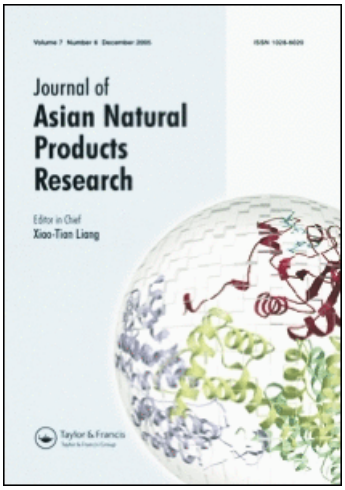

Journal of Asian Natural Products Research

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713454007

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To cite this Article Tian, Xiao-Yan , Wang, Ying-Hong , Yang, Qing-Yun , Liu, Xin , Fang, Wei-Shuo and Yu, Shi-Shan(2006) 'Jacaranone glycosides from *Senecio scandens*', Journal of Asian Natural Products Research, 8: 1, 125 — 132
To link to this Article: DOI: 10.1080/10286020500530912
URL: http://dx.doi.org/10.1080/10286020500530912

Journal of Asian Natural Products Research,
Vol. 8, No. 1–2, January–March 2006, 125–132

Jacaranone glycosides from *Senecio scandens*

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(Received 1 August 2005; revised 7 November 2005; in final form 8 November 2005)

Bioassay-guided fractionation of the ethanol extract of *Senecio scandens* led to the isolation of four new compounds **1**–**4**. These compounds were obtained as tautomeric mixture of α/β epimers, but their structures were confirmed unambiguously by 1D and 2D NMR spectra and LC NMR technology. ^{1}H NMR spectra of pure **1α** and **1β** were furnished by HPLC NMR technology. Compounds **1**–**4** exhibited moderate cytotoxicities against five tumor cell lines.

Keywords: *Senecio scandens*; Benzoquinone; Jacaranone glycosides; Cytotoxicity

1. Introduction

Senecio scandens Buch-Ham is an annual plant distributed in southwestern and southeastern China. It is a folk medicine used for the treatment of inflammatory, bacteria infection, arthritis and rheumatic disease. To our knowledge, no thorough phytochemical investigation about this herb has been reported in the literature. The genus *Senecio* has long been known to contain cytotoxic pyrrolizidine alkaloids and eremophilane sesquiterpenes [1,2]. But in preliminary experiments, the extract showed negative responses to alkaloid detecting agents, such as Dragendorff agent. In our continuing search for new anticancer agents from Chinese folk medicines, the ethanolic extract of *Senecio scandens* was found to demonstrate significant cytotoxic effects. Therefore a bioassay-guided fractionation of the extract was carried out, and four new compounds, jacaranone glycosides **1**–**4**, were isolated. The cytotoxic activities of these compounds were tested, and compounds **1**–**4** exhibited moderate cytotoxicities against five tumor cell lines. The ester glucosides **1**–**3** were isolated as inseparable mixtures due to free terminal C-1″ epimerisation in their sugar parts, whose structures were confirmed unambiguously by 1D and 2D NMR spectra and HPLC NMR

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Journal of Asian Natural Products Research
ISSN 1028-6020 print/ISSN 1477-2213 online © 2006 Taylor & Francis
http://www.tandf.co.uk/journals
DOI: 10.1080/10286020500530912

technology. Their predominant conformations were identical to the calculated energy minimal ones using SYBYL 7.0 software.

2. Results and discussion

Compound **1** was isolated as pale yellow gummy material. When **1** was purified by reversed phase HPLC using MeOH/H_2O (20:80) containing 0.1% CF_3COOH as mobile phase, two major peaks were observed, with retention times at 36 min (**1α**, the major) and 46 min (**1β**, the minor), respectively. However, these two peaks seemed to be inseparable by itinerating purifications. The (+)ESI-MS of **1α** and **1β** showed only one positive quasimolecular ion peak at *m/z* 499.3 ($[M + Na]^+$). In HRFAB-MS a pseudomolecular ion peak $[M + Na]^+$ at *m/z* 499.1212 was identical to formula $C_{23}H_{24}O_{11}$ with unsaturation degrees as 12. Its IR spectrum displayed intense absorption bands at 1670, 1604, 3408 cm^{-1}, indicating the presence of an α,β-unsaturated carbonyl and hydroxyl groups respectively. In the ^1H NMR and ^{13}C NMR spectra, two sets of resolvable signals, with obvious different intensity ratios, were observed. In NMR spectra of compound **1α**, the carbon signals at δ_C 45.9 (C-7), 68.0 (C-4), 128.3 (C-2, 6), 147.0 (C-3, 5), 170.3 (C-8) and 187.5 (C-1) and corresponding proton signals at δ_H 2.73 (s, 2H, H-7), 6.15 (2H, d, $J = 10.5$ Hz, H-2, 6), 7.03 (2H, d, $J = 10.5$ Hz, H-3, 5), typical for jacaranone moiety [3], were observed. In addition, the appearance of a pair of doublets at δ_H 6.33 and 7.62 (each 1H, $J = 15.9$ Hz) representing for a double bond conjugated to a carbonyl group, together with another pair of doublets at δ_H 6.75 (2H, d, $J = 8.7$ Hz) and 7.41 (2H, d, $J = 8.7$ Hz) for aromatic protons on a phenol ring, suggested the presence of a *p*-hydroxyl cinnamoyl moiety in this molecule. The doublet at δ_H 5.24 (1H, $J = 3.6$ Hz) was assigned to the C-1″ proton of the sugar, corresponding to α configuration of the hydroxyl group. Remaining protons in the sugar moiety resonated at δ_H 3.24–4.76. Basic hydrolysis of **1** yielded the aglycones and sugar. The existence of a glucose moiety was confirmed by comparison with an authentic sample of glucose in TLC analysis and the absolute configuration of the glucose was determined as D-type by HPLC analysis [4,5]. All these facts indicated that **1** consisted of jacaranone and *p*-hydroxyl cinnamoyl moieties as well as glucose part.

^1H–^1H COSY and DEPT allowed us to designate all protons and carbons in the sugar, and HMQC enabled the assignments of all proton signals to their attached carbons. In the HMBC spectrum the important cross peak between δ_C 168.8 and δ_H 4.61 prompted us to assign the *p*-hydroxyl cinnamoyl group to C-2″ position in the sugar, and the cross peak between δ_C 170.3 and δ_H 4.18 and 4.33 prompted to assign the jacaranone moiety to C-6″ position in the sugar. Key HMBC correlations are shown in figure 2, which confirmed the structure of **1α** as 2″-(*p*-hydroxyl cinnamoyl)-6″-jacaranone-α-D-glucopyranoside (shown in figure 1).

Compound **1β** is an anomeric isomer of **1α**. All of the spectral data of **1β** were similar to those of **1α** except the differences from the C-1″ anomeric proton and carbon signals. In the ^1H NMR spectrum the signal at 4.64 was attributed to the anomeric proton in **1β**, and a coupling constant of 7.8 indicated the α,β-configuration for the hydroxyl group was β. In the ^{13}C NMR spectrum of **1β**, the signal at δ_C 96.4 was assigned to the anomeric carbon.

The structural relationship between compounds **1α** and **1β** was further confirmed by the HPLC ^1H NMR spectrum. The ^1H NMR spectra of pure **1α** and **1β** were afforded respectively with the help of LC NMR technology. Comparing their ^1H NMR spectra, the chemical shift of anomeric proton in **1α** was obviously different from that in **1β**. In the

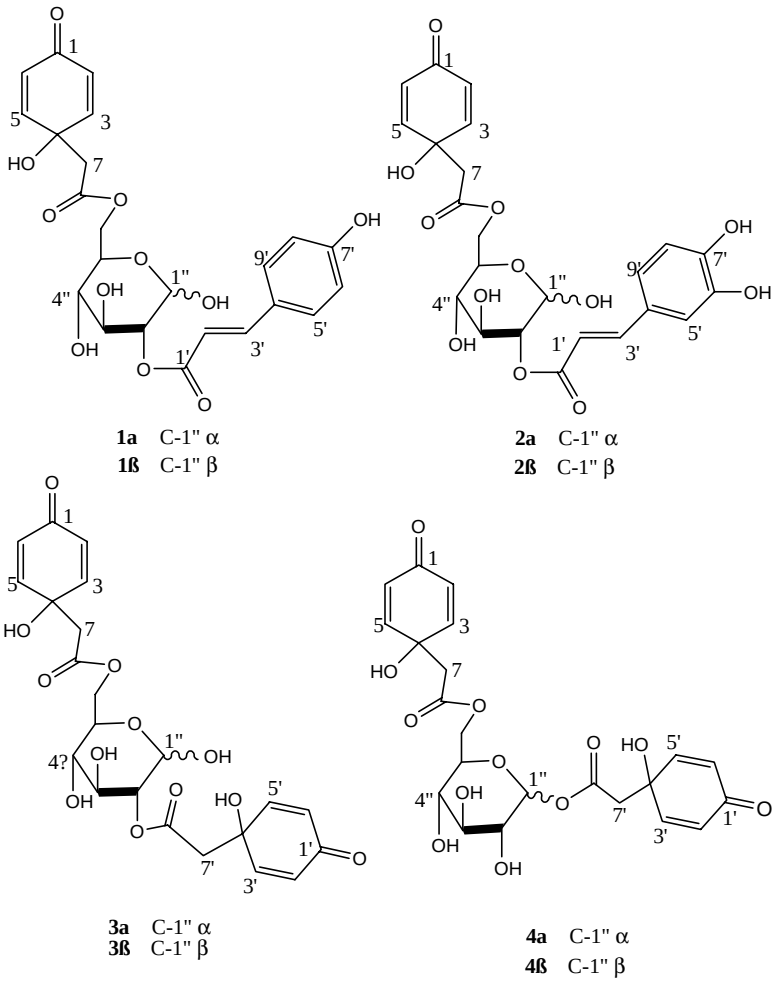

Figure 1. Structures of compounds **1**–**4**.

^{1}H NMR spectrum of **1α**, the anomeric proton was located at 5.24 with a coupling constant of 3.6, while the anomeric proton of **1β** was located at 4.64 ppm with a coupling constant of 7.8. Except for the anomeric proton, the proton signals of **1α** were identical to those of **1β**.

During the purification process, **1α** and **1β** were found to be interconvertable and exist as an epimeric mixture. In order to explain this phenomenon, their energy minimum values were calculated using SYBYL 7.0 software, and the results (see table 1) showed that the α configuration was thermodynamically stable. This conclusion was in agreement with the terminal effect, namely, the lone pair electrons of the bridged oxygen atom in pyranose were

Table 1. Data of energy minimum calculation (kcal/mol).

	1		***2***		***3***	
Configuration	*α*	*β*	*α*	*β*	*α*	*β*
E	−2.640	−2.180	−1.881	−1.047	−5.093	−4.929
Δ*E*	0.460		−0.834		0.164	

repulsive with those of terminal C-1″ hydroxyl group. From the above analysis it was obvious that α was the dominating configuration. However, the energy discrepancy in the two configurations was so small that neither of them could exist in pure form, hence they coexisted in the plant. As a result, it is reasonable that **1** was obtained as α/β epimeric mixture. The ratio of α and β configuration was 3:1, determined by HPLC analysis.

The molecular formula $C_{23}H_{24}O_{12}$ of **2** was calculated on the basis of its (+) ESI-MS ($[M + H]^+$, *m/z* 493.2), and confirmed by its HRESI-MS. This compound was also obtained as an epimeric mixture, and has one more hydroxyl group compared to **1**. The ^{1}H NMR spectrum of **2** was similar to that of **1**, except for two hydroxyl groups on the phenol ring in **2**, which means C-2″ of the sugar was esterified by a caffeoyl group in **2** in place of a *p*-hydroxyl cinnamoyl group in **1**. In the ^{1}H NMR spectrum of **2** an ABX system was shown including a doublet at δ_H 6.79 assigned to H-8′, a broad doublet at δ_H 6.97 ascribed to H-9′, and the broad singlet at δ_H 7.06 attributed to H-5′. Remaining proton signals of **2** were in agreement with those of **1**. Compound **2** was obtained as an α/β mixture with a 3:2 ratio, determined by HPLC analysis.

Compound **3** exhibited a pseudomolecular ion peak at *m/z* 503.0 ($[M + Na]^+$) in its ESI-MS spectrum. Its molecular formula $C_{22}H_{24}O_{12}$ was established by HRESI-MS. The ^{1}H NMR and ^{13}C NMR spectra of **3** revealed that it consisted of two jacaranone moieties and one glucose moiety. The HMBC spectrum showed the important correlations between δ_H 4.13, 4.33, 4.55 (H-6″, 2″) and δ_C 170.3, 169.5 (C-8′, 8) respectively, which indicated that the two jacaranone moieties should be linked to C-2″ and C-6″ positions in the sugar, respectively. The sugar obtained from the basic hydrolysis of **3** was identical to an authentic sample of D-glucose by TLC and HPLC analysis [4,5]. Hence the structure of **3** was confirmed as shown in figure 1. Compound **3** was obtained as an α/β mixture with a 3:2 ratio, determined by HPLC analysis.

Compound **4** exhibited a pseudomolecular ion peak ($[M + Na]^+$) at *m/z* 503.1 in its ESI-MS. A molecular formula $C_{22}H_{24}O_{12}$ was furnished by the aid of HRESI-MS technology. Its ^{1}H NMR and ^{13}C NMR spectra were similar to those of **3**, suggesting it was a regioisomer of **3**. HMBC correlation between H-1″ in sugar and C-8 in jacaranone moiety indicated the anomeric hydroxyl group in sugar was esterified by the carboxyl group in jacaranone. The other jacaranone was linked to C-6″ as in **3**. The reason that **4** was obtained as a mixture different from that of **1**, **2**, and **3** is that its α and β configurations are not interconvertable in the process of purification, but it was extremely difficult to be separated by reversed phase HPLC and other purification methods. The sugar obtained from the basic hydrolysis of **4** was identical to an authentic sample of D-glucose by TLC and HPLC analysis [4,5]. Compound **4** was obtained as an α/β mixture with a 1:6 ratio, determined by HPLC analysis.

3. Experimental

3.1 General experimental procedures

Mass spectra were obtained on an Autospec-Ultima ETOF. ESI-MS measurements were carried out at an Agilent 1100 series LC/MSD Trap SL mass spectrometer. IR spectra were recorded on a Nicolet-Impact 400 IR spectrometer with KBr disk. UV spectra were recorded on an HP 8453 spectrophotometer. NMR experiments were performed on MERCURY-400, or INOVA-500 spectrometers using TMS as internal standard. Silica gel (60–100, 200–300

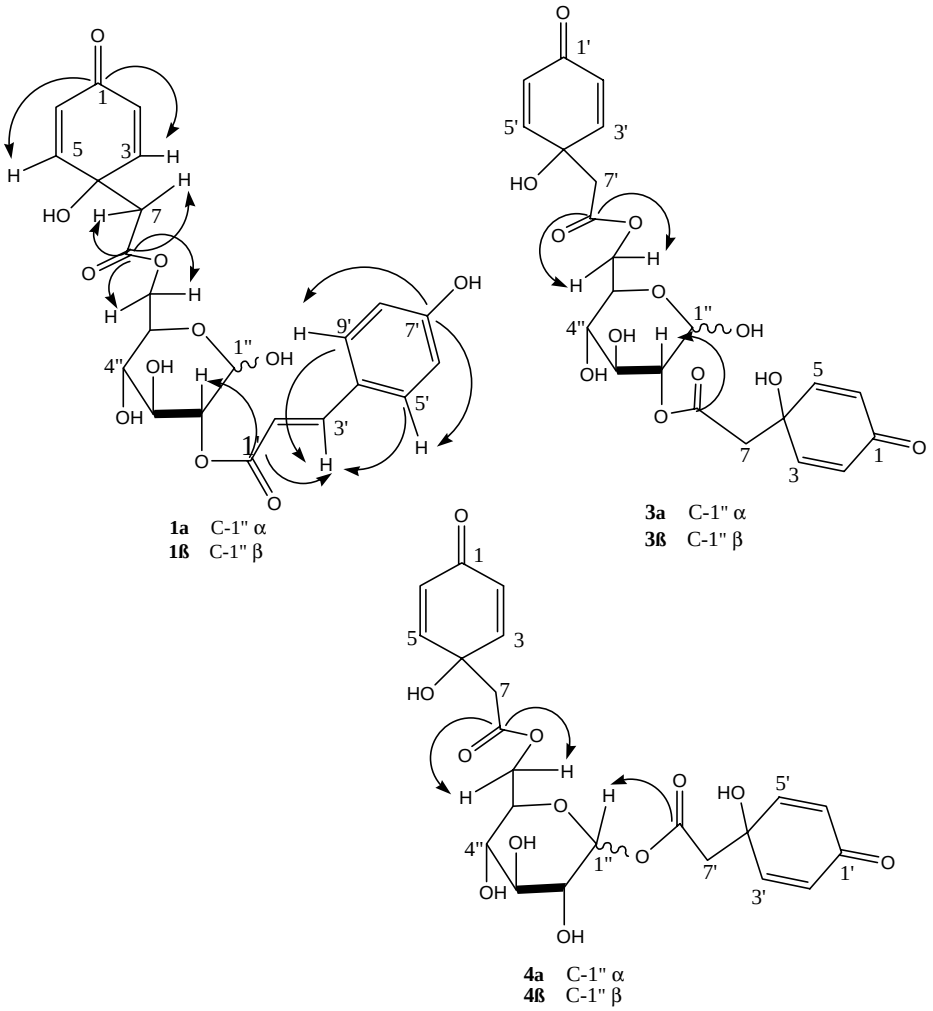

Figure 2. Key HMBC correlations of **1**, **3**, **4**.

mesh) for column chromatography and silica gel GF_{254} for TLC were obtained from Qingdao Marine Chemical Company, Qingdao, Shandong Province, China. RpC-18 (40–60 μ) silica gel was purchased from Fuji Silysica Chemical Ltd. Size-exclusion chromatography was performed using Sigma Lipophilic Sephadex LH-20. Computational chemistry studies were performed using SYBYL 7.0 software on a UNIX IRIS workstation. HPLC was carried out on an Agilent 1100 series. LC NMR was performed on a Varian INOVA-500 spectrometer equipped with $^{1}H\{^{13}C\}$ pulsed field gradient (PFG) LC NMR flow-probe with a 60 μl flow-cell, and HPLC was performed on an Varian 230 using an Inertsil ODS-3 C_{18} column (MeOD/D_2O [15:85] containing 0.1% CF_3COOD as mobile phase).

3.2 Plant material

The aerial parts of *Senecio scandens* Buch-Ham were collected from Dali, Yunnan Province of China, in October 2001. The plant was identified by Professor Guangming Liu, Dali

Medicinal College. The authenticated sample of the plant is deposited at the Herbarium of the Institute of Materia Medica, Chinese Academy of Medical Sciences (No. 817).

3.3 Extraction and isolation

The dried aerial parts (8.0 kg) of *S. scandens* were powdered and extracted with boiling ethanol under reflux. The combined alcohol extracts were concentrated *in vacuo* to yield a dark brown residue (1.2 kg), which was chromatographed on silica gel (60–100 mesh, 4 kg) and eluted with petroleum ether/acetone, acetone, and methanol to provide fractions I (53 g), II (78 g), III (125 g), IV (353 g) and V (200 g), respectively. Bioactive Fr. IV (353 g) was subjected to silica gel CC (1.0 kg) eluting with $CHCl_3$/MeOH (95:5, 12.6 L; 90:10, 9 L; 85:15, 14.5 L; 80:20, 8.5 L; 70:30, 14.0 L; 50:50, 20 L) to afford six fractions (A1, A2, A3, A4, A5, A6). Bioactive Fr. A2 (45.0 g) was subjected to silica gel CC (200–300 mesh, 2 kg) eluting with MeOH/$CHCl_3$ (30:70) to afford 11 fractions (A2-1–A2-11). Fr. A2-1 (1.54 g) was chromatographed on silica gel using $CHCl_3/CH_3OH/H_2O$ (80:20:1, 9.0 L) as eluent to afford six sub-fractions (A2-1-1–A2-1-6). Fr. A2-1-3 (0.885 g) was further separated with Sephadex LH-20 using MeOH as eluent to afford **1** (0.5 g). Compound **1** was purified by HPLC on ODS (YMC-Pack ODS-A C-18, 250 × 20 mm; eluent, 20% MeOH and 0.1% CF_3COOH; flow rate, 5.0 ml/min; detection UV at 210 nm) to yield the mixture of α/β epimer. Fr. A2-4 (19.0 g) was subjected to silica gel CC (800 g) eluting with $CHCl_3/CH_3OH/H_2O$ (85:15:1) to afford eight sub-fractions (A2-4-1–A2-4-8). Fr. A2-4-5 (1.5 g) was further separated over silica gel CC using $CH_3Cl/CH_3OH/H_2O$ (90:10:1) and reversed phase column chromatography using MeOH/H_2O (20:80) as eluent and purified by HPLC on ODS (YMC-Pack ODS-A C-18, 250 × 20 mm; eluent, 20% MeOH and 0.1% CF_3COOH; flow rate, 5.0 ml/min; detection UV at 210 nm) to afford **2** (0.002 g). Fr. A2-4-6 (1.1 g) was chromatographed on silica gel (200–300 mesh, 70 g) using $CH_3Cl/CH_3OH/H_2O$ (90:10:1) and purified by Sephadex LH-20 using CH_3OH as eluent and then by HPLC preparation on ODS (YMC-Pack ODS-A C-18, 250 × 20 mm; eluent, 20% MeOH and 0.1% CF_3COOH; flow rate, 5.0 ml/min; detection UV at 210 nm) to afford **3** (0.019 g), **4** (0.013 g).

3.3.1 Compound 1. Pale yellow gum; $[\alpha]_D^{26}$ + 16 (*c* 0.15, MeOH), UV (MeOH) λ_{max} (log ε) (nm): 232 (3.060), 276 (3.063); IR (KBr) ν_{max} (cm^{-1}): 3408, 1670, 1604, 1561, 1171, 1061; (+)ESI-MS *m/z* 499.3 $[M + Na]^+$; HRFAB *m/z* 499.1212 $[M + Na]^+$ (calcd for $C_{23}H_{24}O_{11}Na$, 499.1216); ^1H NMR and ^{13}C NMR data: see tables 2 and 4, respectively.

3.3.2 Compound 2. Yellow gum; $[\alpha]_D^{26}$ + 6 (*c* 0.15, MeOH); UV (MeOH) λ_{max} (log ε) (nm): 234 (1.156), 302 (1.161); IR (KBr) ν_{max} (cm^{-1}): 3406, 1674, 1188; (−)ESI-MS (*m/z*): 491.5 $[M - H]^-$, (+)ESI-MS (*m/z*): 493.2 $[M + H]^+$; HRESI-MS *m/z* 491.1195 $[M - H]^-$ (calcd for $C_{23}H_{23}O_{12}$, 491.1196); ^1H NMR and ^{13}C NMR data: see tables 2 and 4, respectively.

3.3.3 Compound 3. Pale yellow gum; UV (MeOH) λ_{max} (log ε) (nm): 240 (2.923); IR (KBr) ν_{max} (cm^{-1}): 3384, 1732, 1672, 1626, 1070, 1038; (+)ESI-MS (*m/z*): 503.1 $[M + Na]^+$;

Table 2. ^{1}H NMR assignments for compounds **1** and **2** in CD_3OD [δ_H, mult, intgr, [*J* in Hz)].

	1		***2***	
H	***1α*** *(major)*	***1β*** *(minor)*	***2α*** *(major)*	***2β*** *(minor)*
2	6.12 d (10.5)	6.11 d (10.5)	6.18 d (10)	6.18 d (10)
3	7.03 d (10.5)	7.03 d (10.5)	7.10 d (10)	7.10 d (10)
5	7.03 d (10.5)	7.03 d (10.5)	7.10 d (10)	7.10 d (10)
6	6.12 d (10.5)	6.11 d (10.5)	6.18 d (10)	6.18 d (10)
7	2.73 s	2.73 s	2.80 s	2.80 s
2′	6.33 d (16.5)	6.31 d (16.5)	6.34 d (15.5)	6.32 d (15.5)
3′	7.63 d (16.5)	7.59 d (16.5)	7.64 d (15.9)	7.59 d (15.9)
5′	7.41 d (8.4)	7.41 d (8.4)	7.06 br s	7.06 br s
6′	6.75 d (8.7)	6.75 d (8.7)		
8′	6.75 d (8.7)	6.75 d (8.7)	6.79 d (8.5)	6.82 d (8.5)
9′	7.41 d (8.4)	7.41 d (8.4)	6.97 br d (8)	6.97 d (8)
1″	5.23 d (3.3)	4.64 d (7.8)	5.24 d (3.6)	4.69 d (8.0)
2″	4.61 dd (3.3, 9.9)	4.72 dd (8.1, 9.0)	4.67 m	4.67 m
3″	3.89 dd (9.9, 8.7)	3.89 dd (9.9, 8.7)	3.90 m	3.90 m
4″	3.37 dd (9.9, 9)	3.37 dd (9.9, 9)	3.37 m	3.37 m
5″	3.96 m	3.50 m	3.96 m	3.96 m
6″a	4.18 dd (5.4, 12)	4.18 dd (5.4, 12)	4.42 m	4.22 m
6″b	4.33 dd (2.4, 12)	4.33 dd (2.4, 12)	4.42 m	4.42 m

Chemical shifts are in ppm relative to TMS. Spectra were recorded at 25°C. Proton assignments were aided by ^{1}H–^{1}H COSY, HMQC, HMBC experiments. Compounds **1** and **2** occur in solution as mixtures of two isomers.

HRESI-MS *m/z* 503.1160 $[M + Na]^+$ (calcd for $C_{22}H_{24}O_{12}Na$, 503.1162); ^{1}H NMR and ^{13}C NMR data: see tables 3 and 4, respectively.

3.3.4 Compound 4. Light yellow gum; UV (MeOH) λ_{max} (log ε) (nm): 226 (2.258); IR (KBr) ν_{max} (cm^{-1}): 3384, 1732, 1672, 1626, 1070, 1038; (+)ESI-MS (*m/z*): 503.1 $[M + Na]^+$; HRESI-MS *m/z* 503.1160 $[M + Na]^+$ (calcd for $C_{22}H_{24}O_{12}Na$ 503.1162); ^{1}H NMR and ^{13}C NMR data: see tables 3 and 4, respectively.

Table 3. ^{1}H NMR assignments for compounds **3**, **4** in CD_3OD [δ_H, mult, intgr, [*J* in Hz)].

	3		***4***	
H	***3α*** *(major)*	***3β*** *(minor)*	***4α*** *(major)*	***4η*** *(minor)*
2	6.09 d (8.8)	6.09 d (8.8)	6.10 m	6.10 m
3	7.04 d (9.2)	7.04 d (9.2)	7.01 m	7.01 m
5	7.04 d (8.8)	7.04 d (8.8)	7.01 m	7.01 m
6	6.09 d (8.8)	6.09 d (8.8)	6.10 m	6.10 m
7	2.75 s	2.75 s	2.80 s	2.80 s
2′	6.09 d (8.8)	6.09 d (8.8)	6.10 d (8.8)	6.10 d (8.8)
3′	7.04 d (8.8)	7.04 d (8.8)	7.01 d (8.8)	7.01 d (8.8)
5′	7.04 d (8.8)	7.04 d (8.8)	7.01 d (8.8)	7.01 d (8.8)
6′	6.09 d (8.8)	6.09 d (8.8)	6.10 d (8.8)	6.10 d (8.8)
1″	5.12 Brs	4.59 d (8.4)	5.36 d (4.0)	4.51 d (8.0)
2″	4.54 m	4.57 m	3.33 m	3.33 m
3″	3.80 m	3.90 m	3.33 m	3.33 m
4″	3.41 m	3.37 m	3.33 m	3.33 m
5″	3.86 m	3.86 m	3.45 m	3.45 m
6″a	4.13 m	4.13 m	4.06 m	4.06 m
6″b	4.34 m	4.34 m	4.34 m	4.34 m

Chemical shifts are in ppm relative to TMS. Spectra were recorded at 25°C. Compounds **3** and **4** occurs in solution as mixtures of two isomers.

Table 4. ^{13}C NMR Assignments for compounds **1**–**4** in CD_3OD (in ppm).

Position	***1***		***2***		***3***		***4***	
	1α *(major)*	***1β*** *(minor)*	***2α*** *(major)*	***2β*** *(minor)*	***3α*** *(major)*	***3β*** *(minor)*	***4α*** *(major)*	***4β*** *(minor)*
1	187.5	187.6	186.5	186.4	187.5	187.5	187.5	187.4
2	128.3	128.4	127.3	127.2	128.4	128.4	128.4	128.2
3	147.0	146.7	151.7	151.6	152.7	152.8	152.4	152.4
4	68.0	68.0	67.0	67.0	68.1	70.4	68.1	68.1
5	147.0	146.7	151.7	151.6	152.7	152.8	152.2	152.2
6	128.3	128.4	127.3	127.2	128.4	128.4	128.4	128.2
7	45.9	45.8	44.7	44.7	45.8	45.7	45.6	45.7
8	170.3	170.2	169.2	169.1	170.3	170.3	169.0	169.0
1′	168.8	168.5	167.6	167.3	187.5	187.5	187.5	187.4
2′	114.9	115.3	113.8	114.2	128.4	128.4	128.6	128.6
3′	147.1	146.7	145.9	145.6	152.5	152.8	152.8	152.8
4′	127.2	127.1	127.3	127.2	68.1	70.4	68.1	68.1
5′	131.2	131.1	115.7	115.7	152.5	152.8	152.8	152.8
6′	116.8	116.8	151.6	151.6	128.4	128.4	128.6	128.6
7′	161.3	161.2	161.2	160.1	45.8	45.7	45.9	45.8
8′	116.8	116.8	126.1	126.1	169.5	170.2	170.1	170.1
9′	131.2	131.1	130.1	130.0				
1″	91.3	96.4	90.2	95.3	91.1	96.1	95.7	98.2
2″	75.2	76.0	74.2	74.1	75.6	75.8	71.2	71.6
3″	72.0	70.4	71.0	70.8	75.3	75.3	76.0	75.1
4″	71.9	71.7	70.6	69.3	71.9	71.7	73.7	73.7
5″	75.2	76.4	74.9	75.3	76.9	76.9	77.9	77.7
6″	65.0	65.1	64.0	63.9	65.0	65.0	64.8	64.9

Compounds **1**–**4** occur in solution as mixtures of two isomers.

Acknowledgements

The authors are thankful to the Beijing Municipal Science & Technology Commission of China for the financial support. We also thank Mr Hongyan Liu for the cytotoxicity assay and Ms Xiaohua Ma for energy minimisation calculations.

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