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Three New Dammarane Glycosides from Heat Processed Ginseng

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Three new dammarane glycosides were isolated from the processed ginseng (SG; Sun Ginseng). Their structure were determined to be 3β,12β-dihydroxydammar-20(21),24-diene-3-O-β-D-glucopyranosyl(1 → 2)-β-D-glucopyranoside; 3β,12β-dihydroxydammar-20(21),24-diene-3-O-β-D- glucopyranoside and 3β,6α,12β-trihydroxydammar-20(21),24-diene-6-O-β-D-glucopyranoside based on spectroscopic evidences. The compounds were named as ginsenoside Rk_1, Rk_2, and Rk_3 respectively.

Key words: *Panax ginsneg*, Ginsenoside, Dammarane glycoside

INTRODUCTION

Ginseng (*Panax ginseng* C. A. Meyer, Araliaceae) is one of the most popular herbal medicines in the Orient (Han, 1988). Thousands of papers reported its chemical constituents, biological activities, and cultivation. Two kind of ginseng is commercially available, one is white ginseng and the other is red ginseng. White ginseng is dried ginseng, while red ginseng is steamed and dried ginseng. The most well known chemical constituent of ginseng is ginsenoside, which is a dammarane glycoside. More than 30 ginsenosides were reported from ginseng so far (Baek *et al.*, 1996, Kim *et al.*, 1995, Kim, Baek *et al.*, 1991, Kim, Park *et al.*, 1991, Sanata *et al.*, 1974[a], Sananta *et al.*, 1974[b]). Ginsenosides Rb_1, Rb_2, Rc, Rd, Rg_1, Rg_2, and Re are major constituents of white and red ginsengs, while ginsenosides Rg_3, Rg_5, and Rg_6 are known to be unique constituents of red ginseng (Kim *et al.*, 1996, Kitagawa *et al.*, 1983, Ryu *et al.*, 1997). Recently we reported that steaming ginseng at high temperature increase the radical scavenging and vasodilating activities (Kim *et al.*, 2000). It also exhibited anti-tumor promoting activity (Keum *et al.*, 2000). In the course of study on the chemical constituents of heat processed ginseng (SG; Sun Ginseng), we solated three new dammarane glycosides which have a double bond at C-20(21) position.

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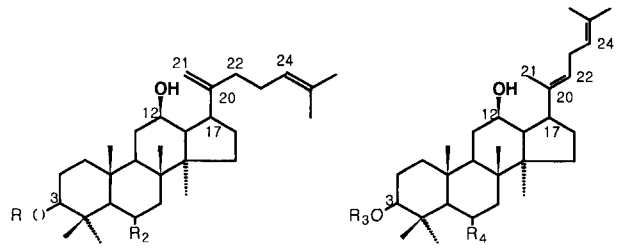
MATERIALS AND METHODS

^{1}H-NMR and ^{13}C-NMR spectra were recorded on AMX 500 NMR spectrometer (Bruker, Rheinstetten Silberstreifen, Germany), LAMBDA 300 spectrometer (Jeol, Tokyo, Japan) or JNM-GSX 400 spectrometer (Jeol, Tokyo, Japan). AX 505WA double focusing mass spectrometer (Jeol, Tokyo, Japan), DIP-360 polarimeter (Jasco, Tokyo, Japan) and 1710 IR spectrometer (Perkin-Elmer, Beaconsfield, U.K.) were used. Ag-impregnated TLC plate was prepared by spraying 3% $AgNO_3$ in MeOH.

Isolation of ginsenosides

Dried rootlet of ginseng (3 kg) was steamed at 120°C for 3 hours in an autoclave. Steamed ginseng was extracted with MeOH (10 L) three times under reflux for 2hrs. The solvent was removed in vacuo to yield 0.4 kg of MeOH extract, which was suspended in water (5 L) and extracted with CH_2Cl_2 (10 L). The remaining aqueous layer was extracted with water-saturated n-BuOH (10 L) three times. The n-BuOH fraction was concentrated in vacuo to yield 0.3 kg of BuOH fraction, which was subjected to silica gel column chromatography. Five fractions were obtained using stepwise gradient elution (EtOAc:MeOH:H_2O = 40:1:1 → 10:1:1).



	R_1	R_2		R_3	R_4
Ginsenoside Rk_1	Glc-Glc-	H	Ginsenoside Rg_5	Glc-Glc-	H
Ginsenoside Rk_2	Glc-	H	Ginsenoside Rh_3	Glc-	H
Ginsenoside Rk_3	H	O-Glc	Ginsenoside Rh_4	H	O-Glc

Fig 1. Structure of ginsenoside Rg_5, Rh_3, Rh_4, Rk_1, Rk_2 and Rk_3

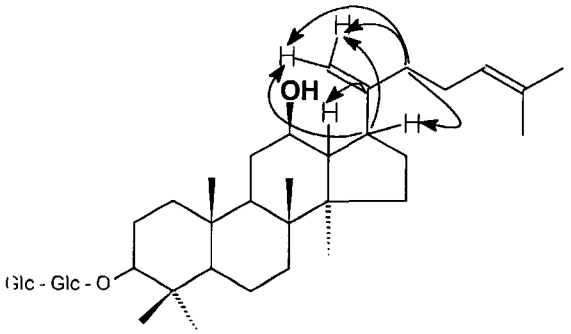


Fig 2. Key long-range ^{13}C-^{1}H NMR (HMBC) for compound **1** (ginsenoside Rk_1)

Isolation of compound 1 (ginsenoside Rk_1)

Fraction 4 was chromatographed over silica gel using EtOAc:MeOH:H_2O=20:1:1 solvent. Compound **1** rich fraction was obtained, which was further purified on Ag-impregnated preparative TLC using EtOAc:MeOH:H_2O = 10:1:1 solvent. The band was visualized by spraying water. Compound **1** was collected from the band of Rf=0.3, which was further purified over semi-preparative HPLC using reverse phase column (LiChrospher 100 RP-18, 250 mm × 10 mm i.d.) with 60% CH_3CN eluent. Thirty mg of purified compound **1** was obtained.

Compound **1** : Amorphous powder, $C_{42}H_{70}O_{12}$, mp: [178-181°C] , $[\alpha]_D$: +11.0° (MeOH, c= 0.2%, 20°C); IR ν_{max} (KBr, cm^{-1}): 3400, 2944, 1655, 1457, 1389, 1078. Mass (FAB$^+$, 6 kV, Xe, glycerol): 789 ([M+Na]$^+$). ^{1}H-NMR (400 MHz, C_5D_5N, ppm) : 0.62 (1H, d, J=11.47 Hz, H-5), 0.72 (3H, s, Me-19), 0.91 (3H, s, Me-30), 1.95 (3H, s, Me-18), 1.02 (3H, s, Me-29), 1.31 (3H, s, Me-28), 1.49 (3H, s, Me-27), 1.61 (3H, s, Me-26), 2.77 (1H, m, H-17), 3.23 (1H, dd, J=11.76, 4.37 Hz, H-3), 3.89 (3H, H-12, 5',5"), 4.83 (1H, d, J=7.53 Hz, H-1), 4.86 (1H, br. s, H-21), 5.13 (1H, br. s, H-21), 5.23 (1H, br.t, J=6.68 Hz, H-24), 5.33 (1H, d, J=7.71 Hz, H-1"). ^{13}C-NMR (125 MHz, C_5D_5N, ppm) : Table I.

Isolation of Compound 2 (ginsenoside Rk_2)

Fraction 2 was chromatographed over silica gel using n-Hexane: Isopropyl alcohol=6:1 solvent. Resulted compound **2** was further purified using semi-preparative HPLC (Column: LiChrospher 100 RP-18, 250 mm × 10 mm i.d., Merck; Eluent: 80% CH_3CN). Twenty mg of compound **2** was obtained.

Compound **2** : $C_{36}H_{60}O_7$, amorphous powder, mp: [163-165°C], $[\alpha]_D$: + 13.1° (MeOH, c= 0.3%, 20°C), IR ν_{max} (KBr, cm^{-1}) : 3423, 2943, 1637, 1458, 1021. Mass (FAB$^+$, 6 kV, Xe, glycerol): 627 ([M+Na]$^+$). ^{1}H-NMR (400 MHz, C_5D_5N, ppm): 0.77 (1H, d, J=10.5, H-5), 0.82 (3H, s, Me-19), 0.99 (3H, s, Me-30), 1.02 (3H, s, Me-29), 1.04 (3H, s, Me-18), 1.33 (3H, s, Me-28), 1.62 (3H, s, Me-27), 1.68 (3H, s, Me-26), 2.85 (1H, m, H-17), 3.40 (1H, dd, J=11.5, 4.5 Hz, H-3), 3.93 (1H, m, H-12), 4.94 (1H, br. s, H-21$_a$), 4.95 (1H, d, J=7.82 Hz, H-1'), 5.19 (1H, br. s, H-21$_b$), 5.31 (1H, br. t, J=6.9 Hz, H-24). ^{13}C-NMR (100 MHz, C_5D_5N, ppm) : Table I.

Isolation of compound 3 and 4 (ginsenoside Rk_3 and ginsenoside Rh_4)

Fraction 3 was chromatographed over silica gel using EtOAc:MeOH:H_2O=40:1:1 solvent. Compound **3** and **4** was obtained as a mixture. Two compounds were separated by Ag-impregnated preparative TLC using EtOAc:MeOH:H_2O=10:1:1 solvent. The bands were visualized by spraying water. Compound **3** and **4** were collected from the band at Rf=0.35 and 0.40, respectively. Two compounds were further purified using semi-preparative HPLC (Econosphere C18, 250 mm × 10 mm , 40% CH_3CN). Twenty mg of compound **3** and 100 mg of compound **4** were obtained.

Compound **3** : $C_{42}H_{70}O_{12}$, amorphous powder, mp : [145-147°C], $[\alpha]_D$: +19.6° (MeOH, c= 0.4%, 20°C), IR ν_{max} (KBr, cm^{-1}) : 3390, 2928, 1652, 1455, 1023. Mass (FAB$^+$, 6kV, Xe, glycerol) : 643 ([M+Na]$^+$). ^{1}H-NMR (500 MHz, C_5D_5N, ppm) : 0.93 (3H, s, Me-30), 1.05 (3H, s, Me-19), 1.30 (3H, s, Me-18), 1.60 (3H, s, Me-29), 1.67 (3H, s, Me-27), 1.74 (3H, s, Me-26), 2.05 (3H, s, Me-28), 2.53 (1H, dd, J=12.76, 3.27 Hz, H-7$_a$), 2.77 (1H, m, H-17), 3.56 (1H, dd, J=11.5, 4.5 Hz, H-3), 3.98 (1H, m, H-12) 4.97 (1H, br. s, H-21$_a$), 5.01 (1H, d, J=7.8 Hz, H-1'), 5.23 (1H, br. s, H-21$_b$), 5.34 (1H, t, J=6.8 Hz, H-24). ^{13}C-NMR (125 MHz, C_5D_5N, ppm) : Table I.

Compound **4** : $C_{42}H_{70}O_{12}$, amorphous powder, mp : [155-157°C], $[\alpha]_D$: +26.9° (MeOH, c=0.5%, 20°C), IR ν_{max} (KBr, cm^{-1}) : 3390, 2928, 1650, 1385, 1022. Mass (FAB$^+$, 6 kV, Xe, glycerol) : 643 ([M+Na]$^+$). ^{1}H-NMR (500 MHz, C_5D_5N, ppm) : 0.80 (3H, s, Me-30), 1.02 (3H, s, Me-19), 1.21 (3H, s, Me-18), 1.56 (3H, s, Me-29), 1.60 (3H, s, Me-27), 1.61

Table I. ^{13}C-NMR chemical shift of ginsenoside Rg_5, Rh_3 and compound **1,2,3,4**

C No.	Rg_5	Compound **1** (Rk1)	Rh_3	Compound **2** (Rk2)	Compound **4** (Rh4)	Compound **3** (Rk3)
1	39.17	39.30	39.22	39.44	39.44	39.50
2	28.00	26.75	28.10	26.92	27.80	27.92
3	88.82	88.95	88.72	88.95	78.52	78.56
4	40.14	39.72	40.22	39.86	40.27	40.37
5	56.29	56.43	56.35	56.57	61.36	61.44
6	18.33	18.45	18.41	18.63	79.97	80.05
7	35.24	35.36	35.29	35.50	45.22	45.31
8	39.60	40.21	39.65	40.38	41.25	41.26
9	50.66	48.23	50.72	51.02	50.50	50.64
10	36.91	37.03	37.02	37.23	39.66	39.71
11	32.10	32.60	32.19	32.88	32.18	32.73
12	72.49	72.47	72.51	72.59	72.51	72.42
13	50.33	52.49	50.41	52.63	50.59	52.07
14	50.91	51.21	50.98	51.38	50.77	51.13
15	32.54	32.67	32.59	32.78	32.47	32.50
16	26.64	30.77	26.70	30.95	28.74	30.71
17	50.80	50.86	50.86	48.44	50.32	48.27
18	16.35	16.45	16.42	15.97	17.31	17.33
19	16.49	15.80	16.75	16.64	17.67	17.73
20	140.06	155.55	140.12	155.71	140.01	155.42
21	13.07	108.15	13.13	108.28	13.07	108.11
22	123.21	33.89	123.78	34.01	123.42	33.70
23	27.35	27.08	27.41	27.22	27.38	27.02
24	123.54	125.33	124.53	125.52	123.78	125.33
25	131.16	131.21	131.22	131.38	131.18	131.18
26	25.60	25.74	25.66	25.92	25.64	25.74
27	17.66	17.74	17.68	17.91	17.67	17.33
28	28.73	28.11	28.80	28.32	31.63	31.70
29	15.72	16.58	15.78	16.95	16.27	16.34
30	16.92	16.98	17.00	17.16	16.73	16.73
1'	105.00	105.09	106.93	107.16	105.87	106.00
2'	83.31	83.45	75.75	75.98	75.34	75.45
3'	78.13	78.19	78.72	78.95	79.50	79.65
4'	71.50	71.65	71.83	72.07	71.71	71.82
5'	77.82	77.96	78.34	78.57	77.98	78.12
6'	62.58	62.76	63.04	63.27	62.96	63.06
1	105.91	106.01				
2	77.00	77.08				
3	78.21	78.34				
4	71.53	71.72				
5	77.98	78.06				
6	62.73	62.87				

(3H, s, Me-26), 1.80 (3H, s, Me-21), 2.05 (3H, s, Me-28), 2.50 (1H, dd, J=12.64, 2.83 Hz, H-7), 2.75 (3H, H-23, 17),

3.5' (1H, dd, J=11.53, 4.6 Hz, H-3), 5.00 (1H, d, J=7.78 Hz, H-1'), 5.20 (1H, br.t, H-24), 5.45 (1H, br.t, H-22). ^{13}C-NMR (75 MHz, C_5D_5N, ppm) : Table I.

RESULTS AND DISCUSSION

Compound 1 (ginsenoside Rk_1)

Compound **1** was isolated as amorphous powder. This compound was not separated from ginsenoside Rg_5 on normal silica gel TLC plate or HPLC using amino column. Compound **1** was separated from ginsenoside Rg_5 on $AgNO_3$-impregnated silicagel TLC plate or reverse phase HPLC. Two anomeric carbon signals at 105.09 and 106.01 ppm, and signals between 60-90 ppm in its ^{13}C-NMR spectrum suggested that compound **1** is a protopanaxadiol type ginsenoside with two sugar moieties. Four olefinic carbon signals at δ_C 155.55, 131.21, 125.33, and 108.15 ppm suggested two double bonds in the molecule. Molecular weight of compound **1** was 766 which is same to that of ginsenoside Rg_5, suggesting compound **1** is a dehydrated compound of ginsenoside Rg_3 (MW=784). ^{13}C-NMR signals of compound **1** are quiet similar to that of ginsenoside Rg_5 (Table I). However, methyl carbon signal arising from C-21 which appeared at 13.07 ppm in Rg_5, was not observed. Methylene carbon signal at δ_C 108.15 ppm showed correlation spots with protons at δ_H 5.13 (H-21) and 4.86 (H-21) ppm in ^{13}C-^{1}H COSY spectrum. These two proton signals showed connections with carbon signals at δ_C 33.89 (C-22), and 50.86 (C-17) ppm in heteronuclear multiple bond connection (HMBC) spectrum. δ_C 33.89 signal showed connection with H-17. Thus, the signals at δ_C 33.89 and 108.15 ppm were assigned to be the signals of C-22 and C-21, respectively. Olefinic carbon at δ_C 155.55 ppm, which was assigned as C-20, showed connections with H-13, H-17, and H-22. Therefore it was concluded that, besides a double bond between C-24 and 25, compound **1** has one more double bond between C-20 and 21. Thus, the structure of compound **1** was elucidated to be 3β,12β-dihydroxydammar-20(21),24-diene-3-O-β-D-glucopyranosyl(12)-β-D-glucopyranoside. Since the compound is not reported yet, we named it as ginsenoside Rk_1.

Compound 2 (ginsenoside Rk_2)

Molecular weight of 2 was 604 corresponding one glucose unit difference, i.e. 162 amu, with compound **1**. ^{13}C and ^{1}H NMR spectra of compound **2** were very similar to that of compound **1** including four olefinic carbon signals at δ_C 155.71, 131.38, 125.52, and 108.28 ppm (Table I). However, compound **2** has only one anomeric carbon signal suggesting one glucose moiety in the molecule. Methylene carbon signal at δ_C 108.28 ppm exhibited correlation spot with protons at δ_H 5.19 (H-21) and 5.31 (H-21) ppm in ^{13}C-^{1}H COSY spectrum. These two proton signals showed connections with carbon signals at δ_C 34.01 (C-22) and δ_C 48.44 (C-17) in HMBC spectrum. Carbon signal at δ_C 34.01 showed correlation with H-23 signal. Thus, two carbon signals at δ_C 34.01 and 108.28 ppm were assigned to be C-22 and C-21, respectively. Carbon signal at δ_C 155.71, which showed correlation with H-13, was assigned to be C-20. Therefore it was concluded that compound **2** is a mono-deglycosylated compound of compound **1**, or dehydrated compound of ginsenoside Rh_2 at C-20 position bearing new double bond between C-20 and 21. Thus, the structure of compound **2** was elucidated to be 3β,12β-dihydroxydammar-20(21),24-diene-3-O-β-D-glucopyranoside and named as ginsenoside Rk_2.

Compound 3 (ginsenoside Rk_3)

Molecular weight of 3 was 620, suggesting one more hydroxyl group than compound **2**, i.e., protopanaxatriol type ginsenoside. Signal at δ_C 80.05 arising from oxygenated carbon at C-6 supported the assumption. One anomeric carbon signal at δ_C 106.00 ppm and signals between δ_C 60-80 ppm suggested that compound 3 has one sugar moiety. Four olefinic carbon signals at δ_C 155.42, 131.18, 125.33, and 108.11 ppm suggested two double bonds at △20(21) and △24(25). Methylene carbon signal at δ_C 108.11 ppm showed correlation with protons at δ_H 5.23 (H-21) and 4.97 (H-21) ppm in ^{13}C-^{1}H COSY spectrum. These two proton signals showed connections with carbon signals at δ_C 33.70 (C-20) and 48.27 (C-17) ppm in HMBC spectrum. Signal at δ_C 33.70 ppm showed connection with H-23 and H-17. Thus, the signals at δ_C 33.70 and 108.11 ppm were assigned as C-22 and C-21, respectively. Olefinic carbon at δ_C 155.42 ppm, which was assigned as C-20, showed connections with H-13, H-17, and H-22. Therefore, the structure of compound **3** was elucidated to be 3β,6α,12β-trihydroxydammar-20(21),24-diene-6-O-β-D-glucopyranoside and named as ginsenoside Rk_3.

Compound 4 (ginsenoside Rh_4)

Molecular weight of compound **4** was same to compound **3**. Only one anomeric carbon signal was observed at δ_C 105.87 ppm and signals at δ_C 60~80 ppm suggested that compound **4** has one sugar moiety (Table I).

Four olefinic carbon signals at δ_C 140.01, 131.18, 123.78, and 123.42 ppm suggested two double bonds at C-20(22) and C-24(25) in the molecule. Thus, this compound is supposed to be an isomer of compound **3**. Signal at δ_H 2.75 ppm showed correlation with olefinic proton at δ_H 5.45 ppm and H-24 proton at δ_H 5.20 ppm in ^{1}H-^{1}H COSY spectrum. Therefore the signals at at δ_H 2.75

ppm and δ_H 5.45 ppm were assigned as H-23 and H-22, respectively. Signal at δ_C 140.01 ppm showed connections with proton signals at δ_H 1.80 (H-21) and δ_H 2.75 (H-17), and signal at δ_C 123.42 ppm with δ_H 1.80 (H-21) and δ_H 2.75 (H-23). Therefore signals at δ_C 140.01 and 123.42 were assigned to be C-20 and C-22, respectively. Above results suggested that compound **4** has a double bond between C-20 and C-22. Thus, the structure of compound **4** was elucidated to be 3β,6α,12β-trihydroxydammar-20(22),24-diene-6-O-β-D-glucopyranoside, which has been reported as ginsenoside Rh_4.

However, compared to ^{13}C-NMR data of ginsenoside Rh4 in the reference (Kim *et al.*, 1995), different signals were observed. Therefore, reassignment was carried out using ^{1}H-^{1}H COSY, ^{13}C-^{1}H COSY, HMBC, proton decoupling, and NOESY spectrum. Connections were observed in (C-21, H-17), (C-29, H-3), (C-27, H-26), (C-23, H-22), (C-8, H-18), (C-7, H-18), (C-17, H-21), (C-6, H-1'), (C-24, H-22), and (C-25, H-23). Ginsenoside Rh_4 and compound **3** were not separated by the method described in the reference. Two compounds were only separated on $AgNO_3$-impregnated silicagel TLC plate or reverse phase HPLC. We believe that ginsenoside Rh_4 in the reference is a mixture of Rh_4 and compound **3**.

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