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A New Cytotoxic Prenylated Dihydrobenzofuran Derivative and Other Chemical Constituents from the Rhizomes of *Atractylodes lancea* DC

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A new prenylated dihydrobenzofuran derivative (**1**), was isolated from the rhizomes of *Atractylodes lancea* DC (Asteraceae), along with ten known compounds, including atractylenolide II (**2**), φ-taraxasteryl acetate (**3**), taraxerol acetate (**4**), β-sitosterol (**5**), stigmasterol (**6**), β-eudesmol (**7**), atractylenolide III (**8**), atractylenolide IV (**9**), daucosterol (**10**), and stigmasterol 3-O-β-D-glucopyranoside (**11**). The structure of the new compound (**1**) was elucidated as *trans*-2-hydroxyisoxypropyl-3-hydroxy-7-isopentene-2,3-dihydrobenzofuran-5-carboxylic acid by the combination of 1D, 2D NMR analysis and mass spectrometry, and it was the first reported 2,3-dihydrobenzofuran derivative having a carboxyl residue at C-5 and an isopentene moiety at C-7 contemporaneously. In addition, compound **1** exhibited significant cytotoxicity against cancer cell lines HCT-116 and MKN-45.

Key words: *Atractylodes lancea*, Asteraceae, Constituent, Atractylenolide, Dihydrobenzofuran, Cytotoxicity

INTRODUCTION

Atractylodes lancea DC (Asteraceae) is distributed only in Maoshan Moutain, Jiangsu province, China. Its rhizomes have been used for eliminating dampness, strengthening thespleen, expelling wind, and clearing away cold in traditional Chinese medicine for centuries (Qian *et al.*, 2006). As for the chemical constituents of the rhizome of *A. lancea*, many sesquiterpenoid glycosides (Kitajima *et al.*, 2003) and essential oil constituents (Takeda *et al.*, 1996; Kohjyouma *et al.*, 1997; Li *et al.*, 2006) were reported. During our research of the phytochemical constituents of the aquous ethanol extract of the rhizomes of *A. lancea*, a new prenylated dihydrobenzofuran derivative and ten known compounds were isolated. This paper describes the isolation and structure elucidation of all of eleven compounds, and the cell growth inhibitory effect on human acute colon cancer HCT-116 cells and human gastric cancer MKN-45 cells is also reported.

MATERIALS AND METHODS

General experimental procedures

Melting points were determined on an XT4A micro-melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer model 241 polarimeter. IR spectra were obtained on a Nicolet Impact infrared spectrophotometer with KBr pellets. NMR spectra were recorded on a Bruker DRX-500 spectrometer, using $CDCl_3$ and DMSO-d_6 as solvents. Chemical shifts are reported on the δ scale in parts per million, downfield from TMS. ESIMS were obtained on an Agilent 110 MSD mass spectrometer. EIMS data were obtained on a Shimadzu QP5050 mass spectrometer. Column chromatography were made on silica gel (100-200 mesh and 200-300 mesh, Marine Chemical Factory in Qingdao) and Sephadex LH-20 (Pharmacia); TLC were performed on precoated silica gel plates (HSG and HSF_{254}, Yantai Chemical Factory), and spots were detected by spraying with sulphuric acid reagent, followed by heating.

Plant material

The rhizomes of *A. lancea* DC was collected in the summer of 2004 from Maoshan Mountain of Jiangsu province, China, and was identified by Prof. Shihui Qian. After collection, the rhizomes were allowed to dry at ambient temperature for about one week and were then crushed and immediately extracted. A voucher specimen (No. JITCM-2004-806) is deposited in the herbarium of Jiangsu Institute of Traditional Chinese Medicine, Nanjing, China.

Extraction and isolation

The air-dried plant material (about 20.0 kg) was extracted

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with 80% ethanol under reflux for three times. After concentration, the dark green solution was partitioned with EtOAc and *n*-BuOH, successively. The *n*-BuOH extract (409.0 g) was chromatographed on a silica gel column with $CHCl_3$-CH_3OH (50:1→0:100, v/v) in a step-wise system. The fractions were pooled into three subfractions according to TLC analysis. Fraction 2 (76.3 g) was subjected to silica gel column chromatography ($CHCl_3$-CH_3OH, 100:1~100:20, v/v) and purified by Sephadex LH-20 (CH_3OH) chromatography to give compound **1** (30 mg). The EtOAc portion (322.0 g) was chromatographed on a silica gel column eluting with petroleum ether/EtOAc (100:1→0:100, v/v), and six fractions were collected according to TLC analysis. Fraction 2 (59.0 g) were subjected to silica gel column chromatography (petroleum ether-EtOAc, 100:2~100:100, v/v) to give **2** (32 mg), **3** (38 mg), and **4** (25 mg), respectively. Fraction 3 (150.0 g) was subjected to silica gel column chromatography (petroleum ether-EtOAc, 100:2~100:100, v/v) to give **5** (985 mg), **6** (78 mg), and **7** (21 mg), respectively. Fraction 4 (150.3 g) was subjected to silica gel column chromatography (CH_2Cl_2-CH_3OH, 100:1~100:20, v/v) to give **8** (35 mg) and **9** (18 mg). Fraction 5 (149.8 g) was also subjected to silica gel column chromatography (CH_2Cl_2-CH_3OH, 100:1~100:20, v/v) to give **10** (750 mg) and **11** (120 mg).

trans-2-Hydroxyisoxypropyl-3-hydroxy-7-isopentene-2,3-dihydrobenzofuran-5-carboxylic acid (1)

White needle (60% CH_3OH); mp 94-96ºC; $[\alpha]_D^{25}$ +45.5º (*c* 0.12, pyridine); UV λ_{max} (CH_3OH) nm (log ε): 211 (4.25), 264 (3.81); HR-ESI-MS *m/z* 329.1375 (calcd for $C_{17}H_{22}O_5Na$ $[M+Na]^+$, 329.1365); ^{1}H-NMR and ^{13}C-NMR see Table 1.

Aractylenolide II (2)

White needle (petroleum ether); mp 100-102ºC; ESI-MS *m/z* 230 $[M]^+$; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.61 (1H, s, H-9), 4.91 (1H, s, H-15), 4.63 (1H, s, H-15), 2.67 (1H, dd, *J*=16.7, 4.03 Hz, H-6α), 2.52 (1H, t, H-6β), 2.36 (1H, m, H-3β), 2.06 (1H, m, H-3α), 1.90 (3H, s, H-13), 1.71 (1H, m, H-2β), 1.66 (1H, m, H-2α), 1.64 (1H, m, H-1β), 1.60 (1H, m, H-1α), 0.94 (3H, s, H-14); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 39.1 (C-1), 22.7 (C-2), 36.2 (C-3), 148.2 (C-4), 48.4 (C-5), 171.3 (C-7), 119.1 (C-8), 148.1 (C-9), 38.1 (C-10), 120.5 (C-11), 179.9 (C-12), 8.5 (C-13), 18.6 (C-14), 107.4 (C-15).

φ-Traxasteryl acetate (3)

White needle (EtOAc); mp 238-240ºC; ESI-MS *m/z* 468 $[M]^+$; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.61 (1H, m, H-21), 4.47 (1H, m, H-3), 2.04 (3H, s, CH_3CO-), 1.04, 1.00, 0.95, 0.88, 0.86, 0.84, 0.74 (21H, m, 7×CH_3). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 38.9 (C-1), 23.5 (C-2), 81.0 (C-3), 37.9 (C-4), 55.6 (C-5), 18.7 (C-6), 33.7 (C-7), 41.3 (C-8), 49.2 (C-9), 37.4 (C-10), 21.3(C-11), 27.8 (C-12), 39.4 (C-13), 42.5 (C-14), 27.2 (C-15), 36.9 (C-16), 34.6 (C-17), 48.8 (C-18), 36.5 (C-19), 140.0 (C-20), 119.1 (C-21), 42.4 (C-22), 28.0 (C-23), 16.6 (C-24), 16.6 (C-25), 16.3 (C-26), 14.9 (C-27), 17.5 (C-28), 22.8 (C-29), 21.8 (C-30), 170.9 (-CO), 21.3 (-CH_3).

Traxerol acetate (4)

White needle ($CHCl_3$); mp 290-292ºC; ESI-MS *m/z* 468 $[M]^+$; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.52 (1H, dd, *J* = 8.4, 3.6 Hz, H-15), 4.45 (1H, dd, *J* = 10.0, 6.4 Hz, H-3), 2.02 (3H, s, CH_3), 1.06, 0.94, 0.92, 0.90, 0. 88, 0.83, 0.79 (24H, s, 8×CH_3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 37.5 (C-1), 23.4 (C-2), 80.9 (C-3), 37.6 (C-4), 55.5 (C-5), 18.6 (C-6), 41.1 (C-7), 38.9 (C-8), 49.1 (C-9), 37.8 (C-10), 17.4 (C-11), 33.3 (C-12), 37.3 (C-13), 157.9 (C-14), 116.9 (C-15), 33.0 (C-16), 38.9 (C-17), 48.6 (C-18), 35.0 (C-19), 29.8 (C-20), 33.6 (C-21), 29.9 (C-22), 27.9 (C-23), 16.5 (C-24), 15.4 (C-25), 25.9 (C-26), 21.3 (C-27), 28.7 (C-28), 35.7 (C-29), 27.9 (C-30), 171.0 (-CO), 21.2 (-CH_3).

β-Sitosterol (5)

White needle ($CHCl_3$); mp 142-143ºC; IR ν_{max}^{KBr} (cm^{-1}): 3352, 2917, 2849, 1463, 1382, 1059, 720, 713; EI-MS *m/z* (rel. int.): 414 (M^+, 87.50), 381 (30.25), 303 (41.21), 255 (32.54), 213 (39.87), 145 (42.69), 57 (63.54), 43 (100.00); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.35 (1H, d, *J* = 5.2 Hz, H-6), 3.51 (1H, m, H-3), 0.7~2.3 (38H, m), 0.99 (3H, s, H-19), 0.90 (3H, d, *J* = 9.5 Hz, H-21), 0.84 (6H, d, *J* = 6.6 Hz, H-26 and H-27), 0.82 (3H, t, *J* = 6.0 Hz, H-29), 0.68 (3H, s, H-18).

Stigmasterol (6)

White needle ($CHCl_3$); mp 168-171ºC; IR ν_{max}^{KBr} (cm^{-1}): 3415, 2956, 2940, 2869, 2854, 1642, 1455, 1382, 1369, 1040, 970; EI-MS *m/z* (rel. int.): 412 (M^+, 95.11), 396 (24.75), 351 (48.47), 300 (39.00), 271 (58.35), 255 (100.00), 229 (23.93), 213 (57.43), 187 (19.65), 173 (27.49), 159 (59.57), 147 (42.97), 133 (48.78)119 (34.62), 107 (43.58), 91 (39.10), 81 (57,13), 69 (44.09), 55 (63.95), 43 (33.60); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.35 (1H, d, *J* = 5.3 Hz, H-6), 4.95~5.20 (2H, m, H-22 and H-23), 3.53 (1H, m, H-3), 0.7~2.3 (34H, m), 0.99 (3H, s, H-19), 0.88 (3H, d, *J* = 9.0 Hz, H-21), 0.84 (3H, d, *J* = 6.1 Hz, H-29), 0.82 (6H, t, *J* = 6.4 Hz, H-26 and H-27), 0.69 (3H, s, H-18). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 37.3 (C-1), 31.7 (C-2), 71.8 (C-3), 39.7 (C-4), 140.8 (C-5), 121.7 (C-6), 42.3 (C-7), 31.9 (C-8), 50.2 (C-9), 36.5 (C-10), 21.1 (C-11), 39.8 (C-12), 42.2 (C-13), 56.9 (C-14), 24.4 (C-15), 28.9 (C-16), 56.0 (C-17), 12.3 (C-18), 19.0 (C-19), 40.5 (C-20), 21.2 (C-21), 138.3 (C-22), 129.3 (C-23), 51.2 (C-24), 31.9 (C-25), 19.4 (C-26 and C-27), 25.4 (C-28), 12.1 (C-29).

β-Eudesmol (7)

White needle (petroleum ether); 76-78ºC; ESI-MS *m/z*: 222 $[M]^+$; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.71 (1H, d, *J* = 1.5 Hz, H-11α), 4.45 (1H, d, *J* = 1.5 Hz, H-11β), 1.20 (6H, s, H-12 and H-13), 0.70 (3H, s, H-15); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 41.2 (C-1), 23.5 (C-2), 36.9 (C-3), 151.2 (C-4), 49.5 (C-5), 25.1 (C-6), 49.9 (C-7), 22.4 (C-8), 41.9 (C-9), 35.9 (C-10), 72.9 (C-11), 27.2 (C-12), 27.2 (C-13), 105.3 (C-14), 16.3 (C-15).

Atractylenolide III (8)

White needle ($CHCl_3$); mp 166-169ºC; ESI-MS *m/z*: 248 $[M]^+$; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.87 (1H, d, *J*=1.4 Hz, H-15), 4.60 (1H, d, *J* = 1.40 Hz, H-15), 2.64 (1H, m, H-6α), 2.44 (1H, m, H-6β), 2.36 (1H,m, H-3β), 2.25 (1H, d, *J* = 13.8 Hz, H-9β), 1.96 (1H, m, H-3α), 1.83 (3H, s, H-13), 1.82 (1H, m, H-5), 1.67 (1H, m, H-2β), 1.66 (1H, m, H-2α), 1.65 (1H, m, H-1β), 1.57 (1H, d, *J* = 4.5 Hz, H-9α), 1.25 (1H, m, H-1α), 1.03 (3H, s, H-14); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 41.4 (C-1), 22.4 (C-2), 36.1 (C-3), 148.5 (C-4), 51.4 (C-5), 24.6 (C-6), 160.6 (C-7), 103.3 (C-8), 51.7 (C-9), 36.7 (C-10), 122.3 (C-11), 171.8 (C-12), 8.2 (C-13), 16.6(C-14), 106.3 (C-15).

Atractylenolide IV (9)

White needle ($CHCl_3$); mp 210-212ºC; ESI-MS *m/z*: 288 $[M]^+$; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.99, 5.03 (1H each, brs, H-15), 2.14 (3H, s, -$COCH_3$), 1.82 (3H, s, H-13), 1.06 (3H, s, H-14); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 38.8(C-1), 21.0 (C-2), 73.8 (C-3), 145.6 (C-4), 49.9 (C-5), 24.2 (C-6), 159.7 (C-7), 103.0 (C-8), 50.6 (C-9), 36.4 (C-10), 122.9 (C-11), 171.6 (C-12), 8.27 (C-13), 16.6 (C-14), 104.7 (C-15), 170.0(-CO).

Daucosterol (10)

White powder; mp 288-290ºC; IR ν_{max}^{KBr} (cm^{-1}): 3414, 2958, 2935, 2869, 1700, 1600, 1464, 1444, 1379, 1161, 1103, 1075, 1024; ESI-MS *m/z*: 576 $[M]^+$; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 5.35 (1H, d, *J* = 5.2 Hz, H-6), 4.22 (1H, d, *J* = 7.7 Hz, H-1'), 2.80~3.70 (m, sugar protons), 3.40 (1H, m, H-3), 0.7~2.3 (38H, m), 0.99 (3H, s, 19-H), 0.90 (3H, d, *J* = 9.5 Hz, H-21), 0.84 (6H, d, *J* = 6.6 Hz, H-26, and H-27), 0.82 (3H, 3H, t, *J* = 6.0 Hz, H-29), 0.68 (3H, s, H-18).

Stigmasterol 3-O-β-D-glucopyranoside (11)

White powder; IR ν_{max}^{KBr} (cm^{-1}): 3390, 2954, 2870, 1455, 1382, 1368, 1164, 1074, 1030, 970; ESI-MS *m/z*: 574 $[M]^+$; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 5.35 (1H, d, *J* = 5.3 Hz, H-6), 4.95~5.20 (2H, m, H-22 and H-23), 4.20 (1H, d, J=7.8 Hz), 2.80~3.70 (m, sugar protons), 3.40 (1H, m, H-3), 0.7~2.3 (34H, m), 0.99 (3H, s, H-19), 0.88 (3H, d, *J* = 9.0 Hz, H-21), 0.84 (3H, d, *J* = 6.1 Hz, H-29), 0.82 (6H, t, *J* = 6.4 Hz, H-26),

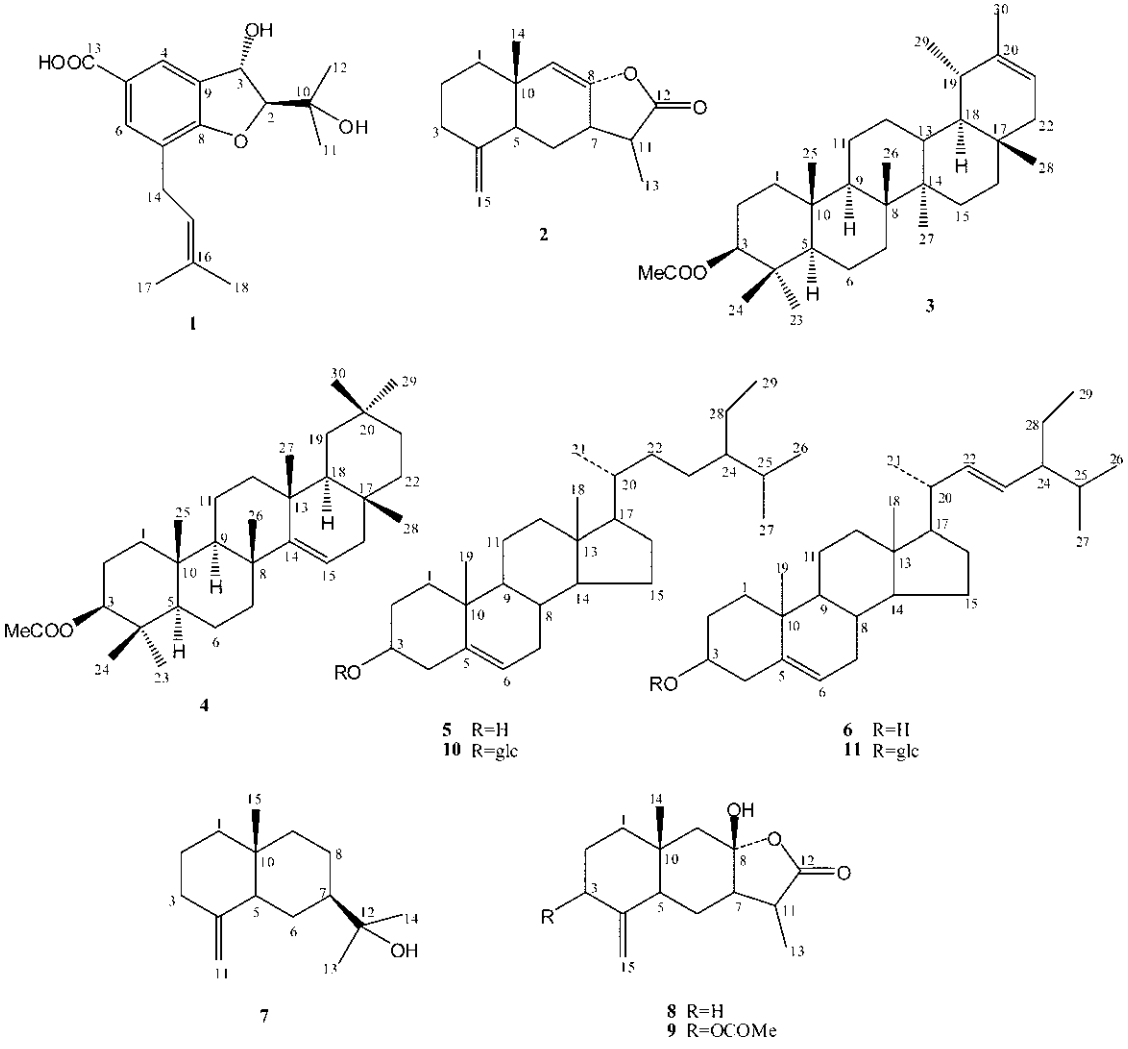

Fig. 1. Structures of **1-11** from the rhizomes of *A. lancea*

0.69 (3H, s, H-18).

Cytotoxicity assay

The cytotoxicity against human colon cancer HCT-116 cells and human gastric cancer MKN-45 cells were evaluated by sulforhodamine B (SRB) protein assay (Skehan *et al*., 1990). Dose response curves were plotted for the samples and the IC_{50} values were calculated as the concentrations of the test compound **1** resulting in 50% reduction of absorption compared to the control cells.

RESULTS AND DISCUSSION

From the 80% ethanol extract of the rhizomes of *A. lancea*, a new prenylated dihydrobenzofuran derivative was isolated, together with ten known compounds (Fig. 1).

Compound **1** was appeared as white needles with mp 94-96 °C and was assigned a molecular formula of $C_{17}H_{22}O_5$ on the basis of positive HR-ESI-MS ($[M+Na]^+$ *m/z* 329.1375). The ^{1}H-NMR spectrum exhibited characteristic signals for a 1,3,4,5-tetrasubstituted aromatic system at δ 7.63 (1H, d, *J* = 1.6 Hz) and 7.75 (1H, d, *J* = 1.3 Hz). Furthermore, two hydroxymethine protons at δ 4.21 (1H, d, *J* = 3.9 Hz) and 5.21 (1H, brd, *J* = 3.6 Hz), and two methyl groups at δ 1.08 (3H, s) and 1.18 (3H, s) were observed. These findings hinted a dihydrobenzofuran skeleton similar to toxol derivatives with a hydroxyl- isopropyl residue at C-2 and a hydroxyl group at C-3 (Bohlmann *et al.*, 1985; Sigstad *et al.*, 1996; Friedrich *et al.*, 2005).

Analysis of ^{1}H- and ^{13}C-NMR spectral data also revealed the presence of an isopentene group (Crichton and Waterman, 1978), the ^{1}H-NMR signals at δ 3.28 (2H, m), 5.28 (1H, m), 1.70 (3H, s), and 1.69 (3H, s), were assigned as H-14, H-15, H-17, and H-18, respectively. The chemical shifts of a methylene carbon at δ 27.7, two olefinic carbons at δ 121.6 and 132.4, and two methyl carbons at δ 25.6 and 17.8, respectively, were assigned as C-14, C-15, C-16, C-17, and C-18 in the HMQC spectrum. The long-range correlation between the methylene protons at δ 3.28 (2H, m) and C-7 (δ 122.8) indicated the isopentene group to be at C-7 (Fig. 2). A ^{13}C-NMR signal at δ 167.3 was assigned to the carboxyl carbon, whereas the carboxyl carbon showed three-bond correlations with H-4 at δ 7.75 (1H, d, *J* = 1.3 Hz) and H-6 at δ 7.63 (1H, d, *J* = 1.6 Hz) in HMBC spectrum (Table 1). These data revealed the presence of a carboxyl moiety at C-5.

The relative stereochemistry of the positions 2 and 3 could be deduced from the coupling constants, which should be 7.0 Hz in case of a *cis*-configuration and <5.0 Hz in *trans*-derivatives (Kawasaki *et al.*, 1984; Sigstad *et al.*, 1996; Friedrich *et al.*, 2005). As a coupling constant of $J_{2,3} < 4.0$ Hz was observed in **1**, the dihydrofuran ring had to be 2,3-*trans*-configurated. All of these data were used to assign **1** as *trans*-2-hydroxyisoxypropyl-3-hydroxy-7-isopentene-2,3-dihydrobenzofuran-5-carboxylic acid. The structure was shown in Fig. 1.

To date, only *trans*-configuration at 2,3-position was reported in 2,3-dihydrobenzofuran derivatives (Bohlmann *et al.*, 1985; Sigstad *et al.*, 1996; Friedrich *et al.*, 2005), and three derivatives with 2-hydroxyisoxypropyl residue and 3-hydroxyl group have been isolated from *Piper hispidum* and *Ophryosporus lorentzii* (Sigstad *et al.*, 1996; Friedrich *et al.*, 2005). To the best of our knowledge, **1** was the first reported 2,3-dihydrobenzofuran derivative having a carboxyl residue at C-5 and an isopentene moiety at C-7 contemporaneously.

Compounds **2-11** were identified as atractylenolide II (**2**; Hikino *et al.*, 1964), φ-taraxasteryl acetate (**3**; Ling *et al.*, 2000), taraxerol acetate (**4**; Patra *et al.*, 1981; Yang *et al.*,

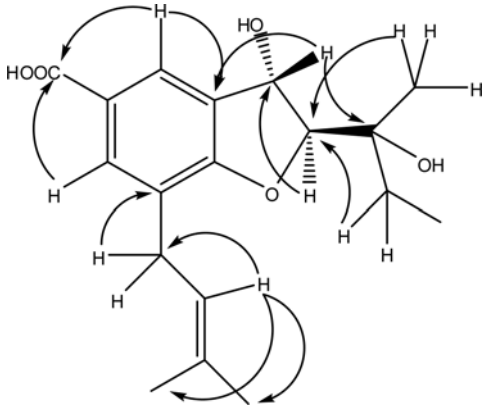

Fig. 2. Selected ^{1}H-^{13}C long-range correlations in HMBC spectrum of **1**

Table 1. ^{1}H- and ^{13}C-NMR spectral assignments (δ/ppm) for compound **1** in DMSO-d_6[a]

Position	δ_C	δ_H	HMBC (HC)
2	97.5	5.21(1H, brd, 3.6)	C-3
3	71.2	4.21(1H, d, 3.9)	C-4, C-10
4	125.0	7.75(1H, d, 1.3)	C-8, C-9, C-13
5	130.5		
6	131.0	7.63(s)	C-4, C-8, C-13, C-14
7	122.8		
8	161.8		
9	122.9		
10	69.9		
11	26.0	1.18 (3H, s)	C-2, C-10, C-12
12	25.0	1.08 (3H, s)	C-2, C-10, C-11
13	167.3		
14	27.7	3.28 (2H, m)	C-7
15	121.6	5.28 (1H, m)	C-14, C-17, C-18
16	132.4		
17	25.6	1.70 (3H, s)	C-15, C-16, C-18
18	17.8	1.69 (3H, s)	C-15, C-16, C-17
HOOC-		12.43 (1H, brs)	

[a] All assignments based on extensive 1D and 2D NMR measurements; TMS was used as the internal standard; integrals, multiplicities and coupling constants (*J* in hertz) in parentheses.

Table 2. Cytotoxicity of compound **1** against HCT-116 and MKN-45 cell lines[a]

Cell lines	1	HCP[b]
HCT-116	0.402±0.012	0.136±0.006
MKN-45	0.525±0.073	0.167±0.016

[a] IC_{50}, μmol/L; IC_{50} is mean of at least 3 determinations±S.D.
[b] 10-Hydroxycamptothecin (HCP) as positive control.

2000), β-sitosterol (**5**; Zheng *et al.*, 2000), stigmasterol (**6**; Bai *et al.*, 1985), β-eudesmol (**7**; Zhao *et al.*, 1995), atractylenolide III (**8**; Hikino *et al.*, 1964), atractylenolide IV (**9**; Hikino *et al.*, 1964), daucosterol (**10**; Jares et al., 1990; Zheng *et al.*, 2000), and stigmasterol 3-O-β-D-glucopyranoside (**11**; Lou *et al.*, 1989) by comparing the spectral data with those of reported in literatures.

The cytotoxicity of **1** against HCT-116 and MKN-45 cancer cells was evaluated in the experiment. Its IC_{50} values were measured on the basis of cell viability after 72 h treatment. Our results (Table 2) indicated that **1** exhibited significant cytotoxicity against the two cell lines with IC_{50} values at 0.402 μM and 0.525 μM, respectively. Based on these initially promising results, **1** is worth to be further studied as potential anticancer agent.

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