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Steric Effects on the Stereochemistry of Old Yellow Enzyme-Mediated Reductions of Unsaturated Diesters: Flipping of the Substrate within the Enzyme Active Site Induced by Structural Modifications

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Abstract: The ene-reductase-mediated reduction of the carbon-carbon double bond of some alkyl 2-substituted butenedioates was investigated. The stereochemical outcome of the reaction was found to be influenced by steric effects. Ethyl and butyl citraconates were converted into the corresponding alkyl (*R*)-2-methylsuccinates with excellent enantioselectivity, whereas ethyl and butyl mesaconates were completely unreactive. Methyl 2-substituted fumarates were reduced to enantiomerically enriched methyl (*S*)-2-substituted succinates, whereas the (*Z*)-stereoisomers were left unreacted by ene-reductases. Labelling experiments were performed to investigate the mechanism of these bioreductions and explain their stereochemical outcome.

Keywords: asymmetric synthesis; baker's yeast; biotransformations; deuterium; enantioselectivity; ene-reductases

The biocatalytic reduction of carbon-carbon double bonds mediated by ene-reductases (ERs) is a very valuable tool for synthetic organic chemists:[1] it occurs with high enantioselectivity and conversion on properly activated substrates, under mild working conditions, without generation of toxic waste. The reduction of unsaturated aldehydes and ketones has been known for a long time,[2] and it has been the object of extensive investigations.[3] In the last years, the availability of isolated ene-reductases, such as *old yellow enzymes* (OYEs), has boosted the search for novel substrates in this kind of reaction, e.g., unsaturated esters[4] and amino acids[5], in order to combine the advantages of the biocatalysed reduction of the carbon-carbon double bond with the synthetic versatility of the carboxylic and amine functionalities. For these types of substrates it is still necessary to collect data regarding the structural requisites that allow the reduction to be performed with high enantioselectivity and yields, in order to investigate and exploit the synthetic potential of the biotransformation.

In the case of unsaturated esters, it has been established that the presence of a second electron-withdrawing group (e.g., a halogen atom at the same carbon atom bearing the carboxylic moiety,[6] or another ester group at the carbon atom in the β position[7]) makes the reaction more likely feasible. There are only a few examples in the literature of successful OYE-mediated bioreductions of unsaturated esters having no additional electron-withdrawing moieties on the carbon-carbon double bond.[8]

We have recently explored the synthetic significance of the bioconversions of α-haloalkenoates **1**: substrates of type (*Z*)-**1** (Figure 1) were converted into enantiomerically pure (*S*)-α-haloalkanoic acids and esters **2**, respectively, by baker's yeast (BY) fermentation and by using isolated enzymes OYE1-3.[9]

We now wish to update the investigation concerning the reduction of unsaturated diesters, which has

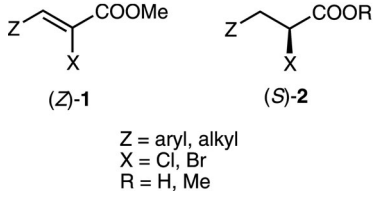

Figure 1. α-Haloacrylates and related reduction products.

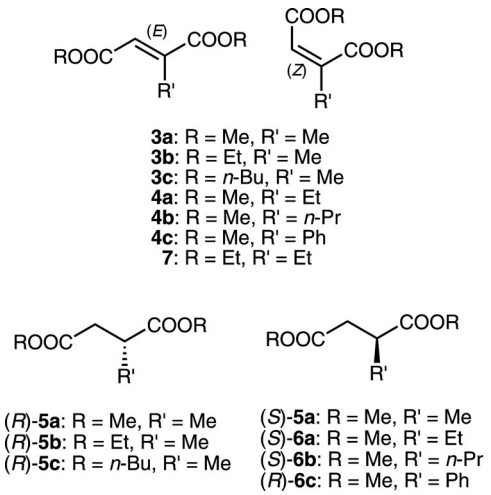

Figure 2. α,β-Unsaturated diesters for ER-mediated reductions and optically active alkyl succinates obtained as products.

been limited up to now to the biotransformation of methyl mesaconate and citraconate: (*E*)- and (*Z*)-**3a**.[7] The steric hindrance either at the alkyl group of the ester moieties, and at the substituent on the carbon-carbon double bond was increased, by preparing alkyl mesaconates and citraconates, (*E*)- and (*Z*)-**3b** and **c**, and 2-substituted fumarates and maleates (*E*)- and (*Z*)-**4a–c** (Figure 2). Their bioreduction could represent a convenient synthetic procedure[10] for the preparation of stereogenic centres bearing two reactive alkoxycarbonyl functionalities.

Derivatives (*E*)- and (*Z*)-**3b** and **3c** were prepared by Fischer esterification of mesaconic and citraconic acid in ethanol and *n*-butanol solution, respectively. The synthesis of compounds (*E*)- and (*Z*)-**4a–c** was accomplished by means of Wittig condensation of the suitable keto ester with methoxycarbonylmethylen-(triphenyl)phosphorane: the two stereoisomers were separated by column chromatography, and submitted separately to biocatalysed reductions. The double bond configuration was established by analysis of the ^{1}H and ^{13}C NMR spectra.

The results of the BY fermentation and OYE1-3 biotransformations are collected in Table 1. The data concerning the reduction of derivatives (*E*)- and (*Z*)-**3a** with OYE1-3 under similar conditions (recycling NADPH) were obtained from the literature.[7]

OYE1-3 had been described to convert methyl mesaconate and citraconate into (*S*)- and (*R*)-methyl 2-methylsuccinate **5a** (Figure 2) with high enantioselectivity, the conversion for the (*E*)-stereoisomer (80–99%) better than that for the (*Z*)-counterpart (30–64%).

When we submitted (*E*)- and (*Z*)- ethyl and butyl esters **3b** and **3c** either to BY fermentation and to

Table 1. Results of BY fermentations and OYE1-3 biotransformations of substrates (*E*)- and (*Z*)-**3** and **4**.

Substrate	BY c[a]	*ee*[c]	OYE1 c[b]	*ee*[c]	OYE2 c[b]	*ee*[c]	OYE3 c[b]	*ee*[c]
R = R′ = Me								
(*E*)-**3a**[d]			99	99 (*S*)	80	99 (*S*)	99	99 (*S*)
(*Z*)-**3a**[d]			58	99 (*R*)	64	99 (*R*)	30	99 (*R*)
R = Et, R′ = Me								
(*E*)-**3b**	0		7		0		2	
(*Z*)-**3b**	31	99 (*R*)	93	99 (*R*)	41	99 (*R*)	60	99 (*R*)
R = *n*-Bu, R′ = Me								
(*E*)-**3c**	0		0		0		0	
(*Z*)-**3c**	21	95 (*R*)	50	99 (*R*)	38	90 (*R*)	44	94 (*R*)
R = Me, R′ = Et								
(*E*)-**4a**	42	98 (*S*)	98	98 (*S*)	80	98 (*S*)	100	96 (*S*)
(*Z*)-**4a**	0		0		0		0	
R = Me, R′ = *n*-Pr								
(*E*)-**4b**	33	99 (*S*)	98	88 (*S*)	44	86 (*S*)	97	77 (*S*)
(*Z*)-**4b**	0		0.5		0		0	
R = Me, R′ = Ph								
(*E*)-**4c**	3		66	99 (*R*)	21	99 (*R*)	15	99 (*R*)
(*Z*)-**4c**	0		47	99 (*R*)	13	96 (*R*)	14	69 (*R*)
R = R′ = Et								
(*E*)-**7**	0		0		0		0	
(*Z*)-**7**	0		0		0		0	

[a] Conversions calculated by GC analysis of the crude mixture after 72 h reaction time.
[b] Conversion calculated by GC analysis of the crude mixture after 24 h reaction time.
[c] Enantiomeric excesses calculated by GC or HPLC analysis on a chiral stationary phase.
[d] Conversions and enantiomeric excess values taken from ref.[7]

OYE1-3 biotransformations, we observed that only the (*Z*)-diastereoisomers were reduced, affording the corresponding (*R*)-enantiomer of succinates **5b** and **5c** in high enantiomeric purity. The (*E*)-stereoisomers were left unreacted.

A different stereochemical course was then observed for substrates (*E*)- and (*Z*)-**4a**–**c**. 2-Substituted methyl fumarates (*E*)-**4a** and **b** were reduced either by BY and by isolated enzymes, to afford the (*S*)-enantiomer of the corresponding reduction products **6** (Figure 2) with good to high enantioselectivity.

OYE1-3 converted derivative (*E*)-**4c** in fairly good yields into nearly enantiomerically pure compound (*R*)-**6c** (Figure 2): the priority of the groups linked to the stereogenic carbon atom is different from that of the other saturated products and it is such that the (*R*)-configuration corresponds to a spatial distribution of substituents which is identical to that of the other (*S*)-enantiomers of type **6**. BY fermentation of substrate (*E*)-**4c** proceeded with very poor yields (3%).

No reduction was obtained when stereoisomers (*Z*)-**4a** and **4b** were employed as substrates under the same reaction conditions either with whole cell system or with isolated enzymes. In the case of derivative (*Z*)-**4c** (diastereoisomeric excess $de = 97\%$), extensive double bond isomerisation was observed in BY fermenting medium and under OYE-reduction conditions: the unreacted starting alkene was invariably recovered as a 1:1 mixture of the two diastereoisomers. No saturated product could be produced by BY reaction, whereas samples of derivative (*R*)-**6c**, showing high enantiomeric enrichment and very likely obtained by conversion of the (*E*)-stereoisomer formed upon isomerisation, were isolated in modest yields from OYE biotransformations.

The absolute configuration of compounds **5b** and **5c** was established by chemical correlation to the corresponding dimethyl ester **5a**; that of derivatives **6a**, **b** and **c** was known in the literature.

Some considerations on the mechanism of these bioreductions were necessary to explain the observed stereochemistry. According to the currently accepted hypothesis,[11] the arrangement of the substrate in the enzyme active site is controlled by the formation of hydrogen bonds between the activating electron-withdrawing group of the alkene and two amino acid residues within the binding pocket. In this situation a hydride ion is transferred from the flavin cofactor to the sp^2 carbon atom in the β position to the activating substituent, and a proton, which is derived from the solvent, is delivered by a tyrosine residue to the α carbon atom, usually on the other stereoheterotopic face of the olefin, thus affording in most cases *anti* hydrogen addition.

Deuterium labelling experiments were performed to establish which ester group of these unsaturated diesters was the activating one, and to confirm the *anti* stereochemistry of the bioreduction.

OYE1-mediated reductions of compounds (*E*)- and (*Z*)-**3a**, (*Z*)-**3b**, and (*E*)-**4a**, were performed in the presence of stoichiometric NADH in deuterium oxide solution,[5] in order to incorporate a deuterium atom, made available by the solvent, at the carbon atom in the α position to the activating electron-withdrawing group. The ester group linked to the prostereogenic carbon atom was always found to be the activating

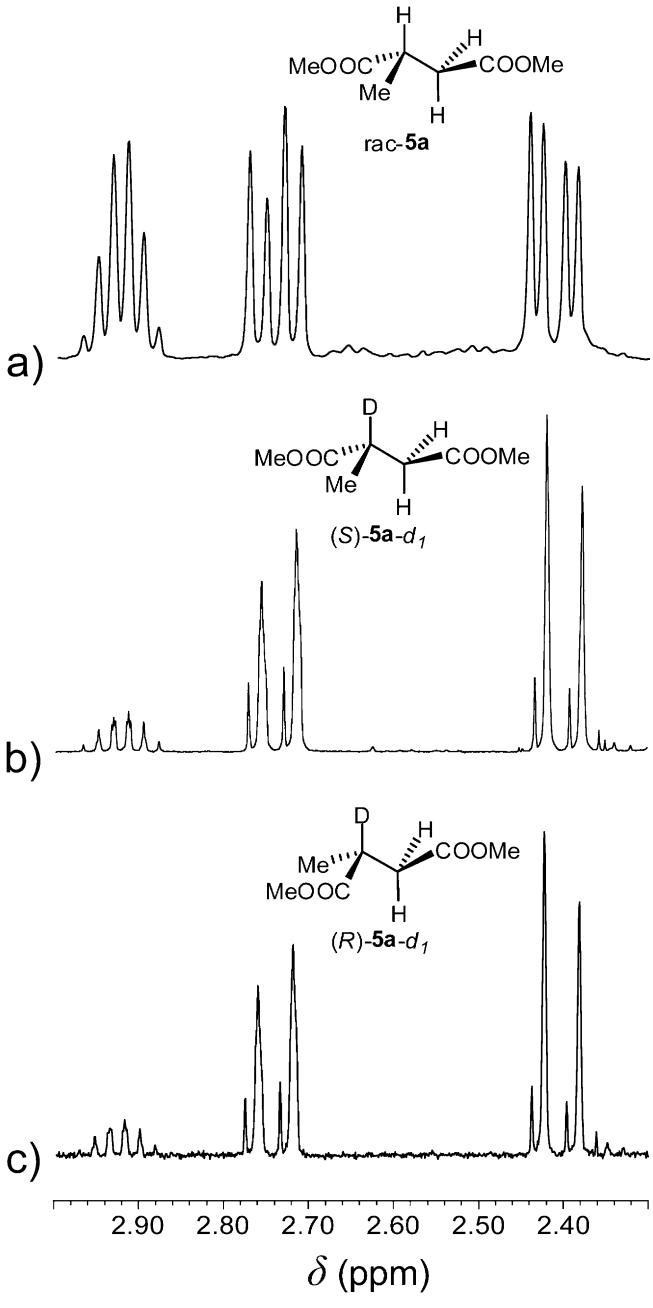

Figure 3. a) ^{1}H NMR spectrum of *rac*-**5a**; b) ^{1}H NMR spectrum of (*S*)-**5a**-d_1 obtained by OYE1 reduction of (*E*)-**3a** in D_2O; c) ^{1}H NMR spectrum of (*R*)-**5a**-d_1 obtained by OYE1 reduction of (*Z*)-**3a** in D_2O.

one: the ^{1}H NMR spectra of the monodeuterated reduced products were all characterised by the nearly complete disappearance of the multiplet due to *CH*COOR, and by the simplification of the signal of the methylene group of the CH_2COOR fragment to an AB system. As a representative example, in Figure 3 the ^{1}H NMR spectra of (*S*)- and (*R*)-**5a**-d_1 are reported and compared to that of the hydrogenated counterpart.

The stereospecificity of hydrogen addition was investigated by performing OYE1 biotransformations in the presence of (*R*)-NADPD (regenerated *in situ* by alcohol dehydrogenase and *i*-PrOH-d_8) in D_2O:[12] under these conditions a D^- anion from the cofactor and a D^+ from the solvent were added to the carbon carbon-double bond. *anti*-Hydrogen addition was established by comparison of the ^{2}H NMR spectra of the doubly deuterated reduced products, obtained from (*E*)- and (*Z*)-**3a**, (*Z*)-**3b** and (*E*)-**4a** by reaction with OYE1, and those of the doubly deuterated species, prepared upon *syn* reduction of the same starting substrates with deuterium gas in the presence of PtO_2 in ethyl acetate solution. Figure 4 collects the results obtained, for instance, for compounds **5b** and **6a**.

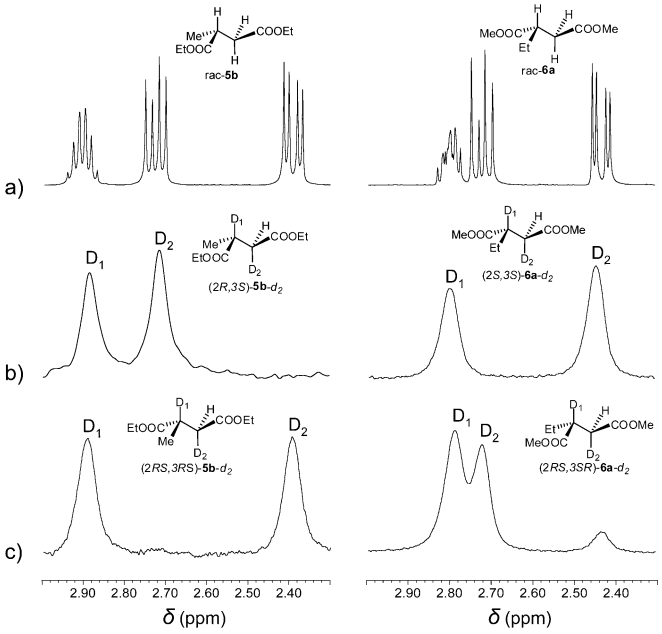

Figure 4. a) ^{1}H NMR spectra of *rac*-**5b**, and *rac*-**6a**; b) ^{2}H NMR spectra of (2*R*,3*S*)-**5b**-d_2, and (2*S*,3*S*)-**6a**-d_2 obtained by enzymatic double deuteration of (*Z*)-**3b** and (*E*)-**4a**, respectively; c) ^{2}H NMR spectra of (2*RS*,3*RS*)-**5b**-d_2, and (2*RS*,3*SR*)-**6a**-d_2 obtained by metal-catalyzed D_2 addition to (*Z*)-**3b** and (*E*)-**4a**, respectively.

The analysis of these ^{2}H NMR spectra clearly show that OYE1-mediated reduction of (*Z*)-**3b** and (*E*)-**4a** afforded the doubly deuterated compounds (2*R*,3*S*)-**5b**-d_2, and (2*S*,3*S*)-**6a**-d_2 (Figure 4, b), which were stereoisomers of the products (2*RS*,3*RS*)-**5b**-d_2, and (2*RS*,3*SR*)-**6a**-d_2, recovered from *syn* chemical deuteration (Figure 4, c) of the same starting alkenes.

The combination of these data, together with the information on the absolute configuration of the resulting succinates, led to the conclusions depicted in Figure 5. The reactive binding arrangements of substrates (*E*)- and (*Z*)-**3a** in the enzyme active site were found to differ from one another by a 180° flipping of the plane of the molecule, with exchange of the stereoheterotopic face of the alkene on which D^+ was delivered.[13] The same situation was found by comparing the results of the bioreduction of (*E*)-**4a** and (*Z*)-**3b**. Common features of the four reactions were the activation due to the most hindered ester group, and the generation of the stereogenic carbon atom in position 3 of the doubly deuterated species in (*S*)-absolute configuration with addition of D^- on C_β-*si* face.

The data of these bioreductions show that this kind of biotransformation suffers from limitations due to steric hindrance. The following considerations may be tentatively drawn, using as references substrates (*E*)- and (*Z*)-**3a**, since they show the minimum steric hindrance either at the substituent on the carbon carbon double bond, and at the ester groups. When the bulkiness of the alkyl group of the ester moieties was increased in substrates (*E*)- and (*Z*)-**3b** and **c**, the (*E*)-stereoisomer became unreactive, and the reaction

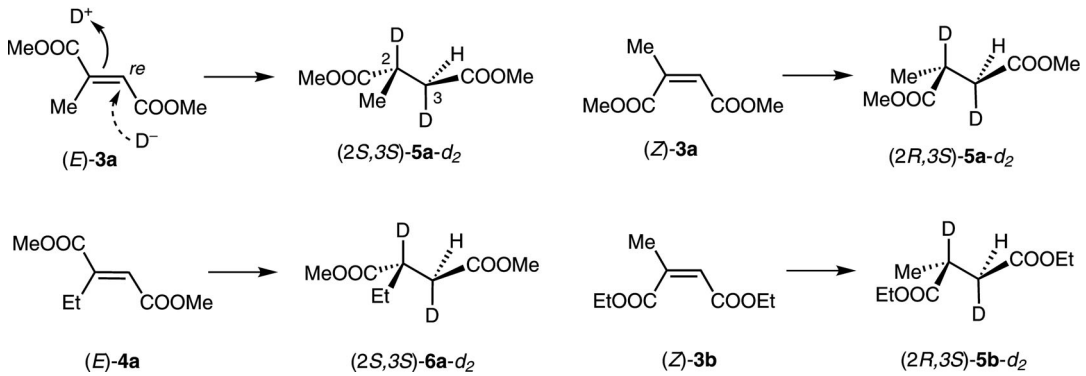

Figure 5. Stereochemical course of ene-reductase reduction of unsaturated diesters.

yields of the (*Z*)-counterpart were found to be lower with R = *n*-Bu with respect to R = Et. When the bulkiness of the substituent on the alkene was increased in substrates (*E*)- and (*Z*)-**4a–c**, the (*Z*)-stereoisomer was no longer reactive, the enantioselectivity of the (*E*)-diastereoisomer reduction decreased from R′ = Et to R′ = *n*-Pr, and conversions diminished from R′ = Et to R′ = Ph.

Substrates (*E*)- and (*Z*)-**7** (Figure 2) were subsequently prepared to investigate the effect of increasing the steric hindrance on the double bond and at the ester groups at the same time, but they were found to be completely unreactive.

This investigation has shown the limits of the synthetic exploitation of the bioreduction of unsaturated diesters: enantioselectivity and conversions are dependent upon steric hindrance, and the practical applicability is quite hindered. Nonetheless, interesting stereochemical data were collected. The two different reactive binding modes deduced from labelling experiments for methyl mesaconate and citraconate represent a sort of optimum prototype for (*E*)- and (*Z*)-stereoisomers of unsaturated diesters. Increasing the bulkiness of the substituent on the double bond, the (*E*)- stereoisomers of compounds **4a–c** are able to maintain an accommodation "(*E*)-**3a**-like", which allows them to react. Derivatives (*Z*)-**4a–c** are prevented by steric reasons from adopting an effectively reactive binding mode "(*Z*)-**3a**-like", which enables the addition of H^- on the C_β-*si* face.

On the contrary, when the size of the alkyl chain at the ester moieties is increased, the (*Z*)- stereoisomers of compounds **3b** and **c** can still adopt the accommodation "(*Z*)-**3a**-like" which is the effectively reacting one. In this case, steric hindrance is such to make (*E*)-stereoisomers unfavourable substrates for ene-reductases: a flipped arrangement similar to that of (*E*)-**3a** cannot be achieved, in order to expose C_β-*si* face to H^- attack.

Unfortunately, the modest reactivity of diesters prevented further investigations. The substitution of one ester group with a nitrile moiety, which shows better electron-withdrawing capability, is now under consideration and the data will be published in due course.

Experimental Section

General Procedure for the OYE-Mediated Bioreduction

The substrate (5 μmol) dissolved in DMSO (10 μL) was added to a KP_i buffer solution (1.0 mL, 50 mM, pH 7.0) containing glucose (20 μmol), $NADP^+$ (0.1 μmol), GDH (4 U) and the required OYE (*ca.* 40 μg dissolved in 100–200 μL H_2O). The mixture was incubated for 24 h in an orbital shaker (160 rpm, 30 °C). The solution was extracted with EtOAc (2 × 250 μL), centrifuging after each extraction (15000 × *g*, 1.5 min), and the combined organic solutions were dried over anhydrous Na_2SO_4.

Bioreduction Procedure for the Preparation of Monodeuterated Samples

The substrate (50 μmol) dissolved in *i*-PrOH (100 μL) was added to a KP_i buffer solution (5.0 mL, 50 mM in D_2O, pH 7.0) containing glucose (20 μmol), NADH (75 μmol) and the required OYE (*ca.* 250 μg, dissolved in 500–700 μL H_2O). The mixture was incubated for 24 h in an orbital shaker (160 rpm, 30 °C). The solution was extracted with EtOAc (3 × 5.0 mL), centrifuging after each extraction (3000 × *g*, 1.5 min), and the combined organic solutions were dried over anhydrous Na_2SO_4.

Bioreduction Procedure for the Preparation of Doubly Deuterated Samples

The substrate (50 μmol) dissolved in *i*-PrOH-d_8 (100 μL) was added to a KP_i buffer solution (5.0 mL, 50 mM in D_2O, pH 7.0) containing $NADP^+$ (15 μmol), TBADH (4 U, 3 mg) and the required OYE (*ca.* 250 μg, dissolved in 500–700 μL H_2O). The mixture was incubated for 24 h in an orbital shaker (160 rpm, 30 °C). The solution was extracted with EtOAc (3 × 5.0 mL), centrifuging after each extraction (3000 × *g*, 1.5 min), and the combined organic solutions were dried over anhydrous Na_2SO_4.

General Procedure for Baker's Yeast Fermentation

A mixture of baker's yeast (100 g) and D-glucose (40 g) in tap water (1 L) was prepared. After 10 min stirring at 30 °C the suitable diester (3.0 g) adsorbed on a hydrophobic resin (60 g, polystyrene XAD-1180N) was added in one portion. The mixture was kept under stirring for 72 h at room temperature and then filtered on a cotton plug. The collected mass was washed with tap water repeatedly, 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.

Supporting Information

Characterisation data of substrates (*E*)- and (*Z*)-**3b** and **3c**, substrates (*E*)- and (*Z*)-**4a–c**, reduced products **5** and **6**, deuterated compounds obtained upon either enzymatic and chemical reduction, analytical procedures for the determination of conversion, and enantiomeric excess are given in the Supporting Information.

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