HETEROCYCLES, Vol. 58, 2002, pp. 191-202, Received, 11th January, 2002

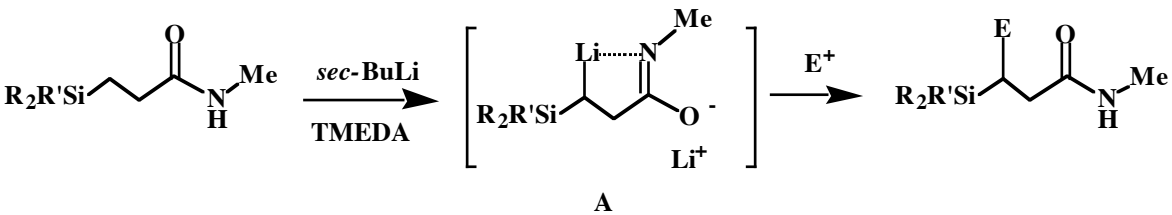
DIASTEREOSELECTIVE REACTIONS OF A HOMOENOLATE GENERATED FROM (*S*)-*N*-(1-PHENYLETHYL)-3-(TRIMETHYLSILYL)PROPANAMIDE: ENANTIOSELECTIVE SYNTHESIS OF (+)-MASSOIALACTONE

Naoko Sadayori, Asako Kawatoh, Ryoko Sakurazawa, Tomoko Utsumi, Miharu Inagaki, and Morio Asaoka*

Department of Chemical and Biological Sciences, Faculty of Science, Japan Women's University, Mejirodai 2-8-1 Bunkyoku, Tokyo 112-8681, Japan

Abstract - Alkylation of the homoenolate generated from (*S*)-*N*-(1-phenylethyl)-3-(trimethylsilyl)propanamide gave the corresponding products with good diastereoselectivity. Starting with one of the alkylated products, enantioselective synthesis of (+)-massoialactone [(+)-**13**] was carried out.

In a previous paper,[1] we reported that the silyl group stabilized amide homoenolate (**A**) was generated by utilizing the complex-induced proximity effect (CIPE)[2] and reacted with some electrophiles (Scheme 1).

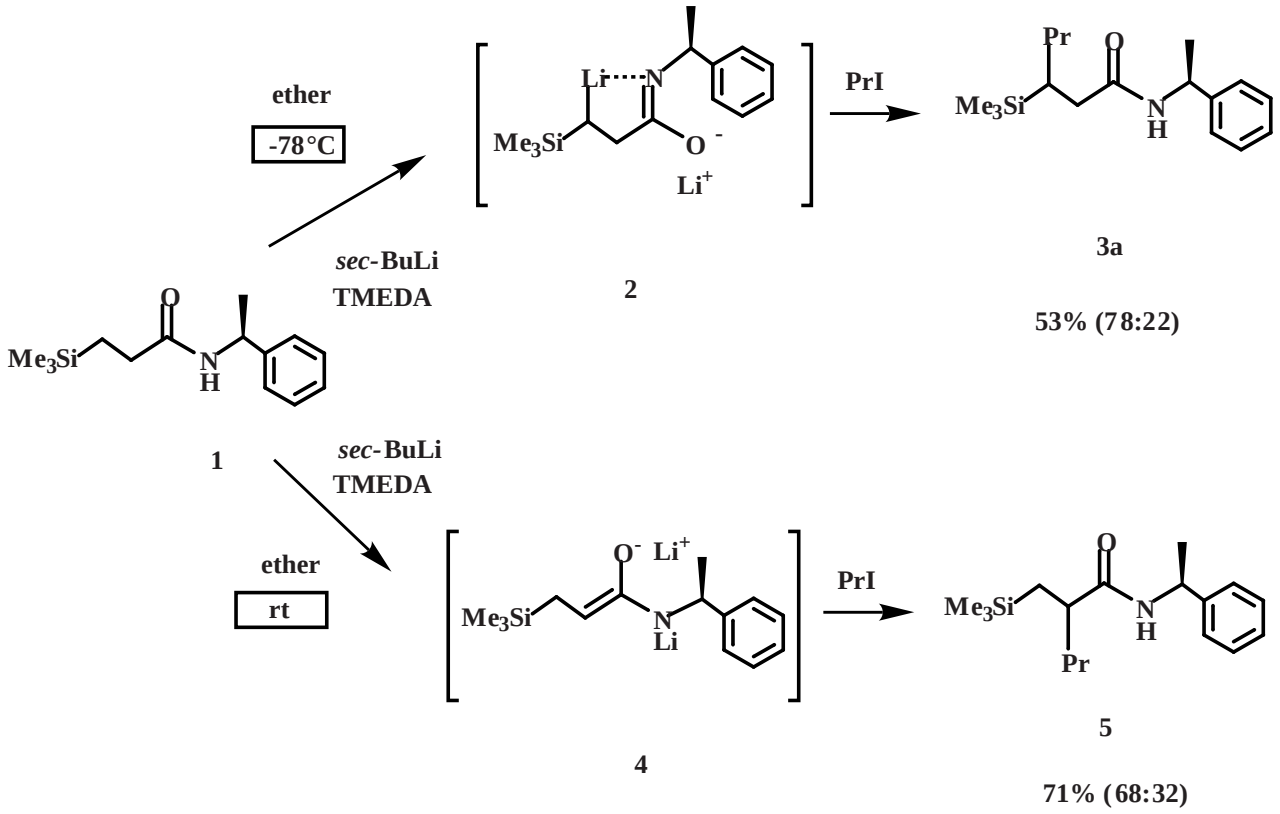


A

Scheme 1

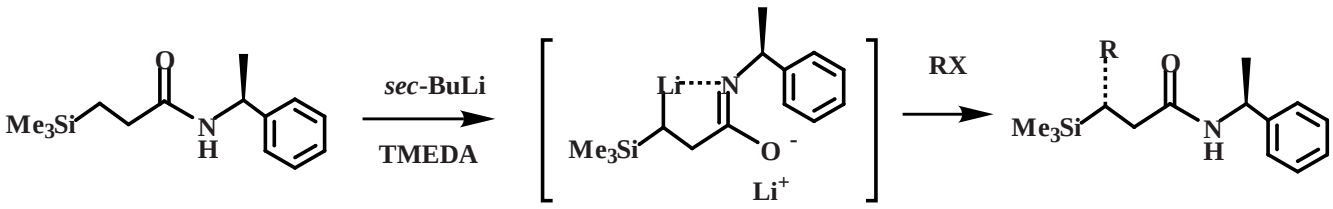
To utilize the above reaction for the enantioselective synthesis of some natural products, chiral group was introduced onto the nitrogen of the amide. Thus, (*S*)-*N*-(1-phenylethyl)-3-(trimethylsilyl)propanamide (**1**) was prepared and the diastereoselectivity

in the alkylation *via* dianion (**2**) was examined. When the dianion generation and the alkylation were carried out at -78°C in ether, β-alkylated product (**3a**) was obtained, whereas α-alkylated product (**5**) was obtained at room temperature (Scheme 2).



Scheme 2

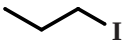
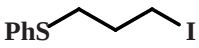
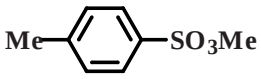
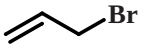
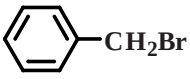
Thus, the alkylation was carried out in ether at -78°C and the results are shown in Table 1. Alkyl iodides reacted with dianion (**2**) to give alkylated products with good to fair diastereoselectivities (Entries 1-3). In the case of methylation, the better selectivity was observed when methyl tosylate was used (Entry 4). However, use of ethyl or allyl tosylate did not give a alkylated product under the same reaction conditions. Although the reason is still obsecure, no diastereoselectivity was observed in the alkylation with allylic or benzylic bromide (Entries 5 and 6). When the alkylation was carried out in dry THF at -78°C, the corresponding products (**3a~d**) were obtained in high (83~92%) yields, however, almost no diastereoselectivity was observed.



1 **2** **3**

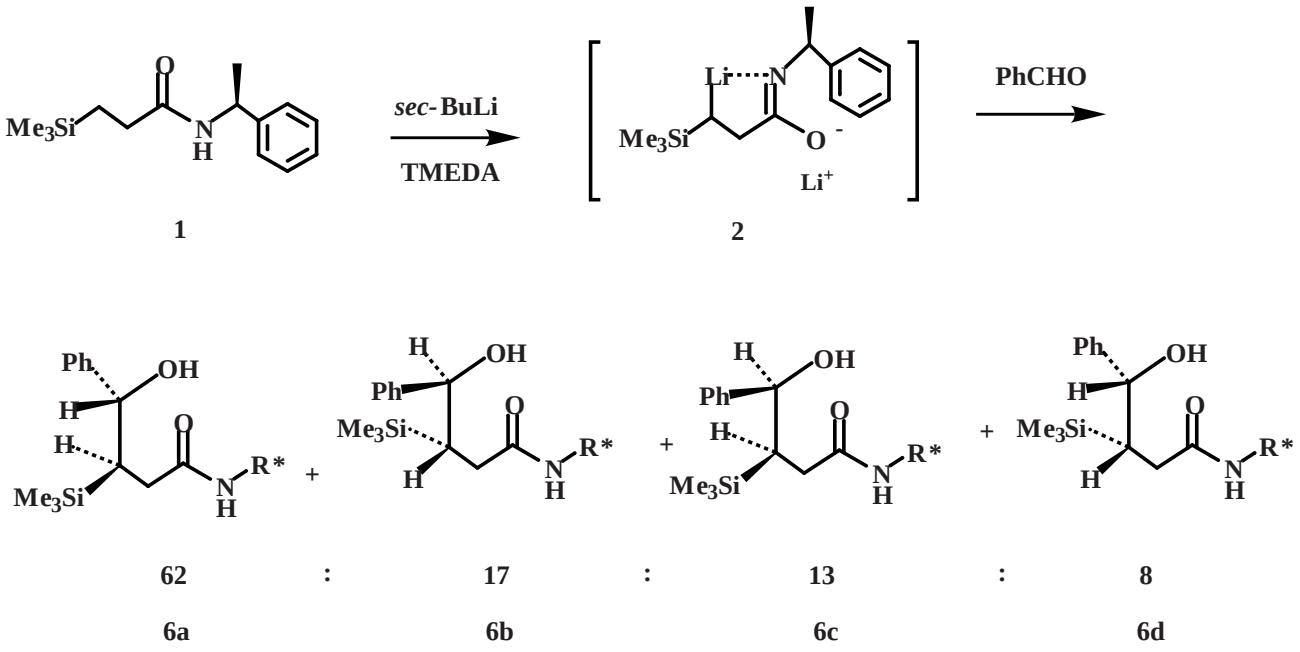
Scheme 3

Table 1 **Alkylation of amide homoenolate (2)**

Entry	RX	3	Yield (%)	Ratio
1		3a	53	78:22
2		3b	52	81:19
3	MeI	3c	65	60:40
4		3c	42	82:18
5		3d	37	50:50
6		3e	30	50:50

Reactions were carried out in dry ether at -78 °C under Ar atmosphere.

The reaction of benzaldehyde with dianion (**2**) in THF at -78°C gave a mixture of four diastereoisomers (**6a**:**6b**:**6c**:**6d**=62:17:13:8) in 64% combined yield (Scheme 4).



Scheme 4

The configuration of **6a~6d** was determined as described below. When the mixture of **6a~6d** was heated at reflux in toluene for 10 h, *trans*-lactones (**7a+b**) were formed and the mixture of **6c**,**d** was recovered due to the sterically unfavorable formation of *cis*-lactone (Figure 1).

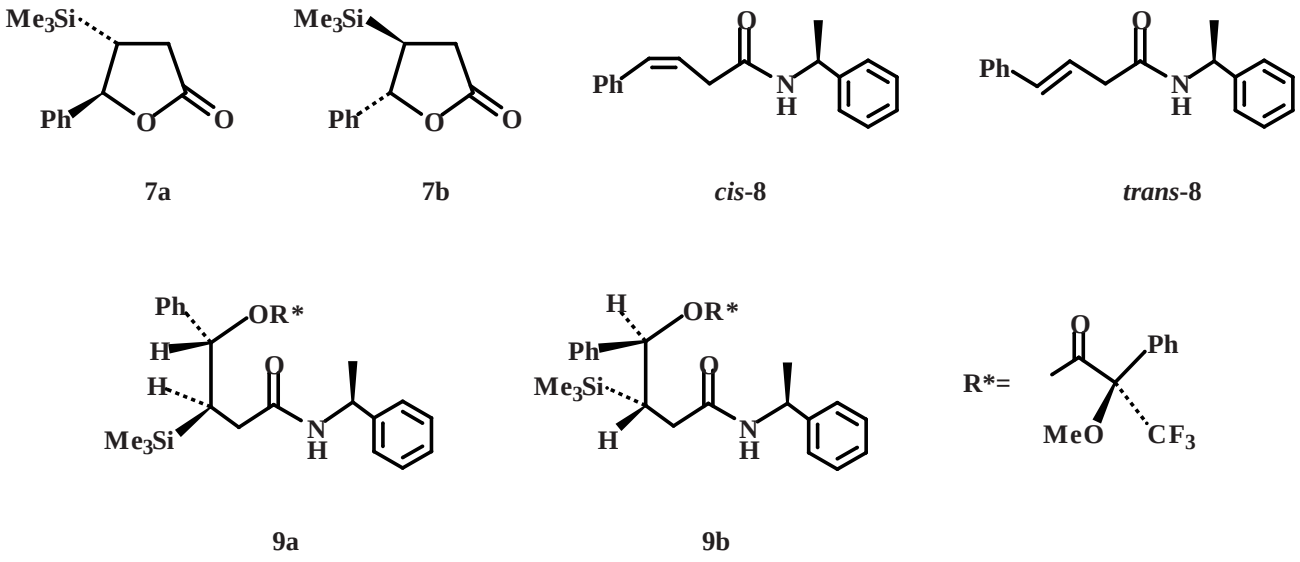
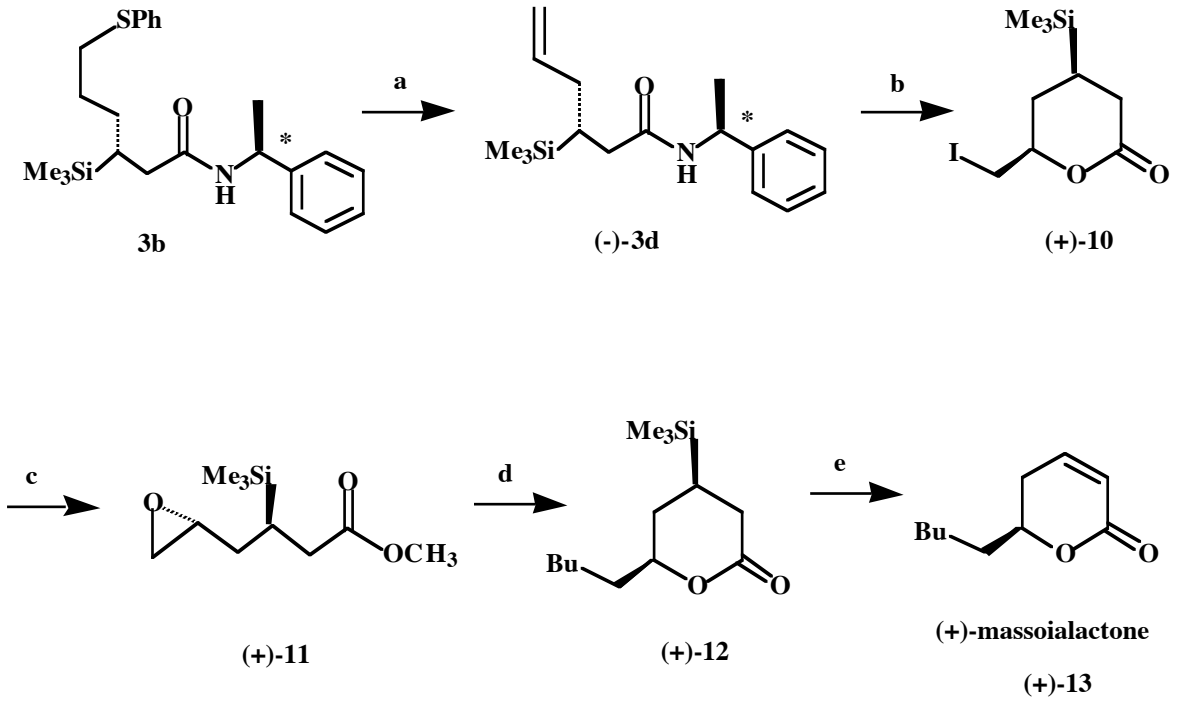


Figure 1

Thus, treatment of the recovered **6c,d** with trifluoroacetic acid gave *cis*-**8** as an exclusive product *via anti*-elimination, whereas the mixture of **6a~6d** gave an 8:2 mixture of *trans*-**8** and *cis*-**8** (Figure 1). According to these results, *syn* or *anti* relationship of C3-C4 was established. The absolute configuration of **6a,b** was assigned after conversion into the corresponding (*R*)-(+)-MTP esters (**9a** and **9b**).[3] On the basis of the ^{1}H NMR spectral data of -OMe (**9a**: δ 3.36, **9b**: δ 3.41) and Me_3Si (**9a**: δ -0.24, **9b**: δ -0.02), the absolute configuration was assigned as shown in Scheme 4.

To utilize the above diastereoselective alkylation as well as to determine the configurations of the alkylated products (**3a-c**), enantioselective synthesis of massoialactone[4,5] was targeted. Since **3d** was not obtained diastereoselectively by the allylation of **1** with allyl bromide, alkylation product (**3b**) was chosen as a starting material (Scheme 5).

Conversion of **3b**, approximately 4 to 1 mixture of diastereoisomers, into the corresponding sulfoxide with sodium metaperiodate followed by thermal degradation at 140°C for 17 h gave **3d** in 64% overall yield. Flash column chromatography followed by recrystallization gave the major diastereoisomer [(-)-**3d**] in a diastereomerically pure form. Iodolactonization with 2 equivalents of I_2 in THF-H_2O gave *cis*-lactone [(+)-**10**] preferentially (66%).[6] A small amount (~2%) of *trans*-lactone was easily separated by column chromatography. Thus, with optically pure iodo lactone [(+)-**10**] in hands, we initially examined a very straightforward method, *i. e.*, displacement of the iodo group with butyl group. However, the reaction of (+)-**10** with Bu_2CuLi under various reaction conditions resulted in failure. Treatment of (+)-**10** with anhydrous Na_2CO_3 in MeOH gave epoxy ester [(+)-**11**] in high (98%) yield[7] and the epoxy ester successfully reacted[8] with large excess of Bu_2CuLi to give expected *cis*-lactone [(+)-**12**] in 95% yield.[5d] Removal of the trimethylsilyl group was carried out by β-bromination *via* enol silyl ether, followed by fluoride ion treatment to give (+)-massoialactone [(+)-**13**] in 56% overall yield (Scheme 5). The spectral (NMR and IR) properties of the synthesized (+)-massoialactone were virtually identical with those previously reported for (+)- or (-)-massoialactone.[5] The sense of the specific rotation, $[\alpha]_D^{22}$ +107.5° (*c* 0.5, $CHCl_3$), indicates that the configuration of the massoialactone synthesized here is 5*S*, which means that the absolute configurations of the synthetic intermediates are (3*R*,5*S*)-**12**, (3*R*,5*R*)-**11**, (3*R*,5*R*)-**10**, (3*R*)-**3d**, and (3*R*)-**3b**. On the basis of these results the absolute configurations of the major products of **3a-c** were assigned as 3*R*.[9] It is noteworthy that the reaction of homoenolate (**2**) with alkyl halides and benzaldehyde preferentially gave products with an opposite sense of configuration at the new carbon-carbon bond.[9,10]



3b **(-)-3d** **(+)-10**

(+)-11 **(+)-12** **(+)-massoialactone (+)-13**

a 1) $NaIO_4$, 2)Δ; b I_2; c K_2CO_3, MeOH; d Bu_2CuLi; e 1) LDA, 2) M e_3SiCl, 3) NBS, 4) TBAF

Scheme 5

EXPERIMENTAL

Melting points were recorded on MITAMURA RIKEN Model 7-12 melting point apparatus. IR spectra were recorded on a HITACHI 260-50 spectrophotometer and recorded in wave number (cm^{-1}). ^{1}H and ^{13}C NMR spectra were taken on a BRUKER AMX400WB (400 MHz) with $CDCl_3$ as solvent. Chemical shifts are reported in ppm (δ value) down field shift from Me_4Si (δ=0 ppm) or residual $CDCl_3$ (δ= 7.26 ppm for ^{1}H or 77.0 ppm for ^{13}C) as internal standard unless otherwise noted. Coupling constants (*J*) are given in Hertz. Flash chromatography was performed with WAKO C-300 silica gel. Analytical TLC was performed on Merck silica plates with F-254 indicator. High resolution MS spectra were taken on a JEOL JMS DX-300. Et_2O and THF were dried and distilled from sodium metal / benzophenone ketyl. All reactions sensitive to oxygen or moisture were conducted under an argon atmosphere in flame dried flasks.

(*S*)-*N*-(1-Phenylethyl)-3-(trimethylsilyl)propanamide (1): To a precooled (0°C) mixture of aqueous NaOH (0.7M, 200 mL, 140 mmol) and (*S*)-(-)-1-phenylethylamine

(15.3 mL, 120 mmol) in ether (200 mL), acryloyl chloride (10.8 mL, 132 mmol) was added dropwise with vigorous stirring. The mixture was left to warm to rt during 3 h. After usual work-up, the crude product was used for the next step without further purification. To the crude product dissolved in AcOEt (200 mL) were added thiophenol (12.3 mL, 120 mmol) and triethylamine (7 mL, 50 mmol). After stirred at rt for 15 h, the reaction mixture was concentrated and the product was purified by flash column chromatography on silica gel (hexane:AcOEt=3:1) to give **(*S*)-*N*-(1-phenylethyl)-3-(phenylthio)-propanamide** (27.6 g, 81%). Recrystallization from hexane gave white crystals (mp 58-60°C). ^{1}H-NMR: δ 1.49 (d, J=6.7 Hz, 3H), 2.48 (t, J=7.2 Hz, 2H), 3.24 (t, J=7.2 Hz, 2H), 5.21 (m, 1H), 5.74 (m, 1H), 7.21-7.27 (m, 10H); IR (KBr): 3300 (NH), 1640 (C=O) cm^{-1}.

A solution of (*S*)-*N*-(1-phenylethyl)-3-(phenylthio)propanamide (8.7 g, 30 mmol) in dry THF (45 mL) was cooled to -78°C and treated with *n*-BuLi (1.58 M, 42 mL, 66 mmol) for 1 h under argon atmosphere. After the addition of Me_3SiCl (8.3 mL, 70 mmol), the reaction mixture was stirred for 0.5 h at this temperature. Usual work-up gave (*S*)-*N*-(1-phenylethyl)-3-phenylthio-3-(trimethylsilyl)propanamide which was used for the following desulfurization step without further purification.

Treatment of the crude product in ethanol (100 mL) with Raney-Ni W2, prepared from 70 g of Raney alloy, at rt for 2 h, followed by filtration, concentration, and purification by flash column chromatography (hexane:AcOEt=5:1) gave (*S*)-*N*-(1-phenylethyl)-3-(trimethylsilyl)propanamide (6.0 g, 80%). mp 38°C (hexane); $[\alpha]_D^{30}$ -75.3° (*c* 2.1, $CHCl_3$); ^{1}H-NMR: δ 0 .00 (s, 9H), 0.84 (m, 2H), 1.49 (d, J=6.8 Hz, 3H), 2.14 (m, 2H), 5.70 (m, 1H), 7.26-7.36 (m, 5H); IR (KBr):3300 (NH), 1640 (C=O) cm^{-1}. HRMS calcd for $C_{14}H_{23}NOSi$ (M^+) 249.1548, found 249.1547. *Anal.* Calcd for $C_{14}H_{23}NOSi$: C, 67.43; H, 9.30; N, 5.62. Found: C, 67.68; H, 9.25; N, 5.52.

***N*-(1-Phenylethyl)-3-(trimethylsilyl)hexanamide (3a):** To a precooled (-78°C) ether (5 mL) solution of **1** (249 mg, 1.0 mmol) and *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA, 170 μL, 1.0 mmol) was added *sec*-BuLi (1.0 M, 2.2 mL, 2.2 mmol). Stirring was continued for 1 h at -78°C to generate the dianion (**2**). After the addition of 1-iodopropane (170 μL, 1.5 mmol) the mixture was stirred at this temperature for 1 h. Usual work-up and purification by flash column chromatography (hexane:AcOEt=10:1) gave a diastereomeric mixture of **3a** (154 mg, 53%). Oil; ^{1}H-NMR: δ -0.13 and -0.11 (s, 9H), 0.71 (m, 3H), 1.07-1.29 (m, 5H), 1.36 (d, J=6.8 Hz, 3H), 1.91 (m, 1H), 2.11 (m, 1H), 5.61 (s, 1H), 7.13-7.22 (m, 5H); IR (NaCl): 3250 (NH), 1640 (C=O) cm^{-1}. HRMS calcd for $C_{17}H_{29}NOSi$ (M^+) 291.2017, found 291.2021.

***N*-(1-Phenylethyl)-6-phenylthio-3-(trimethylsilyl)hexanamide (3b):** oil; ^{1}H-NMR: δ -0.01 (s, 9H), 1.23 (m, 1H), 1.40-1.65 (m, 4H), 1.50 (d, J=6.0 Hz, 3H), 2.01 (m, 1H), 2.23 (m, 1H), 2.84 (m, 2H), 5.15 (m, 1H), 5.69 (br s, 1H), 7.09-7.34 (m, 10H),; IR (NaCl):3280 (NH), 1650 (C=O) cm^{-1}. HRMS calcd for $C_{23}H_{33}NOSSi$ (M^+) 399.2051, found 399.2063.

***N*-(1-Phenylethyl)-3-(trimethylsilyl)butanamide (3c):** ^{1}H-NMR: δ -0.13 and -0.12 (s, 9H), 0.80 and 0.85 (d, J=7.3 and 7.4 Hz, 3H), 1.12 (m, 1H), 1.35 and 1.36 (d, J=3.7 Hz, 3H), 1.79 (m, 1H), 2.22 (m, 1H), 5.04 (m, 1H), 6.38 (s, 1H), 7.05-7.21 (m, 5H); IR (KBr):3280 (NH), 1640 (C=O) cm^{-1}. Recrystallization of the diastereomeric mixture gave the major isomer as white crystals. mp 111°C (hexane); HRMS calcd for $C_{15}H_{25}NOSi$ (M^+)263.1705, found 263.1700. *Anal*. Calcd for $C_{15}H_{25}NOSi$: C, 68.40; H, 9.57; N, 5.32. Found: C, 68.21; H, 9.51; N, 5.47.

***N*-(1-Phenylethyl)-3-trimethylsilyl-5-hexenamide (3d):** semisolid; ^{1}H-NMR: δ 0.00 and 0.03 (s, 9H), 1.14-1.22 (m, 1H), 1.36 (d, J=6.8 Hz, 3H), 1.93-2.07 (m, 4H), 4.77-5.04 (m, 3H), 5.54 (m, 1H), 5.86 (br s,1H), 7.15-7.22 (m, 5H); IR (NaCl): 3440 (NH), 1640 (C=O) cm^{-1}.

Preparation of (3*R*)-(-)-3d from 3b: To a solution of **3b** (460 mg, 1.19 mmol) in MeOH (4 mL)-H_2O (4 mL) was added $NaIO_4$ (430 mg, 2 mmol), the mixture was stirred at rt for 15 h. Extraction with AcOEt and concentration under reduced pressure gave crude sulfoxide. The crude sulfoxide was dissolved into xylene (10 mL) and heated under reflux for 17 h. Purification by column chromatography (hexane:AcOEt=10:1) gave a 4:1 diastereomeric mixture of **3d** (220 mg, 64%). Recrystallization of the diastereomeric mixture gave the major isomer as white crystals. **(3*R*)-(-)-3d :** mp 73~75°C (hexane); $[\alpha]_D^{26}$ -63.1°(*c* 0.8, $CHCl_3$). ^{1}H-NMR: δ 0.03 (s, 9H), 1.33 (m, 1H), 1.49 (d, J=6.8 Hz, 3H), 2.08 (m, 2H), 2.21 (m, 2H), 4.87 (m, 2H), 5.11 (m, 1H), 5.67 (br s, 1H), 5.70 (m, 1H) 7.27 (m, 5H); IR (NaCl):3440 (NH), 1640 (C=O) cm^{-1}. HRMS calcd for $C_{17}H_{27}NOSi$ (M^+) 289.1860, found 289.1859. *Anal*. Calcd for $C_{17}H_{27}NOSi$: C, 70.54; H, 9.41; N, 4.84. Found: C, 70.22; H, 9.51; N 4.97.

The minor isomer of **3d** was isolated by careful column chromatography of the filtrate. Oil; ^{1}H-NMR: δ 0.00 (s, 9H),1.35 (m, 1H), 1.49 (d, J=6.7 Hz, 3H),2.13 (m, 2H), 2.24 (m, 2H), 4.99 (m, 2H), 5.14 (m, 1H), 5.78 (m, 1H), 5.90 (br s, 1H),7.33 (m, 5H); IR (NaCl):3440 (NH), 1640 (C=O) cm^{-1}.

***N*-(1-Phenylethyl)-4-phenyl-3-(trimethylsilyl)butanamide (3e):** oil; ^{1}H-NMR: δ -0.15 and -0.12 (s, 9H), 1.24 and 1.29 (d, J=6.5 and 6.8 Hz, 3H), 1.47 (m, 1H), 1.98-2.04 (m, 2H), 2.43 (m, 1H), 2.64 (dd, J=6.4 and 13.6 Hz, 1H), 4.93 (m, 1H), 5.68 (s, 1H), 7.05-7.21

(m, 10H); IR (KBr):3300 (NH), 1640 (C=O) cm^{-1}; HRMS calcd for $C_{21}H_{29}NOSi$ (M^+) 339.2018, found 339.2007.

***N*-(1-Phenylethyl)-2-(trimethylsilylmethyl)pentanamide (5):** To a stirred solution of **1** (249 mg, 1.0 mmol) and *N,N,N′,N′*-tetramethylethylenediamine (TMEDA, 170 μL, 1.0 mmol) in ether (5 mL) was added *sec*-BuLi (1.0 M, 2.2 mL, 2.2 mmol) at room temperature and the stirring was continued for 1 h. After the addition of 1-iodopropane (170 μL, 1.5 mmol) the mixture was stirred at this temperature for 1 h. Usual work-up and purification by flash column chromatography (hexane:AcOEt=10:1) gave white crystals (diastereomeric mixture of **5,** 206 mg, 71%). ^{1}H-NMR: δ -0.01 and 0.00 (s, 9H), 0.65 and 0.69 (d, J=5.5 and 5.1 Hz, 1H), 0.83 (t, J=7.7 Hz, 3H), 0.94 (q, J=8.3 Hz, 1H), 1.20 (m, 1H), 1.35 (m, 1H), 1.47 (d, J=6.9 Hz, 3H), 2.09 (m, 1H), 5.11 (m, 1H), 5.55(s, 1H), 7.24-7.32 (m, 5H); IR (NaCl): 3400 (NH), 1640 (C=O) cm^{-1}.

***N*-(1-Phenylethyl)-4-hydroxy-4-phenyl-3-(trimethylsilyl)butanamide (6a, 6b, 6c, and 6d):** To a precooled (-78°C) THF (5 mL) solution of **1** (155 mg, 0.62 mmol) and TMEDA (91 μL, 0.62 mmol) was added *sec*-BuLi (1.0 M, 1.35 mL, 1.35 mmol). Stirring was continued for 1 h at -78°C to generate the dianion (**2**). After the addition of benzaldehyde (94.5 μL, 0.93 mmol) the mixture was stirred at this temperature for 10 min. Usual work-up and purification by flash column chromatography (hexane:AcOEt=6:1) gave a mixture of **6a~d** (141 mg, 64%). Careful flash column chromatography of the mixture followed by recrystallization gave diastereomerically pure **6a** and **6b**.

6a: mp 132 °C (hexane); ^{1}H-NMR: δ -0.02 (s, 9H), 1.46 (d, J=7.2 Hz, 3H), 1.58 (m, 1H), 2.27 (dd, J=6.5 and 16.5 Hz, 1H), 2.37 (dd, J=4.5 and 16.5 Hz, 1H), 4.66 (m, 1H), 4.85 (t, J=6.7 Hz, 1H), 5.08 (m, 1H), 5.84 (br s, 1H), 7.23-7.40 (m, 10H); IR (KBr): 1630 (C=O) cm^{-1}.

6b: mp 130 °C (hexane); ^{1}H-NMR: δ -0.07 (s, 9H), 1.47 (d, J=6.5 Hz, 3H), 1.60 (m, 1H), 2.27 (dd, J=6.7 and 15.9 Hz, 1H), 2.37 (dd, J=3.7 and 15.9 Hz, 1H), 4.65 (m, 1H), 4.85 (t, J=6.7 Hz, 1H), 5.07 (m, 1H), 5.89 (br s, 1H), 7.22-7.36 (m, 10H); IR (KBr): 1630 (C=O) cm^{-1}.

6c: oil; ^{1}H-NMR: δ -0.04 (s, 9H), 1.47 (d, J=6.6 Hz, 3H), 1.59 (m, 1H), 2.28 (dd, J=6.7 and 15.9 Hz, 1H), 2.39 (dd, J=3.7 and 15.9 Hz, 1H), 4.65 (m, 1H), 4.85 (t, J=6.8 Hz, 1H), 5.07 (m, 1H), 5.86 (br s, 1H), 7.22-7.36 (m, 10H); IR (KBr): 1630 (C=O) cm^{-1}.

6d: oil; ^{1}H-NMR: δ -0.06 (s, 9H), 1.48 (d, J=6.5 Hz, 3H), 1.59 (m, 1H), 2.25 (dd, J=6.6 and 16.0 Hz, 1H), 2.35 (dd, J=3.7 and 16.0 Hz, 1H), 4.65 (m, 1H), 4.85 (t, J=6.8 Hz, 1H), 5.08 (m, 1H), 5.89 (br s, 1H), 7.22-7.36 (m, 10H); IR (KBr): 1630 (C=O) cm^{-1}.

4-Phenyl-3-(trimethylsilyl)buten-4-olide [*trans*-lactone (7)]: A mixture of **6a~6d** (107 mg, 0.3 mmol) was dissolved into toluene (2 mL) and heated at reflux for 10 h. After removal of toluene, the residue was separated by TLC (hexane:AcOEt=3:1) to give *trans*-lactone (**7**) (42 mg, 60%) and a recovered mixture of **6b,c** (15 mg). **7:** mp 97°C (hexane); ^{1}H-NMR: δ 0.01 (s, 9H), 1.92 (m, 1H), 2.52 (dd, J=12.6 and 17.8 Hz, 1H), 2.75 (dd, J=8.8 and 17.8 Hz, 1H), 5.31 (d, J=10.7 Hz, 1H), 7.37-7.48 (m, 5H); IR (KBr): 1780(C=O) cm^{-1}.

***N*-(1-Phenylethyl)-4-phenyl-3-butenamide (8):** To a mixture of **6a~d** (355 mg, 1 mmol) in dichloromethane (2 mL) was added CF_3COOH (500 μL). After 0.5 h stirring, the reaction was quenched with saturated $NaHCO_3$ solution (3 mL) and extracted with AcOEt. Purification by TLC (hexane:AcOEt=3:2) gave a mixture of *cis*-**8** (40 mg, 15%) and *trans*-**8** (160 mg, 60%).

***cis*-8:** ^{1}H-NMR: δ 1.36 (d, J=6.8 Hz, 3H), 3.18 (d, J=6.2 Hz, 2H), 5.08 (m, 1H), 5.81 (m, 1H), 6.08 (br s, 1H), 6.59 (d, J=11.4 Hz, 1H), 7.15-7.31 (m, 10H); IR (KBr): 1640 (C=O) cm^{-1}.

***trans*-8:** ^{1}H-NMR: δ 1.39 (d, J=7.0 Hz, 3H), 3.07 (d, J=7.0 Hz, 2H), 5.08 (m, 1H), 6.08 (br s, 1H), 6.20 (m, 1H), 6.42 (d, J=15.8 Hz, 1H), 7.15-7.31 (m, 10H); IR (KBr): 1640 (C=O) cm^{-1}.

Typical procedure for the preparation of MTP esters of 6a and 6b: A solution of **6a** (17 mg 0.05 mmol), acid anhydride of (*R*)-(+)-MTP acid (22 mg, 0.05 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (7 mg, 0.05 mmol) in dry dichloromethane (2 mL) was stirred at rt for 30 min, and then triethylamine (2 mL) and saturated $NaHCO_3$ solution (2 mL) were added. Extraction with AcOEt and isolation by TLC (hexane:AcOEt=2:1) gave **9a** (11 mg, 39%).

9a: ^{1}H-NMR: δ -0.24 (s, 9H), 1.41 (d, J=6.8 Hz, 3H), 1.65 (m, 1H), 2.51 (m, 1H), 2.68 (m, 1H), 3.36 (s, 3H), 5.07 (m, 1H), 5.26 (d, J=6.5 Hz, 1H), 5.67 (d, J=6.5 Hz, 1H), 7.25-7.45 (m, 15H).

9b: 22%; ^{1}H-NMR: δ -0.02 (s, 9H), 1.55 (d, J=7.1 Hz, 3H), 1.65 (m, 1H), 2.49 (m, 1H), 2.68 (m, 1H), 3.41 (s, 3H), 5.08 (m, 1H), 5.26 (d, J=6.5 Hz, 1H), 5.68 (d, J=6.5 Hz, 1H), 7.25-7.59 (m, 15H).

(3*R*,5*R*)-6-Iodo-3-(trimethylsilyl)hexan-5-olide [(+)-10]: To a cooled (0°C) solution of **3d** (445 mg, 1.54 mmol) in THF (14 mL)-H_2O (9 mL) was added I_2 (782 mg, 3.08 mmol) and the mixture was stirred at 0°C for 4 h. After the addition of saturated aqueous Na_2SO_3 (2 mL), the mixture was extracted with AcOEt. After removal of the solvent, flash column chromatography (hexane:AcOEt=15:1) gave *cis*-lactone [**(+)-10**] (317 mg, 66%). mp 124-125°C (hexane) ; $[\alpha]_D^{24}$ +27.1° (*c* 0.8, $CHCl_3$); ^{1}H-NMR: δ 0.00 (s, 9H),

1.20 (m, 1H), 1.36 (q, J=13.6 Hz, 1H), 2.05 (dd, J=1.9 and 13.6 Hz, 1H), 2.20 (dd, J=12.5 and 18.0 Hz, 1H), 2.57 (dd, J=3.7 and 18.0 Hz, 1H), 3.32 (m, 2H), 4.26 (m, 1H); IR (KBr):1720 (C=O) cm^{-1}. HRMS calcd for $C_9H_{17}O_2ISi$ (M^+) 312.0043, found 312.0028.

(3*R*,5*S*)-6-Iodo-3-(trimethylsilyl)hexan-5-olide (*trans*-lactone): ^{1}H-NMR: δ 0.06 (s, 9H), 0.85 (m, 1H), 1.25 (m, 1H), 1.94 (m, 1H), 2.24 (dd, J=13.3 and 16.7 Hz, 1H), 2.49 (dd, J=5.4 and 16.7 Hz, 1H), 3.29 (dd, J=7.5 and 10.5 Hz, 1H), 3.40 (dd, J=5.1 and 10.5 Hz, 1H), 4.38 (m, 1H).

Methyl (3*R*,5*R*)-5,6-epoxy-3-(trimethylsilyl)hexanoate [(+)-11]: To a solution of **10** (150 mg, 0.5 mmol) in MeOH (8 mL) was added anhydrous potassium carbonate (2 g) and the suspension was stirred vigorously for 1-2 h at rt. Extraction with AcOEt followed by column chromatography (hexane:AcOEt=8:1) gave epoxy ester [(+)-**11**] (110 mg, 98%). Oil; $[\alpha]_D^{22}$ +15.3° (*c* 1.0, $CHCl_3$); ^{1}H-NMR: δ 0.00 (s, 9H), 1.40 (m, 2H), 1.70 (m, 1H), 2.38 (m, 3H), 2.68 (m, 1H), 2.88 (m, 1H), 3.63 (s, 3H); IR (KBr): 1760 (C=O) cm^{-1}. HRMS calcd for $C_{10}H_{20}O_3Si$ (M^+) 216.1182, found 216.1175.

(3*R*,5*S*)-3-(Trimethylsilyl)decan-5-olide [(+)-12]: To a cooled (-78°C) ether solution (10 mL) of Bu_2CuLi prepared from CuI (390 mg, 2.1 mmol) and *n*-BuLi (1.58 M, 2.66 mL, 4.2 mmol) was added a CH_2Cl_2 solution (2 mL) of **11** (40 mg, 0.21 mmol). After 1.5 h stirring at -78°C, the reaction was quenched by the addition of MeOH (0.5 mL) and saturated NH_4Cl solution. Filtration through short pad of celite, extraction with ether, and purification by column chromatography (hexane:AcOEt=15:1) gave (+)-**12** (50 mg, 95%). Oil; $[\alpha]_D^{22}$ +0.6° (*c* 2.7, $CHCl_3$); ^{1}H-NMR: δ 0.00 (s, 9H), 0.87 (t, J=6.8 Hz, 3H), 1.14-1.81 (m, 11H), 2.19 (dd, J=11.8 and 17.7Hz, 1H), 2.57 (dd, J=6.1 and 17.7 Hz, 1H), 4.23 (m, 1H); ^{13}C-NMR: δ -0.15, 17.93, 22.69, 26.41, 28.43, 33.47, 34.53, 35.56, 40.08, 86.60, 175.57; IR (KBr): 1740 (C=O) cm^{-1}. HRMS calcd for $C_{13}H_{26}O_2Si$ (M^+) 242.1702, found 242.1723. *Anal*. Calcd for $C_{13}H_{26}O_2Si$: C, 64.41; H, 10.81. Found: C, 64.14; H, 10.75.

(*S*)-(+)-Massoialactone [(+)-13]: To a cooled (-78°C) solution of LDA (0.7 mmol) in dry THF (4 mL) was added a THF solution (5 mL) of (+)-**12** (59 mg, 0.22 mmol). After 1 h stirring at this temperature, Me_3SiCl (101 μL, 0.8 mmol) was added, and then, THF solution (3 mL) of *N*-bromosuccinimide (NBS: 285 mg, 1.6 mmol) was added to the reaction mixture. After 15 min, the reaction was quenched with saturated NH_4Cl solution and extracted with ether. After removal of the solvent the crude product was dissolved into dry THF (5 mL) and treated with tetrabutylammonium fluoride (TBAF: 1.0 M inTHF, 0.22 mL, 0.22 mmol) at rt for 0.5 h. Filtration through short pad of silica gel followed by isolation by TLC (hexane:AcOEt=2:1) gave (+)-massoialactone (30 mg, 56%)

Oil; $[\alpha]_D^{22}$ +107.5° (*c* 0.5, $CHCl_3$) [lit., [5f] $[\alpha]_D^{20}$ +110.5° (*c* 2.4, $CHCl_3$)]; ^{1}H-NMR: δ 0.90 (br t, J=4.5 Hz, 3H), 1.32-1.81 (m, 8H), 2.35 (m, 2H), 4.44 (m, 1H), 6.02 (d, J=5.1 Hz, 1H), 6.90 (m, 1H); IR (NaCl):1470 (C=O) cm^{-1}. *Anal*. Calcd for $C_{10}H_{16}O_2$: C, 71.38; H, 9.59. Found: C, 70.83; H, 9.78.

REFERENCES

1. T. Shinozuka, T. Utsumi, M. Inagaki, and M. Asaoka, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2433.
2. (a) P. Beak and A. I. Meyers, *Acc. Chem. Res.*, 1986, **19**, 356; (b) P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, and S. Thayumanavan, *Acc. Chem. Res.*, 1996, **29**, 552; (c) V. Snieckus, *Chem. Rev.*, 1990, **90**, 879.
3. (a) M. Raban and K. Mislow, *Tetrahedron Lett.*, 1965, 4249; (b) G. R. Sullivan, J. A. Dale, and H. S. Mosher, *J. Org. Chem.*, 1973, **38**, 2143; (c) B. M. Trost, J. L. Belletire, S. Godleski, P. G. McDougal, J. M. Balkovec, J. J. Baldwin, M. E. Christy, G. S. Ponticello, S. L. Varga, and P. Springer, *J. Org. Chem.*, 1986, **51**, 2370.
4. Isolation: (a) S. Abe, *J. Chem. Soc. Jpn.*, 1937, **58**, 246; T. M. Meijer, *Recl. Trav. Chim. Pays-Bas.*, 1940, **59**, 191; (b) L. Crombie, *J. Chem. Soc.*, 1955, 1007 and 2535.
5. Asymmetric synthesis: (a) K. Mori, *Agric. Biol. Chem.*, 1976, **40**, 1617; (b) W. H. Pirkle and P. E. Adams, *J. Org. Chem.*, 1980, **45**, 4117; (c) F. Bennett and D. W. Knight, *Heterocycles*, 1989, **29**, 639; (d) M. Asaoka, S. Hayashibe, S. Sonoda, and H. Takei, *Tetrahedron Lett.*, 1990, **31**, 4761; (e) T. Minami, A. Moriyama, and M. Hanaoka, *Synlett*, 1995, 663; (f) G. C. G. Pais, R. A. Fernandes, and P. Kumar, *Tetrahedron*, 1999, **55**, 13445.
6. For some reports on iodolactonization see: (a) G. P. Lutz, H. Du, D. J. Gallagher, and P. Beak, *J. Org. Chem.*, 1996, **61**, 4542; (b) R. W. Hoffman, R. Sturmer, and K. Harms, *Tetrahedron Lett.*, 1994, **35**, 6263 and references cited therein.
7. F. Bennett, D. W. Knight, and G. Fenton, *Tetrahedron Lett.*, 1988, **29**, 4865.
8. For a similar type of lactone formation see: (a); Y. Guindon, C. Yoakim, M. A. Bernstein, and H. E. Morton, *Tetrahedron Lett.*, 1985, **26**, 1185; (b) B. D. Roth and W. H. Roark, *Tetrahedron Lett.*, 1988, **29**, 1255.
9. D. J. Pippel, M. D. Curtis, H. Du, and P. Beak, *J. Org. Chem.*, 1998, **63**, 2.
10. (a) A. Carstens and D. Hoppe, *Tetrahedron*, 1994, **50**, 6097: (b) G. A. Weisenburger and P. Beak, *J. Am. Chem. Soc.*, 1996, **118**, 12218.