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PHYTOCHEMISTRY

Terpenoids and aromatic compounds from *Daphne oleoides* ssp. *oleoides*

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Abstract

The methanol extract of dried stems of *Daphne oleoides* Schreber ssp. *oleoides* afforded two new sesquiterpenoids: 4,10,11-guaiatriene-3-one-15-al and 4, 10, 11-guaiatriene-3,9-dione, named oleodaphnal and oleodaphnone; two new diterpenoids, genkwadaphnin-20-palmitate and gnidicin-20-palmitate; and thirteen known compounds. Their structures were established on the basis of spectroscopic studies. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Terpenoid; Oleodaphnal; Oleodaphnone; Diterpene; Sesquiterpene; *Daphne oleoides* ssp. *oleoides*; Thymelaceae; Daphnane diterpenoids

1. Introduction

Daphne oleoides (Thymelaeaceae) has been used for treatment of malaria and rheumatism in the folk medicinal usage of plants in Turkey (Tabata, Honda, Sezik & Yesilada, 1993; Fujita et al., 1995). In the course of our search for bioactive metabolites from plants (Hayashi, Hayashi, Ujita & Takaishi, 1996; Takaishi, Aihara, Tamai, Nakano & Tomimatsy, 1992; Ujita et al., 1993), we have been interested in the genus *Daphne* and began a study of the chemical components of *D. oleoides* Schreber ssp. *oleoides*. In a previous chemical investigation of *D. oleoides* the occurrence of lignans and coumarins was reported (Thusoo, Raina, Mihaj, Ahmed & Zaman, 1981).

In this paper, we report on the isolation and the structural elucidation of two new guaiane type sesquiterpenoids, oleodaphnal (**1**) and oleodaphnone (**2**), four known diterpenoids **3**–**6**, two new diterpenoids genkwadaphnin-20-palmitate (**7**) and gnidicin-20-palmitate (**8**), and nine other known compounds **9**–**17**.

2. Results and discussion

Column chromatography of the ethyl acetate soluble fraction obtained from the methanol extract of stems of *D. oleoides* Schreber ssp. *oleoides* yielded oleodaphnal (**1**), oleodaphnone (**2**), and two new diterpenoids (**7**, **8**) along with the known compounds genkwadaphnin (**3**) (Kasai, Lee & Huang, 1981), gnidilatidin (**4**) (Kupchan et al., 1976), gnidilatidin-20-palmitate (**5**) (Kupchan et al., 1976), 1, 2-dihydrodaphnetoxin (*6*) (Dagang, Sorg, Adolf, Seip & Hecker, 1991), daphnetin (**9**) (Shimomura, Sashida & Ohshima, 1980), daphnin (**10**) (Niwa et al., 1991), umbelliferone (**11**) (Brown, Asplund & McMahon, 1975), eudesmine (**12**), wikstromol (**13**), matairesinol (**14**) (Ishihara, Tsuneya,

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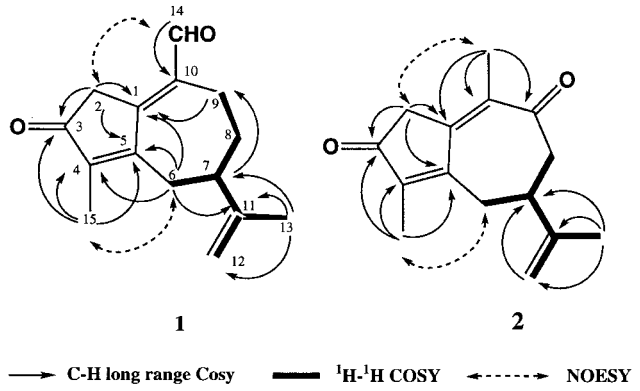


Fig. 1. C–H long range, ^{1}H–^{1}H COSY and NOESY correlations for compounds **1** and **2**.

Shiga & Uneyama, 1991), syringin (**16**) (Brown et al., 1975) and oleanolic acid (**17**).

Oleodaphnal (**1**) was assigned the molecular formula $C_{15}H_{18}O_2$ by HREI mass spectrometry and its IR spectrum showed an unsaturated ketone band at 1703 cm^{-1} and an α, β, γ, δ unsaturated aldehyde at 1675 cm^{-1}. The ^{13}C NMR spectrum exhibited 15 carbon resonances including two methyls, four methylenes, one exo-methylene, one ketone, one aldehyde and two double bonds. From the ^{1}H–^{1}H COSY and ^{13}C–^{1}H COSY spectra of **1**, the presence of partial structures I: CH_3—C═CH_2 and II: —CH_2—CH_2—CH—CH_2— were suggested (Fig. 1). In the C–H long range COSY spectrum, the methyl proton signal at δ_H 1.79 (13-H_3) was correlated with the carbon signals at δ_C 110.0 (C-12), 148.6 (C-11), 42.7 (C-7) and the methine proton signal at δ_H 2.58 (7-H) with the carbon signal at δ_C 21.3 (C-9). These facts clearly indicated the combination of partial structures I and II. Other proton correlations in the C–H long range spectrum are shown in Fig. 1. In the NOESY spectrum of **1**, the methyl proton signal at δ_H 1.91 (15-H_3) was correlated with the proton signal at δ_H 2.88 (6-H_2). From these facts, the assignment at C-4, 5, 6 and 15 was confirmed. The aldehydic proton signal at δ_H 9.96 was correlated with the methylene proton signal at δ_H 3.44 (2-H_2) (Fig. 1). Thus, the ketone moiety was at C-3 and the structure of oleodaphnal was formulated as **1**.

Oleodaphnone (**2**), $C_{15}H_{18}O_2$, showed carbonyl absorptions at 1703 and 1649 cm^{-1} in the IR spectrum. From the same molecular formula of **1** and **2** and the similarity of both spectral data, the structure of **2** was suggested that one aldehyde and one methylene in **1** were replaced by methyl and ketone groups, respectively. In the C–H long range spectrum of **2**, the methyl proton signal at δ_H 1.79 (13-H_3) was correlated with the carbon signals at δ_C 111.1 (C-12), 147.0 (C-11) and 39.0 (C-7), the methyl proton signal at δ_H 1.98 (14-H_3) with the carbon signals at δ_C 144.1 (C-1), 131.6 (C-10) and 200.7 (C-9), the methyl proton signal at δ_H 1.88 (15-H_3) with the carbon signals at δ_C 144.8 (C-4), 162.8 (C-5) and 201.9 (C-3), the methylene proton signal at δ_H 3.08, 3.15 (2-H_2) with the carbon sig-

Table 1
^{1}H NMR spectral data of compounds **3**, **7** and **8** ($CDCl_3$)

Protons	**3**	**7**	**8**
1	7.60 *br s*	7.61 *br s*	
5	4.24 *s*	4.27 *d* (1.5)	4.29 *br s*
7	3.70 *s*	3.58 *s*	3.58 *s*
8	3.72 *d* (2.5)	3.73 *d* (3.4)	3.69 *d* (2.4)
10	3.95 *br s*	3.98 *br s*	3.97 *br s*
11	2.63 *q* (7.3)	2.65 *q* (7.3)	2.59 *q* (7.3)
12	5.31 *s*	5.31 *s*	5.31 *s*
14	5.05 *d* (2.5)	5.01 *d* (2.4)	4.93 *d* (2.4)
16	5.04 *br s*	5.03 *br s*	5.06 *br s*
	5.08 *s*	5.07 *br s*	5.20 *br s*
17	1.92 *s*	1.92 *s*	1.91 *s*
18	1.47 *d* (7.3)	1.46 *d* (7.3)	1.42 *d* (7.3)
19	1.78 *br s*	1.77 *br s*	1.77 *br s*
20	3.85 *d* (12.5)	3.87 *d* (12.2)	3.89 *d* (12.2)
	3.91 *d* (12.5)	4.85 *d* (12.2)	4.84 *d* (12.2)

Table 2
^{13}C-NMR spectral data of compounds **3**, **4**, **7** and **8** ($CDCl_3$)

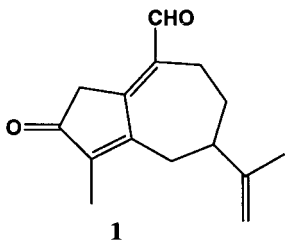
C	**3**[a]	**4**[b]	**7**[c]	**8**[d]
1	160.3 *d*	160.1 *d*	160.1 *d*	160.2 *d*
2	137.1 *s*	136.8 *s*	137.1 *s*	137.1 *s*
3	209.4 *s*	209.3 *s*	209.2 *s*	209.2 *s*
4	78.8 *s*	78.7 *s*	78.9 *s*	78.9 *s*
5	72.0 *d*	71.1 *d*	70.2 *d*	70.2 *d*
6	60.8 *s*	61.0 *s*	59.6 *s*	59.6 *s*
7	64.3 *d*	64.2 *d*	64.2 *d*	64.2 *d*
8	36.0 *d*	35.4 *d*	36.0 *d*	35.7 *d*
9	72.3 *s*	72.5 *s*	72.4 *s*	72.4 *s*
10	47.6 *d*	47.5 *d*	47.6 *d*	47.6 *d*
11	44.3 *d*	44.1 *d*	44.3 *d*	44.3 *d*
12	79.1 *d*	77.9 *d*	79.2 *d*	78.8 *d*
13	84.5 *s*	84.2 *s*	84.5 *s*	84.4 *s*
14	80.9 *d*	80.8 *d*	81.0 *d*	81.0 *d*
15	143.0 *s*	142.9 *s*	143.2 *s*	143.2 *s*
16	113.9 *t*	113.7 *t*	113.9 *t*	113.9 *t*
17	18.9 *q*	18.9 *q*	18.5 *q*	19.0 *q*
18	18.5 *q*	18.3 *q*	19.0 *q*	18.5 *q*
19	9.9 *q*	9.9 *q*	10.0 *q*	10.0 *q*
20	64.9 *t*	65.1 *t*	65.6 *t*	65.6 *t*
—C_6H_5				
1′	117.9 *s*		118.2 *s*	118.2 *s*
2′	129.6 *s*		130.0 *s*	135.5 *s*
3′7′	126.1 *d*		126.3 *d*	
4′6′	128.1 *d*		128.8 *d*	126.2–130.8 *d*
5′	128.1 *d*		129.8 *d*	

[a] (12-Bz; 165.6, 135.4, 129.7, 128.7, 133.4).
[b] [1′—$(CH═CH)_2$—$C_{15}H_{11}$; 117.8, 114.3, 147.1, 126.8, 147.0, 22.4–33.0, 14.0, 12-Bz; 165.1, 135.4, 128.0, 126.0, 129.6].
[c] (12-Bz; 165.6, 135.5, 129.6, 128.2, 133.4, 20-Pal; 173.5, 22.8–34.3, 14.2).
[d] (12-Cin; 165.9, 146.1, 117.5, 134.3, 20-Pal; 173.5, 22.8–34.3, 14.2).

nals at δ_C 144.1 (C-1) and 201.9 (C-3) (Fig. 1). From these facts and analysis of the NOESY spectrum (Fig. 1) the structure of oleodaphnone was formulated as **2**.

Compound **7** showed absorption at 3464 and 1724 cm^{-1} in the IR spectrum. The ^1H NMR spectrum of **7** revealed the presence of two tertiary methyls [δ_H 1.77 (*s*), 1.92 (*s*)], one secondary methyl [δ_H 1.46 (*d, J* = 7.3 Hz)], one methylene [δ_H 3.87, 4.85 (each 1H, *d, J* = 12.2 Hz)] attached to oxygen function, one exo-methylene [δ_H 5.03 (*br s*), 5.07 (*s*)], seven methines [δ_H 2.65 (*q, J* = 7.3 Hz), 3.58 (*s*), 3.73 (*d, J* = 3.4 Hz), 3.98 (*br s*), 4.27 (*br d, J* = 1.5 Hz), 5.01 (*d, J* = 2.4 Hz), 5.31 (*s*)], a saturated fatty acid moiety [δ_H 0.88 (3H, *t, J* = 7.3 Hz), 1.24 (ca 24 H, *br s*), 1.62 (2H, *m*), 2.34 (2H, *t, J* = 7.8 Hz)], one trisubstituted double bond [δ_H 7.61 (*br s*)], and two benzene rings. The spectral data were very similar to those of genkwadaphnin (**3**) except for the presence of a fatty acid moiety (Table 1). The ^{13}C NMR spectrum of **7** was also very similar to that of compound **3** except for the presence of a fatty acid moiety (Table 2). The FAB mass spectrum of **7** showed $[M+Na]^+$ ion peak at *m/z* 863.4346, suggesting the molecular formula of **7** as $C_{50}H_{64}O_{11}$. Thus the structure of **7** was suggested to be the palmitic acid ester of **3**. In the HMBC spectrum of **7**, the carbon signal at δ_C 173.5 was correlated with the proton signals at δ_H 3.87 and 4.85 (each 20-H), 2.34 (2‴-H_2). Accordingly, the ester linkage site of palmitic acid was deduced to be C-20.

Compound **8**, $C_{52}H_{66}O_{11}$ showed almost the same spectral data [IR, ^1H and ^{13}C NMR] as **7** except for the presence of a cinnamoyl ester [δ_H 6.38, 7.65 (each 1H, *d, J* = 16.1 Hz), δ_C 117.5 (*d*), 146.1 (*d*)] in compound **8** in place of the benzoyl ester in compound **7**. The chemical shifts of 12-H and 20-H_2 were almost the same for **7** and **8**, suggesting the presence of palmitate



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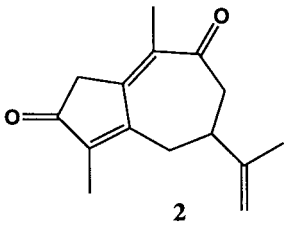

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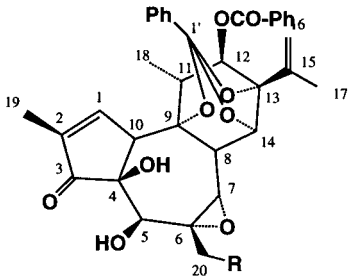
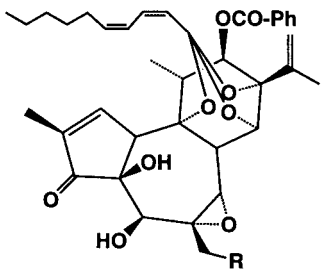
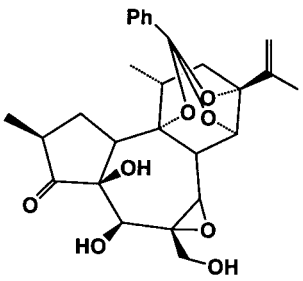


3 : R=OH
7 : R=OCO-$(CH_2)_{14}$-CH_3



4 : R=OH
5 : R=OCO-$(CH_2)_{14}$-CH_3



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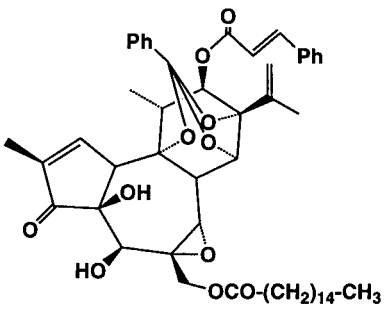

8

and cinnamate esters on C-20 and C-12, respectively. Thus the structure of **8** was deduced to be gnidicin-20-palmitate.

3. Experimental

^{1}H NMR: 270 and 400 MHz with TMS as int. stand; ^{13}C NMR: 100.2 MHz; CC: silica gel 60 (Merck), Sephadex LH-20 (Pharmacia) and TOYO pearl HW-40 (TOSHO); HPLC GPC (H-2002, SHODEX).

3.1. Plant material

Stems of *D. oleoides* Schreber ssp. *oleoides* were collected in August 1994 at Akkisla, Kayseri Turkey. Herbarium specimens (94B027F) are deposited in the herbarium of Kyoto University and Gazi University.

3.2. Extraction and isolation

The dried stems (2.0 kg) of *D. oleoides* Schreber ssp. *oleoides* were extracted with MeOH (15 l × 3) at 60°C. The MeOH extracts were concentrated in vacuo to give a residue (449 g), which was partitioned between EtOAc and H_2O. The EtOAc layer (113 g) was chromatographed on silica gel using solvents of increasing polarity [hexane–EtOAc (3:1, 2:1, 1:1, 1:2), EtOAc, EtOAc–MeOH (19:1, 9:1), MeOH] to give 32 fractions. Fr. 15 (3.8 g) was chromatographed on silica gel [$CHCl_3$-acetone (97:3)] and Toyopearl HW-40 with $CHCl_3$–MeOH (1:1) to give **1** (60 mg), **2** (5 mg) and **15** (105 mg). Fr. 22 (3.3 g) was chromatographed on silica gel with $CHCl_3$ to give five fractions (frs. 22.1–22.5). Fr. 22.3 (0.14 g) was chromatographed on silica gel [hexane–acetone (3:2) and ether] and preparative TLC with hexane–acetone (7:3) to give **3** (4 mg) and **6** (2 mg). Fr. 22.2 (0.14 g) was chromatographed by using HPLC (GPC, $CHCl_3$) and silica gel to give **13** (16 mg). Fr. 19 (2.0 g) was chromatographed on silica gel with $CHCl_3$–acetone (3:1), hexane–acetone (3:1) and Et_2O–hexane (4:1) to give **4** (15 mg) and **14** (15 mg). Fr. 9 (1.4 g) was chromatographed on Toyopearl HW-40 with $CHCl_3$–MeOH (4:1) and silica gel with CH_2Cl_2–acetone (99:1) to give **5** (10 mg). Fr. 10 (2.1 g) was chromatographed on silica gel with CH_2Cl_2–acetone (99:1) and hexane–acetone (4:1), and preparative TLC with $CHCl_3$–MeOH (99:1) to give **7** (2 mg) and **8** (4 mg). Fr. 18 (1.5 g) was chromatographed on silica gel with $CHCl_3$–MeOH (49:1) and Sephadex LH-20 with $CHCl_3$–MeOH (1:2) to give **11** (30 mg). Fr. 20 (3.2 g) was chromatographed on silica gel with $CHCl_3$, hexane–acetone (7:3) and $CHCl_3$–MeOH (19:1) to give **9** (88 mg) and **12** (17 mg). Fr. 32 (2 g) was chromatographed on silica gel with $CHCl_3$–MeOH (9:1) and on Sephadex LH-20 with MeOH to give **10** (30 mg) and **16** (60 mg). Fr. 16 (2.8 g) was chromatographed on silica gel with $CHCl_3$–MeOH (49:1) to give oleanolic acid (**17**) (140 mg).

3.3. Oleodaphnal (*1*)

Oil, $[\alpha]_D^{25}$ + 5.0° ($CHCl_3$ *c* 2.25), IR ν_{max}^{KBr} cm^{-1}: 1703, 1675, 1386, 1286, 893. UV λ_{max}^{MeOH} nm (ϵ): 231 (6500), 303 (10500). ^{1}H NMR: δ ($CDCl_3$): 1.75 (1H, *m*, 8-H), 1.79 (3H, *s*, 13-H_3), 1.91 (3H, *s*, 15-H_3), 1.98 (1H, *m*, 8-H), 2.58 (1H, *ddd, J* = 7.8, 7.8, 5.4 Hz, 7-H), 2.67 (2H, *m*, 9-H_2), 2.88 (2H, *m*, 6-H_2), 3.44 (2H, *s*, 2-H_2), 4.76, 4.77 (each 1H, *s*, 12-H), 9.96 (1H, *s*, 14-H). ^{13}C NMR ($CDCl_3$): 152.6 (*s*, C-1), 37.3 (*t*, C-2), 202.5 (*s*, C-3), 144.2 (*s*, C-4), 166.0 (*s*, C-5), 32.3 (*t*, C-6), 42.7 (*d*, C-7), 31.4 (*t*, C-8), 21.3 (*t*, C-9),135.1 (*s*, C-10), 148.6 (*s*, C-11), 110.0 (*t*, C-12), 20.6 (*q*, C-13), 191.3 (*d*, C-14), 9.0 (*q*, C-15). EIMS *m/z* (rel. int.): 230 $[M]^+$ (47), 187 (40), 160 (100), 91 (75), 77 (45), 41 (40). HR-MS *m/z* 230.1312 $[M]^+$ $C_{15}H_{18}O_2$ required 230.1307.

3.4. Oleodaphnone (*2*)

Oil, $[\alpha]_D^{25}$ +4.1° ($CHCl_3$ *c* 0.93), IR ν_{max}^{KBr} cm^{-1}: 1703, 1649, 1382, 1311, 1092, 898, 757. UV λ_{max}^{MeOH} nm (ϵ): 240 (5300), 300 (6700). ^{1}H NMR: δ ($CDCl_3$): 1.79 (3H, *s*, 13-H_3), 1.88 (3H, *s*, 15-H_3), 1.98 (3H, *s*, 14-H_3), 2.73 (1H, *br t, J* = 12.6 Hz, 7-H), 2.76 (1H, *dd, J* = 14.7, 12.6 Hz, 6-H), 2.89 (2H, *m*, 8-H_2), 2.99 (1H, *br t, J* = 14.7 Hz, 6-H), 3.08, 3.15 (each 1H, *ABq, J* = 21.0 Hz, 2-H), 4.79, 4.82 (each 1H, *s*, 12-H_2). ^{1}H NMR: δ (C_5D_5N): 1.73 (3H, *s*, 12-H_3), 1.81 (3H, *s*, 15-H_3), 1.99 (3H, *s*, 14-H_3), 2.65 (1H, *ddd, J* = 13.2, 13.2, 5.4 Hz, 7-H), 2.68 (1H, *dd, J* = 14.2, 13.2 Hz, 6-H), 2.95 (2H, *m*, 8-H_2), 2.86 (1H, *br t, J* = 14.2 Hz, 6-H), 3.06, 3.16 (each 1H, *ABq, J* = 20.5 Hz, 2-H_2), 4.81, 4.84 (each 1H, *br s*, 13-H_2): ^{13}C NMR ($CDCl_3$): 144.1 (*s*, C-1), 41.1 (*t*, C-2), 201.9 (*s*, C-3), 144.8 (*s*, C-4), 162.8 (*s*, C-5), 35.4 (*t*, C-6), 39.0 (*d*, C-7), 49.8 (*t*, C-8), 200.7 (*s*, C-9), 131.6 (*s*, C-10), 147.0 (*s*, C-11), 111.1 (*t*, C-12), 20.2 (*q*, C-13), 17.4 (*q*, C-14), 9.0 (*q*, C-15). EIMS *m/z* (rel. int.): 230 $[M]^+$ (100), 187 (35), 159 (75), 147 (50), 91 (70), 83 (60), 53 (30), 41 (25). HR-MS *m/z* 230.1306 $[M]^+$ $C_{15}H_{18}O_2$ required 230.1307.

3.5. Genkwadaphnin-20-palmitate (*7*)

Amorphous powder, $[\alpha]_D^{25}$ +37.5° ($CHCl_3$ *c* 1.74), IR ν_{max}^{KBr} cm^{-1}: 3464, 1724, 1631, 1452, 1271, 1177, 1083, 936. UV λ_{max}^{MeOH} nm (ϵ): 223 (18900).^{1}H NMR: δ ($CDCl_3$): Table 1. ^{13}C NMR ($CDCl_3$): Table 2. FAB HR-MS *m/z* 863.4361 $[M+Na]^+$ $C_{50}H_{64}O_{11}Na$ required 863.4346.

3.6. Gnidicin-20-palmitate (**8**)

Amorphous powder, $[\alpha]_D^{25}$ +41.7° ($CHCl_3$ *c* 0.56), IR ν_{max}^{KBr} cm^{-1}: 3469, 1713, 1636, 1452, 1314, 1082, 1012. UV λ_{max}^{MeOH} nm (ϵ): 223 (15900), 280 (15300). ^1H NMR: δ ($CDCl_3$): Table 1. ^{13}C NMR ($CDCl_3$): Table 2. FAB HR-MS *m/z* 889.4597 $[M+Na]^+$ $C_{52}H_{66}O_{11}Na$ required 889.4503.

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