NOVEL CHIRAL SYNTHETIC PATH TO INDOLIZIDINE AND QUINOLIZIDINE ALKALOIDS BY MEANS OF A SAMARIUM DIIODIDE-PROMOTED REDUCTIVE CARBON-NITROGEN CLEAVAGE REACTION: SYNTHESIS OF (+)-(8*R*, 8a*R*)-PERHYDRO-8-INDOLIZIDINOL AND (-)-DEOXYNUPHARIDINE

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Abstract – Novel chiral synthetic procedures for indolizidine and quinolizidine alkaloids were developed, where a samarium diiodide-promoted carbon-nitrogen bond cleavage reaction was employed as a key step. Application of the procedure led to the total synthesis of (+)-(8*R*, 8a*R*)-perhydro-8-indolizidinol and (-)-deoxynupharidine.

Indolizidine and quinolizidine alkaloids, with their wide range of structural and stereochemical features, are large class of natural products that have, over the year, provoked an extraordinary amount of activity by synthetic organic chemists.[1] Recently, we have developed a samarium diiodide-promoted reductive deamination reaction of α-amino esters, where proline derivatives were successfully transformed to the corresponding δ-lactams in good yields.[2] The effectiveness of this reaction for the construction of ring-enlarged lactams[3] leads us to consider its application toward the indolizidine and quinolizidine alkaloids in optically active forms.

Our synthesis of indolizidine alkaloid commenced with the synthesis of the known proline derivative **1**, which was readily accessible via known procedures from (4*R*)-hydroxy-L-proline.[4] Hydroboration of **1** with 9-BBN in THF, followed by oxidative treatment with alkaline hydrogen peroxide gave the primary alcohol (**2**) in 97% yield. Removal of the Boc group of **2** on treatment with zinc bromide[5] in CH_2Cl_2 afforded the desired amino-alcohol (**3**) together with *tert*-butyl ether (**4**), in 71 and 15% yields, respectively. The structure of **4** was confirmed by its alternative preparation from **2** involving an etherification[6] with $(Boc)_2O$ and $Mg(ClO_4)_2$, followed by deprotection of the *N*-Boc group of the resulting ether (**5**) with zinc bromide in CH_2Cl_2. In order to synthesize the bicyclic compound, the precursor for a reductive carbon-nitrogen bond cleavage reaction, the primary alcohol (**3**) was reacted with carbon tetrabromide in the presence of triphenylphosphine in CH_2Cl_2 to give the alkoxyphosphonium salt, which on treatment with triethylamine (TEA) furnished the bicyclic compound (**7**) in 74% yield from **3**.[7] Compound (**7**) was alternatively prepared from **2** by mesylation with methanesulfonyl chloride in CH_2Cl_2, followed by deprotection of the *N*-Boc group of the mesylate (**6**) with zinc bromide in CH_2Cl_2, in 86% overall yield.
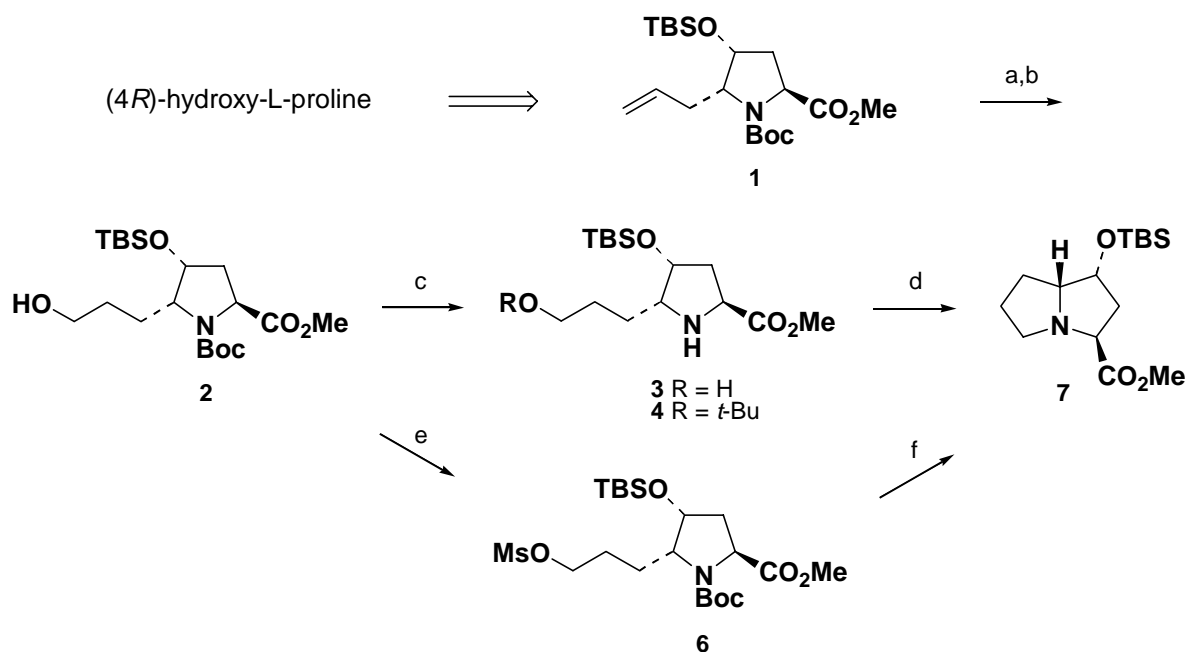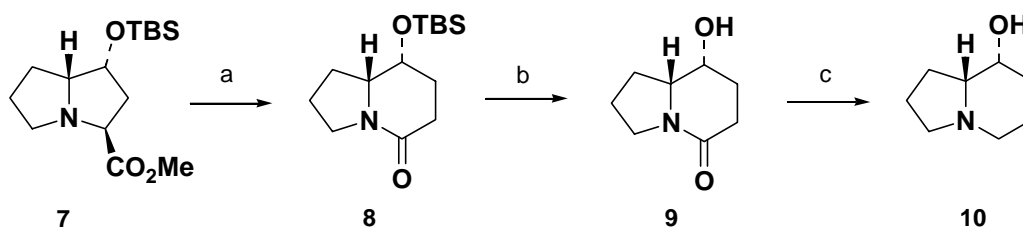

Scheme 1. *Reagents and conditions:* (a) 9-BBN, THF, 0 °C; (b) 3N NaOH, 30% H_2O_2, 0 °C to rt (97%); (c) $ZnBr_2$, CH_2Cl_2, rt (**3**: 71%, **4**: 15%); (d) CBr_4, Ph_3P, CH_2Cl_2, 0 °C then TEA (74%); (e) MsCl, TEA, CH_2Cl_2, 0 °C; (f) $ZnBr_2$, CH_2Cl_2, rt (86% from **2**)
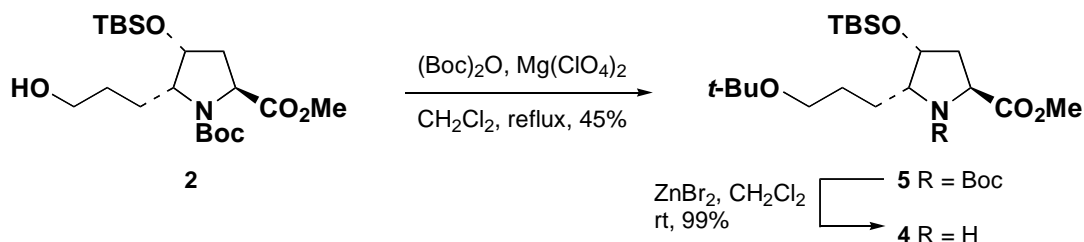
Scheme 2. Structure determination of the compound (**4**)

Since the desired bicyclic ester (**7**) in hands, we focused our attention on the δ-lactam formation by means of a samarium diiodide-promoted reductive carbon-nitrogen bond cleavage reaction. Treatment of **7** with samarium diiodide in THF-HMPA in the presence of methanol as the proton source at 0°C to room temperature for 2 h provided the indolizidinone (**8**) in 86% yield, where a reductive carbon-nitrogen bond cleavage, followed by recyclization of the resulting amino-ester occurred, simultaneously. Deprotection of the silyl group of **8** with tetrabutylammonium fluoride (TBAF) in THF afforded the hydroxy-lactam (**9**),[8] in 97% yield, which was further converted to (+)-(8R, 8aR)-perhydro-8-indolizidinol (**10**) by reduction of the amide function with borane-methylsulfide complex according to the known procedure.[8] The spectroscopic data of **10** were identical with those reported in the literature[8] except for the sign of optical rotation {[α]$_D$ +19.9° (c=1.2, CHCl$_3$); lit.,[8] [α]$_D$ –17.4° (c=1.15, CHCl$_3$)}.
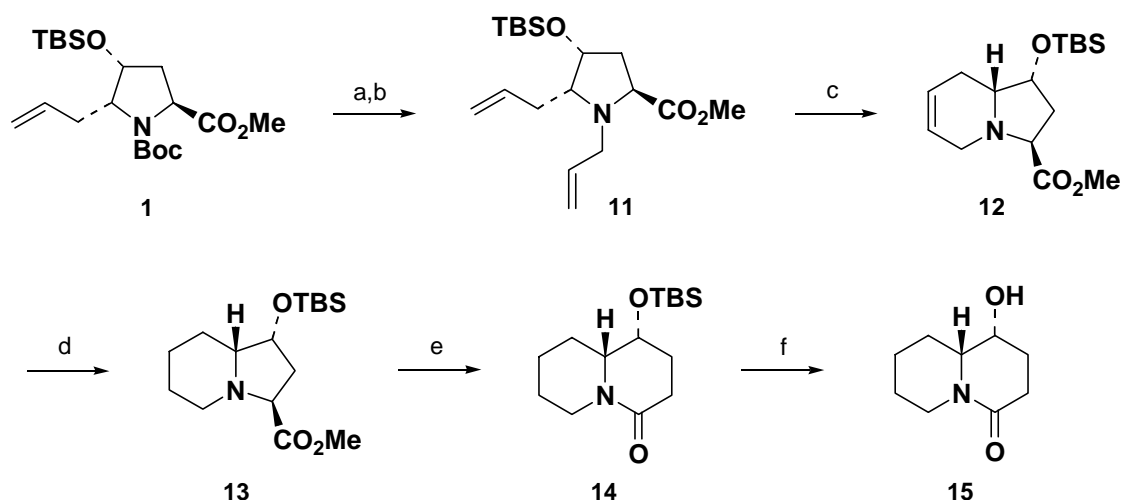

Scheme 3. *Reagents and conditions:* (a) SmI$_2$, THF, HMPA, MeOH, 0 °C to rt (86%); (b) TBAF, THF, rt (97%); (c) BH$_3$-Me$_2$S, THF, 0 °C to rt (83%)

Since we were able to establish a new synthetic procedure for indolizidine alkaloids by employing a samarium diiodide-promoted reductive carbon-nitrogen bond cleavage reaction, as a key step, we planned to extend the utilization of this strategy to the synthesis of quinolizidine alkaloids.

As a model study on the synthesis of quinolizidine alkaloids, a synthesis of 1-hydroxy-4-quinolizidinone was investigated as follows.

Removal of the *N*-Boc group of **1** with zinc bromide in CH$_2$Cl$_2$, followed by allylation of the resulting

amine with allyl bromide in the presence of sodium hydride in DMF gave the *N*-allyl compound (**11**) in

80% from **1**. Ring closing metathesis (RCM)[9] of **11** with 2 mol% of Grubbs' 2nd generation catalyst in

refluxing benzene provided the olefinic bicyclic compound (**12**), in 81% yield, which on catalytic

reduction over palladium on carbon in AcOEt gave the saturated bicyclic compound (**13**) in 94% yield.

Application of a samarium diiodide-promoted reductive carbon-nitrogen bond cleavage reaction to **13**

under the same reaction conditions as described for the synthesis of **10** furnished the desired

quinolizidinone (**14**) in 86% yield. Deprotection of the silyl group of **14** with tetrabutylammonium

fluoride in THF gave the hydroxy-lactam (**15**) in 91% yield. Although the synthesis of the lactam (**15**) has

already been achieved, none of its spectroscopic data were reported in the literature,[10] unfortunately.

Scheme 4. *Reagents and conditions:* (a) ZnBr$_2$, CH$_2$Cl$_2$, rt; (b) allyl bromide, NaH, DMF, 0 °C (80% from **1**); (c) 2 mol% Grubbs' 2nd cat., benzene, 80 °C (81%); (d) H$_2$, 10% Pd-C, AcOEt, rt (94%); (e) SmI$_2$, THF, HMPA, MeOH, 0 °C to rt (86%); (f) TBAF, THF, rt (91%)

In order to synthesize (-)-deoxynupharidine (**16**), a stereoselective construction of the 1-methyl-4-

quinolizidinone ring system in an optically active form would be required. (-)-Deoxynupharidine (**16**) and

(-)-7-*epi*-deoxynupharidine (**17**), isolated from plants of the genus *Nuphar*,[11] are biologically active

sesquiterpene alkaloids based on a quinolizidine core with a furan ring. The dried rhizomes of *Nuphar*

japonicum DC. and *Nuphar pumilum* (TIMM.) DC., are used in folk medicine for tonic, hemostatic and

diuretic purposes in China and Japan. It has also been recognized that (-)-deoxynupharidine exhibited an

immunosuppressive effect,[12] a central paralysis effect[13] and weak anti-metastatic activity,[14] and (-)-7-*epi*-deoxynupharidine showed insecticidal activity.[11]
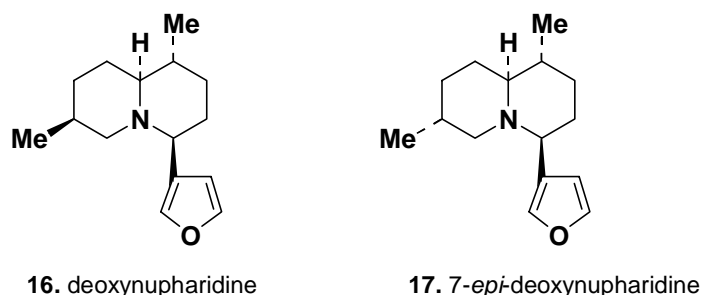

Figure 1. The structures of (-)-deoxynupharidine and (-)-7-*epi*-deoxynupharidine

Thus, methyl *N-tert*-butoxycarbonylpyroglutamate (**18**) was reacted with Bredereck's reagent[15] in toluene at 100°C to give the enaminone (**19**) in 96% yield. Catalytic reduction of **19** over 10% palladium on carbon in *i*PrOH-AcOEt afforded the methylated pyroglutamates (**20** and **21**), in 3 and 91% yields, respectively. Reduction of the major product (**21**) with lithium triethylborohydride in THF at -78°C gave the aminal (**22**), which, on treatment with diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate[16] in THF in the presence of sodium hydride furnished the amide (**23**) in 96% yield from **21**. The stereochemistry at the 5-position of **23** was assumed to be *S*, by comparison of the NMR data of **24** with those of the related compounds prepared by us previously,[4] and finally determined by its conversion to the natural product.
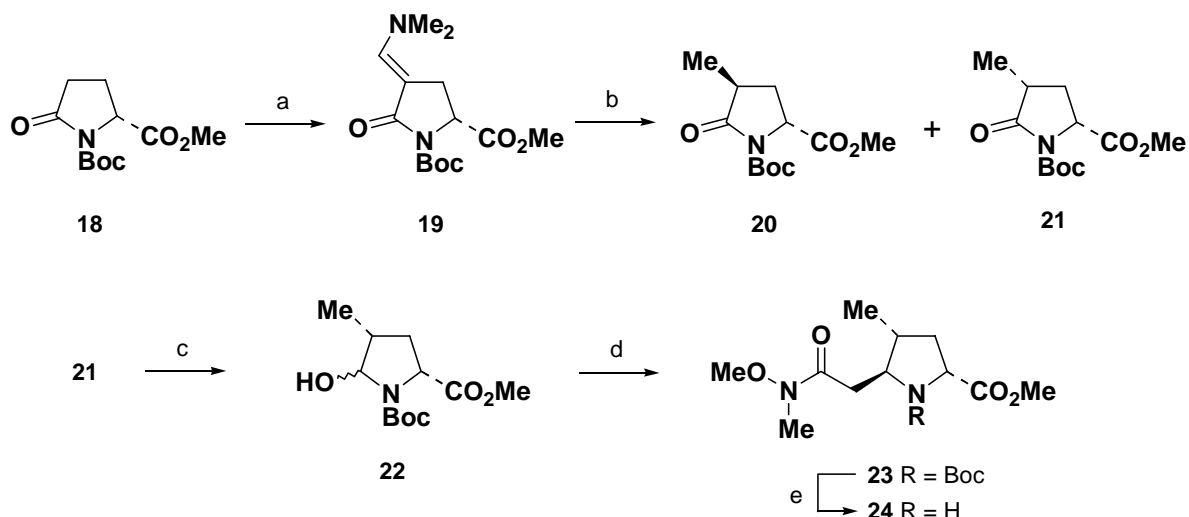

Scheme 5. *Reagents and conditions:* (a) *tert*-BuOCH(NMe₂)₂, toluene, 100 °C (96%); (b) H₂, 10% Pd-C, *i*-PrOH-AcOEt (5:1), rt (**20**: 3%, **21**: 91%) (c) LiEt₃BH, THF, -78 °C; (d) NaH, (EtO)₂P(O)CH₂CON(Me)OMe, THF, rt (96% from **21**); (e) TFA, CH₂Cl₂, 0 °C to rt (90%)

Chemoselective reduction of **23** with DIBAL in THF at -78°C for 0.5 h provided the aldehyde (**25**), which without further purification, was treated with methyltriphenylphosphonium bromide in the presence of sodium hexamethyldisilazide as the base to afforded the alkene (**26**) in 95% yield from **23**. After removal of the *N*-Boc group of **26** with trifluoroacetic acid in CH₂Cl₂, the resulting amine (**27**) was subjected to a samarium diiodide-promoted reductive carbon-nitrogen bond cleavage reaction as described before to provide the ring enlarged lactam (**28**) in 90% yield from **26**. Alkylation of **28** with 3-bromo-2-methylpropene in the presence of sodium hydride in DMF, followed by RCM of the resulting olefin (**29**) with 2 mol% of Grubbs' 2nd generation catalyst in refluxing benzene for 2 h afforded the bicyclic lactam (**30**) in 84% yield from **28**. The lactam (**30**) was alternatively synthesized from **26**, in which the construction of bicyclo-system was carried out prior to a samarium diiodide-promoted reductive deamination, as follows.
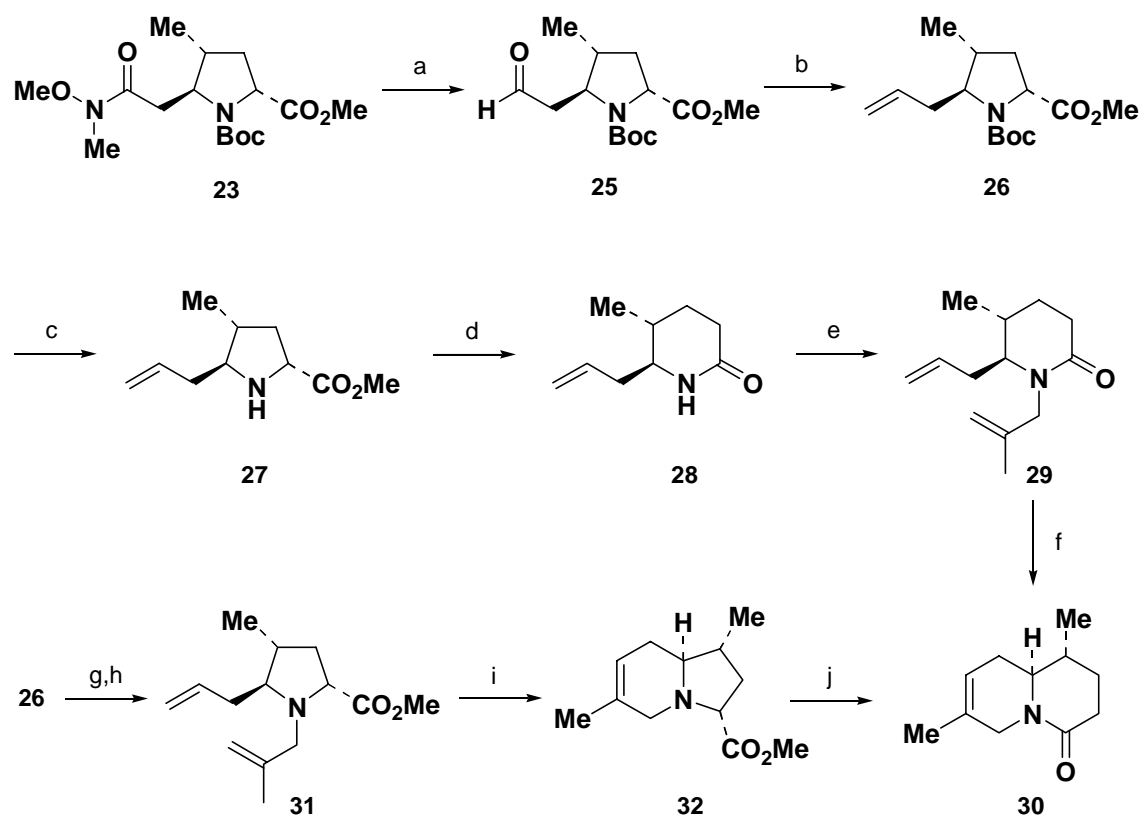
Scheme 6. *Reagents and conditions:* (a) DIBAL, THF, -78 °C; (b) NaHMDS, Ph₃PCH₃⁺Br⁻, THF, -78 °C to rt (95% from **23**); (c) TFA, CH₂Cl₂, 0 °C to rt; (d) SmI₂, THF, HMPA, MeOH, 0 °C to rt (90% from **26**); (e) 3-bromo-2-methylpropene, NaH, DMF, 0 °C to rt (87%); (f) 2 mol% Grubbs' 2nd cat., benzene, 60 °C (96%); (g) TFA, CH₂Cl₂, 0 °C to rt; (h) 3-bromo-2-methylpropene, NaH, DMF, 0 °C to rt (88% from **26**); (i) 2 mol% Grubbs' 2nd cat., benzene, 60 °C (70%); (j) SmI₂, THF, HMPA, MeOH, 0 °C to rt (82%)

Removal of the *N*-Boc group of **26** with trifluoroacetic acid in CH$_2$Cl$_2$, followed by alkylation with 3-bromo-2-methylpropene as described before gave the alkene (**31**) in 88% yield from **26**. RCM of **31** with 2 mol% of Grubbs' 2nd generation catalyst in refluxing benzene for 16 h afforded the bicyclic ester (**32**), in 70% yield. Again, application of a samarium diiodide-promoted carbon-nitrogen bond cleavage reaction to **32** furnished the desired lactam (**30**) in 82% yield. Thus, this reaction was found to be able to apply to both secondary amine and tertiary amine, successfully. Catalytic reduction of **30** over 10% palladium on carbon in methanol gave the lactams (**33**) as a mixture of the diastereomers at the 7-position, in a ration of 7*S*:7*R*=3.4:1.0. Although the lactam (**33**) has already been converted to (-)-deoxynupharidine by Harrity and his co-workers,[17] we decided to adopt an alternative route to (-)-deoxynupharidine, in which we planned to introduce a furyl moiety to the lactam function prior to a reduction of the carbon-carbon double bond.
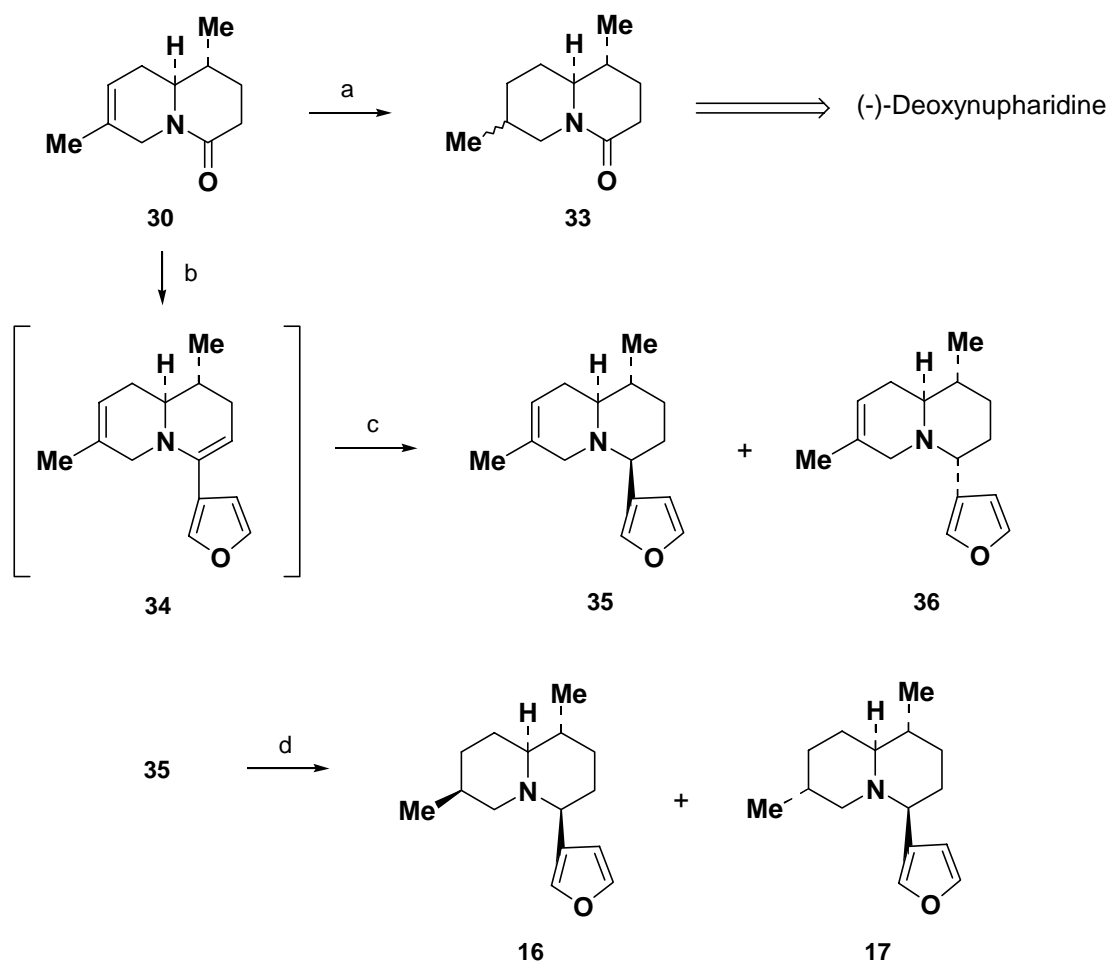
Scheme 7. *Reagents and conditions:* (a) H$_2$, 10% Pd-C, MeOH, rt (90%) (7*S*:7*R* = 3.4:1.0); (b) 3-lithiofuran, THF, -78 °C; (c) NaBH$_4$, MeOH, rt (**35**: 57% from **30**, **36**: 9% from **30**); (d) H$_2$, Pd(OH)$_2$, MeOH, rt (**16**: 68%, **17**: 11%)

Treatment of **30** with 3-lithiofuran in THF at -78°C for 1.5 h, followed by treatment with sodium borohydride in methanol afforded the furyl compounds (**35** and **36**) in 57 and 9% yields, respectively, from **30**. In this conversion, we first attempted DIBAL reduction for the intermediate (**34**) after installation of a furan ring according to the literature reported by Harrity,[17] in which, they proposed a carbinolamine as the intermediate in their synthesis. However, we mentioned that DIBAL was not effective for this reduction, unfortunately, and we could confirm the presence of an enamine as an intermediate by the analysis of its NMR spectra. Our experimental results using sodium borohydride as the reducing agent for the intermediate might support the presence of an enamine (**34**) as the intermediate in our synthesis.

Finally, a catalytic reduction of **35** over palladium hydroxide in methanol gave (-)-deoxynupharidine (**16**) and its 7-epimer (**17**), in 68 and 11% yields, respectively.

In summary, we were able to synthesize both indolizidine and quinolizidine alkaloids by using a samarium diiodide-promoted reductive carbon-nitrogen bond cleavage, as a key step. The strategy developed here would be applicable to the synthesis of a various types of alkaloids, and further extension of this strategy is under investigation in this laboratory.

EXPERIMENTAL

Melting points were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were obtained using a JASCO FT/IR-200 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were obtained on JEOL LAMBDA-270 (^{1}H-NMR: 270 MHz, ^{13}C-NMR: 67.8 MHz) instrument for solutions in CDCl$_3$ unless otherwise noted, and chemical shifts are reported on the δ scale from internal TMS. MS spectra were measured with a JEOL JMS-D 300 spectrometer. Elemental analyses were performed on a Yanaco-MT5.

Methyl (4*R*,5*R*)-1-(*tert*-butoxycarbonyl)-4-(*tert*-butyldimethylsilyloxy)-5-(3-hydroxypropyl)-L-prolinate (2): To a solution of **1** (500 mg, 1.25 mmol) in THF (12.5 mL) was added 9-BBN (0.5 M in THF, 5.0 mL, 2.51 mmol) at 0 °C, and the resulting mixture was stirred for 3 h. To this mixture was added 3N NaOH (3.5 mL) and 30% H$_2$O$_2$ (1.1 mL) at 0 °C. After stirring for 1 h at rt, the mixture was extracted

with AcOEt. The extract was washed with brine, dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography (*n*-hexane:AcOEt, 1:1 v/v) to give the alcohol (**2**) (506 mg, 97%) as a colorless oil; $[\alpha]_D^{27}$ -19.8° (*c* 1.10, $CHCl_3$); IR (thin film): 3450, 2955, 2930, 2860, 1755, 1693, 1392, 1377, 1256, 1204, 1178, 1144, 1116, 840, 786 cm^{-1}; ^{1}H-NMR δ: 4.44-4.57 (m, 1H), 4.21 (and rotamer at 4.26) (dd, *J* = 1.6, 9.2 Hz, 1H), 4.04-4.17 (and rotamer at 3.80-3.95) (m, 1H), 3.73 (s, 3H), 3.59-3.78 (m, 2H), 2.65 (br s, 1H), 1.50-2.24 (m, 6H), 1.39 (and rotamer at 1.47) (s, 9H), 0.88 (s, 9H), 0.07 (br s, 6H); CIMS (*m/z*): 418 (M$^+$+1); *Anal.* Calcd for $C_{20}H_{39}NO_6Si$: C, 57.52; H, 9.41; N, 3.35. Found: C, 57.32, H, 9.52, N, 3.41.

Methyl (4R,5R)-4-(*tert*-butyldimethylsilyloxy)-5-(3-hydroxypropyl)-L-prolinate (3) and

Methyl (4R,5R)-5-(3-*tert*-butoxypropyl)-4-(*tert*-butyldimethylsilyloxy)-L-prolinate (4): To a solution of **2** (500 mg, 1.20 mmol) in CH_2Cl_2 (12.0 mL) was added $ZnBr_2$ (540 mg, 2.40 mmol) and the mixture was stirred for overnight at rt. After removal of insoluble materials by filtration through Celite pad, the filtrate was treated with saturated aqueous $NaHCO_3$, and extracted with $CHCl_3$. The extract was washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography (AcOEt:MeOH, 90:1 v/v) to give the *tert*-butyl ether (**4**) (66.9 mg, 15%) as a colorless oil; $[\alpha]_D^{28}$ -35.3° (*c* 0.65, $CHCl_3$); IR (thin film): 3350, 2950, 2930, 2860, 1740, 1254, 1200, 1085, 835, 775 cm^{-1}; ^{1}H-NMR δ: 4.14-4.23 (m, 1H), 4.03 (t, *J* = 8.2 Hz, 1H), 3.72 (s, 3H), 3.28-3.42 (m, 2H), 2.99-3.09 (m, 1H), 2.19 (br s, 1H), 2.13 (br dd, *J* = 8.2, 13.3 Hz, 1H), 1.99 (ddd, *J* = 4.3, 8.2, 13.3 Hz, 1H), 1.50-1.64 (m, 4H), 1.17 (s, 9H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C-NMR δ: -5.1, -4.6, 17.9, 25.6, 26.2, 27.3, 28.1, 39.9, 51.9, 57.9, 61.4, 63.9, 72.2, 73.2, 175.7; CIMS (*m/z*): 374 (M$^+$+1), HRMS *m/z* calcd for $C_{19}H_{40}NO_4Si$ (M$^+$+1): 374.2726, found: 374.2741. Further elution with the same solvent system afforded the amino-alcohol (**3**) (268 mg, 71%) as a colorless oil; $[\alpha]_D^{29}$ -22.2° (*c* 0.89, $CHCl_3$); IR (thin film): 3320, 2950, 2930, 2855, 1738, 1253, 1214, 1080, 1040, 835, 775 cm^{-1}; ^{1}H-NMR δ: 4.16-4.21 (m, 1H), 4.02 (t, *J* = 8.1 Hz, 1H), 3.72 (s, 3H), 3.54-3.73 (m, 2H), 3.33 (br s, 2H), 2.99 (dt, *J* = 3.6, 8.7 Hz, 1H), 2.13 (ddd, *J* = 2.0, 8.1, 13.5 Hz, 1H), 2.02 (ddd, *J* = 4.6, 8.1, 13.5 Hz, 1H), 1.39-1.81 (m, 4H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C-NMR δ: -5.0, -4.6, 17.9, 25.6, 27.3, 30.7, 39.7, 52.0, 57.5, 62.7, 63.9, 74.2, 175.1; EIMS (*m/z*): 317 (M$^+$); HRMS *m/z* calcd for $C_{15}H_{31}NO_4Si$ (M$^+$):

317.2022, found: 317.2043.

Methyl (4R,5R)-1-(*tert*-butoxycarbonyl)-5-(3-*tert*-butoxypropyl)-4-(*tert*-butyldimethylsilyloxy)-

L-prolinate (5): To a stirred mixture of **2** (200 mg, 0.48 mmol), Mg(ClO$_4$)$_2$ (11.0 mg, 48.0 μmol), and

CH$_2$Cl$_2$ (2 mL) was added (Boc)$_2$O (253 μL, 1.10 mmol), and the resulting mixture was stirred at reflux

for overnight. The reaction mixture was diluted with water and extracted with CH$_2$Cl$_2$. The extract was

concentrated, and the residue was purified by silica gel column chromatography (*n*-hexane:AcOEt, 9:1

v/v) to give the ether (**5**) (101 mg, 45%) as a colorless oil; $[\alpha]_D^{18}$ -14.1° (*c* 0.94, CHCl$_3$); IR (thin film):

2970, 2930, 2860, 1752, 1700, 1392, 1364, 1256, 1200, 1116, 840, 780 cm^{-1}; ^{1}H-NMR δ: 4.40-4.55 (m,

1H), 4.16-4.30 (m, 1H), 3.95-4.07 (and rotamer at 3.84-3.95) (m, 1H), 3.72 (and rotamer at 3.73) (s, 3H),

3.26-3.40 (m, 2H), 1.40-2.23 (m, 6H), 1.38 (and rotamer at 1.46) (s, 9H), 1.17 (s, 9H), 0.89 (s, 9H), 0.06

(br s, 6H); EIMS (*m/z*): 473 (M$^+$); HRMS *m/z* calcd for C$_{24}$H$_{47}$NO$_6$Si (M$^+$): 473.3172, found: 473.3146.

Deprotection of the *N*-Boc group of the ether (5) to the *tert*-butyl ether (4): To a solution of **5** (85.1

mg, 0.18 mmol) in CH$_2$Cl$_2$ (2.0 mL) was added ZnBr$_2$ (81.0 mg, 0.36 mmol) and the mixture was stirred

for overnight at rt. After removal of insoluble materials by filtration through Celite pad, the filtrate was

treated with saturated aqueous NaHCO$_3$, and extracted with CHCl$_3$. The extract was washed with brine,

and dried over Na$_2$SO$_4$. Evaporation of the solvent gave a residue, which was purified by silica gel

column chromatography (AcOEt:MeOH, 90:1 v/v) to give the *tert*-butyl ether (**4**) (66.5 mg, 99%) as a

colorless oil. The spectra were identical with those of the compound prepared above.

(1R,3S,7aR)-1-(*tert*-Butyldimethylsilyloxy)hexahydro-1H-pyrrolizine-3-carboxylate (7):

(Method A) To a mixed solution of **3** (300 mg, 0.95 mmol) and CBr$_4$ (392 mg, 1.18 mmol) in CH$_2$Cl$_2$

(6.0 mL) was added Ph$_3$P (372 mg, 1.42 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min, and

then triethylamine (2.0 mL, 14.2 mmol) was added. After stirring for 10 min, the reaction mixture was

evaporated to give a residue. The residue was extracted with *n*-pentane. The organic layer was

concentrated in vacuo, and the residue was purified by silica gel column chromatography (AcOEt:MeOH,

19:1 v/v) to give the bicyclic ester (**7**) (210 mg, 74%) as a colorless oil; $[\alpha]_D^{28}$ -44.7° (*c* 0.49, CHCl$_3$); IR

(thin film): 2955, 2930, 2860, 1744, 1255, 1198, 1048, 835, 775 cm^{-1}; ^{1}H-NMR δ: 4.10-4.15 (m, 1H),

3.74 (s, 3H), 3.66-3.73 (m, 1H), 3.55 (dd, *J* = 7.4, 9.0 Hz, 1H), 3.04-3.13 (m, 1H), 2.50-2.62 (m, 1H),

2.12-2.17 (m, 2H), 1.80-1.90 (m, 3H), 1.58-1.67 (m, 1H), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C-NMR δ: -5.2, -4.8, 17.8, 24.4, 25.6, 27.3, 41.7, 51.8, 55.2, 66.3, 70.0, 72.4, 175.0; EIMS (*m/z*): 299 (M$^+$); HRMS *m/z* calcd for $C_{15}H_{29}NO_3Si$ (M$^+$): 299.1917, found: 299.1890.

(Method B) To a solution of **2** (99.3 mg, 0.24 mmol) and TEA (50.0 μL, 0.36 mmol) in CH_2Cl_2 (5.0 mL) was added methanesulfonyl chloride (22.0 μL, 0.29 mmol) at 0 °C and the reaction mixture was stirred for 0.5 h. After quenching by addition of saturated aqueous NH_4Cl, the mixture was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product (**6**) was dissolved in CH_2Cl_2 (2.4 mL), and $ZnBr_2$ (108 mg, 0.48 mmol) was added to the solution, and the resulting mixture was stirred for overnight at rt. After removal of insoluble materials by filtration through Celite pad, the filtrate was treated with saturated aqueous $NaHCO_3$, and extracted with $CHCl_3$. The extract was washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography (AcOEt:MeOH, 19:1 v/v) to give the bicyclic ester (**7**) (61.2 mg, 86%) with spectra identical to those of the compound prepared above.

(8R,8aR)-8-(*tert*-Butyldimethylsilyloxy)hexahydroindolizin-5(1H)-one (8): To a stirred solution of **7** (430 mg, 1.44 mmol) in THF (4.0 mL) was added a solution of SmI_2 (0.2 M in THF, 21.6 mL, 4.31 mmol) containing HMPA (750 μL, 4.31 mmol) and MeOH (148 μL, 3.60 mmol) at 0 °C. The solution was gradually warmed up to rt, and stirred for further 2 h at the same temperature. To this solution were added excess of saturated aqueous $NaHCO_3$ and Et_2O, and the whole was stirred for 30 min. After removal of insoluble materials by filtration through Celite pad, the filtrate was extracted with AcOEt, and the extract was washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography (AcOEt:MeOH, 10:1 v/v) to give the indolizidinone (**8**) (333 mg, 86%) as a colorless solid; mp 51-53 °C; $[\alpha]_D^{28}$ +22.5° (*c* 0.37, CHCl$_3$); IR (thin film): 2955, 2930, 2860, 1628, 1460, 1234, 1101, 835, 775 cm^{-1}; ^{1}H-NMR δ: 4.07 (dt, *J* = 1.8, 3.8 Hz, 1H), 3.40-3.62 (m, 3H), 2.50 (ddd, *J* = 7.1, 12.2, 17.8 Hz, 1H), 2.32 (br dd, *J* = 7.1, 17.8 Hz, 1H), 1.65-2.04 (m, 6H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C-NMR δ: -5.1, -4.7, 17.9, 21.9, 25.6, 26.1, 27.8, 28.8, 45.1, 63.0, 64.4, 168.9; CIMS (*m/z*): 270 (M$^+$+1); *Anal.* Calcd for $C_{14}H_{27}NO_2Si$: C, 62.20; H, 10.10; N, 5.20. Found: C, 62.20, H, 10.21, N, 5.25.

(+)-(8*R*, 8a*R*)-8-Hydroxy-5-indolizidinone (9): To a stirred solution of **8** (210 mg, 0.78 mmol) in THF (4.0 mL) was added TBAF (1.0 M in THF, 0.94 mL, 0.94 mmol), and the resulting mixture was stirred at rt for 1.5 h. The volatiles were removed under reduced pressure, and the residue was purified by silica gel column chromatography (AcOEt:MeOH, 10:1 v/v) afforded the hydroxyl-lactam (**9**) (118 mg, 97%) as a colorless solid; mp 100-102 °C; $[\alpha]_D^{28}$ +38.0° (*c* 2.40, CHCl$_3$); IR (KBr): 3390, 2950, 1604, 1483, 1413, 806 cm^{-1}; ^{1}H-NMR δ: 4.07-4.14 (m, 1H), 3.64 (br s, 1H), 3.34-3.54 (m, 3H), 2.46 (ddd, *J* = 7.4, 11.8, 18.4 Hz, 1H), 2.28 (br dd, *J* = 7.4, 18.4 Hz, 1H), 1.58-2.12 (m, 6H); ^{13}C-NMR δ: 21.9, 26.0, 27.4, 28.3, 45.2, 52.5, 63.2, 169.2; CIMS (*m/z*): 156 (M$^+$+1); HRMS *m/z* calcd for C$_8$H$_{14}$NO$_2$ (M$^+$+1): 156.1024, found: 156.1041.

(+)-(8*R*, 8a*R*)-Perhydro-8-indolizinol (10): To a solution of **9** (80.0 mg, 0.52 mmol) in THF (5.0 mL), borane-methyl sulfide complex (0.2 M in THF, 1.0 mL, 2.06 mmol) was added at 0 °C, and the reaction mixture was warmed to rt and stirred for 4 h. The excess of reducing agent was quenched by careful addition of EtOH (2.0 mL) at 0 °C. The solvent was evaporated and the residue was dissolved in EtOH (8.0 mL). The solution was heated under reflux temperature for 2 h, and then cooled to rt. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (*n*-hexane:AcOEt, 2:1 v/v) afforded **10** (60.2 mg, 83%) as a colorless solid; mp 101-103 °C; $[\alpha]_D^{28}$ +19.9° (*c* 1.20, CHCl$_3$); IR (KBr): 3430, 2962, 2365, 1470, 1450, 1180, 1095, 1022, 855 cm^{-1}; ^{1}H-NMR δ: 4.41 (dt, *J* = 4.9, 11.0 Hz, 1H), 3.28-3.40 (m, 1H), 3.13-3.27 (m, 1H), 3.02-3.12 (m, 1H), 2.76 (dt, *J* = 3.6, 12.2 Hz, 1H), 2.56 (dt, *J* = 3.1, 12.2 Hz, 1H), 1.72-2.23 (m, 6H), 1.42-1.68 (m, 2H); ^{13}C-NMR δ: 18.8, 19.8, 22.3, 26.3, 51.7, 64.0, 65.2, 68.7; EIMS (*m/z*): 141 (M$^+$); HRMS *m/z* calcd for C$_8$H$_{15}$NO (M$^+$): 141.1154, found: 141.1157.

Methyl (4*R*,5*R*)-1,5-diallyl-4-(*tert*-butyldimethylsilyloxy)-L-prolinate (11): To a stirred solution of **1** (649 mg, 1.62 mmol) in CH$_2$Cl$_2$ (16.0 mL) was added ZnBr$_2$ (732 mg, 3.25 mmol) at rt, and the mixture was stirred for overnight. After removal of insoluble materials by filtration through Celite pad, the filtrate was treated with saturated aqueous NaHCO$_3$, and extracted with CHCl$_3$. The extract was washed with brine, and dried over Na$_2$SO$_4$ and concentrated under reduced pressure. To the solution of the product in

DMF (4.0 mL), were added allyl bromide (280 μL, 3.24 mmol) and NaH (60% in oil, 97.2 mg, 2.43 mmol) at 0 °C, and the mixture was stirred for 3 h at the same temperature. After quenching by addition of saturated aqueous NH_4Cl, the whole mixture was extracted with AcOEt. The extract was washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography (*n*-hexane:AcOEt, 19:1 v/v) to give *N*-allyl compound (**11**) (442 mg, 80%) as a colorless oil; $[\alpha]_D^{27}$ -44.5° (*c* 1.30, $CHCl_3$); IR (thin film): 2955, 1737, 1640, 1254, 1196, 1165, 1128, 840, 775 cm^{-1}; ^{1}H-NMR δ: 5.76-5.99 (m, 2H), 4.95-5.19 (m, 4H), 4.49 (dt, *J* = 6.7, 6.7 Hz, 1H), 3.72 (dd, *J* = 4.4, 8.1 Hz, 1H), 3.66 (s, 3H), 3.20-3.42 (m, 3H), 2.31-2.44 (m, 1H), 2.16-2.29 (m, 1H), 1.95-2.14 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C-NMR δ: -4.9, -4.5, 18.0, 25.8, 31.7, 38.0, 51.4, 53.2, 61.8 ,65.0, 115.8, 117.0, 136.0, 137.3, 175.1; CIMS (*m/z*): 340 (M$^+$+1); *Anal.* Calcd for $C_{18}H_{33}NO_3Si$: C, 63.67; H, 9.80; N, 4.13. Found: C, 63.38; H, 10.10; N, 4.15.

Methyl (1*R*,3*S*,8a*R*)-1-(*tert*-butyldimethylsilyloxy)-1,2,3,5,8,8a-hexahydroindolizine-3-carboxylate (12): To a stirred solution of **11** (440 mg, 1.30 mmol) in benzene (17.0 mL) was added Grubbs' 2nd generation ruthenium catalyst (22.0 mg, 26.0 μmol) at rt, and the mixture was stirred for 1 h at 80 °C. After concentration, the residue was purified by silica gel column chromatography (*n*-hexane:AcOEt, 15:1 v/v) to give the olefinic bicyclic compound (**12**) (325 mg, 81%) as a colorless oil; $[\alpha]_D^{29}$ +21.5° (*c* 1.90, $CHCl_3$); IR (thin film): 2955, 2930, 1736, 1256, 1194, 1165, 1120, 839, 775 cm^{-1}; ^{1}H-NMR δ: 5.76-5.86 (m, 1H), 5.59-5.68 (m, 1H), 4.51 (ddd, *J* = 2.8, 4.9, 10.7 Hz, 1H), 3.91 (dd, *J* = 3.1, 9.0 Hz, 1H), 3.69 (s, 3H), 3.23-3.32 (m, 2H), 3.12-3.22 (m, 1H), 2.24-2.41 (m, 2H), 2.05 (ddd, *J* = 4.6, 9.0, 13.7 Hz, 1H), 1.82-1.94 (m, 1H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C-NMR δ: -4.9, -4.7, 18.1, 24.7, 25.8, 37.9, 47.4, 51.3, 59.0, 62.4, 72.1, 124.2, 125.0, 174.0; EIMS (*m/z*): 311 (M$^+$); HRMS *m/z* calcd for $C_{16}H_{29}NO_3Si$ (M$^+$): 311.1917, found: 311.1907.

Methyl (1*R*,3*S*,8a*R*)-1-(*tert*-butyldimethylsilyloxy)octahydroindolizine-3-carboxylate (13): To a stirred solution of **12** (320 mg, 1.03 mmol) in AcOEt (15.0 mL) was added 10% Pd-C (7.0 mg), and the mixture was stirred under an atmosphere of H_2 for 2 h. The reaction mixture was filtrated through Celite pad. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography (*n*-hexane:AcOEt, 4:1 v/v) to give the saturated bicyclic compound (**13**) (308 mg, 94%) as a colorless oil;

$[\alpha]_D^{28}$ -37.6° (c 1.65, CHCl$_3$); IR (thin film): 2950, 2935, 1736, 1256, 1192, 1168, 1149, 1120, 1045, 835, 775 cm^{-1}; ^{1}H-NMR δ: 4.38 (ddd, J = 3.3, 5.3, 7.4 Hz, 1H), 3.90 (dd, J = 2.6, 9.0 Hz, 1H), 3.67 (s, 3H), 2.98-3.07 (m, 1H), 2.77 (ddd, J = 3.1, 5.3, 10.4 Hz, 1H), 2.32-2.42 (m, H), 2.30 (ddd, J = 2.6, 7.4, 13.8 Hz, 1H), 2.00 (ddd, J = 3.3, 9.0, 13.8 Hz, 1H), 1.76-1.87 (m, 1H), 1.16-1.62 (m, 5H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C-NMR δ: -4.9, -4.8, 18.2, 23.7, 24.2, 25.4, 25.8, 37.8, 48.3, 51.0, 62.4, 63.7, 72.9, 173.7; EIMS (m/z): 313 (M$^+$); HRMS m/z calcd for C$_{16}$H$_{31}$NO$_3$Si (M$^+$): 313.2073, found: 313.2094.

(1R,9aR)-1-($tert$-Butyldimethylsilyloxy)octahydro-4H-quinolizin-4-one (14): Reductive deamination of **13** was carried out by the same procedure as described for the preparation of **8** using SmI$_2$ (0.2 M in THF, 14.8 mL, 2.95 mmol) to furnish the quinolizidinone (**14**) (239 mg, 86%) as a colorless solid; mp <30 °C; $[\alpha]_D^{28}$ -8.63° (c 1.39, CHCl$_3$); IR (KBr): 2950, 2930, 2855, 1645, 1258, 1104, 1064, 840, 775 cm^{-1}; ^{1}H-NMR δ: 4.69-4.80 (m, 1H), 3.97 (ddd, J = 2.5, 4.1, 6.6 Hz, 1H), 3.21 (dt, J = 3.6, 10.7 Hz, 1H), 2.63 (ddd, J = 5.8, 10.2, 17.2 Hz, 1H), 2.38 (dt, J = 3.0, 12.7 Hz, 1H), 2.30-2.46 (m, 1H), 1.33-2.00 (m, 8H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C-NMR δ: -5.0, -4.7, 17.9, 24.2, 25.2, 25.6, 27.3, 27.8, 27.9, 42.6, 61.4, 67.1, 168.7; EIMS (m/z): 283 (M$^+$); HRMS m/z calcd for C$_{15}$H$_{29}$NO$_2$Si (M$^+$): 283.1967, found: 283.1993.

(1R,9aR)-1-Hydroxy-4-quinolizidinone (15): Deprotection of the silyl group of **14** was carried out by the same procedure as described for the preparation of **9** using TBAF (1.0 M in THF, 399 µL, 0.40 mmol) to furnish the lactam (**15**) (50.8 mg, 91%) as a colorless solid; mp 160-161 °C; $[\alpha]_D^{27}$ -7.25° (c 0.67, CHCl$_3$); IR (KBr): 3260, 2920, 2860, 1605, 1475, 1452, 1334, 1276, 1104 cm^{-1}; ^{1}H-NMR δ: 4.68-4.79 (m, 1H), 4.00-4.09 (m, 1H), 3.30 (dt, J = 2.9, 11.2 Hz, 1H), 2.63 (ddd, J = 5.9, 10.0, 17.3 Hz, 1H), 2.27-2.50 (m, 2H), 2.13 (br s, 1H), 1.35-2.07 (m, 8H); ^{13}C-NMR δ: 24.1, 25.1, 26.8, 27.2, 27.8, 42.7, 60.6, 66.3, 168.7; EIMS (m/z): 169 (M$^+$), HRMS m/z calcd for C$_9$H$_{15}$NO$_2$ (M$^+$): 169.1103, found: 169.1088.

Methyl (2R)-N-($tert$-butoxycarbonyl)-4-(dimethylaminomethylene)pyroglutamate (19): A mixture of **18** (11.0 g, 45.4 mmol), and toluene (88.0 mL), and $tert$-butoxybis(dimethylamino)methane (Bredereck's reagent) (10.0 g, 54.7 mmol) was heated at 100 °C for overnight. The solvent was removed under reduced pressure, and the solid residue crystallized from Et$_2$O to yield the enaminone (**19**) (13.5 g, 96%) as a pale yellow powder; mp 125-127 °C; $[\alpha]_D^{19}$ +41.0° (c 0.54, CHCl$_3$); IR (KBr): 2980, 1766, 1700, 1622, 1318,

1156, 960 cm^{-1}; ^{1}H-NMR δ: 7.12-7.16 (m, 1H), 4.55 (dd, J = 3.8, 10.5 Hz, 1H), 3.75 (s, 3H), 3.19-3.32 (m, 1H), 3.02 (s, 6H), 2.84-2.96 (m, 1H), 1.49 (s, 9H); ^{13}C-NMR δ: 26.2, 27.9, 41.9, 52.3, 55.9, 82.2, 90.8, 146.4, 150.4, 169.4, 172.6; EIMS (m/z): 298 (M^{+}); HRMS calcd for $C_{14}H_{22}N_2O_5$ (M^{+}): 298.1528, found: 298.1513.

Methyl (2R,4R)-N-(tert-butoxycarbonyl)-4-methylpyroglutamate (21) and

Methyl (2R,4S)-N-(tert-butoxycarbonyl)-4-methylpyroglutamate (20): A mixture of **19** (10.5 g, 35.2 mmol) and 10% Pd/C (1.50 g) in iPrOH (250 mL) and AcOEt (50.0 mL) was stirred under an atmosphere of H$_2$ for 5 days at rt. The reaction mixture was filtrated through Celite pad. Evaporation of the solvent afforded an oil, which was purified by silica gel column chromatography (n-hexane:AcOEt, 4:1 v/v) to give the *trans* isomer (**20**) (269 mg, 3.0%) as a colorless oil; $[\alpha]_D^{18}$ +10.2° (c 0.92, CHCl$_3$); IR (KBr): 2980, 1792, 1750, 1716, 1317, 1154 cm^{-1}; ^{1}H-NMR δ: 4.57 (dd, J = 1.3, 9.6 Hz, 1H), 3.78 (s, 3H), 2.60-2.78 (m, 1H), 2.28 (ddd, J = 1.3, 8.7, 13.2 Hz, 1H), 1.93 (ddd, J = 9.6, 11.7, 13.2 Hz, 1H), 1.50 (s, 9H), 1.22 (d, J = 7.2 Hz, 3H); ^{13}C-NMR δ: 14.9, 27.7, 30.2, 36.4, 52.3, 56.7, 83.3, 149.3, 171.6, 175.4; EIMS (m/z): 257 (M^{+}); HRMS calcd for $C_{12}H_{19}NO_5$ (M^{+}): 257.1263, found: 257.1287. Further elution with the same solvent system afforded the *cis* isomer (**21**) (8.2 g, 91%) as a colorless solid; mp 82-84 °C; $[\alpha]_D^{16}$ +39.0° (c 0.56, CHCl$_3$); IR (KBr): 2980, 1792, 1751, 1716, 1320, 1294, 1155 cm^{-1}; ^{1}H-NMR δ: 4.45-4.55 (m, 1H), 3.78 (s, 3H), 2.49-2.68 (m, 2H), 1.60-1.66 (m, 1H), 1.26 (d, J = 6.8 Hz, 3H), 1.49 (s, 9H), 1.26 (d, J = 6.8 Hz, 3H); ^{13}C-NMR δ: 15.8, 27.6, 29.4, 37.2, 52.2, 57.1, 83.3, 149.1, 171.8, 175.4; EIMS (m/z): 257 (M^{+}); *Anal.* Calcd for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44. Found: C, 56.28; H, 7.41; N, 5.47.

Methyl (4R,5S)-1-(tert-butoxycarbonyl)-4-methyl-5-[(N-methoxy-N-methylcarbonyl)methyl]-D-

prolinate (23): To a solution of **21** (2.4 g, 9.34 mmol) in THF (72.0 mL) was added LiBEt$_3$H (1.0 M in THF, 10.3 mL, 10.3 mmol) at -78 °C. After the mixture was stirred for 30 min at the same temperature, it was quenched with saturated aqueous NaHCO$_3$ and warmed to 0 °C. To the above mixture was added 12 drops of a 30% H$_2$O$_2$ aqueous solution at 0 °C and the solution was stirred at 0 °C for 20 min. After removal of THF under reduced pressure, the remaining aqueous layer was extracted with Et$_2$O. The organic extracts were combined, dried over Na$_2$SO$_4$. Evaporation of the solvent gave a crude aminal (**22**),

which was used for the next step without further purification.

A suspension of NaH (65-75% in oil, 450 mg, 11.2 mmol) was diluted with THF (62.0 mL) and treated

dropwise with diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate (2.30 mL, 11.2 mmol) for 1 h

at rt. A solution of **22** in THF (10.0 mL) was added to the mixture, and the whole was further stirred

overnight at rt. The mixture was quenched with saturated aqueous NH_4Cl and extracted with AcOEt. The

combined organic extracts were dried over Na_2SO_4 and the solvent was evaporated to dryness and

purified by silica gel column chromatography (*n*-hexane:AcOEt, 4:1 v/v) to give the amide (**23**) (3.1 g,

96%) as a colorless solid; mp 79-80 °C; $[\alpha]_D^{22}$ +42.8° (*c* 1.11, $CHCl_3$); IR (KBr): 2975, 1751, 1700, 1662,

1390, 1366, 1200, 1178 cm^{-1}; ^{1}H-NMR δ: 4.27 (and rotamer at 4.34) (dd, *J* = 3.8, 9.7 Hz, 1H), 3.94-4.07

(m, 1H), 3.73 (and rotamer at 3.74) (s, 3H), 3.69 (and rotamer at 3.68) (s, 3H), 3.17 (br s, 3H), 3.02 (and

rotamer at 2.94) (dd, *J* = 3.6, 15.7 Hz, 1H), 2.39-2.66 (m, 2H), 2.12-2.34 (m, 1H), 1.58-1.75 (m, 1H), 1.39

(and rotamer at 1.47) (s, 9H), 1.11 (and rotamer at 1.13) (d, *J* = 7.1 Hz, 3H); EIMS (*m/z*): 344 (M$^+$); *Anal.*

Calcd for $C_{16}H_{28}N_2O_6$: C, 55.80; H, 8.19; N, 8.13. Found: C, 55.66; H, 7.97; N, 8.15.

Methyl (4*R*,5*S*)-4-methyl-5-[(*N*-methoxy-*N*-methylcarbonyl)methyl]-D-prolinate (24): To a solution

of **23** (50.0 mg, 0.11 mmol) in CH_2Cl_2 (1.1 mL) was added TFA (84.0 mL, 1.07 mmol) at 0 °C, and the

resulting mixture was stirred for overnight. The reaction solution was washed with saturated aqueous

$NaHCO_3$, dried over Na_2SO_4 and evaporated under reduced pressure to afford a pale yellow oil (**24**) (32

mg, 90%); IR (thin film): 3350, 2960, 1736, 1660, 1456, 1435, 1220, 1152, 1000 cm^{-1}; ^{1}H-NMR δ: 3.85 (t,

J = 7.6 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 3.17 (s, 3H), 3.12-3.23 (m, 1H), 2.70 (dd, *J* = 2.8, 15.9 Hz,

1H), 2.30-2.54 (m, 2H), 1.72-7.94 (m, 1H), 1.53 (ddd, *J* = 7.6, 9.9, 12.5 Hz, 1H), 1.02 (d, *J* = 6.6 Hz, 3H);

^{13}C-NMR δ: 16.6, 31.9, 36.9, 38.0, 39.1, 51.9, 57.9, 60.9, 61.0, 173.1, 175.7; CIMS (*m/z*): 245 (M$^+$+1);

HRMS *m/z* calcd for $C_{11}H_{21}N_2O_4$ (M$^+$+1): 245.1501, found: 245.1510.

Methyl (4*R*,5*S*)-5-allyl-1-(*tert*-butoxycarbonyl)-4-methyl-D-prolinate (26): To a stirred solution of **23**

(500 mg, 1.45 mmol) in THF (58.0 mL), was added DIBAL (0.94 M in hexane, 3.10 mL, 2.91 mmol) at

-78 °C. After the mixture was stirred for 30 min at the same temperature, it was quenched with saturated

aqueous NH_4Cl and warmed to rt. The insoluble material was filtered through Celite pad, and the filtrate

was extracted with AcOEt. The extract was dried over Na_2SO_4. Evaporation of the solvent gave a crude

aldehyde (**25**), which was used for the next step without further purification.

To a stirred solution of methyltriphenylphosphonium bromide (883 mg, 2.47 mmol) in THF (28 mL), was added NaHMDS (1.0 M in THF, 2.18 mL, 2.18 mmol) at -78 °C, and the resulting mixture was stirred for further 30 min at 0 °C. To this solution was added a solution of **25** in THF (10.0 mL) at -78 °C, the solution was gradually warmed up to rt, and stirred for 1 h at the same temperature. The mixture was treated with saturated aqueous NH$_4$Cl, and extracted with AcOEt. The extract was washed with brine and dried over Na$_2$SO$_4$. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography (*n*-hexane:AcOEt, 4:1 v/v) to give the alkene (**26**) (392 mg, 95%) as a colorless oil; $[\alpha]_D^{22}$ +75.5° (*c* 1.87, CHCl$_3$); IR (KBr): 2980, 1752, 1700, 1390, 1365, 1200, 1176 cm^{-1}; ^{1}H-NMR δ: 5.62-5.84 (m, 1H), 4.00-5.14 (m, 2H), 4.21 (and rotamer at 4.27) (dd, *J* = 4.6, 9.4 Hz, 1H), 3.72 (and rotamer at 3.73) (s, 3H), 3.60-3.68 (and rotamer at 3.50-3.58) (m, 1H), 2.32-2.52 (m, 3H), 2.04-2.22 (m, 1H), 1.54-1.66 (m, 1H), 1.40 (and rotamer at 1.48) (s, 9H), 1.06 (d, *J* = 7.1 Hz, 3H); CIMS (*m/z*): 284 (M$^+$+1), HRMS *m/z* calcd for C$_{15}$H$_{26}$NO$_4$ (M$^+$+1): 284.1862, found: 284.1888.

Methyl (4*R*,5*S*)-5-allyl-4-methyl-D-prolinate (27): To a solution of **26** (480 mg, 1.69 mmol) in CH$_2$Cl$_2$ (11.0 mL) was added TFA (1.3 mL, 16.9 mmol) at 0 °C, and the resulting mixture was stirred for overnight. The reaction solution was washed with saturated aqueous NaHCO$_3$, dried over Na$_2$SO$_4$ and evaporated under reduced pressure to give the amine (**27**) as a pale yellow oil; IR (thin film): 3350, 2960, 1736, 1680, 1440, 1200, 1135 cm^{-1}; ^{1}H-NMR δ: 5.76-5.95 (m, 1H), 5.04-5.22 (m, 2H), 3.96(t, *J* = 8.0 Hz, 1H), 3.74 (s, 3H), 3.53 (br s, 1H), 2.86 (dt, *J* = 4.1, 8.6 Hz, 1H), 2.34-2.53 (m, 1H), 2.08-2.24 (m, 1H), 1.75-1.94 (m, 1H), 1.54 (ddd, *J* = 8.0, 10.0, 12.7 Hz, 1H), 1.03 (d, *J* = 6.4 Hz, 3H); ^{13}C-NMR δ: 16.8, 38.0, 38.1, 38.8, 52.1, 57.6, 64.5, 117.0, 135.2, 175.1; CIMS (*m/z*): 184 (M$^+$+1), HRMS *m/z* calcd for C$_{10}$H$_{18}$NO$_2$ (M$^+$+1): 184.1337, found: 184.1331. This compound was used without further purification in the next reaction.

(5*R*,6*S*)-6-Allyl-5-methylpiperidin-2-one (28): To a stirred solution of **27** in THF (4.0 mL) was added a solution of SmI$_2$ (0.2 M in THF, 25.4 mL, 5.09 mmol) containing HMPA (0.89 mL, 5.09 mmol) and MeOH (175 μL, 4.24 mmol) at 0 °C. The solution was gradually warmed up to rt, and stirred for further overnight at the same temperature. To this solution were added excess of saturated aqueous NaHCO$_3$ and

Et$_2$O, and the whole was stirred for 30 min. After removal of insoluble materials by filtration through Celite pad, the filtrate was extracted with AcOEt, and the extract was washed with brine, and dried over Na$_2$SO$_4$. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography (AcOEt:MeOH, 19:1 v/v) to give the lactam (**28**) (234 mg, 90%) as a colorless solid; mp 44-47 °C; [α]$_D^{22}$ +63.9° (*c* 0.70, CHCl$_3$); IR (thin film): 3210, 2930, 1665, 1410, 915 cm^{-1}; ^{1}H-NMR δ: 5.61-5.90 (m, 2H), 5.12-5.26 (m, 2H), 2.99 (dt, *J* = 2.9, 8.7 Hz, 1H), 2.40-2.58 (m, 1H), 2.25-2.44 (m, 2H), 1.99 (dt, *J* = 9.2, 14.0 Hz, 1H), 1.75-1.87 (m, 1H), 1.44-1.64 (m, 2H), 1.50 (d, *J* = 6.1 Hz, 3H); ^{13}C-NMR δ: 17.8, 28.9, 30.9, 32.9, 38.8, 57.8, 119.6, 133.3, 171.9; CIMS (*m/z*): 154 (M$^+$+1); HRMS *m/z* calcd for C$_9$H$_{16}$NO (M$^+$+1): 154.1247, found: 154.1232.

(5*R*,6*S*)-6-Allyl-5-methyl-1-(2-methylprop-2-en-1-yl)piperidin-2-one (29): To a mixed solution of **28** (210 mg, 1.37 mmol) and 3-bromo-2-methylpropene (0.41 mL, 4.11 mmol) in DMF (15.0 mL) was added portionwise NaH (82.0 mg, 2.06 mmol) at 0 °C under argon, and the mixture was allowed to stir for 30 min. After quenching by addition of saturated aqueous NH$_4$Cl, the resulting mixture was extracted with AcOEt, washed with brine, and dried over Na$_2$SO$_4$. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography (AcOEt) to give the olefin (**29**) (248 mg, 87%) as a colorless oil; [α]$_D^{18}$ -37.2° (*c* 1.01, CHCl$_3$); IR (thin film): 3075, 2930, 1644, 1468, 1440, 1419, 1377, 1350, 1283, 1257, 1221, 1185, 1167, 1000, 914 cm^{-1}; ^{1}H-NMR δ: 5.68 (m, 1H), 5.06-5.15 (m, 2H), 4.91 (d, *J* = 1.3 Hz, 1H), 4.83 (dd, *J* = 0.8, 1.3 Hz, 1H), 4.79 (d, *J* = 15.0 Hz, 1H), 3.32 (d, *J* = 15.0 Hz, 1H), 3.06 (ddd, *J* = 3.5, 3.6, 8.7 Hz, 1H), 2.22-2.55 (m, 4H), 1.90-2.08 (m, 2H), 1.69 (t, *J* = 0.7 Hz, 3H), 1.41-1.57 (m, 1H), 1.05 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR δ: 18.3, 19.9, 23.7, 28.7, 28.9, 36.5, 49.1, 60.4, 113.1, 118.0, 133.7, 140.6, 169.9; EIMS (*m/z*): 207 (M$^+$); HRMS *m/z* calcd for C$_{13}$H$_{21}$NO (M$^+$): 207.1623, found: 207.1610.

(5*R*,9a*S*)-1,7-Dimethyl-1,2,3,6,9,9a-hexahydro-4*H*-quinolizin-4-one (30): The bicyclic lactam (**30**) (521 mg, 96%) was synthesized from the olefin (**29**) (630 mg, 3.04 mmol) by the same procedure as described for the preparation of **12**; [α]$_D^{21}$ -168.1° (*c* 1.03, CHCl$_3$); IR (thin film): 2960, 2930, 1730, 1639, 1463, 1449, 1420, 1381, 1348, 1308, 1273, 1235, 1191, 1160, 1039, 952 cm^{-1}; ^{1}H-NMR δ: 5.46 (m, 1H), 4.61 (d, *J* = 18.5 Hz, 1H), 3.33 (d, *J* = 18.5 Hz, 1H), 3.00 (ddd, *J* = 3.6, 6.6, 11.0 Hz, 1H), 2.25-2.54

(m, 3H), 1.90-2.06 (m, 1H), 1.81 (dddd, J = 3.3, 4.6, 5.3, 13.0 Hz, 1H), 1.59-1.74 (m, 4H), 1.50 (ddt, J = 5.3, 10.4, 13.0 Hz, 1H), 1.09 (d, J = 6.6 Hz, 3H); ^{13}C-NMR δ: 18.4, 19.9, 26.8, 31.1, 31.6, 34.1, 45.5, 58.7, 117.7, 130.4, 169.0; EIMS (m/z): 179 (M$^+$); HRMS m/z calcd for C$_{11}$H$_{17}$NO (M$^+$): 179.1310, found: 179.1289.

Methyl (4R,5R)-5-allyl-4-methyl-1-(2-methylprop-2-en-1-yl)-D-prolinate (31): To a solution of **26** (500 mg, 1.77 mmol) in CH$_2$Cl$_2$ (18.0 mL) was added TFA (1.36 mL, 17.7 mmol) at 0 °C, and the resulting mixture was stirred for overnight. The reaction solution was washed with saturated aqueous NaHCO$_3$, dried over Na$_2$SO$_4$ and evaporated under reduced pressure. The product was dissolved in DMF (4.0 mL), 3-bromo-2-methylpropene (535 μL, 5.31 mmol) and NaH (60% in oil, 106 mg, 2.66 mmol) were added at 0 °C, and the mixture was stirred for 30 min. After quenching by addition of saturated aqueous NH$_4$Cl, the resulting mixture was extracted with AcOEt, washed with brine, and dried over Na$_2$SO$_4$. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography (n-hexane:AcOEt, 19:1 v/v) to give the alkene (**31**) (368 mg, 88% from **26**) as a colorless oil; [α]$_D^{26}$ +65.4° (c 0.69, CHCl$_3$); IR (thin film): 2955, 1737, 1456, 1435, 1374, 1360, 1197, 1170, 1146, 900 cm^{-1}; ^{1}H-NMR δ: 5.74-5.90 (m, 1H), 4.98-5.11 (m, 2H), 3.64 (s, 3H), 3.62-3.67 (m, 1H), 3.27 (d, J = 13.3 Hz, 1H), 3.15 (d, J = 13.3 Hz, 1H), 2.85 (dt, J = 3.3, 6.6 Hz, 1H), 2.10-2.24 (m, 1H), 2.25-2.42 (m, 2H), 1.89-2.04 (m, 1H), 1.72-1.73 (m, 3H), 1.39 (ddd, J = 3.5, 5.3, 13.0 Hz, 1H), 1.02 (d, J = 6.8 Hz, 3H); ^{13}C-NMR δ: 19.5, 20.6, 35.3, 35.9, 36.1, 50.9, 54.2, 61.6, 67.4, 112.2, 116.3, 135.4, 143.7, 175.5; CIMS (m/z): 238 (M$^+$+1); HRMS m/z calcd for C$_{14}$H$_{24}$NO$_2$ (M$^+$+1): 238.1807, found: 238.1789.

Methyl (1R,3R,8aS)-1,6-dimethyl-1,2,3,5,8,8a-hexahydroindolizine-3-carboxylate (32): The bicyclic ester (**32**) (93.0 mg, 70%) was synthesized from the alkene (**31**) (150 mg, 0.63 mmol) by the same procedure as described for the preparation of **12**; [α]$_D^{25}$ -64.2° (c 2.20, CHCl$_3$); IR (thin film): 2950, 1746, 1452, 1434, 1377, 1358, 1195, 1170, 1145, 805 cm^{-1}; ^{1}H-NMR δ: 5.40-5.48 (m, 1H), 3.92 (dd, J = 3.9, 9.2 Hz, 1H), 3.70 (s, 3H), 3.07-3.13 (m, 2H), 2.63 (ddd, J = 4.1, 8.1, 9.7 Hz, 1H), 2.43 (dt, J = 9.2, 13.0 Hz, 1H), 2.17-2.30 (m, 1H), 1.72-1.93 (m, 2H), 1.65-1.68 (m, 3H), 1.52 (ddd, J = 3.9, 7.6, 13.0 Hz, 1H), 1.08 (d, J = 6.7 Hz, 3H); ^{13}C-NMR δ: 17.8, 20.7, 31.0, 35.8, 39.4, 50.9, 51.1, 61.9, 63.0, 118.7, 132.1, 174.7; CIMS (m/z): 210 (M$^+$+1); HRMS m/z calcd for C$_{12}$H$_{20}$NO$_2$ (M$^+$+1): 210.1494, found: 210.1496.

Reductive deamination of the bicyclic ester (32) to the bicyclic lactam (30): Following the same procedure as described for the preparation of **8**, the bicyclic ester (**32**) (90.0 mg, 0.43 mmol) was treated with SmI$_2$ (0.2 M in THF, 6.5 mL, 1.29 mmol) to furnish the bicyclic lactam (**30**) (63.0 mg, 82%) as a colorless solid. The spectra were identical with those of an authentic sample.

(1*R*,9a*S*)-1,7-Dimethyloctahydro-4*H*-quinolizin-4-one (33): A mixture of **30** (51.0 mg, 0.28 mmol) and 10% Pd/C (50.0 mg) in MeOH (5.0 mL) was stirred under H$_2$ for 1 hr at rt. The catalyst was filtered on Celite pad and rinsed with AcOEt. Evaporation of the filtrate afforded an oil, which was purified by silica gel column chromatography (*n*-hexane:AcOEt, 1:2 v/v) to give the lactam (**33**) (46.6 mg, 90%) as a colorless oil; IR (thin film): 2930, 1700, 1640, 1466, 1440, 1420, 1261, 970 cm^{-1}; ^{1}H-NMR δ: 4.72 (ddd, *J* = 1.3, 3.9, 13.0 Hz, 0.23H), 4.53 (dt, *J* = 2.2, 13.0 Hz, 0.77H), 2.24-2.85 (m, 4H), 1.30-2.05 (m, 8H), 1.06 (d, *J* = 6.3 Hz, 0.69H), 1.05 (d, *J* = 6.3 Hz, 2.31H), 0.96 (d, *J* = 7.1 Hz, 0.69H), 0.90 (d, *J* = 7.1 HZ, 2.31H); CIMS (*m/z*): 182 (M$^+$+1); HRMS *m/z* calcd for C$_{11}$H$_{19}$NO (M$^+$+1): 182.1545, found: 182.1524.

(1*R*,4*S*,9a*S*)-4-(3-Furyl)-1,7-dimethyl-1,3,4,5,9,9a-hexahydro-2*H*-quinolizine (35)

and diastereoisomer (36): To a mixed solution of 3-bromofuran (0.23 mL, 2.51 mmol) in THF (15.0 mL) was added dropwise *n*-butyllithium (1.5 M solution in hexane, 1.26 mL, 1.88 mmol) at -78 °C under argon, and the mixture was allowed to stir for 30 min. A solution of **30** (225 mg, 1.26 mmol) in THF (2.5 mL x 2) was added to the mixture at -78 °C, and resulting mixture was stirred for 1 h at -78 °C warming to 0 °C. After quenching by addition of saturated aqueous NH$_4$Cl, the mixture was extracted with AcOEt, washed with brine, and dried over Na$_2$SO$_4$. Evaporation of the solvent gave the enamine (**34**); ^{1}H-NMR δ: 7.39 (s, 1H), 7.35 (dd, *J* = 1.6, 1.8 Hz, 1H), 6.41 (dd, *J* = 0.8, 1.8 Hz, 1H), 5.43-5.49 (m, 1H), 4.78 (dd, *J* = 2.3, 6.3 Hz, 1H), 3.52 (d, *J* = 16.8 Hz, 1H), 2.89 (dt, *J* = 1.2, 16.8 Hz, 1H), 2.52 (ddd, *J* = 3.8, 9.7, 9.9 Hz, 1H), 2.19-2.33 (m, 1H), 1.69-2.14 (m, 4H), 1.58 (d, *J* = 0.8 Hz, 3H), 0.98 (d, *J* = 6.4 Hz, 3H); ^{13}C-NMR δ: 18.5, 20.6, 30.9, 31.1, 32.7, 53.9, 60.5, 102.3, 110.7, 119.1, 124.8, 132.2, 138.9, 139.5, 142.3, which, without further purification, was used in the next step.

To a stirred solution of **34** in MeOH (5.0 mL) was added NaBH$_4$ (68.0 mg, 1.79 mmol) at rt. After stirring for 1 h, the reaction mixture was quenched by addition of saturated aqueous NaHCO$_3$, and then removed of MeOH under the reduced pressure. The resulting mixture was extracted with AcOEt, washed with

brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane:AcOEt, 10:1 v/v) to give (*S*)-furyl compound (**35**) (164 mg, 57%) as an amorphous solid as the first eluent; $[\alpha]_D^{19}$ -162.3° (*c* 0.57, CHCl$_3$); IR (thin film): 2925, 2770, 1596, 1573, 1501, 1450, 1439, 1377, 1349, 1330, 1308, 1292, 1250, 1219, 1184, 1163, 1125, 1097, 1070, 1033, 1020, 977, 874 cm^{-1}; ^{1}H-NMR δ: 7.33-7.37 (m, 2H), 6.48 (dd, *J* = 0.8, 1.5 Hz, 1H), 5.36 (m, 1H), 2.93-3.03 (m, 2H), 2.27-2.40 (m, 2H), 1.66-2.02 (m, 5H), 1.35-1.54 (m, 4H), 1.16-1.29 (m, 1H), 0.93 (d, *J* = 6.6 Hz, 3H); ^{13}C-NMR δ: 18.8, 20.7, 31.9, 33.4, 34.4, 37.5, 56.9, 61.2, 64.2, 109.5, 118.3, 128.4, 131.4, 139.3, 142.8; EIMS (*m/z*): 231 (M$^+$); HRMS *m/z* calcd for $C_{15}H_{21}NO$ (M$^+$): 231.1623. found: 231.1646. Further elution with the same solvent system gave (*R*)-furyl compound (**36**) (27.0 mg, 9%) as a light yellow oil as the second eluent; $[\alpha]_D^{26}$ -104.4° (*c* 0.16, CHCl$_3$); IR (thin film): 2930, 2875, 1499, 1458, 1439, 1377, 1261, 1188, 1176, 1160, 1130, 1108, 1061, 1045, 1028, 972, 874 cm^{-1}; ^{1}H-NMR δ: 7.39 (t, *J* = 1.6 Hz, 1H), 7.35 (s, 1H), 6.37 (m, 1H), 5.37 (m, 1H), 4.03 (t, *J* = 4.1 Hz, 1H), 2.94 (dt, *J* = 1.2, 16.6 Hz, 1H), 2.84 (d, *J* = 16.6 Hz, 1H), 2.48 (ddd, *J* = 4.7, 8.2, 9.2 Hz, 1H), 2.18-2.32 (m, 1H), 1.88-2.11 (m, 2H), 1.67-1.79 (m, 1H), 1.35-1.66 (m, 6H), 1.02 (d, *J* = 6.1 Hz, 3H); ^{13}C-NMR δ: 18.9, 20.7, 27.6, 30.6, 31.2, 36.7, 54.4, 54.7, 56.8, 111.9, 118.0, 124.9, 131.5, 139.9, 142.3; EIMS (*m/z*): 231 (M$^+$); HRMS *m/z* calcd for $C_{15}H_{21}NO$ (M$^+$): 231.1623, found: 231.1643.

(-)-Deoxynupharidine (16) and (-)-7-*epi*-deoxynupharidine (17): To a solution of **35** (68.0 mg, 0.29 mmol) in MeOH (3.0 mL) was added Pd(OH)$_2$ (3.4 mg, 5.0% w/w of **35**), and the mixture was allowed to stir for 4 h at rt under H$_2$ atmosphere. After filtration through Celite pad, the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane:AcOEt, 10:1 v/v) to give **16** (46 mg, 68%) as a colorless oil as the first eluent; $[\alpha]_D^{22}$ -108.3° (*c* 0.53, CHCl$_3$), $[\alpha]_D^{26}$ -105.4° (*c* 0.33, EtOH); IR (thin film): 1505, 1463, 1449, 1437, 1391, 1290, 1242, 1180, 1157, 1118, 1093, 1064, 1029, 1018, 972, 875 cm^{-1}; ^{1}H-NMR δ: 7.33 (m, 1H), 7.52 (br s, 1H), 6.38 (br d, *J* = 1.3 Hz, 1H), 2.96 (dd, *J* = 6.1, 6.9 Hz, 1H), 2.63 (ddd, *J* = 1.5, 2.8, 11.4 Hz, 1H), 1.82 (dd, *J* = 3.1, 11.4 Hz, 1H), 1.24-1.77 (m, 1H), 1.04-1.20 (m, 1H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H); ^{13}C-NMR δ: 17.5, 19.1, 25.6, 28.4, 30.4, 33.8, 34.9, 35.6, 58.1, 60.0, 69.5, 109.5, 129.9, 139.1, 142.6; EIMS (*m/z*): 233 (M$^+$); HRMS *m/z* calcd for $C_{15}H_{23}NO$ (M$^+$): 233.1780, found: 233.1788. Further elution with the same solvent system

afforded **17** (7.8 mg, 11%) as a colorless oil as the second eluent; $[\alpha]_D^{22}$ -115.7° (*c* 0.52, CHCl$_3$), $[\alpha]_D^{23}$ -109.3° (*c* 0.46, EtOH); IR (thin film): 2925, 2850, 2770, 1501, 1458, 1437, 1375, 1330, 1311, 1290, 1238, 1174, 1161, 1113, 1066, 1028, 970, 959, 874 cm^{-1}; ^{1}H-NMR δ: 7.35 (m, 1H), 7.29 (dd, *J* = 0.7, 1.5 Hz, 1H), 6.43 (br d, *J* = 1.2 Hz, 1H), 2.89 (dd, *J* = 3.3, 10.5 Hz, 1H), 2.81 (ddd, *J* = 2.1, 3.5, 11.2 Hz, 1H), 1.90-1.99 (m, 1H), 1.61-1.82 (m, 4H), 1.09-1.58 (m, 6H), 0.76-0.95 (m, 1H), 0.90 (d, *J* = 6.3 Hz, 3H), 0.73 (d, *J* = 6.6 Hz, 3H); ^{13}C-NMR δ: 19.2, 19.9, 30.1, 31.1, 33.5, 34.0, 34.9, 36.4, 60.9, 61.3, 69.3, 109.6, 128.9, 139.5, 142.8; EIMS (*m/z*): 233 (M$^+$); HRMS *m/z* calcd for C$_{15}$H$_{23}$NO (M$^+$): 233.1780, found: 233.1788.

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