Tetrahedron: Asymmetry 25 (2014) 340-347

Contents lists available at ScienceDirect

Tetrahedron: Asymmetry

journal homepage: www.elsevier.com/locate/tetasy

Synthesis of new chiral keto alcohols by baker's yeast

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ARTICLE INFO

Article history: Received 20 November 2013 Accepted 14 January 2014

ABSTRACT

Fourteen chiral α - and β -keto alcohols **2a–2r** were synthesized by the asymmetric reduction of their corresponding diketones **1a–1r** via baker's yeast. In addition, ten corresponding racemic α -keto alcohols were synthesized by the benzoin condensation of their corresponding aldehydes, which were used for the determination of the ee values through their chiral resolution on chiral HPLC. Amongst the 15 diketones, **1j** and chiral α -keto alcohols **2i**, **2j** and chiral β -keto alcohol **2r** are novel compounds. Six keto alcohols **2b**, **2c**, **2d**, **2f**, **2h** and **2p** were synthesized by baker's yeast for the first time. There are some studies in the literature where baker's yeast was applied to the diketones **1a**, **1g**, **1e**, **1k** and **1n** under various conditions different to those reported herein. The yields and the ee values of these studies were not as high as ours. All of the keto alcohols synthesized were characterized by IR, NMR (¹H and ¹³C), and MS. The relationship between the structure of the diketone and the yield, diastereoselectivity and enantiomeric excess is also discussed.

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1. Introduction

The asymmetric reduction of carbonyl substrates by biocatalysis is a useful preparative method to obtain chiral compounds, which are necessary for the preparation of natural products and pharmaceuticals.¹ Enzymes are interesting natural bioreactives and biocatalysts in stereoselective reactions.²

Baker's yeast (*Saccharomyces cerevisiae*) is the most frequently used ketoreductase in green chemistry due to its bioavailability, feasibility and inexpensive reaction conditions.^{3,4} 1-Phenyl-1, 2-propanedione can be reduced by thermal pre-heated baker's yeast to its monohydroxypropanone with high enantiomeric excess.⁵ 1-Chloro-2,4-alkanediones react with baker's yeast both regio- and enantioselectively.⁶

Herein we report on the asymmetric synthesis of new chiral α - and β -keto alcohols with different structures via enzymatic baker's yeast reduction of their corresponding diketones that was aimed to be studied in this work; since chiral keto alcohols are valuable building blocks for many applications, pharmaceuticals, flavours, fragrances⁷ and natural products.⁸ α -Hydroxy ketones are found in some antidepressants, Alzheimer's treatment medicals, in antifungal agents and in antitumor antibiotics (epothilones).^{9,10} β -Hydroxy ketones are also synthons for the preparation of various natural compounds such as prelactone V¹¹ and amphidinolides O and P¹² (Scheme 1).

According to the literature, there are only a few studies on the reduction of diketones by baker's yeast, these do not involve satisfying optimizations of the reaction conditions and the structure of the substrates. For this reason fourteen α - and β -keto alcohols were synthesized with high yields and with high ee values.

2. Results and discussion

It was assumed that the asymmetric reduction of diketones with baker's yeast might provide the desired enantiomerically pure keto alcohols. However, the lack of literature on the asymmetric reduction of α - and β -diketones encouraged us to synthesize a series of 15 different chiral α - and β -hydroxy ketones **2a–2r**, and to screen them for enantioselective and regioselective reduction with baker's yeast.

The advantages of some important information on baker's yeast were used.^{13–15} Herein we found that there were many factors that affected the reducibility of baker's yeast reactions. The most important factors were organic solvents, pH, cosubstrates, heating and inhibitors. Benzil 1a was used with different baker's yeast reducing methods in order to determine the best conditions. The first method included a phosphate buffer (pH 7), glucose as the energy source, ethanol as the solvent and heat treatment was carried out.⁵ The second method involved the use of *n*-hexane as organic solvent in diverse organic-water solvent systems. In the third method, glucose was again the energy source and water was used as the solvent at 30 °C. Allyl alcohol was the inhibitor in hexane-Et₂O mixtures with water (Table 1). The use of inhibitor was successful in some cases. Utaka et al.¹⁶ obtained (S)-product with 94% ee, by incubating the yeast suspension with allyl alcohol in the addition of 1-chloro-2.4-alkanediones and glucose, compared to an ee of 47% without the inhibitor.





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Scheme 1. Examples of some chiral synthons bearing α - and β -hydroxy ketones.

Table 1

The reduction of benzil with baker's yeast using different methods



Entry	Heat treatment T (°C)/time (min)	Buffer	Reduction time (h)	Allyl alcohols (mL)	Org. solvent	Conv. (%)	ee (%)	Config.
1	53/60	pH 7	48	_	EtOH	38	5	(<i>S</i>)
2	30-40/30	pH 7	24	-	n-Hexane	53	5	(<i>S</i>)
3	30/30	_	48	-	_	46	27	(<i>R</i>)
4	50/30	_	3	0.1	n-Hexane-Et ₂ O	72	74	(R)
5	50/30	_	3	0.15	n-Hexane-Et ₂ O	43	52	(<i>R</i>)
6	50/30	-	3	0.2	n-Hexane-Et ₂ O	40	48	(<i>R</i>)

Table 2

Effects of sugars in the baker's y	/east reduction of benzil 1a
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Entry	Cosubstrate (g)	Conv. (%)	ee (%)	Config.
1	Glucose (2)	72	74	(R)
2	Galactose (2)	68	54	(<i>R</i>)
3	Xylose (2)	55	22	(<i>R</i>)
4	(−)-1,2:5,6-Di-O-isopropyliden-α-D- glucofuranose (2)	54	66	(<i>R</i>)
5	1,2:3,4-Di-O-isopropyliden-α-D- galactopyranose (2)	40	26	(<i>R</i>)
6	Maltose (2)	73	48	(<i>R</i>)
7	Tartaric acid (2)	0	_	_
8	Succinic acid (2)	0	_	_
9	Glucose (1.5) + tartaric acid (0.5)	85	73	(<i>R</i>)
10	Glucose (1) + tartaric acid (1)	82	66	(<i>R</i>)
11	Glucose (1.5) + succinic acid (0.5)	56	22	(<i>R</i>)

Substrate 0.5 mmol, dry baker's yeast 2 g, water 38 mL, heat treatment at 50 °C for 30 min, alyl alcohol 0.1 mL, *n*-hexane–Et₂O (1:1) 0.5 mL, 3 h.

Amongst these experiments, we observed that the highest ee and yield values were obtained with heat treatment, allyl alcohol (0.1 mL) and *n*-hexane/Et₂O mixture (1:1) as the organic solvent (Table 1, entry 4). The results showed that in the presence of an allyl alcohol, chiral benzoin **2a** was recovered in 40–68% conversion with an ee ranging from 5% to 74%. Moreover the reduction time was decreased from 24 to 3 h.

Table 3				
Effects of org	ganic solvents	in the	BY reduction	of benzil 1a

Entry	Organic solvent	Conv. (%)	ee (%)	Config.
1	Toluene	57	48	(<i>R</i>)
2	Tetrahydrofurane	8	36	(<i>R</i>)
3	n-Pentane	26	24	(<i>R</i>)
4	Dichloromethane	87	12	(S)
5	<i>n</i> -Hexane + Et ₂ O (1:1)	72	74	(<i>R</i>)
6	n-Hexane + EtOAc (1:1)	90	70	(<i>R</i>)
7	<i>n</i> -Heptane + Et ₂ O (1:1)	94	74	(<i>R</i>)
8	<i>n</i> -Heptane + EtOAc (1:1)	93	78	(<i>R</i>)
9	n-Hexadecane + EtOAc (1:1)	45	52	(<i>R</i>)
10	n-Dodecane + EtOAc (1:1)	27	56	(<i>R</i>)

Substrate 0.5 mmol, dry baker's yeast 2 g, water 38 mL, glucose 2 g, heat treatment at 50 $^\circ$ C for 30 min, allyl alcohol 0.1 mL, organic solvent 0.5 mL, 3 h.

In these experiments, screening of several sugars and sugar derivatives as energy sources was investigated (Table 2). In baker's yeast, carbohydrate derivatives such as glucose, fructose, mannose, etc. and also tartaric acid, succinic acid, lactic acid were used as energy sources in the incubation process. Amongst these sugars and mixtures, the highest conversion was found in a mixture where 1.5 g glucose and 0.5 g tartaric acid were used (Table 2, entry 10). However, the ee value was found to be similar when no tartaric acid was used (Table 2, entries 1 and 10), and thus, only glucose was used for the rest of these reactions.

Table 4

The results of enantioselective reduction of aromatic α - and β -diketones by baker's yeast

Entry	Substrate	Product	Yield ^a (%)	ee ^b (%)	Config. ^c
1			85	78	(R)
2			65	98	(R)
3			44	52	(R)
4			62	53	(<i>R</i>)
5			76	84	(R)
6			55	78	(<i>R</i>)
7			57	62	(R)
8			60	72	(R)
9			45	64	(R)
10	0 (CH ₂) ₁₁ CH ₃	OH (CH ₂) ₁₁ CH ₃	65	50	(R)
11			50	100	(R)

Table 4 (continue)	ued)
Fntry	Substrate

Entry	Substrate	Product	Yield ^a (%)	ee ^b (%)	Config. ^c
12		No reaction	-	_	_
13			45	100	(R)
14			62	100 (dr = 100:0) ^d	(1 <i>S</i> ,2 <i>R</i>)
15			74	100 (dr = 3:1) ^d	(1 <i>S</i> ,2 <i>R</i>)

^a Isolated yield of products.

^b The ees were determined by HPLC analysis using literature data and racemic compounds as references.

^c The absolute configuration of the products was assigned by comparing the literature values of the compounds. The absolute configurations of **2i**, **2j**, **2k**, **2p** and **2r** were attributed to have an (*R*)-configuration because they have similar structures with others.

^d The drs were determined by ¹H NMR.

One of the most important factors that limits the benefit of the system in the reductions with baker's yeast is the requirement of an aqueous reaction medium for water-insoluble substances.¹⁷ The water solubility of diketones is very low and they are toxic for baker's yeast whole cells. By using an organic solvent, significantly better enantioselectivity, yield, as well as regioselectivity and chemoselectivity can be obtained.¹⁸

As shown in Table 3, several organic solvents considerably enhanced the enantiomeric excess in favour of the (R)-configuration. The mixtures of a nonpolar solvent such as hexane and heptane and a polar solvent such as ethyl acetate and diethyl ether were more effective than other solvents. The effect of a small amount of organic solvent mixture was important under the conditions of heat-treatment with allyl alcohol, and an (R)-configuration was obtained with 78% ee when using a mixture of n-heptane and ethyl acetate (1:1) (Table 3, entry 8).

The optimal reaction conditions obtained for benzil 1a with baker's yeast were applied to the enantioselective reductions of the α - and β -diketones **1a**–**1r** (Table 4). Ten 1,2-diketones **1b**–**1h** were synthesized from readily available, inexpensive starting materials in two steps through benzoin condensation¹⁹ of their aldehyde derivatives as the first step and oxidation of the benzoin derivatives to diketones.²⁰ Compound **1j** was prepared by a different route; by oxidation of its alkene derivative.²¹ Compounds **1a** and 1k were commercially available 1,2-diketones. The four purchased 1,3-diketones 1m-1r of different structures were reduced to their corresponding keto alcohols 2m-2r by baker's yeast. Except for 1a, 1e, 1g, 1k and 1n, all of the other diketones were reduced to their corresponding keto alcohols using baker's yeast for the first time. From the chiral keto alcohols synthesized, **2a**,¹⁸ **2e**,¹⁸ $2g_{18}^{18}$ $2k^{22}$ and $2n^{23,24}$ were obtained by other baker's yeast procedures.

The ee values and the diastereomeric ratios of the aforementioned chiral keto alcohols were determined by chiral HPLC and were analysed by IR, NMR (¹H and ¹³C) and MS. The configurations of the keto alcohols, except for **2i**, **2j**, **2k**, **2p** and **2r**, were considered according to the data in the literature^{18–24} and were assigned as having an (*R*)-configuration. Baker's yeast gave alcohols with an (*R*)-configuration, which was in agreement with the conditions herein. Therefore, the other keto alcohols reported herein were attributed to have an (R)-configuration due to their similar structures.

The results of the baker's yeast reduction of diketones **1a–1r** are summarized in Table 4. The diketones in the form of benzil, showed enantioselectivities between 50% and 98% and always provided new stereogenic centres with (R)-configurations. The highest ee value was found for (R)-**2b** (ee = 98%).

The other α -diketone **1k** (acenaphthene quinone) which had a different structure from benzil, showed an excellent enantiomeric excess close to 100%. Compound **2k** was obtained by a different baker's yeast procedure,²² although with only 23% ee.

New chiral α -keto alcohols **2i** and **2j** have been synthesized for the first time in this study. They bear different groups on both sides. **2i** has Ph and 5-Me-furyl groups; and **2j** includes *p*-MeOC₆₋ H₅ and *n*-C₁₂H₂₅ as substituents. After bioreduction of these compounds, one of the keto groups was always reduced by baker's yeast. The steric hindrance of electron flow was found to be effective on this reduction.

In the bioreduction of the β -diketones **1n**, **1p** and **1r**, excellent regioselectivity and enantioselectivity except for 1,3-diphenyl **1m** were observed. While nearly 100% ee for **2n**, **2p** and **2r** were found, no reaction was observed for **1m**. Compound **1m** is resistant against bioreduction due to its very stable structure. Compounds **1n**, **1p** and **1r** all have nearly the same skeleton (Scheme 2).

According to the experimental results obtained in this study, only one of the both carbonyl groups is reduced by baker's yeast. In the presence of the inhibitor allyl alcohol, the bioreduction showed only *R*-selectivity. Bioreduction of 1-phenyl-1,3-butadione (**1n**) with baker's yeast previously furnished the (*S*)-enantiomer



Scheme 2. The structures of 1n, 1p and 1r.



Scheme 3. The HPLC chromatograms of racemic and enantiomerically enriched 2e as an example of α -keto alcohol.



Scheme 4. The HPLC chromatograms of racemic and enantiomerically enriched 2n as an example of β -keto alcohol.

with 77% enantiopurity.²⁴ The other β -keto alcohols **2p** and **2r** were synthesized for the first time by baker's yeast reduction.

The absolute configuration of the keto alcohols was determined by using literature data and their retention times on HPLC were compared (Schemes 3 and 4). The (R)-configuration was confirmed by these analyses. However, keto alcohols **2i**, **2j**, **2k**, **2p** and **2r**, which have no literature data were determined to have an (R) configuration by comparing the results from the rest of the findings in this work.

3. Conclusion

The enantioselectivity of the synthesized keto alcohols 2a-2r (Table 4) was controlled by the additives of an enzyme inhibitor, heat treatment and small amounts of organic solvent. The used organic solvent and inhibitor play a role in solubilizing and enhancing the substrate concentration in favour of the (*R*)-selectivity.

Bioreduction by dry baker's yeast presents an excellent example of natural, efficient, green, low energy and compatible multistep synthesis. In addition, water is the solvent of choice for many of the bio-transformations. The economic and easy to handle baker's yeast can be the reagent of choice for biotransformations with high stereoselectivities. We have shown herein that the baker's yeast reduction is a very effective, environmentally sensitive and inexpensive method, especially for synthesizing chiral α - and β -keto alcohols.

4. Experimental

4.1. General

The majority of the chemicals used herein were commercially available from Merck or Aldrich. Commercial baker's yeast, *S.*

cerevisiae as an active and dry solid form was purchased by Sigma (Cat. No: YSC2-500G). α-Diketone 1j were obtained from oxidation of the corresponding alkene using KMnO₄ and a phase transfer agent.²⁵ The racemic α -keto alcohols were prepared via benzoin condensation of the corresponding aldehydes with KCN in ethanol-H₂O. The other α -diketones were synthesized by oxidation of the corresponding racemic keto alcohols using I₂/K₂CO₃ in *t*-BuOH.²³ The racemic β-keto alcohols were prepared by controlled reduction with NaBH₄. Their resolution on chiral HPLC was used for determining the ee values of the chiral β-keto alcohols. The reactions were monitored by TLC using silica gel plates and the products were purified by flash column chromatography on silica gel (Merck; 230-400 mesh) with hexane-ethyl acetate. NMR spectra were recorded at 500 MHz for ¹H and at 125 MHz for ¹³C using Me₄Si as the internal standard in CDCl₃. GC–MS were recorded on Shimadzu/QP2010 Plus. Optical rotations were measured with an Optical Activity AA-55 digital polarimeter at room temperature. IR spectra were recorded on Mattson 1000. Melting points were determined with Buchi melting point B-540. The enantiomeric excesses (ee) of the product chiral alcohols were determined with Shimadzu/DGU-20A₅ HPLC apparatus fitted with a 25 cm Chiralcel OD, Chiralcel OD-H and Chiralpac AD-H chiral columns.

4.2. General procedure using heat-treated baker's yeast with an inhibitor and a small amount of organic solvent

A mixture of dry baker's yeast (2 g), water (38 mL), glucose (2 g) and allyl alcohol (0.1 mL) was stirred at 50 °C for 30 min. After the mixture was cooled to 30 °C, the substrate (0.05 mmol) dissolved in 0.5 mL of organic solvent was added and the reaction was continued to stir at 30 °C for 3 h. The work-up procedure was essentially the same as that described in the foregoing experiment.

4.3. Data for starting diketones synthesized

4.3.1. 1,2-Bis(2-methylphenyl)-1,2-ethanedione 1b²⁶

90% Yield (oily liquid). IR (neat, cm⁻¹): 3061, 2961, 2923, 1676, 1607, 1461, 1269, 1200, 1130, 884, 746 cm⁻¹. ¹H NMR (CDCl₃): δ 2.57 (s, 6H), 7.20 (m, 2H), 7.28 (m, 2H), 7.43 (m, 2H), 7.60 (m, 2H). MS *m/z*: 41, 51, 65, 77, 89, 91, 102, 119, 120, 165, 193, 207, 220, 238 (M⁺).

4.3.2. 1,2-Bis(3-methylphenyl)-1,2-ethanedione 1c²⁶

Mp 102.4–103.4 °C, 95% yield (oily liquid). IR (neat, cm⁻¹): 3038, 2923, 2861, 1669, 1600, 1476, 1515, 1253, 1153, 730 cm⁻¹. ¹H NMR (CDCl₃): δ 2.33 (s, 6H), 7.32 (m, 2H), 7.40 (m, 2H), 7.68 (m, 4H). MS *m*/*z*: 41, 65, 75, 89, 91, 105, 119, 128, 238 (M⁺).

4.3.3. 1,2-Bis(2-methoxyphenyl)-1,2-ethanedione 1d²⁶

Mp 118.2–120 °C, 88% yield. IR (neat, cm⁻¹): 3048, 2938, 2838, 1669, 1600, 1492, 1292, 1281, 1187, 1023, 761 cm⁻¹. ¹H NMR (CDCl₃): δ 3.49 (s, 6H), 6.86 (m, 2H), 7.02 (m, 2H), 7.45 (m, 2H), 8.02 (d, 2H, *J* = 7.8 Hz). MS *m*/*z*: 44, 51, 64, 77, 92, 105, 120, 135, 207, 270 (M⁺).

4.3.4. 1,2-Bis(4-methoxyphenyl)-1,2-ethanedione 1e²⁶

Mp 131.4–132.2 °C, 89% yield. IR (neat, cm⁻¹): 3048, 2923, 2853, 1661, 1600, 1515, 1438, 1269, 1169, 1023, 838 cm⁻¹. ¹H NMR (CDCl₃): δ 3.81 (s, 6H), 6.89 (dd, 4H, J_1 = 1.9 Hz, J_2 = 6.8 Hz), 7.86 (dd, 4H, J_1 = 1.9, Hz, J_2 = 6.8 Hz). MS m/z: 44, 50, 64, 77, 92, 107, 135, 207, 270 (M⁺).

4.3.5. 1-(2-Methylphenyl)-2-phenyl-1,2-ethanedione 1f²⁷

30% Yield (oily liquid). IR (neat, cm⁻¹): 3076, 2976, 2938, 1676, 1600, 1453, 1207, 884, 730 cm⁻¹. ¹H NMR (CDCl₃): δ 2.60 (s, 3H), 7.20 (m, 2H), 7.28 (d, 1H, *J* = 8.3 Hz), 7.45 (m, 3H), 7.55 (m, 2H), 7.91 (ddd, 1H, *J*₁ = 1.5 Hz, *J*₂ = 1.9 Hz, *J*₃ = 6.8 Hz). MS *m*/*z*: 41, 51, 65, 77, 91, 105, 119, 128, 139, 152, 178, 208, 224 (M⁺).

4.3.6. 1,2-Di-2-furanyl-1,2-ethanedione 1g²⁸

Mp 163–165 °C, 850% yield. IR (neat, cm⁻¹): 3069, 2976, 2938, 1676, 1600, 1453, 1284, 1184, 1038, 869, 769 cm⁻¹. ¹H NMR (CDCl₃): δ 6.58 (dd, 2H, J_1 = 1.4 Hz, J_2 = 3.9 Hz), 7.58 (d, 2H, J = 3.9 Hz), 7.72 (d, 2H, J = 1.4 Hz). MS m/z: 40, 51, 62, 67, 78, 95, 105, 134, 162, 176, 190 (M⁺).

4.3.7. 1,2-Bis(5-methyl-2-furanyl)-1,2-ethanedione 1h²⁹

Mp 164–167 °C, 90% yield. IR (neat, cm⁻¹): 3069, 2923, 2938, 1638, 1507, 1453, 1284, 1184, 1038, 815, 769 cm⁻¹. ¹H NMR (CDCl₃): δ 2.40 (s, 2H), 6.18 (dd, 2H, J_1 = 0.9 Hz, J_2 = 3.4 Hz), 7.45 (d, 2H, J = 2.9 Hz). ¹³C NMR (CDCl₃): δ 13.25, 109.13, 125.74, 147.61, 160.24, 175.68. MS *m/z*: 43, 51, 63, 75, 93, 107, 115, 128, 143, 156, 170, 184, 213, 216 (M⁺).

4.3.8. 1-(5-Methyl-furan2-yl)-2-phenyl-ethane-1,2-dione 1i³⁰

Mp 61.2–62.4 °C, 65% yield. IR (neat, cm⁻¹): 3082, 2953, 2860, 1715, 1700, 1607, 1456, 1407, 1302, 1153, 1078, 708, 698 cm⁻¹. ¹H NMR (CDCl₃): δ 2.17 (s, 3H), 6.19 (d, 1H, *J* = 3.4 Hz), 7.11 (d, 1H, *J* = 3.4 Hz), 7.45 (m, 2H), 7.54 (m, 1H), 7.81 (m, 2H). ¹³C NMR (CDCl₃): δ 14.7, 108.4, 108.4, 122.3, 129, 129.7, 134.3, 136.7, 151.4, 157.9, 185, 190.6. MS *m*/*z*: 43, 51, 77, 97, 105, 109, 115, 128, 143, 157, 170, 186, 200, 214, 216 (M⁺).

4.3.9. 1-(4-Methoxyphenyl)-1,2-tetradecanedione 1j²⁵

Mp 35.4–36.7 °C, 20% yield. IR (neat, cm⁻¹): 3038, 2923, 2861, 1715, 1669, 1615, 1469, 1438, 1323, 1269, 1184, 869, 723 cm⁻¹. ¹H NMR (CDCl₃): δ 0.80 (t, 3H, *J* = 7.3 Hz), 1.10–1.70 (m, 22H), 2.78 (t, 2H, *J* = 7.8 Hz), 3.8 (s, 3H), 6.9 (d, 2H, *J* = 9.2 Hz), 7.9 (d, 2H, *J* = 9.2 Hz). ¹³C NMR (CDCl₃): δ 13.96, 22.44, 24.57, 26.85,

28.02–29.63, 37.51, 55.30, 130.00, 131.40, 162.94, 190.71, 202.78. MS m/z: 41, 57, 77, 97, 107, 108, 122, 136, 145, 164, 223, 226, 302, 318, 332 (M⁺). Anal. Calcd for C₂₁H₃₂O₃: C, 75.86; H, 9.70. Found: C, 75.30; H, 10.01.

4.4. Spectroscopic data of the chiral keto alcohols synthesized

4.4.1. (R)-2-Hydroxy-1,2-diphenyl ethanone 2a³¹

Mp 135.4–136.7 °C, $[\alpha]_D^{25} = -81.5$ (*c* 0.27, CH₃COCH₃), {lit.³¹ $[\alpha]_D^{25} = -114$ (*c* 1.5, CH₃COCH₃) for 99% ee, (*R*)-enantiomer}, ee = 78%. HPLC analysis: Chiralcel OD chiral column, mobile phase *iso*-PrOH/hexane: 10:90, flow rate: 1.0 mL/min, wavelength: 210 nm; t_R (retention time): 11.03 min for (*S*)-isomer, 18.87 min for (*R*)-isomer. IR (neat, cm⁻¹): 3415, 3038, 2923, 2853, 1676, 1461, 1438, 1384, 1269, 1092, 753, 700 cm⁻¹. ¹H NMR (CDCl₃): δ 4.45 (br s, 1H), 5.88 (s, 1H), 7.20 (m, 2H), 7.25 (m, 4H), 7.35 (m, 2H), 7.46 (m, 1H), 7.82 (dd, 1H, $J_1 = 8.7$ Hz, $J_2 = 1.5$ Hz).

4.4.2. (R)-2-Hydroxy-1,2-bis(2-methylphenyl)ethanone 2b³¹

Mp 76.4–77.7 °C, $[\alpha]_D^{25} = -112$ (*c* 0.08, CH₃OH) {lit.³¹ $[\alpha]_D^{25} = +47.5$ (*c* 0.5, CH₃OH) for 41% ee, (*S*)-enantiomer}, ee = 98%. HPLC analysis: Chiralcel OD chiral column, mobile phase *iso*-PrOH/hexane: 10:90, flow rate: 1.0 mL/min, wavelength: 210 nm; *t*_R (retention time): 11.59 min for (*S*)-isomer, 13.75 min for (*R*)-isomer. IR (neat, cm⁻¹): 3469, 3061, 2961, 1676, 1607, 1515, 1453, 1392, 1287, 1176, 1084, 738 cm⁻¹. ¹H NMR (CDCl₃): δ 1.18 (s, 1H), 2.63 (s, 6H), 5.95 (s, 1H), 7.18–7.22 (m, 4H), 7.40–7.62 (m, 4H). ¹³C NMR (CDCl₃): δ 20.19, 73.88, 124.82, 124.99, 130.48, 130.88, 131.58, 132.03, 132.59, 140.53, 195.89. MS *m/z*: 41, 51, 65, 77, 89, 91, 119, 128, 152, 165, 178, 206, 224, 238 (M⁺).

4.4.3. (R)-2-Hydroxy-1,2-bis(3-methylphenyl)ethanone 2c³¹

 $[\alpha]_D^{25} = -51$ (*c* 0.14, CH₃OH) {lit.³¹ [α]_D^{25}} = +49.4 (*c* 1, CH₃OH) for 36% ee, (*S*)-enantiomer}, ee = 52%. HPLC analysis: Chiralcel OD chiral column, mobile phase *iso*-PrOH/hexane: 10:90, flow rate: 1.0 mL/min, wavelength: 210 nm; *t*_R (retention time): 8.20 min for (*S*)-isomer, 13.44 min for (*R*)-isomer. IR (neat, cm⁻¹): 3453, 3023, 2923, 1684, 1607, 1492, 1455, 1392, 1284, 1084, 792, 707 cm⁻¹. ¹H NMR (CDCl₃): δ 2.19 (s, 3H), 2.32 (s, 3H), 4.49 (br s, 1H), 5.82 (s, 1H), 6.80–7.20 (m, 6H), 7.65 (m, 2H). ¹³C NMR (CDCl₃): δ 21.54, 21.61, 76.42, 125.20, 126.69, 128.51, 128.73, 129.58, 129.84, 133.80, 134.94, 138.81, 139.11, 139.27, 199.42. MS *m/z*: 41, 51, 65, 77, 89, 91, 119, 128, 152, 165, 195, 206, 222, 238 (M⁺).

4.4.4. (*R*)-2-Hydroxy-1,2-bis(2-methoxyphenyl)ethanone 2d³²

Mp 96.6–98.8 °C, $[\alpha]_D^{25} = -35.4$ (*c* 0.1, CH₃OH) {lit.³³ $[\alpha]_D^{25} = -21.5$ (*c* 0.1, CH₃OH) for 28% ee, (*R*)-enantiomer}, ee = 53%. HPLC analysis: Chiralcel OD-H chiral column, mobile phase *iso*-PrOH/hexane: 10:90, flow rate: 1.0 mL/min, wavelength: 210 nm; *t*_R (retention time): 21.20 min for (*S*)-isomer, 30.38 min for (*R*)-isomer. IR (neat, cm⁻¹): 3469, 3069, 2938, 2892, 1679, 1600, 1492, 1292, 1253, 984, 761 cm⁻¹. ¹H NMR (CDCl₃): δ 3.63 (s, 3H), 3.65 (s, 3H), 4.38 (br s, 1H), 6.03 (s, 1H), 6.66 (dd, 2H, *J*₁ = 8.3 Hz, *J*₂ = 10.7 Hz), 6.71 (dd, 1H, *J*₁ = 0.9 Hz, *J*₂ = 8.3 Hz), 6.84 (dd, 1H, *J*₁ = *J*₂ = 7.8 Hz), 7.06–7.14 (m, 2H), 7.28 (ddd, 1H, *J*₁ = *J*₂ = 14.1 Hz, *J*₃ = 1.9 Hz), 7.62 (dd, 1H, *J*₁ = 1.4 Hz, *J*₂ = 7.3 Hz). ¹³C NMR (CDCl₃): δ 55.10, 55.36, 76.12, 111.10, 111.43, 120.72, 120.74, 125.52, 127.78, 129.79, 130.21, 130.87, 134.07, 157.48, 158.37, 201.86. MS *m/z*: 43, 51, 64, 77, 92, 105, 135, 152, 165, 209, 224, 240, 255, 270 (M⁺).

4.4.5. (*R*)-2-Hydroxy-1,2-bis(4-methoxyphenyl)ethanone 2e³⁴

Mp 103.2–104.4 °C, $[\alpha]_D^{25} = -75$ (*c* 0.25, CH₃OH) {lit.³⁴ $[\alpha]_D^{20} = +88.6$ (*c* 1, CH₃OH) for 98% ee, (*S*)-enantiomer}, ee = 84%. HPLC analysis: Chiralcel OD chiral column, mobile phase *iso*-PrOH/hexane: 10:90, flow rate: 1.0 mL/min, wavelength: 210 nm;

*t*_R (retention time): 21.14 min for (*S*)-isomer, 22.80 min for (*R*)-isomer. IR (neat, cm⁻¹): 3446, 3069, 2930, 1676, 1607, 1515, 1461, 1261, 1176, 1038, 838 cm⁻¹. ¹H NMR (CDCl₃): δ 1.18 (br s, 1H), 3.68 (s, 3H), 3.75 (s, 3H), 5.77 (s, 1H), 6.78 (dd, 4H, J_1 = 6.8 Hz, J_2 = 7.8 Hz), 7.18 (dd, 2H, J_1 = 7.8 Hz, J_2 = 1.9 Hz), 7.82 (dd, 2H, J_1 = 1.9 Hz, J_2 = 6.8 Hz). ¹³C NMR (CDCl₃): δ 54.20, 54.52, 74.22, 112.90, 113.53, 125.32, 127.94, 130.52, 130.78, 158.59, 162.91, 196.36. MS *m*/*z*: 41, 51, 64, 77, 92, 109, 135, 152, 169, 183, 207, 227, 256, 270 (M⁺).

4.4.6. (*R*)-2-Hydroxy-1-(2-methylphenyl)-2-phenyl-ethanone 2f³⁵

Mp 64.5–65.8 °C, $[\alpha]_D^{25} = -160$ (*c* 0.25, CH₃COCH₃), ee = 78%. HPLC analysis: Chiralcel OD-H chiral column, mobile phase *iso*-PrOH/hexane: 10:90, flow rate: 1.0 mL/min, wavelength: 210 nm; t_R (retention time): 16.23 min for (*S*)-isomer, 12.92 min for (*R*)-isomer. IR (neat, cm⁻¹): 3446, 3061, 2961, 2938, 1684, 1600, 1453, 1253, 1184, 1076, 976, 761, 700 cm⁻¹. ¹H NMR (CDCl₃): δ 2.48 (s, 3H), 4.40 (br s, 1H), 5.98 (s, 1H), 6.95 (d, 1H, *J* = 7.8 Hz), 7.02 (m, 2H), 7.10 (m, 2H), 7.32 (m, 2H), 7.41 (m, 1H) 7.75 (dd, 1H, *J*₁ = 0.9 Hz, *J*₂ = 7.3 Hz). ¹³C NMR (CDCl₃): δ 19.53, 74.57, 125.69, 126.96, 128.57, 128.70, 128.93, 128.98, 129.01, 129.14, 131.70, 133.90, 134.06, 136.78, 137.64, 200.21. MS *m/z*: 41, 51, 63, 65, 77, 91, 105, 121, 128, 139, 152, 165, 178, 195, 210, 224 (M⁺).

4.4.7. (*R*)-2-Hydroxy-1,2-bis(2-furanyl)-ethanone 2g³⁴

Mp 133.7–135 °C, $[\alpha]_D^{25} = -96.3$ (*c* 0.08, CHCl₃) {lit.³⁴ $[\alpha]_D^{20} = +123$ (*c* 1, CHCl₃) for 93% ee, (S)-enantiomer}, ee = 62%. HPLC analysis: Chiralcel OD-H chiral column, mobile phase *iso*-PrOH/hexane: 10:90, flow rate: 1.0 mL/min, wavelength: 210 nm; t_R (retention time): 16.94 min for (S)-isomer, 20.89 min for (*R*)-isomer. IR (neat, cm⁻¹): 3423, 3030, 2961, 1653, 1515, 1292, 1100, 1030, 800 cm⁻¹. ¹H NMR (CDCl₃): δ 1.19 (br s, 1H), 5.72 (s, 1H), 6.27 (dd, 1H, J_1 = 1.5 Hz, J_2 = 2.9 Hz), 6.28 (d, 1H, J = 3.4 Hz), 6.46 (dd, 1H, J_1 = 1.4 Hz, J_2 = 3.9 Hz), 7.18 (d, 1H, J = 3.9 Hz), 7.31 (d, 1H, J = 0.9 Hz), 7.54 (s, 1H). ¹³C NMR (CDCl₃): δ 68.29, 108.12, 109.79, 111.59, 119.10, 142.19, 146.67, 148.68, 150.28, 183.40. MS *m/z*: 41, 51, 69, 81, 97, 108, 118, 131, 147, 163, 176, 192 (M⁺).

4.4.8. (R)-2-Hydroxy-1,2-bis(5-methyl-2-furanyl)-ethanone 2h^{13a}

Mp 93–94.2 °C, $[\alpha]_D^{25} = -42.4$ (*c* 0.66, CHCl₃) {lit.^{13a} $[\alpha]_D^{20} = -58$ (*c* 0.1, CHCl₃) for 96% ee, (*R*)-enantiomer}, ee = 72%. HPLC analysis: Chiralcel OD-H chiral column, mobile phase *iso*-PrOH/hexane: 10:90, flow rate: 1.0 mL/min, wavelength: 220 nm; t_R (retention time): 10.73 min for (*S*)-isomer, 13.03 min for (*R*)-isomer. IR (neat, cm⁻¹): 3476, 3123, 2923, 2861, 1676, 1515, 1369, 1215, 1030, 800, 723 cm⁻¹. ¹H NMR (CDCl₃): δ 2.17 (s, 3H), 2.31 (s, 3H), 4.13 (br s, 1H), 5.58 (s, 1H), 5.84 (d, 1H, *J* = 3.4 Hz), 6.07 (d, 1H, *J* = 3.4 Hz), 6.17 (d, 1H, *J* = 2.9 Hz), 7.06 (d, 1H, *J* = 3.4 Hz). ¹³C NMR (CDCl₃): δ 13.76, 14.30, 69.23, 106.96, 109.66, 110.18, 122.41, 148.56, 150.10, 153.28, 159.52, 183.87. MS *m/z*: 43, 53, 67, 83, 95, 111, 121, 145, 161, 175, 204, 205, 220 (M⁺).

4.4.9. (*R*)-2-Hydroxy-1-(5-methyl-2-furanyl)-2-phenyl-ethanone 2i

Mp 125.2–126.5 °C, $[\alpha]_D^{25} = -66.6$ (*c* 0.15, CHCl₃), ee = 64%. HPLC analysis: Chiralcel OD-H chiral column, mobile phase *iso*-PrOH/ hexane: 10:90, flow rate: 1 mL/min, wavelength: 210 nm; *t*₁ (retention time): 12.18 min for major isomer, 16.13 min for minor isomer. IR (neat, cm⁻¹): 3446, 3038, 2923, 1769, 1661, 1515, 1453, 1323, 1289, 1038, 815, 700 cm⁻¹. ¹H NMR (CDCl₃): δ 2.30 (s, 3H), 4.45 (br s, 1H), 5.65 (s, 1H), 6.02 (dd, 1H, *J*₁ = 10.9 Hz, *J*₂ = 3.4 Hz), 7.02 (d, 1H, *J* = 3.4 Hz), 7.22 (m, 1H), 7.35 (m, 2H), 7.38 (m, 2H). ¹³C NMR (CDCl₃): δ 14.31, 75.99, 109.72, 122.32, 127.87, 128.75, 129.06, 139.52, 148.77, 159.28, 186.63. MS *m/z*: 43, 53, 65, 79, 91, 105, 109, 111, 128, 141, 157, 170, 186, 200, 214, 253 (M⁺). Anal. Calcd for C₁₃H₁₂O₃: C, 72.21; H, 5.59. Found: C, 72.53; H, 5.40.

4.4.10. (R)-1-(4-Methoxyphenyl)-2-hydroxy-1-tetradecaneone 2j

Mp 31.3–32.6 °C, $[\alpha]_D^{25} = -28.4$ (*c* 0.12, CHCl₃), ee = 50%. HPLC analysis: Chiralcel OD-H chiral column, mobile phase *iso*-PrOH/ hexane: 2:98, flow rate: 1.0 mL/min, wavelength: 275 nm; *t*_R (retention time): 5.87 min for the major isomer, 6.48 min for the minor isomer. IR (neat, cm⁻¹): 3440, 3069, 2940, 1675, 1607, 1515, 1453, 1284, 1176, 1038, 838 cm⁻¹. ¹H NMR (CDCl₃): δ 0.81 (t, 3H, *J* = 6.8 Hz), 1.18 (m, 15H), 1.48 (m, 8H), 1.93–2.09 (m, 2H), 3.81 (s, 3H), 5.01 (dd, 1H, *J*₁ = 5.8 Hz, *J*₂ = 8.3 Hz), 6.88 (dd, 2H, *J*₁ = 2.4 Hz, *J*₂ = 6.8 Hz), 7.91 (dd, 2H, *J*₁ = 2.4 Hz, *J*₂ = 6.8 Hz). ¹³C NMR (CDCl₃): δ 13.10, 21.67, 25.34, 28.13, 28.33, 28.37, 28.49, 28.58, 28.61, 28.62, 30.90, 32.80, 54.53, 56.67, 112.99, 130.28, 162.97, 191.30. MS *m/z*: 43, 55, 69, 77, 92, 107, 121, 135, 150, 163, 184, 207, 290, 316 (M⁺-H₂O). Anal. Calcd for C₂₁H₃₄O₃: C, 75.41; H, 10.25. Found: C, 74.62; H, 11.05.

4.4.11. (*R*)-1-2-Dihydro-1-hydroxy-2-acenaphthyleneone 2k²³

Mp 211.6–213 °C, $[\alpha]_D^{25} = -73.2$ (*c* 0.41, CHCl₃) {lit.³⁶ $[\alpha]_D^{25} = +60.03$ (*c* 0.5, CHCl₃) for 81% ee, (*S*)-enantiomer}, ee = 100%. HPLC analysis: Chiralpac AD-H chiral column, mobile phase *iso*-PrOH/hexane: 10:90, flow rate: 1.0 mL/min, wavelength: 240 nm; t_R (retention time): not observed (for racemic 12.55 min) for (1) enantiomer, 13.75 min for (2) enantiomer. IR (neat, cm⁻¹): 3438, 3038, 1723, 1607, 1430, 1261, 1069, 1015, 815, 776 cm⁻¹. ¹H NMR (CDCl₃): δ 3.28 (br s, 1H), 5.31 (s, 1H), 7.58–7.65 (m, 3H), 7.80 (d, 1H, *J* = 8.9 Hz), 7.86 (d, 1H, *J* = 6.4 Hz), 8.04 (d, 1H, *J* = 8.4 Hz). ¹³C NMR (CDCl₃): δ 73.58, 120.50, 121.06, 124.41, 127.27, 127.41, 127.73, 129.68, 129.68, 131.11, 135.23, 140.73, 203.13. MS *m/z*: 44, 51, 63, 70, 77, 87, 101, 115, 128, 140, 152, 155, 168, 184 (M⁺).

4.4.12. (*R*)-1-Phenyl-3-hydroxy-1-butanone 2n²⁴

 $[\alpha]_D^{25} = -68.1$ (*c* 0.11, CHCl₃) {lit.²⁴ $[\alpha]_D^{25} = -67.5$ (*c* 1.2, CHCl₃) for 99% ee, (*R*)-enantiomer}, ee = 100%. HPLC analysis: Chiralcel OD-H chiral column, mobile phase *iso*-PrOH/hexane: 5:95, flow rate: 0.8 mL/min, wavelength: 240 nm; t_R (retention time): 15.47 min for (*R*)-isomer, not observed (for racemic 17.69 min) for (*S*)-isomer. IR (neat, cm⁻¹): 3415, 3061, 2923, 2853, 1715, 1684, 1453, 1376, 1284, 1215, 1069, 703 cm⁻¹. ¹H NMR (CDCl₃): δ 1.24 (d, 3H, *J* = 7.3 Hz), 2.12 (s, 1H), 2.98 (dd, 1H, *J*₁ = 18 Hz, *J*₂ = 9.2 Hz), 3.09 (dd, 1H, *J*₁ = 17 Hz, *J*₂ = 2.4 Hz), 4.34 (m, 1H), 7.50 (m, 3H), 7.90 (d, 2H, *J* = 8.3 Hz). ¹³C NMR (CDCl₃): δ 22.64, 46.71, 64.26, 128.30, 128.80, 133.80, 136.95, 201.11. MS *m/z*: 41, 51, 77, 91, 105, 120,140, 164 (M⁺).

4.4.13. (1S,2R)-2-Hydroxycyclohexyl-phenylmethanone 2p³⁷

Mp 74.2–75.5 °C, $[\alpha]_D^{25} = +40$ (*c* 0.1, CHCl₃), 100% ee for *syn* and dr = 100:0, HPLC analysis: Chiralcel OD chiral column, mobile phase *iso*-PrOH/hexane: 10:90, flow rate: 0.5 ml/min, wavelength: 240 nm; t_R (retention time): t_{syn} (major) = 14.37 min, other isomers not observed. IR (neat, cm⁻¹): 3476, 2930, 2853, 1669, 1453, 1353, 1215, 976, 707 cm⁻¹. ¹H NMR (CDCl₃): δ 1.18–1.43 (m, 5H), 1.73–1.90 (m, 4H), 3.36 (m, 1H), 4.40 (m, 1H), 7.40 (m, 2H), 7.56 (m, 1H), 7.85 (m, 2H). ¹³C NMR (CDCl₃): δ 18.62, 23.65, 24.62, 30.95, 47.17, 65.41, 127.39, 132.46, 134.77, 204.99. MS *m/z*: 41, 51, 55, 67, 77, 82, 105, 115, 123, 133, 145, 157, 167, 176, 186, 204 (M⁺).

4.4.14. (1*S*,2*R*)-(2-(1-Hydroxyethyl)-1,2,3,4-tetrahydro-1-oxonaphthalene 2r

100% ee for *syn*, 4% ee for *anti*, and *syn/anti* (dr) = 3:1, HPLC analysis: Chiralcel OD-H chiral column, mobile phase *iso*-PrOH/hexane: 10:90, flow rate: 0.5 ml/min, wavelength: 210 nm; t_R (retention time): $t_{syn}(\text{minor}) = \text{not}$ observed (for racemic 13.647 min), $t_{syn}(\text{major}) = 14.53 \text{ min}$, $t_{anti}(\text{minor}) = 16.13 \text{ min}$, $t_{anti}(\text{major}) = 16.34 \text{ min}$. IR (neat, cm⁻¹): 3430, 3038, 2969, 2930, 1676, 1600, 1461, 1307, 1230, 1115, 869, 753 cm⁻¹. ¹H NMR (CDCl₃):³⁸ major:

δ 1.21 (d, 3H, *J* = 6.8 Hz), 1.75 (m, 2H), 2.20 (m, 1H), 2.40–2.52 (m, 2H), 2.95 (m, 1H), 4.40 (m, 1H), 7.18–7.40 (m, 3H), 7.95 (m, 1H). ¹H NMR (CDCl₃): minor: δ 1.21 (d, 3H, *J* = 6.8 Hz), 1.75–1.90 (m, 2H), 2.20 (m, 1H), 2.40–2.52 (m, 2H), 2.95 (m, 1H), 4.15 (m, 1H), 7.18–7.40 (m, 3H), 7.95 (m, 1H). ¹³C NMR (CDCl₃): δ 19.45, 25.95, 29.32, 54.42, 67.31, 126.91, 127.65, 128.91, 129.02, 133.09, 134.10, 201.13. MS *m/z*: 43, 44, 63, 77, 89, 90, 103, 115, 118, 131, 146, 157, 172, 188, 190 (M⁺). Anal. Calcd for C₁₂H₁₄O₂: C, 75.76; H, 7.42. Found: C, 75.85; H, 7.25.

Acknowledgment

This study was supported by The Istanbul University Department of Scientific Research Project with Project number 22741.

References

- 1. Csuk, R.; Glanzer, B. I. Chem. Rev. 1991, 91, 49-97.
- (a) Nakamura, K.; Yamanaka, R.; Matsuda, T.; Harada, T. Tetrahedron: Asymmetry 2003, 14, 2659–2681; (b) Ni, H. L.; Guan, Y. X.; Yao, S. J. J. Chem. Technol. Biotechnol. 2009, 84, 186–191; (c) Bisogno, F. R.; Lavandera, I.; Kroutil, W.; Gotor, V. J. Org. Chem. 2009, 74, 1730–1732; (d) Ludeke, S.; Richter, M.; Muller, M. Adv. Synth. Catal. 2009, 351, 253–259; (e) Broussy, S.; Cheloha, R. W.; Berkowitz, D. B. Org. Lett. 2009, 11, 305–308; (f) Kosjek, B.; Nti-Gyabaah, J.; Telari, K.; Dunne, L.; Moore, J. C. Org. Proc. Res. Dev. 2008, 12, 584–588; (g) Moore, J. C.; Pollard, D. J.; Kosjek, B.; Devine, P. N. Acc. Chem. Res. 2007, 40, 1412–1419.
- (a) Urdiales, E. G.; Alfonso, I.; Gotor, V. Chem. Rev. 2005, 105, 313; (b) Bortolini, O.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. Recent Res. Dev. Pure Appl. Chem. 1999, 3, 137.
- (a) Patel, R. N.; Banerjee, A.; McNamee, C. G.; Brzozowski, D.; Hanson, R. L.; Szarka, L. J. *Enzyme Microb. Technol.* **1993**, *15*, 1014–1021; (b) Patel, R. N.; McNamee, C. G.; Banerjee, A.; Szarka, L. J. EP-A569998, 1993.; (c) Stewart, D. J. *Curr. Opin. Biotechnol.* **2000**, *11*, 363–368; (d) Sorgedrager, M. J.; Rantwijk, F. Van; Huisman, G. W.; Sheldon, R. A. Adv. Synth. Catal. **2008**, *350*, 2322–2328; (e) Kalaitzakis, D.; Rozzel, J. D.; Smonou, I.; Kambourakis, S. Adv. Synth. Catal. **2006**, *348*, 1958–1969.
- Nakamura, K.; Kondo, S.; Kawai, Y.; Hida, K.; Kitano, K.; Ohno, A. Tetrahedron: Asymmetry **1996**, 7, 409.
- Cui, J. N.; Ema, T.; Sakai, T.; Utaka, M. Tetrahedron: Asymmetry 1998, 9, 2681– 2692.
- Chin-Joe, I.; Nelisse, P. M.; Straathof, A. J. J.; Jongejan, J. A.; Pronk, J. T.; Heijnen, J. J. Biotechnol. Bioeng. 2000, 69, 370.
- (a) Koike, T.; Murata, K.; Ikariya, T. Org. Lett. 2000, 2, 3833; (b) Coppola, G. M.; Schuster, H. F. α-Hydroxy Acids in Enantioselective Synthesis; VCH: Weinheim, 1997; (c) Davies, F. A.; Chen, B. C. Chem. Rev. 1992, 92, 919; (d) Hashiyama, T.; Morikawa, K.; Sharpless, K. B. J. Org. Chem. 1992, 57, 5067; (e) Knight, R. L.; Leeper, F. G. J. J. Chem. Soc., Perkin Trans. 1 1998, 1891; (f) Enders, D.; Breuer, K.; Teles, J. H. Helv. Chim. Acta 1996, 79, 1217; (g) Enders, D.; Breuer, K. In

Comprehensive Asymmetric Catalysis; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; ; Springer: Berlin, 1999; Vol. 2, p 1093.

- (a) Tanaka, T.; Kawase, M.; Tani, S. Bioorg. Med. Chem. 2004, 12, 501–505; (b) Wallace, O. B.; Smith, D. W.; Deshpande, M. S.; Polson, C.; Felsenstein, K. M. Bioorg. Med. Chem. Lett. 2003, 13, 1203–1206; (c) Fang, Q. K.; Han, Z.; Grover, P.; Kessler, D.; Senanayake, C. H.; Wald, S. A. Tetrahedron: Asymmetry 2000, 11, 3659–3663.
- (a) Adam, W.; Lazarus, M.; Saha-Möller, C. R.; Schreier, P. Acc. Chem. Res. 1999, 32, 837–845; (b) Davis, F. A.; Chen, B. C. Chem. Rev. 1992, 92, 919–934.
- Sabitha, G. F.; Padmaja, P.; Reddy, K. B.; Yadav, J. S. *Tetrahedron Lett.* 2008, 49, 919–922.
- 12. Chakraborty, T. K.; Das, S. Chem. Lett. 2000, 80-81.
- (a) Demir, A. S.; Dünnwald, T.; Iding, H.; Pohl, M.; Müller, M. *Tetrahedron: Asymmetry* **1999**, *10*, 4769–4774; (b) Saito, T.; Maruyama, R.; Ono, S.; Yasukawa, N.; Kodaira, K.; Nishizawa, M.; Ito, S.; Inoue, M. *Appl. Biochem. Biotechnol.* **2003**, *111*, 185–190.
- 14. Mahmoodi, N. O.; Mohammadi, H. G. Monatsh. Chem. 2003, 134, 1283-1288.
- (a) Yadav, S. R.; Nainawat, A. K.; Kaushik, S.; Sharma, A.; Sharma, I. K. Asian J. Exp. Sci. 2005, 19, 135–141; (b) Allenmark, S.; Andersson, S. Enzyme Microb. Technol. 1989, 11, 177–179.
- Cui, J. N.; Teraoka, R.; Ema, T.; Sakai, T.; Utaka, M. Tetrahedron Lett. 1997, 38, 3021–3024.
- 17. Ghanem, A.; Aboul-Enein, H. Y. Tetrahedron: Asymmetry 2004, 15, 3331–3335.
- 18. Mahmoodi, N. O.; Noori Navrood, M. Arkivoc 2007, 37-45.
- 19. Adams, R.; Marvel, C. S. Org. Synth. 1941, 1, 94.
- 20. Mori, N.; Togo, H. Tetrahedron 2005, 61, 5915-5925.
- 21. Lee, D. G.; Chang, V. S. J. Org. Chem. 1978, 43, 1532–1536.
- Wang, X. Y.; Cui, J. N.; Ren, W. M.; Li, F.; Lu, C. L.; Qian, X. H. Chin. Chem. Lett. 2007, 18, 681–684.
- 23. Chenevert, R.; Thiboutot, S. Can. J. Chem. 1985, 64, 1599–1601.
- Ahmad, K.; Koul, S.; Taneja, S. C.; Singh, A. P.; Kapoor, M.; Riyaz-ul-Hassan; Vermaand, V.; Qazi, G. N. Tetrahedron: Asymmetry 2004, 15, 1685–1692.
- 25. Yildiz, T.; Yusufoglu, A. S. Monatsh. Chem. 2013, 144, 183–190.
- 26. Bailey, D.; Murphy, J. N.; Williams, V. E. Can. J. Chem. 2006, 84, 659-666.
- 27. McKenzie, A.; Kelman, A. L. J. Chem. Soc. 1934, 412–418.
- 28. Akiba, K.; Ohnari, H.; Ohkata, K. Chem. Lett. 1985, 10, 1577-1580.
- Guirado, A.; Zapata, A.; Andreu, R.; Ramirez de Arellano, C.; Jones, P. G.; Galvez, J. Tetrahedron 2009, 65, 3886–3892.
- Hashmi, A. S. K.; Buehrle, M.; Woelfle, M.; Rudolph, M.; Wieteck, M.; Rominger, F.; Frey, W. Chembiochem 2010, 16, 9846–9854.
- 31. Muthupandi, P.; Sekar, G. Tetrahedron: Asymmetry 2011, 22, 512-517.
- 32. O'Toole, S. E. I.; Connon, S. J. Org. Biol. Chem. 2009, 7, 3584–3593.
- Alamsetti, S. K.; Mannam, S.; Mutupandi, P.; Sekar, G. Chembiochem 2009, 15, 1086–1090.
- 34. Demir, A. S.; Ayhan, P.; Igdir, A. C.; Duygu, A. N. Tetrahedron 2004, 60, 6509–6512.
- Duenkelmann, P.; Kolter-Jung, D.; Nitsche, A.; Demir, A. S.; Siegert, P.; Lingen, B.; Baumann, M.; Pohl, M.; Mueller, M. J. Am. Chem. Soc. 2002, 124, 12084– 12085.
- Tong, L. P.; Cui, J. N.; Ren, W. M.; Wang, X. Y.; Qian, X. H. Chin. Chem. Lett. 2008, 19, 1179–1182.
- Sandoval, C.; Mendez, J. M.; Sanchez-Obregon, R.; Alpizar, C. B.; Barrios, H. Biocatal. Biotransform. 2009, 27, 36–44.
- Zelinski, T.; Liese, A.; Wandreyb, C.; Kula, M. R. Tetrahedron: Asymmetry 1999, 10, 1681–1687.