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anti-Prelog Microbial Reduction of Aryl α-Halomethyl or α-Hydroxymethyl Ketones with *Geotrichum sp.* 38

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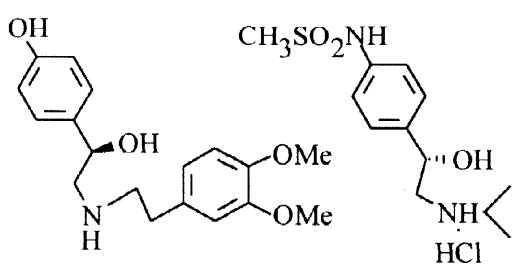
Abstract: Reduction of aryl α-halomethyl ketones **5a-d** and **7a-h** and α-hydroxymethyl ketones **10a-b** by *Geotrichum sp.* 38 affording mostly the *anti*-Prelog alcohols was reported and the stereoselectivities of the reductive products were discussed.

INTRODUCTION

Asymmetric reduction of α-halomethyl or α-hydroxymethyl ketones is potentially a useful process to obtain halohydrins or 1,2-diols, which are valuable synthetic intermediates for the preparation of a range of compounds of biological interest.[1] In this regard, it constitutes an important part in the synthesis of pharmaceutical products[2] such as the substituted 2-amino-1-arylethanols. For example, (*R*)-denopamine (**1**) is the first orally active and long acting positive inotropic agent;[3] *d*-sotalol (**2**) is a β-block that has anti-arrhythmic properties;[4] (*R*)-(-)-clorprenaline (**3**) is a β_2-agonist that is effective for the treatment of diverse disease states such as bronchitis and asthma;[5] R_0 25-8210 (**4**) have been used to prepare inhibitors of the matrix metalloproteinase stromelysin 1.[6]



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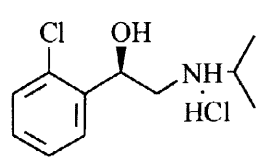

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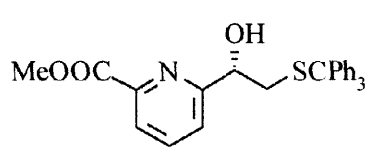

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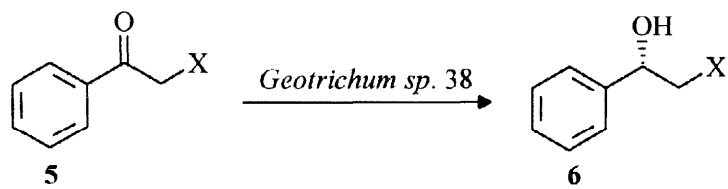
In recent years, this area has been quite extensively investigated by using chemical and biological methods. While the chemical reduction by using such as chiral metal hydrides[7] and chiral organoboranes[8] constitutes a powerful tool, among the most acceptable methods, the biotransformations are undoubtedly considered as powerful accesses due to, in most cases, the high enantio- and chemoselectivities, milder and environmentally compatible reaction conditions. Baker's yeast[9] and other microorganisms or enzymes[10] were used to reduce some α-haloaryl ketones. However, most of these reductions generally follow the Prelog's rule[11] in sense of the outcome of stereochemistry.

In connect with our projects of asymmetric synthesis of some optically active pharmaceuticals, we reported previously the reduction of α-keto esters and the application in the synthesis of (*R*)-denopamine (**1**) subsequently,[12] using *Geotrichum sp.* 38, a high reductive fungus which was obtained by screening tests from a large number of cultures. In this work, *Geotrichum sp.* 38 has been employed in the reduction of aryl α-halomethyl or α-hydroxymethyl ketones in order to synthesize enantiomers of some important pharmaceuticals. An *anti*-Prelog reduction is described and the stereochemical outcome of this reduction is discussed.

RESULTS AND DISCUSSION

To examine which haloacetophenone is accessible for *Geotrichum sp.* 38 reduction, the reduction of different α-halogenated acetophenones **5a-d** in two different incubation media was performed: medium A: tap water without addition of glucose and medium B: 5% glucose solution in tap water. In the meantime the baker's yeast[13] reduction (medium C) was carried out for comparison. The results were shown in Table 1. α-Fluoro and α-chloroacetophenones (**5a**) and (**5b**) were readily reduced by *Geotrichum sp.* 38 to give (*S*)-(+)-2-fluoro-1-phenylethanol (**6a**) and (*S*)-(+)-2-chloro-1-phenylethanol (**6b**) respectively. **6a** was obtained in 65 to 80% yield and 70 to 75% optical purity (entries 1 and 2), and **6b** was obtained in 80 to 86% yield and 87% optical purity (entries 4 and 5). In these two cases, the *Geotrichum sp.* 38 reduction was superior to baker's yeast (entries 3 and 6) both in chemical yields and enantioselectivities. α-Bromo and α-iodoacetophenones (**5c**) and (**5d**) were reduced by *Geotrichum sp.* 38 to (*S*)-(+)-2-bromo-1-phenylethanol (**6c**) and (*S*)-(+)-2-iodo-1-phenylethanol (**6d**) respectively but both in poor yield. The yield was 10 to 15% for **6c** (entries 7 and 8) and ca. 3% for **6d** (entries 10 and 11), though the ee of the resulting bromohydrin **6c** was 80 to 94%. The low chemical yields of bromo- and iodohydrin with *Geotrichum sp.* 38 mediated transformation are similar to those of the control experiments with baker's yeast. However, our results were much different from those reported by Carvalho *et al.* They obtained nearly quantitative mixture of acetophenone and (*S*)-(-)-1-phenylethanol in the reduction of α-iodoacetophenones (**5d**) with baker's yeast.[9a]



5 **6**

a, X = F; **b**, X = Cl; **c**, X = Br; **d**, X = I

Scheme 1

Table 1. Comparison of Reduction of α-Haloacetophenones **5a-d** with *Geotrichum sp.* 38 and Baker's yeast

entry	X	medium [a]	reaction time / h	yield [b] / %	ee [c] / %	$[\alpha]_D$	config.
1	F	A	15	80	70	45°	*S*
2	F	B	15	65	75	47.3°	*S*
3	F	C	24	55 (14)[d]	35[e]	-18.4°	*R*
4	Cl	A	15	80	87	49.3°	*S*
5	Cl	B	15	86	87.4	52.1°	*S*
6	Cl	C	24	6 (40)[d]	68[e]	-32.9°	*R*
7	Br	A	15	10 (20)[d]	80	47.3°	*S*
8	Br	B	15	15 (25)[d]	94	49.8°	*S*
9	Br	C	28	~0 (15)[d]	–	–	–
10	I	A	24	3 (23)[d]	_	25.9°	*S*
11	I	B	24	3 (20)[d]	_	11.4°	*S*
12	I	C	24	~0 (12)[d]	–	–	–

[a] Medium A: *Geotrichum sp.* 38 in tap water; medium B: *Geotrichum sp.* 38 in 5% glucose solution; medium C: baker' yeast in 20% glucose solution. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Yield of recovered substrate. [e] Based on the specific rotation.

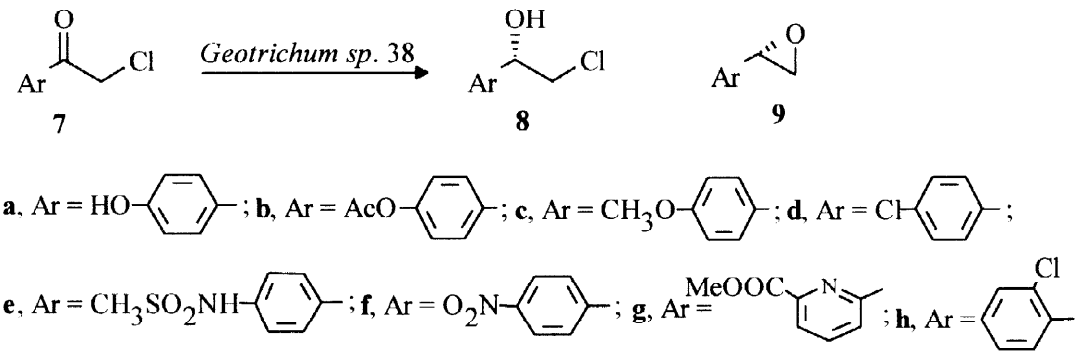
It is noteworthy that in Table 1 all the halohydrins (**6a-d**) obtained with *Geotrichum sp.* 38 mediated reduction (medium A and medium B) are exclusively *S* configuration, while those obtained by baker's yeast (medium C) are *R* configuration. Therefore taking into account that the halomethyl moiety is "effectively smaller" than the phenyl moiety,[10a] *Geotrichum sp.* 38 mediated reduction of α-haloacetophenone afforded the *anti*-Prelog halohydrin product.

As shown in Table 1, α-chloroacetophenone (**5b**) is the best substrate for *Geotrichum sp.* 38 reduction of α-haloacetophenone in the sense of both chemical and optical yields of the product and the results were not much influenced by the reaction medium A or B.

Thus, the reduction of some substituted aryl α-chloromethyl ketones was further investigated in order to obtain more information. Several substituted aryl α-chloromethyl ketones **7a-h** were prepared by conventional methods, *i.e.*, Friedel-Crafts reaction for **7a-e**;[14] Nierenstein reaction for **7f-g**;[15] monochlorination of *o*-chloroacetophenone with sulfuryl chloride for **7h**.[16] The incubation of **7a-h** was carried out with *Geotrichum sp.* 38 (Scheme 2), and the results were summarized in Table 2.

Reduction of α-chloro-*p*-hydroxyacetophenone (**7a**) with *Geotrichum sp.* 38 was taking place slowly. After incubation for 24h, only 15% yield of (*S*)-2-chloro-1-(4-hydroxyphenyl)-1-ethanol (**8a**) was afforded, though in high enantiomeric excess. Most of the substrate **7a** was recovered after flash column chromatography (entry 1). The slow rate of conversion might be rationalized by the existence of phenol moiety in the substrate causing toxicity to the microorganism. Thus, the corresponding acetate (**7b**) was prepared and subjected to microbial reduction. However, to our surprise, the acetate group was hydrolyzed during the reduction of the oxo group of **7b**. The yield and ee of **8a** were 33% and 98% together with 28% of the hydrolyzed product **7a** after incubation

for 24h (entry 2). The absolute configuration and ee of **8a** were deduced by comparing its specific rotation with that reported in the literature.[17] The low yield could be overcome by converting the phenol group in **7a** to its methylether (**7c**). Thus, α-chloro-*p*-methoxyacetophenone (**7c**) was readily reduced by *Geotrichum sp.* 38 to (*S*)-2-chloro-1-(4-methoxyphenyl)-1-ethanol (**8c**) in 76% yield and 90.5% ee (entry 3). The enantiomeric excess was determined by chiral HPLC analysis and the *S* configuration was assigned by comparison of the authentic (*S*)-1-(4-methoxyphenyl)-1-ethanol[18] with that generated by dechlorination of the chlorohydrin (*S*)-**8c** with tributyltin hydride and 2,2'-azoisobutyronitrile (AIBN). α,*p*-Dichloroacetophenone (**7d**) could also be reduced, though the conversion was taken place at slow rate, to produce the corresponding chlorohydrin **8d** in 96.6% ee



Scheme 2

Table 2. Reduction of Substituted Aryl α-Chloromethyl Ketones **7a-h** with *Geotrichum sp.* 38

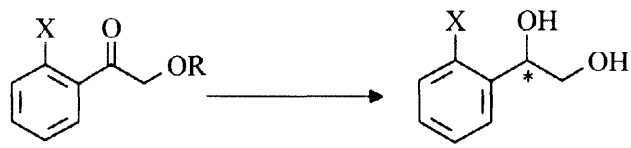
entry	substrate	reaction time / h	yield of **8**[a] / %	ee / %	$[\alpha]_D$	config.
1	**7a**	24	15 (70[b])	>98[c]	28.7°	*S*[c]
2	**7b**	24	[33[d]] [28[e]]	>98[c]	27.5°	*S*[c]
3	**7c**	17	76 (5[b])	90.5[f]	40.2°	*S*[g]
4	**7d**	24	42 (15[b])	96.6[f]	44.2°	*S*[h]
5	**7e**	48	60 (20[b])	87[f]	28.1°	*S*
6	**7f**	13	90 (<3[b])	>98[h]	27.2°	*S*[h]
7	**7g**	18	91 (<3[b])	81[f]	26.2°	*S*[i]
8	**7h**	20	30 (40[b])	7[f]	-2.6°	*R*

[a] Isolated yield. [b] Yield of recovered substrate. [c] Based on the specific rotation reported in the literature[17]. [d] The isolated product was **8a**. [e] Yield of the hydrolyzed product **7a**. [f] Determined by chiral HPLC analysis. [g] Assigned, after converted into *p*-methoxyphenylethanol, by comparison of the sign of the specific rotation with that reported in the literature[18]. [h] Based on the specific rotation,[19] after converted into the corresponding epoxide. [i] Determined after transformed into the corresponding epoxide.[15b]

as determined by chiral HPLC analysis (entry 4). The absolute configuration of **8d** was assigned after converted into the corresponding epoxide (**9d**)[19] by treatment with sodium hydroxide. Similarly, **7e** was also reduced to afford (*S*)-*N*-(4-(1-hydroxy-2-chloroethyl)phenyl)methanesulfonamide (**8e**) in 87% ee (entry 5). Recrystallization of **8e** from methylene chloride-hexane improved the ee up to 93%. Chiral **8e** is a potential

intermediate for chemical synthesis of *d*-sotalol (**2**)[20] which possesses an acidic methylsulfonanilide moiety and exhibits an interesting class III electro-physiological property that is effective against ventricular arrhythmia.[4] The nitrophenyl analog (**7f**), a strong electron withdrawing substituted compound, was smoothly reduced by *Geotrichum sp.* 38 to afford the corresponding (*S*)-alcohol (**8f**) in high yield and optical purity (entry 6). The absolute configuration and ee of **8f** were deduced by converting into the epoxide (**9f**)[19] in the similar manner as that of **8d**. Pyridinyl α-chloromethyl ketone (**7g**) was also readily reduced to provide the corresponding (*S*)-chlorohydrin (**8g**) in 91% yield and 81% ee (entry 7). The ee value can be improved to more than 99% by recrystallization over methylene chloride-hexane. Interestingly, the initial crystals that formed in the crystallization were almost racemic, and the mother liquor contained the enantiomerically enriched material. Chlorohydrin (*S*)-(**8g**) was converted to the corresponding epoxide (**9g**), upon treatment with sodium hydride, which was used to prepare (*S*)-(-)-R_0 25-8210 (**4**) according to the known procedure.[15b] When α,*o*-dichloroacetophenone (**7h**) was incubated with *Geotrichum sp.* 38, to our surprise, the isolated chlorohydrin (**8h**) was in low ee and *R* configuration (entry 8). This is so far the only outcome against with the previous results that the aryl α-halomethyl ketones were reduced by *Geotrichum sp.* 38 to afford the *anti*-Prelog halohydrins (*S*-enantiomer).

Reduction of α-hydroxy ketones, by *Geotrichum sp.* 38 provides useful synthetic intermediates 1,2-diols, which is an alternative approach to halohydrins accessible from α-halo ketones.



10
a X = H, R = H;
b X = Cl, R = H;
c X = H, R = Ac;
d X = Cl, R = Ac.

11
a X = H;
b X = Cl.

Scheme 3

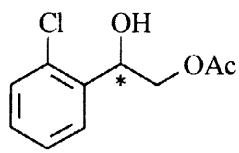
Table 3. Biotransformation of Ketones **10a-d** Using *Geotrichum sp.* 38

entry	substrate	reaction time / h	product	yield [a] / %	ee [b] / %	$[\alpha]_D$	config.
1	**10a**	16	**11a**	60	91.3	37°	*S*
2	**10b**	15	**11b**	77	60	-51.6°	*R*
3[c]	**10b**	20	**11b**	81	65	-45.3°	*R*
4	**10c**	16	**11a**	15 (71[d])	88.6	36.8°	*S*
5	**10d**	15	**11b**[e]	38 (25[d])	66	-56.5°	*R*

[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] Using calcium alginate-immobilized cells[21]. [d] Yield of recovered substrate. [e] With less than 3% yield of **10b** was isolated.

Incubation of phenacyl alcohol (**10a**) and *o*-chlorophenacyl alcohol (**10b**) with *Geotrichum sp.* 38 proceeded smoothly (Scheme 3). The corresponding (*S*)-phenylethanediol (**11a**) obtained in 60% yield and 91.3% ee was the *S* configuration which is in accord with *anti*-Prelog's rule exhibited by *Geotrichum sp.* 38 reduction. To our surprise, the reductive 1,2-diol **11b** was obtained in 77% yield and 60% ee and the configuration is *R*. Incubation of **10b** with calcium alginate-immobilized cells produced **11b** in similar outcome except in a slightly higher ee (65%). These results were summarized in Table 3 (entries 1 to 3).

The effect of chlorine atom at ortho-position of the phenyl group in **10b** leads to the opposite stereoselectivity and low optical purity of the product **11b**, which is as same as the result of reduction of **7h**. In general, the poor stereoselectivity in using intact cell for catalytic reduction of ketones may be caused by two factors. Firstly, the reduction process could be affected by a single enzyme but with different stereoselectivity.[22,23] Secondly, it may be due to participation of more than one oxidoreductase in intact cells which generates alcohols of opposite configuration at different rates.[24,25] In most cases, it turned out that the poor enantioselective reductions emanated from the combined action of competing enzymes exerting in intact cells.[22] These two factors can be readily distinguished from each other by conducting the reduction at different substrate concentrations as the enantioselectivity of the competing oxidoreductases will be influenced by changes in substrate concentrations.[26] Incubation of the acetates **10c** and **10d** with *Geotrichum sp.* 38 led to the products **11a** and **11b** respectively as shown in Table 3 (entries 4 and 5). The conversion rates of **10c** and **10d** were very slow, and the unreacted substrates were dominantly recovered after the same incubating time which were performed with **10a** and **10b**. Moreover, the intermediates **12a** and **12b** were not found during the whole incubation of **10c** and **10d**, while a little (ca. 3%) hydrolyzed intermediate **10b** was isolated after incubation of **10d**. These indicated that the acetates **10c** and **10d** were firstly hydrolyzed mediated by enzyme(s) in *Geotrichum sp.* 38 to 2-hydroxy ketones **10a** and **10b** which were subsequently reduced to 1,2-diols **11a** and

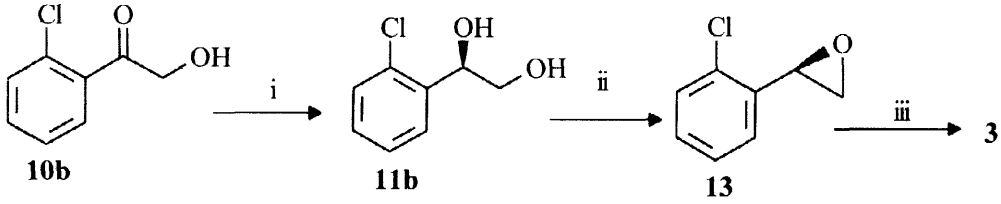


12
a, X = H;
b, X = Cl

11b respectively. This biotransformation procedure is different with that mediated by baker's yeast.[27] Obviously, the substrate concentrations of **10a** and **10b** in direct incubation and in incubation of **10c** and **10d** during which **10a** and **10b** were generated *in situ* are different. As a result, though two different incubations led to the same configuration of the products **11a** and **11b** respectively, there are slight enhancement of the enantioselectivity to the *R* enantiomers (60% to 66% for **11b**) and a little drop of the enantioselectivity to the *S* enantiomers (91.3% to 88.6% for **11a**). Therefore, we can deduce that the opposite configuration of the products **11a** and **11b** and the low optical purity of **11b** resulted from the combined action of competing enzymes in the whole cells which generate alcohols of opposite configuration at different rate.

(*R*)-1-(2-Chlorophenyl)-1,2-ethanediol (**11b**), generated by reduction of **10b** with calcium alginate-immobilized *Geotrichum sp.* 38, can be recrystallized from methylene chloride and its ee was improved to over 85% determined by chiral HPLC analysis. It is interesting to mention again that the initial crystals that formed

in the crystallization were nearly racemic and the mother liquor contained the enantiomerically enriched material. Selective tosylation of the primary hydroxy group of **11b** followed by treatment with alkaline gave the epoxide (*R*)-**13** in 85% yield, which then treated with isopropyl amine to provide (*R*)-clorprenaline (**3**) in 92% yield (Scheme 4).



Scheme 4. *Reagents and conditions*: i. Immobilized *Geotrichum sp.* 38, 5% glucose, 30 °C, 20h. 81%; ii. a) TsCl / Py, 0 °C; b) NaOH / MeOH. 85%; iii. a) $NH_2CH(CH_3)_2$; b) HCl / MeOH. 92%.

In conclusion, we have shown that reduction of aryl α-halomethyl or α-hydroxymethyl ketones (**5a-d**, **7a-g**) and (**10a**) with *Geotrichum sp.* 38 led to *anti*-Prelog halohydrins or 1,2-diol with *S* configuration. Unexpectedly, reduction of *o*-chlorophenacyl chloride (**7h**) or the alcohol (**10b**) led to product with *R* configuration and in low ees. These results might be explained by that there are more than one oxidoreductase in the intact cells which produced alcohols of opposite configuration at different rate as indicated by incubation of acetates **10c** and **10d** with *Geotrichum sp.* 38. However, as whole-cells systems are very complicated and further identification by isolating these oxidoreductases is in progress.

EXPERIMENTAL

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. ^1H and ^{19}F-NMR spectra were recorded on a Varian EM-390 or a Bruker AMX-300 spectrometer with tetramethylsilane as the internal standard for ^1H and CF_3COOH as the external standard for ^{19}F. Chemical shifts are reported in ppm and *J* are in Hz. Optical rotation were measured on a Perkin-Elmer 241 polarimeter. HPLC was carried out using Chiralcel OD or OJ, and Chiralpak AD (0.46 cmϕ x 25 cm) detected at UV 254 nm. TLC were 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.

The substrates for *Geotrichum sp.* 38 reduction, **5d**[28], **7a**[14a], **7b**[14b], **7c**[14c], **7d**[14a], **7e**[14d], **7f**[14a], **7h**[16] and **10c**[27] were prepared according to the procedures reported. *o*-Chloroacetophenone was purchased from TCI (Tokyo) and other reagents were commercially available from local stores.

Baker's yeast was from the local beer corporation.

*Preparation of α-floroacetophenone (**5a**)*

18-Crown-6 (264 mg, 1 mmol) and potassium fluoride (1.8 g, 30 mmol) were dissolved in dry acetonitrile (5 ml). After the mixture was stirred for 30 min at 90°C, α-bromoacetophenone (3.0 g, 15 mmol) was added and then the mixture was stirred for additional 10h. After cooling, ether (30 ml) was added and the salt was removed

by filtration. The organic layer was washed with water and dried. Removal of the solvent and distillation under reduced pressure gave **5a** as a colorless oil, 1.7 g (yield 85%), bp 110-112 °C / 20 mmHg (lit.[29] bp 94-95 °C / 12 mmHg).

Preparation of 6-(chloroacetyl)-2-pyridinecarboxylic acid methyl ester (7g)

To a solution of 6-(chlorocarbonyl)-2-pyridinecarboxylic acid methyl ester (2.3 g) prepared from 2,6-pyridinedicarboxylic acid (2.0 g, 11 mmol) according to the reported procedure [15b] in $CHCl_3$ (15 ml) was added dropwise to a solution of diazomethane (generated from 3.6 g of nitrosomethylurea[30], 35 mmol) in ether (50 ml) at 0 °C. The resultant solution was stirred for 30 min. at 0°C, then warmed to room temperature. After standing overnight, 12 ml of concentrated hydrochloric acid (12M) was gradually added to the reaction mixture cooled in an ice-bath with stirring. After the evolution of nitrogen had ceased, water (20 ml) was added. The organic layer was separated and the water phase was extracted with ethyl acetate (20 x 3 ml). The combined organic layers were washed with brine, dried, filtered and concentrated *in vacuo*. Purification by chromatography with petroleum ether-ethyl acetate (10:1 to 5:1), provided **7g** (2.0 g, 85%) as a white solid. mp. 97-98°C. IR (KBr) 3100, 2950, 1730, 1440, 1390, 1330, 1270, 1210, 1160, 1140, 1080, 1010, 1000, 770 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 4.1 (s, 3H), 5.2 (s, 2H), 8.0-8.5 (m, 3H); HRMS calcd. for $(C_9H_8ClNO_3)^+$ 213.0193, found 213.0229.

Preparation of 2-acetoxy-1-(2-chlorophenyl)ethanone (10d)

To a solution of *o*-chloroacetophenone (7.7 g, 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 1h, and the resulting solution was stirred at room temperature for 25h. 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 (50 x 4 ml). The combined extracts were washed with water, 5% aqueous $NaHSO_3$ and water, then dried. After removal of the solvent, the residue was distilled under reduced pressure to yield *o*-chlorophenacyl bromide 9.3 g (81%), bp 105-108 °C / 1 mmHg. ^{1}H-NMR (90 MHz, CCl_4) δ 4.5 (s, 2H), 7.2-7.6 (m, 4H); MS m/z (rel. intensity): 233 (M^+, 4.64), 141 (52.27), 139 (100), 111 (20.35).

2-Acetoxy-1-(2-chlorophenyl)ethanone (**10d**) was prepared in a same manner as **10c** from *o*-chlorophenacyl bromide (7.0 g, 30 mmol).[27] Purification by chromatography with petroleum ether-ethyl acetate (10:1 to 5:1) obtained **10d** 5.5 g (86%) as a colorless oil. IR (film) 1760, 1720 cm^{-1}; ^{1}H-NMR (90 MHz, CCl_4) δ 2.2 (s, 3H), 5.1 (s, 2H), 7.2-7.5 (m, 4H); MS m/z (rel. intensity): 213 $(M+1)^+$, 141 (38.40), 139 (100), 111 (19.52), 43 (14.13). Anal. Calcd. for $C_{10}H_9ClO_3$: C, 56.48; H, 4.26. Found: C, 56.23; H 4.25.

Preparation of 2-hydroxy-1-phenylethanone (10a) and 2-hydroxy-1-(2-chlorophenyl)ethanone (10b)

To a solution of the acetate (**10c-d**) (12 mmol) in 30 ml of methanol was added eight drops of concentrated hydrochloric acid (12M). The mixture was stirred at 60 °C for 4h. After removal of most of the methanol *in vacuo*, water (20 ml) was added. The mixture was extracted with ethyl acetate (30 x 3 ml), dried, filtered and concentrated. Purification by chromatography with petroleum ether-ethyl acetate (10:1 to 3:1) provided:
10a 1.5 g (90%) as a white solid. mp. 89-90 °C {lit.[31] mp. 89.5-90.5 °C }; IR (KBr) 3400, 1700, 1240 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ 3.5 (bs, 1H), 4.8 (s, 2H), 7.2-7.9 (m, 5H); MS m/z (rel. intensity): 136 (M^+, 55.6), 105 (100). Anal. Calcd. for $C_8H_8O_2$: C, 70.57; H, 5.92. Found: C, 70.58; H 5.7.

10b 1.6 g (80%) as a colorless oil. IR (film) 3400, 1710, 1600, 1440, 1290, 1060, 980, 760 cm^{-1}; ^{1}H-NMR (90 MHz, CCl_4) δ 3.7 (bs, 1H), 4.9 (s, 2H), 7.5-7.9 (m, 4H); MS m/z (rel. intensity): 171([M+1]$^+$, 11.44), 141 (62.21), 139 (100), 111 (20.15), 43 (26.83).

*General procedure for biotransformation of **5a-d**, **7a-h**, **10a-d** with Geotrichum sp. 38*

Geotrichum sp. 38 was cultivated on: glucose (100 g), yeast extract (10 g), urea (1 g) and tap water making up to 1 liter. After 2 days of culture at 30 °C on a reciprocating shaker set at 120 rpm, cells were harvested by centrifugation at 2,600 g for 30min, washed with 0.8% brine, and then were used for biotransformation studies.

Wet mycelium (15 g) was suspended in tap water (medium A, only for **5a-d**) or in 5% glucose solution (medium B) (50 ml). The substrate (1 mmol) in 0.5 ml of DMSO (if it is solid) was added slowly. The mixture was shaken at 30 °C until completion of the biotransformation monitored by TLC. The mycelium was filtered out and washed with ether or ethyl acetate. The filtrate was saturated with sodium chloride and extracted with ethyl acetate or ether (50 x 3 ml). The combined extracts were washed with brine, dried, filtered and evaporated under reduced pressure. The residue was purified by chromatography to give the corresponding alcohols. The yields, the enantiomeric purity and the absolute configuration of the products are summarized in Table 1-3.

*(S)-(+)-2-Floro-1-phenylethanol (**6a**)*

Colorless oil. By medium A: 70% ee, $[\alpha]_D^{22}$ 45° (c 1.3, $CHCl_3$); by medium B: 75% ee, $[\alpha]_D^{22}$ 47.3° (c 1.6, $CHCl_3$). {lit.[11a] $[\alpha]_D^{23}$ -53.2° (c 1.5, $CHCl_3$) (*R*)}. IR (film) 3400, 3050, 3000, 1460, 1080, 1010, 700 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.08 (bs, 1H), 4.41 (double dd, 1H, J = 47.5, 9.6, 8.2 Hz), 4.49 (double dd, 1H, J = 47.5, 9.6, 3.4 Hz), 4.97 (double dd, 1H, J = 14.4, 8.2, 3.4 Hz), 7.36 (s, 5H); ^{19} F-NMR ($CDCl_3$) δ 145 (td, J = 47, 14 Hz); MS m/z (rel. intensity): 140 (M$^+$, 4.75), 107 (100), 79 (71.7), 77 (44.39). The enantiomeric excess was determined by HPLC analysis using Chiralcel OD (eluent, hexane : 2-propanol = 9:1).

*(S)-(+)-2-Chloro-1-phenylethanol(**6b**)*

Colorless oil. By medium A: 87% ee, $[\alpha]_D^{22}$ 49.3° (c 1.73, cyclohexane); by medium B: 87.4% ee, $[\alpha]_D^{22}$ 52.1° (c 1.73, cyclohexane). {lit.[10] $[\alpha]_D^{25}$ -48.1° (c 1.73, cyclohexane) (*R*)}. IR (film) 3400, 3050, 2960, 1455, 1070, 705 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.70 (bs, 1H), 3.65 (dd, 1H, J = 11.1, 8.7 Hz), 3.75 (dd, 1H, J = 11.1, 3.5 Hz), 4.91 (dd, 1H, J = 8.7, 3.5 Hz), 7.3-7.6 (m, 5H); MS m/z (rel. intensity): 156 (M$^+$, 2.53), 107 (100), 79 (51.10), 77 (32.24). The enantiomeric excess was determined by HPLC analysis using Chiralcel OJ (eluent, hexane : 2-propanol = 9:1).

*(S)-(+)-2-Bromo-1-phenylethanol (**6c**)*

Colorless oil. By medium A: 80% ee, $[\alpha]_D^{22}$ 47.3° (c 1.3, $CHCl_3$); by medium B: 94% ee, $[\alpha]_D^{22}$ 49.8° (c 1.3, $CHCl_3$). {lit.[9a] $[\alpha]_D^{25}$ -39.7° (c 8.4, $CHCl_3$) (*R*)}. IR (film) 3400, 3050, 2980, 1460, 1065, 705 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.66 (bs, 1H), 3.55 (dd, 1H, J = 10.2, 9.0 Hz), 3.66 (dd, 1H, J = 10.2, 3.3 Hz), 4.93 (dd, 1H, J = 9.0, 3.3 Hz), 7.3-7.5 (m, 5H); MS m/z (rel. intensity): 200 (M$^+$, 0.95), 107 (100), 79 (40.30), 77 (23.86). The enantiomeric excess was determined by HPLC analysis using Chiralcel OD (eluent, hexane : 2-propanol = 9:1).

*(S)-(+)-2-Iodo-1-phenylethanol (**6d**)*

Colorless oil. By medium A: $[\alpha]_D^{22}$ 25.9° (c 0.23, $CHCl_3$); by medium B: $[\alpha]_D^{22}$ 11.4° (c 0.25, $CHCl_3$). {lit.[32] $[\alpha]_D^{25}$ 36.3° (c 5.29, $CHCl_3$) (*S*)}. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.65 (bs, 1H), 3.41 (dd, 1H, J = 10.3, 8.8 Hz), 3.49 (dd, 1H, J = 10.3, 3.6 Hz), 4.85 (dd, 1H, J = 8.8, 3.6 Hz), 7.3-7.5 (m, 5H); MS m/z (rel. intensity): 248 (M^+, 1.55), 121 (100), 107 (69.03), 77 (86.64).

*(S)-(+)-2-Chloro-1-(4-hydroxyphenyl)ethanol (**8a**)*

White solid; mp. 127-128°C; from **7a**: >98% ee, $[\alpha]_D^{22}$ 28.7° (c 1.1, CH_3COCH_3); from **7b**: >98% ee, $[\alpha]_D^{22}$ 27.5° (c 1.0, CH_3COCH_3); IR (KBr) 3420, 3230, 1620, 1235, 1070 cm^{-1}; ^{1}H-NMR (300 MHz, CD_3COCD_3) δ 3.09 (bs, 2H), 3.60 (dd, 1H, J = 11.0, 7.4 Hz), 3.68 (dd, 1H, J = 11.0, 4.8 Hz), 4.76 (dd, 1H, J = 7.4, 4.8 Hz), 6.8, 7.2 (AB, 4H, J = 6.6 Hz); MS m/z (rel. intensity): 172 (M^+, 7.56), 123 (100), 95 (26.09), 77 (25.39). The optical purity was based on the reported specific rotation. {lit.[17] $[\alpha]_D^{25}$ 26.4° (c 1.5, CH_3COCH_3) for 95% ee, (*S*)}

*(S)-(+)-2-Chloro-1-(4-methoxyphenyl)ethanol (**8c**)*

Colorless oil; 90.5% ee, $[\alpha]_D^{22}$ 40.2° (c 2.2, $CHCl_3$); IR (film) 3400, 2950, 1610, 1520, 1250, 1030, 840, 780 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.26 (bs, 1H), 3.56 (dd, 1H, J = 11.4, 8.7 Hz), 3.62 (dd, 1H, J = 11.4, 3.8 Hz), 3.74 (s, 3H), 4.78 (dd, 1H, J = 8.7, 3.8 Hz), 6.8, 7.2 (AB, 4H, J = 10 Hz); MS m/z (rel. intensity): 186 (M^+, 6.51), 137 (100), 109 (30.98), 94 (24.6), 77 (24.03). The enantiomeric excess was determined by HPLC analysis using Chiralcel OD (eluent, hexane : 2-propanol = 8:2). The absolute configuration was established after converted into (*R*)-1-(4-methoxyphenyl)ethanol.

*(S)-(+)-2-Chloro-1-(4-chlorophenyl)ethanol (**8d**)*

Colorless oil; 96.6% ee, $[\alpha]_D^{22}$ 44.2° (c 2.1, $CHCl_3$); IR (film) 3400, 1600, 1495, 1410, 1090, 1015, 840, 750 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.46 (bs, 1H), 3.60 (dd, 1H, J = 11.2, 8.7 Hz), 3.72 (dd, 1H, J = 11.2, 3.5 Hz), 4.89 (dd, 1H, J = 8.7, 3.5 Hz), 7.3-7.5 (m, 4H); MS m/z (rel. intensity): 190 (M^+, 4.37), 141 (100), 143 (32.09), 77 (94.21). The enantiomeric excess was determined by HPLC analysis using Chiralcel OJ (eluent, hexane : 2-propanol = 9:1). The absolute configuration was established after converted into the corresponding epoxide.

*(S)-(+)-N-(4-(1-Hydroxy-2-chloroethyl)phenyl)methanesulfonamide (**8e**)*

White solid; mp. 88-89°C; 87% ee, while recrystallization from hexane-methylene chloride improved the ee to more than 92%, $[\alpha]_D^{22}$ 28.1° (c 1.1, CH_2Cl_2). {lit.[20b] $[\alpha]_D$ 20° (c 1.0, CH_2Cl_2) (*S*)}. IR (KBr) 3400, 3230, 1620, 1335, 1140, 1080, 985 cm^{-1}; ^{1}H-NMR (300 MHz, CD_3SOCD_3) δ 2.97 (s, 3H), 3.63 (dd, 1H, J = 11.0, 7.1 Hz), 3.73 (dd, 1H, J = 11.0, 4.6 Hz), 4.73 (dd, 1H, J = 7.1, 4.6 Hz), 5.77 (bs, 1H), 7.17, 7.35 (AB, 4H, J = 8.5 Hz), 9.73 (s, 1H); HRMS calcd. for $(C_9H_{12}ClNO_3S+H)^+$ 250.0305, found 250.0320. The enantiomeric excess was determined by HPLC analysis using Chiralpak AD (eluent, hexane : 2-propanol = 85:15).

*(S)-(+)-2-Chloro-1-(4-nitrophenyl)ethanol (**8f**)*

White solid; mp. 87-88 °C; > 98% ee, $[\alpha]_D^{18}$ 37.2° (c 2.0, $CHCl_3$); IR (KBr) 3500, 1610, 1510, 1350, 1080, 860, 740 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.70 (bs, 1H), 3.64 (dd, 1H, J = 11.4, 8.2 Hz), 3.80 (dd, 1H, J = 11.4, 3.6 Hz), 5.05 (dd, 1H, J = 8.2, 3.6 Hz), 7.6, 8.2 (AB, 4H, J = 8.8 Hz); MS m/z (rel. intensity): 204

([M(^{37}Cl)+1]$^+$, 42.57), 202 ([M(^{35}Cl)+1]$^+$, 100), 152 (93.51), 94 (33.82), 78 (33.37). The ee and absolute configuration was established after converted into the corresponding epoxide.

*Methyl (S)-(+)-6-(1-hydroxy-2-chloroethyl)-2-pyridinecarboxylic acid methyl ester (**8g**)*

White solid; mp. 73-74 °C; 81% ee, $[\alpha]_D^{20}$ 26.2° (c 1.1, $CHCl_3$), while recrystallization from methylene chloride-hexane improved the ee to more than 99%, $[\alpha]_D^{22}$ 32.8° (c 1.1, $CHCl_3$); IR (KBr) 3350, 1730, 1600, 1440, 1295, 1220 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.0 (bs, 1H), 3.86 (dd, 1H, J = 11.1, 5.8 Hz), 3.93 (dd, 1H, J = 11.2, 4.4 Hz), 4.00 (s, 3H), 5.08-5.12 (m, 1H), 7.68 (d, 1H, J = 7.7 Hz), 7.91 (t, 1H, J = 7.7 Hz), 8.09 (d, 1H, J = 7.7 Hz); MS m/z (rel. intensity): 214 ([M+1]$^+$, 13.18), 180 (60.99), 166 (100), 134 (56.07), 106 (97.08), 78 (31.97), 77 (34.38). Anal. Calcd. for $C_9H_{10}ClNO_3$: C, 50.13; H, 4.67; N, 6.49. Found: C, 49.97; H 4.66; N, 6.47. The enantiomeric excess was determined by HPLC analysis using Chiralcel OD (eluent, hexane : 2-propanol = 8:2). The absolute configuration was established after converted into the corresponding epoxide.

*(R)-(-)-2-Chloro-1-(2-chlorophenyl)ethanol (**8h**)*

Colorless oil; 7% ee, $[\alpha]_D^{18}$ -2.6° (c 1.0, $CHCl_3$); IR (film) 3400, 1580, 1440, 1080, 750 cm^{-1}; ^{1}H-NMR(300 MHz, $CDCl_3$) δ 2.7 (bs, 1H), 3.52 (dd, 1H, J = 11.3, 8.7 Hz), 3.92 (dd, 1H, J = 11.3, 2.7 Hz), 5.29 (dd, 1H, J = 8.7, 2.7 Hz), 7.2-7.4 (m, 3H), 7.64 (dd, 1H, J = 7.4, 1.8 Hz); MS m/z (rel. intensity): 190 (M$^+$, 3.88), 143 (35.78), 141 (100), 113 (31.9), 77 (61.63). The enantiomeric excess was determined by HPLC analysis using Chiralcel OD (eluent, hexane : 2-propanol = 95:5).

*(S)-(+)-Phenylethanediol (**11a**)*

White solid; mp. 62-63°C; from **10a**: 91.3% ee, $[\alpha]_D^{22}$ 37° (c 1.9, CH_3COCH_3); from **10c**: 88.6% ee, $[\alpha]_D^{22}$ 36.8° (c 1.4, CH_3COCH_3). {lit.[27] $[\alpha]_D$ 40° (c 2.0, CH_3COCH_3) for 94% ee, (*S*)}. Its ^{1}H-NMR, IR, MS spectra were identical with those of an authentic sample. The enantiomeric excess was determined by HPLC analysis using Chiralcel OD (eluent, hexane : 2-propanol = 9:1).

*(R)-(-)-o-Chlorophenylethanediol (**11b**)*

White solid; mp. 98-99°C; from **10b**: 60% ee, $[\alpha]_D^{22}$ -51.6° (c 1.9, EtOH); from **10d**: 66% ee, $[\alpha]_D^{22}$ -56.5° (c 1.8, EtOH); from **10b** using calcium alginate-immobilized cells: 65% ee, $[\alpha]_D^{20}$ -45.3° (c 1.9, EtOH). While recrystallization over methylene chloride improved the ee to 85%, $[\alpha]_D^{22}$ -57° (c 1.8, EtOH) {lit.[33] $[\alpha]_D$ -47.2° (c 1.9, EtOH) for 73% ee, (*R*)}; IR (KBr) 3300, 1635, 1440, 1070, 1040, 760 cm^{-1}; ^{1}H-NMR (300 MHz, CD_3COCD_3) δ 3.39 (dd, 1H, J = 11.2, 7.8 Hz), 3.46 (bs, 2H), 3.69 (dd, 1H, J = 11.2, 3.0 Hz), 5.12 (dd, 1H, J = 7.8, 3.0 Hz), 7.28-7.65 (m, 4H); MS m/z (rel. intensity): 172 (M$^+$, 1.8), 143 (38.02), 141 (100), 113 (24.15), 77 (69.81). The enantiomeric excess was determined by HPLC analysis using Chiralcel OD (eluent, hexane : 2-propanol = 8:2).

*Determination of the absolute configuration of **8c***

A solution of (*S*)-**8c** (120 mg, 0.65 mmol), tributyltin hydride (1.0 ml, 3.25 mmol) and AIBN (100 mg, 0.65 mmol) in benzene (10 ml) was refluxed for 10h. After cooled, 50 ml of ether was added and the mixture was washed with aqueous potassium fluoride solution, brine and then dried. Removal of the solvent and the residue was purified by chromatography with petroleum ether-ethyl acetate (20:1) to obtain (*R*)-1-(4-

methoxyphenyl)ethanol as a colorless oil (75 mg, 76%). The spectra of ^{1}H-NMR and MS were identical with those of an authentic sample in all respects. $[\alpha]_D^{22}$ 35.4° (c 2.6, EtOH) {lit.[18] $[\alpha]_D^{25}$ 31.1° (c 2.54, EtOH), (*R*)}.

*Conversion (S)-**8d** into the epoxide of (S)-1-(4-chlorophenyl)-1,2-epoxypropane (**9d**)*

To a solution of (*S*)-**8d** (55 mg, 0.3 mmol) in methanol (10 ml) at 0 °C was added 20% aqueous NaOH (0.06 ml, 0.3 mmol) and the mixture was stirred at room temperature until TLC showed complete conversion to the epoxide (about 3h). Removal of methanol *in vacuo* followed by CH_2Cl_2 extraction, water wash, drying, and removal of the solvent afforded the residue which was purified by chromatography with petroleum ether-ethyl acetate (20:1) to afford (*S*)-**9d** (30 mg, 70%) with TLC, IR and ^{1}H-NMR identical with those of the authentic sample. $[\alpha]_D^{25}$ 21.8° (c 1.1, $CHCl_3$) {lit.[19] $[\alpha]_D^{20}$ 19.3° (c 1.16, $CHCl_3$), (*S*)}.

*Conversion (S)-**8f** into the epoxide of (S)-1-(4-nitrophenyl)-1,2-epoxypropane (**9f**)*

(*S*)-**8f** (100 mg, 0.5 mmol) was conversed into (*S*)-**9f** (70 mg, 85%) in the same procedure above, with physical and chemical characteristics identical to those of an authentic sample, $[\alpha]_D^{18}$ 38.4° (c 2.0, $CHCl_3$) {lit.[19] $[\alpha]_D^{20}$ 37.6° (c 1.99, $CHCl_3$), (*S*)}.

*Conversion of (S)-**8g** into the epoxide of (S)-6-oxiranyl-2-pyridinecarboxylic acid methyl ester (**9g**)*

(*S*)-**8g** was similarly converted into (*S*)-**9g** according to the procedure reported,[15b] $[\alpha]_D^{20}$ 44° (c 1.1, $CHCl_3$) {lit.[15b] $[\alpha]_D^{22}$ 43.7° (c 1.07, $CHCl_3$), (*S*)}.

*Preparation of (R)-1-(2-chlorophenyl)-1,2-epoxypropane (**13**)*

A solution of *p*-toluenesulfonyl chloride (265 mg, 1.4 mmol) in $CHCl_3$ (2 ml) was added at 0 °C to a solution of (*R*)-**11b** (200 mg, 1.16 mmol, 65% ee) and pyridine (2 ml), and then stirred at room temperature for 48h. The reaction mixture was poured into water (10 ml), extracted with benzene (20 x 3 ml), the organic layer was washed with 1.5N hydrochloric acid, saturated sodium hydrogencarbonate successively, dried, and concentrated. The residue was dissolved in methanol (2 ml). The mixture was cooled in ice-salt bath before the methanolic solution (2.0 ml) of NaOH (50 mg, 1.25 mmol) was added. The reaction mixture was stirred at -10 °C for 4h. After that it was diluted with 50 ml of ether and water (10 ml) was added. The organic layer was separated and washed with water, dried. Removal of the solvent and the residue was purified by chromatography with petroleum ether-ethyl acetate (50:1) to obtain the epoxide (**13**) (150 mg, 85%) as a colorless oil, $[\alpha]_D^{22}$ -43.4° (c 1.5, $CHCl_3$) for 65% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.66 (dd, 1H, J = 5.7, 2.5 Hz), 3.19 (dd, 1H, J = 5.7, 4.2 Hz), 4.21 (dd, 1H, J = 4.2, 2.5 Hz), 7.25-7.35 (m, 4H); MS m/z 154 (M^+).

*Preparation of (R)-2-chloro-α-[(1-methylethyl)aminomethyl]benzenemethanol (clorprenaline) (**3**)*

A solution of (*R*)-**13** (55 mg, 0.35 mmol) in excess isopropyl amine (1 ml) and a drop of water was stirred at room temperature for 2 days, and then the mixture was heated at 60 °C for 5h. After removal of the excess isopropyl amine, the residue was dissolved in 20 ml ether, dried, filtered and concentrated. The solid was recrystallized from n-hexane to afford **3** (69 mg, 92%) as a white solid. mp. 77-78 °C; $[\alpha]_D^{23}$ -61.8° (c 1.3, EtOH). IR (KBr) 3320,3100, 300, 2850, 1460, 1470, 1440, 1390, 1090, 760 cm^{-1}; 1H-NMR (300 MHz, $CDCl_3$) δ 1.08 (dd, 6H, J = 6.2, 4.2 Hz), 2.53 (dd, 1H, J = 12.2, 8.8 Hz), 2.7-3.0 (m, 3H), 3.07 (dd, 1H, J = 12.2, 3.3

Hz), 5.08 (dd, 1H, J = 8.7, 3.3 Hz), 7.2-7.3 (m, 3H), 7.6 (d, 1H, J = 7.7 Hz); MS m/z (rel. intensity): 216 ([M(^{37}Cl)+1]$^+$, 42.44), 215 (17.54), 214 ([M(^{35}Cl)+1]$^+$, 100), 196 (14.73), 77 (19.38), 72 (68.82), 43 (8.71).

The hydrochloride was obtained as follows: **3** was dissolved in methanol (1 ml), and 2 ml of 0.5M HCl in methanol was added; removal of the solvent afforded (*R*)-clorprenaline (**3**·HCl) as a white solid. mp. 191-192 °C; $[\alpha]_D^{22}$ -71.6° (c 1.3, EtOH). Anal. Calcd. for $C_{11}H_{17}Cl_2NO$: C, 52.81; H, 6.85; N, 5.60. Found: C, 52.50; H, 6.82; N, 5.26.

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REFERENCES AND NOTES

1. (a) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1983**, *48*, 1784; (b) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1985**, *50*, 1384; (c) Brown, H. C.; Cho, B. T.; Park, W. S. *J. Org. Chem.* **1988**, *53*, 1231; (d) Srebnik, M.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.* **1988**, *53*, 2918; (e) Brown, H. C.; Srebnik, M.; Ramachandran, P. V. *J. Org. Chem.* **1989**, *54*, 1577.
2. (a) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1990**, *31*, 601; (b) Corey, E. J.; Link, J. O. *J. Org. Chem.* **1991**, *56*, 442; (c) Ramachandran, P. V.; Gong, B.; Brown, H. C. *Chirality* **1995**, *7*, 103.
3. Elks, J.; Ganellin, C. R. *Dictionary of Drugs*; Chapman and Hall; **1990**, pp. 1160.
4. Taggart, P.; Sutton, P.; Donaldson, R. *Clin. Sci.* **1985**, *69*, 631.
5. Tatsumi, K.; Arima, N.; Yamato, C.; Yoshimura, H.; Tsukamoto, H. *Chem. Pharm. Bull.* **1970**, *18*, 1254.
6. Stromelysin 1 (MMP-3) is a member of a family of extracellular matrix-degrading zinc metalloproteases (MMPs) that have been implicated in the tissue destruction associated with a number of diseases, see: Woessner, E. M. *FASEB J.* **1991**, *5*, 2145.
7. Mildland, M. M. *Chem. Rev.* **1989**, *89*, 1553.
8. (a) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861. (b) Bloom, J. D.; Dutia, M. D.; Johnson, B. D.; Wissner, A.; Burns, M. G.; Largis, E. E.; Dolan, J. A.; Claus, T. H. *J. Med. Chem.* **1992**, *35*, 3081. (c) Abdel-Magid, A. F. *Reductions in Organic Synthesis*; ACS Symposium series 641; Washington DC; **1996**, Chapters 5 and 7.
9. (a) Carvalho, M.; Okamoto, M. T.; Moran, P. J. S.; Rodrigues, J. A. R. *Tetrahedron* **1991**, *47*, 2073; (b) Aleixo, L. M.; Carvalho, M.; Moran, P. J. S.; Rodrigues, J. A. R. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1637.
10. (a) Imuta, M.; Kawai, K.; Ziffer, H. *J. Org. Chem.* **1980**, *45*, 3352; (b) Tanner, D. D.; Stein, A. R. *J. Org. Chem.* **1988**, *53*, 1642; (c) Tanner, D. D.; Singh, H. K.; Kharrat, A.; Stein, A. R. *J. Org. Chem.* **1987**, *52*, 2142.
11. Prelog, V. *Pure Appl. Chem.* **1964**, *9*, 119.

12. Gu, J.-X.; Li, Z.-Y.; Lin, G.-Q. *Tetrahedron* **1993**, *49*, 5805.
13. Baker's yeast was from the local beer corporation.
14. (a) Cullinane, N. M.; Edwards, B. F. R. *J. Appl. Chem.* **1959**, *9*, 133; (b) Wilds, A. L.; Johnson, T. L. *J. Am. Chem. Soc.* **1945**, *67*, 287; (c) Miyahara, Y. *J. Het. Chem.* **1979**, *16*, 1147; (d) Lis, R.; Morgan, T. K., Jr.; Devita, R. J.; Davey, D. D.; Lumma, W. C., Jr.; Wohl, R. A.; Diamond, J.; Wong, S. S.; Sullivan, M. E. *J. Med. Chem.* **1987**, *30*, 696.
15. (a) 14a; (b) Hull, K. G.; Visnick, M.; Tautz, W.; Sheffron, A. *Tetrahydron* **1997**, *53*, 12405.
16. Wornhoff, E. W.; Martin, D. G.; Johnson, W. S. *Org. Synth.*; Wiley: New York, **1963**; *Coll. Vol. IV*, pp.162.
17. Gu, J.-X.; Li, Z.-Y.; Lin, G.-Q. *Chinese J. Chem.* **1995**, *13*, 475.
18. Hiratake, J.; Inagaki, M.; Nishioka, T.; Oda, J. *J. Org. Chem.* **1988**, *53*, 6130.
19. Pedragosa-Moreau; Morisseau, C.; Zylber, J.; Achelas, A.; Baratti, J.; Furstoss, R. *J. Org. Chem.* **1996**, *61*, 7402.
20. (a) Brodfuehrer, P. R.; Smith, P.; Dillon, J. L.; Vemishetti, D. *Org. Process Res. Dev.* **1997**, *1*, 176; (b) Patel, R. N.; Banerjee, A.; McNamee, C. G.; Szarka, L. *J. Appl. Microbiol. & Biotechnol.* **1993**, *40*, 241.
21. Woodward, J. *J. Microbiol. Methods* **1988**, *8*, 91.
22. Sih, C. J.; Chen, C. S. *Angew. Chem., Int. Ed. Eng.* **1984**, *23*, 570.
23. MacLeod, R.; Prosser, H.; Fikentscher, L.; Lanyi, J.; Mosher, H. S. *Biochemistry* **1964**, *3*, 838.
24. Shieh, W. R.; Gopalan, A. S.; Sih, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 2993.
25. Chen, C. S.; Zhou, B. M.; Girdaukas, G.; Shieh, W. R.; Van Middles Worth, F.; Gopalan, A. S.; Sih, C. J. *Bioorg. Chem.* **1984**, *12*, 98.
26. Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.
27. Manzocchi, A.; Fiecchi, A.; Santaniello, E. *J. Org. Chem.* **1988**, *53*, 4405.
28. Pasto, D. J.; Garves, K. *J. Org. Chem.* **1967**, *32*, 778.
29. Truce, W. E.; Sack, B. H. *J. Am. Chem. Soc.* **1948**, *70*, 3959.
30. Arndt, F. *Org. Synth.*; Wiley: New York, **1943**; *Coll. Vol. II*, pp. 165.
31. Cadogan, J. I. G.; Ley, S. V.; Pattenden, G.; Raphael, R. A.; Rees, C. W. *Dictionary of Organic Compounds*; Chapman & Hall, London, **1996**; 6th ed., *Vol. 6*, pp. 3562.
32. Soai, K.; Yamanoi, T.; Hikima, H. *J. Organomet. Chem.* **1985**, 290.
33. Hudicky, T.; Boros, E. E.; Boros, C. H. *Tetrahedron: Asymmetry* **1993**, *4*, 1365.