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Enantiomerically pure allylic alcohols: preparation by *Candida parapsilosis* ATCC 7330 mediated deracemisation

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ABSTRACT

Biocatalytic deracemisation of racemic allylic alcohols by whole cells of *Candida parapsilosis* ATCC 7330 resulted in the formation of the (*R*)-enantiomers in high enantiomeric excesses (up to >99%) and isolated yields (up to 79%).

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1. Introduction

Chiral allylic alcohols have attracted considerable attention due to their stereodirecting propensity in diastereoselective reactions.[1] They are considered valuable substrates for both synthetic[2] and mechanistic investigations.[3] These important chiral synthons are used for the synthesis of pharmaceuticals such as verapamil[4] and baclofen.[5] Several methods, chemical[6] and enzymatic,[7] have been reported for the synthesis of these compounds. Enantiopure 4-phenyl-but-3en-2-ol can be obtained either by kinetic resolution of the *rac*-alcohol employing Sharpless epoxidation[8] or via asymmetric hydrogenation of the corresponding ketone.[9] Metal catalysed hydrogen-transfer protocols are not very successful due to insufficient chemodifferentiation between C=C and C=O double bonds.[10] To circumvent this limitation of selectivity, enzymes are recognised to be amongst the most effective catalysts. Biocatalytic preparation of enantiomerically pure allylic alcohols by lipase mediated resolution of racemic allylic alcohols[11] and biocatalytic asymmetric reduction of the precursor prochiral ketones is known.[12] The asymmetric reduction of (3*E*)-phenyl-but-3en-2-one to enantiomerically pure (2*S*,3*E*)-4-phenyl-3-butene-2-ol (>99% ee) by secondary alcohol dehydrogenase from *Thermoanaerobacter ethanolicus* is reported,[13] but whole cells are preferred over isolated enzymes as the need for additional expensive cofactors is unnecessary. Enzymatic resolution is a widely used method but it results in 50% of the unwanted enantiomer unlike biocatalytic deracemisation which ideally gives only one enantiomer in high enantiomeric excess and chemical yield.[14] Dynamic kinetic resolution of (3*E*)-4-phenyl-3-butene-2-ol resulted in (2*R*,3*E*)-4-phenyl-3-butene-2-ol in high enantiomeric excess and yield, but a toxic metal catalyst is used for the racemisation and the time taken for the entire process is more than 24 h.[15] Deracemisation of racemic aryl α- and β-hydroxy esters to the corresponding enantiomerically pure (*S*)-hydroxy esters in high chemical yields (up to 85%) and up to >99% ee by *Candida parapsilosis* ATCC 7330 has previously been reported by our group.[16] These esters include (3*E*)-alkyl-2-hydroxy-4-arylbut-3-enoates,[16e] (3*E*,5*E*)-alkyl-2-hydroxy-6-arylhexa-3,5-dienoates[16g] and (3*E*)-alkyl-4-(hetero-2-yl)-2-hydroxybut-3-enoates.[16h] Extending the substrate specificity of the biocatalyst, herein we report for the first time, the *C. parapsilosis* ATCC 7330 mediated deracemisation of allylic alcohols in high enantiomeric excess (up to >99%) and yields (up to 79%).

2. Results and discussion

2.1. Synthesis of racemic allylic alcohols 2a–2j

Racemic allylic alcohols **2a–2j** were synthesised by the condensation of an aldehyde with acetone[17] followed by sodium borohydride reduction with methanol[7c] (Scheme 1).

2.2. Deracemisation of racemic allylic alcohols 2a–2j using *C. parapsilosis* ATCC 7330

Deracemisation of racemic allylic alcohols by whole cells of *C. parapsilosis* ATCC 7330 was standardised using (3*E*)-4-phenyl-3-butene-2-ol **2a** as the substrate. The (*R*)-enantiomer of the product was obtained in 99% ee and 75% yield. To prove the generality of this deracemisation reaction with respect to the substrate structure, a variety of aryl substituted allylic alcohols were deracemised using *C. parapsilosis* ATCC 7330 (Scheme 2), which resulted in the formation of their (*R*)-enantiomers in >76–99% ee and 68–79% yields. Substrates with different *para*-substituents (Table 1, entries **2b**, **2d** and **2f**) on deracemisation gave 98–99% ee and 70–79% isolated yields of their corresponding (*R*)-enantiomers (Table 2). In the case of the *para*-substituents irrespective of the

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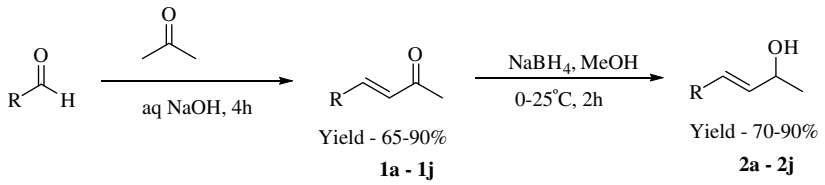
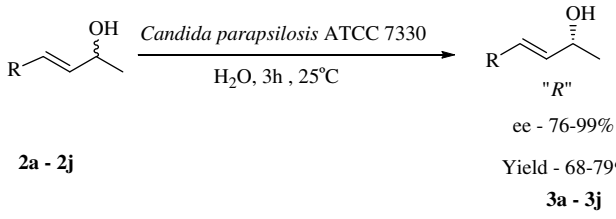


R = Ph, *o*-CH_3Ph, *p*-CH_3Ph, *o*-CH_3OPh, *p*-CH_3OPh, *o*-ClPh, *p*-ClPh, *o*,*p*-ClPh, $C_{10}H_7$ and $C_{14}H_9$

Scheme 1. Synthesis of racemic allylic alcohols **2a–2j**.



R = Ph, *o*-CH_3Ph, *p*-CH_3Ph, *o*-CH_3OPh, *p*-CH_3OPh, *o*-ClPh, *p*-ClPh, *o*,*p*-ClPh, $C_{10}H_7$ and $C_{14}H_9$

Scheme 2. Deracemisation of racemic allylic alcohols **2a–2j** using whole cells of *Candida parapsilosis* ATCC 7330.

Table 1
Synthesis of racemic allylic alcohols **2a–2j**

Entry	R	Yield (%)
2a	Ph	90
2b	*p*-MeC_6H_4	89
2c	*o*-MeC_6H_4	80
2d	*p*-$MeOC_6H_4$	90
2e	*o*-$MeOC_6H_4$	75
2f	*p*-ClC_6H_4	78
2g	*o*-ClC_6H_4	72
2h	*o*,*p*-$Cl_2C_6H_3$	70
2i	1-Naphthyl ($C_{10}H_7$)	85
2j	9-Anthranyl ($C_{14}H_9$)	76

Table 2
Deracemisation of allylic alcohols **2a–2j** using whole cells of *Candida parapsilosis* ATCC 7330

Entries	R	ee (%)[a]	Yield (%)
2a	Ph	>99	75
2b	*p*-MeC_6H_4	98	72
2c	*o*-MeC_6H_4	95	73
2d	*p*-$MeOC_6H_4$	>99	70
2e	*o*-$MeOC_6H_4$	94	69
2f	*p*-ClC_6H_4	>99	79
2g	*o*-ClC_6H_4	92	70
2h	*o*,*p*-$Cl_2C_6H_3$	90	68
2i	1-Naphthyl ($C_{10}H_7$)	76	71
2j	9-Anthranyl ($C_{14}H_9$)	10	78

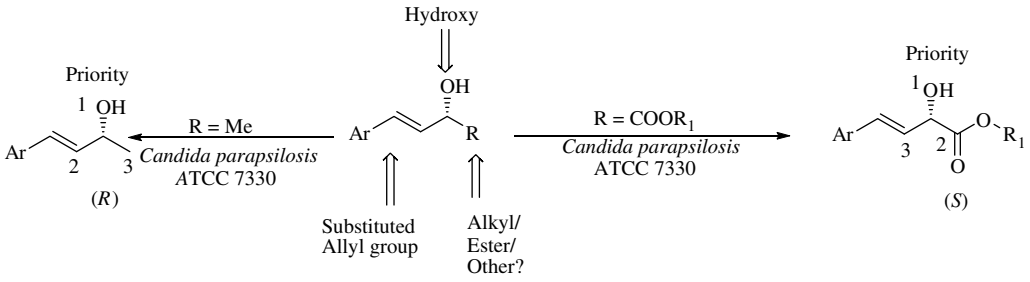
[a] Enantiomeric excess was determined by Chiral HPLC.

Table 3
Retention times of enantiomerically pure allylic alcohols **3a–3j**

Entry	R	Elution of HPLC peaks Retention time in min		Column
		Minor	Major	
3a	Ph	18.5	20.9	OJ-H
3b	*p*-MeC_6H_4	14.0	16.2	OJ-H
3c	*o*-MeC_6H_4	12.1	13.2	OJ-H
3d	*p*-$MeOC_6H_4$	14.0	16.0	OJ-H
3e	*o*-$MeOC_6H_4$	13.3	15.2	OJ-H
3f	*p*-ClC_6H_4	12.2	14.2	OJ-H
3g	*o*-ClC_6H_4	9.9	11.0	OJ-H
3h	*o*,*p*-$Cl_2C_6H_3$	6.2	8.2	OJ-H
3i	1-Naphthyl ($C_{10}H_7$)	19.3	23.2	OJ-H
3j	9-Anthranyl ($C_{14}H_9$)	20.1	22.2	OJ-H

electronic nature of the substituents (methyl, chloro and methoxy), the ee of the deracemised product remained very high (98–99%). Substrates generated from the standard substrate **2a** with an *ortho* substituent (Table 1, entries **2c**, **2e** and **2g**) showed a slight decrease in the (92–95%) of the product. Substrates with bulky groups, for example, (3*E*)-4-(naphthalen-2-yl)but-3-en-2-ol, **2i** and (3*E*)-4-(anthracen-2-yl)but-3-en-2-ol, **2j** gave poor ee whilst the disubstituted (3*E*)-4-(dichlorophenyl)but-3-en-2-ol (Table 1, entry **2h**) on deracemisation gave 90% ee and 68% yield of its (*R*)-enantiomer.

The absolute configuration of the enantiomerically pure enantiomers was assigned to be (*R*) by comparing the specific rotations



Scheme 3. Deracemisation of allylic alcohols and α-hydroxy enoates by *Candida parapsilosis* ATCC 7330.

with the literature data.[18] The elution profile from HPLC was found to be generally in the following order; the (*S*)-enantiomer is the early eluting enantiomer whilst the (*R*)-enantiomer is the late eluting enantiomer (Table 3). The deracemisation of allylic alcohols by *C. parapsilosis* ATCC 7330 possibly follows a stereoinversion mechanism,[19] that is, enantioselective oxidation of one antipode to the ketone intermediate, followed by a complementary enantioselective reduction of the intermediate ketone to give a single enantiomer in high yield and ee. The formation of a ketone intermediate was confirmed by the time course of the deracemisation of racemic (3*E*)-4-phenyl-3-butene-2-ol **2a**, as monitored by HPLC using a reverse phase column. Aliquots of the reaction mixture were taken every 15 min for 3 h. The ketone intermediate was detected at 30 and 45 min. Deracemisation of allylic alcohols using whole cells of *C. parapsilosis* ATCC 7330 yielded the (*R*)-enantiomer whilst the α- and β-hydroxy enaotes[16] gave the (*S*)-enantiomer on deracemisation due to the differences in the prioritisation of the groups for assigning the (*R*)- and (*S*)-configurations (Scheme 3).

3. Conclusion

We have developed a one-pot biocatalytic method for the deracemisation of allylic alcohols using whole cells of *C. parapsilosis* ATCC 7330 to give the (*R*)-allylic alcohols in good yields (68–79%) and high enantiomeric excesses (76–99%) under mild reaction conditions. This method is better than all the reported methods so far, as the biocatalyst shows high enantioselectivity towards racemic allylic alcohols and the entire deracemisation process takes less than 3 h. With appropriate immobilisation of the biocatalyst, this method can be suitably scaled up.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Bruker AV-400 spectrometer operating at 400 and 100 MHz, respectively. Chemical shifts are expressed in ppm values using TMS as an internal standard. HPLC analysis was carried out on a Jasco PU-1580 liquid chromatograph with a PDA detector using Chiralcel OJ-H chiral columns (Daicel, 4.6 × 250 mm). Hexane/isopropanol was used as the mobile phase, however, the proportion of solvents and the flow rate varied for different compounds. Optical rotations were recorded on a Jasco Dip 370 digital polarimeter. TLC was carried out on Kieselger 60 F254 aluminium sheets (Merck1.05554). All other chemicals used were of analytical grade and distilled before use. *C. parapsilosis* ATCC 7330 was purchased from ATCC Manassas, VA 201018, USA. All chemicals for media preparation were purchased locally. All substrates were synthesised as shown in the given schemes.

4.2. Synthesis of substrates

4.2.1. Preparation of various aryl substituted but-3en-2one 1a–1j: Typical procedure for the compound (3*E*) phenylbut-3en-2one 1a

The aldehyde (43.2 mmol) was added gradually to a solution of NaOH (2.2 g) in H_2O (20.0 ml) and ketone (43.3 mmol) in ethanol (12 ml) at 0 °C. The reaction mass was stirred at room temperature for 4 h. After 4 h, satd NH_4Cl solution was added to the flask, followed by extraction with ether. The combined organic layers were dried over Na_2SO_4 and concentrated to give a solid which was washed successively with hexane to give pure enones. (3*E*)-Phenylbut-3en-2one **1a** was obtained as a yellow solid after being purified by column chromatography using hexane/ethyl acetate (95:5) as eluent. The same procedure was followed for all the compounds **1b**–**1j** (Scheme 1).

4.2.2. Synthesis of racemic allylic alcohols (2a–2j). Typical procedure for the (3*E*)-4-phenyl-3-butene-2-ol 2a

Reduction of (3*E*)-4-phenyl-3-butene-2-one **1a** (benzylidene acetone 2.04 g, 0.014 mol) (Scheme 1) was carried out with sodium borohydride (0.56 g, 0.015 mol) in methanol (5 ml) for 2 h at 0–10 °C. After completion of the reaction, the reaction mass was neutralised with dilute HCl (5%) and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and evaporated under vacuum. Compound (3*E*)-4-phenyl-3-butene-2-ol **2a** was obtained as colourless oil in 90% yield (1.9 g) after column purification using hexane/ethyl acetate (90:10) as solvent. The same procedure was followed for the synthesis of all racemic allylic alcohols **2b**–**2j** (Scheme 1, Table 1).

4.3. Growth conditions for *C. parapsilosis* ATCC 7330

C. parapsilosis ATCC 7330 was procured from ATCC 7330, which was grown in yeast malt broth medium (50 ml) in 250 ml Erlenmeyer flasks incubated at 25 °C, 200 rpm. The cells were harvested by centrifuging the 44 h culture broth at 4500 rpm for 15 min and subsequent washing with sterile water. The process was repeated three times, and the wet cells were used for biotransformation.[16b]

4.4. A typical procedure for the deracemisation reaction of (3*E*)-4-phenyl-3-butene-2-ol 2a using the whole cells of *C. parapsilosis* ATCC 7330

To a 250 ml conical flask containing 48g of pelleted *C. parapsilosis* ATCC 7330 cells suspended in 44 ml of sterile distilled water, 144 mg (0.97 mmol) of (3*E*)-4-phenyl-3-butene-2-ol **2a** dissolved in 3.2 ml of ethanol was added. The reaction was carried out in a water bath shaker at 150 rpm and 25 °C for 3 h. After incubation, the reaction mixture was centrifuged at 5000 rpm for 10 min. The product formed was isolated using ethyl acetate (3 × 30 ml) and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed by evaporation and the enantiomerically pure (2*R*,3*E*)-4-phenyl-3-butene-2-ol **3a** was obtained as a colourless solid after purification by silica gel column chromatography using hexane/ethyl acetate (90:10) as a mobile phase eluent. The ee was found to be 99%, as determined using HPLC. The yield of the isolated product, (2*R*,3*E*)-4-phenyl-3-butene-2-ol **3a** was 75% (108 mg). Mp 57–59 °C; $[\alpha]_D^{25} = +33.2$ (*c* 1.02 $CHCl_3$); Spectroscopic data were identical to those reported in literature.[7e] Racemic allylic alcohols **2b**–**2j** were also used as substrates in the same manner (Scheme 2 and Table 2).

4.5. Spectroscopic characterisation of the deracemised allylic alcohols (3b–3j)

4.5.1. (2*R*,3*E*)-4-(4-Methylphenyl)-3-buten-2-ol 3b

Colourless oil; $[\alpha]_D^{25} = +20.9$ (*c* 0.8, $CHCl_3$); Spectroscopic data identical to that reported in the literature.[18b]

4.5.2. (2*R*,3*E*)-4-(2-Methylphenyl)-3-buten-2-ol 3c

Colourless oil; $[\alpha]_D^{25} = +15.4$ (*c* 1.1, $CHCl_3$); Spectroscopic data identical to that reported in the literature.[20a]

4.5.3. (2*R*,3*E*)-4-(4-Methoxyphenyl)-3-buten-2-ol 3d

Colourless oil; $[\alpha]_D^{25} = +9.4$ (*c* 1.1, $CHCl_3$); Spectroscopic data identical to that reported in the literature.[20c]

4.5.4. (2*R*,3*E*)-4-(2-Methoxyphenyl)-3-buten-2-ol 3e

Colourless oil; $[\alpha]_D^{25} = +6.4$ (*c* 1.02, $CHCl_3$); Spectroscopic data identical to that reported in the literature.[20b]

4.5.5. (2*R*,3*E*)-4-(4-Chlorophenyl)-3-buten-2-ol 3f

Colourless solid; mp 60–62 °C; $[\alpha]_D^{25} = +28.1$ (*c* 1.02, $CHCl_3$); Spectroscopic data identical to that reported in the literature.[7e]

4.5.6. (2*R*,3*E*)-4-(2-Chlorophenyl)-3-buten-2-ol 3g

Colourless oil; $[\alpha]_D^{25} = +8.3$ (*c* 0.70, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.29–1.31 (3H, d, $J = 6.4$ Hz), 2.02 (1H, sb), 4.42–4.45 (1H, m), 6.13–6.19 (1H, dd, $J_1 = 15.8$ Hz, $J_2 = 6.3$ Hz), 6.84–6.88 (1H, d, $J = 15.8$ Hz), 7.06–7.12 (2H, m), 7.24–7.26 (1H, d, $J = 7.6$ Hz), 7.42–7.44 (1H, d, $J = 7.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 23.3, 68.8, 125.5, 126.8, 127.5, 128.6, 129.6, 133.1, 134.8, 136.3; IR ν_{max} (neat): 3334, 2970, 2362, 1650, 1470, 1033, 1049 cm^{-1}, HRMS (ESI): found 183.0571, $C_{10}H_{12}OCl$ $[M+H]^+$ requires 183.0577.

4.5.7. (2*R*,3*E*)-4-(2,4-Dichlorophenyl)-3-buten-2-ol 3h

Colourless oil; $[\alpha]_D^{25} = +4.6$ (*c* 0.5 $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.38–1.39 (3H, d, $J = 6.4$ Hz), 2.36 (1H, sb), 4.51–4.54 (1H, m), 6.20–6.26 (1H, dd, $J_1 = 16.4$ Hz, $J_2 = 6.4$ Hz), 6.86–6.90 (1H, d, $J = 16.4$ Hz), 7.18–7.46 (1H, d, $J = 8$Hz), 7.36 (1H, s), 7.44–7.46 (1H, d, $J = 8$Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 23.2, 68.7, 124.4, 127.1, 127.5, 129.3, 133.4, 133.5, 136.9, 136.8; IR ν_{max} (neat): 3338, 2970, 1650, 1585, 1469, 1048 cm^{-1}, HRMS (ESI): found 217.0194, $C_{10}H_{10}OCl_2$ $[M+H]^+$ requires 217.0187.

4.5.8. (2*R*,3*E*)-4-(Naphtha1en-2-yl)-3-buten-2-ol 3i

Colourless oil; $[\alpha]_D^{25} = +7.2$ (*c* 2.0 $CHCl_3$); Spectroscopic data identical to that reported in the literature.[7e]

4.5.9. (2*R*,3*E*)-4-(Anthracen-9-yl)-3-buten-2-ol 3j

Yellow colour solid; mp 98–103 °C; $[\alpha]_D^{25}$ not determined; ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.48–1.50 (3H, d, $J = 6.4$ Hz), 4.47–4.73 (1H, m), 6.04–6.09 (1H, dd, $J_1 = 16.2$ Hz, $J_2 = 6.29$ Hz), 7.25–7.29 (1H, d, $J = 16.2$ Hz), 7.39–7.41 (4H, m), 7.91–7.94 (2H, m), 8.18–8.21 (2H, m), 8.31 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 23.7, 69.1, 124.9, 125.0, 125.3, 125.7, 126.3, 128.6, 129.4, 131.3, 132.1, 142.2; IR ν_{max} (neat): 3339, 2969, 2924, 1670, 1442 cm^{-1}, HRMS (ESI): found 271.1099, $C_{18}H_{16}O$ $[M+Na]^+$ requires 271.1099.

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