Pergamon

Tetrahedron 54 (1998) 13045–13058

TETRAHEDRON

Asymmetric Synthesis of 1-Boc-3- and 4-Hydroxypyrrolidines

Yutaka Aoyagi and Robert M. Williams*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Received 23 July 1998; accepted 25 August 1998

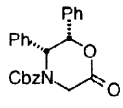
Abstract: Lewis Acid-mediated coupling reactions of (*5R, 6S*)-2-acetoxy-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazine (**2a**) with allylsilanes (**3a-d**) proceeded to give the coupling products (**4a-b**) with moderate to good stereoselectivity. The coupling products (**4a-b**) were effectively converted into 1-Boc-3- and 4-hydroxypyrrolidines (**8a**, *syn*-**b**, and **c**).

Keywords: Amino acids and derivatives; Asymmetric synthesis; Pyrrolidines; Allylation

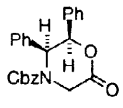
INTRODUCTION

Pyrrolidine alkaloids have been the subject of considerable synthetic, structural and mechanistic study, due to their occurrence in nature as pheromones, toxins and as structural elements in a variety of more complex molecules.[1,2] For example, polyhydroxylated pyrrolidines have been shown to be potent glycosidase inhibitors,[3] which are known to possess a variety of beneficial therapeutic effects against tumor metastasis,[4] metabolic disorder,[5] and viral infections.[6]

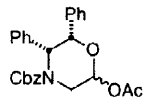
3-Hydroxy-1-butoxycarbonylpyrrolidines are useful precursors for the synthesis of several natural products such as dihydromauritine A[7] and slaframine.[8] Joullié *et al.* have already reported the asymmetric synthesis of 3-hydroxypyrrolidine from L-malic acid[2] and L-glutamic acid.[9] On the other hand, 1-Boc-4-hydroxy-2-hydroxymethylpyrrolidines are also useful intermediates for the synthesis of optically active phosphine ligands,[10] 2,5-diazabicyclo[2.2.1]heptane,[11] 4-purinylpyrrolidine nucleosides,[12] and comformationally restricted chiral spermine analogues.[13] Consequently, facile and effective methods for the enantioselective synthesis of *N*-protected 3-and 4-hydroxypyrrolidines is a worthwhile synthetic objective.



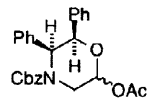
1a



1b



2a



2b

We have extensively demonstrated that (*5S, 6R*)- and (*5R, 6S*)-4-Cbz-5,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-ones (**1a** and **b**)[14] are useful as a chiral, non-racemic glycine templates for the synthesis of structurally diverse α-amino acids.[15] Recently, we have expanded the scope and utility of these substances to

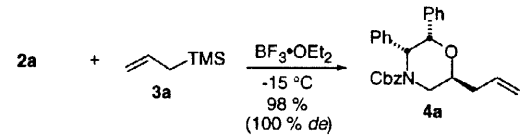
Dedicated to Professor A.I. Meyers on the occasion of his 65th birthday.

FAX: (970)-491-5610; e-mail: rmw@chem.colostate.edu

0040-4020/98/$ - see front matter
PII: S0040-4020(98)00807-2

prepare (5*R*, 6*S*)-and (5*S*, 6*R*)-2-acetoxy-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazines (**2a** and **b**) which have been found to be useful substrates for the synthesis of peptide isosteres *via* Lewis Acid-mediated coupling reactions with organosilanes.[16,17]

We have described that the Lewis Acid-mediated coupling reaction of the hemiacetal **2a** with allyltrimethylsilane proceeded in a diastereoselective manner to give the coupling product **4a** in almost quantitative yield; subsequent manipulation of the allyl group provides access to peptide isosteres. [17]

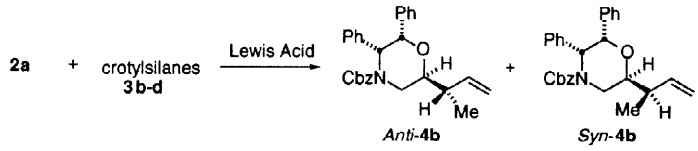


Scheme 1

In this paper, we would like to report the coupling reactions of the hemiacetal **2a** with crotylsilanes and the effective conversion of the coupling products (**4a** and **b**) to 1-Boc-3-hydroxy- and 4-hydroxypyrrolidines.

RESULTS AND DISCUSSION

Danishefsky *et al.* reported the stereoselective Ferrier reactions of glucals with crotylsilanes and the effects of substituents on the silicon atom of crotylsilanes in these reactions.[18] Initially, the coupling reactions of the hemiacetal (**2a**) with crotylsilanes (**3b-d**) under several reaction conditions were examined. As previously reported,[17] a combination of BF_3•OEt_2 and MeCN was found to be effective in the coupling reactions of the hemiacetal (**2a**) with crotylsilanes (**3b**) (Scheme 2 and Table 1, entries 1-3).

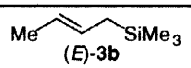
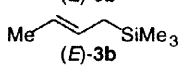
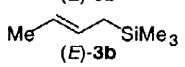
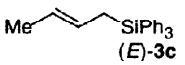
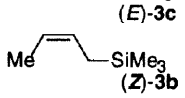
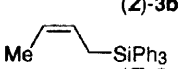
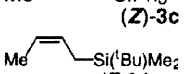


Scheme 2

We have observed that the geometry of the crotylsilanes had a significant impact on the diastereoselectivities of these reactions. Namely, when (*E*)-crotylsilane (**3b**) was employed, *anti*-**4b** was produced predominantly. On the other hand, the coupling reactions of the hemiacetal (**2a**) with (*Z*)-crotylsilanes (**3b-d**) gave *syn*-**4b** as the major product. These coupling products could not be separated by using normal silica gel chromatography but Ag^+-coated silica gel PTLC was found to effect their separation. To determine the stereochemistry of these compounds, ^1H-^1H nOe experiments (*anti*- and *syn*-**4b**) were accomplished. The ^1H-^1H nOe between the 1'-H on the allyl group and 6-H on the oxazine ring was observed for both compounds. As a result, the stereochemistry of the 2-position of both oxazines was found to be (*S*).

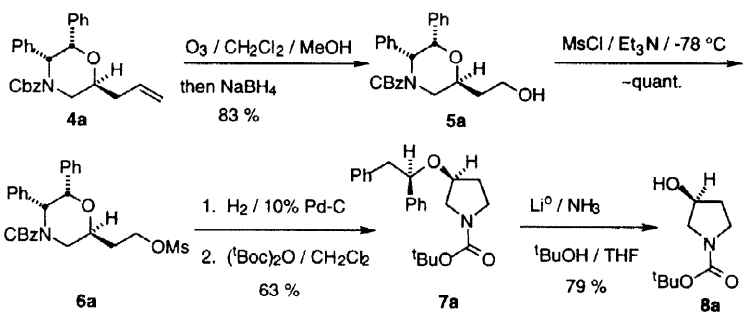
However, the relative configuration at the 1'-position on the allyl side chain proved more difficult to unambiguously assign. Thus, to determine the stereochemistry at the 1'-carbon and to increase the utility of the coupling reactions, these substances were converted into pyrrolidines.

Table 1. Lewis Acid-mediated Coupling Reactions of Hemiacetal (**2a**) with Crotylsilanes (**3b-d**)

Entry	Crotylsilane	Lewis Acid	Temp (°C)	Solvent	time (min)	Yield (%) of **4b** ratio (*anti:syn*)[a]
1	 (*E*)-**3b**	BF_3-OEt_2	-15	MeCN	15	96 (74:26)
2	 (*E*)-**3b**	$TiCl_4$	-15	MeCN	60	48 (74:26)
3	 (*E*)-**3b**	$TiCl_4$	-78→-15	CH_2Cl_2	60	complex mix.
4	 (*E*)-**3c**	BF_3-OEt_2	-15	EtCN	90	54 (84:16)
5	 (*Z*)-**3b**	BF_3-OEt_2	-15	MeCN	15	93 (38:62)
6	 (*Z*)-**3c**	BF_3-OEt_2	-15	EtCN	90	70 (37:63)
7	 (*Z*)-**3d**	BF_3-OEt_2	-15	EtCN	90	81 (39:61)

[a] The ratio was determined on the basis of ^1H nmr.

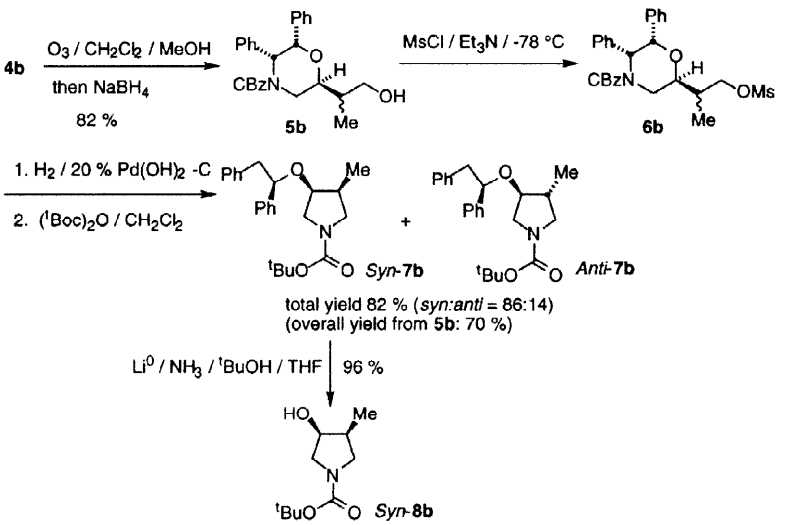
A model experiment was conducted, using compound **4a** as a starting material, (Scheme 3). Ozonolysis of the coupling product (**4a**), followed by reduction with $NaBH_4$ gave an alcohol (**5a**) in 83 % yield. After mesylation of the alcohol (**5a**) with methanesulfonyl chloride in the presence of triethylamine at -78 °C, hydrogenolysis was accomplished to give the corresponding pyrrolidine derivative.



Scheme 3

The pyrrolidine derivative obtained from the reductive cleavage of **6a** proved to be a very polar substance, whose purification by silica gel flash chromatography was facilitated after treatment with $(BOC)_2O$ to afford the corresponding N-BOC-pyrrolidine (**7a**) in 63% overall yield from mesylate (**6a**). We were quite surprised that **6a** had apparently suffered N-CBz deprotection followed by cyclization of the incipient amine

on the mesylate and then chemoselective reduction of the C-N benzylic bond in the presence of the benzylic C-O bond. It was expected that the benzylic C-O bond would reduce faster than the benzylic C-N bond and an explanation for this chemoselectivity can not at present, be clearly put forth. Finally, Birch reduction of compound (**7a**) gave (*S*)-1-Boc-3-hydroxypyrrolidine (**8a**) in 79% yield. The *er* of **8a** was 98.5 : 1.5 on the basis of glc analysis of the corresponding Mosher esters. The overall route from the coupling product (**4a**) includes 5 steps in 41 % overall yield.



Scheme 4

With an effective method for the transformation of the coupling product (**4a**) to a pyrrolidine (**8a**) in hand, we next examined the preparation of 3,4-disubstituted pyrrolidines (Scheme 4). As it proved very difficult to separate the coupling products *syn* and *anti*-**4b**, a diastereomixture of *syn* and *anti*-**4b** was directly utilized. Using the same protocol deployed in Scheme 3, the coupling products **4b** were converted to the corresponding mesylate (**6b**). The hydrogenolysis of the mesylate (**6b**) was accomplished, followed by treatment with $(BOC)_2O$ to give a mixture of pyrrolidines (*syn*- and *anti*-**7b**), which could be easily separated by silica gel flash chromatography. The relative stereochemistry of *syn*- and *anti*-**7b** was elucidated by ^1H-^1H nOe experiments (Figure 1).

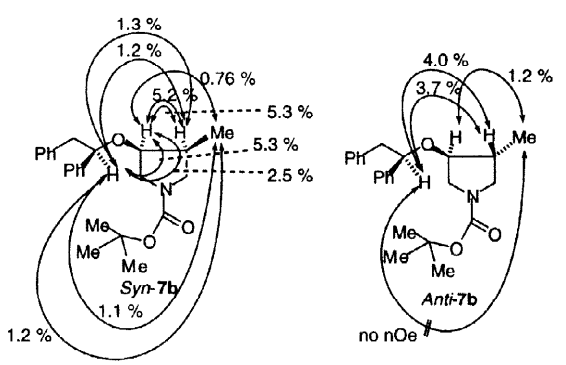


Figure 1

In compound *syn*-**7b** (major product, more polar component), a strong ^{1}H-^{1}H nOe between the 1'-H on the 3-diphenylethoxy group and the 4-H was observed. On the other hand, for *anti*-**7b** (minor product, less polar component), the corresponding ^{1}H-^{1}H nOe was weak. Consequently, the orientation between the 3- and 4-substituents on the pyrrolidine ring is *cis*- in *syn*-**7b**, and *trans*- in *anti*-**7b**. The stereochemistry of the 1'-position on the allyl group of **4b** was determined as shown in Scheme 2. In acyclic systems, it is known that Lewis Acid-mediated coupling reactions of allylic stannanes and silanes exhibits an entirely different stereoselectivity from other crotylmetals. Namely, regardless of the geometry of crotylmetals, both geometrical isomers of crotylsilanes and crotylstannanes furnish the same diastereomers.[19] In the case of cyclic systems such as **4a**, we found that (*E*)-crotylsilanes gave the *anti*-**4b** as a major product and (Z)-crotylsilanes the *syn*-**4b** predominantly. As described previously,[17] it is apparent that these reactions proceed *via* capture of an incipient oxocarbenium ion. Our stereochemical results can thus be rationalized as shown in the Figure 2. Namely, when (*E*)-crotylsilanes are utilized, transition state TS_2 might be more preferable than TS_1 by minimizing steric compression between the CH_2SiR_3 residue and the N-CBz group; TS_2 will thus provide the *anti*-isomer. On the other hand, in the case of the (Z)-isomer, TS_3 can be expected to be favored by reducing steric compression between the CH_2SiR_3 residue and the N-CBz group as well as the methyl group and the methine hydrogens of the oxazinone; TS_3 should therefore provide the corresponding *syn*-isomer.

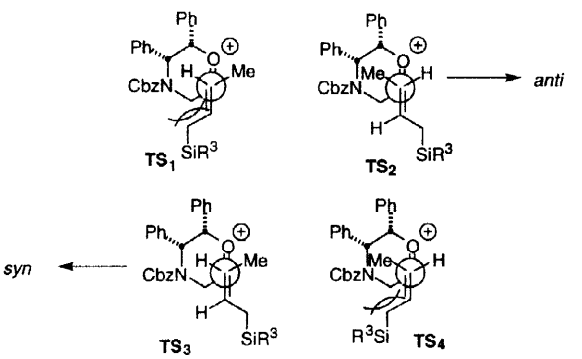
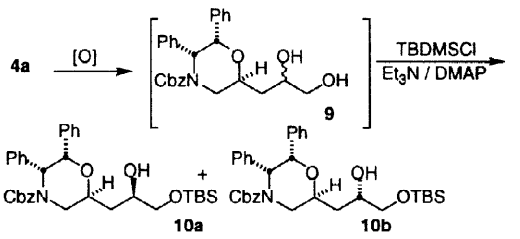


Figure 2

Finally, when Birch reduction of *syn*-**7b** was accomplished, 1-Boc-3-hydroxy-4-methylpyrrolidine (*syn*-**8**) was obtained in 96% yield, with an *er* of >99.5:0.5 on the basis of glc analysis of the Mosher esters.

Next, we examined the asymmetric synthesis of differentially protected 4-hydroxy-2-hydroxymethylpyrrolidine. Asymmetric dihydroxylation (AD reaction)[20] of (**4a**) was conducted as shown in entries 1-3 of Table 2. The diastereomeric excess of the diol could not be determined at this stage. After silylation of the diol with t-butyldimethylsilyl chloride and triethylamine,[21] the ratio was measured by HPLC analysis (Table 2, Scheme 5). The chemical yields and diastereoselectivity proved to be modest and this approach was abandoned.



Scheme 5

Table 2. Dihydroxylation of **4a**

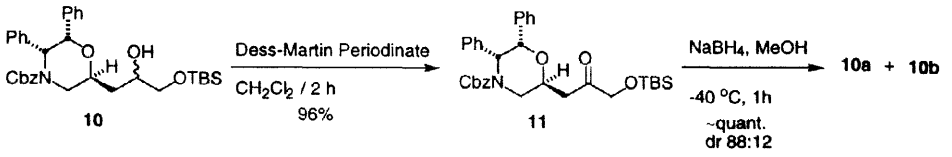
Entry	oxidant	conditions	yield (% of **9**)[1]	yield (% of **10**)[2]
1	AD-mix-α	0°C/*t*-BuOH H_2O, 3 days	78	78 (26:74)
2	AD-mix-β	0°C/*t*-BuOH H_2O, 8h	42	72 (65:35)
3	AD-mix-β	0°C/*t*-BuOH H_2O, 3 days	55	75 (63:37)
4	OsO_4/NMO[3]	rt, MeCN H_2O, 3 days	84	85 (49:51)

1) Total yield of diols. 2) Total yield of **10a** and **b**. The ratio (**10a** and **b**) was determined by HPLC (Column: Partsil® column (Whatman Co Ltd), 9.4 x 500; solvent: hexanes: AcOEt:2-PrOH = 70:29:1; flow rate: 2 mL / min: UV absorption: 254 nm). 3) *N*-methylmorpholine *N*-oxide.

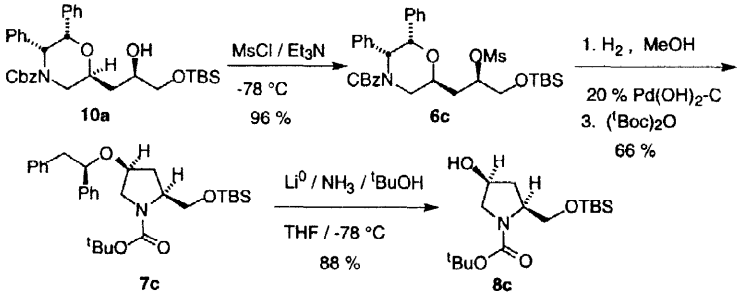
To circumvent the poor facial selectivity of the dihydroxylation, we examined a dihydroxylation sequence and subsequent oxidation of the secondary hydroxyl group followed by asymmetric reduction of the corresponding ketone. Thus, dihydroxylation of (**4a**) with catalytic osmium tetroxide and *N*-methylmorphorine *N*-oxide (NMO) gave the diastereomeric diols in 84% yield. After silylation of the primary hydroxyl group, oxidation of the secondary alcohol was accomplished with Dess-Martin periodinane (96%). A number of hydride reducing agents were examined including: DIBAH, L-Selectride, Red-Al, $ZnBH_4$ and $NaBH_4$ to effect the stereoselective reduction of the carbonyl group of compound (**11**). The best conditions we found entailed treatment of the ketone (**11**) with $NaBH_4$ in MeOH at -40 °C, which afforded the alcohol **10** in quantitative yield with a diastereomer ratio of 88:12. Separation of **10a** and **10b** was accomplished by silica gel flash chromatography. The configuration of the secondary hydroxyl group of **10a** was assigned as *R* on the basis of the empirical Sharpless AD reaction rules [20] and then by the correlation shown below in Schemes 7 and 8.

Alcohol (**10a**) was converted into the pyrrolidine derivative **8c** as shown in Scheme 7. After mesylation of the alcohol (**10a**), hydrogenolysis and *N*-*tert*-butoxycarbonylation were conducted, successively to give the corresponding pyrrolidine derivative (**7c**) in 66 % yield from mesylate (**6c**).

Birch reduction o f compound **7c** gave the differentially protected 1-*t*-BOC-4-hydroxy-2-hydroxymethylpyrrolidine (**8c**) in 88 % yield, with an enantiomeric ratio (*er*) >99.5 : 0.5 on the basis of glc analysis of the corresponding Mosher ester. To establish the stereochemistry of the stereogenic centers of **8c**, an alternative preparation was accomplished as shown in Scheme 8.

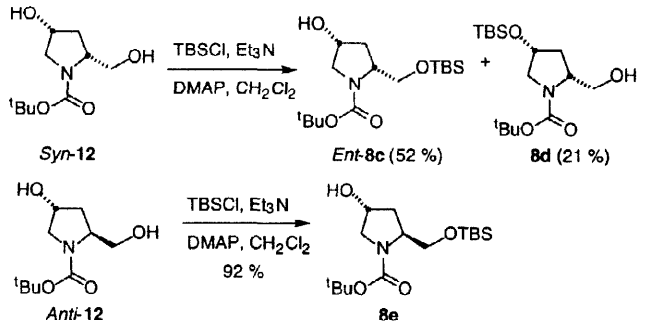


Scheme 6



Scheme 7

Silylation of the known diols *syn*-and *anti*-**12**[13] and comparison with synthetic **8c** was accomplished (Scheme 8). The glc retention time of *ent*-**8c** was identical with that of synthetic **8c** (8.7 min., capillary column: Helifex Phase AT-1 (Alltech Co.); length:15 m. ID 0.25 mm). Injection temp.: 250 °C; Oven temp. 160 °C). Further, the optical rotation value of *ent*-**8c** was +49.2 and that of synthetic **8c**, was -47.0. Consequently, the stereochemistry of synthetic **8c** was established as (*2S, 4S*), and the absolute configuration of the precursor alcohol (**10a**) is thus *R*.



Scheme 8

CONCLUSIONS

We have examined the Lewis Acid-mediated coupling reactions of hemiacetal (**2a**) with several kinds of crotylsilanes. These reactions proceeded with moderate stereoselectivity and good chemical yields. The newly constructed C1′ stereogenic center of the coupling products was governed by the geometry of

crotylsilanes employed. The effective transformation of the coupling products to 1-Boc-3-hydroxy-, 3-hydroxy-4-methyl-, and 4-hydroxy-2-hydroxymethylpyrrolidins was developed. This methodology provides ready access to polysubstituted hydroxypyrrolidines.

Acknowledgment. This work was supported by the National Science Foundation (CHE-9320010).

EXPERIMENTAL SECTION

General Considerations. Melting points were determined in open-ended capillary tubes on a Mel-Temp apparatus and are uncorrected. ^{1}H (300 MHz)-NMR spectra were obtained on a Bruker ACE-300 spectrometer. Chemical shifts are reported in parts per million downfield from the internal standard. Infrared spectra were recorded on a Perkin Elmer 1600 FTIR and were recorded as λ_{max} in cm^{-1}. Optical rotations were obtained on a Rudolph Research automatic polarimeter Autopol III. Specific rotations $[\alpha]_D$ are reported in degrees per decimeter at 25 °C and the concentration (c) is given in grams per 100 mL in the specified solvent. Mass spectra were obtained on a V.G. Micromass Ltd. Model 16F spectrometer or were conducted by UCR Mass Spectrometry Facility, Department of Chemistry, University of California at Irvine, Irvine, CA. Column chromatography and flash chromatography were performed with Merck silica gel Kieselgel 60 (230-400 mesh). Radial chromatography was accomplished with a Harrison Research Chromatotron Model 7924 using Merck silica gel Kieselgel 60 PF-254 containing gypsum; 2 and 4 mm plates were used as needed. Preparative thin layer chromatography (PTLC) was accomplished with Merck Kieselgel 60 F254 precoated glass (either 0.25 or 0.50 mm). Ag^+-coated silica gel PTLC (argentation TLC) was prepared as follows: normal silica gel TLC plates were soaked in 0.25 M $AgNO_3$ aqueous solution and then air-dried in a dark box for couple of days. All solvents were commercial grade and were distilled and dried as follows: tetrahydrofuran (THF) and diethyl ether from sodium benzophenone ketyl; MeCN from P_2O_5; CH_2Cl_2 from CaH_2. The coupling product (**4a**) was prepared according to our previous paper.[17] *cis*- and *trans*-4-hydroxy-2-hydroxymethylpyrrolidines (*syn*- and *anti*-**12**) were prepared according to the literature procedure.[13] The coupling reactions conducted with crotylsilane: 5 equiv. of crotylsilane was arbitrarily chosen as the "excess" amount that was recommended by ref. 18 and has not been optimized for the minimal number of equivalents required to obtain satisfactory yields.

Lewis Acid-Promoted Coupling Reactions of Hemiacetal (2a) with Crotylsilanes. To a MeCN solution (3 mL) of hemiacetal (**2a**) (0.108 g, 0.25 mmol) and crotyltrimethylsilane (0.16 g, 1.25 mmol), BF_3•OEt_2 (0.06 mL, 0.50 mmol) was added at -15 °C under an Ar atmosphere. The reaction mixture was stirred at the same temperature until the starting hemiacetal (**2a**) could not be detected on TLC. After the reaction, sat. $NaHCO_3$ (10 mL) was added, stirred for 20 min at room temperature, and diluted with AcOEt (15 mL). The organic layer was separated, and the aqueous phase was extracted with AcOEt (10 mL x 2). The combined organic layer was washed with sat. NaCl (15 mL x 3), dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to give an oily residue, which was purified by silica gel radial chromatography (hexanes EtOAc = 15 : 1) and Ag^+-coated silica gel PTLC (benzene : CH_2Cl_2 = 8 : 1) to give the corresponding coupling products (*syn*- and *anti*-**4b**).

(*1'R, 2S, 5R, 6S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2-(1'-methyl-2'-propen-1'-yl)-1, 2, 5, 6-tetrahydro-4H-1,4-oxazine (*syn*-4b, less polar component).

25 % yield. Colorless viscous oil. $[\alpha]_D^{25}$ =-53.2 °(CH_2Cl_2, c 0.75). ^{1}H NMR (300 MHz) (393 K, DMSO- d_6) δ TMS: 1.04 (3H, d, J = 6.9 Hz), 2.78 (1H, m), 3.59 (1H, dd, J = 13.7 Hz, 4.8 Hz), 3.88 (1H, dd, J = 13.8 Hz, 4.8 Hz), 4.00 (1H, ddd, J = 9.0 Hz, 4.8 Hz, 4.8 Hz), 5.00-5.14 (2H, m), 5.04 (1H, d, J = 12.3 Hz), 5.11 (1H, d, J = 12.6 Hz), 5.29

(1H, d, J = 3.6 Hz), 5.35 (1H, d, J = 3.6 Hz), 5.77 (1H, ddd, J = 17.4 Hz, 10.4 Hz, 7.8 Hz), 7.05-7.30 (15H, m). IR (NaCl, neat): 1695 (C=O) cm^{-1}. HRMS (FAB+) Calcd for $C_{28}H_{29}NO_3$ (M^+): 427.2147. Found: 427.2152.

(*1'S, 2S, 5R, 6S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-3-(1'-methyl-2'-propen-1'-yl)-1, 2, 5, 6-tetrahydro-4H-1,4-oxazine (*anti*-4b, more polar component).

71 % yield. Colorless viscous oil. $[\alpha]_D^{25}$ =-65.3°(CH_2Cl_2, *c* 1.21). ^1H NMR (300 MHz) (393 K, DMSO- d_6) δ TMS: 1.07 (3H, d, J = 6.6 Hz), 2.75-2.90 (1H, m), 3.63 (1H, dd, J = 13.8 Hz, 4.8 Hz), 3.91 (1H, dd, J = 14.0 Hz, 5.1 Hz), 4.04 (1H, ddd, J = 8.7 Hz, 5.1 Hz, 5.1 Hz), 5.04-5.15 (2H, m), 5.07 (1H, d, J = 12.3 Hz), 5.14 (1H, d, J = 12.9 Hz), 5.32 (1H, d, J = 3.6 Hz), 5.38 (1H, d, J = 3.6 Hz), 5.80 (1H, ddd, J = 17.3 Hz, 10.2 Hz, 8.1 Hz), 7.07-7.35 (15H, m). IR (NaCl, neat): 1699 (C=O) cm^{-1}. HRMS (FAB+) Calcd for $C_{28}H_{30}NO_3$ (M^++H): 428.2226; Found: 428.2224.

(*2S, 5R, 6S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2-(2-hydroxyethan-1-yl)-1, 2, 5, 6-tetrahydro-4H-1,4-oxazine (5a). A solution of **4a** (0.263 g, 0.64 mmol) in CH_2Cl_2 (1.5 mL) and MeOH (3.0 mL) was treated with O_3 at -78 °C until the color of the solution turned to blue (*ca.* 5 min.). After the reaction mixture was purged with Ar gas, $NaBH_4$ (0.144 g, 3.82 mmol) was added carefully at the same temperature. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure and H_2O (20 mL) was added to the residue. The mixture was extracted with AcOEt (15 mL x 3), and the organic layer was washed with H_2O (20 mL x 1), and sat. NaCl (20 mL x 1), successively, dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give an oily residue, which was purified by flash chromatography (hexanes : AcOEt = 1 : 1) to give alcohol (**5a**) as a colorless viscous oil (0.22 g, 83 % yield from compound **4a**). $[\alpha]_D^{25}$ = -76.0 ° (CH_2Cl_2, *c* 0.94). ^1H NMR (300 MHz) (348 K, DMSO- d_6) δ TMS: 1.72-1.83 (1H, m), 1.97-2.09 (1H, m), 3.46-3.57 (2H, m), 3.61 (1H, dd, J = 13.8 Hz, 4.5 Hz), 3.74 (1H, dd, J = 13.7 Hz, 3.8 Hz), 4.26 (1H, t, J = 5.1 Hz), 4.46 (1H, m), 5.06 (1H, d, J = 12.6 Hz), 5.15 (1H, d, J = 12.9 Hz), 5.31 (1H, brd, J = 3.3 Hz), 5.38 (1H, d, J = 3.9 Hz), 7.06-7.35 (15H, m). IR (NaCl, neat): 3458 (OH), 1699 (C=O) cm^{-1}. HRMS (FAB+) Calcd for $C_{26}H_{28}NO_4$(M^++H): 418.2018; Found: 418.2021.

(*1'S and R, 2S, 5R, 6S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2-(1'-methyl-2'-hydroxyethan-1'-yl)-1, 2, 5, 6-tetrahydro-4H-1,4-oxazine (5b, diastereomixture). A solution of **4b** (0.502 g, 1.18 mmol) in CH_2Cl_2 (3.0 mL) and MeOH (6.0 mL) was treated with O_3 at -78 °C until the color of the solution turned to blue (*ca.* 10 min.). After the reaction mixture was purged with Ar gas, $NaBH_4$ (0.267 g, 7.08 mmol) was added carefully at the same temperature. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure and H_2O (20 mL) was added to the residue. The mixture was extracted with AcOEt (15 mL x 3), and the organic layer was washed with H_2O (20 mL x 1), and sat. NaCl (20 mL x 1), and dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give an oily residue, which was purified by flash chromatography (hexanes : AcOEt = 2 : 1) to give alcohol (**5b**) as a colorless oil (0.417 g, 82% yield from compound **4b**): Colorless amorphous solid. ^1H NMR (300 MHz) (348 K, DMSO-d_6) δ TMS: (major) 0.95 (3H, d, J = 6.6 Hz), 3.96 (1H, dd, J = 13.5 Hz, 5.4 Hz), 5.03 (1H, d, J = 12.6 Hz), 5.12 (1H, d, J = 12.6 Hz), 5.25 (1H, d, J = 3.3 Hz), 5.36 (1H, d, J = 3.6 Hz). (minor) 0.93 (3H, d, J = 5.7 Hz), 3.89 (1H, dd, J = 13.8 Hz, 4.5 Hz), 5.04 (1H, d, J = 12.9 Hz), 5.15 (1H, d, J = 12.9 Hz), 5.30 (1H, d, J = 3.0 Hz), 5.41 (1H, d, J = 3.3 Hz). (mix) 2.04-2.25 (1H, m), 3.32-3.61 (2H, m), 3.64-3.75 (1H, m), 4.08-4.33 (2H, m), 7.07-7.29 (15H, m). IR (neat): 3468 (OH), 1698 (C=O) cm^{-1}.

(*1'R, 3S*)-1-Boc-3-(1',2'-diphenylethoxy)pyrrolidine (7a). To a mixture of alcohol (**5a**) (0.703 g, 1.68 mmol), Et_3N (0.256 g, 0.35 mL, 2.53 mmol), and CH_2Cl_2 (20 mL), MsCl (0.212 g, 0.143 mL, 1.85 mmol) was added at -78 °C under an Ar atmosphere. The mixture was stirred at the same temperature for 0.5 h and diluted with Et_2O (20 mL). The mixture was washed with sat. $NaHCO_3$ (10 mL x 1) and sat. NaCl (10 mL x 2), dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give a crude mesylate (**6a**) as a colorless solid (0.83 g, quantitative yield from compound **4a**). Without further purification, mesylate **6a** was employed in the next reaction. A mixture of

the mesylate (**6a**) (0.077g, 0.156 mmol), 10% Pd-C (0.077 g), and THF-EtOH (2 : 1) (7 mL) was stirred under an atmosphere of H_2 (60 psi) at room temperature for 12 h. After filtration through a short pad of Celite 545®, the solvent was evaporated under reduced pressure to give a residue. After addition of H_2O (10 mL), the aqueous solution was adjusted to pH 8 by the addition of solid $NaHCO_3$. The solution was extracted with Et_2O (10 mL x 3). The organic layer was dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give an oily residue. To the residue, $(BOC)_2O$ (0.037 g, 0.172 mmol) and CH_2Cl_2 (2 mL) were added. The resulting mixture was stirred at room temperature for 12 h under an Ar atmosphere. After evaporation of the solvent, the residue was purified by flash chromatography (hexanes : AcOEt = 8 : 1) to give pyrrolidine (**7a**) as a colorless viscous oil (0.036 g, 63% yield from mesylate **6a**). Colorless solid, mp. 71-72 °C (recryst. CH_2Cl_2). $[\alpha]_D^{25}$ = +52.3 ° (CH_2Cl_2, *c* 1.37). ^1H NMR (300 MHz) (340 K, C_6D_6) δ TMS: 1.18-1.30 (1H, m), 1.41-1.56 (1H, m), 1.49 (9H, s), 2.77 (1H, dd, *J* = 13.7 Hz, 4.8 Hz), 2.97 (1H, dd, *J* = 13.8 Hz 8.4 Hz), 3.20 (3H, brs), 3.43 (1H, brs), 3.58 (1H, m), 4.29 (1H, dd, *J* = 8.4 Hz, 4.8 Hz), 7.05-7.20 (10H, m). IR (KBr): 1703 (C=O) cm^{-1}. HRMS (FAB+) Calcd for $C_{23}H_{30}NO_3$ (M^++H): 368.2226; Found: 368.2234.

(1'*R*, 3*S*, 4*S*)-1-Boc-3-(1',2'-diphenylethoxy)-4-methylpyrrolidine (*syn*-7b) and (1'*R*, 3*S*, 4*R*)-1-Boc-3-(1',2'-diphenylethoxy)-4-methylpyrrolidine (*anti*-7b). To a mixture of alcohol (**5b**) (0.331 g, 0.77 mmol), Et_3N (0.117 g, 0.16 mL, 1.16 mmol), and CH_2Cl_2 (10 mL), MsCl (0.097 g, 0.065 mL, 0.85 mmol) was added at -78 °C under an Ar atmosphere. The mixture was stirred at the same temperature for 0.5 h and diluted with Et_2O (20 mL). The mixture was washed with sat. $NaHCO_3$ (10 mL x 1) and sat. NaCl (10 mL x 2), dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give a crude mesylate alcohol (**6b**) as a colorless solid (0.375 g, 96% yield from compound **4b**). Without further purification, mesylate (**6b**) was employed in the next reaction. A mixture of mesylate (**6b**) (0.37 g, 0.156 mmol), 20 % $Pd(OH)_2$ on carbon (0.37 g), and MeOH (10 mL) was stirred under an atmosphere of H_2 (60 psi) at room temperature for 15 h. After filtration through a short pad of Celite 545®, the solvent was evaporated under reduced pressure to give a residue. After addition of H_2O (10 mL), the aqueous solution was adjusted to pH 8 by the addition of solid $NaHCO_3$. The solution was extracted with Et_2O (10 mL x 3). The organic layer was dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give an oily residue. To the residue, $(BOC)_2O$ (0.167 g, 0.78 mmol) and CH_2Cl_2 (5 mL) were added. The resulting mixture was stirred at room temperature for 2 days under an Ar atmosphere. After evaporation of the solvent, the residue was purified by flash chromatography (hexanes : AcOEt = 10 : 1) to give pyrrolidine (*anti*- and *syn*-**7b**).

(1'*R*, 3*S*, 4*R*)-1-Boc-3-(1',2'-diphenylethoxy)-4-methylpyrrolidine (*anti*-7b; less polar component). 13% yield. Colorless semi-solid. $[\alpha]_D^{25}$ = +8.2 ° (CH_2Cl_2, *c* 0.38). ^1H NMR (300 MHz) (300 K, $CDCl_3$) δ TMS: 0.73 (3H, d, *J* = 7.2 Hz), 1.38 (9H, s), 1.94 (1H, m), 2.74 (1H, brs), 2.82 (1H, dd, *J* = 13.8 Hz, 4.5 Hz), 2.98 (1H, dd, *J* = 13.5 Hz, 8.7 Hz), 3.08 (1H, dd, *J* = 11.7 Hz, 3.6 Hz), 3.20 (2H, brs), 3.34 (1H, brq), 4.41 (1H, dd, *J* = 8.7 Hz, 4.8 Hz), 7.13-7.32 (10H, m). IR (NaCl, neat): 1698 (C=O) cm^{-1}. HRMS (FAB+) Calcd for $C_{24}H_{32}NO_3$ (M^++H): 382.2382; Found: 382.2389.

(1'*R*, 3*S*, 4*S*)-1-Boc-3-(1',2'-diphenylethoxy)-4-methylpyrrolidine (*syn*-7b; more polar component). 69% yield. Colorless solid, mp. 81-82 °C (recryst. CH_2Cl_2). $[\alpha]_D^{25}$ = +9.9 ° (CH_2Cl_2, *c* 0.69). ^1H NMR (300 MHz) (300 K, $CDCl_3$) δ TMS: 0.78 (3H, d, *J* = 6.9 Hz), 1.39 (9H, s), 2.07 (1H, m), 2.87 (1H, dd, *J* = 13.7 Hz, 4.7 Hz), 3.00-3.07 (1H, brs), 3.04 (1H, dd, *J* = 13.5 Hz, 8.6 Hz), 3.17 (2H, brs), 3.31 (1H, dd, *J* = 10.4 Hz, 7.4 Hz), 3.67 (1H, dd, *J* = 8.7 Hz), 4.7 Hz), 4.44 (1H, dd, *J* = 8.4 Hz, 5.1 Hz), 7.13-7.34 (10H, m). IR (KBr): 1682 (C=O) cm^{-1}. HRMS (FAB+) Calcd for $C_{24}H_{32}NO_3$ (M^++H): 383.2382; Found: 382.2387.

(*S*)-1-Bocpyrrolidine (8a). To a solution of Li° (0.132 g, 19.0 mmol atom) in liq. NH_3 (20 mL, distilled from Na°), a THF solution (10 mL) of compound (**7a**) (0.29 g, 0.79 mmol) and *tert*-BuOH (0.292 g, 3.95 mmol) was added dropwise at -78 °C. The reaction mixture was stirred at the same temperature for 20 min. To the reaction mixture, excess NH_4Cl was added. The mixture was concentrated to give a residue. After addition of H_2O (20 mL), the aqueous solution was extracted with CH_2Cl_2 (3 x 20 mL). The organic phase was dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give an oily residue, which was purified by flash chromatography (hexanes : AcOEt = 1 : 2) to give pyrrolidine (**8a**) as a colorless solid (0.117 g, 79 % yield from mesylate **7a**). 98.5 : 1.5 *er* on the basis of glc analysis of the corresponding Mosher ester. Colorless solid, Mp. 61-62 °C (recryst. CH_2Cl_2) (lit. 60-62 °C).[9] $[\alpha]_D^{25}$ =+22.0 ° ($CHCl_3$, *c* 0.91) ($[\alpha]_D^{25}$ =+22.75 ° ($CHCl_3$, *c* 1.02)[9] and $[\alpha]_D^{25}$ =+13.6 ° ($CHCl_3$, *c* 0.49)).[2] ^1H NMR (300 MHz) (300 K, $CDCl_3$) δ TMS: 1.46 (9H, s), 1.87-2.02 (3H, m), 3.34 (1H, brd, *J* = 12.0 Hz), 3.44-3.49 (3H, m), 4.44 (1H, m). (1.48 (9H, s), 1.87-2.10 (3H, m), 3.25-3.66 (4H, m), 4.40-4.52 (1H, m)).[9] IR (NaCl, neat): 3419 (OH), 1674 (C=O) cm^{-1}. HRMS (FAB+) Calcd for $C_9H_{18}NO_3$ (M^++H): 188.1287; Found: 188.1292.

(*3S, 4S*)-1-Boc-3-hydroxy-4-methylpyrrolidine (*syn*-8b). To a solution of Li° (0.037 g, 5.35 mmol atom) in liq. NH_3 (8 mL, distilled from Na°), a THF solution (4 mL) of compound (**7a**) (0.085 g, 0.223 mmol) and *tert*-BuOH (0.083 g, 0.11 mL, 1.12 mmol) was added dropwise at -78 °C. The reaction mixture was stirred at the same temperature for 20 min. To the reaction mixture, excess NH_4Cl was added. The mixture was concentrated to give a residue. After addition of H_2O (20 mL), the aqueous solution was extracted with CH_2Cl_2 (3 x 20 mL). The organic phase was dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give an oily residue, which was purified by flash chromatography (hexanes : AcOEt = 1 : 1) to give pyrrolidine (*syn*-**8b**) as a colorless solid (0.043 g, 96% yield from mesylate *syn*-**7b**). >99.5 : 0.5 *er* on the basis of glc analysis of the corresponding Mosher ester. Colorless solid, mp. 71-72 °C (recryst. CH_2Cl_2). $[\alpha]_D^{25}$ =+2.0° (CH_2Cl_2, *c* 0.20). ^1H NMR (300 MHz) (300 K, $CDCl_3$) δ TMS: 1.09 (3H, d, J = 6.9 Hz), 1.47 (9H, s), 1.57 (1H, brs), 2.14-2.29 (1H, m), 3.05 (1H, dd, J = 10.5 Hz, 10.5 Hz), 3.50 (2H, brs), 3.50 (1H, dd, J = 12.3 Hz, 3.3 Hz), 4.19 (1H, brt). IR (NaCl, neat): 3423 (OH), 1675 (CO) cm^{-1}. HRMS (FAB+) Calcd for $C_{10}H_{20}NO_3$ (M^++H): 202.1443; Found: 202.1444.

(*2'R, 2S, 5R, 6S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2-(3'-tert-butyldimethylsilyloxy-2'-hydroxypropan-1'-yl)-1, 2, 5, 6-tetrahydro-4H-1,4-oxazine (10a) and (*2'S, 2S, 5R, 6S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2-(3'-tert-butyldimethylsilyloxy-2'-hydroxypropan-1'-yl)-1, 2, 5, 6-tetrahydro-4H-1,4-oxazine (10b). To a solution of **4a** (0.07 g, 0.17 mmol), N-methylmorpholine N-oxide (NMO) (0.046 g, 0.34 mmol), MeCN (3.0 mL), and H_2O (1.5 mL), a 4% aqueous solution of osmium tetroxide (0.04 mL, 0.017 mmol) was added at room temperature. The mixture was stirred at room temperature for 2 days under an Ar atmosphere. After addition of sat. Na_2SO_3 (5 mL), the resulting mixture was stirred for 0.5 h. The solution was extracted with EtOAc (3 x 10 mL). The organic phase was washed with 1N HCl (2 x 10 mL) and H_2O (2 x 10 mL), successively, and dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give an oily residue, which was purified by flash chromatography (hexanes : AcOEt = 1 : 2) to give diol (**9**) as a colorless solid (0.064 g, 84 % yield from **4a**). To a solution of **9** (0.075 g, 0.168 mmol), DMAP (cat. amount), Et_3N (0.020 g, 0.028 mL, 0.202 mmol) and CH_2Cl_2 (3 mL), TBDMSCl (0.028 g, 0.185 mmol) was added at 0 °C under an Ar atmosphere. The reaction mixture was stirred at room temperature 15 h and diluted with Et_2O (15 mL). The organic layer was washed with H_2O (2x 10 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give an oily residue, which was purified by short silica gel flash chromatography (hexanes : AcOEt = 2 : 1) to give a diastereomixture of **10a** and **10b** (85%). The ratio was determined on the basis of HPLC analysis. Analytical diastereochemically pure samples were obtained by PTLC (hexanes : AcOEt : acetone = 8 : 2 : 1).

(10a: less polar component). Colorless viscous oil. $[\alpha]_D^{25}$ = -49.8 ° (CH_2Cl_2, *c* 1.88). ^1H NMR (300 MHz) (348 K, DMSO- d_6) δ TMS: 0.05 (3H, s), 0.06 (3H, s), 0.90 (9H, s), 1.81-1.90 (1H, m), 1.94-2.03 (1H, m), 3.59-3.50 (2H, m),

3.60-3.67 (2H, m), 3.80 (1H, dd, J = 13.8 Hz, 3.6 Hz), 4.44 (1H, d, J = 4.8 Hz), 4.53-4.61 (1H, m), 5.09 (1H, d, J = 12.6 Hz), 5.17 (1H, d, J = 12.9 Hz), 5.35 (1H, d, J = 3.3 Hz), 5.45 (1H, d, J = 3.6 Hz), 7.09-7.38 (15H, m). IR (neat): 3479 (OH), 1698 (C=O) cm^{-1}. HRMS (FAB+) Calcd for $C_{33}H_{44}NO_5Si$ (M^++H): 562.2989; Found: 562.3002.

(10b: more polar component). Colorless viscous oil. $[\alpha]_D^{25}$ = -64.3 ° (CH_2Cl_2, *c* 1.38). ^1H NMR (300 MHz) (348 K, DMSO- d_6) δ TMS: 0.006 (3H, s), 0.027 (3H, s), 0.85 (9H, s), 1.39 (1H, ddd, J = 14.1 Hz, 9.8 Hz, 4.5 Hz), 2.33 (1H, ddd, J= 14.4 Hz, 9.9 Hz, 3.0 Hz), 3.43 (1H, dd, J = 9.8 Hz, 6.6 Hz), 3.56 (1H, dd, J = 9.8 Hz, 5.1 Hz), 3.65 (1H, dd, J = 13.5 Hz, 4.8 Hz), 3.62-3.68 (1H, m), 3.75 (1H, dd, J = 13.8 Hz, 3.9 Hz), 4.46 (1H, d, J = 5.1 Hz), 4.54-4.62 (1H, m), 5.10 (1H, d, J = 12.9 Hz), 5.19 (1H, d, J = 12.9 Hz), 5.37 (2H, s), 7.09-7.38 (15H, m). IR (neat): 3472 (OH), 1698 (C=O) cm^{-1}. HRMS (FAB+) Calcd for $C_{33}H_{44}NO_5Si$ (M^++H): 562.2989; Found: 562.2999.

(2*S*, 5*R*, 6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2-(2'-oxopropan-1'-yl)-1, 2, 5, 6-tetrahydro-4H-1,4-oxazine (11). A mixture of alcohol **9** (0.097 g, 0.173 mmol), Dess-Martin periodinane (0.09 g, 0.21 mmol), and CH_2Cl_2 (3 mL) were stirred at room temperature for 2 h. After dilution with Et_2O (15 mL), sat. $NaHCO_3$ (15 mL) and $Na_2S_2O_3$ (0.191 g, 1.24 mmol) was added. The reaction mixture was stirred vigorously for 15 min. The organic layer was separated and the aqueous solution was extracted with CH_2Cl_2 (3 x 15 mL). The organic phase was washed with sat. $NaHCO_3$ (1 x 25 mL) and H_2O (2 x 25 mL), successively. The organic layer was dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give an oily residue, which was purified by silica gel chromatography (hexanes : AcOEt = 4 : 1) to give the corresponding ketone (**11**) as a viscous oil (0.093 g, 96 % yield). Colorless viscous oil. $[\alpha]_D^{25}$ = -81.4 ° (CH_2Cl_2, *c* 1.17). ^1H NMR (300 MHz) (348 K, DMSO- d_6) δ TMS: -0.04 (3H, s), -0.02 (3H, s), 0.90 (9H, s), 2.58 (1H, dd, J = 15.9 Hz, 7.2 Hz), 2.84 (1H, dd, J = 16.1 Hz, 6.5 Hz), 3.55 (1H, dd, J = 13.5 Hz, 3.6 Hz), 3.75 (1H, dd, J = 14.4 Hz, 1.8 Hz), 3.93 (2H, s), 4.70 (1H, brs), 5.02 (1H, d, J = 12.3 Hz), 5.22 (1H, d, J = 12.3 Hz), 5.27 (1H, d, J =3.6 Hz), 5.66 (1H, brs), 6.83-7.20 (13H, m), 7.46 (2H, m). IR (neat): 1700 (C=O) cm^{-1}. HRMS (FAB+) Calcd for $C_{33}H_{42}NO_5Si$ (M^++H): 560.2832; Found: 560.2840.

Reduction of Ketone (11) with $NaBH_4$. To a MeOH solution (1 mL) of ketone **11** (0.015 g, 0.027 mmol), $NaBH_4$ (0.004 g, 0.106 mmol) was added in one portion at -40 °C under an Ar atmosphere. The mixture was stirred at -40 °C for 1 h. The solvent was evaporated under reduced pressure. The residue was diluted with Et_2O (20 mL), washed with H_2O (2 x 10 mL), and dried over $MgSO_4$, filtered, and evaporated to give a crude product, which was purified with silica gel PTLC (hexanes : AcOEt = 4 : 1) to give alcohol (**10a**) as a colorless viscous oil (0.017 g, 84 % yield).

(1'*R*, 2*S*, 4*S*)-1-Boc-3-(1',2'-diphenylethoxy)-2-(tert-butyldimethylsilyloxymethyl)pyrrolidine (7c). To a mixture of alcohol **10a** (0.528 g, 0.94 mmol), Et_3N (0.143 g, 0.196 mL, 1.41 mmol), and CH_2Cl_2 (12 mL), MsCl (0.118 g, 0.08 mL, 1.03 mmol) was added at -78 °C under an Ar atmosphere. The mixture was stirred at the same temperature for 0.5 h and diluted with Et_2O (20 mL). The mixture was washed with sat. $NaHCO_3$ (10 mL x 1) and sat. NaCl (10 mL x 2), dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give a crude mesylate (**6c**) as a colorless solid (0.574 g, 96 % yield from compound **10a**). Without further purification, mesylate (**6c**) was employed in the next reaction. A mixture of mesylate (**6c**) (0.322 g, 0.504 mmol), 20 % $Pd(OH)_2$ on carbon (0.322 g), and MeOH (10 mL) was stirred under an atmosphere of H_2 (60 psi) at room temperature for 15 h. After filtration through short pad of Celite 545®, the solvent was evaporated under reduced pressure to give a residue. After addition of H_2O (20 mL), the aqueous solution was adjusted to pH 8 by addition of solid $NaHCO_3$. The solution was extracted with Et_2O (20 mL x 3). The organic layer was dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give an oily residue. To the residue, $(BOC)_2O$ (0.128 g, 0.59 mmol) and CH_2Cl_2 (5 mL) were added. The resulting mixture was stirred at room temperature for 3 days under an Ar atmosphere. After evaporation of the solvent, the residue was purified by flash chromatography (hexanes : AcOEt = 20 : 1) to give pyrrolidine (**7c**) as a colorless viscous oil (0.171 g, 66 % yield from mesylate (**6c**)). $[\alpha]_D^{25}$ = -2.8 ° (CH_2Cl_2, *c*

1.52). ^{1}H NMR (300 MHz) (340 K, C_6D_6) δ TMS: 0.13 (3H, s), 0.14 (3H, s), 1.01 (9H, s), 1.43 (9H, s), 1.66 (1H, ddd, *J* = 13.2 Hz, 6.6 Hz, 6.6 Hz), 2.14 (1H, ddd, *J* = 13.2 Hz, 3.9 Hz, 3.9 Hz), 2.85 (1H, dd, *J* = 13.7 Hz, 6.2 Hz), 3.09 (1H, dd, *J* = 13.7 Hz, 7.1 Hz), 3.32 (1H, dd, *J* = 12.0 Hz, 4.2 Hz), 3.48 (1H, m), 3.67 (1H, ddd, *J* = 9.8 Hz, 6.4 Hz, 4.7 Hz), 3.83 (2H, brs), 3.97 (1H, brs), 4.43 (1H, dd, *J* = 6.6 Hz, 6.6 Hz), 7.02-7.14 (10 H, m). IR (neat): 1698 (C=O) cm^{-1}. HRMS (FAB+) Calcd for $C_{30}H_{46}NO_4Si$ (M^++H): 512.3196; Found: 512.3202.

(2*S*, 4*S*)-1-Boc-2-(tert-butyldimethylsilyloxymethyl)-3-hydroxypyrrolidine (8c). To a solution of Li° (0.054 g, 7.75 mmol atom) in liq. NH_3 (10 mL, distilled from Na°), a THF solution (5 mL) of compound **7c** (0.165 g, 0.323 mmol) and *tert*-BuOH (0.120 g, 1.62 mmol) were added dropwise at -78 °C. The reaction mixture was stirred at the same temperature for 20 min. To the reaction mixture, excess NH_4Cl was added. The mixture was concentrated to give a residue. After addition of H_2O (20 mL), the aqueous solution was extracted with CH_2Cl_2 (3 x 20 mL). The organic phase was dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give an oily residue, which was purified by flash chromatography (hexanes : AcOEt = 4 : 1) to give pyrrolidine **8c** as a colorless viscous oil (0.094 g, 88% yield from mesylate **7c**). >99.5 : 0.5 *er* on the basis of glc analysis of Mosher esters. Colorless viscous oil. $[\alpha]_D^{25}$ = -47 ° (CH_2Cl_2, *c* 1.1). ^{1}H NMR (300 MHz) (348 K, DMSO- d_6) δ TMS: 0.056 (6H, s), 0.89 (9H, s), 1.41 (9H, s), 1.86 (1H, m), 2.01-2.10 (1H, m), 3.03 (1H, dd, *J* = 11.4 Hz, 3.6 Hz), 3.50 (1H, dd, *J* = 11.3 Hz, 5.9 Hz), 3.74 (2H, brs), 3.72 (1H, m), 4.18 (1H, m), 4.70 (1H, d, *J* = 4.2 Hz). IR (neat): 3427 (OH), 1698 (C=O) cm^{-1}. HRMS (FAB+) Calcd for $C_{16}H_{34}NO_4Si$ (M^++H): 332.2257; Found: 332.2256.

Silylation of *Syn*-12. To a solution of *syn*-**12**[13] (0.16 g, 0.74 mmol), DMAP (cat. amount), Et_3N (0.089 g, 0.124 mL, 0.89 mmol) and CH_2Cl_2 (5 mL), TBDMSCl (0.123 g, 0.81 mmol) was added at 0 °C under an Ar atmosphere. The reaction mixture was stirred at room temperature for 2 days and diluted with Et_2O (15 mL). The organic layer was washed with H_2O (2x 10 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give an oily residue, which was purified by short silica gel flash chromatography (hexanes : AcOEt = 3 : 1) to give the monosilylated compounds *ent*-**8c** and **8d**.

(2*R*, 4*R*)-1-Boc-2-(tert-butyldimethylsilyloxymethyl)-3-hydroxypyrrolidine (*ent*-8c). Colorless viscous oil. $[\alpha]_D^{25}$ = +49.2 ° (CH_2Cl_2, *c* 0.75). ^{1}H NMR and IR spectra of *ent*-**8c** were identical with those of compound **8c**.

(2*R*, 4*R*)-1-Boc-3-(tert-butyldimethylsilyloxy)-2-(hydroxymethyl)pyrrolidine (8d). Colorless viscous oil. $[\alpha]_D^{25}$ = +14.1 ° (CH_2Cl_2, *c* 1.02). ^{1}H NMR (300 MHz) (348 K, DMSO- d_6) δ TMS: 0.07 (3H, s), 0.08 (3H, s), 0.88 (9H, s), 1.41 (9H, s), 1.87 (1H, ddd, *J* = 13.2 Hz, 4.1 Hz, 4.1 Hz), 2.09 (1H, ddd, *J* = 13.4 Hz, 8.1 Hz, 5.4 Hz), 3.03 (1H, dd, *J* = 11.1 Hz, 3.9 Hz), 3.43-3.66 (3H, m), 3.70-3.78 (1H, m), 4.30-4.38 (2H, m). IR (neat): 3434 (OH), 1697 (C=O) cm^{-1}. HRMS (FAB+) Calcd for $C_{16}H_{34}NO_4Si$ (M^++H): 332.2257; Found: 332.2261.

Silylation of *Anti*-12. By following the same procedure as described above, 0.237 g (92% yield) of monosilylated product **8e** was obtained. Colorless viscous oil. $[\alpha]_D^{25}$ = -53.9 ° (CH_2Cl_2, *c* 0.83). ^{1}H NMR (300 MHz) (348 K, DMSO- d_6) δ TMS: 0.026 (3H, s), 0.036 (3H, s), 0.88 (9H, s), 1.41 (9H, s), 1.85 (1H, ddd, *J* = 12.4 Hz, 8.4 Hz, 4.3 Hz), 1.96-2.04 (1H, m), 3.25 (2H, d, *J* = 3.9 Hz), 3.62 (1H, dd, *J* = 9.9 Hz, 3.0 Hz), 3.71 (1H, brs), 3.83 (1H, m), 4.26 (1H, m), 4.62 (1H, d, *J* = 3.9 Hz). IR (neat): 3428 (OH), 1698, 1674 (C=O) cm^{-1}. HRMS (FAB+) Calcd for $C_{16}H_{34}NO_4Si$ (M^++H): 332.2257; Found: 332.2256.

REFERENCES AND NOTES

1. (a) Pinder, A. R. *Nat. Prod. Rep.* **1992**, *9*, 17 and references cited therein. (b) Michael, J. P. *Nat. Prod. Rep.* **1992**, *9*, 17 and references cited therein.
2. Bhat, K. L.; Flanagan, D. M.; Joullié, M. M. *Synth. Commun.* **1985**, *15*, 587 and references cited therein. Interestingly, different optical rotation values for 1-Boc-3-hydroxypyrrolidine are reported by the same authors (compare ref. 9).
3. (a) Sinnot, M. L. *Chem. Rev.* **1990**, *90*, 1170 and references cited therein. (b) Razavi, H.; Polt, R.*Tetrahedron Lett.* **1998**, *39*, 3371 and references cited therein. (c) Ryu, Y.; Kim, G. *J.Org. Chem.* **1995**, *60*, 103 and references cited therein. (d) Blanco, M.-J.; Sardina, F. J. *J. Org. Chem.* **1996**, *61*, 4748 and references cited therein. (e) Burley, I.; Hewson, T. *Tetrahedron Lett.* **1994**, *38*, 7099 and references cited therein.
4. Humphries, M. J.; Matsumoto, K.; White, S. L.; Olden, K. *Cancer Res.* **1986**, *46*, 5215.
5. (a) Elbein, A. D. *Annu. Rev. Biochem.* **1987**, *56*, 497. (b) Truscheit, E.; Frommer, W.; Junge, B.; Müller, L.; Schmidt, D. D.; Wingender, W. *Angew. Chem., Int. Ed. Engl.*. **1981**, *20*, 744.
6. Gruters, R. A.; Neefjes, J. J.; Tersmette, M.; De Goede, R. E. Y.; Tulp, A.; Huisman, H. G.; Miedema, F.; Ploegh, H. L. *Nature* **1987**, *330*, 74.
7. Nutt, R. F.; Joullié, M. M. *J. Am. Chem. Soc.* **1982**, *104*, 5852.
8. Schneider, M. J.; Harris, T. M. *J. Org. Chem.* **1984**, *49*, 3681.
9. Harris, B. D.; Bhat, K. L.; Joullié , M. M. *Synth. Commun.* **1986**, *16*, 1815.
10. Baker, G. L.; Fritschel, S. J.; Stille, J. R.; Still, J. K. *J. Org. Chem.* **1981**, *46*, 2954.
11. Jordis, U.; Sauter, F.; Siddiqi, S. M.; Küenburg, B.; Bhattacharya, K. *Synthesis* **1990**, 925.
12. Peterson, M. L.; Vince, R. *J. Med. Chem.* **1991**, *34*, 2787.
13. Rajeev, K. G.; Sanjayan, G. J.; Ganesh, K. N. *J. Org. Chem.* **1997**, *62*, 5169.
14. The requisite diphenyloxazines **1a-d** are commercially available from Aldrich Chemical Co.; **1a**: catalog #33185-6 (CAS Registry #105228-46-4); the antipode **1b**: catalog #33187-2 (CAS Registry #100516-54-9); **1c**: catalog #33181-3 (CAS Registry #112741-50-1); the antipode **1d**: catalog #33184-8 (CAS Registry #112741-49-8).
15. Williams, R. M. *Aldrichimica Acta* **1992**, *25*, 11 and references cited therein.
16. Williams, R. M.; Colson, P. -J.; Zhai, W. *Tetrahedron Lett.* **1994**, *35*, 9371.
17. Aoyagi, Y.; Williams, R. M. *Tetrahedron*, **1998**, *54*, 10419.
18. (a) Danishefsky, S. J.; DeNinno, S.; Lartey, P. *J. Am. Chem. Soc.* **1987**, *109*, 2082. (b) Danishefsky, S. J.; Selnick, H. G.; Zelle, R. E.; DeNinno, M. P. *J. Am. Chem. Soc.*, **1988**, *110*, 4368. (c) Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc.* **1989**, *111*, 2967.
19. Yamamoto, Y.; Yatagai, H.; Ishihara, Y.; Maeda, N.; Maruyama, K. *Tetrahedron* **1984**, *40*, 2246.
20. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. -S.; Kwong, H. -L.; Morikawa, K.; Wang, Z. -M.; Xu, D.; Zhang, X. -L. *J. Org. Chem.* **1992**, *57*, 2768.
21. Guindon, Y.; Yuakin, C; Bernstein, M. A.; Morton, H. E. *Tetrahedron Lett.* **1985**, *26*, 1185.