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Construction of 4a,8a-*cis*-Octahydroquinolin-7-one Core Using an Intramolecular Aldol Type of Cyclization: An Application to Enantioselective Total Synthesis of Lepadin B

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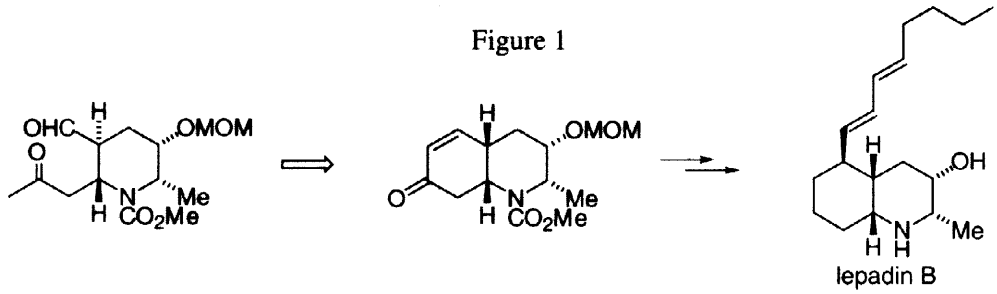
Abstract: An intramolecular aldol type of cyclization of the piperidine derivative **1** proceeded in highly stereoselective manner to afford the desired 4a,8a-*cis*-octahydroquinolin-7-one. This key step involves a feature of the use of $A^{(1,3)}$ strain as a control element, in biasing **1** towards the conformer desired for the above cyclization. An application of this aldol reaction to enantioselective total synthesis of the marine alkaloid lepadin B is also described.

The decahydroquinoline alkaloids represent one of the major classes of amphibian alkaloids,[1] and more recently these alkaloids have been found in the extracts of virgin queens of a myrmicine ant.[2] These alkaloids display interesting biological activities, therefore the extensive studies for the enantioselective construction of this ring system have been explored. These methods involve the strategies starting with the intramolecular Diels-Alder reaction of an acyclic *N*-acyl-*N*-dienyltriene,[3] biomimetic approach based on an iminium cyclization,[4] the enantioselective Birch reduction and reductive alkylation of anthranilic acid derivative,[5] ruthenium-catalyzed hydration of nitrile and transformation of δ-keto nitrile to ene-lactam,[6] the construction of 2,6-*cis*-disubstituted 4-piperidone ring system by using nice chiral 1-acylpyridinium chemistry,[7] an aqueous intramolecular acylnitroso Diels-Alder reaction,[8] palladium catalyzed intramolecular reductive cyclization of an ene-yne compound,[9] a highly diastereoselective lithium amide 1,4-conjugate addition to a dienoic ester,[10] the cyclization reaction of 3-aminoacrylate.[11]

In our continuous studies on the development of the synthesis of biologically and structurally interesting alkaloid,[12] we designed the new strategy for the construction of 4a,8a-*cis*-octahydroquinolin-7-one core, which would serve as a promising intermediate for the synthesis of decahydroquinoline alkaloid (Figure 1).

Figure 1



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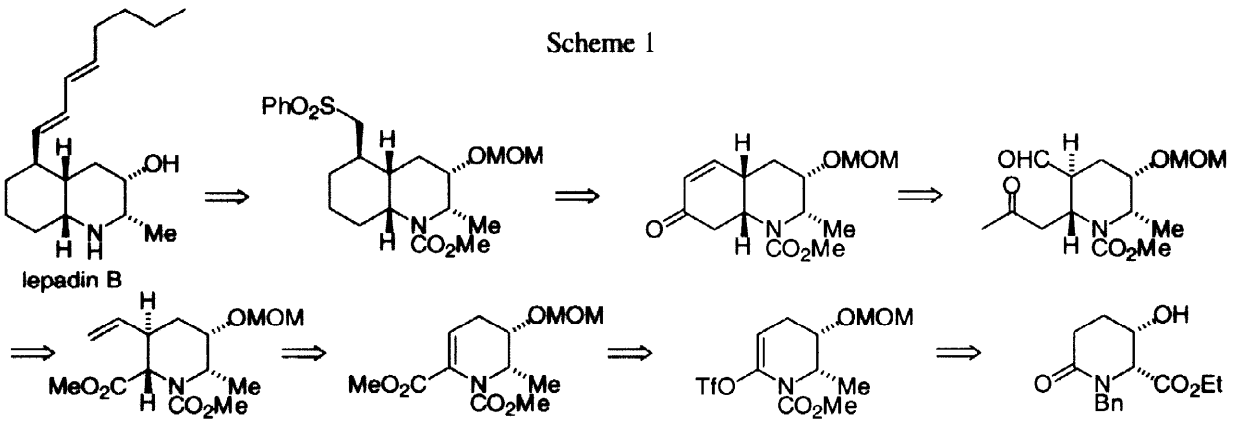
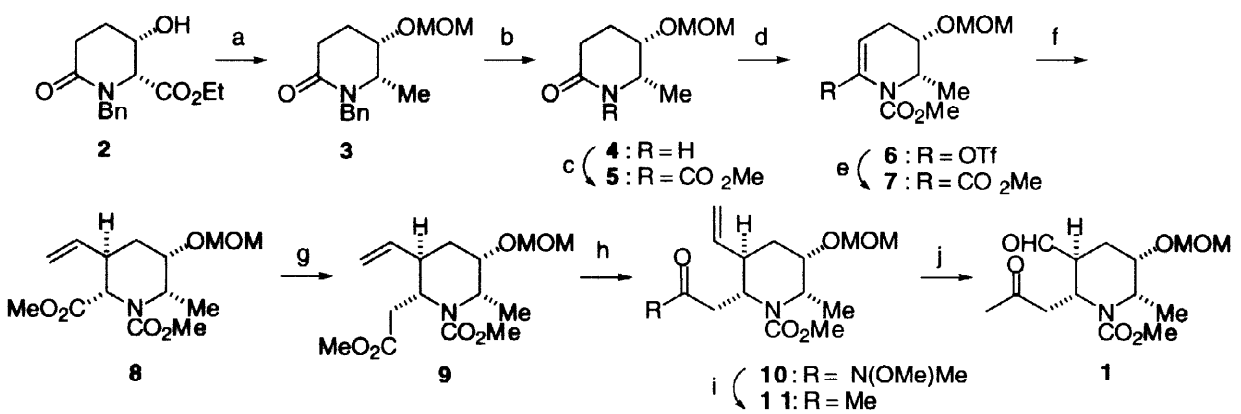
According to the above strategy, we achieved the enantioselective total synthesis of the marine alkaloid lepadin B, and here wish to report a full detail of this synthesis.[13] The synthetic plan followed the retrosynthetic analysis shown in Scheme 1.

Scheme 1



Birch reduction of **3**, which was obtained from enantiopure hydroxy ester **2**[12a] in 4 steps, gave piperidone **4**. Treatment of **4** with *n*-BuLi at -78 °C followed by the addition of $ClCO_2Me$ to the resulting anion afforded the carbamate **5**. Enol triflation of **5** with LiHMDS and *N*-(5-chloro-2-pyridyl)triflimide (Comins reagent)[14] proceeded smoothly to provide vinyl triflate **6** in good yield. The vinyl triflate **6** was converted to enecarbamate **7** by the use of Cacchi's protocol.[15] Copper-mediated 1,4-addition of vinyllithium to **7** gave the addition product **8** in high yield as a single isomer.[16] The carbon chain on the 2 position was elongated by an Arndt-Eistert sequence to afford the homologated ester **9**. Hydrolysis of the ester **9** with aqueous LiOH at 60 °C followed by the reaction of the resulting carboxylic acid with 1,1'-carbonyldiimidazole and then with *O*,*N*-dimethylhydroxylamine hydrochloride in the presence of Et_3N provided the Weinreb's amide[17] **10**. Reaction of **10** with MeMgBr afforded the methyl ketone **11**, whose terminal alkene was cleaved oxidatively to give the aldehyde **1** (Scheme 2).

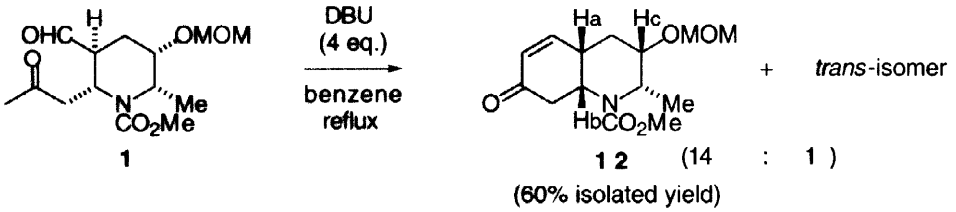
Scheme 2



Reagents and conditions: a: 85% overall yield from **3**; b: Na, liquid NH_3-THF (91%); c: *n*-BuLi, $ClCO_2Me$, THF, -78 °C to rt (77%); d: LiHMDS, *N*-(chloro-2-pyridyl)trifimide, THF, -78 to -50 °C (80%); e: $Pd(PPh_3)_4$, Et_3N, Ph_3P, MeOH, CO balloon, DMF, rt (74%); f: vinyllithium, CuI, Et_2O, -78 to -30 °C (89%); g: LiOH·H_2O, MeOH-H_2O (3:1), 60 °C; $ClCO_2Et$, Et_3N, THF, 0 °C; CH_2N_2, Et_2O; $PhCO_2Ag$, Et_3N, MeOH (71% in 4 steps); h: LiOH·H_2O, MeOH-H_2O (3:1) 60 °C; 1,1'-carbonyldiimidazole, Et_3N, *O*,*N*-dimethylhydroxylamine·hydrochloride, CH_2Cl_2, 0 °C to rt (83% in 2 steps); i: MeMgBr, THF, 0 °C to rt (97%); j: OsO_4, $NaIO_4$, dioxane-H_2O (1:1), rt (84%)

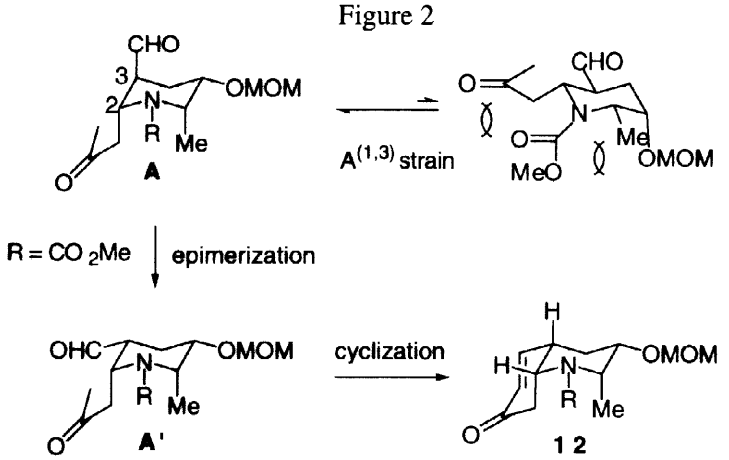
Of the reaction conditions examined for the above cyclization,[18] the use of 4 equivalents of DBU as a base in refluxing benzene gave the best result, and the 4a,8a-*cis*- and *trans*-octahydroquinolin-7-one was formed in a ratio of 14:1 which was estimated from the NMR spectrum of the crude product. The major product **12** was isolated in 60% yield by SiO_2 column chromatographic separation. The stereochemistry of **12** was determined to be desired *cis*-hexahydroquinolinone based on the observation of NOEs between Ha and Hb, Ha and Hc in the NOESY experiment (Scheme 3).

Scheme 3



The selective formation of desired 4a,8a-*cis*-enone **12** during the intramolecular aldol-type of cyclization of **1** can be rationalized as shown below. The conformation of **1** will be restricted to conformer **A** owing to $A^{(1,3)}$ strain between both substituents on α- and α'-positions and methoxylcarbonyl group on nitrogen,[19] so the appendages on C-2 and C-3 in conformer **A** lie in non-cyclizable *trans* diaxial orientation. Thus, the epimerization on C-3 will occur first to afford the conformer **A'**, which will cyclize smoothly to give the *cis*-enone **12** (Figure 2).

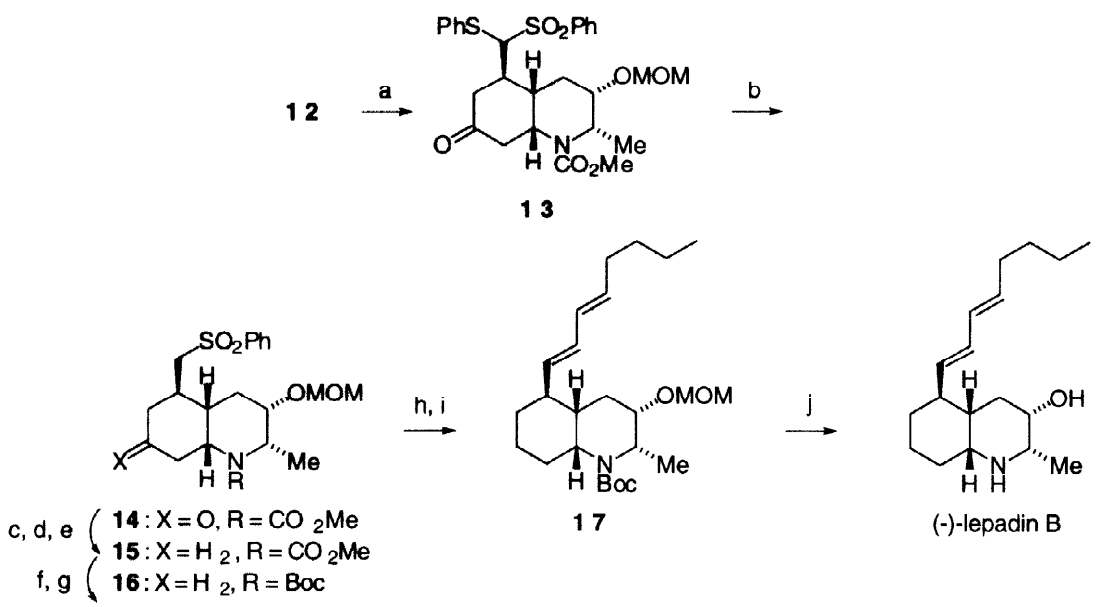
Figure 2



Next we examined the construction of octadienyl moiety by using the Julia coupling[20] on the C-5 position of enone **12**. Conjugate addition reaction of the anion of methyl phenyl sulfone, generated from the reaction of methyl phenyl sulfone with *n*-BuLi at -78 °C, with **12** gave not desired 1,4-addition product but the 1,2-addition product, exclusively.[21] Thus, we were forced to examine the addition reaction with another nucleophile. We chose phenylthiomethyl phenyl sulfone as a softer nucleophile. The reaction of the anion of phenylthiomethyl phenyl sulfone, generated from the reaction with *n*-BuLi at -78 °C, with **12** proceeded smoothly to provide the 1,4-addition product **13** as a 2:1 mixture of the diastereomers in high yield, which was subjected to the radical reduction of the phenylthio moiety with *n*-Bu_3SnH in the presence of the catalytic amount of AIBN to give the sulfone **14** as a single stereoisomer. Thus, the 1,4-addition reaction on the C-5 position of **12** was highly

stereoselective.[22] Reduction of **14** with $NaBH_4$ followed by thiocarbonylation of the resulting alcohol using 1,1'-thiocarbonyldiimidazole in refluxing $ClCH_2CH_2Cl$ afforded the Barton's ester,[23] radical reduction of which with *n*-Bu_3SnH gave the deoxygenated product **15**. Deprotection of methoxycarbonyl group under Corey's procedure[24] provided the amine, which was protected with $(Boc)_2O$ to give the Boc urethane **16**. Finally, Julia coupling of **16** with 2-heptenal under the standard condition afforded the diene **17**, which was treated with conc. hydrochloric acid in refluxing MeOH to furnish lepadin B (Scheme 4).

Scheme 4



Reagents and conditions: a: $PhSCH_2SO_2Ph$, *n*-BuLi, THF, -78 to -10 °C (78%); b: *n*-Bu_3SnH, AIBN, benzene, reflux (85%); c: $NaBH_4$, CH_2Cl_2-MeOH (10:1), 0 °C; d: 1,1'-thiocarbonyldiimidazole, $ClCH_2CH_2Cl$, reflux (75% in 2 steps); e: *n*-Bu_3SnH, toluene, reflux (84%); f: *n*-PrSLi, HMPA-THF, rt; g: $(Boc)_2O$, benzene, reflux (59% in 2 steps); h: *n*-BuLi, THF, -78 to -70 °C then 2-heptenal, -78 to -50 °C; i: Na-Hg, Na_2HPO_4, MeOH, rt (49% in 2 steps); j: concd HCl, MeOH, reflux (85%)

The spectral data for trifluoroacetate salt of synthetic lepadin B {$[\alpha]^{26}D$ -92.6 (MeOH)} were identical with those for trifluoroacetate salt of natural lepadin B {$[\alpha]D$ -96 (MeOH)}.[25]

In summary, the first total synthesis of lepadin B was accomplished by using the intramolecular aldol cyclization of the tetrasubstituted piperidine **1** as the key step, and the absolute stereochemistry of (-)-lepadin B was verified to be 2*S*, 3*S*, 4a*S*, 5*S*, 8a*R* by the present chiral synthesis.

Experimental

Microanalyses were performed by Microanalysis Center of Toyama Medical & Pharmaceutical University. ^1H NMR spectra were recorded at the indicated field strength as solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are given in parts per million (ppm, δ) downfield from TMS and are referenced to $CHCl_3$ (7.26 ppm) as internal standard. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR spectra were recorded at the indicated field strength as solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are given in parts per million (ppm, δ) downfield from TMS and are referenced to the center line of $CDCl_3$ (77.0 ppm) as internal standard. Carbon signals were assigned by a DEPT pulse sequence, q = methyl, t = methylene, d = methine, and s = quaternary carbons. Infrared spectra

(IR) were measured with a Perkin-Elemer 1600 series FT-IR spectrophotometer. Mass spectra (MS) and high-resolution mass spectra (HRMS) were measured on a JEOL JMS D-200 or JMS-AX505HD mass spectrometer. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. Column chromatography was performed on Merck silica gel 60 (No 7734-5B) or (No 9385).

Methyl 6-Methyl-5-(methoxymethoxy)-2-oxopiperidinecarboxylate (5): Metallic sodium (2 g, 87.0 mmol atm) was added to a stirred liquid NH_3 (150 mL) at -78 °C in a small portion, and the resulting deep blue solution was stirred at -78 °C for 0.5 h. To the solution was added **3** (2.1 g, 7.99 mmol) in THF (8 mL) at -78 °C, and then the resulting mixture was stirred under reflux for 0.5 h. The NH_3 was removed at 0 °C, and then the residue was diluted with $CHCl_3$. To the resulting solution was added H_2O carefully, and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (10 mL x 6), and the $CHCl_3$ layer and extracts were combined, washed with 10% HCl, brine, dried, and evaporated to give the amide **4** as a pale yellow solid (1.25 g, 91%), which was used directly in the next step.

To a stirred solution of the amide obtained above (1.25 g, 7.23 mmol) in THF (30 mL) was added *n*-BuLi (4.98 mL, 7.95 mmol, 10% w/v in hexane) at -78 °C, and the resulting solution was stirred at -78 °C for 0.5 h. To the resulting solution was added $ClCO_2Me$ (0.61 mL, 7.97 mmol) at the same temperature, and the solution was stirred at -78 °C for 0.5 h, then at -10 °C for 5 min. The reaction was quenched with satd. $NaHCO_3$, and the aqueous mixture was extracted with CH_2Cl_2 (40 mL x 2). The extracts were combined, dried, and evaporated to give a pale yellow oil, which was fractionated by column chromatography on SiO_2 (30 g, hexane:acetone=10:1~8:1) to afford **5** (1.29 g, 77%) as a colorless oil.

IR (neat) 2955, 1772, 1718 cm^{-1}; ^1H NMR (500 MHz) δ 1.17 (3H, dt, J = 7.0, 1.5 Hz), 1.88-1.94 (1H, m), 1.99 (3H, s), 2.14-2.23 (1H, m), 2.49-2.56 (1H, m), 2.71 (1H, dm, J = 17.5 Hz), 3.99-4.06 (2H, m), 4.10 (1H, d, J = 14.5 Hz), 4.21 (1H, d-like, J = 6.0 Hz), 4.95 (1H, d, J = 14.5 Hz), 5.10-5.15 (1H, quint-like, J = 6.0 Hz), 7.17-7.20 (2H, m), 7.23-7.29 (3H, m); ^{13}C NMR (125 MHz) δ 14.02 (q), 20.67 (t), 22.93 (t), 28.82 (q), 49.58 (t), 59.89 (d), 61.51 (t), 67.01 (d), 127.70 (d), 128.47 (d), 128.57 (d), 135.70 (s), 168.78 (s), 168.88 (s), 169.62 (s); MS 320 (M^++1), 319 (M^+), 91 (100); HRMS Calcd. for $C_{17}H_{21}NO_5$: 319.1420, Found 319.1441; $[\alpha]^{26}_D$ +22.8 (*c* 1.87, $CHCl_3$).

Methyl 6-[(Trifluoromethyl)sulfonyloxy]-2-methyl-3-(methoxymethoxy)-2*H*,3*H*,4*H*-azinecarboxylate (6): To a stirred solution of **5** (570 mg, 2.47 mmol) in THF (13 mL) was added LiHMDS (3.3 mL, 3.27 mmol, 1M in THF) at -78 °C, and the resulting solution was stirred at -78 °C for 0.5 h. To the resulting solution was added *N*-(5-chloro-2-pyridyl)triflimide (1.28 g, 3.27 mmol) in THF (5 mL) at -78 °C, and then the reaction mixture was stirred at -78 ~-50 °C for 0.5 h. The reaction was quenched with satd. NH_4Cl, and the aqueous mixture was extracted with Et_2O (40 mL x 2). The organic extracts were combined, dried, and evaporated to give a pale yellow solid, which was chromatographed on SiO_2 column (20 g, hexane:acetone=30:1) to afford **6** (713 mg, 80%) as a colorless oil.

IR (neat) 2957, 1733, 1683, 1281 cm^{-1}; ^1H NMR (500 MHz) δ 1.14 (3H, d, J = 6.8 Hz), 2.14 (1H, ddd, J = 18.2, 9.9, 3.2 Hz), 2.54 (1H, ddd, J = 18.2, 6.8, 4.1 Hz), 3.37 (3H, s), 3.78-3.82 (1H, m), 3.79 (3H, s), 4.63 & 4.65 (2H, ABq, J = 6.8 Hz), 4.65-4.68 (1H, m), 5.22 (1H, t, J = 3.9 Hz); ^{13}C NMR (125 MHz) δ 9.42 (q), 25.96 (t), 52.04 (d), 53.68 (q), 55.71 (q), 71.05 (d), 95.87 (t), 104.45 (d), 137.14 (s), 153.64 (s); MS 364 (M^++1), 363 (M^+), 68 (100); HRMS Calcd. for $C_{11}H_{16}F_3NO_7S$: 363.0599, Found 363.0615; $[\alpha]^{26}_D$ +57.8 (*c* 2.34, $CHCl_3$).

Methyl 2-Methyl-3-(methoxymethoxy)-6-(methoxycarbonyl)-2*H*,3*H*,4*H*-azinecarboxylate (7): To a stirred solution of **6** (2.525 g, 6.96 mmol) in DMF (30 mL) were added $Pd(PPh_3)_4$ (241 mg, 0.21 mmol) and Ph_3P (365 mg, 1.39 mmol), and the resulting solution was stirred at room temperature under CO balloon pressure for 10 min. To the mixture were added Et_3N (3.9 mL, 27.8 mmol) and MeOH (11.3 mL, 278.0 mmol), and the mixture was stirred under CO balloon presure for 1.5 h. The reaction mixture was diluted with H_2O (150 mL) and the aqueous mixture was extracted with Et_2O (50 ml x 4). The organic layers were combined, dried and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 column (50 g, hexane:acetone=20:1~15:1) to afford **7** (1.48 g, 74%) as a colorless oil.

IR (neat) 2953, 1717, 1652, 1043 cm^{-1}; ^1H NMR (500 MHz) δ 1.02 (3H, d, J = 6.8 Hz), 2.06 (2H, ddd, J = 19.4, 9.9, 3.5 Hz), 2.49 (1H, ddd, J = 19.4, 6.6, 4.1 Hz), 3.33 (3H, s), 3.66 (3H, br s), 3.70 (3H, s), 3.77-3.82 (1H, m), 4.56 (1H, br), 4.61 & 4.63 (2H, ABq, J = 6.8 Hz), 5.94 (1H, t, J = 3.7 Hz); ^{13}C NMR (125 MHz) δ 9.72 (q), 27.02 (t), 49.33 (d), 52.05 (q), 53.10 (q), 55.53 (q), 71.45 (d), 95.57 (t), 120.14 (d), 129.10 (s), 154.02 (s), 164.71 (s); MS 274 (M^++1), 273 (M^+), 59 (100); HRMS Calcd. for $C_{12}H_{16}NO_6$: 273.1212, Found 273.1192; $[\alpha]^{26}_D$ +58.4 (*c* 1.88, $CHCl_3$).

Methyl 3-Vinyl-6-methyl-5-(methoxymethoxy)-2-(methoxycarbonyl)piperidinecarboxylate (8): To a stirred solution of tetravinyltin (0.3 mL, 1.83 mmol) in Et_2O (5 mL) was added MeLi (7.33 mL, 7.33 mmol, 1M in Et_2O) at 0 °C, and the resulting mixture was stirred at 0 °C for 15 min. To a stirred suspension of CuI (698 mg, 3.66 mmol) in Et_2O (5 mL) was added the above vinyllithium solution in Et2O at -78 °C. The temperature was gradually raised to -35 °C and then recooled to -78 °C. To the suspension was added **7** (200 mg, 0.73 mmol) in Et_2O (5 mL) at -78 °C, and the temperature was gradually raised to -30 °C. The reaction was quenched with satd. NH_4Cl, and the insoluble material was removed by filtration through a Celite pad and washed with CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL x 3). The organic extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on SiO_2 column (20 g, hexane:acetone=20:1) to afford **8** (196 mg, 89%) as a colorless oil along with the starting material (14 mg, 7% recovered).

IR (neat) 2952, 1700, 1559, 1046 cm^{-1}; ^1H NMR (500 MHz) δ 1.02 (3H, t, J = 7.1 Hz), 1.70 (1H, dt, J = 13.2, 3.6 Hz), 1.92 (1H, td, J = 13.2, 5.1 Hz), 3.26 (1H, br), 3.33 (3H, s), 3.70 (3H, s), 3.74 (3H, s), 3.79-3.83 (1H, m), 4.48 (1H, br), 4.59 (2H, s), 4.83 (1H, br), 5.09-5.15 (2H, m), 5.79-5.86 (1H, m); ^{13}C NMR (125 MHz) δ 11.56 (q), 27.04 (t), 36.72 (d), 50.07 (d), 52.24 (q), 53.11 (q), 54.04 (d), 55.51 (q), 69.83 (d), 95.02 (t), 115.48 (t), 138.76 (d), 156.75 (s), 172.46 (s); MS 302 (M^++1), 301 (M^+), 242 (100); HRMS Calcd. for $C_{14}H_{23}NO_6$: 301.1525, Found 301.1536; $[\alpha]^{26}_D$ -66.2 (*c* 2.81, $CHCl_3$).

Methyl 2-[3-Vinyl-6-methyl-5-(methoxymethoxy)-1-(methoxycarbonyl)-2-piperidyl]acetate (9): To a stirred solution of **8** (390 mg, 1.30 mmol) in MeOH (3 mL) and H_2O (1 mL) was added $LiOH•H_2O$ (110 mg, 2.62 mmol) at 0 °C, and the resulting mixture was stirred at 60 °C for 1 h. After cooling, MeOH was removed in vacuo, and the aqueous residue was acidified with 10% HCl. The aqueous mixture was extracted with EtOAc (10 mL x 5). The combined EtOAc layer was dried and evaporated to give a colorless oil, which was used directly in the next step.

To a stirred solution of the above carboxylic acid in THF (9 mL) were added $ClCO_2Et$ (0.14 mL, 1.43 mmol) and Et_3N (0.20 mL, 1.43 mmol) at 0 °C, and the resulting suspension was stirred at same temperature for 1 h. The insoluble material was removed by filtration through a Celite pad and washed with Et_2O. The organic layer was concentrated in vacuo to give a colorless oil, which was used directly in the next step.

To a stirred solution of the above oil in Et_2O (5 mL) was added an excess of CH_2N_2 in Et_2O at 0 °C, and the resulting solution was stirred at room temperature for 10 h. The solvent was evaporated and the resulting oil was disolved in MeOH (10 mL). To the solution were added Et_3N (0.36 mL, 2.59 mmol) and silver benzoate (40 mg, 0.17 mmol), and then the suspension was stirred at room temperature for 15 h in the dark. The insolble material was filtered off and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 column (15 g, hexane:acetone=25:1) to afford **9** (290 mg, 71% in 4 steps) as a colorless oil.

IR (neat) 2953, 1734, 1700, 1653, 1045 cm^{-1}; ^1H NMR (500 MHz) δ 1.15 (3H, d, J = 7.1 Hz), 1.70 (1H, dt, J = 13.5, 3.8 Hz), 1.93 (1H, td, J = 13.5, 4.8 Hz), 2.49 (1H, br), 2.54 (1H, dd, J = 15.2, 4.5 Hz), 2.69 (1H, dd, J = 15.2, 10.3 Hz), 3.35 (3H, s), 3.66 (3H, s), 3.69 (3H, s), 3.84-3.88 (1H, m), 4.46 (1H, br), 4.61 (2H, s), 5.08-5.13 (2H, m), 5.80-5.87 (1H, m); ^{13}C NMR (125 MHz) δ 14.53 (q), 25.75 (t), 36.59 (t), 39.63 (d), 49.16 (d), 49.96 (d), 52.24 (q), 51.76 (q), 52.86 (q), 55.52 (q), 69.71 (d), 95.01 (t), 115.36 (t), 139.60 (d), 156.35 (s), 171.49 (s); MS 316 (M^++1), 315 (M^+), 242 (100); HRMS Calcd. for $C_{15}H_{25}NO_6$: 315.1682, Found 315.1651; $[\alpha]^{26}_D$ +11.1 (*c* 1.98, $CHCl_3$).

Methyl 3-Vinyl-6-methyl-5-(methoxymethoxy)-2-[(*N*-methyl-*N*-methoxycarbamoyl)methyl]-piperidinecarboxylate (10): To a stirred solution of **9** (278 mg, 0.88 mmol) in MeOH (3 mL) and H_2O (1 mL) was added $LiOH•H_2O$ (75 mg, 1.78 mmol) at 0 °C, and the resulting mixture was stirred at 60 °C for 1 h. After cooling, MeOH was removed in vacuo, and the aqueous residue was acidified with 10% HCl. The aqueous mixture was extracted with EtOAc (10 mL x 5). The combined EtOAc layer was dried and evaporated to give a colorless oil, which was used directly in the next step. To a stirred solution of the above oil in CH_2Cl_2 (5 mL) was added 1,1'-carbonyldiimidazole (186 mg, 1.15 mmol) at 0 °C, and the resulting solution was stirred at room temperature for 0.5 h. To the reaction mixture was added *O*,*N*-dimethylhydroxylamine•HCl (113 mg, 1.15 mmol) and Et_3N (0.16 mL, 1.15 mmol), and the reaction mixture was stirred at room temperature for 16 h. The solvent was evaporated , and the residue was chromatographed on SiO_2 column (20 g, hexane:acetone=6:1) to afford **10** (254 mg, 83%) as a colorless oil.

IR (neat) 2945, 1734, 1696, 1560, 1045 cm^{-1}; ^1H NMR (500 MHz) δ 1.16 (3H, d, J = 7.1 Hz), 1.69 (1H, dt, J = 13.5, 3.6 Hz), 1.94 (1H, td, J = 13.5, 4.6 Hz), 2.51-2.54 (2H, br),2.84-2.89 (1H, br), 3.13 (3H, br s), 3.33 (3H, s), 3.67 (3H, s), 3.68 (3H, s), 3.84-3.89 (1H, m), 4.48-4.50 (1H, br), 4.60 (2H, s), 4.62-4.65 (1H, br), 5.05-5.12 (2H, m), 5.80-5.87 (1H, m); ^{13}C NMR (125 MHz) δ 14.55 (q), 25.59 (t), 32.02 (q), 36.99 (t), 39.29 (d), 49.07 (d), 49.72 (d), 52.75 (q), 55.44 & 55.46 (each q, due to rotamers), 61.19 (q), 69.77 (d), 94.95 (t), 115.12 (t), 139.83 & 139.86 (each d, due to rotamers), 156.34 (s), 171.73 (s); MS 345 (M^++1), 344 (M^+), 180 (100); HRMS Calcd. for $C_{16}H_{28}N_2O_6$: 344.1948, Found 344.1947; $[\alpha]^{26}_D$ +13.2 (*c* 2.97, $CHCl_3$).

Methyl 3-Vinyl-6-methyl-5-(methoxymethoxy)-2-(2-oxopropyl)piperidinecarboxylate (11): To a stirred solution of **10** (307 mg, 0.89 mmol) in THF (8 mL) was added MeMgBr (1.4 mL, 1.4 mmol, 1.0 M in THF) at 0 °C, and the resulting solution was stirred at room temperature for 0.5 h. The reaction was quenched with satd. NH_4Cl, and the aqueous mixture was extracted with CH_2Cl_2 (10 mL x 4), and the organic layer was combined, dried, and evaporated to give a colorless oil, which was chromatographed on SiO_2 column (15 g, hexane:acetone=15:1) to afford **11** (260 mg, 97%) as a colorless oil.

IR (neat) 2949, 1694, 1559, 1044 cm^{-1}; ^1H NMR (500 MHz) δ 1.12 (3H, d, J = 7.1 Hz), 1.65 (2H, m), 2.51 (1H, dt, J = 13.5, 3.4 Hz), 1.88 (1H, td, J = 13.5, 4.7 Hz), 2.14 (3H, s), 2.37 (1H, br), 2.59 (1H, dd, J = 15.9, 3.1 Hz), 2.78 (1H, dd, J = 15.9, 10.3 Hz), 3.32 (3H, s), 3.67 (3H, s), 3.81-3.86 (1H, m), 4.45 (1H, t-

like, J = 6.4 Hz), 4.58-4.60 (1H, br), 4.59 (2H, s), 5.05-5.11 (2H, m), 5.79-5.86 (1H, m); ^{13}C NMR (125 MHz) δ 14.43 (q), 25.58 (t), 29.94 (q), 39.59 (d), 48.92 (d), 49.05 (d), 49.12 (t), 52.78 (q), 55.45 & 55.47 (each q, due to rotamers), 69.70 (d), 94.98 (t), 115.28 (t), 139.63 & 139.66 (each t, due to rotamers), 156.29 (s), 206.17 (s); MS 300 (M^++1), 299 (M^+), 102 (100); HRMS Calcd. for $C_{15}H_{25}NO_5$: 299.1733, Found 299.1739; $[\alpha]^{26}_D$ +47.2 (*c* 3.14, $CHCl_3$).

Methyl 3-Formyl-6-methyl-5-(methoxymethoxy)-2-(2-oxopropyl)-piperidinecarboxylate (1): To a stirred solution of **11** (260 mg, 0.87 mmol) in dioxane (4 mL) and H_2O (4 mL) were added OsO_4 (5 drops, 4% aqueous solution). After 10 min., $NaIO_4$ (372 mg, 1.74 mmol) was added in two portions over a period of 15 min. The resulting suspension was stirred at room temperature for 1 h and quenched with 10% $Na_2S_2O_3$ in satd. $NaHCO_3$. The aqueous mixture was extracted with CH_2Cl_2 (10 mL x 4), and the organic layer was combined, dried, and evaporated to give a colorless oil, which was chromatographed on SiO_2 column (15 g, hexane:acetone=8:1~5:1) to afford **1** (219 mg, 84%) as a colorless oil along with the starting alkene (8 mg, 3% recovered). This aldehyde was used in the next step immediately.

Methyl 2-Aza-3-methyl-4-(methoxymethoxy)-9-oxobicyclo[4.4.0]dec-7-ene-2-carboxylate (12): To a stirred solution of **1** (219 mg, 0.73 mmol) in benzene (20 mL) was added DBU (0.41 mL, 2.91 mmol), and the resulting solution was refluxed for 24 h. After cooling, the reaction mixture was washed with 10% HCl and H_2O. The organic layer was dried and evaporated to give a colorless oil, which was chromatographed on SiO_2 column (15 g, hexane:acetone=20:1) to afford **12** (124 mg, 60%) as a colorless oil. IR (neat) 2953, 1699, 1683, 1559, 1041 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.20 (3H, d, J = 7.1 Hz), 1.70 (1H, q, J = 12.6 Hz), 1.98 (1H, dt, J = 13.0, 3.6 Hz), 2.56-2.66 (3H, br), 3.40 (3H, s), 3.72 (3H, s), 3.77-3.81 (1H, m), 4.50-4.62 (1H, br), 4.66 (1H, br), 4.70 (2H, s), 6.04 (1H, d, J = 10.3 Hz), 6.87 (1H, dd, J = 10.3, 5.6 Hz); ^{13}C NMR (125 MHz) δ 14.25 & 14.78 (each q, due to rotamers), 25.73 (t), 34.51 & 35.96 (each d, due to rotamers), 40.10 & 40.94 (each t, due to rotamers), 48.14 (d), 48.57 (d), 52.84 & 52.90 (each q, due to rotamers), 55.57 (q), 73.46 & 73.98 (each d, due to rotamers), 95.00 & 95.22 (each t, due to rotamers), 129.02 (d), 150.62 (d), 155.68 (s), 197.75 (s); MS 284 (M^++1), 283 (M^+), 221 (100); HRMS Calcd. for $C_{14}H_{21}NO_5$: 283.1420, Found 283.1387; $[\alpha]^{26}_D$ +10.4 (*c* 1.08, $CHCl_3$).

Methyl 2-Aza-3-methyl-4-(methoxymethoxy)-9-oxo-7-[(phenylsulfonyl)phenylthiomethyl]-bicyclo[4.4.0]decane-2-carboxylate (13): To a stirred solution of phenylthiomethyl phenyl sulfone (164 mg, 0.62 mmol) in THF (8 mL) was added *n*-BuLi (0.40 mL, 0.62 mmol, 10% w/v in hexane) at -78 °C, and the resulting solution was stirred at -78 °C for 30 min. To the reaction mixture was added the enone **12** (147 mg, 0.52 mmol) in THF (2 mL) at -78 °C, and the reaction temperature was gradually raised to -10 °C. The reaction was quenched with satd. NH_4Cl and the aqueous mixture was extracted with CH_2Cl_2 (10 mL x 4). The organic layer was combined, dried, and evaporated to give a colorless oil, which was chromatographed on SiO_2 column (10 g, hexane:acetone=10:1~5:1) to afford **13** (222 mg, 78%) as a colorless oil as a mixture of the diastereomers along with starting enone **12** (20 mg, 14%).

Methyl 2-Aza-3-methyl-4-(methoxymethoxy)-9-oxo-7-[(phenylsulfonyl)methyl]bicyclo-[4.4.0]decane-2-carboxylate (14): To a stirred solution of **13** (423 mg, 0.77 mmol) in benzene (20 mL) were added *n*-Bu_3SnH (0.45 mL, 1.59 mmol) and AIBN (10 mg, 0.06 mmol), and the resulting solution was refluxed for 2 h. After cooling, the solvent was evaporated and the residue was diluted with MeCN. The MeCN layer was washed with hexane and evaporated to give a colorless oil, which was chromatographed on SiO_2 column (20 g, hexane:acetone=5:1) to afford **14** (287 mg, 85%) as a colorless oil.

IR (neat) 2956, 1694, 1041, 752 cm^{-1}; ^1H NMR (500 MHz) δ 1.18 (3H, d, J = 7.1 Hz), 1.87 (1H, br), 1.96 (1H, q, J = 12.0 Hz), 2.11 (1H, br), 2.32 (1H, br t-like, J = 15.0 Hz), 2.48-2.69 (3H, br m), 2.82 (1H, br), 2.95-3.05 (2H, m), 3.39 (3H, s), 3.68 & 3.69 (3H, each br s), 3.77-3.82 (1H, m), 4.27-4.61 (2H, br m), 4.68 (2H, s), 7.58-7.60 (2H, br), 7.68 (1H, br), 7.88-7.90 (2H, br); ^{13}C NMR (125 MHz) δ 14.94 & 15.55 (each q, due to rotamers), 26.70 (t), 33.92 & 34.25 (each d, due to rotamers), 38.05 (d), 41.54 (t), 43.34 & 44.25 (each t, due to rotamers), 48.79 (d), 48.88 & 48.96 (each d, due to rotamers), 52.91 & 53.03 (each q, due to rotamers), 55.67 (q), 59.17 & 59.26 (each t, due to rotamers), 73.82 & 73.32 (each d, due to rotamers), 94.98 & 95.20 (each t, due to rotamers), 127.78 (d), 129.42 & 129.55 (each d, due to rotamers), 134.11 (d), 139.41 (s), 155.33 & 155.75 (each s, due to rotamers), 206.43 & 206.74 (each s, due to rotamers); MS 440 (M^++1), 439 (M^+), 102 (100); HRMS Calcd. for $C_{21}H_{29}NO_7S$: 439.1664, Found 439.1666; $[\alpha]^{26}_D$ -17.9 (*c* 2.43, $CHCl_3$).

Methyl 2-Aza-3-methyl-4-(methoxymethoxy)-7-[(phenylsulfonyl)methyl]bicyclo[4.4.0]-decane-2-carboxylate (15): To a stirred solution of **14** (64 mg, 0.146 mmol) in CH_2Cl_2 (5 mL) and MeOH (5 mL) was added $NaBH_4$ (8 mg, 0.212 mmol) at 0 °C and the resulting solution was stirred at 0 °C for 2 h. The reaction was quenched with satd. NH_4Cl and the aqueous mixture was diluted with CH_2Cl_2. The mixture was dried and evaporated to give a colorless oil, which was used directly in the next step. To a stirred solution of the oil obtained above in $ClCH_2CH_2Cl$ (5 mL) was added 1,1'-thiocarbonyldiimidazole (104 mg, 0.58 mmol) and the resulting solution was refluxed for 7 h. After cooling the solvent was evaporated to give a pale yellow oil, which was chromatographed on SiO_2 column (5 g, hexane:acetone=5:1) to afford the thioester (60 mg, 75% in 2 steps) as a colorless oil as a mixture of diastereomers. To a solution of *n*-Bu_3SnH (0.06 mL, 0.218 mmol) in refluxing toluene (8 mL) was added dropwise slowly a solution of the thioester obtained above (60 mg, 0.109 mmol) in toluene and the resulting mixture refluxed for 2 h. After cooling, the solvent was evaporated and the residue was diluted with MeCN. The MeCN layer was washed with hexane and evaporated to give a colorless oil, which was chromatographed on SiO_2 column (5 g, hexane:acetone=8:1) to afford **15** (39 mg, 84%) as a colorless oil.

IR (neat) 2951, 1697, 1147, 1086, 1040, 754 cm^{-1}; ^1H NMR (500 MHz) δ 1.14 (3H, d, J = 6.8 Hz), 1.21-1.30 (2H, m), 1.53-1.69 (4H, m), 1.74-1.77 (2H, m), 1.90 (1H, quint, J = 12.6 Hz), 2.41 & 2.51 (1H, each br), 3.13-3.24 (2H, m), 3.37 & 3.38 (3H, each s), 3.60-3.66 (1H, m), 3.68 (3H, s), 3.82-3.88 & 4.02-4.06 (1H, each m), 4.34 & 4.48 (1H, each quint, each J = 6.8 Hz), 4.64 & 4.65 (2H, each s), 7.58 (2H, q, J = 7.4 Hz), 7.67 (1H, q, J = 7.4 Hz), 7.92 (2H, t, J = 7.4 Hz); ^{13}C NMR (125 MHz) δ 15.19 & 15.77 (each q, due to rotamers), 20.55 (t), 25.30 (t), 26.97 & 27.30 (each t, due to rotamers), 34.21 & 34.32 (each t, due to rotamers), 34.43 & 34.56 (each d, due to rotamers), 39.11 (d), 48.88 & 48.95 (each d, due to rotamers), 49.24 (d), 52.52 & 52.66 (each q, due to rotamers), 55.43 & 55.53 (each q, due to rotamers), 59.52 (t), 73.95 & 74.33 (each d, due to rotamers), 94.71 & 94.96 (each t, due to rotamers), 127.72 & 127.81 (each d, due to rotamers), 129.21 & 129.34 (each d, due to rotamers), 133.72 (d), 139.56 & 139.81 (each s, due to rotamers), 155.93 & 156.11 (each s, due to rotamers); MS 425 (M^+), 102 (100); HRMS Calcd. for $C_{21}H_{31}NO_6S$: 425.1872, Found 425.1868; $[\alpha]^{26}_D$ +1.97 (*c* 1.95, $CHCl_3$).

***tert*-Butyl 2-Aza-3-methyl-4-(methoxymethoxy)-7-[(phenylsulfonyl)methyl]bicyclo[4.4.0]-decane-2-carboxylate (16):** To a stirred solution of *n*-PrSH (0.4 mL, 4.47 mmol) in HMPA (2.5 mL) was added *n*-BuLi (10w/v % in hexane, 2.7 mL, 4.25 mmol) at 0 °C, and then the resulting solution was stirred at 0 °C for 30 min. To the solution was added a solution of **15** (178 mg, 0.42 mmol) in THF (2 mL) at 0 °C,

and the reaction mixture was stirred at room temperature for 48 h. The reaction was quenched with NH_3 (aq), and the aqueous mixture was extracted with Et_2O (5 mL x 10). The organic extracts were combined, dried over K_2CO_3, and evaporated to give a pale yellow oil, which was used directly in the next step. To a stirred solution of the oil obtained above in benzene was added $(Boc)_2O$ (274 mg, 1.26 mmol), and the resulting solution was refluxed for 2 h. After cooling the solvent was evaporated to give a colorless oil, which was chromatographed on SiO_2 column (10 g, hexane:acetone=15:1) to afford **16** (115 mg, 59% in 2 steps) as a colorless oil.

IR (neat) 2934, 1685, 1448, 1306, 1147, 1040 cm^{-1}; ^1H NMR (500 MHz) δ 1.11 (3H, d, J = 7.1 Hz), 1.25-1.31 (2H, m), 1.44 (9H, s), 1.51-1.61 (6H, br m), 1.70 (1H, d-like, J = 12.2 Hz), 1.84-1.91 (1H, m), 2.34 & 2.51 (1H, each br), 3.12-3.22 (2H, m), 3.35 & 3.38 (3H, each s), 3.61-3.66 (1H, m), 3.78-3.80 & 3.96-3.98 (1H, each m), 4.27 & 4.42 (1H, each quint, each J = 6.5 Hz), 4.62 & 4.65 (2H, each s), 7.55-7.61 (2H, m), 7.64-7.68 (1H, m), 7.90-7.93 (2H, m); ^{13}C NMR (125 MHz) δ 15.18 & 15.64 (each q, due to rotamers), 20.57 (t), 25.30 (t), 27.11 (t), 28.30 & 28.38 (each q, due to rotamers), 34.26 & 34.37 (each t, due to rotamers), 39.20 (d), 48.23 (d), 48.67 & 49.11 (each d, due to rotamers), 55.45 & 55.46 (each d, due to rotamers), 59.57 (t), 74.55 & 74.71 (each d, due to rotamers), 79.72 (s), 94.77 & 95.01 (each t, due to rotamers), 127.70 & 127.75 (each d, due to rotamers), 129.21 & 129.38 (each d, due to rotamers), 133.72 (d), 139.93 (s), 154.91 (s); $[\alpha]^{26}_D$ -0.53 (*c* 4.05, $CHCl_3$).

***tert*-Butyl 2-Aza-3-methyl-4-(methoxymethoxy)-7-octa-1,3-dienylbicyclo[4.4.0]decane-2-carboxylate (17):** To a stirred solution of **16** (80 mg, 0.17 mmol) in THF (3 mL) was added *n*-BuLi (10w/v % in hexane, 0.16 mL, 0.26 mmol) at -78 °C, and then the resulting solution was stirred at -78~-70 °C for 30 min. To the solution was added 2-heptenal (0.025 mL, 0.0.19 mmol) at -78 °C, and the reaction mixture was stirred at -78~-50 °C for 1 h. The reaction was quenched with satd. NH_4Cl (aq), and the aqueous mixture was extracted with CH_2Cl_2 (5 mL x 6). The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was used directly in the next step. To a stirred solution of the oil obtained above in MeOH (5 mL) were added Na_2HPO_4 (220 mg, 1.55 mmol), and 5% Na-Hg (1.8 g), and the resulting solution was stirred at room temperature for 2 h. The reaction was quenched with satd. NH_4Cl (aq), and then the aqueous mixture was extracted with CH_2Cl_2 (5 mL x 5). The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on SiO_2 column (10 g, hexane:acetone=200:1) to afford **17** (35 mg,49% in 2 steps) as a colorless oil.

IR (neat) 2930, 1685, 1654, 1365, 1148, 1043 cm^{-1}; ^1H NMR (500 MHz) δ 0.89 (3H, *t*, J = 7.1 Hz), 1.14 (3H, d, J = 6.6 Hz), 1.26-1.39 (4H, br m), 1.45 (9H, s), 1.41-1.1.60 (6H, br m), 1.68-1.82 (2H, m), 1.89-1.96 (1H, m), 2.03-2.10 (2H, br m), 2.35 & 2.75 (1H, each br), 3.36 & 3.38 (3H, each s), 3.69-3.73 (1H, m), 4.00-4.20 (1H, br m), 4.30 & 4.47 (1H, each quint-like, each J = 6.4 Hz), 4.65 & 4.67 (2H, each s), 5.56-5.83 (2H, br m), 5.94-6.25 (2H, br m); ^{13}C NMR (125 MHz) δ 13.92 (q), 15.31 & 15.71 (each q, due to rotamers), 21.07 (t), 22.21 (t), 25.97 (t), 27.45 & 27.83 (each t, due to rotamers), 28.36 & 28.48 (each q, due to rotamers), 31.49 (t), 32.26 & 32.58 (each t, due to rotamers), 39.70 & 39.81 (each d, due to rotamers), 42.61 & 42.80 (each t, dute to rotamers), 48.36 (d), 49.30 & 49.95 (each d, due to rotamers), 55.44 & 55.46 (each d, due to rotamers), 74.56 & 75.09 (each d, due to rotamers), 79.44 (s), 94.80 & 95.04 (each t, due to rotamers), 130.10 (d), 130.20 & 130.31 (each d, due to rotamers), 133.25 & 133.45 (each d, due to rotamers), 134.42 & 134.63 (each d, due to rotamers), 154.99 (s); $[\alpha]^{26}_D$ +4.86 (*c* 1.34, $CHCl_3$).

5-Aza-4-methyl-10-octa-1,3-dienylbicyclo[4.4.0]decan-3-ol (lepadin B): To a stirred solution of **17** (12 mg, 0.0285 mmol) in MeOH (1 mL) was added c. HCl (one drop), and then the resulting mixture was refluxed for 3 h. After cooling, the solvent was evaporated to give lepadin B as the hydrochloride salt. Recrystallization of the salt from Et_2O-MeOH gave pure hydrochloride salt of lepadin B as a colorless solid. To a stirred suspension of the salt obtained above in $CHCl_3$ (5 mL) was added solid K_2CO_3 (100 mg), and the resulting suspension was stirred at room temperature for 1 h. Filtration and evaporation gave (-)-lepadin B (6.5 mg, 85%) as a colorless paste.

^1H NMR (500 MHz) δ 0.89 (3H, *t*, J = 7.1 Hz), 1.11 (3H, d, *J* = 6.6 Hz), 1.26-1.39 (4H, br m), 1.42-1.51 (2H, m), 1.57 (2H, d-like, *J* = 9.5 Hz), 1.59-1.72 (3H, m), 1.74 (1H, d, *J* = 6.2 Hz), 2.05 (2H, q-like, *J* = 7.0 Hz), 2.11 (1H, d-like, *J* = 15.0 Hz), 2.60 (1H, qd-like, *J* = 9.0, 4.0 Hz), 2.78 (1H, qd, *J* = 6.6, 1.5 Hz), 2.94 (1H, br), 3.54 (1H, m), 5.37 (1H, dd *J* = 15.0, 9.0 Hz), 5.59 (1H, dt, J = 15.0, 7.0 Hz), 6.00 (1H, ddt-like, *J* = 15.0, 10.0, 2.0 Hz), 6.08 (1H, dd, *J* = 15.0, 10.0 Hz); ^{13}C NMR (75.5 MHz) δ 14.08 (q), 18.50 (q), 20.87 (t), 22.40 (t), 31.62 (t), 32.41 (t), 33.11 (t), 34.19 (t), 34.27 (t), 38.74 (d), 41.16 (d), 56.13 (d), 56.68 (d), 68.81 (d), 130.22 (d), 130.74 (d), 132.67 (d), 137.01 (d); MS 278 (M^++1), 277 (M^+), 168 (100); $[\alpha]^{26}_D$ -70.7 (*c* 0.185, MeOH).

Trifluoroacetate salt of (-)-lepadin B: ^1H NMR (500 MHz) δ 0.90 (3H, *t*, J = 7.1 Hz), 1.06 (1H, m), 1.28-1.38 (4H, br m), 1.41 (3H, d, *J* = 6.8 Hz), 1.43-1.66 (5H, br m), 1.75 (1H, d, *J* = 13.5 Hz), 2.06 (2H, q, *J* = 6.6 Hz), 2.11 (1H, d, *J* = 8.8 Hz), 2.30 (1H, d-like, *J* = 13.9 Hz), 2.78 (1H, q-like, *J* = 11.8 Hz), 3.37 (1H, br), 3.51 (1H, br), 3.60 (1H, br), 3.90 (1H, br), 5.28 (1H, dd, *J* = 15.1, 8.8 Hz), 5.65 (1H, dt, *J* = 15.0, 7.0 Hz), 5.98 (1H, dd, *J* = 15.0, 10.5 Hz), 6.12 (1H, dd, *J* = 15.1, 10.5 Hz), 7.33 (1H, br), 9.93 (1H, br); ^{13}C NMR (125 MHz) δ 14.07 (q), 15.04 (q), 19.65 (t), 22.38 (t), 29.01 (t), 31.50 (t), 32.31 (t), 32.41 (t), 33.11 (t), 36.95 (d), 39.87 (d), 56.79 (d), 57.41 (d), 66.61 (d), 129.69 (d), 132.29 (d), 134.03 (d), 134.11 (d); $[\alpha]^{26}_D$ -92.6 (*c* 0.194, MeOH).

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