Note

Lignan Diesters of Canangafruticoside A from the Leaves of *Cananga odorata* var. *odorata*

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From the leaves of *Cananga odorata* var. *odorata*, three relatively large molecules, namely two aryl naphthalene lignan diesters of canangafruticoside A and one cyclobutane lignan diester of canangafruticoside A, were isolated along with four known compounds. The structures of the new compounds were elucidated based on spectroscopic evidence.

Key words *Cananga odorata* var. *odorata*; Annonaceae; lignan; canangafruticoside A

Parkinson's disease (PD) is a common neurodegenerative disorder. More than 10 genes have been identified as causing familial PD.[1] However, in idiopathic PD, which accounts for over 90% of PD cases, endogenous and exogenous environmental factors are believed to be crucial for the onset of symptoms.[2,3] In 1999, Caparros and Elbaz suggested the high prevalence of atypical Parkinsonism in the Caribbean island of Guadeloupe was linked to consumption of Annonaceous fruits and herbal tea prepared from *Annona muricata* and *A. squamosa*.[4] A related Annonaceous plant, *Canagna odorata*, is used as an herbal medicine for treating fevers and symptoms of malaria,[5] and ylang-ylang is an essential oil obtained from the flowers of *C. odorata*. This oil has euphoric and sedative effects on the nervous system and its fragrant components have been well analyzed. However, there has been little phytochemical study of the non-oil constituents in *Cananga* species; thus, *Cananga* species attracted our attention. *C. odorata* (Lam.) Hooker f. & Thomson var. *odorata* is called fragrant cananga or wild cananga, and megastigmane glucoside has been isolated from this plant.[6] Further investigation of this plant resulted in the isolation of three relatively large molecules, namely, lignan canangafruticoside A diesters (**1**–**3**) (Fig. 1), along with one known lignan glucoside, (+)-isolariciresinol 3a-*O*-*β*-D-glucopyranoside (**4**),[7] and three known flavonol glycosides, kaempferol 3-*O*-neohesperidoside (**5**),[8] quercetin 3-*O*-neohesperidoside (**6**),[9] and 3-*O*-robinoside (**7**).[10] 10-*O*-*p*-Coumaroyl and 10-*O*-caffeoyl esters of canangafruticoside A (**8**), namely canangafruticosides C (**9**) and E (**10**), respectively, which have been isolated from *C. odorata* var. *fruticosa*, were also obtained.[11] In this paper, we describe the structural elucidation of these new lignan derivatives by intensive inspection of one- and two-dimensional NMR spectroscopic data.

Results and Discussion

Air-dried leaves of *C. odorata* var. *odorata* were extracted with MeOH three times and the concentrated MeOH extract was partitioned with solvents of increasing polarity. The 1-BuOH-soluble fraction was separated by various chromatographic procedures, including column chromatography (CC) on a highly porous synthetic resin (Diaion HP-20), normal silica gel and reversed-phase octadecyl silica gel (ODS) CC, droplet counter-current chromatography (DCCC), and HPLC to afford three new compounds (**1**–**3**) (Fig. 1).

Compound **1** ($[\alpha]_D^{25}$+17.5) was isolated as an amorphous powder and its elemental composition was determined as $C_{50}H_{60}O_{23}$ by high-resolution (HR) electrospray-ionization (ESI) MS. The IR spectrum exhibited absorptions corresponding to hydroxy groups (3367 cm^{-1}), ester functional groups (1720 cm^{-1}), and aromatic rings (1604, 1513 cm^{-1}). UV absorptions at 286, 311, and 330 also indicated the presence of aromatic rings. The ^{1}H-NMR spectrum included three singlet aromatic signals (δ_H 6.87, 7.31, 8.29) and two characteristic signals [δ_H 6.89 (2H, d), 7.10 (2H, d)], coupled in an AA′BB′ system, along with anomeric protons [δ_H 4.47 (2H)], two sets of *cis*-olefinic protons, and two close aldehyde signals (Table 1). In the ^{13}C-NMR, 16 overlapping or binary signals were ob-

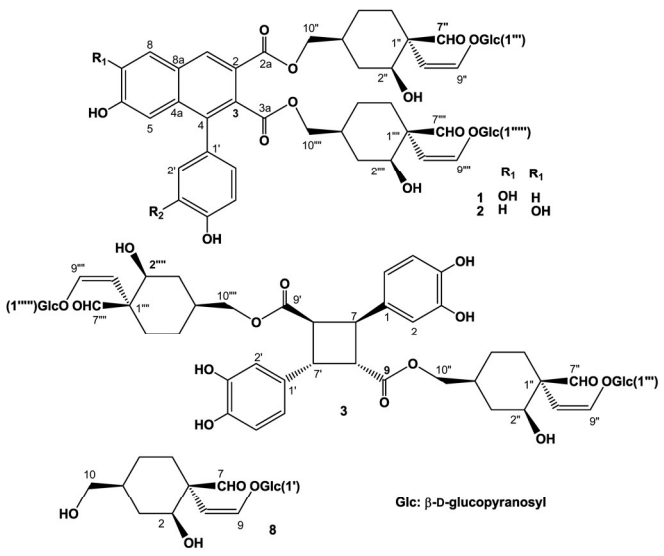

Fig. 1. Structures of New Compounds Isolated and Canangafruticoside A (**8**)

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Table 1. ^{1}H-NMR Spectroscopic Data for Compounds **1**, **2**, and **3** (CD_3OD, 400 MHz)

H	**1**	**2**	**3**
1	8.29 s	8.47 s	—
2	—	—	6.74 d 1.1
5	6.87 s	6.94 d 2.2	6.72 d 8.2
6	—	—	6.62 dd 8.1, 1.1
7	—	7.18 d 8.8, 2.2	4.22 m
8	7.31 s	7.93 d 8.8	3.74–3.77 m
2′	7.10 d 8.5	6.74 d 1.5	6.74 d 1.1
3′	6.89 d 8.5	—	—
5′	6.89 d 8.5	6.87 d 8.0	6.72 d 8.2
6′	7.10 d 8.5	6.61 dd 8.0, 1.5	6.62 dd 8.2, 1.1
7′	—		4.22 m
8′	—		3.74–3.77 m
2″, 2‴	3.74 dd 11.5, 4.1	3.66 m	3.70–3.79 2H m
	3.79 m	3.74 m	
3″, 3‴	1.25–1.34 2H m	1.42–1.44 2H m	1.09 m, 1.12 m
	1.79–1.96 2H m	1.96–2.05 2H m	1.66–1.69 2H m
4″, 4‴	1.95 2H m	1.96–2.05 2H m	1.29–1.32 2H m
5″, 5‴	1.29–1.32 2H m	1.36–1.44 2H m	0.98–1.01 2H m
	1.65 2H m	1.67–1.75 2H m	1.22–1.26 2H m
6″, 6‴	1.29–1.32 2H m	1.29–1.44 2H m	1.22–1.26 2H m
	2.38 2H m	2.31–2.45 2H m	2.26 m, 2.28 m
7″, 7‴	9.77 s	9.83 s	9.76 s
	9.84 s	9.77 s	9.76 s
8″, 8‴	4.59 d 6.6	4.59 d 6.6	4.58 d 6.6
	4.64 d 6.6	4.63 d 6.6	4.58 d 6.6
9″, 9‴	6.44 d 6.6	6.44 d 6.5	6.43 d 6.6
	6.47 d 6.6	6.47 d 6.5	6.43 d 6.6
10″, 10‴	3.72–3.80 2H m	3.84–3.87 2H m	3.70–3.79 4H m
	4.17–4.20 2H m	4.00–4.21 1H m	
1‴, 1⁗	4.47 2H d 7.8	4.49 2H d 7.6	4.48 d 8.2
2‴, 2⁗	3.25 2H dd 9.1, 7.8	3.26 2H m	3.26 dd 8.9, 8.2
3‴, 3⁗	3.30–3.31 2H m	3.30–3.32 2H m	3.30–3.32 2H m
4‴, 4⁗	3.30–3.31 2H m	3.30–3.32 2H m	3.30–3.32 2H m
5‴, 5⁗	3.35 2H m	3.35 2H m	3.35 2H m
6‴, 6⁗	3.66 2H dd 12.0, 4.5	3.66 2H dd 11.4, 4.4	3.66 2H dd 11.9, 4.4
	3.86 2H dd 12.0, 2.1	3.86 2H dd 11.4, 1.1	3.86 2H dd 11.9, 1.4

served, which resembled those of canangafruticoside A (**8**) or the canangafruticoside A region of an aryldihydronaphthalene lignan dicarboxylic acid diester of canangafruticoside A (**11**) isolated from a related plant, *C. odorata* var. *fruticosa*[11] (Table 2). The remaining 16 ^{13}C-NMR signals, two of which were of double strength, comprised 14 sp^2 carbons and two carbonyl carbons. Based on these results, the structure of compound **1** was expected to be the arylnaphthalene lignan dicarboxylic acid diester of canangafruticoside A with a *para*-substituted benzene ring bearing one hydroxy functional group (δ_C 158.3) and the naphthalene skeleton bearing two hydroxy functional groups (δ_C 149.4, 150.9). Because the three aromatic protons appeared as singlets in the ^{1}H-NMR spectrum, the positions of the two hydroxy groups on the naphthalene skeleton could only be at C-6 and C-7. This was substantiated by the heteronuclear multiple bond correlations (HMBC) between H-1 and C-2a, C-4a and C-8, H-5 and C-4 and C-7, and H-8 and C-1 and C-6 (Fig. 2), and those from H_2-10″ and H_2-10⁗ and C-2a and C-3a established the ester linkages between two canangafruticoside A units and the lignan dicarboxylic acid. Therefore, the structure of **1** was assigned as shown in Fig. 1.

Compound **2** ($[\alpha]_D^{25}$+12.8), was isolated as an amorphous powder and its elemental composition was determined as $C_{50}H_{60}O_{23}$ by HR-ESI-MS. The IR and UV spectra were similar to those of **1**. The NMR spectra also indicated the presence of two units of canangafruticoside A and 16 sp^2 and two carbonyl carbons. In the ^{1}H-NMR spectrum, two sets of aromatic protons coupled in an ABX system and one singlet aromatic proton was observed. Thus, the *para*-substituted aromatic ring present in **1** was replaced by a 1,3,4-trisubstituted ring and only one hydroxy group was present on the naphthalene ring. In the HMBC spectrum, H-5 [δ_H 6.94 (d, J=2.2 Hz)] showed a correlation cross peak with C-4 and H-8 [δ_H 7.93 (d, J=8.8 Hz)] and C-1, and their coupling constants showed that C-7 bears a hydrogen atom. Therefore, the hydroxy group was on C-6 and the structure was elucidated as shown in Fig. 1.

Compound **3** ($[\alpha]_D^{25}$+13.5) was isolated as an amorphous powder and its elemental composition was determined as $C_{50}H_{64}O_{24}$ by HR-ESI-MS. The IR spectrum of **3** was similar to the spectra of **1** and **2**, and overlapping and binary signals corresponding to two units of canangafruticoside A were also observed in the NMR spectrum. Three aromatic protons signals, each corresponding to two protons, were coupled in an ABX system, and of the remaining 18 ^{13}C-NMR signals, 12

Table 2. ^{13}C-NMR Spectroscopic Data for Compounds **1**, **2**, and **3** (CD_3OD, 100 MHz)

C	**1**	**2**	C	**3**	**8**[a)]
1	130.0	132.1	1	131.96	
2	129.7	138.1	2	115.97	
2a	167.8	167.6	3	146.2	
3	123.1	132.6	4	145.5	
3a	171.8	171.5	5	116.4	
4	137.8	138.0	6	120.19	
4a	130.1	138.1	7	42.5	
5	110.1	109.0	8	48.6	
6	150.9	159.9	9	173.80	
7	149.4	121.2	1′	131.98	
8	112.0	132.4	2′	116.00	
8a	132.1	128.5	3′	146.3	
1′	129.9	129.8	4′	145.6	
2′	132.6	118.9	5′	116.4	
3′	116.0	146.48	6′	120.16	
4′	158.3	146.46	7′	42.5	
5′	116.0	116.3	8′	48.7	
6′	132.6	123.3	9′	173.81	
1″, 1‴	56.23	56.2	1″, 1‴	56.19	56.32
	56.24	56.3		56.24	56.32
2″, 2‴	75.7	75.7	2″, 2‴	75.59	75.5
	75.8	75.8		75.65	75.8
3″, 3‴	35.9	35.92	3″, 3‴	35.7	35.7
	36.0	35.93		35.9	35.9
4″, 4‴	36.9	36.9	4″, 4‴	37.0	37.35
	37.3	37.4		37.0	37.39
5″, 5‴	26.1	26.2	5″, 5‴	25.9	26.0
	26.2	26.3		26.2	26.1
6″, 6‴	31.0	31.1	6″, 6‴	31.06	31.3
	31.1	31.2		31.15	31.4
7″, 7‴	206.9	206.99	7″, 7‴	206.88	206.89
	206.9	207.03		206.9	206.94
8″, 8‴	110.2	110.1	8″, 8‴	110.1	110.17
	110.2	110.2		110.2	110.21
9″, 9‴	146.1	146.1	9″, 9‴	146.0	146.1
	146.3	146.3		146.1	146.2
10″, 10‴	70.4	70.5	10″, 10‴	69.7	69.8
	70.7	70.9		69.9	70.2
1‴, 1⁗	104.2	104.3	1‴, 1⁗	104.2	104.3
2‴, 2⁗	74.6	74.6	2‴, 2⁗	74.6	74.6
3‴, 3⁗	78.5	78.5	3‴, 3⁗	78.5	78.6
4‴, 4⁗	71.3	71.3	4‴, 4⁗	71.3	71.3
5‴, 5⁗	78.0	78.0	5‴, 5⁗	78.0	78.0
6‴, 6⁗	62.6	62.7	6‴, 6⁗	62.6	62.7

a) Canangafruticoside A region of canangafruticoside A diester of aryldihydronaphthalene lignan dicarboxylic acid.[7)]

sp^2 carbon signals were assigned to the two 1,3,4-trisubstituted benzene rings, two to carbonyl carbons, and four to methine carbons, indicating a dimeric phenyl propanoid skeleton. The lack of protons demanded one more ring system, and four characteristic methine carbons (δ_C 42.5×2, 48.6, 48.7) can form a cyclobutane ring. The cyclobutane ring can form through the dimerization of phenylpropanoids with a double bond at the 7-position, and the possible stereoisomers of the phenylpropanoids are shown in Fig. 3.[12)] Because the ^{13}C-NMR signals for the lignan skeleton appeared as sets, stereoisomers that possess a C2 symmetric axis (**E**, **F**, **G**, **H**) were eliminated as candidates. Improbable dimerization products between *trans*- and *cis*-phenylpropanoids are so far unknown and these isomers (**C**, **D**, **I**, **J**) were eliminated. The correlation peaks of H-2 (or 2′) and H-6 (or 6′) with H-8 and H-8′ in the phase-sensitive nuclear Overhauser enhancement spectroscopy eliminated **A**. The remaining two candidates, **B** and **K**, could be formed through the dimerization of *trans*-phenylpropanoids. The ^{13}C-NMR chemical shifts reported for truxinic acid, **B** (δ_C 44.6, 45.1, 45.9, 46.2)[13)] do not match those of **3** (Table 2), whereas those of the cyclobutane ring carbons (δ_C 42.1, 42.8, 48.0, 48.7) of shimobashiric acid (**K**), a truxillic acid isolated from *Keiskea japonica*, closely resembled those of **3**.[14)] Therefore, the structure of **3** was assigned as shown in Fig. 1.

Three large molecules were isolated from the leaves of *C. odorata* var. *odorata*. The compounds were the arylnaphtha-

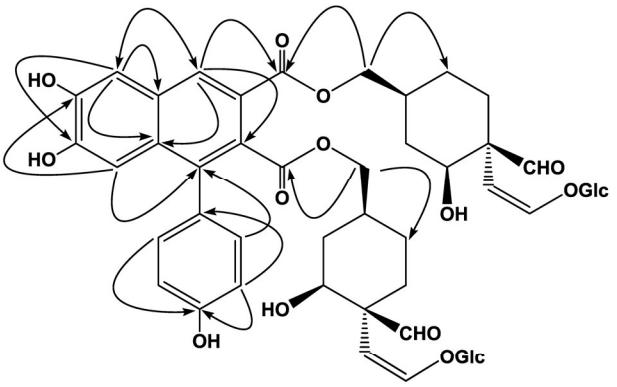

Fig. 2. HMBC Correlations of Compound **1**

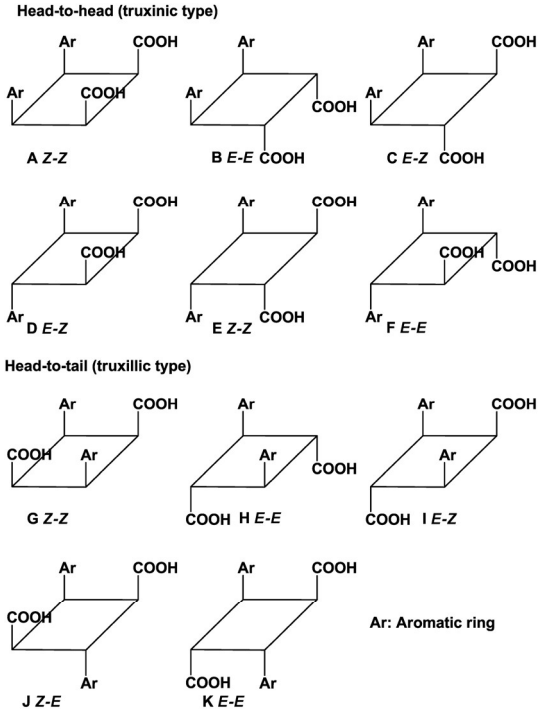

Fig. 3. Possible Isomers of Cyclobutane Derivatives

lene lignan dicarboxylic acid diesters of an unusual monoterpene glucoside, canangafruticoside A (**8**) and a truxillic acid diester of canangafruticoside A. Canangafruticoside A was first isolated from a related species, *C. odorata* var. *fruticosa* and its stereochemistry was extensively examined.[11] Because 10-*O*-acyl esters of canangafruticoside A, namely canangafruticosides C and E, were also isolated from the title plant, the stereochemistry of the canangafruticoside A moiety in **1**, **2**, and **3** must be the same as that isolated from *C. odorata* var. *fruticosa*.

Experimental

General Experimental Procedures Optical rotations were measured on a polarimeter (P-1030, JASCO, Tokyo, Japan). IR and UV spectra were measured on IR and UV/Vis spectrophotometers (FT-710, Horiba, Kyoto, Japan and V-520, JASCO, respectively). ^{1}H- and ^{13}C-NMR spectra were recorded on a spectrometer (JNM α-400, JEOL, Tokyo, Japan) at 400 and 100 MHz, respectively, with tetramethylsilane as an internal standard. Positive-ion HR-ESI-MS was performed by nanospray ESI-TOF-MS (QSTAR XL, Applied Biosystems, Foster City, CA, U.S.A.). Silica gel CC was performed on silica gel 60 (Merck, Darmstadt, Germany; 70–230 mesh), and reversed-phase (ODS) open CC on Cosmosil 75C_{18}-OPN (Nacalai Tesque, Kyoto, Japan; Φ=50 mm, L=25 cm). DCCC (Tokyo Rikakikai, Tokyo, Japan) used 500 glass columns (Φ=2 mm, L=40 cm), and the lower and upper layers of the solvent mixture $CHCl_3$–MeOH–H_2O–1-PrOH (9 : 12 : 8 : 2) were used as the mobile and stationary phases, respectively. Fractions (5 g each) were collected and numbered according to their order of elution with the mobile phase. HPLC was performed on an ODS column (Inertsil; GL Sciences Inc., Tokyo, Japan; Φ=6 mm, L=25 cm).

Plant Material Leaves of *C. odorata* var. *odorata* (Annonaceae) were collected in March 2005 from a cultivated plant in the Botanical Garden, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand.

Extraction and Isolation Dried leaves of *C. odorata* var. *odorata* (541 g) were extracted three times with MeOH (4.5 L×3) at 25°C for one week each and the total extracts were concentrated to 3 L *in vacuo*. The extracts were washed with *n*-hexane (3 L; hexane-soluble fraction: 20.1 g) and the MeOH layer was concentrated to a gummy mass. The gummy mass was suspended in water (3 L) and then extracted with EtOAc (3 L) to give an EtOAc-soluble fraction (14.0 g), and with 1-BuOH (3 L) to give a 1-BuOH-soluble fraction (27.4 g). The remaining water-layer was concentrated to furnish a water-soluble fraction (70.3 g).

The 1-BuOH-soluble fraction (27.0 g) was subjected to CC (Diaion HP-20, Mitsubishi Kagaku, Tokyo, Japan; Φ=40 mm, L=50 cm), using H_2O–MeOH (4 : 1, 3 L; 2 : 3, 3 L; 3 : 2, 3 L; 1 : 4, 3 L), and MeOH (3 L), and 500 mL fractions were collected. The residue (8.61 g) in fractions 14–18 (H_2O–MeOH, 2 : 3, 3 : 2) was subjected to silica gel CC (250 g) with elution by $CHCl_3$–MeOH (19 : 1, 1.5 L; 17 : 3, 1.5 L; 3 : 1, 1.5 L) and 300 mL fractions were collected. The residue (2.13 g) in fractions 14–18 was separated by ODS open CC (linear gradient: MeOH–H_2O 1 : 9, 500 mL→9 : 1, 500 mL, 10 g fractions), and the residue (282 mg) was subjected to DCCC. The residue (73.4 mg) in fractions 30–34 was purified by HPLC (H_2O–MeOH, 3 : 2; 1 mL/min) to give **5** (13.4 mg) from the peak at 35 min. The residue (44.7 mg) in fractions 42–48 was purified by HPLC (H_2O–MeOH, 13 : 7; 1 mL/min) to give **4** (6.5 mg) from the peak at 15 min. The residue (160 mg) in fractions 72–86 obtained on ODS open CC was purified by HPLC (H_2O–MeOH, 11 : 9; 1 mL/min) to give **10** (33.0 mg) from the peak at 30 min. The residue (636 mg) obtained on silica gel CC was separated by DCCC and the residue (288 mg) in fractions 54–59 was separated by HPLC (H_2O–MeOH, 1 : 1; 1 mL/min) to afford **6** (16.7 mg), **7** (6.3 mg), **3** (8.1 mg), and **1** (7.0 mg) from the peaks at 12, 22, 39, and 80 min, respectively.

The residue (3.94 g) in fractions 19–22 obtained by Diaion HP-20 CC was subjected to silica gel CC (120 g) with elution by $CHCl_3$–MeOH (19 : 1, 800 mL; 9 : 1, 800 mL; 4 : 1, 800 mL; 7 : 3, 800 mL; 3 : 2, 800 mL) and $CHCl_3$–MeOH–H_2O (6 : 4 : 1, 800 mL), and 100 mL fractions were collected. The residue (0.50 g) in fractions 12–19 was separated by ODS open CC (linear gradient: MeOH–H_2O, 1 : 9, 600 mL→9 : 1, 600 mL, 2 g fractions) to give **9** (23.7 mg) in fractions 148–151. The residue in fractions 25–45 (1.49 g) was separated by ODS open CC

(linear gradient: MeOH–H_2O, 1 : 9, 600 mL→9 : 1, 600 mL, 2 g fractions), and the residue in fractions 339–352 (140 mg) was purified by HPLC (H_2O–MeOH, 1 : 1; 1 mL/min) to give **2** (10.2 mg) from the peak at 88 min.

Compound **1**

Amorphous powder, $[\alpha]_D^{25}$+17.5 (c=0.70, MeOH); IR ν_{max} (film) cm^{-1}: 3367, 2929, 1720, 1708, 1604, 1513, 1257, 1171, 1074, 1042; UV λ_{max} (MeOH) nm (log ε): 227 (4.15), 255 (4.26), 286 (3.93), 311 (3.84), 330 (3.79); ^{1}H-NMR (CD_3OD, 400 MHz): Table 1; ^{13}C-NMR (CD_3OD, 100 MHz): Table 2; HR-ESI-MS (positive-ion mode) m/z: 1051.3404 $[M+Na]^+$ (Calcd for $C_{50}H_{60}O_{23}Na$: 1051.3418).

Compound **2**

Amorphous powder, $[\alpha]_D^{25}$+12.8 (c=1.02, MeOH); IR ν_{max} (film) cm^{-1}: 3384, 2931, 1710, 1654, 1617, 1516, 1437, 1261, 1208, 1075, 1044; UV λ_{max} (MeOH) nm (log ε): 251 (4.16), 286 (3.95), 309 (3.90), 327 (3.83), 350 (3.41); ^{1}H-NMR (CD_3OD, 400 MHz): Table 1; ^{13}C-NMR (CD_3OD, 100 MHz): Table 2; HR-ESI-MS (positive-ion mode) m/z: 1051.3397 $[M+Na]^+$ (Calcd for $C_{50}H_{60}O_{23}Na$: 1051.3418).

Compound **3**

Amorphous powder, $[\alpha]_D^{25}$+13.5 (c=0.81, MeOH); IR ν_{max} (film) cm^{-1}: 3367, 2935, 1720, 1708, 1604, 1513, 1444, 1285, 1200, 1075, 1040; UV λ_{max} (MeOH) nm (log ε): 227 (4.02), 253 (3.78), 286 (3.76); ^{1}H-NMR (CD_3OD, 400 MHz): Table 1; ^{13}C-NMR (CD_3OD, 100 MHz): Table 2; HR-ESI-MS (positive-ion mode) m/z: 1071.3650 $[M+Na]^+$ (Calcd for $C_{50}H_{64}O_{24}Na$: 1071.3680).

Sugar Analysis Compounds **1**–**3** were hydrolyzed with 1 M HCl at 90°C for 2 h. The hydrolysates were analyzed with a chiral detector (OR-2090plus, JASCO) on an amino column [Asahipak NH_2P-50 4E; CH_3CN–H_2O, 4 : 1, 1 mL/min] to give peaks for D-glucose at 13.7 min. All peaks showed positive optical rotation signs. Peaks were identified by co-chromatography with authentic D-glucose.

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Conflict of Interest The authors declare no conflict of interest.

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