Graphical Abstract.

Asymmetric chemoenzymatic synthesis of *N*-acetyl-α-amino esters based on lipase-catalyzed kinetic resolutions through interesterification reactions

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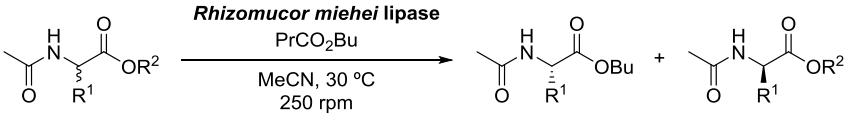

Chemical synthesis

R^1= Bn, 4-OMe-Bn, 4-Me-Bn, 4-Cl-Bn, 4-NO_2-Bn, 3-NO_2-Bn, 2-NO_2-Bn, 2-Naphthyl-CH_2

R^2=Me, allyl

Tetrahedron
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Asymmetric chemoenzymatic synthesis of *N*-acetyl-α-amino esters based on lipase-catalyzed kinetic resolutions through interesterification reactions

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Keyword_1: Amino acids
Keyword_2: Asymmetric synthesis
Keyword_3: Interesterification
Keyword_4: Kinetic resolution
Keyword_5: Lipases

ABSTRACT

Several phenylalanine analogs have been synthesized through a four-step route starting from easily available ethyl acetamidocyanoacetate. In a first reaction, and making use of phase transfer catalysts, this compound reacted with several alkyl halides, being benzyltributylammonium chloride identified as the best one for the production of a series of quaternary amino acids in moderate to excellent yields (52-95%). Then, the corresponding *N*-acetyl-phenylalanine methyl and allyl ester derivatives were obtained through acidic hydrolysis, esterification, and *N*-acetylation. *Rhizomucor miehei* lipase was found as a versatile enzyme for the resolution of these amino esters, finding the best results through interesterification reactions with butyl butyrate in acetonitrile. A great influence in the stereoselectivity was found depending on the chemical structure of the compound, achieving for the non- or *para*-substituted in the phenyl ring excellent stereoselectivities, being moderate for the *meta*-nitro derivative, while the *ortho*-nitro amino ester did not react.

1. Introduction

α-Amino acids are essential to life as building blocks of peptides, proteins, hormones, and as a source of low-molecular weight nitrogenated substances with enormous biological importance such as glutathione, taurine, nitric oxide, polyamines, etc. The applicability of amino acids is also well documented as agrochemicals, antibacterial agents, fungicides, neuroactive compounds, food supplements, enzyme inhibitors and pharmaceutical materials.[1] They are involved in the synthesis of a great number of organic substances as a source of chiral raw materials, as synthetic targets, and as reagents and/or catalysts in asymmetric synthesis.[2] For all these reasons, the development of synthetic strategies for the preparation of amino acids has been object of intense investigation.[1] Particularly, optically active phenylalanine analogs are interesting compounds because of their synthetic possibilities as chiral building blocks of more complex structures with relevance in the area of medicinal chemistry, as for instance, enzyme inhibitors.[3]

In the last years, many efforts have been focused on the introduction of unnatural amino acids in peptidic chains to afford peptidomimetics designed to improve their binding potency to a desired biological target, their chemical and/or biological stability, and their pharmacokinetic properties compared to the natural compounds, providing useful information for the elucidation of different enzymatic mechanisms.[4]

Biocatalytic and chemoenzymatic methods have been described for the production of unnatural or non-proteinogenic amino acids through many routes,[5] receiving hydrolase-catalyzed reactions great attention due to their easy manipulation and commercial availability.[6] Particularly, lipases (EC 3.1.1.3) have largely demonstrated their applicability with synthetic purposes, being the most employed enzymes in industrial processes in the last three decades. This fact is mainly based on their wide availability in nature and their broad substrate acceptance. Significantly this class of hydrolases acts with high levels of selectivity in the transformation of achiral but also racemic, prochiral or *meso*-compounds, their usefulness being extensively demonstrated through hydrolytic or synthetic processes in both aqueous and organic media.[7]

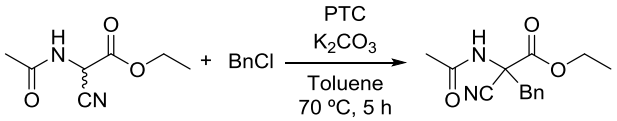
Candida antarctica lipase B (CAL-B) is probably the most versatile catalyst,[8] although others such as *Pseudomonas cepacia* lipase (PSL or PCL) or *Rhizomucor miehei* lipase (RML)[9] have also shown excellent activities in a series of synthetic transformations such as aminolysis, esterification and transesterification reactions. Although less employed, the interconversion between two reacting esters (interesterification), is another process that can be successfully used operating with lipases.[10] Herein, we wish to report our latest results in the field of asymmetric synthesis of amino acids. For that reason, a family of amino esters was chemically prepared to later explore their

kinetic resolution (KR), RML being found as the most versatile enzyme for interesterification reactions.

2. Results and discussion

Due to the relevance of phenylalanine analogs, a series of *N*-acetylated *O*-esterified derivatives was synthesized through a four-step methodology. Starting from a common precursor, racemic ethyl acetamidocyanoacetate (**1**), firstly the alkylation at its α-position was carried out using the desired alkyl halide in order to afford the corresponding quaternary esters. These intermediates will be hydrolyzed, esterified and acetylated in the subsequent steps, giving access to the target compounds. With that purpose and considering that phase transfer catalysis is a highly demanded strategy for the synthesis of amino acids through alkylation reactions,[11] this approach was applied to the transformation of commercially available **1** with two equivalents of benzyl chloride (**2**), thus producing the *N*-acetyl amino ester (±)-**3a** in the presence of potassium carbonate at 70 ºC. A panel of phase transfer catalysts (PTCs) was employed such as benzyltriethylammonium bromide (BTAB), tetrabutylammonium hydrogen sulfate (TBAH), dodecyltrimethylammonium chloride (DTMAC), cetyltrimethylammonium bromide (CTMAB), benzyltributylammonium bromide (BTBAB) or benzyltributylammonium chloride (BTBAC), Aliquat or 18-crown-6, obtaining in all cases moderate to good yields of (±)-**3a** as the unique product when 10 mol% of the PTC was used (Table 1). The best results were achieved using the chloride salt BTBAC, so at this point benzyl bromide (**4a**) was used in order to improve the conversion of the process. Satisfyingly, the reaction with **4a** led to a further improvement in the isolated yield of **3a** in comparison with the reaction with **2** as alkylating agent (from 75 to 95% isolated yield, see entry 1 in Table 2).

Table 1. Alkylation of (±)-**1** with **2** (2 equivalents) and a phase transfer catalyst (10 mol%) in toluene and potassium carbonate (1 equivalent) for 5 h at 70 ºC.

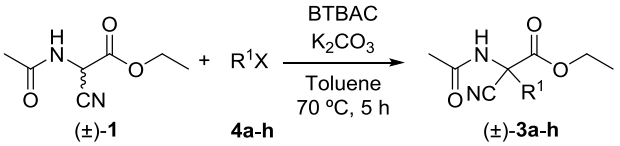


Entry	PTC	Isolated yield **3a** (%)[a]
1	BTAB	62
2	TBAH	59
3	DTMA	65
4	CTMA	64
5	BTBAB	63
6	BTBAC	75
7	Aliquat	66
8	18-Crown-6	66

[a] Isolated yield after flash chromatography.

These conditions were then extended to other alkyl halides, selecting the bromide halides when they were commercially available. The results are summarized in Table 2, observing a slower reactivity for the 4-methoxybenzyl chloride (**4b**) in comparison with bromide salts **4a**,**c**-**h**, all the amino esters being obtained with good to very high yields after 5 h. In addition, *para*-substituted derivatives with methyl (**3c**) or chloro substitution (**3d**) were achieved in 78-80% yield (entries 3 and 4). Compounds bearing a nitro functionality led to excellent results independently of the substituent position (**3e**-**g**, entries 5-7), while the most hindered naphtyl derivative **3h** was isolated in 89% yield (entry 8).

Table 2. Alkylation of (±)-**1** with 2 equivalents of alkyl halides (**4a**-**h**) and BTBAC (10 mol%) as PTC in toluene and potassium carbonate (1 equivalent) for 5 h at 70 ºC.

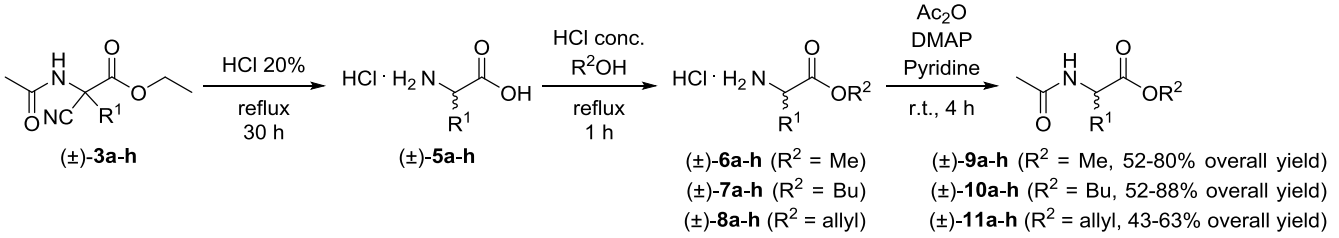


Entry	R^1X	Isolated yield **3a-h** (%)[a]
1	Benzyl bromide (**4a**)	95
2	4-Methoxybenzyl chloride (**4b**)	52
3	4-Methybenzyl bromide (**4c**)	78
4	4-Chlorobenzyl bromide (**4d**)	80
5	4-Nitrobenzyl bromide (**4e**)	93
6	3-Nitrobenzyl bromide (**4f**)	94
7	2-Nitrobenzyl bromide (**4g**)	92
8	2-(Bromomethyl)naphthalene (**4h**)	89

[a] Isolated yield after flash chromatography.

The corresponding amino acid derivatives **3a-h** were then subjected to a chemical sequence based on their acidic hydrolysis,[12] subsequent esterification reaction using different alcohols (i.e. methanol, butanol or allyl alcohol), and final *N*-acetylation protection (Scheme 1), leading to racemic compounds **9a-h**, **10a-h** and **11a-h** in a straightforward manner. In general moderate to good yields were obtained for the global three-step process, the poorer results being found with the allylic derivatives.

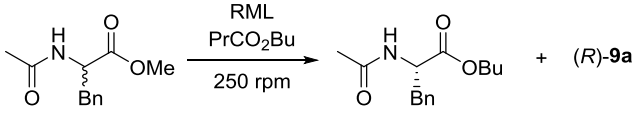
Next, the enzymatic kinetic resolution of methyl *N*-acetylated amino ester **9a** was studied. It must be mentioned that previous reports have appeared in the literature leading to the preparation of optically active *N*-acylated phenylalanine derivatives by means of highly selective hydrolytic processes,[13] while transesterification reactions led to the desired compounds with high selectivity but modest conversions.[14] For this reason, we decided to explore an alternative such as the interesterification reaction.[10] Thus, butyl butyrate was selected as both resolving agent and solvent. A set of hydrolases including *Candida antarctica* lipase type A (CAL-A), *Candida antarctica* lipase type B (CAL-B), *Candida rugosa* lipase (CRL), porcine pancreas lipase (PPL), *Pseudomonas cepacia* lipase (PSL-IM), *Rhizomucor miehei* lipase (RML), lipase AK from *Pseudomonas fluorescens* (AK) and *Thermomyces lanuginosus* lipase (TLL) were tested in this reaction at 30 and 60 ºC. Only RML was able to produce the butyl ester in 53% conversion and 80% *ee* after 8.2 h at 60 ºC (Table 3, entry 1), while no reaction was observed with the other lipases after 24 h.



Scheme 1. Chemical synthesis of racemic *N*-acetylated amino esters (±)-**9**-**11**.

Then, the reaction was analyzed studying the influence of the temperature and the enzyme loading in the lipase catalysis. A slightly better enantiopreference was observed when the reaction was carried out in milder conditions (30 ºC, entry 2), attaining 50% conversion after 48 h. In order to improve the reaction rate, enzyme loading was doubled leading to a similar conversion value at 24 h (entry 3).

Table 3. Interesterification reaction of (±)-**9a** (120 mM) using butyl butyrate and RML.



Entry	Enzyme:**9a**[a]	T (ºC)	*t* (h)	ee_s (%)[b]	ee_p (%)[b]	*c* (%)[c]	*E*[d]
1	1:1	60	8.2	89	80	53	27
2	1:1	30	48	86	85	50	34
3	2:1	30	24	90	87	51	44

[a] Ratio of RML:amino ester **9a** in weight/weight.
[b] Enantiomeric excess of substrate and product determined by HPLC.
[c] Conversion value: $c= ee_s/(ee_s+ee_p)$.
[d] Enantioselectivity value: $E= \ln[1-c(1+ee_p)]/\ln[1-c(1-ee_p)]$.

Looking at these results, we turned our attention to the solvent effect in the RML-catalyzed reaction. By this, tetrahydrofuran, 1,4-dioxane, *tert*-butyl methyl ether, toluene, acetonitrile, *n*-hexane and diethyl ether were tested using 5 equivalents of butyl butyrate (Table 4). The results were compared with the reaction carried out with $PrCO_2Bu$ as solvent (entry 1). Aliquots were regularly taken at intervals between 1 and 72 h, and the most representative results are shown. Reactions carried out at 30 ºC in THF, *n*-hexane and diethyl ether led almost to 50% conversion after 24 h with moderate enantioselectivity (*E* <50, entries 2-4), while in 1,4-dioxane the RML activity was lower with a similar selectivity (entry 5).

Biotransformations in TBME and toluene (entries 6 and 7) showed the fastest reaction rates, attaining 47% conversion after only 8 h. Finally, an excellent selectivity was observed when the reaction was performed in acetonitrile, unfortunately the conversion value was not synthetically useful. For that reason, interesterification was carried out with 10 equivalents of butyl butyrate, but no changes were observed in the conversion. At this point, we decided to explore new insights in these processes, combining the use of different organic solvents with a lower temperature (4 ºC), trying in this way to obtain better stereoselectivities (entries 9-12). This goal was reached, and a remarkable conversion value of 48% was attained with MTBE (entry 11), while a better selectivity was observed for toluene (entry 12), although it decreased at longer reaction times.

Table 4. Interesterification reaction of (±)-**9a** using butyl butyrate in different organic solvents.[a]

Entry	Solvent	T (ºC)	*t* (h)	ee_s (%)[b]	ee_p (%)[b]	*c* (%)[c]	*E*[d]
1	$PrCO_2Bu$	30	24	90	87	51	44
2	THF	30	24	17	95	50	50
3	*n*-Hexane	30	24	75	83	47	25
4	Et_2O	30	24	83	88	49	39
5	Dioxane	30	72	44	94	32	50
6	MTBE	30	8	79	88	47	38
7	Toluene	30	8	79	93	47	38
8	MeCN	30	24	16	>99	14	>200
9	*n*-Hexane	4	24	41	89	32	35
10	Et_2O	4	24	31	96	24	63
11	MTBE	4	24	83	92	48	64
12	Toluene	4	24	96	49	34	89

[a] Reaction conditions: 5 equivalents of butyl butyrate and RML (ratio 2:1 of enzyme:**9a**), 120 mM substrate concentration at 250 rpm.
[b] Enantiomeric excess of substrate and product determined by HPLC.
[c] Conversion value: $c= ee_s/(ee_s+ee_p)$.
[d] Enantioselectivity value: $E= \ln[1-c(1+ee_p)]/\ln[1-c(1-ee_p)]$.

Once that the potential of the interesterification reaction was demonstrated in the resolution of the *N*-acetylated phenylalanine methyl ester, we decided to study the effect of the ester moiety making use of the allyl ester **11a** as starting material. Due to the fact that the best selectivity achieved for **9a** and $PrCO_2Bu$ was achieved employing MeCN as organic solvent, we decided to compare the effect of the substrate under these conditions (entries 1 and 2, Table 5). As can be observed, a very high stereoselectivity towards the formation of the butyl ester (*S*)-**10a** and the allyl derivative (*R*)-**11a** was reached after 72 h of reaction. This trend was shared in all cases, the reactivity of the allyl amino esters (**11**) being much higher than the ones from the corresponding methylated derivatives (**9**). There was just one exception for the hindered *ortho*-nitrobenzyl compounds (**9g** and **11g**), which did not shown appreciable activity (entries 13 and 14). Allyl *para*-substituted derivatives with methoxy (**b**), methyl (**c**), chloro (**d**) or nitro (**e**) functionalities produced the butyl esters in enantiopure form and gratifyingly with conversions close to 50% (47-48%, entries 4, 6, 8 and 10). For the 3-nitrobenzyl ester (**11f**) and the 2-naphthylmethyl ester (**11h**) a significant lost of stereoselectivity was observed, but still better activities were achieved than for the methyl counterparts.

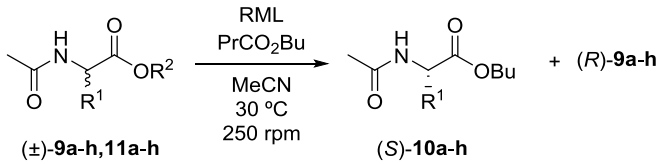
3. Conclusions

The selective synthesis on non-proteinogenic amino acid derivatives has been the focus of many efforts by organic chemists during the last years due to the novel properties attained when introduced in proteins and peptides. In this sense, while both enantiomers of phenylalanine could be obtained through

hydrolase-catalyzed resolutions through transesterification or hydrolysis processes,[13a,b,14] the synthesis of other phenylalanine analogs has been scarcely studied.[13c,d] Herein we show a methodology applicable for a series of phenylalanine derivatives making use of an interesterification reaction as a versatile approach to obtain them in an enantioenriched form.

Twenty-four *N*-acetyl amino esters have been chemically prepared from easily accessible ethyl acetamidocyanoacetate (**1**) following a phase transfer catalytic *C*-alkylation, acidic hydrolysis and later esterification and acetylation sequence. Several phase transfer catalysts were tested in the reaction between **1** and alkyl halides, finding the best results with benzyltributylammonium chloride (BTBAC). The obtained methyl amino esters were then subjected to enzymatic kinetic resolution using a set of lipases as biocatalysts. *Rhizomucor miehei* lipase was found as a versatile enzyme for the asymmetric synthesis of the corresponding *N*-acetyl protected amino esters. The best results were found when carrying out interesterification reactions with butyl butyrate in acetonitrile as solvent at 30 ºC. A great influence in the activity and stereoselectivity has been observed depending on the chemical structure of the amino ester. Allyl esters reacted faster than the corresponding methyl esters, achieving, with the exception of the *ortho*-nitro amino ester, excellent stereoselectivities for the non- or *para*-substituted analogs in the phenyl ring, while moderate ones for the *meta*-nitro or a bulky naphthalene derivative.

Table 5. Interesterificaton reaction of (±)-**9a-h** and **11a-h** (120 mM) using butyl butyrate and RML (ratio 2:1 in weight respect to the amino ester) in MeCN at 30 ºC and 250 rpm.



(±)-**9a-h,11a-h** (*S*)-**10a-h**

Entry	Substrate	*t* (h)	ee_s (%)[a]	ee_p (%)[a]	*c* (%)[b]	*E*[c]
1	**9a**	24	16	>99	14	>200
2	**11a**	72	90	98	48	>200
3	**9b**	24	44	>99	31	>200
4	**11b**	57	90	>99	48	>200
5	**9c**	240	75	>99	43	>200
6	**11c**	72	91	>99	48	>200
7	**9d**	240	78	>99	44	>200
8	**11d**	64	89	>99	47	>200
9	**9e**	120	86	98	47	>200
10	**11e**	30	90	>99	48	>200
11	**9f**	144	48	84	37	18
12	**11f**	72	81	87	48	35
13	**9g**	240	<3	<3	<3	n.d[d]
14	**11g**	24	<3	<3	<3	n.d[d]
15	**9h**	120	27	92	23	31
16	**11h**	120	81	78	49	19

[a] Enantiomeric excess of substrate and product determined by HPLC.
[b] Conversion value: $c=ee_s/(ee_s+ee_p)$.
[c] Enantioselectivity value: $E= \ln[1-c(1+ee_p)]/\ln[1-c(1-ee_p)]$.
[d] n.d.: Not determined.

4. Experimental section

4.1. General considerations

Chemical reagents were purchased from different commercial sources and used without further purification. Solvents were distilled over an adequate desiccant under nitrogen. *Candida antarctica* lipase type B (CAL-B, Novozyme 435, 7300 PLU/g) was a gift from Novozymes. *Pseudomonas cepacia* lipase currently known as *Burkhlolderia cepacia* lipase (PSL-IM, 1638 U/g solid) and *Pseudomonas fluorescens* lipase (AK, 22100 U/g) were acquired from Sigma-Aldrich. *Candida antarctica* lipase A (CAL-A, 2.6 U/mg solid) was purchased from Codexis. Pancreas porcine lipase (PPL, 46 U/mg solid), *Candida rugose* lipase (CRL, 1.41 U/g) and *Candida cylindracea* lipase (CCL, 1.41 U/mg solid) were obtained from Sigma. *Rhizomuccor miehei* lipase (RML, 150 IUN/g) and *Thermomyces lanuginosus* lipase (TLL, 250 IUN/g) were purchased from Novozymes.

Flash chromatography was performed using silica gel 60 (230-240 mesh). Melting points were taken on samples in open capillary tubes and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1720-X F7 using NaCl plates or KBr pellets in. ^{1}H, ^{13}C NMR, and DEPT were obtained using AV-300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz) and AV-400 (^{1}H, 400.13 MHz and ^{13}C, 100.6 MHz) spectrometers. The chemical shifts are given in delta (δ) values and the coupling constants (*J*) in Hertz (Hz). High resolution mass spectra (HRMS) experiments were carried out by ESI$^+$ using a BrukerMicroTofQ spectrometer. Measurement of the optical rotation was done in a Perkin-Elmer 241 polarimeter. High performance liquid chromatography (HPLC) analyses were carried out in a Hewlett Packard 1100 chromatograph with a UV detector at 210 nm using a Chiralpak AS column (25 cm × 4.6 mm I.D.), Chiralpak IC (25 cm × 4.0 mm I.D.) and Chiralcel OB-H column (25 cm × 4.6 mm I.D.).

*4.2. General procedure for the alkylation of racemic ethyl acetamidocyanoacetate (**1**) with alkyl halides **4a-h***

A suspension of (±)-**1** (511 mg, 3 mmol), BTBAC (31 mg, 0.1 mol), the corresponding alkyl halides (**2** or **4a-h**, 6 mmol), and potassium carbonate (415 mg, 3 mmol) were heated in toluene (5 mL) for 5 h at 70 ºC under magnetic stirring. The reaction mixture was cooled to room temperature and diluted with $CHCl_3$ (20 mL), then the solution was washed with water (3 x 40 mL). The organic phase was dried with Na_2SO_4, filtered and the solvent evaporated under reduced pressure, obtaining a crude product that was purified by *flash* chromatography on silica gel (30-100% EtOAc/hexane). The amino esters **3a-h** were obtained as solids in 52-95% isolated yield (see Table 2).

Spectroscopical data of ethyl 2-acetylamino-2-cyano-3-phenylpropanoate (3a): Solid. R_f (50% EtOAc/hexane): 0.38. Mp: 121-122 °C. IR (NaCl): *v* 3277, 1753, 1668, 1527 and 1220 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 1.23 (t, 3H, *J*= 14.3 Hz), 2.07 (s, 3H), 3.38 (d, 1H, *J*= 13.4 Hz), 3.52 (d, 1H, *J*= 13.4 Hz), 4.16-4.30 (m, 2H), 6.87 (s, 1H), 7.23 (s, 1H) and 7.26-7.37 (m, 5H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 13.8 (CH_3), 22.6 (CH_3), 41.6 (CH_2), 57.9 (C), 63.7 (CH_2), 116.4 (C), 128.6 (CH), 128.9 (2CH), 130.1 (2CH), 131.7 (C), 165.8 (C) and 170.1 (C). HRMS [ESI$^+$, *m/z*] calcd for $C_{14}H_{16}N_2O_3$[Na$^+$] 283.1059, found 283.1054.

Spectroscopical data of ethyl 2-acetylamino-2-cyano-3-(4-methoxyphenyl)propanoate (3b): Solid. R_f (50% EtOAc/hexane): 0.16. Mp: 181-184 °C. IR (NaCl): *v* 3250, 1697, 1633, 1512 and 1248 cm^{-1}. ^{1}H NMR (300.13 MHz, Py-d5) δ (ppm): 1.20 (t, 3H, *J*= 7.0 Hz), 2.23 (s, 3H), 3.76-3.89 (m, 5H), 4.32-4.40 (m, 2H), 7.13 (dd, 2H, *J*= 11.4 and 3.0 Hz) and 7.62

(dd, 2H, *J*= 11.2 and 2.4 Hz). ^{13}C NMR (75.5 MHz, Py-d5) δ (ppm): 14.6 (CH_3), 22.8 (CH_3), 42.2 (CH_2), 55.9 (C), 60.8 (CH_3), 63.7 (CH_2), 115.1 (2CH), 119.0 (C), 125.5 (C), 132.7 (2CH), 160.8 (C), 168.0 (C) and 171.6 (C). HRMS [ESI$^+$, *m/z*] calcd for $C_{15}H_{18}N_2O_4$[Na^+] 313.1164, found 313.1161.

Spectroscopical data of ethyl 2-acetylamino-3-(4-methylphenyl)-2-cyanopropanoate (3c): Solid. R_f (50% EtOAc/hexane): 0.3. Mp: 149.5-150.1 °C. IR (NaCl) *v* 3404, 3250, 1730, 1697, 1512 and 1248 cm^{-1}. ^{1}H NMR (300.13 MHz, MeOD) δ (ppm): 1.10 (t, 3H, *J*= 6.0 Hz), 2.05 (s, 3H), 2.34 (s, 3H), 4.06-4.12 (q, 2H, *J*= 6.0 Hz), 4.27-4.34 (m, 1H) and 7.18 (s, 4H). ^{13}C NMR (75 MHz, MeOH) δ (ppm): 14.1 (CH_3), 21.2 (CH_3), 21.9 (CH_3), 42.5 (CH_2), 60.5 (CH_2), 64.1 (C), 118.1 (C), 130.2 (2CH), 130.3 (C), 131.3 (2CH), 139.4 (C), 167.6 (C) and 173.2 (C). HRMS [ESI$^+$, *m/z*] calcd for $C_{15}H_{18}N_2O_3$[Na^+] 297.1215, found 297.1209.

Spectroscopical data of ethyl 2-acetylamino-3-(4-chlorophenyl)-2-cyanopropanoate (3d): Solid. R_f (50% EtOAc/hexane): 0.28. Mp: 151-152 °C. IR (NaCl) *v* 3250, 1730, 1697, 1512, 1248 and 1032 cm^{-1}. ^{1}H NMR (300.13 MHz, MeOD) δ (ppm): 1.13 (t, 3H, *J*= 7.1 Hz), 2.05 (s, 3H), 3.27 (d, 1H, *J*= 13.4 Hz), 3.40 (d, 1H, *J*= 13.3 Hz), 4.09-4.15 (q, 2H, *J*= 7.1 Hz), 7.30 (d, 2H, *J*= 8.7 Hz) and 7.38 (d, 2H, *J*= 8.7 Hz). ^{13}C NMR (75.5 MHz, MeOD) δ (ppm): 14.1 (CH_3), 21.8 (CH_3), 41.9 (CH_2), 60.2 (C), 64.2 (CH_2), 117.8 (C), 129.8 (2CH), 132.3 (C), 133.0 (2CH), 135.5 (C), 167.4 (C) and 173.2 (C). HRMS [ESI$^+$, *m/z*] calcd for $C_{14}H_{15}N_2O_3Cl$[Na^+] 317.0669, found 317.0666.

Spectroscopical data of ethyl 2-acetylamino-2-cyano-3-(4-nitrophenyl)propanoate (3e): Solid. R_f (60% EtOAc/hexane): 0.31. Mp: 141-143 °C. IR (NaCl) *v* 3244, 3034, 1743, 1656, 1528 and 1211 cm^{-1}. ^{1}H NMR (300.13 MHz, Py-d5) δ (ppm): 1.07 (t, 3H, *J*= 7.2 Hz), 2.11 (s, 3H), 3.81 (d, 1H, *J* = 13.3 Hz), 3.92 (d, 1H, *J*= 13.1 Hz), 4.24 (q, 2H, *J*= 7.2 Hz), 7.70 (d, 2H, *J*= 8.8 Hz) and 8.23 (d, 2H, *J*= 8.8 Hz). ^{13}C NMR (75.5 MHz, Py-d5) δ (ppm): 14.3 (CH_3), 22.6 (CH_3), 41.7 (CH_2), 59.9 (C), 63.9 (CH_2), 118.2 (C), 124.4 (2CH), 132.5 (2CH), 141.1 (C), 148.7 (C), 167.3 (C) and 171.6 (C). HRMS [ESI$^+$, *m/z*] calcd for $C_{14}H_{15}N_3O_5$[Na^+] 328.0909, found 328.0909.

Spectroscopical data of ethyl 2-acetylamino-2-cyano-3-(3-nitrophenyl)propanoate (3f): Solid. R_f (EtOAc/Hexane:MeOH 4:5:1): 0.33. Mp: 120-123 °C. IR (NaCl) *v* 3244, 3043, 1759, 1656, 1530 and 1204 cm^{-1}. ^{1}H NMR (300.13 MHz, Py-d5) δ (ppm): 1.04 (t, 3H, *J*= 7.2 Hz), 2.07 (s, 3H), 3.78-3.93 (m, 2H), 4.18-4.25 (q, 2H, *J*= 7.2 Hz), 7.52 (apparent t, 1H, *J*= 7.9 Hz), 7.90 (d, 1H, *J*= 7.6 Hz), 8.19 (dd, 1H, *J*= 8.3 and 1.5 Hz) and 8.44 (s, 1H). ^{13}C NMR (75 MHz, Py-d5) δ (ppm): 14.1 (CH_3), 22.3 (CH_3), 41.3 (CH_2), 59.9 (C), 63.7 (CH_2), 117.9 (C), 125.9 (CH), 130.3 (CH), 135.5 (CH), 137.4 (CH), 148.8 (C), 167.1 (C) and 171.4 (C). HRMS [ESI$^+$, *m/z*] calcd for $C_{14}H_{15}N_3O_5$[Na^+] 328.0909, found 328.0915.

Spectroscopical data of ethyl 2-acetylamino-2-cyano-3-(2-nitrophenyl)propanoate (3g): Solid. R_f (60% EtOAc/hexane): 0.31. Mp: 140-143 °C. IR (NaCl) *v* 3241, 3045, 1755, 1659, 1529 and 1202 cm^{-1}. ^{1}H NMR (300.13 MHz, Py-d5) δ (ppm): 1.05 (t, 3H, *J*= 7.3 Hz), 2.07 (s, 3H), 4.18-4.23 (m, 3H), 4.42 (d, 1H, *J*= 8.4 Hz), 7.44 (dd, 1H, *J*= 4.9 Hz, *J*= 0.9 Hz), 7.57 (apparent t, 1H, *J*= 3.7 Hz), 7.74 (d, 1H, *J*= 4.6 Hz) and 8.07 (d, 1H, *J*= 4.8 Hz). ^{13}C NMR (75.5 MHz, Py-d5) δ (ppm): 14.6 (CH_3), 23.0 (CH_3), 38.4 (CH_2), 60.1 (C), 64.4 (CH_2), 118.4 (C), 124.7 (CH), 126.7 (CH), 128.9 (CH), 130.8 (CH), 134.4 (C), 135.2 (C), 167.6 (C) and 171.8 (C). HRMS [ESI$^+$, *m/z*] calcd for $C_{14}H_{15}N_3O_5$[Na^+] 328.0909, found 328.1001.

Spectroscopical data of ethyl 2-acetylamino-2-cyano-3-(naphthalen-2-yl)propanoate (3h): Solid. R_f (50% EtOAc/hexane): 0.21. Mp: 170-172 °C. IR (NaCl) *v* 3293, 1752, 1666, 1528 and 1224 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.25 (t, 3H, *J*= 7.3 Hz), 2.04 (s, 3H), 3.51 (d, 1H, *J*= 8.2 Hz), 3.77 (d, 1H, *J*= 8.1 Hz), 4.22-4.33 (q, 2H, *J*= 7.3 Hz), 6.43 (s, 1H) and 7.27-7.35 (m, 1H), 7.51 (m, 2H), 7.69 (s, 1H), 7.82 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 13.9 (CH_3), 22.7 (CH_3), 41.6 (CH_2), 57.5 (C), 64.0 (CH_2), 116.3 (C), 126.6-133.3 (10 C_{Ar}), 165.9 (C) and 169.7 (C). HRMS [ESI$^+$, *m/z*] calcd for $C_{18}H_{18}N_2O_3$[Na^+] 333.1215, found 333.1214.

*4.3. General procedure for the hydrolysis of amino esters **3a-h** and subsequent esterification and N-acetylation reactions*

A suspension of amino ester **3a-h** (0.3 M) in an aqueous 20% HCl solution (20 mL), was refluxed for 30 h, obtaining the amino acid salts **5a-h** as white solids, which were washed with Et_2O (30 mL). Then a solution of **5a-h** (0.03 M) in the corresponding alcohol (methanol, butanol or allyl alcohol, 30 mL) was prepared and a catalytic amount of a concentrated HCl solution (0.03 mL) was added. The solution was stirred at reflux for 1 h, and after that time the solvent was evaporated under reduced pressure, and the crude product was washed with Et_2O (30 mL). The resulting solid without further purification was subjected to *N*-acetylation reaction, by dissolving it in CH_2Cl_2 (5 mL, 0.25 M), and then acetic anhydride (2.3 mL, 24.3 mmol), pyridine (1.0 mL, 12 mmol) and DMAP (30.5 mg, 0.25 mmol) were added. The reaction was stirred at room temperature for 4 h, and then diluted with CH_2Cl_2 (30 mL) and washed with a 10% $CuSO_4$ aqueous solution (3 x 30 mL). The reaction mixture was concentrated under reduced pressure and the reaction crude products were purified by *flash* chromatography on silica gel. The corresponding esters were obtained as follows: **9a-h** (52-80% isolated yield), **10a-h** (52-88% isolated yield) and **11a-h** (43-63% isolated yield), see Scheme 1 and Supporting Information for further details.

*4.4. General procedure for the lipase-catalyzed interesterification of **11a-h***

To a suspension of the corresponding allylated amino ester **11a-h** (20 mg, 0.09 mmol) and RML (40 mg) in dry MeCN (0.75 mL), butyl butyrate (75 μL, 0.45 mmol) was added under nitrogen atmosphere. The resulting suspension was shaken at 30 ºC and 250 rpm in an orbital shaker, following the time course of the reactions by HPLC analysis (see further details in the Supporting Information). After the adequate time, the reaction was stopped, and the enzyme filtered off and washed with CH_2Cl_2 (15 mL). The solvent was evaporated under reduced pressure and the reaction crude purified by *flash* chromatography on silica gel (10-70% EtOAc/hexane), yielding (*S*)-**11a-h** and (*R*)-**10a-h**, and their enantiomeric excess (see Table 5) were determined by HPLC.

Spectroscopical data of methyl 2-acetylamino-3-phenylpropanoate (9a): Solid. R_f (50% EtOAc/hexane): 0.15. Mp: 88-90 ºC. IR (NaCl): *v* 3280, 1744, 1656, 1544 and 1217 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.93 (s, 3H), 3.03 (dd, 1H, *J*= 5.9 and 5.8 Hz), 3.10 (dd, 1H, *J*= 5.9 and 5.8 Hz), 3.68 (s, 3H), 4.84 (ddd, 1H, *J*= 6.9, 6.8 and 6.0 Hz), 6.19 (br d, 1H, *J*= 7.3 Hz), 7.07 (m, 2H) and 7.20-7.27 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 23.1 (CH_3), 37.9 (CH_2), 52.4 (CH), 53.3 (CH_3), 127.2 (CH), 128.6 (2CH), 129.3 (2CH), 136.0 (C), 169.9 (C) and 172.3 (C). HRMS [ESI$^+$, *m/z*] calcd for $C_{12}H_{15}NO_3$[Na^+] 244.095, found 244.0989. $[\alpha]_D^{20}$= -83.5 (*c* 1.0, $CHCl_3$) for 82% *ee* of the (*R*)-enantiomer. Lit $[\alpha]_D^{20}$= -96.3 (*c* 1.0, $CHCl_3$) for

90% *ee* of the (*R*)-enantiomer.[15] Lit $[\alpha]_D^{20}$= -99.3 (*c* 1.0, $CHCl_3$) for 94% *ee* of the (*R*)-enantiomer.[16]

Spectroscopical data of butyl 2-acetylamino-3-phenylpropanoate (10a): Oil. R_f (50% EtOAc/hexane): 0.38. IR (NaCl) *v* 3282, 2960, 1740, 1659, 1549 and 1211 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.90 (t, 3H, *J*= 14.8 Hz), 1.28-1.35 (m, 2H), 1.54-1.60 (m, 2H), 1.97 (s, 3H), 3.06-3.14 (m, 2H), 4.04-4.13 (m, 2H), 4.85 (m, 1H), 6.02 (br d, 1H, *J*= 7.0 Hz), 7.09 (m, 2H) and 7.21-7.28 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 13.8 (CH_3), 19.2 (CH_2), 23.3 (CH_3), 30.6 (CH_2), 38.2 (CH_2), 53.4 (CH), 65.6 (CH_2), 127.2 (CH), 128.7 (2CH), 129.5 (2CH), 136.1 (C), 169.8 (C) and 172.0 (C). HRMS [ESI^+, *m/z*] calcd for $C_{15}H_{21}NO_3[Na^+]$ 286.1419, found 286.1383. $[\alpha]_D^{20}$= +7.5 (*c* 1.0, $CHCl_3$) for 98% *ee* (*S*).

Spectroscopical data of allyl 2-acetylamino-3-phenylpropanoate (11a): Oil. R_f (50% EtOAc/hexane): 0.28. IR (NaCl) *v* 3283, 1743, 1659, 1539 and 1230 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 2.01 (s, 3H), 3.16 (m, 2H), 4.63 (d, 2H, *J*= 6.0 Hz), 4.93 (d, 1H, *J*= 7.5 Hz), 5.31 (m, 2H), 5.88 (m, 1H), 5.97 (br d, 1H, *J*= 6.5 Hz), 7.12 (m, 2H) and 7.27-7.32 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 23.3 (CH_3), 38.0 (CH_2), 53.3 (CH), 66.3 (CH_2), 119.3 (CH_2), 127.3 (CH), 128.7 (2CH), 129.5 (2CH), 131.5 (CH), 135.9 (C), 169.8 (C) and 171.5 (C). HRMS [ESI^+, *m/z*] calcd for $C_{14}H_{17}NO_3[Na^+]$ 270.1106, found 270.1101. $[\alpha]_D^{20}$= -58.2 (*c* 1.0, $CHCl_3$) for 90% *ee* (*R*).

Spectroscopical data of methyl 2-acetylamino-3-(4-methoxyphenyl)propanoate (9b): Solid. R_f (50% EtOAc/hexane): 0.16. Mp: 106-107 ºC. IR (NaCl): *v* 3280, 1748, 1640, 1511 and 1223 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 2.00 (s, 3H), 3.01-3.14 (m, 2H), 3.74 (s, 3H), 3.80 (s, 3H), 4.85 (dd, 1H, *J*= 7.2 and 5.7 Hz), 5.92 (br d, 1H, *J*= 7.2 Hz), 6.83 (d, 2H, *J*= 8.6 Hz) and 7.02 (d, 2H, *J*= 8.6 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 23.0 (CH_3), 37.1 (CH_2), 52.2 (CH), 53.1 (CH_3), 55.2 (CH_3), 114.1 (2CH), 127.8 (C), 130.2 (2CH), 158.7 (C), 169.8 (C) and 172.0 (C). HRMS [ESI^+, *m/z*] calcd for $C_{13}H_{17}NO_4[Na^+]$ 274.1055, found 274.1052. $[\alpha]_D^{20}$= -45.2 (*c* 1.0, $CHCl_3$) for 44% *ee* of the (*R*)-enantiomer. Lit $[\alpha]_D^{20}$= +82.3 (*c* 1.0, $CHCl_3$) for 84.5% *ee* of the (*S*)-enantiomer.[15] Lit $[\alpha]_D^{20}$= +102.5 (*c* 1.0, $CHCl_3$) for >99% *ee* of the (*S*)-enantiomer.[17]

Spectroscopical data butyl 2-acetylamino-3-(4-methoxyphenyl)propanoate (10b): Oil. R_f (50% EtOAc/hexane): 0.23. IR (NaCl): *v* 3276, 1752, 1648, 1527 and 1221 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 0.92 (t, 3H, *J*=7.3 Hz), 1.28-1.40 (m, 2H), 1.55-1.64 (m, 2H), 1.98 (s, 3H), 2.99-3.17 (m, 2H), 3.78 (s, 3H), 3.99-4.12 (m, 2H), 6.0 (br d, 1H, *J*= 7.4 Hz), 6.82 (d, 2H, *J*= 8.4 Hz), 7.02 (d, 2H, *J*= 8.5 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 13.8 (CH_3), 19.2 (CH_2), 23.3 (CH_3), 30.7 (CH_2), 37.3 (CH_2), 53.5 (CH), 55.4 (CH_3), 65.5 (CH_2), 114.1 (2CH), 128.0 (C), 130.4 (2CH), 158.9 (C), 169.8 (C) and 172.1 (C). HRMS [ESI^+, *m/z*] calcd for $C_{16}H_{23}NO_4[Na^+]$ 316.1525, found 316.1523. $[\alpha]_D^{20}$= +53.7 (*c* 0.8, $CHCl_3$) for >99% *ee* (*S*).

Spectroscopical data of allyl 2-acetylamino-3-(4-methoxyphenyl)propanoate (11b): Oil. R_f (50% EtOAc/hexane): 0.18. IR (NaCl): *v* 3280, 1759, 1642, 1521 and 1232 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 1.98 (s, 3H), 3.07 (dd, 2H, *J*= 6.8 and 3.5 Hz), 3.78 (s, 3H), 4.61 (d, 2H, *J*= 5.5 Hz), 4.86 (d, 1H, *J*= 7.7 Hz), 5.25-5.34 (m, 2H), 5.88 (m, 1H), 5.99 (s, 1H), 6.81 (d, 2H, *J*= 8.5 Hz) and 7.01 (d, 2H, *J*= 8.5 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 23.3 (CH_3), 37.2 (CH_2), 53.5 (CH), 55.4 (CH_3), 66.2 (CH_2), 114.2 (2CH), 119.3 (CH_2), 127.9 (CH), 130.5 (2CH), 131.6 (2CH), 158.9 (C), 169.9 (C) and 171.6 (C). HRMS [ESI^+, *m/z*] calcd for $C_{15}H_{19}NO_4[Na^+]$ 300.1212, found 320.1210. $[\alpha]_D^{20}$= -39.1 (*c* 0.6, $CHCl_3$) for 90% *ee* (*R*).

Spectroscopical data of methyl 2-acetylamino-3-(4-methylphenyl)propanoate (9c): Solid. R_f (50% EtOAc/hexane): 0.28. Mp: 123-123.6 °C. IR (NaCl): *v* 3273, 1747, 1662, 1521 and 1207 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 1.96 (s, 3H), 2.30 (s, 3H), 2.99-3.13 (m, 2H), 3.71 (s, 3H), 4.81-4.88 (m, 1H), 6.07 (br d, 1H, *J*= 7.4 Hz), 6.97 (d, 2H, *J*= 7.8 Hz) and 7.08 (d, 2H, *J*= 7.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 21.1 (CH_3), 23.1 (CH_3), 37.4 (CH_2), 52.3 (CH), 53.2 (CH_3), 129.1 (2CH), 129.3 (2CH), 132.7 (C), 136.7 (C), 169.7 (C) and 172.2 (C). HRMS [ESI^+, *m/z*] calcd for $C_{13}H_{17}NO_3[Na^+]$ 258.1106, found 258.1059. $[\alpha]_D^{20}$= -43.8 (*c* 1.0, CH_2Cl_2) for 75% *ee* (*R*).

Spectroscopical data of butyl 2-acetylamino-3-(4-methylphenyl)propanoate (10c): Solid. R_f (50% EtOAc/hexane): 0.37. Mp: 62.7-63.0 ºC. IR (NaCl) *v* 3270, 1756, 1642, 1559 and 1211 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 0.94 (t, 3H, *J*= 7.3 Hz), 1.27-1.42 (m, 2H), 1.56-1.66 (m, 2H), 2.00 (s, 3H), 3.01-3.13 (m, 2H), 3.79 (s, 3H), 4.09-4.15 (m, 2H), 4.81-4.87 (m, 1H), 5.92 (br d, 1H, *J*= 7.9 Hz), 6.83 (dd, 2H, *J*= 6.8 and 2.0 Hz) and 7.02 (dd, 2H, *J*= 6.7 and 2.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 13.8 (CH_3), 19.2 (CH_2), 23.3 (CH_3), 30.7 (CH_2), 37.3 (CH_2), 53.5 (CH), 55.4 (CH_3), 65.5 (CH_2), 114.1 (2CH), 128.0 (C), 130.5 (2CH), 158.9 (C), 169.7 (C) and 172.0 (C). HRMS [ESI^+, *m/z*] calcd for $C_{16}H_{23}NO_3[Na^+]$ 300.1576, found 300.1553. $[\alpha]_D^{20}$= +45.4 (*c* 1.0, $CHCl_3$) for >99% *ee* (*S*).

Spectroscopical data of allyl 2-acetylamino-3-(4-methylphenyl)propanoate (11c): Oil. R_f (75% EtOAc/hexane): 0.48. IR (NaCl) *v* 3259, 1749, 1640, 1211 and 891 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 1.99 (s, 3H), 2.31 (s, 3H), 3.09 (m, 2H), 4.61 (d, 2H, *J*= 5.7 Hz), 4.88 (ddd, 1H, *J*= 7.5, 6.7 and 5.8 Hz), 5.30 (m, 2H), 5.89 (m, 1H), 6.02 (br d, 1H, *J*= 7.5 Hz), 6.99 (d, 2H, *J*= 7.9 Hz) and 7.09 (d, 2H, *J*= 7.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 21.2 (CH_3), 23.3 (CH_3), 37.6 (CH_2), 53.4 (CH), 66.2 (CH_2), 119.3 (CH_2), 129.4 (2CH), 129.5 (2CH), 131.6 (CH), 132.8 (C), 136.9 (C), 170.0 (C) and 171.7 (C). HRMS [ESI^+, *m/z*] calcd for $C_{15}H_{19}NO_3[Na^+]$ 284.1263, found 284.1220. $[\alpha]_D^{20}$= -53.9 (*c* 0.7, $CHCl_3$) for 91% *ee* (*R*).

Spectroscopical data of methyl 2-acetylamino-3-(4-chlorophenyl)propanoate (9d): Oil. R_f (50% EtOAc/hexane): 0.49. IR (NaCl) *v* 3267, 1748, 1691, 1503, 1201 and 1049 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 1.99 (s, 3H), 3.09 (dd, 1H, *J*= 14.0 and 5.8 Hz), 3.13 (dd, 1H, *J*= 14.0 and 6.0 Hz), 3.73 (s, 3H), 4.87 (ddd, 1H, *J*= 7.4, 6.0 and 5.8 Hz), 6.05 (br d, 1H, *J*= 7.4 Hz), 7.03 (d, 2H, *J*= 8.4 Hz) and 7.26 (d, 2H, *J*= 8.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 23.3 (CH_3), 37.5 (CH_2), 52.6 (CH_3), 53.3 (CH), 128.9 (2CH), 130.8 (2CH), 133.3 (C), 134.6 (C), 169.9 (C) and 172.1 (C). HRMS [ESI^+, *m/z*] calcd for $C_{12}H_{14}NO_3Cl[Na^+]$ 278.0560, found 278.0559. $[\alpha]_D^{20}$= -101.9 (*c* 1.0, $CHCl_3$) for 78% *ee* (*R*).

Spectroscopical data of butyl 2-acetylamino-3-(4-chlorophenyl)propanoate (10d): Oil. R_f (50% EtOAc/hexane): 0.35. IR (NaCl) *v* 3259, 1750, 1683, 1512 and 1021 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 0.92 (t, 3H, *J*= 7.1 Hz), 1.26-1.38 (m, 2H), 1.53-1.63 (m, 2H), 1.99 (s, 3H), 3.02-3.15 (m, 2H), 4.03-4.17 (m, 2H), 4.82-4.88 (m, 1H), 6.13 (br d, 1H, *J*= 7.5 Hz), 7.04 (d, 2H, *J*= 7.9 Hz) and 7.25 (d, 2H, *J*= 8.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 13.8 (CH_3), 19.2 (CH_2), 23.3 (CH_3), 30.6 (CH_2), 37.6 (CH_2), 53.3 (CH), 65.8 (CH_2), 128.9 (2CH), 130.8 (2CH), 133.2 (C), 134.7 (C), 170.0 (C) and 171.9 (C). HRMS [ESI^+, *m/z*] calcd for $C_{15}H_{20}NO_3Cl[Na^+]$ 320.1029, found 320.0994. $[\alpha]_D^{20}$= +77.6 (*c* 0.5, $CHCl_3$) for >99% *ee* (*S*).

Spectroscopical data of allyl 2-acetylamino-3-(4-chlorophenyl)propanoate (11d): Solid. R_f (50% EtOAc/hexane): 0.42. Mp: 140-141.2 °C. IR (NaCl) *v* 1754, 1699, 1523, 1225 and 1046 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 2.00 (s, 3H), 3.04-3.18 (m, 2H), 4.62 (d, 2H, *J*=5.9 Hz), 4.89 (m, 1H), 5.26-5.36 (m, 2H), 5.81-5.89 (m, 1H), 6.26 (br d, 1H, *J*= 7.6 Hz), 7.06 (d, 2H, *J*= 8.3 Hz) and 7.26 (d, 2H, *J*= 8.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 23.0 (CH_3), 37.3 (CH_2), 53.2 (CH), 66.2 (CH_2), 119.3 (CH_2), 128.7 (2CH), 130.7 (2CH), 131.3 (CH), 133.0 (C), 134.5 (C), 169.9 (C) and 171.2 (C). HRMS [ESI^+, *m/z*] calcd for $C_{14}H_{16}NO_3Cl[Na^+]$ 304.0716, found 304.0710. $[\alpha]_D^{20}$= -24.9 (*c* 0.7, $CHCl_3$) for 89% *ee* (*R*).

Spectroscopical data of methyl 2-acetylamino-3-(4-nitrophenyl)propanoate (9e): Solid. R_f (EtOAc): 0.45. Mp: 112-113 °C. IR (NaCl): *v* 3278, 1743, 1654, 1352, 1219 and 736 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 2.02 (s, 3H), 3.19 (dd, 1H, *J*= 13.9 and 5.7 Hz), 3.32 (dd, 1H, *J*= 13.7 and 6.1 Hz), 3.76 (s, 3H), 4.94 (ddd, 1H, *J*= 7.4, 7.3 and 5.8 Hz), 6.03 (br d, 1H, *J*= 6.8 Hz), 7.30 (d, 2H, *J*= 8.7 Hz) and 8.17 (d, 2H, *J*= 8.6 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 25.1 (CH_3), 39.9 (CH_2), 54.6 (CH_3), 54.9 (CH), 125.7 (2CH), 132.2 (2CH), 145.8 (C), 149.2 (C), 171.7 (C) and 173.5 (C). HRMS [ESI^+, *m/z*] calcd for $C_{12}H_{14}N_2O_5[Na^+]$ 289.0800, found 289.0801. $[\alpha]_D^{20}$= -83.6 (*c* 0.7, $CHCl_3$) for 86% *ee* (*R*).

Spectroscopical data of butyl 2-acetylamino-3-(4-nitrophenyl)propanoate (10e): Solid. R_f (EtOAc/Hexane/MeOH 4:5:1): 0.5. Mp: 102.9-103.4 °C. IR (NaCl) *v* 3271, 3060, 1759, 1670, 1536 and 1209 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 0.93 (t, 3H, *J*= 7.2 Hz), 1.27-1.39 (m, 2H), 1.55-1.65 (m, 2H), 2.03 (s, 3H), 3.16-3.33 (m, 2H), 4.06-4.21 (m, 2H), 4.95 (m, 1H), 6.07 (br d, 1H, *J*= 7.2 Hz), 7.31 (d, 2H, *J*= 8.7 Hz) and 8.17 (d, 2H, *J*= 8.7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 15.6 (CH_3), 21.0 (CH_2), 25.1 (CH_3), 32.5 (CH_2), 40.0 (CH_2), 54.9 (CH), 67.8 (CH_2), 125.6 (2CH), 132.2 (2CH), 145.9 (C), 149.2 (C), 171.7 (C) and 173.2 (C). HRMS [ESI^+, *m/z*] calcd for $C_{15}H_{20}N_2O_5[Na^+]$ 331.1270, found 331.1295. $[\alpha]_D^{20}$= +93.1 (*c* 1.0, $CHCl_3$) for 98% *ee* (*S*).

Spectroscopical data of allyl 2-acetylamino-3-(4-nitrophenyl)propanoate (11e): Solid. R_f (EtOAc/Hexane:MeOH 4:5:1): 0.78. Mp: 92-94 °C. IR (NaCl): *v* 3280, 1761, 1650, 1529 and 1355 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 2.01 (s, 3H), 3.19 (dd, 1H, *J*= 13.7 and 5.7 Hz), 3.31 (dd, 1H, *J*= 13.8 and 6.3 Hz), 4.62 (d, 2H, *J*= 5.8 Hz), 4.94 (m, 1H), 5.27-5.35 (m, 2H), 5.80-5.93 (m, 1H), 6.04 (br d, 1H, *J*= 7.2 Hz), 7.30 (d, 2H, *J*= 8.5 Hz) and 8.14 (d, 2H, *J*= 8.5 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 23.3 (CH_3), 38.0 (CH_2), 53.1 (CH), 66.6 (CH_2), 119.9 (CH_2), 123.9 (2CH), 130.4 (2CH), 131.2 (2CH), 144.0 (C), 147.4 (C), 169.9 (C) and 171.0 (C). HRMS [ESI^+, *m/z*] calcd for $C_{14}H_{16}N_2O_5[Na^+]$ 315.0957, found 315.0955. $[\alpha]_D^{20}$= -37.0 (*c* 0.7, $CHCl_3$) for 90% *ee* (*R*).

Spectroscopical data of methyl 2-acetylamino-3-(3-nitrophenyl)propanoate (9f): Oil. R_f (50% EtOAc/hexane): 0.47. IR (NaCl): *v* 3280, 1744, 1658, 1530 and 1352 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 2.00 (s, 3H), 3.17 (dd, 1H, *J*= 13.7 and 5.8 Hz), 3.31 (dd, 1H, *J*= 13.9 and 5.7 Hz), 3.76 (s, 3H), 4.92 (m, 1H), 6.23 (br d, 1H, *J*= 6.8 Hz), 7.48 (d, 2H, *J*= 5.2 Hz), 7.98 (s, 1H) and 8.11 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 25.0 (CH_3), 39.6 (CH_2), 54.6 (CH_3), 55.0 (CH), 124.2 (CH), 126.2 (CH), 131.5 (CH), 137.4 (CH), 140.2 (C), 150.2 (C), 171.9 (C) and 173.6 (C). HRMS [ESI^+, *m/z*] calcd for $C_{12}H_{14}N_2O_5[Na^+]$ 289.0800, found 289.0803. $[\alpha]_D^{20}$= -90.6 (*c* 1.0, CH_2Cl_2) for 60% *ee* (*R*).

Spectroscopical data of butyl 2-acetylamino-3-(3-nitrophenyl)propanoate (10f): Solid. R_f (50% EtOAc/hexane): 0.38. Mp: 103-105 °C. IR (NaCl) *v* 3280, 3071, 1740, 1659, 1531 and 1211 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 0.88 (t, 3H, *J*= 7.6 Hz), 1.23-1.35 (m, 2H), 1.52-1.61 (m, 2H), 1.96 (s, 3H), 3.13 (dd, 1H, *J*= 13.9 and 6.1 Hz), 3.26 (dd, 1H, *J*= 13.7 and 6.0 Hz), 4.09 (t, 2H, *J*= 6.6 Hz), 4.83-4.89 (m, 1H), 6.47 (br d, 1H, *J*= 7.2 Hz), 7.41-7.49 (m, 2H), 7.97 (s, 1H) and 8.06 (d, 1H, *J*= 7.4 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 15.6 (CH_3), 21.0 (CH_2), 24.9 (CH_3), 32.4 (CH_2), 39.6 (CH_2), 55.1 (CH), 67.7 (CH_2), 124.1 (CH), 126.2 (CH), 131.4 (CH), 137.5 (CH), 140.4 (C), 150.2 (C), 172.0 (C) and 173.3 (C). HRMS [ESI^+, *m/z*] calcd for $C_{15}H_{20}N_2O_5[Na^+]$ 331.1270, found 331.1267. $[\alpha]_D^{20}$= +51.9 (*c* 0.9, $CHCl_3$) for 87% *ee* (*S*).

Spectroscopical data of allyl 2-acetylamino-3-(3-nitrophenyl)propanoate (11f): Oil. R_f (60% EtOAc/hexane): 0.34. IR (NaCl): *v* 3277, 1743, 1659, 1531 and 1352 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 1.99 (s, 3H), 3.17 (dd, 1H, *J*= 13.9 and 6.0 Hz), 3.30 (dd, 1H, *J*= 13.9 and 5.9 Hz), 4.62 (m, 2H), 4.92 (m, 1H), 5.25-5.34 (m, 2H), 5.87 (m, 1H), 6.33 (br d, 1H, *J*= 7.4 Hz), 7.43-7.51 (m, 2H), 7.98 (d, 1H, *J*= 2.0 Hz) and 8.08 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 23.3 (CH_3), 37.9 (CH_2), 53.4 (CH), 68.7 (CH_2), 120.0 (CH_2), 122.5 (CH), 124.6 (CH), 129.7 (CH), 131.3 (CH), 135.9 (CH), 138.5 (C), 148.5 (C), 170.2 (C) and 171.2 (C). HRMS [ESI^+, *m/z*] calcd for $C_{14}H_{16}N_2O_5[Na^+]$ 315.0957, found 315.0954. $[\alpha]_D^{20}$= -67.9 (*c* 0.8, $CHCl_3$) for 81% *ee* (*R*).

Spectroscopical data of methyl 2-acetylamino-3-(2-nitrophenyl)propanoate (9g): Oil. R_f (60% EtOAc/hexane): 0.23. IR (NaCl): *v* 3278, 1740, 1659, 1541 and 1339 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 1.94 (s, 3H), 3.33 (dd, 1H, *J*= 13.9 and 8.0 Hz), 3.52 (dd, 1H, *J*= 13.9 and 6.0 Hz), 3.72 (s, 3H), 4.92 (dt, 1H, *J*= 7.9 and 5.8 Hz), 6.32 (br d, 1H, *J*= 7.7 Hz), 7.39-7.45 (m, 2H), 7.57 (dt, 1H, *J*= 7.8 and 1.4 Hz) and 7.92 (dd, 1H, *J*= 7.9 and 1.4 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 23.3 (CH_3), 35.0 (CH_2), 53.0 (CH), 53.3 (CH_3), 125.3 (CH), 128.6 (CH), 131.9 (C), 133.1 (CH), 133.5 (CH), 150.3 (C), 170.3 (C) and 172.1 (C). HRMS [ESI^+, *m/z*] calcd for $C_{12}H_{14}N_2O_5[Na^+]$ 289.0800, found 289.0767.

Spectroscopical data of butyl 2-acetylamino-3-(2-nitrophenyl)propanoate (10g): Solid. R_f (50% EtOAc/hexane): 0.34. Mp: 94-96 °C. IR (NaCl) *v* 3263, 3059, 1752, 1657, 1522 and 1203 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 0.90 (t, 3H, *J*= 7.4 Hz), 1.23-1.34 (m, 2H), 1.51-1.58 (m, 2H), 1.92 (s, 3H), 3.31 (dd, 1H, *J*= 13.6 and 8.1 Hz), 3.49 (dd, 1H, *J*= 13.8 and 6.1 Hz), 4.01-4.16 (m, 2H), 4.91 (apparent dt, 1H, *J*= 8.1 and 6.1 Hz), 6.32 (br d, 1H, *J*= 7.6 Hz), 7.41 (m, 2H), 7.55 (dd, 1H, *J*= 7.7 and 1.3 Hz) and 7.92 (d, 1H, *J*= 8.4 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 14.0 (CH_3), 19.4 (CH_2), 23.3 (CH_3), 30.8 (CH_2), 35.2 (CH_2), 53.4 (CH), 66.1 (CH_2), 125.2 (CH), 128.6 (CH), 132.0 (C), 133.1 (CH), 133.4 (CH), 149.8 (C), 170.2 (C) and 171.8 (C). HRMS [ESI^+, *m/z*] calcd for $C_{15}H_{20}N_2O_5[Na^+]$ 331.1270, found 331.1269.

Spectroscopical data of allyl 2-acetylamino-3-(2-nitrophenyl)propanoate (11g): Oil. R_f (50% EtOAc/hexane): 0.71. IR (NaCl): *v* 3250, 1749, 1660, 1556 and 1341 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 1.95 (s, 3H), 3.35 (dd, 1H, *J*= 13.6 and 8.1 Hz), 3.55 (dd, 1H, *J*= 13.8 and 6.1 Hz), 4.55-4.68 (m, 2H), 4.91 (apparent dt, 1H, *J*= 8.1 and 6.1 Hz), 5.24-5.32 (m, 2H), 5.79-5.93 (m, 1H), 6.23 (br d, 1H, *J*= 7.9 Hz), 7.42 (m, 2H), 7.55 (m, 1H) and 7.92 (dd, 1H, *J*= 8.4 and 1.7 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 22.9 (CH_3), 37.2 (CH_2), 53.3 (CH), 68.0 (CH_2), 116.6 (CH_2), 125.2 (CH), 128.6 (CH), 129.4 (CH), 132.0 (C), 133.1 (CH), 133.4 (CH), 150.4 (C), 166.3 (C) and

170.1 (C). HRMS [ESI$^+$, *m/z*] calcd for $C_{14}H_{16}N_2O_5[Na^+]$ 315.0957, found 315.0949.

Spectroscopical data of methyl 2-acetylamino-3-(naphthalen-2-yl)propanoate (9h): Solid. R_f (50% EtOAc/hexane): 0.35. Mp= 93-95 ºC. IR (NaCl) *v* 3277, 3056, 1745, 1655, 1544 and 1219 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 1.95 (s, 3H), 3.22 (dd, 1H, *J*= 20.2 and 6.3 Hz), 3.30 (dd, 1H, *J*= 19.9 and 6.0 Hz), 3.71 (s, 3H), 4.97 (apparent dt, 1H, *J*=6.9 and 6.0 Hz), 6.37 (br d, 1H, *J*= 7.7 Hz), 7.24 (dd, 1H, *J*= 8.0 and 1.6 Hz), 7.42-7.49 (m, 2H), 7.58 (s, 1H) and 7.77 (d, 3H, *J*= 3.4 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 23.3 (CH_3), 38.3 (CH_2), 52.7 (CH_3), 53.7 (CH), 126.2-133.9 (10 C_{Ar}), 170.4 (C) and 172.6 (C). HRMS [ESI$^+$, *m/z*] calcd for $C_{16}H_{17}NO_3[Na^+]$ 294.1106, found 294.1068. $[\alpha]_D^{20}$= -28.2 (*c* 1.0, $CHCl_3$) for 27% *ee* of the (*R*)-enantiomer. Lit $[\alpha]_D^{20}$= +91.5 (*c* 1.0, $CHCl_3$) for 86% *ee* for the (*S*)-enantiomer.[15] Lit $[\alpha]_D^{20}$= -104.7 (*c* 0.99, $CHCl_3$) for >99% *ee* for the (*R*)-enantiomer.[18]

Spectroscopical data of butyl 2-acetylamino-3-(naphthalen-2-yl)propanoate (10h): Solid. R_f (50% EtOAc/hexane): 0.43. Mp: 148-150 °C. IR (NaCl) *v* 3280, 3056, 1739, 1659, 1545 and 1202 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 0.86 (t, 3H, *J*= 7.2 Hz), 1.21-1.31 (m, 2H), 1.50-1.59 (m, 2H), 1.97 (s, 3H), 3.21-3.33 (m, 2H) 4.10 (t, 2H, *J*= 6.6 Hz), 4.97 (apparent dt, 1H, *J*= 7.1 and 6.0 Hz), 6.23 (br d, 1H, *J*= 7.7 Hz), 7.26 (dd, 1H, *J*= 8.3 and 1.9 Hz), 7.46 (m, 2H), 7.57 (s, 1H) and 7.73-7.86 (m, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (ppm): 13.6 (CH_3), 19.0 (CH_2), 23.1 (CH_3), 30.5 (CH_2), 38.2 (CH_2), 53.3 (CH), 65.4 (CH_2), 125.3-133.6 (10 C_{Ar}), 169.8 (C) and 171.9 (C). HRMS [ESI$^+$, *m/z*] calcd for $C_{19}H_{23}NO_3[Na^+]$ 336.1576, found 336.1544. $[\alpha]_D^{20}$= +90.2 (*c* 0.5, $CHCl_3$) for 92% *ee* (*S*).

Spectroscopical data of allyl 2-acetylamino-3-(naphthalen-2-yl)propanoate (11h): Oil. R_f (50% EtOAc/hexane): 0.42. IR (NaCl): *v* 1739, 1699, 1510 and 1374 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ (ppm): 1.99 (s, 3H), 3.24-3.37 (m, 2H), 4.63 (d, 2H, *J*= 6.0 Hz), 5.01 (apparent dt, 1H, *J*= 13.0 and 5.8 Hz), 5.22-5.34 (m, 2H), 5.80-5.93 (m, 1H), 6.09 (br d, 1H, *J*= 7.5 Hz), 7.26 (dd, 1H, *J*= 9.0 and 1.6 Hz), 7.48 (m, 2H), 7.58 (s, 1H) and 7.74-7.82 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 23.3 (CH_3), 38.2 (CH_2), 53.5 (CH), 66.4 (CH_2), 119.5 (CH_2), 126.0-133.5 (10 C_{Ar}), 133.6 (CH), 170.1 (C) and 171.7 (C). HRMS [ESI$^+$, *m/z*] calcd for $C_{18}H_{19}NO_3[Na^+]$ 320.1263, found 320.1260. $[\alpha]_D^{20}$= -74.6 (*c* 0.5, $CHCl_3$) for 81% *ee* (*R*).

Acknowledgments

The authors thank to the Brazilian and Spanish agencies CAPES-DGU (Process: 149/07), CNPq, FUNCAP, PRONEX, and Spanish Ministerio de Ciencia e Innovación (MICINN, Project CTQ 2011-24237) for fellowships and financial support. I. L. also thanks MICINN for personal funding (Ramón y Cajal Program).

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Supplementary Material

HPLC analysis conditions, and copies of ^{1}H and ^{13}C NMR experiments are available in the supplementary material.