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Acyclic Phenylalkanediols as Substrates for the Study of Enzyme Recognition: Synthesis of Substrates and Enzymatic Resolution via Hydrolysis and Transesterification

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Abstract

Different racemic or prochiral phenyl alkane (1,*n*)-diols were synthesized, and their resolution was carried out by two different strategies: enzymatic transesterification with vinyl acetate, or enzymatic hydrolysis of their corresponding diacetates, in both cases catalysed by porcine pancreatic lipase (PPL). The absolute configuration of the optically enriched reaction products was determined by formation of Mosher's esters or by the use of the Benzene Sector and Benzene Chirality Rules as obtained from the Circular Dichroism spectra.

Keywords: Phenylalkanediols; Porcine Pancreatic Lipase; Transesterification; Hydrolysis; Absolute Configuration.

Introduction

Optically active diols are very useful compounds as chiral building blocks in the synthesis of natural products,[1-3] drugs or drug synthetic intermediates.[4-7] Thus, many chemical methods have been described in the modern literature for obtaining this kind of product, such as hydroboration of allylic alcohols followed by an oxidative step,[8] hydrosilylation-oxidation of alkenes,[9] diastereo or enantiofacial osmylation of olefins,[10] or diastereoselective reduction of hydroxyketones[11] and prochiral diones,[12] amongst many others.

The use of enzymatic methodologies for the preparation of homochiral diols or their corresponding monoacetates has also been documented,[13-15] either starting from the racemic (or prochiral) diols *via* an acyl transfer process, or by a hydrolysis of their corresponding diesters. For these purposes, lipases (E.C.3.1.1.3) are especially suitable biocatalysts,[16] due to their excellent enantioselectivity, activity and stability in water, in mixtures of water and a water-immiscible organic solvent and in organic solvents.[13]

Porcine pancreatic lipase (PPL) is one of the most frequently used enzymes in biotransformations.[15, 16] Nevertheless, there is still a great lack of knowledge about the substrate-recognition pattern followed by this enzyme, and no generally applicable rule to predict the fast-reacting enantiomer in PPL-catalyzed resolution of primary alcohols exists.[16] Thus, with the aim of furthering this topic, in this paper we present the synthesis of some acyclic phenylalkane (1,n)-diols (some of them described for the first time),and their resolution using PPL, *via* transesterification with vinyl acetate or by hydrolysis of the corresponding diacetates. The results observed for the resolution of these compounds was used to clarify the substrate-recognition pattern of this enzyme.

Thus we have used three different families of diols and their diacetyl derivatives as substrates for PPL:

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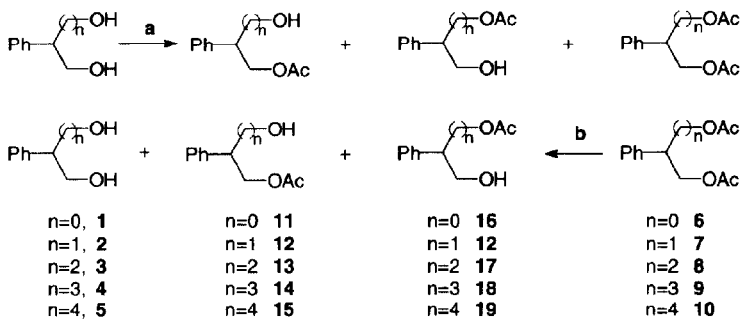
a) 1-phenyl-1,2-ethanediol (±)-**1** (commercial product) and its diacetyl derivative 1-phenyl-1,2-diacetoxyethane (±)-**6**, for determining the chemoselectivity of PPL when faced with a primary and a secondary hydroxyl group; *b.)* 2-phenyl-1,3-propanediol, **2**, and its diacetyl derivative, 2-phenyl-1,3-diacetoxypropane, **7**, as prochiral substrates to be asymmetrised by PPL, and *c.)* 2-phenyl-1,4-butanediol (±)-**3**, 2-phenyl-1,5-butanediol (±)-**4** and 2-phenyl-1,6-hexanediol (±)-**5**, (and the diacetyl compounds 2-phenyl-1,4-diacetoxybutane (±)-**8**, 2-phenyl-1,5-diacetoxypentane (±)-**9**, and 2-phenyl-1,6-diacetoxyhexane (±)-**10**, respectively) which may be considered excellent substrates to test PPL's ability to discriminate between two different primary alcohol moieties.

Scheme 1 shows two different strategies used for the resolution of these substrates: enzymatic acylation of the racemic diols **1** to **5** using vinyl acetate (path **a**), or enzymatic hydrolysis of the corresponding diacetates (**6** to **10**), path **b**.

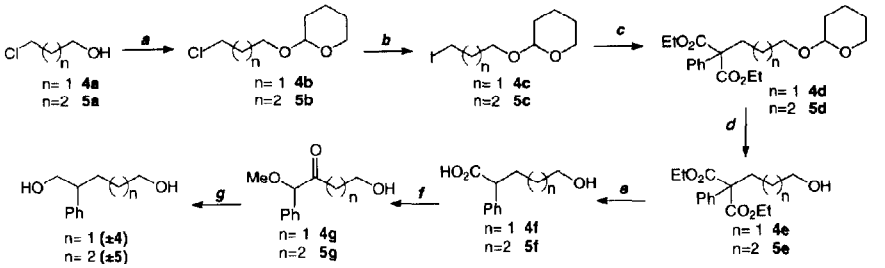


Scheme 1. Overall reaction scheme: (a) PPL-catalysed acetylation of diols. (b) PPL-catalysed hydrolysis of the diacetoxy derivatives.

Results and Discussion.

The prochiral 2-phenyl-1,3-propanediol **2** and racemic 2-phenyl-1,4-butanediol (±)-**3** were prepared according to the procedure described in the literature,[17] starting from diethyl phenylmalonate and diethyl 2-phenylsuccinate (see Experimental Section). In this paper we report the first chemical synthesis of compounds (±)-**4** and (±)-**5**, obtained as summarized in Scheme 2, in a synthetic route which could be extrapolated for all the longer-chain racemic acyclic (1,*n*)-diols. Thus, the starting chlorine-derivatives **4b** and **5b** were prepared by treating the commercially available substrates 3-chloro-1-propanol (**4a**) and 3-chloro-1-butanol (**5a**), respectively , with 3,4-dihydro-2H-pyran (DHP) in the presence of Amberlyst H-15 resin in *n*-hexane. Conversion to the iodine-derivatives **4c** and **5c** was achieved by treating **4b** or **5b** with NaI in dry acetone. The precursors **4d** and **5d** were obtained by alkylation of the iodine derivatives (**4c** or **5c**) with diethyl phenylmalonate and NaH in dry DMF. The further conversion of **4d** and **5d** to **4f** and **5f** was completed in two steps: i) deprotection of the alcohol group with Amberlyst H-15 in MeOH and ii) hydrolysis of diethyl ester (**4e**) followed by decarboxylation. Finally, 2-phenyl-1,5-pentanediol (±)-**4** and 2-phenyl-1,6-hexanediol (±)-**5** were prepared by reduction of the methyl esters of **4f** and **5f** with $LiAlH_4$ in dry Et_2O.

The diacetoxy derivatives (**6** to **10**) of the corresponding diols were obtained by a chemical acylation with acetic anhydride and dry pyridine (Experimental Section).



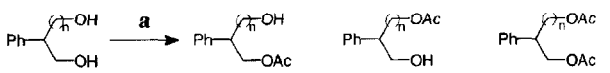
a) DHP, Amberlyst H-15, hexane, r.t.; **4b** (76%); **5b** (82%). *b*) NaI, dry acetone, reflux, 24h; **4c** (64%); **5c** (56%). *c*) Diethyl phenylmalonate, NaH, dry DMF, 80°C, 2h; **4d** (95%); **5d** (81%). *d*) MeOH, Amberlyst H-15, 60°C, 2h; **4e** (90°C); **5e** (95%). *e*) H_2O, OH (3h) // H^+/Δ (4h); **4f** (90%); **5f** (81%). *f*) MeOH, H^+ (4h); 4g (96%); 5g (95%). *g*) $LiAlH_4$, dry Et_2O, r.t. (1h) and reflux (1h); (±)-**4** (81%); (±)-**5** (78%).

Scheme 2. Synthesis of 2-phenyl-1,5-pentanediol (±)-**4** and 2-phenyl-1,6-hexanediol (±)-**5**.

The results obtained in the resolution of the diols (±)-**1** to (±)-**5** and the diacetates (±)-**6** to (±)-**10** are shown in Tables 1 and 2.

Table 1

PPL-catalysed acylation of diols (±)-1 to (±)-5.



n	diol	t (χ_{50})[a] (h)	Overall Yield (%)	Residual diol (%)	ee(%)/ config.	monoac./ (%)	ee(%)/ config.	monoac./ (%)	ee(%)/ config.	diacetate/ (%)	ee(%)/ config.
0	±1	32.5	47	53	13(S)	**16** / 47	19(*R*)	nd	----	nd	----
1	2	1	58	42	----[b]	**12** / 58	>95(*R*)	----	----	**7** / <5	----[b]
2	±3	4	44	56	<5	**13** / 4	>95(*S*)	**17** / 31	25(*R*)	**8** / 9	55(*S*)
3	±4	5	48	52	<5	**14** / 5	>95(*S*)	**18** / 34	<5	**9** / 9	27.5(*S*)
4	±5	6	50	50	11(*S*)	**15** / 6	47(*S*)	**19** / 34	<5	**10** / 10	34(*S*)

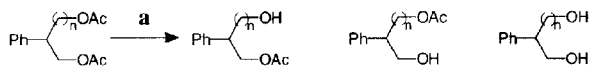
[a] Time to consume approx. 50% of the starting diol. [b] Prochiral compound. nd, not detected.

The determination of the enantiomeric purity of the remaining diols, monoacetates and diacetates, the sign of the optical rotation of the enantiomers, as well as the absolute configuration of the reaction products were established by different methods:

a) literature data. Thus, the absolute configuration of monoacetate **12** is based on literature data.[17-19] Similarly, the diols ***R*** and ***S*-1**, as well as the monoacetates ***R*** and ***S*-11** were assigned according to the optical rotation signs previously described,[20] and the same procedure was followed for ***R*** and ***S*-3**.[21]

Table 2

PPL-catalysed hydrolysis of the diacetoxy derivatives (±)-6 to (±)-10.



n	diac.	t (χ_{50}) [a] (h)	Overall Yield (%)	Residual diac. (%)	ee(%)/ config.	monoac./ (%)	ee(%)/ config.	monoac./ (%)	ee(%)/ config.	Diol	ee(%)/ config.
0	**±6**	1.7	52	48	<5	**11** / 20	<5	**16** / 32	10(*S*)	nd	----
1	**7**	1.2	48	52	----[b]	**12** / 48	65(*S*)	nd	nd	**7** / 2	----b
2	**±8**	2.2	51	49	<5	**13** / 31	42(*R*)	**17** / 20	63(*S*)	**8** / 9	55(*S*)
3	**±9**	2.2	49	51	nd	**14** / 30	nd	**18** / 19	12(*S*)	**9** / 9	27.5(*S*)
4	**±10**	4.5	48	52	<5	**15** / 18	35(*R*)	**19** / 18	33(*S*)	**10** / 10	34(*S*)

[a] Time to consume aprox. 50% of the starting diacetate. [b] Prochiral compound. nd, not detected.

b) ^{1}H-NMR spectra of the corresponding Mosher's esters, treating the diols with *R* or *S* -α-methoxy-α-trifluoromethyl-phenylacetyl chloride, and monitoring the upfield shift of the internal α-OMe group in the diastereoisomeric esters, produced by the matching aryl group of the substrates. The differences observed in the chemical shifts in both diastereoisomers allowed us to obtain the configurational correlation according to the model developed by Dale and Mosher.[22] Thus, this method was used extensively for the determination of the absolute configuration of monoacetates **11**, **17**, **18** and **19**, and acyclic (1,*n*)-diols **1**, **3**, **4** and **5**, monitoring the differences in chemical shifts of the α-OMe group in Mosher's esters in these compounds, which are considerably large and can be used for establishing configurational assignments.

c) HPLC using a chiral stationary phase (see Experimental Section),

d) recording the CD spectra of the optically enriched compounds obtained during the reaction course. The absolute configuration was established by measuring the sign of the Cotton effect for the maximum absorption (around 260 nm, due to the UV ^1L_b absorption band[23]). Table 3 summarises the CD spectra of the products obtained in the course of the PPL-catalysed acylation of the diols (±)-**1** to (±)-**5**.

The Benzene Sector and Benzene Chirality Rules, as defined for aromatic compounds with asymmetric benzylic C atoms possessing one hydrogen atom on the stereocentre,[24] were used to establish the absolute configuration of the products. Thus, different studies (empirical potential function[25] and molecular orbital calculations,[26-28] as well as X-ray,[26,29] proton nuclear magnetic resonance,[27,30-32] gas electron diffraction,[33] and jet laser[34] spectroscopy) for benzene compounds with a contiguous chiral centre incorporating a hydrogen atom indicate that the preferred conformation of this type of compound is that shown in Scheme 3, where the hydrogen atom at the chiral centre eclipses or almost eclipses the phenyl ring plane. Thus, by studying the CD spectra of several compounds possessing the monosubstituted benzene chromophore, Lorentzen *et al.*[35] defined the quadrant projection shown in Scheme 3, which shows the sign of the vibronic contribution to the ^1L_b Cotton effects caused by the substituents lying in sectors either in front of (near sectors) or behind (far sectors) the benzene ring plane, defining the boundaries by the attachment bond of the chiral centre and the benzene plane. The sum of the contributions gives the sign to the observed Cotton effects of the ^1L_b band since for benzene compounds with only

one substituents these effects are solely the results of the vibronic bestowal.[36] Thus, a ranking of rotatory contributions was defined.[24] Following this methodology, we have assigned a similar ranking for the different substituents around the stereocentre of our compounds on the sighs of the Cotton effects observed. Table 4 summarises the assignments, which were estimated as follows: as the absolute configurations of some of the reaction products was established either from literature data (compounds **1**, **3**, **11**, **12**[17-21]) or by the Mosher's esters

Table 3
Circular dichroism spectra of the reaction products.

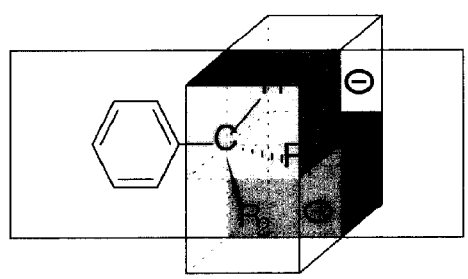
Product[a]	Cotton Effect		[C], mM	[θ]
	λ(nm)	Δε (mdeg)		deg·cm²·mol⁻¹
1[b]	2606	-711	213	$-6.660\cdot10^{1}$
3[b]	2600	-238	319	$-1.439\cdot10^{1}$
4[b]	-----[c]	-----[c]	32.4	-----
5[b]	-----[c]	-----[c]	28.6	-----
8	259.6	4.77	21.2	$+4.505\cdot10^{1}$
9	260.2	9.34	36.7	$+5.090\cdot10^{1}$
10	260	7.39	19.6	$+7.549\ 10^{1}$
11	260.4	27.43	28.6	$+1.920\cdot10^{2}$
12	2606	144	306	$+9.401\cdot10^{1}$
13	259.2	2.71	12.7	$+4.276\cdot10^{1}$
14	260.4	9.76	25.2	$+7.748\cdot10^{1}$
15	259.6	11.84	33.8	$+6.995\cdot10^{1}$
16	260.5	-3.54	56.3	$-1.260\cdot10^{1}$
17	260.8	3.77	24.2	$+3.109\cdot10^{1}$
18	-----[c]	-----[c]	27	-----
19	-----[c]	-----[c]	24.3	-----

[a] Non-racemic enantiomeric mixtures. [b] Remaining diols. [c] Low signal/noise ratio.

(compounds **1**, **3**, **11** and **17**), it is possible to define a first sequence of rotatory contributions, considering that:

a) *-CH_2OH* > *-OH* (from **1**);
b) *-$(CH_2)_2OH$* > *-CH_2OH* (from **3**);
c) *-CH_2OAc* > *-OH* (from **11**);
d) *-CH_2OH* > *-CH_2OAc* (from **12**);
e) *-CH_2OH* > *-$(CH_2)_2OAc$* (from **17**).

Therefore, this first sequence would be:



Scheme 3. Vibronic contributions to the ^1L_b Cotton effect for atoms or groups at the chiral centre for substituted benzylic chromophores.

$$-(CH_2)_2OH > -CH_2OH > -(CH_2)_2OAc > -CH_2OAc > -OH$$

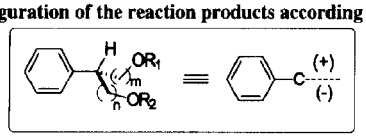
which shows:

1.- the greater effect of an hydroxyalkyl group versus an acetoxyalkyl (in accordance with the general ranking reported by Smith[24]), and

2.- the higher the number of methylene groups, the higher the effect.

Table 4

Absolute configuration of the reaction products according to the CD spectra.



Compound	n	m	R_1	R_2	Cotton effect	Contribution of Groups
***R*-1**[a,b]	0	1	-H	-H	positive	$-CH_2OH > -OH$
***S*-1**[a,b]	1	0	-H	-H	negative	
***R*-3**[a,b]	2	1	-H	-H	negative	$-(CH_2)_2OH > -CH_2OH$
***S*-3**[a,b]	1	2	-H	-H	positive	
***R*-8**	2	1	-Ac	-Ac	negative	$-(CH_2)_2OAc > -CH_2OAc$
***S*-8**	1	2	-Ac	-Ac	positive	
***R*-9**	3	1	-Ac	-Ac	negative	$-(CH_2)_3OH > -CH_2OAc$
***S*-9**	1	3	-Ac	-Ac	positive	
***R*-10**	4	1	-Ac	-Ac	negative	$-(CH_2)_4OAc > -CH_2OAc$
***S*-10**	1	4	-Ac	-Ac	positive	
***R*-11**[a,b]	0	1	-Ac	-H	positive	$-CH_2OAc > -OH$
***S*-11**[a,b]	1	0	-H	-Ac	negative	
***R*-12**[b]	1	1	-H	-Ac	positive	$-CH_2OH > -CH_2OAc$
***S*-12**[b]	1	1	-Ac	-H	negative	
***R*-13**	2	1	-Ac	-H	negative	$-(CH_2)_2OH > -CH_2OAc$
***S*-13**	1	2	-H	-H	positive	
***R*-14**	3	1	-H	-Ac	negative	$-(CH_2)_3OH > -CH_2OAc$
***S*-14**	1	3	-Ac	-H	positive	
***R*-15**	4	1	-H	-Ac	negative	$-(CH_2)_4OH > -CH_2OAc$
***S*-15**	1	4	-Ac	-H	positive	
***R*-16**	0	1	-H	-Ac	positive	$-CH_2OH > -OAc$
***S*-16**	1	0	-Ac	-H	negative	
***R*-17**[a]	2	1	-H	-Ac	positive	$-CH_2OH > -(CH_2)_2OAc$
***S*-17**[a]	1	2	-Ac	-H	negative	

[a] Configuration also assigned by Mosher´s esters. (See Experimental Section) [b] Configuration also confirmed by literature data.[17-21]

Hence, it seems reasonable to suppose the contributions of the other groups:

f) $(CH_2)_nOAc$ >-CH_2OAc (to assign **8**, **9** and **10**);

g) -$(CH_2)_nOH$ >-CH_2OAc (to assign **13**, **14** and **15**);

h) CH_2OH >-OAc (to assign **16**);

i) -CH_2OAc >-OAc (to assign **6**).

Once the absolute configuration of the reaction products were assigned, the analysis of the enzymatic regio and enantioselectivities shown in Tables 1 and 2 confirms that PPL always reacts on the -OH group furthest from the asymmetric carbon, regardless of the strategy used (acylation or hydrolysis), except in the hydrolysis of **10**, where equimolar amounts of **15** and **19** are obtained. Nevertheless, the acyl-transfer approach renders some amounts of diacetates (except for the acylation of **1**), while the hydrolytic operational method only leads to some amount of diol for **10**, maybe because of the shorter reaction times of this last strategy.

Another point to be considered is the stereoselectivity, which is excellent in organic medium for the asymmetrisation of the prochiral diol **2** and for the formation of the minor monoacetates **13** and **14**, while the hydrolytic pathways does not give adequate optical purities, except for the hydrolysis of the prochiral diacetate **7** (although with smaller enantiomeric excess (66%) than the acyl-transfer methodology (>95%)). The higher enantioselectivity of the acyl-transfer methodology *versus* the hydrolytic process is a common feature in lipase-catalysed reactions, and it has been attributed to the high concentration of water solvent in the second methodology.[37] Moreover, substantial changes of the intrinsic enantioselectivity properties of enzymes upon replacement of water by organic (co)solvents have been claimed.[38-40] In fact, it can be observed from Tables 1 and 2 that the enzymatic stereorecognition is inversed between the two strategies, that is, in each step of the reaction pathway, if an *R* (or *pro-R*) configuration is preferred in the hydrolytic fashion, an *S* (or pro-S) will be preferred in the acyl-transfer process, and *vice versa*.

To summarise the work of this paper, the synthesis of different racemic and prochiral diols and diacetates has been described. Moreover, the characterisation of all the reaction products obtained in the resolution with PPL has been reported, therefore opening the way to their resolution with some other lipases. In order to deepen the knowledge of the enzymatic recognition of the substrates, we have actually studied the acyl-transfer process (more enantioselective) to explore the enzymatic regio- (differences between acylation in both -OH groups) and enantioselectivity, and to rationalise it according to the microcrystalline enzymatic structure for further publication.[41]

Experimental Section

General remarks. Melting points were determined on the Gallenkamp melting point apparatus. Thin-layer chromatography (TLC) was done on Merck silica gel 60 F_{254}. Column chromatography was done on Merck silica gel 60 (230-240 mesh ASTM). ^1H NMR and ^{13}C NMR spectra were recorded on Bruker AC-200 and Bruker AC-300. HPLC analysis was performed with a chiral column Chiralcel OD (25 cm× 0.46 cm i.d.) using equipment made by Thermo/Separation ConstaMetric® 4100 Quaternary Solvent Delivery Systems, a SpectroMonitor® 5000 equipped with a Photo Diode Array Detector and a Knauer Chiral Detector A1000. CD spectra were recorded on a Jasco (J-710) spectropolarimetre using 0.5 cm optical path length cuvettes. The solvent used for solubilising the compounds (obtained before reaction time = 9 h) was *n*-hexane/*i*-propanol 90/10, v/v. Spectral data were acquired over the range 230-290 nm.

Materials. Lipases (E.C.3.1.1.3.) from Porcine Pancreas, crude (Steapsin), type II, and purified, type VI, were obtained from Sigma. The racemic alcohol phenyl-1,2-ethanediol (**±1**) and all the reagents and solvents used were

purchased from Aldrich Chemical Co., Alcobendas, Spain.

2-Phenyl-1,3-propanediol (2). To a suspension of $LiAlH_4$ (10.5 mmol, 388 mg) in dry Et_2O (100 ml) a solution of diethyl phenylmalonate (4.2 mmol, 991 mg) in dry Et_2O (50 ml) was added at 0°C. The reaction mixture was stirred at room temperature for 1 h after which it was refluxed for 1 h. Dilute HCl was carefully added to acidic pH; the aqueous phase was extracted with ethyl acetate and the combined organic extracts were washed successively with a saturated solution of $NaHCO_3$ and water. The organic phase was dried over $MgSO_4$ anhydrous and concentrated under reduced pressure. Flash chromatography on silica gel by eluting with hexane-ethyl acetate (1:3) afforded 2-phenyl-1,3-propanediol **2** (83%) as a white solid, m.p. 51-53°C (Lit. m.p. 53-54°C)[17].

(±)-2-Phenyl-1,4-butanediol (±3). The procedure was similar to above, with the following change: To a suspension of $LiAlH_4$ (10.5 mmol, 388.5 mg) in dry Et_2O (100 ml) a solution of diethyl-2-phenyl-succinate (4.2 mmol, 1.05 mg) in dry Et_2O (50 ml) was added at 0°C. The conditions of reaction and work-up were similar to previous procedure for compound **2**. Column chromatography eluting with hexane-ethyl acetate (1:3) afforded (±)-2-phenyl-1,4-butanediol (±)-**3** (663 mg, 95%) as a white solid, m.p. 66-68°C. ν_{max} (KBr): 3345, 2395, 1494, 1050 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.86 (1H, m, H-3_A), 2.00 (1H, m, H-3_B), 2.92 (1H, m, H-2), 3.49 (2H, m, H-4_A), 3.57 (s br, OH), 3.60 (1H, m, H-4_B), 3.72 (2H, d, J=6.8 Hz, H-1), 7.15 (2H, d, J=8.0 Hz, H-2'), 7.20 (1H, t, J=8.0 Hz, H-4'), 7.30 (2H, t, J=8.0 Hz, H-3'). δ_C (75 MHz, $CDCl_3$): 35.94 (C-3), 46.05 (C-2), 61.61 (C-4),67.18 (C-1), 126.94 (C-4'), 127.93 (C-2'), 128.84 (C-3'), 142.43 (C-1'). [Found, C, 72.20; H, 8.41.$C_{10}H_{14}O_2$: requires C, 72.26; H, 8.49].

2-(3-chloropropoxy)tetrahydropyran (4b) and 2-(4-chlorobutoxy)tetrahydropyran (5b) See Scheme 2. A solution of 3-chloro-1-propanol (**4a**) (106 mmol, 9.97 g), or 4-chloro-1-butanol (**5a**) (106 mmol, 11.45 g), and 3,4-dihydro-2H-pyran (150 mmol, 12.6 g) in 20 ml of hexane was added to a suspension of Amberlyst H-15 (20 meq., 5 g) in 20 ml of hexane and the mixture was stirred for 1h. The resin was then filtered off and the solvent removed under reduced pressure. The crude mixture was purified by column chromatography eluting with hexane-ethyl acetate (10:1) to give 2-(3-chloropropoxy)tetrahydropyran **4b** (14.34 g ,76%) or 2-(4-chlorobutoxy)tetrahydropyran **5b** (16.69 g, 82%). Compound **4b**: Colourless oil. ν_{max}: 2941, 2870, 1442, 1122, 1033 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.48 (4H, m), 1.65 (2H, m), 1.98 (2H, m), 3.40 (2H, m), 3.55 (2H, t, J=6.3 Hz), 3.65 (2H, m), 4.48 (1H, t, J=3.0 Hz). δ_C (75 MHz, $CDCl_3$): 19.50 (CH_2), 25.46 (CH_2), 30.62 (CH_2), 32.80 (CH_2), 41.97 (CH_2), 62.16 (CH_2), 63.90 (CH_2) and 98.83 (CH). [Found, C, 53.7; H, 8.5.; $C_8H_{15}ClO_2$: requires C, 53.8; H, 8.5, Cl, 19.8]. Compound **5b**: Colourless oil. ν_{max}: 2942, 2869, 1444, 1119, 1034 cm^{-1}. δ_H (300 MHz, $CDCl_3$):1.4-1.9 (10H, m), 3,38 (2H, m), 3.52 (2H, t, J=6.3 Hz), 3.70 (2H, m), 4.51 (1H, t, J=3.0 Hz). δ_C (75 MHz, $CDCl_3$):19.55 (CH_2), 25.41 (CH_2), 27.08 (CH_2), 29.49 (CH_2), 30.65 (CH_2), 44.90 (CH_2) 62.28 (CH_2), 66.54 (CH_2), 98.78 (CH). [Found, C, 56.02; H, 8.80;. $C_9H_{17}ClO_2$: requires C, 56.10; H, 8.89].

2-(3-iodopropoxy)tetrahydropyran (4c) and 2-(4-iodobutoxy)tetrahydropyran (5c). A mixture of **4b** (62 mmol, 11.04 g) or **5b** (62 mmol, 11.90 g), NaI (70 mmol, 10.5 g) and dry acetone (25 ml) was heated at reflux overnight. After filtration of NaCl and removal of solvent, the final residue was purified by column chromatography by eluting with hexane-ethyl acetate (10:1) to give a 80:20 mixture of **4b**:**4c** (63% overall yield), and the same mixture of **5b**:**5c** (56% overall yield). Compound **4c**: Colourless oil. ν_{max}: 2941, 2865, 1440, 1132, 1030 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.60 (4H, m), 1.80 (2H, m), 2.10 (2H, m), 3.26 (2H, t, J=6.5 Hz), 3.48 (2H, m), 3.85 (2H, m), 4.55 (1H, t, J=3.0 Hz). δ_C (75 MHz, $CDCl_3$): 3.60 (CH_2), 19.58 (CH_2), 25.51 (CH_2), 30.69 (CH_2), 33.64 (CH_2), 62.40 (CH_2), 66.92 (CH_2), 99.00 (CH). Compound **5c**: Colourless oil. ν_{max}: 2940, 2869, 1440, 1133, 1033 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.4-1.9 (m, 10H), 3.18 (t, J=6.3 Hz, 2H), 3.39 (m, 2H), 3.70 (m, 2H), 4.53 (t, J=3.0 Hz, 1H). δ_C (75 MHz, $CDCl_3$): 6.65 (CH_2), 19.44 (CH_2), 25.32 (CH_2), 26.97 (CH_2), 29.51 (CH_2), 30.54 (CH_2), 62.11 (CH_2), 66.04 (CH_2), 98.62 (CH).

2-phenyl 2[3(2-tetrahydropyranoxy)propyl] diethyl malonate (4d) and 2-phenyl 2[4(2-tetrahydropyranoxy)butyl] diethyl malonate (5d). A solution of diethyl phenylmalonate (33.9 mmol, 8.0 g) in 10 ml of anhydrous DMF was added dropwise into a stirred suspension of sodium hydride (60% in silicon oil; 34 mmol, 1.36 g) in 15 ml of anhydrous DMF. After the addition, hydrogen evolution quickly stopped as stirring was

continued for 30 min at rt. Then, (**4c**) (34 mmol, 8.1 g) or **5c** (34 mmol, 8.57 g) in 10 ml of anhydrous DMF were added dropwise at 80ºC. The mixture was poured into ice water and was extracted with ethyl acetate. The combined extracts were washed twice with NaCl solution, dried over Na_2SO_4 anhydrous and the solvent evaporated under reduced pressure. The residue was purified by column chromatography eluting with hexane- AcOEt (10:1) to give 2-phenyl 2[3(2-tetrahydropyranoxy)propyl] diethyl malonate **4d** (12.22 g, 95%) and 2-phenyl 2[4(2-tetrahydropyranoxy)butyl] diethyl malonate **5d** (10.81 g, 81%). Compound **4d**: Colourless oil. ν_{max}: 2940, 1732, 1235, 1033 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.25 (t, J=7.0 Hz, 6H), 1.4-1.9 (8H, m), 2.39 (2H, m), 3.42 (2H, m), 3.73 (2H, m), 4.20 (4H, q, J=7.0 Hz), 4.52 (1H, t, J=3.0 Hz), 7.28 (1H, td, J=6.5 and 2.5 Hz), 7.30 (2H, dd, J=8.5 and 6.5 Hz), 7.43 (2H, dd, J=8.5 and 2.5 Hz). δ_C (75 MHz, $CDCl_3$): 14.04 (2×CH_3), 19.80 (CH_2), 25.13 (CH_2), 25.51 (CH_2), 30.73 (CH_2), 32.46 (CH_2), 61.53 (2×CH_2), 62.20 (CH_2), 62.39 (C), 67.17 (CH_2), 98.62 (CH), 127.5 (CH), 128.13 (2×CH), 128.21 (2×CH), 136.90 (C), 170.74 (2×CO). [Found, C, 66.70; H, 7.81;. $C_{21}H_{30}O_6$: requires C, 66.65; H, 7.79]. Compound **5d**: Colourless oil. ν_{max}: 2938, 1732.5, 1234, 1032 cm^{-1} δ_H (300 MHz, $CDCl_3$): 1.22 (6H, t, J=7.0 Hz,), 1.4 1.9 (10H, m), 2.3 (2H, m), 3.35 (2H, m), 3.70 (2H, m), 4.20 (4H, q, J=7.0Hz), 4.50 (1H, t, J=3.0 Hz), 7.23 (1H, t, d, J=6.5 and 2.5 Hz), 7.28 (2H, dd, J=8.5 and 6.5 Hz), 7.40 (2H, dd, J=8.5 and 2.5 Hz). δ_C (75 MHz, $CDCl_3$): 13.86 (2x CH_3), 19.41 (CH_2), 21.32 (CH_2), 24.93 (CH_2), 29.81(CH_2), 30.60 (CH_2), 35.45 (CH_2), 61.29 (2x CH_2), 62.05 (CH_2),98.56 (CH), 127.26 (CH), 127.93 (4x CH), 136.96 (C), 170.59 (2x CO). [Found, C, 67.35; H, 8.20; $C_{22}H_{32}O_6$: requires C, 67.32; H, 8.22].

2-phenyl 2(3-hydroxypropyl) diethyl malonate (4e) and 2-phenyl 2(4-hydroxybutyl) diethyl malonate (5e). Amberlyst H-15 (3.5 g, 11.5 meq.) was added to a solution of the compound **4d** (11.5 mmol, 4.347 g) or **5d** (11.5 mmol, 4.508 g) dissolved in methanol (250 ml), and the mixture was heated at 60ºC for 2h. The resin was then filtered off and the solvent removed under reduced pressure. The residue was then chromatographed on silica gel by eluting with hexane- ethyl acetate (6:1) to give 2-phenyl 2(3-hydroxypropyl) diethyl malonate **4e** (3.05 g, 90%) or 2-phenyl 2(4-hydroxybutyl) diethyl malonate **5e** (3.37 g, 95%). Compound **4e**: Colourless oil. ν_{max}: 3426, 2938, 1731, 1242 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.20 (6H, t, J=7.0 Hz), 1.49 (2H, m), 2.35 (2H, m), 3.55 (2H, m), 4.18 (4H, q, J=7.0 Hz), 7.2-7.4 (5H, m). δ_C (75 MHz, $CDCl_3$): 13.75 (2x CH_3), 27.83 (CH_2), 31.99 (CH_2),61.41 (2x CH_2), 61.83 (C), 62.25 (CH_2), 127.20 (CH), 127.81 (2x CH), 127.92 (2×CH), 136.79 (C), 170.51 (2x CO). [Found, C, 65.32, H, 7.50; $C_{16}H_{22}O_5$: requires C, 65.29; H, 7.53]. Compound **5e**: Colourless oil.ν_{max}: 3430, 2940, 1732, 1241 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.19 (6H, t, J=7.0 Hz), 1.23 (2H, m), 1.51 (2H, m), 2.25 (2H, m), 3.51 (2H, t, J=7.0 Hz), 4.18 (4H, q, J=7.0 Hz), 7.2-7.4 (5H, m). δ_C (75 MHz, $CDCl_3$): 13.80 (2x CH_3), 20,84 (CH_2), 32.55 (CH_2), 35.28 (CH_2), 61.35 (2x CH_2), 62.04 (CH_2), 62.49 (C), 127.28 (CH), 127.81 (2x CH), 127.95 (2x CH), 136.95 (C), 170.62 (2x CO). [Found, C, 66.19, H, 7.91; $C_{17}H_{24}O_5$: requires C, 66.21; H, 7.84].

2-phenyl 5-hydroxy pentanoic acid (4f) and 2-phenyl 6-hydroxy hexanoic acid (5f). A solution of compound **4e** (13.6 mmol, 4.01g) or **5e** (13.6 mmol, 4.20 g), in EtOH (10 ml) was added to a solution of KOH (30g) in water (40 ml). When all the ester has been added, the solution was boiled for 3h, until hydrolysis was complete, and diluted with 100 ml of water. Then, the alcohol formed in the hydrolysis was distilled. H_2SO_4 (conc.) was slowly added to the cold residue with stirring, and the mixture of reaction was refluxed for 4h. The aqueous phase was extracted with ethyl acetate and the combined organic extracts were washed with NaCl solution, dried over $NaSO_4$ anhydrous and the solvent evaporated under reduced pressure. The residue was purified by column chromatography by eluting with CH_2Cl_2/ MeOH (15:1) to give 2-phenyl 5-hydroxy pentanoic acid **4f** (2.64 g, 85%) and 2-phenyl 6-hydroxy hexanoic acid **5f** (2.29 g, 81%). Compound **4f**: Waxy solid. oil. ν_{max}: (Nujol): 3500-3100, 1708, 1455, 1274 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.51 (2H, m), 1.82 (1H, m), 2.10 (1H, m), 3.58 (2H, t, J=7.0 Hz), 3.60 (1H, dd, J=6.8 and 6.0 Hz), 7.2-7.4 (5H, m). δ_C (75 MHz, $CDCl_3$): 29.44 (CH_2), 30.43 (CH_2), 51.34 (CH), 62.39 (CH_2), 127.60 (CH), 128.11 (2×CH), 128.82 (2×CH), 138.56 (C), 179.0 (CO). [Found, C, 68.06, H, 7.21; $C_{11}H_{14}O_3$: requires C, 68.02; H, 7.26]. Compound **5f**: Waxy solid.ν_{max}: (Nujol): 3500-3100, 1710, 1452, 1271 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.35 (2H, m), 1.56 (2H, m), 1.80 (1H, m), 2.12 (1H, m), 3.54 (1H, t, J=6 Hz), 3.59 (2H, t, J=6 Hz), 7.2-7.4 (5H, m), 7.80 (s br, OH). δ_C (75 MHz, $CDCl_3$): 23.67 (CH_2), 32.10 (CH_2), 32.82 (CH_2), 51.50 (CH), 62.42 (CH_2), 127.39 (CH), 127.94 (2x CH), 128.64 (2x CH),138.49 (C), 179.28 (CO),[Found, C, 69.18, H, 7.75; $C_{12}H_{16}O_3$: requires C, 68.02; H, 7.26].

2-phenyl 5-hydroxy methyl pentanoate (4g) and 2-phenyl 6-hydroxy methyl hexanoate (5g). A solution of **4f** (10.3 mmol, 2 g) or **5f** (10.3 mmol, 2.14 g) in MeOH (100 ml) and H_2SO_4 conc. (0.5 ml) was refluxed for 4h, until esterification was completed. The solvent was distilled under reduced pressure and the residue was dissolved in CH_2Cl_2 (150 ml). The organic layer was washed successively with saturated $NaHCO_3$ and water, dried with $MgSO_4$ anhydrous and concentrated under reduced pressure to give 2-phenyl 5-hydroxy methyl pentanoate **4g** (2.06 g, 96%) and 2-phenyl 6-hydroxy methyl hexanoate **5g** (2.18 g, 95%). Compound **4g**: Syrup. ν_{max}: 3437, 1714, 1454, 1167 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.46 (2H, m), 1.77 (1H, m), 2.10 (1H, m), 3.36 (3H, m), 3.51 (1H, t, J=7.7 Hz), 3.55 (2H, t, J=7.7 Hz), 6.10 (s br, OH), 7.2-7.3 (5H, m). δ_C (75 MHz, $CDCl_3$): 29.24 (CH_2), 30.09 (CH_2), 50.06 (CH_3), 51.18 (CH), 61.95 (CH_2), 127.86 (2x CH), 128.54 (2x CH), 138.63 (C), 177.93 (CO). [Found, C, 69.27, H, 7.71; $C_{12}H_{16}O_3$ requires C, 69.21; H, 7.75]. Compound **5f**: Syrup. ν_{max}: 3439, 1716, 1452, 1168 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.29 (2H, m), 1.53 (2H, m), 1.79 (1H, m), 2.08 (1H, m), 3.53 (1H, t, J=7.7 Hz), 3.56 (2H, t, J=7.7 Hz), 3.62 (3H, s), 7.2-7.3 (5H, m). δ_C (75 MHz, $CDCl_3$): 23.71 (CH_2), 32.27 (CH_2), 33.16 (CH_2), 51.50 (CH), 51.88 (CH_3), 62.38 (CH_2), 127.17 (CH), 127.78 (2x CH), 128.54 (2x CH), 138.97 (C), 174.47 (CO). [Found, C, 70.21, H, 8.23; $C_{13}H_{18}O_3$ requires C, 70.24; H, 8.26].

Preparation of (±)-2-Phenyl-1,5-pentanediol (±)-4 and (±)-2-Phenyl-1,6-hexanediol (±)-5. To a suspension of $LiAlH_4$ (4.81 g, 13.0 mmol) in dry ether (100 ml) a solution of compound **4g** (1.0 g, 4.5 mmol) or **5g** (0.87 g, 4.5 mmol) in dry ether (40 ml) was slowly added at 0°C. The reaction mixture was stirred at room temperature for 1h. Diluted HCl was carefully added to acidic pH; usual workup (ether) and chromatography by eluting with hexane-AcOEt (1:3) afforded (±)-2-phenyl-1,5-pentanediol (±)-**4** (0.66 g, 81%) and (±)-2-phenyl-1,6-hexanediol (±)-**5** (0.68 g, 78%) Compound (±)-**4**: colourless oil. ν_{max}: 3338, 2937, 1452, 1053 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.38 (2H, m, H-4), 1.54 (1H, m, H-3_A), 1.85 (1H, m, H-3_B), 2.79 (1H, m, H-2), 3.38 (s br, OH), 3.58 (2H, t, J=6.2 Hz, H-5), 3.74 (2H, d, J=6.5 Hz, H-1), 7.15 (2H, d, J=8.0 Hz, H-2'), 7.20 (1H, t, J=8.0 Hz, H-4'), 7.29 (2H, d, J=8.0 Hz, H-3'). δ_C (75 MHz, $CDCl_3$): 28.23 (C-3), 30.50 (C-4), 48.45 (C-2), 62.81 (C-5), 67.58 (C-1), 126.94 (C-4'), 128.14 (C-2'), 128.82 (C-3'), 142.20 (C-1'). [Found, C, 73.35; H, 8.91. $C_{11}H_{16}O_2$ requires: C, 73.30; H, 8.95.] Compound (±)-**5**: colourless oil. ν_{max}: 3330, 2934, 1452, 1050 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.20 (2H, m, H-4), 1.48 (2H, m, H-5), 1.53 (1H, m, H-3_A), 1.72 (1H, m, H-3_B), 2.78 (1H, m, H-2), 3.57 (2H, t, J=6.4 Hz, H-6), 3.73 (2H, d, J=6.2 Hz, H-1), 7.15 (2H, d, J=8.0 Hz, H-2'), 7.20 (1H, t, J=8.0 Hz, H-4'), 7.30 (2H, t, J=8.0 Hz, H-3'). δ_C (75 MHz, $CDCl_3$): 23,65 (C-4), 31.87 (C-3), 32.77 (C-5), 48.74 (C-2), 62.78 (C-6), 67.58 (C-1), 126. 87 (C-4'), 128.15 (C-2'), 128.78 (C-3'), 142.39 (C-1').[Found, C, 74.22; H, 9.31. $C_{12}H_{18}O_2$: requires C, 74.19; H, 9.34.].

Chemical Acylation of (1,n)-diols: General Procedure A solution of diols **1-5** (10 mmol) in dry pyridine (20 ml) and acetic anhydride (10 ml) was stirred at room temperature overnight. Then, ethyl acetate (200 ml) was added and the organic extract was washed with HCl (10%) and dried with $MgSO_4$ anhydrous. Then, the solvent was evaporated "in vacuo" to give quantitatively the diacetoxy derivatives **6** to **10**.

1-Phenyl-1,2-diacetoxyethane (±6): Colourless oil. ν_{max}: 1740, 1230, 1037 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 2.06 (3H, s), 2.12 (3H, s), 4.30 (2H, m), 6.01 (1H, m), 7.2-7.4 (5H, m). δ_C (75 MHz, $CDCl_3$): 66.20 (CH_2), 73.42 (CH), 126.79 (2x CH), 128.73 (CH), 128.75 (2x CH), 156.58 (C), 170.19 (C). [Found, C, 64.79; H, 6.39. $C_{12}H_{14}O_4$: requires C, 64.85; H, 6.35.].

2-Phenyl-1,3-diacetoxypropane (7): Colourless oil. ν_{max}: 1741, 1229, 1038 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 2.02 (6H, s, 2×CH_3), 3.32 (1H, m, H-2), 4.32 (4H, d, J= 6.6 Hz, H-1 and H-3), 7.2-7.4 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 20.98 (2×CH_3), 43.83 (CH), 64.97 (2×CH_2), 127.55 (CH), 128.06 (2×CH), 128.78 (2×CH), 138.44 (C), 171.01 (2×CO).[Found, C, 66.01.20; H, 6.79. $C_{13}H_{16}O_4$: requires C, 66.09; H, 6.83.].

2-Phenyl-1,4-diacetoxybutane (±8): Colourless oil. ν_{max}: 1741, 1238, 1040 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1,90-2.20 (2H, m, H-3), 1.99 (3H, s, CH_3), 2.01 (3H, s, CH_3), 3.06 (1H, m, H-2), 3.97 (2H, m, H-4), 4.22 (2H, d, J=6.9 Hz, H-1), 7.1-7.4 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 21.00 (2×CH_3), 31.36 (CH_2), 41.90 (CH), 62.46 (CH_2), 68.21 (CH_2), 127.23 (CH), 127,87 (2×CH), 28.80 (2×CH), 140.55 (C), 171.06 (2×CO). [Found, C, 67.21; H, 7.30. $C_{14}H_{28}O_4$ requires C, 67.18; H, 7.25].

2-Phenyl-1,5-diacetoxypentane (±9): Colourless oil. ν_{max}: 1739, 1242, 1039 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.4-1.9 (4H, m, H-3 and H-4), 2.00 (3H, s, CH_3), 2.02 (3H, s, CH_3), 2.93 (1H, m, H-2), 4.01 (2H, t, J=6.6 Hz, H-5), 4.19 (2H, d, J=6.9 Hz, H-1), 7.1-7.4 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 21.03 (CH_3), 21.07 (CH_3), 26.44 (CH_2), 28.79 (CH_2), 44.73 (CH), 64.40 (CH_2), 68.45 (CH), 127.05 (CH), 127.91 (2×CH), 128.71 (2×CH), 141.29 (C), 171.13 (CO), 171.23 (CO).[Found, C, 68.10; H, 7.69. $C_{15}H_{20}O_4$ requires C, 68.16; H, 7.63.].

2-Phenyl-1,6-diacetoxyhexane (±10): Colourless oil. ν_{max}: 1738, 1239, 1037 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.2-1.8 (6H, m, H-3, H-4 and H-5), 1.99 (3H, s, CH_3), 2.00 (3H, s, CH_3), 2.90 (1H, m, H-2), 3.99 (2H, t, J=6.7 Hz, H-6), 4.19 (2H, d, J=7.0 Hz, H-1), 7.1-7.4 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 21.04 (CH_3), 21.08 (CH_3), 23.63 (CH_2), 28.60 (CH_2), 32.05 (CH_2), 44.92 (CH), 64.33 (CH_2), 68.51 (CH_2), 126.90 (CH), 127.91 (2×CH), 128.62 (2×CH), 141.66 (C), 171.17 (CO), 171.27 (CO).[Found, C, 68.98; H, 7.99. $C_{16}H_{22}O_4$ requires C, 69.04; H, 7.97].

PPL-Catalysed Transesterification of Racemic 2-Phenyl-1,n-alkanediols: General Procedure. A solution of diols (**1-5**) (6 mmol) and vinyl acetate (4.13 g, 48 mmol) in diisopropyl ether (15 ml) was stirred at 25 °C with PPL (300mg commercial powder). Then, aliquots of 0.1 ml were taken from the solution (at different times) and added to 0.9 ml of a 80/20 n-hexane/isopropanol mixture; after microfiltration, they were analysed by HPLC. The spectrophotometrical quantification (λ=254 nm) of products concentration and the enantiomeric excess of the products were calculated using an external standard method.

PPL-Catalysed Hydrolysis of Racemic 2-Phenyl-1,n-diacetoxyalkanes: General Procedure. A suspension of the diacetoxy derivatives (±)-**6** to (±)-**10** (1 mmol) in a 0.02 M phosphate buffer (10 ml) at pH= 7.0 was incubated with PPL (110 mg) and stirred at room temperature. The hydrolysis was monitored by titration with a 1M sodium hydroxide solution, and was stopped after comsumption of 1 equivalent of alkali. After that, the crude reaction mixture was extracted with dichloromethane. The organic phase was dried on $MgSO_4$, concentrated and analysed by TLC. The purification of compounds **1**, **3**, **4** and **5** and derivatives were carried out by flash chromatography eluting with a mixture *n*-hexane/ethyl acetate (2:1), and a mixture *n*-hexane/ethyle acetate (3:1) was used for the purification of compound **2** and derivatives.

HPLC Analysis Analysis conditions for the products were as follows:

i) For the resolution of mixtures of **1**, ***R*-11**, ***S*-11**, ***R*-16**, ***S*-16**, ***R*-6** and ***S*-6**: isocratic mixture of n-hexane/isopropanol (97/3), flow rate=0.7 ml/min (P≈400 psi). Retention time: (***S*-1**), t= 46 min; (***R*-1**), t= 41 min; (***R*-11**), t= 34 min; (***S*-11**), t=30 min; (***S*-16**), t=27.5 min; (***R*-16**), t=26 min; (***R*-6**)-(***S*-6**), t=10-12 min.

ii) For the resolution of mixtures of **2**, **12** and **7**: isocratic mixture of n-hexane/isopropanol (97/3), flow rate=0.7 ml/min (P≈400 psi). Retention times: **2**, t=34 min; (***R*-12**), t=24 min; **7**, t= 13 min.

iii) For the resolution of mixtures of **3**, **13**, **17** and **8**: n-hexane/isopropanol gradient: t=0 min, flow rate=0.5 ml/min, 98/2 n-hexane/isopropanol; t=30 min, flow rate=1 ml/min, 97/3 n-hexane/isopropanol. Retention times: (***R*-3**), t=58 min; (***S*-3**), t=56 min; (***R*-13**), t= 42 min; (***S*-13**), t= 40 min; (***S*-17**), t=48 min; (***R*-8**), t= 28 min; (***S*-8**), t=21 min.

iv) For the resolution of mixtures of **4**, **14**, **18** and **9**: n-hexane/isopropanol gradient: t=0 min, flow rate= 0.5 ml/min, 98/2 n-hexane/isopropanol; t=25 min, flow rate= 0.6 ml/min, 97/3 n-hexane/isopropanol; t=29 min, flow rate=1 ml/min, 97/3 n-hexane/isopropanol. Retention times: **4**, t=57 min (only one peak); **14**, t= 40 min (only one peak); (***S*-18**), t=46 min; (***R*-9**) , t=22 min; (***S*-9**), t=20 min.

v) For the resolution of mixtures of **5**, **15**, **19** and **10**: the same above mentioned solvents gradient was used. Retention times: (***S*-5**), t=68 min; (***R*-5**), t=64 min; (***S*-15**), t=47 min; (***R*-15**), t=45 min; (***S*-19**), t=53 min; (***R*-19**), t=50 min, (***S*-10**), t=19 min; (***R*-10**), t=17 min.

At a convenient fixed reaction time, the crude reaction mixture, after removal of the enzyme by filtration, was concentrated and the remaining residue was chromatographically separated on a silica gel column (hexane: EtOAc 1:2), obtaining fractions containing the monoacetates, (major and minor) the diacetates and the remnant diols, which structures were confirmed by ^{1}H-NMR and ^{13}C-NMR and microanalysis.

Characterization of the Reaction Products.

2-acetoxy-1-hydroxy-1-phenylethane (11): Colourless oil. ν_{max}: 3441, 1739, 1242, 1039 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 2.11 (3H, s, $\underline{CH_3}$), 4.16 (1H, dd, J=11.6 and 8.4 Hz, $\underline{H\text{-}2_A}$), 4.29 (1H, dd, J=11.6 and 3.3 Hz, $\underline{H\text{-}2_B}$), 4.97 (1H, dd, J=8.4 and 3.3 Hz, H-1), 7.3-7.4 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 21.03 (CH_3), 69.46 (CH_2), 72.54 (CH), 126.24 (2×CH), 128.38 (CH), 128.72 (2×CH), 139.81 (C), 171.30 (CO). [Found, C, 66.59 H, 6.73. $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.71].

1-acetoxy-3-hydroxy-2-phenylpropane (12): Colourless oil. ν_{max}: 3426, 1737, 1249, 1037 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 2.01 (3H, s, $\underline{CH_3}$), 3.12 (1H, m, H-2), 3.80 (2H, dd, J=6.1 and 6.1 Hz, H-1), 4.36 (2H, d, J=6.6 Hz, H-3), 7.2-7.4 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 21.05 (CH_3), 47.36 (CH), 64.00 (CH_2), 65.06 (CH_2), 127.49 (CH), 128.22 (2×CH), 128.90 (2×CH), 138.99 (C), 171.45 (CO). [Found, C, 67.93 H, 7.27. $C_{11}H_{14}O_3$ requires C, 68.02; H, 7.26].

1-acetoxy-4-hydroxy-2-phenylbutane (13): Colourless oil. ν_{max}: 3406, 1738, 1245, 1051 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.8-2.2 (2H, m, H-3), 1.98 (3H, s, $\underline{CH_3}$), 2.91 (1H, m, H-2), 3.75 (2H, d, J=6.6 Hz, H-1), 3.98 (2H, m, H-4), 7.1-7.4 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 21.01 (CH_3), 31.00 (CH_2), 45.44 (CH), 62.77 (CH_2), 67.34 (CH_2), 127.18 (CH), 128.06 (2×CH), 128.93 (2×CH), 141.23 (C), 171.22 (CO). [Found, C, 69.18; H, 7.79. $C_{12}H_{16}O_3$ requires C, 69.21; H, 7.74].

1-acetoxy-5-hydroxy-2-phenylpentane (14): Colourless oil. ν_{max}:3420, 1738, 1242, 1038 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.5-1.9 (4H, m, H-3 and H-4), 2.02 (3H, s, $\underline{CH_3}$), 2.79 (1H, m, H-2), 3.74 (2H, d, J=6.0 Hz, H-1), 4.01 (2H, t, J=6.5 Hz, H-5), 7.1-7.4 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 21.01 (CH_3), 26.60 (CH_2), 28.37 (CH_2), 48.42 (CH), 64.48 (CH_2), 67.57 (CH_2), 127.05 (CH), 128.12 (2×CH), 128.87 (2×CH), 141.84 (C), 171.33 (CO). [Found, C, 70.28; H, 8.19. $C_{13}H_{18}O_3$ requires C, 70.25; H, 8.16].

1-acetoxy-6-hydroxy-2-phenylhexane (15): Colourless oil. ν_{max}: 3407, 1738, 1240, 1036 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.27 (2H, m, H-4), 1.67 (4H, m, H-3 and H-5), 2.00 (3H, s, $\underline{CH_3}$), 2.77 (1H, m, H-2), 3.72 (2H, d, J=7.4 Hz, H-1), 3.99 (2H, t, J=6.7 Hz, H-6), 7.1-7.4 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 21.09 (CH_3), 23.77 (CH_2), 28.65 (CH_2), 31.65 (CH_2), 48.67 (CH), 64.40 (CH_2), 67.59 (CH_2), 126.90 (CH), 128.13 (2×CH), 128.79 (2×CH), 142.21 (C), 171.37 (CO). [Found, C, 71.12; H, 8.49. $C_{14}H_{20}O_3$ requires C, 71.16; H, 8.53].

1-acetoxy-2-hydroxy-1-phenylethane (16): Colourless oil. ν_{max}: 3419, 1732, 1239, 1046 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 2.14 (3H, s, $\underline{CH_3}$), 3.80 (1H, dd, J=12 and 4.3 Hz, $\underline{H\text{-}2_A}$), 3.88 (1H, dd, J=12 and 7.3 Hz, $\underline{H\text{-}2_B}$), 5.85 (1H, dd, J=7.3 and 4.3 Hz, H-1), 7.4 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 20.1 (CH_3), 69.37 (CH_2), 81.40 (CH), 127.44 (2×CH), 127.68 (CH), 128.74 (2×CH), 140.95 (C), 171.32 (CO). [Found, C, 66.61 H, 6.75. $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.71].

4-acetoxy-1-hydroxy-2-phenylbutane (17): Colourless oil. ν_{max}: 3428, 1738, 1244, 1042 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.8-2.1 (2H, m, H-3), 1.99 (3H, s, $\underline{CH_3}$), 3.11 (1H, m, H-2), 3.54 (2H, m, H-4), 4.22 (2H, d, J=6.9 Hz, H-1), 7.2-7.4 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 21.01 (CH_3), 35.27 (CH_2), 41.53 (CH), 60.47 (CH_2), 68.43 (CH_2), 127.06 (CH), 127.94 (2×CH), 128.90 (2×CH), 141.28 (C), 171.29 (CO). [Found, C, 69.27; H, 7.71. $C_{12}H_{16}O_3$ requires C, 69.21; H, 7.74].

5-acetoxy-1-hydroxy-2-phenylpentane (18): Colourless oil. ν_{max}: 3428, 1736, 1244, 1040 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.42 (2H, m, H-4), 1.66 (1H, m, $\underline{H\text{-}3_A}$), 1.83 (1H, m, $\underline{H\text{-}3_B}$), 1.99 (3H, s, $\underline{CH_3}$), 2.92 (1H, m, H-2), 3.57 (2H, t, J=6.4 Hz, H-5), 4.20 82H, d, J=7.0 Hz, H-1), 7.1-7.4 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 21.04 (CH_3), 28.65 (CH_2), 30.41 (CH_2), 44.85 (CH), 62.74 (CH_2), 68.60 (CH_2), 126.94 (CH), 128.13 (2×CH), 128.65 (2×CH), 141.61 (C), 171.31 (CO). [Found, C, 70.29; H, 8.21. $C_{13}H_{18}O_3$ requires C, 70.25; H, 8.16].

6-acetoxy-1-hydroxy-2-phenylhexane (19): Colourless oil. γ_{max}: 3434, 1738, 1245, 1045 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 1.26 (2H, m, H-4), 1.50-1.80 (4H, m, H-3 and H-5), 1.99 (3H, s, $\underline{CH_3}$), 2.91 (1H, m, H-2), 3.57 (2H, t, J=6.5 Hz, H-6), 4.18 (2H, d, J=7.0 Hz, H-1), 7.1-7.4 (5H, m, Ar-H). δ_C (75 MHz, $CDCl_3$): 21.06 (CH_3), 23.52 (CH_2), 32.27 (CH_2), 32.77 (CH_2), 45.04 (CH), 62.82 (CH_2), 68.57 (CH_2), 126.87 (CH), 127.93 (2×CH), 128.61

(2×CH), 141.82 (C), 171.26 (CO). [Found, C, 71.20; H, 8.50. $C_{14}H_{20}O_3$ requires C, 71.16; H, 8.53].

General Procedure for Preparation of Mosher's Esters

To a solution of the corresponding alcohol or (1,n)-diol (0.005 mmol) and DMAP (12.2 mg, 0.10 mmol) in 3 ml of CH_2Cl_2 was added the corresponding α-methoxy-α-trifluoromethyl phenylacetyl chloride [(*R*) and (*S*)] (10 μl, 0.06 mmol) and the mixture stirred until complete reaction by TLC (≈1h). The solution was then passed through a short pad of silica and washed through with CH_2Cl_2. The resulting solution was concentrated under reduced pressure to give the products which were analyzed by ^{1}H-NMR.

MTPA-diesters: (*R*)-MTPA of (***R***)-**1**: δ_H 3.28 (s br, OCH_3), 3.34 (s br, OCH_3), 6.21 (dd, J=8.0 and 3.5 Hz, CH). (*R*)-MTPA of (***S***)-**1**: δ_H 3.26 (s br, OCH_3), 3.39 (s br, OCH_3), 6.09 (dd, J=8.6 and 2.8 Hz, CH). (*R*)-MTPA of (***R***)-**3**: δ_H 3.36 (s br, OCH_3), 3.52 (s br, OCH_3). (*R*)-MTPA of (***S***)-**3**: δ_H 3.40 (s br, OCH_3), 3.52 (s br, OCH3). (*R*)-MTPA of (***R***)-**4:** δ_H 3.35 (s br, OCH_3), 3.51 (s br, OCH_3). (*R*)-MTPA of (***S***)-**4**: δ_H 3.38 (s br, OCH_3), 3.51 (s br, OCH_3). (*R*)-MTPA of (***R***)-**5**: δ_H 3.35 (s br, OCH_3), 3.46 (s br, OCH_3). (*R*)-MTPA of (***S***)-**5**: δ_H 3.38 (s br, OCH_3), 3.46 (s br, OCH_3).

MTPA-monoesters: (*R*)-MTPA of (***R***)-**11**: δ_H 1.99 (s, CH_3CO), 3.48 (s br, OCH_3), 6.37 (dd, J=11.1 and 5.8 Hz, CH). (*R*)-MTPA of (***S***)-**11**: δ_H 2.08 (s ,CH_3CO), 3.60 (s br, OCH_3), 6.23 (dd, J=13.1 and 4.4 Hz, CH). (*R*)-MTPA of (***R***)-**17**: δ_H 3.37 (s br, OCH_3). (*R*)-MTPA of (***S***)-**17**: δ_H 3.41 (s br, OCH_3). (*R*)-MTPA of (***R***)-**18**: δ_H 3.36 (s br, OCH_3). (*R*)-MTPA of (***S***)-**18**: δ_H 3.40 (s br, OCH_3). (*R*)-MTPA of (***R***)-**19**: δ_H 3.36 (s br, OCH_3). (*R*)-MTPA of (***S***)-**19**: δ_H 3.40 (s br, OCH_3).

In order to confirm the validity of these assignations, similar experiments were carried out using the (*R*)-MTPA-Cl for the corresponding diols and monoacetates, observing, as expected, similar chemical shifts for the enantiomeric counterparts.

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