Thiacrown Ether Technology in Lipase-Catalyzed Reaction: Scope and Limitation for Preparing Optically Active 3-Hydroxyalkanenitriles and Application to Insect Pheromone Synthesis

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Both reaction rate and enantioselectivity in *Pseudomonas cepacia* lipase (PCL)-catalyzed hydrolysis of 3-hydroxyalkanenitrile acetates were significantly changed by the addition of catalytic amounts of thiacrown ether (1,4,8,11-tetrathiacyclotetradecane). Although the reaction rate of various nitriles was accelerated, the enantioselectivity greatly depended on the nature of the substrate. Among 10 substrates tested, thiacrown ether offered highest enantioselectivity in PCL-catalyzed hydrolysis of 1-(cyanomehtyl)propyl acetate. Forty or more times this crown ether, molarity based on the enzyme, was required to attain an acceptably high reaction rate and enantioselectivity. Applying this technology, we succeeded in synthesizing the optically pure attractant pheromone of ant *Myrmica scabrinodis* (A), (*R*)-3-octanol and its antipode of (*S*)-isomer in good overall yields.

Introduction

Lipases are the most frequently used enzymes in organic synthesis because of their stability, availability, and acceptance of a broad range of substrates.[2] The synthetic value of lipases has been well recognized because their reactions proceed efficiently and selectively under mild conditions. Since only a limited number of lipase-catalyzed reactions are applicable for practical optical resolution, several methods were recommended to improve their reaction performance:[3] optimization of reaction conditions, modification of substrate,[4] selection of nonaqueous media,[2b,5] and use of additive that regulates lipase reactivity.[6] Crown ethers are promising candidates as additives and are known to be complexing agents for several proteins.[7] Reinhoudt et al. reported that serine proteases were activated by crown ethers, especially by 18-crown-6.[8] We also found that some crown ethers had the potential to enhance both the enantioselectivity and reaction rate in the lipase-catalyzed hydrolysis of 2-cyano-1-methylethyl acetate (**1a**).[1a] In particular, 1,4,8,11-tetrathiacyclotetradecane (**4**) was confirmed as the best additive among 35 types of crown ethers and their acyclic analogues tested.[1a] To determine the scope and limitation of this thiacrown ether additive technology in lipase-catalyzed reaction for preparing optically active 3-hydroxyalkanenitriles, 10 acetates of hydroxyalkanenitriles were examined as substrates. We wish to report here that the enantioselectivity of this reaction greatly depended on the nature of the substrate when 5 mol % of thiacrown ether **4** was added. Among the tested substrates, this thiacrown ether offered the highest enantioselectivity in the lipase-catalyzed hydrolysis of 1-(cyanomethyl)propyl acetate (**1b**). We applied this technology in synthesizing the optically pure attractant pheromone of ant *Myrmica scabrinodis* (A), (*R*)-3-octanol (**5**).[9]

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Table 1. Effect of Thiacrown Ether 4 on PCL-Catalyzed Hydrolysis of 1

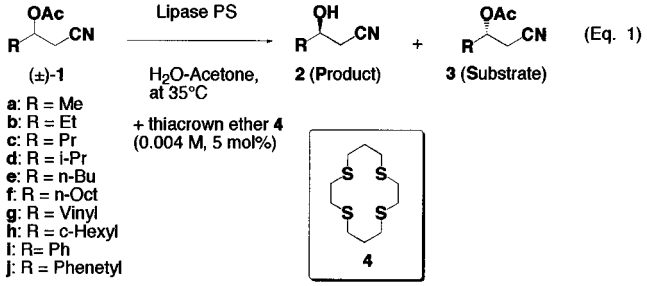
entry	substrate	R	additive (mol %)	time (h)	% ee of **2** (% yield)	% ee of **3** (% yield)	% convn[c]	rate	*E* value
1	**1a**	Me	0	60	80 (3.5)	16 (40)	38	0.6	16
2	**1a**	Me	5	14	71 (39)	99 (40)	59	4.2	37
3	**1b**	Et	0	11	90 (29)	86 (29)	49	4.5	53
4	**1b**	Et	5	8	>99 (49)	94 (35)	49	6	>700
5	**1c**	*n*-Pr	0	4.7	54 (40)	43 (41)	44	9.4	5
6	**1c**	*n*-Pr	5	4.3	67 (39)	52 (37)	44	10.2	8
7	**1d**	*i*-Pr	0	360	75 (37)	59 (42)	44	0.1	13
8	**1d**	*i*-Pr	5	168	80 (44)	62 (51)	44	0.3	17
9	**1e**	*n*-Bu	0	4.8	56 (39)	37 (49)	40	8.3	5
10	**1e**	n-Bu	5	3	39 (37)	39 (43)	50	13.9	3
11	**1f**	*n*-Oct	0	2	22 (50)	26 (29)	54	27	2
12	**1f**	*n*-Oct	5	1.8	30 (30)	20 (29)	40	27.8	2
13	**1g**	vinyl	0	5.5	69 (50)	60 (41)	47	8.5	10
14	**1g**	vinyl	5	3.5	73 (47)	67 (49)	48	14.3	13
15	**1h**	c-hexyl	0	10	97 (39)	76 (61)	44	4.4	152
16	**1h**	c-hexyl	5	12	99 (49)	82 (51)	45	3.8	501
17	**1i**	Ph	0	34.5	>99 (49)	75 (47)	43	1.3	449
18	**1i**	Ph	5	78	>99 (48)	>99 (50)	50	0.6	>1057
19	**1j**	$PhCH_2CH_2$	0	15.2	50 (49)	34 (41)	40	2.6	4
20	**1j**	$PhCH_2CH_2$	5	11	40 (42)	35 (46)	47	4.3	3

[a] Optical purity of the product shows >99% ee when no isomer was detected by GLC analysis. [b] Rate shows percent conversion per reaction time (h).

Results and Discussion

Effect of Thiacrown Ether Additive on PCL-Catalyzed Hydrolysis of Various 3-Hydroxyalkanenitriles. We chose acetates **1** as model substrates and PCL as the enzyme because 3-hydroxyalkanenitriles are employable chiral building blocks and PCL is applicable to various substrates.[10] Racemic 3-hydroxyalkanenitriles, (±)-**2**, were prepared through two different pathways, the first one being the reaction of potassium cyanide with oxiranes.[1a,11] Three types of 3-hydroxyalkanenitriles, **2a**,[1a] **2b**, and **2e**, were thus prepared in 54−74% yield.[5] This method is very convenient for preparing the corresponding 3-hydroxyalkanenitriles from oxiranes, though limited types of oxiranes are commercially available. The second method is nucleophilic addition of lithioacetonitrile to aldehydes.[4a] Seven types of acetates, **1c,d,f**−**j**, were prepared through this path, though the reaction required expensive butyllithium as a lithiation reagent and should be carried out very carefully under argon atmosphere. The alcohols obtained were converted to the corresponding acetates **1b**−**j** in almost quantitative yields by treatment with acetyl chloride in the presence of pyridine as base.

The hydrolysis of (±)-**1** was carried out in a nonbuffered aqueous solution to exclude any effect of complexation between this thiacrown ether **4** and metal cation (eq 1). When 2-cyano-1-methylethyl acetate (**1a**) was



employed as substrate, the optimum value was obtained in the presence of 5 and 33 mol % of the thiacrown ether to the substrate.[1a] Therefore, we decided to use 5 mol % of thiacrown ether toward the substrate. The reaction was typically carried out as follows: 12.5 mL of an aqueous lipase solution was added to a solution of (±)-**1** (1.25 mmol), together with a crown ether **4** additive (5 mol % toward the substrate) in 1.25 mL of acetone. The resulting mixture was stirred at 35 °C, and the reaction was stopped when the mole ratio of acetate **1** and alcohol **2** became equal. The alcohol (*R*)-**2** produced and remaining ester (*S*)-**1** were extracted with ethyl acetate and separated by silica gel TLC (hexane/ethyl acetate = 2:1). The enantiomeric excess of the remaining acetate (*S*)-**1** was determined by capillary GLC analysis using chiral stationary phase (Chiraldex G-Ta). The enantiomeric excess of alcohol (*R*)-**2** was also determined by the GLC analysis of the corresponding acetate. Because this reaction is a kinetic resolution of the racemic substrate, the optical purity of the producing alcohol and remaining acetate depends on the reaction conversion. The effect of this crown ether on enantioselectivity was evaluated by comparison of *E* values, which were calculated by the equation proposed by Sih.[12] The relative rate was calculated from the percentage conversion per reaction time. These results obtained for the reaction at 35 °C are summarized in Table 1, and Figure 1a,b.

There were marked differences of the additive effect on the enantioselectivity among the substrates employed (Figure 1a), while thiacrown ether only slightly influenced the reaction rate (Figure 1b). The most significant enhancement in enantioselectivity was observed when the reaction was carried out using 1-(cyanomethyl)propyl acetate (**1b**: R = Et) as the substrate (Table 1, entry 4). Although the hydrolysis of **1b** proceeded with modest enantioselectivity ($E = 53$) without the additive (Table 1, entry 3), the addition of 5 mol % thiacrown ether **4** to the substrate significantly enhanced enantioselectivity, reaching a higher level for practical use ($E = 700$) (Table 1, entry 4). The enantioselectivities of the reactions of **1h** and **1i** were similarly enhanced about two to three times by the addition of thiacrown **4** (Table 1, entries 15−

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(10) Weissfloch, A. N. E.; Kazlauskas, R. J. *J. Org. Chem.*, **1995**, *60*, 6959.
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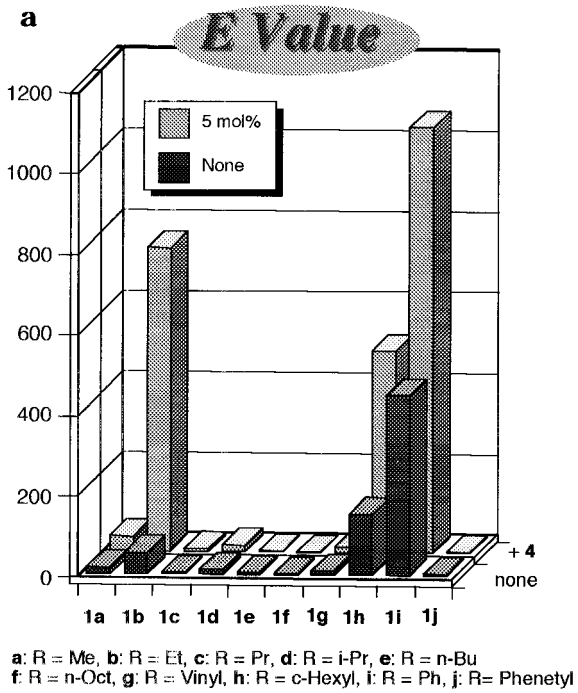


Figure 1. (a) Enantioselectivity of PCL-catalyzed hydrolysis of various acetates **1** in the presence of 5 mol % of thiacrown ether **4**. (b) Relative rate change of PCL-catalyzed hydrolysis of various acetates **1** in the presence of 5 mol % of thiacrown ether **4**.

18). On the contrary, no marked enhancement in enantioselectivity was observed when acetates **1e** (R = *n*-Bu), **1f** (R = *n*-Oct), and **1j** (R = phenethyl) were used (Table 1, entries 9−12, 19, and 20). With substrates **1a,d,g**, the enantioselectivity was slightly enhanced (Figure 1a). These results obviously suggest that this crown ether additive cannot change the original stereochemistry of the product but does enhance its potential ability to a level at which the reaction can be used practically.

Figure 2a, shows the results of the hydrolysis of acetate **1a** under different temperature conditions. The addition of only 5 mol % of thiacrown ether accelerated the hydrolysis rate of both enantiomers with a similar magnitude of increase at each temperature. It is quite interesting that the hydrolysis proceeded even at 0 °C and reached 27% conversion after 24 h in the presence of thiacrown ether **4**, though the hydrolysis conversion of 24 h reaction was only 3% in the absence of the crown ether (Figure 2a).

We performed these reactions in nonbuffered aqueous media; the reaction rate gradually lowered in the reaction course and *E* values obtained were greatly reduced at over 40% conversion.[1a] This seems to be a result of inactivation of enzyme by lower pH or a reverse reaction. Figure 3 show results of the hydrolysis of acetate (±)-**1b** in the presence and absence of thiacrown ether **4** at 35 °C; pH values of both of the solutions reached 3.4−3.5 after 20 h because the reactions were carried out under conditions of no pH control. The reaction was dramatically accelerated by the crown ether additive as shown in Figure 3. The hydrolysis did not stop after 30 h when 5 mol % of **4** was present, while the reaction stopped after 25 h in the absence of thiacrown ether **4**. It should be emphasized that the enzymatic reaction proceeded in the pH range of 3.4−3.5 in the presence of thiacrown ether **4**. Addition of thiacrown ether clearly had an impact on the lipase activity.

Why does the crown ether modify lipase performance? Crown ethers bind metal cations with varying strength depending on structural variations. The lipase solution employed was confirmed to contain the following alkali and alkaline earth metal cations: Na^+, 6.5×10^{-4} mol/L; K^+, 4.6×10^{-4} mol/L; Mg^{2+}, 6×10^{-4} mol/L; and Ca^{2+}, 6.3×10^{-4} mol/L.[1a] The amounts are believed to be too small to affect the enzyme reactivity, and it is well-known that thiacrown ether does not possess strong affinity with these alkali metal cations.[13] Some metal salts were recently reported to influence the catalytic activities of enzymes,[6c−f] but in that case crown ether−metal cation complexation may not be involved. Recently, Reinhoudt and his colleagues reported that 18-crown-6 activated some enzymes; in that case, 18-crown-6 might modify the conformation of the enzyme by trapping water molecules at the active site or the enzyme surface.[8f]

We have proposed the following mechanism for enhanced enantioselectivity by thiacrown ether additive:[1a] when lipophilic thiacrown ethers remain at the entrance of the lipase, they may modify the local conformation of the lipase; this increases fitness of the substrate introduced to the active site of the enzyme, traps the product alcohol, and accelerates the diffusion of the alcohol into the bulk water phase. ^{13}C NMR binding experiments support the possibility that thiacrown ether can trap the alcohol. When thiacrown ether **4** was added to a $CDCl_3$ solution of the product alcohols, **2b** and **2f**, large ^{13}C NMR spectral changes were observed at the carbon signals at the 3-position of both products (Figure 4), while no significant induced chemical shift change was observed for substrate **1b** or **1f** (Table 2). An induced chemical shift of nitrile carbon for **2f** was −0.24 ppm, while no significant induced chemical shift was observed for that of **2b** ($\Delta\delta$ = +0.002 ppm). These results may suggest that nitriles **2b** and **2f** interact with thiacrown ether in different fashions. Because the enzymatic reaction was performed in water, a ^{13}C NMR experiment was also carried out in D_2O. Due to the low solubility of the thiacrown ether **4** in D_2O, however, no spectral change

(13) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1991**, *91*, 1721.

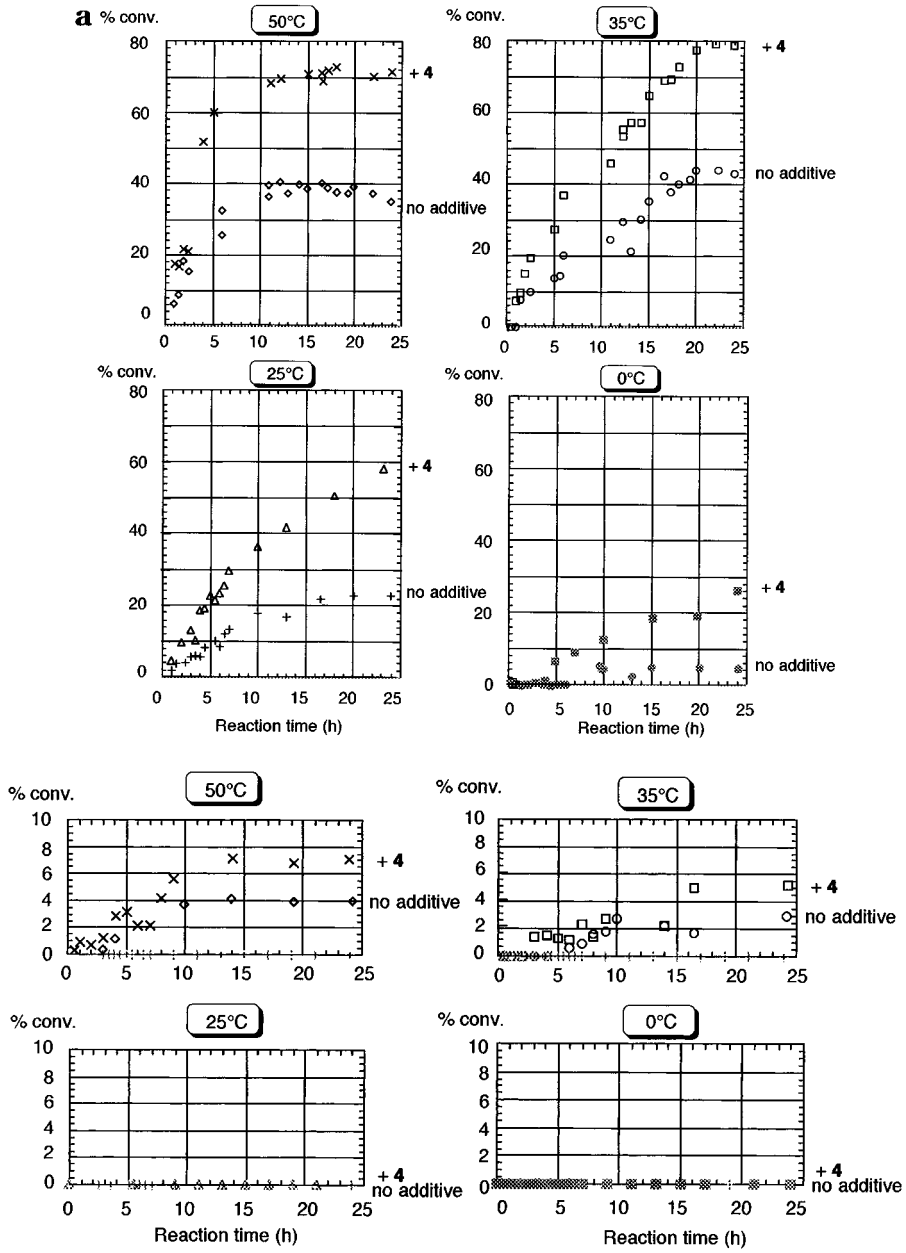


Figure 2. (a) Reaction course of the hydrolysis of (*R*)-**1a** in the presence of thiacrown ether **4**. (b) Reaction course of the hydrolysis of (*S*)-**1a** in the presence of thiacrown ether **4**.

was detected in the ^{13}C NMR signal of the monoacetate. To confirm this hypothesis, the conformational change of the enzyme by thiacrown ether should be investigated, though the change may be too small to be seen using the present analytical instrument. It has been reported that the conformational change in the protein is reflected in the CD spectra.[14] However, we have observed no significant spectral change when the CD spectra of the PCL aqueous solution were measured in the presence of 5−33 mol % of thiacrown ether **4**. Although we have not yet elucidated the mechanism of this enhancement completely, these results provided interesting application in organic synthesis, especially for the synthesis of chiral natural products.

Synthesis of an Attractant Pheromone of the Ant *M. scabrinodis*. We described above that thiacrown ether technology in the PCL-catalyzed reaction led to the highly efficient optical resolution of racemic **1b**; this provided 3-hydroxypentanenitrile **2b** in optically pure form (>99% ee). Applying this, the facile synthesis of the attractive pheromone of the ant *M. scabrinodis* (A) was accomplished using (*R*)-**2b** as a starting material (Scheme 1).

An aqueous lipase solution (100 mL, including ca. 700 mg of PCL) was added to a solution of (±)-**1b** (1.41 g, 9.99 mmol), together with thiacrown ether **4** (5 mol % toward the substrate) in 10 mL of acetone. The resulting mixture was stirred at 35 °C, and the reaction was stopped when ester and alcohol became equal-to-mole ratio by gas chromatography analysis. Alcohol (*R*)-**2b** produced and ester (*S*)-**1b** remaining were extracted with ethyl acetate and separated by silica gel flash column chromatography (hexane/ethyl acetate 2:1); this gave (*R*)-**2b** (4.94 mmol, 49%) and (*S*)-**1b** (4.55 mmol, 46%). The enantiomeric excess of these compounds was confirmed as >99% ee by GLC analysis using chiral capillary

(14) Colton, I. J.; Sharmin, N. A.; Kazlauskas, R. J. *J. Org. Chem.* **1995**, *60*, 212.

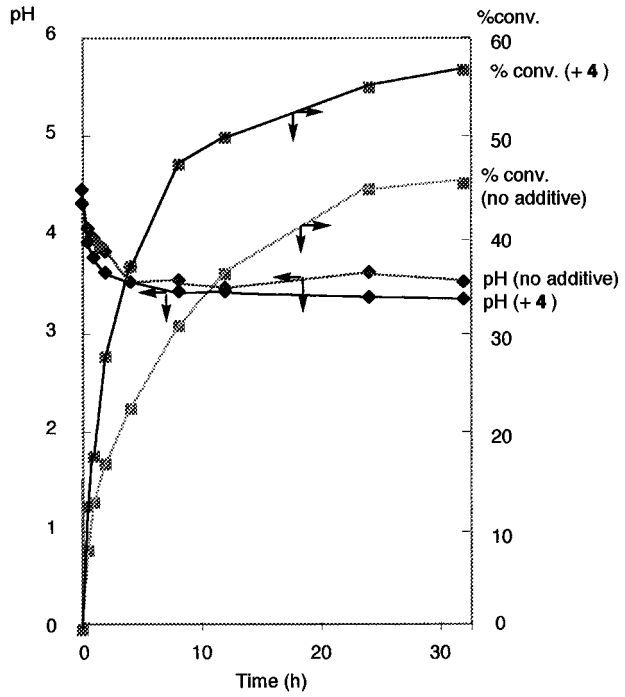


Figure 3. pH response of PCL-catalyzed hydrolysis of (±)-**1b** in the presence of 5 mol % of thiacrown ether **4**.

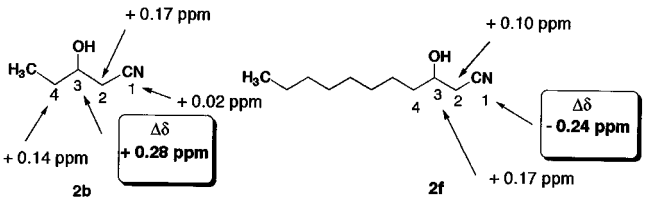


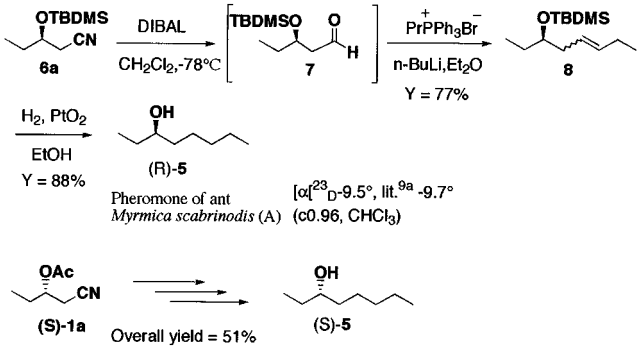
Figure 4. Induced ^{13}C NMR (50 MHz) spectral change. The values $\Delta\delta$ (ppm) mean differences in ^{13}C NMR chemical shifts in the absence and in the presence of 2.0 equiv of thiacrown ether **4** in 0.05 M $CDCl_3$.

column. (*R*)-**2b** was converted to *tert*-butyldimethylsilyl ether (*R*)-**6b** in 97% yield. Carbon elongation of (*R*)-**6b** was successfully achieved through the Wittig reaction[15] protocol; (*R*)-**6b** was treated with diisobutylalminum hydride (DIBAL) at −78 °C giving the corresponding aldehyde **7**, which was used without isolation for subsequent Wittig reaction; silyl ether (*R*)-**8** was thus obtained in 77% overall yield from (*R*)-**2b**. Finally, hydrogenation of (*R*)-**8** released the target molecule (*R*)-**5** ($[\alpha]^{23}_D$ −9.5° (*c* 0.96, $CHCl_3$), lit.[9a] [α^{23}_D −9.7°), the attractant pheromone of the ant *M. scabrinodis* (A), in 88% yield (66% overall yield from (*R*)-**2b**). The antipode of this pheromone, (*S*)-**5**, was also synthesized from (*S*)-**1b** through the same reaction sequences in 51% overall yield.

It should be emphasized that the key step of this synthesis is a pollution-free chemical reaction using a natural enzymatic system. Lipase-catalyzed reactions are particularly useful even for large-scale preparative organic synthesis. In particular, *Pseudomonas cepacia* lipase is commercially available and not very expensive; hence, the present protocol can undoubtedly allow us to evolve a smarter and more convenient synthesis of pheromone compounds.

(15) Wittig, G. *Angew. Chem.* **1956**, *68*, 505.

Scheme 1. Synthesis of the Attractant Pheromone of Ant *Myrmica scabrinodis* (A)



Experimental Section

Materials. Crown ethers were purchased from Aldrich and used without further purification. *P. cepacia* lipase was provided by Amano Pharmaceutical Co., Ltd. (Japan).

3-Hydroxypentanenitrile (2b). To a solution of 1,2-epoxybutane (10.8 g, 150 mmol) in ethanol (22 mL) under argon atmosphere at 50−60 °C was added 32% KCN aqueous solution (150 mmol, 21 mL) and 30% CH_3CO_2H aqueous solution (150 mmol, 21 mL) dropwise at the same time. The mixture was stirred for 3 h, keeping the pH value at around 7. After being cooled to room temperature, the mixture was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated. Kugelrohr distillation afforded **2b** (11.0 g, 111.0 mmol) as a colorless oil in 74% yield: R_f 0.29 (hexane/ethyl acetate 2:1); bp 145 °C/45 Torr (Kugelrohr); ^1H NMR (200 MHz, δ, $CDCl_3$, J = Hz), 0.95 (3H, t, J = 7.4), 1.59 (2H, dq, J = 7.5, 7.4), 2.51 (2H, dd, J = 17.0, 5.3), 2.90 (1H, s, OH), 3.8−3.9 (1H, m); ^{13}C NMR (50 MHz, ppm, $CDCl_3$, J = Hz) 9.56, 25.51, 29.33, 68.81, 117.87; IR (neat, cm^{-1}) 3400, 2900, 2250, 1460, 1405, 1105, 980. Anal. Calcd for C_5H_9NO: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.39; H, 9.38; N, 13.28.

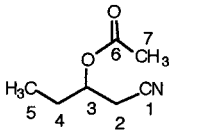
(*R*)-**2b** (>99% ee): $[\alpha]^{25}_D$ −0.8 (*c* 1.51, $CHCl_3$) (*S*)-**2b** (>99% ee): $[\alpha]^{25}_D$ +1.6 (*c* 0.66, $CHCl_3$). Using the same procedure, γ-hydroxyheptanenitrile **2e** was also prepared from the corresponding epoxide.

Caution: Potassium cyanide is very toxic so that the reaction must be carried out in a well-ventilated area.

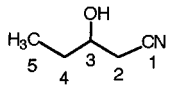
3-Hydroxyheptanenitrile (2e): R_f 0.17 (hexane/ethyl acetate 4:1); bp 160 °C/43 Torr (Kugelrohr); ^1H NMR (200 MHz, δ, $CDCl_3$, J = Hz) 0.93 (3H, t, J = 7.1), 1.36−1.59 (4H, m), 2.45 (1H, dd, J = 16.6, 6.4), 2.56 (1H, dd, J = 16.6, 4.9) 2.84 (1H, brs, OH), 3.93 (1H, dt, J = 17.4, 5.8); ^{13}C NMR(50 MHz, ppm, $CDCl_3$) 13.64, 18.51, 25.98, 38.45, 67.27, 117.83; IR (neat, cm^{-1}) 3440, 2950, 2240, 1460, 1415, 1120, 1015. Anal. Calcd for $C_7H_{13}NO$: C, 66.11; H, 10.30; N, 11.01. Found: C, 65.91; H, 10.32; N, 11.00.

3-Hydroxy-4-pentenenitrile (2 g). To a solution of diisopropylamine (3.04 g, 30.04 mmol) in THF (30 mL) under argon atmosphere at −10 °C was added a solution of *n*-BuLi in hexane (1.62 M, 17.0 mL, 27.54 mmol). The mixture was stirred at 10 °C for 1 h and cooled to −78 °C, and then a solution of CH_3CN (1.23 g, 29.96 mmol) in THF (15 mL) was added. The mixture was stirred at −78 °C for 1 h, a solution of propionaldehyde (1.40 g, 24.97 mmol) in THF (15 mL) was added, and the mixture was again stirred at −78 °C for 3 h. The reaction was quenched with saturated aqueous NH_4Cl and treated with aqueous 2 M HCl. The mixture was extracted with Et_2O, and the combined organic layers were dried over $MgSO_4$, filtered, and evaporated. The obtained yellow oily residue was purified by flash column chromatography (gradient elution hexane/ethyl acetate 8:1−4:1) to give an alcohol **2g** as a colorless oil (2.23 g, 23.0 mmol) in 92% yield: R_f 0.27 (hexane/ethyl acetate 2:1); bp 150 °C/42 Torr (Kugelrohr); ^1H NMR (200 MHz, δ, $CDCl_3$, J = Hz) 2.58 (2H, dd, J = 16.7, 5.9), 3.03 (1H, brs, OH), 4.43 (1H, dt, J = 16.4, 5.3), 5.26 (1H, dt, J = 10.4, 1.3), 5.37 (1H, dt, J = 16.4, 1.3), 5.89 (1H, ddd, J = 16.4, 10.4, 5.9); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 25.87,

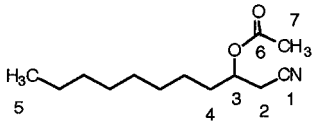
Table 2. Chemical Shift Changes of 50 MHz ^{13}C NMR Spectra (in 0.05 M $CDCl_3$) of 1b,f, and 2b,f in the Presence of Thiacrown Ether 4 (2 Mol Equiv)



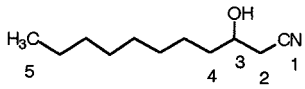
1b



2b



1f



2f

compd	amt of **4** (equiv)	C5 (ppm)	C7 (ppm)	C4 (ppm)	C2 (ppm)	C3 (ppm)	C1 (CN) (ppm)	C6 (CO) (ppm)
1b (OAc)	0.00	9.26	20.76	22.34	26.18	69.78	116.23	170.19
1b (OAc)	2.0	9.35	20.85	22.42	26.24	69.84	116.23	170.27
	$\Delta\delta$	+0.09	+0.09	+0.08	+0.06	+0.06	±0.00	+0.08
2b (OH)	0.00	9.57		25.50	29.33	68.81	117.86	
2b (OH)	2	9.61		25.64	29.50	69.09	117.88	
	$\Delta\delta$	+0.04		**+0.14**	**+0.17**	**+0.28**	+0.02	
1f (OAc)	0.00	14.02	20.85	22.81	33.08	68.66	116.29	170.24
1f (OAc)	2.0	14.02	20.88	22.84	33.11	68.69	116.27	170.26
	$\Delta\delta$	±0.00	0.03	0.03	0.03	0.03	−0.02	0.02
2f (OH)	0.00	14.01		25.31	36.44	67.64	117.79	
2f (OH)	2.0	14.03		25.32	36.54	67.81	117.55	
	$\Delta\delta$	+0.02		+0.01	**+0.10**	**+0.17**	**−0.24**	

68.34, 117.26, 68.81, 117.40, 137.21; IR (neat, cm^{-1}) 3410, 2880, 2240, 1640, 1410, 1120, 930. Anal. Calcd for C_5H_7NO: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.77; H, 7.34; N, 14.24.

Using the same procedure, hydoxyalkanenitriles **2c**−**j**were also prepared from the corresponding aldehydes.

3-Hydroxyhexanenitrile (2c): R_f 0.27 (hexane/ethyl acetate 3:1); bp 108 °C/2 Torr (Kugelrohr); ^1H NMR (200 MHz, δ, $CDCl_3$, J = Hz) 0.89 (3H, t, J = 6.9), 1.29−1.36 (4H, m), 1.51−1.58 (2H, m), 2.50 (2H, dd, J = 16.7, 4.9), 2.81 (1H, brs, OH), 3.90 (1H, m); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 13.81, 22.29, 25.95, 27.39, 36.06, 67.51, 117.86; IR (neat, cm^{-1}) 3420, 2925, 2240, 1465, 1410, 1120, 1020. Anal. Calcd for $C_6H_{11}NO$: C, 63.69; H, 9.80; N, 12.38. Found: C, 63.30; H, 9.81; N, 11.98.

3-Hydroxy-4-methylpentanenitrile (2d): R_f 0.40 (hexane/ethyl acetate 2:1); bp 115 °C/4 Torr (Kugelrohr); ^1H NMR (200 MHz, δ, $CDCl_3$, J = Hz) 0.94 (6H, t, J = 6.5, 6.3), 1.79 (1H, dq, J = 13.3, 6.7), 2.50 (1H, d, J = 3.1), 2.53 (1H, d, J = 1.4), 2.63−2.77 (1H, brs, OH), 3.63−3.71 (1H, m); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 17.24, 18.40, 23.52, 33.16, 72.42, 118.28; IR (neat, cm^{-1}) 3460, 2970, 2250, 1470, 1420, 1130, 1060. Anal. Calcd for $C_6H_{11}NO$: C, 63.69; H, 9.80; N, 12.38. Found: C, 63.81; H, 10.35; N, 12.40.

3-Hydroxyundecanenitrile (2f): R_f 0.25 (hexane/ethyl acetate 4:1); bp 150 °C/3.5 Torr (Kugelrohr); ^1H NMR (200 MHz, δ, $CDCl_3$, J = Hz) 0.86 (3H, t, J = 6.5), 1.23 (12H, s), 1.55 (2H, t, J = 6.4), 2.51 (2H, m), 2.78 (1H, brs, OH), 3.8−4.0 (1H, m); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 14.01, 22.57, 25.31, 26.01, 29.12, 29.25, 29.36, 31.74, 36.45, 67.64, 117.79; IR (neat, cm^{-1}) 3420, 2920, 2240, 1460, 1410, 1120, 1075. Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 73.91; H, 11.64; N, 7.23.

3-Hydroxy-3-cyclohexylpropanenitrile (2h): R_f 0.54 (hexane/ethyl acetate 2:1); bp 156 °C/2.8 Torr (Kugelrohr); ^1H NMR (200 MHz, δ, $CDCl_3$, J = Hz) 0.88−1.33 (4H, m), 1.37−1.58 (1H, m), 1.58−1.95 (6H, m), 2.43 (1H, s, OH), 2.48 (1H, dd, J = 16.9, 6.9), 2.58 (1H, dd, J = 16.9, 4.9), 3.62−3.71 (1H, m); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 23.51, 25.61, 25.77, 26.03, 27.77, 28.81, 42.74, 71.83, 118.24; IR (neat, cm^{-1}) 3455, 2925, 2250, 1450, 1060, 1040. Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.70; H, 10.07; N, 9.05.

3-Hydroxy-3-phenylpropanenitrile (2i):[4a] R_f 0.32 (hexane/ethyl acetate 2:1); bp 161 °C/2 Torr (Kugelrohr); ^1H NMR (200 MHz, δ, $CDCl_3$, J = Hz) 2.50−2.53 (1H, brs, OH), 2.74 (2H, d, J = 6.2), 5.02 (1H, t, J = 6.2), 7.38 (5H, s); ^{13}C NMR (50 MHz, ppm, $CDCl_3$, J = Hz) 27.88, 70.02, 117.29, 125.48, 128.78, 128.88, 140.97; IR (neat, cm^{-1}) 3440, 2900, 2250, 1500, 1450, 1060, 760, 700.

3-Hydroxy-5-phenylpentanenitrile (2j):[4a] R_f 0.29 (hexane/ethyl acetate 2:1); bp 172 °C/2.5 Torr (Kugelrohr); ^1H NMR (200 MHz, δ, $CDCl_3$, J = Hz) 1.83−1.95 (2H, m), 2.48−2.62 (3H, m), 2.65−2.82 (2H, m), 3.93 (1H, dt, J = 13.2, 5.7), 7.17−7.34 (5H, m); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 26.21, 31.52, 37.85, 66.82, 117.65, 126.17, 128.32, 128.54, 140.67; IR (neat, cm^{-1}) 3420, 2910, 2240, 1590, 1490, 1450, 1410, 1050, 750, 700.

1-(Cyanomethyl)prop-2-enyl acetate (1g). To 3-hydroxy-4-pentenenitrile (**2g**) solution (963 mg, 9.92 mmol) in CH_2Cl_2 (20 mL) and pyridine (1.0 mL) was added a CH_2Cl_2 solution (20 mL) of acetyl chloride (1.56 g, 19.9 mmol) at 0 °C, and the solution was stirred at room temperature for 3 h. The reaction was quenched by the addition of crushed ice, extracted with CH_2Cl_2, dried over $MgSO_4$, and evaporated. The crude product was purified by flash column chromatography (hexane/ethyl acetate 10:1) to provide acetate **2g** (1.24 g, 8.91 mmol) in 90% yield: R_f 0.53 (hexane/ethyl acetate 2:1); bp 155 °C/45 Torr (Kugelrohr); ^1H NMR (200 MHz, δ, $CDCl_3$, J = Hz) 0.93 (3H, t, J = 7.4), 1.6−1.9 (2H, m), 2.07 (3H, s), 2.57 (2H, dd, J = 17.2, 5.4), 2.63 (2H, dd, J = 17.2, 5.4), 4.8−5.0 (1H, m); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 9.27, 20.76, 22.34, 26.18, 69.78, 116.23; IR (neat, cm^{-1}) 2950, 2200, 2250, 1720, 1220, 1050. Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.36; H, 6.59; N, 9.91.

Using the same procedure, 1-alkyl-2-cyano acetates **1b**−**j** were also prepared from the corresponding hydoxyalkanenitriles.

1-(Cyanomethyl)propyl acetate (1b): R_f 0.53 (hexane/ethyl acetate 2:1); bp 155 °C/45 Torr (Kugelrohr); ^1H NMR (200 MHz, δ, $CDCl_3$, J = Hz) 0.93 (3H, t, J = 7.4), 1.6−1.9 (2H, m), 2.07 (3H, s), 2.57 (1H, dd, J = 17.2, 5.4), 2.63 (1H, dd, J = 17.2, 5.4), 4.8−5.0 (1H, m); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 9.27, 20.76, 22.34, 26.18, 69.78, 116.23, 170.19; IR (neat, cm^{-1}) 2950, 2200, 1720, 1220, 1050. Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 58.89; H, 8.14; N, 9.87.

(*R*)-**1b** (>99% ee): $[\alpha]^{25}_D$ +79.2 (*c* 1.765, $CHCl_3$).

(*S*)-**1b** (>99% ee): $[\alpha]^{25}_D$ −80.0 (*c* 1.050, $CHCl_3$).

Table 3. Results of GLC Analysis and $[\alpha]_D$ Values of Acetates 1

compd	R	$[\alpha]_D$ (*c* in $CHCl_3$)	GLC t_R	GLC *k*	GLC α	GLC column temp (°C)
(*R*)-**1a**	Me	$[\alpha]^{25}_D$ +48.9 (*c* 1.15), 91% ee	5.2	1.1		100
(*S*)-**1a**	Me	$[\alpha]^{25}_D$ −51.4 (*c* 1.23), 94% ee	9.4	2.8	2.5	100
(*R*)-**1b**	Et	$[\alpha]^{21}_D$ +66.0 (*c* 1.81), >99% ee	7.3	2.7		100
(*S*)-**1b**	Et	$[\alpha]^{21}_D$ −67.3 (*c* 1.76), 94% ee	11.2	4.6	1.8	100
(*R*)-**1c**	*n*-Pr	$[\alpha]^{23}_D$ +24.8 (*c* 1.26), 67% ee	10.5	4.3		100
(*S*)-**1c**	*n*-Pr	$[\alpha]^{23}_D$ −25.6 (*c* 0.90), 52% ee	15.3	6.6	1.6	100
(*R*)-**1d**	*i*-Pr	$[\alpha]^{22}_D$ −52.2 (*c* 0.76), 79 % ee	10.3	4.1		100
(*S*)-**1d**	*i*-Pr	$[\alpha]^{23}_D$ +42.7 (*c* 0.83), 62 % ee	19.0	8.5	2.1	100
(*R*)-**1e**	*n*-Bu	$[\alpha]^{16}_D$ +20.9 (*c* 0.69), 39 % ee	17.2	7.6		100
(*S*)-**1e**	*n*-Bu	$[\alpha]^{16}_D$ −17.2 (*c* 0.85), 39 % ee	25.4	11.7	1.5	100
(*R*)-**1f**	*n*-Oct	$[\alpha]^{23}_D$ +9.6 (*c* 1.62), 30 % ee	26.7	12.4		130
(*S*)-**1f**	*n*-Oct	$[\alpha]^{23}_D$ −2.3 (*c* 1.65), 20 % ee	35.1	16.5	1.3	130
(*R*)-**1g**	vinyl	$[\alpha]^{23}_D$ −8.3 (*c* 0.99), 73 % ee	6.3	2.1		100
(*S*)-**1g**	vinyl	$[\alpha]^{23}_D$ +14.2 (*c* 1.03), 67 % ee	8.3	3.2	1.5	100
(*R*)-**1h**	c-Hex	$[\alpha]^{23}_D$ −31.4 (*c* 0.52), 99 % ee	13.6	5.5		130
(*S*)-**1h**	c-Hex	$[\alpha]^{23}_D$ +33.33 (*c* 0.74), 82% ee	16.6	7.3	1.3	130
(*R*)-**1i**	Ph	$[\alpha]^{23}_D$ −67.3 (*c* 0.65), >99% ee	15.8	6.9		130
(*S*)-**1i**	Ph	$[\alpha]^{23}_D$ +72.8 (*c* 0.64), >99% ee	17.2	7.6	1.1	130
(*R*)-**1j**	$PhCH_2CH_2$	$[\alpha]^{23}_D$ −7.7 (*c* 0.81), 50% ee	16.8	7.4		150
(*S*)-**1j**	$PhCH_2CH_2$	$[\alpha]^{23}_D$ +17.9 (*c* 1.03), 34% ee	19.0	8.5	1.1	150

[a] GLC analysis for determination of % ee of (±)-**1** was carried out using a capillary column on chiral phase; Chiraldex G-TA (∅ 0.25 × 20 M).

1-(Cyanomethyl)butyl acetate (1c): R_f 0.41 (hexane/ethyl acetate 2:1); bp 172 °C/43 Torr (Kugelrohr); ^{1}H NMR (200 MHz, δ, $CDCl_3$, *J* = Hz) 0.92 (3H, t, *J* = 7.2), 1.31−1.67 (2H, m), 1.58−1.72 (2H, m), 2.06 (3H, s), 2.56 (1H, dd, *J* = 16.8, 5.4), 2.70 (1H, dd, *J* = 16.8, 5.4), 4.96 (1H, tt, *J* = 5.0, 4.9); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 13.49, 18.24, 20.78, 22.78, 35.09, 68.33, 116.27, 170.18; IR (neat, cm^{-1}) 2950, 2240, 1740, 1225, 1025. Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.21; H, 8.48; N, 8.98.

1-(Cyanomethyl)-2-methylpropyl acetate (1d): R_f 0.39 (hexane/ethyl acetate 4:1); bp 122 °C/ 3.5 Torr (Kugelrohr); ^{1}H NMR (200 MHz, δ, $CDCl_3$, *J* = Hz) 0.95 (6H, d, *J* = 6.9), 2.03 (1H, dq, *J* = 13.6, 6.8), 2.10 (3H, s), 2.59 (1H, dd, *J* = 17.1, 5.8), 2.64 (1H, dd, *J* = 17.1, 4.0), 4.74−4.83 (1H, m); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 17.68, 18.13, 20.61, 20.75, 30.85, 72.96, 116.48, 170.25; IR (neat, cm^{-1}) 2970, 2250, 1745, 1375, 1235,1030. Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.83; H, 8.54; N, 8.95.

1-(Cyanomethyl)pentyl acetate (1e): R_f 0.50 (hexane/ethyl acetate 3:1); bp 122 °C/3 Torr; ^{1}H NMR (200 MHz, δ, $CDCl_3$, *J* = Hz) 0.88 (3H, t, *J* = 6.6), 1.26−1.34 (4H, m), 1.61−1.73 (2H, m), 2.07 (3H, s), 2.56 (1H, dd, *J* = 16.9, 5.0), 2.70 (1H, dd, *J* = 16.9, 5.0) 4.95 (1H, tt, *J* = 5.4, 5.3); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 13.73, 20.81, 22.15, 22.77, 27.05, 32.75, 68.60, 116.28, 170.22; IR (neat, cm^{-1}) 2950, 2240, 1735, 1460, 1420, 1370, 1235, 1025. Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.75; H, 8.94; N, 8.28.

1-(Cyanomethyl)nonyl acetate (1f): R_f 0.50 (hexane/ethyl acetate 4:1); bp 158 °C/2.5 Torr (Kugelrohr); ^{1}H NMR (200 MHz, δ, $CDCl_3$, *J* = Hz) 0.86 (3H, t, *J* = 6.5), 1.25 (12H, s), 1.66−1.76 (2H, m), 2.08 (3H, s), 2.57 (1H, dd, *J* = 17.0, 5.2), 2.70 (1H, dd, *J* = 17.0, 5.2), 4.96 (1H, tt, *J* = 5.4, 5.3); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 14.00, 20.85, 22.54, 22.80, 29.12, 29.06, 29.24, 31.70, 33.07, 68.65, 116.28, 170.24; IR (neat, cm^{-1}) 2920, 2240, 1740, 1460, 1415, 1370, 1230, 1025. Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.19; H, 10.28; N, 6.23.

2-Cyano-1-cyclohexylethyl acetate (1h): R_f 0.48 (hexane/ethyl acetate 4:1); bp 166 °C/3.2 Torr (Kugelrohr); ^{1}H NMR (200 MHz, δ, $CDCl_3$, *J* = Hz) 0.85−1.41 (5H, m), 1.63−1.80 (6H, m), 2.10 (3H, s), 2.60 (1H, dd, *J* = 17.1, 5.7), 2.70 (1H, dd, *J* = 17.1, 5.0), 4.75−4.84 (1H, m); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 20.58, 20.77, 25.46, 25.59, 25.93, 28.15, 40.17, 72.30, 116.52, 170.30; IR (neat, cm^{-1}) 2930, 2250, 1745, 1450, 1370, 1230, 1030. Anal. Calcd for $C_{11}H_{18}NO_2$: C, 67.32; H, 9.24; N, 7.14. Found: C, 67.53; H, 9.17; N, 7.21.

2-Cyano-2-phenylethyl acetate (1i):[4a] R_f 0.59 (hexane/ethyl acetate 2:1); mp 115−117 °C; ^{1}H NMR (200 MHz, δ, $CDCl_3$, *J* = Hz) 2.15 (3H, s), 2.89 (2H, d, *J* = 5.8), 5.97 (1H, t, *J* = 6.1), 7.39 (5H, s); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 20.86, 25.49, 70.39, 115.98, 126.06, 128.89, 128.99, 137.11, 169.55; IR (neat, cm^{-1}) 2940, 2250, 1740, 1490, 1450, 1240, 1050, 760, 710.

1-(Cyanomethyl)-3-phenylpropyl acetate (1j):[4a] R_f 0.54 (hexane/ethyl acetate 2:1); bp 182 °C/2.8 Torr (Kugelrohr); ^{1}H NMR (200 MHz, δ, $CDCl_3$, *J* = Hz) 1.98−2.05 (2H, m), 2.08 (3H, s), 2.66 (4H, ddd, *J* = 31.8, 17.0, 5.1), 5.00 (1H, dt, *J* = 13.5, 5.0), 7.14−7.33 (5H, m); ^{13}C NMR (50 MHz, ppm, $CDCl_3$, *J* = Hz) 20.78, 22.90, 31.30, 34.59, 68.04, 116.12, 126.28, 128.20, 128.54, 140.04, 170.19; IR (neat, cm^{-1}) 2920, 2240, 1740, 1600, 1490, 1450, 1230, 1040, 750, 710.

Lipase-Catalyzed Hydrolysis. A typical example is described below: To an acetone solution (10 mL) of ester (±)-**1b** (1.41 g, 10.0 mmol) and thiacrown ether **4** (134 mg, 0.5 mmol) was added lipase PS aqueous solution (100 mL), and the resulting mixture was incubated at 35 °C. The progress of the reaction was monitored by GLC analysis using Quadlex MS (∅ 0.25 × 25 M). The reaction was stopped by the addition of small pieces of ice, and then the mixture was extracted with ethyl acetate, dried over $MgSO_4$, and evaporated to dryness. The product **2b** and remaining substrate (−)-**1b** were separated by silica gel TLC (hexane/ethyl acetate 2:1). The lipase solution was prepared in the following way: A boltex shaking suspension of lipase PS (705 mg) in deionized water (110 mL) was centrifuged at 3000 rpm for 5 min at room temperature, and then 100 mL of the supernatant was immediately used as the enzyme solution. GLC analysis for determination of % ee of (±)-**1b** was carried out using a capillary column on chiral phase; Chiraldex G-TA, ∅ 0.25 mm × 20 m; carrier gas, He 40 mL/min; *T* (°C) 100 or 130; inlet pressure 1.35 kg/cm^2; amount 400 ng; detection FID. The results of GLC analyses of racemic **1a**−**h** are summarized in Table 3.

The Attractive Pheromone of the Ant *M. scabrinodis* (A): (*R*)-3-Octanol (5).[9] To a solution of (*R*)-**1b** (1.03 g, 10.4 mmol, >99% ee) in dry DMF (20 mL) was added a DMF (15 mL) solution of *tert*-butyldimethylsilyl chloride (2.74 g, 19.2 mmol) and imidazole (1.23 g, 18.1 mmol) in DMF (5 mL) at 0 °C. After the mixture was stirred for 5 h at room temperature, the reaction was quenched by crushed ice and extracted with ether. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and evaporated to dryness. Silica gel column chromatography (hexanes−ethyl acetate = 10:1) gave **6b** (2.14 g, 10.06 mmol) in 97% yield as a colorless liquid. Under argon atmosphere, to a CH_2Cl_2 (10 mL) solution of **6b** (346 mg, 1.6 mmol) was added DIBAL (1.6 mmol, 1.2 mL as 1.5 M toluene solution) at −78 °C and the resulting mixture was stirred for 4 h at the same temperature. The reaction was quenched by 5 mL of water containing 1 g of SiO_2 powder. After further stirred for 15 min at room temperature, silica gel was filtered off through a sintered glass filter. The

resulting solution was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and evaporated to give aldehyde (*R*)-**7** (315 mg), which was immediately used for further Wittig reaction. To a solution of propyltriphenylphosphonium bromide (578 mg, 1. 5 mmol) in ether (5 mL) was added *n*-BuLi (1.5 mmol as 1.6 M hexane solution) at 0 °C to form an orange solution. To this mixture was added an ether (5 mL) solution of (*R*)-**7** (315 mg) at 0 °C, and the whole was stirred for 4 h at room temperature. The reaction was quenched by the addition of aqueous NH_4Cl solution and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated to give the crude oil. Silica gel flash column chromatography (hexanes/ether 20: 1) gave silyl ether (*R*)-**8** (280 mg, 1.23 mmol) in 77% yield from **6b**. Silyl ether (*R*)-**8** (114 mg, 0. 56 mmol) was hydrogenated using PtO_2 (12 mg) as catalyst under H_2 (1 atm) in ethanol (3.0 mL) at room temperature for 2 days. Silica gel flash column chromatography (hexanes/ethyl acetate 50:1−20:1) gave (*R*)-**5** (64.2 mg, 0.49 mmol) in 88% yield.

(*R*)-(*E/Z*)-6-[(*tert*-Butyldimethylsilyl)oxy]-3-octene (8): R_f 0.85 (hexane/ethyl acetate 10:1); bp 80 °C/15 Torr (Kugelrohr); $[\alpha]^{23}_D$ +16.1 (*c* 0.84, $CHCl_3$); ^{1}H NMR (200 MHz, δ, $CDCl_3$, J = Hz) 0.05 (6H, s), 0.84−1.00 (6H, m), 0.87 (9H, s), 2.03 (2H, dd, J = 14.0, 6.0) 2.17 (2H, dd, J = 12.7, 6.2), 3.60 (1H, dt, J = 11.6, 5.9), 5.38 (1H, m) 5.41 (1H, m); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 9.73, 14.24, 18.17, 20.72, 25.69, 25.93, 29.49, 34.70, 40.21, 73.58, 73.74, 125.39, 125.77, 133.03, 134.12; IR (neat, cm^{-1}) 2960, 1460, 1250, 1040, 840, 770. Anal. Calcd for $C_{14}H_{30}OSi$: C, 69.35; H, 12.47. Found: C, 69.00; H, 12.50.

(*R*)-3-Octanol (5):[9a] R_f 0.19 (hexane/ethyl acetate 10:1);bp 88 °C/30 Torr (Kugelrohr); $[\alpha]^{23}_D$ −9.5 (*c* 0.960, $CHCl_3$) (lit.[9a] $[\alpha]^{23}_D$ −9.7); ^{1}H NMR (200 MHz, δ, $CDCl_3$, J = Hz) 0.88−0.97 (6H, m), 1.16−1.50 (10H, m), 1.52 (1H, s, OH), 3.51−3.54 (1H, m); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 9.87, 14.04, 22.64, 25.33, 30.11, 31.91, 36.90, 73.34; IR (neat, cm^{-1}) 3350, 2930, 2860, 1460, 1380, 1250.

(*S*)-**5** ($[\alpha]^{23}_D$ +8.8 (*c* 0.490, $CHCl_3$)) was prepared by the procedure described above. The spectroscopic data were the same as (*R*)-**5**.

NMR Binding Experiments. ^{13}C NMR binding studies (Table 2 and Figure 4) were carried out with a Varian VXR-200 spectrometer (SC NMR Laboratory of Okayama University). The substrate was dissolved in $CDCl_3$ at a concentration of 0.05 mol/L in the presence of thiacrown ether **4**.

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Supporting Information Available: IR, ^{1}H NMR, and ^{13}C NMR spectra for **1b**−**j**, **2b**−**j**, (*R*)-**8**, and (*R*)-**5** (60 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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