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Two new aromatic compounds and a new D-arabinitol ester from the mushroom *Hericium erinaceum*

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ABSTRACT

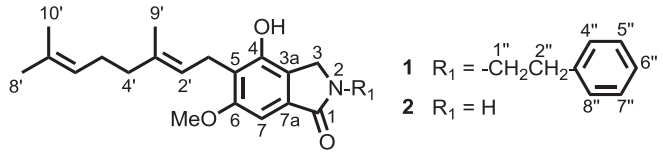
Two new aromatic compounds (**1**, **2**), new D-arabinitol ester (**3**), and two known compounds (**4**, **5**) were isolated from mushroom *Hericium erinaceum*. The structures of **1**–**5** were elucidated on the basis of spectral data. Compounds **1**, **2**, **4**, and **5** exhibited α-glucosidasae inhibitory activity.

1. Introduction

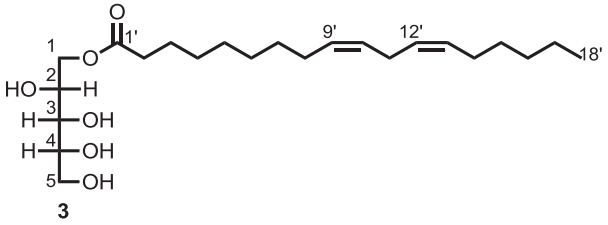
Mushrooms have been not only used as food materials with their unique flavor and texture, but also recognized as an important source of biologically active compound of medicinal value.[1] In recent years, there is increased medical and pharmaceutical interest in mushrooms as sources of novel immunomodulators,[2] antitumor agents,[3] antibiotics,[4] and antihypertensives.[5] *Hericium erinaceum* (Yamabushitake in Japanese) is known as an edible mushroom that belongs to the Hericiaceae family and grows on dead trunks of hard woods such as narra, oak, and beech in Japan, China, Europe. In regarding to chemical components of *H. erinaceum*, various constituents such as hericene, hericerin, hericenone erinacine, erinacerin, and polysaccharides have been reported as the chemical components.[6–12] Its fruiting bodies have been used for the treatment of dyspepsia, gastric ulcer, and enervation in China. This mushroom has some beneficial effects, including antioxidant,[13] antitumor,[14–16] antimicrobial,[17,18] pollen tube germination/growth inhibition,[19] and the stimulating the synthesis of nerve growth factor (NGF).[20] These results suggest the usefulness of *H. erinaceum*, thus, we investigated chemical component of *H. erinaceum*.

2. Result and discussion

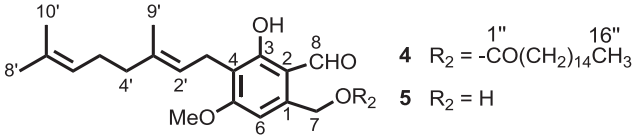
The fruiting bodies of *H. erinaceum* were extracted with EtOAc. The solvent was filtered and then removed in vacuo to give a brown crude extract. The extract was fractionated by silica gel column chromatography. As a consequence, two new aromatic compounds (**1**, **2**), new D-arabinitol ester (**3**), and two known compounds (**4**, **5**) were isolated from this mushroom.



1 R_1 = -CH_2CH_2-
2 R_1 = H



3



4 R_2 = -$CO(CH_2)_{14}CH_3$ (1" … 16")
5 R_2 = H

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Compound **1** was isolated as colorless prisms. Its molecular formula of **1** was determined as $C_{27}H_{33}O_3N$ by HREIMS [*m*/*z* 419.2470 $[M]^+$ (calcd for $C_{27}H_{33}O_3N$, 419.2480)]. The presence of a hydroxyl group (3419 cm^{-1}), a γ-lactam (1646 cm^{-1}), and an aromatic ring (1589 cm^{-1}) were confirmed by IR spectral data. Carbon NMR, including DEPT, indicated nine quaternary carbons (δ_C 169.0, 158.4, 150.4, 139.1, 138.7, 132.1, 132.0, 121.1, and 118.1). The connectivity of carbon and hydrogen atoms was established from the HSQC spectrum. Proton NMR spectrum indicated a methoxy group (δ_H 3.83), aromatic protons (δ_H 7.26 (2H), 7.22 (2H), 7.19 (1H), 6.95 (1H)), three methyl groups (δ_H 1.80, 1.66 and 1.58), six methylenes (δ_H 4.17, 3.84, 3.49, 2.97, 2.10, 2.05) and, two trisubstituted olefins (δ_H 5.24, 5.03). Also signal observed at δ_H 6.52 (1H, s), which had no HSQC correlation with any carbon signals, was assignable to phenolic proton (4-OH) (Table 1). Comparison of ^1H, ^{13}C NMR including DEPT and IR spectra with those of known compound hericerin suggested that this molecule involves isoindolinone skeleton.

The partial structure was determined by interpretation of the HMBC spectrum revealed correlations as shown in Fig. 1. The connection between nitrogen atom and phenylethyl group was indicated by HMBC correlations from H-1″ to C-1 and C-3. Isoindoline-1-one substructure was disclosed by HMBC correlations from H-7 to C-1 and H-3 to C-4. On the other hand, in the case of hericerin, NOE was observed between the signal at aromatic proton and methylene proton of isoindolinone skeleton.[19] These results indicated that chemical structure of compound **1** is different from that of hericerin, thus, we named compound **1** isohericerin.

Table 1
^1H and ^{13}C NMR spectra data for compounds **1**,**2** and **4**,**5** (500 MHz for ^1H; 125 MHz for ^{13}C)

Position	**1** δ_H (*J* in Hz)	δ_C	**2** δ_H (*J* in Hz)	δ_C
1		169.0		170.5
2				
3	4.17 s	48.2	4.19 s	43.2
3a		132.1		131.7
4		150.4		150.3
5		118.1		120.0
6		158.4		158.5
7	6.95 s	97.5	6.73 s	96.4
7a		121.1		123.4
1′	3.49 d (6.8)	22.8	3.31 d (7.1)	22.5
2′	5.24 br t (6.8)	22.8	5.12 t (7.1)	122.5
3′		139.1		134.2
4′	2.05 m	39.6	1.89 t (7.6)	39.5
5′	2.10 m	26.3	1.99 td (7.6, 7.0)	26.4
6′	5.03 br t (6.8)	123.7	5.02 t (7.0)	124.3
7′		132.0		130.8
8′	1.66 s	25.7	1.58 s	25.7
9′	1.80 s	16.1	1.72 s	16.1
10′	1.58 s	17.7	1.51 s	17.7
1″	3.84 br t (7.2)	44.2		
2″	2.97 t (7.2)	34.8		
3″		138.7		
4″, 8″	7.22 dd (7.2, 1.7)	128.6		
5″, 7″	7.26 dd (7.2, 7.2)	128.6		
6″	7.19 dd (7.2, 1.7)	126.4		
4-OH	6.52 s		9.42 s	
6-OMe	3.83 s	56.0	3.79 s	56.0
NH			8.36 s	
Position	**4** δ_H (*J* in Hz)	δ_C	**5** δ_H (*J* in Hz)	δ_C
1		138.4		143.3
2		112.9		112.6
3		162.9		163.7
4		118.1		103.5
5		163.5		163.0
6	6.52 s	105.6	6.52 s	103.5
7	5.32 s	62.9	4.94 s	62.7
8	10.11 s	193.1	10.21 s	193.6
1	3.24 d (7.0)	21.3	3.33 d (7.2)	21.3
2′	5.17 br t (7.0)	121.2	5.17 t (7.2)	121.5
3′		135.7		131.5
4′	1.95 t (7.0)	39.8	1.95 t (7.6)	39.8
5′	2.04 m	26.7	2.04 m	26.7
6′	5.05 br t (6.8)	124.3	5.06 br t (6.8)	124.4
7′		131.2		131.4
8′	1.63 s	25.6	1.64 s	25.7
9′	1.77 s	16.1	1.77 s	16.0
10′	1.57 s	17.6	1.57 s	17.6
1″		173.2		
2″	2.33 t (7.6)	34.2		
3″	1.61 tt (7.6, 7.6)	25.6		
4″-15″	1.23–1.32 m	22.7–31.9		
16″	0.88 t (7.6)	14.1		
3-OH	12.36 s		12.37 s	
5-OMe	3.91 s	55.9	3.92 s	55.8

In $CDCl_3$ for **1**, **4**, and **5**; in DMSO for **2**.

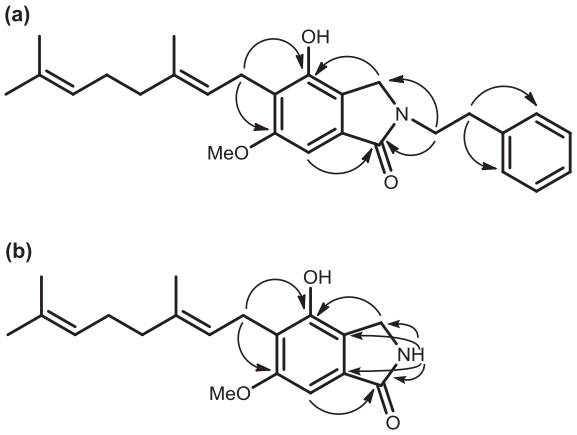

Fig. 1. (a) Key HMBC correlations (H→C) of **1**. (b) Key HMBC correlations (H→C) of **2**.

Compound **2** was isolated as an amorphous powder. The molecular formula of **2** was determined to be $C_{19}H_{25}O_3N$ by HREIMS [*m*/*z* 315.1829 $[M]^+$ (calcd for $C_{19}H_{25}O_3N$, 315.1759)].

The presence of a hydroxyl group (3263 cm^{-1}), a γ-lactam (1667 cm^{-1}), and an aromatic ring (1625, 1593 cm^{-1}) were confirmed by IR spectral data. The ^1H and ^{13}C NMR spectra were almost similar to those of **1** (Table 1). It was suggested that **2** is isohericerin analogues compound without the phenylethyl moiety. The HMBC showed correlations for H_2-3/C-1, H_2-3/C-4, H-2/C-1, H-2/C-3, H-2/C-3a, H-2/C-7a, and H-7/C-1 (Fig. 1). Compound **2** was determined as *N*-De phenylethyl isohericerin by ^1H, ^{13}C NMR, HSQC, HMBC analyses.

Compound **3** was isolated as a white powder. The IR spectrum indicated the presence of OH (3322 cm^{-1}) and C=O (1735 cm^{-1}). The ^{13}C NMR spectrum including DEPT displayed 23 carbon resonances, comprising 3 sp^3 methines, 14 sp^3 methylenes, 1 sp^3 methyl, 4 sp^2 methines, and a carbonyl. The $^1H-^1H$ COSY spectrum of compound **3** showed the partial structure −O−CH_2−CHOR−CHOR−CHOR−CH_2−O−. Therefore, we assumed that compound **3** is sugar alcohol ester. Pursuant to this, we hydrolyzed compound **3** to obtain D-arabinitol and methyl linoleate. These compounds were identified with NMR data, specific rotation and MS spectrum and retention index (RI).[21–23] Moreover, HMBC spectrum revealed the correlation from methylene proton of sugar alcohol to carbonyl carbon. The result indicated that a linoleoyl group linked to carbon atom of C-1 or C-5. To confirm the linoleoyl group connected C-1 or C-5 position, we synthesized 1-D-arabinitol-monolinoleate. Compound **3** was confirmed as 1-D-arabinitol-monolinoleate by comparing the NMR data of 1-D-arabinitol-monolinoleate synthesized with that of compound **3**. Compounds **4**

and **5** were identified as hericene A and 4-[3′,7′-dimethyl-2′,6′-octadienyl]-2-formyl-3-hydroxy-5-methyoxybenzylalcohol, respectively, by comparing with previous spectral data.[24] Arone et al., obtained compound **5** by methanolysis of hericenes A–C,[24] however, there is no report as the isolated compound **5** from natural source. We isolated compound **5** as a natural compound from *H. erinaceum* for the first time.

Compounds **1**–**5** were evaluated in α-glucosidase inhibitory activity assay. Compounds **1**, **2**, **4**, and **5** exhibited α-glucosidase inhibitory activity. Fifty percent inhibition (IC_{50}) values of **1**, **2**, **4**, and **5** were 11.7, 12.5, 12.3, and 12.3 μM, respectively (Table 2). This result indicated that chemical components of *H. erinaceum* effects on α-glucosidase inhibitory activity.

Table 2
Inhibitory activity of compounds **1**–**5** against α-glucosidase

Compound	IC_{50} (μM)[a]	Compound	IC_{50} (μM)[a]
1	12.3±1.3	**5**	12.5±1.3
2	12.3±6.2	1-Deoxynojirimycin[b]	278.0±1.7
3	>300	Acarbose[b]	907.5±2.2
4	11.7±0.2		

[a] Data represents means of ±SD of triplicate samples.
[b] These compounds were used as reference compounds.

3. Experimental

3.1. General

Thin layer chromatographies (TLC) were performed on precoated plates (silica gel $60F_{254}$, 0.25 mm, Merk, Darmstadt, Germany). Column chromatographies were carried out using 70–230 mesh silica gel (Kieselgel 60, Merck, Germany). ^{1}H NMR spectra were recorded at 400 MHz on a JEOL ECA-400 spectrometer, or at JEOL ECA-500 spectrometer or at JEOL ECA-700 spectrometer in D_2O, $CDCl_3$, and DMSO-d_6 with DSS as internal standard for D_2O and TMS for $CDCl_3$ and DMSO-d_6. ^{13}C NMR spectra were recorded at 100 MHz on a JEOL ECA-400 spectrometer, at JEOL ECA-500 spectrometers or at JEOL ECA-700 spectrometer. For gas chromatography mass spectrometry (GC–MS), an Agilent Technologies 6890N (Agilent Technologies (Tokyo, Japan)) gas chromatograph equipped with a split injector was directly coupled to Agilent Technologies-5973N-MSD (Agilent Technologies (Tokyo, Japan)) mass spectrometer and an HP-5MS capillary column (30 m length, 0.25 mm i.d.) (Agilent Technologies (Tokyo, Japan)); a split injection of 10:1 was used. Helium at 1.8 ml/min was used as a carrier gas. The temperature of the ion source was 280 °C, and the electron energy was70 eV. The oven temperature was programmed from 40 to 260 °C at 4 °C/min. The injection temperature was 270 °C and the detector temperature 280 °C. The electron impact (EI) mode was used. The retention index (RI) was calculated using a homologous series of *n*-alkane C_5–C_{28} for HP-5MS column. High-resolution EIMS (HREIMS) was obtained on a JEOL the Tandem MS station JMS-700 (Japan). IR spectra were determined with a JASCO FT/IR-470 plus Fourier transform infrared spectrometer.

Melting points (mp) were measured on an MP-5000D melting-point apparatus. Alpha-glucosidase (EC 3.2.1.20) was purchased from Oriental Yeast Co., Ltd (Tokyo, Japan). *p*-Nitrophenyl-α-D-glucopyranoside was purchased from Wako Pure Chemistry (Osaka, Japan). All solvents were purchased from Kanto Chemical (Tokyo, Japan).

3.2. Fungus materials

The fruiting bodies of *H. erinaceum* were collected in Hokkaido, Japan, in January 2010 and identified by the biotechnology laboratory at Kinki University.

3.3. Extraction and isolation

The fruiting bodies of *H. erinaceum* (1.2 kg) were extracted with EtOAc (3 l, two times) for 3 h. The solution was concentrated under reduced pressure. The EtOAc-soluble part (28.0 g) was fractionated by silica gel column chromatography with a hexane/EtOAc (17:3, 1:1, MeOH, v/v) to obtain four fractions: 1 (10.2 g), 2 (6.2 g), 3 (1.8 g), 4 (9.8 g). Fraction 1 (10.2 g) was separated by SiO_2 column chromatography with a CH_2Cl_2/EtOAc (9:1, v/v) to obtain five fractions. Compound **4** (840 mg) was obtained from fractions 1 to 4 (1.6 g) by crystallization (diethylether/ethanol). Compound **4** was identified as hericene A. Fraction 3 (1.8 g) was separated by SiO_2 column chromatography with CH_2Cl_2/EtOAc (9:1, 4:1, 0:1, MeOH, v/v) to obtain four fractions. Fraction 3-2 (240 mg) was further separated by SiO_2 column chromatography with a hexane/EtOAc (4:1, v/v) to afford compound **5** (40 mg). Fraction 3-3 (780 mg) was further separated by SiO_2 column chromatography with CH_2Cl_2/EtOAc (4:1, v/v) to afford compound **1** (172 mg). Fraction 4 (9.8 g) was further separated by SiO_2 column chromatography with hexane/acetone (4:1, 3:2, MeOH, v/v) to obtain three fractions. Fraction 4-3 (7.8 g) was further separated by SiO_2 column chromatography with CH_2Cl_2/acetone (4:1, 7:3, 3:2, MeOH, v/v) to obtain four fractions. Fraction 4-3-2 (426 mg) was further separated by SiO_2 column chromatography with CH_2Cl_2/acetone (3:2, v/v) to obtain two fractions. Compound **2** (72 mg) was obtained from fraction 4-3-2-1 (148 mg) by crystallization (hexane/acetone). Fraction 4-3-3 (1.5 g) was further separated by SiO_2 column chromatography with CH_2Cl_2/acetone (3:2, v/v) to obtain three fractions. Compound **3** was obtained from fraction 4-3-3-1 (420 mg) by crystallization (CH_2Cl_2/acetone).

3.4. Hydrolysis of compound 3

Compound **3** (132 mg, 0.32 mmol) was dissolved in 1 ml of methanol and 28% sodium methoxide (260 μl, 1.28 mmol) was added. The mixture was stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure to give white solid. The white solid was separated by silica gel column chromatography with a CH_2Cl_2/MeOH (9:1) repeatedly, to give D-arabinitol (39 mg, 0.26 mmol) and methyl linoleate (88 mg, 0.30 mmol). D-Arabinitol was identified by comparing with NMR data and specific rotation, while methyl linoleate was identified by comparing with MS spectrum and retention index (RI).

3.5. Synthesis of 1-D-arabinitol-monolinoleate

A mixture of D-arabinose (2.0 g, 13.3 mmol), tritylchloride (4.1 g, 14.7 mmol), triethylamine (3.3 ml, 24.0 mmol), dimethylaminopyridine (81.0 mg, 0.67 mmol), and THF (20 ml) was stirred at room temperature for 1 h. The mixture was poured into water and extracted with ethylacetate three times. The organic layer was washed with water, and dried on anhydrous sodium sulfate and the solvent was evaporated to afford 5-*O*-trityl-D-arabinose (2.0 g, yield 38.0%). 5-*O*-Trityl-D-arabinose (2.0 g, 5.1 mmol) was added to a mixture of methanol (20 ml) and ethanol (7 ml). The solution was kept in an ice bath at 0 °C and $NaBH_4$ (94 mg, 2.6 mmol) was added in small portions over a period of 30 min with constant stirring. After keeping it for 90 min, solvent was evaporated to afford pale yellow solid. The obtained solid was purified by column chromatography (CH_2Cl_2/MeOH, 9:1, v/v) on silica gel to afford 5-*O*-trityl-D-arabinitol (1.29 g, 64.0%). To a stirred solution of 5-*O*-trityl-D-arabinitol (500 mg, 1.27 mmol), linoleoyl chloride (490 μl, 1.52 mmol) in dichloromethane (15 ml) was added dimethylaminopyridine (8 mg, 0.065 mmol), and stirred at room temperature for 18 h. The solvent was evaporated under reduced pressure to give pale yellow solid. The obtained solid was column chromatographed on SiO_2

with CH_2Cl_2/MeOH (9:1, v/v) to give 1-linoleoyl-5-*O*-trityl-D-arabinitol (396 mg, 47%). 1-Linoleoyl-5-*O*-trityl-D-arabinitol (486 mg, 1 mmol) was added to a mixture of ethylacetate (4 ml) and formic acid (2 ml) and stirred at room temperature for 30 min. The reaction mixture was diluted with ethylacetate (10 ml), after neutralization with saturated sodium hydrogencarbonate solution, extracted with ethylacetate. The solvent was removed in vacuo and the remaining residue subjected to chromatography (silica gel, ethyl acatate/acetone=80:20) to afford 1-D-arabinitol-monolinoleate (200 mg, 58%) as white solid. Furthermore, 1-D-arabitniol-monolinoleate was crystallized from hexane/acetone.

3.6. Bioassay

3.6.1. α-Glucosidase inhibitory activity. α-Glucosidase inhibitory activity was determined using the modified version of the method according to Li et al.[25] α-Glucosidase (25 μl, 0.2 U/ml), 25 μl of various concentrations of samples, and 175 μl of 50 mM sodium phosphate buffer (pH 7.0) were mixed at room temperature for 10 min. The reaction was started by the addition of 25 μl of 2.5 mM *p*-nitrophenyl-α-D-glucopyranoside. The reaction mixture was incubated for 10 min at 37 °C. The activities of glucosidase were detected in 96-well plate, and the absorbance was determined at 405 nm (for *p*-nitrophenol) in a microplate reader (Corona Electric Co., Ltd). Control sample contained 25 μl DMSO in place of test samples. Percentage of enzyme inhibition was calculated as $(1-B/A)\times 100$, where A represents absorbance of control without test samples, and B represents absorbance in presence of test samples. All the tests were run in duplicate. Acarbose and 1-deoxynojirimycin were used as the positive control in this study. The fifty percent inhibitory concentration (IC_{50}) values were expressed as mean±SD, (n=3).

3.7. Compound 1

Isohericerin: colorless prisms; mp 157–158.5 °C; IR ν_{max} (KBr, cm^{-1}): 3419, 1646, 1589; HREIMS *m*/*z*: 419.2470 (calcd for $C_{27}H_{33}O_3N$: 419.2480, M^+). ^1H and ^{13}C NMR shown in Table 1.

3.8. Compound 2

N-De phenylethyl isohericerin: amorphous powder; mp 171–174 °C; IR ν_{max} (KBr, cm^{-1}): 3263, 1625, 1593; HREIMS *m*/*z*: 315.1829 (calcd for $C_{19}H_{25}O_3N$: 315.1759, M^+). ^1H and ^{13}C NMR shown in Table 1.

3.9. Compound 3

1-D-Arabinitol-monolinoleate: white amorphous powder; mp 100–102 °C; IR ν_{max} (KBr) cm^{-1}: 3304, 1731, 1593, 1447. $[\alpha]_D$ −0.99 (*c* 0.98, MeOH). ^1H NMR (DMSO-d_6, 700 MHz): 0.86 (3H, t, *J*=7.2 Hz, H-18′), 1.26–1.28 (10H, m, H-4′, H-5′, H-6′, H-16′, H-17′), 1.28–1.34 (4H, m, H-7′ and H-15′), 1.51 (2H, m, H-3′), 2.02 (4H, m, H-8′, H-14′), 2.28 (2H, t, *J*=7.4 Hz, H-2′), 2.74 (2H, m, H-11′), 3.24 (1H, m, H-3), 3.39 (1H, dd, *J*=11.2, 5.1 Hz, H-5a), 3.47 (1H, m, H-4), 3.59 (1H, dd, *J*=11.2, 3.4 Hz, H-5b), 3.88(1H, m, H-2), 3.97 (1H, dd, *J*=10.8, 5.6 Hz, H-1a), 4.01 (1H, dd, *J*=10.8, 7.4 Hz, H-1b), 5.31–5.34 (4H, m, H-9′, H-10′, H-12′ and H-13′). ^{13}C NMR (DMSO-d_6, 175 MHz): 14.1 (C-18′), 22.1 and 28.6–31.0 (C-4′, C-5′, C-6′, C-7′, C-15′, C-16′, C-17′), 24.6 (C-3′), 25.4 (C-11′), 26.8 (C-8′ and C-14′), 33.7 (C-2′), 63.7 (C-1), 65.9 (C-5), 67.5 (C-2), 70.8 (C-3), 71.2 (C-4), 127.9 and 129.9 (C-9′, C-10′, C-12′ and C-13′), 173.0 (C-1′).

3.10. Compound 4

Hericene A: white powder; mp 41–42 °C; IR ν_{max} (KBr, cm^{-1}): 3450, 1730, 1625, 1572; HREIMS *m*/*z*: 556.4132 (calcd for$C_{35}H_{56}O_5$: 556.4128, M^+). ^1H and ^{13}C NMR shown in Table 1.

3.11. Compound 5

4-[3′,7′-Dimethyl-2′,6′-octadienyl]-2-formyl-3-hydroxy-5-methyoxybenzylalcohol: yellow oil; IR ν_{max} (film, cm^{-1}): 3364, 1620; HREIMS *m*/*z* 318.4149 (calcd for $C_{19}H_{26}O_4$: 318.4144, M^+). ^1H and ^{13}C NMR shown in Table 1.

3.12. D-Arabinitol

$[\alpha]_D$ −6.8 (*c* 1.25, MeOH). ^1H NMR (D_2O 400 MHz): 3.45 (1H, dd, *J*=8.0, 2.0 Hz, H-3), 3.50–3.54 (3H, m, H-1a, H-1b, H-5a), 3.62 (1H, m, H-4), 3.70 (1H, dd, *J*=12.0, 2.0 Hz, H-5b), 3.80 (1H, m, H-2). ^{13}C NMR (D_2O, 100 MHz): 65.6 (C-5), 65.7 (C-1), 72.9 (C-2), 73.1 (C-3), 73.6 (C-4).

3.13. Methyl linoleate

MS (EI) *m*/*z* (%) 294$[M]^+$ (12), 263 (9), 164 (7), 150 (9), 136 (9), 124 (11), 123 (13), 110 (21), 109 (26), 96 (37), 95 (57), 81 (87), 67 (100), 55 (60), 41 (56). RI: 2093.

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