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Chemoenzymatic preparation of optically active 4-aryl-5-carboxy-6-methyl-3,4-dihydro-2(1*H*)-pyridone derivatives

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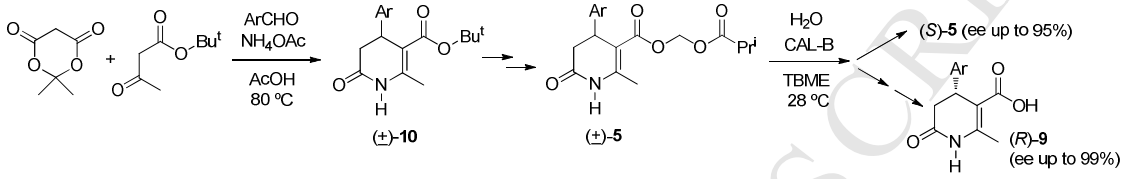

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ABSTRACT

A series of racemic 4-aryl-5-(*tert*-butoxycarbonyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridones have been prepared by means of a modified Hantzsch reaction using commercially available starting materials. An easy removal of the *tert*-butyl group of these pyridones and subsequent reaction with cesium carbonate and chloromethyl 2-methylpropanoate provided us suitable substrates (±)-**5** to be used in lipase-catalyzed hydrolysis reactions. Lipase B from *Candida antarctica* (CAL-B) was the most adequate lipase in the hydrolysis of (±)-**5**. Despite the low enantioselectivity values obtained ($E \leq 12$), several optically active pyridone derivatives were finally isolated with high enantiomeric excesses (ee ≥ 91%) and moderate yields.

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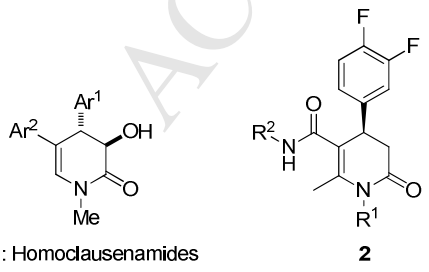
1. Introduction

The 3,4-dihydro-2(1*H*)-pyridone (3,4-DHP-2-one) core is present in natural products such as the homoclausenamide alkaloids **1**,[1] and the structural analogy of these heterocycles with 1,4-dihydropyridines making them good candidates for the development of calcium channel modulators.[2] In addition, different functionalized 3,4-DHP-2-ones have been used as precursors in the synthesis of biologically active molecules[3] (Figure 1). For instance, several carboxamide derivatives **2** have shown to be potent and selective α_{1a} receptor antagonists, and they could be used for the treatment of benign prostatic hyperplasia. In this case, the (*R*)-(–) enantiomer was significantly more active than its (*S*)-(+)-counterpart.[3b]



1: Homoclausenamides **2**

Figure 1. Some representative 3,4-dihydro-2(1*H*)-pyridone derivatives.

Given that the biological activity of a compound is closely related to the configuration of its chiral centres, the synthesis of optically active 3,4-DHP-2-ones is necessary to investigate their pharmacological activities. In this sense, methods for the preparation of enantioenriched 3,4-DHP-2-ones are scarce. Among them, the resolution by preparative enantioselective HPLC of a racemic mixture allowed to obtain an optically active precursor of **2**.[3b] Recently, the asymmetric synthesis of a 4-(*p*-fluorophenyl)-5-carboxy-3,4-DHP-2-one derivative by means of an organocatalyst has been published,[4] as well as the preparation of a wide variety of optically active 4-substituted-5-(alkoxycarbonyl or cyano)-3,4-DHP-2-ones derivatives by *N*-heterocyclic carbene catalyzed aza-Claisen reactions.[5]

Taking the importance of the development of green procedures into account, we decided to investigate the utility of hydrolytic enzymes for the resolution of 3,4-DHP-2-one derivatives. Nowadays, enzymes are recognized as excellent tools for preparing optically active compounds, either by kinetic resolution (KR) of racemic mixtures or by desymmetrization of *meso* compounds.[6] We report herein an efficient method to prepare a set of racemic 4-aryl-5-carboxy-3,4-DHP-2-ones, which have been subsequently converted into adequate substrates to carry out its resolution via lipase-catalyzed hydrolysis reactions. The resulting optically active compounds could be used as precursors of benzodiazepine-dihydropyridine hybrid molecules with potential activity as neuroprotective agents.[2c]

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2. Results and discussion

2.1. *Preparation of racemic 3,4-DHP-2-one derivatives.*

The syntheses of some racemic 4-aryl-6-methyl-5-(methoxycarbonyl)-3,4-DHP-2-ones (±)-**3** and their ethyl ester analogues (±)-**4** have previously been published.[7] Some initial attempts to carry out the hydrolysis of these esters using different lipases (Enz-OH) were unsuccessful (Figure 2). This absence of reactivity may be due to both steric and electronic factors. The steric congestion around the ester function could avoid the adequate fitting of the substrate in the active site of the enzyme. In addition, the high electronic density at the olefinic C-5 position[7a] could diminish the electrophilic character of the adjacent carbonyl carbon. These facts agree with the difficulties previously found in the enzymatic hydrolysis of related esters derived from 4-aryl-1,4-dihydropyridines.[8] Similarly to those cases, the hydrolysis resistance could be circumvented by introducing a spacer such as, for instance, the isobutyryloxymethyl unit beyond the carboxyl group. With these new substrates (±)-**5** (Fig. 2), the enzyme could be able to catalyze the reaction of the outer ester group, the pyridone ring being accommodated in the nucleophile binding site, and not in the acyl donor site. Moreover, this outer ester function is activated because it contains an optimal leaving group, which spontaneously loses formaldehyde with the concomitant formation of the corresponding non-racemic 4-aryl-5-carboxy-6-methyl-3,4-DHP-2-one **9**.

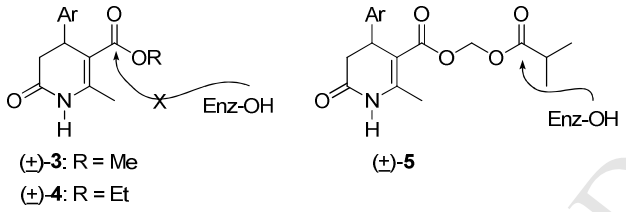
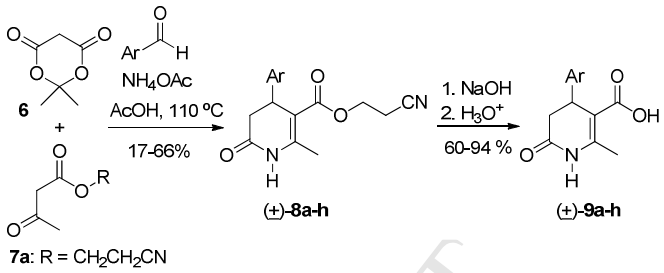


Figure 2. 4-Aryl-5-carboxy-6-methyl-3,4-DHP-2-one esters derivatives.

To obtain diesters (±)-**5** the corresponding carboxylic acids (±)-**9** are required as starting materials. However, several attempts to carry out the basic hydrolysis of the easily available compounds (±)-**3** and (±)-**4** failed. Thus, the treatment at room temperature with NaOH or LiOH in a water-methanol mixture was ineffective and the starting materials were recovered unaltered after 48 h of reaction. Higher reaction temperatures led to a complex mixture of products. On the other hand, some of these acids have been prepared on a small scale (0.50 mmol) by means of a four-step solid-phase synthesis.[9]

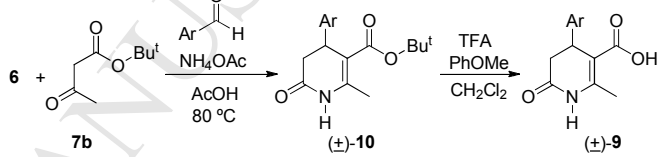
With the idea to develop a straightforward and expeditious alternative to the synthesis of carboxylic acids (±)-**9**, we initially decided to prepare the 2-cyanoethyl ester derivatives (±)-**8** (Scheme 1). In the presence of a base this kind of esters experiences a β-elimination[10] (initiated by the removal of the proton α to the cyano group) affording the corresponding carboxylate. Synthesis of (±)-**8** was carried out similarly to the preparation of (±)-**3** or (±)-**4**, by means of a modified Hantzsch reaction using the Meldrum's acid **6**.[11] The four-component reaction among equimolar amounts of **6**, 2-cyanoethyl acetoacetate **7a**, and the appropriate aromatic aldehyde, as well as 1.5 equivalents of ammonium acetate in acetic acid at 110 ºC, gave the corresponding 2-cyanoethyl esters (±)-**8** with low to moderate yields (Scheme 1). The removal of the cyanoethyl group, and thus the conversion of esters (±)-**8** into acids (±)-**9**, easily took place by treatment with NaOH (4 equiv) in a water-acetone mixture. Although in almost all cases the yields of this last step were high (>75%), the poor results of the first step cut down the overall yields of the products (±)-**9** (15-59%).



Scheme 1. Synthesis of (±)-**9a-h** from 2-cyanoethyl esters (±)-**8a-h**. The Ar groups for **8** and **9** are the same shown in Table 1.

With the idea to enhance the yields of acids (±)-**9**, we decided to check other esters whose conversion into acids does not imply a nucleophilic attack to the carbonyl group. Thus, we planned to access to compounds (±)-**9** through the *tert*-butyl esters derivatives (±)-**10** (Table 1).

Table 1. Synthesis of (±)-**9** and *tert*-butyl esters (±)-**10**.[a]



Entry	Ar	(±)-**10**	Yield (%)[b]	(±)-**9**	Yield (%)[c]
1	Ph	**10a**	61	**9a**	52
2	2-NO_2-C_6H_4	**10b**	69	**9b**	52
3	3-NO_2-C_6H_4	**10c**	72	**9c**	58
4	4-NO_2-C_6H_4	**10d**	73	**9d**	50
5	2-Cl-5-NO_2-C_6H_3	**10e**	74	**9e**	53
6	4-Br-C_6H_4	**10f**	88	**9f**	65
7	3-CH_3O-C_6H_4	**10g**	84	**9g**	76
8	1-Naphthyl	**10h**	92	**9h**	83

[a]Reactions were carried out using an equimolecular amount of **6**, **7b**, and the aldehyde, and 50% excess of ammonium acetate in AcOH as the solvent. [b]Isolated yields for (±)-**10** after recrystallization or flash-chromatography. [c]Overall two-steps yields for (±)-**9**.

The four component reaction among **6**, *tert*-butyl acetoacetate **7b**, the corresponding aldehyde, and ammonium acetate, all of them commercially available, happened at lower reaction temperature (80 ºC) than the reaction using **7a**. Consequently, the formation of side compounds decreased drastically, and the *tert*-butyl esters (±)-**10** were obtained in higher yields (Table 1) than those of (±)-**8** (Scheme 1). After testing several reaction conditions for the removal of the *tert*-butyl group of (±)-**10**, the best results were obtained at 0 ºC using trifluoroacetic acid and anisole as a cation scavenger.[12] Thus, acids (±)-**9** were finally isolated in 50-83% overall yields (Table 1).

Transformation of carboxylic acids (±)-**9** into the diesters (±)-**5** was easily carried out in one pot process by treatment with cesium carbonate (1.6 equiv) in DMF, and subsequent reaction of the carboxylate with a slight excess of chloromethyl isobutyrate,

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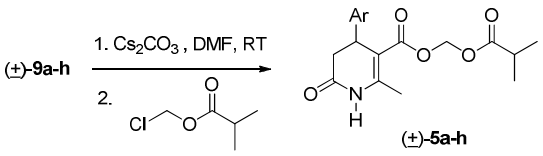
at room temperature (Scheme 2). Isolated yields after the purification of (±)-**5** by flash-chromatography were very high (78-91%).

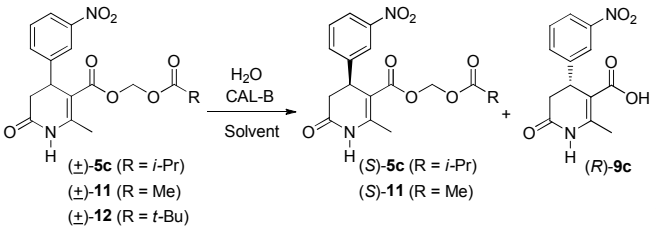


Scheme 2. Synthesis of diesters (±)-**5a-h**.

2.2. *Enzymatic hydrolysis of (±)-5.*

In order to check the enzymatic kinetic resolution of diesters (±)-**5**, the 3-nitrophenyl derivative (±)-**5c** was chosen as a substrate model. To improve the dissolution of the diester, the enzymatic hydrolysis reactions were carried out in organic solvents. Several combinations of lipases (PSL, CRL, CAL-A, and CAL-B) and organic solvents were tested and a selection of the results obtained is included in Table 2, entries 1-5. The best results were achieved with CAL-B in *tert*-butyl methyl ether (TBME), at 28 ºC (entry 3). In these conditions, the enantiomeric excess (ee) of either the remaining substrate and the product was only moderate, the enantioselectivity value being low (E = 12).[13]

Table 2. Enzymatic hydrolysis of diesters (±)-**5c** and (±)-**11**.[a]



Entry	R	Solvent	t, h	ee_S (%)[b]	ee_P (%)[c]	c[d]	E[e]
1	*i*-Pr	1,4-Dioxane	9	58	32	64	3
2	*i*-Pr	DIPE	24	78	42	65	5
3	*i*-Pr	TBME	9	80	67	54	12
4	*i*-Pr	TBME[f]	9	44	64	41	7
5	*i*-Pr	TBME[g]	3	44	72	38	9
6	Me	1,4-Dioxane	2	35	13	73	2
7	Me	TBME	2	91	49	65	9

[a]Reactions were carried out at 28 ºC and 200 rpm using 25 mg of substrate and the following solvents: water-saturated diisopropyl ether (15 mL) or TBME (2.5 mL); or a mixture of 1,4-dioxane (1.0 mL) and H_2O (50 µL). [b]The ee of remaining substrates **5c** or **11** (ee_S) was determined by enantioselective HPLC analysis. [c]The ee of the produced acid **9c** (ee_P) was determined after treatment with diazomethane, and then enantioselective HPLC analysis of the resulting methyl ester derivative **3c**. [d]The degree of conversion (%) was calculated from ee_S and ee_P: $c = 100ee_S / (ee_S + ee_P)$. [e]See Ref. 13. [f]Reaction was carried out at 10 ºC. [g]A two-phase 3:1 v/v system TBME-H_2O was used.

Other diesters such as the acetyl (±)-**11** and pivaloyl (±)-**12** derivatives (Table 2) were also prepared and checked in the enzymatic hydrolysis. Whereas pivaloyl derivative was not transformed, the enzyme catalyzed the hydrolysis of the acetyl derivative (±)-**11** quicker than that of (±)-**5c**, but with a slightly lower E value (Table 2, entry 7). Besides hydrolysis, several enzymatic transesterifications and aminolysis reactions of (±)-**5c** were essayed in the presence of CAL-B, but the results were always poorer than those attained in the hydrolysis reaction.

Next, the best enzymatic hydrolysis conditions were applied to all the diesters (±)-**5a-h** (for the nature of each Ar substituent, see Table 1). Some of the results obtained are collected in Table 3. Reactions using (±)-**5b**,**d,e,h** as starting materials happened with $E \leq 2$ and therefore were not included in Table 3. The E value obtained in the reaction with substrate (±)-**5a** (Ar = Ph) was also very low (Table 3, entry 1), the ee for the remaining substrate (*S*)-**5a** and the product (*R*)-**9a** being very low (32% and 47% ee, respectively). However, taking advantage of the different solubility of the racemic diester (±)-**5a** and the enantiopure form, it was possible to access to (*S*)-**5a** with very high ee after a simple recrystallization of the moderately enantioenriched sample (see below in the text).

Results achieved in the CAL-B-catalyzed hydrolysis of (±)-**5f** and (±)-**5g** (Table 3, entries 3 and 4) were similar to those obtained with **5c**, the ee for both substrate and product being moderate at a degree of conversion near to 50% (E = 10). Nevertheless, from these reactions happening with E values near to 10, the remaining substrates can be reached with high ee at degrees of conversion around 65%. Effectively, when enzymatic hydrolysis of (±)-**5c**,**f**,**g** were conducted to longer reaction times (Table 3, entries 5-7) substrates (*S*)-**5c,f,g** were isolated with high ee (93-95%) and moderate yields (30-31%), considering the maximal 50% yield of a kinetic resolution. It is worth noting that isolation of optically active compounds (*S*)-**5** and (*R*)-**9** was easily carried out by base-acid extraction.

On the other hand, we also try to enhance the ee of these compounds by recrystallization of the enantioenriched samples, seeing as the racemates usually crystallize better than the corresponding optically active samples. Based on this fact, substrate (*S*)-**5c** (ee = 73%), isolated from the enzymatic hydrolysis reaction (Table 3, entry 2), was recrystallized in diethyl ether. After a slow crystallization, the solid was filtered and the enantiomeric excesses of both the solid and the product recovered from the filtrate were measured by enantioselective HPLC. Whereas the crystallized solid (22% of recovering) was almost racemic (ee = 2%), the ee of the compound (*S*)-**5c** obtained from the filtrate (71% of recovering) was very high (95% ee). This highly enantioenriched (*S*)-**5c** was obtained as a viscous oil, with an overall yield (taking the two steps, enzymatic hydrolysis and crystallization, into account) of 32%. These values (ee and yield) are similar to those obtained from the kinetic resolution at c = 64% (Table 3, entry 5). In addition, recrystallization of (*S*)-**5a** with 32% ee (Table 3, entry 1) allowed us to access to a 13% overall yield of almost enantiopure (*S*)-**5a** (99% ee). However, when this method was applied to enantioenriched (*S*)-**5f,g** of 71 and 69% ee, respectively, the same trends was observed in both cases, but the ee of the resulting samples were lower than 90%. From these results we can conclude that the most adequate method to obtain the enantioenriched esters (*S*)-**5c**,**f**,**g** (ee >90%) is by means of enzymatic hydrolysis to degrees of conversion around 65%.

Several attempts to enhance the ee of the carboxylic acids (*R*)-**9** isolated from the enzymatic reactions were also carried out. Since the recrystallization attempts failed for compounds (*R*)-**9**, we decided to convert the enantioenriched samples (*R*)-**9c,f,g** into the esters (*R*)-**5c,f,g** and submit these substrates to enzymatic hydrolysis again. Thus, after 2-3 h of reaction, the new acids (*R*)-**9c,f,g** were isolated with very high ee (>90%) and moderate yields (Table 3, entries 8-10). Considering the three steps (KR-esterification-KR), the overall yields for these acids were in the 20-25% range.[14]

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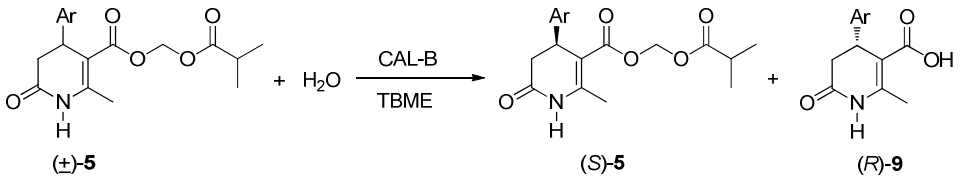
Table 3. Enzymatic hydrolysis of diesters (±)-**5**.[a]



(±)-**5** (*S*)-**5** (*R*)-**9**

Entry	Starting diester	Ar	Time (h)	Remaining substrate			Product			*c* (%)	*E*
				Substrate	Yield (%)	ee$_S$ (%)[b]	Product	Yield (%)	ee$_P$ (%)[c]		
1	(±)-**5a**	Ph	9	(*S*)-**5a**	56	32[d]	(*R*)-**9a**	39	47	41	4
2	(±)-**5c**	3-NO$_2$-C$_6$H$_4$	9	(*S*)-**5c**	47	73[e]	(*R*)-**9c**	48	71	51	12
3	(±)-**5f**	4-Br-C$_6$H$_4$	11	(*S*)-**5f**	46	71	(*R*)-**9f**	46	64	52	10
4	(±)-**5g**	3-CH$_3$O-C$_6$H$_4$	7	(*S*)-**5g**	48	69	(*R*)-**9g**	48	66	51	10
5	(±)-**5c**	3-NO$_2$-C$_6$H$_4$	16	(*S*)-**5c**	31	**95**	(*R*)-**9c**	62	53	64	11
6	(±)-**5f**	4-Br-C$_6$H$_4$	18	(*S*)-**5f**	31	**93**	(*R*)-**9f**	59	48	66	9
7	(±)-**5g**	3-CH$_3$O-C$_6$H$_4$	12	(*S*)-**5g**	30	**95**	(*R*)-**9g**	61	50	65	10
8	(*R*)-**5c**[f]	3-NO$_2$-C$_6$H$_4$	3				(*R*)-**9c**	52 (24)[i]	**95**		
9	(*R*)-**5f**[g]	4-Br-C$_6$H$_4$	2.5				(*R*)-**9f**	41 (20)[i]	**93**		
10	(*R*)-**5g**[h]	3-CH$_3$O-C$_6$H$_4$	2				(*R*)-**9g**	49 (25)[i]	**91**		

[a]Reactions were carried out at 100-1000 mg scale amount (see Experimental Section) using TBME saturated with water as solvent, at 28 ºC and 200 rpm. The degree of conversion (*c*, %) and the *E* values were calculated as in Table 2.

[b]Determined by enantioselective HPLC analysis (see Sec. 4.14). High ee values are bolded.

[c]Determined by enantioselective HPLC analysis after treatment of products **9** with diazomethane (see Sec. 4.14). High ee values are bolded.

[d](*S*)-**5a** almost enantiopure (99% ee) was isolated after submitting this sample to crystallization (see Sec. 4.10.1).

[e]Recrystallization of this sample afforded to (*S*)-**5c** with 95% ee (see Sec. 4.11.1).

[f]An enantioenriched sample of (*R*)-**5c** with ee$_o$ = 67% was used as substrate.

[g]An enantioenriched sample of (*R*)-**5f** with ee$_o$ = 62% was used as substrate.

[h]An enantioenriched sample (*R*)-**5g** with ee$_o$ = 57% was used as substrate.

[i]The corresponding overall yield calculated from racemic 5 is given between brackets.

Finally, optically active esters (*S*)-**5** were smoothly converted into the acids (*S*)-**9** by conventional basic hydrolysis (aq 3N NaOH, acetone, RT). No racemization took place in these reactions as proven by enantioselective HPLC.

In order to establish the enantiopreference of the lipase in these process, product **9f** (ee = 93%, see Table 3, entry 9) was treated with cesium carbonate in DMF and then with methyl iodide. The resulting methyl ester (–)-**3f** ($[\alpha]_D^{20}$ = –100.6 (*c* 1.05, $CHCl_3$)) retained the ee as shown by the enantioselective HPLC analysis. Comparison of the sign of the optical rotation of this ester with the published value[5] establishes the (*R*) configuration for (–)-**3f** and thus, for the acid **9f** proceeding from the enzymatic reaction. That means that CAL-B preferently catalyzes the hydrolysis of the (*R*) enantiomer of the diester **5f**. Based on the structural resemblance among all the substrates reported here, we have tentatively assigned the (*R*) configuration to the other produced acids **9**. In addition the (*S*) configuration for the remaining optically active substrates **5a,c,g** was also assigned.

3. Conclusion

We have developed an efficient method to obtain some carboxylic acids derived from 3,4-DHP-2-ones, as well as several acyloxymethyl ester derivatives which are suitable substrates to be used in lipase-catalyzed hydrolysis reactions. Lipase B from *Candida antarctica* catalyzed the hydrolysis of the acyloxymethyl esters, but the *E* values obtained for these processes were low. The remoteness between the asymmetric carbon and the reactive carbonyl function could be the reason for this poor enantioselectivity.[15] Nevertheless, compounds with high enantiomeric excesses and moderate yields were prepared by combining either the enzymatic resolution with a selective crystallization process or two consecutive KRs. As a result, both enantiomers of the pyridone-carboxylic acids have been achieved. The biological activities of these optically active pyridone-carboxylic acids as well as some of their derivatives are currently under study.

4. Experimental section

Lipase B from *Candida antarctica* (CAL-B, Novozyme 435, available immobilized on polyacrylamide, 7300 PLU/g) was gifted by Novo Nordisk Co. Immobilized lipase A from *Candida 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. Melting points were taken on samples in open capillary tubes and are uncorrected. For the enzymatic hydrolysis reaction *tert*-butyl methyl (TBME) 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

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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: $CDCl_3$, 76.95; DMSO-d_6, 39.52 ppm) or the residual solvent partially or non-deuterated (^{1}H: $CHCl_3$, 7.26; DMSO-d_5, 3.50 ppm).

In Figure 3 we show the 4-aryl-3,4-DHP-2-one unit with the numbering used in the assignation of the NMR signals.

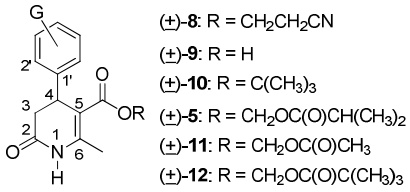

Figure 3. 4-Aryl-3,4-DHP-2-one derivatives.

4.1. *2-Cyanoethyl 2-oxobutanoate (**7a**).*

A solution of 1,3-dioxin-4-one (10.0 mL, 76.5 mmol) and 3-hydroxypropanonitrile (5.5 mL, 80 mmol) in toluene (15 mL) was heated at reflux during 24 h. Elimination of the solvents under reduced pressure yielded **7a** (11.3 g, 95%). Spectroscopic data for **7a** are in good agreement with those previously published.[16]

4.2. *General procedure for the synthesis of 2-cyanoethyl esters (±)-**8**.*

To a solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (4.73 g, 32.8 mmol) in acetic acid (9.5 mL), the aromatic aldehyde (32.8 mmol), 2-cyanoethyl 3-oxobutanoate (5.09 g, 32.8 mmol), and ammonium acetate (3.78 g, 49.1 mmol) were added. After refluxing during 7-16 h, the reaction mixture was poured into ice-water, and the precipitation of (±)-**8** took place. The solid was filtered and successively washed with water and cold diethyl ether yielding the corresponding ester (±)-**8**, which was purified by flash chromatography (hexane/ethyl acetate mixtures).

*4.2.1. (±)-5-[(2-Cyanoethyl)oxycarbonyl]-6-methyl-4-phenyl-3,4-dihydro-2(1*H*)-pyridone [(±)-**8a**]*

Reaction time: 14 h. White solid; mp 110-111 ºC; yield 17%; ν_{max}(KBr) 3226, 1705, 1690, 1635, and 1525 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 2.43 (s, 3H, CH_3), 2.77-2.47 (m, 3H, CH_2CN and *H*H-3), 2.96 (dd, 1H, ^3J 8.2, $|^2J|$ 16.6 Hz, H*H*-3), 4.33-4.15 (m, 3H, O-CH_2 and H-4), 7.36-7.12 (m, 5H, Ph), 7.83 (br s, 1H, NH); δ_C (75.5 MHz, $CDCl_3$) 17.9 (*C*H_2-CN), 19.0 (CH_3), 37.8 (C-4), 38.1 (C-3), 58.4 (O-CH_2), 105.8 (C-5), 117.0 (C≡N), 126.6 (CH), 127.1 (C-4'), 128.8 (CH), 141.9 (C), 148.4 (C), 166.0 (CO), 171.4 (C-2); HRMS (ESI$^+$): MH^+, found: 385.1234. $C_{16}H_{17}N_2O_3$ requires 385.1219.

*4.2.2. (±)-5-[(2-Cyanoethyl)oxycarbonyl]-6-methyl-4-(2-nitrophenyl)-3,4-dihydro-2(1*H*)-pyridone [(±)-**8b**]*

Reaction time: 14 h. White solid; m.p.: 146-149 ºC; yield 26%; ν_{max}(KBr) 3223, 1710, 1698, 1636, 1522, 1491, and 1342 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 2.58-2.42 [m + s, 5H, CH_2CN and singlet centered to 2.49 corresponding to CH_3], 2.84 (br d, 1H, $|^2J|$ 16.5 Hz, *H*H-3), 3.09 (dd, 1H, ^3J 9.2, $|^2J|$ 17.2 Hz, H*H*-3), 4.16 (m, 2H, O-CH_2), 4.74 (br d, 1H, ^3J 9.0 Hz, H-4), 7.33-7.19 (m, 1H, H-6'), 7.40 [td, 1H, ^3J 7.7 (t), ^4J 1.1 (d) Hz, H-4'], 7.52 [td, 1H, ^3J 7.7 (t), ^4J 0.9 (d) Hz, H-5'], 7.84 (dd, 1H, ^3J 8.1, ^4J 1.0 Hz, H-3'); δ_C (75.5 MHz, $CDCl_3$) 17.2 (*C*H_2-CN), 18.5 (CH_3), 33.3 (C-4), 37.1 (C-3), 58.9 (O-CH_2), 103.0 (C-5), 118.1 (C≡N), 124.7 (C-3'), 127.8 (CH), 128.3 (CH), 133.7 (CH), 136.6 (C-1'), 148.6 (C-2'), 150.9 (C-6), 165.5 (CO), 168.9 (C-2); HRMS (ESI$^+$): MH^+, found: 330.1084. $C_{16}H_{16}N_3O_5$ requires 330.1069.

*4.2.3. (±)-5-[(2-Cyanoethyl)oxycarbonyl]-6-methyl-4-(3-nitrophenyl)-3,4-dihydro-2(1*H*)-pyridone [(±)-**8c**]*

Reaction time: 16 h. White solid; m.p.: 158-160 ºC; yield 51%; ν_{max}(KBr) 3213, 1707, 1687, 1623, 1527, 1485, and 1350 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 2.49 (s, 3H, CH_3), 2.63 (m, 2H, CH_2CN), 2.73 (br d, 1H, $|^2J|$ 16.6 Hz, *H*H-3), 3.03 (dd, 1H, ^3J 7.6, $|^2J|$ 16.6 Hz, H*H*-3), 4.28 (m, 2H, O-CH_2), 4.38 (br d, 1H, ^3J 7.6 Hz, H-4), 7.60-7.43 (m, 2H, H-5' and H-6'), 7.79 (br s, 1H, NH), 8.03 (t, 1H, ^4J 1.7 Hz, H-2'), 8.11 (dt, 1H, ^3J 7.7, ^4J 1.4 Hz, H-4'); δ_C (75.5 MHz, $CDCl_3$) 18.2 (*C*H_2-CN), 19.8 (CH_3), 37.8 (C-3), 37.9 (C-4), 58.8 (O-CH_2), 105.0 (C-5), 116.9 (C≡N), 121.8 (C-4'), 122.6 (C-2'), 130.2 (C-5'), 133.2 (C-6'), 144.1 (C-1'), 148.8 (C-3'), 149.2 (C-6), 165.7 (CO), 169.6 (C-2); MS (EI), *m/z* (%) = 329 ($M^{\bullet+}$, 83), 312 (100), 259 (64), 231 (93); HRMS (ESI$^+$): MH^+, found: 330.1084. $C_{16}H_{16}N_3O_5$ requires 330.1094.

*4.2.4. (±)-5-[(2-Cyanoethyl)oxycarbonyl]-6-methyl-4-(4-nitrophenyl)-3,4-dihydro-2(1*H*)-pyridone [(±)-**8d**]*

Reaction time: 13 h. White solid; m.p.: 118-119 ºC; yield 27%; ν_{max}(KBr) 3220, 1697, 1631, 1567, 1417, and 1349 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 2.46 (s, 3H, CH_3), 2.75-2.50 [m + br d, 3H, CH_2CN and doublet centered to 2.68 corresponding to *H*H-3 ($|^2J|$ 16.7 Hz)], 3.02 (dd, 1H, ^3J 8.3, $|^2J|$ 16.6 Hz, H*H*-3), 4.43-4.15 [m + br d, 3H, O-CH_2 and doublet centered to 4.37 corresponding to H-4 (^3J 8.1 Hz)], 7.36 (d, 2H, ^3J 8.3 Hz, H-2' and H-6'), 8.15 (d, 2H, ^3J 8.4 Hz, H-3' and H-5'), 8.54 (br s, 1H, NH); δ_C (75.5 MHz, $CDCl_3$) 18.2 (*C*H_2-CN), 19.6 (CH_3), 37.7 (C-3), 38.0 (C-4), 58.8 (O-CH_2), 104.9 (C-5), 117.0 (C≡N), 124.4 (CH), 127.8 (CH), 147.3 (C), 149.2 (C), 149.5 (C), 165.6 (CO), 170.2 (C-2); HRMS (ESI$^+$): MH^+, found: 330.1084. $C_{16}H_{16}N_3O_5$ requires 330.1071.

*4.2.5. (±)-4-(2-Chloro-5-nitrophenyl)-5-[(2-cyanoethyl)oxycarbonyl]-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(±)-**8e**]*

Reaction time: 13 h. White solid; m.p.: 161-163 ºC; yield 66%; ν_{max}(KBr) 3222, 1705, 1685, 1643, 1525, and 1350 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 2.79-2.49 [m + s, 5H, CH_2CN and singlet centered to 2.55 corresponding to CH_3], 2.72 (br d, 1H, $|^2J|$ 16.8 Hz, *H*H-3), 3.01 (dd, 1H, ^3J 8.6, $|^2J|$ 16.8 Hz, H*H*-3), 4.30-4.15 (m, 2H, O-CH_2), 4.78 (br d, 1H, ^3J 8.3 Hz, H-4), 7.60 (br d, 1H, ^3J 8.7 Hz, H-3'), 7.86 (d, 1H, ^4J 2.6 Hz, H-6'), 8.07 (dd, 1H, ^4J 2.6, ^3J 8.7 Hz, H-4'), 8.16 (br s, 1H, NH); δ_C (75.5 MHz, $CDCl_3$) 18.1 (*C*H_2-CN), 19.6 (CH_3), 35.4 (C-4), 35.9 (C-3), 58.9 (O-CH_2), 103.8 (C-5), 116.6 (C≡N), 122.4 (CH), 123.8 (CH), 131.5 (C-3'), 140.4 (C), 140.4 (C), 147.1 (C-2'), 150.6 (C-5'), 165.3 (CO), 169.2 (C-2); HRMS (ESI$^+$): MH^+, found: 364.0695. $C_{16}H_{15}ClN_3O_5$ requires 364.0687.

*4.2.6. (±)-4-(4-Bromophenyl-5-[(2-cyanoethyl)oxycarbonyl]-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(±)-**8f**]*

Reaction time: 14 h. White solid; m.p.:144-146 ºC; yield 47%; ν_{max}(KBr) 3209, 1705, 1690, 1630, and 1487 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 2.44 (s, 3H, CH_3), 2.72-2.50 (m, 3H, CH_2CN and *H*H-3), 2.95 (dd, 1H, ^3J 8.2, $|^2J|$ 16.6 Hz, H*H*-3), 4.35-4.15 (m, 3H, O-CH_2 and H-4), 7.06 [d, 2H, ^3J 8.4 Hz, H-2' and H-6'], 7.41 [d, 2H, ^3J 8.5 Hz, H-3' and H-5'], 8.00 (br s, 1H, NH); δ_C (75.5 MHz, $CDCl_3$) 18.2 (*C*H_2-CN), 19.6 (CH_3), 37.6 (C-4), 38.1 (C-3), 58.7 (O-CH_2), 105.7 (C-5), 117.0 (C≡N), 121.1 (C), 128.6 (C-2' and C-6'), 132.2 (C-3' and C-5'), 141.0 (C), 148.5 (C), 165.9 (CO), 170.6 (C-2); HRMS (ESI$^+$): MH^+, found: 363.0339. $C_{16}H_{16}BrN_2O_3$ requires 363.0339.

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*4.2.7. (±)-5-[(2-Cyanoethyl)oxycarbonyl]-4-(3-methoxyphenyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(±)-**8g**]*

Reaction time: 14 h. White solid; m.p.: 123-124 ºC; yield 34%; ν_{max}(KBr) 3550, 3475, 3414, 3224, 1705, 1692, 1620, 1579, and 1489 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 2.42 (s, 3H, CH_3), 2.74-2.47 (m, 3H, CH_2CN and *H*H-3), 2.94 (dd, 1H, ^3J 8.2, $|^2J|$ 16.6 Hz, H*H*-3), 3.77 (s, 3H, O-CH_3), 4.33-4.15 (m, 3H, O-CH_2 and H-4), 6.73-6.69 (m, 1H, Ph), 6.80-6.73 (m, 2H, Ph), 7.21 (t, 1H, ^3J 7.9 Hz, H-5'), 8.27 (br s, 1H, NH); δ_C (75.5 MHz, $CDCl_3$) 18.2 (*C*H_2-CN), 19.5 (CH_3), 38.1 (C-4), 38.3 (C-3), 55.3 (O-CH_3), 58.6 (O-CH_2), 105.9 (C-5), 112.0 (CH), 113.0 (CH), 117.1 (C≡N), 119.1 (CH), 130.1 (CH), 143.7 (C), 148.3 (C), 160.0 (C-3'), 166.1(CO), 170.8 (C-2); HRMS (ESI^+): MNa^+, found: 337.1159. $C_{17}H_{18}N_2NaO_4$ requires 337.1151.

*4.2.8. (±)-5-[(2-Cyanoethyl)oxycarbonyl]-6-methyl-4-(1-naphthyl)-3,4-dihydro-2(1*H*)-pyridone [(±)-**8h**]*

Reaction time: 7h. White solid; m.p.: 197-198 ºC; yield 52%; ν_{max}(KBr) 3227; 1707; 1695; 1633; 1527 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 2.58-2.20 [m + s, 5H, CH_2CN and singlet centered to 2.52 corresponding to CH_3], 2.80 (br d, 1H, $|^2J|$ 17.3 Hz, *H*H-3), 3.09 (dd, 1H, ^3J 8.6, $|^2J|$ 17.3 Hz, H*H*-3), 4.14-3.97 (m, 1H, O-C*H*H), 4.27-4.14 (m, 1H, O-CH*H*), 5.14 (br d, 1H, ^3J 8.3 Hz, H-4), 7.18 (d, 1H, ^3J 7.7 Hz, H-2'), 7.35 (t, 1H, ^3J 7.7 Hz, H-3'), 7.66-7.43 [m, 2H, H-6' and H-7'], 7.75 (d, 1H, ^3J 8.2 Hz, H-4'), 7.89 (d, 1H, ^3J 7.8 Hz, H-5'), 7.96 (br s, 1H, NH), 8.08 (d, 1H, ^3J 8.4 Hz, H-8'); δ_C (75.5 MHz, $CDCl_3$) 17.9 (*C*H_2-CN), 19.4 (CH_3), 33.7 (C-4), 37.5 (C-3), 58.5 (O-CH_2), 105.7 (C-5), 116.8 (C≡N), 122.7 (C-8'), 123.1 (C-2'), 125.5 (C-3'), 125.8 (C-6'), 126.6 (C-7'), 128.1 (C-4'), 129.4 (C-5'), 130.6 (C), 134.6 (C), 136.4 (C), 149.1 (C), 166.1 (CO), 170.7 (C-2); HRMS (ESI^+): MH^+, found: 335.1390. $C_{20}H_{19}N_2O_3$ requires 335.1554.

4.3. *General procedure for the hydrolysis of 2-cyanoethyl esters (±)-**8**.*

To a solution of the cyanoethyl ester (±)-**8** (5.0 mmol) in acetone (70 mL), aq 3 M NaOH (20 mmol) and water (140 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 dichloromethane (2 x 30 mL). After, aq 3 M HCl was added to the aqueous phase until pH was 1-2. The resulting acid aqueous phase was extracted with ethyl acetate (3 x 60 mL). The organic layers were combined, washed with brine (50 mL), dried with Na_2SO_4, and evaporated under reduced pressure to give the corresponding carboxylic acid (±)-**9** as a pure product. Spectroscopic data for **9a-d** (white solids) are in good agreement with those previously published.[17] Yields obtained were: **9a** (90%), **9b** (88%), **9c** (60%), and **9d** (78%).

*4.3.1. (±)-5-Carboxy-4-(2-chloro-5-nitrophenyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(±)-**9e**]*

White solid, m.p.: 220-221 ºC; yield 90%; ν_{max}(KBr) 3245; 1709; 1676; 1622; 1525 cm^{-1}; δ_H (300.13 MHz, DMSO-d_6) 2.33 (d, 1H, $|^2J|$ 16.3 Hz, *H*H-3), 2.42 (s, 3H, CH_3), 3.10 (dd, 1H, ^3J 8.3, $|^2J|$ 16.5 Hz, H*H*-3), 4.54 (d, 1H, ^3J 8.0 Hz, H-4), 7.76 (d, 1H, ^4J 2.7 Hz, H-6'), 7.82 (br d, 1H, ^3J 8.7, H-4'), 8.13 (dd, 1H, ^4J 2.7, ^3J 8.7 Hz, H-3'), 10.10 (s, 1H, NH), 12.17 (br s, 1H, COOH); δ_C (75.5 MHz, DMSO-d_6) 18.1 (CH_3), 35.4 (C-4), 35.8 (C-3), 103.6 (C-5), 121.7 (CH), 123.7 (CH), 131.6 (C-3'), 139.5 (C), 141.3 (C), 146.7 (C), 149.8 (C), 167.6 (CO), 168.8 (C-2); HRMS (ESI^+): MH^+, found: 311.0429. $C_{13}H_{12}ClN_2O_5$ requires 311.0399.

*4.3.2. (±)-4-(4-Bromophenyl)-5-carboxy-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(±)-**9f**]*

White solid, m.p.: 199-201 ºC; yield 94%; ν_{max}(KBr) 3414; 1694; 1676; 1639; 1488 cm^{-1}; δ_H (300.13 MHz, DMSO-d_6) 2.31 (s, 3H, CH_3), 2.36 (d, 1H, $|^2J|$ 16.1 Hz, *H*H-3), 2.92 (dd, 1H, ^3J 7.8, $|^2J|$ 16.2 Hz, H*H*-3), 4.08 (d, 1H, ^3J 7.2 Hz, H-4), 7.10 (d, 2H, ^3J 8.4 Hz, H-2', H-6'), 7.48 (d, 2H, ^3J 8.5 Hz, H-3', H-5'), 9.84 (s, 1H, NH), 12.01 (s, 1H, COOH); δ_C (75.5 MHz, DMSO-d_6) 18.2 (CH_3), 37.1 (C-4), 38.2 (C-3), 105.0 (C-5), 119.5 (C-4'), 129.0 (C-2' and C-6'), 131.4 (C-3' and C-5'), 142.2 (C-1'), 148.0 (C-6), 168.1 (CO), 169.6 (C-2); MS ($APCI^+$), *m/z* (%) = 266 ($[(M+H) - CO_2]^+$, 100). Anal. calc. for $C_{13}H_{12}BrNO_3$: C, 50.34; H, 3.90; N, 4.52. Found: C, 50.12; H, 3.99; N, 4.78.

*4.3.3. (±)-5-Carboxy-4-(3-methoxyphenyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(±)-**9g**]*

White solid m.p.: 204-205 ºC; yield 76%; ν_{max}(KBr) 3448, 3212, 1695, 1673, 1639, 1599, 1489, and 1367 cm^{-1}; δ_H (300.13 MHz, DMSO-d_6) 2.31 (s, 3H, CH_3), 2.39 (d, 1H, $|^2J|$ 15.9 Hz, *H*H-3), 2.90 (dd, 1H, ^3J 7.8, $|^2J|$ 16.1 Hz, H*H*-3), 3.71 (s, 3H, OCH_3), 4.07 (d, 1H, ^3J 7.3 Hz, H-4), 6.80-6.65 (m, 3H, H-2', H-4', and H-6'), 7.20 (t, 1H, ^3J 7.9 Hz, H-5'), 9.78 (s, 1H, NH), 11.96 (s, 1H, COOH); δ_C (75.5 MHz, DMSO-d_6) 18.2 (CH_3), 37.5 (C-4), 38.4 (C-3), 54.9 (OCH_3), 105.3 (C-5), 111.3 (CH), 112.9 (CH), 118.7 (CH), 129.6 (CH), 144.4 (C), 147.6 (C), 159.4 (C-3'), 168.2 (CO), 169.7 (CO); HRMS (ESI^+): MH^+, found: 262.1074. $C_{14}H_{16}NO_4$ requires 262.1060.

*4.3.4. (±)-5-Carboxy-6-methyl-4-(1-naphthyl)-3,4-dihydro-2(1*H*)-pyridone [(±)-**9h**]*

White solid, m.p.: 200-201 ºC; yield 90%; ν_{max}(KBr) 3550, 3478, 3414, 3219, 1691, 1640, 1606, and 1486 cm^{-1}; δ_H (300.13 MHz, DMSO-d_6) 2.74-2.13 (m + s, 4H, *H*H-3 and singlet centered to 2.43 corresponding to CH_3), 3.10 (dd, 1H, ^3J 8.4, $|^2J|$ 16.1 Hz, H*H*-3), 4.97 (d, 1H, ^3J 8.0, H-4), 7.14 (d, 1H, ^3J 7.0 Hz, H-2'), 7.41 (t, 1H, ^3J 7.5 Hz, H-3'), 7.73-7.48 [m, 2H, H-6' and H-7'], 7.80 (d, 1H, ^3J 8.2 Hz, H-4'), 7.96 (d, 1H, ^3J 7.5 Hz, H-5'), 8.17 (d, 1H, ^3J 8.2 Hz, H-8'), 9.86 (s, 1H, NH), 11.92 (s, 1H, COOH); δ_C (75.5 MHz, DMSO-d_6) 18.3 (CH_3), 33.6 (C-4), 37.8 (C-3), 105.0 (C-5), 122.7 (CH), 123.1 (CH), 125.5 (CH), 125.6 (CH), 126.3 (CH), 127.2 (CH), 128.9 (CH), 130.2 (C), 134.0 (C), 137.1 (C), 148.7 (C), 168.2 (C-2), 169.5 (CO); HRMS (ESI^+): MH^+, found: 282.1125. $C_{17}H_{16}NO_3$ requires 282.1121.

4.4. *Synthesis of tert-butyl esters (±)-**10**.*

tert-Butyl esters (±)-**10** (up to a scale of 5.0 mmol) were prepared from *tert*-butyl acetoacetate (**7b**) following the procedure described for the synthesis of (±)-**8**, except that reactions were conducted at 80 ºC.

*4.4.1. (±)-5-(*tert*-Butoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydro-2(1*H*)-pyridone [(±)-**10a**]*

Reaction time: 11 h. White solid; mp 155-156 ºC; yield 61%; ν_{max}(KBr) 3414, 3218, 1690, 1634, 1483, 1384, and 1366 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 1.35 (s, 9H, Bu^t); 2.36 (s, 3H, CH_3), 2.68 (dd, 1H, ^3J 2.7, $|^2J|$ 16.5 Hz, *H*H-3), 2.92 (dd, 1H, ^3J 8.1, $|^2J|$ 16.5 Hz, H*H*-3), 4.18 (br d, 1H, ^3J 7.8 Hz, H-4), 7.32-7.12 (m, 5H, Ph), 7.56 (br s, 1H, NH); δ_C (75.5 MHz, $CDCl_3$) 19.1 (CH_3), 28.3 (3 × CH_3), 38.3 (C-3), 38.6 (C-4), 80.6 (C), 109.1 (C-5), 126.8 (CH), 126.9 (C-4'), 128.9 (CH), 142.7 (C), 144.7 (C), 166.3 (CO), 171.0 (C-2); HRMS (ESI^+): MH^+, found: 288.1594. $C_{17}H_{22}NO_3$ requires 288.1595.

*4.4.2. (±)-5-(*tert*-Butoxycarbonyl)-6-methyl-4-(2-nitrophenyl)-3,4-dihydro-2(1*H*)-pyridone [(±)-**10b**]*

Reaction time: 7 h. White solid; mp: 193-194 ºC (dec.); yield 69%; ν_{max}(KBr) 3480, 3416, 3220, 1699, 1671, 1638, 1524, and

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1365 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 1.20 (s, 9H, Bu^t); 2.44 (s, 3H, CH_3), 2.83 (dd, 1H, ^3J 2.7, $|^2J|$ 17.1 Hz, *H*H-3), 3.09 (dd, 1H, ^3J 9.2, $|^2J|$ 17.1 Hz, H*H*-3), 4.67 (br d, 1H, ^3J 9.1 Hz, H-4), 7.28 (dd, 1H, ^4J 1.4, ^3J 7.9 Hz, H-6'), 7.38 [dt, 1H, ^4J 1.4 (d), ^3J 8.1 (t), H-4'], 7.52 [dt, 1H, ^4J 1.4 (d), ^3J 7.9 (t), H-5'], 7.79 (br s, 1H, NH), 7.89 (dd, 1H, ^4J 1.4, ^3J 8.1 Hz, H-3'); δ_C (75.5 MHz, $CDCl_3$) 18.9 (CH_3), 28.1 (3 × CH_3), 34.6 (C-4), 37.4 (C-3), 80.9 (C), 107.7 (C-5), 125.0 (CH), 128.0 (CH), 128.4 (CH), 133.5 (CH), 137.8 (C), 146.8 (C), 149.1 (C), 165.5 (CO), 170.4 (C-2); HRMS (ESI^+): MH^+, found: 333.1445. $C_{17}H_{21}N_2O_5$ requires 333.1427.

*4.4.3. (±)-5-(*tert*-Butoxycarbonyl)-6-methyl-4-(3-nitrophenyl)-3,4-dihydro-2(1*H*)-pyridone [(±)-**10c**]*

Reaction time: 9 h. White solid; mp: 173-173.4 ºC; yield 72%; ν_{max}(KBr) 3554, 3470, 3414, 3227, 1701, 1640, 1618, 1526, 1366, and 1347 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 1.38 (s, 9H, Bu^t); 2.40 (s, 3H, CH_3), 2.69 (dd, 1H, ^3J 1.7, $|^2J|$ 16.7 Hz, *H*H-3), 2.99 (dd, 1H, ^3J 8.2, $|^2J|$ 16.7 Hz, H*H*-3), 4.29 (br d, 1H, ^3J 8.2 Hz, H-4), 7.57-7.40 (m, 2H, H-6' and H-5'), 7.71 (br s, 1H, NH), 8.14-8.02 (m, 2H, H-2' and H-4'); δ_C (75.5 MHz, $CDCl_3$) 19.3 (CH_3), 28.3 (3 × CH_3), 37.8 (C-3), 38.3 (C-4), 81.2 (C), 107.9 (C-5), 122.1 (CH), 122.2 (CH), 129.9 (CH), 133.0 (CH), 144.8 (C), 145.9 (C), 148.6 (C), 165.8 (CO), 170.2 (C-2); HRMS (ESI^+): MH^+, found: 333.1445. $C_{17}H_{21}N_2O_5$ requires 333.1435.

*4.4.4. (±)-5-(*tert*-Butoxycarbonyl)-6-methyl-4-(4-nitrophenyl)-3,4-dihydro-2(1*H*)-pyridone [(±)-**10d**]*

Reaction time: 9 h. White solid; mp 230-232 ºC; yield 73%; ν_{max}(KBr) 3413, 3223, 1698, 1637, 1521, and 1349 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 1.36 (s, 9H, Bu^t); 2.40 (s, 3H, CH_3), 2.65 (dd, 1H, ^3J 1.6, $|^2J|$ 16.6 Hz, *H*H-3), 2.98 (dd, 1H, ^3J 8.3, $|^2J|$ 16.6 Hz, H*H*-3), 4.29 (br d, 1H, ^3J 8.2 Hz, H-4), 7.35 (d, 2H, ^3J 8.6 Hz, H-2' and H-6'), 7.71 (br s, 1H, NH), 8.16 (d, 2H, ^3J 8.6 Hz, H-3' and H-5'); δ_C (75.5 MHz, $CDCl_3$) 19.3 (CH_3), 28.3 (3 × CH_3), 37.7 (C-3), 38.6 (C-4), 81.2 (C), 107.8 (C-5), 124.2 (CH), 127.8 (CH), 145.8 (C), 147.1 (C), 150.3 (C), 165.8 (CO), 170.1 (C-2); HRMS (ESI^+): MH^+, found: 333.1445. $C_{17}H_{21}N_2O_5$ requires 333.1449.

*4.4.5. (±)-5-(*tert*-Butoxycarbonyl)-4-(2-chloro-5-nitrophenyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(±)-**10e**]*

Reaction time: 5 h. White solid, mp 226-228 ºC; yield 74%; ν_{max}(KBr) 3551, 3473, 3413, 3224, 1700, 1630, 1523, and 1343 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 1.31 (s, 9H, Bu^t); 2.49 (s, 3H, CH_3), 2.66 (br d, 1H, $|^2J|$ 16.8 Hz, *H*H-3), 2.96 (dd, 1H, ^3J 8.6, $|^2J|$ 16.8 Hz, H*H*-3), 4.68 (br d, 1H, ^3J 8.2 Hz, H-4), 7.57 (d, 1H, ^3J 8.7 Hz, H-3'), 7.59 (br s, 1H, NH), 7.89 (d, 1H, ^4J 2.6 Hz, H-6'), 8.06 (dd, 1H, ^4J 2.6, ^3J 8.7 Hz, H-4'); δ_C (75.5 MHz, $CDCl_3$) 19.1 (CH_3), 28.2 (3 × CH_3), 35.97 (C-3), 36.02 (C-4), 81.1 (C), 106.6 (C-5), 122.5 (CH), 123.4 (CH), 131.1 (CH), 140.4 (C), 141.4 (C), 147.1 (C), 147.4 (C), 165.4 (CO), 169.6 (C-2); HRMS (ESI^+): MH^+, found: 367.1055. $C_{17}H_{20}ClN_2O_5$ requires 367.1063.

*4.4.6. (±)-4-(4-Bromophenyl)-5-(*tert*-butoxycarbonyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(±)-**10f**]*

Reaction time: 4 h. White solid, mp 186-187 ºC; yield 88%; ν_{max}(KBr) 3216, 1687, 1630, 1484, 1380, and 1365 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 1.36 (s, 9H, Bu^t); 2.36 (s, 3H, CH_3), 2.62 (dd, 1H, ^3J 1.9, $|^2J|$ 16.5 Hz, *H*H-3), 2.91 (dd, 1H, ^3J 8.1, $|^2J|$ 16.5 Hz, H*H*-3), 4.14 (br d, 1H, ^3J 8.1 Hz, H-4), 7.05 (d, 2H, ^3J 8.4 Hz, H-2' and H-6'), 7.39 (d, 2H, ^3J 8.4 Hz, H-3' and H-5'), 7.64 (br s, 1H, NH); δ_C (75.5 MHz, $CDCl_3$) 19.3 (CH_3), 28.3 (3 × CH_3), 38.06 (C-3), 38.11 (C-4), 80.9 (C), 108.6 (C-5), 120.8 (C), 128.6 (2 × CH), 131.9 (2 × CH), 141.6 (C), 144.9 (C), 166.1 (CO), 170.3 (C-2); HRMS (ESI^+): MH^+, found: 366.0699. $C_{17}H_{21}BrNO_3$ requires 366.0683.

*4.4.7. (±)-5-(*tert*-Butoxycarbonyl)-4-(3-methoxyphenyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(±)-**10g**]*

Reaction time: 10 h. White solid; mp: 145-146 ºC; yield 84%; ν_{max}(KBr) 3480, 3414, 3219, 1699, 1686, and 1634 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 1.36 (s, 9H, Bu^t); 2.35 (s, 3H, CH_3), 2.67 (dd, 1H, ^3J 2.6, $|^2J|$ 16.5 Hz, *H*H-3), 2.90 (dd, 1H, ^3J 8.1, $|^2J|$ 16.5 Hz, H*H*-3), 3.77 (s, 3H, O-CH_3), 4.16 (br d, 1H, ^3J 8.1 Hz, H-4), 6.81-6.69 (m, 3H, H-2', H-4', and H-6'), 7.19 (t, 1H, ^3J 7.9 Hz, H-5'), 7.53 (br s, 1H, NH); δ_C (75.5 MHz, $CDCl_3$) 19.2 (CH_3), 28.3 (3 × CH_3), 38.2 (C-3), 38.6 (C-4), 55.3 (O-CH_3), 80.6 (C), 109.0 (C-5), 111.9 (CH), 113.0 (CH), 119.2 (CH), 129.8 (CH), 144.3 (C), 144.7 (C), 159.9 (C-3') 166.3 (CO), 170.8 (C-2); HRMS (ESI^+): MH^+, found: 318.1700. $C_{18}H_{24}NO_4$ requires 318.1704.

*4.4.8. (±)-5-(*tert*-Butoxycarbonyl)-6-methyl-4-(1-naphthyl)-3,4-dihydro-2(1*H*)-pyridone [(±)-**10h**]*

Reaction time: 6 h. White solid, mp: 235-236 ºC; yield 92%; ν_{max}(KBr) 3216, 1694, 1645, 1526, 1366, and 1347 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 1.15 (s, 9H, Bu^t); 2.46 (s, 3H, CH_3), 2.76 (dd, 1H, ^3J 2.6, $|^2J|$ 16.4 Hz, *H*H-3), 3.05 (dd, 1H, ^3J 8.7, $|^2J|$ 16.4 Hz, H*H*-3), 5.06 (br d, 1H, ^3J 8.7 Hz, H-4), 7.21 (d, 1H, ^3J 6.9 Hz, H-2'), 7.35 (dd, 1H, ^3J 7.3, 8.0 Hz, H-3'), 7.60-7.44 (m, 2H, H-6' and H-7'), 7.62 (br s, 1H, NH), 7.73 (d, 1H, ^3J 8.1 Hz, H-4'), 7.86 (dd, 1H, ^3J 7.8, ^4J 1.5 Hz, H-5'), 8.06 (d, 1H, ^3J 8.4 Hz, H-8'); δ_C (75.5 MHz, $CDCl_3$) 19.1 (CH_3), 28.1 (3 × CH_3), 34.3 (C-4), 37.6 (C-3), 80.5 (C), 108.7 (C-5), 122.8 (CH), 123.2 (CH), 125.6 (2 × CH), 126.3 (CH), 127.7 (CH), 129.3 (CH), 130.8 (C), 134.5 (C), 137.2 (C), 145.6 (C), 166.2 (CO), 170.6 (C-2); HRMS (ESI^+): MH^+, found: 338.1751. $C_{21}H_{24}NO_3$ requires 318.1745.

4.5. *General procedure for tert-butyl group removing of (±)-**10**.*

A solution of the corresponding *tert*-butyl ester (±)-**10** (1.0 mmol) in dichloromethane (2.0 mL) was cooled at 0 ºC, and anisole (0.48 mL, 4.4 mmol) and trifluoroacetic acid (1.89 mL) were added. The solution was stirred at 0 ºC until disappearance of the starting material (TLC monitoring). Then, organic solvent and trifluoroacetic acid were eliminated under reduced pressure. The resulting residue was dissolved in dichloromethane (15 mL) and extracted with aq saturated $NaHCO_3$ (2 × 10 mL). The organic phase was discarded. Conc. aq HCl was added to the aqueous phase until pH was 1-2. The resulting acid aqueous phase was extracted with dichloromethane (3 x 15 mL). The organic layers were combined, washed with brine (20 mL), dried with Na_2SO_4, and evaporated under reduced pressure to give the corresponding carboxylic acid (±)-**9** as a pure product. Yields obtained were: **9a** (85%), **9b** (76%), **9c** (81%), **9d** (68%), **9e** (72%), **9f** (74%), **9g** (91%), and **9h** (90%).

4.6. *General procedure for the synthesis of diesters (±)-**5**.*

Carboxylic acid (±)-**9** (5.18 mmol) was dissolved in *N*,*N*-dimethylformamide (15.5 mL). Cesium carbonate (4.14 mmol) was added to the solution and the suspension was stirred during 2-3 min after which chloromethyl 2-methylpropanoate (6.73 mmol) was added. After stirring at room temperature during 18-24 h, dichloromethane (30 mL) was added to the mixture and the resulting organic phase was successively washed with water (3 x 20 mL) and brine (3 x 20 mL). Organic solvent was eliminated and the residue was submitted to flash chromatography (hexane/ethyl acetate mixtures) to yield the corresponding diester (±)-**5.**

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*4.6.1. (±)-6-Methyl-5-[(2-methylpropanoyloxy)methyloxycarbonyl]-4-phenyl-3,4-dihydro-2(1H)-pyridone [(±)-**5a**]*

Reaction time: 22 h. White solid, mp 157-160 ºC; yield 83%; ν_{max}(KBr) 3210; 1758; 1716; 1690; 1628; 1492 cm^{-1}, δ_H (300.13 MHz, $CDCl_3$) 1.13-1.02 [6H, two overlapped d centered to 1.09 (^3J 7.0 Hz) and 1.06 (^3J 7.0 Hz), CH-(C*H*$_3$)$_2$], 2.52-2.39 [m + s, 4H, C*H*$(CH_3)_2$ and singlet centered to 2.42 corresponding to CH_3], 2.71 (br d, 1H, $|^2J|$ 16.6 Hz, *H*H-3), 2.94 (dd, 1H, ^3J 8.2, $|^2J|$ 16.6 Hz, H*H*-3), 4.26 (br d, 1H, ^3J 7.9 Hz, H-4), 5.75 (AB system, $|^2J|$ 5.5 Hz, O-CH_2-O), 7.30-7.11 (m, 5H, Ph), 7.80 (br s, 1H, NH); δ_C (75.5 MHz, $CDCl_3$) 18.7 (CH_3), 19.5 (CH_3), 33.8 (CH), 37.7 (C-4), 38.1 (C-3), 79.0 (CH_2), 106.0 (C-5), 126.8 (CH), 127.2 (C-4'), 129.0 (CH), 141.9 (C), 148.7 (C-6), 165.3 (CO), 171.1 (C-2), 175.9 (CO); HRMS (ESI^+): MH^+, found: 332.1492. $C_{18}H_{22}NO_5$ requires 332.1446.

*4.6.2. (±)-6-Methyl-5-[(2-methylpropanoyloxy)methyloxycarbonyl]-4-(2-nitrophenyl)-3,4-dihydro-2(1H)-pyridone [(±)-**5b**]*

Reaction time: 18 h. White solid, mp 155-156 ºC; yield 78%; ν_{max}(KBr) 3436; 3312; 1745; 1714; 1703; 1624; 1527 cm^{-1}, δ_H (300.13 MHz, DMSO-d_6) 1.00-0.88 [6H, two overlapped d centered to 0.96 (^3J 7.0 Hz) and 0.93 (^3J 7.0 Hz), CH-(C*H*$_3$)$_2$], 2.50-2.33 [m + s, 5H, C*H*$(CH_3)_2$, *H*H-3, and singlet centered to 2.39 corresponding to CH_3], 3.18 (dd, 1H, ^3J 8.9, $|^2J|$ 16.5 Hz, H*H*-3), 4.50 (br d, 1H, ^3J 8.6 Hz, H-4), 5.57 (AB system, $|^2J|$ 5.9 Hz, O-CH_2-O), 7.25 (dd, 1H, ^4J 1.3, ^3J 7.7 Hz, H-6'), 7.50 [dt, 1H, ^4J 1.3 (d), ^3J 8.0 (t), H-4'], 7.64 [dt, 1H, ^4J 1.4 (d), ^3J 7.7 (t), H-5'], 7.93 (dd, 1H, ^4J 1.3, ^3J 8.0 Hz, H-3'), 10.26 (br s, 1H, NH); δ_C (75.5 MHz, DMSO-d_6) 18.2 (CH_3), 18.4 (CH_3), 32.8 (CH), 33.2 (C-4), 37.0 (C-3), 78.8 (CH_2), 102.3 (C-5), 124.8 (CH), 127.8 (CH), 128.3 (CH), 133.7 (CH), 136.5 (C), 148.4 (C), 152.3 (C), 164.4 (CO), 168.9 (C-2), 174.6 (CO); MS (EI), *m/z* (%) = 259 ([M – $OCH_2OC(O)^iPr]^+$, 97), 197 (100), 71 (98). Anal. calc. for $C_{18}H_{20}N_2O_7$: C, 57.44; H, 5.36; N, 7.44. Found: C, 57.72; H, 5.27; N, 7.53.

*4.6.3. (±)-6-Methyl-5-[(2-methylpropanoyloxy)methyloxycarbonyl]-4-(3-nitrophenyl)-3,4-dihydro-2(1H)-pyridone [(±)-**5c**]*

Reaction time: 24 h. White solid; m.p. 126-127 ºC; yield 85%; ν_{max}(KBr) 3229; 1749; 1719; 1631; 1531 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 1.07 [m, 6H, (C*H*$_3$)$_2$CH], 2.59-2.39 [m + s, 4H, C*H*$(CH_3)_2$ and singlet centered to 2.47 corresponding to CH_3], 2.71 (br d, 1H, ^2J 16.7 Hz, *H*H-3), 3.03 (dd, 1H, ^3J 8.3, $|^2J|$ 16.6 Hz, H*H*-3), 4.38 (br d, 1H, ^3J 7.9 Hz, H-4), 5.73 (AB system, $|^2J|$ 5.7 Hz, O-CH_2-O), 7.57-7.47 (m, 2H, H-5' and H-6'), 8.01 (s, 1H, H-2'), 8.09 (dd, 1H, ^3J 7.7, ^4J 0.9 Hz, H-4'), 8.16 (br s, 1H, NH); δ_C (75.5 MHz, $CDCl_3$) 18.7 (CH_3), 19.7 (CH_3), 33.8 (CH), 37.6 (C-4), 37.8 (C-3), 79.2 (CH_2), 104.9 (C-5), 121.8 (C-4'), 122.5 (C-2'), 130.1 (C-5'), 133.2 (C-6'), 144.1 (C-1'), 148.8 (C-3'), 149.7 (C-6), 164.9 (CO), 170.0 (C-2), 175.8 (CO); MS (EI), *m/z* (%) = 376 ($M^{\bullet+}$, 11) 259 ([M – $OCH_2OC(O)^iPr]^+$, 100); HRMS (EI): $M^{\bullet+}$ found: 376.1281. $C_{18}H_{20}N_2O_7$ requires 376.1271.

*4.6.4. (±)-6-Methyl-5-[(2-methylpropanoyloxy)methyloxycarbonyl]-4-(4-nitrophenyl)-3,4-dihydro-2(1H)-pyridone [(±)-**5d**]*

Reaction time: 22 h. White solid, m.p. 155-156 ºC; yield 84%; ν_{max}(KBr) 3318; 1753; 1735; 1692; 1634; 1516 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 1.12-1.00 [6H, two overlapped d centered to 1.08 (^3J 7.0 Hz) and 1.05 (^3J 7.0 Hz), CH-(C*H*$_3$)$_2$], 2.54-2.40 [m + s, 4H, C*H*$(CH_3)_2$ and singlet centered to 2.46 corresponding to CH_3], 2.70 (br d, 1H, $|^2J|$ 16.8 Hz, *H*H-3), 3.01 (dd, 1H, ^3J 8.4, $|^2J|$ 16.8 Hz, H*H*-3), 4.36 (br d, 1H, ^3J 8.3 Hz, H-4), 5.74 (AB system, $|^2J|$ 5.7 Hz, O-CH_2-O), 7.34 (d, 2H, ^3J 8.6 Hz, H-2' and H-6'), 8.12 (br s, 1H, NH), 8.14 (d, 2H, ^3J 8.6 Hz, H-3' and H-5'); δ_C (75.5 MHz, $CDCl_3$) 18.7 (CH_3), 19.8 (CH_3), 33.8 (CH), 37.5 (C-3), 37.8 (C-4), 79.1 (CH_2), 104.9 (C-5), 124.3 (CH), 127.9 (CH), 147.3 (C), 149.46 (C), 149.50 (C), 164.9 (CO), 169.9 (C-2), 175.9 (CO); HRMS (ESI): MH^+ found: 377.1343. $C_{18}H_{21}N_2O_7$ requires 377.1335.

*4.6.5. (±)-4-(2-Chloro-5-nitrophenyl)-6-methyl-5-[(2-methylpropanoyloxy)methyloxycarbonyl]- 3,4-dihydro-2(1H)-pyridone [(±)-**5e**]*

Reaction time: 23 h. White solid, 154-155 ºC, yield 81%; ν_{max}(KBr) 3420; 1759; 1709; 1681; 1636; 1524 cm^{-1}; δ_H (300.13 MHz, DMSO-d_6) 0.97-0.85 [6H, two overlapped d centered to 0.93 (^3J 7.0 Hz) and 0.90 (^3J 6.9 Hz), CH-(C*H*$_3$)$_2$], 2.51-2.31 [m + s, 5H, C*H*$(CH_3)_2$, *H*H-3, and singlet centered to 2.44 corresponding to CH_3], 3.16 (dd, 1H, ^3J 8.5, $|^2J|$ 16.7 Hz, H*H*-3), 4.55 (br d, 1H, ^3J 8.1 Hz, H-4), 5.62 (AB system, $|^2J|$ 5.8 Hz, O-CH_2-O), 7.72 (d, 1H, ^4J 2.7 Hz, H-6'), 7.81 (d, 1H, ^3J 8.7 Hz, H-3'), 8.13 (dd, 1H, ^4J 2.7, ^3J 8.7 Hz, H-4'), 10.35 (s, 1H, NH), δ_C (75.5 MHz, DMSO-d_6) 18.2 (CH_3), 18.3 (CH_3), 32.8 (CH), 34.9 (C-4), 35.6 (C-3), 78.8 (CH_2), 101.4 (C-5), 121.5 (CH), 123.6 (CH), 131.6 (CH), 139.4 (C), 140.9 (C), 146.6 (C), 152.7 (C), 164.3 (CO), 168.6 (C-2), 174.7 (CO); HRMS (ESI^+): MH^+, found: 411.0954. $C_{18}H_{20}ClN_2O_7$ requires 411.0931.

*4.6.6. (±)-4-(4-Bromophenyl)-6-methyl-5-[(2-methylpropanoyloxy)methyloxycarbonyl]- 3,4-dihydro-2(1H)-pyridone [(±)-**5f**]*

Reaction time: 24 h. White solid, 134-135 ºC; yield 83%; ν_{max}(KBr) 3418; 1760; 1721; 1695; 1626; 1490 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 1.14-1.00 [6H, two overlapped d centered to 1.09 (^3J 7.0 Hz) and 1.07 (^3J 7.0 Hz), CH-(C*H*$_3$)$_2$], 2.55-2.39 [m + s, 4H, C*H*$(CH_3)_2$ and singlet centered to 2.43 corresponding to CH_3], 2.66 (br d, 1H, $|^2J|$ 16.6 Hz, *H*H-3), 2.94 (dd, 1H, ^3J 8.1, $|^2J|$ 16.6 Hz, H*H*-3), 4.21 (br d, 1H, ^3J 7.8 Hz, H-4), 5.74 (AB system, $|^2J|$ 5.6 Hz, O-CH_2-O), 7.03 (d, 2H, ^3J 8.3 Hz, H-2' and H-6'), 7.38 (d, 2H, ^3J 8.5 Hz, H-3' and H-5'), 7.69 (br s, 1H, NH); δ_C (75.5 MHz, $CDCl_3$) 18.7 (CH_3), 19.6 (CH_3), 33.8 (CH), 37.3 (C-4), 37.9 (C-3), 79.0 (CH_2), 105.5 (C-5), 121.1 (C), 128.6 (2 × CH), 132.0 (2 × CH), 140.9 (C), 149.0 (C), 165.1 (CO), 170.8 (C-2), 175.9 (CO); HRMS (ESI): MH^+ found: 410.0598. $C_{18}H_{21}BrNO_5$ requires 410.0606.

*4.6.7. (±)-4-(3-Methoxyphenyl)-6-methyl-5-[(2-methylpropanoyloxy)methyloxycarbonyl]- 3,4-dihydro-2(1H)-pyridone [(±)-**5g**]*

Reaction time: 18 h. White solid; mp 105-107 ºC; yield 91%; ν_{max}(KBr) 3412; 1752; 1714; 1694; 1629; 1585 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 1.14-1.03 [6H, two overlapped d centered to 1.09 (^3J 7.0 Hz) and 1.07 (^3J 7.0 Hz), CH-(C*H*$_3$)$_2$], 2.42 (s, 3H, CH_3), 2.25 [septet, 1H, ^3J 7.0 Hz, C*H*$(CH_3)_2$], 2.71 (br d, 1H, $|^2J|$ 16.6 Hz, *H*H-3), 2.93 (dd, 1H, ^3J 8.1, $|^2J|$ 16.6 Hz, H*H*-3), 3.77 (s, 3H, O-CH_3), 4.24 (br d, 1H, ^3J 8.1 Hz, H-4), 5.75 (AB system, $|^2J|$ 5.6 Hz, O-CH_2-O), 6.80-6.65 (m, 3H, H-2', H-4', and H-6'), 7.18 (t, 1H, ^3J 7.9 Hz, H-5'), 7.65 (br s, 1H, NH); δ_C (75.5 MHz, $CDCl_3$) 18.7 (2 × CH_3), 19.5 (CH_3), 33.8 (CH), 37.7 (CH), 38.1 (C-3), 55.2 (O-CH_3), 79.0 (CH_2), 105.8 (C-5), 111.9 (CH), 113.1 (CH), 119.1 (CH), 129.9 (CH), 143.5 (C), 148.9 (C), 159.9 (C-3') 165.3 (CO), 171.1 (C-2), 175.9 (CO); HRMS (ESI): $[M+Na]^+$ found: 384.1418. $C_{19}H_{23}NNaO_6$ requires 384.1426.

*4.6.8. (±)-6-Methyl-5-[(2-methylpropanoyloxy)methyloxycarbonyl]-4-(1-naphthyl)-3,4-dihydro-2(1H)-pyridone [(±)-**5h**]*

Reaction time: 24 h. White solid, mp 164-166 ºC; yield 79%; ν_{max}(KBr) 3413; 1750; 1710; 1703; 1675; 1631 cm^{-1}; δ_H (300.13 MHz, $CDCl_3$) 0.96-0.81 [6H, two d centered to 0.92 (^3J 7.0 Hz)

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and 0.87 (^3J 7.0 Hz), CH-(CH_3)$_2$], 2.27 [septet, 1H, ^3J 7.0 Hz, CH(CH$_3$)$_2$], 2.50 (s, 3H, CH$_3$), 2.81 (br d, 1H, $|^2J|$ 16.4 Hz, *H*H-3), 3.07 (dd, 1H, ^3J 8.6, $|^2J|$ 16.4 Hz, H*H*-3), 5.13 (br d, 1H, ^3J 8.6 Hz, H-4), 5.63 (s, 2H, O-CH$_2$-O), 7.15 (d, 1H, ^3J 6.6 Hz, H-2'), 7.33 (dd, 1H, ^3J 7.2, 8.2 Hz, H-3'), 7.64-7.43 (m, 2H, H-6' and H-7'), 7.73 (d, 1H, ^3J 8.2 Hz, H-4'), 7.87 (dd, 1H, ^3J 7.9, ^4J 1.4 Hz, H-5'), 8.04 (d, 1H, ^3J 8.4 Hz, H-8'), 8.14 (br s, 1H, NH); δ_C (75.5 MHz, CDCl$_3$) 18.5 (CH$_3$), 19.6 (CH$_3$), 33.56 (CH), 33.62 (CH), 37.4 (C-3), 79.3 (CH$_2$), 105.5 (C-5), 122.8 (CH), 123.1 (CH), 125.5 (CH), 125.7 (CH), 126.6 (CH), 128.1 (CH), 129.3 (CH), 130.6 (C), 134.7 (C), 135.9 (C), 149.5 (C), 165.3 (CO), 170.5 (C-2), 175.6 (CO); HRMS (ESI): MH$^+$ found: 382.1649. $C_{22}H_{24}NO_5$ requires 382.1650.

4.7. *(±)-5-(Acetoxymethyloxycarbonyl)-6-methyl-4-(3-nitrophenyl)-3,4-dihydro-2-(1*H*)-pyridone [(±)-**11**]*

It was obtained from (±)-**9a** (1.1 mmol) and chloromethyl acetate (1.4 mmol) following the general procedure for the synthesis of diesters (±)-**5**. Flash chromatography (hexane/ethyl acetate 2:1) yielded pure (±)-**11** (230 mg, 60%) as a white solid; mp 131-132 ºC; ν_{max}(KBr) 3229; 1752; 1720; 1628; 1517 cm^{-1}; δ_H (300.13 MHz, CDCl$_3$) 2.01 (s, 3H, CH$_3$), 2.48 (s, 3H, CH$_3$), 2.72 (br d, 1H, ^2J 16.7 Hz, *H*H-3), 3.02 (dd, 1H, ^3J 8.2, $|^2J|$ 16.7 Hz, H*H*-3), 4.37 (br d, 1H, ^3J 7.9 Hz, H-4), 5.73 (s, 2H, O-CH$_2$-O), 7.57-7.46 (m, 2H, H-5' and H-6'), 7.86 (br s, 1H, NH), 8.01 (s, 1H, H-2'), 8.09 (br d, 1H, ^3J 7.9 Hz, H-4'); δ_C (75.5 MHz, CDCl$_3$) 18.5 (CH$_3$), 20.3 (CH$_3$), 36.9 (C-4), 37.7 (C-3), 78.7 (CH$_2$), 102.5 (C-5), 121.3 (C-4'), 121.8 (C-2'), 130.2 (C-5'), 133.4 (C-6'), 144.9 (C-1'), 148.0 (C-3'), 151.8 (C-6), 164.7 (CO), 169.2 (C), 169.3 (C); MS (EI), *m/z* (%) = 348 (M$^{\bullet+}$, 14), 259 ([M – OCH$_2$OC(O)CH$_3$]$^+$, 100); HRMS (CI): MH$^+$ found 349.1035. $C_{16}H_{17}N_2O_7$ requires 349.1036.

4.8. *(±)-5-[(2,2-Dimethylpropanoyloxy)methyloxycarbonyl]-6-methyl-4-(3-nitrophenyl)-3,4-dihydro-2(1*H*)-pyridone [(±)-**12**]*

It was prepared as described for (±)-**5c** from (±)-**9a** (0.60 mmol) and chloromethyl 2,2-dimethylpropanoate (0.78 mmol). Flash chromatography (hexane/ethyl acetate 2:1) yielded pure (±)-**12** (103 mg, 44%) as a white solid; mp 168-170 ºC; ν_{max}(KBr) 3211; 1749; 1725; 1631; 1510 cm^{-1}; δ_H (300.13 MHz, DMSO-d$_6$) 0.97 (s, 9H, Bu^t), 2.38 (s, 3H, CH$_3$), 2.55-2.44 (m, 1H, *H*H-3), 3.05 (dd, 1H, ^3J 8.0, $|^2J|$ 16.6 Hz, H*H*-3), 4.28 (br d, 1H, ^3J 7.7 Hz, H-4), 5.67 (AB system, $|^2J|$ 5.8 Hz, O-CH$_2$-O), 7.65-7.55 (m, 2H, H-5' and H-6'), 8.01 (br s, 1H, H-2'), 8.08 (m, 1H, H-4'), 10.20 (br s, 1H, NH),); δ_C (75.5 MHz, CDCl$_3$) 18.4 (CH$_3$), 26.3 (3 × CH$_3$), 36.9 (C-4), 37.8 (C-3), 38.0 (C), 78.9 (CH$_2$), 102.4 (C-5), 121.2 (C-4'), 121.8 (C-2'), 130.2 (C-5'), 133.4 (C-6'), 144.9 (C-1'), 147.9 (C-3'), 151.7 (C-6), 164.7 (CO), 169.2 (C-2), 176.2 (CO); MS (EI), *m/z* (%) = 390 (M$^{\bullet+}$, 8), 259 ([M – OCH$_2$OC(O)^{t}Bu]$^+$, 100), 57 (^{t}Bu$^+$, 54); HRMS (CI): MH$^+$ found 391.1517. $C_{19}H_{23}N_2O_7$ requires 391.1505.

4.9. *General procedure for the enzymatic hydrolysis reactions.*

Compound (±)-**5** was dissolved in *tert*-butyl methyl ether (TBME) previously saturated with water. CAL-B was added to this solution, and the mixture was shaken at 28 ºC and 200 rpm. After the time collected in Table 3, the enzyme was filtered and thoroughly washed with methanol. Solvents were eliminated under reduced pressure and the residue was dissolved with ethyl acetate. 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$_2$SO$_4$ and concentrated in *vacuo* to give the optically active remaining substrate (*S*)-**5**. On the other hand, the basic aqueous phase containing the produced carboxylic acid (*R*)-**9** was acidified with aq 3 M HCl (pH = 1-2) and subsequently extracted with ethyl acetate (three times). The normal work-up of this new organic phase gave the corresponding acid (*R*)-**9**.

4.10. *Enzymatic hydrolysis of (±)-**5a*** (Table 3, entry 1).

To a solution of (±)-**5a** (100 mg, 0.30 mmol) in TBME (10 mL), CAL-B (100 mg) was added and the mixture was shaken at 28 ºC and 200 rpm during 9 h. After, the general procedure was followed. Thus, the remaining substrate (*S*)-**5a** was isolated with 56% yield (56 mg) and 32% ee. The product (*R*)-**9a** was isolated with 39% yield (27 mg) and 47% ee.

*4.10.1. Enantioenrichment of the enzymatically produced (S)-**5a** and (R)-**9a**.*

Substrate (*S*)-**5a** (55 mg, 32% ee) was dissolved in diethyl ether (2.0 mL) at room temperature. After cooling at –15 ºC during 30 min, the formed solid was filtered. The ee of this solid (40 mg) was 5% (*S*). In addition, from the removal of the solvent of the filtrate, 13 mg of enantioenriched (*S*)-**5a** (99% ee) was recovered as a viscous oil: $[\alpha]_D^{20}$ +64.9 (*c* 0.65, CHCl$_3$).

The product (*R*)-**9a** (26 mg, 47% ee) was dissolved in methanol (3.0 mL). After cooling at –15 ºC during 4 h, the formed solid was filtered. The ee of this solid (8 mg) was 31% (*R*). In addition, from the removal of the solvent of the filtrate, 17 mg of slightly enantioenriched (*R*)-**9a** (55% ee) was recovered as white solid, $[\alpha]_D^{20}$ –17.4 (*c* 0.85, DMSO), ee 55%.

4.11. *Enzymatic hydrolysis of (±)-**5c*** (Table 3, entry 2)

To a solution of (±)-**5c** (1.00 g, 2.66 mmol) in TBME (100 mL), CAL-B (1.00 g) was added and the mixture was shaken at 28 ºC and 200 rpm during 9 h. After following the general procedure, the remaining substrate (*S*)-**5c** was isolated with 47% yield (470 mg) and 73% ee. The product (*R*)-**9c** was isolated with 48% yield (352 mg) and 71% ee.

*4.11.1. Enantioenrichment of the enzymatically produced (S)-**5c** and (R)-**9c**.*

A solution of (*S*)-**5c** (469 mg, 73% ee) in diethyl ether (13 mL) was maintained at room temperature during 36 h. The crystallized solid was filtered (90 mg, 2% ee). Removal of the solvent of the filtrate gave 319 mg of compound (*S*)-**5c** with 95% ee; $[\alpha]_D^{20}$ = +101.5 (*c* 1.0, CHCl$_3$).

A partially enantioenriched sample of product (*R*)-**9c** (408 mg, 1.48 mmol, 67% ee) was converted into (*R*)-**5c** (484 mg, 87% yield) as described for the racemic mixture. After incubation of a solution of (*R*)-**5c** (482 mg, ee$_o$ = 67%) in TBME (48 mL) with CAL-B (482 mg) during 3 h (Table 3, entry 8), the acid (*R*)-**9c** (184 mg, 52% yield) was isolated with 95% ee, $[\alpha]_D^{20}$ = –142.6 (*c* 0.50, MeOH).

4.12. *Enzymatic hydrolysis of (±)-**5f*** (Table 3, entries 3 and 6)

To a solution of (±)-**5f** (200 mg, 0.488 mmol) in TBME (20 mL), CAL-B (200 mg) was added and the mixture was shaken at 28 ºC and 200 rpm during 11 h (Table 3, entry 3). After following the general procedure, the remaining substrate (*S*)-**5f** was isolated with 46% yield (92 mg) and 71% ee. The product (*R*)-**9f** was isolated with 46% yield (70 mg) and 64% ee.

When the enzymatic hydrolysis of (±)-**5f** (100 mg) was maintained during 18 h (Table 3, entry 6), the remaining substrate (*S*)-**5f** (31 mg, 31% yield) was isolated with 93% ee; $[\alpha]_D^{20}$ = +73.6 (*c* 1.0, CHCl$_3$).

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*4.12.1. Enantioenrichment of the enzymatically produced (R)-**9f**.*

A partially enantioenriched sample of acid (*R*)-**9f** (99 mg, 0.32 mmol, 62% ee) was converted into (*R*)-**5f** (106 mg, 81% yield) as described for the racemic mixture. After incubation of a solution of (*R*)-**5f** (105 mg, ee_o = 62%) in TBME (10 mL) with CAL-B (105 mg) during 2.5 h (Table 3, entry 9), the acid (*R*)-**9f** (33 mg, 41% yield) was isolated with 93% ee, $[\alpha]_D^{20}$ = –82.3 (*c* 0.40, MeOH).

4.13. *Enzymatic hydrolysis of (±)-**5g*** (Table 3, entries 4 and 7)

To a solution of (±)-**5g** (100 mg, mmol) in TBME (10 mL), CAL-B (100 mg) was added and the mixture was shaken at 28 ºC and 200 rpm during 7 h (Table 3, entry 4). After following the general procedure, the remaining substrate (*S*)-**5g** was isolated with 48% yield (48 mg) and 69% ee. The product (*R*)-**9c** was isolated with 48% yield (35 mg) and 66% ee.

When the enzymatic hydrolysis of (±)-**5g** (100 mg) was allowed to react during 12 h (Table 3, entry 7), the substrate (*S*)-**5g** (30 mg, 30% yield) was isolated with 95% ee; $[\alpha]_D^{20}$ = +72.6 (*c* 0.50, $CHCl_3$).

*4.13.1. Enantioenrichment of the enzymatically produced (R)-**9g**.*

A partially enantioenriched sample of acid (*R*)-**9g** (120 mg, 0.460 mmol, 57% ee) was converted into (*R*)-**5g** (148 mg, 89% yield) as described for the racemic mixture. After incubation of a solution of (*R*)-**5g** (148 mg, ee_o = 57%) in TBME (15 mL) with CAL-B (148 mg) during 2 h (Table 3, entry 10), the acid (*R*)-**9g** (52 mg, 49% yield) was isolated with 91% ee, $[\alpha]_D^{20}$ = –64.2 (*c* 0.90, DMSO).

4.14. *Determination of the enantiomeric excesses.*

Enantioselective HPLC was used for the determination of the enantiomeric excesses of compounds **5** and **9**. Previously to the measurement, carboxylic acids **9** were transformed into the corresponding methyl ester **3** by treatment with diazomethane. HPLC-conditions and chromatograms are included in the Supplementary Material.

4.15. *Assignment of the configuration: synthesis of (R)-**3f**.*

Optically active (*R*)-**9f** (ee = 93%; 29 mg, 0.094 mmol) was dissolved in DMF (0.30 mL) and cesium carbonate (24 mg, 0.15 mmol) was added. After ten minutes, methyl iodide (0.023 mL, 0.37 mmol) was added and the solution was allowed to react during 4h at RT. Then, dichloromethane (10 mL) was added. The organic phase was successively washed with water (5 mL) and brine (5 mL) to yield the methyl ester (*R*)-**3f**, which was purified by flash chromatography using hexane/ethyl acetate 5:2 (23 mg, 76%); $[\alpha]_D^{20}$ = –100.6 (*c* 1.05, $CHCl_3$).

Acknowledgments

Financial support from the Spanish MICINN (CTQ2011-24237) is gratefully acknowledged. S. Y. Torres thanks to the University of Oviedo for a grant.

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14. Recrystallization of esters (*R*)-**5c**,**f**,**g** also allows their enantioenrichment in some extension, but either the overall yields and enatiomeric excesses attained for the acids were lower than those achieved following the three steps KR-derivatization-KR.
15. For a recent example about the influence of the remote stereogenic centre on the enantioselectivity of the lipase-catalyzed reactions, see: Schönstein, L.; Forró, E.; Fülop, F. *Tetrahedron: Asymmetry* **2013**, *24*, 202-206.
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Supplementary Material

Copy of the HPLC chromatograms of the racemic and optically active compounds.

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Chemoenzymatic preparation of optically active 4-aryl-5-carboxy-6-methyl-3,4-dihydro-2(1*H*)-pyridone derivatives

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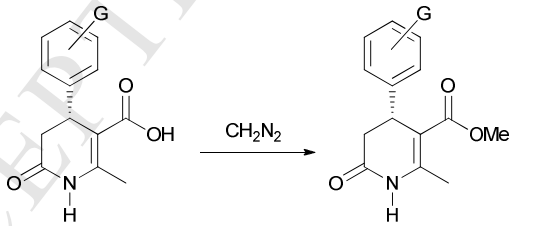
Table of Contents:

I. *General procedure for the derivatization of the carboxylic acids with diazomethane.*

An excess of a solution of diazomethane in a mixture of diethyl ether/methanol (40 mM) was added to a sample of 1.0 mg of the corresponding carboxylic acid. After 2-3 min. solvents were evaporated and the resulting methyl ester was analysed by enantioselective HPLC. The optically active carboxylic acids (isolated from the enzymatic reactions) and the methyl esters derivatives are collected in Scheme I.



(*R*)-**9a** (G = H) (*R*)-**3a** (G = H)
(*R*)-**9c** (G = 3-NO_2) (*R*)-**3c** (G = 3-NO_2)
(*R*)-**9f** (G = 4-Br) (*R*)-**3f** (G = 4-Br)
(*R*)-**9g** (G = 3-OMe) (*R*)-**3g** (G = 3-OMe)

Scheme I. Methyl esters derivatives

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II. Enantioselective HPLC conditions and chromatograms:

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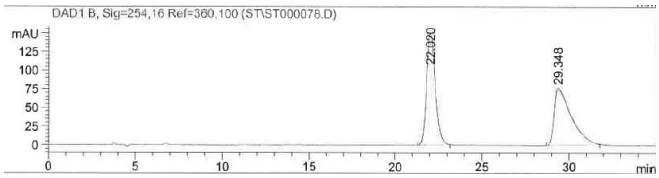
*1. Enzymatic hydrolysis of (±)-**5a** and recrystallization of the resulting (S)-**5a** and (R)-**9a**.*

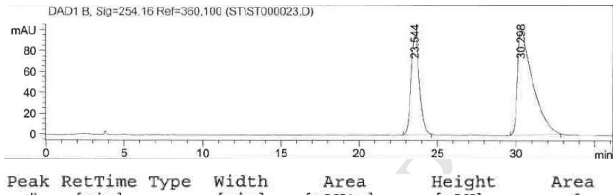
HPLC conditions for remaining substrate **5a**: Chiralpak IA; hexane/propan-2-ol 95:5, 0.8 mL/min, 254 nm, 30 °C; t_R = 22.0 (*R*) and 29.3 (*S*) min; R_S = 5.0.

(±)-**5a**



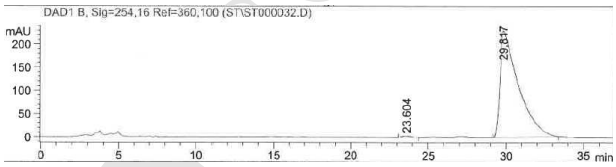
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.020	BB	0.5247	5185.01855	150.22017	49.7787
2	29.348	BB	0.9318	5231.11475	77.27405	50.2213

(*S*)-**5a** with ee = 32% (Table 3, entry 1)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.544	BB	0.5655	6573.82715	177.74718	33.9080
2	30.298	BB	0.9057	1.28134e4	190.26399	66.0920

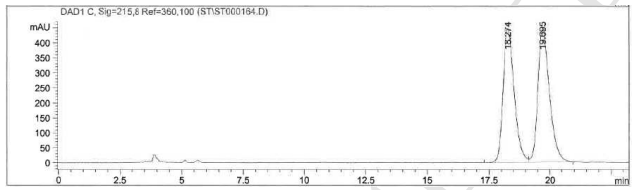
(*S*)-**5a** with ee = 99% (isolated from the filtrate of the crystallization step



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.604	BB	0.4338	98.16917	2.85071	0.5175
2	29.817	BB	1.1086	1.88727e4	230.65884	99.4825

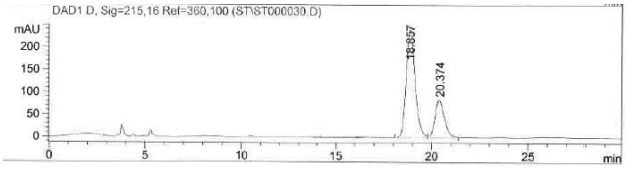
Product **9a** was transformed into the methyl ester **3a** (Scheme 1)
HPLC conditions for **3a**: Chiralpak IA; hexane/propan-2-ol 95:5, 0.8 mL/min, 215 nm, 30 °C; t_R = 18.3 (*R*) and 19.7 (*S*) min; R_S = 1.4.

(±)-**3a**



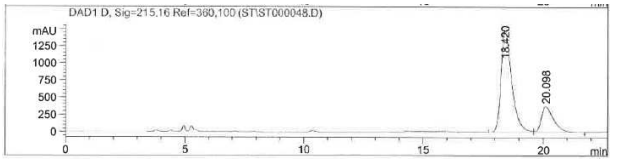
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.274	VV	0.5115	1.45621e4	447.64224	49.3422
2	19.695	VB	0.5129	1.49504e4	446.17844	50.6578

(*R*)-**3a** with ee = 47% (Table 3, entry 1)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.857	BV	0.5037	7812.32813	240.01505	73.6600
2	20.374	VB	0.5015	2793.60010	84.11499	26.3400

(*R*)-**3a** with ee = 55% (isolated from the filtrate of the crystallization step)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.420	PV	0.4671	4.58536e4	1481.53284	77.4050
2	20.098	VB	0.5293	1.33849e4	376.04913	22.5950

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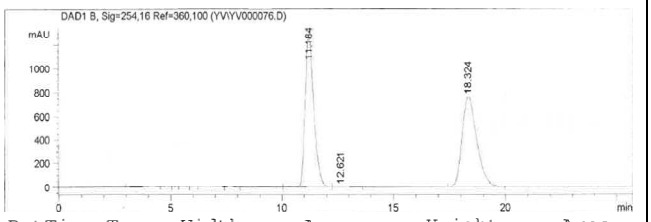
*2. Enzymatic hydrolysis reactions of (±)-**5c** and (R)-**5c*** (ee_o = 67%).

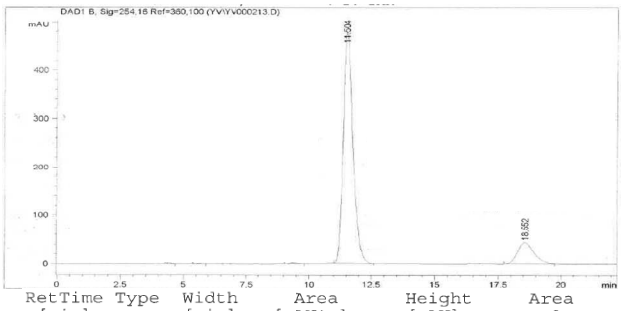
HPLC conditions for remaining substrate **5c**: Chiralcel OD; hexane/propan-2-ol 70:30, 0.8 mL/min, 254 nm, 20 °C; t_R = 11.2 (*S*) and 18.3 (*R*) min; R_S = 6.4.

(±)-**5c**



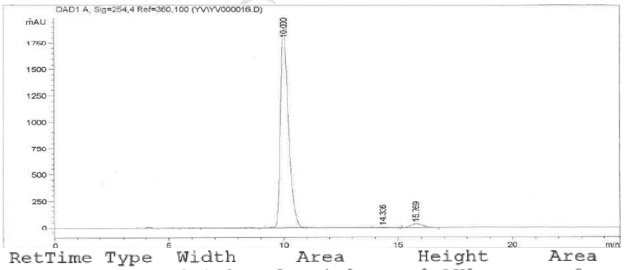
RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
11.184	VB	0.4185	3.44227e4	1276.90735	48.5035
12.621	BB	0.4833	148.33438	4.40006	0.2090
18.324	BB	0.6906	3.42078e4	760.72662	48.2006

(*S*)-**5c** with ee = 73% (Table 3, entry 2)



RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
11.504	BP	0.3924	1.28235e4	478.93378	86.1842
18.552	BB	0.6862	1968.61670	43.98365	13.2306

(*S*)-**5c** with ee = 95% (Table 3, entry 5)

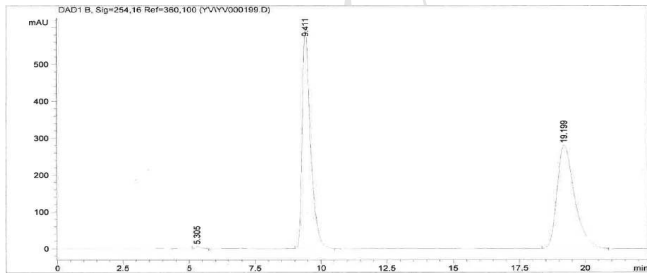


RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
10.000	BB	0.3667	4.56417e4	1897.13293	96.1450
14.336	BB	0.4322	135.94363	4.40332	0.2864
15.769	BB	0.5562	1268.88733	34.09512	2.6729

Product **9c** was transformed into the methyl ester **3c** (Scheme 1)

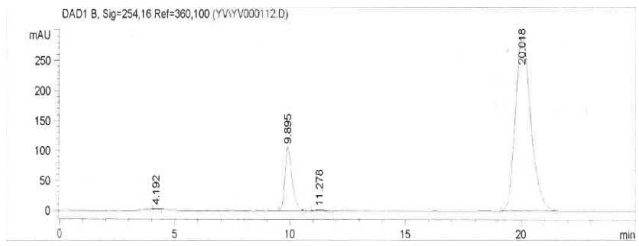
HPLC conditions for **3c**: Chiralcel OD; hexane/propan-2-ol 70:30, 0.8 mL/min, 254 nm, 20 °C; t_R = 9.4 (*S*) and 19.2 (*R*) min; R_S = 9.5.

(±)-**3c**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.305	BB	0.2031	94.68458	6.69163	0.3612
2	9.411	PB	0.3287	1.30981e4	595.30481	49.9713
3	19.199	BB	0.6974	1.30185e4	281.58432	49.6674

(*R*)-**3c** with ee = 71% (Table 3, entry 2)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.192	BB	0.2066	23.68604	1.60143	0.1487
2	9.895	BB	0.3209	2288.15186	106.39953	14.3672
3	11.278	PB	0.3564	49.52195	2.03124	0.3109
4	20.018	BB	0.6757	1.35649e4	290.00415	85.1731

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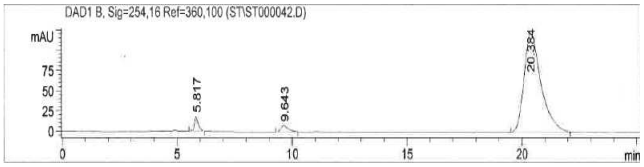
(*R*)-**3c** with ee = 95% (Table 3, entry 8)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.817	BP	0.1517	193.23401	18.23020	2.8931
2	9.643	BB	0.3277	176.92209	7.88745	2.6489
3	20.384	BB	0.7722	6308.92529	122.23524	94.4580

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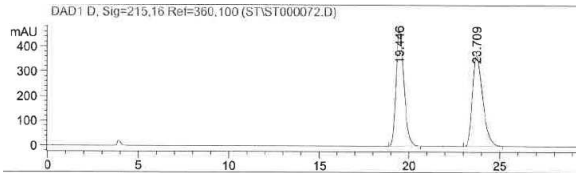
*3. Enzymatic hydrolysis reactions of (±)-**5f** and (R)-**5f*** (ee_o = 62%).

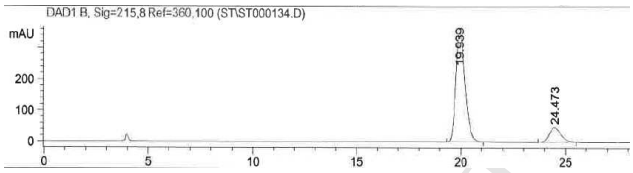
HPLC conditions for remaining substrate **5f**: Chiralpak IC; hexane/propan-2-ol 90:10, 0.8 mL/min, 215 nm, 30 °C; t_R = 19.4 (*S*) and 23.7 (*R*) min; R_S = 4.0.

(±)-**5f**



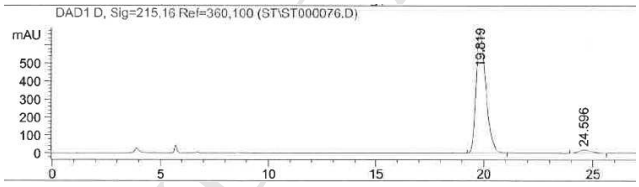
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.446	BB	0.4818	1.44277e4	462.71384	49.9663
2	23.709	BB	0.5981	1.44472e4	367.94470	50.0337

(*S*)-**5f** with ee = 71% (Table 3, entry 3)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.939	BB	0.4852	1.09557e4	350.03357	85.5180
2	24.473	PB	0.6049	1855.29553	47.37258	14.4820

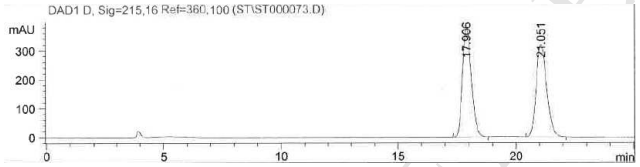
(*S*)-**5f** with ee = 93% (Table 3, entry 6)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.819	PB	0.4943	2.13817e4	662.96161	96.3290
2	24.596	BB	0.5725	814.82910	20.64551	3.6710

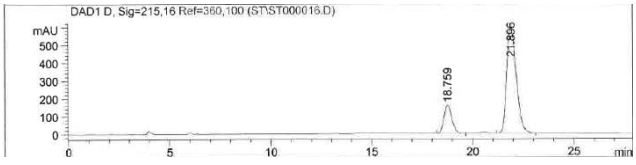
Product **9f** was transformed into the methyl ester **3f** (Scheme 1)
HPLC conditions for **3f**: Chiralpak IC; hexane/propan-2-ol 90:10, 0.8 mL/min, 215 nm, 30 °C; t_R = 17.9 (*S*) and 21.1 (*R*) min; R_S = 3.6.

(±)-**3f**



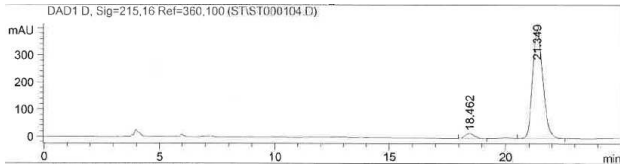
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.906	BB	0.4067	9923.40234	380.00369	50.0141
2	21.051	BB	0.4816	9917.79199	319.99875	49.9859

(*R*)-**3f** with ee = 64% (Table 3, entry 3)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.759	BB	0.4198	4262.73730	157.46225	18.1059
2	21.896	VB	0.5088	1.92807e4	590.74359	81.8941

(*R*)-**3f** with ee = 93% (Table 3, entry 9)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.462	BB	0.4093	454.70847	16.93338	3.5090
2	21.349	VB	0.4818	1.25037e4	400.99399	96.4910

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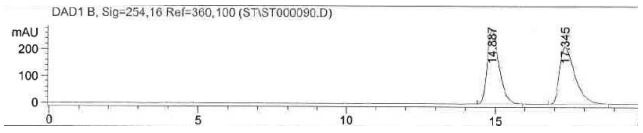
*4. Enzymatic hydrolysis reactions of (±)-**5g** and (R)-**5g*** (ee_o = 57%).

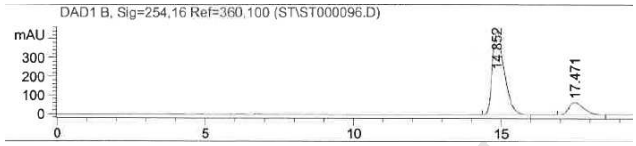
HPLC conditions for remaining substrate **5g**: Chiralpak IC; hexane/propan-2-ol 75:25, 0.8 mL/min, 254 nm, 20 °C; t_R = 14.9 (*S*) and 17.3 (*R*) min; R_S = 2.6.

(±)-**5g**



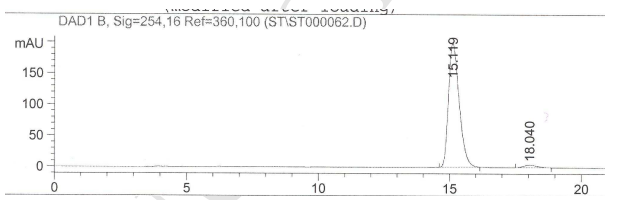
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.887	BB	0.4253	7587.05322	273.79974	50.0911
2	17.345	BB	0.5354	7559.45703	213.32549	49.9089

(*S*)-**5g** with ee = 69% (Table 3, entry 4)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.852	PB	0.4254	1.21955e4	439.92117	84.4784
2	17.471	BB	0.5246	2240.72632	65.25600	15.5216

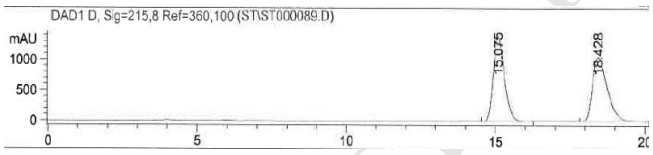
(*S*)-**5g** with ee = 95% (Table 3, entry 7)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.119	BB	0.4374	5638.01318	198.46317	97.2975
2	18.040	BB	0.4555	156.60188	4.31412	2.7025

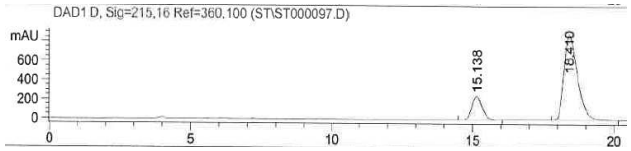
Product **9g** was transformed into the methyl ester **3g** (Scheme 1)
HPLC conditions for **3g**: Chiralpak IC; hexane/propan-2-ol 75:25, 0.8 mL/min, 215 nm, 20 °C; t_R = 15.1 (*S*) and 18.4 (*R*) min; R_S = 3.9.

(±)-**3g**



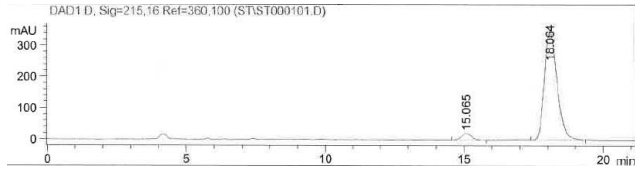
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.075	PB	0.4014	3.60888e4	1387.89526	49.9404
2	18.428	BB	0.5289	3.61749e4	1052.63049	50.0596

(*R*)-**3g** with ee = 66% (Table 3, entry 4)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.138	VB	0.3879	6191.68066	247.46048	17.2026
2	18.410	BB	0.5132	2.98011e4	893.25208	82.7974

(*R*)-**3g** with ee = 91% (Table 3, entry 10)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.065	VV	0.3921	541.04089	20.89438	4.6413
2	18.064	VB	0.4820	1.11161e4	352.45908	95.3587