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Lipase-catalysed kinetic resolution as the key step in the synthesis of a new class of optically active 5,6-*trans*-9,10-dihydrophenanthroline derivatives

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ABSTRACT

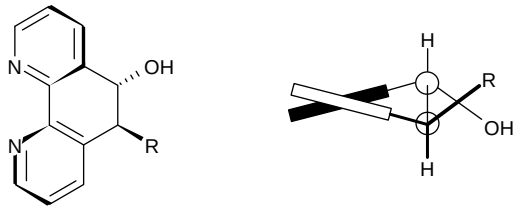
New atropisomeric 5,6-*trans*-9,10-dihydrophenanthroline amino- and hydroxy-derivatives **3**–**7** possessing two additional stereogenic centres were obtained in high enantiomeric purity by lipase-catalysed kinetic resolution of the corresponding easily accessible racemates. Lipase from *Pseudomonas fluorescens* (Lipase AK) showed good enantioselectivity ($E > 200$) in the esterification reaction of *trans*-5-azido-6-hydroxyl derivative (±)-**7**, giving access to the enantioforms (+)- and (−)-**7** isolated with ee = 97% and ee >98%, respectively. The chemical reduction of azide group furnished the homochiral amino derivatives (+)- and (−)-**4** without a loss in enantiomeric purity. For all the substrates investigated, lipase AK revealed a stereopreference for the enantiomer with a (*P*,*R*,*R*)-configuration.

1. Introduction

Chiral homo- and heterobidentate organic ligands containing nitrogen and/or oxygen atoms are successfully employed in asymmetric metal catalysis. When using C_2-symmetrical chiral diols, excellent results have been obtained in the enantioselective addition of diethylzinc to aldehydes, 1,4-conjugate additions and Diels–Alder reactions.[1] Enantiomerically pure amino alcohols are efficient ligands in the asymmetric transfer hydrogenation of ketones, as well as in the catalytic addition of alkyl groups to aldehydes.[2] Conversely, bidentate chiral chelating agents containing two endocyclic nitrogen atoms suitable for metal coordination such as 2,2′-bipyridines or 1,10-phenanthrolines, are employed in the asymmetric copper-catalysed cyclopropanation of alkenes and allylic oxidations, palladium-catalysed allylic substitution, addition of organozinc reagent to carbonyl compounds and rhodium-catalysed reduction of prochiral ketones.[3]

In this context, *trans*-5,6-dihydro-9,10-phenanthrolines can be considered as interesting ligands due to their particular stereochemistry concerning both axial and central chirality, as well as their high and versatile metal ions chelating power due to the presence of sp^2 nitrogen donors and additional active groups, such as dihydroxy- or amino-, directly bonded to the stereogenic centres.

Chiral non-racemic 2,2′-bipyridines and 1,10-phenanthrolines are commonly synthesised either by inserting chiral subunits in a pre-existing framework, or by coupling reactions of single heterocycle units containing stereocentres in the side chains.



R = OH or NH_2

The lipase's ability to work in organic solvent makes these catalysts useful in asymmetric organic synthesis due to their high versatility in accepting intricate stereochemical organic substrates. Excellent results have been obtained in the enantiodifferentiation of molecules having multiple stereocentres, and in recognition of rigid structures containing single axial, helical or planar chirality or combinations thereof.[4] As part of our research work concerning the chemoenzymatic preparation of stereochemically complex molecules, we have seen a noteworthy lipase efficiency in the stereodiscrimination of substrates with axial chirality.[5] Recently, we verified that the lipase from *Pseudomonas fluorescens* is stereoselective in the esterification reaction of racemic *trans*-5-hydroxy-6-methoxy-9,10-dihydrophenanthroline, a molecule containing both helical and central chirality.[6]

Since the nucleophilic ring-opening reaction of commercial epoxide **1** enables easy access to a series of dihydrophenanthroline derivatives (Scheme 1), we have prepared a set of amino hydroxy- and dihydroxy-dihydrophenanthrolines, potentially active as ligands for asymmetric catalysis, and realised a lipase chemoenzymatic procedure for their enantiomeric resolution, which is reported and discussed below.

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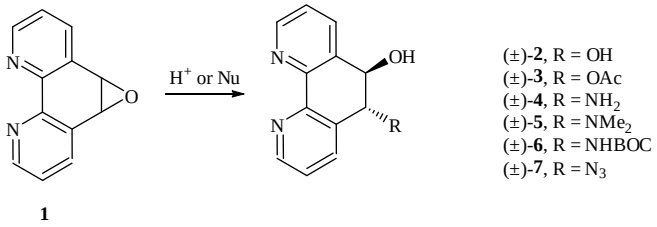

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Scheme 1.

2. Results and discussion

2.1. Enzymatic resolution

In our previous work, the lipase-catalysed resolution of racemic *trans*-5-hydroxy-6-methoxy-9,10-dihydrophenanthroline was performed using lipase AK in a methanol/vinyl acetate mixture as the reaction medium.[7] Over the course of that investigation, a spontaneous esterification reaction of the parent dihydroxyl-derivative (±)-**2** was evidenced; thus, at that time, its biocatalytic resolution was not considered further. However, enzymatic resolution of (±)-**2** could be achieved in a double sequential esterification if an enantiodiscrimination on the racemic monoester intermediate[8] is operative. This was the case, with the lipase-catalysed esterification of (±)-**2**, when dissolved in a 20% methanol/vinyl acetate mixture, and gave a nearly racemic monoacetate (±)-**3**. Prolonging the reaction time furnished a diester and unreacted monoester that were both enantiomerically enriched, thus indicating enzyme enantioselectivity in the second step of the esterification. On this basis, considering the higher solubility in hydrophobic solvents, (±)-**3** was thought to be a very suitable starting material to attempt the enantiomeric separation of (±)-**2**. With this intention (±)-**3**, prepared in high chemical yield by treatment of **1** with acetic acid, was subjected to esterification in 5% methanol/vinyl acetate; at 48% of conversion, diacetylated product (−)-**3a** and unreacted (+)-**3** with 92% and 90% ee, respectively, were obtained as result of a valuable enzymatic enantioselectivity (Table 1, entry 1).

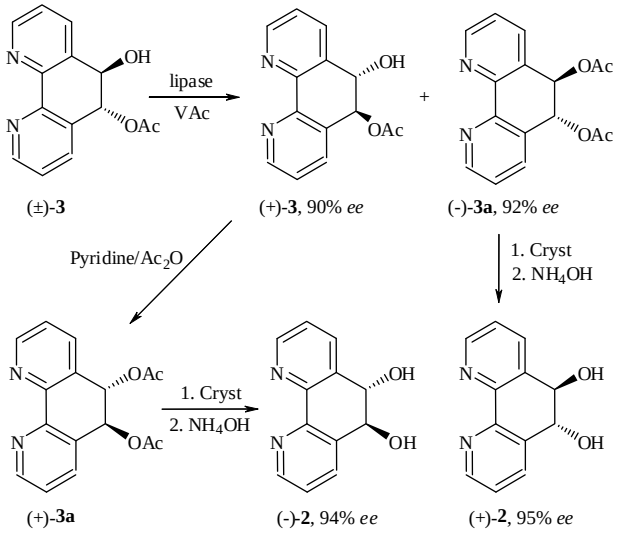
Table 1
Lipase-catalysed resolution[a] of racemic dihydrophenanthroline derivatives

Entry	*rac*-Compounds	Solvent	% ee[b] substrate	% ee product	*E*[c]
1	**3** (R = OAc)	5% MeOH/VAc	90	92	74
2	**4** (R = NH_2)	5% MeOH/VAc	—	—	—
3	**5** (R = NMe)	5% MeOH/VAc	26	42	3
4	**6** (R = NHBOC)	5% MeOH/VAc	89	90	57
5	**7** (R = N_3)	TBME	>98	97	>200

[a] The reactions were carried out in the presence of Lipase AK at 45 °C and 300 rpm.
[b] The enantiomeric excesses were determined by chiral HPLC using a Chiralcel OD® column eluting with *n*-hexane/2-propanol mixture.
[c] Ref. 7.

The enantiomeric purities of both enantioforms were improved to 95% and 94% by crystallization of diacetyl derivatives (−)-**3a** and (+)-**3a**, the latter obtained by conventional acetylation of (+)-**3**. Hydrolysis of (−)-**3a** and (+)-**3a** with aqueous ammonium hydroxide gave the corresponding homochiral alcohols (+)-**2** and (−)-**2** in quantitative yields (Scheme 2).

The amino derivative *trans*-5-amino-6-hyhydroxy-9,10-dihydrophenanthroline (±)-**4** was then considered and prepared by treating epoxide **1** with aqueous ammonium hydroxide. The attempt to resolve this racemate by the same enzymatic procedure



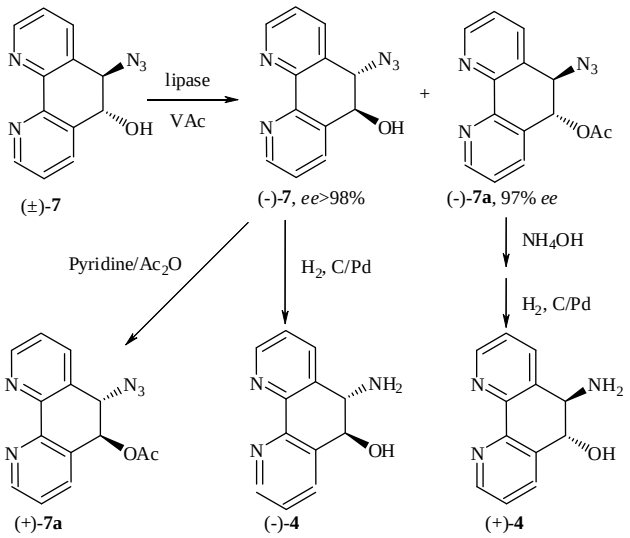
Scheme 2.

as described above for (±)-**3**, was ineffective. As a result of the biocatalysed esterification, substrate disappearance was observed and only trace of the diacetylated product were detected in solution. This behaviour is perhaps due to the addition of the substrate with the acetaldehyde generated in the collateral rapid esterification of methanol with vinyl acetate. Esterification of (±)-**4** carried out using a mixture of methanol/isopropenylacetate as solvent, did not give a substantial improvement in the performance of the reaction. To avoid this drawback, derivative (±)-**5**, obtained from **1** by epoxide ring opening with dimethylamine in 1,4-dioxane, was chosen as an alternative, considering that the amine moiety was not available for further imine formation. The reaction was carried out in 5% methanol/vinyl acetate mixture in the presence of lipase AK, but in this case a low enzymatic enantioselectivity was detected ($E = 3$) (Table 1, entry 3).

In order to assess if the low lipase activity could be related to the presence of the amino function, (±)-**4** was converted into the related *tert*-butoxycarbonyl-derivative (BOC) (±)-**6**, which was then subjected to an enzymatic reaction under the same conditions. Despite the large steric hindrance due to the presence of a *tert*-butoxy group vicinal to the hydroxyl, the reaction afforded 49% substrate conversion after 4 days with a satisfactory enantioselectivity of $E = 57$; the alcohol residue (+)-**6** and the corresponding acetyl derivative were recovered with 89% ee and 90% ee, respectively (Table 1, entry 4).

In view of the results obtained, the neutral *trans*-5-azido-6-hydroxyl derivative (±)-**7**, a direct precursor of corresponding amino alcohol (±)-**4**, was considered as a useful substrate and prepared from epoxide **1**, by treatment with sodium azide in a 1,4-dioxane/water mixture. Thanks to the better solubility of the azide derivative, a preliminary enzymatic reaction of (±)-**7** was performed in methyl *tert*-butyl ether, a more useful solvent for the lipase catalysis.

After 24 h, 18% substrate conversion was detected by HPLC analysis and a $E > 200$ value was calculated for this resolution process. In a preparative scale esterification of (±)-**7**, the lipase transformed 49% of the substrate, to furnish product (−)-**7a** and residue (−)-**7** possessing 97% ee and ee > 98%, respectively (Table 1, entry 5) after eight days. Ester (−)-**7a**, previously hydrolysed by heating in aqueous ammonium hydroxide, and subjected to a reduction of the azide group, quantitatively furnished the homochiral aminoderivative (+)-**4**. In a similar way, reduction of (−)-**7** gave amino derivative (−)-**4** (Scheme 3).



Scheme 3.

2.2. Determination of the absolute configuration

The absolute configurations of all the products obtained were assigned by ^{1}H NMR and CD spectroscopy. The aromatic rings in bridged 3,3′-bipyridines, such as 2,2′-bridged biphenyl, are non-coplanar and chiroptical properties are correlated to the twist angle of the atropisomeric aromatic system. The sign of the CD band in the region of 210–235 nm is diagnostic of the helicity of biphenyl chromophore and *P* or *M* helicity is associated with a positive or negative band, respectively. The absolute configurations of benzylic C-9 and C-10 in dihydrophenanthrene derivatives were assigned by the combination of helicity with the conformational diaxial or diequatorial orientation of substituents as deduced by ^{1}H NMR analysis of J_{9-10} coupling constant.[8] Taking into account these considerations and the similarity observed in the CD spectra of dihydrophenanthrolines with 9,10-dihydrophenanthrene systems, the absolute configurations of chiral compounds here obtained were determined by the same method. However, it should be noted that the helical conformation in phenanthrene derivatives is strongly solvent dependent;[9] since the compounds prepared were soluble in methanol, their configurations were assigned in this solvent.

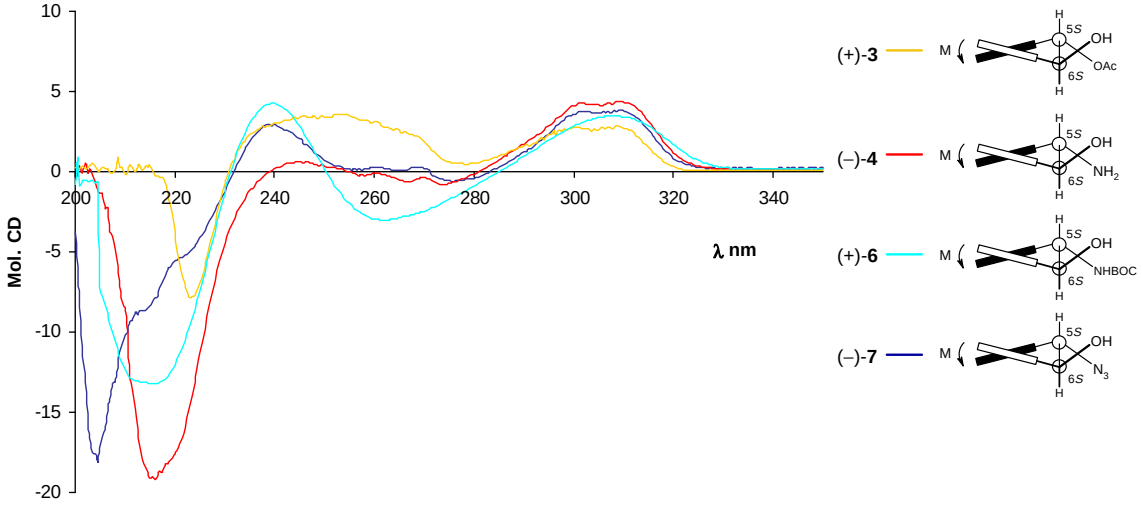


Figure 1. CD spectra recorded in methanol for (+)-**3**; (−)-**4**; (+)-**6** and (−)-**7**.

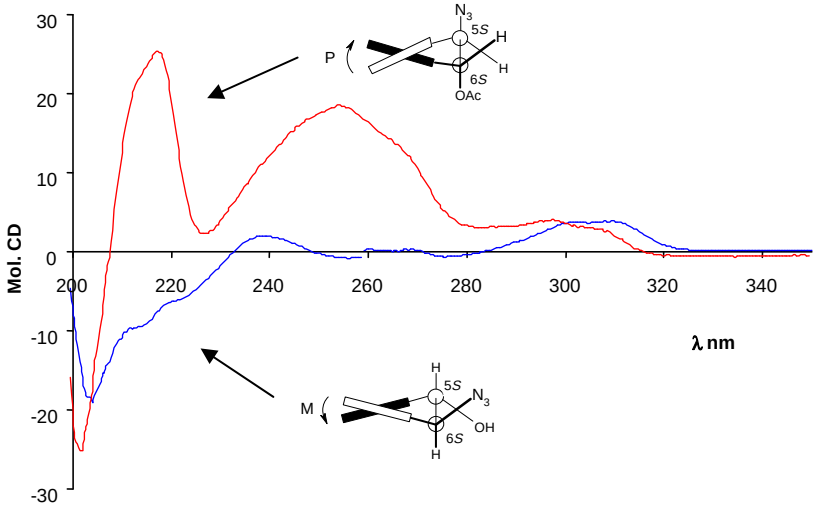


Figure 2. CD spectra recorded in methanol for (−)-**7** and its acetyl derivative (+)-**7a**.

The axial *M* and central (5*S*,6*S*)-absolute configuration determined for all the alcohol residues of the enzymatic reactions showed a lipase preference for the enantiomer possessing stereochemistry *P*,5*R*,6*R*, in agreement with behaviour observed in lipase-catalysed enantiomeric resolution of *trans*-5-hydroxy-6-methoxy-9,10-dihydrophenanthroline previously reported[6] (Fig. 1 and Table 2).

The CD spectra were registered too for the acetyl derivatives to acquire conformational information on the preferred helicity and related orientation of benzylic substituents. According to results Lakshman et al.[8b] reported for the corresponding phenanthrene derivatives, a change of sign in the CD band at 210–230 nm was observed in this case for azidoacetoxy-derivative (+)-**7a** with respect to azidohydroxy- and aminohydroxy-derivatives (−)-**7** and (−)-**4** (Fig. 2). This conformational switch was caused by the shift of the benzylic groups from the equatorial to the more stable pseudoaxial orientation and was confirmed by a lower coupling constant value measured in the ^{1}H NMR spectrum of (+)-**7a** (6.6 Hz) when compared with (−)-**7** (9.6 Hz) or (−)-**4** (9.3 Hz) (Table 2, entries 5 and 2).

Table 2
CD data and absolute configurations of dihydrophenanthroline derivatives

Entry	Compounds	CD band (210-235 nm)	Helicity	$J_{5\text{-}6}$ (Hz)	C5 and C6 chirality
1	(+)-**3** (OAc, OH)	–	M	8.0	(*S*,*S*) *eq*
2	(−)-**7** (N_3, OH)	–	M	9.6	(*S*,*S*) *eq*
3	(−)-**4** (NH_2, OH)	–	M	9.3	(*S*,*S*) *eq*
4	(+)-**6** (NHBOC, OH)	–	M	8.2	(*S*,*S*) *eq*
5	(+)-**7a** (N_3, OAc)	+	P	6.6	(*S*,*S*) *ax*
6	(+)-**3a** (OAc, OAc)	+	P	4.8	(*S*,*S*) *ax*

The CD spectra and ^{1}H NMR were registered in methanol and CD_3OD, respectively.

A helicity change of the bipyridine chromophore was also observed for (+)-**3** after chemical acetylation, in fact the spectrum of diester (+)-**3a** showed an inversion of the CD band at 223 nm. Moreover, its ^{1}H NMR spectrum showed a lower coupling constant $J_{5\text{–}6}$ (4.8 Hz), measured on a satellite band, confirming a favoured pseudoaxial orientation of benzylic substituents (Table 2, entry 6), probably due to adverse steric interactions between the two acetyl groups. Finally, a chemical hydrolysis of (+)-**3** to (−)-**2** did not cause any conformational change in the bipyridine chromophore so that a negative sign of CD band in the spectrum at 224 nm was detected (Fig. 3).

3. Conclusion

A lipase-catalysed esterification reaction in organic solvent was found to be effective for obtaining both enantiomers of *trans*-5,6-dihydroxy-9,10-phenanthroline and *trans*-5-amino-6-hydroxy-9,10-dihydrophenantroline, versatile potential ligands in asymmetric chemical catalysis. The lipase AK from *P. fluorescens* showed good enantioselectivity, even in the detrimental medium conditions adopted, consisting of a methanol/vinyl acetate mixture. The absolute configurations of the new chiral compounds were assigned in methanol by means of CD and NMR analyses; furthermore, an interesting conformational switch of helical chirality was seen for isomers (+)-**3** and (−)-**7** as a consequence of the hydroxyl group acetylation.

4. Experimental

4.1. Materials and methods

Amano Lipase AK from *P. fluorescens* was purchased from Aldrich and used as received. Thin-layer chromatography (TLC) was performed on Silica Gel 60-F_{254} aluminium sheets eluting with ethyl acetate/2-propanol/NH_4OH mixtures. Preparative chromatography was carried out using Silica Gel® Si 60 (0.04–0.063 mm) from Merck.

^{1}H and ^{13}C NMR spectra were recorded in CD_3OD unless otherwise specified, on a Bruker Avance™ 400 instrument at 400.13 and 100.03 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to TMS and coupling constants (J) in Hertz. Optical rotations were recorded on a DIP 135 JASCO instrument using a φ 3.5 × 100 mm cell. The enantiomeric excesses and substrate conversions were determined by chiral HPLC analysis using a Chiralcel® OD (Daicel Chemical Industries) column eluting with *n*-hexane/2-propanol 1:1 mixture at 0.5 ml/min flow rate at 25 °C with simultaneous detection at λ 225, 250, 275 and 300 nm. CD spectra were registered at room temperature in MeOH (0.1 cm cell length) on a JASCO J-810 spectropolarimeter.

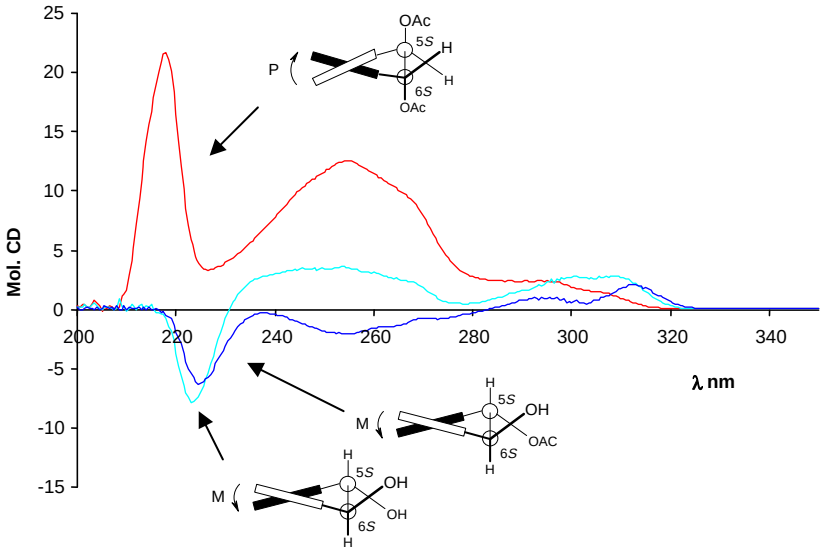


Figure 3. CD spectra recorded in methanol for (−)-**2** and its monoacetyl and diacetyl derivatives (+)-**3** and (+)-**3a**.

4.2. Chemical synthesis and enzymatic resolution of (±)-3

The 5,6-epoxy-1,10-dihydrophenanthroline **1** (500 mg 2.5 mmol) was dissolved in 8 ml of acetic acid/water 2:1 (v/v) mixture and the suspension was stirred at 50 °C for two days. After complete conversion of the substrate, as detected by TLC analysis eluting with ethyl acetate/2-propanol/NH_4OH 6:1:1 mixture, the solvent was evaporated in vacuo. Product (±)-**3** was isolated by crystallisation from ethyl acetate/*n*-hexane mixture in 87% yield (567 mg, 2.2 mmol). ^{1}H NMR in CD_3OD δ 2.14 (s, 3H), 5.00 (d, 1H, J = 8.1), 6.12 (d, 1H, J = 8.1), 7.44 (m, 2H), 7.80 (d, 1H, J = 7.6), 8.02 (d, 1H, J = 7.6), 8.64 (m, 2H); ^{13}C NMR in CD_3OD δ 19.5, 69.0, 73.0, 124.3, 124.6, 130.3, 133.8, 135.7, 135.9, 149.2, 149.3, 149.6, 149.8, 170.2. Chiral HPLC analysis: t_R/min 17.03 for (+)-**3** and 20.6 for (−)-**3**.

To a solution of (±)-**3** (300 mg, 1.1 mm ol) in 5:95 (v/v) methanol/vinyl acetate (60 ml), 1.5 g of lipase AK was added and then the suspension was shaken at 45 °C and 300 rpm. After six days, at 48% of substrate conversion, the reaction was stopped by filtering off the enzyme. The products were isolated by preparative chromatography eluting with AcOEt/acetone/TEA 6:1:1.

Compound (+)-**3**: 41% yield (103 mg, 0.4 mmol) 90% ee: $[\alpha]_D^{25} = +75.0$ (c 0.6, CH_3OH); CD: (c 2.2×10^{-4}) λ_{ext} 207 ($\Delta\varepsilon$ +0.08), 213 ($\Delta\varepsilon$ +10.65), 218 ($\Delta\varepsilon$ +21.63), 221 ($\Delta\varepsilon$ +10.6), 226 ($\Delta\varepsilon$ +3.32), 239 ($\Delta\varepsilon$ +7.32), 254 ($\Delta\varepsilon$ +12.51), 271 ($\Delta\varepsilon$ +6.81), 277 ($\Delta\varepsilon$ +3.43), 317 ($\Delta\varepsilon$ +0.14).

Compound (−)-**3a**: 38% yield (111.7 mg, 0.42 mmol) and 95% ee recovered from mother liquor after crystallisation with AcOEt/*n*-hexane: $[\alpha]_D^{25} = -211.4$ (c 0.3, CH_3OH); ^{1}H NMR δ: 1.98 (s, 6H), 6.18 (s, 2H), 7.46 (dd, 2H, J = 4.8 and 7.7), 7.94 (dd, 2H, J = 1.6 and 7.7), 8.73 (dd, 2H, J = 1.6 and 4.8); ^{13}C NMR in $CDCl_3$ δ: 20.7, 69.5, 124.2, 128.4, 137.7, 150.7, 151.3, 169.7. CD: (c 1.4×10^{-4}) λ_{ext} 209 ($\Delta\varepsilon$ +1.13), 218 ($\Delta\varepsilon$ +21.64), 225 ($\Delta\varepsilon$ +3.62), 255 ($\Delta\varepsilon$ +12.55), 279 ($\Delta\varepsilon$ +2.88), 313 ($\Delta\varepsilon$ +0.49).

Chiral HPLC analysis of diacetyl derivative (±)-**3a** gave: t_R/min 14.6 and 62.74, respectively, for (+)-**3a** and (−)-**3a**.

4.3. Preparation of (+)-2

Diacetate (−)-**3a** was recovered with 95% ee from the mother liquors of crystallisation from AcOEt/*n*-hexane mixture. The diol (+)-**2** was obtained in quantitative yield by chemical hydrolysis of (−)-**3a** carried out in NH_4OH/MeOH at 50 °C for 3h: $[\alpha]_D^{25} = +77.8$ (c 0.2, CH_3OH); ^{1}H NMR δ: 4.78 (s, 2H), 7.48 (dd, 2H, J = 4.8 and 7.6), 8.10 (d, 2H, J = 7.6), 8.65 (d, 2H, J = 4.8); ^{13}C NMR δ: 73.2, 124.6, 136.1, 136.3, 150.1, 150.7. CD: (c 6.4×10^{-5}) λ_{ext} 210 ($\Delta\varepsilon$ +0.18), 225 ($\Delta\varepsilon$ −6.28), 230 ($\Delta\varepsilon$ −0.30), 254 ($\Delta\varepsilon$ −2.09), 279 ($\Delta\varepsilon$ −0.34), 313 ($\Delta\varepsilon$ +2.04).

4.4. Preparation of (−)-2

Monoacetate (+)-**3** was acetylated by conventional acetylation procedure using pyridine/Ac_2O mixture. The obtained (+)-**3a** was crystallised as reported procedure for (−)-**3a** and after chemical hydrolysis (−)-**2** was recovered with 94% ee: $[\alpha]_D^{25} = -75.1$ (c 0.4, CH_3OH).

4.5. Chemical synthesis of (±)-4

A solution of **1** (300 mg, 1.4 mmol) in NH_4OH (8 ml) was stirred overnight at 50 °C. The reaction was stopped when TLC analysis (AcOEt/2-propanol/NH_4OH 5:1:1) showed total conversion of substrate. The solvent was evaporated in vacuo and (±)-**4** was recovered by precipitation from AcOEt/*n*-hexane: ^{1}H NMR δ: 4.40 (d, 1H, J = 9.3), 4.98 (d, 1H, J = 9.3), 7.52 (m, 2H), 8.09 (m, 2H), 8.70 (m, 2H); ^{13}C NMR δ: 55.9, 71.6, 125.8, 126.1, 136.2, 136.3, 136.5, 149.9, 150.5, 151.1.

4.6. Chemical synthesis of (±)-5

To a solution of **1** (300 mg, 1.2 mmol) in 1,4-dioxane (6 ml) was added 3 ml of dimethylamine. The reaction mixture was stirred overnight at 50 °C to complete conversion of substrate, then the solvent was evaporated and (±)-**5** was recovered in quantitative yield as a solid residue: ^{1}H NMR δ: 2.24 (s, 6H), 3.86 (d, 1H, J = 5.3), 5.07 (d, 1H, J = 5.3), 7.42 (m, 2H), 7.92 (m, 2H), 8.63 (m, 2H); ^{13}C NMR δ: 42.6, 68.6, 69.5, 125.3, 125.8, 132.6, 136.5, 137.6, 140.1, 150.2, 150.4, 150.9, 151.8.

Chiral HPLC analysis: t_R/min 10.7 and 16.8 for (±)-**5** and 11.1 and 19.6 for the corresponding racemic acetyl derivative.

4.7. Chemical synthesis and enzymatic resolution of (±)-6

To a solution of (±)-**4** (500 mg, 2.3 mmol) in MeOH (4 ml) were added 0.5 ml of TEA and 0.5 ml of *t*-butoxycarbonyl chloride. The reaction mixture was stirred at 45 °C for 1 h, after which complete substrate conversion was detected by TLC analysis. The product was isolated in 91% yield (670 mg, 2.1 mmol) by preparative chromatography eluting with AcOEt/2-propanol/NH_4OH 5:1:1 mixture. ^{1}H NMR in $CDCl_3/CD_3OD$ 1:3 (v:v)[10] δ: 1.42 (s, 9H), 4.97 (d, 1H, J = 10.1), 5.01 (d, 1H, J = 10.1), 7.59 (dd, 1H, J = 5.2 and 7.6), 7.65 (dd, 1H, J = 5.2 and 7.6), 8.02 (d, 1H, J = 7.6), 8.31 (d, 1H, J = 7.6), 8.65 (m, 2H); ^{13}C NMR δ: 28.7, 56.4, 70.8, 80.7, 125.7, 134.3, 136.3, 136.5, 136.8, 150.1, 150.3, 150.6, 151.2, 158.6.

Enzymatic acetylation was carried out dissolving (±)-**6** (300 mg, 0.9 mmol) in a 5:95 (v/v) methanol/vinyl acetate in the presence of 1.5 g of lipase AK. The reaction was shaken at 45 °C and 300 rpm for 4 days when a 47% of substrate conversion was detected. The products were isolated by preparative chromatography (6:1 AcOEt/TEA).

Compound (+)-**6**: 42% yield (126 mg, 0.38 mmol) and 96% ee after crystallisation from CH_2Cl_2/*n*-hexane. $[\alpha]_D^{25} = +51.9$ (c 0.2, $CHCl_3$); CD: (c 7.5×10^{-4}) λ_{ext} 203 ($\Delta\varepsilon$ −5.11), 214 ($\Delta\varepsilon$ −13.18), 227 ($\Delta\varepsilon$ −5.01), 239 ($\Delta\varepsilon$ +4.24), 262 ($\Delta\varepsilon$ −3.03), 307 ($\Delta\varepsilon$ +3.46). Chiral HPLC analysis was carried out after conventional acetylation (see (−)-**6a**).

Compound (−)-**6a**: 43% yield (144 mg, 0.39 mmol), 90% ee: $[\alpha]_D^{25} = -68.9$ (c 0.3, MeOH); ^{1}H NMR δ: 1.46 (s, 9H), 2.14 (s, 3H), 5.10 (d, 1H, J = 8.1), 6.19 (d, 1H, J = 8.1), 7.46 (m, 2H), 7.87 (m, 2H), 8.68 (m, 2H); ^{13}C NMR δ: 20.7, 28.7, 53.5, 72.4, 80.9, 125.6, 125.8, 131.6, 132.9, 137.2, 137.5, 150.6, 150.9, 151.1, 151.2, 157.9, 171.7. Chiral HPLC analysis: t_R/min 24.37 for (+)-**6a** and 33.12 for (−)-**6a**.

4.8. Chemical synthesis and enzymatic resolution of (±)-7

To a solution of **1** (500 mg, 2.5 mmol) in a 2:3 1,4-dioxane/H_2O mixture (20 ml) was added sodium azide (200 mg, 3.1 mmol). The reaction mixture was stirred overnight at room temperature until complete substrate conversion was detected by TLC analysis (AcOEt/2-propanol/NH_4OH 6:0.5:0.5). Product (±)-**7** was recovered in 75% yield (519 mg, 1.87 mmol) by preparative chromatography. ^{1}H NMR in $CDCl_3/CD_3OD$ 1:3 (v:v) mixture:[10] δ: 5.09 (d, 1H, J = 10.0), 5.14 (d, 1H, J = 10.0), 7.81 (dd, 1H, J = 5.2 and 7.8), 7.93 (dd, 1H, J = 5.4 and 7.7), 8.36 (d, 1H, J = 7.7), 8.57 (d, 1H, J = 7.8), 8.76 (m, 2H); ^{13}C NMR in $CDCl_3$ δ: 65.3, 71.8, 124.2, 124.5, 129.5, 133.2, 134.1, 134.9, 149.5, 150.1, 150.4, 150.6. Chiral HPLC analysis: t_R/ min 13.57 for (+)-**7** and 15.03 for (−)-**7**.

The lipase-catalysed resolution of (±)-**7** was carried out by dissolving the substrate (300 mg, 1.23 mmol) in 40 ml of TBME in the presence of 1.5 g of lipase AK. The reaction was started by addition

of 2 ml of vinyl acetate and shaken at 45 °C and 300 rpm for 8 days, then the enzyme was filtered off and the products were recovered by preparative chromatography (7:0.5:0.5 AcOEt/2-propanol/NH_4OH).

Compound (−)-**7**: 44% yield (135 mg, 0.55 mmol) and ee > 98%. $[\alpha]_D^{25} = -67.5$ (*c* 0.6, $CHCl_3$); CD: (*c* 9.6×10^{-5}) λ_{ext} 204 ($\Delta\varepsilon$ −18.2), 219 ($\Delta\varepsilon$ −5.96), 239 ($\Delta\varepsilon$ +2.85), 262 ($\Delta\varepsilon$ +0.20), 305 ($\Delta\varepsilon$ +3.66).

Compound (−)-**7a**: 39% yield (137 mg, 0.48 mmol), 97% ee: $[\alpha]_D^{25} = -264.5$ (*c* 0.6, MeOH); ^{1}H NMR in δ: 2.05 (s, 3H), 5.15 (d, 1H, *J* = 5.7), 6.11 (d, 1H, *J* = 5.7), 7.50 (dd, 1H, *J* = 4.8 and 7.7), 7.55 (dd, 1H, *J* = 4.8 and 7.7), 7.94 (dd, 1H, *J* = 1.4 and 7.7), 8.03 (dd, 1H, *J* = 1.4 and 7.7), 8.75 (dd, 1H, *J* = 1.4 and 4.8), 8.78 (dd, 1H, *J* = 1.4 and 4.8); ^{13}C NMR in $CDCl_3$ δ 20.73, 61.1, 70.5, 124.2, 127.8, 128.5, 136.0, 136.3, 150.2, 151.2, 169.8. CD: (*c* 4.3×10^{-5}) λ_{ext} 202 ($\Delta\varepsilon$ −24.2), 209 ($\Delta\varepsilon$ +6.33), 217 ($\Delta\varepsilon$ +26.2), 227 ($\Delta\varepsilon$ +3.25), 254 ($\Delta\varepsilon$ +19.43), 382 ($\Delta\varepsilon$ +3.96), 301 ($\Delta\varepsilon$ +4.30), 325 ($\Delta\varepsilon$ +0.31. Chiral HPLC analysis: t_R/min 17.32 for (+)-**7a** and 34.26 for (−)-**7a**.

4.9. Preparation of (−)-4 and (+)-4

To a solution of (−)-**7** (100 mg, 0.4 mmol, ee > 98%) in ethanol (5 ml) was added a catalytic amount of C/Pd. The reaction was carried out for 4 h under 2 atm hydrogen pressure, then the catalyst was filtered off and the solvent evaporated in vacuo.

Compound (−)-**4**: 100% yield (86.4 mg, 0.4 mmol). $[\alpha]_D^{25} = -51.9$ (*c* 0.1, MeOH); ^{1}H NMR δ: 4.4 (d, 1H, *J* = 9.3), 4.89 (d, 1H, *J* = 9.3), 7.52 (m, 2H), 8.09 (m, 2H), 8.70 (m, 2H); ^{13}C NMR δ: 55.8, 71.6, 125.8, 126.0, 136.2, 136.1, 136.3, 136.4, 136.6, 149.9, 150.5, 151.1. CD: (*c* 1.6×10^{-4}) λ_{ext} 203 ($\Delta\varepsilon$ +0.15), 210 ($\Delta\varepsilon$ −8.64), 216 ($\Delta\varepsilon$ −19.21), 228 ($\Delta\varepsilon$ −6.78), 245 ($\Delta\varepsilon$ +0.60), 274 ($\Delta\varepsilon$ −0.80), 305 ($\Delta\varepsilon$ +4.19), 329 ($\Delta\varepsilon$ +0.11).

Compound (+)-**4** was obtained from (−)-**7a** (97% ee) by chemical hydrolysis using NH_4OH/MeOH mixture at 50 °C overnight and successive catalytic hydrogenation in the same condition above reported for (−)-**4**.

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10. Due to the overlap with water resonance, the H_5 and H_6 coupling constant of (−)-**7** and (+)-**6** were measured in a 1:3 $CDCl_3/CD_3OD$ mixture.