NOVEL CHIRAL SYNTHETIC PATH TO INDOLIZIDINE AND QUINOLIZIDINE ALKALOIDS BY MEANS OF A SAMARIUM DIIODIDE-PROMOTED REDUCTIVE CARBON-NITROGEN CLEAVAGE REACTION: SYNTHESIS OF (+)-(8R, 8aR)-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 (+)-(8R, 8aR)-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. 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. The effectiveness of this reaction for the construction of ring-enlarged lactams 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 (4R)-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\(_2\)Cl\(_2\) 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)\(_2\)O and Mg(ClO\(_4\))\(_2\), followed by deprotection of the N-Boc group of the resulting ether (5) with zinc bromide in CH\(_2\)Cl\(_2\). 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\(_2\)Cl\(_2\) 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\(_2\)Cl\(_2\), followed by deprotection of the N-Boc group of the mesylate (6) with zinc bromide in CH\(_2\)Cl\(_2\), in 86% overall yield.

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\text{Scheme 1. Reagents and conditions: (a) 9-BBN, THF, 0 °C; (b) 3N NaOH, 30% H\(_2\)O\(_2\), 0 °C to rt (97%); (c) ZnBr\(_2\), CH\(_2\)Cl\(_2\), rt (3: 71%, 4: 15%); (d) CBr\(_4\), Ph\(_3\)P, CH\(_2\)Cl\(_2\), 0 °C then TEA (74%); (e) MsCl, TEA, CH\(_2\)Cl\(_2\), 0 °C; (f) ZnBr\(_2\), CH\(_2\)Cl\(_2\), rt (86% from 2)}
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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), 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. The spectroscopic data of 10 were identical with those reported in the literature except for the sign of optical rotation \([\alpha]_D +19.9^\circ (c=1.2, \text{CHCl}_3); \text{lit.}, [\alpha]_D -17.4^\circ (c=1.15, \text{CHCl}_3)\).

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 CH₂Cl₂, 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.

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,\textsuperscript{12} a central paralysis effect\textsuperscript{13} and weak anti-metastatic activity,\textsuperscript{14} and (-)-7-\textit{epi}-deoxynupharidine showed insecticidal activity.\textsuperscript{11}

Figure 1. The structures of (-)-deoxynupharidine and (-)-7-\textit{epi}-deoxynupharidine

Thus, methyl \textit{N-}\textit{tert}-butoxycarbonylpyroglutamate (18) was reacted with Bredereck’s reagent\textsuperscript{15} in toluene at 100°C to give the enaminone (19) in 96% yield. Catalytic reduction of 19 over 10% palladium on carbon in \textit{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 (\textit{N}-methoxy-\textit{N}-methylcarbamoylmethyl)phosphonate\textsuperscript{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 \textit{S}, by comparison of the NMR data of 24 with those of the related compounds prepared by us previously,\textsuperscript{4} and finally determined by its conversion to the natural product.

Scheme 5. \textit{Reagents and conditions:} (a) \textit{tert}-BuOCH(NMe\textsubscript{2})\textsubscript{2}, toluene, 100 °C (96%); (b) \text{H}_2, 10\% \text{Pd}-\text{C}, \textit{i}-\text{PrOH-AcOEt} (5:1), \text{rt} (20: 3\%, 21: 91\%); (c) \text{LiEt}_3\text{BH}, \text{THF}, -78 °C; (d) \text{NaH}, (\text{EtO})\textsubscript{2}\text{P(O)}\text{CH}_2\text{CON(Me)}\text{OMe}, \text{THF, rt (96\% from 21)}; (e) \text{TFA, CH}_2\text{Cl}_2, 0 °\text{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, Ph₃PCH₂Br⁻, 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 CH₂Cl₂, 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 ratio of 7S:7R=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.

\[ \text{Scheme 7. Reagents and conditions: (a) H₂, 10% Pd-C, MeOH, rt (90%) (7S:7R = 3.4:1.0); (b) 3-lithiofuran, THF, -78 °C; (c) NaBH₄, MeOH, rt (35: 57% from 30, 36: 9% from 30); (d) H₂, Pd(OH)₂, MeOH, rt (16: 68%, 17: 11%)} \]
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, 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 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. 1H- and 13C-NMR spectra were obtained on JEOL LAMBDA-270 (1H-NMR: 270 MHz, 13C-NMR: 67.8 MHz) instrument for solutions in CDCl₃ 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 (4R,5R)-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% H₂O₂ (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 Na₂SO₄. 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; [α]D° -19.8° (c 1.10, CHCl₃); IR (thin film): 3450, 2955, 2930, 2860, 1755, 1693, 1392, 1377, 1256, 1204, 1178, 1144, 1116, 840, 786 cm⁻¹; ¹H-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⁺); Anal. Calcd for C₂₀H₃₉NO₆Si: 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 CH₂Cl₂ (12.0 mL) was added ZnBr₂ (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 NaHCO₃, and extracted with CHCl₃. The extract was washed with brine, and dried over Na₂SO₄. 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; [α]D° -35.3° (c 0.65, CHCl₃); IR (thin film): 3350, 2950, 2930, 2860, 1740, 1254, 1200, 1085, 835, 775 cm⁻¹; ¹H-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); ¹³C-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⁺); HRMS m/z calcd for C₁₉H₄₀NO₄Si (M⁺): 374.2741. Further elution with the same solvent system afforded the amino-alcohol (3) (268 mg, 71%) as a colorless oil; [α]D° -22.1° (c 0.89, CHCl₃); IR (thin film): 3320, 2950, 2930, 2855, 1738, 1253, 1214, 1080, 1040, 835, 775 cm⁻¹; ¹H-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); ¹³C-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 C₁₅H₃₁NO₄Si (M⁺):
Methyl (4\(R\),5\(R\))-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 \(\mu\)mol), and CH\(_2\)Cl\(_2\) (2 mL) was added (Boc)\(_2\)O (253 \(\mu\)L, 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 \(\delta\): 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.

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

\(\text{Method A}\) 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 \(\delta\): 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); 13C-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 C13H29NO3Si (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 CH₂Cl₂ (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 NH₄Cl, the mixture was extracted with AcOEt. The extract was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product (6) was dissolved in CH₂Cl₂ (2.4 mL), and ZnBr₂ (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 NaHCO₃, and extracted with CHCl₃. The extract was washed with brine, and dried over Na₂SO₄. 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 SmI₂ (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 NaHCO₃ and Et₂O, 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 Na₂SO₄. 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; [α]D28 +22.5° (c 0.37, CHCl₃); IR (thin film): 2955, 2930, 2860, 1628, 1460, 1234, 1101, 835, 775 cm⁻¹; 1H-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); 13C-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 C14H27NO2Si: C, 62.20; H, 10.10; N, 5.20. Found: C, 62.20, H, 10.21, N, 5.25.
(+)-(8R, 8aR)-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; [α]D28 +38.0° (c 2.40, CHCl3); IR (KBr): 3390, 2950, 1604, 1483, 1413, 806 cm⁻¹; ¹H-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); 13C-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 C₈H₁₄NO₂ (M⁺+1): 156.1024, found: 156.1041.

(+)-(8R, 8aR)-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; [α]D28 +19.9° (c 1.20, CHCl3); IR (KBr): 3430, 2962, 2365, 1470, 1450, 1180, 1095, 1022, 855 cm⁻¹; ¹H-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); ¹³C-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 C₈H₁₅NO (M⁺): 141.1154, found: 141.1157.

Methyl (4R,5R)-1,5-diallyl-4-((tert-butyldimethylsilyloxy)-L-prolinate (11): To a stirred solution of 1 (649 mg, 1.62 mmol) in CH₂Cl₂ (16.0 mL) was added ZnBr₂ (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 NaHCO₃, and extracted with CHCl₃. The extract was washed with brine, and dried over Na₂SO₄ 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 NH₄Cl, the whole mixture was extracted with AcOEt. The extract was washed with brine, and dried over Na₂SO₄. 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; [α]D²⁷⁻₄₄.₅° (c 1.30, CHCl₃); IR (thin film): 2955, 1737, 1640, 1254, 1196, 1165, 1128, 840, 775 cm⁻¹; ¹H-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); ¹³C-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 C₁₈H₃₃NO₃Si: C, 63.67; H, 9.80; N, 4.13. Found: C, 63.38; H, 10.10; N, 4.15.

**Methyl (1R,3S,8aR)-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; [α]D²⁹⁺₂₁.₅° (c 1.90, CHCl₃); IR (thin film): 2955, 2930, 1736, 1256, 1194, 1165, 1120, 839, 775 cm⁻¹; ¹H-NMR δ: 5.76-5.86 (m, 1H), 5.59-5.68 (m, 1H), 4.51 (dd, 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 (dd, J = 4.6, 9.0, 13.7 Hz, 1H), 1.82-1.94 (m, 1H), 0.89 (s, 9H), 0.05 (s, 6H); ¹³C-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 C₁₆H₂₉NO₃Si (M⁺): 311.1917, found: 311.1907.

**Methyl (1R,3S,8aR)-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 H₂ 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;
[α]D<sup>28</sup> -37.6° (c 1.65, CHCl<sub>3</sub>); IR (thin film): 2950, 2935, 1736, 1256, 1192, 1168, 1149, 1120, 1045, 835, 775 cm<sup>-1</sup>; <sup>1</sup>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); <sup>13</sup>C-NMR δ: -4.9, -4.8, 18.2, 23.7, 24.2, 25.4, 25.8, 27.3, 27.8, 27.9, 42.6, 61.4, 67.1, 168.7; EIMS (m/z): 313 (M<sup>+</sup>); HRMS m/z calcd for C<sub>16</sub>H<sub>31</sub>NO<sub>3</sub>Si (M<sup>+</sup>): 313.2073, found: 313.2094.

(1R,9aR)-1-(tert-Butyldimethylsilyloxy)octahydro-4H-quinoliniz-4-one (14): Reductive deamination of 13 was carried out by the same procedure as described for the preparation of 8 using Sml<sub>2</sub> (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; [α]D<sup>28</sup> -8.63° (c 1.39, CHCl<sub>3</sub>); IR (KBr): 2950, 2930, 2855, 1645, 1258, 1104, 1064, 840, 775 cm<sup>-1</sup>; <sup>1</sup>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); <sup>13</sup>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<sup>+</sup>); HRMS m/z calcd for C<sub>15</sub>H<sub>29</sub>NO<sub>2</sub>Si (M<sup>+</sup>): 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; [α]D<sup>27</sup> -7.25° (c 0.67, CHCl<sub>3</sub>); IR (KBr): 3260, 2920, 2860, 1605, 1475, 1452, 1334, 1276, 1104 cm<sup>-1</sup>; <sup>1</sup>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); <sup>13</sup>C-NMR δ: 24.1, 25.1, 26.8, 27.2, 27.8, 27.9, 42.6, 66.3, 168.7; EIMS (m/z): 169 (M<sup>+</sup>); HRMS m/z calcd for C<sub>9</sub>H<sub>15</sub>NO<sub>2</sub> (M<sup>+</sup>): 169.1103, found: 169.1088.

Methyl (2R)-N-(tert-butoxycarbonyl)-4-(dimethylaminomethylene)pyroglutamate (19): A mixture of 18 (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<sub>2</sub>O to yield the enaminone (19) (13.5 g, 96%) as a pale yellow powder; mp 125-127 °C; [α]D<sup>19</sup> +41.0° (c 0.54, CHCl<sub>3</sub>); IR (KBr): 2980, 1766, 1700, 1622, 1318,
1156, 960 cm⁻¹; ¹H-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); ¹³C-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 C₁₄H₂₂N₂O₅ (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 H₂ 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; [α]D⁺ 18 +10.2° (c 0.92, CHCl₃); IR (KBr): 2980, 1792, 1750, 1716, 1317, 1154 cm⁻¹; ¹H-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); ¹³C-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 C₁₂H₁₉NO₅ (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; [α]D⁺ 16 +39.0° (c 0.56, CHCl₃); IR (KBr): 2980, 1792, 1751, 1716, 1320, 1294, 1155 cm⁻¹; ¹H-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); ¹³C-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 C₁₂H₁₉NO₅: 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 LiBEt₃H (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 NaHCO₃ and warmed to 0 °C. To the above mixture was added 12 drops of a 30% H₂O₂ 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 Et₂O. The organic extracts were combined, dried over Na₂SO₄. 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 NH₄Cl and extracted with AcOEt. The combined organic extracts were dried over Na₂SO₄ 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; [α]D22 +42.8° (c 1.11, CHCl₃); IR (KBr): 2975, 1751, 1700, 1662, 1390, 1366, 1200, 1178 cm⁻¹; ¹H-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⁺);

**Methyl (4R,5S)-4-methyl-5-[((N-methoxy-N-methylcarbamoyl)methyl]-D-prolinate (24):** To a solution of 23 (50.0 mg, 0.11 mmol) in CH₂Cl₂ (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 NaHCO₃, dried over Na₂SO₄ 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; ¹H-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); ¹³C-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⁺); HRMS m/z calcd for C₁₁H₂₁N₂O₄ (M⁺): 245.1501, found: 245.1510.

**Methyl (4R,5S)-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 NH₄Cl and warmed to rt. The insoluble material was filtered through Celite pad, and the filtrate was extracted with AcOEt. The extract was dried over Na₂SO₄. 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 NH4Cl, and extracted with AcOEt. The extract was washed with brine and dried over Na2SO4. 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; [α]D22 +75.5° (c 1.87, CHCl3); IR (KBr): 2980, 1752, 1700, 1390, 1365, 1200, 1176 cm-1; 1H-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 calcld for C15H26NO4 (M+1): 284.1862, found: 284.1888.

Methyl (4R,5S)-5-allyl-4-methyl-D-prolinate (27): To a solution of 26 (480 mg, 1.69 mmol) in CH2Cl2 (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 NaHCO3, dried over Na2SO4 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; 1H-NMR δ: 5.76-5.95 (m, 1H), 5.04-5.22 (m, 2H), 3.96(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); 13C-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 calcld for C10H18NO2 (M+1): 184.1337, found: 184.1331. This compound was used without further purification in the next reaction.

(5R,6S)-6-Allyl-5-methylpiperidin-2-one (28): To a stirred solution of 27 in THF (4.0 mL) was added a solution of SmI2 (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 NaHCO3 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; $[\alpha]_D^{22}$ +63.9° (c 0.70, CHCl$_3$); IR (thin film): 3210, 2930, 1665, 1410, 915 cm$^{-1}$; $^1$H-NMR $\delta$: 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 $\delta$: 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$^+$): 154.1247, found: 154.1232.

(5R,6S)-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; $[\alpha]_D^{18}$ -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 $\delta$: 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 (dd, $J = 3.5$, 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 $\delta$: 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.

(5R,9aS)-1,7-Dimethyl-1,2,3,6,9a-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; $[\alpha]_D^{21}$ -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 $\delta$: 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 (dddt, 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 \(\mu\)L, 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; \([\alpha]_D^{26} +65.4^\circ\) (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 (dddt, 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; \([\alpha]_D^{25} -64.2^\circ\) (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 (dddt, 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 (dddt, 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 SmI₂ (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.

\[(1R,9aR)-1,7-Dimethyl-octahydro-4H-quinolinizin-4-one (33):\] 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 H₂ 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 \(\delta\): 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.

\[(1R,4S,9aS)-4-(3-Furyl)-1,7-dimethyl-1,3,4,5,9,9a-hexahydro-2H-quinolizine (35) and diastereoisomer (36):\] 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 \(\delta\): 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); \(^1\)\(^3\)C-NMR \(\delta\): 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 NaBH₄ (68.0 mg, 1.79 mmol) at rt. After stirring for 1 h, the reaction mixture was quenched by addition of saturated aqueous NaHCO₃, and then removed of MeOH under the reduced pressure. The resulting mixture was extracted with AcOEt, washed with
brine, dried over Na₂SO₄, 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; \([\alpha]_D^{19} -162.3^\circ\) (c 0.57, CHCl₃); IR (thin film): 2925, 2770, 1596, 1573, 1501, 1450, 1377, 1349, 1330, 1308, 1292, 1250, 1219, 1184, 1163, 1125, 1097, 1070, 1033, 1020, 977, 874 cm⁻¹; \(^1\)H-NMR: 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: 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 C₁₅H₂₁NO (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; \([\alpha]_D^{26} -104.4^\circ\) (c 0.16, CHCl₃); IR (thin film): 2930, 2875, 1499, 1458, 1377, 1261, 1188, 1176, 1160, 1130, 1061, 1045, 1028, 972, 874 cm⁻¹; \(^1\)H-NMR: 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: 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 C₁₅H₂₁NO (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 H₂ 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; \([\alpha]_D^{22} -108.3^\circ\) (c 0.53, CHCl₃), \([\alpha]_D^{26} -105.4^\circ\) (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: 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: 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 C₁₅H₂₃NO (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; \([\alpha]_D^{22} -115.7^\circ \; (c \; 0.52, \; \text{CHCl}_3), \; [\alpha]_D^{23} -109.3^\circ \; (c \; 0.46, \; \text{EtOH}); \) IR (thin film): 2925, 2850, 2770, 1501, 1437, 1375, 1330, 1311, 1290, 1238, 1174, 1161, 1113, 1066, 1028, 970, 959, 874 cm\(^{-1}\); \(^1\)H-NMR \(\delta\): 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 \(\delta\): 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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REFERENCES AND NOTE

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