Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 13, pp. 2175–2187, 1997

Printed in Great Britain
PII: S0957-4166(97)00218-8
0957-4166/97 $17.00 + 0.00

Enzyme catalysed asymmetrization of pyridyl substituted 1,3-propanediols and of the corresponding diacetates

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Abstract: 2-(4-pyridyl)- and 2-(2-pyridyl)-1,3-propanediols **1** and **4** were prepared and asymmetrized by enantioselective acetylation in organic solvent catalysed by hydrolytic enzymes, the best being supported pig pancreatic lipase, to give new valuable heterocyclic chiral building blocks. The asymmetrization of diacetate **6**, catalysed by pig pancreatic lipase is also described. © 1997 Elsevier Science Ltd

Pyridine, as well as its hydrogenated derivatives, are very common structural units present in many natural substances of biological interest.[2] Many of these products are chiral and therefore their synthesis in enantiomerically pure form is an important goal. Moreover, some of them have shown to behave as very effective chiral catalysts or chiral auxiliaries and, for this purpose, they have been used extensively in many asymmetric syntheses.[3] One of the main difficulties in devising efficient preparations of optically active compounds of these classes lies in the limited number of naturally available "chiral building blocks" characterized by such heteroaromatic rings. Thus classical or enzymatic resolutions have been often employed for achieving enantiomerically enriched compounds.[4]

In the course of a research project aimed towards the enantioselective synthesis of new chiral building blocks with the aid of hydrolytic enzymes,[5] we have now studied the preparation of optically active 1,3-propanediol monoacetates characterized by the presence of a pyridine ring at position 2. The asymmetric centre of these compounds is expected to be useful not only for the construction of pyridines, bearing chiral side-chains, but also as control element for the diastereoselective functionalization of the heterocyclic ring, for example through nucleophilic additions to it.[6]

The requisite diols **1** and **4** were prepared in one step from commercially available 4-picoline and 2-picoline by reaction with excess 37% aqueous formaldehyde.[7] While the reaction of 4-picoline with formaldehyde was performed at reflux, the reaction with 2-picoline needed to be performed in a closed vial at 120°C in order to obtain a significant amount of desired diol **4** (Scheme 1). The yields of this reaction were always low; however, the low cost of 4- and 2-picoline makes the preparation of **1** and **4** convenient. In any case the formation of the diols was always accompanied by some by-products. The main of them were the 2-(heteroaryl)ethanols, the 2-(heteroaryl)-2-hydroxymethyl-1,3-propanediols and products deriving from elimination reactions of the diols. Finally, both diols were crystalline products. The preparation of the diacetates **3** and **6**, was done by conventional acetylation of **1** and **4**; but, while **6** was obtained in satisfactory yields, diacetate **3** is somewhat unstable and underwent an extended decomposition process, upon attempted chromatography. Decomposition is presumed to occur through elimination of one of the acetate groups.

We first explored the asymmetrization of the diols using different lipases. In particular diol **1** was acetylated in the presence of various lipases: from *Candida cylindracea* (CCL), Amano AY (from *Candida* sp., AYL) Amano 6 (from *Aspergillus niger*, ANL), Amano PS (from *Pseudomonas cepacia*, PSL). All of these enzymes showed a slight preference for the formation of *R*-**2**, but the enantiomeric excess was in all cases not satisfactory (Table 1).

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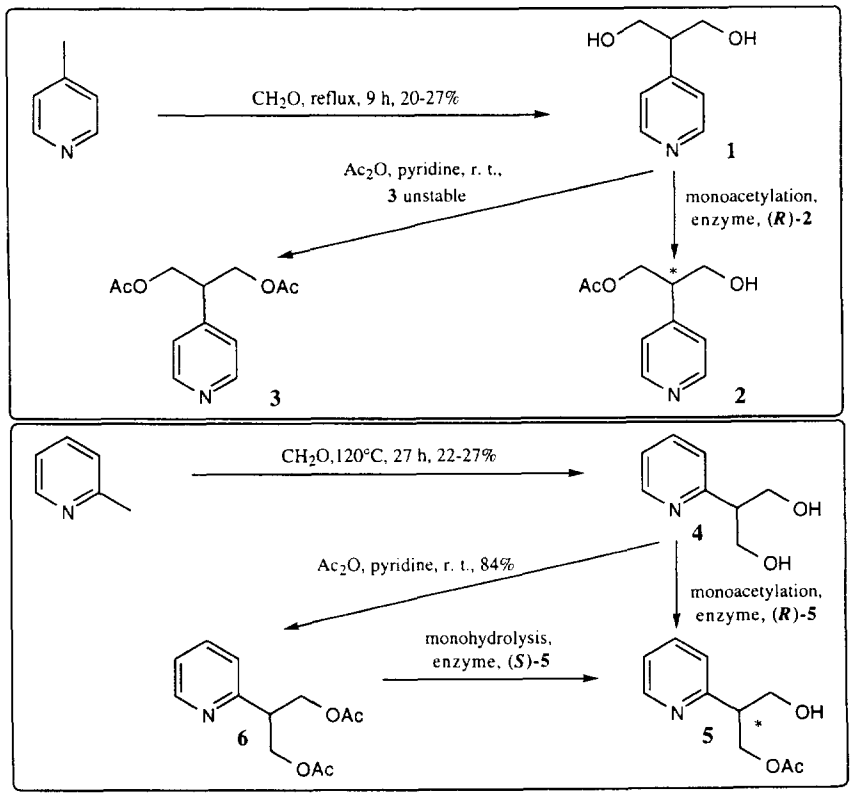


Scheme 1.

Table 1. Monoacetylation of diols **1** and **4** catalysed by various enzymes[a]

Entry	*Diol*	*Enzyme (mg/mmol)*	*Temp. (°C)*	*Time (min.)*	*Conversion*[b]	*1: 2: 3* (from **1**) *4: 5: 6* (from **4**)	*Isolated yield*	*e.e.*[c] *%*	*Conf.*
1	**1**	CCL (251)	20°	1440	43.0	29.9 : 54.2 : 15.9	53%	11.3	*R*
2	**1**	AYL (250)	20°	1415	18.5	66.4 : 30.1 : 3.5	16%	14.9	*R*
3	**1**	ANL (150)	20°	3195	7.9	84.6 : 15.0 : 0.4	6.9%	//	//
4	**1**	PSL (150)	20°	1415	55.6	1.3 : 86.2 : 12.5	85%	13.8	*R*
5	**1**	CAL (80)	0°	395	≈ 70[d]	10.2 : 46.4 : 43.4[d]	46%	69.1	*S*
6	**4**	CAL (80)	0°	300	55.6	12.8 : 63.3 : 23.9	65%	39.1	*S*

[a] Reactions were carried out on 0.1 M solution of substrate in vinyl acetate (both as solvent and acylating agent), in the presence of 3 Å powdered mol. sieves. [b] For a definition of conversion see ref. 5b. [c] Determined by ^{1}H-n.m.r. in the presence of Eu(hfc)$_3$. [d] Due to the instability of **3**, when it is present in a considerable amount, it was difficult to determine the percentage and, consequently, the conversion reported was estimated; the ratio of **3** reported in table was calculated after the experimental determination of **1** and **2** ratios.

Moreover, using AYL and ANL, the reaction was very slow, particularly with the second lipase (entry 3). We then tried the recombinant lipase from *Candida antarctica* (CAL). This enzyme showed a very efficient catalytic activity so that the reactions were performed at 0°C, instead than 20°C. However, the substrate selectivity was in this case lower: we always observed the formation of considerable amounts of diacetate (entries 5, 6), also before complete consumption of the diol. Interestingly, with this enzyme both diols **1** and **4** were transformed into the corresponding *S* monoacetates, while the

Table 2. PPL catalysed monoacetylation of diols **1** and **4**[a]

Entry	*Diol*	*Solvent*	*SPPL/diol (mg/mmol)*	*Temp.*	*Time (min.)*	*Conversion*	*1: 2: 3* (from **1**) *4: 5: 6* (from **4**)	*Isolated yield*	*e.e. %*
1	**1**	VA/THF 8:2	285	20°C	225	36.9%	26.9 : 72.5 : 0.6	65%	94.8
2	**1**	VA/THF 8:2	285	20°C	312	45.9%	7.5 : 90.0 : 2.5	75%	93.0
3	**1**	VA/THF 8:2	285	20°C	480	54.2%	0 : **91.6** : 8.4	84%	**96.0**[8]
4	**4**	VA	285	20°C	300	30.7%	39.3 : 60.0 : 0.7	58%	90.9
5	**4**	VA	285	20°C	450	49.5%	4.9 : 91.2 : 3.9	86%	90.5
6	**4**	VA	285	20°C	630	54.5%	0 : 90.9 : 9.1	80%	94.7
7	**4**	VA	285	20°C	900	56.9%	0 : **86.2** : 13.8	81%	**98.2**
8	**4**	VA	285	20°C	1440	59.1%	0 : 81.8 : 18.2	77%	97.1
9	**4**	VA	285	20°C	2880	73.7%	0 : 52.5 : 47.5	50%	91.8
10	**4**	VA/iPr_2O 1:3	285	20°C	450	46.4%	12.3 : 82.7 : 5	79%	94.6
11	**4**	VA/iPr_2O 1:3	285	20°C	900	52.8%	2.2 : 90.0 : 7.8	80%	95.5

[a] Reactions were carried out on 0.1 M solution of substrate using supported PPL SPPL-4 (see ref. 5d), in the presence of 3 Å powdered mol. sieves. VA = vinyl acetate. The major enantiomer was always (*R*).

other tested lipases gave always *R* enantiomer. The e.e.s however were moderate for **2**, and low for **5**, making also this enzyme unsuitable.

On the other hand, using pig pancreatic lipase (PPL), under the conditions recently optimized by us,[5d,9] both monoacetates *R*-**2** and *R*-**5** were obtained in good yields and high enantiomeric excesses (entries 3[8] and 7, Table 2). In all cases allowing the reactions to go over 50% conversion was beneficial, leading to an increase in enantioselectivity, due to the synergic intervention of kinetic resolution on monoacetates **2** and **5**. But, when we let the conversion to go much more over 50% (entries 7–9), that is using very long reaction times (entry 9), we observed that the e.e. dropped, probably due to acetyl scrambling between the two hydroxymethyl groups, which provoked some racemization of the monoacetate.

For diol **1** we always used a mixture of solvents; actually, in vinyl acetate alone the reaction was slightly slower. On the contrary the solvent had no appreciable influence on the asymmetrization of **4** neither in terms of reaction rate nor in terms of enantioselectivity, as showed in Table 2.

When we started with our project we were interested in the preparation of both enantiomers of monoacetates **2** and **5** with an appreciable enantiomeric excess. The data collected in Tables 1 and 2 show that, while the *R* enantiomers can be obtained with excellent chemical yields and enantiomeric excess, we can't say the same for the *S* enantiomers.

A well known way to obtain the enantiomer of a monoacetate derived from the asymmetrization of the corresponding diol, is the monohydrolysis of the diacetate, catalysed by the same enzyme. Of course this procedure was unsuitable for diacetate **3**, due to the instability of this compound. However, diacetate **6**, a completely stable product, was a good substrate for studying its asymmetrization through a hydrolysis procedure; the most significant data are collected in Table 3.

As previously observed with 1,3-diacetoxypropanes bearing an aryl in position 2,[10] if the reaction is performed in water as the only solvent, reaction rate was slower; moreover, the e.e. is usually enhanced in the presence of an organic co-solvent.[11] Although the presence of an organic co-solvent was always beneficial with respect to e.e., the reaction was not always faster (i.e. using CH_3CN reaction was very slow). Also under optimized conditions the e.e.s were only moderate, never being higher than 80%. Besides we observed that longer reaction times had a negative effect: the reaction always stopped around 50% conversion and e.e. dropped. Also in this case the acetyl scrambling could be invoked

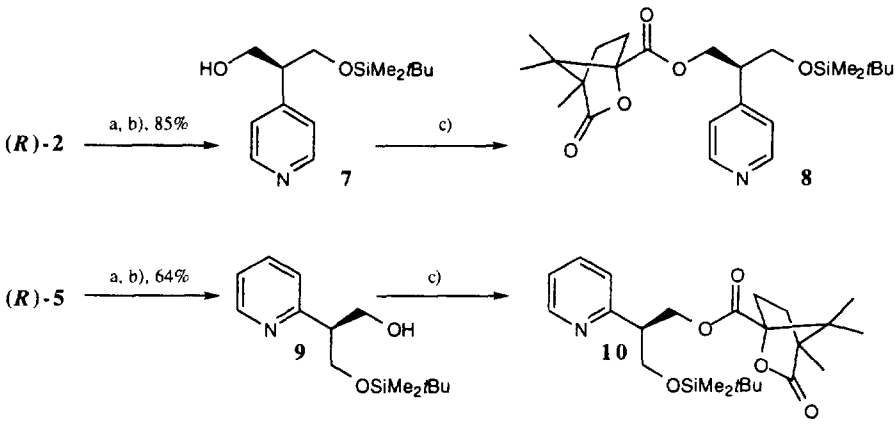
Table 3. PPL catalysed monohydrolysis of diacetate **6**[a]

Entry	*Solvent*	*PPL/5 (mg/mmol)*	*Time (min.)*	*Conversion*	*4: 5: 6*	*Isolated yield*	*e.e. %*
1	H_2O	209	1120	45.0	1.0 : 88.0 : 11.0	86	42.5
2	H_2O/*i*Pr_2O 85:15	208	135	42.8	0.5 : **84.6** : 14.9	75	**77.0**
3	H_2O/*i*Pr_2O 85:15	100	910	50.0	5.7 : 88.7 : 5.6	93	65.0
4	H_2O/*t*BuOH 85:15	201	465	41.0	1.3 : **79.5** : 19.2	74	**77.9**
5	H_2O/dioxane 85:15	214	260	30.4	0.2 : 60.4 : 39.4	50	68.9
6	H_2O/CH_3CN 85:15	208	1525	33.0	1.8 : 62.5 : 35.7	58	71.3
7	H_2O/heptane 85:15	200	240	44.1	0.8 : 86.6 : 12.6	75	56.1

[a]All reactions were performed at room temperature, and pH was maintained at 7 by addition of 0.1 N NaOH from an automatic burette.

to explain the observed decrease of enantiomeric excess. In conclusion the best conditions were the ones using diisopropyl ether or *t*-butanol as co-solvents, as reported in entries 2 and 4 (Table 3).

In order to perform a first check of the chemical and configurational stability of the monoacetates **2** and **5**, we converted them into the monosilylethers **7** and **9** by a two step sequence (Scheme 2). The enantiomeric excess of these monosilylated diols was measured by conversion into both the camphanoates, obtained by reaction of the diols with the (*R*)- and (*S*)-camphanoyl chlorides. ^{1}H NMR analysis indicated that no racemization had occurred.

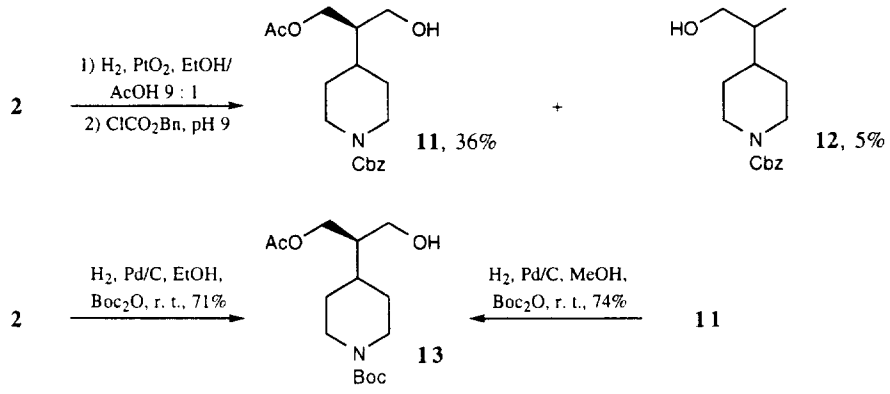


a) Me_2*t*BuSiCl, imidazole, DMF, r. t.; b) KOH, MeOH/H_2O, 0°C; c) (*R*)- or (*S*)-camphanic chloride, pyridine, r.t.

Scheme 2.

The absolute configuration of **2** was determined by chemical correlation with the analogous piperidine derivative, recently prepared in our group (Scheme 3).[4d] As a first choice, we tried the direct transformation of **2** into **11**, by hydrogenation of the pyridine ring, followed by protection of the secondary amine as carbobenzyloxyderivative. To our surprise we isolated **11** in low yield and, most of all, it was almost completely racemic, as demonstrated by the very low value of $[\alpha]_D$ and by the ^{1}H-NMR analysis of both diastereomeric Mosher's esters obtained from **11**. An explanation for this behaviour may be the possibility of the formation of an achiral tautomeric form of **2**, whose formation could be facilitated by the presence of acetic acid in reaction medium. This fact can also explain the formation, as by-product, of **12**, obtained as a racemic mixture.

We circumvented this problem by a one-pot procedure in which di-*tert*-butyl dicarbonate was added during the hydrogenation. In this way, as soon as the pyridine ring was reduced, the corresponding



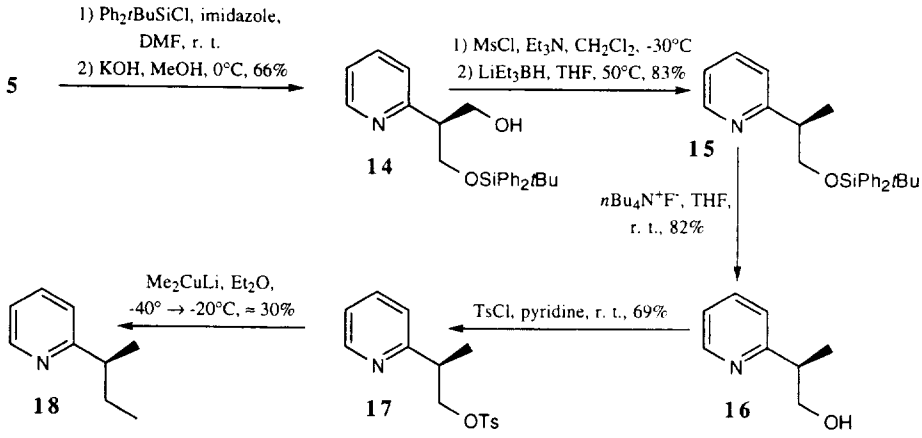
Scheme 3.

piperidine was immediately transformed into the carbamate **13**. The direct transformation of **2** into **13** was very advantageous; actually, while conventional hydrogenation was usually sluggish and required many hours to be complete,[12] the one-pot transformation was faster and more reproducible, being complete in about 4–5 h; moreover, Pd instead of PtO_2 can be used and the yields were much more satisfactory. Probably, the reaction between the secondary amine and Boc_2O, substracting a basic reagent from medium, prevents the co-ordination of the piperidine with the catalyst, a fact responsible for its inhibition.[13] Finally this procedure showed only a slight degree of racemization, not more than 5–10%, determined on the corresponding Mosher's esters. By the same one-pot procedure a sample of **11**, of known absolute configuration, obtained as described in Ref.[4d], was transformed into **13**, without appreciable racemization. By comparison of the sign of optical rotation of **13**, obtained either from **2** or from **11**, and by ^{1}H-NMR analysis of the Mosher's esters of **13**, we concluded that both monoacetates have been converted into the same enantiomer. Then **2**, obtained through PPL-catalysed monoacetylation of **1**, must have the *R* configuration.

For the determination of the absolute configuration of **5** we performed the transformation into compound **18** (Scheme 4). This synthetic sequence is also a demonstration of the potentiality of these monoacetates in the preparation of chiral pyridine derivatives. In order to synthesize **18**, we had to remove both the oxygenated functionalities and to perform a one-carbon homologation. Monosilylether **14**, obtained by conventional procedures, was transformed into the corresponding mesylate, a suitable precursor for the first deoxygenation process. This was realized using Super-Hydride® and we had to optimize temperature and reaction times in order to minimize the partial reduction of the pyridine ring. The final homologation step was performed on the tosylate **17**, readily prepared starting from the deprotected alcohol **16**, by reaction with Me_2CuLi.[14] In this way we obtained **18** in moderate yield [probably due also to the relative volatility of this compound and the small scale employed (<0.5 mmols)]. The positive sign of the specific rotation, compared with the one reported in literature[15] indicated an *S* absolute configuration.[16]

The obtainment of the *R* monoacetates during the monoacetylation of the diols **1** and **4** is in agreement with our usual observed trend for PPL-catalysed acetylation of 2-substituted 1,3-propanediols.[5d] This reaction indeed furnishes, with few exceptions, the *R* monoacetate.[5c]

In conclusion we have developed efficient protocols for the two-step synthesis, in high e.e.s, of a new family of heterocyclic chiral building blocks through a chemoenzymatic methodology, starting from inexpensive starting materials. These synthons are of particular interest, due to their intrinsic enantiodivergency, which makes them suitable for the transformation into both the enantiomers of a possible target, just using a correct protection–deprotection sequence of the two alcoholic functions.[5b] We hope that the stereogenic centre of these compounds can serve as a control element in the



Scheme 4.

stereoselective functionalization of the heteroaromatic ring to give dihydropyridine derivatives. Studies toward this goal are in progress.[17]

Experimental

NMR spectra were taken, unless otherwise indicated, in $CDCl_3$, at 200 MHz (^1H), and at 50 MHz (^{13}C). Chemical shifts are reported in ppm (δ scale), coupling constants are reported in Hertz. Peak assignment in ^1H NMR spectra, was also made with the aid of double resonance experiments. Peak assignment in ^{13}C spectra was made with the aid of DEPT experiments. GC-MS were carried out on a HP-5971A instrument, using an HP-1 column (12 m long, 0.2 mm wide) and electron impact at 70 eV as ionization method. Analyses were performed with a constant He flow of 0.9 ml/min. $[\alpha]_D$ Values were measured on a Jasco DIP 181 instrument, usually as $CHCl_3$ (containing 0.75% EtOH) solutions; concentrations of the samples are calculated in g/100 ml. I.R. spectra were measured with a Perkin-Elmer 881 instrument as $CHCl_3$ solutions, unless otherwise stated. T.l.c. analyses were carried out on silica gel plates, which were developed by these detection methods: **A**) U.V.; **B**) dipping into a solution of $(NH_4)_4MoO_4 \cdot 4H_2O$ (21g) and $Ce(SO_4)_2 \cdot 4H_2O$ (1g) in H_2SO_4 (31 cc) and H_2O (469 cc) and warming; **C**) spraying with 48% HBr, warming, then dipping into a ninhydrin solution (900 mg in 300 ml *n*BuOH+9 ml AcOH), warming. R_f were measured after an elution of 7–9 cm. Chromatographies were carried out on 220–400 mesh silica gel using the "flash" methodology. Petroleum ether (40–60°C) is abbreviated as PE. In extractive work-up, aqueous solutions were always reextracted thrice with the appropriate organic solvent. Organic extracts were dried over Na_2SO_4 and filtered, before evaporation of the solvent under reduced pressure. All reactions employing dry solvents were carried out under a nitrogen (or argon, where indicated) atmosphere. The purity of all compounds was established by t.l.c., ^1H NMR, GC-MS. Enzymes were obtained as follows: CCL was purchased from Fluka; AYL, ANL, PSL were a gift from Amano Company; CAL was a gift from Novo Nordisk Company; crude PPL was purchased from Sigma.

2-(4-Pyridyl)propan-1,3-diol ***1*** *and 2-(2-pyridyl)propan-1,3-diol* ***4***

50.6 mmols (7 ml) of 4- or 2-picoline were dissolved in 37% aqueous formaldehyde (16.6 ml, 202 mmols) and heated at reflux (4-picoline) or at 120°C in a sealed vial (2-picoline) for about 9 h (4-picoline) or 27 h (2-picoline). Excess formaldehyde was removed under reduced pressure; crude reaction mixture was taken up with methanol (about 200 ml) and solvent was removed again *in vacuo*. Chromatography with AcOEt/MeOH 9:1 → 8:2 furnished **1** as a white solid, with a yield of 20–27%. Diol **4** was purified through a double chromatography using CH_2Cl_2/MeOH 98:2 → 8:2 and

AcOEt/EtOH 95:5 → 75:25 as eluents and it was obtained in 22–27% overall yield as a white solid. Finally, both diols were crystallized from THF/Et_2O mixtures.

Characterization of 1: R_f 0.18 (AcOEt/MeOH 9:1, det. A). P. f.=74.9°–75.2°C (THF/Et_2O). I.R.: ν_{max} 3681, 3616, 3006, 2954, 2883, 2392, 1601, 1411, 1192, 1065, 1038, 732. GC-MS: R_t 6.96 min (init. temp. 70°C, init. time 2 min, rate 20°C/min, final temp. 220°C; inj. temp. 200°C); *m/z* (E.I. 180°C) 153 (M^+; 1.1); 135 (0.38, -H_2O); 106 (34); 105 (100); 104 (11); 94 (4.6); 93 (13); 79 (3.9); 78 (7.8); 65 (3.2); 51 (4.1); 39 (3.1); 31 (4.8). ^{1}H-NMR: δ 3.06 [1H, quintuplet, J=6.1, >C*H*CH_2OH]; 3.68 [2H, broad s, -O*H*]; 3.98 and 4.04 [4H, AB part of ABX system, 2 -CH_2OH, J_{AB}=8.5, J_{AX} and J_{BX}=3.0, 4.5]; 7.21 [2H, X part of AA′XX′ system, *H* meta to N]; 8.48 [2H, A part of AA′XX′ system, *H* ortho to N].

Characterization of 4: R_f 0.35 (AcOEt/EtOH 8:2, det. A). P. f.=75.3°–75.9°C (THF/Et_2O). I.R.: ν_{max} 3611, 3384, 2994, 2958, 2878, 2434, 1597, 1570, 1470, 1434, 1246, 1150, 1070, 1021, 1006, 977, 953, 911, 659. GC-MS: R_t 6.51 min (init. temp. 70°C, init. time 2 min, rate 20°C/min, final temp. 250°C; inj. temp. 250°C); *m/z* (E.I. 175°C) 136 (M^+-H_2O, 4.6); 123 (23); 122 (100, -CH_2OH); 106 (34); 105 (31); 104 (12); 94 (10); 93 (35); 92 (5.6); 79 (23); 78 (13); 65 (5.6); 52 (6.6); 51 (8.8); 39 (5.6); 31 (6.4). ^{1}H-NMR: δ 3.04 [1H, quintuplet, >C*H*CH_2OH, J=4.8]; 3.68 [2H, broad s, -O*H*]; 4.07 and 4.16 [4H, AB part of ABX system, 2 -CH_2OH, J_{AB}=11.1, J_{AX} and J_{BX}=4.7, 4.9]; 7.20 [1H, dt, *H* para to the side chain, J=1.1, 4.8]; 7.23 [1H, broad d, *H* ortho to the side chain, J=4.8]; 7.68 [1H, dt, *H* para to N, J=1.9, 7.8]; 8.50 [1H, dt, *H* ortho to N, J=1.0, 3.8].

(R)- and (S)-3-(Acetoxy)-2-(4-pyridyl)propan-1-ol **2** *and (R)- and (S)-3-(Acetoxy)-2-(2-pyridyl)-propan-1-ol* **5** *by monoacetylation of the corresponding diols*

A 0.1 M solution of the diol (**1** or **4**) in the opportune solvent (see Tables 1 and 2) was treated with powdered 3 Å molecular sieves (0.06 mg/mg diol) and stirred at r.t. for 15 min under nitrogen. The enzyme was added and stirring continued at the reported temperature for the desired time. The enzyme was filtered off, the solution was concentrated *in vacuo* and crude product was chromatographed with AcOEt/MeOH 9:1 (**2**) or AcOEt → AcOEt/EtOH 95:5 (**5**); both monoacetates are colourless oils. Isolated yields, conversion and e.e.s were reported in Tables 1 and 2. In all cases the *R* enantiomer prevailed, with the exceptions of the reactions catalysed by CAL, in which the *S* enantiomer was obtained. For reactions using supported PPL the enzyme was prepared as described in Ref.[5d].

Characterization of 2: R_f 0.41 (AcOEt/MeOH 8:2, det. A). $[\alpha]_D$=+8.15 (c 2.0, $CHCl_3$, measured on a sample with 97.5% e.e., obtained from a PPL-catalysed reaction). I.R.: ν_{max} 3607, 3211, 3075, 2962, 2466, 1939, 1727, 1601, 1556, 1368, 1195, 1028, 881, 814. GC-MS: R_t 7.24 min (init. temp. 80°C, init. time 2 min, rate 20°C/min, final temp. 260°C; inj. temp. 220°C); *m/z* (E.I. 176°C) 195 (M^+, 0.44); 165 (1.2); 135 (2.6, -AcOH); 122 (8.3, -CH_2OAc); 107 (5.0); 106 (65); 105 (100, -H_2O; -AcOH); 104 (8.6); 93 (13); 80 (5.3); 78 (6.3); 43 (36). ^{1}H-NMR: δ 2.06 [3H, s, -COCH_3]; 3.14 [1H, quintuplet, >C*H*CH_2OH, J=6.2]; 3.88 [2H, d, -CH_2OH, J=5.9]; 4.42 [2H, d, -CH_2OAc, J=6.5]; 7.21 [2H, X part of AA′XX′ system, *H* meta to N]; 8.54 [2H, A part of AA′XX′ system, *H* ortho to N].

Characterization of 5: R_f 0.46 (AcOEt/MeOH 95:5, det. A). $[\alpha]_D$=+6.67 (c 0.7, $CHCl_3$, measured on a sample with 98.2% e.e., obtained from a PPL-catalysed reaction). I.R.: ν_{max} 3672, 3611, 3375, 2963, 2395, 2304, 1735, 1597, 1572, 1435, 1386, 1368, 1248, 1150, 1098, 1031, 895, 662. GC-MS: R_t 7.28 min (init. temp. 70°C, init. time 2 min, rate 20°C/min, final temp. 200°C; inj. temp. 250°C); *m/z*: (E.I. 175) 165 (M^+-CH_2O, 4.8); 152 (7.8); 136 (31), 134 (6.6); 123 (7.7); 122 (100); 118 (11); 107 (5.3); 106 (65); 105 (27); 104 (11); 94 (6.1); 93 (17); 79 (14); 78 (8.2); 43 (14). ^{1}H-NMR: δ 2.05 [3H, s, -COCH_3]; 3.21 [1H, centre of m, >C*H*CH_2OH]; 4.02 and 4.08 [2H, AB part of ABX system, -CH_2OH, J_{AB}=11.2, J_{AX} and J_{BX}=3.0, 4.6]; 4.44 and 4.47 [2H, AB part of ABX system, -CH_2OAc, J_{AB}=10.9, J_{AX} and J_{BX}=6.5, 7.8]; 7.18–7.25 [2H, m, *H* para and *H* ortho to the side chain]; 7.68 [1H, dt, *H* para to N, J=1.9, 7.7]; 8.52 [1H, dt, *H* ortho to N, J=1.9, 5.7].

(S)-3-(Acetoxy)-2-(2-pyridyl)propan-1-ol **5** *by monohydrolysis of* **6**

A 0.067 M pH 7 buffer solution (17 ml) was added to a solution of **6** (120 mg, 0.506 mmols) in the organic solvent (3 ml, see Table 3). After the addition of crude PPL the mixture was vigorously stirred at r.t., while pH was constantly maintained at 7 by addition of 0.1 N NaOH from an automatic burette. After the required reaction time the enzyme was filtered and the two-layer solution was saturated with NaCl and extracted with AcOEt. Finally, chromatography with AcOEt → AcOEt/MeOH 9:1, gave **5** as a colourless oil. Additional data (reaction times, conversion, e.e.s, yields) were reported in Table 3. $[\alpha]_D=-3.79$ (c 3.4, $CHCl_3$, measured on a sample with 77.9% e.e.).

2-(2-Pyridyl)-1,3-diacetoxypropane **6**

A solution of **4** (904 mg, 5.90 mmols) was dissolved in dry pyridine (3 ml) and cooled to 0°C. Acetic anhydride (1.67 ml, 17.70 mmols) was added and the reaction was stirred at r.t. for 1 h. The solution was diluted with water and extracted with Et_2O, while pH of the aqueous layer was maintained at 8. After solvent removal, residual pyridine was eliminated azeotropically by adding heptane. Chromatography with AcOEt/PE 6:4 → 7:3, gave 1.18 g of **6** as a pale yellow oil (yield 84%). R_f 0.75 (AcOEt/MeOH 9:1, det. A). I.R.: ν_{max} 3674, 3454, 2964, 2456, 1954, 1733, 1593, 1572, 1467, 1436, 1382, 1367, 1247, 1150, 1029, 993, 900, 817, 659, 604. GC-MS: R_t 7.87 min (init. temp. 70°C, init. time 2 min, rate 20°C/min, final temp. 200°C; inj. temp. 250°C); *m/z* (E.I. 175°C) 179 (M^+-58, 5.2); 178 (44); 164 (18); 135 (13); 134 (100); 122 (64); 118 (46); 106 (34); 105 (21); 104 (11); 93 (8.0); 79 (16); 78 (8.8); 43 (44). ^{1}H-NMR: δ 2.01 [6H, s, -COCH_3]; 3.48 [1H, quintuplet, >CHCH$_2$OAc, J=6.8]; 4.45 and 4.45 [4H, AB part of ABX system, -CH_2OAc, J_{AB}=11.4, J_{AX} and J_{BX}=7.0, 7.0]; 7.16–7.22 [2H, m, *H* para and *H* ortho to N]; 7.65 [1H, dt, *H* para to N, J=1.8, 7.7]; 8.58 [1H, dt, *H* ortho to N, J=1.8, 3.8].

(S)-3-(t-Butyldimethylsilyl)oxy-2-(4-pyridyl)propan-1-ol **7** *and (S)-3-(t-butyldimethylsilyl)oxy-2-(2-pyridyl)propan-1-ol* **9**

a) *Silylation reaction*: monoacetate **2** or **5** (100 mg, 0.512 mmols) was dissolved in dry DMF (1.5 ml) and the solution was cooled to 0°C, before adding imidazole (60 mg, 0.88 mmols) and *t*-butyldimethylsilyl chloride (101 mg, 0.670 mmols). After 5 min the reaction was stirred at r.t. for 1 h. The solution was diluted with $NH_4Cl/NaHCO_3$ 1:1 (saturated aqueous solutions) and extracted with Et_2O. Crude products [from **2**: R_f 0.60 (AcOEt, det. A); from **5**: R_f 0.89 (AcOEt/MeOH 95:5, det. A)] were used as such in the next reactions. b) *Saponification of the acetate group*: products from the previous reaction were dissolved in MeOH (1 ml) and cooled to 0°C. A 1 M solution of KOH in MeOH (1 ml) was added and the resulting mixture was stirred at the same temperature for about 2 h. The reaction was quenched with saturated NH_4Cl solution and concentrated *in vacuo*. The residue was taken up with water and extracted with Et_2O.

Isolation and characterization of 7: chromatography with AcOEt/MeOH 96:4 furnished 116 mg of **7** as a colourless oil (overall yield 85%). R_f 0.20 (AcOEt, det. A). $[\alpha]_D=-6.84$ (c 2.0, $CHCl_3$). I.R.: ν_{max} 3620, 3496, 3066, 2957, 2929, 2857, 1601, 1463, 1408, 1390, 1192, 1084, 1063, 1032, 1005, 907, 831. GC-MS: R_t 8.40 min (init. temp. 80°C, init. time 2 min, rate 20°C/min, final temp. 220°C; inj. temp. 200°C); *m/z* (E.I. 180°C) 267 (M^+; 0.29); 252 (2.0, -Me); 211 (13); 210 (79, -CH_2=C(CH_3)$_2$); 180 (6.6); 136 (56, -OTBDMS); 118 (16); 106 (7.5); 105 (14); 77 (5.8); 76 (7.4); 75 (100); 73 (16); 47 (5.2). ^{1}H-NMR: δ 0.04 [6H, s, -Si(CH_3)$_2$C(CH_3)$_3$]; 0.88 [9H, s, -C(CH_3)$_3$]; 3.02 [1H, quintuplet, >CHCH$_2$OH, J=6.1]; 3.93 [2H, d, -CH_2OH, J=6.1]; 3.93 and 4.04 [2H, AB part of ABX system, -CH_2OTBDMS, J_{AB}=10.9, J_{AX} and J_{BX}=6.9, 7.0]; 7.18 [2H, X part of AA′XX′ system, *H* meta to N]; 8.52 [2H, A part of AA′XX′ system, *H* ortho to N].

Isolation and characterization of 9: chromatography with AcOEt/PE 7:3 furnished 88.0 mg of **9** as a colourless oil (overall yield 64%). R_f 0.49 (AcOEt/PE 7:3, det. A). $[\alpha]_D=+2.58$ (c 1.3, $CHCl_3$); I.R.: ν_{max} 3005, 2923, 2853, 2395, 1727, 1507, 1414, 1194, 1034, 919, 662. GC-MS: R_t 6.97 min. (init. temp. 100°C, init. time 2 min, rate 20°C/min, final temp. 260°C; inj. temp. 250°C); *m/z* (E.I. 175°C)

267 (M^+; 0.27); 252 (3.1, -Me); 211 (15); 210 (92, -CH_2=C(CH_3)$_2$); 194 (19); 192 (11); 178 (12); 136 (26, -OTBDMS); 122 (9.3); 118 (13); 106 (26); 105 (14); 104 (5.8); 93 (6.1); 79 (10); 78 (11); 77 (7.6); 76 (8.0); 75 (100); 73 (28); 59 (9.2); 57 (8.7); 51 (5.7); 47 (9.7); 45 (14); 43 (6.3); 41 (13); 39 (6.8); 31 (9.3). ^{1}H-NMR: δ −0.05 [3H, s, -Si(C*H*$_3$)CH_3*t*Bu]; −0.01 [3H, s, -Si(CH_3)C*H*$_3$*t*Bu]; 0.84 [9H, s, -C(C*H*$_3$)$_3$]; 3.06 [1H, centre of m, >C*H*CH_2OH]; 3.92 and 4.02 [2H, AB part of ABX system, -C*H*$_2$OH, J_{AB}=9.9, J_{AX} and J_{BX}=4.5, 6.7]; 4.07 and 4.10 [2H, AB part of ABX system, -C*H*$_2$OTBDMS, J_{AB}=8.4, J_{AX} and J_{BX}=4.1, 4.5]; 7.17 [1H, ddd, *H* para to the side chain, J=1.2, 4.9, 7.5]; 7.22 [1H, broad d, *H* ortho to the side chain, J=7.8]; 7.63 [1H, dt, *H* para to N, J=1.8, 7.6]; 8.49 [1H, broad d, *H* ortho to N, J=4.1].

General procedure for the preparation of camphanic esters of primary alcohols ***7*** *(to give* ***8****),* ***9*** *(to give* ***10****),* ***14*** *and* ***16***

Alcohols **7**, **9**, **14** or **16** (56.09 μmols) were dissolved in dry CH_2Cl_2 (1 ml) and treated, at 0°C, with 250 μl of dry pyridine, 4-*N*,*N*-dimethylaminopyridine (6.8 mg, 56.09 μmols) and camphanic chloride (36.5 mg, 168.3 μmols; the reaction was performed using both *R* and *S* enantiomers of the chloride). After 1 h the solution was partitioned between water and Et_2O and then extracted with Et_2O. After solvent evaporation under reduced pressure, pyridine was removed azeotropically with heptane. The esters were purified by preparative t.l.c., using Et_2O as eluent. Isolated yields are in the range 77–91%. Compound **8**: R_f 0.51 (Et_2O, det. A). Compound **10**: R_f 0.64 (PE/Et_2O 1:1, det. A). Camphanic ester from **14**: R_f 0.73 (PE/Et_2O 9:1, det. A). Camphanic ester from **16**: R_f 0.48 (Et_2O, det. A).

(R)-3-(Acetoxy)-2-[4-(1-benzyloxycarbonyl)piperidinyl]propan-1-ol ***11***

a) *Hydrogenation of the pyridine ring*: monoacetate **2** (56.7 mg, 0.290 mmols) was dissolved in 5 ml of 96% EtOH/AcOH 9:1, treated with PtO_2 (10 mg) and hydrogenated at atmospheric pressure for 22.5 h. The catalyst was filtered and the solvent mixture was evaporated. R_f 0.18 ($CHCl_3$/EtOH/NH_3 50:50:1). b) *Protection of the secondary aminic function*: the residue of the previously described hydrogenation was taken up with 1 ml of water and, after cooling to 0°C, it was treated with 1 N NaOH (0.640 mmols, 640 μl) and benzyl chloroformate (95%, 52 μl, 0.348 mmols). The mixture was stirred at r.t. for 4 h 40 min, maintaining the pH at a constant value of 9. Additional benzyl chloroformate (120 μl, 0.798 mmols) was used in order to complete the reaction. After 2.4 h the aqueous layer was saturated with NaCl and extracted with AcOEt. Chromatography with AcOEt/PE 1:1 gave 35 mg of pure **11** as a colourless oil (yield 36%). R_f 0.55 (AcOEt/PE 8:2, det. B); $[\alpha]_D$=+0.96 (c 1.2, $CHCl_3$) [lit[4d]]+9.1, c 1.1, $CHCl_3$]; I.R.: ν_{max} 3689, 3006, 2926, 2854, 2394, 1685, 1602, 1416, 1189, 1032, 924, 666, GC-MS: R_t 11.57 min (init. temp. 100°C, init. time 2 min, rate 20°C/min, final temp. 260°C; inj. temp. 250°C); *m/z* (E.I. 177°C) 232 (M^+−103, 2.9); 201 (5.9); 200 (51); 140 (4.7); 124 (3.2); 92 (8.6); 91 (100); 82 (4.2); 65 (5.2); 55 (2.4); 43 (9.9); 42 (3.4). ^{1}H-NMR: δ 1.10–1.45 [2H, m, 2*H* of piperidine ring]; 1.50–1.95 [4H, m, 3*H* of piperidine ring and >C*H*CH_2OH]; 2.08 [3H, s, -COC*H*$_3$]; 2.77 [2H, broad t, 2*H* α to N, J=12.8]; 3.59 and 3.68 [2H, AB part of ABX system (after exchange with D_2O), J_{AB}=11.1, J_{AX} and J_{BX}=3.4, 5.8]; 4.10–4.35 [2H, m, 2*H* α to N]; 4.17 and 4.28 [2H, AB part of ABX system, J_{AB}=11.4, J_{AX} and J_{BX}=3.9, 6.0]; 5.12 [2H, s, -C*H*$_2$Ph]; 7.28–7.43 [5H, aromatics of Cbz].

(R)-3-(Acetoxy)-2-[4-(1-t-butoxycarbonyl)piperidinyl]propan-1-ol ***13***

a) *Starting from* ***2*** (with 93.2% e.e.): a solution of **2** (49.4 mg, 0.253 mmols) in EtOH (2.5 ml), was treated with di-*t*-butyl dicarbonate 174 μl, 0.759 mmols) and with 10% Pd/C (12 mg). After 4.5 h the catalyst was filtered and the resulting solution was concentrated. The residue was diluted with H_2O/Et_2O and extracted. Crude product was chromatographed with Et_2O to give 54.1 mg of **13** as a colourless oil (yield 71%). $[\alpha]_D$=+9.44° (c 1.1, $CHCl_3$). Racemization observed by ^{1}H-NMR analysis of the corresponding Mosher's esters: about 5–10%. b) *Starting from* ***11*** (with 69.2% e.e.): the reaction was performed as above described, using MeOH as solvent. Compound **13** was obtained in 74% overall yield. $[\alpha]_D$=+6.37 (c 1.8, $CHCl_3$). No racemization was observed by ^{1}H-NMR analysis

of the corresponding Mosher's esters. R_f 0.56 (Et_2O, det. C). I.R.: ν_{max} 3688, 3009, 2975, 2931, 2873, 2403, 1683, 1600, 1514, 1422, 1383, 1193, 1110, 1042, 925, 719. GC-MS: R_t 9.07 min (init. temp. 100°C, init. time 2 min, rate 20°C/min, final temp. 260°C; inj. temp. 250°C); *m/z* (E.I. 175°C) 244 (M^+-57, 7.6); 200 (30); 185 (6.2); 167 (7.4); 158 (7.9); 142 (38); 140 (5.2); 128 (8.9); 127 (8.1); 126 (76); 124 (9.0); 110 (6.6); 85 (19); 84 (17); 82 (21); 58 (6.3); 57 (100); 56 (17); 55 (13); 44 (12); 43 (30); 42 (12); 41 (22); 39 (6.7); 31 (8.2). ^{1}H-NMR: δ 1.14–1.38 [2H, m, 2*H* of piperidine ring]; 1.46 [9H, s, -C(CH_3)$_3$]; 1.49–1.79 [4H, m, 3*H* of piperidine ring and >C*H*CH_2OH]; 2.09 [3H, s, -COCH_3]; 2.66 [2H, broad t, 2*H* α to N, J=12.9]; 3.60 and 3.69 [2H, AB part of ABX system (after exchange with D_2O), J_{AB}=11.4, J_{AX} and J_{BX}=3.9, 6.0]; 4.12–4.21 [2H, m, 2*H* α to N]; 4.17 and 4.30 [2H, AB part of ABX system, J_{AB}=11.4, J_{AX} and J_{BX}=3.9, 6.1].

General procedure for the preparation of Mosher's esters of primary alcohols ***11*** *and* ***13***

A solution of the desired alcohol (10 μmols) was dissolved in dry CH_2Cl_2 (0.5 ml) and cooled to 0°C. 4-*N*,*N*-dimethylaminopyridine (60 μmols) was added, followed by Mosher's chloride (30 μmols). The solution was stirred at r.t. for 1.5 h. Crude mixture was directly purified over a silica gel plate using PE/AcOEt 7:3 as eluent. Ester from **11**: R_f 0.40 (PE/AcOEt 7:3, det. A, B). Ester from **13**: R_f 0.54 (PE/AcOEt 7:3, det. A, B).

(S)-3-(t-Butyldiphenylsilyl)oxy-2-(2-pyridyl)propan-1-ol ***14***

a) *Silylation reaction*: starting from 792 mg of **2** (4.06 mmols, 95.1% e.e.) the reaction was performed as above described for the preparation of the TBDMS derivatives, using *t*-butyldiphenylsilyl chloride. b) *Saponification of the acetate group*: as above described for the preparation of **7** and **9**. Chromatography with Et_2O/PE 8:2 → Et_2O gave 1.22 g of **14** as a colourless oil (77% overall yield). R_f 0.48 (AcOEt/PE 4:6, det. A). $[\alpha]_D$=−2.97 (c 1.8, $CHCl_3$). I.R.: ν_{max} 3346, 2958, 2931, 2858, 2398, 1910, 1595, 1570, 1463, 1426, 1385, 1362, 1200, 1109, 1007, 984, 922, 818, 608. GC-MS: R_t 11.94 min (init. temp. 100°C, init. time 2 min, rate 20°C/min, final temp. 260°C; inj. temp. 250°C); *m/z* (E.I. 175°C) 334 (M^+-57, 11); 302 (39); 258 (5.4); 257 (20); 256 (100); 242 (4.5); 226 (8.8); 200 (5.4); 199 (27); 197 (4.5); 181 (5.3); 135 (3.6); 106 (3.7); 105 (3.3); 77 (4.4). ^{1}H-NMR: δ 1.01 [9H, s, -C(CH_3)$_3$]; 3.10 [1H, centre of m, >C*H*CH_2OH]; 3.94 and 4.10 [2H, AB part of ABX system, -CH_2OTBDPS, J_{AB}=10.0, J_{AX} and J_{BX}=6.5, 7.6]; 4.04–4.17 [2H, m, -CH_2OH]; 4.45 [1H, broad s, -O*H*]; 7.11–7.66 [13H, m, -Si(C_6H_5)$_2$*t*Bu and 2*H* meta and *H* para to N]; 8.46 [1H, broad d, *H* ortho to N, J=5.8].

(R)-1-[(t-Butyldiphenylsilyl)oxy]-2-(2-pyridyl)propane ***15***

a) (*R*)-3-[(*t*-Butyldiphenylsilyl)oxy]-2-(2-pyridyl)propyl methanesulfonate: a solution of **14** (428 mg, 1.09 mmols, e.e.>95% as determined from ^{1}H-NMR analysis of the corresponding camphanoate) was dissolved in dry CH_2Cl_2 (16 ml) and cooled to −30°C. Triethylamine (183 μl, 1.31 mmols) and mesyl chloride (93 μl, 1.20 mmols) were added and the mixture was stirred at the same temperature for 1.5 h. Due to incomplete reaction, an equivalent amount of triethylamine and of mesyl chloride was added and stirring continued for an additional hour. The solution was diluted with saturated aqueous NH_4Cl and extracted with Et_2O. After solvent removal crude product was directly used for the reduction process. R_f 0.82 (AcOEt/PE 4:6). b) *Reduction of mesylate*: crude mesylate, obtained as above described was dissolved in 10 ml of dry THF and treated, at r.t., with $LiEt_3BH$ (Super-Hydride®, 1 M sol in THF, 3.0 ml, 3.0 mmols). The solution was heated at 50°C for 10 min. Then additional two portions of $LiEt_3BH$ were added every 30 min (first 2.0 ml, then 1.0 ml). The solution was diluted with saturated aqueous NH_4Cl and extracted with Et_2O. Chromatography with Et_2O/PE 2:8 → Et_2O furnished 339 mg of **15** as a colourless oil (overall yield 83%). R_f 0.62 (Et_2O/PE 4:6, det. A, B). I.R.:ν_{max} 3674, 3041, 2959, 2929, 2857, 2392, 1727, 1592, 1571, 1466, 1424, 1388, 1187, 1112, 927, 734, 606. GC-MS: R_t 10.45 min (init. temp. 100°C, init. time 2 min, rate 20°C/min, final temp. 260°C; inj. temp. 250°C); *m/z* (E.I. 175°C) 375 (M^+, 0.10); 320 (6.8); 319 (26); 318 (100); 302 (8.4); 240 (3.2); 199 (6.3); 197 (3.2); 181 (4.8); 135 (3.6); 120 (8.0); 105 (3.3); 77 (3.3). ^{1}H-NMR: δ 0.96 [9H, s, -C(CH_3)$_3$]; 1.33 [3H, d, >CHCH_3, J=7.0]; 3.16 [1H, hexuplet, >C*H*CH_3, J=6.8]; 3.83

and 3.89 [2H, AB part of ABX system, -C*H*$_2$OTBDPS, J_{AB}=10.0, J_{AX} and J_{BX}=7.3, 7.4]; 7.12 [1H, ddd, *H* para to the side chain, J=1.1, 4.9, 7.5]; 7.19 [1H, broad d, *H* ortho to the side chain, J=7.9]; 7.28–7.63 [11H, m, -Si(C$_6$*H*$_5$)$_2$ and *H* para to N]; 8.54 [1H, broad d, *H* ortho to N, J=4.7].

(R)-2-(2-Pyridyl)propan-1-ol ***16***

A solution of **15** (261 mg, 0.695 mmols) in dry THF (10 ml) was treated, at r.t., with *n*Bu$_4$N$^+$F$^-$ (1 M sol in THF, 2.1 ml, 2.08 mmols) and stirred for 1 h. The solution was diluted with brine and extracted with AcOEt. Chromatography with Et$_2$O/AcOEt 9:1 → 8:2 furnished 78.6 mg of **16** as a colourless oil (yield 83%). R_f 0.11 (Et$_2$O/PE 6:4). $[\alpha]_D$=+27.38 (c 3.4, CHCl$_3$). I.R.: ν_{max} 3613, 3341, 3084, 2968, 2874, 1760, 1594, 1577, 1434, 1037, 993, 873, 764. GC-MS: R_t 3.08 min (init. temp. 100°C, init. time 2 min, rate 20°C/min, final temp. 260°C; inj. temp. 250°C); *m/z* (E.I. 172°C) 136 (M$^+$−1, 3.5); 122 (-CH$_3$, 39); 121 (6.9); 120 (68); 119 (12); 118 (20); 107 (59); 106 (100); 104 (5.5); 94 (6.1); 93 (15); 80 (5.8); 79 (26); 78 (34); 77 (11); 53 (6.9); 52 (15); 51 (17); 50 (7.6); 44 (7.3); 38 (7.4); 32 (7.1); 31 (8.9). ^{1}H-NMR: δ 1.33 [3H, d, >CHC*H*$_3$, J=7.0]; 3.08 [1H, centre of m, >C*H*CH$_3$]; 3.84 and 3.94 [2H, AB part of ABX system, -C*H*$_2$OH, J_{AB}=10.8, J_{AX} and J_{BX}=3.8, 6.7]; 7.13–7.22 [2H, m, 2*H* meta to N]; 7.65 [1H, dt, *H* para to N, J=1.8, 7.8]; 8.50 [1H, broad d, *H* ortho to N, J=4.8].

(R)-2-(2-Pyridyl)propyl p-toluenesulfonate ***17***

A solution of **16** (78.6 mg, 0.573 mmols, e.e.>95% as determined from ^{1}H-NMR analysis of the corresponding camphanoate) in dry pyridine (1.5 ml) was cooled to 0°C and treated with tosyl chloride (328 mg, 1.72 mmols). The solution was then allowed to react at r.t. for 4 h. After dilution with water the reaction was extracted with Et$_2$O, and residual pyridine was removed azeotropically with heptane. Chromatography with Et$_2$O/PE 1:1 → 7:3 gave 115 mg of pure **17** as a white solid (yield 69%). R_f 0.71 (Et$_2$O, det. A). $[\alpha]_D$=−1.22 (c 3.1, CHCl$_3$). I.R.: ν_{max} 3680, 3041, 2965, 2402, 1593, 1433, 1358, 1170, 1096, 972, 683. GC-MS: R_t 9.38 min (init. temp. 100°C, init. time 2 min, rate 20°C/min, final temp. 260°C; inj. temp. 250°C); *m/z* (E.I. 172°C) 292 (M$^+$+1, 0.04); 197 (8.8); 155 (6.0); 137 (8.6); 136 (100); 120 (21); 118 (7.4); 107 (13); 106 (28); 92 (4.8); 91 (21); 79 (4.8); 78 (9.7); 65 (9.9). ^{1}H-NMR: δ 1.28 [3H, d, >CHC*H*$_3$, J=7.0]; 2.44 [3H, s, -SO$_2$(C$_6$H$_4$)C*H*$_3$]; 3.25 [1H, hexuplet, >C*H*CH$_3$, J=6.9]; 4.20 and 4.32 [2H, AB part of ABX system, >CHC*H*$_2$OTs, J_{AB}=9.4, J_{AX} and J_{BX}=6.4, 7.2]; 710–7.17 [2H, m, *H* ortho and para to the side chain]; 7.28 [2H, X part of AA′XX′ system, 2*H* meta to -SO$_2$-]; 7.60 [1H, dt, *H* para to N, J=1.8, 7.7]; 7.66 [2H, A part of AA′XX′ system, 2*H* ortho to -SO$_2$-]; 8.42 [1H, dt, *H* ortho to N, J=1.5, 4.3].

(S)-2-(2-Pyridyl)butane ***18***

a) *Preparation of Me$_2$CuLi*: A suspension of anhydrous CuI (986 mg, 5.18 mmols) in dry Et$_2$O (8 ml), under an argon atmosphere, was cooled to −10°C and treated with MeLi (1.6 M sol in Et$_2$O, 6.4 ml, 10.24 mmols). The initially formed yellow precipitate slowly dissolved to give a nearly colourless solution, which was stirred for additional 10 min at the same temperature. b) *Reaction*: a solution of tosylate **17** (115 mg, 0.395 mmols) in dry Et$_2$O (4 ml), under argon, was cooled to −40°C and treated with 2.7 ml (about 2.33 mmols) of the above prepared cuprate solution. After 10 min the solution was allowed to raise to 10°C over a period of 4 h. The reaction was diluted with saturated aqueous NH$_4$Cl (10 ml) and 10% NH$_4$OH (10 ml), and transferred into a beaker. The mixture was vigorously stirred until the two layers were perfectly separated. Extraction was performed with Et$_2$O. Solvent was removed under reduced pressure, using a Claisen equipped with a Vigreux column. The residue was purified by chromatography, using pentane/Et$_2$O 9:1 as eluent. The solvent was removed again by the same procedure. Product **18** was obtained in about 30% yield. R_f 0.61 (Et$_2$O/PE 1:1). $[\alpha]_D$=+15.01 (c 0.69, EtOH).[16] I.R.: ν_{max} 3678, 3597, 3025, 2958, 2925, 2853, 2393, 1726, 1601, 1505, 1423, 1192, 1093, 1013, 928, 698. GC-MS: R_t 3.81 min (init. temp. 60°C, init. time 2 min, rate 20°C/min, final temp. 160°C; inj. temp. 130°C); *m/z* (E.I. 172°C) 135 (M$^+$, 2.4); 134 (5.9); 121 (6.6); 120 (-CH$_3$, 73); 118 (8.8); 108 (7.8); 107 (100); 106 (75); 104 (5.3); 93 (14); 92 (12); 80 (5.2); 79 (18); 78 (23); 77 (7.5); 53 (5.7); 52 (11); 51 (13); 39 (7.6). ^{1}H-NMR: δ 0.84 [3H, t, -CH$_2$C*H*$_3$, J=7.5]; 1.28 [3H,

d, >CHCH_3, J=6.9]; 1.55–1.84 [2H, m, -CH_2CH$_3$]; 2.79 [1H, hexuplet, >CHCH$_3$, J=7.0]; 7.07–7.15 [2H, m, 2*H* meta to N]; 7.60 [1H, dt, *H* para to N, J=1.8, 7.7]; 8.54 [1H, broad s, *H* ortho to N].

Acknowledgements

We wish to thank Amano and Novo-Nordisk for the generous gift of some enzymes, and Ms Sara Perrozzi for her collaboration to this work, which was financially assisted by M.U.R.S.T. and C.N.R. (Progetto Strategico Tecnologie Chimiche Innovative).

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8. We also observed that the resolution of monoacetate **2** (e.e. 88%) catalysed by supported PPL and performed following conditions used in entry 3 (Table 2), is very efficient and the e.e. have been enhanced to 97.5%, after a 4.5% conversion.
9. PPL catalysed acetylation of **4** was already reported (Cesti, P.; Zaks, A.; Klibanov, A. M. *Appl. Biochem. Biotechnol.* **1985**, *11*, 401–407). However the e.e. was not determined.
10. Guanti, G.; Riva, R. unpublished results.
11. We have already demonstrated that in monohydrolysis of a some diesters, using PLE as enzyme, the rate and the enantioselectivity are strongly influenced by the presence of an organic co-solvent (Ref. Guanti, G.; Banfi, L.; Narisano, E.; Riva, R.; Thea, S. *Tetrahedron Lett.* **1986**, *27*, 4639–4642).
12. Authors of Ref. 4d experienced the same behaviour during the hydrogenation of **1** to give the corresponding pyperidine diol; that's the reason why they prepared that diol using a completely different approach.
13. To prevent this undesired process, usually the hydrogenation is conduced in the presence of an acid (Ref. Keay, J. in *Comprehensive Organic Synthesis*, Trost, B. M. Ed. **1991**, vol. 8, 579–602, Pergamon Press, Oxford).
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16. We proved that the synthetic sequence was non-racemizing until **16**, through ^{1}H-NMR analysis of the camphanoates of the alcohol. The $[\alpha]_D$ of this was lower than the one reported, but, due to the volatility of this compound, we did not strip away all the solvent.
17. Some preliminary results were already presented in the symposium: *Biocatalisi e Sintesi Organica*, Acquafredda di Maratea (I), **1996**, May, 3–5.

(Received in UK 22 April 1997)