Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 271–283

TETRAHEDRON: *ASYMMETRY*

Baker's yeast mediated stereoselective biotransformation of 1-acetoxy-3-aryloxypropan-2-ones

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Received 12 November 1997; accepted 8 December 1997

Abstract

A series of 1-acetoxy-3-aryloxypropan-2-ones **1a–m** were synthesized and subjected to biotransformation by baker's yeast yielding optically active monoacetates **5** or *ent*-**5** and/or diols **4** of moderate to excellent enantiomeric purity. The dependence of the reduction/hydrolysis ratio and stereoselectivity on the size and substitution pattern of the aromatic moiety in the substrate is also discussed. © 1998 Elsevier Science Ltd. All rights reserved.

3-Aryloxypropane-1,2-diols **4a–m** in enantiomerically pure form are versatile compounds of interest as intermediates in syntheses of pharmaceuticals such as β-receptor blockers, or as chiral fragments in optically active crown ethers. Lipase catalyzed acylation has proved to be a useful tool for enantiomer separation of racemic 3-aryloxypropane-1,2-diol derivatives.[1,2] This kinetic resolution using lipase catalyzed sequential transesterification was found to be highly enantiomer selective for diols having *m*- or *p*-substituted aromatic moieties, whereas the most sterically hindered *o*-substituted derivatives showed decreased enantiomer selectivity or were not accepted as substrates. Without racemization of the remaining enantiomer, however, even highly enantiomer selective processes can provide only 50% of the starting racemate in optically active form.

Alternatively, an enantiotope selective method, such as reduction of a prochiral ketone, might yield an optically active product quantitatively. Since acetoxymethyl ketones with phenyl,[3] benzyloxymethyl,[4] or azidomethyl[5] moieties resulted in the corresponding monoacetates of high enantiomeric purity by reduction with baker's yeast, it seemed worthwhile to investigate the analogous biotransformation of 3-aryloxy-1-acetoxypropan-2-ones **1a–m**. Here we report our results on the preparation and baker's yeast mediated stereoselective biotransformation of these ketones.

The 3-aryloxy-1-acetoxypropan-2-ones **1a–m** were prepared by alkylation of the corresponding phenols (**3a–m**) with racemic 3-chloropropane-1,2-diol *rac*-**2**, followed by acetylation of the primary

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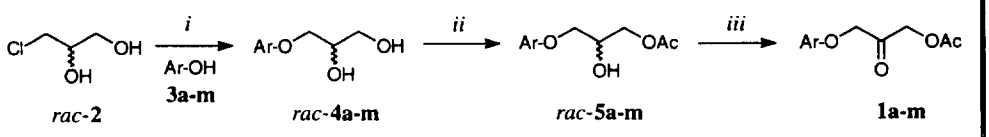
PII: S0957-4166(97)00626-5

Table 1
Preparation of 3-aryloxy-1-acetoxypropan-2-ones (**1a–m**)



rac-**2** *rac*-**4a-m** *rac*-**5a-m** **1a-m**

	Ar	*rac*-**4a-m** Yield (%)	*rac*-**5a-m** Yield (%)	**1a-m** Yield (%)
a	phenyl	81	79	94
b	1-naphthyl	82	78	93
c	2-naphthyl	79	75	90
d	2-isopropylphenyl	77	83	91
e	2-chlorophenyl	74	73	88
f	3-chlorophenyl	55	69	94
g	4-chlorophenyl	81	62	94
h	2-methylphenyl	79	66	90
i	3-methylphenyl	66	75	90
j	4-methylphenyl	71	75	89
k	3-nitrophenyl	26	68	87
l	2,6-dimethylphenyl	98	43	79
m	2,4,6-trichlorophenyl	99	42	71

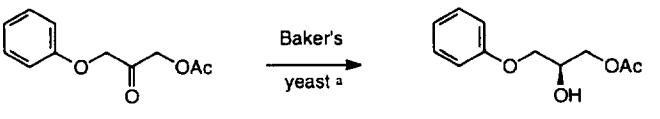
Reagents: i.) NaOH; *ii.)* Ac_2O, DMAP, pyridine; *iii.)* oxalyl chloride, DMSO, Et_3N; yields refer to isolated pure products

hydroxyl moiety of the resulting diols (*rac*-**4a–m**) and Swern-oxidation of the monoacetates *rac*-**5a–m** (Table 1).

Having the desired ketones in hand, the effect of the reaction conditions on enantiotope selectivity of the baker's yeast reduction of 1-acetoxy-3-phenoxypropan-2-one **1a** was investigated (Table 2). Under various conditions, the reaction yielded the expected optically active monoacetate **5a** without noticeable hydrolysis, in accordance with the results of the analogous baker's yeast reductions.[3–5]

In baker's yeast mediated enantiotope selective reduction of carbonyl compounds there may be two factors responsible for the incomplete stereoselectivity. Firstly, it may be due to participation of more than one reductase enzyme with different kinetic parameters and eventually opposite selectivity,[6–8] or secondly, the process may be catalyzed by a single enzyme but with incomplete selectivity.[9] In the majority of cases, it turned out that competing enzymes of opposite selectivity was the factor responsible for poor selectivity. Since the kinetic behavior of these competing enzymes is different, the selectivity may be controlled by the reaction conditions. The most frequently used modifications for influencing the selectivity are e.g.: modification of pH;[10,11] application of lyophilized yeast instead of the row cake form;[12,13] use of various additives such as metal salts;[14] allylic alcohol or α,β-unsaturated carbonyl compounds;[12,15] ethyl chloroacetate and similar compounds.[16] In Table 2 the effect of these factors on the enantiotope selectivity is shown. The reaction performed by wet caked baker's yeast at pH 7 (entry 2) provided the best selectivity. This selectivity remained practically unaltered at pH 8, or by adding some salts or allylic alcohol (entries 3 and 5–7). On the other hand, decreased selectivity was observed in the

Table 2
Effect of the reaction conditions on the selectivity of reduction of the 1-acetoxy-3-phenoxypropan-2-one **1a**



1a **5a**

Entry	Yeast	pH	Time	Additive	E.e. %
1	Wet Caked	n.b. [b]	3	-	52
2	Wet Caked	7	1	-	80
3	Wet Caked	8	1	-	78
4	Lyophilized	7	1.5	-	64
5	Wet Caked	7	1	0.1 M K_2SO_4	79
6	Wet Caked	7	1	0.1 M $MgSO_4$	80
7	Wet Caked	7	2	0.3 M allylic alcohol	79
8	Wet Caked	7	2	0.15 M ethyl chloroacetate	37

[a] *Reaction conditions:* **1a**, 500 mg; media (0.15M sodium phosphate buffer), 200 ml; baker's yeast, wet (12 g) or lyophilized (2.5 g); sucrose, 5 g. [b] Non buffered tap water.

non-buffered reaction (entry 1), by using lyophilized yeast (entry 4) or by adding ethyl chloroacetate (entry 8).

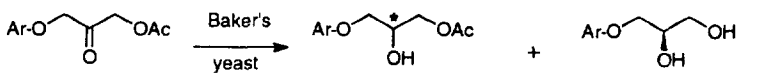
Hence, baker's yeast mediated biotransformations of further 1-acetoxy-3-aryloxypropan-2-ones **1a–k** were performed under the conditions which gave the best selectivity with the unsubstituted phenoxy derivative **1a**. The results of these reactions are summarized in Table 3.

Surprisingly, only the unsubstituted phenoxy-derivative **1a** was reduced without noticeable amounts of hydrolysis. The 2-naphthyloxy-derivative **1b** was not reduced at all, and all the other ketones **1c–m** were transformed not only into the corresponding monoacetates **5** or *ent*-**5** but partially or even fully into the corresponding diols **4** indicating the enzyme action of some hydrolases beside oxidoreductases in these reactions. The differences between the enantiomeric purities or even the configuration of the produced monoacetates **5** or *ent*-**5** and diols **4** imply that in these reactions more than one type of selectivity may be decisive. Analysis of the possible pathways and selectivities is shown in Fig. 1.

The original enantiomeric composition of the monoacetate fraction **5** versus *ent*-**5** is determined by the enantiotope selectivity of the direct reduction ($k_{1,R}$ versus $k_{1,ent\text{-}R}$). The formation of the diol fraction **4** and *ent*-**4** may proceed *via* two alternative routes. The first possible way is the hydrolysis of the monoacetate fraction (**5** and *ent*-**5**) by which the original enantiomeric composition may be altered by the enantiomer selectivity ($k_{2,H}$ versus $k_{2,ent\text{-}H}$) of the hydrolysis. The second alternative way to diols **4** and *ent*-**4** is the non-stereoselective hydrolysis ($k_{1,H}$) of the achiral acetoxy ketone **1** followed by an enantiotope selective reduction ($k_{2,R}$ versus $k_{2,ent\text{-}R}$) of the forming hydroxy ketone **6**.

The reactions of the 1-acetoxy-3-aryloxypropan-2-ones **1a–m** (Table 3) in buffered (pH 7) media with fermenting baker's yeast resulted, with the exception of the 2-isopropyloxyphenoxy compound **1d**, (*S*)-monoacetates **5a,f–j,l,m** and/or of the (*R*)-diols **4b,d–m** indicating the same geometric preference for both products. In the case of the sterically most demanding 1-naphthyl **1b** or phenyl derivatives with at least one substituent in the *o*-position **1d,e,h,l,m**, the formation of the diol **4d,e,h,l,m** of high (>90%

Table 3
Baker's yeast mediated biotransformation of 1-acetoxy-3-aryloxypropan-2-ones (**1a–k**)[a]



1a-m (*ent*)-**5a-m** **4a-m**

	Ar	Time (h)	Monoacetate **5** or *ent*-**5** [b] Yield (%)	%e.e. (config.)	Diol **4** Yield (%)	%e.e. (config.)
a	phenyl	1	84	83 [c] (*S*)	-	-
b	1-naphthyl	2	-	-	78	>95 [d] (*R*)
c	2-naphthyl	16	no reaction		no reaction	
d	2-isopropylphenyl	1	36	28 (*R*)	55	93 [e] (*R*) [d]
e	2-chlorophenyl	2	-	-	82	>95 [e] (*R*)
f	3-chlorophenyl	2	38	93 (*S*)	48	81 [e] (*R*)
g	4-chlorophenyl	2	65	61 (*S*)	25	63 [e] (*R*)
h	2-methylphenyl	2	32	65 (*S*)	47	>95 [e] (*R*)
i	3-methylphenyl	2	66	77 (*S*)	26	82 [e] (*R*)
j	4-methylphenyl	2	36	52 (*S*)	40	68 [e] (*R*) [d]
k	3-nitrophenyl	4	-	-	80	>95 [d] (*R*)
l	2,6-dimethylphenyl	1.5	60	>95 (*S*)	32	>95 [d] (*R*)
m	2,4,6-trichlorophenyl	6	58	95 (*S*)	34	92 [d] (*R*)

[a] *Reaction conditions:* **1a-m**, 500 mg; potassium phosphate buffer (0.15M, pH 7), 200 ml; wet baker's yeast, 12 g; sucrose, 5 g. [b] Configuration and enantiomeric purity of the monoacetates (**5**) were determined from the specific rotation of the corresponding diols (**4**); [c] From ^{1}H-NMR spectra of the MTPA ester of **5a**; [d] From optical rotation of the diol [(*R*)-**4**] obtained by alkylating the corresponding phenol (**3**) with (*R*)-3-chloropropane-1,2-diol [(*R*)-**2**, 95 % e.e.][17]; [e] From ^{1}H-NMR spectra of the di-MTPA ester of the diol.

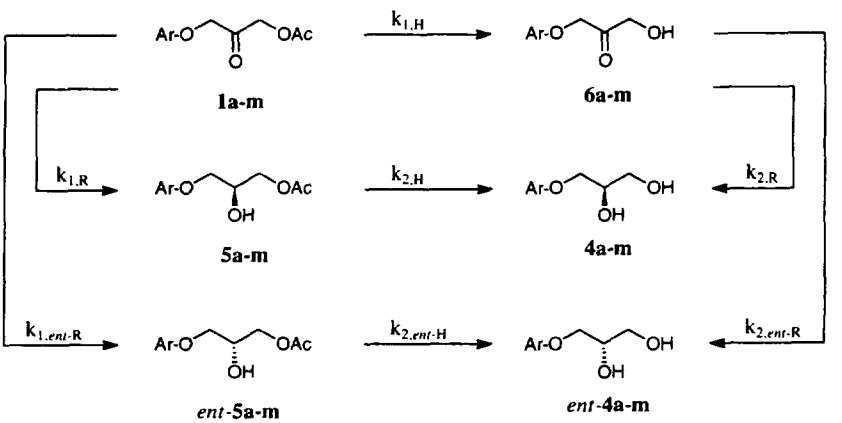


Fig. 1. Baker's yeast mediated reaction of 1-acetoxy-3-aryloxypropan-2-ones **1a–m**

e.e.) enantiomeric purity is common. The reaction of ketone with the more bulky *m*-nitrophenyl moiety **1k** proceeded also with high selectivity, while the compounds with smaller *m*-substitutents of the phenyl moiety **1f,i** were transformed with less remarkable stereoselectivities. The lowest selectivities were found in the reactions of the compounds with *p*-substituted phenyl rings **1g,j**. In three cases, the diol **4b,e,k** was the sole product, while in the other reactions, both the non-hydrolyzed monoacetate *ent*-**5d, 5f–j,l,m** and the diol **4d,f–j,l,m** were obtained with variable enantiomeric compositions. These results might be best interpreted by assuming first a fast enantiotope selective reduction of the acetoxy ketones **1** with variable degree of (*S*)-enantiomer preference ($k_{1,R}>k_{1,ent\text{-}R}$), followed by an enantiomer selective hydrolysis ($k_{2,H}>k_{2,ent\text{-}H}$) with preference towards the (*R*)-diols **4**.[18] By this assumption, formation of the (*R*)-monoacetate *ent*-**5d** of low enantiomeric excess can also be interpreted without assuming the unlikely configuration-preference change of the reduction within the series of acetoxy ketones **1**. Accordingly, this reaction may be the result of the reduction of the acetoxy ketone **1d** with moderate (*S*)-enantiotope selectivity followed by hydrolysis with high enantiomer selectivity towards the (*R*)-diol **4d**, leaving the non-hydrolyzed (*R*)-monoacetate *ent*-**5d** in excess in the remaining monoacetate fraction.

In conclusion, baker's yeast mediated reaction of the 1-acetoxy-3-aryloxypropan-2-ones **1a–m** proved to be a useful method for the preparation of optically active 3-aryloxypropan-1,2-diol derivatives. This transformation showed high selectivities with the ketones of sterically hindered aryl moieties, while lower selectivities were found for the less hindered ketones with *m*- or *p*-substituted phenyl moieties. Since the opposite tendency (i.e. higher selectivity for the less hindered compounds) was found by the lipase-catalyzed enantiomer selective acylation processes of the similar 3-aryloxypropan-1,2-diol derivatives, the present baker's yeast mediated method seems to be useful for preparing such diols bearing a sterically hindered aryl moiety.

1. Experimental

The ^{1}H NMR spectra were recorded on a Bruker AW-250 spectrometer operating at 250 MHz. ^{1}H NMR spectra for enantiomeric excess determinations were recorded at 500 MHz on a Bruker DRX-500 spectrometer. All spectra were taken in $CDCl_3$ solution and chemical shift values are expressed in ppm values from TMS as internal standard on δ scale. IR spectra of thin film samples were taken on a Specord 2000 spectrometer. Optical rotations were determined on a Perkin–Elmer 241 polarimeter. Thin layer chromatography was carried out using Merck Kieselgel 60 F_{254} alumina sheets applying hexane:acetone=10:4 (A) or chloroform:methanol=10:0.5 (B) mixtures for elution. Spots were visualized by treatment with 5% ethanolic phosphomolybdic acid solution and heating of the dried plates. Preparative chromatographic separations were performed using vacuum-chromatography[19] on Merck Kieselgel 60 (0.063–0.200 mm). Phenols, racemic 3-chloropropane-1,2-diol and acetic anhydride were products of FLUKA or Aldrich. All solvents used were freshly distilled. Wet cake or lyophilized form of baker's yeast were from a local store.

1.1. Preparation of 3-aryloxypropane-1,2-diols rac-***4a–m***

To the solution of the phenol derivative **3a–m**, 0.1 mol in ethanol (60 ml) a solution of NaOH (5.0 g, 0.125 mol) in water (20 ml) was added and the resulting mixture was heated under reflux for 10 minutes. Then a solution of racemic 3-chloropropane-1,2-diol *rac*-**2**, 13.3 g, 0.12 mol in ethanol (10 ml) was added within 5 minutes and the mixture was further heated under reflux for between 1 and 2 hours (the progress of the reaction was monitored by TLC; solvent A). After cooling, the volume of the resulting

mixture was reduced to about one third by a rotary evaporator followed by addition of water (60 ml) and extraction with diethyl ether (2×75 ml). The combined organic layers were dried over Na_2SO_4 and the solvent was removed. The resulting diols **4a–m** were usually purified by recrystallization from a 1:1 mixture of hexane and diethyl ether. For yields, see Table 1.

1.1.1. rac-*3-Phenoxypropane-1,2-diol* rac-***4a***

^{1}H NMR: 3.65–3.85 (m, 2H, CH_2–OH), 4.0 (m, 1H, CH), 4.10–4.22 (m, 2H, ArO–CH_2), 6.84–7.25 (m, 5H, ArH). IR: 3450 (br), 2910, 1600, 1590, 1500, 1460, 1170, 1120, 1060, 1050, 880, 750, 690 cm^{-1}. Calcd for $C_9H_{12}O_3$: C 64.27, H 7.19. Found: C 64.46, H 7.17.

1.1.2. rac-*3-(1-Naphthyloxy)propane-1,2-diol* rac-***4b***

^{1}H NMR: 3.86 (m, 2H, CH_2), 4.02–4.14 (m, 3H, CH and ArO–CH_2), 6.75–8.24 (m, 7H, ArH). IR: 3290 (br), 2940, 1730, 1580, 1510, 1470, 1390, 1270, 1240, 1130, 1110, 1040, 990, 890, 790, 770 cm^{-1}. Calcd for $C_{13}H_{14}O_3$: C 71.54, H 6.47. Found: C 71.68, H 6.46.

1.1.3. rac-*3-(2-Naphthyloxy)propane-1,2-diol* rac-***4c***

^{1}H NMR: 3.77 (m, 2H, CH_2–OH), 3.92 (m, 1H, CH), 4.07–4.26 (m, 2H, ArO–CH_2), 7.09–7.73 (m, 7H, ArH). IR: 3400 (br), 2940, 1630, 1600, 1510, 1460, 1260, 1220, 1180, 1060, 1000, 840, 740 cm^{-1}. Calcd for $C_{13}H_{14}O_3$: C 71.54, H 6.47. Found: C 71.25, H 6.50.

1.1.4. rac-*3-(2-Isopropylphenoxy)propane-1,2-diol* rac-***4d***

^{1}H NMR: 1.24 (d, 6H, $2CH_3$), 3.16, (m, 1H, CH–Ar), 3.74 (m, 2H, CH_2–OH), 4.03 (m, 1H, CH), 4.07–4.18 (m, 2H, ArO–CH_2), 6.81–7.25 (m, 4H, ArH). IR: 3300 (br), 2960, 2870, 1600, 1500, 1460, 1380, 1240, 1080, 1050, 930, 760 cm^{-1}. Calcd for $C_{12}H_{18}O_3$: C 68.55, H 8.63. Found: C 68.28, H 8.66.

1.1.5. rac-*3-(2-Chlorophenoxy)propane-1,2-diol* rac-***4e***

^{1}H NMR: 3.78 (m, 2H, CH_2–OH), 4.07 (m, 1H, CH), 4.10 (m, 2H, ArO–CH_2), 6.88–7.31 (m, 4H, ArH). IR: 3300 (br), 2940, 1590, 1490, 1450, 1300, 1250, 1130, 1070, 1030, 740 cm^{-1}. Calcd for $C_9H_{11}O_3Cl$: C 53.35, H 5.47. Found: C 53.40, H 5.46.

1.1.6. rac-*3-(3-Chlorophenoxy)propane-1,2-diol* rac-***4f***

^{1}H NMR: 3.75 (m, 2H, CH_2–OH), 3.96 (m, 1H, CH), 4.07 (m, 2H, ArO–CH_2), 6.69–7.24 (m, 4H, ArH). IR: 3300 (br), 2930, 1600, 1470, 1430, 1280, 1230, 1120, 1060, 890, 860, 770, 680 cm^{-1}. Calcd for $C_9H_{11}O_3Cl$: C 53.35, H 5.47. Found: C 53.37, H 5.45.

1.1.7. rac-*3-(4-Chlorophenoxy)propane-1,2-diol* rac-***4g***

^{1}H NMR: 3.78 (m, 2H, CH_2–OH), 4.01 (m, 1H, CH), 4.10 (m, 2H, ArO–CH_2), 6.79–7.26 (m, 4H, ArH). IR: 3300 (br), 2920, 1600, 1490, 1450, 1280, 1240, 1110, 1050, 880, 820 cm^{-1}. Calcd for $C_9H_{11}O_3Cl$: C 53.35, H 5.47. Found: C 53.33, H 5.49.

1.1.8. rac-*3-(2-Methylphenoxy)propane-1,2-diol* rac-***4h***

^{1}H NMR: 2.23 (s, 3H, CH_3), 3.76 (m, 2H, CH_2–OH), 4.01 (m, 1H, CH), 4.12 (m, 2H, ArO–CH_2), 6.78–7.18 (m, 4H, ArH). IR: 3260 (br), 2930, 1610, 1500, 1460, 1310, 1250, 1120, 1050, 990, 750 cm^{-1}. Calcd for $C_{10}H_{14}O_3$: C 65.92, H 7.74. Found: C 65.69, H 7.72.

1.1.9. rac-*3-(3-Methylphenoxy)propane-1,2-diol* rac-***4i***

^{1}H NMR: 2.27 (s, 3H, CH_3), 3.76 (m, 2H, CH_2–OH), 4.00 (m, 1H, CH), 4.08 (m, 2H, ArO–CH_2), 6.67–7.18 (m, 4H, ArH). IR: 3290 (br), 2930, 1610, 1590, 1490, 1450, 1290, 1260, 1160, 1060, 910, 860, 770, 690 cm^{-1}. Calcd for $C_{10}H_{14}O_3$: C 65.92, H 7.74. Found: C 65.74, H 7.73.

1.1.10. rac-*3-(4-Methylphenoxy)propane-1,2-diol* rac-***4j***

^{1}H NMR: 2.25 (s, 3H, CH_3), 3.72–4.00 (m, 2H, CH_2–OH), 3.96 (m, 1H, CH), 4.13 (m, 2H, ArO–CH_2), 7.24–7.87 (m, 4H, ArH). IR: 3390 (br), 1580, 1520, 1440, 1360, 1320, 1250, 1140, 1080, 1010, 870, 820 cm^{-1}. Calcd for $C_{10}H_{14}O_3$: C 65.92, H 7.74. Found: C 65.99, H 7.74.

1.1.11. rac-*3-(3-Nitrophenoxy)propane-1,2-diol* rac-***4k***

^{1}H NMR: 3.72–4.00 (m, 2H, CH_2), 4.13 (m, 3H, CH_2 and CH), 7.24–7.87 (m, 4H, ArH). IR: 3390 (br), 1580, 1520, 1440, 1360, 1320, 1250, 1140, 1080, 1010, 870, 820, 740 cm^{-1}. Calcd for $C_9H_{11}NO_5$: C 50.71, H 5.20, N 6.57. Found: C 50.56, H 5.22, N 6.59.

1.1.12. rac-*3-(2,6-Dimethylphenoxy)propane-1,2-diol* rac-***4l***

^{1}H NMR: 2.21 (s, 6H, CH_3), 3.78 (m, 4H, CH_2–OH and CH_2–OAr), 4.07 (m, 1H, CH), 6.80–7.00 (m, 3H, ArH). IR: 3384 (br), 2925, 1592, 1477, 1264, 1201, 1026, 768 cm^{-1}. Calcd for $C_{11}H_{16}O_3$: C 67.32, H 8.22. Found: C 67.38, H 8.19.

1.1.13. rac-*3-(2,4,6-Trichlorophenoxy)propane-1,2-diol* rac-***4m***

^{1}H NMR: 3.50–4.55 (m, 5H, CH_2–OH, CH_2–OAr and CH), 7.25 (s, 2H, ArH). IR: 3312 (br), 2943, 1572, 1553, 1447, 1256, 1053, 858 cm^{-1}. Calcd for $C_9H_9Cl_3O_3$: C 39.81, H 3.34. Found: C 39.67, H 3.39.

1.2. Preparation of 1-acetoxy-3-aryloxypropan-2-ols rac-***5a–m***

To a solution of 3-aryloxypropane-1,2-diol *rac*-**4a–m**, 50 mmol, pyridine (60 mmol) and (4-*N,N*-dimethylamino)pyridine (100 mg) in methylene chloride (100 ml) acetic anhydride (50 mmol) was added dropwise and the resulting solution was stirred for between 10 and 60 minutes. Then the mixture was washed with 5% hydrochloric acid (2×20 ml), saturated $NaHCO_3$ solution (20 ml) and brine (15 ml). After drying over Na_2SO_4 the solvent was removed by rotary evaporation. The residue was purified by preparative vacuum-chromatography by eluting with hexane:acetone 10:1→10:3. Yields of the products *rac*-**5a–m** are given in Table 1.

1.2.1. rac-*1-Acetoxy-3-phenoxypropan-2-ol* rac-***5a***

^{1}H NMR: 2.04 (s, 3H, CH_3COO), 4.05 (m, 2H, ArO–CH_2), 4.09 (m, 1H, CH), 4.08–4.17 (m, 2H, AcO–CH_2), 6.76–7.22 (m, 5H, ArH). IR: 3450 (br), 2940, 1740, 1600, 1500, 1370, 1240, 1050, 760 cm^{-1}. Calcd for $C_{11}H_{14}O_4$: C 62.85, H 6.71. Found: C 62.66, H 6.70.

1.2.2. rac-*1-Acetoxy-3-(1-naphthyloxy)propan-2-ol* rac-***5b***

^{1}H NMR: 2.14 (s, 3H, CH_3COO), 4.19 (m, 2H, ArO–CH_2), 4.28–4.46 (m, 3H, AcO–CH_2 and CH), 6.77–8.25 (m, 7H, ArH). IR: 3450 (br), 1710, 1580, 1460, 1400, 1370, 1270, 1240, 1110, 1050, 950, 790, 270 cm^{-1}. Calcd for $C_{15}H_{16}O_4$: C 69.22, H 6.20. Found: C 69.43, H 6.19.

1.2.3. rac-*1-Acetoxy-3-(2-naphthyloxy)propan-2-ol* rac-***5c***

^{1}H NMR: 2.12 (s, 3H, CH_3COO), 4.14 (m, 2H, ArO–CH_2), 4.31 (m, 3H, CH and AcO–CH_2), 7.13–7.78 (m, 7H, ArH). IR: 3450 (br), 2940, 1740, 1630, 1600, 1510, 1460, 1390, 1260, 1220, 1180, 1050, 840 cm^{-1}. Calcd for $C_{15}H_{16}O_4$: C 69.22, H 6.20. Found: C 69.35, H 6.22.

1.2.4. rac-*1-Acetoxy-3-(2-isopropylphenoxy)propan-2-ol* rac-***5d***

^{1}H NMR: 1.10 (d, 6H, $2CH_3$), 2.10 (s, 3H, CH_3COO), 3.17 (m, 1H, CH–Ar), 3.84 (m, 2H, ArO–CH_2), 4.16 (m, 3H, CH and AcO–CH_2), 6.67–7.11 (m, 4H, ArH). IR: 3460 (br), 2960, 2870, 1740, 1490, 1250, 1370, 1240, 1090, 1050, 750 cm^{-1}. Calcd for $C_{14}H_{20}O_4$: C 66.65, H 7.99. Found: C 66.45, H 8.02.

1.2.5. rac-*1-Acetoxy-3-(2-chlorophenoxy)propan-2-ol* rac-***5e***

^{1}H NMR: 1.94 (s, 3H, CH_3COO), 3.91 (m, 2H, ArO–CH_2), 4.16 (m, 3H, CH and AcO–CH_2), 6.74–7.21 (m, 4H, ArH). IR: 3440 (br), 2950, 1740, 1590, 1490, 1450, 1370, 1250, 1130, 1060 cm^{-1}. Calcd for $C_{11}H_{13}O_4Cl$: C 54.00, H 5.36. Found: C 54.16, H 5.34.

1.2.6. rac-*1-Acetoxy-3-(3-chlorophenoxy)propan-2-ol* rac-***5f***

^{1}H NMR: 1.97 (s, 3H, CH_3COO), 3.81 (m, 2H, ArO–CH_2), 4.11 (m, 3H, CH and AcO–CH_2), 6.62–7.09 (m, 4H, ArH). IR: 3440 (br), 2950, 1740, 1600, 1480, 1370, 1230, 1070, 1050, 860 cm^{-1}. Calcd for $C_{11}H_{13}O_4Cl$: C 54.00, H 5.36. Found: C 53.89, H 5.38.

1.2.7. rac-*1-Acetoxy-3-(4-chlorophenoxy)propan-2-ol* rac-***5g***

^{1}H NMR: 2.06 (s, 3H, CH_3COO), 3.98 (m, 2H, ArO–CH_2), 4.07 (m, 1H, CH), 4.25 (m, 2H, AcO–CH_2), 6.77–7.23 (m, 4H, ArH). IR: 3450 (br), 2950, 1740, 1600, 1490, 1370, 1240, 1170, 1090, 1050, 850 cm^{-1}. Calcd for $C_{11}H_{13}O_4Cl$: C 54.00, H 5.36. Found: C 54.12, H 5.35.

1.2.8. rac-*1-Acetoxy-3-(2-methylphenoxy)propan-2-ol* rac-***5h***

^{1}H NMR: 2.02 (s, 3H, CH_3COO), 2.22 (s, 3H, CH_3), 3.95 (m, 2H, ArO–CH_2), 4.08 (m, 1H, CH), 4.25 (m, 2H, AcO–CH_2), 6.75–7.12 (m, 4H, ArH). IR: 3450 (br), 2950, 1740, 1600, 1500, 1460, 1380, 1240, 1190, 1120, 1050, 750 cm^{-1}. Calcd for $C_{12}H_{16}O_4$: C 64.27, H 7.19. Found: C 64.40, H 7.20.

1.2.9. rac-*1-Acetoxy-3-(3-methylphenoxy)propan-2-ol* rac-***5i***

^{1}H NMR: 1.96 (s, 3H, CH_3COO), 2.16 (s, 3H, CH_3), 3.79 (m, 2H, ArO–CH_2), 3.90–4.10 (m, 3H, CH and AcO–CH_2), 6.56–7.00 (m, 4H, ArH). IR: 3450 (br), 2926, 1740, 1600, 1590, 1490, 1460, 1370, 1260, 1160, 1050, 780 cm^{-1}. Calcd for $C_{12}H_{16}O_4$: C 64.27, H 7.19. Found: C 64.18, H 7.18.

1.2.10. rac-*1-Acetoxy-3-(4-methylphenoxy)propan-2-ol* rac-***5j***

^{1}H NMR: 1.89 (s, 3H, CH_3COO), 2.10 (s, 3H, CH_3), 3.80 (m, 2H, ArO–CH_2), 4.04–4.11 (m, 3H, CH and AcO–CH_2), 6.62–6.91 (m, 4H, ArH). IR: 3450 (br), 2930, 1740, 1610, 1510, 1460, 1370, 1240, 1180, 1050, 820 cm^{-1}. Calcd for $C_{12}H_{16}O_4$: C 64.27, H 7.19. Found: C 64.21, H 7.18.

1.2.11. rac-*1-Acetoxy-3-(3-nitrophenoxy)propan-2-ol* rac-***5k***

^{1}H NMR: 2.12 (s, 3H, CH_3COO), 3.72–4.00 (m, 2H, ArO–CH_2), 4.14 (m, 1H, CH), 4.31 (m, 2H, AcO–CH_2), 7.25–7.83 (m, 4H, ArH). IR: 3330 (br), 2950, 1740, 1620, 1530, 1350, 1240, 1050, 1030, 820, 740 cm^{-1}. Calcd for $C_{11}H_{13}O_6N$: C 51.77, H 5.13, N 5.49. Found: C 51.56, H 5.12, N 5.51.

1.2.12. rac-*1-Acetoxy-3-(2,6-dimethylphenoxy)propan-2-ol* rac-***5l***

^{1}H NMR: 2.12 (s, 3H, CH_3COO), 2.30 (s, 6H, CH_3), 3.80 (m, 2H, ArO–CH_2), 3.95 (m, 1H, CH), 4.30 (m, 2H, AcO–CH_2), 6.90–7.10 (m, 3H, ArH). IR: 3456 (br), 2926, 1740, 1592, 1375, 1243, 1201, 1092, 1046, 771 cm^{-1}. Calcd for $C_{13}H_{18}O_4$: C 65.53, H 7.61. Found: C 64.97, H 7.72.

1.2.13. rac-*1-Acetoxy-3-(2,4,6-trichlorophenoxy)propan-2-ol* rac-***5m***

^{1}H NMR: 2.05 (s, 3H, CH_3COO), 4.10 (m, 3H, ArO–CH_2 and CH), 4.30 (m, 2H, AcO–CH_2), 7.30 (s, 2H, ArH). IR: 3448 (br), 3076, 2953, 1741, 1553, 1448, 1248, 1047, 1005, 857, 809 cm^{-1}. Calcd for $C_{11}H_{11}Cl_3O_4$: C 42.14, H 3.54, Cl 33.92. Found: C 42.25, H 3.50.

1.3. Preparation of 1-acetoxy-3-aryloxy-propan-2-ones ***1a–m*** *by Swern-oxidation*

To a solution of oxalyl chloride (1.35 ml, 15.0 mmol) in methylene chloride (25 ml) dimethyl sulfoxide (2.3 ml, 32.0 mol) in methylene chloride (5.0 ml) was added dropwise at −60°C. After stirring the resulting mixture for 10 minutes, racemic 1-acetoxy-3-aryloxypropan-2-ol *rac*-**5a–m**, 10 mmol in methylene chloride (10 ml) was added at −60°C followed by stirring for 20 minutes at −60°C. Then triethylamine (7.0 ml, 50 mmol) was added and the temperature was increased to room temperature within 30 min. The resulting mixture was washed with water (30 ml) and the aqueous layer was extracted with methylene chloride (20 ml). The combined organic solutions were washed with 5% hydrochloric acid (20 ml), saturated $NaHCO_3$ solution (15 ml) and brine (15 ml). After drying over Na_2SO_4 and the solvent was removed in vacuo. The resulting product was usually pure enough for the next step. In several cases the product was purified by preparative vacuum-chromatography using hexane:acetone 10:0.5→10:1 for the elution. For yields of the resulting ketones **1a–m**, see Table 1.

1.3.1. 1-Acetoxy-3-phenoxypropan-2-one ***1a***

^{1}H NMR: 2.15 (s, 3H, CH_3COO), 4.63 (s, 2H, CH_2), 4.98 (s, 2H, CH_2), 6.87–7.35 (m, 5H, ArH). IR: 1740, 1600, 1500, 1430, 1380, 1240, 1160, 1070, 760, 690 cm^{-1}. Calcd for $C_{11}H_{12}O_4$: C 63.45, H 5.81. Found: C 63.58, H 5.79.

1.3.2. 1-Acetoxy-3-(1-naphthyloxy)propan-2-one ***1b***

^{1}H NMR: 2.11 (s, 3H, CH_3COO), 4.62 (s, 2H, ArO–CH_2), 4.96 (s, 2H, AcO–CH_2), 6.48–8.17 (m, 7H, ArH). IR: 1740, 1630, 1580, 1510, 1420, 1400, 1370, 1310, 1240, 1110, 1040, 1020, 980, 860, 790, 770 cm^{-1}. Calcd for $C_{15}H_{14}O_4$: C 69.76, H 5.46. Found: C 69.48, H 5.44.

1.3.3. 1-Acetoxy-3-(2-naphthyloxy)propan-2-one ***1c***

^{1}H NMR: 2.21 (s, 3H, CH_3COO), 4.75 (s, 2H, ArO–CH_2), 5.02 (s, 2H, AcO–CH_2), 7.04–7.81 (m, 7H, ArH). IR: 1750, 1730, 1630, 1600, 1510, 1430, 1410, 1370, 1300, 1260, 1250, 1220, 1180, 1110, 1080, 1030, 1000, 840, 810, 740 cm^{-1}. Calcd for $C_{15}H_{14}O_4$: C 69.76, H 5.46. Found: C 69.57, H 5.45.

1.3.4. 1-Acetoxy-3-(2-isopropylphenoxy)propan-2-one ***1d***

^{1}H NMR: 1.15 (d, 6H, $2CH_3$), 2.03 (d, 6H, $2CH_3$), 3.25 (m, 1H, CH–Ar), 4.51 (s, 2H, ArO–CH_2), 4.92 (s, 2H, AcO–CH_2), 6.58–7.19 (m, 4H, ArH). IR: 2960, 1740, 1600, 1590, 1490, 1450, 1370, 1240, 1170, 1090, 1070, 750 cm^{-1}. Calcd for $C_{14}H_{18}O_4$: C 67.18, H 7.25. Found: C 67.42, H 7.25.

1.3.5. 1-Acetoxy-3-(2-chlorophenoxy)propan-2-one ***1e***

^{1}H NMR: 2.01 (s, 3H, CH_3COO), 4.57 (s, 2H, ArO–CH_2), 5.0 (s, 2H, AcO–CH_2), 6.72–7.31 (m, 4H, ArH). IR: 1740, 1590, 1480, 1420, 1400, 1370, 1300, 1240, 1160, 1070, 750 cm^{-1}. Calcd for $C_{11}H_{11}O_4Cl$: C 54.45, H 4.57. Found: C 54.57, H 4.55.

1.3.6. 1-Acetoxy-3-(3-chlorophenoxy)propan-2-one ***1f***

^{1}H NMR: 2.05 (s, 3H, CH_3COO), 4.60 (s, 2H, ArO–CH_2), 4.88 (s, 2H, AcO–CH_2), 6.62–7.22 (m, 4H, ArH). IR: 2930, 1740, 1590, 1480, 1430, 1380, 1290, 1230, 1170, 1070, 1020, 860, 770, 680 cm^{-1}. Calcd for $C_{11}H_{11}O_4Cl$: C 54.45, H 4.57. Found: C 54.61, H 4.58.

1.3.7. 1-Acetoxy-3-(4-chlorophenoxy)propan-2-one ***1g***

^{1}H NMR: 2.05 (s, 3H, CH_3COO), 4.56 (s, 2H, ArO–CH_2), 4.87 (s, 2H, AcO–CH_2), 6.73–7.21 (m, 4H, ArH). IR: 1740, 1600, 1490, 1430, 1370, 1280, 1240, 1160, 1070, 1020, 830 cm^{-1}. Calcd for $C_{11}H_{11}O_4Cl$: C 54.45, H 4.57. Found: C 54.39, H 4.57.

1.3.8. 1-Acetoxy-3-(2-methylphenoxy)propan-2-one ***1h***

^{1}H NMR: 2.10 (s, 3H, CH_3COO), 2.23 (s, 3H, CH_3), 4.60 (s, 2H, ArO–CH_2), 4.95 (s, 2H, AcO–CH_2), 6.64–7.09 (m, 4H, ArH). IR: 1750, 1600, 1590, 1490, 1430, 1400, 1370, 1240, 1160, 1120, 1060, 850, 810, 750 cm^{-1}. Calcd for $C_{12}H_{14}O_4$: C 64.85, H 6.35. Found: C 64.59, H 6.34.

1.3.9. 1-Acetoxy-3-(3-methylphenoxy)propan-2-one ***1i***

^{1}H NMR: 2.02 (s, 3H, CH_3COO), 2.17 (s, 3H, CH_3), 4.51 (s, 2H, ArO–CH_2), 4.87 (s, 2H, AcO–CH_2), 6.54–7.07 (m, 4H, ArH). IR: 2920, 1740, 1600, 1590, 1490, 1430, 1370, 1290, 1230, 1150, 1070, 1030, 880, 780, 690 cm^{-1}. Calcd for $C_{12}H_{14}O_4$: C 64.85, H 6.35. Found: C 64.90, H 6.35.

1.3.10. 1-Acetoxy-3-(4-methylphenoxy)propan-2-one ***1j***

^{1}H NMR: 2.11 (s, 3H, CH_3COO), 2.21 (s, 3H, CH_3), 4.57 (s, 2H, ArO–CH_2), 4.95 (s, 2H, AcO–CH_2), 6.61–7.03 (m, 4H, ArH). IR: 2930, 1740, 1610, 1510, 1430, 1410, 1380, 1290, 1240, 1160, 1070, 1020, 820 cm^{-1}. Calcd for $C_{12}H_{14}O_4$: C 64.85, H 6.35. Found: C 64.71, H 6.33.

1.3.11. 1-Acetoxy-3-(3-nitrophenoxy)propan-2-one ***1k***

^{1}H NMR: 2.11 (s, 3H, CH_3COO), 4.78 (s, 2H, ArO–CH_2), 4.91 (s, 2H, AcO–CH_2), 7.19–7.87 (m, 4H, ArH). IR: 1750, 1730, 1530, 1480, 1410, 1350, 1240, 1100, 1030, 870, 810, 740 cm^{-1}. Calcd for $C_{11}H_{11}O_6N$: C 52.18, H 4.38, N 5.53. Found: C 52.03, H 4.39, N 5.52.

1.3.12. 1-Acetoxy-3-(2,6-dimethylphenoxy)propan-2-one ***1l***

^{1}H NMR: 2.05 (s, 3H, CH_3COO), 2.14 (s, 6H, CH_3), 4.36 (s, 2H, ArO–CH_2), 4.99 (s, 2H, AcO–CH_2), 6.92 (m, 3H, ArH). IR: 2937, 1750, 1734, 1475, 1396, 1231, 1168, 1075, 1058, 788 cm^{-1}. Calcd for $C_{13}H_{16}O_4$: C 66.09, H 6.83. Found: C 66.01, H 6.79.

1.3.13. 1-Acetoxy-3-(2,4,6-trichlorophenoxy)propan-2-one ***1m***

^{1}H NMR: 2.18 (s, 3H, CH_3COO), 4.60 (s, 2H, ArO–CH_2), 5.20 (s, 2H, AcO–CH_2), 7.34 (s, 2H, ArH). IR: 3066, 2934, 1739, 1728, 1554, 1456, 1422, 1281, 1259, 1070, 1015, 858, 769 cm^{-1}. Calcd for $C_{11}H_9Cl_3O_4$: C 42.41, H 2.91. Found: C 42.36, H 2.95.

1.4. Optimization of the reaction conditions for reduction of 1-acetoxy-3-phenoxypropan-2-one **1a**

To 200 ml of media (as indicated in Table 2) 1-acetoxy-3-phenoxypropan-2-one **1a**, 500 mg, sucrose (5.0 g), baker's yeast (wet cake 12 g; or lyophilized 2.5 g) and additive (as indicated in Table 2) were added and the resulting mixture was stirred at room temperature for a period indicated in Table 2. Then the reaction mixture was extracted with ethyl acetate (2×150 ml), the combined organic layers were washed with brine (20 ml) and dried over Na_2SO_4. After removing the solvent the residue was subjected to preparative vacuum-chromatography (hexane:acetone 10:1→10:5) to yield 75–85% of pure monoacetate **5a**. The enantiomeric composition of the product **5a** (Table 2) was determined by esterification with (*R*)-MTPA-Cl [0.05 mmol scale; triethylamine, cat. DMAP, in CCl_4, 50°C, 3 h] and ^{1}H NMR analysis of the **5a**-MTPA-ester [characteristic signals: 2.001 (s, $COCH_3$) for (*S*)-**5a**-MTPA ester; 2.065 (s, $COCH_3$) for (*R*)-**5a**-MTPA ester].

1.5. Preparation of optically active 1-acetoxy-3-aryloxypropan-2-ols **5** or ent-**5** and/or 3-aryloxypropane-1,2-diols (**4** or ent-**4**) by baker's yeast reaction

General procedure: To 200 ml of sodium phosphate buffer (0.15 M, pH 7) 1-acetoxy-3-aryloxypropan-2-one **1a–k**, 0.5 g, sucrose (5.0 g) and baker's yeast (12.0 g wet) were added and the resulting mixture was stirred at room temperature for a period indicated in Table 3. Work up and chromatographic separation was carried out similarly as described in the preceding section and yielded monoacetate **5** or *ent*-**5** and/or diol **4** or *ent*-**4** fractions. The IR and ^{1}H NMR spectra of the resulting 1-acetoxy-3-aryloxypropan-2-ols **5** or *ent*-**5** and/or 3-aryloxypropan-1,2-diols **4** or *ent*-**4** were similar to those of the corresponding racemic compounds. For yield, enantiomeric composition and configuration of the products, see Table 3.

Enantiomeric composition of several diols **4d–j** were determined from ^{1}H NMR spectra of the corresponding di-MTPA derivatives [esterification with (*R*)-MTPA-Cl: triethylamine, cat. DMAP, in CCl_4, 50°C, 3 h; characteristic signals: di-MTPA ester of (*R*)-**4d**: 5.638 (mc, CH–O); di-MTPA ester of (*S*)-**4d**: 5.699 (mc, CH–O); di-MTPA ester of (*R*)-**4e**: 5.669 (mc, CH–O); di-MTPA ester of (*S*)-**4e**: 5.713 (mc, CH–O); di-MTPA ester of (*R*)-**4f**: 5.620 (mc, CH–O); di-MTPA ester of (*S*)-**4f**: 5.665 (mc, CH–O); di-MTPA ester of (*R*)-**4g**: 5.627 (mc, CH–O); di-MTPA ester of (*S*)-**4g**: 5.645 (mc, CH–O); di-MTPA ester of (*R*)-**4h**: 5.641 (mc, CH–O); di-MTPA ester of (*S*)-**4h**: 5.705 (mc, CH–O); di-MTPA ester of (*R*)-**4i**: 5.630 (mc, CH–O); di-MTPA ester of (*S*)-**4i**: 5.675 (mc, CH–O); di-MTPA ester of (*R*)-**4j**: 5.627 (mc, CH–O); di-MTPA ester of (*S*)-**4j**: 5.655 (mc, CH–O)].

For determination of configuration, several (*R*)-diols **4** were prepared from (*R*)-3-chloropropane-1,2-diol [(*R*)-**2**, 95% e.e.] by coupling with the corresponding phenol **3** [(*R*)-**2**: 1.2 mmol, **3**: 1.5 mmol; according to the procedure used for the preparation of the racemic diols].

For direct comparison of the specific rotations, the monoacetate fractions **5** were saponified [1.2 M NaOMe/MeOH, r.t., 10 min, 80–95% yields] to diols **4** (Table 4).

Acknowledgements

The Hungarian OTKA Foundation (Project Nos: 1759 and 14894) is gratefully acknowledged for financial support. J.B. thanks the Zoltán Magyary Foundation for a postdoctoral fellowship.

Table 4

4	Ar	Solvent (c= 1)	$[\alpha]_D$ (conf.)		
			[from 5]	[diol fraction]	[from (*R*)-2]
a	phenyl [a]	ethanol	-9.0 (*R*)		-10.5 (*R*)
b	1-naphthyl [b]	methanol		-6.8 (*R*)	-6.5 (*R*)
d	2-isopropylphenyl [c]	hexane-isopropanol	-4.2 (*S*)	13.2 (*R*)	14.1 (*R*)
e	2-chlorophenyl [d]	hexane-ethanol 4:1		13.3 (*R*)	
f	3-chlorophenyl [e]	ethanol	-9.0 (*R*)	-7.9 (*R*)	
g	4-chlorophenyl [f]	methanol	-8.3 (*R*)	-8.7 (*R*)	
h	2-methylphenyl [g]	hexane-isopropanol	12.1 (*R*)	17.5 (*R*)	
i	3-methylphenyl [h]	ethanol	-6.1 (*R*)	-6.5 (*R*)	
j	4-methylphenyl [i]	hexane-isopropanol	6.5 (*R*)	8.6 (*R*)	12.1 (*R*)
k	3-nitrophenyl [c]	ethanol		-13.7 (*R*)	-12.3 (*R*)
l	2,6-dimethylphenyl [c]	acetone	2.2 (*R*)	2.2 (*R*)	2.1 (*R*)
m	2,4,6-trichlorophenyl [c]	acetone	2.3 (*R*)	2.2 (*R*)	2.3 (*R*)

[a] Lit. [1]: (*R*)-**4a** (98 %e.e.): $[\alpha]_D$= -10.8 (1, EtOH), (*S*)-**4a** (91 %e.e.): $[\alpha]_D$= 10.2 (1, EtOH); [b] Lit.: (*R*)-**4b**: $[\alpha]_D$= -6.76 (1, MeOH)[20], -8.1 (1, MeOH)[21], -8.5 (4.5, MeOH)[22], (*S*)-**4b**: $[\alpha]_D$= 6.7 (1, MeOH)[20], 6.9 (1, MeOH)[21], 7.6 (1, MeOH)[23], 7.7 (1, MeOH)[24], 8.4 (4.5, MeOH)[22]; [c] No published optical rotation data were found; [d] Lit. [1]: (*R*)-**4e** (99 %e.e.): $[\alpha]_D$= 14.0 (1, hexane-EtOH 4:1), (*S*)-**4e** (99 %e.e.): $[\alpha]_D$= -13.4 (1, hexane-EtOH 4:1); [e] Lit. [1]: (*R*)-**4f** (>99 %e.e.): $[\alpha]_D$= -12.7 (1, EtOH), (*S*)-**4f** (98 %e.e.): $[\alpha]_D$= 13.7 (1, EtOH); [f] Lit. [1]: (*R*)-**4g** (95 %e.e.): $[\alpha]_D$= -11.8 (1, EtOH), (*S*)-**4g** (97 %e.e.): $[\alpha]_D$= 12.3 (1, EtOH); [g] Lit. [1]: (*R*)-**4h** (>99 %e.e.): $[\alpha]_D$= 19.8 (0.9, hexane-*i*-PrOH 4:1), (*S*)-**4h** (>99 %e.e.): $[\alpha]_D$= -19.3 (0.9, hexane-*i*-PrOH 4:1); [h] Lit. [1]: (*R*)-**4i** (>99 %e.e.): $[\alpha]_D$= -9.3 (1, EtOH), (*S*)-**4i** (97 %e.e.): $[\alpha]_D$= 9.5 (1, EtOH); [i] Lit. [1]: (*R*)-**4j** (97 %e.e.): $[\alpha]_D$= -9.2 (1, EtOH), (*S*)-**4j** (71 %e.e.): $[\alpha]_D$= 7.5 (1, EtOH).

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