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Regio- and Enantioselective Esterifications of Polyoxygenated Compounds Catalyzed by Lipases

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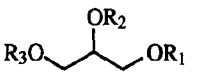
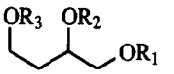
Abstract: The lipase catalyzed esterifications of derivatives of propane-1,2,3-triol and butane-1,2,4-triol in organic solvents have been studied. The influence of several factors (lipase source, organic solvent, additives and structural variations in the substrates) on the selectivity have been investigated. Good levels of regio- and enantioselectivity have been achieved, providing practical methods for the synthesis of these chiral building blocks.

Current endeavors in our group require practical synthesis of derivatives of both enantiomers of propane-1,2,3-triol (chiral glycerol derivatives; e.g., **A**) and butane-1,2,4-triol (e.g., **B**) as chiral building blocks for the EPC-synthesis[1] of functionalized lactones,[2] sugar analogues[3] and polyoxygenated natural products.[4] Whereas one of the two enantiomers of these chiral building blocks can be prepared from natural carbohydrates and hydroxy acids,[5] the existence of these natural products in only one enantiomeric form makes the synthesis of the other enantiomer of **A** and **B** quite problematic.



A



B

With the objective of obtaining both enantiomers of **A** and **B**, we decided to employ the kinetic resolution of readily available racemic materials. If the kinetic resolution were efficient, it would allow to get both enantiomers in good yields and high enantiomeric purities.

Lipases have proved to be efficient mediators to achieve this goal.[6] This kind of ester hydrolases are inexpensive, do not require cofactors, can accept a broad variety of structural types of organic compounds as substrates and are remarkably stable in organic solvents. Although the natural function of lipases is the hydrolysis of esters of glycerol,[7] it have been demonstrated that the reaction can be reversed in poor water-

content organic media, furnishing esters from an alcohol and an acylating agent.[8] The use of an organic solvent provides the opportunity to modulate the selectivity of the reaction catalyzed by lipase upon changes in the nature of the solvent.[9,10]

Continuing with our studies on the synthetic applications of lipases in organic solvents, [10,11] we report herein our results on the lipase catalyzed transesterification of (±)-1-O-benzylpropane-1,2,3-triol (**1a, Scheme 1** and **Scheme 4**), (±)-1-O-acetyl-3-O-benzylpropane-1,2,3-triol (**1b, Scheme 3**) and (±)-4-hydroxymethyl-1,3-dioxane-2-aryl substituted (**2a, 3a, 4a, 5a, 6a, Scheme 5**).

RESULTS AND DISCUSSION

SYNTHESIS OF C_3 CHIRAL BUILDING BLOCKS

Chiral derivatives of propane-1,2,3-triol (chiral glycerol derivatives, **A**) have been amply used in organic synthesis.[12,13,14] In connection with a project on the synthesis of modified nucleosides, we need derivatives of both enantiomers of 1-O-benzylpropane-1,2,3-triol (**1a**). These chiral building blocks, which have been previously used in the synthesis of a variety of biologically active compounds,[15,16] have been prepared through lengthy procedures from D-mannitol,[17] L-serine,[18] or L-ascorbic acid.[19] As an alternative we searched for a lipase catalyzed kinetic resolution of readily available (±)-**1a**. With this diol as substrate, two issues have to be considered, namely, the control of regioselectivity[20] and enantioselectivity of the process. We have found that the reaction of (±)-**1a** with vinyl acetate as acylating agent[21] catalyzed by several lipases is highly regioselective, affording (±)-1-O-acetyl-3-O-benzylpropane-1,2,3-triol [(±)-**1b**] in high yield (**Scheme 1**). Furthermore, we have submitted (±)-**1b** to a second lipase catalyzed acetylation (**Scheme 3**), this transformation goes with moderate to good enantioselectivity (as indicated by the value of the parameter E, as defined by Sih and Wu[6c]). Finally, we have combined the two steps [the regioselective acylation of (±)-**1a** and the enantioselective acylation of (±)-**1b**] in a "one-pot" sequence (**Scheme 4**), which allows to obtain derivatives of both enantiomers of 1-O-benzylpropane-1,2,3-triol in a practical manner.[22]

Regioselective acetylation of (±)-1-O-benzylpropane-1,2,3-triol (1a).

The results of the regioselective lipase catalyzed acetylation of (±)-**1a** using vinyl acetate as acyl-transfer agent (**Scheme 1**) are collected in **Table 1**.

Scheme 1

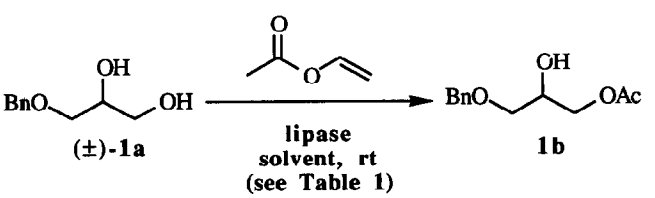


Table 1. Results of the regioselective lipase catalyzed transesterification of (±)-**1a**.

Entry	Lipase [a] (Amount) [b]	Solvent [c]	Vinyl acetate (moleq.) [d]	Time (h)	%c [e]	Diol (1a) %y [f]	Monoacetate (1b) %ee (%y) [g]
1	PPL (4500)	wet $CHCl_3$	2.5	74	59	(±)-**1a** 38	(±)-**1b** (47)
2	PPL (4000)	toluene	2.5	21.5	43	(-)-**1a** 49	(+)-**1b** 27 (42)
3	PFL (100)	toluene	5.0	6.25	44	(-)-**1a** 40	(+)-**1b** 14 (40)
4	PFL (240)	toluene	5.0	18.5	94	(-)-**1a** 3	(+)-**1b** *ca.* 3 (80)
5	PFL (200)	$CHCl_3$	5.0	5.75	20	(+)-**1a** 57	(-)-**1b** 16 (37)
6	PFL (200)	wet $CHCl_3$	5.0	14.5	48	(+)-**1a** 39	(-)-**1b** 19 (47)
7	PFL (200)	THF	5.0	7	29	(±)-**1a** 53	(±)-**1b** (25)
8	PFL (200)	hexane-THF (1:1)	2.5	2.75	85 [h]	(+)-**1a** 7	(-)-**1b** *ca.* 5 (75)
9	PFL (230)	vinyl acetate	34	3.25	48	(±)-**1a** 51	(±)-**1b** (47)
10	PFL (200)	vinyl acetate	30	23	90	**1a** [i]	(±)-**1b** (88)
11	PFL (390) [k]	vinyl acetate	46	46	>95 [l]		(±)-**1b** (92)
12	PFL (200)	acetonitrile	5.0	26.5	70	(+)-**1a** 23	(-)-**1b** 9 (67)
13	LPA (1500)	THF	5.0	17	>95 [m]		(±)-**1b** (78)

a) All the enzymes are commercially available (crude PPL from Sigma, PFL from Fluka and LPA from Amano). PPL refers to hog pancreas lipase (specific activity: 17.5 U/mg); PFL denotes *Pseudomonas fluorescens* lipase (specific activity: 31.5 U/mg); LPA signifies lipase P from Amano (a lipase from *Pseudomonas cepacia* with 30.0 U/mg specific activity). An unit of PFL corresponds to the amount of enzyme which liberates 1 μmol oleic acid per minute at pH 8.0 and 40°C (as described in Fluka catalogue). An unit of PPL hydrolizes 1 μmol of olive oil in one hour at pH 7.7 at 37°C (as indicated in Sigma catalogue). b) In units of enzyme per mmol of (±)-**1a**. c) All the solvents were of *puriss.* quality (Fluka or Aldrich). Wet solvents refer to water-saturated solvents. d) The amount of vinyl acetate relative to (±)-1a. e) The conversion degree was determined by ^{1}H-NMR in D_2O-containing $CHCl_3$. f) Isolated yield after flash-chromatography. The enantiomeric excesses were not determined. g) Isolated yield after flash-chromatography. The enantiomeric excesses (%ee) were determined by ^{1}H-NMR in the presence of Eu(hfc)$_3$ (ref. 23). h) A trace of diacetate 1c was detected in the ^{1}H-NMR spectrum of the crude. i) Not isolated. k) PFL recovered from the reaction reported in entry 9 was used. l) 3% of (+)-1c (>95% ee) was isolated. m) *ca.* 7% of diacetate was detected by ^{1}H-NMR (not isolated).

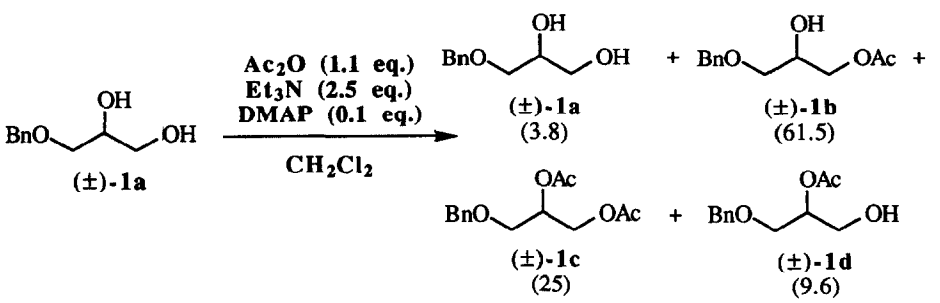
The lipases from *Candida cylindracea* (CCL), hog pancreas (PPL), *Pseudomonas fluorescens* (PFL) and *Pseudomonas cepacia* (lipase P from Amano, LPA) have been screened for activity and selectivity. The lipase from *Candida cylindracea* (CCL) shows very low regioselectivity, giving a 60:28:2:10 mixture of starting material (**1a**), primary monoacetate (**1b**), secondary monoacetate (**1d**) and diacetate (**1c**).[24] The lipase from hog pancreas (PPL) have been examined using wet chloroform and toluene as solvents (entries 1 and 2, **Table 1**). In both solvents, the reaction is highly regioselective, giving **1b** as the only acetylated product. While the reaction in wet chloroform affords racemic materials [(±)-**1a** and (±)-**1b**], independent of the conversion degree, the reaction in toluene furnishes (+)-**1b** with a slight enantiomeric excess.[25] The lipase from *Pseudomonas fluorescens* (PFL) shows low (entries 3-6, 8 and 12, **Table 1**) or null (entries 7, 9-11, **Table 1**) enantioselectivity. Although the enantioeselectivity is very low, it is worth noting that there is a

reversal in the stereochemical preference of the enzyme upon a change in the solvent; thus, while in chloroform (entries 5 and 6, **Table 1**), hexane-THF (1:1) (entry 8, **Table 1**) and acetonitrile (entry 12, **Table 1**) the (S)-enantiomer of (±)-**1a** is preferently acylated; the (R)-enantiomer of (±)-**1a** is acetylated in toluene. Up to very recently,[26] this reversal in the stereochemical outcome in enzyme catalyzed reactions upon a change in the solvent had not been reported; and, up to the best of our knowledgement, this is the third case where this phenomenon has been observed. Although in the present paper as well as in the reported examples,[26] the enantioselectivity is low, the prospect to alter the steric course of the reaction upon change in the reaction media opens new synthetic possibilities to enzyme mediated transformations and provides interesting data in order to understand the behavior of enzyme in aqueous solvents (non-aqueous enzymology [27]). The lipase P from Amano (LPA), related to PFL, has been briefly examined (entry 13, **Table 1**); this reaction is also highly regioselective, providing (±)-**1b** in good yield.

For the purpose of organic synthesis, the most useful feature of the acylation reported in **Scheme 1** and **Table 1** is that the reaction is highly regioselective, affording **1b** as the only monoacetate.[28] After some experimentation, we have found that the optimal conditions for performing the transformation of (±)-**1a** into (±)-**1b** in multigram scale was using vinyl acetate as solvent and PFL as catalyst (entry 10, **Table 1**). Furthermore, the enzyme has been recovered with the same activity and selectivity, and has been reused (entry 11, **Table 1**).

For the shake of comparison, the non-enzymatic acetylation of (±)-**1a** have been studied. As it is shown in **Scheme 2**, the reaction was non-regioselective affording a 61.5:9.6 mixture of the two monoacetates (±)-**1b** and (±)-**1d**, along 25% of the diacetate (±)-**1c** and 3.8% of the starting material.[24]

Scheme 2



Enantioselective acetylation of (±)-1-O-acetyl-3-O-benzylpropane-1,2,3-triol [(±)-1b].

With a ready access to (±)-**1b** in hand, we have tried the lipase catalyzed acetylation of this compound using vinyl acetate as acylating agent (**Scheme 3**). The results are collected in **Table 2**.

Scheme 3

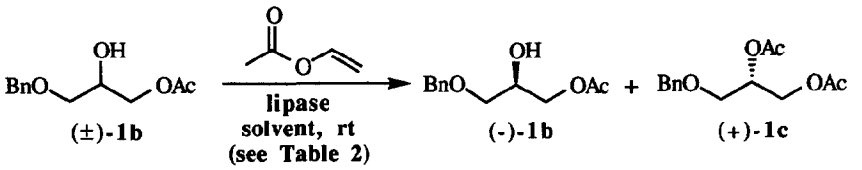


Table 2. Results of the lipase catalyzed transesterification of (±)-**1b**.

Entry	Lipase [a] (Amount)[b]	Solvent [c]	Vinyl acetate (moleq.)[d]	Time (h)	%c [e]	(-)-1b %ee[f] (%y)[g]	(+)-1c %ee[h] (%y)[g]	E [i]
1	LPA (1200)	$CHCl_3$	6.5	96	53	70 (43)	68 (35)	10.8
2	LPA (1200)	vinyl acetate	35	25	59	75 (35)	52 (45)	6.9
3	LPA (1000) [k]	vinyl acetate	20	101	65	92 (33)	50 (48)	9.1
4	LPA (1500)	pyridine	5.0	576	47	37 (45)	42 (37)	3.4
5	PFL (500)	toluene	5.0	122	53	69 (44)	60 (49)	8.0
6	PFL (200)	benzene	5.0	236	48	58 (49)	63 (34)	7.8
7	PFL (1000)	$CHCl_3$	5.0	358	50	61 (49)	62 (38)	7.8
8	PFL (800)	wet $CHCl_3$	5.0	192	46	40 (49)	48 (33)	4.1
9	PFL (420)	vinyl acetate	48	336	57	86 (41)	66 (46)	13.1
10	PFL (1000)	vinyl acetate	80	97	48	63 (53)	69 (36)	10.3
11	PFL (200)	THF	5.0	553	36	53 (61)	>95 (33)	>50
12	PFL (1000)	hexane-THF (2:1)	5.7	44	54	>95 (44)	81 (47)	>35

a) All the enzymes are commercially available (PFL from Fluka and LPA from Amano). PFL denotes *Pseudomonas fluorescens* lipase (specific activity: 31.5 U/mg); LPA signifies lipase P from Amano (a lipase from *Pseudomonas cepacia* with 30.0 U/mg specific activity). An unit of PFL corresponds to the amount of enzyme which liberates 1 μmol oleic acid per minute at pH 8.0 and 40°C (as described in Fluka catalogue). b) In units of enzyme per mmol of (±)-**1a**. c) All the solvents were of *puriss.* quality (Fluka or Aldrich). Wet solvents refer to water-saturated solvents. d) The amount of vinyl acetate relative to (±)-**1a**. e) The conversion degree was calculated by the expression $c = ee_S/(ee_S+ee_P)$ (ref. 6c). f) The enantiomeric excesses (%ee) were determined by ^{1}H-NMR in the presence of $Eu(hfc)_3$ (ref. 23). g) Isolated yield after flash-chromatography. h) The enantiomeric excesses (%ee) were determined by ^{1}H-NMR in the presence of $Eu(tfc)_3$ (ref. 23). i) Calculated according to ref. 6c. k) The enzyme recovered from the reaction reported in entry 2 was used.

CCL, PPL, LPA and PFL have been screened as catalysts in this transformation. With CCL and PPL as catalysts, the reactions are very slow and with low enantioselectivity E (data not shown). The transesterifications promoted by LPA (entries 1-4, **Table 2**) and PFL (entries 5-12, **Table 2**) show the same stereochemical outcome; but, meanwhile LPA is moderately enantioselective, PFL gives more satisfactory results. The enantioselectivity of the transesterifications catalyzed by PFL can be modulated upon changes in

the nature of the solvent, as we have previously shown with unrelated substrates to (±)-**1b**.[10] This have also been the case in the kinetic resolution of (±)-**1b**, where the enantioselectivity depends on the nature of the solvent (entries 5-12, **Table 2**). Although a exhaustive study has not been carried out, it has been found that high values of E are achieved when THF (entry 11, **Table 2**) or a 2:1 hexane-THF mixture (entry 12, **Table 2**) are used as solvents, what allows to obtain (-)-(R)-1-O-acetyl-3-O-benzylpropane-1,2,3-triol [(-)-**1b**] (entry 11, **Table 2**) and (+)-(S)-1,2-di-O-acetyl-3-O-benzylpropane-1,2,3-triol [(+)-**1c**] (entry 12, **Table 2**) in high enantiomeric purities and good chemical yields.

"One-pot" sequential regioselective and enantioselective acetylation from (±)-1-O-benzylpropane-1,2,3-triol [(±)-1a].

Having achieved satisfactory results on the regioselective acetylation of (±)-**1a** and the enantioselective acetylation of (±)-**1b**, we have combined both transformations in a "one-pot" sequence using LPA and PFL as catalysts in organic solvents (**Scheme 4**). The results are collected in **Table 3**.

Scheme 4

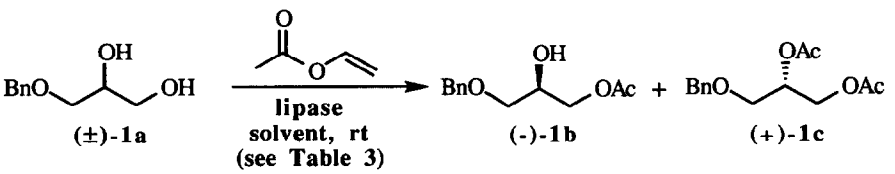


Table 3. Results of the lipase catalyzed acetylation of (±)-**1a** to give (-)-**1b** and (+)-**1c**.

Entry	Lipase [a] (Amount) [b]	Solvent [c]	Vinyl acetate (moleq.) [d]	Time (h)	(-)-1b %ee [e] (%y) [f]	(+)-1c %ee [g] (%y) [f]
1	LPA (1200)	$CHCl_3$	5.0	16 [h]	18 (53)	87 (15)
2	LPA (1200)	vinyl acetate	35	40.5 [h]	66 (43)	60 (42)
3	LPA (1000) [i]	vinyl acetate	20	4.5	23 (76)	79 (19)
4	LPA (1200)	THF	5.0	16 [k]	27 (75)	91 (22)
5	LPA (1500)	acetonitrile	5.6	744	67 (30)	84 (33)
6	PFL (1000)	THF-hexane (1:1)	5.0	35.5 [h]	>92 (43)	80 (46)

a) All the enzymes are commercially available (PFL from Fluka and LPA from Amano). PFL denotes *Pseudomonas fluorescens* lipase (specific activity: 31.5 U/mg); LPA signifies lipase P from Amano (a lipase from *Pseudomonas cepacia* with 30.0 U/mg specific activity). An unit of PFL corresponds to the amount of enzyme which liberates 1 μmol oleic acid per minute at pH 8.0 and 40°C (as described in Fluka catalogue). b) In units of enzyme per mmol of (±)-**1a**. c) All the solvents were of *puriss.* quality (Fluka or Aldrich). d) The amount of vinyl acetate relative to (±)-**1a**. e) The enantiomeric excesses (%ee) were determined by ^{1}H-NMR in the presence of Eu(hfc)$_3$ (ref. 23). f) Isolated yield after flash-chromatography. g) The enantiomeric excesses (%ee) were determined by ^{1}H-NMR in the presence of Eu(tfc)$_3$ (ref. 23). h) *ca.* 5% of **1a** were isolated (ee and absolute configuration were not determined). i) The enzyme used was recovered from the reaction reported in entry 2. k) *ca.* 3% of **1a** were isolated (ee and absolute configuration were not determined).

Although the methodology has not been optimized, the results shown in **Table 3** points out that it is possible to get in a practical manner (-)-(R)-1-O-acetyl-3-O-benzylpropane-1,2,3-triol [**(-)-1b**] (entry 6, **Table 3**) and (+)-(S)-1,2-di-O-acetyl-3-O-benzylpropane-1,2,3-triol [**(+)-1c**] (entry 4, **Table 3**) from (±)-1-O-benzylpropane-1,2,3-triol [**(±)-1a**] in a "one-pot" reaction from racemic 1-O-benzylpropane-1,2,3-triol.

SYNTHESIS OF C_4 CHIRAL BUILDING BLOCKS

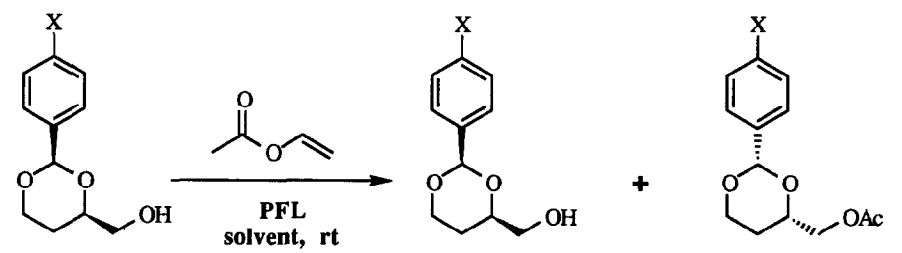
Derivatives of both enantiomers of butane-1,2,4-triol [e. g., **(-)-2a-6a** and **(+)-2b-6b**, **Scheme 5**] are useful chiral building blocks for the synthesis of natural products[29] and chiral auxiliaries for asymmetric synthesis.[30] In the course of our work on the synthesis of biologically active compounds[2b] we need practical routes to these chiral building blocks. Although derivatives of (S)-butane-1,2,4-triol can be prepared from readily available (S)-malic acid,[31] the synthesis of derivatives of the (R)-enantiomer involves the use of expensive (R)-malic acid.[32,33] Due to this inconvenience we have searched for an alternative route to these compounds, finding that lipase mediated transformations of the readily available acetals (±)-**2a-6a**,[34] derived from racemic butane-1,2,4-triol, permits to reach this goal efficiently.

We have recently reported our preliminary studies on the kinetic resolution of the parent acetal (±)-**2a** through a transesterification with vinyl acetate in organic solvents.[11] We have found that the enantioselectivity of the kinetic resolution depends on both the lipase source as well as on nature of the solvent. The most satisfactory results have been achieved when the lipase from *Peudomonas fluorescens* (PFL) was used. In this paper we present some additional results on the PFL-catalyzed kinetic resolution of (±)-**2a**, as well as our studies on the PFL-catalyzed acetylation of the related acetals (±)-**3a**, (±)-**4a**, (±)-**5a** and (±)-**6a**.

Enantioselective acetylation of (±)-4-hydroxymethyl-2-phenyl-1,3-dioxane [(±)-2a].

The results of the PFL-catalyzed acetylation of (±)-**2a** in organic solvents using vinyl acetate as acylating agent (**Scheme 5**) are depicted in **Table 4**.

Scheme 5



(±)-**2a**; X= H
(±)-**3a**; X= Me
(±)-**4a**; X= iPr
(±)-**5a**; X= F
(±)-**6a**; X= OMe

(-)-**2a**; X= H
(-)-**3a**; X= Me
(-)-**4a**; X= iPr
(-)-**5a**; X= F
(-)-**6a**; X= OMe

(+)-**2b**; X= H
(+)-**3b**; X= Me
(+)-**4b**; X= iPr
(+)-**5b**; X= F
(+)-**6b**; X= OMe

Table 4. Results of the *Pseudomonas fluorescens* lipase catalyzed transesterification of (±)-**2a**.[a]

Entry	Amount [b]	Solvent [c]	Time (h)	%c [d]	(-)-**2a** %ee (%y) [e]	(+)-**2b** %ee (%y) [e]	E [f]
1	195	toluene	9	54	90 (35)	77 (46)	23.3
2	200	wet toluene	6	52	81 (39)	76 (49)	18.1
3	200 [g]	wet toluene	3	30	37 (66)	85 (29)	17.7
4	510 [h]	wet toluene	2.5	45	61 (43)	78 (42)	14.4
5	410	$CHCl_3$	72	64	39 (30)	71 (46)	4.5
6	200	$CHCl_3$ [i]	480	20 [k]	n. d. [l]	n. d.	n.d.
7	120	wet $CHCl_3$	80	47	74 (41)	84 (41)	25.7
8	200	CH_2Cl_2	504	36	43 (47)	78 (31)	12.3
9	230	wet CH_2Cl_2	28	50	70 (42)	69 (46)	11.2
10	220	Et_2O	9	48	68 (36)	74 (39)	13.3
11	220	wet Et_2O	67	45	59 (34)	72 (38)	11.1
12	230	THF	5	31	42 (49)	93 (29)	42.0
13	210	THF	45	54	>97 (39)	82 (48)	44.0
14	360	THF	6	46	74 (46)	86 (41)	31.5
15	340	THF [m]	24	56	95.5 (33)	75 (51)	26.0
16	750	THF [n]	17	54	79 (33)	67 (42)	12.0
17	525	THF	5	51	83 (46)	81 (42)	24.5
18	525	THF [o]	36	53	88 (47)	78 (44)	23.2
19	230	THF/H20 (200:1)	32	49	84 (41)	88 (45)	42.0
20	200	THF/H20 (200:1) [p]	38	59	>97 (34)	68 (35)	23.0
21	200	THF-H_2O (50:1)	168	25 [q]	n. d.	n. d.	n. d.
22	230	THF-hexane (1:1)	15	56	>99 (32)	77 (50)	45.8
23	210	THF-hexane (1:2)	22	51	91 (41)	87 (46)	45.8
24	230	vinyl acetate [r]	23	59	95 (33)	66 (52)	17.3
25	130	acetone	23	49	72 (38)	74 (36)	14.4
26	205	acetone [i]	79.5	51	84 (37)	82 (47)	25.5

a) The enzyme was purchased from Fluka. The specific activity of this enzyme is 31.5 U/mg. An unit corresponds to the quantity of enzyme which liberates 1 µmol oleic acid per minute at pH 8.0 and 40°C (as defined in Fluka catalogue). Unless otherwise indicated, all the reactions were carried out using 2.5 moleq. of vinyl acetate [related to (±)-**2a**]. b) The amount refers to units of PFL per mmol of (±)-**2a**. c) All the solvents were of *purissimum* quality (Fluka). Wet solvent means water-saturated solvents. d) The conversion degree was calculated by the expression $c = ee_S/(ee_S+ee_P)$ (ref. 6c). e) %ee were determined by ^{1}H-NMR spectroscopy in the presence of Eu(hfc)$_3$ (ref. 23). All the yields refer to isolated compounds after flash-chromatography. f) Calculated according to ref. 6c. g) The enzyme recovered from the reaction reported in entry 2 was reused. h) The enzyme was previously used 3 times. i) The reaction was carried out in the presence of 0.5 masseq. [relative to (±)-**1a**] of powered 3 Å molecular sieves. k) The reaction stopped after *ca.* 80 hours. The reaction products were not isolated. The conversion degree was estimated by ^{1}H-NMR. l) n.d.= not determined. m) 1.0 moleq. of vinyl acetate was used. n) 0.6 moleq. of vinyl acetate were used. o) The reaction was carried out in the presence of 0.4 masseq. [relative to (±)-**1a**] of powered 3 Å molecular sieves. p) The reaction was carried out at 40°C. q) The reaction stopped after *ca.* 70 hours. Acetic acid was detected. The reaction products were not isolated. The conversion was estimated by ^{1}H-NMR. r) 48 moleq. of vinyl acetate were used.

In all the solvents tested the enzyme catalyze preferentially the acetylation of the (S,S)-enantiomer of (±)-**2a**, giving (-)-**2a** and (+)-**2b**.[35] The effectiveness of the process has been calibrated by the value of the enantioselectivity E.[6c] A remarkable fact of this reaction is that the enantioselectivity (and the velocity) can be modulated upon changes in the experimental conditions (polarity and hidrophobicity of the solvent, water-content of the solvent, amount of enzyme, amount of acylating agent and addition of molecular sieves). The

values of E ranges from the modest (4.5; entry 5, **Table 4**) to excelent (> 30; entries 12, 13, 14, 19, 22 and 23, **Table 4**)].

We have previously reported that the enantioselectivity of the PFL-catalyzed acetylation of (±)-**2a** in "nearly" anhydrous solvent is dependent on the hydrophobicity and polarity of the solvent in a semi-quantitative way.[10] Wishing to get a deeper knowledgement on the performance of this enzyme in organic solvents, we have examined the effect of different experimental conditions on the enantioselectivity of the reaction.

The consequences of the addition of water and molecular sieves on the velocity and enantioselectivity of the transesterification have been studied using toluene, chloroform, methylene chloride, diethyl ether, tetrahydrofuran and acetone as solvents. The reaction is slightly faster and the enantioselectivity is slightly lower in wet toluene than in "dry" toluene (entries 1 and 2, **Table 4**). When the reaction is conducted in wet toluene, the enzyme sticks on the wall of the flask. This enzyme, "immobilized" on the glassware, is used in the experiment reported in entry 3; this "immobilized" enzyme possesses essentially the same activity and enantioselectivity than the unmodified lipase. This enzyme can be reused several times (entry 3).[36] The effect of adding water to chloroform is dramatic: much faster and more enantioselective reactions have been obtained in wet chloroform than in dry chloroform (entries 5 and 7). On the other hand, when the reaction is carried out in chloroform in the presence of molecular sieves, the reaction is very slow, and the enzyme becomes deactivated after several hours (entry 6, **Table 4**), probably most of the water surrounding the surface of the enzyme (*essential water* [27]) is stripped off, disturbing seriously the most active conformation of the enzyme. There is a high augment in the velocity of the reaction when wet methylene chloride was used instead of the solvent, but no effect on the enantioselectivity of the transesterification is observed (entries 8 and 9, **Table 4**). The opposite tendency was observed when dry diethyl ether was replaced by wet diethyl ether: the reaction was slower in the wet solvent than in the nearly anhydrous solvent, but no appreciable change in the enantioselectivity was observed (entries 10 and 11). Small addition of water to THF does not have any effect on the velocity and selectivity of the reaction (entries 12, 13 and 19, **Table 4**); but when the ratio of water increases (entry 21) the reaction is very slow, acetic acid is formed,[37] and the enzyme becomes deactivated. When the reaction in THF is carried out in the presence of molecular sieves, a slower reaction is produced and the enantioselectivity is nearly the same (compare entries 17 and 18). The selectivity of the PFL-catalyzed acetylation of (±)-**2a** in acetone increases when the reaction is carried out in the presence of molecular sieves, although the reaction is slower (entries 25 and 26, **Table 4**).

Because our preliminary studies[10] have indicated that the reactions in THF are the most selective, we have briefly examined other experimental variables (namely, the amounts of lipase and acylating agent) on the selectivity[38] of the acetylation of (±)-**2a**. It is observed that higher amounts of PFL causes faster reactions and less selective transformation (entries 13, 14 and 17, **Table 4**). The use of smaller amounts of vinyl acetate makes the reaction slower and slightly less enantioselective (entries 14 and 15). Thus, when big amounts of PFL and small quantities of vinyl acetate are used, only a modest enantioselectivity is achieved (entry 16, **Table 4**).

Finally the reaction in mixed solvents has been tested. We has found that a THF-hexane mixture is a suitable solvent for this transformation, which proceeds with excellent selectivity and relatively fast. Furthermore, the reaction is insensible to the solvent's ratio (entries 22 and 23, **Table 4**).

Enantioselective acetylation of (±)-2-aryl-4-hydroxymethyl-1,3-dioxanes.

As a part of our programm to elucidate the structure-selectivity relationship in lipase catalyzed reactions, we have carried out a study on the *Pseudomonas fluorescens* catalyzed acetylation of the acetals (±)-**3a**, (±)-**4a**, (±)-**5a** and (±)-**6a**, which are structurally related to (±)-**2a** (**Scheme 5**). Although the structural difference between (±)-**2a** and these compounds is far away from the reacting group in the transesterification, we have observed some striking differences regarding the selectivity. The results are collected in **Table 5**.

On comparing with the results obtained in the kinetic resolution of the parent acetal (±)-**2a** (**Table 4**), the selectivity increases with the steric size of the substituent in the position 4- of the aromatic ring [substrates (±)-**3a**, (±)-**4a** and (±)-**6a**] when the reaction is carried out in "nearly" anhydrous solvents (entries 1, 3, 4, 11, 13, 16 and 17, **Table 5**). On the contrary, the selectivity decreases when (±)-**5a** is the substrate in "nearly" anhydrous solvents (entries 8, 9 and 10). When wet chloroform is the solvent, no correlation can be found, finding that the selectivity relative to (±)-**2a** increases with (±)-**6a** (entries 14 and 15, **Table 5**) and decreases with (±)-**4a** (entry 5), being nearly the same with (±)-**3a** and (±)-**5a** (entries 2, 6 and 7).

Also from a practical point of view, it is worth noting that when the reaction is carried out in wet chloroform (or in wet toluene as indicated above), the enzyme sticks on the wall of the glass, and this immobilized enzyme is reused. Thus the same batch of PFL have been consecutively used in the acetylation of (±)-**5a** in wet chloroform (entry 6), hexane-THF (2:1) (entry 8), wet chloroform (entry 7) and vinyl acetate (entry 10, **Table 5**), without decreasing activity and selectivity; and, even, a slight increase in activity and selectivity have been observed in vinyl acetate.

Although with the data currently available, we can not determine the structural factors responsible of the enantioselectivity in the PFL-catalyzed transesterification, the results with the alcohols **2a**-**6a** show that relatively distant groups from the reacting moiety in the substrate are still very important in determining the selectivity of the reaction.

Summarizing, the results reported in **Tables 4** and **5** show that it is possible to get high enantioselectivities in the PFL-catalyzed acetylation of these acetals, what allows to obtain derivatives of both enantiomers of butane-1,2,4-triol.

CONCLUSION

Chiral derivatives of both propane-1,2,3-triol and butane-1,2,4-triol have been obtained through lipase catalyzed acetylations in organic solvents. The applications of these chiral building blocks in the synthesis of nucleoside analogues and polyoxygenated natural products is currently investigated.

In this paper, we demonstrate that the enantioselectivity can be modulated upon changes in the nature of the solvent (*media engineering*),[27a] what provides a straightforward method to achieve efficient kinetic resolutions.[39] Furthermore the data reported in the present paper can help to understand the behavior of enzymes in organic solvents.

Work is in progress in order to fully understand the role of the solvent in lipase catalyzed esterifications as well as to know the structural requirement of the substrates in order to achieve high selectivity.[40]

Table 5. Results of the *Pseudomonas fluorescens* lipase (PFL) catalyzed transesterification of (±)-**3a**, (±)-**4a**, (±)-**5a** and (±)-**6a**.[a]

Entry	Starting material	Amount [b]	Solvent [c]	Time (h)	%c [d]	Alcohol %ee (%y) [e]	Ester %ee (%y) [e]	E [f]
1	(±)-**3a**	205	toluene	5.75	50	(-)-**3a** 90 (48)	(+)-**3b** 90 (46)	>50
2	(±)-**3a**	180	wet $CHCl_3$	14.75	48	(-)-**3a** 74 (41)	(+)-**3b** 81 (40)	21.0
3	(±)-**3a**	230	vinyl acetate [g]	3.5	50	(-)-**3a** 80 (45)	(+)-**3b** 81 (49)	23.2
4	(±)-**4a**	200	toluene	3.25	53	(-)-**4a** >94 (38)	(+)-**4b** 84 (47)	>40
5	(±)-**4a**	240	wet $CHCl_3$	16	29	(-)-**4a** 34 (65)	(+)-**4b** 82 (28)	14.1
6	(±)-**5a**	220	wet $CHCl_3$	18.5	47	(-)-**5a** 72 (44)	(+)-**5b** 83 (39)	23.1
7	(±)-**5a**	165 [h]	wet $CHCl_3$	18.5	34	(-)-**5a** 44 (55)	(+)-**5b** 87 (27)	22.2
8	(±)-**5a**	185 [i]	hexane-THF (2:1)	5	53	(-)-**5a** 90 (33)	(+)-**5b** 79 (40)	26.0
9	(±)-**5a**	200	vinyl acetate [k]	9	33	(-)-**5a** 28 (60)	(+)-**5b** 55 (33)	4.5
10	(±)-**5a**	200 [l]	vinyl acetate [k]	6.5	43	(-)-**5a** 53 (55)	(+)-**5b** 71 (32)	9.9
11	(±)-**6a**	200	toluene	4.5	50	(-)-**5a** 91 (38)	(+)-**5b** 90 (40)	>50
12	(±)-**6a**	215	wet toluene	3.5	58	(-)-**5a** >98.5 (41)	(+)-**5b** 72 (47)	29.1
13	(±)-**6a**	240	$CHCl_3$	256	52	(-)-**5a** >98 (42)	(+)-**5b** 90 (48)	>50
14	(±)-**6a**	240	wet $CHCl_3$	8	48	(-)-**5a** 86 (52)	(+)-**5b** 94 (40)	>50
15	(±)-**6a**	240	wet $CHCl_3$	20	54	(-)-**5a** >98 (44)	(+)-**5b** 83 (44)	>50
16	(±)-**6a**	215	vinyl acetate [m]	6.75	48	(-)-**5a** 76 (50)	(+)-**5b** 84 (41)	26.2
17	(±)-**6a**	230	acetone	51	55	(-)-**5a** >98 (40)	(+)-**5b** 83 (41)	>50

a) The enzyme was purchased from Fluka. The specific activity of this enzyme is 31.5 U/mg. An unit corresponds to the quantity of enzyme which liberates 1 μmol oleic acid per minute at pH 8 0 and 40°C (as defined in Fluka catalogue). Unless otherwise indicated, all the reactions were carried out using 2.5 moleq. of vinyl acetate (related to the racemic starting alcohol). b) The amounts refer to units of PFL per mmol of racemic starting alcohol. c) All the solvents were of *purissimum* quality (Fluka). Wet solvent means water-saturated solvents. d) The conversion degree was calculated by the expression $c = ee_S/(ee_S+ee_P)$ (ref. 6c). e) %ee were determined by ^{1}H-NMR spectroscopy in the presence of of Eu(hfc)$_3$ (ref. 23). All the yields refer to isolated compounds after flash-chromatography. f) Calculated according to ref. 6c. g) 43 moleq. of vinyl acetate were used. h) The enzyme was recovered from the reaction reported in entry 8 (third use of the lipase, see text). i) The enzyme was recovered from the reaction reported in entry 6 (second use of the lipase, see text). k) 52 moleq. of vinyl acetate were used. l) The enzyme was recovered from the reaction reported in entry 7 (fourth use of the lipase). m) 43 moleq. of vinyl acetate were used.

EXPERIMENTAL

General. All the lipases are commercially available (PPL from Sigma, PFL from Fluka and LPA from Amano), and were used as received. All the solvents and chemicals are commercially available (Fluka or Aldrich), and unless otherwise indicated were used as received. Pyridine was distilled over CaH_2 under argon, and kept over molecular sieves. ^{1}H-NMR and ^{13}C-NMR spectra were measured in *Varian-XL-300* or *Varian-Gemini-200* ; chemical shift are reported in parts per million (δ) relative to TMS, and the coupling constants are indicated in Hz. The multiplicity of the signals in the ^{13}C-NMR spectra have been determined by ATP or DEPT experiments. Microanalysis were performed by E. Barbero (Instituto de Química Orgánica). Low-resolution electron-impact (70eV) mass spectra were recorded in a *RMU-GMG* spectrometer from *Hitachi-Perkin-Elmer*. The optical rotations were measured in a *Perkin-Elmer 241 MC* polarimeter; all the optical rotations were measured in $CHCl_3$ solution at room temperature (21-24°C).

Regioselective acetylation of (±)-1a. Synthesis of 1-O-acetyl-3-O-benzylpropane-1,2,3-triol [(±)-1b].(Table 1, entry 10). A representative procedure is as follows. 94.5 mg (2970 units, 200 U/mmol) of PFL were added to a solution of 2.71 g (14.9 mmol) of **(±)-1a** in 4.5 ml of vinyl acetate. The mixture was stirred at room temperature for 23 hours. The mixture was diluted with CH_2Cl_2, and filtered to afford 92 mg of PFL, which was reused. The solvent was removed under reduced pressure to give a crude material which was flash-chromatographed (hexane-EtOAc, 2:3) to afford 2.94 g of **(±)-1b** (88% yield). MS: m/e= 224 (0.3), 181 (3.6), 107 (14.9), 103 (12.5), 92 (21.1), 91 (100), 43 (26.7). ^{1}H-NMR (300 MHz, $CDCl_3$): δ= 7.33 (m, 5H), 4.56 (s, 2H), 4.19 (dd, J= 11.4, 4.5, 1H), 4.13 (dd, J= 11.4, 6.0, 1H), 4.04 (m, 1H), 3.56 (dd, J= 9.6, 4.2, 1H), 3.50 (dd, J= 9.6, 6.1, 1H), 2.50 (br s, 1H), 2.08 (s, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ= 170.9 (s), 137.6 (s), 128.3 (2C, d), 127.65 (d), 127.57 (2C, d), 73.3 (t), 70.8 (t), 66.5 (d), 65.4 (t), 20.6 (q). Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.28%; H, 7.14%. Found: C, 64.13%; H, 7.40%.

Synthesis of enantiomerically pure (S)-1-O-acetyl-3-O-benzylpropane-1,2,3-triol [(+)-1b]. (equation 1, footnote 25). The procedure reported above was followed. The amounts used were 97 mg of enantiomerically pure (R)-1-O-benzylpropane-1,2,3-triol **[(+)-1a]**, 3.4 mg of PFL and 2.0 ml of vinyl acetate. 107 mg of **(+)-1b** (90% yield), identical to the racemic material, were obtained. $[\alpha]_D$= +4.1 ($CHCl_3$, c= 1.04).

Synthesis of (+)-(S)-1,2-di-O-acetyl-3-O-benzylpropane-1,2,3-triol [(+)-1c]. (equation 2, footnote 25). Excess acetic anhydride (1.0 ml) was dropwise added to a solution of 70 mg (0.26 mmol) of **(+)-1a** in 2.5 ml of pyridine at 0°C. The mixture was allowed to evolve to room temperature overnight, and poured over a saturated aqueous solution of $NaHCO_3$ at 0°C. After stirring for 30 minutes, the solution was extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O, half-saturated aqueous $CuSO_4$ and H_2O. After drying ($MgSO_4$), evaporation of the solvent gave 99 mg of pure **(+)-1c** (97% yield). An analytical sample was obtained by flash-chromatography (hexane-ethy acetate, 3:1). $[\alpha]_D$= +14.0 ($CHCl_3$ c= 0.5) [Literature for the R-enantiomer:[17b] $[\alpha]_D$= -16.37 (MeOH, c= 4.56)]. MS: m/e= 266 (0.2), 223 (4.1), 159 (13.9), 117 (25.9), 107 (10.1), 105 (14.3), 100 (32.7), 91 (100), 43 (60.9). ^{1}H-NMR (300 MHz, $CDCl_3$): δ= 7.36-7.30 (m, 5H), 5.22 (m, 1H), 4.57 (d, J= 12.2, 1H), 4.52 (d, J=12.2, 1H), 4.34 (dd, J=11.9, 3.8, 1H), 4.19 (dd, J= 11.9, 6.3, 1H), 3.60 (d, J= 5.1, 2H), 2.09 (s, 3H), 2.04 (s, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ= 171.8 (s), 170.7 (s), 138.2 (s), 128.9 (2C, d), 128.3 (d), 128.1 (2C, d), 73.7 (t),

70.7 (d), 68.5 (t), 63.3 (t), 21.5 (q), 21.2 (q). Anal. Calcd. for $C_{14}H_{18}O_5$: C, 63.16%; H, 6.77%. Found: C, 63.26%; H= 7.00%.

Enantioselective acetylation of (±)-1b.(Table 2, entry 6). A typical procedure is as follow. 9.3 mg (292 U, 200 U/mmol) of PFL were added to a solution of 330 mg (1.47 mmol) of **(±)-1b** in 4 ml of benzene. After stirring for 5 minutes, 0.68 ml of vinyl acetate were added. The mixture was stirred at room temperature. The progress of the reaction was readily followed by ^{1}H-NMR (singlets at 2.09 and 2.04 ppm for the diacetate and 2.08 ppm for the monoacetate). After 236 hours the reaction mixture was diluted with CH_2Cl_2 and the enzyme was filtered off. The solvent was removed under reduced pressure to give a crude product which was flash-chromatographed [hexane-EtOAc (3:1) and hexane-EtOAc (2:3)] to give 133 mg (34% yield) of **(+)-1c** and 159 mg (49% yield) of **(-)-1b**.

Determination of the enantiomeric excess of (R)-1-O-acetyl-2-O-benzylpropane-1,2,3-triol [(-)-1b]. A typical procedure is as follows. A mixture of 3.0 mg of enantiomerically enriched **(-)-1b** (of 63% ee, from the reaction reported in the entry 10 of **Table 2**) and 14.4 mg (0.9 moleq) of $Eu(hfc)_3$ was dissolved in *ca.* 0.6 ml of $CDCl_3$. After *ca.* 30 minutes, a ^{1}H-NMR spectrum was taken, showing peaks (4.32:1 ratio) at 2.679 ppm (for the main diastereoisomer) and at 2.649 ppm (for the major diastereoisomer) for the methyl protons of the acetyl group.

Determination of the enantiomeric excess of (S)-1,2-O-diacetyl-3-O-benzyl-propane-1,2,3-triol [(+)-1c]. A typical procedure is as follows. A mixture of 1.85 mg of enantiomerically enriched **(+)-1c** (of 63% ee, from the reaction reported in the entry 10 of **Table 2**) and 6.9 mg (1.1 moleq) of $Eu(tfc)_3$ was dissolved in *ca.* 0.6 ml of $CDCl_3$. After *ca.* 1 hour, a ^{1}H-NMR spectrum was taken, showing peaks (1:5.8:1.1:5.7 ratio) at 3.697, 3.691, 3.680 and 3.674 ppm. The signals at 3.697 and 3.680 ppm are for the minor diastereoisomer and the peaks at 3.691 and 3.674 ppm are for the major diastereoisomer for the doublet of H-2.

"One-pot" sequential regio- and enantioselective acetylations of (±)-1a, (Table 3, entry 6). A typical procedure is as follow. 13.6 mg (428 U, 1000 U/mmol) of PFL were added to a solution of 78 mg (0.43 mmol) of **(±)-1a** in 2 ml of THF-hexane (1:1). After stirring for 5 minutes, 0.20 ml (2.15 mmol, 5.0 eq.) of vinyl acetate were added. The mixture was stirred at room temperature. The progress of the reaction was followed by ^{1}H-NMR (singlets at 2.09 and 2.04 ppm for the diacetate and 2.08 ppm for the monoacetate). After 35.5 hours the reaction mixture was diluted with CH_2Cl_2 and the enzyme was filtered off. The solvent was removed under reduced pressure to give a crude product which was flash-chromatographed [hexane-EtOAc (3:1), hexane-EtOAc (2:3) and EtOAc] to give 52 mg (46% yield) of **(+)-1c,** 41 mg (43% yield) of **(-)-1b**, and 4 mg (5% yield) of **1a** (stereochemistry not determined).

General procedure for the PFL-catalyzed acetylation of (±)-2a-6a. Vinyl acetate (the moleq. indicated in either **Table 4** or **Table 5**) was added to a mixture of **(±)-2a-6a** and PFL (the amount indicated in either **Table 4** or **Table 5**) in the corresponding solvent (when the reaction was carried out in the presence of powdered molecular sieves, it was added before vinyl acetate). The mixture was stirred at room temperature. The reactions were readily followed by ^{1}H-NMR. When the desired conversion degree was achieved, the mixture was diluted with CH_2Cl_2. The enzyme was filtered off and thoroughly washed with CH_2Cl_2. Evaporation of the solvents gave a crude material, which was chromatographed [hexane-EtOAc, 3:1 and 2:3; for the purification of **(+)-4b** and **(-)-4a**, hexane-EtOAc, 4:1 and 1:1 was used] affording the ester **(+)-2b-6b** and the alcohol **(-)-2a-6a**.

(R,R)-4-Hydroxymethyl-2-phenyl-1,3-dioxane [(-)-2a] (>98% ee). $[\alpha]_D$= -10.0 ($CHCl_3$, c= 1.18). MS: m/e= 194 (41.7), 193 (65.1), 163 (72.5), 123 (7.8), 117 (7.2), 107 (44.7), 106 (18.4), 105 (100), 91 (47.5), 79 (75.2), 78 (24.8), 77 (68.8), 71 (47.7), 57 (35.8), 43 (24.8). Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02%; H, 7.27%. Found: C, 67.78%; H, 7.60.

(S,S)-4-Acetoxymethyl-2-phenyl-1,3-dioxane [(+)-2b] (>98% ee). $[\alpha]_D$= +27.1 ($CHCl_3$, c= 1.2). MS: m/e= 236 (19.1), 235 (22.2), 193 (2.7), 176 (3.8), 163 (28.0), 114 (39.4), 105 (100), 91 (33.2), 79 (29.9), 77 (44.2), 43 (76.4). ^{1}H-NMR (200 MHz, $CDCl_3$): δ= 7.61-7.46 (m, 2H), 7.32 (m, 3H), 5.53 (s, 1H), 4.25-4.09 (m, 1H), 4.25-4.09 (m, 3H), 4.00 (dt, J= 4.0, 12.7, 1H), 2.11 (s, 3H), 2.05-1.80 (m, 1H), 1.62-1,49 (m, 1H). ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ= 171.4 (s), 138.7 (s), 129.2 (d), 128.6 (2C, d), 126.5 (2C, d), 101.5 (d), 75.1 (d), 66.8 (2C, t), 27.7 (t), 21.1 (q).

(R,R)-4-Hydroxymethyl-2-(4-methylphenyl)-1,3-dioxane [(-)-3a]. (>98% ee). $[\alpha]_D$= -8.0 ($CHCl_3$, c= 0.96). MS: m/e= 208 (34.5), 207 (47.2), 193 (20.7), 177 (49.3), 121 (36.2), 119 (100), 105 (37.1), 93 (38.6), 91 (92.1), 77 (26.9), 71 (38.1),65 (22.0), 57.1 (24.8), 43 (17.9). ^{1}H-NMR (200 MHz, $CDCl_3$): δ= 7.38 (d, J= 8.1, 2H), 7.19 (d, J= 8.1, 2H), 5.53 (s, 1H), 4.30 (ddd, J= 11.5, 5.1, 1.1, 1H), 4.04-3.94 (m, 2H), 3.68 (m, 2H), 2.35 (s, 3H), 2.05 (br s, 1H), 2.00-1.86 (m, 1H), 1.48 (m, 1H). ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ= 138.7 (s), 135.6 (s), 128.9 (d), 126.0 (d), 101.3 (d), 77.5 (d), 66.5 (t), 65.7 (t), 26.8 (t), 21.2 (q).

(S,S)-4-Acetoxymethyl-2-(4-methylphenyl)-1,3-dioxane [(-)-3a]. (84% ee). $[\alpha]_D$= +25.2 ($CHCl_3$, c= 1.05). MS: m/e= 250 (24.5), 177 (17.8), 119 (100), 114 (30.3), 105 (24.4), 91 (46.4), 43 (50.7). ^{1}H-NMR (200 MHz, $CDCl_3$): δ= 7.38 (d, J= 7.8, 2.0, 2H), 7.17 (d, J= 7.8, 2.0, 2H), 5.50 (s, 1H), 4.30 (dd, J= 11.4, 4.9, 1H), 4.18-4.10 (m, 3H), 3.98 (dt, J= 11.8, 2.1, 1H), 2.34 (s, 3H), 2.09 (s, 3H), 1.89 (m, 1H), 1.52 (m, 1H). ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ= 170.9 (s), 138.6 (s), 135.5 (s), 128.8 (d), 126.0 (d), 101.3 (d), 74.7 (d), 66.6 (t), 66.5 (t), 27.5 (t), 21.2 (q), 20.8 (q).

(R,R)-4-Hydroxymethyl-2-(4-isopropylphenyl)-1,3-dioxane [(-)-4a]. (34% ee). $[\alpha]_D$= -4.0 ($CHCl_3$, c= 1.51). MS: m/e= 236 (50.4), 205 (63.1), 193 (35.0), 149 (51.2), 148 (20.3), 147 (44.9), 133 (68.9), 105 (100), 91 (45.9), 79 (54.9), 77 (49.2), 71 (71.3), 57 (48.0), 43 (99.2), 41 (45.1). ^{1}H-NMR (200 MHz, $CDCl_3$): δ= 7.45-7.41 (m, 2H), 7.27-7.23 (m, 2H), 5.54 (s, 1H), 4.31 (ddd, J= 10.1, 5.2, 1.3, 1H), 4.04-3.94 (m, 2H), 3.71-3.63 (m, 2H), 2.92 (m, 1H), 2.00-1.85 (br. s, 1H), 1.94 (m, 1H), 1.49-1.44 (m, 1H), 1.24 (d, J= 6.9, 6H). ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ= 150.3 (s), 136.4 (s), 127.0 (s), 126.9 (2C, d), 126.6 (2C, d), 101.9 (d), 78.0 (d), 67.1 (t), 66.2 (t), 34.5 (d), 27.3 (t), 24.5 (2C, q). Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16%; H, 8.53%. Found: C, 70.60%; H, 9.02.

(S,S)-4-Acetoxymethyl-2-(4-isopropylphenyl)-1,3-dioxane [(+)-4b]. (82% ee). $[\alpha]_D$= +20.9 ($CHCl_3$, c= 0.6). MS: m/e= 278 (74.0), 235 (16.6), 205 (37.0), 164 (21.8) 147 (92.8), 133 48.5), 131 (26.0), 119 (21.3), 114 (75.3), 105 (57.9), 91 (21.3), 43 (100). ^{1}H-NMR (200 MHz, $CDCl_3$): δ= 7.42 (m, 2H), 7.23 (m, 2H), 5.51 (s, 1H), 4.31 (ddd, J= 11.4, 5.1, 1.4, 1H), 4.20-4.11 (m, 3H), 3.98 (dt, J= 2.6, 11.9, 1H), 2.90 (m, 1H), 2.09 (s, 3H), 2.08-1.80 (m, 1H), 1.59-1.49 (m,1H), 1.22 (d, J= 6.9, 6H). ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ= 170.8 (s), 149.6 (s), 135.8 (s), 126.2 (2C, d), 126.0 (2C, d), 101.2 (d), 74.7 (d), 66.5 (t), 66.4 (t), 35.7 (d), 27.4 (t), 23.7 (2C, q), 20.7 (q). Anal. Calcd. for $C_{16}H_{22}O_4$: C, 67.64%; H, 8.33%. Found: C, 68.00%; H, 8.45%.

(R,R)-2-(4-Fluorophenyl)-4-hydroxymethyl-1,3-dioxane [(-)-5a]. (28% ee). $[\alpha]_D$= -3.4 ($CHCl_3$, c= 0.7). MS: m/e= 212 (7.4), 181 (19.3), 125 (33.8), 123 (100), 109 (23.2), 97 (65.0), 95 (67.9), 75 (36.5),

57 (64.2), 43 (39.1). ^{1}H-NMR (200 MHz, $CDCl_3$): δ= 7.52-7.43 (m, 2H), 7.12-7.01 (m, 2H), 5.53 (s, 1H), 4.34-4.26 (m, 1H), 4.11-3.92 (m, 2H), 3.80-3.60 (m, 2H), 2.2-1.7 (broad, 1H), 1.91 (m, 1H), 1.46 (m, 1H). ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ= 163.5 (d, J_{C-F}= 247 Hz), 134.8 (s), 128.5 (2C, dd, J_{C-F}= 8.3 Hz), 115.6 (dd, J_{C-F}= 21.5 Hz), 101.1 (s), 77.7 (d), 67.1 (t), 66.2 (t), 27.2 (t).

(S,S)-4-Acetoxymethyl-2-(4-fluorophenyl)-1,3-dioxane [(+)-5b]. (35% ee). $[\alpha]_D$= +9.7 ($CHCl_3$, c= 1.65). MS: m/e= 254 (15.8), 253 (30.0), 181 (41.7), 125 (29.0), 124 (27.7), 123 (98.7), 114 (70.3), 109 (30.0), 97 (24.0), 95 (25.0), 71 (30.3), 43 (100). ^{1}H-NMR (200 MHz, $CDCl_3$): δ= 7.45 (m, 2H), 7.05 (m, 2H), 5.51 (s, 1H), 4.29 (m, 1H), 4.22-4.08 (m, 3H), 3.97 (dt, J= 2.5, 12.0, 1H), 2.09 (s, 3H), 1.88 (m, 1H), 1.58 (m, 1H). ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ= 171.5 (s), 163.5 (d, J_{C-F}= 247 Hz), 134.7 (d, J_{C-F}= 2.9 Hz), 128.5 (2C, dd, J_{C-F}= 8.5 Hz), 115.6 (dd, J_{C-F}= 21.5 Hz), 101.0 (s), 75.3 (d), 67.0 (2C, t), 27.9 (t), 21.4 (q).

(R,R)-4-Hydroxymethyl-2-(4-methoxyphenyl)-1,3-dioxane [(-)-6a]. (>98% ee). $[\alpha]_D$= -10.3 ($CHCl_3$, c= 1.45). MS: m/e= 224 (17.6), 223 (27.3), 193 (27.6), 135 (100), 109 (22.4), 108 (23.8), 77 (45.1), 71 (48.6), 57 (46.5), 55 (30.5), 43 (71.5), 41 (55.2). ^{1}H-NMR (200 MHz, acetone-d_6): δ= 7.39 (m, 2H), 6.90 (m, 2H), 5.49 (s, 1H), 4.25-3.90 (m, 3H), 3.79 (s, 3H), 3.59 (m, 2H), 2.86 (s, 1H), 1.78-1.69 (m, 1H), 1.57 (m, 1H). ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ= 160.5 (s), 131.3 (s), 127.8 (2C, d), 114.0 (2C, d), 101.5 (s), 77.8 (d), 66.8 (t), 66.0 (t), 55.6 (q), 27.0 (t).

(S,S)-4-Acetoxymethyl-2-(4-methoxyphenyl)-1,3-dioxane [(+)-6b]. (90% ee). $[\alpha]_D$= +25.1 ($CHCl_3$, c= 0.77). MS: m/e= 266 (17.2), 265 (20.0), 193 (26.3), 152 (21.0), 135 (100), 43 (64.7). ^{1}H-NMR (200 MHz, $CDCl_3$): δ= 7.42 (m, 2H), 6.90 (m, 2H), 5.49 (s, 1H), 4.30 (dd, J= 11.5, 4.0, 1H), 4.20-4.08 (m, 3H), 3.97 (dt, J= 2.5, 11.8, 1H), 3.80 (s, 3H), 2.09 (s, 3H), 1.89 (m, 1H), 1.51 (m, 1H).^{13}C-NMR (50.3 MHz, $CDCl_3$): δ= 171.3 (s), 160.4 (s), 131.2 (s), 127.8 (2C, d), 113.9 (2C, d), 101.4 (d), 75.0 (d), 66.9 (t), 66.8 (t), 55.5 (q), 27.7 (t), 21.1 (q). Anal. Calcd. for $C_{14}H_{18}O_5$: C, 63.14%; H, 6.81%. Found: C, 63.30%; H, 7.21%.

Determination of the enantiomeric excess of (R,R)-4-hydroxymethyl-2-phenyl-1,3-dioxane [(-)-2a]. A typical procedure is as follows. A mixture of 4.4 mg of enantiomerically enriched **(-)-2a** (of 61% ee, from the reaction reported in entry 4, **Table 4**) and 13.6 mg (0.5 moleq) of Eu(hfc)$_3$ was dissolved in *ca.* 0.6 ml of $CDCl_3$. After 15-20 minutes, a ^{1}H-NMR spectrum was taken, showing peaks (1:4.13 ratio) at 7.095 ppm (for the minor diastereoisomer) and at 7.047 ppm (for the main diastereoisomer) for the acetalic protons.

Determination of the enantiomeric excess of (S,S)-4-acetoxymethyl-2-phenyl-1,3-dioxane [(+)-2b]. A typical procedure is as follows. A mixture of 8.8 mg of enantiomerically enriched **(+)-2** (of 78% ee, from the reaction reported in entry 4, **Table 4**) and 17.9 mg (0.4 moleq) of Eu(hfc)$_3$ was dissolved in *ca.* 0.6 ml of $CDCl_3$. After 15-20 minutes, a ^{1}H-NMR spectrum was taken, showing peaks (8.09:1 ratio) at 3.790 ppm (for the main diastereoisomer) and at 3.730 ppm (for the minor diastereoisomer) for the methyl groups.

Determination of the enantiomeric excess of (R,R)-4-hydroxymethyl-2-(4-methylphenyl)-1,3-dioxane [(-)-3a]. A typical procedure is as follows. A mixture of 3.0 mg of enantiomerically enriched **(-)-3a** (of 80% ee, from the reaction reported in entry 3, **Table 5**) and 6.7 mg (0.4 moleq) of Eu(hfc)$_3$ was dissolved in *ca.* 0.6 ml of $CDCl_3$. After 15-20 minutes, a ^{1}H-NMR spectrum was taken, showing peaks (1:8.63 ratio) at 6.445 ppm (for the minor diastereoisomer) and at 6.412 ppm (for the main diastereoisomer) for the acetalic protons.

Determination of the enantiomeric excess of (S,S)-4-acetoxymethyl-2-(4-methyphenyl)-1,3-dioxane [(+)-3b]. A typical procedure is as follows. A mixture of 3.3 mg of enantiomerically enriched **(+)-3b** (of 81% ee, from the reaction reported in entry 3, **Table 5**) and 6.2 mg (0.4 moleq) of $Eu(hfc)_3$ was dissolved in *ca.* 0.6 ml of $CDCl_3$. After 15-20 minutes, a ^{1}H-NMR spectrum was taken, showing peaks (9.31:1 ratio) at 3.309 ppm (for the main diastereoisomer) and at 3.265 ppm (for the minor diastereoisomer) for the methyl of the acetyl groups.

Determination of the enantiomeric excess of (R,R)-4-hydroxymethyl-2-(4-isopropylphenyl)-1,3-dioxane [(-)-4a]. A typical procedure is as follows. A mixture of 2.63 mg of enantiomerically enriched **(-)-4a** (of 34% ee, from the reaction reported in entry 5, **Table 5**) and 6.1 mg (0.45 moleq) of $Eu(hfc)_3$ was dissolved in *ca.* 0.6 ml of $CDCl_3$. After 15-20 minutes, a ^{1}H-NMR spectrum was taken, showing peaks (1:2.03 ratio) at 6.436 ppm (for the minor diastereoisomer) and at 6.407 ppm (for the main diastereoisomer) for the acetalic protons.

Determination of the enantiomeric excess of (S,S)-4-acetoxymethyl-2-(4-isopropylphenyl)-1,3-dioxane [(+)-4b]. A typical procedure is as follows. A mixture of 3.94 mg of enantiomerically enriched **(+)-4b** (of 82% ee, from the reaction reported in entry 5, **Table 5**) and 5.11 mg (0.3 moleq) of $Eu(hfc)_3$ was dissolved in *ca.* 0.6 ml of $CDCl_3$. After 15-20 minutes, a ^{1}H-NMR spectrum was taken, showing peaks (10.07:1 ratio) at 2.843 ppm (for the main diastereoisomer) and at 2.814 ppm (for the minor diastereoisomer) for the methyl of the acetyl groups.

Determination of the enantiomeric excess of (R,R)-2-(4-fluorophenyl)-4-hydroxymethyl-1,3-dioxane [(-)-5a]. A typical procedure is as follows. A mixture of 3.13 mg of enantiomerically enriched **(-)-5a** (of 72% ee, from the reaction reported in entry 6, **Table 5**) and 8.81 mg (0.5 moleq) of $Eu(hfc)_3$ was dissolved in *ca.* 0.6 ml of $CDCl_3$. After 15-20 minutes, a ^{1}H-NMR spectrum was taken, showing peaks (1:6.13 ratio) at 6.890 ppm (for the minor diastereoisomer) and at 6.850 ppm (for the main diastereoisomer) for the acetalic protons.

Determination of the enantiomeric excess of (S,S)-4-acetoxymethyl-2-(4-fluorophenyl)-1,3-dioxane [(+)-5b]. A typical procedure is as follows. A mixture of 4.18 mg of enantiomerically enriched **(+)-5b** (of 83% ee, from the reaction reported in entry 6, **Table 5**) and 9.57 mg (0.5 moleq) of $Eu(hfc)_3$ was dissolved in *ca.* 0.6 ml of $CDCl_3$. After 15-20 minutes, a ^{1}H-NMR spectrum was taken, showing peaks (10.9:1 ratio) at 3.588 ppm (for the main diastereoisomer) and at 3.534 ppm (for the minor diastereoisomer) for the methyl groups.

Determination of the enantiomeric excess of (R,R)-4-hydroxymethyl-2-(4-methoxyphenyl)-1,3-dioxane [(-)-6a]. A typical procedure is as follows. A mixture of 3.6 mg of enantiomerically enriched **(-)-6a** (of 76% ee, from the reaction reported in entry 16, **Table 5**) and 10.6 mg (0.55 moleq) of $Eu(hfc)_3$ was dissolved in *ca.* 0.6 ml of $CDCl_3$. After 15-20 minutes, a ^{1}H-NMR spectrum was taken, showing peaks (1:7.23 ratio) at 7.053 ppm (for the minor diastereoisomer) and at 7.003 ppm (for the main diastereoisomer) for the acetalic protons.

Determination of the enantiomeric excess of (S,S)-4-acetoxymethyl-2-(4-methoxyphenyl)-1,3-dioxane [(+)-6b]. A typical procedure is as follows. A mixture of 1.4 mg of enantiomerically enriched **(+)-6b** (of 84% ee, from the reaction reported in entry 16, **Table 5**) and 9.57 mg (0.5 moleq) of $Eu(hfc)_3$ was dissolved in *ca.* 0.6 ml of $CDCl_3$. After 15-20 minutes, a ^{1}H-NMR spectrum was taken, showing peaks

(10.95:1 ratio) at 2.982 ppm (for the main diastereoisomer) and at 2.949 ppm (for the minor diastereoisomer) for the methyl of the acetyl groups.

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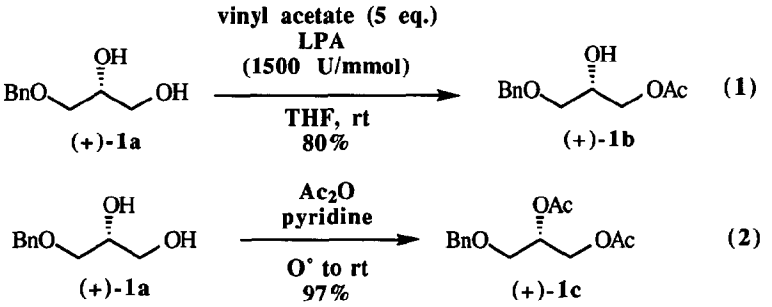
24) This ratio was determined by ^{1}H-NMR analysis of the crude material. The products were not isolated.

25) The absolute configuration of the reaction products have been determined by correlation with the known (R)-1-O-benzylpropane-1,2,3-triol [**(+)-1a**].[15] Thus, **(+)-1a** have been converted into **(+)-1b** and **(+)-1c** as indicated in equations 1 and 2.



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34) These acetals have been synthesized in multigram scale (>25 g, 60-85% yield, >98% diastereoselectivity, >90% regioselectivity) through the reaction of the racemic triol and the corresponding aldehydes [or dimetyl acetal of p-anisaldehyde for the preparation of (±)-**6a**] catalyzed by p-toluenesulfonic acid in refluxing toluene under a soxhlet charged with molecular sieves. We have found that using molecular sieves for removing water is more efficient than the Dean-Stark device in terms of higher yields and selectivity, as well as faster reactions and reproducibility when the reaction is scaled-up. For an example, see: Herradón, B.; Seebach, D. *Helv. Chim. Acta* **1989**, 72, 690-711. Currently, we are preparing a full account on the scope of the method: Herradón, B.; Cueto, S.; Valverde, S. manuscript in preparation.

35) The absolute configuration have been established by comparison with compouds prepared from (S)-malic acid.

36) We are currently studying the properties on this "immobilized" lipase.

37) Most likely acetic acid is formed from vinyl acetate, although the hydrolysis of **2b** can not be ruled out.

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