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Three anti-tumor saponins from *Albizia julibrissin*

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Abstract—Three new triterpenoid saponins, julibroside J_{29} (**1**), julibroside J_{30} (**2**), and julibroside J_{31} (**3**), were isolated from the stem bark of *Albizia julibrissin* Durazz. (Leguminosae) by using chromatographic method. Their structures were established by spectroscopic methods. Compounds **1**, **2**, and **3** displayed significant anti-tumor activities in vitro against PC-3M-1E8, HeLa, and MDA-MB-435 cancer cell lines at 10 μM assayed by SRB and MTT methods.

The stem bark of *Albizia julibrissin* (Leguminosae) has been recorded in Chinese Pharmacopoeia as a sedative drug and an anti-inflammatory for treating swelling and pain of the lungs, skin ulcers, and wounds.[1] In the previous research, the novel and complex triterpenoid saponins with cytotoxic activities were isolated and identified.[2,3] On our continuing study, three minor saponins obtained from the *n*-BuOH soluble part of the hot water extract from the stem bark of *A. julibrissin* showed significant inhibitory activity in vitro against human tumor cell lines. Isolation[4] of the active extract led to the separation of compounds **1**, **2**, and **3**. Their structures, named julibroside J_{29} (**1**), julibroside J_{30} (**2**), and julibroside J_{31} (**3**), were determined by NMR spectra, including ^{1}H–^{1}H COSY, HSQC, and HMBC techniques.[5] Compounds **1**, **2**, and **3** displayed significant anti-tumor activities against PC-3M-1E8, MDA-MB-435, and HeLa cancer cell lines in vitro at 10 μM assayed by SRB and MTT methods.

Julibroside J_{29} (**1**), white powder, gave positive Molish reaction and Liebermann–Burchard reaction. The UV spectrum showed a maximum absorption at 216 nm. ESI-TOF-MS showed the quasi-molecular ion peak at *m/z* 1939 $[M+H+K]^{+}$. Upon acidic hydrolysis with 2.0 M HCl, **1** gave an acacic acid lactone unit, which was identified with an authentic sample, and compound **1** also gave glucosamine hydrochloride, glucose, xylose, fucose, rhamnose, arabinose, and quinovose, which were identified by co-TLC with authentic samples.[6] Its ^{1}H NMR spectrum showed seven methyl signals at δ 0.92 (3H, s), 1.01 (6H, s), 1.06 (3H, s), 1.14 (3H, s), 1.16 (3H, s), and 1.87 (3H, s), one olefinic proton signal at δ 5.57 (1H, br s), and sugar proton signals at δ 3.5–6.0. ^{13}C NMR spectrum showed two olefinic carbon signals at δ 123.0 and 143.3, suggesting that **1** was an oleanane type triterpenoid saponin. One- and two-dimensional NMR techniques permitted assignments of ^{1}H and ^{13}C NMR signals of **1** (Table 1). In a comparison of the ^{13}C NMR signals for aglycone of **1** with those of known saponin prosapogenin-10 (**4**, Table 1),[7] all signals due to the aglycone of **1** were almost superimposable with those of **4**, indicating the aglycone of **1** was same as that of **4**, which was acacic acid (3β, 16α, 21β-trihydroxyolean-12-ene-28-oic acid) and its 3, 21-hydroxy groups and 28-carbonyl group carried a sugar moiety, respectively. ^{13}C NMR spectrum gave eight anomeric carbon signals at δ 95.6, 99.3, 101.8, 103.3, 104.7, 105.7, 106.9, and 111.0, four methyl carbon signals at δ 17.2, 18.9, 18.8, and 23.6, a carbonyl signal at δ 170.1, and a typical amide carbon signal at δ 57.9. Eight anomeric proton signals at δ 4.83 (1H, d, J = 8.0 Hz), 4.98 (1H, d, J = 7.5 Hz), 5.02 (1H, d, J = 8.5 Hz), 5.07 (1H, d, J = 6.5 Hz), 5.32 (1H, d, J = 7.5 Hz), 5.87 (1H, s), 6.03 (1H, d, J = 8.0 Hz), and 6.26 (1H, br s) were assigned by direct correlation from HSQC spectrum. In the HMBC spectrum, the correlations were observed between δ 2.10 (3H, s), 8.9 (NH), and δ 170.1, indicating the presence of an acetamido sugar. Based on the ^{1}H and ^{13}C NMR data of **1**, the

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Table 1. ^{13}C NMR chemical shifts for compounds **1**–**3** (py-d_5)

Carbon	1	2	3	4	5	6
Aglycon						
C-1	38.7	39.3	38.9	38.7		
2	26.5	26.6	26.9	26.6		
3	88.8	88.8	88.5	88.2		
4	39.3	39.4	39.6	39.4		
5	55.9	56.0	56.0	55.8		
6	18.6	18.4	18.6	18.5		
7	33.6	33.6	33.6	33.4		
8	40.1	40.1	40.1	40.0		
9	47.1	47.1	47.1	47.0		
10	37.0	37.1	37.1	36.9		
11	23.7	23.8	23.8	23.8		
12	123.0	123.1	123.0	122.9		
13	143.3	143.3	143.4	143.2		
14	42.0	42.0	42.0	41.8		
15	35.8	35.9	35.9	35.7		
16	73.9	73.9	73.9	73.7		
17	51.5	51.6	51.6	51.5		
18	40.9	40.8	40.9	40.8		
19	47.8	47.9	47.9	47.7		
20	35.4	35.4	35.4	35.3		
21	76.8	76.8	76.8	76.5		
22	36.3	36.4	36.0	36.2		
23	28.1	28.1	28.1	28.0		
24	17.0	17.2	16.9	17.0		
25	15.8	15.8	15.9	15.7		
26	17.3	17.3	17.2	17.2		
27	27.2	27.3	27.3	27.1		
28	174.4	174.4	174.4	174.3		
29	29.1	29.2	29.2	29.0		
30	19.1	19.1	19.1	19.0		
MT[a]						
C-1	167.5	167.5	167.5	167.4		
2	133.7	133.8	133.7	133.5		
3	145.3	145.2	145.3	145.3		
4	23.5	23.6	23.6	23.4		
5	40.8	41.0	40.8	40.7		
6	79.4	79.6	79.5	79.4		
7	144.0	144.0	143.4	143.8		
8	114.8	115.0	114.8	114.7		
9	56.2	56.3	56.2	56.1		
10	23.5	23.7	23.7	26.6		
C-21 qui					xyl	
1	99.3	100.4	99.3	99.1	100.9	
2	75.4	75.3	75.5	75.3	75.9	
3	78.3	78.5	78.3	78.2	78.8	
4	77.0	71.2	76.8	76.7	72.0	
5	72.5	67.1	72.1	72.4	67.4	
6	18.8		18.9	18.7		
Sugar (C-3)						
glc or glc-2-NHAc						
1	104.7	104.8	104.9	106.5		104.7
2	57.9	57.9	82.8	75.5		82.6
3	75.8	75.9	76.9	78.2		76.8
4	72.2	72.5	71.8	71.4		71.5
5	77.4	77.5	77.1	77.3		77.4
6	69.9	69.4	69.8	69.8		69.6
C=O	170.1	170.0				
$COCH_3$	23.6	23.7				
glc′ (1 → 2) glc						
1			105.7			105.5
2			75.9			75.7
3			78.1			78.0
4			71.3			71.1
5			78.2			78.0
6			61.9			62.3
fuc (1 → 6) glc						
1	103.3	103.4	103.4	103.1		103.2
2	82.0	82.0	82.3	81.9		82.0
3	75.2	75.4	75.4	75.2		75.2
4	72.5	72.2	72.6	72.0		72.4
5	71.2	71.1	71.4	71.0		71.0
6	17.2	17.2	17.3	17.0		17.2
xyl (1 → 2) fuc						
1	106.9	107.2	107.0	106.7		106.8
2	75.4	75.9	76.4	75.6		76.3
3	78.0	78.5	77.6	77.8		77.8
4	70.8	70.8	70.4	70.6		70.6
5	67.1	67.1	67.2	67.0		67.0
C-28						
glc″1	95.6	95.7	95.7	95.5		95.5
2	76.8	76.8	76.8	78.9		78.9
3	78.1	78.1	77.0	76.9		76.8
4	71.7	71.3	71.9	71.6		72.0
5	78.9	79.0	78.9	78.2		78.2
6	61.9	62.5	62.5	62.4		62.6
rha (1 → 2) glc″						
1	101.8	101.8	101.8	101.6		101.7
2	70.5	70.5	70.7	70.3		70.3
3	82.1	82.2	82.0	78.7		78.8
4	79.0	79.1	79.0	84.2		84.2
5	69.1	69.2	69.2	69.0		69.0
6	18.9	18.9	18.9	18.7		18.7
glc‴ (1 → 3) rha						
1	105.7	105.8	105.9	105.5		105.5
2	75.4	75.2	75.2	75.0		75.0
3	78.3	78.2	77.9	78.0		77.9
4	71.3	71.9	71.2	71.1		71.1
5	78.3	78.7	78.2	78.2		78.2
6	62.7	62.8	62.8	62.6		62.6
ara (1 → 4) rha						
1	111.0	111.1	110.9	110.8		110.8
2	84.4	84.6	84.5	81.9		81.8
3	78.0	78.4	78.3	78.2		78.2
4	85.4	85.5	85.4	85.2		85.2
5	62.5	62.9	62.8	61.8		61.8

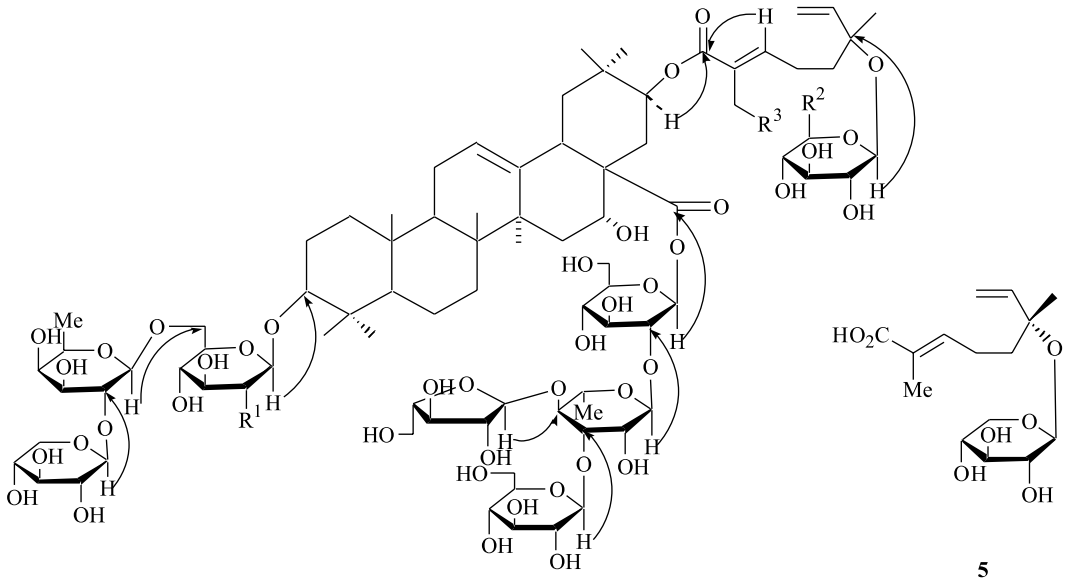
[a] MT, monoterpenoid acid moiety.

anomeric configurations of the sugar moieties were determined as β-configuration for glucose, 2-deoxy-2-acetamidoglucose, fucose, xylose, and quinovose, and α-configuration for rhamnose and arabinose. ^{13}C NMR spectrum of **1** showed four olefinic carbon signals at δ 133.7, 145.3, 144.0, and 114.8, an α, β-unsaturated carbonyl carbon at δ 167.5, and a methylene carbon at δ 56.2, ^{1}H NMR spectrum showed methyl proton signal at δ 1.49 (3H, s), methylene proton signal at δ 4.70 (2H, s), olefinic proton signal at δ 7.03 (1H, t, J = 7.5 Hz), and a group of one-substituted olefin proton signals at δ 6.17 (1H, dd, J = 18.0, 11.0 Hz), 5.14 (1H, d, J = 11.0 Hz), and 5.35 (1H, d, J = 18.0 Hz), indicating **1** had one monoterpene moiety. The linkages among aglycone, sugars, and monoterpene moieties

were determined on the basis of HMBC experiments (Fig. 1). When the ^{1}H and ^{13}C NMR signals of **1** were compared with those of **4**, the ^{1}H and ^{13}C NMR data of monoterpene moiety of **1** were in agreement with those of **4**, and sugar signals were similar to those of **4**, except for the appearance of 2-deoxy-2-acetamidoglucopyranosyl signals linked to C-3 instead of glucopyranosyl signals. Therefore, the structure of **1** was determined as 3-*O*-[β-D-xylopyranosyl-(1 → 2)-β-D-fucopyranosyl-(1 → 6)-β-D-2-deoxy-2-acetamidoglucopyranosyl]-21-*O*-[(6*S*)-2-*trans*-2-hydroxymethyl-6-methyl-6-*O*-β-D-quinovopyranosyl-2,7-octadienoyl]-acacic acid-28-*O*-β-D-glucopyranosyl(1 → 3)-[α-L-arabinofuranosyl-(1 → 4)]-α-L-rhamnopyranosyl-(1 → 2)]-β-D-glucopyranosyl ester. Compound **1** was a new saponin, named julibroside J_{29}.

Julibroside J_{30} (**2**), white powder, gave positive Molish reaction and Liebermann–Burchard reaction. ESI-TOF-MS showed the quasi-molecular ion peak at *m/z* 1904 $[M+H+NH_4]^+$. Upon acidic hydrolysis with 2.0 M HCl, **2** gave an acacic acid lactone unit, which was identified with an authentic sample, and **2** also furnished glucosamine hydrochloride, glucose, xylose, fucose, rhamnose, and arabinose, which were identified by co-TLC with authentic samples. In a comparison of the ^{13}C NMR signals for aglycone and monoterpene moiety of **2** with those of **1** (Table 1), all signals due to the aglycone and monoterpene moiety of **1** were almost superimposable with those of **1**, indicating that the aglycone and monoterpene moiety of **1** was same as that of **1**. In the ^{13}C NMR spectrum, the sugar signals of **2** were similar to those of **1**, except for the appearance of xylopyranosyl signals instead of quinovopyranosyl signals. The xylopyranosyl signals in **2** were in agreement with those of (6*S*)-menthiafolic acid-6-*O*-β-D-xyloside (**5**)[8] (Table 1), indicating that the xylose can be determined to be linked at C-6 of the monoterpenoic acid attached at C-21 of aglycone. Thus, the structure of **2** was established to be 3-*O*-[β-D-xylopyranosyl-(1 → 2)-β-D-fucopyranosyl-(1 → 6)-β-D-2-deoxy-2-acetamidoglucopyranosyl]-21-*O*-[(6*S*)-2-*trans*-2-hydroxymethyl-6-methyl-6-*O*-β-D-xylopyranosyl-2,7-octadienoyl]-acacic acid-28-*O*-β-D-glucopyranosyl(1 → 3)-[α-L-arabinofuranosyl-(1 → 4)]-α-L-rhamnopyranosyl-(1 → 2)]-β-D-glucopyranosyl ester. Compound **2** was a new saponin, named julibroside J_{30}.

Julibroside J_{31} (**3**), white powder, gave positive Molish reaction and Liebermann–Burchard reaction. The positive ESI-TOF-MS showed the quasi-molecular ion peak at *m/z* 2021 $[M+H]^+$. Upon acidic hydrolysis with 2.0 M HCl, **3** gave an acacic acid lactone unit, which was identified with an authentic sample, and **3** also afforded glucose, xylose, fucose, rhamnose, arabinose, and quinovose, which were identified by co-TLC with authentic samples. In a comparison of the ^{13}C NMR data of **3** with those of **1**, all signals due to the aglycone, monoterpene moiety and sugar moieties attached at C-21 and C-28 in **3** were in agreement with those in **1**. The sugar signals linked at C-3 in **3** were similar to those of **1**, except for the appearance of two glucose signals instead of 2-deoxy-2-acetamidoglucose signals (Table 1). The ^{13}C NMR data of the sugar moieties attached to C-3 of the aglycone were identical with those of prosapogenin-8 (**6**).[7] Thus, compound **3** was elucidated as



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	R^1	R^2	R^3
Julibroside J_{29} (**1**)	NHAc	Me	OH
Julibroside J_{30} (**2**)	NHAc	H	OH
Julibroside J_{31} (**3**)	O-glc	Me	OH
Prosapogenin-10 (**4**)	OH	Me	OH
Prosapogenin-8 (**6**)	O-glc	Me	H

Figure 1. The structures of **1**–**6** and the HMBC of **1**–**3**.

Table 2. The inhibitory rate to cancer cell lines (10 μM)

Cancer cell lines	PC-3M-1E8	MDA-MB-435	HeLa	HL-60	BGC823	Bel-7402
1	85.37	84.47	94.90	25.35	52.90	67.14
2	84.98	75.68	91.65	25.59	46.66	57.49
3	80.85	80.41	83.48	39.33	15.16	46.61

Table 3. The inhibitory rate to cancer cell lines (10 μM)

Cancer cell lines	PC-3M-1E8	Bel-7402	HeLa
Adriamycin	91.61	51.26	76.96
1	81.40	50.37	87.75
2	75.96	61.87	92.19
3	94.71	44.34	64.33

3-*O*-{β-D-glucopyranosyl-(1 → 2)-[β-D-xylopyranosyl-(1 →2)-β-D-fucopyranosyl-(1 → 6)]-β-D-glucopyranosyl}-21-*O*-[(6*S*)-2-*trans*-2-hydroxymethyl-6-methyl–6-*O*-β-D-quinovopyranosyl-2,7-octadienoyl]-acacic acid-28-*O*-β-D-glucopyranosyl(1 → 3)-[α-L-arabinofuranosyl-(1 → 4)]-α-L-rhamnopyranosyl-(1 → 2)]-β-D-glucopyranosyl ester. Compound **3** was a new saponin, named julibroside J_{31}.

Julibroside J_{29} (**1**), julibroside J_{30} (**2**), and julibroside J_{31} (**3**) showed marked inhibitory activities against PC-3M-1E8, MDA-MB-435, and HeLa cancer cell lines in vitro at 10 μM assayed by SRB and MTT methods (Tables 2 and 3).

Acknowledgment

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4. Extraction and isolation. The air-dried powder of the stem bark of *A. julibrissin* Durazz. (20 kg) was sliced into chips, extracted three times with boiling water, and concentrated under reduced pressure. The water extract was partitioned with *n*-BuOH and water. The *n*-BuOH extract (1200.0 g) was subjected to silica gel column chromatography and eluted with $CHCl_3$–MeOH–H_2O (65:35:10, v/v) to yield fractions A and B. Fraction A was chromatographed over HP-20 macroporous resin column by eluting gradient solvent system (30% MeOH → 90% MeOH) to give fractions 1–6. Fraction 4 was subjected to Rp C_{18} silica gel column chromatography (60 → 80% MeOH) and preparative HPLC (74:26 MeOH–H_2O, 2.8 mL/min, 216 nm detection) to afford **1** (30 mg), **2** (25 mg), and **3** (20 mg).
5. Julibroside J_{29} (**1**), White powder, ESI-TOF-MS *m*/*z* 1939 $[M+H+K]^+$; ^1H NMR (500 MHz, py-d_6): δ 0.92 (3H, s, CH_3), 1.01 (6H, s, CH_3), 1.06 (3H, s, CH_3), 1.14 (3H, s, CH_3), 1.16 (3H, s, CH_3), 1.87 (3H, s, CH_3), 5.02 (1H, d, *J*=8.5 Hz, glc H-1), 8.9 (NH), 4.98 (1H, d, *J* = 7.5 Hz, fuc H-1), 5.07 (1H, d, *J* = 6.5 Hz, xyl H-1), 6.03 (1H, d, *J* = 8.0 Hz, glc′ H-1), 5.87 (1H, s, rha H-1), 6.26 (1H, br s, araf H-1), 5.32 (1H, d, *J* = 7.5 Hz, glc″ H-1), 4.83 (1H, d, *J* = 8.0 Hz, qui H-1), 2.10 (3H, s, $COCH_3$), 1.75 (3H, d, *J* = 5.5 Hz, rha H-6), 1.46 (3H, d, *J* = 6.0 Hz, fuc H-6), 1.57 (3H, d, *J* = 5.0 Hz, qui H-6), 7.03 (1H, t, *J* = 7.5 Hz, MT H-3), 6.17 (1H, dd, *J* = 11.0, 18.0 Hz, MT H-7), 5.14 (1H, t, *J* = 11.0 Hz, MT H-8a), 5.35 (1H, t, *J* = 18.0 Hz, MT H-8b), 1.49 (3H, s, MT H-10). ^{13}C NMR (125 MHz, py-d_6) data, see Table 1. Acid hydrolysis of **1**: A small amount of **1** was hydrolyzed by 2 M HCl in 100 °C for 6 h. After filtration of the reaction mixture, the filtrate was neutralized with $BaCO_3$ to give a residue, which was identified as glucosamine hydrochloride, glucose, xylose, fucose, rhamnose, arabinose, and quinovose on TLC (2-propanol–H_2O, 9:1), reagent: 20% H_2SO_4. Julibroside J_{30} (**2**), white powder, ESI-TOF-MS *m*/*z* 1904 $[M+H+NH_4]^+$, ^1H NMR (500 MHz, py-d_6): δ 0.94 (3H, s, CH_3), 1.03 (6H, s, CH_3), 1.06 (3H, s, CH_3), 1.16 (3H, s, CH_3), 1.17 (3H, s, CH_3), 1.89 (3H, s, CH_3), 5.03 (1H, d, *J* = 8.0 Hz, 2-NHAc-glc H-1), 5.00 (1H, d, *J* = 7.5 Hz, fuc H-1), 5.08 (1H, d, *J* = 6.5 Hz, xyl H-1), 6.06 (1H, d, *J* = 8.0 Hz, glc′ H-1), 5.95 (1H, s, rha H-1), 6.28 (1H, br s, araf H-1), 5.37 (1H, d, *J* = 8.5 Hz, glc″ H-1), 4.84 (1H, d, *J* = 7.5 Hz, xyl H-1), 2.11 (3H, s, $COCH_3$), 1.48 (1H, d, *J* = 6.5 Hz, fuc H-6), 1.78 (3H, d, *J* = 6.0 Hz, rha H-6), 7.03 (1H, t, *J* = 7.4 Hz, MT H-3), 6.17 (1H, dd, *J* = 11.0, 18.0 Hz, MT H-7), 5.18 (1H, t, *J* = 11.0 Hz, MT H-8a), 5.39 (1H, t, *J* = 18.0 Hz, MT H-8b), 1.43 (3H, s, MT H-10). ^{13}C NMR (125 MHz, py-d_6) data, see Table 1. Julibroside J_{31} (**3**), White powder, ESI-TOF-MS *m*/*z* 2021 $[M+H]^+$, ^1H NMR (500 MHz, py-d_6): δ 0.96 (3H, s, CH_3), 1.01 (3H, s, CH_3), 1.06 (3H, s, CH_3), 1.13 (3H, s, CH_3), 1.14 (3H, s, CH_3), 1.26 (3H, s, CH_3), 1.86 (3H, s, CH_3), 4.87 (1H, d, *J* = 7.0 Hz, glc H-1), 4.95 (1H, d, *J* = 8.0 Hz, fuc H-1), 5.04 (1H, d, *J* = 7.0 Hz, xyl H-1), 5.32 (1H, d, *J* = 8.0 Hz, glc′ H-1), 6.04 (1H, d, *J* = 8.0 Hz, glc″ H-1), 5.84 (1H, br s, rha H-1), 6.25 (1H, br s, araf H-1), 5.40 (1H, d, *J* = 7.5 Hz, glc″ H-1), 4.84 (1H, d, *J* = 8.0 Hz, qui H-1), 1.47 (3H, d, *J* = 6.5 Hz, fuc H-6), 1.77 (3H, d, *J* = 5.5 Hz, rha H-6), 1.57 (3H, d, *J* = 4.5 Hz, qui H-6), 7.06 (1H, t, *J* = 7.4 Hz, MT H-3), 6.18 (1H, dd, *J* = 11.0, 18.0 Hz, MT H-7), 5.14 (1H, t, *J* = 11.0 Hz, MT H-8a), 5.39 (1H, t, *J* = 18.0 Hz, MT H-8b), 1.43 (3H, s, MT H-10). ^{13}C NMR (125 MHz, py-d_6) data, see Table 1.
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