Two New Lignans and Anti-HBV Constituents from *Illicium henryi*

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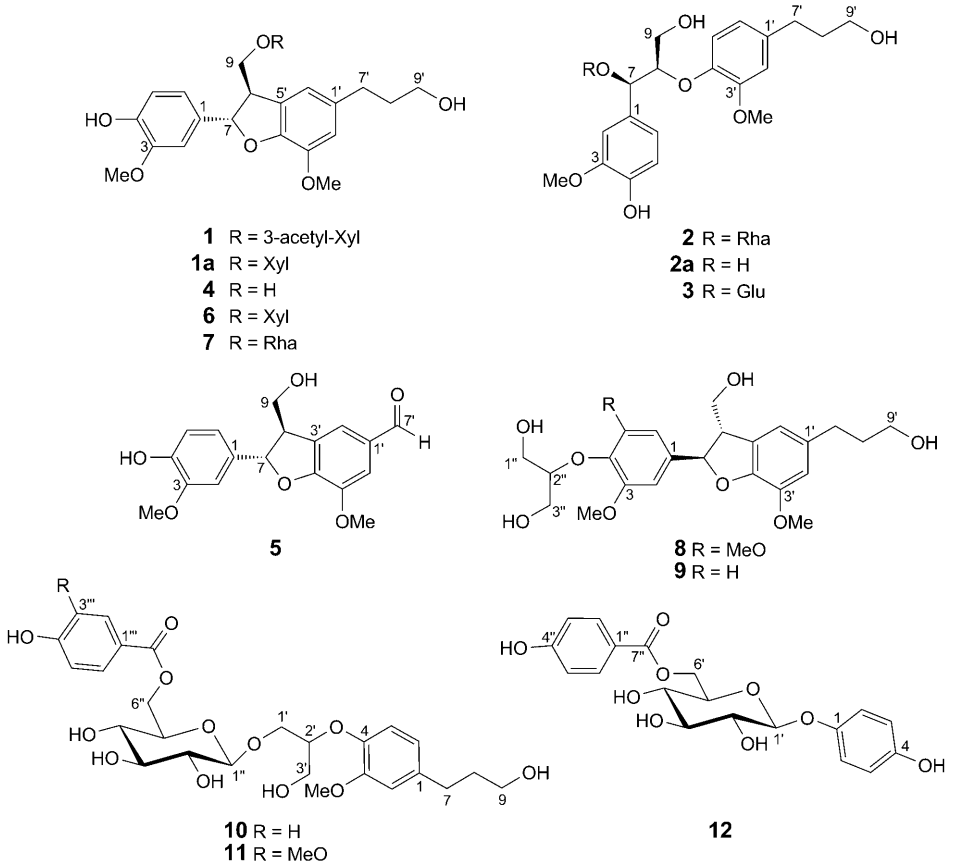
Two new lignans, dihydrodehydrodiconiferyl alcohol 9-*O*-*β*-D-(3′′-*O*-acetyl)-xylopyranoside (**1**) and *threo*-4,9,9′-trihydroxy-3,3′-dimethoxy-8-*O*-4′-neolignan 7-*O*-*α*-rhamnopyranoside (**2**) were isolated from *Illicium henryi*, together with ten known compounds, **3**–**12**. Their structures were elucidated by extensive spectroscopic analyses. The anti-hepatitis B virus (anti-HBV) activity of compounds **1**–**12** inhibiting HBV surface antigen (HBsAg) and HBV e antigen (HBeAg) secretion on Hep G2.2.15 cell line was evaluated. (−)-Dihydrodehydrodiconiferyl alcohol (**4**) showed moderate inhibitory activity on both HBsAg and HBeAg secretion with IC_{50} values of 0.06 and 0.53 mM, respectively.

Introduction. – The genus *Illicium* belongs to the single-genus family Illiciaceae. Previous chemical investigations on this genus yielded prenylated C_6-C_3 compounds, neolignans, and a large number of unique sesquiterpene lactones exhibiting neurotoxic and neurotrophic activities [1–3]. From a chemotaxonomic point of view, the *Illicium* species are interesting sources, rich in biosynthetically unique sesquiterpenes which are considered to be characteristic chemical markers [4]. In addition, the prenylated C_6-C_3 compounds, referred to as phytoquinoids, are also considered to be characteristic constituents, some of which are found to increase choline acetyltransferase activity [5]. *I. henryi* is a shrub distributed in the southwestern part of China, and its bark and roots have been used as a folk-medicinal herb for dispelling wind-evil and assuaging pain [6]. In the previous studies, sesquiterpene lactones [7] and flavonoids [8] had been isolated from the title plant. Here, we describe the isolation and structure elucidation of two new lignans, **1** and **2**, along with ten known compounds, **3**–**12**, which were isolated from the EtOH extract of the stems and roots of *I. henryi* for the first time, and the assessment of their anti-HBV activity.

Results and Discussion. – 1. *Structure Elucidation.* Compound **1** was obtained as white amorphous powder. HR-ESI-MS showed the $[M+Cl]^-$ ion peak at *m*/*z* 569.1775 (calc. 569.1789) in accordance with the molecular formula $C_{27}H_{34}O_{11}$, indicating eleven degrees of unsaturation. The IR spectrum showed the presence of OH (3430 cm^{-1}) and CO (1733 cm^{-1}) groups, as well as aromatic rings (1610, 1500, 1464 cm^{-1}). The ^{1}H-NMR spectrum displayed *ABX* spin-system signals at δ(H) 6.97 (*s*, 1 H), 6.83 (*dd*,



$J = 8.0, 1.6, 1$ H), and 6.74 (overlapped, 1 H), aromatic H-atom signals at δ(H) 6.76 (*s*, 1 H), 6.72 (*s*, 1 H), two MeO signals at δ(H) 3.81 (*s*), 3.84 (*s*), and an anomeric H-atom signal at δ(H) 4.38 (*d*, $J = 7.5$). The ^{13}C-NMR (DEPT; *Table 1*) spectrum revealed the presence of three Me, five CH_2, and twelve CH groups, and eight quaternary C-atoms. The CO C-atom signal at δ(C) 172.6 and a Me signal at δ(C) 21.1 suggested the presence of an AcO moiety in compound **1**. Analysis of NMR spectra revealed that compound **1** was almost identical with dihydrodehydrodiconiferyl alcohol 9-*O*-β-D-xylopyranoside (**6**) [9], except for the presence of the signals due to an AcO moiety. The cross-peak between H–C(3″) and C(1‴) (δ(C) 172.6) observed in the HMBC spectrum indicated that the AcO group was linked to C(3″) (*Fig.*). Hydrolysis of compound **1** with 1M NaOH gave **1a**. The NMR data of **1a** were identical to those of **6**. The value of coupling constant of H–C(7)[1]) ($J = 6.4$ Hz) along with the ROESY correlation H–C(7)/H–C(9) (*Fig.*) indicated that H–C(7) and H–C(8) were in a *trans*-configuration [10][11]. The β-configuration of the anomeric C-atom was established by

[1]) Numbering as indicated in the *Formulae*; for systematic names, *cf.* the *Exper. Part*.

Table 1. *^{1}H- and ^{13}C-NMR Data of Compounds* **1** *and* **2**. Recorded at 400 and 100 MHz, respectively, in CD_3OD; δ in ppm, J in Hz.

Position[1])	**1**		**2**	
	δ(H)	δ(C)	δ(H)	δ(C)
1	–	129.5 (*s*)	–	129.7 (*s*)
2	6.97 (*s*)	110.6 (*d*)	7.33 (*d*, *J* = 1.5)	112.5 (*d*)
3	–	149.0 (*s*)	–	148.6 (*s*)
4	–	147.4 (*s*)	–	148.1 (*s*)
5	6.74 (overlapped)	116.0 (*d*)	7.21 (*d*, *J* = 8.1)	116.2 (*d*)
6	6.83 (*dd*, *J* = 8.0, 1.6)	119.7 (*d*)	7.14 (*d*, *J* = 8.0)	122.1 (*s*)
7	5.53 (*d*, *J* = 6.4)	89.0 (*d*)	5.69 (*d*, *J* = 5.4)	76.2 (*d*)
8	3.57–3.61 (*m*)	52.9 (*d*)	4.96–4.99 (*m*)	84.4 (*d*)
9	3.88–3.92 (*m*), 3.27–3.30 (*m*)	72.2 (*t*)	4.29–4.30 (*m*), 3.38–3.40 (*m*)	61.0 (*t*)
1′	–	137.0 (*s*)	–	136.4 (*s*)
2′	6.72 (*s*)	114.0 (*d*)	6.85 (*d*, *J* = 1.7)	113.4 (*d*)
3′	–	145.2 (*s*)	–	150.9 (*s*)
4′	–	147.4 (*s*)	–	146.9 (*s*)
5′	–	134.5 (*s*)	7.25 (*d*, *J* = 8.2)	117.3 (*d*)
6′	6.76 (*s*)	118.0 (*t*)	6.77 (*dd*, *J* = 8.2, 1.6)	121.0 (*d*)
7′	2.61 (*t*, *J* = 7.6)	32.9 (*t*)	2.76 (*t*, *J* = 7.3)	32.4 (*t*)
8′	1.78–1.82 (*m*)	35.8 (*t*)	1.97–2.04 (*m*)	35.7 (*t*)
9′	3.56 (*t*, *J* = 6.4)	62.2 (*t*)	3.86 (*t*, *J* = 6.4)	61.4 (*t*)
1″	4.38 (*d*, *J* = 7.5)	104.6 (*d*)	5.36 (br. *s*)	98.4 (*d*)
2″	3.34–3.36 (*m*)	73.0 (*d*)	4.61–4.65 (*m*)	73.0 (*d*)
3″	4.85–4.87 (*m*)	78.7 (*d*)	4.59–4.61 (*m*)	72.5 (*d*)
4″	3.58–3.63 (*m*)	69.4 (*d*)	4.30–4.33 (*m*)	74.2 (*d*)
5″	3.98–4.02 (*m*), 3.81–3.84 (*m*)	66.7 (*t*)	4.67–4.71 (*m*)	70.5 (*d*)
6″	–	–	1.68 (*d*, *J* = 6.1)	18.9 (*q*)
1‴	–	172.6 (*s*)	–	–
2‴	2.10 (*s*)	21.1 (*q*)	–	–
MeO	3.81 (*s*)	56.4 (*q*)	3.60 (*s*)	55.7 (*q*)
MeO	3.84 (*s*)	56.7 (*q*)	3.65 (*s*)	55.8 (*q*)

the coupling constant of H–C(1″) (J = 7.5 Hz) as observed in the ^{1}H-NMR spectrum [9]. Thus, compound **1** was deduced as dihydrodehydrodiconiferyl alcohol 9-*O*-β-D-(3″-*O*-acetyl)xylopyranoside.

Compound **2** was isolated as white amorphous powder. HR-ESI-MS exhibited the $[M+Cl]^-$ ion peak at m/z 559.1961 (calc. 559.1946), indicating the molecular formula $C_{26}H_{36}O_{11}$. The IR spectrum suggested the presence of a OH group (3416 cm^{-1}) and an aromatic ring (1607, 1513, 1454 cm^{-1}). The ^{1}H-NMR spectrum displayed the signals of one C_3 unit at δ(H) 2.01 (*m*, CH_2(8′)), 2.76 (*t*, J = 7.3, CH_2(7′)), and 3.86 (*t*, J = 6.4, CH_2(9′)), two MeO groups (δ(H) 3.60 (*s*), 3.65 (*s*)), two CH groups (δ(H) 4.98 (*m*, H–C(8)), 5.69 (*d*, J = 5.4, H–C(7)), a rhamnosyl moiety, and six aromatic H-atoms (two *ABX*-type spin systems). The ^{13}C-NMR (DEPT; *Table 1*) spectra revealed the presence of three Me, four CH_2, and 13 CH groups, and six quaternary C-atoms, suggesting the presence of two C_6-C_3 units and a sugar moiety. Comparing the NMR data of compound **2** with those of *threo*-4,9,9′-trihydroxy-3,3′-dimethoxy-8-*O*-4′-neolignan 7-*O*-β-D-glucopyranoside (**3**) [12], indicated that they were similar except

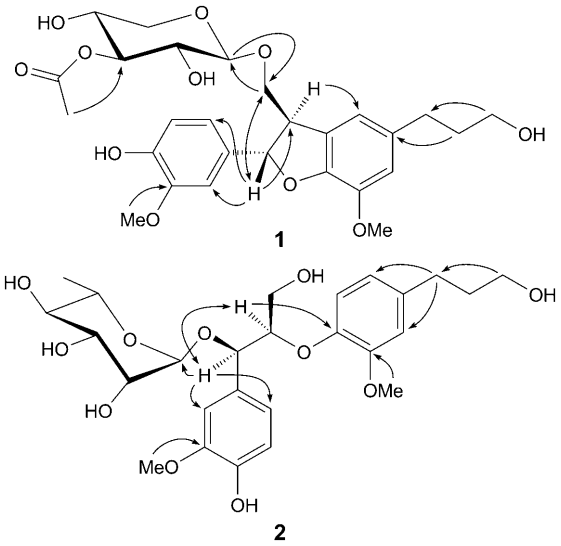


Figure. *Key HMBC* (→) *and ROESY* (↔) *correlations of* **1** *and* **2**

for the signals of the sugar moiety. The acid hydrolysis of compound **2** with 2M HCl afforded rhamnose and the aglycone **2a**. The rhamnose was identified by HP-Si-TLC with authentic sample. The α-configuration of the rhamnosyl residue was confirmed by ^{1}H,^{13}C-NMR data [13][14]. The configuration of C(7) and C(8) was determined as *threo* based on the large coupling constant (J(7,8) = 7.2) in the ^{1}H-NMR spectrum of **2a** [12], which was also supported by the ROESY correlation of H–C(7) and H–C(8), as shown in the *Figure*. Consequently, the structure of compound **2** was determined to be *threo*-4,9,9′-trihydroxy-3,3′-dimethoxy-8-*O*-4′-neolignan 7-*O*-α-rhamnopyranoside.

The known compounds, *threo*-4,9,9′-trihydroxy-3,3′-dimethoxy-8-*O*-4′-neolignan 7-*O*-β-D-glucopyranoside (**3**) [12], (−)-dihydrodehydrodiconiferyl alcohol (**4**) [15], ficusal (**5**) [16], dihydrodehydrodiconiferyl alcohol 9-*O*-β-D-xylopyranoside (**6**) [9], dihydrodehydrodiconiferyl alcohol 9-*O*-α-L-rhamnopyranoside (**7**) [17], sakuraresinol (**8**) [18], 2,3-dihydro-2-[3′-methoxy-4′-(1″,3″-dihydroxy-2″-propyloxy)phenyl]-3-(hydroxymethyl)-7-methoxybenzofuran-5-propanol (**9**) [10], 4-*O*-[2′-hydroxy-1′-(hydroxymethyl)ethyl]dihydroconiferyl alcohol 6″-(*p*-hydroxybenzoyl)-β-D-glucopyranoside (**10**) [19], 4-*O*-[2′-hydroxy-1′-(hydroxymethyl)ethyl]dihydroconiferyl alcohol vanilloyl-glucoside (**11**) [13], and breynioside A (**12**) [20] were identified by comparison of their spectroscopic data with those reported.

2. *Anti-HBV Assay.* The isolated compounds **1**–**12** were evaluated for their anti-HBV activity on the HBV-transfected Hep G 2.2.15 cell line *in vitro* according to our previous report [21]. The results including their activities and cytotoxicities were compiled in *Table 2*. The results show that the benzofuran lignans exhibited anti-HBV activities with reduced cytotoxicities for the glycoside derivatives **1**, **6**, and **7**. (−)-Dihydrodehydrodiconiferyl alcohol (**4**) was the most active showing moderate inhibitory activity (IC_{50} = 0.06 mM, SI = 8.8) on HBV surface antigen (HBsAg)

secretion in Hep G2.2.15 cells. The new compound dihydrodehydrodiconiferyl alcohol 9-*O*-*β*-D-(3′′-*O*-acetyl)xylopyranoside (**1**) possessed weak activity against HBsAg secretion with an IC_{50} value of 0.58 mM and CC_{50} value of 0.92 mM.

Table 2. *Anti-HBV Activities of Compounds* **1**–**12**[a])

Compounds	CC_{50} [mM]	HBsAg[b])		HBeAg[c])	
		IC_{50} [mM]	SI[d])	IC_{50} [mM]	SI[d])
1	0.92	0.58	1.6	>2.40	<0.4
2	>1.85	>1.85	–	>1.85	–
3	1.15	0.59	1.9	0.80	1.4
4	0.53	0.06	8.8	0.50	1.1
5	0.27	0.15	1.8	0.52	0.5
6	>2.15	1.67	>1.3	>2.15	–
7	1.76	0.93	1.9	2.45	0.7
8	0.95	0.95	1.0	>2.59	<0.4
9	4.52	3.62	1.2	4.56	1.0
10	>1.93	>1.93	–	>1.93	–
11	>2.87	1.65	>1.7	>2.87	–
12	1.17	1.28	0.9	1.43	0.8
3TC[e])	28.0	10.0	2.8	20.0	1.4

[a]) All values are the means of two independent experiments. [b]) HBsAg: HBV surface antigen. [c]) HBeAg: HBV e antigen. [d]) CC_{50}: 50% Cytotoxic concentration, IC_{50}: 50% inhibition concentration against HBV synthesis, $SI = CC_{50}/IC_{50}$. [e]) 3TC: Lamivudine, an antiviral agent used as a positive control.

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Experimental Part

General: Column chromatography (CC): Silica gel (SiO_2; 200–300 mesh; *Qingdao Meigao Chemical Company*, Qingdao, P. R. China), D_{101} macroporous resin (*Tianjin Pesticide Chemical Company*, Tianjin, P. R. China), *Lichrospher Rp-18 gel* (40–63 μm; *Merck Chemicals Ltd.*, Germany), and *Sephadex LH-20* (20–150 μm; *Pharmacia Fine Chemical Co. Ltd.*, Sweden). Prep. HPLC: *Waters 600* (*Waters*, Milford, USA), with a *Waters Xterra Prep RP-18* (7.8 × 300 mm, 10 μm) column (*Waters*, Ireland). Optical rotations: Horiba *SEPA-300* polarimeter (*Horiba*, Tokyo, Japan). UV Spectra: *Shimadzu UV-210A* spectrophotometer (*Shimadzu*, Kyoto, Japan). IR Spectra: *Bio-Rad FTS-135* spectrometer (*Bio-Rad*, California, USA); as KBr pellets. 1D- and 2D-NMR spectra: *Bruker AM-400* NMR and *DRX-500* spectrometers with TMS as internal standard (*Bruker*, D-Bremerhaven). MS: *VG Auto Spec-3000* spectrometer (*VG*, GB-Manchester) and *API Qstar Pulsar* (*Applied Biosystems*, Foster City, USA); in *m*/*z*.

Plant Material. The stems and roots of *Illicium henryi* Diels. were collected in Wenshan, Yunnan Province, P. R. China, in July 2006, and identified by Prof. *Ligong Lei* from Kunming Institute of Botany, Chinese Academy of Sciences. A voucher specimen (2006-07-01) was deposited with the Laboratory of Antivirus and Natural Medicinal Chemistry, Kunming Institute of Botany.

Extraction and Isolation. Dried and powdered plant material (9 kg) was extracted with 95% EtOH (40 l) under reflux for three times, 2 h for each time. The extract was concentrated *in vacuo*, and then partitioned between $CHCl_3$, BuOH, and H_2O successively. The BuOH fraction (200 g) was dissolved in H_2O. The H_2O-soluble fraction was passed through a D_{101} macroporous adsorptive resin column and was eluted with H_2O/EtOH (100:0, 80:20, 60:40, 40:60, 20:80, 0:100 (*v*/*v*)) to yield ten fractions, *Frs. 1–10*. The *Fr. 3* (10 g) was repeatedly subjected to CC (SiO_2 (5 × 41 cm, 350 g); $CHCl_3$/Me_2CO 90:10, 80:20, 70:30, 50:50, 30:70 (*v*/*v*; each 4 l) to give five fractions, *Frs. 3a–3e*. By further purification on *Rp-18* gel (2.5 × 33 cm, 120 g) with MeOH/H_2O (30:70, 40:60, 50:50, 60:40 (*v*/*v*; each 500 ml), compounds **1** (15 mg), **2** (13 mg), and **6** (40 mg) were obtained from *Fr. 3b*. *Fr. 4* (8 g) was subjected to CC (*Rp-18* gel (2.5 × 33 cm, 120 g); MeOH/H_2O 10:90, 80:20, 40:60, 60:40, 80:20, 0:100 (*v*/*v*)) to afford seven fractions, *Frs. 4a–4g*. *Fr. 4b* was subjected to CC (SiO_2 (2 × 35 cm, 50 g); $CHCl_3$/MeOH 90:10) to yield compound **7** (9 mg). *Fr. 4f* was separated by repeated SiO_2 CC to yield compound **3** (12 mg) eluted with $CHCl_3$/MeOH 90:10, followed by AcOEt/MeOH 95:5. *Fr. 5* (12 g) was subjected to CC (SiO_2 (5 × 35 cm, 260 g); $CHCl_3$/Me_2CO 100:0, 90:10, 80:20 (*v*/*v*); each 3 l) to afford five fractions, *Frs. 5a–5e*. *Fr. 5a* (1.2 g), *Fr. 5b* (1 g), and *Fr. 5d* (1.8 g) were further separated by CC (SiO_2 (3 × 25 cm, 70 g); petroleum ether (PE)/Me_2CO 75:25, PE/AcOEt 60:40, and $CHCl_3$/Me_2CO 85:15, resp.) to furnish compounds **4** (6 mg), **5** (8 mg), and **8** (8 mg). *Fr. 7* (5 g) was further separated by CC (SiO_2 (3 × 30 cm, 85 g); PE/Me_2CO 85:15, 70:30, 50:50, 30:70 (*v*/*v*); each 700 ml) to give six fractions, *Frs. 7a–7f*. *Fr. 7c* was further purified by CC (*Rp-18* (2.5 × 33 cm, 120 g); MeOH/H_2O 65:35) to provide compound **10** (11 mg). *Fr. 7d* (50 mg) and *Fr. 7f* (50 mg) were further purified by CC (*Sephadex LH-20* (1.4 × 150 cm, 48 g), MeOH), then purified by semi-prep. HPLC, using a *Waters XTerra Prep RP-18* column, eluted with MeOH/H_2O 40:60 (flow rate 4.5 ml/min; detection at 254 nm) to obtain compounds **11** (4 mg, t_R 20 min) and **12** (19 mg, t_R 35 min), resp.

*Dihydrodehydrodiconiferyl Alcohol 9-*O*-β-*D*-(3′′-*O*-Acetyl)xylopyranoside* (= *[(2*S*,3*R*)-2,3-Dihydro-2-(4-hydroxy-3-methoxyphenyl)-5-(3-hydroxypropyl)-7-methoxy-1-benzofuran-3-yl]methyl 3-*O*-Acetyl-β-*D*-xylopyranoside*; **1**). White amorphous powder. $[\alpha]_D^{27.9} = -4.6$ ($c = 0.215$, MeOH). UV ($CHCl_3$): 282 (3.73). IR (KBr): 3430, 2934, 1733, 1610, 1518, 1500, 1464, 1244, 1213, 1039, 974, 755. ^{1}H- and ^{13}C-NMR: see *Table 1*. HR-ESI-MS: 569.1775 ($[M+Cl]^-$, $C_{27}H_{34}ClO_{11}^-$; calc. 569.1789).

threo-*4,9,9′-Trihydroxy-3,3′-dimethoxy-8-*O*-4′-neolignan 7-*O*-α-Rhamnopyranoside* (= *(1*R*,2*R*)-3-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-2-[4-(3-hydroxypropyl)-2-methoxyphenoxy]propyl 6-Deoxy-α-*L*-mannopyranoside*; **2**). White amorphous powder. $[\alpha]_D^{26.1} = -36.4$ ($c = 0.055$, MeOH). UV ($CHCl_3$): 224 (4.16), 280 (3.71). IR (KBr): 3416, 2930, 1607, 1513, 1454, 1273, 1129, 1035, 983, 812. ^{1}H- and ^{13}C-NMR: see *Table 1*. FAB-MS (neg.): 523 ($[M-H]^-$), 359, 329, 283. HR-ESI-MS: 559.1961 ($[M+Cl]^-$, $C_{26}H_{36}ClO_{11}^-$; calc. 559.1946).

Hydrolysis of Compound **1**. 2M NaOH (1 ml) was added to a soln. of **1** (7 mg) in MeOH (1 ml), which was stirred for 12 h at r.t. The mixture was diluted with 1M HCl (5 ml) and extracted with AcOEt (3 × 5 ml). The AcOEt layer was washed with brine (10 ml), dried (Na_2SO_4), and concentrated under reduced pressure to give a crude residue, which was purified by CC (SiO_2; $CHCl_3$/MeOH 90:10) to yield **1a** (3 mg).

Hydrolysis of Compound **2**. The mixture of **2** (6 mg), 2M HCl (1 ml), and MeOH (1 ml) was heated in a water bath at 50° for 12 h. After reaction, the mixture was diluted with H_2O (10 ml) and extracted with AcOEt (3 × 5 ml). The AcOEt layer was washed with brine (10 ml) and dried ($MgSO_4$), and concentrated under reduced pressure to give a crude residue which was purified by CC (SiO_2; $CHCl_3$/MeOH 95:5) to provide **2a** (2 mg). The aq. layers were evaporated to dryness under reduced pressure. The sugar was identified to be rhamnose by comparison with an authentic sample on HP-Si-TLC.

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