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Preparation of isoxazolidinyl nucleoside enantiomers by lipase-catalysed kinetic resolution

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ABSTRACT

An efficient biocatalytic procedure to obtain chiral N,O-nucleoside derivatives consisting of a lipase-catalysed resolution of the corresponding racemates in organic solvent has been developed. Enantioselective esterification of thymine and cytosine derivatives, (±)-**9a** and (±)-**9b**, has been investigated by comparing the efficiency of different lipases and acyl donors. Since esterification of (±)-**9a** and (±)-**9b**, occurred with low enantioselectivity ($E \leqslant 14$) in the presence of the lipases considered, for preparative purposes we resorted, with success, to a double sequential kinetic resolution, using Lipozyme IM as the best catalyst. This approach enables us to obtain all the enantiomers with ee $\geqslant$ 95%. The absolute configuration of the new chiral *N*-acetyl cytosine derivative **9b** was established by circular dichroism spectroscopy.

1. Introduction

N,O-Nucleosides constitute a particular class of modified nucleoside bearing a heterocyclic system (isoxazolidine) instead of the ribose ring. These compounds have been shown to be endowed with important biological properties:[1,2] ADFU **1** is a good inductor of apoptosis on lymphoid and monocytoid cells, acting as a strong potentiator of Fas-induced cell death[3] and phosphonated N,O-nucleosides **2** are potent reverse transcriptase inhibitors on different retroviruses[4] (Fig. 1). Recently, compounds **2**, synthesised as a racemic mixture from the corresponding tosylated N,O-nucleoside by Arbuzov reaction,[5] have been proposed to ensure long lasting control of HTLV-1, an oncogen retrovirus associated with adult Leukemia/Limphoma (ATLL) and with myelopathy, tropical spastic Paraparesis.[6]

Several asymmetric routes have been reported for the synthesis of enantiopure N,O-nucleosides, such as; (i) the 1,3-dipolar cycloaddition of chiral nitrones;[7,8] (ii) nucleophilic addition of enolates to α-alkoxy- and α-aminonitrones;[9] and (iii) the Michael addition of *N*-methyl hydroxylamine to unsaturated esters and lactones.[10] However, the reported strategies do not constitute as a general way for the synthesis of β-D and β-L enantiopure N,O-nucleosides since the stereochemical result is strictly correlated to the structural features of the reagents, the chosen route and the experimental conditions, and in many instances the undesired α-anomer predominates.[11,7c]

Lipases are able to catalyse asymmetric transesterification reactions in a wide range of hydrophobic substrates. The use of these enzymes as chiral catalysts has useful applications in preparative organic chemistry, so that the chemo-enzymatic approach for asymmetric synthesis is largely accepted in synthetic design.[12] To the best of our knowledge, nothing has been reported for the enzymatic resolution of racemic N,O-nucleosides, whereas the lipase resolution has been applied for a few classes of modified nucleosides, such as carbanucleosides and 2′-deoxynucleosides.[13]

Herein, we report an efficient method for the preparation of enantiopure chiral isoxazolidine nucleosides **9a** and **9b** via lipase-catalysed transesterification reactions in an organic solvent.

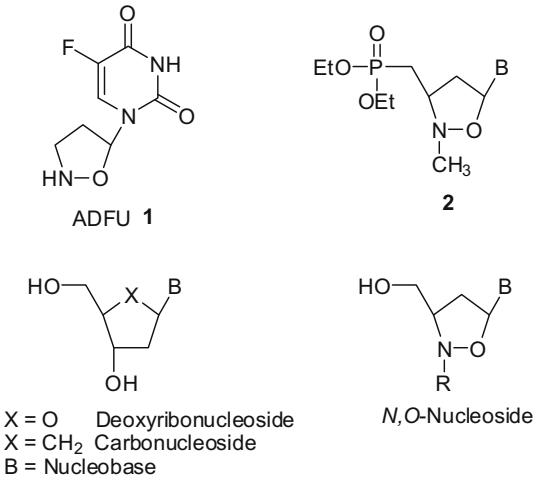

Figure 1. Modified nucleosides.

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2. Results and discussion

2.1. Synthesis of racemic N,O-nucleosides (±)-9a,b

Racemic compounds (±)-**9a** and (±)-**9b** were synthesised by a three-step procedure starting from the nitrone **3** as previously reported.[5] Thus, the 1,3-dipolar cycloaddition of nitrone **3** with vinyl acetate, performed in anhydrous ether at room temperature in 3 h afforded a mixture of isoxazolidines (±)-**4** and (±)-**5** with a 90% yield. The crude mixture of isoxazolidines was subjected to nucleosidation with silylated thymine or *N*-acetyl cytosine in dry acetonitrile in the presence of 0.4 equiv of TMSOTf as a catalyst. The α- and β-anomers have been separated by flash chromatography and the *cis*-adducts (±)-**7a**,**b** were treated with TBAF in THF to give the corresponding nucleosides (±)-**9a** and (±)-**9b** (Scheme 1).

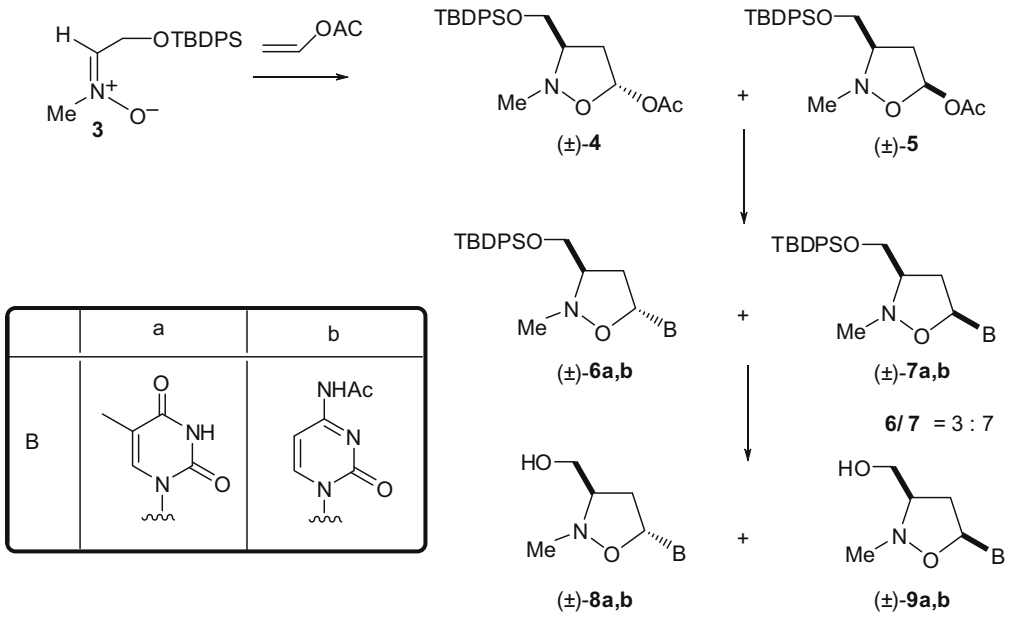
2.2. Lipase-catalysed resolution of (±)-9a and (±)-9b

A preliminary esterification screening for the resolution of thymine, (±)-**9a,** and acetyl cytosine, (±)-**9b,** derivatives was carried out using three native lipases from *Pseudomonas cepacia*, *Pseudomonas fluorescens* (lipase AK) and *Candida rugosa* and five as immobilised form *P. cepacia* (PS-C, PSC-I and PS-D), *Mucor miehei* (Lipozyme IM) and *Candida antarctica* (Novozyme 435). Due to the scarce solubility of (±)-**9a** and (±)-**9b** in the organic solvents of ordinary use in lipase catalysis we chose 1,4-dioxane as the reaction medium, and vinyl acetate was exploited as acyl donor. All the lipases used catalysed the esterification of substrates but lacking enantioselectivity, probably due to the distance between the hydroxyl function and the stereogenic centre, as reported for the chiral recognition of primary alcohols.[14] The best one was Lipozyme IM allowing $E = 7$ for (±)-**9a** and $E = 8$ for (±)-**9b**.[15]

Generally, it proved to be difficult to attain highly enantioselective resolution by lipase-catalysed reaction when E <20. To improve the enantiomeric discrimination, several strategies concerning physical and/or chemical modifications of the enzyme or of the substrate have been proposed.[16] One of these consists of a change of acyl donor in order to induce a favourable conformational variation of substrate-binding site, so resulting in an improvement in enzymatic enantioselectivity. With this intention, the lipozyme-assisted esterification in 1,4-dioxane of (±)-**9a** and (±)-**9b** was repeated using vinyl propionate and vinyl benzoate as acyl donors, and the results concerning the influence of the acyl donor are summarised in Table 1.

The use of vinyl propionate instead of vinyl acetate in the esterification of (±)-**9a** has a positive influence on reaction rate but not on the enantioselectivity. Conversely, the use of the bulkier benzoate did not affect the reaction rate but gave a significant enhancement in enantioselectivity (Table 1, entry 3). The change of acyl donor in the esterification of (±)-**9b** leads to a consequent decline in enantioselectivity although a very fast reaction is observed using vinyl propionate (Table 1, entries 5 and 6).

Considering these poor results, in order to access our enantiopure compounds we resorted to trying a double kinetic resolution

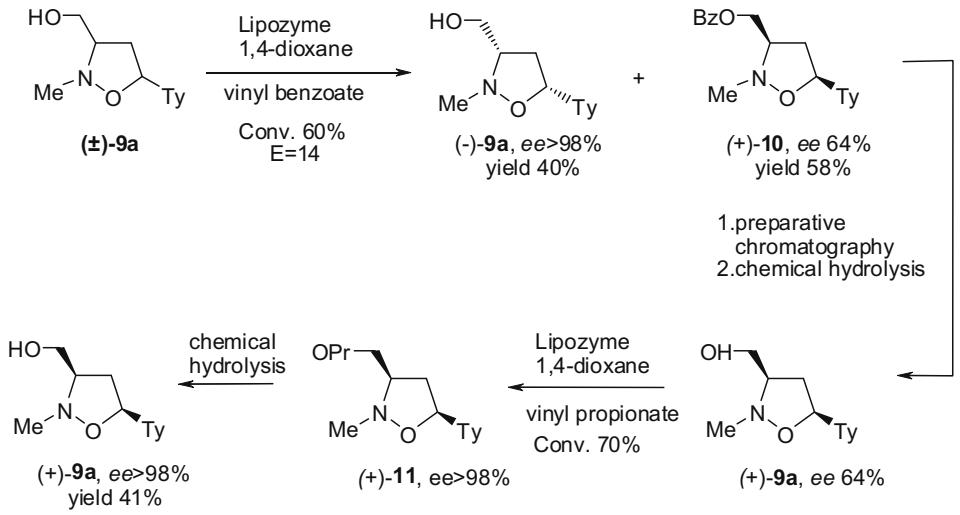


Scheme 1. Synthesis of racemic N,O-nucleosides (±)-**9a** and (±)-**9b**.

Table 1
Acyl donor influence on the enantioselectivity of biocatalysed resolution[a] of (±)-**9a** and (±)-**9b**

Entry	Substrate	Acyl donor	Time (h)	Conv.[b] (%)	ee % alcohol	ee % ester	E[c]
1	(±)-**9a**	Vinyl acetate	3	38	40	65	7
2	(±)-**9a**	Vinyl propionate	1	47	56	63	8
3	(±)-**9a**	Vinyl benzoate	3	32	39	81	14
4	(±)-**9b**	Vinyl acetate	1.5	25	24	72	8
5	(±)-**9b**	Vinyl propionate	0.5	46	45	53	5
6	(±)-**9b**	Vinyl benzoate	3	37	25	43	3

[a] The reactions were performed in the presence of Lipozyme IM in 1,4-dioxane at 45 °C and shaken at 300 rpm.
[b] Substrate conversions and enantiomeric excesses were determined by chiral HPLC analysis using a Chiralcel OJ column.
[c] See Ref. 15.



Scheme 2. Double enzymatic kinetic resolution of (±)-**9a**.

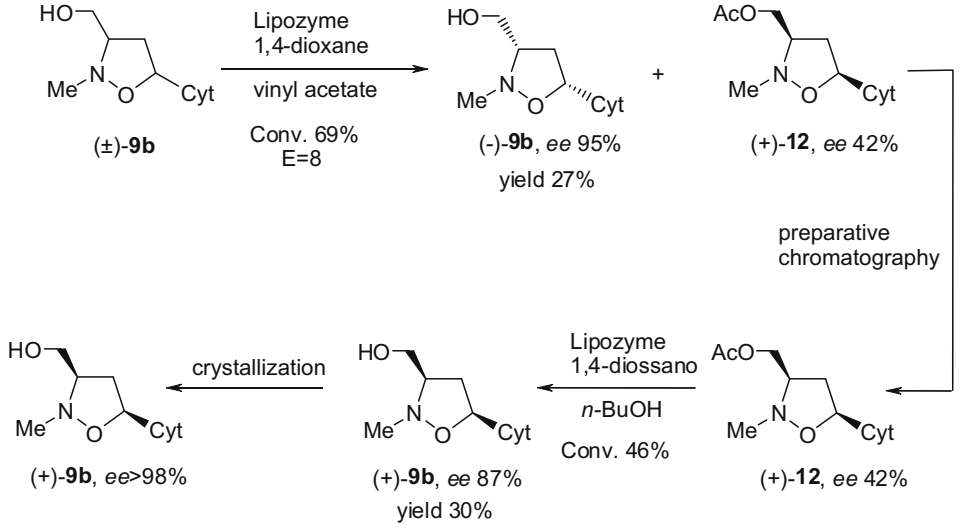
procedure. This, in theory, is realisable by a lipase-assisted sequential acylation followed by deacylation. Alternatively, if the biocatalysed alcoholysis step is not efficient, the enantioenriched ester can be transformed by chemical hydrolysis into the corresponding alcohol, and subjected to a second lipase-assisted esterification.

To this end, (±)-**9a** was subjected to an esterification reaction, catalysed by Lipozyme IM in 1,4-doxane using vinyl benzoate as the acyl donor (Scheme 2). The reaction was monitored by HPLC chiral analysis and the residue (−)-**9a** was obtained with ee >98% (yield 40%) by protracting the reaction to 60% conversion. The benzoate derivative (+)-**10** after chromatographic purification (ee 64%, yield 58%) was dissolved in 1,4-dioxane and an alcoholysis using *n*-butanol in the presence of Lipozyme IM was attempted. Unfortunately, this reaction occurred very slowly giving a negligible amount of the desired product after 3 days. As a consequence of this result, in order to have the desired (+)-**9a** in satisfactory enantiomeric excess, the ester (+)-**10** was transformed into alcohol (+)-**9a** with 64% ee, by a chemical hydrolysis with aqueous NH_4OH/methanol mixture, so in the presence of Lipozyme IM and vinyl propionate, (+)-**9a** was subjected to a new resolution cycle. Since this substrate was enantioenriched, the use of vinyl propionate instead of vinyl benzoate does not compromise the efficiency of the resolution, while it allows us to have the ester (+)-**11** in high enantiomeric excess (ee >98%) and 41% overall yield in a shorter time. Alkaline hydrolysis of (+)-**11**, carried out in aqueous NH_4OH /methanol mixture, gave the desired product (+)-**9a** quantitatively.

In the resolution of the *N*-acetyl-cytosine derivative (±)-**9b**, the first step of a biocatalysed esterification was realised by choosing vinyl acetate as an acyl donor, but due to the low enantioselectivity (E = 8, Table 1, entry 4) the reaction required to reach 69% conversion to give the unreacted alcohol (−)-**9b** with a satisfactory 95% ee. Preparative column chromatography furnished (−)-**9b** in 27% yield and acetyl derivative (+)-**12** with 42% ee. In the second step of the reaction, ester (+)-**12** was subjected to alcoholysis in presence of Lipozyme IM using *n*-butanol as nucleophile, (Scheme 3). After 42 h, a 46% substrate conversion was reached and chiral HPLC analysis of the reaction evidenced the alcohol (+)-**9b** possessing 87% ee. After chromatographic purification and crystallisation, alcohol (+)-**9b** possessing ee >98% was recovered from the mother liquor.

2.3. Determination of absolute configurations

An absolute configuration of (3*R*,5*S*) was assigned to compound (−)-**9a** by comparing its specific rotation to the literature value[9] so



Scheme 3. Double enzymatic kinetic resolution of (±)-**9b**.

that a stereopreference (*S*) of Lipozyme IM was determined. The absolute configuration at C3 and C5 of (−)-**9b** was unknown, therefore it was determined by comparison of a CD spectrum with that of (−)-**9a** whose configuration was known. The CD spectra of these compounds are shown in Figure 2. Since the spectrum obtained for (−)-**9b** was found to be a good approximation matching to that registered for (3*R*,5*S*)-isomer (−)-**9a**, the same absolute configuration was assigned to the stereogenic centres of (−)-**9b**. Moreover these data obtained from CD analysis were in agreement with the stereopreference of the lipase showing an (*S*)-selectivity in the esterification of a $-CH_2OH$ group at C3 of (±)-**9a**.

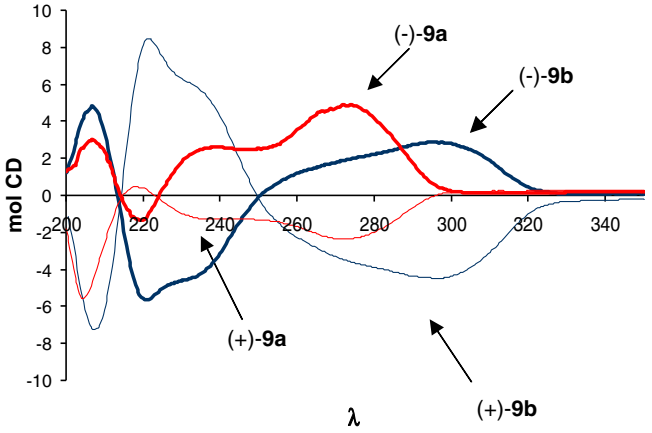


Figure 2. CD spectra recorded in methanol of **9a** and **9b** enantiomers.

3. Conclusions

In this work we have applied, for the first time, an enzymatic kinetic resolution procedure to obtain chiral non-racemic N,O-nucleosides. Despite the low enantioselectivity shown by the lipases investigated due to large distance between the –OH groups and the stereogenic centres, single enantiomers of (±)-**9a** and (±)-**9b** have been anyway obtained in high enantiomer purity by developing a lipase-catalysed double sequential kinetic resolution route. The absolute configuration of new (3*R*,5*S*)-(−)-**9b** was assigned by CD analysis by comparison of its spectrum with that of known (−)-**9a**. Since (+)-**9a** and (+)-**9b** displayed the same C-3 stereochemistry, it could be deduced that the lipase recognition was mainly affected by the isoxazolidine moiety with less influence for the chemical nature of the pyrimidine base.

4. Experimental

4.1. Materials and methods

Lipases from *P. cepacia*, *P. fluorescens* (lipase AK), *C. rugosa*, immobilised *P. cepacia* (PS-C, PSC-I and PS-D), *M. miehei* (Lipozyme IM) and *C. antarctica* (Novozyme 435) were purchased from Aldrich and were used as received. Optical rotations were recorded on a DIP 135 JASCO instrument using a ϕ 3.5 × 100 mm cell. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, on a Varian 300 instrument. Chemical shifts (δ) are reported in ppm relative to TMS and coupling constants (*J*) in hertz. The enantiomeric excesses and substrate conversions were determined by chiral HPLC analysis using a Chiralcel® OJ (Daicel Chemical Industries) column eluting with *n*-hexane/ethanol mixtures with simultaneous detection at λ 225, 250, 275 and 300 nm. Chiral HPLC conditions: Chiralcel® OJ column eluting with a 7:3 *n*-hexane/EtOH mixture at 0.7 ml/min^{-1} for 20 min and then 1.3 ml/min flow rate was used for alcohol (±)-**9a** (t_R 12.9 and 14.4 min for (3*R*,5*S*)- and (3*S*,5*R*)-enantiomer), for the benzoate **(±)-10** (t_R 35.2 and 45.2 min for (3*R*,5*S*)- and (3*S*,5*R*)-enantiomer) and for the propionate (±)-**11** (t_R 27.1 and 47.5 min for (3*R*,5*S*)- and (3*S*,5*R*)-enantiomer). A 7:3 *n*-hexane/EtOH mixture and a 0.7 ml/min^{-1} flow rate were employed for the alcohol (±)-**9b** (t_R 11.5 and 13.6 min for (3*R*,5*S*)- and (3*S*,5*R*)-enantiomer) and for the acetyl derivative (±)-**12** (t_R 25.1 and 28.6 min for (3*R*,5*S*)- and (3*S*,5*R*)-enantiomer).

CD spectra were registered at 20 °C in MeOH (0.1 cm cell length) on a JASCO J-810 spectropolarimeter.

4.2. General procedure for analytical enzyme-catalysed esterification of (±)-9a and (±)-9b

To a solution of substrates **9a** and **9b** (0.04) in 1,4-dioxane (6 ml) were added vinyl ester (0.25 mmol) and lipase (100 mg). The mixture incubated at 45 °C was shaken at 300 rpm. At regular times, aliquots of the mixtures were analysed by chiral HPLC, and the reactions stopped at desired substrate conversion (in range of 30–50%).

4.3. Preparative resolution procedure of (±)-9a

Substrate (±)-**9a** (250 mg, 1 mmol) was dissolved in 150 ml of 1,4-dioxane containing 2.5 g of Lipozyme IM and vinyl benzoate (0.138 ml, 1 mmol) was added. The obtained mixture was incubated at 45 °C and shaken (300 rpm) until 60% of substrate conversion detected by HPLC analysis. Then the reaction was stopped by filtering off the lipase and the mixture chromatographed on silica gel eluting with CH_2Cl_2/MeOH 98:2, to furnish (+)-**10** yield 58% and ee 64% (194 mg, 0.58 mmol) and (−)-**9a** yield 40% (97 mg, 0.40 mmol) ee >98%.

Specific rotation data of (−)-**9a**: $[\alpha]_D^{25} = -113.5$ (*c* 0.8, EtOH) and $[\alpha]_D^{25} = -8.1$ (*c* 0.8, $CHCl_3$) {lit.[9] $[\alpha]_D^{20} = -11$ (*c* 0.8 $CHCl_3$)}; CD (*c* 6.3 × 10^{-4} M, CH_3OH): λ_{ext} 202 ($\Delta\varepsilon$ +1.59), 219 ($\Delta\varepsilon$ −1.31), 238 ($\Delta\varepsilon$ +2.59), 254 ($\Delta\varepsilon$ +2.67), 274 ($\Delta\varepsilon$ +4.87), 300 ($\Delta\varepsilon$ +0.23), 346 ($\Delta\varepsilon$ +0.21).

The NMR spectra and elemental analysis were identical with the literature data.[17]

Ester (+)-**10** was dissolved in NH_4OH/MeOH and hydrolysed by heating at 50 °C for 8 h. After removal of the solvents under reduced pressure, the residue was dissolved in CH_2Cl_2 and then extracted with water containing $NaHCO_3$. The organic layer was dried over anhydrous sodium sulfate and concentrated to obtain (+)-**9a** (ee >98%) quantitatively.

To a solution of (+)-**9a** (140 mg, 0.58 mmol) in 1,4-dioxane (100 ml) containing Lipozyme IM (1.9 g) was added vinyl propionate (0.170 ml, 1.56 mmol) and shaken at 45 °C and 300 rpm until 70% of substrate conversion detected by HPLC analysis. The reaction was stopped and the mixture purified by chromatography using CH_2Cl_2/MeOH 95:5 mixture as eluent to give ester (+)-**11** ee >98%. Chemical hydrolysis, carried out in NH_4OH/MeOH mixture, gave (99 mg, 0.41 mmol) of the homochiral alcohol (+)-**9a** in 41% overall yield.

4.4. Preparative resolution procedure for (±)-9b

Alcohol (±)-**9b** (300 mg, 1.3 mmol) was dissolved in 45 ml of 1,4-dioxane containing vinyl acetate (0.245 ml, 2.6 mmol) then the reaction was started by the addition of lipase Lipozyme IM (1.5 g). After 7 h at 300 rpm and 45 °C the reaction was stopped, at 69% substrate conversion detected by chiral HPLC analysis. The enzyme was filtered off and the mixture was chromatographed on silica gel column eluting with CH_2Cl_2/2-propanol 6:1 to obtain the alcohol (−)-**9b** with ee 95% and yield 27% (80 mg, 0.35 mmol). After crystallisation from CH_2Cl_2/2-propanol (−)-**9b** was obtained with ee >98%: $[\alpha]_D^{25} = -19.8$ (*c* 0.2 EtOH). ^{1}H NMR (500 MHz,

$CDCl_3$): δ 2.31 (s, 3H), 2.48 (ddd, 1H, J = 4.3, 9.5, and 13.5 Hz), 2.91 (s, 3H), 2.92 (m, 1H), 3.12 (ddd, 1H, J = 6.5, 7.2 and 13.5 Hz), 3.62 (dd, 1H, J = 4.0 and 12.0 Hz), 3.73 (dd, 1H, J = 4.0 and 12.0 Hz), 5.30 (br s, 1H), 6.06 (dd, 1H, J = 4.3 and 6.5 Hz), 7.45 (d, 1H, J = 8.0 Hz), 8.40 (d, 1H, J = 8.0 Hz). ^{13}C NMR (500 MHz, $CDCl_3$): δ 23.6, 39.2, 43.5, 60.1, 68.4, 88.9, 95.5, 141.65, 155.2, 162.8, 171.5. HRMS (EI) for (M^+): 268.1164. Anal. Calcd for $C_{11}H_{16}N_4O_4$: C, 49.25; H, 6.01; N, 20.88. Found: C, 49.31; H, 6.15; N, 21.04.

CD: (c 1.7 $\times$ 10^{-4} M) λ_{ext} 202 ($\Delta\varepsilon$ +2.53), 207 ($\Delta\varepsilon$ +4.56), 214 ($\Delta\varepsilon$ −0.26), 221 ($\Delta\varepsilon$ −5.70), 235 ($\Delta\varepsilon$ −4.26), 250 ($\Delta\varepsilon$ −0.24), 296 ($\Delta\varepsilon$ +2.86), 318 ($\Delta\varepsilon$ +0.66), 370 ($\Delta\varepsilon$ +0.10).

The isolated ester (+)-**12** (256 mg, 0.90 mmol) was dissolved in 1,4-dioxane (40 ml) and then Lipozyme IM (1.2 g) was added. The reaction was started by addition of *n*-butanol (0.084 ml, 0.95 mmol) and shaken at 45 °C and 300 rpm. The reaction was monitored by chiral HPLC and stopped at 46% substrate conversion. The alcohol (+)-**9b** was isolated with ee 87% and 30% overall yield (90 mg, 0.40 mmol) by preparative chromatography eluting with CH_2Cl_2/2-propanol 6:1. After crystallisation from CH_2Cl_2/*n*-hexane (+)-**9b** was obtained with ee >98%.

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