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Tetrahedron 60 (2004) 6197–6216
Tetrahedron

Stereodivergent synthesis of the 2,3,5,6-tetrasubstituted piperidine ring system: an application to the synthesis of alkaloids 223A and 205B from poison frogs

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Received 5 April 2004; accepted 10 May 2004

Available online 9 June 2004

Abstract—Stereodivergent synthesis of the 2,3,5,6-tetrasubstituted piperidine ring system has been achieved by sequential stereocontrolled Michael-type conjugate addition reaction of appropriate enaminoesters. This methodology has been applied to the total syntheses of the poison frog alkaloids **223A** and **205B**. The relative stereochemistry of natural **223A** at the 6-position was revised, and the absolute stereochemistry of natural **205B** was determined by the present synthesis.

1. Introduction

Alkaloids containing a piperidine ring are abundant in nature. 2,6-Disubstituted piperidine ring systems especially, are a major structural element found in these natural products.[1] Many of these alkaloids exhibit intriguing biological activities. Accordingly, numerous efforts to construct this heterocycle have been reported to date.[2] The 2,3,5,6-tetrasubstituted piperidine system, which is found in some natural products, is generally more difficult to synthesize and few general methods exist to control the relative stereochemistry of the four substituents. As part of a program aimed at developing syntheses of biologically active alkaloids,[3] we present here a full account of the stereodivergent construction of two 2,3,5,6-tetrasubstituted piperidine ring systems.[4]

Our basic strategy for the stereodivergent construction of the 2,3,5,6-tetrasubstituted piperidine ring core is shown in Figure 1. The strategy involves the sequential use of Michael-type conjugate addition reaction to an enaminoester. The stereodiversity is a consequence of using an acyclic or cyclic carbamate functionality to provide total conformational control of the substrate in the second addition reaction.

2. Results and discussion

The synthesis of a 3,5-*cis*-type 2,3,5,6-tetrasubstituted piperidine core started with known amide **1**.[5] Treatment of **1** with *n*-BuLi and $ClCO_2Me$ provided methyl carbamate **2**, which was converted in high yield to enoltriflate **3** using

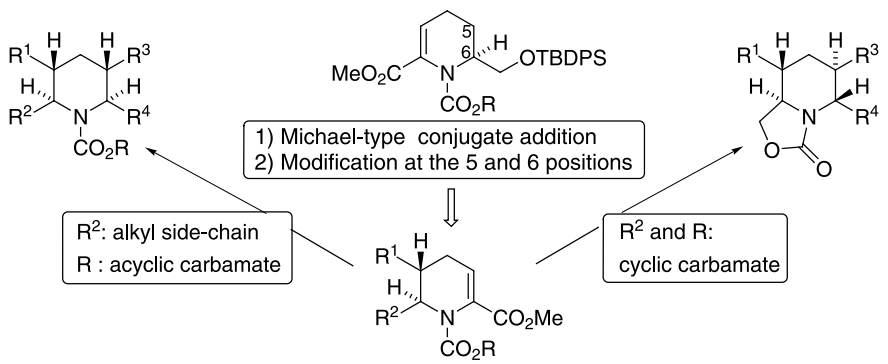

Figure 1.

Keywords: Alkaloids; Comins' triflating agent; Piperidones.
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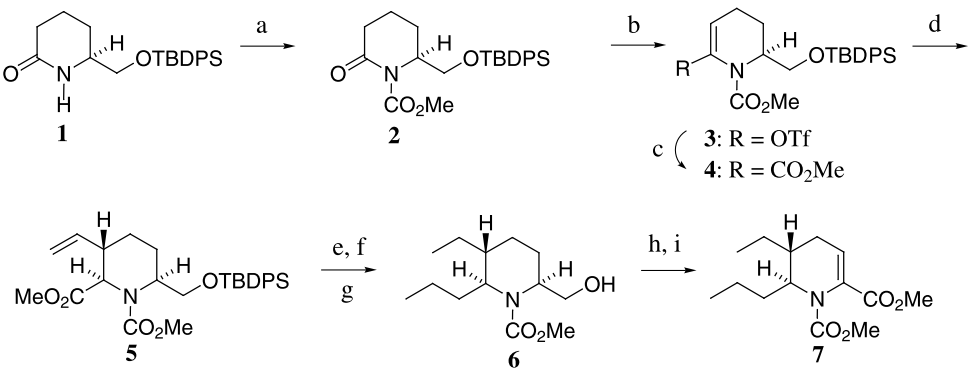
doi:10.1016/j.tet.2004.05.039



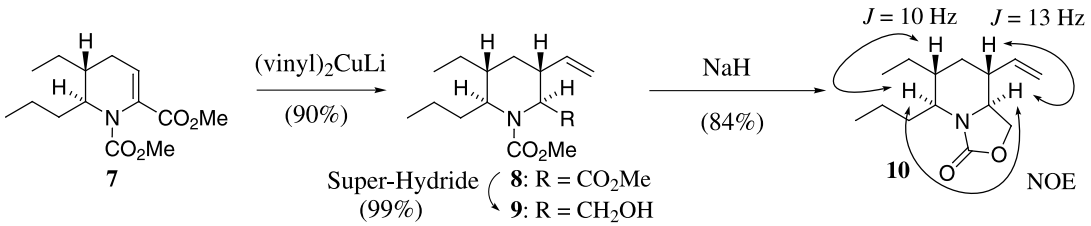
Scheme 1. (a) *n*-BuLi, $ClCO_2Me$ (98%); (b) LiHMDS, 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (Comins' reagent) (96%); (c) CO, $Pd(Pl_3P)_4$, Et_3N, MeOH (88%); (d) $(vinyl)_2CuLi$ (96%); (e) Supper-Hydride (96%); (f) Swern ox. then *n*-BuLi, $EtP^+Ph_3Br^-$ (79%); (g) 5% Pd–C, H_2 then TBAF (77%); (h) swern ox. then $NaClO_2$ then CH_2N_2 (90%); (i) LiHMDS, PhSeCl (77%).

Comins' triflating agent.[6] Palladium-catalyzed CO insertion reaction in the presence of MeOH[7] gave rise to enaminoester **4**. The first Michael-type conjugate addition reaction[8] to **4** proceeded smoothly to afford the adduct **5** as a single isomer. For the key, second Michael-type conjugate addition reaction of divinyllithium cuprate, the adduct **5** was transformed into the second enaminoester **7** via the alcohol **6** as shown in Scheme 1.

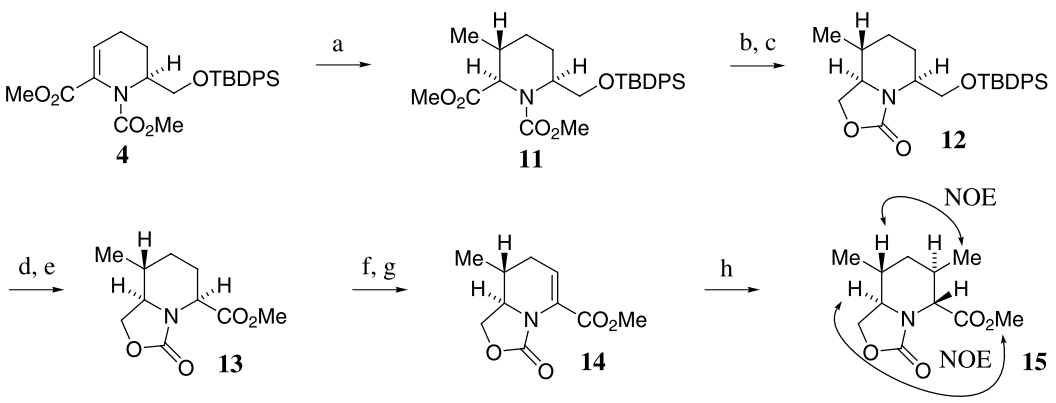
With the requisite enaminoester **7** in hand, we next investigated the second and key conjugate addition reaction. Accordingly, treatment of **7** with divinyllithium cuprate provided the tetrasubstituted piperidine **8**, again as a single isomer. The expected 3,5-*cis*-stereochemistry of **8** was confirmed by the coupling constants indicated and an NOE experiment on the corresponding oxazolizinone derivative **10**, prepared via the alcohol **9** as shown in Scheme 2.

From the synthesis of **205B** we required the cyclic enaminoester **14**. The previously obtained enaminoester **4** was converted to the trisubstituted piperidine **11** using our original Michael-type conjugate addition reaction, which was transformed into the oxazolizinone **12**. Removal of the silyl protecting group and a two-step oxidation of the resulting alcohol followed by esterification with diazomethane provided the methyl ester **13**. This ester was converted to **14** using the protocol developed by Matsumura et al.[9] The key, second Michael-type conjugate addition reaction of **14** proceeded smoothly to give rise to the tetrasubstituted piperidine **15** in high yield and as a single isomer. The 3,5-*trans*-stereochemistry of **15** was confirmed by the NOE experiment, whose results are shown in Scheme 3.

The observed, remarkable stereoselectivity of the conjugate addition reactions of **7** and **14** can be rationalized by the stereoelectronic effect[10] and is also consistent with Cieplak's hypothesis,[11] both illustrated in Figure 2.



Scheme 2.



Scheme 3. (a) $(Me)_2CuLi$ (98%); (b) Super-Hydride (92%); (c) NaH (99%); (d) TBAF (99%); (e) Swern ox. then $NaClO_2$ then CH_2N_2 (86%); (f) LiHMDS, PhSSPh (99%); (g) *m*-CPBA, 2,6-lutidine (85%); (h) $(Me)_2CuLi$ (93%).

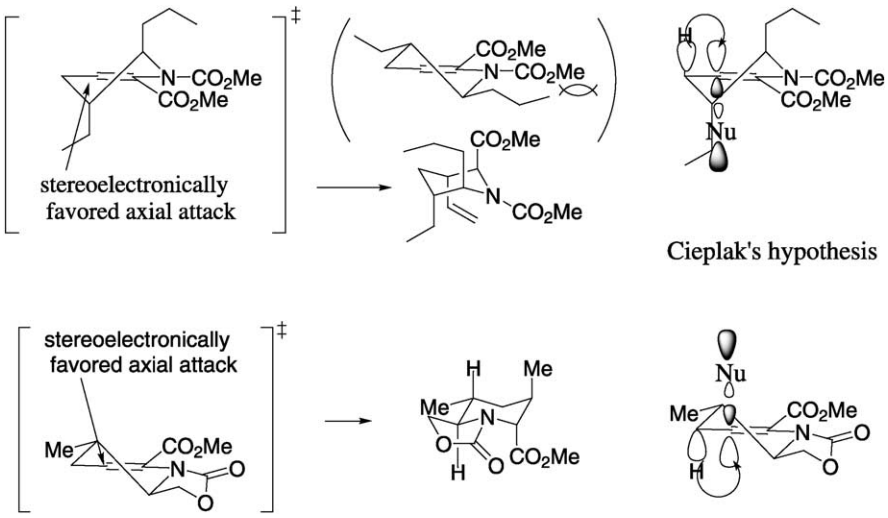
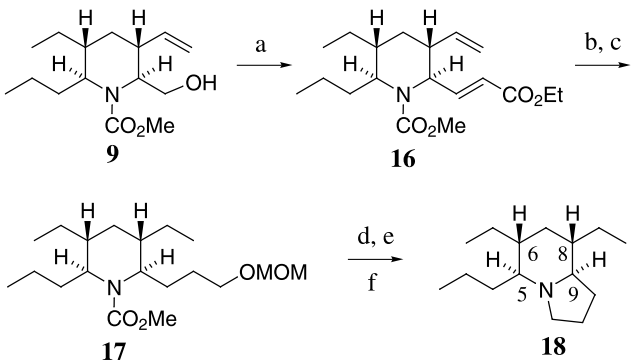


Figure 2.

Thus, we achieved the stereodivergent synthesis of the 2,3,5,6-tetrasubstituted piperidine ring core with complete stereoselection. To illustrate the efficacy of our protocol for the construction of tetrasubstituted piperidines, syntheses of poison frog alkaloids **223A** and **205B** were undertaken. Alkaloid **223A** was isolated from a skin extract of a Panamanian population of the frog *Dendrobates pumilio* Schmidt (Dendrobatidae) in 1997, and it was the first member of a new trialkyl-substituted indolizidine class of amphibian alkaloids to be characterized.[12] In a preliminary report, the configuration of the ethyl group at C-6 position was revised.[4] The tetrasubstituted piperidine **9** was converted to the unsaturated ester **16**, whose double bonds were hydrogenated over Pd–C. Reduction of the ester moiety with Super-Hydride followed by protection of the resulting alcohol with MOMCl in the presence of Hünig's base provided the MOM ether **17**. Finally, removal of the methoxycarbonyl and MOM groups, followed by indolizidine cyclization of the intermediate propyl bromide furnished the desired indolizidine **18** (Scheme 4).



Scheme 4. (a) Swern ox. then $(EtO)_2P(O)CH_2CO_2Et$, NaH (96%); (b) 10% Pd–C, H_2, then Super-Hydride (89%); (c) MOMCl, Hünig's base (86%); (d) *n*-PrSLi, HMPA; (e) c. HCl, MeOH; (f) CBr_4, Ph_3P, Et_3N (52%).

The ^1H and ^{13}C NMR and IR spectra of **18** were not identical with those for the natural product, nor was the GC retention time. The close similarity of the Bohlmann bands in the vapor phase FTIR spectra of **18** and natural **223A** indicated the same 5,9-*Z* configuration for both compounds. In ^1H NMR spectra, our synthetic DCl salt of **18** showed a nicely separated quartet-like signal at δ 1.01 with a *J* of 12.5 Hz for the H-7 axial proton. This observation means that the quartet-like signal with three large and approximately equal couplings for the H-7 axial proton must include two *trans*-diaxial vicinal couplings with H-6 and H-8 protons and one geminal coupling with the H-7 equatorial proton, and thus both ethyl-substituents at the 6- and 8-positions should be of the equatorial orientation as shown in Figure 3. A quartet at this chemical shift was not seen in the natural material. On the other hand, the H-5 proton in **18** and natural **223A** was a doublet of triplet with *J* values of 11, 2.5 and 11, 4.7 Hz, respectively, in the ^1H NMR spectrum. We now conclude the hindered rotation at C-5 in the C-6 epimer **30** of proposed structure for natural **223A** (**18**) leads to a large (11-Hz J_{5-10}) coupling and does not reflect an originally assumed *trans*-diaxial J_{5-6} coupling.

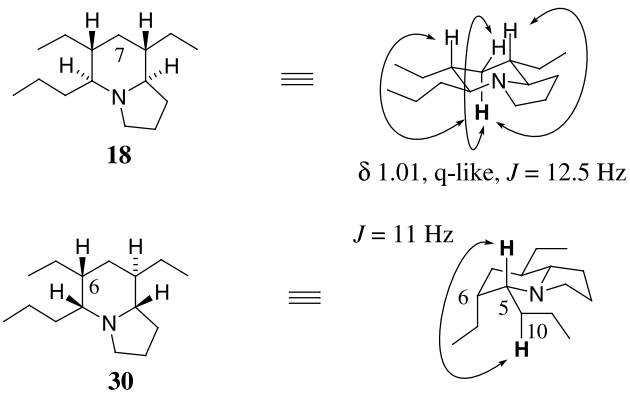
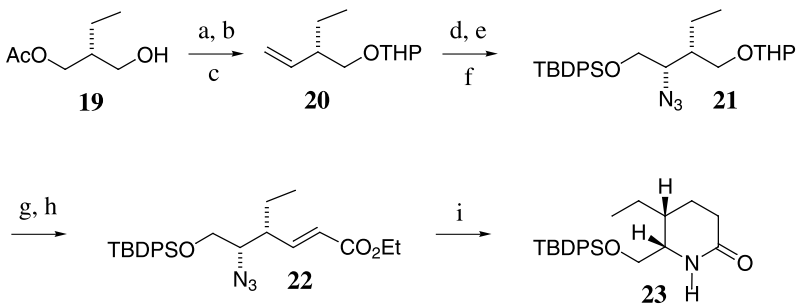
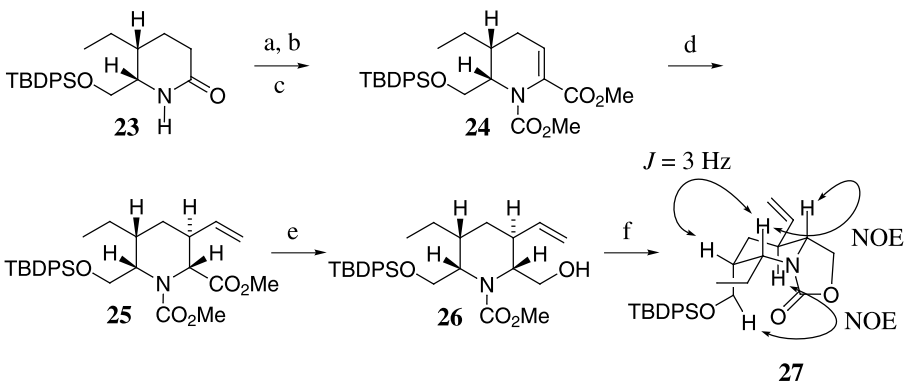


Figure 3.

Therefore, we commenced the synthesis of the 6-epimer (**30**) of initially proposed structure for **223A**. For the synthesis of **30**, we needed the *cis*-substituted piperidone **23**. Synthesis of **23** began with the known 2*R* mono-acetate **19**,[13] which was converted to the olefin **20**. A $(DHQD)_2$-PYR ligand-induced AD reaction[14] of **20** followed by protection of the primary hydroxyl group gave the secondary alcohol, which was transformed into the azide **21** via the mesylate. Removal of the THP protecting group



Scheme 5. (a) DHP, PPTS; (b) K_2CO_3, MeOH; (c) Swern ox then $PH_3P^+CH_3Br^-$, *n*-BuLi (76%); (d) AD-mix β-$(DHQD)_2PYR$ ligand (80%); (e) TBDPSCl, Et_3N, DMAP (98%); (f) MsCl, Et_3N then NaN_3 (83%); (g) PPTS, EtOH; (h) Swern ox then NaH, $(EtO)_2P(O)CH_2CO_2Et$ (88%); (i) 10% Pd–C, H_2 (73%).



Scheme 6. (a) *n*-BuLi, $ClCO_2Me$ (97%); (b) LiHMDS, Comins' reagent (97%); (c) CO, $Pd(Ph_3P)_4$, Et_3N, MeOH (75%); (d) $(vinyl)_2CuLi$ (95%); (e) Super-Hydride (96%); (f) NaH (94%).

with PPTS, and Swern oxidation followed by the Horner–Emmons reaction provided the unsaturated ester **22**. Hydrogenation of **22** over Pd–C under medium pressure gave rise to desired piperidone **23** (Scheme 5).

This piperidone was transformed into the enaminoester **24** in the same manner as the synthesis of **4**. The key Michael-type conjugate addition reaction to **24** was achieved by treatment of **24** with divinyllithium cuprate to give the 3,5-*trans*-adduct **25** as a single isomer. The stereochemistry of **25** was determined to be that of the desired intermediate for the synthesis of **30** by the coupling constant indicated and the NOE cross peaks of the oxazolidinone **27** derived from the alcohol **26** as shown in Scheme 6.

Stereoselectivity of this conjugate addition reaction can also be explained as shown in Figure 4. Attack of the vinyl anion is preferred from the stereoelectronically favored β-axial orientation on the conformation **24-A** to form **25**. The alternative conformation **24-B** is unlikely due to $A^{(1,3)}$ strain.[15]

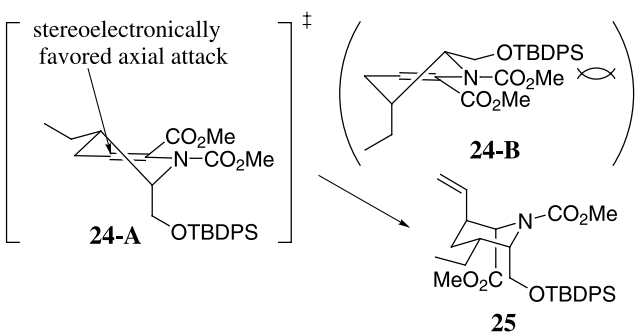
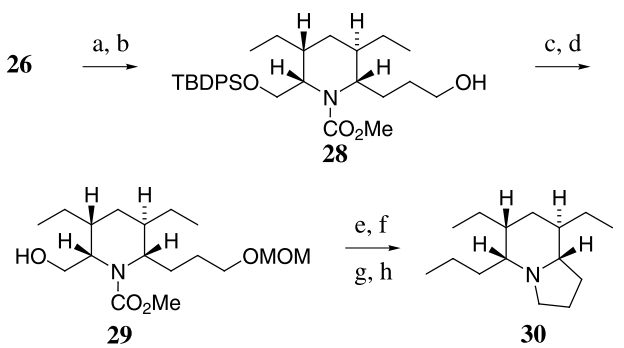


Figure 4.

The alcohol **26** was converted to the 2-carbon-homologated alcohol **28**. Protection of the hydroxyl group in **28** followed by removal of the silyl group provided the alcohol **29**. After carbon-chain elongation of **29** at the α-position, a three-step indolizidine cyclization reaction gave rise to indolizidine **30**,[16] whose spectral data were completely in accord with those for natural **223A** (Scheme 7).

Thus the structure of natural **223A** was revised to **30**,[4] and the relative stereochemistry of this natural product was



Scheme 7. (a) Swern ox. then $(EtO)_2P(O)CH_2CO_2Et$, NaH (92%); (b) 10% Pd–C, H_2 then Super-Hydride (98%); (c) MOMCl, Hünig base (89%); (d) TBAF (79%); (e) Swern ox. then *n*-BuLi, $EtP^+Ph_3Br^-$ (83%); (f) 10% Pd–C, H_2; (g) *n*-PrSLi, HMPA then c. HCl, MeOH; (h) CBr_4, Ph_3P, Et_3N (51%).

determined to be $5R^*,6R^*,8R^*,9S^*$ by the present synthesis.

Alkaloid **205B**, isolated from skin extracts of the Panamanian frog *Dendrobates pumilio*, possesses an unusual and unique 8b-azaacenaphthylene ring system.[17] In addition to this unique structure, the alkaloid contains five asymmetric centers in its compact, fourteen-carbon-atom tricycle. The structure of alkaloid **205B** was first reported to be **A**, and recently revised to be **B** based on FTIR, NMR, and MS spectral data.[18] At present, no synthesis of this alkaloid has been reported, and the absolute stereochemistry is still unknown (Fig. 5).

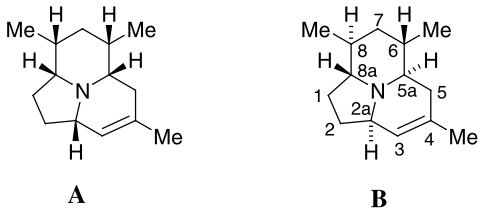


Figure 5.

We applied our tetrasubstituted piperidine synthesis illustrated in Figure 1 to the synthesis of alkaloid **205B**. The side chain on the 6-position of **15** was homologated by the Arndt–Eistert sequence to afford the ester **31**, which was converted to methyl ketone **33** via Weinreb's amide[19] **32** in good yield. After protection of the carbonyl group in **33**, the oxazolizinone ring was hydrolyzed by treatment with 2 M KOH in *i*-PrOH at 120 °C in a sealed tube followed by protection of the resulting amino alcohol with Boc_2O in the presence of NaOH to give rise to **34**. Swern oxidation of **34** followed by the Horner–Emmons reaction of the resulting aldehyde yielded the unsaturated ester **35**. Hydrogenation of the double bond in **35** and reduction of the ester moiety with DIBAL provided the aldehyde, which was subjected to an intramolecular Mannich-type cyclization reaction by treatment with *p*TsOH to provide the tricyclic ketone **36** along with its acetal **37** (Scheme 8).

The stereochemical outcome of this cyclization can be explained as depicted in Figure 6.

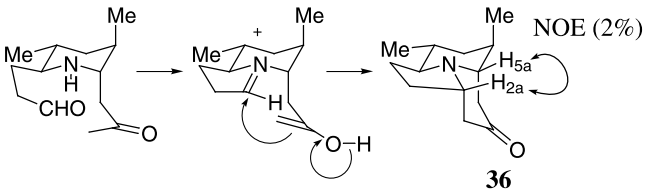
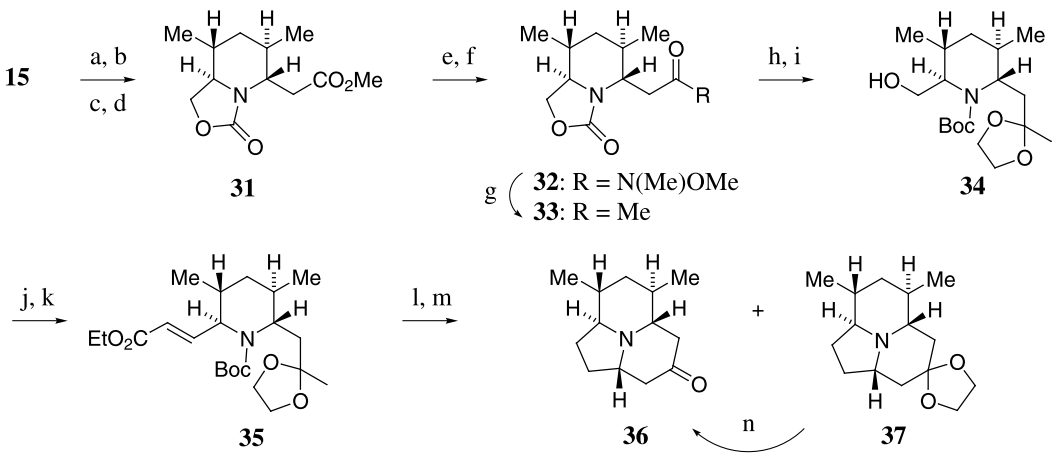


Figure 6.

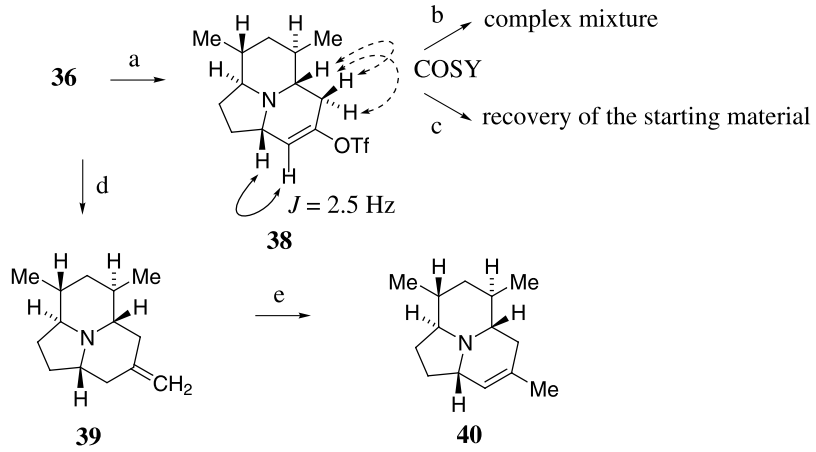
Regioselective enolization of the ketone precursor to **36** in the presence of a chiral lithium amide base was performed to give the enol triflate as a 3:1 mixture of regioisomers, and major product **38** resulted in 54% yield. The tricyclic ketone **38** was confirmed to have the desired stereochemistry as shown in Scheme 9. Attempts to convert **38** into final product **40** under the Takai and Nozaki's protocol[20] or McMurry's reaction conditions[21] led only to a complex mixture or recovered starting material, respectively. On the other hand, the acid-catalyzed isomerization of the exo-olefin **39**, derived from **36** by Wittig olefination was quite effective,[22] and led to the desired endo-olefin **40** in 63% yield. The spectroscopic data of **40** were identical with those for the natural product. The absolute sterochemistry of natural **205B** was unambiguously determined to be an antipode of our synthetic **40** by comparison of optical rotations.

3. Conclusion

In summary, we have succeeded in stereodivergent syntheses of two 2,3,5,6-tetrasubstituted piperidine ring systems with complete stereoselection by sequential use of Michael-type conjugate addition reaction to enaminoesters. Using this methodology, we completed the first total synthesis of the alkaloids **223A** and **205B** both of which possess the above tetrasubstituted piperidine ring structural element. The original structure for alkaloid **223A** has been



Scheme 8. (a) LiOH, MeOH–H_2O; (b) $ClCO_2Et$, Et_3N: (c) CH_2N_2; (d) $PhCO_2Ag$, Et_3N, MeOH (71%); (e) LiOH, MeOH–H_2O; (f) 1,1′-carbonyldiimidazole then E_3tN, (MeO)MeNH·HCl (98%); (g) MeMgBr (73%); (h) ethylene glycol *p*-TsOH (86%); (i) 2 M KOH in *i*-PrOH, 120 °C then Boc_2O, NaOH (74%); (j) Swern ox.; (k) $(EtO)_2P(O)CH_2CO_2Et$, NaH (74%); (l) 10% Pd–C, H_2 then DIBAL; (m) *p*-TsOH, benzene–acetone (**36**; 62%, **37**; 15%); *n*-TsOH, acetone (80%).



Scheme 9. (a) *R*-(*R**, *R**)-(+)-bis(α-methylbenzyl)amine, *n*-BuLi then Comins' reagent (54%); (b) $Pd(Ph_3P)_4$, Me_3Al; (c) $(Me)_2CuLi$; (d) $MeP^+Ph_3I^-$, *n*-BuLi (84%); (e) *p*-TsOH, benzene, reflux (63%).

revised to **30**, and the absolute stereochemistry of **205B** was determined to be 2a*R*,5a*R*,6*S*,8*S*,8a*R* by the present total synthesis.

4. Experimental

4.1. General

Melting points were determined with a Yanaco micro melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were taken on a Varian Gemini 300 or Unity Plus 500 spectrometer. ^1H NMR spectra were recorded at the indicated field strength as solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are given in parts per million (ppm, δ) downfield from TMS and are referenced to $CHCl_3$ (7.26 ppm) as internal standard. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR spectra were recorded at the indicated field strength as solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are given in parts per million (ppm, δ) downfield from TMS and are referenced to the center line of $CDCl_3$ (77.0 ppm) as internal standard. Carbon signals were assigned by a DEPT pulse sequence, q=methyl, t=methylene, d=methyne, and s=quaternary carbons. Infrared spectra (IR) were measured with a Perkin–Elmer 1600 series FT-IR spectrophotometer. Mass spectra (MS) and high-resolution mass spectra (HRMS) were measured on a JEOL JMS-AX505HAD mass spectrometer. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. Column chromatography was performed on Merck silica gel 60 (No 7734-5B) or (No 9385). Elemental analysis were performed by the micro analytical laboratory of this University.

4.1.1. Methyl (6*S*)-(−)-2-(*tert*-butyldiphenylsilyloxymethyl)-6-oxopiperidine-1-carboxylate (2). To a stirred solution of **1** (1.85 g, 5.40 mmol) in THF (22 mL) was added a solution of *n*-BuLi (1.6 m in hexane, 3.5 mL, 5.54 mmol) at −78 °C, and the resulting mixture was stirred at −78 °C for 30 min. To the reaction mixture was added $ClCO_2Me$ (0.43 mL, 5.54 mmol) at −78 °C, and then the reaction mixture was warmed to 0 °C for 2 h. The reaction was quenched with satd. $NaHCO_3$ (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (50 mL×1, 15 mL×2). The organic extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (50 g, hexane:acetone=30:1–20:1) to give **2** (2.10 g, 98%) as a colorless solid (mp 97–102 °C).

IR (KBr) 2958, 1718, 1113 cm^{-1}; ^1H NMR (500 MHz) δ 1.06 (9H, s), 1.69–1.75 (1H, m), 1.86–1.99 (2H, m), 2.12–2.17 (1H, m), 2.49–2.52 (2H, m), 3.72–3.76 (2H, m), 3.76 (3H, s), 4.41–4.44 (1H, m), 7.37–7.45 (6H, m), 7.63–7.67 (4H, m); ^{13}C NMR (125 MHz) δ 17.44 (t), 18.96 (s), 24.18 (t), 26.63 (q), 34.64 (t), 53.52 (q), 56.16 (d), 64.10 (t), 127.60 (d), 129.65 and 129.68 (each d), 132.63 and 132.81 (each s), 135.36 and 135.42 (each d), 154.69 (s), 171.69 (s); MS: 425 (M^+), 115 (100); HRMS: Calcd for $C_{24}H_{31}NO_4Si$ 425.2022. Found 425.2006. Anal. Calcd for $C_{24}H_{31}NO_4Si$ C, 67.73; H, 7.34; N, 3.29. Found C, 67.73; H, 7.39; N, 3.32; $[\alpha]_D^{26}$=41.6 (*c* 5.67, $CHCl_3$).

4.1.2. Mehtyl (6*S*)-(−)-2-(*tert*-butyldiphenylsilyloxymethyl)-6-trifluoromethanesulfonyloxy-3,4-dihydro-2*H*-pyridine-1-carboxylate (3). To a stirred solution of hexamethyldisilazane (1.5 mL, 6.97 mmol) in THF (5 mL) was added a solution of *n*-BuLi (1.6 M in hexane, 4.4 mL, 6.97 mmol) at 0 °C, and the resulting solution was stirred at 0 °C for 30 min. To a stirred solution of **2** (2.47 g, 5.81 mmol) in THF (15 mL) was added a solution of LiHMDS prepared above at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. To the above reaction mixture was added a solution of 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]5-chloropyridine (Comins' reagent) (97%, 2.73 g, 6.97 mmol) in THF (6 mL) at −78 °C, and the resulting mixture was warned to −40 °C for 1 h. The reaction was quenched with satd. NH_4Cl (aq.), and the aqueous mixture was extracted with Et_2O (20 mL×4). The organic extracts were combined, dried, and evaporated to give pale yellow solid, which was chromatographed on SiO_2 (60 g, hexane:acetone=100:1–50:1) to give **3** (3.0 g, 96%) as a colorless oil.

IR (neat) 2962, 1733, 1423, 1213, 1114 cm^{-1}; ^1H NMR (500 MHz) δ 1.06 (9H, s), 1.69–1.76 (1H, m), 1.91–2.04 (2H, br m), 2.13–2.19 (1H, m), 3.57 (2H, dd, *J*=10.2, 8.1 Hz), 3.79 (3H, s), 4.64–4.68 (1H, m), 5.17 (1H, t,

J=3.8 Hz), 7.37–7.46 (6H, m), 7.63–7.67 (4H, m); ^{13}C NMR (125 MHz) δ 19.09 (t), 19.29 (s), 22.22 (t), 26.81 (q), 53.69 (q), 55.63 (d), 60.79 (t), 106.05 (d), 127.63 (d), 129.69 (d), 133.06 and 133.11 (each s), 135.42 and 135.44 (each d), 138.05 (s), 154.69 (s); MS: 557 (M^+), 422 (100); HRMS: Calcd for $C_{25}H_{30}F_3NO_6Si$ 557.1515. Found 557.1518; $[\alpha]_D^{26}$=−18.8 (*c* 1.57, $CHCl_3$).

4.1.3. Dimethyl (*S*)-(−)-6-(*tert*-butyldiphenylsilyloxymethyl)-5,6-dihydro-4*H*-pyridine-1,2-dicarboxylate (4). To a stirred solution of the above **3** (5.30 g, 9.52 mmol) in DMF (25 mL) was added $Pd(Ph_3P)_4$ (550 mg, 0.48 mmol), and the resulting mixture was stirred at room temperature under CO balloon pressure for 30 min. To the reaction mixture were added Et_3N (5.3 mL, 38.1 mmol) and MeOH (15.4 mL, 381.0 mmol), and then the reaction mixture was stirred at 70 °C under CO balloon pressure for 15 h. After cooling, the reaction mixture was diluted with H_2O (100 mL) and brine (25 mL), and the aqueous mixture was extracted with Et_2O (50 mL×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (80 g, hexane:acetone=50:1–30:1) to give **4** (3.91 g, 88%) as a colorless oil.

IR (neat) 2968, 1732, 1652, 1240 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.05 (9H, s), 1.77–1.85 (1H, m), 1.91–1.99 (1H, br m), 2.04–2.16 (2H, m), 3.52 (1H, dd, J=10.2, 8.5 Hz), 3.70 (3H, s), 3.71 (3H, s), 3.77 (1H, dd, J=10.2, 6.3 Hz), 4.55 (1H, br), 5.96 (1H, t, J=3.5 Hz), 7.37–7.45 (6H, m), 7.65–7.67 (4H, m); ^{13}C NMR (125 MHz) δ 19.43 (t), 19.55 (s), 22.48 (t), 26.95 (q), 52.16 (q), 52.69 (d), 53.30 (q), 61.39 (t), 121.98 (s), 127.72 (d), 129.72 and 129.75 (each d), 130.59 (s), 133.31 and 133.41 (each s), 135.58 (d), 154.52 (s), 165.49 (s); MS: 467 (M^+, 100); HRMS: Calcd for $C_{26}H_{33}NO_5Si$ 467.2128. Found 467.2134; $[\alpha]_D^{26}$=−53.3 (*c* 1.33, $CHCl_3$).

4.1.4. Dimethyl (2*R*,3*S*,6*S*)-(+)-6-(*tert*-butyldiphenylsilyloxymethyl)-3-vinylpiperidine-1,2-dicarboxylate (5). To a stirred suspension of CuI (1.71 g, 9.00 mmol) in Et_2O (15 mL) was added a solution of vinyl lithium, prepared from tetravinyltin (0.37 mL, 4.50 mmol) and MeLi (1.0 M in Et_2O, 18 mL, 18.0 mmol) in Et_2O (15 mL) at 0 °C for 30 min, at −78 °C, and the resulting suspension was warmed to −35 °C for 20 min. The resulting suspension was re-cooled to −78 °C, and a solution of **4** (1.05 g, 2.25 mmol) in Et_2O (5 mL) was added to the resulting suspension. The reaction mixture was warmed to −30 °C for 1 h, and the reaction was quenched with satd. NH_4Cl (aq.). The aqueous mixture was diluted with CH_2Cl_2 (100 mL), and the resulting suspension was filtered. The filtrate was separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL×2). The organic layer and extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (40 g, hexane:acetone=40:1–30:1) to give **5** (1.07 g, 96%) as a colorless oil.

IR (neat) 3071, 2935, 2890, 1750, 1705, 1113 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.05 (9H, s), 1.41–1.43 (1H, m), 1.59 (1H, br), 1.74–1.81 (1H, br m), 1.85–1.88 (1H, m), 3.00 (1H, br), 3.45 (3H, s), 3.65 (3H, s), 3.67–3.70 (1H, m), 4.28 (1H, br), 4.78 (1H, br), 5.09–5.30 (2H, m), 5.81–5.88 (1H, m), 7.36–7.44 (6H, m), 7.65–7.67 (4H, m); ^{13}C NMR (125 MHz) δ 18.68 (t), 19.56 (s), 21.03 (t), 27.15(q), 37.06 (d), 52.27 (d), 52.34 (q), 53.19 (q), 56.05 (d), 62.34 (t), 115.56 (t), 127.74 (d), 129.72 (d), 133.76 (s), 135.63 (d), 138.91 (d), 157.63 (s), 172.66 (s); MS: 495 (M^+); HRMS: Calcd for $C_{28}H_{37}NO_5Si$ 495.2441. Found 495.2464; $[\alpha]_D^{26}$=+2.1 (*c* 1.57, $CHCl_3$).

4.1.5. Methyl (2*R*,3*S*,6*S*)-(+)-6-(*tert*-butyldiphenylsilyloxymethyl)-2-hydroxymethyl-3-vinylpiperidine-1-carboxylate. To a stirred solution of **5** (2.0 g, 4.04 mmol) in THF (15 mL) was added Super-Hydride (1 M in THF, 8.9 mL, 8.9 mmol) at 0 °C, and the resulting solution was stirred at 0 °C for 1 h. The reaction was quenched with satd. $NaHCO_3$ (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (15 mL×6). The organic extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (40 g, hexane:acetone=30:1–6:1) to give an alcohol (1.8 g, 96%) as a colorless oil.

IR (neat) 3449, 3070, 2937, 2862, 1679 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.05 (9H, s), 1.26–1.39 (2H, m), 1.63–1.70 (1H, m), 1.79–1.86 (1H, br m), 2.35 (1H, br), 2.96 (1H, br), 3.55–3.69 (4H, m), 3.67 (3H, br s), 4.25–4.29 (1H, m), 4.39 (1H, br), 5.06–5.12 (2H, m), 5.79–5.86 (1H, m), 7.39–7.46 (6H, m), 7.66–7.72 (4H, m); ^{13}C NMR (125 MHz) δ 19.03 (s), 19.95 (t), 21.27 (t), 26.67 and 26.72 (each q), 36.70 (d), 50.83 (d), 52.72 (q), 56.14 (d), 64.43 (t), 64.88 (t), 115.05 (t), 127.67 and 127.70 (each d), 129.74 (d), 132.93 and 133.02 (each s), 135.44 and 135.49 (each d), 140.18 (d), 157.97 (s); MS: 410 (M^+−57), 378 (100); HRMS: Calcd for $C_{23}H_{28}NO_4Si$ 410.1787. Found 410.1807; $[\alpha]_D^{26}$=+19.7 (*c* 1.53, $CHCl_3$).

4.1.6. Methyl (2*S*,3*S*,6*S*)-(−)-6-(*tert*-butyldiphenylsilyloxymethyl)-2-propenyl-3-vinylpiperidine-1-carboxylate. To a stirred solution of $(COCl)_2$ (0.24 mL, 2.77 mmol) in CH_2Cl_2 (5 mL) was added DMSO (0.38 mL, 5.43 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 10 min. To the mixture was added a solution of the alcohol prepared above (857 mg, 1.84 mmol) in CH_2Cl_2 (4 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. Triethylamine (1.1 mL, 7.98 mmol) at −78 °C, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (10 mL×4). The organic extracts were combined, dried and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred suspension of $EtP^+Ph_3Br^-$ (2.73 g, 7.35 mmol) in THF (15 mL) was added a solution of *n*-BuLi (1.6 M in hexane, 4 mL, 6.4 mmol) at 0 °C, and the resulting orange solution was stirred at 0 °C for 30 min. To the solution was added a solution of the above oil in THF (6 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (15 mL×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (30 g, hexane:acetone=100:1–80:1) to give an olefin (691 mg, 79% in 2 steps) as a colorless oil.

IR (neat) 3070, 2938, 2860, 1697 cm^{-1}; ^1H NMR (500 MHz) δ 1.06 (9H, s), 1.33–1.38 (1H, m), 1.67 (3H, t-like, J=6.8 Hz), 1.69–1.75 (2H, br m), 1.81–1.88 (1H, m), 2.19 (1H, br), 3.58–3.69 (2H, m), 3.63 (3H, br s), 4.35 (1H, m), 4.90 (1H, d-like, J=9.4 Hz), 5.05–5.10 (2H, m), 5.29–5.33 (1H, m), 5.38–5.43 (1H, m), 5.85–5.91 (1H, m), 7.38–7.45 (6H, m), 7.67–7.68 (4H, m); ^{13}C NMR (125 MHz) δ 13.02 (q), 19.18 (s), 19.47 (t), 20.73 (t), 26.78 (q), 41.73 (d), 51.01 (d), 51.71 (d), 52.46 (q), 64.35 (t), 114.70 (t), 127.62 (d), 129.62 (d), 131.10 (d), 133.50 and 133.64 (each s), 135.56 and 135.59 (each d), 140.22 (d), 156.81 (s); MS: 420 (M^+-57), 423 (100); HRMS: Calcd for $C_{25}H_{30}NO_3Si$ 420.1995. Found 420.2017; $[\alpha]_D^{26}=-64.5$ (c 2.09, $CHCl_3$).

4.1.7. Methyl (2*S*,3*R*,6*S*)-(−)-3-ethyl-6-hydroxymethyl-2-propylpiperidine-1-carboxylate (6). To a solution of the above olefin (704 mg, 1.48 mmol) in EtOAc (15 mL) was added 5% Pd–C (50 mg), and the resulting suspension was hydrogenated under hydrogen atmosphere at 1 atm for 48 h. The catalyst was removed by filtration, and the filtrate was evaporated to give colorless oil, which was used directly in the next step.

To a stirred solution of the above oil in THF (10 mL) was added a solution of TBAF (1 M in THF, 1.9 mL, 1.9 mmol) at 0 °C, and the resulting solution was stirred at room temperature for 1 h. The reaction was quenched with satd. NH_4Cl (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (10 mL×8). The organic extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (20 g, hexane:acetone=20:1–7:1) to give **6** (276 mg, 77% in 2 steps) as a colorless oil.

IR (neat) 3447, 2956, 2872, 2672 cm^{-1}; ^1H NMR (500 MHz) δ 0.87–0.91 (6H, m), 1.23–1.59 (9H, br m), 1.71–1.81 (2H, m), 2.94 (1H, br), 3.57–3.64 (2H, m), 3.68 (3H, s), 3.92 (1H, br), 4.25 (1H, br); ^{13}C NMR (125 MHz) δ 11.96 (q), 13.98 (q), 19.92 (t), 20.15 (t), 25.73 (t), 37.93 (d), 38.87 (t), 52.67 (q), 52.89 (d), 54.46 (d), 52.46 (q), 65.77 (t), 158.85 (s); MS: 243 (M^+), 131 (100); HRMS: Calcd for $C_{13}H_{25}NO_3$ 243.1833. Found 243.1821; $[\alpha]_D^{26}=-21.8$ (c 1.05, $CHCl_3$).

4.1.8. Dimethyl (2*S*,5*R*,6*S*)-(−)-5-ethyl-6-propylpiperidine-1,2-dicarboxylate. To a stirred solution of $(COCl)_2$ (0.53 mL, 6.12 mmol) in CH_2Cl_2 (12 mL) was added DMSO (0.88 mL, 12.38 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 10 min. To the mixture was added a solution of **6** (1 g, 4.12 mmol) in CH_2Cl_2 (9 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. Triethylamine (2.6 mL, 18.47 mmol) at −78 °C, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (20 mL×4). The organic extracts were combined, dried and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred suspension of NaH_2PO_4 (4.9 g, 40.83 mmol), 2-methyl-2-butene (8.8 mL, 82.5 mmol), and the above oil in t-BuOH (20 mL) was added a solution of $NaClO_2$ (80%, 2.7 g, 24.3 mmol) in H_2O (8 mL), and the resulting suspension was stirred at room temperature for 45 min. The reaction was quenched with satd. $NaHSO_3$ (aq.) and 10% HCl at 0 °C, and the aqueous mixture was extracted with EtOAc (15 mL×10). The organic extracts were combined, dried, and evaporated to give colorless oil, which was used directly in the next step.

To a stirred solution of the above oil in EtOAc (20 mL) was added a solution of CH_2N_2 in Et_2O at 0 °C, and the reaction mixture was stirred at room temperature for 20 h. The solvent was evaporated, and the residue was chromatographed on SiO_2 (40 g, hexane:acetone=20:1) to give a methyl ester (1.008 g, 90% in 3 steps) as a colorless oil.

IR (neat) 2957, 2872, 1740, 1701 cm^{-1}; ^1H NMR (500 MHz) δ 0.86 (6H, t-like, J=6.8 Hz), 1.24–1.42 (7H, br m), 1.46–1.52 (1H, m), 1.71–1.87 (2H, m), 1.96 (1H, br), 3.66 (3H, s), 3.69 (3H, br s), 3.88–4.05 (1H, br), 4.63 and 4.84 (1H, br); ^{13}C NMR (125 MHz) δ 11.87 (q), 13.86 (q), 19.91 (t), 20.31 (t), 25.02 (t), 36.19 (t), 37.75 (d), 51.92 (q), 52.72 (q), 54.79 (d), 157.80 (s), 173.24 (s); MS: 271 (M^+), 228 (100); HRMS: Calcd for $C_{14}H_{25}NO_4$ 271.1784. Found 271.1816; $[\alpha]_D^{26}=-65.1$ (c 2.17, $CHCl_3$).

4.1.9. Dimethyl (5*R*,6*S*)-(+)-5-ethyl-6-propyl-5,6-dihydro-4*H*-pyridine-1,2-dicarboxylate (7). To a stirred solution of hexamethyldisilazane (0.32 mL, 1.5 mmol) in THF (3 mL) was added a solution of n-BuLi (1.6 M in hexane, 0.94 mL, 1.5 mmol) at 0 °C, and the resulting solution was stirred at 0 °C for 30 min. To a stirred solution of the above methyl ester (271 mg, 1 mmol) in THF (2 mL) was added a solution of LiHMDS prepared above at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. To a stirred solution of PhSeCl (610 mg, 3 mmol) in THF (5 mL) was added a solution of Li enolate prepared above at −78 °C, and the resulting suspension was stirred at room temperature for 20 h. The solvent was evaporated and the residue was chromatographed on SiO_2 (30 g, hexane:acetone=40:1–35:1) to give **7** (207 mg, 77%) as a colorless oil.

IR (neat) 2958, 2874, 1708, 1646 cm^{-1}; ^1H NMR (500 MHz) δ 0.91 and 0.93 (each 3H, each t, J=7.2 Hz), 1.17–1.34 (4H, br m), 1.42–1.51 (3H, m), 1.99 (1H, dd, J=19.2, 3.9 Hz), 2.27 (1H, ddd, J=19.2, 7.3, 3.9 Hz), 3.70 (3H, br s), 3.76 (3H, s), 4.26 (1H, br), 5.97 (1H, t, J=3.9 Hz); ^{13}C NMR (125 MHz) δ 11.91 (q), 14.02 (q), 19.30 (t), 25.12 and 26.20 (each t), 33.04 (t), 36.30 (t), 37.99 and 38.66 (each d), 52.10 (q), 53.07 (q), 55.29 (d), 121.05 (d), 129.05 and 129.28 (each s), 155.49 (s), 165.40 (s); MS: 269 (M^+, 100); HRMS: Calcd for $C_{14}H_{23}NO_4$ 269.1627. Found 269.1604; $[\alpha]_D^{26}=+63.4$ (c 0.68, $CHCl_3$).

4.1.10. Dimethyl (2*S*,3*R*,5*R*,6*S*)-(−)-5-ethyl-6-propyl-3-vinylpiperidine-1,2-dicarboxylate (8). To a stirred suspension of CuI (622 mg, 3.27 mmol) in Et_2O (5 mL) was added a solution of vinyl lithium, prepared from tetravinyltin (0.31 mL, 1.63 mmol) and MeLi (1.01 M in Et_2O, 6.5 mL, 6.6 mmol) in Et_2O (3 mL) at 0 °C for 30 min, at −78 °C, and the resulting suspension was warmed to −35 °C for 20 min. The resulting suspension was re-cooled to −78 °C, and a solution of **7** (176 mg, 0.65 mmol) in Et_2O (4 mL) was added to the resulting suspension. The reaction mixture was warmed to 0 °C for 1 h, and the reaction was quenched with

satd. NH_4Cl (aq.). The aqueous mixture was diluted with CH_2Cl_2 (50 mL), and the resulting suspension was filtered. The filtrate was separated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL×2). The organic layer and extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (20 g, hexane:acetone=70:1–40:1) to give **8** (174 mg, 90%) as a colorless oil.

IR (neat) 2957, 2873, 1747, 1702 cm^{-1}; ^1H NMR (500 MHz) δ 0.88 and 0.89 (each 3H, each t, J=7.3 Hz), 0.96 (1H, q, J=12 Hz), 1.24–1.46 (6H, br m), 1.62–1.70 (1H, m), 1.70–1.77 (1H, m), 2.64 (1H, q-like, J=8 Hz), 3.67 (3H, s), 3.69 (3H, s), 3.92 (1H, br), 4.29 (1H, br), 5.00–5.08 (2H, m), 5.71–5.78 (1H, m); ^{13}C NMR (125 MHz) δ 11.31 (q), 13.98 (q), 19.86 (t), 29.56 (t), 31.76 (t), 39.68 (d), 40.50 (t), 40.86 (d), 51.73 (q), 52.81 (q), 55.40 (d), 59.78 (d), 115.31 (t), 139.95 (d), 157.35 (s), 173.20 (s); MS: 254 (M^+-43, 100); HRMS: Calcd for $C_{13}H_{20}NO_4$ ($M^+-C_3H_7$) 254.1392. Found 254.1353; $[\alpha]_D^{26}=-65.9$ (c 0.91, $CHCl_3$).

4.1.11. Methyl (2*S*,3*R*,5*R*,6*S*)-(−)-5-ethyl-2-hydroxymethyl-6-propyl-3-vinylpiperidine-1-carboxylate (9). To a stirred solution of **8** (45 mg, 0.15 mmol) in THF (1 mL) was added a solution of Super-Hydride (1 M in THF, 0.4 mL, 0.4 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h. The reaction was quenched with satd $NaHCO_3$ (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (10 mL×5). The organic extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (10 g, hexane:acetone=30:1–15:1) to give **9** (41 mg, 99%) as a colorless oil.

IR (neat) 3456, 3078, 2958, 2873, 1672 cm^{-1}; ^1H NMR (500 MHz) δ 0.88 and 0.92 (each 3H, each t, J=7.3 Hz), 1.00 (1H, q, J=10.7 Hz), 1.28–1.47 (6H, br m), 1.53–1.59 (1H, m), 1.62–1.66 (2H, m), 2.12 (1H, br q-like, J=9.8 Hz), 3.54–3.59 (1H, m), 3.71 (3H, s), 3.72–3.85 (1H, br), 3.97 (2H, br), 5.03–5.29 (2H, m), 5.69 (1H, ddd, J=17.1, 9.8, 8.1 Hz); ^{13}C NMR (125 MHz) δ 11.22 (q), 13.88 (q), 19.65 (t), 29.56 (t), 32.50 (t), 40.51 (d), 41.63 (t), 41.74 (d), 52.98 (q), 55.65 (d), 60.40 (d), 67.09 (t), 115.63 (t), 141.02 (d); MS: 238 (M^+-31), 117 (100); HRMS: Calcd for $C_{14}H_{24}NO_2$ (M^+-MeO), 238.1808. Found 238.1792; $[\alpha]_D^{26}=-93.4$ (c 1.86, $CHCl_3$).

4.1.12. (5*S*,6*R*,8*R*,9*S*)-(−)-6-Ethyl-5-propyl-8-vinylhexahydrooxazolo[3,4-*a*]pyridin-3-one (10). To a stirred solution of **9** (41 mg, 0.15 mmol) in THF (1 mL) was added NaH (60%, 7.9 mg, 0.20 mmol) at 0 °C, and the resulting suspension was stirred at 0 °C for 1 h. The reaction was quenched with 10% AcOH, and the aqueous mixture was extracted with CH_2Cl_2 (5 mL×4). The organic extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (10 g, hexane:acetone=20:1) to give **10** (30.3 mg, 84%) as a colorless oil.

IR (neat) 3078, 2962, 2872, 1751 cm^{-1}; ^1H NMR (500 MHz) δ 0.87 (3H, t, J=7.5 Hz), 0.93 (3H, t, J=7.3 Hz), 1.06–1.16 (2H, m), 1.26–1.33 (1H, br m), 1.51 (1H, qm, J=11.5 Hz), 1.54–1.62 (2H, m), 1.73–1.80 (1H, m), 1.97 (1H, dt, J=13, 3.5 Hz), 2.17 (1H, qm, J=11 Hz), 2.21–2.29 (1H, m), 2.82 (1H, td, J=10, 3.5 Hz), 3.24 (1H, ddd, J=13, 7, 3 Hz), 3.96 (1H, dd, J=8, 3 Hz), 4.16 (1H, dd, J=8, 7 Hz), 5.10–5.14 (2H, m), 5.52 (1H, ddd, J=16.5, 10, 8 Hz); ^{13}C NMR (125 MHz) δ 10.20 (q), 14.01 (q), 19.49 (t), 24.19 (t), 29.34 (t), 35.98 (t), 39.97 (d), 44.78 (d), 61.16 (d), 61.20 (d), 64.87 (t), 117.44 (t), 137.61 (d), 155.82 (s); MS: 237 (M^+, 100); HRMS: Calcd for $C_{14}H_{23}NO_2$, 237.1728. Found 237.1740; $[\alpha]_D^{26}=-31.9$ (c 1.52, $CHCl_3$).

4.1.13. Dimethyl (2*R*,3*R*,6*S*)-(+)-6-(*tert*-butyldiphenylsilyloxymethyl)-3-methylpiperidine-1,2-dicarboxylate (11). To a stirred suspension of CuI (5.95 g, 31.25 mmol) in Et_2O (20 mL) was added a solution of MeLi (1.14 M in Et_2O, 55 mL, 62.5 mmol) at −78 °C, and the resulting suspension was stirred at −78 to −35 °C for 20 min. The resulting solution was cooled to −78 °C, and a solution of **4** (2.92 g, 6.25 mmol) in Et_2O (10 mL) was added to the above reaction mixture at −78 °C. The temperature was gradually raised to −35 °C, and then the reaction was quenched with satd. NH_4Cl (aq.). The reaction mixture was diluted with CH_2Cl_2, and the insoluble material was removed through a celite pad. The filtrate was separated and the aqueous layer was extracted with CH_2Cl_2. The filtrate and organic layers were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (60 g, hexane:acetone=30:1–20:1) to give **11** (2.96 g, 98%) as a colorless oil.

IR (neat) 2955, 1861, 1708 cm^{-1}; ^1H NMR (500 MHz) δ 1.05 (9H, s), 1.07 (3H, d, J=6.8 Hz), 1.18–1.25 (1H, m), 1.54–1.57 (1H, br), 1.81–1.85 (2H, m), 2.45 (1H, br), 3.45 (3H, s), 3.49 (1H, t-like, J=9.9 Hz), 3.65 (3H, s), 3.68 (1H, dd, J=9.9, 4.3 Hz), 4.28 (1H, br), 4.44 (1H, br), 7.35–7.44 (6H, m), 7.64–7.68 (4H, m); ^{13}C NMR (125 MHz) δ 17.98 (q), 18.13 (t), 19.19 (s), 21.87 (t), 26.78 (q), 28.02 (d), 51.77 (q), 52.06 (d), 52.80 (q), 58.48 (d), 127.53 and 127.56 (each d), 129.53 and 129.54 (each d), 133.58 and 133.63 (each s), 135.47 (d), 157.36 (s), 172.82 (s); MS: 483 (M^+), 426 (100); HRMS: Calcd for $C_{23}H_{28}NO_5Si$ ($M^+-C_4H_9$) 426.1736. Found 426.1744; $[\alpha]_D^{26}=+13.6$ (c 5.12, $CHCl_3$).

4.1.14. Methyl (2*R*,3*R*,6*S*)-(+)-6-(*tert*-butyldiphenylsilyloxymethyl)-2-hydroxymethyl-3-methylpiperidine-1-carboxylate. To a stirred solution of **11** (2.96 g, 6.13 mmol) in THF (15 mL) was added a solution of Super-Hydride (1 M in THF, 13.5 mL, 13.48 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h. The reaction was quenched with satd. $NaHCO_3$ (aq.), and the aqueous mixture was extracted with CH_2Cl_2. The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (45 g, hexane:acetone=30:1–6:1) to give an alcohol (2.58 g, 92%) as a colorless oil.

IR (neat) 3450, 3070, 2956, 1680 cm^{-1}; ^1H NMR (500 MHz) δ 1.04 (9H, s), 1.05 (3H, d, J=7.7 Hz), 1.15–1.18 (1H, m), 1.43 (1H, br), 1.58–1.64 (1H, m), 1.78–1.90 (2H, m), 2.99 (1H, br), 3.53–3.64 (4H, m), 3.67 (3H, s), 4.01–4.04 (1H, m), 4.39 (1H, br), 7.37–7.46 (6H, m), 7.66–7.72 (4H, m); ^{13}C NMR (125 MHz) δ 18.98 (q), 19.14 (s), 19.49 (t), 22.37 (t), 26.63 (q), 27.28 (d), 50.81 (d), 52.63 (q), 58.79 (d), 64.89 (t), 127.62 and 127.65 (each d), 129.68 and

129.69 (each d), 133.03 (s), 135.39 and 135.45 (each d), 158.32 (s); MS: 398, 366 (100); HRMS: Calcd for $C_{22}H_{28}NO_4Si$ ($M^+-C_4H_9$) 398.1787. Found 398.1787; $[\alpha]_D^{26}=+19.8$ (*c* 1.89, $CHCl_3$).

4.1.15. (5*S*,8*R*,9*R*)-(−)-5-(*tert*-Butyldiphenylsilyloxymethyl)-8-methylhexahydrooxazolo[3,4-*a*]pyridin-3-one (12). To a stirred solution of the above alcohol (493 mg, 1.08 mmol) in THF (8 mL) was added NaH (60%, 48 mg, 1.19 mmol) at 0 °C, and the resulting suspension was stirred at 0 °C for 1 h. The reaction was quenched with 10% AcOH (aq.), and the aqueous mixture was extracted with CH_2Cl_2. The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (15 g, hexane:acetone=30:1–15:1) to give **12** (456 mg, 99%) as a colorless solid (mp 81–83 °C).

IR (KBr) 2958, 2859, 1751, 757 cm^{-1}; ^1H NMR (500 MHz) δ 0.88 (3H, d, *J*=6.4 Hz), 1.03 (9H, s), 1.11–1.20 (1H, m), 1.41–1.48 (2H, m), 1.90 (1H, dq, *J*=13.7, 3.4 Hz), 2.07 (1H, dq, *J*=13.4, 3.4 Hz), 3.12–3.20 (2H, m), 3.89 (1H, dd, *J*=8.6, 7.3 Hz), 4.18 (1H, dd, *J*=10.2, 8.1 Hz), 4.33 (1H, dd, *J*=8.6, 7.7 Hz), 4.48 (1H, dd, *J*=10.2, 4.3 Hz), 7.36–7.43 (6H, m), 7.66–7.69 (4H, m); ^{13}C NMR (125 MHz) δ 16.87 (q), 19.14 (s), 26.75 (q), 28.39 (t), 31.72 (t), 35.09 (t), 56.93 (d), 62.38 (d), 63.16 (t), 66.64 (t), 127.48 (d), 129.45 (d), 133.38 and 133.50 (each s), 135.40 and 135.46 (each d), 156.20 (s); MS: 366 (100); HRMS: Calcd for $C_{21}H_{24}NO_3Si$ ($M^+-C_4H_9$) 366.1526. Found 366.1526. Anal. Calcd for C25H33NO3Si C, 70.88; H, 7.85; N, 3.31. Found C, 70.71; H, 7.92; N, 3.39; $[\alpha]_D^{26}=-43.5$ (*c* 1.46, $CHCl_3$).

4.1.16. (5*S*,8*R*,9*R*)-(−)-5-Hydroxymethyl-8-methylhexahydrooxazolo[3,4-*a*]pyridin-3-one. To a stirred solution of **12** (1.49 g, 3.51 mmol) in THF (20 mL) was added a solution of TBAF (1 M in THF, 4.6 mL, 4.6 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with satd. NH_4Cl (aq.), and the aqueous mixture was extracted with $CHCl_3$. The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (18 g, hexane:acetone=10:1–4:1) to give an alcohol (648 mg, 99%) as a colorless oil.

IR (neat) 3420, 2930, 2875, 1723 cm^{-1}; ^1H NMR (500 MHz) δ 0.78–0.83 (3H, m), 1.06–1.16 (1H, m), 1.26–1.37 (2H, m), 1.51–1.57 (1H, m), 1.76–1.82 (1H, m), 3.04–3.13 (1H, m), 3.13–3.21 (1H, m), 3.66–3.71 (1H, m), 3.73–3.84 (1H, m), 3.86–3.91 (1H, m), 4.37–4.41 (1H, m), 4.57–4.62 (1H, m); ^{13}C NMR (125 MHz) δ 16.52 (q), 27.46 (t), 31.40 (t), 35.70 (d), 58.44 (d), 62.02 (d), 63.23 (t), 67.52 (t), 157.40 (s); MS: 185 (M^+), 155 (100); HRMS: Calcd for $C_9H_{15}NO_3$ 185.1052. Found 185.1050; $[\alpha]_D^{26}=-39.7$ (*c* 1.32, $CHCl_3$).

4.1.17. Methyl (5*S*,8*R*,9*R*)-(−)-8-methyl-3-oxohexahydrooxazolo[3,4-*a*]pyridine-5-carboxylate (13). To a stirred solution of $(COCl)_2$ (0.65 mL, 7.47 mmol) in CH_2Cl_2 (10 mL) was added DMSO (1.1 mL, 15.41 mmol) at −78 °C, and the resulting mixture was stirred at −78 °C for 5 min. To the mixture was added a solution of the above alcohol (923 mg, 4.99 mmol) in CH_2Cl_2 (5 mL) via canule at −78 °C, and then stirring was continued for 30 min. To the reaction mixture was added Et_3N (3.1 mL, 22.62 mmol) at −78 °C, and the temperature was gradually raised to 0 °C. The reaction mixture was diluted with Et_2O and water, and the organic layer was separated. The aqueous layer was extracted with Et_2O and the organic layer and extracts were combined, dried, and evaporated to give a pale yellow oil, which was used directly in the next step. To a stirred solution of the above oil in *t*-BuOH (21 mL) were added $NaHPO_4$ (5.9 g, 49.17 mmol) and 2-methyl-2-butene (21 mL, 192.92 mmol) at room temperature, and then a solution of $NaClO_2$ (80%, 3.3 g, 29.18 mmol) in water (8 mL) was added dropwise to the reaction mixture at 0 °C. The resulting suspension was stirred at room temperature for 30 min, and the reaction was quenched with satd. $NaHSO_3$ (aq.) at 0 °C. To the mixture was added 10% HCl (aq.), and the aqueous mixture was saturated with NaCl. The aqueous mixture was extracted with EtOAc, and the organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was used direcly in the next step.

To a stirred solution of the above pale yellow oil in EtOAc (10 mL) was added a solution of CH_2N_2 in Et_2O (10 mL) at 0 °C, and then the resulting solution was stirred at room temparature for 23 h. The solvent was evaporated and the residue was chromatographed on SiO_2 (40 g, hexane:acetone=15:1–12:1) to give **13** (1.06 g, 86% in 2 steps) as a colorless solid (mp 74–76 °C).

IR (KBr) 2960, 2932, 1762, 1205 cm^{-1}; ^1H NMR (500 MHz) δ 0.90 (3H, d, *J*=6.4 Hz), 1.13 (1H, qd, *J*=12.8, 3.4 Hz), 1.54–1.60 (1H, m), 1.71–1.80 (1H, m), 1.88–1.98 (2H, m), 3.14–3.20 (1H, m), 3.67 (1H, dd, *J*=11, 3.5 Hz), 3.77 (3H, s), 3.95 (1H, t-like, *J*=8.5 Hz), 4.41 (1H, t-like, *J*=8.5 Hz); ^{13}C NMR (125 MHz) δ 16.88 (q), 27.70 (t), 30.66 (t), 34.08 (d), 52.44 (q), 55.82 (d), 61.40 (d), 67.97 (t), 156.79 (s), 170.36 (s); MS: 213 (M^+), 211 (100); HRMS: Calcd for $C_{10}H_{15}NO_4$ 213.0101. Found 213.0991; $[\alpha]_D^{26}=-96.7$ (*c* 1.08, $CHCl_3$).

4.1.18. Methyl (8*R*,9*R*)-(−)-8-methyl-3-oxo-5-phenylsulfanylhexahydrooxazolo[3,4-*a*]pyridine-5-carboxylate. To a stirred solution of hexamethyldisilazane (1.01 mL, 4.73 mmol) in THF (6 mL) was added *n*-BuLi (1 M in hexane, 3.0 mL, 4.73 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 30 min. To a stirred solution of **7** (871 mg, 4.09 mmol) in THF (6 mL) was added a solution of LiHMDS in THF prepared above at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. To the reaction mixture was added a solution of $(PhS)_2$ in THF (4 mL) via canule at −78 °C, and the temperature was gradually raised to 0 °C. The volatiles were removed and the residue was chromatographed on SiO_2 (50 g, hexane:acetone=10:1) to give a phenylthio ether (1.3 g, 99%) as a colorless oil.

IR (neat) 2956, 1762, 1269, 1202, 758 cm^{-1}; ^1H NMR (500 MHz) δ 0.94 (3H, d, *J*=6.4 Hz), 1.52–1.59 (1H, m), 1.65–1.73 (2H, m), 1.87 (1H, dt-like, *J*=14.5, 3 Hz), 2.05–2.11 (1H, m), 3.65–3.70 (1H, m), 3.74 (3H, s), 3.88 (1H, t-like, *J*=8.5 Hz), 4.40 (1H, t-like, *J*=8.5 Hz), 7.25–7.29 (2H, m), 7.31–7.33 (1H, m), 7.66–7.68 (2H, m); ^{13}C NMR (125 MHz) δ 16.74 (q), 27.93 (t), 32.82 (t), 34.59 (d), 53.08 (q), 57.42 (d), 67.96 (t), 71.98 (s), 128.57 (d), 129.25 (s),

129.57 (d), 137.10 (d), 155.17 (s), 169.56 (s); MS: 321 (M^+), 213 (100); HRMS: Calcd for $C_{16}H_{19}NO_4S$ 321.1035. Found 321.1038; $[\alpha]_D^{26}=-13.3$ (*c* 1.38, $CHCl_3$).

4.1.19. Methyl (8*R*,9*R*)-(−)-8-methyl-3-oxo-1,7,8,8a-tetrahydrooxazolo[3,4-*a*]pyridine-5-carboxylate (14). To a stirred solution of the above phenylthio ether (160 mg, 0.50 mmol) in CH_2Cl_2 (2 mL) was added 2,6-lutidine (0.15 mL, 1.29 mmol), and then *m*CPBA (65%, 320 mg, 1.20 mmol) was added to the resulting mixture in four portions in 15 min interval at room temperature. The reaction was quenched with 10% $Na_2S_2O_3$ in satd. $NaHCO_3$ (aq.), and the aqueous mixture was diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The organic layer and extracts were combined, washed with brine, 10% HCl, and brine, successively, dried and evaporated to give a colorless oil, which was chromatographed on SiO_2 (15 g, hexane:acetone=10:1) to give **14** (89 mg, 85%) as a colorless solid (mp 101–103 °C).

IR (KBr) 2989, 2956, 1763, 1730, 1411, 1249, 1214 cm^{-1}; ^1H NMR (500 MHz) δ 1.01 (3H, d, *J*=6.4 Hz), 1.85–1.87 (1H, m), 1.89–1.96 (1H, m), 2.48 (1H, dt, *J*=19.7, 5.1 Hz), 3.39–3.44 (1H, m), 3.83 (3H, s), 4.23 (1H, dd, *J*=9.0, 3.0 Hz), 4.55 (1H, t-like, *J*=8.5 Hz), 6.25 (1H, dd, *J*=4.9, 2.8 Hz); ^{13}C NMR (125 MHz) δ 16.43 (q), 30.64 (d), 31.42 (t), 52.44 (q), 57.98 (d), 123.56 (d), 154.76 (s), 163.25 (s); MS:211 (M^+); HRMS: Calcd for $C_{10}H_{13}NO_4$ 211.0844. Found 211.0870; $[\alpha]_D^{26}=-34.4$ (*c* 0.46, $CHCl_3$).

4.1.20. Methyl (5*R*,6*R*,8*R*,9*R*)-(−)-6,8-dimethyl-3-oxo-hexahydrooxazolo[3,4-*a*]pyridine-5-carboxylate (15). To a stirred suspension of CuI (744 mg, 3.91 mmol) in Et_2O (25 mL) was added a solution of MeLi (1.18 M in Et_2O, 6.6 mL, 7.82 mmol) at −78 °C, and the reaction mixture was warmed to −35 °C for 30 min. To a solution of **14** (165 mg, 0.78 mmol) in Et_2O (70 mL) was added a solution of $(Me)_2CuLi$, prepared above, at −78 °C, and the reaction mixture was warmed to −10 °C for 1 h. The reaction was quenched with satd. NH_4Cl (aq.), and the aqueous mixture was diluted with CH_2Cl_2 (300 mL). The resulting suspension was filtered, and the filtrate was separated. The aqueous layer was extracted with CH_2Cl_2 (10 mL×2), and the filtrate and organic extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on SiO_2 (15 g, hexane:acetone=14:1) to give **15** (165 mg, 93%) as a colorless oil.

IR (neat) 2961, 1748, 1420, 1272, 1243 cm^{-1}; ^1H NMR (500 MHz) δ 0.84 (3H, d, *J*=6.4 Hz), 1.13 (3H, d, *J*=7.3 Hz), 1.28 (1H, td, *J*=13, 4.3 Hz), 1.53 (1H, dt, *J*=14, 3 Hz), 1.65–1.72 (1H, m), 2.49–2.51 (1H, m), 3.59 (1H, dt, *J*=10, 8 Hz), 3.74 (3H, s), 3.97 (1H, t-like, *J*=8.5 Hz), 4.26 (1H, br), 4.52 (1H, t-like, *J*=8.5 Hz); ^{13}C NMR (125 MHz) δ 17.18 (q), 18.17 (q), 29.51 (d), 29.73 (d), 34.82 (t), 52.39 (q), 57.21 (d), 57.67 (d), 68.12 (t), 157.68 (s), 170.97 (s); MS: 227 (M^+), 169 (100); HRMS: Calcd for $C_{11}H_{17}NO_4$ 227.1158. Found 227.1168; $[\alpha]_D^{26}=-36.4$ (*c* 0.96, $CHCl_3$).

4.1.21. Methyl (2*S*,3*R*,5*R*,6*S*)-(−)-2-(2-ethoxycarbonyl-vinyl)-5-ethyl-6-propyl-3-vinylpiperidine-1-carboxylate (16). To a stirred solution of $(COCl)_2$ (0.11 mL, 1.26 mmol) in CH_2Cl_2 (2 mL) was added DMSO (0.18 mL, 2.52 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 10 min. To the mixture was added a solution of **9** (150 mg, 0.56 mmol) in CH_2Cl_2 (3 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. Triethylamine (0.52 mL, 3.78 mmol) at −78 °C, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (10 mL×4). The organic extracts were combined, dried and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred suspension of NaH (60%, 25 mg, 0.61 mmol) in THF (2 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (0.12 mL, 0.59 mmol) at 0 °C, and the resulting solution was stirred at 0 °C for 15 min. To the reaction mixture was added a slolution of the above oil in THF (4 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with CH_2Cl_2 (10 mL×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (12 g, hexane:acetone=80:1) to give **16** (181 mg, 96%) as a colorless oil.

IR (neat) 3078, 2958, 2873, 1697 cm^{-1}; ^1H NMR (500 MHz) δ 0.86–0.92 (6H, m), 1.00 (1H, q, *J*=11.1 Hz), 1.25 (3H, t, *J*=7.3 Hz), 1.29–1.45 (7H, br m), 1.51–1.58 (1H, m), 1.68–1.72 (1H, m), 2.30 (1H, q-like, *J*=11.1 Hz), 3.67 (3H, s), 4.16 (2H, q, *J*=7.3 Hz), 4.18 (1H, br), 5.03–5.07 (2H, m), 5.59–5.66 (1H, m), 5.79–5.87 (1H, m), 6.77 (1H, dd, *J*=15.8, 6.9 Hz); ^{13}C NMR (125 MHz) δ 11.20 (q), 13.80 (q), 14.15 (q), 19.76 (t), 29.70 (t), 32.23 (t), 41.17 (t), 41.51 (d), 41.82 (d), 52.69 (q), 55.37 (d), 58.29 (d), 60.35 (t), 116.19 (t), 122.33 (d), 139.72 (d), 147.09 (d), 157.17 (s), 166.42 (s); MS: 337 (M^+), 294 (100); HRMS: Calcd for $C_{19}H_{31}NO_4$, 337.2253. Found 337.2231; $[\alpha]_D^{26}=-42.1$ (*c* 1.08, $CHCl_3$).

4.1.22. Methyl (2*R*,3*S*,5*R*,6*S*)-(−)-3,5-diethyl-2-(3-hydroxypropyl)-6-propylpiperidine-1-carboxylate. To a solution of **16** (200 mg, 0.59 mmol) in EtOAc (10 mL) was added 5% Pd–C (50 mg), and the resulting suspension was hydrogenated under hydrogen atmosphere at 1 atm for 72 h. The catalyst was removed by filtration, and the filtrate was evaporated to give colorless oil, which was used directly in the next step.

To a stirred solution of the above in THF (8 mL) was added a solution of Super-Hydride (1 M in THF, 1.3 mL, 1.3 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h. The reaction was quenched with satd $NaHCO_3$ (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (10 mL×5). The organic extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (20 g, hexane:acetone=30:1–8:1) to give an alcohol (157 mg, 89%) as a colorless oil.

IR (neat) 3448, 2957, 2872, 1674 cm^{-1}; ^1H NMR (500 MHz) δ 0.63 (1H, q-like, *J*=11.1 Hz), 0.86–0.89 (9H, m), 1.18–1.66 (15H, br m), 2.60 (1H, br), 3.59–3.65 (2H, br), 3.63 (3H, s), 3.76 (1H, br), 3.92 (1H, br); ^{13}C NMR (125 MHz) δ 11.46 (q), 14.02 (q), 20.09 (t), 28.45 (t), 28.82

(t), 29.73 (t), 30.60 (t), 34.41 (t), 40.46 (t), 42.12 (d), 52.43 (q), 55.23 (d), 56.74 (d), 62.70 (t), 158.40 (s); MS: 299 (M^+), 256 (100); HRMS: Calcd for $C_{17}H_{33}NO_3$, 299.2460. Found 299.2459; $[\alpha]_D^{26}=-7.2$ (*c* 3.00, $CHCl_3$).

4.1.23. Methyl (2*R*,3*S*,5*R*,6*S*)-(+)-3,5-diethyl-2-(3-methoxymethoxypropyl)-6-propylpiperidine-1-carboxylate (17). To a stirred solution of the above alcohol (217 mg, 0.73 mmol) in $CHCl_3$ (5 mL) were added MOMCl (0.22 mL, 2.9 mmol) and Hünig base (0.56 mL, 3.19 mmol), and the resulting mixture was refluxed for 2 h. After cooling, the solvent was evaporated and the residue was chromatographed on SiO_2 (15 g, hexane:acetone=30:1) to give **17** (215 mg, 86%) as a colorless oil.

IR (neat) 2955, 2873, 1693, 1110 cm^{-1}; ^1H NMR (500 MHz) δ 0.60 (1H, q-like, *J*=8.8 Hz), 0.83–0.86 (9H, m), 1.19–1.62 (15H, br m), 3.30 (3H, br s), 3.46 (2H, br), 3.60 (3H, br s), 3.71 (1H, br), 3.91 (1H, br), 4.55 (2H, br s); ^{13}C NMR (125 MHz) δ 11.42 (q), 14.00 (q), 20.10 (t), 27.17 (t), 28.60 (t), 30.60 (t), 34.38 (t), 40.21 (t), 42.08 (d), 52.22 (q), 54.91 (q), 56.76 (d), 67.52 (t), 96.20 (t), 158.13 (s); MS: 343 (M^+), 300 (100); HRMS: Calcd for $C_{19}H_{37}NO_4$, 343.2721. Found 343.2709; $[\alpha]_D^{26}=+0.126$ (*c* 6.28, $CHCl_3$).

4.1.24. (5*S*,6*R*,8*S*,9*R*)-(+)-6,8-Diethyl-5-propyloctahydroindolizine (18). To a stirred solution of *n*-PrSLi, prepared from *n*-PrSH (0.11 mL, 1.17 mmol) and *n*-BuLi (1.6 M in hexane, 0.69 mL, 1.13 mmol) in HMPA (0.5 mL) at 0 °C for 30 min. To the reaction mixture was added a solution of **17** (40 mg, 0.17 mmol) in THF (2 mL) at 0 °C, and the resulting solution was stirred at room temperature for 48 h. The reaction was quenched with NH_3 (aq.), and the aqueous mixture was extracted with Et_2O (5 mL×10). The organic extracts were combined, dried over K_2CO_3, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred solution of the above oil in MeOH (4 mL) was added c. HCl (3 drops), and the resulting mixture was refluxed for 1 h. After cooling, the solvent was evaporated, and the residue was washed with Et_2O. To the residue was added NH_3 (aq.), and the aqueous mixture was extracted with $CHCl_3$ (5 mL×8). The organic extracts were combined, dried over K_2CO_3, and evaporated to give colorless oil, which was used directly in the next step.

Carbontetrabromide (55 mg, 0.16 mmol) and Ph_3P (46 mg, 0.17 mmol) were added to a solution of the above oil in CH_2Cl_2 (1 mL) at 0 °C, and the reaction mixture was stirred at 0 °C for 2 h. To the reaction mixture was added Et_3N (0.26 mL, 1.87 mmol) at 0 °C, and the resulting suspension was stirred at 0 °C for 10 min. The solvent was evaporated, and the residue was extracted with *n*-pentane (5 mL×5). The organic extracts were combined and evaporated to give colorless solid, which was chromatographed on SiO_2 (7 g, hexane:acetone:Et_3N=50:1:5 drops) to give **18** (14 mg, 52%) as a pale yellow oil.

IR (neat) 2959, 2872, 2778, 1461, 1379, 1324, 1247, 1172, 934, 901, 733 cm^{-1}; ^1H NMR (500 MHz) δ 0.61 (1H, q-like, *J*=12 Hz), 0.89 (9H, t, *J*=7 Hz), 1.07 (2H, m), 1.20–1.80 (13H, br m), 1.93 (3H, br dt-like, *J*=13, 3.5 Hz), 3.18 (1H, br); ^{13}C NMR (75 MHz) δ 11.08 (q), 14.76 (q), 18.00 (t), 20.71 (t), 24.71 (t), 26.03 (t), 28.80 (t), 32.98 (t), 35.23 (t), 39.94 (d), 52.06 (t), 67.49 (d); MS: 223 (M^+), 190 (100); $[\alpha]_D^{26}=+60.4$ (*c* 0.25, $CHCl_3$).

DCl salt. ^1H NMR (500 MHz, D_2O) δ 0.84–0.91 (9H, m), 1.01 (1H, q-like, *J*=12.5 Hz), 1.23 (3H, m), 1.39 (1H, m), 1.55 (3H, br m), 1.65 (2H, m), 1.75 (2H, m), 1.94 (1H, quint-like, *J*=11 Hz), 2.05 (2H, dm, *J*=14 Hz), 2.33 (1H, m), 2.89 (1H, dt-like, *J*=12, 2.5 Hz), 2.93 (1H, m), 3.03 (1H, q-like, *J*=10 Hz), 3.65 (1H, td-like, *J*=10, 3 Hz); ^{13}C NMR (75 MHz, D_2O) δ 9.79 (q), 9.99 (q), 13.79 (q), 16.49 (t), 19.45 (t), 23.74 (t), 25.13 (t), 27.12 (t), 30.15 (t), 33.20 (t), 38.53 (d), 40.21 (d), 51.42 (t), 67.89 (d), 71.87 (d); $[\alpha]_D^{26}=+17.2$ (*c* 0.3, $CHCl_3$).

4.1.25. (2*S*)-2-(2-Ethylbut-3-enyloxy)tetrahydropyran (20). To a stirred solution of (2*R*)-2-(hydroxymethyl)butyl acetate (**19**, 730 mg, 5 mmol) in CH_2Cl_2 (5 mL) were added 3,4-dihydro-2*H*-pyran (0.55 mL, 6 mmol) and PPTS (251 mg, 1 mmol), and the resulting mixture was stirred at room temperature for 2 h. The reaction was quenched with satd $NaHCO_3$ (a), and the aqueous mixture was extracted with CH_2Cl_2 (10 mL×4). The organic extracts were combined, dried, and evaporated to give colorless oil, which was used directly in the next step.

To a stirred solution of the above oil in MeOH (5 mL) was added solid K_2CO_3 (414 mg, 3 mmol) at 0 °C, and the resulting suspension was stirred at room temperature for 3 h. The reaction was quenched with 10% AcOH, and the aqueous mixture was extracted with $CHCl_3$ (10 mL×6). The organic extracts were combined, dried, and evaporated to give colorless oil, which was used directly in the next step.

To a stirred solution of $(COCl)_2$ (0.65 mL, 7.5 mmol) in CH_2Cl_2 (7 mL) was added DMSO (1.06 mL, 15.0 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 10 min. To the mixture was added a solution of the above oil in CH_2Cl_2 (6 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. Triethylamine (3.1 mL, 22.5 mmol) at −78 °C, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (15 mL×4). The organic extracts were combined, dried and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred suspension of $MeP^+Ph_3Br^-$ (8.08 g, 20.0 mmol) in THF (20 mL) was added a solution of *n*-BuLi (1.6 M ih hexane, 12 mL, 19.0 mmol) at 0 °C, and the resulting orange solution was stirred at 0 °C for 30 min. To the solution was added a solution of the above oil in THF (10 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 1.5 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (25 mL×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (40 g, hexane:acetone=100:1–80:1) to give **20** (695 mg, 76% in 4 steps) as a colorless oil.

^1H NMR (500 MHz) δ 0.88 (3H, t, *J*=7.3 Hz), 1.22–1.35 (1H, m), 1.46–1.62 (5H, br m), 1.69 (1H, m), 1.80 (1H, m),

2.22 (1H, br), 3.31 (1H, m), 3.50 (1H, br), 3.68 (1H, m), 3.80 (1H, m), 4.59 (1H, br), 5.07 (2H, m), 5.63 (1H, m).

4.1.26. (2*R*,3*R*)-3-(Tetrahydropyran-2-yloxymethyl)-pentane-1,2-diol. To a stirred solution of **20** (690 mg, 3.75 mmol) in *t*-BuOH (10 mL) and H_2O (10 mL) was added AD-mix β (4 g), prepared from $(DHQD)_2PYR$ (0.5 g), $K_2OsO_4{\cdot}2H_2O$ (40.5 mg), $K_3Fe(CN)_6$ (54.7 g), and K_2CO_3 (22.9 g), at 0 °C, and the resulting suspension was stirred at 0 °C for 24 h. The reaction was quenched with Na_2SO_3 (4 g), and the reaction mixture was extracted with EtOAc (20 mL×5). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (20 g, hexane:acetone=10:1–4:1) to give a diol (654 mg, 80%) as a colorless oil.

IR (neat) 3405, 2940, 2877, 1124 cm^{-1}; ^1H NMR (500 MHz) δ 0.91–0.94 (3H, m), 1.31–1.78 (9H, br m), 2.22 and 2.28 (1H, each br), 3.46–3.65 (3H, m), 3.66–3.72 (3H, m), 3.78 (1H, br), 3.82–3.93 (2H, br m), 4.52 and 4.57 (1H, each br), 3.91 (1H, br); ^{13}C NMR (125 MHz) δ 11.60 and 11.61 (each q), 19.37 and 19.76 (each t), 21.22 and 21.43 (each t), 25.13 (t), 30.41 and 30.55 (each t), 42.13 and 42.27 (each d), 62.38 and 62.99 (each t), 65.11 (t), 67.74 and 68.15 (each t), 73.61 and 73.59 (each d), 98.88 and 99.74 (each d).

4.1.27. (2*R*,3*R*)-1-(*tert*-Butyldiphenylsilyloxy)-3-(tetrahydropyran-2-yloxymethyl)-pentan-2-ol. To a stirred solution of the above diol (590 mg, 2.71 mmol) in CH_2Cl_2 (5 mL) were added TBDPSCl (0.8 mL, 2.98 mmol), Et_3N (0.5 mL, 3.52 mmol), and DMAP (70 mg, 0.54 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 20 h. The solvent was evaporated and the redisue was chromatographed on SiO_2 (30 g, hexane:acetone=50:1–30:1) to give a silyl ether (1.21 g, 98%) as a colorless oil.

IR (neat) 3486, 3069, 2935, 2864, 1113 cm^{-1}; ^1H NMR (500 MHz) δ 0.95 and 0.96 (3H, each t, each J=7.7 Hz), 1.06 (9H, s), 1.42–1.76 (9H, br m), 3.01–3.05 (1H, m), 3.44–3.52 (2H, m), 3.72–3.95 (5H, br m), 4.52 (1H, br), 7.40–7.46 (6H, m), 7.69–7.72 (4H, m); ^{13}C NMR (125 MHz) δ 11.62 and 11.76 (each q), 19.12 and 19.14 (each t), 19.32 (s), 21.02 and 21.08 (each t), 25.24 and 25.27 (each t), 26.77 (q), 30.38 and 30.41 (each t), 41.57 (d), 61.77 and 61.82 (each t), 66.33 (t), 66.97 (t), 73.18 and 73.24 (each d), 98.55 and 99.12 (each d), 127.61 (d), 129.61 and 129.62 (each d), 133.27 and 133.28 (each s), 135.47 (d).

4.1.28. (2*S*,3*S*)-1-(*tert*-Butyldiphenylsilyloxy)-3-(tetrahydropyran-2-yloxymethyl)pentan-2-azide (21). To a stirred solution of the above silyl ether (1.49 g, 3.27 mmol) in CH_2Cl_2 (4 mL) were added MsCl (0.28 mL) and Et_3N (0.68 mL) at 0 °C, and the resulting suspension was stirred at 0 °C for 1 h. The reaction was quenched with satd $NaHCO_3$ (aq.), and aqueous mixture was extracted with CH_2Cl_2 (10 mL×4). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred solution of the above oil in DMF (10 mL) was added NaN_3 (2.1 g, 32.65 mmol), and the resulting suspension was stirred at 80 °C for 15 h. After cooling, the insoluble material was filtered, washed with CH_2Cl_2, and filtrate was evaporated to give pale yellow oil, which was chromatographed on SiO_2 (30 g, hexane:acetone=50:1–40:1) to give **21** (1.3 g, 83%) as a colorless oil.

IR (neat) 3070, 2936, 2098, 1112, 1032 cm^{-1}; ^1H NMR (500 MHz) δ 0.88 and 0.90 (3H, each t, each J=7.3 Hz), 1.10 (9H, s), 1.44–1.75 (9H, br m), 3.22–3.29 (1H, m), 3.44–3.52 (1H, m), 3.66–3.83 (5H, br m), 4.46 and 4.51 (1H, each br), 7.39–7.47 (6H, m), 7.70–7.74 (4H, m); ^{13}C NMR (125 MHz) δ 11.82 and 11.91 (each q), 19.06 and 19.14 (each t), 19.42 (s), 20.09 and 20.26 (each t), 25.35 and 25.38 (each t), 26.66 (q), 30.45 and 30.49 (each t), 41.26 and 41.32 (each d), 61.76 and 62.22 (each t), 65.49 and 65.55 (each d), 65.68 (t), 66.19 (t), 66.83 (t), 98.32 and 99.35 (each d), 127.70 (d), 129.70 and 129.72 (each d), 133.03 and 133.14 (each s), 135.58 and 135.60 (each d).

4.1.29. Ethyl (4*R*,5*S*)-5-azide-6-(*tert*-butyldiphenylsilyloxy)-4-ethyl-2-hexenoate (22). To a stirred solution of **21** (1.1 g, 2.29 mmol) in EtOH (5 mL) was added PPTS (115 mg, 0.46 mmol), and the reaction mixture was stirred at 60 °C for 2 h. After cooling, the reaction was quenched with satd $NaHCO_3$ (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (20 mL×4). The organic extracts were combined, dried, and evaporated to give colorless oil, which was used directly in the next step.

To a stirred solution of $(COCl)_2$ (0.3 mL, 3.43 mmol) in CH_2Cl_2 (6 mL) was added DMSO (0.5 mL, 6.86 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 10 min. To the mixture was added a solution of the above alcohol in CH_2Cl_2 (8 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. Triethylamine (1.4 mL, 10.29 mmol) at −78 °C, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (15 mL×4). The organic extracts were combined, dried and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred suspension of NaH (60%, 100 mg, 2.52 mmol) in THF (5 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (0.5 mL, 2.52 mmol) at 0 °C, and the resulting solution was stirred at 0 °C for 15 min. To the reaction mixture was added a solution of the above aldehyde in THF (6 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with CH_2Cl_2 (15 mL×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (25 g, hexane:acetone=80:1) to give **22** (935 mg, 88% in 3 steps) as a colorless oil.

IR (neat) 3070, 2962, 2934, 2861, 1720, 1110 cm^{-1}; ^1H NMR (500 MHz) δ 0.84–0.92 (3H, m), 1.11 (9H, s), 1.31 (3H, t, J=6.0 Hz), 1.33–1.40 (1H, m), 1.69–1.77 (1H, m), 2.30–2.44 (1H, m), 3.36–3.40 (1H, m), 3.56–3.74 (1H, m), 3.78–3.81 (1H, m), 4.21 (2H, q, J=6.0 Hz),5.83 (1H, d, J=15.4 Hz), 6.63 (1H, dd, J=15.4, 7.7 Hz), 7.40–7.48 (6H, m), 7.69–7.73 (4H, m); ^{13}C NMR (125 MHz) δ 11.35 (q), 14.17 (q), 19.00 (s), 23.36 (t), 26.62 (q), 44.97 (d), 60.28 (t),

65.37 (t), 66.12 (d), 123.73 (d), 127.71 and 127.75 (each d), 129.78 and 129.80 (each d), 132.64 and 132.66 (each s), 135.47 and 135.50 (each d), 139.33 (d), 147.35 (d), 165.79 (s).

4.1.30. (5*R*,6*S*)-(+)-6-(*tert*-Butyldiphenylsilyloxymethyl)-5-ethylpiperidin-2-one (23). To a solution of **22** (3.88 g, 8.34 mmol) in EtOAc (100 mL) was added 10% Pd–C (800 mg), and the resulting suspension was hydrogenated under hydrogen atmosphere at 4 atm for 72 h. The catalyst was removed by filtration, and the filtrate was evaporated to give colorless oil, which was chromatographed on SiO_2 (80 g, hexane:acetone=40:1–8:1) to give **23** (2.4 g, 73%) as a colorless oil.

IR (neat) 3402, 3206, 2933, 1666, 1108 cm^{-1}; ^1H NMR (500 MHz) δ 0.81 (3H, t, J=7.5 Hz), 1.05 (9H, s), 1.17–1.26 (2H, m), 1.66–1.70 (2H, m), 1.72–1.76 (1H, m), 2.30–2.39 (2H, m), 3.53–3.57 (1H, m), 3.58 (1H, t-like, J=9 Hz), 3.63 (1H, dd, J=9, 3 Hz), 6.20 (1H, br), 7.37–7.46 (6H, m), 7.62–7.65 (4H, m); ^{13}C NMR (125 MHz) δ 11.57 (q), 19.05 (s), 21.19 (t), 23.00 (t), 26.73 (q), 29.48 (t), 35.73 (d), 56.78 (d), 64.42 (t), 127.79 and 127.81 (each d), 129.85 and 129.88 (each d), 132.79 (s), 135.44 and 135.46 (each d), 171.89 (s); MS: 338 (M^+-57), 199 (100); HRMS: Calcd for $C_{20}H_{24}NO_2Si$ ($M^+-C_4H_9$) 338.1577. Found 338.1592; $[\alpha]_D^{26}$=+28.2 (*c* 2.94, $CHCl_3$).

4.1.31. Methyl (2*S*,3*R*)-(−)-2-(*tert*-butyldiphenylsilyloxymethyl)-3-ethyl-6-oxopiperidine-1-carboxylate. To a stirred solution of **23** (1.7 g, 4.30 mmol) in THF (15 mL) was added a solution of *n*-BuLi (1.6 M in hexane, 3.0 mL, 4.80 mmol) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. To the reaction mixture was added $ClCO_2Me$ (0.5 mL, 6.33 mmol) at −78 °C, and the resulting mixture was warmed to 0 °C for 1 h. The reaction was quenched with satd. $NaHCO_3$ (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (20 mL×4). The organic extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (30 g, hexane:acetone=20:1–15:1) to give an imide (1.88 g, 97%) as a colorless oil.

IR (neat) 3069, 3049, 2957, 2883, 2860, 1774, 1719, 1108 cm^{-1}; ^1H NMR (300 MHz) δ 0.93 (3H, t, J=7.4 Hz), 1.02 (9H, s), 1.23–1.44 (2H, m), 1.81–1.88 (2H, m), 1.99–2.06 (1H, m), 2.49–2.70 (2H, m), 3.73 (1H, dd, J=11, 3.3 Hz), 3.80 (3H, s), 3.83 (1H, dd, J=11, 4.4 Hz), 4.28 (1H, br), 7.35–7.47 (6H, m), 7.61–7.68 (4H, m); ^{13}C NMR (75 MHz) δ 12.02 (q), 18.96 (s), 24.53 (t), 25.68 (t), 26.71 (q), 34.38 (t), 39.11 (d), 53.69 (q), 59.25 (d), 61.48 (t), 127.55 and 127.58 (each d), 129.62 (d), 132.08 and 132.63 (each s), 135.41 and 135.52 (each d), 154.82 (s), 171.78 (s); MS: 396 (M^+-57), 84 (100); HRMS: Calcd for $C_{22}H_{26}NO_4Si$ ($M^+-C_4H_9$) 396.1631. Found 396.1631; $[\alpha]_D^{26}$=−34.9 (*c* 3.38, $CHCl_3$).

4.1.32. Methyl (2*S*,3*R*)-(−)-2-(*tert*-butyldiphenylsilyloxymethyl)-3-ethyl-6-trifluoromethanesulfonyl-oxy-3,4-dihydro-2*H*-pyridine-1-carboxylate. To a stirred solution of hexamethyldisilazane (1.03 mL, 4.87 mmol) in THF (8 mL) was added a solution of *n*-BuLi (1.6 M in hexane, 3.03 mL, 4.86 mmol) at 0 °C, and the resulting solution was stirred at 0 °C for 30 min. To a stirred solution of the above imide (1.84 g, 4.06 mmol) in THF (10 mL) was added a solution of LiHMDS prepared above at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. To the above reaction mixture was added a solution of 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]5-chloropyridine (Comins' reagent) (97%, 1.96 g, 4.85 mmol) in THF (6 mL) at −78 °C, and the resulting mixture was warned to −45 °C for 1 h. The reaction was quenched with satd. NH_4Cl (aq.), and the aqueous mixture was extracted with Et_2O (20 mL×4). The organic extracts were combined, dried, and evaporated to give pale yellow solid, which was chromatographed on SiO_2 (40 g, hexane:acetone=50:1–40:1) to give an enol triflate (2.3 g, 97%) as a colorless oil.

IR (neat) 3070, 2959, 2933, 2887, 2860, 1733, 1684, 1213, 1111 cm^{-1}; ^1H NMR (300 MHz) δ 0.83 (3H, t, J=7.4 Hz), 1.06 (9H, s), 1.13–1.30 (2H, m), 1.60–1.81 (2H, m), 2.32 (1H, dm, J=16.4 Hz), 3.57–3.63 (1H, m), 3.71–3.78 (1H, m), 3.85 (3H, s), 4.61–4.67 (1H, m), 5.23 (1H, t, J=3.4 Hz), 7.38–7.48 (6H, m), 7.67–7.75 (4H, m); ^{13}C NMR (75 MHz) δ 11.89 (q), 19.11 (s), 25.44 (t), 26.49 (t), 26.59 (q), 37.62 (d), 53.46 (q), 59.25 (d), 58.43 (t), 59.75 (d), 105.51 (d), 127.51 and 127.56 (each d), 129.52 and 129.60 (each d), 133.09 and 133.14 (each s), 135.42 and 135.51 (each d), 138.13 (s), 153.80 (s); MS: 528 (M^+-57), 308 (100); HRMS: Calcd for $C_{23}H_{25}NO_6F_3SiS$ ($M^+-C_4H_9$) 528.1124. Found 528.1115; $[\alpha]_D^{26}$=−43.8 (*c* 5.73, $CHCl_3$).

4.1.33. Dimethyl (5*R*,6*S*)-(−)-6-(*tert*-butyldiphenylsilyloxymethyl)-5-ethyl-5,6-dihydro-4*H*-pyridine-1,2-dicarboxylate (24). To a stirred solution of the above enol triflate (2.3 g, 3.93 mmol) in DMF (15 mL) was added $Pd(Ph_3P)_4$ (230 mg, 0.20 mmol), and the resulting mixture was stirred at room temperature under CO balloon pressure for 30 min. To the reaction mixture were added Et_3N (2.2 mL, 15.73 mmol) and MeOH (6.4 mL, 157.26 mmol), and then the reaction mixture was stirred at 70 °C under CO balloon pressure for 14 h. After cooling, the reaction mixture was diluted with H_2O (50 mL) and brine (10 mL), and the aqueous mixture was extracted with Et_2O (50 mL×4). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (40 g, hexane:acetone=40:1–20:1) to give **24** (1.46 g, 75%) as a colorless oil.

IR (neat) 3048, 2955, 2882, 2859, 1919, 1650 cm^{-1}; ^1H NMR (500 MHz) δ 0.87 (3H, t, J=7.5 Hz), 1.04 (9H, s), 1.18–1.32 (2H, m), 1.66–1.72 (1H, m), 1.82–1.86 (1H, m), 2.27–2.33 (1H, m), 3.59–3.71 (2H, m), 3.74 (3H, s), 3.75 (3H, s), 4.54 (1H, br), 6.01 (1H, br), 7.36–7.45 (6H, m), 7.66–7.73 (4H, m); ^{13}C NMR (125 MHz) δ 11.80 (q), 19.14 (s), 26.02 (t), 26.55 (q), 27.43 (t), 37.51 (d), 51.89 (q), 53.04 (q), 56.29 (d), 59.14 (t), 121.34 (d), 127.43 and 127.46 (each d), 129.41 and 129.47 (each d), 133.28 (s), 133.26 (s), 135.44 and 135.47 (each d), 154.42 (s), 165.58 (s); MS: 438 (M^+-57), 68 (100); HRMS: Calcd for $C_{24}H_{28}NO_5Si$ ($M^+-C_4H_9$) 438.1736. Found 438.1741; $[\alpha]_D^{26}$=−47.1 (*c* 4.22, $CHCl_3$).

4.1.34. Dimethyl (2*R*,3*S*,5*R*,6*S*)-(+)-6-(*tert*-butyldiphenylsilyloxymethyl)-5-ethyl-3-vinylpiperidine-1,2-dicarboxylate (25). To a stirred suspension of CuI (2.69 g,

14.14 mmol) in Et_2O (15 mL) was added a solution of vinyl lithium, (prepared from tetravinyltin (1.2 mL, 7.07 mmol) and MeLi (1.0 M in Et_2O, 28 mL, 28.0 mmol) in Et_2O (10 mL) at 0 °C for 30 min), at −78 °C, and the resulting suspension was warmed to −35 °C for 20 min. The resulting suspension was re-cooled to −78 °C, and a solution of **24** (1.4 g, 2.82 mmol) in Et_2O (8 mL) was added to the resulting suspension. The reaction mixture was warmed to −20 °C for 1 h, and the reaction was quenched with satd. NH_4Cl (aq.). The aqueous mixture was diluted with CH_2Cl_2 (100 mL), and the resulting suspension was filtered. The filtrate was separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL×2). The organic layer and extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (30 g, hexane:acetone=50:1–30:1) to give **25** (1.41 g, 95%) as a colorless oil.

IR (neat) 3070, 2954, 2860, 1704, 1112 cm^{-1}; ^1H NMR (500 MHz) δ 0.80 (3H, t-like, J=7 Hz), 1.05 (9H, s), 1.11–1.18 (1H, m), 1.36 (1H, quint-like, J=7.2 Hz), 1.52 (1H, d-like, J=13.7 Hz), 1.64 (1H, td, J=13.2, 4.7 Hz), 1.72–1.77 (1H, m), 3.09 (1H, br), 3.45 (3H, s), 3.63 (2H, d, J=6.8 Hz), 3.70 (3H, br s), 4.40 (1H, br), 4.98 (1H, br), 5.07–5.13 (2H, m), 5.79–5.85 (1H, m), 7.36–7.45 (6H, m), 7.68–7.69 (4H, br); ^{13}C NMR (75 MHz) δ 11.91 (q), 19.21 (s), 25.70 (t), 26.83 (q), 27.81 (t), 34.63 (d), 36.99 (d), 52.00 (q), 52.97 (q), 54.80 (d), 61.18 (t), 115.07 (t), 127.46 (d), 129.49 (d), 133.34 and 133.39 (each s), 135.42 (d), 139.15 (d), 156.91 (s), 172.52 (s); MS: 466 (M^+-57, 100); HRMS: Calcd for $C_{26}H_{32}NO_5Si$ ($M^+-C_4H_9$) 466.2050. Found 466.2035; $[\alpha]_D^{26}$=+26.6 (*c* 5.52, $CHCl_3$).

4.1.35. Methyl (2*S*,3*R*,5*S*,6*R*)-(+)-2-(*tert*-butyldiphenylsilyloxymethyl)-3-ethyl-6-hydroxymethyl-5-vinylpiperidine-1-carboxylate (26). To a stirred solution of **25** (1.38 g, 2.64 mmol) in THF (15 mL) was added a solution of Super-Hydride (1 M in THF, 6 mL, 6.0 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h. The reaction was quenched with satd. $NaHCO_3$ (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (15 mL×6). The organic extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on SiO_2 (25 g, hexane:acetone=40:1–15:1) to give **26** (1.26 g, 96%) as a colorless oil.

IR (neat) 3459, 3071, 2957, 2932, 1692, 1111 cm^{-1}; ^1H NMR (500 MHz) δ 0.53 and 0.64 (3H, br), 0.90–0.99 (2H, br), 1.02 (9H, s), 1.40–1.44 (1H, br), 1.56 (1H, td, J=13.7, 4.7 Hz), 1.71–1.77 (1H, br), 2.30 and 2.41 (1H, br), 3.61–3.91 (8H, br), 4.44–4.69 (2H, br), 5.00–5.14 (2H, m), 5.83–5.90 (1H, m), 7.39–7.46 (6H, m), 7.65–7.88 (4H, m); ^{13}C NMR (75 MHz) δ 11.04 (q), 18.95 (s), 25.11 (t), 26.65 (q), 27.43 (t), 33.67 (d), 36.62 (d), 52.81 (q), 54.61 (d), 61.95 (t), 64.36 (t), 114.75 (t), 127.58 and 127.69 (each d), 129.68 and 129.78 (each d), 132.66 (s), 135.21 (d), 140.12 (d), 157.90 (s); MS: 438 (M^+-57), 407 (100); HRMS: Calcd for $C_{25}H_{32}NO_4Si$ ($M^+-C_4H_9$) 438.2101. Found 438.2099; $[\alpha]_D^{26}$=+22.7 (*c* 2.37, $CHCl_3$).

4.1.36. (5*S*,6*R*,8*R*,9*R*)-(−)-5-(*tert*-Butyldiphenylsilyloxymethyl)-6-ethyl-8-vinyl-hexahydrooxazolo[3,4-*a*]pyridin-3-one (27). To a stirred solution of **26** (50 mg, 0.10 mmol) in THF (0.5 mL) was added NaH (60%, 4.8 mg, 0.12 mmol) at 0 °C, and the resulting suspension was stirred at 0 °C for 1 h. The reaction was quenched with 10% AcOH, and the aqueous mixture was extracted with CH_2Cl_2 (10 mL×4). The organic extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (10 g, hexane:acetone=40:1–25:1) to give **27** (44 mg, 94%) as a colorless oil.

IR (neat) 3070, 2958, 2933, 1753, 1110 cm^{-1}; ^1H NMR (500 MHz) δ 0.92 (3H, t, J=7.4 Hz), 1.09 (9H, s), 1.25–1.32 (1H, m), 1.41 (1H, ddd, J=15, 12, 5 Hz), 1.49–1.57 (1H, m), 2.01–2.05 (2H, m), 2.27 (1H, ddd, J=12, 10, 5 Hz), 3.35 (1H, ddd, J=10.5, 8.5, 5 Hz), 3.42 (1H, ddd, J=8.5, 5.5, 3 Hz), 3.94 (1H, dd, J=8.5, 5 Hz), 4.25 (1H, t, J=8.5 Hz), 4.32 (1H, dd, J=10.5, 8.5 Hz), 4.35 (1H, dd, J=10.5, 5.5 Hz), 5.05–5.16 (2H, m), 5.48–5.55 (1H, m), 7.37–7.45 (6H, m), 7.65–7.73 (4H, m); ^{13}C NMR (75 MHz) δ 11.89 (q), 18.25 (t), 19.34 (s), 26.99 (q), 32.81 (t), 35.42 (d), 40.53 (d), 59.77 (d), 60.11 (d), 60.42 (t), 66.44 (t), 117.09 (t), 127.55 (d), 129.55 (d), 133.35 and 133.42 (each s), 135.41 and 135.44 (each d), 137.46 (d), 156.38 (s); MS: 406 (M^+-57, 100); HRMS: Calcd for $C_{24}H_{28}NO_3Si$ ($M^+-C_4H_9$) 406.1839. Found 406.1841; $[\alpha]_D^{26}$=−32.8 (*c* 2.03, $CHCl_3$).

4.1.37. Methyl (2*S*,3*R*,5*S*,6*R*)-(−)-2-(*tert*-butyldiphenylsilyloxymethyl)-3,5-diethyl-6-(2-ethoxycarbonylvinyl)-piperidine-1-carboxylate. To a stirred solution of $(COCl)_2$ (0.26 mL, 3.03 mmol) in CH_2Cl_2 (8 mL) was added DMSO (0.43 mL, 6.06 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 10 min. To the mixture was added a solution of **26** (1.0 g, 2.02 mmol) in CH_2Cl_2 (10 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. Triethylamine (1.26 mL, 9.09 mmol) at −78 °C, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (20 mL×4). The organic extracts were combined, dried and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred suspension of NaH (60%, 90 mg, 2.22 mmol) in THF (10 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (0.44 mL, 2.22 mmol) at 0 °C, and the resulting solution was stirred at 0 °C for 15 min. To the reaction mixture was added a solution of the above oil in THF (10 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with CH_2Cl_2 (30 mL×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (30 g, hexane:acetone=80:1–40:1) to give an α,β-unsaturated ester (1.05 g, 92%) as a colorless oil.

IR (neat) 3070, 2957, 2932, 1703, 1111 cm^{-1}; ^1H NMR (500 MHz) δ 0.62 (3H, br t-like, J=7 Hz), 0.95 (2H, quint-like, J=7.5 Hz), 1.07 (9H, s), 1.20 (3H, t, J=7.5 Hz), 1.44 (1H, d-like, J=14 Hz), 1.60 (1H, td, J=13, 4.7 Hz), 1.76 (1H, br), 2.71 (1H, br), 3.49 (1H, dd, J=11, 5.2 Hz), 3.64–3.76 (5H, br m), 4.10–4.24 (2H, m), 4.40–4.65 (1H, br), 5.09–5.28 (2H, m), 5.88–5.94 (1H, m), 6.16 (1H, d-like, J=16 Hz), 7.26 (1H, d-like, J=16 Hz), 7.36–7.45 (6H, m), 7.67–7.81 (4H, m); ^{13}C NMR (75 MHz) δ 11.30 (q), 14.27

(q), 19.01 (s), 25.29 (t), 26.71 (q), 27.46 (t), 33.70 (d), 39.16 (d), 52.81 (q), 53.41 (d), 54.32 (d), 60.16 (t), 60.37 (t), 115.15 (t), 121.36 (d), 129.42 and 129.50 (each d), 133.35 (s), 135.38 (d), 139.62 (d), 149.26 (d), 157.15 (s), 166.12 (s); MS: 506 (M^+-57), 69 (100); HRMS: Calcd for $C_{29}H_{36}NO_5Si$ ($M^+-C_4H_9$) 506.2363. Found 506.2363; $[\alpha]_D^{26}=-10.8$ (*c* 4.43, $CHCl_3$).

4.1.38. Methyl (2*S*,3*R*,5*R*,6*S*)-(+)-2-(*tert*-butyldiphenylsilyloxymethyl)-3,5-diethyl-6-(3-hydroxypropyl)piperidine-1-carboxylate (28). To a solution of the above α,β-unsaturated ester (1.0 g, 1.78 mmol) in EtOAc (30 mL) was added 5% Pd–C (100 mg), and the resulting suspension was hydrogenated under hydrogen atmosphere at 1 atm for 72 h. The catalyst was removed by filtration, and the filtrate was evaporated to give colorless oil, which was used directly in the next step.

To a stirred solution of the above in THF (12 mL) was added a solution of Super-Hydride (1 M in THF, 4.0 mL, 4.0 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 1 h. The reaction was quenched with satd $NaHCO_3$ (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (15 mL×5). The organic extracts were combined, dried, and evaporated to give colorless oil, which was chromatographed on SiO_2 (25 g, hexane:acetone=40:1–12:1) to give **28** (913 mg, 98%) as a colorless oil.

IR (neat) 3448, 2998, 2962, 2839, 1738, 1240 cm^{-1}; ^1H NMR (500 MHz) δ 0.76–0.95 (6H, m), 1.04 (9H, s), 1.15–1.86 (11H, br m), 1.98–2.23 (1H, br), 2.72 (1H, br), 3.58–3.71 (4H, br m), 3.62 (3H, s), 3.91–4.08 (1H, br), 4.41–4.45 (1H, br), 7.39–7.41 (6H, m), 7.63–7.69 (4H, m); ^{13}C NMR (75 MHz) δ 11.89 (q), 12.38 and 12.54 (each q), 19.16 (s), 22.67 (t), 25.53 (t), 25.71 (t), 26.78 (q), 29.53 (t), 31.16 (t), 33.51 (d), 33.67 (d), 52.59 (q), 53.54 (d), 54.74 (d), 59.25 (t), 61.99 (t), 127.50 and 127.56 (each d), 129.49 and 129.58 (each d), 133.21 and 133.35 (each s), 135.33 and 135.41 (each d), 158.23 (s); MS: 468 (M^+-57), 256 (100); HRMS: Calcd for $C_{27}H_{38}NO_4Si$ ($M^+-C_4H_9$) 468.2570. Found 468.2568; $[\alpha]_D^{26}=+10.6$ (*c* 1.57, $CHCl_3$).

4.1.39. Methyl (2*S*,3*R*,5*R*,6*S*)-(−)-2-(*tert*-butyldiphenylsilyloxymethyl)-3,5-diethyl-6-(3-methoxymethoxypropyl)piperidine-1-carboxylate. To a stirred soultion of **28** (913 mg, 1.74 mmol) in $CHCl_3$ (12 mL) were added MOMCl (0.52 mL, 6.96 mmol) and Hünig base (1.4 mL, 7.66 mmol), and the resulting mixture was refluxed for 2 h. After cooling, the solvent was evaporated and the residue was chromatographed on SiO_2 (25 g, hexane:acetone=40:1) to a MOM ether (878 mg, 89%) as a colorless oil.

IR (neat) 2932, 1692, 1111 cm^{-1}; ^1H NMR (500 MHz) δ 0.73 and 0.79 (3H, each t, each *J*=7.3 Hz), 0.90 (3H, t-like, *J*=7.3 Hz), 1.02 (9H, s), 1.14–1.77 (12H, br m), 3.30 (3H, s), 3.41–3.45 (1H, m), 3.49–3.58 (1H, m), 3.64 (3H, s), 3.61–3.69 (2H, m), 3.93 and 4.12 (1H, m), 4.42 and 4.68 (1H, m), 4.57 (2H, s), 7.37–7.44 (6H, m), 7.67–7.78 (4H, m); ^{13}C NMR (75 MHz) δ 11.70 and 11.86 (each q), 12.36 and 12.48 (each q), 19.09 (s), 25.47 (t), 25.66 (t), 26.70 (q), 27.81 (t), 31.81 (t), 33.41 and 33.77 (each d), 37.59 and 38.01 (each d), 52.39 (q), 54.38 (d), 54.75 (d), 54.98 (q), 62.12 (t), 67.70 (t), 96.27 (t), 127.43 and 127.48 (each d), 129.41 (d), 133.27 and 133.37 (each s), 135.28 and 135.33 (each d), 157.53 (s); MS: 512 (M^+-57, 100); HRMS: Calcd for $C_{29}H_{42}NO_5Si$ ($M^+-C_4H_9$) 512.2832. Found 512.2829; $[\alpha]_D^{26}=-0.98$ (*c* 3.37, $CHCl_3$).

4.1.40. Methyl (2*S*,3*R*,5*R*,6*S*)-(+)-3,5-diethyl-2-hydroxymethyl-6-(3-methoxymethoxypropyl)-piperidine-1-carboxylate (29). To a stirred solution of the above MOM ether (240 mg, 0.42 mmol) in THF (8 mL) was added a solution of TBAF (1 M in THF, 1.5 mL, 1.5 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 22 h. The reaction was quenched with satd. NH_4Cl (aq.), and the aqueous mixture was extracted with $CHCl_3$ (10 mL×5). The organic extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on SiO_2 (15 g, hexane:acetone=30:1–6:1) to give **29** (110 mg, 79%) as a colorless oil.

IR (neat) 3461, 2955, 2878, 1680, 1114, 1042 cm^{-1}; ^1H NMR (500 MHz) δ 0.86 (3H, t-like, *J*=7.3 Hz), 0.90 (3H, t, *J*=7.2 Hz), 1.12 (1H, m), 1.22–1.38 (2H, m), 11.40–1.59 (3H, m), 1.61–1.72 (5H, m), 2.17 (1H, br), 2.46 (1H, br), 3.32 (3H, s), 3.50 (2H, m), 3.57–3.66 (1H, m), 3.67 (3H, s), 3.69–3.76 (1H, br), 3.93–4.14 (1H, br), 4.31–4.46 (1H, br), 4.58 (2H, s); ^{13}C NMR (75 MHz) δ 11.93 (q), 12.30 (q), 25.29 (t), 25.50 (t), 27.43 (t), 32.15 (t), 33.28 (d), 37.94 (d), 52.84 (q), 54.43 (d), 55.11 (q), 55.21 (d), 62.12 (t), 67.47 (t), 96.25 (t), 159.39 (s); MS: 330 (M^+-1), 300 (100); HRMS: Calcd for $C_{17}H_{32}NO_5$ (M^+-H) 330.2279. Found 330.2291; $[\alpha]_D^{26}=+3.6$ (*c* 4.85, $CHCl_3$).

4.1.41. Methyl (2*S*,3*R*,5*R*,6*S*)-(+)-3,5-diethyl-2-(3-methoxymethoxypropyl)-6-propenylpiperidine-1-carboxylate. To a stirred solution of $(COCl)_2$ (0.12 mL, 1.41 mmol) in CH_2Cl_2 (4 mL) was added DMSO (0.2 mL, 2.82 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 10 min. To the mixture was added a solution of **29** (311 mg, 0.94 mmol) in CH_2Cl_2 (4 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. Triethylamine (0.58 mL, 4.23 mmol) at −78 °C, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (10 mL×4). The organic extracts were combined, dried and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred suspension of $EtP^+Ph_3Br^-$ (1.7 g, 4.70 mmol) in THF (15 mL) was added a solution of *n*-BuLi (1.6 M ih hexane, 2.6 mL, 4.22 mmol) at 0 °C, and the resulting orange solution was stirred at 0 °C for 30 min. To the solution was added a solution of the above oil in THF (6 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (15 mL×3). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (20 g, hexane:acetone=100:1–30:1) to give an olefin (266 mg, 83% in 2 steps) as a colorless oil.

IR (neat) 2929, 1693 cm^{-1}; ^1H NMR (500 MHz) δ 0.80 (3H, t, *J*=7.3 Hz), 0.86 (3H, m), 1.01–1.08 (1H, m), 1.09–1.15 (1H, m), 1.22–1.74 (12H, br m), 1.77 (1H, d-like,

J=6 Hz), 3.31 (3H, s), 3.44–3.48 (2H, br), 3.63 and 3.66 (3H, each s), 3.94 and 4.27 (1H, each br), 4.56 (2H, s), 4.93 and 5.11 (1H, each br), 5.48 (1H, q-like, J=9.4 Hz), 5.54 (1H, br); ^{13}C NMR (75 MHz) δ 11.44 (q), 12.38 (q), 13.19 and 13.63 (each q), 25.37 and 25.42 (each t), 25.76 (t), 26.99 and 27.20 (each t), 32.60 (t), 34.14 (d), 38.07 and 38.65 (each d), 49.96 (d), 52.38 (q), 54.15 (d), 55.01 (q), 67.54 (t), 96.17 (t), 126.28 and 126.51 (each d), 127.37 and 128.42 (each d), 156.83 (s); MS: 341 (M^+), 239 (100); HRMS: Calcd for $C_{19}H_{35}NO_4$ 341.2564. Found 341.2583; $[\alpha]_D^{26}$=+34.7 (c 1.50, $CHCl_3$).

4.1.42. (5*R*,6*R*,8*R*,9*S*)-(−)-6,8-Diethyl-5-propyloctahydroindolizine (30). To a solution of the above olefin (120 mg, 0.35 mmol) in EtOAc (12 mL) was added 5% Pd–C (100 mg), and the resulting suspension was hydrogenated under hydrogen atmosphere at 1 atm for 84 h. The catalyst was removed by filtration, and the filtrate was evaporated to give colorless oil, which was used directly in the next step.

To a stirred solution of *n*-PrSLi, prepared from *n*-PrSH (0.32 mL, 3.50 mmol) and *n*-BuLi (1.6 M in hexane, 2.1 mL, 3.33 mmol) in HMPA (3 mL) at 0 °C for 30 min. To the reaction mixture was added a solution of the above oil in THF (3 mL) at 0 °C, and the resulting solution was stirred at room temperature for 60 h. The reaction was quenched with NH_3 (aq.), and the aqueous mixture was extracted with Et_2O (10 mL×10). The organic extracts were combined, dried over K_2CO_3, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred solution of the above oil in MeOH (10 mL) was added c. HCl (8 drops), and the resulting mixture was refluxed for 2 h. After cooling, the solvent was evaporated, and the residue was washed with Et_2O. To the residue was added NH_3 (aq.), and the aqueous mixture was extracted with $CHCl_3$ (10 mL×8). The organic extracts were combined, dried over K_2CO_3, and evaporated to give colorless oil, which was used directly in the next step.

Carbontetrabromide (163 mg, 0.49 mmol) and Ph_3P (138 mg, 0.53 mmol) were added to a solution of the above oil in CH_2Cl_2 (6 mL) at 0 °C, and the reaction mixture was stirred at 0 °C for 2 h. To the reaction mixture was added Et_3N (0.77 mL, 5.60 mmol) at 0 °C, and the resulting suspension was stirred at 0 °C for 30 min. The solvent was evaporated, and the residue was extracted with *n*-pentane (10 mL×5). The organic extracts were combined and evaporated to give colorless solid, which was chromatographed on SiO_2 (15 g, hexane:acetone:Et_3N=50:1:5 drops) to give **30** (40 mg, 51%) as a pale yellow oil.

IR (neat) 2958, 2874, 2776, 1460, 1378, 1316, 1180, 1112, 928, 888 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.86 (3H, t, J=7.5 Hz), 0.87 (3H, t, J=7.5 Hz), 0.91 (3H, t, J=7 Hz), 0.97–1.06 (1H, m), 1.13–1.21 (1H, m), 1.21–1.52 (11H, br m), 1.55–1.62 (1H, m), 1.70–1.77 (1H, m), 1.86 (1H, q, J=9 Hz), 1.86–1.92 (1H, m), 1.94 (1H, dt, J=13, 3 Hz), 1.95–1.99 (1H, m), 3.12 (1H, td, J=8, 2 Hz); ^{13}C NMR (75 MHz) δ 11.23 (q), 12.56 (q), 14.68 (q), 18.45 (t), 19.17 (t), 20.49 (t), 26.00 (t), 29.29 (t), 32.49 (t), 33.51 (t), 37.28 (d), 37.86 (d), 52.13 (t), 66.82 (d), 71.34 (d); MS: 223 (M^+, 100); $[\alpha]_D^{26}$=−100.9 (c 1.76, $CHCl_3$).

DCl salt. ^{1}H NMR (500 MHz, D_2O) δ 0.83–0.89 (9H, m), 1.10–1.23 (4H, m), 1.32–1.39 (1H, m), 1.42–1.51 (2H, br m), 1.53–1.62 (3H, m), 1.66–1.74 (1H, m), 1.85–2.01 (3H, m), 2.07 (1H, dm, J=13.5 Hz), 2.27–2.34 (1H, m), 2.85 (1H, td-like, J=11, 6 Hz), 2.94 (1H, q-like, J=10 Hz), 3.14 (1H, dm, J=11 Hz), 3.58 (1H, tm, J=10 Hz); ^{13}C NMR (75 MHz, D_2O) δ 9.47 (q), 11.10 (q), 12.77 (q), 16.57 (t), 17.35 (t), 18.27 (t), 24.06 (t), 26.39 (t), 29.43 (t), 29.48 (t), 34.92 (d), 35.00 (d), 51.08 (t), 66.13 (d), 71.82 (d); $[\alpha]_D^{26}$=−40.9 (c 0.25, $CHCl_3$).

4.1.43. Methyl (5*S*,6*R*,8*R*,9*R*)-(−)-(6,8-dimethyl-3-oxohexahydrooxazolo[3,4-*a*]pyridin-5-yl)acetate (31). To a stirred solution of **15** (211 mg, 0.93 mmol) in MeOH (3 mL) and H_2O (1 mL) was added LiOH·H_2O (84 mg, 1.99 mmol), and the resulting solution was refluxed for 2 h. After cooling, the MeOH was evaporated, and the aqueous residue was acidified with 10% HCl and saturated with NaCl. The aqueous layer was extracted with EtOAc (10 mL×7), and the organic extracts were combined, dried, and evaporated to give a colorless oil, which was used directly in the next step.

To a stirred solution of the above oil in THF (8 mL) were added $ClCO_2Et$ (0.15 mL, 1.56 mmol) and Et_3N (0.23 mL, 1.66 mmol) at 0 °C, and the resulting suspension was stirred at 0 °C for 1 h. The insoluble material was filtered off, and the filtrate was evaporated to give a colorless oil, which was used directly in the next step.

To a stirred solution of the above oil in Et_2O (15 mL) was added a solution of CH_2N_2 in Et_2O at 0 °C, and the resulting mixture was stirred at room temperature for 19 h. The solvent was evaporated to give a pale yellow oil, which was used directly in the next step.

To a stirred solution of the above oil in MeOH (10 mL) were added $PhCO_2Ag$ (48 mg, 0.21 mmol) and Et_3N (0.3 mL, 2.17 mmol) at 0 °C, and the resulting suspension was stirred in the dark at room temperature for 27 h. The insoluble material was filtered, and the filtrate was evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (15 g, hexane:acetone=14:1) to give **31** (160 mg, 71% in 4 steps) as a colorless oil.

IR (neat) 2960, 2923, 1750 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.85 (3H, d, J=6.8 Hz), 1.08 (3H, d, J=7.3 Hz), 1.42–1.53 (2H, m), 1.64–1.70 (1H, m), 1.84–1.89 (1H, m), 2.53 (1H, dd, J=14.5, 7.7 Hz), 2.61 (1H, dd, J=14.5, 8.2 Hz), 3.28–3.34 (1H, m), 3.66 (3H, s), 3.95 (1H, dd, J=8.5, 6.4 Hz), 4.09 (1H, t-like, J=7.9 Hz), 4.41 (1H, t-like, J=8.5 Hz); ^{13}C NMR (125 MHz) δ 17.25 (q), 18.56 (q), 29.95 (d), 30.85 (d), 33.46 (t), 36.15 (t), 51.70 (d), 51.94 (q), 56.32 (d), 67.34 (t), 157.16 (s), 170.96 (s); MS: 241 (M^+), 197 (100); HRMS: Calcd for $C_{12}H_{19}NO_4$ 241.1314. Found 241.1312; $[\alpha]_D^{26}$=−37.7 (c 1.01, $CHCl_3$).

4.1.44. (5*S*,6*R*,8*R*,9*R*)-(−)-2-(6,8-Dimethyl-3-oxohexahydrooxazolo[3,4-*a*]pyridin-5-yl)-*N*-methoxy-*N*-methylacetamide (32). To a stirred solution of **31** (267 mg, 1.11 mmol) in MeOH (3 mL) and H_2O (1 mL) was added LiOH·H_2O (94 mg, 2.22 mmol), and the resulting solution was refluxed for 1 h. After cooling, the MeOH was

evaporated, and the aqueous residue was acidified with 10% HCl and saturated with NaCl. The aqueous layer was extracted with EtOAc (10 mL×8), and the organic extracts were combined, dried, and evaporated to give a colorless oil, which was used directly in the next step.

To a stirred solution of the above oil in CH_2Cl_2 (5 mL) was added 1,1′-carbonyldiimidazole (234 mg, 1.44 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 30 min. To the reaction mixture were added Me(MeO)NH·HCl (141 mg, 1.44 mmol) and Et_3N (0.2 mL, 1.44 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 22 h. The solvent was evaporated and the rsidue was chromatographed on SiO_2 (15 g, hexane:acetone=10:1–4:1) to give **32** (292 mg, 98%) as a colorless oil.

IR (neat) 2961, 2926, 1746, 1656, 1416 cm^{-1}; ^1H NMR (500 MHz) δ 0.86 (3H, d, J=6.4 Hz), 1.09 (3H, d, J=7.3 Hz), 1.49–1.50 (2H, m), 1.64–1.68 (1H, m), 1.93–1.95 (1H, m), 2.62 (1H, dd, J=13.7, 7.6 Hz), 2.73 (1H, dd, J=13.7, 7.7 Hz), 3.15 (3H, s), 3.39 (1H, q-like, J=8.1 Hz), 3.72 (3H, s), 3.92 (1H, t-like, J=7.3 Hz), 4.10 (1H, t-like, J=7.2 Hz), 4.42 (1H, t-like, J=7.3 Hz; ^{13}C NMR (125 MHz) δ 17.26 (q), 18.65 (q), 30.07 (d), 30.74 (d), 32.14 (q), 33.56 (t), 34.31 (t), 51.36 (d), 56.60 (d), 61.41 (d), 67.52 (t), 157.27 (s), 171.23 (s); MS: 270 (M^+), HRMS: Calcd for $C_{13}H_{22}N_2O_4$ 270.1578. Found 270.1563; $[\alpha]_D^{26}$=−53.3 (c 1.28, $CHCl_3$).

4.1.45. (5*S*,6*R*,8*R*,9*R*)-(−)-6,8-Dimethyl-5-(2-oxopropyl)-hexahydrooxazolo[3,4-*a*]pyridin-3-one (33). To a stirred solution of **32** (51 mg, 0.19 mmol) in THF (2 mL) was added a solution of MeMgBr (0.9 m in THF, 0.31 mL, 0.28 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with satd. NH_4Cl (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (10 mL×3). The organic extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on SiO_2 (10 g, hexane:acetone=10:1–7:1) to give **33** (31 mg, 73%) as a colorless solid (mp 53–56 °C).

IR (KBr) 2962, 1748 cm^{-1}; ^1H NMR (500 MHz) δ 0.83 (3H, d, J=6.4 Hz), 1.07 (3H, d, J=7.3 Hz), 1.40–1.50 (2H, m), 1.62–1.69 (1H, m), 1.82–1.84 (1H, br), 2.13 (3H, s), 2.63 (1H, dd, J=15.4, 7.6 Hz), 2.68 (1H, dd, J=15.4, 7.7 Hz), 3.23–3.28 (1H, m), 3.95 (1H, dd, J=8.5, 6.4 Hz), 4.12 (1H, t-like, J=7.7 Hz), 4.36 (1H, dd, J=8.5, 6.4 Hz); ^{13}C NMR (125 MHz) δ 17.22 (q), 18.52 (q), 29.68 (q), 29.77 (d), 30.86 (d), 33.40 (t), 45.30 (t), 50.99 (d), 56.41 (d), 67.25 (t), 157.24 (s), 206.19 (s); MS: 225 (M^+), 182 (100); HRMS: Calcd for $C_{12}H_{19}NO_3$ 225.1364. Found 225.1364; $[\alpha]_D^{26}$=−13.9 (c 1.48, $CHCl_3$).

4.1.46. (5*S*,6*R*,8*R*,9*R*)-(−)-6,8-Dimethyl-5-(2-methyl-[1,3]dioxolan-2-ylmethyl)hexahydrooxazolo[3,4-*a*]pyridin-3-one. To a stirred solution of **33** (161 mg, 0.72 mmol) in benzene (15 mL) were added p-TsOH·H_2O (30 mg, 0.16 mmol) and ethyleneglycol (0.3 mL, 5.39 mmol), and the reaction mixture was refluxed using Dean–Stark apparatus for 18 h. After cooling, the reaction was quenched with satd. $NaHCO_3$ (aq.) and the organic layer was separated. The aqueous layer was extracted with benzene (10 mL×3), and the organic layer and extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on SiO_2 (20 g, hexane:acetone=10:1–7:1) to give an acetal (166 mg, 86%) as a colorless solid (mp 82–84 °C).

IR (KBr) 2961, 2922, 1740, 1060 cm^{-1}; ^1H NMR (500 MHz) δ 0.82 (3H, d, J=6.5 Hz), 1.04 (3H, d, J=7.3 Hz), 1.33 (3H, s), 1.45–1.47 (2H, m), 1.63–1.69 (1H, m), 1.76 (1H, dd, J=14.5, 4.7 Hz), 1.83–1.88 (1H, m), 2.06 (1H, dd, J=14.5, 9 Hz), 3.28–3.33 (1H, m), 3.87–3.99 (6H, m), 4.36 (1H, t-like, J=8.5 Hz); ^{13}C NMR (125 MHz) δ 17.35 (q), 18.34 (q), 23.76 (q), 30.16 (d), 32.20 (d), 33.75 (t), 39.65 (t), 50.72 (d), 56.25 (d), 64.26 (t), 66.91 (t), 109.03 (s), 157.09 (s); MS: 269 (M^+), 254 (100); HRMS: Calcd for $C_{14}H_{23}NO_4$ 269.1627. Found 269.1641. Anal. Calcd for C14H23NO4 C, 62.43; H, 8.61; N, 5.20. Found C, 62.59; H, 8.67; N, 5.14; $[\alpha]_D^{26}$=−20.4 (c 1.59, $CHCl_3$).

4.1.47. 2-Methyl-2-propyl (2*R*,3*R*,5*R*,6*S*)-(+)-2-hydroxymethyl-3,5-dimethyl-6-(2-methyl-[1,3]dioxolan-2-ylmethyl)piperidine-1-carboxylate (34). A solution of 2 M KOH in i-PrOH (50 mL) was added to the above acetal (1.9 g, 7.06 mmol), and the resulting mixture was heated at 120 °C in the sealed tube for 2 days. After cooling, the solvent was evaporated, and the residue was dissolved in H_2O. The aqueous mixture was extracted with $CHCl_3$ (20 mL×10), and the organic extracts were combined, dried over K_2CO_3, and evaporated to give pale yellow oil, which was used directly in the next step.

To a stirred solution of the above oil in H_2O (24 mL) and dioxane (48 mL) were added NaOH (950 mg, 23.75 mmol) and Boc_2O (4.8 g, 21.99 mmol) at 0 °C, and the resulting solution was stirred at room temperature for 18 h. The aqueous layer was extracted with $CHCl_3$ (10 mL×5). The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (50 g, hexane:acetone=20:1) to give **34** (1.8 g, 74% in 2 steps) as a colorless oil.

IR (neat) 3425, 2963, 2928, 1669 cm^{-1}; ^1H NMR (500 MHz) δ 0.91 (3H, d, J=6.4 Hz), 0.98 (3H, d, J=6.8 Hz), 1.33 (3H, s), 1.38–1.42 (2H, br), 1.44 (9H, s), 1.72 (1H, br), 1.76 (1H, dd, J=14.5, 4.1 Hz), 2.00–2.16 (2H, br), 2.83 (1H, br), 3.89 (2H, br), 3.92 (4H, m), 4.19 (1H, br), 5.29 (1H, br); ^{13}C NMR (125 MHz) δ 18.34 (q), 18.95 (q), 23.88 (q), 26.58 (d), 28.37 (q), 33.42 (d), 36.36 (t), 41.79 (t), 55.75 (d), 60.60 (t), 61.31 (d), 64.31 (t), 64.51 (t), 79.92 (s), 109.53 (s), 157.60 (s); MS: 343 (M^+), 212 (100); HRMS: Calcd for $C_{18}H_{33}NO_5$ 343.2357. Found 343.2345; $[\alpha]_D^{26}$=+22.8 (c 9.84, $CHCl_3$).

4.1.48. (2*R*,3*R*,5*R*,6*S*)-(+)-2-Methyl-2-propyl 2(2-ethoxycarbonylvinyl)-3,5-dimethyl-6-(2-methyl-[1,3]-dioxolan-2-ylmethyl)piperidine-1-carboxylate (35). To a stirred solution of $(COCl)_2$ (0.7 mL, 8.06 mmol) in CH_2Cl_2 (20 mL) was added DMSO (1.2 mL, 17.0 mmol) at −78 °C, and the resulting solution was stirred at −78 °C for 10 min. To the mixture was added a solution of **12** (1.8 g, 5.25 mmol) in CH_2Cl_2 (10 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. Triethylamine

(3.3 mL, 23.92 mmol) was added to the reaction mixture at −78 °C, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (20 mL×5). The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was used directly in the next step.

To a stirred suspension of NaH (60%, 330 mg, 8.05 mmol) in THF (20 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (1.6 mL, 7.87 mmol) at 0 °C, and the resulting solution was stirred at 0 °C for 30 min. To the mixture was added a solution of the above aldehyde in THF (9 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 6 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with CH_2Cl_2 (20 mL×4). The organic extracts were combined, dried, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (50 g, hexane:acetone=20:1) to give **35** (2.16 g, 73% in 2 steps) as a colorless oil.

IR (neat) 2972, 2929, 2881, 1716, 1690 cm^{-1}; ^1H NMR (500 MHz) δ 0.81 (3H, d, J=6.4 Hz), 0.98 (3H, d, J=6.8 Hz), 1.26 (3H, t, J=7.2 Hz), 1.33 (3H, s), 1.35–1.42 (1H, m), 1.40 (9H, s), 1.80–1.86 (4H, m), 2.14–2.18 (1H, m), 3.46 (1H, t-like, J=8.5 Hz), 3.88–3.95 (5H, m), 4.18 (2H, q, J=7.2 Hz), 5.80 (1H, d, J=15.8 Hz), 7.10 (1H, dd, J=15.8, 7.7 Hz); ^{13}C NMR (125 MHz) δ 14.18 (q), 18.67 (q), 18.85 (q), 23.82 (q), 28.28 (q), 29.28 (d), 31.70 (d), 35.36 (t), 39.46 (t), 55.18 (d), 60.06 (t), 64.24 (t), 64.34 (t), 79.87 (s), 109.32 (s), 120.12 (d), 148.59 (d), 155.75 (s), 166.58 (s); MS: 411 (M^+), 253 (100); HRMS: Calcd for $C_{22}H_{37}NO_6$ 411.2619. Found 411.2932; $[\alpha]_D^{26}$=+37.0 (*c* 1.39, $CHCl_3$).

4.1.49. (2a*S*,5a*S*,6*R*,8*R*,8a*S*)-(+)-6,8-Dimethyldecahydropyrrolo[2,1,5-de]quinolizin-4-one (14) and its acetal (36). To a stirred solution of **35** (165 mg, 0.40 mmol) in EtOAc (20 mL) was added 10% Pd–C (50 mg), and the resulting suspension was hydrogenated under hydrogen atmosphere at 1 atm for 45 h. The catalyst was removed by filtration and the filtrate was evaporated to give a colorless oil, which was used directly in the next step.

To a stirred solution of the above oil in CH_2Cl_2 (2 mL) was added a solution of DIBAL (0.93 M in hexane, 0.43 mL, 0.4 mmol) at −78 °C, and the resulting mixture was stirred at −78 °C for 30 min. The reaction was quenched with MeOH (1 mL) and satd. Rochelle solution in H_2O (1 mL). The organic layer was seperated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL×3). The organic layer and extracts were combined, dried, and evaporated to give a colorless oil, which was used directly in the next step.

To a stirred solution of the above oil in benzene (24 mL) and acetone (4 mL) was added p-TsOH·H_2O (228 mg, 1.2 mmol), and the reaction mixture was heated at reflux using Dean–Stark apparatus for 5 h. After cooling, the reaction was quenched with satd. $NaHCO_3$ (aq.), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (10 mL×5), and the organic layer and extracts were combined, dried over K_2CO_3, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (20 g, hexane:acetone=30:1–15:1) to give **36** (52 mg, 62% in 3 steps) as a colorless solid (mp 57–58 °C) and its acetal **37** (15 mg, 15% in 3 steps) as a pale yellow oil.

Ketone **36**. IR (KBr) 2959, 2920, 2867, 1707 cm^{-1}; ^1H NMR (500 MHz) δ 0.91 (3H, d, J=6.3 Hz), 1.18 (3H, d, J=7 Hz), 1.38–1.53 (4H, m), 1.63 (1H, m), 1.75 (1H, m), 2.02–2.08 (2H, m), 2.13–2.20 (2H, m), 2.29 (1H, dd, J=13.5, 11 Hz), 2.58 (1H, td, J=10, 6.4 Hz), 2.64 (1H, t, J=13 Hz), 3.08 (1H, dt, J=12, 2.5 Hz), 3.39 (1H, m); ^{13}C NMR (125 MHz) δ 18.74 (q), 20.42 (q), 28.88 (t), 29.00 (t), 32.13 (d), 33.23 (d), 35.68 (t), 42.67 (t), 45.14 (t), 59.59 (d), 61.05 (d), 61.55 (d), 210.34 (s); MS: 207 (M^+), 91 (100); HRMS: Calcd for $C_{13}H_{21}NO$ 207.1622. Found 207.1642; $[\alpha]_D^{26}$=+27.1 (*c* 2.29, $CHCl_3$).

Acetal **37**. IR (neat) 2951, 2921, 2878, 1152 cm^{-1}; ^1H NMR (500 MHz) δ 0.84 (3H, d, J=6.4 Hz), 1.15 (3H, d, J=7.3 Hz), 1.27–1.39 (5H, m), 1.42–1.44 (1H, m), 1.51–1.56 (2H, m), 1.68 (1H, br), 1.83 (1H, t, J=12.8 Hz), 1.94 (1H, m), 2.04 (1H, m), 2.44 (1H, m), 3.00 (1H, d-like, J=12.7 Hz), 3.26 (1H, m), 3.96 (4H, s-like); ^{13}C NMR (125 MHz) δ 18.82 (q), 20.42 (q), 28.07 (t), 28.95 (t), 32.18 (d), 32.93 (d), 34.19 (t), 36.36 (t), 36.57 (t), 57.33 (d), 57.73 (d), 58.96 (d), 63.83 (t), 64.41 (t), 109.17 (s); MS: 251 (M^+), 250 (100); HRMS: Calcd for $C_{15}H_{25}NO_2$ 251.1884. Found 251.1889; $[\alpha]_D^{26}$=−4.6 (*c* 1.48, $CHCl_3$).

Deprotection of **37** with acid. To a stirred solution of **37** (179 mg, 0.71 mmol) in acetone (20 mL) was added p-TsOH·H_2O (1 g, 5.71 mmol), and the reaction mixture was heated at reflux for 20 h. After cooling, the reaction was quenched with satd. $NaHCO_3$ (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (20 mL×4). The organic extracts were combined, dried over K_2CO_3, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (15 g, hexane:acetone=30:1–15:1) to give **36** (118 mg, 80%) as a colorless solid, whose spectral data were identical with those of the authentic sample.

4.1.50. (2a*S*,5a*S*,6*R*,8*R*,8a*R*)-(−)-6,8-Dimethyl-2,2a,5,5a,6,7,8,8a-octahydro-1*H*-pyrrolo[2,1,5-de]-quinolizin-4-yl trifluoromethanesulfonate (38). To a stirred solution of *R*-(*R**,*R**)-(+)-bis(α-methylbenzyl)amine (110 mg, 0.49 mmol) in THF (1 mL) was added *n*-BuLi (1.6 M in hexane, 0.3 mL, 0.49 mmol) at 0 °C, and the resulting solution was stirred at 0 ° C for 30 min. To the above solution was added a solution of **36** (66 mg, 0.32 mmol) in THF (2 mL) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. To the reaction mixture was added a solution of 2[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridie (Comins' reagent) (194 mg, 0.49 mmol) at −78 °C, and the reaction mixture was warmed to −40 °C for 30 min. The reaction was quenched with satd. $NaHCO_3$ (aq.), and the aqueous mixture was extracted with CH_2Cl_2 (15 mL×5). The organic extracts were combined, dried over K_2CO_3, and evaporated to give pale yellow oil, which was chromatographed on SiO_2 (20 g, hexane:acetone=150:1) to give **38** (58 mg, 54%) as a colorless oil.

IR (neat) 2947, 2926, 2875, 1283 cm^{-1}; ^1H NMR (500 MHz) δ 0.88 (3H, d, J=6.4 Hz), 1.20 (3H, d, J=7.3 Hz), 1.34–1.46 (4H, m), 1.52 (1H, m), 1.78 (1H, m), 1.99 (2H, m), 2.10 (1H, td, J=10, 5 Hz), 2.20 (1H, m),

2.59 (1H, m), 3.11 (1H, dd, J=11, 5 Hz), 3.99 (1H, dd-like, J=7, 2.5 Hz), 5.62 (1H, t-like, J=2.5 Hz); ^{13}C NMR (125 MHz) δ 18.77 (q), 20.03 (q), 26.65 (t), 27.86 (t), 29.19 (t), 32.22 (d), 35.19 (t), 57.23 (d), 57.46 (d), 60.79 (d), 100.57 (s), 121.95 (d), 144.71 (s); MS: 339 (M^+), 69 (100); HRMS: Calcd for $C_{14}H_{20}F_3NO_3S$ 339.1115. Found 339.1137; $[\alpha]_D^{26}$=−13.8 (*c* 1.84, $CHCl_3$).

4.1.51. (2a*S*,5a*S*,6*R*,8*R*,8a*S*)-(+)-3,5-Dimethyl-7-methylenedecahydropyrrolo[2,1,5-de]quinolizine (39). To a stirred suspension of $MeP^+Ph_3Br^-$ (1.22 g, 3.01 mmol) in THF (5 mL) was added *n*-BuLi (1.6 M in hexane, 1.65 mL, 2.63 mmol) at 0 °C, and the resulting yellow suspension was stirred at 0 °C for 15 min. To the suspension was added a solution of **36** (78 mg, 0.38 mmol) in THF (2 mL) at 0 °C, and the resulting suspension was stirred at room temperature for 21 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (15 mL×4). The organic extracts were combined, dried over K_2CO_3, and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (15 g, hexane:acetone=100:1) to give **39** (65 mg, 84%) as a colorless oil.

IR (neat) 3070, 2954, 2927, 2791 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.86 (3H, d, J=6.9 Hz), 1.14 (3H, d, J=7.3 Hz), 1.34–1.38 (4H, m), 1.54 (1H, m), 1.74 (1H, br), 1.85 (1H, d, J=11.5 Hz), 1.96–2.07 (4H, m), 2.32 (1H, t, J=12.4 Hz), 2.59 (1H, q-like, J=6.9 Hz), 2.74 (1H, dm, J=12.4 Hz), 3.05 (1H, br), 4.66 (2H, br); ^{13}C NMR (125 MHz) δ 18.79 (q), 20.49 (q), 28.54 (t), 29.11 (t), 32.31 (d), 33.25 (d), 35.13 (t), 36.52 (t), 37.60 (t), 59.45 (d), 61.58 (d), 61.92 (d), 106.48 (t), 148.42 (s); MS: 205 (M^+), 150 (100); HRMS: Calcd for $C_{14}H_{23}N$ 205.1829. Found 205.1844; $[\alpha]_D^{26}$=+12.4 (*c* 3.01, $CHCl_3$).

4.1.52. (2a*S*,5a*S*,6*R*,8*R*,8a*S*)-(+)-3,5,7-Trimethyl-2,2a,3,4,5,5a,6,8a-octahydro-1*H*-pyrrolo[2,1,5-de]-quinolizidine (205B, 40). To a stirred solution of **39** (60 mg, 0.29 mmol) in benzene (6 mL) was added *p*-TsOH·H_2O (167 mg, 0.88 mmol), and the reaction mixture was heated at reflux for 24 h. After cooling, the reaction was quenched with satd. $NaHCO_3$ (aq.), and the organic layer was separated. The aqueous layer was extracted with Et_2O (10 mL×4), the organic layer and extracts were combined, dried over K_2CO_3, and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (15 g, hexane:acetone=100:1) to give **40** (38 mg, 63%) as a pale yellow oil.

IR (neat) 2956, 2905, 2790, 1660, 1458, 1375, 1317, 1216, 1169 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.86 (3H, d, J=6.4 Hz), 1.19 (3H, d, J=7.3 Hz), 1.27–1.52 (6H, br m), 1.64 (3H, s), 1.72 (1H, m), 1.92 (1H, m), 2.12–2.18 (3H, m), 3.00 (1H, dd, J=11.2, 4.5 Hz), 3.80 (1H, br), 5.20 (1H, br); ^{13}C NMR (125 MHz) δ 18.83 (q), 20.19 (q), 23.56 (q), 28.35 (t), 28.38 (t), 29.22 (t), 32.44 (d), 32.55 (d), 35.42 (d), 56.49 (d), 58.04 (d), 60.46 (d), 125.52 (d), 129.52 (d); MS: 205 (M^+), 71 (100); HRMS: Calcd for $C_{14}H_{23}N$ 205.1829. Found 205.1828; $[\alpha]_D^{26}$=+8.1 (*c* 1.05, $CHCl_3$).

Acknowledgements

We would like to thank Drs. John W. Daly, Thomas F. Spande, and H. Martin Garraffo, NIH, for very valuable suggestions and discussions about this paper. We are also grateful to Dr. Yoshihiko Hirose, Amano Pharmaceutical Co., Ltd., for the generous gift of lipase AK used in the synthesis of **19**. We also thank Professors Shigetoshi Kadota and Yasuhiro Tezuka for recording the NOE spectra of **38**.

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