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Trichosporon cutaneum-promoted deracemization of (±)-2-hydroxindan-1-one: a mechanistic study

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Abstract—A mechanistic study of the deracemization of (±)-2-hydroxy-1-indanone mediated by the yeast *Trichosporon cutaneum* to afford pure (1*S*,2*R*)-1,2-indandiol is reported. The key aspect of the study was the use of pure (*R*)- and (*S*)-2-hydroxy-1-indanone enantiomers to ensure reliable conclusions. Experiments in the absence of yeast cells or using dead cells disclosed that the pure enantiomers were not racemized, which suggest that the whole dynamic kinetic resolution process is enzymatic in character. When living yeast cells were used the (*R*)-substrate was smoothly converted to (1*S*,2*R*)-1,2-indandiol, whilst the (*S*)-2-hydroxy-1-indanone was converted to the same diol through a more complex fashion, which requires a more lengthy oxidation–reduction pathway having the 1,2-indanedione as an achiral intermediate. An unexpected observation was that 1,2-indanone acts as a moderate inhibitor of the reductive enzymes acting in the conversion of (*R*)-2-hydroxy-1-indanone to (1*S*,2*R*)-1,2-indandiol.

1. Introduction

Enantiomerically pure 1,2-diols are an important commonly occurring functional group pattern in natural products such as carbohydrates and polyketides in chiral ligands used in asymmetric catalysis, and the literature details a number of methods for their synthesis.[1] Therefore, much effort has been invested in the development of stereoselective methods for 1,2-diol synthesis. A very powerful one for preparing *syn*-1,2-diols is the Sharpless asymmetric dihydroxylation of *trans*-disubstituted olefins.[2]

Optically active amino alcohols are also important structural building blocks found in a plethora of natural products.[3] Their stereoselective synthesis has been a subject of recent interest.[4] In addition, 1,2-amino alcohol residues are also present in many important commercial drugs as chloramphenicol,[5] ephedrine,[6] and indinavir,[7] and can be prepared from a 1,2-diol through a Ritter reaction.[8]

Nowadays, a versatile environmentally friendly alternative to prepare enantiopure compounds involves biocatalytic resolution of racemates by microbial enzymes. The deracemization with kinetic resolution method often provides compounds with high enantiomeric excess although the maximum theoretical yield of product or substrate is only 50% in such a process.[9] This limitation of kinetic resolution can be overcome by employing a deracemization technique known as dynamic kinetic resolution (DKR). DKR has recently become not only an alternative to traditional kinetic resolution, but also a new procedure for asymmetric synthesis.[10] It is one of the most useful and reliable methods to prepare a single chiral compound bearing two or more stereocenters starting from a racemate, with a theoretical yield of 100%. Several examples were reported employing this dynamic kinetic resolution (DKR).[11]

Recently, we reported a biocatalytic synthesis of (1*S*,2*R*)-1,2-indandiol **2** from 1,2-indanone with high stereoselectivity, using resting whole cells of the yeast *Trichosporon cutaneum*.[12] Monitoring of the reaction profile by chiral GC analysis disclosed that the biocatalytic reduction of the 1,2-indandione was not a simple one-step stereoselective reduction. In fact, it was observed that the

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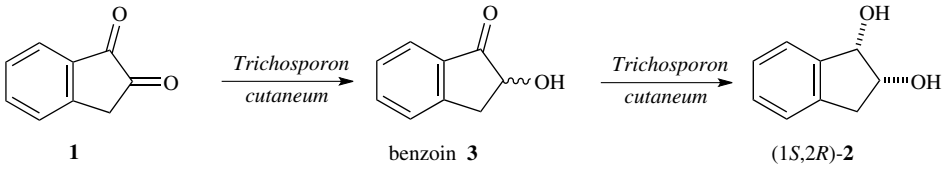


Scheme 1.

(±)-2-hydroxy-1-indanone was being formed as a racemate (Scheme 1). Therefore, the results indicate that the reactive enantiomer is being depleted by the stereoselective reduction to give **2** and the equilibrium (*R*)-**3**/(*S*)-**3** concentrations are constantly re-adjusted until the complete conversion of the substrate occurred. In the mechanism proposed, the unreactive enantiomer (*S*)-**3** is isomerized to (*R*)-**3**, in a concomitant step. As a result, the clean dynamic kinetic resolution (DKR) of the racemic 2-hydroxy-1-indanone **1** afforded enantiomerically pure (1*S*,2*R*)-1,2-indandiol (**2**) in high yield (90%) and with an excellent ee (>99%).

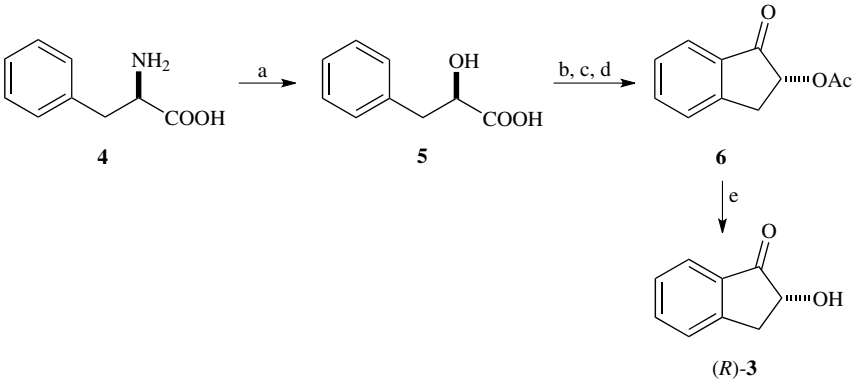
2. Results and discussion

In order to better understand the microbial deracemization of the title compound, it was imperative to undertake a systematic study of the bio-reduction reaction, using pure enantiomers of 2-hydroxy-1-indanone as substrates. The (*R*)- and (*S*)-2-hydroxy-1-indanone (**3**) were readily available from (*R*)- and (*S*)-phenylalanine in 35% (98% ee) and 32% (97% ee) isolated yield, through the method previously described by Kajiro et al.[13] (Scheme 2). Attempts to use a different less expensive catalyst for the last step in the synthesis (acetate **6** hydrolysis) were fruitless.

The first step to understand the biotransformation of (±)-**3** by *T. cutaneum* was to find the origin of the stereoinversion of the starting material observed in the proposed dynamic kinetic resolution (DKR) process. Thus, to establish whether the conversion of (*S*)- to the (*R*)-**3** enantiomer was induced by some component of the reaction media or mediated by an enzyme present in yeast, we carried out some simple control experiments. These experiments were conducted in parallel reactions for each enantiomer using the following conditions: (a) in the absence of *T. cutaneum* cells, each substrate, (*R*)-**3** or (*S*)-**3**, was independently suspended in distilled water; (b) each substrate, (*R*)-**3** or (*S*)-**3**, was treated with dead *T. cutaneum* cells (yeast cells were killed by treatment with ethanol and acetone); (c) each substrate, (*R*)-**3** or (*S*)-**3**, was treated with dead *T. cutaneum* cells (cells were heated in an autoclave at 121 °C for 30 min). All three experiments were performed on an orbital shaker (170 rpm) at 28 °C for a week.

The mixtures were then extracted with ethyl acetate and after concentration the resulting residues were promptly analyzed by chiral GC. In all cases, the analysis shows no isomerization of the pure substrates (*R*)-**3** or (*S*)-**3**, which indicates that the dynamic kinetic resolution observed in the biotransformation of dione **1** by *T. cutaneum* is enzymatic as a whole. Since a stereoinversion of (*S*)-**3** to (*R*)-**3** is required to explain the formation of (1*S*,2*R*)-**2** as the major product (90% yield), the expression by *T. cutaneum* of a racemase that would act on the isomerization of enantiomer (*S*)-**3** was initially postulated.[12] To investigate this hypothesis, we planned and performed new experiments to evaluate the details of the biotransformation of pure enantiomers (*R*)- or (*S*)-**3** separately. Accordingly, the experiments were carried out in distilled water using resting cells of *T. cutaneum* and pure (*R*)- or (*S*)-**3** as substrates.

The biotransformations were conducted on an orbital shaker (170 rpm) at 28 °C until complete conversion of the substrate. Reactions were periodically monitored through sample analysis by chiral GC. We observed that the (*R*)-**3** was biotransformed by *T. cutaneum* in 22 h in a clean fashion (no by products such as indanone **1** were detected) giving ultimately (1*S*,2*R*)-diol **2** as the sole product in both



Scheme 2. Reagents and conditions: (a) $NaNO_2$, 1 mol L^{-1} H_2SO_4, 0 °C to rt; (b) Ac_2O/pyridine, 0 °C to rt, 12 h; (c) $SOCl_2$, rt to 50 °C, 3 h; (d) $AlCl_3$/CH_2Cl_2, rt, 3 h; (e) $Sc(OTf)_3$ (20 mol %) MeOH–H_2O, rt, 61 h.

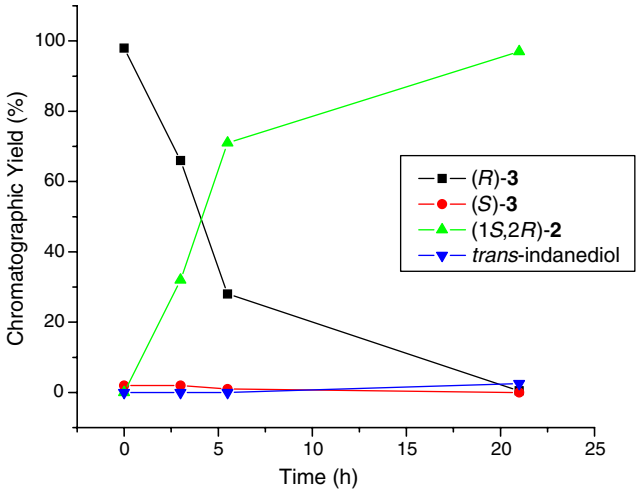
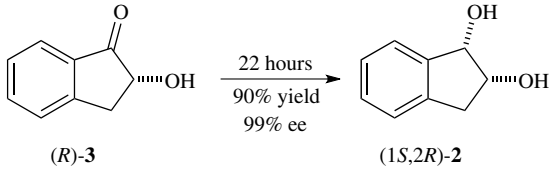


Figure 1. Relative percentage of substrate and products as a function of time for the reduction of (*R*)-**3** by yeast *Trichosporon cutaneum* in water at 28 °C.



Scheme 3.

high yield and enantiomeric excess (90% and 99%, respectively) as shown in Figure 1 and Scheme 3. It is important to stress that (*R*)-**3** was not isomerized to (*S*)-**3** by the yeast under such experimental conditions.

After complete conversion of the substrate, the cells were removed by centrifugation and crude product **2** was isolated from the aqueous layer by extraction with ethyl acetate. Purification was achieved by flash chromatography to give (1*S*,2*R*)-**2** in 90% yield and 99% ee (Scheme 3).

On the other hand, the biotransformation of (*S*)-**3** to (1*S*,2*R*)-**2** took place through a different route than that observed for (*R*)-**3** enantiomer. Detailed analysis of the results of the experiments show that substrate (*S*)-**3** was isomerized to form enantiomer (*R*)-**3** through the intermediate formation of dione **1** by oxidation followed by further reduction of the dione by *T. cutaneum* to afford (1*S*,2*R*)-diol **2** as previously reported by us.[12] Therefore, the biotransformation of (*S*)-**3** requires the existence of an equilibrium-controlled reduction–oxidation sequence rather than the action of a single enzyme (like a racemase). Faber and co-workers also observed a similar reduction–oxidation sequence when studying the racemization of (*R*)-2-hydroxy-1-indanone **3** by *Lactobacillus paracasei* DSM 20207.[14] In addition, they found that alkaline medium (pH lower than 10) favored the oxidation of the substrate.

The complete conversion of (*S*)-**3** by *T. cutaneum* was accomplished only after 42 h and in spite of the longer reaction time, the product (1*S*,2*R*)-diol **2** was also isolated in both high yield and ee (85% and 99%, respectively).

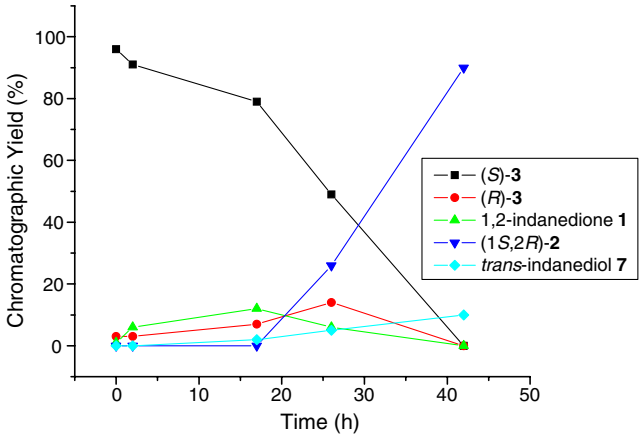
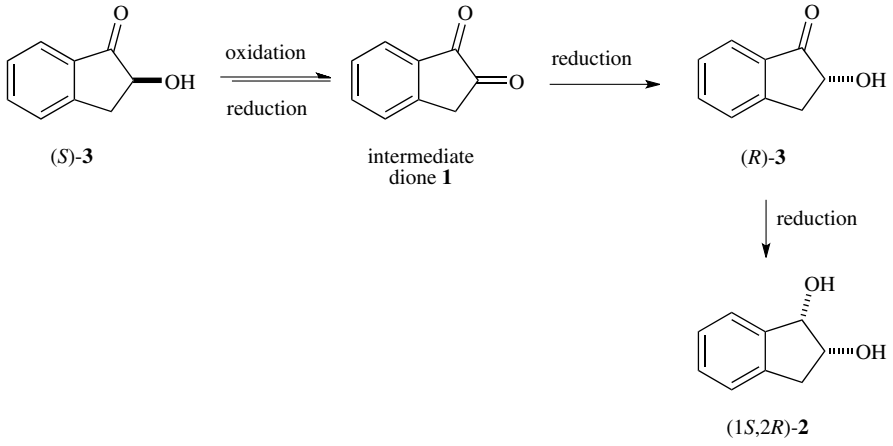


Figure 2. Relative percentage of substrate and products as a function of time for the reduction of (*S*)-**3** by yeast *Trichosporon cutaneum* in distilled water at 28 °C.



Scheme 4. Proposed general mechanism for the biotransformation of (*S*)-**3** by resting cells of *Trichosporon cutaneum* in distilled water at 28 °C.

Figure 2 summarizes the complex biotransformation profile of (*S*)-**3** by *T. cutaneum* and Scheme 4 depicts a proposed general mechanism for the biotransformation.

In order to better understand the oxidation–reduction equilibrium proposed above, we re-investigated the bioreduction of dione **1** (50 mg scale) by resting cells of *T. cutaneum*. The experiments were carried out at 28 °C in distilled water and incubated in an orbital shaker (170 rpm). Periodical analyses of samples were performed by chiral GC. The reaction profile of the biotransformation is shown in Figure 3. Accordingly, after 10 min of reaction, dione **1** has already been extensively reduced to (*R*)-**3**. However, it is worth mentioning that traces of dione **1** are detected through-out the reaction, which reinforces the existence of an oxidation–reduction equilibrium between dione **1** and (*S*)-**3**, as proposed in Scheme 4. In spite of the presence of (*R*)-**3** in the medium in relatively high amounts, the formation of (1*S*,2*R*)-diol **2** was curiously observed only after 50 h of incubation. In addition, as already observed by us, the biotransformation of dione **1** was sluggish and took 120 h to completion.

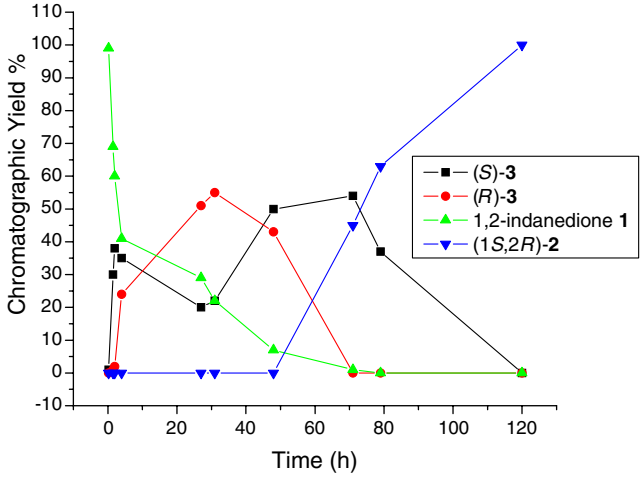


Figure 3. Relative percentage of substrate and products as a function of time during the reduction of **1** by yeast *Trichosporon cutaneum* in water at 28 °C.

Taking in account the delay for the start of the reduction (*R*)-**3** to form (1*S*,2*R*)-diol **2** and the time-consuming biotransformation of dione **1**, we considered the possibility that one of the components of the reaction medium is acting as a reductase inhibitor. In order to check such a possibility, we carried out some new experiments with *T. cutaneum* using the most reactive enantiomer (*R*)-**3** as a substrate with concomitant introduction of different amounts of dione **1** as shown in Table 1.

The results obtained shed some light on the process. As can be seen in Table 1, increasing amounts of dione **1** played a paramount effect on the biotransformation profile of (*R*)-**3** by *T. cutaneum*. In the absence of dione **1** the reaction was quickly completed in 22 h (entry 1), even when starting with a larger amount of the substrate (entry 2). No effects on the biotransformation of (*R*)-**3** were observed until 20 mg of dione **1** was added to the medium. The larger amounts of dione **1** imparted a moderate to intense delay of the reduction of the substrate and in consequence, the time required to complete the conversion increased almost threefold and fivefold (entries 5 and 6, respectively) compared to entry 2. It is clear that the delay observed to complete the conversion of the substrate due to increasing amounts of dione **1** in the medium cannot be simply associated with the larger concentration of (*R*)-**3** coming from the reduction of dione **1** since a larger starting amount of substrate (entry 2) did not change the time required for full conversion of 50 mg of (*R*)-**3** (entry 1). Therefore, it is reasonable to propose that in fact dione **1** acts as an inhibitor of the reductase involved in the biotransformation of (*R*)-**3**.

Table 1. Evaluation of the inhibitory profile of 1,2-indandione (**1**) on the biotransformation of substrate (*R*)-**3** by resting cells of *T. cutaneum*

Entry	Amount of (*R*)-**3** (mg)	Amount of **1** added (mg)	Time to full conversion (h)
1	50	0	22
2	80	0	22
3	50	5	22
4	50	10	22
5	50	20	60
6	50	30	120

We propose the hypothesis that the dione imparts an inhibitory effect by competing with compound **3** for the active site of the enzyme since the compounds are similar in structure. The inhibitory effect of dione **1** on the bio-reduction of (*R*)-**3** is further evidenced through the analysis of the chiral GC chromatograms depicted in Figure 4. Accordingly, the final product (1*S*,2*R*)-diol **2** starts to appear only after 29 h when dione **1** has nearly disappeared from the medium. We believe that this unexpected behavior is only reasonably explained if dione **1** truly acts as an inhibitor of (*R*)-**3** reductase.

3. Conclusion

In summary, evidence regarding the mechanism of the *T. cutaneum*-mediated deracemization of compound (±)-**3** using pure enantiomers (*R*)-**3** and (*S*)-**3** as substrates has been provided. The fact that no isomerization occurred in the absence of living cells of the yeast proved the enzymatic character of the inversion of the configuration of (*S*)-**3** required to form (1*S*,2*R*)-diol **2** as the main product. In addition, it was shown that the biotransformation of (*S*)-**3** formed 1,2-indandione **1** as an intermediate, which strongly suggests the existence of an equilibrium-controlled reduction–oxidation sequence rather than the action of a single enzyme in the isomerization step the biotransformation. Finally, it was demonstrated that dione **1** acts as an inhibitor of the (*R*)-**3** reductase. As such, this compound should be avoided as a substrate if the intention is to obtain (1*S*,2*R*)-diol **2** in high yield in shorter time. Therefore, it is reasonable to conclude that (±)-2-hydroxindan-1-one (**3**) should be the starting material of choice for the best results.

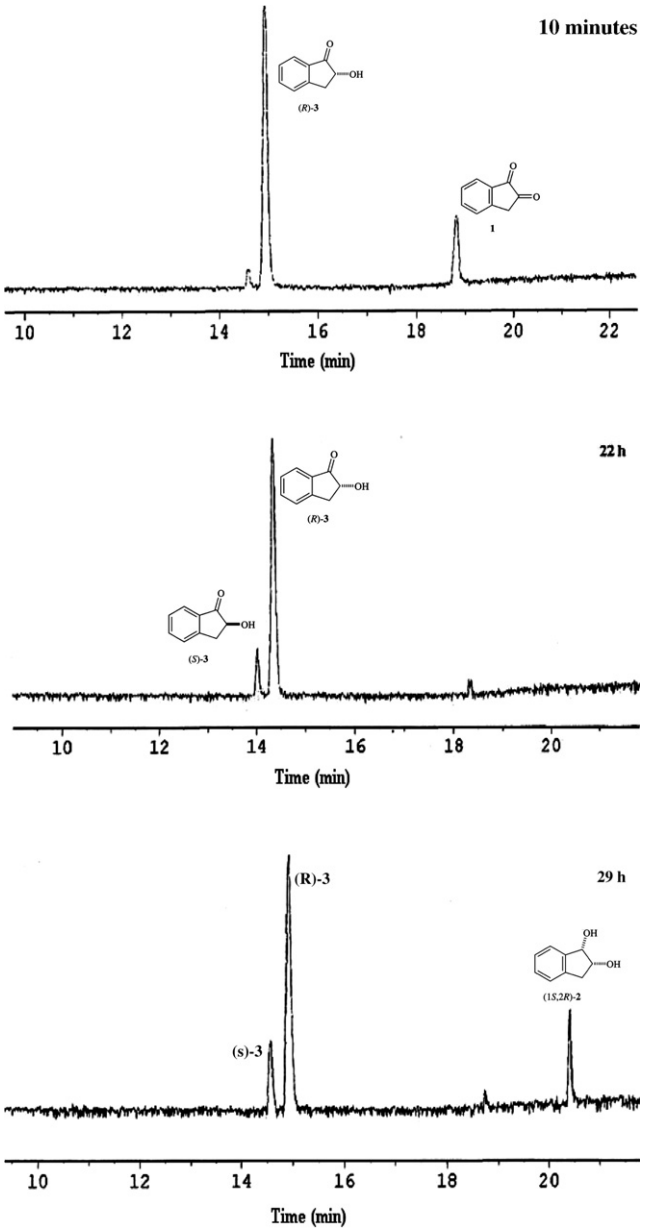


Figure 4. Chiral GC chromatograms obtained at different times for the biotransformation of (*R*)-**3** by resting cells of *T. cutaneum*, in the presence of 20 mg of dione **1**.

4. Experimental

4.1. General

All reagents and solvents were obtained from commercial sources. ^{1}H and ^{13}C NMR spectra were recorded on Varian INOVA-500 Gemini 300 spectrometers. Optical rotations were measured on a Perkin Elmer Polarimeter 341. Melting points were measured on a Microquimica MQ APF-301 equipment. GC–MS analysis and mass spectra acquisition were carried out on QP 5000-SHIMADZU or AGILENT CG 6890/HEWLETT PACKARD 5973 gas chromatographs equipped with a HP-5MS (5% phenylmethylpolysiloxane, 30 m × 250 μm × 0.25 μm) or a Macherey 212117/91 Hydrodex-β 3P fused silica capillary columns (25 m × 250 μm × 0.25 μm) with helium or hydrogen as carrier gases (1.0 mL min^{-1}). The strain of *T. cutaneum* (CCT 1903) was purchased from the "André Tosello" Research Foundation (Brazil). Culture media were purchased from Biobrás (Brazil). Flash column chromatography was carried out on silica (200–400 mesh, Merck).

4.2. (*R*)-2-Hydroxy-3-phenylpropanoic acid 5

Aqueous $NaNO_2$ (21 g, 300 mmol, in 50 mL of H_2O) and H_2SO_4 (3.2 mol L^{-1} aqueous solution, 50 mL) were added to a solution of D-(*R*)-phenylalanine **4** (10 g, 61 mmol) in H_2SO_4 (1 mol L^{-1}, 200 mL) over 30 min at 0 °C. The reaction mixture was stirred for 75 min at 0 °C and then extracted with EtOAc (3 × 100 mL). The organic layer was washed with brine (2 × 100 mL), dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by recrystallization (EtOAc–hexane 4:1) to give (*R*)-2-hydroxy-3-phenylpropanoic acid **5** (7.7 g, 77% yield, >99% ee) as colorless crystals. Enantiomeric excess of (*R*)-**5** was determined after conversion to its methyl ester: diazomethane was added dropwise (0.5 mL, ethyl ether solution) to a solution of (*R*)-**5** (10 mg) in MeOH (5 mL). The resulting mixture was concentrated under reduced pressure. The residue was dissolved in EtOH and analyzed by GC–MS using a chiral column.

Mp 118.4–121.5 °C (lit.[15] 126.0–127.0 °C); $[\alpha]_D^{20} = +25.4$ (*c* 1.0, H_2O) (lit.[3] $[\alpha]_D^{20} = +20.4$ (*c* 1.0, H_2O)). Spectroscopic data for compound (*R*)-**5** were in agreement with those previously reported.

Starting with L-(*S*)-phenylalanine and using the same methodology (*S*)-2-hydroxy-3-phenylpropanoic acid (*S*)-**5** was obtained in 75% yield, >99% ee. Mp 118.4–121.5 °C (lit.[3] 126.0–127.0 °C); $[\alpha]_D^{20} = -27.0$ (*c* 1.0, H_2O) (lit.[3] $[\alpha]_D^{20} = -20.0$ (*c* 1.0, H_2O)). Spectroscopic data for compound (*S*)-**5** were in agreement with those previously reported.

4.3. (*R*)-2-Acetoxy-1-indanone 6

Acetic anhydride (5.3 mL, 56 mmol) at 0 °C was added to a solution of (*R*)-2-hydroxy-3-phenylpropanoic acid (**5**) (7.7 g, 46.4 mmol) in pyridine (50 mL). The resulting mixture was stirred at 25 °C for 12 h before concentration under reduced pressure. The residue was redissolved in EtOAc (30 mL), washed with HCl (1 mol L^{-1}, 2 × 50 mL), dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure to afford (*R*)-2-acetoxy-3-phenylpropanoic acid as an amber-colored oil (9.4 g, 97% yield). This crude product was used in the next step without further purification.

A solution of crude (*R*)-2-acetoxy-3-phenylpropanoic acid (9.4 g, 45 mmol), in thionyl chloride (17 mL, 0.15 mol) was stirred at room temperature for 20 min and then heated at 50 °C for 3 h. Removal of all volatile materials under reduced pressure furnished the crude product, (*R*)-2-acetoxy-3-phenylpropanoyl chloride (9.2 g, 38.25 mmol, 90% yield), as an amber-colored oil. This crude product

was used in the next step without further purification. Thus, $AlCl_3$ (13 g, 97 mmol). was added in one portion to a solution of the oil in CH_2Cl_2 (400 mL) The resulting mixture was stirred at 25 °C for 80 min and treated with an ice-water mixture (300 mL). The organic layer was removed and the aqueous layer was further extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc 4:1) to give compound (*R*)-**6** (5 g, 65% yield, >99% ee) as an off-white solid. Mp 81.3–81.5 °C; (lit.[2] 80.5–81.5 °C). IR (KBr) 1728, 1607, 1372, 1252, 1223, 1184 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 2.19 (s, 3H), 3.04 (dd, $J = 4.7$ and 17.1 Hz, 1H), 3.66 (dd, $J = 8.0$ and 17.1 Hz, 1H), 5.42 (dd, $J = 4.7$ and 8.0 Hz, 1H), 7.39–7.46 (m, 2H), 7.64 (t, $J = 7.2$ Hz, 1H), 7.78 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.8, 33.4, 74.0, 124.3, 126.5, 128.0, 134.3, 135.7, 150.2, 170.2, 200.3; $[\alpha]_D^{20} = -19.0$ (*c* 1.0, MeOH) (lit.[2] $[\alpha]_D^{20} = -19.0$ (*c* 1.0, MeOH)).

The (*S*)-2-acetoxy-1-indanone (*S*)-**6** was prepared from (*S*)-2-hydroxy-3-phenylpropanoic acid (*S*)-**5** using the same methodology (54% yield, >99% ee). $[\alpha]_D^{20} = +18.7$ (*c* 1.0, MeOH).

4.4. (*R*)-2-hydroxy-1-indanone 3

An aqueous solution of $Sc(OTf)_3$ (2.6 g, 5.3 mmol) in 50 mL of distilled water was added to a solution of (*R*)-2-acetoxy-1-indanone **6** (5 g, 26 mmol) in MeOH (200 mL). The resulting mixture was stirred at 30 °C for 60 h and then concentrated under reduced pressure. The residue was diluted in distilled water (50 mL) and extracted with EtOAc (3 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc 7:3) to give compound (*R*)-**3** (3.2 g, 82% yield, 98% ee) as a colorless solid.

Mp 79.9–81.0 °C; (lit.[2] 82.4–83.7 °C). IR (KBr) 3418, 1716, 1609, 1585, 1303, 1207, 1091, 912, 753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 3.02 (dd, $J = 5.1$ and 16.4 Hz, 1H), 3.58 (dd, $J = 7.8$ and 16.4 Hz, 1H), 3.74 (s, 1H), 4.58 (dd, $J = 5.1$ and 7.8 Hz, 1H), 7.37–7.47 (m, 2H), 7.60–7.66 (m, 1H), 7.75 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (125 MHz $CDCl_3$) δ: 35.2, 74.2, 124.3, 126.6, 127.8, 133.9, 135.7, 150.8, 206.5; $[\alpha]_D^{20} = -53.0$ (*c* 1.0, MeOH) (lit.[2] $[\alpha]_D^{20} = -57.0$ (*c* 1.0, MeOH)).

The (*S*)-2-Hydroxy-1-indanone **3** was prepared from (*S*)-2-acetoxy-1-indanone (*S*)-**6** using the same procedure described above. Data: 80% yield, 97% ee, $[\alpha]_D^{20} = +54.0$ (*c* 1.0, MeOH).

4.5. Growth conditions of *T. cutaneum* CCT 1903

T. cutaneum CCT 1903 was incubated in sterile SDB (Sabouraud dextrose broth, 1 L) at 166 rpm at 30 °C on an orbital shaker for 3 days. After suitable biomass accumulation, the cells were harvested by centrifugation (5000 rpm, 6 min) prior to use in the reactions.

4.6. Typical procedure for the biotransformation of the substrates

A solution of 50 mg of the substrate, that is, (±)-**3**, (*R*)-**3**, (*S*)-**3** or diketone **1** in ethanol (0.5 mL) was added to a slurry of *T. cutaneum* CCT 1903 (3 g, wet weight) in sterile distilled water (50 mL). The resulting suspension was stirred on an orbital shaker (166 rpm) at 28 °C until the total consumption of the substrate. After centrifugation (5000 rpm), the supernatant and cell pellet were thoroughly extracted with ethyl acetate. The organic extracts were combined, dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. All the substrates tested presented (1*S*,2*R*)-1,2-indanediol **2** as the major product. Purification was achieved by flash column chromatography on silica gel (hexane/EtOAc 1:1) to furnish desired diol (1*S*,2*R*)-**2** (90% yield, >99% ee) as white crystals.

Mp 94–98 °C (lit.[16] 98 °C). IR (KBr): 3529, 3439, 3298, 3153, 2923, 1459, 1337, 1187, 1155, 987, 737, 634 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ: 2.76 (dd, $J = 15.6$ and 3.7 Hz, 1H), 2.92 (dd, $J = 15.6$ and 5.6 Hz, 1H), 4.24–4.27 (m, 1H), 4.58 (d, $J = 4.9$ Hz, 1H), 4.78 (dd, $J = 6.7$ and 4.9 Hz, 1H), 4.99 (d, $J = 6.7$ Hz, 1H), 7.17–7.20 (m, 3H), 7.30 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 38.28, 72.90, 75.05, 124.76, 124.83, 126.29, 127.62, 140.57, 143.96.

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