DOI: 10.1002/ejoc.200901006

Baker's Yeast Reduction of β-Hydroxy Ketones

Daniela Acetti,[a] Elisabetta Brenna,*[a] Claudio Fuganti,[a] Francesco G. Gatti,[a] and Stefano Serra[b]

Keywords: Enzymes / Baker's yeast / Reduction / Asymmetric synthesis / 1,3-Diols / Ketones

Reduction of β-hydroxy ketones to the corresponding 1,3-diols by baker's yeast was investigated, in order to develop methods for simultaneous control over the configurations of multiple stereogenic centres. The reactions were found to be enantiospecific and generally characterised by good diastereoselectivity. Substrates with a substituent at the carbon atom in the α position were also considered. When the substituent at the α-carbon atom was part of a ring, higher selectivity was observed.

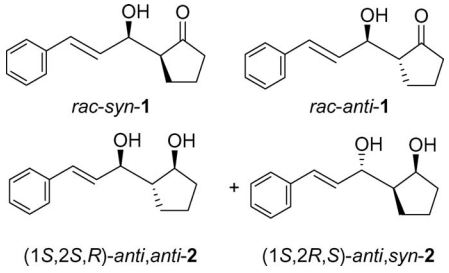
Introduction

Stereoselective reduction of carbonyl moieties is a very useful tool for the introduction of stereogenic centres into chiral synthons, which are necessary for the preparation of natural products and pharmaceuticals.[1] Chemical methodologies such as metal hydride reduction, catalytic hydrogenation or hydrogen-transfer reactions,[2] as well as biocatalytic approaches using either isolated enzymes or whole-cell systems[3] have been optimised for transformations of this kind .

The prerequisites for the ideal reagent or catalyst should be the following: broad substrate acceptance, predictability of access to enantiomers and/or diastereoisomers, minimal environmental burden, and possibly at the lowest cost.[4] Enzymes are very interesting candidates as choices of appropriate reducing agents, and this has recently prompted a renewal of interest in the application of baker's yeast and isolated ketoreductases in stereoselective reactions.[5]

The chiral molecules that organic chemists are called on to prepare today show such stereochemical complexity that the configuration of more than one stereogenic centre often has to be controlled.[6] The synthesis of configurationally defined steric sequences such as 1,3-diols or 2-alkyl-1,3-diols, for example, is a challenging task that can be achieved through highly stereoselective 1,3-diketone or 3-hydroxy ketone reductions.[7] The concomitant formation of stereogenic centres of precise configuration in one-pot transformations is of great advantage from a synthetic point of view. Some biocatalytic reductions have shown potential for simultaneous control over the configurations of multiple stereogenic centres with high enantio- and diastereoselectivity.[8]

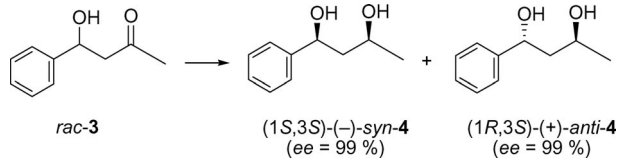
We have recently been involved in investigations of baker's yeast reductions[9] of *syn*- and *anti*-**1** (Scheme 1), which afforded a 1:1 mixture of the enantiomerically pure diols (1*S*,2*S*,*R*)-*anti*,*anti*-**2** and (1*S*,2*R*,*S*)-*anti*,*syn*-**2**. This was quite a novel finding because β-hydroxy ketones are typically the final products of baker's yeast reductions of β-diketones,[5g,10] and in most cases they are not further transformed.



Scheme 1.

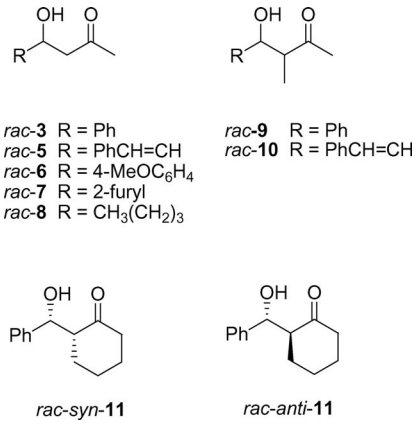
Chênevert,[11] for example, described the extraordinary selectivity of the baker's yeast reduction of 1-phenylbutane-1,3-dione to optically pure (*S*)-3-hydroxy-1-phenylbutan-1-one. The reaction was found to be unexpectedly chemoselective, with only the carbonyl group at the 3-position being affected, in spite of the fact that baker's yeast was known to reduce acetophenone. The reaction was also enantiospecific, with only the (*S*)-(+) enantiomer of the final hydroxy ketone being obtained. In 2004[12] the conversion of the hydroxy ketone **3** (Scheme 2) into (1*S*,3*S*)-(–)-*syn* and (1*R*,3*S*)-(+)-*anti* diol **4** in a reduction mediated by *Saccharomyces cerevisiae* was described.

[a] Politecnico di Milano, Dipartimento di Chimica, Materiali, Ingegneria Chimica,
Via Mancinelli 7, 20131 Milano, Italy
Fax: +39-02-23993180
E-mail: elisabetta.brenna@polimi.it
[b] Istituto CNR per la Chimica del Riconoscimento Molecolare, Dipartimento di Chimica, Materiali, Ingegneria Chimica, Politecnico di Milano,
Via Mancinelli 7, 20131 Milano, Italy



Scheme 2. Baker's-yeast-mediated reduction of hydroxy ketone **3** as in ref.[12]

The importance of simultaneous control over more than one stereogenic centre through baker's yeast fermentation prompted us to investigate this transformation further with the hydroxy ketones **3** and **5**–**11** (Scheme 3), including with substrates containing substituents at their α carbon atoms.



Scheme 3. Hydroxy ketones subjected to baker's yeast fermentation conditions.

We envisaged the possibility of employing this enzymatic procedure to obtain synthons for the preparation of suitable natural compounds (Scheme 4), including i) prelactone V[13] (**I**), which has a C_6 1,3-diol steric sequence in a definite absolute configuration embedded in its structure and can be prepared by one-carbon homologation of the C_5 chiral fragment obtained by bioreduction of ketone **10**, and ii) compound with structure of type **II** containing a C_5 1,3-diol sequence, a key fragment in the synthesis of amphidinolides O and P,[14] that can be prepared from the reduction products of ketone **10**.

For all the β-hydroxy ketones employed as starting materials in this work (except for the aliphatic compound *rac*-**8**) we intentionally chose the regioisomer with the carbonyl group not adjacent to the aromatic ring. The results of our investigation are reported here.

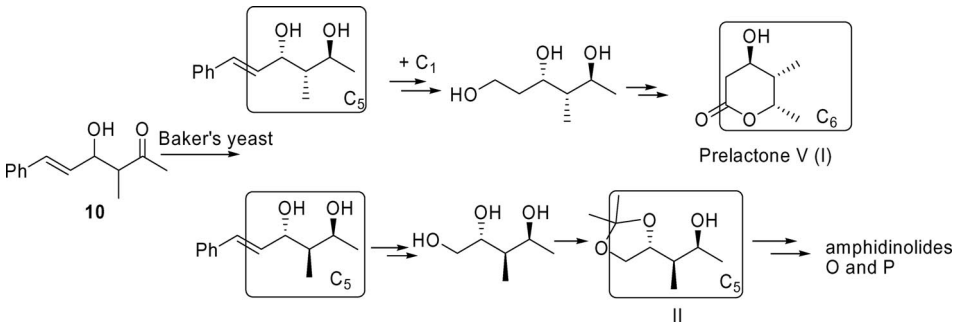
Results and Discussion

The hydroxy ketones **3** and **5**–**11** were prepared from readily available, cheap starting materials through aldol condensations, promoted by catalytic amounts of aqueous NaOH (40%) in methanol as a solvent. Only *rac*-**8** was obtained by a different route, by ozonolysis of 2-methyloct-1-en-4-ol. The derivatives *rac*-**9** and *rac*-**10** were each obtained as a mixture of two racemic diastereoisomers, in a ratio of 0.7:1 for *syn*-**9**/*anti*-**9** and of 0.5:1 for *syn*-**10**/*anti*-**10**. They were subjected to baker's yeast fermentation as such without isomer separation. The two diastereoisomers of *rac*-**11** could be separated by column chromatography and subjected separately to enzyme reduction.

The results of baker's yeast fermentation of the hydroxy ketones **3** and **5**–**11** are summarised in Tables 1 and 2. The reductions of the carbonyl moieties showed high enantioselectivity and always afforded new stereogenic centres of *S* configuration. Enantiomeric excesses or optical purity values in the 95–99% range were observed for the final diols. The only low value was found for (1*S*,3*S*)-*syn*-**14** (*ee* = 68%).

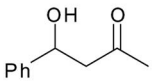
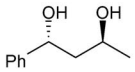
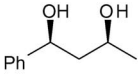
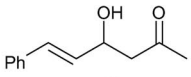
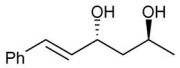
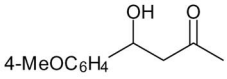
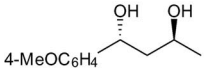
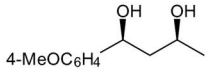
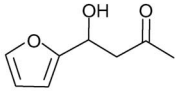
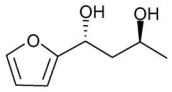
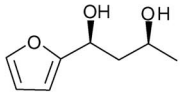
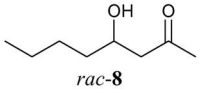
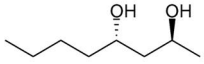
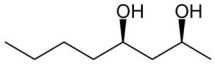
In our hands, baker's yeast reduction of the hydroxy ketone **3** proved to be more stereoselective (*de* = 70%) than the transformation described by Taneja et al. (*de* = 33%).[12] In the reduction of the β-hydroxy ketones **3** and **5**–**7** a preference for the formation of the *anti* diols was observed: diastereoisomeric excess values, calculated from the ^{1}H NMR spectra of the crude reaction mixtures, ranged from 43% for *anti*-/*syn*-**13**, to 70–74% for *anti*-/*syn*-**4** and **-14**, to >99% for *anti*-**12**. The reduction of *rac*-**8** gave the corresponding *syn* and *anti* diols in nearly 1:1 ratio, with a slight preference for the *syn* diol.

In the cases of the α-substituted β-hydroxy ketones **9**–**11** the formation of the *anti* diols was generally preferred: diastereoisomeric excess values of 56 and 35% were found for the *anti* diols **16** and **17** (*anti* diol = *syn*,*anti* + *anti syn*; *syn* diol = *anti*,*anti* + *syn*,*syn*), but >99% for *anti*,*syn*-**18**, the only product of *anti*-**11** reduction. In the reduction of *syn*-**11** nearly equimolar amounts of *syn* and *anti* diols were obtained.



Scheme 4. Chiral synthons for natural products.

Table 1. Baker's yeast reductions of the β-hydroxy ketones **3** and **5**–**8** to afford the diols **4** and **12**–**15**.

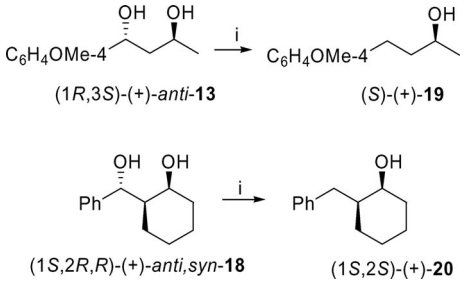
Substrate	Yield[a] (time)	Products *anti*-diol	Products *syn*-diol	*anti*/*syn*[b]
 *rac*-**3**	40% (48 h)	 (1*R*,3*S*)-*anti*-**4** *ee* = 98% (GC)	 (1*S*,3*S*)-*syn*-**4** *ee* = 97% (GC)	5.7/1
 *rac*-**5**	23% (48 h)	 (2*S*,4*R*)-*anti*-**12** single diastereoisomer o.p. = 99%		–
 *rac*-**6**	22.4% (72 h)	 (1*R*,3*S*)-*anti*-**13** *ee* = 99% (HPLC)	 (1*S*,3*S*)-*syn*-**13** *ee* = 99% (HPLC)	2.5/1
 *rac*-**7**	24% (48 h)	 (1*R*,3*S*)-*anti*-**l4** *ee* = 95% (GC)	 (1*S*,3*S*)-*syn*-**14** *ee* = 68% (GC)	6.7/1
 *rac*-**8**	44% (72 h)	 (2*S*,4*S*)-*anti*-**15** o.p.>99%	 (2*S*,4*R*)-*syn*-**15** o.p.>99%	1/1.2

[a] Percentages of total diols in the crude reaction mixtures calculated from ^{1}H NMR spectra. [b] Ratios between *anti* and *syn* diols calculated from the ^{1}H NMR spectra of the crude reaction mixtures.

In the reduction of *rac*-**9**, which was richer in the *anti* diastereoisomer, the diastereoisomeric distribution of products was in favour (1.8:1) of those showing the *syn* arrangement at the stereogenic centres already present in the starting material, whereas the same ratio (2:1) was maintained in the reduction of *rac*-**10**. When the mixture of *syn*- and *anti*-**1** was subjected to the fermentation conditions, only the *anti* diastereoisomer was transformed.

The diols obtained from the baker's yeast reductions were separated from the reaction mixtures by column chromatography and characterised. The absolute configurations of the diols (1*R*,3*S*)-*anti*-**4**, (2*S*,4*R*)-*anti*-**12**, (2*S*,4*S*)-*anti*-**15**, (2*S*,4*R*)-*syn*-**15**, (1*R*,2*S*,3*S*)-*syn*,*anti*-**16**, (1*R*,2*R*,3*S*)-*anti*,*syn*-**16**, (2*S*,3*R*,4*S*)-*anti*,*syn*-**17** and (2*S*,3*S*,4*R*)-*anti*,-*anti*-**17** were assigned by comparison with the specific optical rotatory data reported in the literature (See Experimental Section).

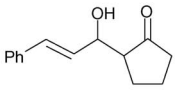
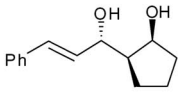
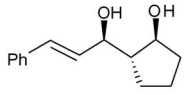
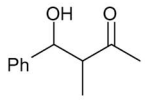
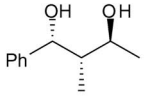
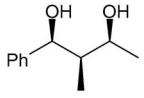
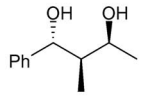
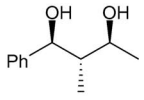
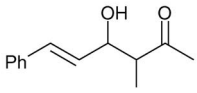
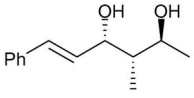
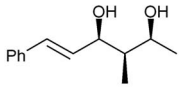
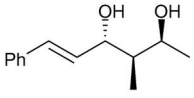
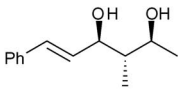
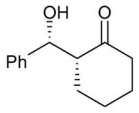
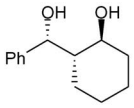
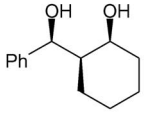
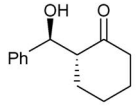
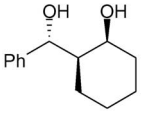
The absolute configurations of (1*R*,3*S*)-*anti*-**13**, (1*R*,3*S*)-*anti*-**l4** and (1*S*,2*R*,*R*)-*anti*,*syn*-**18** were determined by chemical correlation. Compounds (1*R*,3*S*)-(+)-*anti*-**13** and (1*S*,2*R*,*R*)-(+)-*anti*,*syn*-**18** were subjected to hydrogenolysis (Scheme 5) in methanol solution in the presence of catalytic amounts of Pd/C, to give (*S*)-(+)-**19** and (1*S*,2*S*)-(+)-**20**, respectively.



Scheme 5. i) Pd/C, MeOH, room temp., H_2, 80 psi.

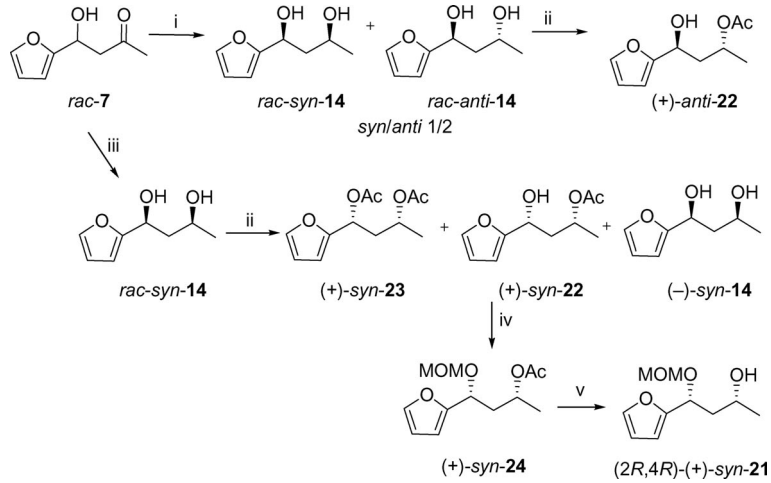
For diol **14**, lipase-PS-mediated acetylation also had to be investigated (Scheme 6), in order to establish the absolute configurations of the baker's-yeast-mediated reduction products. A search in the literature showed that the absolute

Table 2. Baker's yeast reductions of the α-substituted-β-hydroxy ketones **1** and **9**–**10** to afford the diols **2** and **16**–**18**.

Substrate	Yield[a] (time)	Product *anti*-diol	Product *syn*-diol	*anti*/*syn*[b]
 *rac*-**1**	30 % (48 h)	 (1*S*,2*R*,*S*)-*anti*,*syn*-**2**	 (1*S*,2*S*,*R*)-*anti*,*anti*-**2** *ee* > 99%	1
 *rac*-**9** *syn*/*anti* 0.7/1	23.3 % (48 h)	 (1*R*,2*S*,3*S*)-*syn*,*anti*-**16** o.p. = 96% 4.8	 (1*S*,2R,3*S*)- *syn*,*syn*-**16** 1	3.5/1
		 (1*R*,2*R*,3*S*)-*anti*,*syn*-**16** o.p. = 97% 2.2	 (1*S*,2*S*,3*S*)-*anti*,*anti*-**16** 1	
 *rac*-**10** *syn*/*anti* 0.5/1	22.7 % (48 h)	 (2*S*,3*S*,4*S*) *syn*,*anti*-**17** 2	 (2*S*,3*R*,4*R*)- *syn*,*syn*-**17** 1	2.1/1
		 (2*S*,3*R*,4*S*)- *anti*,*syn*-**17** *ee* = 99% (HPLC) 4.4	 (2*S*,3*S*,4*R*)- *anti*,*anti*-**17** *ee* = 99% (HPLC) 2	
 *rac*-*syn*-**11**	42.5 % (48 h)	 (1*S*,2*S*,*R*)- *syn*,*anti*-**18** *ee* = 99% (HPLC)	 (1*S*,2*R*,*S*) - *syn*,*syn*-**18** *ee* = 99% (HPLC)	1.4/1
 *rac*-*anti*-**11**	44.4 % (72 h)	 (1*S*,2*R*,*R*)-*anti*,*syn*-**18** *ee* = 99% (HPLC) single diastereoisomer		

[a] Percentages of total diols in the crude reaction mixtures calculated from ^{1}H NMR spectra. [b] Ratios between *anti* and *syn* diols calculated from the ^{1}H NMR spectra of the crude reaction mixtures (*anti* diols: *syn*,*anti* + *anti*,*syn*; *syn* diols: *syn*,*syn* + *anti*,*anti*). The molar ratios of the single diastereoisomers with respect to the less abundant ones are reported under each structure.

configuration of the derivative (+)-*syn*-**21** was known,[15] and we envisaged the possibility of functionalising the two hydroxy groups of diol **14** with high regioselectivity and enantioselectivity by enzyme-catalysed tranesterification. When a 1:2 mixture of *syn*/*anti* diols **14**, obtained upon $NaBH_4$ reduction of the corresponding hydroxy ketone, was treated with lipase PS in *tert*-butyl methyl ether solution in the presence of vinyl acetate, the monoacetate (+)-*anti*-**22**



Scheme 6. i) $NaBH_4$, $MeOH/CH_2Cl_2$; ii) Lipase PS, *tert*-butyl methyl ether, vinyl acetate; column chromatography; iii) diethylmethoxyborane, THF/CH_3OH, –78 °C; $NaBH_4$; iv) MOMCl, iPr_2NEt, CH_2Cl_2; v) KOH, MeOH.

could be recovered as a single pure compound, showing *de* = 99% and *ee* = 99% (GC of the corresponding acetonide on a chiral column).

When *rac*-*syn*-**14**, obtained by treatment of the corresponding hydroxy ketone with diethylmethoxyborane followed by $NaBH_4$, was treated with lipase PS under the same conditions, the following derivatives could be isolated from the reaction mixture by column chromatography: the diacetate (+)-*syn*-**23** (*ee* = 99%, GC of the corresponding acetonide on a chiral column), the monoacetate (+)-*syn*-**22** (*ee* = 99%, GC of the corresponding acetonide on a chiral column) and the unreacted diol (–)-*syn*-**14** (*ee* = 99%, GC of the corresponding acetonide on a chiral column).

The GC analysis of the corresponding acetonides on chiral columns allowed us to establish that compound (+)-*syn*-**23** was the diacetate derivative of the enantiomer of the diol *syn*-**14**, of configuration opposite to that of the *syn* diol obtained by baker's yeast reduction of the hydroxy ketone **7**. The configuration of the monoacetate (+)-*syn*-**22** could be established by chemical correlation by the synthetic sequence shown in Scheme 6. Compound (+)-*syn*-**22** was converted into the methoxymethyl ether derivative (+)-*syn*-**24**, which was then hydrolysed to afford compound (+)-*syn*-**21**, the absolute configuration of which was known to be (2*R*,4*R*).[15]

The relative *syn* and *anti* configurations of the diols **13** were verified by conversion of racemic *syn*-**13** into the corresponding acetonide. Its ^1H NMR spectrum was consistent with a diequatorial arrangement of the aryl and methyl groups [H–C(1): δ = 4.76 ppm, J = 11.1, 1.9 Hz, dd; H–C(3): δ = 4.04 ppm, J = 11.7, 5.7, 2.2 Hz, dqd] and the ^{13}C NMR resonances for the acetonide methyl groups were observed at δ = 30.3 and 19.8 ppm, which are characteristic values of *syn* acetonides.[16]

Conclusions

Baker's yeast reduction of β-hydroxy ketones has been shown to be possible when the carbonyl moiety is not adjacent to the aromatic ring, and also in aliphatic compounds such as *rac*-**8**. The reactions are enantiospecific and are generally characterised by good diastereoselectivity. When the substituent at the α-carbon atom is part of to a ring (i.e., *rac*-**1** vs. *rac*-**10**, and *rac*-**11** vs. *rac*-**9**) higher selectivity is observed: *rac*-*syn*-**1** was not affected by baker's yeast fermentation and *rac*-*anti*-**11** gave only (1*S*,2*R*,*R*)-*anti*,*syn*-**18**.

The synthetic advantage of the transformation that we describe is that the enantioselective reduction of the carbonyl group occurs with diastereoselective discrimination through the configurations of the stereocentres already present in the starting racemic hydroxy ketones. These derivatives can be readily prepared through aldol condensations, and by this one-pot procedure they can be converted into optically active 1,3-diols with simultaneous control over the stereochemistry of two or three stereogenic carbon atoms. The method represents an alternative to the two-step sequence based on the diastereoselective reduction of optically active hydroxy ketones, which is well documented in the literature.[17]

This work might also serve to inspire others to look more closely at bioreductions of hydroxy ketones in the presence of more specific bioreagents, such as isolated and/or overexpressed enzymes or engineered strains with higher reductase activity towards carbonyl groups. Nonetheless, the cheap and easily handled baker's yeast can still be the reagent of choice when it so happens that the complex multi-enzyme system operating during fermentation can perform biotransformations with high stereoselectivities.

Experimental Section

General Methods: Baker's yeast from Lesaffre Italia (code number 30509) was employed. TLC analyses were performed on Merck Kieselgel 60 F254 plates. All the chromatographic separations were carried out with silica gel columns. ^1H and ^{13}C NMR spectra were recorded with a 400 MHz spectrometer. The chemical shift scale was based on internal tetramethylsilane. GC–MS analyses were performed with a HP-5MS column (30 m × 0.25 mm × 0.25 μm).

The following temperature program was employed: 60 °C (1 min)/6 °C min^{-1}/150 °C (1 min)/12 °C min^{-1}/280 °C (5 min). The enantiomeric excess values were determined by GC or HPLC analysis. GC analysis was performed with a Chirasil DEX CB column (Chrompack, 25 m × 0.25 mm), installed on a DANI HT 86.10 gas chromatograph, under the following conditions:

a) Diacetate derivatives of *syn*- and *anti*-**4**: 60 °C (3 min)/1.5 °C min^{-1}/180 °C; diacetate of (1*R*,3*S*)-*anti*-**4** t_R = 39.25 min; diacetate of (1*S*,3*R*)-*anti*-**4** t_R = 39.49 min; diacetate of (1*S*,3*S*)-*syn*-**4** t_R = 40.28 min; diacetate of (1*R*,3*R*)-*syn*-**4** t_R = 40.39 min.

b) Acetonide derivatives of diols *anti*- and *syn*-**14**: 60 °C (3 min)/1.5 °C min^{-1}/180 °C; acetonide of (1*R*,3*S*)-*anti*-**14** t_R = 14.02 min; acetonide of (1*S*,3*R*)-*anti*-**14** t_R = 14.32 min; acetonide of (1*R*,3*R*)-*syn*-**14** t_R = 15.32 min; acetonide of (1*S*,3*S*)-*syn*-**14** t_R = 15.52 min.

HPLC analyses were performed with a Chiralcel OD column, installed on a Merck–Hitachi L-7100 instrument with a Merck–Hitachi L-4250 UV/Vis detector, under the following conditions:

a) Diacetate derivatives of diols *syn*- and *anti*-**13**: hexane/propan-2-ol 98:2, flow 0.6 mL min^{-1}, 210 nm; diacetate of (1*S*,3*S*)-*syn*-**13** t_R = 9.60 min; diacetate of (1*R*,3*R*)-*syn*-**13** t_R = 10.25 min; diacetate of (1*R*,3*S*)-*anti*-**13** t_R = 11.27 min; diacetate of (1*S*,3*R*)-*anti*-**13** t_R = 12.47 min.

b) Diol derivatives *anti*,*syn*-**17** and *anti*,*anti*-**17**: hexane/propan-2-ol 90:10, flow 0.6 mL min^{-1}, 254 nm; (+)-*anti*,*syn*-**17** t_R = 9.12 min, (–)-*anti*,*syn*-**17** t_R = 12.59 min, (–)-*anti*,*anti*-**17** t_R = 10.80 min, (+)-*anti*,*anti*-**17** t_R = 14.22 min.

c) Diols **18**: hexane/propan-2-ol 95:5, flow 0.4 mL min^{-1}, 210 nm; (1*R*,2*R*,*S*)-*syn*,*anti*-**18** t_R = 38.49 min; (1*S*,2*S*,*R*)-*syn*,*anti*-**18** t_R = 52.30 min; (1*R*,2*S*,*R*)-*syn*,*syn*-**18** t_R = 42.32 min; (1*S*,2*R*,*S*)-*syn*,*syn*-**18** t_R = 75.26 min; (1*R*,2*S*,*S*)-*anti*,*syn*-**18** t_R = 32.87 min, (1*S*,2*R*,*R*)-*anti*,*syn*-**18** t_R = 48.08 min.

d) Hydroxy ketone *anti*-**11**: hexane/propan-2-ol 98:2, flow 0.6 mL min^{-1}, 210 nm; (2*S*,*R*)-*anti*-**11** t_R = 33.7 min; (2*R*,*S*)-*anti*-**11** t_R = 54.5 min;

Optical rotations were measured with a Dr. Kernchen Propol digital automatic polarimeter at 589 nm and are given in 10^{-1} deg cm^2 g^{-1}.

Synthesis of Hydroxy Ketones 3, 5–7 and 9–11: The hydroxy ketones **3**, **5**–**7** and **9**–**11** were prepared through aldol condensations of suitable commercially available starting materials by the following procedure, demonstrated for the hydroxy ketone **11**.

A stirred solution of cyclohexanone (12.2 g, 0.125 mol) and benzaldehyde (13.2 g, 0.125 mol) in methanol (100 mL) was treated at –10 °C with aqueous sodium hydroxide (40%, 1 mL). After 15 min the slightly yellow solution was poured into excess ice/water containing acetic acid (2 mL). The reaction mixture was extracted with an ethyl acetate/hexane mixture (2:1). The organic phase was washed with sat. $NaHCO_3$ solution and dried with sodium sulfate. The residue obtained upon evaporation of the solvent was chromatographed with increasing amounts of ethyl acetate in hexane, affording *syn*-**11** (6.12 g, 24%) and *anti*-**11** (5.36 g, 21%).

4-Hydroxy-4-phenylbutan-2-one (*rac*-3):[12] This compound was obtained from benzaldehyde (13.2 g, 0.125 mol) and acetone (7.25 g, 0.125 mol): 11.1 g (54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.22 (m, 5 H, aromatic H), 5.12 (dd, *J* = 9.1, 3.4 Hz, 1 H, *CH*OH), 2.87 (dd, *J* = 17.3, 9.1 Hz, 1 H, *CH*H), 2.77 (dd, *J* = 17.3, 3.4 Hz, 3 H, *CH*H), 2.16 (s, 3 H, CO*CH*$_3$) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 207.8, 142.8, 127.6, 126.6, 124.9, 68.9, 51.3, 29.6 ppm.

(*E*)-4-Hydroxy-6-phenylhex-5-en-2-one (*rac*-5):[18] This compound was obtained from cinnamaldehyde (16.5 g, 0.125 mol) and acetone (7.25 g, 0.125 mol): 13.5 g (57%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.20 (m, 5 H, aromatic H), 6.64 (dd, *J* = 15.9, 1.1 Hz, 1 H, Ph*CH*=), 6.20 (dd, *J* = 15.9, 6.1 Hz, 1 H, =*CH*CH), 4.76 (dq, *J* = 6.4, 1.1 Hz, 1 H, *CH*OH), 2.76 (d, *J* = 6.4 Hz, 1 H, *CH*$_2$), 2.22 (s, 3 H, CO*CH*$_3$) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 208.1, 136.1, 130.4, 129.5, 125.9, 127.1, 128.1, 67.8, 49.7, 30.2 ppm.

4-Hydroxy-4-(4-methoxyphenyl)butan-2-one (*rac*-6):[18,19] This compound was obtained from 4-methoxybenzaldehyde (17.0 g, 0.125 mol) and acetone (7.25 g, 0.125 mol): 13.4 g (55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (m, 2 H, aromatic H), 6.87 (m, 2 H, aromatic H), 5.09 (dd, *J* = 9.2, 3.3 Hz, 1 H, Ar*CH*OH), 3.79 (s, 3 H, O*CH*$_3$), 2.88 (dd, *J* = 17.3, 9.2 Hz, 1 H, *CH*H), 2.77 (dd, *J* = 17.3, 3.3 Hz, 1 H, *CH*H), 2.17 (s, 3 H, CO*CH*$_3$) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 208.0, 158.3, 135.1, 126.4, 113.1, 68.8, 54.4, 51.5, 29.9 ppm.

4-(Furan-2-yl)-4-hydroxybutan-2-one (*rac*-7):[20] This compound was obtained from 2-furylaldehyde (7.50 g, 0.049 mol) and acetone (7.25 g, 0.125 mol): 8.28 g (43%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (m, 1 H, α furan H), 6.32 (m, 1 H, β furan H), 6.26 (m, 1 H, β furan H), 5.16 (dd, *J* = 8.6, 3.7 Hz, 1 H, *CH*OH), 3.05 (dd, *J* = 17.9, 8.6 Hz, 1 H, *CH*H), 2.91 (dd, *J* = 17.9, 3.7 Hz, 1 H, *CH*H), 2.23 (s, 3 H, CO*CH*$_3$) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 209.5, 156.6, 142.9, 110.9, 107.1, 63.8, 52.7, 31.4 ppm.

4-Hydroxyoctan-2-one (rac-8): Compound *rac*-**8** was obtained by treatment of 2-methyloct-1-en-4-ol (17.0 g, 0.120 mol, prepared as in ref.[21]) with O_3 at –78 °C in CH_2Cl_2/MeOH (2:1, 500 mL) with quenching of the reaction mixture with PPh_3. The usual reaction workup afforded, after purification by column chromatography with elution with hexane and increasing amounts of AcOEt, *rac*-**8** (10.9 g, 63%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.02 (m, 1 H, C*H*–OH), 2.60 [dd, *J* = 17.0, 3.2 Hz, 1 H, H–C(3)], 2.53 [dd, *J* = 17.0, 8.7 Hz, 1 H, H–C(3)], 2.17 (*s*, 3 H, CO*CH*$_3$), 1.56–1.22 (m, 6 H, *CH*$_2$*CH*$_2$*CH*$_2$), 0.90 (t, *J* = 7.1 Hz, 3 H, C*H*$_3$–CH$_2$) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 208.6, 66.9, 49.7, 35.9, 29.9, 26.9, 21.8, 13.1 ppm.

***syn*- and *anti*-4-Hydroxy-3-methyl-4-phenylbutan-2-one (*rac*-9):**[22] This compound was obtained from benzaldehyde (13.2 g, 0.125 mol) and butan-2-one (9.0 g, 0.125 mol); a 0.7:1 mixture of *syn*- and *anti*-**9** was obtained (12.9 g, 58%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.26 (m, aromatic H), 5.09 (d, *J* = 3.8 Hz, 1 H, *CH*OH *syn*), 4.74 (d, *J* = 8.4 Hz, 1 H, *CH*OH *anti*), 2.93 (m, 1 H, *CH*CH$_3$ *anti*), 2.83 (m, 1 H, *CH*H *syn*), 2.21 (s, 3 H, CO*CH*$_3$, *anti*), 2.14 (s, 3 H, CO*CH*$_3$, *syn*), 1.09 (d, *J* = 7.4 Hz, CH*CH*$_3$ *syn*), 0.94 (d, *J* = 7.4 Hz, CH*CH*$_3$ *anti*) ppm.

***syn*- and *anti*-(*E*)-4-Hydroxy-3-methyl-6-phenylhex-5-en-2-one (*rac*-10):**[23] This compound was obtained from cinnamaldehyde (16.5 g, 0.125 mol) and butan-2-one (9.0 g, 0.125 mol); a 0.5:1 mixture of *syn*- and *anti*-**10** was obtained (13.5 g, 53%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.15 (m, aromatic H), 6.70–6.55 (m, Ph*CH*=), 6.20–6.10 (m, =*CH*–CH), 4.65 (ddd, *J* = 5.6, 3.8, 1.5 Hz, *CH*OH *syn*), 4.38 (t, *J* = 7.4 Hz, *CH*OH *anti*.), 2.90–2.65 (m, *CH*CH$_3$), 2.23 (s, *CH*$_3$CO *anti*), 2.22 (s, *CH*$_3$CO *syn*), 1.20 (d, *J* = 7.3 Hz, *CH*$_3$CH *syn*), 1.14 (d, *J* = 7.1 Hz, *CH*$_3$CH *anti*) ppm.

***syn*- and *anti*-2-[Hydroxy(phenyl)methyl]cyclohexanone (*rac*-11):**[24] This compound was obtained from benzaldehyde (13.2 g, 0.125 mol) and cyclohexanone (12.2 g, 0.125 mol); a 1:1 mixture of *syn*- and *anti*-**11** was obtained. The two diastereoisomers could be separated by column chromatography, with elution with hexane and increasing amounts of ethyl acetate.

Compound *syn*-11:[24] 6.12 g (24%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.28 (m, 5 H, aromatic H), 5.38 (d, J = 2.6 Hz, 1 H, *CH*OH), 2.60 (m, 1 H, H cyclohexanone ring), 2.45 (m, 1 H, H cyclohexanone ring), 2.36 (m, 1 H, H cyclohexanone ring), 2.07 (m, 1 H, H cyclohexanone ring), 1.88–1.46 (m, 5 H, H cyclohexanone ring) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 213.3, 141.7, 127.5, 126.2, 125.3, 69.9, 56.6, 41.8, 27.0, 25.5, 24.1 ppm.

Compound *anti*-11:[24] 5.36 g (21%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.28 (m, 5 H, aromatic H), 4.79 (d, J = 8.7 Hz, 1 H, *CH*OH), 2.61 (m, 1 H, H cyclohexanone ring), 2.46 (m, 1 H, H cyclohexanone ring), 2.36 (m, 1 H, H cyclohexanone ring), 2.07 (m, 1 H, H cyclohexanone ring), 1.88–1.22 (m, 5 H, H cyclohexanone ring) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 214.6, 140.7, 127.7, 126.5, 125.3, 73.8, 56.8, 41.8, 30.1, 27.2, 23.9 ppm.

Baker's Yeast Reduction of Hydroxy Ketones 3 and 5–11: The hydroxy ketones **3** and **5**–**11** were subjected to baker's yeast fermentation conditions in the following procedure, demonstrated for *syn*-**11**. A solution of the ketone *syn*-**11** (5.0 g, 0.024 mol) in ethanol (10 mL) was added dropwise at 30 °C to a stirred mixture of baker's yeast (100 g) and D-glucose (40 g) in tap water (1 L). After the system had been kept for 48 h under these conditions, acetone (500 mL) was added, followed by ethyl acetate/hexane (4:1, 500 mL). The mixture was filtered in a large Buchner funnel through a thick Celite pad previously washed with acetone. The two phases were then separated and the aqueous phase was extracted twice with an ethyl acetate/hexane mixture. The oily residue obtained upon concentration of the washed and dried organic phase was chromatographed with increasing amounts of ethyl acetate in hexane, to provide the starting hydroxy ketone *syn*-**11** (2.39 g, 49%), (1*S*,2*R*,*S*)-*syn*,*syn*-**18** (0.618 g, 12.5%) and (1*S*,2*S*,*R*)-*syn*,*anti*-**18** (0.939 g, 19%). The 1,3-diols prepared by baker's yeast reduction were isolated from the corresponding mixtures by column chromatography.

Baker's Yeast Reduction of *rac*-3: Compound *rac*-**3** (10.0 g, 0.061 mol) was subjected to baker's yeast fermentation. After 48 h, the reaction was worked up and the corresponding crude mixture showed the following composition (NMR): the starting hydroxy ketone **3** (60%), (1*R*,3*S*)-*anti*-**4** (34%) and (1*S*,3*S*)-*syn*-**4** (6%). Column chromatography allowed the recovery of (+)-*anti*-**4** as a single pure compound.

(1*R*,3*S*)-1-Phenylbutane-1,3-diol [(+)-*anti*-4]:[12] 2.93 g (29%); *ee* = 98% (GC of the corresponding diacetate on a chiral column). $[\alpha]_D$ = +58.6 (c = 1.12, $CHCl_3$) {ref.[12] $[\alpha]_D$ = +60.1 (c = 0.9, $CHCl_3$) for (1*R*,3*S*)-*anti*-**4** with *ee* = 99%}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.20 (m, 5 H, aromatic H), 5.00 (dd, J = 7.7, 3.7 Hz, 1 H, Ph*CH*OH), 4.04 (m, 1 H, CH_3*CH*OH), 1.84 (m, 2 H, CH_2), 1.21 (d, J = 6.3 Hz, 3 H, CHCH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 144.4, 128.4, 127.3, 125.5, 71.6, 65.3, 46.1, 23.4 ppm.

Baker's Yeast Reduction of *rac*-5: Compound *rac*-**5** (10.0 g, 0.053 mol) was subjected to baker's yeast fermentation. After 48 h, the reaction was worked up and the corresponding crude mixture showed the following composition (NMR): the starting hydroxy ketone **5** (77%) and (+)-(2*S*,4*R*)-*anti*-**12** (23%). Column chromatography allowed the recovery of (+)-*anti*-**4** as a single pure compound.

(2*S*,4*R*,*E*)-6-Phenylhex-5-ene-2,4-diol [(+)-*anti*-12]:[23] 1.83 g (18%). $[\alpha]_D$ = +39.7 (c = 1.15, $CHCl_3$) {ref.[23] $[\alpha]_D$ = +40.5 (c = 1.13, $CHCl_3$) for (2*S*,4*R*)-*anti*-**12**}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.20 (m, 5 H, aromatic H), 6.64 (dd, J = 15.9, 1.0 Hz, 1 H, Ph*CH*), 6.28 (dd, J = 15.9, 6.1 Hz, 1 H, =*CH*CH), 4.64 (qd, J = 6.1, 1.0 Hz, 1 H, =CH*CH*OH), 4.20 (m, 1 H, *CH*CH_3), 1.81 (m, 2 H, CH_2), 1.26 (d, J = 6.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 136.8, 132.0, 130.0, 128.6, 127.6, 126.5, 70.4, 65.4, 44.4, 23.7 ppm.

Baker's Yeast Reduction of *rac*-6: Compound *rac*-**6** (10.0 g, 0.052 mol) was subjected to baker's yeast fermentation. After 72 h, the reaction was worked up and the corresponding crude mixture showed the following composition (NMR): the starting hydroxy ketone **6** (77.6%), (–)-(1*S*,3*S*)-*syn*-**13** (6.4%) and (+)-(1*R*,3*S*)-*anti*-**13** (16%). Column chromatography allowed the recovery of (+)-*anti*-**13** and (–)-*syn*-**13** as single pure compounds.

(1*S*,3*S*)-1-(4-Methoxyphenyl)butane-1,3-diol [(–)-*syn*-13]:[25] 0.359 g (3%); *ee* = 99% (HPLC of the corresponding diacetate). $[\alpha]_D$ = –18.3 (c = 1.05, $CHCl_3$) of a sample of 82% purity (NMR). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (m, 2 H, aromatic H), 6.88 (m, 2 H, aromatic H), 4.90 (dd, J = 9.9, 2.9 Hz, 1 H, Ar*CH*OH), 4.12 (m, 1 H, *CH*CH_3), 3.80 (s, 3 H, OCH_3), 1.88 (dt, J = 14.6, 9.9 Hz, 1 H,*CH*H), 1.74 (dt, J = 14.6, 2.9 Hz, 1 H, *CH*H), 1.23 (d, J = 6.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 158.9, 136.7, 126.8, 113.7, 74.5, 68.4, 55.1, 46.9, 23.8 ppm.

A racemic sample of *syn*-**13** was converted into the corresponding acetonide by treatment with 2,2-dimethoxypropane in the presence of pyridinium *p*-toluenesulfonate to verify the relative *syn* configuration: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (m, 2 H, aromatic H), 6.80 (m, 2 H, aromatic H), 4.76 (dd, J = 11.1, 2.0 Hz, 1 H, Ar*CH*O), 4.04 (dqd, J = 11.7, 5.7, 2.0 Hz, 1 H, *CH*CH_3), 3.71 (s, 3 H, OCH_3), 1.61 (dt, J = 13.0, 2.0 Hz, 1 H, C*H*H), 1.37 (m, 1 H, C*H*H), 1.48 (s, 3 H, CCH_3), 1.41 (s, 3 H, CCH_3), 1.13 (d, J = 6.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 159.1, 134.7, 127.2, 113.8, 98.9, 71.4, 65.3, 55.2, 40.9, 30.3, 22.1, 19.8 ppm.

(1*R*,3*S*)-1-(4-Methoxyphenyl)butane-1,3-diol [(+)-*anti*-13]:[25] 1.43 g (12%); *ee* = 99% (HPLC of the corresponding diacetate). $[\alpha]_D$ = +58.6 (c = 0.95, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (m, 2 H, aromatic H), 6.89 (m, 2 H, aromatic H), 5.00 (dd, J = 7.6, 3.7 Hz, 1 H, Ar*CH*OH), 4.07 (m, 1 H, *CH*CH_3), 3.80 (s, 3 H, OCH_3), 1.87 (m, 2 H,CH_2), 1.24 (d, J = 6.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 158.9, 136.6, 126.8, 113.8, 71.3, 65.3, 55.2, 46.2, 23.4 ppm.

Hydrogenolysis of (+)-*anti*-13: A solution of (+)-*anti*-**13** (0.500 g, 2.55×10^{-3} mol) in ethanol (20 mL) was treated with H_2 (80 psi) at room temperature for 48 h in the presence of Pd/C (50 mg). The reaction mixture was filtered and concentrated under reduced pressure, to give a residue that was purified by column chromatography to afford (+)-**19** (0.372 g, 81%): $[\alpha]_D$ = +13.9 (c = 0.98, $CHCl_3$) {ref.[26] $[\alpha]_D$ = +12.8 (c = 2.41, $CHCl_3$) for (*S*)-**19** with *ee* = 91%}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (m, 2 H, aromatic H), 6.82 (m, 2 H, aromatic H), 3.81 (m, 1 H, *CH*OH), 3.78 (s, 3 H, OCH_3), 2.65 (m, 2 H, CH_2), 1.74 (m, 2 H, CH_2), 1.22 (d, J = 6.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 157.8, 134.1, 129.2, 113.8, 67.4, 55.2, 41.0, 31.1, 23.6 ppm.

Baker's Yeast Reduction of *rac*-7: Compound *rac*-**7** (7.50 g, 0.049 mol) was subjected to baker's yeast fermentation. After 48 h, the reaction was worked up and the corresponding crude mixture showed the following composition (NMR): the starting hydroxy ketone **7** (76.0%), (1*R*,3*S*)-*anti*-**14** (20.8%) and (1*S*,3*S*)-*syn*-**14** (3.2%). Column chromatography allowed the recovery of (+)-*anti*-**14** as a single pure compound.

(1*R*,3*S*)-1-(Furan-2-yl)butane-1,3-diol [(+)-*anti*-14]: 1.21 g (16%); *ee* = 95% (GC of the corresponding acetonide). $[\alpha]_D$ = +56.7 (c = 1.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (m, 1 H, α furan H), 6.33 (m, 1 H, β furan H), 6.26 (m, 1 H, β furan H), 5.04

(dd, J = 7.6, 3.2 Hz, 1 H, Fu–*CH*–OH), 4.13 (m, 1 H, CH_3*CH*–OH), 2.04–1.87 (m, 2 H, CH_2), 1.27 (d, J = 6.4 Hz, CH_3CH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 156.8, 141.6, 110.0, 105.5, 65.0, 64.9, 42.8, 23.2 ppm.

The assignment of the relative configuration of diol *anti*-**14** was based on the ^{1}H and ^{13}C NMR spectra of the corresponding acetonide, prepared by treatment with 2,2-dimethoxypropane in acetone in the presence of pyridinium *p*-toluenesulfonate. A comparison was made with the ^{1}H and ^{13}C NMR spectra of the acetonide of diol *syn*-**14** reported in the literature.[15]

Acetonide of Diol *anti*-14: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (m, 1 H, α furan H), 6.32 (m, 1 H, β furan H), 6.25 (m, 1 H, β furan H), 4.92 (dd, J = 8.3, 6.4 Hz, 1 H, Fu–*CH*–O), 4.15 (m, 1 H, *CH*OCH_3), 2.22 (m, 1 H, *CH*H), 1.78 (m, 1 H, *CH*H), 1.45 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 1.25 (d, J = 6.1 Hz, CH_3CH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 154.3, 142.3, 110.1, 107.1, 100.3, 62.9, 62.6, 36.7, 26.1, 24.2, 21.7 ppm. GC/MS: = t_R = 11.96 min, m/z 196 (12) $[M]^+$, 181 (15), 121 (100).

Acetonide of Diol *syn*-14: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (m, 1 H, α furan H), 6.33 (m, 1 H, β furan H), 6.28 (m, 1 H, β furan H), 4.96 (m, 1 H, Fu–*CH*–O), 4.10 (m, 1 H, *CH*OCH_3), 1.73 (m, 2 H, CH_2), 1.56 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 1.24 (d, J = 6.0 Hz, CH_3CH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 154.5, 142.1, 110.0, 106.5, 99.0, 65.2, 64.9, 36.6, 30.1, 22.0, 19.6 ppm. GC/MS: t_R = 12.47 min, m/z 196 (12) $[M]^+$, 181 (12), 121 (100).

Lipase-Mediated Acetylation of Diols *syn*- and *anti*-14: In a typical experiment, a solution of diol **14** (3.12 g, 0.020 mol) in vinyl acetate/*tert*-butyl methyl ether (1:1, 40 mL) was stirred at room temperature for 2 d with lipase Amano PS (*Burkholderia cepacia*, 3.0 g). The filtered solution was concentrated and the residue was chromatographed with increasing amounts of ethyl acetate in hexane.

Under these conditions, the 1:2 mixture of *syn*/*anti*-**14** (3.12 g, 0.020 mol) obtained by $NaBH_4$ reduction of hydroxy ketone **7** in CH_2Cl_2/MeOH solution at 0 °C afforded the monoacetate derivative (+)-*anti*-**22** (0.396 g, 10%), followed by an inseparable mixture of other isomeric monoacetates and, finally, by the unconverted starting diols (1.28 g, 41%).

(2*R*,4*S*)-4-(Furan-2-yl)-4-hydroxybutan-2-yl Acetate [(+)-*anti*-22]: *ee* = 95% (HPLC of the corresponding acetonide). $[\alpha]_D$ = +8.6 (c = 0.56, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (m, 1 H, α furan H), 6.29 (m, 1 H, β furan H), 6.22 (m, 1 H, β furan H), 5.14 (dqd, J = 8.8, 6.2, 3.5 Hz, 1 H, CH_3*CH*OAc), 4.40 (dd, J = 9.1, 4.4 Hz, 1 H, Fu–*CH*–OH), 2.02 (m, 2 H, CH_2), 1.99 (s, 3 H, CH_3COO), 1.26 (d, J = 6.2 Hz, CH_3CH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.2, 156.1, 141.7, 109.9, 105.5, 67.9, 63.8, 41.8, 20.9, 20.3 ppm.

Under the same conditions, the diol *syn*-**14** (5.10 g, 0.033 mol, obtained upon stereoselective reduction of the corresponding hydroxy ketone **7** by treatment with diethylmethoxyborane[27] followed by $NaBH_4$) afforded the diacetate (+)-*syn*-**23** (1.82 g, 23%), the monoacetate (+)-*syn*-**22** (1.04 g, 16%) and the diol (–)-*syn*-**14** (2.01 g, 39%).

(1*R*,3*R*)-1-(Furan-2-yl)butane-1,3-diyl Diacetate [(+)-*syn*-23]: *ee* = 99% (GC of the corresponding acetonide). $[\alpha]_D$ = +106.1 (c = 1.04, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (m, 1 H, α furan H), 6.31 (m, 2 H, 2 β furan H), 5.92 (t, J = 7.6 Hz, 1 H, Fu–*CH*–OAc), 4.81 (sextuplet, J = 6.4 Hz, 1 H, CH_3*CH*OAc), 2.27 (ddd, J = 13.9, 7.6, 6.4 Hz, 1 H, *CH*H), 2.16 (ddd, J = 13.9, 7.6, 6.1 Hz, 1 H, *CH*H), 2.04 (s, 3 H, CH_3COO), 1.99 (s, 3 H, CH_3COO), 1.24 (d, J = 6.4 Hz, CH_3CH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 170.0, 169.7, 151.6, 142.4, 110.1, 108.7, 67.6, 65.7, 38.4, 20.9,20.8, 19.9 ppm.

(2*R*,4*R*)-4-(Furan-2-yl)-4-hydroxybutan-2-yl Acetate [(+)-*syn*-22]: *ee* = 99% (GC of the corresponding acetonide). $[\alpha]_D$ = +13.5 (c = 1.58, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (m, 1 H, α furan H), 6.30 (m, 1 H, β furan H), 6.20 (m, 1 H, β furan H), 4.95 (sextuplet, J = 6.0 Hz, 1 H, CH_3*CH*OAc), 4.75 (t, J = 6.7 Hz, 1 H, Fu–*CH*–OH), 2.18 (m, 1 H, *CH*H), 2.00 (m, 1 H, *CH*H), 1.96 (s, 3 H, CH_3COO), 1.24 (d, J = 6.4 Hz, CH_3CH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 170.6, 155.9, 141.8, 110.0, 105.8, 68.4, 64.8, 41.3, 21.0, 19.8 ppm.

(1*S*,3*S*)-1-(Furan-2-yl)butane-1,3-diol [(–)-*syn*-14]: *ee* = 99% (GC of the corresponding acetonide). $[\alpha]_D$ = –31.8 (c = 0.66, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (m, 1 H, α furan H), 6.32 (m, 1 H, β furan H), 6.24 (m, 1 H, β furan H), 4.94 (dd, J = 9.4, 3.8 Hz, 1 H, Fu–*CH*–OH), 4.09 (m, 1 H, CH_3*CH*–OH), 2.04–1.87 (m, 2 H, CH_2), 1.23 (d, J = 6.4 Hz, CH_3CH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 156.3, 141.7, 110.0, 105.5, 67.9, 67.7, 43.1, 23.7 ppm.

Determination of the Absolute Configuration of the Monoacetate (+)-*syn*-22. Preparation of (2*R*,4*R*)-4-(Furan-2-yl)-4-(methoxymethoxy)butan-2-yl Acetate [(+)-*syn*-24]: The monoacetate (+)-*syn*-**22** (0.900 g, 4.55×10^{-3} mol) was treated with MOMCl (0.805 g, 0.010 mol) and iPr$_2$Net (1.81 g, 0.014 mol) in CH_2Cl_2 (50 mL). The reaction mixture was stirred at room temperature for 12 h and was then diluted with AcOEt and saturated $NaHCO_3$. The mixture was extracted with AcOEt, dried and concentrated under reduced pressure. The residue was purified by column chromatograph with elution with hexane/ethyl acetate to afford the MOM derivative (+)-*syn*-**24** (0.793 g, 72%): $[\alpha]_D$ = +101 (c = 1.21, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (m, 1 H, α furan H), 6.32 (m, 1 H, β furan H), 6.26 (m, 1 H, β furan H), 4.84 (m, 1 H, CH_3*CH*–OAc), 4.69 (t, J = 6.9 Hz, 1 H, Fu–*CH*–OMOM), 4.58 (d, J = 6.9 Hz, 1 H, O*CH*HO), 4.50 (d, J = 6.9 Hz, 1 H, O*CH*HO), 3.35 (s, 3 H, OCH_3), 2.26 (m, 1 H, *CH*H), 2.06 (m, 1 H, *CH*H), 1.99 (s, 3 H, COCH_3), 1.23 (d, J = 6.4 Hz, CH_3CH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 170.0, 152.9, 142.4, 109.9, 108.5, 93.8, 67.95, 67.90, 55.4, 39.9, 20.9, 19.8 ppm.

(2*R*,4*R*)-4-(Furan-2-yl)-4-(methoxymethoxy)butan-2-ol [(+)-*syn*-21]:[15] The MOM derivative (+)-*syn*-**24** (0.650 g, 2.68×10^{-3} mol) was treated with KOH (0.226 g, 4.03×10^{-3} mol) in MeOH (50 mL), to afford compound (+)-*syn*-**21** (0.444 g, 83%): $[\alpha]_D$ = +180 (c = 1.45, $CHCl_3$) {ref.[15] $[\alpha]_D$ = +177 (c = 1.21, $CHCl_3$) for (2*R*,4*R*)-*syn*-**21**}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (m, 1 H, α furan H), 6.22 (m, 2 H, 2 β furan H), 4.76 (dd, J = 8.2, 6.0 Hz, 1 H, Fu–*CH*–OMOM), 4.51 (d, J = 6.7 Hz, 1 H, O*CH*HO), 4.41 (d, J = 6.7 Hz, 1 H, O*CH*HO), 3.77 (m, 1 H, CH_3*CH*–OH), 3.26 (s, 3 H, OCH_3), 2.15 (dt, J = 13.9, 8.2 Hz, 1 H, *CH*H), 1.80 (ddd, J = 13.9, 6.0, 3.2 Hz, 1 H, *CH*H), 1.21 (d, J = 6.0 Hz, CH_3CH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 153.0, 142.2, 109.8, 108.2, 93.5, 69.7, 65.7, 55.2, 42.6, 23.2 ppm.

Baker's Yeast Reduction of *rac*-8: Compound *rac*-**8** (10.0 g, 0.069 mol) was subjected to baker's yeast fermentation. After 72 h, the reaction was worked up and the corresponding crude mixture showed the following composition (NMR): the hydroxy ketone **8** (56%), (+)-(2*S*,4*S*)-*anti*-**15** (20%) and (+)-(2*S*,4*R*)-*syn*-**15** (24%). Column chromatography allowed the recovery of (+)-*anti*-**15** and (+)-*syn*-**15** as single pure compounds.

(2*S*,4*R*)-Octane-2,4-diol [(+)-*syn*-15]:[28] 1.41 g (14%). $[\alpha]_D$ = +6.5 (c = 1.17, EtOH) {ref.[28] $[\alpha]_D$ = –1.3 (c = 1.40, EtOH) for (2*R*,4*S*)-*syn*-**15** with *ee* = 24%}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.91 (m,

1 H, C*H*–OH), 3.70 (m, 1 H, C*H*–OH), 1.49–1.14 (m, 8 H, 4 × CH_2), 1.08 (d, J = 6.4 Hz, 3 H, CH_3–CH), 0.80 (t, J = 6.9 Hz, CH_2CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 72.4, 68.5, 44.3, 37.5, 27.3, 23.7, 22.4, 13.7 ppm.

(2*S*,4*S*)-Octane-2,4-diol [(+)-*anti*-15]:[28] 1.81 g (18%). $[\alpha]_D$ = +21.8 (c = 0.66, EtOH) {ref.[28] $[\alpha]_D$ = –5.4 (c = 1.40, EtOH) for (2*R*,4*R*)-*syn*-**15** with *ee* = 25%}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.10 (sextuplet, J = 6.0 Hz, 1 H, C*H*–OH), 3.87 (m, 1 H, C*H*–OH), 1.54 (t, J = 6.0 Hz, CH_2), 1.51–1.22 (m, 6 H, 3 × CH_2), 1.18 (d, J = 6.4 Hz, 3 H, CH_3–CH), 0.87 (t, J = 6.9 Hz, CH_2CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 69.1, 65.1, 44.1, 37.0, 27.9, 23.3, 22.6, 13.9 ppm.

Baker's Yeast Reduction of the 0.7:1 Mixture of Racemic *syn*- and *anti*-9: Compound *rac*-**9** (10.0 g, 0.056 mol) was subjected to baker's yeast fermentation. After 48 h, the reaction was worked up and the corresponding crude mixture showed the following composition (NMR): the hydroxy ketone **9** (*syn*-**9** 28.5%, *anti*-**9**, 48.2%), (1*S*,2*R*,3*S*)-*syn*,*syn*-**16** (2.6%), (1*R*,2*S*,3*S*)-*syn*,*anti*-**16** (12.4%), (1*R*,2*R*,3*S*)-*anti*,*syn*-**16** (5.7%) and (1*S*,2*S*,3*S*)-*anti*,*anti*-**16** (2.6%). Column chromatography allowed the recovery of (+)-*syn*,*anti*-**16** and (–)-*anti*,*syn*-**16** as single pure compounds.

(1*R*,2*S*,3*S*)-2-Methyl-1-phenylbutane-1,3-diol [(+)-*syn*,*anti*-16]:[29] 0.907 g (9%). $[\alpha]_D$ = +50.9 (c = 1.02, CH_2Cl_2) {ref.[29] $[\alpha]_D$ = +52.3 (c = 1.12, CH_2Cl_2) for (1*R*,2*S*,3*S*)-*syn*,*anti*-**16** with *ee* = 99%}; optical purity = 96%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.20 (m, 5 H, aromatic H), 5.06 (d, J = 3.0 Hz, 1 H, Ph*CH*OH), 3.78 (quintet, J = 6.4 Hz, 1 H, CH_3CHOH), 1.80 [m, 1 H, *CH*C(2)], 1.25 (d, J = 6.4 Hz, 3 H, CH_3CHOH), 0.77 [d, J = 6.9 Hz, 3 H, CH_3C(2)] ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 142.7, 128.0, 127.0, 126.1, 74.7, 70.9, 45.7, 21.9, 11.3 ppm.

(1*R*,2*R*,3*S*)-2-Methyl-1-phenylbutane-1,3-diol [(–)-*anti*,*syn*-16]:[29] 0.302 g (3%). $[\alpha]_D$ = –24.7 (c = 1.04, CH_2Cl_2) {ref.[29] $[\alpha]_D$ = +25.2 (c = 1.1, CH_2Cl_2) for (1*S*,2*S*,3*R*)-*anti*,*syn*-**16** with *ee* = 99%}; optical purity 97%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.20 (m, 5 H, aromatic H), 4.70 (d, J = 7.1 Hz, 1 H, Ph*CH*OH), 4.05 (qd, J = 6.4, 2.1 Hz, 1 H, CH_3CHOH), 1.95 [m, 1 H, *CH*C-(2)], 1.22 (d, J = 6.5 Hz, 3 H, CH_3CHOH), 0.82 [d, J = 6.9 Hz, 3 H, CH_3C(2)] ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 143.7, 128.2, 127.6, 126.4, 77.7, 68.9, 44.4, 18.9, 12.0 ppm.

Baker's Yeast Reduction of the 0.5:1 Mixture of Racemic *syn*- and *anti*-10: Compound *rac*-**10** (10.0 g, 0.049 mol) was subjected to baker's yeast fermentation. After 48 h, the reaction was worked up and the corresponding crude mixture showed the following composition (NMR): the starting hydroxy ketone **10** (*syn*-**10** 28.3%, *anti*-**10** 49.0%), (2*S*,3*R*,4*R*)-*syn*,*syn*-**17** (2.4%), (2*S*,3*S*,4*S*)-*syn*,*anti*-**17** (4.8%), (2*S*,3*R*,4*S*)-*anti*,*syn*-**17** (10.7%) and (2*S*,3*S*,4*R*)-*anti*,*anti*-**17** (4.8%). Column chromatography allowed the recovery of (+)-*anti*,*syn*-**17** and (+)-*anti*,*anti*-**17** single pure compounds.

(2*S*,3*R*,4*S*,*E*)-3-Methyl-6-phenylhex-5-ene-2,4-diol [(+)-*anti*,*syn*-17]:[23] 0.807 g (8%). *ee* = 99% (HPLC). $[\alpha]_D$ = +8.01 (c = 1.05, $CHCl_3$) {ref.[23] $[\alpha]_D$ = +7.36 (c = 0.92, $CHCl_3$) for (2*S*,3*R*,4*S*)-*anti*,*syn*-**17** with *ee* = 97%}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.20 (m, 5 H, aromatic H), 6.63 (d, J = 15.7 Hz, 1 H, Ph*CH*=), 6.25 (dd, J = 15.7, 6.7 Hz, 1 H, PhCH=*CH*CH), 4.32 (t, J = 6.7 Hz, 1 H, =CH*CH*OH), 4.18 (qd, J = 6.4, 2.2 Hz, 1 H, CH_3CHOH), 1.78 (dquintuplet, J = 2.8, 7.1 Hz, 1 H, *CH*CH_3), 1.23 (d, J = 6.4 Hz, 3 H, CH_3CHOH), 0.96 (d, J = 7.1 Hz, 3 H, CHCH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 136.7, 131.5, 131.1, 128.6, 127.6, 126.5, 76.5, 69.2, 43.4, 19.6, 11.5 ppm.

(2*S*,3*S*,4*R*,*E*)-3-Methyl-6-phenylhex-5-ene-2,4-diol [(+)-*anti*,*anti*-17]:[23] 0.302 g (3%); *ee* = 99% (HPLC). $[\alpha]_D$ = +15.9 (c = 1.15, $CHCl_3$) {ref.[23] $[\alpha]_D$ = +16.5 (c = = 1.31, $CHCl_3$) for (2*S*,3*S*,4*R*,*E*)-*anti*,*anti*-**17** with *ee* > 99%}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.20 (m, 5 H, aromatic H), 6.58 (d, J = 15.7 Hz, 1 H, Ph*CH*=), 6.21 (dd, J = 15.7, 8.0 Hz, 1 H, PhCH=*CH*CH), 4.23 (t, J = 8.0 Hz, 1 H, =CH*CH*OH), 3.85 (dq, J = 8.0, 6.2 Hz, 1 H, CH_3CHOH), 1.68 (m, 1 H, *CH*CH_3), 1.25 (d, J = 6.1 Hz, 3 H, CH_3CHOH), 0.82 (d, J = 6.7 Hz, 3 H, CHCH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 136.6, 131.9, 131.0, 128.5, 127.6, 126.5, 78.6, 72.6, 45.5, 21.6, 13.2 ppm.

Baker's Yeast Reduction of *syn*-11: Compound *rac*-*syn*-**11** (5.0 g, 0.024 mol) was subjected to baker's yeast fermentation. After 48 h, the reaction was worked up and the corresponding crude mixture showed the following composition (NMR): the starting hydroxy ketone *syn*-**11** (57.5%), (1*S*,2*R*,*S*)-*syn*,*syn*-**18** (17.5%) and (1*S*,2*S*,*R*)-*syn*,*anti*-**18** (25%). Column chromatography allowed the recovery of (–)-*syn*,*syn*-**18** and (+)-*syn*,*anti*-**18** as single pure compounds.

(1*S*,2*R*)-2-[(*S*)-Hydroxy(phenyl)methyl]cyclohexanol [(–)-*syn*,*syn*-18]:[30] M.p. 95 °C. 0.618 g (12.5%); *ee* = 99% (HPLC). $[\alpha]_D$ = –13 (c = 0.99, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.28 (m, 5 H, aromatic H), 4.97 (d, J = 3.3 Hz, Ph*CH*OH), 4.16 (m, 1 H, *CH*OH of the ring), 1.83–1.03 (m, 9 H, 9H of the ring) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 143.2, 127.9, 126.9, 125.8, 122.2, 77.8, 71.2, 47.7, 33.7, 25.6, 19.6, 18.4 ppm.

(1*S*,2*S*)-2-[(*R*)-Hydroxy(phenyl)methyl]cyclohexanol [(+)-*syn*,*anti*-18]:[30] M.p. 101 °C. 0.939 g (19%); *ee* = 99% (HPLC). $[\alpha]_D$ = +32 (c = 0.95, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.28 (m, 5 H, aromatic H), 4.96 (d, J = 3.3 Hz, Ph*CH*OH), 3.52 (td, J = 10.3, 4.4 Hz, 1 H, *CH*OH of the ring), 1.99–0.80 (m, 9 H, 9H of the ring) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 141.9, 127.8, 126.9, 126.6, 126.1, 76.2, 71.2, 50.1, 35.4, 25.7, 25.2, 24.3 ppm.

Baker's Yeast Reduction of *anti*-11: Compound *rac*-*anti*-**11** (5.0 g, 0.024 mol) was subjected to baker's yeast fermentation. After 48 h, the reaction was worked up and the corresponding crude mixture showed the following composition (NMR): the starting hydroxy ketone *anti*-**11** (55.6%, showing *ee* = 73% by HPLC analysis) and (1*S*,2*R*,*R*)-*anti*,*syn*-**18** (44.4%). Column chromatography allowed the recovery of (+)-*anti*,*syn*-**18** as a single pure compound.

(1*S*,2*R*)-2-[(*R*)-Hydroxy(phenyl)methyl]cyclohexanol [(+)-*anti*,*syn*-18]: 1.92 g (39%); *ee* = 99% (HPLC). $[\alpha]_D$ = +40.4 (c = 1.25, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.26 (m, 5 H, aromatic H), 4.73 (d, J = 5.1 Hz, Ph*CH*OH), 4.10 (m, 1 H, *CH*OH of the ring), 1.80–1.16 (m, 9 H, 9H of the ring) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 143.6, 128.0, 127.0, 126.1, 76.8, 66.9, 46.9, 32.7, 25.1, 24.5, 20.2 ppm.

Hydrogenolysis of (+)-*anti*,*syn*-18: A solution of (+)-*anti*,*syn*-**18** (0.500 g, 2.43 × 10^{-3} mol) in ethanol (20 mL) was treated with H_2 (80 psi) at room temperature for 48 h in the presence of Pd/C (50 mg). The reaction mixture was filtered and concentrated under reduced pressure to give a residue that was purified by column chromatography to afford (+)-**20** (0.392 g, 85%): $[\alpha]_D$ = +27.5 (c = 1.05, $CHCl_3$) {ref.[31] $[\alpha]_D$ = +28 (c = 1.0, $CHCl_3$) for (1*S*,2*S*)-(+)-**20**}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.26 (m, 5 H, aromatic H), 3.78 (m, 1 H, *CH*OH), 2.72 (dd, J = 13.3, 7.3 Hz, Ph*CH*H), 2.54 (dd, J = 13.3, 7.6 Hz, Ph*CH*H), 1.81–1.14 (m, 9 H, 9H of the ring) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 141.0, 129.0, 128.1, 125.7, 68.5, 43.5, 38.6, 33.3, 26.4, 25.2, 20.3 ppm.

[1] a) V. Malathong, S. D. Rychnovsky, *Org. Lett.* **2009**, *11*, 4220–4223; b) S. Raghavan, K. Rathore, *Synlett* **2009**, 1285–1288; c) G. Sabitha, P. Gopal, J. S. Yadav, *Tetrahedron: Asymmetry*

2009, *20*, 1493–1499; d) J. E. D. Martins, M. Wills, *Tetrahedron* **2009**, *65*, 5782–5786; e) N. Hayashi, T. Suzuki, K. Usui, M. Nakada, *Tetrahedron* **2009**, *65*, 888–895.
[2] a) R. H. Morris, *Chem. Soc. Rev.* **2009**, *38*, 2282–2291; b) C. A. Sandoval, Y. Li, K. Ding, R. Noyori, *Chem. Asian J.* **2008**, *3*, 1801–1810; c) Y. L. Ren, X. Z. Tian, K. P. Sun, J. Xu, X. L. Xu, S. J. Lu, *Tetrahedron Lett.* **2006**, *47*, 463–465; W. H. Zhang, Y. Cai, X. Liu, Y. Fang, J. H. Xu, *Prog. Chem.* **2007**, *19*, 1537–1552.
[3] a) T. Matsuda, R. Yamanaka, K. Nakamura, *Tetrahedron: Asymmetry* **2009**, *20*, 513–557; b) B. T. Grau, P. N. Devine, L. N Di Michele, B. Kosjek, *Org. Lett.* **2007**, *9*, 4951–4954; c) J. C. Moore, D. J. Pollard, B. Kosjek, P. N. Devine, *Acc. Chem. Res.* **2007**, *40*, 1412–1419; d) I. A. Kaluzna, J. D. Rozzell, S. Kambourakis, *Tetrahedron: Asymmetry* **2005**, *16*, 3682–3689.
[4] M. T. Reetz, *J. Org. Chem.* **2009**, *74*, 5767–5778.
[5] a) K. Nakamura, R. Yamanaka, T. Matsuda, T. Harada, *Tetrahedron: Asymmetry* **2003**, *14*, 2659–2681; b) H. L. Ni, Y. X. Guan, S. J. Yao, *J. Chem. Technol. Biotechnol.* **2009**, *84*, 186–191; c) F. R. Bisogno, I. Lavandera, W. Kroutil, V. Gotor, *J. Org. Chem.* **2009**, *74*, 1730–1732; d) S. Ludeke, M. Richter, M. Muller, *Adv. Synth. Catal.* **2009**, *351*, 253–259; e) S. Broussy, R. W. Cheloha, D. B. Berkowitz, *Org. Lett.* **2009**, *11*, 305–308; f) B. Kosjek, J. Nti-Gyabaah, K. Telari, L. Dunne, J. C. Moore, *Org. Proc. Res. Devel.* **2008**, *12*, 584–588; g) J. C. Moore, D. J. Pollard, B. Kosjek, P. N. Devine, *Acc. Chem. Res.* **2007**, *40*, 1412–1419.
[6] D. A. Evans, L. Kvaerno, T. B. Dunn, A. Beauchemin, B. Raymer, J. A. Mulder, E. J. Olhava, M. Juhl, K. Kagechika, D. A. Favor, *J. Am. Chem. Soc.* **2008**, *130*, 16295–16315; B. M. Trost, J. Waser, A. Meyer, *J. Am. Chem. Soc.* **2008**, *130*, 16424–16434; K. C. Nicolaou, *J. Org. Chem.* **2009**, *74*, 951–972.
[7] L. C. Dias, C. D. S. Goncalves, *Adv. Synth. Catal.* **2008**, *350*, 1017–1021; G. E. Keck, R. L. Giles, V. J. Cee, C. A. Wager, T. Yu, M. B. Kraft, *J. Org. Chem.* **2008**, *73*, 9675–9691; M. Helliwell, S. Karim, E. R. Parmee, E. J. Thomas, *Org. Biomol. Chem.* **2005**, *3*, 3636–3653; A. A. Salaskar, N. V. Mayekar, A. Sharma, S. K. Nayak, A. Chattopadhyaya, S. Chattopadhyay, *Synthesis-Stuttgart* **2005**, 2777–2781.
[8] R. N. Patel, A. Banerjee, C. G. McNamee, D. Brzozowski, R. L. Hanson, L. J. Szarka, *Enzyme Microb. Technol.* **1993**, *15*, 1014–1021; R. N. Patel, C. G. McNamee, A. Banerjee, L. J. Szarka, EP-A569998, 1993; D. J. Stewart, *Curr. Opin. Biotechnol.* **2000**, *11*, 363–368; M. J. Sorgedrager, F. van Rantwijk, G. W. Huisman, R. A. Sheldon, *Adv. Synth. Catal.* **2008**, *350*, 2322–2328; D. Kalaitzakis, J. D. Rozzell, I. Smonou, S. Kambourakis, *Adv. Synth. Catal.* **2006**, *348*, 1958–1969.
[9] D. Acetti, E. Brenna, C. Fuganti, F. G. Gatti, L. Malpezzi, S. Serra, *Eur. J. Org. Chem.* **2008**, 5125–5134.
[10] S. Servi, *Synthesis* **1990**, 1–25.
[11] R. Chênevert, S. Thiboutot, *Can. J. Chem.* **1986**, *64*, 1599–1601.
[12] K. Ahmad, S. Koul, S. C. Taneja, A. P. Singh, M. Kapoor, R.-ul-Hassan, V. Verma, G. N. Qazi, *Tetrahedron: Asymmetry* **2004**, *15*, 1685–1692.
[13] G. F. Sabitha, P. Padmaja, K. B. Reddy, J. S. Yadav, *Tetrahedron Lett.* **2008**, *49*, 919–922.
[14] T. K. Chakraborty, S. Das, *Chem. Lett.* **2000**, 80–81.
[15] Y. Kobayashi, M. Matsuumi, *J. Org. Chem.* **2000**, *65*, 7221–7224.
[16] S. D. Rychnovsky, D. J. Skalitzky, *Tetrahedron Lett.* **1990**, *31*, 945–948; D. A. Evans, D. L. Rieger, J. R. Gage, *Tetrahedron Lett.* **1990**, *31*, 7099–7100.
[17] G. E. Keck, C. A. Wager, *Org. Lett.* **2000**, *2*, 2307; P. R. Chopade, T. A. Davis, E. Prasad, R. A. Flowers, *Org. Lett.* **2004**, *6*, 2685; O. Labeeuw, C. Roche, P. Phansavath, J.-P. Genet, *Org. Lett.* **2007**, *9*, 105; J. L. Vicario, D. Badia, L. Carrillo, E. Dominguez, M. Rodriguez, *J. Org. Chem.* **2000**, *65*, 3754.
[18] H. Shulman, C. Makarov, A. K. Ogawa, F. Romesberg, E. Keinan, *J. Am. Chem. Soc.* **2000**, *122*, 10743–10753.
[19] A. Crdova, K. D. Janda, *J. Am. Chem. Soc.* **2001**, *123*, 8248–8259.
[20] R. Fernandez-Lopez, J. Kofoed, M. Machuqueiro, T. Darbre, *Eur. J. Org. Chem.* **2005**, 5268–5276.
[21] B. Janza, A. Studer, *J. Org. Chem.* **2005**, *70*, 6991–6994.
[22] *syn*-**9**: T. Yakura, Y. Yoshimoto, C. Ishida, S. Mabuchi, *Tetrahedron* **2007**, *63*, 4429–4438; *anti*-**9**: M. Sato, S. Sunami, Y. Sugita, C. Kaneko, *Heterocycles* **1995**, *41*, 1435–1444.
[23] A. Abate, E. Brenna, A. Costantini, C. Fuganti, F. G. Gatti, L. Malpezzi, S. Serra, *J. Org. Chem.* **2006**, *71*, 5228–5240.
[24] J.-R. Chen, H.-H. Lu, X.-Y. Li, L. Cheng, J. Wan, W.-J. Xiao, *Org. Lett.* **2005**, *7*, 4543–4545.
[25] T. Cohen, I. H. Jeong, B. Mudryk, M. Bhupathy, M. M. A. Awad, *J. Org. Chem.* **1990**, *55*, 1528–1536.
[26] M. M. Musa, K. I. Ziegelmann-Fjield, C. Vieille, J. G. Zeikus, R. S. Phillips, *J. Org. Chem.* **2007**, *72*, 30–34.
[27] K.-M. Chen, G. E. Hardtmann, K. Prasad, O. Repič, M. J. Shapiro, *Tetrahedron Lett.* **1987**, *28*, 155–158.
[28] K. Edegger, W. Stampfer, B. Seisser, K. Faber, S. F. Mayer, R. Oehrlein, A. Hafner, W. Kroutil, *Eur. J. Org. Chem.* **2006**, 1904–1909.
[29] A. Abate, E. Brenna, C. Fuganti, F. G. Gatti, T. Giovenzana, L. Malpezzi, S. Serra, *J. Org. Chem.* **2005**, *70*, 1281–1290.
[30] S. H. J. Thompson, M. F. Mahon, K. C. Molloy, M. S. Hadley, T. Gallagher, *J. Chem. Soc. Perkin Trans. 1* **1995**, 379–383.
[31] G. Fronza, G. Fogliato, C. Fuganti, S. Lanati, R. Rallo, S. Servi, *Tetrahedron Lett.* **1995**, *36*, 123–124.

Received: September 3, 2009
Published Online: November 17, 2009

