Enzymatic Kinetic Resolution of [4](1,2)Ferrocenophane Derivatives

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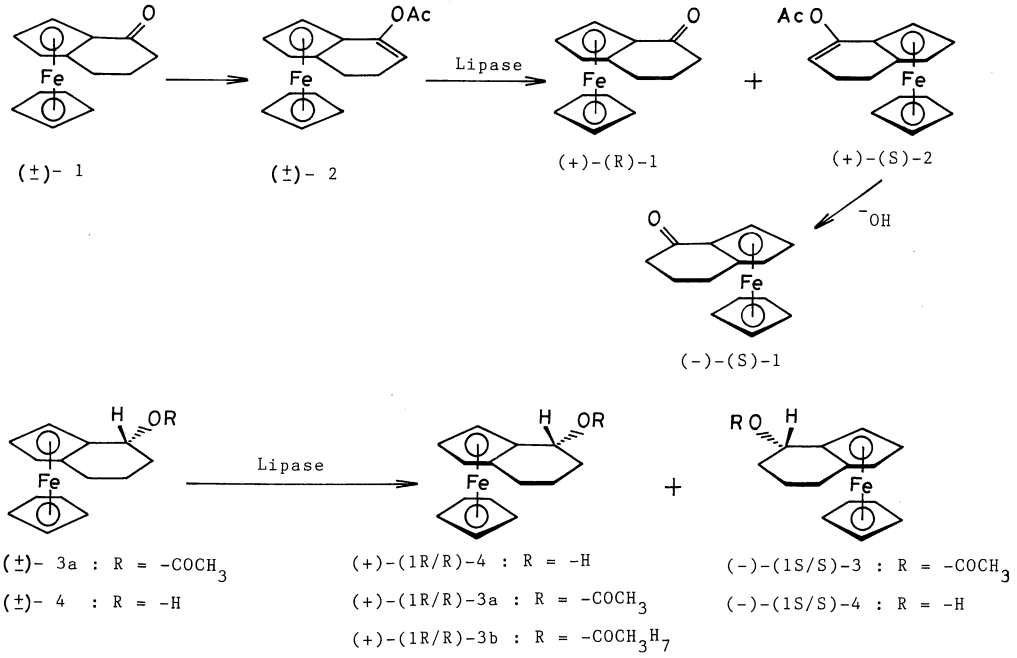
The enol acetate of (±)-[4](1,2)ferrocenophan-1-one was enantioselectively hydrolyzed by using lipase PS to afford (+)-(*R*)-[4](1,2)ferrocenophan-1-one and (+)-(*S*)-1-acetoxy[4](1,2)ferrocenophan-1-ene. By using lipase PS or lipozyme, (±)-1-acetoxy[4](1,2)ferrocenophane was resolved into the (+)-(1*R*)-alcohol and the (−)-(1*S*)-acetate. The lipase-mediated transesterification and esterification of (±)-1-hydroxy[4](1,2)ferrocenophane led to the formation of the (+)-(1*R*)-ester and the (−)-(1*S*)-alcohol.

Application of enzymes to effect selective transformations of synthetic substrates is a useful method to provide optically pure intermediates for synthesis.[1] Particularly, readily available enzymes such as baker's yeast, pig liver esterase, and porcine pancreatic lipase have been recognized as powerful synthetic tools for the preparation of optically active compounds. However, most of the previous studies were concerned with central chirality. On the other hand, enzyme-mediated asymmetric transformation of planar chiral organometallic compounds is one of the most interesting research subjects[2] in modern organic synthesis, because many such species are known to be useful chiral auxiliaries in asymmetric reactions.[3]

Previously, we reported that the enantioselective reduction of formyl[4](1,1′)ferrocenophane with bakers' yeast afforded the optically active planar chiral alcohol and aldehyde, and that the [4](1,1′)ferrocenophane units do not inhibit the penetration of substrates in the yeast cells.[4] In this paper, we wish to report the resolution of (±)-[4](1,2)ferrocenophan-1-one(**1**), (±)-1-acetoxy[4](1,2)ferrocenophane (**3a**), and (±)-1-hydroxy-[4](1,2)ferrocenophane (**4**) using lipases.

Results and Discussion

It has been shown that reduction of α-substituted ketones by an electron-withdrawing group with actively fermenting bakers' yeast (*Saccharomyces cerevisiae*) leads to the formation of the corresponding optically active alcohols in good chemical and high optical yields.[5] In the initial attempt, reduction of (±)-**1** was tried via incubation with fermenting bakers' yeast for 14 days at 30 °C. However, baker's yeast did not act on (±)-**1** and the reduction of **1** did not proceed. Matsumoto et al.[6] recently reported enantioface-differentiating hydrolysis of α-substituted ketone enol esters with the aid of a micro organism. In view of the



Scheme 1.

unique stereoselectivity of this reaction, enol acetate **2** derived from the ketone **1** was subjected to hydrolysis by commercial lipases. When enol acetate **2** was incubated with the lipase of *Pseudomonas fluorescens* (Lipase PS, Amano) in phosphate buffer (pH, 7.4), the hydrolysis proceeded rapidly to afford optically active (+)-(*R*)-**1**, of which the optical purity was not so high (ee 24%). On the other hand, the enantiomeric excess (ee) of the recovered enol acetate (+)-(*S*)-**2** was very high (ee >99%). The absolute configuration of (+)-(*S*)-**2** was definitely determined by conversion to (−)-(*S*)-**1** with alkaki hydrolysis, and the ee value was measured by ^{1}H NMR analysis using Eu(hfc)$_3$ as a chiral shift reagent.

Lipase-catalyzed hydrolysis of the racemic acetate **3** was performed in 0.2 M phosphate buffer solution at 23 °C for 20 d. The illustrative results are summarized in Table 1. *Porcine pancreatic* lipase (PPL, Sigma Type II) and *Candida cylindracea* lipase (CCL, Sigma Type VII) exhibited very low catalytic activities in the hydrolysis of (±)-acetate **3a**, and did not afford the enzymatically hydrolyzed products (Entries 3 and 4). In a mixture of hexane and toluene (2 : 1), lipase PS was also inert in the hydrolysis of (±)-**3** (Entry 1). In diisopropyl ether, however, lipase PS was active, and the substrate(±)-**3a** was hydrolyzed to (+)-(1*R*)-1-hydroxy-(*R*)-[4](1,2)ferrocenophane (+)-(1*R*/*R*)- **4** and (−)-(1*S*)-1-acetoxy-(*S*)-[4](1,2)ferrocenophane (−)-(1*S*/*S*)-**3a** (Entry 2). Among the lipases tested, lipase-MY (*Candida cylindrasea*, Meito Sangyo) in diisopropyl ether was the best, and the lipase MY-catalyzed hydrolysis of (±)-**3a** was found to be highly enantioselective, with an *E* value[7] of 400 (Entry 5). Recently, the use of enol esters such as vinyl acetate[8] and isopropenyl acetate[9] for irreversible acyl transfer has been proposed. In the presence of vinyl acetate or vinyl butyrate, the lipase-catalyzed transesterification of (±)-**4** proceeded smoothly to afford (+)-(1*R*)-1-acetoxy-(*R*)-[4](1,2)ferrocenophane (+)-(1*R*/*R*)-**3a** or (+)-(1*R*)-1-butyryloxy-(*R*)-[4](1,2)ferrocenophane (+)-(1*R*/*R*)-**3b** and (−)-

Table 1. Enzymatic Hydrolysis of the Acetate (±)-**3a**

Entry	Enzyme	Solvent[a]	Time	Conversion[b]	Product alcohol: (+)-(1*R*/*R*)-**4**[c]		Unhydrolyzed acetate: (−)-(1*S*/*S*)-**3a**[c]		*E*
			d	%	Yield/%	ee/%	Yield/%	ee/%	
1	Lipase PS	A	21	—	—	—	—	—	—
2	Lipase PS	B	21	30	6	87	49	72	20
3	PPL	B	20	—	—	—	—	—	—
4	CCL	A	20	—	—	—	—	—	—
5	Lipase MY	B	20	40	19	99	40	30	400

a) A: a mixture (20 cm^3) of hexane and toluene (2 : 1); B: diisopropyl ether (20 cm^3). b) Determined by HPLC (hexane/AcOEt). c) The ee value was determined by chiral HPLC analysis with a Daicel chiralcel OG column.

Table 2. Lipase-Catalyzed Transesterification of (±)-Alcohol **4** Using Vinyl Esters

Entry	Enzyme	Solvent[a]	Acyl donor[b]	Time	Conversion[c]	Product ester: (+)-(1*R*/*R*)-**3**[d]		Recovered alcohol: (−)-(1*S*/*S*)-**4**[d]		*E*
				d	%	Yield/%,	ee/%	Yield/%,	ee/%	
6	Lipase PS	A	E	21	25	**3a**: 15,	56	84	19	4
7	Lipase PS	B	E	21	25	**3a**: 15,	78	83	17	10
8	Lipase PS	C	E	11	44	**3a**: 46,	81	56	67	18
9	PPL	C	E	21	6	**3a**: 5,	68	94	4	6
10	CCL	C	E	20	10	**3a**: 4,	47	70	6	3
11	Lipase MY	C	E	20	6	**3a**: 5,	44	80	3	2
12	Lipozyme	B	E	21	40	**3a**: 31,	81	62	59	16
13	Lipozyme	C	E	12	40	**3a**: 30,	80	64	51	16
14	Lipase PS	D	F	1	42	**3b**: 38,	99	51	71	430
15	PPL	D	F	2	32	**3b**: 25,	80	66	37	13
16	CCL	D	F	14	20	**3b**: 19,	95	64	35	50
17	Lipase MY	D	F	13	20	**3b**: 13,	88	61	19	19
18	Lipozyme	D	F	1	22	**3b**: 86,	73	24	17	18

a) A: diisopropyl ether (20 cm^3); B: a mixture (20 cm^3) of hexane and toluene (2 : 1); C: a mixture (20 cm^3) of hexane and toluene (2 : 1) in the presence of 4-A molecular sieve powder (400 mg); D: diisopropyl ether (20 cm^3) in the presence of 4-A molecular sieve powder (400 mg). b) E: vinyl acetate; F: vinyl butyrate. c) Determined by HPLC (benzene/AcOEt). d) **3a**: (+)-(1*R*)-1-acetoxy-(*R*)-[4](1,2)ferrocenophane (+)-(1R/*R*)-**3a**; 3b: (+)-(1*R*)-1-butyryloxy-(*R*)-[4](1,2)ferrocenophane (+)-(1*R*/*R*)-**3b**; (−)-(1*S*/*S*)-**4**: (−)-(1*S*)-1-hydroxy-(*S*)-[4](1,2)ferrocenophane. The ee values of (+)-(1*R*/*R*)-**3a**, (+)-(1*R*/*R*)-**3b**, and (−)-(1*S*/*S*)-**4** were determined by chiral HPLC analysis with a Daicel OG column.

Table 3. Lipase-Catalyzed Esterification of (±)-Alcohol **4** Using Butyric Anhydride

Entry	Enzyme	Solvent[a]	Time	Conversion[b]	Product butyrate: (+)-(1*R*/*R*)-**3b**[c]		Recovered alcohol: (−)-(1*S*/*S*)-**4**[c]		*E*
			d	%	Yield/%	ee/%	Yield/%	ee/%	
19	Lipase PS	A	4	47	47	99	48	94	580
20	PPL	A	21	23	23	90	57	31	25
21	CCL	A	21	39	39	94	54	80	60
22	Lipase MY	A	21	30	30	91	70	57	30

a) A: diisopropyl ether (20 cm³). b) Determined by HPLC (benzene/AcOEt). c) The ee value was determined by chiral HPLC analysis with a Daicel chiralcel OG column.

(1S)-1-hydroxy-(S)-[4](1,2)ferrocenophane (−)-(1*S*/*S*)-**4**. The absolute configuration of (+)-(1*R*/*R*)-**3b** was established by comparison of the optical rotation with the literature data, after hydrolysis to the corresponding alcohol (+)-(1*R*/*R*)-**4**.[10] The ee values of the acetate (+)-(1*R*/*R*)-**3a**, butyrate (+)-(1*R*/*R*)-**3b**, and alcohol (−)-(1*S*/*S*)-**4** were determined by chiral HPLC analysis with a chiralcel column. The results are summarized in Table 2.

The transesterification of (±)-**4** by lipase PS proceeded with low degrees of enantioselectivity, with *E* values ranging from 4 to 10 (Entries 6 and 7). However, the addition of molecular sieves had a dramatic effect on the reaction rate. In the lipase PS-catalyzed reaction of (±)-**4** in the presence of molecular sieves, the enantioselectivity was not significantly different compared with that in the absence of molecular sieves, however, the reaction rate was about two times faster (Entry 8). The rate for the lipozyme-catalyzed reaction of (±)-**4** was also about two times faster than that with no molecular sieves (Entries 11 and 12). The effect can be explained on the basis of molecular sieves adsorbing the acetaldehyde that is released in the reaction.[8,11]

$$\mathbf{4} + CH_2{=}CH{-}OAcyl \longrightarrow \mathbf{4}\text{-}OAcyl + CH_3CHO$$

The enzymatic transesterification of (±)-**4** using other lipases, therefore, was performed with the addition of molecular sieve powder. As shown in Table 2, in the lipase PS- and CCL-mediated reactions of (±)-**4**, the order of the effect of the acyl donors on the enantioselectivity was found to be vinyl butyrate>vinyl acetate (Entries 8, 14, and 10, 16). In all tested lipase-catalyzed reactions using vinyl butyrate as an acyl donor, the rate of esterification was about 2—10 times faster than that using vinyl acetate. The same phenomena were reported by Wang et al.,[12] Sonnet,[13] and Sih et al.[14] The lipase PS-catalyzed reaction using vinyl butyrate in diisopropyl ether provided the most high enantioselectivity products (Entry 14).

Recently, Bianchi et al.[15] proposed the use of acid anhydrides as acylation agents for lipase-catalyzed esterification of racemic alcohols, in which the reaction rates are higher than those obtained in the equivalent esterification or transesterification processes.

The resolition of (±)-**4** was accomplished by lipase-catalyzed acylation using butyric anhydride as shown in Table 3. The acylation of (±)-**4** was efficiently accomplished with a stoichiometric amount of butyric anhydride in dry diisopropyl ether, and it was always found that the enzyme preferentially utilized the (+)-(1*R*/*R*)-form; consequently, at the end of the reaction, the unesterified alcohol was enriched in the (−)-(1*S*/*S*) form. Except for the reaction using lipase PS, the reaction rates of asymmetric acylation were not significantly different, compared with those of the transesterification of (±)-**4** using vinyl butyrate. However, enzymatic acylation with butyric anhydride afforded products with greater ee values than those of the transesterification using vinyl ester (Enries 20, 21, and 22). As shown in Table 3, the fastest rate and the highest ee ($E > 580$) were observed when lipase PS was used as the enzyme (Entry 19).

Experimental

All melting points were taken with a Gallenkamp melting point apparatus and uncorrected. IR spectra were recorded on Hitachi 260-10 spectrometer, and ^{1}H NMR spectra were obtained with a Hitachi R-90H spectrometer, using TMS as an internal standard. Mass spectra were run on a Hitachi RMU-6M mass spectrometer. Optical rotations were measured on a JASCO DIP-140 digital polarimeter.

1-[4](1,2)Ferrocenophan-1-one (**1**), 1-acetoxy[4](1,2)ferrocenophane (**3a**), and 1-hydroxy[4](1,2)ferrocenophane (**4**) were prepared by methods described in the literature,[16] and the endo-form was used as substrate.

Porcine pancreatic lipase (Type II, PPL) and *Candida Cyclindracea* lipase (Type VII, 700—1500 μ/mg, CCL) were obtained from Sigma Chemical Co.; *Pseudomonas fluorescens* lipase (Lipase PS), lipase from *Candida cyclindracea* (Lipase MY, 52000 μ/mg) and immobilized lipase from *Mucor sp.* (Lipozyme) were purchased from Amano Pharmaceutical Co., Meito Sangyo Co., and Novo Industry, respectively.

Preparation of 1-Acetoxy[4](1,2)ferrocenophan-1-ene (2). A mixture of **1** (3.0 g, 11.8 mmol), isopropenyl acetate (6.9 ml, 62.6 mmol), and *p*-toluenesulfonic acid (0.17 g, 1.0 mmol) was refluxed for 24 h under a nitrogen atmosphere. After benzene (200 ml) was added to the reaction mixture, the benzene solution was washed successively with water, a saturated sodium hydrogencarbonate solution, and water. The benzene extracts were dried over $MgSO_4$ and evaporated to dryness under reduced pressure. The residue was recrystallized from ethanol and afforded reddish crystals of **2** (2.1 g,

65%), mp 68—69 °C; IR (KBr) 3090, 1745 (C=O), 1650, 1210, 1105, and 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.16 (3H, s, -COC$\underline{H}_3$), 2.22—2.65 (4H, m, -C$\underline{H}_2$-), 4.06 (3H, br-s, Fc-$\underline{H}$), 4.12 (5H, s, Fc-$\underline{H}$), and 5.37 (1H, t, -C=C-$\underline{H}$); MS (70 eV) m/z 296 [M^+].

Found: C, 64.96; H, 5.58%. Calcd for $C_{16}H_{16}FeO_2$: C, 64.89; H, 5.44%, M, 296.

Enzymatic Hydrolysis of Enol Acetate 2 Using Lipase PS. Potassium dihydrogenphosphate buffer (0.2 M, pH 7.4, 7.0 ml, 1 M=1 moldm^{-3}), 2 wt % aqueous poly(vinylalcohol) solution (7.5 ml), and lipase PS (900 mg) were added successively to a solution of enole acetate **2** (300 mg, 1.0 mmol) in ethanol (1.2 ml) and diisopropyl ether (15 ml). The mixture was stirred vigorously at 23 °C and the conversion was monitored by TLC analysis (silica gel, benzene). When the appropriate degree of conversion was accomplished (9 h), the reaction was stopped by addition of a mixture of benzene and acetone (1 : 1, 500 ml). The enzyme was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The residue was chromatographed rapidly on silica gel (benzene) to give reddish crystals of (+)-(*S*)-1-acetoxy-[4](1,2)ferrocenophan-2-ene [(+)-(*S*)-**2**] (61.2 mg, 20%), and reddish yellow crystals of(+)-(*R*)-[4](1,2)ferrocenophan-1-one [(+)-(*R*)-**1**] (182.8 mg, 71%). Spectroscopic and analytical data of the products were as follows:

(+)-(*S*)-**2**: Mp 68—70 °C; $[\alpha]_D^{20}$ +988° (*c* 0.52, EtOH); the IR and ^1H NMR analyses were in good agreement with the racemic enol acetate **2**.

Found: C, 64.86 H, 5.51%. Calcd for $C_{16}H_{16}FeO_2$: C, 64.89; H, 5.49%.

The absolute configuration of (+)-(*S*)-**2** was secured by conversion into the known (−)-(*S*)-[4](1,2)ferrocenophan-1-one (−)-(*S*)- **1** [mp 77—79 °C, $[\alpha]_D^{20}$ −578° (*c* 0.06, EtOH), lit,[17] $[\alpha]_D$ −580°, EtOH] by hydrolysis with 0.1 M sodium hydroxide solution, and the ee value (99%) of (+)-(*S*)-**2** was measured by ^1H NMR analysis in the presence of Eu(tfc)$_3$ as a chiral shift reagent.

(+)-(*R*)-**1**: Mp 78—81 °C, $[\alpha]_D^{20}$ +141.5° (*c* 0.05, EtOH); IR (KBr) 3050, 1100, 1000, 815 (ferrocene ring), and 1660 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ=1.80—3.00 (m, 6H, -C$\underline{H}_2$-), 4.15 (s, 5H, Fc-$\underline{H}$), 4.43 (d, 2H, Fc-$\underline{H}$), and 4.57 (t, 1H, Fc-$\underline{H}$); MS (70 eV) m/z 254 [M^+].

Found: C, 65.92 H, 5.48%. Calcd for $C_{14}H_{14}FeO_2$: C, 66.17; H, 5.55%; M, 254.

The absolute configuration was established by comparison of the optical rotation of (+)-(*R*)-**1** with literature data ($[\alpha]_D$ +580 °, EtOH; mp 78—80 °C).[18] The ee value (24%) was determined by chiral HPLC analysis with a Daicel chiralcel OG column.

Alkaline Hydrolysis of Enol Ester (+)-(*S*)-2. The enol acetate, (+)-(*S*)-**2** ($[\alpha]_D^{20}$ +988°, 61.2 mg), was dissolved in a 0.1 M solution of sodium hydroxide in a mixture (50 ml) of methanol and water (1 : 1). After stirring for 1 h at 70 °C, the reaction mixture was evaporated under reduced pressure and benzene (80 ml) was added. The benzene layers were washed with water, dried with $MgSO_4$, and evaporated to dryness. Column chromatography on silica gel with benzene as eluant afforded (−)-(*S*)-**1**, reddish yellow crystals, mp 76—79 °C, $[\alpha]_D^{20}$ −578.7° (*c* 0.06, EtOH) (lit,[17] $[\alpha]$ −580°). ^1H NMR and IR analyses were in good agreement with racemic **1**, and the ee value of (−)-(*S*)-**1** was determined by chiral HPLC analysis with a Daicel chiralcel OG column.

Enzymatic Resolution of the Acetate (±)-3a: General Procedure. Potassium dihydrogemophosphate buffer (0.2 M, pH 7.4, 7.0 ml), 2 wt% aqueous poly(vinyl alcohol) solution (7.5 ml) and lipase (800 mg) were added successively to a solution of the acetate (±)-**3a** (300 mg, 1.0 mmol) in ethanol (1.2 ml) and the solvent (15 ml). The mixture was stirred vigorously at 23 °C, and the conversion was monitored by TLC analysis (alumina, benzene). The reaction was stopped at approximately 50% conversion by addition of a mixture of benzene and acetone (1 : 1, 500 ml). The enzyme and poly(vinyl alcohol) were removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The residue was chromatographed on deactivated alumina with benzene as eluant to afford (−)-(1*S*/*S*)-**3a** and (+)-(1*R*/*R*)-**4**.

Spectroscopic and analytical data of the products were as follows:

(−)-(1*S*/*S*)-**3a** (ee 72%, Entry 2): Reddish yellow oil; $[\alpha]_D^{20}$ −216.8° (*c* 0.68, EtOH); IR (neat film): 3080, 1100, 1000, 820 (ferrocene ring), and 1710 cm^{-1} (ester); ^1H NMR ($CDCl_3$) δ=1.20—2.82 (m, 6H, -C$\underline{H}_2$-), 2.10 (s, 3H, -COC$\underline{H}_3$-), 4.03 (s, 5H, Fc-$\underline{H}$), 4.08 (br-s, 3H, Fc-$\underline{H}$), and 5.44 (t, 1H, -C$\underline{H}$-O-); MS (70 eV) m/z 298.

Found: C, 64.36; H, 5.87%. Calcd for $C_{16}H_{18}FeO_2$: C, 64.45; H, 6.08%.

The absolute configuration was assigned after conversion into the known alcohol (−)-(1*S*/*S*)-**4** ($[\alpha]_D^{20}$ −30.7°, EtOH, lit,[10] $[\alpha]_D$ −43°) by hydrolysis, and the ee value was measured by chiral HPLC analysis with a Daicel chiralcel OG column.

(+)-(1*R*/*R*)-**4** (ee>99%, Entry 5); Reddish yellow oil; $[\alpha]_D^{20}$ +42.9° (*c* 0.66, EtOH) (lit,[10] $[\alpha]_D$ +43°); IR (neat film) 3440 (-OH), 3090, 1105, 1000, and 815 cm^{-1} (ferrocene ring); ^1H NMR ($CDCl_3$) δ=1.06—2.80 (m, 3H, -C$\underline{H}_2$-+-C$\underline{H}$-) and 3.90—4.60 (m, 9H, Fc-$\underline{H}$+-O$\underline{H}$); MS m/z 298 [M^+].

Found: C, 65.52; H, 6.20%. Calcd for $C_{14}H_{16}FeO$: C, 65.65; H, 6.29%.

The ee value was determined by chiral HPLC analysis with a Daicel chiralcel OG column. The results are summarized in Table 1.

Stereoselective Acylation of the Alcohol (±)-4 with Enol Ester: General Procedure. The alcohol (±)-**4** (410 mg, 1.6 mmol) was dissolved in dry solvent (20 ml). Lipase (800 mg) and vinyl acetate (0.20 ml, 2.2 mmol) or vinyl butyrate (0.27 ml, 2.2 mmol) were added successively to the solution. The mixture was stirred vigorously at 23 °C, and the conversion was monitored by TLC analysis (alumina, benzene). The reaction was stopped at approximately 50% conversion by filtration of the enzyme, and the filtrate was evaporated to dryness under reduced pressure. The ester (+)-(1*R*/*R*)-**3a** or (+)-(1*R*/*R*)-**3b** and the unesterified alcohol (−)-(1*S*/*S*)-**4** were separated by column chromatography on deactivated alumina with benzene as eluent. The results are given in Table 2.

Spectroscopic and analytical data of the products were as follows:

(+)-(1*R*/*R*)-**3a** (ee 80%, Entry 13); Reddish yellow oil; $[\alpha]_D^{20}$ +298.2° (*c* 1.38, EtOH), (lit, $[\alpha]_D$ +330°); ^1H NMR and IR analyses were in good agreement with the racemic acetate (±)-**3a**. The ee value was measured by chiral HPLC analysis with a Daicel chiralcel OG column.

(+)-(1*R*/*R*)-**3b** (ee 99%, Entry 14): Reddish yellow oil, $[\alpha]_D^{20}$ +271.9° (*c* 0.78, EtOH); IR (neat film) 3090, 1105, 1005, 820 (Fc ring), and 1730 cm^{-1} (ester); ^1H NMR ($CDCl_3$) δ=1.02 (t, 3H, -C$\underline{H}_3$), 1.40—2.85 (m, 8H, -C$\underline{H}_2$-), 2.38 (t, 2H, -C$\underline{H}_2$-CO-), 3.99 (br-s, 3H, Fc-$\underline{H}$), 4.08 (s, 5H, Fc-$\underline{H}$), and 5.47 (t, 1H, -C$\underline{H}$-O-); MS (70 eV) m/z 326 [M^+].

Found C, 66.11; H, 6.72%. Calcd for $C_{18}H_{22}FeO_2$: C, 66.23; H, 6.79%; M, 326.

The absolute configuration of (+)-(1*R*/*R*)-**3b** was determined after hydrolysis with alkali to the corresponding alcohol (+)-(1*R*/*R*)-**4**, and the ee value was determined by chiral HPLC analysis with a Daicel chiralcel OG column.

(−)-(1*S*/*S*)-**4** (ee 71%, Entry 14): Reddish yellow oil, $[\alpha]_D^{20}$ −30.7° (*c* 0.81, EtOH), (lit,[10] $[\alpha]_D$ −43°). ^{1}H NMR and IR analyses were in good agreement with the racemic acetate (±)-**4**.

Found: C, 65.58; H, 6.18%. Calcd for $C_{14}H_{16}FeO$: C, 65.65; H, 6.29%.

The ee value of (−)-(1*S*/*S*)-**4** was determined by chiral HPLC analysis with a Daicel chiralcel OG column.

Alkali Hydrolysis of Butyrate (+)-(1*R*/*R*)-3b. Optically active butyrate (+)-(1*R*/*R*)-**3b**, $[\alpha]_D^{20}$ +271.9° (*c* 0.78, EtOH), (420 mg) was dissolved in a 1 M solution of sodium hydroxide in absolute ethanol (20 ml). The solution was stirred for 5 h at 30 °C. The solvent was then evaporated under reduced pressure. Column chromatography on deactivated alumina with benzene as eluent afforded (+)-(1*R*/*R*)-**4**, $[\alpha]_D^{20}$ +42.8° (*c* 0.24, FtOH) (280 mg, 85%), (lit,[10] $[\alpha]_D$ +43°). The ee value (99%) was determined by chiral HPLC analysis with a Daicel chiralcel OG column.

Stereoselective Butylation of (±)-4 with Butyric Anhydride: General Procedure. Lipase (800 mg) was added to a solution of (±)-**4** (400 mg, 1.56 mmol) and butyric anhydride (0.24 ml, 1.57 mmol) in dry diisopropyl ether (209 ml). The reaction mixture was stirred at 23 °C and the conversion was monitored by TLC analysis (alumina, benzene). The reaction was stopped at 50% conversion by filtration of the enzyme, and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in chloroform (80 ml) and the chloroform layer was washed with 5% aqueous sodium carbonate solution (20 ml), dried over anhydrous magnesium sulfate and evaporated to dryness. Chromatography on deactivated alumina with benzene as eluent afforded (+)-(1*R*)-1-butyryloxy-(*R*)-[4](1,2)ferrocenophane (+)-(1*R*/*R*)-**3b** and (−)-(1*S*)-1-hydrnxy-(*S*)-[4](1,2)ferrocenophane (−)-(1*S*/*S*)-**4**. To determine the absolute configuration, (+)-(1*R*/*R*)-**3b** was transformed to (−)-(1*R*/*R*)-**4** by hydrolysis with 1 M sodium hydroxide. The results are summarized in Table 3.

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