Synthesis Y. Yamashita et al. Feature

Ex Situ Enantioconvergent Approaches for the Effective Use of Undesired Isomers: Stereochemical Convergence of a Substrate with Multiple Chiral Centers and Recycling of a Decarboxylated Byproduct

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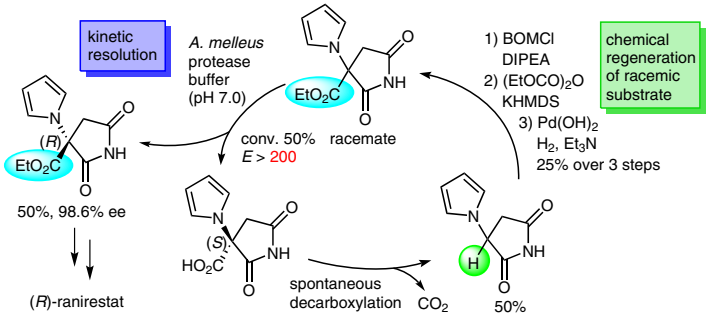

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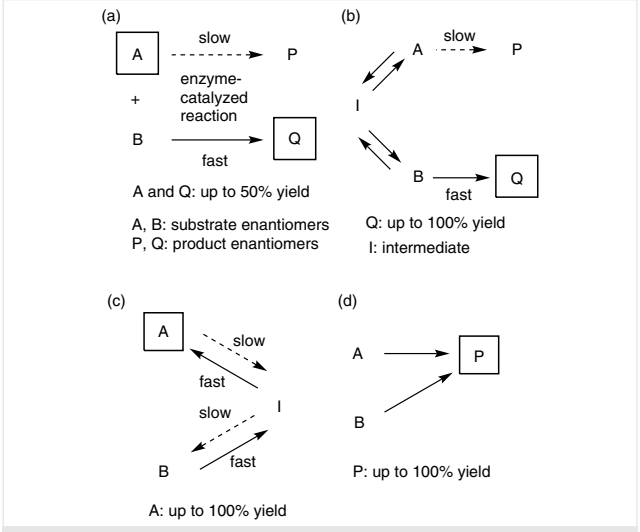
Abstract Enzyme-mediated kinetic resolution of racemic starting materials is a valuable and convenient tool for the preparation of enantioenriched compounds. To overcome the 50% yield limitation in conventional kinetic resolution, diverse enantioconvergent approaches have been developed. After a brief introduction of the recently developed '*in situ* deracemization' and '*ex situ* enantioconvergent approach', we present unique *ex situ* enantioconvergent approaches to solve two difficult cases: 1) In the synthesis of ethyl (3*R*,4*S*,5*R*)-shikimate, a diastereomeric (3*R**,4*S**,5*S**)-substrate containing multiple chiral centers was applied in an enzyme-catalyzed acetylation, and both the enzyme-catalyzed product and unreacted substrate converted into ethyl (3*R*,4*S*,5*R*)-shikimate via partial stereochemical inversions. 2) The enzyme-catalyzed kinetic resolution of a ranirestat precursor and the regeneration of the racemic substrate from a decarboxylated byproduct are described in detail. Since in the latter study, the products spontaneously decarboxylated after hydrolysis of the ester groups, the *in situ* regeneration of the racemic substrates was of significant difficulty. We successfully installed an ethoxycarbonyl group on the byproduct by *ex situ* sequential derivatization to overcome the 50% yield limitation.

Key words enzyme catalysis, kinetic resolution, convergence, undesired stereoisomers

1 Short Review of Enantioconvergent Approaches

Enzyme-mediated kinetic resolution is a valuable and convenient tool for the preparation of enantiomerically enriched compounds on both laboratory and industrial preparative scales if the racemic precursors are readily available. The principle of conventional kinetic resolution is briefly illustrated in Scheme 1 (a). In the conventional kinetic resolution of a racemate, the yield of the required en-



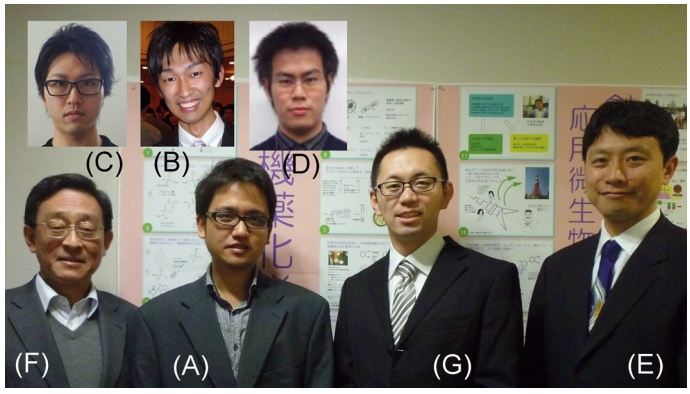
Scheme 1 Principles of enzyme-catalyzed kinetic resolution and deracemization approaches

antiomer is limited to a maximum of 50%. To overcome this inevitable constraint, *in situ* deracemization approaches in which the product is converted into a single enantiomer have been intensively studied.[1–19] These approaches are classified into three types: dynamic kinetic resolution (Scheme 1, b), *in situ* stereoinversion (Scheme 1, c), and enantioconvergent (Scheme 1, d).[20] Interestingly, it has recently been reported that sulfatases and epoxide hydrolases can be applied in an *in situ* enantioconvergent approach, resulting in the convergence of racemic sulfate esters and epoxides into the corresponding enantioenriched alcohols and diols, respectively.[20]

The *ex situ* inversion of the stereochemistry in an undesired stereoisomer after the completion of a kinetic resolution is another possible method to overcome the 50% yield limitation. In lipase-catalyzed kinetic resolutions starting from both esters and alcohols, the convergence of products into a single enantiomer of the esters or alcohols can be accomplished via the introduction of a leaving group and successive stereoinversion (Scheme 2).

Herein, we present resolution, *ex situ* enantioconvergent approaches to overcome the 50% yield limitation in two difficult cases where the above-mentioned deracemization approach cannot be successfully applied. The first case is the convergence of a racemate containing multiple chiral centers into a single product via several partial stereoinversions (Section 2). The second case involves nonenzymatic C–C bond cleavage in the product, via decarboxylation, immediately after the enzyme-catalyzed hydrolysis (Section 3).

Biographical Sketches



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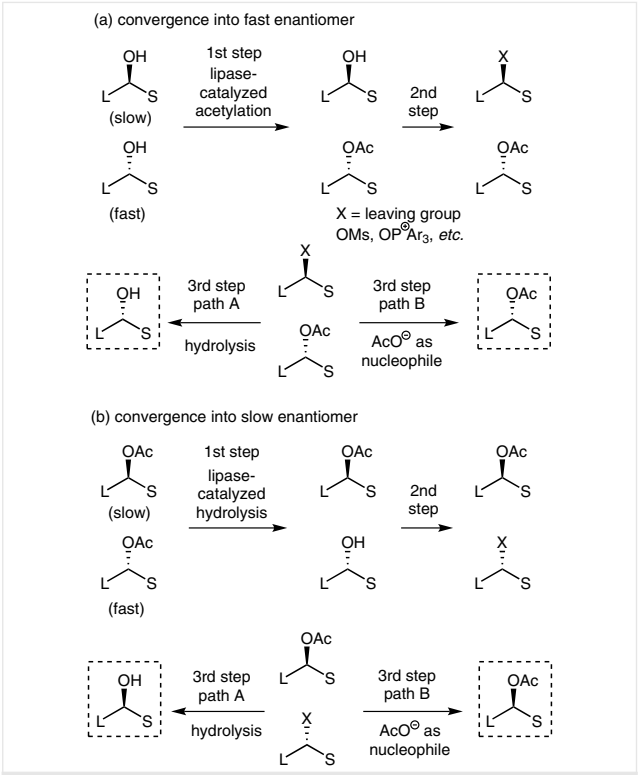
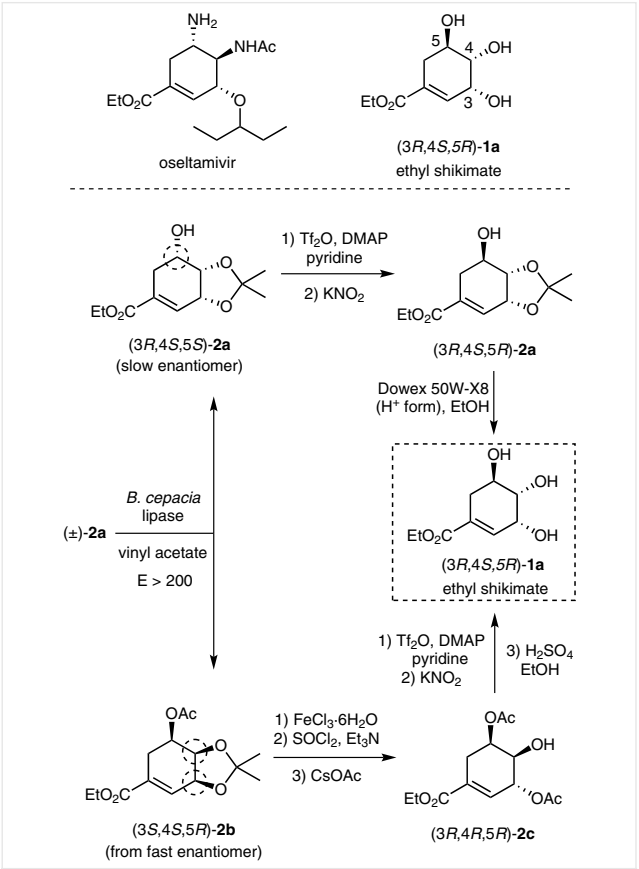


Scheme 2 Convergence of racemic secondary alcohols (a) and their esters (b) into a single enantiomer in three steps involving lipase-catalyzed kinetic resolution (1st step), introduction of a leaving group (2nd step), and stereoinversion/hydrolysis (3rd step); L: large substituents, S: small substituents.

2 Resolution of a Substrate with Multiple Chiral Centers

Ethyl shikimate [(3*R*,4*S*,5*R*)-**1a**], an important intermediate for the synthesis of oseltamivir phosphate, has three chiral centers. Therefore, the above-mentioned deracemization approaches including a simple stereoinversion at a specific secondary alcohol afford only the diastereomer of the desired stereoisomer, not the single enantiomer. We designed a secondary alcohol (3*R**,4*S**,5*S**)-(±)-**2a**, having a diastereomeric relationship with ethyl shikimate, as a substrate for lipase-mediated kinetic resolution.[21] Alcohol (3*R**,4*S**,5*S**)-(±)-**2a** was prepared on a large scale by the Diels–Alder reaction of furan with acryloyl chloride and the subsequent introduction of oxygen functional groups.

Among the three commercially available lipases [*Burkholderia cepacia* lipase (Amano, PS-IM), *Candida antarctica* lipase B (Novozym 435), and *Candida rugosa* lipase (Meito OF)], the use of *B. cepacia* lipase resulted in an excellent *E* value (>200) and robust catalytic activity under the reaction conditions. Both products obtained from the *B. cepacia* lipase-catalyzed resolution, alcohol (3*R*,4*S*,5*S*)-**2a** and acetate (3*S*,4*S*,5*R*)-**2b**, were merged into (3*R*,4*S*,5*R*)-**1a** via (3*R*,4*S*,5*R*)-**2a** and (3*R*,4*R*,5*R*)-**2c**, respectively, thus establishing a new *ex situ* enantioconvergent route, as shown in Scheme 3.[21]

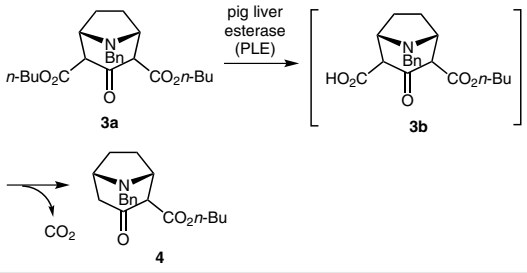


Scheme 3 Convergence of (3*R*,4*S*,5*S*)-**2a** (slow enantiomer) and (3*S*,4*S*,5*R*)-**2b** (from fast enantiomer) into ethyl shikimate [(3*R*,4*S*,5*R*)-**1a**]

3 Resolution Based on Enzyme-Mediated Hydrolysis Accompanied by Nonenzymatic C–C Bond Cleavage

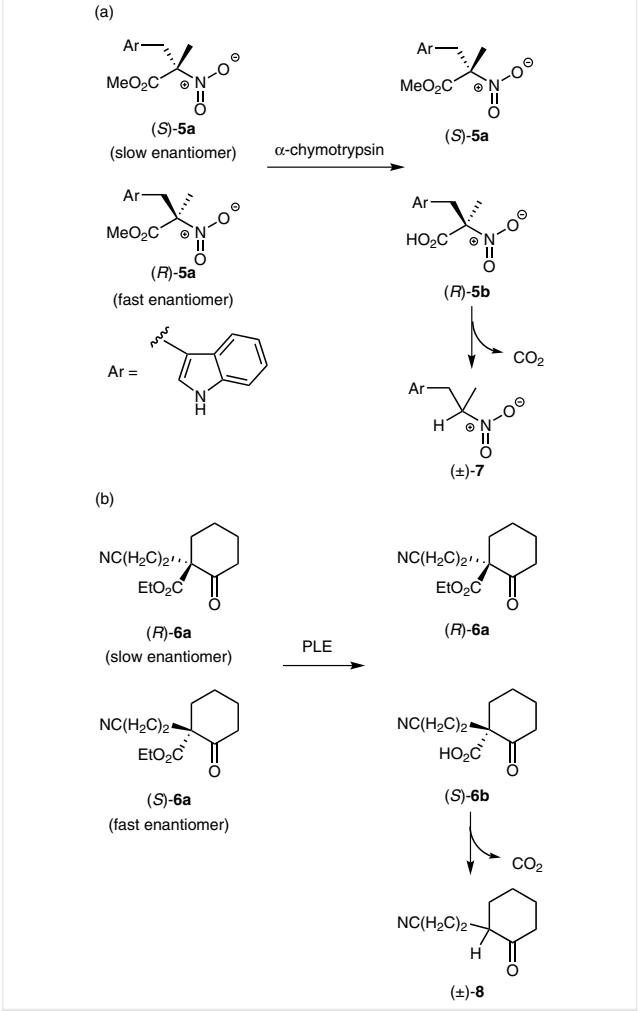
In the enzyme-mediated hydrolysis of esters bearing adjacent electron-withdrawing groups, such as in β-oxo esters, subsequent decarboxylation can occur during the progress of the enzyme-mediated hydrolysis. The sequential reaction can be advantageous for the desymmetrization approach from **3a** to **4**[22] (Scheme 4).

On the other hand, in kinetic resolution, *in situ* decarboxylation is disadvantageous for maximum yield; the decarboxylated products are difficult to reconvert *in situ* into the racemic substrates by the above-mentioned deracemization approaches. In the typical examples shown in Scheme 5,α-nitro ester **5a**[23] and oxo ester **6a**[24] were hydrolyzed and subsequently decarboxylated, producing nitroal-



Scheme 4 Enzyme-catalyzed hydrolysis of β-oxo ester **3a** with spontaneous decarboxylation[22a]

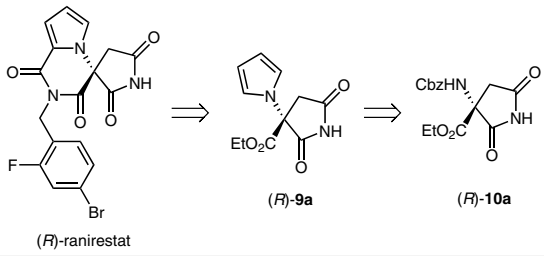
kane (±)-**7** and ketone (±)-**8**, respectively. Because only slow enantiomers are available for the subsequent synthesis, the fast enantiomer-derived products were generally discarded.



Scheme 5 Kinetic resolution by enzyme-catalyzed hydrolysis of α-nitro ester **5a**[23] (a) and oxo ester **6a**[24] (b) accompanied by the decarboxylation of the products derived from the fast enantiomers

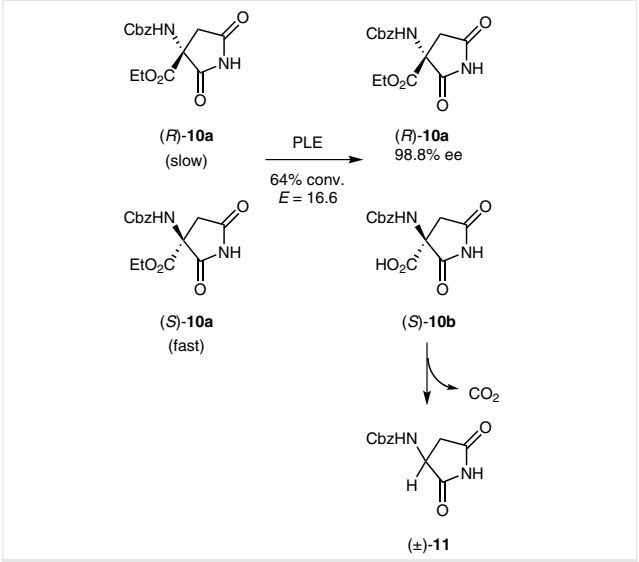
For the effective use of a waste decarboxylated product, the regeneration of the racemic substrate by introducing the lost functional groups after the kinetic resolution is a powerful approach. In the preparation of the synthetic precursor of ranirestat (AS-3201, Scheme 6), enzymes were screened, and the substrate structure was optimized in the kinetic resolution. Finally, the undesired products in the kinetic resolution were recycled. These results are now described in detail.

Ranirestat has been developed as a drug for the treatment of diabetic neuropathy,[25] a complication of diabetes, by Sumitomo Dainippon Pharma Co., Ltd. It is a highly potent aldose reductase inhibitor that suppresses the accumulation of sorbitol in neural tissues.[25a,b] Ranirestat has a unique stereocenter on its succinimide ring; the nitrogen atom of a pyrrole ring is directly attached to the tetrasubstituted stereogenic center. The (*R*)-isomer of ranirestat shows 10 times more potent inhibitory activity against aldose reductase *in vitro* and 500 times more potent *in vivo* inhibitory activity than the (*S*)-isomer.[25a] Thus, enantiomerically enriched 2,2-disubstituted succinimide (*R*)-**9a** (Scheme 6) is crucial for the synthesis of (*R*)-ranirestat.[25a]



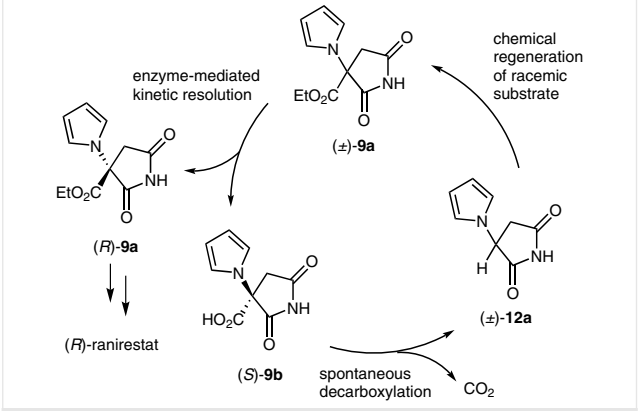
Scheme 6 (*R*)-Ranirestat and its synthetic precursors

To access (*R*)-**9a** with a high enantiomeric excess, Negoro and co-workers prepared enantioenriched (*R*)-**10a**, the precursor of (*R*)-**9a**, by recrystallization of the cinchonidine salt.[25a] Owing to the high therapeutic potency of ranirestat, more practical synthetic methods were needed, and alternative asymmetric syntheses of (*R*)-**9a** have been developed. Shibasaki and co-workers reported the asymmetric amination of a succinimide derivative with a lanthanum-based ternary catalyst.[26] Seki and Kawase reported the asymmetric alkylation of an α-cyano ester using a phase-transfer catalyst.[27] On the other hand, Kudo and Yamada accomplished the kinetic resolution of **10a** by pig liver esterase (PLE)-mediated hydrolysis (Scheme 7), in which (*S*)-**10a** (the fast enantiomer) was hydrolyzed more rapidly than (*R*)-**10a** (the slow enantiomer), and a moderate *E* value of 16.6 was obtained.[28] Although (*R*)-**10a** was obtained in 98.8% ee, no data exist for (*S*)-**10b**. This compound may have spontaneously decarboxylated to afford (±)-**11** under the reaction conditions.



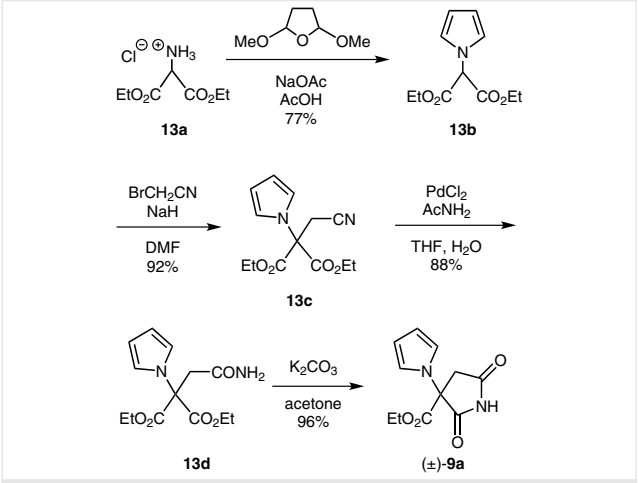
Scheme 7 Kudo and Yamada's kinetic resolution of **10a**

Because the pyrrole ring in **9a** is smaller than the Cbz group in **10a**,[28] reducing the steric repulsion between **9a** and enzymes, an improvement in the reactivity and enantioselectivity of the kinetic resolution of **9a** was expected. First, the synthesis of racemic substrate (±)-**9a** and the kinetic resolution of **9a** with several enzymes were investigated. Second, the effects of the size of the ester moiety on the enantioselectivity and reaction rate were studied. Finally, the chemical regeneration of (±)-**9a** from the undesired (*S*)-isomer by *ex situ* convergence via the ethoxycarbonylation of (±)-**12a** was investigated (Scheme 8).



Scheme 8 Our kinetic resolution and reuse of the undesired isomer (*ex situ* convergence)

The racemic substrate **9a** used for the kinetic resolution was prepared as shown in Scheme 9. Malonate **13b**, prepared by the Clauson-Kaas reaction of diethyl aminomalonate (**13a**),[25a] was alkylated with bromoacetonitrile, providing nitrile **13c**. Palladium-catalyzed hydration of the cyano group with acetamide[29] afforded amide **13d**. Using our procedure, amide **13d** can be prepared in two steps, one step shorter than the method used by Negoro and co-workers.[25a] Finally, the subsequent base-mediated intramolecular cyclization of **13d** afforded succinimide (±)-**9a**. Compared to previous reports on the syntheses of kinetic resolution substrates, succinimide (±)-**9a** can be prepared from commercially available diethyl aminomalonate (**13a**) in fewer steps; the total yield was >60% over four steps. Moreover, all the reactions are easy to manipulate, indicating suitability for large-scale synthesis.

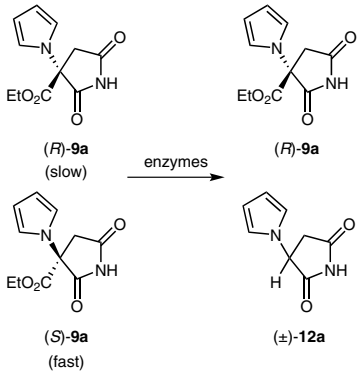


Scheme 9 Preparation of racemic substrate **9a**

The enzyme-mediated kinetic resolutions of (±)-**9a** were conducted under hydrolytic conditions (Table 1). In all cases, (*S*)-**9a** was hydrolyzed preferentially, as in the case of (*S*)-**10a**, affording **12a** via the spontaneous decarboxylation of (*S*)-**9b**. The stereochemistry of the slow enantiomer, (*R*)-**9a**, was confirmed by comparing optical rotation values [(*R*)-**9a**: $[\alpha]_D^{25}$ –56.4 (Lit.[25a] $[\alpha]_D^{26}$ –59.5)]. When (±)-**9a** was treated with PLE, the *E* value (11.3) was slightly lower than that of **10a**, contrary to our expectations. The hydrolysis of **9a** proceeded faster than that of **10a**, indicating that the reactivity of the (*R*)-isomer increased by more than that of the (*S*)-isomer upon replacing the NHCbz group by the pyrrole ring. Thus, three other enzymes, *C. antarctica* lipase B (Novozym 435), *B. cepacia* lipase (Amano, PS-IM), and *Aspergillus melleus* protease (Nagase, XP-488), were applied. The two lipases are solid-supported enzymes that are highly stable in aqueous and organic solvents and can be easily removed from reaction mixtures by simple filtration. *A. melleus* protease has been developed for the modification of food properties by Nagase ChemteX Corporation (Japan) and applied in the kinetic resolution of ethyl tetrahydrofurancarboxylate and dihydropyridine derivatives,[30] which are structurally similar to **9a**. In contrast to the sluggish hydro-

lysis of **9a** with the two lipases, *A. melleus* protease showed a fast reaction rate and excellent enantioselectivity ($E > 200$).

Table 1 Kinetic Resolution of (±)-**9a** by Enzyme-Mediated Hydrolysis



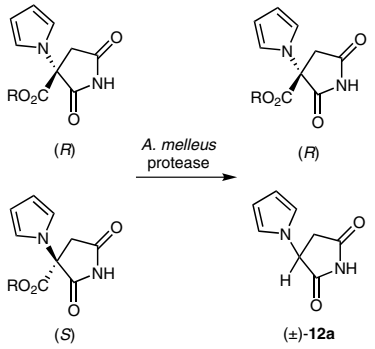
Enzyme	Time (h)	Conv. (%)	*E*
Pig liver esterase (PLE, Sigma)	1.0	62.6	11.3
C. antarctica lipase B (Novozym 435)	24	0	ND[a]
B. cepacia lipase (Amano, PS-IM)	24	0	ND[a]
A. melleus protease (Nagase, XP-488)	1.5	50.0	>200

[a] ND: not determined.

To further establish the relationship between the reactivity, selectivity, and substrate structures in *A. melleus* protease-mediated kinetic resolution, other substrates with a more hindered ester group, such as isobutyl and isopropyl, were used (Table 2). It was expected that the reaction rate of the slow enantiomers would decrease owing to the steric hindrance of their alkoxy moieties, thus improving the enantioselectivity. Substrates **9c** and **9d** were prepared by the Ti(O*i*-Pr)$_4$-catalyzed transesterification of **9a** with the corresponding alcohols.[31] In the case of isobutyl ester **9c**, the enantioselectivity seemed to be slightly lower than that of ethyl ester **9a** based on a simple calculation of the data. The bulkier isopropyl ester group in **9d** significantly decreased both the enantioselectivity ($E = 5.4$) and reactivity. The fast enantiomer was more affected by the steric hindrance of the ester moiety than the slow enantiomer. These results proved that (±)-**9a** is a better substrate for *A. melleus* protease-mediated kinetic resolution in terms of both synthetic accessibility and enantioselectivity.

As noted above, the kinetic resolution of (±)-**9a** ($E > 200$) was successfully carried out using *A. melleus* protease, affording (*R*)-**9a** in 50% yield and with 98.6% ee. While (*R*)-**9a** was used for the synthesis of (*R*)-ranirestat, undesired (±)-**12a** would normally be discarded. Therefore, for the effective use of undesired product (±)-**12a** and to overcome the

Table 2 Effect of the Structure of the Ester Moiety on Kinetic Resolution

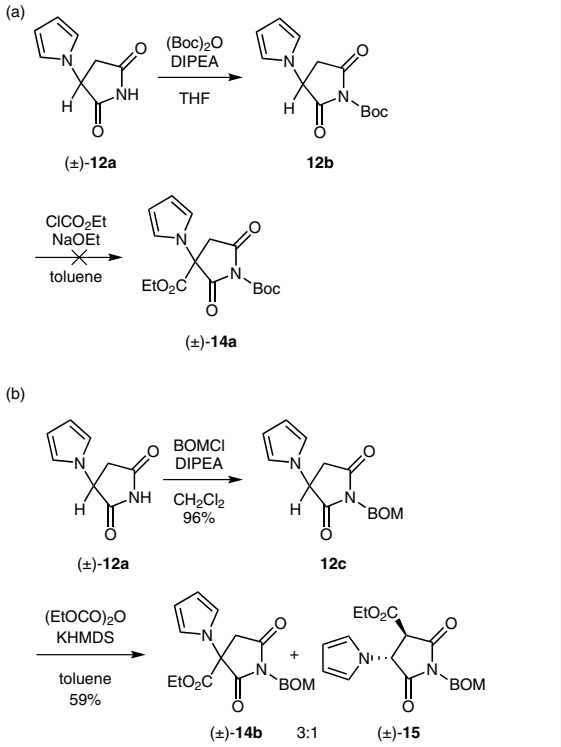


Substrate	R	Time (h)	Conv. (%)	*E*
9a	Et	1.5	50.0	>200
9c	*i*-Bu	2.0	47.8	>200
9d	*i*-Pr	2.0	29.8	5.4

50% yield limitation, the regeneration of racemic substrate (±)-**9a** from (±)-**12a** was investigated. Our regeneration strategy for (±)-**9a** was as follows: protection of the imide nitrogen in (±)-**12a**; subsequent ethoxycarbonylation at the C-3 position and deprotection to afford (±)-**9a**.

Because the acidic proton of the imide nitrogen would interfere with deprotonation of the C-3 position in the ethoxycarbonylation step, a Boc group was introduced on the imide nitrogen, affording **12b** (Scheme 10, a). The imide ring in **12b** was expected to be unstable owing to the electron-withdrawing properties of the Boc group; thus, **12b** was used in the subsequent ethoxycarbonylation step without further purification. The reaction conditions were adopted from a procedure developed by Crider and co-workers,[32] in which a similar compound bearing a cyclic imide group and an aromatic ring was used. Unfortunately, this resulted in decomposition of the imide ring by the nucleophilic attack of ethoxide anion. This result indicated that electron-withdrawing groups such as carbamate-type protecting groups are not suitable as protecting groups for the imide nitrogen, and that bulky bases should be used for the ethoxycarbonylation.

Next, various protecting groups, such as a *tert*-butyl, *p*-methoxyphenyl, *p*-methoxybenzyl, or allyl group, were introduced on the nitrogen atom of the imide ring. Disappointingly, the removal of these groups was difficult owing to the high sensitivity of the pyrrole ring under various reaction conditions, including acidic, oxidative, and transition-metal-mediated conditions. These findings prompted us to use the benzyloxymethyl (BOM) group, which can be removed by hydrogenolysis; BOM imide **12c** was prepared from **12a** in a high yield (Scheme 10, b). When weakly nucleophilic bases such as NaH and KH were used with **12c**,

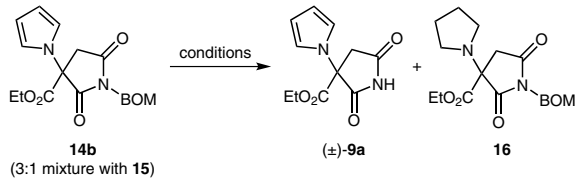


Scheme 10 (a) Attempted ethoxycarbonylation of *N*-Boc-succinimide **12a**, and (b) ethoxycarbonylation of imide **12c** bearing a BOM group

ethoxycarbonylated compound was obtained in negligible amounts. Finally, the reaction was accomplished using potassium hexamethyldisilazide and diethyl dicarbonate, affording **14b** as a 3:1 inseparable mixture with regioisomer **15** in a moderate yield.

For the removal of the BOM group, initially, hydrogenolysis conditions were applied by using a palladium catalyst adsorbed on carbon (Table 3, entries 1 and 2) or synthetic polymers[33] (entries 3 and 4). These attempts, however, resulted in reduction of the pyrrole ring, producing the undesired pyrrolidine **16** as the major product. To suppress the reduction of the pyrrole ring, palladium on Diaion® CR11 polymer[34] bearing an iminodiacetate-chelating group was used; however, imide **9a** was not obtained at all (Table 3, entry 5). The addition of Et_3N[35] suppressed the reduction of the pyrrole ring, affording (±)-**9a** (Table 3, entry 6). After further investigation of the reaction conditions, a combination of $Pd(OH)_2$ and Et_3N was found to be a superior catalyst for the selective hydrogenolytic cleavage of the BOM group (Table 3, entry 7). The inseparable impurity (±)-**15** was also reduced under these conditions, and the reduced compound could be separated in this step. Using this method, the *ex situ* convergence of (±)-**12a** into (±)-**9a** was accomplished. The overall yield was 25% over three steps, and the cycle for the effective use of the undesired isomer was completed.

Table 3 Hydrogenolysis of the BOM Group in **14b**



Entry	Catalyst (wt%)	Et_3N (mol%)	Ratio **9a**/**16**[a]	Yield (%) of **9a**
1	10% Pd/C (50)	–	1:2	ND[b]
2	20% $Pd(OH)_2$/C (50)	–	1:5	ND[b]
3	ASCA-2®[c] (200)	–	1:2	ND[b]
4	10% Pd/HP20[d] (80)	–	1:2	ND[b]
5	8% Pd/CR11[e] (80)	–	0:1	ND[b]
6	10% Pd/C (116)	80	ND[b]	56
7	20% $Pd(OH)_2$/C (213)	60	ND[b]	63

[a] Determined from the ^1H NMR spectrum of the crude mixture.
[b] ND: not determined.
[c] N.E. CHEMCAT Ltd.
[d] Pd on Diaion® HP20 polymer (Mitsubishi Chemical Co. Ltd., on polystyrene–polyvinylbenzene-based synthetic adsorbent).
[e] Pd on Diaion® CR11 polymer (Mitsubishi Chemical Co. Ltd., on iminodiacetate-based chelating resin).

4 Conclusions

In this study, we have attempted to solve difficult cases of kinetic resolutions where *in situ* deracemization approaches cannot be applied to overcome the 50% yield limitation. These examples prove that not only *in situ* deracemization, but also *ex situ* synthetic derivatization after kinetic resolution, namely a *ex situ* enantioconvergent approach, can play an important role in the efficient chemoenzymatic transformation of organic compounds. In Section 2 we described the enzyme-catalyzed kinetic resolution of a 'diastereomeric substrate' bearing multiple chiral centers and chemical convergence to the desired stereoisomer. The design of a racemic substrate having a diastereomeric relationship with ethyl shikimate was the key for the success of the enantioconvergent approach. In Section 3 we described the regeneration of the racemic substrate from a decarboxylated product in an enzyme-catalyzed hydrolytic kinetic resolution. Although the total yield of this regeneration sequence was as low as 25%, for the first time the lost functional group was reintroduced into the undesired product derived from the fast enantiomer, which would normally be discarded.

We hope that our findings will inspire chemists and more unique chemoenzymatic transformations are developed, thus not waiting for the development of better enzymes by enzymologists.

Melting points were recorded on a Yanaco MP-J3 micro melting point apparatus and are uncorrected. IR spectra were measured as ATR on a Jeol FT-IR SPX60 spectrometer. ^{1}H NMR spectra were measured at 400 MHz on a Varian 400-MR or at 500 MHz on an Agilent Inova-500 spectrometer, and ^{13}C NMR spectra were measured at 100 MHz on a Varian 400-MR or at 125 MHz on an Agilent Inova-500 spectrometer. High-resolution mass spectra were recorded on a Jeol JMS-T100LP AccuTOF spectrometer. HPLC data were recorded using Jasco MD-2010 multichannel detectors and a Shimadzu SPD-20A diode array detector. Optical rotation values were recorded on a Jasco P-1010 polarimeter. Merck silica gel 60 F_{254} thin-layer plates (1.05744, 0.5-mm thickness) were used for preparative TLC. Silica gel 60 (spherical and neutral; 100–210 µm, 37560-79) from Kanto Chemical Co. and SNAP silica gel cartridges and an Isolera One flash purification system from Biotage (Sweden) were used for column chromatography. *Aspergillus melleus* protease (XP-488), *Candida antarctica* lipase B (Novozym 435), and *Burkholderia cepacia* lipase (PS-IM) were gifts from Nagase & Co., Novozymes Japan, and Amano Enzyme Inc., respectively.

Diethyl 2-(Cyanomethyl)-2-(1*H*-pyrrol-1-yl)malonate (13c)

To a stirred suspension of NaH (252 mg, 10.5 mmol) in anhydrous DMF (7.0 mL) was added ester **13b**[25a] (2.00 g, 8.88 mmol) at 0 °C, and the mixture was stirred for 1 h at r.t. Then, to the mixture was added dropwise bromoacetonitrile (700 µL, 10.0 mmol) at 0 °C, and the mixture was further stirred at r.t. for 4 h. The reaction was quenched with saturated aq NH_4Cl solution, and the organic materials were extracted with EtOAc (3 ×). The combined organic layer was washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (100 g; hexane/EtOAc, 5:1) to afford **13c** (2.15 g, 92%) as a colorless oil.

IR (ATR): 2985, 1741, 1250, 721 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.1 Hz, 6 H), 3.35 (s, 2 H), 4.35 (q, *J* = 7.1 Hz, 2 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 6.25 (dd, *J* = 2.1, 2.3 Hz, 2 H), 6.81 (dd, *J* = 2.1, 2.3 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 26.2, 63.8, 68.9, 110.0, 115.0, 120.0, 165.2.

Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.08; H, 6.11; N, 10.59.

Diethyl 2-(Carbamoylmethyl)-2-(1*H*-pyrrol-1-yl)malonate (13d)

A solution of **13c** (500 mg, 1.89 mmol), $PdCl_2$ (42 mg, 0.24 mmol), and acetamide (1.12 g, 19.0 mmol) in a mixture of THF and H_2O (1:1, 15 mL) was stirred at r.t. for 24 h. The mixture was filtered through a short column of Celite® and the column was washed with EtOAc. The combined filtrate and washings was washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (4 g; hexane/EtOAc, 5:1) to afford **13d** (468 mg, 88%) as a colorless solid; mp 94.0–95.0 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.2 Hz, 6 H), 3.33 (s, 2 H), 4.29 (q, *J* = 7.2 Hz, 2 H), 4.30 (q, *J* = 7.2 Hz, 2 H), 5.34 (br s, 1 H), 5.56 (br s, 1 H), 6.17 (dd, *J* = 2.2, 2.4 Hz, 2 H), 6.84 (dd, *J* = 2.2, 2.4 Hz, 2 H); the ^{1}H NMR spectrum was identical with that reported previously.[25a]

Ethyl 2,5-Dioxo-3-(1*H*-pyrrol-1-yl)pyrrolidine-3-carboxylate (9a)

To a stirred solution of **13d** (500 mg, 1.77 mmol) in acetone (7.5 mL) was added K_2CO_3 (25 mg, 0.18 mmol), and the mixture was refluxed for 24 h. After cooling, the mixture was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in EtOAc and washed with saturated aq NH_4Cl solution, H_2O, and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (2.5 g; hexane/EtOAc, 5:1) to afford **9a** (400 mg, 96%) as a colorless oil.

(±)-**9a**: HPLC [Daicel Chiralpak AY-H, 0.46 cm × 25 cm; hexane/*i*-PrOH (5:1), 0.5 mL/min; detected at 206 nm]: t_R (min) = 21.1 [(*S*)-**9a**], 25.0 [(*R*)-**9a**].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 3 H), 3.35 (d, *J* = 17.9 Hz, 1 H), 3.61 (d, *J* = 17.9 Hz, 1 H), 4.28 (q, *J* = 7.2 Hz, 2 H), 6.27 (dd, *J* = 2.1, 2.2 Hz, 2 H), 6.93 (dd, *J* = 2.1, 2.2 Hz, 2 H), 8.10 (br s, 1 H); the ^{1}H NMR spectrum was identical with that reported previously.[25a]

Isobutyl 2,5-Dioxo-3-(1*H*-pyrrol-1-yl)pyrrolidine-3-carboxylate (9c)

To a stirred solution of ethyl ester **9a** (200 mg, 0.85 mmol) in *i*-BuOH (2.0 mL) was added Ti(O*i*-Pr)$_4$ (110 µL, 0.37 mmol), and the mixture was refluxed for 2.5 h. After cooling, the mixture was filtered through a short column of Celite® and the column was washed with EtOAc. The combined filtrate and washings was concentrated in vacuo. The residue was dissolved in EtOAc, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (1.5 g; hexane/EtOAc, 10:1) to afford **9c** (164 mg, 73%) as a colorless solid; mp 69.0–70.0 °C.

(±)-**9c**: HPLC [under the same conditions as for (±)-**9a**]: t_R (min) = 19.5 [(*S*)-**9c**], 25.7 [(*R*)-**9c**].

IR (ATR): 3209, 3082, 2962, 2873, 2779, 1716 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85 (d, *J* = 6.7 Hz, 6 H), 1.90 (ddqq, *J* = 6.4, 6.8, 6.7, 6.7 Hz, 1 H), 3.37 (d, *J* = 18.0 Hz, 1 H), 3.62 (d, *J* = 18.0 Hz, 1 H), 3.97 (dd, *J* = 6.8, 10.8 Hz, 1 H), 4.00 (dd, *J* = 6.4, 10.8 Hz, 1 H), 6.28 (dd, *J* = 2.0, 2.5 Hz, 2 H), 6.95 (dd, *J* = 2.0, 2.5 Hz, 2 H), 8.49 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.6, 27.5, 41.9, 68.6, 73.4, 110.0, 120.1, 167.0, 170.6, 172.8.

Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.18; H, 6.14; N, 10.48.

Isopropyl 2,5-Dioxo-3-(1*H*-pyrrol-1-yl)pyrrolidine-3-carboxylate (9d)

In the same manner as described for **9c**, **9a** (300 mg, 1.28 mmol) was treated with Ti(O*i*-Pr)$_4$ (140 µL, 0.47 mmol) in *i*-PrOH (3.0 mL) at reflux for 2.5 h. After a similar workup, the residue was purified by silica gel column chromatography (2 g; hexane/EtOAc, 10:1) to afford **9d** (256 mg, 80%) as a colorless solid; mp 94.0–94.5 °C.

(±)-**9d**: HPLC [under the same conditions as for (±)-**9a**]: t_R (min) = 15.5 [(*S*)-**9d**], 18.6 [(*R*)-**9d**].

IR (ATR): 3240, 3101, 2987, 1708 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (d, *J* = 6.2 Hz, 3 H), 1.25 (d, *J* = 6.2 Hz, 3 H), 3.34 (d, *J* = 18.0 Hz, 1 H), 3.55 (d, *J* = 18.0 Hz, 1 H), 5.08 (qq, *J* = 6.2, 6.2 Hz, 1 H), 6.25 (dd, *J* = 2.0, 2.2 Hz, 2 H), 6.92 (dd, *J* = 2.0, 2.2 Hz, 2 H), 8.73 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 21.4, 41.9, 68.7, 72.3, 110.1, 120.0, 166.2, 170.4, 172.5.

Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.70; H, 5.66; N, 11.04.

PLE-Catalyzed Hydrolysis of (±)-9a

To a solution of (±)-**9a** (20.9 mg, 88.5 µmol) in a mixture of phosphate buffer (0.1 M, pH 7.0; 200 µL) and acetone (50 µL), PLE (Sigma, E2884; 50 µL) was added, and the mixture was stirred for 1 h at 30 °C. The progress of the reaction was monitored by TLC analysis [silica gel,

hexane/EtOAc (1:1), by the detection of the deethoxycarbonylated product **12a** (R_f = 0.38)]. The reaction was quenched with 2 M HCl to pH 2, and the organic materials were extracted with EtOAc (3 ×). The combined extract was dried over Na_2SO_4 and concentrated in vacuo. The residue (16.7 mg) was purified by preparative TLC (hexane/EtOAc, 1:1) to afford (*R*)-**9a** (7.8 mg, 33 μmol, 37.3%) and **12a** (9.1 mg, 55 μmol, 62.6%).

(*R*)-**9a**: $[\alpha]_D^{25}$ –56.4 (*c* 0.32, MeOH) [Lit.[25a] $[\alpha]_D^{26}$ –59.5 (*c* 1.0, MeOH), for (*R*)-**9a**].

HPLC: t_R (min) = 22.5 [(*S*)-**9a**, 3.3%], 26.1 [(*R*)-**9a**, 96.7%]; 93.4% ee.

The ^{1}H NMR spectrum of (*R*)-**9a** was identical with that of (±)-**9a**.

Identification of 12a

An authentic sample of **12a** was prepared in the following manner: Ester **9a** (289 mg, 1.23 mmol) was dissolved in THF (2 mL). After cooling to 0 °C, aq NaOH solution (2.0 M; 700 μL, 1.40 mmol) was added, and the mixture was stirred for 27 h at 0 °C. The reaction was quenched with saturated aq NH_4Cl solution, and the organic materials were extracted with EtOAc (3 ×). The combined extract was washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (15 g; hexane/EtOAc, 3:1) to afford **12a** (129 mg, 64%).

IR (ATR): 3240, 3095, 1785, 1702, 1172 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.00 (dd, *J* = 5.7, 18.6 Hz, 1 H), 3.34 (dd, *J* = 9.6, 18.6 Hz, 1 H), 5.08 (dd, *J* = 5.7, 9.6 Hz, 1 H), 6.25 (dd, *J* = 2.1, 2.2 Hz, 2 H), 6.92 (dd, *J* = 2.1, 2.2 Hz, 2 H), 8.19 (br s, 1 H); the ^{1}H NMR spectrum of the sample derived from the PLE-catalyzed hydrolysis was identical with that of this authentic sample.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.8, 57.7, 110.3, 119.5, 173.1, 173.6.

Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.65; H, 4.99; N, 16.85.

Comparison with Other Hydrolytic Enzymes

A 2-mL sample tube was charged with (±)-**9a** (20 mg), phosphate buffer (0.1 M, pH 7.0; 0.20 mL), and acetone (50 μL). To this, a 20-mg portion of one of the hydrolytic enzymes, *A. melleus* protease (Nagase, XP-488), *C. antarctica* lipase B (Novozymes, Novozym 435), or *B. cepacia* lipase PS (Amano, PS-IM), was added, and the mixture was stirred for 24 h at 30 °C. The reaction was monitored by TLC analysis, as described above. Of the three enzymes tested, only *A. melleus* protease showed a certain progress of the hydrolysis.

A. melleus Protease-Catalyzed Hydrolysis of (±)-9a

In a similar manner as described for the hydrolysis with PLE, to a solution of (±)-**9a** (21.4 mg, 90.6 μmol) in a mixture of phosphate buffer (0.1 M, pH 7.0; 200 μL) and acetone (50 μL), *A. melleus* protease (20 mg) was added. The mixture was stirred for 1.5 h at 30 °C. By the same workup and purification, ester (*R*)-**9a** (10.7 mg, 45.3 μmol, 50%) and **12a** (8.1 mg, 49.3 μmol, quant.) were obtained.

(*R*)-**9a**: $[\alpha]_D^{25}$ –61.5 (*c* 0.38, MeOH).

HPLC: t_R (min) = 22.3 [(*S*)-**9a**, 0.7%], 26.1 [(*R*)-**9a**, 99.3%]; 98.6% ee.

A. melleus Protease-Catalyzed Hydrolysis of (±)-9c

In a similar manner, by the treatment of (±)-**9c** (20.3 mg, 76.8 μmol) with *A. melleus* protease for 2.0 h, (*R*)-**9c** (10.6 mg, 40.1 μmol, 52.2%) was obtained.

(*R*)-**9c**: $[\alpha]_D^{26}$ –42.9 (*c* 0.48, MeOH).

HPLC: t_R (min) = 18.6 [(*S*)-**9c**, 4.2%], 24.3 [(*R*)-**9c**, 95.8%]; 91.6% ee.

A. melleus Protease-Catalyzed Hydrolysis of (±)-9d

In a similar manner, by the treatment of (±)-**9d** (19.8 mg, 79.1 μmol) with *A. melleus* protease for 2 h, (*R*)-**9d** (13.9 mg, 58.8 μmol, 55.5%) was obtained.

(*R*)-**9d**: $[\alpha]_D^{26}$ –16.2 (*c* 0.53, MeOH).

HPLC: t_R (min) = 16.3 [(*S*)-**9d**, 37.0%], 19.6 [(*R*)-**9d**, 63.0%]; 26.0% ee.

1-(*tert*-Butoxycarbonyl)-3-(1*H*-pyrrol-1-yl)pyrrolidine-2,5-dione (12b)

A solution of **12a** (12 mg, 0.074 mmol), Boc_2O (40 μL, 0.154 mmol), and DIPEA (40 μL, 0.23 mmol) in THF (100 μL) was stirred for 20 h at 40 °C. The reaction was quenched with H_2O, and the organic materials were extracted with EtOAc (3 ×). The combined extract was washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo to give **12b**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56 (s, 9 H), 3.03 (dd, *J* = 6.4, 18.5 Hz, 1 H), 3.35 (dd, *J* = 9.5, 18.5 Hz, 1 H), 5.06 (dd, *J* = 6.4, 9.5 Hz, 1 H), 6.24 (dd, *J* = 2.0, 2.2 Hz, 2 H), 6.70 (dd, *J* = 2.0, 2.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.6, 36.8, 56.7, 87.1, 110.3, 119.6, 145.7, 146.7, 169.1, 169.6.

1-(Benzyloxymethyl)-3-(1*H*-pyrrol-1-yl)pyrrolidine-2,5-dione (12c)

To a solution of **12a** (602 mg, 3.67 mmol) and DIPEA (959 μL, 5.51 mmol) in CH_2Cl_2 (15 mL) was added dropwise benzyl chloromethyl ether (554 μL, 4.03 mmol) over 15 min at 0 °C, and the mixture was stirred for 30 min at 0 °C. Then, the mixture was washed with aq NH_4Cl solution, H_2O, and brine (20 mL each). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (SNAP Ultra, 25 g; hexane/EtOAc, 9:1 to 0:1) to afford **12c** (1000 mg, 96%) as a colorless solid.

IR (ATR): 3128, 3008, 2945, 2926, 2879, 1794, 1757, 1716, 1387, 1365, 1323, 1194, 1072 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.86 (dd, *J* = 18.5, 5.8 Hz, 1 H), 3.17 (dd, *J* = 18.5, 9.5 Hz, 1 H), 4.64 (d, *J* = 12.8 Hz, 1 H), 4.68 (d, *J* = 12.8 Hz, 1 H), 4.81 (dd, *J* = 9.5, 5.8 Hz, 1 H), 5.11 (s, 2 H), 6.23 (dd, *J* = 2.1, 2.2 Hz, 2 H), 6.60 (dd, *J* = 2.1, 2.2 Hz, 2 H), 7.29–7.38 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.6, 56.5, 68.2, 72.5, 110.2, 119.5, 127.6, 128.0, 128.5, 137.4, 173.1, 173.4.

HRMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{16}N_2NaO_3$: 307.1059; found: 307.1074.

Ethyl 1-(Benzyloxymethyl)-2,5-dioxo-3-(1*H*-pyrrol-1-yl)pyrrolidine-3-carboxylate (14b) and Ethyl 1-(Benzyloxymethyl)-2,5-dioxo-4-(1*H*-pyrrol-1-yl)pyrrolidine-3-carboxylate (15)

To a solution of **12c** (352 mg, 1.24 mmol) in anhydrous toluene (10 mL) was added KHMDS solution in toluene (0.5 M; 2.73 mL, 1.36 mmol), and the mixture was stirred at r.t. for 5 min. To the reaction mixture was added diethyl dicarbonate (206 μL, 1.42 mmol), and the mixture was stirred at r.t. for 20 min. The mixture was then diluted with EtOAc (30 mL), and the solution was washed with aq NH_4Cl solution, H_2O, and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (15 g; hexane/EtOAc, 10:1 to 5:1) to afford an inseparable mixture of **14b** and **15** (3:1) as a yellow oil (262 mg, 59%).

IR (ATR): 3027, 2981, 2939, 2908, 2871, 1797, 1759, 1716, 1344, 1325, 1227, 1086, 1076 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (signals attributed to **14b**) = 1.23 (t, *J* = 7.2 Hz, 3 H), 3.23 (d, *J* = 7.8 Hz, 1 H), 3.56 (d, *J* = 7.8 Hz, 1 H), 4.26 (q, *J* = 7.2 Hz, 2 H), 4.61 (s, 2 H), 5.10 (d, *J* = 10.6 Hz, 1 H), 5.43 (d, *J* = 6.6 Hz, 1 H), 6.28 (dd, *J* = 2.2, 2.1 Hz, 2 H), 6.95 (dd, *J* = 2.2, 2.1 Hz, 2 H), 7.27–7.38 (m, 5 H).

^{1}H NMR (400 MHz, $CDCl_3$): δ (signals attributed to **15**) = 1.34 (t, *J* = 7.2 Hz, 3 H), 3.82 (d, *J* = 6.6 Hz, 1 H), 4.28 (q, *J* = 7.2 Hz, 2 H), 4.65 (d, *J* = 13.2 Hz, 1 H), 4.68 (d, *J* = 13.2 Hz, 1 H), 5.09 (d, *J* = 10.6 Hz, 1 H), 5.14 (d, *J* = 10.6 Hz, 1 H), 5.43 (d, *J* = 6.6 Hz, 1 H), 6.28 (dd, *J* = 2.3, 2.2 Hz, 2 H), 6.95 (dd, *J* = 2.3, 2.2 Hz, 2 H), 7.27–7.38 (m, 5 H).

Regeneration of (±)-9a

To a solution of **14b** and **15** (75 mg) in EtOH (1 mL) was added 20% $Pd(OH)_2/C$ (50% in H_2O, 61 mg) and Et_3N (6 µL, 0.042 mmol). The mixture was stirred for 3.5 h at r.t. under hydrogen atmosphere, and then was filtered. The filtrate and washings were concentrated in vacuo, and the residue was dissolved in EtOH (1 mL). To the solution was again added 20% $Pd(OH)_2/C$ (50% in H_2O, 114 mg) and Et_3N (12 µL, 0.084 mmol), and the resulting mixture was stirred for a further 7.5 h under hydrogen atmosphere. The mixture was filtered, and the combined filtrate and washings was concentrated. The residue was purified by silica gel column chromatography (4 g; hexane/EtOAc, 5:1) to afford (±)-**9a** (23 mg, 63%) as a colorless oil.

The ^{1}H NMR spectrum was identical with that of authentic **9a**.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561620.

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