Sphingolipid and Other Constituents from Almond Nuts (*Prunus amygdalus* Batsch)

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One sphingolipid, 1-*O*-β-D-glucopyranosyl-(2*S*,3*R*,4*E*,8*Z*)-2-[(2*R*)-2-hydroxyhexadecanoylamino]-4,8-octadecadiene-1,3-diol, and four other constituents, β-sitosterol, daucosterol, uridine, and adenosine, have been isolated from the nuts of almond (*Prunus amygdalus*). Complete assignments of the proton and carbon chemical shifts for the sphingolipid were accomplished on the basis of high-resolution 1D and 2D NMR data. All of these compounds are being reported from almond nuts (*P. amygdalus*) for the first time.

KEYWORDS: Almond nuts; *Prunus amygdalus*; sphingolipid; constituents

INTRODUCTION

Sphingolipids are compounds with a sphingoid base backbone, an amide linked nonpolar aliphatic "tail", and a polar headgroup. There are more than 70 different sphingoid base backbones that vary in alkyl chain lengths (from 14 to 22 carbon atoms), degree of saturation and position of the double bonds, presence of a hydroxyl group at position 4, and branching of the alkyl chain. The amino group of the sphingoid base is usually substituted with a long-chain fatty acid. The fatty acids vary in chain length (14−30 carbon atoms), degree of unsaturation, and presence or absence of a hydroxyl group on the carbon atom. Subsequent addition of a double bond at the 4,5 carbon−carbon bond of the sphingonine backbone results in the formation of ceramide (N-acyl-sphingosine). More complex sphingolipids are formed when polar headgroups are added at position 1 of ceramide (*1, 2*).

Sphingolipids are located in cellular membranes, lipoproteins (especially LDL), and other lipid-rich structures, such as skin. They are constituents of most foods, especially foods of mammalian origin, which have a wide spectrum of complex sphingolipids (sphingomyelins, cerebrosides, globosides, gangliosides, or sulfatides). The complex sphingolipids of plants are mainly cerebrosides (mono- and oligohexosylceramides) with glucose, galactose, mannose, and inositol (*2*). It was reported that both the sphingomyelin (SM) and glycosphingolipids of milk have been shown to inhibit early stages of colon cancer (appearance of aberrant crypt foci, ACF) and to decrease the proportion of adenocarcinomas vs adenomas in 1,2-dimethylhydrazine (DMH)-treated female CF1 mice (*3−5*). Studies with experimental animals have also shown that consumption of sphingolipids reduces serum low-density lipoprotein cholesterol, and elevates high-density lipoproteins (*6, 7*). All of these reports suggest that sphingolipids are "functional" components of food. However, the sphingolipid content and component of foods has not been widely studied. In the course of our studies on bioactive sphingolipid from foods, we have investigated the chemical constituents of almond nuts.

Almond is one of the most popular tree nuts on a worldwide basis and ranks number one in tree nut production. They are typically used as snack foods and as ingredients in a variety of processed foods, especially in bakery and confectionery products. The United States is the largest almond producer in the world and most of the U. S. almonds are grown in California in an area that stretches over 400 miles from Bakersfield to Red Bluff (*8*). Over 7,000 individual growers cultivate more than 400,000 acres of almonds. Almonds are California's largest tree crop based on dollar value, acreage, and world distribution. Five major varieties of almonds grown in California include Nonpareil, Mission, California, Ne Plus Ultra, and Peerless. Of the five groups listed, most almond production (about 90%) falls into three major marketing categories of Nonpareil, California, and Mission. In this report, we describe the isolation and structure elucidation of one sphingolipid, 1-*O*-β-D-glucopyranosyl-(2*S*,3*R*,4*E*,8*Z*)-2-[(2*R*)-2-hydroxyhexadecanoylamino]-4,8-octadecadiene-1,3-diol (**1**), together with four other constituents, β-sitosterol (**2**), daucosterol (**3**), uridine (**4**), and adenosine (**5**), from the nuts of almond (*Prunus amygdalus*) (**Figure 1**).

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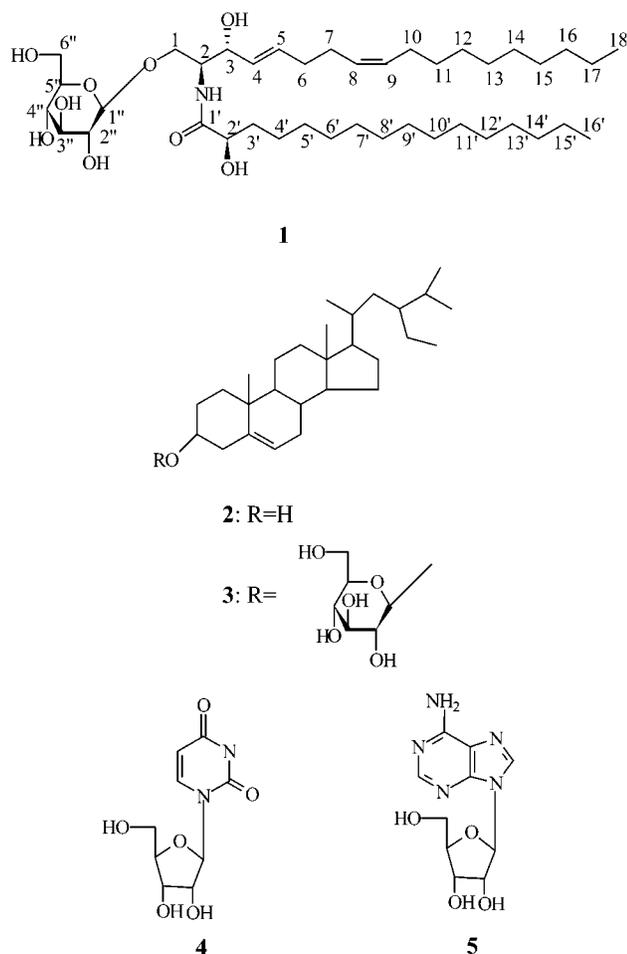‡ Osaka City University.
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Figure 1. Structures of compounds **1–5**.

MATERIALS AND METHODS

General Procedures. The ^{1}H, ^{13}C, and 2D NMR spectra were recorded on a Varian Unity plus 500 (500 MHz) and Varian AM-600 NMR spectrometer (Palo Alto, CA), with TMS as internal standard. HRFAB-MS was run on a JEOL HX-110 double-focusing mass spectrometer in the Department of Biochemistry, Michigan State University. The atmospheric pressure chemical ionization mass spectrometry (APCI-MS) was performed on a Fisons/VG Platform II mass spectrometer (Micromass Co., Beverly, MA) equipped with a Digital DECPC XL560 computer for data analysis. Thin-layer chromatography was performed on Sigma-Aldrich TLC plates (250 μm thickness, 2–25 μm particle size), with compounds visualized by spraying with 5% (v/v) H_2SO_4 in ethanol solution.

Plant Material. Almond nuts were supplied by the California Almond Board. A voucher specimen (HS17) was deposited in the Department of Food Science, Cook College, Rutgers University.

Extraction and Isolation Procedures. The dried almond nuts powders (14 kg) were extracted successively with hexane (10 L × 2) and 95% EtOH (10 L × 3). After evaporation of ethanol in vacuo, the residue (60 g) was subjected to silica gel column chromatography with a hexanes−ethyl acetate (6:1) solvent system first to give fractions 1−3, then with ethyl acetate to give fraction 4, then with an ethyl acetate− MeOH−H_2O (20:1.2:0.8, 10:1.2:0.8, 5:1.2:0.8, and 0:0:1) solvent system to give fractions 5−11. Fraction 2 eluted by hexanes−ethyl acetate (6:1) was subjected to Sephadex LH-20 column chromatography with 95% EtOH to give compound **2** (200 mg). Fraction 5 eluted by ethyl acetate−MeOH−H_2O (20:1.2:0.8) was subjected to RP C-18 column chromatography with 95% MeOH to give compounds **1** (120 mg) and **3** (500 mg). Fraction 6 eluted by ethyl acetate−MeOH−H_2O (20:1.2:0.8) was subjected to Sephadex LH-20 and eluted by 95% EtOH to afford 15 mg of compound **4** and 25 mg of compound **5**.

Spectral Identification of Compounds 1−5. *Compound 1*. White powder; $[\alpha]_D23$ +6.6° (c 0.43, MeOH/CHCl$_3$ 3:2). Positive-ion

Table 1. NMR Spectral Data for Compound 1 (C_5D_5N) (δ in ppm, J in Hz)

	^{1}H	^{13}C	COSY	HMBC (H→C)
1a	4.20 dd 3.7, 10.5	70.1	2, 1b	2, 3, 1″
1b	4.68 dd 5.9, 10.5		2, 1a	
2	4.78 dddd 3.7, 5.9, 6.3, 9.0	54.6	1, 3, NH	1, 3, 1′
3	4.73 dd 6.3, 6.5	72.2	2, 4	1, 2, 4, 5
4	5.97 dd 6.5, 15.5	132.1	3, 5	2, 3, 5, 6
5	5.88 dt 6.0, 15.5	132.0	4, 6	3, 4, 6, 7
6	2.12 m	32.8	5, 7	
7	2.15 m	27.2	6, 8	
8	5.45 m	129.3	7	6, 7, 9, 10
9	5.45 m	130.5	10	7, 8, 10, 11
10	2.04 m	27.5	9, 11	
11	1.35 m	29.5	10, 12	
12	1.30 m	29.9	11	
13–15	1.20 m	29.5–29.9		
16	1.20 m	32.0	17	
17	1.21 m	22.9	16, 18	
18	0.92 t 6.5	14.2	17	16, 17
1′		175.6		
2′	4.54 dd 3.7, 7.8	72.4	3′a, 3′b	1′, 3′, 4′
3′a	2.16 m	35.5	2′, 3′b, 4′	
3′b	1.96 m		2′, 3′a, 4′	
4′	1.80 m	25.8	3′a, 3′b, 5′	
	1.68 m		3′a, 3′b, 5′	
5′	1.36 m	29.8	4′, 6′	
6′	1.30 m	29.9	5′	
7′-13′	1.20 m	29.5–29.9		
14′	1.20 m	32.0	15′	
15′	1.21 m	22.9	14′, 16′	
16′	0.92 t 6.5	14.2	15′	14′, 15′
1″	4.88 d 7.5	105.6	2″	1, 2″, 3″
2″	4.00 dd 7.5, 9.0	75.0	1″, 3″	1″, 3″
3″	4.18 m	78.3	2″, 4″	2″, 4″
4″	4.18 m	71.4	3″, 5″	3″, 5″, 6″
5″	3.87 m	78.5	4″, 6″a, 6″b	3″, 4″
6″a	4.48 dd 12.0, 2.5	62.5	5″, 6″b	4″, 5″
6″b	4.32 dd 12.0, 5.5		5″, 6″a	
NH	8.35 d 9.0		2	1, 2, 3, 1′, 2′

HRFAB-MS: [M + H]$^+$ at m/z 714.5489 for $C_{40}H_{76}NO_9$, calcd. for $C_{40}H_{76}NO_9$, 714.5520. ^{1}H NMR (C_5D_5N, 500 MHz): see **Table 1**. ^{13}C NMR (C_5D_5N, 125 MHz): see **Table 1**.

β-sitosterol (2). White powder. APCI-MS, m/z 413 [M − H]$^-$. ^{1}H NMR (CDCl$_3$, 600 MHz) δ 5.17 (1H, m), 3.50 (1H, m), 0.98 (3H, s), 0.90 (3H, d, J = 6.0 Hz), 0.82 (3H, t, J = 6.6 Hz), 0.81 (3H, d, J = 6.6 Hz), 0.78 (3H, d, J = 7.2 Hz), 0.65 (3H, s). ^{13}C NMR (CDCl$_3$) δ 141.0 (s), 121.9 (d), 72.0 (d), 57.0 (d), 56.3 (d), 50.3 (d), 46.0 (d), 42.5 (s), 40.0 (t), 37.5 (t), 36.9 (s), 36.7 (d), 34.2 (t), 32.1 (t), 31.8 (d), 29.3 (d), 28.4 (t), 26.3 (t), 24.5 (t), 23.3 (t), 21.3 (t), 20.0 (q), 19.5 (q), 19.2 (q), 19.0 (q), 12.2 (q), 12.1 (q). (Identical to that reported in the literature (*9, 10*)).

Daucosterol (3). White powder. APCI-MS, m/z 575 [M − H]$^-$. ^{1}H NMR (C_5D_5N, 600 MHz) δ 5.60 (1H, m), 5.28 (1H, d, J = 7.8 Hz), 4.80 (1H, dd, J = 2.4, 12.0 Hz), 4.65 (1H, dd, J = 5.4, 12.0 Hz), 4.52 (2H, m), 4.29 (1H, t, J = 7.8 Hz), 4.21 (2H, m), 2.97 (1H, m), 2.72 (1H, t, J = 11.4 Hz), 2.37 (1H, m), 2.23 (1H, m), 1.24 (3H, d, J = 6.6 Hz), 1.18 (3H, s), 1.15 (3H, t, J = 7.2 Hz), 1.13 (3H, d, J = 6.6 Hz), 1.1 (3H, d, J = 7.2 Hz), 0.91 (3H, s). ^{13}C NMR (C_5D_5N) δ 140.9 (s), 121.9 (d), 102.5 (d), 78.6 (d), 78.4 (d), 78.1 (d), 75.3 (d), 71.6 (d), 62.8 (t), 56.8 (d), 56.2 (d), 50.3 (d), 46.0 (d), 42.4 (s), 39.9 (t), 39.3 (t), 37.4 (t), 36.9 (s), 36.4 (d), 34.2 (t), 32.1 (t), 32.0 (d), 30.2 (t), 29.4 (d), 28.5 (t), 26.3 (t), 24.5 (t), 23.4 (t), 21.3 (t), 20.0 (q), 19.4 (q), 19.2 (q), 19.0 (q), 12.1 (q), 12.0 (q). (Identical to that reported in the literature (*11, 12*)).

Uridine (4). White powder. APCI-MS, m/z 245 [M + H]$^+$. ^{1}H NMR (CD$_3$OD, 600 MHz) δ 8.04 (1H, d, J = 8.4 Hz), 5.94 (1H, d, J = 4.8 Hz), 5.74 (1H, d, J = 8.4 Hz), 4.17 (1H, t, J = 4.8 Hz), 4.14 (1H, t, J = 4.8 Hz), 3.99 (1H, m), 3.82 (1H, dd, J = 3.6, 13.2 Hz), 3.72 (1H, dd, J = 3.0, 10.8 Hz). ^{13}C NMR (CD$_3$OD) δ 166.3 (s), 152.6 (s), 142.9 (d), 102.9 (d), 90.9 (d), 86.5 (s), 75.8 (d), 71.4 (d), 62.4 (t). (Identical to that reported in the literature (*13, 14*)).
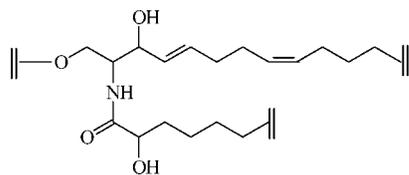
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Figure 2. Partial structure of compound **1**.

Adenosine (5). White powder. APCI-MS, *m/z* 268 [M + H]⁺, ¹H NMR (DMSO, 600 MHz) δ 8.33 (1H, s), 8.12 (1H, s), 7.32 (NH₂, brs), 5.86 (1H, d, *J* = 6.0 Hz), 5.42 (−OH, d, *J* = 6.0 Hz), 5.39 (−OH, dd, *J* = 4.8, 7.2 Hz), 5.16 (−OH, d, *J* = 4.8 Hz), 4.60 (1H, dd, *J* = 6.0, 11.4 Hz), 4.13 (1H, dd, *J* = 4.8, 7.2 Hz), 3.95 (1H, dd, *J* = 2.0, 6.0 Hz), 3.65 (1H, m), 3.54 (1H, m). ¹³C NMR (DMSO) δ 156.1 (s), 152.4 (d), 149.0 (d), 139.9 (d), 119.3 (s), 87.9 (d), 85.9 (d), 73.4 (d), 70.6 (d), 61.6 (t). (Identical to that reported in the literature (*12, 14*)).

RESULTS AND DISCUSSION

The extraction of almond nuts was chromatographed successively on silica gel, Sephadex LH-20, and RP C-18 columns to afford compounds **1**−**5**. Their structures were established by interpretation and full assignments of 1D and 2D NMR spectroscopic data and comparison with literature data.

Compound **1** was assigned a molecular formula of C₄₀H₇₅-NO₉ determined by positive-ion HRFAB-MS ([M + H]⁺ at *m/z* 714.5489 for C₄₀H₇₆NO₉, calcd. for C₄₀H₇₆NO₉, 714.5520), as well as from its ¹³C NMR data. The ¹H and ¹³C NMR spectral data of **1** showed the presence of two aliphatic long chains, an amide linkage, and a sugar moiety, strongly suggesting the glycosphingolipid nature of **1**. In the ¹H NMR spectrum, two terminal methyl groups at δ 0.92 (t, *J* = 6.5 Hz) and an intense signal at δ 1.20 indicated the presence of either two long aliphatic chains or a single branched aliphatic chain. A signal of a carbon attached to nitrogen was observed at δ 54.6, and an amide carbonyl signal appeared at δ 175.6 in the ¹³C NMR spectrum. According to the ¹H−¹H COSY, TOCSY (5 bonds), and HMBC, the partial structure shown in **Figure 2** was established. The 4,5 alkene bond was found to be trans, by the large vicinal coupling constants (*J₄,₅* = 15.5 Hz). The trans geometry of this double bond was also supported by the chemical shift of C-6 (δ 32.8). Usually, the signals of carbons next to a trans double bond appear at δ 32−33, whereas those of a cis double bond appear at δ 27−28 (*15*). The olefinic protons at 8,9 were equivalent, but as evidenced by the carbon signals of C-7 (δ 27.2) and C-10 (δ 27.5), the geometry of the 8,9 alkene bond was determined to be cis. Furthermore, the ¹H NMR spectrum of **1** showed one anomeric proton at δ 4.88, d, *J* = 7.5 Hz. The ¹³C NMR spectrum exhibited the signals for the glucopyranose unit (δ 105.6, d, C-1″; δ 75.0, d, C-2″; δ 78.3, d, C-3″; δ 71.4, d, C-4″; δ 78.5, d, C-5″; and δ 62.5, t, C-6″). The β-anomeric configuration for the glucose was judged from its large ³*J*₍H1,H2₎ coupling constants (*J* = 7.5 Hz) (*16*). HMBC correlation between H-1″/C-1 suggested that the β-glucopyranose unit was attached at the C-1 position of the amide acyl chain. This was also supported by the cross-peaks between H-1a/H-1″ and H-1b/H-1″ in the ROESY spectrum. The relative configurations of C-2, C-3, and C-2′ of **1** were established on the basis of the NMR data and the optical rotation data in agreement with those published for the synthetic 1-*O*-β-D-glucopyranosyl-(2*S*,3*R*,4*E*,8*Z*)-2-[(2*R*)-2-hydroxyhexadecanoylamino]-4,8-octadecadiene-1,3-diol (*17, 18*). Thus, compound **1** was determined as shown in **Figure 1**. Full assignments of the ¹H and ¹³C NMR signals were accomplished using ¹H-¹H COSY, TOCSY, ROESY, HMQC, and HMBC experiments

(**Table 1**). This compound is also known as the major constituent of soyacerebroside II. It has been reported that simple monoglucocerebrosides containing sphinga-4,8-dienine in the hydrophobic moiety exhibit significant activities, such as antiulcerogenic activity (*19*), ionophoretic activity for Ca²⁺ ion (20), repellent activity against the Blue Mussel, *Mytilus edulis* (*21*), and antihepatotoxic effect on CCl₄-induced cytotoxicity in primary cultured rat hepatoxytes (*22*).

In addition to the sphingolipid (**1**), four known constituents, β-sitosterol (**2**), dancosterol (**3**), uridine (**4**), and adenosine (**5**), have also been isolated in this study. Their structures were identified by comparison of their NMR and MS data with those reported in the literature (*9*−*14*). All of these compounds are being reported from this species (*P. amygdalus)* for the first time.

It is notable that in vivo studies have shown that whole almonds and almond fractions reduce aberrant crypt foci (ACF) in a rat model of colon carcinogenesis (*23*). So almond consumption may provide a measure of protection from the risk of colon cancer. As mentioned above, recent research has revealed that sphingolipids have the capacity to inhibit the development of early stages of colon cancer in mice and decrease the proportion of adenocarcinomas vs adenomas in 1,2-dimethylhydrazine (DMH) treated CF1 mice (*3*−*5, 24*). The studies of sphingolipid digestion, uptake, and elimination have been conducted with rodents, and they suggest that both sphingomyelin and glucosylceramide are digested in the small intestine, but significant amounts reach the colon (*25*−*27*). Therefore, compound **1** could be the major active compound in almond nuts responsible for the suppression of aberrant colonic crypt foci formation. Further in vivo studies will be necessary for this pure compound.

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