Syntheses of New Optically Active Organosilanes and Their Applications for the Optical-Purity-Determining Agents

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New optically active organosilicon compounds such as (benzylmethylphenylsilyl)acetic acid (**1**) and (ethylmethylphenylsilyl)acetic acid (**2**) were synthesized. Application of these acids as the optical purity determining agents for chiral amines and alcohols were successfully carried out. In addition, it was also revealed that optically active (benzylmethylphenylsilyl)methylamine (**3**) and [benzylmethyl(*o*-tolyl)silyl]methylamine (**4**) are able to be used as the optical purity determining agents for chiral carboxylic acids.

It is well-known that the method of optical purity determination of chiral organic compounds by using NMR spectrometer is one of the most convienient methods. A variety of agents for this purpose have been proposed.[1] One of the most useful agents is α-methoxy-α-trifluoromethylphenylacetic acid, Mosher agent.[2] These agents, however, do not always have a suitable group which shows a par of diastereomeric peaks in its ^{1}H NMR spectrum. In that case, the possibility for determining the optical purity has to depend on the structure of the chiral substrate to be estimated.

On the other hand, in the course of our studies on the syntheses of new optically active carbon-functional organosilanes, it was found that some of them were suitable for the enantiomer-ratio-determining agents.[3]

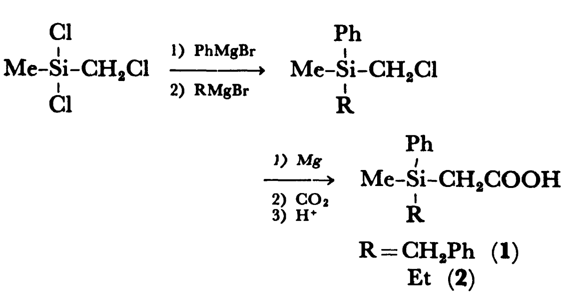
The advantages of these carbon-functional optically active organosilanes as optical-purity-determining agents over the agents which have been developed for this purpose are;

a) One of the most convienient analytical instruments, ^{1}H NMR spectrometer, can be used.

b) The Si–Me signal in the ^{1}H NMR spectra appears in the region of δ 0.1—0.4, where any other signal of ordinary organic compounds rarely appears.

c) The shape of the Si–Me signal is always observed as a sharp singlet.

d) These carbon-functional organosilicon compounds never reacemize during leading them to a pair of diastereomers.



$$\mathrm{Me\text{-}SiCl_2\text{-}CH_2Cl} \xrightarrow[\text{2) RMgBr}]{\text{1) PhMgBr}} \mathrm{Me\text{-}Si(Ph)(R)\text{-}CH_2Cl} \xrightarrow[\text{2) } CO_2 \text{ 3) } H^+]{\text{1) Mg}} \mathrm{Me\text{-}Si(Ph)(R)\text{-}CH_2COOH}$$

R = CH$_2$Ph (**1**)
Et (**2**)

Scheme 1.

Results and Discussion

Synthesis and Resolution. Racemic silylacetic acid derivatives **1** and **2** were obtained by the three steps of Grignard reactions starting from dichloro(chloromethyl)methylsilane in a good yield (Scheme 1).

Resolution of **1** was carried out by the fractional crystallization using 1-phenylethylamine(PEA) as a resolving agent (Fig. 1). Optically pure (+)-**1** was obtained by four times recrystallization of the diastereomer salt of **1** with (+)-PEA from appropriate ratio of benzene–hexane mixed solvent. Then (−)-rich **1** salt was recovered from the filtrates, and the acid was liberated. The acid recovered was treated with (−)-PEA and the diastereomer salt was recrystallized from

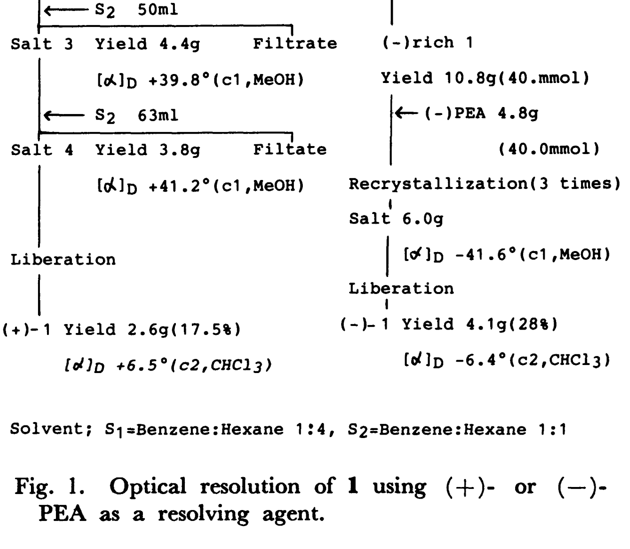


Fig. 1. Optical resolution of **1** using (+)- or (−)-PEA as a resolving agent.

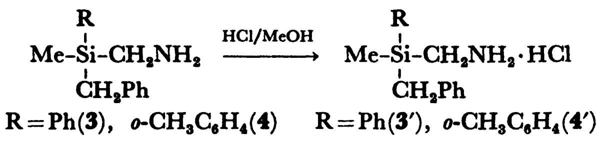
the same solvent descrived above.

Optically active (+)- and (−)-**2** were obtained by using optically active PEA as a resolving agent in a similar manner to that descrived above. It is noted that optically pure **1** can be obtained rather easier than **2**.

Optically active silylmethylamine derivatives **3** and **4** were obtained by a modified method descrived in the previous paper.[4] Then these optically active amines were converted into salts with hydrochloric acid in order to make them easier to be dealt with (Scheme 2).

The physical properties of optically active **1**, **2**, **3′**, and **4′** are listed in Table 1.

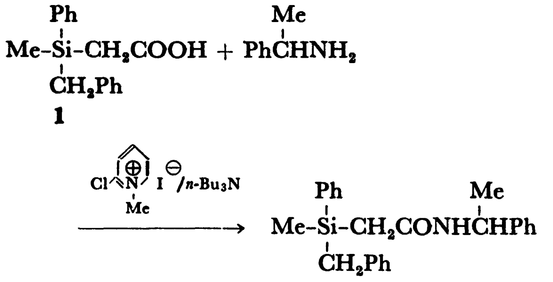
Application of the Enantiomer-Ratio-Determining Agent for a Amine. Optically pure (+)-**1** was treated with (±)- and (−)-PEA in the presence of a condensation agent, 2-chloro-1-methyl-pyridinium iodide,[5] to give the corresponding diastereomeric amides (Scheme 3).



$$\mathrm{Me\text{-}\overset{R}{\underset{CH_2Ph}{Si}}\text{-}CH_2NH_2} \xrightarrow{\mathrm{HCl/MeOH}} \mathrm{Me\text{-}\overset{R}{\underset{CH_2Ph}{Si}}\text{-}CH_2NH_2\cdot HCl}$$

R=Ph(**3**), *o*-$CH_3C_6H_4$(**4**) R=Ph(**3′**), *o*-$CH_3C_6H_4$(**4′**)

Scheme 2.



Scheme 3.

Proton NMR spectrum of the amide of (+)-**1** with racemic PEA shows two equivalent Si–Me peaks at δ 0.30 and 0.34, but that of with (−)-PEA shows only one peak at δ 0.34 (Fig. 2). These data suggest that optically active **1** is able to be used as an optical-purity-determining agent for the chiral amine. In the diastereomeric amide method, one of the most important points is that the two NMR peaks of an amide derived from racemic amine may not appear in equal intensity, mainly due to the difference in the diastereomeric selectivity of the reaction between the optically active determining agent and the chiral amine. If it happens, the NMR peaks of the diaster-

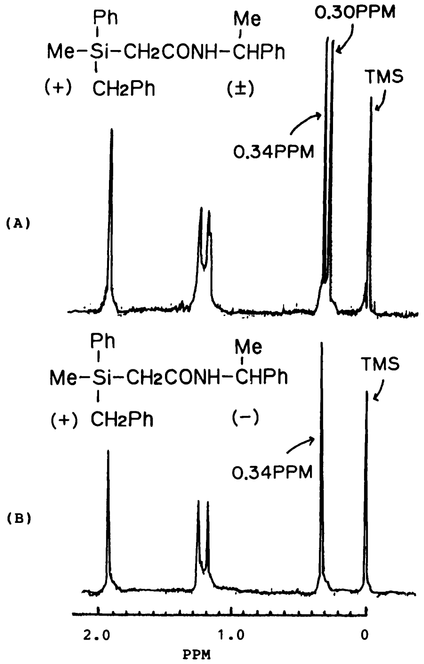


Fig. 2. ^{1}H-NMR spectra of the amides of (+)-**1** with (±)-PEA(A) and with (−)-PEA(B) measured at 90 MHz.

Table 1. The Physical Properties of Optically Active **1**, **2**, **3′**, and **4′**

Compound	Mp(Bp)(°C/Torr†)	Specific Rotation
Ph Me-Si-CH$_2$COOH (**1**) CH$_2$Ph	69—70	$[\alpha]_D$ +6.5° (*c* 2, $CHCl_3$)
Ph Me-Si-CH$_2$COOH (**2**) Et	(154—157/0.9)	$[\alpha]_D$ +7.9° (*c* 1, MeOH)
Ph Me-Si-CH$_2$NH$_2$·HCl (**3′**) CH$_2$Ph	166.5—167	$[\alpha]_D$ +45.0° (*c* 1, MeOH)
o-tolyl Me-Si-CH$_2$NH$_2$·HCl (**4′**) CH$_2$Ph	186—186.5	$[\alpha]_D$ +35.2° (*c* 1, MeOH)

†1 Torr=133.322 Pa.

eomeric amide never reflect the correct enantiomer compositions of the chiral amine. In order to check this point, appropriate grade samples of optically active PEA were prepared, and the values of optical purity measured by a Polarimeter were compared with those calculated from the NMR method (Fig. 3). These results indicate that the correlation between both methods is fairly good. Although the balance of the diastereotopic Si–Me chemical shifts(Δδ 0.04) is rater small, it is clear that the estimation of the optical purity of the amine can be done in a significant accuracy based on the unique characters of Si–Me peak: the peak appears in a paticular region and the shape is always sharp singlet, in the NMR spectra.

Then the diastereomeric amides of (+)-**1** with a number of racemic and optically active amines were prepared, and the chemical shifts of Si–Me of the diastereomeric amides were investigated. These results are summarized in Table 2.

In a similar manner, Si–Me chemical shifts of the diastereomeric amides of (+)-**2** with a number of

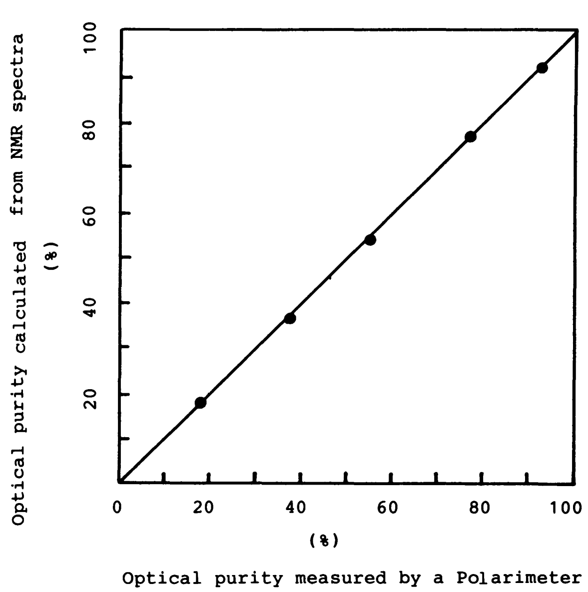
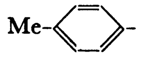
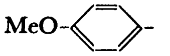
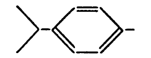
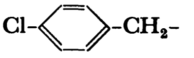
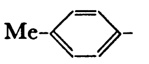
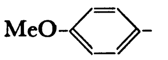
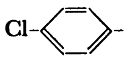
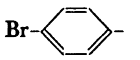
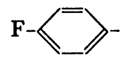


Fig. 3. Correlation of the values of optical purity measured by a polarimeter and calculated from the NMR method.

Table 2. Chemical Shifts of Si–Me of Diastereomeric Amides of (+)-**1** and (+)-**2** with Chiral Amines

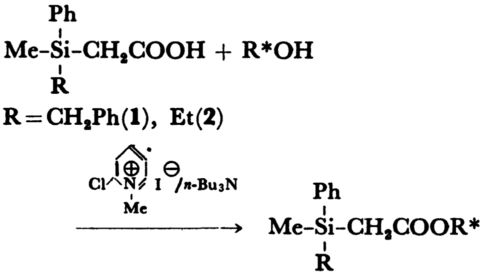
Amine Structure		Chemical Shift of the Amide of (+)-**1** (PPM)			Chemical Shift of the Amide of (+)-**2** (PPM)		
$R_1R_2CHNH_2$		(+)-(+)	(+)-(−)	Δδ[a)]	(+)-(+)	(+)-(−)	Δδ[a)]
R_1	R_2						
Ph	Me	0.30	0.34	−0.04	0.39	0.33	+0.06
	Me	0.38	0.35	+0.03	—	—	—
	Me	0.32	0.35	−0.03	—	—	—
	Me	0.30/0.35[b)]		(0.05)	—		—
Ph	Et	0.23/0.31[b)]		(0.08)	0.26/0.38[b)]		(0.11)
Ph	*n*-Pr	0.26/0.33[b)]		(0.09)	0.26/0.38[b)]		(0.09)
Ph	*i*-Pr	0.23/0.32[b)]		(0.09)	0.27/0.37[b)]		(0.10)
Ph	Allyl	0.29/0.33[b)]		(0.04)	0.32/0.38[b)]		(0.06)
Ph		0.21/0.23[b)]		(0.02)	—		—
$PhCH_2$	CH_2OH	(0.28/0.32)[c)]		—	—		—
Me_2CHCH_2	COOMe	(0.35/0.38)[c)]		—	—		—
Me	Et	(0.36)[d)]		—	—		—
$R_1R_2CHCH_2NH_2$							
R_1	R_2						
Ph	*i*-Pr	0.24	0.21	+0.03	0.24	0.27	−0.03
	*i*-Pr	0.25	0.21	+0.03	0.25	0.28	−0.03
	*i*-Pr	0.25	0.22	+0.04	0.25	0.28	−0.03
	*i*-Pr	0.25	0.22	+0.03	0.25	0.28	−0.03
	*i*-Pr	0.24	0.21	+0.03	0.25	0.28	−0.03
	*i*-Pr	0.25	0.21	+0.04	0.25	0.28	−0.03
1-Np	*i*-Pr	0.11	0.14	−0.03	—	—	—

a) The balance of the chemical shifts of the diasteromeric amides of the same and the opposite sign of rotation. b) The data used only racemic amines. c) The separation of the Si–Me peaks was observed after the addition of a little amount of $Eu(fod)_3$. d) The separation of the Si–Me peaks was not observed.

chiral amines were investigated. These results are also summarized in Table 2.

As listed in Table 2, it is clear that most of the pairs of diastereomeric amides of (+)-**1** and (+)-**2** with chiral amines have different chemical shifts. These results suggest that these silylacetic acid derivatives are useful as optical-purity-determining agents for these chiral amines, except for *s*-butylamine.

If the separation of the Si–Me chemical shifts is not observed, addition of a little amount of shift agent, i. e. Eu(fod)3, is often effective, although somewhat broadening of the Si–Me peak result.



Scheme 4.

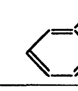
The values of the separation degree (Δδ) were calculated from differences in the chemical shifts of the diastereomeric amides obtained from (+)-**1** and (+)-amines, and those of the amides obtained from (+)-**1** and (−)-amines. It seems that the signs of the separation degree have a definite tendency dependent on the structures of (+)-**1** or (+)-**2** and chiral amines. It is of interest to investigate the correlations between the absolute configurations of the amines and the signs of the separation degrees, although we do not have enough data yet.

The diastereomeric esters of chiral alcohols with (+)-**1** and (+)-**2** were prepared (Scheme 4).

Although the differences in the chemical shifts of the Si–Me of these esters are rather smaller than those of diasteromeric amides, determination of optical purity of these chiral alcohols seems to be possible (Table 3). Actually the optical purity of 2-(2-chlorophenyl)-3-methyl-1-butanol, a new optically active alcohol, was successfully estimated by using (+)-**1**.[6]

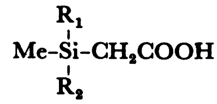
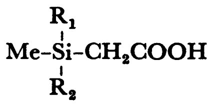
Another silylacetic acid derivatives as shown in

Table 3. Chemical Shifts of Si–Me of Diastereomeric Esters of (+)-**1** and (+)-**2** with Chiral Alcohols

Alcohol Structure		Chemical Shift of the Esters of (+)-**1** (PPM)			Chemical Shift of the Esters of (+)-**2** (PPM)		
R_1R_2CHOH		(+)-(+)	(+)-(−)	Δδ[a)]	(+)-(+)	(+)-(−)	Δδ[a)]
R_1	R_2						
Ph	Me	0.29/0.31[b)]		(0.02)	0.32/0.35[b)]		(0.03)
Ph	Et	0.26/0.29[b)]		(0.03)	0.30/0.33[b)]		(0.33)
Ph	*n*-Bu	0.26/0.28[b)]		(0.02)	0.30/0.32[b)]		(0.02)
$PhCH_2$	*n*-Bu	0.32/0.33[b)]		(0.01)	—		—
o-$CH_3C_6H_4$	*n*-C_5H_{11}	0.28/0.30[b)]		(0.02)	0.32/0.34[b)]		(0.02)
n-C_5H_{11}	Et	(0.35)[c)]		—	—		—
$R_1R_2CHCH_2OH$							
R_1	R_2						
	*i*-Pr	0.19	0.18	+0.01	—		—

a) The balance of the chemical shifts of the diastereomeric esters of the same and the opposite sign of rotation. b) The data used only racemic alcohol. c) The separation of the peaks was not observed.

Table 4. Chemical Shifts of Si–Me of Diastereomeric Amides of (±)-PEA with Racemic Chiral Organosilanes

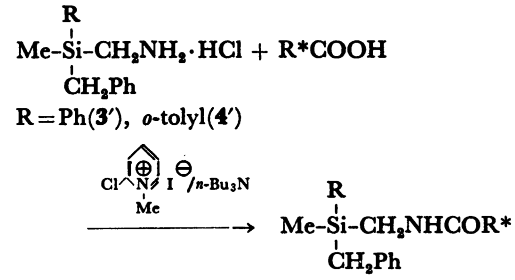
 $\mathrm{Me\text{-}\overset{R_1}{\underset{R_2}{Si}}\text{-}CH_2COOH}$		Chemical Shift of the Amide of PEA (PPM)		 $\mathrm{Me\text{-}\overset{R_1}{\underset{R_2}{Si}}\text{-}CH_2COOH}$		Chemical Shift of the Amide of PEA (PPM)	
R_1	R_2		Δδ[a)]	R_1	R_2		Δδ[a)]
Ph	*n*-Pr	0.34/0.40	0.06	*o*-$CH_3C_6H_4$	*n*-Pr	0.39/0.45	0.06
Ph	*n*-Bu	0.34/0.41	0.07	*p*-$CH_3C_6H_4$	Et	0.32/0.37	0.05
$PhCH_2$	Et	0.03/0.05	0.02	*o*-$CH_3OC_6H_4$	Et	0.31/0.38	0.07
$PhCH_2$	*n*-Pr	0.03/0.05	0.02	*o*-$CH_3OC_6H_4$	Allyl	0.34/0.39	0.05
o-$CH_3C_6H_4$	Et	0.39/0.45	0.06	1-Naphtyl	Et	0.35/0.60	0.07

a) The balance of the chemical shifts of the diastereomeric amides.

Table 4, were synthesized. The Si–Me chemical shifts of the diastereomeric amides of these acids with racemic PEA were investigated. The chemical shifts differences of some of these amides reveal rather larger than those of **1** and **2**, but, unfortunately, we have not found out the adequate resolving agent for these acids. The investigation of optical resolution of these acids are in progress.

Application of the Enantiomer-Ratio-Determining Agent for a Carboxylic Acid. The diasteromeric amides of **3′** and **4′** with a number of chiral caboxylic acids were prepared in a similar manner to that described above (Scheme 5).

The chemical shifts of Si–Me of these diastereomeric amides were also measured (Table 5). The most of the Si–Me chemical shifts of the two pairs of diastereomeric amides were separated. It is clear that both **3** and **4** have high potentials enough to estimate the enantiomer ratio of a number of chiral carboxylic acids.



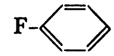
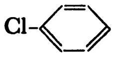
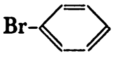
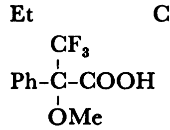
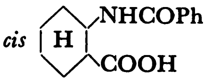
Scheme 5.

Experimental

The melting points and boiling points are uncorrected. The IR spectra were determined with JASCO IR-A 302 spectrometer. The NMR spectra were determined at 60MHz and 90MHz with a JEOL 60Si and FX90Q spectrometer, in $CDCl_3$ using TMS as an internal standard. The optical rotations were measured with a JASCO DIP-360 polarimeter. All the reactions of the Grignard reagents and the preparations of amides and esters were carried out under dry nitrogen atmosphere. All optically active amines and carboxylic acids were prepared by the procedures described in the literatures.[7]

(Benzylmethylphenylsilyl)acetic Acid (1). In a two-necked flask, equipped with a reflux condenser and an additional funnel, magnesium (3.3 g, 0.14 mol) and dry tetrahydrofuran(THF)(90 ml) were placed. A solution of (benzylmethylphenylsilyl)methyl chloride[3] (30.0 g, 0.12 mol) in THF (20 ml) was added to the solution slowly. An exothermic reaction took place. The reaction mixture was refluxed for 3 h after the addition was completed. The reaction mixture was poured into a excess amount of Dry Ice, and then the mixture was allowed to stand at room temperature until the chips of the Dry Ice disappeared. To the mixture, dil. HCl was added and the organic layer was separated from the aqueous solution. The aqueous layer was extracted with ether (30 ml×2). The combined organic and ether layer was washed with water, and then extracted with 10% aq K_2CO_3 (50 ml×3). The alkaline layer was

Table 5. Chemical Shifts of Si–Me of Diastereomeric Amides of (+)-**3** and (+)-**4** with Chiral Carboxylic Acids

Carboxylic Acid Structure		Chemical Shift of the Amide of (+)-**3** (PPM)			Chemical Shift of the Amide of (+)-**4** (PPM)		
$R_1R_2CHCOOH$		(+)-(+)	(+)-(−)	$\Delta\delta$[a]	(+)-(+)	(+)-(−)	$\Delta\delta$[a]
R_1	R_2						
Ph	OH	0.20	0.17	+0.03	0.23	0.21	+0.02
Ph	*i*-Pr	0.17	0.15	+0.02	0.22	0.17	+0.05
p-$CH_3C_6H_4$	*i*-Pr	0.18	0.16	+0.02	0.23	0.19	+0.04
	*i*-Pr	0.20	0.16	+0.04	0.25	0.18	+0.07
	*i*-Pr	0.20	0.17	+0.03	0.25	0.18	+0.07
	*i*-Pr	0.20	0.17	+0.03	0.25	0.16	+0.09
Me	Cl	(0.59/0.62)[b]		—	(0.72/0.80)[b]		—
Et	Cl	(0.56/0.60)[b]		—	(0.52/0.55)[c]		—
 $Ph\text{-}\overset{CF_3}{\underset{OMe}{C}}\text{-}COOH$		(0.18/0.22)[b]			0.33	0.30	+0.03
cis 		0.27	0.28	−0.01	0.33	0.30	+0.03

a) The balance of the chemical shifts of the diastereomeric amides of the same and opposite sign of rotation.
b) The separation of the Si–Me peaks was observed after the addition of a little amount of Eu(fod)$_3$.

washed with ether (50 ml), and 3 M†† HCl was added to the solution until the solution changes to acidic. The resulted carboxylic acid was extracted with ether (50 ml×3). The combined extracts was dried over Na_2SO_4, and subsequent evaporation gave **1** in 26.3 g (80%) yield. Mp 36—38 °C. IR (neat) 2900 cm^{-1} (s, COOH), 1680 cm^{-1}. ^{1}H NMR δ=0.38 (s, 3, Si-CH_3), 2.12 (s, 2, -CH_2C=O), 2.43 (s, 2, -CH_2Ph), 6.7—7.6 (m, 10, Ph), 9.0 (s, 1, COOH). Found: C, 71.33; H, 6.81%. Calcd for $C_{16}H_{18}O_2Si$: C, 71.07; H, 6.71%.

(Ethylmethylphenylsilyl)acetic Acid (2). The phenylmagnesium bromide and the ethylmagnesium bromide were prepared from magnesium (3.3 g, 0.14 mol) and bromobenzene(19.2 g, 0.12 mol) in dry ether (50 ml), and from magnesium (3.3 g, 0.14mol) and bromoethane (13.3 g, 0.12 mol) in dry ether (50 ml), respectively. The phenyl Grinard reagent was added to a solution of (dichloromethylsilyl)methyl chloride[3] (20.0 g, 0.12 mol) in dry ether (30 ml). The mixture was refluxed for 4 h with stirring. Then, the ethyl Grinard reagent was added to the reaction mixture, and it was refluxed for 4 h with stirring. Saturated NH_4Cl was added to the reaction mixture with external cooling. The organic layer was separated and the aqueous layer was extracted with ether (30 ml×2). The combined organic layer was dried (Na_2SO_4). Subsequent evaporation and distillation gave (ethylmethylphenylsilyl)methyl chloride in 17.8 g (73%) yield. Bp 130—135 °C/20 Torr (1 Torr =133.322 Pa). ^{1}H NMR δ=0.37 (s, 3, Si-CH_3), 1.0—1.2 (m, 5, Et), 2.86 (s, 2, CH_2Cl), 7.1—7.6 (m, 5, Ph).

In a two-necked flask, equipped with a condeser and an additional funnel, magnesium (3.1 g, 0.13 mol) and THF (35 ml) was placed. A solution of (ethylmethylphenylsilyl) methyl chloride (17.0 g, 0.89 mol) in THF (35 ml) was added to the flask. An exothermic reaction took place. After the addition was completed, the reaction mixture was refluxed for 4 h with stirring. The reaction mixture was allowed to stand at room temperature until the chips of Dry Ice disappeared. Workup of the reaction mixture in the similar manner descrived above, and subsequent distillation gave **2** in 12.3 g (69%) yield. Bp 154—157°C/0.9 Torr. IR (neat) 2990 cm^{-1} (s, COOH), 1680 cm^{-1} (s, C=O). ^{1}H NMR δ=0.41 (s, 3, Si-CH_3), 0.94—1.0 (m, 5, Et), 2.15 (s, 2, CH_2C=O), 7.2—7.5 (m, 5, Ph), 9.6 (broad s, 1, COOH). Found: C, 63.42; H, 7.74%. Calcd for $C_{11}H_{16}O_2Si$: C, 63.30, H, 7.60%.

Another Silylacetic Acid Derivatives. All silylacetic acid derivatives listed in Table 4 were prepared in the similar manner described above. The yield and boiling points of the (alkylarylmethylsilyl)methyl chlorides are as follows; Compound; Yield(%), BP(°C/Torr): MePh(*n*-Pr)$SiCH_2Cl$; 73, 145—150/20: *n*-BuMePh$SiCH_2Cl$; 82, 130/13: BzEtMe$SiCH_2Cl$; 89, 117—119/5: BzMe(*n*-Pr)$SiCH_2Cl$; 87, 95/3: EtMe(*o*-$CH_3C_6H_4$)$SiCH_2Cl$; 72, 108/3: Me(*n*-Pr)(*o*-$CH_3C_6H_4$)$SiCH_2Cl$; 84, 106/2: EtMe(*p*-$CH_3C_6H_4$)$SiCH_2Cl$; 76, 95/3: EtMe(*o*-$CH_3OC_6H_4$)$SiCH_2Cl$; 70, 110/1: AllylMe(*o*-$CH_3C_6H_4$)$SiCH_2Cl$; 76, 120/4: Et(1-Np)Me$SiCH_2Cl$; 73, 140/3.

The yield and NMR spectra data of the silylacetic acid derivatives are as follows; Compound; Yield(%), Bp(°C/Torr): MePh(*n*-Pr)$SiCH_2COOH$; 51, -, ^{1}H NMR δ=0.40 (s, 3, Si-CH_3), 0.8—1.3 (m, 7, Pr), 2.15 (s, 2, CH_2), 7.0—7.5 (m, 5, Ph), 12.0 (broad s, 1, COOH): *n*-BuMePh$SiCH_2COOH$; 18, -, ^{1}H NMR δ=0.40 (s, 3, Si-CH_3), 0.7—1.5 (m, 9, Bu), 2.10 (s, 2, CH_2), 7.0—7.5 (m, 5, Ph), 11.0 (broad s, 1, COOH): BzEtMe$SiCH_2COOH$; 75, -, ^{1}H NMR δ=0.06 (s, 3, Si-CH_3), 0.6—1.4 (m, 5, Et), 1.80 (s, 2, CH_2C=O), 2.16 (s, 2, CH_2Ph), 6.7—7.3 (m, 5, Ph), 12.0 (broad s, 1, COOH): BzMe(*n*-Pr)$SiCH_2COOH$; 65, -, ^{1}H NMR δ=0.06 (s, 3, Si-CH_3), 0.5—1.7 (m, 7, Pr), 1.80 (s, 2, CH_2C=O), 2.16 (s, 2, CH_2Ph), 6.8—7.3 (m, 5, Ph), 11.5 (broad s, 1, COOH): EtMe(*o*-$CH_3C_6H_4$)-$SiCH_2COOH$; 71, 170/0.6, ^{1}H NMR δ=0.45 (s, 3, Si-CH_3), 0.99 (s, 5, Et), 2.15 (s, 2, CH_2), 2.45 (s, 3, CH_3), 6.9—7.5 (m, 4, Ar), 12.5 (broad s, 1, COOH); Me(*n*-Pr)(*o*-$CH_3C_6H_4$)-$SiCH_2COOH$; 38, -, ^{1}H NMR δ=0.45 (s, 3, Si-CH_3), 0.8—1.6 (m, 7, Pr), 2.10 (s, 2, CH_2), 2.45 (s, 3, CH_3), 6.9—7.5 (m, 4, Ar), 11.5 (broad s, 1, COOH): EtMe (*p*-$CH_3C_6H_4$)-$SiCH_2COOH$; 49, 155/0.3, ^{1}H NMR δ=0.40 (s, 3, Si-CH_3), 0.9—1.1 (m, 5, Et), 2.05 (s, 2, CH_2), 2.35 (s, 3, CH_3), 6.9—7.5 (m, 4, Ar), 11.5 (broad s, 1, COOH): (*o*-$CH_3OC_6H_4$)-EtMe$SiCH_2COOH$; 53, -, ^{1}H NMR δ=0.36 (s, 3, Si-CH_3), 0.95 (s, 5, Et), 2.10 (s, 2, CH_2), 3.75 (s, 3, O-CH_3), 6.5—7.5 (m, 4, Ar), 11.5 (broad s, 1, COOH): Allyl (*o*-$CH_3OC_6H_4$)-Me$SiCH_2COOH$; 19, -, ^{1}H NMR δ=0.35 (s, 3, Si-CH_3), 1.90 (d, 2, CH_2), 2.05 (s, 2, CH_2C=O), 3.74 (s, 3, O-CH_3), 4.6—5.0 (m, 2, =CH_2), 5.2—6.2 (m, 1, CH=), 6.5—7.5 (m, 4, Ar), 10.5 (broad s, 1, COOH): EtMe(1-Np)$SiCH_2COOH$; 44, -, ^{1}H NMR δ=0.59 (s, 3, Si-CH_3), 1.0—1.2 (m, 5, Et), 2.85 (s, 2, CH_2), 7.2—8.0 (m, 7, Ar), 11.5 (broad s, 1, COOH).

Optical Resolution of 1. A solution of (+)-PEA (6.6 g, 54.4 mmol) in a mixed solvent (benzene:hexane 1:4, 50 ml) was added to a solution of (±)-**1**(14.7 g, 54.4 mmol) in the same mixed solvent (100 ml). The solution was allowed to stand over night at room temperature. The salt precipitated was collected by filtration (Salt **1**, yield 18.7 g). The salt **1** was recrystallized from a mixed solvent(benzene-hexane 1:1, 120 ml)(Salt **2**, yield 5.1 g). Further twice recrystallizations were carried out by using the same solvent (Salt **3**, yield 4.4 g) (Salt **4**, yield 3.8 g, $[\alpha]_D$ +41.2° (*c* 1, MeOH)). (+)-**1** was liberated from (+)-PEA and extracted with ether (30 ml×2). The ether solution was dried over Na_2SO_4. Evaporation gave optically pure (+)-**1** in 2.6 g (17.5%) yield. Mp 68—69.5 °C. $[\alpha]_D$ +6.5°(*c* 2, $CHCl_3$).

The first and second filtrates were collected and (−)-rich **1**, was liberated from the solution. (−)-Rich **1** was treated with an equimolar amount of (−)-PEA, and subsequent four times fractional crystallization were carried out. Optically pure salt was obtained in 6.0 g (28%) yield. $[\alpha]_D$ −41.6° (*c* 1, MeOH). Subsequent liberation of the acid, extraction, and evaporation gave optically pure (−)-**1** in 4.1 g (28%) yield. Mp 69—70.5 °C. $[\alpha]_D$ −6.4° (*c* 2, $CHCl_3$).

Optical Resolution of 2. A solution of (+)-PEA in a mixed solvent (benzene-hexane 1:4, 50 ml) was added to a solution of (±)-**2** in the same solvent (100 ml). The solution was allowed to stand over night at room temperature. The precipitated crystalls were collected by filtration. Yield 20.1 g (72%). $[\alpha]_D$ +4.9° (*c* 1, MeOH). The crystalline solid was recrystallized from a mixed solvent (benzene-hexane 1:1). Yield 13.6 g (68%). $[\alpha]_D$ +6.2° (*c* 1, MeOH). It was recrysallized from the same mixed solvent (136 ml). Yield 9.1 g (71%). $[\alpha]_D$ +7.0° (*c* 1, MeOH). It was further recrystallized from the same solvent (180 ml). Yield 7.5 g (55%). $[\alpha]_D$ +7.9° (*c* 1, MeOH). Then, it was recrystallized from benzene (75 ml). Yield 5.8 g (77%). $[\alpha]_D$ +8.0° (*c* 1, MeOH). The salt was recrystallized from benzene (86 ml)

[††] 1 M=1 mol dm^{-3}.

again. Yield 4.3 g (75%). $[\alpha]_D$ +8.0° (*c* 1, MeOH). Liberation and subsequent usual work-up gave (+)-**2** in 2.7 g (14%) yield. $[\alpha]_D$ +7.9° (*c* 1, MeOH). Optical purity of this (+)-**2** was estimated as 99% by NMR method using optically pure (+)-PEA.

The enantiomer of **2**, which has oppsite sign of rotation, was recovered from the filtrates. Optically pure (−)-**2** was obtained in a similar manner described above, by several times fractional crystallization of its (−)-PEA salt from appropriate solvents.

Optically Active (Benzylmethylphenylsilyl)methylamine Hydrochloride Salt (3′). To a solution of optically active (+)-**3** (1.0 g, 4.1 mmol), $[\alpha]_D$ +12.6° (*c* 1, Et_2O) in MeOH (5 ml), 3 M HCl (5 ml) was added. The mixture was evaporated and the residue was recrystallized from a mixed solvent (benzene–hexane 2:1, 90 ml). White crystalline salt was obtained in 1.2 g (99%) yield. Mp 166.5—167 °C. $[\alpha]_D$ +45.0 ° (*c* 1, MeOH). ^{1}H NMR δ=0.50 (s, 3, Si–CH_3), 2.57 (m, 4, $SiCH_2N$, $SiCH_2Ph$), 7.0—7.5 (m, 10, Ph), 9.0 (broad s, 3, NH_3).

Optically Active (Benzylmethyl-*o*-tolylsilyl)methylamine Hydrochloride Salt(4′). To a solution of (+)-**4** (1.0 g, 3.9 mmol), $[\alpha]_D$ +4.3° (*c* 4, Et_2O) in MeOH (5 ml), 3 M HCl (5 ml) was added. The solvent was evaporated and the residue was recrystallized from benzene (50 ml). The salt of (+)-**4** was obtained in 1.0 g (89%) yield. Mp 186.5—187 °C. $[\alpha]_D$ +35.2° (*c*1, MeOH). ^{1}H NMR δ=0.55 (s, 3, Si–CH_3), 2.36 (s, 3, Ph–CH_3), 2.47—2.65 (m, 4, CH_2–N, CH_2ph), 7.0-8.0 (m, 9, Ar), 8.2 (broad s, 3, NH_3).

Preparation of the Diastereomeric Amide of (+)-1 with (±)-PEA. In a flask, equipped with a condenser, a solution of 2-chloro-1-methylpridinium iodide (56 mg, 0.22 mmol) in dry dichloromethane (0.5 ml) was placed. A mixture of (+)-**1** (51 mg, 0.19 mmol), (±)-PEA(22 mg, 0.19 mmol), and tributylamine (82 mg, 0.44 mmol) in dry dichloromethane (0.5 ml) was added to the solution. The reaction mixture was refluxed for 1 h with stirring. Subsequent evaporation and purification by TLC(benzene–ethylacetate 5:1, R_f=0.6) gave the diastereomeric amide in 57 mg (80%) yield. ^{1}H NMR δ=0.34 (two s, 3, Si–CH_3), 1.21, 1.22, 1.28, 1.29 (a pair of d, 3, CH_3), 1.96 (s, 2, CH_2C=O), 2.44 (s, 2, CH_2Ph), 4.6—5.2 (a pair of q, 1, CH), 5.12 (broad s, 1, NH), 7.0—7.5 (m, 15, Ph).

All the amides listed in Tables 2 and 4 were prepared in a similar manner described above. Most of the amides were obtained in the range from 50 to 80% yields.

Preparation of Diastereomeric Ester of (+)-2 with (±)-1-Phenylethanol. In a flask, equipped with a condenser, a solution of 2-chloro-1-methylpyridinium iodide (112 mg, 0.44 mmol) in dry dichloromethane (1 ml) was placed. A mixture of (+)-**2** (83 mg, 0.4 mmol), (±)-1-phenylethanol (49 mg, 0.4 mmol) and tributylamine (160 mg, 0.88 mmol) was added to the flask. The reaction mixture was refluxed for 3 h with stirring. Evaporation and purification by TLC (bnzene, R_f=0.5—0.6) gave the ester in 60 mg (48%) yield. ^{1}H NMR δ=0.32, 0.35 (two s, 3, Si–CH_3), 0.85—1.0 (m, 5, Et), 1.36, 1.37, 1.43, 1.45 (a pair of d, 3, CH_3), 2.15 (s, 2, CH_2), 7.0—7.5 (m, 10, Ph).

All the esters listed in Table 3 were prepared in a similar manner described above. Most of the esters were obtained in the range of 40 to 70% yields.

Preparation of Diastereomeric Amide of (+)-3 with (±)-2-(4-Methylphenyl)-3-methylbutanoic Acid. In a flask, equipped with a condenser, a solution of 2-chloro-1-methylpyridinium iodide (31 mg, 0.12 mmol) in dichloromethane (1 ml) was placed. A mixture of (benzylmethylphenylsilyl) methylamine hydrochloride (28 mg, 0.10 mmol), tributylamine (60 mg, 0.32 mmol), and (±)-2-(4-methylphenyl)-3-methylbutanoic acid (20 mg, 0.10 mmol) was added to the flask. The reaction mixture was refluxed for 1 h with stirring. Evaporation and purification by TLC (dichloromethane, R_f=0.6—0.7) gave the diastereomeric amide in 20.6 mg (50%) yield. ^{1}H NMR δ=0.16, 0.18 (two s, 3, Si–CH_3), 0.60, 0.67, 0.87, 0.94 (a pair of d, 6, CH_3). 2.30 (s, 3, Ar–CH_3), 2.35 (s, 2, Ph–CH_2), 2.1—2.4 (m, 2, CH), 2.9—3.0 (m, 2, CH_2N), 6.9—7.4 (m, 14, Ar).

All diastereomeric amides listed in Table 5 were prepared in a similar manner described above. Most of the amides were obtained in the range of 50—80% yields.

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