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Highly Stereoselective Construction of *trans*(2,3)-*cis*(2,6)-Trisubstituted Piperidines: An Application to the Chiral Synthesis of *Dendrobates* Alkaloids

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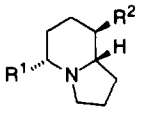
Abstract: A general and flexible route to the 5,8-disubstituted indolizidine and 1,4-disubstituted quinolizidine system found in *Dendrobates* alkaloids has been developed. The key step for this synthesis is the highly stereoselective Michael reaction of a didehydropiperidinecarboxylate (**1**) to afford a *trans*(2,3)-*cis*(2,6)-trisubstituted piperidine. In this manner, the chiral formal synthesis of indolizidines 207A and 209B and the total synthesis of indolizidines 223J, 235B' and C1-epimer of quinolizidine 207I have been achieved. © 1997 Elsevier Science Ltd.

Introduction

Poison frogs of the family *Dendrobatidae* have provided a rich source of novel pharmacologically active alkaloids, including a variety of bicyclic nitrogen heteroalicycles, such as azaspiro[5.5]undecanols (histrionicotoxins), decahydroquinolines, pyrrolizidines, indolizidines, and quinolizidines.[1] The 5,8-disubstituted indolizidines and the 1,4-disubstituted quinolizidines constitute two subclasses of izidine alkaloids, which occur not only in *Dendrobatid* frogs, but in one genus of *Mantelline* frogs and one genus of *Bufonid* toads.[1] Structures or tentative structures of members of these subclasses, which are based on mass and infrared spectra and in some cases NMR spectra, are shown in Figure 1.[1,2] Several structures have been confirmed by synthesis.[3,4]

5,8-Disubstituted indolizidines



203A $R^1 = CH_2CH{=}CHC{\equiv}CH$ (cis), $R^2 = CH_3$

205A $R^1 = (CH_2)_3C{\equiv}CH$, $R^2 = CH_3$

207A * $R^1 = (CH_2)_3CH{=}CH_2$, $R^2 = CH_3$

209B * $R^1 = (CH_2)_4CH_3$, $R^2 = CH_3$

209I $R^1 = (CH_2)_2CH_3$, $R^2 = (CH_2)_2CH_3$ (Tentative)

217B $R^1 = CH_2CH{=}CHC{\equiv}CH$ (cis), $R^2 = CH_2CH_3$ (Tentative)

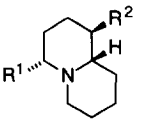
221I $R^1 = C_5H_9$ (internal double bond), $R^2 = CH_2CH_3$ (Tentative)

223J $R^1 = (CH_2)_3CH_3$, $R^2 = (CH_2)_2CH_3$ (Tentative)

235B' * $R^1 = (CH_2)_5CH{=}CH_2$, $R^2 = CH_3$

235B" * $R^1 = (CH_2)_3CH{=}CHCH_2CH_3$ (cis), $R^2 = CH_3$ (formerly **235B**)

1,4-Disubstituted quinolizidines

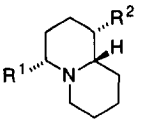


217A $R^1 = CH_2CH{=}CHC{\equiv}CH$ (cis), $R^2 = CH_3$

231A $R^1 = CH_2CH{=}CHC{\equiv}CH$ (cis), $R^2 = CH_2CH_3$ (Tentative)

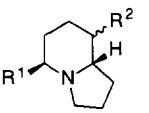
233A $R^1 = (CH_2)_3C{\equiv}CH$ (cis), $R^2 = CH_2CH_3$ (Tentative)

235E' $R^1 = C_6H_{11}$ (internal double bond), $R^2 = CH_3$ (Tentative)



207I $R^1 = CH_2CH{=}CH_2$, $R^2 = CH_2CH_3$ (Tentative)

Atypical 5,8-disubstituted indolizidine



223I $R^1 = (CH_2)_2CH_3$, $R^2 = (CH_2)_3CH_3$ (Tentative)

Figure 1. Structures of indolizidine and quinolizidine alkaloids from amphibian skin. Structures based only on MS and FTIR data are indicated as tentative. Structures proposed for **207I, 223I**, and **223J** are based on data in the present paper. Structures that have been confirmed by synthesis[4, 6] are indicated with an asterisk. The specific rotations for **223I** and **223J** have not been determined.

A recently developed enantiodivergent synthesis of a *cis, cis*-trisubstituted 3-piperidinol[5] provided a new approach to 5,8-disubstituted indolizidines.[4d] The strategy involved elimination of a 3-acetoxy group, followed by a highly stereoselective introduction of a methyl group into the core piperidine ring at the 3-position. This strategy allows the introduction of various alkyl, alkenyl and alkynyl groups stereoselectively in the 3-position of the core piperidine ring to provide *trans*-(2,3)-*cis*-(2,6)-trisubstituted piperidines. Further elaboration at the 2-and 6-positions would lead to 5,8-disubstituted indolizidine and 1,4-disubstituted quinolizidine alkaloids

(Figure 2). We now report the application of this general and versatile route to the chiral synthesis of indolizidine and quinolizidine alkaloids.

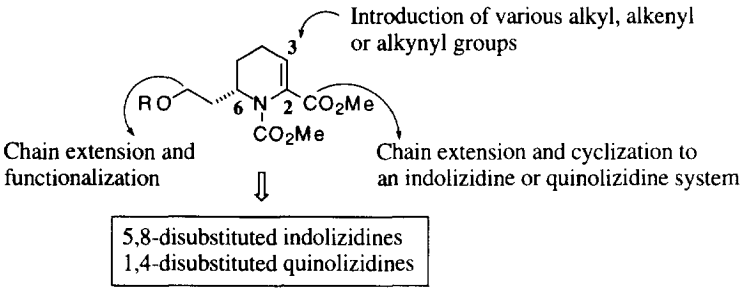


Figure 2. A general route to 5,8-disubstituted indolizidines and 1,4-disubstituted quinolizidines

Results and Discussion

First, we examined the Michael reaction of **1** (R=TBS or MOM), which was derived from **2** (R=TBS or MOM) by treatment with a base (Scheme 1), with various alkyl or alkenyl species. The reactant, solvent, and yields of (+)-**3a-e** are reported in Table 1. All reactions proceeded smoothly and the desired trisubstituted piperidines (+)-**3a-e** were obtained in high yield in each case as a single stereoisomer.

Scheme 1

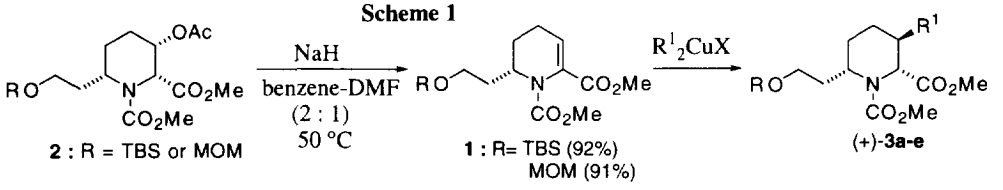
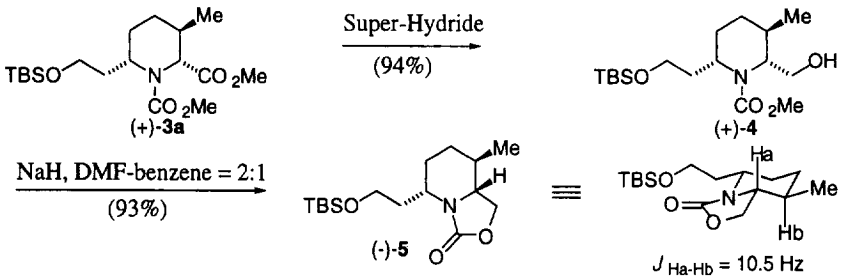


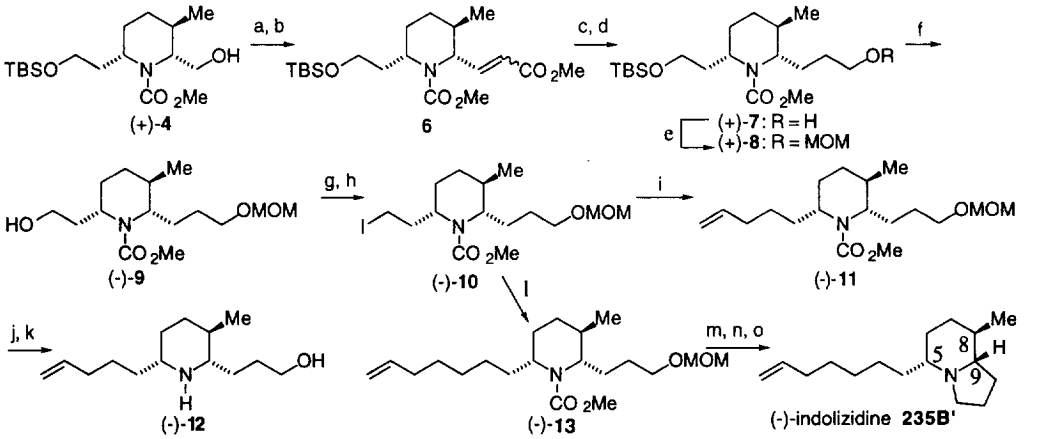
Table 1	R^1	X	R	solvent	yield (%)
(+)-**3a**	Me	Li	TBS	Et_2O	92
(+)-**3b**	Et	MgBr	TBS	THF	96
(+)-**3c**	vinyl	Li	MOM	Et_2O	91
(+)-**3d**	allyl	MgCl	MOM	THF	80
(+)-**3e**	*n*-Bu	Li	TBS	Et_2O	94

The exclusive formation of (+)-**3** can be rationalized as the result of a preferred α-axial attack of the alkyl or alkenyl anion, leading not to a boat-like but to a chair-like intermediate[6] where the C-6 side-chain occupies a quasi-axial orientation owing to an $A^{(1,3)}$ strain.[7].

The piperidine (+)-**3a** was transformed into the oxazolidinone (–)-**5** *via* a sequence of first a Super-Hydride reduction and then treatment of the resulting alcohol (+)-**4** with sodium hydride. The relative stereochemistry of the new asymmetric center of the piperidine (+)-**3a** was determined to be trans to the centers at C-2 and C-6 by analysis of the coupling constant between H_a and H_b in the ^1H NMR spectrum of (–)-**5**. It was assumed that all of the ring appendages in (–)-**5** lie in the equatorial orientation. The absolute stereochemistry of (–)-**5** is 2*R*,3*R*,6*S*, as shown below.

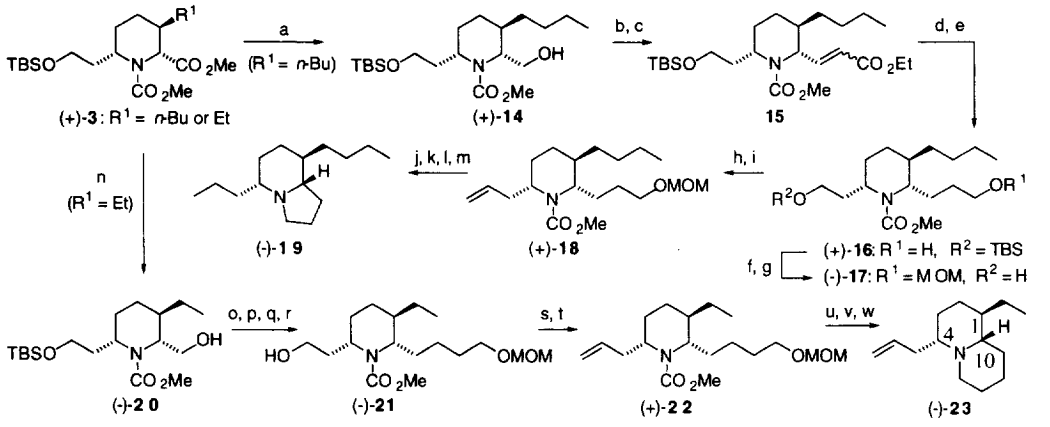


We then examined the chiral synthesis of indolizidine and quinolizidine alkaloids. Swern oxidation of the alcohol (+)-**4**, followed by a Wittig-Horner reaction of the resulting aldehyde, gave the α,β-unsaturated ester **6** as a 4:1 mixture of *E*- and *Z*-isomers in 90% yield (Scheme 2). Catalytic hydrogenation of the mixture of *E*- and *Z*-**6** with 5% Pd-C and subsequent Super-Hydride reduction afforded the homologated alcohol (+)-**7** in 91% yield. Protection of the hydroxyl in (+)-**7** by treatment with MOMCl gave (+)-**8** in 93% yield, and deprotection of (+)-**8** with TBAF gave the alcohol (–)-**9** in 95% yield. The carbon chain homologation of (–)-**9** at the 6-position was performed *via* a sequence of mesylation of the hydroxyl, substitution of the resulting mesyloxyl with NaI to the iodide (–)-**10** and subsequent cross coupling with allylmagnesium chloride in the presence of CuI, providing the olefin (–)-**11** in 74% yield. Deprotection at the methoxycarbonyl group in (–)-**11** with *n*-PrSLi,[8] followed by treatment of the resulting amine with acid, furnished the amino alcohol (–)-**12** in 65% yield. The amino alcohol (–)-**12** had been previously synthesized by another route and then converted *via* the Kibayashi ring closure to the indolizidines **207A** and **209B**[9] (see Figure 1), two members of the 5,8-disubstituted indolizidine subclass of izidine alkaloids. The spectral data for (–)-**12** were in good accord with those reported by Shishido and Kibayashi.[9] In a similar manner the iodide (–)-**10** was converted to the amino alcohol (–)-**13**. Application of the Kibayashi indolizidine closure to (–)-**13** provided (–)-indolizidine **235B'** (see Figure 1), another member of the 5,8-disubstituted subclass of izidine alkaloids. Spectral data for the synthetic (–)-indolizidine **235B'** (Scheme 2) were in good accord with the data reported for the natural alkaloid.[10] The natural alkaloid is the (–)-enantiomer. It had been previously synthesized by another route.[9]



Scheme 2: *Reagents and conditions*: (a) Swern oxidn.; (b) NaH, $(EtO)_2P(O)CH_2CO_2Me$ (90% in 2 steps); (c) H_2, 5% Pd-C, MeOH; (d) Super-Hydride, rt (91% in 2 steps); (e) MOMCl, Hünig base (93%); (f) TBAF (95%); (g) MsCl, Et_3N, 0 °C; (h) NaI, acetone (85% in 2 steps); (i) CH_2=$CHCH_2MgCl$, CuI, -30 °C (74%); (j) *n*-PrSLi, HMPA; (k) c. HCl, MeOH, reflux (65% in 2 steps); (l) CH_2=$CH(CH_2)_3MgBr$, CuI, -30 °C (82%); (m) *n*-PrSLi, HMPA; (n) c. HCl, MeOH, reflux; (o) Ph_3P, CBr_4, Et_3N (63% in 3 steps)

We then applied the chiral syntheses towards the natural indolizidine **223I** and quinolizidine **207I** (see Figure 1). The strategy for the synthesis, starting, respectively, with (+)-**3e** and (+)-**3b**, of indolizidine (–)-**19** and quinolizidine (–)-**23** (Scheme 3), the structures assigned tentatively to these alkaloids, respectively, was similar to that for the synthesis of (–)-indolizidine **235B'**.



Scheme 3: *Reagents and conditions*: (a) Super-Hydride THF, 0 °C (95%); (b) Swern oxidn.; (c) NaH, $(EtO)_2P(O)CH_2CO_2Me$ (81% in 2 steps); (d) H_2, 5% Rh-C, EtOAc, 4 atm; (e) Super-Hydride THF, 0 °C (86% in 2 steps); (f) MOMCl, Hünig base (86%); (g) TBAF (89%); (h) Swern oxidn.; (i) $CH_3P^+Ph_3Br^-$, *n*-BuLi, THF (81% in 2 steps); (j) H_2, 5% $Pd(OH)_2$; (k) *n*-PrSLi, HMPA; (l) c. HCl, MeOH, reflux; (m) Ph_3P, CBr_4, Et_3N (43% in 4 steps); (n) Super-Hydride THF, 0 °C (92%); (o) Swern oxidn.; (p) $MOMO(CH_2)_3P^+Ph_3Br^-$, *n*-BuLi, THF (89% in 2 steps); (q) H_2, 5% Pd-C, MeOH, 4 atm; (r) TBAF (89% in 2 steps); (s) Swern oxidn.; (t) $CH_3P^+Ph_3Br^-$, *n*-BuLi, THF (64% in 2 steps); (u) *n*-PrSLi, HMPA; (v) c. HCl, MeOH, reflux; (w) Ph_3P, CBr_4, Et_3N (63% in 3 steps)

Natural indolizidines **223I** and **223J** have not fully been fractionated because of low levels present in frog skin extracts and the structures proposed were, therefore, tentative, based only on mass spectral properties.[1] Subsequent FTIR spectral analyses revealed that alkaloid **223I** was not a typical 5,8-disubstituted indolizidine (unpublished data), since the Wenkert-Bohlmann band region (2800-2600 cm^{-1}) differs significantly from that of other well-characterized natural 5,8-disubstituted indolizidines, all of which have the 5-H and 9-H in a *cis* relationship and consequently show an intense (and sharp) Wenkert-Bohlmann band.[11,12] This intense band is not present in the FTIR spectrum of **223I** (Figure 3), but is present in indolizidine (–)-**19**. Alkaloid **223I** may prove to be an 8-butyl-5-propylindolizidine with the 5-H and 9-H in a trans-relationship (Figure 1), but this is only a tentative assignment. The natural alkaloid **223I** and (–)-**19** are well separated on RTX-5 or HP-5 capillary columns (data not shown). The indolizidine (–)-**19** and the natural 5-butyl-8-propylindolizidine **223J** have virtually identical FTIR spectra (Figure 3) suggesting that they both have the same relative configuration, certainly at C-5 and C-9.

Tentative structures for alkaloids of a 1,4-disubstituted quinolizidine subclass have been proposed based on characteristic features of their mass and FTIR spectra.[10,11] Such alkaloids exhibit, in addition to a base peak formed by α-cleavage, a significant fragment at m/z 110 due to a retro-Diels-Alder loss from the base peak. In addition, such alkaloids show a strong peak in the Wenkert-Bohlmann band region; the peak is broader than the corresponding peak in 5,8-disubstituted indolizidines. Recently, by NMR spectral analysis has been confirmed the tentative structure of one such 1,4-disubstituted quinolizidine, namely **217A**.[2] The relative configuration

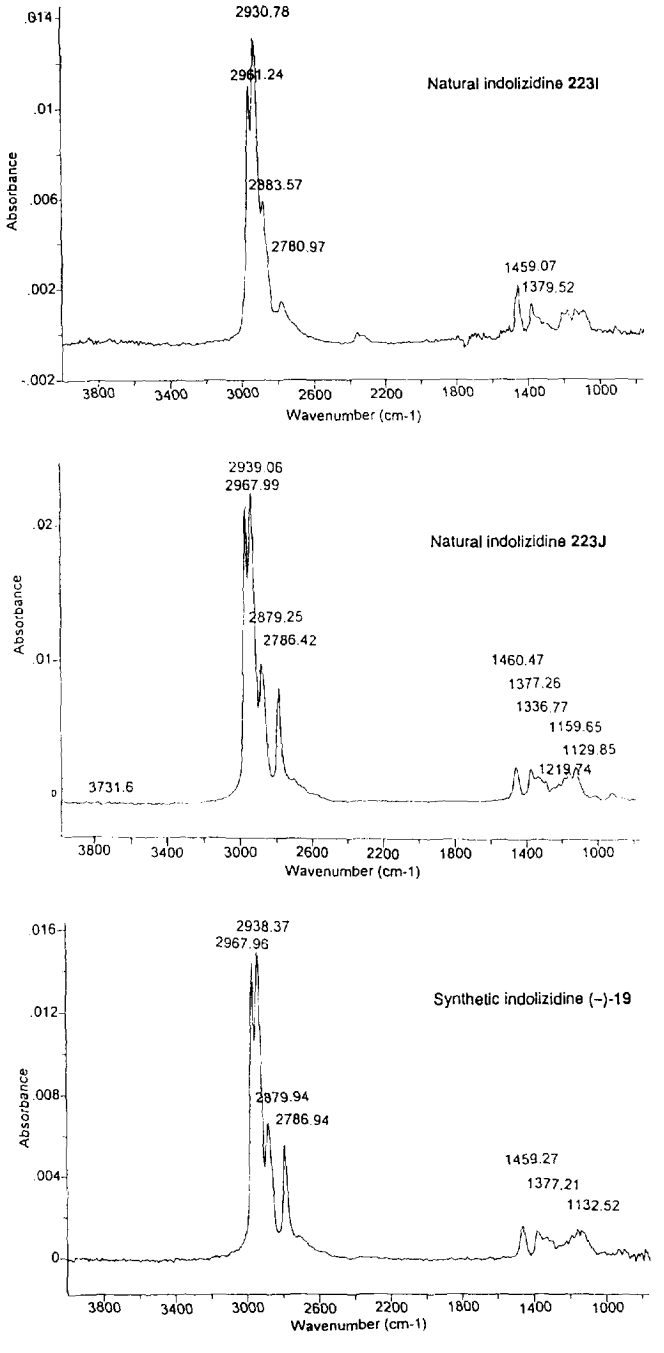


Figure 3: GC-FTIR spectra of natural indolizidines 223I and 223J, and synthetic indolizidine (–)-**19**.

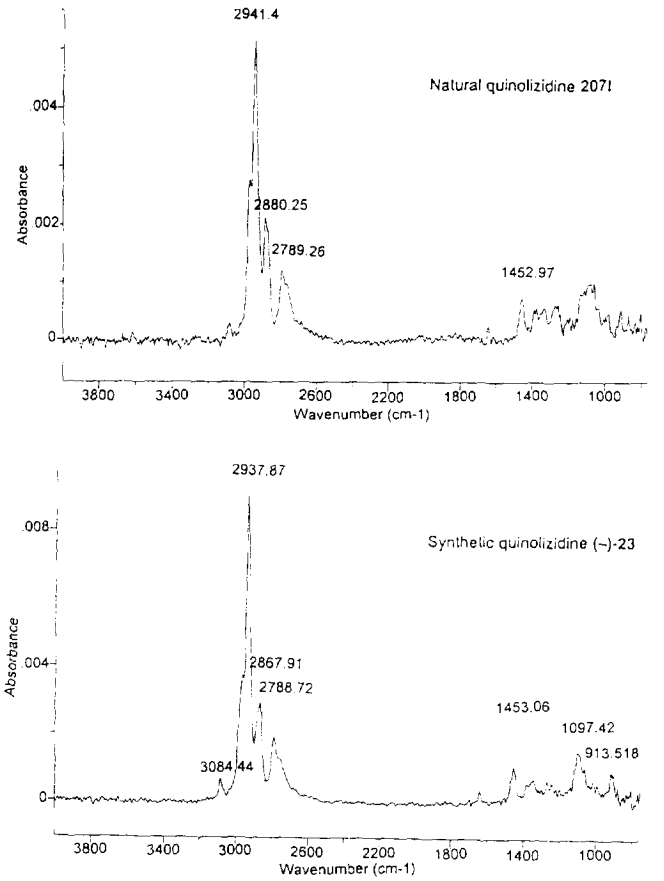


Figure **4**: GC-FTIR spectra of natural quinolizidine 207I and synthetic quinolizidine (–)-**23**.

corresponds to that of (–)-**23**, but the absolute configuration is unknown. FTIR spectral analyses of other alkaloids, previously proposed[1] to be 1,4-disubstituted quinolizidines, have confirmed that four alkaloids have Wenkert-Bohlmann bands corresponding to those in quinolizidine **217A** and, thus, appear to be 1,4-disubstituted quinolizidines with the hydrogens on C-4 and C-10 *cis* to each other.[2] Tentative structures are shown in Figure 1, where the configuration at C-1 remains undefined except for **217A**. Comparision of (–)-**23** with natural **207I** revealed that the two are not identical. They had slightly different retention times (10 min 57 sec for (–)-**23** and 10 min 53 sec for **207I**) on a 30 m RTX-5 capillary column. In addition, the ion trap mass spectra showed very small, but consistent differences in the relative intensities of the ion fragments at m/z lower than 110. FTIR spectra were very similar but not identical (Figure 4). The pattern in the Wenkert-Bohlmann band region is very similar, indicating both (–)-**23** and **207I** have the same relative configuration at C-4 and C-10. Thus, the most probable difference between those diastereomers is the relative configuration at C-1, and the structure of **207I** is most likely that of (1*S*,4*S*,10*S*)- or (1*R*,4*R*,10*R*)-4-allyl-1-ethylquinolizidine, since (–)-**23** is (1*R*,4*S*,10*S*)-4-allyl-1-ethylquinolizidine. Structures shown for quinolizidines **217A** and **207I** in Figure 1 are based on NMR spectral analysis[2] and comparison with (–)-**23**, respectively.

Conclusion

We have achieved highly stereoselective syntheses of *trans*-(2,3)-*cis*-(2,6)-trisubstituted piperidines (**3a-c**) starting with a Michael reaction on **1**. The utility of such compounds as chiral building blocks for synthesis was demonstrated by chiral synthetic routes to natural indolizidines **207A, 209B, 235B'**, and (–)-**19** and to quinolizidine (–)-**23**. The relative stereochemistry of natural indolizidine **223J** is concluded to be the same as synthetic indolizidine (–)-**19**, based on virtually identical FTIR spectra. Natural indolizidine **223I** is a diastereomer of indolizidine (–)-**19**, probably with the opposite relative configuration at C-5, based on the difference in the Wenkert-Bohlmann band region in the FTIR spectra. The relative stereochemistry of natural quinolizidine **207I** is concluded to be of a *cis*-(1,4)-*cis*-(1,10) configuration, based on comparison of GC-mass and GC-FTIR spectra with (–)-**23**, which has a *trans*-(1,4)-*trans*-(1,10) configuration.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were recorded at the indicated field strength using $CDCl_3$ as solvent unless otherwise indicated. Chemical shifts are reported 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 using $CDCl_3$ as solvent unless otherwise indicated. Chemical shifts are reported in parts per million (ppm, δ) downfield from TMS and are referenced to the center line of $CDCl_3$ (77.0) as an internal standard. Carbon signals were assigned by a DEPT pulse sequence and are designated as u = methyl or methine, d = methylene, and s = quaternary. GC-MS analysis used an RTX-5 fused silica bonded capillary column (Restek, 30 m x 0.25 mm i.d.) in a Varian model 3400 gas chromatograph programmed from 100°-280° at a rate of 10°/min, interfaced with a Finnigan ion-trap model 800. GC-MS-FTIR spectra were obtained using a Hewlett-Packard model 5890 gas chromatograph having a 25 m x 0.32 mm HP-5 (polymer of 5% diphenylsiloxane and 95% dimethylsiloxane) fused silica bonded capillary column with the same program as used above for the GC-MS analysis, interfaced with a Hewlett-Packard model 5971 series mass selective detector and a Hewlett-Packard model 5965B IR instrument with a narrow band (4000-750 cm^{-1}) detector. A Hewlett-Packard MS/IR ChemStation (DOS based) was used to generate the chromatograms, and the EIMS and FTIR spectra of GC peaks.

Methyl (2*R*,3*R*,6*S*)-(+)-3-Acetoxy-6-{2-(*t*-butyldimethylsiloxy)ethyl}-1-(methoxycarbonyl)-piperidine-2-carboxylate (2, R=TBS): To a stirred solution of methyl (2*R*,3*R*,6*S*)-(-)-3-acetoxy-6-(2-hydroxyethyl)-1-(methoxycarbonyl)piperidine-2-carboxylate[5] (1.3 g, 4.29 mmol) in CH_2Cl_2 (5 mL) were added TBSCl (750 mg, 4.98 mmol), Et_3N (0.75 mL, 5.36 mmol) and DMAP (52 mg, 0.43 mmol) at 0 ℃, and the reaction mixture was stirred for 19 h at room temperature. Water (10 mL) was added to the mixture, and the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2 (20 mL x 3), and the extracts were combined, dried over $MgSO_4$ and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (60 g, hexane:acetone=30:1~20:1) to afford (+)-**2**, R = TBS, 1.7 g, 95%, as a colorless oil.

IR (neat) 2954, 2857, 1750, 1707, 1444, 1406, 1362, 1320, 1294, 1236, 1196, 1173, 1091, 1052, 1006, 940, 836, 776 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.05 (6H, s), 0.89 (9H, s), 1.67-2.11 (6H, m), 2.01 (3H, s), 3.60-3.70 (2H, m), 3.71 (6H, s), 4.28-4.36 (1H, br), 4.90-5.02 (1H, m), 5.07 (1H, d-like, J = 6.9 Hz); ^{13}C NMR (125

MHz) δ -5.49 & -5.46 (each u, due to rotamers), 18.15 (s), 20.89 & 20.93 (each u, due to rotamers), 25.31 (d), 25.32 (d), 25.81 (u), 35.90 (d), 48.24 (u), 51.87 (u), 53.01 (u), 54.76 (u), 60.88 (d), 69.03 (u), 169.98 & 170.53 (each s, due to rotamers), MS; 418 (M^++1), 417 (M^+), 360 (M^+-57), 200 (100); HRMS Calcd. for $C_{19}H_{35}NO_7Si$: 417.2181, Found 417.2178; $[\alpha]^{26}_D$ +2.7 (*c* 3.2, $CHCl_3$).

Methyl (2*R*, 3*R*, 6*S*)-(-)-3-Acetoxy-1-(methoxycarbonyl)-6-{2-(methoxymethoxy)ethyl}-piperidine-2-carboxylate (2, R=MOM): Methoxymethyl chloride (0.19 mL, 2.48 mmol) and Hünig base (0.52 mL, 3.3 mmol) were added to a stirred solution of methyl (2*R*,3*R*,6*S*)-(-)-3-acetoxy-6-(2-hydroxyethyl)-1-(methoxycarbonyl)piperidine-2-carboxylate[5] (500 mg, 1.65 mmol) in CH_2Cl_2 (5 mL) at 0 ℃, and the reaction mixture was stirred for 19 h at room temperature. Water (5 mL) was added to the mixture, and the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2 (10 mL x 3). The extracts were combined, dried over $MgSO_4$ and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (15 g, hexane:acetone=15:1~10:1) to afford (-)-**2**, R = MOM, 528 mg, 92%, as a colorless solid (mp 68.5~70 ℃).

IR (KBr) 2954, 2884, 1747, 1703, 1444, 1364, 1330, 1293, 1237, 1169, 1149, 1110 cm^{-1}; ^1H NMR (270 MHz) δ 1.70-2.12 (9H, br m, including at δ 2.06, 3H, s), 3.36 (3H, s), 3.56 (2H, t, *J* = 6.5 Hz), 3.72 (6H, s), 4.35 (1H, br), 4.62 (2H, s), 4.93-5.02 (1H, br m), 5.00 (1H, d-like, *J* = 6.8 Hz); ^{13}C NMR (67.5 MHz) δ 20.78 (u), 20.96 (d), 25.56 (d), 33.14 (d), 47.92 (u), 51.80 (u), 52.96 & 53.00 (each u, due to rotamers), 54.77 & 54.99 (each u, due to rotamers), 55.04 (u), 65.41 (d), 68.81 (u), 96.28 (d), 156.26 (s), 169.78 (s), 170.32 (s); MS 348 (M^++1), 347 (M^+), 138 (100); HRMS Calcd. for $C_{15}H_{25}NO_8$: 347.1579, Found 347.1593; Anal. Calcd. for $C_{15}H_{25}NO_8$: C, 51.86; H, 7.25; N, 4.03. Found: C, 51.75; H, 7.31; N, 3.97; $[\alpha]^{26}_D$ -14.6 (*c* 1.10, $CHCl_3$).

Methyl (6*S*)-(-)-6-{2-(*t*-Butyldimethylsiloxy)ethyl}-1-(methoxycarbonyl)-2,3-dehydro-piperidine-2-carboxylate (1, R=TBS): To a stirred suspension of NaH (60%, 280 mg, 7.0 mmol) in DMF (6 mL) was added (+)-**2**, (R = TBS, 1.46 g, 3.5 mmol) in benzene (3 mL) at 0 ℃, and the resulting suspension was stirred at 50 ℃ for 1.5 h. After cooling, the reaction was quenched with 10 % AcOH in H_2O (30 mL). The aqueous layer was extracted with benzene (20 mL x 5), and the extracts were combined, dried over $MgSO_4$ and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (50 g, hexane:acetone=40:1~30:1) to afford (-)-**1**, R = TBS, 1.15 g, 92%, as a colorless oil.

IR (neat) 2952, 2929, 2884, 2856, 1716, 1647, 1472, 1442, 1402, 1349, 1330, 1294, 1275, 1239, 1193, 1159, 1082, 109, 837, 776, 746 cm^{-1}; ^1H NMR (500 MHz) δ 0.03 & 0.04 (each 3H, each s), 0.88 (9H, s), 1.50 (1H, m), 1.68-1.77 (2H, m), 1.80-1.88 (1H, m), 2.12-2.26 (2H, m), 3.65-3.75 (8H, br m, including δ 3.69 & 3.74, each 3H, each s), 4.53-4.57 (1H, m), 6.08 (1H, t-like, *J* = 3.6 Hz); ^{13}C NMR (125 MHz) δ -5.55 & -5.46 (each u, due to rotamers), 18.22 (s), 19.67 & 19.73 (each d, due to rotamers), 25.83 (d), 25.86 (u), 32.77 (d), 48.39 (u), 52.03 (u), 53.04 (u), 60.12 (d), 122.62 (u), 129.68 (s), 154.65 (s), 165.61 (s); MS 358 (M^++1), 357 (M^+), 300 (M^+-57), 73 (100); HRMS Calcd. for $C_{17}H_{31}NO_5Si$: 357.1970, Found 357.1987; $[\alpha]^{26}_D$ -54.8 (*c* 2.6, $CHCl_3$).

Methyl (6*S*)-(-)-1-(Methoxycarbonyl)-6-{2-(methoxymethoxy)ethyl}-2,3-dehydropiperidine-2-carboxylate (1, R=MOM): To a stirred suspension of NaH (46 mg, 1.15 mmol) in DMF (3 mL) was added (-)-**2**, (R = MOM, 200 mg, 0.576 mmol) in DMF (1 mL) and benzene (2 mL) at 0 ℃, and the resulting suspension was heated at 50 ℃ for 3 h. After cooling, the reaction was quenched with 10% AcOH in H_2O (20 mL), and the aqueous layer was extracted with benzene (10 mL x 5). The extracts were combined, dried

over $MgSO_4$ and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (10 g, hexane:acetone=12:1) to afford (-)-**1**, R = MOM, 151 mg, 91%, as a colorless oil.

IR (neat) 2952, 1718, 1648, 1442, 1401, 1330, 1276, 1238, 1193, 1148, 1111, 1040 cm^{-1}; ^1H NMR (270 MHz) δ 1.50-1.64 (1H, br m), 1.71-1.96 (3H, br m), 2.10-2.27 (2H, br m), 3.38 (3H, s), 3.63 (2H, t-like, J = 5.6 Hz), 3.71 (3H, s), 3.76 (3H, s), 4.55-4.70 (3H, br, including δ 4.64, 2H, s), 6.10 (1H, t-like, J = 3.7 Hz); ^{13}C NMR (67.5 MHz) δ 19.36 (d), 25.70 (d), 29.73 (d), 48.25 (u), 51.77 (u), 52.81 (u), 54.84 & 54.87 (each u, due to rotamers), 64.55 (d), 96.44 (d), 122.07 (s), 129.68 (u), 154.39 (s), 165.28 (s); MS 288 (M^++1), 287 (M^+), 59 (100); HRMS Calcd. for $C_{13}H_{21}NO_6$: 287.1367, Found 287.1336; $[\alpha]^{26}_D$ -75.2 (*c* 2.38, $CHCl_3$).

General Procedure for the Michael Reaction of the ester (1, R=TBS or MOM) To a stirred suspension of CuI (5 eq) in the ether solvent (see Table 1) was added R^1X (10 eq, see Table 1) at -35~-40 ℃, and the resulting suspension was stirred for 20 min at -35~-40 ℃. To the suspension was added the ester (**1**) in the same ether solvent at -78℃, and the temperature was gradually raised to -30 ℃. The reaction was quenched with 10% HCl, and 10% $Na_2S_2O_3$ in satd. $NaHCO_3$ in H_2O was added. The aqueous layer was extracted with CH_2Cl_2, and the extracts were dried over $MgSO_4$ and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 to afford the adduct **3** as a colorless oil in 80~96% yield (see Table 1).

Methyl (2*R*,3*R*,6*S*)-(+)-6-{2-(*t*-Butyldimethylsiloxy)ethyl}-1-methoxycarbonyl-3-methylpiperidine-2-carboxylate (3a, R^1=Me, R=TBS): IR (neat) 2953, 2857, 1738, 1704, 1445, 1406, 1360, 1331, 1301, 1256, 1198, 1160, 1100, 1007, 837, 813, 776 cm^{-1}; ^1H NMR (500 MHz) δ 0.03 & 0.04 (each 3H, each s), 0.88 (9H, s), 1.07 (3H, d, J = 7.1 Hz), 1.21-1.26 (1H, m), 1.39-1.44 (1H, m), 1.53-1.60 (1H, m), 1.77-1.91 (3H, br m), 2.50-2.57 (1H, m), 3.57-3.65 (2H, m), 3.70 (3H, s), 3.72 (3H, s), 4.28-4.33 (1H, m), 4.56 (1H, br s); ^{13}C NMR (125 MHz) δ -5.43 & -5.38 (each u, due to rotamers), 18.20 (s), 18.29 (u), 22.08 (d), 22.40 (d), 25.85 (u), 27.82 (u), 35.66 (d), 48.63 (u), 52.06 (u), 52.87 (u), 57.97 (u), 60.76 (d), 173.20 (s); MS 374 (M^++1), 373 (M^+), 316 (M^+-57), 89 (100); HRMS Calcd. for $C_{18}H_{35}NO_5Si$: 373.2282, Found 373.2295; $[\alpha]^{26}_D$ +71.2 (*c* 0.7, $CHCl_3$).

Methyl (2*R*,3*R*,6*S*)-(+)-6-{2-(*t*-Butyldimethylsiloxy)ethyl}-3-ethyl-1-methoxycarbonylpiperidine-2-carboxylate (3b, R^1=Et, R=TBS): IR (neat) 2954, 2857, 1737, 1704, 1444, 1253, 1214, 1195, 1102, 837, 775 cm^{-1}; ^1H NMR (500 MHz) δ -0.001 & 0.003 (each 3H, each s), 0.85 (9H, s), 0.90 (3H, t-like, J = 7.2 Hz), 1.28-1.39 (3H, m), 1.45 (1H, sixtet-like, J = 7.2 Hz), 1.54 (1H, sextet-like, J = 6.9 Hz), 1.69-1.83 (3H, m), 2.20 (1H, br), 3.54-3.61 (2H, m), 3.65 (3H, s), 3.69 (3H, s), 4.24 (1H, br m), 4.68 (1H, br); ^{13}C NMR (67.5 MHz) δ -5.51 & -5.44, 11.72 & 11.87, 18.11, 20.17 & 20.22, 22.29 & 22.30, 24.41 & 24.50, 25.15, 25.60 & 25.96, 26.40, 34.91, 35.07 & 35.50, 48.79 & 48.86, 51.92, 52.08 & 52.70, 55.86, 60.42, 173.39; MS 387 (M^+), 330 (100); HRMS Calcd. for $C_{19}H_{37}NO_5Si$: 387.2439, Found 387.2411; $[\alpha]^{26}_D$ +60.6 (*c* 13.0, $CHCl_3$).

Methyl (2*R*,3*R*,6*S*)-(+)-6-{2-(*t*-Butyldimethylsiloxy)ethyl}-3-butyl-1-methoxycarbonylpiperidine-2-carboxylate (3c, R^1=*n*-Bu, R=TBS): IR (neat) 2953, 2930, 2857, 1737, 1704, 1444, 1361, 1256, 1105, 837, 776 cm^{-1}; ^1H NMR (500 MHz) δ 0.027 & 0.031 (each 3H, each s), 0.88 (12H, br s), 1.26-1.47 (8H, br m), 1.53-1.60 (1H, m), 1.68-1.85 (3H, br m), 2.31 (1H, br), 3.56-3.64 (2H, m), 3.69 (3H, s), 3.72 (3H, br s), 4.27 (1H, m), 4.68 (1H, br); ^{13}C NMR (67.5 MHz) δ -5.53 & -5.48 (each u, due to rotamers), 13.93 (u), 18.09 (s), 20.44 (d), 22.28 (d), 22.52 (d), 25.75 (u), 29.41 (d), 31.32 (d), 33.11 (u), 35.54 (d), 48.82 (u), 51.95 (u), 52.72 (u), 56.22 (u), 60.70 (u), 157.33 (s), 173.29 (s); MS 416 (M^++1), 415

(M^+), 359 (100); HRMS Calcd. for $C_{21}H_{41}NO_5Si$: 415.2752, Found 415.2791; $[\alpha]^{26}_D$ +54.7 (*c* 4.88, $CHCl_3$).

Methyl (2*R*, 3*R*, 6*S*)-(+)-3-Allyl-1-methoxycarbonyl-6-{2-(methoxymethoxy)ethyl}piperidine-2-carboxylate (3d, R^1=allyl, R=MOM): IR (neat) 3074, 2950, 1734, 1700, 1654, 1639, 1445, 1406, 1362, 1314, 1211, 1151, 1110, 1040 cm^{-1}; ^1H NMR (500 MHz) δ 1.33-1.41 (2H, br m), 1.59 (1H, sextet, *J* = 7.0 Hz), 1.75-1.86 (2H, m), 1.91 (1H, sextet, *J* = 7.2 Hz), 2.08 (1H, quint-like, *J* = 7.0 Hz), 2.18 (1H, quint-like, *J* = 7.2 Hz), 2.20 (1H, br), 3.34 (3H, s), 3.49-3.57 (2H, m), 3.69 (3H, s), 3.72 (3H, br s), 4.34 (1H, br), 4.59 & 4.60 (2H, ABq, *J* = 6.2 Hz), 4.71 (1H, br), 5.01-5.07 (2H, m), 5.75 (1H, ddt, *J* = 16.1, 8.9, 7.0 Hz); ^{13}C NMR (67.5 MHz) δ 20.55 (d), 22.81 (d), 32.70 (d), 33.02 (u), 36.18 (d), 48.76 (u), 52.13 (u), 52.90 (u), 55.18 (u), 55.21 (u), 65.47 (d), 96.46 (d), 117.29 (u), 136.08 (u), 157.24 (s), 173.23 (s); MS 330 (M^++1), 329 (M^+), 270 (100); HRMS Calcd. for $C_{16}H_{27}NO_6$: 329.1837, Found 329.1815; $[\alpha]^{26}_D$ +25.9 (*c* 1.65, $CHCl_3$).

Methyl (2*R*, 3*R*, 6*S*)-(+)-1-Methoxycarbonyl-6-{2-(methoxymethoxy)ethyl}-3-vinylpiperidine-2-carboxylate (3e, R^1=vinyl, R=MOM): IR (neat) 3080, 2951, 2882, 1737, 1698, 1445, 1406, 1361, 1341, 1315, 1288, 1211, 1152, 1110, 1040, 918 cm^{-1}; ^1H NMR (500 MHz) δ 1.38-1.42 (1H, m), 1.43-1.47 (1H, m), 1.59 (1H, sextet-like, *J* = 6.8 Hz), 1.80-1.92 (3H, br m), 3.06 (1H, br), 3.31 (3H, s), 3.48-3.56 (2H, br m), 3.68 (3H, s), 3.70 (3H, s), 4.32 (1H, br), 4.57 (2H, s), 4.88 (1H, br), 5.08 (1H, dq-like, *J* = 17.5, 1.1 Hz), 5.10 (1H, dq-like, *J* = 17.5, 1.1 Hz), 5.82 (1H, dddd, *J* = 17.5, 10.7, 6.0, 1.3 Hz); ^{13}C NMR (67.5 MHz) δ 21.76 (d), 23.55 (d), 33.16 (d), 37.23 (u), 49.12 (u), 52.78 (u), 53.54 (u), 55.74 (u), 55.86 (u), 66.01 (d), 97.03 (d), 115.93 (d), 139.53 (u), 157.61 (s), 173.40 (s); MS 316 (M^++1), 315 (M^+), 256 (100); HRMS Calcd. for $C_{15}H_{25}NO_6$: 315.1680, Found 315.1699; $[\alpha]^{26}_D$ +35.4 (*c* 1.19, $CHCl_3$).

Methyl (2*R*, 3*R*, 6*S*)-(+)-6-{2-(*t*-Butyldimethylsiloxy)ethyl}-2-(hydroxymethyl)-3-methylpiperidine-1-carboxylate (4): Super-Hydride (1 M in THF, 2 mL) was added to a stirred solution of (+)-**3** (R^1 = Me, R = TBS, 336 mg, 0.9 mmol) in THF (10 mL) at 0 ℃, and the reaction mixture was stirred at 0 ℃ for 1 h. The reaction was quenched with H_2O (3 mL), and the aqueous layer was extracted with CH_2Cl_2 (20 mL x 5). The extracts were combined, dried over $MgSO_4$ and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (20 g, hexane:acetone=12:1) to afford (+)-**4** (292 mg, 94%) as a colorless oil.

IR (neat) 3446, 2954, 2858, 1694, 1673, 1447, 1407, 1362, 1310, 1255, 1192, 1101, 1047, 1005, 930, 836, 775 cm^{-1}; ^1H NMR (500 MHz) δ 0.01 & 0.02 (each 3H, each s), 0.85 (9H, s), 1.01 (3H, d, *J* = 6.8 Hz), 1.13-1.19 (1H, m), 1.33-1.38 (1H, m), 1.62-1.91 (3H, br m), 2.31 (1H, br), 3.07 (1H, br, exchangeable with D_2O), 3.55-3.59 (1H, br), 3.60-3.68 (5H, br, including δ 3.66, 3H, s), 3.96-3.99 (1H, br), 4.27 (1H, br); ^{13}C NMR (125 MHz) δ -5.60 & -5.52 (each u, due to rotamers), 18.22 (s), 19.35 (u), 22.31 (d), 23.15 (d), 25.81 (u), 27.60 (u), 38.46 (d), 48.71 (u), 52.60 (u), 58.89 (u), 61.93 (d), 65.01 (d), 158.24 (s); MS 346 (M^++1), 345 (M^+), 313 (M^+-32), 288 (M^+-57), 89 (100); HRMS Calcd. for $C_{17}H_{35}NO_4Si$: 345.2333, Found 345.2310; $[\alpha]^{26}_D$ +17.9 (*c* 2.4, $CHCl_3$).

(-)-Oxazolidinone (5): The alcohol (+)-**4** (70 mg, 0.2 mmol) in benzene (1 mL) was added to a stirred suspension of NaH (16 mg, 0.4 mmol) in DMF (2 mL) at 0 ℃, and the resulting suspension was stirred at 50 ℃ for 1 h. After cooling, the reaction was quenched with 10 % AcOH in H_2O (10 mL), and the aqueous layer was extracted with benzene (10 mL x 5). The extracts were combined, dried over $MgSO_4$ and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (10 g, hexane:acetone=20:1~15:1) to afford (-)-**5** (59 mg, 93%) as a colorless oil.

IR (neat) 2955, 2929, 2856, 1756, 1472, 1461, 1439, 1421, 1388, 1363, 1338, 1255, 1224, 1188, 1113, 1093, 1049, 1007, 942, 837, 812, 777 cm^{-1}; ^1H NMR (500 MHz) δ 0.03 & 0.04 (each 3H, each s), 0.86 (3H, d, J = 7.0 Hz), 0.87 (9H, s), 1.19 (1H, qd-like, J = 12.2, 3.9 Hz), 1.43 (1H, qd-like, J = 12.2, 3.9 Hz), 1.46-1.54 (1H, m), 1.69 (1H, dq, J = 13.0, 3.0 Hz), 1.78-1.85 (1H, m), 1.89 (1H, dq, J = 13.5, 3.5 Hz), 2.67-2.74 (1H, m), 3.10 (1H, ddd, J = 10.5, 7.7, 4.5 Hz), 3.25-3.31 (1H, m), 3.73-3.76 (2H, m), 3.94 (1H, dd, J = 8.5, 4.5 Hz), 4.25 (1H, dd, J = 8.5, 7.5 Hz); ^{13}C NMR (125 MHz) δ -5.44 & -5.39 (each u, due to rotamers), 17.10 (u), 18.27 (s), 25.91 (u), 31.00 (d), 32.78 (d), 34.19 (d), 34.63 (u), 53.74 (u), 60.21 (d), 63.51 (u), 65.57 (d), 156.11 (s); MS 314 (M^++1), 313 (M^+), 298 (M^+-15), 257 (100), 256 (M^+-57); HRMS Calcd. for $C_{16}H_{31}NO_3Si$: 313.2071, Found 313.2065; $[\alpha]^{26}_D$ -10.9 (*c* 1.7, $CHCl_3$).

Methyl (2*R*, 3*R*, 6*S*)-6-{2-(*t*-Butyldimethylsiloxy)ethyl}-1-(methoxycarbonyl)-3-methylpiperidine-2-prop-α-enoate (6): Dimethyl sulfoxide (0.18 mL, 2.5 mmol) was added to a stirred solution of $(COCl)_2$ (0.11 mL, 1.27 mmol) in CH_2Cl_2 (5 mL) at -78 ℃, and the mixture was stirred for 5 min. The alcohol (+)-**4** (R^1 = Me, R = TBS, 291 mg, 0.84 mmol) in CH_2Cl_2 (3 mL) was added at -78 ℃, and the reaction mixture was stirred at -78 ℃ for 30 min, and Et_3N (0.53 mL, 3.8 mmol) was added at -78 ℃. The resulting mixture was warmed to 0 ℃ for 1 h, and H_2O (30 mL) and Et_2O (50 mL) was added to the mixture. The organic layer was separated, and the aqueous layer was extracted with Et_2O (10 mL x 4). The organic rayer and extracts were combined, dried over $MgSO_4$ and evaporated to give the aldehyde as a pale yellow oil, which was used directly in the next step. The phosphono ester $(EtO)_2P(O)CH_2CO_2Me$ (0.23 mL, 1.27 mmol) was added to a stirred suspension of NaH (44 mg, 1.1 mmol) in THF (5 mL) at 0 ℃, and the resulting mixture was stirred at 0 ℃ for 10 min. The above aldehyde in THF (3 mL) was added at 0 ℃, and the mixture was stirred at room temperature for 2 h. The reaction was quenched with H_2O (5 mL), and the aqueous layer was extracted with CH_2Cl_2 (15 mL x 4). The organic extracts were combined, dried over $MgSO_4$ and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (20 g, hexane:acetone=50:1~40:1) to afford **6** (303 mg, 90% in 2 steps, a 4 : 1 mixture of *E* and *Z* stereoisomers) as a colorless oil.

IR (neat) 2953, 2857, 1728, 1698, 1654, 1443, 1403, 1360, 1302, 1258, 1194, 1150, 1100, 1041, 1007, 992, 837, 775 cm^{-1}; ^1H NMR (500 MHz) δ 0.01 & 0.02 (each 2.4H, each s), 0.03 & 0.04 (each 0.6H, each s), 0.87 (7.2H, s), 0.88 (1.8H, s), 1.06 (2.4H, d, J = 7.0 Hz), 1.10 (0.6H, d, J = 7.0 Hz), 1.22-1.33 (1H, m), 1.41-1.49 (1H, m), 1.64-2.03 (5H, br m), 3.57-3.66 (2.6H, m, including at δ 3.63, 0.6H, s), 3.68 (2.4H, s), 3.71 (2.4H, s), 3.72 (0.6H, s), 4.26-4.28 (0.2H, m), 4.30-4.34 (0.8H, m), 4.54 (0.8H, br), 5.39 (0.2H, d-like, J = 8.8 Hz), 5.75 (0.2H, dd, J = 11.9, 1.8 Hz), 5.92 (0.8H, dd, J = 15.9, 1.8 Hz), 6.37 (0.2H, dd, J = 11.9, 9.0 Hz), 6.95 (0.8H, dd, J = 15.9, 6.0 Hz); MS 400 (M^++1), 399 (M^+), 342 (M^+-57), 89 (100); HRMS Calcd. for $C_{20}H_{37}NO_5Si$: 399.2439, Found 399.2460.

Methyl (2*S*, 3*R*, 6*S*)-(+)-6-{2-(*t*-Butyldimethylsiloxy)ethyl}-2-{3-(hydroxy)propyl}-3-methylpiperidine-1-carboxylate (7): To a solution of **6** (65 mg, 0.16 mmol) in MeOH (2 mL) was added 5% Pd/C (10 mg), and the resulting suspension was hydrogenated at 4 atm for 6 h. The catalyst was removed through a celite pad and washed with CH_2Cl_2 (10 mL x 5). The organic layer and washings were combined and evaporated to give the reduced ester, which was essentially pure and used directly in the next step. The analytical sample was obtained by chromatography on SiO_2 (5 g, hexane:acetone=40:1) as a colorless oil.

IR (neat) 2953, 2857, 1741, 1694, 1443, 1411, 1361, 1310, 1256, 1191, 1170, 1100, 836, 775 cm^{-1}; ^1H NMR (500 MHz) δ 0.02 & 0.03 (each 3H, each s), 0.87 (9H, s), 0.99 (3H, d, J = 7.0 Hz), 1.14-1.19 (1H, m), 1.20 (1H, br), 1.70-1.78 (3H, m), 1.80-1.89 (4H, m), 2.26-2.37 (2H, m), 3.64 & 3.65 (each 3H, each s),

3.86 (1H, br), 4.24 (1H, br); ^{13}C NMR (125 MHz) δ -5.47 & -5.46 (each u, due to rotamers), 18.20 (s), 19.14 (u), 21.58 (d), 22.14 (d), 25.83 (u), 30.97 (u), 31.11 (d), 31.59 (d), 38.18 (d), 48.34 (u), 51.51 (u), 52.43 (u), 55.99 (u), 60.89 (d), 157.39 (s), 173.73 & 173.74 (each s); MS 402 (M^++1), 401 (M^+), 344 (M^+-57), 89 (100); HRMS Calcd. for $C_{20}H_{39}NO_5Si$: 401.2595, Found 401.2582; $[\alpha]^{26}_D$ +6.8 (*c* 3.3, $CHCl_3$).

Super-Hydride (0.36 mL, 0.36 mmol) was added to a stirred solution of the above ester in THF (2 mL) at 0 ℃, and the resulting mixture was stirred at room temperature for 2 h. The reaction was quenched with H_2O (2 mL), and the aqueous layer was extracted with CH_2Cl_2 (10 mL x 6). The extracts were combined, dried over $MgSO_4$ and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (10 g, hexane:acetone=10:1) to afford (+)-**7** (56 mg, 91% in 2 steps) as a colorless oil.

IR (neat) 3446, 2953, 2858, 1694, 1682, 1446, 1410, 1361, 1312, 1256, 1191, 1102, 1007, 925, 836, 775, 734 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.03 (6H, s), 0.87 (9H, s), 1.00 (3H, d, *J* = 7.0 Hz), 1.18 (1H, quint-like, *J* = 4.8 Hz), 1.20 (1H, br), 1.45-1.66 (3H, br m), 1.73-1.80 (3H, m), 1.81-1.86 (2H, m), 1.99 (1H, br), 2.55-2.80 (1H, br, exchangeable with D_2O), 3.55-3.64 (7H, br, including δ 3.66, 3H, s), 3.80-3.95 (1H, br), 4.20 (1H, br); ^{13}C NMR (125 MHz) δ -5.46 & -5.42 (each u, due to rotamers), 18.21 (s), 19.22 (u), 21.10 (d), 21.74 (d), 25.83 (u), 29.59 (d), 30.23 (u), 32.30 (d), 38.07 (d), 47.98 (u), 52.49 (u), 56.09 (u), 60.96 (d), 62.27 (d), 157.67 (s); MS 374 (M^++1), 373 (M^+), 316 (M^+-57), 182 (100); HRMS Calcd. for $C_{19}H_{39}NO_4Si$: 373.2646, Found 373.2622; $[\alpha]^{26}_D$ +21.0 (*c* 2.8, $CHCl_3$).

Methyl (2*S*, 3*R*, 6*S*)-(+)-6-{2-(*t*-Butyldimethylsiloxy)ethyl}-2-{3-(methoxymethoxy)propyl}-3-methylpiperidine-1-carboxylate (8): Methoxymethyl chloride (21 μL, 0.28 mmol) and Hünig base (53 μL, 0.30 mmol) were added to a stirred solution of (+)-**7** (54 mg, 0.145 mmol) in CH_2Cl_2 (2 mL) at 0 ℃, and the mixture was stirred at room temperature for 20 h. Direct chromatography of the reaction mixture on SiO_2 (10 g, hexane:acetone=30:1) afforded the MOM ether (56 mg, 93%) as a colorless oil.

IR (neat) 2952, 2858, 1695, 1443, 1360, 1309, 1255, 1149, 1103, 1044, 837, 775 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.027 & 0.029 (each 3H, each s), 0.87 (9H, s), 0.99 (3H, d, *J* = 7.0 Hz), 1.16 (1H, quint-like, *J* = 5.1 Hz), 1.19 (1H, br), 1.52-1.66 (3H, m), 1.76 (3H, q-like, *J* = 6.9 Hz), 1.81-1.86 (3H, m), 3.34 (3H, s), 3.46-3.56 (1H, m), 3.57-3.67 (5H, br, including δ 3.65, 3H, s), 3.75-3.94 (1H, br), 4.21 (1H, br), 4.59 (2H, s); ^{13}C NMR (125 MHz) δ -5.46 (u), 18.22 (s), 19.24 (u), 21.52 (d), 22.24 (d), 25.86 (u), 27.46 (d), 30.51 (u), 32.87 (d), 38.26 (d), 52.38 (u), 55.06 (u), 56.61 (u), 67.56 (d), 96.32 (d), 157.39 (s); MS 418 (M^++1), 417 (M^+), 360 (M^+-57), 182 (100); HRMS Calcd. for $C_{21}H_{43}NO_5Si$: 417.2908, Found 417.2926; $[\alpha]^{26}_D$ +9.4 (*c* 2.6, $CHCl_3$).

Methyl (2*S*,3*R*, 6*S*)-(-)-6-(2-Hydroxyethyl)-2-{3-(methoxymethoxy)propyl}-3-methylpiperidine-1-carboxylate (9): Tetrabutylammonium fluoride (1M in THF, 0.84 mmol, 0.84 mmol) was added to a stirred solution of (+)-**8** (335 mg, 0.80 mmol) in THF (8 mL) at 0 ℃, and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with satd. NH_4Cl (2 mL), and the aqueous layer was extracted with CH_2Cl_2 (15 mL x 4). The extracts were combined, dried over $MgSO_4$ and evaporated to give a colorless oil, which was chromatographed on SiO_2 (15 g, hexane:acetone=5:1) to afford (-)-**9** (236 mg, 97%) as a colorless oil.

IR (neat) 3460, 2948, 2872, 1668, 1447, 1410, 1362, 1308, 1191, 1147, 1108, 1040, 919, 773 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.00 (3H, d, *J* = 7.0 Hz), 1.22 (1H, dq-like, *J* = 9.5, 3.9 Hz), 1.30-1.36 (1H, m), 1.50-1.68 (5H, br m), 1.74-1.86 (2H, m), 1.89 (1H, br), 1.99 (1H, br), 3.33 (3H, s), 3.48-3.50 (3H, m), 3.57 (1H, br), 3.69 (3H, s), 3.80 (1H, br, exchangeable with D_2O), 3.97 (1H, br), 4.38 (1H, br), 4.59 (2H, s); ^{13}C

NMR (125 MHz) δ 19.16 (u), 21.48 (d), 23.73 (d), 27.55 (d), 30.33 (u), 32.67 (d), 38.50 (d), 46.91 (u), 52.98 (u), 55.09 (u), 58.87 (d), 67.33 (d), 96.34 (d), 156.97 (s); MS 304 (M^++1), 303 (M^+), 226 (100); HRMS Calcd. for $C_{15}H_{29}NO_5$: 303.3204, Found 303.3219; $[\alpha]^{26}_D$ -13.8 (*c* 7.0, $CHCl_3$).

Methyl (2*S*, 3*R*, 6*S*)-(-)-6-(2-Iodoethyl)-2-{3-(methoxymethoxy)propyl}-3-methylpiperidine-1-carboxylate (10): Methanesulfonyl chloride (0.1 mL, 1.3 mmol) and Et_3N (0.24 mL, 1.73 mmol) were added to a stirred solution of (-)-**9** (140 mg, 0.46 mmol) in CH_2Cl_2 (4 mL) at 0 ℃, and the mixture was stirred at 0 ℃ for 30 min. Water (10 mL) was added to the mixture, and the aqueous layer was extracted with CH_2Cl_2 (10 mL x 4). The extracts were combined, dried over $MgSO_4$ and evaporated to give a pale yellow oil, which was used directly in the next step. Sodium iodide (350 mg, 2.33 mmol) was added to a stirred solution of the above oil in acetone (10 mL), and the resulting mixture was stirred at 50 ℃ for 1 h. After evaporation, the residue was diluted with 10% $Na_2S_2O_3$ in satd. $NaHCO_3$ (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (10 mL x 4). The extracts were combined, dried over $MgSO_4$ and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (15 g, hexane:acetone=30:1) to afford (-)-**10** (162 mg, 85% in 2 steps) as a pale yellow oil.

IR (neat) 2947, 2871 , 1694, 1443, 1409, 1360, 1295, 1188, 1148, 1108, 1040 cm^{-1}; ^1H NMR (500 MHz) δ 1.00 (3H, d, *J* = 6.9 Hz), 1.17-1.22 (1H, m), 1.28-1.35 (1H, br m), 1.51-1.66 (3H, br m), 1.71 (1H, br), 1.74-1.93 (3H, m), 1.98-2.06 (1H, m), 2.16-2.23 (1H, m), 3.07 (1H, td, *J* = 9.1, 6.5 Hz), 3.16 (1H, td, *J* = 9.1, 5.5 Hz), 3.35 (3H, s), 3.49-3.56 (2H, m), 3.68 (3H, s), 3.78-3.94 (1H, br), 4.19 (1H, br), 4.61 (2H, s); ^{13}C NMR (125 MHz) δ 2.13 (d), 19.29 (u), 21.70 (d), 22.23 (d), 27.46 (d), 30.59 (u), 32.92 (d), 39.92 (d), 51.88 (u), 52.59 (u), 55.17 (u), 56.71 (u), 67.40 (d), 96.34 (d), 157.54 (s); $[\alpha]^{26}_D$ -22.0 (*c* 1.4, $CHCl_3$).

Methyl (2*S*, 3*R*, 6*R*)-(-)-2-{3-(Methoxymethoxy)propyl}-3-methyl-6-(pent-4-enyl)piperidine-1-carboxylate (11): Allylmagnesium chloride (2M in THF, 0.52 mL, 1.05 mmol) was added to a stirred suspension of CuI (100 mg, 0.53 mmol) in THF (5 mL) at -40 ℃, and the suspension was stirred at -40 ℃ for 15 min. The iodide (-)-**10** (87 mg, 0.21 mmol) in THF (5 mL) was added to the suspension at -40 ℃, and the mixture was stirred at -30 ℃ for 2 h. The reaction was quenched with satd. NH_4Cl (5 mL), and the aqueous layer was extracted with CH_2Cl_2 (15 mL x 3). The extracts were combined, dried over $MgSO_4$ and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (15 g, hexane:acetone=30:1) to afford (-)-**11** (51 mg, 74%) as a pale yellow oil and the starting iodide (11 mg, 13%) as a pale yellow oil.

IR (neat) 3071, 2940, 1694, 1639, 1443, 1411, 1362, 1308, 1190, 1147, 1108, 1041, 918 cm^{-1}; ^1H NMR (500 MHz) δ 1.00 (3H, d, *J* = 7.0 Hz), 1.12-1.19 (1H, m), 1.30-1.44 (3H, m), 1.45-1.63 (5H, br m), 1.71-1.89 (4H, m), 1.98-2.09 (2H, m), 3.34 (3H, s), 3.47-3.55 (2H, m), 3.66 (3H, s), 3.72-3.92 (1H, br), 4.03-4.13 (1H, br), 4.60 (2H, s), 4.93 (1H, dq-like, *J* = 9.9, 1.0 Hz), 4.98 (1H, dq, *J* = 16.1, 1.7 Hz), 5.78 (1H, ddt, *J* = 16.1, 9.9, 6.5 Hz); ^{13}C NMR (125 MHz) δ 19.32 (u), 21.67 (d), 22.18 (d), 26.46 (d), 27.48 (d), 30.72 (u), 32.94 (d), 33.61 (d), 34.83 (d), 50.76 (u), 52.38 (u), 55.07 (u), 56.66 (u), 67.57 (d), 96.32 (d), 114.48 (d), 138.68 (u), 157.57 (s); MS 328 (M^++1), 327 (M^+), 154 (100); HRMS Calcd. for $C_{18}H_{33}NO_4$: 327.2408, Found 327.2441; $[\alpha]^{26}_D$ -10.9 (*c* 0.95, $CHCl_3$).

(2*S*,3*R*,6*R*)-(-)-2-(3-Hydroxypropyl)-3-methyl-6-(pent-4-enyl)piperidine (12): To a stirred solution of *n*-PrSH (0.11 mL, 1.22 mmol) in HMPA (0.6 mL) was added *n*-BuLi (0.74 mL, 1.16 mmol) at 0 ℃, and the mixture was stirred at 0 ℃ for 30 min. The carbamate (-)-**11** (40 mg, 0.122 mmol) in THF (0.6 mL) was added to the mixture at 0 ℃, and the mixture was stirred at room temperature for 24 h. The reaction was quenched with 33% NH_3 in H_2O (5 mL), and the aqueous layer was extracted with Et_2O (10 mL x 8). The

extracts were combined, dried over K_2CO_3 and evaporated to give a pale yellow oil, which was used directly in the next step. A catalytic amount of c. HCl was added to a stirred solution of the above oil in MeOH (1 mL), and the mixture was refluxed for 1 h. After evaporation of the solvent, the residue was washed with Et_2O (2 mL x 3). Aueous ammonia was added, and the aqueous layer was extracted with $CHCl_3$ (10 mL x 8). The extracts were combined, dried over K_2CO_3 and evaporated to give a colorless oil, which was chromatographed on Al_2O_3 (20 g, $CHCl_3$:MeOH=100:1) to afford (-)-**12** (18 mg, 65% in 2 steps) as a colorless oil.

IR (neat) 3384, 3075, 2925, 2851, 1639, 1458, 1376, 1339, 1287, 1201, 1118, 1060, 990, 909 cm^{-1}; ^1H NMR (500 MHz) δ 0.85 (3H, d, J = 6.5 Hz), 1.02-1.13 (2H, m), 1.31-1.47 (7H, m), 1.52-1.82 (6H, br m), 2.01-2.07 (2H, m), 2.22 (1H, ddd, J = 10.0, 6.9, 2.5 Hz), 2.48-2.54 (1H, m), 3.52 (1H, ddd, J = 11.2, 7.8, 2.0 Hz), 3.59 (1H, ddd, J = 11.2, 6.9, 2.9 Hz), 4.94 (1H, dm, J = 10.8 Hz), 4.99 (1H, dq-like, J = 17.8, 1.8 Hz), 5.79 (1H, ddt, J = 17.8, 10.8, 7.0 Hz); ^{13}C NMR (125 MHz) δ 18.53 (u), 25.19 (d), 29.25 (d), 32.63 (d), 33.29 (d), 33.79 (d), 33.83 (d), 34.56 (u), 36.42 (d), 56.61 (u), 62.15 (u), 62.87 (d), 114.64 (d), 138.64 (u); MS 226 (M^++1), 225 (M^+), 224 (M^+-1), 182 (M^+-43), 166 (M^+-59), 156 (M^+-69), 138 (M^+-87), 71 (100); $[\alpha]^{26}_D$ -16.4 (*c* 0.75, $CHCl_3$), lit.[9] $[\alpha]^{25}_D$ -16.5 (*c* 0.85, $CHCl_3$).

Methyl (2*S*, 3*R*, 6*R*)-(-)-6-(Hept-6-enyl)-2-{3-(methoxymethoxy)propyl}-3-methylpiperidine-1-carboxylate (13): 4-Pentenylmagnesium bromide (prepared from 4-pentenylbromide and magnesium in THF, 1.82 mmol) was added to a stirred suspension of CuI (173 mg, 0.91 mmol) in THF (6 mL) at - 40 ℃, and the resulting suspension was stirred at -40 ℃ for 15 min. The iodide (-)-**10** (94 mg, 0.23 mmol) in THF (5 mL) was added to the suspension at - 40 ℃, and the reaction mixture was stirred at -30 ℃ for 2 h. The reaction was quenched with satd. NH_4Cl (5 mL), and the aqueous layer was extracted with CH_2Cl_2 (20 mL x 3). The extracts were combined, dried over $MgSO_4$ and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (25 g, hexane:acetone=50:1) to afford (-)-**13** (66 mg, 82%) as a pale yellow oil.

IR (neat) 3074, 2933, 2859, 1693, 1639, 1443, 1410, 1361, 1310, 1189, 1147, 1108, 1042, 918 cm^{-1}; ^1H NMR (500 MHz) δ 1.00 (3H, d, J = 7.0 Hz), 1.12-1.18 (1H, m), 1.20-1.40 (7H, br m), 1.46-1.63 (5H, br m), 1.70-1.88 (4H, br m), 2.02 (2H, q-like, J = 7.4 Hz), 3.34 (3H, s), 3.47-3.55 (2H, m), 3.66 (3H, s), 3.72-3.92 (1H, br), 3.93-4.15 (1H, br), 4.60 (2H, s), 4.92 (1H, dq, J = 10.0, 1.0 Hz), 4.98 (1H, dq-like, J = 16.8, 2.0 Hz), 5.79 (1H, ddt, J = 16.8, 10.0, 6.7 Hz); ^{13}C NMR (75 MHz) δ 19.32 (u), 21.68 (d), 22.08 (d), 27.03 (d), 27.45 (d), 28.79 (d), 28.98 (d), 30.73 (u), 32.93 (d), 33.69 (d), 35.28 (d), 50.87 (u), 52.29 (u), 55.01 (u), 56.63 (u), 67.55 (d), 96.27 (d), 114.15 (d), 138.98 (u), 157.51 (s); MS 356 (M^++1), 355 (M^+), 253 (100); HRMS Calcd. for $C_{20}H_{37}NO_4$: 355.2721, Found 355.2738; $[\alpha]^{26}_D$ -6.5 (*c* 1.02, $CHCl_3$).

(5*R*,8*R*,9*S*)-(-)-Indolizidine 235B': To a stirred solution of *n*-PrSH (0.27 mL, 2.98 mmol) in HMPA (1.5 mL) was added *n*-BuLi (1.8 mL, 2.84 mmol) at 0 ℃, and the mixture was stirred at 0 ℃ for 30 min. The carbamate (-)-**13** (106 mg, 0.3 mmol) in THF (2 mL) was added at 0 ℃, and the mixture was stirred at room temperature for 36 h. The reaction was quenched with 33% NH_3 in H_2O (5 mL), and the aqueous layer was extracted with Et_2O (10 mL x 8). The extracts were combined, dried over K_2CO_3 and evaporated to give a pale yellow oil, which was used directly in the next step. A catalytic amount of c. HCl was added to a stirred solution of the above oil in MeOH (2 mL), and the mixture was refluxed for 1 h. After evaporation, the residue was washed with Et_2O (2 mL x 3). Aqueous ammonia was added, and the aqueous layer was extracted with $CHCl_3$ (10 mL x 8). The extracts were combined, dried over K_2CO_3 and evaporated to give a colorless oil. Carbon tetrabromide (124 mg, 0.37 mmol) and Ph_3P (118 mg, 0.45 mmol) were added to a stirred solution of the above oil in CH_2Cl_2 (1 mL) at 0 ℃, and the mixture was stirred at 0 ℃ for 30 min. Triethylamine (0.66

mL, 4.78 mmol) was added at 0 ℃, and the mixture was stirred for 10 min and evaporated. The residue was extracted with *n*-pentane (10 mL x 2), and the pentane layers were combined and evaporated to give a pale yellow solid, which was chromatographed on Al_2O_3 (20 g, hexane:$CHCl_3$=3:1) to afford (-)-indolizidine 235B' (44 mg, 63% in 3 steps) as a colorless oil.

IR (neat) 3075, 2926, 2856, 2777, 2700, 1639, 908 cm^{-1}; ^1H NMR (500 MHz) δ 0.85 (3H, d, J = 6.5 Hz), 0.94 (1H, m), 1.16-1.50 (10H, br m), 1.58-1.77 (5H, br m), 1.80-1.97 (4H, br m), 2.03 (2H, q-like, J = 7.0 Hz), 3.25 (1H, td, J = 9.0, 2.0 Hz), 4.92 (1H, dm, J = 10.0 Hz), 4.98 (1H, dm, J = 17.0 Hz), 5.80 (1H, ddt, J = 17.0, 10.0, 6.9 Hz); ^{13}C NMR (125 MHz) δ 18.88 (u), 20.33 (d), 25.66 (d), 28.87 (d), 29.04 (d), 29.53 (d), 31.22 (d), 33.68 (d), 33.74 (d), 34.56 (d), 36.56 (u), 51.83 (u), 63.49 (u), 71.31 (u), 114.16 (d), 139.14 (u); MS 236 (M^++1), 235 (M^+), 234 (M^+-1), 194 (M^+-41), 178 (M^+-57), 164 (M^+-71), 139 (M^+-96), 138 (M^+-97), 96 (100); $[\alpha]^{26}_D$ -98.8 (*c* 0.89, MeOH), lit.[10] $[\alpha]^{25}_D$ -61 (*c* 0.5, MeOH).

Hydrochloride: mp: 132~134 ℃; IR (KBr) 3080, 2956, 2920, 2864, 2597, 2548, 2435, 1637, 1471, 1456, 1388, 1338, 1299, 1271, 1214, 1143, 1067, 1049, 1004, 974, 902, 807, 731 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 1.02 (3H, d, J = 10.0 Hz), 1.20-2.18 (19H, br m), 2.24-2.41 (1H, br), 2.84 (1H, m), 3.04 (2H, m), 3.73 (1H, m), 4.84-5.02 (2H, m), 5.80 (1H, m); ^{13}C NMR (75 MHz, CD_3OD) δ 19.16 (u), 20.88 (d), 26.84 (d), 29.13 (d), 30.59 (d), 30.69 (d), 30.91 (d), 33.38 (d), 33.82 (d), 35.47 (d), 36.64 & 36.72 (each u), 52.84 (u), 66.25 (u), 74.42 (u), 115.75 (d), 140.64 (u); MS 271 (M^+), 139 (100); HRMS Calcd. for $C_{16}H_{30}NCl$: 271.2067, Found 271.2102; $[\alpha]^{26}_D$ -50.0 (*c* 1.04, MeOH).

Methyl (2*R*, 3*R*, 6*S*)-(+)-3-Butyl-6-{2-(*t*-butyldimethylsiloxy)ethyl}-2-(hydroxymethyl)-piperidine-1-carboxylate (14): To a stirred solution of (+)-**3** (R^1 = *n*-Bu, R = TBS, 300 mg, 0.72 mmol) in THF (10 mL) was added Super-Hydride (1.6 mL, 1.59 mmol) at 0 ℃, and the mixture was stirred for 1 h at 0 ℃. The reaction was quenched with ice-water, and the aqueous layer was extracted with CH_2Cl_2 (10 mL x 5). The extracts were combined, dried over $MgSO_4$ and evaporated to give a colorless oil, which was chromatographed on SiO_2 (15 g, hexane:acetone=12:1~10:1) to afford (+)-**14** (266 mg, 95%) as a colorless oil.

IR (neat) 3446, 2954, 2857, 1694, 1674, 1447, 1362, 1316, 1255, 1101, 836, 775 cm^{-1}; ^1H NMR (500 MHz) δ 0.012 & 0.025 (each 3H, each s), 0.86 (12H, br s), 1.18-1.86 (14H, br m), 3.51-3.67 (7H, br m, including δ 3.66, 3H, s), 4.11 (1H, br), 4.23 (1H, br); ^{13}C NMR (75 MHz) δ -5.59 & -5.50 (each u, due to rotamers), 13.99 (u), 18.26 (s), 20.64 (d), 22.64 (d), 23.75 (d), 25.84 (u), 29.47 (d), 32.85 (d), 33.43 (u), 38.55 (d), 48.87 (u), 52.58 (u), 57.23 (u), 61.36 (d), 65.27 (d), 158.32 (s); MS 388 (M^++1), 387 (M^+), 330 (100); HRMS Calcd. for $C_{20}H_{41}NO_4Si$: 387.2802, Found 387.2844; $[\alpha]^{26}_D$ +16.3 (*c* 4.45, $CHCl_3$).

Ethyl (2*R*, 3*R*, 6*S*)-3-Butyl-6-{2-(*t*-butyldimethylsiloxy)ethyl}-1-(methoxycarbonyl)-piperidine-2-prop-α-enoate (15): To a stirred solution of $(COCl)_2$ (0.16 mL, 1.94 mmol) in CH_2Cl_2 (2 mL) was added DMSO (0.27 mL, 3.88 mmol) at -78 ℃, and the mixture was stirred for 5 min at -78 ℃. To the mixture was added (+)-**14** (375 mg, 0.97 mmol) in CH_2Cl_2 (2 mL) at -78 ℃, and the mixture was stirred at -78 ℃ for 30 min. Triethylamine (0.8 mL, 5.81 mmol) was added, and the temperature was gradually raised to -20 ℃. The reaction was quenched with H_2O, and the aqueous layer was extracted with Et_2O (15 mL x 4). The extracts were combined, dried over $MgSO_4$ and evaporated to give the corresponding aldehyde as a pale yellow oil, which was used directly in the next step. To a stirred solution of $(EtO)_2P(O)CH_2CO_2Et$ (0.25 mL, 1.26 mmol) in THF (5 mL) was added NaH (46 mg, 1.16 mmol) at 0 ℃, and the resulting mixture was stirred at 0 °C for 30 min. The aldehyde was added in THF (4 mL) at 0 ℃, and the mixture was stirred at room temperature for 6 h. The reaction was quenched with H_2O, and the aqueous layer was extracted with CH_2Cl_2

(10 mL x 6). The extracts were combined, dried over $MgSO_4$ and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (20 g, hexane:acetone = 50:1) to afford **15** (357 mg, 81%, a 5:1 mixture of *E*- and *Z*-isomers) as a colorless oil.

^1H NMR (500 MHz) δ 0.011 & 0.018 (each 3H, each s), 0.88 (12H, br s), 1.26-1.91 (16H, br m, including δ 1.28, 3H, t, J = 7.0 Hz), 3.60 (2H, m), 3.64 & 3.69 (each 3H, each s), 4.18 (2H, q, J = 7.0 Hz), 4.27 (1H, br m), 4.68 (1H, br), 5.74 (0.17H, dd, J = 11.6, 1.2 Hz), 5.91 (0.83H, dd, J = 16.0, 1.5 Hz), 6.38 (0.17H, dd, J = 11.6, 9.0 Hz), 6.97 (0.83H, dd, J = 16.0, 6.0 Hz).

Methyl (2*S*,3*R*,6*S*)-(+)-3-Butyl-6-{2-(*t*-butyldimethylsiloxy)ethyl}-2-(3-hydroxypropyl)piperidine-1-carboxylate (16): To a solution of **15** (600 mg, 1.32 mmol) in EtOAc (10 mL) was added 5% Rh/C (100 mg), and the resulting suspension was hydrogenated at 4 atm for 8 h. The catalyst was removed by filtration, and the filtrate was evaporated to give a colorless oil. To a stirred solution of the above oil in THF (10 mL) was added Super-Hydride (2.7 mL, 2.7 mmol) at 0 ℃, and the resulting mixture was stirred at 0 ℃ for 1 h. The reaction was quenched with ice-water, and the aqueous layer was extracted with CH_2Cl_2 (15 mL x 6). The extracts were combined, dried over $MgSO_4$ and evaporated to give a colorless oil, which was chromatographed on SiO_2 (30 g, hexane:acetone=12:1~10:1) to afford (+)-**16** (472 mg, 86%) as a colorless oil.

IR (neat) 3447, 2953, 2930, 2858, 1675, 1448, 1106, 836, 755 cm^{-1}; ^1H NMR (500 MHz) δ 0.018 & 0.02 (each 3H, each s), 0.87 (12H, br s), 1.18-1.82 (17H, br m), 2.75 (1H, br), 3.57-3.70 (7H, br m, including δ 3.65, 3H, s), 4.00 (1H, br), 4.17 (1H, br); ^{13}C NMR (75 MHz) δ -5.45 & -5.42 (each u, due to rotamers), 14.02 (u), 18.21 (s), 19.53 (d), 22.32 (d), 22.72 (d), 25.84 (u), 29.52 (d), 29.74 (d), 32.35 (d), 32.55 (d), 35.86 (u), 38.15 (d), 48.13 (u), 52.45 (u), 54.40 (u), 60.86 (d), 62.20 (d), 157.57 (s); MS 416 (M^++1), 415 (M^+), 84 (100); HRMS Calcd. for $C_{22}H_{45}NO_4Si$: 415.3115, Found 415.3149; $[\alpha]^{26}_D$ +23.0 (*c* 4.59, $CHCl_3$).

Methyl (2*S*,3*R*,6*S*)-(+)-3-Butyl-6-{2-(*t*-butyldimethylsiloxy)ethyl}-2-{3-(methoxymethoxy)-propyl}piperidine-1-carboxylate: To a stirred solution of (+)-**16** (370 mg, 0.89 mmol) in CH_2Cl_2 (5 mL) were added MOMCl (0.14 mL, 1.78 mmol) and Hünig base (0.34 mL, 1.96 mmol), and the mixture was stirred at room temperature for 14 h. The mixture was evaporated, and the residue was chromatographed on SiO_2 (20 g, hexane:acetone=40:1~30:1) to afford the MOM ether (353 mg, 86%) as a colorless oil.

IR (neat) 2930, 2858, 1696, 1443, 1362, 1315, 1255, 1045, 837, 775 cm^{-1}; ^1H NMR (500 MHz) δ 0.013 (6H, s), 0.86 (12H, br s), 1.18-1.80 (17H, br m), 3.32 (3H, s), 3.45-3.66 (7H, br m, including δ 3.64, 3H, s), 3.85 & 4.00 (1H, br), 4.15 (1H, br), 4.58 (2H, s); ^{13}C NMR (75 MHz) δ -5.44 (u), 14.02 (u), 18.19 (s), 20.05 (d), 22.72 (d), 25.84 (u), 27.42 (d), 29.70 (d), 32.63 (d), 32.66 (d), 32.96 (d), 36.21 (u), 38.34 (d), 48.23 (u), 52.31 (u), 54.95 & 55.03 (each u, due to rotamers), 60.93 (d), 67.53 (d), 96.30 (d), 157.27 (s); MS 460 (M^++1), 459 (M^+), 402 (100); HRMS Calcd. for $C_{24}H_{49}NO_5Si$: 459.3396, Found 459.3396; $[\alpha]^{26}_D$ +11.1 (*c* 4.04, $CHCl_3$).

Methyl (2*S*,3*R*,6*S*)-(-)-3-Butyl-6-(2-hydroxyethyl)-2-{3-(methoxymethoxy)propyl}piperidine-1-carboxylate (17): To a stirred solution of the silyl ether from the previous step (346 mg, 0.75 mmol) in THF was added TBAF (0.83 mL, 0.83 mmol) at 0 ℃, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with satd. NH_4Cl, and the aqueous layer was extracted with CH_2Cl_2 (10 mL x 6). The extracts were combined, dried and evaporated to give a colorless oil, which was chromatographed on SiO_2 (20 g, hexane:acetone=6:1~5:1) to afford (-)-**17** (231 mg, 89%) as a colorless oil.

IR (neat) 3448, 2932, 1670, 1448, 1364, 1111, 1045 cm^{-1}; ^1H NMR (500 MHz) δ 0.89 (3H, t, J = 7.0 Hz), 1.20-1.98 (16H, br m), 3.35 (3H, s), 3.51 (2H, br), 3.59 (1H, br m), 3.71 (3H, s), 3.91 (1H, t-like, J = 6.2

Hz), 4.00 (1H, dd-like, J = 10.0, 3.5 Hz), 4.38 (1H, br m), 4.59 (2H, s); ^{13}C NMR (75 MHz) δ 13.95 (u), 19.94 (d), 22.61 (d), 24.19 (d), 27.45 (d), 29.56 (d), 32.35 (d), 32.61 (d), 35.95 (u), 38.51 (d), 47.06 (u), 52.92 (u), 55.01 (u), 55.07 (u), 58.82 (d), 67.23 (d), 96.27 (d), 158.72 (s); MS 346 (M^++1), 345 (M^+); HRMS Calcd. for $C_{18}H_{35}NO_5$: 345.2513, Found 345.2501; $[\alpha]^{26}_D$ -3.4 (*c* 3.24, $CHCl_3$).

Methyl (2*S*,3*R*,6*S*)-(+)-3-Butyl-2-{3-(methoxymethoxy)propyl}-6-(prop-2-enyl)piperidine-1-carboxylate (18): To a stirred solution of $(COCl)_2$ (0.11 mL, 1.33 mmol) in CH_2Cl_2 (2 mL) was added DMSO (0.19 mL, 2.67 mmol) at -78 ℃, and the mixture was stirred for 5 min at -78 ℃. To the mixture was added (-)-**17** (230 mg, 0.67 mmol) in CH_2Cl_2 (2 mL) at -78 ℃, and the stirring was continued at -78 ℃ for 30 min. Triethylamine (0.55 mL, 4.0 mmol) was added , and the temperature was gradually raised to -20 ℃. The reaction was quenched with H_2O, and the aqueous layer was extracted with Et_2O (15 mL x 4). The extracts were combined, dried over $MgSO_4$ and evaporated to give the corresponding aldehyde as a pale yellow oil, which was used directly in the next step. To a stirred suspension of $CH_3P^+Ph_3Br^-$ (1.2 g, 3.36 mmol) in THF (10 mL) was added *n*-BuLi (1.8 mL, 3.0 mmol) at 0 ℃, and the resulting mixture was stirred at 0 ℃ for 30 min. The above aldehyde in THF (4 mL) was added at 0 ℃, and the resulting mixture was stirred at room temperature for 6 h. The reaction was quenched with H_2O, and the aqueous layer was extracted with Et_2O (10 mL x 6). The extracts were combined, dried over $MgSO_4$ and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (25 g, hexane:acetone=30:1) to afford (+)-**18** (184 mg, 81% in 2 steps) as a pale yellow oil.

IR (neat) 3076, 2930, 2871, 1694, 1640, 1444, 1361, 1321, 1296, 1149, 1110, 1044, 919 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.86 (3H, t, J = 7.0 Hz), 1.20-1.81 (15H, br m), 2.23 (1H, m), 2.34 (1H, br), 3.33 (3H, s), 3.50 (2H, m), 3.66 (3H, s), 3.80-4.25 (2H, br), 4.59 (2H, s), 5.00 (2H, m), 5.72 (1H, br); ^{13}C NMR (75 MHz) δ 13.99 (u), 19.86 (d), 21.68 (d), 22.70 (d), 27.44 (d), 29.68 (d), 32.63 (d), 33.07 (d), 36.15 (u), 39.71 (d), 50.61 (u), 52.34 (u), 54.95 (u), 55.03 (u), 67.55 (d), 96.33 (d), 116.69 (d), 136.02 (u), 157.33 (s); MS 341 (M^+), 269 (100); HRMS Calcd. for $C_{19}H_{35}NO_4$: 341.2564, Found 341.2592; $[\alpha]^{26}_D$ +3.8 (*c* 3.25, $CHCl_3$).

(5*R*,8*R*,9*S*)-(-)-5-Propyl-8-butylindolizidine (19): To a stirred solution of (+)-**18** (90 mg, 0.26 mmol) in MeOH (2 mL) was added $Pd(OH)_2$ (10 mg), and the resulting suspension was hydrogenated at 1 atm for 8 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 *n*-PrSH (0.24 mL, 2.64 mmol) in HMPA (1.4 mL) was added *n*-BuLi (1.6 mL, 2.51 mmol) at 0 ℃, and the mixture was stirred at 0 ℃ for 30 min. The above oil in THF (2 mL) was added at 0 ℃, and the mixture was stirred at room temperature for 36 h. The reaction was quenched with 33% NH_3 in H_2O (5 mL), and the aqueous layer was extracted with Et_2O (10 mL x 8). The extracts were combined, dried over K_2CO_3 and evaporated to give a pale yellow oil, which was used directly in the next step. Concentrated HCl (3 drops) was added to a stirred solution of the above oil in MeOH (4 mL), and the resulting mixture was refluxed for 2 h. After evaporation of the mixture, the residue was washed with Et_2O (2 mL x 3). Aqueous ammonia was added, and the aqueous layer was extracted with $CHCl_3$ (10 mL x 8). The extracts were combined, dried over K_2CO_3 and evaporated to give a colorless oil. Carbon tetrabromide (110 mg, 0.33 mmol) and Ph_3P (110 mg, 0.40 mmol) were added to a stirred solution of the above oil in CH_2Cl_2 (2 mL) at 0 ℃, and the resulting mixture was stirred at 0 ℃ for 30 min. Triethylamine (0.60 mL, 4.22 mmol) was added at 0 ℃, and the mixture was stirred for 10 min, and the volatiles were removed. The residue was extracted with *n*-pentane (10 mL x 2), and the extracts were combined and evaporated to give a pale yellow

solid, which was chromatographed on SiO_2 (10 g, hexane:acetone=50:1) to afford (-)-**19** (25.4 mg, 43% in 4 steps) as a colorless oil (mp 192~195 ℃ as a hydrochloride from EtOAc-EtOH).

Natural Indolizidine 223I: Ion-trap EIMS m/z 224 (M^++1, 7), 223 (2), 222 (5), 208 (<1), 194 (6), 180 (100), 166 (5), 152 (8), 138 (4), 124 (4), 122 (1), 112 (2), 110 (2), 98 (2), 96 (7), 84 (3), 82 (2), 81 (3), 70 (4), 69 (3), 68 (3), 67 (3), 55 (5); EIMS m/z 223 (M^+, 3), 222 (1), 208 (2), 194 (10), 180 (100), 166 (10), 152 (13), 138 (8), 136 (2), 125 (2), 124 (3), 112 (5), 110 (3), 96 (9), 82 (3), 81 (2), 70 (5), 69 (6), 68 (4), 67 (4), 56 (4), 55 (11), 54 (2), 53 (2); FTIR cm^{-1} 2961 (83), 2931 (100), 2884 (45), 2781 (12), 1459 (15), 1380 (10).

Natural Indolizidine 223J: Ion-trap EIMS m/z 223 (M^+, 2), 222 (2), 166 (100), 110 (3), 96 (28), 70 (9), 55 (3); EIMS m/z 223 (M^+, 1), 222 (1), 194 (1), 180 (3), 166 (100), 152 (1), 138 (2), 122 (2), 120 (3), 110 (3), 96 (11), 70 (9), 55 (5); FTIR cm^{-1} 2968 (95), 2939 (100), 2879 (43), 2786 (37), 1460 (10), 1377 (9), 1160 (9), 1130 (9).

Synthetic (5*R*,8*R*,9*S*)-5-propyl-8-butylindolizidine, (-)-19: Ion-trap EIMS m/z 224 (M^++1, 16), 222 (9), 180 (100), 136 (2), 124 (2), 122 (3), 110 (3), 96 (18), 70 (1); EIMS m/z 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); FTIR cm^{-1} 2968 (96), 2938 (100), 2880 (44), 2787 (34), 1459 (10).

IR (neat) 2957, 2930, 2871, 2778, 1654, 1560, 1542, 1508, 1458, 1378, 1193, 1132, 927 cm^{-1}; ^1H NMR (500 MHz) δ 0.82-0.91 (1H, br m), 0.87 (3H, t, *J* = 7.0 Hz), 0.90 (3H, t, *J* = 7.0 Hz), 0.98-1.06 (1H, m), 1.12-1.36 (7H, m), 1.37-1.46 (3H, m), 1.52-1.58 (1H, m), 1.59-1.66 (2H, m), 1.69-1.79 (2H, m), 1.80-1.87 (3H, m), 1.88-1.97 (2H, m), 3.25 (1H, td, *J* = 8.5, 2.0 Hz); ^{13}C NMR (75 MHz) δ 14.04 (u), 14.52 (u), 19.06 (d), 20.44 (d), 22.99 (d), 28.76 (d), 29.21 (d), 30.53 (d), 31.20 (d), 33.01 (d), 36.95 (d), 41.46 (u), 51.89 (d), 63.40 (u), 70.21 (u); HRMS Calcd. for $C_{15}H_{29}N$: 223.2299, Found 223.2304; $[\alpha]^{26}_D$ -131.9 (*c* 0.50, $CHCl_3$).

Hydrochloride: mp: 192~195 ℃; IR (KBr) 2949, 2931, 2871, 2457, 1560, 1509, 1466, 1458, 1432, 1389, 1050 cm^{-1}; ^1H NMR (500 MHz) δ 0.90 (3H, d, *J* = 7.0 Hz), 0.95 (3H, d, *J* = 7.0 Hz), 1.04-1.14 (2H, m), 1.20-1.38 (5H, br m), 1.43-1.56 (3H, m), 1.74-1.81 (1H, m), 1.90-1.98 (1H, m), 2.00-2.12 (4H, m), 2.16-2.34 (4H, m), 2.51 (1H, br quint-like, *J* = 9.0 Hz), 2.60-2.69 (2H, br m), 3.88-3.94 (1H, br m); ^{13}C NMR (125 MHz) δ 13.75, 13.95, 18.97, 19.37, 22.93, 27.27, 27.87, 28.03, 28.99, 32.46, 33.42, 37.90, 50.83, 65.27, 72.48.

Methyl (2*R*, 3*R*, 6*S*)-(+)-6-{2-(*t*-Butyldimethylsiloxy)ethyl}-3-ethyl-2-(hydroxymethyl)piperidine-1-carboxylate (20): To a stirred solution of (+)-**3** (R^1 = Et, R = TBS, 460 mg, 1.19 mmol) in THF (13 mL) was added Super-Hydride (2.6 mL, 2.6 mmol) at 0 ℃, and the resulting mixture was stirred for 1 h at 0 ℃. The reaction was quenched with ice-water, and the aqueous layer was extracted with CH_2Cl_2 (10 mL x 5). The extracts were combined, dried over $MgSO_4$ and evaporated to give a colorless oil, which was chromatographed on SiO_2 (25 g, hexane:acetone=10:1) to afford (+)-**20** (394 mg, 92%) as a colorless oil.

IR (neat) 3446. 2955, 2858, 1694, 1447, 1362, 1315, 1256, 1100, 836, 775 cm^{-1}; ^1H NMR (500 MHz) δ 0.028 & 0.040 (each 3H, each s), 0.87 (12H, br s), 1.17-1.48 (5H, br m), 1.63-1.90 (4H, br m), 2.80 (1H, br), 3.58-3.69 (7H, br m, including δ 3.67, 3H, s), 4.15 (1H, br t-like, *J* = 12.5 Hz), 4.26 (1H, br); ^{13}C NMR (75 MHz) δ -5.58 & -5.50 (each u, due to rotamers), 11.76 (u), 18.26 (s), 20.49 & 20.52 (each d, due to rotamers), 23.78 & 23.90 (each d, due to rotamers), 25.84 (u), 25.98 (d), 35.39 (u), 38.64 (d), 49.08 & 49.15 (each u, due to rotamers), 52.58 (u), 56.89 (u), 61.43 & 61.48 (each d, due to rotamers), 65.41 & 65.53 (each

d, due to rotamers), 158.36 (s); MS 360 (M^++1), 359 (M^+), 302 (100); HRMS Calcd. for $C_{18}H_{37}NO_4Si$: 359.2490, Found 359.2455; $[\alpha]^{26}_D$ +17.8 (*c* 6.74, $CHCl_3$).

Methyl (2*R*, 3*R*, 6*S*)-6-{2-(*t*-Butyldimethylsiloxy)ethyl}-3-ethyl-2-{4-(methoxymethoxy)but-1-enyl}piperidine-1-carboxylate: To a stirred solution of $(COCl)_2$ (0.27 mL, 3.27 mmol) in CH_2Cl_2 (5 mL) was added DMSO (0.45 mL, 6.47 mmol) at -78 ℃, and the mixture was stirred for 5 min at -78 ℃. To the mixture was added (+)-**20** (520 mg, 1.45 mmol) in CH_2Cl_2 (4 mL) at -78 ℃, and the mixture was stirred at -78 ℃ for 30 min. Triethylamine (1.4 mL, 10.14 mmol) was added, and the temperature was gradually raised to -20 ℃. The reaction was quenched with H_2O, and the aqueous layer was extracted with Et_2O (15 mL x 4). The extracts were combined, dried over $MgSO_4$ and evaporated to give the corresponding aldehyde as a pale yellow oil, which was used directly in the next step. To a stirred suspension of $MOMO(CH_2)_3P^+Ph_3Cl^-$ (3.5 g, 8.74 mmol) in THF (10 mL) was added *n*-BuLi (2.8 mL, 4.37 mmol) at 0 ℃, and the resulting mixture was stirred at 0 ℃ for 30 min. The above aldehyde in THF (5 mL) was added at 0 ℃, and the resulting mixture was stirred at room temperature for 6 h. The reaction was quenched with H_2O, and the aqueous layer was extracted with Et_2O (10 mL x 6). The extracts were combined, dried over $MgSO_4$ and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (40 g, hexane:acetone=40:1) to afford the corresponding olefin (570 mg, 89%) as a colorless oil.

IR (neat) 2954, 2930, 2858, 1759, 1695, 1443, 1106, 1037, 836, 775 cm^{-1}; ^1H NMR (500 MHz) δ 0.003 (3H, s), 0.88 (9H, s), 0.91 (3H, t, *J* = 7.5 Hz), 1.26-1.52 (6H, br m), 1.73-1.89 (6H, m), 2.34-2.55 (3H, m), 3.36 (3H, s), 3.51-3.64 (4H, m), 3.66 (3H, s), 4.24 (1H, m), 4.62 (2H, s), 4.79 (1H, br d, *J* = 9.0 Hz), 5.45 (1H, m), 5.73 (1H, tt-like, *J* = 10.0, 1.8 Hz); MS 444 (M^++1), 443 (M^+), 386 (100); HRMS Calcd. for $C_{23}H_{45}NO_5Si$: 443.3064, Found 443.3072.

Methyl (2*S*, 3*R*, 6*S*)-(-)-3-Ethyl-6-(2-hydroxyethyl)-2-{4-(methoxymethoxy)butyl}piperidine-1-carboxylate (21): To a solution of the olefin (550 mg, 1.24 mmol) from the previous step in MeOH (10 mL) was added 5% Pd/C (100 mg), and the resulting suspension was hydrogenated at 4 atm for 8 h. The catalyst was removed by filtration, and the filtrate was evaporated to give a colorless oil. To a stirred solution of the oil in THF (10 mL) was added TBAF (1.4 mL, 1.4 mmol) at 0 ℃, and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with satd. NH_4Cl, and the aqueous layer was extracted with CH_2Cl_2 (15 mL x 6). The extracts were combined, dried over $MgSO_4$ and evaporated to give a colorless oil, which was chromatographed on SiO_2 (30 g, hexane:acetone=7:1~6:1) to afford (-)-**21** (367 mg, 89% in 2 steps) as a colorless oil.

IR (neat) 3456, 2938, 2872, 1691, 1667, 1448, 1363, 1110, 1045 cm^{-1}; ^1H NMR (500MHz) δ 0.83 (3H, t, *J* = 7.2 Hz), 1.20-1.90 (19H, br m), 3.29 (3H, s), 3.45 (3H, br t-like, *J* = 7.0 Hz), 3.54 (1H, br), 3.64 (3H, s), 3.86 (1H, br t-like, *J* = 7.0 Hz), 3.98 (1H, br d-like, *J* = 6.0 Hz), 4.30 (1H, br), 4.55 (2H, s); ^{13}C NMR (75 MHz) δ 11.80 (u), 19.55 (d), 23.82 (d), 24.08 (d), 25.38 (d), 29.31 (d), 35.68 (d), 37.56 (u), 38.45 (d), 46.99 (u), 52.86 (u), 54.68 (u), 54.92 (u), 58.78 (d), 67.33 (d), 96.20 (d), 158.68 (s); MS 318 (M^++1), 317 (M^+), 86 (100); HRMS Calcd. for $C_{16}H_{31}NO_5$: 317.2200, Found 317.2239; $[\alpha]^{26}_D$ -5.4 (*c* 6.68, $CHCl_3$).

Methyl (2*S*, 3*R*, 6*S*)-(+)-3-Ethyl-2-{4-(methoxymethoxy)butyl}-6-(prop-2-enyl)piperidine-1-carboxylate (22): To a stirred solution of $(COCl)_2$ (0.19 mL, 2.24 mmol) in CH_2Cl_2 (2 mL) was added DMSO (0.32 mL, 4.47 mmol) at -78 ℃, and the mixture was stirred for 5 min at -78 ℃. To the mixture was added (-)-**21** (370 mg, 1.11 mmol) in CH_2Cl_2 (2 mL) at -78 ℃, and the mixture was stirred at -78 ℃ for 30 min. Triethylamine (0.93 mL, 6.70 mmol) was added, and the temperature was gradually raised to -20 ℃.

The reaction was quenched with H_2O, and the aqueous layer was extracted with Et_2O (15 mL x 4). The extracts were combined, dried over $MgSO_4$ and evaporated to give the corresponding aldehyde as a pale yellow oil, which was used directly in the next step. To a stirred suspension of $CH_3P^+Ph_3Br^-$ (1.99 g, 5.59 mmol) in THF (15 mL) was added *n*-BuLi (3.2 mL, 5.03 mmol) at 0 ℃, and the resulting mixture was stirred at 0 ℃ for 30 min. The above aldehyde in THF (5 mL) was added at 0 ℃, and the resulting mixture was stirred at room temperature for 6 h. The reaction was quenched with H_2O, and the aqueous layer was extracted with Et_2O (10 mL x 6). The extracts were combined, dried over $MgSO_4$ and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 (40 g, hexane:acetone=30:1) to afford (+)-**22** (235 mg, 64% in 2 steps) as a pale yellow oil.

IR (neat) 3075, 2872, 1694, 1640, 1444, 1362, 1321, 1109, 1045 cm^{-1}; ^1H NMR (500 MHz) δ 0.85 (3H, t-like, J = 7.5 Hz), 1.19-1.79 (19H, br m), 2.21 (1H, m), 2.33 (1H, br), 3.32 (3H, s), 3.48 (2H, t-like, J = 6.5 Hz), 3.64 (s, 3H), 3.80-4.20 (br, 2H), 4.58 (s, 2H), 5.00 (m, 2H), 5.71 (br, 1H); ^{13}C NMR (75 MHz) δ 11.94 (u), 19.51 (d), 21.64 (d), 23.82 (d), 25.65 (d), 29.56 (d), 36.24 (d), 37.80 (u), 39.74 & 39.80 (each d, due to rotamers), 39.87 & 39.90 (each d, due to rotamers), 50.59 (u), 52.29 (u), 54.65 (u), 55.00 (u), 67.58 (d), 96.30 (d), 116.67 (t), 136.03 (d), 157.28 (s); MS 327 (M^+), 254 (100); HRMS Calcd. for $C_{18}H_{33}NO_4$: 327.2408, Found 327.2440; $[\alpha]^{26}_D$ +2.6 (*c* 3.26, $CHCl_3$).

(1*R*,4*S*,10*S*)-(-)-4-Allyl-1-ethylquinolizidine (23): To a stirred solution of *n*-PrSH (0.28 mL, 3.06 mmol) in HMPA (1.5 mL) was added *n*-BuLi (1.86 mL, 2.91 mmol) at 0 ℃, then the mixture was stirred at 0 ℃ for 30 min. The carbamate (+)-**22** (100 mg, 0.31 mmol) in THF (2 mL) was added to the mixture at 0 ℃, and the mixture was stirred at room temperature for 48 h. The reaction was quenched with 33% NH_3 in H_2O (5 mL), and the aqueous layer was extracted with Et_2O (10 mL x 10). The extracts were combined, dried over K_2CO_3 and evaporated to give a pale yellow oil, which was used directly in the next step. Concentrated HCl (3 drops) was added to a stirred solution of the above oil in MeOH (4 mL), and the mixture was refluxed for 1 h. After evaporation of the mixture, the residue was washed with Et_2O (2 mL x 5). Aqueous ammonia was added to the mixture, and the aqueous layer was extracted with $CHCl_3$ (10 mL x 8). The extracts were combined, dried over K_2CO_3 and evaporated to give a colorless oil. Carbon tetrabromide (145 mg, 0.44 mmol) and Ph_3P (120 mg, 0.46 mmol) were added to a stirred solution of the oil in CH_2Cl_2 (2 mL) at 0 ℃, and the mixture was stirred at 0 ℃ for 30 min. Triethylamine (0.68 mL, 4.89 mmol) was added to the mixture at 0 ℃, and the mixture was stirred at 0 ℃ for 10 min. and evaporated. The residue was extracted with *n*-pentane (10 mL x 2), and the pentane layers were combined and evaporated to give a pale yellow solid, which was chromatographed on SiO_2 (20 g, hexane:acetone=50:1) to afford (-)-**23** (40 mg, 63% in 3 steps) as a colorless oil.

Natural Quinolizidine 207I: Ion-trap EIMS: m/z 208 (M^++1,1), 206 (1), 166 (100), 152 (3), 150 (1), 138 (1), 136 (3), 134 (2), 122 (2), 120 (1), 110 (34), 96 (2), 94 (3), 93 (2), 85 (7), 84 (8), 83 (12), 82 (8), 81 (6), 80 (4), 79 (5), 70 (3), 69 (4), 68 (6), 67 (11), 56 (7), 55 (20), 54 (8), 53 (7); FTIR cm^{-1}: 3084 (4), 2970(52), 2941 (100), 2880 (38), 2789 (18), 1453 (10).

Synthetic (1*R*,4*S*,10*S*)-4-allyl-1-ethylquinolizidine, (-)-23: Ion-trap EIMS m/z 208 (M^++1, 3), 206 (5), 178 (1), 166 (100), 136 (3), 134 (1), 124 (1), 122 (2), 110 (34), 94 (3), 84 (2), 82 (5), 81 (3), 80 (1), 79 (1), 67 (5), 56 (3), 55 (5), 54 (4), 53 (3); FTIR cm^{-1}: 3084 (6), 2967 (38), 2938 (100), 2868 (30), 2789 (18), 1453 (10), 1097 (13).

IR (neat) 3073, 2929, 2856, 2784, 1637, 1449, 1376, 1346, 1266, 1089, 1058, 992, 909 cm^{-1}; ^1H NMR (500 MHz) δ 0.83 (3H, d, J = 8.0 Hz), 0.99 (1H, qd, J = 12.0, 4.0 Hz), 1.04-1.13 (1H, m), 1.14-1.25 (3H, m),

1.36 (1H, qm, J = 14.0 Hz), 1.47-1.65 (4H, br m), 1.67-1.77 (4H, m), 1.90-1.97 (2H, m), 2.14 (1H, dtt-like, J = 14.0, 7.2, 1.0 Hz), 2.41 (1H, dm, J = 14.0 Hz), 3.28 (1H, dm, J = 11.0 Hz), 4.99-5.05 (2H, m), 5.77-5.85 (1H, m); ^{13}C NMR (75 MHz) δ 10.45 (u), 24.63 (d), 24.99 (d), 26.13 (d), 29.42 (d), 29.80 (d), 31.35 (d), 38.77 (d), 41.88 (u), 51.70 (d), 62.83 (u), 67.36 (u), 116.12 (d), 136.26 (u); HRMS Calcd. for $C_{14}H_{25}N$: 207.1986, Found 207.1992; $[\alpha]^{26}_D$ -97.9 (*c* 0.55, $CHCl_3$).
Hydrochloride: mp: 205~207 ℃ (EtOAc-Et_2O); IR (KBr) 3082, 2954, 2932, 2876, 2707, 2671, 2547, 2512, 1638, 1447, 1376, 1299, 1212, 1038, 997, 969, 916, 812 cm^{-1}.

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