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Biocatalytic Synthesis of Enantiopure β-Methoxy-β-arylalanine Derivatives

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Chiral β-hydroxy-β-arylalanine and β-methoxy-β-arylalanine derivatives, which occur widely in marine nature products, were stereoselectively synthesized with ≥99 % *ee* values. The two *erythro* isomers were prepared by L- or D-aminoacylase-catalyzed resolution of the corresponding *N*-acetyl derivatives, whereas the two *threo* isomers were obtained only by D-aminoacylase-catalyzed resolution of the derivatives. *erythro*-β-Hydroxy-β-arylalanine derivatives were prepared by diastereoselective hydrogenation of ethyl 2-(hydroxyimino)-3-oxo-3-arylpropanoates, which were in turn acquired by the oximation of ethyl 3-oxo-3-arylpropanoates with ethyl nitrite in the presence of nano-K_2CO_3 with yields of 72 % to 80 %. β-Methoxy-β-arylalanine derivatives were synthesized through Williamson reactions between the corresponding β-hydroxy-β-arylalanines and iodomethane with silver oxide as base.

Introduction

Chiral β-hydroxy-β-arylalanine and β-methoxy-β-arylalanine derivatives, as nonproteinogenic amino acids, are found in numerous natural products and perform key functions in biological activity.[1] For example, scutianine E, which contains β-phenylserine, exhibits wide-spectrum antimicrobial activity,[1f] and callipeltin B, which contains β-methoxytyrosine, is cytotoxic against various human carcinoma cells in vitro[1c] (Figure 1). Additionally, these nonproteinogenic amino acids can serve as useful synthetic building blocks and chiral auxiliaries in organic synthesis.[2] Extensive studies on the preparation of these amino acids have been performed because of their importance in biological systems and organic synthesis. Recently, several strategies such as asymmetric metal-catalyzed syntheses,[3] chiral-auxiliary-induced syntheses,[4] and chiral pool syntheses have been formulated.[5] However, the main difficulties encountered in the current protocols involve the control of the stereochemistry at the α- and β-positions and the low yields caused by the long reaction routes.

Thanks to the specificity and efficiency of enzymes, biocatalysis provides an interesting alternative way. We therefore envisaged using aminoacylase-catalyzed resolution to furnish enantiopure β-hydroxy (or β-methoxy) β-arylalanine derivatives. Aminoacylases, including L- and D-aminoacylase, have been used in the production of enantiopure L-amino and D-amino compounds from the corresponding *N*-acetyl derivatives,[6] almost invariably to prepare amino compounds containing single chiral centers.[7] However, the aminoacylase-catalyzed resolution of amino acids containing two consecutive chiral centers has only rarely been reported. Inoue et al. accomplished the total

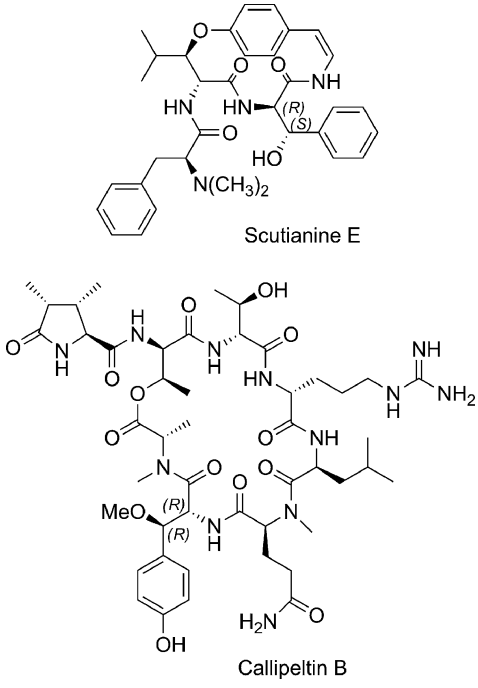

Figure 1. Structures of scutianine E and callipeltin B.

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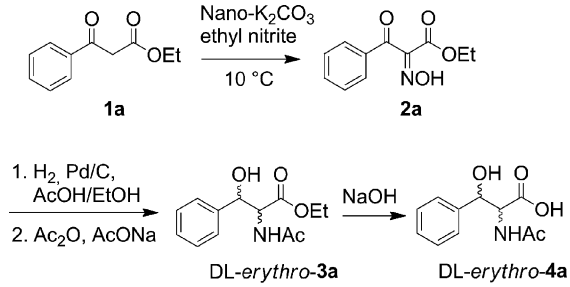
synthesis of (2*R*,3*S*)-3-(4-methoxyphenyl)glycidic ester by using (2*S*,3*S*)-β-hydroxy-β-(4-methoxyphenyl)alanine as starting material.[8] In this paper we report a general, expeditious, and practical synthesis of enantiopure β-hydroxy-β-arylalanine and β-methoxy-β-arylalanine derivatives containing two chiral centers, by L- or D-aminoacylase-catalyzed hydrolysis of *N*-acetylamino acids. Here we report for the first time the reaction behavior of aminoacylases with the substrates (±)-*threo*-*N*-acetyl-β-hydroxy-β-phenylalanine and (±)-*erythro*-*N*-acetyl-β-methoxy-β-arylalanine derivatives.

Results and Discussion

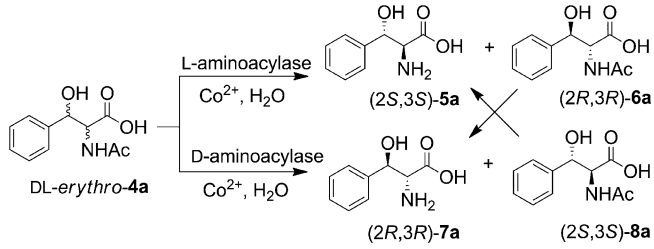
Synthesis of the Four Optically Pure Isomers of β-Hydroxy-β-phenylalanine

The four optically pure isomers of β-hydroxy-β-phenylalanine were obtained by aminoacylase-catalyzed hydrolysis of (±)-*erythro*- and (±)-*threo*-*N*-acetyl-β-hydroxy-β-phenylalanine. A convenient synthetic method for (±)-*erythro*-**3a** was initially examined (Scheme 1). The intermediate oxime **2a** was successfully produced by the oximation of **1a** with ethyl nitrite in the presence of the new, efficient, and safe base nano-K_2CO_3, developed by the authors.[9] Subsequently, a convenient approach to converting compound **2a** into *erythro*-**3a** in one-pot fashion was developed. The process involved two reaction steps. Diastereoselective hydrogenation of oxime **2a** in the presence of Pd/C and AcOH yielded ethyl *erythro*-β-hydroxy-β-phenylalanine with 98% selectivity, and *N*-acetylation occurred in Ac_2O/AcONa. The method resulted in a 90% yield, higher than that in the literature.[10]



Scheme 1. Synthesis of (±)-*erythro*-β-hydroxy-β-phenylalanine.

To obtain enantiopure β-hydroxy-β-phenylalanine, the selective hydrolysis of (±)-*erythro*-**4a** in the presence of aminoacylase as catalyst was investigated. Enantiopure (2*S*,3*S*)-β-hydroxy-β-phenylalanine (**5a**) was obtained successfully by L-aminoacylase-catalyzed hydrolysis either of (±)-*erythro*-**4a** or of **8a** in the presence of Co^{2+} at pH 7.5 (Scheme 2). The resolution process can be performed on a gram scale, and a high *ee* (>99%) and excellent conversion (>99%) were achieved (Table 1, Entry 1). Meanwhile, compound **8a** was also hydrolyzed with 1% hydrochloric acid solution to yield the product **5a**. (2*R*,3*R*)-β-Hydroxy-β-phenylalanine (**7a**) was obtained by D-aminoacylase-catalyzed hydrolysis either of (±)-*erythro*-**4a** or of **6a** under similar conditions. The result was similar to that above, with *ee* > 99% and conversion > 99% (Table 1, Entry 2). The enantioselectivity and conversion were confirmed by HPLC, specific rotation, and ^1H NMR spectroscopy.



Scheme 2. Aminoacylase-catalyzed synthesis of (2*S*,3*S*)- and (2*R*,3*R*)-β-hydroxy-β-phenylalanine.

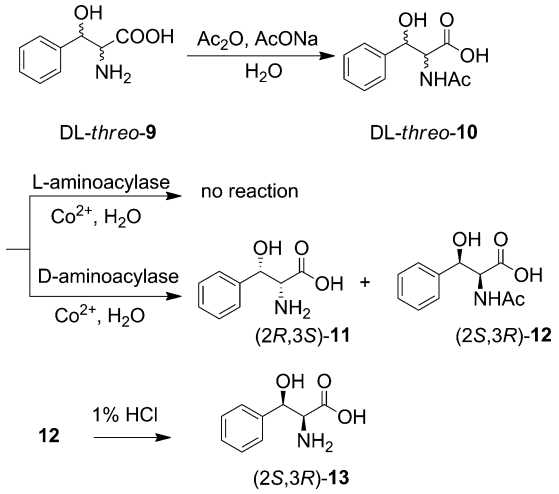
Table 1. Aminoacylase-catalyzed hydrolysis of *erythro*- and *threo*-*N*-acetyl-β-hydroxy-β-phenylalanine.

Entry	Substrate	Acylase	Conversion [%][a]	*ee* [%][b]
1	*erythro*	l	>99	>99
2	*erythro*	d	>99	>99
3	*threo*	l	–[c]	–[c]
4	*threo*	d	>99	>99

[a] The conversion was calculated as 0.5 molar quantity of *rac*-substrate. [b] Determined by HPLC on a chiral stationary phase. [c] No reaction was observed.

Compound **10**, (±)-*threo*-*N*-acetyl-β-hydroxy-β-phenylalanine, was prepared selectively through the thermodynamically controlled aldol reaction between glycine and benzaldehyde under alkaline conditions,[11] followed by *N*-acetylation (Scheme 3). Use of the same approach to hydrolyze the (±)-*threo* isomer **10** to prepare compound **13** was unexpectedly unsuccessful. L-Aminoacylase does not work with the substrate (2*S*,3*R*)-*N*-acetyl-β-hydroxy-β-phenylalanine. However, D-aminoacylase can work well with (2*R*,3*S*)-*N*-acetyl-β-hydroxy-β-phenylalanine (Scheme 3). Therefore, the hydrolysis of (±)-*threo*-*N*-acetyl-β-hydroxy-β-phenylalanine was catalyzed selectively by D-aminoacylase to achieve the resolution of the (±)-*threo* isomer to yield the optical pure product (2*R*,3*S*)-β-hydroxy-β-phenylalanine with excellent conversion (>99%), whereas (2*S*,3*R*)-amino acid **13** was obtained by hydrolysis of (2*S*,3*R*)-*N*-acetyl-β-hydroxy-β-phenylalanine with 1% HCl.

In summary, the resolution of *N*-acetyl-β-hydroxy-β-phenylalanine can be performed by enzyme-catalyzed hydrolysis to yield the corresponding optically pure products. However, both L- and D-aminoacylase showed good activity towards (±)-*erythro*-*N*-acetyl-β-hydroxy-β-phenylalanine as substrate, whereas only D-aminoacylase worked well with the (±)-*threo* isomers as substrate.

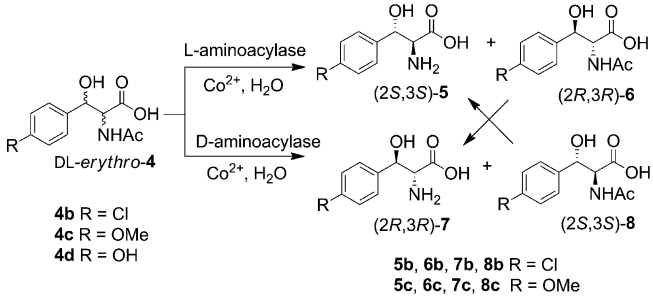


Scheme 3. Aminoacylase-catalyzed hydrolysis of *threo*-*N*-acetyl-β-hydroxy-β-phenylalanine.

Synthesis of (2*S*,3*S*)- and (2*R*,3*R*)-β-Hydroxy-β-arylalanine Derivatives

In view of the good results exhibited by the aminoacylase-catalyzed enantioselective hydrolysis of the *erythro* substrates, extension of the scope of *erythro* substrates was further investigated. The *erythro* substrates were obtained by the same preparation method as used for **4a**, and the resolution results are shown in Table 2. As predicted, the substrates, with *p*-chloro substitution and *p*-methoxy substitution on benzene (*erythro*-**4b** and -**4c**), could be enantioselectively hydrolyzed by L- or D-aminoacylase catalysis with excellent *ee* values and good levels of conversion (Table 2, Entries 1 to 4). The results indicated that the different electronic effects of the substituents on the aromatic ring have

Table 2. Aminoacylase-catalyzed hydrolysis of *erythro*-*N*-acetyl-β-hydroxy-β-arylalanine derivatives.



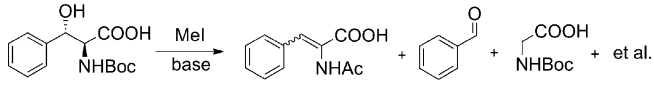
Entry	*p*-Substituent	Acylase	Conversion [%][a]	*ee* [%][b]
1	Cl	l	>99	>99
2	Cl	d	>99	>99
3	OMe	l	>95	>99
4	OMe	d	>93	>99
5	OH	l	–[c]	–
6	OH	d	–[c]	–

[a] The conversion was calculated as 0.5 molar quantity of *rac*-substrate. [b] Determined by HPLC on a chiral stationary phase. [c] Decomposition of the substrate under the enzyme catalysis conditions was found.

no noticeable influence on the molecular recognition by the aminoacylase. Notably, however, when a 4-hydroxy substituent was present – in compound **4d** – the enzyme-catalyzed hydrolysis did not yield the predicted products (Table 2, Entries 5 and 6). *p*-Hydroxybenzaldehyde and glycine, the products of the *retro*-aldol reaction of **4d**, were formed, which might be due to the more strongly electron-donating effect of the phenol hydroxy group enhancing the by-reaction.

Synthesis of (2*S*,3*S*)-β-Methoxy-β-phenylalanine

To obtain enantiopure β-methoxy-β-phenylalanine, the β-hydroxy group in *N*-Boc-β-hydroxy-β-phenylalanine was methylated. A series of different bases, including Na_2CO_3, K_2CO_3, and NaH, was tried, but dehydration and *retro*-aldol reactions were the main results (Scheme 4).



Scheme 4. Methylation of Boc-protected enantiopure β-hydroxy-β-phenylalanine.

The unsuccessful results led us to revise our research strategy; that is, we attempted to hydrolyze *erythro*-*N*-acetyl-β-methoxyphenylalanine directly with aminoacylase as catalyst. Initially, methylation of the β-hydroxy group in (±)-*erythro*-*N*-acetyl-β-methoxyphenylalanine (**7a**) was investigated. Classical Williamson reactions were conducted with MeI as methylation reagent in the presence of different bases (Table 3, Entries 1 to 4), but the results were similar to those of Scheme 3, with the dehydration and *retro*-aldol products being obtained. In view of the fact that the by-reaction occurred under basic conditions, diazomethane was selected as methylation reagent to complete the reaction, and the desired product **14a** was obtained in a low yield of 10% (Table 3, Entry 5). Although the yield of the diazomethane method is considerably lower, the approach may prevent the by-reaction. Finally, a heterogeneous methylation of **7a** with iodomethane with use of silver oxide as base in CH_2Cl_2 was selected. The result showed that the methylation of hydroxy group was completed in good yield (Table 3, Entry 6).

Furthermore, the enzyme-catalyzed hydrolysis of compounds (±)-*erythro*-**15** was investigated. (2*S*,3*S*)-*N*-Acetyl-β-OMe-amino acids could be enantioselectively hydrolyzed by L-aminoacylase to afford the corresponding (2*S*,3*S*)-β-OMe-amino acid products with excellent *ee* values (Table 4, Entries 1, 3, and 5). However, D-aminoacylase did not work on the corresponding isomer substrates (Table 4, Entries 2, 4, and 6). The L-aminoacylase-catalyzed reaction of (±)-*erythro*-**15a** was found to be more difficult than that of (±)-*erythro*-**4a**, and the level of conversion of (±)-*erythro*-**15a** into (2*S*,3*S*)-**16a** was only 49% under the same reaction conditions (Table 4, Entry 1). The *O*-methylation products

Table 3. Methylation conditions.

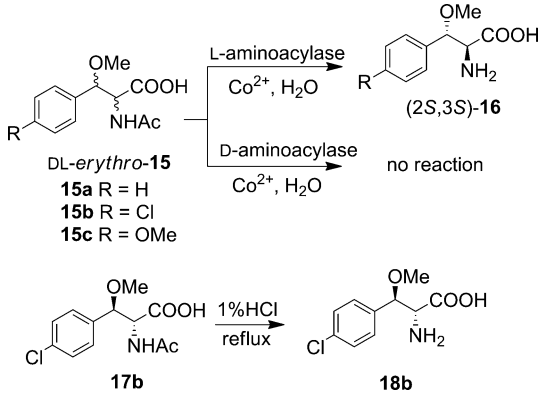
DL-*erythro*-**7a** DL-*erythro*-**14a**

Entry	Reagent	Catalyst	Solvent	Conditions	Yield [%][a]
1	MeI	Na	THF	0 °C	0
2	MeI	NaH	THF	r.t	0
3	MeI	K_2CO_3	CH_3CN	reflux	0
4	MeI	Na_2CO_3	CH_3CN	reflux	0
5	CH_2N_2	$Et_2O{\cdot}BF_3$	$(CH_3)_2CO$	r.t	10
6	MeI	Ag_2O	CH_2Cl_2	reflux	75

[a] Yield of the isolated product.

of *erythro*-*N*-acetyl-β-hydroxy-β-arylalanine derivatives exhibited characteristics different from those of their non-methylated counterparts in the presence of aminoacylases. Specifically, D-aminoacylase was inactive with the substrates (2*R*,3*R*)-*N*-acetyl-β-OMe-β-arylalanine. The different responses with aminoacylases probably reflect different hydrogen-bonding interactions of the aminoacylases with the methylated and non-methylated. The corresponding (2*R*,3*R*)-amino acid isomers, such as (2*R*,3*R*)-**18b**, were readily obtained by chemical hydrolysis.

Table 4. Aminoacylase-catalyzed hydrolysis of *erythro*-*N*-acetyl-β-methoxy-β-arylalanine derivatives.



Entry	*p*-Substituent	Acylase	Conversion [%][a]	*ee* [%][b]
1	H	L	49	>99[b]
2	H	D	–[c]	–
3	Cl	L	>99	>99
4	Cl	D	–[c]	–
5	OMe	L	79	>99
6	OMe	D	–[c]	–

[a] The conversion was calculated as 0.5 molar quantity of *rac*-substrate. [b] Determined by HPLC on a chiral stationary phase. [c] No reaction was observed.

Conclusions

In conclusion, we describe an expeditious and practical route based on aminoacylase catalysis for the synthesis of enantiopure β-hydroxy(or methoxy)-β-arylalanine derivatives containing two consecutive asymmetric centers. L-Aminoacylase was able to catalyze the hydrolysis of all (2*S*,3*S*)-*N*-acetyl-amino acids examined, whereas D-aminoacylase could only hydrolyze (2*R*,3*R*)-*N*-acetyl-β-hydroxy-β-arylalanine derivatives. In contrast, D-aminoacylase functioned well with (±)-*threo*-*N*-acetyl-β-hydroxy-β-phenylalanine, but L-aminoacylase did not work with this substrate. Additionally, large-scale aminoacylase-catalyzed resolution of β-hydroxy/methoxy-β-arylalanine derivatives is being developed in our laboratory.

Experimental Section

General Methods and Materials: ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker Advance II 500 instrument at 500 and 126 MHz, respectively. Chemical shifts are given as δ values (ppm) with tetramethylsilane as the internal standard, and coupling constants (J) are given in Hertz (Hz). Melting points were determined with an X4 apparatus and are uncorrected. The optical rotations were measured with a polarimeter at the sodium D line. HPLC was performed with a Dionex UltiMate-3000 HPLC, with Daicel Chem. Ind. Crownpak CR(+) as stationary phase and MeOH/H_2O 1:7 at pH 1.0 ($HClO_4$) as mobile phase. HPLC-MS was performed with a Thermo Finnigan LCQ-Advantage mass spectrometer. Reactions were monitored by thin-layer chromatography on silica gel plates (GF254). Flash chromatography was performed with silica gel (200 mesh–400 mesh).

L-Aminoacylase from *Aspergillus oryzae* (EC 3.5.1.4) and D-aminoacylase (recombinant) from *Escherichia coli* (EC 3.5.1.81) were purchased from Sigma–Aldrich (Shanghai). Most reagents were commercially available reagent-grade chemicals and were used without further purification, unless noted otherwise. The preparation of nano-K_2CO_3: commercial anhydrous K_2CO_3 (200 g) and absolute ethyl alcohol (200 mL) were placed in a high frequency resonance grinding machine. The mixture was ground for 5 h. The nano-K_2CO_3 was collected by centrifugation and then directly used for the next reaction.

Ethyl 3-Oxo-3-phenylpropanoate (1a): Acetophenone (3.6 g, 30 mmol) was added at 0 °C to a suspension of NaH (3.6 g, 150 mmol) in DMF (20 mL), and the mixture was stirred for 30 min. Then, diethyl carbonate (17.7 g, 150 mmol, dissolved in 20 mL DMF) was added dropwise. The mixture was stirred at room temperature for 12 h, and the reaction mixture was then quenched with ice/water and extracted with Et_2O (50 mL × 3). The extracts were combined, washed with water, dried with anhydrous $MgSO_4$, and distilled in vacuo after removal of ether to yield ethyl 3-oxo-3-phenylpropanoate as a pale yellow oil with b.p. 140–142 °C (4 Torr), yield (34.6 g, 60%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.94–7.96 (m, 2 H), 7.59–7.60 (m, 1 H), 7.47–7.50 (m, 2 H), 4.22 (q, J = 7.0 Hz, 2 H), 3.99 (s, 2 H), 1.26 (t, J = 7.0 Hz, 3 H) ppm.

Compounds **1b**, **1c**, and **1d** were prepared according to the procedure used for **2a**.

Ethyl 3-(4-Chlorophenyl)-3-oxopropanoate (1b): Yield (65%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.88 (d, J = 10.5 Hz, 2 H), 7.45 (d, J = 10.5 Hz, 2 H), 4.21 (q, J = 7.0 Hz), 3.96 (s, 2 H), 1.26 (t, J = 7.0 Hz, 3 H) ppm.

Ethyl 3-(4-Methoxyphenyl)-3-oxopropanoate (1c): Yield (63%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.93 (d, J = 9.0 Hz, 2 H), 6.95 (d, J = 9.0 Hz, 2 H), 4.21 (q, J = 7.0 Hz), 3.94 (s, 2 H), 3.88 (s, 3 H), 1.26 (t, J = 7.0 Hz, 3 H) ppm.

Methyl 3-[4-(Benzyloxy)phenyl]-3-oxopropanoate (1d): Yield (67%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.84 (d, J = 9.0 Hz, 2 H), 7.40–7.42 (m, 5 H), 7.05 (d, J = 9.0 Hz, 2 H), 5.15 (s, 2 H), 3.85 (s, 3 H) ppm.

Ethyl 2-(Hydroxyimino)-3-oxo-3-phenylpropanoate (2a): Nano-K_2CO_3 (0.6 mol, 83.5 g) was added to a solution of ethyl 3-oxo-3-phenylpropanoate (**1a**, 52 mmol, 10 g) in ethanol (52 mL). Then, the mixture was cooled to 10 °C. Separately, a solution of sodium nitrite (78 mmol, 5.4 g) in water (26 mL) and ethanol (4 mL) was placed in a 100 mL one-port flask. Then, a solution of sulfuric acid (31 mmol, 3.1 g) in water (52 mL) and ethanol (3 mL) was added dropwise slowly to generate ethyl nitrite. Ethyl nitrite was introduced into the reactor through a drying tube. Stirring was maintained for 3 h at a low temperature after the sulfuric acid solution had been added. The reaction mixture was then concentrated to remove ethanol. Cold water (30 mL) was then added to the residue, and the pH of the solution was adjusted to 6 with hydrochloric acid (0.5 M). The solution was extracted with ethyl acetate (3× 50 mL), and the organic phase was dried with anhydrous $MgSO_4$. Ethyl acetate was removed under reduced pressure to yield solid product **2a** (9.2 g, 80%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.88–7.89 (m, 2 H), 7.63–7.67 (m, 1 H), 7.51–7.54 (m, 2 H), 4.33 (q, J = 7.0 Hz, 2 H), 1.29 (t, J = 7.0 Hz, 3 H) ppm.

Compounds **2b**, **2c**, and **2d** were prepared similarly according to the procedure used for **2a**.

Ethyl 3-(4-Chlorophenyl)-2-(hydroxyimino)-3-oxopropanoate (2b): Yield (72%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.82 (d, J = 8.5 Hz, 2 H), 7.50 (d, J = 8.5 Hz, 2 H), 4.32 (q, J = 7.0 Hz, 2 H), 1.27 (t, J = 7.0 Hz, 3 H) ppm.

Ethyl 2-(Hydroxyimino)-3-(4-methoxyphenyl)-3-oxopropanoate (2c): Yield (77%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 9.52 (br., 1 H), 7.85 (d, J = 8.5 Hz, 2 H), 6.98 (d, J = 8.5 Hz, 2 H), 4.31 (q, J = 7.0 Hz, 2 H), 1.27 (t, J = 7.0 Hz, 3 H) ppm.

Methyl 3-[4-(Benzyloxy)phenyl]-2-(hydroxyimino)-3-oxopropanoate (2d): Yield (74%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.85 (d, J = 9.0 Hz, 2 H), 7.35–7.43 (m, 5 H), 7.06 (d, J = 9.0 Hz, 2 H), 5.15 (s, 2 H), 3.86 (s, 3 H) ppm.

***erythro*-Ethyl 2-Acetamido-3-hydroxy-3-phenylpropanoate (3a):** Pd/C catalyst (10%, 1.0 g) was added to a solution of **2a** (50.7 mmol, 11.2 g) in ethanol (91 mL) and acetic acid (3 mL), and the nitrogen atmosphere was replaced by hydrogen. The reaction mixture was stirred (atmospheric pressure) at room temperature for 24 h. The pH of the reaction was adjusted to 7.0 by the addition of NaOH, and then acetic anhydride (146.9 mmol, 15.0 g) was added. The reaction mixture was stirred at room temperature overnight and then filtered. The filtrate was concentrated, and then water was added. Finally, the mixture was filtered to give **3a** (11.5 g, 90%), m.p. 147–148 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.24 (d, J = 8.5 Hz, 1 H), 7.24–7.37 (m, 5 H), 5.79 (d, J = 3.0 Hz, 1 H), 4.73 (d, J = 4.5 Hz, 1 H), 4.46 (d, J = 4.5 Hz, 1 H), 4.04 (q, J = 6.0 Hz, 2 H), 1.72 (s, 3 H), 1.12 (t, J = 6.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.7, 169.4, 139.2, 128.3, 125.9, 75.3, 62.1, 59.3, 22.9, 14.0 ppm. HRMS: calcd. for $C_{13}H_{18}NO_4$ [M + H]$^+$ 252.1236; found 252.1226.

Compounds **3b**, **3c**, and **3d** were prepared similarly according to the procedure used for **3a**.

***erythro*-Ethyl 2-Acetamido-3-(4-chlorophenyl)-3-hydroxypropanoate (3b):** Yield (85%), m.p. 113–115 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.31 (d, J = 8.0 Hz, 1 H), 7.17 (d, J = 8.0 Hz, 1 H), 6.25 (d, J = 4.5 Hz, 1 H), 5.27 (dd, J = 3.0, 6.0 Hz, 1 H), 4.97 (dd, J = 3.0, 6.5 Hz, 1 H), 4.70 (d, J = 6.0 Hz, 1 H), 4.22 (q, J = 7.0 Hz, 2 H), 2.04 (s, 3 H), 1.27 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.8, 169.2, 139.1, 133.7, 128.2, 125.9, 75.1, 62.0, 22.9, 14.0 ppm. HRMS: calcd. for $C_{13}H_{17}ClNO_4$ [M + H]$^+$ 286.0846; found 286.0823.

***erythro*-Ethyl 2-Acetamido-3-hydroxy-3-(4-methoxyphenyl)propanoate (3c):** Yield (86%), m.p. 146–148 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.15 (dd, J = 2.0, 7.0 Hz, 2 H), 6.85 (dd, J = 2.0, 7.0 Hz, 2 H), 6.25 (d, J = 7.0 Hz, 1 H), 5.22 (dd, J = 3.5, 5.5 Hz, 1 H), 4.96 (dd, J = 3.5, 6.5 Hz, 1 H), 4.44 (d, J = 5.5 Hz, 1 H), 4.20 (q, J = 7.5 Hz, 2 H), 2.04 (s, 3 H), 1.27 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.7, 169.5, 159.4, 131.2, 127.1, 113.7, 74.9, 62.0, 59.3, 55.2, 22.9, 14.1 ppm. HRMS: calcd. for $C_{14}H_{20}NO_5$ [M + H]$^+$ 282.1341; found 282.1329.

***erythro*-Methyl 2-Acetamido-3-hydroxy-3-(4-hydroxyphenyl)propanoate (3d):** Yield (41%). ^{1}H NMR (DMSO, 500 MHz): δ = 9.31 (s, 1 H), 8.15 (d, J = 9.0 Hz, 1 H), 7.14 (d, J = 8.5 Hz, 2 H), 6.88 (d, J = 8.5 Hz, 2 H), 5.60 (d, J = 5.0 Hz, 1 H), 4.61 (dd, J = 5.0, 8.5 Hz, 1 H), 4.40 (t, J = 8.5 Hz, 1 H), 3.61 (s, 3 H), 1.70 (s, 3 H) ppm.

(2*S*,3*S*)-2-Amino-3-hydroxy-3-phenylpropanoic Acid (5a): A solution of **7a** (30 mmol, 7.6 g) in a mixture of ethanol (65 mL) and NaOH (4 N, 10 mL) was stirred for 1.5 h and then concentrated under reduced pressure until the volume was approximately 10 mL. The residue was acidified with concentrated HCl and extracted with ethyl acetate. The extracts were combined, dried with anhydrous $MgSO_4$, and then concentrated to yield the product **8a** as a white solid (5.9 g, 90%). A suspension of **4a** in water (250 mL) was converted into a solution by adjusting its pH to 7.5 with NaOH (2 M). Acylase (120 mg) and $CoCl_2$ (0.05 M, 5 mL) were added at 37 °C to this magnetically stirred solution. The reaction pH was adjusted to 7.0 by adding NaOH (0.5 M), and this pH was maintained for 36 h. The reaction mixture was concentrated under reduced pressure until the volume was approximately 30 mL, acidified with concentrated HCl until the pH was about 1, and extracted with ethyl acetate (100 mL × 3). The extracts were washed with HCl (2%, 30 mL × 2) and were then combined, dried with anhydrous $MgSO_4$, and concentrated to yield *N*-acetyl-β-phenylserine (**6a**, 2.5 g). The aqueous layer was adjusted to pH 6 with aq. NaOH and concentrated until the volume was 5 mL. The precipitated crystals were collected on a filter, washed with a small amount of water, and dried to give **5a** (2.1 g, 79%) as a tan solid, m.p. 173–175 °C (dec.). $[\alpha]_D^{20}$ = 61.0 (c = 0.4, 6 N HCl). [lit[4b] $[\alpha]_D^{20}$ = 60.7 (c = 0.4, 6 N HCl).]. HPLC: column: Daicel Chem. Ind. Crownpak CR(+), mobile phase: MeOH/H_2O 1:7 at pH 1.0 ($HClO_4$), 25 °C, flow rate: 0.4 mL min^{-1}, retention time: 6.7 min. ^{1}H NMR (D_2O, 500 MHz): δ = 7.24–7.49 (m, 5 H), 5.38 (d, J = 4.0 Hz, 1 H), 4.11 (d, J = 4.0 Hz, 1 H) ppm. HRMS: calcd. for $C_9H_{12}NO_3$ [M + H]$^+$ 182.0817; found 182.0810.

(2*R*,3*R*)-2-Amino-3-hydroxy-3-phenylpropanoic Acid (7a): Similarly, **11a** was obtained by use of D-aminoacylase according to the procedure described above (yield 71%). $[\alpha]_D^{20}$ = –60.9 (c = 0.4, 6 N HCl). [ref.[4b] $[\alpha]_D^{20}$ = –63.2 (c = 0.65, 6 N HCl)]. HPLC: column: Daicel Chem. Ind. Crownpak CR(+), mobile phase: MeOH/H_2O 1:7 at pH 1.0 ($HClO_4$), 25 °C, flow rate: 0.4 mL min^{-1}, retention time: 5.8 min.

Compounds **5b** and **5c** were prepared similarly according to the procedure used for **5a**, whereas compounds **7b** and **7c** were prepared similarly according to the procedure used for **7a**.

(2*S*,3*S*)-2-Amino-3-(4-chlorophenyl)-3-hydroxypropanoic Acid (5b): Yield (68%), m.p. 175–177 °C. $[\alpha]_D^{20}$ = 32.5 (c = 0.2, H_2O). HPLC:

column: Daicel Chem. Ind. Crownpak CR(+), mobile phase: MeOH/H_2O 1:7 at pH 1.0($HClO_4$), 25 °C, flow rate: 0.3 mL min^{-1}, retention time: 7.1 min. ^{1}H NMR (D_2O, 500 MHz): δ = 7.40 (d, J = 8.5 Hz, 2 H), 7.32 (d, J = 8.5 Hz, 2 H), 5.29 (d, J = 4.0 Hz, 1 H), 4.02 (d, J = 4.0 Hz, 1 H) ppm. HRMS: calcd. for $C_9H_{11}ClNO_3$ [M + H]$^+$ 216.0427; found 216.0421.

(2*R*,3*R*)-2-Amino-3-(4-chlorophenyl)-3-hydroxypropanoic Acid (7b): Yield (69%). $[a]_D^{20}$ = –30.1 (c = 0.2, H_2O). HPLC: column: Daicel Chem. Ind. Crownpak CR(+), mobile phase: MeOH/H_2O 1:7 at pH 1.0 ($HClO_4$), 25 °C, flow rate: 0.3 mL min^{-1}, retention time: 6.1 min.

(2*S*,3*S*)-2-Amino-3-hydroxy-3-(4-methoxyphenyl)propanoic Acid (5c): Yield (63%), m.p. 164–166 °C (dec). $[a]_D^{20}$ = –2.76 (c = 0.4, methanol/H_2O 1:1). [ref.[8] $[a]_D^{20}$ = –2.73 (c = 0.586, methanol/H_2O 1:1)]. HPLC: column: Daicel Chem. Ind. Crownpak CR(+), mobile phase: MeOH/H_2O 1:7 at pH 1.0 ($HClO_4$), 6 °C, flow rate: 0.3 mL min^{-1}, retention time: 9.5 min. ^{1}H NMR (D_2O, 500 MHz): δ = 7.36 (d, J = 8.5 Hz, 2 H), 7.32 (d, J = 8.5 Hz, 2 H), 5.33 (d, J = 4.0 Hz, 1 H), 4.07 (d, J = 4.0 Hz, 1 H) 3.87 (s, 3 H) ppm. HRMS: calcd. for $C_{10}H_{14}NO_4$ [M + H]$^+$ 212.0923; found 212.0921.

(2*R*,3*R*)-2-Amino-3-hydroxy-3-(4-methoxyphenyl)propanoic Acid (7c): Yield (60%), m.p. 164–166 °C (dec). $[a]_D^{20}$ = +2.65 (c = 0.4, MeOH/H_2O 1:1). HPLC: column: Daicel Chem. Ind. Crownpak CR(+), mobile phase: MeOH/H_2O 1:7 at pH 1.0 ($HClO_4$), 6 °C, flow rate: 0.3 mL min^{-1}, retention time: 11.8 min.

Compounds **7a, 7b**, **5a**, and **5b** were also obtained by hydrolysis of the corresponding *N*-acetyl-enantiomers with HCl (1%).

A suspension of **8a** (0.9 g, 4 mmol) in HCl (1%, 80 mL) was heated at reflux for 4 h. The reaction mixture was cooled and washed with ethyl acetate, and then concentrated under reduced pressure until the volume was 2 mL. The aqueous layer was adjusted to pH 6 with aqueous NaOH. The precipitated crystals were collected on a filter, washed with a small amount of water, and dried to give **5a** (yield 0.55 g, 76%) as a tan solid.

***threo*-2-Amino-3-hydroxy-3-phenylpropanoic Acid (9):** Compound **9** was prepared as described in the literature.[10]

***threo*-2-Acetamido-3-hydroxy-3-phenylpropanoic Acid (10):** Acetic anhydride (45 mmol, 4.6 g) was added dropwise to a solution of **9** (15 mmol, 2.7 g) and sodium acetate (60 mmol, 4.9 g) in water (66 mL) at 0 °C. The reaction mixture was stirred at room temperature overnight, and then concentrated until the volume was 5 mL. The mixture was acidified with concentrated HCl until the pH was approximately equal to 1 and was then filtered to give **16** (2.4 g, 77%), m.p. 164–167 °C. ^{1}H NMR (MeOD, 500 MHz): δ = 7.38–7.41 (m, 2 H), 7.29–7.32 (m, 2 H), 7.21–7.24 (m, 1 H), 5.29 (d, J = 3.0 Hz, 1 H), 4.71 (d, J = 3.0 Hz, 1 H), 1.87 (s, 3 H) ppm.

(2*R*,3*S*)-2-Amino-3-hydroxy-3-phenylpropanoic Acid (11): Compound **11** was obtained by use of D-aminoacylase according to the procedure used for **7a** (yield 72%), m.p. 182–185 °C (dec). $[a]_D^{20}$ = +31.4 (c = 0.5, H_2O). [ref.[4a] $[a]_D^{20}$ = +31.0 (c = 1.28, H_2O).]. HPLC: column: Daicel Chem. Ind. Crownpak CR(+), mobile phase: MeOH/H_2O 1:7 at pH 1.0 ($HClO_4$), 25 °C, flow rate: 0.4 mL min^{-1}, retention time: 5.2 min. ^{1}H NMR (D_2O, 500 MHz): δ = 7.43–7.48 (m, 5 H), 5.32 (d, J = 4.0 Hz, 1 H), 3.93 (d, J = 4.0 Hz, 1 H) ppm. ^{13}C NMR (D_2O, 125 MHz): δ = 171.9. 139.2. 128.9. 128.6. 125.9. 71.3. 60.9 ppm. HRMS: calcd. for $C_9H_{12}NO_3$ [M + H]$^+$ 182.0817; found 182.0809.

(2*S*,3*R*)-2-Amino-3-hydroxy-3-phenylpropanoic Acid (13): Compound **13** was obtained by hydrolysis of the corresponding *N*-acetyl-enantiomer **12** with HCl (1%) as in the case of **7a** (yield 76%), m.p. 182–184 °C (dec). $[a]_D^{20}$ = –30.6 (c = 0.5, H_2O). [ref.[4a] $[a]_D^{20}$ = –30.0 (c = 1.0, H_2O).]. HPLC: column: Daicel Chem. Ind. Crownpak CR(+), mobile phase: MeOH/H_2O 1:7 at pH 1.0 ($HClO_4$), 25 °C, flow rate: 0.4 mL min^{-1}, retention time: 5.6 min.

***erythro*-Ethyl 2-Acetamido-3-methoxy-3-phenylpropanoate (14a):** Ag_2O (3.8 g, 16.4 mmol) was added to a solution of **7a** (5.8 g, 23.3 mmol) and MeI (3.4 mL) in CH_2Cl_2 (50 mL). The reaction mixture was heated at reflux for 24 h in darkness under nitrogen and then filtered. The filtrate was concentrated in vacuo and purified by chromatography (hexane/EtOAc 2.7:1) to afford **12a** as a white solid (4.6 g, 75%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.27–7.38 (m, 5 H), 6.16 (d, J = 8.5 Hz, 1 H), 4.94 (dd, J = 4.5, 8.5 Hz, 1 H), 4.61 (d, J = 4.5 Hz, 1 H) 4.04–4.09 (m, 2 H), 3.35 (s, 3 H), 2.02 (s, 3 H), 1.11 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 169.8, 169.7, 137.0, 128.5, 126.8, 83.6, 61.4, 57.9, 57.1, 23.3, 13.9 ppm. HRMS: calcd. for $C_{14}H_{20}NO_4$ [M + H]$^+$ 266.1392; found 266.1381.

Compounds **14b** and **14c** were prepared similarly according to the procedure used for **14a**.

***erythro*-Ethyl 2-Acetamido-3-(4-chlorophenyl)-3-methoxypropanoate (14b):** Yield (71%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.28–7.38 (m, 5 H), 6.13 (d, J = 8.0 Hz, 1 H), 4.94 (dd, J = 4.0, 9.0 Hz, 1 H), 4.60 (d, J = 4.0 Hz, 1 H), 4.06 (q, J = 7.0 Hz, 2 H), 3.35 (s, 3 H), 2.02 (s, 3 H), 1.11 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 169.8, 169.7, 137.0, 128.5, 128.3, 126.8, 83.5, 61.4, 57.9, 57.1, 23.3, 13.9 ppm. HRMS: calcd. for $C_{14}H_{19}ClNO_4$ [M + H]$^+$ 300.1003; found 300.0989.

***erythro*-Ethyl 2-Acetamido-3-methoxy-3-(4-methoxyphenyl)propanoate (14c):** Yield (73%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.20 (d, J = 8.5 Hz, 2 H), 6.89 (d, J = 8.5 Hz, 2 H), 4.91 (dd, J = 4.5, 9.0 Hz, 1 H), 4.54 (d, J = 4.5 Hz, 1 H), 4.08–4.13 (m, 2 H), 3.81 (s, 3 H), 3.31 (s, 3 H), 2.00 (s, 3 H), 1.16 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.1, 169.7, 159.7, 128.9, 128.0, 113.9, 83.1, 61.4, 57.6, 57.1, 55.3, 23.3, 14.1 ppm. HRMS: calcd. for $C_{15}H_{22}NO_5$ [M + H]$^+$ 296.1498; found 296.1486.

(2*S*,3*S*)-2-Amino-3-methoxy-3-phenylpropanoic Acid (16a): Similarly, **16a** was obtained by use of L-aminoacylase according to the procedure described above (yield 32%), m.p. 190–192 °C. $[a]_D^{20}$ = +36.3 (c = 0.6, H_2O). [ref.[5c] $[a]_D^{20}$ = +34.5 (c = 0.6, H_2O)]. HPLC: column: Daicel Chem. Ind. Crownpak CR(+), mobile phase: H_2O at pH 1.0 ($HClO_4$), 25 °C, flow rate: 0.4 mL min^{-1}, retention time: 12.2 min. ^{1}H NMR (D_2O, 500 MHz): δ = 7.45–7.49 (m, 3 H), 7.36–7.37 (m, 2 H), 4.93 (d, J = 2.5 Hz, 1 H), 4.11 (d, J = 2.5 Hz, 1 H), 3.41 (s, 3 H) ppm. ^{13}C NMR (D_2O, 125 MHz): δ = 171.0, 134.6, 129.1, 128.9, 127.1, 80.6, 58.9, 56.8 ppm. HRMS: calcd. for $C_{10}H_{14}NO_3$ [M + H]$^+$ 196.0974; found 196.0966.

(2*S*,3*S*)-2-Amino-3-(4-chlorophenyl)-3-methoxypropanoic Acid (16b): Yield (70%), m.p. 198–202 °C. $[a]_D^{20}$ = +29.0 (c = 0.4, H_2O). HPLC: column: Daicel Chem. Ind. Crownpak CR(+), mobile phase: MeOH/H_2O 1:7 at pH 1.0 ($HClO_4$), 6 °C, flow rate: 0.4 mL min^{-1}, retention time: 9.3 min. ^{1}H NMR (D_2O, 500 MHz): δ = 7.47–7.49 (m, 3 H), 7.37–7.38 (m, 2 H), 4.92 (d, J = 4.0 Hz, 1 H), 4.18 (d, J = 4.0 Hz, 1 H), 3.42 (s, 3 H) ppm. ^{13}C NMR (D_2O, 125 MHz): δ = 170.9, 134.5, 128.9, 128.5, 127.0, 80.6, 58.8, 56.8 ppm. HRMS: calcd. for $C_{10}H_{13}ClNO_3$ [M + H]$^+$ 230.0584; found 230.0575.

(2*R*,3*R*)-2-Amino-3-(4-chlorophenyl)-3-methoxypropanoic Acid (18b): (Removal of acetyl group with 1% HCl), yield (72%), m.p. 198–202 °C. $[a]_D^{20}$ = –26.9 (c = 0.4, H_2O). HPLC: column: Daicel Chem. Ind. Crownpak CR(+), mobile phase: MeOH/H_2O 1:7 at

pH 1.0 ($HClO_4$), 6 °C, flow rate: 0.4 mL min^{-1}, retention time: 8.3 min.

(2*S*,3*S*)-2-Amino-3-(4-methoxyphenyl)-3-methoxypropanoic Acid (16c): Yield 63%, m.p. 177–180 °C (dec). $[a]_D^{20}$ = +55.7 (*c* = 0.4, H_2O). HPLC: column: Daicel Chem. Ind. Crownpak CR(+), mobile phase: MeOH/H_2O 1:7 at pH 1.0 ($HClO_4$), 25 °C, flow rate: 0.4 mL min^{-1}, retention time: 18.6 min. ^{1}H NMR (D_2O, 500 MHz): δ = 7.31 (d, *J* = 8.5 Hz, 2 H), 7.06 (d, *J* = 8.5 Hz, 2 H), 4.88 (d, *J* = 4.0 Hz, 1 H), 4.16 (d, *J* = 4.0 Hz, 1 H), 3.87 (s, 3 H), 3.89 (s, 3 H) ppm. ^{13}C NMR (D_2O, 125 MHz): δ = 171.0, 159.3, 128.6, 126.9, 114.4, 80.1, 58.8, 56.7, 55.5 ppm. HRMS: calcd. for $C_{11}H_{16}NO_4$ $[M + H]^+$ 226.1079; found 226.1069.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra and HPLC chromatograms of products.

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