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Four new norlignan glycoside isomers from the twigs of *Cephalotaxus oliveri* Mast.

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ABSTRACT

Four novel isomers of norlignan glycoside were isolated from *Cephalotaxus oliveri* Mast.. Their structures were elucidated as 3*S*-4″-*O*-*β*-D-glucopyranosylnyasol **1**, 3*S*-4′-*O*-*β*-D-glucopyranosylnyasol **2**, 3*S*-4″-*O*-*β*-D-glucopyranosylhinokiresinol **3**, 3*S*-4′-*O*-*β*-D-glucopyranosylhinokiresinol **4** by extensive spectroscopic methods including 1D and 2D NMR experiments (^{1}H, ^{13}C, DEPT, ^{1}H–^{1}H COSY, HSQC, HMBC, ROESY) along with HR-ESIMS and comparison to literature data. Their absolute configurations were elucidated through CD spectra coupled with the quantum chemical CD calculations.

1. Introduction

Cephalotaxus oliveri Mast. (Cephalotaxaceae) is mainly distributed in Vietnam, and the Southeast and Southwest regions of China.[1] Phytochemical investigations showed that alkaloids including cephalotaxine type and homoerythrina type alkaloids were the main constituents of *Cephalotaxus* genus. Lactones, flavonoids, essential oil and other natural compounds were also found from *C. oliveri* and other plants of *Cephalotaxus* genus.[2–5] Recent studies have revealed that the bioactive components from *Cephalotaxus*-genus have pharmacological activities, such as anti-tumor, anti-oxidant, anti-inflammatory, and anti-phytoviral activities.[5–11] Some cephalotaxine type alkaloids, such as homoharringtonine, showed potent anti-cancer activity. Homoharringtonine had been approved by the Food and Drug Administration of USA for the treatment of chronic myeloid leukemia in the chronic phase or accelerated phase.

Herein, we report the isolation of four new norlignan glycoside isomers from *C. oliveri*. Their structures were elucidated by extensive spectroscopic methods including 1D and 2D NMR experiments (^{1}H, ^{13}C, DEPT, ^{1}H–^{1}H COSY, ROESY, HSQC, HMBC) along with HR-ESIMS and comparison of CD spectra with quantum chemical calculated CD spectra.

2. Results and discussion

The molecular formula of compound **1** was determined to be $C_{23}H_{26}O_7$ in agreement with its HR-ESIMS data (*m*/*z* 432.2003 $[M+NH_4]^+$, calcd for $C_{23}H_{30}O_7N$ 432.2022 and *m*/*z* 413.1585 $[M-H]^-$, calcd for $C_{23}H_{25}O_7$ 413.1600). The ^{1}H NMR spectrum of **1** showed the signals of two *para*-disubstituted aromatic rings [*δ* 7.11 (d, 2H, *J* = 8.5 Hz), 7.04 (d, 2H, *J* = 8.7 Hz); 7.14 (d, 2H, *J* = 8.7 Hz), 6.73 (d, 2H, *J* = 8.5 Hz)] and those of a vinyl group [*δ* 5.12 (br d, 1H, *J* = 16.7 Hz), 5.12 (br d, 1H, *J* = 10.8 Hz) and 6.01 (ddd, 1H, *J* = 16.7, 10.8, 6.1 Hz)] and a vinylene (*δ* 6.49, d, 1H, *J* = 11.4 Hz; 5.65, dd, 1H, *J* = 11.4, 9.7 Hz). The signals at *δ* 6.01 and 5.65 are further coupled with a hydrogen at *δ* 4.50 (dd, 1H, *J* = 9.7, 6.4 Hz), which indicated the existence of a 1,4-pentadiene group. The 1,4-pentadiene 1,3-disubstituted by two *para*-disubstituted aromatic rings were confirmed by the correlation between the hydrogen at *δ* 4.50 (dd, 1H, *J* = 9.7, 6.1 Hz) and a quaternary carbon at *δ* 138.8, and the correlation between the hydrogen at *δ* 6.49 (d, 1H, *J* = 11.4 Hz) and a quaternary carbon at *δ* 129.8 in the HMBC spectrum. Due to the coupling constant between H-1 and H-2 (*J* = 11.4 Hz), the configuration of the double bond was determined as *Z*. A doublet at *δ* 4.88 (d, 1H, *J* = 7.4 Hz) whose ^{13}C NMR signals at *δ* 102.3, indicated the existence of a *β*-glucopyranosyl. Based on the information above, compound **1** was deduced to be a glucoside of nyasol. The glycosidic linkage is hard to determine by HMBC due to the very closely chemical shifts of C-4′ and C-4″ (*δ* 157.7 and 157.6). However, the correlation between the anomeric hydrogen of the glucopyranosyl and the H-3″, 5″ could be observed in the

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ROSEY spectrum, which suggested that the glucopyranosyl should be substituted at C-4″. Its absolute configuration was determined as D-glycopyranosyl by HPLC analysis of the derivative of its acid hydrolyzed residue.[12] These data indicated that compound **1** had the same planar structure as mononyasine A (4″-*O*-*β*-D-glucopyranosylnyasol).[13]

Compound **2** gave a same molecular formula $C_{23}H_{26}O_7$ from its HR-ESIMS spectrum (*m*/*z* 432.2002 $[M+NH_4]^+$, calcd for $C_{23}H_{30}O_7N$ 432.2022 and *m*/*z* 413.1587 $[M-H]^-$, calcd for $C_{23}H_{25}O_7$ 413.1600). When comparing the ^1H and ^{13}C NMR spectra of **2** and **1**, they give similar NMR data, which indicates that compound **2** was the isomeric compound of compound **1**. In the ROSEY spectrum of compound **2**, the correlation between the anomeric hydrogen of the glucopyranosyl and the H-3′, 5′ indicated that the glucopyranosyl was substituted at C-4′. Compound **2** had the same planar structure as mononyasine B.[13]

Compounds **3** and **4** also gave the same molecular formula, $C_{23}H_{26}O_7$, in their HR-ESIMS spectrum. Their NMR data were also similar to those of compounds **1** and **2**, except that the coupling constants between H-1 and H-2 were 15.9 Hz, which indicated that they were the glycosides of hinokiresinol, a pair of *E*-isomers of compounds **1** and **2**. The attachments of glycopyranosyl moiety of compounds **3** to C-4″, and to C-4′ for compound **4**, were indicated by the HMBC correlations of H-glu-1 to the corresponding carbon, respectively. The glycopyranosyl moieties were also determined as having a D-configuration by HPLC analysis of the derivatives of their acid hydrolyzed residues.

Herein, the absolute configurations of **1**–**4** were determined by the CD spectra coupled with the quantum chemical CD calculations in Gaussian 09 software and comparison of their physicochemical properties. Four absolute configurations (*ZS*/*ZR* and *ES*/*ER*) of aglycone were selected randomly for the systematically conformational analysis in the SYBYL 8.1 program by using MMFF94's molecular force field. Among the obtained conformers, eight and ten lowest-energy conformers were selected for optimization and further time-dependent DFT [CAM-B3LYP/6-31 + G(d)//B3LYP/6-31+G(d)] computations, respectively. The predicted CD spectra of *ZS* and *ES* revealed good agreement with the experimental ones of **1**, **2** (Fig. 2A) and **3**, **4** (Fig. 2B), respectively. Therefore, the absolute configurations of **1**, **2** and **3**, **4** were, respectively, established as (1*Z*,3*S*) and (1*E*,3*S*). Consequently, these four norlignan glycoside isomers were elucidated as 3*S*-4″-*O*-*β*-D-glucopyranosylnyasol **1**, 3*S*-4′-*O*-*β*-D-glucopyranosylnyasol **2**, 3*S*-4″-*O*-*β*-D-glucopyranosylhinokiresinol **3**, 3*S*-4′-*O*-*β*-D-glucopyranosylhinokiresinol **4**.

The isolation and planar structures of mononyasines A and B were reported in 1989.[13] However, the absolute configurations of mononyasines A and B have not been determined until now. Compounds **1** and **2** share the same planar structures as mononyasines A and B, but have opposite specific rotation values. Compounds **1**

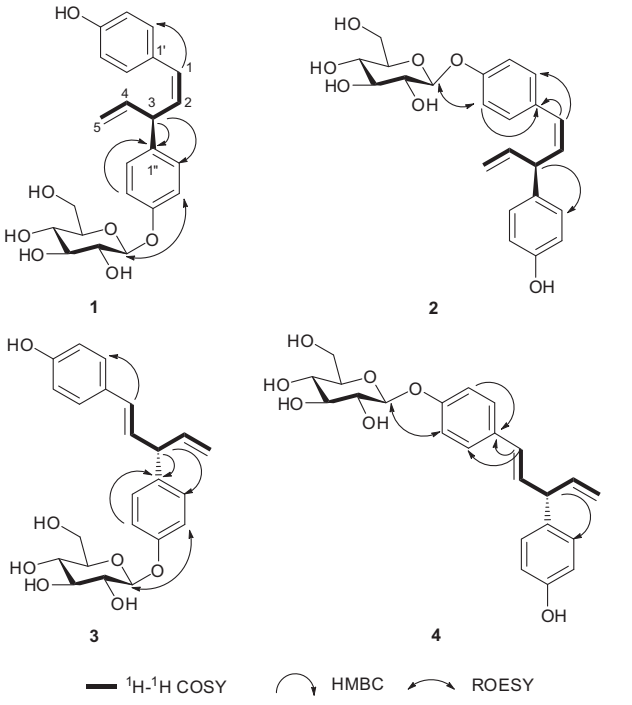

Figure 1. Structures of compounds **1**–**4** and their key ^{1}H–^{1}H COSY, HMBC and ROESY correlations.

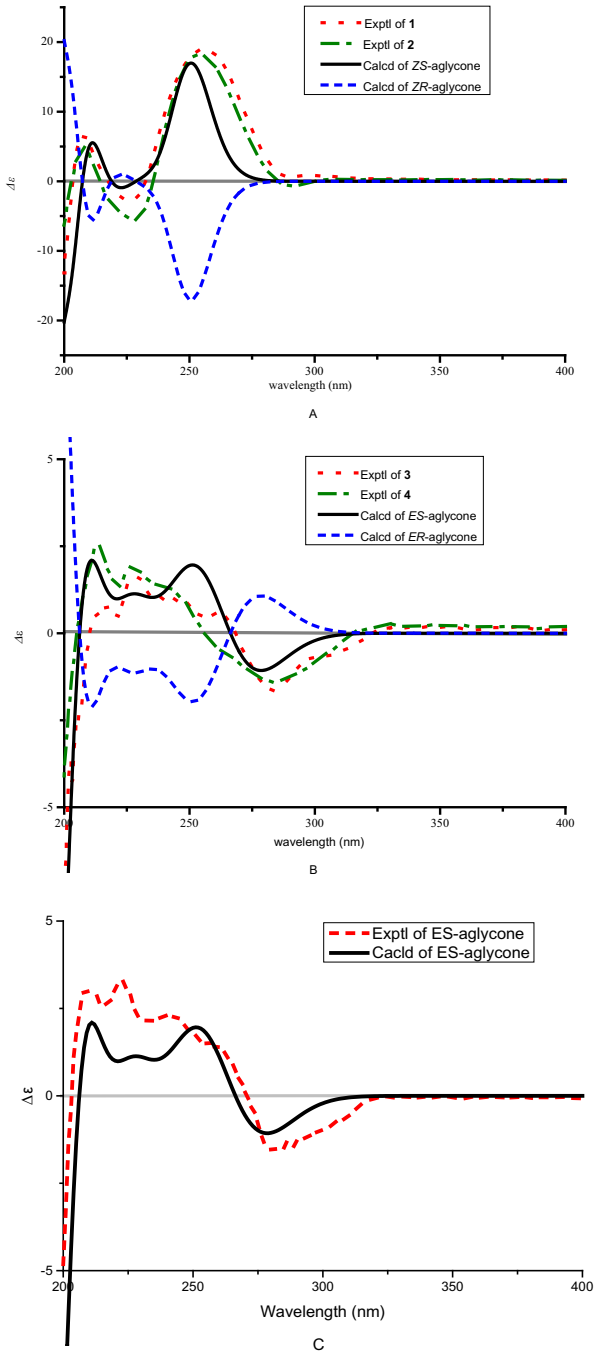

Figure 2. Calculated and experimental CD spectra of compounds **1**, **2** (A), compounds **3**, **4** (B) and reference (3*S*)-hinokiresinol (C).

and **2** are the epimers of mononyasines A and B, respectively. Thus, mononyasines A and B would have a (3*R*)-configuration. The aglycones of compounds **1**–**4**, naysol and hinokiresinol, have been isolated and their enantioselective synthesis were also achieved.[14–16] There are no ambiguities in the assignment of the absolute configuration of (−)- and (+)-nyasol. It was reported that synthetic (+)-nyasol has an (*S*)-stereogenic center[14] and (−)-nyasol has an (*R*)-stereogenic center.[15] Their CD data were also reported.[17] However, the reports about the absolute configuration determination of hinokiresinol were often contradictory.[17–19] Hinokiresinol was first reported from *Chamaecyparis obtusa* by Hirose et al.[20] A (3*S*)-configuration was reported by chemical transformation.[21] Minami et al.[17] claimed a (3*S*)-configuration for (−)-hinokiresinol followed by Lassen et al.[18] who synthesized the hinokiresinol racemates and then separated them on a chiral column. Lassen et al. assigned (3*S*) and (3*R*) for (−) and (+)-hinokiresinol, respectively. The synthesized (*R*)-hinokiresinol by Hamilton et al.[16] had a negative specific rotation. Commercial (3*S*)-hinokiresinol exhibited a positive specific rotation {$[\alpha]_D^{20}$ = +3.5, (*c* 1.2, acetone)} and its CD spectrum was in good agreement with the predicted one (Fig. 2C), which supported Hamilton's result.[16]

3. Conclusion

A chemical investigation on the twigs of *Cephalotaxus oliveri* Mast. led to the isolation of four new norlignan glycosides **1**–**4** (Fig. 1). Compounds **1** and **2** are epimers of mononyasine A and mononyasine B, respectively. Compounds **3** and **4** are the *E*-isomers of compounds **1** and **2**. The absolute configurations of their aglycones were determined by comparing the experimental and calculated ECD spectra, and those of the glucopyranosyl were determined by analysis their derivatives using HPLC method.

4. Experimental

4.1. General

HR-ESIMS measurements were carried out on Thermo LTQ Orbitrap XL mass spectrometer (Thermo Electron, Bremen, Germany). IR spectra were recorded on a PerkinElmer Spectrum 100 FT-IR Spectrometer with KBr pellets (PerkinElmer, Waltham, USA). Optical rotations were measured on a PerkinElmer Model 341 polarimeter at the sodium D line at 20.0 °C (PerkinElmer, Waltham, USA). UV spectra were obtained on a HACH DR-6000 UV/VIS spectrophotometer (HACH, Loveland, USA). 1D and 2D NMR spectra were recorded on a Bruker Ascend 600 spectrometer (CD_3OD used as solvent and TMS as an internal standard, Fallanden, Switzerland). HPLC was performed on an Agilent 1200 Chromatograph equipped with a 250 mm × 4.6 mm i.d. Cosmosil 5C18-AR-II column (Nacalai Tesque Inc., Kyoto, Japan) at 25 °C. Column chromatography was performed on silica gel (200–300 mesh, Qingdao Marine Chemical Group Co., Qingdao, China) and Sephadex LH-20 (Pharmacia, USA); the solvents of analytical grade used for extraction and gel chromatography were supplied by Kaitong Chemical Co. Ltd. (Tianjin, China). Solvents applied for preparative column and HPLC analysis were of HPLC grade and purchased from Merck (Darmstadt, Germany). Distilled water was purified with a Millipore Milli Q-Plus system (Millipore, Milford, MA, USA). (3*S*)-Hinokiresinol was purchased from Shanghai Yihe Biological Technology Co., Ltd. (Shanghai, China).

4.2. Plant material

The twigs of *Cephalotaxus oliveri* Mast. were collected in Jiujiang, Jiangxi province, China in April 2014, and authenticated by Professor Qing-Qian Zeng (Guangdong Research Institute of Traditional Chinese Medicine). A voucher specimen was deposited in the Guangdong Research Institute of Traditional Chinese Medicine.

4.3. Extraction and isolation

Dried twigs of *C. oliveri* were powdered and percolated with 95% ethanol. The ethanol extract was dissolved in 2% hydrochloric acid and then extracted with $CHCl_3$. The acidic layer was basified to pH 10 with aqueous ammonia and then extracted with $CHCl_3$. The $CHCl_3$ solution was concentrated to give a residue (20 g), which was separated by a silica gel column using $CHCl_3$-MeOH (1:0 → 1:1) as eluent, affording 5 fractions (Fr1-5). Fr-4 (4.8 g) was subjected to silica gel column using $CDCl_3$-MeOH (30:1 → 5:1) as a gradient eluent to afford 6 sub-fractions 1–6.

Table 1
^1H (600 MHz, δ in ppm, *J* in Hz) and ^{13}C NMR (150 MHz, δ in ppm) data of compounds **1**–**4** in CD_3OD

	1		**2**		**3**		**4**	
	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
1	130.0	6.49 (d, 11.4)	129.2	6.52 (d, 11.4)	131.2	6.30 (d, 15.9)	130.5	6.33 (d, 15.9)
2	132.0	5.65 (dd, 11.4, 9.7)	133.6	5.71 (dd, 11.4, 10.0)	130.0	6.19 (dd, 15.9, 6.8)	132.0	6.28 (dd, 15.9, 6.7)
3	48.5	4.50 (dd, 9.7, 6.1)	48.4	4.44 (dd, 10.0, 6.2)	53.1	4.13 (dd, 6.8, 6.8)	53.1	4.10 (dd, 6.7, 6.7)
4	142.4	6.01 (ddd, 16.7, 10.8, 6.1)	142.6	6.00 (ddd, 15.9, 10.7, 6.2)	142.2	6.08 (ddd, 17.1, 10.1, 6.8)	142.3	6.08 (ddd, 17.2, 10.2, 6.7)
5	115.1	5.12 (br d, 16.7) 5.12 (br d, 10.8)	114.9	5.11 (br d, 15.9) 5.10 (br d, 10.7)	115.2	5.12 (br d, 10.1) 5.07 (br d, 17.1)	115.1	5.11 (br d, 10.2) 5.06 (br d, 17.2)
1′	129.8		132.7		130.4		133.3	
2′, 6′	130.9	7.11 (d, 8.5)	130.8	7.23 (d, 8.7)	128.4	7.20 (d, 8.6)	128.2	7.30 (d, 8.7)
3′, 5′	116.0	6.73 (d, 8.5)	117.4	7.06 (d, 8.7)	116.3	6.70 (d, 8.6)	117.7	7.02 (d, 8.7)
4′	157.7[a]		158.1		158.0[b]		158.4	
1″	138.8		135.4		138.3		135.0	
2″, 6″	129.6	7.14 (d, 8.7)	129.6	7.02 (d, 8.5)	130.0	7.17 (d, 8.7)	130.0	7.06 (d, 8.5)
3″, 5″	117.8	7.04 (d, 8.7)	116.3	6.72 (d, 8.5)	117.7	7.06 (d, 8.7)	116.2	6.74 (d, 8.5)
4″	157.6[a]		157.0		157.7[b]		157.0	
Glu-1	102.3	4.88 (d, 7.4)	102.1	4.92 (d, 7.4)	102.3	4.89 (d, 7.4)	102.2	4.88 (d, 7.4)
Glu-2	74.9	3.45 (m)	74.9	3.46 (m)	74.9	3.45 (m)	74.9	3.45 (m)
Glu-3	78.0	3.44 (m)	78.0	3.45 (m)	77.9	3.44 (m)	77.9	3.44 (m)
Glu-4	71.3	3.38 (m)	71.3	3.39 (m)	71.3	3.39 (m)	71.3	3.39 (m)
Glu-5	78.1	3.42 (m)	78.1	3.44 (m)	78.1	3.42 (m)	78.1	3.42 (m)
Glu-6	62.5	3.88 (dd, 12.1, 2.1) 3.69 (dd, 12.1, 5.5)	62.5	3.90 (dd, 12.1, 2.1) 3.69 (dd, 12.1, 5.6)	62.5	3.89 (dd, 12.1, 2.1) 3.69 (dd, 12.1, 5.5)	62.4	3.89 (dd, 12.1, 2.1) 3.69 (dd, 12.1, 5.5)

[a,b] Interchangeable.

Sub-fraction 4 (1.1 g) was subjected to silica gel column chromatography with the solvent system $CHCl_3$-MeOH (15:1 → 10:1) to give 4 sub-fractions. Further chiral separation of sub-fraction 3 was performed on an Agilent 1200 HPLC equipped with a 250 mm × 4.6 mm Lux® Cellulose-3 5 μm column (CH_3CN:H_2O 25:75). Finally, compound **1** (1.0 mg), **2** (2.0 mg), **3** (2.9 mg) and **4** (4.0 mg) were obtained.

4.3.1. (3*S*)-4″-*O*-β-D-Glucopyranosylnyasol 1

Amorphous powder, $C_{23}H_{26}O_7$, $[\alpha]_D^{20}$ = +119.0 (*c* 0.03, MeOH), IR (KBr) ν_{max}: 3133, 2926, 2855, 1660, 1611, 1510, 1401, 1234, 1074 cm^{-1}; UV (MeOH) λ_{max} (log ε): 207 (4.02), 257 (3.76) nm; HR-ESIMS *m*/*z* 432.2003 $[M+NH_4]^+$ (calcd for $C_{23}H_{30}O_7N$, 432.2022) and *m*/*z* 413.1585 $[M-H]^-$ (calcd for $C_{23}H_{25}O_7$, 413.1600); CD (MeOH): $[\theta]_{228}$ −8800, $[\theta]_{255}$ +62400; ^1H NMR (CD_3OD, 600 MHz) and ^{13}C NMR (CD_3OD, 150 MHz) data see Table 1.

4.3.2. (3*S*)-4′-*O*-β-D-Hlucopyranosylnyasol 2

Amorphous powder, $C_{23}H_{26}O_7$, $[\alpha]_D^{20}$ = +95.0 (*c* 0.1, MeOH), IR (KBr) ν_{max}: 3274, 2931, 2859, 1664, 1614, 1405, 1231 1077 cm^{-1}; UV (MeOH) λ_{max} (log ε): 206 (3.93), 252 (3.72) nm; HR-ESIMS *m*/*z* 432.2000 $[M+NH_4]^+$ (calcd for $C_{23}H_{30}O_7N$, 432.2022) and *m*/*z* 413.1586 $[M-H]^-$ (calcd for $C_{23}H_{25}O_7$, 413.1600); CD (MeOH): $[\theta]_{228}$ −18500, $[\theta]_{254}$ +55900, $[\theta]_{290}$ −2100; ^1H NMR (CD_3OD, 600 MHz) and ^{13}C NMR (CD_3OD, 150 MHz) data see Table 1.

4.3.3. (3*S*)-4″-*O*-β-D-Glucopyranosylhinokiresinol 3

Amorphous powder, $C_{23}H_{26}O_7$, $[\alpha]_D^{20}$ −16.6 (*c* 0.05, MeOH), IR (KBr) ν_{max}: 3168, 2928, 2858, 1654, 1624, 1414, 1247, 1085 cm^{-1}; UV (MeOH) λ_{max} (log ε): 206 (4.30) nm; HR-ESIMS *m*/*z* 432.2001 $[M+NH_4]^+$ (calcd for $C_{23}H_{30}O_7N$, 432.2022), *m*/*z* 459.1639 $[M+HCOO]^-$ (calcd for $C_{24}H_{27}O_9$, 459.1655) and *m*/*z* 413.1585 $[M-H]^-$ (calcd for $C_{23}H_{25}O_7$, 413.1600); CD (MeOH): $[\theta]_{229}$ +5300, $[\theta]_{242}$ +3200, $[\theta]_{261}$ +2000, $[\theta]_{284}$ −5400; ^1H NMR (CD_3OD, 600 MHz) and ^{13}C NMR (CD_3OD, 150 MHz) data see Table 1.

4.3.4. (3*S*)-4′-*O*-β-D-glucopyranosylhinokiresinol 4

Amorphous powder, $C_{23}H_{26}O_7$, $[\alpha]_D^{20}$ −38.3 (*c* 0.13, MeOH), IR (KBr) ν_{max}: 3138, 2935, 2848, 1651, 1616, 1406, 1242, 1081 cm^{-1}; UV (MeOH) λ_{max} (log ε): 208 (4.04), 261 (4.01) nm; HR-ESIMS *m*/*z* 432.2002 $[M+NH_4]^+$ (calcd for $C_{23}H_{30}O_7N$, 432.2022) and *m*/*z* 413.1587 $[M-H]^-$ (calcd for $C_{23}H_{25}O_7$, 413.1600); CD (MeOH): $[\theta]_{227}$ +6400, $[\theta]_{240}$ +4600, $[\theta]_{284}$ −4700; ^1H NMR (CD_3OD, 600 MHz) and ^{13}C NMR(CD_3OD, 150 MHz) data see Table 1.

4.4. Acid hydrolysis

Compounds **1**–**4** (each 0.5–2 mg) were hydrolyzed in 2 mL of 2 mol/L HCl at 80 °C water-bath for 2 h. After remove the solvent, the residues were dissolved in 0.5 mL pyridine containing 5 mg of L-cysteine methyl ester. The mixtures were then kept at 60 °C water-bath for 1 h, after which *O*-tolyl isothiocyanate (5 mg) was added and heated for 1 h.[13] Finally, the solutions were passed through a 0.45 μm syringe filter for HPLC analysis (Agilent 1200, 250 mm × 4.6 mm i.d. Cosmosil 5C18-AR-II, acetonitrile: 0.5% aqueous trifluoroacetic acid solution 25:75, 0.8 mL/min, 250 nm). The standard solutions of glucose (5 mg) were treated as described above. The peaks of glucose derivative were observed at t_R (min): **1** D-glucose 20.23, **2** D-glucose 20.21, **3** D-glucose 20.18, **4** D-glucose 20.16 (reference L-glucose 18.38, D-glucose 20.14).

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetasy.2017.10.017.

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