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Alkylresorcinol Derivatives and Sesquiterpene Lactones from *Cichorium spinosum*†

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One new alkylresorcinol derivative, cichoriol B, and a mixture of three other ones, cichoriols A, C, and D, were isolated from the dichloromethane extract of *Cichorium spinosum*, a plant that is used traditionally in the Cretan diet. The methanol extract afforded one new sesquiterpene lactone, (4*R*)-3,4-dihydrolactucopicrin. The structures of the new compounds were determined by spectroscopic methods, mainly by the concerted application of 1D and 2D NMR techniques (HMQC, HMBC, NOESY).

KEYWORDS: ***Cichorium spinosum*; alkylresorcinols; cichoriols A−D; 3,4-dihydrolactucopicrin; lactucopicrin; terpenoids**

INTRODUCTION

The genus *Cichorium*, belonging to the family Asteraceae, is comprised of three species: *C. intybus*, *C. endivia*, and *C. spinosum* (*1*). The first two species are widely cultivated as salad plants in Europe, and their chemical constituents have been studied several times (*2*−*5*). *C. spinosum* is a perennial plant found around the Mediterranean region. It is characterized by its spine-like and nonflowering upper branches, which are developed after the first flowering period. In Greece, it can be found in southern coastal regions and especially in Crete, where it is widely consumed. During the winter, the young fresh leaves are used as a bitter salad, with olive oil and vinegar, but in many cases the leaves are also cooked or salted.

The traditional Cretan diet is the richest diet in fruits and legumes in the Western world and is generally recognized as the best example of Mediterranean diet for prevention of cardiovascular diseases (*6*). The population of Crete has the greatest life expectancy in the Western world. Our interest in plants used in the famous Cretan diet (*7*) led us to the chemical investigation of the aerial parts of *C. spinosum*. To our knowledge, no previous phytochemical works have been recorded for this species.

MATERIALS AND METHODS

General Experimental Procedures. Optical rotations were measured with a Perkin-Elmer 341 polarimeter. The IR spectra were obtained on a Perkin-Elmer Paragon 500 instrument. NMR spectra were recorded on Bruker DRX 400 and Bruker AC 200 spectrometers [^{1}H (400 and 200 MHz) and ^{13}C (50 MHz)]; chemical shifts are expressed in ppm downfield from TMS. The ^{1}H−^{1}H and ^{1}H−^{13}C NMR experiments were performed using standard Bruker microprograms. GC−MS analysis was carried out on a Hewlett-Packard 6890-5973 system operating in EI mode, equipped with a 30-m × 0.25-mm-i.d., 0.25-μm HP-5 MS capillary column; temperature program from 60 (5 min) to 280 °C at a rate of 3 °C/min; injection temperature 200 °C. CI-MS spectra were determined on a Finnigan GCQ *Plus* ion-trap mass spectrometer using CH_4 as the CI ionization reagent, and HRMS spectra were obtained on a AEI MS-90 spectrometer. Circular dichroism spectra were recorded in MeOH on a JASCO-700 spectrometer. Medium-pressure liquid chromatography (MPLC) was performed with a Büchi model 688 apparatus on columns containing silica gel 60 (Merck, 20−40 μm). Thin-layer chromatography (TLC) was performed on plates coated with silica gel 60 F_{254} (Merck, 0.25 mm). Molecular calculations were performed using the MM+ force field. The Polak-Ribiere (conjugate gradient) minimization method, with an energy convergence criterion of 0.01 kcal/mol, was used for geometry optimization.

Plant Material. Plant material was collected at Tybaki (Crete, Greece) in May 2000 and identified by Dr. Eleftherios Kalpoutzakis. A voucher specimen (KL011) is deposited in the herbarium of the Laboratory of Pharmacognosy, University of Athens, Greece.

Extraction and Isolation. Air-dried, pulverized aerial parts of *C. spinosum* (1.8 kg) were extracted for 48 h with CH_2Cl_2 (3 × 2 L) and then with MeOH (3 × 2 L). After evaporation of the solvent from the dichloromethane extract, the residue (34.4 g) was submitted to MPLC chromatography on a column containing silica gel 60 (Merck, 20−40 μm) with cyclohexane/CH_2Cl_2 (from 100:0 to 50:50 gradient), to afford 60 fractions of 200 mL each. Portions of fractions 28−31 (300 mg of 1.9 g) were rechromatographed by MPLC with cyclohexane/CH_2Cl_2 (80:20) to afford taraxasterol acetate (29 mg) (*8*), lupenol acetate (40 mg) (*9*), and ψ-taraxasterol acetate (19 mg) (*8*, *9*). Portions of fractions 32−37 (250 mg of 1.8 g) were rechromatographed by MPLC with cyclohexane/CH_2Cl_2 (from 80:20 to 50:50 gradient) to afford taraxerone (21 mg) (*10*), lupenone (30 mg) (*9*), bauerenone (3 mg) (*11*), taraxasterone (5 mg) (*12*), the new alkylresorcinol cichoriol B (**1**) (11 mg), and an inseparable mixture of cichoriols A, C, and D (**2**−**4**) (3 mg). Portions of fractions 38−43 (250 mg of 1.9 g) were rechromatographed by MPLC with cyclohexane/CH_2Cl_2 (50:50) to afford β-sitosterol (20 mg) (*13*), stigmasterol (10 mg) (*14*), lupenol (75 mg) (*9*), bauerenol (9 mg) (*15*), and taraxasterol (60 mg) (*16*). The methanol extract (41.7 g) was also chromatographed by MPLC (CH_2-

† Part 6 in the series Plants from Crete. For part 5, see: Papandreou, V.; Magiatis, P.; Skaltsounis, A.-L. Paeonicluside, a new salicylic glycoside from the Greek endemic species *Paeonia clusii*. *Z. Naturforsch.* **2002**, *57c*, 235−238.

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Cl_2/MeOH from 100:0 to 90:10 gradient) to afford 40 fractions of 200 mL each. Fractions 21−36 (1.2 g) were rechromatographed by MPLC with CH_2Cl_2/MeOH (97:3) to afford lactucopicrin (**5**) (230 mg) and the new sesquiterpene lactone 3,4-dihydrolactucopicrin (**6**) (170 mg). All the known compounds were identified by comparison of their NMR and MS data with the literature values. All the fractions of the columns were estimated by TLC using eluent systems similar to those used in the relative column chromatographies.

Cichoriol B, 3-methyl ether of 5-heneicosyl-2-methylresorcinol (1): amorphous compound; UV ($CHCl_3$) λ_{max} (log ϵ) 241 (3.46), 271 (2.97), 280 (sh) nm; IR ν_{max} ($CHCl_3$) 3400, 3000, 1618, 1591, 1250 cm^{-1}; ^1H NMR ($CDCl_3$/TMS, 400 MHz, δ ppm, J in Hz) 6.30 (2H, s, H-4,6), 4.61 (1H, s, 1-OH), 3.80 (3H, s, 3-OCH_3), 2.51 (2H, t, $J = 8$ Hz, H-1′), 2.07 (3H, s, 2-CH_3), 1.56 (4H, br s, H-2′,19′), 1.29 (34H, br s, H-3′−18′,20′), 0.87 (3H, t, $J = 7$ Hz, H-21′); ^{13}C NMR ($CDCl_3$/TMS, 50 MHz, δ ppm) 158.41 (C-3), 154.11 (C-1), 141.83 (C-5), 109.01 (C-2), 107.95 (C-6), 103.43 (C-4), 55.65 (OCH_3), 36.06 (C-1′), 31.94 (C-2′), 31.46 (C-19′), 29.70 (C-3′-18′), 22.72 (C-20′), 14.15 (C-21′), 7.76 (2-CH_3); EIMS (70 eV) *m/z* (relative intensity) 432 ($M^{\bullet+}$), 165, 152 (100); CI-MS *m/z* 433 $(M + H)^+$; HREIMS *m/z* 432.3961 $[M]^+$(calculated 432.3967).

Cichoriol A, 3-methyl ether of 5-nonadecyl-2-methylresorcinol (2): EIMS (70 eV) *m/z* (relative intensity) 404 ($M^{\bullet+}$), 165, 152 (100); CI-MS *m/z* 405 $(M + H)^+$; HREIMS *m/z* 404.3649 $[M]^+$(calculated 404.3654).

Cichoriol C, 3-methyl ether of 5-docosyl-2-methylresorcinol (3): EIMS (70 eV) *m/z* (relative intensity) 446 ($M^{\bullet+}$), 165, 152 (100); CI-MS *m/z* 447 $(M + H)^+$; HREIMS *m/z* 446.4120 $[M]^+$(calculated 446.4124).

Cichoriol D, 3-methyl ether of 5-tricosyl-2-methylresorcinol (4): EIMS (70 eV) *m/z* (relative intensity) 460 ($M^{\bullet+}$), 165, 152 (100); CI-MS *m/z* 461 $(M + H)^+$; HREIMS *m/z* 460.4285 $[M]^+$(calculated 460.4280).

3,4-Dihydrolactucopicrin (6): $[\alpha]^{25}_D$ +11.3° (*c* 0.2, MeOH); IR ν_{max} (MeOH, CaF) 1764, 1738, 1702, 1606 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz, δ ppm, J in Hz) 7.13 (2H, d, $J = 8.5$ Hz, H-2′,6′), 6.75 (2H, d, $J = 8.5$ Hz, H-3′,5′), 5.90 (1H, d, $J = 3.1$ Hz, H-13a), 5.25 (1H, d, $J = 2.6$ Hz, H-13b), 4.86 (1H, ddd, $J = 11.0$, 10.3, 2.0 Hz, H-8), 3.88 (1H, t, $J = 10.3$ Hz, H-6), 3.73 (1H, dd, $J = 11.0$, 4.2 Hz, H-15a), 3.62 (2H, s, $OCOCH_2$), 3.59 (1H, dd, $J = 11.0$, 5.7 Hz, H-15b), 3.31 (1H, tdd, $J = 10.3$, 3.1, 2.6 Hz, H-7), 3.12 (H, br d, H-5), 2.72 (1H, dd, $J = 13.2$, 11.0 Hz, H-9_{ax}), 2.53 (2H, m, H-4,3a), 2.45 (1H, dd, $J = 13.2$, 2.0 Hz, H-9_{eq}), 2.38 (1H, m, H-3b), 2.33 (3H, s, H-14); ^{13}C NMR (CD_3OD, 50 MHz, δ ppm) 207.26 (C-2), 172.49 (OCO), 170.47 (C-12), 157.86 (C-4′), 150.62 (C-10), 138.75 (C-11), 137.80 (C-1), 131.51 (C-2′,6′), 125.59 (C-1′), 121.84 (C-13), 116.48 (C-3′,5′), 82.52 (C-6), 70.94 (C-8), 65.69 (C-15), 55.73 (C-7), 47.34 (C-5), 45.69 (C-9), 43.16 (C-3), 41.47 ($OCOCH_2$), 37.86 (C-4), 22.39 (C-14); CI-MS *m/z* 413 $(M + H)^+$; HRFABMS *m/z* 413.1609 $[M + H]^+$-(calculated 413.1600).

RESULTS AND DISCUSSION

Investigation of the CH_2Cl_2 extract of the aerial parts of *C. spinosum* led to the identification of several known triterpenes. Although in the whole genus there is only one report of tritepenes isolated from *C. intybus* (*17*), it should be noted that almost the whole of the extract was comprised of triterpenes and phytosterols. Among them, lupenol, taraxasterol, their esters, and the corresponding ketones were the most abundant. When the fractions of the extract were estimated by TLC, it was apparent that they contained minor quantities of phenolic compounds, which gave a vivid red color after spraying with a vanillin solution. Purification of these fractions led to the isolation of the major phenol, the 3-methyl ether of 5-heneicosyl-2-methylresorcinol (**Figure 1**), for which the trivial name cichoriol B (**1**) is proposed. Three other alkylresorcinols, cichoriols A, C, and D (**2**−**4**), were obtained and studied as an inseparable mixture.

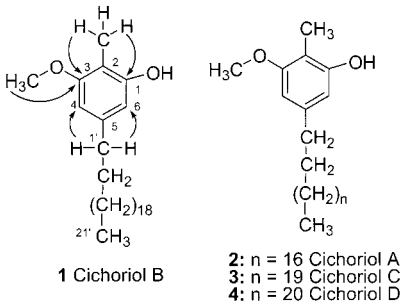

Figure 1. Structures of cichoriols A–D (**1**–**4**) and important HMBC correlations of **1**.

Cichoriol B (**1**) was isolated as a white amorphous compound, and its molecular formula was determined by HRMS as $C_{29}H_{52}O_2$. The EI-MS spectrum showed a quasi-molecular ion at *m/z* 432, a fragment at *m/z* 417 corresponding to the loss of a terminal methyl group, and 19 consecutive fragments differing by 14 amu. This fragmentation pattern suggested a molecule containing a long aliphatic chain. The structure of **1** was determined unambiguously by NMR studies. The ^1H NMR spectrum of **1** showed a broad singlet at 4.61 ppm which was exchanged with D_2O, corresponding to a hydroxyl group. The HMQC spectrum showed that a two-proton singlet at 6.30 ppm corresponded to two different carbons, observed at 107.95 and 103.43 ppm. The two aforementioned carbons, in combination with four deshielded quaternary carbons at 158.41, 154.11, 141.83, and 109.01 ppm, constituted a tetrasubstituted aromatic ring, with two oxygenated carbons.

Additionally, the ^1H NMR spectrum showed two three-proton singlets at 3.80 and 2.07 ppm. In the HMQC spectrum, the singlet at 3.80 ppm was correlated with a carbon at 55.65 ppm and consequently was a methoxy group. The second singlet at 2.07 ppm was correlated with a carbon at 7.76 ppm. From the DEPT spectrum, this carbon corresponded to an aromatic methyl group.

Finally, the ^1H NMR spectrum showed a triplet ($J = 8$ Hz) at 2.51 ppm, integrating for two protons, a broad singlet at 1.56 ppm, integrating for four protons, a broad singlet at 1.29 ppm, integrating for 18 protons, and a triplet ($J = 7$ Hz) at 0.87 ppm, integrating for three protons. The COSY spectrum showed that all these protons were cross-coupled, confirming the presence of a long aliphatic chain, as suggested by the EI-MS spectrum. The alkyl chain was concluded to be unbranched because in the DEPT spectrum only one terminal methyl group (14.15 ppm) was observed. The most deshielded alkyl chain protons were observed at 2.51 ppm, indicating that the alkyl chain was directly connected to the aromatic ring.

From these data, it was evident that **1** contained an aromatic ring, substituted with a hydroxyl group, a methoxy group, a methyl group, and an unbranched aliphatic chain with 21 carbons. The arrangement of these groups on the aromatic ring was established by the HMBC spectrum.

In the HMBC spectrum (**Figure 1**), the protons of the aromatic methyl group had a strong ^3J correlation with the aromatic oxygenated carbon bearing the methoxy group and a strong ^3J correlation with the aromatic oxygenated carbon bearing the hydroxy group. Consequently, the methyl group was placed in an ortho position between the methoxy and hydroxy groups. The H-1′ protons of the aliphatic chain were correlated in the HMBC spectrum with both protonated aromatic carbons C-4 and C-6, indicating that the aliphatic chain should be placed at C-5. The final structure of cichoriol B (**1**) was confirmed by the NOESY spectrum, in which the methyl protons were

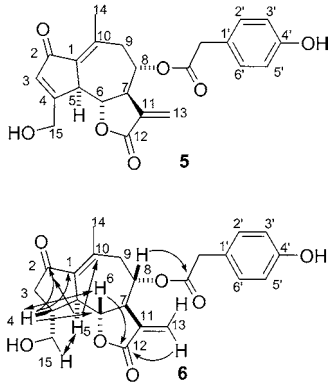

Figure 2. Structures of lactucopicrin (**5**) and (4*R*)-3,4-dihydrolactucopicrin (**6**) and important HMBC (→) and NOESY (↔) correlations of **6**.

correlated with the hydroxyl proton and not with any of the aromatic protons. These protons were correlated with the protons of the aliphatic chain.

Cichoriols A, C, D (**2**−**4**) were obtained as a mixture that could not be separated due to its limited quantity. The NMR profile of the mixture was identical to that of cichoriol B, but when it was studied by GC−MS in the EI and CI modes, it was found to contain three different compounds in a ratio of 2:1: 2. Each compound showed exactly the same fragmentation pattern in the EI-MS as in the case of **1**, except for a difference in the molecular ion. Cichoriol A (**2**) showed a molecular ion at 404 amu, cichoriol C (**3**) at 446 amu, and cichoriol D (**4**) at 460 amu. These differences correspond to homologous differences of the aliphatic side chain. The four described alkylresorcinols, cichoriols A−D, are new natural products. It must be noted that *C. spinosum* represents a new source of alkylresorcinols. Natural products of this category have been found in only 11 families of higher plants and in only four other members of the Asteraceae family (*18*). Alkyresorcinols possess biological activities, such as antimicrobial, antiparasitic, antiinflammatory, protective against cellular lipid oxidation, etc., and their identification in edible plants such as *C. spinosum* is very interesting.

Separation of the methanol extract of the aerial parts of *C. spinosum* led to the isolation of two major constituents. The first was identified as the known compound lactucopicrin (**5**), isolated previously from the other two *Cichorium* species (*3*). The second compound was also identified as a guaianolide-type sesquiterpene lactone (**Figure 2**).

3,4-Dihydrolactucopicrin (**6**) was isolated as an amorphous compound, and its molecular formula was determined by HRFABMS as $C_{23}H_{24}O_7$. The IR spectrum revealed the presence of a γ-lactone (1764 cm^{-1}), an ester (1738 cm^{-1}), and a conjugated ketone (1702 cm^{-1}). In the ^1H NMR spectrum, two *exo*-methylene protons (5.90, 5.25 ppm), two protons corresponding to an oxygenated methylene (3.73, 3.59 ppm), two protons corresponding to two oxygenated methines (4.86, 3.88 ppm), one deshielded methyl group (2.33 pppm), and two pairs of protons corresponding to a para-substituted aromatic ring (7.13, 6.75 ppm) were observed. The ^{13}C NMR and DEPT spectra showed the presence of three carbonyl groups, an olefinic methylene, an oxygenated methylene, a methylene directly attached to an aromatic ring, two other methylenes, two oxygenated methines, three other methines, two pairs of aromatic methines, a methyl group, three quaternary olefinic carbons, and two quaternary aromatic carbons, one of them oxygenated. The ^{13}C NMR spectrum of **6** was very similar to that described for lactucopicrin (*19*), with one very important difference: the absence of the double bond between positions 3 and 4. Carbon 3 was observed at 43.16 ppm as an aliphatic methylene, corresponding to the α-position of a ketone. Carbon 4 was observed at 37.86 ppm as a methine correlated with C-2, C-1, and C-6 in the HMBC spectrum (**Figure 2**). The site of esterification was C-8, as established by the ^3J correlation of H-8 with the ester carbonyl. The guaianolide-type structure was confirmed by the characteristic ^3J correlation of H-5 with C-2 and C-10. The lactone moiety was confirmed by the ^3J correlations of H-6 and H-13 with C-12.

The relative stereochemistry was deduced from the coupling constants and interpretation of the NOESY spectrum. The large coupling constants between H-5, H-6, H-7, and H-8 indicated that all these protons were placed in trans-axial positions. With respect to H-4, in the NOESY spectrum it was found to be correlated with H-6. Although H-4 overlapped with one of the H-3 protons, the molecular model of **6** showed that in the lowest energy conformer, the distance between H-6 and both of the H-3 protons is more than 4 Å, and consequently the NOESY cross-peak corresponds to the correlation of H-6 with H-4β. The stereochemistry of C-4 was also confirmed by the NOE correlation of H-5α with H-15.

The absolute stereochemistry of **6**, as well as that of **5**, was determined by the study of their circular dichroism spectra. Both compounds showed a positive Cotton effect at 233 nm and a negative Cotton effect at 269 nm, revealing that the four corresponding carbons C5, C6, C7, and C8 had the same configuration. The first positive Cotton effect, corresponding to the $\pi\pi^*$ transition of the lactone chromophore, as described by Youssef and Frahm (*20*), is characteristic for the *R* configuration of C-7 when C-8 is bearing a nonsaturated ester moiety. Based on the aforementioned relative stereochemistry, the absolute stereochemistry of **6** is 4*R*,5*S*,6*R*,7*R*,8*S*. (4*R*)-3,4-Dihydrolactucopicrin (**6**) is a new natural product, closely related to a compound recently identified from *C. intybus*, in which the C-15 is an aldehyde instead of a hydroxymethylene group (*2*).

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