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TETRAHEDRON

Hypervalent λ^n-Iodane-Mediated Fragmentation of Tertiary Cyclopropanol Systems II: Application to Asymmetric Syntheses of Piperidine and Indolizidine Alkaloids

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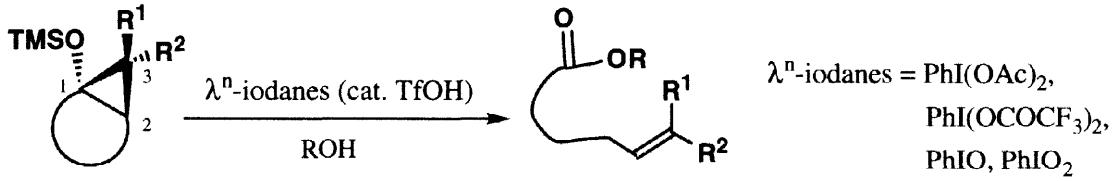
Abstract: The asymmetric synthesis of (-)-pinidine and its enantiomer was accomplished by starting from norgranatanone *via* the asymmetric enolization, stereoselective cyclopropanation, and oxidative ring cleavage of the resulting cyclopropanol system with a hypervalent λ^n-iodane as key steps. Formal asymmetric synthesis of (+)-indolizidine 223AB was also performed *via* the asymmetric enolization and oxidative ring cleavage of the resulting cyclopropanol system as key steps.

Keywords: Fragmentation reactions; Hypervalent elements; Cyclopropanes; Asymmetric synthesis

1. INTRODUCTION

Tertiary cyclopropyl silyl ethers (**1**), available from the cyclopropanation of enol silyl ethers, act as important synthons in organic synthesis. Recently, we found that the reaction of **1** with hypervalent λ^n-iodanes in a protic solvent caused oxidative bond cleavage at both C_1-C_2 and C_1-C_3 leading to alkenoic acids or their corresponding esters (**2**) in high yields.[1-3] In the cases of the compounds bearing an alkyl group on the cyclopropane-ring, the *endo*-compound (**1a**) gave only the (*Z*)-alkene (**2a**) while the *exo*-compound (**1b**) gave only the (*E*)-alkene (**2b**) (**Scheme 1**).



1a (R^1=Me, R^2=H)
1b (R^1=H, R^2=Me)

Scheme 1

2a (R^1=Me, R^2=H)
2b (R^1=H, R^2=Me)

We applied this stereospecific fragmentation to the asymmetric synthesis of the piperidine alkaloid, pinidine[4,5], bearing the (*E*)-olefin moiety and reported this result in a preliminary communication.[6] This paper describes the full details of this work and the formal asymmetric synthesis of indolizidine 223AB.[7]

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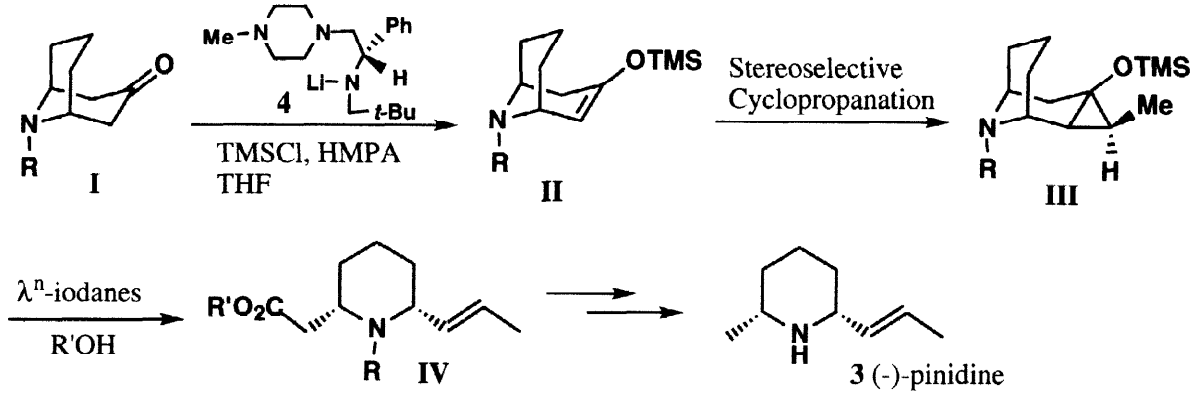
2. ASYMMETRIC SYNTHESIS OF ENANTIOMERIC PAIRS OF PINIDINE

SYNTHETIC STRATEGY

Our synthetic plan for pinidine (**3**) is depicted in **Scheme 2**. Recently, our group developed asymmetric syntheses of 2,6-*cis*-substituted piperidine alkaloids and 2,5-*cis*-substituted pyrrolidine alkaloids using chiral enol silyl ethers of ω-azabicyclo[3.*n*.1]alkan-3-one.[8-11] We planned to apply this procedure to the asymmetric synthesis of pinidine. Asymmetric enolization of a 9-azabicyclo[3.3.1]nonan-3-one (*N*-protected norgranatanone) (**I**) by Koga's chiral lithium amide (**4**)[12,13] will afford the chiral enol silyl ether (**II**), and subsequent cyclopropanation will provide the key chiral 10-azatricyclo[4.3.1.$0^{2,4}$]decan-4-ol (**III**). Stereoselective cyclopropanation affording the *exo* methyl compound (**III**) is required because pinidine (**3**) has an (*E*)-olefin moiety. The hypervalent λ^n-iodane-mediated fragmentation of **III** will give the chiral 2,6-*cis*-substituted-piperidine intermediate (**IV**) which is easily transformed into (-)-pinidine (**3**).



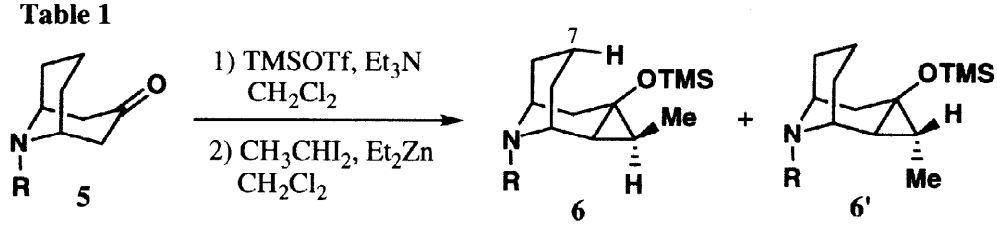
Scheme 2

RESULTS AND DISCUSSION

First, we examined the stereoselective cyclopropanation of (±)-3-(trimethylsilyloxy)-9-azabicyclo-[3.3.1]nonenes that were easily prepared from the reaction of 9-azabicyclo[3.3.1]nonan-3-ones (**5**) (*N*-protected norgranatanone) with trimethylsilyl trifluoromethanesulfonate. The cyclopropanation of the enol silyl ethers using diethylzinc and 1,1-diiodoethane took place only at the β-face of the enol ethers to afford 3-methyl-4-(trimethylsilyloxy)-10-azatricyclo[4.3.1.$0^{2,4}$]decanes (**6** and **6'**) in all cases because the 'fork head' axial proton (C7 ax.-H) blocked the α-face from an attack by the carbenoid. The results are summarized in **Table 1**.

A 1:1 mixture of 3-*exo*-methyl-4-(trimethylsilyloxy)-10-azatricyclo[4.3.1.$0^{2,4}$]decanes (**6**) and 3-*endo*-compounds (**6'**) was obtained in the cases of *N*-protected norgranatanones (**5**) bearing an alkoxycarbonyl or an acyl group on the bridged nitrogen (entries 1-4). Fortunately, in the cases of the substrates bearing an *N*-sulfonyl group, the cyclopropanation proceeded stereoselectively to give the desired *exo*-methyl compounds **6** predominantly (entries 5 and 6).

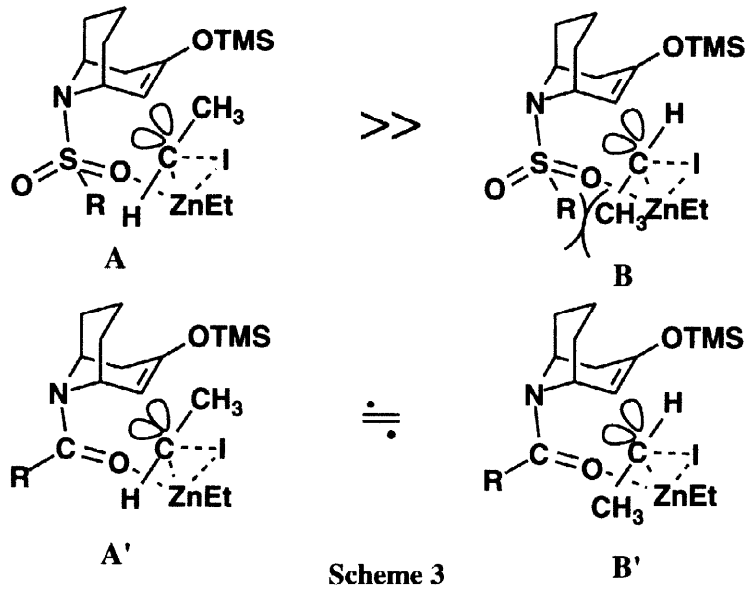
Table 1



Entry	5	R	Yields of 6 and 6' (%)	exo (6) : endo (6') *
1	5a	CO_2Me	89	1 : 1
2	5b	Cbz	78	1 : 1
3	5c	$COCF_3$	63	1 : 1
4	5d	Bz	43	1 : 1
5	5e	Ms	51	4 : 1
6	**5f**	**Ts**	**99**	**10 : 1**

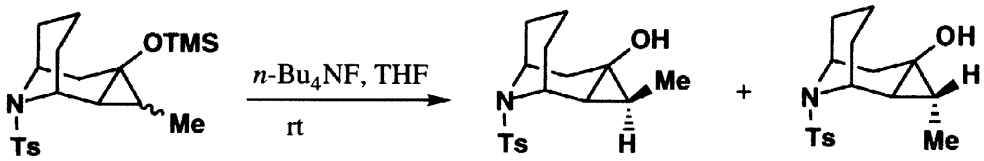
* Determined by ^{1}H-NMR.

It is apparent that the sulfonamide moiety in **5** plays an important role in the stereoselectivity. We assume that the sulfonamide oxygen coordinated with the zinc on the carbenoid and that the carbenoid attacks the double bond in a less hindered fashion (**A**) as shown in **Scheme 3**. The fact that the tosylated compound **5f** (entry 6) exhibits better stereoselectivity than does the mesylated one **5e** (entry 5) strongly supports our postulate. On the other hand, in the case of **5a-5d**, the coordination of zinc/carbenoid with the carbonyl oxygen causes no steric interaction between "R" and the methyl of the carbenoid.



Scheme 3

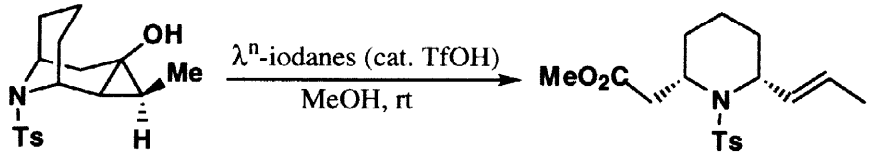
Although **6** and **6'** could not be separated in all cases, the alcohols (**7f** and **7f'**, desilylated compounds of **6f** and **6f'**) could be separated using column chromatography on silica gel. (**Scheme 4**).



6f and **6f'** **Scheme 4** **7f** (81%) **7f'** (9%)

Next, we examined the stereospecific fragmentation of **7f** by hypervalent λ^n-iodanes. The results are summarized in **Table 2**. The (*E*)-isomer (**8**) was obtained stereospecifically and no (*Z*)-isomer was obtained in all cases.[14] The best result was obtained when **7f** was treated with phenyliodine(III) bistrifluoroacetate (PIFA) in the presence of a catalytic amount of trifluoromethanesulfonic acid (TfOH)(run 3 in **Table 2**).

Table 2

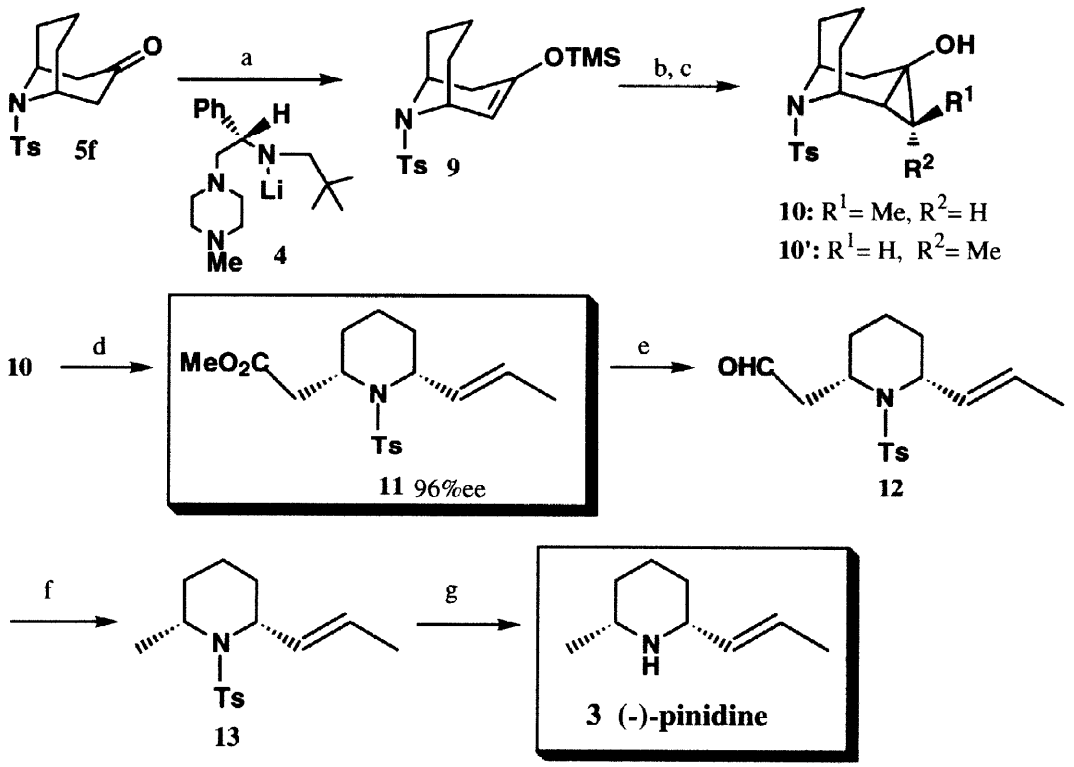


7f **8**

run	reaction conditions	yield of **8** (%)
1	$PhI(OAc)_2$	53
2	$PhI(OAc)_2$, cat. TfOH	65
3	**$PhI(OCOCF_3)_2$, cat. TfOH**	**69**
4	PhIO, cat. TfOH	60
5	$PhIO_2$, cat. TfOH	50

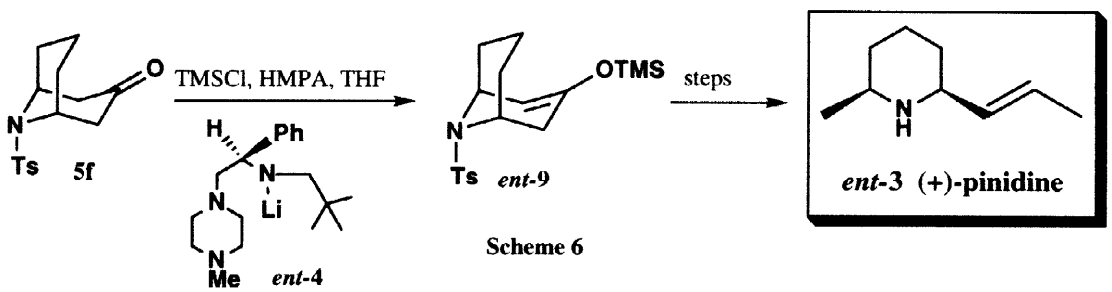
We then examined the asymmetric enolization of *N*-tosylated norgranatanone (**5f**). The reaction of **5f** with a chiral lithium amide (**4**) and chlorotrimethylsilane (TMSCl) gave the corresponding chiral enol silyl ether (**9**). The cyclopropanation of **9** and subsequent desilylation afforded the *exo*-methyl compound (**10**) and the *endo*-methyl compound (**10'**). The PIFA oxidation of **10** in methanol in the presence of a catalytic amount of TfOH gave the desired (*E*)-alkene (**11**). At this stage, the optical purity of **11** was determined by high-performance liquid chromatography (HPLC), and it turned out to be over 96% ee.[15] The reduction of **11** with diisobutylaluminum hydride afforded an aldehyde (**12**), and the decarbonylation of **12** with Wilkinson's complex gave *N*-tosylpinidine (**13**). The spectral data and specific rotation of **13** were identical with those reported.[5] Deprotection of **13** according to Kibayashi's method[5] afforded (-)-pinidine (**3**). (**Scheme 5**).

Scheme 5



Reagents and conditions: a) lithium amide (**4**), TMSCl, THF, HMPA, -100°C (94%); b) CH_3CHI_2, Et_2Zn, CH_2Cl_2, rt; c) nBu_4NF, THF (81% for **10**, 9% for **10'** in 2 steps); d) PIFA, cat. TfOH, MeOH, rt (69%); e) DIBAL, CH_2Cl_2, -78°C (91%); f) $RhCl(PPh_3)_3$, C_6H_6, reflux (89%); g) Na, liq. NH_3, EtOH, -78°C (81%).

(+)-Pinidine (***ent*-3**), the enantiomer of **3**, was also synthesized from **5f** *via* the asymmetric enolization using the enantiomeric amide ***ent*-4** in the same manner as described above (**Scheme 6**).

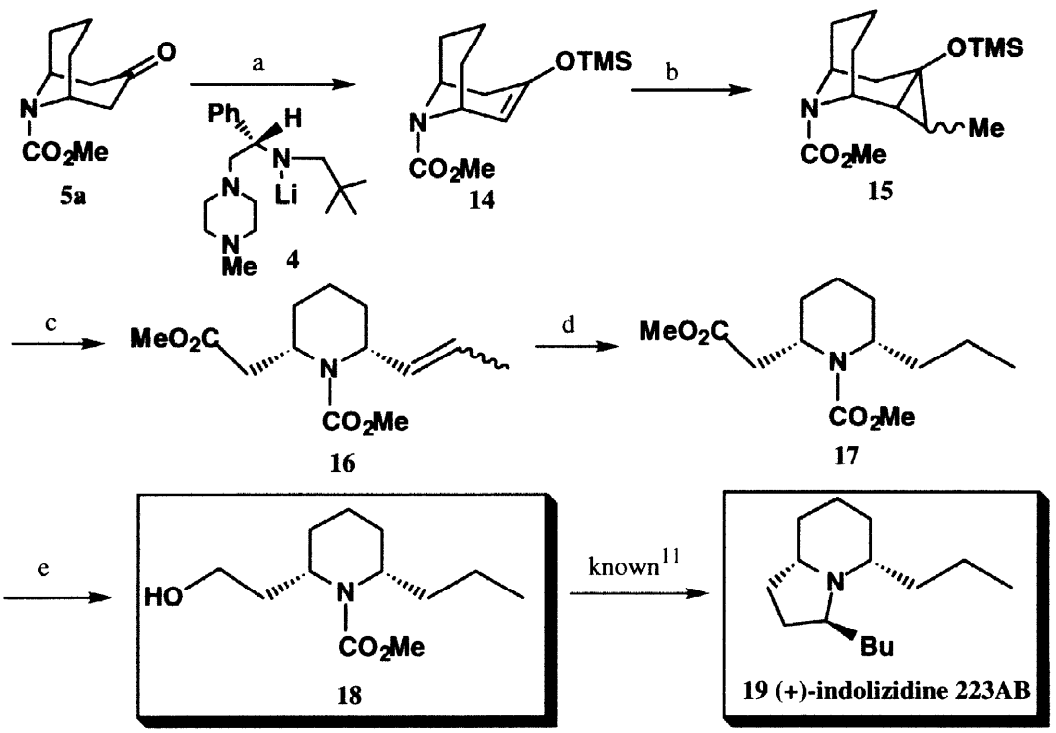


Scheme 6

3. FORMAL ASYMMETRIC SYNTHESIS OF (+)-INDOLIZIDINE 223AB

We synthesized the known key intermediate (**18**) for the synthesis of (+)-indolizidine 223AB (**19**) from **5a** in 5 steps (51% overall yield) as depicted in **Scheme 7**.[16] The reaction of **5a** with **4** and TMSCl afforded the chiral enol silyl ether (**14**). The cyclopropanation of **14** using diethylzinc and 1,1-diiodoethane afforded 3-methyl-4-(trimethlysilyloxy)-10-azatricyclo[4.3.1.$0^{2,4}$]decanes [**15** (the 1:1 mixture of the chiral **6** and the chiral **6'**)]. The reaction of **15** with PIFA in methanol in the presence of a TfOH-catalyst provided the chiral 2,6-*cis*-disubstituted-piperidine (**16**) as a mixture of *Z* and *E* isomers. The catalytic hydrogenation of **16** over 5% Pd-C and subsequent reduction with Super-Hydride furnished the desired key intermediate (**18**). The synthesis of (+)-indolizidine 223AB from **18** had already been established by our group.[11]

Scheme 7



Reagents and conditions: a) lithium amide (**4**), TMSCl, THF, HMPA, -100°C (91%); b) CH_3CHI_2, Et_2Zn, CH_2Cl_2, rt (86%) c) PIFA, cat. TfOH, MeOH, rt (67%); d) H_2 (1 atm) 5% Pd-C, MeOH, rt (99%); e) Super-Hydride, THF, rt (98%).

4. CONCLUSION

We have described the efficient asymmetric synthesis of the piperidine-alkaloid, pinidine, and the formal asymmetric synthesis of indolizidine-alkaloid indolizidine 223AB using the hypervalent λ^n-iodane-mediated fragmentation of tertiary cyclopropanol systems.

ACKNOWLEDGMENT

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EXPERIMENTAL SECTION

General: Optical rotations were measured with a JASCO DIP-140 polarimeter and are recorded as 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrophotometer. NMR spectra were taken on either a Varian Gemini 300 or a Varian UNITY plus 500 spectrometer. All the NMR spectra were taken using $CDCl_3$ solutions with tetramethylsilane as internal standard, and coupling constants (*J*) are given in hertz (Hz). Low-resolution and high-resolution mass spectra (electron impact) were recorded on either a JEOL D-200 or a JEOL AX505 spectrometer. Melting points were determined with a Yanagimoto micro-melting point apparatus and are uncorrected. Column chromatography was performed on silica gel (Merck Kieselger 60). Hypervalent λ^3-iodanes (PIDA, PIFA, PhIO) were purchased from Tokyo Kasei Kogyo Co. Iodoxybenzene ($PhIO_2$) was prepared according to the literature.[17]

Methyl 3-oxo-9-azabicyclo[3.3.1]nonane-9-carboxylate (5a)

Prepared according to the literature.[10]

Benzyl 3-oxo-9-azabicyclo[3.3.1]nonane-9-carboxylate (5b)

Prepared according to the literature.[10]

***N*-Trifluoroacetyl-9-azabicyclo[3.3.1]nonan-3-one (5c)**

The hydrochloric salt of 9-azabicyclo[3.3.1]nonan-3-one was prepared from *N*-benzyl-9-azabicyclo[3.3.1]-nonan-3-one, according to the literature.[10] To a solution of 9-azabicyclo[3.3.1]nonan-3-one (367.3 mg, 2.64 mmol) and pyridine (0.32 ml, 4.0 mmol) in dichloromethane (8 ml) was added trifluoroacetic anhydride (0.56 ml, 3.96 mmol) at room temperature under an inert atmosphere. The resulting mixture was stirred for 12 hr. Saturated aqueous sodium bicarbonate (10 ml) was added and the resulting mixture was extracted with dichloromethane (30 ml x3). The combined extract was dried over anhydrous sodium sulfate and the solvent was evaporated. The residue was purified using column chromatography (*n*-hexane: ethyl acetate = 3:1) to afford the pure product (190.5 mg, 31%) as colorless crystals.

mp: 70-73°C (*n*-hexane / ether). IR (KBr) cm^{-1}: 2965, 1680, 1460; ^{1}H-NMR ($CDCl_3$) δ: 1.57-1.95 (6H, m), 2.48-2.57 (2H, m), 2.65-2.75 (2H, m), 4.60 (1H, brs), 5.11-5.18 (1H, m); MS (m/z) 235 (M^+); Anal. calcd. for $C_{10}H_{12}NO_2F_3$: C, 51.10; H, 5.14; N, 5.96. found: C, 51.36; H, 5.30; N, 5.86.

***N*-Benzoyl-9-azabicyclo[3.3.1]nonan-3-one (5d)**

To a solution of 9-azabicyclo[3.3.1]nonan-3-one (354.2 mg, 2.55 mmol) in dichloromethane (8 ml) was added a solution of benzoyl cyanide (0.453 ml, 3.82 mmol) in dichloromethane (3 ml) at -10°C under an inert atmosphere. The resulting mixture was stirred under the same conditions for 7 hr. Aqueous sodium hypochlorite (3 ml) was added, and the mixture was extracted with dichloromethane (20 ml x3). The combined extract was dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was purified

using column chromatography (*n*-hexane: ethyl acetate = 3:1) to afford the pure product (190.5 mg, 31%) as a colorless oil.
IR (neat) cm^{-1}: 2938, 1707, 1628, 1420, 1102, 704; ^{1}H-NMR ($CDCl_3$) δ: 1.60-1.99 (6H, m), 2.33 (1H, d, *J*=16.2 Hz), 2.48-2.56 (2H, m), 2.79-2.86 (1H, dd, *J*= 16.6, 6.7 Hz), 4.32 (1H, brs), 5.27 (1H, brs), 7.45 (5H, s); HRMS calcd. for $C_{15}H_{17}NO_2$ (M^+): 243.1259 , found 243.1243.

N-Methylsulfonyl-9-azabicyclo[3.3.1]nonan-3-one (5e)

To a solution of 9-azabicyclo[3.3.1]nonan-3-one hydrochloride (334.2 mg, 1.90 mmol) in water (5 ml) was added dichloromethane (5 ml) and sodium carbonate (710.6 mg, 6.76 mmol) at room temperature. The mixture was cooled to 0°C and methanesulfonyl chloride (0.28 ml, 3.62 mmol) was added slowly. The mixture was stirred at room temperature for 12 hr. The reaction mixture was extracted with dichloromethane (30 ml x 3), and the extract was dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was purified using column chromatography (*n*-hexane: ethyl acetate = 1:1) to afford the pure product (128.9 mg, 31%) as colorless crystals.
mp: 127-128°C (EtOH). IR (KBr) cm^{-1}: 3004, 2938, 2876, 1718, 1326, 1184; ^{1}H-NMR ($CDCl_3$) δ: 1.61-1.94 (6H, m), 2.41 (1H, s), 2.47 (1H, s), 2.78 (1H, d, *J*= 7.1 Hz), 2.83 (1H, d, *J*= 6.6 Hz), 3.00 (3H, s), 4.47 (2H, brs); MS (m/z) 217 (M^+); Anal. calcd. for $C_9H_{15}NO_3S$: C, 49.70; H, 6.96; N, 6.45. found: C, 49.82; H, 6.97; N, 6.27.

N-*p*-Tolylsulfonyl-9-azabicyclo[3.3.1]nonan-3-one (5f)

To a solution of 9-azabicyclo[3.3.1]nonan-3-one hydrochloride (1.80 g, 10.3 mmol) in water (20 ml) were added dichloromethane (10 ml) and sodium carbonate (3.55 g, 33.5 mmol) at room temperature. The mixture was cooled to 0°C and a solution of *p*-toluenesulfonyl chloride (2.94 g, 15.4 mmol) in dichloromethane (10 ml) was added dropwise slowly. The mixture was stirred at room temperature for 12 hr. The reaction mixture was extracted with dichloromethane (50 ml x 3), and the extract was dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was purified using column chromatography (*n*-hexane: ethyl acetate = 5:1) to afford the pure product (2.84 g, 95%) as colorless crystals.
mp: 149-151°C (EtOH). IR (KBr) cm^{-1}: 2953, 2924, 1712, 1468, 1443; ^{1}H-NMR ($CDCl_3$) δ: 1.37-1.75 (6H, m), 2.28 (2H, d, *J*=16.5 Hz), 2.36 (3H, s), 2.60 (2H, dd, *J*=16.5, 6.5 Hz), 4.43 (2H, brs), 7.25 (2H, d, *J*=8.5 Hz), 7.71 (2H, d, *J*=8.5 Hz); MS (m/z) 293 (M^+); Anal. calcd. for $C_{15}H_{19}NO_3S$: C, 61.40; H, 6.53; N, 4.77. found: C, 61.54; H, 6.50; N, 4.76.

Representative procedure for the preparation of 6 and 6' from 5

To a solution of **5a** (56.3 mg, 0.287 mmol) and triethylamine (80.0 μl, 0.574 mmol) in dichloromethane (3 ml) was added trimethylsilyl trifluoromethanesulfonate (83.4 μl, 0.431 mmol) at 0°C under an inert atmosphere. The reaction mixture was stirred for 30 min at 0°C. Saturated aqueous sodium bicarbonate (1 ml) was added and the mixture was extracted with ether (40 ml x 3). The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated to afford the crude product of the enol silyl ether. The crude enol silyl ether was dissolved in dichloromethane, and a solution of diethylzinc in hexane (0.98 M, 0.88 ml, 0.862 mmol) was added to the solution at room temperature under an inert atmosphere. The mixture was cooled to 0°C and 1,1-diiodoethane (0.14 ml, 1.15 mmol) was added over 10 min. The reaction mixture was

stirred at room temperature for 1 hr. Saturated aqueous ammonium chloride (3 ml) and dichloromethane (50 ml) were added to the reaction mixture and the mixture was filtered using Celite. The organic layer was separated and dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was purified using column chromatography (*n*-hexane: ethyl acetate = 10:1) to afford the inseparable 1:1 mixture of **6a** and **6a'** (75.5 mg, 89%) as a yellow oil.

Methyl (1*RS*, 2*RS*, 3*SR*, 4*SR*, 6*SR*)-3-Methyl-4-trimethylsilyloxy-10-azatricyclo-[4.3.1.0^{2,4}]decane-10-carboxylate (6a) and Methyl (1*RS*, 2*RS*, 3*RS*, 4*SR*, 6*SR*)-3-Methyl-4-trimethylsilyloxy-10-azatricyclo[4.3.1.0^{2,4}]decane-10-carboxylate (6a')

IR (neat) cm^{-1}: 2938, 1700, 1654, 1458, 1412, 1364, 1108; ^{1}H-NMR ($CDCl_3$) δ: 0.17 (9H, s), 0.23-0.31 (1H, m), 0.43-0.49 (1H, m), 1.08 (1.5H, d, *J*= 2.7 Hz), 1.10 (1.5H, d, *J*= 2.7 Hz), 1.50-1.74 (6H, m), 2.04-2.18 (1H, m), 2.36-2.49 (1H, m), 3.65 (1.5H, s), 3.66 (1.5H, s), 4.03 (0.5H, brs), 4.15 (0.5H, brs), 4.27 (0.5H, brs), 4.40 (0.5H, brs); HRMS calcd. for $C_{15}H_{27}NO_3Si$ (M^+): 297.1760, found 297.1794.

Inseparable 1:1 mixture of Benzyl (1*RS*, 2*RS*, 3*SR*, 4*SR*, 6*SR*)-3-Methyl-4-trimethylsilyloxy-10-azatricyclo[4.3.1.0^{2,4}]decane-10-carboxylate (6b) and Benzyl (1*RS*, 2*RS*, 3*RS*, 4*SR*, 6*SR*)-3-Methyl-4-trimethylsilyloxy-10-azatricyclo[4.3.1.0^{2,4}]decane-10-carboxylate (6b')

a colorless oil; IR (neat) cm^{-1}: 2948, 1700, 1425, 1320, 1250; ^{1}H-NMR ($CDCl_3$) δ: 0.09 (9H, s), 0.14-0.23 (1H, m), 0.36-0.42 (1H, m), 0.99 (1.5H, d, *J*= 2.2 Hz), 1.01 (1.5H, d, *J*= 2.2 Hz), 1.40-1.69 (6H, m), 1.95-2.10 (1H, m), 2.28-2.47 (1H, m), 4.07 (1H, m), 4.30 (0.5H, brs), 4.34 (0.5H, brs), 4.95-5.10 (2H, m), 7.21-7.30 (5H, m); HRMS calcd. for $C_{21}H_{31}NO_3Si$ (M^+): 373.2071, found 373.2071.

Inseparable 1:1 mixture of (1*RS*, 2*RS*, 3*SR*, 4*SR*, 6*SR*)-*N*-Trifluoroacetyl-3-methyl-4-trimethylsilyloxy-10-azatricyclo[4.3.1.0^{2,4}]decane (6c) and (1*RS*, 2*RS*, 3*RS*, 4*SR*, 6*SR*)-*N*-Trifluoroacetyl-3-methyl-4-trimethylsilyloxy-10-azatricyclo[4.3.1.0^{2,4}]decane (6c')

a colorless oil; IR (neat) cm^{-1}: 2953, 2875, 1688, 1457, 1252, 1218, 1187, 872, 843; ^{1}H-NMR ($CDCl_3$) δ: 0.19 (9H, s), 0.25-0.40 (1H, m), 0.58-0.65 (1H, m), 1.09 (1.5H, d, *J*= 2.5 Hz), 1.12 (1.5H, d, *J*= 2.5 Hz), 1.25-2.40 (6H, m), 2.13-2.30 (1H, m), 2.43-2.55 (1H, m), 3.95 (0.5H, brs), 4.23 (0.5H, brs), 4.50 (0.5H, brs), 4.77 (0.5H, brs); HRMS calcd. for $C_{15}H_{24}NO_2F_3Si$ (M^+): 335.1528, found 335.1502.

Inseparable 1:1 mixture of (1*RS*, 2*RS*, 3*SR*, 4*SR*, 6*SR*)-*N*-Benzoyl-3-methyl-4-trimethylsilyloxy-10-azatricyclo[4.3.1.0^{2,4}]decane (6d) and (1*RS*, 2*RS*, 3*RS*, 4*SR*, 6*SR*)-*N*-Benzoyl-3-methyl-4-trimethylsilyloxy-10-azatricyclo[4.3.1.0^{2,4}]decane (6d')

a colorless oil; IR (neat) cm^{-1}: 2938, 1614, 1434, 753; ^{1}H-NMR ($CDCl_3$) δ: 0.02 (4.5H, s), 0.03 (4.5H, s), 0.40-0.50 (1H, m), 1.08 (1.5H, d, *J*= 3.0 Hz), 1.15 (1.5H, d, *J*= 3.0 Hz), 1.33-1.37 (1H, m), 1.50-2.00 (6H, m), 2.12-2.65 (2H, m), 3.60 (0.5H, brs), 3.95 (0.5H, brs), 4.68 (0.5H, brs), 4.93 (0.5H, brs), 7.31-7.40 (5H, m); HRMS calcd. for $C_{20}H_{29}NO_2Si$ (M^+): 343.1991, found 343.1955.

Inseparable 4:1 mixture of (1*RS*, 2*RS*, 3*SR*, 4*SR*, 6*SR*)-3-Methyl-*N*-methylsulfonyl-4-trimethylsilyloxy-10-azatricyclo[4.3.1.0^{2,4}]decane (6e) and (1*RS*, 2*RS*, 3*RS*, 4*SR*, 6*SR*)-3-Methyl-*N*-methylsulfonyl-4-trimethylsilyloxy-10-azatricyclo[4.3.1.0^{2,4}]decane (6e')

a colorless oil; IR (neat) cm^{-1}: 2951, 2873, 1331, 1314, 1155; ^{1}H-NMR ($CDCl_3$) δ: 0.17 (9H, s), 0.47 (1H, d, *J*= 6.2 Hz), 0.63 (1H, quintet, *J*= 6.2 Hz), 1.12 (2.4H, d, *J*= 6.2 Hz), 1.13 (0.6H, d, *J*= 6.2 Hz), 1.57-1.90 (6H, m), 2.12-2.22 (1H, m), 2.48 (1H, dd, *J*=14.1 and 8.2 Hz), 2.86 (3H, s), 3.82 (1H, brs), 4.11 (0.8H, brs), 4.18 (0.2H, brs); HRMS calcd. for $C_{14}H_{27}NO_3SSi$ (*M*$^+$): 317.1481, found 317.1507.

Inseparable 10:1 mixture of (1*RS*, 2*RS*, 3*SR*, 4*SR*, 6*SR*)-3-Methyl-*N*-(*p*-tolylsulfonyl)-4-trimethylsilyloxy-10-azatricyclo[4.3.1.0^{2,4}]decane (6f) and (1*RS*, 2*RS*, 3*RS*, 4*SR*, 6*SR*)-3-Methyl-*N*-(*p*-tolylsulfonyl)-4-trimethylsilyloxy-10-azatricyclo[4.3.1.0^{2,4}]decane (6f')

a colorless oil; IR (neat) cm^{-1}: 2926, 1160; ^{1}H-NMR ($CDCl_3$) δ: 0.16 (9H, s), 0.42 (1H, d, *J*= 6.1 Hz), 0.63 (1H, quintet, *J*= 6.1 Hz), 1.09 (3H, d, *J*= 6.1 Hz), 1.30-1.60 (6H, m), 1.77-2.19 (2H, m), 2.41 (3H, s), 3.80-3.88 (0.91 H, m), 3.89-3.95 (0.09H, m), 4.19 (0.91H, brs), 4.28 (0.09H, brs), 7.27 (2H, d, *J*= 8.2 Hz), 7.68 (2H, d, *J*= 8.2 Hz); HRMS calcd. for $C_{20}H_{31}NO_3SSi$ (*M*$^+$): 393.1794, found 393.1793.

(1*RS*, 2*RS*, 3*SR*, 4*SR*, 6*SR*)-4-Hydroxy-3-methyl-*N*-(*p*-tolylsulfonyl)-10-azatricyclo-[4.3.1.0^{2,4}]decane (7f) and (1*RS*, 2*RS*, 3*RS*, 4*SR*, 6*SR*)-4-Hydroxy-3-methyl-*N*-(*p*-tolylsulfonyl)-10-azatricyclo[4.3.1.0^{2,4}]decane (7f')

A tetrahydrofuran solution of tetra-*n*-butylammonium fluoride (1.00M, 3.81 ml, 3.81 mmol) was added to a solution of **6f** and **6f'** (10:1 mixture, 999 mg, 2.54 mmol) in tetrahydrofuran (30 ml) at room temperature. The reaction mixture was stirred for 20 min at room temperature. Saturated aqueous ammonium chloride (12 ml) was added to the mixture, and the resulting mixture was extracted with dichloromethane (50 ml x 3). The extract was dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was purified using column chromatography (*n*-hexane: ethyl acetate = 3:1) to afford **7f** (661.1 mg, 81%) as colorless crystals and **7f'** (73 mg, 9%) as a colorless oil.

7f: mp: 127-128°C (hexane/ether). IR (KBr) cm^{-1}: 3519-3490, 2948, 2920, 2875, 2853, 1325, 1303, 1155, 1088; ^{1}H-NMR ($CDCl_3$) δ: 0.50 (1H, dd, *J*= 6.0, 1.3 Hz), 0.63-0.65 (1H, m), 1.11 (3H, *J*= 6.2 Hz), 1.36-1.82 (6H, m), 1.94-2.11 (1H, m), 2.41 (3H, s), 2.45-2.48 (1H, m), 3.85-3.87 (1H, m), 4.11 (1H, brs), 7.26 (2H, d, *J*= 8.1 Hz), 7.67 (2H, d, *J*= 8.1 Hz); ^{13}C-NMR ($CDCl_3$) δ: 11.17, 15.81, 21.40, 21.69, 29.99, 30.72, 31.49, 37.61, 45.86, 48.23, 54.41, 126.95, 129.80, 139.24, 143.00; MS (m/z) 321 (M^+); HRMS calcd. for $C_{17}H_{23}NO_3S$ (*M*$^+$): 321.1399, found 321.1360; Anal. calcd. for $C_{17}H_{23}NO_3S$: C, 63.50; H, 7.21; N, 4.36. found: C, 63.22; H, 7.23; N, 4.21.

7f': IR (neat) cm^{-1}: 3587-3447, 2938, 1330, 1313, 1158, 1096; ^{1}H-NMR ($CDCl_3$) δ: 0.78-0.82 (1H, m), 1.13 (3H, d, *J*= 2.7 Hz), 1.21-1.48 (6H, m), 1.85 (1H, d, *J*= 14.8 Hz), 1.95-2.16 (1H, m), 2.42 (3H, s), 2.60 (1H, dd, *J*= 14.8, 6.6 Hz), 3.94-3.98 (1H, m), 4.31 (1H, brs), 7.27 (2H, d, *J*= 8.2 Hz), 7.70 (2H, d, *J*= 8.2 Hz); ^{13}C-NMR ($CDCl_3$) δ: 7.26, 16.13, 21.70, 23.22, 26.89, 29.52, 29.87, 34.21, 46.38, 46.68, 53.40, 127.16, 129.86, 139.47, 143.08; HRMS calcd. for $C_{17}H_{23}NO_3S$ (*M*$^+$): 321.1399, found 321.1386.

Methyl (2*RS*, 6*SR*)-2-[(*E*)-1-Propenyl]-*N*-(*p*-tolylsulfonyl)piperidine-6-ethanoate (8)

To a stirred solution of **7f** (111.0 mg, 0.346 mmol) in methanol (4 ml) was added phenyliodine bistrifluoroacetate (164 mg, 0.380 mmol) and one drop of trifluoromethanesulfonic acid at room temperature. The reaction mixture was stirred for 5 min, and water (3 ml) was added to the reaction mixture. The mixture was extracted with dichloromethane (20 ml x 2). The combined extract was dried over anhydrous magnesium sulfate and the solvent evaporated. The residue was purified using column chromatography (*n*-hexane: ethyl acetate = 12:1) to afford **8** (83.8 mg, 69%) as a colorless oil.

IR (neat) cm^{-1}: 2947, 2869, 1783, 1437, 1396, 1319, 1163, 1099, 1068, 1018, 976, 937, 884, 817, 755, 710, 678; ^{1}H-NMR ($CDCl_3$) δ: 1.30-1.80 (9H, m), 2.41 (3H, s), 2.63-2.80 (2H, m), 3.66 (3H, s), 4.43-4.46 (1H, m), 4.61 (1H, brs), 5.52-5.66 (2H, m), 7.27 (2H, d, *J*= 8.2 Hz), 7.72 (2H, d, *J*= 8.2 Hz); ^{13}C-NMR ($CDCl_3$) δ: 13.98, 18.03, 21.60, 27.35, 27.41, 39.19, 49.23, 51.80, 52.37, 126.92, 127.27, 129.72, 132.11, 138.53, 143.06, 171.67; HRMS calcd. for $C_{18}H_{25}NO_4S$ (M^+): 351.1504, found 351.1497.

(1*R*, 5*S*)-*N*-(*p*-Tolylsulfonyl)-3-(trimethylsilyloxy)-9-azabicyclo[3.3.1]non-2-ene (9)

To a stirred solution of (*S*)-[2-(4-methylpiperazinyl)-1-phenylethyl](2,2-dimethylpropyl)amine (4.30 g, 14.9 mmol) in tetrahydrofuran (30 ml) was added *n*-butyllithium (1.6 M in hexane, 13.0 ml, 20.8 mmol) and hexamethylphosphorictriamide (3.62 ml, 20.8 mmol) at -100°C under an inert atmosphere. The resulting mixture was warmed to room temperature for 1 hr and then recooled to -100°C. To the cooled mixture were added chlorotrimethylsilane (2.64 ml, 20.8 mmol) and then **5f** (872 mg, 2.98 mmol) in tetrahydrofuran (10 ml) at -100°C, and the reaction mixture was stirred for 40 min at -100°C. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate (9 ml) to the mixture, after which the aqueous layer was separated and extracted with ether (30 ml x 3). The combined extract was dried over anhydrous magnesium sulfate and the solvent was evaporated. The residue was purified using column chromatography (*n*-hexane: ethyl acetate = 8:1) to afford **9** (1.02 g, 94%) as a colorless oil.

$[\alpha]_D^{24}$ +9.9° (*c* 0.13, $CHCl_3$); IR (neat) cm^{-1}: 2924, 1162, 1092, 876; ^{1}H-NMR ($CDCl_3$) δ: 0.07 (9H, s), 1.42-1.84 (6H, m), 1.70 (1H, d, *J*= 17.8 Hz), 2.23 (1H, dd, *J*= 17.8, 7.4 Hz), 2.39 (3H, s), 4.21-4.24 (1H, m), 4.52-4.53 (1H, m), 4.67 (1H, d, *J*= 5.5 Hz), 7.23 (2H, d, *J*= 8.2 Hz), 7.71 (2H, d, *J*= 8.2 Hz); HRMS calcd for $C_{18}H_{27}NO_3SSi$ (M^+): 365.1481, found 365.1452.

(1*R*, 2*R*, 3*S*, 4*S*, 6*S*)-4-Hydroxy-3-methyl-*N*-(*p*-tolylsulfonyl)-10-azatricyclo[4.3.1.0^{2,4}]-decane (10) and (1*R*, 2*R*, 3*R*, 4*S*, 6*S*)-4-Hydroxy-3-methyl-*N*-(*p*-tolylsulfonyl)-10-azatricyclo[4.3.1.0^{2,4}]decane (10')

According to the same procedure for the preparation of **7f** and **7f'**, **10** and **10'** were synthesized from **9**.

10: mp: 127-128°C (hexane / ether). $[\alpha]_D^{26}$ -22.6° (*c* 1.91, $CHCl_3$); The spectral data for this sample were identical with those of **7f**.

10': $[\alpha]_D^{27}$ -10.6° (*c* 1.31, $CHCl_3$); The spectral data for this sample were identical with those of **7f'**.

Methyl (2*R*, 6*S*)-2-[(*E*)-1-Propenyl]-*N*-(*p*-tolylsulfonyl)piperidine-6-ethanoate (11)

According to the same procedure for the preparation of **8**, **11** was synthesized from **10**.

11: $[\alpha]_D^{27}$ +17.4° (*c* 1.06, $CHCl_3$); The spectral data for this sample were identical with those of **8**.

(2*R*, 6*S*)-6-Formylmethyl-2-[(*E*)-1-propenyl]-*N*-(*p*-tolylsulfonyl)piperidine (12)

To a stirred solution of **11** (222 mg, 0.632 mmol) in dichloromethane (10 ml) was added diisobutylaluminum hydride (0.98 M, hexane solution, 0.645 ml, 0.632 mmol) at -78°C under an inert atmosphere. The resulting mixture was stirred for 10 min under the same condition. Saturated aqueous ammonium chloride (2 ml) was added to the reaction mixture at -78°C and the mixture was warmed to room temperature. Ether (20 ml) was added and the resulting mixture was stirred for 1.5 hr. Anhydrous magnesium sulfate was added and the mixture was filtered using Celite. The filtrate was evaporated and the residue was purified using column chromatography (*n*-hexane: ethyl acetate = 5:1) to afford **12** (185 mg, 91%) as a colorless oil.

$[\alpha]_D^{25}$ +35.7° (*c* 1.28, $CHCl_3$); IR (neat) cm^{-1}: 3030, 2941, 2860, 2733, 1723, 1654, 1598, 1449, 1334, 1162; ^{1}H-NMR ($CDCl_3$) δ: 1.23-1.74 (6H, m), 1.67 (3H, d, *J*= 6.0 Hz), 2.38 (3H, s), 2.60-2.86 (2H, m), 4.54-4.60 (2H, m), 5.47-5.68 (2H, m), 7.25 (2H, d, *J*= 8.2 Hz), 7.67 (2H, d, *J*= 8.2 Hz), 9.70 (1H, t, *J*= 1.9 Hz); ^{13}C-NMR ($CDCl_3$) δ: 14.07, 18.03, 21.67, 27.12, 27.94, 47.38, 48.35, 52.40, 127.01, 127.77, 129.91, 132.00, 138.50, 143.32, 201.03; HRMS calcd. for $C_{17}H_{23}NO_3S$ (M^+): 321.1398, found 321.1396.

(2*R*, 6*R*)-6-Methyl-2-[(*E*)-1-propenyl]-*N*-(*p*-tolylsulfonyl)piperidine (13)

A solution of **12** (107 mg, 0.333 mmol) in benzene (10 ml) was heated under reflux, and a solution of Wilkinson's complex (308 mg, 0.333 mmol) in benzene (20 ml) was added to the solution under an inert atmosphere. The reaction mixture was stirred under the same conditions for 12 hr. The mixture was cooled to room temperature and filtered using Celite. The filtrate was evaporated and the residue was purified using column chromatography (*n*-hexane: ethyl acetate = 10:1) to afford **13** (87.1 mg, 89%) as a colorless oil.

$[\alpha]_D^{26}$ +35.1° (*c* 1.34, $CHCl_3$). lit.[5] $[\alpha]_D^{25}$ +35.7° (*c* 0.96, $CHCl_3$).

The spectral data for this sample were identical with those in the literature.[5]

(-)-Pinidine (3)

According to the literature,[5] an 81% yield (11.0 mg) of (-)-pinidine (**3**) was obtained from **13** (34.3 mg, 0.117 mmol).

$[\alpha]_D^{28}$ -10.7° (*c* 0.14, EtOH). lit.[5] $[\alpha]_D^{25}$ -10.5° (*c* 1.880, EtOH).

The spectral data for this sample were identical with those in the literature.[5]

(-)-Pinidine Hydrochloride

mp 244-246°C (EtOH/ether). lit.[5] 244-246°C. $[\alpha]_D^{28}$ -9.5° (*c* 0.055, EtOH). lit.[5] $[\alpha]_D^{23}$ -9.5° (*c* 5.3, EtOH).

The spectral data for this sample were identical with those in the literature.[5]

(1*S*, 5*R*)-*N*-(*p*-Tolylsulfonyl)-3-(trimethylsilyloxy)-9-azabicyclo[3.3.1]non-2-ene (*ent*-9)

By the same procedure as that described for the preparation of **9**, a 63% yield of ***ent*-9** (485 mg) was obtained from **5f** (616.2 mg, 2.10 mmol), ***ent*-4** (2.431 g, 8.41 mmol), *n*-butyllithuim (1.6 M in hexane, 5.26 ml), hexamethylphosphorictriamide (2.20 ml, 12.6 mmol) and chlorotrimethylsilane (1.60 ml, 12.6 mmol).

$[\alpha]_D^{27}$ -10.5° (*c* 1.10, $CHCl_3$).

The spectral data for this sample were identical with those of **9**.

(1*S*, 2*S*, 3*R*, 4*R*, 6*R*)-4-Hydroxy-3-methyl-*N*-(*p*-tolylsulfonyl)-10-azatricyclo[4.3.1.$0^{2,4}$]-decane (*ent*-10) and (1*S*, 2*S*, 3*S*, 4*R*, 6*R*)-4-Hydroxy-3-methyl-*N*-(*p*-tolylsulfonyl)-10-azatricyclo[4.3.1.$0^{2,4}$]decane (*ent*-10')

According to the same procedure for the preparation of **7f** and **7f'**, ***ent*-10** and ***ent*-10'** were synthesized from ***ent*-9**.

***ent*-10**: mp 127-128°C (hexane/ether); $[\alpha]_D^{27}$ +22.1° (*c* 0.98, $CHCl_3$); The spectral data for this sample were identical with those of **7f**.

***ent*-10'**: $[\alpha]_D^{27}$ +10.9° (*c* 0.61, $CHCl_3$); The spectral data for this sample were identical with those of **7f'**.

Methyl (2*S*, 6*R*)-2-[(*E*)-1-Propenyl]-*N*-(*p*-tolylsulfonyl)piperidine-6-ethanoate (*ent*-11)

According to the same procedure for the preparation of **8**, ***ent*-11** was synthesized from ***ent*-10**.

***ent*-11**: $[\alpha]_D^{24}$ -18.3° (*c* 0.31, $CHCl_3$); The spectral data for this sample were identical with those of **8**.

(2*S*, 6*R*)-6-Formylmethyl-2-[(*E*)-1-propenyl]-*N*-(*p*-tolylsulfonyl)piperidine (*ent*-12)

According to the same procedure for the preparation of **12**, ***ent*-12** was synthesized from ***ent*-11**.

***ent*-12**: $[\alpha]_D^{25}$ -35.9° (*c* 1.21s, $CHCl_3$); The spectral data for this sample were identical with those of **12**.

(2*S*, 6*S*)-6-Methyl-2-[(*E*)-1-propenyl]-*N*-(*p*-tolylsulfonyl)piperidine (*ent*-13)

According to the same procedure for the preparation of **13**, ***ent*-13** was synthesized from ***ent*-12**.

***ent*-13**: $[\alpha]_D^{29}$ -36.5° (*c* 1.21s, $CHCl_3$). lit.[5] $[\alpha]_D^{24}$ -36.7° (*c* 1.67, $CHCl_3$).

The spectral data for this sample were identical with those in the literature.[5]

(+)-Pinidine (*ent*-3)

According to the literature,[5] (+)-pinidine (***ent*-3**) was obtained from ***ent*-13**.

$[\alpha]_D^{27}$ +9.9° (*c* 0.23, EtOH). lit.[5] $[\alpha]_D^{23}$ +10.2° (*c* 6.0, EtOH).

The spectral data for this sample were identical with those in the literature.[5]

(+)-Pinidine Hydrochloride

mp 243°C (EtOH/ether). lit.[5] 243-244°C. $[\alpha]_D^{26}$ +9.5° (*c* 0.13, EtOH). lit.[5] $[\alpha]_D^{24}$ +9.5° (*c* 0.20, EtOH).

The spectral data for this sample were identical with those in the literature.[5]

Methyl (1*R*,5*S*)-3-trimethylsilyloxy-9-azabicyclo[3.3.1]non-2-ene-9-carboxylate (14)

According to a similar procedure for the preparation of **9**, **14** (261.3 mg, 91%) was synthesized from **5a** (210.3 mg, 1.07 mmol) as a colorless oil.

$[\alpha]_D^{26}$ +17.1° (*c* 1.22, $CHCl_3$).

The spectral data of this sample were identical with those of the enantiomer of **14** (***ent*-14**)[10].

An 1:1 mixture of Methyl (1*R*,2*R*,3*S*,4*S*,6*S*)-3-Methyl-4-trimethylsilyloxy-10-azatricyclo-[4.3.1.0^{2,4}]decane-10-carboxylate and Methyl (1*R*, 2*R*, 3*R*, 4*S*, 6*S*)-3-Methyl-4-trimethylsilyloxy-10-azatricyclo[4.3.1.0^{2,4}]decane-10-carboxylate (15)

According to a similar procedure for the preparation of **6a** and **6a'**, **15** (282.6 mg, 86%) was synthesized from **14** (297.5 mg, 1.11 mmol) as a yellow oil.

The spectral data of this sample were identical with those of a 1:1 mixture of **6a** and **6b**.

A mixture of Methyl (2*S*,6*R*)-2-{*N*-(methoxycarbonyl)-6-[(*Z*)-1-propenyl]-2-piperidyl)-ethanoate and Methyl (2*S*,6*R*)-2-{*N*-(methoxycarbonyl)-6-[(*E*)-1-propenyl]-2-piperidyl)-ethanoate (16)

To a stirred mixture of **15** (228.0 mg, 0.767 mmol) in methanol (8 ml) was added phenyliodine bistrifluoroacetate (363.0 mg, 0.844 mmol) and one drop of trifluoromethanesulfonic acid at room temperature. The reaction mixture was stirred for 5 min, and water (7 ml) was added to the reaction mixture. The mixture was extracted with dichloromethane (30 ml x 2). The combined extract was dried over anhydrous magnesium sulfate and the solvent evaporated. The residue was purified using column chromatography (*n*-hexane: ethyl acetate = 10:1) to afford **16** (131.6 mg, 67%) as a colorless oil.

IR (neat) cm^{-1}: 3015, 2950, 2867, 1736, 1696, 1444, 1400, 1364, 1311, 1284, 1192, 1103, 1065, 1033, 970, 754; ^{1}H-NMR ($CDCl_3$) δ: 1.45-1.84 (9H, m), 2.51 (1H, dd, *J* = 14.8, 5.0 Hz), 2.63 (1H, dd, *J* = 14.8, 9.8 Hz), 3.66 (3H, s), 3.69 (3H, s), 4.62-4.68 (1H, m), 4.68-4.77 (1H, brs), 5.45-5.58 (2H, m); MS (*m/z*): 255 (*M*$^+$), 240 [(*M*-CH_3)$^+$], 224 [(*M*-OCH_3)$^+$], 196 [(*M*-CO_2CH_3)$^+$]; HRMS calcd. for $C_{13}H_{21}NO_4S$ (*M*$^+$) :255.1538, found 255.1586.

Methyl (2*S*,6*S*)-2-[*N*-(methoxycarbonyl)-6-propyl-2-piperidyl]ethanoate (17)

To a stirred solution of **16** (75.0 mg, 0.29 mmol) in methanol (10 ml) was added 5% Pd-C (45 mg), and the resulting suspension was stirred for 2 days under a hydrogen atmosphere. The catalyst was filtered off, and the filtrate was evaporated. The residue was purified using column chromatography (*n*-hexane: ethyl acetate = 10:1) to afford **17** (75.0 mg, 99%) as a colorless oil.

$[\alpha]_D^{26}$ +27.4° (*c* = 1.36, $CHCl_3$); IR (neat) cm^{-1}: 2954, 2871, 1738, 1694, 1443, 1406, 1365, 1312, 1272, 1192, 1101, 1024, 773; ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, *J* = 7.26 Hz), 1.19-1.25 (1H, m), 1.27-1.35 (1H, m), 1.41-1.56 (4H, m), 1.57-1.65 (4H, m), 2.50 (1H, dd, *J* = 15.0, 4.9 Hz), 2.60 (1H, dd, *J* = 15.0, 10.3 Hz), 3.65 (3H, s), 3.66 (3H, s), 4.08-4.17 (1H, br), 4.59-4.65 (1H, br); MS (*m/z*): 257 (*M*$^+$), 226 [(*M*-OCH_3)$^+$], 198 [(*M*-CO_2CH_3)$^+$]; HRMS calcd. for $C_{13}H_{23}NO_4S$ (*M*$^+$): 257.1627, found 257.1598.

Methyl (2*S*,6*S*)-2-(2-hydroxyethyl)-6-propylpiperidine-1-carboxylate (18)

To a stirred solution of **17** (45.0 mg, 0.18 mmol) in tetrahydrofuran (3 ml) was added Super-Hydride (0.35 ml, 0.25 mmol) at 0°C and the resulting mixture was stirred for 3 h at room temperature. The reaction was quenched by the addition of water (3 ml) to the mixture, after which the aqueous layer was separated and extracted with dichloromethane (15 ml x 3). The organic extracts were combined, dried and evaporated. The residue was purified using column chromatography (*n*-hexane: acetone = 5:1) to afford **18** (39.1 mg, 98%) as a colorless oil.

$[\alpha]_D^{23}$ -7.9° (*c* 0.16, $CHCl_3$). lit.[11] $[\alpha]_D^{26}$ -7.4° (*c* 0.58, $CHCl_3$).

The spectral data of this sample were identical with those of the authentic sample.[11]

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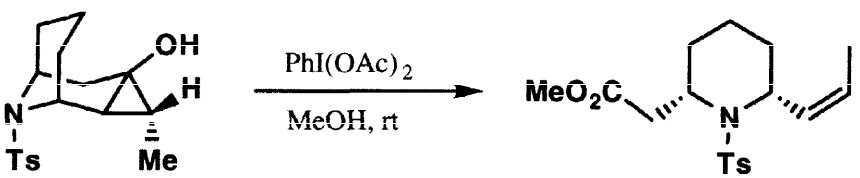
14. The reaction of **7f'** with phenyliodine diacetate afforded (*Z*)-isomer (**8'**) stereospecifically.

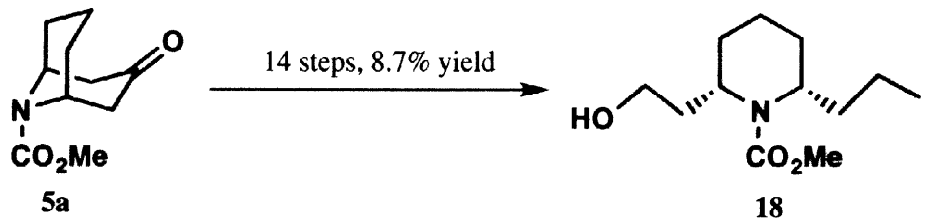


7f' **8'** (48%)

8': a colorless oil, IR (neat) cm^{-1}: 2941, 1738, 1437, 1319, 1162, 1102, 972, 908, 816, 709, 662; ^{1}H-NMR ($CDCl_3$) δ: 1.30-1.70 (6H, m), 1.76 (3H, dd, *J*= 6.6 and 1.6 Hz), 2.41 (3H, s), 2.61 (1H, dd, *J*= 15.5 and 3.3 Hz), 2.77 (1H, dd, *J*= 15.5, and 11.0 Hz), 3.65 (3H, s), 4.43-4.48 (1H, m), 4.97-5.04 (1H, m), 5.48-5.78 (2H, m), 7.27 (2H, d, *J*= 8.0 Hz), 7.73 (2H, d, *J*= 8.0 Hz); ^{13}C-NMR ($CDCl_3$) δ: 13.26, 14.13, 21.69, 27.30, 29.81, 39.50, 48.84, 49.02, 51.93, 126.99, 127.17, 129.77, 130.01, 138.45, 143.15, 171.68; HRMS calcd. for $C_{18}H_{25}NO_4S$ (M^+): 351.1504, found 351.1496.

15. The conditions for HPLC analysis: DAICEL CHIRALPAC AS, hexane / *i*-PrOH = 10 / 1.

16. As reported in a previous paper,[11] our group synthesized **18** from **5a** in 14 steps with an 8.7% yield.



5a **18**

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