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Microbial Transformation of 2-Hydroxy and 2-Acetoxy Ketones with *Geotrichum* sp.

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Abstract—Biotransformation of a series of *o*-, *m*- and *p*-substituted α-hydroxy- and α-acetoxyphenylethanones **1a–h** and **9a–g** with *Geotrichum* sp. led to the corresponding 1,2-diols **2** and/or monoacetates **10** in moderate to excellent enantiomeric excesses. α-Hydroxy- and α-acetoxyphenylethanones and their *m*- and *p*-derivatives gave preponderantly the *S*-configuration products while in the case of the *o*-derivatives *R*-alcohol was provided as the major enantiomer. The results of stereoselectivity were discussed. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

Optically active 1,2-diols are versatile and important synthetic intermediates in fine organic synthesis, in particular for the preparation of biologically active compounds.[1] The necessity of preparing such target molecules in an optically pure form has triggered much research, leading to the emergence of various synthetic methods based on either conventional chemistry or enzyme catalyzed reactions.[2,3] Among these methods, the most important one is the asymmetric dihydroxylation of olifelins.[2] Another potentially powerful route into optically active 1,2-diols is the asymmetric reduction of the α-hydroxy ketones.[3] Compared with the usual chemical methods,[2a,3a–e] the advantages of biological methods are the higher enantio- and chemoselectivity, milder and environmentally friendly reaction conditions.

Though a variety of 1,2-diols have been prepared by microbial catalyzed reduction of α-hydroxy ketones,[3f,g] the microorganisms employed for this purpose are without exception baker's yeast. So far, due to the stereochemical preference of baker's yeast mediated reduction expressed as the Prelog rule,[4] the low availability of the other configuration enantiomers still remains as an unsolved problem. In the previous paper,[5] we reported an *anti*-Prelog reduction of extensive α-halo ketones and only two α-hydroxy ketones mediated by a high reductive fungus *Geotrichum* sp. We report herein our further results on the microbial reduction of the α-hydroxy ketones.

Results and Discussion

The substituted phenacyl alcohols **1a–d** were prepared by replacement of bromine in the corresponding phenacyl bromide with potassium acetate,[6] followed by acidic hydrolysis; **1e–h** were produced by hydrolysis of the corresponding phenacyl bromide in the presence of silver nitrate.[7] Having the desired α-hydroxy ketones in hand, the incubations of **1a–h** were carried out with *Geotrichum* sp. (Scheme 1). The results are summarized in Table 1.

As shown in Table 1, all of the substituted phenacyl alcohols **1a–h** could be reduced to the corresponding 1,2-diols **2a–h** by *Geotrichum* sp. Phenacyl alcohol **1a** and *p*-substituted phenacyl alcohols **1d**, **1g** and **1h** are very good substrates for *Geotrichum* sp. reduction as the corresponding (*S*)-1,2-diols were obtained with high yield and excellent enantiomeric excess (91–100%) (entries 1, 4, 7 and 8). *m*-Substituted phenacyl alcohols **1c** and **1f** are still good substrates for *Geotrichum* sp. reduction and the corresponding (*S*)-1,2-diols **2c** and **2f** were obtained in good yield and moderate to high enantiomeric excess (entries 3 and 6). When *o*-substituted phenacyl alcohols **1b** and **1e** were incubated with *Geotrichum* sp., to our surprise, the isolated 1,2-diols **2b** and **2e** were in relatively low e.e. and *R* configuration (entries 2 and 5).

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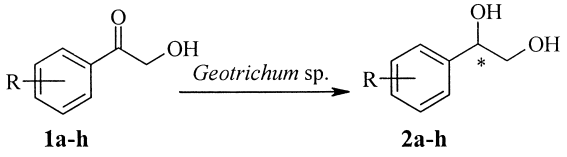


Scheme 1.

Therefore, the resulting selectivities markedly depend on the nature and the position of the substituent group. First of all, the position of the substituent had remarkable effects on the enantioselectivity of *Geotrichum* sp. mediated reduction, as yields, e.e.s and even the configuration of the 1,2-diols obtained were quite different in reduction of different position-substituted phenacyl alcohols. *o*-Substituted ketones gave (*R*)-1,2-diols preponderantly in moderate enantiomeric excess whereas (*S*)-1,2-diols were obtained by reduction of *m*- and *p*-substituted phenacyl alcohols (Table 1). The steric bulk of the substituent may also have some effects on the reduction mediated by *Geotrichum* sp. For example, **1h** with the bulky *p*-methanesulfonamide group on the phenyl ring was reduced in slow rate as only 67% yield of (*S*)-1-(4-methanesulfonamidephenyl)ethanediol (**2h**) was afforded after incubation for two days, though in excellent optical purity. There was still 13% of the starting material **1h** isolated after purification (entry 8). On the other hand, the electronic properties of the substituent group may also have some effects on the reduction. The electron-withdrawing substituent on the *p*- or *m*-position of the phenyl ring is favorable to the *Geotrichum* sp. mediated reduction. Thus, the *p*-nitrophenacyl alcohol **1g** is an excellent substrate for *Geotrichum* sp. reduction. After scale up, 10 g of **1g** can efficiently be reduced to (*S*)-**2g** with 60 g of wet mycelium (equivalent to ca. 15 g of dry biomass) without losing the yield and optical purity of the product after incubation for a day. Therefore, it will have potential perspective in industrial application.

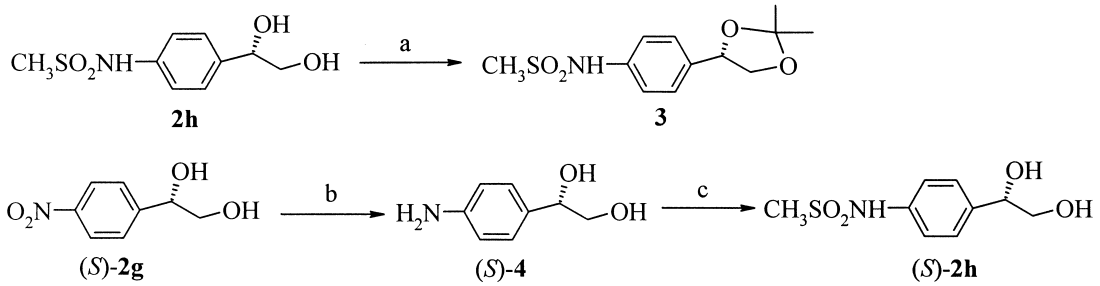
All of the enantiomeric excesses of the 1,2-diols were directly determined by chiral HPLC analysis using the racemic compounds as comparison except **2h**, which was converted to the corresponding acetonide derivative **3** (Scheme 2) and then submitted to the HPLC analysis using Chiralpak AD column, revealing that **2h** was enantiomerically pure (> 99% ee).

The absolute configurations of the 1,2-diols **2a**–**d** and **2g** were assigned by comparison of their specific rotations with the reported values (see Experimental). The absolute configurations of **2e**, **2f** and **2h** were elucidated by chemical correlations as shown in Schemes 2 and 3, respectively. The (*S*)-(+)-1-(4-nitrophenyl)ethanediol (**2g**) was hydrogenated using platinic oxide as catalyst under atmospheric hydrogen to give (*S*)-**4** quantitatively. Selective mesylation of the amino group of (*S*)-**4** gave the optically pure (*S*)-(+)-**2h**. By comparison of the specific rotation of **2h**, obtained by *Geotrichum* sp. reduction of **1h** (entry 8), with that of (*S*)-**2h**, obtained from chemical transformations of (*S*)-**2g** (Scheme 2), the absolute configuration of **2h** from *Geotrichum* sp. mediated reduction was shown to be *S*. Selective tosylation of the primary hydroxy groups of **2e** and **2f** followed by treatment with excess sodium borohydride gave **7** and **8**, respectively (Scheme 3). Thus, the stereochemistry of **2e**

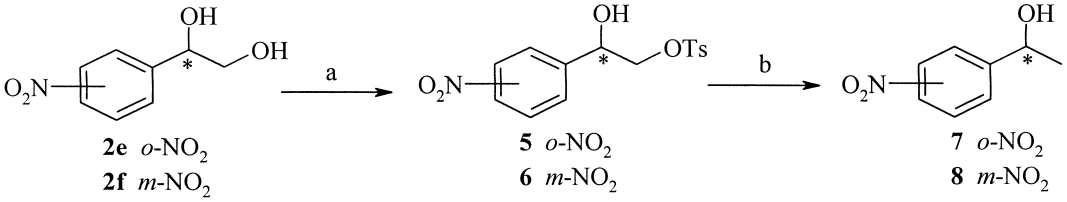
Table 1. *Geotrichum* sp. mediated reduction of α-hydroxy ketones **1a**–**h**

Entry	Substrate **1**	R	Time (h)	Yield (%)[a]	ee (%)[b]	Configuration
1	**1a**	H	16	62	91	*S*
2	**1b**	*o*-Cl	15	77	60	*R*
3	**1c**	*m*-Cl	12	93	77	*S*
4	**1d**	*p*-Cl	12	91	96	*S*
5	**1e**	*o*-NO_2	15	37 (31[c])	47	*R*
6	**1f**	*m*-NO_2	12	84	98.5	*S*
7	**1g**	*p*-NO_2	10	95	100	*S*
8	**1h**	*p*-CH_3SO_2NH	48	67 (13[c])	99.5[d]	*S*

[a]Isolated yield.
[b]Determined by chiral HPLC analysis.
[c]Yield of recovered starting material.
[d]Determined by chiral HPLC analysis after conversion to **3**.



Scheme 2. Reaction conditions: (a) 2,2-Dimethoxypropane, PTS, rt, 16 h, 89%; (b) H_2, PtO_2, EtOH, rt, 4 h, 98%; (c) CH_3SO_2Cl, Py, CH_2Cl_2, −10 °C, 63%.

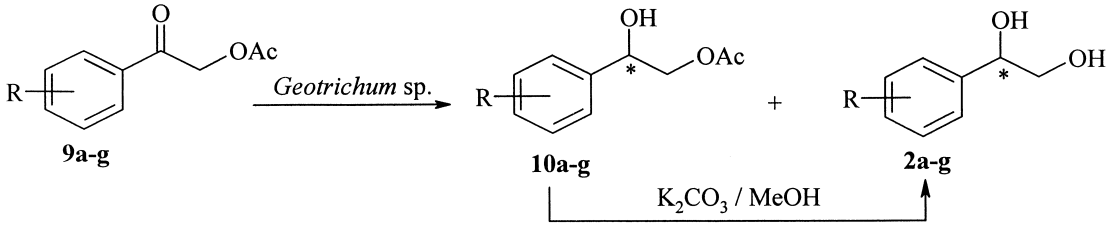


Scheme 3. Reaction conditions: (a) TsCl, Py, CH_2Cl_2, 0 °C; (b) $NaBH_4$, DMSO, 50 °C.

and **2f** was ascertained to be *R* and *S*, respectively, by comparison of the specific rotations of **7** and **8** with the reported values (see Experimental).

Santaniello et al. have reported[6] that yeast mediated reduction of phenacyl alcohol esters leads to products with stereochemistry opposite to those obtained by reduction of phenacyl alcohol itself. Thus, in order to investigate the stereochemistry of *Geotrichum* sp. mediated reduction of phenacyl alcohol ester, biotransformations of phenacyl alcohol acetates **9a**–**g** using *Geotrichum* sp. were performed under standard conditions (Scheme 4). The results are summarized in Table 2.

As shown in Table 2, all 2-acetoxy-1-arylethanones **9**, with the exception of **9e**, were transformed not only into the corresponding monoacetates **10**, but also into the corresponding 1,2-diols **2**. This indicated the presence of hydrolase(s) beside oxidoreductase(s) in these biotransformations. The absolute configurations and enantiomeric excesses of the monoacetates **10a**–**g** were determined after saponification to the corresponding 1,2-diols **2a**–**g** with potassium carbonate in methanol (Table 2). By comparison of Tables 1 and 2, it can be seen that *Geotrichum* sp. mediated reduction of phenacyl alcohols **1a**–**g** and the acetates **9a**–**g** with similar enantioselectivity, as each 1,2-diol **2a**–**g**, obtained from reduction of **1a**–**g**, and each monoacetate **10a**–**g**, obtained from reduction of **9a**–**g**, have the same configuration, respectively. It is interesting to point out that *Geotrichum* sp. mediated transformation of α-hydroxy ketones and α-acetoxy ketones with an *o*-substituent on the phenyl ring generally led to the corresponding 1,2-diols or monoacetates in low enantiomeric purity and opposite stereoselectivity with others (entries 2 and 5 in Tables 1 and 2). In general, the poor stereoselectivity in using intact cells for catalytic reduction of ketones may be caused by two factors. Firstly, the reduction process may be affected by a single enzyme but with different stereoselectivity.[8,9] Secondly, it may be due to participation of more than one oxidoreductase in intact cells which may generate alcohols of opposite configuration at different rate.[10–12] In most cases, it turned out that the poor enantioselective reductions emanated from the combined action of competing oxidoreductases of opposite stereoselectivity in intact cells.[8] Though there have been several methods developed to influence the selectivity, e.g., mediation of pH,[13] use of lyophilized cell or microbial dried cell,[14] and use of additives or inhibitors,[15] etc., they are not suited to distinguish the two factors as they may influence the selectivity of the reduction even if catalyzed by only one oxidoreductase.



Scheme 4.

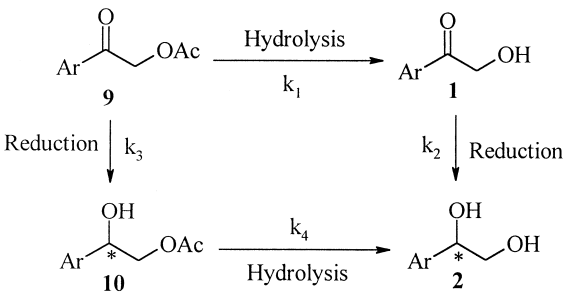
Table 2. *Geotrichum* sp. mediated biotransformation of 2-acetoxy-1-arylethanones **9a**–**g**

Entry	Substrate **9**	R	Time (h)	Monoacetate **10**			Diol **2**		
				Yield (%)[a]	e.e. (%)[b]	Configuration[c]	Yield (%)[a]	e.e. (%)	Configuration
1	**9a**	H	18	⩽3	85	*S*	53	83	*S*
2	**9b**	*o*-Cl	18	⩽3	41	*R*	51	66	*R*
3	**9c**	*m*-Cl	15	13	76	*S*	59	55	*S*
4	**9d**	*p*-Cl	15	21	86	*S*	54	83	*S*
5	**9e**	*o*-NO_2	16	0	—	—	15[d]	36	*R*
6	**9f**	*m*-NO_2	16	18	93	*S*	59	92	*S*
7	**9g**	*p*-NO_2	20	25	90	*S*	57	69	*S*

[a]Isolated yield.
[b]Determined by chiral HPLC analysis after saponified to the corresponding 1,2-diol.
[c]Determined by saponification of the monoacetate **10** to the corresponding diol **2** with K_2CO_3 in methanol.
[d]With 13% yield of starting material **9e** and 27% yield of hydrolyzed product **1e**.

While these two factors could be readily distinguished from each other by conducting the reduction at different substrate concentrations, as the enantioselectivity is independent of changes in substrate concentration if the reduction was catalyzed by a single oxidoreductase while the enantioselectivities of the competing oxidoreductase will be influenced by changes in substrate concentration.[12] It could be seen that the enantiomeric excesses of each produced monoacetate **10** and 1,2-diol **2** were different. Generally, the optically active 1,2-diols **2** produced by *Geotrichum* sp. reduction of the α-acetoxy ketones **9** may undergo various pathways as shown in Scheme 5. The formation of the 1,2-diol may proceed via two alternative processes. The first possible route is that the α-acetoxy ketone **9** was firstly non-stereoselectively hydrolyzed by hydrolase(s) in *Geotrichum* sp. to α-hydroxy ketone **1** (k_1), which was subsequently enantioselectively reduced to 1,2-diol **2** mediated by oxidoreductase(s) (k_2). The second possible route is the enantioselective reduction of the α-acetoxy ketone **9** (k_3) followed by hydrolysis of the formed optically active monoacetate **10** (k_4).

As shown in Table 2, biotransformation of the 2-acetoxy-1-arylethanones **9a–g** with *Geotrichum* sp. led to correspondingly the monoacetates **10a–g** and 1,2-diols **2a–g** of the same configuration, respectively. However, the enantiomeric excesses of each corresponding pair of the monoacetate **10** and 1,2-diol **2** obtained from reduction of **9** were different. The enantiomeric purity of monoacetates **10** was generally higher than that of the 1,2-diols **2** produced from **9**, in each case of biotransformation of the α-acetoxy ketones **9**, with the exception of **9b** and **9e** with an *o*-substituent on the phenyl ring (entries 2 and 5 in Table 2). These results might be caused by the α-acetoxy ketones **9** being enantioselectively reduced to the monoacetates **10** firstly with moderate (*S*)-enantiotope selectivities which were enantioselectively hydrolyzed subsequently to leave the non-hydrolyzed (*S*)-monoacetates with high optical purities in the remaining monoacetate fractions, while the enantiomeric composition of the original 1,2-diols may be altered by the hydrolyzed 1,2-diols. However, this kind of hydrolysis was not enantioselective, as when the racemic 1-(4-nitrophenyl)ethanediol monoacetate (*rac*-**10g**) was performed to the *Geotrichum* sp. transformation, both the hydrolyzed 1,2-diol and recovered monoacetate were racemic after nearly half hydrolysis of the starting racemic monoacetate. Therefore, the

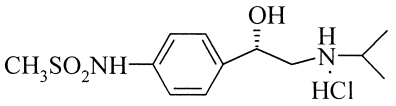


Scheme 5. Possible pathways of *Geotrichum* sp. reduction of 2-acetoxy-1-arylethanones **9a–g**.

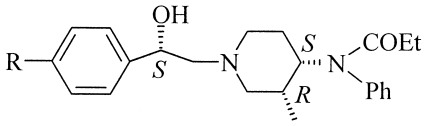
1,2-diols **2** with lower enantiomeric excesses were obtained predominantly by reduction of the corresponding α-hydroxy ketones **1** produced in situ from non-enantioselective hydrolysis of α-acetoxy ketones **9**, instead of by hydrolysis of the corresponding monoacetates **10** which had higher enantiomeric excesses, i.e. $k_4 < k_2$, k_1, k_3 (Scheme 5). This process may be further confirmed by the isolation of 27% yield of the hydrolyzed α-hydroxy ketone **1e** in the biotransformation of **9e** (entry 5 in Table 2). That is to say that, when 2-acetoxy-1-arylethanones **9a–g** were submitted to *Geotrichum* sp. mediated transformation, the monoacetates **10a–g** were produced by direct reduction with higher (*S*)-enantioselectivities, while the 1,2-diols were produced predominantly by lower (*S*)-enantioselective reduction of the α-hydroxy ketones **1** which were produced in situ from hydrolysis of the acetoxy ketones **9**, with the exception of **9b** and **9e**. Obviously, the concentrations of each hydroxy ketone **1a–g** in the direct incubation and in the incubation of the α-acetoxy ketones **9a–g** during which the hydroxy ketones **1** were generated in situ should be different. As a result, though two different incubations led to the same enantiotope selectivities of the 1,2-diols **2**, respectively, the enantiomeric purities were remarkably different. There are noticeable drop of the enantiomeric excesses of each 1,2-diol in *S* configuration and slight enhancement of the enantiomeric excesses of (*R*)-1,2-diols (from Table 1 to Table 2), with the exception of (*R*)-*o*-nitrophenylethanediol (**2e**) which might be interpreted by the factor that the hydroxy ketone **1e** with a bulky nitro-substituent on *o*-position of the phenyl ring was not a good substrate for *Geotrichum* sp. transformation and, as a result, could not be reduced efficiently (entries 5 in Tables 1 and 2). Therefore, it could be deduced that the different configuration and the various optical purity of *Geotrichum* sp. mediated reduction should be resulted from the combined action of the competing oxidoreductases in the intact cells which generate alcohols of opposite configuration at different rate. It is interesting to point out that this biotransformation procedure is much different from that mediated by baker's yeast.[6,13c]

The optically active arylethanediols and their monoacetates are versatile intermediates in synthesis of pharmaceuticals. For example, *d*-sotalol (**11**) which possesses an acidic methylsulfonanilide moiety and exhibits an interesting class III electro-physiological property that is effective against ventricular arrhythmia.[16] Ohmefentanyl (OMF) (**12a**) is one of the most potent analgesic agents and tool drugs for opioid receptor research due to its high affinity and selectivity for the μ receptor.[17] The pharmacological research showed that different stereoisomers exhibited extremely different analgesic activity, μ receptor binding affinity and selectivity. *Cis*-(+)-(2′*S*,3*R*,4*S*)-OMF was found to be the most potent compound among the stereoisomers of OMF and 13,110 times active than that of morphine in mice hot plate test.[18] As 3-methylfentanyl isothiocyanate, an opioid δ receptor irreversible inhibitor, also exhibited high receptor enantioselectivity,[19] therefore, synthesis of optically pure opioid receptor ligands, such as ohmefentanyl isothiocyanate (**12b**), and study of their biological

activities are required. These pharmaceuticals could be stereoselectively synthesized from (*S*)-1-(4-nitrophenyl)-ethanediol (**2g**) and the results will be published elsewhere.



11 *d*-(+)-Sotalol



12a R = H Ohmefentanyl (OMF)
12b R = SCN OMF isothiocyanate

Conclusion

We have shown that *Geotrichum* sp. mediated reduction of α-hydroxy- and α-acetoxyarylethanones **1** and **9** led to the corresponding 1,2-diols **2** and monoacetates **10** with *anti*-Prelog selectivity with the exception of **1b**, **9b** and **1e**, **9e** with a substitution on the *ortho* position which inverts the enantioselectivity of the bioreduction in comparison with those substituted derivatives on *meta* and *para* positions. The differences in stereoselectivity might be due to the combined action of multiple competing oxidoreductases in the intact cells, as the enantiomeric excesses of the product were dependent on the incubation concentrations of the substrate. The optically active (*S*)-arylethanediols and their monoacetate derivatives are useful synthetic intermediates.

Experimental

General methods

All melting points are uncorrected. IR spectra were recorded on a Shimadzu IR-440 spectrometer. EI mass spectra (MS) were run on an HP-5989A mass spectrometer and high resolution mass spectra (HRMS) were recorded on a Finnigan MAT-4021 instrument. ^{1}H NMR spectra were recorded on a Varian EM-390 (90 MHz) or a Bruker AMX-300 (300 MHz) spectrometer with tetramethylsilane as the internal standard. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. HPLC was carried out using Chiralcel OD and OJ columns, and Chiralpak AD column (0.46 cm×25 cm) detected at UV 254 nm, rate of flow 0.7 mL/min. TLC was carried out using HSG F_{254} silica gel plates and silica gel (200–400 mesh) was used for chromatography. Organic extracts were dried over anhydrous sodium sulfate.

2-Acetoxy-1-arylethanones 9a–g. To a solution of the corresponding acetophenone (50 mmol) in 100 mL of glacial acetic acid at room temperature was added bromine (2.6 mL, 50 mmol) in 10 mL of glacial acetic acid over a period of 1 h, and the resulting solution was stirred at room temperature for 15–25 h. After removal of most of the acetic acid in vacuo, the reaction mixture was poured into 100 mL of water and extracted with methylene chloride or ethyl acetate (50 mL×4). The combined extracts were washed with water, 5% aqueous $NaHSO_3$ and water, then dried. After removal of the solvent, the residue was the corresponding crude phenacyl bromide which was used in next reaction without further purification.

2-Acetoxy-1-arylethanones **9c–g** were prepared in a similar manner as **9a** and **9b** from the corresponding phenacyl bromides according to the reported procedure.[5,6] Purification by chromatography with petroleum ether:ethyl acetate obtained the desired products. The yields for two steps and the physical and chemical characteristics of **9c–g** are given as follows.

2-Acetoxy-1-(3-chlorophenyl)ethanone (9c). Yield, 57%; white solid, mp 35–36 °C. IR (film) 1760, 1710 cm^{-1}. ^{1}H NMR (90 MHz, CCl_4) δ 8.0–7.2 (m, 4H), 5.2 (s, 2H), 2.2 (s, 3H). Anal. calcd for $C_{10}H_9ClO_3$: C, 56.49; H, 4.27. Found: C, 56.42; H 4.10.

2-Acetoxy-1-(4-chlorophenyl)ethanone (9d). Yield, 74%; white solid, mp 67–68 °C. IR (KBr) 1740, 1695 cm^{-1}. ^{1}H NMR (90 MHz, CCl_4) δ 7.8 and 7.4 (AB, 4H, J = 9 Hz), 5.2 (s, 2H), 2.2 (s, 3H). Anal. calcd for $C_{10}H_9ClO_3$: C, 56.49; H, 4.27. Found: C, 56.49; H 4.21.

2-Acetoxy-1-(2-nitrophenyl)ethanone (9e). Yield, 72%; light yellow oil. IR (film) 1760, 1730 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$) δ 8.2 (d, 1H, J = 8 Hz), 8.0–7.3 (m, 3H), 5.0 (s, 2H), 2.1 (s, 3H). Anal. calcd for $C_{10}H_9NO_5$: C, 53.82; H, 4.06; N, 6.28. Found: C, 53.78; H 4.33; N, 6.16.

2-Acetoxy-1-(3-nitrophenyl)ethanone (9f). Yield, 51%; light yellow solid, mp 48–49 °C. IR (film) 1750, 1710 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$) δ 8.8 (s, 1H), 8.6 (d, 1H, J = 8 Hz), 8.4 (d, 1H, J = 8 Hz), 7.9 (t, 1H, J = 8 Hz), 5.5 (s, 2H), 2.3 (s, 3H). Anal. calcd for $C_{10}H_9NO_5$: C, 53.82; H, 4.06; N, 6.28. Found: C, 53.67; H 4.06; N, 6.41.

2-Acetoxy-1-(4-nitrophenyl)ethanone (9g). Yield, 75%; light yellow solid, mp 125–126 °C {lit.[20] mp 125 °C}. IR (film) 1750, 1705 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$) δ 8.4 and 8.1 (AB, 4H, J = 9 Hz), 5.4 (s, 2H), 2.3 (s, 3H). MS m/z (rel. intensity): 224 ($[M+1]^+$, 0.54), 151 (14.1), 150 (100), 120 (8.6), 104 (23.0), 92 (11.7), 76 (18.1).

1-Aryl-2-hydroxyethanones 1a–d. 2-Hydroxy-1-phenylethanone (**1a**) and 1-(2-chlorophenyl)-2-hydroxyethanone (**1b**) were prepared by previous method.[5] **1c** and **1d** were prepared as follows with an improved procedure.

The mixture of **9c** or **9d** in methanol and drops of concentrated sulfuric acid was stirred under reflux for 6 h. After removal of the solvent, the residue was dissolved in ethyl acetate and washed with saturated brine, dried and purified by chromatography with petroleum ether: ethyl acetate (2:1).

1-(3-Chlorophenyl)-2-hydroxyethanone (1c). Yield, 82%; white solid, mp 94–95 °C. IR (KBr) 3400, 1680 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ 8.1–7.4 (m, 4H), 4.9 (s, 2H), 3.0 (br s, 1H). Anal. calcd for $C_8H_7ClO_2$: C, 56.32; H, 4.14. Found: C, 56.47; H 4.14.

1-(4-Chlorophenyl)-2-hydroxyethanone (1d). Yield, 79%; white solid, mp 114–115 °C. IR (KBr) 3400, 1680 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ 7.9, 7.5 (AB, 4H, $J=9$ Hz), 4.8 (s, 2H), 3.2 (br s, 1H). Anal. calcd for $C_8H_7ClO_2$: C, 56.32; H, 4.14. Found: C, 56.61; H 4.16.

1-Aryl-2-hydroxyethanones 1e–h. Produced by hydrolysis of the corresponding phenacyl bromide obtained above in the presence of silver nitrate according to the reported method.[7]

2-Hydroxy-1-(2-nitrophenyl)ethanone (1e). Yield, 20% of **1e**, and 68% of unreacted starting material; light yellow oil. IR (film) 3350, 1710 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ 8.2 (d, 1H, $J=9$ Hz), 8.0–7.3 (m, 3H), 4.7 (s, 2H), 3.1 (br s, 1H).

2-Hydroxy-1-(3-nitrophenyl)ethanone (1f).[21] Yield, 63%; light yellow solid, mp 69–70 °C. IR (film) 3300, 1710 cm^{-1}. ^1H NMR (90 MHz, CD_3COCD_3) δ 8.8 (s, 1H), 8.5 (t, 2H, $J=8$ Hz), 8.0 (t, 1H, $J=8$ Hz), 5.0 (s, 2H), 3.4 (br s, 1H).

2-Hydroxy-1-(4-nitrophenyl)ethanone (1g). Its physical and chemical characteristics were identical to those reported.[7]

***N*-(4-(2-Hydroxy-1-oxoethyl)phenyl)methanesulfonamide (1h).** Yield, 45%; white solid, mp 145–146 °C. IR (KBr) 3450, 3100, 2900, 1670, 1600, 1490, 1390, 1330, 1270, 1230, 1140, 1000, 960, 910, 830 cm^{-1}. ^1H NMR (90 MHz, CD_3COCD_3) δ 8.0, 7.5 (AB, 4H, $J=8$ Hz), 4.9 (s, 2H), 3.3 (s, 2H), 3.1 (s, 3H). HRMS calcd for $(C_9H_{11}NO_4S)^+$ 229.0409, found 229.0413.

Biotransformation of 1a–h and 9a–g. *Geotrichum* sp. was cultivated on: glucose (100 g), yeast extract (10 g), urea (1 g) and tap water making up to 1 L. After 2 days of culture at 30 °C on a reciprocating shaker set at 120 rpm, cells were filtered out and washed with 0.8% brine. Wet mycelium (5 g) was suspended in 5% glucose solution (50 mL). The substrate (1 mmol) in 0.5 mL of DMF (if it is solid) was added slowly. The mixture was shaken at 30 °C. After completion of the biotransformation, the mycelium was filtered out and washed with ethyl acetate. The filtrate was saturated with sodium chloride and extracted with ethyl acetate (50 mL×4). The combined extracts were washed with brine, dried, filtered and evaporated under reduced pressure. The residue was purified by chromatography. The yields, the enantiomeric purity and the absolute configuration of the products are summarized in Tables 1 and 2.

(*S*)-(+)-1-Phenyl-1,2-ethanediol (2a). Obtained from **1a**: white solid, mp 62–63 °C; $[\alpha]_D^{22}$ +37 (*c* 1.9, CH_3COCH_3) {lit.[6] $[\alpha]_D$ +40 (*c* 2.0, CH_3COCH_3) for 94% ee, (*S*)}. Its ^1H NMR, IR and MS spectra were identical with those of an authentic sample. The enantiomeric excess was determined by HPLC analysis using Chiralcel OD column (eluent, hexane:2-propanol = 9:1).

(*R*)-(−)-1-(2-Chlorophenyl)-1,2-ethanediol (2b). Obtained from **1b**: white solid, mp 98–99 °C; $[\alpha]_D^{25}$ −50 (*c* 2.0, EtOH) {lit.[22] $[\alpha]_D$ −47.2 (*c* 1.9, EtOH) for 73% ee, (*R*)}. Its ^1H NMR, IR and MS spectra were identical with those of an authentic sample. The enantiomeric excess was determined by HPLC analysis using Chiralcel OD column (eluent, hexane:2-propanol = 8:2).

(*S*)-(+)-1-(3-Chlorophenyl)-1,2-ethanediol (2c). Obtained from **1c**: light yellow oil. $[\alpha]_D^{20}$ +17 (*c* 1.4, EtOH) {lit.[23] $[\alpha]_D$ +24.05 (*c* 1.24, EtOH) for 95% ee, (*S*)}. Its spectral data were identical with those reported.[23] The enantiomeric excess was determined by HPLC analysis using Chiralcel OD column (eluent, hexane:2-propanol = 9:1).

(*S*)-(+)-1-(4-Chlorophenyl)-1,2-ethanediol (2d). Obtained from **1d**: white solid; $[\alpha]_D^{20}$ +26 (*c* 2.1, EtOH) {lit.[22] $[\alpha]_D$ −27.6 (*c* 0.96, EtOH) for 79% ee, (*R*)}. Its spectral data were identical with those reported.[22] The enantiomeric excess was determined by HPLC analysis using Chiralcel OD column (eluent, hexane:2-propanol = 95:5).

(*R*)-(+)-1-(2-Nitrophenyl)-1,2-ethanediol (2e). Obtained from **1e**: light yellow solid, mp 99–101 °C; $[\alpha]_D^{20}$ +9 (*c* 0.8, MeOH) {lit.[23] mp 94–96 °C}. ^1H NMR (300 MHz, CD_3COCD_3) δ 7.91–7.86 (m, 2H), 7.73 (t, 1H, $J=7.8$ Hz), 7.53 (t, 1H, $J=7.8$ Hz), 5.28 (dd, 1H, $J=7.0$, 4.0 Hz), 3.74 (dd, 1H, $J=11.1$, 4.0 Hz), 3.60 (dd, 1H, $J=11.1$, 7.0 Hz), 3.45 (br s, 2H). MS *m*/*z* (rel. intensity): 184 ($[M+1]^+$, 1.1), 166 (21.1), 152 (88.0), 135 (52.3), 104 (100), 91 (53.6), 79 (69.1), 77 (87.6). The enantiomeric excess was determined by HPLC analysis using Chiralcel OJ column (eluent, hexane:2-propanol = 9:1).

(*S*)-(+)-1-(3-Nitrophenyl)-1,2-ethanediol (2f). Obtained from **1f**: white solid, mp 73–74 °C; $[\alpha]_D^{20}$ +26 (*c* 1.5, MeOH) {lit.[24] mp 80 °C}. ^1H NMR (300 MHz, CD_3COCD_3) δ 8.28 (s, 1H), 8.10 (d, 1H, $J=8.2$ Hz), 7.83 (d, 1H, $J=7.5$ Hz), 7.61 (t, 1H, $J=8.2$ Hz), 4.87 (t, 1H, $J=5.7$ Hz), 3.70–3.50 (m, 2H), 3.4 (br s, 2H). MS *m*/*z* (rel. intensity): 184 ($[M+1]^+$, 5.1), 166 (70.1), 152 (100), 136 (34.4), 105 (59.8), 91 (15.8), 77 (51.8). The enantiomeric excess was determined by HPLC analysis using Chiralcel OD column (eluent, hexane:2-propanol = 9:1).

(*S*)-(+)-1-(4-Nitrophenyl)-1,2-ethanediol (2g). Obtained from **1g**: white solid, mp 89–90 °C; $[\alpha]_D^{21}$ +23 (*c* 1.0, MeOH) {lit.[25] $[\alpha]_D^{20}$ −20.0 (*c* 1.15, MeOH), 96% ee, (*R*)}. ^1H NMR (300 MHz, CD_3COCD_3) δ 8.18, 7.69 (AB, 4H, $J=8.7$ Hz), 4.85 (dd, 1H, $J=6.7$, 4.9 Hz), 3.66 (dd, 1H, $J=11.1$, 4.9 Hz), 3.58 (dd, 1H, $J=11.1$, 6.7 Hz), 3.45 (br s, 2H). MS *m*/*z* (rel. intensity): 184 ($[M+1]^+$, 10.7), 153 (36.6), 152 (100), 136 (14.2), 106 (23.2), 105 (20.6), 91 (17.5), 77 (23.5). The enantiomeric excess was determined by HPLC analysis using Chiralcel OD column (eluent, hexane:2-propanol = 9:1).

(*S*)-(+)-*N*-(4-(1,2-Dihydroxyethyl)phenyl)methanesulfonamide (2h). Obtained from **1h**: white solid, mp 135–136 °C; $[\alpha]_D^{25}$ +35 (*c* 1.0, CH_3COCH_3). IR (KBr) 3250, 1630, 1510, 1390, 1320, 1215, 1150, 1080, 1050, 990, 765 cm^{-1}. ^1H NMR (300 MHz, CD_3COCD_3) δ 7.37, 7.28 (AB, 4H, *J* = 8.5 Hz), 4.68 (dd, 1H, *J* = 7.6, 4.4 Hz), 3.60 (dd, 1H, *J* = 11.0, 4.4 Hz), 3.52 (dd, 1H, *J* = 11.0, 7.6 Hz), 3.41 (s, 2H), 2.94 (s, 3H). MS *m*/*z* (rel. intensity): 231 (M^+, 1.1), 200 (100), 184 (12.6), 121 (30.9), 120 (14.8), 106 (10.5), 92 (24), 77 (9.6). Anal. calcd for $C_9H_{13}NO_4S$: C, 46.74; H, 5.67; N, 6.06; S, 13.87. Found: C, 46.58; H, 5.65; N, 5.95; S, 14.15.

(*S*)-(+)-2-Acetoxy-1-phenylethanol (10a). Obtained from **9a**: colorless oil; $[\alpha]_D^{25}$ +28 (*c* 1.1, CH_3COCH_3) {lit.[6] $[\alpha]_D$ +28 (*c* 2.0, CH_3COCH_3), 94% ee, (*S*)}. IR (film) 3400, 1730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.35 (m, 5H), 4.95 (dd, 1H, *J* = 8.5, 3.3 Hz), 4.28 (dd, 1H, *J* = 11.7, 3.3 Hz), 4.15 (dd, 1H, *J* = 11.7, 8.5 Hz), 2.75 (br s, 1H), 2.09 (s, 3H).

(*R*)-(−)-2-Acetoxy-1-(2-chlorophenyl)ethanol (10b). Obtained from **9b**: colorless oil; $[\alpha]_D^{25}$ −19.3 (*c* 1.2, $CHCl_3$). IR (film) 3450, 1730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (dd, 1H, *J* = 7.6, 1.7 Hz), 7.4–7.2 (m, 3H), 5.39 (dd, 1H, *J* = 7.9, 2.9 Hz), 4.33 (dd, 1H, *J* = 11.6, 2.9 Hz), 4.17 (dd, 1H, *J* = 11.6, 7.9 Hz), 2.4 (br s, 1H), 2.11 (s, 3H). Anal. calcd for $C_{10}H_{11}ClO_3$: C, 55.96; H, 5.16. Found: C, 55.57; H, 5.01.

(*S*)-(+)-2-Acetoxy-1-(3-chlorophenyl)ethanol (10c). Obtained from **9c**: colorless oil; $[\alpha]_D^{20}$ +29 (*c* 1.3, $CHCl_3$). IR (film) 3400, 1720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.5–7.1 (m, 4H), 4.92 (dd, 1H, *J* = 8.1, 3.4 Hz), 4.23 (dd, 1H, *J* = 11.7, 3.4 Hz), 4.11 (dd, 1H, *J* = 11.7, 8.1 Hz), 2.9 (br s, 1H), 2.07 (s, 3H). Anal. calcd for $C_{10}H_{11}ClO_3$: C, 55.96; H, 5.16. Found: C, 55.71; H, 5.30.

(*S*)-(+)-2-Acetoxy-1-(4-chlorophenyl)ethanol (10d). Obtained from **9d**: colorless oil; $[\alpha]_D^{20}$ +33 (*c* 1.9, $CHCl_3$). IR (film) 3400, 1730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.6–7.1 (m, 4H), 4.92 (dd, 1H, *J* = 8.2, 3.4 Hz), 4.22 (dd, 1H, *J* = 11.5, 3.4 Hz), 4.10 (dd, 1H, *J* = 11.5, 8.2 Hz), 2.7 (br s, 1H), 2.08 (s, 3H). Anal. calcd for $C_{10}H_{11}ClO_3$: C, 55.96; H, 5.16. Found: C, 55.67; H, 5.14.

(*S*)-(+)-2-Acetoxy-1-(3-nitrophenyl)ethanol (10f). Obtained from **9f**: white solid, mp 74–76 °C; $[\alpha]_D^{20}$ +40.3 (*c* 1.1, $CHCl_3$). IR (film) 3300, 1720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.30 (t, 1H, *J* = 1.7 Hz), 8.18 (d, 1H, *J* = 8.1 Hz), 7.75 (d, 1H, *J* = 7.7 Hz), 7.56 (t, 1H, *J* = 8.0 Hz), 5.09 (dd, 1H, *J* = 7.8, 3.3 Hz), 4.33 (dd, 1H, *J* = 11.6, 3.3 Hz), 4.16 (dd, 1H, *J* = 11.6, 7.8 Hz), 2.65 (br s, 1H), 2.12 (s, 3H). Anal. calcd for $C_{10}H_{11}NO_5$: C, 53.34; H, 4.92; N, 6.22. Found: C, 53.17; H, 5.01; N, 6.40.

(*S*)-(+)-2-Acetoxy-1-(4-nitrophenyl)ethanol (10g). Obtained from **9g**: white solid; $[\alpha]_D^{23}$ +27 (*c* 1.4, $CHCl_3$) {lit.[24] mp 121–122 °C}. IR (film) 3400, 1710 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.24, 7.60 (AB, 4H, *J* = 8.7 Hz), 5.10 (dd, 1H, *J* = 7.8, 3.3 Hz), 4.36 (dd, 1H, *J* = 11.7, 3.3 Hz), 4.16 (dd, 1H, *J* = 11.7, 7.8 Hz), 2.8 (br s, 1H), 2.12 (s, 3H). MS *m*/*z* (rel. intensity): 226 ($[M+1]^+$, 3.7), 208 (73.4), 165 (13.1), 153 (30.7), 135 (12.9), 106 (14.6), 74 (22.5), 43 (100).

(*S*)-(+)-*N*-(4-(2,2-Dimethyl-1,3-dioxolan-4-yl)phenyl)-methanesulfonamide (3). A mixture of **2h** (50 mg, 0.22 mmol), acetone (0.5 mL), 2,2-dimethoxypropane (0.5 mL, 4.1 mmol) and *p*-toluene sulfonic acid (5 mg) was stirred at room temperature for 16 h. After that, 30 mL of ethyl acetate was added. The organic phase was washed with aqueous sodium bicarbonate, saturated brine, dried, filtered and evaporated under reduced pressure. The residue was purified by chromatography with petroleum ether:ethyl acetate (5:2) to give **3** (52 mg, 89%) as a white solid, mp 81–82 °C; $[\alpha]_D^{25}$ +59 (*c* 0.7, CH_3COCH_3). IR (KBr) 3350, 2980, 1635, 1515, 1460, 1400, 1330, 1290, 1220, 1150, 1070, 980, 920, 870, 830 cm^{-1}. ^1H NMR (300 MHz, CD_3COCD_3) δ 7.39, 7.32 (AB, 4H, *J* = 8.5 Hz), 5.06 (dd, 1H, *J* = 7.7, 6.4 Hz), 4.29 (dd, 1H, *J* = 8.1, 6.4 Hz), 3.60 (t, 1H, *J* = 7.9 Hz), 2.96 (s, 3H), 1.46 (s, 3H), 1.39 (s, 3H). Anal. calcd for $C_{12}H_{17}NO_4S$: C, 53.12; H, 6.32; N, 5.16. Found: C, 53.09; H, 6.38; N, 5.03. The enantiomeric excess was 99.5%, determined by HPLC analysis using Chiralpak AD column (eluent, hexane:2-propanol = 9:1) using the racemic **3** as comparison.

(*S*)-(+)-1-(4-Aminophenyl)-1,2-ethanediol (4). A mixture of (*S*)-**2g** (150 mg, 0.82 mmol), ethanol (10 mL) and $PtO_2 \cdot 2H_2O$ (20 mg) was stirred at room temperature under atmospheric hydrogen for 5 h. After filtration the solvent was removed under reduced pressure and the residue was purified by chromatography with methylene chloride:acetone (3:1) to give **4** (123 mg, 98%) as a light yellow solid, mp 107–108 °C; $[\alpha]_D^{25}$ +39 (*c* 1.5, CH_3COCH_3) {lit.[24] mp 98–99 °C}. ^1H NMR (300 MHz, CD_3COCD_3) δ 7.08, 6.63 (AB, 4H, *J* = 8.5 Hz), 4.54 (dd, 1H, *J* = 7.9, 4.4 Hz), 3.52 (dd, 1H, *J* = 11.0, 4.4 Hz), 3.45 (dd, 1H, *J* = 11.0, 7.9 Hz), 3.25 (s, 4H). MS *m*/*z* (rel. intensity): 153 (M^+, 9.9), 122 (100), 106 (10.4), 94 (42), 77 (30).

Conversion of (*S*)-4 to (*S*)-2h. 75 mg (0.5 mmol) of (*S*)-**4** was dissolved in methylene chloride (1 mL) and pyridine (0.2 mL). The mixture was cooled to −10 °C and methanesulfonyl chloride (40 μL, 0.51 mmol) was added slowly. The mixture was stirred at −10 °C for 1 h, then warmed to room temperature and stirred for further 4 h. After that 50 mL of ethyl acetate was added and the mixture was washed with brine and dried. After filtration the solvent was removed under reduced pressure and the residue was purified by chromatography with methylene chloride:acetone (4:1) to give (*S*)-**2h** (71 mg, 63%), $[\alpha]_D^{26}$ +32 (*c* 0.8, CH_3COCH_3).

Determination of the absolute configuration of 2e and 2f. To a mixture of **2e** (**2f**) (120 mg, 0.66 mmol), DMAP (10 mg) and CH_2Cl_2 (3 mL) was added slowly at 0 °C a solution of *p*-toluenesulfonyl chloride (170 mg, 0.9 mmol) in 2 mL of CH_2Cl_2. After that the mixture was stirred at 10 °C for a day. The solvent was removed

and the residue was dissolved in ethyl acetate (50 mL). The mixture was washed with brine and dried. After filtration the solvent was removed under reduced pressure and the residue was used for the next step reaction without further purification.

A mixture of crude **5** (**6**) obtained from above, DMSO (3 mL) and sodium borohydride (370 mg, 15 equiv) was stirred at 40 °C for 20 h. After that 50 mL of ethyl acetate was added and the mixture was washed with brine and dried. After filtration the solvent was removed under reduced pressure and the residue was purified by chromatography with petroleum ether:ethyl acetate (5:1) to give **7** (**8**).

(*S*)-(+)-1-(2-Nitrophenyl)ethanol (7). 38 mg (35%, for two steps); light yellow solid, mp 58–60 °C; $[\alpha]_D^{20}$ +12 (*c* 1.3, $CHCl_3$) {lit.[26] mp 60–61 °C, $[\alpha]_D^{27}$ +54.2 (*c* 0.98, $CHCl_3$), (*S*)}. Its spectral data were identical with those of an authentic sample.

(*R*)-(+)-1-(3-Nitrophenyl)ethanol (8). 48 mg (44%, for two steps); light yellow solid, mp 58–59 °C; $[\alpha]_D^{20}$ +20.6 (c 0.54, $CHCl_3$). {lit.[27] (*S*)-configuration for (−)-**8**}. Its spectral data were identical with those of an authentic sample.

General procedure for saponification of 2-acetoxy-1-arylethanols (10): determination of the absolute configuration and enantiomeric excess. The monoacetates **10** were saponified to the corresponding 1,2-diols **2** with potassium carbonate (1 equiv) in methanol at room temperature for 3 h. By direct comparison of the specific rotations and chiral HPLC analysis, the absolute configurations and optical purities were assigned as shown in Table 2.

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