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On the stereochemistry of the Baker's Yeast-mediated reduction of regioisomeric unsaturated aldehydes: Examples of enantioselectivity switch promoted by substrate-engineering

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ABSTRACT

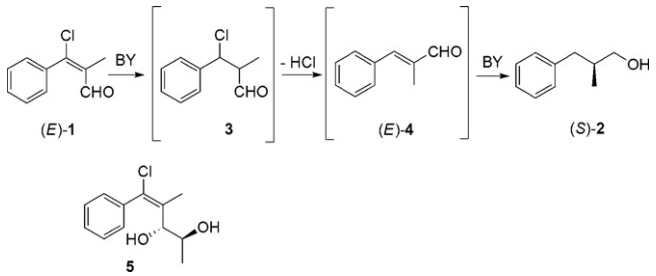
The Baker's Yeast (BY) reduction of (*Z*)-2-chloromethyl-3-arylacrylaldehydes was found to afford (*R*)-2-methyl-3-aryl-propanols showing high enantiomeric excess values. Deuterium incorporation experiments were performed, in order to investigate the mechanism of the bioreduction: the formation of the corresponding substituted 2-benzylacrylaldehydes, as intermediates to be effectively reduced by Baker's Yeast, was suggested. These intermediates were synthesized and submitted to BY reduction to afford the corresponding saturated (*R*)-alcohols, thus confirming the conclusions drawn from labelling experiments. The enantioselectivity of their bioreduction was found to be opposite with respect to that observed for the corresponding regioisomeric 2-methylcinnamaldehydes. The preparation of the two enantiomers of 2-methyl-3-aryl-propanols by fermentation of two regioisomers represents an interesting example of substrate-controlled enantioselective reaction.

1. Introduction

Since the early seventies the growing interest for small chiral molecules, to be used as building blocks for the synthesis of more complex enantiopure compounds, [1] has promoted the study of microbial transformations of non conventional substrates [2–4]. However, the major drawback of this approach is that biocatalysed reactions usually afford only one enantiomer of the final molecule with high enantioselectivity. If the other enantiomer is needed, efforts have to be devoted to obtain it by acting on the choice of the biocatalyst or on the structure of the starting substrate. In the case of secondary alcohols, derived from the reduction of a prochiral ketone, useful results were obtained by growing cultures from different strains of the same microorganism [5], or using different microorganisms on the same substrate [6–8] or the same microorganism on modified substrates [9].

Among chiral compounds prepared by enzyme-mediated reduction of the double bond of activated olefins, a remarkable example is that of (*Z*)- and (*E*)-methyl 2,4,4-trichloro-2-butenoates, transformed by fermenting Baker's Yeast (BY) [10], and by isolated ene-reductases [11] into (*S*)- and (*R*)-2,4,4-trichlorobutanoic acids, respectively. In 2007 Faber et al. reported the bioreduction of the dimethyl esters of citraconic and mesaconic acid into the (*R*)- and (*S*)-enantiomers of methyl 2-methylsuccinate by means of isolated enzymes [12].

Recently, we have been interested in the BY fermentation of chloro aldehydes. We found that aldehyde (*E*)-**1** (Scheme 1) was converted by Baker's Yeast into saturated alcohol (*S*)-**2** with an enantiomeric excess (ee) value of 70% [13]. Deuterium incorporation experiments showed that the conversion of compound **1** into derivative **2** proceeded through intermediate **3**, which gave upon dehydroalogenation in the fermentation medium α-methylcinnamaldehyde ((*E*)-**4**), the real substrate for the BY



Scheme 1. BY reduction of chloro aldehyde (*E*)-**1**.

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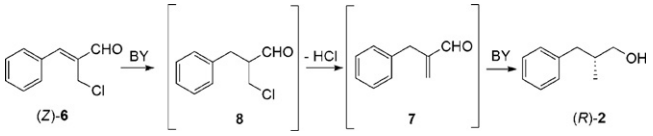
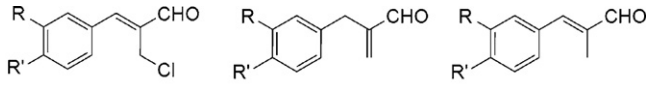


Scheme 2. BY reduction of chloro aldehyde (*Z*)-**6**.



(*Z*)-**9** R = H, R' = Cl
(*Z*)-**10** R = OMe, R' = H
11 R = H, R' = Cl
12 R = OMe, R' = H
13 R = H, R' = Cl
14 R = OMe, R' = H

Scheme 3. Substrates for bioreductions.

production of (*S*)-**2** [14]. Yeast fermentation of **1** afforded also diol **5** by reduction of the hydroxy ketone, which was generated in the acyloin-type condensation promoted by BY on unsaturated aldehyde **1** [15].

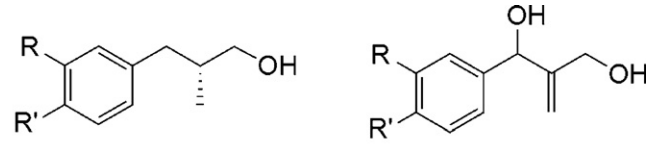
We now report on the conversion of chloromethyl cinnamaldehyde (*Z*)-**6** (Scheme 2), a regioisomer of compound **1**, into saturated alcohol (*R*)-**2** by BY fermentation, likely through the formation of intermediate benzylacrylaldehyde **7**, which is a regioisomer of compound **4**. Aldehyde **7** can be generated by dehydrohalogenation of saturated chloro aldehyde **8** in the reaction medium.

The same behaviour under BY fermentation is herein described also for chloro aldehydes (*Z*)-**9** and (*Z*)-**10** (Scheme 3), and the results of labelling experiments are presented to confirm that substituted benzylacrylaldehydes **7**, **11** and **12** are the intermediates effectively reduced by BY. The hypothesis, that the different enantioselectivity observed in the reduction of (*E*)-**1** and (*Z*)-**6** is due to the formation of two regioisomeric unsaturated aldehydes, has induced us to further investigate the role played on the stereochemical course of the reaction by the position of the conjugated C=C double bond with respect to the aldehydic moiety. Thus, aldehydes **7**, **11** and **12** have been synthesised on purpose, and submitted to BY fermentation. The results of their reduction are herein compared with the data regarding the BY-mediated reduction of the corresponding cinnamaldehydes (*E*)-**4**, (*E*)-**13**, and (*E*)-**14** (Scheme 3).

2. Results and discussion

2.1. Baker's Yeast reduction of chloro aldehydes (*Z*)-6, (*Z*)-9, and (*Z*)-10 and deuterium incorporation experiments.

In the biocatalysed reduction of chloro aldehydes (*Z*)-**6**, (*Z*)-**9**, and (*Z*)-**10** different results were observed according to the mode employed for adding the substrate to fermenting BY. When the chloro aldehydes were adsorbed on a hydrophobic resin (polystyrene XAD-1180N, 1:15 w/w), and then suspended in the aqueous medium, only the (*R*)-enantiomers of the corresponding saturated alcohols **2**, **15** and **16** (Scheme 4) were obtained in high enantiomeric excess (Table 1). These feeding conditions are known



(*R*)-**2** R = H, R' = H
(*R*)-**15** R = H, R' = Cl
(*R*)-**16** R = OMe, R' = H

17 R = R' = H
18 R = H, R' = Cl
19 R = OMe, R' = H

Scheme 4. Products of BY reduction of chloroaldehydes (*Z*)-**6**, **9**, and **10**.

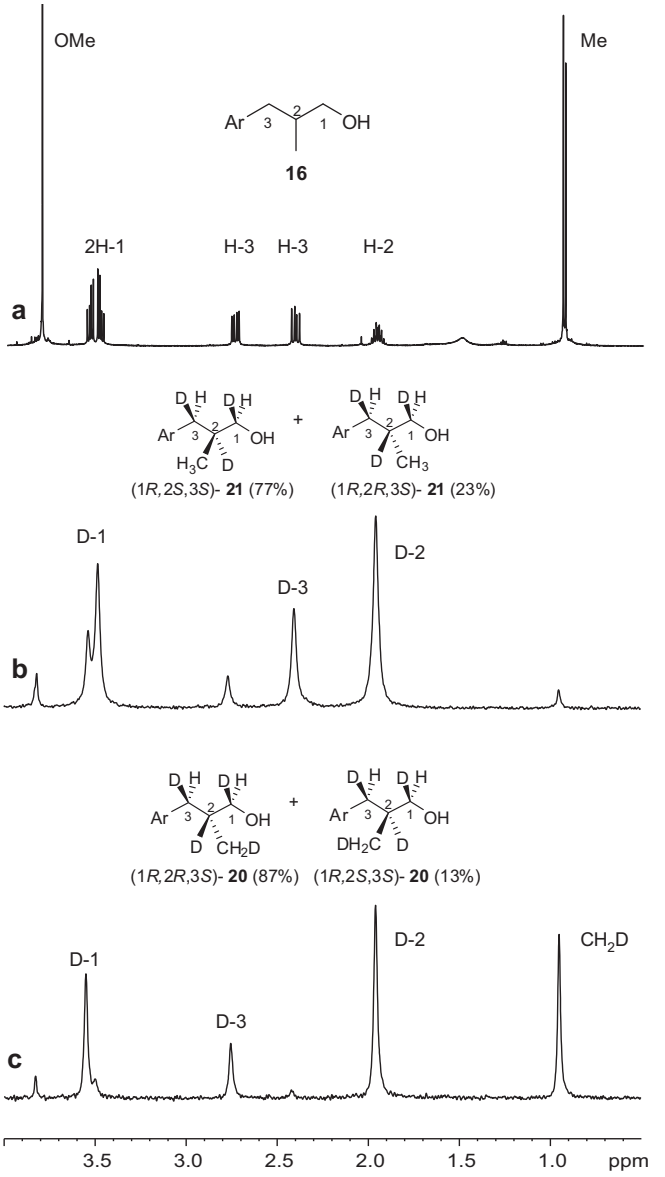


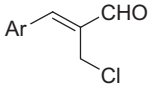
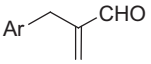
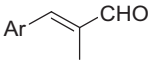
Fig. 1. (a) Proton spectrum ($CDCl_3$) of racemic **16**; (b) deuterium spectrum ($CHCl_3$) of (1*R*,2*S*,3*S*)-**21** (main product) obtained by BY reduction of (*E*)-**4** in H_2O/D_2O 1%; (c) deuterium spectrum ($CHCl_3$) of (1*R*,2*R*,3*S*)-**20** (main product) obtained by BY reduction of (*Z*)-**10** in H_2O/D_2O 1% (Ar = 3-methoxyphenyl).

to ensure very low substrate concentration in the fermentation medium [16].

Conversely, when the aldehydes were added as an ethanolic solution, racemic diols **17–19** (Scheme 4) were obtained in *ca.* 1:2 mixture with the corresponding saturated (*R*)-alcohol showing low ee.

To support the mechanism outlined in Scheme 2 for the conversion of unsaturated chloromethyl aldehydes (*Z*)-**6**, (*Z*)-**9**, and (*Z*)-**10** into saturated (*R*)-alcohols **2**, **15**, and **16**, deuterium incorporation experiments were performed. Aldehyde (*Z*)-**10** was treated with fermenting Baker's Yeast in the presence of D_2O, and the resulting deuterated reduction product **20** was submitted to ^2H NMR studies (Fig. 1). This compound was chosen for the interpretation of ^2H NMR spectra, because it showed the natural abundance signal of the O-methyl group at 3.81 ppm intense enough to allow a proper evaluation of the contribution of deuterium natural abundance to the intensity of the signals of the deuterium atoms incorporated during the bioreduction.

Table 1
Conversion (*c*) and enantiomeric excess (ee) values for the bioreduction of aldehydes (*Z*)-**6**, (*Z*)-**9**, (*Z*)-**10**, **7**, **11**, **12**, (*E*)-**4**, (*E*)-**14**, (*E*)-**15** to afford the corresponding alcohols **2**, **15**, and **16**.

	*c*[a] [%]	ee[a] [%]		*c*[a] [%]	ee[a] [%]		*c* [%]	ee [%]
(*Z*)-**6** Ar = Ph	49	99 (*R*)	**7** Ar = Ph	60	95 (*R*)	(*E*)-**4** Ar = Ph	12[b]	70[b] (*S*)
(*Z*)-**9** Ar = 4-ClC_6H_4	29	96 (*R*)	**11** Ar = 4-ClC_6H_4	33	69 (*R*)	(*E*)-**14** Ar = 4-ClC_6H_4	13	78[c] (*S*)
(*Z*)-**10** Ar = 3-$MeOC_6H_4$	21	98 (*R*)	**12** Ar = 3-$MeOC_6H_4$	28	94 (*R*)	(*E*)-**15** Ar = 3-$MeOC_6H_4$	44[d]	54[d] (*S*)

[a] Conversion (*c*) and enantiomeric excess values (ee) are referred to the reaction performed with the substrate adsorbed on resins, and they are calculated by GC analysis (on a chiral stationary phase) of the crude mixture after 48 h reaction time; conversion is expressed as percentage of the saturated alcohol in the reaction mixture.
[b] Isolated yields and ee value from Ref. [13].
[c] Conversion values determined by GC analysis and ee value from Ref. [26].
[d] Conversion (*c*) and enantiomeric excess values (ee) are referred to the reaction performed with the substrate dissolved in ethanol, conversion is calculated by GC/MS analysis of the crude mixture after 48 h reaction time; ee value is determined by HPLC analysis (on a chiral stationary phase).

The ^{2}H NMR spectrum of **20** (Fig. 1c) was compared with that of the deuterated saturated alcohol **21** (Fig. 1b) obtained by BY fermentation of the corresponding cinnamaldehyde (*E*)-**14** [17]. The signal assignment was performed by considering the ^{1}H NMR spectrum of the synthetic saturated alcohol **16** (Fig. 1a).

The spectrum of **21** (Fig. 1b) is characterised by three intense signals at 1.96 ppm (2*S*-D), 2.42 ppm (3*S*-D) and 3.49 ppm (1*R*-D), while that of compound **20** (Fig. 1c) shows four intense deuterium peaks at 0.94 ppm (methyl group at position 2), 1.96 ppm (2*R*-D), 2.74 ppm (3*S*-D) and 3.54 ppm (1*R*-D). Each spectrum shows also less intense signals belonging to the diastereotopic nuclei at positions 1 and 3, because the ^{2}H NMR spectra were recorded on the compounds recovered from fermentation reactions performed in the absence of resins. These materials were obtained in higher yields, but lower stereoisomeric purity (enantiomeric purity when the reaction was performed in water; diastereoisomeric purity when the reaction was carried out in the presence of D_2O, with de = 54% for **21** and 74% for **20**). The peaks at 3.81 ppm in Fig. 1b and c, and that at 0.94 ppm in Fig. 1b are due to the natural abundance deuterium nuclei of the methoxy and methyl groups, respectively.

The absolute configuration of compounds **20** and **21** was assigned on the basis of these considerations. In a previous work [13], the BY-mediated reduction of (*E*)-**4** to saturated alcohol (*S*)-**2** was established to occur according to an *anti* mechanism, with the substrate in a flipped binding mode, in order to account for the (*S*) configuration of the resulting compound [18]. The *anti* addition was established by comparison of the ^{2}H NMR spectrum of the deuterated product recovered from BY fermentation with those of stereospecifically deuterated synthetic species. Thus, as for cinnamaldehyde (*E*)-**14**, the addition to C_β-*re* face of a D^- from the cofactor (which has exchanged the hydrogen to be delivered in the reduction with deuterated water [19]) and of a D^+ to C_α-*re* face from the solvent gave the deuterated saturated aldehyde shown in Scheme 5a, which was then reduced by one of the alcohol dehydrogenases active in fermenting BY to afford compound **21**. The absolute configuration of the stereogenic centres C_2 and C_3 in compound **21** was thus assigned to be (2*S*,3*S*), while that of C_1 was established to be *R* on the basis of the known mode of BY reduction of the carbonyl group of cinnamaldehyde [20,21]. The sample contained also 23% of the diastereoisomer (1*R*,2*R*,3*S*)-**21**, due to the lower stereoselectivity of the bioreduction when the substrate was added in ethanol solution.

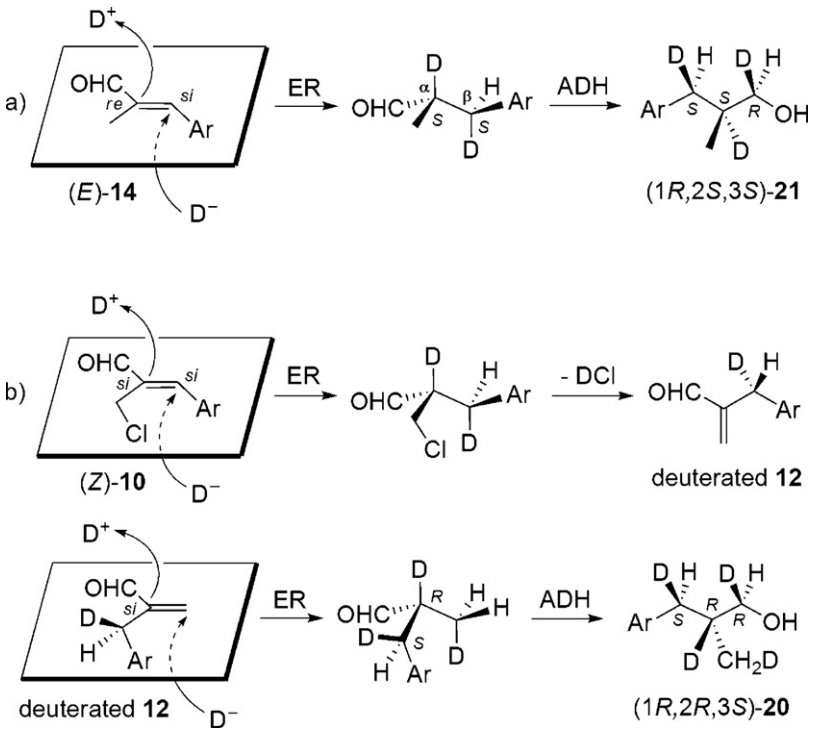
The ^{2}H NMR spectrum of compound **20** (Fig. 1c) showed the presence of four deuterium atoms in position 1, 2, 2′ and 3, and absolute configuration (1*R*,2*R*,3*S*) was tentatively established for the main component by comparison with the deuterium spectrum of (1*R*,2*S*,3*S*)-**21**.

The first observation is that the two compounds have opposite configuration at C_2, because the experimental evidence is that BY-mediated reduction afforded saturated alcohols (*S*)- and (*R*)-**16** from (*E*)-**14** and (*Z*)-**10**, respectively. Fig. 1b and c clearly show that the chemical shifts of D-1 and D-3 in alcohol **20** are different from those of the corresponding deuterium atoms in derivative **21**, where they are both characterised by *anti* arrangement with respect to D-2. Thus, a *syn,syn* relative configuration can be established for D-1, D-2, and D-3 in compound **20**. The configuration of C_1 is in agreement with the known mode of BY-mediated reduction of the carbonyl group of cinnamaldehyde.

The second important consideration is that compound **20** is characterised by the incorporation of four deuterium atoms, whereas only three of them are inserted in the structure of derivative **21**. In particular, the labelling of the methyl group in position 2 of compound **20**, together with the presence of a deuterium atom at C_2, supports the formation of methoxybenzyl acrylaldehyde **12** as intermediate in the generation of the corresponding saturated alcohol from (*Z*)-**10**.

Scheme 5b shows the steps of deuterium incorporation in the BY reduction of (*Z*)-**10** to (1*R*,2*R*,3*S*)-**20**, which are in agreement with the absolute configuration obtained by the analysis of the deuterium spectrum. In the first step deuterium addition occurs to the C=C double bond of chloro aldehyde (*Z*)-**10** with *anti* stereochemistry: D^- is delivered to C_β-*re* face, and D^+ to C_α-*si* face. This latter deuterium atom in indeed lost in the dehydrohalogenation step, to afford deuterated **12**. The configuration of C_3 requires a flipped binding mode of the starting substrate in the enzyme active site [18]. The same *anti* stereochemistry of double bond reduction occurs in the following step: the addition of a D^- from the cofactor to C_β, and a of D^+ from the solvent to C_α-*si* face of deuterated **12** finally gives (1*R*,2*R*,3*S*)-**20**, as the main product.

As mentioned earlier, alcohols **2**, **15**, and **16** were the only transformation products when aldehydes (*Z*)-**6**, **9** and **10** were administered to fermenting BY loaded on adsorption resins, with no trace of those *vic*-diols produced by reduction of the acyloin intermediates, usually obtained from a variety of α,β-unsaturated and aromatic aldehydes [22]. However, when aldehydes (*Z*)-**6**, **9** and **10** were administered to Baker's Yeast in ethanolic solution, they provided 1,3-diols, shown to possess structural formulas **17**, **18** and **19** by spectroscopic studies and comparison with reported data [23], in *ca.* 1:2 ratio with the saturated (*R*)-alcohols **2**, **15**, and **16**. These diols showed small negative optical rotation values. In particular,



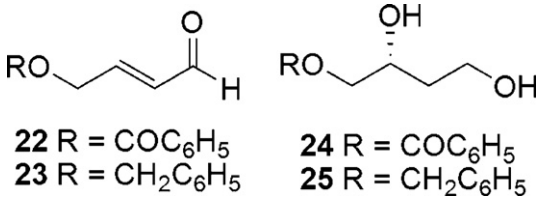
Scheme 5. Deuterium incorporation in the BY reduction products of (a) (*E*)-**14** and of (b) (*Z*)-**10** in D_2O (ER = ene-reductase; ADH = alcohol dehydrogenase; Ar = 3-methoxyphenyl).

diol **17** displayed $[\alpha]_D = -1.6$ (*c* 1, $CHCl_3$), and no baseline-resolved peaks could be obtained for these products by either HPLC or GC analysis on a chiral stationary phase.

The formation of structurally related 1,3-diols from α,β-unsaturated aldehydes in fermenting Baker's Yeast is not new. The benzoyl and the benzyl derivatives of 4-hydroxy crotonaldehyde **22** and **23** (Scheme 6), respectively, provided diols (*R*)-**24** and **25** showing good enantiomeric purity [24]. The BY generation of these diols was explained from the mechanistic point of view by a stereospecific reversible water addition β to the carbonyl group of **22** and **23**, mediated by a lyase, followed by reduction of the intermediate β-hydroxy aldehyde by yeast alcohol dehydrogenase. When regiospecifically deuterated **22** was incubated with BY, partial loss and scrambling of the label in the position of derivative **24** corresponding to position 2 of the precursor **22** was observed.

The generation of **17**, **18** and **19** from (*Z*)-**6**, **9** and **10** follows a pathway similar to the one suggested for **24** and **25** from **22** and **23**, as it is outlined in Scheme 7 for the conversion of (*Z*)-**10** into diol **19**. An initial Michael-type addition of water in position 3 of the unsaturated aldehyde **10** provides (step **a**) β-hydroxy aldehyde **26**. The hydrogen atom in position 2 of this kind of intermediates should be very labile, as one can judge from the extended loss of deuterium in the suggested intermediate for the conversion of **22** into **24**. Accordingly, dehydrohalogenation of **26** (step **b**) affords unsaturated aldehyde **27**. Finally, in step **c** the carbonyl group of aldehyde **27** is reduced to provide diol **19**. At the moment, the reasons for the low or nil enantiomeric enrichment of **17**, **18** and **19**, as compared with **24** and **25**, are obscure.

Evidence supporting this mechanistic proposal arose from ^2H NMR studies of the product obtained by biotransformation of (*Z*)-**10** in deuterated water. Fig. 2a shows the proton NMR spectrum of **19**, obtained from (*Z*)-**10** in tap water, with the corresponding signal assignment, while Fig. 2b is the ^2H NMR spectrum of **28**, deuterated analogue of **19**, produced from (*Z*)-**10** in the presence of deuterated water. The incorporation of one deuterium in position 1 of **28** (Fig. 2b) (signals at 4.01 and 3.85 ppm) thus demonstrates that step **c** of Scheme 7 is biocatalysed, with addition of a D^- to C_1 from the reduced cofactor. The stereospecificity of yeast alcohol dehydrogenase carbonyl reduction (which should have provided (*R*)-**28** is well established. Thus, the nearly 1:1 ratio of the deuterium signals of Fig. 2b should lead to the conclusion that water addition to the double bond of **10** is not stereospecific. However, steps **a** and **c** of Scheme 7 must be under enzymatic control, since aldehyde **10** was recovered unaltered from 7 days incubation in water/ethanol in the presence of D-glucose, at the same temperature and dilution used in the yeast transformation.

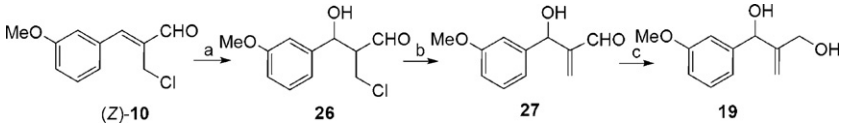


Scheme 6. Products obtained by BY reduction of 4-oxygen substituted crotonaldehyde.

2.2. Baker's Yeast reduction of substituted benzylacrylaldehydes **7**, **11**, and **12**

Substituted benzylacrylaldehydes **7**, **11**, and **12** were synthesised and their bioreduction was investigated, in order to further support the hypothesis of their formation as intermediates in the BY mediated conversion of chloromethyl arylacrylaldehydes into saturated alcohols.

The BY reduction of benzylacrylaldehyde **7** had been already described in the literature [25] to afford modest yields (20%) of nearly enantiomerically pure (*R*)-**2** (ee = 98%) through a slow addition (96 h) of an ethanolic solution of the substrate to the reaction medium.



Scheme 7. Steps in the conversion of (*Z*)-**10** into **19**.

Substrates **7**, **11**, and **12** were adsorbed on a hydrophobic resin (polystyrene XAD-1180 N, 1:15 w/w), and suspended in fermenting BY. After 48 h, saturated (*R*)-alcohols **2**, **15**, and **16** were recovered: the conversion and ee values are reported in Table 1. As for compound **7**, complete consumption of the starting aldehyde was observed, with formation of a 6:4 mixture of (*R*)-**2** (ee = 95%) and of the corresponding allylic alcohol. 45% of aldehyde **11** was still present after 48 h, together with 33% of alcohol (*R*)-**15** (ee = 69%) and 22% of the allylic alcohol. When aldehyde **12** was the substrate, (*R*)-**16** (ee = 98%) was obtained in 28%, together with 33% of the unreacted starting aldehyde and 39% of the allylic alcohol. The stereochemistry of the reduction was the same observed in the conversion of chloromethyl cinnamaldehydes, and opposite to that found in the BY reduction of (*E*)-cinnamaldehydes **4**, **13** [26] and **14** (Table 1).

The absolute configuration of (*R*)-(+)-**2** was known [13], and that of the saturated alcohols **15** and **16** was tentatively assigned by considering the accepted stereochemistry for the reduction of α-methylcinnamaldehydes (Ref. [26] for (*S*)-(−)-**15** obtained from (*E*)-**13**, this work for (*S*)-(−) and (*R*)-(+)-**16**, respectively obtained from (*E*)-**14** and **11**)

The stereochemical outcome of the two sets of regioisomeric aldehydes, *i.e.* **7**, **11**, **12** and **4**, **13**, **14**, allowed for some considerations to be made on the possibility to drive the enantioselectivity of BY carbon carbon double bond reduction by a careful choice of the structure of the starting substrates. The two sets of regioisomeric aldehydes are bound in the active site of the enzyme according to the same mode, as it is drawn in Scheme 5a and b for 3-methoxy derivatives (*E*)-**14** and **12**. However, the position of the double bond is such that the addition of the proton from the solvent occurs on C_α-*re* face and C_α-*si* face, respectively.

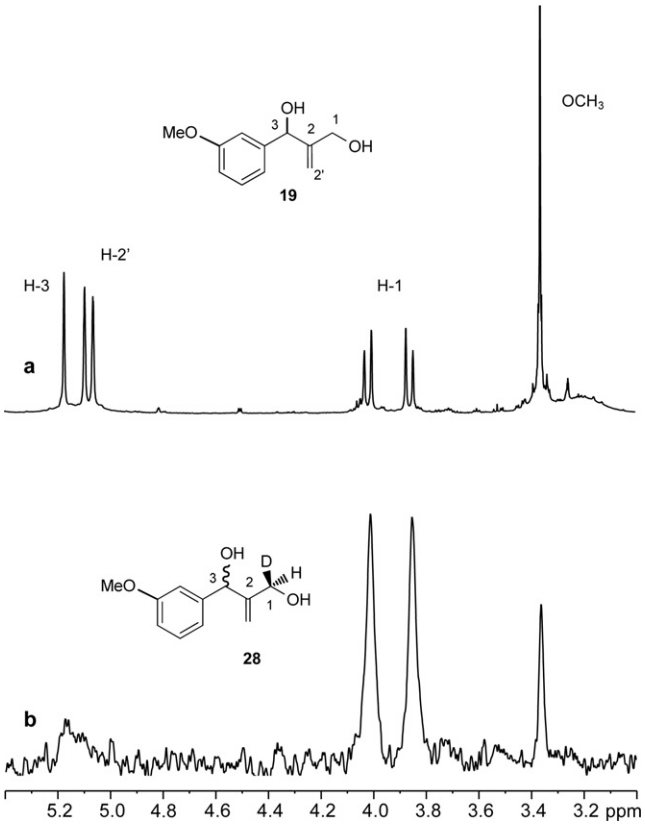


Fig. 2. (a) Proton spectrum (C_6D_6) of **19** and (b) deuterium spectrum (C_6H_6) of **28** obtained by BY reduction of (*Z*)-**10** in H_2O/D_2O 1%. The signals at 3.36 and 5.06–5.17 ppm are due to the natural abundance deuterium present, respectively, at the OCH_3, H-2′ and H-3 positions.

3. Conclusion

The investigation of the mechanism of BY reduction of chloromethyl aldehydes (*Z*)-**6**, **9**, and **10** by deuterium incorporation experiments, and the comparison with the behaviour of chloro aldehyde (*E*)-**1** under the same reaction conditions allowed us to make some considerations on the stereochemistry of carbon carbon double bond bioreduction. In particular, we could put into evidence the importance of the position of the double bond to be reduced with respect to the activating aldehydic group. The hypothesis that the different enantioselectivity was due to the formation of two regioisomeric intermediates, *i.e.* **4** and **7**, was further supported by the analysis of the stereochemical outcome of two sets of regioisomeric aldehydes, *i.e.* **7**, **11**, **12** and **4**, **13**, **14**.

The results of this research demonstrate also the utility of fermenting Baker's Yeast in the discovery of new multienzymatic transformations of non-conventional substrates, leading to synthetically useful unexpected products. For example, saturated alcohol (*R*)-**16** is now available by BY reduction, and it can be used as starting material for the synthesis of the pain-relief therapeutic agent (1*R*,2*R*)-tapentadol (Nucynta) [27].

4. Experimental

TLC analyses were performed on Merck Kieselgel 60 F254 plates. All the chromatographic separations were carried out on silica gel columns. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer. The chemical shift scale was based on internal tetramethylsilane. GC–MS analyses were performed using a HP-5MS column (30 m × 0.25 mm × 0.25 μm). The following temperature program was employed: 60° (1 min)/6°/min/150° (1 min)/12°/min/280° (5 min). The enantiomeric excess values of the samples of saturated alcohol **2** and **15** were determined by GC analysis performed using a DAcTBSil.BetaCDX 0.25 μm × 0.25 mm × 25 m column (Mega, Italy), according to the following conditions: (i) compound **2**: 80 °C (2 min)/1 °C min^{-1}/120 °C/30 °C min^{-1}/220 °C: (*R*)-**2** t_R = 16.1 min, (*S*)-**2** t_R = 16.5 min; (ii) compound **15**: 90 °C (2 min)/1 °C min^{-1}/140 °C/30 °C min^{-1}/220 °C: (*R*)-**15** t_R = 40.6 min, (*S*)-**15** t_R = 41.0 min. The enantiomeric excess values of the samples of saturated alcohol **16** were determined by HPLC analysis using a Chiralcel OD column, according to the following conditions: hexane: isopropanol 9:1, flow 0.6 ml/min, λ = 210 nm; t_R (*S*)-**16** = 13.42 min, t_R (*R*)-**17** = 16.17 min.

4.1. Acquisition of the ^{2}H spectra

The ^{2}H spectra were measured on a Bruker Avance 500 spectrometer equipped with a 10-mm probe head and ^{19}F lock channel

under CPD (Waltz 16 sequence) proton decoupling conditions at the temperature of 305 K. The solutions were prepared dissolving 20–100 mg of material in *ca.* 3.0 mL of $CHCl_3$ or C_6H_6 adding about 40 μL of C_6F_6 for the lock. The spectra were run collecting 1024–4096 scans depending on the solution concentration using the following acquisition parameters: 5.4 s acquisition time, 1530 Hz spectral with, 16 K time domain and 1 s delay. The spectra were Fourier transformed with a line broadening of 0.3 Hz, manually phased and integrated after an accurate correction of the base line. For partially overlapped signals the peak areas were determined through the deconvolution routine of the Bruker TopSpin NMR software using a Lorentzian line shape.

4.2. Synthesis of chloromethyl aldehydes (Z)-6, (Z)-9, and (Z)-10

These substrates were prepared according to this sequence: the Baylis–Hillman adducts, obtained by reaction of the corresponding aromatic aldehyde and methyl acrylate in the presence of DABCO (1,4-diazabicyclo[2.2.2]octane), were treated with CCl_4/PPh_3 to afford the corresponding chloromethyl esters. These derivatives were submitted to DIBAH (diisobutylaluminium hydride) reduction to afford the allylic alcohols, which gave upon MnO_2 oxidation the desired chloromethyl aldehydes.

4.2.1. General procedure for the preparation of the Baylis–Hillman adducts [28]

Neat aldehyde (100.0 mmol) was added to a stirred solution of methyl acrylate (12.91 g, 150 mmol) and DABCO (11.15 g, 100 mmol) and left to stir overnight at room temperature. After 24–48 h the reaction was complete. The reaction mixture was diluted with diethyl ether (500 mL) and washed twice with 2 N HCl (100 mL), 2 N NaOH (50 mL) and brine (2 × 50 mL). The organic layer was separated and dried (Na_2SO_4). The oily residue obtained upon evaporation of the solvent was chromatographed on a silica gel column with increasing amounts of ethyl acetate in hexane.

Methyl 2-(hydroxy(phenyl)methyl)acrylate. Yield 80%; spectroscopic data for this compound are in agreement with those reported in literature [29].

Methyl 2-((4-chlorophenyl)(hydroxy)methyl)acrylate. Yield 78%; spectroscopic data for this compound are in agreement with those reported in literature [30].

Methyl 2-(hydroxy(3-methoxyphenyl)methyl)acrylate. Yield 91%; δ_H (400 MHz; $CDCl_3$) 7.25 (1H, m, aromatic hydrogen), 6.94–6.95 (2H, m, aromatic hydrogens), 6.82 (1H, dd, *J* 7.8 and 1.4 Hz, aromatic hydrogen), 6.33 (1H, m, C*H*H=), 5.83 (1H, m, C*H*H=), 5.53 (1H, s, PhC*H*OH), 3.79 (3H, s, OMe), 3.72 (3H, s, COOMe); δ_C (100.91 MHz; $CDCl_3$) 51.9, 55.2, 73.0, 112.0, 113.3, 118.8, 126.2, 129.4, 141.7, 142.9, 159.6, 166.7; GC/MS t_R 21.29 min, *m/z* 222 (M^+, 60), 190 (50), 162 (50), 135(100), 109 (50).

4.2.2. General procedure for the conversion of the Baylis–Hillman adducts into the corresponding 2-chloromethyl-3-arylacrylates [31]

The Baylis–Hillman esters (70.0 mmol) were refluxed 3 h in CCl_4 (60 mL) with PPh_3 (80.0 mmol). The reaction mixture was cooled to 0 °C and the solution was recovered. Diethyl ether (150 mL) was added and the mixture was scratched until triphenyl phosphine oxide separated in crystalline form. The mixture was filtered by suction and the solid was washed with diethyl ether. The combined organic phase was evaporated to dryness and chromatographed on a silica gel column with increasing amounts of ethyl acetate in hexane.

(*Z*)-*Methyl 2-*(*chloromethyl*)*-3-phenylacrylate*. Yield 90%; spectroscopic data for this compound are in agreement with those reported in literature [32].

(Z)-Methyl 2-chloromethyl-3-(4-chlorophenyl)acrylate. Yield 54%; spectroscopic data for this compound are inagreement with those reported in literature [28].

(Z)-Methyl 2-chloromethyl-3-(3-methoxyphenyl)acrylate. Yield 50%; δ_H (400 MHz; $CDCl_3$) 7.85 (1H, s, C*H*=), 7.35 (1H, m, aromatic hydrogen), 7.12–7.10 (2H, m, aromatic hydrogens), 6.96–6.94 (1H, m, aromatic hydrogen), 4.48 (2H, s, CH_2Cl), 3.88 (3H, s, OMe), 3.84 (3H, s, COOMe); δ_C (100.91 MHz; $CDCl_3$; Me_4Si) 39.1, 52.4, 55.2, 114.2, 115.8, 121.9, 128.5, 129.8, 135.3, 143.7, 159.7, 166.6; GC/MS t_R 22.68 min, *m/z* 242 (M^+ +2, 50), 240 (M^+, 50), 208 (40), 180 (40), 145(100), 131 (15), 115 (30).

4.2.3. General procedure for the conversion of 2-chloromethyl-3-arylacrylates in the corresponding 2-chloromethyl-3-arylpropenols

The ester prepared above (50 mmol) in toluene (150 mL) under stirring at −10 °C in a N_2 atmosphere was treated dropwise with a 25% DIBAH solution in toluene (120 mmol). After 16 h acetone (10 mL) was added dropwise, followed by a sat. solution of potassium sodium tartrate (1.5 vol). After stirring overnight the organic phase was separated and the aqueous layer was extracted with toluene. The combined organic phase was washed with water, dil. cold HCl and brine. The oily residue obtained upon evaporation of the dried organic phase and chromatographed on a silica gel column with increasing amounts of ethyl acetate in hexane.

(Z)-2-Chloromethyl-3-phenylprop-2-en-1-ol. Yield 90%; δ_H (400 MHz; $CDCl_3$) 7.40–7.25 (5H, m, aromatic hydrogens), 6.76 (1H, s, C*H*=C), 4.39 (2H, m, CH_2OH or CH_2Cl), 4.29 (2H, s, CH_2Cl or CH_2OH); δ_C (100.91 MHz; $CDCl_3$) 40.8, 64.9, 127.7, 128.5, 128.6, 130.9, 135.7, 136.1; GC–MS t_R = 19.20 min *m/z* 184 (M^+ +2, 35), 182 (M^+, 50), 147 (20), 133 (70), 115 (100), 91 (80).

(Z)-2-Chloromethyl-3-(4-chlorophenyl)prop-2-en-1-ol. Yield 70%; δ_H (400 MHz; $CDCl_3$;) 7.25 (2H, m, aromatic hydrogens), 7.19 (2H, m, m, aromatic hydrogens), 6.60 (1H, s, C*H*=), 4.28 (2H, s, CH_2OH or CH_2Cl), 4.14 (2H, s, CH_2OH or CH_2Cl); δ_C (100.91 MHz; $CDCl_3$; Me_4Si) 40.5, 64.7, 128.8, 129.5, 129.9, 133.6, 134.1, 137.5; GC–MS t_R = 21.85 min *m/z* 218 (M^+ +2, 50), 216 (M^+, 50), 181 (25), 167 (80), 151 (70), 115 (100).

(Z)-2-Chloromethyl-3-(3-methoxyphenyl)prop-2-en-1-ol. Yield 80%; δ_H (400 MHz; $CDCl_3$) 7.28 (1H, m, m, aromatic hydrogens), 6.94–6.93 (2H, m, m, aromatic hydrogens), 6.86–6.84 (1H, m, H(Ar)), 6.72 (1H,s, C*H*=), 4.37 (2H, s, CH_2OH or CH_2Cl), 4.28 (2H, s, CH_2Cl or CH_2OH), 3.81 (3H, s, OMe); δ_C (100.91 MHz; $CDCl_3$; Me_4Si) 40.8, 55.2, 64.7, 113.5, 113.8, 121.1, 129.6, 130.8, 129.6, 137.0, 159.6; GC–MS t_R = min 22.22 min *m/z* 214 (M^+ +2, 30), 212 (M^+, 100), 176 (40), 159 (95), 145 (60), 115 (70), 91 (40).

4.2.4. General procedure for the oxidation of 2-chloromethyl-3-arylpropenols to 2-chloromethyl-3-arylacrylaldehydes

The allylic alcohol (35 mmol) was dissolved in dichloromethane (50 mL) and treated with 4 parts by weight of activated MnO_2 under stirring overnight at r.t. The reaction mixture was filtered by suction over a Celite™ pad. The mass on the filter was washed repeatedly with dichloromethane. The oily residue obtained upon evaporation of the solvent was chromatographed on a silica gel column with increasing amounts of ethyl acetate in hexane.

(Z)-2-(Chloromethyl)-3-phenylacrylaldehyde ((Z)-6) [33] Yield 70%; δ_H (400 MHz; $CDCl_3$) 9.56 (s, 1H, C*H*O), 7.67–7.64 (m, 2H, aromatic hydrogens), 7.51–7.47 (m, 3H, aromatic hydrogens), 7.44 (s, 1H, C*H*=), 4.40 (s, 2H, CH_2Cl); δ_C (100.91 MHz; $CDCl_3$) 34.9, 128.2, 128.9, 130.1, 130.7, 137.2, 152.4, 192.3; GC–MS t_R = 18.69 min *m/z* 182 (M^+ +2, 33), 180 (M^+, 75), 179 (90), 145 (25), 115 (100), 91 (25).

(Z)-2-(Chloromethyl)-3-(4-chlorophenyl)acrylaldehyde ((Z)-9). Yield 70%; δ_H (400 MHz; $CDCl_3$) 9.59 (1H, s, C*H*O), 7.61 (2H, m, aromatic hydrogens), 7.48 (2H, m, aromatic hydrogens), 7.41 (1H,

s, C*H*=), 4.39 (2H, s, CH_2Cl); δ_C (100.91 MHz; $CDCl_3$) 34.7, 129.4, 131.4, 131.8, 137.1, 137.8, 150.8, 192.1; GC–MS t_R = 21.34 min *m/z* 216 (M^+ +2, 15), 214 (M^+, 25), 179 (100), 151 (30), 115 (100).

(Z)-2-(Chloromethyl)-3-(3-methoxyphenyl)acrylaldehyde ((Z)-10). Yield 91%; δ_H (400 MHz; $CDCl_3$) 9.58(1H, s, C*H*O), 7.43 (s, 1H, C*H*=), 7.40 (1H, t, *J* 8.4 Hz, aromatic hydrogen), 7.23–7.21 (2H, m, aromatic hydrogens), 7.02–7.01 (1H, m, aromatic hydrogens), 4.41 (2H, s, CH_2Cl), 3.86 (3H, s, O*Me*); δ_C (100.91 MHz; $CDCl_3$) 35.1, 55.3, 114.9, 116.9, 122.6, 130.1, 134.6, 137.6, 152.4, 159.9, 192.3; GC–MS t_R = min 21.92 min *m/z* 212 (M^+ +2, 20), 210 (M^+, 60), 179 (40), 147 (100), 131 (35), 115 (45), 91 (10).

4.3. Synthesis of substituted benzylacrylaldehydes 7, 11, and 12

Benzylacrylaldehyde **7** was prepared following the synthetic sequence described in Ref. [25]. Aldehydes **11**, and **12** were prepared according to the following path: the suitable Baylis–Hillman adduct obtained by reaction of the aromatic aldehyde with methyl acrylate in the presence of DABCO (according to procedure 4.2.1) was submitted to HBr rearrangement. The corresponding 2-bromomethyl-3-arylacrylates were treated with DABCO and $NaBH_4$ to afford substituted benzylacrylates which were reduced to the corresponding propenols. These latter substrates gave the corresponding substituted benzylacrylaldehydes by MnO_2 oxidation.

4.3.1. General procedure for the conversion of the Baylis–Hillman adducts into the corresponding 2-bromomethyl-3-arylacrylates [34]

To a stirred solution of the suitable Baylis–Hillman adduct (80 mmol) in CH_2Cl_2 (150 mL) was added dropwise HBr 48% (26 mL) and then concentrated H_2SO_4 (23.2 mL) at 0 °C. After stirring overnight at r.t., the reaction mixture was carefully diluted with CH_2Cl_2 and water. The mixture was extracted with CH_2Cl_2; the organic phase was washed twice with water, dried (Na_2SO_4), and concentrated under reduced pressure, to give a residue which was chromatographed on a silica gel column with increasing amounts of ethyl acetate in hexane.

(Z)-Methyl 2-(bromomethyl)-3-(4-chlorophenyl)acrylate. Yield 71%; δ_H (400 MHz; $CDCl_3$) 7.76 (1H, s, C*H*=), 7.51 (2H, m, aromatic hydrogens), 7.43 (2H, m, aromatic hydrogens), 4.35 (2H, s, CH_2Brl), 3.88 (3H, s, COOMe); δ_C (100.91 MHz; $CDCl_3$) 26.2, 52.5, 129.2, 130.9, 131.2, 131.6, 132.6, 141.5, 166.3; GC/MS t_R 23.51 min, *m/z* 288 (M^+, 6), 209 (100), 149 (75), 115 (87).

(Z)-Methyl 2-(bromomethyl)-3-(3-methoxyphenyl)acrylate. Yield 76%; δ_H (400 MHz; $CDCl_3$) 7.80 (1H, s, C*H*=), 7.35 (1H, m, aromatic hydrogen), 7,15 (2H, m, aromatic hydrogens), 6.97 (1H, m, aromatic hydrogen), 4.40 (2H, s, CH_2Br), 3.87 (3H, s, OMe), 3.85 (3H, s, COOMe); δ_C (100.91 MHz; $CDCl_3$) 26.8, 52.4, 55.3, 114.2, 115.8, 122.0, 128.8, 129.8, 135.5, 142.9, 159.8, 166.5; GC/MS t_R 23.95 min, *m/z* 284 (M^+, 14), 205 (68), 145(100).

4.3.2. General procedure for the conversion of the 2-bromomethyl-3-arylacrylates into the corresponding substituted benzylacrylates [35]

The bromomethylacrylate (60 mmol) was dissolved in 1:1 THF/water (60 mL) and treated with DABCO (60 mmol). After stirring 15 min at r.t., $NaBH_4$ (60 mmol) was added. After 15 min, the reaction mixture was poured in HCl 1 M, and extracted with ethyl acetate. The organic phase was washed with water, dried (Na_2SO_4), and concentrated under reduced pressure to give a residue which was chromatographed on a silica gel column with increasing amounts of ethyl acetate in hexane.

Methyl 2-(4-chlorobenzyl)acrylate. Yield 85%; δ_H (400 MHz; $CDCl_3$) 7.25 (2H, m, aromatic hydrogens), 7.13 (2H, m, aromatic hydrogens), 6.23 (1H, m, C*H*H=), 5.48 (1H, m, C*H*H=), 3.73 (3H, s, COOMe), 3.59 (2H, s, CH_2); δ_C (100.91 MHz; $CDCl_3$) 37.5, 51.9, 126.4, 128.5, 130.3, 131.2, 137.2, 139.7, 167.1; GC/MS t_R 18.74 min, *m/z* 210 (M^+, 67), 179 (29), 150 (100), 115 (100).

Methyl 2-(3-methoxybenzyl)acrylate. Yield 81%; δ_H (400 MHz; $CDCl_3$) 7.19 (1H, m, aromatic hydrogen), 6.82–6.72 (3H, m, aromatic hydrogens), 6.23 (1H, m, C*H*H), 5.48 (1H, m, C*H*H), 3.78 (3H, s, OMe), 3.73 (3H, s, COOMe), 3.61 (2H, s, CH_2); δ_C (100.91 MHz; $CDCl_3$) 38.1, 51.8, 55.1, 111.7, 114.7, 121.3, 126.2, 129.3, 139.9, 140.2, 159.6, 167.2; GC/MS t_R 19.53 min, *m/z* 206 (M^+, 50), 174 (24), 146 (100).

4.3.3. General procedure for the conversion of the substituted benzylacrylates into the corresponding substituted benzylpropenols

The reduction of substituted benzylacrylates to substituted benzylpropenols was performed according to procedure 4.2.3.

2-(4-Chlorobenzyl)prop-2-en-1-ol. Yield 68%; δ_H (400 MHz; $CDCl_3$) 7.22 (2H, m, aromatic hydrogens), 7.08 (2H, m, aromatic hydrogens), 5.08 (1H, m, C*H*H=), 4.83 (1H, m, C*H*H=), 3.95 (2H, s, CH_2OH), 3.31 (2H, s, CH_2Ar); δ_C (100.91 MHz; $CDCl_3$) 38.9, 64.8, 111.7, 128.4, 130.2, 131.9, 137.4, 147.5; GC/MS t_R 18.10 min, *m/z* 182 (M^+, 5), 164 (7), 129 (100), 115 (20).

2-(3-Methoxybenzyl)prop-2-en-1-ol. Yield 72%; δ_H (400 MHz; $CDCl_3$) 7.19 (1H, m, aromatic hydrogen), 6.82–6.72 (3H, m, aromatic hydrogens), 5.12 (1H, m, C*H*H), 4.91 (1H, m, C*H*H), 4.03 (2H, s, CH_2OH), 3.78 (3H, s, OMe), 3.38 (2H, s, CH_2Ar); δ_C (100.91 MHz; $CDCl_3$) 39.9, 55.1, 65.2, 111.5, 111.6, 114.6, 121.3, 129.3, 140.6, 147.9, 159.7; GC/MS t_R 18.84 min, *m/z* 178 (M^+, 100), 159 (27), 121 (67).

4.3.4. General procedure for the conversion of the substituted substituted benzylpropenols into the corresponding substituted benzylacrylaldehydes

The oxidation of substituted benzylpropenols to substituted benzylacrylaldehydes was performed according to procedure 4.2.4.

2-(4-Chlorobenzyl)acrylaldehyde (11). Yield 65%; δ_H (400 MHz; $CDCl_3$) 9.57 (1H, s, C*H*O), 7.24 (2H, m, aromatic hydrogens), 7.10 (2H, m, aromatic hydrogens), 6.11 (1H, m, C*H*H=), 6.06 (1H, m, C*H*H=), 3.52 (2H, s, CH_2Ar); δ_C (100.91 MHz; $CDCl_3$) 33.5, 128.6, 130.43, 132.2, 135.1, 136.6, 149.2, 193.6; GC/MS t_R 16.3 min, *m/z* 180 (M^+, 11), 145 (100), 125 (15), 115 (56).

2-(3-Methoxybenzyl)acrylaldehyde (12). Yield 64%; δ_H (400 MHz; $CDCl_3$) 9.60 (1H, s, C*H*O), 7.20 (1H, m, aromatic hydrogen), 6.80–6.68 (3H, m, aromatic hydrogens), 6.11 (1H, m, C*H*H), 6.06 (1H, m, C*H*H), 3.78 (3H, s, OMe), 3.53 (2H, s, CH_2Ar); δ_C (100.91 MHz; $CDCl_3$) 34.1, 55.1, 111.8, 114.9, 121.5, 129.5, 135.1, 139.7, 149.6, 159.8, 193.9; GC/MS t_R 17.42 min, *m/z* 176 (M^+, 100), 145 (33), 108 (40).

4.4. General procedure for Baker's Yeast reduction of aldehydes

(a) Substrate adsorbed on the resin (for aldehydes (Z)-6, (Z)-9, (Z)-10, 7, 11, and 12). A mixture of 100 g of Baker's Yeast (Lesaffre) and 50 g of D-glucose in 1 L of tap water was prepared. After 30 min stirring at 30 °C the aldehyde (2.5 g) adsorbed on 37.5 g of hydrophobic resins (polystyrene XAD-1180N) was added within 10 min. The mixture was kept under stirring 48 h at r.t. and then filtered on a cotton plug. The collected mass was washed repeatedly with tap water to remove most of the cells. The resin was then collected and extracted twice in sequence with acetone (200 mL) and ethyl acetate (200 mL). The organic phase was concentrated to 1/3 and then washed with brine. The residue obtained upon evaporation of the dried (Na_2SO_4) extract was chromatographed on a silica gel column with increasing amounts of ethyl acetate in hexane.

(b) Substrate Added in Solution (for aldehydes (Z)-6, (Z)-9, (Z)-10, and (E)-14). To the fermenting yeast mixture described above (100 g yeast) the suitable aldehyde (2.5 g) dissolved in 25 mL of ethanol

was added dropwise within 10 min. After 48 h stirring, acetone (1 L) was added to the mixture. After stirring overnight, ethyl acetate (1 L) was added and the mixture was stirred 1 h. The two phases were separated in a separatory funnel and the aqueous phase was extracted twice with a 9:1 mixture of ethyl acetate-hexane. The combined organic phase was concentrated under vacuum to a small volume. After addition of 10 vol of ethyl acetate–hexane 9:1, the organic phase was washed repeatedly with water and brine. The oily residue obtained upon evaporation of the dried (Na_2SO_4) organic phase was chromatographed on a silica gel column obtaining with *ca.* 15–20% ethyl acetate in hexane the saturated alcohols **2, 15** and **16** and with neat ethyl acetate the diols **17**, **18** and **19**.

Deuterium Incorporation Experiments. The reactions were carried out exactly as described above, with the only modification that *ca.* 1% of 99% D_2O was added at the beginning to the reaction mixture.

(R)-2-Methyl-3-phenylpropan-1-ol ((R)-2). δ_H (400 MHz; $CDCl_3$): 7.33–7.10 (5H, m, aromatic hydrogens), 3.51 (1H, dd, *J* 5.8 and 10.6 Hz, C*H*HOH), 3.45 (1H, dd, *J* 5.8 and 10.3 Hz, CH*H*OH), 2.75 (1H, dd, *J* 6.4 and 13.5 Hz, PhC*H*H), 2.40 (1H, dd, *J* = 8.0 and 13.5 Hz, PhCH*H*), 1.93 (1H, m, *CH*CH_3), 0.90 (3H, d, *J* 6.7 Hz, *CH*$_3$). δ_C (100.91 MHz; $CDCl_3$): 16.3, 37.6, 39.6, 67.5, 125.8, 128.2, 129.1, 140.6. The material recovered (33% isolation yields) from the reduction of (*Z*)-**6** loaded on the resin showed $[\alpha]_D$ =+10.9 (*c* 1.22, $CHCl_3$) with ee = 99% [lit. Ref. [36]: $[\alpha]_D = -10$. (*c* 0.84, $CHCl_3$) for the (*S*) enantiomer (ee = 87%)]. The material recovered (45% isolation yields) from the reduction of **7** loaded on the resin showed $[\alpha]_D$ = +10.4 (*c* 1.22, $CHCl_3$).

(R)-2-Methyl-3-(4-chloro-phenyl)propan-1-ol ((R)-15). δ_H (400 MHz; $CDCl_3$): 7.40–7.05 (5H, m, aromatic hydrogens), 3.49 (2H, m, C*H*$_2$OH), 2.75 (1H, dd, *J* 6.1 and 13.5 Hz, ArC*H*H), 2.39 (1H, dd, *J* 8.3 and 13.5 Hz, ArCH*H*), 1.91 (1H, m, *CH*CH_3), 0.90 (3H, d, *J* 6.7 Hz, *CH*$_3$); δ_C (100.91 MHz; $CDCl_3$): 16.2, 37.6, 38.9, 67.4, 128.3, 130.5, 131.7, 139.0. The material recovered (15% isolation yields) from the reduction of (*Z*)-**9** loaded on the resin showed $[\alpha]_D$ = +11.5 (*c* 3.5, $CHCl_3$), with ee = 96%. The material recovered (20% isolations yields) from the reduction of **11** loaded on the resin showed $[\alpha]_D$ = +8.4 (*c* 3.0, $CHCl_3$), with ee = 69%.

(R)-2-Methyl-3-(3-methoxy-phenyl)propan-1-ol ((R)-16). δ_H (500 MHz; $CDCl_3$): 7.21 (1H, m, aromatic hydrogens), 6.79–6.71 (3H, m, aromatic hydrogens), 3.81 (3H, s, O*CH*$_3$), 3.54 (1H,dd, *J* 10.5 and 5.8 Hz, C*H*HOH), 3.49 (1H, dd, *J* 10.5 and 6.0 Hz, CH*H*OH), 2.74 (1H, dd, *J* 6.5 and 13.5 Hz, ArC*H*H), 2.42 (1H, dd, *J* 7.9 and 13.5 Hz, ArCH*H*), 1.96 (1H, m, *CH*CH_3), 0.94 (3H, d, *J* 6.8, *CH*$_3$); δ_D (75.77 MHz, $CHCl_3$): 3.81 (OCH_2*D*), 3.54 (C*D*HOH), 2.75 (PhC*D*H), 0.94 (CH2*D*) (major isomer); 3.50 (CH*D*OH), 2.42 (PhCH*D*) (minor isomer) (see Fig. 1c); δ_C (100.91 MHz; $CDCl_3$):16.4, 37.6, 39.8, 55.1, 67.6, 111.1, 114.9, 121.6, 129.1, 142.3, 159.6. The material recovered (13% isolation yields) from the reduction of (*Z*)-**10** loaded on the resin showed $[\alpha]_D$ = +10.1 (*c* 1.1, $CHCl_3$) with ee = 98% (HPLC). The material recovered (19% isolation yields) from the reduction of **12** loaded on the resin showed $[\alpha]_D$ = +9.4 (*c* 1.02, $CHCl_3$) with ee = 94% (HPLC). The material recovered (32% isolation yields) from the reduction of (*E*)-**15** dissolved in ethanol showed $[\alpha]_D = -5.7$ (*c* 1.05, $CHCl_3$) with ee = 54% (HPLC).

2-(1-Hydroxy-1-phenyl)methyl-prop-2-en-1-ol (17). Yield 15%. δ_H (400 MHz; $CDCl_3$): 7.40–7.23 (m, 5H, aromatic hydrogens), 5.35 (1H, s, *PhCH*OH)), 5.21 (2H, s, =C*H*$_2$), 4.14 (1H, d, *J* 13.2 Hz, C*H*OH), 4.04 (1H, d, *J* 13.2 Hz, C*H*OH). δ_C (100.91 MHz; $CDCl_3$; Me_4Si): 64.0, 76.3, 113.4, 126.3, 127.7, 128.4, 141.8, 149.3.

2-(1-hydroxy-1-(4-chloro-phenyl))methyl-prop-2-en-1-ol (18). Yield 8%. It was purified and characterised as the corresponding diacetate, prepared by reaction with acetic anhydride in pyridine. δ_H (400 MHz; $CDCl_3$): 7.30 (m, 4H, aromatic hydrogens), 6.29 (1H, s, *PhCH*OAc)), 5.34 (1H, s, =C*H*), 5.31 (1H, s, =C*H*), 4.58 (1H, d, *J* 13.5, C*H*OAc), 4.42 (1H, d, *J* 13.2, C*H*OAc). δ_C (100.91 MHz; $CDCl_3$; Me_4Si): 21.1, 21.4, 64.3, 75.1, 116.3, 129.0, 129.1, 134.7, 136.6, 142.2, 169.9, 170.7.

2-(1-hydroxy-1-(3-methoxy-phenyl))-methyl-prop-2-en-1-ol (12). Yield 6%. δ_H (500 MHz; C_6D_6): 7.09 (2H, m, aromatic hydrogens), 6.94 (1H, m, aromatic hydrogens), 6.72 (1H, m, aromatic hydrogens), 5.14 (1H, s, Ar*CH*OH)), 5.10 (1H, br s, =C*H*H), 5.05 (1H, br s, =CH*H*), 4.00 (1H, d, *J* 13.4 Hz, C*H*HOH), 3.82 (1H, d, *J* 13.4 Hz, CH*H*OH), 3.35 (3H, s, OCH_3); δ_D (75.77 MHz; C_6H_6;) 4.01 (C*D*HOH), 4.85 (CH*D*OH), 3.36 (OCH2*D*) (see Fig. 2b); δ_C (100.91 MHz, $CDCl_3$): 55.2, 63.9, 76.2, 111.8, 113.2, 113.5, 118.6, 129.5, 143.5, 149.3, 159.8.

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