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An efficient enzymatic preparation of rhinovirus protease inhibitor intermediates

Carlos A. Martinez, Daniel R. Yazbeck and Junhua Tao*

Pfizer Global Research and Development, La Jolla Laboratories, 4215 Sorrento Valley Boulevard, La Jolla, CA 92121, USA

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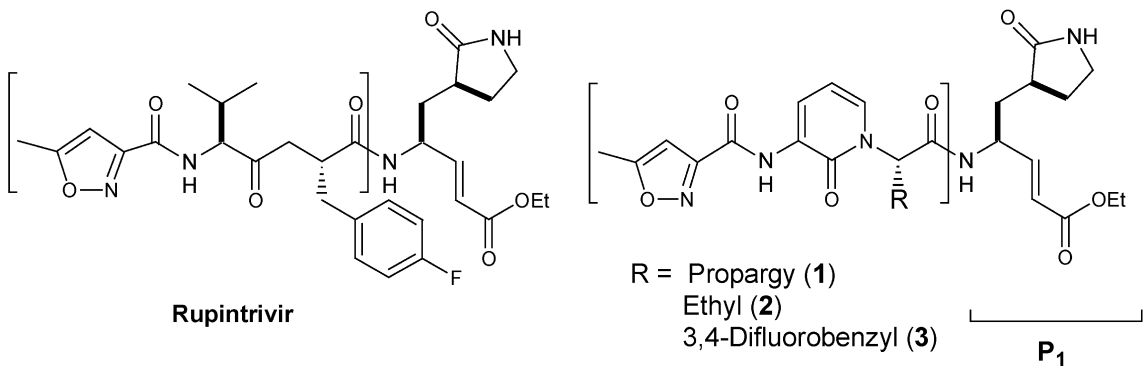
Abstract—The development of an efficient route for the preparation of (2*S*)-2-[3-{[(5-methylisoxazol-3-yl)carbonyl]amino}-2-oxopyridin-1(2*H*)-yl]pent-4-ynoic acid (**4**), a key intermediate in the synthesis of a human rhinovirus (HRV) protease inhibitor, is presented. In the presence of 40% acetonitrile, the alkaline protease from *Bacillus lentus* can catalyze the kinetic resolution of racemic ester **7** to afford (*S*)-acid **4** in 49% chemical yield/per cycle with 98% ee and >98% HPLC purity. The (*R*)-ester can then be readily recycled via a DBU catalyzed epimerization. The enzymatic preparation described here is superior to the existing chemical resolution route, exhibiting lower costs as well as higher yields, enantioselectivity, and substrate loads. In addition, this protease displays broad substrate specificity toward this class of compounds and can be easily extended to the preparation of other tripeptide mimetics of rhinovirus protease inhibitors.

1. Introduction

Currently, no effective therapy exists to directly treat the common cold. Since the condition is mainly caused by rhinovirus infections, the use of inhibitors that target the 3C protease, a protein required for viral replication, has been reported. The design and development of substrate-derived tripeptidyl Michael acceptor-containing human rhinovirus protease inhibitors have been extensively investigated.[1] A series of promising compounds including Rupintrivir™ and other related molecules (**1**–**3**, Scheme 1) have emerged as the lead candidates for this ailment entering human clinical trials. All of these molecules share the same right wing piece (P_1).[2] One of the most difficult issues in the synthesis of these compounds is to install the desired chiral center in the tripeptide mimetics [bracketed] with high optical purity.[3]

In this paper, we report an efficient and cost-effective enzymatic preparation of a key intermediate **4** towards the synthesis of compound **1** (Scheme 2). The method relies on enzymatic kinetic resolution of a racemic ester precursor using a protease isolated from a *Bacillus* species strain also known as *Bacillus lentus*.[4] The enzyme is a very inexpensive and commercially available serine protease,



Scheme 1.

Keywords: Rhinovirus protease inhibitor; Kinetic resolution; Enzymatic hydrolysis; Process development; Solvent engineering; *Bacillus lentus* protease; Substrate recycling.
* Corresponding author. Tel.: +1-858-622-3228; fax: +1-858-678-8277; e-mail address: junhua.tao@pfizer.com

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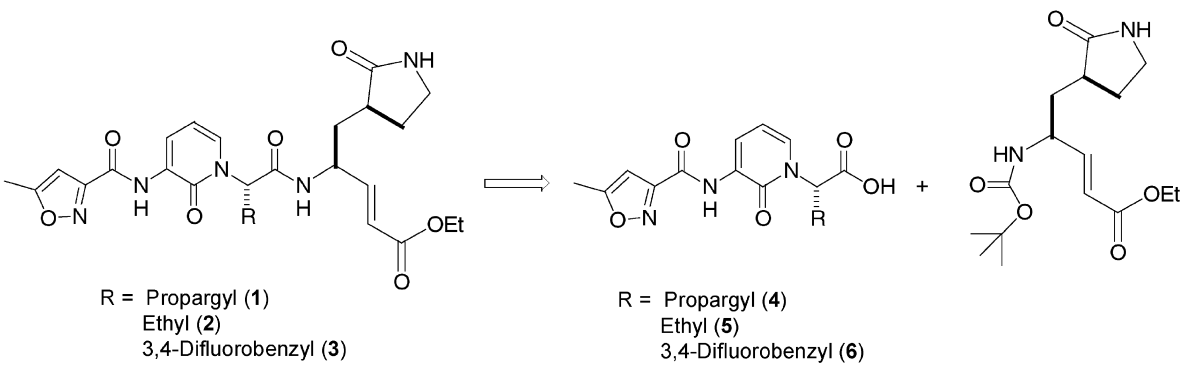


Scheme 2.

which is used in the detergent industry to remove protein-based stains and in the textile industry for wool finishing. However, in view of its ease of availability and low cost, the enzyme appears to be underused as a preparative catalyst. The enzymatic resolution strategy presented displays broad substrate range and could be easily extended to the preparation of tripeptide mimetics **5** and **6** needed for the synthesis of other rhinovirus protease inhibitors **2** and **3**.

Herein, we describe the screening performed in order to identify the enzyme, as well as process optimization carried out to improve the yield, enantioselectivity and substrate load. The dramatic solvent effect revealed during optimization of enzyme selectivity as well as the details on the development of a repetitive batch process to recycle unreacted ester with wrong stereochemistry, will be described. Finally, enzymatic and chemical processes will be compared.

2. Results and discussion

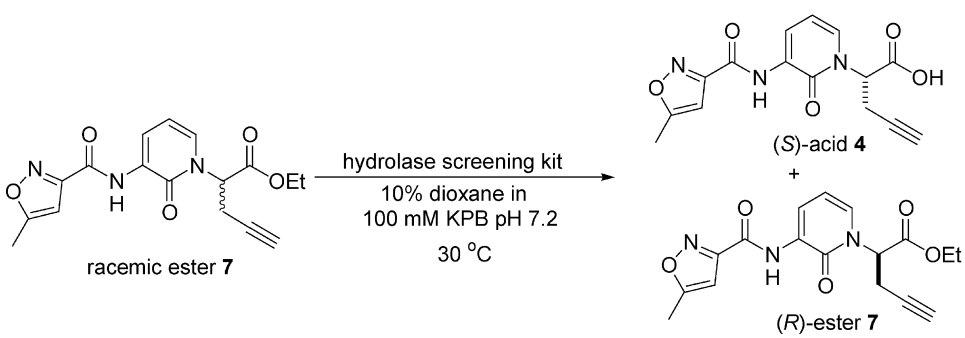
The development of a process for the resolution of racemic ester **7**[5] (Scheme 3) will be used to illustrate the strategy. The process development involved three main steps: (1) screen for an enzyme from an internal collection containing most commercially available lipases, proteases and esterases, (2) perform reaction optimization primarily to improve enantioselectivity of the enzyme hits found and subsequently to determine the optimal pH, temperature and substrate loads, and (3) development of a procedure for the regeneration of racemic ester from enriched unreacted ester (recovered after one kinetic resolution cycle) in order to perform a repetitive batch process with yields greater than 50%.

2.1. Enzyme screening

The most suitable catalyst for the kinetic resolution of racemic ester **7** was identified by using an unbiased screening of commercially available hydrolases. A general high-throughput enzyme screening method was used to screen the enzymes.[6] After initial screening using 10% dioxane, several hydrolases were identified as hits for the enzymatic hydrolysis of the racemic substrate **7**. The active enzymes found were pig liver esterase, subtilisin carlsberg, *Candida antarctica* lipase-A, *Candida antarctica* lipase-B, *Aspergillus oryzae* lipase, *Aspergillus* species protease, *Bacillus lentus* protease, *Bacillus subtilis* protease, *Aspergillus oryzae* protease, *Aspergillus melleus* protease and the acylase from *Aspergillus* species. Most of them showed good reactivities but unfortunately poor enantioselectivities ($E<5$). *Candida antarctica* lipase-B carried out the reaction with very good enantioselectivity (>98% ee at 50% conversion), however the reaction was very slow with only 0.5% w/v substrate loads being possible. Although process optimization was attempted initially with this enzyme, no major improvements in terms of reactivity were obtained afterwards. The substrate loads and the cost of the enzyme could not compete with the existing chemical process, where the racemic acid from ester **7** upon chemical hydrolysis was resolved using chiral norephedrine (see discussions below).

2.2. Optimization of enantioselectivity through the use of organic co-solvents

The use of solvent engineering to improve the enantioselectivity of enzymes has been extensively well documented.[6,7] A comprehensive study was thus initiated to



Scheme 3.

Table 1. Effect of dioxane contents on reactivity and enantioselectivity of proteases[a] (for the hydrolysis of substrate **7**)

Enzyme	[Dioxane] (%)	ee (%)	Conversion (%)	*E*
Bacillus lichenformis protease (subtilisin Carlsberg)	5	5	49	1.2
	35	48	45	4.1
	40	60	43	6.2
	45	66	41	7.6
	50	68	22	6.3
Aspergillus species protease	5	4	45	1.2
	35	70	12	6.2
	40	66	5.6	5.1
	45	72	2.4	6.3
	50	60	2	4.1
Bacillus lentus protease	5	30	43	2.3
	35	97	49	>200
	40	98	48	>200
	45	98	43	144
	50	98	28	143

[a] Reactions were conducted at pH 7.2, 5 mg/mL substrate **7**, 10% v/v enzymes, 30 °C and 5–50% solvent content. The reactions were allowed to proceed for 1 h and then quenched and analyzed by HPLC.

study the effects of solvent content on the enantioselectivity of the enzyme hits, which were reacted under various concentrations of 1,4-dioxane at constant pH 7.2. Both solvents and solvent contents showed intriguing effect on the enantioselectivity of the catalyzed hydrolysis of ester **7** by the three very inexpensive protease hits, which displayed relatively good reactivity (Tables 1 and 2). Subtilisin carlsberg, *Aspergillus* species protease and *Bacillus lentus* protease exhibited an enhanced *E* value as the solvent contents in the reaction mixture was increased. Moreover, *Bacillus lentus* protease (BLP) exhibited a dramatic solvent content effect, having an *E* value of >200 at 40% solvent content compared to an *E* value of only 2.3 at 5% 1,4-dioxane. As stated previously, this solvent effect has been found to be quite general for a variety of potential processes,[6] further emphasizing the need for a routine implementation of a thorough solvent study in every enzyme screening. Once an appropriate solvent content was identified, other solvents were screened at that content in order to identify potentially more reactive and environmentally friendly solvents while retain high enantioselectivity of the enzyme. As can be seen from Table 2, although the enzyme was still very enantioselective in most solvents at 40% solvent content, the reactivity differed significantly, with some reactions not proceeding at all notably in protic solvents (glycerol, MeOH, EtOH) and nonpolar solvents (methylene chloride, THF, toluene and hexanes). Acetone and acetonitrile were used in further optimization studies.

Table 2. Effect of solvents on reactivity and enantioselectivity of BLP[a] (for the hydrolysis of substrate **7**)

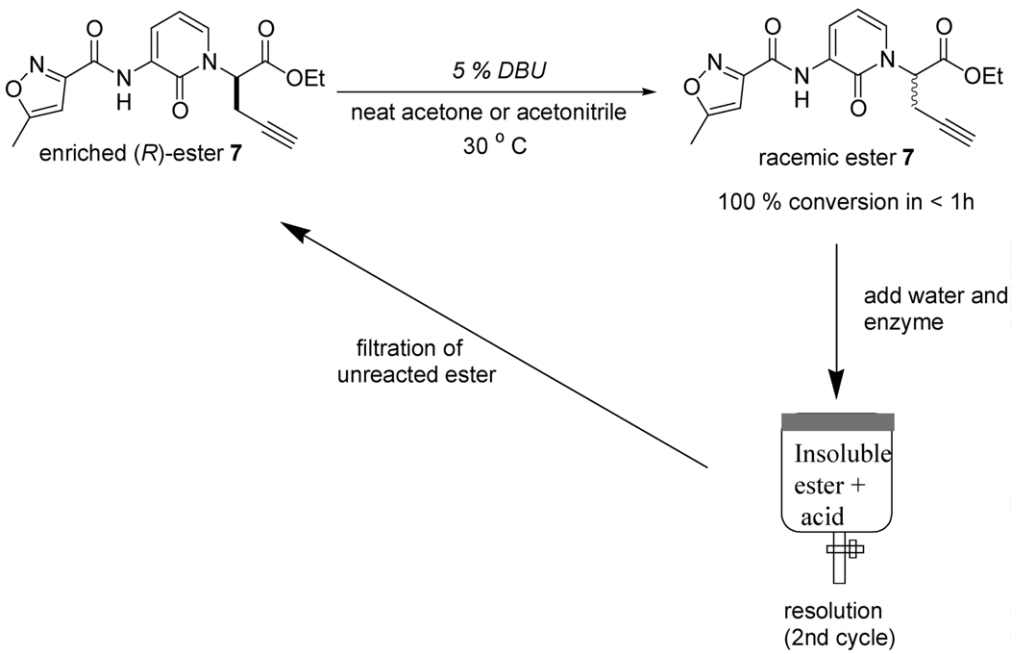
Solvent	Conversion (%)	ee (%)
50% Glycerol	<5	>99
Methanol	<5	>99
Ethanol	<5	>99
Isopropanol	29.6	99.2
Acetonitrile	41.8	98.8
Methyl-*t*-butyl ether	27	98.7
Methylene chloride	No reaction	—
Tetrahydrofuran	No reaction	—
1,4-Dioxane	48	98.8
Acetone	46	97.7
Toluene	<5	>99
Hexane	<5	>99

[a] Reactions were conducted at pH 7.2, 5 mg/mL substrate **7**, 10 mg/mL of enzyme, 30 °C, and 40% solvent content. The reactions were allowed to proceed for 1 h and then quenched and analyzed by HPLC.

2.3. Other optimization studies

Further optimization studies were performed in order to determine parameters such as maximum substrate load, optimum pH and temperature. Substrate load as high as 10% (100 mg/mL) required approximately 24 h reaction time. It was observed that proper stirring is very important since most of the substrate remained out of solution after saturation at 30 g/L concentration. The fact that the reaction was performed in a heterogeneous system was in fact advantageous since removal of the leftover ester only involved a simple filtration once the kinetic resolution was complete. Under these conditions, a batch process was chosen for simplicity. BLP is an enzyme that remains active in a broad pH range (6–11) with greater activity at higher pH. The background chemical hydrolysis was significant (>1%) at pH values above 8.5. Therefore a pH of 8.25 was optimum in terms of having maximum activity in the absence of deleterious background hydrolysis leading to low ee's. The enzyme-catalyzed reaction was studied at temperatures ranging from 20–50 °C. Temperatures above 37 °C favored background hydrolysis at the optimum pH mentioned above. Since the reaction was fast enough, there was no need to increase temperature above 30 °C. The amount of enzyme to be used was also studied by varying the amount of enzyme from 0.1–50% v/v. It was found that 10% enzyme content was the optimum protein concentration with minimal complication in the workup.

The enzyme catalyzed kinetic resolution to afford (*S*)-**4** was thus optimized to reach 49% chemical yield/cycle, >98% HPLC purity and 98% ee. BLP catalyzes the selective hydrolysis of the (*S*)-ester of the racemic mixture of **7** in the presence of 40% acetonitrile as co-solvent. After the reaction is over, the remaining ester (*R*)-**7** is filtered from the reaction mixture and the acid is recovered from the aqueous mother liquor after acidification to pH 3.5 without further purification.



Scheme 4.

2.4. Repetitive batch process

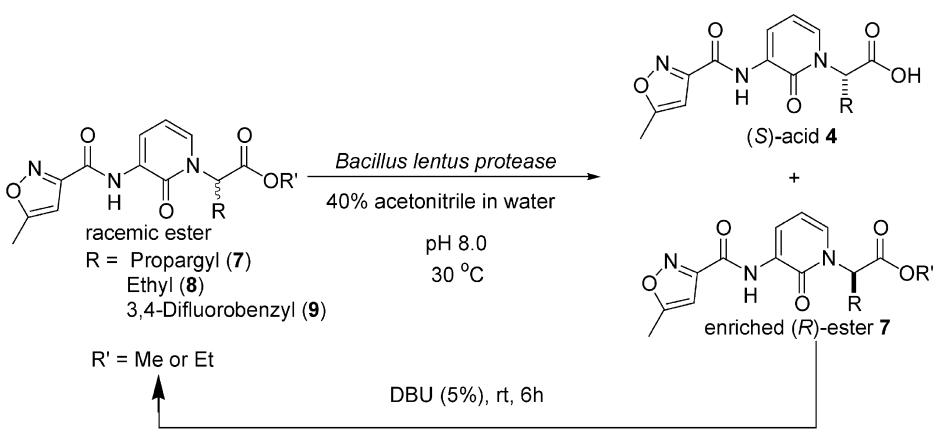
Due to the limitations associated with performing a kinetic resolution, a method for the recovery or in situ conversion of the remaining ester (*R*)-**7** was explored. A dynamic resolution process was attempted, however it was not possible to find conditions in which racemization took place efficiently under the optimum conditions catalyzed by BLP. However, the wrong enantiomer could be easily racemized under non-aqueous conditions (Scheme 4), thus allowing a repetitive batch approach for the preparation of (*S*)-**4**. The ester was epimerized by a catalytic amount of DBU (5 mol%) in 100% acetone or acetonitrile. The second resolution cycle continues after the addition of enzyme and water to the mixture under optimized conditions. The small amount of DBU did not produce any observable effect on the activity of the enzyme in the second cycle.

2.5. Scope of the method

Considering the attractiveness of the above process to resolve **7** using BLP, the kinetic resolution of **8** and **9** to prepare **5** and **6** was investigated under similar conditions optimized for substrate **7** (Scheme 5). Both methyl and ethyl esters were studied as suitable substrates. The remarkable solvent effect on enantioselectivity was also observed at concentrations above 30%. Both compounds were good substrates for the enzyme with enantiopurities of the products **5** and **6** being >97% after half of the racemic substrate was hydrolyzed. The base catalyzed racemization procedure outlined above for (*R*)-**7** could also be applied to substrates **8** and **9**, thus allowing a repetitive batch process as well. The enzyme accommodates both methyl and ethyl esters and displays very similar reactivities and enantioselectivities.

3. Summary

In summary, an efficient preparation of intermediate **4** has been described using *Bacillus lentus* protease (BLP). As seen from Table 3, this enzymatic preparation is superior to



Scheme 5.

Table 3. Comparison of chemical and enzymatic processes for the production of (*S*)-**4**

	Chemical	Enzymatic
Substrate	*rac*-**4**	*rac*-**7**
Method	Diastereomeric salt formation (norephedrin)	BLP catalyzed hydrolysis
Substrate load (g/L)	100	100
Yield/cycle (%)	33	49
ee of acid (%)	96	98
Catalyst load	84 g/L	100 ml/L
Catalyst price (per kg)	$315	<$50
Recyclability	Complicated: CDI-base treatment	Simple: filtration-DBU treatment

the chemical resolution approach. First of all, the enzyme BLP is significantly cheaper than chemical resolving agent norephedrine. In addition, the enzymatic process has much higher yields (49% vs 33% per resolution cycle). The high yielding makes the enzymatic route far more attractive considering it is the penultimate step of the overall synthesis of the drug candidate. Furthermore, removal of the leftover ester involved simple filtration once the kinetic resolution was complete, and efficient racemization allowed for the development of a repetitive batch process. In contrast, the chemical recycling is much more complicated involving activation of the undesired acid followed by epimerization. In the BLP catalyzed process described herein, >4000 mol of ester are converted per mole of enzyme per batch. The enzyme has high stability under a wide range of pH, temperature, and high organic solvent contents (40%). Remarkably, this bacterial enzyme also displayed broad substrate specificity and could be extended to the preparation of chiral precursors **5** and **6** needed for the synthesis of rhinovirus protease inhibitors **2** and **3**. While BLP shows similar reactivity toward both methyl and ethyl esters ignoring the difference among propargyl (**4**), ethyl (**5**) and difluorobenzyl (**6**) substituents, it differentiates each enantiomer stereochemically with kinetic perfection. The preparation of these types of densely functionalized optically active compounds with high molecular weight is a difficult task that still presents a major challenge in organic synthesis in the pharmaceutical industry. Through the use of a very robust hydrolytic enzyme such as BLP, a challenging chemical process has been resolved in a matter of weeks resulting in an efficient and environmentally acceptable route with great savings.

4. Experimental

4.1. Materials

The majority of enzymes utilized in the preparation of screening kits were obtained from various enzyme suppliers including Amano (Nagoya, Japan), Roche (Basel, Switzerland), Novo Nordisk (Bagsvaerd, Denmark), Altus Biologics Inc (Cambridge, MA), Biocatalytics (Pasadena, CA), Toyobo (Osaka, Japan), Sigma and Fluka (see Ref. 5 for details on preparation of screening plates, including specific enzyme sources for each enzyme, as well as a detailed description of the screening methodology). HPLC analysis of the screened samples was performed on an Agilent 220 HPLC auto sampler. Reactions were performed in an Eppendorf thermomixer-R (VWR). Solvents utilized during optimization were obtained from EM Science (Gibbstown, NJ) and were of the highest purity available. Chiral HPLC columns used in analysis were obtained from Chiral Technologies (Exton, PA) and Phenomenex (Torrance, CA). Commercially available *Bacillus lentus* protease was purchased from Altus Biologics (Boston, MA) as Altus 53 in crude form. A semi-purified form of the enzyme can also be obtained from Sigma as Savinase. This preparation showed no significant difference in the resolution, both in terms of reactivity and enantioselectivity when compared to Altus 53 preparations. HPLC methods: chiral method using detector wavelength: 254 nm; Chiralcel OJ-R, 3μ, C18, 4.6×100 mm; flow rate 0.5 mL/min; injection volume: 10 μL; mobile phases: (A) 25 mM NaH_2PO_4 pH 2.0; (B) Acetonitrile; isocratic: 40% B for 31 min, 3 min post run. Every HPLC sample was made by taking 5×200 μL from the reaction slurry, then combined and diluted with 4 ml of acetonitrile. 100 μL of that solution were further diluted with 400 μL of acetonitrile and injected in the HPLC.

4.2. Procedure for enzyme screening

The resolution of ester intermediate **7** was carried out as following. A 96-well plate screening kit prepared in house[6] was thawed for 5 min. 80 μL of potassium phosphate buffer (0.1 M, pH 7.2) was then dispensed into the wells using a multi-channel pipette. 10 μL of the substrate stock solution (50 mg of **7**/mL dioxane) was then added to each well via a multichannel pipette, and the 96 reactions were incubated at 30 °C and 750 rpm. The reactions were sampled after 1 and 16 h by the transfer of 25 μL of the reaction mixture into a new 96-well plate, which was then quenched by the addition of 150 μL of acetonitrile. The 96-well plate was then centrifuged, and the organic supernatant transferred from each well into another 96-well plate. Sampled reactions were then sealed using a penetrable mat cover and transferred to an HPLC system for analysis. The same plate was used to analyze the samples for both reactivity and enantioselectivity using alternating columns on the HPLC simultaneously.

4.2.1. Procedure for the preparation of compound 4. To a 150 mL jacketed flask equipped with a pH electrode, an overhead stirrer and a base addition line, was added the racemic ester **7** (10 g, 29.12 mmol, 1.00 equiv.) and acetone (40 mL). A 718 Stat Titrino-Metrohm pH titrator (Brinkman instruments, Inc.) was used to control the pH of the reaction. The resulting slurry was stirred at 30 °C for 5 min. A mixture of *B. lentus* protease (10 mL from commercial Altus 53 solution) and distilled water (50 mL) was added to the reaction flask. The suspension was then stirred at the

same temperature for 24 h maintaining the pH of the reaction constant at 8.2 using 1 M NaOH. Both the conversion and ee's of the reaction was monitored by RP-HPLC following the product, and stopped after 50% starting material was consumed (approximately 24 h under these conditions). The heterogeneous mixture was filtered and the remaining ester was recovered as white crystals, washed once with distilled water and dried under vacuum to afford 4.81 g of (*R*)-ester (48% yield, >98% ee). The remaining aqueous solution was extracted once with 50 mL of ethyl acetate to remove any traces of starting material, acidified to pH 3.5 with 1 M HCl, and extracted three times with 50 mL of ethyl acetate. The acid fractions were pooled, dried with sodium sulfate and concentrated in vacuum. The crude solid was washed once with hot water, filtered and dried overnight. Compound **4** was obtained as white crystals (4.68 g, 98% ee, 49% yield, >98% UV purity). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.44 (s, 1H), 8.31 (dd, J=1.67, 7.38 Hz, 1H), 7.54 (dd, J=1.72, 7.02 Hz, 1H), 6.72 (d, J=0.91 Hz, 1H), 6.42 (t, J=7.17 Hz, 1H), 5.28 (dd, J=4.55, 10.68 Hz, 1H), 3.19 (ddd, J=2.65, 10.72, 17.46 Hz, 1H), 2.97 (ddd, J=2.70, 4.55, 17.47 Hz, 1H), 2.84 (t, J=2.59 Hz, 1H), 2.50 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.77, 169.17, 158.83, 157.15, 156.84, 132.88, 127.64, 123.54, 105.67, 101.60, 80.03, 73.67, 60.81, 19.37, 12.17. Mp 175–182 °C; IR (KBr) ν_{max}/cm^{-1}: 3301, 1752, 1645, 1542, 1459, 1221, 1188; HRMS (CI) *m/z*: 316.0940 (316.0933 calculated for $C_{15}H_{14}N_30_5$).

4.2.2. Data for compound 5. Compound **5** was obtained as white crystals from the resolution of racemic ester **8** with 97% ee, 48% yield, >98% UV purity. ^{1}H NMR (700 MHz, $CDCl_3$): δ 9.58 (s, 1H), 8.49 (dd, J=1.7, 7.5 Hz, 1H), 7.11 (dd, J=1.9, 7.2 Hz, 1H), 6.82 (s-broad, 1H), 6.49 (s, 1H), 6.38 (t, J=7.4 Hz, 1H), 5.38 (dd, J=5.1, 10.1 Hz, 1H), 2.5 (s, 3H), 2.34 (m, 1H), 2.05 (m, 1H), 0.93 (t, J=7.7 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 172.7, 171.8, 158.7, 157.9, 157.7, 129.2, 128.6, 123.8, 107.3, 101.4, 61.5, 23.7, 12.5, 10.6. Mp 158–160 °C; IR (KBr) ν_{max}/cm^{-1}: 3345, 1744, 1699, 1643, 1534, 11459, 1202; HRMS (CI) *m/z*: 305.2940 (305.2933 calculated for $C_{14}H_{15}N_30_5$).

4.2.3. Data for compound 6. Compound **6** was obtained as white crystals from the resolution of racemic ester **9** with 97% ee, 45% yield, >98% purity. ^{1}H NMR (700 MHz, $CDCl_3$): δ 9.50 (s, 1H), 8.45 (dd, J=1.5, 7.5 Hz, 1H), 7.63 (s-broad, 1H), 7.00 (m, 1H), 6.92 (m, 1H), 6.82 (dd, J=7.2, 1.5 Hz, 1H), 6.77 (m, 1H), 6.49 (s, 1H), 6.24 (t, J=7.2 Hz, 1H), 5.28 (dd, J=4.9, 10.2 Hz, 1H), 3.55 (dd, J=14.8, 5.0 Hz, 1H), 3.41 (dd, J=14.8, 10.5 Hz, 1H), 2.50 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 171.9, 171.2, 158.2, 157.9, 157.3, 132.9, 130.4, 128.7, 125.2, 124.3, 107.4, 101.4, 63.7, 34.8, 12.5. Mp 152–155 °C; IR (KBr) ν_{max}/cm^{-1}: 3347, 1718, 1650, 1594, 1535, 1460, 1286, 1213; HRMS (CI) *m/z*: 403.0940 (403.1033 calculated for $C_{19}H_{15}F_2N_30_5$).

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