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AN ASYMMETRIC TOTAL SYNTHESIS OF (-)-SUPINIDINE

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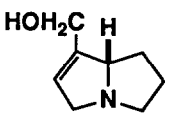
Abstract *By starting from the N-alkenylurethane* ***4****, the epoxy urethane ent-****5****, and the pyrrolidine ent-****6*** *available from the Katsuki-Sharpless kinetic resolution of N-benzyloxycarbonyl-3-hydroxy-1-pentenylamine* ***(2)*** *has been elaborated (-)-supinidine* ***(1)***

The total synthesis of pyrrolizidine alkaloids including $\Delta^{1,2}$-unsaturated necine bases has been an attractive subject for synthetic organic chemists due to their unique structure and intriguing biological activities such as carcinogenicity and antitumor activity [1] Accordingly, much attention is focussed on their asymmetric synthesis during the past decade [2] In most of the syntheses reported, however, chiral building blocks derived from L-proline derivatives, malic acid, or carbohydrates are used as homochiral precursors Recent investigation in this laboratory has revealed that chiral urethanes readily accessible from the Katsuki-Sharpless asymmetric oxidation of racemic *N*-protected 3-hydroxy-4-pentenylamines (**2** or **3**) serve as new and versatile chiral building blocks in the preparation of pyrrolidine or indolizidine alkaloids [3] In connection with our program directed towards development for the asymmetric synthesis of biologically active nitrogen-containing compounds, we wish to report a total synthesis of a necine base (-)-supinidine (**1**)[4] starting from our urethane precursors as chiral educts



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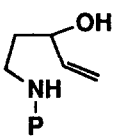
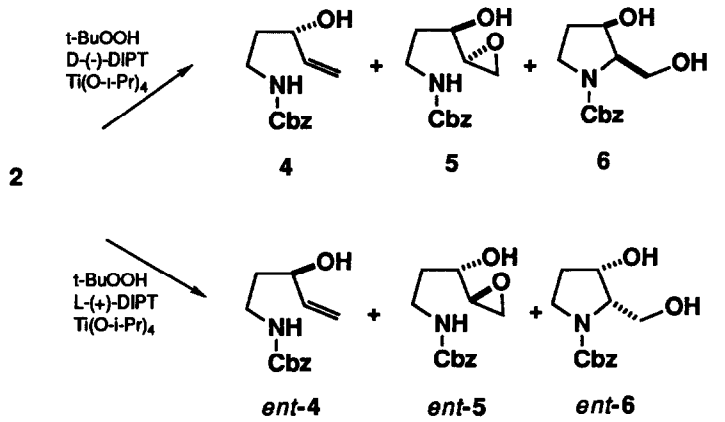


2 P=Cbz
3 P=Boc

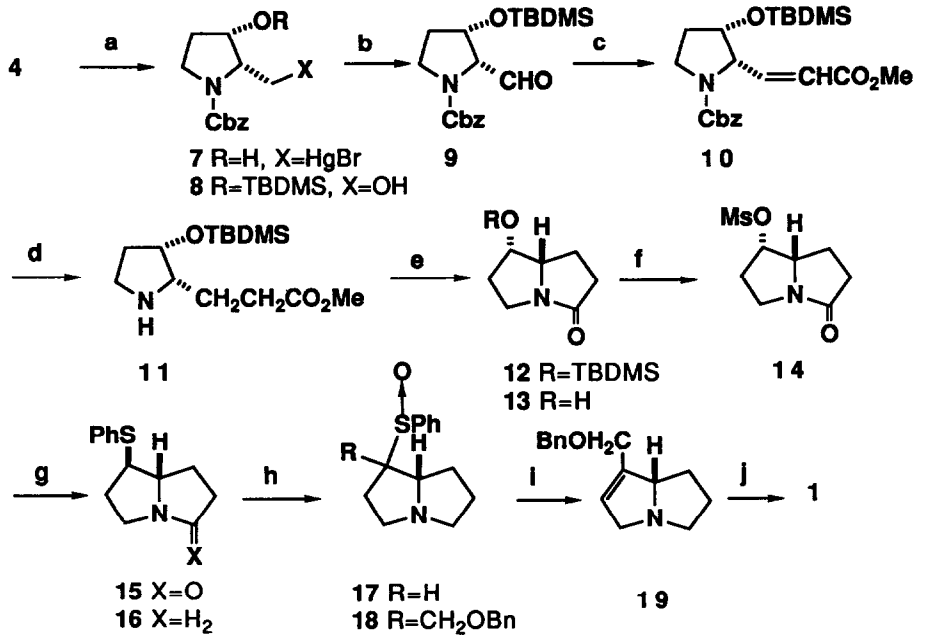
Recent work [3] from our laboratory has shown that the Katsuki-Sharpless kinetic resolution based on the asymmetric epoxidation[5] of *N*-benzyloxycarbonyl-3-hydroxy-1-pentenylamine (**2**) [*tert*-butyl hydroperoxide (TBHP) (0 6 equiv), D-(-)-diisopropyl tartrate (D-(-)-DIPT) (1 2 equiv) or L-(+)-DIPT, Ti(O-i-Pr)4 (1 equiv), molecular sieves (3 Å)/CH_2Cl_2/-20 °C/8 days] gives three kinds of urethanes {the olefin [**4** (44%) or *ent*-**4** (32%)], the epoxy alcohol [**5** (34%) or *ent*-**5** (24%)], and the pyrrolidine [**6** (12%) or *ent*-**6** (12%)]} in good optical purity (Scheme 1) Our approach to **1** utilized **4**, *ent*-**5**, and *ent*-**6** as starting materials



Scheme 1

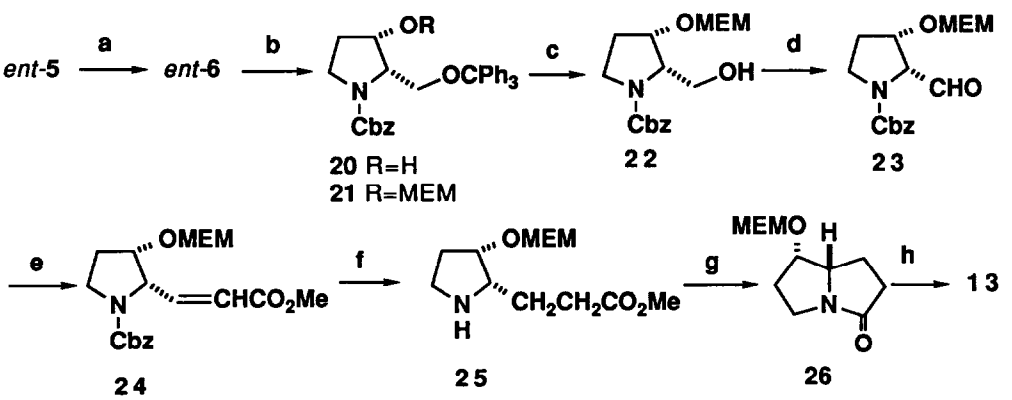
Our synthesis of **1** began with the stereoselective intramolecular amidomercuration of **4**, the initial step of the procedure recently developed by us [6] Reaction of **4** with mercuric acetate in tetrahydrofuran (THF) followed by treatment with sodium bromide gave the *cis*-2,3-substituted pyrrolidine **7** in 81% yield *tert*-Butyldimethylsilylation (TBDMSCl/imidazole/DMF) of **7** followed by reductive oxygenation (O_2/$NaBH_4$/DMF) by the protocol of Whitesides[7] provided the pyrrolidine alcohol **8** as a single product in 67% overall yield from **7** The oxidation (pyridine-sulfur trioxide complex/Et_3N/DMSO)[8] of **8** gave the aldehyde **9** The elongation of C_2 unit on **9** for enabling the construction of a pyrrolizidine ring was performed by the Hornor-Emmons reaction to furnish the α,β-unsaturated ester **10** in 56% overall yield from **8**. Exposure of **10** to palladium hydroxide under an atmosphere of hydrogen in methanol caused both debenzyloxycarbonylation and reduction of the olefinic linkage, providing the amino ester **11** in 94% yield without accompanying spontaneous annulation [9] The intramolecular amidation of **11** was performed by the Weinreb's procedure[10] utilizing trimethylaluminum to give the pyrrolizidinone **12** in 85% yield. Removal of the TBDMS protecting group with 4% HCl in methanol gave the alcohol **13** in 99% yield, which was transformed, in 76% overall yield, to the sulfide **15** *via* mesylation and sulfidation Reduction of **15** with $LiAlH_4$ provided the pyrrolizidine **16** in 89% yield. The hydrochloride of **16** was oxidized with m-CPBA to afford the sulfoxide **17** in 96% yield, which was converted, by introducing the hydroxymethyl unit with LDA/benzyloxychloromethane, into **18** in 69% yield [11] Heating of **18** under reflux in xylene underwent the pyrolysis of the sulfoxide to provide **19**, which was debenzylated with Na/NH_3 to give the desired (-)-supinidine (**1**) $[\alpha]_D^{24}$ -11 30° (*c* 0 23, EtOH), Lit ,[4a] $[\alpha]_D^{18}$ -10 3° (*c* 1 65, EtOH)] in 73% yield from **18** Its spectral data (^1H- and ^{13}C-NMR and IR) were consistent with the values reported [4b]

Next, an alternative route to **13** from *ent*-**5** was developed Exposure of *ent*-**5** to D-camphor-10-sulfonic acid (D-CSA) as an acid catalyst caused aminocyclization, providing *ent*-**6** in 76% yield The selective tritylation at the primary hydroxyl on *ent*-**6** followed by treatment with MEMCl/Hunig base gave the *O*-protected pyrrolidine **21** in 35% overall yield from *ent*-**6** [12] The detachment of the trityl group was performed with *p*-TsOH in methanol to afford the monohydroxy compound **22** in 69% yield Transformation of **22** into **13** was achieved in 55% overall yield in five steps by a procedure similar to that for the elaboration of **8** to **13** as shown in Scheme 3 Accordingly, this method constitutes a new entry to (+)-supinidine[13] from **5** and **6**



a) i, $Hg(OAc)_2$/THF, ii, $NaHCO_3$/NaBr, iii, TBDMSCl/imidazole/DMF, iv, $O_2/NaBH_4$/DMF, b) Py-SO_3 /DMSO/Et_3N, c) $(EtO)_2POCH_2CO_2Me$/NaH, d) $H_2/Pd(OH)_2$, e) i, $AlMe_3$, ii, H^+/MeOH, f) MsCl/Py, g) i, NaSPh/DMF, ii, $LiAlH_4$, h) i, mCPBA, ii, LDA/$BnOCH_2Cl$, i) 150 °C, J) Na/NH_3

Scheme 2



a) D-CSA, b) i, Trytyl chloride/Et_3N, ii, MEMCl/(i-Pr)$_2$NEt, c) p-TsOH/MeOH, d) Py-SO_3/DMSO/Et_3N, e) $(EtO)_2POCH_2CO_2Me$/NaH, f) $H_2/Pd(OH)_2$, g) $AlMe_3$, h) HCl/MeOH

Scheme 3

In summary, we have demonstrated the utility of the chiral urethanes **4**, *ent*-**5**, and *ent*-**6**, prepared readily by the Katsuki-Sharpless oxidation of **2**, as the versatile starting materials in a new asymmetric synthesis of (-)-supinidine (**1**) Thus, the readily available pyrrolidines **9** and **23** would serve as useful chirons in the enantiomeric synthesis of other $\Delta^{1,2}$-unsaturated necine bases such as retronecine, heliotridine, and crotanecine, and their results will be achieved in due course

Experimental Part

Melting points were determined with a Yanaco micro melting point apparatus and are not corrected Microanalyses were performed by Microanalysis Center of Toyama Medical & Pharmaceutical University Infrared spectra (IR) were measured with a JASCO A 102 spectrophotometer or a Perkin-Elmer 1600 series FTIR spectrophotometer Proton magnetic resonance (^{1}H NMR) spectra were recorded either at 60 MHz on a JEOL PMX-60 instrument or at 270 MHz on a JEOL-FX270 instrument with tetramethylsilane as an internal standard Carbon-13 NMR spectra were determined on a Varian XL-200 instrument with tetramethylsilane as an internal standard unless otherwise specified Mass spectra (MS) and high resolution mass spectra (HRMS) were measured on a JEOL JMS D-200 spectrometer Optical rotations were measured on a JASCO DIP-140 instrument Column chromatography was performed on silica gel (Fuji-Davision BW-200, Merck 60 (No 9385) , or Nakarai 60) with a medium pressure apparatus and a mixture of ethyl acetate and hexane was used as eluant unless otherwise specified. The extracts were dried over Na_2SO_4 unless otherwise specified

General Procedure for Sharpless Oxidation of the Racemic 2. To a mixture of the racemic **4** (10 mmol) and Molecular Sieves (3Å) (20 mmol%) in CH_2Cl_2 (88 mL) was added freshly distilled D-(-)- or L-(+)-DIPT (12 mmol) After being cooled to -20 °C, Ti(O-*i*-Pr)$_4$ (10 mmol) was added to the mixture and then the resulting mixture was stirred for 30 min *tert*-Butyl hydroperoxide [TBHP, 6 mmol, 3 M in 2,2,4-trimethylpentane, dried with MS (3Å)] was added to the mixture and then the resulting mixture was kept at -20 °C for 8 days A solution of $FeSO_4$ $7H_2O$ (6 mmol) and citric acid (12 mmol) in H_2O (26 mL) was added to the reaction mixture at 0 °C After being stirred at room temperature for 30 min, the Molecular Sieves was removed by filtration The organic phase of the filtrate was separated and then the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL) The combined organic layers were washed with brine (40 mL), dried, and evaporated To a solution of the residue in ether (16 mL) was added a solution of NaOH (7 89 g) and NaCl (1 32 g) in H_2O (23 7 mL) at 0 °C and then the resulting mixture was vigorously stirred for 1 h After addition of H_2O (5 mL), the organic phase was separated The aqueous phase was extracted with ether (3 x 10 mL) The combined organic layers were washed with brine, dried, and evaporated The residue was chromatographed to yield optically active **4**, **5**, and **6**, or *ent*-**4**, *ent*-**5**, and *ent*-**6**, respectively

(*S*)-*N*-Benzyloxycarbonyl-3-hydroxy-4-pentenylamine (4) An oil, $[\alpha]_D^{25}$ +2 64° (*c* 2 975, $CHCl_3$), Enantiomeric excess was determined on the basis of ^{19}F NMR analysis for the corresponding (+)-α-methoxy-α-trifluorophenylacetic ethyl ester, which indicated the optical purity to be 92%ee IR (neat) 3350, 1700 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 1 51-1 80 (m, 2 H), 2 75-2 85 (br s, 1 H), 3 17-3 52 (m, 2 H), 4 12-4 23 (m, 1 H), 5 04 -5 34(m, 5 H), 5 74-5 95 (m, 1 H), 7 35 (s, 5 H) HRMS calcd for $C_{13}H_{17}NO_3$ 235 1183, found 235 1206

(3*R*,4*S*)-1-[(*N*-Benzyloxycarbonyl)amino]-4,5-epoxypentane (5). An oil, $[\alpha]_D^{25}$ -5 93° (*c* 1 065, $CHCl_3$), IR (neat) 3350, 1690 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 1 49-1 67 (m, 1 H), 1 67-1 81 (m, 1 H),

2 60-2 68 (m, 2 H), 2.88 (br s, 1 H), 3 20-3 39 (m, 2 H), 3 57-3 68 (m, 1 H), 3 90 (br s, 1 H), 5 02 (s, 2 H), 5 97 (m, 1 H), 7 26 (s, 5 H), HRMS calcd for $C_{13}H_{17}NO_4$ 251 1156, found 251 1134

(2*R*,3*R*)-1-(Benzyloxycarbonyl)-3-hydroxy-2-(hydroxymethyl)pyrrolidine (6) An oil, $[\alpha]_D^{25}$ -35 96° (*c* 3 705, $CHCl_3$), IR (neat) 3420, 1675 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1 53-2.01 (m, 2 H), 3 18-4 05 (m, 5 H), 4 29-4 64 (m, 1 H), 5 04-5 14 (m, 2 H), 7 31 (s, 5 H), HRMS calcd for $C_{13}H_{17}NO_4$ 251 1158, found 251.1170

***(R)*-*N*-Benzyloxycarbonyl-3-hydroxy-4-pentenylamine (*ent*-4)** The chromatographic properties and spectral data were identical with those of **4**, $[\alpha]_D^{25}$ -2 60° (*c* 1 08, $CHCl_3$)

(3*S*,4*R*)-1-[(*N*-Benzyloxycarbonyl)amino]-4,5-epoxypentane (*ent*-5). The chromatographic properties and spectral data were identical with those of **5**, $[\alpha]_D^{25}$ +5 93° (c 1 065, $CHCl_3$)

(2*S*,3*S*)-1-(Benzyloxycarbonyl)-3-hydroxy-2-(hydroxymethyl)pyrrolidine (*ent*-6). The chromatographic properties and spectral data were identical with those of **6**, $[\alpha]_D^{25}$ +35 01° (*c* 1 13, $CHCl_3$) The specific rotation of (2*S*,3*S*)-1-(*tert*-butoxycarbonyl)-3-hydroxy-2-(hydroxymethyl)pyrrolidine prepared from ***ent*-6** (1 H_2/Pd(OH)$_2$, 2· Boc_2O/Et_3N) showed $[\alpha]_D^{25}$+ 30.2° Enantioselectivity of ***ent*-6** was determined by comparison with the specific rotation ($[\alpha]_D^{25}$ +30 9° /91% ee) of the authentic sample[3a] to be 89% ee

(2*S*,3*S*)-1-(Benzyloxycarbonyl)-2-[(bromomercuri)methyl]-3-hydroxypyrrolidine (7) A mixture of **4** (470 mg, 2 mmol) and $Hg(OAc)_2$ (956 mg, 3 mmol) in THF (22 mL) was stirred at room temperature for 24 h The mixture was added to saturated $NaHCO_3$ (50 mL), and the resulting mixture was stirred at room temperature for 0 5 h To the mixture was added saturated KBr (50 mL), and the resulting mixture was stirred at room temperature for 1 5 h The organic phase was separated, the aqueous phase was extracted with CH_2Cl_2 three times The combined organic extracts were washed with brine, dried, and evaporated The residue was subjected to chromatography to yield **7** (836 mg, 81 2%) as an oil, $[\alpha]_D^{25}$ +19 0° (*C* 3 175, $CHCl_3$), IR (neat) 3396, 1684 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1 50-2 33 (m, 4 H), 3 23-3 90 (m, 3 H), 3 90-4 65 (m, 2 H), 5 20 (s, 2 H), 7 42 (s, 5 H)

(2*S*,3*S*)-1-(Benzyloxycarbonyl)-3-[(*tert*-butyldimethylsilyl)oxy]-2-(hydroxymethyl)-pyrrolidine (8). A mixture of **7** (515 mg, 1 mmol), imidazole (170 mg, 2 5 mmol), DMAP (29 5 mg, 1 mmol), and TBDMSCl (226 mg, 1 5 mmol) in DMF (4 mL) was stirred at room temperature for 24 h Ether (1 5 mL) was added to the reaction mixture, and the resulting mixture was successively washed with brine, 5% HCl, 5% $NaHCO_3$, and brine The organic phase was dried and evaporated The residue was subjected to chromatography to yield (2*S*,3*S*)-1-(benzyloxycarbonyl)-2-[(bromomercuri)methyl]-3-[(*tert*-butyldimethylsilyl)-oxy]pyrrolidine (547 mg, 86 8%) as an oil, $[\alpha]_D^{25}$ +10 24° (*c* 4 04, $CHCl_3$), IR ($CHCl_3$) 1690 cm^{-1}, ^1H NMR ($CDCl_3$) δ 0 01 (s, 6 H), 0 81 (s, 9 H), 1 37-2 03 (m, 4 H), 3 03-3 46 (m, 2 H), 3 80-4 39 (m, 2 H), 5 01 (s, 2 H), 7 22 (s, 5 H) Oxygen was bubbled into a suspension of $NaBH_4$ (46 mg, 1 20 mmol) in DMF (13 mL) for 0 5 h While oxygen was bubbled through the mixture, a solution of the above *tert*-butyldimethylsilylated compound (547 mg 0 87 mmol) in DMF (42 mL) was added dropwise over 2 h Oxygen bubbling was continued for 1 h, and ether was added The precipitate was removed by filtration through Celite, and the filtrate was evaporated *in vacuo* The residue was subjected to chromatography to yield **8** (244 mg, 76.8%) as an oil, $[\alpha]_D^{25}$ +34 54° (*c* 2, 22, $CHCl_3$), IR (neat) 3448, 1701 cm^{-1}, ^1H NMR ($CDCl_3$) δ 0 07 (s, 6 H), 0 87 (s, 9 H), 2 17-2 64 (m, 2 H), 3 27-3 62 (m, 2 H), 3 64-4 22 (m, 4 H), 4 22-4 64 (m, 1 H), 5 08 (s, 2 H), 7 29 (s, 5 H), HRMS calcd for $C_{19}H_{31}NO_4Si$ 365 2021, found 365 1975

Methyl 3-[(2*S*,3*S*)-1-(Benzyloxycarbonyl)-3-[(*tert*-butyldimethylsilyl)oxy]pyrrolidin-2-yl]-2-propenoate (10) A solution of sulfur trioxide pyridine complex (1 767g, 11 1 mmol) in DMSO (10 mL) was added to a solution of **8** (1 35g, 3 71 mmol) and triethylamine (1 55 mL, 11 1 mmol) in CH_2Cl_2 (10 mL) with ice-cooling. The reaction was stirred at room temperature for 1.5 h and then diluted with ether (20 mL). A 10% citric acid solution was added to the mixture to be adjusted to pH 4 The organic phase was separated and the aqueous phase was extracted with ether three times The combined extracts were washed with brine, dried, and evaporated to leave an oil, which was subjected to column chromatography with silica gel using n-hexane-ethyl acetate as eluant to provide **9** (1 09 g, 81%) as an oil, IR (neat) 1735, 1706 cm^{-1}, ^1H NMR ($CDCl_3$) δ 0.10 (s, 6H), 0.90 (s, 9 H), 1 73-2 17 (m, 2 H), 3 60-4 00 (m, 2 H), 4 00-4 37 (m, 1 H), 4.63-4 93 (m, 1 H), 5.20 (br s, 2 H), 7.41 (br s, 5 H), 9 50 (br s, 1 H). To a suspension of sodium hydride (172 mg, 4 29 mmol) in THF (7 6 mL) was added methyl diethylphosphonoacetate (796 μL, 4 29 mmol) over 5 min at -20 °C After being stirred for 20 min, a solution of **9** (779 mg, 2.14 mmol) was added to the mixture, and the whole mixture was stirred for 2 h at -10 °C Saturated NH_4Cl (3 mL) was added to the reaction mixture After separation, the aqueous phase was extracted with CH_2Cl_2 three times The combined extracts were washed with brine, dried, and evaporated to give an oil, which was chromatographed on silica gel using a mixture of n-hexane and ethyl acetate (10 1) as an eluant to give **10** (625 mg, 69 5%) (*E*:*Z*=3 1) as an oil, ***E*-10**, $[\alpha]_D^{25}$ +14.09° (*c* 1 125, $CHCl_3$), IR (neat) 1706, 1662 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0 00 (s, 6 H), 0 81 (s, 9 H), 1 75-1.82 (m, 1 H), 1.88-1.97 (m, 1 H), 3.39-3.49 (m, 2 H), 3 66 (s, 3 H), 4.29-4.43 (m, 2 H), 4.97-5.13 (m, 2 H), 5 71-5.88 (m, 1 H), 6 82-6 92 (m, 1 H), 7.20-7 29 (m, 5 H); HRMS calcd for $C_{22}H_{33}NO_5Si$ 419 2126, found 419 2106.

(7*S*,8*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-3-oxopyrrolizidine (12) A suspension of **10** (521 mg, 1 24 mmol) and palladium hydroxide (96 mg) in methanol (6.4 mL) was stirred under a hydrogen atmosphere for 4 h The insoluble materials were removed by filtration and the filtrate was evaporated to give the crude **11** (336 mg, 94 1%) as an oil, which was taken in CH_2Cl_2 (20 mL) To the solution was added 1N trimethylaluminum in hexane (1.35 mL, 1 34 mmol) The reaction mixture was stirred for 1 h at room temperature and then refluxed for 18 h A 0.5% HCl aqueous solution was slowly added to the mixture with ice-cooling and the organic phase was separated The aqueous phase was extracted with CH_2Cl_2 three times The combined organic layers were washed with brine, dried, and evaporated. The residue was subjected to column chromatography on silica gel using ethyl acetate as an eluant to give **12** (242 mg, 84.7%) as an oil, $[\alpha]_D^{25}$ +32 81° (*c* 1 045, $CHCl_3$), IR (neat) 1696cm^{-1}, ^1H NMR ($CDCl_3$) δ 0 06 (s, 3 H), 0.07 (s, 3 H), 0 87 (s, 9 H), 1 97-2.18 (m, 4 H), 2.37-2 49 (m, 1 H), 2 58-2.73 (m, 1 H), 3 04-3 15 (m, 1 H), 3 55-3.69 (m, 1 H), 3 80-3 89 (m, 1 H), 4 03-4.07 (m, 1 H); HRMS calcd for $C_{13}H_{25}NO_2Si$ 255 1654, found 255 1684.

(2*S*,3*S*)-1-(Benzyloxycarbonyl)-3-[(methoxyethoxymethyl)oxy]-2-(triphenylmethoxymethyl)pyrrolidine (21) A solution of *ent*-**5** (1 69 g, 6 76 mmol) and D-camphor-10-sulfonic acid (156 mg, 0 67 mmol) in CH_2Cl_2 (69 5 mL) was stirred for 4 h After addition of triethylamine (0 35 mL), the mixture was stirred for 0 5 h The mixture was washed with brine, dried, and evaporated The residue was subjected to column chromatography on silica gel using a mixture of n-hexane and ethyl acetate (1 1) as an eluant to yield *ent*-**6** (1 29 g, 75.6%) as an oil To a solution of *ent*-**6** (1 52 g, 6 mmol) in CH_2Cl_2 (22 mL) was added successively triethylamine, DMAP (29 mg), and chlorotriphenylmethane (1 85 g) with ice-cooling and then the reaction mixture was stirred for 20 h at room temperature The mixture was washed with brine, dried, evaporated The residue was subjected to column chromatography on silica gel using a mixture of n-hexane and

ethyl acetate (7 1) as an eluant to yield **20** (2 3 g, 77 5%) as an oil; $[\alpha]_D^{25}$ +47 2° (*c* 0.845, $CHCl_3$), IR (neat) 3442, 1698 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1 93-2 14 (m, 2 H), 2 76 (d, *J*=6 1 Hz, 1 H), 3.26-3 70 (m, 4 H), 3 87-4.07 (m, 1 H), 4.47-4.58 (m, 1 H), 4.99 (s, 1 H), 5 09 (s, 1 H), 7 20-7 39 (m, 20 H) To a solution of **20** (1 98 g, 4 02 mmol) in CH_2Cl_2 (40 4 mL) was added MEMCl (1 83 mL) and *N,N*-diisopropylethylamine (2 8 mL) and then the mixture was refluxed for 20 h The reaction mixture was washed with brine three times, dried, and evaporated. The residue was subjected to column chromatography on silica gel using a mixture of n-hexane and ethyl acetate (7.1) as an eluant to yield **21** (1 045 g, 44.7%) as an oil, $[\alpha]_D^{25}$ +9.57° (*c* 4 45, $CHCl_3$), IR (neat) 3058, 2887, 1702, 1597 cm^{-1}, ^1H NMR ($CDCl_3$) δ 2 04-2.19 (m, 1 H), 2 20-2 33 (m, 1 H), 3 38 (s, 3 H), 3.29-3 66 (m, 6 H), 3 69-3 72 (m, 2 H), 3 96-4 16 (m, 1 H), 4 33 (dd, *J*=6 84, 14 4 Hz, 1 H), 4 62 (d, *J*=7 08 Hz, 1 H), 4 70 (d, *J*=7 32, 1 H), 4 83-4 96 (m, 0 5 H), 5 04-5 18 (m, 1 5 H), 7 08-7 27 (m, 14 H), 7 27-7.43 (m, 6 H), HRMS calcd for $C_{36}H_{38}NO_6$ (M^+-1) 580 2699, found 580.2664

(2*S*,3*S*)-1-(Benzyloxycarbonyl)-2-(hydroxymethyl)-3-[(methoxyethoxymethyl)oxy]-pyrrolidine (22) A mixture of **21** (90 4 mg, 0 155 mmol) and pTsOH (1 5 mg, 0 07 mmol) in methanol (2 mL) was stirred for 3 h at room temperature After addition of triethylamine (0 1 mL), the mixture was evaporated. The residue was subjected to column chromatography on silica gel using a mixture of n-hexane and ethyl acetate (1 1) as an eluant to yield **22** (36 3 mg, 68 8%) as an oil, $[\alpha]_D^{25}$ +73 42° (*c* 1.46, $CHCl_3$), IR (neat) 3448, 2896, 1699 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1 87-2 40 (m, 2 H), 3 51 (s, 3 H), 3 52-4 30 (m, 9 H), 4 36-4 65 (m, 1 H), 4 80 (br s, 1 H), 4 92 (s, 2 H), 5 33 (s, 2 H), 7 52 (s, 2 H), HRMS calcd for $C_{16}H_{22}NO_5$ (M^+-CH_2O) 308 1260, found 308 1261

Methyl 3-[(2*S*,3*S*)-1-(Benzyloxycarbonyl)-3-[(methoxyethoxymethyl)oxy]pyrrolidin-2-yl]-2-propenoate (24) A solution of sulfur trioxide-pyridine complex (1 767g, 11 1 mmol) in DMSO (10 mL) was added to a solution of **22** (420 mg, 1 23 mmol) and triethylamine (1 55 mL, 11 1 mmol) in CH_2Cl_2 (10 mL) with ice-cooling The reaction mixture was stirred at room temperature for 1 5 h and then diluted with ether (20 mL) A 10% citric acid solution was added to the mixture to be adjusted to pH 4 The organic layer was separated and the aqueous layer was extracted with ether three times The combined extracts were washed with brine, dried, and evaporated to leave an oil, which was purified by column chromatography on silica gel using n-hexane-ethyl acetate as eluant to provide **23** (415 mg, 99%) To a suspension of sodium hydride (172 mg, 4 29 mmol) in THF (7 6 mL) was added methyl diethylphosphonoacetate (796 μl, 4 29 mmol) over 5 min at -20 °C After being stirred for 20 min, a solution of **23** (415 mg, 1 23 mmol) was added to the mixture and the whole mixture was stirred for 2 h at -10 °C Saturated NH_4Cl (3 mL) was added to the reaction mixture After separation, the aqueous layer was extracted with CH_2Cl_2 three times The combined extracts were washed with brine, dried, and evaporated to give an oil, which was chromatographed on silica gel using a mixture of n-hexane and ethyl acetate (10 1) as an eluant to give **24** (484 mg, 68%) (*E* *Z*=7 3) as an oil, $[\alpha]_D^{24}$ +10.1° (*c* 2 06, $CHCl_3$), IR (neat) 2950, 2891, 1705, 1661 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1 86-2 19 (m, 2 H), 3 37 (s, 3 H), 3 39-3 77 (m, 6 H), 3 73 (s, 3 H), 4 11-4 38 (m, 1 H), 4 60-4 83 (m, 3 H), 5 06-5 16 (m, 2 H), 5 42-5 60 (m, 0 3 H), 5 80-5 97 (m, 0 7 H), 6 08-6 32 (m, m, 0 3 H), 6 88-6 96 (m, 0 7 H), 7 30-7 35 (m, 5 H), HRMS calcd for $C_{20}H_{28}NO_7$ 394.1864, found 394 1834

(7*S*,8*S*)-7-[(Methoxyethoxymethyl)oxy]-3-oxopyrrolizidine (26) A suspension of **24** (484 mg, 1 20 mmol) and palladium hydroxide (96 mg) in methanol (6 4 mL) was stirred under a hydrogen atmosphere for 4 h The insoluble materials were removed by filtration and the filtrate was evaporated to give the crude **25** (336 mg, 94 1%) as an oil To a solution of the crude **25** in CH_2Cl_2 (20 mL) was added 1N

trimethylaluminum in hexane (1.35 mL, 1 34 mmol) The reaction mixture was stirred for 1 h at room temperature and then refluxed for 18 h A 0 5% aqueous HCl solution was slowly added to the mixture with ice-cooling and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 three times The combined organic layers were washed with brine, dried, and evaporated to give a residue, which was subjected to column chromatography on silica gel using ethyl acetate as an eluant to give **26** (194 mg, 68 9%) as an oil, $[\alpha]_D^{25}$ +34 5° (*c* 0 605, $CHCl_3$), IR (neat) 2892, 1685cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 1 96-2 34 (m, 4 H), 2 39-2 51 (m, 1 H), 2 60-2 73 (m, 1 H), 3.12 (t, *J*=10 3 Hz, 1 H), 3 39 (s, 3 H), 3 53-3 63 (m, 3 H), 3 65-3 70 (m, 2 H), 3 89-3.96 (m, 1 H), 4 04-4 07 (m, 1 H), 4 71 (d, *J*=7 1 Hz, 1 H), 4 79 (d, *J*=7.1 Hz, 1 H), HRMS calcd for $C_{11}H_{19}NO_4$ 229 1313, found 229 1276

(7*S*,8*S*)-7-Hydroxy-3-oxopyrrolizidine (13) a) From **12**, A solution of **12** (242 mg, 0 95 mmol) in 4% HCl-methanol (4 04 mL) was stirred for 2 h at 30 °C After removal of the solvent, the residue was subjected to column chromatography on silica gel using a mixture of ethyl acetate and methanol (10 1) as an eluant to give **13** (133 mg, 99 4%) as an oil, $[\alpha]_D^{25}$ +44 5° (*c* 1 59, $CHCl_3$), IR (KBr) 3293, 1655 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 2 02-2 14 (m, 1 H), 2 25-2 43 (m, 3 H), 2 67-2 92 (m, 2 H), 3 14-3.23 (m, 1 H), 3 64-3 75 (m, 1 H), 3 96-4.04 (m, 1 H), 4 16 (br d, *J*=1 96 Hz, 1 H), 6 79 (br s, 1 H), HRMS calcd for $C_7H_{11}NO_2$ 141 0789, found 141 0799 b) From **26**, A solution of **26** (242 mg, 0 95 mmol) in 4% HCl-methanol (4 04 mL) was stirred for 2 h at 30 °C After removal of the solvent, the residue was subjected to column chromatography on silica gel using a mixture of ethyl acetate and methanol (10 1) as an eluant to give **13** (133 mg, 81 4%) as an oil, $[\alpha]_D^{24}$ +41 07° (*c* 1 55, $CHCl_3$) The chromatographic and spectral properties were identical with those of a sample obtained in a).

(7*S*,8*S*)-7-[(Methylsulfonyl)oxy]-3-oxopyrrolizidine (14) Methanesulfonyl chloride (230 μL, 2 97 mmol) was added to a solution of **13** (133 mg, 0 94 mmol) in pyridine (4 14 mL) and the reaction mixture was stirred for 1 5 h at room temperature After addition of water (0 5 mL), the mixture was evaporated to give the residue, which was subjected to column chromatography on silica gel using a mixture of $CHCl_3$ and methanol (15 1) as an eluant to provide **14** (167 mg, 80 6%) as an oil, $[\alpha]_D^{25}$ +3 93° (*c* 0 5, $CHCl_3$), IR (KBr) 1678 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 2 14-2 23 (m, 2 H), 2 34-2 55 (m, 3 H), 2 63-2 72 (m, 1 H), 3 06 (s, 3 H), 3 16-3 24 (m, 1 H), 3 66-3 77 (m, 1 H), 4 06 (td, *J*=2 93, 6 72 Hz, 1 H), 5 08 (br t, *J*=3 18 Hz, 1 H), HRMS calcd for $C_8H_{12}NO_4S$ (M^+-H) 219 0485, found 218 0462

(7*R*,8*S*)-7-(Phenylthio)-3-oxopyrrolizidine (15) A solution of NaSPh [prepared from thiophenol (126 μL, 1 23 mmol) and sodium hydroxide (45 7 mg, 1 14 mmol) in DMF (2 12 mL)] was added to a solution of **14** (167 mg, 0 76 mmol) in DMF (0 55 mL) and then the mixture was stirred for 2 h at 50 °C After removal of the solvent, the residue was subjected to column chromatography on silica gel using a mixture of n-hexane and ethyl acetate (3.1) as an eluant to give **15** (163 5 mg, 93 3%) as an oil,$[\alpha]_D^{25}$ -64 5° (*c* 2 045, $CHCl_3$), IR (neat) 1700 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 1 52-1 67 (m, 1 H), 1 98-2 16 (m, 2 H), 2 30-2 41 (m, 1 H), 2 44-2 57 (m, 1 H), 2 61-2 67 (m, 1 H), 3 05-3 22 (m, 2 H), 3 57-3 67 (m, 1 H), 3 77-3 85 (m, 1 H), 7 30-7 36 (m, 3 H), 7 45-7 48 (m 2 H), HRMS calcd for $C_{13}H_{15}NOS$ 233 0784, found 233 0849

(1*R*,8*S*)-1-(Phenylthio)pyrrolizidine (16) A solution of **15** (160 mg, 0 686 mmol) in THF (2 mL) was added to a suspension of $LiAlH_4$ (105 mg) in THF (11 2 mL) and then the suspension was refluxed for 4 h Water (52 5 mL), 20% NaOH aqueous solution (37 3 mL), and water (191 mL) were added successively to the suspension The insoluble materials were filtered off and then the filtrate was evaporated to give a residue Column chromatography of the residue using a mixture of $CHCl_3$ and 1% NH_3 in methanol (10 1) as an eluant

gave **16** (134 mg, 88 8%) as an oil, $[\alpha]_D^{25}$ -34.60° (*c* 1.495, $CHCl_3$), IR (neat) 2961, 2867 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1 44-1 51 (m, 1 H), 1 68-1 80 (m, 1 H), 1 85-1 96 (m, 1 H), 2 25-2 32 (m 1 H), 2 50-2 66 (m, 2 H), 2 97-3 05 (m, 1 H), 3 16-3 28 (m, 2 H), 3 37-3 44 (m 1 H), 7.22-7.31 (m, 3 H), 7 40-7 43 (m, 2 H), HRMS calcd for $C_{13}H_{16}NS(M^+-H)$ 218 1002, found 218 1000

(8*S*)-*O*-Benzylsupinidine (19) To a solution of **16** (100 mg, 0 456 mmol) in methanol (1 39 mL) was added 8%-HCl-methanol (0 73 mL) with ice-cooling and then the mixture was stirred for 0 5 h After removal of the solvent, the residue was taken in CH_2Cl_2 (14 9 mL) To the mixture was added mCPBA (82 6 mg, 0 479 mmol) at -36 °C After being stirred for 0 5 h, a 10% KOH solution (5 mL) was added to the reaction mixture The organic phase was separated and then the aqueous phase was extracted with CH_2Cl_2 three times The combined organic layers were washed with brine, dried, and evaporated Column chromatography of the residue using a mixture of $CHCl_3$ and 1% NH_3 in methanol (10 1) as eluant gave **17** (104 mg, 96.5%) as an oil A solution of **17** (100 mg, 0 42 mmol) in THF (0 92 mL) and HMPA (0 92 mL) was added to a solution of LDA [prepared from 15% n-BuLi (0 53 mL, 0 82 mmol) in n-hexane and diisopropylamine (122 μL, 0 84 mmol) in THF (0 92 mL)] at -78 °C and then the mixture was stirred for 2 h at the same temperature Benzyl chloromethyl ether (83 μL, 0 6 mmol) was added to the mixture at -78 °C and then the temperature of the reaction mixture was raised to -5 °C After addition of water (3 mL), the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 three times The combined organic layers were washed with brine, dried, and evaporated. Column chromatography of the residue using a mixture of $CHCl_3$ and 1% NH_3 in methanol (10 1) as an eluant gave **18** (104 mg, 68 9%) as an oil A solution of **18** (100 mg, 0 28 mmol) in xylene (2 5 mL) was refluxed for 20 min After removal of the solvent, the residue was subjected to column chromatography on silica gel using a mixture of $CHCl_3$ and 1% NH_3 in methanol (10 1) as an eluant to provide **19** (47 5 mg, 73 6%) as an oil, $[\alpha]_D^{25}$ -42 26° (*c* 1 335, $CHCl_3$), ^1H NMR ($CDCl_3$) δ 1 46-1 58 (m, 1 H), 1 70-1 80 (m, 2 H), 1 90-2 02 (m, 1 H), 2 44-2 50 (m, 1 H), 3 07-3 15 (m, 1 H), 3 35 (ddd, *J*=1 95, 4 63, 13 7 Hz, 1 H), 3 89 (ddd, *J*=1 71, 3 17, 13 9 Hz, 1 H), 4 09 (br s, 2 H), 4 16 (br s, 1 H), 4 52 (ABq, *J*=16 85 2 H), 5 60 (d, *J*=1 71 Hz, 1 H), 7 32-7 35 (m, 5 H),HRMS calcd for $C_{15}H_{19}NO$ 229 1466, found 229 1452

(-)-Supinidine (1) To a solution of **19** (45 mg, 0 19 mmol) in liquid ammonia (1 94 mL) and THF (1 28 mL) was added sodium metal (15 8 mg, 0 68 mmol) The mixture was stirred for 5 min and then quenched with aqueous ammonium chloride (1 mL) After evaporation of ammonia, the mixture was extracted with ether three times The extracts were dried and evaporated The residue was subjected to chromatography using a mixture of $CHCl_3$ and 1% NH_3-methanol (10 1) as an eluant to yield **1** (27 mg, 98 9%) as an oil,$[\alpha]_D^{24}$ -11 30° (*c* 0 23, EtOH), [lit , [4a] $[\alpha]_D^{18}$ -10 3° (*c* 1 65, EtOH)], IR ($CHCl_3$) 3640, 3360, 2980, 2890, 1455, 1120, 1085, 1050 cm^{-1}, ^1H NMR ($CDCl_3$) δ 1 43-1 56 (m, 1 H), 1 70-1 77 (m, 2 H), 1 87 (br s, 1 H), 1 80-2 02 (m, 1 H), 2 47-2 56 (m, 1 H), 3 03-3 10 (m, 1 H), 3 31 (ddd, *J*=1 96, 4 40, 12 9 Hz, 1 H), 3 86 (br d, *J*=15 4 Hz, 1 H), 4 12-4 26 (m, 3H), 5 50 (br s, 1 H), ^{13}C NMR ($CDCl_3$) δ 25 60, 30 20, 56 36, 59 74, 61 70, 70 87, 120 88, 143 87, HRMS calcd for $C_8H_{13}NO$ 139 0997, found 139 0947

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