Highly Oxygenated Monoterpenes from *Chenopodium ambrosioides*

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Three new monoterpenes (**3**−**5**) were isolated from an organic extract of the aerial parts of *Chenopodium ambrosioides*. Structures were established on the basis of MS and NMR spectroscopic (^{1}H, ^{13}C, ^{1}H−^{1}H COSY, HMQC and HMBC) data.

The genus *Chenopodium* consists of 120 species, nine of which are found in Egypt.[1] The genus is abundant in the tropics and adjacent warmer regions, especially in tropical America and Africa.[2] Chemical investigations of members of this genus have been concerned with essential oils,[3] sesquiterpenes,[4,5] ecdysteroids,[6] flavonoids,[7,8] and saponins.[9] The importance of *Chenopodium* species is due to their wide variety of medicinal properties.[10,11] Although, the crude extract of *C. ambrosioides* showed antifungal activity, little work has been carried out on its chemical constituents.[2,7] Investigation of an Egyptian collection of this species afforded six monoterpenes of which three were new natural products, **3**−**5**.

An extract of the aerial parts of *C. ambrosioides* L. (= *C. anthelminticum* L.) (Chenopodiaceae) was subjected to Si gel column chromatography, followed by Sephadex LH-20 column chromatography, to give six monoterpenes. The identities of two compounds, thymol and **1**, were deduced from comparison of their NMR spectra with the published data,[12] while the structures of the new compounds were established by two-dimensional homonuclear correlation spectroscopy (^{1}H−^{1}H COSY) and heteronuclear ^{1}H-detected ^{13}C multiple quantum coherence (HMQC and HMBC) experiments.

The NMR data of **1** ($C_{10}H_{18}O_2$) and **2** ($C_{10}H_{18}O_2$) were identical, respectively, with a monoterpene formed by biotransformation of α-terpinene and a monoterpene reported from *Ferula jaechkeana*.[12,13] Although, the stereochemistry of the previously reported compounds was suggested by formation of acetonide derivatives, the optical rotations were of opposite sign. Compound **1**, which has been isolated from *F. jaechkeana*[12] showed a negative optical rotation, opposite that of the same compound of the biotransformation products.[13] Additionally, compound **2**, from *C. ambrosioides*, gave a negative optical rotation, while the biotransformation compound showed a positive optical rotation. This is the first report of **2** from natural sources.

The molecular formula of compound **3** ($C_{10}H_{18}O_2$) was identical with that of **1** and **2**. A third isomeric natural compound was suggested from the observation of two olefinic protons appearing as double doublets at δ 5.59 (H-2) and 5.70 (H-3), which were coupled with each other (J = 10 Hz) and showed a *W* coupling with H-6 (J = 1.5 Hz) and H-5 (J = 1.5 Hz), respectively, in the ^{1}H−^{1}H COSY experiment. Moreover, these two protons were correlated with two carbons at δ 135.4 and 133.4, in HMQC. The remaining protons and carbons were easily assigned by similar experiments and with the aid of ^{1}H−^{1}H COSY. The two quaternary carbons (C-1 and C-4) were distinguished from each other by 2D long-range correlation (HMBC). The stereochemistry of **3** was suggested from NOE experiments; irradiation of the methyl group at δ 1.32 (H-7) enhanced the signals at δ 5.70 (H-3) and 1.88 (H-5_{ax}), and irradiation of the signal at δ 5.59 (H-2) enhanced the signal at δ 1.70 (H-8). An epimeric synthetic compound has been reported by chemical reduction of ascaridol.[14,15] Ascaridol has also been reported from the Brazilian collection of *C. ambrosioides*,[2] and compound **3** could be formed by bioreduction of that compound.

The molecular formula of **4** was deduced from its ^{13}C, DEPT, and CIMS data. The CIMS displayed a peak at *m*/*z* 187 $[M - H_2O]^+$ ($C_{10}H_{20}O_4$), followed by fragments at *m*/*z* 169 $[M - 2H_2O]^+$ and 151 $[M - 3H_2O]^+$, while HREIMS yielded an $[M - H_2O]^+$ ion at *m*/*z* 187.1330 ($C_{10}H_{19}O_3$). The^{13}C and DEPT experiments showed four carbons bearing oxygen; two quaternary carbons and two secondary oxygen-bearing carbons. The secondary alcoholic carbons correlated (HMQC) with two protons in an AB system at δ 3.75 (H-2) and 3.53 (H-3), respectively. The coupling constant (9 Hz) between H-2 and H-3 was in accord with an axial−axial orientation of both protons. The isopropyl group was detected as two methyl doublets at δ 0.97 (H-9) and 0.96 (H-10) and the methine proton (H-8) at δ 2.00. Acetylation of compound **4** gave the diacetyl derivative **4a**. The ^{1}H NMR spectrum of the acetylation product afforded signals for two acetyl substituents at δ 2.04 and 2.05. Characteristic changes in the chemical shifts of the neighboring protons, H-2 and H-3, were also observed. Additionally, a *W* coupling (1.5 Hz) was detected between H-2 and H-6, as well as between H-3 and H-5, in the ^{1}H−^{1}H COSY experiment. The stereochemistry of **4a** was proved by NOESY spectroscopy. The location of the methyl group at C-1, in the equatorial position, was suggested from a cross-peak between this methyl (H-7) and H-3_{ax} and by the absence of a cross-peak with H-2_{ax}. Also, the stereochemistry at C-4 was deduced from the observed cross-peak between H-2_{ax} and the two methyl doublets at δ 0.96 and 0.92 (H-9 and H-10, respectively).

The ^{1}H and ^{13}C NMR spectra of compound **5** differed markedly from those of compounds **1**−**4**. However, the isopropyl signals were evident at δ 2.40 (dqq, H-8), 1.24 (d, H-9), and 1.17 (d, H-10). In the ^{1}H−^{1}H COSY spectrum, three protons forming an ABX system were detected at δ 2.82, 2.69, and 5.42, suggesting the partial structure O=C−CH_2−CH(O). Additionally, a methyl ketone was present at δ 2.27, and the corresponding carbons appeared at δ 31.1 and 209.8, respectively. A narrow triplet was found at δ 5.81 (H-3), which showed allylic coupling with the methine protons at δ 2.40 (H-8, J = 1.5 Hz) and 5.42 (H-5, J = 1.5 Hz) in the ^{1}H−^{1}H COSY experiment. This

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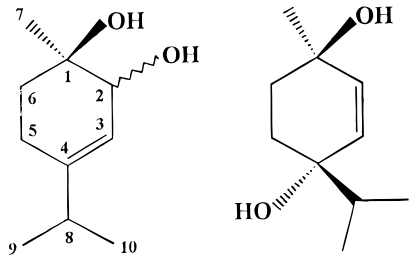
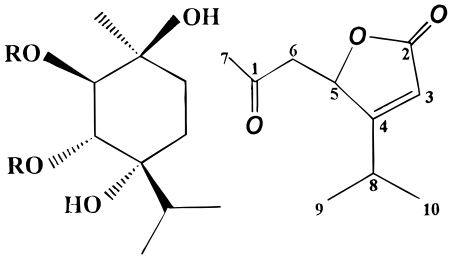


1 β-OH
2 α-OH

3



4 R=H
4a R=Ac

5

signal showed correlation with an olefinic carbon at δ 114.67, in HMQC. These data, together with the chemical shifts of the 10 carbon signals determined in ^{13}C and DEPT experiments suggested that **5** was a monoterpene with a furanone ring. The proposed structure was supported by 2D long-range heteronuclear correlation (HMBC). Important correlations were observed between H-6 and C-4, C-5, and C-7 and between H-3 and C-2, C-4, and C-5. Furthermore, HREIMS yielded an $[M]^+$ ion at *m/z* 182.0929 ($C_{10}H_{14}O_3$). Compound **5** has been given the name chenopanone, and a scheme outlining its possible biogenetic formation is given in the Supporting Information.

Experimental Section

General Experimental Procedures. NMR studies employed a JEOL JNM EX-400 spectrometer operating at 400 MHz for ^1H and 100 M for ^{13}C, including COSY, NOESY, HMQC, and HMBC. Optical rotations were obtained using a JASCO-20C automatic recording spectropolarimeter. The IR spectra (films, $CHCl_3$) were obtained on a Shimadzu IR 470 spectrometer. Mass spectra (EIMS and HREIMS) were recorded on a JEOL JMS-D300 mass spectrometer using a direct inlet and electron impact ionization (70 eV).

Plant Material. The aerial parts of *C. ambrosioides* were collected from Assiut Province, Egypt, in July 1995. A voucher specimen (Ahmed 7/95) has been deposited at the Department of Botany, University of El-Minia.

Extraction and Isolation. Air-dried leaves (1.2 kg) were ground and extracted at room temperature with *n*-hexane−Et_2O−MeOH (1:1:1) and the solvent evaporated in vacuo. The extract (20 g) was prefractionated as reported,[16] by column chromatography (6 × 100 cm) on Si gel eluting with *n*-hexane (2 L) followed by a gradient of *n*-hexane−Et_2O up to 100% Et_2O, and then Et_2O−MeOH (2 L each) into five fractions: A (*n*-hexane−Et_2O, 3:1), B (*n*-hexane−Et_2O, 1:1), C (*n*-hexane−Et_2O, 1:3), D (Et_2O 100%), and E (Et_2O−MeOH, 9:1). Fraction B was subjected to a Sephadex LH-20 column (4 × 60 cm) eluted with *n*-hexane−CH_2Cl_2−MeOH (5:9:1) to afford thymol (20 mg), **1** (10 mg), and **2** (8 mg). Fractions C and D were combined and further separated by column chromatography (4 × 80 cm) on Sephadex LH-20 eluted with *n*-hexane−CH_2Cl_2−MeOH (5:9:1) to give **3** (30 mg) and **5** (9 mg). Fraction E was subjected to column chromatography (4 × 50) on Sephadex LH-20 eluted with *n*-hexane−Et_2O−MeOH (4:7:1.5) to give **4** (19 mg).

(−)(1*R,4*S**)−1,4-Dihydroxy-*p*-menth-2-ene (3):** $[\alpha]^{25}_D$ −2.6 (*c* 0.13, $CHCl_3$); IR ($CHCl_3$) ν_{max}: 3600, 2925, 1660; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.70 (1H, dd, *J* = 10, 1.5 Hz, H-3), 5.59 (1H, dd, *J* = 10, 1.5 Hz, H-2), 1.88 (1H, ddd, *J* = 14, 14, 3.5 H-5_a), 1.82 (1H, ddd, *J* = 14, 14, 3.5 Hz, H-6_a), 1.68 (1H, dddd, *J* = 14, 3.5, 3, 1 Hz, H-6_b), 1.70 (1H, qq, *J* = 7, 7 Hz, H-8), 1.52 (1H, dddd, *J* = 14, 3.5, 3, 1 Hz, H-5_b), 1.32 (3H, s, H-7), 0.94 (3H, d, *J* = 7 Hz, H-9), 0.86 (3H, d, *J* = 7 Hz,, H-10); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 67.2 (s, C-1), 135.4 (d, C-2), 133.4 (d, C-3), 71.5 (s, C-4) 27.0 (t, C-5), 33.4 (t, C-6), 29.5 (q, C-7), 37.3 (d, C-8), 16.3 (q, C-9), 17.5 (q, C-10); CIMS *m/z* $[M - H_2O]^+$ 153 (100), $[M - 2H_2O]^+$ 135 (85); FDMS *m/z* $[M]^+$ 170 (43), $[M - OH]^+$ 153 (100), $[M - C_3H_7]^+$ 127 (52); HRCI *m/z* 153.127343 $[M - H_2O]^+$ (calcd for $C_{10}H_{18}O_2$, 153.127940).

(−)(1*R, 2*S**, 3*S**, 4*S**)-1,2,3,4-Tetrahydroxy-*p*-menthane (4):** $[\delta]^{25}_D$ −1.6 (*c* 0.06, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3560, 3550, 3545; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.75 (1H, br d, *J* = 9 Hz, H-2), 3.53 (1H, br d, *J* = 9 Hz, H-3), 2.00 (1H, qq, *J* = 7, 7 Hz, H-8), 1.98 (3H, m, H-6, H-5_a), 1.36 (3H, s, H-7),1.26 (1H, dddd, *J* = 14, 3.5, 3, 1 Hz, H-5_b), 0.97 (3H, d, *J* = 7 Hz, H-9), 0.96 (3H, d, *J* = 7 Hz, H-10); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 91.2 (s, C-1), 70.3 (d, C-2), 73.4 (d, C-3), 84.5 (s, C-4) 29.1 (t, C-5), 25.0 (t, C-6), 20.0 (q, C-7), 32.7 (d, C-8), 17.6 (q, C-9), 17.5 (q, C-10); CIMS *m/z* $[M - H_2O]^+$ 187 (86), $[M - 2H_2O]^+$ 169 (100); $[M - 3H_2O]^+$ 151 (49); HRCI *m/z* 187.133006 $[M - H_2O]^+$ (calcd for $C_{10}H_{19}O_3$, 187.133420).

Acetylation of 4. Compound **4** (15 mg) was refluxed with Ac_2O, at 70 °C for 1 h. The mixture was decomposed by distilled H_2O and was extracted with CH_2Cl_2. The organic layer was concentrated and separated by TLC (hexane−Et_2O, 1:2) affording 11 mg of the diacetate derivative **4a** as a colorless gum: ^1H NMR ($CDCl_3$, 400 MHz) δ 4.99 (1H, dd, *J* = 9, 1.5 Hz, H-3), 4.75 (1H, dd, *J* = 9, 1.5 Hz, H-2), 2.12 (2H, m, H-6_a, H-5_a), 2.05 (3H, s, AcO), 2.04 (3H, s, AcO), 2.01 (1H, qq, *J* = 7, 7 Hz, H-8), 1.54 (1H, m, H-6_b), 1.42 (1H, m, H-5_b),1.38 (3H, s, H-7), 0.96 (3H, d, *J* = 7 Hz, H-9), 0.92 (3H, d, *J* = 7 Hz, H-10); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 83.9 (s, C-1), 73.4 (d, C-2), 70.2 (d, C-3), 89.8 (s, C-4) 27.0 (t, C-5), 30.5 (t, C-6), 19.9 (q, C-7), 32.4 (d, C-8), 17.4 (q, C-9), 17.3 (q, C-10); CIMS *m/z* $[M + H]^+$ 289 (23), $[M - CH_3CO]^+$ 246 (85); $[CH_3CO]^+$ 43 (100).

Chenopanone (5): $[\alpha]^{25}_D$ −7.5° (*c* 0.025, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3560, 3550, 3545; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.81 (1H, dd, *J* = 1.5, 1.5 Hz, H-3), 5.42 (1H, ddd, *J* = 8.5, 3.5, 1.5 Hz, H-5), 2.82 (1H, dd, *J* = 16.5, 3.5 Hz, H-6_a), 2.69 (1H, dd, *J* = 8.5, 6.8 Hz, H-6_b), 2.40 (1H, dqq, *J* = 7, 7, 1.5 Hz, H-8), 2.27 (3H, s, H-7), 1.24 (3H, d, *J* = 7 Hz, H-9), 1.17 (3H, d, *J* = 7 Hz, H-10); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 209.8 (s, C-1), 178.3 (s, C-2), 114.6 (d, C-3), 117.4 (s, C-4) 79.0 (d, C-5), 45.6 (t, C-6), 31.0 (q, C-7), 27.8 (d, C-8), 20.6 (q, C-9), 21.9 (q, C-10); CIMS *m/z* $[M - H_2O]^+$ 153 (100), $[M - 2H_2O]^+$ 135 (85); HREIMS *m/z* 182.0929 (45) (calcd for $C_{10}H_{14}O_3$, 182.0942), $[M - CH_3CO]^+$ 139 (52), $[M - (CH_2CO + C_3H_7)]^+$ 85 (52), $[CH_3CO]^+$ 43 (100).

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Supporting Information Available: The possible biogenetic formation of compound **5** is available free of charge via the Internet at http://pubs.acs.org.

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