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Tetrahedron: *Asymmetry* 17 (2006) 2220–2234
Tetrahedron: Asymmetry

Kinetic and chemical resolution of different 1-phenyl-2-propanol derivatives

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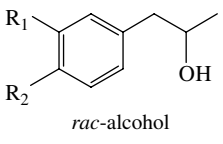
Received 20 June 2006; accepted 17 July 2006

Abstract—Seven chiral target molecules containing a hydroxy group have been resolved by both biocatalytic and chemical means. The lipase-catalyzed acylation mainly yielded the acylated derivative of the (*R*)-alcohols with moderate enantiomeric excess and the enantiopure (*S*)-alcohols. In the course of the chemical resolution, first the dicarboxylic acid monoesters of the target molecules were synthesized and the resolution of these monoesters was attempted by different homochiral bases. By re-resolution and/or optimization of the reaction time and/or recrystallization, respectively, each molecule was produced in very high enantiomeric purity.

1. Introduction

Benzodiazepines explain their therapeutically effect (anxiolitic, sedatohipnotic, anticonvulsive and muscle relaxant) on the benzodiazepine binding site of the $GABA_A$ receptor: they enhance the GABA-erg neurotransmission in the central nervous system. Herein we report the kinetic and chemical resolution of seven compounds (Scheme 1: 1-phenyl-2-propanol **1**, 1-benzo[1,3]dioxol-5-yl-2-propanol **2**, 1-(3-chloro-phenyl)-2-propanol **3**, 1-(4-chloro-phenyl)-2-propanol **4**, 1-(3,4-dichloro-phenyl)-2-propanol **5**, 1-(4-fluoro-phenyl)-2-propanol **6**, 1-(3-bromo-4-methoxy-phenyl)-2-propanol **7**) as starting materials for new derivatives of benzodiazepines, which are chiral structures, thus their enantiomers are of interest.



rac-alcohol

racemic alkohol	R_1	R_2
rac-**1**	H	H
rac-**2**	benzo[1.3]dioxole	
rac-**3**	Cl	H
rac-**4**	H	Cl
rac-**5**	Cl	Cl
rac-**6**	H	F
rac-**7**	Br	CH_3O

Scheme 1. The target molecules.

Enantiomerically pure compounds can be obtained by classical resolution techniques via diastereoisomers,[1] enantioselective reduction of the corresponding ketones by chiral hydride donors,[2] micro-organisms[3] or oxidoreductases,[4] or by enantioselective hydrolases of the corresponding esters using hydrolases or micro-organisms.[5] The tremendous potential of enzymes as practical catalysts is well recognized.[6,7] In particular, they are being increasingly exploited for asymmetric synthetic transformation,[8] fuelled by the growing demand for enantiopure pharmaceuticals.[9] Today, kinetic resolution of racemic substrates by enzyme catalysis has become a standard reaction in organic synthesis.[7,10] Enzymes, especially lipases,[11,12] have some advantages for use in stereoselective transformations since they are highly selective, environmentally friendly and easy to work with.

Resolution via diastereoisomeric salt formation is usually based on the separation of diastereoisomers by fractional crystallization.[2] When a racemate contains a basic or an acidic group, its resolution can generally be accomplished by diastereoisomeric salt formation as among the large number of basic or acidic resolution agents at least one effective resolution agent can be found.[1,13] Resolution of

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doi:10.1016/j.tetasy.2006.07.019

alcohols is more complicated. One can attempt to prepare an acidic or basic derivative and seek a salt forming resolving agent. The separated and purified enantiomers can be then converted back to the starting molecule.

There are several reports on the lipase-catalyzed resolution of the racemic 1-phenyl-2-propanol *rac*-**1** and successful resolution procedures of this alcohol by kinetic reaction have been described.[14–18] We found only some reports available for the preparation of the enantiomers of 1-phenyl-2-propanol derivatives,[19–27] but no paper on the chemical resolution has been found in the literature. Racemic **1** is commercially available, and compounds **2**, **3**, **4**, **5**, **6** and **7** are available by the reduction of the corresponding propanones (1-benzo[1,3]dioxol-5-yl-2-propanone, 1-(3-chloro-phenyl)-2-propanone, 1-(4-chloro-phenyl)-2-propanone, 1-(3,4-chloro-phenyl)-2-propanone, 1-(4-fluoro-phenyl)-2-propanone and 1-(3-bromo-4-methoxy-phenyl)-2-propanone, respectively). Except for compounds **1** and **2**, no biocatalytic resolution has been reported, although it can be a highly selective, easily manageable, economical and environmentally friendly method. In addition, they have not been found to be resolved by chemical means, which can be very useful in the pharmaceutical practice. Herein we report on their lipase-catalyzed acylation and resolution via diastereoisomeric salt formation.

2. Results and discussion

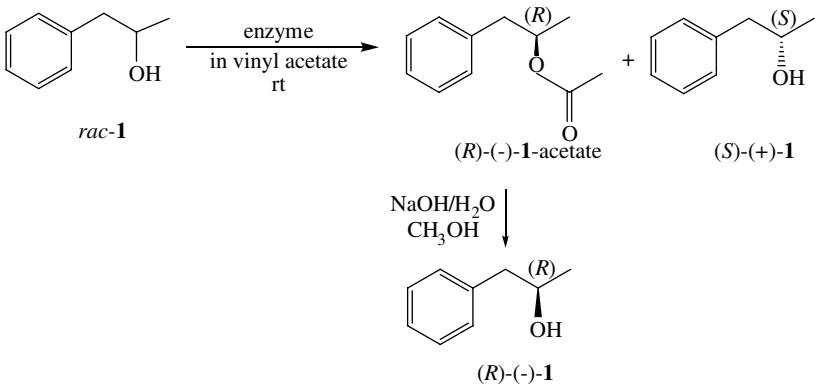
In the course of the investigation of the resolution by biocatalytic method first, for **1**, several enzymes were tested in vinyl acetate. The results are shown in Table 1.

In all cases the (*R*)-enantiomer was preferentially acylated, and a mixture of the unreacted (*S*)-alcohol and the (*R*)-acetate was obtained. As it can be seen in Table 1, high enantiomer separation was obtained by Amano AK, Amano PS-C, PfL and Novozym 435. Further investigations were elaborated with Amano PS-C enzyme: the effect of different solvents and acylating agent on the separation of the enantiomers was examined. The solvents were hexane and tetrahydrofuran, the acylating agents were vinyl propionate and vinyl butyrate. The results are summarized in Table 2.

As it can be seen in Table 2, enantiomer separation was not improved when other solvents and acylating agent were employed.

Amano PS-C enzyme preparation has been found to be appropriate for the other compounds, therefore, further investigations were elaborated in vinyl acetate with this enzyme. The results are shown in Table 3. As it can be seen in Table 3, moderate enantiomer separation was obtained with compounds **2**–**7** by Amano PS-C.

Table 1. Enzymatic acetylation of **1**: screening with six commercially available enzyme preparations



rac-**1** (*R*)-(-)-**1**-acetate (*S*)-(+)-**1** (*R*)-(-)-**1**

Enzyme name (mg)	Time (h)	Hydrolyzed alcohol (*R*)-(−)-**1**		Remaining alcohol (*S*)-(+)-**1**		
		Y [%]	ee[b] (%)	*Y* (%)	ee[b] (%)	*E*[c]
Amano AK[a] (20)	68	85	97	104	81	>100
Amano PS[a] (20)	191	92	82	97	77	23
Amano PS-C[a] (20)	48	97	93	92	>99	>100
PfL[a] (20)	68	81	>99	108	41	>100
Novozym 435[a] (100)	3	79	>99	110	85	>100
CrL[a] (100)	191	46	64	142	19	5

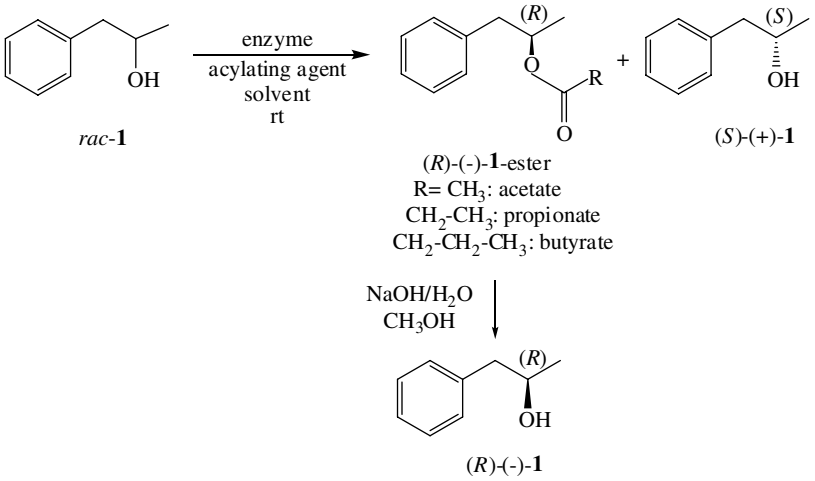
[a] Amano AK: lipase AK from *Pseudomonas fluorescens*; Amano PS: lipase from *Burkholderia cepacia*; Amano PS-C: lipase from *Burkholderia cepacia* immobilized on ceramic particles (>1000 U/g);[1] PfL: lipase from *Pseudomonas fluorescens*; Novozym 435: lipase B from *Candida antarctica* immobilized on acrylic resin; CrL: lipase from *Candida rugosa (cylindracea)*.

[b] The enantiomeric excess of the alcohol was determined by GC.

[c] $E = \frac{\ln[(1-c)(1-ee_S)]}{\ln[(1-c)(1+ee_S)]}, \quad c = \frac{ee_S}{ee_S + ee_P}.$

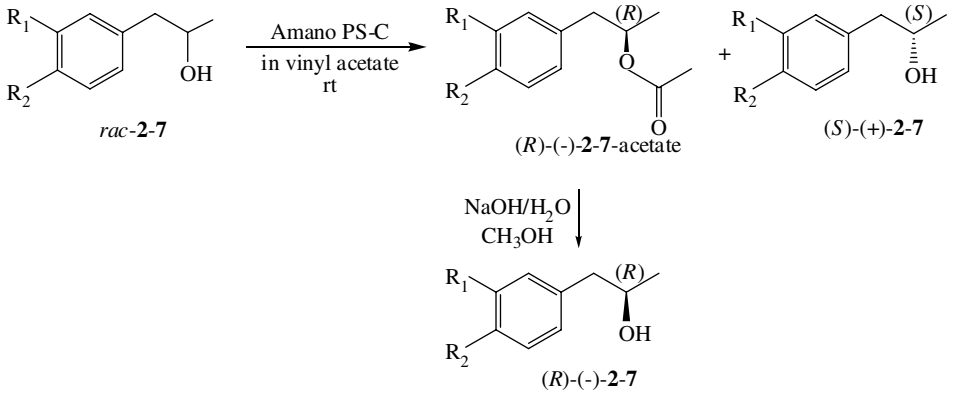
ee_S = enantiomeric excess of substrate, ee_P = enantiomeric excess of product.

Table 2. Enzymatic acylation of **1** with various solvents and acylating agent



Compound	Time (h)	Acylating agent/solvent	Hydrolyzed alcohol (*R*)-(−)-**1**		Remaining alcohol (*S*)-(+)-**1**		
			Y (%)	ee (%)	*Y* (%)	ee (%)	*E*
1	48	Vinyl acetate/hexane	89	96	97	>99	>100
	48	Vinyl acetate/THF	91	97	101	96	>100
	48	Vinyl propionate/hexane	98	97	91	>99	>100
	48	Vinyl butyrate/hexane	97	98	93	>99	>100

Table 3. Enzymatic acetylation of **2**–**7**



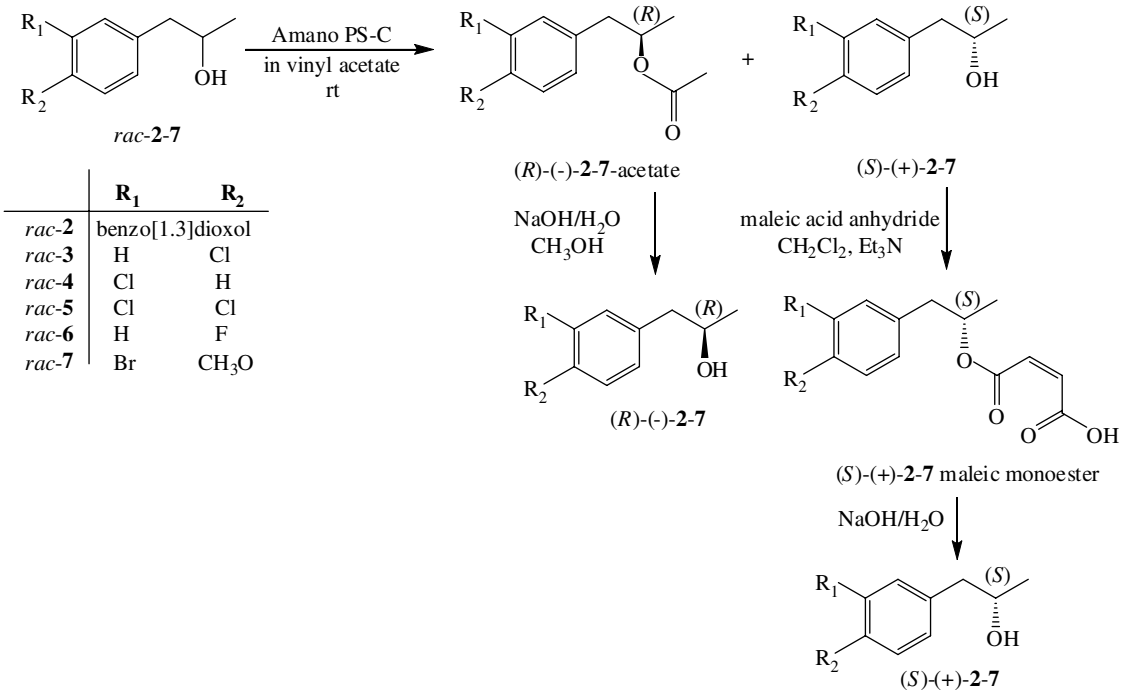
Compound	Time (h)	Hydrolyzed alcohol (*R*)-(−)-**2**–**7**		Remaining alcohol (*S*)-(+)-**2**–**7**		
		Y (%)	ee[a] (%)	*Y* (%)	ee[a] (%)	*E*
2	18	81	86	106	89	40
3	32	90	85	89	92	40
4	48	99	84	94	85	31
5	48	105	62	80	89	12
6	13	95	53	70	99	15
7	48	74	93	15	111	65

[a] The enantiomeric excess of the **2**–**6** alcohols was determined by GC. The enantiomeric excess of **7** alcohol was determined by polarimeter, the specific rotation of the pure enantiomer: $[\alpha]_D^{25} = +32.2$ (*c* 2, chloroform).

2.1. Enantiopure substances

The enantiomers of compounds **2**–**7** could be obtained by Amano PS-C enzyme preparation in vinyl acetate with optimization of the reaction time. The work-up method was also changed, as described below (Scheme 2).

Compounds (*S*)-(+)-**2**–**7** were obtained with 100% enantiomeric excess by preparing the maleic acid monoester of the residual alcohol from the enzymatic reaction. Hydrolysis of the acetate gave (*R*)-(−)-**2**–**7** with high overall yield but its enantiomeric purity is not so high. The results are shown in Table 4.



	R_1	R_2
rac-**2**	benzo[1.3]dioxol	
rac-**3**	H	Cl
rac-**4**	Cl	H
rac-**5**	Cl	Cl
rac-**6**	H	F
rac-**7**	Br	CH_3O

Scheme 2. Resolution of (*S*)- and (*R*)-**2**–**7**.

Table 4. Enzymatic acetylation of racemic **2**–**7** by Amano PS-C with optimization

Compound	Time (h)	(*R*)-(−)-Enantiomer			(*S*)-(+)-Enantiomer			
		Acetate	Alcohol		Maleic acid monoester	(*S*)-(+)-Alcohol		
		Y (%)	*Y* (%)	ee (%)	*Y* (%)	*Y* (%)	ee (%)	*E*
2	6	97	92	82	90	81	100	52
3	36	120	116	58	75	67	100	18
4	48	155	147	28	43	39	100	7
5	30	110	107	65	78	69	100	23
6	15	119	96	64	79	59	100	22
7	30	115	113	64	79	68	100	22

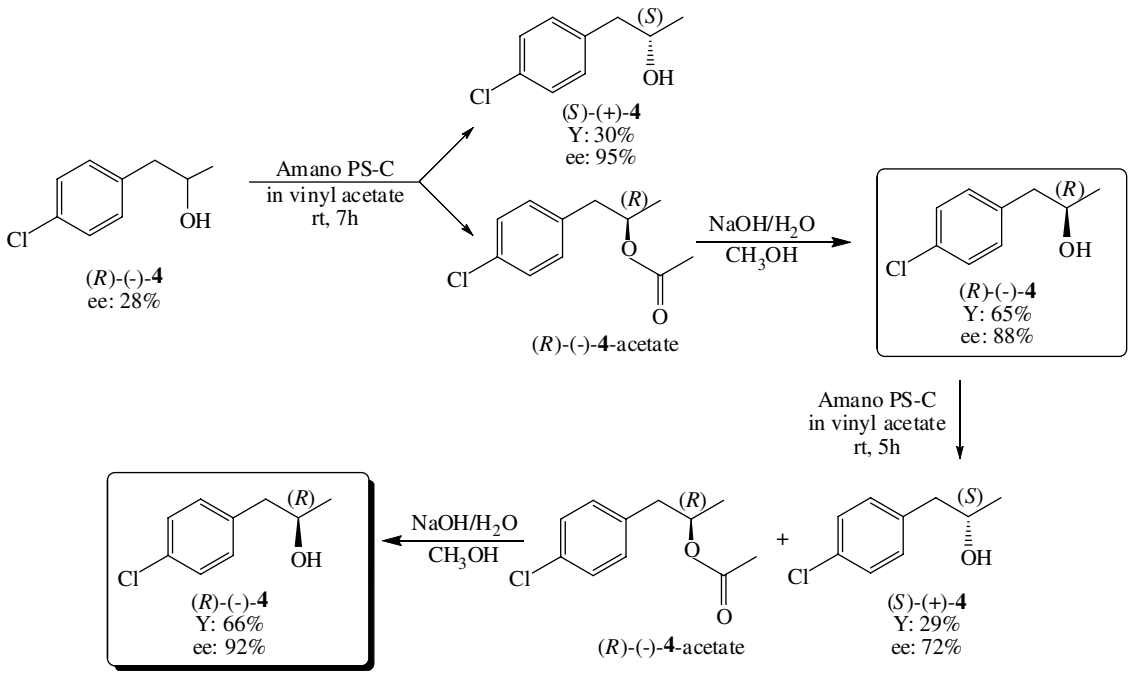
Compounds (*R*)-(−)-**2**–**7** were obtained by the Amano PS-C catalyzed acetylation from the acetate fraction with moderate enantiomeric excess and high overall yield. The remaining alcohols were converted into maleic acid monoesters and their hydrolysis yielded pure (*S*)-(+)-**2**–**7**.

The enantiopure (*S*)-(+)-alcohols were obtained by the Amano PS-C catalyzed acetylation with optimization of the reaction time, but very high enantiomeric excess could also be obtained by lipase-catalyzed re-resolution.

Compound (*R*)-(−)-**4** was obtained by Amano PS-C catalyzed acetylation from the acetate fraction. It was subjected to acetylation by Amano PS-C again, yielding (*R*)-(−)-**4** with moderate yield and 92% enantiomeric excess (Scheme 3).

Table 5. Lipase-catalyzed re-resolution of (*R*)-(−)-alcohol

Initial alcohol [ee (%)]	Enzyme/acylating agent	Time (h)	(*S*)-(+)-Alcohol		(*R*)-(−)-Enantiomer		
					Acetate	Alcohol	
			Y (%)	ee (%)	*Y* (%)	*Y* (%)	ee (%)
(*R*)-(−)-**5** [28]	0.4 × Amano PS-C/4 × vinyl acetate	7	30	95	68	65	88
(*R*)-(−)-**5** [88]	0.2 × Amano PS-C/4 × vinyl acetate	1.5	28	72	67	66	92
(*R*)-(−)-**7** [57]	0.05 × Novozym 435/3 × vinyl acetate	11	20	86	78	76	96.5
(*R*)-(−)-**7** [96.5]	0.02 × Novozym 435/3 × vinyl acetate	6	31	92	66	61	97.2
(*R*)-(−)-**7** [97.2]	0.1 × Novozym 435/3 × vinyl acetate	1.5	30	86	68	63	99



Scheme 3. Re-resolution of (*R*)-(−)-**4**.

Racemic **7** was acetylated by Amano PS-C, affording (*S*)-(+)-**7**- and (*R*)-(−)-**7**-acetates, both of moderate enantiomeric purity. (*R*)-(−)-**7**-Acetate was then hydrolyzed, yielding (*R*)-(−)-**7**. Afterwards it was purified by repeated lipase-catalyzed re-resolution with Novozym 435, yielding (*R*)-(−)-**7** with 99.2% enantiomeric excess (Scheme 4).

In the course of the investigation of the resolution by chemical means, some dicarboxylic acid monoesters of the target molecules were synthesized (Scheme 5). The maleic acid monoesters, succinic acid monoesters and phthalic acid monoesters were prepared at 83–99% yield.

Resolution of these monoesters was attempted by different homochiral bases (Table 6). Successful separation was obtained with the maleic acid, succinic acid and phthalic acid monoesters resolved by (*S*)-(−)- and (*R*)-(+)-phenylethylamine **26** and **27**, (+)-dehydroabiethylamine **28**, quinine **29**, (*R*,*R*)-(−)-1-(4-nitro-phenyl)-2-amino-1,3-propanediol **30** and (*S*)-(+)-benzyl-aminobutanol **31** in different solvents and solvent mixtures.

The maleic acid monoesters were successfully resolved by (*S*)-(−)-phenylethylamine **26**, (*R*)-(+)-phenylethylamine **27** and (+)-dehydroabiethylamine **28** too. The results are summarized in Table 7. As it can be seen in Table 7, during the resolution of *rac*-**8** by (*S*)-(−)-phenylethylamine **26**, the more stable diastereoisomeric salt was formed with the (*S*)-enantiomer. It was recrystallized twice from ethyl acetate, and after salt splitting followed by hydrolysis, (*S*)-**2** was obtained at moderate overall yield but with very high enantiomeric excess. Good results were obtained by (+)-dehydroabiethylamine **28** without recrystallization.

The succinic acid monoesters were successfully resolved by (*R*)-(+)-phenylethylamine **27** (+)-dehydroabiethylamine **28**, and quinine **29**. The results are summarized in Table 8.

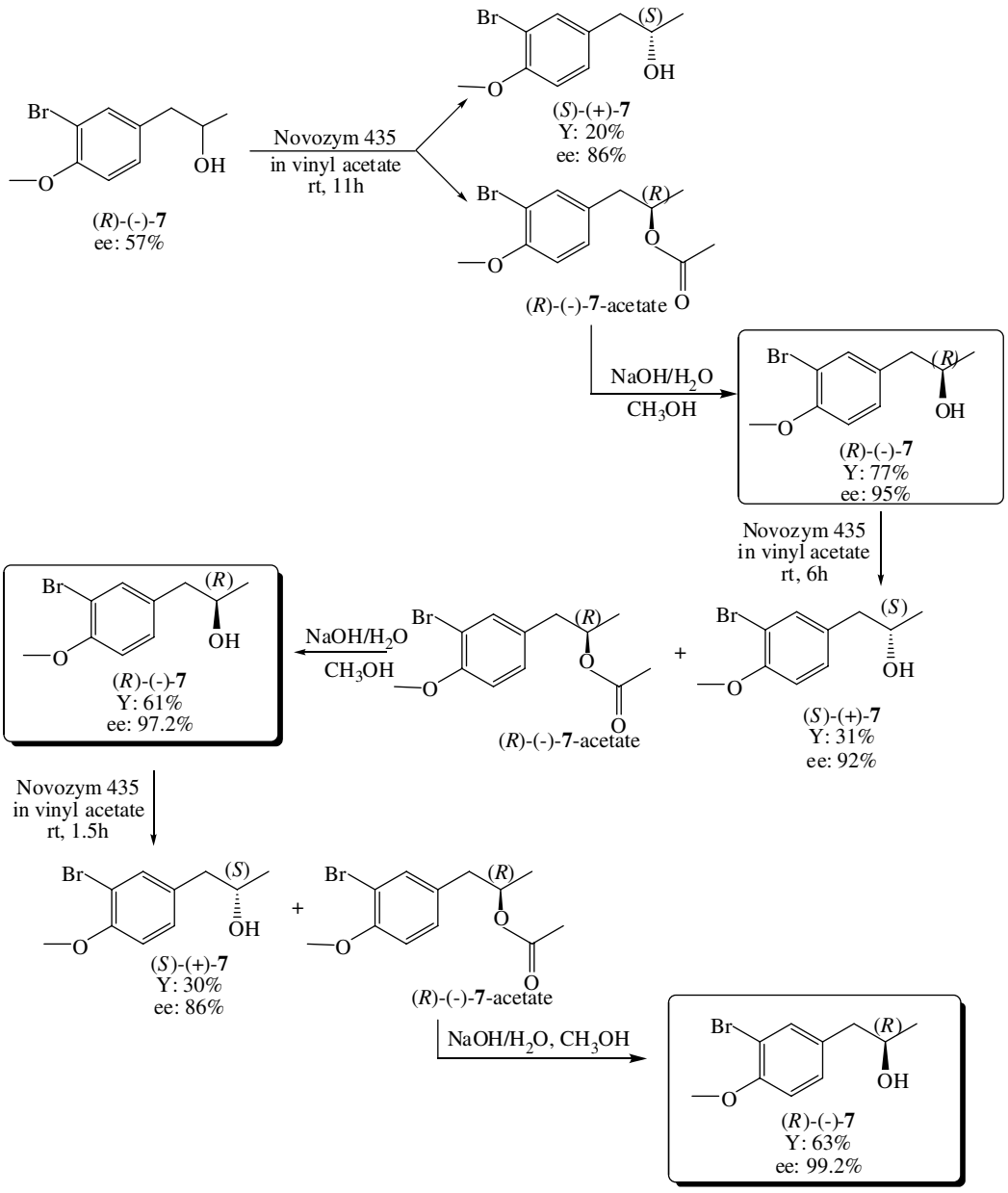
Compounds (*S*)-**4**, (*R*)-**5** and (*S*)-**7** were obtained after salt splitting followed by hydrolysis with quite moderate enantiomeric excesses.

The phthalic acid monoesters were successfully resolved by (*S*)-(−)-phenylethylamine **26**, (*R*,*R*)-(−)-1-(4-nitro-phenyl)-2-amino-1,3-propanediol **30** and (*S*)-(+)-benzyl-aminobutanol **31**. The results are summarized in Table 9.

Compounds (*S*)-**4**, (*S*)-**5** and (*R*)-**7** were obtained after salt splitting followed by hydrolysis also with low enantiomeric excess. Nevertheless, during the resolution of *rac*-**25** by (*S*)-(+)-benzyl-aminobutanol **31**, (*S*)-**7** was obtained from the mother liquor with 70% enantiomeric excess and moderate overall yield.

Enantiomeric enrichment can be accomplished by re-resolution of the enantiomers or recrystallization of the diasteroisomeric salts. We evaluated the re-resolution of the alcohol enantiomers. First, the required (*S*)- and (*R*)-monoesters were prepared from the (*S*)- and (*R*)-alcohols, and these monoesters were resolved by the same resolving agent as described above. The results are summarized in Table 10.

As it can be seen in Table 10, for re-resolving (−)-**8** by (*R*)-(+)-phenylethylamine **27**, the diastereoisomeric salt was recrystallized twice from ethyl acetate and after salt splitting followed by hydrolysis, (−)-**2** was obtained with very good enantiomeric excess but quite moderate overall yield. Good re-resolution results were achieved for (−)-**11** with both (*R*)-(+)-phenylethylamine **27** and (+)-dehydroabiethylamine **28** as resolving agents. The diastereoisomeric salt

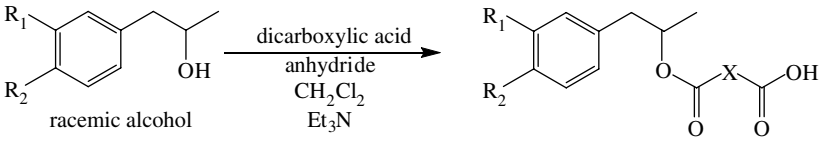


Scheme 4. Re-resolution of (*R*)-(−)-**7**.

was recrystallized from methanol in case of (*R*)-(+)-phenylethylamine **27** as a resolving agent, and after salt splitting and hydrolysis, (−)-**3** was obtained with moderate enantiomeric excess. In case of dehydroabiethylamine **28** as a resolving agent, the diastereoisomeric salt was recrystallized twice from acetone. After salt splitting followed by hydrolysis, (−)-**3** was obtained with very good enantiomeric excess. In both cases, the overall yield was rather low. Compound (−)-**15** with moderate enantiomeric excess was re-resolved with (*S*)-(−)-phenylethylamine **26**. The diastereoisomeric salt was recrystallized twice from acetone and after salt splitting followed by hydrolysis, (−)-**4** was obtained with 100% enantiomeric excess and moderate overall yield. In case of re-resolution of (+)-**4**, (−)-**5** and (−)-**7**, we found the alcohol enantiomers were obtained with 88% enantiomeric excesses.

Enantiomeric enrichment can also be accomplished by recrystallization of the monoester or alcohol enantiomers. This can only be considered when the alcohol or the monoester is solid. We examined the recrystallization of the monoester and alcohol enantiomers, and the results are summarized in Table 11.

During the recrystallization of (−)-**8** from toluene, the (−)-alcohol was prepared from the mother liquor. Compound (−)-**5** was recrystallized three times, once from hexane and twice from a mixture of hexane and toluene, and the (−)-alcohol was obtained with 100% enantiomeric excess from the crystalline phase. Compounds (−)-**7** and (+)-**7** were also recrystallized from a mixture of hexane and toluene. In case of (−)-**7**, the enantiopure alcohol was prepared from the mother liquid. Furthermore, (+)-**7**



R_1	R_2	racemic alcohol	X = CH=CH	X = CH_2-CH_2	X = C_6H_4
benzo[1.3]dioxole		*rac*-**2**	*rac*-**8**	*rac*-**9**	*rac*-**10**
Cl	H	*rac*-**3**	*rac*-**11**	*rac*-**12**	*rac*-**13**
H	Cl	*rac*-**4**	*rac*-**14**	*rac*-**15**	*rac*-**16**
Cl	Cl	*rac*-**5**	*rac*-**17**	*rac*-**18**	*rac*-**19**
F	H	*rac*-**6**	*rac*-**20**	*rac*-**21**	*rac*-**22**
Br	CH_3O	*rac*-**7**	*rac*-**23**	*rac*-**24**	*rac*-**25**

Scheme 5. Monoesters of the 1-phenyl-2-propanol derivatives.

Table 6. Chiral bases as resolving agents

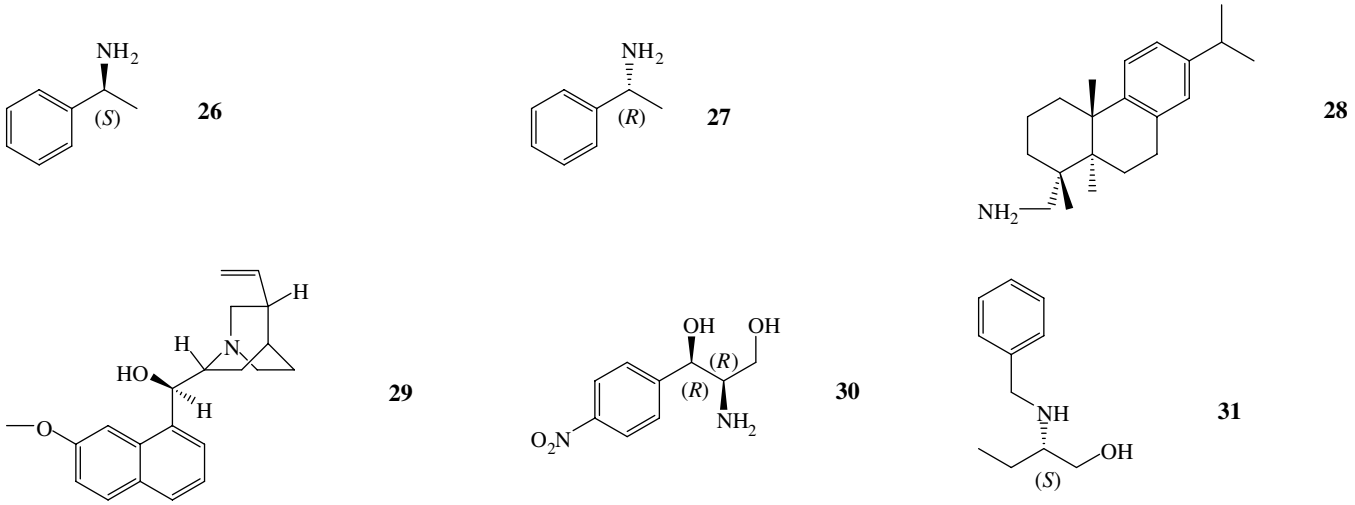


Table 7. Resolution of maleic acid monoesters

Racemate	Resolving agent	Solvent	Diastereoisomeric salt				Mother liquor		
			Config.	*Y* (%)	ee (%)	S	Config.	*Y* (%)	ee (%)
rac-**8**	0.60 × **26**	1.4 × Ethyl acetate	(*S*)	48	98	0.47	(*R*)	117	48
rac-**8**	0.65 × **28**	3 × Ethyl acetate	(*R*)	55	72	0.40	(*S*)	73	67
rac-**11**	0.75 × **28**	5 × Ethyl acetate 0.25 × Ethyl acetate	(*R*)	47	80	0.38	(*S*)	66	59
rac-**11**	0.65 × **27**	0.25 × Acetone 4.5 × Diisopropyl-ether	(*R*)	35	31	0.11	(*S*)	135	9
rac-**17**	0.75 × **28**	3 × Ethyl acetate	(*R*)	33	65	0.21	(*S*)	58	35
rac-**17**	0.75 × **27**	2 × Acetone	(*R*)	71	4	0.3	(*S*)	65	4
rac-**23**	0.65 × **28**	2 × Ethyl acetate	(*R*)	45	64	0.29	(*S*)	78	45

was obtained with good enantiomeric excess from the crystal.

3. Conclusion

We can conclude that lipase-catalyzed kinetic resolution is suitable for preparing the homochiral substances at very high enantiomeric purity. Although the use of the lipases is limited by their relatively high price, the excellent enantiomeric purity can compensate for the price of the biocatalyst. Furthermore, lipase-catalyzed kinetic resolution is an easily manageable, economical and environmentally friendly method. The monoester resolution by homochiral bases has also proved itself by being appropriate for each of the racemic alcohols. It was possible to find a working

Table 8. Resolution of succinic acid monoesters

Racemic	Resolving agent	Solvent	Diastereoisomeric salt				Mother liquor		
			Config.	*Y* (%)	ee (%)	S	Config.	*Y* (%)	ee (%)
rac-**15**	1.00 × **27**	2 × Ethyl acetate	(*S*)	48	35	0.17	(*R*)	114	14
rac-**15**	0.75 × **29**	6 × Ethyl acetate	(*S*)	76	12	0.9	(*R*)	64	12
rac-**18**	0.75 × **28**	2 × Ethyl acetate	(*R*)	42	17	0.7	(*S*)	101	11
rac-**24**	1.00 × **27**	1 × Ethyl acetate	(*S*)	11	6	0.1	(*R*)	51	4

Table 9. Resolution of phthalic acid monoesters

Racemic	Resolving agent	Solvent	Diastereoisomeric salt				Mother liquor		
			Config.	*Y* (%)	ee (%)	S	Config.	*Y* (%)	ee (%)
rac-**16**	0.60 × **30**	1 × Ethyl acetate	(*S*)	87	17	0.15	(*R*)	97	15
rac-**19**	0.75 × **27**	4 × Diisopropyl-ether	(*S*)	24	29	0.7	(*R*)	72	25
rac-**25**	0.65 × **27**	2 × Ethyl acetate	(*R*)	87	5	0.4	(*S*)	45	9
rac-**25**	0.65 × **31**	3 × Ethyl acetate	(*R*)	74	31	0.23	(*S*)	39	70

Table 10. Enantiomeric enrichment by re-resolution of the enantiomers

Initial compound [ee_0 (%)]	Resolving agent	Solvent	Diastereoisomeric salt				Mother liquor		
			Config.	*Y* (%)	ee (%)	S	Config.	*Y* (%)	ee (%)
(−)-**8** [48]	0.60 × **27**	1 × Ethyl acetate	(*R*)	24	97	0.23	(*R*)	50	14
(−)-**11** [58]	1.00 × **27**	5 × Diethyl ether	(*R*)	11	74	0.8	(*R*)	61	45
(−)-**11** [58]	1.00 × **28**	5 × Ethyl acetate	(*R*)	18	97	0.17	(*R*)	60	34
(−)-**15** [52]	1.50 × **26**	1 × Acetone	(*R*)	21	100	0.21	(*R*)	59	33
(+)-**15** [96]	1.00 × **27**	5 × Ethyl acetate	(*S*)	62	99	0.61	(*S*)	23	79
(−)-**19** [65]	1.00 × **26**	4 × Diisopropyl-ether	(*R*)	26	88	0.23	(*R*)	46	34
(−)-**23** [64]	1.00 × **28**	1 × Ethyl acetate	(*R*)	25	97	0.24	(*R*)	18	10

Table 11. Purification by recrystallization of the enantiomers

Initial compound [ee_0 (%)]	Solvent	Crystal phase				Mother liquid		
		Config	*Y* (%)	ee (%)	S	Config.	*Y* (%)	ee (%)
(−)-**8** [48]	2 × Toluene	(*R*)	23	14	0.3	(*R*)	66	59
(−)-**5** [61]	1 × Hexane	(*R*)	66	80	0.53	(*R*)	34	27
(−)-**5** [80]	1 × Hexane/1 × toluene	(*R*)	55	98,6	0.54	(*R*)	44	58
(−)-**5** [98.6]	3 × Hexane/1 × toluene	(*R*)	84	100	0.84	(*R*)	7	90
(−)-**7** [57]	2.2 × Hexane/0.8 × toluene	(*R*)	85	76	0.65	(*R*)	13	100
(+)-**7** [86]	2 × Hexane/1 × toluene	(*S*)	73	89	0.65	(*S*)	26	82

monoester/chiral base combination for five racemic alcohols.

4. Experimental

The gas chromatographic measurements were completed on an Agilent 4890D instrument using FID. Separations were achieved on a 30 m × 0.250 mm HP Chiral (20% permethylated β-cyclodextrin) and ALPHA DEX™ 120 chiral stationery phases. The carrier gas was H_2 and injections were made in split mode. Optical rotation values were determined on a Perkin–Elmer 241 polarimeter. Thin-layer chromatography (TLC) was made using Merck Kieselgel 60 F_{254} alumina sheets. Spots were visualized by treatment with 5% ethanolic phosphomolybdic acid solution and heating of the dried plates. Preparative vacuum-chromatography was performed using Merck Kieselgel 60 F_{254}. CrL enzyme was obtained from Sigma. Amano enzymes were courtesy of Amano. Novozym was courtesy of Novo Nordisk. Vinyl acetate, vinyl propionate and vinyl butyrate were products of Fluka. All solvents used were freshly distilled.

4.1. Lipase-catalyzed acylation of racemic 1-phenyl-2-propanol *rac*-1 by various enzymes: general procedure

To a solution of racemic 1-phenyl-2-propanol *rac*-**1** (200 mg) in vinyl acetate (2 mL), enzyme (for amount, see Table 1) was added and the resulting suspension was stirred at room temperature (for reaction time, see Table 1). The reaction was monitored by TLC and was

stopped by filtering out the enzyme. Vinyl acetate was evaporated in vacuum and the residue was separated by preparative vacuum column chromatography (hexane–ethyl acetate = 10:2) to obtain (+)-**1** and (−)-**1**-acetate. The acetate fraction was hydrolyzed with NaOH in water and methanol. For yields and enantiomeric excesses, see Table 1.

4.2. Lipase-catalyzed acylation of racemic 1-phenyl-2-propanol *rac*-1 by Amano PS-C enzyme preparation with various acylating agents in various solvents: general procedure

To a solution of racemic 1-phenyl-2-propanol *rac*-**1** (200 mg) in the chosen solvent (1 mL, for solvents, see Table 2), the chosen enzyme (0.1 × Amano PS-C) and the acylating agent (1 mL, for acylating agents see Table 2) were added, and the resulting suspension was stirred at room temperature. Work-up of the products was carried out as described in the previous section.

For reaction times, yields and enantiomeric composition, see Table 2.

4.3. Lipase-catalyzed acylation of racemic 1-phenyl-2-propanol derivatives *rac*-2–7 by Amano PS-C enzyme preparation: general procedure

To a solution of racemic 1-phenyl-2-propanol derivatives (*rac*-**2**–**7**) (200–250 mg) in vinyl acetate (5×), enzyme (0.1 × for **2** and 0.3× for **3**–**7**) was added and the resulting suspension was stirred at room temperature. Work-up of the products was carried out as described in the previous section.

For reaction times, yields and enantiomeric composition, see Table 3.

4.4. Preparation of enantiopure substances: general procedure

Racemic alcohol and Amano PS-C (0.3× for **2**, **4**, **6** and 0.085× for **3**, **5**, **7**) were dissolved in vinyl acetate (5× for **2**, **4**, **6** and 3× for **3**, **5**, **7**) and the resulting suspension was stirred at room temperature. The reaction was stopped by filtering out the enzyme, then it was washed by vinyl acetate, and vinyl acetate was evaporated in vacuo to obtain a mixture of (*S*)-(+)-alcohol and (*R*)-(−)-acetate.

The mixture of (*S*)-(+)-alcohol and (*R*)-(−)-acetate was dissolved in dichloromethane (2.5–3×), and triethylamine (1.3×) and maleic acid anhydride (1.0–1.2×) were added. The solution was heated and its colour turned into dark brown. It was stirred for 5 min. After cooling to room temperature, it was extracted by 1.5 M HCl solution and water. Then the organic phase was extracted by 1 M Na_2CO_3 solution. The combined aqueous phase was extracted again by dichloromethane. (The aqueous phase contains the sodium salt of the (*S*)-(+)-alcohol maleic acid monoester.) The combined organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford a yellow oil of (*R*)-(−)-acetate.

(*R*)-(−)-Acetate and NaOH (0.3×) were dissolved in water (0.65–1.5×) and methanol (0.7–1×). The mixture was boiled for 5 min and after cooling to room temperature, methanol was evaporated in vacuo. It was extracted by diethyl ether. The combined organic phase was dried over Na_2SO_4 and the solvent was evaporated to yield (*R*)-(−)-alcohol.

The aqueous phase containing the sodium salt of the (*S*)-(+)-alcohol maleic acid monoester was added to 37% HCl and it was extracted by dichloromethane. The combined dichloromethane phase was dried over Na_2SO_4 and the solvent was evaporated to yield (*S*)-(+)-alcohol maleic acid monoester.

(*S*)-(+)-Alcohol maleic acid monoester and NaOH (0.5×) were dissolved in water (1.5–3×). The mixture was boiled for 1 min and after cooling to room temperature it was extracted by diethyl ether. The combined organic phase was dried over Na_2SO_4 and the solvent was evaporated to yield (*S*)-(+)-alcohol. For reaction times, yields and enantiomeric compositions, see Table 4.

4.5. Lipase-catalyzed re-resolution of (*R*)-(−)-alcohol: general procedure

(*R*)-(−)-Alcohol (for enantiomer excess, see Table 5) and Amano PS-C (for amount, see Table 5) were dissolved in vinyl acetate (for amount, see Table 5), and the resulting suspension was stirred at room temperature (for reaction time, see Table 5). The reaction was stopped by filtering out the enzyme, then it was washed by vinyl acetate, and vinyl acetate was evaporated in vacuo to obtain a mixture of (*S*)-(+)-alcohol and (*R*)-(−)-acetate.

The mixture of (*S*)-(+)-alcohol and (*R*)-(−)-acetate was separated by preparative vacuum column chromatography (hexane–ethyl acetate = 10:1) to obtain (*S*)-(+)-alcohol and (*R*)-(−)- acetate.

(*R*)-(−)-Acetate and NaOH (0.35) were dissolved in water (0.5–2×) and methanol (1–2×). The mixture was boiled up and it was stirred for half an hour. The methanol was evaporated in vacuo and the residue was extracted by diethyl ether. The combined organic phase was dried over Na_2SO_4 and the solvent was evaporated to yield (*R*)-(−)-alcohol. For yields and enantiomeric compositions, see Table 5.

4.6. Preparation of the monoesters of racemic 1-phenyl-2-propanol derivatives: general procedure

To a solution of racemic 1-benzo[1,3]dioxol-5-yl-2-propanol *rac*-**1** (60.00 g, 332.96 mmol) in dichloromethane (240 mL), triethylamine (50 mL, 359.2 mmol, $d = 0727$) was added and the mixture was stirred at room temperature. Then maleic acid anhydride (33.00 g, 336.53 mmol) was added to the solution and the mixture was heated up while the colour of the solution turned into dark brown. It was stirred and refluxed for 10 min. After cooling to room temperature, it was extracted with 1 × 300 mL and 1 × 60 mL 1.5 M HCl solution and 1 × 60 mL water. The organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo yielding a dense brown oil of race-

mic 1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester *rac*-**8** (90.50 g, 325.23 mmol, *Y*: 98%). Later the oil was solidified (bp: 93–96 °C).

4.7. Resolution of racemic monoesters with chiral bases: resolution of racemic 1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester *rac*-8 with (*S*)-(−)-phenylethylamine 26

Racemic 1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester *rac*-**8** (90.30 g, 324.51 mmol) was dissolved in ethyl acetate (125 mL), and (*S*)-(−)-phenylethylamine **26** (23.60 g, 194.75 mmol) was added to the solution. The solution was stirred for 20 min, diethyl ether (271 mL) was added to the clear solution and it was inoculated with some diastereoisomeric salt. The crystals were placed at 1 °C overnight and then were filtered, washed with diethyl ether (3 × 45 mL) and dried to afford the solid diastereoisomeric salt: (+)-1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (+)-**8** (*S*)-(−)-phenylethylamine salt (47.40 g, 118.7 mmol, *Y*: 73.1%), brownish crystal.

The diastereoisomeric salt (47.0 g) was dissolved in hot ethyl acetate (94 mL) and cooled to room temperature slowly. It was allowed to crystallize for 1 h and the crystals were filtered, washed with diethyl ether (3 × 25 mL) and dried to afford the solid recrystallized diastereoisomeric salt: (+)-1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (+)-**8** (*S*)-(−)-phenylethylamine salt (42.10 g, 105.40 mmol, *Y*: 65.0%), brownish crystal.

The recrystallized diastereoisomeric salt (41.7 g) was dissolved in hot ethyl acetate (83 mL) and cooled to room temperature slowly once again. It was allowed to crystallize for 1 h and the crystals were filtered, washed with diethyl ether (3 × 25 mL) and dried to afford the solid twice recrystallized diastereoisomeric salt: (+)-1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (+)-**8** (*S*)-(−)-phenylethylamine salt (36.80 g, 92.13 mmol, *Y*: 56.8%), brownish crystal, {$[\alpha]_D^{25} = +6.9$ (*c* 2, glacial acetic acid)}; mp: 155–160 °C, it frizzled up from 95 °C.

The crystals (36.4 g) were suspended in ethyl acetate (300 mL), and 20% HCl (25 mL) was added and the solution was stirred for 30 min (clear two-phase solution). The phases were separated and the organic phase was washed with 1.5 M HCl solution (2 × 20 mL), then it was dried over Na_2SO_4 and the solvent was removed in vacuo to afford an oil of (+)-1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (+)-**8** (23.92 g, 86.00 mmol, *Y*: 53.0%) {$[\alpha]_D^{25} = +11.9$ (*c* 2, $CHCl_3$)}.

The monoester was removed: (+)-1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (+)-**8** (23.47 g) was heated with a mixture of water (45 mL) and NaOH (15 g) for 1 min and it was allowed to cool to room temperature. The aqueous phase was washed with diethyl ether (4 × 45 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (+)-1-benzo[1,3]dioxol-5-yl-2-propanol (+)-**2** (14.04 g, 77.91 mmol, *Y*: 48.0%) {$[\alpha]_D^{25} = +31.5$ (*c* 2, $CHCl_3$)}, ee: 98%.

The resolution mother liquid was washed with 1.5 M HCl solution (1 × 65 mL and 2 × 10 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (−)-1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (−)-**8** (59.04 g, 213.47 mmol, *Y*: 131.6%) {$[\alpha]_D^{25} = -11.0$ (*c* 2, $CHCl_3$)}.

The monoester was removed: (−)-1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (−)-**8** (59.04 g) was heated with a mixture of water (100 mL) and NaOH (25 g) for 1 min and it was allowed to cool to room temperature. The aqueous phase was washed with diethyl ether (4 × 100 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (−)-1-benzo[1,3]dioxol-5-yl-2-propanol (−)-**2** (34.1 g, 116.7 mmol, *Y*: 116.7%) {$[\alpha]_D^{25} = -15.3$ (*c* 2, $CHCl_3$)}, ee: 48%.

4.8. Resolution of racemic 1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester *rac*-8 with (+)-dehydroabiethylamine 28: general procedure

Racemic 1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester *rac*-**8** (4.65 g, 16.72 mmol) and (+)-dehydroabiethylamine **28** (3.10 g, 10.86 mmol) were dissolved in ethyl acetate (14 mL) during heating. The solution was placed at 15 °C overnight and the crystals were filtered, washed with ethyl acetate (4 × 3 mL) and dried to afford the solid diastereoisomeric salt: (+)-1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (+)-**8** (+)-dehydroabiethylamine salt (4.14 g, 7.34 mmol, *Y*: 87.9%), {$[\alpha]_D^{25} = +9.9$ (*c* 2, glacial acetic acid)}, mp: 139–141 °C.

The crystals (4.14 g) were suspended in ethyl acetate (10 mL), and 1 M Na_2CO_3 solution (1 × 10, 1 × 5 mL) was added. The phases were separated and the combined aqueous phase was washed with ethyl acetate (2 × 5 mL), it was acidified with 37% HCl (2 mL) and then it was extracted with ethyl acetate (3 × 10 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (−)-1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (−)-**8** (1.63 g, 5.85 mmol, *Y*: 70.1%) {$[\alpha]_D^{25} = -10.7$ (*c* 10, CH_3OH)}.

The monoester was removed: (+)-1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (−)-**8** (1.63 g) was heated with mixture of methanol (1 mL), water (3 mL) and NaOH (1 g) for 1 min and it was allowed to cool to room temperature. Water (10 mL) was added and the methanol was removed in vacuo. The residue was extracted with ethyl acetate (4 × 10 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (−)-1-benzo[1,3]dioxol-5-yl-2-propanol (−)-**2** (0.83 g, 4.61 mmol, *Y*: 55.1%) {$[\alpha]_D^{25} = -23.1$ (*c* 2, $CHCl_3$)}, ee: 72%.

The resolution mother liquid was extracted with 1 M Na_2CO_3 solution (1 × 15 mL and 1 × 5 mL). The combined aqueous phase was washed with ethyl acetate (2 × 5 mL), it was acidified with 37% HCl (2 mL) and then it was extracted with ethyl acetate (3 × 10 mL). The combined organic phase was dried over Na_2SO_4 and the solvent

was removed in vacuo to afford (+)-1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (+)-**8** (2.32 g, 8.33 mmol, *Y*: 99.8%) {($[\alpha]_D^{25} = +11.1$ (*c* 10, CH_3OH)}.

The monoester was removed: (+)-1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (+)-**8** (2.32 g) was heated with a mixture of methanol (1 mL), water (3 mL) and NaOH (1 g) for 1 min and it was allowed to cool to room temperature. Water (10 mL) was added and the methanol was removed in vacuo. The residue was extracted with ethyl acetate (4 × 10 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (+)-1-benzo[1,3]dioxol-5-yl-2-propanol (+)-**2** (1.32 g, 6.10 mmol, *Y*: 73.1%) $[\alpha]_D^{25} = +21.5$ (*c* 2, $CHCl_3$), ee: 67%.

4.9. Resolution of racemic 1-(3-chloro-phenyl)-2-propanol maleic acid monoester *rac*-11 with (*R*)-(+)-phenylethylamine 27: general procedure

Racemic 1-(3-chloro-phenyl)-2-propanol maleic acid monoester *rac*-**11** (1.00 g, 3.72 mmol) was dissolved in the mixture of ethyl acetate (0.25 mL), acetone (0.25 mL) and diisopropyl ether (4.5 mL), and (*R*)-(+)-phenylethylamine **27** (0.30 g, 2.48 mmol) was added to the solution. The solution was inoculated with some diastereoisomeric salt and the crystals were placed for 24 h. The crystals were filtered, washed with diisopropyl ether (2 × 1 mL) and dried to afford the solid diastereoisomeric salt: (−)-1-(3-chloro-phenyl)-2-propanol maleic acid monoester (−)-**11** (*R*)-(+)-phenylethylamine salt (0.28 g, 0.72 mmol, *Y*: 38.7%).

The crystals (0.28 g) were suspended in ethyl acetate (10 mL), and 1.5 M HCl (5 mL) was added and the solution was stirred for 5 min. The phases were separated and the organic phase was washed with 1.5 M HCl solution (2 × 5 mL), then it was dried over Na_2SO_4 and the solvent was removed in vacuo to afford an oil of (−)-1-(3-chloro-phenyl)-2-propanol maleic acid monoester (−)-**11** (0.18 g, 0.67 mmol, *Y*: 36.0%) {$[\alpha]_D^{25} = -10.8$ (*c* 2, $CHCl_3$)}.

The monoester was removed: (−)-1-(3-chloro-phenyl)-2-propanol maleic acid monoester (−)-**11** (0.18 g) was heated with a mixture of water (5 mL) and NaOH (0.8 g) for 1 min and it was allowed to cool to room temperature. The aqueous solution was extracted with diethyl ether (4 × 5 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (−)-1-(3-chloro-phenyl)-2-propanol (−)-**3** (0.11 g, 0.64 mmol, *Y*: 34.6%) {$[\alpha]_D^{25} = -10.8$ (*c* 2, $CHCl_3$)}, ee: 31%.

Ethyl acetate (10 mL) was added to the resolution mother liquid and it was washed with 1.5 M HCl solution (3 × 5 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (+)-1-(3-chloro-phenyl)-2-propanol maleic acid monoester (+)-**11** (0.79 g, 2.94 mmol, *Y*: 158.0%) {$[\alpha]_D^{25} = +2.6$ (*c* 2, $CHCl_3$)}.

The monoester was removed: (+)-1-(3-chloro-phenyl)-2-propanol maleic acid monoester (+)-**11** (2.32 g) was heated with a mixture of water (5 mL) and NaOH (0.8 g) for 1 min and it was allowed to cool to room temperature. The aqueous solution was extracted with ethyl acetate (4 × 10 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (+)-1-(3-chloro-phenyl)-2-propanol (+)-**3** (0.43 g, 2.52 mmol, *Y*: 135.4%) {$[\alpha]_D^{25} = +3.2$ (*c* 2, $CHCl_3$)}, ee: 9%.

4.10. Resolution of racemic 1-(4-chloro-phenyl)-2-propanol succinic acid monoester *rac*-15 with quinine 29

Racemic 1-(4-chloro-phenyl)-2-propanol succinic acid monoester *rac*-**15** (1.00 g, 3.69 mmol) was dissolved in ethyl acetate (6 mL) and quinine **29** (0.90 g, 2.77 mmol) was added to the solution. The solution was inoculated with some diastereoisomeric salt and the crystals were placed for 24 h. The crystals were filtered, washed with ethyl acetate (2 × 1 mL) and dried to afford the solid diastereoisomeric salt: (+)-1-(4-chloro-phenyl)-2-propanol succinic acid monoester (+)-**15** quinine salt (1.07 g, 1.80 mmol, *Y*: 97.3%).

The crystals (1.07 g) were suspended in ethyl acetate (10 mL), and 1 M Na_2CO_3 solution (1 × 10 mL) was added, and the solution was stirred for 5 min. The phases were separated and the aqueous phase was washed with ethyl acetate (2 × 10 mL), it was acidified with 1.5 M HCl (20 mL) and then it was extracted with diethyl ether (3 × 10 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (+)-1-(4-chloro-phenyl)-2-propanol succinic acid monoester (+)-**15** (0.39 g, 1.44 mmol, *Y*: 78.0%).

The monoester was removed: (+)-1-(4-chloro-phenyl)-2-propanol succinic acid monoester (+)-**15** (0.39 g) was heated with a mixture of water (5 mL) and NaOH (0.8 g) for 1 min and it was allowed to cool to room temperature. The aqueous solution was extracted with diethyl ether (4 × 5 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (+)-1-(4-chloro-phenyl)-2-propanol (+)-**4** (0.24 g, 1.41 mmol, *Y*: 76.1%) {$[\alpha]_D^{25} = +3.8$ (*c* 2, $CHCl_3$)}, ee: 12%.

Ethyl acetate (10 mL) and 1 M Na_2CO_3 solution (10 mL) was added to the resolution mother liquid and the solution was stirred for 5 min. The phases were separated, the aqueous phase was extracted with 1 M Na_2CO_3 solution (2 × 5 mL), it was acidified with 1.5 M HCl (20 mL) and then it was extracted with diethyl ether (3 × 10 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (−)-1-(4-chloro-phenyl)-2-propanol succinic acid monoester (−)-**15** (0.35 g, 1.29 mmol, *Y*: 70.0%).

The monoester was removed: (−)-1-(4-chloro-phenyl)-2-propanol succinic acid monoester (−)-**15** (0.35 g) was heated with a mixture of water (5 mL) and NaOH (0.8 g) for 1 min and it was allowed to cool to room temperature. The aqueous solution was extracted with diethyl ether (4 × 5 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (−)-1-(4-chloro-phenyl)-2-propanol (−)-**4** (0.20 g, 1.17 mmol, *Y*: 63.5%) {$[\alpha]_D^{25} = -3.9$ (*c* 2, $CHCl_3$)}, ee: 12%.

4.11. Resolution of racemic 1-(4-chloro-phenyl)-2-propanol phthalic acid monoester *rac*-16 with (*R*,*R*)-(−)-1-(4-nitro-phenyl)-2-amino-1,3-propanediol 30

Racemic 1-(4-chloro-phenyl)-2-propanol phthalic acid monoester *rac*-**16** (3.40 g, 10.67 mmol) was dissolved in ethyl acetate (3.4 mL), and (*R*,*R*)-(−)-1-(4-nitro-phenyl)-2-amino-1,3-propanediol **30** (1.36 g, 6.41 mmol) was added to the solution and it was heated. After cooling to room temperature, diethyl ether (13.6 mL) was added to the solution and the solution was placed for 48 h. The crystals were filtered, washed with diethyl ether and dried to afford the solid diastereoisomeric salt: (+)-1-(4-chloro-phenyl)-2-propanol phthalic acid monoester (+)-**16** quinine salt (2.65 g, 4.99 mmol, *Y*: 93.6%).

The crystals (2.65 g) were suspended in ethyl acetate (35 mL), and 1.5 M HCl (20 mL) was added and the solution was stirred for 5 min. The phases were separated and the organic phase was washed with 1.5 M HCl solution (2 × 20 mL), then it was dried over Na_2SO_4 and the solvent was removed in vacuo to afford an oil of (+)-1-(4-chloro-phenyl)-2-propanol phthalic acid monoester (+)-**16** (1.58 g, 4.96 mmol, *Y*: 92.9%).

The monoester was removed: (+)-1-(4-chloro-phenyl)-2-propanol phthalic acid monoester (+)-**16** (1.58 g) was heated with a mixture of water (20 mL) and NaOH (3 g) for 1 min and it was allowed to cool to room temperature. The aqueous solution was extracted with diethyl ether (4 × 25 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (+)-1-(4-chloro-phenyl)-2-propanol (+)-**4** (0.79 g, 4.63 mmol, *Y*: 86.8%), {$[\alpha]_D^{25} = +5.2$ (*c* 2, $CHCl_3$)}, ee: 17%.

Ethyl acetate (35 mL) was added to the resolution mother liquid and it was washed with 1.5 M HCl solution (3 × 20 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (−)-1-(4-chloro-phenyl)-2-propanol phthalic acid monoester (−)-**16** (1.75 g, 5.49 mmol, *Y*: 102.9%).

The monoester was removed: (−)-1-(4-chloro-phenyl)-2-propanol phthalic acid monoester (−)-**16** (1.75 g) was heated with a mixture of water (20 mL) and NaOH (3 g) for 1 min and it was allowed to cool to room temperature. The aqueous solution was extracted with diethyl ether (4 × 35 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (−)-1-(4-chloro-phenyl)-2-propanol (−)-**4** (0.88 g, 5.16 mmol, *Y*: 96.7%) {$[\alpha]_D^{25} = -4.6$ (*c* 2, $CHCl_3$)}, ee: 15%.

4.12. Resolution of racemic 1-(3-bromo-4-methoxy-phenyl)-2-propanol phthalic acid monoester *rac*-25 with (*S*)-(+)-benzyl-aminobutanol 31

Racemic 1-(3-bromo-4-methoxy-phenyl)-2-propanol phthalic acid monoester *rac*-**25** (1.00 g, 2.54 mmol) was dissolved in ethyl acetate (3 mL), and (*S*)-(+)-benzyl-aminobutanol **31** (0.30 g, 1.67 mmol) was added to the solution. The solution was inoculated with some diastereoisomeric salt and the crystals were placed for 24 h. The crystals were filtered, washed with diethyl ether (3 × 1 mL) and dried to afford the solid diastereoisomeric salt: (−)-1-(3-bromo-4-methoxy-phenyl)-2-propanol phthalic acid monoester *rac*-**25** (*S*)-(+)-benzyl-aminobutanol salt (0.89 g, 1.55 mmol, *Y*: 122.3%).

The crystals (0.89 g) were suspended in ethyl acetate (10 mL), and 1.5 M HCl (5 mL) was added and the solution was stirred for 5 min. The phases were separated and the organic phase was washed with 1.5 M HCl solution (2 × 5 mL), then it was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (−)-1-(3-bromo-4-methoxy-phenyl)-2-propanol phthalic acid monoester (−)-**25** (0.56 g, 1.42 mmol, *Y*: 112.0%), $[\alpha]_D^{25} = -7.4$ (*c* 2, $CHCl_3$).

The monoester was removed: (−)-1-(3-bromo-4-methoxy-phenyl)-2-propanol phthalic acid monoester (−)-**25** (0.56 g) was heated with a mixture of water (5 mL) and NaOH (0.8 g) for 1 min and it was allowed to cool to room temperature. The aqueous solution was extracted with diethyl ether (4 × 5 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (−)-1-(3-bromo-4-methoxy-phenyl)-2-propanol (−)-**7** (0.23 g, 0.94 mmol, *Y*: 73.8%), {$[\alpha]_D^{25} = -7.8$ (*c* 2, $CHCl_3$)}, ee: 31%.

Ethyl acetate (10 mL) was added to the resolution mother liquid and it was washed with 1.5 M HCl solution (3 × 5 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (+)-1-(3-bromo-4-methoxy-phenyl)-2-propanol phthalic acid monoester (+)-**25** (0.35 g, 0.89 mmol, *Y*: 70.0%), {$[\alpha]_D^{25} = +13.1$ (*c* 2, $CHCl_3$)}.

The monoester was removed: (+)-1-(3-bromo-4-methoxy-phenyl)-2-propanol phthalic acid monoester (+)-**25** (0.35 g) was heated with a mixture of water (5 mL) and NaOH (0.8 g) for 1 min and it was allowed to cool to room temperature. The aqueous solution was extracted with diethyl ether (4 × 10 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (+)-1-(3-bromo-4-methoxy-phenyl)-2-propanol (+)-**7** (0.12 g, 0.89 mmol, *Y*: 38.5%) $[\alpha]_D^{25} = -17.5$ (*c* 2, $CHCl_3$), ee: 70%.

4.13. Re-resolution of the enantiomers with chiral bases: resolution of racemic (−)-1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (−)-8 with (*R*)-(+)-phenylethylamine 27: general procedure

(−)-1-Benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (−)-**8** (10.00 g, 35.94 mmol, ee: 48%) was dissolved in ethyl acetate (10 mL) with heating, and (*R*)-(+)-phenylethylamine **27** (2.5 g, 20.63 mmol) and diethyl ether (30 mL) were added to the solution. The solution was inoculated with some diastereoisomeric salt and the crystals were placed for 2 h at room temperature. The crystals were filtered, washed with diethyl ether (4 × 4 mL) and dried to afford the solid diastereoisomeric salt:

(−)-1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (−)-**8** (*R*)-(+)-phenylethylamine salt (6.78 g, 16.97 mmol, *Y*: 47.2%), off-white crystals.

The diastereoisomeric salt (6.78 g) was dissolved in hot ethyl acetate (20 mL) and cooled to room temperature slowly. It was allowed to crystallize for 1 h and the crystals were filtered, washed with ethyl acetate (3 × 2.5 mL) and dried to afford the solid recrystallized diastereoisomeric salt: (−)-1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (−)-**8** (*R*)-(+)-phenylethylamine salt (6.08 g, 15.22 mmol, *Y*: 42.3%), off-white crystals.

The recrystallized diastereoisomeric salt (6.08 g) was dissolved in hot ethyl acetate (18 mL) and cooled to room temperature slowly once again. It was allowed to crystallize for 1 h and the crystals were filtered, washed with ethyl acetate (3 × 2.5 mL) and dried to afford the solid twice recrystallized diastereoisomeric salt: (−)-1-benzo-[1,3]dioxol-5-yl-2-propanol maleic acid monoester (−)-**8** (*R*)-(+)-phenylethylamine salt (5.27 g, 13.19 mmol, *Y*: 36.7%), off-white crystal, {$[\alpha]_D^{25} = -6.1$ (*c* 2, glacial acetic acid)}.

The crystals (4.87 g, 12.19 mmol) were suspended in ethyl acetate (40 mL), and 20% HCl (5 mL) was added and the solution was stirred for 15 min (clear two-phase solution). The phases were separated and the organic phase was washed with 1.5 M HCl solution (3 × 5 mL), then it was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (−)-1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (−)-**8** (3.38 g, 12.14 mmol, *Y*: 33.8%) {$[\alpha]_D^{25} = -15.3$ (*c* 2, $CHCl_3$)}.

The monoester was removed: (−)-1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (−)-**8** (2.98 g, 10.70 mmol) was heated with a mixture of water (4.5 mL) and NaOH (1.5 g) for 1 min and it was allowed to cool to room temperature. The aqueous phase was washed with diethyl ether (4 × 40 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (−)-1-benzo[1,3]dioxol-5-yl-2-propanol (−)-**2** (1.52 g (after vacuo distillation), 8.43 mmol, *Y*: 23.5%) {$[\alpha]_D^{25} = -31.3$ (*c* 2, $CHCl_3$)}, ee: 97%.

The resolution mother liquid was washed with 1.5 M HCl solution (1 × 15 mL and 2 × 5 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (−)-1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (−)-**8** (6.19 g, 22.24 mmol, *Y*: 61.9%) {$[\alpha]_D^{25} = -3.8$ (*c* 2, $CHCl_3$)}.

The monoester was removed: (−)-1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (−)-**8** (6.19 g) was heated with a mixture of water (9 mL) and NaOH (3 g) for 1 min and it was allowed to cool to room temperature. The aqueous phase was washed with diethyl ether (4 × 100 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (−)-1-benzo[1,3]dioxol-5-yl-2-propanol (−)-**2** (3.23 g, 17.92 mmol, *Y*: 49.9%) {$[\alpha]_D^{25} = -4.4$ (*c* 2, $CHCl_3$)}, ee: 14%.

4.14. Re-resolution of (−)-1-(3-chloro-phenyl)-2-propanol maleic acid monoester (−)-11 with (+)-dehydroabiethylamine 28: general procedure

(−)-1-(3-Chloro-phenyl)-2-propanol maleic acid monoester (−)-**11** (16.00 g, 59.54 mmol, ee: 58%) was dissolved in ethyl acetate (80 mL) and (+)-dehydroabiethylamine **28** (28.0 g, 59.0 mmol). The solution was inoculated with some diastereoisomeric salt and the crystals were placed for 10 h. The crystals were filtered, washed with ethyl acetate (5 × 5 mL) and dried to afford the solid diastereoisomeric salt: (−)-1-(3-chloro-phenyl)-2-propanol maleic acid monoester (−)-**11** (+)-dehydroabiethylamine salt (13.13 g, 23.69 mmol, *Y*: 39.8%).

The diastereoisomeric salt (13.13 g) was dissolved in hot acetate (350 mL), then it was evaporated to 86 g, cooled to room temperature slowly and was allowed to crystallize for 1 h. The crystals were filtered, washed with ethyl acetate (5 × 5 mL) and dried to afford the solid recrystallized diastereoisomeric salt: (−)-1-(3-chloro-phenyl)-2-propanol maleic acid monoester (−)-**11** (+)-dehydroabiethylamine salt (10.20 g, 18.40 mmol, *Y*: 30.9%).

The recrystallized diastereoisomeric salt (10.20 g) was dissolved in hot acetone (300 mL), then it was evaporated to 63 g, cooled to room temperature slowly and was allowed to crystallize for 1 h. The crystals were filtered, washed with diethyl ether (5 × 5 mL) and dried to afford the solid twice recrystallized diastereoisomeric salt: (−)-1-(3-chloro-phenyl)-2-propanol maleic acid monoester (−)-**11** (+)-dehydroabiethylamine salt (7.97 g, 14.38 mmol, *Y*: 24.2%), {$[\alpha]_D^{25} = -10.9$ (*c* 2, CH_3OH)}, mp: 140–143 °C.

The crystals (7.97 g) were suspended in methanol (25 mL), and a mixture of water (5 mL) and NaOH (0.8 g), then water (100 mL) were added to the solution. It was extracted with dichloromethane (3 × 30 mL), then it was acidified with 37% HCl solution (3 mL) and extracted with dichloromethane (3 × 30 mL) again. The combined organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (−)-1-(3-chloro-phenyl)-2-propanol maleic acid monoester (−)-**11** (3.34 g, 12.43 mmol, *Y*: 20.9%).

The monoester was removed: (−)-1-(3-chloro-phenyl)-2-propanol maleic acid monoester (−)-**11** (3.34 g) was heated with a mixture of water (6 mL) and NaOH (2.5 g) for 1 min and it was allowed to cool to room temperature. The solution was extracted with diethyl ether (4 × 20 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (−)-1-(3-chloro-phenyl)-2-propanol (−)-**3** (1.82 g, 10.67 mmol, *Y*: 17.9%), {$[\alpha]_D^{25} = -33.8$ (*c* 2, $CHCl_3$)}, ee: 97%.

The solvent was removed in vacuo from the resolution mother liquid, and methanol (35 mL), a mixture of water (10 mL) and NaOH (1 g) and then water (100 mL) were added to the residue. The solution was extracted with dichloromethane (3 × 50 mL), it was acidified with 37% HCl (5 mL) and then it was extracted with dichloromethane (4 × 25 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to

afford (−)-1-(3-chloro-phenyl)-2-propanol maleic acid monoester (−)-**11** (10.22 g, 38.04 mmol, *Y*: 63.9%).

The monoester was removed: (−)-1-(3-chloro-phenyl)-2-propanol maleic acid monoester (−)-**11** (10.22 g) was heated with a mixture of water (20 mL) and NaOH (5 g) for 1 min and it was allowed to cool to room temperature. The solution was extracted with diethyl ether (4 × 20 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (−)-1-(3-chloro-phenyl)-2-propanol (−)-**3** (6.08 g, 35.63 mmol, *Y*: 59.8%) {$[\alpha]_D^{25} = -11.7$ (*c* 2, $CHCl_3$)}, ee: 34%.

4.15. Purification by recrystallization of the enantiomers

4.15.1. Purification of (−)-1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (−)-8 enantiomer with recrystallization. (−)-1-Benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (−)-**8** (10.00 g, 35.94 mmol, ee: 48%) was dissolved in toluene (20.0 mL) with heating. The solution was inoculated with pure (−)-1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (−)-**8** and stirred for 3 h at room temperature. The crystals were filtered, washed with toluene (3 × 2 mL) and hexane (3 × 2 mL), and dried to afford: (−)-1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (−)-**8** (2.50 g, 8.98 mmol, *Y*: 25%), off white crystals, {$[\alpha]_D^{25} = -2.7$ (*c* 2, $CHCl_3$)}.

The monoester was removed: (−)-1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (−)-**8** (2.50 g) was heated with a mixture of water (4 mL) and NaOH (1.2 g) for 1 min and it was allowed to cool to room temperature. The aqueous phase was washed with diethyl ether (4 × 10 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (−)-1-benzo[1,3]dioxol-5-yl-2-propanol (−)-**2** (1.46 g, 8.10 mmol, *Y*: 22.5%), oil, {$[\alpha]_D^{25} = -4.5$ (*c* 2, $CHCl_3$)}, ee: 14%.

The mother liquid was evaporated: (−)-1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (−)-**8** (7.45 g, 26.77 mmol, *Y*: 74.5%), dun oil, {$[\alpha]_D^{25} = -12.7$ (*c* 2, $CHCl_3$)}.

The monoester was removed: (−)-1-benzo[1,3]dioxol-5-yl-2-propanol maleic acid monoester (−)-**8** (7.45 g) was heated with a mixture of water (11 mL) and NaOH (3.8 g) for 1 min and it was allowed to cool to room temperature. The aqueous phase was washed with diethyl ether (4 × 10 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo to afford (−)-1-benzo[1,3]dioxol-5-yl-2-propanol (−)-**2** (4.24 g, 23.53 mmol, *Y*: 65.5%), oil, $[\alpha]_D^{25} = -19.1$ (*c* 2, $CHCl_3$), ee: 59%.

4.15.2. Purification of (−)-1-(3,4-dichloro-phenyl)-2-propanol (−)-5 enantiomer with recrystallization: general procedure. (−)-1-(3,4-Dichloro-phenyl)-2-propanol (−)-**5** (6.75 g, 32.91 mmol, ee: 61%) was dissolved in hot hexane (6.8 mL). The solution was divided into two phases during the cooling to 20 °C. The two-phase solution was inoculated with pure (−)-1-(3,4-dichloro-phenyl)-2-propanol (−)-**5** and it was stirred for 20 min. The crystals were filtered, washed with hexane (3 × 2 mL) and dried to afford: (−)-1-(3,4-dichloro-phenyl)-2-propanol (−)-**5** (4.43 g, 21.60 mmol, *Y*: 65.6%), white crystals, {$[\alpha]_D^{25} = -23.1$ (*c* 2, $CHCl_3$)}, ee: 80%.

The mother liquid was evaporated: (−)-1-(3,4-dichloro-phenyl)-2-propanol (−)-**5** (2.27 g, 11.07 mmol, *Y*: 33.6%), {$[\alpha]_D^{25} = -7.8$ (*c* 2, $CHCl_3$)}, ee: 27%.

Acknowledgements

The Hungarian OTKA Foundation (Project No. T042725 E.F.) is gratefully acknowledge for financial support. V.K. thanks Gedeon Richter Ltd, for doctoral fellowship.

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