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SYNTHESIS OF PROTECTED (2*S*,6*S*,8*S*)-INDOLIZIN-9-ONE AMINO ACID†

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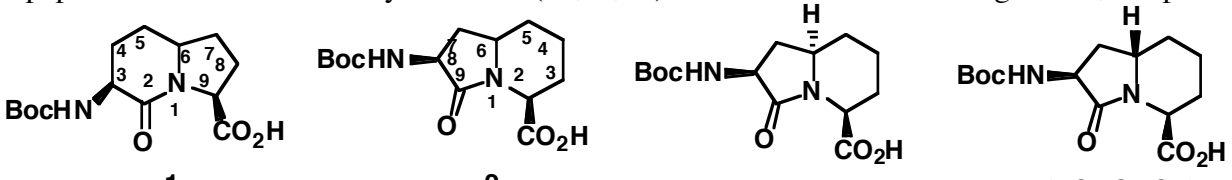
Abstract-First synthesis of (2*S*,6*S*,8*S*)-indolizidin-9-one amino acid starting from 1,6-heptadiene has been described.

The design of peptidomimetic derivatives is currently an area of active investigation and has generated a considerable amount of work in the synthesis of high affinity and selective new therapeutic agents.[1] The spatial requirement for protein chemistry and biology may be explored through the employment of indolizidine amino acids as building blocks for the construction of conformationally rigid surrogates of peptide structures.[2] The unique dipeptide analogues can be used to restrain the backbone geometry and side-chain conformations of the native peptide in order to probe and elucidate structure-activity relationships. Much attention was focused on synthesis and design of indolidin-2-one amino acid (**1**) of bicyclic peptidomimetics based on proline of two indolizidinone amino acids.[3] On the contrary, the synthesis of indolizidin-9-one amino acid based on pipecolic acid (**2**) is rare. So far, an asymmetric synthesis of (2*S*,6*R*,8*S*)-indolizidin-9-one amino acid (**2**) has been reported once time,[4] whereas that of its stereoisomer (2*S*,6*S*,8*S*)-indolizidin-9-one amino acid (**2**) has not been done. Accordingly, we were stimulated to the development of a comprehensive synthetic program for these amino acids. Our interest in this field has been directed to the potential strategies based on the enantiomeric enhancement caused by the twofold or more application of the Sharpless asymmetric dihydroxylation (AD) reactions.[5] In this paper we describe the first synthesis of (2*S*,6*S*,8*S*)-**2** *via* iterative AD starting with 1,6-heptadiene.



1 **2** (2*S*,6*R*,8*S*)-**2** (2*S*,6***S***,8*S*)-**2**

Figure 1

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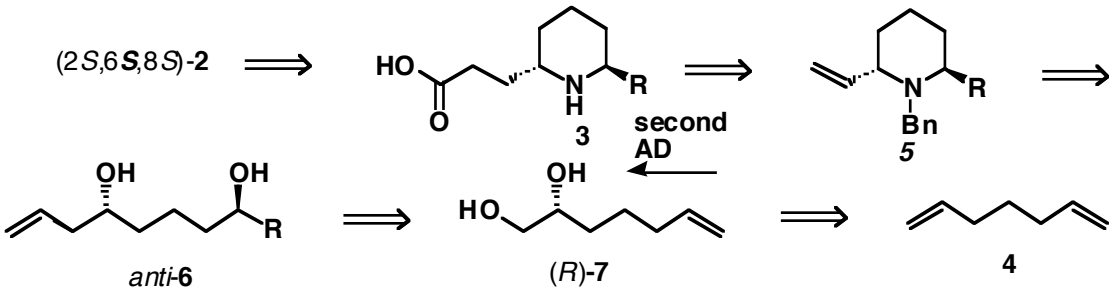
†This paper is dedicated to Professor Yuichi Kanaoka of his 75 th birthday.

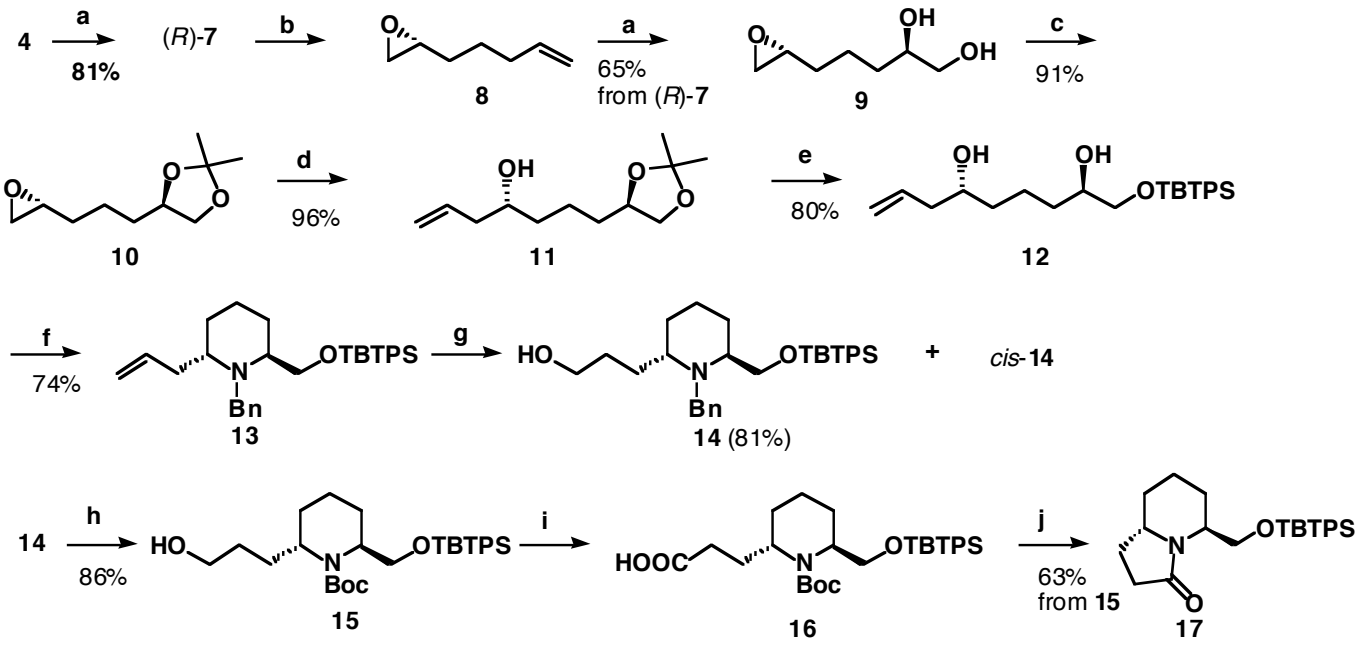
We considered (2*S*,6*S*,8*S*)-**2** would be obtained from *trans*-2,6-disubstituted piperidine (**3**). Recently, we developed a general access to *trans*-2,6-disubstituted piperidine *via* double or a sequence of two-fold AD reactions starting from an achiral 1,6-heptadiene (**4**).[6,7] According to a similar concept, our retrosynthetic plan is outlined in Scheme 1. Access to *trans*-2,6-disubstituted piperidine (**5**) is viewed to be possible by manipulation *via* cyclic amination of *anti*-1,5-diol (*anti*-**6**) using benzylamine, respectively. This strategy has two key characteristics. The first one is the installation of the selective hydroxylation of olefins with two AD reactions. That is to say, the dual AD reactions using same ligand (DHQD-based ligand) provide the *anti*-diol (**4** → **7** → *anti*-**6**). Second one is as follows; in general, when the products prepared by dual AD reaction are acyclic and their asymmetric centers (1,5-relationship) are remote, it is difficult to separate two diastereomers. The transformation of acyclic compounds (**6**) to cyclic derivatives (**5**) provides rigid conformation and causes close proximity (1,3-relationship) between two chiral centers. Therefore, it would be expected to greatly facilitate a separation of two diastereomers.



Scheme 1

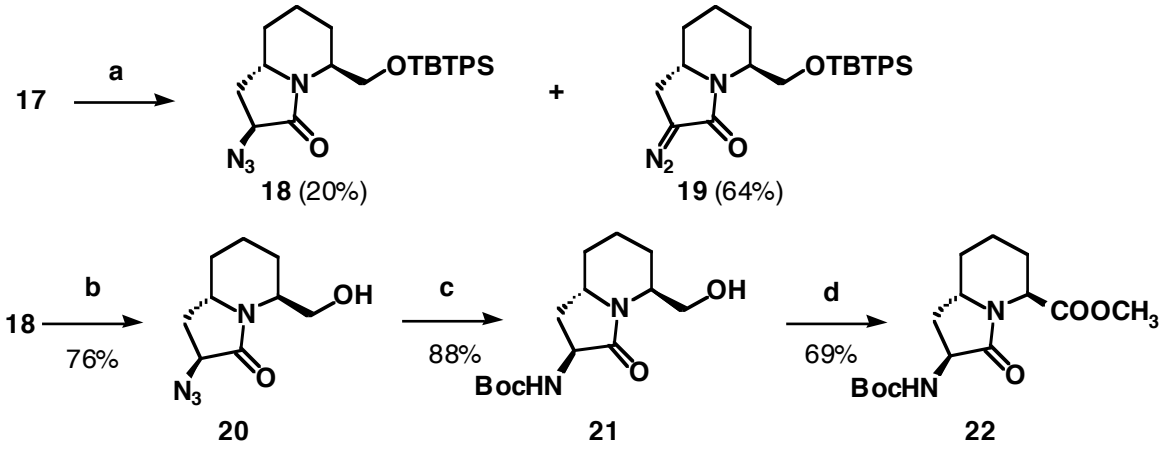
Our synthetic approach to **2** began with the single AD of **4**. The $(DHQD)_2$-PYR ligand-derived AD reaction of **4** afforded the diol (*R*)-**7** (85% ee) in 81% yield.[6] The diol (*R*)-**7** was converted into the epoxide (**8**) by the Sharpless one-pot procedure.[8] Without further purification, second $(DHQD)_2$-PYR ligand-derived AD was performed to afford the diol (**9**)[9] in 65% yield from diol (*R*)-**7**.

Regioselective cleavage of the epoxide ring of **9** with vinylmagnesium bromide in combination with cuprous bromide-dimethyl sulfide complex resulted in unsuccessful. We considered free two hydroxyl groups would disturb this reaction. Consequently, **9** was protected to convert the acetal (**10**), which was treated with vinylmagnesium bromide in presence of cuprous bromide-dimethyl sulfide complex to convert to **11**. Deprotection of acetal group followed by selective protection of primary hydroxyl group of the resulting triol with *tert*-butyldiphenylsilyl chloride (TBDPSCl) gave the diol (**12**). The diol (**12**) was successively subjected to ditosylation of secondary hydroxyl groups and cyclic amination with benzylamine to give a diastereomeric isomers of piperidines (**13**). Unfortunately, in this stage, a separation of diasteromes is unsuccessful. Hydroboration followed by oxidation treatment of **13** gave *trans*-disubstituted piperidinol as a major diasteromer (**14**) and its *cis*-isomer in a ratio (6.3:1). Exchange of *N*-protecting group from benzyl to *tert*-butoxycarbonyl (Boc) group was perfomed in a two-step sequence (debenzylation and carbamation) afforded **15**. Oxidation of **15** with cat. $RuCl_3$ provided the carboxylic acid (**16**), which was cyclized with Aldrithiol™-2 in the presence of Ph_3P[10] to yield bicylic lactam (**17**).



Scheme 2: a) cat. $(DHQD)_2$-PYR, cat. K_2OsO_4; b) i $CH_3C(OCH_3)_3$, PPTS; ii $(C_2H_5)_3N$, CH_3COBr; iii NaOH; c) $(CH_3)_2C(OCH_3)_2$, PPTS, MS 5A; d) vinylmagnesium bromide, CuBr-$(CH_3)_2S$; e) i HCl; ii TBTPSCl. imidazole; f) i TsCl, $(C_2H_5)_3N$; ii $PhCH_2NH_2$; g) i 9-BBN; ii NaOH, H_2O_2; h) i H_2, cat. $Pd(OH)_2$; ii Boc_2O, K_2CO_3; i) cat. $RuCl_3$, $NaIO_4$; j) i CF_3COOH; ii 2,2'-dipyridyl disulfide, Ph_3P

With **17** in hand, we tried an introduction of amino groups to □-position of lactam carbonyl. First amination using di-*tert*-butyl azodicarboxylate[11] for **17** was carried out to result in unsuccessful. Next, azidation of **17** with 2,4,6-triisopropylbenzenesulfonyl azide[12] using lithium diisopropylamide as a base was examined to yield the desired azide (**18**) in 20% yield. However, the undesired diazo (**19**) was also obtained in 64% yield. In this stage, a stereochemistry of **18** remains unknown. Fortunately, desilylation of **18** gave the crystallized product (**20**), of which stereochemistry was determined by its X-Ray crystallographic analysis to be *S* configuration (Figure 2). Exposure of **20** to hydrogen in the presence of cat. $Pd(OH)_2$ followed by protection with Boc_2O of the resulting amine gave **21** in 88% yield. Finally, treatment of hydroxyl with cat. $RuCl_3$ in the presence of $NaIO_4$ as co-oxidant provide the carboxylic acid (**2**), which was methylated with diazomethane to yield the desired **22** in 69% yield.



Scheme 3: a) Trisyl azide, LDA; b) TBAF; c) i H_2, cat. $Pd(OH)_2$; ii Boc_2O, $(C_2H_5)_3N$; d) i cat. $RuCl_3$; $NaIO_4$; ii CH_2N_2

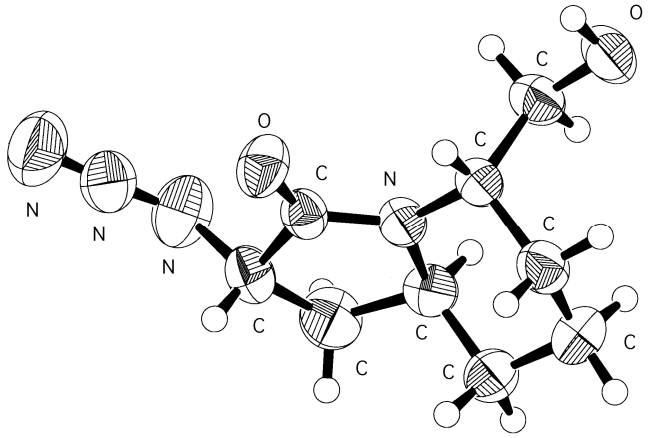


Figure 2. ORTEP diagram of **20**

In summary, the first synthesis of methyl ester of (2*S*,6*S*,8*S*)-indolizidin-9-one amino acid (**2**) was performed using the iterative AD reaction starting from 1,6-heptadiene. This procedure would be applied to the synthesis of (2*S*,6*R*,8*S*)-**2**.

EXPERIMENTAL

Melting points were determined by Yanaco micro melting point apparatus and are uncorrected. IR spectra were obtained in the range 4000-500 cm^{-1} on a Perkin-Elmer 1600 Series FTIR spectrophotometer. ^{1}H NMR spectra were recorded at 500 MHz on a Varian-Unity-500 instrument with $CHCl_3$ (7.26 ppm) as an internal standard. ^{13}C NMR spectra were recorded on a Varian-Unity-500 instrument with $CDCl_3$ (77.2 ppm) as an internal standard. MS and HRMS spectra were measured on a JEOL JMS AX-505 HAD spectrometer. Optical rotations were recorded on a JASCO DIP-140 instrument. Microanalyses were performed by Microanalysis Center of Toyama Medical & Pharmaceutical University. Chromatography was performed on a silica gel column (Merck 60-No.9385 or No.7734). The extracts were dried over Na_2SO_4.

(2*R*,6*R*)-6,7-Epoxyheptane-1,2-diol (9). A mixture of (*R*)-**7** (874 mg, 6.71 mmol), pyridinium *p*-toluenesulfonate (PPTS) (18 mg, 0.07 mmol), and trimethyl orthoacetate (1.11 mL, 8.72 mmol) in CH_2Cl_2 (8.4 mL) was stirred for 1 h at rt. After the solvent was removed by rotary evaporation, triethylamine (0.09 mL, 0.67 mmol), CH_2Cl_2 (8.4 mL) and acetyl bromide (0.74 mL, 10.1 mmol) were successively added to the resulting residue. After vigorous stirring for 45 min, the reaction mixture was added to 1M HCl solution (13.6 mL). The mixture was extracted with CH_2Cl_2. The extract was dried and evaporated. A mixture of ether (16.4 mL) and methanol (0.39 mL) was added to the residue and pulverized NaOH (590 mg, 14.8 mmol)) were successively added to the resulting residue. After stirring for 2.5 h, the mixture was filtered through on K_2CO_3-packed glass-filter. The filtrate was removed at an atmosphere to yield the crude epoxide **(8).** The olefin **(8)** was added to a mixture of AD-mix (8.52 g), prepared from $K_2O_SO_4 \cdot 2H_20$ (38 mg), $(DHQD)_2PYR$ (0.49 g), $K_3Fe(CN)_6$ (5.3 g), and K_2CO_3 (2.2 g) in *tert*-BuOH (33.6 mL), and H_2O (33.6 mL) at 0 °C. After the reaction mixture was

stirred for 14 h at the same temperature, sodium sulfite (10.3 g) was added to the mixture. After stirring for 30 min, the mixture was filtered through a Celite pad. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (60 mL) five times. The combined organic layers were washed with brine, dried, and evaporated. The residue was chromatographed using *n*-hexane: acetone (5:1) as eluent to yield a diasteromeric mixture (633 mg, 65%) of (2*R*,6*R*)-**9** as a major product as an oil; IR (neat) 3386, 2935, 1458, 1410, 1072, 914, 845, 754 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.47-1.66 (6H, m), 2.31(1H, br s), 2.49 (1H, dd, *J* = 4.9 Hz, 2.8Hz), 2.57 (1H, br s) , 2.75-2.78 (1H, m), 2.90-2.96 (1H, m), 3.41-3.47 (1H, m), 3.63-3.72 (2H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 22.55, 32.54, 32.96, 47.36, 52.56, 66.97, 72.22 ; MS (m/z) 115(M^+-31).

(2*R*,6*R*)-6,7-Epoxyheptane-1,2-acetonide (10) A suspension of **9** (663 mg, 4.33 mmol, molecular sieves 5Å (10.8 g) acetone dimethyl acetal (0.8 mL, 6.50 mmol), and PPTS (108 mg, 0.43 mmol) in CH_2Cl_2 (47.6 mL) was stirred at rt for 20 h. The reaction mixture was filtered through Celite and the filtrate was evaporated. The residue was chromatographed using (*n*-hexane:ethyl acetate = 7:1) as an eluent to yield a diastereomeric mixture (736 mg, 91%) of (2*R*,6*R*)-**10** as a major product as an oil; IR (neat) 2986, 1458, 1369, 1216, 1160, 1062, 851, 757 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.35 (3H, s), 1.40 (3H, s), 1.43-1.69 (6H, m), 2.4 7 (1H, dd, *J* = 4.9 Hz, 2.8 Hz), 2.75 (1H, t, *J* = 4.7 Hz), 2.88-2.92 (1H, m), 3.48-3.54 (1H, m), 4.01-4.13 (2H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 22.54, 22.69, 25.98, 27.21, 32.58, 32.75, 33.49, 33.63, 47.27, 52.36, 69.58, 76.08, 108.86 ; MS (m/z) 187(M^++1).

(2*R*,6*R*)-8-Nonen-6-ol-1,2-acetonide (11) To a suspension of cuprous bromide-dimethyl sulfide complex (15.4 g, 7.50 mmol) in THF (37.6 mL) was added 1M vinylmagnesium bromide (30 mL, 30.0 mmol) in THF solution at -78 °C and the reaction mixture was warmed to -30 °C with stirring. A solution of **10** (1.40 g, 7.50 mmol) was added to the mixture and stirred at the same temperature for 1.5 h. The reaction mixture was diluted with ether. The mixture was successively washed with saturated ammonium chloride, water, and brine and evaporated. The residue was chromatographed using (n-hexane:ethyl acetate = 5:1) as an eluent to yield a diasteromeric mixture (1.545 g, 96%) of (2*R*,6*R*)-**11** as a major product as an oil; IR (neat) 3447, 2936, 1370, 1217, 1157, 1059, 916, 860, 756 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.35 (3H, s), 1.40 (3H, s), 1.43-1.57 (4H, m), 1.61-1.71 (2H, m), 2.09-2.19 (1H, m), 2.26-2.35 (1H, m), 3.47-3.54 (1H, m), 3.62-1.71 (2H, m), 2.09-2.19 (1H, m), 2.26-2.35 (1H, m), 3.47-3.54 (1H, m), 3.62-3.66 (1H, m), 4.01-4.13 (2H, m), 5.10-5.17 (2H, m), 5.75-5.89 (1H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 22.37, 26.03, 27.23, 33.78, 36.94, 42.25, 69.69, 70.63, 76.23, 108.81, 118.39, 134.79 ; MS (m/z) 213(M^+-1).

(2*R*,6*R*)-1-(*tert*-Butyldiphenylsilyloxy)non-8-ene-2,6-diol (12) 1*N* HCl (7.25 mL) was added to a solution of **11** (622 mg, 2.90 mmol) in THF (7.25 mL) and the mixture was stirred at the rt for 2 h. Saturated $NaHCO_3$ was added to the reaction mixture at 0 °C and then the mixture was saturated with NaCl. The mixture was filtered through Celite and the filtrate was extracted with a mixture of

chlorofolm : 2-propanol (5:1). The extract was dried and evaporated. The residue was chromatographed using ethyl acetate:methanol (50:1) as an eluent to yield a diasteromeric mixture of triol (488 mg, 97%) as an oil; IR (neat) 3352, 2935, 1437, 1031, 914, 870 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.32-1.62 (6H, m), 2.12-2.28 (2H, m), 3.38-3.44(2H, m), 3.54-3.64 (3H, m), 4.05 (1H, br s), 4.27 (1H, br s), 5.06-5.11 (2H, m), 5.74-5.87 (1H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 21.81, 32.81, 33.10, 36.45, 36.73, 42.25, 42.34, 66.76, 66.87, 70.67, 70.84, 72.13, 72.40, 117.77, 134.99; MS (m/z) 143 (M^+-31). A solution of triol (448 mg, 2.80 mmol), imidazole, and *tert*-butyldiphenylsilyl chloride (TBDPSCl) (0.78 mL, 3.36 mmol) in DMF (2.4 mL) was stirred at rt for 5 h. A large amount of water was added to the reaction mixture and the mixture was extracted with CH_2Cl_2. The extract was successively washed with 20% $KHSO_4$, saturated $NaHCO_3$, and brine. The organic layer was dried and evaporated. The residue was chromatographed using *n*-hexane : ethyl acetate (4:1) as an eluent to yield a diasteromeric mixture (948 mg, 82%) of **12** as major as an oil; IR (neat) 3384, 2931, 1428, 1113, 913, 824, 758, 702 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.07 (9H, s), 1.32-1.55 (6H, m), 1.77 (1H, br s), 2.08-2.18 (1H, m), 2.24-2.33 (1H, m), 2.60 (1H, m), 3.49 (1H, dd, *J* = 9.9 Hz, 7.7 Hz), 3.61-3.73 (3H, m), 5.09-5.15 (2H, m), 5.75-5.89 (1H, m), 7.36-7.48 (6H, m), 7.65-7.68 (4H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 19.52, 21.79, 21.99, 27.11, 32.78, 36.88, 42.11, 42.17, 68.19, 70.61, 72.03, 118.18, 127.86, 129.89, 133.17, 133.21, 134.88, 135.60; MS (m/z) 355(M^+-57).

(2*S*,6*S*)-*N*-Benzyl-6-allyl-2-[(*tert*-butyldiphenylsilyloxy)methyl]piperidine (13) To a solution of **12** (2.23 g, 5.40 mmol) in CH_2Cl_2 (9.35 mL) was successively added *p*-toluenesulfonyl chloride (*p*-TsCl) (4.42 g, 21.6 mmol), triethylamine (3.01 mL, 21.6 mmol), and 4-*N*,*N*-dimethylaminopyridine (264 mg, 2.16 mmol) with ice cooling. The reaction was stirred for 2 days at rt and then diluted with a large amount of ether. The solvent was filtered through Celite. The filtrate was washed with brine, dried, and evaporated. The residue was chromatographed to yield the ditosylate (3.66 g, 94%) as a pale yellow oil; IR (neat) 2934, 1362, 1178, 1109, 907, 817, 743, 703, 664 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.00 (3H, s), 1.06-1.17 (2H, m), 1.44-1.70 (4H, m), 2.27 (2H, m), 2.41 (6H, s), 3.57 (2H, ddd, *J* = 20.9 Hz, 11.9 Hz, 4.6 Hz), 4.41-4.50 (2H, m), 4.97-5.03 (2H, m), 5.51-5.64 (1H, m), 7.25 (2H, d, *J* = 9.3 Hz), 7.29 (2H, d, *J* = 7.7 Hz), 7.34-7.47 (6H, m), 7.55-7.59 (2H, m), 7.69 (2H, d, *J* = 8.2 Hz), 7.75 (2H, d, *J* = 8.2 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 19.44. 20.08, 21.90, 26.97, 30.90, 33.51, 38.71, 64.41, 82.39, 82.47, 118.87, 127.74, 127.83, 129.81, 129.91, 132.12, 132.83, 132.97, 134.16, 132.26, 135.54, 135.61, 144.60, 144.66. A mixture of the ditosylate (3.66 g, 5.08 mmol) and benzylamine (16.65 mL, 152 mmol) was heated at 70 ˚C for 2 days. The reaction was diluted with *n*-pentane (100 mL) at 0 ˚C and 2*N* NaOH (150 mL) was added to the dilute solution. The organic layer was separated and the aqueous layer was extracted with n-pentane (40 mL) four times. The combined organic layers were dried with K_2CO_3 and evaporated. The residue was chromatographed using 4% ethyl acetate /*n*-hexane as eluent to yield **13** as a diastereomeric mixture (1.94 g, 79 %); IR (neat) 2931, 1428, 1109, 736, 702 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.00 (0.7H, s), 1.03 (3H, s), 1.30-1.70 (6H, m), 2.11-2.38 (2H, m), 2.69-2.81 (1H, m),

2.88-2.96 (1H, m), 3.41 (0.25H, dd, *J* = 10.3 Hz, 7.4 Hz), 3.63-3.90 (4H, m), 4.88-5.00 (2H, m), 5.63-5.77 (1H, m), 7.15-7.45 (11H, m), 7.54-7.65 (4H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 19.49, 20.02, 22.05, 24.98, 26.54, 27.12, 29.53, 34.66, 39.37, 52.33, 55.58, 57.08, 64.18, 65.23, 115.81, 116.17, 126.13, 126.40, 127.57, 127.68, 127.99, 128.12, 128.25, 129.59, 133.84, 133.88, 135.64, 135.67, 136.72, 137.02, 141.45; MS (m/z) 482(M^+-1); HRMS:calcd for $C_{32}H_{41}NOSi$ (M^+) 483.2957, found 483.2972.

(2*S*,6*S*)-*N*-Benzyl-2-[(*tert*-butyldiphenylsilyloxy)methyl]-6-(3-hydroxypropyl)piperidine (*trans*-14). To a 0.5 M 9-borabicyclo[3.3.1]nonane (12.9 mL, 6.44 mmol) in THF solution was added a solution of **13** (1.56 g, 3.22 mmol) in THF (3.86 mL) at 0 °C and the reaction mixture was stirred at rt for 2 h. 3*N* NaOH (35.4 mL) and 30% H_2O_2 (17.6 mL) were successively added to the mixture at 0 °C and the reaction mixture was stirred at the rt for 1 h. The mixture was extracted with ethyl acetate. The extract was washed with brine, dried, and evaporated. The residue was chromatographed using 16% ethyl acetate /n-hexane as eluent to yield **14** (1.305 g, 81 %) and its *cis* isomer (13%). **14**; $[\alpha]^{26}_D$ -0.5˚ (*c* 0.89, $CHCl_3$) ; IR (neat) 3356, 2932, 1463, 1109, 820, 702 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.02(9H, s), 1.23-1.80(11H, m), 2.70-2.72 (1H, m), 3.02-3.04 (1H, m), 3.45-3.59 (2H, m), 3.73-3.85 (4H, m), 7.21-7.44 (11H, m), 7.59-7.64 (4H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 19.52, 20.44, 22.11, 25.56, 27.14, 29.25, 30.58, 51.07, 55.20, 56.08, 63.19, 65.23, 126.81, 127.69, 128.30, 128.87, 129.62, 133.70, 135.66, 139.98; MS (m/z) 500(M^+-1), 444(M^+-57); HRMS:calcd for $C_{32}H_{43}NO_2Si$ (M^+) 501.3063, found 501.3026.

(2*S*,6*S*)-*N*-(*tert*-Butoxycabonyl)-2-[(*tert*-butyldiphenylsilyloxy)methyl]-6-(3-hydroxypropyl)-piperidine (15) A suspension of **14** (772 mg, 1.54 mmol) and $Pd(OH)_2$ (55 mg) in MeOH (12.4 mL) under a hydrogen atmosphere was stirred for 1 h. The mixture was filtered through a Celite pad, and the filtrate was evaporated. To the residue in a mixture of THF (11.3 mL) and H_2O (11.3 mL) was successively added K_2CO_3 (275 mg, 2.00 mmol) and di-*tert*-butyl dicarbonate (Boc_2O) (0.71 mL, 3.08 mmol) at 0 ˚C. After being stirred at rt for 5 h, the organic solvent was removed *in vacuo*. After the residue was acidified with 20% $KHSO_4$, the mixture was extracted with ethyl acetate. The extract was dried and evaporated. The residue was chromatographed using 17% ethyl acetate-hexane as eluent to give **15** (675 mg, 86%) as an oil; $[\alpha]^{25}_D$ -36.3˚ (*c* 1.54, $CHCl_3$); IR (neat) 3447, 2932, 1672, 1473, 1428, 1391, 1174, 1113, 825, 756, 702 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.06 (9H, s), 1.36 (9H, s), 1.42-1.86 (10H, m), 2.01-2.05 (1H, m), 3.50-3.92 (6H, m), 7.35-7.46 (6H, m), 7.65-7.68 (4H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.71, 19.52, 21.60, 23.86, 27.09, 28.65, 29.55, 30.43, 50.42, 53.03, 62.21, 64.82, 79.67, 127.72, 129.72, 133.62, 133.68, 135.58, 155.48; Anal. Calcd for $C_{30}H_{45}NO_4Si$: C, 70.41, H, 8.86, N, 2.74, found C, 70.50, H, 8.82, N, 2.37.

(2*S*,6*S*)-2-[(*tert*-Butyldiphenylsilyloxy)methyl]-9-oxo-1-azabicyclo[4.3.0]nonane (17) To a solution of **15** (675 mg, 1.32 mmol) in carbon tetrachloride (4.42 mL), acetonitrile (2.95 mL) and water (4.42 mL) was added $NaIO_4$ (847 mg, 3.96 mmol). After the mixture was stirred for 3 min, ruthenium(III) chloride hydrate (6.8 mg, 2,2 mol%) was added to the reaction mixture. The mixture

was vigorously stirred for 3 h. The mixture was extracted with CH_2Cl_2. The extract was dried and evaporated. Et_2O was added to the residue. The mixture was filtrated through Celite. The filtrate was evaporated to leave the residue. CH_2Cl_2 (6.2 mL) and trfluoroacetic acid (6.2 mL) were added to the residue. The mixture was stirred for 1 h and evaporated to leave the crude carboxylic acid (**16**). 2,2'-Dipyridinyl disulfide (348 mg, 1.58 mmol) and triphenylphosphine (414 mg, 1.58 mmol) were added to a solution of the residue in acetonitrile (3 mL) and the reaction mixture was stirred at rt for 3 h. The mixture was evaporated and Et_2O was added to the residue. The mixture was filtered through a Celite pad and the filtrate was evaporated. The residue was chromatographed using 18% ethyl acetate-hexane as eluent to give **17** (337 mg, 63%) as an oil; $[\alpha]^{30}_{D}$ -52.0˚ (*c* 1.58, $CHCl_3$) ; IR (neat) 2936, 1683, 1423, 1110, 749, 704 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.05 (9H, s), 1.40-1.64 (5H, m), 1.75-1.80 (1H, m), 1.88-1.92 (1H, m), 2.03-2.14 (1H, m), 2.24-2.32 (2H, m), 3.33-3.42 (1H, m), 3.66 (2H, d, *J* = 6.9 Hz), 4.34-4.40 (1H, m), 7.36-7.45 (6H, m), 7.64-7.67 (4H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 19.11, 19.29, 24.16, 25.73, 26.78, 48.93, 54.17, 61.66, 127.45, 127.48, 129.47, 133.08, 135.41, 173.57; MS (m/z) 350(M^+-57); Anal. Calcd for $C_{25}H_{33}NO_2Si$: C, 73.66, H, 8.16, N, 3.44, found C, 73.63, H, 8.20, N, 3.56.

(2*S*,6*S*,8*S*)-8-Azido-2-[(*tert*-butyldiphenylsilyloxy)methyl]-9-oxo-1-azabicyclo[4.3.0]nonane (18) and (2*S*,6*S*)-2-[(*tert*-Butyldiphenylsilyloxy)methyl]-8-diazo-9-oxo-1-azabicyclo[4.3.0]nonane (19) 1.6 M *n*-Butyllithium (2.13 mL, 3.40 mmol) in *n*-hexane solution was added to a solution of diisopropylamine (0.48 mL, 3.40 mmol) in THF (4.10 mL) at –78 °C and the mixture was stirred at the same temperature for 20 min. A solution of **17** (555 mg, 1.36 mmol) in THF (3.0 mL) was added to the mixture at –78 °C and the reaction mixture was stirred at the same temperature for 20 min. A solution of trisyl azide (1.26 g, 4.08 mmol) in THF (2.0 mL) was added to the mixture at –78 °C and the reaction mixture was stirred at the same temperature for 10 min. Acetic acid (0.58 mL, 10.2 mmol) was added to the mixture at –78 °C and the mixture was stirred at rt for 1 h. The reaction was diluted with ethyl acetate and the mixture was washed with brine. The organic layer was dried and evaporated. The residue was chromatographed using 14% ethyl acetate-hexane as eluent to give **18** (119 mg, 20%) and **19** (376 mg, 64%) as oils; **18** ; $[\alpha]_{30\ D}$ -167.9˚ (*c* 0.60, $CHCl_3$); IR (neat) 2937, 2106, 1696, 1428, 1253, 1110, 822, 742, 704 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.06 (9H, s), 1.23-1.30 (1H, m), 1.39-1.49 (2H, m), 1.53-1.60 (1H, m), 1.71-1.89 (3H, m), 2.00 (1H, ddd, *J* = 17.4 Hz, 7.3 Hz, 3.7 Hz), 3.46-3.56 (1H, m), 3.65-3.75 (2H, m), 4.09 (1H, dd, *J* = 8.5 Hz, 3.6 Hz), 4.32-4.37 (1H, m), 7.37-7.46 (6H, m), 7.65-7.68 (4H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 19.08, 19.38, 24.35, 26.71, 32.47, 33.12, 49.51, 52.24, 59.10, 62.11, 127.51, 129.52, 132.83, 132.92, 135.39, 169.11 ; MS (m/z) 448(M^+), 391(M^+-57) ; HRMS:calcd for $C_{21}H_{21}N_4O_2Si$ (M^+-57) 391.1590, found 391.1521. **19**; $[\alpha]^{30}_{D}$ -70.4˚ (*c* 1.34, $CHCl_3$); IR (neat) 2941, 2120, 1709, 1428, 1245, 1110, 824, 740, 704 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.06 (9H, s), 1.49-1.65 (3H, m), 1.73 (1H, dd, *J* = 13.7 Hz, 6.9 Hz), 1.82-1.91 (2H, m), 2.35 (1H, dd, *J* = 13.7 Hz,

6.6 Hz), 3.43-3.52 (1H, m), 3.70 (2H, d, *J* = 6.6 Hz), 4.30-4.34 (1H, m), 7.37-7.46 (6H, m), 7.64-7.67 (4H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 19.08, 19.29, 24.48, 26.71, 32.62, 38.67, 49.78, 50.25, 62.39, 79.62, 127.56, 129.60, 132.74, 135.34, 135.37, 165.52; MS (m/z) 433(M^+), 405 (M^+-28), 377 (M^+-56) ; HRMS:calcd for $C_{25}H_{31}N_3O_2Si$ (M^+) 433.2186, found 433.2175.

(2*S*,6*S*,8*S*)-8-Azido-2-hydroxymethyl-9-oxo-1-azabicyclo[4.3.0]nonane (20) 1M Tetrabutylammonium fluoride (TBAF) (0.254 mL, 0.254 mmol) was added to a solution of **18** (76 mg, 0.169 mmol) in THF (1.94 mL) at 0 °C and the reaction mixture was stirred at rt for 2.5 h. Saturated $NaHCO_3$ (1.76 mL) was added to the mixture at 0 °C and the mixture was extracted with CH_2Cl_2. The extract was dried and evaporated. The residue was chromatographed using 25% ethyl acetate-hexane as eluent to give **20** (27 mg, 76%) as a white solid; mp 72.5-74.5 ˚C (diisopropyl ether); $[\alpha]^{30}_D$ -262.8˚ (*c* 1.05, $CHCl_3$) ; IR (KBr) 3408, 2941, 2107, 1683, 1445, 1254, 1057 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.12 (1H, ddd, *J* = 24.4 Hz, 12.4 Hz, 3.6 Hz), 1.48-1.67 (3H, m), 1.71-1.95 (4H, m), 2.12 (1H, ddd, *J* = 13.9 Hz, 6.9 Hz, 2.9 Hz), 3.65-3.82 (3H, m), 4.13 (1H, dd, *J* = 8.2 Hz, 2.7 Hz), 4.29-4.36 (1H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 19.37, 24.09, 32.68, 32.88, 50.32, 52.02, 59.27, 61.24, 170.35; MS (m/z) 210(M^+), 179 (M^+-31); Anal. Calcd for $C_9H_{14}N_4O_2$: C, 51.42, H, 6.71, N, 26.65, found C, 51.47, H, 6.63, N, 26.49.

Single-Crystal X-Ray Diffraction of 20.

A colorless plate crystal of $C_9H_{14}N_4O_2$ having approximate dimensions of 0.03 x 0.47 x 0.51 mm was mounted on a glass fiber. All measurements were mode on a Rigaku AFC7R diffractometer with graphite monochromated Mo-Kα radiation and a rotating anode generator. The structure was solved by direct methods (SIR92). The non-hydrogen atoms were refined anisotropically. Crystal data for $C_9H_{14}N_4O_2$: *M*=210.24, orthorhombic, a=8.585(2) Å, b=17.547(3) Å, c=6.946(3) Å, *V*=1046.3(5) Å^3, *T*=20±1°C, space group $P2_12_12_1$ (no.19), *Z*=4, μ(MoKα) 0.98 cm^{-1}, *Dcalc*=1.334g/cm^3, 1424 reflections measured, 1423 unique (R_{int}=0.288). Full-matrix least-squares refinement was based on 728 observed reflections (*I*>3.00s(*I*)) and 137 variable parameters. R=0.034, Rw=0.048, GOF=1.09.

(2*S*,6*S*,8*S*)-8-[*N*-(*tert*-Butoxycarbonyl)amino]-2-hydroxymethyl-9-oxo-1-azabicyclo[4.3.0]nonane (21) A suspension of **20** (26 mg, 0.124 mmol) and $Pd(OH)_2$ (15 mg) in MeOH (1.0 mL) under a hydrogen atmosphere was stirred for 30 min. The mixture was filtered through a Celite pad, and the filtrate was evaporated. To the residue in a mixture of THF (0.9 mL) and H_2O (0.9 mL) were successively added K_2CO_3 (22 mg, 0.161 mmol) and Boc_2O (57 μL, 0.248 mmol) at 0 ˚C. After being stirred at rt for 2.5 h, the organic solvent was removed *in vacuo*. After the residue was acidified with 20% $KHSO_4$, the mixture was extracted with ethyl acetate. The extract was dried and evaporated. The residue was chromatographed using 50% ethyl acetate-hexane as eluent to give **21** (31 mg, 88%)

as a viscous oil; $[\alpha]^{30}_{D}$ -11.8˚ (*c* 1.42, $CHCl_3$) ; IR (neat) 3321, 2939, 1680, 1531, 1451, 1367, 1252, 1170, 1057, 754 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.10-1.34 (1H, m), 1.42 (9H, s), 1.54-1.71 (4H, m), 1.99 (1H, br d, *J* = 13.5 Hz), 1.98-2.08 (1H, m), 2.14-2.23 (1H, m), 3.47 (1H, br s), 3.53-3.56 (1H, m), 3.83-4.41 (3H, m), 4.38-4.41 (1H, m), 5.73 (1H, d, *J* = 5.8 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 19.97, 24.42, 28.28, 33.23, 33.40, 50.74, 51.78, 52.02, 60.84, 80.20, 155.84, 171.76; MS (m/z) 284 (M^+), 253 (M^+-31), 228(M^+-56); HRMS:calcd for $C_{10}H_{15}N_2O_4$ (M^+-57) 227.1032, found 227.1044.

(2*S*,6*S*,8*S*)-Methyl 8-[*N*-(*tert*-Butoxycarbonyl)amino]-9-oxo-1-azabicyclo[4.3.0]nonane-2-carboxylate (22) To a solution of **21** (16 mg, 0.056 mmol) in carbon tetrachloride (0.22 mL), acetonitrile (0.16 mL), and water (0.22 mL) was added $NaIO_4$ (36 mg, 0.169 mmol). After the mixture was stirred for 3 min, ruthenium(III) chloride hydrate (0.3 mg, 2,2 mol%) was added to the reaction mixture. The mixture was vigorously stirred for 3 h. The mixture was extracted with CH_2Cl_2. The extract was dried and evaporated. Et_2O was added to the residue. The mixture was filtrated through Celite. The filtrate was evaporated. THF (0.43 mL) was added to the residue. To the mixture was added a solution of diazomethane in Et_2O prepared from *N*-methylnitrosourea (88 mg). After being stirred for 30 min, the mixture was evaporated. The residue was chromatographed using 30% ethyl acetate-hexane as eluent to give **22** (12 mg, 69%) as a solid; mp 142-144 ˚C (diisopropyl ether); $[\alpha]^{28}_{D}$ -39.7˚ (*c* 0.14, $CHCl_3$); IR (KBr) 3282, 2976, 1685, 1514, 1442, 1299, 1229, 1166 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.12-1.38 (2H, m), 1.45 (9H, s), 1.54-1.62 (1H, m), 1.77-1.86 (2H, br m), 2.14-2.23 (3H, m), 3.75 (4H, m), 4.27-4.29 (1H, br m), 4.87 (1H, d, *J* = 6.0 Hz), 4.99 (1H, br s); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 20.89, 26.21, 28.28, 31.74, 33.72, 51.34, 51.63, 52.41, 52.73, 79.85, 155.50, 170.55, 171.34; MS (m/z) 312 (M^+), 256 (M^+-56) ; HRMS:calcd for $C_{15}H_{24}N_2O_5$ (M^+) 312.1685, found 312.1656.

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