Tetrahedron: *Asymmetry* 23 (2012) 395–400

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Enzymatic synthesis of both enantiomeric forms of 3-allyloxy-propane-1,2-diol

Silvana Casati [a], Enzo Santaniello [b], Pierangela Ciuffreda [a,*]

[a] Università degli Studi di Milano, Dipartimento di Scienze Cliniche 'L. Sacco', via G.B. Grassi 74, 20157 Milano, Italy
[b] Università degli Studi di Milano, Dipartimento di Medicina, Chirurgia e Odontoiatria, via A. di Rudinì 8, 20142 Milano, Italy

ARTICLE INFO

Article history:
Received 15 February 2012
Accepted 13 March 2012
Available online 5 April 2012

ABSTRACT

The stereoselective synthesis of (*S*)- and (*R*)-3-allyloxy-propane-1,2-diol has been accomplished in four steps from (*RS*)-3-allyloxy-propane-1,2-diol. Only one intermediate, namely 1-benzoyloxy-3-allyloxy-2-propanone has been prepared by a chemical reaction, that is, pyridinium chlorochromate oxidation of 1-benzoyloxy-3-allyloxypropan-2-ol. All of the remaining reactions (regioselective acylations, asymmetric bioreduction of prochiral ketones, and enzymatic alcoholysis) have been carried out in the presence of biocatalysts.

1. Introduction

Glycerol derivatives are common building blocks for a number of chiral natural and synthetic products.[1] A general chemical approach to these requires selective blocking of a primary hydroxyl group in the 1,2-diol system and further manipulation, including protection–deprotection steps. This process is not always totally selective and proceeds in variable yield.[2,3] Recently, the use of enzymes has been reported for the preparation of chiral glycerol derivatives.[4]

Herein we report a novel and simple chemo-enzymatic approach for the preparation of both (*S*)- and (*R*)-3-allyloxy-propane-1,2-diol [(*S*)-**1** and (*R*)-**1**], a glycerol derivative that has been used as an intermediate for further elaboration to more complex chiral molecules such as an analogue of the platelet-activating factor (PAF)[5] or plasmenylcholine.[6]

The usefulness of allyl ethers in asymmetric organic synthesis is well established; therefore the 3-allyl ether moiety in compound **1** makes this glycerol derivative particularly attractive, due to the stability of the allyl group during further synthetic manipulations and to the increasing number of methods available for the removal of this protecting group.[7]

2. Results and discussion

2.1. Lipase-catalyzed acylation of 3-allyloxy-propane-1,2-diol 1

In order to obtain both the enantiomeric forms of 3-allyloxy-propane-1,2-diol, (*S*)-**1** and (*R*)-**1**, we tested a few lipases with well recognized stereoselective transesterification activity in organic solvents using vinyl acetate (VA)[8] or vinyl benzoate (VB)[9] as acyl transfer reagents. We have applied both reagents to the biocatalytic asymmetric synthesis of chiral glycerol intermediates[10] as well as to enzymatic benzoylation and debenzoylation.[11,12]

Specifically, microbial lipases from *Pseudomonas cepacia* (PCL), *Muchor miehei* (MML), and *Candida antarctica* (CAL-B) were selected as biocatalysts. *tert*-Butyl methyl ether (*t*BuOMe) was selected as a sole solvent, due to its frequent use in several synthetic applications involving lipases.

The transesterifications were carried out using a millimole of commercially available diol **1**, and stopped at <50% conversion to monoacetate **2** or monobenzoate **3**. In all cases products with moderate enantiomeric excess (ee, maximum 57% and 60% respectively for acetate **2** and benzoate **3**) were formed (Scheme 1 and Table 1).

As a general comment, with VA a fast esterification (0.15–1.5 h for 32–37% conversion to the monoacetate **2**) was observed. The rate of the enzymatic benzoylation with VB depends on the lipase and MML catalyzed the fastest reaction (0.5 h for 40% conversion to the monobenzoate **3**).

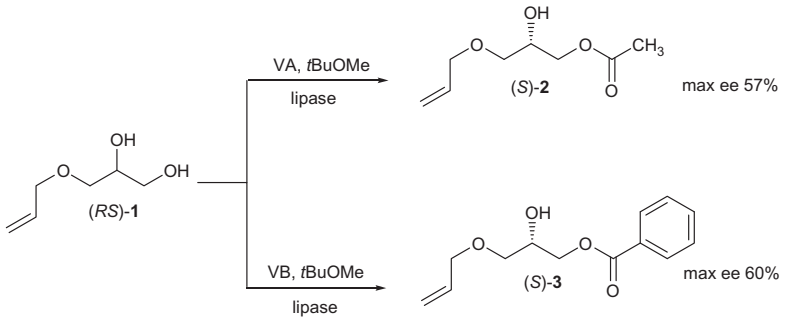
The (*S*)-configuration was assigned to the products of the enzymatic acylation, by preparing the corresponding Mosher esters with (*R*) or (*S*)-α-methoxy-α-trifluoromethylphenylacetic acid according to a well established protocol.[13]

For (*S*)-monoacetates **2** the ee (38–57%) of the enzymatic procedure was established by recording and analyzing the ^{1}H NMR spectra of the MTPA esters of each enzymatic preparation. In the case of the (*S*)-monobenzoates **3** the ee (54–60%) was established by GC using a chiral column.

The ee of the above procedure could be eventually improved using different experimental conditions, testing other lipases or applying other resolution conditions reported for the enzymatic transesterification of 1,2-diol systems.[14] However, this approach is time consuming and so we preferred to investigate another chemo-enzymatic approach for the preparation of both enantiomeric forms of 3-allyloxy-propane-1,2-diol, (*S*)-**1** and (*R*)-**1**.

* Corresponding author.
E-mail address: pierangela.ciuffreda@unimi.it (P. Ciuffreda).

0957-4166/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetasy.2012.03.008

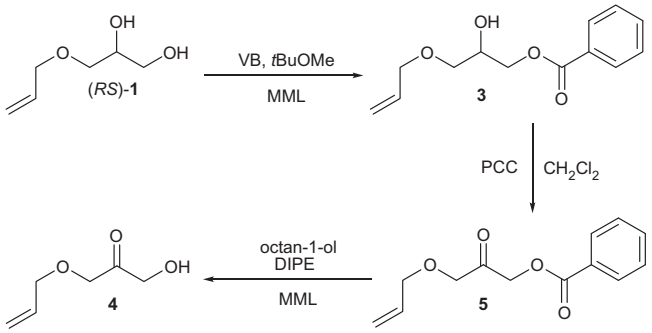


Scheme 1. Enzymatic resolution of (*RS*)-3-allyl-propane-1,2-diol **1** to (*S*)-acetate **2** or (*S*)-benzoate **3**.

Table 1
Lipase-catalyzed acetylation and benzoylation of 3-allyloxy-propane-1,2-diol **1** in *t*BuOMe

Enzyme	Acylating agent[a]	Conversion (%)	Time (h)	Product[b]	ee[c]
PCL	VA	37	1.5	*S*-2	40[d]
MML	VA	36	0.15	*S*-2	57[d]
CAL	VA	32	0.15	*S*-2	38[d]
PCL	VB	39	24	*S*-3	56[e]
MML	VB	40	0.5	*S*-3	60[e]
CAL	VB	36	2.3	*S*-3	54[e]

[a] 3 equiv.
[b] Configuration determined from ^{1}H NMR spectrum of the MTPA ester.
[c] Determined for the product.
[d] % ee were determined from ^{1}H NMR spectrum of the MTPA ester.
[e] % ee were calculated using GC chiral column.

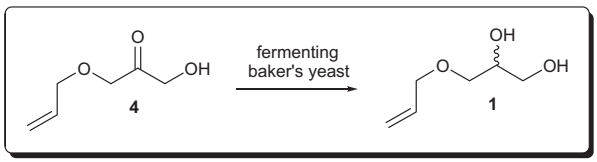


Scheme 3. Chemo-enzymatic synthesis of 3-allyloxy-1-hydroxypropan-2-one **4**.

2.2. Fermenting baker's yeast bioreduction of hydroxyketone 4 and its esters

We considered the asymmetric bioreduction of a suitable hydroxyketone (or that of the corresponding esters) since the bioreduction of carbonyl compounds has been investigated extensively due to its high stereoselectivity, mild reaction conditions and environmental compatibility.[15] The most commonly used biocatalyst in asymmetric reduction is baker's yeast. This microorganism is commercially available, easy to handle, and able to be used in the asymmetric reduction of a wide range of carbonyl functionalities.[16] The bioreduction of hydroxyketones and related esters has also been applied in the preparation of optically active 1,2-diols or to chiral mono-protected glycerol.[17]

For the preparation of one enantiomer of 3-allyloxy-propane-1,2-diol **1** by baker's yeast bioreduction, the hydroxyketone **4** was required (Scheme 2).



Scheme 2. Baker's yeast-mediated bioreduction of 3-allyloxy-1-hydroxypropan-2-one **4**.

The hydroxyketone **4** was prepared by a chemo-enzymatic approach as shown in Scheme 3. Thus, the starting diol (*RS*)-3-allyloxy-propane-1,2-diol (*RS*)-**1** was converted into the stable monobenzoate **3** by an enzymatic regioselective monobenzoylation in the presence of lipase from *Muchor miehei* (MML) in *t*BuOMe using VB as an acyl transfer agent.[9] The reaction proceeded smoothly at room temperature to provide exclusively 1-benzoyloxy-3-allyloxypropan-2-ol **3** with greater than 95% yield. The ketone **5** was obtained from its hydroxy precursor **3** by oxidation with PCC (64% yield).

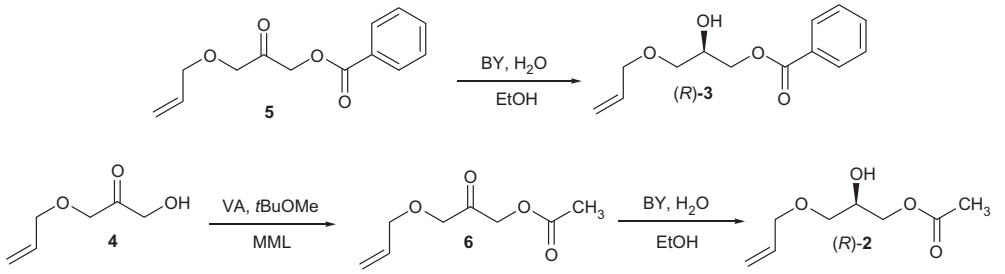
A smooth debenzoylation of ketone **5** to the required hydroxyketone **4** was achieved enzymatically with MML in diisopropyl ether (DIPE), using octan-1-ol as the acceptor of the benzoyl group.[12]

The bioreduction of 3-allyloxy-1-hydroxypropan-2-one **4** gave the corresponding alcohol (*R*)-**1** in 2.0 h in high yields (68%). However, the enantioselectivity of the bioreduction was not satisfactory (75% ee), and this could be tentatively explained by considering that baker's yeast has a plurality of reducing enzymes.[18] Thus, we cannot exclude that an oxidoreductase with opposite stereoselectivity is present in the reducing medium. Another possible explanation for the observed, non-complete enantioselectivity could rely on a partial tautomerization of the hydroxyketone **4** to the corresponding (*RS*)-hydroxyaldehyde and reduction of this compound to (*RS*)-**1**.[19]

In order to investigate the preparation of (*S*)-**1**, we relied on the observation that, by altering the size of the substituents on the keto group, a reverse enantioselectivity of baker's yeast reduction can be observed. This has also been broadened to ketoesters[18] or hydroxyketones.[20]

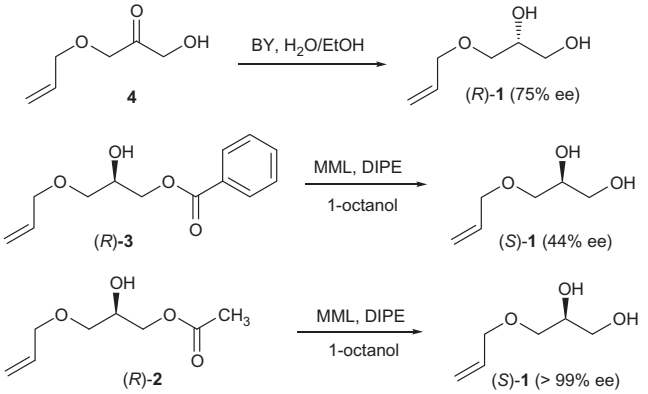
We therefore decided to submit the previously prepared 1-benzoyloxyderivative **5** to the baker's yeast bioreduction. The corresponding alcohol (*R*)-**3**[21] was obtained in 3.5 h in good yields (78%), but the reduction proceeded with only moderate selectivity (44%).

The acetate of the hydroxyketone **4** was quantitatively prepared by a lipase mediated acetylation of **5** using MML and VA in *t*BuOMe. The acetoxy derivative **6** proved to be a better substrate for the asymmetric reduction with baker's yeast than the benzoyloxy derivative **5** or the hydroxyketone **4**. In fact, when 1-acetoxy-3-allyloxypropan-2-one **6** was submitted to an asymmetric reduction with baker's yeast, the corresponding alcohol (*R*)-**2** was obtained in 3.5 h in high yields (76%) and high ee (>98%) (Scheme 4).



Scheme 4. Baker's yeast mediated reduction of 1-benzoyloxy-3-allyloxypropan-2-one **5** and 1-acetoxy-3-allyloxypropan-2-one **6**.

In conclusion, the reduction of the hydroxyketone **4** affords directly the (*R*)-diol **1** (75% ee). The enantiomeric (*S*)-3-allyloxy-propane-1,2-diol **1** can be prepared by MML-catalyzed deacylation of (*R*)-1-benzoyloxy-3-allyloxypropan-2-ol **3** and (*R*)-1-acetoxy-3-allyloxy-propan-2-ol **2** (44 and >99% ee, respectively; see Scheme 5).



Scheme 5. Enzymatic synthesis of enantiomerically enriched (*R*)-**1** and (*S*)-**1**.

In order to assign unequivocally the configuration of the C(2)-secondary alcohol of glycerol derivatives (compounds **1**–**3**) obtained by the asymmetric bioreduction of prochiral ketones **4**, **5,** and **6**, we applied the modified Mosher's method[13] to the products of the baker's yeast reduction. Treatment of compounds **1**, **2,** and **3** with (*R*)- and (*S*)-α-methoxy-α-trifluoromethylphenyl acetic acid (MTPA) in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine in dichloromethane afforded the corresponding (*R*)- and (*S*)-MTPA esters.[10]

The $\Delta\delta$ (δ_S–δ_R) values, expressed in Hertz, obtained from ^{1}H NMR spectra at 500 MHz, are shown in Table 2. All protons of the allyl moiety have $\Delta\delta$ >0 values while the C(1)-methylene protons and acyl group (in Table 2 depicted with R) have a $\Delta\delta$ <0 values. According to the model adopted to determine the absolute configuration of secondary alcohols,[13] we conclude that the configuration of the alcohol in all cases is (*R*). This result confirmed the original configurational assignment that was based on chemical correlations by alcoholysis to the corresponding alcohol **1** and the measurement of its specific rotation.

3. Conclusion

In conclusion, a selective and facile strategy to prepare both (*S*)- and (*R*)- 3-allyloxy-propane-1,2-diol has been developed. The most satisfactory result, in terms of enantioselectivity, was obtained by the baker's yeast bioreduction of 1-acetoxy-3-allyloxypropan-2-one **6** from which enantiomerically pure (*S*)-**1** could be prepared. Compound (*R*)-**1** can be prepared by two different biocatalytical approaches, that is, enzymatic transesterification of the racemic diol **1** (maximum 60% ee) or the fermentation route carried out on the hydroxyketone **4** (75% ee). Moreover, (*R*)-3-allyloxy-propane-1,2-diol (*R*)-**1** (maximum 60%) has been obtained by the alcoholysis of the (*S*)-acetate **2** and (*S*)-benzoate **3** by the MML-catalyzed acylation of (*RS*)-**1**.

Finally, it is noteworthy that the only chemical step in the whole synthetic approach corresponds to the PCC oxidation of 1-benzoyloxy-3-allyloxypropan-2-ol **3** to 1-benzoyloxy-3-allyloxy-propan-2-one **5**. A few attempts to carry out the oxidation step enzymatically using commercial NAD(P)$^+$-dependent oxidoreductases[22] have been, at present, unsuccessful.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded at 298 K in the indicated deuterated solvents on a Bruker AVANCE 500 spectrometer equipped with a 5 mm broadband reverse probe with field *z*-gradient operating at 500.13 MHz for ^{1}H and 125.76 MHz for ^{13}C. Chemical shifts (δ) are given as parts per million relative to the residual solvent peak and coupling constants (*J*) are in Hertz. The splitting pattern abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, and bs, broad peak. Column chromatography was performed on Silica Gel 60 (70–230 mesh) using the specified eluents. Optical rotations were measured on a Perkin-Elmer 241 polarimeter (sodium D line at 25 °C). Melting points were determined with a Stuart Scientific SMP3 melting point apparatus and are uncorrected.

The progress of the reactions was monitored by analytical thin-layer chromatography (TLC) on pre-coated glass plates (silica gel 60 F254-plate-Merck, Darmstadt, Germany) and the products were visualized by UV light.

Purity of all compounds ($\geqslant$99%) was verified by thin layer chromatography and NMR measurements. The enantiomeric purity of alcohols (*S*)-**1** and (*R*)-**1** was determined by ^{1}H NMR analysis of their Mosher's ester prepared as previously described.[10]

The enantiomeric excess (ee) of the enantiomerically enriched monobenzoate **3** was determined by a HP 6890 series split/less GC, equipped with chiral column, HP chiral 20% permethylated B-cyclodextrin (30 m × 0.32 mm × 0.25 μm), and FID detector. The following conditions were used for the chiral separation: injector 200 °C, detector 200 °C, carrier gas nitrogen, column flow: 1.00 ml/min, maximum temperature 220 °C, and temperature program: start 180 °C, hold time 3 min, rate 50 °C/min to 200 °C hold time 15.00 min. Retention times of (*R*)- and (*S*)-**3** were found to be 16.8 and 16.3 min.

Elemental analyses were obtained for all intermediates and are within ±0.4% of theoretical values.

The chemicals and solvents, including diol **1**, were obtained from Sigma–Aldrich and used without further purification.

Lipase from *Pseudomonas* sp. (Lipase PS 'Amano', 30 U/mg solid) was purchased from Amano Pharmaceutical. *Candida antarctica* lipase (Novozym 435®, acrylic resin supported lipase, 11.4 U/mg

Table 2
$\Delta\delta = \delta_S - \delta_R$ values, expressed in Hertz[a] of the (*S*)-MTPA and (*R*)-MTPA esters

Substrate	H-1a	H-1b	R	H-3	$CH_2CH{=}CH_2$	$CH{=}CHH$	$CH{=}CHH$	$CH{=}CHH$
(*R*)-**1**	−60	−30	—	+45	+40	+25	+15	+10
(*R*)-**2**	−10	−50	−10	+45	+45	+35	+30	+25
(*R*)-**3**	−45	−35	−5; −10; −20	+35	+40	+30	+30	+20

[a] Obtained from ^{1}H NMR spectrum at 500 MHz.

solid) was purchased from Novo Nordisk Bioindustrial Group. Lipase from *Muchor miehei* (Chirazyme® L-9,c.-f., C2, lyo, carrier-fixed lipase, 8 U/mg solid) was purchased from Roche Diagnostics GmbH. Baker's yeast by *Saccharomyces cerevisiae* was purchased from a local store. There are no rules to define the amount of the enzyme to be used in organic solvents and, therefore, we decided to rely upon the hydrolytic activity of the lipases expressed as units.

4.2. General procedure for lipase-mediated benzoylation and acetylation of 3-allyloxy-propane-1,2-diol 1

Substrates (1.0 mmol), VA or VB, (3.0 mmol) and lipase (PCL 80 mg; MML 100 mg; CAL 200 mg) were suspended in 10.0 ml of *t*BuOMe. The mixture was stirred at rt and the formation of the acetylated or benzoylated compounds was monitored by GC analysis. The reaction was stopped at the reported conversion (see Table 1) by filtration of the enzyme and evaporation of the solvent at reduced pressure. The residue was then purified by chromatography. For time, see Table 1.

4.2.1. (*S*)-1-Acetoxy-3-allyloxy-propan-2-ol 2[23]

According to the general procedure, compound **2** was prepared from (*RS*)-3-allyloxy-propane-1,2-diol **1** and purified by column chromatography (petroleum ether/ethyl acetate 7:3). Viscous liquid; R_f (40% ethyl acetate/petroleum ether) 0.40; ^{1}H NMR ($CDCl_3$) δ 2.10 (3H, s, $COCH_3$), 3.46 (1H, dd, J = 6.2, 9.7 Hz, 3-C*H*HO), 3.53 (1H, dd, J = 4.2, 9.7 Hz, 3-CH*H*O), 4.00–4.05 (3H, m, 2-C*H*OH and $OCH_2CH{=}CH_2$), 4.12 (1H, dd, J = 6.2, 11.8 Hz, 3-C*H*HO), 4.18 (1H, dd, J = 4.9, 11.8 Hz, 3-CH*H*O), 5.20 (1H, dd, J = 2.0, 10.4 Hz, (*Z*)-CH=C*H*H), 5.28 (1H, dd, J = 2.0, 17.3 Hz, (*E*)-CH=CH*H*), 5.91 (1H, ddt J = 7.2, 10.4, 17.3 Hz, C*H*=CH_2); ^{13}C NMR δ 20.4 (CH_3), 65.6 (1-C), 68.8 (2-C), 70.9 (3-C), 72.4 ($OCH_2CH{=}CH_2$), 117.5 ($CH{=}CH_2$), 134.3 (*C*H=CH_2), 171.2 (CO).

4.2.2. 1-Benzoyloxy-3-allyloxypropan-2-ol 3[24]

According to the general procedure, compound **3** was prepared from (*RS*)-3-allyloxy-propane-1,2-diol **1** and purified by column chromatography (petroleum ether/ethyl acetate 8:2). Viscous liquid; R_f (20% ethyl acetate/petroleum ether) 0.31; ^{1}H NMR ($CDCl_3$) δ 3.56 (1H, dd, J = 5.5, 9.7 Hz, 3-C*H*HO), 3.62 (1H, dd, J = 6.2, 9.7 Hz, 3-CH*H*O), 4.05 (2H, d, J = 5.6 Hz, $OCH_2CH{=}CH_2$), 4.18 (1H, dddd, J = 4.8, 5.5, 6.2, 7.6 Hz, 2-C*H*OH), 4.38–4.45 (2H, m, part AB of ABX system, 1-CH_2O), 5.20 (1H, dd, J = 2.0, 10.4 Hz, (*Z*)-CH=C*H*H), 5.29 (1H, dd, J = 2.0, 17.3 Hz, (*E*)-CH=CH*H*), 5.90 (1H, ddt J = 7.2, 10.4, 17.3 Hz, C*H*=CH_2), 7.43 (2H, dd, J = 7.0, 7.0 Hz, *m*-Ph H), 7.55 (1H, t, J = 7.0, *p*-Ph H), 8.05 (2H, d, J = 7.0, *o*-Ph H); ^{13}C NMR δ, 66.0 (1-C), 68.9 (2-C), 71.0 (3-C), 72.4 ($OCH_2CH{=}CH_2$), 117.5 ($CH{=}CH_2$), 128.4 (*m*-PhCH), 129.7 (*o*-PhCH), 129.9 (Ph*C*), 133.1 (*p*-PhCH), 134.3 (*C*H=CH_2), 166.6 (CO).

4.3. 1-Benzoyloxy-3-allyloxypropan-2-one 5

PCC (5.0 g; 24 mmol) was added to a solution of **3** (1.32 g, 5.6 mmol) in dichloromethane (20 ml). The mixture was stirred at room temperature for 24 h, then filtered on a Celite pad. Evaporation of the solvent and purification on column chromatography (petroleum ether/ethyl acetate 8:2) gave **5**. Yield: 840 mg, 64% of viscous liquid. R_f (20% ethyl acetate/petroleum ether) 0.58; ^{1}H NMR ($CDCl_3$) δ 4.11 (2H, d, J = 5.6 Hz, $OCH_2CH{=}CH_2$), 4.22 (2H, s, 3-CH_2), 5.14 (2H, s, 1-CH_2), 5.27 (1H, dd, J = 1.4, 10.0 Hz, (*Z*)-CH=C*H*H), 5.34 (1H, dd, J = 1.4, 17.3 Hz, (*E*)-CH=CH*H*), 5.99 (1H, ddt J = 5.6, 10.0, 17.3 Hz, CH=CH_2), 7.47 (2H, dd, J = 7.0, 7.0 Hz, *m*-Ph H), 7.60 (1H, t, J = 7.0, *p*-Ph H), 8.10 (2H, d, J = 7.0, *o*-Ph H); ^{13}C NMR δ, 67.3 (1-C), 72.6 ($OCH_2CH{=}CH_2$), 73.8 (3-C), 118.3 ($CH{=}CH_2$), 128.4 (*m*-PhCH), 129.2 (Ph*C*), 129.9 (*o*-PhCH), 133.4 (*p*-PhCH), 133.5 (*C*H=CH_2), 165.9 (OCOPh), 202.0 (CO). Anal. Calcd for $C_{13}H_{14}O_4$ (234.09): C, 66.66; H, 6.02. Found: C, 66.79; H, 6.14.

4.4. 1-Acetoxy-3-allyloxypropan-2-one 6

Compound **4** (130 mg, 1.0 mmol), vinyl acetate (3.0 mmol), and MML (100 mg) were suspended in 10.0 ml of *t*BuOMe. The mixture was stirred at rt for 4 h until GC analysis showed up to 100% conversion. The mixture was filtered and evaporated at reduced pressure. Yield 169 mg (98%) of viscous liquid. R_f (20% ethyl acetate/petroleum ether) 0.42; ^{1}H NMR ($CDCl_3$) δ 2.16 (3H, s, $COCH_3$), 4.06 (2H, d, J = 5.6 Hz, $OCH_2CH{=}CH_2$), 4.13 (2H, s, 3-CH_2), 4.89 (2H, s, 1-CH_2), 5.25 (1H, dd, J = 1.4, 10.0 Hz, (*Z*)-CH=C*H*H), 5.35 (1H, dd, J = 1.4, 17.3 Hz, (*E*)-CH=CH*H*), 5.89 (1H, ddt J = 5.6, 10.0, 17.3 Hz, CH=CH_2); ^{13}C NMR δ 20.5 (CH_3), 67.0 (1-C), 72.5 ($OCH_2CH{=}CH_2$), 73.7 (3-C), 118.4 ($CH{=}CH_2$), 133.4 (*C*H=CH_2), 170.5 ($OCOCH_3$), 202.2 (CO). Anal. Calcd for $C_8H_{12}O_4$ (172.18): C, 55.81; H, 7.02. Found: C, 55.89; H, 7.14.

4.5. General procedure for the microbial reduction

A suspension of baker's yeast (20 g) and sucrose (20 g) in water (100 ml) was preincubated at 38 °C for 20 min. Thereafter, a solution of the ketone (1.5 mmol) in EtOH (2 ml) was added and the resulting mixture was stirred magnetically at 38 °C for 2 h, until GC analysis showed up 95% conversion. The mixture was filtered on a Celite pad and extracted with ethyl acetate (3 × 30 ml). The solvent was removed under reduced pressure and the residue was purified by column chromatography to afford the desired alcohol which was recovered as an oil.

4.5.1. (*R*)-1-Benzoyloxy-3-allyloxypropan-2-ol (*R*)-3[5]

(*R*)-**3** was prepared from 1-benzoyloxy-3-allyloxypropan-2-one **5** (350 mg, 1.5 mmol), purified by column chromatography (petroleum ether/ethyl acetate 8:2) to yield 276 mg (78%); $[\alpha]_D^{20} = -1.3$ (*c* 1, $CHCl_3$), 44% ee. R_f (20% ethyl acetate/ petroleum ether) 0.31.

4.5.2. (*R*)-3-Allyloxypropane-1,2-diol (*R*)-1[25]

Compound (*R*)-**1** was prepared from 3-allyloxy-1-hydroxypropan-2-one **4** (195 mg, 1.5 mmol), purified by column chromatography (petroleum ether/ethyl acetate 7:3) to yield 135 mg (68%); viscous liquid. $[\alpha]_D^{20} = +5.5$ (*c* 1, $CHCl_3$), 75% ee {lit.[25] $[\alpha]_D^{25} = +7.5$ (*c* 0.11)}. R_f (40% ethyl acetate/petroleum ether) 0.12; ^{1}H NMR ($CDCl_3$) δ 3.43 (1H, dd, J = 5.5, 9.7 Hz, 3-C*H*HO), 3.47 (1H, dd, J = 4.2, 9.7 Hz, 3-CH*H*O), 3.54 (1H, dd, J = 6.2, 11.8 Hz, 1-C*H*HO),

3.62 (1H, dd, J = 3.5, 11.8 Hz, 3-CH*H*O), 3.81 (1H, dddd, J = 3.5, 4.2, 5.5, 6.2, Hz, 2-C*H*OH), 3.98 (2H, d, J = 6.2 Hz, OCH_2CH=CH$_2$), 5.16 (1H, dd, J = 2.0, 10.4 Hz, (*Z*)-CH=C*H*H), 5.24 (1H, dd, J = 2.0, 17.3 Hz, (*E*)-CH=CH*H*), 5.86 (1H, ddt J = 6.2, 10.4, 17.3 Hz, CH=CH_2); ^{13}C NMR δ, 63.7 (1-C), 70.9 (2-C), 71.5 (3-C), 72.3 (OCH_2CH=CH$_2$), 117.4 (CH=CH_2), 134.2 (C*H*=CH$_2$).

4.5.3. (*R*)-1-Acetoxy-3-allyloxy-propan-2-ol (*R*)-2[23]

(*R*)-**2** was prepared from 1-acetoxy-3-allyloxypropan-2-one **6** (258 mg, 1.5 mmol), purified by column chromatography (petroleum ether/ethyl acetate 7:3) yield 198 mg (76%); viscous liquid. $[\alpha]_D^{20} = +1.4$ (c 1, CHCl$_3$), >98% ee.

4.6. General procedure for lipase-mediated alcoholysis

To a solution of benzoate or acetate (1.0 mmol) in DIPE (10.0 ml) containing octan-1-ol (2.5 mmol) MML (200 mg) was added. The suspension was stirred vigorously at room temperature and the progress of the reaction monitored until a TLC analysis (petroleum ether/ethyl acetate 80:20) showed up 100% conversion. After 20 h the reaction mixture was filtered to remove lipase. The filtrate was diluted with AcOEt and washed with saturated aq NaHCO$_3$, the organic layer washed with saturated aq NaCl and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography

4.6.1. 3-Allyloxy-1-hydroxypropan-2-one 4

Compound **4** was prepared from 1-benzoyloxy-3-allyloxypropan-2-one **5** (350 mg, 1.5 mmol), purified by column chromatography (petroleum ether/ethyl acetate 8:2) yield 126 mg (65%); viscous liquid. R_f (40% ethyl acetate/petroleum ether) 0.44; ^{1}H NMR (CDCl$_3$) δ 4.07 (2H, d, J = 5.6 Hz, OCH_2CH=CH$_2$), 4.18 (2H, s, 3-CH_2), 4.48 (2H, s, 1-CH_2), 5.27 (1H, dd, J = 1.4, 10.0 Hz, (*Z*)-CH=C*H*H), 5.33 (1H, dd, J = 1.4, 17.3 Hz, (*E*)-CH=CH*H*), 5.90 (1H, ddt J = 5.6, 10.0, 17.3 Hz, CH=CH_2); ^{13}C NMR δ, 66.7 (1-C), 72.7 (OCH_2CH=CH$_2$), 73.3 (3-C), 118.4 (CH=CH_2), 133.6 (C*H*=CH$_2$) 208.8 (CO). Anal. Calcd for $C_6H_{10}O_3$ (130.06): C, 55.37; H, 7.74. Found: C, 55.49; H, 7.84.

4.6.2. (*S*)-3-Allyloxy-propane-1,2-diol (*S*)-1[25]

According to the general procedure, compound (*S*)-**1** was obtained from (*R*)-1-benzoyloxy-3-allyloxypropan-2-ol (*R*)-**3** (1.5 mmol) or from (*R*)-1-acetoxy-3-allyloxypropan-2-ol (*R*)-**2** (1.5 mmol), purified by column chromatography (petroleum ether/ethyl acetate 7:3) to yield 130 mg (66%) From (*R*)-**3** $[\alpha]_D^{20} = -3.1$ (c 1, CHCl$_3$), 44% ee. From (*R*)-**2** $[\alpha]_D^{20} = -7.2$ (c 1, CHCl$_3$), >98% ee.

4.6.3. (*R*)-MTPA ester of 3-allyloxy-propane-1,2-diol 1

Colorless oil; ^{1}H NMR (CDCl$_3$) representative signals δ 3.54 (2H, d, J = 5.6, 3-CH_2O), 3.90 (2H, d, J = 5.6, OCH_2CH=CH$_2$), 4.46 (1H, dd, J = 6.9, 12.4 Hz, 1-C*H*HO), 4.77 (1H, dd, J = 3.5, 12.4 Hz, 1-CH*H*O), 5.18 (1H, dd, J = 1.4, 10.4 Hz, (*Z*)-CH=C*H*H), 5.23 (1H, dd, J = 1.4, 17.4 Hz, (*E*)-CH=CH*H*), 5.50–5.54 (1H, m, 2-C*H*), 5.79 (1H, ddt J = 5.6, 10.4, 17.4 Hz, C*H*=CH$_2$).

4.6.4. (*S*)-MTPA ester of 3-allyloxy-propane-1,2-diol 1

Colorless oil; ^{1}H NMR (CDCl$_3$) representative signals δ 3.58–3.65 (2H, m, part AB of ABX system, 3-CH_2O), 3.93–4.00 (2H, m, part AB of ABX system, OCH_2CH=CH$_2$), 4.40 (1H, dd, J = 6.9, 12.4 Hz, 1-C*H*HO), 4.65 (1H, dd, J = 3.5, 12.4 Hz, 1-CH*H*O), 5.20 (1H, dd, J = 1.4, 10.4 Hz, (*Z*)-CH=C*H*H), 5.26 (1H, dd, J = 1.4, 17.4 Hz, (*E*)-CH=CH*H*), 5.50–5.54 (1H, m, 2-C*H*), 5.84 (1H, ddt J = 5.6, 10.4, 17.4 Hz, C*H*=CH$_2$).

4.6.5. (*R*)-MTPA ester of 1-acetoxy-3-allyloxypropan-2-ol 2

Colorless oil; ^{1}H NMR (CDCl$_3$) representative signals δ 2.07 (3H, s, CH$_3$), 3.57–3.60 (2H, m, part AB of ABX system, 3-CH_2O), 3.90–3.97 (2H, m, part AB of ABX system, OCH_2CH=CH$_2$), 4.22 (1H, dd, J = 6.9, 12.4 Hz, 1-C*H*HO), 4.47 (1H, dd, J = 3.5, 12.4 Hz, 1-CH*H*O), 5.18 (1H, dd, J = 1.4, 10.4 Hz, (*Z*)-CH=C*H*H), 5.23 (1H, dd, J = 1.4, 17.4 Hz, (*E*)-CH=CH*H*), 5.50–5.54 (1H, m, 2-C*H*), 5.81 (1H, ddt J = 5.6, 10.4, 17.4 Hz, C*H*=CH$_2$).

4.6.6. (*S*)-MTPA ester of 1-acetoxy-3-allyloxypropan-2-ol 2

Colorless oil; ^{1}H NMR (CDCl$_3$) representative signals δ 2.01 (3H, s, CH$_3$), 3.65–3.70 (2H, m, part AB of ABX system, 3-CH_2O), 3.99–4.07 (2H, m, part AB of ABX system, OCH_2CH=CH$_2$), 4.16 (1H, dd, J = 6.9, 12.4 Hz, 1-C*H*HO), 4.37 (1H, dd, J = 3.5, 12.4 Hz, 1-CH*H*O), 5.23 (1H, dd, J = 1.4, 10.4 Hz, (*Z*)-CH=C*H*H), 5.29 (1H, dd, J = 1.4, 17.4 Hz, (*E*)-CH=CH*H*), 5.50–5.54 (1H, m, 2-C*H*), 5.88 (1H, ddt J = 5.6, 10.4, 17.4 Hz, C*H*=CH$_2$).

4.6.7. (*R*)-MTPA ester of 1-benzoyloxy-3-allyloxypropan-2-ol 3

Colorless oil; ^{1}H NMR (CDCl$_3$) representative signals δ 3.69 (2H, d, J = 5.6 Hz, 3-CH_2), 3.98 (2H, d, J = 5.6 Hz, OCH_2CH=CH$_2$), 4.54 (1H, dd, J = 7.6, 12.5 Hz, 1-C*H*HO), 4.66 (1H, dd, J = 3.5, 12.5 Hz, 1-CH*H*O), 5.19 (1H, dd, J = 1.4, 10.4 Hz, (*Z*)-CH=C*H*H), 5.26 (1H, dd, J = 1.4, 17.4 Hz, (*E*)-CH=CH*H*), 5.66–5.71 (1H, m, 2-C*H*), 5.83 (1H, ddt J = 5.6, 10.4, 17.4 Hz, C*H*=CH$_2$), 7.46 (2H, dd, J = 7.0, 7.0 Hz, *m*-Ph H), 7.60 (1H, t, J = 7.0, *p*-Ph H), 8.02 (2H, d, J = 7.0, *o*-Ph H).

4.6.8. (*S*)-MTPA ester of 1-benzoyloxy-3-allyloxypropan-2-ol 3

Colorless oil; ^{1}H NMR (CDCl$_3$) representative signals δ 3.73–3.79 (2H, m, part AB of ABX system, 3-CH_2O), 4.06 (2H, d, J = 5.6 Hz, OCH_2CH=CH$_2$), 4.47 (1H, dd, J = 7.6, 12.5 Hz, 1-C*H*HO), 4.58 (1H, dd, J = 3.5, 12.5 Hz, 1-CH*H*O), 5.23 (1H, dd, J = 1.4, 10.4 Hz, (*Z*)-CH=C*H*H), 5.31 (1H, dd, J = 1.4, 17.4 Hz, (*E*)-CH=CH*H*), 5.66–5.71 (1H, m, 2-C*H*), 5.90 (1H, ddt J = 5.6, 10.4, 17.4 Hz, C*H*=CH$_2$), 7.45 (2H, dd, J = 7.0, 7.0 Hz, *m*-Ph H), 7.58 (1H, t, J = 7.0, *p*-Ph H), 7.98 (2H, d, J = 7.0, *o*-Ph H).

Acknowledgment

This work has been financially supported by the Università degli Studi di Milano (Fondi PUR).

References

1. (a) Behr, A.; Eilting, J.; Irawadi, K.; Leschinski, J.; Lindner, F. *Green Chem.* **2008**, *10*, 13–30; (b) Beatriz, A.; Araújo, Y. J. K.; de Lima, D. P. *Quim. Nova* **2011**, *34*, 306–319; (c) Sakakura, A.; Umemura, S.; Ishihara, K. *Adv. Synth. Catal.* **2011**, *353*, 1938–1942; (d) Acosta, A.; Filice, M.; Fernandez-Lorente, G.; Palomo, J. M.; Guisan, J. M. *Bioresource Technol.* **2011**, *102*, 507–512.
2. Ashton, W. T.; Canning, L. F.; Reynolds, G. F.; Tolman, R. L.; Karkas, J. D.; Liou, R.; Davies, M. M.; DeWitt, C. M.; Perry, H. C.; Field, A. K. *J. Med. Chem.* **1985**, *28*, 926–933.
3. (a) Hirth, G.; Saroka, H.; Bannwarth, W.; Barner, R. *Helv. Chim. Acta* **1983**, *66*, 1210–1240; (b) VanBoeckel, C. A. A.; van der Marel, G. A.; Westerduin, P.; VanBoom, J. H. *Synthesis* **1982**, 399–402.
4. (a) Duclos, R. I., Jr.; Johnston, M.; Vadivel, S. K.; Makriyannis, A.; Glaser, S. T.; Gatley, S. J. *J. Org. Chem.* **2011**, *76*, 2049–2055; (b) Sun, S.; Yang, G.; Bi, Y.; Xiao, F. *Biotechnol. Lett.* **2009**, 1885–1889; (c) Kristinsson, B.; Haraldsson, G. G. *Synlett* **2008**, 2178–2182; (d) Cateni, F.; Bonivento, P.; Procida, G.; Zacchigna, M.; Gabrielli Favretto, L.; Scialino, G.; Banfi, E. *Bioorg. Med. Chem.* **2007**, *15*, 815–826.
5. Mickeleit, M.; Wieder, T.; Arnold, M.; Geilen, C. C.; Mulzer, J.; Reutter, W. *Angew. Chem., Int. Ed.* **1998**, *37*, 351–353.
6. Shin, J.; Thompson, D. H. *J. Org. Chem.* **2003**, *68*, 6760–6766.
7. (a) Yuan, C.; Hollingsworth, R. I. *Tetrahedron Lett.* **2011**, *52*, 5421–5423; (b) Enugala, R.; Carvalho, L. C. R.; Marques, M. M. B. *Synlett* **2010**, 2711–2716; (c) Tsukamoto, H.; Suzuki, T.; Sato, M.; Kondo, Y. *Tetrahedron Lett.* **2007**, *48*, 8438–8441.
8. Sontakke, J. B.; Yadav, G. D. *Ind. Eng. Chem. Res.* **2011**, *50*, 12975–12983.
9. Santaniello, E.; Ciuffreda, P.; Casati, S.; Alessandrini, L.; Repetto, A. *J. Mol. Catal. B-Enzym.* **2006**, *40*, 81–85.

10. Casati, S.; Ciuffreda, P.; Santaniello, E. *Tetrahedron: Asymmetry* **2011**, *22*, 658–661.
11. Santaniello, E.; Casati, S.; Ciuffreda, P.; Gamberoni, L. *Tetrahedron: Asymmetry* **2004**, *15*, 3177–3179.
12. Santaniello, E.; Casati, S.; Ciuffreda, P.; Gamberoni, L. *Tetrahedron: Asymmetry* **2005**, *16*, 1705–1708.
13. (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549; (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.
14. For representative reviews, see: (a) Theil, F. *Chem. Rev.* **1995**, *95*, 2203–2227; (b) Theil, F. *Catal. Today* **1994**, *22*, 517–536.
15. (a) Khor, G. K.; Uzir, M. H. *Yeast* **2011**, *28*, 93–107; (b) Moore, J. C.; Pollard, D. J.; Kosjek, B.; Devine, P. N. *Accounts Chem. Res.* **2007**, *40*, 1412–1419; (c) Johanson, T.; Katz, M.; Gorwa-Grauslund, M. F. *FEMS Yeast Res.* **2005**, *5*, 513–525; (d) Patel, R. N. *Adv. Synth. Catal.* **2001**, *343*, 527–546.
16. Csuk, R.; Glanzer, B. I. In *Stereoselective Biocatalysis*; Patel, R. N., Ed.; Marcel Dekker: New York, 2000; pp 527–578.
17. (a) Nakamura, K.; Yamanaka, R.; Matsudab, T.; Haradab, T. *Tetrahedron: Asymmetry* **2003**, *14*, 2659–2681; (b) Wei, Z.-L.; Lin, G.-Q.; Li, Z.-Y. *Bioorg. Med. Chem.* **2000**, *8*, 1129–1137; (c) Lee, L. G.; Whitesides, G. M. *J. Org. Chem.* **1986**, *51*, 25–36.
18. (a) Zhou, B.; Gopalan, A. G.; VanMiddlesworth, F.; Shieh, W.-R.; Sih, C.-J. *J. Am. Chem. Soc.* **1983**, *105*, 5925–5926; (b) Shieh, W.-R.; Gopalan, A. G.; Sih, C.-J. *J. Am. Chem. Soc.* **1985**, *107*, 2993–2994.
19. The NMR spectrum of the hydroxyketone **4** in $CDCl_3$ shows no trace of an aldehyde signal, but a partial tautomerization of the hydroxyketone **4** to the corresponding (*RS*)-hydroxyaldehyde in the fermentation medium cannot be excluded.
20. Manzocchi, A.; Fiecchi, A.; Santaniello, E. *J. Org. Chem.* **1988**, *53*, 4405–4407.
21. Note that for derivative **3** there is a change in the CIP preference with regards to diol **1**.
22. (a) Yan, Z.; Nie, Y.; Xu, Y.; Liu, X.; Xiao, R. *Tetrahedron Lett.* **2011**, *52*, 999–1002; (b) Musa, M. M.; Ziegelmann-Fjeld, K. I.; Vieille, C.; Zeikus, J. G.; Phillips, R. S. *J. Org. Chem.* **2007**, *72*, 30–34; (c) Kroutil, W.; Mang, H.; Edegger, K.; Faber, K. *Curr. Opin. Chem. Biol.* **2004**, *8*, 120–126; (d) van Deursen, R.; Stampfer, W.; Edegger, K.; Faber, K.; Kroutil, W. *J. Mol. Catal. B-Enzym.* **2004**, *31*, 159–163.
23. Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Shaibani, R. *Tetrahedron* **2004**, *60*, 6105–6111.
24. Khalafi-Nezhad, A.; Soltani Rad, M. N.; Khoshnood, A. *Synthesis* **2003**, 2552–2558.
25. Sugawara, F.; Nakayama, H.; Strobel, G. A.; Ogawa, T. *Agric. Biol. Chem.* **1986**, *50*, 2261–2271.