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ARTICLE

Chemoenzymatic synthesis of optically active phenolic 3,4-dihydropyridin-2-ones: a way to access enantioenriched 1,4-dihydropyridine and benzodiazepine derivatives†‡

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A chemoenzymatic approach for the synthesis of optically active 4-(3-acetoxyphenyl)-5-(alkoxycarbonyl)-6-methyl-3,4-dihydropyridin-2-ones (3,4-DHP-2-ones) and their hydroxyphenyl derivatives has been developed, the key step being a *Candida rugosa* lipase (CRL)-catalyzed hydrolysis reaction. As a result, different optically active 3,4-DHP-2-ones have been prepared with very high enantiomeric excesses (ee = 94-99%) and good yields. The enantioenriched 3,4-DHP-2-ones have easily been converted into highly functionalized (*R*)- and (*S*)-1,4-dihydropyridines (1,4-DHPs) by means of a Vilsmeier-Haack reaction. Finally, the coupling of the 1,4-DHPs with benzene-1,2-diamine using TFA as an acid promoter provided us the corresponding optically active hybrid 1,5-benzodiazepine-1,4-dihydropyridine (BZD-DHP) derivatives. No racemization took place in these processes and all optically active compounds were obtained in excellent yields.

Introduction

3,4-Dihydropyridin-2-ones (3,4-DHP-2-ones, Figure 1) are components of natural products[1] and essential structural units in medicinal and synthetic chemistry. As an example, some carboxamide derivatives exhibit activities as Rho kinase inhibitors,[2] selective α_{1a} adrenergic receptor antagonists,[3] P2X7 receptor antagonists[4] or G protein-coupled kinase receptor antagonists.[5] In addition, these structures can be easily converted into other valuable compounds such as 1,4-dihydropyridines (1,4-DHPs) and 1*H*-1,5-benzodiazepine-1,4-dihydropyridine derivatives (BZD-DHPs, Figure 1).[6] 1,4-DHPs are recognized as privileged pharmacophores widely used in clinics for the treatment of cardiovascular and cerebrovascular diseases[7] and in the synthesis of natural products,[8] while the hybrid BZD-DHP is a multi-target-directed ligand whose potential as a neuroprotective agent is under study.[9] The concept of a single compound that may be able to hit multiple targets is an emerging strategy for the treatment of complex diseases like neurodegenerative syndromes.[10]

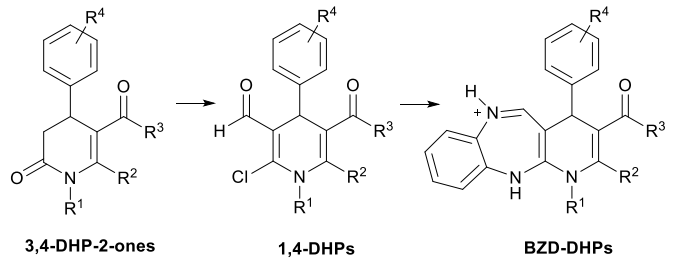

Figure 1. Representative structures.

Despite the close relationship between biological activity and stereochemistry, the preparation of optically pure 3,4-DHP-2-ones and thus their derivatives have scarcely been described. Besides the resolution of racemic mixtures by preparative chiral HPLC,[2a] the asymmetric synthesis of a 5-carboxy-4-(*p*-fluorophenyl)-3,4-DHP-2-one and its methyl ester derivative have been described by desymmetrization of a *meso* anhydride using an optically active thiourea as an organocatalyst.[3b,11] Also, a series of 4-substituted-5-(alkoxycarbonyl or cyano)-3,4-DHP-2-ones has been synthesized via an enantioselective NHC-catalyzed aza-Claisen rearrangement.[12]

In a previous report, as a part of our research on the chemoenzymatic preparation of optically active 3,4-DHP-2-ones and hybrid BZD-DHPs, we described the enantioselective hydrolysis of acyloxymethyl esters derived from 3,4-DHP-2-ones (Figure 2) using the Lipase B from *Candida antarctica*.[13] The acyloxymethyl ester derivatives were required as substrates after checking the absence of reactivity of the alkyl (methyl or ethyl) ester analogues due to both steric and electronic factors.[14] Still, poor enantioselectivities were achieved in these processes and the enantiomeric excess of the resulting products had to be improved by combining either the enzymatic resolution with a selective crystallization process, or by means of two consecutive kinetic resolutions.

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†Dedicated to Prof. Vicente Gotor on the occasion of his 70th birthday.

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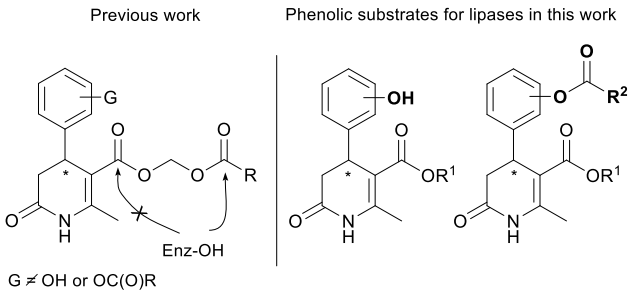


Figure 2. Non-phenolic and phenolic 3,4-DHP-2-ones capable of being transformed by lipases.

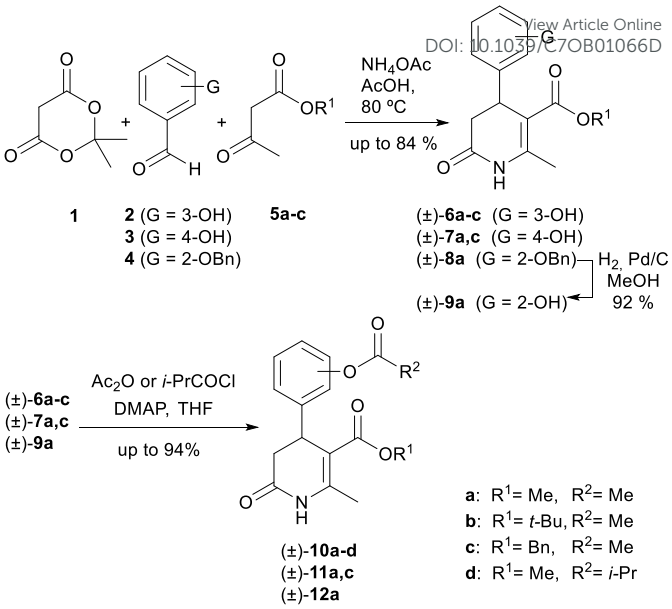
Here, we have focused on the synthesis and resolution of new 3,4-DHP-2-one derivatives bearing a phenolic unit in their structure (Figure 2). The presence of the phenolic hydroxyl group as such or as ester derivative will allow to address the resolution of these heterocycles from a different place in the molecule, which could have a beneficial effect on the enantioselectivity of the lipase. In addition, the presence of these functional groups may facilitate a further derivatization of the molecule. On the other hand, phenols and their ester derivatives have been much less studied than alcohols as substrates in lipase or esterase catalyzed processes, even though, some resolutions of binaphthols,[15] biphenols,[16] and other phenolic esters present in compounds with remote hindered stereogenic centers[17] or in chiral phosphines and sulphoxides[18] have been reported.

Results and discussion

Synthesis and enzymatic resolution of racemic 5-(alkoxycarbonyl)-4-(hydroxyphenyl)-6-methyl-3,4-DHP-2-one derivatives

Several racemic 5-(alkoxycarbonyl)-4-(hydroxyphenyl)-6-methyl-3,4-DHP-2-ones (±)-**6a-c**, (±)-**7a**,**c**, and (±)-**9a** were synthesized by a multicomponent reaction using the Meldrum's acid (**1**), the corresponding hydroxybenzaldehyde and the β-ketoester **5a-c**, in the presence of ammonium acetate following the previously reported procedure (Scheme 1).[13,19] In these conditions, the desired *meta*- and *para*-substituted phenolic derivatives (±)-**6a-c** and (±)-**7a**,**c**, respectively, were obtained in good or moderate yields, but the method failed starting from the *o*-hydroxybenzaldehyde. Nevertheless, the *ortho* derivative (±)-**9a** could be obtained in 54% overall yield using *o*-benzyloxybenzaldehyde (**4**) in the multicomponent process, followed by a hydrogenation under standard conditions.

Although the lipase-catalyzed acylation reaction had shown scarce utility to carry out the resolution of phenols and related compounds,[15b-c,16] we decided to start our study testing the activity of different lipases in the acylation of the phenolic 3,4-DHP-ones using vinyl acetate as an acyl donor. Previous results obtained in the regioselective acetylation of polyphenols with vinyl acetate showed that the regioselectivity of lipases towards phenolic hydroxyls usually paralleled their chemical reactivity, favouring the less hindered positions.[20] Based on



Scheme 1. Synthesis of substrates (±)-**10a-d** (*meta*), (±)-**11a,c** (*para*), and (±)-**12a** (*ortho*).

this finding, we selected the unhindered *meta*-phenolic derivative (±)-**6a** as a model substrate to test the enzymatic acylation. Several commercially available lipases [*Candida antarctica* (CAL-A and CAL-B), *Burkholderia cepacia* (PSL-IM), and *Candida rugose* (CRL)] were tested as catalyst. The processes were carried out in 2-methyltetrahydrofurane (2-Me-THF) as the solvent and using 5.0 equiv of vinyl acetate, or also using the vinyl acetate as the solvent. Selection of 2-Me-THF was based on the high solubility of the substrate in this solvent and also considering its advantages in terms of health and environment.[21] However, no satisfactory results were found in any of the proposed experiments, and no traces of the product were detected after a prolonged reaction time (up to 3 days at 28 °C).

Taking these disappointing results into account, we focused our study on the enzymatic hydrolytic processes. For this, the acylated derivatives (±)-**10a-d** (*meta*), (±)-**11a,c** (*para*), and (±)-**12a** (*ortho*) were synthesized by conventional chemical methods (Scheme 1).

The initial experiments were designed to find the most suitable lipase for catalysing the hydrolysis of the *meta*-acetyl derivative (±)-**10a** as a model substrate. In a first set of experiments, lipases CAL-B, PSL-IM, and CRL were checked as catalysts (Table 1). Due to the low solubility of the substrate in an aqueous medium, 2-Me-THF was again chosen as the solvent and a little amount of water (1.0% v/v) was added as the reagent.

Hydrolysis reactions of (±)-**10a** were carried out at 28 °C, on a 5 mg (screening) or up to 100 mg (preparative) scale amount. The processes were allowed to react until the conversion was near 50% (TLC monitoring) or when hardly further progress was observed. The obtained results have

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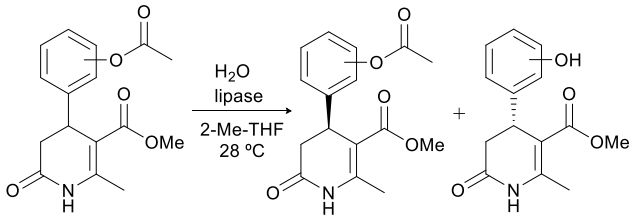
Table 1. Lipase-catalyzed hydrolysis of (±)-**10a**, (±)-**11a**, and (±)-**12a** in 2-Me-THF.



(±)-**10a** (*meta*) (*S*)-**10a** (*R*)-**6a**
(±)-**11a** (*para*) (*S*)-**11a** (*R*)-**7a**
(±)-**12a** (*orto*) (*S*)-**12a** (*R*)-**9a**

Entry	Substrate[a]	Lipase[b]	*t* (h)	ee$_s$ (%)[c]	ee$_p$ (%)[c]	*c* (%)[d]	*E*[d]
1	(±)-**10a**	CAL-B	9.0	12	32	27	2
2	(±)-**10a**	PSL-IM	5.5	45(*R*)	42(*S*)	52	4
3	(±)-**10a**	CRL	5.5	66	94	41	64
4	(±)-**10a**	CRL	7.0	94	90	51	67
5	(±)-**11a**	CRL	0.25	16	12	57	~1
6	(±)-**12a**	CRL	432	8	10	44	~1

[a] Reactions were carried out using 5 mg (entries 1, 2, 5, and 6), 77 mg (entry 3) or 86 mg (entry 4); 100 μL of solvent/mg of substrate and H_2O (1.0% v/v) were used. [b] Weight ratio enzyme/substrate 1:1. [c] Enantiomeric excess of remaining substrates **10a**-**12a** (ee$_s$) and products **6a**, **7a**, and **9a** (ee$_p$) were determined by chiral HPLC; all enzymes showed the stereochemical preference indicated in the scheme, except PSL-IM. [d] Conversion, c = ee$_s$/(ee$_s$ + ee$_p$), and enantiomeric ratio, $E = \ln[(1-c)(1-ee_s)]/\ln[(1-c)((1+ee_s)]$ as indicated in ref. 22.

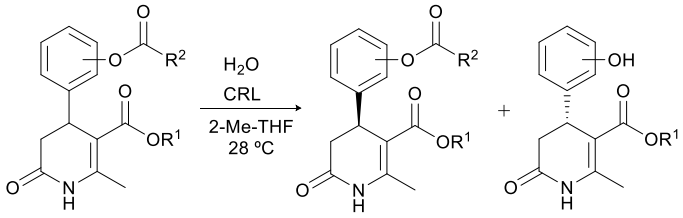
been summarized in Table 1 (entries 1-3). The reaction rate was considerably fast in the processes catalyzed by PSL-IM and CRL, and moderate in the case of CAL-B, but only CRL showed simultaneously a high enantiomeric ratio[22] (*E* = 64, entry 3). This *E* value is high enough to allow us to obtain either the remaining substrate (*S*)-**10a** and the product (*R*)-**6a** in good yields and high enantiomeric excesses, by simply an adequate control of the extent of the conversion. Thus, both (*R*)-**6a** and (*S*)-**10a** were isolated with 94% ee after 5.5 and 7 h of incubation, respectively (Table 1, entries 3 and 4). Moreover, it can be noted that the resulting enantioenriched compounds were recovered without significant loss of material after a flash chromatography column (see experimental section).

All enzymes shown the same stereochemical preference except PSL-IM (Table 1, entry 2). The assignment of the absolute configuration of the enantioenriched products and the remaining substrates is described later on this text.

Once the efficacy of the CRL lipase in the resolution of substrate (±)-**10a** was demonstrated, the same reaction conditions were applied to the resolution of the isomeric (±)-**11a** (*para*) and (±)-**12a** (*ortho*) but, for both substrates, the reaction proceeded with a *E* value near to 1 (Table 1, entries 5 and 6). Regarding the reactivity, the same trend described in the regioselective hydrolysis of polyphenolic esters[20] was observed in the processes with **10a**-**12a**, the reaction rate decreasing in the order *para*>*meta*>>*ortho*.

To check the influence of the substrate structure on the enantioselectivity of the enzymatic hydrolysis, some structural changes were incorporated in the model compound **10a**. All results achieved with the new substrates are summarized in Table 2 and, for an easier comparison among them, those obtained with (±)-**10a** have been included again (entry 1). Firstly, the isobutyryl derivative (±)-**10d** with a higher steric demand in the phenolic ester was prepared (Scheme 1) and examined in the enzymatic hydrolysis. In this case, the reaction was very slow and the enantioselectivity of the process decreased considerably (*E* = 4, Table 2, entry 2). This result discouraged us to try the same structural modification with the *para* and *ortho* isomers.

Table 2. CRL-catalyzed hydrolysis of substrates (±)-**10a-d** and (±)-**11c** in 2-Me-THF.



(±)-**10a-d** (*meta*) (*S*)-**10a-d** (*R*)-**6a-c**
(±)-**11c** (*para*) (*S*)-**11c** (*R*)-**7c**

Entry	Substrate[a]	R^1	R^2	*t* (h)	Remaining Substrate	ee$_s$ (%)[c]	Yield (%)[d]	Product	ee$_p$ (%)[c]	Yield$_p$(%)[d]	*c* (%)[e]	*E*[e]
1	(±)-**10a**	Me	Me	7.0	(*S*)-**10a**	94	45	(*R*)-**6a**	90	45	51	67
2	(±)-**10d**	Me	*i*-Pr	103	(*S*)-**10d**	41	--	(*R*)-**6a**	43	--	49	4
3	(±)-**10b**	*t*-Bu	Me	8.3	(*S*)-**10b**	58	38	(*R*)-**6b**	88	11	40	28
4	(±)-**10c**	Bn	Me	15	(*S*)-**10c**	63	55	(*R*)-**6c**	96	37	40	93
5	(±)-**10c**	Bn	Me	44	(*S*)-**10c**	99	43	(*R*)-**6c**	89	50	53	89
6	(±)-**11c**	Bn	Me	2.0	(*S*)-**11c**	15	--	(*R*)-**7c**	17	--	47	2

[a] Reactions were carried out at 77-150 mg scale amount, except in entries 2 and 6 (5 mg). [b] Weight ratio enzyme/substrate 1:1. [c] Determined by chiral HPLC. [d] Isolated yield. [e] Conversion (*c*) and enantiomeric ratio (*E*) determined as in Table 1.

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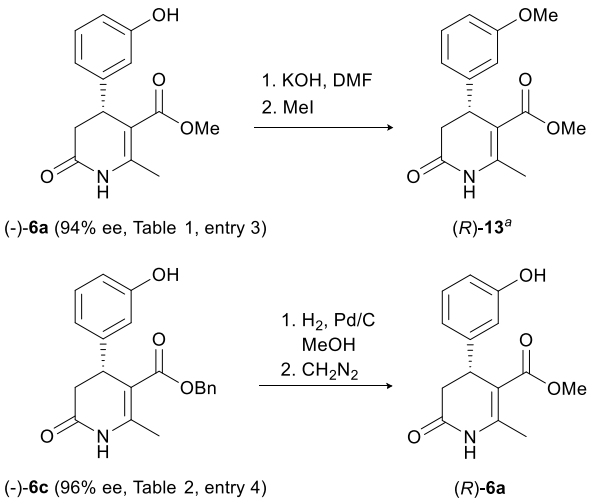
Next, we planned to change the methyl ester at the 5-position of the pyridone ring by the *t*-butyl or benzyl ester, [(±)-**10b** and (±)-**10c**, respectively]. This modification could improve the enantioselectivity of the enzyme due to the increased size of one of the substituents of the chiral center. Furthermore, it has the additional attractiveness of the greater synthetic versatility of the new esters. As it was demonstrated in a previous paper,[13] whereas the hydrolysis of the methyl ester in both conventional basic and enzymatic hydrolyses are ineffective, the *t*-butyl or benzyl ester can be easily converted into the carboxylic acids because this transformation does not imply a nucleophilic attack to the carbonyl group.

Once synthesized esters (±)-**10b** and (±)-**10c** (Scheme 1), their enzymatic hydrolyses were investigated in the already described reaction conditions, using 2-Me-THF as the solvent and CRL as catalyst. No satisfactory results were found in the hydrolysis of the *t*-butyl ester (±)-**10b**. The reaction rate was slightly lower than that of the methyl ester (±)-**10a**, and the enantioselectivity decreased (*E* = 28, Table 2, entry 3). Another drawback to this reaction was the poor performance of the chromatographic separation of the resulting mixture (*R*)-**6b** and (*S*)-**10b**, which led to a loss of yield as can be appreciated in the data shown in Table 2. On the contrary, a considerable enhancement of enantioselectivity (*E* = 93) was observed in the CRL-catalyzed hydrolysis of the benzyl analogue (±)-**10c** (Table 2, entry 4), which allowed us to isolate the product (*R*)-**6c** with very high ee (96%) and high yield after 15 h of incubation. After a larger reaction time, a slightly higher 50% conversion was reached and the remaining substrate (*S*)-**10c** was isolated with 99% ee (Table 2, entry 5).

In view of the results obtained using the benzyl ester (±)-**10c**, the analogue *para*-substituted (±)-**11c** was also prepared (Scheme 1) and tested in the same conditions but, in this case, no improvement in the enantioselectivity of the process was observed (Table 2, entry 6). The preparation of the analogue benzyl *ortho* derivative was discarded in the light of the observed decreasing of the reaction rate with both **10c** and **11c**. This fact would have a dramatical consequence on the hydrolysis process considering the extremely slow hydrolysis of the methyl *ortho* derivative **12a** (Table 1, entry 6).

Assignment of the absolute configuration of the compounds isolated from the lipase catalyzed hydrolyses, and thus the enantiopreference shown by the lipases in these processes, was determined as follows: product (−)-**6a** (94% ee), which was obtained from the CRL-catalyzed hydrolysis of (±)-**10a** (see Table 1, entry 3), was treated with KOH in DMF, followed by methyl iodide, affording the methoxy derivative (−)-**13** (Scheme 2). The *R* configuration for this compound was established after comparison of its chiral-HPLC chromatogram with that one reported for (*R*)-**13**.[13] Therefore, the *R* configuration was also assigned to the preceding (−)-**6a**. This indicates that CRL shows preference towards the *R*-enantiomer of the substrate (±)-**10a**, and that the isolated optically active remaining **10a** has the *S* configuration. The (*R*)-preference of CRL towards the benzyl analogue **10c** was also



Scheme 2. Assignment of the absolute configuration to the enzymatically produced compounds. [a] Its chiral-HPLC chromatogram was compared with a known sample.

established by chemical correlation. Thus, the hydrogenolysis of the benzylic ester of the product (−)-**6c** (see Table 2, entry 4) and the subsequent esterification of the resulting carboxylic acid with diazomethane gave **6a** (Scheme 2), which showed the same chiral-HPLC chromatogram as (*R*)-**6a**. Taking into account the (*R*)-enantiopreference of the CRL towards the esters (±)-**10a** and (±)-**10c**, we have tentatively assigned the *R* configuration to the enantioenriched product **6b** and the *S* configuration for the remaining ester **10b**, both compounds isolated in the CRL-catalyzed hydrolysis of (±)-**10b** (Table 2, entry 3).

Synthesis of optically active 6-chloro-5-formyl-1,4-DHP derivatives and their hybrids 1,5-BZD-1,4-DHPs.

In order to address the synthesis of optically active hybrid BZD-DHPs with potential therapeutic interest,[9] the transformation of the optically active 3,4-DHP-2-ones into the highly functionalized 6-chloro-5-formyl-1,4-DHP derivatives is required. To this aim, the enantioenriched 3,4-DHP-2-ones (*R*)-**6a,c** and (*S*)-**10a,c** (ee ≥94%) were submitted to a Vilsmeier-Haack (V-H) reaction (Scheme 3).[23] When the acetylated compounds (*S*)-**10a,c** were used as starting materials, the corresponding 1,4-DHP derivatives (*S*)-**14a,c** were isolated in excellent yields (86-92%). However, when the V-H reaction was applied to (*R*)-**6a,c**, which contain the free hydroxyl group, the reactions resulted in low yields due to the partial formylation of this group. To avoid this undesired reaction, previously to the V-H reaction, compounds (*R*)-**6a,c** were converted into the corresponding acetates (*R*)-**10a,c** by a conventional acetylation and then, transformed into the 1,4-DHP (*R*)-**14a,c**. No racemization was observed in any of the involved synthetic steps, as it was proven by chiral-HPLC analysis.

Considering that the racemic 1,4-DHP phenolic acetates (±)-**14a-c** are also susceptible to be hydrolysed by lipases,

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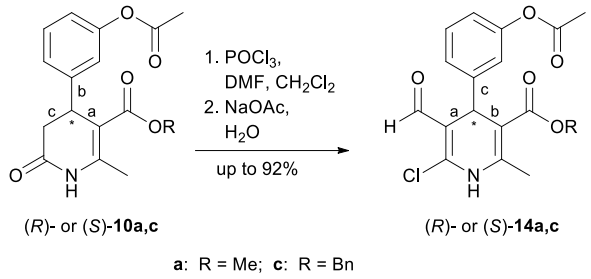


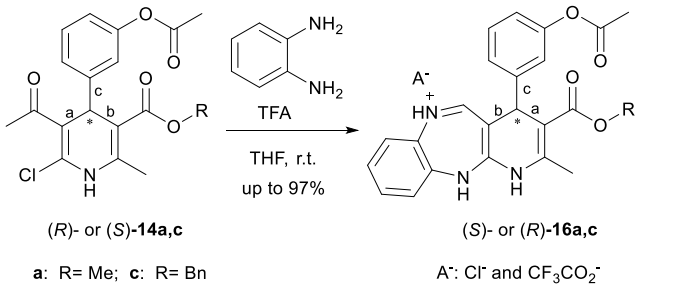
Scheme 3. Synthesis of optically active 4-(3-acetoxyphenyl)-1,4-DHPs **14a,c**. The priority order of the substituents of the chiral C-4 according to Cahn-Ingold-Prelog rule is given (a>b>c).

these 1,4-DHPs were prepared from the racemic 3,4-DHP-2-ones (±)-**10a-c** and evaluated as substrates. The lipases CAL-B, PSL-IM, and CRL were tested as catalysts and the hydrolysis processes conducted in the conditions described above for (±)-**10a-c**. The most representative results obtained in these reactions are summarized in Table 3.

When CRL was used as the catalyst, the reaction rates and enantioselectivities were lower than for the corresponding 3,4-DHP-2-ones (±)-**10a-c** (entries 1,3,5). On the contrary, the PSL-IM-catalyzed hydrolysis of substrate (±)-**14c** showed better enantioselectivity (*E* = 17, Table 3, entry 6) than that obtained in the analogous hydrolysis of its precursor (±)-**10c** (*E* = 3, this value is not shown in tables). Nevertheless, this result did not improve what was obtained in the resolution of (±)-**10c** with CRL (*E* = 93, Table 2, entry 4). Thus, although a further optimization of the enzymatic resolution of the 1,4-DHP derivatives can be performed, from the study carried out so far, it can be concluded that the best approach to the preparation of optically active 1,4-DHPs is the resolution at the 3,4-DHP-2-one stage.

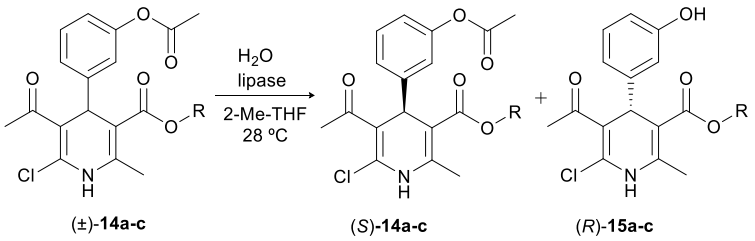
Absolute configuration of the enzymatically produced 1,4-DHPs (Table 3) and thereby, the opposite enantiopreference of both employed lipases, was established by comparison of the chiral-HPLC chromatogram of each sample with that of the optically active 1,4-DHPs (*S*)-**14a** and (*S*)-**14c** previously synthesized (Scheme 3).

Finally, the last objective of this work was the transformation of the enantioenriched 1,4-DHPs (*R*)- and (*S*)-**14a,c** (ee ≥94%) into the corresponding hybrids BZD-DHPs. The coupling reaction between (*R*)- and (*S*)-**14a,c** and benzene-1,2-diamine was carried out using trifluoroacetic acid (TFA) as an acid promoter (Scheme 4), following our previously developed method.[6b] In this way, the corresponding hybrids (*R*)- and (*S*)-**16a,c** were isolated in almost quantitative yield (95-97%) as an approximately 2:1 mixture of hydrochloride and trifluoroacetic salts. Quantification of the presence of the counterion in the structure of each BZD-DHP was carried out by ^{1}H- and ^{19}F-RMN analyses using 1-chloro-3-fluoropropan-2-ol as an internal reference.[6b] As it can be expected, taking the mild reaction conditions and the non-involvement of the chiral centre in the coupling reaction into account, the chiral-HPLC analyses confirmed that no racemization took place in the process.



Scheme 4. Synthesis of optically active phenolic BZD-DHP derivatives.

Table 3. Lipase-catalyzed hydrolysis of (±)-**14a-c** in 2-Me-THF.



Entry	Substrate[a]	R	Lipase[b]	*t* (h)	ee$_s$ (%)[c]	Configuration	ee$_p$ (%)[c]	Configuration	*c* (%)[d]	*E*[d]
1	(±)-**14a**	Me	CRL	98	43	*S*	83	*R*	34	16
2	(±)-**14a**	Me	PSL-IM	127	3	*R*	20	*S*	13	1
3	(±)-**14b**	*t*-Bu	CRL	144	-	-	-	-	<5	-
4	(±)-**14b**	*t*-Bu	PSL-IM	144	18	*R*	67	*S*	21	6
5	(±)-**14c**	Bn	CRL	72	15	*S*	79	*R*	16	10
6	(±)-**14c**	Bn	PSL-IM	7.5	47	*R*	83	*S*	36	17

[a] Reactions were carried out using 5 mg scale amount. [b] Weight ratio enzyme/substrate 1:1. [c] Determined by chiral HPLC. [d] Conversion, $c = ee_s/(ee_s + ee_p)$, enantiomeric ratio, $E = \ln[(1 - c)(1 - ee_s)]/\ln[(1 - c)((1 + ee_s)]$.[22]

Conclusions

An efficient chemoenzymatic procedure to obtain valuable optically active phenolic 3,4-DHP-2-ones, highly functionalized 1,4-DHPs, and their hybrids BZD-DHPs has been developed. In this strategy the key step was an enantioselective hydrolysis of the 3,4-DHP-2-one acetyl derivatives catalyzed by the commercially available *Candida rugose* lipase. The mild reaction conditions of the subsequent transformations required to access to the 1,4-DHP and BZD-DHP derivatives ensures the maintenance of the optical purity of the products, which have been obtained in excellent yields.

Several aspects are noteworthy in this procedure. Firstly, the high value of the synthesized optically active compounds, whose biological activities are currently under study. Secondly, the involvement of a biocatalytic step in the synthetic strategy which improves the scalability of the process and affords additional benefits from the sustainability point of view; this feature was taken into account for the selection of 2-Me-THF as the solvent of that step. Finally, focusing on the enzymatic catalysis, the results presented here highlight the efficacy of using the transformation of a phenolic ester to address the resolution of a remote and sterically hindered stereogenic centre.

Experimental Protocols

General. Enzymatic reactions were carried out in a Gallenkamp incubatory orbital shaker. Immobilized *Candida antarctica* lipase B, CAL-B (Novozym 435, 7300 PLU/g), was a gift from Novo Nordisk co., immobilized CAL-A (lipase IMMCALA-T2-150, 3000 U/g) from Chiralvision*, C. rugosa* lipase was purchased from Sigma-Aldrich (CRL type VII, 700 U/mg), and immobilized *Burkholderia cepacia* (PSL-IM, 783 U/g) is commercialized by Amano Pharmaceutical Co. Chemical reagents were supplied by Aldrich, Merck, ACROS organics or Alfa Aesar. Solvents were distilled over an appropriate desiccant under nitrogen. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh). Optical rotations were measured using a Perkin-Elmer 343 polarimeter and are quoted in units of 10^{-1} deg cm^2 g^{-1}. For the protonated BZD a low concentration was used due to the intense color of the solution. So, solutions of c = 1.0 (g/100 mL) were prepared and they were successively diluted until to obtain a good measurement of the optical deviation. ^{1}H-NMR, ^{13}C-NMR, DEPT, and ^{19}F-NMR spectra were recorded in a Bruker AC-300 or DPX-300 (^{1}H, 300.13, ^{13}C, 75.5, and ^{19}F, 254.99 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; CD_3OD, 49.00; DMSO-d_6, 39.52 ppm), the residual solvent partially or non-deuterated (^{1}H: $CHCl_3$, 7.26; CHD_2OD, 3.31; DMSO-d_5, 2.50 ppm), or an externalreference (^{19}F: CF_3COOH, –76.55 ppm). HRMS were measured in ESI$^+$ mode with a Bruker micrOTOF spectrometer. IR spectra were recorded in a FT-IR Rayleigh (WQF-510). The enantiomeric excesses were determined by chiral HPLC analysis on a Hewlett-Packard 1100, LC liquid chromatograph, using a CHIRALPAK IA column (4.6 × 250 mm), CHIRALCEL OD column (4.6 × 250 mm), and CHIRALPAK AD-H column (4.6 × 250 mm). In Figure 3 we show the numbering used in the assignation of the NMR signals in the different structures.

General procedure for the synthesis of racemic 4-(hydroxyphenyl)-3,4-DHP-2-ones (±)-6a-c, (±)-7a,c, and (±)-8a. To a solution of 2,2-dimethyl-1,3-dioxane-4,6-dione **1** (4.73 g, 32.8 mmol) in acetic acid (9.5 mL), the aromatic aldehyde **2**, **3** or **4** (32.8 mmol), the β-ketoester **5a-c** (32.8 mmol), and ammonium acetate (3.78 g, 49.1 mmol) were added. The resulting mixture was stirred for 22-24 h at 80 °C. Then, 15 mL of water were added and the resulting mixture was extracted with ethyl acetate (3 x 15 mL). The organic layer was successively washed with aq saturated $NaHCO_3$ (10 mL), water (2 x 10 mL), and brine (10 mL), dried with Na_2SO_4, and evaporated under reduced pressure to give the corresponding 4-(hydroxyphenyl)-3,4-DHP-2-one, which was purified by flash chromatography (hexane:EtOAc mixtures).

(±)-4-(3-Hydroxyphenyl)-5-(methoxycarbonyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(±)-6a]. Reaction time: 22 h. White solid; mp 189-191 °C; yield 82%; ν_{max}(KBr) 3274, 1685, 1657, 1627, 1525 cm^{-1}; ^{1}H-NMR (CD_3OD, 300.13 MHz): δ 2.40 (d, 3H, ^5J 0.7 Hz, CH_3), 2.53 (dd, 1H, ^3J 1.8, $|^2J|$ 16.3 Hz, *H*H-3), 2.94 (dd, 1H, ^3J 8.0, $|^2J|$ 16.3 Hz, H*H*-3), 3.63 (s, 3H, OCH_3), 4.16 (br d, 1H, ^3J 7.5 Hz, H-4), 6.75-6.51 (m, 3H, H-2', H-4', H-6'), 7.14-7.03 (m, 1H, H-5'); ^{13}C-NMR (CD_3OD, 75.5 MHz): δ 18.6 (CH_3), 39.1 (C-4), 39.4 (C-3), 51.7 (OCH_3), 107.6 (C-5), 114.5 (CH),114.7 (CH), 118.9 (C-6'), 130.7 (C-5'), 145.1 (C-1'), 149.1 (C-6), 158.8 (C-3'), 169.1 (CO), 172.7 (C-2); HRMS-ESI$^+$ calcd. for $[C_{14}H_{15}NNaO_4]^+$ (MNa)$^+$ 284.0893 *m/z*, found 284.0900.

(±)-5-(*tert*-Butoxycarbonyl)-4-(3-hydroxyphenyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(±)-6b]. Reaction time: 22 h. White solid; mp 187-188 °C; yield 81%; ν_{max}(KBr) 3406, 1617, 1599, 1481 cm^{-1}; ^{1}H-NMR (CD_3OD, 300.13 MHz): δ 1.35 (s, 9H, Bu^t), 2.34 (d, 3H, ^5J 0.9 Hz, CH_3), 2.51 (dd, 1H, ^3J 2.5, $|^2J|$ 16.3 Hz, *H*H-3), 2.91 (dd, 1H, ^3J 8.2, $|^2J|$ 16.3 Hz, H*H*-3), 4.16-4.03 (m, 1H, H-4), 6.70-6.55 (m, 3H, H-2', H-4', H-6'), 7.13-7.02 (m, 1H, H-5'); ^{13}C-NMR (CD_3OD, 75.5 MHz): δ 18.4 (CH_3), 28.4 [(CH_3)$_3$C], 39.4 (C-3), 39.8 (C-4), 81.4 [C(CH_3)$_3$], 109.6 (C-5), 114.6 (CH), 114.7 (CH), 119.0 (C-6'), 130.7 (C-5'), 145.8 (C-1'), 147.3 (C-6), 158.7 (C-3'), 168.1 (CO), 172.7 (C-2); HRMS-ESI$^+$ calcd. for $[C_{17}H_{21}NNaO_4]^+$ (MNa)$^+$ 326.1363 *m/z*, found 326.1358.

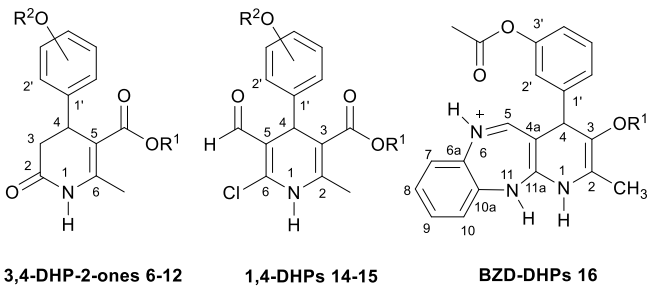


Figure 3. Numbering used in the assignation of the NMR signals.

(±)-5-(Bencyloxycarbonyl)-4-(3-hydroxyphenyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(±)-6c]. Reaction time: 23 h. White solid; mp 130-132 °C; yield 84%; ν_{max}(KBr) 3310, 1709, 1676, 1634, 1598 cm^{-1}; ^{1}H-NMR (CD_3OD, 300.13 MHz): δ 2.40 (s, 3H, CH_3), 2.53 (dd, 1H, ^3J 1.7, $|^2J|$ 16.2 Hz, *H*H-3), 2.96 (dd, 1H, ^3J 8.2, $|^2J|$ 16.3 Hz, H*H*-3), 4.20 (br d, 1H, ^3J 7.9 Hz, H-4), AB system (δ_A 5.04, δ_B 5.11, $|^2J_{A,B}|$ 12.7 Hz, CH_2), 6.69-6.57 (m, 3H, Ar), 7.17-7.01 (m, 3H, Ar), 7.31-7.17 (m, 3H, Ar); ^{13}C-NMR (CD_3OD, 75.5 MHz): δ 18.6 (CH_3), 39.3 (C-4), 39.4 (C-3), 66.7 (CH_2), 107.5 (C-5), 114.6 (CH), 114.8 (CH), 119.1 (C-6'), 128.6 (2 x CH), 128.8 (CH), 129.4 (2 x CH), 130.8 (CH), 137.8 (C-1"), 145.4 (C-1'), 149.6 (C-6), 158.8 (C-3'), 168.3 (CO), 172.6 (C-2); HRMS-ESI$^+$ calcd. for $[C_{20}H_{20}NO_4]^+$ $(M+H)^+$ 338.1387 *m/z*, found 338.1371.

(±)-4-(4-Hydroxyphenyl)-5-(methoxycarbonyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(±)-7a]. Reaction time: 24 h. White solid; mp 195-197 °C; yield 64%; ν_{max}(KBr) 3341, 1749, 1638, 1598, 1481 cm^{-1}; ^{1}H-NMR (CD_3OD, 300.13 MHz): δ 2.38 (d, 3H, ^5J 0.6 Hz, CH_3), 2.50 (dd, 1H, ^3J 1.9, $|^2J|$ 16.2 Hz, *H*H-3), 2.91 (dd, 1H, ^3J 7.8, $|^2J|$ 16.2 Hz, H*H*-3), 3.63 (s, 3H, OCH_3), 4.14 (br d, 1H, ^3J 7.8 Hz, H-4), 6.68 (d, 2H, ^3J 8.6, H-3', H-5'), 6.97 (d, 2H, ^3J 8.5, H-2', H-6'); ^{13}C-NMR (CD_3OD, 75.5 MHz): δ 18.5 (CH_3), 38.4 (C-4), 39.7 (C-3), 51.7 (CH_3), 108.2 (C-5), 116.4 (C-3' and C-5'), 128.7 (C-2' and C-6'), 134.2 (C-1'), 148.8 (C-6), 157.3 (C-4'), 169.2 (CO), 172.9 (C-2); HRMS-ESI$^+$ calcd. for $[C_{14}H_{15}NNaO_4]^+$ $(MNa)^+$ 284.0893 *m/z*, found 284.0897.

(±)-5-(Bencyloxycarbonyl)-4-(4-hydroxyphenyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(±)-7c]. Reaction time: 24 h. White solid; mp 166-167 °C; yield 54%; ν_{max}(KBr) 3367, 3235, 2949, 1694, 1628 cm^{-1}; ^{1}H-NMR (CD_3OD, 300.13 MHz): δ 2.39 (s, 3H, CH_3), 2.50 (dd, 1H, ^3J 1.9, $|^2J|$ 16.3 Hz, *H*H-3), 2.93 (dd, 1H, ^3J 8.0, $|^2J|$ 16.3 Hz, H*H*-3), 4.18 (br d, 1H, ^3J 7.5 Hz, H-4), AB system (δ_A 5.02, δ_B 5.13, $|^2J_{A,B}|$ 12.7 Hz, CH_2), 6.68 (d, 2H, ^3J 8.6 Hz, Ar), 6.96 (d, 2H, ^3J 8.6 Hz, Ar), 7.20-7.10 (m, 2H, Ph), 7.31-7.22 (m, 3H, Ph); ^{13}C-NMR (CD_3OD, 75.5 MHz): δ 18.6 (CH_3), 38.5 (C-4), 39.6 (C-3), 66.7 (CH_2), 108.0 (C-5), 116.4 (2 x CH), 128.6 (2 x CH), 128.81 (C-6'), 128.84 (2 x CH), 129.3 (2 x CH), 134.5 (C), 137.8 (C), 149.1 (C-6), 157.3 (C), 168.3 (CO), 172.8 (C-2); HRMS-ESI$^+$ calcd. for $[C_{20}H_{19}NNaO_4]^+$ $(M+Na)^+$ 360.1220 *m/z*, found 360.1204.

(±)-4-(2-Hydroxyphenyl)-5-(methoxycarbonyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(±)-9a]. Once the pyridone (±)-**8a** was obtained after a reaction time of 23 h and purification by flash chromatography (hexane:EtOAc 3:1), this compound (351 mg, 1.0 mmol) was dissolved in methanol (69 mL) and 10% Pd-C (96 mg) was added. The mixture was stirred at room temperature for 4 days. After this time, the catalyst was filtered through a pad of Celite® and washed with methanol. The solvents were evaporated giving (±)-**9a** as a white solid; mp 191-192 °C; overall yield 54%; ν_{max}(KBr) 3250, 1684, 1583, 1431, 1343 cm^{-1}; ^{1}H-NMR (CD_3OD, 300.13 MHz): δ 2.38 (d, 3H, ^5J 0.5 Hz, CH_3), 2.67 (dd, 1H, ^3J 2.1, $|^2J|$ 16.3 Hz, *H*H-3), 2.77 (dd, 1H, ^3J 7.7, $|^2J|$ 16.3 Hz, H*H*-3), 3.55 (s, 3H, OCH_3), 4.51 (br d, 1H, ^3J 6.9 Hz, H-4), 6.65 (td, 1H, ^4J (d) 1.2, ^3J (t) 7.5 Hz, Ar), 6.74 (dd, 1H, ^4J 1.2, ^3J 8.0 Hz, Ar), 6.81 (dd, 1H, ^4J 1.8, ^3J 7.7 Hz, Ar), 6.98 (td, 1H, ^4J (d) 1.7, ^3J (t) 7.9 Hz, Ar); ^{13}C-NMR (CD_3OD, 75.5 MHz): δ 18.5 (CH_3), 33.4 (C-4), 37.3 (C-3), 51.7 (OCH_3), 107.0 (C-5), 116.2 (C-3'), 120.3 (C-5'), 127.5 (C-4'), 128.1 (C-1'), 128.9 (C-6'), 149.7 (C-6), 156.0 (C-2'), 169.2 (CO), 173.4 (C-2); HRMS-ESI$^+$ calcd. for $[C_{14}H_{16}NO_4]^+$ $(M+H)^+$ 262.1074 *m/z*, found 262.1069.

General procedure for the acylation of 4-(hydroxyphenyl)-3,4-DHP-2-ones. To a solution of the corresponding phenolic (±)-**6a-c,** (±)-**7a,c**, or (±)-**9a** (0.77 mmol) in THF (5 mL), DMAP (94 mg, 0.77 mmol) and acetic anhydride (109 μL, 1.16 mmol) or 2-methylpropanoyl chloride (123 μL, 1.16 mmol), were added under an inert atmosphere. The mixture was stirred at room temperature for 4 h. Then, EtOAc (20 mL) was added and the solution was successively washed with aq 1N HCl (15 mL), water (2 x 15 mL) and brine (15 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. No further purification was necessary.

(±)-4-(3-Acetoxyphenyl)-5-(methoxycarbonyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(±)-10a]. White solid; mp 196-197 °C; yield 88%; ν_{max}(KBr) 3217, 3123, 1768, 1705, 1689, 1636 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 2.27 (s, 3H, CH_3), 2.40 (s, 3H, CH_3COO), 2.71 (dd, 1H, ^3J 1.2, $|^2J|$ 16.6 Hz, *H*H-3), 2.92 (dd, 1H, ^3J 8.0, $|^2J|$ 16.6 Hz, H*H*-3), 3.66 (s, 3H, OCH_3), 4.26 (br d, 1H, ^3J 7.2 Hz, H-4), 6.89 (t, 1H, ^4J 2.0 Hz, Ar), 6.96 (ddd, 1H, ^5J 0.9, ^4J 2.2, ^3J 8.0 Hz, Ar), 7.05 (br d, 1H, ^3J 7.8 Hz, Ar), 7.28 (t, 1H, ^3J 7.9 Hz, Ar), 7.91 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 19.5 (CH_3), 21.3 (CH_3COO), 37.7 (C-4), 38.0 (C-3), 51.7 (OCH_3), 106.7 (C-5), 120.0 (CH), 120.4 (CH), 124.2 (C-6'), 129.8 (C-5'), 143.8 (C-1'), 146.7 (C-6), 151.1 (C-3'), 167.3 (CO), 169.4 (CH_3COO), 170.4 (C-2); HRMS-ESI$^+$ calcd. for $[C_{16}H_{17}NNaO_5]^+$ $(MNa)^+$ 326.0999 *m/z*, found 326.1007.

(±)-4-(3-Acetoxyphenyl)-5-(*tert*-butoxycarbonyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(±)-10b] White solid; mp 133-134 °C; yield 82%; ν_{max}(KBr) 3222, 3125, 1767, 1703, 1632 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 1.36 (s, 9H, Bu^t), 2.27 (s, 3H, CH_3), 2.35 (s, 3H, CH_3COO), 2.66 (dd, 1H, ^3J 2.6, $|^2J|$ 16.7 Hz, *H*H-3), 2.91 (dd, 1H, ^3J 8.2, $|^2J|$ 16.7 Hz, H*H*-3), 4.18 (dd, 1H, ^3J 2.6 Hz, ^3J 8.5 Hz, H-4), 6.89 (t, 1H, ^3J 1.9 Hz, Ar), 6.94 (ddd, 1H, ^5J 0.9 Hz, ^4J 2.2, ^3J 8.0 Hz, Ar), 7.05 (d, 1H, ^3J 7.8 Hz, Ar), 7.28 (t, 1H, ^3J 7.9 Hz, Ar), 7.59 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 18.9 (CH_3), 21.3 (CH_3COO), 28.2 [$(CH_3)_3C$], 37.9 (C-3), 38.3 (C-4), 80.7 [$C(CH_3)_3$], 108.4 (C-5), 120.0 (CH), 120.2 (CH), 124.1 (C-6'), 129.7 (C-5'), 144.5 (C-1'), 145.3 (C-6), 151.0 (C-3'), 166.1 (CO), 169.3 (CH_3COO), 171.1 (C-2); HRMS-ESI$^+$ calcd. for $[C_{19}H_{23}NNaO_5]^+$ $(MNa)^+$ 368.1468 *m/z*, found 368.1488.

(±)-4-(3-Acetoxyphenyl)-5-(bencyloxycarbonyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(±)-10c]. White solid; mp 128-130 °C; yield 94%; ν_{max}(KBr) 3216, 3117, 1763, 1692, 1632 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 2.25 (s, 3H, CH_3), 2.40 (s, 3H, CH_3COO), 2.68 (dd, 1H, ^3J 1.3, $|^2J|$ 16.6 Hz, *H*H-3), 2.92 (dd, 1H, ^3J 8.2, $|^2J|$ 16.7 Hz, H*H*-3), 4.27 (br d, 1H, ^3J 7.6 Hz, H-4), AB system (δ_A 5.08, δ_B 5.10, $|^2J_{A,B}|$ 12.6 Hz, CH_2), 6.87 (t, 1H, ^4J 1.9 Hz, Ar), 6.97 (ddd, 1H, ^5J 0.8 Hz, ^4J 2.3, ^3J 8.0 Hz, Ar), 7.02 (d, 1H, ^3J 7.8 Hz, Ar), 7.19-7.09 (m, 2H, Ar), 7.33-7.21 (m, 4H, Ar), 8.67 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 19.2 (CH_3), 21.3 (CH_3COO), 37.7 (C-4), 37.9 (C-3), 66.1 (CH_2), 106.4 (C-5), 120.0 (CH), 120.4 (CH), 124.2 (CH), 127.9 (CH), 128.0 (CH), 128.5 (CH), 129.8 (CH), 136.2 (C-1"), 144.0 (C-1'), 147.4 (C-6), 151.1 (C-3'), 166.5 (CO), 169.3 (CH_3COO), 171.1 (C-2); HRMS-

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ESI$^+$ calcd. for $[C_{22}H_{21}NNaO_5]^+$ (MNa)$^+$ 402.1312 *m/z*, found 402.1325.

(±)-5-(Methoxycarbonyl)-6-methyl-4-[3-(2-methylpropanoyloxy)phenyl)]-3,4-dihydro-2(1*H*)-pyridone [(±)-10d]. White solid; mp 178-180 °C; yield 89%; ν_{max}(KBr) 3431, 3224, 1754, 1693, 1639 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 1.30 [d, 6H, $(CH_3)_2CH$], 2.41 (d, 3H, ^5J 0.5 Hz, CH_3), 2.86-2.67 [m, 2H, *H*H-3 and C*H*$(CH_3)_2$], 2.91 (dd, 1H, ^3J 8.0, $|^2J|$ 16.6 Hz, H*H*-3), 3.66 (s, 3H, CH_3O), 4.26 (br d, 1H, ^3J 7.9 Hz, H-4), 6.89 (t, 1H, ^4J 1.9 Hz, Ar), 6.95 (ddd, 1H, ^5J 1.0, ^4J 2.2, ^3J 8.0 Hz, Ar), 7.02 (br d, 1H, ^3J 7.8 Hz, Ar), 7.31-7.23 (m, 2H, Ar overlapped with $CHCl_3$), 7.49 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 19.0 [$(CH_3)_2CH$], 19.2 (CH_3), 34.3 [$(CH_3)_2CH$], 37.6 (C-4), 38.0 (C-3), 51.6 (OCH_3), 106.6 (C-5), 120.0 (CH), 120.3 (CH), 123.8 (C-6'), 129.8 (C-5'), 143.7 (C-1'), 147.0 (C-6), 151.3 (C-3'), 167.3 (CO), 171.0 (CH_3COO), 175.5 (C-2); HRMS-ESI$^+$ calcd. for $[C_{18}H_{21}NNaO_5]^+$ (MNa)$^+$ 354.1312 *m/z*, found 354.1308.

(±)-4-(4-Acetoxyphenyl)-5-(methoxycarbonyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(±)-11a]. White solid; mp 178-180 °C; yield 71%; ν_{max}(KBr) 3213, 1765, 1685, 1631, 1430 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 2.28 (s, 3H, CH_3), 2.40 (s, 3H, CH_3COO), 2.69 (dd, 1H, ^3J 1.3, $|^2J|$ 16.5 Hz, *H*H-3), 2.92 (dd, 1H, ^3J 7.9, $|^2J|$ 16.6 Hz, H*H*-3), 3.65 (s, 3H, CH_3O), 4.25 (br d, 1H, ^3J 7.4 Hz, H-4), 6.99 (d, 2H, H-3', H-5'), 7.18 (d, 2H, H-2', H-6'), 8.15 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 19.4 (CH_3), 21.3 (CH_3COO), 37.3 (C-4), 38.1 (C-3), 51.6 (OCH_3), 107.1 (C-5), 121.9 (C-3', C-5'), 127.9 (C-2', C-6'), 139.5 (C-1'), 146.6 (C-6), 149.7 (C-4'), 167.3 (CO), 169.6 (CH_3COO), 170.8 (C-2); HRMS-ESI$^+$ calcd. for $[C_{16}H_{17}NNaO_5]^+$ (MNa)$^+$ 326.0999 *m/z*, found 326.0996.

(±)-4-(4-Acetoxyphenyl)-5-(bencyloxycarbonyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(±)-11c]. White solid; mp 163-164 °C; yield 91%; ν_{max}(KBr) 3221, 3112, 2974, 1759, 1693, 1633 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 2.29 (s, 3H, CH_3), 2.41 (s, 3H, CH_3COO), 2.67 (dd, 1H, ^3J 1.1, $|^2J|$ 16.6 Hz, *H*H-3), 2.93 (dd, 1H, ^3J 8.2, $|^2J|$ 16.6 Hz, H*H*-3), 4.28 (br d, 1H, ^3J 7.7 Hz, H-4), AB system (δ_A 5.07, δ_B 5.11, $|^2J_{A,B}|$ 12.6 Hz, CH_2), 6.98 (d, 2H, ^3J 8.6 Hz, Ar), 7.22-7.08 (m, 4H, Ar), 7.35-7.25 (m, 3H, Ar), 8.41 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 19.3 (CH_3), 21.3 (CH_3COO), 37.5 (C-4), 38.1 (C-3), 66.1 (CH_2), 106.8 (C-5), 121.9 (2 x CH), 127.9 (2 x CH), 128.0 (2 x CH), 128.1 (C), 128.6 (2 x CH), 136.2 (C), 139.7 (C), 147.2 (C-6), 149.7 (C), 166.5 (CO), 169.6 (CH_3COO), 170.9 (C-2); HRMS-ESI$^+$ calcd. for $[C_{22}H_{21}NNaO_5]^+$ (MNa)$^+$ 402.1312 *m/z*, found 402.1315.

(±)-4-(2-Acetoxyphenyl)-5-(methoxycarbonyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(±)-12a]. White solid; mp 167-169 °C; yield 88%; ν_{max}(KBr) 3210, 1723, 1710, 1628, 1548 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 2.35 (s, 3H, CH_3), 2.42 (s, 3H, CH_3COO), 2.62 (dd, 1H, ^3J 1.3, $|^2J|$ 16.6 Hz, *H*H-3), 2.87 (dd, 1H, ^3J 8.6, $|^2J|$ 16.7 Hz, H*H*-3), 3.57 (s, 3H, OCH_3), 4.39 (br d, 1H, ^3J 7.9 Hz, H-4), 7.17-6.98 (m, 3H, Ar), 7.34-7.18 (m, 1H, H-3'), 8.54 (br s, 1H, NH). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 19.1 (CH_3), 21.2 (CH_3COO), 32.2 (C-4), 36.9 (C-3), 51.6 (OCH_3), 105.9 (C-5), 123.1 (C-3'), 126.5 (CH), 127.3 (CH), 128.3 (CH), 133.4 (C-1'), 147.4 (C-6), 148.1 (C-2'), 167.1 (CO), 169.2 (CH_3COO), 170.8 (C-2); HRMS-ESI$^+$ calcd. for $[C_{16}H_{17}NNaO_5]^+$ (MNa)$^+$ 326.0999 *m/z*, found 326.1003.

General procedure for the enzymatic hydrolysis. At the screening processes scale, the reaction mixture containing the corresponding acylated substrate (5.0 mg), the lipase (5.0 mg), H_2O (5.0 μL, 1% v/v) in 2-Me-THF (0.50 mL) was shaken at 28 °C and 250 rpm in an orbital shaker. The progress of the reaction was monitored by TLC and chiral HPLC until the achievement of the required conversion. The same ratio of substrate, enzyme, and solvent was employed in the preparative scale processes. The reaction was carried out in the same conditions until the required conversion was achieved. Then, the enzyme was removed by filtration and washed with MeOH. The crude residue was purified by flash chromatography on silica gel (hexane:EtOAc 3:1 as the eluent).

(*R*)-4-(3-Hydroxyphenyl)-5-(methoxycarbonyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(*R*)-6a]. Yield 45%; $[\alpha]_D^{20}$ −92.5 (*c* 0.57, MeOH), ee 94%.

(*S*)-4-(3-Acetoxyphenyl)-5-(methoxycarbonyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(*S*)-10a]. Yield 45%; $[\alpha]_D^{20}$ +84.1 (*c* 0.64, $CHCl_3$), ee 94%.

(*R*)-5-(*tert*-Butoxycarbonyl)-4-(3-hydroxyphenyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(*R*)-6b]. Yield 11%; $[\alpha]_D^{20}$ −162.8 (*c* 0.44, MeOH), ee 88%.

(*S*)-4-(3-Acetoxyphenyl)-5-(*tert*-butoxycarbonyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(*S*)-10b]. Yield 38%; $[\alpha]_D^{20}$ +66.0 (*c* 0.75, $CHCl_3$), ee 58%.

(*R*)-5-(Bencyloxycarbonyl)-4-(3-hydroxyphenyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(*R*)-6c]. Yield 37%; $[\alpha]_D^{20}$ −74.5 (*c* 0.72, MeOH), ee 96%.

(*S*)-4-(3-Acetoxyphenyl)-5-(bencyloxycarbonyl)-6-methyl-3,4-dihydro-2(1*H*)-pyridone [(*S*)-10c]. Colourless oil. Yield 43%; $[\alpha]_D^{20}$ +81.1 (*c* 0.68, $CHCl_3$), ee >99%.

Acetylation of optically active 4-(hydroxyphenyl)-3,4-DHP-2-ones. The optically active 4-(hydroxyphenyl)-3,4-DHP-2-ones (*R*)-**6a** and (*R*)-**6c** were acetylated in the same conditions used for the racemic samples, thus affording the corresponding (*R*)-**10a** (yield 85%; $[\alpha]_D^{20}$ −81.1 (*c* 1.41, $CHCl_3$), ee 94%) and (*R*)-**10c** (yield 90%; $[\alpha]_D^{20}$ −77.4 (*c* 0.66, $CHCl_3$), ee 96%).

Synthesis of optically active 1,4-DHPs 14a and 14c. (*R*)-**14a**, (*S*)-**14a**, (*R*)-**14c**, and (*S*)-**14c** were prepared from the corresponding optically active 3,4-DHP-2-ones (*R*)-**10a**, (*S*)-**10a**, (*R*)-**10c**, and (*S*)-**10c**, respectively, following the procedure described in Ref. 13. Purification of the products was carried out by flash chromatography (hexane:EtOAc 3:1 as the eluent).

Methyl (*S*)-4-(3-acetoxyphenyl)-6-chloro-5-methanoyl-2-methyl-1,4-dihydropyridine-3-carboxylate [(*S*)-14a]. Yellow solid; yield 86 %; $[\alpha]_D^{20}$ +3.4 (*c* 1.37, $CHCl_3$), ee 94%. ν_{max}(KBr) 3407, 3259, 1763, 1661, 1492 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 2.27 (s, 3H, CH_3), 2.42 (s, 3H, CH_3COO), 3.63 (s, 3H, CH_3O), 5.16 (s, 1H, H-4), 6.51 (br s, 1H, NH), 6.92 (d, 1H, ^3J 8.0 Hz, Ar), 6.99 (s, 1H, H-2'), 7.13 (d, 1H, ^3J 7.8 Hz, Ar), 7.24 (t, ^3J 7.9 Hz, H-5' overlapped with $CHCl_3$), 9.78 (s, 1H, HC=O). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 18.9 (CH_3), 21.4 (CH_3COO), 38.1 (C-4), 51.6 (OCH_3), 105.8 (C-5), 112.6 (C-3) 120.1 (C-4'), 120.9 (C-2'), 125.3 (C-6'), 129.2 (C-5'), 142.3 (C-1'), 144.6 (C-2), 146.7 (C-6), 150.7 (C-3'), 167.1 (CO), 169.7 (CH_3COO), 187.6 (CHO).

HRMS-ESI$^+$ calcd. for $[C_{17}H_{16}ClNNaO_5]^+$ $(MNa)^+$ 372.0609 *m/z*, found 372.0608.

(*R*)-14a. Yield 84 %; $[\alpha]_D^{20}$ −3.1 (*c* 1.32, $CHCl_3$), ee 93%.

Benzyl (*S*)-4-(3-Acetoxyphenyl)-6-chloro-5-methanoyl-2-methyl-1,4-dihydropyridine-3-carboxylate [(*S*)-14c]. Yellow solid; yield 92 %; $[\alpha]_D^{20}$ −14.9 (*c* 1.02, $CHCl_3$), ee >99%; mp 75-77 °C; ν_{max}(KBr) 3441, 3240, 3219, 1767, 1705, 1634, 1595, 1489 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 2.27 (s, 3H, CH_3), 2.42 (s, 3H, *C*H_3COO), AB system (δ_A 5.03, δ_B 5.09, $|^2J_{A,B}|$ 12.5 Hz, CH_2), 5.17 (s, 1H, H-4), 6.40 (br s, 1H, NH), 6.99-6.89 (m, 2H, Ar), 7.17-7.06 (m, 3H, Ar), 7.21 (t, 1H, ^3J 7.8 Hz, Ar), 7.31-7.26 (m, 3H, Ar), 9.76 (s, 1H, HC=O). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 19.3 (CH_3), 21.4 (*C*H_3COO), 38.3 (C-4), 66.3 (CH_2), 105.9 (C-5), 113.0 (C-3) 120.2 (C-4'), 121.1 (C-2'), 125.63 (C-6'), 128.1 (C-3", C-4", C-5"), 128.6 (C-2", C-6"), 129.2 (C-5'), 136.0 (C-1"), 141.4 (C-1'), 144.6 (C-2), 146.6 (C-6), 150.8 (C-3'), 166.2 (CO), 169.5 (CH_3*C*OO), 187.4 (CHO). HRMS-ESI$^+$ calcd. for $[C_{23}H_{20}ClNNaO_5]^+$ $(MNa)^+$ 448.0922 *m/z*, found 448.0913.

(*R*)-14c. Yield 84 %; $[\alpha]_D^{20}$ +13.1 (*c* 1.14, $CHCl_3$), ee 96%.

Synthesis of optically active hybrid BZD-DHPs 16a and 16c. Following an analogous procedure to that described in Ref. 6b, (*S*)-**16a**, (*R*)-**16a**, (*S*)-**16c**, and (*R*)-**16c** were prepared from the optically active (*R*)-**14a**, (*S*)-**14a**, (*R*)-**14c**, and (*S*)-**14c**, respectively (notice the change of the priority order of the substituents of the chiral C-4 according to Cahn-Ingold-Prelog rule, see Scheme 4): To a solution of the corresponding 1,4-DHP **14** (0.10 mmol) in anhydrous THF (1.4 mL), bencene-1,2-diamine (12 mg, 0.11 mmol) and TFA (7.7 μL, 0.10 mmol) were added. The resulting solution was stirred at r.t. for 7–8 h. The specific reaction time is indicated in each case. All benzodiazepines were isolated by filtration or by previous removing of the solvent. The resulting solid was finally washed with a hexane-diethyl ether mixture to yield the salt derivative **16** as dark red solids.

(*R*)-4-(3-Acetoxyphenyl)-3-(methoxycarbonyl)-2-methyl-4,11-dihydro-1*H*-benzo[*b*]pyrido[2,3-*e*][1,4]diazepin-6-ium chloride/trifluoroacetate (2:1) mixed salt [(*R*)-16a]. Reaction time 8.0 h; Yield 97 %; $[\alpha]_D^{20}$ −50.0 (*c* 0.03, MeOH), ee 94%. ν_{max}(KBr) 3423, 3227, 3145, 1764, 1704, 1643, 1617 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 300.13 MHz): δ 2.25 (s, 3H, CH_3), 2.35 (s, 3H, CH_3COO), 3.57 (s, 3H, CH_3O), 4.48 (s, 1H, H-4), 6.64-6.46 (m, 2H, H-7, H-10), 7.04-6.90 (m, 4H, H-5, H-8, H-9, Ar), 7.14 (d, 2H, ^3J 7.8 Hz, Ar), 7.36 (t, 1H, ^3J 7.8 Hz, H-5'), 10.14 (br d, 2H, ^3J 8.1 Hz, H-6, NH), 11.01 (br s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 75.5 MHz): δ 17.9 (CH_3), 20.9 (*C*H_3COO), 41.1 (C-4), 51.6 (CH_3O), 94.5 (C-4a), 107.7 (C-3), 119.3 (C-4'), 120.5 (C-2'), 122.4 and 122.8 (C-7, C-10), 123.4 (C-6'), 127.7 and 128.0 (C-8, C-9), 130.1 (C-5'), 131.7 (C-10a), 135.8 (C-6a), 142.2 (C-2), 147.1 (C-1'), 150.9 (C-3'), 159.6 (C-11a), 160.1 (C-5), 165.9 (CO), 169.2 (CH_3*C*OO). ^{19}F-NMR (DMSO-d_6, 254.99 MHz): δ −74.51. HRMS-ESI$^+$ calcd. for $[C_{23}H_{22}N_3O_4]^+$ $(MH)^+$ 404.1605 *m/z*, found 404.1606 (the symbol M has been used for the no protonated molecule).

(*S*)-16a. Reaction time 8.0 h; yield 95 %; $[\alpha]_D^{20}$ +48.0 (*c* 0.03, MeOH), ee 93%.

(*R*)-4-(3-Acetoxyphenyl)-3-(benzyloxycarbonyl)-2-methyl-4,11-dihydro-1*H*-benzo[*b*]pyrido[2,3-*e*][1,4]diazepin-6-ium chloride/trifluoroacetate (5:2) mixed salt [(*R*)-16c]. Reaction time 7.0 h; yield 97 %; $[\alpha]_D^{20}$ −36.7 (*c* 0.03, MeOH), ee >99%. ν_{max}(KBr) 3413; 3220; 1767; 1714; 1646; 1616 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 300.13 MHz): δ 2.25 (s, 3H, CH_3), 2.37 (s, 3H, CH_3COO), 4.51 (s, 1H, H-4), AB system (δ_A 5.00, δ_B 5.13, $|^2J_{A,B}|$ 12.9 Hz, CH_2), 6.65-6.47 (m, 2H, H-7, H-10), 7.31-6.80 (m, 11H, Ar and H-5), 7.35 (t, 1H, ^3J 7.9 Hz, H-5'), 10.14 (br d, 2H, ^3J 7.5 Hz, H-6, NH), 11.04 (br s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 75.5 MHz): δ 17.9 (CH_3), 20.9 (*C*H_3COO), 41.2 (C-4), 65.6 (CH_2), 94.6 (C-4a), 107.5 (C-3), 119.4 (C-4'), 120.5 (C-2'), 122.3 and 122.9 (C-7, C-10), 123.5 (C-6'), 127.4 (C-3", C-5"), 127.7, 127.8 and 128.0 (C-4", C-8, C-9), 128.3 (C-2", C-6"), 130.1 (C-5'), 131.8 (C-10a), 135.8 (C-6a), 136.0 (C-1"), 142.8 (C-2), 147.3 (C-1'), 150.9 (C-3'), 159.6 (C-11a), 160.3 (C-5), 165.2 (CO), 169.1 (CH_3*C*OO). ^{19}F-NMR (DMSO-d_6, 254.99 MHz): δ −74.05. HRMS-ESI$^+$ calcd. For $[C_{29}H_{26}N_3O_4]^+$ $(M)^+$ 480.1918 *m/z*, found 480.1916 (the symbol M has been used for the no protonated molecule).

(*S*)-16c. Reaction time 7.5 h; yield 96 %; $[\alpha]_D^{20}$ +38.1 (*c* 0.05, MeOH), ee 96%.

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Table of contents information

Kinetic resolution of 3,4-DHP-2-ones with *Candida rugose* lipase (CRL) has been possible due to the presence of a reactive phenolic ester in a remote position.