Fungal Transformation of (1*R*,2*S*,5*R*)-(−)-Menthol by *Cephalosporium aphidicola*

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Incubation of (1*R*,2*S*,5*R*)-(−)-menthol (**1**) with *Cephalosporium aphidicola* for 12 days yielded the six oxidized metabolites: 10-acetoxymenthol (**2**), 7-hydroxymenthol (**3**), 4α-hydroxymenthol (**4**), 3α-hydroxymenthol (**5**), 9-hydroxymenthol (**6**), and 10-hydroxymenthol (**7**). The structures of the novel compounds **2**, **4**, **5**, and **7** were assigned by interpretation of their spectral data.

The biotransformation of various classes of terpenoids by *Cephalosporium aphidicola* has been studied extensively.[1−6] Our work on the biotransformation of 7α-hydroxyfrullanolide and sclareolide by *Aspergillus* species and *Culvularia lunata* has resulted in the production of several interesting metabolites that would have been difficult to obtain synthetically.[7,8]

The monoterpenoid menthol is the main constituent of peppermint oil, and it exhibits anesthetic, disinfectant, and photoprotective effects.[9] We now report the biotransformation of (1*R*,2*S*,5*R*)-(−)-menthol (**1**) by *Cephalosporium aphidicola* (IMI 68981) to yield four new metabolites characterized as 10-acetoxymenthol (**2**), 4α-hydroxymenthol (**4**), 3α-hydroxymenthol (**5**), and 10-hydroxymenthol (**7**) and two known compounds identified as 7-hydroxymenthol (**3**) and 9-hydroxymenthol (**6**).[10,11] The structures of these metabolites were established through detailed physical and spectroscopic studies.

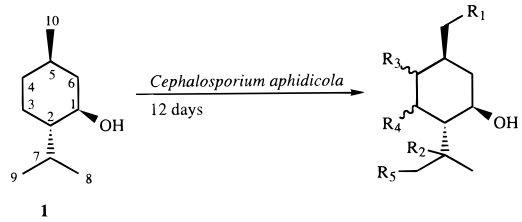
Results and Discussion

The prime investigation aimed at the metabolic transformation of (1*R*,2*S*,5*R*)-(−)-menthol (**1**) by fermentation with *C. aphidicola* has resulted in the production of six polar compounds as detected by TLC. Column chromatography of the crude material yielded compounds **2**−**7**.

The EIMS of compound **2** showed a molecular ion at *m*/*z* 214, which was confirmed by positive ion FABMS, while its HREIMS displayed a molecular ion at *m*/*z* 214.1559 corresponding to the molecular formula $C_{12}H_{22}O_3$. The IR spectrum displayed absorptions at 3595 (OH) and 1722 (acetoxy carbonyl) cm^{-1}. The ^1H NMR spectrum ($CDCl_3$, 300 MHz) was similar to that of menthol (**1**) but displayed an acetyl methyl signal at δ 2.04. These observations suggested the introduction of an acetoxy group in the menthol molecule. The presence of the acetoxy group at C-10 was confirmed by the absence of the CH_3-10 doublet in the ^1H NMR spectrum, the absence of the CH_3-10 carbon signal in the ^{13}C NMR spectrum, and the appearance of the carbon signals at δ 171.2 (−O*CO*) and 22.1 (−OCO−*CH*$_3$). The complete ^1H NMR and ^{13}C NMR assignments of **2** are presented in Tables 1 and 2, respectively.

The EIMS of **3** showed a molecular ion at *m*/*z* 172, which was confirmed by positive ion FABMS. The exact molecular mass of the compound was found to be 172.1445, which corresponds to the molecular formula $C_{10}H_{20}O_2$ with one degree of unsaturation. A 6H singlet at δ 1.21 was observed in the ^1H NMR of the compound, which resonated due to the two methyls of an isopropyl moiety. This suggested that hydroxylation took place at the C-7 tertiary carbon atom in the molecule. The position of the OH group at C-7 was further confirmed by the appearance of the C-7 quaternary carbon at low field in the ^{13}C NMR spectrum at δ 75.1. The ^1H NMR and ^{13}C NMR spectral assignments of **3** in comparison of those of menthol (**1**) are summarized in Tables 2 and 3. The synthesis of compound **3** has been previously reported.[10]

Scheme 1. Microbial oxidation of menthol (1).



1

2 R_1=OAc, R_2=R_3=R_4=R_5=H
3 R_2=OH, R_1=R_3=R_4=R_5=H
4 R_3=αOH, R_1=R_2=R_4=R_5=H
5 R_4=αOH, R_1=R_2=R_3=R_5=H
6 R_5=OH, R_1=R_2=R_3=R_4=H
7 R_1=OH, R_2=R_3=R_4=R_5=H

Compound **4** showed a molecular ion at *m*/*z* 172, which was confirmed by positive ion FABMS. The exact molecular mass of the compound was determined by HREIMS and found to be *m*/*z* 172.1188, which corresponds to the molecular formula $C_{10}H_{20}O_2$. The IR spectrum displayed an absorption at 3355 cm^{-1} (OH). The ^1H NMR spectrum ($CDCl_3$, 500 MHz) exhibited a downfield methine signal at δ 3.18 (1H, dt, J = 4.3, 10.6 Hz). This observation suggested the introduction of an OH group at one of the CH_2 groups, that is, C-3, C-4, or C-6. The assignments of all the protons were accomplished from the interpretation of the HMQC spectrum. The COSY 45° interactions of H-5 (δ 1.41) and H-3 (δ 1.05, 1.83) with the newly oxygenated methine proton (δ 3.48) suggested the introduction of a hydroxyl group at C-4. The multiplicity of the H-4 signal at δ 3.18 (dt, J = 4.3, 10.6 Hz, H-4) suggested the β-orientation (equatorial) of H-4 and, hence, of an α (axial) orientation of the newly introduced OH group at C-4.

The metabolite **5**, which was isolated as colorless crystals, displayed a molecular ion peak at *m*/*z* 172 in the EIMS. The positive ion FABMS showed a peak at *m*/*z* 173 and confirmed the molecular mass of the compound to be

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Table 1. ^{1}H NMR Assignments of Menthol (**1**) and Its Microbial Transformation Products (**2**−**7**) (δ ppm, J Hz)

proton (s)	**1**	**2**	**3**	**4**	**5**	**6**	**7**
1α	3.38 (dt, 4.5, 10.5)	3.42 (m,$W_{1/2}$ = 25.2)	3.70 (dt, 4.3, 10.8)	3.48 (dt, 4.4, 10.7)	3.75 (dt, 4.4, 10.8)	3.44 (dt, 4.3, 10.5)	3.43 (dt, 3.8, 10.6)
2β	1.08 (ddt, 13.5, 10.5, 3.5)	1.15 (m)	1.37 (m)	1.30 (m)	1.97 (m)	1.34 (m)	1.18 (m)
3β	0.93 (m)	0.90 (m)	0.95 (m)	1.05 (m)	3.99 (ddd, 6.2, 10.8, 13.4)	0.94 (m)	0.95 (m)
3α	1.39 (m)	1.65 (m)	1.67 (m)	1.83 (dt, 7.6, 3.9)		1.60 (m)	1.10 (m)
4β	0.83 (m)	0.85 (m)	1.60 (m)	3.18 (dt, 4.3, 10.6)	0.95 (m)	0.82 (m)	0.80 (m)
4α	1.58 (qd, 13.0, 3.5)	1.65 (m)	1.00 (m)		1.20 (m)	1.66 (m)	1.62 (tt, 2.0, 3.9)
5α	1.64 (dtd, 9.0, 6.5, 3.5)	1.41 (m)	1.70 (m)	1.41 (m)	1.25 (m)	1.42 (m)	1.50 (m)
6β	0.98 (m)	1.10 (m)	1.06 (m)	1.10 (m)	1.10 (m)	0.98 (m)	1.00 (m)
6α	1.94 (dtd, 12.0, 3.5, 2.0)	1.95 (m)	1.92 (dtd, 12.2, 4.1, 2.1)	1.95 (dt, 4.0, 12.7)	1.75 (m)	1.98 (m)	2.05 (m)
7	2.15 (dtd, 14.0, 7.0, 3.0)	2.13 (m)		2.13 (dtd, 14.0, 7.0, 2.85)	2.08 (m)	2.08 (m)	2.15 (dtd, 14.1, 7.1, 2.8)
8	0.79 (d, 7.0)	0.81 (d, 4.2)	1.21 (s)	0.85 (d, 4.2)	1.24 (d, 4.2)	0.855 (d, 7.1)	0.77 (d, 7)
9	0.90 (d, 7.0)	0.95 (d, 7.0)	1.21 (s)	0.95 (d, 7)	0.85 (d, 6.9)	3.57 (dd, 5.3, 10.5) 3.50 (dd, 7.5, 10.5)	0.90 (d,7)
10	0.89 (d, 7.0)	4.00 (dd, 8.5, 9.7) 3.90 (dd, 4.5, 8.5)	0.90 (d, 6.5)	1.03 (d, 6.5)	0.93 (d, 7.0)	0.90 (s)	3.38 (m, $W_{1/2}$ = 18.5)
$OCOCH_3$		2.04 (s)					

Table 2. ^{13}C NMR Assignments of Menthol (**1**) and Its Microbial Transformation Products (**2**−**7**) (δ ppm)

carbon	multiplicities	**1**	**2**	**3**	**4**	**5**	**6**	**7**
1	CH	71.5	71.0	72.9	70.7	72.3	72.0	71.4
2	CH	50.2	50.3	53.4	48.6	50.1	46.0	50.6
3	CH_2	23.3	22.6	27.1	32.4	68.5	25.6	22.9
4	CH_2	34.6	34.3	34.4	76.0	38.4	34.3	29.0
5	CH	31.7	30.9	31.4	38.3	30.3	31.6	39.5
6	CH_2	45.1	39.2	44.6	42.5	48.2	45.1	39.3
7	CH	25.9	25.9	75.1	25.8	25.9	36.0	26.0
8	CH_3	16.2	16.1	23.7	15.9	16.2	13.0	16.2
9	CH_3	21.0	20.9	30.1	20.9	20.9	66.7	21.0
10	CH_3	22.2	68.7	22.0	18.1	23.8	22.0	68.0
$OCOCH_3$			171.2					
$OCOCH_3$			22.1					

172. The molecular formula of the compound was found to be $C_{10}H_{20}O_2$ by recording the HREIMS, which showed an exact mass at m/z 172.1428. A hydroxyl absorption at 3385 cm^{-1} was observed in the IR spectrum of **5**. The ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of **5** exhibited a diagnostic CH proton signal at δ 3.99 (1H, ddd, J = 6.2, 10.8, 13.4 Hz), which provided evidence of hydroxylation at C-3, C-4, or C-6. The position of the new hydroxyl group was established as C-3 on the basis of COSY 45° NMR interactions of H-3 (δ 3.99) with H-2 (δ 1.97) and H-4 (δ 1.20, 1.95). This was further confirmed by HMBC correlations between H-3α (δ 3.95) and C-2 (δ 50.1). The new methine proton exhibited a doublet of double doublets at δ 3.99 (J = 6.2, 10.8, 13.4 Hz), which provided evidence for the 3β (axial) orientation of H-3, and hence the 3α (equatorial) orientation of the newly introduced OH was confirmed. The complete ^{1}H NMR and ^{13}C NMR assignments of **5** are summarized in Tables 1 and 3.

The EIMS of compound **6** showed a molecular ion at m/z 172, which was confirmed by FABMS. The exact molecular mass of the compound as determined by HREIMS was found to be m/z 172.1504, which corresponds to the molecular formula $C_{10}H_{20}O_2$. The IR spectrum displayed an absorption at 3392 cm^{-1} (OH). The ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) was distinctly similar to that of menthol (**1**) and displayed an AB double doublet at δ 3.57 and 3.50 due to an oxygen-bearing CH_2, while the CH_3-9 signal of menthol did not appear in the spectrum. The position of the newly introduced OH group at C-9 was indicated by the absence of the CH_3-9 signal at δ 21.0 and the appearance of the CH_2-9 signal at δ 66.7 in the ^{13}C NMR spectrum. The complete ^{1}H and ^{13}C NMR assignments of **6** are presented in Tables 1 and 2. A synthetic compound **6** has been previously reported.

Compound **7** showed a molecular ion at m/z 172, which was confirmed by positive ion FABMS. The exact molecular mass was found to be m/z 172.1454 by HRMS, corresponding to the molecular formula $C_{10}H_{20}O_2$. An absorption at 3415 cm^{-1} in the IR spectrum of **7** was observed showing the presence of hydroxyl groups in the menthol. A multiplet at δ 3.43(2H) and the disappearance of the CH_3-10 signal provided information of the conversion of C-10 methyl to C-10 CH_2OH. This was further confirmed by the presence of a CH_2-10 oxygen-bearing carbon at low field, that is, at δ 68.6, and the absence of a CH_3-10 signal at δ 22.2 in the ^{13}C NMR spectrum. The complete ^{1}H and ^{13}C NMR assignments of **7** are presented in Tables 2 and 3.

Experimental Section

General Experimental Procedures. Bruker AMX 500, AM 400, AM 300, and AC 300 NMR spectrometers were used to record ^{1}H NMR spectra, and the same instruments operating at 125, 100, and 75 MHz were used to record ^{13}C NMR spectra. A Varian MAT 311A mass spectrometer connected to a Masspec Data system was used to record mass spectra. FABMS and HREIMS spectra were recorded on a JEOL-JMS HX 110 mass spectromter with a glycerin matrix. The IR spectra were recorded on a JASCO IR A-302 IR spectrophotometer, and UV spectra were recorded on a Hitachi UV-3200 UV/vis spectrophotometer. Optical rotations were measured on a JASCO DIP 360 digital polarimeter. Melting points were taken on a Buchi 535 melting point apparatus. The purity of the samples was checked on precoated plates (Si gel 60 F_{254}, 0.2 mm, Merck). The metabolites were purified by column chromatography on flash Si gel and on precoated plates (Si gel 60 F_{254}, 0.2 mm, Merck). (1*R*,2*S*,5*R*)-(−)-Menthol was purchased from Aldrich.

Preparation of Medium. A medium for *C. aphidicola* (IMI 68981) was prepared by mixing glucose (100 g), KH_2PO_4 (2 g), $MgSO_4{\cdot}7H_2O$ (4 g), KCl (2 g), glycine (4 g), and *Gibberella* trace element solution [$Co(NO_3)_2$ (0.01% w/v), $FeSO_4{\cdot}7H_2O$ (0.1%), $CuSO_4{\cdot}5H_2O$ (0.1%), $ZnSO_4{\cdot}7H_2O$ (0.161%), $MnSO_4{\cdot}H_2O$ (0.01%), $Mn(NO_3)_2{\cdot}4H_2O$ (0.01%), H_2O (100 mL)] (4-mL portion of mixture) into distilled H_2O (2 L).

Cultivation of *C. aphidicola*. Two-day-old spores of *C. aphidicola* were aseptically transferred into a broth medium flask (250 mL) containing 100 mL of freshly prepared and autoclaved medium. The seed flask thus obtained was incubated on a shake table at 30 °C for 2 days.

Innoculation of the Cultures. A 2-day-old broth culture from a 1-mL seed flask was innoculated aseptically into 20 media flasks (250 mL) containing 100 mL of medium and fermentation was continued for a further 2 days.

Fermentation of (1*R*,2*S*,5*R*)-(−)-Menthol. (1*R*,2*S*,-5*R*)-(−)-Menthol (**1**) (1.0 g) was diluted with Me_2CO (10 mL), and the resulting solution was evenly distributed among 20 conical flasks having shake cultures, and the fermentation was continued for 12 days. The mycelium was filtered, washed with EtOAc (1 L), and the broth thus obtained was extracted with EtOAc (10 L). The extract was dried over anhydrous sodium sulfate and concentrated in vacuo to afford a brown gum (2 g) that was absorbed on flash Si gel (5.0 g), subjected to column chromatography containing flash Si gel (50 g), and eluted with various solvent gradients of petroleum ether, EtOAc, and MeOH.

Compound 1. Elution with EtOAc−petroleum ether (1:4) afforded residual menthol (**1**) (6.0%); mp 43 °C; $[\alpha]^{25}_D$ 507° (*c* 0.06, MeOH); UV (MeOH) λ_{max} (log ϵ) 215 nm (2.1); IR ($CHCl_3$) ν_{max} 3595 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) data, see Table 1; ^{13}C NMR ($CDCl_3$, 100 MHz) data, see Table 2; positive ion FABMS *m*/*z* 157; EIMS (70 eV) *m*/*z* 155 (1.5) $[M - 1]^+$, 138 (29) $[M - H_2O]^+$, 95 (64), 71 (100)

Compound 2. Elution with EtOAc−petroleum ether (40−60) (3:17) afforded impure fractions that were mixed and purified by TLC on precoated plates (Si gel 60 F_{254} 0.2 mm, Merck) using EtOAc−petroleum ether (2:3) as mobile phase where two pure compounds (**2** and **3**) were obtained. A colorless crystalline solid with R_f 0.4 has been identified as 10-acetoxymenthol (**2**) (3.0%): mp 68 °C; $[\alpha]^{20}_D$ 24° (*c* 0.13, MeOH); UV (MeOH) λ_{max} (log ϵ) 208 (2.20), 273.2 (2.04) nm; IR ($CHCl_3$) λ_{max} 3600 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) data, see Table 1; ^{13}C NMR ($CDCl_3$, 125 MHz) data, see Table 2; positive ion FABMS *m*/*z* 215; EIMS (70 eV) *m*/*z* 213 (3) $[M - 1]^+$, 165 (5), 154 (70), 136 (81), 112 (74), 55 (100); HREIMS *m*/*z* 214.1559 $[M]^+$, calcd for $C_{12}H_{22}O_3$ 214.1569.

Compound 3. The second compound obtained by TLC (see compound **2**) was a colorless crystalline solid with R_f 0.2, and identified as 7-hydroxymenthol (**3**) (4.8%); mp 58.9 °C; $[\alpha]^{25}_D$ 50° (*c* 0.06, MeOH); UV (MeOH) λ_{max} (log ϵ) 220 (2.7) nm; IR ($CHCl_3$) λ_{max} 3440 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) data, see Table 1; ^{13}C NMR ($CDCl_3$, 125 MHz) data, see Table 2; positive ion FABMS *m*/*z* 173; EIMS (70 eV) *m*/*z* 172 (0.08) $[M]^+$ 154 (2) $[M - 18]^+$, 139 (12), 121 (9), 96 (65), 81 (100), 59 (92); HREIMS *m*/*z* 172.1445 $[M]^+$, calcd for $C_{10}H_{20}O_2$, 172.1463.

Compound 4. Elution with EtOAc−petroleum ether (3:7) afforded impure fractions that were loaded on TLC precoated plates (Si gel 60 F_{254} 0.2 mm, Merck) and eluted with EtOAc−petroleum ether (1:1) to yield a colorless crystalline solid, R_f 0.7, identified as 4β-hydroxymenthol (**4**) (7.5%): mp 55 °C; $[\alpha]^{25}_D$ 20° (*c* 0.108, MeOH); UV (MeOH) λ_{max} (log ϵ) 220 (2.5) nm; IR ($CHCl_3$) υ_{max} 3400 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) data, see Table 1; ^{13}C NMR ($CDCl_3$, 125 MHz) data, see Table 2; positive ion FABMS *m*/*z* 173; EIMS (70 eV) *m*/*z* 155 (11), 154 (94) $[M - 18]^+$, 139 (100), 97 (81), 55 (79); HREIMS *m*/*z* 172.1188 $[M]^+$, calcd for $C_{10}H_{20}O_2$ 172.1463.

Compound 5. Elution with EtOAc−petroleum ether (7:13) afforded impure fractions that were mixed and loaded on precoated plates (Si gel 60 F_{254} 0.2 mm, Merck) using EtOAc−petroleum ether (1:1) as mobile phase to yield a crystalline solid with R_f 0.3, identified as 3α-hydroxymenthol (**5**) (2.3%): mp 59 °C; $[\alpha]^{25}_D$ 34° (*c* 0.072, MeOH); UV (MeOH) λ_{max} (log ϵ) 200 (2.5) nm; IR ($CHCl_3$) υ_{max} 3400 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) data, see Table 1; ^{13}C NMR ($CDCl_3$, 125 MHz) data, see Table 2; positive ion FABMS *m*/*z* 173; EIMS (70 eV) *m*/*z* 154 (4), 134 (6), 94 (100), 79 (64); HREIMS *m*/*z* 172.1428 $[M]^+$ calcd for $C_{10}H_{20}O_2$ 172.1463.

Compound 6. Elution with EtOAc−petroleum ether (2:3) afforded a white crystalline solid identified as 9-hydroxymenthol (**6**) (14.0%); mp 79.5 °C; $[\alpha]^{25}_D$ −20° (*c* 0.2, MeOH); UV (MeOH) λ_{max} (log ϵ) 220 (1.6) nm; IR ($CHCl_3$) υ_{max} 3400 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) data, see Table 1; ^{13}C NMR ($CDCl_3$, 125 MHz) data, see Table 2; positive ion FABMS *m*/*z* 172.1; EIMS (70 eV) *m*/*z* 172 (5) $[M]^+$ 154 (11) [M - 18]$^+$, 112 (29), 95.1 (43), 81 (100), 71 (82), 55 (86); HREIMS *m*/*z* 172.1504 $[M]^+$, calcd for $C_{10}H_{20}O_2$, 172.1463.

Compound 7. Elution with EtOAc−petroleum ether (1:1) afforded impure fractions that were mixed and loaded on to precoated plates (Si gel 60 F_{254} 0.2 mm, Merck) and eluted with EtOAc−petroleum ether (1:1). This afforded a white crystalline solid with R_f 0.2, identified as 10-hydroxymenthol (**7**) (21.5%): mp 88.4 °C; $[\alpha]^{25}_D$ 57.0 (*c* 0.06, MeOH); UV (MeOH) λ_{max} (log ϵ) 230 (2.2) nm; IR ($CHCl_3$) υ_{max} 3400 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) data, see Table 1; ^{13}C NMR ($CDCl_3$, 75 MHz) data, see Table 2; positive ion FABMS *m*/*z* 173; EIMS (70 eV) *m*/*z* 172 (68) $[M]^+$, 154 (12) $[M - 18]^+$, 123 (95), 81 (100), 55 (89); HREIMS *m*/*z* 172.1454 $[M]^+$, calcd for $C_{10}H_{20}O_2$ 172.1463.

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