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Enantiomerically Pure Cage-Shaped (1*S*,4*S*,5*R*)-4-Hydroxy-2,6-diazabicyclo[3.3.0]octane and (1*S*,4*R*,5*R*)-4-Hydroxy-2-oxa-6-azabicyclo[3.3.0]octane: Synthesis and Test for Enantioselective Catalysis

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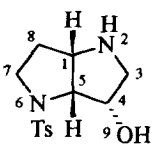
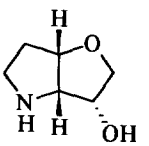
Abstract: A synthesis of cage-shaped compounds-(*1S,4S,5R*)-4-hydroxy-2,6-diazabicyclo[3.3.0]octane and (*1S,4R,5R*)-4-hydroxy-2-oxa-6-azabicyclo[3.3.0]octane described. The test for enantioselective catalysis also reported.

The synthesis of polyhydroxylated pyrrolidines, piperidines and indolizidines has been still remained as a challenging target for synthetic chemists[1,2] due to their interesting bioactivities, such as the glycosidase and HIV inhibitors. Nevertheless, the synthesis of the compounds bearing perhydro-pyrrolo[3,2b]pyrrole (pyrrolidylpyrrolidine) or tertrahydrofuro[3,2b]pyrrolidine skeleton is rather rare.[3,4] The compounds containing tetrahydrofuro[3,2b]pyrrolidine are suitable chiral intermediates for synthesis of many pyrrolidines and pyrrolizidines etc.[5]

The development of new methods for the synthesis of the chiral amino alcohols is of continuing interest since these compounds have found enormous applications as chiral ligands in metal-mediated organic reactions.[6] The hydroxylated perhydro-pyrrolo[3,2b]pyrrolidine or tetrahydrofuro[3,2b]pyrrolidines such as **2** and **3** could be considered as a kind of amino alcohols, and these might act as chiral ligands for catalysis in some asymmetric reactions.



1



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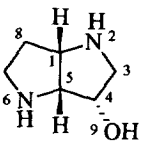
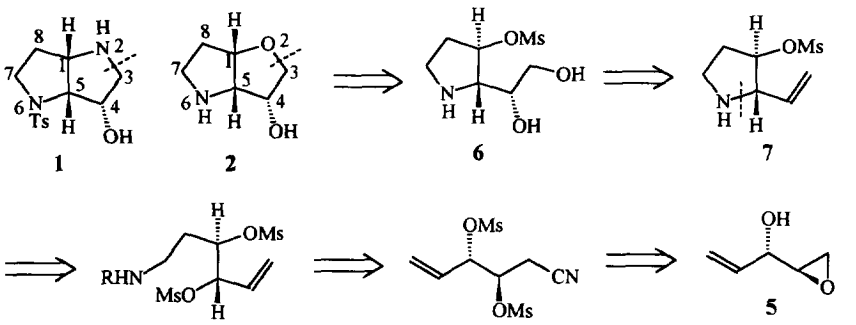


3

Due to these two reasons, we are interested in some cage-shaped hydroxylated bipyrrolidines. We have communicated the design and synthesis of (*1S,4S,5R*)-*N*-tosyl-4-hydroxy-2,6-diazabicyclo[3.3.0]octane (**1**).[7] Here, we hope to report the full detail of synthesis of (*1S,4S,5R*)-*N*-tosyl-4-hydroxy-2,6-diazabicyclo[3.3.0]octane (**1**), (*1S,4R,5R*)-4-hydroxy-2-oxa-6-azabicyclo[3.3.0]octane (**2**) and (*1S,4S,5R*)-4-hydroxy-2,6-diazabicyclo[3.3.0]octane (**3**). The conformational analysis of **1**, **2**, **3** using Quanta CHARMM 4.0, the complexation of **1** with metal observed by ^{1}H NMR and ^{13}C NMR spectra, and the test for the use of **1** and **2** as chiral ligand are also reported.

Our retrosynthetic analysis of **1** and **2** indicate that the chiral 1,2-epoxy-4-penten-3-ol (**5**) generated by asymmetric epoxidation of the divinylcarbinol (**4**)[8,9] is a suitable starting material as outlined in Scheme 1.

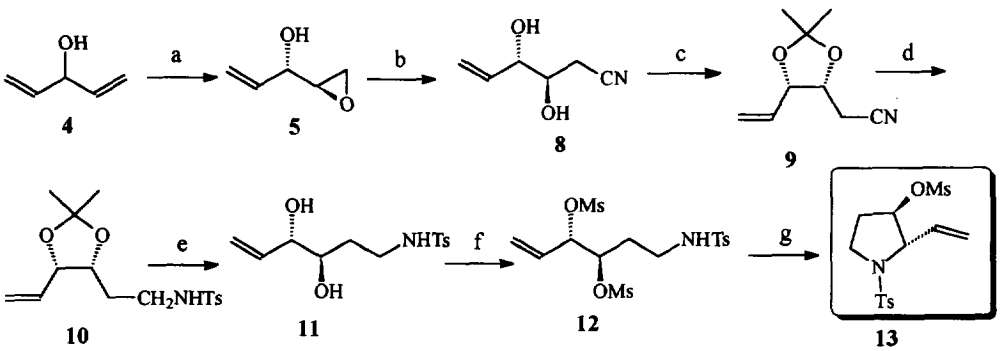
Retrosynthetic Analysis



Scheme 1

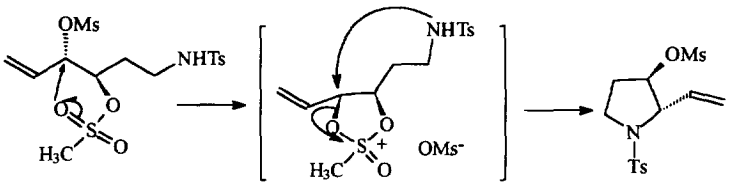
As shown in Scheme 2, epoxidation of **4** using L-(+)-DIPT as the chiral ligand gave the (*2R,3S*)-1,2-epoxy-4-penten-3-ol (**5**) with 98% de and 97% ee, which was then treated without purification with KCN in methanol to produce the dihydroxy cyanide (**8**) in 75% yield from **4**. Protection of the diol in **8** with 2,2-dimethoxy propane gave **9** in 98% yield. Reduction of **9** with LAH followed by protection of the amine with *p*-TsCl produced **10** (67%). Deprotection of the diol with *p*-TsOH and 2 N HCl gave **11**, which was followed by mesylation to afford the dimesylate **12** in 89% overall yield. Treatment of **12** with K_2CO_3 or KOH in methanol afforded the important intermediate **13** in quantitative yield (Scheme 2). Surprisingly, even though the structure of **13** was supported by ^{1}H NMR, ^{13}C NMR, ^{1}H-^{1}H Cosy and ^{1}H-^{13}C Cosy, there was no correlation between 2-H and 3-H in the ^{1}H-^{1}H Cosy of **13** indicating the 2H-3H *trans* in **13** instead of being in 2H-3H *cis* form. Finally, the configuration of **13** was determined by its X-ray analysis (Fig. 1). X-ray structure showed that 2-H and 3-H was *trans* and their dihedral angle was nearly 90°.

The retention of the configuration of C-3 in **13** is rationalized by the process through double S_N2 attack as shown in Scheme 3.



Reaction conditions: a: L-(+)-DIPT, TBHP, $Ti(OPr^i)_4$, CH_2Cl_2, 4Å M.S., -20°C, 10 days. b: KCN, acetone/water, r.t., 75% from 8. c: 2,2-dimethoxy propane, *p*-TSA, CH_2Cl_2, 98%. d: 1) LAH, Et_2O, r.t., 2) Et_3N, *p*-TsCl, CH_2Cl_2, r.t., 67%. e: *p*-TSA, MeOH, 2N HCl aq., r.t., 91%. f: pyridine, MsCl, CH_2Cl_2, 98%. g: K_2CO_3 or KOH, MeOH, r.t., 100%, >98% de.

Scheme 2



Scheme 3

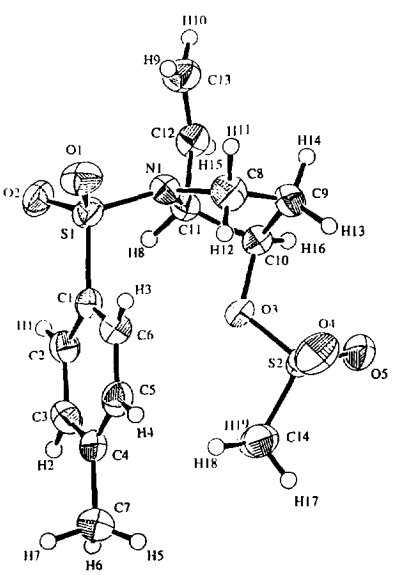
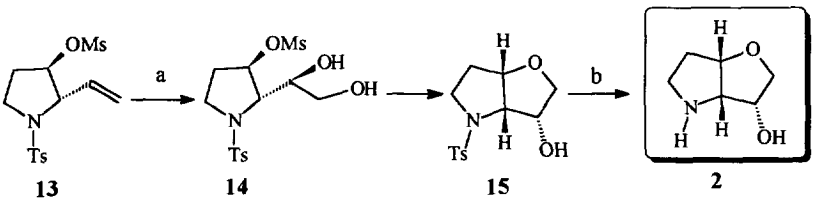


Fig. 1

The ent-**13,** the enantiomer of **13** was thus readily obtained from divinylcarbinol (**4**) using D-(-)-DIPT as chiral ligand as the same manner in the preparation of **13**.

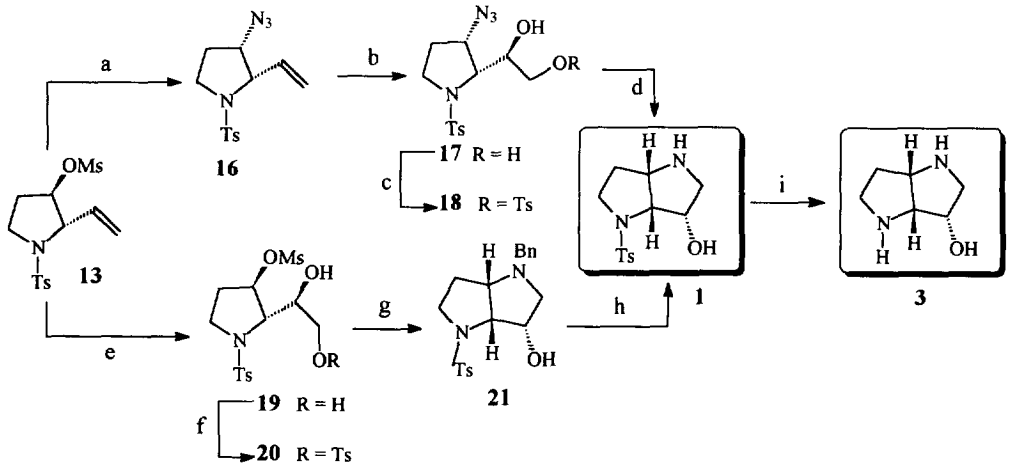
Transformation of **13** to **2** was performed as the following (Scheme 4). Dihydroxylation of **13** using $(DHQD)_2PHAL$ as the chiral ligand in the presence of excess K_2CO_3 (6 eq.) provided the tetrahydro-furo[3,2b]pyrrolidine compound (**15**) with 56% yield. The presence of the excess K_2CO_3 immediately convert the diol (**14**) to **15**. The detosylation of **15** with sodium/naphthalene in DME gave the title compound **2** with 75% yield.



Reaction conditions: a: OsO_4 (cat), $K_3Fe(CN)_6$, K_2CO_3, $(DHQD)_2PHAL$, t-BuOH/H_2O=1/1, r.t., 56%.
b: Na/naphthalene/DME, -60°C ~ -70°C, 75%.

Scheme 4

There are two ways to complete the synthesis of **1** from **13** (Scheme 5). Treatment of **13** with NaN_3 in DMF at 80°C gave the azide (**16**) in 82% yield. Dihydroxylation of **16** using $(DHQD)_2PHAL$ as the chiral



Reaction conditions: a:NaN_3, DMF, 80°C, 82%. b: OsO_4(cat), $K_3Fe(CN)_6$, K_2CO_3, $(DHQD)_2PHAL$, t-BuOH/H_2O=1/1, r.t., 85%. c: pyridine, *p*-TsCl, CH_2Cl_2, 0°C, 91%. d: 10% Pd/C, H_2, MeOH, r.t., 85%. e: b, 81%. f: c, 91%. g: benzylamine, MeOH, r.t., 95%. h: 10% Pd/C, H_2, MeOH, 75%. i: Na/naphthalene/DME, -60°C, 80%.

Scheme 5

ligand easily produce the diol **(17)** with 85% yield. Tosylation of the primary alcohol in **17** with *p*-toluenesulfonyl chloride at 0°C gave **18** in 91% yield. Hydrogenation of the azide (10% Pd/C, H_2) gave the amine, which spontaneously attacked the carbon with tosyloxy group as leaving group to afford *N*-tosyl-4-hydroxy-2,6-diazabicyclo[3.3.0]octane (**1**) with 85% yield. The structure of **1** was confirmed by ^{1}H NMR, ^{13}C NMR, ^{1}H-^{1}H Cosy spectra in all respects. **1** was also synthesized from **13** as the following. Dihydroxylation of **13** using $(DHQD)_2PHAL$ as the chiral ligand gave the diol **(19)** in 81% yield. The monotosylate **(20)** from **19** was treated with benzylamine at room temperature for 24 hr to afford perhydro-pyrrolo[3,2b]pyrrole **(21)** in 95% yield. Hydrogenation of **21** (10% Pd/C, H_2) afforded **1** (75%). Deprotection of the tosyl group in **1** with sodium/naphthalene in DME gave **3** in 80% yield.

Thus, (*1S,4R,5R*)-tetrahydroxyfuro[3,2b]pyrrolidine (**2**) was prepared from divinylcarbiol (**4**) over 8 steps in 18.4% total yield, and (*1S,4S,5R*)-*N*-tosyl-4-hydroxy-2,6-diazabicyclo[3.3.0]octane **3** was obtained from **4** over 11 steps in 18.4% total yield.

In order to get better understanding of conformational behavior of **1**, **2** and **3**, molecular modeling of them were performed using a Quanta CHARMM 4.0 program. The result showed that the distance of N(2)-N(6), N(6)-O, N(2)-O in **1** was 3.52 Å, 2.72 Å and 2.88 Å respectively; those of N(6)-O(2), N(6)-O(9) and O(2)-O(9) in **2** were 3.41 Å, 2.75 Å and 3.32 Å respectively, and those of N(2)-N(6), N(6)-O, N(2)-O in **3** were 3.47 Å, 2.66 Å and 3.03 Å respectively. This means that the cavity of the N-N-O in **1**, **3** and N-O-O in **2** should be large enough to hold atom such as B (r=0.82 Å), Zn (r= 1.25 Å), Ti (r=1.32 Å) and Pd (r=1.28 Å) etc. (r: covalent radius).

Complexation study of **1** was performed by ^{1}H NMR and ^{13}C NMR spectra in CD_3OD. To a solution of **1** in CD_3OD (*ca.*, 0.14M), the excess metal halide (BBr_3, $ZnCl_2$ and $TiCl_4$) was added (*ca.*, 1.5 eq.). After the mixture was shaken for 15 min, ^{1}H NMR and ^{13}C NMR spectra were taken. The result was shown in Table 1 and Table 2. Obviously, the presence of B, Zn, Ti induced the downfield shift of these protons nearby the cavity of the *cis*-fused pyrrolidine rings (see the chemical shift changes of 1-H, 3-H, 4-H and 5-H). Whereas, there are no significant change with the ^{13}C chemical shifts. It means that the B, Zn and Ti can easily get into the N-N-O cavity, which effected the proton shifts, but with slight effect on the ^{13}C NMR because the carbon atoms are far away from the metal in comparison with the hydrogen atoms.

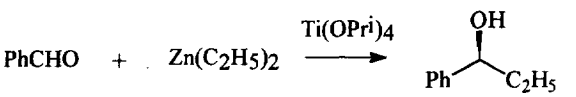
Table 1: Change of ^{1}H NMR Chemical Shift of 1 by Addition of BBr_3, $TiCl_4$ and $ZnCl_2$ *.

	1-H	3-H	3'-H	4-H	5-H	7-H and 7'-H	8-H	8'-H
1	3.79(dt)	3.10(dd)	3.10(dd)	4.35(m)	4.35(m)	3.67(m)	1.88(m)	1.70(m)
1+$ZnCl_2$	4.00(m)	3.29(dd)	3.39(d)	4.49(m)	4.49(m)	3.67(m)	2.16(m)	1.89(m)
1+BBr_3	4.26(m)	3.62(m)	3.62(m)	4.69(dd)	4.60(m)	3.64, 3.82(m)	2.31(dt)	2.02(dt)
1+$TiCl_4$	4.20(dt)	3.52(m)	3.52(m)	4.64(dd)	4.54(dd)	3.61, 3.75(m)	2.23(dt)	1.91(dt)

Table 2. Change of ^{13}C NMR Chemical Shift of 1 by Addition of $TiCl_4$ and $ZnCl_2$ (ppm)

	1-C	3-C	4-C	5-C	7-C	8-C
1	63.466	51.524	73.478	68.472	55.123	32.965
1+ $TiCl_4$	63.620	52.025	72.835	68.864	56.733	31.610
1+ $ZnCl_2$	63.799	51.489	71.911	68.316	56.490	31.176

Finally, the test was conducted using **1** and **2** as catalyst in the addition of diethylzinc to benzaldehyde as shown in Scheme 6. As usual, the reaction was performed with 5% of the catalyst, 1.5 eq. $Ti(OPr^i)_4$ in toluene



22

Ligand	
1	36% ee, S
2	24% ee, S

Scheme 6

solution[10]. Under this condition the reaction was effectively catalyzed, the yield of the 1- phenyl-1-propanol (**22**) exceeded 86% in each case. The ee value of **22** are 24% (**2** as the ligand) and 36% (**1** as the ligand) determined by chiral GC analysis. Although the ee value is not so good, we still can deduce from the result that the metal (Ti) was inserted into the cage of ligand **1** and **2** to produce a complex, which acted as a chiral ligand in this asymmetric reaction. Modification of these reactions is in process.

Experimental:

The melting points were measured on a Büchi 535 Micro Melting Points Apparatus and are uncorrected. Infrared spectra were recorded on a Shimadzu IR-440 Spectrometer or Bio-RAD FTS-20E, Bio-RAD FTS-185 Spectrometer and only the strongest/structurally most important peaks are listed in cm^{-1}. ^1H NMR spectra, ^{13}C NMR, ^1H-^1H cosy, ^1H-^{13}C cosy were also obtained at Bruker AM 300 spectrometer. Routine mass spectra were run on a HP-5989A mass spectrometer. HRMS were run on Finnigan MAT-8430 spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at the sodium D line and 25°C. GC analysis was carried out using a HP 5880 spectrometer fitted with a CYDEX-B chiral column. X-ray structure was measured on Rigaku AFC 5R 4-circle diffractometer. The elemental analysis was performed by the Heraeus CHN-O-RAPID spectrometer. Flash column chromatography were carried out using silica gel (200~300 mesh, made in Shanghai, China). All reactions were carried out under positive nitrogen pressure.

(*3S,4R*)-3,4-dihydroxy-5-cyano-1-pentene (8). To a mixture of 3 g of 4 Å molecular sieves and 75 ml of dried CH_2Cl_2, was added subsequently 4.5 ml of L-(+)-DIPT (21.1 mmol), 40 ml of TBHP (4.5 M in CH_2Cl_2) and 5.25 ml of $Ti(OPr^i)_4$ (17.8 mmol) at -20°C under positive N_2 pressure. After being stirred for 0.5 h, 6 ml of divinylcarbinol (61.7 mmol) was added *via* syringe. The mixture was kept in a refrigerator at -20°C for 10 days. Then 150 ml of 10% water in acetone was added and stirring was continued for 2 h. The mixture was filtered through a pad of celite and was dried over anhydrous Na_2SO_4. Removal of solvent gave a residue, which was dissolved in 20 ml of acetone and 20 ml of water. Then 8.05 g of KCN (123.8 mmol) was added. The resultant mixture was stirred at r.t. for 15 h. Removal of acetone gave a mixture, which was extracted with ethyl acetate (4 times). The EtOAc layer was dried over anhydrous Na_2SO_4 and purified by flash column chromatography (petroleum ether / ethyl acetate = 1/2) to produce 5.88 g of **8** as a pale viscous oil (75%). $[\alpha]_D$ -40.0 (c 0.86 in MeOH). IR (film) ν_{max}: 3342 (-OH); 2981; 2252; 1540 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.58 (2H, m, 5-H); 3.80 (1H, dd, J=8.6, 4.8 Hz, 4-H); 4.10 (3H, m, 3-H and 2 x -OH); 5.28 (1H, d, J=10.5 Hz, 1-H); 5.39 (1H, d, J=17.2 Hz, 1'-H); 6.85 (1H, m, 2-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.94 (5-C); 69.99 (4-C); 74.76 (3-C); 118.22 (1-C); 118.87 (2-C); 135.30 (5-C) ppm. MS (m/z %): 127 (M^+, 11.2); 85 (32.6).

(*3S,4R*)-3,4-*O*-Isopropylidene-5-cyano-1-pentene (9). To a solution of 2.7 g of **8** (21.3 mmol) in 5 ml of CH_2Cl_2, 400 mg of *p*-TSA (2.1 mmol) and 3.14 ml of 2,2-dimethoxy propane (25.5 mmol) were added subsequently. The resultant mixture was stirred at r.t. and the reaction was monitored by TLC. After the completion of the reaction, 150 mg of $NaHCO_3$ was added to quench the reaction and the stirring was continued for 15 min. The mixture was then diluted with 300 ml of CH_2Cl_2, washed with water and sat. aq. NaCl, dried over anhydrous Na_2SO_4. Finally, removal of CH_2Cl_2 gave a residue, which was subjected to flash column chromatography (petroleum ether/ethyl acetate = 8/1) to generate 3.48 g of **9** as a pale viscous oil (98%). $[\alpha]_D$ +7.4 (c 0.3 in $CHCl_3$). IR (film) ν_{max}: 2980; 2900; 2200 (-CN); 1380; 1240 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (3H, s, $-CH_3$); 1.44 (3H, s, $-CH_3$); 2.59, 2.75 (2H, ABX, J=17.5, 4.8 Hz, 5-H); 3.82(1H, m, 4-H); 4.20(1H, m, 3-H); 5.32(1H, d, J=10.3 Hz, 1-H); 5.44(1H, d, J=16.7 Hz, 1'-H); 5.80(1H, m, 2-H) ppm. MS (m/z %): 168(M^++1, 1.4); 167(M^+, 9.1); 152(32.4).

(*4R,5S*)-*N*-Tosyl-4,5-*O*-isopropylidene-5-ene-hexylamine (10). To a suspension of 3.0 g of LAH (78.9 mmol) in 20 ml of Et_2O, 3.3 g of **9** (19.8 mmol) in 15 ml of Et_2O was added dropwise. The mixture was stirred at r.t. for 1.5 h, 20 ml of 10% NaOH aq. was added slowly to quench the reaction. The mixture was filtered through a pad of silica gel. The residue was washed with EtOAc (3 times). The EtOAc layer was dried over anhydrous Na_2SO_4. Removal of EtOAc gave a residue, which was dissolved in 15 ml of CH_2Cl_2. Then 15 ml of NEt_3 (107.6 mmol) and 10.5 g of *p*-TsCl (98.2 mmol) were added subsequently at r.t.. The resultant mixture was stirred at r.t. and the reaction was monitored by TLC. After 30 min, the mixture was diluted with 400 ml

of CH_2Cl_2, washed with water, sat. aq. NaCl and dried over anhydrous Na_2SO_4. Flash column chromatography of the rude product (petrolum ether / ethyl acetate = 6/1) gave 4.27 g of **10** as a pale viscous oil (67%). $[\alpha]_D$ +1.5 (c 1.45 in $CHCl_3$). IR(film) ν_{max}: 3250; 2960; 1720; 1600; 1420; 1380; 1320 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (6H, s, 2 x CH_3); 1,48 (2H, m, 2-H); 2.48(3H, s, -phCH_3); 3.08(1H, m, 1-H); 3.18(1H, m, 1'-H); 4.49(1H, t, J=6.7 Hz, 3-H); 5.02(1H, dd, J=7.0, 4.4 Hz, 4-H); 5.25(1H, d, J=10.2 Hz, 6-H); 5.35(1H, d, J=17.2 Hz, 6'-H); 5.74(1H, m, 5-H); 7.29(2H, d, J=8.2 Hz, 2H of phenyl); 7.76(2H, d, J=8.2 Hz, 2H of phenyl) ppm. MS (m/z %): 325(M^+, 3.4); 310(16.1); 149(base); 91(-Bn, 94.9). HRMS: Calcd for $C_{16}H_{23}NSO_4$ 325.1348; Found: 325.1345.

***(4R,5S)*-*N*-Tosyl-4,5-dihydroxy-5-ene-hexylamine (11).** To a solution of 2.32 g of **10** (7.15 mmol) in 4 ml of methanol, were added 2.08 g of *p*-TSA (10.9 mmol) and 10 ml of 5% aq. HCl at r.t.. The mixture was stirred at r.t. and the reaction was monitored by TLC. After 30 min, 2.0 g of $NaHCO_3$ (23.8 mmol) was added to quench the reaction and the stirring was continued for 15 min, 40 ml of water was added to solve the $NaHCO_3$ and the methanol was removed in vacuo. The mixture was then extracted with EtOAc 4 times. The EtOAc layer was washed with sat. aq. NaCl, dried over anhydrous Na_2SO_4 and purified by flash column chromatography (petroleum ether / ethyl acetate = 1/1) to obtain 1.82 g of **11** as a white solid (91%). m.p.: 61.0°C. $[\alpha]_D$ -2.9 (c 0.6 in $CHCl_3$). IR (KBr disc) ν_{max}: 3410; 2920; 1640; 1440; 1320; 1150 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.66 (2H, m, 2-H); 2.45 (3H, s, -CH_3); 3.08 (1H, m, 1-H); 3.22 (1H, m, 1'-H); 3.62 (1H, m, 3-H); 3.91 (1H, m, 4-H); 5.11 (1H, br, -NH); 5.26 (1H, d, J=10.1 Hz, 6-H); 5.36 (1H, d, J=16.9 Hz, 6'-H); 5.80 (1H, m, 5-H); 7.31 (2H, d, J=7.6 Hz, 2H of phenyl); 7.76 (2H, d, J=7.6 Hz, 2H of phenyl) ppm. MS (m/z %): 286 (M^++H_2O, 6.2); 268 (M^+, 13.1); 228 (18.2); 155 (-Ts, 94.4); 91(-Bn, 96.4). HRMS: Calcd for $C_{13}H_{18}NSO_3$ 268.1008; Found: 268.0949. Microanalysis: Calcd: C 54.74; H 6.67; N 4.91; Found: C 54.84; H 6.67; N 4.92.

***(4R,5S)*-*N*-Tosyl-4,5-dimesyloxy-5-ene-hexylamine (12).** Compound **11** (1.74 g, 6.49 mmol) was dissolved in 15 ml of CH_2Cl_2. Then, 8 ml of pyridine (0.1 mol) and 1.9 ml of methanesulfonyl chloride (24.5 mmol) were added at r.t.. The resultant mixture was stirred at r.t. for 2h. The mixture was diluted with 250 ml of CH_2Cl_2, washed with 5% aq. HCl, with brine and dried over anhydrous Na_2SO_4. Removal of CH_2Cl_2 gave a residue, which was purified by flash column chromatography (petroleum ether/ethyl acetate = 1/1) to generate 2.69 g of **12** as a wax-like solid (98%), which is not so stable. $[\alpha]_D$ -30.7 (c 0.26 in $CHCl_3$). IR (film) ν_{max}: 3350; 1710; 1600; 1340; 1160 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.96 (1H, m, 2-H); 2.15(1H, m, 2'-H); 2.47 (3H, s, -CH_3); 3.07 (3H, s, -CH_3); 3.12 (2H, m, 1-H); 3.19 (3H, s, -CH_3); 4.90 (1H, m, 3-H); 5.35 (1H, d, J= 10.3 Hz, 4-H); 5.50 (1H, d, J=10.2 Hz, 6-H); 5.60 (1H, d, J=17.4 Hz, 6'-H); 5.81(1H, m, 5-H); 7.32 (2H, d, J=8.1 Hz, 2H of phenyl); 7.73(2H, d, J=8.1 Hz, 2H of phenyl) ppm.

(*2S,3R*)-*N*-Tosyl-2-vinyl-3-mesyloxy-pyrrolidine (13). To a solution of 2.16 g of **12** (5.1 mmol) in 20 ml of acetone and 15 ml of water, 1.6 g of KOH (28.6 mmol) or 3.5 g of K_2CO_3 (25.4 mmol) was added. The resultant mixture was stirred at r.t. overnight. Removal of acetone gave a mixture, which was extracted with EtOAc (3 x 150 ml). The EtOAc layer was washed with sat. aq. NaCl, dried over anhydrous Na_2SO_4 and purified by flash column chromatography (petroleum ether/ethyl acetate=2/1) to produce 1.69 g of **13** as a white solid (100%). m.p.: 129.6~130.8°C. $[\alpha]_D$ -35.1 (c 0.76 in $CHCl_3$). IR (KBr disc) ν_{max}: 2920; 1596; 1342; 1324 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$); δ 2.15 (2H, m, 4-H); 2.43 (3H, s, $-CH_3$); 2.70 (3H, s, $-SO_2CH_3$); 3.38 (1H, m, 5-H); 3.65 (1H, dt, J=7.8, 2.4 Hz, 5'-H); 4.44 (1H, d, J=4.1 Hz, 2-H); 4.88 (1H, d, J=2.0 Hz, 3-H); 5.34 (1H, d, J=9.9 Hz, CH=C<u>H</u>$_2$); 5.55 (1H, d, J=16.8 Hz, -CH=C<u>H</u>$_2$); 5.80 (1H, m, -C<u>H</u>=CH_2); 7.33(2H, d, J=8.2 Hz, 2 H of phenyl); 7.77 (2H, d, J=8.2 Hz, 2H of phenyl) ppm. ^{13}C NMR and DEPT (75 MHz, $CDCl_3$): δ 21.46 (CH_3); 30.01(CH_2); 38.34 (CH_3); 46.15 (CH_2); 67.56 (CH); 82.54(CH); 118.64 (CH_2); 127.89 (CH); 129.61 (CH); 134.10(CH); 134.43(C); 143.68 (C) ppm. MS (m/z %): 346 (M^++1, 0.91); 345 (M^+, 1.52); 266 (M-Ms, 75.2); 155 (-Ts, base). HRMS: Calcd for $C_{14}H_{19}NS_2O_5$ 345.0705; Found: 345.0750. Microanalysis: Calcd: C 48.7; H 5.5; N 4.1; Found: C 48.6; H 5.4; N 3.9.

The procedure for the synthesis of ent-**13** was the same as the procedure of synthesis of **13**. The spectra of ent-**8**, ent-**9**, ent-**10**, ent-**11**, ent-**12** and ent-**13** were as same as the compounds **8**, **9**, **10**, **11**, **12** and **13.** The sign of their optical activities was just opposite.

(*1S,4R,5R*)-*N*-Tosyl-4-hydroxy-2-oxa-6-azabicyclo[3.3.0]octane (15). To a solution of 300 mg of **13** (0.87 mmol) in 10 ml of t-BuOH and 10 ml of water, were added subsequently 1.14 g of $K_3Fe(CN)_6$ (3.5 mmol), 1.48 g of K_2CO_3 (10.7 mmol) and 60 mg of $(DHQD)_2PHAL$ (0.077 mmol) at r.t.. Then 0.8 ml solution of OsO_4 (0.5 g OsO_4 in 40 ml of t-BuOH) was added dropwise *via* syringe to the mixture. The resultant mixture was stirred at r.t. for 24 h. Then 3.0 g of Na_2SO_3 (23.8 mmol) was added to quench the reaction. The mixture was extracted with ethyl acetate (4 times). The EtOAc layer was dried over anhydrous Na_2SO_4 and purified by flash column chromatography (petroleum ether/ethyl acetate=1/1) to afford 136 mg of **15** as a white solid (56%). m.p. 87.5~88.5°C. $[\alpha]_D$ +102.4 (c 0.39 in $CHCl_3$). IR (KBr disc) ν_{max}: 3427; 2904; 1598; 1496; 1330; 1158 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$); δ 1.41 (1H, m, 8-H); 1.91(1H, m, 8'-H); 2.45 (3H, s, $-CH_3$); 3.39 (1H, m, 7-H); 3.51 (1H, dd, J=10.3, 6.1 Hz, 7'-H); 3.65 (2H, dt, J=8.2, 3.1 Hz, 3-H); 4.16 (1H, m, 5-H); 4.35 (2H, m, 2-H and 4-H); 7.32 (2H, d, J=8.1 Hz, 2H of phenyl); 7.70(2H, d, J=8.1 Hz, 2H of phenyl) ppm. MS (m/z %): 284 (M^++1, 15.5); 283 (M^+, 2.3); 223 (84.8); 155 (-Ts, 43.8), 128 (base); 91 (-Bn, 82.3). HRMS: Calcd for $C_{13}H_{17}NSO_4$ 283.0878; Found: 283.0847. Microanalysis: Calcd: C 55.1; H 6.0; N 4.9; Found: C 55.2; H 6.2; N 5.2.

***(1S,4R,5R)*-4-Hydroxy-2-oxa-6-azabicyclo[3.3.0]octane (2).** To a solution of 240 mg of naphthalene (1.87 mmol) in 2 ml of DME (redistilled), was added 200 mg of Na (8.69 mmol). The mixture was stirred at r.t. for 45 min to form the Na/naphthalene/DME solution. To a solution of 92 mg of **15** (0.33 mmol) in 3 ml of DME, was added 0.8 ml of pre-prepared Na/naphthalene/DME solution at -60~-70°C. The color of solution turned from white to blue. The mixture was stirred at -60~-70°C for 30 min and the reaction was quenched by the addition of 10 ml of water. Removal of DME gave a residue, which was extracted with ethyl acetate (3 times). Removal of water layer in vacuo gave a residue, which was purified by flash column chromatography (CH_2Cl_2/MeOH = 12/1 to CH_2Cl_2/MeOH = 4/1 and trace of NH_3/H_2O) to produce 31 mg of **2** as a white solid (75%). m.p. 85°C. $[\alpha]_D$ +10.1 (c 0.06 in MeOH). IR (KBr disc) ν_{max}: 3398; 3135; 1496; 1438; 1400; 1211; 1180 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ 2.13(1H, m, 8-H); 2.25(1H, m, 8'-H); 3.30(1H, m, 7-H); 3.46(1H, m, 7'-H); 3.67(1H, dd, J=9.8, 4.8 Hz, 5-H); 4.05(1H, dd, J=5.0, 1.9 Hz, 3-H); 4.13(1H, dd, J=9.8, 5.1 Hz, 4-H); 4.53(1H, m, 3'-H); 4.85(1H, t, J=5.6 Hz) ppm. MS (m/z %): 129(M^+, 36.3); 111(M^+-H_2O, 26.5).

***(2S,3S)*-*N*-Tosyl-2-vinyl-3-azide-pyrrolidine (16).** To a solution of 804 mg of **13** (2.33 mmol) in 5 ml of DMF, was added 1.5 g of NaN_3 (23.1 mmol). The resultant mixture was stirred at 90°C for 24 h. The mixture was then filtered through a pad of silica gel to remove the excess NaN_3. Removal of DMF gave a residue, which was subjected to flash column chromatography (petroleum ether/ethyl acetate = 15/1) to produce 558 mg of **16** as a pale viscous oil (82%). $[\alpha]_D$ -83.2 (c 0.29 in $CHCl_3$). IR (film) ν_{max}: 2920; 2100; 1600; 1350; 1160 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ, 1.79 (1H, m, 4-H); 2.09 (1H, m, 4'-H); 2.45 (3H, s, $-CH_3$); 3.28 (1H, m, 5-H); 3.58 (1H, m, 5'-H); 3.84(1H, m, 3-H); 4.08 (1H, d, J=5.2 Hz, 2-H); 5.28 (1H, d, J=10.1 Hz, $=CH_2$); 5.47 (1H, d, J=17.0 Hz, =CH2); 5.82 (1H, m, CH=); 7.36(2H, dd, J=8.0, 4.9 Hz, 2H of phenyl); 7.74 (2H, dd, J=10.5, 8.0 Hz, 2H of phenyl) ppm. MS (m/z %): 293 (M^++1, 0.73); 291(M^+-1, 0.54); 237(M^+-CHN_3, 35.7); 155(-Ts, 59.4); 91(-Bn, base). HRMS: Calcd for M-CHN_3 ($C_{12}H_{15}NSO_2$) 237.0823; Found: 237.0828.

***(2R,3S,2'R)*-*N*-Tosyl-2-(1',2'-dihydroxyethyl)-3-azide-pyrrolidine (17).** To a solution of 468 mg of **16** (1.6 mmol) in 8 ml of t-BuOH and 8 ml of water, were added subsequently 1.62 g of $K_3Fe(CN)_6$ (4.9 mmol), 681 mg of K_2CO_3 (4.9 mmol) and 100 mg of $(DHQD)_2PHAL$(0.128 mmol) at r.t.. Then 1.17 ml of OsO_4 solution (0.5 g OsO_4 in 40 ml of t-BuOH) was added dropwise *via* syringe to the mixture. The resultant mixture was stirred at r.t. for 24 h. Then the reaction was quenched by the addition of 2.5 g of Na_2SO_3 (19.8 mmol). The mixture was extracted with EtOAc (4 times). The EtOAc layer was dried over anhydrous Na_2SO_4 and purified by flash column chromatography (petroleum ether/ethyl acetate=1/2) to afford 447 mg of **17** as a wax-like solid (85%). $[\alpha]_D$ -107.8 (c 1.15 in MeOH). IR (KBr disc) ν_{max}: 3520; 2980; 2105; 1597; 1494 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$); δ 1.68 (1H, m, 4-H); 2.23 (1H, m, 4'-H); 2.45(3H, s, $-CH_3$); 2.54(2H, br, 2 x-OH); 3.20(1H, m, 5-H); 3.40 (1H, m, 5'-H); 3.51 (2H, m, 2-H and 3-H); 3.72 (1H, m, $-CH_2OH$); 3.85 (1H, m, -

CH_2OH); 4.14 (1H, m, -CHOH); 7.36 (2H, d, J=8.3 Hz, 2H of phenyl); 7.75 (2H, d, J=8.3 Hz, 2H of phenyl) ppm. MS (m/z %): 327 (M^++1, 9.5); 326 (M^+, 2.5); 309 (M^++1-H_2O, 4.3); 265 (base); 155 (-Ts, 40.6); 91(-Bn, 67.5). HRMS: Calcd for $C_{13}H_{18}N_4SO_4$ 326.1049; Found: 326.1102.

(*2R,3S,2'R*)-*N*-Tosyl-2-(1'-tosyloxy-2'-hydroxy-ethyl)-3-azide-pyrrolidine (18). The solution of 497 mg of **17** (1.52 mmol) in 5 ml of CH_2Cl_2 was cooled to 0°C, 2.5 ml of pyridine (31.2 mmol) and 1.2 g of *p*-TsCl (6.3 mmol) were then added subsequently at this temperature. The resultant mixture was stirred at 0°C and the reaction was monitored by TLC. After 2 h, the mixture was diluted with 200 ml of CH_2Cl_2, washed with 5% aq. HCl, brine and dried over anhydrous Na_2SO_4. Removal of CH_2Cl_2 gave a residue, which was subjected to flash column chromatography (petroleum ether/ethyl acetate = 3/1) to produce 665 mg of **18** as a wax-like solid (91%). $[\alpha]_D$ -85.6 (c 0.42 in MeOH). IR (KBr disc) ν_{max}: 3400; 2920; 2060; 1580; 1340 cm^{-1}. ^1H NMR (300 M Hz, $CDCl_3$); δ 1.22 (1H, m, 4-H); 1.70 (1H, m, 4'-H); 2.20 (2H, m, 5-H); 2.44 (3H, s, $-CH_3$); 2.46 (3H, s, $-CH_3$); 3.50 (2H, m, 2-H and 3-H); 4.00 (1H, m, -CHOH); 4.21(2H, m, $-CH_2OTs$); 7.34 (2H, d, J=8.7 Hz); 7.36(2H, d, J=8.7 Hz); 7.70 (2H, m, 2H of phenyl); 7.84 (2H, d, J=8.7 Hz) ppm. MS (m/z %): 481(M^++1, 1.5); 463(M^++1-H_2O, 1.9); 265 (base); 155 (-Ts, 51.3); 91 (-Bn, 84.8).

(*1S,4S,5R*)-*N*-Tosyl-4-hydroxy-2,6-diazabicyclo[3.3.0]octane (1) (path a). To a solution of 115 mg of **18** (0.24 mmol) in 6 ml of methanol was added 74 mg of 10% Pd/C. The mixture was stirred under H_2 atmosphere at r.t. for 24 h. The mixture was then filtered to remove the Pd/C. Removal of methanol gave a residue, which was subjected to flash column chromatography ($CHCl_3$/MeOH = 15/1) to generate 77.3 mg of **1** as a white solid (85%). m.p.: 117.9~118.1°C. $[\alpha]_D$ -96.9 (c 0.65 in MeOH). IR (KBr disc) ν_{max}: 3541; 3347; 1599; 1342 cm^{-1}. ^1H NMR (300 M Hz, CD_3OD): δ, 1.70(1H, m, 8-H); 1.88(1H, m, 8'-H); 2.63 (3H, s, $-PhCH_3$); 3.10 (2H, dd, J=8.1 and 4.2 Hz, 3-H); 3.67(2H, m, 7-H); 3.79(1H, dt, J=8.6, 5.2 Hz, 1-H); 4.35(2H, m, 4-H and 5-H); 7.61(2H, d, J=8.2 Hz, 2H of phenyl); 7.97(2H, d, J=8.2 Hz, 2H of phenyl) ppm. ^{13}C NMR(75 MHz, CD_3OD): 21.49(CH_3); 32.64(CH_2); 51.23(CH2); 54.77(CH_2); 63.09(CH); 68.13(CH); 73.15(CH); 127.29(CH); 129.60(CH); 134.79(C); 144.10(C) ppm. HRMS: Calcd for $C_{13}H_{18}N_2SO_3$ 282.1038; Found: 282.1053.

(*2S,3R,2'R*)-*N*-Tosyl-2-(1',2'-dihydroxyethyl)-3-mesyloxypyrrolidine (19). To a solution of 480 mg of 7 (1.39 mmol) in 30 ml of t-BuOH and 30 ml of water, were added subsequently 1.78 g of $K_3Fe(CN)_6$ (5.14 mmol), 758 mg of K_2CO_3 (5.5 mmol) and 100 mg of $(DHQD)_2PHAL$ (0.128 mmol). Then, 1.25 ml of OsO_4 solution (0.5 g of OsO_4 in 40 ml of t-BuOH) was added *via* syringe to the mixture. The resultant mixture was stirred at r.t. for 48 h. The reaction was quenched by the addition of 2.5 g of Na_2SO_3 (19.8 mmmol). The mixture was extracted with EtOAc (3 x 200 ml). The EtOAc layer was dried over anhydrous Na_2SO_4 and purified by flash column chromatography (petroleum ether / ethyl acetate=1/4) to generate 429 mg of **19** as a

wax-like solid (81%). $[\alpha]_D$ +60.3 (c 0.45 in $CHCl_3$). IR (KBr disc) ν_{max}: 3423; 1718; 1598; 1331; 1240 cm^{-1}. ^1H NMR (300 M Hz, $CDCl_3$): δ 2.03 (1H, m, 4-H); 2.30 (1H, m, 4'-H); 2.43 (3H, s, $-CH_3$); 2.71(3H, s, $-CH_3$); 3.15 (2H, br, 2 x -OH); 3.26 (1H, m, 5-H); 3.56(2H, m, 2-H and 5'-H); 3.78 (1H, m, $-CH_2OH$); 3.90 (1H, d, J=6.1 Hz, $-CH_2OH$); 4.07 (1H, m, -CHOH); 5.29 (1H, br, 3-H); 7.35(2H, d, J=7.8 Hz, 2H of phenyl); 7.75 (2H, d, J=7.8 Hz, 2H of phenyl) ppm. MS (m/z %): 380(M^++1, 1.7); 318(M-$CHOHCH_2OH$, 43.5); 223(56.6); 155(-Ts, 57.2); 91(-Bn, base). HRMS: Calcd for M-$C_2H_5O_2$ ($C_{12}H_{16}NS_2O_5$) 318.0470; Found: 318.0474.

(*2S,3R,2'R*)-*N*-Tosyl-2-(1'-tosyloxy-2'-hydroxyethyl)-3-mesyloxypyrrolidine (20). To a solution of 240 mg of **19** (0.63 mmol) in 10 ml of CH_2Cl_2, were added 6 ml of pyridine (25.0 mmol) and 1.6 g of *p*-TsCl (3.1 mmol) subsequently at 0°C. The resultant mixture was stirred at 0°C for 2 h, then diluted with 150 ml of CH_2Cl_2, washed with 5% aq. HCl, brine and dried over anhydrous Na_2SO_4. Removal of CH_2Cl_2 gave a residue, which was subjected to flash column chromatography (petroleum ether/ethyl acetate = 1.5/1) to produce 311 mg of **20** as a wax-like solid (91%). $[\alpha]_D$ +54.1 (c 0.65 in $CHCl_3$). IR (KBr disc) ν_{max}: 3320; 1678; 1598; 1480; 1340 cm^{-1}. ^1H NMR (300 M Hz, $CDCl_3$) δ 1.60(1H, br, -OH); 2.04(1H, m, 4-H); 2.29(1H, m, 4'-H); 2.44(3H, s, $-CH_3$); 2.47(3H, s, $-CH_3$); 2.73(3H, s, $-CH_3$); 3.26(1H, m, 5-H); 3.59(1H, m, 5'-H); 3.78(1H, d, J=5.2 hz, 2-H); 4.03(1H, m, -CHOH); 4.19(1H, dd, J=10.8, 7.1 Hz, $-CH_2OTs$); 4.39(1H, dd, J=10.8, 3.9 Hz, $-CH_2OTs$); 5.20(1H, d, J= 3.9 Hz, 3-H); 7.37(4H, t, J=8.8 Hz); 7.72(2H, d, J=8.2 Hz); 7.84(2H, d, J=8.2 Hz) ppm. MS (m/z %): 534(M^++1, 0.7); 438(2.5); 318(M-$CH(OH)CH_2OTs$, 72.1); 155(-Ts, 64.8); 91(-Bn, base). HRMS: Calcd for M-$CH(OH)CH_2OTs$ ($C_{12}H_{16}NS_2O_5$) 318.0470; Found: 318.0467.

(*1S,4S,5R*)-N^2-Benzyl-N^6-tosyl-4-hydroxy-2,6-diazabicyclo[3.3.0]octane (21). To a solution of 85 mg of **20** (0.16 mmol) in 2 ml of methanol, were added 0.15 ml of benzylamine (1.38 mmol) and 100 mg of K_2CO_3 (0.72 mmol) at r.t.. The resultant mixture was stirred at r.t. for 24 h. Removal of methanol gave a residue, which was extracted with EtOAc (3 times). The EtOAc layer was washed with sat.aq. NaCl, dried over anhydrous Na_2SO_4 and purified by flash column chromatography (petroleum ether / ethyl acetate = 4/1) to generate 58 mg of **21** as a white solid (95%). m.p. 128°C. $[\alpha]_D$ +102.7 (c 0.72 in $CHCl_3$). IR (KBr disc) ν_{max}: 3525; 2928; 1598; 1494; 1455; 1332; 1156 cm^{-1}. ^1H NMR (300 M Hz, $CDCl_3$): δ 1.20 (1H, m, 8-H); 1.66(1H, m, 8'-H); 2.43 (3H, s, $-CH_3$); 2.46(1H, dd, J=10.7, 4.4 Hz, 3-H); 2.86(1H, br, -OH); 3.06 (2H, d, J=10.7 Hz, 3'-H containing 1H, m, 5-H); 3.50(2H, m, 7-H); 3.46, 3.71(2H, AB, J= 13.3 Hz, $-CH_2Ph$); 4.09(1H, dd, J=7.7, 6.7 Hz, 5-H); 4.24(1H, dt, J=4.5, 1.4 Hz, 4-H); 7.26(5H, m, -Ph); 7.32(2H, d, J=8.2 Hz, 2H of phenyl); 7.75(2H, d, J= 8.2 Hz, 2H of phenyl) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.55(CH_3); 30.19(CH_2); 50.06(CH_2); 58.13(CH_2); 61.22(CH_2); 66.66(CH); 68.05(CH); 69.79(CH); 127.21(CH); 127.53(CH); 128.31(CH); 128.88(CH); 129.91(CH); 134.91(C); 138.00(C); 143.99(C) ppm.

(*1S,4S,5R*)-*N*-Tosyl-4-hydroxy-2,6-diazabicyclo[3.3.0]octane (1) (path b). To a solution of 56 mg of **21** (0.15 mmol) in 2 ml of methanol, was added 20 mg of 10% Pd/C. The resultant mixture was stirred under H_2 atmosphere and r.t. for 24 h. The mixture was then filtered to remove the Pd/C. Removal of methanol gave a residue, which was subjected to flash column chromatography ($CHCl_3$/MeOH = 15/1) to produce 32 mg of **1** as a white solid (75%).

(*1S,4S,5R*)-4-Hydroxy-2,6-diazabicyclo[3.3.0]octane (3). To a solution of 240 mg of naphthalene (1.88 mmol) in 2 ml of DME (redistilled), was added 300 mg of Na (13.0 mmol). The resultant mixture was stirred at r.t. for 1 h to generate a blue Na/naphthalene/DME solution. To a solution of 54 mg of **1** (0.19 mmol) in 1.5 ml of DME, was added 0.6 ml of Na/naphthalene/DME solution (pre-prepared) to the mixture at -60 ~ -70°C. The resultant mixture was stirred at -60 ~ -70°C for 30 min. The reaction was quenched by the addition of 2 ml of sat. aq. NH_4Cl and 10 ml of water. Removal of DME gave a residue, which was extracted with EtOAc (2 x 25 ml). The water layer was concentrated to give a residue, which was purified by a column of Dowex 50 x 8 resin, eluting with CH_3OH, H_2O then NH_3/H_2O to produce 19.8 mg of **3** as a white solid (80%). m.p. 88.5°C. $[\alpha]_D$ -20.9 (c 0.1 in MeOH). IR (KBr disc) ν_{max}: 3137(-br); 3050; 1564; 1581; 1465 cm^{-1}. ^1H NMR (300 M Hz, CD_3OD): δ 2.43(2H, m, 8-H); 3.36 (2H, m, 7-H); 3.52 (1H, m, 3-H); 3.57(1H, m, 3'-H); 4.27(1H, m, 1-H); 4.61(1H, m, 5-H); 4.70(1H, m, 4-H) ppm. MS (m/z %): 129(M^++1, 17.8); 128(M^+, 4.4); 110 (M^+-H_2O, 56.0); 69 (base). HRMS: Calcd for M^+-H_2O ($C_6H_{10}N_2$) 110.1088; Found: 110.1104.

General procedure of test for enatioselective catalysis. To a solution of 20 mg of **1** (0.085 mmol) or 20 mg of **2** (0.085 mmol) in 1.5 ml of anhydrous toluene, was added 0.8 ml of $Ti(OPr^i)_4$ (2.71 mmol). The resultant mixture was stirred at 50°C for 30 min. The mixture was cooled to -78°C, then 2 ml of 1.0 M $(C_2H_5)_2Zn$ (2.0 mmol) in hexane was added dropwise *via* syringe to the mixture. After 20 min of stirring, 0.1 ml of PhCHO (0.98 mmol) was added to the mixture at -78°C. The resultant mixture was stirred and gradually warmed to r.t. for 15 h. The reaction was quenched with 5% aq. HCl. The mixture was extracted with EtOAc (3 times), washed with sat. aq. NaCl and dried over anhydrous Na_2SO_4. Removal of EtOAc gave a residue, which was purified by flash column chromatography (petroleum ether/ethyl acetate=14/1) to generate 114.5 mg of **22** as a pale viscous oil (86%). The ee value was determined by GC with CYDEX-B column.

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