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Enantioselective syntheses of two 5, 9*E* diastereomers of 223V, an alkaloid from the poison frog *Dendrobates pumilio*

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Abstract—Enantioselective syntheses of two 5, 9*E* diastereomers (**1** and **2**) of **223V** (**3**) are described. Neither corresponded on GC–MS and GC-FTIR analyses to alkaloid **223I**, previously tentatively proposed to be a 5,8-disubstituted indolizidine of the unusual 5, 9*E* relative stereochemistry. Synthetic (−)-(5, 9*Z*)-5-*n*-propyl-8-*n*-butylindolizidine (**3**) corresponds on GC–MS and GC-FTIR analyses to the natural indolizidine **223V** found in a *pumilio* from 'Split Hill', Panama.

1. Introduction

5,8-Disubstituted indolizidines represent a major class of alkaloids found in skins of poison frogs.[1] Over 60 such alkaloids have been proposed. Some structures are tentative, being based only on their GC–MS, dominated by a base peak due to α-cleavage of the 5-substituent, followed by a *retro*-Diels–Alder loss to yield a characteristic fragment at *m/z* 96.[2] Several of the 5,8-disubstituted indolizidines have been isolated from frog skin in sufficient quantities to allow structure confirmation by NMR spectral analysis. These include (−)-**203A**,[13] (−)-**205A**,[14] (−)-**207A**,[15] **233D**,[13] (−)-**235B′** and (+)-**235B″** (formerly **235B**).[14,15] Structures are shown in Figure 1. The structures of (−)-**207A**, (−)-**235B′**, and (+)-**235B″** have been confirmed by enantioselective synthesis.[3,16,17] The relative stereochemistry of **205A** is depicted on the basis of comparison with synthetic racemic material.[18] The structure and absolute stereochemistry of natural **209I**[15] was confirmed (unpublished results) by comparison to synthetic racemic material,[19] and the synthetic (−)-unnatural enantiomer.[20] Several laboratories have reported syntheses of (−)-**209B**.[18,21,22] Virtually all alkaloids of this class possess a 5, 9*Z* structure as shown by a characteristic sharp and intense Bohlmann

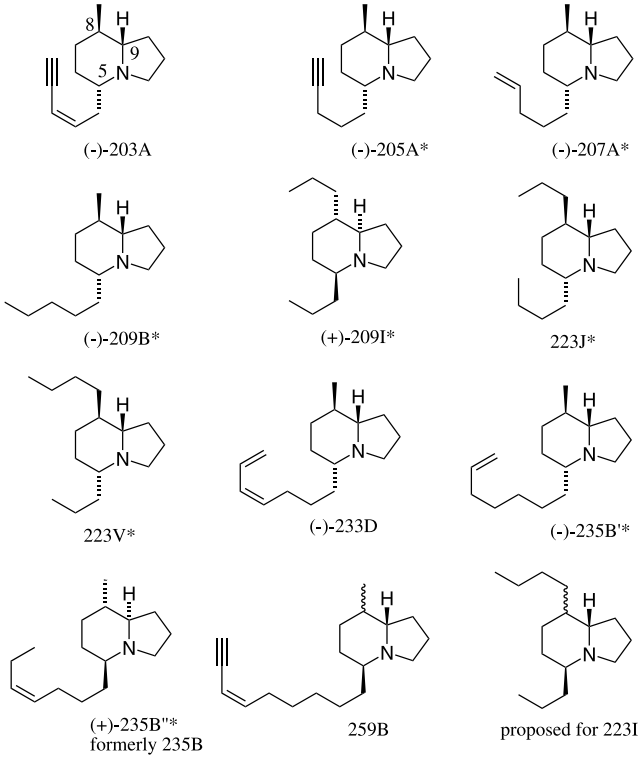

Figure 1. Alkaloids of the 5,8-disubstituted indolizidine class: structures of **203A**, **205A**, **207A**, **233D**, **235B′** and **235B″** were established by NMR spectral analysis, while structures indicated by an asterisk have been synthesized (see text). Absolute configurations have been established for the indicated alkaloids.

Keywords: Enantioselective syntheses; Diastereomers; Alkaloid.
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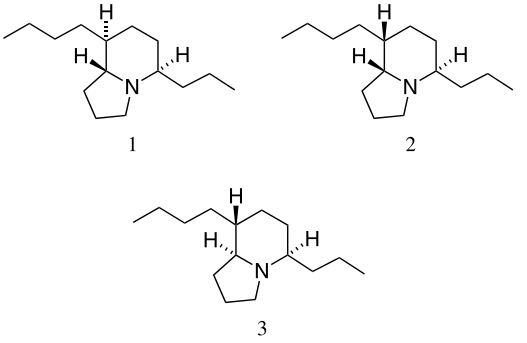
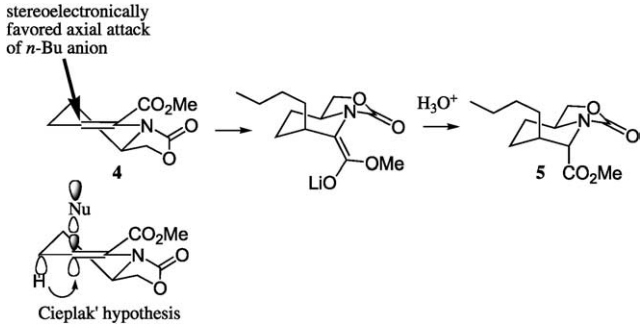
band near 2790 cm^{-1} in their GC-FTIR spectra.[2] Only two alkaloids have been tentatively proposed to be (5, 9*E*)-5,8-disubstituted indolizidines, based on GC–MS and a weak absorbance in the Bohlmann band region on GC-IR.[1] One of these is alkaloid **259B** from one population of *Dendrobates pumilio* with an EI-MS showing the α-cleavage expected of a 5-C_9H_{13}-8-CH_3-indolizidine, followed by *retro*-Diels–Alder cleavage of the fragment at *m/z* 138 to yield a significant diagnostic ion at *m/z* 96. The second was alkaloid **223I** from another population of the poison frog *D. pumilio*, tentatively proposed to have a (5, 9) *E*-5-propyl-8-butylindolizidine structure even though the diagnostic peak in EI-MS at *m/z* 96 was much weaker than expected.

In this paper, we would like to report the enantioselective syntheses of two 8-epimers of (5, 9*E*) 5-propyl-8-butyl-indolizidine (**1**, **2**) and comparison to alkaloid **223I**. In addition, a previously synthesized (−)-(5, 9*Z*) 5-propyl-8-butylindolizidine[3] (**3**) has now been shown to be identical in GC–MS and GC-FTIR to alkaloid **223V** from yet another population of the same poison frog, *D. pumilio* from 'Spilit Hill', Panama.



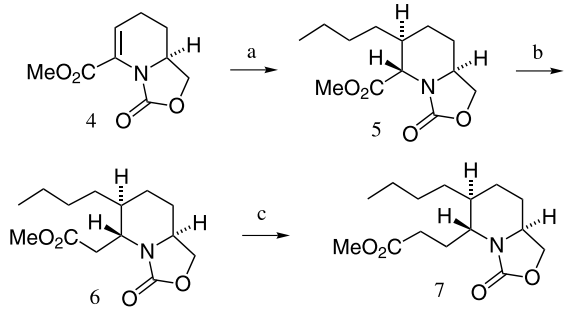
2. Results and discussion

The stereoselective synthesis of **3** has been described.[3] The synthesis of **1** began with the enaminoester **4**,[4] which was treated with lithium dibutylcuprate to afford the adduct **5** as a single isomer.[5] The stereoselectivity of this addition reaction can be explained by the stereoelectronic effect[6] and Cieplak's hypothesis[7] as shown below (Scheme 1).

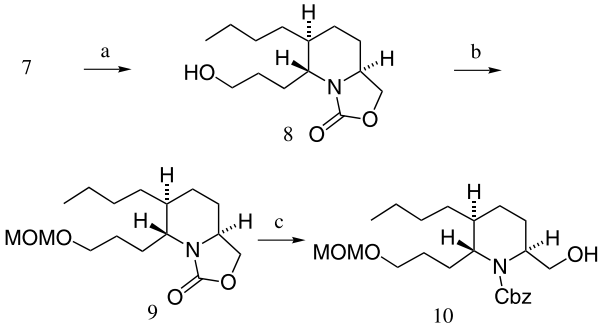


Scheme 1.

The carbon chain at the α-position of **5** was elongated by two Arndt–Eistert reactions to provide the two-carbon homologated ester **7**, which was converted to the methoxymethyl ether **9** by reduction of the ester moiety of **7** with Super-Hydride, followed by protection of the resulting alcohol **8** as shown in Schemes 2 and 3.

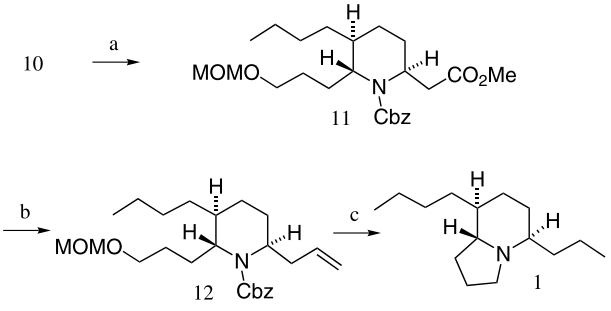


Scheme 2. (a) *n*-Bu_2CuLi, −78 to −10 °C (96%); (b) (1) LiOH, MeOH–H_2O, reflux; (2) $ClCO_2Et$, Et_3N, THF, 0 °C; (3) CH_2N_2; (4) $PhCO_2Ag$, Et_3N, MeOH, rt (80% in 4 steps); (c) same as (b) (86% in 4 steps).



Scheme 3. (a) Super-Hydride, THF, 0 °C (88%); (b) MOMCl, Hünig base, CH_2Cl_2, rt (87%); (c) (1) 2 M KOH/*i*-PrOH, 120 °C, sealed tube; (2) CbzCl, K_2CO_3, H_2O–CH_2Cl_2, rt (82% in 2 steps).

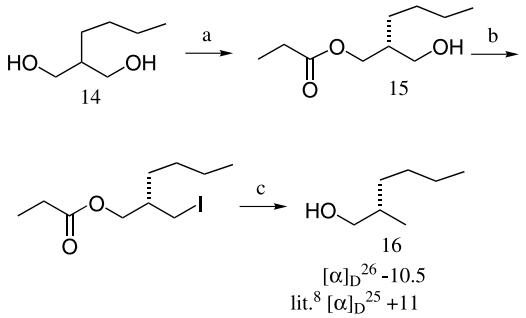
Hydrolysis of the oxazolizinone ring in **9** with KOH in a sealed tube, and protection of the resulting amino alcohol with CbzCl provided the alcohol **10**. Two-step oxidation of the alcohol **10** followed by Arndt–Eistert reaction afforded the methyl ester **11** (Scheme 4), which was reduced with DIBAL. Wittig olefination of the resulting aldehyde intermediate provided the olefin **12**. Hydrogenation of the double bond and hydrogenolysis of the Cbz-protecting group of **12**, and then removal of the methoxymethyl group with acid followed by indolizidine formation from the



Scheme 4. (a) (1) Swern ox.; (2) $NaClO_2$, H_2O–*t*-BuOH, 0 °C–rt; (3) $ClCO_2Et$, Et_3N, THF, 0 °C; (4) CH_2N_2; (5) $PhCO_2Ag$, Et_3N, MeOH, rt (54% in 5 steps); (b) (1) DIBAL, CH_2Cl_2, −78 °C (2) Witting reagent (57% in 2 steps); (c) (1) 10% Pd–C, H_2, EtOAc, 1 atm; (2) conc. HCl, MeOH, reflux; (3) CBr_4, Ph_3P, CH_2Cl_2, rt then Et_3N (67% in 3 steps).

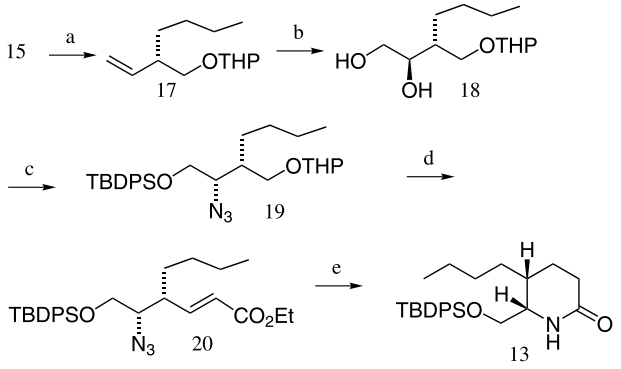
resulting amino alcohol via an intermediate bromide furnished the desired indolizidine **1** as shown in Scheme 4.

Synthesis of the indolizidine **2** was as follows: Lipase-mediated transesterification of the *meso*-diol **14** afforded the mono-propanoate **15**, which was transformed into the known 2-methyl-1-hexanol **16** via an intermediate iodide in a 3-step sequence as shown in Scheme 5. The enantiomeric excess of **15** was determined to be 95% ee using a GC chiral column and by comparison of the optical rotation of synthetic **16** with a reported value for the (+)-enantiomer.[8]



Scheme 5. (a) Lipase from *Pseudomonas cepacia* (Amano PS), vinyl propanoate MeCN (90%, 95% ee); (b) (1) MsCl, pyridine, CH_2Cl_2 (99%); (2) NaI, acetone (94%); (c) $LiAlH_4$, THF (69%).

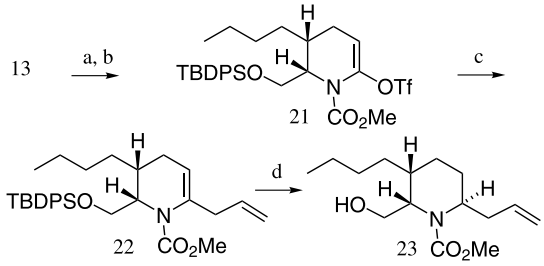
The mono-propanoate **15** was converted to the olefin **17**, which was subjected to $(DHQD)_2PYR$ ligand-induced Sharpless asymmetric dihydroxylation reaction[9] to give the diol **18** as shown in Scheme 6.



Scheme 6. (a) (1) DHP, PPTS, CH_2Cl_2; (2) K_2CO_3, MeOH; (3) Swern ox.; (4) $CH_3P^+Ph_3I^-$, *n*-BuLi, THF (80% in 4 steps) (b) $(DHQD)_2PYR$, K_2OsO_4, $K_3Fe(CN)_6$, K_2CO_3, H_2O–*t*-BuOH, 0 °C (84%); (c) (1) TBDPSCl, Et_3N, DMAP, CH_2Cl_2 (99%); (2) MsCl, Et_3N, CH_2Cl_2, 0 °C; (3) NaN_3, DMF 80 °C (73% in 2 steps); (d) (1) PPTS, EtOH, 60 °C; (2) Swern ox.; (3) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF (88% in 3 steps, 9:1 mixture of diastereomers); (e) 10% Pd–C, H_2, EtOAc, 4 atm (56%) isolated yield); only major diastereomers of **18**, **19**, and **20** are shown here.

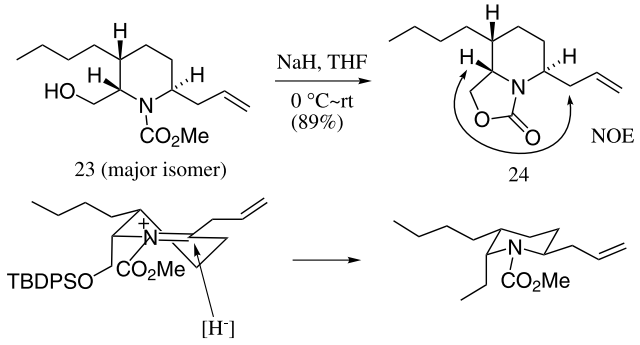
Protection of the primary hydroxyl group in **18** followed by substitution of the secondary hydroxyl group with NaN_3 via its mesylate provided azide **19**, which was transformed into the unsaturated ester **20**. Hydrogenation of **20** gave rise to 5,6-*cis*- and *trans*-piperidones. The desired 5,6-*cis*-piperidone **13** was isolated in 56% yield.

After conversion of **13** to the corresponding methyl urethane, the urethane was treated with Comins' triflating reagent[10] to yield the enoltriflate **21** as shown in Scheme 7.



Scheme 7. (a) *n*-BuLi, $ClCO_2Me$, THF, −78–0 °C (98%); (b) LiHMDS, 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine, THF, −78 to −40 °C (96%); (c) LiCl, allyltributyltin, $Pd(Ph_3P)_4$, THF, rt (92%); (d) TFA, $NaBH_3CN$, CH_2Cl_2, −45 °C (65% isolated yield, 2,6-*trans*/*cis* = 11:1).

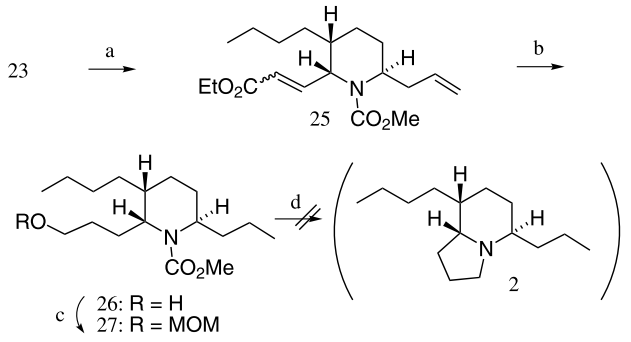
The triflate **21** was subjected to a Stille-type coupling reaction[11] using allyltributyltin to provide the olefin **22**. A stereoselective reduction of **22** with $NaBH_3CN$ under acidic conditions gave rise to the reduction product as an 11:1 mixture. The major isomer **23** was isolated in 65% yield. The stereochemistry of **23** was determined to be that of the desired 2,6-*trans* piperidine, based on the NOE spectrum of the corresponding oxazolizinone **24**. The stereochemical course of the attack of the hydride on the iminium salt generated from **22** under the acidic condition can be explained by $A^{(1,2)}$ strain and a stereoelectronic effect[6] as shown below (Scheme 8).



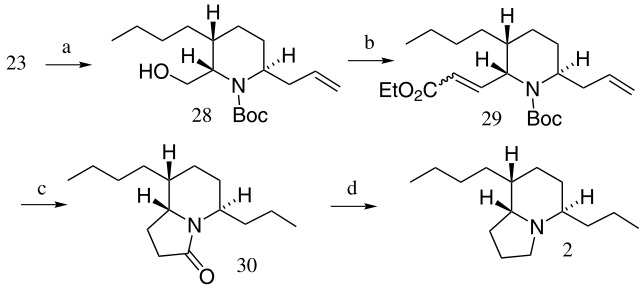
Scheme 8.

The carbon-chain on the 2-position of **23** was elongated by Swern oxidation followed by Horner–Emmons reaction to give **25**. Hydrogenation of **25** over Pd–C and reduction of the resulting ester with Super-Hydride afforded the alcohol **26** whose hydroxyl group was protected with methoxymethyl chloride in the presence of Hünig base to give **27**. Finally, the ether **27** was subjected to a 3-step indolizidine ring closure reaction, but no indolizidine formation was observed (Scheme 9).

A conversion of **23** to the desired indolizidine **2** was then attempted via the bicyclic lactam **30** as shown in Scheme 10. The methyl urethane **23** was converted to Boc-urethane **28** in two-step sequence and the carbon-chain on the 2-possition of **28** was elongated same as **25** in Scheme 9 to give rise to **29**. Hydrogenation of **29**, hydrolysis of the resulting ester, followed by removal of the Boc group with



Scheme 9. (a) (1) Swern ox.; (2) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF (*E*/*Z*= 4:1, 87% in 2 steps); (b) (1) 10% Pd–C, H_2, EtOAc; (2) Super-Hydride, THF, 0 °C (96% in 2 steps); (c) MOMCl, Hünig base, CH_2Cl_2, rt (94%); (d) (1) *n*-PrSLi, HMPA–THF, 0 °C–rt; (2) conc. HCl, MeOH, reflux; (3) CBr_4, Ph_3P, then Et_3N, CH_2Cl_2, 0 °C.



Scheme 10. (a) (1) 2 M KOH/*i*PrOH, 120 °C sealed tube; (2) Boc_2O, NaOH, dioxane–H_2O (70% in 2 steps); (b) (1) Swern ox.; (2) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF (*E*/*Z*=4: 1, 95% in 2 steps) (c) (1) 10% Pd–C, H_2, EtOAc, 1 atm; (2) LiOH, H_2O–EtOH, 60 °C; (3) TFA, CH_2Cl_2, rt; (4) DEPC, Et_3N, DMF, rt (91% in 4 steps); (d) $LiAlH_4$, THF, reflux (81%).

CF_3CO_2H and lactam formation using the Shioiri's reagent[12] gave rise to **30**. Reduction of the lactam moiety in **30** with $LiAlH_4$ furnished the desired indolizidine **2**.

3. Conclusion

The synthesis and properties of indolizidine **3** have been reported.[3] It proved on GC–MS {223 (M^+, 1), 222 (1), 180 (100), 166 (1), 138 (1), 136 (1), 126 (1), 124 (2), 110 (2), 108 (1), 96 (12), 70 (9), 55 (4)} and GC-FTIR (2968, 2938, 2880, 2787, 1459, 1377, 1133 cm^{-1}) analysis to be identical to natural indolizidine **223V**.

Synthesis of the 5, 9*E*-indolizidines **1** and **2** provided clear proof that alkaloid **223I** was not a 5, 9*E*-indolizidine. Both **1** and **2** had an appreciable *retro*-Diels–Alder fragment at *m*/*z* 96, while **223I** did not. The structure of natural **223I** should be revised, but further studies are required for the determination of the structure of natural product and results will be reported in due course.

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 an 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 ppm, (δ) downfield from TMS and are referenced to the centre line of $CDCl_3$ (77.0 ppm) as an internal standard. Carbon signals were assigned by a DEPT pulse sequence, q=methyl, t=methylene, d=methine, 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 with Merck silica gel 60 (No 7734-5B) or (No 9385). GC–MS was performed with a Finnigan GCQ instrument fitted with a Restek Amine5x column (30 m×0.25 mm) and a program 100 °C (1 min hold time) to 280 °C at 10 °C. GC-FTIR spectra were obtained with a narrow band HP model 5981 GC-FTIR infrared spectrophotometer interfaced with both an HP MSD, model 5971 and an HP 5890 gas chromatograph using the same temperature program as above and fitted with the same column except 0.32 mm i.d.

4.1.1. (5*S*,6*S*,9*S*)-(+)-6-Butyl-3-oxohexahydrooxazolo[3,4-*a*]pyridine-5-carboxylic acid methyl ester (5). To a stirred solution of the enaminoester **4**[4] (950 mg, 4.82 mmol) in Et_2O (150 mL) was added a solution of the dibutyllithium cuprate, prepared from *n*-BuLi (1.6 M in hexane, 24 mL, 38.6 mmol) and CuI (3.44 g, 18.1 mmol) in Et_2O (60 mL) at −50 to −30 °C, and the resulting suspension was warmed to −10 °C for 1 h. The reaction was quenched with satd. NH_4Cl (aq). The aqueous mixture was diluted with CH_2Cl_2 (300 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 a colorless oil, which was chromatographed on silica gel (40 g, hexane/acetone=20:1–10:1) to give **5** (1.18 g, 96%) as a colorless oil.

IR (neat) 2935, 2863, 1745, 1255 cm^{-1}; ^1H NMR (500 MHz) δ 0.89 (3H, t-like, J=6.9 Hz, 1.30–1.39 (5H, m), 1.46–1.56 (3H, m), 1.63 (1H, m), 1.67 (1H, m), 2.20 (1H, br), 3.74 (3H, s), 3.90 (1H, t, J=8.5 Hz), 4.06 (1H, m), 4.35 (1H, s), 4.49 (1H, *t*, J=8.5 Hz); ^{13}C NMR (125 MHz) δ 13.89 (q), 22.38 (t), 23.62 (t), 24.04 (t), 29.50 (t), 30.22 (t), 34.08 (d), 51.66 (d), 52.29 (q), 55.90 (d), 69.00 (t), 157.62 (s), 171.19 (s); MS: 255 (M^+); HRMS: Calcd for $C_{13}H_{21}NO_4$ 255.1469; Found 255.1447; $[\alpha]_D^{26}$ +7.5° (*c* 0.92, $CHCl_3$).

4.1.2. (5*R*,6*S*,9*S*)-(−)-(6-Butyl-3-oxohexahydrooxazolo[3,4-*a*]pyridin-5-yl)acetic acid methyl ester (6). To a stirred solution of **5** (590 mg, 2.31 mmol) in MeOH (9 mL) and H_2O (3 mL) was added $LiOH\cdot H_2O$ (200 mg, 4.73 mmol), and the resulting solution was refluxed for

2 h. After cooling, the MeOH was evaporated and the residue was acidified with 10% HCl solution (aq). The aqueous mixture was extracted with EtOAc (10 mL×5). The organic extracts were combined, dried, and evaporated to give a colorless paste, which was used directly in the next step. To a stirred solution of the above paste in THF (6 mL) were added $ClCO_2Et$ (0.29 mL, 3.03 mmol) and Et_3N (0.42 mL, 3.03 mmol) at 0 °C, and the resulting suspension was stirred at 0 °C for 1 h. The reaction mixture was diluted with Et_2O (20 mL) and $Et_3N{\cdot}HCl$ was removed by filtration. 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 (10 mL) was added a solution of CH_2N_2 in Et_2O at 0 °C, and the reaction was stirred at room temperature for 20 h. The solvent was evaporated to give a pale yellow oil, which was dissolved in MeOH (10 mL). To the MeOH solution were added $PhCO_2Ag$ (53 mg, 0.23 mmol) and Et_3N (0.64 mL, 4.63 mmol), and the resulting suspension was stirred at room temperature for 18 h. The reaction mixture was diluted with EtOAc and the insoluble material was removed by filtration. The filtrate was evaporated to give a pale yellow oil, which was chromatographed on silica gel (20 g, hexane/acetone=30:1–10:1) to give **6** (500 mg, 80%) as a colorless oil.

IR (neat) 2932, 2864, 1746, 1417, 1256 cm^{-1}; ^1H NMR (500 MHz) δ 0.88 (3H, t, J=7 Hz), 1.25–1.38 (5H, br m), 1.46–1.51 (2H, m), 1.53–1.66 (3H, m), 1.69–1.76 (1H, m), 2.57 (1H, dd, J=14.5, 7.7 Hz), 2.65 (1H, dd, J=14.5, 8.1 Hz), 3.67 (3H, s), 3.76–3.82 (1H, m), 3.88 (1H, dd, J=8.1, 6.9 Hz), 4.19 (1H, t-like, J=6.1 Hz), 4.40 (1H, t-like, J=8.1 Hz); ^{13}C NMR (125 MHz) δ 13.91 (q), 22.28 (t), 22.52 (t), 24.91 (t), 29.56 (t), 30.85 (t), 35.29 (d), 36.11 (t), 50.39 (d), 51.84 (q), 68.43 (t), 157.19 (s), 170.95 (s); MS: 269 (M^+); HRMS: Calcd for $C_{14}H_{23}NO_4$ 269.1626; Found 269.1648; $[\alpha]_D^{26}$ −12.7° (*c* 1.07, $CHCl_3$).

4.1.3. (5*R*,6*S*,9*S*)-(−)-3-(6-Butyl-3-oxohexahydrooxazolo[3,4-*a*]pyridin-5-yl)propionic acid methyl ester (7). To a stirred solution of **6** (445 mg, 1.65 mmol) in MeOH (6 mL) and H_2O (2 mL) was added $LiOH{\cdot}H_2O$ (141 mg, 3.33 mmol), and the resulting solution was refluxed for 2 h. After cooling, the MeOH was evaporated and the residue was acidified with 10% HCl solution (aq). The aqueous mixture was extracted with EtOAc (10 mL×5). The organic extracts were combined, dried, and evaporated to give a colorless paste, which was used directly in the next step. To a stirred solution of the above oil in THF (6 mL) were added $ClCO_2Et$ (0.21 mL, 2.19 mmol) and Et_3N (0.30 mL, 2.19 mmol) at 0 °C, and the resulting suspension was stirred at 0 °C for 1 h. The reaction mixture was diluted with Et_2O (20 mL) and $Et_3N{\cdot}HCl$ was removed by filtration. 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 (8 mL) was added a solution of CH_2N_2 in Et_2O at 0 °C, and the reaction was stirred at room temperature for 25 h. The solvent was evaporated to give a pale yellow oil, which was dissolved in MeOH (8 mL). To the MeOH solution were added $PhCO_2$-Ag (48 mg, 0.21 mmol) and Et_3N (0.46 mL, 3.33 mmol), and the resulting suspension was stirred at room temperature for 20 h. The reaction mixture was diluted with EtOAc and the insoluble material was removed by filtration. The filtrate was evaporated to give a pale yellow oil, which was chromatographed on silica gel (20 g, hexane/acetone=15:1–12:1) to give **7** (405 mg, 86%) as a colorless oil.

IR (neat) 2932, 2864, 1743, 1253 cm^{-1}; ^1H NMR (500 MHz) δ 0.87 (3H, t, J=6.8 Hz), 1.22–1.34 (5H, m), 1.41–1.46 (1H, m), 1.48–1.63 (4H, br m), 1.70–1.80 (2H, m), 2.09–2.17 (1H, m), 2.33–2.43 (2H, m), 3.65 (3H, s), 3.69 (1H, dd, J=10.7, 4.5 Hz), 3.76–3.82 (1H, m), 3.89 (1H, dd, J=8.6, 5.6 Hz), 4.37 (1H, t-like, J=8.6 Hz); ^{13}C NMR (125 MHz) δ 13.94 (q), 22.42 (t), 22.55 (t), 25.27 (t), 26.39 (t), 29.73 (t), 30.90 (t), 31.07 (t), 36.13 (d), 50.06 (d), 51.62 (q), 53.67 (d), 68.36 (t), 157.79 (s), 173.73 (s); MS: 283 (M^+); HRMS: Calcd for $C_{15}H_{25}NO_4$ 283.1782; Found 283.1759; $[\alpha]_D^{26}$ −32.4° (*c* 0.87, $CHCl_3$).

4.1.4. (5*R*,6*S*,9*S*)-(−)-6-Butyl-5-(3-hydroxypropyl)hexahydrooxazolo[3,4-*a*]pyridin-3-one (8). To a stirred solution of **7** (558 mg, 1.97 mmol) in THF (12 mL) was added a solution of Super-Hydride (1 M in THF, 4.4 mL, 4.4 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 2 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 a colorless oil, which was chromatographed on silica gel (25 g, hexane/acetone=10:1–2:1) to give **8** (444 mg, 88%) as a colorless oil.

IR (neat) 3427, 2931, 2864, 1733, 1063 cm^{-1}; ^1H NMR (500 MHz) δ 0.82 (3H, t-like, J=6.4 Hz), 1.17–1.27 (6H, br m), 1.35–1.54 (7H, br m), 1.68–1.79 (2H, m), 2.90 (1H, br), 3.58 (2H, br), 3.64 (1H, m), 3.74 (1H, m), 3.83 (1H, m), 4.36 (1H, m); ^{13}C NMR (125 MHz) δ 13.87 (q), 22.12 (t), 22.49 (t), 25.31 (t), 27.37 (t), 29.04 (t), 29.65 (t), 30.86 (t), 35.61 (d), 50.09 (d), 53.51 (d), 61.89 (t), 68.44 (t), 157.88 (s); MS: 255 (M^+); HRMS: Calcd for $C_{14}H_{25}NO_3$ 255.1833; Found 255.1855; $[\alpha]_D^{26}$ −17.2° (*c* 1.05, $CHCl_3$).

4.1.5. (5*R*,6*S*,9*S*)-(−)-6-Butyl-5-(3-methoxymethoxypropyl)hexahydrooxazolo[3,4-*a*]pyridin-3-one (9). To a stirred solution of **8** (444 mg, 1.74 mmol) in CH_2Cl_2 (5 mL) were added MOMCl (0.29 mL, 3.83 mmol) and Hünig base (0.87 mL, 5 mmol), and the reaction mixture was stirred at room temperature for 48 h. The volatiles were evaporated and the residue was chromatographed on silica gel (25 g, hexane/acetone=10:1–7:1) to give **9** (438 mg, 87%) as a colorless oil.

IR (neat) 2931, 2868, 1746, 1040 cm^{-1}; ^1H NMR (500 MHz) δ 0.80 (3H, t-like, J=6.8 Hz), 1.17–1.25 (6H, br m), 1.35–1.58 (7H, br m), 1.67–1.74 (2H, m), 3.26 (3H, s), 3.46 (2H, br), 3.62 (1H, br), 3.70 (1H, br), 3.79–3.80 (1H, m), 4.30–4.33 (1H, m), 4.52 (2H, s); ^{13}C NMR (125 MHz) δ 13.83 (q), 22.30 (t), 22.45 (t), 25.30 (t), 26.44 (t), 27.69 (t), 29.66 (t), 30.82 (t), 35.58 (d), 50.03 (d), 53.36 (d), 54.89 (q), 67.00 (t), 68.21 (t), 96.14 (t), 157.53 (s); MS: 299 (M^+); HRMS: Calcd for $C_{16}H_{29}NO_4$ 299.2095; Found 299.2098; $[\alpha]_D^{26}$ −18.4° (*c* 7.56, $CHCl_3$).

4.1.6. (2*R*,3*S*,6*S*)-(−)-3-Butyl-6-hydroxymethyl-2-(3-methoxymethoxypropyl)piperidine-1-carboxylic acid benzyl ester (10). A solution of 2 M KOH in *i*-PrOH

(25 mL) was added to **9** (432 mg, 1.44 mmol), and the resulting mixture was heated at 120 °C in a sealed tube for 48 h. After cooling, the solvent was evaporated, and the residue was dissolved in H_2O. 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 a pale yellow oil, which was used directly in the next step. To a stirred solution of the above oil in H_2O (6 mL) and $CHCl_3$ (15 mL) were added CbzCl (0.42 mL, 2.89 mmol) and K_2CO_3 (800 mg, 5.78 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 3 h. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (10 mL×5). The organic layer and extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (30 g, hexane/acetone=18:1–13:1) to give **10** (483 mg, 82%) as a colorless oil.

IR (neat) 3456, 2931, 1680, 1112, 1040 cm^{-1}; ^1H NMR (500 MHz) δ 0.82 (3H, t-like, J=6.9 Hz), 1.20 (5H, br), 1.34–1.38 (3H, m), 1.45–1.57 (4H, br m), 1.74–1.90 (3H, br m), 3.28 (1H, br), 3.33 (3H, s), 3.46–3.51 (2H, m), 3.81 (3.89 (2H, m), 4.19–4.23 (1H, m), 4.52 (1H, br), 4.57 (2H, s), 5.05 (2H, ABq, J=12 Hz), 7.29–7.38 (5H, m); ^{13}C NMR (125 MHz) δ 14.09 (q), 22.80 (t), 23.72 (t), 24.29 (t), 26.47 (t), 27.54 (t), 29.95 (t), 31.67 (t), 37.10 (d), 55.08 (q), 55.74 (d), 57.36 (d), 64.27 (t), 67.08 (t), 67.24 (t), 96.29 (t), 127.85 (d), 127.89 (d), 128.31 (d), 136.28 (s), 156.17 (s); MS: 407 (M^+); HRMS: Calcd for $C_{23}H_{37}NO_5$ 407.2670; Found 407.2659; $[\alpha]_D^{26}$ −24.7° (*c* 1.22, $CHCl_3$).

4.1.7. (2*R*,3*S*,6*S*)-(−)-3-Butyl-6-methoxycarbonylmethyl-2-(3-methoxymethoxypropyl)-piperidine-1-carboxylic acid benzyl ester (11). To a stirred solution of $(COCl)_2$ (0.16 mL, 1.78 mmol) in CH_2Cl_2 (3 mL) was added DMSO (0.26 mL, 3.56 mmol) at −78 °C, and the resulting solution was stirred for 10 min. To the mixture was added a solution of **10** (483 mg, 1.19 mmol) in CH_2Cl_2 (1 mL×2) at −78 °C, and the reaction mixture was stirred for 30 min. Triethylamine (0.74 mL, 5.34 mmol) was added 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×3). 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 $NaH_2PO_4 \cdot 2H_2O$ (1.85 g, 11.86 mmol), 2-methyl-2-butene (2.5 mL, 23.6 mmol), and the above oil in *t*-BuOH (10 mL) was added a solution of $NaClO_2$ (80%, 810 mg, 7.16 mmol) in H_2O (5 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 (aq) at 0 °C, and the aqueous mixture was extracted with EtOAc (10 mL×10). 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 solution of the above oil in THF (3 mL) were added $ClCO_2Et$ (0.15 mL, 1.54 mmol) and Et_3N (0.21 mL, 1.54 mmol) at 0 °C, and the resulting suspension was stirred at 0 °C for 1 h. The reaction mixture was diluted with Et_2O (10 mL) and $Et_3N \cdot HCl$ was removed by filtration. The filtrate 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 Et_2O (5 mL) was added a solution of CH_2N_2 in Et_2O at 0 °C, and the reaction solution was stirred at room temperature for 20 h. The solvent was evaporated to give a pale yellow oil, which was dissolved in MeOH (6 mL). To the MeOH solution were added $PhCO_2Ag$ (54 mg, 0.24 mmol) and Et_3N (0.33 mL, 2.34 mmol), and the resulting suspension was stirred at room temperature for 16 h. The reaction mixture was diluted with EtOAc and the insoluble material was removed by filtration. The filtrate was evaporated to give a pale yellow oil, which was chromatographed on silica gel (20 g, hexane/acetone=35:1–30:1) to give **11** (278 mg, 54%) as a colorless oil.

IR (neat) 2931, 1740, 1039 cm^{-1}; ^1H NMR (500 MHz) δ 0.83–0.86 (3H, m), 1.22–1.95 (16H, br m), 2.58–2.62 (1H, m), 3.35 (3H, s), 3.49–3.59 (2H, m), 3.64 (3H, s), 3.78 (1H, br), 4.00 (1H, br), 4.60 (2H, s), 5.07 (2H, s), 7.28–7.36 (5H, m); ^{13}C NMR (125 MHz) δ 13.98 (q), 22.64 (t), 22.72 (t), 24.40 (t), 26.37 (t), 26.94 (t), 28.12 (t), 29.71 (t), 32.58 (t), 37.50 (d), 38.68 (t), 49.02 (d), 51.40 (q), 54.99 (q), 66.56 (t), 67.33 (t), 67.37 (t), 96.22 (t), 127.78 (d), 127.83 (d), 127.92 (d), 128.30 (d), 136.73 (s), 156.40 (s), 172.21 (s); MS: 449 (M^+); HRMS: Calcd for $C_{25}H_{39}NO_6$ 449.2775; Found 449.2759; $[\alpha]_D^{26}$ −15.5° (*c* 4.27, $CHCl_3$).

4.1.8. (2*R*,3*S*,6*S*)-(+)-6-Allyl-3-butyl-2-(3-methoxymethoxypropyl)piperidine-1-carboxylic acid benzyl ester (12). To a stirred solution of **11** (83 mg, 0.18 mmol) in CH_2Cl_2 (1 mL) was added a solution of DIBAL (0.93 M in hexane, 0.2 mL, 0.18 mmol) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. The reaction was quenched with MeOH (0.3 mL) and with satd. potassium sodium tartrate solution (aq). The aqueous mixture was extracted with CH_2Cl_2 (5 mL×3). The organic extracts were combined, dried, and evaporated to give a colorless oil, which was used directly in the next step. To a stirred suspension of $CH_3P^+Ph_3I^-$ (374 mg, 0.92 mmol) in THF (2 mL) was added a solution of *n*-BuLi (1.6 M in hexane, 0.52 mL, 0.83 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. To the mixture was added a solution of the above aldehyde in THF (2 mL) at 0 °C, and the orange suspension was stirred at room temperature for 22 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (10 mL×3). The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (15 g, hexane/acetone=80:1–30:1) to give **12** (44 mg, 57%) as a colorless oil.

IR (neat) 3070, 2930, 2869, 1699, 1110, 1042 cm^{-1}; ^1H NMR (500 MHz) δ 0.87 (3H, t-like, J=6.8 Hz), 1.18–1.82 (15H, br m), 2.39 (1H, br), 2.78 (1H, br), 3.36 (3H, s), 3.44–3.55 (3H, br m), 3.73 (1H, br), 4.60 (2H, s), 5.00–5.15 (4H, m), 5.73–5.81 (1H, m), 7.28–7.39 (5H, m); ^{13}C NMR (125 MHz) δ 14.03 (q), 22.80 (t), 24.44 (t), 26.74 (t), 28.49 (t), 29.62 (t), 33.04 (t), 37.51 (t), 37.94 (d), 53.16 (d), 55.04 (q), 58.40 (d), 66.56 (t), 67.48 (t), 96.27 (t), 116.40 (t), 127.79 (d), 127.86 (d), 128.36 (d), 136.24 (d), 136.92 (s), 156.80 (s); MS: 417 (M^+); HRMS: Calcd for $C_{25}H_{39}NO_4$ 417.2877; Found 417.2883; $[\alpha]_D^{26}$ +2.9° (*c* 2.24, $CHCl_3$).

4.1.9. (5*R*,8*S*,9*R*)-(+)-8-Butyl-5-propyloctahydroindolizine (1). To a solution of **12** (135 mg, 0.32 mmol) in EtOAc (15 mL) was added 10% Pd–C (100 mg), and the

resulting suspension was hydrogenated under a hydrogen atmosphere at 4 atm for 40 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 oil above in MeOH (6 mL) was added conc. HCl (aq) (4 drops), and the reaction mixture was refluxed for 1 h. After cooling, the solvent was evaporated and the residue was washed with Et_2O. To the hydrochloride salt was added NH_3 (aq), and the aqueous mixture was extracted with $CHCl_3$ (5 mL×10). The organic extracts were combined, dried over K_2CO_3, and evaporated to give a colorless oil, which was used directly in the next step. Carbon tetrachloride (150 mg, 0.45 mmol) and Ph_3P (127 mg, 0.49 mmol) were added to a solution of the above oil in CH_2Cl_2 (4 mL) at 0 °C, and the reaction mixture was stirred at 0 °C for 2 h. To the reaction mixture was added Et_3N (0.72 mL, 5.18 mmol) at 0 °C, and the resulting suspension was stirred for 30 min. The volatiles were evaporated, and the residue was extracted with *n*-pentane (10 mL×4). The organic extracts were combined and evaporated to give a pale orange solid, which was chromatographed on silica gel (10 g, hexane/acetone/Et_3N=50:1:5 drops-20:1:5 drops) to give **1** (48 mg, 67%) as a pale yellow oil.

IR (neat) 2928, 2865, 2803, 1657, 1460, 1376, 1259, 1219, 1170, 1142, 1101, 905, 754 cm^{-1}; ^1H NMR (500 MHz) δ 0.89 (3H, t, J=6.8 Hz), 0.92 (3H, t, J=6.8 Hz), 1.01–1.67 (14H, br m), 1.56–1.70 (3H, m), 1.72–1.82 (1H, m), 1.87–1.94 (1H, m), 2.07–2.11 (1H, m), 2.63 (1H, q, J=8.5 Hz), 2.80 (1H, td, J=8.6, 2.9 Hz), 2.95–2.99 (1H, m); ^{13}C NMR (125 MHz) δ 14.06 (q), 14.40 (q), 20.65 (t), 20.94 (t), 23.00 (t), 24.28 (t), 24.83 (t), 27.88 (t), 28.88 (t), 29.68 (t), 33.06 (t), 42.45 (d), 48.92 (t), 54.94 (d), 60.29 (d); MS: 223 (M^+); HRMS: Calcd for $C_{15}H_{29}N$ 223.2299; Found 223.2290; $[\alpha]_D^{26}$ +31.0° (*c* 2.14, $CHCl_3$).

4.1.10. (*R*)-(+)-Propionic acid 2-hydroxymethylhexyl ester (15). To a stirred solution of **14** (3 g, 22 mmol) in MeCN (300 mL) were added vinyl propanoate (4.55 g, 45 mmol) and lipase PCL (Amano PS) (1.5 g), and the resulting suspension was stirred at room temperature for 20 h. The lipase catalyst was removed by filtration, and the volatiles were evaporated to give a colorless oil, which was chromatographed on silica gel (60 g, hexane/EtOAc=3:1) to give **15** (3.72 g, 90%) as a colorless oil. The enantiomeric excess was determined to be 95% ee by the GC analysis using a cyclodextrin-β-236M-19 chiral column.

IR (neat) 3449, 2931, 2868, 1736, 1193 cm^{-1}; ^1H NMR (500 MHz) δ 0.88 (3H, t, J=6.6 Hz), 1.13 (3H, t, J=7.6 Hz), 1.26–1.34 (6H, br), 1.76–1.81 (1H, m), 2.21–2.27 (1H, m), 2.33 (2H, q, J=7.6 Hz), 3.44–3.61 (2H, m), 4.07 (1H, dd, J=11, 6.6 Hz), 4.19 (1H, dd, J=11, 4.7 Hz); ^{13}C NMR (125 MHz) δ 9.24 (q), 14.00 (q), 22.90 (t), 27.56 (t), 27.64 (t), 29.17 (t), 40.52 (d), 62.71 (t), 64.51 (t), 174.87 (s); MS: 188 (M^+); HRMS: Calcd for $C_{10}H_{20}O_3$ 188.1411; Found 188.1432; $[\alpha]_D^{26}$ +10.6° (*c* 1.96, $CHCl_3$).

4.1.11. (*S*)-(+)-Propionic acid 2-iodomethylhexyl ester. To a stirred solution of **15** (188 mg, 1 mmol) in CH_2Cl_2 (5 mL) were added MsCl (0.12 mL, 1.5 mmol) and pyridine (0.15 mL, 1.8 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated and the residue was chromatographed on Silica gel (10 g, hexane/acetone=12:1–8:1) to give the mesylate (265 mg, 99%) as a colorless oil.

IR (neat) 2938, 2867, 1738, 1355, 1178 cm^{-1}; ^1H NMR (500 MHz) δ 0.89 (3H, t, J=7.2 Hz), 1.13 (3H, t, J=7.7 Hz), 1.30–1.40 (6H, br m), 2.04–2.09 (1H, m), 2.34 (2H, q, J=7.7 Hz), 3.01 (3H, s), 4.03 (1H, dd, J=11.1, 6.8 Hz), 4.13 (1H, dd, J=11.1, 4.7 Hz), 4.16–4.23 (2H, m); ^{13}C NMR (125 MHz) δ 8.97 (q), 13.77 (q), 22.54 (t), 27.15 (t), 27.35 (t), 28.63 (t), 37.09 (q), 37.61 (d), 63.00 (t), 69.16 (t), 174.19 (s); MS: 266 (M^+); HRMS: Calcd for $C_{11}H_{22}O_5S$ 266.1187; Found 266.1199; $[\alpha]_D^{26}$ +3.9° (*c* 4.74, $CHCl_3$).

To a stirred solution of the mesylate obtained above (265 mg, 1 mmol) in acetone (10 mL) was added NaI (1.5 g, 9.96 mmol), and the resulting solution was stirred at room temperature for 14 h and at reflux for 2 h. After cooling, the reaction mixture was diluted with Et_2O. The ethereal layer was washed with 10% $Na_2S_2O_3$ in satd. $NaHCO_3$ (aq), dried and evaporated to give a colorless oil, which was chromatographed on silica gel (10 g, hexane/acetone=100:1–80:1) to give the iodide (280 mg, 94%) as a colorless oil.

IR (neat) 2956, 2931, 2863, 1740 cm^{-1}; ^1H NMR (500 MHz) δ 0.88 (3H, t, J=7.2 Hz), 1.12 (3H, t, J=7.4 Hz), 1.26–1.35 (6H, br), 1.52–1.58 (1H, m), 2.30 (2H, q, J=7.4 Hz), 3.23 (1H, dd, J=9.9, 5.2 Hz), 3.29 (1H, dd, J=9.9, 6.6 Hz), 3.89 (1H, dd, J=11, 7.1 Hz), 4.08 (1H, dd, J=11, 4.6 Hz); ^{13}C NMR (125 MHz) δ 9.18 (q), 11.10 (t), 13.95 (q), 22.62 (t), 27.52 (t), 28.61 (t), 30.97 (t), 38.49 (d), 66.44 (t), 173.90 (s); MS: 298 (M^+); HRMS: Calcd for $C_{10}H_{19}IO_2$ 298.0430; Found 298.0442; $[\alpha]_D^{26}$ +5.3° (*c* 2.00, $CHCl_3$).

4.1.12. (*S*)-(+)-2-Methylhexan-1-ol (16). To a stirred solution of the iodide (280 mg, 0.94 mmol) in Et_2O (20 mL) was added $LiAlH_4$ (380 mg, 10 mmol), and the resulting suspension was refluxed for 16 h. After cooling, the reaction was quenched with 10% NaOH (aq), and the aqueous mixture was extracted with Et_2O (10 mL×4). The organic extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on silica gel (10 g, hexane/acetone=15:1–10:1) to give **16** (75 mg, 69%) as a colorless oil.

IR (neat) 3445, 2935, 2862 cm^{-1}; ^1H NMR (500 MHz) δ 0.89–0.92 (6H, m), 1.06–1.13 (1H, m), 1.20–1.43 (5H, m), 1.57–1.64 (1H, m), 1.91 (1H, br), 3.39–3.42 (1H, m), 3.48–3.81 (1H, m); ^{13}C NMR (125 MHz) δ 14.04 (q), 16.52 (q), 22.93 (t), 29.15 (t), 32.79 (t), 35.66 (d), 68.28 (t); $[\alpha]_D^{26}$ −10.5° (*c* 2.01, $CHCl_3$), lit.[8] $[\alpha]_D^{26}$ +11° (*c* 2.5, $CHCl_3$).

4.1.13. (*S*)-(+)-2-(2-Butylbut-3-enyloxy)tetrahydropyran (17). To a stirred solution of **15** (1.814 g, 9.65 mmol) in CH_2Cl_2 (20 mL) were added DHP (1.32 mL, 14.5 mmol) and PPTS (485 mg, 1.93 mmol), and the reaction mixture was stirred at room temperature for 6 h. The reaction was quenched with satd. $NaHCO_3$ (aq), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (20 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 MeOH (12 mL) was added K_2CO_3 (803 mg, 5.82 mmol), and the resulting suspension was stirred at room temperature for 19 h. The reaction mixture was diluted with H_2O, and the aqueous mixture was extracts with CH_2Cl_2 (15 mL×6). 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 $(COCl)_2$ (1.25 mL, 14.33 mmol) in CH_2Cl_2 (15 mL) was added DMSO (2.05 mL, 28.89 mmol) at −78 °C, and the reaction mixture was stirred for 5 min. To the reaction mixture was added a solution of the alcohol obtained above in CH_2Cl_2 (3 mL×2) at −78 °C, and the reaction mixture was stirred for 30 min. Triethylamine (6 mL, 43.37 mmol) was added to the reaction mixture at −78 °C, and the reaction was warmed to 0 °C for 1 h. The reaction mixture was diluted with H_2O and Et_2O, and the organic layer was separated. The aqueous layer was extracted with Et_2O (20 mL×2). 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 suspension of $CH_3P^+Ph_3I^-$ (15.7 g, 38.8 mmol) in THF (35 mL) was added a solution of *n*-BuLi (1.6 M in hexane, 22.9 mL, 36.6 mmol) at 0 °C, and the resulting orange suspension was stirred at 0 °C for 30 min. To the suspension was added a solution of the aldehyde obtained above in THF (10 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 22 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (20 mL×3). The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (30 g, hexane/acetone=100:1–80:1) to give **17** (1.63 g, 80%) as a colorless oil.

IR (neat) 3075, 2934, 2866, 1642, 1127, 1071, 1032 cm^{-1}; ^1H NMR (500 MHz) δ 0.88 (3H, t, J=7.3 Hz), 1.20–1.33 (5H, m), 1.44–1.61 (5H, m), 1.66–1.72 (1H, m), 1.78–1.85 (1H, m), 2.26–2.33 (1H, m), 3.28–3.32 (1H, m), 3.47–3.52 (1H, m), 3.65 (1H, dd, J=9.4, 6.8 Hz), 3.83–3.88 (1H, m), 4.56–4.59 (1H, m), 5.02–5.07 (2H, m), 5.62–5.70 (1H, m); ^{13}C NMR (125 MHz) δ 13.98 (q), 19.37 (t), 19.43 (t), 22.71 (t), 25.44 (t), 29.12 (t), 29.14 (t), 30.55 (t), 30.90 (t), 43.83 (d), 44.04 (d), 61.96 (t), 62.03 (t), 70.86 (t), 70.95 (t), 98.57 (d), 98.77 (d), 115.20 (t), 115.27 (t), 140.29 (d), 140.44 (d); MS: 212 (M^+); HRMS: Calcd for $C_{13}H_{24}O_2$ 212.1775; Found 212.1784; $[\alpha]_D^{26}$ +8.8° (*c* 16.20, $CHCl_3$).

4.1.14. 3-(Tetrahydropyran-2-yloxymethyl)heptane-1,2-diol (18). To a stirred solution of **17** (1.63 g, 7.69 mmol) in *t*-BuOH (30 mL) and H_2O (30 mL) was added AD-mix with $(DHQD)_2PYR$ (14 g) at 0 °C, and the resulting suspension was stirred at 0 °C for 17 h. The reaction was quenched with Na_2SO_3 (10 g), and the reaction mixture was extracted with EtOAc (30 mL×5). The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (40 g, hexane/acetone=10:1–4:1) to give **18** (1.58 g, 84%) a colorless oil consisting of a diastereomeric mixture.

^1H NMR (500 MHz) δ 0.91 (3H, t-like, J=6.8 Hz), 1.27–1.49 (5H, m), 1.55–1.63 (4H, m), 1.72–1.86 (4H, m), 2.56–2.63 (1H, m), 3.40–3.98 (8H, br m), 4.58–4.62 (1H, m).

4.1.15. 2-Azido-1-(*tert*-butyldiphenylsilanyloxy)-3-(tetrahydropyran-2-yloxymethyl)heptane (19). To a stirred solution of **18** (700 mg, 2.85 mmol) in CH_2Cl_2 (5 mL) were added Et_3N (0.51 mL, 3.7 mmol), DMAP (69 mg, 0.57 mmol), and TBDPSCl (0.82 mL, 3.13 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 45 h. The volatiles were evaporated and the residue was chromatographed on silica gel (30 g, hexane/acetone=50:1–30:1) to give the silyl ether (1.37 g, 99%) as a colorless oil consisting of a diastereomeric mixture.

^1H NMR (500 MHz) δ 0.91 (3H, t-like, J=6 Hz), 1.09 (9H, s), 1.22–1.83 (14H, br m), 3.01–3.04 (1H, m), 3.38–3.56 (2H, m), 3.70–3.94 (4H, m), 4.51–4.53 (1H, m), 7.38–7.47 (6H, m), 7.70–7.76 (4H, m).

To a stirred solution of the silyl ether obtained above (1.37 g, 2.83 mmol) in CH_2Cl_2 (5 mL) were added MsCl (0.24 mL, 3.11 mmol) and Et_3N (0.59 mL, 4.25 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 1 h. 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×2). The organic layer and extracts were combined, dried, and evaporated to give the mesylate, which was used directly in the next step. To a stirred solution of the mesylate obtained above in DMF (5 mL) was added NaN_3 (1.84 g, 28.31 mmol), and the resulting suspension was heated at 80 °C for 15 h. After cooling, the insoluble material was removed by filtration, and the solvent was evaporated to give a pale yellow oil, which was chromatographed on silica gel (25 g, hexane/acetone=50:1–40:1) to give **19** (1.05 g, 73%) as a colorless oil containing a diastereomeric mixture.

^1H NMR (500 MHz) δ 0.87–0.91 (3H, m), 1.10 (9H, s), 1.10–1.75 (13H, br m), 3.22–3.29 (1H, m), 3.46–3.56 (1H, m), 3.64–3.84 (5H, m), 4.48–4.52 (1H, m), 7.40–7.48 (6H, m), 7.71–7.74 (4H, m).

4.1.16. 5-Azido-6-(*tert*-butyldiphenylsilanyloxy)-4-butyl-2-hexenoic acid ethyl ester (20). To a stirred solution of **19** (1.05 g, 2.06 mmol) in EtOH (5 mL) was added PPTS (104 mg, 0.41 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 (10 mL×5). 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 $(COCl)_2$ (0.27 mL, 3.09 mmol) in CH_2Cl_2 (6 mL) was added DMSO (0.44 mL, 6.19 mmol) at −78 °C, and the reaction mixture was stirred for 5 min. To the reaction mixture was added a solution of the oil obtained above in CH_2Cl_2 (2 mL) at −78 °C, and the resulting mixture was stirred at −78 °C for 30 min. Triethylamine (1.3 mL) was added to the reaction mixture, and the reaction was warmed to 0 °C for 1 h. The reaction mixture was then diluted with H_2O and Et_2O, and the organic layer was separated. The aqueous layer was extracted with Et_2O (20 mL×2). 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 suspension of NaH (60%, 99 mg, 2.48 mmol) in THF (5 mL) was added (EtO) $_2$P(O)CH_2CO_2Et (0.5 mL, 2.48 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. To the mixture was added a solution of the aldehyde obtained above in THF (4 mL) at 0 °C, and then 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×4). The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (25 g, hexane/acetone=100:1–50:1) to give **20** (890 mg, 88%) as a colorless oil as a 9:1 mixture of diastereomers.

^{1}H NMR (500 MHz) δ 0.89 (3H, t-like, J=7.2 Hz), 1.10 (9H, s), 1.11–1.38 9H, m, including at δ 1.32, 3H, t, J=7.3 Hz), 2.36–2.42 (1H, m), 3.34–3.38 (1H, m), 3.50–3.67 (1H, m), 3.68–3.80 (1H, m), 4.20 (2H, q, J=7.3 Hz), 5.81 (1H, d, J=15.4 Hz), 6.63 (1H, dd, J=15.4, 9.4 Hz), 7.40–7.48 (6H, m), 7.68–7.72 (4H, m).

4.1.17. (5*R*,6*S*)-(+)-5-Butyl-6-(*tert*-butyldiphenylsilanyloxymethyl)piperidin-2-one (13). To a solution of **20** (1.77 g, 3.59 mmol) in EtOAc (60 mL) was added 10% Pd–C (400 mg), and the resulting suspension was hydrogenated with 4 atm of hydrogen for 48 h. The catalyst was removed by filtration, and the filtrate was evaporated to give a colorless oil, which was chromatographed on silica gel (30 g, hexane/acetone=12:1–7:1) to give **13** (852 mg, 56%) as a colorless oil.

IR (neat) 3206, 3070, 2931, 2860, 1666 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.84 (3H, t, J=7.3 Hz), 1.07 (9H, s), 1.08–1.27 (7H, m), 1.68 (2H, q-like, J=6.4 Hz), 2.33–2.39 (2H, m), 3.53–3.67 (3H, br m), 6.27 (1H, br), 7.39–7.48 (6H, m), 7.66–7.67 (4H, m); ^{13}C NMR (125 MHz) δ 13.82 (q), 19.00 (s), 22.54 (t), 23.50 (t), 26.69 (q), 28.05 (t), 29.11 (t), 29.56 (t), 33.97 (d), 56.76 (d), 64.34 (t), 127.74 (d), 127.75 (d), 129.80 (d), 129.83 (d), 132.68 (s), 132.73 (s), 135.40 (d), 135.42 (d), 171.88 (s); MS: 423 (M^+); HRMS: Calcd for $C_{26}H_{37}NO_2Si$ 423.2591; Found 423.2597; $[\alpha]_D^{26}$ +25.4° (*c* 1.04, $CHCl_3$).

4.1.18. (2*S*,3*R*)-(−)-3-Butyl-2-(*tert*-butyldiphenylsilanyloxymethyl)-6-trifluoromethane-sulfonyloxy-3,4-dihydro-2*H*-pyridine-1-carboxylic acid methyl ester (21). To a stirred solution of **13** (1.06 g, 2.50 mmol) in THF (7 mL) was added a solution of *n*-BuLi (1.6 M in hexane, 1.72 mL, 2.75 mmol) at −78 °C, and the reaction mixture stirred at −78 °C for 30 min. To the reaction mixture was added $ClCO_2Me$ (0.22 mL, 2.75 mmol), and the solution 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×3). The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (30 g, hexane/acetone=30:1–10:1) to give the methyl urethane (1.17 g, 98%) as a colorless oil.

IR (neat) 1743, 1641, 3017, 2954, 2932, 2860, 1773, 1719, 1284 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.89 (3H, t, J=6.9 Hz), 1.04 (9H, s), 1.25–1.37 (6H, m), 1.81–1.87 (1H, m), 1.95–1.98 (1H, m), 2.01–2.08 (1H, m), 2.54–2.61 (1H, m), 2.64–2.66 (1H, m), 3.76 (1H, dd, J=11.1, 2.9 Hz), 3.82 (3H, s), 3.86 (1H, dd, J=11.1, 3.9 Hz), 4.28 (1H, br), 7.39–7.48 (6H, m), 7.64–7.71 (4H, m); ^{13}C NMR (125 MHz) δ 13.84 (q), 18.85 (s), 22.61 (t), 24.79 (t), 26.61 (q), 29.33 (t), 32.33 (t), 34.31 (t), 37.16 (d), 53.66 (q), 59.42 (d), 61.50 (t), 127.64 (d), 127.67 (d), 129.73 (d), 132.16 (s), 132.73 (s), 135.53 (d), 135.64 (d), 154.99 (s), 172.03 (s); MS: 424 (M^+−57); HRMS: Calcd for $C_{24}H_{30}NO_4Si$ 424.1942; Found 424.1961; $[\alpha]_D^{26}$ −27.4° (*c* 3.02, $CHCl_3$).

To a stirred solution of the methyl urethane obtained above (633 mg, 1.32 mmol) in THF (2 mL) was added a solution of LiHMDS, prepared from hexamethyldisilazane (0.33 mL, 1.6 mmol) and *n*-BuLi (1.6 M in hexane, 1 mL, 1.6 mmol) in THF (2 mL) at 0 °C for 30 min, at −78 °C, and the reaction mixture was stirred at the same temperature for 30 min. To the resulting mixture was added a solution of 2-[*N*,*N*-bis(trifluoromethanesulfonyl)amino]-5-chloropyridine (Comins' reagent, 640 mg, 1.6 mmol) in THF (2 mL) at −78 °C, and the reaction temperature was warmed to −40 °C for 30 min. The reaction was quenched with satd. NH_4Cl (aq), and the organic layer was separated. The aqueous layer was extracted with Et_2O (10 mL×3), and the organic layer and extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (30 g, hexane/acetone=50:1–40:1) to give **21** (772 mg, 96%) as a colorless oil.

IR (neat) 3069, 2956, 2932, 2860, 1733, 1424, 1328, 1272, 1215, 1114 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.91 (3H, t, J=6.9 Hz), 1.13 (9H, s), 1.15–1.36 (6H, br m), 1.68–1.75 (1H, m), 1.89 (1H, br), 2.31–2.37 (1H, m), 3.68 (1H, d-like, J=8.9 Hz), 3.85 (1H, t-like, J=6.8 Hz), 3.90 (3H, s), 4.70 (1H, br), 5.29 (1H, t, J=3.4 Hz), 7.45–7.51 (6H, m), 7.74–7.84 (4H, m); ^{13}C NMR (125 MHz) δ 13.67 (q), 18.89 (s), 22.42 (t), 26.41 (q), 26.59 (t), 29.22 (t), 31.97 (t), 35.64 (d), 53.27 (q), 58.26 (t), 59.87 (d), 105.64 (d), 117.01 (s), 119.55 (s), 127.56 (d), 127.59 (d), 129.56 (d), 129.67 (d), 133.14 (s), 133.17 (s), 135.45 (d), 135.59 (d), 138.13 (s), 153.89 (s); MS: 613 (M^+); HRMS: Calcd for $C_{29}H_{38}NO_6F_3SSi$ 613.2139; Found 613.2118; $[\alpha]_D^{26}$ −30.5° (*c* 8.45, $CHCl_3$).

4.1.19. (2*S*,3*R*)-(−)-6-Allyl-3-butyl-2-(*tert*-butyldiphenylsilanyloxymethyl)-3,4-dihydro-2*H*-pyridine-1-carboxylic acid methyl ester (22). To a stirred solution of **21** (1.18 g, 1.92 mmol) in THF (20 mL) were added allyltributyltin (1.2 mL, 3.8 mmol), $Pd(PPh_3)_4$ (222 mg, 0.19 mmol), and LiCl (480 mg, 11.32 mmol), and the resulting mixture was heated at 70 °C for 4 h. After cooling, the reaction mixture was diluted with Et_2O. The insoluble materials were removed by filtration, and the filtrate was evaporated to give a pale brown oil, which was chromatographed on silica gel (30 g, hexane/acetone=100:1) to give **22** (900 mg, 92%) as a pale yellow oil.

IR (neat) 3070, 2954, 2928, 2858, 1709, 1660, 1111 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.87 (3H, t, J=6.8 Hz), 1.09 (9H, s), 1.12–1.50 (6H, m), 1.51–1.56 (1H, m), 1.82–1.91 (1H, m), 2.11–2.16 (1H, m), 3.13–3.17 (1H, m), 3.56 (1H, br), 3.60–3.63 (1H, m), 3.73 (1H, t-like, J=9.4 Hz), 3.78 (3H, s), 4.58 (1H, br), 5.00–5.08 (2H, br), 5.13 (1H, t-like, J=17 Hz), 5.85–5.94 (1H, m), 7.42–7.49 (6H, m), 7.71–7.78 (4H, m);

^{13}C NMR (125 MHz) δ 13.98 (q), 19.16 (s), 22.70 (t), 26.65 (q), 27.73 (t), 29.29 (t), 33.02 (t), 36.02 (d), 39.43 (t), 52.44 (q), 57.60 (d), 58.78 (t), 112.11 (d), 115.70 (t), 127.43 (d), 129.37 (d), 129.47 (d), 133.40 (s), 133.56 (s), 135.36 (d), 135.51 (d), 136.22 (d), 154.78 (s); MS: 505 (M^+); HRMS: Calcd for $C_{31}H_{43}NO_3Si$ 505.3010; Found 505.3025; $[\alpha]_D^{26}$ −62.6° (*c* 2.91, $CHCl_3$).

4.1.20. (2*S*,3*R*,6*S*)-(−)-6-Allyl-3-butyl-2-hydroxymethylpiperidine-1-carboxylic acid methyl ester (23). To a stirred solution of **22** (700 mg, 1.39 mmol) in CH_2Cl_2 (15 mL) were added $NaBH_3CN$ (95%, 460 mg, 6.95 mmol) at −78 °C, and then TFA (1.07 mL, 13.9 mmol) at −78 °C, and the resulting suspension was stirred at −78 to −45 °C for 3 h. The reaction was quenched with satd. $NaHCO_3$ (aq), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (15 mL×5). The organic layer and extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on silica gel (20 g, hexane/acetone=30:1–10:1) to give **23** (242 mg, 65%) as a colorless oil.

IR (neat) 3447, 3074, 1678 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.91 (3H, t-like, J=6.8 Hz), 1.21–1.41 (7H, br m), 1.73–1.89 (3H, m), 1.93–1.97 (1H, br), 2.18–2.24 (1H, m), 2.50–2.55 (1H, m), 3.18 (1H, br), 3.69–3.73 (1H, m), 3.74 (3H, s), 3.80–3.88 (2H, m), 4.06–4.09 (1H, m), 5.05–5.11 (2H, m), 5.71–5.78 (1H, m); ^{13}C NMR (125 MHz) δ 14.11 (q), 21.49 (t), 22.25 (t), 22.85 (t), 29.50 (t), 32.73 (t), 34.69 (d), 38.87 (t), 51.79 (d), 52.76 (q), 57.71 (d), 64.27 (t), 116.93 (t), 135.39 (d), 158.27 (s); MS: 269 (M^+); HRMS: Calcd for $C_{15}H_{27}NO_3$ 269.1989; Found 269.1999; $[\alpha]_D^{26}$ −25.6° (*c* 1.72, $CHCl_3$).

4.1.21. (5*S*,8*R*,9*S*)-(−)-5-Allyl-8-butylhexahydrooxazolo[3,4-*a*]pyridin-3-one (24). To a stirred solution of **23** (54 mg, 0.2 mmol) in THF (2 mL) was added NaH (60%, 8.8 mg, 0.22 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with 10% AcOH (aq), and the aqueous mixture was extracted with CH_2Cl_2 (5 mL×3). The organic extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on silica gel (10 g, hexane/acetone=30:1–10:1) to give **24** (42 mg, 89%) as a colorless oil.

IR (neat) 3075, 2933, 2866, 1746 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.90 (3H, t-like, J=6.8 Hz), 1.15–1.17 (1H, m), 1.20–1.40 (6H, br m), 1.62–1.81 (4H, m), 2.25–2.30 (1H, m), 2.40–2.45 (1H, m), 3.93–3.96 (1H, m), 3.98–4.01 (1H, m), 4.14–4.19 (1H, m), 4.23–4.27 (1H, m), 5.05–5.10 (2H, m), 5.71–5.80 (1H, m); ^{13}C NMR (125 MHz) δ 13.96 (q), 20.38 (t), 21.07 (t), 22.69 (t), 22.87 (t), 29.31 (t), 34.43 (d), 34.99 (t), 48.41 (d), 53.95 (d), 64.34 (t), 117.38 (t), 134.57 (d), 157.20 (s); MS: 237 (M^+); HRMS: Calcd for $C_{14}H_{23}NO_2$ 237.1728; Found 237.1724; $[\alpha]_D^{26}$ −45.9° (*c* 2.58, $CHCl_3$).

4.1.22. (2*S*,3*R*,6*S*)-6-Allyl-3-butyl-2-(2-ethoxycarbonylvinyl)piperidine-1-carboxylic acid methyl ester (25). To a stirred solution of $(COCl)_2$ (0.12 mL, 1.41 mmol) in CH_2Cl_2 (3 mL) was added DMSO (0.2 mL) at −78 °C, and the reaction mixture was stirred for 5 min. To the reaction mixture was added a solution of **23** (253 mg, 0.94 mmol) in CH_2Cl_2 (2 mL), at −78 °C, and the reaction was stirred for 30 min. Triethylamine (0.59 mL) was added at −78 °C, and the reaction was warmed to 0 °C for 1 h. The reaction was quenched with H_2O, and the mixture was extracted with Et_2O (15 mL×3). 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%, 45 mg, 1.13 mmol) in THF (4 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (0.23 mL, 1.13 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. To the reaction mixture was added a solution of the aldehyde obtained above in THF (2 mL) at 0 °C, and the resulting mixture was stirred at room temperature for 10 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with CH_2Cl_2 (10 mL×4). The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on Silica gel (10 g, hexane/acetone=50:1) to give **25** (276 mg, 87%) as a colorless oil.consisting of a 4:1 mixture of *E*- and *Z*-isomers.

4.1.23. (2*R*,3*R*,6*R*)-(−)-3-Butyl-2-(3-hydroxypropyl)-6-propylpiperidine-1-carboxylic acid methyl ester (26). To a stirred solution of **25** (270 mg, 0.8 mmol) in EtOAc (20 mL) was added 10%Pd–C (250 mg), and the resulting suspension was hydrogenated at 1 atm for 20 h. The catalyst was removed by filtration, and the filtrate evaporated to give a colorless oil, which was used directly in the next step. To a stirred solution of the ester obtained above in THF (10 mL) was added a solution of Super-Hydride (1 M in THF, 1.8 mL, 1.8 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with CH_2Cl_2 (10 mL×5). The organic extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on Silica gel (15 g, hexane/acetone=30:1–8:1) to give **26** (229 mg, 96%) as a colorless oil.

IR (neat) 3447, 2931, 2865, 11689 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.87–0.93 (6H, m), 1.15–1.35 (9H, br m), 1.44–1.81 (10H, br m), 2.48 (1H, br), 3.52 (1H, br), 3.67 (3H, s), 3.62–3.71 (2H, br), 4.02 (1H, br); ^{13}C NMR (125 MHz) δ 14.14 (q), 20.58 (t), 22.91 (t), 23.14 (t), 25.10 (t), 25.92 (t), 29.40 (t), 33.23 (t), 36.60 (t), 37.20 (d), 52.07 (q), 52.44 (d), 55.17 (d), 62.50 (t), 156.81 (s); MS: 299 (M^+); HRMS: Calcd for $C_{17}H_{33}NO_3$ 299.2459; Found 299.2434; $[\alpha]_D^{26}$ −28.2° (*c* 2.33, $CHCl_3$).

4.1.24. (2*R*,3*R*,6*R*)-(−)-3-Butyl-2-(3-methoxymethoxypropyl)-6-propylpiperidine-1-carboxylic acid methyl ester (27). To a stirred solution of **26** (55 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) were added MOMCl (0.084 mL, 1.10 mmol) and Hünig base (0.26 mL, 1.47 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 28 h. The volatiles were evaporated, and the residue was chromatographed on silica gel (10 g, hexane/acetone=30:1–20:1) to give **27** (59 mg, 94%) as a colorless oil.

IR (neat) 2930, 2867, 1699 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.87–0.92 (6H, m), 1.15–1.38 (9H, br m), 1.46–1.83 (10H, br m), 3.35 (3H, s), 3.39 (1H, br), 3.52 (2H, br), 3.65 (3H, s), 4.03 (1H, br), 4.61 (2H, s); ^{13}C NMR (125 MHz) δ 14.11 (q), 14.16 (q), 20.63 (t), 22.90 (t), 24.01 (t), 25.08 (t), 26.03

(t), 26.81 (t), 29.37 (t), 33.02 (t), 36.54 (t), 37.64 (d), 51.87 (q), 52.68 (d), 55.04 (q), 55.79 (d), 67.70 (t), 96.25 (t), 156.68 (s); MS: 343 (M^+); HRMS: Calcd for $C_{19}H_{37}NO_4$ 343.2721; Found 343.2749; $[\alpha]_D^{26}$ −23.1° (*c* 2.86, $CHCl_3$).

4.1.25. (2*S*,3*R*,6*S*)-(−)-6-Allyl-3-butyl-2-hydroxymethylpiperidine-1-carboxylic acid *tert*-butyl ester (28). 2 M Potassium hydroxide in *i*-PrOH (25 mL) was added to **23** (429 mg, 1.59 mmol), and the resulting solution was heated at 120 °C in a sealed tube for 48 h. After cooling, the solvent was evaporated, and the residue was dissolved in H_2O. The aqueous mixture was saturated with K_2CO_3, and extracted with $CHCl_3$ (10 mL×10). The organic extracts were combined, dried over K_2CO_3, and evaporated to give a pale yellow oil, which was used directly in the next step.

To a stirred solution of the oil obtained above in dioxane (20 mL) and H_2O (10 mL) were added NaOH (270 mg, 6.75 mmol) at 0 °C, and then Boc_2O (1.1 g, 5.04 mmol) at the same temperature. The reaction mixture was stirred at room temperature for 12 h, then it was extracted with CH_2Cl_2 (15 mL×5), and the organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (20 g, hexane/acetone=40:1–30:1) to give **28** (350 mg, 70%) as a colorless oil.

IR (neat) 3446, 3074, 2931, 2867, 1665, 1173 cm^{-1}; ^1H NMR (500 MHz) δ 0.92 (3H, t-like, J=6.9 Hz), 1.18–1.23 (1H, m), 1.27–1.39 (6H, m), 1.50 (9H, s), 1.74–1.84 (3H, m), 1.92–1.97 (1H, m), 2.16–2.22 (1H, m), 2.49–2.53 (1H, m), 3.45 (1H, br), 3.62–3.67 (1H, m), 3.78–3.86 (2H, m), 4.08–4.11 (1H, m), 5.05–5.11 (2H, m), 5.73–5.81 (1H, m); ^{13}C NMR (125 MHz) δ 14.11 (q), 21.28 (t), 21.97 (t), 22.88 (t), 28.54 (q), 29.53 (t), 33.36 (t), 34.59 (d), 39.29 (t), 51.86 (d), 57.08 (d), 64.69 (t), 80.24 (s), 116.75 (t), 135.68 (d), 157.45 (s); MS: 311 (M^+); HRMS: Calcd for $C_{18}H_{33}NO_3$ 311.2459; Found 311.2463; $[\alpha]_D^{26}$ −35.4° (*c* 1.52, $CHCl_3$).

4.1.26. (2*S*,3*R*,6*S*)-6-Allyl-3-butyl-2-(2-ethoxycarbonylvinyl)piperidine-1-carboxylic acid *tert*-butyl ester (29). To a stirred solution of $(COCl)_2$ (0.055 mL, 0.63 mmol) in CH_2Cl_2 (2 mL) was added DMSO (0.089 mL, 1.25 mmol) at −78 °C, and the reaction mixture was stirred at −78 °C for 5 min. To the reaction mixture was added a solution of **18** (130 mg, 0.42 mmol) in CH_2Cl_2 (2 mL), and the resulting mixture was stirred at −78 °C for 30 min. Triethylamine was added to the reaction mixture, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with H_2O and Et_2O was added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (10 mL×2). 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 suspension of NaH (60%, 22 mg, 0.54 mmol) in THF (5 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (0.11 mL, 0.54 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. To the reaction mixture was added a solution of the aldehyde obtained above in THF (2 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 12 h. The reaction was quenched with H_2O, and the aqueous layer was extracted with CH_2Cl_2 (10 mL×3). The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (20 g, hexane/acetone=80:1–70:1) to give **29** (150 mg, 95%) as a colorless oil consisting of a 4:1 mixture of *E*- and *Z*-isomers.

4.1.27. (5*R*,8*R*,9*R*)-(−)-8-Butyl-5-propylhexahydroindolizin-3-one (30). To a stirred solution of **29** (150 mg, 0.40 mmol) in EtOAc (10 mL) was added 10% Pd–C (100 mg), and the resulting suspension hydrogenated at 1 atm for 20 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 ester obtained above in EtOH (3 mL) and H_2O (1 mL) was added $LiOH\cdot H_2O$ (33 mg, 0.79 mmol), and the reaction mixture was heated at 60 °C for 2 h. After cooling, the solvent was evaporated, and the residue was extracted with EtOAc (5 mL×10). 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 carboxylic acid obtained above in CH_2Cl_2 (2 mL) was added TFA (0.18 mL, 2.37 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 5 h. The volatiles were evaporated to give a pale yellow oil, which was used directly in the next step. To a stirred solution of the amine obtained above in DMF (2 mL) were added Et_3N (0.16 mL, 1.19 mmol) and DEPC (0.09 mL, 0.59 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 1 h. The volatiles were evaporated, and the residue was chromatographed on silica gel (15 g, hexane/acetone=30:1–10:1) to give **30** (86 mg, 90%) as a pale yellow oil.

IR (neat) 2933, 2867, 1682 cm^{-1}; ^1H NMR (500 MHz) δ 0.83–0.90 (6H, m), 1.10–1.42 (10H, br m), 1.55–1.67 (5H, m), 1.72–1.83 (1H, m), 1.94–1.99 (1H, m), 2.22–2.34 (2H, m), 3.76–3.81 (1H, m), 4.12–4.19 (1H, br); ^{13}C NMR (125 MHz) δ 14.10 (q), 14.19 (q), 19.71 (t), 20.44 (t), 21.46 (t), 22.25 (t), 22.98 (t), 23.09 (t), 29.58 (t), 30.68 (t), 32.59 (t), 37.25 (d), 47.49 (d), 56.61 (d), 173.48 (s); MS: 237 (M^+); HRMS: Calcd for $C_{15}H_{27}NO$ 237.2091; Found 237.2076; $[\alpha]_D^{26}$ −38.4° (*c* 3.96, $CHCl_3$).

4.1.28. (5*R*,8*R*,9*R*)-(−)-8-Butyl-5-propyloctahydroindolizine (2). To a stirred solution of **30** (79 mg, 0.33 mmol) in THF (10 mL) was added $LiAlH_4$ (126 mg, 3.33 mmol), and the resulting suspension was refluxed for 15 h. After cooling, the reaction was quenched with 10% NaOH (aq), and the aqueous mixture was extracted with Et_2O (10 mL×5). The organic extracts were combined, dried over K_2CO_3, and evaporated to give a colorless oil, which was chromatographed on Silica gel (15 g, hexane/acetone/Et_3N=450:15:10 drops) to give **2** (60 mg, 81%) as a colorless oil.

IR (neat) 2954, 2927, 2868, 2796, 1461, 1375, 1268, 1187, 1059, 899 cm^{-1}; ^1H NMR (500 MHz) δ 0.88–0.93 (6H, m), 1.12–1.31 (10H, br m), 1.35–1.47 (1H, m), 1.48–1.66 (5H, br m), 1.78–1.84 (2H, m), 1.94 (1H, br), 2.11–2.15 (1H, m), 2.66–2.72 (1H, m), 3.00–3.05 (1H, m), 3.15–3.19 (1H, m); ^{13}C NMR (125 MHz) δ 14.19 (q), 14.63 (q), 19.40 (t), 20.95 (t), 21.44 (t), 23.01 (t), 25.29 (t), 29.48 (t), 31.29 (t), 33.35 (t), 36.78 (d), 37.00 (t), 50.43 (t), 54.19 (d), 64.17 (d) (s);

MS: 223 (M^+); HRMS: Calcd for $C_{15}H_{29}N$ 223.2299; Found 223.2292; $[\alpha]_D^{26}$ −29.0° (*c* 2.99, $CHCl_3$).

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