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Stereochemical Course of Baker's Yeast Mediated Reduction of the Tri- and Tetrasubstituted Double Bonds of Substituted Cinnamaldehydes

Giovanni Fronza,[a] Claudio Fuganti,[b] and Stefano Serra*[a]

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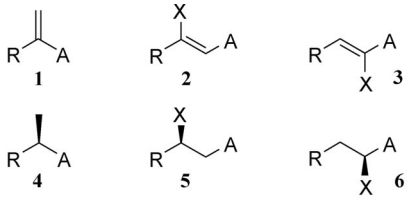
A comprehensive study of the stereochemical course of baker's yeast mediated reduction of substituted cinnamaldehydes is reported. Hydride addition to the β position of β-methylcinnamaldehydes preferentially afforded isomers of (3*S*)-3-phenylbutan-1-ol. The reduction of (*E*)-2,3-dimethylcinnamaldehyde (**15**) produced a mixture of (2*S*,3*S*)- and (2*R*,3*S*)-2-methyl-3-phenylbutan-1-ol (**13** and **14**), respectively, with 93 % *ee*. Conversely (*Z*)-2,3-dimethylcinnamaldehyde (**16**) afforded a mixture of **13** and **14** with 33 % *ee*. Accordingly, the reduction of trisubstituted β-methylcinnamaldehydes **34** and **35** proceeded with the same stereochemical preference and with higher enantioselectivity to give (*S*)-3-phenylbutan-1-ol (**37**). In addition, deuterium incorporation and ^{2}H NMR studies demonstrated that the addition of the second hydrogen atom to the α position proceeded with very low stereochemical control and the overall process is formally a mixture of *cis*/*trans* hydrogen addition to the double bond. Alternatively, α-methylcinnamaldehyde is reduced to (*S*)-2-methyl-3-phenylpropan-1-ol (**24**) with preferential addition of the hydride to the opposite β face with good stereochemical control of the *trans* addition of hydrogen to the double bond.

Introduction

Baker's yeast mediated reduction of activated olefins is a process that has been known for a long time. The first studies in this area go back to the work of Fischer,[1] who described in 1940 the reduction of a number of unsaturated aldehyde and ketone derivatives. This research did not consider the enantioselectivity of this kind of transformation which was considered a biochemical curiosity until the 1970s when this type of reaction received renewed interest in the context of the preparation of chiral synthetic intermediates to increase the pool of chiral compounds prevalent in nature.[2a–2c] Indeed, the asymmetric reduction of a double bond allows the creation of up to two stereogenic centres and is a pivotal reaction in organic synthesis. In the field of microbial biocatalysis, baker's yeast is the most commonly employed for the reduction of prochiral double bonds because it is cheap and commercially available and the transformations usually proceed with high enantioselectivity.

Moreover, for olefins of the type **1**–**3** the stereochemical course of the reduction is by now predictable, invariably affording saturated compounds of the type **4**–**6**, respectively (Figure 1). Thus, by these means, a large number of enantioenriched compounds have been prepared,[2b,2c] some of which we have used in the stereoselective syntheses of compounds belonging to quite different structural classes.[3]



A = activating group: CHO, $CH(OR)_2$, CH_2OH, CO_2R, NO_2
X = methyl, halogen

Figure 1. Substrates and products of the baker's yeast mediated asymmetric reduction of activated alkenes.

To determine the mechanism of the "biohydrogenation" of carbonyl-activated double bonds using baker's yeast or isolated enzymes, a number of isotopic studies[4] have been performed that pointed to a process involving first the addition of a hydride [delivered from NAD(P)H] to the carbon atom at the β position with respect to the activating group followed by the addition of a proton from the medium to the α position.

Thus, the overall process is formally an asymmetric *trans* hydrogenation. This aspect is very significant because the asymmetric reduction of olefins using transition-metal catalysts and chiral ligands is a stereospecific *cis* hydrogenation.[5] Therefore, the two processes could be complementary and different studies on the use of isolated reductases

[a] C.N.R. Istituto di Chimica del Riconoscimento Molecolare, Via Mancinelli 7, 20131 Milano, Italy
Fax: +39-02-2399-3180
E-mail: stefano.serra@polimi.it
[b] Dipartimento di Chimica, Materiali ed Ingegneria Chimica del Politecnico, Via Mancinelli 7, 20131 Milano, Italy

as catalysts for biohydrogenation have recently been described.[6] Moreover, a comprehensive understanding of the stereochemical course of the biocatalytic reduction might afford a number of new synthetic and analytical applications. The stereoselective bioreduction of tetrasubstituted olefins is clearly a most challenging synthetic procedure because it could afford products not available by chemical catalytic hydrogenation. In addition, knowledge of the mechanism of this biochemical transformation, which is quite widespread in Nature, would be helpful in studies designed to determine the origin of substances of practical interest for the flavour industry.[7]

To the best of our knowledge, the only reported study on baker's yeast reduction of an activated tetrasubstituted olefin relates to a nitroalkene, in which *cis* hydrogenation prevailed.[8] This is not the only exception to the generally accepted *anti* addition rule mentioned above. Some other examples of *cis* reduction of carbonyl-activated double bonds mediated by baker's yeast have been reported.[9] At first glance, these discordant results have been explained by supposing that a number of different reducing enzymes operate in a whole-cell-mediated transformation thus affording different results on the basis of their specific enzyme/substrate affinity. However, through deuterium-labelling experiments, we have recently shown[7d] that the chiral α,β-unsaturated aldehyde perillaldehyde is reduced by baker's yeast in either a *trans* or *cis* fashion depending upon its absolute configuration. More recently,[10] this latter transformation has been reinvestigated by using NADPH as the reducing agent and Ltb4 dehydrogenase as the biocatalyst, which unequivocally demonstrated that the same enzyme mediates a net *trans* addition of hydrogen across the double bond of (*R*)-perillaldehyde, but a *cis* process for the (*S*) enantiomer, thus confirming the previous findings. Seen together, the results described above would suggest that the "*trans* addition rule" is not of general validity. Accordingly, we have performed a detailed (isotopic) study of the stereochemical course of baker's yeast mediated reduction of tetra- and trisubstituted aldehydes, selecting tetrasubstituted cinnamaldehydes **7c** in addition to trisubstituted **7a** and **7b**, which have previously been shown[3c,3e,4a] to provide saturated alcohols of type **8** and **9**, respectively (Figure 2). More specifically, we employed methylcinnamaldehydes (Ar = Ph, R^1 and/or R^2 = Me), which are easily accessible in good isomeric purity by chemical synthesis.

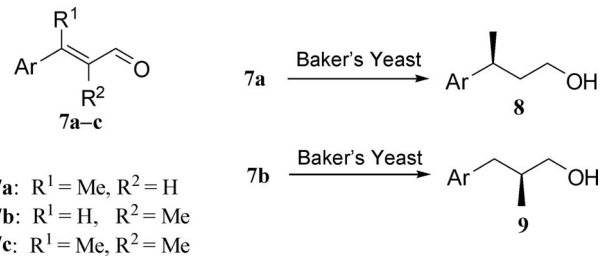


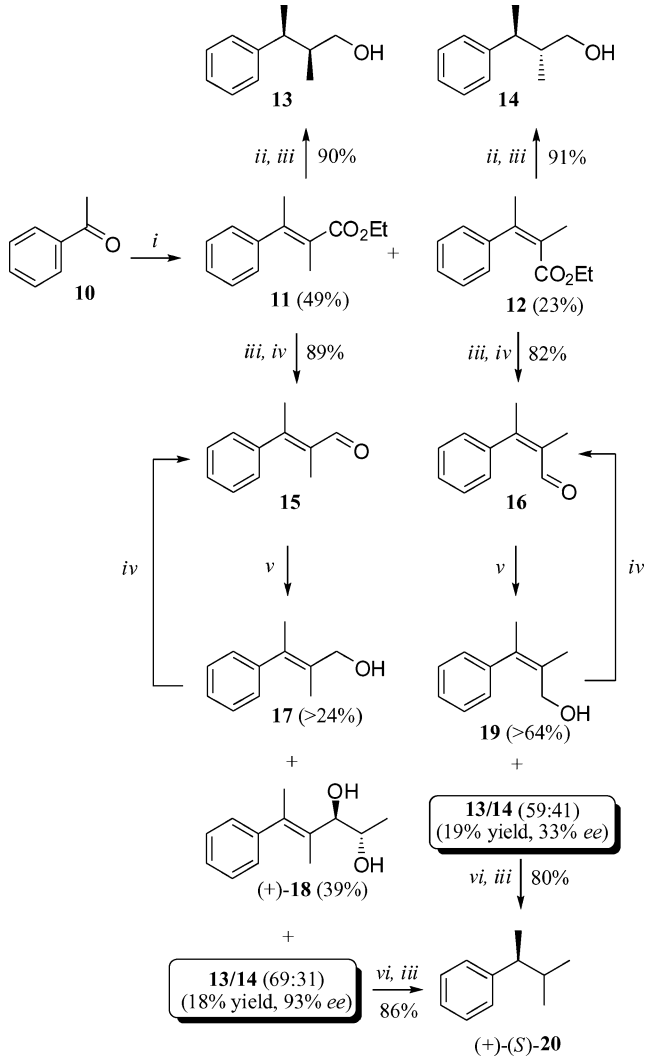
Figure 2. Substituted cinnamaldehydes and the products of their baker's yeast mediated asymmetric reduction.

Results and Discussion

As mentioned above our study of baker's yeast mediated reduction of methylcinnamaldehydes requires the use of an isomerically pure substrate. Indeed, the stereochemical course of the reduction could also be affected by the geometry of the double bond. Because isomeric methylcinnamaldehydes are not easily separable by the usual laboratory methods, we prepared them by starting from the corresponding substituted ethyl cinnamates prepared in turn by Horner condensation of acetophenone with the appropriate phosphonate esters and separated by chromatography. The desired aldehydes were obtained from the cinnamates by $LiAlH_4$ reduction followed by MnO_2 oxidation. In this way, methylcinnamaldehydes were obtained in isomerically pure form and free of any saturated impurity.

According to the general consideration described above, Horner condensation of acetophenone (**10**) with triethyl 2-phosphonopropionate[11] gave chromatographically separable esters **11** and **12** (Scheme 1). These compounds were hydrogenated using palladium on charcoal as the catalyst and the saturated esters obtained were reduced with $LiAlH_4$ to give racemic diastereoisomers **13** and **14**,[12] respectively, which were used as reference materials in the biological reduction of 2,3-dimethylcinnamaldehydes. Indeed, the reduction of esters **11** and **12** with $LiAlH_4$ followed by oxidation with MnO_2 gave aldehydes **15** and **16**, respectively, which were incubated with fermenting baker's yeast at a concentration of 2.5 g/L substrate for 4 d.

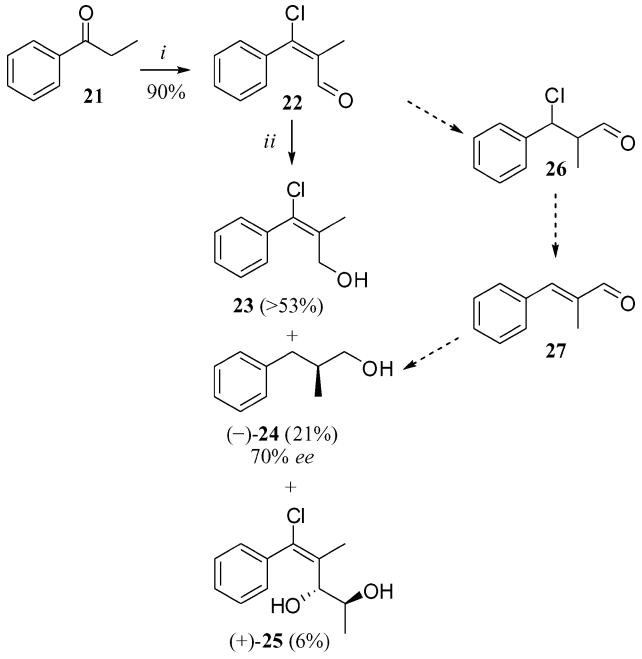
Solvent extraction provided a mixture composed of allylic alcohols, saturated alcohols and, in the case of **15**, the C_6-C_5 methyl-diol **18**, formed by reduction of the α-ketol of acyloin condensation of C_6-C_3 starting aldehyde with a C_2 unit.[13] The reduction of (*E*)-aldehyde **15** gave allylic alcohol **17** (24%), enantio- and diastereoisomerically pure diol (+)-**18** (39%) and a mixture of saturated alcohols **13** and **14** (18%, ratio 69:31, respectively) both with 93% *ee*. However, the reduction of (*Z*)-aldehyde **16** did not give a detectable amount of a diol like **18**, the main products being the allylic alcohol **19** (64%) and a mixture of the saturated alcohols **13** and **14** (19%, ratio 59:41, respectively), both showing 33% *ee*. The absolute configurations of alcohols **13** and **14** were determined by chemical correlation with the known (1,2-dimethylpropyl)benzene (**20**).[14] Accordingly, in separate runs, the two mixtures of diastereoisomeric alcohols were treated with *p*-toluenesulfonyl chloride and the derived tosylates with $LiAlH_4$. In both cases we obtained samples of (+)-(*S*)-**20**, the *ee*s of which were identical to those measured for the starting alcohols. These results prove that both aldehydes are reduced with preferential hydride delivery to the same face of the β position of the double bond. However, in the case of the reduction of (*E*)-aldehyde **15** the process is highly enantioselective, whereas the transformation of (*Z*)-aldehyde **16** is less selective. As far as the second step of the reduction is concerned, that is, the delivery of a proton to the α position, there is a modest and a low stereocontrol, respectively.



Scheme 1. Preparation of isomers of α,β-dimethylcinnamaldehydes and their baker's yeast mediated asymmetric reduction. Reagents and conditions: *i*) triethyl 2-phosphonopropionate, NaOEt, EtOH; *ii*) H_2, Pd/C, EtOAc; *iii*) $LiAlH_4$, Et_2O; *iv*) MnO_2, $CHCl_3$, reflux; *v*) Baker's yeast, glucose, water; *vi*) TsCl, Py, CH_2Cl_2.

We then examined the transformation of a tetrasubstituted cinnamaldehyde by yeast by using 3-chloro-2-methylcinnamaldehyde (**22**; Scheme 2), obtained as a 92:8 mixture of *E*/*Z* isomers by the action of phosphoryl chloride and DMF on propiophenone (**21**).[15] The reduction of **22** with fermenting baker's yeast afforded allylic alcohol **23** (53%), (*S*)-2-methyl-3-phenylpropan-1-ol (**24**; 21%)[16] and the enantio- and diastereoisomerically pure diol (+)-**25** without any trace of the expected saturated chloro alcohol. We interpreted the formation of chlorine-free **24** to be the result of a three-step process involving enzyme-mediated saturation of the double bond of **22** to provide **26**, which, by spontaneous elimination of hydrochloric acid, yields **27**, which is finally reduced to 2-methyl-3-phenylpropan-1-ol, shown to contain around 85% of the (2*S*) enantiomer **24**.

To verify the above mechanistic proposal for the generation in baker's yeast of **24** from **22** the following deuterium-labelling experiments were performed. Aldehydes **22** and **27**



Scheme 2. Preparation of 3-chloro-2-methylcinnamaldehyde and its baker's yeast mediated asymmetric reduction. Reagents and conditions: *i*) DMF, $POCl_3$; *ii*) Baker's yeast, glucose, water.

were incubated, as above, in tap water containing 1% deuteriated water. The chemically identical saturated alcohols isolated in the two experiments were shown to contain around 85% of the (2*S*) enantiomer **24**. For spectroscopic reasons, these materials were converted into the corresponding acetate esters. The ^2H NMR spectra of the derivatives of **24** obtained from **22** and **27** in baker's yeast are presented in parts A and B of Figure 3, whereas part C shows the spectrum of the trideuteriated material composed of a 1:1 racemic mixture of (1*RS*,2*SR*,3*RS*)- and (1*SR*,2*SR*,3*RS*)-[1,2,3-$^2H_3$]-2-methyl-3-phenylpropan-1-ol (**30**; Scheme 3), obtained by catalytic reduction of the aldehyde **27** with deuterium gas.

Inspection of spectra A and B indicates that the products of bioreduction incorporated deuterium atoms at all three positions of the side-chain. The deuterium atom present at the 1-position is delivered in the reduction of the aldehydic moiety of 2-methyl-3-phenylpropanal, the putative ultimate intermediate in the process, supposedly mediated by yeast alcohol dehydrogenase. If we take into account the result obtained in the case of the reduction of cinnamaldehyde,[4a] we can assign the absolute configuration *R* to the carbon atom at the 1-position of **24**. As far as the deuterium atoms introduced during the saturation of the double bond are concerned, we expect that the deuterium present at the 3-position should have been delivered from the reduced form of the nicotine cofactor, which exchanges hydrogen atom(s) with the deuteriated solvent,[17] whereas the deuterium at the 2-position derives from the medium.

Examination of the spectrum of (2*S*)-**24** (0.7 *ee*; Figure 3, B) produced directly from **27** indicates that this material is approximately an 85:15 mixture of (1*R*,2*S*,3*S*)-[1,2,3-$^2H_3$]-

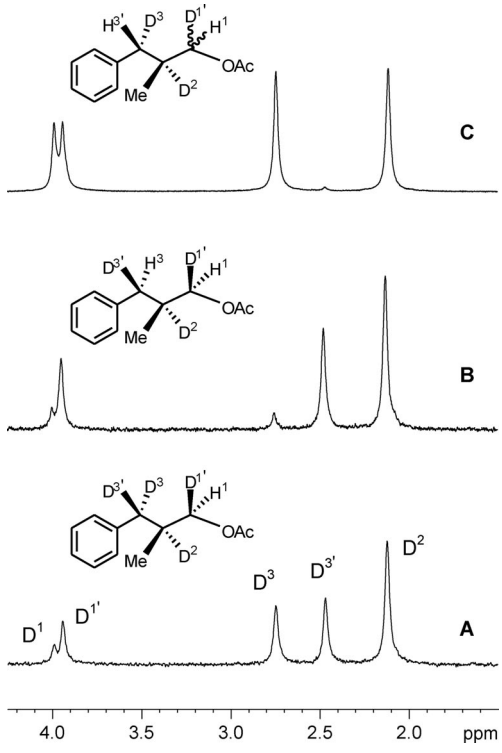
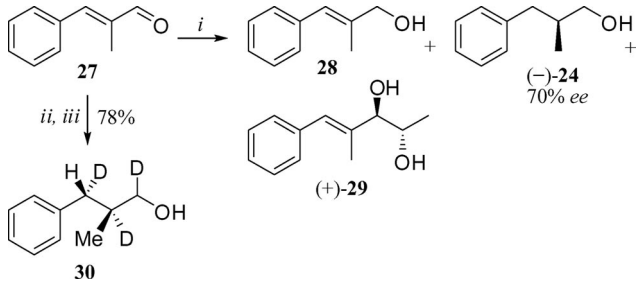


Figure 3. ^{2}H NMR spectra of the acetates of 2-methyl-3-phenylpropan-1-ol obtained from labelling experiments: A) bioreduction of the chloro aldehyde **22** providing the (1*R*,2*S*)-[1,2,3,3-$^2H_4$] derivative as the major distereoisomer; B) bioreduction of aldehyde **27** providing the (1*R*,2*S*,3*S*)-[1,2,3-$^2H_3$] derivative as the major diastereoisomer; (C) catalytic reduction with deuterium gas of the aldehyde **27** affording the racemic mixture (2*SR*,3*RS*)-[1,2,3-$^2H_3$] of the acetate of **30**.



Scheme 3. Baker's yeast mediated asymmetric reduction of α-methylcinnamaldehyde and preparation of (2*RS*,3*SR*)-2,3-dideuterio-2-methyl-3-phenylpropan-1-ol. Reagents and conditions: *i*) baker's yeast, glucose, water; *ii*) D_2, Pd/C, EtOAc; *iii*) H_2O.

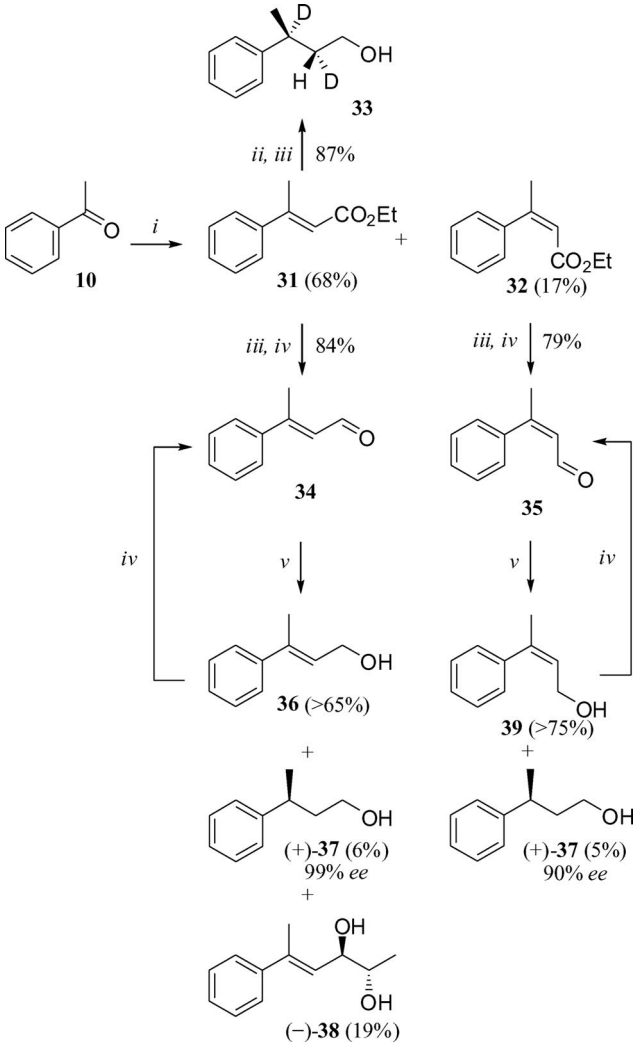
and (1*R*,2*R*,3*R*)-[1,2,3-$^2H_3$]-2-methyl-3-phenylpropan-1-ol, as pictorially illustrated in Figure 3. Conversely, (2*S*)-**24** formed from the chloro aldehyde **22** bears two deuterium labels of equal intensity at the benzylic position (Figure 3, A). An economic interpretation of this observation is that of the two diastereotopic deuterium atoms, the one possessing the (3*R*) configuration is incorporated into **22** when the latter is transformed into 3-chloro-2-methyl-3-phenylpropanal (**26**; Scheme 2). This deuterium atom is then retained when [2,3-$^2H_2$]-**26**, upon elimination of hydrochloric acid, provides [3-^{2}H]-**27**. This product is then reduced and like the protium counterpart **27** incorporates three deuterium atoms. The (3*S*) deuterium atom present in A (the second deuterium in that position) is introduced in this way. Thus, (1*R*,2*S*)-[1,2,3,3-$^2H_4$]-2-methyl-3-phenylpropan-1-ol is the prevalent (85%) deuteriated diastereoisomer of **24** derived from **22**, whereas the minor one (15%) is the (1*R*,2*R*) isomer. The above-mentioned events are represented in Scheme 3, including the production of the diol **29** alongside **28** and **24**.

To obtain further information on the cryptic stereochemistry of the yeast-mediated reduction of substituted cinnamaldehydes we investigated in some detail the reduction of (*E*)- and (*Z*)-3-methylcinnamaldehydes (**34** and **35**), respectively. The condensation of acetophenone (**10**) with triethyl phosphonoacetate gave separable esters **31** and **32** (Scheme 4). The double bond of the (*E*)-ester **31** was saturated with deuterium gas (Pd/C, ethyl acetate) and the resulting product reduced with $LiAlH_4$ to provide racemic (2*RS*,3*SR*)-[2,3-$^2H_2$]-**33**, which was used as a reference compound in subsequent studies. The reduction of esters **31** and **32** with $LiAlH_4$ followed by oxidation with MnO_2 gave aldehydes **34** and **35**, respectively, which were incubated with fermenting baker's yeast using the same experimental conditions as described for the reduction of tetrasubstituted aldehydes. The reduction of (*E*)-aldehyde **34** gave allylic alcohol **36** (65%), enantiopure saturated alcohol (+)-**37**[18] (6%) and diastereoisomerically pure diol (–)-**38** (19%). However, the reduction of (*Z*)-aldehyde **35** did not give a detectable amount of a diol similar to **38**. The main products were allylic alcohol **39** (75%) and the saturated alcohol (+)-**37** showing 90% *ee*.

These results indicate that both aldehydes were reduced by preferential hydride addition to the same face of the double bond with an enantioselectivity that ranges from very high to high in the transformations of the *E* and *Z* regioisomers, respectively. Thus, the mode of reduction of (*E*)-**34** is identical to that of (*E*)-**15** as far as the direction of hydride delivery at the β position is concerned and opposite to that of α-methylcinnamaldehyde (**27**), as revealed by the deuterium-labelling experiments described above. Consequently, to gain information on the mode of α-protonation in the reduction of **34** we submitted the latter compound to baker's yeast incubation in the presence of deuteriated water and determined the mode of labelling of the resulting saturated alcohol **37** through ^{2}H NMR studies.

In the deuterium spectrum of saturated alcohol **37** there are separate signals for the five hydrogen atoms of the side-chain backbone. The ^{2}H NMR spectra of racemic (2*RS*,3*SR*)-[2,3-$^2H_2$]-**33** and (*S*)-**37** obtained in baker's yeast/D_2O from **34** are presented in Figure 4, C and A.

As in the case of **24** from **27** (Figure 3, A) the formation in baker's yeast of **37** from **34** led to the incorporation of deuterium at all three positions of the side-chain. However, inspection of C and comparison with A indicates that labelled (*S*)-**37** isolated from the reduction of **34** is the (1*R*,3*S*)-



Scheme 4. Preparation of isomers of β-methylcinnamaldehydes and their baker's yeast mediated asymmetric reduction as well as the synthesis of (2*RS*,3*SR*)-2,3-dideuterio-3-phenylbutan-1-ol (**33**). Reagents and conditions: *i*) triethyl phosphonoacetate, NaH, THF; *ii*) D_2, Pd/C, EtOAc; *iii*) $LiAlH_4$, Et_2O; *iv*) MnO_2, $CHCl_3$, reflux; *v*) Baker's yeast, glucose, water.

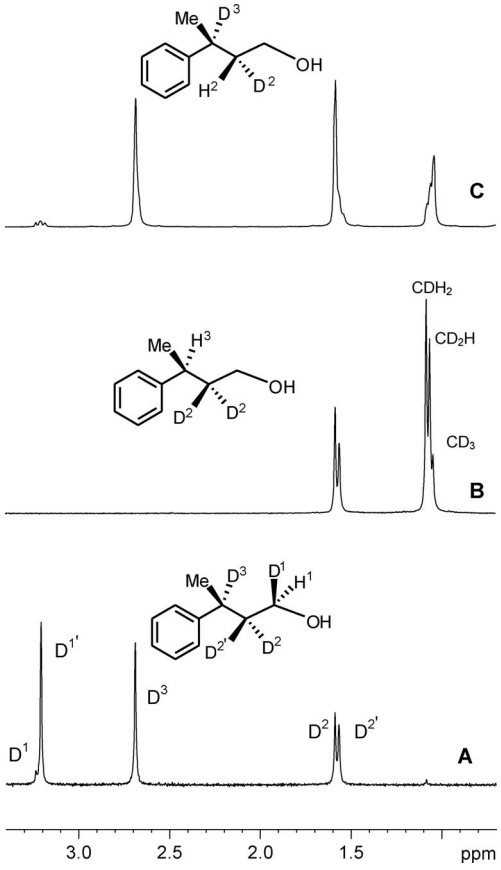


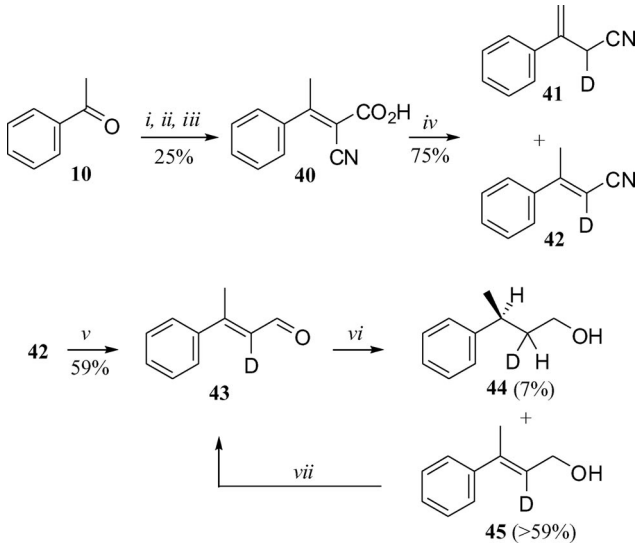
Figure 4. ^2H NMR spectra of 3-phenylbutan-1-ol obtained from the labelling experiments: A) bioreduction of aldehyde **34** in H_2O/D_2O (1%) to afford the diastereoisomer (1*R*,3*S*)-[1,2,2,3-$^2H_4$]-**37**; B) bioreduction of the deuteriated aldehyde **43** in H_2O showing the lack of sterespecificity at the 2-position of alcohol **44**; C) catalytic reduction (D_2–Pd/C then $LiAlH_4$) of the ester **31** providing the racemic (2*RS*,3*SR*)-[2,3-$^2H_2$] alcohol **33**.

[1,2,2,3-$^2H_4$] diastereoisomer, which suggests a lack of stereospecificity in the protonation at the α position in the latter conversion.

To clarify this point, specifically labelled [2-^{2}H]-**43** was synthesized (Scheme 5) and submitted to the yeast reduction.

Condensation of acetophenone (**10**) with ethyl cyanoacetate gave ethyl (1-phenylethylidene)cyanoacetate[19] as a mixture of *Z*/*E* isomers, which, after hydrolysis of the ester group and fractional crystallization of the resulting mixture, afforded pure acid **40**.[20] The latter compound was stirred with D_2O and the solvent was removed under reduced pressure, repeating the operation twice. The acid obtained was heated at 200 °C until the evolution of carbon dioxide had ceased, thus providing a mixture of nitriles **41** and **42**. The α,β-unsaturated nitrile **42** was isolated by chromatography and reduced with DIBAH to provide the desired aldehyde **43**, which, as a consequence of the mode of preparation, is deuterium-labelled in the β-methyl group. Yeast reduction of labelled **43** in tap water provided enantiopure (*S*)-**44** and the allylic alcohol **45**. The ^2H NMR spectrum of alcohol **44** (Figure 4, B) shows two deuterium signals arising from the methylene group at 1.58 (2-D) and 1.56 ppm (2′-D) (ratio 55:45). This result confirms the above findings, that is, the yeast reduction of **34** to **37** proceeds with stereospecific hydride addition at the β position, but with random protonation at the α position. As reported above, baker's yeast reduction of aldehyde **34** affords in addition to the alcohols **36** and (+)-**37** the diastereoisomerically pure 5-phenylhex-4-en-2,3-diol [(–)-**38**].

The deuterium spectrum of **38** shows incorporation of deuterium labels at the 1- and 2-positions (Figure 5). The formation of **38** occurs by addition of a C_2 unit derived from pyruvate onto the carbonyl carbon of **34** to provide an α-hydroxy ketone, subsequently reduced to the *anti*-diol actually isolated. The formation of the precursor pyruvate and the stereospecific yeast reduction fully accounts for the incorporation of deuterium in **38**.



Scheme 5. Preparation of 2-deuterio-3-methylcinnamaldehyde and its baker's yeast mediated asymmetric reduction. Reagents and conditions: *i*) ethyl cyanoacetate, NH_4OAc, AcOH; *ii*) NaOH, MeOH then HCl; *iii*) recrystallization from EtOAc; *iv*) D_2O, stirring then drying and warming at 200 °C; *v*) DIBAH, toluene, –60 °C; *vi*) Baker's yeast, glucose, water; *vii*) MnO_2, $CHCl_3$, reflux.

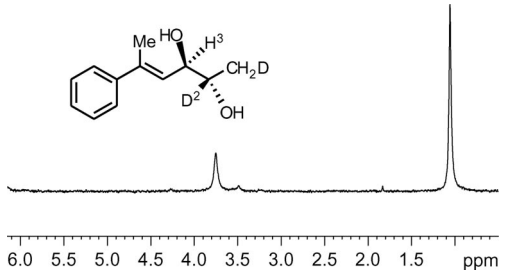
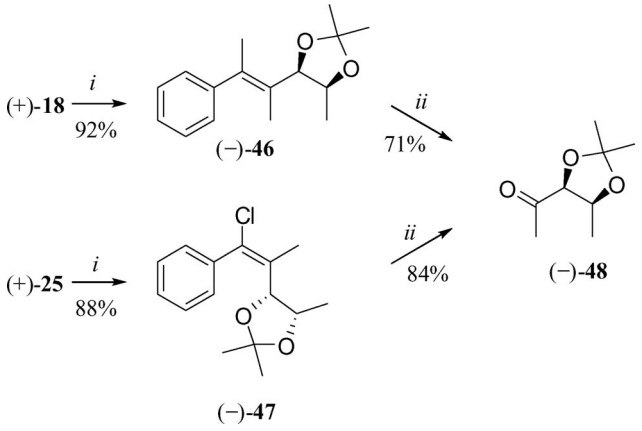


Figure 5. Deuterium spectrum of diol **38** showing incorporation of deuterium labels at the 1- and 2-positions.

Finally, note that the modest extent to which α,β-dimethylcinnamaldehydes **15** and **16** and β-methylcinnamaldehydes **34** and **35** afforded saturated alcohols (19–18 and 7–5%, respectively) is in apparent contrast to the results obtained in previous studies[3c,3e] with similar compounds, in which the saturated products were obtained in over 50% yield. This is due to the different experimental conditions employed in the latter reductions; we performed the microbial process on substrates adsorbed on a non-polar resin that slowly released the aldehyde into the aqueous medium and at the same time adsorbed the transformation product(s). The low concentrations of the substrates in the aqueous medium favoured the saturation of the double bond and reduced the formation of allylic alcohols and methyldiols. However, in this study we have focused on the stereochemical features of the bioreduction. The biotransformations were performed without resin and thus without optimization of the yields, but by using the same conditions for each experiment.

The stereochemical assignments of diols **18** and **25** were made by chemical correlation with the known compound **48** (Scheme 6). Thus, **18** and **25** were converted into the corresponding 1,3-dioxolanes **46** and **47**, respectively, which, after ozonolysis and treatment with Ph_3P, provided in both cases the known ketone **48** in enantiopure form. Therefore, the diols (+)-**18** and (+)-**25** have the absolute configuration (2*S*,3*R*), the same as the known diols (+)-**29**[16] and (–)-**38**.[21] These experiments have demonstrated that (*E*)-methylcinnamaldehydes are good substrates in baker's yeast mediated acyloin condensation and reduction, whereas carbon–carbon coupling does not occur with the (*Z*) isomers.[13]



Scheme 6. Chemical correlation of diols (+)-**18** and (+)-**25** with 1-[(4*S*,5*S*)-2,2,5-trimethyl-1,3-dioxolan-4-yl]ethanone. Reagents and conditions: *i*) 2,2-dimethoxypropane, PPTS, MeOH; *ii*) O_3, CH_2Cl_2/MeOH then Ph_3P.

Conclusions

This work further confirms that baker's yeast mediated reduction of substituted cinnamaldehydes proceeds with a stereochemical course strongly dependent on the structure of the substrate. Aldehydes with a β-methyl substituent are invariably reduced with preferential formation of the (3*S*)-3-phenylbutan-1-ol isomers. This step is highly enantioselective for trisubstituted (*E*)- and (*Z*)-β-methylcinnamaldehydes (**34** and **35**). In the case of tetrasubstituted aldehydes the reduction of the (*E*) isomer **15** is again highly enantioselective, whereas the same step proceeds with low enantioselectivity with the (*Z*) isomer **16**.

In the reduction of tetrasubstituted α,β-dimethylcinnamaldehydes the addition of the second hydrogen atom to the α position proceeds with low stereochemical control [7:3 and 6:4, respectively, for the (*E*) and (*Z*) isomers **15** and **16**], but in a *cis* fashion. Deuterium-labelling experiments revealed that protonation at the α-position in the case of (*E*)-β-methylcinnamaldehyde (**34**) proceeds without stereochemical control.

Conversely, (*E*)-α-methylcinnamaldehyde (**27**) is reduced with preferential addition of the hydride to the opposite β face with fairly good (85:15) *anti* stereochemical control, as indicated by deuterium-labelling experiments.

In future works, the use of enzymes isolated from baker's yeast and able to catalyze the reduction of activated double bonds will clarify in detail the results obtained with the whole cell system (this work).

Experimental Section

General: All moisture-sensitive reactions were carried out under a static atmosphere of nitrogen. All reagents were of commercial quality. TLC: Merck silica gel 60 F254 plates. Column chromatography (CC): silica gel. GC–MS analyses: HP-6890 gas chromatograph equipped with a 5973 mass detector and a HP-5MS column (30 m × 0.25 mm, 0.25 μm firm thickness; Hewlett–Packard) with the following temp. program: 60 °C (1 min)–6 °C/min–150 °C (1 min)–12 °C/min–280 °C (5 min); carrier gas: He; constant flow 1 mL/min; split ratio: 1:30; t_R(**11**) = 17.45, t_R(**12**) = 16.66, t_R(**13**) = 14.62, t_R(**14**) = 14.79, t_R(**15**) = 15.19, t_R(**16**) = 15.36, t_R(**18**) = 20.43, t_R(**20**) = 8.51, t_R(**22**, *Z* isomer) = 15.97, t_R(**22**, *E* isomer) = 16.06, t_R(**24**) = 13.05, t_R(**25**) = 21.81, t_R(**31**) = 18.16, t_R(**32**) = 15.94, t_R(**34**) = 15.32, t_R(**35**) = 13.70, t_R(**37**) = 12.92, t_R(**38**) = 17.76, t_R(**46**) = 20.39, t_R(**47**) = 21.36, t_R(**48**) = 6.35 min. MS (ESI) analyses: Bruker Esquire 3000 PLUS spectrometer (ESI Ion Trap LC/MSn System). Chiral GC analyses: DANI-HT-86.10 gas chromatograph; enantiomer excesses determined on a Chirasil DEX CB column with the following temp. program: compound **13**: 70 °C (0 min)–1 °C/min–88 °C (15 min)–30 °C/min–180 °C (0 min); t_R[(2*S*,3*S*)-**13**] = 27.1, t_R[(2*R*,3*R*)-**13**] = 27.7 min; compound **20**: 35 °C (0 min)–0.3 °C/min–45 °C (0 min)–30 °C/min–180 °C (0 min); t_R[(+)-(*S*)-**20**] = 24.1, t_R[(–)-(*R*)-**20**] = 25.1 min. Optical rotations: Jasco-DIP-181 digital polarimeter. ^{1}H and ^{13}C NMR spectra: $CDCl_3$ solutions at room temp.; Bruker AC-400 spectrometer at 400 and 100 MHz, respectively; chemical shifts in ppm relative to $SiMe_4$ as an internal standard (δ = 0 ppm), *J* values in Hz. IR spectra: Perkin–Elmer 2000 FT-IR spectrometer; $\tilde{\nu}$ in cm^{-1}. Melting points: Reichert apparatus equipped with a Reichert microscope values are uncorrected.

Acquisition of the ^{2}H NMR Spectra: The ^{2}H NMR spectra were recorded with a Bruker Avance 500 spectrometer equipped with a 10 mm probe head and a ^{19}F lock channel under CPD (Waltz 16 sequence) proton decoupling conditions at a temperature of 305 K. The solutions were prepared by dissolving 20–100 mg of material in $CHCl_3$ or C_6H_6 (ca. 3.0 mL) adding about C_6F_6 (40 μL) for the lock. The spectra were recorded by performing 64–2048 scans depending on the solution concentration and the deuteriation grade using the following acquisition parameters: 5.4 s acquisition time, 1530 Hz spectral width, 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 accurate correction of the base line. For partially overlapped signals the peak areas were determined by the deconvolution routine of the Bruker TopSpin NMR software using a Lorentzian line shape.

The spectra of the products obtained by incubation of the aldehydes with baker's yeast in tap water with 1% D_2O show the presence of molecules with several deuteriated sites. However, due to the low concentration of D_2O they are not polydeuteriated molecules but rather an assembly of monodeuteriated species. For this reason their ^{2}H NMR spectra do not exhibit mutual isotope effects on the chemical shifts of the deuterium nuclei. On the contrary, polydeuteriated molecules were obtained by chemical reduction with their ^{2}H NMR spectra exhibiting line-broadening and signal multiplicity due to isotope effects. The isotope shifts are of the order of 0.02 ppm upfield for nuclei separated by two bonds and about 0.008 ppm for nuclei separated by three bonds. For instance, the partially deuteriated methyl groups of 3-phenylbutan-1-ol show separate signals for the CH_2D, CHD_2 and CD_3 groups (see parts B and C in Figure 4).

Synthesis of Substrates and Reference Materials. Ethyl (2*E*)- and (2*Z*)-2-Methyl-3-phenylbut-2-enoate (11 and 12): Triethyl 2-phosphonopropionate (100 g, 420 mmol) was added to a stirred solution of NaOEt (29 g, 426 mmol) in ethanol (400 mL). After 10 min, acetophenone (42 g, 350 mmol) was added dropwise and the reaction was heated at reflux for 24 h. After cooling, the mixture was poured onto ice/water and extracted with diethyl ether (3 × 200 mL). The organic phase was washed with brine (2 × 100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography with hexane/diethyl ether (95:5–9:1) as eluent to afford pure esters **11** (35.1 g, 49%) and **12** (16.7 g, 23%).

11: Colourless oil, 99% purity (by GC). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (t, *J* = 7.1 Hz, 3 H), 1.75 (q, *J* = 1.5 Hz, 3 H), 2.25 (q, *J* = 1.5 Hz, 3 H), 4.26 (q, *J* = 7.1 Hz, 2 H), 7.11–7.39 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.2, 17.3, 23.0, 60.2, 124.9, 126.9, 127.2, 128.3, 143.5, 145.3, 169.9 ppm. GC–MS (EI): *m*/*z* (%) = 204 (100) $[M]^+$, 175 (34), 159 (85), 131 (66), 115 (55), 105 (8), 91 (47), 77 (13).

12: Colourless oil, 96% purity (by GC). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.82 (t, *J* = 7.1 Hz, 3 H), 2.02 (q, *J* = 1.0 Hz, 3 H), 2.08 (q, *J* = 1.0 Hz, 3 H), 3.83 (q, *J* = 7.1 Hz, 2 H), 7.10–7.15 (m, 2 H), 7.18–7.30 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.4, 16.2, 21.5, 59.9, 126.1, 126.7, 126.8, 127.8, 142.7, 144.2, 170.4 ppm. GC–MS (EI): *m*/*z* (%) = 204 (100) $[M]^+$, 175 (35), 159 (69), 131 (60), 115 (53), 105 (8), 91 (47), 77 (13).

Ethyl (2*E*)- and (2*Z*)-3-Phenylbut-2-enoate (31 and 32): Triethyl phosphonoacetate (90 g, 401 mmol) was added dropwise under nitrogen over a period of 2 h to a stirred suspension of NaH (60% in mineral oil; 16.2 g, 405 mmol) in dry THF (300 mL) at room temp. A solution of acetophenone (40 g, 333 mmol) in dry THF (100 mL) was slowly added to the resulting mixture and the reaction mixture was heated at reflux for 3 h. After cooling, the mixture was poured onto ice/water and extracted with diethyl ether (3 × 200 mL). The organic phase was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography with hexane/diethyl ether (95:5–9:1) as eluent to afford pure esters **31** (43 g, 68%) and **32** (9.5 g, 17%).

31: Colourless oil, 99% purity (by GC). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.31 (t, *J* = 7.1 Hz, 3 H), 2.57 (d, *J* = 1.3 Hz, 3 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 6.13 (q, *J* = 1.3 Hz, 1 H), 7.30–7.40 (m, 3 H), 7.43–7.50 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.3, 17.9, 59.8, 117.2, 126.3, 128.4, 128.9, 142.3, 155.4, 166.8 ppm. GC–MS (EI): *m*/*z* (%) = 190 (80) $[M]^+$, 175 (6), 161 (47), 145 (100), 115 (70), 102 (8), 91 (25), 77 (7).

32: Colourless oil, 97% purity (by GC). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.06 (t, *J* = 7.1 Hz, 3 H), 2.16 (d, *J* = 1.4 Hz, 3 H), 3.98 (q, *J* = 7.1 Hz, 2 H), 5.90 (q, *J* = 1.4 Hz, 1 H), 7.16–7.40 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.8, 27.0, 59.6, 117.8, 126.8, 127.6, 127.8, 140.8, 155.0, 165.8 ppm. GC–MS (EI): *m*/*z* (%) = 190 (83) $[M]^+$, 175 (6), 161 (49), 145 (100), 115 (74), 102 (9), 91 (28), 77 (9).

(2*SR*,3*SR*)- and (2*RS*,3*SR*)-2-Methyl-3-phenylbutan-1-ol (13 and 14): A solution of ester **11** (1 g, 4.9 mmol) in EtOAc (50 mL) was hydrogenated at atmospheric pressure using 10% Pd/C (100 mg) as the catalyst. After the reaction was complete (1 h), the catalyst was filtered and the solution was concentrated in vacuo. The residue

was dissolved in dry ether (80 mL) and then treated with $LiAlH_4$ (190 mg, 5 mmol). Work-up with 5% aq. HCl (80 mL) afforded an oil that was purified by chromatography to give pure alcohol **13** (0.72 g, 90%) as a colourless oil (98% purity by GC). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.98 (d, J = 6.9 Hz, 3 H), 1.24 (d, J = 6.9 Hz, 3 H), 1.37 (br. s, 1 H), 1.76–1.88 (m, 1 H), 2.68 (quint., J = 7.3 Hz, 1 H), 3.27 (dd, J = 6.4, 10.6 Hz, 1 H), 3.44 (dd, J = 5.1, 10.6 Hz, 1 H), 7.14–7.21 (m, 3 H), 7.23–7.31 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.1, 18.0, 41.7, 42.2, 66.7, 126.0, 127.4, 128.3, 146.5 ppm. GC–MS (EI): m/z (%) = 164 (11) $[M]^+$, 146 (9), 131 (13), 117 (5), 105 (100), 91 (25), 77 (10).

The procedure described above was repeated starting from ester **12** (1 g, 4.9 mmol) to afford alcohol **14** (0.73 g, 91%) as a colourless oil (96% purity by GC). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.79 (d, J = 6.9 Hz, 3 H), 1.29 (d, J = 7.1 Hz, 3 H), 1.49 (br. s, 1 H), 1.77–1.89 (m, 1 H), 2.78 (quint., J = 7.1 Hz, 1 H), 3.51 (dd, J = 6.1, 10.7 Hz, 1 H), 3.61 (dd, J = 5.2, 10.7 Hz, 1 H), 7.14–7.21 (m, 3 H), 7.23–7.31 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.5, 19.1, 41.5, 41.7, 66.1, 126.0, 127.9, 128.1, 145.4 ppm. GC–MS (EI): m/z (%) = 164 (20) $[M]^+$, 146 (15), 131 (13), 117 (10), 105 (100), 91 (40), 77 (18).

(2*SR*,3*RS*)-1,2,3-Trideuterio-2-methyl-3-phenylpropan-1-ol (30): A solution of 2-methylcinnamaldehyde (1 g, 6.8 mmol) in EtOAc (50 mL) was stirred in the presence of deuterium at atmospheric pressure using 10% Pd/C (100 mg) as the catalyst. After the reaction was complete (24 h), the catalyst was filtered and the solution was stirred with water (50 mL) for 1 h. Then the organic phase was separated, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by chromatography to give alcohol **30** (0.81 g, 78%), which was quantitatively transformed into the acetyl derivative. ^{1}H NMR ($CDCl_3$ 500 MHz): δ = 0.93 (s, 3 H, CH_3), 2.07 (s, 3 H, $COCH_3$), 2.44 (br. s, 0.9 H, 3-H), 2.73 (d, J = 13.4 Hz, 0.1 H, 3′-H), 3.90 (br. s, 0.4 H, 1′-H), 3.94 (br. s, 0.4 H, 1-H), 7.31–7.15 (m, 5 H, Ph) ppm. ^{2}H NMR ($CHCl_3$ 76.7 MHz): δ = 2.12 (br. s, 1 D, 2-D), 2.74 (br. s, 1 D, 3-D), 3.94 (br. s, 0.5 D, 1′-D), 3.99 (br. s, 0.5 D, 1-D ppm (see Figure 3, C).

(2*RS*,3*SR*)-2,3-Dideuterio-3-phenylbutan-1-ol (33): A solution of ester **31** (1 g, 5.3 mmol) in EtOAc (50 mL) was stirred in the presence of deuterium at atmospheric pressure using 10% Pd/C (100 mg) as the catalyst. After the reaction was complete (2 h), the catalyst was filtered and the solution was concentrated in vacuo. The residue was dissolved in dry diethyl ether (80 mL) and then treated with $LiAlH_4$ (200 mg, 5.3 mmol). Work-up with 5% aq. HCl (80 mL) afforded an oil that was purified by chromatography to give pure alcohol **33** (0.70 g, 87%). ^{1}H NMR (C_6D_6 500 MHz): δ = 0.66 (br. s, 1 H, OH), 1.12 (s, 2.5 H, CH_3), 1.66–1.57 (m, 1.32 H, 2-H, 2′-H), 2.73 (quint., J = 7.0 Hz, 0.38 H, 3-H), 3.31–3.23 (m, 2 H, 1-H, 1′-H), 7.18–7.05 (m, 5 H, Ph) ppm. ^{2}H NMR (C_6H_6 76.7 MHz): δ = 1.08–1.04 (CH_2D + CHD_2 + CD_3), 1.59 (br. s, 2-D), 2.69 (br. s, 3-D) ppm (see Figure 4, C).

(2*E*)-2-Methyl-3-phenylbut-2-enal (15): The ester **11** (20 g, 98 mmol) as a solution in dry diethyl ether (300 mL) was reduced with $LiAlH_4$ (3.7 g, 97 mmol) at 0 °C. The reaction was quenched by dropwise addition of ethyl acetate (50 mL) followed by the addition of 5% aq. HCl (350 mL). The organic phase was separated and the aqueous layer extracted with ethyl acetate (2 × 100 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude allylic alcohol was dissolved in $CHCl_3$ (250 mL) and treated at reflux with MnO_2 (40 g, 460 mmol) for 6 h. The residue obtained upon filtration and evaporation of the solvent was purified by chromatography to give pure aldehyde **15** (13.9 g, 89%) as a colourless oil (98% purity by GC). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.66 (q, J = 1.4 Hz, 3 H), 2.46 (q, J = 1.4 Hz, 3 H), 7.15–7.20 (m, 2 H), 7.29–7.43 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 12.9, 19.3, 126.7, 127.8, 128.4, 133.2, 142.8, 155.3, 191.7 ppm. GC–MS (EI): m/z (%) = 160 (50) $[M]^+$, 159 (100), 145 (22), 131 (16), 115 (32), 103 (4), 91 (24), 77 (10).

(2*Z*)-2-Methyl-3-phenylbut-2-enal (16): The procedure described above was repeated starting from ester **12** (15 g, 73.5 mmol) to afford aldehyde **16** (9.7 g, 82%) as a colourless oil (95% purity by GC). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.92 (q, J = 1.0 Hz, 3 H), 2.27 (q, J = 1.0 Hz, 3 H), 7.18–7.25 (m, 2 H), 7.31–7.41 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 11.1, 23.4, 128.2, 128.7, 134.4, 140.2, 157.4, 193.5 ppm. GC–MS (EI): m/z (%) = 160 (57) $[M]^+$, 159 (100), 145 (22), 131 (17), 115 (32), 103 (4), 91 (25), 78 (10).

(2*E*)-3-Phenylbut-2-enal (34): The procedure described above was repeated starting from ester **31** (20 g, 105.3 mmol) to afford aldehyde **34** (12.9 g, 84%) as a colourless oil (97% purity by GC). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.56 (d, J = 1.2 Hz, 3 H), 6.38 (dq, J = 7.6, 1.2 Hz, 1 H), 7.38–7.44 (m, 3 H), 7.50–7.57 (m, 2 H), 10.17 (d, J = 7.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.3, 126.2, 127.2, 128.7, 130.0, 140.6, 157.4, 191.0 ppm. GC–MS (EI): m/z (%) = 146 (44) $[M]^+$, 145 (100), 131 (24), 115 (41), 103 (14), 91 (17), 78 (10).

(2*Z*)-3-Phenylbut-2-enal (35): The procedure described above was repeated starting from ester **32** (10 g, 52.6 mmol) to afford aldehyde **35** (6.1 g, 79%) as a colourless oil (95% purity by GC). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.30 (d, J = 1.3 Hz, 3 H), 6.13 (dq, J = 8.2, 1.3 Hz, 1 H), 7.26–7.33 (m, 2 H), 7.37–7.42 (m, 3 H), 9.47 (d, J = 8.2 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.3, 128.2, 128.3, 129.0, 129.1, 138.4, 161.8, 193.1 ppm. GC–MS (EI): m/z (%) = 146 (47) $[M]^+$, 145 (100), 131 (25), 115 (42), 103 (16), 91 (17), 78 (12).

3-Chloro-2-methylcinnamaldehyde (22): Dry DMF (90 mL) was added dropwise whilst stirring to phosphorus oxychloride (70 mL, 765 mmol) at 0 °C. The resulting solution was stirred for a further 1 h and then propiophenone (50 g, 373 mmol) was added dropwise. The mixture was kept at 0 °C for 5 h and then at room temp. for 2 h. The reaction was quenched by the addition of crushed ice and extracted with diethyl ether (2 × 200 mL). The organic phase was washed with saturated aq. Na_2CO_3 and then with brine and then dried (Na_2SO_4). The solvent was removed in vacuo and the residue distilled (b.p. 78–80 °C/0.1 Torr) to give aldehyde **22** (60.4 g, 90%) as a pale-yellow oil as a 92:8 mixture (by GC analysis) of *E*/*Z* isomers.

(*E*) Isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.08 (s, 3 H), 7.39–7.47 (m, 5 H), 9.48 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.2, 128.4, 130.0, 130.2, 135.8, 136.3, 154.2, 190.1 ppm. GC–MS (EI): m/z (%) = 182 (18) $[M]^+$, 181 (42), 180 (52) $[M]^+$, 179 (100), 145 (14), 115 (88), 91 (13), 74 (5), 63 (9).

(1-Phenylethylidene)cyanoacetic Acid (40): Ethyl cyanoacetate (38 g, 336 mmol), acetophenone (40 g, 333 mmol), ammonium acetate (6 g, 78 mmol) and acetic acid (16 g, 266 mmol) were heated at reflux in benzene (100 mL) removing the water formed in a Dean–Stark apparatus. After cooling, the reaction was quenched by dilution with diethyl ether (100 mL) and the addition of water (300 mL). The organic phase was washed with saturated aq. Na_2CO_3 and brine. The solvent was evaporated and the residue was dissolved in methanol (140 mL) and stirred at room temp. with a solution of NaOH (13.3 g, 332 mmol) in water (60 mL). After 8 h, the reaction was diluted with water (300 mL) and extracted with

diethyl ether (100 mL). The organic phase was discarded and the aqueous phase was acidified by addition of 10% aq. HCl (150 mL) followed by extraction with ethyl acetate (2 ×150 mL). The organic solvent was dried (Na_2SO_4) and concentrated under reduced pressure. The residue, consisting of a mixture of isomers, was recrystallized from ethyl acetate to give pure acid **40** (15.5 g, 25%) as yellow crystals (98% purity by GC analysis of the corresponding methyl ester); m.p. 176–177 °C. ^{1}H NMR [$(CD_3)_2SO$, 400 MHz]: δ = 2.62 (s, 3 H), 7.45–7.54 (m, 5 H), 13.80 (br. s, 1 H) ppm. ^{13}C NMR [$(CD_3)_2SO$ 100 MHz]: δ = 22.8, 105.5, 116.5, 127.0, 128.4, 129.9, 140.3, 163.2, 171.0 ppm. MS (ESI): *m*/*z* = 210.1 $[M + Na]^+$.

2-Deuterio-3-phenylbut-3-enenitrile (41) and 2-Deuterio-3-phenylbut-2-enenitrile (42): A sample of acid **40** (15 g, 80.2 mmol) was stirred with D_2O at 50 °C for 1 h. The mixture was then dried under reduced pressure and the above procedure was repeated three times. The deuterium-enriched acid obtained was slowly heated to 200 °C and then left at this temperature until evolution of carbon dioxide was complete (1 h). After cooling, the residue was purified by chromatography using hexane/diethyl ether (95:5–9:1) as eluent to afford nitriles **41** and **42** (8.7 g, 75%).

41: Obtained as a mixture of partially deuteriated molecules. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.53 (m, 1 H), 5.54–5.52 (m, 0.6 H), 5.64–5.62 (m, 0.6 H), 7.42–7.32 (m, 5 H) ppm. ^{2}H NMR ($CDCl_3$ 76.7 MHz): δ = 3.53 (s), 3.54 (s), 5.60 (s), 5.69 (s) ppm.

42: Obtained as a mixture of partially deuteriated molecules. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.48–2.44 (m, 1.57 H), 5.65 (br. s, 0.4 H), 7.48–7.37 (m, 5 H) ppm. ^{2}H NMR ($CDCl_3$ 76.7 MHz): δ = 2.50–2.46 (CH_2D + CHD_2 + CD_3), 5.68 (br. s, 1 D) ppm.

2-Deuterio-3-phenylbut-2-enal (43): DIBAH (21 mL of 1.2 M solution in toluene) was added dropwise under nitrogen to a stirred solution of nitrile **42** (3 g, 20.8 mmol) in dry toluene (50 mL) at –60 °C. The reaction was stirred at 0 °C for 3 h, then diluted with diethyl ether (50 mL) and quenched with a saturated solution of aq. NH_4Cl (50 mL) stirring vigorously for 1 h at room temp. The reaction was extracted with diethyl ether (2 × 100 mL) and the combined organic phases were concentrated under reduced pressure. The residue was purified by chromatography eluting with hexane/diethyl ether (95:5–9:1) to give pure aldehyde **43** (1.81 g, 59%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.56–2.52 (m, 1.5 H), 6.37 (m, 0.4 H), 7.54–7.38 (m, 5 H), 10.15 (s, 1 H) ppm. ^{2}H NMR ($CDCl_3$ 76.7 MHz): δ = 2.54–2.50 (CH_2D + CHD_2 + CD_3), 6.38 (br. s, 1 D) ppm.

General Procedure for Baker's Yeast Reduction of Aldehydes. Reduction of (2*E*)-2-Methyl-3-phenylbut-2-enal (15): A 5 L open cylindrical glass vessel equipped with a mechanical stirrer was charged with tap water (3 L) and glucose (100 g). Fresh baker's yeast (0.5 kg) was added in small pieces to the stirred mixture and the fermentation was allowed to proceed for 1 h. A solution of the aldehyde **15** (10 g, 62.5 mmol) in ethanol (25 mL) was added dropwise. The vigorous stirring was continued for 4 d at room temperature. During this time further baker's yeast (100 g) and glucose (20 g) were added after 24 h, and again after 48 h after the fermentation had started. The reaction was then interrupted by the addition of Celite (100 g) and ethyl acetate (400 mL) followed by filtration through a Buchner funnel through a Celite pad. The aqueous phase was extracted with ethyl acetate (3 × 150 mL) and the combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to give an oil (15 g). The latter was purified by chromatography with hexane/diethyl ether (95:5–1:1) as eluent to afford a mixture of allylic alcohol **17** and saturated alcohol **13/14** (4.5 g) followed by diol (+)-**18** (5.0 g, 39%).

(*E*)-(2*S*,3*R*)-4-Methyl-5-phenylhex-4-ene-2,3-diol [(+)-18]: Colourless crystals, 97% purity (by GC); m.p. 78–79 °C. $[\alpha]_D^{20}$ = +41.5 (*c* = 2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.30 (d, *J* = 6.3 Hz, 3 H), 1.59 (q, *J* = 1.4 Hz, 3 H), 2.01 (q, *J* = 1.4 Hz, 3 H), 2.03 (br. s, 2 H), 3.94 (quint., *J* = 6.3 Hz, 1 H), 4.64 (d, *J* = 6.0 Hz, 1 H), 7.06–7.13 (m, 2 H), 7.19–7.25 (m, 1 H), 7.28–7.36 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.4, 18.5, 20.8, 69.4, 74.7, 126.3, 127.9, 128.2, 130.0, 135.9, 144.7 ppm. MS (ESI): *m*/*z* = 229.1 $[M + Na]^+$.

The mixture of alcohol **17** and saturated alcohols **13/14** was dissolved in $CHCl_3$ (70 mL) and treated with MnO_2 (20 g, 230 mmol), stirring at reflux for 5 h. The residue obtained upon filtration and evaporation of the organic phase was purified by column chromatography using hexane/ethyl acetate (9:1 to 3:1) as eluent to give recovered aldehyde **15** (2.4 g, 15 mmol) and a mixture of alcohols **13** and **14** (1.85 g, 18%) as a pale-yellow oil (97% purity by GC) in a **13/14** ratio of 69:31 (by GC). $[\alpha]_D^{20}$ = +22.4 (*c* = 2, $CHCl_3$); 93% *ee* (by chiral GC).

Reduction of (2*Z*)-2-Methyl-3-phenylbut-2-enal (16): The reduction of aldehyde **16** (5 g, 31.2 mmol) performed according to the general procedure gave recovered aldehyde **16** (3.6 g, 20 mmol) and a mixture of alcohols **13** and **14** (0.96 g, 19%) as a pale-yellow oil (98% purity by GC) in a ratio of **13/14** of 59:41 (by GC). $[\alpha]_D^{20}$ = +8.2 (*c* = 2, $CHCl_3$); 33% *ee* (by chiral GC). No diols were detected in the reaction mixture.

Reduction of 3-Chloro-2-methylcinnamaldehyde (22): The reduction of the aldehyde **22** (15 g, 83.3 mmol) performed according to the general procedure gave recovered aldehyde **22** (8 g, 44.4 mmol), saturated alcohol (–)-**24** (2.6 g, 21%) and diol (+)-**25** (1.1 g, 6%).

(*S*)-2-Methyl-3-phenylpropan-1-ol [(–)-24]: Colourless oil, 96% purity (by GC). $[\alpha]_D^{20}$ = –8.5 (*c* = 1, $CHCl_3$) {ref.[22] $[\alpha]_D^{25}$ = –10.1 (*c* = 0.8, $CHCl_3$)}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.89 (d, *J* = 6.7 Hz, 3 H), 1.84–1.98 (m, 1 H), 2.11 (br. s, 1 H), 2.38 (dd, *J* = 8.2, 13.5 Hz, 1 H), 2.74 (dd, *J* = 6.1, 13.5 Hz, 1 H), 3.42 (dd, *J* = 6.1, 10.5 Hz, 1 H), 3.48 (dd, *J* = 5.9, 10.5 Hz, 1 H), 7.11–7.20 (m, 3 H), 7.22–7.29 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.3, 37.6, 39.6, 67.4, 125.7, 128.1, 129.0, 140.6 ppm. GC–MS (EI): *m*/*z* (%) = 150 (22) $[M]^+$, 132 (23), 117 (66), 104 (3), 92 (56), 91 (100), 77 (5), 65 (10), 51 (4), 41 (5).

(*Z*)-(2*S*,3*R*)-5-Chloro-4-methyl-5-phenylpent-4-ene-2,3-diol [(+)-25]: Pale-yellow crystals, 98% purity (by GC); m.p. 63–65 °C. $[\alpha]_D^{20}$ = +8.9 (*c* = 2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.29 (d, *J* = 6.4 Hz, 3 H), 1.79 (s, 3 H), 2.70 (br. s, 2 H), 4.08–4.20 (m, 1 H), 4.99 (d, *J* = 4.9 Hz, 1 H), 7.26–7.43 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 15.6, 18.1, 69.3, 74.9, 127.7, 128.2, 128.3, 129.0, 133.5, 138.9 ppm. MS (ESI): *m*/*z* = 251.0 $[M + Na]^+$, 249.0 $[M + Na]^+$.

Reduction of (2*E*)-2-Methylcinnamaldehyde: The reduction of aldehyde **27** (10 g, 68.5 mmol) performed according to the general procedure gave diol (+)-**29** (1.95 g, 15%), recovered aldehyde **27** (5.5 g, 55%) and saturated alcohol (–)-**24** (1.2 g, 12%) showing 97% purity (by GC) and $[\alpha]_D^{20}$ = –8.9 (*c* = 1, $CHCl_3$).

(*E*)-(2*S*,3*R*)-4-Methyl-5-phenylpent-4-ene-2,3-diol [(+)-29]: Colourless crystals, 98% purity (by GC); m.p. 106–107 °C (ref.[16] m.p. 106–107 °C). $[\alpha]_D^{20}$ = +31.9 (*c* = 1, EtOH) {ref.[16] $[\alpha]_D^{20}$ = +32 (*c* = 1, EtOH}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.22 (d, *J* = 6.4 Hz, 3 H), 1.90 (d, *J* = 1.2 Hz, 3 H), 2.05 (br. s, 1 H), 2.28 (br. s, 1 H), 3.95–4.05 (m, 1 H), 4.16 (d, *J* = 4.6 Hz, 1 H), 6.60 (s, 1 H), 7.20–7.37 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.6, 17.3, 68.9, 80.4, 126.6, 127.1, 128.1, 129.0, 136.9, 137.2 ppm. MS (ESI): *m*/*z* = 215.1 $[M + Na]^+$.

Reduction of (2*E*)-3-Phenylbut-2-enal (34): The reduction of the aldehyde **34** (3 g, 20.5 mmol) performed according to the general procedure gave recovered aldehyde **34** (1.95 g, 65%), saturated alcohol (+)-**37** (0.185 g, 6%) and diol (–)-**38** (0.75 g, 19%).

(*S*)-3-Phenylbutan-1-ol [(+)-37]: Colourless oil, 98% purity (by GC). $[\alpha]_D^{20}$ = +28.6 (*c* = 2, $CHCl_3$) {ref.[18] $[\alpha]_D^{25}$ = +25.5 (*c* = 1.52, $CHCl_3$)}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.26 (br. s, 1 H), 1.27 (d, *J* = 7.0 Hz, 3 H), 1.85 (q, *J* = 6.8 Hz, 2 H), 2.82–2.93 (m, 1 H), 3.48–3.61 (m, 2 H), 7.15–7.32 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.3, 36.5, 41.0, 61.2, 126.1, 126.9, 128.4, 146.9 ppm. GC–MS (EI): *m*/*z* (%) = 150 (11) $[M]^+$, 132 (18), 117 (46), 105 (100), 91 (28), 77 (16), 65 (3), 51 (6).

(*E*)-(2*S*,3*R*)-5-Phenylhex-4-ene-2,3-diol [(–)-38]: Colourless oil, 96% purity (by GC). $[\alpha]_D^{20}$ = –4.8 (*c* = 2, $CHCl_3$) {ref.[21] $[\alpha]_D^{20}$ = –6.7 (*c* = 1, $CHCl_3$)}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.19 (d, *J* = 6.4 Hz, 3 H), 2.12 (d, *J* = 1.3 Hz, 3 H), 2.15 (br. s, 2 H), 3.94 (dq, *J* = 3.7, 6.4 Hz, 1 H), 4.49 (dd, *J* = 3.7, 8.7 Hz, 1 H), 5.84 (dq, *J* = 8.7, 1.3 Hz, 1 H), 7.23–7.36 (m, 3 H), 7.37–7.44 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.5, 17.5, 70.4, 72.5, 125.6, 125.8, 127.5, 128.3, 139.7, 142.8 ppm. GC–MS (EI): *m*/*z* (%) = 174 (17) $[M - H_2O]^+$, 159 (1), 131 (100), 115 (16), 103 (4), 91 (35), 77 (6).

Reduction of (2*Z*)-3-Phenylbut-2-enal (35): The reduction of aldehyde **35** (3.2 g, 21.9 mmol) performed according to the general procedure gave recovered aldehyde **35** (2.4 g, 16.4 mmol) and saturated alcohol (+)-**37** (0.16 g, 5%) showing 97% purity (by GC) and $[\alpha]_D^{20}$ = +25.0 (*c* = 2, $CHCl_3$). No diol was detected in the reaction mixture.

Reduction of 2-Deuterio-3-phenylbut-2-enal (43): The reduction of aldehyde **43** (1 g, 6.8 mmol) performed according to the general procedure gave saturated alcohol (+)-**44** (75 mg, 7%) and recovered aldehyde **43** (0.59 g, 4 mmol).

(3*S*)-[2,2-^{2}H$_2$]-3-Phenylbutan-1-ol [(+)-44]: ^{1}H NMR (C_6D_6 500 MHz): δ = 0.57 (br. s, 1 H, OH), 1.13–1.07 (m, 2.3 H, CH_3 + CH_2D + CHD_2), 1.67–1.57 (m, 1.8 H, 2-H, 2′-H), 2.76–2.70 (m, 1 H, 3-H), 3.31–3.23 (m, 2 H, 1-H + 1′-H), 7.18–7.05 (m, 5 H, Ph) ppm. ^{2}H NMR (C_6D_6, 76.7 MHz): δ = 1.08–1.04 (CH_2D + CHD_2 + CD_3), 1.56 (s, 2′-D), 1.59 (s, 2-D) ppm (ratio 2-D/2′-D = 55:45; see Figure 4, B).

General Procedure for Baker's Yeast Reduction of Aldehydes in the Presence of D_2O. Reduction of (2*E*)-3-Phenylbut-2-enal (34): A 3 L open cylindrical glass vessel equipped with a mechanical stirrer was charged with tap water (1 L), D_2O (13 mL) and glucose (50 g). Fresh baker's yeast (0.2 kg) was added in small pieces to the stirred mixture and the fermentation was allowed to proceed for 1 h. A solution of aldehyde **34** (2 g, 13.7 mmol) in ethanol (10 mL) was added dropwise. The vigorous stirring was continued for 3 d at room temperature. During this time further baker's yeast (50 g) and glucose (10 g) were added after 24 h, and again after 48 h after the fermentation had started. The reaction was then interrupted by the addition of Celite (50 g) and ethyl acetate (200 mL) followed by filtration through a Buchner funnel through a Celite pad. The aqueous phase was extracted with ethyl acetate (2 × 100 mL) and the combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to give an oil (3.5 g). The latter was purified by chromatography with hexane/diethyl ether (95:5–1:1) as eluent to afford a mixture of allylic alcohol **36** and saturated alcohol (+)-**37** (1.4 g) followed by diol (–)-**38** (0.48 g, 18%). This mixture was dissolved in $CHCl_3$ (50 mL) and treated with MnO_2 (5 g, 57.5 mmol), stirring at reflux for 5 h. The residue obtained upon filtration and evaporation of the organic phase was purified by column chromatography using hexane/ethyl acetate (9:1 to 3:1) as eluent to give recovered aldehyde **34** (1.3 g, 8.9 mmol) and saturated alcohol (+)-**37** (0.13 g, 6%).

(1*R*,3*S*)-[1,2,2,3-^{2}H$_4$]-3-Phenylbutan-1-ol [(+)-37]: ^{1}H NMR (C_6D_6 500 MHz): δ = 0.67 (br. s, 1 H, OH), 1.12 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.67–1.57 (m, 2 H, 2-H, 2′-H), 2.74 (qt, *J* = 7.0 Hz, 3-H), 3.31–3.23 (m, 2 H, 1-H, 1′-H), 7.18–7.05 (m, 5 H, Ph) ppm. ^{2}H NMR (C_6D_6, 76.7 MHz): δ = 1.57 (s, 0.43 D, 2′-D), 1.59 (s, 0.45 D, 2-D), 2.69 (s, 1 D, 3-D), 3.21 (s, 1 D, 1′D), 3.24 ppm (see Figure 4, A).

(*E*)-(2*S*,3*R*)-[1,2-^{2}H$_2$]-5-Phenylhex-4-ene-2,3-diol [(–)-38]: ^{1}H NMR (C_6D_6 500 MHz): δ = 1.08 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.68 (br. s, 2 H, 2 OH), 1.87 (d, *J* = 1.4 Hz, 3 H, CH_3), 3.78 (qd, *J* = 6.4, 3.6 Hz, 1 H, 2-H), 4.29 (dd, *J* = 8.6, 3.9 Hz, 1 H, 3-H), 5.89 (dq, *J* = 8.6, 1.3 Hz, 1 H, 4-H), 7.30–7.07 (m, 5 H, Ph) ppm. ^{2}H NMR (C_6D_6, 76.7 MHz): δ = 1.06 (s, CH_3), 3.75 (s, 2-D) ppm (see Figure 5).

Reduction of (2*Z*)-3-Phenylbut-2-enal (35): The reduction of the aldehyde **35** (2 g, 13.7 mmol) performed according to the general procedure gave recovered aldehyde **35** (1.2 g, 8.2 mmol) and saturated alcohol (+)-**37** (0.11 g, 5%). No diol was detected in the reaction mixture.

(1*R*,2*S*)-[1,2,3,3-^{2}H$_4$]-2-Methyl-3-phenylpropyl Acetate: ^{1}H NMR ($CDCl_3$ 500 MHz): δ = 0.94 (d, *J* = 6.7 Hz, 3 H, CH_3), 2.07 (s, 3 H, $COCH_3$), 2.13 (m, 1 H, 2-H), 2.47 (dd, *J* = 7.8, 13.4 Hz, 1 H, 3′-H), 2.75 (dd, *J* = 6.4, 13.4 Hz, 3-H), 3.93 (dd, *J* = 6.4, 10.8 Hz, 1 H, 1′-H), 3.98 (dd, *J* = 6.2, 10.8 Hz, 1 H, 1-H), 7.15–7.31 (m, 5 H, Ph) ppm. ^{2}H NMR ($CHCl_3$ 76.7 MHz): δ = 2.13 (br. s, 1 D, 2-D), 2.47 (br. s, 0.52 D, 3′-D), 2.75 (br. s, 0.48 D, 3-D), 3.94 (br. s, 0.75 D, 1′-D), 3.98 (br. s, 0.25 D, 1-D) ppm (see Figure 3, A). The minor signal (1-D, ca. 25%) belongs to the isotopomer (1*R*,2*R*)-[1,2,3-^{2}H$_3$]-2-methyl-3-phenylpropan-1-ol acetate.

(1*R*,2*S*,3*S*)-[1,2,3-^{2}H$_3$]-2-Methyl-3-phenylpropyl Acetate: ^{1}H NMR ($CDCl_3$ 500 MHz): δ = 0.94 (d, *J* = 6.7 Hz, 3 H, CH_3), 2.07 (s, 3 H, $COCH_3$), 2.13 (m, 1 H, 2-H), 2.47 (dd, *J* = 7.8, 13.4 Hz, 1 H, 3′-H), 2.75 (dd, *J* = 6.4, 13.4 Hz, 3-H), 3.93 (dd, *J* = 6.4, 10.8 Hz, 1 H, 1′-H), 3.98 (dd, *J* = 6.2, 10.8 Hz, 1 H, 1-H), 7.15–7.31 (m, 5 H, Ph) ppm. ^{2}H NMR ($CHCl_3$ 76.7 MHz): δ = 2.13 (br. s, 1 D, 2-D), 2.47 (br. s, 0.85 D, 3′-D), 2.75 (br. s, 0.15 D, 3-D), 3.94 (br. s, 0.85 D, 1′-D), 3.98 (br. s, 0.15 D, 1-D) ppm (see Figure 3, B). The minor signals (ca. 15%) belong to the isotopomer (1*R*,2*R*)-[1,2,3-^{2}H$_3$]-2-methyl-3-phenylpropan-1-ol acetate.

General Procedure for the Determination of the Absolute Configurations of Alcohols 13 and 14: A solution of *p*-toluenesulfonyl chloride (0.63 g, 3.3 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of the mixture of alcohols **13** and **14** {0.5 g, 3 mmol; $[\alpha]_D^{20}$ = +22.4 (*c* = 2, $CHCl_3$)} in pyridine (5 mL). After 4 h, the mixture was diluted with diethyl ether (90 mL) and washed in turn with 1 N aq. HCl solution (100 mL), saturated $NaHCO_3$ solution (50 mL) and brine. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in dry diethyl ether (20 mL) and added dropwise to a solution of $LiAlH_4$ (0.15 g, 3.9 mmol) at reflux in diethyl ether (50 mL). After 1 h, the reaction was cooled (0 °C) and quenched by dropwise addition of water (1 mL) and a 20% aqueous solution of NaOH (5 mL). The diethyl ether layer was separated, washed with brine, dried (Na_2SO_4) and the solvent evaporated in vacuo. The residue was purified by chromatography with hexane/diethyl ether (95:5) as eluent and the product was further purified by bulb-to-bulb distillation to afford pure (+)-**20** (0.39 g, 86%).

(*S*)-(1,2-Dimethylpropyl)benzene [(+)-20]: Colourless oil, 98% purity (by GC). $[\alpha]_D^{20}$ = +28.4 (*c* = 2.5, CCl_4) {ref.[14a] $[\alpha]_D^{23.5}$ = –27.2

(c = 2.39, CCl_4)} for the (*R*) isomer. ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.75 (d, J = 6.8 Hz, 3 H), 0.93 (d, J = 6.8 Hz, 3 H), 1.23 (d, J = 7.0 Hz, 3 H), 1.70–1.83 (m, 1 H), 2.41 (quint., J = 7.2 Hz, 1 H), 7.11–7.18 (m, 3 H), 7.22–7.30 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 18.7, 20.1, 21.1, 34.4, 46.9, 125.7, 127.6, 128.0, 147.1 ppm. GC–MS (EI): m/z (%) = 148 (55) $[M]^+$, 115 (9), 105 (100), 91 (31), 77 (25), 65 (4), 51 (7).

The procedure described above was repeated starting from the mixture of alcohols **13** and **14** (0.45 g, 2.8 mmol) showing $[\alpha]_D^{20}$ = +8.2 (c = 2, $CHCl_3$) to give (+)-**20** (0.33 g, 80%; 96% purity by GC). $[\alpha]_D^{20}$ = +10.5 (c = 2.5, CCl_4).

General Procedure for the Determination of the Absolute Configuration of Diols (+)-18 and (+)-25: A solution of diol (+)-**18** (2 g, 9.7 mmol) in methanol (20 mL) and 2,2-dimethoxypropane (30 mL) was treated with pyridinium *p*-toluenesulfonate (0.1 g, 0.4 mmol) stirring at room temp. for 12 h. The reaction was then diluted with CH_2Cl_2 (100 mL), washed with saturated aq. Na_2CO_3 and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography with hexane/diethyl ether (95:5–9:1) as eluent to afford pure (–)-**46** (2.2 g, 92%).

(4*S*,5*R*)-2,2,4-Trimethyl-5-[(*E*)-1-methyl-2-phenylpropenyl]-1,3-dioxolane [(–)-46]: Colourless oil, 98% purity (by GC). $[\alpha]_D^{20}$ = –34.6 (c = 2, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.19 (d, J = 6.4 Hz, 3 H), 1.41 (s, 3 H), 1.53 (s, 3 H), 1.58 (q, J = 1.3 Hz, 3 H), 1.93 (q, J = 1.3 Hz, 3 H), 4.54 (quint., J = 6.6 Hz, 1 H), 5.17 (d, J = 7.2 Hz, 1 H), 7.06–7.12 (m, 2 H), 7.17–7.25 (m, 1 H), 7.26–7.35 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 16.1, 16.8, 20.6, 24.8, 27.0, 74.1, 77.7, 107.6, 126.2, 128.0, 128.2, 129.6, 133.5, 144.9 ppm. GC–MS (EI): m/z (%) = 246 (1) $[M]^+$, 202 (55), 187 (63), 171 (26), 156 (18), 144 (24), 129 (100), 115 (15), 103 (5), 86 (15), 77 (7).

A solution of **46** (2.1 g, 8.5 mmol) in CH_2Cl_2 (100 mL) and MeOH (20 mL) was treated with a stream of ozone at –78° until the appearance of a persistent blue colour. Nitrogen was then bubbled through the solution until it turned colorless and the reaction was treated with a solution of Ph_3P (3 g, 11.4 mmol) in CH_2Cl_2 (30 mL). The solution obtained was gradually warmed to room temp. and then concentrated at reduced pressure. The residue was purified by chromatography with hexane/diethyl ether (95:5 to 8:2) as eluent and the product was further purified by bulb-to-bulb distillation to afford pure (–)-**48** (0.95 g, 71%).

1-[(4*S*,5*S*)-2,2,5-Trimethyl-1,3-dioxolan-4-yl]ethanone [(–)-48]: Colourless oil, 98% purity (by GC). $[\alpha]_D^{20}$ = –83.7 (c = 1.5, $CHCl_3$) {ref.[16] $[\alpha]_D^{20}$ = –80 (c = 1, $CHCl_3$)}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.16 (d, J = 6.4 Hz, 3 H), 1.38 (s, 3 H), 1.60 (s, 3 H), 2.21 (s, 3 H), 4.36 (d, J = 7.7 Hz, 1 H), 4.52 (dq, J = 7.7, 6.4 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 15.8, 24.8, 27.0, 28.1, 73.7, 83.1, 109.7, 209.5 ppm. GC–MS (EI): m/z (%) = 143 (32) $[M – Me]^+$, 115 (100), 99 (51), 74 (9), 59 (96), 43 (85).

The transformation of diol (+)-**25** (0.6 g, 2.6 mmol) performed according to the general procedure gave ketal (–)-**47** (0.62 g, 2.3 mmol, 88%).

(4*R*,5*S*)-4-[(*Z*)-2-Chloro-1-methyl-2-phenylvinyl]-2,2,5-trimethyl-1,3-dioxolane [(–)-47]: Colourless oil, 97% purity (by GC). $[\alpha]_D^{20}$ = –66.4 (c = 1.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.23 (d, J = 6.3 Hz, 3 H), 1.42 (s, 3 H), 1.53 (s, 3 H), 1.75 (s, 3 H), 4.67 (quint., J = 6.5 Hz, 1 H), 5.36 (d, J = 7.2 Hz, 1 H), 7.27–7.40 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 15.7, 17.5, 24.7, 26.9, 74.0, 78.4, 108.0, 126.8, 128.3, 128.3, 129.1, 133.3, 138.8 ppm. GC–MS (EI): m/z (%) = 266 (<1) $[M]^+$, 251 (3), 222 (20), 187 (100), 173 (16), 159 (14), 145 (5), 129 (57), 115 (19), 86 (4), 77 (4).

The above described compound was ozonized to give (–)-**48** (0.31 g, 84%; 98% purity by GC). $[\alpha]_D^{20}$ = –81.9 (c = 1.5, $CHCl_3$).

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