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A chemo-enzymatic route to diastereoisomers of 2-methyl-1-phenyl-1,3-butanediol: the dual role of microorganisms

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Abstract—Diastereoisomers (1*S*,2*R*,3*S*)-, (1*R*,2*R*,3*S*)-, (1*R*,2*S*,3*S*)- and (1*S*,2*S*,3*S*)-2-methyl-1-phenyl-1,3-butanediols were prepared by simple and convenient strategies using two different chemo-enzymatic approaches for the reduction of racemic 2-methyl-1-phenyl-1,3-butanedione, both involving in situ racemization. The first method comprised a one-pot microbial reduction coupled with a chemical reduction, while in the second method, stepwise chemo-enzymatic reductions were performed.

1. Introduction

Natural products with a 1,3-diol framework have interesting pharmacological attributes. In particular, propionate-based compounds with 1,3-polyol moieties are valuable building blocks for the synthesis of ionophore antibiotics and macrolides.[1] The preparation of an optically active 1,3-diol can involve reduction of the corresponding 1,3-diketone by a chemo-enzymatic method using a lipase or by a chemical method.[2] 1,3-Diols may also be obtained from α,β-unsaturated ketones via chiral epoxy alcohols or via β-hydroxyketone reduction using hydride. A β-hydroxyketone with a defined stereochemistry may be obtained by an aldol condensation or by reduction of corresponding 1,3-diketone.[3] The specific stereochemistry of a β-hydroxyketone will influence the stereochemistry of the final 1,3-diols via chiral induction during formation of the new stereogenic centre. Both *syn* and *anti* diastereoisomers of 1,3-diols can be prepared using a suitable reducing agent,[4] e.g., $NaBH_4$ reduction of β-hydroxyketones in the presence of alkoxydialkylborane produces *syn* diols due to an internal hydride transfer, whereas tetramethylammonium triacetoxyborohydride gives predominantly *anti* diols.[1b,4c] Our attempts to synthesize the optically active diastereoisomers of 1-phenyl-1,3-diols by chemo-enzymatic routes resulted in the development of a one-pot method wherein chemical reduction of the intermediate β-hydroxyketone formed during the bioreduction was successfully achieved in the presence of a microorganism.[5] Encouraged by the earlier results, we decided to study one-pot transformations of racemic 2-methyl-1-phenyl-1,3-butanedione **1**. In situ racemization (deracemization) during bioreduction of (±)-**1** may also influence the course of reaction and formation of isomers of 2-methyl-1-phenyl-1,3-butanediol. The influence of in situ racemization was expected due to the presence of a configurationally labile C2 stereocentre.

Due to their importance, various methods for the preparation of optically active 2-methyl-1-phenyl-1,3-butanediols are reported in the literature.[6] A mixture of 1,3-*syn*- and *anti*-, i.e., (1*S*,2*R*,3*S*)- and (1*R*,2*S*,3*S*)-2-methyl-1-phenyl-1,3-butanediol was synthesized by sodium borohydride reduction of 3-hydroxy-2-methyl-1-phenylbutanone, which was prepared by chiral resolution using lipases.[6a] Bodnar et al. and later Jose Vicario et al. used borane dimethyl sulfide complex in THF for the formation of *syn*-1,3-diol, while $LiBH_4$ was used for the preparation of the *anti* isomer.[6b] In another study, chiral ruthenium reagents were employed for a dynamic kinetic resolution during chiral reduction of racemic 2-methyl-1-phenyl-1,3-butanedione.[3a] In a significant and recent development, Baneditti et al. prepared an equimolar complex between 1,3-diketones and bovine serum albumin (BSA) while using $NaBH_4$ as the reducing agent to produce 1,3-diols in a diastereoselective manner.[7] The proposed one-pot chemo-enzymatic approach for the preparation of diastereoisomers of 2-methyl-1-phenyl-1,3-butanediols may provide a facile and efficient method for their synthesis.

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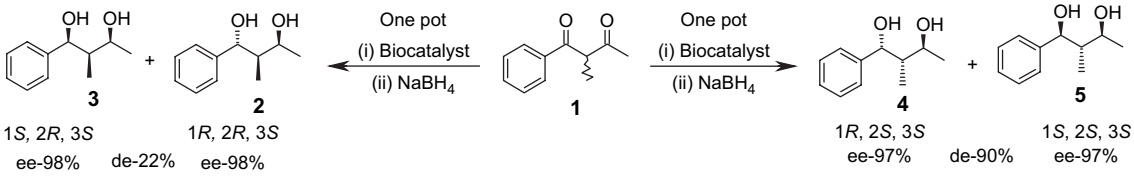
2. Results and discussion

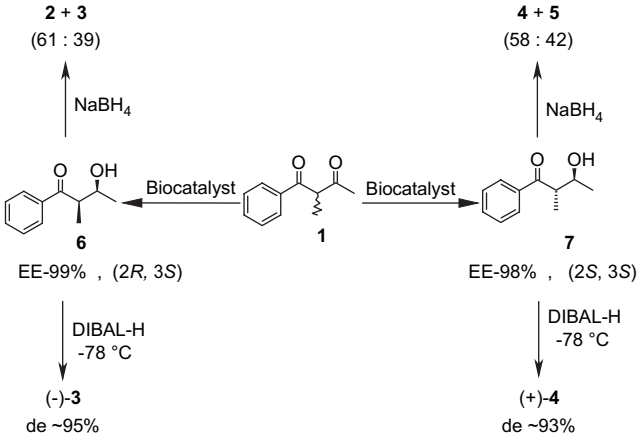
When (±)-2-methyl-1-phenyl-1,3-butanedione **1** was subjected to enzymatic reduction with a panel of microorganisms bearing oxido-reductases followed by $NaBH_4$ reduction in one-pot, 1,3-diols with high as well as low de's were obtained. The results of these experiments may be divided into two groups based on the products formed, i.e., pairs of diastereoisomers, (1*R*,2*R*,3*S*)-2-methyl-1-phenyl-1,3-butanediol **2**; (1*S*,2*R*,3*S*)-2-methyl-1-phenyl-1,3-butanediol **3** (ee∼98%, de∼20–24%) and (1*R*,2*S*,3*S*)-2-methyl-1-phenyl-1,3-butanediol **4**; (1*S*,2*S*,3*S*)-2-methyl-1-phenyl-1,3-butanediol **5** (ee∼96–98%, de∼88–90%), respectively (Scheme 1). All four diastereoisomers were separated by column chromatography. The results with different microorganisms are summarized in Table 1.



Scheme 1. One-pot chemo-enzymatic reduction of (±)-**1**.

In these transformations, the influence of in situ racemization was apparent due to higher isolated yields (55–83%) of the final products (Table 1). It was also confirmed by HPLC, which indicated that ratio of (+)-**1** and (−)-**1** remained equal (1:1) throughout the course of the reaction. Dynamic kinetic resolution involving in situ substrate racemization in molecules bearing 1,3-diketo functions is now an important aspect of stereoselective synthesis, which is increasingly being exploited as only one stereoisomer amongst many possible stereoisomers is formed.[8–11]

In order to compare the results of one pot as well as two pot (stepwise) reductive transformations and to understand the course of reaction during in situ racemization, (±)-**1** was first subjected to simple bioreduction studies by incubating it with the same set of microorganisms (Scheme 2). It was observed that simple biocatalytic reduction of (±)-**1** afforded either *syn*-(2*R*,3*S*)-3-hydroxy-2-methyl-1-phenylbutanone **6** or *anti*-(2*S*,3*S*)-3-hydroxy-2-methyl-1-phenylbutanone **7** with complete deracemization and high optical purity and yield (Table 2). Thus *Pichia farinosa*, *Bacillus pseudomegaterium* and *Zygosaccharomyces rouxii* furnished predominantly *anti*-(2*S*,3*S*)-3-hydroxy-2-methyl-1-phenylbutanone **7**, whereas *Candida crusei* and *Serratia marcescens* gave *syn*-(2*R*,3*S*)-3-hydroxy-2-methyl-1-phenylbutanone **6** as the major product. Thus by selecting the proper microorganism it is possible to obtain either *syn* or *anti* products.



Scheme 2. Stepwise reduction experiments with (±)-**1**.

The intermediate **7** (ee>98%), isolated after bioreduction of (±)-**1** was subjected to $NaBH_4$ reduction under controlled conditions (0 °C ambient temperature, methanol/water), resulting in the formation of a mixture of diastereoisomers **4** and **5** in an average ratio of 58:42 (de=16%). Similarly, on borohydride reduction under similar conditions, compound **6** gave a mixture of **2** and **3** with an average ratio of 61:39 (de=22%) (Scheme 2).

Alternatively, reduction of **7** with DIBAL-H at −78 °C in THF gave **4** as the major product (ee=97%, de >93%, yield ∼82%) whereas **6** with DIBAL-H produced **3** as the main product (ee=98%, de >95%, yield ∼80%) (Scheme 2).

Table 1. One-pot chemo-enzymatic reduction of racemic 2-methyl-1-phenyl-1,3-butanedione (**1**)

Microorganism	Ratio[a], *anti*:*syn*		Major isomer[c]	Minor isomer	Total yield (%)	$[\alpha]_D^{25}$[b]
	2:**3**	**4**:**5**	ee (%) conf.	ee (%) conf.		
Bacillus pseudomegaterium	—	95:5	97 (1*R*,2*S*,3*S*)	97 (1*S*,2*S*,3*S*)	75	+37.5
Candida crusei	60:40	—	98 (1*R*,2*R*,3*S*)	96 (1*S*,2*R*,3*S*)	55	—
Pichia farinosa	—	94:6	96 (1*R*,2*S*,3*S*)	96 (1*S*,2*S*,3*S*)	83	+34.5
Serratia marcescens	62:38	—	99 (1*R*,2*R*,3*S*)	99 (1*S*,2*R*,3*S*)	82	—
Zygosaccharomyces rouxii	—	95:5	98 (1*R*,2*S*,3*S*)	98 (1*S*,2*S*,3*S*)	83	+36.5

[a] Diastereomeric ratio of 1,3-*syn* and *anti* diols calculated on the basis of chiral HPLC and ^{1}H NMR.
[b] Specific rotation of major isomer in chloroform (c=1.0).
[c] Time required for the completion of the first step is given in Table 2.

Table 2. Bioreduction of (±)-**1** for the preparation of β-hydroxyketones **6** and **7**

S. no.	Microorganism	Ratio (ketols), *syn*:*ant*[a]	Time (h)	Major isomer, ee (%) conf.	$[\alpha]_D^{25}$ [b]	Yield[c] (%)
1	*Bacillus pseudomegaterium*	02:98	48	98 (2*S*,3*S*)	+68.3	78
2	*Candida crusei*	97:03	54	>99 (2*R*,3*S*)	−16.0	58
3	*Pichia farinosa*	04:96	56	98 (2*S*,3*S*)	+66.5	85
4	*Serratia marcescens*	99:01	60	>99 (2*R*,3*S*)	−16.3	85
5	*Zygosaccharomyces rouxii*	03:97	48	98 (2*S*,3*S*)	+67.5	83

[a] *syn*:*anti* ratio determined by ^{1}H NMR and chiral HPLC data.
[b] The specific rotation values correspond to the diastereomeric mixture with *c*=1.0 and chloroform as a solvent.
[c] Isolated yields after cc on silica gel with a mixture of *n*-hexane/ethyl acetate (19:1) as eluent.

The absolute stereochemical assignments of the final products **2** and **3**, as well as of the intermediate **6**, were established on the basis of NMR data and by comparison of the signs of optical rotations with those reported in the literature.[6a,6c,3a] Similarly, the absolute configuration of **4** was determined on the basis of a combination of NMR data and the stereochemical assignment of intermediate **7** (Scheme 1 and Table 2).[6a,12] The absolute configuration of **5** was established only by comparison of optical rotation values.[6a]

On comparing the results obtained from the two different approaches of reduction of (±)-**1**, i.e., one pot and stepwise reductions, it becomes evident that diastereoisomer **4** was always obtained with a higher de % in the one-pot transformations, whereas for diastereoisomers **2** and **3**, both methods gave similar results. The use of DIBAL-H was preferable for higher diastereoselectivity in the stepwise reactions. It may also be construed from these results that presence of the 3-hydroxy group led to the formation of predominantly 1,3-*anti* products with $NaBH_4$ as a reducing agent while the 2-methyl group had little or no influence; on the other hand, when DIBAL-H was used as the reducing agent, it was the 2-methyl group, which guided diastereoselectivity thus giving 1,2-*syn* products.[4b]

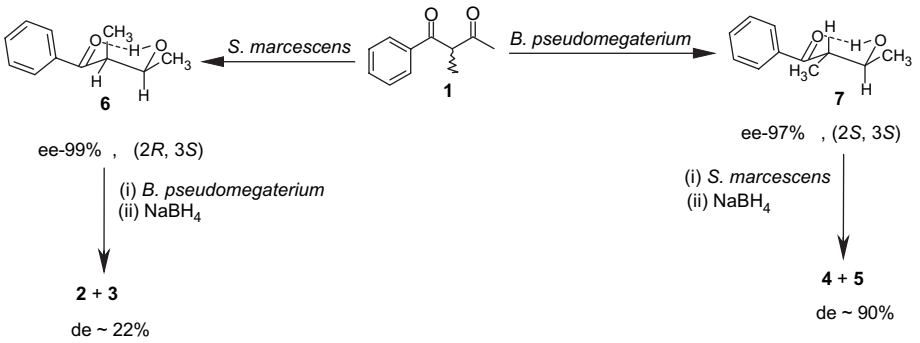
Table 3. Reported and observed $[\alpha]_D$ values of diastereoisomers of 2-methyl-1-phenyl-1,3-butanediol

Compound	$[\alpha]_{D\ reported}$	$[\alpha]_{D\ observed}$	Reference
(1*R*,2*R*,3*S*) **2**	+15.8 (*c* 0.1, CH_2Cl_2)	+38.5 (*c* 1.0, $CHCl_3$)	6b
(1*S*,2S,3*R*) **2**[a]	-44.6 (*c* 0.40, $CHCl_3$)		6c
	+25.2 (*c* 1.1, $CHCl_3$)		6a
(1*S*,2*R*,3*S*) **3**	+12.4 (*c* 0.1, CH_2Cl_2)	-35.2 (*c* 1.0, $CHCl_3$)	6b
	-27.7 (*c* 0.7, $CHCl_3$)		6a
(1*R*,2*S*,3*R*) **3**[a]	-12.3 (*c* 0.2, CH_2Cl_2)		6b
	+35.5 (0.46, $CHCl_3$)		6c
(1*R*,2S,3*S*) **4**	+15.6 (*c* 0.1, CH_2Cl_2)	+37.5 (*c* 1.0, $CHCl_3$)	6b
	+52.3 (*c* 1.12, CH_2Cl_2)		6a
(1*S*,2S,3*S*) **5**	—	-29.8 (*c* 1.0, $CHCl_3$)	
(1*R*,2*R*,3*R*) **5**[a]	+27.8 (*c* 1.0, $CHCl_3$)		6a

[a] Reported $[\alpha]_D$ values of the enantiomer.

A summary of the specific rotations of the various diastereoisomers of 2-methyl-1-phenyl-1,3-butanediol (**2**–**5**) prepared by these chemo-enzymatic routes is presented in Table 3 together with their literature values. It may be noted here that some of the observed $[\alpha]_D$ values of diastereoisomers are different from those reported in the literature.

Two cross experiments were also performed to demonstrate that during $NaBH_4$ reduction in the presence of a microorganism, conformations (*syn*/*anti*) of two methyls in the intermediates **6** and **7**, directly influenced the diastereoselectivity of the final products. In the first experiment, (±)-**1** after bioreduction with *S. marcescens* was chemically reduced in the presence of *B. pseudomegaterium*, to give a diastereoisomer pair **2** and **3** in the ratio of 61:39 (de∼22%); while in the other experiment, **7** derived from *B. pseudomegaterium* after $NaBH_4$ reduction in the presence of *S. marcescens*, produced a diastereoisomeric pair **4** and **5**, where **4** again is the major diastereoisomer (de∼90%). These results which are similar to those depicted in Scheme 1, clearly demonstrated that conformations of methyl groups in the intermediate bioproduct determined the formation of the final product during $NaBH_4$ reduction, irrespective of the microorganism used (Scheme 3).



Scheme 3. Cross experiments and possible mode of reductions.

3. Conclusions

In conclusion, the preparation of optically active diastereoisomers of 2-methyl-1-phenyl-1,3-butanediol was achieved by chemo-enzymatic methods using two different modes of reduction. In both methods, in situ racemization during bioreduction played an important role. The results of these experiments indicated that there is a clear difference between one pot and stepwise reduction methods. At this stage it is not possible to explain this through a rational mechanism, however, it is apparent that the presence of microorganisms has a definite influence on diastereoselectivity of the final products during $NaBH_4$ reductions. There are reports of reduction of 1,3-diketones in the presence of non-redox proteins such as BSA where the protein functioning as a template/guide facilitated the induction of diastereoselectivity during $NaBH_4$ reduction.[7,13] Though it is not possible to derive any analogy to BSA due to the complex nature of microorganisms, nonetheless, their dual role in diastereoselective reductions is apparent.

4. Experimental section

4.1. General

^{1}H NMR spectra were recorded as δ values at 200 MHz NMR and ^{13}C NMR at 50 MHz using $CDCl_3$ as a solvent and TMS as internal standard. Infrared spectra were recorded as KBr pellets in cm^{-1} on a Hitachi 270-30 spectrophotometer. Mass spectra were recorded on JEOL MSD-300 mass spectrophotometer. Optical rotations were measured on Perkin–Elmer 241 polarimeter in $CHCl_3$ solution. Chiral HPLC was performed on a Shimadzu LC-10 AT model on a Diacel OD-H chiral column.

4.1.1. Cultivation of the microorganisms. For the general preparation of biomass, following solution was used (g L^{-1}); yeast 3 g, dextrose 20 g, peptone 10 g and pH adjusted to 6.5. The medium was autoclaved at 120 °C for 20 min. The dextrose solution autoclaved separately and used prior to inoculation. The flask (1000 mL) filled with 250 mL of the medium inoculated and cultivated under CO_2 atmosphere on a rotary shaker (200–220 rpm) at a temperature of 30 °C. The optical density (OD) of the medium was observed at 610 nm and the medium centrifuged (8000 rpm) at 10–15 °C for 8–10 min. The pellet was washed with autoclaved distilled water and centrifuged again. The cell pellet thus obtained was used as such for biotransformation studies.

4.1.2. One-pot chemo-enzymatic preparation of (1*R*,2*S*, 3*S*)-2-methyl-1-phenyl-1,3-butanediol 4. In a typical experiment, ethanolic solution of (±)-**1** (100 mg, 0.57 mmol in 1 mL) was added to a suspension of *B. pseudomegaterium* (wet pellet, 4.5 g) in distilled water (55 mL) containing glucose (3 g) and the contents shaken at 28 °C using a bubbler. After the completion of the reaction (48 h), the ee % of the intermediate **7** was analyzed on Diacel OD-H (chiral column), using isopropanol/hexane=0.2:99.8 as eluent at a flow rate of 3 mL/min. Thereafter, the contents of the reaction mixture were cooled to 15 °C and $NaBH_4$ (30 mg) was added in three small portions while stirring. After the completion of the reaction (1.5 h), HPLC analysis of the mixture showed formation of two products **4** (95%) and **5** (5%), de=90% and ee=97% (major product). Purification of the mixture over silica gel afforded a product (1*R*,2*S*, 3*S*)-2-methyl-1-phenyl-1,3-butanediol **4** as a white solid (73 mg, 0.41 mmol), mp 83 °C; $[\alpha]_D^{25}$ +37.5 (*c* 1.0, $CHCl_3$); IR (KBr): 3356, 2972, 2927, 1493, 1452, 701 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.26–7.33 (5H, m, Ar-H), 5.09 (1H, d, *J*=2.2 Hz, PhC*H*OH), 3.80 (1H, quintet, *J*=6.2 Hz, CH_3C*H*OH), 1.82 (1H, d quintet, *J*=6.3, 2.7 Hz, CHC(2)), 1.28 (3H, d, *J*=6.3 Hz, CH_3CHOH), 0.79 (3H, d, *J*=7.0 Hz, CH_3C(2)); ^{13}C NMR (50 MHz): δ 142.6, 128.7, 128.4, 128.0, 127.0, 126.2, 75.0(C1), 70.8(C3), 45.5(C2), 21.9(C4), 11.5(CH_3); MS *m*/*z* (%): 181 (1), 162 (3), 118 (5), 117 (7), 107 (100), 105 (9), 91 (5), 79 (28), 77 (20), 57 (56); Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.22; H, 9.16.

4.1.3. One-pot chemo-enzymatic preparation of (1*R*, 2*R*,3*S*)-2-methyl-1-phenyl-1,3-butanediol 2 and (1*S*, 2*R*,3*S*)-2-methyl-1-phenyl-1,3-butanediol 3. In an experimental process described as above, reaction of (±)-**1** with *C. crusei* afforded the intermediate **6** (time 54 h) (ee∼99%, calculated by chiral HPLC). In the same pot $NaBH_4$ reduction of **6** at 15 °C followed by normal processing and separation on a silica gel column gave (1*R*,2*R*,3*S*)-2-methyl-1-phenyl-1,3-butanediol **2** as a semi-solid (31 mg, 0.17 mmol, 31% yield); $[\alpha]_D^{25}$ +38.5 (*c* 1.0, $CHCl_3$) (98% ee); IR (KBr): 3356, 3063, 2974, 2933, 1493, 1453, 1416, 1126, 1001, 927, 701 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.22–7.28 (5H, m, Ar-H), 4.61 (1H, d, *J*=7.3 Hz, PhC*H*OH), 3.96 (1H, qd, *J*=6.6, 2.2 Hz, CH_3C*H*OH), 1.86 (1H, d quintet, *J*=7.2, 2.2 Hz, CHC(2)), 1.13 (3H, d, *J*=6.3 Hz, CH_3CHOH), 0.73 (3H, d, *J*=7.1 Hz, CH_3C(2)); ^{13}C NMR (50 MHz): δ 143.0, 128.3, 128.0, 127.5, 126.4, 125.6, 78.0(C1), 69.2(C3), 44.4(C2), 19.2(C4), 12.1(CH_3); MS *m*/*z* (%): 181 (1), 162 (7), 147 (4), 117 (52), 107 (100), 105 (28), 91 (5), 79 (28), 77 (20); Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.18; H, 9.11; and (1*S*,2*R*,3*S*)-2-methyl-1-phenyl-1,3-butanediol **3** as a semi-solid (24 mg, 0.13 mmol, 24% yield); $[\alpha]_D^{25}$ −35.2 (*c* 1.0, $CHCl_3$ (96% ee); IR (KBr): 3356, 2972, 1453, 1126, 1056, 1021, 1001, 701, 669 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.19–7.28 (5H, m, Ar-H), 4.99 (1H, d, *J*=2.8 Hz, PhC*H*OH), 4.17 (1H, qd, *J*=6.4, 2.5 Hz, CH_3C*H*OH), 1.88 (1H, d quintet, *J*=7.1, 2.6 Hz, CHC(2)), 1.15 (3H, d, *J*=6.5 Hz, CH_3CHOH), 0.75 (3H, d, *J*=7.0 Hz, CH_3C(2)); ^{13}C NMR (50 MHz): δ 143.0, 128.3, 128.0, 126.9, 126.1, 125.5, 78.4(C1), 72.0(C3), 45.0(C2), 21.8(C4), 11.4(CH_3); MS *m*/*z* (%): 181 (3), 163 (2), 147 (7), 118 (44), 107 (100), 105 (20); Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.14; H, 9.18.

4.1.4. DIBAL-H reduction of 6: preparation of 3. In a typical experiment, to a solution of (2*R*,3*S*)-3-hydroxy-2-methyl-1-phenylbutanone **6** (178 mg, 1 mmol) in THF (25 mL) at −78 °C, DIBAL-H (3 mmol, 1 mol/L THF solution) was added dropwise while maintaining the temperature. After stirring for 3.5 h, the mixture was quenched with 5% HCl solution. The reaction mixture was extracted with solvent ether and washed with NaCl solution. The ethereal solution was dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography

on silica gel to give a semi-solid (1*S*,2*R*,3*S*)-2-methyl-1-phenyl-1,3-butanediol **3** (149 mg, 83% yield), $[\alpha]_D^{25}$ −35.2 (*c* 1.0, $CHCl_3$) (97% ee, 95% de).

4.1.5. DIBAL-H reduction of 7: preparation of 4. THF solution of (2*S*,3*S*)-3-hydroxy-2-methyl-1-phenylbutanone **7** (178 mg, 1 mmol) was reduced with DIBAL-H (3 mmol, 1 mol/L THF solution) at −78 °C as described above. After the completion of the reaction (3.5 h) and processing, purification of the crude product by column chromatography on silica gel gave (1*R*,2*S*,3*S*)-2-methyl-1-phenyl-1,3-butanediol **4** as a white solid, mp 82 °C (153 mg, 85% yield), $[\alpha]_D^{25}$ +37.5 (*c* 1.0, $CHCl_3$) (97% ee, 93% de).

4.1.6. $NaBH_4$ reduction of 7: preparation of 4 and 5. In a methanolic solution of **7** (125 mg, 0.70 mmol, 50 mL), $NaBH_4$ (19 mg, 0.5 mmol) was added slowly at 0 °C and the reaction monitored by TLC. After the completion of the reaction and usual processing, the products were separated by chromatography over silica gel to give (1*R*,2*S*,3*S*)-2-methyl-1-phenyl-1,3-butanediol **4** as a white solid, mp 83 °C (36 mg, 29% yield), $[\alpha]_D^{25}$ +36.8 (ee 97%) and (1*S*,2*S*,3*S*)-2-methyl-1-phenyl-1,3-butanediol **5** as a white solid, mp 86 °C (27 mg, 21% yield); $[\alpha]_D^{25}$ −29.8 (*c* 1.0, $CHCl_3$) (97% ee); IR (KBr): 3356, 3057, 2974, 2933, 1490, 1453, 1416, 1126, 1020, 759, 705 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.21–7.30 (5H, m, Ar-H), 4.48 (1H, d, *J*=9.2 Hz, PhC*H*OH), 3.91 (1H, qd, *J*=8.2, 6.1 Hz, CH_3CHOH), 1.83 (1H, m, CHC(2)), 1.24 (3H, d, *J*=6.1 Hz, CH_3CHOH), 0.68 (3H, d, *J*=7.1 Hz, $CH_3C(2)$); ^{13}C NMR (50 MHz): δ 142.2, 128.7, 127.8, 127.0, 126.0, 125.5, 77.1(C1), 71.2(C3), 46.1(C2), 21.7(C4), 13.0(CH_3); MS *m*/*z* (%): 181 (1), 162 (5), 133 (4), 125 (7), 107 (100), 105 (5), 91 (3), 79 (30), 57 (50), 43 (10); Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.39; H, 9.08.

4.1.7. Preparation of racemic 3-hydroxy-2-methyl-1-phenylbutanone. Racemic 2-methyl-1-phenyl-1,3-butanediol (900 mg, 5 mmol), obtained as a result of $NaBH_4$ reduction of diketone (±)-**1**, was reacted with pyridinium dichromate (1.880 g, 5 mmol) in dimethyl formamide (10 mL), the contents stirred at 0 °C for 2.5 h and the reaction monitored by TLC. After completion of the reaction, the mixture diluted with solvent ether (150 mL), filtered and the solid washed with solvent ether (2×50 mL). The combined organic layer was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel to give a mixture of *syn*- and *anti*-3-hydroxy-2-methyl-1-phenylbutanone as an oil (360 mg, 40% yield) in the ratio of 40:60 as analyzed from ^1H NMR.

4.1.8. Biocatalytic reduction of 2-methyl-1-phenyl-1,3-butanedione 1.

4.1.8.1. Preparation of (2*R*,3*S*)-3-hydroxy-2-methyl-1-phenylbutanone 6. In a typical experiment, to a suspension of *S. marcescens* (wet pellet, 4.5 g) in distilled water (55 mL) containing glucose (3.0 g), an ethanolic solution of compound (±)-**1** (100 mg, 0.57 mmol in 1 mL) was added and the contents shaken at 28 °C using a bubbler. The progress of the reaction was monitored by TLC. After the completion of the reaction (54 h), the contents were centrifuged and the supernatant and cell pellet extracted separately with solvent ether (3×70 mL). The combined organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure to furnish a crude product, which on purification by column chromatography on silica gel and elution with hexane/ethyl acetate (85:15) afforded (2*R*,3*S*)-3-hydroxy-2-methyl-1-phenylbutanone **6** as a semi-solid (85 mg, 85% yield); $[\alpha]_D^{25}$ −16.3 (*c* 1.0, $CHCl_3$) (99% ee); IR (KBr): 3442, 2974, 1677, 1448, 1215, 972, 910, 707 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.94 (2H, d, *J*=8.1 Hz, Ar-H), 7.50–7.56 (3H, m, Ar-H), 4.24 (1H, qd, *J*=6.0, 3.1 Hz, CH_3CHOH), 3.42 (1H, qd, *J*=7.5, 3.1 Hz, CHC(2)), 1.26 (3H, d, *J*=7.4 Hz, CH_3CHOH), 1.18 (3H, d, *J*=6.4 Hz, $CH_3C(2)$); ^{13}C NMR (50 MHz): δ 205.8(C1), 135.9, 133.4, 128.7(2C), 128.4(2C), 67.5(C3), 45.8(C2), 20.3(C4), 11.2(CH_3); MS *m*/*z* (%): 179 (0.7), 178 (0.2), 160 (11), 133 (30), 123 (34), 106 (10), 105 (100); Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.19; H, 7.79.

4.1.8.2. Preparation of (2*S*,3*S*)-3-hydroxy-2-methyl-1-phenylbutanone 7. To a suspension of *Z. rouxii* (wet pellet, 4.5 g) in distilled water (55 mL) containing glucose (3 g), an ethanolic solution of compound (±)-**1** (100 mg, 0.57 mmol in 1 mL) was added and the contents shaken at 28 °C using a bubbler. Reaction was monitored by TLC. After the completion of the reaction (48 h) and processing, purification by column chromatography over silica gel gave a white solid (2*S*,3*S*)-3-hydroxy-2-methyl-1-phenylbutanone **7**, mp 43–45 °C (83 mg, 83% yield); $[\alpha]_D^{25}$ +67.5 (*c* 1.0, $CHCl_3$) (98% ee); IR (KBr): 3441, 2973, 1678, 1448, 1376, 1112, 911, cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.99 (2H, d, *J*=7.3 Hz, Ar-H), 7.52–7.58 (3H, m, Ar-H), 4.14 (1H, quintet, *J*=6.4 Hz, CH_3CHOH), 3.51 (1H, quintet, *J*=7.0 Hz, CHC(2)), 1.31 (3H, d, *J*=6.4 Hz, CH_3CHOH), 1.26 (3H, d, *J*=7.3 Hz, $CH_3C(2)$); ^{13}C NMR (50 MHz): δ 205.2(C1), 136.4, 133.2, 128.6(2C), 128.3(2C), 69.7(C3), 47.6(C2), 20.7(C4), 15.2(CH_3); MS *m*/*z* (%): 179 (0.3), 178 (0.3), 164 (0.5), 163 (1), 160 (5), 145 (1), 133 (27), 123 (34), 105 (100), 91 (2); Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.21; H, 7.84.

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