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ENZYME CATALYZED MONOHYDROLYSIS OF 2-ARYL-1,3-PROPANEDIOL DIACETATES. A STUDY OF STRUCTURAL EFFECTS OF THE ARYL MOIETY ON THE ENANTIOSELECTIVITY

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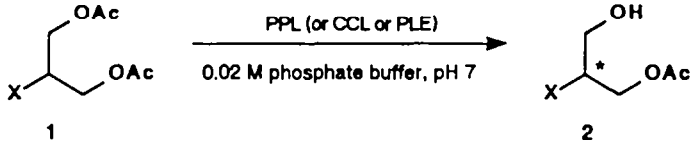
Summary. - PPL catalyzed monohydrolysis of 2-aryl substituted 1,3-propanediol diacetates afforded the corresponding monoacetates in acceptable to fair chemical and optical yields. Electronic effects in the aromatic ring were examined. Elaboration of some 2-arylpropanediol monoacetates to optically active 2-arylpropanols and propanoic acids was performed.

Optically active 2-substituted 1,3-propanediol monoacetates 2 are important chiral building blocks suitable as starting material for the asymmetric synthesis of many natural products. However, only a limited number of such derivatives is easily available and for this reason many efforts are currently made to find new strategies of access to these molecules.[1] Enzymes are particularly attractive catalysts and in the last years many reports have appeared describing their ability to discriminate between two enantiotopic groups of a symmetrical substrate.[2] Following this concept some prochiral 1,3-propanediol diacetates 1 have been hydrolyzed enantioselectively in the presence of enzymes to afford in some cases important chiral polyfunctionalized building



1 2

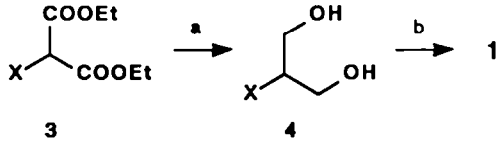
a: X = Ph	e: X = 4-$NO_2C_6H_4$	i : X = 4-MeCONHC_6H_4	o: X = 1-Naphthyl
b: X = 4-MeC_6H_4	f : X = 4-OHC_6H_4	l : X = 4-PhCONHC_6H_4	p: X = 2-Naphthyl
c: X = 4-MeOC_6H_4	g: X = 4-Ph$CH_2OC_6H_4$	m: X = 4-PhCH_2OCONHC_6H_4	q: X = 2-Thienyl
d: X = 4-ClC_6H_4	h: X = 4-$NH_2C_6H_4$	n : X = 4-Pyridyl	r : X = 3-Thienyl

Scheme 1

blocks of type 2 with X = OBn,[3a] alkyl,[3b, c] alkenyl,[3d] alkoxymethyl,[3d] and NO_2.[3e] As far as aromatic derivatives 1 (X = Ar) are concerned, enzymatic studies have been performed only for X = Ph,[3c] using purified immobilized PPL, although aromatic building blocks of type 2 are not commercially available while many natural products containing a chiral arylidene moiety are known. Furthermore, substituted aromatic rings can undergo suitable manipulations to afford new chiral C-units.

Continuing our studies on the use of enzymes in organic synthesis,[3d] we have investigated the enzyme catalyzed hydrolysis of a series of 2-aryl substituted 1,3-propanediol diacetates **1a-r** to optically active monoacetates (Scheme 1). This research was aimed both at obtaining suitable optically active units to be used in the synthesis of valuable targets and at collecting information on the effect of structural (electronic and steric) changes in the substrate on enzyme enantioselectivity.[4]

Substrates **1a-r** were generally prepared as outlined in Scheme 2: diacetates **1a-d, n-r** were directly accessed to through acetylation of the corresponding diols **4a-d, n-r**, in turn obtained by reduction of the corresponding diethyl malonates **3a-d, o-r** (only for **4n** a different synthetic pathway was followed: see Experimental). Diacetate **1f** was obtained by deblocking the methyl ether functionality in **1c**. Nitration of **1a** gave **1e**, whose reduction gave **1h**. Diacetates **1f** and **1h** were used to obtain **1g** and **1i-m** respectively.



3 4

a) $LiAlH_4$, THF. b) Ac_2O, pyridine.

Scheme 2

Enzymatic hydrolyses were performed using three different enzymes (PPL, PLE, and CCL) in aqueous medium at constant pH and followed by titration with 1 N NaOH by means of a pH-stat apparatus. In order to obtain comparable data, runs were always stopped at 50% conversion. Data for enzymatic hydrolyses are reported in Table 1. In few cases, when PPL (entries 15, 18, and 20 in Table 1) or CCL (entries 3, 12, 31, and 37 in Table 1) were used as catalyst, the hydrolysis stopped spontaneously before consuming 1 eq of NaOH. It is apparent that PPL is the enzyme of choice, as PLE generally showed very low enantioselectivity, while CCL only tolerated small variations in substrate structure; on the contrary, PPL accepted reasonably wide structural changes in the substrate, usually matched by high enantioselectivity and good reproducibility of behaviour, while PLE gave erratic results. Moreover, when using PLE or CCL, substantial amounts of diol **4** were usually formed, while PPL catalyzed hydrolyses almost spontaneously stopped at the monoacetate stage (it is well known that the rate of PPL catalyzed lipolysis follows the order: triglycerides > diglycerydes > monoglycerides).[5]

Table 1. Enzymes catalyzed monohydrolysis of diacetates 1

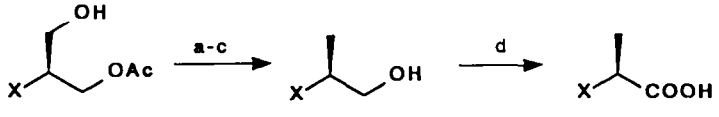
Entry	Cpd	time (h) PPL / PLE / CCL	yield[a] (%) PPL / PLE / CCL	α]D (*c* 1 - 2, $CHCl_3$) PPL	ee[b] (%) PPL / PLE / CCL	abs conf PPL / PLE / CCL
1	1a	4.5	80	- 15.4°[c]	92	*S*
2		1	63		12	*R*
3		17[d]	54		24	*S*
4	1b	6	77	- 16.2°	96	*S*
5		2	34		28	*R*
6		15	49		48	*S*
7	1c	7	79	- 14.1°	92	*S*
8		2.3	57		26	*R*
9		14	56		24	*S*
10	1d	4	67	- 11.6°	>96	e
11		3	35		12	e
12		24[d]	44		52	e
13	1e	11	65	- 4.4°	88	*S*
14		3.2	20		14	*S*
15	1f	21[d,f]	20	- 5.5°	38	e
16		2.3	42		22	e
17		g	-		-	e
18	1g	41[d]	64	- 10.9°	94	e
19		g	-		-	-
20	1h	31[d,h]	23	- 8.6°	50	*S*
21		i	-		-	-
22	1i	g	-	-	-	-
23		5	79		36	e
24		g	-		-	-
25	1l	g	-	-	-	-
26		g	-		-	-
27		g	-		-	-
28	1m	g	-	-	-	-
29	1n	72	34	e	20	e
30		3	42		28	e
31		33	4		e	e
32	1o	l,m	-	-	-	-
33		11	34		40	e
34		g	-		-	-
35	1p	22[d]	30	- 11.8°	>96	*S*
36		8.5	5		6	*R*
37		49[d]	44		14	*S*
38	1q	2	67	-12.7°	88	e
39	1r	3.5	78	- 19.5°	90	e

[a] Monoacetate isolated yields. [b] Determined by n.m.r. spectroscopy ($CDCl_3$) in the presence of $Eu(HFC)_3$. [c] $\alpha]_{365}$ -59.6° (see ref. 3c). [d] Reaction stopped spontaneously before consuming 1 eq of NaOH. [e] Not determined. [f] Addition of THF (THF : buffer 15 : 85) had a negligible effect. [g] No reaction was observed within a 10 h period. [h] Di-*iso*-propyl ether (*i*-Pr_2O : buffer 15 : 85) was added to the reaction mixture before adding PPL. [i] Monoacetate 2h was found to be unstable under the reaction conditions. [l] 360 mg PPL/mmol diacetate were used. [m] Extremely slow reaction.

Results obtained using PLE or CCL are too poorly significant to deserve any comment, while perusal of Table 1 indicates that using PPL a fair to excellent enantioselectivity was generally observed regardless of the nature of substituent in the aromatic ring. Only diacetates **1f** (entry 15), **1h** (entry 20), and **1n** (entry 29) gave low enantioselectivity, accompanied by longer reaction times and lower chemical yields: a reasonable explanation could be that substrates containing such 'acidic' or 'basic' groups bind in some alternative way to enzyme,[6] thus causing a less

stereospecific hydrolysis. Only sparse reports have appeared on the influence of this type of functional groups in similar reactions. In the PLE catalyzed hydrolysis of *meso* diesters, a reversal of enantioselectivity was observed depending on the protecting group of an amine function.[7] On the contrary, a free hydroxyl group seems to play just a minor role in PPL catalyzed hydrolysis of cyclopentanoid meso diacetates,[8] while a notable influence of a free or protected hydroxyl group was reported in the α-chymotrypsin catalyzed hydrolysis of malonates.[9] In our case, protection of hydroxy group of **1f** had a beneficial effect (entries 7, 18) while the amide-type protections of the amino group of **1h** (entries 22, 25, 28) seemed to inhibit the ester hydrolysis. No electronic effect is apparent from this series of substrates, having either an electronic 'poor' or 'rich' aromatic ring (π system) near to prochiral centre. Comparison of entries 1 and 4 with entries 32 and 35 suggests that a rate retarding steric effect is operating: a bicyclic aromatic ring slows down the hydrolysis rate, especially when the second ring is *'ortho'* fused (*cfr.* entries 35 and 32). In the case of diacetates **1f** and **1h** addition of an organic cosolvent was tried, although with a modest success.

As for enantioselectivity, it is worth noting that in all cases examined but one (**1e**) the opposite configuration is obtained passing from PPL to PLE, as previously observed by other authors.[10] However, the enantiomeric excesses and the chemical yields obtained with PLE are much less satisfactory and therefore the *ent*-**2** is better achieved from **2** (*via* PPL) by selective functional group manipulation.[11] In order to assess the absolute configuration of some representative monoacetates **2** and to exploit their synthetic handiness, we performed some suitable chemical transformations. Thus, **2a** was transformed into (+)-(*R*) tropic acid[12] through oxidation of hydroxyl group and basic hydrolysis of the acetate functionality (chemical and optical yields were not optimized); (-)-**2e** and (-)-**2h** were correlated each other through catalytic hydrogenation of the former, and to (-)-**2a**, *via* protection of the hydroxy group of **2a** as benzyloxycarbonyl derivative, nitration, and successive catalytic hydrogenation: these chemical correlations indicate that **2a**, **2e**, and **2h** all possess the *S* configuration. On the other hand, monoacetates (-)-**2b**, (-)-**2c**, and (-)-**2p** were converted into the corresponding (+)-(*R*)-2-arylpropan-1-ols **5b**,[13] **5c**,[14] and **5p**,[15] and then into the the corresponding (-)-(*R*)-2-arylpropanoic acids **6b**[16] **6c**,[17] and **6p**, without appreciable racemisation, as outlined in Scheme 3. It is noteworthy that 2-arylpropanoic acids (and in some instances also 2-arylpropanols) are known to be a valuable class of potent antiinflammatory drugs,[18] and *ent*-**5b**, (-)-(*S*)-2-(4-methylphenyl)propan-1-ol, has been recently used as precursor in the synthesis of (+)-α-cuparenone.[19]



(-)-**2b, c, p** (+)-(*R*)-**5b, c, p** (-)-(*R*)-**6b, c, p**

a) 4-$MeC_6H_4SO_2Cl$ (TsCl), Et_3N, DMAP, CH_2Cl_2. b) $NaBH_4$, DMSO. c) 1 N NaOH, MeOH-THF. d) Jones' oxidation (CrO_3, H_2SO_4, Me_2CO).

Scheme 3

Besides the before mentioned transformations, other exploitations of some herein reported chiral building blocks in the synthesis of biologically active targets are in progress in our laboratory.

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EXPERIMENTAL

General

N.m.r. spectra were recorded as $CDCl_3$ or CD_3COCD_3 solutions on a Varian FT 80 or Gemini 200 spectrometer using tetramethylsilane (TMS) as internal standard; chemical shifts (δ) are in ppm, coupling constants (*J*) are in Hz. I.r. frequencies are reported in cm^{-1}. N.m.r. data for diethyl arylmalonates **3b-d, o-r** are reported in Table 2, data for 2-arylpropane-1,3-diols **4a-d, n-r** in Table 3, data for 1,3-diacetoxy-2-arylpropanes **1a-r** in Table 4, and data for 2-aryl-3-acetoxypropan-1-ols **2a-i, n-r** in Table 5; analytical and i.r. data for compounds **2a-i, n-r** are reported in Table 6.

'Usual workup' means that the given reaction mixture was extracted (Et_2O, CH_2Cl_2, or AcOEt), the organic layer was washed with brine and dried (Na_2SO_4), filtered, and evaporated to dryness under reduced pressure.

Tetrahydrofuran (THF) was always freshly distilled from K/Ph_2CO, CH_2Cl_2 and Et_2O were distilled from CaH_2. Dimethylsulfoxide (DMSO) was stored over 4 A molecular sieves. All reactions requiring dry conditions were run under an inert atmosphere (N_2).

Column chromatographies were run following the method of 'flash chromatography',[20] using 230 - 400 mesh silica gel (Merck).

Diethyl phenylmalonate **3a** was a commercial specimen; commercially available

Table 2. N.m.r. data[a] for diethyl arylmalonates **3b-d, o-r**

Cpd	CH (s, 1 H)	2 x CH_2 (q,[b] 4 H)	CH_3 (t,[b] 2 H)	Ar*H* (m)	Others
3b	4.70	4.28 (7.0)	1.35 (7.0)	7.22 - 7.57 (4 H)	2.35 (s, 3 H, *Me*Ar)
3c	4.55	4.15 - 4.26 (m)	1.25 (7.1)	6.87 - 6.91 (2 H), 7.30 - 7.35 (2 H)	3.80 (s, 3 H, *Me*O)
3d	4.67	4.30 (7.0)	1.27 (7.0)	7.47 (s, 4 H)	-
3o	5.58	4.37 (7.3)	1.30 (7.3)	7.53 - 8.27 (7 H)	-
3p	4.88	4.32 (7.3)	1.27 (7.3)	7.40 - 8.28 (7 H)	-
3q	4.90	4.24 (7.1)	1.27 (7.1)	6.92 - 7.34 (3 H)	-
3r	4.74	4.22 (7.1)	1.26 (7.1)	7.12 - 7.34 (3 H)	-

[a] $CDCl_3$, TMS [b] *J* (Hz) in parentheses

3-thienylmalonic acid was converted to diethyl ester **3r**[21] through a conventional method (absolute EtOH, H_2SO_4). Diethyl 4-methylphenylmalonate **3b**,[22] 4-methoxyphenylmalonate **3c**,[23] 4-chlorophenylmalonate **3d**,[23] 1-naphthylmalonate **3o**,[23] and 2-naphthylmalonate **3p**[23] were prepared starting from the the corresponding commercially available arylacetic acids *via* a conventional esterification and a crossed Claisen condensation with diethyl oxalate, followed by decarbonylation, according to a reported procedure.[24] 2-Thienylmalonate **3r**[25] was similarly prepared starting from commercially available ethyl 2-thienylacetate.

Enzymes were purchased from Sigma (PPL, L3126; PLE, E3128; CCL, L1754) and used without further purification.

4-Pyridylpropane-1,3-diol **4n** was prepared according to a reported procedure.[26]

All compounds gave satisfactory spectroscopic and analytical data.

Synthesis of 2-arylpropane-1,3-diols **4a-d, o-r.**

To a suspension of $LiAlH_4$ (2.2 mmol) in dry Et_2O (2 ml) a THF (2 ml) solution of diethyl arylmalonate **3a-d, o-r** (1 mmol) was added at 0°C. Cooling bath was removed and reaction mixture stirred at room temperature for 15 min. Diluted HCl was carefully added to acidic pH; usual workup (Et_2O and AcOEt) and chromatography (petroleum ether - AcOEt) afforded 2-arylpropane-1,3-diol **4a**,[27] **4b**, **4c**,[28] **4d**,[29] **4o**, **4p**, **4q**, and **4r** (50 - 90% yield).

Synthesis of 1,3-diacetoxy-2-arylpropanes **1a-d, n-r.**

To a solution of diol **4a-d, n-r** (1 mmol) in dry CH_2Cl_2 (8 ml) at 0°C, triethylamine (3.0 mmol), acetic anhydride (3.1 mmol), and a catalytic amount of 4-dimethylaminopyridine (DMPA) were sequentially added. Cooling bath was removed and reaction mixture stirred at room temperature for 1h. Saturated aqueous $NaHCO_3$ was added, and reaction mixture worked up as usual

Table 3. N.m.r. data[a] for 2-arylpropane-1,3-diols **4a-d, n-r**

Cpd	CH (m or app quint,[b] 1 H)	2 x C*H*$_2$ (m or app d,[d] 4 H)	Ar*H* (m)	Others
4a	2.99 - 3.15	3.99 - 4.10	7.29 - 7.38 (5 H)	-
4b	3.02 - 3.15	3.87 - 4.05	7.15 (b s, 4 H)	2.33 (s, 3 H, *Me* Ar)
4c	3.00 - 3.14	3.82 - 4.01	6.87 - 6. 91 (2 H), 7.15 - 7.29 (2 H)	3.80 (s, 3 H, *Me* O)
4d	2.97 - 3.10	3.83 - 3.98	7.14 - 7.32 (4 H)	-
4n	2.94 - 3.07	3.77 - 3.94	7.32 - 7.35 (2 H), 8.43 - 8.46 (2 H)	-
4o	3.89 - 4.12 (m, 5 H)		7.22 - 7.24 (4 H), 7.70 - 7.85 (2 H), 8.09 - 8.13 (1 H)	-
4p	3.22 - 3.35	4.01 - 4.18	7.35 - 7.53 (3 H), 7.71 (b s, 1 H), 7.81 - 7.86 (3 H)	-
4q	3.36 (6.1)	3.95 (5.9)	6.93 - 7.23 (3 H)	-
4r	3.22 (6.1)	3.96 (6.1)	6.97 - 7.37 (3 H)	-

[a] $CDCl_3$, TMS [b] *J* (Hz) in parentheses [c] In CD_3COCD_3

(CH_2Cl_2). Column chromatography (petroleum ether - AcOEt) afforded 1,3-diacetoxy-2-arylpropane **1a-d,n-o, q-r** (oils), and **1p** (white solid) in 85 - 95% yield.

Synthesis of 1,3-diacetoxy-2-(4-nitrophenyl)propane 1e.

90% Nitric acid (10 ml) was added to 1,3-diacetoxy-2-phenylpropane **1a** (1 mmol) at -20°C. After 20 min, reaction mixture was poured into a mixture of crushed ice and water. A precipitate formed and was collected by filtration. Column chromatography (petroleum ether - AcOEt 7 : 3) afforded pure **1e** as a white solid (68%), mp 49 - 50°C (after crystallization from AcOEt).

Synthesis of 1,3-diacetoxy-2-(4-aminophenyl)propane 1h.

A solution of **1e** (1 mmol) in absolute EtOH (7 ml) was hydrogenated at normal pressure in the presence of a catalytic amount of PtO_2 or 10% Pd/C. After 2h, reaction mixture was filtered through a celite pad, washing with AcOEt, the filtrate was concentrated under reduced pressure and the residue chromatographed (petroleum ether - AcOEt 3 : 7) to give **1h** as a white solid (92%), mp 73 - 75°C (after crystallization from AcOEt - petroleum ether).

Synthesis of 1,3-diacetoxy-2-(4-acetamidophenyl)propane 1i.

To **1h** (1 mmol) glacial acetic acid (0.5 ml) was added and the reaction mixture was refluxed for 3h. Solvent was removed under reduced pressure and the residue chromatographed (petroleum ether - AcOEt 7 : 3) to give **1i** as a white solid (61%), mp 99 - 102°C (after crystallization from AcOEt - petroleum ether).

Synthesis of 1,3-diacetoxy-2-(4-benzamidophenyl)propane 1l.

To a mixture of **1h** (1 mmol) and pyridine (1 mmol) at 0°C, benzoyl chloride (1.1 mmol) was added and reaction mixture was stirred for 15 min, then diluted with CH_2Cl_2, washed with 1 N HCl and 0.5 N NaOH, and brine; the organic phase was dried (Na_2SO_4), filtered, and evaporated to dryness. Column chromatography (petroleum ether - AcOEt 1 : 1) of the residue afforded **1l** as a white solid (94%), mp 123 - 124°C (after crystallization from AcOEt - petroleum ether).

Synthesis of 1,3-diacetoxy-2-[(4-benzyloxycarbonylamino)phenyl]propane 1m.

To a mixture of **1h** (1 mmol) and pyridine (1 mmol) at 0°C, benzyl chlorocarbonate (1.1 mmol) was added. After 15 min, reaction mixture was worked up as above described for the synthesis of **1l**. Column chromatography (petroleum ether - AcOEt 1 : 1) afforded **1m** as a white solid (80%), mp 96 - 98°C (after crystallization from AcOEt).

Synthesis of 1,3-diacetoxy-2-(4-hydroxyphenyl)propane 1f.

To a solution of **1c** (1 mmol) in dry CH_2Cl_2 (6 ml) at -78°C, 3 ml of a 1M solution of BBr_3 in hexane (3 mmol) were added and reaction mixture was stirred at -78°C for 30 min, the allowed to reach room temperature over a period of 20 min. Ethyl ether and water were added and reaction mixture was worked up as usual (Et_2O). Column chromatography (petroleum ether - AcOEt 1 : 1) afforded **1f** as an oil (85%).

Synthesis of 1,3-diacetoxy-2-(4-benzyloxyphenyl)propane 1g.

To a solution of **1f** (1 mmol) in dry acetone (3 ml), anhydrous K_2CO_3 (2 mmol) and benzyl chloride (1.5 mmol) were sequentially added. Reaction mixture was stirred overnight at 25 - 30°C, then poured into water and worked up as usual (AcOEt). Column chromatography (petroleum ether - AcOEt 4 : 1) afforded **1g** as a white solid (79%), mp 40 - 42°C.

General experimental procedure for enzymatic hydrolyses.

Diacetate **1** (1 mmol) was dispersed in 0.02 M phosphate buffer (pH 7, 12 ml), PPL (110 - 120 mg) or PLE (120 µl) or CCL (60 mg) was added, and the reaction mixture was stirred at room

Table 4. N.m.r. data[a] for 1,3-acetoxy-2-arylpropanes **1a-r**

Cpd	2 x *Me*CO (s, 6 H)	CH (m or app quint,[b] 1 H)	2 x CH_2OAc (m or app d,[b] 4 H)	Ar*H* (m)	Others
1a	2.03	3.25 - 3.83	4.23 - 4.54	7.22 - 7.35 (5 H)	-
1b	2.03	3.28 (6.6)	4.31 (6.6)	7.14 (b s, 4 H)	2.34 (s, 3 H, *Me*Ar)
1c	2.03	3.20 - 3.33	4.30 (6.6)	6.85 - 7.19 (4 H)	3.80 (s, 3 H, *Me*O)
1d	2.02	3.23 - 3.77	4.40 (6.6)	7.16 - 7.34 (4 H)	-
1e	2.03	3.40 - 3.53	4.26 - 4.47	7.41 - 7.46 (2 H), 8.19 - 8.25 (2 H)	-
1f	2.03	3.26 (6.6)	4.30 (6.6)	6.76 - 6.83 (2 H), 7.08 - 7.15 (2 H)	-
1g	2.03	3.20 - 3.34	4.30 (6.6)	6.93 - 6.97 (2 H), 7.15 - 7.19 (2 H), 7.32 -7.43 (5 H)	5.06 (s, 2 H, PhCH_2)
1h	2.03	3.20 (6.6)	4.28 (6.6)	6.63 - 6.69 (2 H), 7.00 - 7.07 (2 H)	-
1i	2.02	3.29 (6.6)	4.30 (6.6)	7.18 - 7.22 (2 H), 7.54 - 7.49 (2 H)	2.18 (s, 3 H, *Me*CONH), 7.22 (b s, 1 H, N*H*)
1l	2.03	3.32 (6.6)	4.32 (6.6)	7.23 - 7.27 (2 H),7.49 - 7.64 (5 H),7.84 - 7.89 (2 H)	7.81 (b s 1 H, N*H*)
1m	2.02	3.21 - 3.34	4.17 - 4.43	7.16 - 7.42 (9 H)	5.09 - 5.32 (m, 2 H, PhCH_2), 6.66 (b s, 1H, N*H*)
1n	2.03	3.34 (6.5)	4.27 - 4.42	7.20 - 7.23 (2 H), 8.58 - 8.61 (2 H)	-
1o	1.86	4.03 - 4.15	4.25 - 4.41	7.21 - 7.45 (4 H), 7.61 - 7.74 (2 H), 7.96 - 8.01 (1 H)	-
1p	2.02	3.49 (6.1)	4.42 (6.1)	7.34 - 7.53 (3 H), 7.69 (b s, 1 H), 7.79 - 7.85 (3 H)	-
1q	2.06	3.46 - 3.76	3.96 - 4.67	6.92 - 7.23 (3 H)	-
1r	2.04	3.27 - 3.60	4.32 (6.3)	6.98 - 7.35 (3 H)	-

[a] $CDCl_3$, TMS. [b] *J* (Hz) in parentheses.

Table 5. N..m.r. data[a] for 3-acetoxy-2-arylpropan-1-ols 2a-i, n-r

Cpd	*Me*CO (s, 3 H)	CH (m or app quint,[b] 1 H)	C*H*$_2$OH (m, 2 H)	C*H*$_2$OAc (m or app d,[b] 2 H)	Ar*H* (m)	Others
2a	2.06	3.18 - 3.23	3.84 - 3.90	4.39 (6.2)	7.24 - 7.50 (5 H)	-
2b	2.07	3.10 - 3.16	3.83 - 3.86	4.35 - 4.39	7.04 - 7.29 (4 H)	2.34 (s, 3 H, *Me*Ar)
2c	2.06	3.05 - 3.18	3.80 - 3.86	4.35 (6.3)	6.87 - 6. 91 (2 H), 7.17 - 7.21 (2 H)	3.80 (s, 3 H, *Me*O)
2d	2.06	3.08 - 3.20	3.81 - 3.87	4.37 (6.5)	7.18 - 7.35 (4 H)	-
2e	2.06	3.22 - 3.35	3.77 - 4.03	4.31 - 4.56	7.44 - 7.51 (2 H), 8.19 - 8.26 (2 H)	-
2f	2.07	3.07 - 3.16	3.80 - 3.87	4.33 - 4.38	6.80 - 7.18 (4 H)	-
2g	2.07	3.05 - 3.18	3.78 - 3.89	4.28 - 4.39	6.94 - 6.99 (2 H), 7.15 - 7.21 (2 H), 7.33 - 7.46 (5 H)	5.06 (s, 2 H, PhC*H*$_2$)
2h	2.06	2.99 - 3.13	3.75 - 3.86	4.25 - 4.40	6.63 - 6.70 (2 H), 7.01 - 7.09 (2 H)	-
2i	1.99	3.10 - 3.23	3.74 - 3.82	4.30 (6.7)	7.05 - 7.16 (2 H), 7.37 - 7.48 (2 H)	2.08 (s, 3 H, *Me*CONH), 8.48 (b s, 1 H, N*H*)
2n	2.17	2.93 - 3.07	3.83 (6.0)	4.37 (6.6)	7.13 - 7.23 (2 H), 8.37 - 8.45 (2 H)	-
2o	2.05	4.01 - 4.03 (m, 4 H)		4.50 - 4.57	7.40 - 8.18 (m, 7 H)	
2p	2.06	3.25 - 3.40	3.93 - 3.99	4.49 (6.5)	7.37 - 7.60 (4 H), 7.72 - 7.90 (2 H) 8.10 - 8.15 (1 H)	-
2q	2.11	3.42 - 3.54	3.83 - 3.89	4.32 - 4.49	6.96 - 7.04 (2 H), 7.23 - 7.28 (1 H)	-
2r	2.08	3.23 - 3.35	3.80 - 3.86	4.30 - 4.64	7.02 - 7.05 (1 H), 7.14 - 7.15 (1 H), 7.31 - 7.35 (1 H)	-

[a] $CDCl_3$, TMS [b] *J* (Hz) in parentheses

temperature while pH was kept constant by addition of 1 N NaOH by means of a pH-stat machine. After reaction either consumed 1 eq of NaOH or stopped consuming NaOH (see Text) the reaction mixture was worked up as usual (AcOEt); column chromatography (petroleum ether - AcOEt) gave the pure monoacetate **2**. In PPL catalyzed reactions, except for entries 6, 7, and 8 of Table 1, yields of the recovered diacetate **1** were always less than 5%, while yields of diol were less than 10% in all cases. When PLE or CCL were used as catalyst, substantial amounts (15 - 50%) of diol **4** were usually formed.

Optically rotatory power $(\alpha]_D$) was determined as 1 - 2% $CHCl_3$ solutions. Enantiomeric excess (ee) was determined by n.m.r. spectroscopy ($CDCl_3$) in the presence of tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium(III) [Eu(hfc)$_3$] (5 - 15 mg/mg of **2**) using *Me*COO signal as diagnostic peak. Blank experiments were run on racemic **2**.

Synthesis of racemic 3-acetoxy-2-arylpropan-1-ols 2a-h, m-r.

Diacetate **1a-h, m-r** (0.5 mmol) was dissolved in 12 ml of 10 : 1 THF - MeOH (v/v) at room

Table 6. Analytical and i.r. data for 3-acetoxy-2-arylpropan-1-ols **2a-i, n-r**

Cpd	Formula	H%		C%		N%		I.r.
		Calcd	Found	Calcd	Found	Calcd	Found	(cm^{-1})
2a	$C_{11}H_{14}O_3$	7.27	7.19	68.02	67.89	-	-	1738, 3434[a]
2b	$C_{12}H_{16}O_3$	7.74	7.69	69.21	69.11	-	-	1736, 3423[a]
2c	$C_{12}H_{16}O_4$	7.19	7.10	64.27	64.41	-	-	1738, 3442[b]
2d	$C_{11}H_{13}ClO_3$	5.73	5.77	57.78	57.72	-	-	1722, 3436[b]
2e	$C_{11}H_{13}NO_5$	5.48	5.50	55.23	55.31	5.85	5.77	1738, 3442[a]
2f	$C_{11}H_{14}O_4$	6.71	7.69	62.85	62.70	-	-	1734, 3353[b]
2g	$C_{18}H_{20}O_4$	6.71	6.69	71.98	71.62	-	-	1724, 3392[c]
2h	$C_{11}H_{15}NO_3$	7.23	7.21	63.14	62.98	6.69	6.65	1716, 3471[b]
2i	$C_{13}H_{17}NO_4$	6.82	6.86	62.14	62.48	5.57	5.58	1725, 3380[b]
2n	$C_{10}H_{13}NO_3$	6.71	6.70	61.53	61.58	7.17	7.11	1722, 3420[b]
2o	$C_{15}H_{16}O_3$	6.60	6.51	73.75	73.73	-	-	1737, 3440[b]
2p	$C_{15}H_{16}O_3$	6.60	6.55	73.75	73.70	-	-	1700, 3488[b]
2q	$C_9H_{12}O_3S$	6.04	6.00	53.98	53.87	-	-	1738, 3411[a]
2r	$C_9H_{12}O_3S$	6.04	5.99	53.98	53.98	-	-	1736, 3437[a]

[a] Neat. [b] $CHCl_3$. [c] Nujol.

temperature and 2.5 ml of 0.1 N NaOH were added. After 2 - 10 min, diluted HCl was added to acidic pH and reaction mixture was worked up as usual (AcOEt). Column chromatography (petroleum ether - AcOEt) of the residue afforded pure racemic monoacetate **1a-h, m-r**.

Synthesis of (+)-(R)-tropic acid.

(-)-3-Acetoxy-2-phenylpropan-1-ol (-)-**2a** (1 mmol) was dissolved in 2 ml of acetone and treated at room temperature with a small excess (*ca.* 0.5 ml) of Jones' reagent (2.5 M solution of H_2CrO_3 in H_2SO_4 - H_2O). The oxidation was complete in few minutes. Reaction mixture was filtered through a celite pad, washing with AcOEt; the organic phase was separated, washed with H_2O, and extracted with 0.1 N NaOH; aqueous phase was acidified with 6 N HCl, and subjected to usual workup (AcOEt). 3-Acetoxy-2-phenylpropionic acid was obtained as a colourless oil (83%), $[\alpha]_D$ + 46.1° (*c* 1, $CHCl_3$), n.m.r. (CD_3COCD_3) 1.95 (s, 3 H, *Me*CO), 3.89 - 4.69 (m, 3 H, C*H*$_2$OAc + C*H*), 7.36 (b s, 5 H, *Ph*), i.r. (neat) 1721, 3450.

(+)-3-Acetoxy-2-phenylpropionic acid (0.5 mmol) was dissolved in 10 ml of THF - MeOH (5 : 1 v/v) and treated with 1.5 ml of 1 N NaOH. After 10 min, reaction mixture was acidified with diluted HCl and worked up as usual (AcOEt). Tropic acid (3-hydroxy-2-phenylpropionic acid)[12] was obtained as a white solid (90%), $[\alpha]_D$ + 45.1° (*c* 2, absolute EtOH), ee 68%, as checked by n.m.r. analysis of its Mosher's esters (prepared using either (-)-(*R*)- or (+)-(*S*)-*alpha*-methoxy-*alpha*-trifluoromethylphenylacetylchloride).

Synthesis of (-)-(R)-2-arylpropanoic acids 6b, 6c, and 6p.

Monoacetate **2** (1 mmol) was dissolved in dry CH_2Cl_2 (50 ml) at room temperature and triethylamine (3 mmol), p-toluenesulfonylchloride (3 mmol), and 4-dimethylaminopyridine (catalytic amount) were sequentially added. Reaction mixture was stirred at room temperature overnight, then saturated NH_4Cl was added and usual workup was performed (CH_2Cl_2). Crude product was rapidly passed through a short silica gel column, eluting with petroleum ether - AcOEt 7 : 3, to give pure 1-acetoxy-2-aryl-3-(4-methylphenylsulfonyloxy)propane (90-97%). This compound (0.7 mmol) was dissolved in dry DMSO (30 ml) and $NaBH_4$ (7 mmol) was added. The reaction mixture

was heated at 60°C for 4 h, then cooled to O°C, treated with saturated NH_4Cl, and worked up as usual (Et_2O). Column chromatography (petroleum ether - AcOEt 9 : 1) afforded 1-acetoxy-2-arylpropane (60 - 70%), which (0.4 mmol) was dissolved in 6 ml of THF - MeOH 10 : 1 at room temperature and added with 0.4 ml of 1 N NaOH. After stirring overnight, saturated NH_4Cl was added and the reaction mixture worked up as usual (AcOEt), to give pure (+)-2-arylpropan-1-ols **5b**, **5c**, and **5p** (quantitative yield), n.m.r. ($CDCl_3$) 1.26 (d, *J* 7.4 Hz, 3 H, *Me*CH), 2.36 (s, 3 H, *Me*Ar), 2.84 - 3.01 (m, 1 H, C*H*Me), 3.64 - 3.72 (m, 2 H, CH_2), 7.15 (b s, 4 H, Ar*H*) for **5b**, 1.25 (d, *J* 7.1 Hz, 3 H, *Me*CH), 2.83 - 3.00 (m, 1 H, C*H*), 3.64 - 3.71 (m, 2 H, CH_2), 3.80 (s, 3 H, *Me*O), 6.86 - 6.91 (m, 2 H, Ar*H*), 7.15 - 7.19 (m, 2 H, Ar*H*) for **5c**, 1.38 (d, *J* 7.0 Hz, 3 H, *Me*CH), 3.05 - 3.22 (m, 1 H ,C*H*), 3.79 - 3.85 (m, 2 H, CH_2), 7.37 - 7.52 (m, 3 H, Ar*H*), 7.69 (b s, 1 H, Ar*H*), 7.80 - 7.86 (m, 3 H, Ar*H*) for **5p**. In the case of **5b**, optical purity was confirmed by converting **5b** into its Mosher's esters, using either (-)-(*R*)- or (+)-(*S*)-*alpha*-methoxy-*alpha*-trifluoromethyl-phenylacetylchloride, and analyzing them by both ^1H and ^{13}C n.m.r. spectroscopy.

(+)-2-Arylpropan-1-ols (0.4 mmol) were subjected to Jones' oxidation as above described in the synthesis of tropic acid, to give (-)-2-arylpropanoic acids **6b**, **6c**, and **6p** (50 - 60%), which were converted into their methyl esters (CH_2N_2, Et_2O) and analyzed by n.m.r. spectroscopy in the presence of Eu(hfc)$_3$; n.m.r. ($CDCl_3$) 1.50 (d, *J* 7.1 Hz, 3 H, *Me*CH), 2.33 (s, 3 H, *Me*Ar), 3.71 (q, *J* 7.1 Hz, 1 H, C*H*Me), 7.12 - 7.24 (m, 4 H, Ar*H*) for **6b**, 1.50 (d, *J* 7.2 Hz, 3 H, *Me*CH), 3.70 (q, *J* 7.2 Hz, 1 H, C*H*Me), 3.80 (s, 3 H, *Me*O), 6.85 - 6.89 (m, 2H, Ar*H*), 7.23 - 7.27 (m, 2 H, Ar*H*) for **6c**, 1.61 (d, *J* 7.2 Hz, 3 H, *Me*CH), 3.92 (q, *J* 7.2 Hz, 1 H, C*H*Me), 7.43 - 7.48 (m, 3 H, Ar*H*), 7.76 - 7.84 (m, 4 H, Ar*H*) for **6p**; i.r. ($CHCl_3$) 1715, 3035 for **6b**, 1710, 3100 for **6c**, 1712, 3150 for **6p**.

Synthesis of (-)-3-acetoxy-2-(4-aminophenyl)propan-1-ol (-)-2h.

A) Starting from (-)-3-acetoxy-2-phenylpropan-1-ol (-)-2a.

Monoacetate (-)-**2a** (1 mmol) was dissolved in pyridine (4 ml) at 0°C and benzyl chloroformate (3 mmol) was added. Cooling bath was removed and, after 40 min, reaction mixture was evaporated to dryness under reduced pressure. Column chromatography (petroleum ether - AcOEt 9 : 1) of the residue gave 1-acetoxy-3-benzyloxycarbonyloxy-2-phenylpropane (60%) as a colourless oil, $[\alpha]_D$ - 2.8° (*c* 1, $CHCl_3$), n.m.r. ($CDCl_3$) 2.01 (s, 3H, *Me*CO), 3.29 - 3.42 (m, 1 H, C*H*), 4.33 - 4.44 (m, 4 H, CH_2OAc + CH_2OCOOBn), 5.13 (s, 2 H, PhCH_2O), 7.20 - 7.36 (m, 10 H, 2 x *Ph*).

(-)-1-Acetoxy-3-benzyloxycarbonyloxy-2-phenylpropane (0.5 mmol) was treated at O°C with 90% nitric acid (3 ml). After 30 min, reaction mixture was poured into crushed ice - water, and then subjected to usual workup (Et_2O). Column chromatography (petroleum ether - AcOEt 8 : 2) afforded 1-acetoxy-3-(4-nitrobenzyloxycarbonyloxy)-2-(4-nitrophenyl)propane in 30% yield, along with a mixture of isomers (35%), $[\alpha]_D$ - 5.3° (*c* 0.4, $CHCl_3$), n.m.r. ($CDCl_3$) 2.03 (s, 3 H, *Me*CO), 3.43 - 3.57 (m, 1 H, C*H*), 4.37 - 4.50 (m, 4 H, CH_2OAc + CH_2OCOOBn), 5.22 (s, 2 H, ArCH_2O), 7.42 - 7.54 (m, 4 H, Ar*H*), 8.14 - 8.26 (m, 4 H, Ar*H*).

(-)-1-Acetoxy-3-(4-nitrobenzyloxycarbonyloxy)-2-(4-nitrophenyl)propane (0.1 mmol) was dissolved in AcOEt (10 ml) and hydrogenated at normal pressure in the presence of a catalytic amount of 10% Pd/C. After 20 min, reaction mixture was filtered, evaporated to dryness, and chromatographed (petroleum ether - AcOEt 4 : 6) to give 1-acetoxy-2-(4-aminophenyl)propan-1-ol

2h (60%), $[\alpha]_D$ - 4.0° (*c* 1, $CHCl_3$).

B) Starting from (-)-1-acetoxy-2-(4-nitrophenyl)propan-1-ol (-)-2e.

Monoacetate (-)-**2e** (1 mmol) was dissolved in AcOEt (30 ml) and hydrogenated at normal pressure in the presence of a catalytic amount of 10% Pd/C for 2 h. Reaction mixture was filtered and evaporated to dryness to give **2h** (63%), $[\alpha]_D$ - 16.0° (*c* 1, $CHCl_3$).

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