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Guaiane-type Sesquiterpene Lactones from *Chrysophthalmum montanum*

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Abstract: Four new guaiane-type sesquiterpene glycosides (**1-4**), 4*α*-hydroxy-guai-1(10)-en-12,8*α*-olide 2*β*-*O*-*β*-D-glucopyranoside (**1**), 4*α*-hydroxy-guai-1(10)-en-12,8*α*-olide 2*β*-*O*-(6′-*trans*-caffeoyl)-*β*-D-glucopyranoside (**2**), 10*α*-hydroxy-guai-1(2)-en-12,8*α*-olide 4*α*-*O*-*β*-D-glucopyranoside (**3**) and 10*α*-hydroxy-guai-12,8*α*-olide 4*β*-*O*-*β*-D-glucopyranoside (**4**) and three known guaiane-type sesquiterpenes (**5-7**), 4*α*,6*α*-dihydroxy-1*β*,5*α*,7*αH*-guaia-9(10),11(13)-dien-12,8*α*-olide (**5**), 6*α*-acetoxy-4*α*-hydroxy-1*β*H-guaia-9(10),11(13)-dien-12,8*α*-olide (**6**), and 4*β*-10*α*-Dihydroxy-5*α*-guai-1(2),11(13)-dien-12,8*α*-olide (**7**) were isolated from the aerial parts of *Chrysophthalmum montanum* (DC) Boiss. The structures of the compounds were elucidated by extensive 1D- and 2D-NMR spectroscopic analysis in combination with MS experiments.

Keywords: *Chrysophthalmum montanum*; Asteraceae; sesquiterpene lactone glycosides; guaianolides.

1. Introduction

The genus *Chrysophthalmum* (Asteraceae), which is the element of the South-East Turkey and Iran region, comprises four species worldwide and three species in the flora of Turkey [1, 2]. *C. montanum* is used in Turkish folk medicine to ease respiration in common cold [3] and to cure eye diseases and wounds of both human beings and animals [4]. Antimicrobial activities of *C. montanum* is also reported [5]. While the chemistry of many genera of Inuleae group has been studied nothing is known about that of *Chrysophthalmum*. Different types of sesquiterpene lactones; guaianolides, eudesmanolides, germacranes, pseudo-guaianolides have been reported from *Inula* species which is the most close genus to *Chrysophytalmum* [6-9]. It is noteworthy that some of these sesquiterpene lactones showed cytotoxic, antibacterial, immunomodulatory and anti-inflammatory activities [10-13]. In the course of a search for sesquiterpene lactones in the Asteraceae, we have examined *C. montanum* a plant on which extensive phytochemical studies have not been previously conducted. Herein we report on the isolation and structure characterization four new sesquiterpene glycosides along with three known sesquiterpene lactones (Figure 1).

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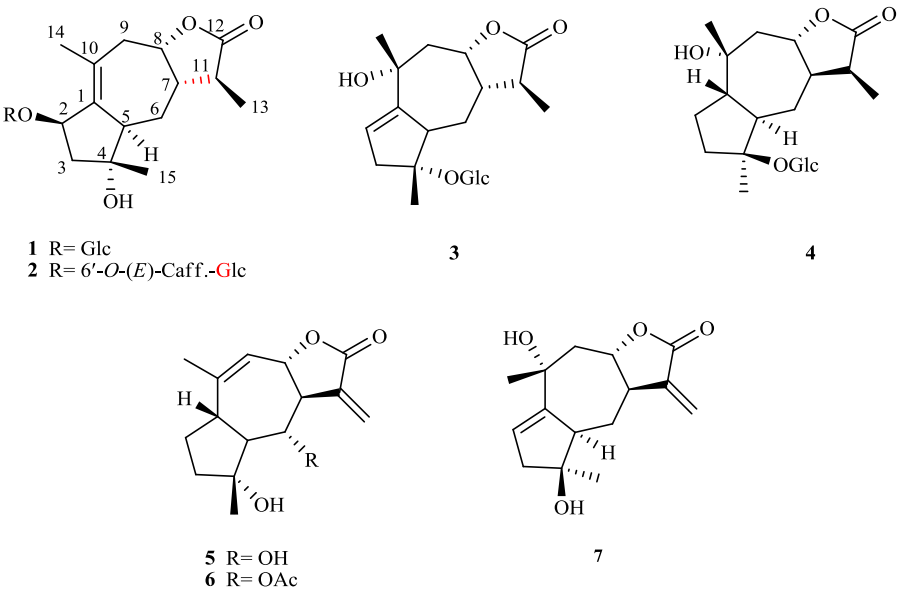


Figure 1. Structures of Compounds **1-7**

2. Materials and Methods

2.1. General experimental procedures

NMR (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR, both use TMS as internal standard) were measured on a Bruker AM 400 spectrometer and MS spectra on a LC/MS High Resolution Time of Flight (TOF) Agilent 1200/6530 instrument; CC, silica gel 60 (Merck); GPC (General Permeation Chromatography, Sephadex LH-20). IR spectra were recorded on a Perkin Elmer 400 FT-IR infrared spectrometer, and UV spectra on a UV-1800 UV-VIS recording spectrometer (Shimadzu, Japan).

2.2 Plant material

Aerial parts of *Chrysophthalmum montanum* (DC.) Boiss were collected in Niğde, Ulukışla, between Madenköy-Alihoca at 1350 m altitude of calcareous rock clefts on July 2011. Plants were identified by Assist. Prof. Mehmet Yavuz Paksoy. A voucher specimen (PAKSOY 1301) has been deposited in the Herbarium of Fırat University, Elazığ, Turkey.

2.3. Extraction and isolation

The dried powdered herb of *C. montanum* (900 g) was extracted with methanol (2.5 L x 7) by maceration at room temperature. After evaporation of the solvent (yield 11.11%), 100 g of the residue was suspended in 100 mL of water and partitioned with chloroform (250 mLx8), n-BuOH (150 mL x 7), respectively, yielding after evaporation of the solvents chloroform (34 g), n-BuOH (18 g) and the remaining water (41 g) extracts.

The n-BuOH extract was submitted to column chromatography on polyamide, eluted with a gradient system (MeOH-H_2O 0:100, 20:80, 40:60, 60:40, 80:20, MeOH) yielding 8 main fractions (Fr. 1-8) [FR1: 11 g, FR2: 394 mg, FR3: 684 mg, FR4: 167 mg, FR5: 256 mg, FR6: 330 mg, FR7: 740 mg, FR8: 203 mg].

FR3 (684 mg) was submitted to column on sephadex LH-20 eluted with a MeOH to afford two subfractions FR3.01-02. Then FR3.01 was applied to column on silica gel, eluted with a gradient system ($CHCl_3$-MeOH 90:10) yielding compound **2** (35 mg).

FR1 (10 g) submitted on reversed phase silica gel RP-18 (MeOH-H_2O 100:0, 5:95, 7.5:92.5, 10:90, 12.5:87.5, 15:85) to give 17 subfractions (FR1.01-17). Further separation of FR1.16, FR1.08, FR1.09 were performed by on silica gel column ($CHCl_3$-MeOH-H_2O 90:10:0, 90:10.5:0.5, 90:10:1) yielding compounds **1** (24 mg), **3** (40 mg), **4** (10.8 mg) successively.

The $CHCl_3$ extract was submitted to column chromatography on silica gel, eluted with a gradient system (PE:EtOAc 90:10→ 0:100) yielding 9 main fractions (Fr. 1-9) [FR1: 1.6 g, FR2: 714 mg, FR3: 1.09 g, FR4: 3.4 g, FR5: 3.1 g, FR6: 1.4 g, FR7: 2.2 g, FR8: 2.2 g, FR9: 1.3 g].

FR4 (3.4 g) was submitted to column on silica gel eluted with a gradient system (PE:EtOAc 1:1→2:3) to afford five subfractions FR4.01-05. Then FR4.04 (700 mg) was crystallized and yielded compound **6** (150 mg). FR4.02-3 was submitted to column on Sephadex LH-20 eluted with a gradient system (PE:Et_2O 2:8) to afford compound **5** (20 mg).

FR7 (2.2 g) was submitted to column on silica gel eluted with a gradient system (EtOAc: MeOH: H_2O 100:5:1→100:30:13) to afford three subfractions FR7.01-03. Then FR7.02 (200 mg) and FR7.03 (110 mg) were submitted on reversed –phase silica gel RP-18 (ACN-H_2O 0/100→30/70 in 40 min) respectively to give compound **7** (30 mg).

4*α*-hydroxy-guai-1(10)-en-12,8α*α*-olide 2*β*-*O*-*β*-D-glucopyranoside (**1**).

White amorphous solid; mp 122-126 °C; UV (CH_3OH): λ_{max}: 258, 275, 286, 300 nm; IR νmax (ATR) cm^{-1}: 3297, 2968, 2877, 1745, 1634, 1512, 1448; for ^1H and ^{13}C NMR spectroscopic data, see Table 1; HRESIMS m/z 473.20395 $[M+HCOO]^-$, calcd. 473.20229.

4*α*-hydroxy-guai-1(10)-en-12,8α-olide 2*β*-*O*-(6′-*trans*-caffeoyl)-*β*-D-glucopyranoside (**2**).

White amorphous solid; mp 134-136 °C; UV (CH_3OH): λ_{max} : 257, 293, 350; IR νmax (ATR) cm^{-1}: 3326, 2927, 1736, 1701, 1630, 1598, 1513, 1443; for ^1H and ^{13}C NMR spectroscopic data, see Table 1; HRESIMS m/z 589.22984 $[M-H]^-$, calcd. 589.22850.

10*α*-hydroxy-guai-1(2)-en-12,8*α*-olide 4*α*-*O*-*β*-D-glucopyranoside (**3**).

Viscous liquid; IR ν_{max} (ATR) cm^{-1}:3661, 3343, 2987, 2460, 2213, 2136, 1932, 1751, 1393; for ^1H and ^{13}C NMR spectroscopic data, see Table 1; HRESIMS m/z 473.20512 $[M+HCOO]^-$, calcd. 473.20229

10*α*-hydroxy-guai-12-8*α*-olide 4*β*-*O*-*β*-D-glucopyranoside (**4**).

Viscous liquid; IR ν_{max} (ATR) cm^{-1}: 3663, 3344, 2987, 2458, 2215, 2135, 1927, 1749, 1393; for ^1H and ^{13}C NMR spectroscopic data, see Table 1; HRESIMS m/z 475.22119 $[M+HCOO]^-$, calcd. 475.21794.

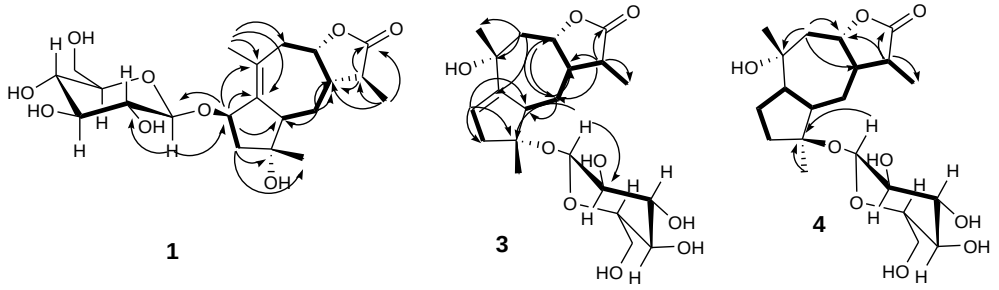


Figure 2. Observed key HMBC (H → C) and ^1H-^1H COSY (—) correlation for compounds **1, 3** and **4**

3. Results and Discussion

In this study, the aerial parts of *Chrysophytalmum montanum* has yielded four new compounds (**1-4**) from the *n*-butanol-soluble extract, in addition to the three known compounds 4*α,6α*-dihydroxy-1*β*,5*α*,7*αH*-guai-9(10),11(13)-dien-12,8*α*-olide (**5**) [14, 15], 6*α*-acetoxy-4*α*-hydroxy-1*βH*-guai-9(10),11(13)-dien-12,8*α*-olide (**6**) [16], and 4*β*-10*α*-dihydroxy-5*α*-guai-1(2),11(13)-dien-12,8*α*-olide (**7**) [17, 18] from the chloroform-soluble extract.

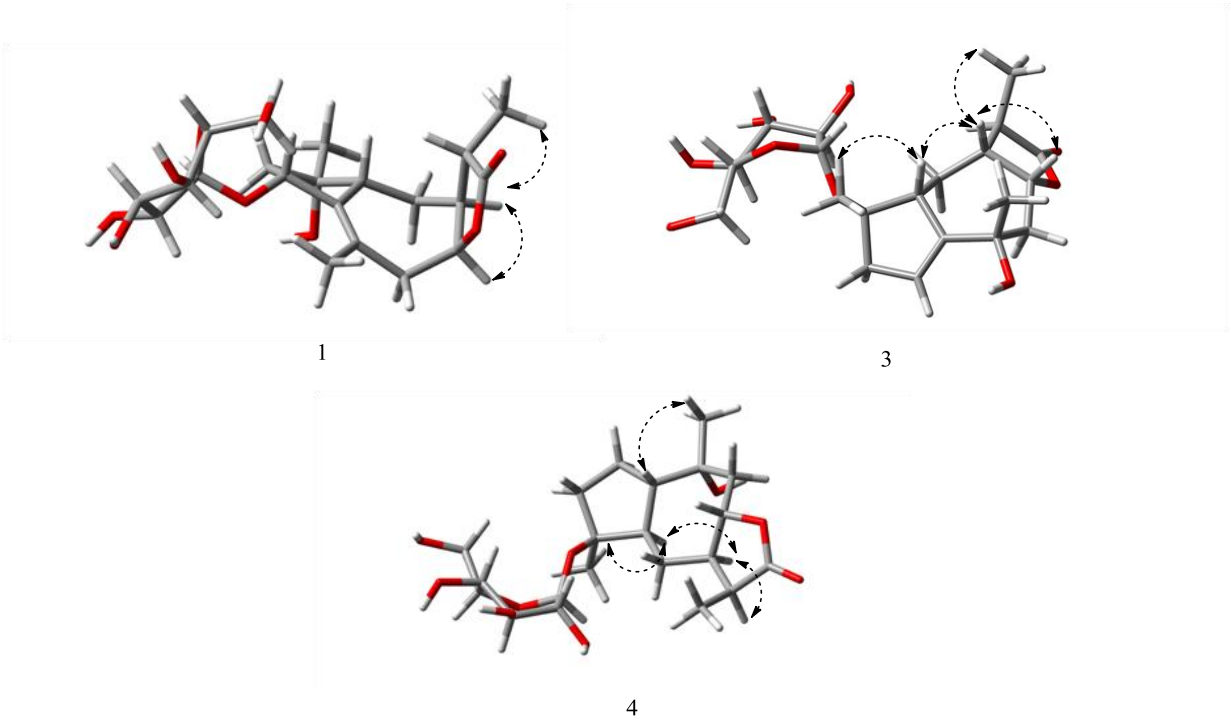
Compound **1** (Figure 1) was isolated as white powder, and its molecular formula was determined to be $C_{21}H_{32}O_9$ from its HRESIMS (*m/z* 473.20395 $[M+HCOO]^-$, calcd. 473.20229). In the IR spectrum, absorption bands of hydroxyl (3297 cm^{-1}) and the ester carbonyl (1745 cm^{-1}) were observed. The ^1H-NMR spectrum showed two *tert*- methyl singlets at δ_H 1.68, 0.82, a *sec*-methyl at δ_H 1.13 (3H, d, *J*=7.1 Hz), two oxygenated methines at δ_H 4.77-4.91 (1H, m) and 4.21-4.49 (1H, m)

and an anomeric proton at δ_H 4.15 (1H, d, *J*= 7.8 Hz). The ^{13}C and DEPT (90 and 135) NMR spectroscopic data of **1** showed the presence of two *tert*- methyls at δ_C 23.21 (C-14) and 22.52 (C-15) , a *sec*-methyl at δ_C 13.13 (C-13), three methylenes at δ_C 48.68 (C-3), 22.04 (C6) and 37.71 (C-9), five methines (two of which were oxygenated) at δ_C 80.39 (C-8), 78.08 (C-2), 52.64 (C-5), 39.38 (C-11) and 37.30 (C-7), a quaternary carbon at δ_C 77.31 (C-4), a tetrasubstituted double bond at δ_C 130.50, 138.87 (C-1 and C-10) and a carbonyl group at δ_C 180.28 (C-12) in addition to the *β*-D-glucopyranosyl moiety (according to the *J* values of the anomeric protons) observed at δ_C 102.97, 73.98, 77.20, 70.59, 77.13 and 61.62. The linkage position of the sugar moiety was established by observation of HMBC correlations (Figure 2) between C-2 (δ_C 78.08) of the aglycone and H-1 (δ_H 4.15) of Glc. The reverse HMBC correlations of the signals further proved the linkage positions. In the NOESY spectrum, correlation was observed between H-7 and H-8 indicating of the *cis*-fused lactone ring. Cross-peak between H-7 and H-13 and absence of cross-peak between H-7 and H-5 and H-5 and H_3-15 indicated the relative configurations of H-5 and H_3-15 as α and *β*, respectively. The relative configuration of OH group at C-2 was determined to be *β* based on the absence of cross-peak between H-2 and H_3-15 in the NOESY spectrum. Consequently, compound **1** was identified as the 4*α*-hydroxy-guai-1(10)-en-12,8*α*-olide 2*β*-*O*-*β*-D-glucopyranoside.

The molecular formula of sesquiterpene lactone **2** was deduced to be $C_{30}H_{38}O_{12}$ from its HRESIMS (*m/z* 589.22984 [M-H] $^-$, calcd. 589.22850). Compound **2** was obtained as a white solid. The IR absorptions showed the presence of hydroxyl (3326 cm^{-1}) and carbonyl (1736 and 1701 cm^{-1}). The ^{1}H and ^{13}C NMR data of **2** (Table 1) were found to be very similar to sesquiterpene lactone **1,** with additional signals due to the a *trans*-caffeoyl group**.** Major differences in the ^{1}H NMR spectrum of **2** showed the presence of 1,3,4-trisubstituted aromatic ring [δ_H 7.02 (1H, d, *J*= 1.8 Hz, H-5"), 6.73 (1H, *J*= 8.2 Hz, H-8") and 6.98 (1H, dd, *J*= 1.8, 8.4 Hz, H-9")], a trans-double bond [(δ_H 7.47 (1H, d, *J*= 15.8 Hz, H-2"), 6.24 (1H, *J*= 15.8 Hz, H-3")]. The ^{13}C NMR data (Table 1) also supported structure of guaiane-type sesquiterpene lactone glycoside **2**. HMBC correlation between H-6' and the carbonyl carbon at 166.88 ppm of the *trans*-caffeoyl unit was indicated the location of the acyl unit at the 6' position of the glucose moiety. By detailed analysis of its NOESY spectrum, the relative configuration of **2** was also elucidated to be the same as that of **1**. Based on these data, **2** was defined as 4*α*-hydroxy-guai-1(10)-en-12,8*α*-olide 2*β*-*O*-(6′-*trans*-caffeoyl)-*β*-D-glucopyranoside.

The molecular formula of compound **3** was deduced to be $C_{21}H_{32}O_9$ from its HRESIMS (*m/z* 473.20512 [M+HCOO] $^-$, calcd. 473.20229). The ^{13}C, DEPT and HSQC NMR spectroscopic data exhibited 21 carbon signals including six signals due to the *β*-D-glucopyranosyl moiety. ^{13}C NMR spectral data of **3** showed the presence of two *tert*-methyls at δ_C 25.96 (C-14) and 21.80 (C-15), a *sec*-methyl δ_C 9.33 (C-13), three methylenes δ_C 43.31 (C-3), 21.47 (C-6) and 42.16 (C-9), four methines (one oxygenated) δ_C 53.62 (C-5), 41.67 (C-7), 78.29 (C-8) and 39.22 (C-11), two oxygenated quaternary carbons δ_C 88.89 (C-4) and 70.01 (C-10), a trisubstituted double bond δ_C 150.69 (C-1) and 119.86 (C-2) and a carbonyl δ_C 179.94 (C-12), in addition to the *β*-D-glucopyranosyl moiety δ_C 98.57, 73.74, 76.34, 70.08, 76.69 and 61.35. The ^{1}H NMR spectrum of **3** showed characteristic signals two tertiary methyls at δ_H 1.31and 1.34 indicated that these methyl groups should be adjacent to oxygen functions, a secondary methyl at δ_H 1.17 (3H, d, *J*= 7.3 Hz), oxygenated methine at 4.86-4.72 (1H, m), an olefinic proton at δ_H 5.68 (1H, bd, *J*= 2.2) and an anomeric proton at δ_H 4.47 (1H, d, *J*= 7.8 Hz). *J* value of anomeric proton of glucose was characteristic for *β*-D-configuration in the pyranosyl form. The glycosidic linkage position at C-4 was determined by the HMBC spectrum based on the obvious correlation between H-1' (δ_H 4.47) and C-4 (δ_C 88.89).

The stereochemistry of **3** was determined on the basis of NOESY experiment (Figure 3). The strong NOESY correlation of H-7 and H-8, compound **3** should contain a *cis*-fused lactone ring and NOESY correlations between H_3-15 and H-5, H-5 and H-7, H-5 and H_3-14 and the correlation between H-13 and H-7 protons indicated the relative configurations of H_3-15, H-5, H-7, H-8, H_3-13 and H_3-14 as *β*. Therefore, the structure of **3** was 10*α*-hydroxy-guai-1(2)-en-12,8*α*-olide 4*α*-*O*-*β*-D-glucopyranoside and their chemical shifts were compared in the literature with similar guaianolides [9, 19].



1 3

4

Figure 3. Key NOESY (◄- - -►) correlations of **1, 3** and **4** (geometry-optimized conformation).

Table 1. NMR spectroscopic data of compounds **1**–**4** [in (400 MHz for ^{1}H and 100 MHz for ^{13}C, δ in ppm and J in Hz].

	1[a]		**2**[a]		**3**[b]		**4**[b]	
Position	**δ_C**	**δ_H**	**δ_C**	**δ_H**	**δ_C**	**δ_H**	**δ_C**	**δ_H**
1	130.5		130.6		150.6		47.3	2.06-1.92 (m)
2	78.0	4.21-4.49 (m)	77.0	4.27-4.35 (m)	119.8	5.68 (d, 2.2)	23.1	1.92-1.80 (m) 1.55-1.69 (m)
3	48.6	2.09 (dd, 7.5, 13.1) 1.78 (dd, 6.8, 13.1)	49.0	2.06 (dd, 7.7, 13.0) 1.77 (dd, 7.0, 13.4)	43.3	2.69 (d, 15.8) 2.32 (m)	38.1	1.55-1.84(m) 1.55-1.84 (m)
4	77.3		77.0		88.8		86.8	
5	52.6	2.40 (bd, 11.5)	52.7	2.39 (bd, 11.5)	53.6	2.87 (d, 12)	52.0	1.92-1.80 (m)
6	22.0	1.67-1.63 (m) 1.38-1.26 (m)	22.2	1.61-1.66 (m) 1.28-1.35 (m)	21.4	1.77 (bd, 13.2) 1.24 (bd, 13.2)	27.5	1.93-2.03 (m) 1.30 (overlapped)
7	37.3	2.81-2.67 (m)	37.3	2.70-2.79 (m)	41.6	2.71 (m)	49.6	2.13-2.23 (m)
8	80.3	4.77-4.91 (m)	80.5	4.52-4.74 (m)	78.2	4.86-4.72 (m)	79.4	4.58 (t, 10.8)
9	37.7	2.16 (dd, 2.0, 16.0) 2.64 (bd, 14.9)	37.8	2.15 (d, 14.0) 2.59-2.71 (m)	42.1	2.27 (dd, 13.4, 6.4) 1.98 (dd, 13.1, 11)	48.3	2.34 (bd, 13.4) 2.00 (d, 14.2)
10	138.8		138.7		70.0		72.6	
11	39.3	2.81-2.67 (m)	39.3	2.79-2.70 (m)	39.2	3.11-3.01 (m)	40.5	2.68 (dd, 7.7, 15.4)
12	180.2		180.2		179.9		181.0	
13	13.1	1.13 (d, 7.1)	13.5	1.12 (d, 7.1)	9.3	1.17 (d, 7.3)	9.7	1.19 (d, 7.8)
14	22.5	1.68 (s)	23.2	0.75 (s)	25.9	1.34 (s)	23.4	1.29 (s)
15	23.2	0.82 (s)	22.5	1.69 (s)	21.8	1.31 (s)	19.4	1.26 (s)
1'	102.9	4.15 (d, 7.8)	103.0	4.22 (d, 7.8)	98.5	4.47 (d, 7.8)	98.4	4.42 (d, 7.8)
2'	73.9	2.96-2.85 (m)	73.9	2.90-3.00 (m)	73.7	3.19-3.12 (m)	73.7	3.11 (dd, 7.8, 9.1)
3'	77.2	3.18-2.98 (m)	76.1	3.10-3.03 (m)	76.3	3.28 (m)	76.1	3.30-3.23 (m)
4'	70.5	3.18-2.98 (m)	70.8	3.10-3.03(m)	70.0	3.28 (m)	70.8	3.30-3.23 (m)
5'	77.1	3.18-2.98 (m)	76.1	3.10-3.03(m)	76.6	3.37 (dd, 12, 5.3)	76.8	3.33-3.40 (m)
6'	61.6	3.64 (dd, 3.5, 11.7) 3.41 (dd, 5.7, 11.4)	63.8	4.11 (dd, 7.3, 11.7) 3.79-3.61 (m)	61.3	3.84 (dd, 11.9, 1.8) 3.66 (dd, 11.8, 5.3)	61.3	3.84 (bd, 12.0) 3.63 (dd, 5.4, 11.8)

NMR data of caffeoyl moiety: ^{13}C NMR (DMSO-*d6*, 100 MHz), δ 166.88 (C-1"), 116.2 (C-2"), 146.03 (C-3"), 121.79 (C-4"), 114.39 (C-5"), 145.66 (C-6"), 148.92 (C-7"), 115.29 (C-8"), 125.82 (C-9"); ^{1}H NMR (DMSO-*d6*, 400 MHz), δ 7.47 (1H, d, J = 15.8 Hz, H-2"), 6.24 (1H, d, J = 15.8 Hz, H-3"), 7.02 (1H, d, J = 1.8 Hz, H-5"), 6.73 (1H, d, J = 8.2 Hz, H-8"), 6.98 (1H, dd, J = 1.8/8.4 Hz, H-9")

[a] Recorded in DMSO-d_6

[b] Recorded in methanol-d_4

Last compound **4** is saturated form 10*α*-hydroxy-guai-1(2)-en-12,8*α*-olide 4*α*-*O*-*β*-D-glucopyranoside (**3**). This was clearly seen from their mass spectra. The HRESIMS of **4** exhibited a peak at *m/z* 475.22119 $[M+HCOO]^-$ corresponding to $C_{21}H_{34}O_9$, whereas the HRESIMS of **3** afforded a peak at *m/z* 473.20512 $[M+HCOO]^-$ corresponding to $C_{21}H_{32}O_9$. The ^{13}C and DEPT (90 and 135) NMR spectroscopic data of **4** showed the presence of two *tert*- methyls at δ_C 23.48 (C-14) and 19.43 (C-15) , a *sec*-methyl at δ_C 9.73 (C-13), four methylenes at δ_C 23.19 (C-2), 38.16 (C-3), 27.53 (C-6) and 48.32 (C-9), five methines (one of which were oxygenated) at δ_C 47.34 (C-1), 52.03 (C-5), 49.68 (C-7), 79.48 (C-8) and 40.50 (C-11), two quaternary carbons at δ_C 86.88 (C-4) and 72.65 (C-10), and one carbonyl group at δ_C 181.05 (C-12) in addition to the *β*-D-glucopyranosyl moiety (according to the *J* values of the anomeric proton) at δ_C 98.42, 76.83, 76.17, 73.78, 70.81, 61,31. ^1H-^1H-COSY correlations of H-1/H-2/H-3, H-5/H-6/H-7, H-8/H-9/H-7 and H-7/H-11/H-13 supported the structure of compound **4**. The sugar moiety connected to the five member ring at C-4 which was evident from the HMBC cross-peaks between H-1' (δ_H 4.42) and C-4 (δ_C 86.88).

The relative configuration of compound **4** was studied by means of a NOESY experiment (Figure 3). In the NOESY spectrum, no correlation was detected between H-7 and H-8 indicating of the *trans*-fused lactone ring. Cross-peaks between H_3-15 and H-5, H-5 and H-7, H-7 and H-11 and absence of cross-peak between H-5 and H-1 indicated the relative configurations of H_3-15, H-5, H-7 and H-1 as α, α, α and *β*, respectively. Configuration of methyl group (H_3-14) was proposed to be *β* based on the NOESY cross-peak between H-1 and H-14, respectively. Consequently, the structure of **4** was concluded to be 10*α*-hydroxy-guai-12-8*α*-olide 4*β*-*O*-*β*-D-glucopyranoside.

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Supporting Information

Supporting Information accompanies this paper on http://www.acgpubs.org/RNP

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