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Diterpene glycosides from *Aster homochlamydeus*

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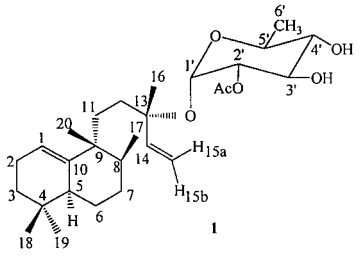
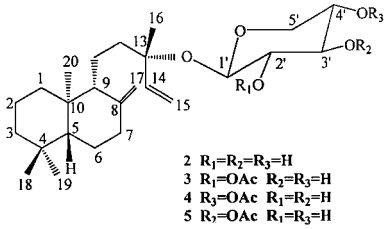
A new diterpene glycoside **1** was isolated from the whole plant of *Aster homochlamydeus* Hand-mazz (Compositae), along with four known diterpene glycosides **2**–**5**. Their structures were elucidated by spectroscopic methods, MS, IR, NMR and X-ray crystallographic analyisis. Antibacterial activity of compounds **1**–**5** was observed.

1. Introduction

The genus *Aster* (Compositae) has long been used in Chinese folk medicine as apophlegmatic, antitussive, anticarcinogenic and antibiotic drugs (Chinese Medicine Dictionary 1977; Shao Y, et al. 1997). Triterpene glycosides have been reported as the most widespread main constitutents in the genus (Sakai et al. 1999; Nagao et al. 1993; Nagao et al. 1990; Akihsa et al. 1998). From the whole plant of *Aster homochlamydeus* Hand-mazz, five diterpene glycosides were obtained and, their structures were elucidated by spectroscopic methods and X-ray crystallographic analyisis. We describe herein the isolation and structural elucidation of a new diterpene glycoside (**1**) and four known ones (**2**–**5**). Moreover, the antibacterial activities of compounds **1**–**5** against *Bacillus subtilis*, *Staphylococcus aureus* and *Escherichia coli* were also assayed according to the paper-disk method (Xu et al. 1982). The results indicated that compound **1** has significant antibacterial activity against *S. aureus*, *B. subtilis* and *E. coli* and compound **5** shows significant antibacterial activity against *S. aureus*, while the others exhibit weak antibacterial activity.



1



2 $R_1=R_2=R_3=H$
3 $R_1=OAc$ $R_2=R_3=H$
4 $R_3=OAc$ $R_1=R_2=H$
5 $R_3=OAc$ $R_1=R_3=H$

2. Investigations, results and discussion

From the EtOH extract of the whole plant of *A. homochlamydeus,* a new diterpene glycoside named astern-13(*R*)-1(10),14-diene-13-*O*-α-L-2′-acetylrhamnopyranoside (**1**) was isolated and elucidated, together with four known ones: ent-manool-13-*O*-β-D-xylopyransyl (**2**) (Urzua et al. 1995), ent-manool-13-*O*-β-D-2′-acetylxylopyranoside (**3**) (Li et al. 2004), ent-manool-13-*O*-β-D-4′-acetylxylpyranoside (**4**) (Urzua et al. 1995), and ent-manool-13-*O*-β-D-3′-acetylxylpyranoside (**5**) (Urzua et al. 1995). The structures of the known compounds **2**–**5** were elucidated by comparison of their spectral data ($[\alpha]_D^{21}$, EIMS, FABMS, IR, ^{1}H NMR and ^{13}C NMR) with those published in the literature, respectively.

Compound **1** was obtained as colorless needle-like crystals with a molecular formula of $C_{28}H_{46}O_6$, deduced from its FABMS (which gave $[M + Na]^+$ at m/z 501 and $[M + Li]^+$ at m/z 485), together with ^{13}C NMR and DEPT data (Table 1). From its IR (KBr) spectrum, the absorptions of hydroxyl (3483, 3377 cm^{-1}), carboxyl (1729 cm^{-1}) and double bond (976, 934, 842 cm^{-1}) can be found. The ^{13}C NMR and DEPT spectra (Table 1) revealed 28 carbon signals (including $7 \times CH_3$, $7 \times CH_2$, $9 \times CH$, $5 \times C$), among these signals, the signals of δ_C 68.0–93.1 and 17.5 ppm, together with δ_H 3.30–4.90 and 1.29 ppm in the ^{1}H NMR spectrum were very similar to those of L-rhamnose. However, C-2′ was shifted downfield to δ_C 73.9 ppm and H-2′ appeared at δ_H 4.84 ppm, while C-3′ appeared upfield at δ_C 70.1 ppm (Gerl et al. 1994). Meanwhile, δ_C 171.0, 20.3 and δ_H 2.12 (s, 3 H) showed the presence of an acetoxyl which was attached to C-2′, supported by the HMBC correlation of δ_C 171.0 with δ_H 4.84 (H-2′) and a strong ion peak at m/z 272 in the EIMS corresponding to the loss of a terminal acetyl hexose ($C_8H_{14}O_6$) unit. The α configuration of the anomeric carbon of the sugar was deduced from the anomeric proton signal at δ_H 4.87 (s, 1 H). Since C-13 appeared downfield

Table 1: ^{13}C NMR and DEPT (100 MHz) data of compounds 1–5 ($CDCl_3$, TMS, δ, ppm)

No	1	2	3	4	5
1	119.7 d	39.2 t	39.2 t	39.1 t	39.2 t
2	32.8 t	19.6 t	19.6 t	19.4 t	19.5 t
3	28.5 t	42.4 t	42.4 t	42.1 t	42.3 t
4	31.3 s	33.8 s	33.7 s	33.7 s	33.8 s
5	43.3 d	55.7 d	55.7 d	55.6 d	55.6 d
6	24.0 t	24.6 t	24.6 t	24.4 t	24.6 t
7	32.4 t	38.5 t	38.5 t	38.4 t	38.4 t
8	39.8 d	148.8 s	148.7 s	148.5 s	148.7 s
9	42.9 s	57.5 d	57.4 d	57.5 d	57.6 d
10	142.0 s	40.0 s	40.0 s	40.1 s	39.9 s
11	23.1 t	17.9 t	17.7 t	17.8 t	17.7 t
12	36.4 t	40.7 t	41.2 t	41.1 t	40.9 t
13	79.1 s	81.4 s	81.5 s	81.4 s	81.3 s
14	143.2 d	142.7 d	142.8 d	142.5 d	142.7 d
15	114.5 t	116.1 t	116.6 t	116.4 t	116.3 t
16	23.1 q	22.5 q	22.9 q	22.7 q	22.8 q
17	15.3 q	106.7 t	106.7 t	106.4 t	106.6 t
18	28.5 q	33.7 q	33.7 q	33.5 q	33.8 q
19	22.3 q	21.9 q	21.9 q	21.8 q	21.5 q
20	27.7 q	14.7 q	14.7 q	14.6 q	14.7 q
1′	93.1 d	98.3 d	95.6 d	96.1 d	97.8 d
2′	73.9 d	73.3 d	73.6 d	72.0 d	71.7 d
3′	70.1 d	76.2 d	75.0 d	71.5 d	77.7 d
4′	73.7 d	69.9 d	70.1 d	71.3 d	68.1 d
5′	68.8 d	65.1 t	63.7 t	60.7 t	64.3 t
6′	17.5 q				
$\underline{C}OCH_3$	171.0 s		171.1 s	170.9 s	171.0 s
$CO\underline{C}H_3$	20.3 q		20.4 q	20.3 q	20.1 q

at δ_C 79.1 ppm in the ^{13}C NMR spectrum (Almqvist et al. 1975), together with the HMBC correlation of H-1′ with C-13, the acetyl hexose was definitely located at C-13. As regards the aglycone of compound **1**, its ^{1}H NMR spectrum exhibited the signals of a terminal double bond at δ_H 5.72 (1 H, dd, J = 10.8, 17.6 Hz, H-14), 5.16 (1 H, d, J = 17.6 Hz, H-15a), 5.21 (1 H, d, J = 10.8 Hz, H-15b) and another olefinic proton at δ_H 5.31 (1 H, brs), five methyl signals, including four quaternary methyls at δ_H 0.83, 0.86, 0.87 and 1.33 (each 3 H, s) and one tertiary methyl at δ_H 0.79 (3 H, d, J = 7.0 Hz). From the above data, the remaining 20 carbon signals except an acetyl hexose in the ^{13}C NMR spectrum formed a dicyclic diterpene skeleton as given, which was further supported by the HMBC correlations: H-18, 19/C-4, 5; H-1/C-5, 9, 10; H-17/C-8; H-20/C-9; H-5/C-1, 10; H-8/C-9, 17; H-14/C-13, 15, 16. Moreover, a NOESY experiment showed the correlations of $C\underline{H}_3$-20/$C\underline{H}_3$-17, 18; H-5/H-2α, 8, $C\underline{H}_3$-19, which indicated the relative stereochemistry of **1** except C-13. Finally, X-ray crystallographic analysis solved the stereochemistry of C-13 assigned as *R* and further confirmed the exact structure of **1**; it was a new labdan diterpenoid and was named astern-13(*R*)-1(10),14-diene-13-*O*-α-L-2′-acetylrhamnopyranoside. The compounds were tested for antibacterial activity; the results are given in Table 2.

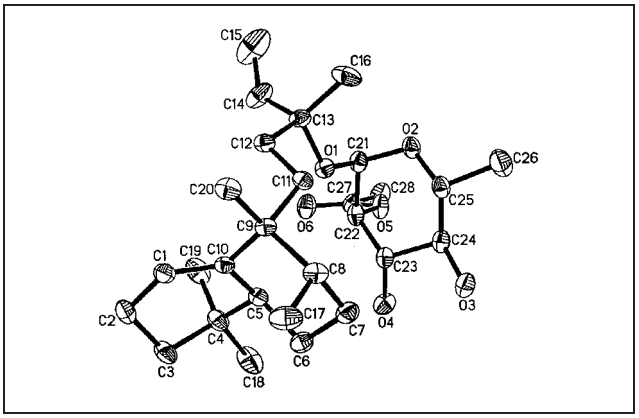


Fig.: ORTEP diagram of the crystal structure of compound **1**

Table 2: Antibacterial activity of compounds 1–5

Compound	*E. coli*	*B. subtilis*	*S. aureus*
1	++	+++	+++
2	+	++	+
3	+	+	++
4	+	++	++
5	+	++	+++
Chloramphenicol (100 μg/ml)	+++	+++	+++

Antibacterial circle: +++ > 17 mm; ++ 13–16 mm; + < 12 mm.

3. Experimental

3.1. Apparatus

Optical rotations: Perkin-Elmer 341 Polarimeter; IR: Nicolet NEXUS 670 FT-IR instrument; EIMS: HP 5988A GC/MS instrument; FABMS data: VG-ZAB-HS mass spectrometer (at 70 eV); NMR (^{1}H NMR, ^{13}C NMR, NOESY, HMBC): Bruker AM 400 FT-NMR instrument; Silica gel (200–300 mesh) for column chromatography and GF254 (10–40 μ) for TLC were supplied by the Qingdao Marine Chemical factory, Qingdao, P. R. China; Spots were detected on TLC under UV lamp and by heating after spraying with 5% H_2SO_4 in C_2H_5OH or 5% $FeCl_3$ in C_2H_5OH; Melting points were determined on a Kefler melting point apparatus and are uncorrected.

3.2. Plant material

The whole plant of *Aster homochlamydeus* Hand-mazz was collected in Zhang county, Gansu province, P.R. China, in August 2001. It was identified by Prof. Guoliang Zhang, School of Life Science, Lanzhou University. A voucher specimen (No. 10811) was deposited in the College of Chemistry and Chemical Engineering, Lanzhou University.

3.3. Extraction and isolation

Dried and ground whole plant of *A. homochlamydeus* (4.5 kg) was extracted with 95% EtOH (13500 ml) three times at room temperature (each time for 7 days) and then concentrated under reduced pressure. The resulting residue (0.41 kg) was dissolved in H_2O (1000 ml) and extracted with petroleum ether (60–90 °C) (1500 ml × 3), followed with EtOAc (1000 ml × 3) and *n*-BuOH (700 ml × 3). The EtOAc extract (25 g) was chromatographed on a silica gel (300 g) column (4.0 × 50 cm) using a gradient of $CHCl_3$–EtOAc (1 : 0, 50 : 1, 30 : 1, 20 : 1, 10 : 1, 5 : 1 and 1 : 1, 1500 ml for each eluent). Seven fractions ($F_1 \rightarrow F_7$) were obtained according to differences in composition indicated by TLC analysis. F_2 ($CHCl_3$–EtOAc, 50 : 1, 200 mg) was separated by CC over a silica gel colum (10 g) using a gradient of $CHCl_3$–MeOH (100 : 1, 50 : 1, 30 : 1, 20 : 1, 10 : 1 and 5 : 1, 50 ml each eluent) to give crude **1** (15 mg, 30 : 1) and purified by recrystallization ($CHCl_3$–Me_2CO). F_3 ($CHCl_3$–EtOAc, 30 : 1, 558 mg) was rechromatographed on a silica gel column (20 g) eluting with $CHCl_3$–MeOH (50 : 1, 30 : 1, 20 : 1, 10 : 1, 5 : 1 and 1 : 1, 100 ml each eluent) to yield **2** (36 mg, 20 : 1) and **3** (27 mg, 10 : 1). After rechromatography on a silica gel column ($CHCl_3$–MeOH, 50 : 1 → 1 : 1, 25 ml each eluent) from F_4, a mixture of **4** and **5** (70 mg, 10 : 1) was obtained. It was separated by repeated preparative TLC with $CHCl_3$–EtOAc (30 : 1, three times) to yield **4** (5 mg, R_f = 0.45) and **5** (7 mg, R_f = 0.29).

3.3.1. Astern-13(R)-1(10),14-diene-13-O-α-L-2′-acetylrhamnopyranoside (**1**)

Colorless crystals; molecular formula: $C_{28}H_{46}O_6$; m.p. 146–147 °C ($CHCl_3$); $[\alpha]_D^{21}$: +33.0° (c 0.40, $CHCl_3$); FABMS m/z (sgly): 501 $[M + Na]^+$, 485 $[M + Li]^+$, 273 [M-rhamnose-acetyl]$^+$; EIMS m/z (rel int): 272 [M-rhamnose-acetyl]$^+$ (9), 257 [M-rhamnose-acetyl-CH_3]$^+$ (4), 191 (76), 171 (16), 135 (12), 121 (13), 81 (26), 43 (100); IR (ν_{max}^{KBr}, cm^{-1}): 3483, 3377 (hydroxyl), 1729 (carboxyl), 976, 934, 842 (double bond); ^{1}H NMR δ ppm ($CDCl_3$, 400 MHz): 0.79 (3 H, d, J = 7.0 Hz, Me-17), 0.83 (3 H, s, Me-19), 0.87 (3 H, s, Me-18), 0.86 (3 H, s, Me-20), 1.33 (3 H, s, Me-16), 2.12 (3 H, s, COMe), 5.72 (1 H, dd, 10.8, 17.6 Hz, H-14), 5.16 (1 H, d, 17.6 Hz, H-15a), 5.21 (1 H, d, 10.8 Hz, H-15b) , 5.31 (1 H, brs, H-1), 4.87

(1 H, s, H-1′), 4.84 (1 H, br s, H-2′), 3.99 (1 H, d, J = 6.6 Hz, H-3′), 4.13 (1 H, d, J = 4.2 Hz, H-4′), 3.79 (1 H, dd, J = 5.7, 9.0 Hz, H-5′), 1.29 (3 H, d, J = 6.0 Hz, H-6′); ^{13}C NMR data: see Table 1.

3.3.2. X-Ray crystallographic analysis of **1**

Crystal data: $C_{28}H_{46}O_6$, formula wt: 478.65; T = 293(2) K; wavelength: 0.71073 Å; crystal system: monoclinic; space group: P2(1); unit cell dimensions: a = 11.542(2) Å, b = 8.793(2) Å, c = 14.095(2) Å, $\alpha = \gamma = 90°$, $\beta = 102.14°$, V = 1398.6(4) Å^3, Z = 2; $D_c = 1.137$ Mg/m^3; range for data collection: $1.48° \leq \theta \leq 27.09°$; limiting indices $0 \leq h \leq 14$, $0 \leq k \leq 11$, $-18 \leq = l \leq = 17$; F(000): 524; reflections collected: 3283, independent reflections: 3289 [R(int) = 0.0201]; refinement method: full-matrix least-squares on F^2; goodness-of-fit on F^2: 0.813; final R indices [I > 2 sigma (I)]: R1 = 0.0376, wR2 = 0.0734; R indices (all data): R1 = 0.0759, wR2 = 0.0822; largest diff. peak and hole: 0.122 and −0.126 e.Å^3; audit creation method: SHELXL = 97.

3.3.3. ent-Manool-13-O-β-D-xylopyranosyl (**2**)

Gum; molecular formula: $C_{25}H_{42}O_5$; $[\alpha]_D^{21}$: −50.0° (c 2.50, $CHCl_3$); FABMS m/z (sgly): 405 $[M + H]^+$; EIMS m/z (rel int): 272 [M-xylose-acetyl]$^+$ (6), 204 (8), 189 (5), 137 (28), 43 (100); IR (ν_{max}^{KBr}, cm^{-1}): 3575, 3450, 1042 (hydroxyl), 1633 (double bond); ^{1}H NMR δ ppm ($CDCl_3$, 400 MHz): 0.65 (3 H, s, Me-20), 0.79 (3 H, s, Me-19), 0.85 (3 H, s, Me-18), 1.32 (3 H, s, Me-16), 2.10 (3 H, s, COMe), 5.16 (1 H, d, J = 17.2 Hz, H-15a), 5.27 (1 H, d, J = 8.4 Hz, H-15b), 5.78 (1 H, dd, J = 8.4, 17.2 Hz, H-14), 4.79 (1 H, br s, H-17a), 4.35 (1 H, br s, H-17b), 4.34 (1 H, d, J = 6.8 Hz, H-1′), 3.45 (1 H, br t, J = 7.5 Hz, H-2′), 3.29 (1 H, br t, J = 7.5 Hz, H-3′), 3.60 (1 H, dd, J = 8.8, 14.4 Hz, H-4′), 3.87 (1 H, br d, J = 8.8 Hz, H-5′a), 3.15 (1 H, br t, J = 9.6, 13.2 Hz, H-5′b); ^{13}C NMR data: see Table 1.

3.3.4. ent-Manool-13-O-β-D-2′-acetylxylopyranoside (**3**)

Gum; molecular formula: $C_{27}H_{44}O_6$; $[\alpha]_D^{21}$: −43.0° (c 0.51, $CHCl_3$); FABMS m/z (sgly): 465 $[M + H]^+$; EIMS m/z (rel int): 272 [M-xylose-acetyl]$^+$ (7), 204 (4), 189 (5), 137 (31), 43 (100); IR (ν_{max}^{KBr}, cm^{-1}): 3500, 1041 (hydroxyl), 1739 (carboxyl), 1640 (double bond); ^{1}H NMR δ ppm ($CDCl_3$, 400 MHz): 0.66 (3 H, s, Me-20), 0.79 (3 H, s, Me-19), 0.86 (3 H, s, Me-18), 1.36 (3 H, s, Me-16), 2.10 (3 H, s, COMe), 5.20 (1 H, d, J = 16.0 Hz, H-15a), 5.28 (1 H, d, J = 10.0 Hz, H-15b), 5.79 (1 H, dd, J = 10.0, 16.0 Hz, H-14), 4. 80 (1 H, br s, H-17a), 4.48 (1 H, br s, H-17b). 4.53 (1 H, d, J = 6.7 Hz, H-1′), 4.69 (1 H, dd, J = 6.0, 7.8 Hz, H-2′), 3.50 (1 H, br t, J = 6.9 Hz, H-3′), 3.67 (1 H, m, H-4′), 3.22 (1 H, dd, J = 6.8, 11.6 Hz, H-5′a), 3.92 (1 H, dd, J = 4.8, 11.6 Hz, H-5′b); ^{13}C NMR data: see Table 1.

3.3.5. ent-Manool-13-O-β-D-4′-acetylxylopyranoside (**4**)

Gum; molecular formula: $C_{27}H_{44}O_6$; $[\alpha]_D^{21}$: −45.8° (c 0.52, $CHCl_3$); FABMS m/z (sgly): 465 $[M + H]^+$; EIMS m/z (rel int): 272 [M-xylose-acetyl]$^+$ (5), 204 (6), 189 (5), 137 (30), 43 (100); IR (ν_{max}^{KBr}, cm^{-1}): 3550, 1040 (hydroxyl), 1740 (carboxyl), 1222 (CH_3COR), 1650 (double bond); ^{1}H NMR δ ppm ($CDCl_3$, 400 MHz): 0.65 (3 H, s, Me-20), 0.79 (3 H, s, Me-19), 0.85 (3 H, s, Me-18), 1.34 (3 H, s, Me-16), 2.11 (3 H, s, COMe), 5.20 (1 H, d, J = 16.0 Hz, H-15a), 5.27 (1 H, d, J = 10.4 Hz, H-15b), 5.78 (1 H, dd, J = 10.4, 16.0 Hz, H-14), 4.78 (1 H, br s, H-17a), 4.48 (1 H, br s, H-17b), 4.50 (1 H, d, J = 6.8 Hz, H-1′), 3.51 (1 H, br t, J = 5.2 Hz, H-2′), 3.70 (1 H, br t, J = 7.2 Hz, H-3′), 3.83 (1 H, m, H-4′), 3.36 (1 H, dd, J = 7.2, 12.0 Hz, H-5′a), 4.06 (1 H, dd, J = 4.8, 12.0 Hz, H-5′b); ^{13}C NMR data: see Table 1.

3.3.6. ent-Manool-13-O-β-D-3′-acetylxylopyranoside (**5**)

Gum; molecular formula: $C_{27}H_{44}O_6$; $[\alpha]_D^{21}$: −48.9° (c 0.11, $CHCl_3$); FABMS m/z (sgly): 465 $[M + H]^+$; EIMS m/z (rel int): 272 [M-xylose-acetyl]$^+$ (4), 204 (5), 189 (5), 43 (100); IR (ν_{max}^{KBr}, cm^{-1}): 3450, 1040 (hydroxyl), 1745 (carboxyl), 1655 (double bond); ^{1}H NMR δ ppm ($CDCl_3$, 400 MHz): 0.66 (3 H, s, Me-20), 0.79 (3 H, s, Me-19), 0.85 (3 H, s, Me-18), 1.35 (3 H, s, Me-16), 2.10 (3 H, s, COMe), 5.21 (1 H, d, J = 15.6 Hz, H-15a), 5.26 (1 H, d, J = 10.0 Hz, H-15b), 5.78 (1 H, dd, J = 10.0, 15.6 Hz, H-14), 4.79 (1 H, br s, H-17a), 4.45 (1 H, br s, H-17b), 4.41 (1 H, d, J = 6.8 Hz, H-1′), 3.48 (1 H, dd, J = 6.8, 8.8 Hz, H-2′), 4.82 (1 H, br t, J = 8.8 Hz, H-3′), 3.83 (1 H, m, H-4′), 3.26 (1 H, dd, J = 10.0, 11.6 Hz, H-5′a), 3.98 (1 H, dd, J = 4.8, 11.6 Hz, H-5′b); ^{13}C NMR data: see Table 1.

3.4. Anti-bacterial assays

The anti-bacterial activity assay was carried out using the cup-plate method. Chloramphenicol was used as a positive control. Three strains of bacteria: *Bacillus subtilis*, *Escherichia coli* and *Staphylococcus aureus*, were cultured in beef broth and incubated at 37 °C for 24 h. After dilution of the beef broth, the three bacteria were cultured in agar medium dishes respectively, six cups (8 × 10 mm) were put onto the dishes, and each test compound (0.2 ml of 100 μg/ml) was respectively added into the cups under aseptic conditions. Then the dishes were cultured at 37 °C for 24 h. The zone of inhibition of the growth of bacteria, produced by diffusion of the compounds from the cup into the surrounding medium, was measured to evaluate the anti-bacterial activity. Each test was performed in duplicate.

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