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Stereochemical control in microbial reduction. Part 31: Reduction of alkyl 2-oxo-4-arylbutyrates by baker's yeast under selected reaction conditions

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Abstract

Treatment of baker's yeast with phenacyl chloride in an aqueous–organic solvent has been proven to be an effective method of inhibiting the enzymes that afford (*S*)-enantiomers of α-hydroxy esters in the reduction of α-keto esters. The procedure is effective for the whole-cell system to produce the (*R*)-product with high chemical yield and high enantiomeric excess.

1. Introduction

The asymmetric production of bioactive compounds starting from chiral building blocks has been well documented for their advantages.[1–3] The availability and cost of these chiral reagents is highly dependent on their method of production, and much effort has been made in the common interest of obtaining cheaper optically active compounds of high purity and yield.[1,4] One prime example is the preparation of the chiral reagent alkyl (*R*)-2-hydroxy-4-phenylbutanoate, a versatile key intermediate for the synthesis of a variety of angiotensin converting enzyme (ACE) inhibitors from their corresponding prochiral precursors, alkyl 2-oxo-4-phenylbutanoates.[5–7] Often, the biotechnological preparation of chiral molecules such as alkyl (*R*)-2-hydroxy-4-phenylbutanoates[5,8–10] is the method of choice rather than just the chemical approach.[11,12] Microbial reduction of ethyl 2-oxo-4-phenylbutanoate to ethyl (*R*)-2-hydroxy-4-phenylbutanoate with excellent chemical yield (90%) and ee (>99%) under the catalysis of *Daucus carota* cells has already been reported.[10] The same reaction under the catalysis of baker's yeast

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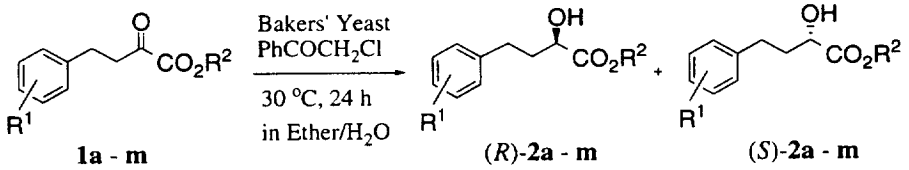
(*Saccharomyces cerevisiae*), which has long been recognized as a valuable reagent in organic asymmetric synthesis, has also been reported recently by us to give high chemical yield (80–90%) with excellent ee (>90%)[13] by selecting reaction conditions such as medium, temperature, addition of a third reagent and so on.[14–17]

In order to extend the scope of the reduction, we studied the reduction of alkyl 2-oxo-4-arylbutanoates **1** to the corresponding alkyl 2-hydroxy-4-arylbutanoates **2** mediated by baker's yeast (Scheme 1) under the influence of the third reagent added to the reaction system.[13] We now wish to report the effect of substituents on the phenyl ring with respect to chemical yield and ee of the product. In addition, we would also like to exploit the potential of our technique in the yeast-mediated reduction of other aromatic α-keto esters such as alkyl phenylformates and phenylpyruvates. It has been reported that, although the reduction of phenylformate affords (*R*)-mandelate in 60–70% chemical yield with 98% ee, the reduction of phenylpyruvate affords racemic product in 40–50% chemical yield.[18] Of course, the disadvantages in chemical yield and enantioselectivity have been resolved with the use of isolated enzyme systems.[19,20]



1a - m (*R*)-**2a - m** (*S*)-**2a - m**

a : R^1=H , R^2=C_2H_5
b : R^1=*o*-CH_3 , R^2=C_2H_5
c : R^1=*m*-CH_3 , R^2=C_2H_5
d : R^1=*p*-CH_3 , R^2=C_2H_5
e : R^1=*p*-CH_3O , R^2=C_2H_5
f : R^1=*p*-F , R^2=C_2H_5
g : R^1=*p*-F , R^2=C_3H_7
h : R^1=*p*-F , R^2=$(CH_3)_2CHCH_2$
i : R^1=*o*-Cl , R^2=C_2H_5
j : R^1=*m*-Cl , R^2=C_2H_5
k : R^1=*p*-Cl , R^2=C_2H_5
m: R^1=*p*-NO_2 , R^2=C_2H_5

Scheme 1.

2. Results and discussion

2.1. Syntheses of materials

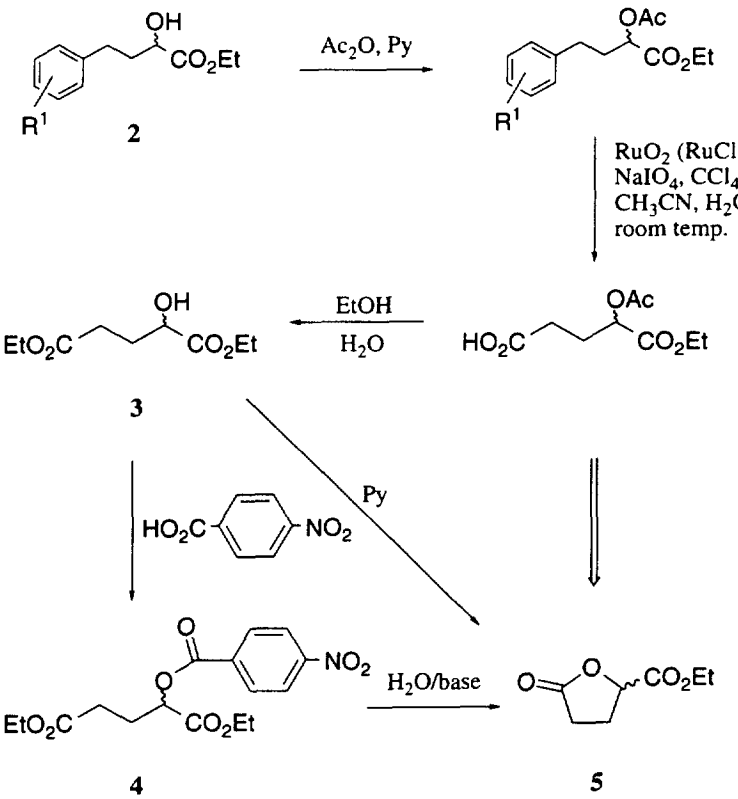
Ethyl 2-oxo-4-phenylbutanoate substituted by *o*-, *m*- and *p*-methyl, *o*-, *m*- and *p*-chloro, and *p*-fluoro, as well as *p*-methoxy groups were all prepared by converting the alcohols to the corresponding

bromides,[21–24] which were then coupled with diethyl oxalate through the Grignard reactions.[25,26] Propyl 2-oxo-4-*p*-fluorophenylbutanoate **1g** and isobutyl 2-oxo-4-*p*-fluorophenylbutanoate **1h** were prepared by acid-catalyzed exchange reactions from ethyl 2-oxo-4-*p*-fluorophenylbutanoate **1f** with appropriate alcohols, respectively. Ethyl 2-oxo-4-*p*-nitrophenylbutanoate **1m** was prepared by oxidation of ethyl 2-hydroxy-4-*p*-nitrophenylbutanoate **2m** with pyridinium dichromate,[27,28] which was prepared from 4-(*p*-nitrophenyl)butyric acid by the Hell–Volhard–Zelinski procedure.[29,30]

2.2. *Determination of configuration*

The configuration of the *o*-, *m*- and *p*-chloro compounds **2i**, **j** and **k** were determined by reductive dechlorination at the aromatic moiety using Pd/C.[31,32] The configurations of the products **2a** were elucidated by comparing their retention times on HPLC with a chiral stationary phase to that of the authentic sample of the (*R*)-configuration. The *m*-methyl, *p*-methoxy, *p*-fluoro and *p*-nitro derivatives **2c**, **e**, **f** and **m** were initially acetylated to protect the α-hydroxy group and oxidized by ruthenium tetroxide to give the monoethyl α-acetoxy glutarate.[33–36] The monoethyl ester was converted to the corresponding *p*-nitrobenzoate **4**, through diethyl α-hydroxy glutarate **3**, for convenience in chromatography. The configuration of **4** thus obtained was then compared to that derived from **2a**.

Liberation of the secondary alcohol moiety by removal of the *p*-nitrobenzoyl group or standing **3** in pyridine inherently causes intramolecular cyclization to yield a lactone **5**, another useful chiral building block, in 76–90% chemical yield (Scheme 2). The chiral lactone **5** is also available by yeast-mediated reduction of 3-benzoylpropionic acid[37,38] followed by the oxidation with ruthenium tetroxide.[33–36]



Scheme 2.

2.3. Substituent effect

Substitution of an electron-withdrawing group retards the reaction as seen in Table 1. It is interesting to note that a chlorine substituent at any position of the phenyl ring exerts good stereoselectivity. The effect of the steric size of a molecule is also seen in the reductions of propyl and isobutyl esters **1g** and **h** when they are compared to the reduction of the corresponding ethyl ester, **1f**.[13]

When the microbe is incubated in the presence of phenacyl chloride, stereochemical results are improved appreciably for all the substrates studied, as has been reported previously for the reduction of unsubstituted substrate, **1a**.[13] It is obvious that phenacyl chloride inactivates the enzyme(s) that afford the (*S*)-isomer of the product, because, in most cases, an increase in the stereoselectivity of the (*R*)-isomer is improved at the sacrifice of chemical yield after prolonged incubation time with this reagent. In addition, since we know that changing the ethyl group at the alcohol moiety to a butyl or a higher alkyl group improves the selectivity to a satisfactory level (90% ee), we believe that the present results appear satisfactory except for **1b**, a substrate with an *ortho*-substituent. Clearly, the selectivity results, in the presence of phenacyl chloride, are satisfactory for the *m*-methyl-, *p*-methoxy-, *p*-fluoro- and *m*- and *p*-chloro-substituents, whilst the effect is less sensitive for the *p*-methyl- and *p*-nitro-substituents. It seems that a moderately bulky group (or atom) at the *para*-position is required to be sensitive to the effects of phenacyl chloride. Electronic effects from the substituents on the phenyl ring seem to play little part in controlling the selectivity under the influence of phenacyl chloride. Although an electron-withdrawing *p*-fluoro-substituted substrate with a bulky alcohol moiety, **1h**, exerts excellent stereoselectivity, the chemical yield from this substrate is far from being satisfactory. Because the chemical yield is defined as that after 24 h of reaction and we observed no other product than **2** on HPLC, there is no doubt that prolonged reaction time and/or an increase in the amount of baker's yeast may improve the chemical yield to a satisfactory level.

2.4. Effect of carbon chain length

The use of phenacyl chloride as a 'stereochemical regulator' has so far demonstrated its potential effectiveness in controlling the stereochemical outcome of the reduction. To verify further the effectiveness of this reagent, we tested its ability to effect the stereochemical control of the baker's yeast reduction of other α-keto esters having different carbon chain length in the acid moiety. The results are summarized in Table 2, which again proves that the use of a stereochemical regulator is an effective method for controling the stereochemical result of the reduction.

Although methyl and ethyl benzoylformates are reduced with high ee under standard conditions, addition of phenacyl chloride has greatly enhanced the selectivity further. The length of the carbon chain in the acid moiety of the esters so far studied does not affect the stereochemical result or chemical yield appreciably: they are all satisfactory. Thus, it has been proven that the treatment of the yeast cells in aqueous diethyl ether in the presence of phenacyl chloride is an effective device to control the stereochemical course of the reduction, affording the corresponding (*R*)-enantiomer of the hydroxy ester. Since the reactivity of the microbe decreases, there is no doubt that phenacyl chloride inhibits the enzyme(s) responsible for the production of the (*S*)-enantiomer of the ester.

Table 1
Effect of substituent on stereoselectivity in the reduction of alkyl 2-oxo-4-arylbutanoate **1** mediated by baker's yeast

R^1	R^2	Phenacyl Chloride (mg)	Chemical Yield (%)[a] / Ee (%) Preincubation Time (h) Control[b]	2	6	10	$[\alpha]_D^{24}$	Configuration
H	C_2H_5	6	97/62	98/73	97/76[c]	89/80	-21.6[d]	*R*
		10		96/78	92/81	94/81	-15.7[e]	
o-CH_3	C_2H_5	6	93/65	61/83	84/74	45/43	–	*R*[f]
		10		92/77	69/69	58/60		
m-CH_3	C_2H_5	6	94/68	92/87	82/92	79/94	-9.2[g]	*R*
		10		95/89	86/90	77/92		
p-CH_3	C_2H_5	6	92/62	90/69	92/71	30/80	–	*R*[f]
		10		83/74	99/88	25/80		
p-CH_3O	C_2H_5	6	98/70	96/79	98/86	65/93	-17.2[h]	*R*
		10		93/81	96/86	53/92		
p-F	C_2H_5	6	63/51	95/68	93/69	73/85	-14.5[i]	*R*
		10		96/69	90/73	63/83	-12.2[j]	
p-F	C_3H_7	6	68/60	–	48/79	40/85	–	*R*[k]
		10		–	25/85	21/86		
p-F	$(CH_3)_2CHCH_2$	6	36/66	34/86	23/88	14/99	-2.4[l]	*R*[k]
		10		30/90	25/90	12/99		
o-Cl	C_2H_5	6	76/89	78/93	55/92	28/86	-12.4[m]	*R*
		10		73/95	51/91	34/88		
m-Cl	C_2H_5	6	48/96	56/95	55/97	51/96	-11.2[n]	*R*
		10		52/94	47/96	40/98		
p-Cl	C_2H_5	6	34/91	27/86	22/90	18/89	-18.6[o]	*R*
		10		22/93	24/84	14/96		
p-NO_2	C_2H_5	6	73/36	–	76/51	75/48	–	*R*
		10		–	78/53	61/49		

[a] After 24 h. [b] Reaction without pretreatment by phenacyl chloride. [c] 86/96 for the corresponding butyl ester.[13] [d] 99% ee (c=1.01, $CHCl_3$). [e] 80% ee (c=1.02, $CHCl_3$). [f] Configuration was assigned by comparing the retention time on HPLC with those of (*R*)-**2a**, **c**, and **j**. [g] 91% ee (c=1.01, $CHCl_3$). [h] 92% ee (c=1.01, $CHCl_3$). [i] 99% ee (c=1.00, $CHCl_3$). [j] 86% ee (c=1.03, $CHCl_3$). [k] Configuration was determined after converting the product to the ethyl ester, **2f**. [l] 99% ee (c=0.51, $CHCl_3$). [m] 90% ee (c=0.70, $CHCl_3$). [n] 96% ee (c=1.01, $CHCl_3$). [o] 99% ee (c=1.02, $CHCl_3$).

Table 2
Reduction of α-keto esters having different carbon chain lengths

Substrate R and n in $Ph(CH_2)_nCOCO_2R$	Chemical Yield (%)[a] / Ee (%) Phenacyl Chloride (mg) Control[b]	2	6	10	$[\alpha]_D^{24}$	Configuration
n=0, R=CH_3	89/90	90/94	88/95	81/98	-140.6[c]	*R*[d]
n=0, R=C_2H_5	77/93	77/93	64/96	66/96	-41.2[e]	*R*[d]
n=1, R=C_2H_5	96/67	94/77	95/81	93/85	18.9[f]	*R*
n=2, R=C_2H_5	97/62	97/73	97/76[g]	96/80	-21.6[h]	*R*
n=3, R=C_2H_5	89/76	59/80	62/82	59/84	–	*R*[i]

[a] After 24 h. [b] Reaction without pretreatment by phenacyl chloride. [c] >97% ee (c=1.00, $CHCl_3$). [d] Configuration was determined by comparing the retention time on HPLC of (*R*)-mandelate. [e] 96% ee (c=1.03, $CHCl_3$). [f] 84% ee (c=1.03, $CHCl_3$). [g] 86/96 for the corresponding butyl ester.[13] [h] 99% ee(c=1.02, $CHCl_3$). [i] Configuration was assigned by comparing the retention time on HPLC with that of (*R*)-**2a**.

Table 3
Medium-scale preparation of α-hydroxy esters[a]

Substrate	Product	Chemical Yield (mg)	Chemical Yield (%)	Ee (%)
1c	(*R*)-**2c**	177.5	71	91
1e	(*R*)-**2e**	135.0	54	92
1f	(*R*)-**2f**	192.5	77	82

[a] Substrate, 250 mg: Bakers' yeast, 22 g: Diethyl ether/Water, 240 ml/12 ml: Phenacyl chloride, 130 mg: Preincubation, 10 h at 30 °C: Reduction, 24 h at 30 °C.

2.5. *Medium-scale preparation*

It is important to confirm that the method is practically applicable to organic syntheses, and the reduction was run with a substrate of laboratory-scale amount. Results, summarized in Table 3, have been found satisfactory.

3. Experimental section

3.1. *Instruments*

Liquid-phase chromatograms (HPLC) were obtained on a Hitachi 655 using a Chiralcel OD 25+5 (Daicel) with hexane:isopropanol as the eluent. ^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Varian VXR 200 FT-NMR spectrometer in $CDCl_3$ (TMS and Cl_3CF as internal standards). Optical rotations

were measured on a JASCO DIP-181 digital polarimeter. Infrared analysis was performed with a JASCO FT-IR 5300 spectrophotometer. Elemental analyses were conducted using a Yanaco MT-5 elemental analyzer. Melting points were measured with a Yanagimoto micro melting point apparatus, and were not corrected.

3.2. Materials and methods

Reagents were purchased from Nacalai Tesque Inc., Wako Pure Chemical Industries Ltd, and the Aldrich Chemical Co. unless otherwise stated. Baker's yeast (*Saccharomyces cerevisiae*) was purchased from the Oriental Yeast Co. and stored in a refrigerator. Column chromatography was performed on silica gel using the solvent mixtures indicated. Both diethyl ether and THF were dried over $CaCl_2$ and finally distilled over Na with benzophenone ketyl as an indicator. Benzene and CH_2Cl_2 were distilled on CaH_2 or dried over 4 Å molecular sieves. All other solvents were of analytical grade. Dried and distilled solvents were employed whenever necessary. Preparation of 2-oxo-4-phenylbutanoate, **1a**, was described in a previous paper from our laboratory.[13] The purity of all the reagents employed for the reactions were confirmed by ^1H NMR spectroscopy and gave satisfactory results.

3.3. Preparation alkyl 2-oxo-4-arylbutanoates

As a typical run, (4-fluorophenyl)acetic acid was reduced to 2-(4-fluorophenyl)ethyl alcohol by $LiAlH_4$, and the alcohol was converted into the corresponding bromide by bromination with PBr_3.[21–24]

2-(4-Fluorophenyl)ethyl alcohol: ^1H NMR (δ from TMS in $CDCl_3$): 2.20 (bs, 1H), 2.84 (t, 2H, J=6.6 Hz), 3.84 (t, 2H, J=6.6 Hz), 6.99 (m, 2H), 7.18 (m, 2H).

2-(4-Fluorophenyl)ethyl bromide: ^1H NMR (δ from TMS in $CDCl_3$): 2.95 (t, 2H, J=7.5 Hz), 3.39 (t, 2H, J=7.5 Hz), 7.01 (m, 2H), 7.18 (m, 2H).

To a 100 ml two-necked round-bottomed flask containing 0.38 g (15.6 mmol) Mg equipped with a magnetic stirrer and a Dimroth condenser connected to an argon balloon was added a solution of 3.4 g (16.7 mmol) of the halide in 20 ml diethyl ether via a syringe. External heating with good agitation may be needed to initiate the reaction. The solution was then refluxed for 30–40 min with gentle heating; it was then cooled to room temperature before conveying it to a second vessel, containing 1.9 g (13.0 mmol) of diethyl oxalate in 20 ml diethyl ether, equipped with a magnetic stirrer, a dropping funnel and a Dimroth condenser protected from the air by a $CaCl_2$ tube. The Grignard reagent was discharged slowly into the reaction mixture with vigorous stirring in an ice-bath (1 h), then for a further 10 h or overnight at room temperature, and was completed with 30–40 min reflux. Ethyl 2-oxo-(4-fluorophenyl)butanoate, **1f**, (78% yield) was liberated after acidification of the reaction mixture with 2 M (1 M=1 mol dm^{-3}) HCl at 0°C and usual work-up.[25,26] The ester was purified on a silica gel column with hexane:EtOAc=5:1 as an eluent (R_f=0.51). ^1H NMR (δ from TMS in $CDCl_3$): 1.35 (t, 3H, J=7.2 Hz), 2.94 (t, 2H, J=7.1 Hz), 3.15 (t, 2H, J=7.1 Hz), 4.34 (q, 2H, J=7.2 Hz), 6.95 (m, 2H), 7.15 (m, 2H). Anal. calcd for $C_{12}H_{13}FO_3$: C, 64.28; H, 5.84%. Found: C, 64.37; H, 5.88%.

The propyl and isobutyl 2-oxo-(4-fluorophenyl)butanoates, **1g** and **1h**, were prepared by ester exchange reactions from the ethyl ester and the corresponding alcohols, respectively.

1g: ^1H NMR (δ from TMS in $CDCl_3$): 0.97 (t, 3H, J=7.2 Hz), 1.75 (m, 2H), 2.96 (t, 2H, J=7.2 Hz), 3.15 (t, 2H, J=6.8 Hz), 4.20 (t, 2H, J=6.8 Hz), 6.95 (m, 2H) and 7.15 (m, 2H). Anal. calcd for $C_{13}H_{15}FO_3$: C, 65.54; H, 6.35%. Found: C, 65.64; H, 6.39%.

1h: ^{1}H NMR (δ from TMS in $CDCl_3$): 0.96 (d, 6H, J=7.0 Hz), 2.03 (m, 1H), 2.93 (t, 2H, J=7.1 Hz), 3.15 (t, 2H, J=7.1 Hz), 4.01 (d, 2H, J=7.1 Hz), 6.96 (m, 2H) and 7.15 (m, 2H). Anal. calcd for $C_{14}H_{17}FO_3$: C, 66.65; H, 6.79%. Found: C, 66.48; H, 6.91%.

All other esters were prepared by methods similar to above in 30–78% yields.

1b: ^{1}H NMR (δ from TMS in $CDCl_3$): 1.35 (t, 3H, J=7.1 Hz), 2.32 (s, 3H), 2.94 (m, 2H), 3.13 (m, 2H), 4.31 (q, 2H, J=7.1 Hz) and 7.14 (s, 4H). Anal. calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32%. Found: C, 70.93; H, 7.44%.

1c: ^{1}H NMR (δ from TMS in $CDCl_3$): 1.28 (t, 3H, J=7.1 Hz), 2.31 (s, 3H), 2.92 (t, 2H, J=7.1 Hz), 3.12 (t, 2H, 7.1 Hz), 4.20 (q, 2H, J=7.1 Hz), 6.99 (m, 3H) and 7.16 (m, 1H). Anal. calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32%. Found: C, 70.77; H, 7.38%.

1d: ^{1}H NMR (δ from TMS in $CDCl_3$): 1.34 (t, 3H, J=7.1 Hz), 2.31 (s, 3H), 2.91 (t, 2H, J=7.1 Hz), 3.15 (t, 2H, J=7.1 Hz), 4.29 (q, 2H, J=7.1 Hz) and 7.09 (m, 4H). Anal. calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32%. Found: C, 71.02; H, 7.43%.

1e: ^{1}H NMR (δ from TMS in $CDCl_3$): 1.35 (t, 3H, J=7.1 Hz), 2.90 (t, 2H, J=7.2 Hz), 3.14 (t, 2H, J=7.1 Hz), 3.78 (s, 3H), 4.30 (q, 2H, J=7.2 Hz), 6.83 (d, 2H, J=8.6 Hz), 7.11 (d, 2H, J=8.6 Hz). Anal. calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83%. Found: C, 66.28; H, 6.96%.

1i: ^{1}H NMR (δ from TMS in $CDCl_3$): 1.35 (t, 3H, J=7.1 Hz), 3.05 (t, 2H, J=6.6 Hz), 3.17 (t, 2H, J=6.6 Hz), 4.31 (q, 2H, J=7.1 Hz) and 7.12–7.38 (m, 4H). Anal. calcd for $C_{12}H_{13}ClO_3$: C, 59.88; H, 5.44%. Found: C, 60.10; H, 5.39%.

1j: ^{1}H NMR (δ from TMS in $CDCl_3$): 1.35 (t, 3H, J=7.1 Hz), 2.93 (t, 2H, J=7.2 Hz), 3.18 (t, 2H, J=7.2 Hz), 4.31 (q, 2H, J=7.1 Hz), 7.06 (m, 1H) and 7.20 (m, 3H). Anal. calcd for $C_{12}H_{13}ClO_3$: C, 59.88; H, 5.44%. Found: C, 60.02; H, 5.57%.

1k: ^{1}H NMR (δ from TMS in $CDCl_3$): 1.34 (t, 3H, J=7.2 Hz), 2.92 (t, 2H, J=7.2 Hz), 3.16 (t, 2H, J=7.2 Hz), 4.32 (q, 2H, J=7.2 Hz), 7.12 (d, 2H) and 7.25 (d, 2H). Anal. calcd for $C_{12}H_{13}ClO_3$: C, 59.88; H, 5.44%. Found: C, 60.11; H, 5.53%.

1m: To a 100 ml round-bottomed flask equipped with a magnetic stirring bar was added 1.0 g (4.0 mmol) of ethyl 2-hydroxy-(4-nitrophenyl)butanoate **2m**, 40 ml of CH_2Cl_2 and 9.0 g (24.0 mmol) of pyridinium dichromate.[27,28] The reaction, under vigorous stirring at room temperature, was run for 3.5 days to reach near completion as gauged by TLC (R_f=0.45, hexane:EtOAc=3:1) to afford, after work-up and through silica gel column chromatography, ethyl 2-oxo-(4-nitrophenyl)butanoate **1m** in 34% yield. ^{1}H NMR (δ from TMS in $CDCl_3$): 1.29 (t, 3H, J=7.1 Hz), 2.81 (t, 2H, J=6.5 Hz), 3.38 (t, 2H, J=6.5 Hz), 4.18 (q, 2H, J=7.1 Hz), 8.14 (d, 2H, J=8.9 Hz) and 8.31 (d, 2H, J=8.9 Hz). Anal. calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58%. Found: C, 57.39; H, 5.28; N, 5.52%.

Methyl and ethyl benzoylformate were prepared by an acid catalyzed exchange reaction of benzoylformic acid (2.5 g, 16.7 mmol) with appropriate alcohols (15 ml) in near-quantitative yields after work-up (silica gel column, hexane:EtOAc=5:1, R_f=0.50 and 0.57, respectively). ^{1}H NMR spectra are identical to the authentic samples.

Ethyl phenylpyruvate was obtained in 40% yield by the Grignard reaction[25,26] with benzyl chloride (5.0 g, 39.5 mmol) and diethyl oxalate (5.2 g, 35.6 mmol). ^{1}H NMR (δ from TMS in $CDCl_3$): 1.36 (t, 3H, J=7.2 Hz), 4.34 (q, 2H, J=7.2 Hz), 6.45 (s, 1H), 7.21–7.42 (m, 4H) and 7.78 (d, 2H, J=7.3 Hz).

Ethyl 2-oxo-5-phenylpentanoate in 67% yield was prepared from 1-bromo-3-phenylpropane (6.0 g, 30.1 mmol) and diethyl oxalate (3.7 g, 25.3 mmol) in a similar manner. ^{1}H NMR (δ from TMS in $CDCl_3$): 1.29 (t, 3H, J=7.1 Hz), 1.92 (m, 2H), 2.59 (t, 2H, J=7.5 Hz), 2.81 (t, 2H, J=7.3 Hz), 4.25 (q, 2H, J=7.1 Hz) and 7.15 (m, 5H). Anal. calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32%. Found: C, 70.76; H, 7.40%.

3.4. Preparation of alkyl 2-hydroxy-4-arylbutanoates

As a typical run, ethyl 2-hydroxy-(4-fluorophenyl)butanoate, **2f**, was prepared in 76% yield by $NaBH_4$ reduction of **1f** in THF at 0°C under stirring for 4–6 h. ^1H NMR (δ from TMS in $CDCl_3$): 1.26 (t, 3H, J=7.2 Hz), 1.81–1.98 (m, 1H), 1.99–2.18 (m, 1H), 2.74 (t, 2H, J=7.2 Hz), 2.95 (bs, 1H), 4.15 (m, 1H), 4.21 (q, 2H, J=7.2 Hz), 6.96 (m, 2H), 7.15 (m, 2H): ^{19}F NMR (δ from Cl_3CF in $CDCl_3$): −117.6. Anal. calcd for $C_{12}H_{15}FO_3$: C, 63.71; H, 6.68%. Found: C, 63.75; H, 6.60%.

2g: ^1H NMR (δ from TMS in $CDCl_3$): 0.95 (t, 3H, J=7.2 Hz), 1.66 (m, 2H), 1.81–1.98 (m, 1H), 1.99–2.17 (m, 1H), 2.74 (m, 2H), 2.84 (bs, 1H), 4.13 (t, 2H, J=7.2 Hz), 4.16 (m, 1H), 6.96 (m, 2H) and 7.14 (m, 2H). Anal. calcd for $C_{13}H_{17}FO_3$: C, 64.99; H, 7.13%. Found: C, 65.04; H, 7.21%

2h: ^1H NMR (δ from TMS in $CDCl_3$): 0.95 (d, 6H, J=7.0 Hz), 1.83–1.98 (m, 2H), 1.99–2.18 (m, 1H), 2.74 (m, 2H), 2.87 (bs, 1H), 3.96 (d, 2H, J=7.0 Hz), 4.17 (m, 1H), 6.95 (m, 2H) and 7.15 (m, 2H). Anal. calcd for $C_{14}H_{19}FO_3$: C, 66.12; H, 7.53%. Found: C, 66.32; H, 7.58%.

All other phenyl substituted esters were prepared by methods similar to above in 56–85% yields.

2b: ^1H NMR (δ from TMS in $CDCl_3$): 1.29 (t, 3H, J=7.1 Hz), 1.81–1.98 (m, 1H), 1.99–2.16 (m, 1H), 2.32 (s, 3H), 2.75 (m, 2H), 2.91 (bs, 1H), 4.21 (m, 1H), 4.23 (q, 2H, J=7.1 Hz) and 7.13 (m, 4H). Anal. calcd for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16%. Found: C, 70.34; H, 8.25%.

2c: ^1H NMR (δ from TMS in $CDCl_3$): 1.27 (t, 3H, J=7.1 Hz), 1.83–1.98 (m, 1H), 1.99–2.19 (m, 1H), 2.31 (s, 3H), 2.73 (t, 2H, J=7.2 Hz), 2.91 (bs, 1H), 4.15 (m, 1H), 4.20 (q, 2H, J=7.1 Hz), 6.98 (m, 3H) and 7.15 (m, 1H). Anal. calcd for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16%. Found: C, 70.28; H, 8.18%.

2d: ^1H NMR (δ from TMS in $CDCl_3$): 1.29 (t, 3H, J=7.1 Hz), 1.81–1.98 (m, 1H), 1.99–2.23 (m, 1H), 2.31 (s, 3H), 2.74 (m, 2H), 2.83 (bs, 1H), 4.16 (m, 1H), 4.20 (q, 2H, J=7.1 Hz) and 7.10 (m, 4H). Anal. calcd for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16%. Found: C, 70.43; H, 8.17%.

2e: ^1H NMR (δ from TMS in $CDCl_3$): 1.29 (t, 3H, J=7.1 Hz), 1.81–1.98 (m, 1H), 1.99–2.18 (m, 1H), 2.70 (t, 2H, J=7.4 Hz), 2.85 (bs, 1H), 3.78 (s, 3H), 4.16 (m, 1H), 4.21 (q, 2H, J=7.1 Hz), 6.83 (d, 2H, J=8.6 Hz) and 7.11 (d, 2H, J=8.6 Hz). Anal. calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61%. Found: C, 65.74; H, 7.72%.

2i: ^1H NMR (δ from TMS in $CDCl_3$): 1.29 (t, 3H, J=7.1 Hz), 1.86–1.99 (m, 1H), 2.00–2.20 (m, 1H), 2.88 (t, 2H, J=7.9 Hz), 2.98 (bs, 1H), 4.20 (m, 1H), 4.21 (q, 2H, J=7.1 Hz) and 7.09–7.27 (m, 4H). Anal. calcd for $C_{12}H_{15}ClO_3$: C, 59.39; H, 6.23%. Found: C, 59.80; H, 6.27%.

2j: ^1H NMR (δ from TMS in $CDCl_3$): 1.30 (t, 3H, J=7.1 Hz), 1.83–1.99 (m, 1H), 2.00–2.19 (m, 1H), 2.74 (t, 2H, J=8.4 Hz), 2.96 (bs, 1H), 4.15 (m, 1H), 4.21 (q, 2H, J=7.1 Hz), 7.07 (m, 1H) and 7.19 (m, 3H). Anal. calcd for $C_{12}H_{15}ClO_3$: C, 59.39; H, 6.23%. Found: C, 59.58; H, 6.25%.

2k: ^1H NMR (δ from TMS in $CDCl_3$): 1.28 (t, 3H, J=7.2 Hz), 1.81–1.98 (m, 1H), 1.99–2.17 (m, 1H), 2.73 (t, 2H, J=6.8 Hz), 2.89 (bs, 1H), 4.13 (m, 1H), 4.20 (q, 2H, J=7.2 Hz), 7.12 (m, 2H) and 7.26 (m, 2H). Anal. calcd for $C_{12}H_{15}ClO_3$: C, 59.39; H, 6.23%. Found: C, 59.40; H, 6.27%.

2m: To a 200 ml round-bottomed flask fitted with a mechanical stirrer and a Dimroth condenser was added 50 ml of benzene, 10 g (48.0 mmol) of 4-(4-nitrophenyl)butyric acid, 0.6 ml (0.8 g, 5.82 mmol) of phosphorous trichloride and 2.5 ml (7.64 g, 48.0 mmol) of bromine. The resulting solution was refluxed for 1–2 days until the initial bromine color was discharged. At this stage the benzene was distilled off by replacing the condenser with a collecting side-arm. The removal of the solvent left a black oil which, on cooling to room temperature, was added slowly to 3 M NaOH (150 ml) under good stirring in an ice-bath. The reaction was run for 8–10 h at 0°C and then overnight at room temperature. The solution was transferred to a 500 ml conical flask and was acidified with slow addition of 2 M HCl at 0°C. Extraction with diethyl ether (5×50 ml) and usual work-up gave crude 2-hydroxy-4-(4-nitrophenyl)butyric acid

(R_f=0.10, eluent: hexane:EtOAc=1:2). ^{1}H NMR (δ from TMS in $CDCl_3$): 1.86–2.03 (m, 1H), 2.04–2.22 (m, 1H), 2.77–2.93 (m, 2H), 4.16 (bs, 1H), 7.35 (d, 2H, J=8.9 Hz) and 8.14 (d, 2H, J=8.9 Hz)

The product was difficult to purify by column chromatography on silica gel with several organic solvent mixtures as eluents or by recrystallization, due to contamination caused by the remaining α-bromo acid and 3-(4-nitrophenyl)propanol [^{1}H NMR (δ from TMS in $CDCl_3$): 2.02 (m, 2H), 2.40 (t, 2H, J=6.8 Hz), 2.89 (t, 2H, J=7.0 Hz), 7.35 (d, 2H, J=8.9 Hz) and 8.15 (d, 2H, J=8.9 Hz), R_f=0.25] formed by decarboxylation from 4-(4-nitrophenyl)butyric acid. Hence, acid catalyzed esterification of the crude α-hydroxy acid in 30–40 ml anhydrous ethanol afforded **2m** after usual work-up in 40% yield,[29,30] which was purified much more easily than the corresponding acid by column chromatography on silica gel with hexane:EtOAc=3:1 as the eluent (R_f=0.29). ^{1}H NMR (δ from TMS in $CDCl_3$): 1.31 (t, 3H, J=7.1 Hz), 1.88–2.05 (m, 1H), 2.05–2.24 (m, 1H), 2.78–2.95 (m, 2H), 4.17 (m, 1H), 4.18–4.30 (q, 2H, J=7.1 Hz), 7.37 (d, 2H, J=8.9 Hz) and 8.15 (d, 2H, J=8.9 Hz); mp: 60–62°C. Anal. calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53%. Found: C, 56.88; H, 5.98; N, 5.60%.

The methyl and ethyl mandelates were obtained commercially. Similarly, D- and L-ethyl phenyllactate were obtained from D- and L-phenyllactic acids, without racemization, in quantitative yields (hexane:EtOAc=5:1, R_f=0.35). ^{1}H NMR (δ from TMS in $CDCl_3$): 1.26 (t, 3H, J=7.2 Hz), 2.78 (bs, 1H), 2.94 (dd, 1H, J=13.8 Hz, J=6.8 Hz), 3.13 (dd, 1H, J=13.8 Hz, J=4.8 Hz), 4.21 (q, 2H, J=7.2 Hz), 4.43 (dd, 1H, J=6.8 Hz, J=4.8 Hz) and 7.25 (m, 5H).

Ethyl 5-phenyl-2-hydroxypentanoate was prepared by the reduction of the corresponding keto ester with $NaBH_4$, as mentioned above, in 82% yield after the work-up [silica gel column, hexane:EtOAc=5:1, 3:1 then 1:1, R_f (5:1)=0.40]. ^{1}H NMR (δ from TMS in $CDCl_3$): 1.21 (t, 3H, J=7.1 Hz), 1.60–1.88 (m, 4H), 2.58 (m, 2H), 2.74 (bs, 1H), 4.17 (m, 1H), 4.19 (q, 2H, J=7.1 Hz) and 7.18 (m, 5H). Anal. calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16%. Found: C, 70.02; H, 8.10%.

3.5. Acetylation of α-hydroxy ester

To a 50 ml round-bottomed flask equipped with a magnetic stirrer, was added 1.5 g (7.2 mmol) (*R*)-**2a**, 1.10 g (10.8 mmol) acetic anhydride, and 3–4 ml pyridine. The esterification was run for 5–6 h at room temperature, as checked by TLC (R_f=0.44, hexane:EtOAc=5:1 as an eluent). After usual work-up and purification of the product through silica gel column chromatography, the acetylated product **2a**-OAc was obtained in 94% yield. ^{1}H NMR (δ from TMS in $CDCl_3$): 1.26 (t, 3H, J=7.1 Hz), 2.15 (s, 3H), 2.09–2.21 (m, 2H), 2.74 (t, 2H, J=7.3 Hz), 4.19 (q, 2H, J=7.1 Hz), 4.98 (t, 1H, J=6.5 Hz) and 7.13–7.28 (m, 5H).

In a similar procedure, other hydroxy esters were also esterified in 86–95% yields.

2c-OAc: ^{1}H NMR (δ from TMS in $CDCl_3$): 1.26 (t, 3H, J=7.1 Hz), 2.10–2.22 (m, 2H), 2.15 (s, 3H), 2.31 (s, 3H), 2.72 (t, 2H, J=7.2 Hz), 4.19 (q, 2H, J=7.1 Hz), 4.99 (t, 1H, J=6.4 Hz), 6.98 (d, 3H) and 7.15 (m, 1H).

2e-OAc: ^{1}H NMR (δ from TMS in $CDCl_3$): 1.28 (t, 3H, J=7.1 Hz), 2.08–2.19 (m, 2H), 2.14 (s, 3H), 2.82 (t, 2H, J=8.1 Hz), 3.78 (s, 3H), 4.20 (q, 2H, J=7.1 Hz), 4.98 (t, 1H, J=6.3 Hz), 6.82 (d, 2H, J=8.6 Hz) and 7.11 (d, 2H, J=8.6 Hz).

2f-OAc: ^{1}H NMR (δ from TMS in $CDCl_3$): 1.27 (t, 3H, J=7.2 Hz), 2.05–2.18 (m, 2H), 2.16 (s, 3H), 2.70 (t, 2H, J=7.3 Hz), 4.19 (q, 2H, J=7.2 Hz), 4.95 (t, 1H, J=6.4 Hz), 6.95 (m, 2H) and 7.13 (m, 2H).

2m-OAc: ^{1}H NMR (δ from TMS in $CDCl_3$): 1.30 (t, 3H, J=7.1 Hz), 2.10–2.21 (m, 2H), 2.16 (s, 3H), 2.87 (m, 2H), 4.22 (q, 2H, J=7.1 Hz), 5.01 (t, 1H, J=6.3 Hz), 7.38 (d, 2H, J=8.9 Hz) and 8.15 (d, 2H, J=8.9 Hz).

3.6. Oxidation of phenyl group to carboxylic acid with ruthenium tetroxide

To a 100 ml round-bottomed flask equipped with a magnetic stirrer, was added **2a**-OAc (0.5 g, 2.0 mmol), carbon tetrachloride (7 ml), acetonitrile (7 ml), water (10.5 ml) and sodium periodate (3.1 g, 14.5 mmol). The contents of the flask were stirred at room temperature until both phases became clear. To the flask, either ruthenium(III) chloride or ruthenium(II) oxide (2.2 mol%) was added and stirring was continued until no aromatic compound could be detected by TLC or HPLC. Normally, the reaction required about 2–3 h depending on the stirring rate. The reaction mixture was then cooled to 0°C with an ice-bath, and CH_2Cl_2 (15 ml) was added with vigorous stirring for 10 min. A deep black color appeared at this moment. The mixture was then transferred to a 100 ml separating funnel and the organic phase was separated. The aqueous layer was then extracted with CH_2Cl_2 (3×15 ml). The combined organic layers were washed with brine (2×10 ml), dried with anhydrous $MgSO_4$, filtered, and concentrated to give crude monoethyl α-acetoxy glutarate,[33–36] which was then esterified to the corresponding diethyl ester **3** followed by immediate deacetylation to give **4** as a brownish orange oil in 57–94% chemical yield before purification by column chromatography on silica gel with hexane:EtOAc=5:1 as an eluent.

4: ^{1}H NMR (δ from TMS in $CDCl_3$): 1.20–1.41 (m, 6H), 1.82–2.02 (m, 1H), 2.09–2.28 (m, 1H), 2.43–2.52 (m, 2H), 2.95–3.06 (bs, 1H), 4.08–4.38 (m, 4H) and 4.21–4.41 (m, 1H). IR (cm^{-1}, CCl_4): ν 3495 (broad, O–H), 2939 (C–H), 1738 (C=O) and 1216 (C–O). Anal. calcd for $C_9H_{16}O_5$: C, 52.93; H, 7.90%. Found: C, 52.94; H, 7.91%.

For ease of detection on HPLC (Chiralcel OD 25+5), the α-hydroxy group of **3** (50 mg, 0.25 mmol) was esterified by *p*-nitrobenzoic acid (ca. 50 mg, 0.29 mmol) in refluxing diethyl ether for 30 min. The product **4**, obtained in 70–90% chemical yield, was subjected to column chromatography on silica gel with hexane:EtOAc=3:1 as an eluent (R_f=0.36). ^{1}H NMR (δ from TMS in $CDCl_3$): 1.20–1.41 (m, 6H), 1.81–1.99 (m, 1H), 2.00–2.28 (m, 1H), 2.62–2.78 (m, 2H), 4.09–4.40 (m, 5H), 6.96 (m, 2H) and 7.14 (m, 2H). Anal. calcd for $C_{16}H_{19}NO_8$: C, 54.39; H, 5.42; N, 3.96%. Found; C, 54.46; H, 5.45; N, 3.91%. Retention times of (*R*)- and (*S*)-**4** were 20.50 and 17.06 min, respectively. Both **3** and **4** were cyclized to lactone **5** by either standing in pyridine for 2–3 days or gentle refluxing for 1–2 h in ethyl alcohol (5 ml) with a catalytic amount of *p*-toluenesulfonic acid monohydrate. Pure lactone **5** was obtained in 76–90% chemical yield after column chromatography on silica gel with hexane:EtOAc=1:1 as an eluent (R_f=0.50).

^{1}H NMR (δ from TMS in $CDCl_3$): 1.30 (t, 3H, J=7.1 Hz), 2.20–2.44 (m, 1H), 2.48–2.70 (m, 1H), 2.53–2.60 (d, 2H, J=6.3 Hz), 4.26 (q, 2H, J=7.1 Hz) and 4.95 (m, 1H). IR (cm^{-1}, CCl_4): ν 3000 (C–H), 1780 (C=O) and 1769 (C=O). Anal. calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37%. Found: C, 53.14; H, 6.45%.

For chlorinated hydroxy esters **2i, j** and **k**, the following procedure was employed. To a 30 ml dried two-necked round-bottomed flask fitted with a magnetic stirrer were added 50 mg of Pd/C and 0.2 g NaOH which was dissolved in 2.0 ml ethanol, and the solution was cooled to room temperature. Then, about 200 mg (0.83 mmol) of either **2i**, **2j** or **2k** in 1.0 ml ethanol was added to the mixture. The flask was then flushed with hydrogen to displace the inside air and was stirred under a hydrogen atmosphere at room temperature. The reaction was gauged with TLC until most of the chloro derivative was converted into **2a**.[31,32] The product, obtained in 42–57% chemical yield, was then checked by TLC and optical rotation, and compared to the results obtained from the known (*R*)-(−)-**2a**.

3.7. Reduction of α-keto esters to α-hydroxy esters by baker's yeast

The procedure was essentially the same as described previously.[13] To a 25×150 mm glass tube, fitted with a Teflon® cap, containing 1.0 g of baker's yeast, 10 ml of diethyl ether or a mixture of diethyl

ether and an appropriate amount of water, was added ethyl 2-oxo-4-phenylbutanoate (**1a**; 12 mg, 0.058 mmol). The mixture was agitated at 130 rpm at 30°C for 24 h. The organic portions were then collected by filtration and the yeast was washed with either ethyl acetate or diethyl ether (4×10 ml) and the extracts were combined with the filtrate. The combined organic portions were concentrated under reduced pressure. The residue was subjected to Extrelut and silica gel to remove involatile materials prior to gas chromatographic analysis using an HR-20M column for the measurement of chemical yield, and a CP-cyclodextrin column for determination of enantiomeric excess.

The chemical yield of the product and the amount of the starting material remaining were evaluated by comparing the signal area of the product to that of the starting material under the standard conditions. No other product was detected on VPC/HPLC. Whenever necessary, preincubation and reaction times were changed appropriately.

It was also found that the addition of an appropriate amount of phenacyl chloride to the preincubation system is effective at improving the enantiomeric excess of the product. For measuring the effect of the stereocontroller, the microbe was preincubated in the presence of an appropriate amount of the reagent. The efficiency of the third reagent was tested under the g/l unit, instead of using the mole unit, for expressing the amount of the reagent added to the reaction system, because the former unit seems more practical for synthetic purpose than the latter.

3.8. Medium-scale reduction of some keto esters

To a 500 ml three-necked flask containing 240 ml of diethyl ether and 12 ml of water, fitted with a mechanical stirrer, a thermometer and a reflux condenser, was added 130 mg phenacyl chloride and 22 g of baker's yeast. The mixture was preincubated for either 6 or 10 h at 30°C with an agitation rate of 130 rpm. Then, 250 mg of either **1c**, **e** or **f** was added and the reduction was allowed to proceed for 24 h. The organic portion was separated by filtration from the yeast and the yeast was washed with ethyl acetate (4×60 ml). The washings were combined with the filtrate and the combined solution was concentrated in vacuo to give an odorous yellow viscous residue. The residue was subsequently washed with water (3×5 ml), then brine (2×5 ml) and dried over $MgSO_4$ before it was subjected to Extrelut® to remove yeast materials. It was then purified by column chromatography on silica gel with hexane:EtOAc=5:1 or 3:1 as an eluent. Chemical yields and enantiomeric excesses are listed in Table 3.

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