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Chemoenzymatic approach to optically active 1,4-dihydropyridine derivatives

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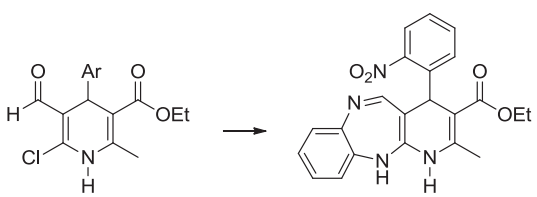
ABSTRACT

A series of racemic (2-methyl)propanoyloxymethyl 4-aryl-6-chloro-5-methanoyl-2-methyl-1,4-dihydropyridine-3-carboxylates [(±)-**5a**–**h**] have been prepared by a four step sequence including a multicomponent Hantzsch process and a Vilsmeier–Haack reaction. The subsequent resolution of (±)-**5a**–**h** was carried out by means of lipase-catalyzed hydrolysis, the most adequate enzymes being lipases from *Candida rugosa* (CRL) and *Candida antarctica* (CAL-B). The moderate to high enantioselectivities values (*E* up to >200) obtained in most cases allowed us to obtain the corresponding optically active 1,4-dihydropyridine derivatives with high enantiomeric excesses (ee≥94%) and yields.

1. Introduction

Nowadays, 1,4-dihydropyridines (1,4-DHPs) are recognized as privileged pharmacophores widely used in clinics for the treatment of cardiovascular diseases.[1] Structural modification led to a large family of hybrid drugs containing the 1,4-DHP moiety.[2] This is the case of the recently published BZD-DHP hybrid molecule **2**, which is obtained from the racemic 1,4-DHP ethyl ester derivative **1b** (Fig. 1). Compound **2** is a potential multi-target neuroprotective agent, since it protects mitochondria and prevents ischemic insult-mediated neural cell death in vitro.[3]



1b: Ar = 2-NO_2-C_6H_4 **2**

Fig. 1. Highly functionalized 1,4-DHP **1b** and its 1*H*-1,5-BZD derivative **2**.

On the other hand, 1,4-DHPs have proven to be valuable compounds in organic synthesis. They are NADH mimics[4] and as such they are used as the hydrogen source for the asymmetric hydrogenation of C=C, C=N, and C=O in the presence of an optically active organocatalyst or a metal–ligand complex.[5] Analogously, optically pure C4-substituted 1,4-DHPs have shown a high enantioselectivity in the reduction of activated ketones in the presence of Mg(II) ions.[6]

Optically active 1,4-DHPs were prepared using chiral auxiliaries,[7] by means of organocatalytic asymmetric synthesis procedures,[6a,8] or by separation of enantiomers from racemates either by preparative enantioselective HPLC[9] or by formation of diastereomeric salts (using the *Cinchona* alkaloids cinchonidine and quinidine[10] or L-tartaric acid[11]). In addition, enzymatic methods were successfully applied to the asymmetrization of prochiral 1,4-DHP-3,5-dicarboxylates.[12] In this sense, when employing lipase as catalyst, the presence of a spacer in the carboxylic function such as the acyloxymethyl group was required, because this kind of enzymes do not have the capability of acting on the carboxylic function directly joined to the 1,4-DHP. Although results obtained in the lipase-catalyzed kinetic resolution of racemic 1,4-DHP derivatives[12,13] were usually poorer than those of the asymmetrization, an efficient kinetic resolution of a series of 6-alkylsulfanyl-1,4-DHPs has recently been published.[14]

Based on these results and considering that the absolute configuration of the asymmetric center of chiral 1,4-DHPs has a crucial influence on their biological activity,[10,15] we thought it would be

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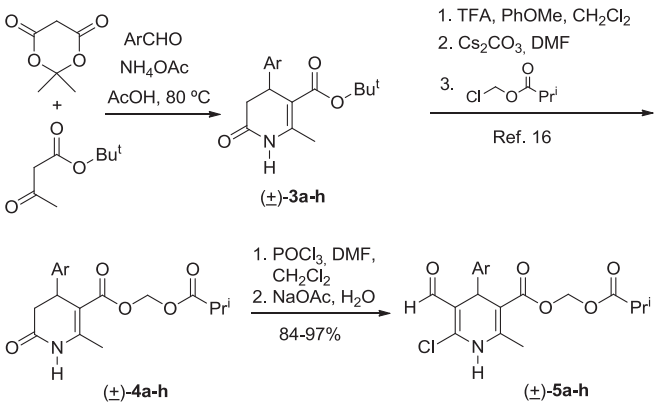
interesting to investigate the potential of lipases and some esterases in the resolution of the adequate precursors of 1,4-DHPs **1**. Besides compound **2**, the highly functionalized optically active 1,4-DHPs **1** could be used in the preparation of other interesting optically active hybrid drugs.

2. Results and discussion

The first objective was the synthesis of the appropriate substrates (±)-**5** to be submitted to hydrolysis reaction with lipases and esterases. As mentioned before, lipases require a spacer at the carboxylic function. An advantage of using the acyloxymethyl group[12] to this end is that the hydrolysis of the outer ester function of substrates (±)-**5** directly affords the corresponding 1,4-DHP-3-carboxylic acids **6** due to a spontaneous loss of formaldehyde.

Recently, we have described the synthesis of pyridones (±)-**4a**–**h** following the strategy collected in Scheme 1.[16] A multicomponent Hantzsch-type reaction led to pyridones (±)-**3a**–**h** whose *tert*-butyl group was easily removed with trifluoroacetic acid (TFA) and anisole as a scavenger. The subsequent treatment of the resulting carboxylic acids with cesium carbonate and chloromethyl isobutyrate gave pyridones (±)-**4a**–**h**, which were transformed into the required racemic 1,4-DHPs (±)-**5a**–**h** by means of a Vilsmeier–Haack reaction.[17] The isolated yields of (±)-**5a**-**h** after purification by flash-chromatography were very high (84–97%).

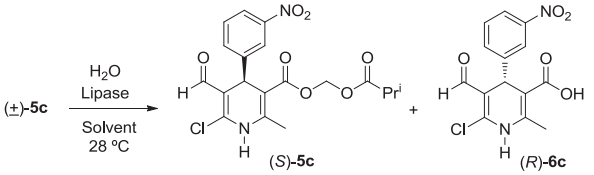


Scheme 1. Synthesis of 1,4-DHPs (±)-**5a**–**h**. The Ar groups for **5** are shown in Table 2.

As is shown in Scheme 1, the immediate precursors of 1,4-DHPs (±)-**5** are compounds (±)-**4**, which are also susceptible to be resolved by lipases. Our previous study with (±)-**4** established the lipase B from *Candida antarctica* (CAL-B)-catalyzed hydrolysis as the best option.[16] However, the obtained enantioselectivity values[18] were so low (E<12) that the method only allowed us to prepare three of the eight chosen substrates with high enantiomeric excesses and moderate yields. For this reason, we decided to explore the enzymatic resolution in the 1,4-DHP stage.

Firstly, the 3-nitrophenyl derivative (±)-**5c** was used as a substrate model. We tested the potential of some esterases [pig liver (PLE-1 and PLE-5), *Nocardia farcinica*, *Methylobacterium populi*, and *Pelobacter propionicus*][19] to catalyze the hydrolysis of the model substrate, but very poor results were obtained in all the cases. For instance, the highest enantioselectivity value (E=4) was obtained with esterase from *M. populi*. In addition, several lipase and organic solvent combinations were also assayed, and the best results are collected in Table 1. Lipase A from *C. antarctica* (CAL-A) and porcine pancreatic lipase (PPL) did not show either catalytic or enantioselective activity. CAL-B catalyzed the hydrolysis in *tert*-butyl methyl ether (TBME) but with a low E value (Table 1, entry 1), which was slightly lower than that obtained in the resolution of its precursor

Table 1
Enzymatic hydrolysis of (±)-**5c**[a]



Entry	Lipase	Solvent	t, h	ee$_S$[b] (%)	ee$_P$[c] (%)	c[d]	E[e]
1	CAL-B	TBME	3.8	49	67	42	8
2	PSL	TBME	26	42	84	33	17
3	CRL	TBME	0.22	74	88	46	34
4	CRL	EtOAc	1.3	82	90	48	48

[a] Reactions were carried out at 28 °C and 200 rpm using 10 mg of substrate, 10 mg of lipase, and water-saturated TBME (1.0 mL) or EtOAc (0.25 mL).
[b] The ee of remaining substrate **5c** (ee$_S$) was determined by enantioselective HPLC analysis.
[c] The ee of the produced acid **6c** (ee$_P$) was determined after treatment with diazomethane, and then enantioselective HPLC analysis of the resulting methyl ester derivative.
[d] The degree of conversion (%) was calculated from ee$_S$ and ee$_P$: c=100ee$_S$/(ee$_S$+ee$_P$).
[e] The enantioselectivity value (E) was calculated according to Ref. 18.

pyridone (±)-**4c** (E=12).[16] The lipase from *C. rugosa* (CRL) was the most efficient and it preferably catalyzed the hydrolysis of (*R*)-**5c** with moderate-high enantioselectivity in both TBME and ethyl acetate (EtOAc). Although reaction in EtOAc was slower than that in TBME, we selected EtOAc as the best solvent due to the higher enantioselectivity exhibited by the CRL (Table 1, entry 4). It is noteworthy that when (±)-**5c** was incubated with CAL-B using EtOAc as the solvent, less than 5% of conversion was attained after 28 h of reaction.

CRL was very efficient in EtOAc, in spite of the fact that this solvent is also susceptible to be hydrolyzed by the lipase. To demonstrate to what extension EtOAc is hydrolyzed by the lipases used, incubations of water-saturated EtOAc with CRL and CAL-B were carried out. After 1 h of reaction at 28 °C, no acetic acid was observed in the reaction with CRL, less than 0.1% was present after 2 h, and the amount was slowly increasing until 4.5% upon reaching 27 h of reaction. This shows that hydrolysis of EtOAc in the presence of CRL is very slow, and no inhibition problems are expected by the acetic acid released in that time range. However, CAL-B hydrolyzed an 8.1% of EtOAc after 1 h of reaction, 9.4% after 5 h, and the amount of acetic acid remained practically constant (10.3%) after 24 h of reaction. The high activity of CAL-B toward EtOAc as well as the high amount of acetic acid released to the reaction medium could be the cause for the low activity exhibited for this lipase towards substrate **5c**. In spite of this fact, CAL-B continued showing its enantioselective properties in this solvent towards other substrates (vide infra).

Once CRL and EtOAc were established as the best choice for the kinetic resolution of (±)-**5c**, these conditions were applied to the hydrolysis of the other racemic 1,4-DHPs (±)-**5**. Results are shown in Table 2. Processes were allowed to react until a near 50% degree of conversion was reached, the required time being highly dependent of the substitution in the aromatic ring. Thus, the presence of substituents at the C-2 position of phenyl group had a beneficial effect on the reaction rate. In addition, enantioselectivity was also strongly influenced by the aryl substituent, electron-withdrawing groups such as nitro and chlorine at the *ortho*- and/or *meta*-positions giving the best results. The highest enantioselectivity value (E>200) was obtained in the hydrolysis of the 2-chloro-5-nitro derivative (±)-**5e**. In this process, both the remaining substrate (*R*)-**5e** and the product (*S*)-**6e** were obtained with very high ee and yields (Table 2, entry 5). Also, the very good results achieved in the

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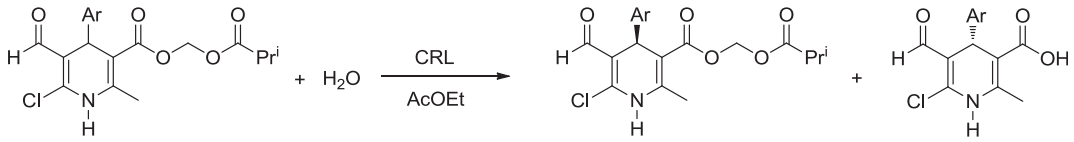
Table 2
Enzymatic hydrolysis of racemic 1,4-DHP derivatives (±)-**5**[a]



(±)-**5a-h** (*S*)-**5a-d,f-h** (*R*)-**5e** (*R*)-**6a-d,f-h** (*S*)-**6e**

Entry	Starting diester	Ar	Time (h)	Remaining substrate			Product			*c* (%)	*E*
				Substrate	Yield (%)	ee$_S$[b] (%)	Product	Yield (%)	ee$_P$[c] (%)		
1	(±)-**5a**	Ph	8	(*S*)-**5a**	48	57	(*R*)-**6a**	42	60	49	7
2	(±)-**5b**	2-NO_2-C_6H_4	0.7	(*S*)-**5b**	51	84	(*R*)-**6b**	45	*95*	47	*103*
3	(±)-**5c**	3-NO_2-C_6H_4	1.5	(*S*)-**5c**	49	89	(*R*)-**6c**	46	88[d]	50	46
4	(±)-**5d**	4-NO_2-C_6H_4	5	(*S*)-**5d**	41	88	(*R*)-**6d**	53	69	56	15
5	(±)-**5e**	2-Cl-5-NO_2-C_6H_3	0.8	(*R*)-**5e**	50	*95*	(*S*)-**6e**	44	*98*	49	*>200*
6	(±)-**5f**	4-Br-C_6H_4	23	(*S*)-**5f**	47	60	(*R*)-**6f**	43	58	51	7
7	(±)-**5g**	3-CH_3O-C_6H_4	10	(*S*)-**5g**	58	40	(*R*)-**6g**	32	62	39	6
8	(±)-**5h**	Naphthyl	2.5	(*S*)-**5h**	51	84	(*R*)-**6h**	43	*97*	46	*175*
9	(±)-**5b**	2-NO_2-C_6H_4	1.6	(*S*)-**5b**	43	*>99*	(*R*)-**6b**	51	90	52	>100
10	(±)-**5c**	3-NO_2-C_6H_4	2.3	(*S*)-**5c**	42	*97*	(*R*)-**6c**	50	82	54	41
11	(±)-**5h**	Naphthyl	5.5	(*S*)-**5h**	45	*99*	(*R*)-**6h**	48	94	51	170

[a] Reactions were carried out at 100–1000 mg scale amount (see Experimental section) using EtOAc saturated with water as solvent, at 28 °C and 200 rpm. The degree of conversion (*c*, %) and the *E* values were calculated as in Table 1.
[b] Determined by enantioselective HPLC analysis (see Section 4.6). High ee values are given in italicsface.
[c] Determined by enantioselective HPLC analysis after treatment of products **6** with diazomethane (see Section 4.6). High ee values are given in italicsface.
[d] A 31% yield of (*R*)-**6c** with 97% ee was isolated after submitting this sample to a selective pH-controlled crystallization (see Section 4.4.3.1).

reaction with naphthyl derivative (±)-**5h** were noticeable. In this case, the optically active product (*R*)-**6h** was isolated with very high ee (97%) and yield (Table 2, entry 8).

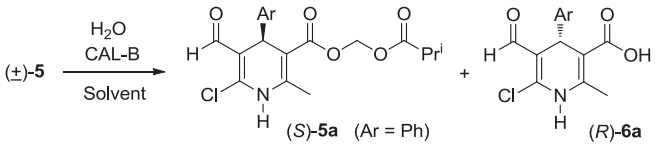
The moderate to high enantioselectivity (*E*>40) exhibited by the CRL toward 1,4-DHPs **5b**, **5c**, and **5h** enables the preparation of these substrates with very high ee (≥97%) and high isolated yields (≥42%) if the hydrolysis reactions are allowed to attain degrees of conversion slightly higher than 50% (see Table 2, entries 9–11).

Isolation of both product and remaining substrate of each enzymatic hydrolysis was easily carried out by base–acid extraction. Once partitioned substrate **5** and product **6** between EtOAc and an saturated aqueous solution of $NaHCO_3$, the recovery of the carboxylic acid **6** from the aqueous medium was carried out by addition of aq HCl until pH=1–2 and subsequent extraction with EtOAc. The efficiency of this procedure was very high as judged by the very high overall yield of both components in all the cases (90–96%).

During the acidification of the aqueous basic solution, the carboxylic acids usually began to precipitate at pH 4–5. Based on this fact and considering that the racemic sample of some pyridones **4** (Scheme 1) crystallizes better than the corresponding optically active sample,[16] we tried to enhance the ee of the enzymatically prepared carboxylic acids (*R*)-**6** by carrying out their crystallization at pH 4–5. This method was successfully applied to the enantioenrichment of (*R*)-**6c**. Thus, the sample of (*R*)-**6c** with 88% ee (Table 2, entry 3) was dissolved in saturated aq $NaHCO_3$ (see Experimental section) and aq HCl was added until pH=4–5. After a slow crystallization, the filtered solid showed, as expected, a low ee (26%, HPLC). Then, the pH of the filtrate was lowered to 1–2 and extracted with EtOAc to attain (*R*)-**6c** with 97% ee and 31% yield (calculated from the starting racemic **5c**). However, by applying this methodology the enantiomeric excesses of (*R*)-**6a** and (*R*)-**6d** were enhanced from 60% to 92% and from 69% to 95%, respectively. Nevertheless, the yields of both enantioenriched samples were very poor (~10%, see Sections 4.4.1.1 and 4.4.4.1). In addition, no satisfactory results were obtained with the acids (*R*)-**6f** and (*R*)-**6g**.

Seeing that the crystallization methodology had failed for the acids **6f** and **6g**, and considering that CAL-B had shown some catalytic activity in the resolution of pyridones **4f** and **4g**,[16] we decided to come back to the enzymatic approach. Thus, we tested CAL-B in the hydrolysis of (±)-**5f,g**, and also in those of (±)-**5a** and (±)-**5d**, for which CRL had shown a low enantioselectivity. After carrying out the reactions in water-saturated TBME and EtOAc, no improvement was achieved with the 4-nitro derivative **5d**, a similar *E* value was reached with **5a**, but satisfactory results were obtained with **5f** and **5g** (see Table 3). So, product (*R*)-**6f** with 89% ee and 39% yield was obtained from the hydrolysis of (±)-**5f** in EtOAc (Table 3, entry 3). Moreover, the highest enantioselectivity value shown by CAL-B toward **5g** (*E*=63) allowed us to isolate (*R*)-**6g** with 95% ee and 33% yield (Table 3, entry 6). CAL-B preferably transformed the same enantiomer than CRL in all the cases.

Table 3
CAL-B catalyzed hydrolysis of (±)-**5a,f,g**[a]



(±)-**5** (*S*)-**5a** (Ar = Ph) (*R*)-**6a**
(*S*)-**5f** (Ar = 4-Br-C_6H_4) (*R*)-**6f**
(*S*)-**5g** (Ar = 3-CH_3O-C_6H_4) (*R*)-**6g**

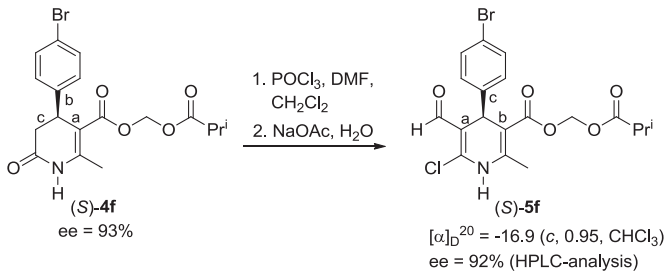
Ent.	Substrate	Solvent	*t*, h	Remaining (*S*)-**5** ee$_S$[b] (%)	Product (*R*)-**6** ee$_P$[b] (%)	*c*[c]	*E*[c]
1	(±)-**5a**	TBME	24	*89*	60	60	11
2	(±)-**5f**	TBME	6	75	85	47	27
3	(±)-**5f**	EtOAc	25	67	*89*	43	34
4	(±)-**5f**	TBME	14	*97*	72	57	24
5	(±)-**5g**	TBME	9	62	88	41	29
6	(±)-**5g**	EtOAc	21	49	*95*	34	63
7	(±)-**5g**	TBME	19	*94*	80	54	31

[a] Reactions conditions: 150–200 mg scale amount (see Experimental section), water-saturated TBME (100 μL/mg of substrate) or EtOAc (50 μL/mg of substrate), CAL-B (1.0 mg/mg of substrate).
[b] The ee for each remaining substrate **5a,f,g** (ee$_S$) as well as the ee for each produced carboxylic acid **6a,f,g** (ee$_P$) were determined as in Table 2 (high ee values are given in italicsface).
[c] The degree of conversion (*c*, %) and the *E* values were calculated as in Table 1.

In order to obtain the remaining substrates with high ee, hydrolysis of (±)-**5f** and (±)-**5g** has to be carried out to a high degree

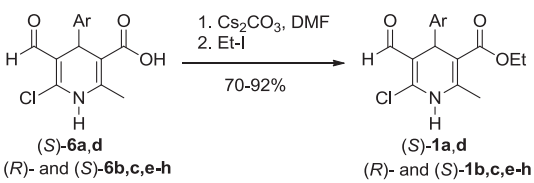
of conversion. This means that reaction times have to be longer than 25 h if EtOAc is chosen as the solvent. As the activity of CAL-B in EtOAc is significantly lowered after 24 h of reaction (as a consequence of the acetic acid released to the reaction medium, see above), we decided to use TBME to this end. Finally, remaining substrates (*S*)-**5f** (Table 3, entry 4) and (*S*)-**5g** (Table 3, entry 7) were obtained with high ee and moderate-high yields (37% and 43%, respectively).

In order to establish the enantiopreference of both CRL and CAL-B in the hydrolysis reactions, both the retention time of the HPLC-analysis and the optical rotation of the remaining substrate **5f** [isolated from the enzymatic hydrolysis of (±)-**5f** (Table 2, entry 6 and Table 3, entry 4)] were compared with those values obtained for a sample of (*S*)-**5f**, which was prepared from the configurationally known pyridone (*S*)-**4f**[16] (Scheme 2). From this comparison, the (*S*) configuration was assigned to the remaining substrate **5f**. That means that both lipases preferentially catalyze the hydrolysis of the (*R*) enantiomer of **5f**. Based on the structural resemblance among all the substrates reported here, we have tentatively assigned the (*R*) configuration to the other produced acids **6**, except to the acid **6e**, for which the absolute configuration is (*S*) due to a change of priority of the substituents of its chiral center. In addition, we have also assigned the (*S*) configuration for all the remaining optically active substrates, except newly for **5e**, for which it was (*R*).



Scheme 2. Synthesis of (*S*)-**5f** from the configurationally known (*S*)-**4f** (see Ref. 16).

Finally, optically active esters **5** were smoothly converted into the acids **6** by conventional basic hydrolysis (aq 3 N NaOH, acetone, rt). No racemization took place in these reactions as was proven by enantioselective HPLC-analysis. In addition, most of the enantioenriched carboxylic acids **6**, particularly those with high ee (≥88%), were easily transformed into the ethyl esters **1** by reaction with cesium carbonate and ethyl iodide in *N*,*N*-dimethylformamide (DMF) as the solvent (Scheme 3). These DHPs **1** are the starting materials for the synthesis, among other derivatives,[17a,20] of the hybrids BZP-DHP **2** (see Fig. 1).



Scheme 3. Synthesis of optically active 1,4-DHP ethyl esters derivatives **1**. The Ar groups for **6** and **1** are the same shown in Table 2.

3. Conclusion

We have developed an efficient chemoenzymatic procedure to obtain a series of highly functionalized 1,4-DHP derivatives with very high yields and enantiomeric excesses, the key step being a lipase-catalyzed hydrolysis reaction. In spite of the remoteness between the asymmetric carbon and the reactive carbonyl function of the substrates used, enantioselectivity values obtained in most enzymatic processes were moderate to very high, especially when CRL was the catalyst. The involvement of very cheap catalysts and the possibility to work to a gram scale are interesting characteristics of this chemoenzymatic method. Transformation of optically active 1,4-DHP derivatives **1** into hybrids with potential biological activity is currently under study.

4. Experimental section

4.1. General

Pig liver esterases (isoenzymes 1 and 5) as well as esterases from *Nocardia farcinica*, *M. populi*, and *P. propionicus* were purchased from Enzymicals. Lipase B from *C. antarctica* (CAL-B, Novozyme 435, available immobilized on polyacrylamide, 7300 PLU/g) was gifted by Novo Nordisk Co. Immobilized lipase A from *C. antarctica* (CAL-A, NZL-101, 6.2 U/g) was purchased from Codexis. Immobilized lipase from *Burkholderia cepacia* (PSL-IM, 783 U/g), which previously was classified as *Pseudomonas cepacia*, was purchased from Amano Pharmaceutical Co. *C. rugosa* lipase was purchased from Sigma–Aldrich (CRL type VII, ≥700 U/mg). Melting points were taken on samples in open capillary tubes and are uncorrected. For the enzymatic hydrolysis reaction TBME or EtOAc saturated with water was used. IR spectra were recorded using KBr pellets. ^{1}H NMR and proton-decoupled ^{13}C NMR spectra ($CDCl_3$ solutions) were obtained using AC-300 or DPX300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz) spectrometers using the δ scale (ppm) for chemical shifts. Calibration was made on the signal of the solvent (^{13}C: $CDCl_3$, 77.16; DMSO-d_6, 39.52 ppm) or the residual solvent partially or non-deuterated (^{1}H: $CHCl_3$, 7.26; DMSO-d_5, 2.50 ppm).

In Fig. 2 we show the 4-aryl-1,4-DHP unit with the numbering used in the assignation of the NMR signals.

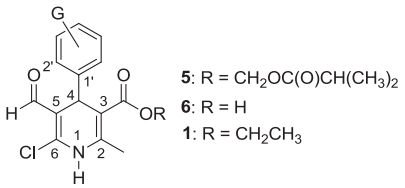


Fig. 2. 1,4-DHP derivatives.

4.2. General procedure for the synthesis of (±)-5

An analogous procedure as that described by Martín, Seoane et al.[21] was followed. Anhydrous DMF (2.45 mL, 31.6 mmol) was cooled at 0 °C, and $POCl_3$ (2.90 mL, 31.6 mmol) was slowly added for 10 min. After 30 min, a solution of (±)-**4** (7.89 mmol) in anhydrous dichloromethane (32 mL) was added, and the resulting solution was stirred at room temperature for 20–25 h. Then, an aqueous 6.5 M sodium acetate solution (59 mL) was added. After 1 h, the mixture was partitioned between water and CH_2Cl_2, and the aqueous phase was extracted with EtOAc (3×15 mL). The organic phases were mixed and successively washed with water and brine, dried with Na_2SO_4, and concentrated in vacuo. Flash chromatography of the crude material (hexane/EtOAc 3:1) gave compounds (±)-**5**, which were isolated with 84–97% yield.

*4.2.1. (±)-[2-(Methyl)propanoyloxy]methyl 6-chloro-5-methanoyl-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate [(±)-**5a**].* Yellow solid; mp 127–128 °C; yield 92%; ν_{max} (KBr) 3269; 1722; 1637; 1603; 1489 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 1.14–1.00 [6H, two overlapped d centered to 1.07 (^{3}J 7.0 Hz) and 1.09 (^{3}J

7.0 Hz), CH(CH_3)$_2$], 2.54–2.33 [m+s, 4H, C*H*(CH_3)$_2$ and singlet centered to 2.43 corresponding to CH_3], 5.11 (s, 1H, H-4), 5.73 (s, 2H, O–CH_2–O), 6.44 (br s, 1H, NH), 7.33–7.09 (m, 5H, Ph), 9.78 (s, 1H, HC=O); δ_C (75.5 MHz, $CDCl_3$) 18.7 (2×CH_3), 19.4 (CH_3), 33.8 (CH), 38.4 (C-4), 79.0 (CH_2), 105.4 (C-5), 113.5 (C-3), 127.0 (C-4′), 128.0 (C-2′ and C-6′), 128.4 (C-3′ and C-5′), 141.6 (C-2), 144.9 (C-1′), 145.8 (C-6), 165.2 (CO), 175.8 (CO), 187.6 (CHO); HRMS (ESI$^+$): MNa$^+$, found: 400.0922. $C_{19}H_{20}ClNNaO_5$ requires 400.0888.

*4.2.2. (±)-[2-(Methyl)propanoyloxy]methyl 6-chloro-5-methanoyl-2-methyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3-carboxylate [(±)-**5b**].* Yellow solid, mp 134–135 °C; yield 84%; ν_{max} (KBr) 3269; 3191; 1728; 1714; 1658; 1535; 1491 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 1.13–0.99 [6H, two overlapped *d* centered to 1.06 (^3J 7.0 Hz) and 1.07 (^3J 7.0 Hz), CH(CH_3)$_2$], 2.53–2.33 [m+s, 4H, C*H*(CH_3)$_2$ and singlet centered to 2.41 corresponding to CH_3], 5.67 (AB system, $|^2J|$ 5.5 Hz, O–CH_2–O), 5.93 (s, 1H, H-4), 6.68 (br s, 1H, NH), 7.34–7.27 (m, 1H, H-6′), 7.54–7.44 (m, 2H, H-4′ and H-5′), 7.75 (d, 1H, ^3J 7.8 Hz, H-3′), 9.69 (s, 1H, CHO); δ_C (75.5 MHz, $CDCl_3$) 18.6 (CH_3), 18.7 (CH_3), 19.2 (CH_3), 33.7 (CH), 34.5 (C-4), 79.4 (CH_2), 104.6 (C-5), 112.7 (C-3), 124.5 (C-3′), 127.7 (C-4′), 131.3 (C-6′), 133.0 (C-5′), 139.5 (C-2), 143.0 (C-6), 147.2 (C-2′), 148.5 (C-1′), 165.0 (CO), 175.7 (CO), 187.7 (CHO); HRMS (ESI$^+$): MH$^+$, found: 423.0954. $C_{19}H_{20}ClN_2O_7$ requires 423.0968.

*4.2.3. (±)-[2-(Methyl)propanoyloxy]methyl 6-chloro-5-methanoyl-2-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate [(±)-**5c**].* Yellow solid; mp 149–150 °C; yield 96%; ν_{max} (KBr) 3304; 1729; 1720; 1657; 1645; 1529; 1486 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 1.07 (t, 6H, ^3J 6.8 Hz, CH(CH_3)$_2$), 2.55–2.38 [m+s, 4H, C*H*(CH_3)$_2$ and singlet centered to 2.47 corresponding to CH_3], 5.21 (s, 1H, H-4), 5.72 (s, 2H, O–CH_2–O), 6.63 (br s, 1H, NH), 7.41 (t, 1H, ^3J 7.8 Hz, H-5′), 7.72 (d, 1H, ^3J 7.7 Hz, H-6′), 8.08–7.99 (m, 2H, H-2′ and H-4′), 9.77 (s, 1H, HC=O); δ_C (75.5 MHz, $CDCl_3$) 18.1 (CH_3), 18.17 (CH_3), 18.22 (CH_3), 32.8 (CH), 37.8 (C-4), 78.7 (CH_2), 102.3 (C-5), 110.9 (C-3), 121.7 (C-4′), 121.9 (C-2′), 129.9 (C-5′), 134.1 (C-6′), 143.0 (C-2), 147.3 (C), 147.6 (C), 148.7 (C-1′), 164.3 (CO), 174.8 (CO), 186.7 (CHO); HRMS (ESI$^+$): MNa$^+$, found: 445.0773. $C_{19}H_{19}ClN_2NaO_7$ requires 445.0779.

*4.2.4. (±)-[2-(Methyl)propanoyloxy]methyl 6-chloro-5-methanoyl-2-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3-carboxylate [(±)-**5d**].* Yellow solid; mp 150–152 °C; yield 94%; ν_{max} (KBr) 3462; 3265; 1757; 1724; 1631; 1477 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 1.06 [t, 6H, ^3J 7.0 Hz, CH(CH_3)$_2$], 2.58–2.33 [m+s, 4H, C*H*(CH_3)$_2$ and singlet centered to 2.47 corresponding to CH_3], 5.21 (s, 1H, H-4), 5.80–5.65 (m, 2H, O–CH_2–O), 6.58 (br s, 1H, NH), 7.46 (d, 2H, ^3J 7.9 Hz, H-2′ and H-6′), 8.10 (d, 2H, ^3J 7.9 Hz, H-3′ and H-5′), 9.77 (s, 1H, HC=O); δ_C (75.5 MHz, $CDCl_3$) 18.7 (2×CH_3), 19.7 (CH_3), 33.8 (CH), 38.8 (C-4), 79.1 (CH_2), 104.5 (C-5), 112.7 (C-3), 123.8 (C-3′ and C-5′), 129.2 (C-2′ and C-6′), 141.5 (C-2), 146.4 (C), 146.9 (C), 151.8 (C-1′), 164.6 (CO), 175.7 (CO), 187.1 (CHO); HRMS (ESI$^+$): MNa$^+$, found: 445.0773. $C_{19}H_{19}ClN_2NaO_7$ requires 445.0746.

*4.2.5. (±)-[2-(Methyl)propanoyloxy]methyl 6-chloro-4-(2-chloro-5-nitrophenyl)-5-methanoyl-2-methyl-1,4-dihydropyridine-3-carboxylate [(±)-**5e**].* Yellow solid; mp 185–186 °C; yield 90%; ν_{max} (KBr) 3464; 3305; 1753; 1724; 1649; 1604; 1491 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 1.14–1.10 [6H, two overlapped d centered to 1.07 (^3J 7.0 Hz) and 1.08 (^3J 7.0 Hz), CH(CH_3)$_2$], 2.55–2.35 [m+s, 4H, C*H*(CH_3)$_2$ and singlet centered to 2.42 corresponding to CH_3], 5.52 (s, 1H, H-4), 5.70 (AB system, $|^2J|$ 5.6 Hz, O–CH_2–O), 6.76 (br s, 1H, NH), 7.45 (d, 1H, ^3J 8.8 Hz, H-3′), 7.95 (dd, 1H, ^4J 2.7, ^3J 8.8 Hz, H-4′), 8.22 (d, 1H, ^4J 2.7 Hz, H-6′), 9.74 (s, 1H, HC=O); δ_C (75.5 MHz, $CDCl_3$) 18.7 (2×CH_3), 19.7 (CH_3), 33.8 (CH), 38.1 (C-4), 79.4 (CH_2), 104.0 (C-5), 112.2 (C-3), 122.8 (CH), 126.8 (CH), 130.8 (CH), 140.5 (C), 142.2 (C), 144.1 (C), 146.6 (C), 146.8 (C), 164.7 (CO), 175.6 (CO), 187.2 (CHO); HRMS (ESI$^+$): MNa$^+$, found: 479.0383. $C_{19}H_{18}Cl_2N_2NaO_7$ requires 479.0371.

*4.2.6. (±)-[2-(Methyl)propanoyloxy]methyl 4-(4-bromophenyl)-6-chloro-5-methanoyl-2-methyl-1,4-dihydropyridine-3-carboxylate [(±)-**5f**].* Yellow solid; mp 77–78 °C; yield 94%; ν_{max} (KBr) 3467; 1757; 1718; 1637; 1597; 1483 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 1.13–1.01 [6H, two overlapped d centered to 1.07 (^3J 6.9 Hz) and 1.09 (^3J 6.9 Hz), CH(CH_3)$_2$], 2.54–2.36 [m+s, 4H, C*H*(CH_3)$_2$ and singlet centered to 2.43 corresponding to CH_3], 5.06 (s, 1H, H-4), 5.72 (AB system, $|^2J|$ 5.6 Hz, O–CH_2–O), 6.42 (br s, 1H, NH), 7.15 (d, 2H, ^3J 8.5 Hz, H-2′ and H-6′), 7.34 (d, 2H, ^3J 8.5 Hz, H-3′ and H-5′), 9.76 (s, 1H, HC=O); δ_C (75.5 MHz, $CDCl_3$) 18.7 (2×CH_3), 19.5 (CH_3), 33.8 (CH), 38.2 (C-4), 78.9 (CH_2), 105.1 (C-5), 113.3 (C-3), 121.0 (C), 129.9 (2×CH), 131.5 (2×CH), 141.2 (C), 143.9 (C), 145.8 (C), 165.0 (CO), 175.8 (CO), 187.4 (CHO); HRMS (ESI$^+$): MNa$^+$, found: 478.0027. $C_{19}H_{19}BrClNNaO_5$ requires 478.0014.

*4.2.7. (±)-[2-(Methyl)propanoyloxy]methyl 6-chloro-5-methanoyl-4-(3-methoxyphenyl)-2-methyl-1,4-dihydropyridine-3-carboxylate [(±)-**5g**].* Yellow solid; mp 114–115 °C; yield 94%; ν_{max} (KBr) 3467; 3269; 1766; 1687; 1631; 1483 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 1.14–0.98 [6H, two overlapped d centered to 1.07 (^3J 6.9 Hz) and 1.09 (^3J 6.9 Hz), CH(CH_3)$_2$], 2.53–2.35 [m+s, 4H, C*H*(CH_3)$_2$ and singlet centered to 2.43 corresponding to CH_3], 3.78 (s, 3H, OCH_3), 5.10 (s, 1H, H-4), 5.74 (s, 2H, O–CH_2–O), 6.40 (br s, 1H, NH), 6.75–6.65 (m, 1H, H-2′), 6.90–6.77 (m, 2H, H-4′ and H-6′), 7.15 (t, 1H, ^3J 7.9 Hz, H-5′), 9.79 (s, 1H, HC=O); δ_C (75.5 MHz, $CDCl_3$) 18.6 (2×CH_3), 19.2 (CH_3), 33.8 (CH), 38.3 (C-4), 55.2 (OCH_3), 79.0 (CH_2), 105.1 (C-5), 111.8 (C-4′), 113.2 (C-3), 114.2 (C-2′), 120.4 (C-6′), 129.3 (C-5′), 142.1 (C-2), 146.2 (C), 146.5 (C), 159.6 (C-3′), 165.3 (CO), 175.8 (CO), 187.8 (CHO); HRMS (ESI$^+$): MNa$^+$, found: 430.1028. $C_{20}H_{22}ClNNaO_6$ requires 430.1026.

*4.2.8. (±)-[2-(Methyl)propanoyloxy]methyl 6-chloro-5-methanoyl-2-methyl-4-(1-naphthyl)-1,4-dihydropyridine-3-carboxylate [(±)-**5h**].* Yellow solid; mp 89–91 °C; yield 97%; ν_{max} (KBr) 3465; 1716; 1637; 1599; 1464 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 1.04–0.90 [6H, two overlapped d centered to 0.97 (^3J 7.0 Hz) and 0.98 (^3J 7.0 Hz), CH(CH_3)$_2$], 2.36–2.21 [m, 1H, C*H*(CH_3)$_2$], 2.41 (s, 3H, CH_3), 5.53 (AB system, $|^2J|$ 5.6 Hz, O–CH_2–O), 5.89 (s, 1H, H-4), 6.57 (br s, 1H, NH), 7.51–7.30 (m, 3H, H-3′, H-6′and H-7′), 7.65–7.56 (m, 1H, H-2′), 7.67 (dd, 1H, ^4J 1.7, ^3J 7.4 Hz, H-4′), 7.74 (d, 1H, ^3J 7.6 Hz, H-5′), 8.72 (d, 1H, ^3J 8.6 Hz, H-8′), 9.74 (s, 1H, HC=O); δ_C (75.5 MHz, $CDCl_3$) 18.5 (CH_3), 18.6 (CH_3), 19.2 (CH_3), 33.65 (CH), 33.68 (C-4), 79.0 (CH_2), 107.1 (C-5), 114.7 (C-3), 125.2 (CH), 125.5 (CH), 125.7 (CH), 126.2 (CH), 127.0 (CH), 127.9 (CH), 128.1 (CH), 130.9 (C), 133.5 (C), 141.4 (C), 143.8 (C-2), 145.0 (C-6), 165.4 (CO), 175.6 (CO), 188.0 (CHO); HRMS (ESI$^+$): MNa$^+$, found: 450.1079. $C_{23}H_{22}ClNNaO_5$ requires 450.1051.

4.3. General procedure for the preparation of racemic 1,4-DHP-3-carboxylic acids (±)-6

To a solution of racemic 1,4-DHP (±)-**5** (0.438 mmol) in acetone (7.7 mL), aq 3 M NaOH (1.75 mmol) and water (15.4 mL) were added. The solution was stirred at room temperature until disappearance of the starting material (TLC control). Then, acetone was eliminated under reduced pressure and the basic aqueous phase extracted with CH_2Cl_2 (2×7 mL). After, aq 3 M HCl was added to the aqueous phase until pH was 1–2, and the precipitation took place. The resulting solid was filtered and washed with water to give the corresponding carboxylic acid (±)-**6** in a pure form.

*4.3.1. (±)-6-Chloro-5-methanoyl-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylic acid [(±)-**6a**].* Reaction time: 4 h.

Yellow solid; mp 254–255 °C; yield 95%; ν_{max} (KBr) 3467; 1682; 1628; 1599; 1491 cm^{-1}; δ_H (300.13 MHz, DMSO-d_6) 2.33 (s, 3H, CH_3), 4.93 (s, 1H, H-4), 7.32–7.05 (m, 5H, Ph), 9.69 (s, 1H, HC=O), 10.25 (br s, 1H, NH), 12.14 (br s, 1H, CO_2H); δ_C (75.5 MHz, DMSO-d_6) 17.7 (CH_3), 37.8 (C-4), 105.5 (C-5), 111.0 (C-3), 126.4 (C-4′), 127.3 (2×CH), 128.2 (2×CH), 142.8 (C-2), 144.6 (C), 145.7 (C), 168.0 (CO_2H), 186.6 (CHO); HRMS (ESI$^+$): MNa^+, found: 300.0398. $C_{14}H_{12}ClNNaO_3$ requires 300.0355.

*4.3.2. (±)-6-Chloro-5-methanoyl-2-methyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid [(±)-**6b**].* Reaction time: 6 h. Yellow solid; mp 187–190 °C; yield 90%; ν_{max} (KBr) 3467; 1672; 1606; 1525; 1460 cm^{-1}; δ_H (300.13 MHz, DMSO-d_6) 2.28 (s, 3H, CH_3), 5.67 (s, 1H, H-4), 7.52–7.23 (m, 2H, H-4′ and H-6′), 7.62 (t, 1H, ^3J 7.4 Hz, H-5′), 7.74 (d, 1H, ^3J 7.9 Hz, H-3′), 9.60 (s, 1H, HC=O), 10.31 (br s, 1H, NH), 12.16 (br s, 1H, CO_2H); δ_C (75.5 MHz, DMSO-d_6) 17.8 (CH_3), 34.1 (C-4), 105.4 (C-5), 110.6 (C-3), 123.9 (C-5′), 127.6 (C-3′), 130.8 (C-4′), 133.2 (C-6′), 139.9 (C-2), 143.6 (C-6), 144.7 (C-2′), 148.0 (C-1′), 167.6 (CO_2H), 186.5 (CHO); HRMS (ESI$^+$): MH^+, found: 323.0429. $C_{14}H_{12}ClN_2O_5$ requires 323.0417.

*4.3.3. (±)-6-Chloro-5-methanoyl-2-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid [(±)-**6c**].* Reaction time: 2 h. Yellow solid; mp 228–229 °C; yield 96%; ν_{max} (KBr) 3491; 3292; 1684; 1630; 1591; 1473 cm^{-1}; δ_H (300.13 MHz, DMSO-d_6) 2.36 (s, 3H, CH_3), 5.05 (s, 1H, H-4), 7.66–7.50 (m, 2H, H-5′ and H-6′), 7.96 (s, 1H, H-2′), 8.03 [dt, 1H, ^4J 2.0 (d), ^3J 7.6 (t) Hz, H-4′], 9.69 (s, 1H, HC=O), 10.47 (br s, 1H, NH), 12.30 (br s, 1H, CO_2H); δ_C (75.5 MHz, DMSO-d_6) 17.8 (CH_3), 38.1 (C-4), 104.6 (C-5), 110.2 (C-3), 121.6 (C-4′), 121.7 (C-2′), 129.9 (C-5′), 134.1 (C-6′), 143.4 (C-2), 145.6 (C), 147.67 (C), 147.68 (C), 167.6 (CO_2H), 186.6 (CHO); HRMS (ESI$^+$): MNa^+, found: 345.0249. $C_{14}H_{11}ClN_2NaO_5$ requires 345.0239.

*4.3.4. (±)-6-Chloro-5-methanoyl-2-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3-carboxylic acid [(±)-**6d**].* Reaction time: 4 h. Yellow solid; mp 224–226 °C (dec); yield 98%; ν_{max} (KBr) 3462; 1680; 1630; 1600; 1522; 1487 cm^{-1}; δ_H (300.13 MHz, DMSO-d_6) 2.35 (s, 3H, CH_3), 5.04 (s, 1H, H-4), 7.42 (d, 2H, ^3J 8.8 Hz, H-2′ and H-6′), 8.13 (d, 2H, ^3J 8.8 Hz, H-3′ and H-5′), 9.67 (s, 1H, HC=O), 10.40 (br s, 1H, NH), 12.30 (br s, 1H, CO_2H); δ_C (75.5 MHz, DMSO-d_6) 17.9 (CH_3), 38.3 (C-4), 104.5 (C-5), 110.0 (C-3), 123.6 (C-3′ and C-5′), 128.6 (C-2′ and C-6′), 143.4 (C-2), 145.6 (C-6), 146.1 (C-4′), 152.9 (C-1′), 167.6 (CO_2H), 186.5 (CHO); HRMS (ESI$^+$): MH^+, found: 323.0429. $C_{14}H_{12}ClN_2O_5$ requires 323.0398.

*4.3.5. (±)-6-Chloro-4-(2-chloro-5-nitrophenyl)-5-methanoyl-2-methyl-1,4-dihydropyridine-3-carboxylic acid [(±)-**6e**].* Reaction time: 2 h. Yellow solid; mp 190–192 °C; yield 97%; ν_{max} (KBr) 3467; 1682; 1637; 1601; 1522; 1464 cm^{-1}; δ_H (300.13 MHz, DMSO-d_6) 2.29 (s, 3H, CH_3), 5.32 (s, 1H, H-4), 7.61 (d, 1H, ^3J 8.8 Hz, H-3′), 8.00 (dd, 1H, ^4J 2.8, ^3J 8.8 Hz, H-4′), 8.08 (d, 1H, ^4J 2.8 Hz, H-6′), 9.63 (s, 1H, HC=O), 10.45 (br s, 1H, NH), 12.24 (br s, 1H, CO_2H); δ_C (75.5 MHz, DMSO-d_6) 17.8 (CH_3), 38.4 (C-4), 104.4 (C-5), 109.7 (C-3), 122.8 (CH), 126.1 (CH), 130.9 (CH), 139.2 (C), 144.0 (C), 144.7 (C), 145.2 (C), 146.2 (C), 167.4 (CO_2H), 186.6 (CHO); HRMS (ESI$^+$): MNa^+, found: 378.9859. $C_{14}H_{10}Cl_2N_2NaO_5$ requires 378.9846.

*4.3.6. (±)-4-(4-Bromophenyl)-6-chloro-5-methanoyl-2-methyl-1,4-dihydropyridine-3-carboxylic acid [(±)-**6f**].* Reaction time: 5 h. Yellow solid; mp 215–217 °C; yield 98%; ν_{max} (KBr) 3745; 1682; 1633; 1589; 1489 cm^{-1}; δ_H (300.13 MHz, DMSO-d_6) 2.32 (s, 3H, CH_3), 4.89 (s, 1H, H-4), 7.09 (d, 2H, ^3J 8.4 Hz, H-2′ and H-6′), 7.44 (d, 2H, ^3J 8.5 Hz, H-3′ and H-5′), 9.67 (s, 1H, HC=O), 10.30 (br s, 1H, NH), 12.20 (br s, 1H, CO_2H); δ_C (75.5 MHz, DMSO-d_6) 17.8 (CH_3), 37.6 (C-4), 105.0 (C-5), 110.6 (C-3), 119.5 (C), 129.5 (2×CH), 131.1 (2×CH), 143.0 (C), 144.9 (C), 145.0 (C), 167.8 (CO_2H), 186.5 (CHO); HRMS (ESI$^+$): MNa^+, found: 377.9503. $C_{14}H_{11}BrClNNaO_3$ requires 377.9509.

*4.3.7. (±)-6-Chloro-5-methanoyl-4-(3-methoxyphenyl)-2-methyl-1,4-dihydropyridine-3-carboxylic acid [(±)-**6g**].* Reaction time: 5 h. Yellow solid; mp 241–242 °C; yield 93%; ν_{max} (KBr) 3234; 3159; 1682; 1624; 1593; 1487 cm^{-1}; δ_H (300.13 MHz, DMSO-d_6) 2.33 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 4.91 (s, 1H, H-4), 6.76–6.63 (m, 3H, H-2′, H-4′ and H-6′), 7.16 (t, 1H, ^3J 7.9 Hz, H-5′), 9.69 (s, 1H, HC=O), 10.32 (br s, 1H, NH), 12.15 (br s, 1H, CO_2H); δ_C (75.5 MHz, DMSO-d_6) 17.7 (CH_3), 37.6 (C-4), 54.9 (OCH_3), 105.3 (C-5), 110.8 (C-3), 111.0 (C-4′), 113.5 (C-2′), 119.4 (C-6′), 129.3 (C-5′), 142.9 (C-2), 144.7 (C-1′), 147.1 (C-6), 159.1 (C-3′), 167.9 (CO_2H), 186.6 (CHO); HRMS (ESI$^+$): MH^+, found: 308.0684. $C_{15}H_{15}ClNO_4$ requires 308.0655.

*4.3.8. (±)-6-Chloro-5-methanoyl-2-methyl-4-(1-naphthyl)-1,4-dihydropyridine-3-carboxylic acid [(±)-**6h**].* Reaction time: 5 h. Yellow solid; mp 172–174 °C; yield 94%; ν_{max} (KBr) 3425; 1684; 1628; 1597; 1491 cm^{-1}; δ_H (300.13 MHz, DMSO-d_6) 2.34 (s, 3H, CH_3), 5.69 (s, 1H, H-4), 7.38–7.29 (m, 1H, H-2′), 7.62–7.38 (m, 3H, H-3′, H-6′ and H-7′), 7.73 (d, 1H, ^3J 8.0 Hz, H-4′), 7.82 (d, 1H, ^3J 7.4 Hz, H-5′), 8.64 (d, 1H, ^3J 8.6 Hz, H-8′), 9.65 (s, 1H, HC=O), 10.32 (br s, 1H, NH), 12.01 (br s, 1H, CO_2H); δ_C (75.5 MHz, DMSO-d_6) 17.7 (CH_3), 33.5 (C-4), 107.6 (C-5), 112.3 (C-3), 125.36 (2×CH), 125.40 (CH), 125.9 (CH), 126.4 (CH), 127.1 (CH), 127.8 (CH), 130.3 (C), 132.9 (C), 142.8 (C), 143.3 (C-2), 144.6 (C-6), 168.0 (CO_2H), 186.8 (CHO); HRMS (ESI$^+$): MNa^+, found: 350.0554. $C_{18}H_{14}ClNNaO_3$ requires 350.0555.

4.4. General procedure for the lipase-catalyzed hydrolysis reactions

Compound (±)-**5** was dissolved in the organic solvent (EtOAc or TBME) previously saturated with water. Then, lipase (CRL or CAL-B) was added to this solution, and the mixture was shaken at 28 °C and 200 rpm. After the time collected in Table 2 or 3, the enzyme was filtered and thoroughly washed with methanol. Solvents were eliminated under reduced pressure and the residue was dissolved with EtOAc. The organic solution was extracted three times with aq saturated $NaHCO_3$. The organic phase was successively washed with water and brine, dried with Na_2SO_4 and concentrated in vacuo to give the optically active remaining substrate **5**. On the other hand, the basic aqueous phase containing the produced optically active carboxylic acid **6** was acidified (pH=1–2) with aq 3 M HCl and subsequently extracted with EtOAc (three times). The normal work-up of this new organic phase gave the corresponding acid **6**. The best approach for each substrate is described below.

*4.4.1. Enzymatic hydrolysis of (±)-**5a** (Table 3, entry 1).* To a solution of (±)-**5a** (200 mg, 0.530 mmol) in TBME (20 mL), CAL-B (200 mg) was added and the mixture was shaken at 28 °C and 200 rpm during 24 h. After, the general procedure was followed. Thus, the remaining substrate (*S*)-**5a** was isolated with 39% yield (78 mg) and 89% ee; $[\alpha]_D^{20}$ −19.6 (*c* 1.0, $CHCl_3$).

The product (*R*)-**6a** was isolated with 57% yield (82 mg) and 60% ee.

*4.4.1.1. Enantioenrichment of the enzymatically produced (R)-**6a**.* A partially enantioenriched sample of acid (*R*)-**6a** (80 mg, 60% ee) was dissolved in aq saturated $NaHCO_3$ (40 mL). Then, aq 3 M HCl was added until pH=4–5. After 12 h at 5 °C, the solid formed was filtered off and the pH of the resulting aqueous solution adjusted to 1. Extraction with EtOAc allowed us to isolate a small amount of highly enantioenriched (*R*)-**6a** (18 mg); $[\alpha]_D^{20}$ −24.6 (*c* 0.40, DMSO), 92% ee.

*4.4.2. Enzymatic hydrolysis of (±)-**5b** (Table 2, entries 2 and 9).* To a solution of (±)-**5b** (1.00 g, 2.37 mmol) in EtOAc (25 mL), CRL

(1.00 g) was added and the mixture was shaken at 28 °C and 200 rpm for 43 min (Table 2, entry 2). After following the general procedure, the remaining substrate (*S*)-**5b** was isolated with 51% yield (512 mg) and 84% ee. The product (*R*)-**6b** was isolated with 45% yield (346 mg); $[\alpha]_D^{20}$ +104.6 (*c* 0.38, DMSO), 95% ee.

When the enzymatic hydrolysis of (±)-**5b** (500 mg) was maintained for 95 min (Table 2, entry 9), the remaining substrate (*S*)-**5b** (217 mg, 43% yield) was isolated with ee >99%; $[\alpha]_D^{20}$ −201.9 (*c* 0.52, $CHCl_3$); mp 155–157 °C.

*4.4.3. Enzymatic hydrolysis of (±)-**5c** (Table 2, entries 3 and 10).* To a solution of (±)-**5c** (650 mg, 1.54 mmol) in EtOAc (16 mL), CRL (650 mg) was added and the mixture was shaken at 28 °C and 200 rpm for 90 min (Table 2, entry 3). After following the general procedure, the remaining substrate (*S*)-**5c** was isolated with 49% yield (317 mg) and 89% ee. The product (*R*)-**6c** was isolated with 46% yield (228 mg) and 88% ee.

When the enzymatic hydrolysis of (±)-**5c** (700 mg) was maintained for 140 min (Table 2, entry 10), the remaining substrate (*S*)-**5c** (294 mg, 42% yield) was isolated with 97% ee; $[\alpha]_D^{20}$ −57.1 (*c* 1.02, $CHCl_3$); mp 122–123 °C.

*4.4.3.1. Enantioenrichment of the enzymatically produced (R)-**6c**.* To a sample of acid (*R*)-**6c** (227 mg, 0.703 mmol, 88% ee) was applied the method described for the enantioenrichment of (*R*)-**6a** (see Section 4.4.1.1). Thus, (*R*)-**6c** (154 mg, 0.477 mmol) with 97% ee was obtained [31% yield calculated from the starting (±)-**5c**]; $[\alpha]_D^{20}$ +12.7 (*c* 0.52, DMSO), mp 205–206 °C.

*4.4.4. Enzymatic hydrolysis of (±)-**5d** (Table 2, entry 4).* To a solution of (±)-**5d** (200 mg, 0.473 mmol) in EtOAc (5.0 mL), CRL (200 mg) was added and the mixture was shaken at 28 °C and 200 rpm for 5 h. After following the general procedure, the remaining substrate (*S*)-**5d** was isolated with 41% yield (82 mg) and 88% ee; $[\alpha]_D^{20}$ −19.5 (*c* 1.01, $CHCl_3$).

The product (*R*)-**6d** was isolated with 53% yield (81 mg) and 69% ee.

*4.4.4.1. Enantioenrichment of the enzymatically produced (R)-**6d**.* Applying the method described in Section 4.4.1.1 to a sample of acid (*R*)-**6d** (80 mg, 69% ee), 21 mg of enantioenriched (*R*)-**6d** (95% ee) was isolated; $[\alpha]_D^{20}$ +12.8 (*c* 1.01, DMSO).

*4.4.5. Enzymatic hydrolysis of (±)-**5e** (Table 2, entry 5).* To a solution of (±)-**5e** (200 mg, 0.438 mmol) in EtOAc (5.0 mL), CRL (200 mg) was added and the mixture was shaken at 28 °C and 200 rpm for 50 min. After following the general procedure, the remaining substrate (*R*)-**5e** was isolated with 50% yield (100 mg) and 95% ee; $[\alpha]_D^{20}$ −86.6 (*c* 0.52, $CHCl_3$).

The product (*S*)-**6e** was isolated with 44% yield (69 mg) and 98% ee; $[\alpha]_D^{20}$ +80.3 (*c* 0.51, DMSO); mp 176–178 °C.

*4.4.6. Enzymatic hydrolysis of (±)-**5f** (Table 3, entries 3 and 4).* To a solution of (±)-**5f** (150 mg, 0.328 mmol) in EtOAc (7.5 mL), CAL-B (150 mg) was added and the mixture was shaken at 28 °C and 200 rpm for 25 h (Table 3, entry 3). After following the general procedure, the remaining substrate (*S*)-**5f** was isolated with 53% yield (80 mg) and 67% ee. The product (*R*)-**6f** was isolated with 39% yield (46 mg) and 89% ee; $[\alpha]_D^{20}$ −59.0 (*c* 0.50, MeOH).

When the enzymatic hydrolysis of (±)-**5f** (150 mg) was carried out in TBME (15 mL) and CAL-B (150 mg) for 14 h (Table 3, entry 4), the substrate (*S*)-**5f** (56 mg, 37% yield) was isolated with 97% ee; $[\alpha]_D^{20}$ −19.9 (*c* 0.70, $CHCl_3$).

*4.4.7. Enzymatic hydrolysis of (±)-**5g** (Table 3, entries 6 and 7).* To a solution of (±)-**5g** (200 mg, 0.490 mmol) in EtOAc (10 mL), CAL-B (200 mg) was added and the mixture was shaken at 28 °C and 200 rpm during 21 h (Table 3, entry 6). After following the general procedure, the remaining substrate (*S*)-**5g** was isolated with 62% yield (124 mg) and 49% ee. The product (*R*)-**6g** was isolated with 33% yield (50 mg) and 95% ee; $[\alpha]_D^{20}$ −79.7 (*c* 0.82, MeOH).

When the enzymatic hydrolysis of (±)-**5g** (200 mg) was carried out with CAL-B (200 mg) in TBME (20 mL), (*S*)-**5g** (86 mg, 43%) was isolated with 94% ee after 19 h of reaction (Table 3, entry 7); $[\alpha]_D^{20}$ −25.3 (*c* 0.95, $CHCl_3$).

*4.4.8. Enzymatic hydrolysis of (±)-**5h** (Table 2, entries 8 and 11).* To a solution of (±)-**5h** (300 mg, 0.701 mmol) in EtOAc (7.5 mL), CRL (300 mg) was added and the mixture was shaken at 28 °C and 200 rpm for 2.5 h (Table 2, entry 8). After following the general procedure, the remaining substrate (*S*)-**5h** was isolated with 51% yield (153 mg) and 84% ee. The product (*R*)-**6h** was isolated with 43% yield (98 mg) and 97% ee; $[\alpha]_D^{20}$ +90.5 (*c* 0.63, MeOH); mp 160–161 °C (dec).

When the enzymatic hydrolysis of (±)-**5h** (300 mg) was allowed to react for 5.5 h (Table 2, entry 11), the substrate (*S*)-**5h** (135 mg, 45% yield) was isolated with 99% ee; $[\alpha]_D^{20}$ −12.7 (*c* 1.0, $CHCl_3$); mp 93–94 °C.

4.5. Typical procedure for the synthesis of optically active 1,4-DHPs ethyl ester 1

To a solution of the corresponding optically active carboxylic acid **6**[22] (0.30 mmol) in DMF (1.6 mL), cesium carbonate (0.39 mmol) was added. After stirring the suspension for 2–3 min, ethyl iodide (96 μL, 1.2 mmol) was added and the mixture was maintained at room temperature for 1–3 h. After this time, CH_2Cl_2 (20 mL) was added and the resulting organic phase was successively washed with water (3×10 mL) and brine (3×10 mL). Organic solvent was eliminated and the residue was submitted to flash chromatography. Spectroscopic data for optically active **1a**–**d** and **1g** are in good agreement with those previously published for the corresponding racemic compound [(±)-**1a**,**b**[23] and (±)-**1c**,**d**,**g**[24]].

*4.5.1. Ethyl (S)-6-chloro-5-methanoyl-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate [(S)-**1a**].* It was obtained from (*S*)-**6a** (47 mg, 0.17 mmol, 88% ee). Reaction time: 2 h. Purification of the crude material by flash chromatography (CH_2Cl_2 as the eluant) gave (*S*)-**1a** (42 mg) as a yellow solid; 81% yield; $[\alpha]_D^{20}$ +16.3 (*c* 0.75, $CHCl_3$), 88% ee.

*4.5.2. Ethyl 6-chloro-5-methanoyl-2-methyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (**1b**).* Reaction time with both enantiomers: 1 h. After purification by flash chromatography (hexane/EtOAc 5:1), both enantiomers of **1b** were obtained as yellow solids.

Compound (*S*)-**1b** was obtained from (*S*)-**6b** (153 mg, 0.474 mmol, >99% ee) with 78% yield (130 mg); mp 155–157 °C; $[\alpha]_D^{20}$ −242.4 (*c* 0.51, $CHCl_3$), 99% ee.

Compound (*R*)-**1b** was obtained from (*R*)-**6b** (220 mg, 0.682 mmol, 95% ee) with 75% yield (179 mg); $[\alpha]_D^{20}$ +254.7 (*c* 0.52, $CHCl_3$), 98% ee.

*4.5.3. Ethyl 6-chloro-5-methanoyl-2-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (**1c**).* Reaction time: 2 h. After purification by flash chromatography (hexane/EtOAc 5:1), both enantiomers of **1c** were obtained as yellow solids.

Compound (*S*)-**1c** was obtained from (*S*)-**6c** (100 mg, 0.310 mmol, 97% ee) with 88% yield (96 mg); $[\alpha]_D^{20}$ −36.8 (*c* 0.49, $CHCl_3$), 97% ee.

Compound (*R*)-**1c** was obtained from (*R*)-**6c** (130 mg, 0.403 mmol, 97% ee) with 92% yield (130 mg); mp 156–157 °C; $[\alpha]_D^{20}$ +37.0 (*c* 0.50, $CHCl_3$), 99% ee.

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*4.5.4. Ethyl (S)-6-chloro-5-methanoyl-2-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3-carboxylate [(S)-**1d**].* It was obtained from (*S*)-**6d** (56 mg, 0.174 mmol, 88% ee). Reaction time: 1 h. Purification of the crude material by flash chromatography (hexane/EtOAc 5:1) gave (*S*)-**1d** (43 mg) as a yellow solid; 70% yield; $[\alpha]_D^{20}$ −28.2 (*c* 0.73, $CHCl_3$), 87% ee.

*4.5.5. Ethyl 6-chloro-4-(2-chloro-5-nitrophenyl)-5-methanoyl-2-methyl-1,4-dihydropyridine-3-carboxylate (**1e**).* Reaction time for both enantiomers: 4 h. Purification of the corresponding crude material was carried out by flash chromatography (hexane/EtOAc 4:1). Yellow solid; ν_{max} (KBr) 3289; 1709; 1684; 1643; 1600; 1487; 1348 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 1.18 (t, 3H, CH_3CH_2), 2.41 (s, 3H, CH_3), 4.18–3.96 (m, 2H, CH_3CH_2), 5.53 (s, 1H, H-4), 6.57 (br s, 1H, NH), 7.45 (d, 1H, ^3J 8.8 Hz, H-3′), 7.96 (dd, 1H, ^4J 2.7, ^3J 8.8 Hz, H-4′), 8.23 (d, 1H, ^4J 2.7 Hz, H-6′), 9.74 (s, 1H, HC=O); δ_C (75.5 MHz, $CDCl_3$) 14.2 (CH_3CH_2), 19.1 (CH_3), 38.4 (C-4), 60.7 (CH_3CH_2), 105.3 (C-5), 111.6 (C-3), 122.8 (CH), 126.9 (CH), 130.8 (CH), 140.4 (C), 143.2 (C), 144.4 (C), 144.9 (C), 146.7 (C), 166.2 (CO), 187.6 (CHO); HRMS (ESI^+): MNa^+, found: 407.0172. $C_{16}H_{14}Cl_2N_2NaO_5$ requires 407.0145.

Compound (*R*)-**1e** was obtained from (*R*)-**6e** (71 mg, 0.20 mmol, 95% ee) with 86% yield (66 mg); mp 182–184 °C; $[\alpha]_D^{20}$ −52.8 (*c* 0.50, $CHCl_3$), 99% ee.

Compound (*S*)-**1e** was obtained from (*S*)-**6e** (58 mg, 0.16 mmol, 98% ee) with 80% yield (50 mg); $[\alpha]_D^{20}$ +60.4 (*c* 1.0, $CHCl_3$), 97% ee.

*4.5.6. Ethyl 4-(4-bromophenyl)-6-chloro-5-methanoyl-2-methyl-1,4-dihydropyridine-3-carboxylate (**1f**).* Reaction time for both enantiomers: 2 h. Purification of the corresponding crude material was carried out by flash chromatography (hexane/EtOAc 5:1). Yellow solid; ν_{max} (KBr) 3282; 1699; 1635; 1590; 1479 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 1.18 (t, 3H, ^3J 7.1 Hz, CH_3CH_2), 2.42 (s, 3H, CH_3), 4.07 (q, 2H, ^3J 7.1 Hz, CH_3CH_2), 5.08 (s, 1H, H-4), 6.26 (br s, 1H, NH), 7.17 (d, 2H, ^3J 8.4 Hz, H-2′ and H-6′), 7.35 (d, 2H, ^3J 8.4 Hz, H-3′ and H-5′), 9.76 (s, 1H, HC=O); δ_C (75.5 MHz, $CDCl_3$) 14.3 (CH_3CH_2), 19.1 (CH_3), 38.4 (C-4), 60.5 (CH_3CH_2), 106.5 (C-5), 112.8 (C-3), 120.8 (C), 129.9 (2×CH), 131.4 (2×CH), 142.0 (C), 143.8 (C), 144.3 (C), 166.5 (CO), 187.6 (CHO); HRMS (ESI^+): MH^+, found: 383.9997. $C_{16}H_{16}BrClNO_3$ requires 383.9987.

Compound (*S*)-**1f** was obtained from (*S*)-**6f** (42 mg, 0.12 mmol, 96% ee) with 74% yield (34 mg); $[\alpha]_D^{20}$ +10.6 (*c* 1.0, $CHCl_3$), 95% ee.

Compound (*R*)-**1f** was obtained from (*R*)-**6f** (40 mg, 0.11 mmol, 89% ee) with 77% yield (93 mg); $[\alpha]_D^{20}$ −9.4 (*c* 0.95, $CHCl_3$), 89% ee.

*4.5.7. Ethyl 6-chloro-5-methanoyl-2-methyl-4-(3-methoxyphenyl)-1,4-dihydropyridine-3-carboxylate (**1g**).* Reaction time: 3 h. After purification by flash chromatography (hexane/EtOAc 3:1), both enantiomers of **1g** were obtained as yellow solids.

Compound (*S*)-**1g** was obtained from (*S*)-**6g** (60 mg, 0.19 mmol, 96% ee) with 76% yield (50 mg); mp 148–149 °C; $[\alpha]_D^{20}$ +12.8 (*c* 0.90, $CHCl_3$), 98% ee.

Compound (*R*)-**1g** was obtained from (*R*)-**6g** (47 mg, 0.15 mmol, 95% ee) with 78% yield (40 mg); $[\alpha]_D^{20}$ −12.1 (*c* 0.85, $CHCl_3$), 95% ee.

*4.5.8. Ethyl 6-chloro-5-methanoyl-2-methyl-4-(1-naphthyl)-1,4-dihydropyridine-3-carboxylate (**1h**).* Reaction time for both enantiomers: 3 h. Purification of the corresponding crude material was carried out by flash chromatography using CH_2Cl_2 as eluant. Yellow solid; ν_{max} (KBr) 3429; 3261; 1703; 1637; 1593; 1489 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 0.89 (t, 3H, ^3J 7.1 Hz, CH_3CH_2), 2.41 (s, 3H, CH_3), 4.03–3.70 (m, 2H, CH_3CH_2), 5.89 (s, 1H, H-4), 6.38 (br s, 1H, NH), 7.50–7.30 (m, 3H, H-3′, H-6′ and H-7′), 7.63–7.53 (m, 1H, H-2′), 7.68 (d, 1H, ^3J 7.6 Hz, H-4′), 7.76 (d, 1H, ^3J 8.2 Hz, H-5′), 8.75 (d, 1H, ^3J 8.6 Hz, H-8′), 9.76 (s, 1H, HC=O); δ_C (75.5 MHz, $CDCl_3$) 14.0 (CH_3CH_2), 18.9 (CH_3), 33.8 (C-4), 60.3 (CH_3CH_2), 108.7 (C-5), 114.5 (C-3), 125.5 (CH), 125.58 (CH), 125.63 (CH), 125.8 (CH), 127.0 (CH), 127.8 (CH), 128.1 (CH), 130.9 (C), 133.4 (C), 141.5 (C), 142.8 (C-2), 144.2 (C-6), 166.8 (CO), 188.0 (CHO); HRMS (ESI^+): MH^+, found: 356.1048. $C_{20}H_{19}ClNO_3$ requires 356.1036.

Compound (*S*)-**1h** was obtained from (*S*)-**6h** (81 mg, 0.25 mmol, 95% ee) with 75% yield (66 mg); $[\alpha]_D^{20}$ −85.3 (*c* 0.90, $CHCl_3$), 95% ee.

Compound (*R*)-**1h** was obtained from (*R*)-**6h** (90 mg, 0.27 mmol, 95% ee) with 80% yield (78 mg); $[\alpha]_D^{20}$ +87.1 (*c* 1.0, $CHCl_3$), 95% ee.

4.6. Determination of the enantiomeric excesses

Enantioselective HPLC was used for the determination of the enantiomeric excesses of compounds **5** and **6**. Previously to the measurement, carboxylic acids **6** were transformed into the corresponding methyl ester by treatment with diazomethane. HPLC-conditions and chromatograms are included in Supplementary data.

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Supplementary data

Copy of the HPLC chromatograms of the racemic and optically active compounds. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.04.047.

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