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Lipase-catalyzed kinetic resolution of ethyl 3-aryl-3-hydroxypropionate: preparation of the side chain of a novel carbapenem, J-114,870

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Abstract

An optically active 3-aryl-3-hydroxypropionate **3a** was prepared by lipase-catalyzed kinetic hydrolysis of a diastereomeric mixture of 3-aryl-3-(α-chloroacetoxy)propionate **6** in good conversion yield with adequate purity (>95% de). This enzymatic reaction proceeded with great efficiency as measured by reaction rate, chemical yield and stereoselectivity. The compound **3a** was converted to J-114,870 **1a**, a novel ultra-broad spectrum carbapenem, without significant epimerization.

1. Introduction

In the course of investigating new carbapenems, we synthesized J-114,870 **1a** which possesses a unique *trans*-3,5-disubstituted pyrrolidin-3-ylthio side-chain at the C-2 position of the 1β-methylcarbapenem[1] nucleus, and found that this novel carbapenem had an ultra-broad antimicrobial spectrum covering clinically important strains such as methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*.[2] Using (2*R*,4*R*)-4-hydroxy-2-phenylpyrrolidine derivative **4** as a precursor,[3] the side chain of J-114,870 was synthesized using lipase as a biocatalyst, or by chemical asymmetric synthesis.[4]

Biocatalysts have often played an important role in the preparation of homochiral compounds that are not obtained easily by conventional chemical reactions. In particular, lipase[5] has been applied to many transformations such as kinetic resolution of racemic compounds[6] and asymmetric synthesis of chiral 1,3-propanediols[7] because of its wide susceptibility of substrates, stability under various conditions, and commercial availability. Enzymatic resolution of a diastereomeric mixture of ethyl 3-aryl-3-hydroxy propionate **3** was considered to be a practical method for preparing homochiral thiol **2a**, a side chain of J-114,870 **1a** (Fig. 1). Herein, we describe in detail the lipase-mediated resolution of a diastereomeric mixture of 3-aryl-3-hydroxypropionate **3** and the following transformation to a side chain of J-114,870.

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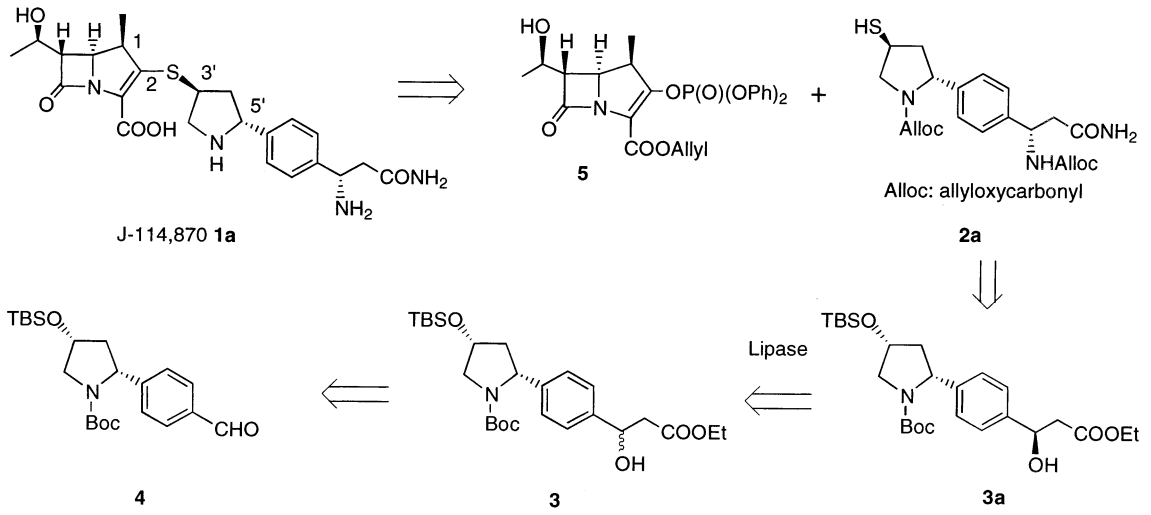
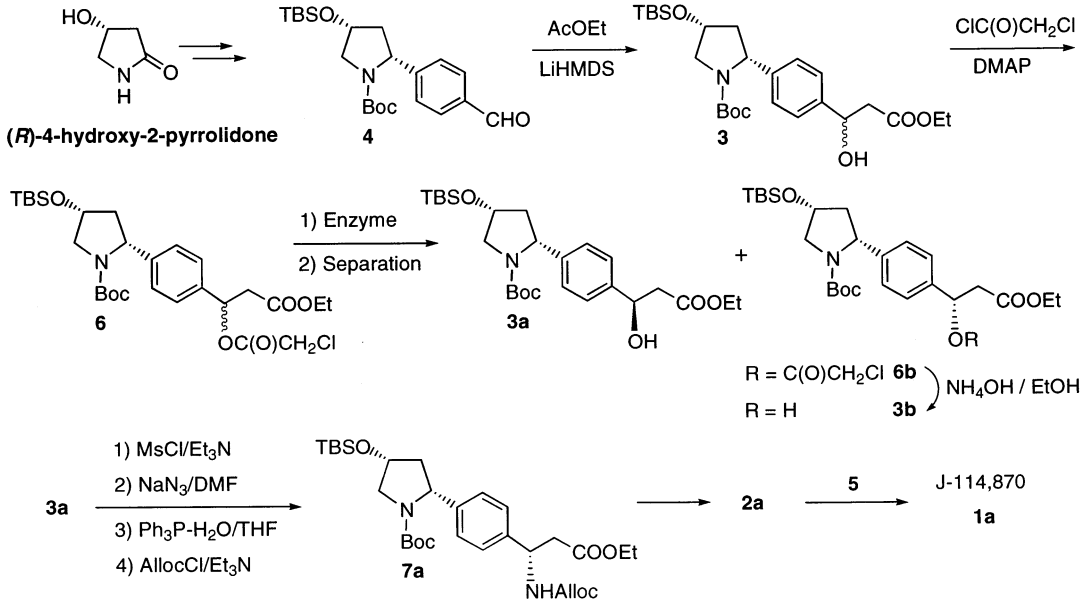


Figure 1. Synthesis of J-114,870 **1a**

2. Results and discussion

2.1. Synthesis and enzymatic resolution of the chloroacetates *6*

Commercially available (*R*)-4-hydroxy-2-pyrrolidone was converted into 2,4-*cis*-disubstituted pyrrolidine **4** with high enantiomeric purity (>99.5% de) according to our previous report.[3] The aldehyde **4** was subjected to aldol condensation with ethyl acetate by the action of lithium hexamethyldisilazide (LHMDS) at −78°C to provide a diastereomeric mixture of 3-aryl-3-hydroxypropionate **3** (ca. 10% de) (Scheme 1).



Scheme 1. Synthesis of key intermediate **3a** and conversion into J-114,870 **1a**

Enzyme-catalyzed acylation of alcohol **3** using vinyl acetate, isopropenyl acetate or acetic anhydride as an acetylating agent did not proceed with acceptable yield or selectivity. Enzyme hydrolysis of acetylated **3** afforded similar unsatisfactory results.

Next, diastereomers **3** were converted into the corresponding chloroacetates **6** by treatment with chloroacetyl chloride and 4-dimethylaminopyridine (DMAP), and the resulting chloroacetates **6** were hydrolyzed by using several enzymes in phosphate buffer (Table 1). When lipase LIP[8] was used (entry 1), the reaction proceeded with the highest selectivity (E value[9] = 747) and ended within 2 hours. It should be noted that prolonged reaction time did not diminish the diastereomeric excess of the hydrolyzed product. Sufficient diastereomeric excesses were also obtained by lipase PS[10] (entry 5), lipase MY (entry 10) and lipase Type VII (entry 13) with a longer reaction time (14 h).

Lipase-catalyzed hydrolysis of chloroacetates **6** was carried out using buffer solutions between pH 5 and 9 (Table 2). The results showed that the appropriate pH for this lipase-catalyzed reaction was 7.0–8.5, which provided both diastereomers **3a** and **6b** with sufficient enantiomeric purity (>95% de). Reactions conducted below pH 6.5 did not complete and the remaining **6b** showed moderate diastereomeric excess.

2.2. Application to the large scale synthesis

Thus, a diastereomeric mixture of benzyl alcohol **3** was successfully resolved by the lipase-catalyzed hydrolysis of the corresponding chloroacetates **6** with good diastereoselectivity to afford the hydrolyzed product **3a** with (*R*)-configuration and intact **6b**. Under optimized conditions, hydrolysis of 1000 g of alcohol **3** took place smoothly to provide **3a** (400 g) and **6b** (390 g), both of which showed excellent enantiomeric purity (>99% de). Chloroacetate **6b** was easily hydrolyzed by means of aqueous ammonia in ethanol to yield (*S*)-alcohol **3b**. The optically active alcohol **3a** thus obtained could be converted into Alloc-protected amino compound **7a** by the conventional procedure, as described in Scheme 1, without any appreciable epimerization of the resolved stereogenic center. Amino ester **7a** was transformed into J-114,870 **1a** according to reported procedures,[4] including coupling reaction of the side chain thiol **2a** with allyl-protected 1β-methylcarbapenem diphenylphosphate **5**.

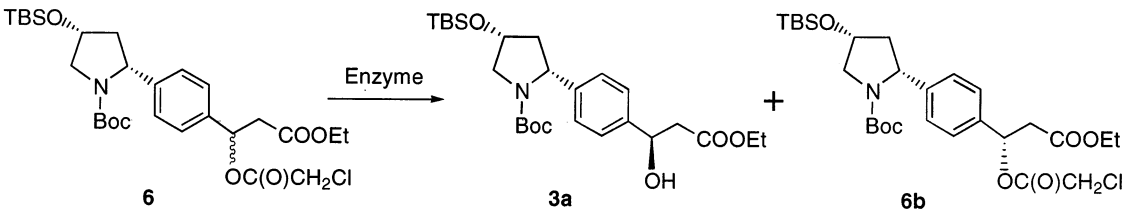
*2.3. Determination of the stereochemistry of alcohols **3a** and **3b***

Absolute configuration of the stereogenic center (C7′) of **3a** and **3b** was determined by the application of the advanced Mosher's method[11] to the MTPA esters **8a** and **8b**, which were obtained from the secondary alcohols **3a** and **3b**, respectively, by acylation with (+)-MTPA-Cl in the presence of DMAP and successive removal of the Boc group by TFA (Fig. 2). Comparison of the ^{1}H NMR spectrum of the MTPA esters **8a** and **8b** indicated that the resolved stereogenic center of **3a** was (*R*)- and hence **3b** had (*S*)-configuration (Fig. 2, Table 3).

3. Conclusions

A diastereomeric mixture of the 3-aryl-3-(α-chloroacetoxy)propionate **6** was successfully converted into the enantiopure 3-aryl-3-hydroxypropionates **3a** and **3b** in good conversion yield via the lipase-catalyzed kinetic resolution process. Of all the enzymes tested, lipase LIP was the

Table 1
Effect of the enzyme[a]



Entry	Enzyme	Source	Time (h)	**3a** % de[j] (% yield)	**6b** % de[m] (% yield)	*E* value[n]
1	Lipase LIP[b]	*Pseudomonas aeruginosa*	2	99 (44)	95 (38)	747
2	Lipase LIP[b,c]	*Pseudomonas aeruginosa*	14	98 (42)	76 (48)	228
3	Lipase LIP[b,d]	*Pseudomonas aeruginosa*	14	98 (32)	35 (62)	140
4	Lipase LIP[b,e]	*Pseudomonas aeruginosa*	14	N.D.[k]		
5	Lipase PS[f]	*Pseudomonas cepacia*	14	96 (47)	96 (36)	194
6	Lipase M10[f]	*Mucor javanicus*	14	N.R.[l]		
7	Lipase A6[f]	*Aspergillus niger*	14	N.R.[l]		
8	Lipase F-AP15[f]	*Rhizopus javanicus*	14	N.R.[l]		
9	Newlase F[f]	*Rhizopus niveus*	14	N.R.[l]		
10	Lipase MY[g]	*Candida cylindracea*	14	94 (42)	97 (30)	136
11	Lipase[h]	*Steapsin*	14	N.R.[l]		
12	Lipase Type II[i]	*Porcine pancreas*	14	N.D.[k]		
13	Lipase Type VII[i]	*Candida cylindracea*	14	98 (42)	93 (34)	340

[a] Standard conditions: **6** 50 mg, enzyme 50 mg, acetone 0.5 ml, phosphate buffer (0.1 M, pH 7.0) 1.0 ml.
[b] Purchased from TOYOBO.
[c] Enzyme 25 mg.
[d] Enzyme 5 mg.
[e] Enzyme 1 mg.
[f] Purchased from AMANO.
[g] Purchased from MEITO.
[h] Purchased from TOKYO KASEI.
[i] Purchased from SIGMA.
[j] Determined by HPLC analysis using the chiral phase column (CHIRALCEL OD-H, DAICEL).
[k] Not determined.
[l] No reaction.
[m] Determined by HPLC (see footnote j) of the corresponding alcohol **3b**.
[n] $E=\ln\{1-c[1+\mathbf{3a}(\mathrm{ee})]\}/\ln\{1-c[1-\mathbf{3a}(\mathrm{ee})]\}$, $c=\mathbf{6b}(\mathrm{ee})/[\mathbf{6b}(\mathrm{ee})+\mathbf{3a}(\mathrm{ee})]$ (Ref. 9).

most efficient catalyst as measured by stereoselectivity, reaction time and feasibility of large-scale preparation. In addition, enantiopure alcohol **3a** could be converted into J-114,870 **1a**, a novel ultra-broad spectrum carbapenem, without appreciable epimerization.

Table 2
Effect of pH[a]

$$\mathbf{6} \xrightarrow{\text{Lipase LIP}^{a}} \mathbf{3a} + \mathbf{6b}$$

pH	5	5.5	6	6.5	7	7.5	8	8.5	9
% de of **3a**	95.2	97.0	98.8	99.1	98.9	98.8	99.4	98.9	98.3
% de of **6b**	5.7	3.8	18.2	71.0	95.4	95.4	>99.8[b]	>99.8[b]	>99.8[b]
E value	41	68	237	425	747	747	>2293	>1171	>869

[a] Conditions: **6** 50 mg, lipase LIP 50 mg, acetone 0.5 ml, phosphate buffer (0.1 M) 1.0 ml.
[b] **3a** was not detectable by HPLC analysis.

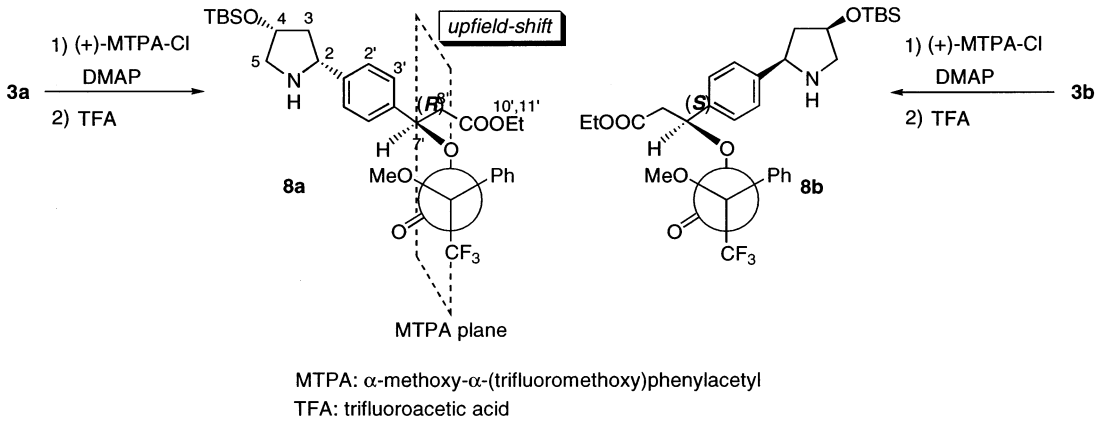


Figure 2. Conversion of **3a** and **3b** into MTPA ester **8a** and **8b**

4. Experimental

4.1. General methods

The ^{1}H NMR spectra were recorded on a Varian VXR-300 (300 MHz) spectrometer and a JEOL JNM-A500 (500 MHz) spectrometer with tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectra were recorded on a JEOL JNM-A500 (500 MHz). IR absorption spectra were recorded on a Horiba FT-200 spectrometer. Specific rotations were measured on a Jasco DIP-370 polarimeter. Mass spectra (MS) were measured on a JEOL JMS-SX102A spectrometer. The silica-gel TLC was performed with Merck Kieselgel F_{254} precoated plates. The silica gel used for column chromatography was WAKO gel C-300. All reactions involving air-sensitive reagents were performed under a nitrogen atmosphere using syringe-septum cap techniques.

Table 3
^{1}H NMR of MTPA esters **8a** and **8b**

Proton	2	3	4	5	2′	3′	7′	8′	10′	11′
8a	4.112	2.412	4.462	2.932 3.051	7.439	7.352	6.404	2.735 3.014	4.034 4.061	1.177
8b	4.080	2.412	4.457	2.923 3.041	7.370	7.197	6.344	2.740	4.117 4.152	1.227
$\Delta\delta \times 10^{-3}$ ppm	−32	±0	−5	−9 −10	−69	−155	−60	+5 +10	+83 +91	+50

4.2. Synthesis of the substrates **6**

4.2.1. (2R,4R)-1-tert-Butoxycarbonyl-4-tert-butyldimethylsiloxy-2-[4-(1-hydroxy-2-(ethoxycarbonyl)ethyl)phenyl]pyrrolidine **3**

To a solution of LHMDS (1 M in THF, 308 ml, 308 mmol) in THF (300 ml), EtOAc (31.5 ml, 323 mmol) was added dropwise at −78°C. After stirring for 1 h at −78°C, a solution of **4** (50.0 g, 123 mmol) in THF (200 ml) was added dropwise to the mixture over 1 h at −78°C. The reaction mixture was poured into H_2O and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 7:1–3:1) to give **3** (55.5 g, 91%) as a yellow oil. IR (KBr) ν_{max} 2931, 1736, 1697, 1398, 1367, 1254, 1159, 1093, 839, 777 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (6H, s), 0.79 (9H, s), 1.15 (6H, s), 1.27 (3H, t, J = 7.4 Hz), 1.44 (3H, s), 1.87 (1H, m), 2.48 (1H, m), 2.70 (2H, m), 3.41 (1H, m), 3.84 (1H, m), 4.18 (2H, q, J = 7.4 Hz), 4.37 (1H, m), 4.72 (0.7H, m), 4.88 (0.3H, m), 5.11 (1H, m), 7.23 (2H, d, J = 8.2 Hz), 7.28 (2H, d, J = 9.6 Hz); FAB-HRMS calcd for $C_{26}H_{43}NO_6SiNa$ $(M+Na)^+$: 516.2757. Found 516.2783.

4.2.2. (2R,4R)-1-tert-Butoxycarbonyl-4-tert-butyldimethylsiloxy-2-[4-(1-chloroacetoxy-2-(ethoxycarbonyl)ethyl)phenyl]pyrrolidine **6**

To a solution of **3** (1032 g, 2.09 mol) and DMAP (1268 g, 10.4 mol) in CH_2Cl_2 (2000 ml), chloroacetyl chloride (1056 g, 9.35 mol) was added under a nitrogen atmosphere at 0°C. After the completion of the reaction, 6N hydrochloric acid was added to the reaction mixture to quench excess DMAP. The organic phase was washed with a saturated solution of $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 5:1) to give **6** (922 g, 77%) as a yellow oil. IR (KBr) ν_{max} 2956, 1743, 1697, 1396, 1365, 1257, 1172, 1093, 837, 777 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (6H, s), 0.78 (9H, s), 1.14 (6H, s), 1.24 (3H, t, J = 7.1 Hz), 1.45 (3H, s), 1.87 (1H, m), 2.47 (1H, m), 2.76 (1H, m), 3.01 (1H, m), 3.42 (1H, m), 3.80 (1H, m), 4.02 (2H, dd, J = 17.4, 14.7 Hz), 4.14 (2H, q, J = 7.1 Hz), 4.37 (1H, m), 4.72 (0.7H, m), 4.93 (0.3H,

m), 6.23 (1H, dd, $J=9.3$, 4.7 Hz), 7.26 (4H, m); FAB-HRMS calcd for $C_{28}H_{44}ClNO_7SiNa$ $(M+Na)^+$: 592.2473. Found 592.2477.

4.3. Enzymatic resolution of the substrates **6**

4.3.1. (2R,4R)-1-tert-Butoxycarbonyl-4-tert-butyldimethylsiloxy-2-[4-((R)-1-hydroxy-2-(ethoxycarbonyl)ethyl)phenyl]pyrrolidine **3a** and (2R,4R)-1-tert-butoxycarbonyl-4-tertbutyldimethylsiloxy-2-[4-((S)-1-chloroacetoxy-2-(ethoxycarbonyl)ethyl)phenyl]pyrrolidine **6b**

To a solution of **6** (922 g, 1.62 mol) in acetone (9.2 l) and 0.1 M phosphate buffer (18.4 l, pH 8.0), lipase LIP (TOYOBO, 1.0 kg) was added and the mixture was stirred for 22 h at room temperature. After lipase was removed by filtration through a pad of Celite®, the filtrate was diluted with H_2O (10 l) and extracted three times with EtOAc (40 l). The organic layer was washed with brine (10 l), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 7:1–3:1) to give **6b** (389 g, 42%) as a yellow oil and **3a** (407 g, 52%, >99% de by HPLC) as a yellow oil. **6b**: $[\alpha]_D^{20}$ −13.2 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 2956, 1741, 1697, 1396, 1365, 1255, 1162, 1092, 837, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (6H, s), 0.79 (9H, s), 1.16 (6H, s), 1.24 (3H, t, $J=7.3$ Hz), 1.46 (3H, s), 1.87 (1H, m), 2.47 (1H, m), 2.75 (1H, m), 3.01 (1H, m), 3.40 (1H, m), 3.81 (1H, m), 4.02 (2H, dd, $J=17.3$, 14.6 Hz), 4.14 (2H, q, $J=7.3$ Hz), 4.37 (1H, m), 4.72 (0.7H, m), 4.93 (0.3H, m), 6.24 (1H, dd, $J=9.1$, 4.8 Hz), 7.26 (4H, m); FAB-HRMS calcd for $C_{28}H_{44}ClNO_7SiNa$ $(M+Na)^+$: 592.2473. Found 592.2476. **3a**: $[\alpha]_D^{20}$ +54.2 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 2933, 1734, 1697, 1398, 1367, 1254, 1159, 1093, 837, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (6H, s), 0.79 (9H, s), 1.16 (6H, s), 1.27 (3H, t, $J=7.4$ Hz), 1.44 (3H, s), 1.86 (1H, m), 2.50 (1H, m), 2.70 (2H, m), 3.39 (1H, m), 3.84 (1H, m), 4.18 (2H, q, $J=7.4$ Hz), 4.37 (1H, m), 4.72 (0.7H, m), 4.89 (0.3H, m), 5.11 (1H, m), 7.23 (2H, d, $J=8.7$ Hz), 7.28 (2H, d, $J=10.0$ Hz); FAB-HRMS calcd for $C_{26}H_{43}NO_6SiNa$ $(M+Na)^+$: 516.2757. Found 516.2756. The enantiomeric purity of **3a** was determined by HPLC analysis: column, Chiralcel OD-H (Daicel, 4.6ϕ×250 mm); eluent, *n*-hexane:*i*-PrOH = 95:5; flow rate, 1.0 ml/min; detection, UV 250 nm; rt, 9.3 min (**3b**) and 11.3 min (**3a**).

4.3.2. (2R,4R)-1-tert-Butoxycarbonyl-4-tert-butyldimethylsiloxy-2-[4-((S)-1-hydroxy-2-(ethoxycarbonyl)ethyl)phenyl]pyrrolidine **3b**

To a solution of **6b** (389 g, 683 mmol) in EtOH (2 l), 25% aqueous ammonia (800 ml) was added and the mixture was stirred for 0.5 h at 15°C. The reaction mixture was poured into H_2O (5 l) and the whole was extracted with EtOAc (6 l). The organic layer was washed successively with 1N HCl (5 l), a saturated solution of $NaHCO_3$ (5 l) and brine (5 l), and then dried over $MgSO_4$. After evaporation under reduced pressure, the residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 5:1–3:1) to give **3b** (310 g, 92%, >99% de by HPLC) as a yellow oil; $[\alpha]_D^{20}$ +12.8 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 2931, 1734, 1697, 1398, 1367, 1254, 1159, 1092, 837, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (6H, s), 0.79 (9H, s), 1.16 (6H, s), 1.25 (3H, t, $J=7.4$ Hz), 1.44 (3H, s), 1.87 (1H, m), 2.50 (1H, m), 2.70 (2H, m), 3.41 (1H, m), 3.84 (1H, m), 4.18 (2H, q, $J=7.4$ Hz), 4.37 (1H, m), 4.72 (0.7H, m), 4.88 (0.3H, m), 5.11 (1H, m), 7.23 (2H, d, $J=8.5$ Hz), 7.28 (2H, d, $J=8.9$ Hz); FAB-HRMS calcd for $C_{26}H_{43}NO_6SiNa$ $(M+Na)^+$: 516.2757. Found 516.2739.

4.4. Synthesis of the MTPA esters **8a** and **8b** for determination of absolute configuration

4.4.1. (2R,4R)-4-tert-Butyldimethylsiloxy-2-[4-((R)-1-[(R)-(α-methoxy-α-(trifluoromethyl)-phenylacetoxy]-2-(ethoxycarbonyl)ethyl)phenyl]pyrrolidine **8a**

To a solution of **3a** (327 mg, 0.662 mmol) in CH_2Cl_2 (10 ml), DMAP (324 mg, 2.65 mmol) and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride ((*S*)-(+)-MTPA-Cl, 247 μl, 1.32 mmol) were added at room temperature. After being stirred for 1 h at the same temperature, H_2O was added to the reaction mixture. The organic phase was separated and the aqueous phase was extracted with $CHCl_3$. The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 5:1) to give a colorless oil (405 mg, 86%).

To a solution of the material obtained above (100 mg, 0.141 mmol) in CH_2Cl_2 (2 ml), TFA (100 μl) was added at 0°C and the mixture was stirred for 1 h at same temperature and then for 1.5 h at room temperature. The mixture was poured into H_2O and the whole mixture was extracted with EtOAc. The organic layer was washed with a saturated solution of $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 10:1) to give **8a** (39 mg, 45%) as a yellow oil. $[\alpha]_D^{20}$ +52.8 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 2954, 1749, 1257, 1173, 1122, 1020, 837, 777, 721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (6H, s), 0.90 (9H, s), 1.17 (3H, t, J = 7.1 Hz), 1.73 (1H, m), 2.42 (1H, m), 2.73 (1H, dd, J = 16.2, 4.5 Hz), 2.93 (1H, dd, J = 11.7, 4.4 Hz), 3.02 (2H, m), 3.41 (3H, s), 4.07 (3H, m), 4.45 (1H, m), 6.40 (1H, dd, J = 9.7, 4.4 Hz), 7.35 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 18.0, 25.8, 40.7, 44.1, 55.3, 56.9, 60.8, 61.9, 73.6, 74.3, 84.2, 122.0, 124.3, 127.1, 127.38, 127.42, 128.1, 129.4, 132.1, 136.4, 145.1, 165.4, 169.1; FAB-HRMS calcd for $C_{31}H_{43}F_3NO_6Si$ $(M+H)^+$: 610.2812. Found 610.2803.

4.4.2. (2R,4R)-4-tert-Butyldimethylsiloxy-2-[4-((S)-1-[(R)-(α-methoxy-α-(trifluoromethyl)-phenylacetoxy]-2-ethoxycarbonyl)ethyl)phenyl]pyrrolidine **8b**

By using the same procedure for preparing **8a** described above, **3b** (391 mg, 0.792 mmol) was condensed with (*S*)-(+)-MTPA-Cl to give a colorless oil (505 mg, 90%). The obtained material (100 mg, 0.141 mmol) was then treated with TFA to afford **8b** (44 mg, 51%) as a yellow oil. $[\alpha]_D^{20}$ +22.8 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 2956, 1749, 1257, 1171, 1122, 1022, 837, 777, 721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (6H, s), 0.90 (9H, s), 1.23 (3H, t, J = 7.1 Hz), 1.73 (1H, m), 2.41 (1H, m), 2.74 (1H, dd, J = 16.5, 4.0 Hz), 2.92 (1H, dd, J = 11.7, 4.6 Hz), 3.03 (2H, m), 3.51 (3H, s), 4.12 (3H, m), 4.46 (1H, m), 6.35 (1H, dd, J = 10.0, 3.9 Hz), 7.29 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 18.0, 25.8, 41.0, 44.1, 55.5, 56.9, 60.9, 62.0, 73.7, 74.5, 84.4, 122.0, 124.3, 126.7, 127.23, 127.24, 128.1, 129.4, 132.0, 136.4, 144.9, 165.2, 169.5; FAB-HRMS calcd for $C_{31}H_{43}F_3NO_6Si$ $(M+H)^+$: 610.2812. Found 610.2806.

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References

1. Ito, Y.; Terashima, S. *J. Syn. Org. Chem. Jpn.* **1989**, *47*, 606–618.
2. (a) Imamura, H.; Ohtake, N.; Shimizu, A.; Jona, H.; Sato, H.; Nagano, R.; Ushijima, R.; Yamada, K.; Hashizume, T.; Morishima, H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 109–113. (b) Imamura, H.; Ohtake, N.; Shimizu, A.; Sato, H.; Sugimoto, Y.; Sakuraba, S.; Kiyonaga, H.; Suzuki-Sato, C.; Nagano, M.; Nagano, R.; Yamada, K.; Hashizume, T.; Morishima, H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 115–118.
3. Imamura, H.; Shimizu, A.; Sato, H.; Sugimoto, Y.; Sakuraba, S.; Nakano, R.; Yamada, K.; Hashizume, T.; Morishima, H. *J. Antibiot.* **2000**, *53*, 314–316.
4. Imamura, H. et al. *Tetrahedron* **2000**, *56*, 7705–7713.
5. (a) Iwai, M. *Lipases*: *Their Foundation and Application*; Saiwai Shobou: Tokyo, 1991. (b) Schmid, R. D.; Verger, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1609–1633. (c) Chen, C.-S.; Liu, Y.-C. *J. Jpn. Oil Chem. Soc.* **1992**, *41*, 724–733. (d) Robert, S. M., Ed.; *Preparative Biotransformations: Whole Cell and Isolated Enzymes in Organic Synthesis*; John Wiley & Sons Ltd: Chichester, England, 1992.
6. (a) Otera, J. *Chem. Rev.* **1993**, *93*, 1449–1470. (b) Ogasawara, K. *J. Syn. Org. Chem. Jpn.* **1996**, *54*, 15–26.
7. (a) Yokomatsu, T.; Minowa, T.; Murano, T.; Shibuya, S. *Tetrahedron* **1998**, *54*, 9341–9356. (b) Guanti, G.; Narisano, E.; Riva, R. *Tetrahedron: Asymmetry* **1998**, *9*, 1859–1862. (c) Itoh, T.; Takagi, Y.; Tsukube, H. *J. Mol. Catal. B: Enzym.* **1997**, *3*, 259–270. (d) Achiwa, K. *Yakugaku Zasshi* **1995**, *115*, 681–699. (e) Banfi, L.; Guanti, G.; Mugnoli, A.; Riva, R. *Tetrahedron: Asymmetry* **1998**, *9*, 2481–2492.
8. (a) Mizuguchi, E.; Suzuki, T.; Achiwa, K. *Synlett* **1996**, 743–744. (b) Kita, Y.; Naka, T.; Imanishi, M.; Akai, S.; Takebe, Y.; Matsugi, M. *Chem. Commun.* **1998**, 1183–1184. (c) Sugahara, T.; Ogasawara, K. *Synlett* **1996**, 319–320. (d) Sakai, T.; Miki, Y.; Nakatani, M.; Ema, T.; Uneyama, K.; Utaka, M. *Tetrahedron Lett.* **1998**, *39*, 5233–5236. (e) Yoshida, N.; Kamikubo, T.; Ogasawara, K. *Tetrahedron: Asymmetry* **1998**, *9*, 3325–3329.
9. Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.
10. (a) Amano Pharmaceutical Co., Ltd; Amano Enzyme USA Co., Ltd; Amano Enzyme Europe Ltd *Lipases for Resolution and Asymmetric Synthesis*; 1995. (b) Nakamura, K.; Hirose, Y. *J. Syn. Org. Chem. Jpn.* **1995**, *53*, 668–677. (c) Sugahara, T.; Ogasawara, K. *Tetrahedron Lett.* **1996**, *37*, 205–208. (d) Bianchi, D.; Battistel, E.; Bosetti, A.; Cesti, P.; Fekete, Z. *Tetrahedron: Asymmetry* **1993**, *4*, 777–782.
11. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.