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Enzymatic Preparation of Optically Active Silylmethanol Derivatives Having A Stereogenic Silicon Atom by Hydrolase-catalyzed Enantioselective Esterification

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Abstract: Kinetic resolution of ethylmethylphenylsilylmethanol, a primary alcohol having a stereogenic silicon atom, was tried by hydrolase-catalyzed enantioselective reactions. Among twenty kinds of hydrolases examined, a commercial crude papain preparation was found to exhibit the highest enantioselectivity with moderate activity toward the silicon-containing alcohol on esterification with 5-phenylpentanoic acid in an organic solvent system, and the (+)-enantiomer of 92 %ee was obtained as the remaining substrate. Several silylmethanol derivatives could be also resolved by this enantioselective esterification, even though it was difficult to synthesize such chiral quaternary silanes with high optical purity by chemical methods due to the absence of leaving groups on the silicon atom. These results demonstrate that enzymes can recognize the configuration not only of carbon atoms but also of silicon atoms, and indicate the usefulness of biocatalysts for preparing optically active silanes.

INTRODUCTION

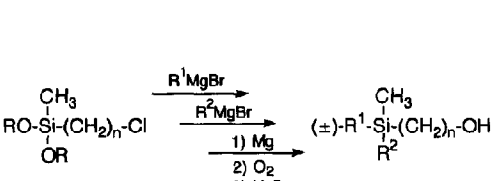
Silicon is the second most abundant element in the Earth's crust, and it is always found in combination with oxygen as silica or metal silicates. Although silicon belongs to the same group as carbon in the periodic table and has some properties similar to carbon, such as making tetrahedral sp^3-hybridized bonds, organosilicon compounds possessing silicon-carbon bonds have never been known to occur in nature. The organosilicon compounds show unique chemical and physical properties compared to conventional organic compounds due to the specific characteristics of silicon, and therefore they are used as important reagents in synthetic chemistry and in the chemical industry.[1]

We have examined the introduction of such organosilicon compounds into bioconversion systems as unconventional substrates,[2] and carried out enantioselective conversions of racemic trimethylsilylpropanols with alcohol dehydrogenase[2c-d] and hydrolases.[2e] The results demonstrated that the enzymatic systems can be promising methods for the preparation of optically active organosilicon compounds by utilizing the selectivity of biocatalysts.

In this paper, the preparation of optically active silanes having a stereogenic silicon atom with enzymes was attempted. This is important because recent interest has focused on the use of such chiral silanes[3] as new synthetic reagents,[4] biologically active compounds,[5] and their precursors. It was reported that silicon-analogues of antimuscarinic drugs having a chiral silanol structure were found to exhibit higher pharmacological activity than their corresponding carbon analogues, and that their enantiomers showed a stereoselectivity of antimuscarinic action *in vitro*.[5b-c]

We selected ethylmethylphenylsilylmethanol (**1**) and its derivatives (**2-9**), which are primary alcohols having a stereogenic silicon atom, as substrates for enzymes (Scheme 1) and tried their kinetic resolution by

enantioselective esterification and transesterification with hydrolases in an organic solvent system (Scheme 2). It is interesting to see whether enzymes can recognize the configuration of the silicon atom or not, and to investigate the behavior of enzymes toward these organosilicon compounds. Furthermore, chemical synthesis of chiral quaternary silanes having no leaving groups attached to the silicon atom with high optical purity is generally difficult, in spite of well developed chemical methods for preparing optically active organosilicons.[3] So the use of biocatalysts would provide a new useful procedure for organosilicon chemistry for the preparation of optically active silanes.



Entry	n	R	R^1	R^2
1	1	Et	Ph	Et
2	2	Me	Ph	Et
3	3	Me	Ph	Et
4	1	Et	Ph	Pr
5	1	Et	Ph	*n*-C_6H_{13}
6	1	Et	*p*-Me-Ph	Et
7	1	Et	*p*-F-Ph	Et
8	1	Et	*n*-C_6H_{13}	Et
9	1	Et	Pr	Et

Fig. 1. Preparation of racemic alcohols having a stereogenic silicon atom.

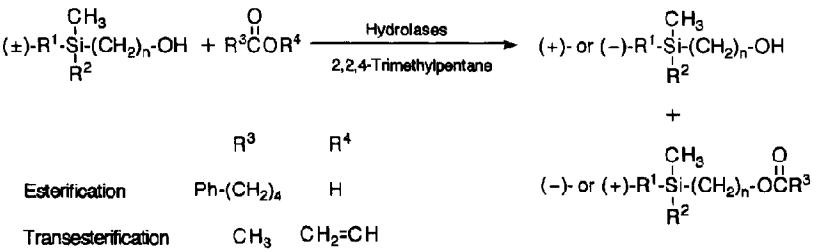


Fig. 2. Enantioselective esterification and transesterification of racemic alcohols having a stereogenic silicon atom catalyzed by hydrolases in an organic solvent system.

RESULTS AND DISCUSSION

Screening of hydrolases

Twenty kinds of commercially available hydrolases including lipases, a lipoprotein lipase, a cholesterol esterase, and proteases from various sources were examined to screen for highly active and enantioselective enzymes towards **1** on esterification with 5-phenylpentanoic acid in water-saturated 2,2,4-trimethylpentane (Table 1). Many of the hydrolases exhibited the esterification activity except for lipases from bacteria and proteases from *Bacillus* sp., but the enantiomeric excess of remaining **1**, determined by HPLC, was not very high in general. While there have been many successful reports of kinetic resolutions of racemic secondary alcohols with hydrolases,[6] the chiral recognition of primary alcohols was generally difficult for both enzymatic and chemical methods due to the lower bulkiness around the hydroxyl group compared to secondary alcohols.

Table 1. Screening of hydrolases for enantioselective esterification of ethylmethylphenylsilylmethanol (1) with 5-phenylpentanoic acid in organic solvent

Hydrolase	Source	Time (h)	Conv.[a] (%)	%ee[b]	Optical[c] activity
Lipase	*Candida antarctica*	32	12	1	
Lipase	*Candida cylindracea*	11	45	10	(+)
Lipase AY	*Candida rugosa*	45	44	0	
Lipase OF 360	*Candida cylindracea*	12	56	14	(+)
Lipase Type VII	*Candida cylindracea*	25	61	3	
Lipase A	*Aspergillus niger*	143	34	2	
Lipase CE	*Humicola langinosa*	94	60	22	(+)
Lipase Saiken 100	*Rhizopus japonicus*	25	50	47	(+)
Lipase AK	*Pseudomonas* sp.	94	2	–	
Lipase LKIP-001	*Pseudomonas* sp.	24	0	–	
Lipase PS	*Pseudomonas* sp.	94	2	–	
Lipase T-01	*Chromobacterium viscosum*	24	0	–	
Lipase(Steapsin)	Hog pancreas	15	51	23	(-)
Lipase Type II	Hog pancreas	94	46	10	(-)
Lipase Type II	Porcine pancreas	11	43	14	(-)
Lipoprotein lipase Type A	*Pseudomonas* sp.	4	48	25	(-)
Cholesterol esterase Type A	*Pseudomonas* sp.	16	54	26	(-)
Papain	*Papaya* latex	36	60	92	(+)
Subtilisin Carlsberg	*Bacillus licheniformis*	72	2	–	
Thermolysin	*Bacillus thermoproteolyticus*	72	2	–	

The reaction was carried out with 5-phenylpentanoic acid and 20 mg hydrolase adsorbed on Celite in water-saturated 2,2,4-trimethylpentane.
[a] Conversion ratio determined by GLC.
[b] %ee of the remaining alcohols determined by HPLC.
[c] Optical activity of the remaining alcohols

Table 2. Screening of hydrolases for enantioselective transesterification of 1 with vinyl acetate in organic solvent

Hydrolase	Time (h)	Conv.[a] (%)	%ee[b]	Optical[c] activity
Lipase AY	1	67	10	(-)
Lipase OF 360	2	56	4	
Lipase Type VII	2	52	0	
Lipase A	147	50	5	(+)
Lipase CE	147	44	1	
Lipase Saiken 100	168	13	1	
Lipase AK	120	50	4	
Lipase PS	48	64	6	(-)
Lipase(Steapsin)	168	28	2	
Lipase Type II	144	16	0	
Lipoprotein lipase Type A	71	46	7	(-)
Cholesterol esterase Type A	1	76	23	(-)
Papain	144	54	49	(+)
Subtilisin Carlsberg	96	3	–	
Thermolysin	96	0	–	

The reaction was carried out with vinyl acetate and 20 mg hydrolase in water-saturated 2,2,4-trimethylpentane.
[a] Conversion ratio determined by GLC.
[b] %ee of the remaining alcohols determined by HPLC.
[c] Optical activity of the remaining alcohols.

In fact, many hydrolases showed only a low enantioselectivity toward **1** despite their esterification activity. Only one enzyme, a commercial crude papain preparation, was found to exhibit a high enantioselectivity and moderate activity toward **1**, resulting in highly optically active (+)-**1** (92 %ee).

Enantioselective transesterification of **1** with vinyl acetate in water-saturated 2,2,4-trimethylpentane was also tried (Table 2). Vinyl acetate and related enol esters are very useful acyl donors because the enols produced after transesterification rapidly tautomerize to the corresponding aldehydes or ketones, thus preventing the back reactions.[7] Fifteen kinds of hydrolases were tested and thirteen hydrolases, including lipases from bacteria, exhibited transesterification activity towards **1**. However, high optical purity of remaining **1** was not obtained; 49 %ee showed by crude papain was the highest value in this series of experiments.

Thus, the enantioselective esterification with 5-phenylpentanoic acid catalyzed by crude papain was selected for further study because of the high enantioselectivity toward **1**.

Effect of chain length between the hydroxyl group and the silicon atom

The chain length between the hydroxyl group and the silicon atom was changed from **1** to 3 (**1-3**), and its effect on the activity and enantioselectivity of crude papain was investigated. It is clearly shown in Table 3 that **1** was the most reactive among the three substrates examined and that the reaction rate decreased with increasing chain length. A similar phenomenon was also observed in the case of $Me_3Si(CH_2)_nOH$ (n=1-3) which were used as acyl acceptors in lipase-catalyzed esterification.[2a] One of the factors that caused these phenomena was supposed to arise from the decreasing enhanced nucleophilicity of the hydroxyl group with increasing distance from the electropositive silicon atom.

The enantioselectivity of crude papain toward **1-3**, shown as E* values (relative rate of the fast reacting enantiomer toward the slow one)[8] in Table 3, decreased upon increasing the chain length between the hydroxyl group and the silicon atom. The enantiomeric recognition became more difficult for the enzyme with increasing the distance of the functional group from the stereogenic center in the substrates. Only a silylmethanol derivative, **1**, was recovered with high enantiomeric excess (92 %ee).

Table 3. Effect of chain length between the hydroxyl group and the silicon atom on enantioselective esterification catalyzed by crude papain preparation with 5-phenylpentanoic acid

	$EtMePhSi(CH_2)_nOH$			Alcohol		Ester		
Alcohol	n	Time (h)	Conv. (%)	%ee	$[\alpha]_D$[a]	%ee	$[\alpha]_D$[a]	E*[b]
1	1	38	58[c]	92[d]	+5.7	67[d]	-2.2	16
2	2	62	59[c]	62[e]	+1.2	43[e]	-1.1	5
3	3	186	53[f]	0[g]	0.0	0[g]	0.0	1

The reaction was carried out with 5-phenylpentanoic acid and 100 mg crude papain adsorbed on Celite in water-saturated 2,2,4-trimethylpentane.

[a] Specific rotation measured at 20 % (w/v) in $CHCl_3$.

[b] $E = \ln\{(1-c)(1-ee_s)\}/\ln\{(1-c)(1+ee_s)\}$, where c is conversion ratio and ee_s is %ee of the remaining alcohol.[8]

[c] Conversion ratio determined from %ee of the alcohols and the esters.

[d] %ee determined by HPLC.

[e] %ee determined by ^{19}F-NMR after derivatization with (*S*)-cyanofluorophenylacetic acid.[16]

[f] Conversion ratio determined by GLC.

[g] %ee estimated from the specific rotation.

The high reaction rate was incompatible with high enantioselectivity as observed with lipase-catalyzed esterification using conventional compounds as substrates,[6a, 9] but this experience is not correct in the case of unconventional substrates, organosilicon compounds.

Effect of the substituent groups attached to the silicon atom

Various silylmethanol derivatives, that is, analogues of **1** having different substituent groups instead of the phenyl or ethyl group on the silicon atom, $R^1R^2MeSiCH_2OH$ (**4-9**), were synthesized as racemic compounds and examined in the enantioselective esterification catalyzed by crude papain (Table 4). When R^1 was the phenyl group and R^2 was an *n*-alkyl group (**1**, **4**, and **5**), the reaction rate of the esterification decreased with increase in chain length of R^2 (38 h for **1**, 137 h for **4**, and 456 h for **5** until 54-58 % conversion), probably due to the increased steric hindrance at the R^2 position. Although the enantioselectivity of the enzyme towards **4** (E^*=15) was still as high as that towards **1**, the enantiomeric excesses of the alcohol and the ester were very low in the reaction of **5** (E^*=3). Compound **6**, which had a *p*-methylphenyl group instead of the phenyl group, was esterified slower, but the E^* value was a little larger than the case of **1**. These results suggested that steric hindrance around the silicon atom decreased the reaction rate, but that a difference of the bulkiness between R^1 and R^2 was necessary for crude papain to recognize the chirality of the silylmethanol derivatives.

Introduction of a fluorine atom at the *p*-position of the benzene ring (**7**) enhanced the reactivity. Due to the electron-attracting fluorine atom, the molecule would be more strongly polarized and the nucleophilicity of the oxygen atom would be increased in this case, resulting in the higher reactivity of **7** compared to **1**. This substitution increased not only the reactivity but also the enantioselectivity of the enzyme; the E^* value was 28 and the enantiomeric excess of remaining **7** reached 99 %ee. In this reaction system, **7** was the most efficiently resolved compound among the silicon-containing alcohols used here.

Table 4. Effect of substituent groups attached to the silicon atom on enantioselective esterification catalyzed by crude papain preparation with 5-phenylpentanoic acid

Alcohol	$R^1R^2MeSiCH_2OH$		Time (h)	Conv.[a] (%)	Alcohol		Ester		E^{*d}
	R^1	R^2			%ee[b]	$[\alpha]_D^c$	%ee[b]	$[\alpha]_D^c$	
1	Ph	Et	38	58	92	+5.7	67	-2.2	16
4	Ph	Pr	137	58	93	+1.6	64	-1.1	15
5	Ph	n-C_6H_{13}	456	54	34	+1.4	30	-0.7	3
6	*p*-Me-Ph	Et	72	59	97	+5.4	68	-1.6	20
7	*p*-F-Ph	Et	28	59	99	+5.5	70	-2.2	28
8	n-C_6H_{13}	Et	384	60	40[e]	+0.2	27[e]	-0.1	2
9	Pr	Et	963	24[f]	–	–	–	–	–

The reaction was carried out with 5-phenylpentanoic acid and 100 mg crude papain adsorbed on Celite in water-saturated 2,2,4-trimethylpentane.

[a] Conversion ratio determined from %ee of the alcohols and the esters.

[b] %ee determined by HPLC.

[c] Specific rotation measured at 20 % (w/v) in $CHCl_3$.

[d] $E^*=\ln\{(1-c)(1-ee_s)\}/\ln\{(1-c)(1+ee_s)\}$, where c is conversion ratio and ee_s is %ee of the remaining alcohol.[8]

[e] %ee determined by ^{19}F-NMR after derivatization with (*S*)-cyanofluorophenylacetic acid.[16]

[f] Conversion ratio determined by GLC.

Drastic decrease of the reaction rate was observed when a linear *n*-alkyl group was substituted for the phenyl group (**8** having *n*-C_6H_{13} and **9** having Pr at R^1 position). The reaction time required to achieve 60 % conversion was 384 h for **8**, that is, 10 times longer compared to **1**. In the case of **9**, the conversion ratio was only 24% after 963 h and never reached 50 % even after prolonged reaction time. Frurthermore, the enantioselectivity of crude papain toward **8** was very low (E^*=2). The aromatic ring on the silicon atom was essential to express both the high esterification activity and high enantioselectivity for the enzyme. Interaction between the aromatic ring and a binding pocket of the enzyme must play an important role in incorporation of the substrates and recognition of the chirality through the reaction.

As a result, several kinds of highly optically active silylmethanol derivatives having a stereogenic silicon atom (**1**, **4**, **6**, and **7**)[10] were successfully obtained, and other related silanes will be also resolved by using this reaction system. It is generally difficult to prepare such chiral quaternary silanes with high enantiomeric excess by chemical methods.[3a-b] Chemical kinetic resolution and asymmetric synthesis require leaving groups attached to the silicon atom, and furthermore, enantiomeric excesses attained are not high in these cases. Stereospecific substitution of optically active halogenosilanes with carbon nucleophiles is a potent method for preparing the chiral quaternary silanes, but synthesis of the chiral halogenosilanes with desired structure is very complicated.[3a-b] However, enzymatic kinetic resolution enables the convenient preparation of such chiral quaternary silanes from the racemic compounds which are easily synthesized by traditional methodology.

Recent research has developed a biologically active quaternary silane ([(1,2,4-triazol-1-yl)methyl]silane, Flusilazole) as a fungicidal agrochemical.[5c, 11] The optically active silylmethanols prepared by the crude papain-catalyzed enantioselective reaction will be applicable to the synthesis of optically active analogues of such useful quaternary organosilicon compounds.

In conclusion, this study has revealed that enzymes can recognize the configuration not only of carbon atoms but also of silicon atoms, and this fact indicates the usefulness of enzymes for preparing optically active silanes. This is the first report, in our knowledge, of the enzymatic resolution of organosilicons having a stereogenic silicon atom.

EXPERIMENTAL SECTION

Analyses. ^{1}H-NMR spectra were measured with a JEOL PMX-60 NMR spectrometer, ^{19}F-NMR spectra with a JEOL JNM-A500 NMR spectrometer, EI mass spectra with a JEOL DX-300 spectrometer, and IR spectra with a JASCO IR-810 spectrometer. GLC analyses were carried out using a Shimadzu GC-14A equipped with a flame-ionization detector, and HPLC analyses were done using a Hitachi L-6000 instrument equipped with an L-4200 UV-Vis detector. Specific rotations were determined with a JASCO DIP-140 polarimeter.

Chemicals. (Chloromethyl)diethoxymethylsilane, (2-chloroethyl)dichloromethylsilane, and (3-chloropropyl)-dimethoxymethylsilane were purchased from Petrarch Systems, Levittown, PA, USA and 5-Phenylpentanoic acid was from Aldrich, Milwaukee, WI, USA. Celite No. 535 was a product of Johns-Manville, Denver, CO, USA and 3,5-dinitrophenyl isocyanate was purchased from Sumika Chemical Analysis Service, Osaka, Japan. All other chemicals were also obtained from commercial sources.

Enzymes. The enzymes used in this study were as follows: Lipase from *Candida antarctica* (Novo Nordisk, Copenhagen, Denmark); lipases from *Candida cylindracea*, A, AK, AY, CE, and PS (Amano Seiyaku, Nagoya, Japan); lipase LKIP-001 (Kurita Kogyo, Tokyo, Japan); lipase OF 360 (Meito Sangyo, Tokyo, Japan); lipase Saiken 100 (Osaka Saikin Kenkyusho, Osaka, Japan); lipase(Steapsin) (Tokyo Kasei, Tokyo,

Japan); lipase T-01 (Toyo Jozo, Tokyo, Japan); lipase Type II, Type VII, papain, and subtilisin Carlsberg (Sigma, St.Louis, MO, USA); lipoprotein lipase Type A and cholesterol esterase Type A (Toyobo, Osaka, Japan); thermolysin (Daiwa Kasei, Osaka, Japan). These enzymes were used without further purification. Some of the enzymes were obtained from commercial sources and the others were kindly donated by several companies.

Preparation of substrates: Ethylmethylphenylsilylmethanol (1). To a solution of phenylmagnesium bromide in 150 ml dry tetrahydrofuran (THF) prepared from magnesium (2.4 g, 100 mmol) and phenyl bromide (17.3 g, 110 mmol) under an N_2 atmosphere, (chloromethyl)diethoxymethylsilane (15.5 g, 85 mmol) was added dropwise at 0 °C and stirred for 6 h. 10 % NH_4Cl (100 ml) was added slowly and the mixture was warmed to room temperature. The organic layer was separated and the aqueous layer was extracted with diethyl ether (50 ml x 3). The combined organic layer was washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated in vacuo. The residue was distilled under reduced pressure (3 mmHg) followed by the fractionation at bp 78-80 °C to give crude (chloromethyl)ethoxymethylphenylsilane as colorless oil (15.5 g, 84 %): ^{1}H-NMR (60 MHz, $CDCl_3$) δ 0.53 (s, 3H, $SiCH_3$), 1.23 (t, 3H, *J*=8 Hz, OCH_2CH_3), 3.02 (s, 2H, $SiCH_2Cl$), 3.82 (q, 2H, *J*=8 Hz, OCH_2CH_3), 7.3-7.7 (m, 5H, SiC_6H_5).

(Chloromethyl)ethoxymethylphenylsilane was added dropwise to a solution of ethylmagnesium bromide in 150 ml dry THF prepared from magnesium (3.8 g, 160 mmol) and ethyl bromide (18.5 g, 170 mmol) under an N_2 atmosphere, and the mixture was refluxed for 8 h. After cooling to room temperature, the mixture was worked up in the same procedure described above and distilled. The fractionation at bp 78-81 °C (3 mmHg) gave crude (chloromethyl)ethylmethylphenylsilane as colorless oil (13.0 g, 90 %): ^{1}H-NMR (60 MHz, $CDCl_3$) δ 0.43 (s, 3H, $SiCH_3$), 0.98 (m, 5H, SiC_2H_5), 2.98 (s, 2H, $SiCH_2Cl$), 7.2-7.6 (m, 5H, SiC_6H_5); IR (neat) 2950, 1425, 1258, 1115, 1005, 797, 695 cm^{-1}.

To a stirred mixture of magnesium (1.94 g, 80 mmol) and 100 ml dry THF, (chloromethyl)ethylmethylphenylsilane was added dropwise under an N_2 atmosphere. Ethyl bromide (0.22 g, 2 mmol) was added as an initiator, and the mixture was refluxed for 2 h and cooled to 0 °C. Dry oxygen gas was slowly introduced into the mixture[12] followed by addition of 10 % NH_4Cl (80 ml). After stirring for 1 h at room temperature, the organic layer was separated and the aqueous layer was extracted with diethyl ether (50 ml x 3). The combined organic layer was washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel 60 (No.7734, Merck, Darmstadt, FRG) (mobile phase; *n*-hexane/diethyl ether, 4:1 v/v) and distilled under reduced pressure to give **1** (bp 87-88 °C, 4 mmHg) as colorless oil (8.1 g, 69 %): ^{1}H-NMR (60 MHz, $CDCl_3$) δ 0.32 (s, 3H, $SiCH_3$), 0.8-1.0 (m, 5H, SiC_2H_5), 1.29 (s, 1H, OH), 3.53 (s, 2H, $SiCH_2OH$), 7.1-7.5 (m, 5H, SiC_6H_5); IR (neat) 3350, 2950, 2870, 1425, 1250, 1110, 1000, 815, 730, 695 cm^{-1}; MS, m/z 180 (M^+), 149, 121, 89; Anal. Calcd for $C_{10}H_{16}OSi$: C, 66.61; H, 8.94. Found: C, 66.63; H, 8.79.

The other substrates shown in Fig.1 were prepared by the same procedure. **1** and **4-9** were synthesized from chloromethyldiethoxymethylsilane, **2** from (2-chloroethyl)dimethoxymethylsilane[13], and **3** from (3-chloropropyl)dimethoxymethylsilane. Spectral data are given below.

2-(Ethylmethylphenylsilyl)ethanol (2). Bp 108-110 °C (3 mmHg); ^{1}H-NMR (60 MHz, $CDCl_3$) δ 0.28 (s, 3H, $SiCH_3$), 0.8-1.0 (m, 5H, SiC_2H_5), 1.15 (t, 2H, *J*=8 Hz, $SiCH_2CH_2OH$), 1.61 (s, 1H, OH), 3.66 (t, 2H, *J*=8 Hz, $SiCH_2CH_2OH$), 7.1-7.5 (m, 5H, SiC_6H_5)); IR (neat) 3320, 2950, 2860, 1425, 1250, 1110, 1035, 790, 730, 695 cm^{-1}; MS, m/z 176 (M^+-H_2O), 137, 121; Anal. Calcd for $C_{11}H_{18}OSi$: C, 67.98; H, 9.34. Found: C, 67.99; H, 9.14.

3-(Ethylmethylphenylsilyl)propanol (3). Bp 125-126 °C (3 mmHg); ^{1}H-NMR (60 MHz, $CDCl_3$) δ 0.26 (s, 3H, $SiCH_3$), 0.6-1.2 (m, 7H, SiC_2H_5 and $SiCH_2CH_2CH_2OH$), 1.3-1.7 (m, 2H, $SiCH_2CH_2CH_2OH$), 1.90 (s, 1H, OH), 3.46 (t, 2H, J=6 Hz, $SiCH_2CH_2CH_2OH$), 7.0-7.4 (m, 5H, SiC_6H_5); IR (neat) 3340, 2950, 2930, 2870, 1425, 1255, 1115, 1055, 1010, 785, 735, 700 cm^{-1}; MS, m/z 208 (M^+), 179, 137, 121; Anal. Calcd for $C_{12}H_{20}OSi$: C, 69.17; H, 9.67. Found: C, 69.11; H, 9.51.

Methylphenyl-n-propylsilylmethanol (4). Bp 96-98 °C (10 mmHg); ^{1}H-NMR (60 MHz, $CDCl_3$) δ 0.33 (s, 3H, $SiCH_3$), 0.9-1.7 (m, 8H, SiC_3H_7 and OH), 3.53 (s, 2H, $SiCH_2OH$), 7.1-7.6 (m, 5H, SiC_6H_5); IR (neat) 3350, 2950, 2860, 1425, 1248, 1110, 1062, 995, 820, 732, 695 cm^{-1}; MS, m/z 198 (M^+), 167, 139; Anal. Calcd for $C_{11}H_{18}OSi$: C, 67.98; H, 9.34. Found: C, 67.90; H, 9.62.

n-Hexylmethylphenylsilylmethanol (5). Bp 132-133 °C (6 mmHg); ^{1}H-NMR (60 MHz, $CDCl_3$) δ 0.31 (s, 3H, $SiCH_3$), 0.6-1.6 (m, 14H, SiC_6H_{13} and OH), 3.52 (s, 2H, $SiCH_2OH$), 7.1-7.6 (m, 5H, SiC_6H_5); IR (neat) 3335, 2950, 2918, 2850, 1428, 1250, 1113, 1000, 800, 732 698 cm^{-1}; MS, m/z 194 (M^+), 163, 135, 89; Anal. Calcd for $C_{14}H_{24}OSi$: C, 71.12; H, 10.23. Found: C, 71.19; H, 10.32.

Ethylmethyl(p-methylphenyl)silylmethanol (6). Bp 97 °C (3 mmHg); ^{1}H-NMR (60 MHz, $CDCl_3$) δ 0.30 (s, 3H, $SiCH_3$), 0.7-1.0 (m, 5H, SiC_2H_5), 1.08 (s, 1H, OH), 2.32 (s, 3H, CH_3), 3.55 (s, 2H, $SiCH_2OH$), 7.0-7.5 (m, 4H, SiC_6H_4); IR (neat) 3350, 2945, 2865, 1600, 1455, 1388, 1245, 1102, 1003, 790 cm^{-1}; MS, m/z 194 (M^+), 163, 121; Anal. Calcd for $C_{11}H_{18}OSi$: C, 67.98; H, 9.34. Found: C, 67.96; H, 9.55.

Ethyl(p-fluorophenyl)methylsilylmethanol (7). Bp 102-103 °C (3 mmHg); ^{1}H-NMR (60 MHz, $CDCl_3$) δ 0.32 (s, 3H, $SiCH_3$), 0.8-1.1 (m, 5H, SiC_2H_5), 1.23 (s, 1H, OH), 3.56 (s, 2H, $SiCH_2OH$), 6.8-7.7 (m, 4H, SiC_6H_4); IR (neat) 3350, 2948, 2865, 1582, 1495, 1228, 1158, 1100, 1003, 820 cm^{-1}; MS, m/z 236 (M^+), 205, 151, 121; Anal. Calcd for $C_{10}H_{15}OFSi$: C, 60.57; H, 7.62; F, 9.58. Found: C, 60.47; H, 7.54; F, 9.64.

Ethyl-n-hexylmethylsilylmethanol (8). Bp 94-95 °C (7 mmHg); ^{1}H-NMR (60 MHz, $CDCl_3$) δ 0.02 (s, 3H, $SiCH_3$), 0.4-1.5 (m, 19H, SiC_2H_5, SiC_6H_{13}, and OH), 3.36 (s, 2H, $SiCH_2OH$); IR(neat) 3330, 2950, 2915, 2850, 1427, 1250, 1110, 998, 800, 725, 695 cm^{-1}; MS, m/z 188 (M^+), 129, 73; Anal. Calcd for $C_{10}H_{24}OSi$: C, 63.76; H, 12.84. Found: C, 63.65; H, 12.56.

Ethylmethyl-n-propylsilylmethanol (9). Bp 154 °C; ^{1}H-NMR (60 MHz, $CDCl_3$) δ 0.03 (s, 3H, $SiCH_3$), 0.5-1.5 (m, 12H, SiC_2H_5 and SiC_3H_7), 1.77 (s, 1H, OH), 3.38 (s, 2H, $SiCH_2OH$); IR (neat) 3330, 2948, 2860, 1455, 1248, 1060, 992, 818 cm^{-1}; MS, m/z 128 (M^+-H_2O), 115, 73; Anal. Calcd for $C_7H_{18}OSi$: C, 57.47; H, 12.40. Found: C, 57.21; H, 12.39.

Adsorption of enzymes on Celite. Enzyme preparation (100 mg) suspended in 100 μl deionized water was mixed thoroughly with 250 mg Celite No. 535.

Screening of hydrolases. The reaction mixture for esterification was composed of Celite-adsorbed hydrolase (corresponding to 20 mg enzyme) and 2 ml water-saturated 2,2,4-trimethylpentane containing 100 mM (±)-**1** and 100 mM 5-phenylpentanoic acid. The reaction was carried out in 15 ml test tube at 30 °C with shaking (120 strokes·min^{-1}). The ester was quantitatively determined by GLC using a glass column (diameter 3.0 mm x 1.0 m) packed with silicon SE-30 supported on Chromosorb W AW-DMCS (Nishio Kogyo, Tokyo, Japan) (carrier gas, N_2; flow rate, 60 ml·min^{-1}). *n*-Icosane was used as the internal standard. The optical purity of the remaining alcohols after the reaction was determined with HPLC using two columns of Sumichiral OA-4600 (diameter 4.0 mm x 250 mm, Sumika Chemical Analysis Service) in series after derivatization with 3,5-dinitrophenyl isocyanate.[14] The mobile phase was *n*-hexane/2-propanol, 98:2 v/v and the flow rate was 1.0 ml·min^{-1}. The eluent was monitored at 254 nm. The enantiomeric excess (%ee) was calculated from the peak

areas of both the enantiomers.

The reaction mixture for transesterification was composed of 20 mg hydrolase (without adsorption on Celite) and 2 ml water-saturated 2,2,4-trimethylpentane containing 100 mM (±)-1 and 250 mM vinyl acetate. The ester formed and the optical purity of the remaining alcohols were determined by the same procedures described above.

Enantioselective esterification catalyzed by crude papain. Celite-adsorbed crude papain (corresponding to 100 mg enzyme) and 10 ml water-saturated 2,2,4-trimethylpentane containing 100 mM racemic alcohol shown in Fig. 1 and 100 mM 5-phenylpentanoic acid were mixed in 100 ml flask and shaken (120 strokes·min^{-1}) at 30 °C. The ester was determined by GLC as described above. The mixture was filtered off to stop the reaction at more than 50 % conversion, and the filtrate was concentrated. The ester and the alcohol were isolated by column chromatography on silica gel 60 (mobile phase; *n*-hexane/diethyl ether, 10:1 v/v for the ester and 4:1 v/v for the alcohol). Each enantiomer of **1**, **4**, **5**, **6**, and **7** was separated by HPLC as described above and the enantiomeric excesses of these alcohols and esters were determined.[15] In the cases of **2** and **9**, the enantiomeric excesses were determined with ^{19}F-NMR after derivatization with (*S*)-cyanofluorophenylacetic acid (CFPA) as reported by Takeuchi *et al.*[16] Specific rotation of the alcohols and the esters isolated was measured in $CHCl_3$ at 20 °C.

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