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Lipase catalyzed asymmetrization of quinolyl substituted 1,3-propanediols

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Abstract

2-(2-Quinolyl)- and 2-(4-quinolyl)-1,3-propanediols **3** and **4** were prepared and asymmetrized by enantioselective acetylation in organic solvent catalyzed by lipases. While monoacetate **5** was best obtained using Celite-supported pig pancreatic lipase (PPL) (97.3% e.e.) as the (*R*)-enantiomer, both enantiomers of **6** have been obtained using different enzymes: (*R*)-**6** using lipase from *Aspergillus niger* (84.0% e.e.) and (*S*)-**6** using lipase from *Candida antarctica* (97.5% e.e.). The absolute configuration of both monoacetates **5** and **6** has been determined by anomalous X-ray dispersion methodology on the corresponding *p*-bromobenzoates **11** and **12**.

1. Introduction

The preparation of unnatural chiral building blocks is a very important goal, since they can be used as precursors in the synthesis of complex organic molecules. This can be easily accomplished using chemical or enzymatic methodologies. In particular, asymmetrization of 2-substituted 1,3-propanediols and of their corresponding diacetates using lipases have been extensively studied by us;[1] in fact, the corresponding monoacetates, usually obtained in very high enantiomeric excess and chemical yield, can be readily transformed, thanks to their enantiodivergency,[1a] into both enantiomers of a given target just by using the correct protection–deprotection strategy for the two alcoholic functionalities. Among the

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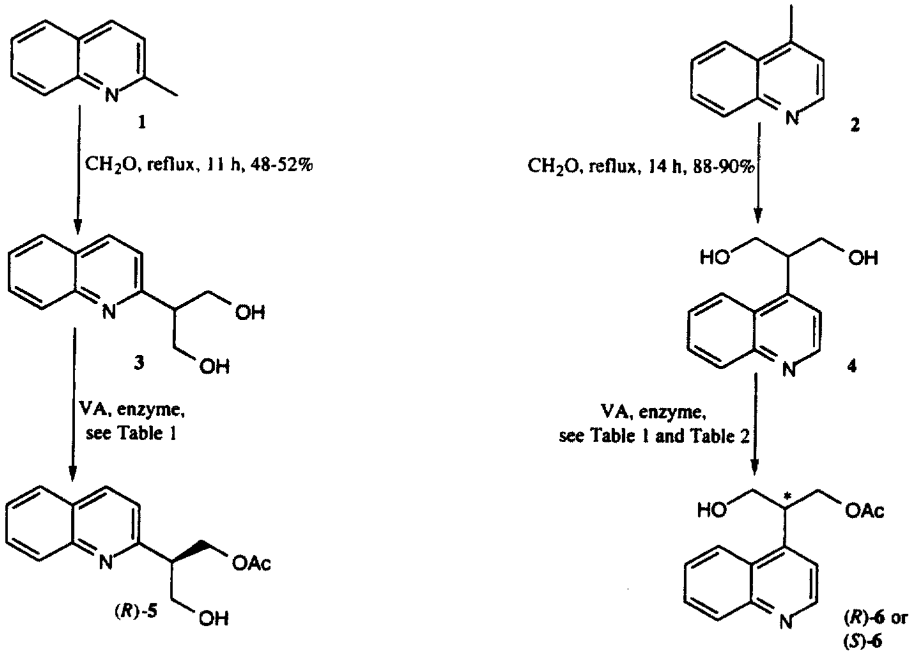
asymmetrized substrates, diols bearing heterocycles, such as piperidine[1c] and pyridine[1g] have also been studied by us.

Chiral N-heterocycles and, in particular, pyridine and quinoline derivatives, are very important chiral building blocks, since they can be used for the synthesis of many natural products of biological interest;[2] moreover, they have shown interesting properties as chiral auxiliaries or catalysts in asymmetric synthesis.[3]

Continuing our research in the field of enzyme catalyzed asymmetrization of prochiral substrates useful for synthetic applications, we report here our research on the lipase catalyzed acetylation of 2- and 4-quinoline substituted 1,3-propanediols.

2. Results and discussion

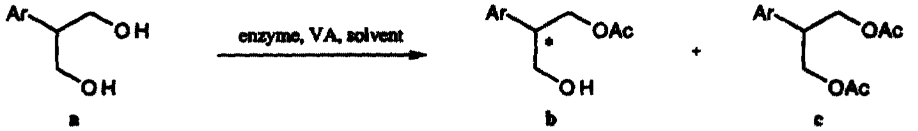
The preparation of **3** and **4** was accomplished by a one-step procedure starting from the commercially available quinaldine **1** and lepidine **2**, which were refluxed in the presence of 37% aqueous formaldehyde. Under these conditions **1** afforded **3** in moderate yield, accompanied by monoalcohol[2-(2-quinolyl)ethanol], triol [2-(2-quinolyl)-2-hydroxymethyl-1,3-propanediol] and the products deriving from elimination of water from the monoalcohol and **3** (Scheme 1). The behaviour was thus similar to that experienced with 2-picoline and 4-picoline.[1g] However, in this case the yield was higher and, in particular, the formation of triol was less pronounced. The reaction was best stopped before completion in order to minimize the elimination products. On the other hand, diol **4** was obtained in excellent yield (88–90%). The high yield in this case is probably due to the *peri* interaction which disfavours further reaction of the diol **4** through sp^2 intermediates to give the elimination products.



Scheme 1.

We first explored the asymmetrization of these substrates using supported pig pancreatic lipase (PPL), under the conditions recently optimized by us[1d] (Table 1). This enzyme proved to be excellent for diol

Table 1
PPL catalyzed monoacetylation of diols 3 and 4[a]



Entry	*Diol*	*Solvent*	*SPPL[a]/diol (mg/mmol)*	*Temp. (°C)*	*Time (min.)*	*Conversion[b] (%)*	*a : b : c*	*Isolated yield of b (%)*	*e.e.[c] (%)*
1	3	VA	205	20	480	32.3	35.4 : 64.6 : 0	49	94.5
2	3	VA	205	20	1050	47.7	7.5 : 89.7 : 2.8	85	96.3
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	4	VA/THF 2:1	708	37	3840	38.7	24.3 : 74.0 : 1.7	65	22.7
5	4	VA/THF 2:1	1145	37	3300	37.0	27.8 : 70.4 : 1.8	60	11.9

a Reactions were carried out on 0.06 M substrate for diol 3 and on 0.1 M substrate for diol 4 using supported PPL SPPL-4 (see ref. 1d), in the presence of 4 Å powdered mol. sieves. VA = vinyl acetate. b Conversion means the ratio (mmols of acetylated OH) / (initial mmols of OH). c Determined by ^{1}H-n.m.r. in the presence of Eu(hfc)$_3$. The major enantiomer was always *R*.

3, leading to the corresponding monoacetate in good yields and high enantiomeric excess also at a low degree of conversion (entry 1). Moreover, letting the reactions go over 50% conversion was beneficial, leading to an increase in enantioselectivity (entry 3). On the other hand, diol 4 turned out to be less reactive and the e.e.s were poor (entries 4 and 5). Actually, this result was not completely unexpected and agrees with the empirical model previously proposed by us to rationalize the enantioselectivity in PPL catalyzed reactions.[1a] The structure of 4 indeed resembles a 2-(alkenyl)-1,3-propanediol with substituents both in the *Z* and *E* positions, and we have previously shown that these kind of compounds are poor substrates for PPL.[1a,b,4]

In view of possible interesting uses of asymmetrized monoacetate 6 in the field of enediyne antibiotics of the Dynemicin family,[2c,5,6] we sought to overcome the low efficiency of PPL catalyzed acetylation by exploring different enzymes (Table 2). After various unsuccessful attempts we found two promising enzymes: *Aspergillus niger* lipase[7] (entry 9) and *Candida antarctica* lipase (entries 10–16),[8] which, interestingly, afforded opposite enantiomers. Of the two, the best in terms of reaction rate was without doubt the latter, which also allowed (*S*)-6 to be obtained with excellent enantiomeric excess. In this case the degree of conversion had little influence. Thus *Candida antarctica* lipase seems to be promising as a PPL substitute for the asymmetrization of 2-substituted-1,3-propanediols in those cases where, due to structural limitations, PPL fails both in term of catalytic activity and/or enantioselectivity.

In order to perform a first check of the chemical and configurational stability of these monoacetates, we converted them into the monosilylethers 7 and 8 by the two step sequence depicted in Scheme 2. The enantiomeric excess of these monosilylated diols was measured by conversion into both the camphanoates, obtained by reaction with the (1*R*)- and (1*S*)-camphanoyl chlorides. ^{1}H-NMR analysis indicated that no racemization had occurred.

The transformation of 5 into 7 had a beneficial effect: for 5 we observed a tendency to eliminate the acetate moiety, giving the corresponding allylic alcohol, which is always present, although in small amounts, during the enzymatic reaction. We suspect that this process is favoured by an intramolecular hydrogen bond between the hydroxy group of 5 and the nitrogen of quinoline.[9] On the other hand silyl ether 7 is absolutely stable and did not show any tendency to give elimination products.

Table 2
Monoacetylation of diol 4 catalyzed by various enzymes[a]

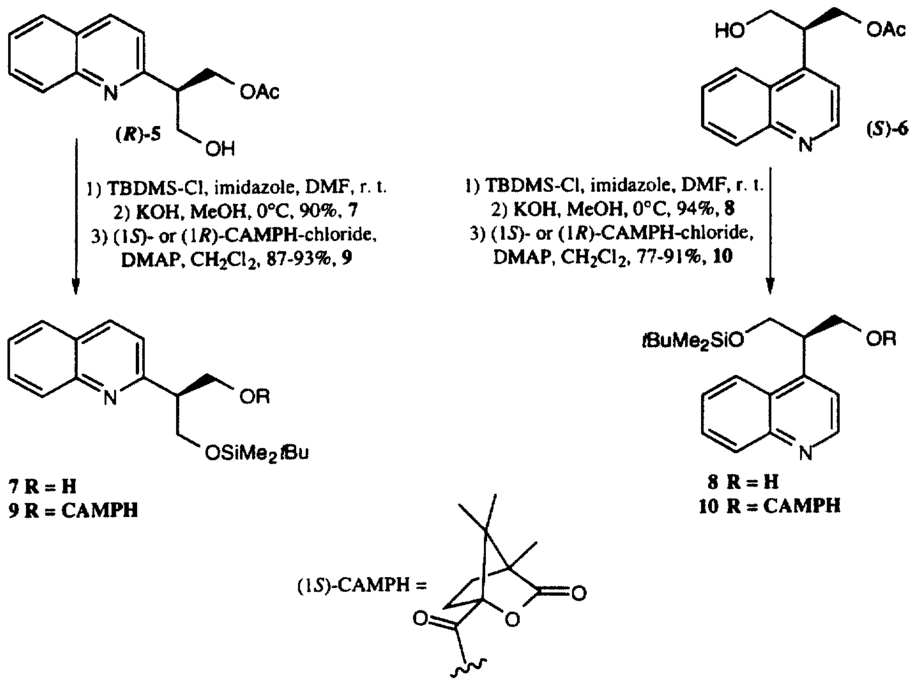
Entry	*Enzyme*[b]	*Enzyme quantity (mg/mmol 4)*	*Temp. (°C)*	*Time (min.)*	*Conv.*[c] *(%)*	*a : b : c*	*Isolated yield of b (%)*	*e.e.*[d] *(%)*	*Conf.*
1	SPPL[e]	708	37	3840	38.7	24.3 : 74.0 : 1.7	65	22.7	*R*
2	CCL[e]	105	37	4320	14.3	71.9 : 27.5 : 0.6	21	41.7	*S*
3	AYL[e]	517	37	2880	32.5	39.8 : 55.5 : 4.7	48	25.0	*S*
4	AYL[f]	605	37	1710	40.1	29.3 : 61.2 : 9.5	53	20.5	*R*
5	AYL[g]	603	37	7200	< 5	n.d.	n.d.	n.d.	n.d.
6	PSL	343	37	1440	46.5	11.4 : 84.2 : 4.4	75	62.3	*S*
7	AOP	448	37	10020	<5	n.d.	n.d.	n.d.	n.d.
8	MJL	284	37	2725	8.0	84.1 : 15.9 : 0	13	39	*R*
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	CAL	362	37	345	90.8	0 : 18.3 : 81.7	16	86.2	*S*
11	CAL	92	20	240	62.5	0 : 75 : 25	67	95.0	*S*
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13	CAL	56	0	432	12.8	74.4 : 25.6 : 0	20	90.0	*S*
14	CAL	90	0	820	46.4	17.3 : 72.5 : 10.2	65	96.6	*S*
15	CAL	103	0	1204	59.0	0 : 81.9 : 18.1	74	96.0	*S*
16	CAL	98	0	963	57.2	0 : 85.6 : 14.4	73	95.9	*S*

a Reactions were carried out on 0.1 M substrate in vinyl acetate (unless where otherwise noted) in the presence of 4 Å powdered mol. sieves. **b** SPPL = supported PPL SPPL-4 (see ref. 1d); CCL = *Candida cylindracea* lipase (Sigma, cat. L-1754); AYL = Amano AY lipase (from *Candida*); PSL = Amano P lipase (from *Pseudomonas*); AOP = Protease from *Aspergillus oryzae* (Sigma, cat. P4032). MJL = *Mucor javanicus* lipase (Fluka, cat. 62304); ANL = *Aspergillus niger* lipase (Fluka cat. 62301); CAL = *Candida antarctica* lipase. **c** Conversion means the ratio (mmols of acetylated OH) / (initial mmols of OH). **d** Determined by ^{1}H-n.m.r. in the presence of Eu(hfc)$_3$. **e** These reactions were carried out in THF/vinyl acetate 2:1. **f** This reaction was carried out in toluene/vinyl acetate 1:0.06. **g** This reaction was carried out in acetone/vinyl acetate 1:0.1.

Since only very few optically active simple quinolyl derivatives are known, a chemical correlation of both **5** and **6** with compounds of known absolute configuration seemed to be very difficult. We first attempted a spectroscopic correlation,[10] similar to Mosher's method for the determination of the absolute configuration of secondary alcohols;[11] this method is based on the estimation of the anisotropic effects in a suitable amidic derivative of the compound of unknown absolute configuration. For this purpose we had first to oxidize the $-CH_2OH$ group into $-CO_2H$. This reaction was very sluggish and the only product we isolated derived form decarboxylation of the corresponding acid.[12]

Thus, the absolute configuration of these new chiral building blocks was determined by X-ray analysis. The two monoacetates were then acylated at the free hydroxy group to give the corresponding *p*-bromobenzoates **11** and **12**, used for the configurational assignment (Scheme 3).

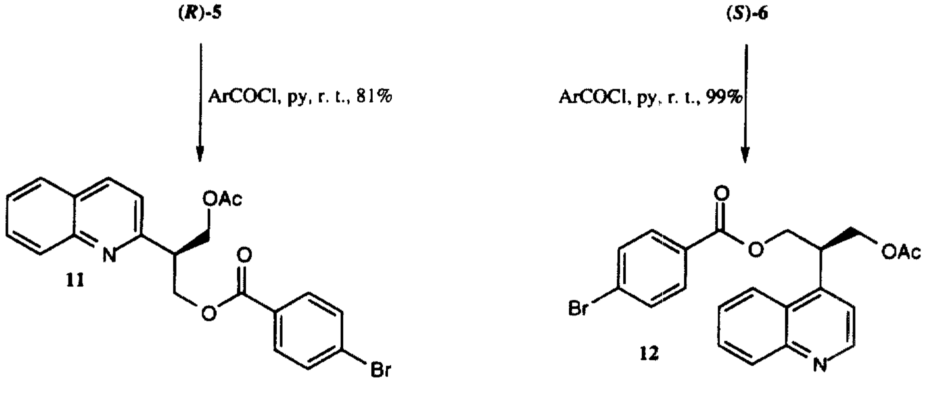
Both crystal structures were solved by direct methods (SIR92)[13] and refined on F^2 data by means of an anisotropic full-matrix least-squares process (SHELXL97).[14] The absolute stereochemistry at C11 for compound **11** (see Fig. 1) and at C11A and C11B for compound **12** (see Fig. 2) has been determined unambiguously as *S* (**11**) and *R* (**12**), the Flack parameters[15] being −0.006(8) and −0.011(9), respectively.



Scheme 2.

The position of the hydrogen atoms bonded to the chiral centres C11, C11A, C11B was determined experimentally from difference Fourier syntheses.

All geometry calculations were performed with the program PARST97.[16] Ranges of esds on bond lengths and bond angles between heavier atoms are 0.002–0.007 Å and 0.2–0.5° for **11** and 0.005–0.011 Å and 0.4–0.8° (not considering the disordered acetyl group) for **12**, respectively. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC).[17]



Scheme 3.

In this way we proved that PPL catalyzed acetylation afforded in both cases the (*R*)-monoacetate, while CAL, when used on **4**, afforded the enantiomeric (*S*)-antipode. This stereochemical outcome is in agreement with the usual observed trend for PPL and CAL catalyzed acetylation of 2-substituted 1,3-propanediols.[1d] In fact, with few exceptions, the (*R*)-enantiomer was obtained using PPL, while *Candida anctartica* lipase gave the opposite enantiomer.

In conclusion, we have prepared two new heterocyclic chiral building blocks, both characterized by the property of enantiodivergency, which make them suitable as starting materials for both enantiomers of a possible target. The new asymmetric centre of these compounds can serve as a control element in the stereoselective elaboration of the two C-branches as well as of the heteroaromatic ring.[6,18] Studies toward this goal are in progress.

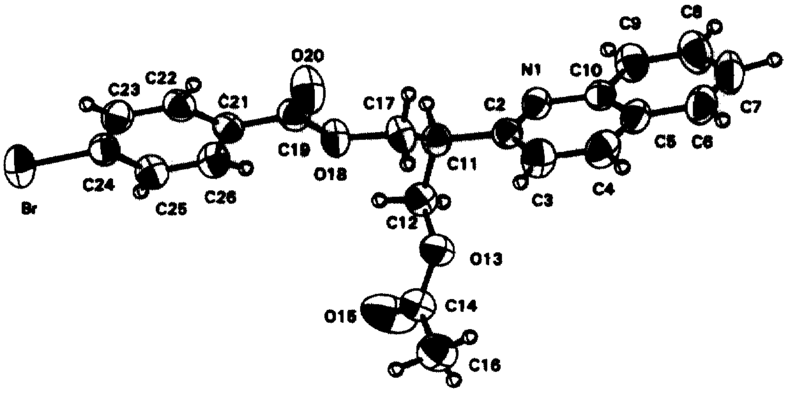


Fig. 1. ORTEP view of the structure of **11** with numbering of atoms. Thermal ellipsoids are drawn at the 50% probability level; hydrogen atoms, treated as isotropic, are on an arbitrary scale

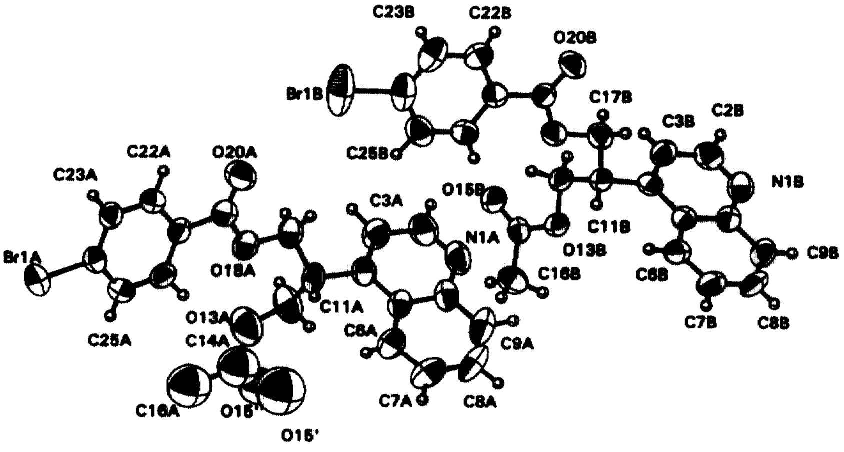


Fig. 2. ORTEP drawing of the asymmetric unit of **12**. The labelling of atoms, reported only partially for the sake of clarity, is analogous to that used for **11**. Thermal ellipsoids are drawn at the 50% probability level. Atoms C14A, O15′, O15″ and C16A, affected by disorder, have been treated as isotropic

3. 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 ^{13}C spectra was made with the aid of DEPT experiments. GC–MS was carried out on an HP-5971A instrument, using an HP-1 column (12 m long, 0.2 mm wide) and electron impact at 70 eV as the ionization method at 175°C. If not otherwise described, the following GC conditions were used: constant He flow of 0.9 ml/min, init. temp. 100°C, init. time 2 min, rate 20°C/min, final temp. 260°C, final time 4 min, inj. temp. 250°C. Values of $[\alpha]_D$ 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. IR spectra were measured with a Perkin–Elmer 881 instrument as $CHCl_3$ solutions, unless otherwise stated. TLC analyses were carried out on silica gel plates and spots were detected with a UV lamp. Values of R_f were measured after an elution of 7–9 cm. Chromatography was 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 three times 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 atmosphere. The purity of all compounds was established by TLC, ^{1}H-NMR and GC–MS. Enzymes were obtained as follows: ANL, CCL and MJL were purchased from Fluka; crude PPL and AOP were purchased from Sigma; AYL and PSL were a gift from Amano Company; CAL was a gift from Novo Nordisk Company.

3.1. 2-(2-Quinolyl)propan-1,3-diol 3 and 2-(4-quinolyl)propan-1,3-diol 4

A quantity (37.8 mmol, 5 ml) of quinaldine **1** or lepidine **2** was dissolved in 37% aqueous formaldehyde (11.3 ml, 151.2 mmol) and heated at reflux for about 11 h (quinaldine) or 14 h (lepidine). Excess formaldehyde was removed under reduced pressure; the crude reaction mixture was taken up with methanol (about 200 ml) and solvent was again removed *in vacuo*.

3.1.1. Purification and characterization of 3

Chromatography with AcOEt:MeOH 9:1 → 8:2 gave **3** as a white solid, with a yield of 48–52%; this compound was crystallized from THF:Et_2O mixtures. R_f 0.37 (AcOEt:MeOH 95:5). Mp=114.3–115.3°C (THF:Et_2O). IR (KBr): ν_{max} 1604, 1428, 1328, 1204, 1042, 865. GC–MS: R_t 7.84 min; *m/z* 203 (M^+, 0.40); 173 (26); 172 (100); 168 (5.0); 156 (28); 155 (13); 154 (6.8); 144 (9.4); 143 (30); 129 (13); 128 (14); 115 (6.0); 77 (6.9). ^{1}H-NMR: δ 3.21 [1H, centre of m, $-CH(CH_2OH)_2$]; 4.06 [2H, broad s, $-OH$]; 4.16 and 4.29 [4H, AB part of ABX system, $-CH(CH_2OH)_2$, J_{AB}=11.1, J_{AX} and J_{BX}=4.4, 4.8]; 7.37 [1H, d, H_3, J=8.4]; 7.53 [1H, ddd, H_6 or H_7, J=1.2, 8.0, 8.1]; 7.71 [1H, ddd, H_6 or H_7, J=1.6, 7.0, 8.4]; 7.81 [1H, broad d, H_5, J=7.8]; 8.01 [1H, d, H_4 or H_8, J=8.4]; 8.15 [1H, d, H_4 or H_8, J=8.4]. ^{13}C-NMR (DMSO-d_6): 53.13 [$-CH(CH_2OH)_2$]; 62.03 [$-CH(CH_2OH)_2$]; 122.06 [C_3]; 125.62 [C_6]; 126.70 [C_{4a}]; 127.60 [C_5]; 128.41 and 129.10 [C_7 and C_8]; 135.56 [C_4]; 147.15 [C_{8a}]; 162.68 [C_1].

3.1.2. Purification and characterization of 4

Chromatography with AcOEt:EtOH 9:1 → 8:2 gave **4** in 88–90% overall yield as a white solid. Finally, **4** was crystallized from THF. R_f 0.42 (AcOEt:EtOH 9:1). Mp=127.6–128.2°C (THF). IR (KBr): ν_{max} 1590, 1577, 1510, 1039, 763. GC–MS: R_t 8.51 min; *m/z* 203 (M^+, 32); 155 (100); 154 (92); 144 (11); 143 (24); 142 (5.8); 130 (7.9); 129 (5.3); 128 (7.0); 127 (8.1); 115 (11); 101 (4.9); 77 (7.5); 31 (6.2). ^{1}H-NMR: δ 3.12 [2H, broad s, $-OH$]; 3.89–4.01 [1H, m, $-CH(CH_2OH)_2$]; 4.15 and 4.19 [4H, AB part of ABX system, $-CH(CH_2OH)_2$, J_{AB}=10.8, J_{AX} and J_{BX}=4.0, 7.9]; 7.24 [1H, d, H_3, J=4.5]; 7.60 [1H, ddd, H_6 or H_7, J=1.3, 6.9, 8.4]; 7.70 [1H, ddd, H_6 or H_7, J=1.5, 6.8, 8.4]; 8.04 [1H, broad d, H_5 or H_8, J=8.2]; 8.11 [1H, broad d, H_5 or H_8, J=8.3]; 8.59 [1H, d, H_2, J=4.6]. ^{13}C-NMR (DMSO-d_6): 44.43 [$-CH(CH_2OH)_2$]; 61.94 [$-CH(CH_2OH)_2$]; 119.44 [C_3]; 123.59 [C_6]; 126.05 [C_5]; 127.68 [C_{4a}]; 128.62 and 129.61 [C_7 and C_8]; 147.73 and 147.83 [C_4 and C_{8a}]; 149.76 [C_1].

*3.2. (*R*)-3-(Acetoxy)-2-(2-quinolyl)propan-1-ol* **5** *and (*R*)- and (*S*)-3-(acetoxy)-2-(2-quinolyl)propan-1-ol* **6**

A 0.06 M solution of diol **3** or a 0.1 M solution of diol **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 and the solution was concentrated *in vacuo*. Isolated yields, conversion and e.e.s are reported in Tables 1 and 2, together with the absolute configuration of the monoacetates. For reactions using supported PPL the enzyme was prepared as described in the literature.[1d]

3.2.1. Purification and characterization of **5**

Chromatography with AcOEt:ETP 6:4 → 7:3 gave **5** as a white solid, which was crystallized from Et_2O. R_f 0.62 (AcOEt:ETP 7:3). $[\alpha]_D=-36.5$ (c 1.50, $CHCl_3$, measured on a sample with 97.3% e.e., obtained from a PPL catalyzed reaction). Mp=65.8–66.0°C (Et_2O). IR: ν_{max} 3422, 3001, 2922, 2854, 1722, 1600, 1555, 1418, 1244, 1103, 1020, 919, 820. GC–MS: R_t 10.65 min; *m/z*: 245 (M^+, 0.42); 215 (7.2); 186 (38); 184 (7.1); 173 (11); 172 (100); 168 (17); 157 (5.8); 156 (46); 155 (14); 154 (7.9); 144 (6.9); 143 (21); 129 (13); 128 (14); 77 (5.2); 43 (18). ^{1}H-NMR: δ 2.06 [3H, s, $-COCH_3$]; 3.39 [1H, centre of m, $>CHCH_2OH$]; 4.11 and 4.22 [2H, AB part of ABX system, $-CH_2OH$, $J_{AB}=11.2$, J_{AX} and $J_{BX}=2.8$, 4.3]; 4.56 [2H, d, $-CH_2OAc$, J=7.1]; 7.36 [1H, d, H_3, J=8.4]; 7.54 [1H, dt, H_6 or H_7, J=1.0, 7.4]; 7.72 [1H, ddd, H_6 or H_7, J=1.6, 7.1, 8.5]; 7.82 [1H, broad d, H_5, J=8.0]; 8.03 [1H, d, H_4 or H_8, J=8.4]; 8.15 [1H, d, H_4 or H_8, J=8.4]. ^{13}C-NMR: 20.66 [$-COCH_3$]; 47.17 [$>CHCH_2OH$]; 62.24 and 64.45 [$-CH_2O-$]; 121.46 [C_3]; 126.25 [C_6]; 126.94 [C_{4a}]; 127.39 [C_5]; 128.72 and 129.57 [C_7 and C_8]; 136.67 [C_4]; 147.08 [C_{8a}]; 160.92 [C_2]; 170.75 [$>CO$].

3.2.2. Purification and characterization of **6**

Chromatography with AcOEt → AcOEt:MeOH 9:1 gave **6** as a white solid, which was crystallized from Et_2O. R_f 0.56 (AcOEt:MeOH 95:5). $[\alpha]_D=-14.6$ (c 1.31, $CHCl_3$, measured on a sample with 97.5% e.e., obtained from a *Candida antarctica* lipase catalyzed reaction). Mp=84.9–86.2°C (Et_2O). IR: ν_{max} 3620, 2961, 1735, 1590, 1368, 1196, 1042. GC–MS: R_t 7.74 min; *m/z*: 245 (M^+, 5.5); 185 (5.9); 172 (12); 167 (12); 156 (42); 155 (100); 154 (71); 144 (5.8); 143 (8.1); 130 (10); 127 (5.9); 115 (5.5); 43 (33). ^{1}H-NMR: δ 2.06 [3H, s, $-COCH_3$]; 4.00–4.15 [3H, m, $>CHCH_2OH$ and $>CHCH_2OH$]; 4.56 [2H, d, $>CHCH_2OAc$, J=6.1]; 7.36 [1H, d, H_3, J=4.6]; 7.61 [1H, ddd, H_6 or H_7, J=1.2, 6.8, 8.3]; 7.74 [1H, ddd, H_6 or H_7, J=1.6, 6.9, 8.4]; 8.12 [1H, dd, H_5 or H_8, J=1.2, 8.1]; 8.13 [1H, dd, H_5 or H_8, J=1.3, 7.8]; 8.81 [1H, d, H_2, J=4.6]. ^{13}C-NMR: 20.71 [$-COCH_3$]; 41.15 [$>CHCH_2OH$]; 62.60 and 64.02 [$-CH_2O-$]; 119.13 [C_3]; 122.73 [C_6]; 126.75 [C_5]; 127.27 [C_{4a}]; 129.19 and 129.87 [C_7 and C_8]; 145.67 [C_4]; 147.91 [C_{8a}]; 149.52 [C_2]; 171.07 [$>CO$].

*3.3. (*S*)-3-(t-Butyldimethylsilyl)oxy-2-(2-quinolyl)propan-1-ol* **7** *and (*R*)-3-(t-butyldimethylsilyl)oxy-2-(4-quinolyl)propan-1-ol* **8**

(a) *Silylation reaction*: Monoacetate (*R*)-**5** or (*S*)-**6** (100 mg, 408 μmol) was dissolved in dry DMF (1.5 ml) and the solution was cooled to 0°C, before adding imidazole (47 mg, 694 μmol) and *t*-butyldimethylsilyl chloride (80 mg, 530 μmol). 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 **5**: R_f 0.61 (AcOEt:PE 3:7); from **6**: R_f 0.77 (AcOEt)] were used as such in the next reactions.

(b) *Saponification of the acetate group*: Products from the previous reaction were dissolved in dry 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.

3.3.1. Purification and characterization of **7**

Chromatography with AcOEt:PE (2:8) gave 116 mg of **7** as a colourless oil (overall yield 90%). R_f 0.73 (AcOEt:PE 25:75). $[\alpha]_D$=+45.9 (c 0.50, $CHCl_3$). IR: ν_{max} 3357, 2954, 2930, 2882, 2856, 1619, 1600, 1562, 1463, 1195, 1108, 1076, 1045. GC–MS: R_t 9.24 min; *m/z*: 317 (M^+, 0.17); 286 (8.2); 262 (5.8); 261 (21); 260 (100); 228 (7.5); 186 (32); 168 (11); 167 (5.1); 157 (5.4); 156 (32); 155 (8.0); 154 (5.8); 143 (5.2); 142 (5.8); 129 (8.4); 128 (9.4); 75 (37); 73 (14). ^1H-NMR: δ −0.023 [3H, s, $-CH_3$]; 0.024 [3H, s, $-CH_3$]; 0.87 [9H, s, $-C(CH_3)_3$]; 3.25 [1H, centre of m, $>CHCH_2OH$]; 4.05 and 4.16 [2H, AB part of ABX system, $-CH_2O-$, J_{AB}=10.0, J_{AX} and J_{BX}=6.3, 7.7]; 4.13 and 4.23 [2H, AB part of ABX system, $-CH_2O-$, J_{AB}=11.3, J_{AX} and J_{BX}=3.6, 4.7]; 7.38 [1H, d, H_3, J=8.5]; 7.52 [1H, ddd, H_6 or H_7, J=1.2, 6.8, 8.1]; 7.70 [1H, ddd, H_6 or H_7, J=1.5, 6.9, 8.4]; 7.80 [1H, dd, H_5, J=1.1, 8.1]; 8.03 [1H, d, H_4 or H_8, J=8.4]; 8.11 [1H, d, H_4 or H_8, J=8.4]. ^{13}C-NMR: 5.62 [2 $-CH_3$]; 18.14 [$-C(CH_3)_3$]; 25.78 [$-C(CH_3)_3$]; 50.67 [$>CHCH_2OH$]; 63.08 and 64.67 [$-CH_2O-$]; 122.23 [C_3]; 126.05 [C_6]; 126.95 [C_{4a}]; 127.42 [C_5]; 128.82 and 129.42 [C_7 and C_8]; 136.14 [C_4]; 147.16 [C_{8a}]; 162.50 [C_2].

3.3.2. Purification and characterization of **8**

Chromatography with AcOEt:PE (7:3) gave 122 mg of **8** as a colourless oil (overall yield 94%). R_f 0.46 (AcOEt:PE 7:3). $[\alpha]_D$=+35.6 (c 1.50, $CHCl_3$). IR: ν_{max} 3487, 2955, 2930, 2883, 2857, 1590, 1464, 1069. GC–MS: R_t 9.68 min; *m/z*: 317 (M^+, 0.05); 260 (7.6); 242 (6.1); 186 (20); 169 (13); 168 (100); 167 (9.9); 154 (11); 142 (10); 75 (45); 73 (14). ^1H-NMR: δ 0.04 [3H, s, $-CH_3$]; 0.05 [3H, s, $-CH_3$]; 0.90 [9H, s, $-C(CH_3)_3$]; 2.98 [1H, broad s, $-OH$]; 3.94 [1H, centre of m, $>CHCH_2OH$]; 3.74 [1H, d, $-CH_2OH$, J=5.9]; 4.10 and 4.21 [2H, AB part of ABX system, $-CH_2OTBDMS$, J_{AB}=10.8, J_{AX} and J_{BX}=6.8, 10.5]; 7.28 [1H, d, H_3, J=4.7]; 7.60 [1H, ddd, H_6 or H_7, J=1.4, 6.9, 8.2]; 7.72 [1H, ddd, H_6 or H_7, J=1.4, 6.8, 8.4]; 8.11 [1H, dd, H_5 or H_8, J=1.4, 3.3]; 8.15 [1H, dd, H_5 or H_8, J=1.5, 3.8]; 8.82 [1H, d, H_2, J=4.5]. ^{13}C-NMR: 5.60 and 5.63 [2 $-CH_3$]; 18.07 [$-C(CH_3)_3$]; 25.72 [$-C(CH_3)_3$]; 43.64 [$>CHCH_2OH$]; 64.78 and 65.44 [$-CH_2O-$]; 119.15 [C_3]; 122.89 [C_6]; 126.60 [C_5]; 127.36 [C_{4a}]; 129.05 and 130.23 [C_7 and C_8]; 146.31 [C_4]; 148.21 [C_{8a}]; 149.69 [C_2].

3.4. General procedure for the preparation of camphanic esters **9** and **10**

Alcohols **7** and **8** (15 mg, 47.2 μmol) were dissolved in dry CH_2Cl_2 (1 ml) and treated, at 0°C, with 250 μl of dry pyridine, 4-*N*,*N*-dimethylaminopyridine (5.8 mg, 47.2 μmol) and camphanic chloride (30.8 mg, 141.6 μmol; 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 TLC, using Et_2O as eluent. Isolated yields are in the range 77–93%. Compound **9**: R_f 0.51 (AcOEt:PE 1:2). Compound **10**: R_f 0.61 (AcOEt:PE 6:4).

*3.5. (S)-2-(2-Quinolyl)-3-[(acetoxy)oxy]propyl 4-bromobenzoate **11** and (R)-2-(4-quinolyl)-3-[(acetoxy)oxy]propyl 4-bromobenzoate **12***

A solution of (*R*)-**5** or (*S*)-**6** (500 mg, 2.04 mmol) in dry pyridine (5 ml) was treated with 4-bromobenzoyl chloride (537 mg, 2.45 mmol) and stirred at r.t. for 4 h. The solution was diluted with water and extracted with Et_2O. The solvent was removed *in vacuo* and pyridine was removed azeotropically with heptane.

*3.5.1. Purification and characterization of **11***

Chromatography with Et_2O:PE (1:1) gave 705 mg of **11** as a white solid (yield 81%). Compound **11** was then crystallized from Et_2O. Crystal growth of **11**: crystals were obtained by slowly cooling a saturated solution of **11** in Et_2O. R_f 0.78 (AcOEt:PE 1:1). Mp=79.6–80.4°C (Et_2O). $[\alpha]_D$=+38.1 (c 2.60, $CHCl_3$). IR: ν_{max} 3007, 2961, 1723, 1619, 1591, 1268, 1117, 1103, 1070, 1035, 1012. GC–MS: R_t 12.33 min (usual conditions but with final temp. 290°C and final time 8 min); *m/z*: 370 (M^+−OAc; ^{81}Br, 1.1); 368 (M^+−OAc; ^{79}Br, 1.1); 228 (21); 185 (33); 184 (100); 183 (20); 172 (15); 168 (27); 157 (12); 156 (12); 155 (16); 129 (11); 128 (10); 76 (8.1); 75 (5.8); 43 (16). ^{1}H-NMR: δ 2.01 [3H, s, $-COCH_3$]; 3.82 [1H, quintuplet, $>CHCH_2OAc$, J=6.7]; 4.66 [2H, d, $-CH_2O-$, J=7.0]; 4.81 [2H, d, $-CH_2O-$, J=6.6]; 7.38 [1H, d, H_3, J=8.4]; 7.49–7.57 [3H, m, H_6 or H_7 and 2*H* ortho to Br]; 7.72 [1H, ddd, H_6 or H_7, J=1.5, 6.9, 8.5]; 7.80 [2H, dt, 2*H* meta to Br, J=2.0, 8.6]; 8.06 [1H, d, H_4 or H_8, J=8.4]; 8.14 [1H, d, H_4 or H_8, J=8.4].

*3.5.2. Purification and characterization of **12***

Chromatography with Et_2O:PE (8:2) gave 864 mg of **12** as a white solid (yield 99%). Compound **12** was then crystallized from Et_2O:pentane. Crystal growth of **12**: crystals were obtained by slowly cooling a saturated solution of **12** in Et_2O:pentane. R_f 0.40 (Et_2O:PE 8:2). Mp=71.8–72.1°C (Et_2O:pentane). $[\alpha]_D$=+21.8 (c 2.40, $CHCl_3$). IR: ν_{max} 3033, 2959, 1723, 1591, 1267, 1114, 1103, 1070, 1041, 1012. GC–MS: R_t 12.56 min (usual conditions but with final temp. 290°C and final time 8 min); *m/z*: 429 (M^+; ^{81}Br, 0.74); 427 (M^+; ^{79}Br, 0.69); 185 (33); 183 (33); 168 (14); 167 (100); 166 (6.2); 157 (11); 156 (14); 155 (18); 154 (19); 76 (6.1); 43 (25). ^{1}H-NMR: δ 2.00 [3H, s, $-COCH_3$]; 4.41 [1H, quintuplet, $-CHCH_2OH$, J=6.3]; 4.54 and 4.62 [2H, AB part of ABX system, $-CH_2O-$, J_{AB}=11.1, J_{AX} and J_{BX}=6.30, 6.33]; 4.71 and 4.75 [2H, AB part of ABX system, $-CH_2O-$, J_{AB}=11.2, J_{AX} and J_{BX}=6.2, 6.4]; 7.38 [1H, d, H_3, J=4.5]; 7.54 [2H, dt, 2*H* ortho to Br, J=2.0, 8.6]; 7.65 [1H, ddd, H_6 or H_7, J=1.4, 6.8, 8.2]; 7.73–7.82 [3H, m, H_6 or H_7 and 2*H* meta to Br]; 8.16–8.23 [2H, m, H_5 and H_8]; 8.91 [1H, d, H_2, J=4.6].

3.6. Crystal data, structure solution and refinement

For both compounds **11** and **12** the X-ray data were recorded on an Enraf-Nonius CAD4 diffractometer with graphite monochromated MoKα (λ=0.7107 Å) radiation. Cell constants were determined by least-squares refinement of diffractometer angles for 25 automatically centred reflections. During the data collection the centring of six reflections was repeated periodically for both structures to test the crystal orientation, and two reflections were monitored every 60 min to check the crystal stability.

After every reflection the Friedel opposite was immediately measured at the negative 2θ position, in order to minimize residual absorption errors and effects of crystal decay or X-ray intensity fluctuations. Absorption corrections were applied by means of ψ-scan measurements.

Compound 11, $C_{21}H_{18}BrNO_4$, *M*=428.3. Monoclinic, *a*=10.150(2), *b*=7.101(2), *c*=13.785(2) Å, β=105.43(1)°, *V*=957.7(4) Å^3, space group $P2_1$, *Z*=2, D_c=1.485 g cm^{-3}. Crystal dimensions

0.26×0.36×0.38 mm, μ=2.17 mm^{-1}; max, min transmission factors=1.00, 0.72; ω/θ scan mode, scan width 1.43°, scan speed 0.9–16.2 min^{-1}; 4392 unique reflections measured ($2.5 \le \theta \le 27.5°$). Heavy atom positions were determined from an E-map and refined anisotropically; all the H atoms, obtained from difference syntheses, were refined isotropically. Final reliability factors are R_1=0.035 on 3580 $F_o \ge 4\sigma(F_o)$, wR_2=0.088 on all 4392 data and 316 parameters (goodness of fit=1.001). In the last difference Fourier map the highest peak and the deepest hole are near to the Br atom (ρ=0.26 and −0.46 eÅ^{-3}, respectively).

Compound 12, $C_{21}H_{18}BrNO_4$, M=428.3. Monoclinic, a=14.634(5), b=7.188(2), c=19.577(6) Å, β=110.30(2)°, V=1931(1) Å^3, space group P2$_1$, Z=4, D_c=1.473 g cm^{-3}. Crystal dimensions 0.18×0.34×0.38 mm, μ=2.15 mm^{-1}; max, min transmission factors=1.00, 0.72; $\omega/2\theta$ scan mode, scan width 1.72°, scan speed 0.9–16.2 min^{-1}; 6824 unique reflections measured ($2.5 \le \theta \le 25°$). Heavy atom positions were determined from an E-map. In molecule A the acetyl group is disordered, the oxygen atom O15 being split over two positions. Correspondingly the atoms C14A, O15′, O15″ and C16A were treated as isotropic. All other non-H atoms were refined anisotropically. The hydrogen atoms bonded to C16A were not determined; of the remaining 33 H atoms of the two molecules in the asymmetric unit, 16 were determined by difference syntheses and refined, whereas 17 were located in calculated positions. Final reliability factors are R_1=0.048 on 5076 $F_o \ge 4\sigma(F_o)$, wR_2=0.125 on all 6824 data and 528 parameters (goodness of fit=1.018). In the last difference Fourier map the highest peak and the deepest hole are near to the disordered region (ρ=0.39 and −0.38 eÅ^{-3}, respectively).

With the exception of a few rather tight intermolecular distances (in **11**, C12· · ·C16 in $x, y-1, z$, 3.68 Å; in **12**, Br1A· · ·C17B in $x-1, y, z-1$, 3.55 Å) there are no contacts significantly shorter than the sum of the involved van der Waals radii.

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