Components of the Ether-Insoluble Resin Glycoside Fraction from the Seed of *Cuscuta australis*[1]

Xiao-Ming Du,[†] Ning-Yi Sun,[†] Masatoshi Nishi,[†] Toshio Kawasaki,[†] Yong-Tian Guo,[‡] and Kazumoto Miyahara*[,†]

Faculty of Pharmaceutical Sciences, Setsunan University, 45-1, Nagaotoge-cho, Hirakata, Osaka 573-0101, Japan, and Institute of Medical and Pharmaceutical Sciences Dalian, Chunyangjie 21, Dalian 116013, China

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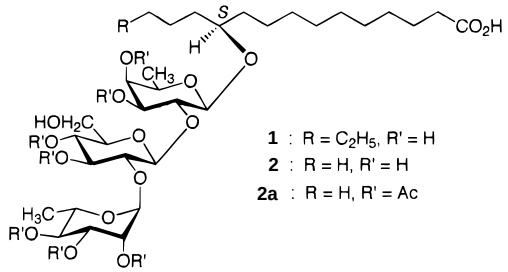
An ether-insoluble resin glycoside fraction was obtained from the seeds of *Cuscuta australis*. Identification and characterization of alkaline hydrolysis products by means of GC, FABMS, and ^{1}H, ^{13}C, and 2D NMR revealed the material to be composed of three new glycosidic acids, cuscutic acids A_1−A_3 (**1**−**3**); triglycosides with (11*S*)-jalapinolic or (11*S*)-convolvulinolic acid as the aglycon; and acetic, isobutyric, (2*S*)-2-methylbutyric, tiglic, and (2*R*,3*R*)-nilic acids. The resin glycoside is considered to be a complex mixture of glycosidic ester-type oligomers (up to heptamers) with a core consisting of a number of the above cuscutic acids each acylated with one or two carboxylic acid moieties.

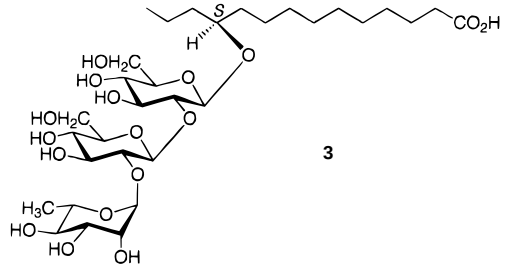
Cuscuta Semen is a well-known Chinese traditional medicine used as a tonic.[2] The Chinese Pharmacopoeia[3] specifies the seeds of *Cuscuta chinensis* Lam (Convolvulaceae) as its origin. However, several species belonging to the same genus, such as *C. australis* and *C. japonica*, are commercialized as substitutes under the same name in the Chinese market.[4] In a preceding paper, we reported two acylated trisaccharides, cus-1 and cus-2, closely related to the so-called resin glycoside,[5] and four glycosidic acids along with acetic acid, propionic acid, (2*S*)-2-methylbutyric, tiglic, (2*R*,3*R*)-nilic, (11*S*)-convolvulinolic, and (11*S*)-jalapinolic acids obtained by alkaline hydrolysis of the ether-insoluble resin glycoside-like fraction of the seeds of *C. chinensis*.[6] To clarify the relation of the chemical constituents of *C. chinensis* and other members of the *Cuscuta* genus, we examined the resin glycosides of the seeds of *C. australis* and obtained a complex mixture of ether-insoluble resin glycosides with relatively high molecular weights. This paper describes the characterization of several component glycosidic acids and organic acids obtained by alkaline hydrolysis of the ether-insoluble resin glycoside fraction.

Results and Discussion

Powdered seeds of *C. australis* were percolated with Me_2CO at room temperature. The extract was defatted with *n*-hexane, and the residue was partitioned with the mixture $CHCl_3$−MeOH−H_2O (1:1:1). The lower layer was concentrated and treated with ether. The residue was subjected to LH-20 column chromatography to give an ether-insoluble resin glycoside fraction, 0.15% based on the seeds. The matrix-assisted laser desorption ionization time-of-flight (MALDI TOF) MS showed many peaks around *m*/*z* 1585, 2406, 3193, 3989, 4793, and 5580, similar to that of *C. chinensis*.[6] Every effort to isolate individual components was unsuccessful.

Alkaline hydrolysis of the ether-insoluble resin glycoside fraction yielded low molecular weight carboxylic acid and glycosidic acid fractions. The former was methylated with diazomethane, and gas chromatography (GC) revealed the presence of acetic, isobutyric, 2-methylbutyric, tiglic, and nilic (3-hydroxy-2-methylbutyric) acids. The absolute configurations of 2-methylbutyric and 3-hydroxy-2-methylbutyric acids were determined as 2*S* and 2*R*,3*R*, respectively, by comparison of the specific rotations of their 4-bromophenacyl esters with those obtained from *C. chinensis*.[5,6] Reversed-phase column chromatography and HPLC of the glycosidic acid fraction gave three new glycosidic acids named cuscutic acids A_1 (**1**), A_2 (**2**), and A_3 (**3**).





Compound **1** was obtained as a white powder, mp 173−176 °C, $C_{34}H_{62}O_{16}$, from aqueous MeOH. On complete acidic hydrolysis, **1** furnished (11*S*)-jalapinolic acid[7] (11*S*-hydroxyhexadecanoic acid), D-fucose, D-glucose, and L-rhamnose in a ratio of about 1:1:1. The absolute configurations of the hydroxy fatty acids and the sugars were determined by the Mosher method[7] and the Hara method,[8] respectively. The negative ion FABMS of **1** showed a quasi molecular ion peak at *m*/*z* 725 $[M - H]^-$ along with fragment peaks at *m*/*z* 579 [725 − 146 ($C_6H_{10}O_4$, methylpentose unit)]$^-$, 417 [579−162 ($C_6H_{10}O_5$, hexose unit)]$^-$, and 271 [417 − 146, jalapinolic acid − H]$^-$, indicating that **1** was a glycoside composed of jalapinolic acid, fucose, glucose, and rhamnose (1:1:1:1) and that the sequence of the sugar moiety was either rhamnosyl−glucosyl−fucose or fucosyl−glucosyl−rhamnose.

* To whom correspondence should be addressed. Tel.: + 720-66-3138. Fax: +720-66-3139, E-mail: miyahara@pharm.setsunan.ac.jp.
† Faculty of Pharmaceutical Sciences.
‡ Institute of Medical and Pharmaceutical Sciences.

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Table 1. NMR Spectra Data for Compounds **1**, **2a**, and **3** (Pyridine-d_5)[a]

	1		**2a**	**3**	
	^{1}H[b]	^{13}C[c]	^{1}H[b]	^{1}H[b]	^{13}C[c]
Fuc-1	4.76 d (7.7)	102.6	4.78 d (7.7)		
2	4.49 dd (7.7, 9.3)	78.2	4.47 dd (7.7, 9.1)		
3	4.33 dd (9.3, 3.6)	76.2	5.31 dd (9.1, 3.3)		
4	3.81 br d (3.6)	72.6	5.67 dd (3.3, 1.0)		
5	3.71 br q (6.4)	71.0	3.92 dq (1.0, 6.3)		
6	1.46 d (3H, 6.4)	17.2	1.23 d (3H, 6.3)		
Glc-1				4.99 d (7.8)	102.5
2				4.33 dd (7.8, 9.3)	80.0
3				4.51 dd (9.3, 9.3)	79.4
4				4.12 dd (9.3, 9.3)	72.0
5				3.90 ddd (9.3, 5.3, 2.7)	77.9
6				4.32 dd (5.3, 11.5)	62.8
				4.46 dd (11.5, 2.7)	
Glc′-1	5.63 d (7.7)	102.3	5.32 d (7.7)	5.81 d (7.7)	102.2
2	4.22 dd (7.7, 9.3)	78.4	4.09 dd (7.7, 9.5)	4.26 dd (7.7, 9.4)	79.8
3	4.16 dd (9.3, 9.3)	79.3	5.82 dd (9.5, 9.5)	4.23 dd (9.4, 9.4)	79.3
4	4.03 dd (9.3, 9.3)	72.6	5.41 dd (9.5, 9.5)	4.08 dd (9.4, 9.4)	72.6
5	3.62 ddd (9.3, 5.2, 3.2)	77.1	4.04 ddd (9.5, 4.3, 2.6)	3.85 ddd (9.4, 5.2, 2.7)	77.5
6	4.17 dd (5.2, 11.7)	63.2	4.58 dd (4.3, 12.1)	4.27 dd (5.2, 11.5)	63.3
	4.26 dd (11.7, 3.2)		4.33 dd (12.1, 2.6)	4.44 dd (11.5, 2.7)	
Rha-1	6.32 d (1.5)	101.9	5.42 d (1.6)	6.32 dd (1.5)	102.2
2	4.73 dd (1.5, 3.2)	72.4	5.60 dd (1.6, 3.2)	4.74 dd (1.5, 3.2)	72.3
3	4.72 dd (3.2, 8.9)	72.7	5.66 dd (3.2, 10.3)	4.67 dd (3.2, 9.1)	72.6
4	4.30 dd (8.9, 8.9)	74.4	5.62 dd (10.3, 10.3)	4.30 dd (9.1, 9.1)	74.4
5	4.99 dq (8.9, 6.1)	69.6	4.60 dq (10.3, 6.3)	5.00 dq (9.1, 6.2)	69.7
6	1.82 d (3H, 6.1)	19.0	1.61 d (3H, 6.3)	1.79 d (3H, 6.2)	19.0
Ag-1		176.1			176.4
2	2.50 t (2H, 7.5)	34.9	2.56 t (2H, 7.4)	2.51 t (2H, 7.5)	35.1
11	3.89 m	80.2	3.84 m	3.96 m	80.5
14			0.92 t (3H, 7.3)	0.87 t (3H, 7.5)	14.5
16	0.83 t (3H, 7.5)	14.2			

[a] All assignments are based on ^{1}H−^{1}H COSY, NOESY, and ^{1}H−^{13}C COSY spectra. Coupling constants (J) are in parentheses. Fuc, fucopyranosyl; Glc, glucopyranosyl; Rha, rhamnopyranosyl; Ag, aglycon (jalapinolic or convolvulinolic acid); br, broad. [b] At 600 MHz. [c] At 150 MHz.

The ^{1}H and ^{13}C NMR signals of **1** were assigned with the aid of COSY, NOESY, and C−H COSY experiments. The spectra included signals for a terminal methyl and equivalent methylene groups ascribable to the aglycon (jalapinolic acid) at δ_H 0.83 (3H, t)/δ_C 14.2 and δ_H 2.50 (2H, t)/δ_C 34.9. The component sugar moieties were determined to be β-fucopyranosyl (Fuc) in $^4C_1$, β-glucopyranosyl (Glc) in $^4C_1$ and α-rhamnopyranosyl (Rha) in $^1C_4$ conformation, respectively, by vicinal ^{1}H−^{1}H coupling constants (Table 1). Their modes of the glycosidic linkage were supported by $^1J_{C1-H1}$[9] (Fuc, 156 Hz; Glc, 158 Hz; Rha, 171 Hz).

Comparing the ^{13}C NMR chemical shifts of **1** and the methyl pyranosides in the literature,[10] glycosydation shifts were observed at C-2 of Fuc (+6.2 ppm) and C-2 of Glc (+3.5 ppm) (Table 1). The NOESY spectrum of **1** revealed cross peaks between H-1 of Rha/H-2 of Glc, H-1 of Glc/H-2 of Fuc, and H-1 of Fuc/H-11 of the aglycon. These data implied that the linkages of **1** are Rha-(1→2)-Glc-(1→2)-Fuc-(1→11)-aglycon. Accordingly, **1** was characterized as (11*S*)-jalapinolic acid 11-*O*-α-L-rhamnopyranosyl-(1→2)-*O*-*β*-D-glucopyranosyl-(1→2)-*β*-D-fucopyranoside. The structure corresponds to that of the glycosidic acid moiety of tricolorin G and unit A of tricolorin H of *Ipomoea tricolor*.[11]

Compound **2**, mp 178−180 °C, $C_{32}H_{58}O_{16}$, gave (11*S*)-convolvulinolic acid, D-fucose, D-glucose, and L-rhamnose on acidic hydrolysis. The negative FABMS showed the [M − H]$^-$ ion peak at *m*/*z* 697 along with fragment peaks at *m*/*z* 551, 389, and 243, all of which were 28 mass units (C_2H_4) less than those of **1**, thus **2** is composed of 1 unit each of convolvulinolic acid[7] (11-hydroxytetradecanoic acid), D-fucose, D-glucose, and L-rhamnose, with the sugar moiety similar to that of compound **1**. The ^{1}H and ^{13}C NMR spectra of **2** were superimposable on those of **1** except for signals due to the convolvulinolic acid moiety. Moreover, comparing the ^{1}H NMR spectral data between **2** and its peracetate (**2a**), the signals at 3-H and 4-H of fucose, and those of glucose, were shifted downfield by 0.98, 1.86, 1.66, and 1.38 ppm, respectively, whereas those of 2-H were shifted upfield by 0.02 and 0.13 ppm, respectively. Therefore, the sugar moieties of **1** and **2** are identical, including their conformation. Thus, **2** is (11*S*)-convolvulinolic acid 11-*O*-α-L-rhamnopyranosyl-(1→2)-*O*-*β*-D-glucopyranosyl-(1→2)-*β*-D-fucopyranoside.

Compound **3**, a white powder, mp 185−188 °C, $C_{32}H_{58}O_{17}$, afforded, on acidic hydrolysis, (11*S*)-convolvulinolic acid, and D-glucose and L-rhamnose in the ratio 2:1. Its negative FABMS showed the [M − H]$^-$ ion peak at *m*/*z* 713 and fragment peaks at *m*/*z* 567 [713 − 146]$^-$, 405[567 − 162]$^-$ and 243 [405 − 162]$^-$, so that **3** was suggested to be a triglycoside consisting of 1 mol each of convolvulinolic acid and rhamnose, and 2 mol of glucose, in which the inner D-fucose of **2** is substituted by D-glucose in **3**. The NOESY and ^{13}C NMR spectra demonstrated that the glycosidic linkages are at the 2-OH of Glc, 2-OH of Glc′, and the 11-OH of the convolvulinolic acid moiety, and further, the glycosidic linkages of Rha, Glc, and Glc′ were determined to be α in $^1C_4$, β in $^4C_1$, and β in $^4C_1$, respectively, the same as for **1** (Table 1). Thus, the structure of **3** was defined as (11*S*)-convolvulinolic acid 11-*O*-α-L-rhamnopyranosyl-(1→2)-*O*-*β*-D-glucopyranosyl-(1→2)-*β*-D-glucopyranoside.

The glycosidic acids from *C. australis* are all triglycosides, although those from *C. chinensis*, cuscutic acids A−D, are tetraglycosides. Neither free jalapinolic nor convolvulinolic acids, nor the trisaccharides obtained as components in the alkaline hydrolysate of the resin from *C. chinensis*,[5,6] were found in *C. australis*. Taking the

features of the MALDI-TOF MS into account, the resin glycoside from this plant is considered to be a complex mixture of ester-type oligomers (up to heptamer), which consist of a variety of glycosidic acids each acylated with one or two organic acids such as acetic, isobutyric, (2*S*)-2-mehylbutyric, tiglic, and (2*R*,3*R*-)-nilic acids.

Experimental Section

General Experimental Procedures. Melting points were determined on a Yanaco MP−S3 apparatus and are uncorrected. Specific rotations were determined on a JASCO DIP-140 polarimeter at 17 °C. ^{1}H, ^{13}C, and 2D NMR spectra were recorded on a GE Omega 600 spectrometer at 26 °C using pyridine-d_5 as a solvent unless otherwise cited. EIMS and FABMS were measured on a JEOL JMS DX-300 spectrometer, and MALDI TOF MS was performed on a Perceptive Voyager Elite spectrometer. Triethanolamine was used as a matrix for the FABMS measurements. Analytical GC was carried out on a Shimadzu GC-8A gas chromatograph for organic and hydroxy fatty acids and on a Hitachi G-3000 gas chromatograph for sugars, equipped with FID.

Plant Material. The seeds of *C. australis*, whose host plant was *Sesamum indicum* DC., were collected in Inner Mongolia, China, in August 1992, and verified by Mr. Daixian Chen, Institute for Drug Control of Dalian, China. The voucher specimen (CONV-022) has been deposited in the herbarium of the Botanical Garden of the Faculty of Pharmaceutical Sciences, Setsunan University.

Extraction and Purification of the Ether-Insoluble Resin Glycoside Fraction. Powdered seeds of *C. australis* (1.2 kg) were percolated with Me_2CO (7 L) at room temperatures and the extract was evaporated under reduced pressure to afford a brown syrup (65 g). This was defatted with *n*-hexane (100 mL × 3), and the residue (10.8 g) was partitioned with $CHCl_3$−MeOH−H_2O (1:1:1, 300 mL). Concentration of the lower layer furnished a powder (2.32 g), which was treated with ether (25 mL × 2). The residue (2.12 g) was subjected to Sephadex LH-20 column chromatography (80 × 3.5 cm i.d., MeOH) to provide an ether-insoluble resin glycoside fraction (1.77 g, 0.15%), as a white powder, MALDI TOF MS (matrix; sinapic acid) major peaks at *m*/*z* 1585, 2406, 3193, 3989, 4793, and 5580.

Alkaline Hydrolysis of the Ether-Insoluble Fraction. The ether-insoluble resin glycoside fraction (1.5 g) was dissolved in 3% KOH (10 mL) and allowed to stand at 37 °C for 5 h. The mixture was adjusted to pH 4 with 1M HCl, and then extracted with Et_2O (5 mL × 3). The combined Et_2O layers were washed with H_2O and dried over Na_2SO_4. Evaporation of the Et_2O gave an oil (organic acid fraction, 137 mg). The H_2O layer was chromatographed over Mitsubishi chemical CHP 20P (25 × 5 cm i.d., H_2O → MeOH), and the MeOH eluate gave a white powder (glycosidic acid fraction, 1.18 g).

Identification of Organic Acids. The organic-acid fraction (1 mg) was examined by GC [condition 1: 2 m × 3.2 mm i.d. packed with Unisol 30T (5%); isothermal 110 °C; N_2 at 0.5 kg cm^{-2}], t_R (min) 2.13 (acetic acid), 3.59 (isobutyric acid), 5.97 (2-methylbutyric acid), 14.12 (tiglic acid). The organic-acid fraction (1 mg) was methylated with CH_2N_2 in the usual way and analyzed by GC under the same conditions as above except for column temperature: 100 °C, R_t (min) 7.59 (methyl nilate).

A solution of the organic-acid fraction (130 mg) in dry Me_2CO (5 mL) was neutralized with triethylamine. 4-Bromophenacyl bromide (110 mg) was added, and the mixture was allowed to stand at room temperature for 1 h. After removal of the solvent, the residue was diluted with H_2O (5 mL) and extracted with Et_2O (5 mL × 3). The combined Et_2O layer was concentrated and then chromatographed over Si gel using *n*-hexane−EtOAc (10:1) → EtOAc to afford 4-bromophenacyl (2*S*)-2-methylbutyrate (8.5 mg): colorless needles, mp 41−42 °C, $[\alpha]_D$ +9.8° (*c* 0.8, $CHCl_3$) and 4-bromophenacyl (2*R*,3*R*)-nilate (11.7 mg), colorless needles, mp 70−72 °C, $[\alpha]^{17}_D$ −14.3° (*c* 1.1, $CHCl_3$). These were identical in all respects to known standards (^{1}H NMR, EIMS, and specific rotation).[6]

Isolation of Cuscutic Acids A_1 (1), A_2 (2), and A_3 (3). The glycosidic acid fraction (100 mg) was purified over Nacalai Tesque Cosmosil 75 C18-opn (28 × 2 cm i.d., 75% MeOH) and then subjected to HPLC on GL Sciences Inertsil ODS (250 × 20 mm i.d., 83% MeOH) to afford **1** (11 mg), **2** (61 mg), and **3** (15 mg), respectively.

Cuscutic Acid A_1 (1): obtained as a white powder (MeOH−H_2O); mp 173−176 °C, $[\alpha]^{17}_D$ −38.7° (*c* 1.1, MeOH); negative ion FABMS *m*/*z* 725, 579, 417, 271; *anal.* C 56.09%, H 8.76%, calcd for $C_{34}H_{62}O_{16}$, C 56.18%, H 8.60%; ^{1}H and ^{13}C NMR δ, see Table 1; $^1J_{C1-H1}$ Hz 156 (Fuc), 158 (Glc), 171 (Rha).

Cuscutic Acid A_2 (2): obtained as a white powder (MeOH−H_2O), mp 178−180 °C; $[\alpha]^{17}_D$ −41.5° (*c* 5.5, MeOH); negative ion FABMS *m*/*z* 697, 551, 389, 243; *anal.* C 54.89%, H 8.25%, calcd for $C_{32}H_{58}O_{16}$, C 55.00%, H 8.37%; ^{1}H and ^{13}C NMR δ, see Table 1; $^1J_{C1-H1}$ Hz 156 (Fuc), 157 (Glc), 172 (Rha).

Cuscutic Acid A_3 (3): obtained as a white powder (MeOH−H_2O), mp 185−188 °C; $[\alpha]^{17}_D$ −79.2° (*c* 0.95, MeOH); negative ion FABMS *m*/*z* 713, 567, 405, 243; *anal.* C 53.63%, H 8.29%, calcd for $C_{32}H_{58}O_{17}$, C 53.77%, H 8.18%, ^{1}H and ^{13}C NMR δ, see Table 1; $^1J_{C1-H1}$ Hz 157 (Glc), 159 (Glc′), 171 (Rha).

Acidic Hydrolysis of 1, 2, and 3. Compounds **1** (9 mg), **2** (11 mg), and **3** (10 mg) were separately dissolved in 5% H_2SO_4 (2 mL) and heated at 95 °C for 1 h. The reaction mixture in each case was diluted with H_2O (2 mL), then extracted with Et_2O. The Et_2O layer was treated with CH_2N_2, then the product was examined by GC [condition 2: column, 2 m × 3.2 mm i.d. packed with silicone OV-17 (2%); N_2 at 1 kg cm^{-2}; isothermal 240 °C; t_R (min) 4.53 (methyl convolvulinolate) for **2** and **3**, 7.23 (methyl jalapinolate) for **1**]. A mixture of methyl jalapinolate (2 mg from **1**), (−)-1-methoxy-1-trifluoromethylphenylacetyl (MTPA) chloride (4 mg), dicyclohexylcarbodiimide (6 mg), and 4-(dimethylamino)pyridine (2 mg) in Et_2O (1.5 mL) was stirred at room temperature overnight. The solvent was removed under a stream of N_2, and the residue was purified over a Si gel column chromatography using *n*-hexane−Et_2O (10:1) to give the (−)-MTPA ester (3 mg) as a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.84 (3H, t, J = 6.9 Hz, H_3-16), 2.30 (2H, t, J = 7.5 Hz, H_2-2), 3.56 (3H, q, J = 1.2 Hz, OCH_3), 3.67 (3H, s, $COOCH_3$), 5.08 (1H, tt, J = 5.5, 6.7 Hz, H-11). These data were identical with those of an authentic (−)-MTPA ester of methyl (11*S*)-jalapinolate [cf. (+)-MTPA ester δ 0.88 (3H, t, J = 6.9 Hz, H_3-16)[7]]. In the same manner as above, the methyl convolvulinolate (each 2 mg from **2** and **3**) was transformed to the (−)-MTPA ester to afford a colorless oil, respectively: ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.85 (3H, t, J = 7.3 Hz, H_3-14), 2.30 (2H, t, J = 7.5 Hz, H_2-2), 3.55 (3H, q, J = 1.2 Hz, OCH_3), 3.67 (3H, s, $COOCH_3$), 5.10 (1H, tt, J = 5.3, 7.0 Hz, H-11). The ^{1}H NMR in each case was superimposable on that of an authentic sample of the (−)-MTPA ester of methyl (11*S*)-convolvulinolate [cf. (+)-MTPA ester δ 0.92 (3H, t, J = 6.9 Hz, H_3-14)[7]].

Each aqueous layer was neutralized with $Ba(OH)_2$, and the precipitates were filtered off. The filtrate was concentrated, and the residue was subjected to LH-20 column chromatography (MeOH) to afford a sugar mixture as a syrup (5 mg from **1**, 6 mg from **2**, and 5 mg from **3**). The samples were analyzed by GC according to the method of Hara et al.[8] (condition 3: WCOT, GL Sciences OV-17, 50 m × 0.25 mm i.d.; isothermal 220 °C; He at 1.5 kg cm^{-2}); t_R (min) 19.18 (L-rhamnose), 19.77 (D-fucose), and 26.99 (D-glucose) from **1** and **2** in a ratio of ca. 1:1:1, respectively, and 19.19 (L-rhamnose) and 27.01 (D-glucose) from **3** (ca. 1:2).

Acetylation of 2. A solution of **2** (20 mg) in Ac_2O−pyridine (1:1) was heated at 50 °C, for 2 h. The mixture was evaporated under an N_2 stream, and the residue was purified over Si gel using *n*-hexane−Me_2CO (2:1) to give a white powder (**2a**, 28 mg). EIMS *m*/*z* 791, 561, 289, 273. ^{1}H NMR δ, see Table 1.

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