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Rare Thioglycosides from the Roots of *Wasabia japonica*

Chung Sub Kim,[†] Joonseok Oh,[‡,§] Lalita Subedi,[⊥,∥] Sun Yeou Kim,[⊥,∥] Sang Un Choi,[#] and Kang Ro Lee*[,†]

[†]Natural Products Laboratory, School of Pharmacy, Sungkyunkwan University, Suwon 16419, Republic of Korea

[‡]Department of Chemistry, Yale University, New Haven, Connecticut 06520, United States

[§]Chemical Biology Institute, Yale University, West Haven, Connecticut 06516, United States

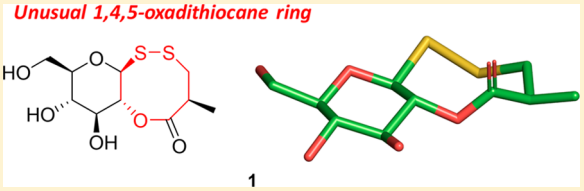
[⊥]Gachon Institute of Pharmaceutical Science, Gachon University, Incheon 21936, Republic of Korea

[∥]College of Pharmacy, Gachon University, #191, Hambakmoero, Yeonsu-gu, Incheon 21936, Republic of Korea

[#]Korea Research Institute of Chemical Technology, Daejeon 34114, Republic of Korea

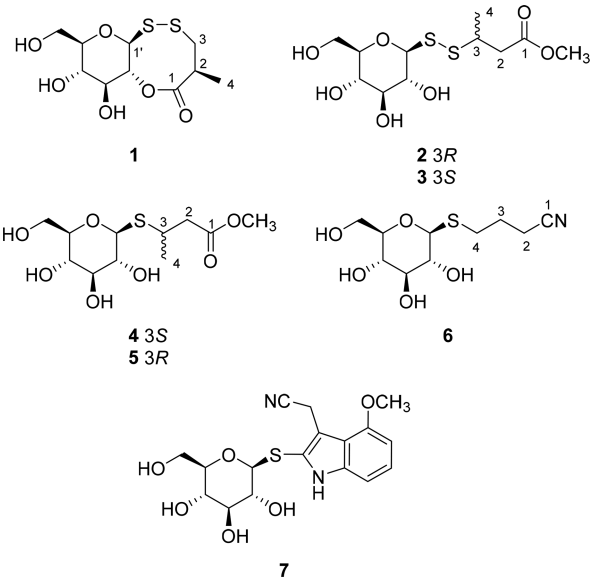
Supporting Information

ABSTRACT: Six new thioglycosides (**1**−**6**) were characterized from the roots of *Wasabia japonica* along with a known analogue (**7**). Of these compounds, **1**−**3** possess a disulfide bridge connecting the carbohydrate motif and the aglycone, which is extremely rare in Nature. In particular, compound **1** forms an unusual 1,4,5-oxadithiocane ring system. The structures of the isolated compounds were determined through conventional NMR and HRMS data analysis procedure, and computational methods with advanced statistics were used for the configurational assignments of **1** and two pairs of inseparable epimers, **2**/**3** and **4**/**5**. All compounds were evaluated for their anti-inflammatory, neuroprotective, and cytotoxic activities, with **1** showing weak anti-inflammatory activity (IC_{50} 41.2 μM).



Thioglycosides are rare in Nature and so far have been reported from plants in the family Brassicaceae, several microorganisms, and a marine sponge, *Clathria pyramida*.[1−6] In plants, glucosinolate derivatives featuring structurally an *O*-sulfated thiohydroximate of 1-thio-β-D-glucopyranose are the major class found among all thioglycosides,[1,7] while several different types of thioglycosides have been also reported, such as afrostyraxthioside A,[5] raphanuside,[6] isatindigotindolosides C−E,[4] indole-3-acetonitrile-2-*S*-β-D-glucopyranoside, indole-3-acetonitrile-4-methoxy-2-*S*-β-D-glucopyranoside, and *N*-methoxyindole-3-acetonitrile-2-*S*-β-D-glucopyranoside.[3] Moreover, no thioglycoside with a disulfide bond has been discovered apart from one compound, desulfo-4-(β-D-glucopyranosyldisulfanyl)butylglucosinolate, from *Eruca sativa*.[8]

Wasabia japonica (Miq.) Matsum., also commonly known as wasabi, belongs to the family Brassicaceae and has been used widely for a long time as a pungent spice for sushi and sashimi.[9,10] Since desulfosinigrin, possessing an allyl isothiocyanate motif with a pungent flavor, is the only thioglycoside identified from wasabi, we have searched for other thioglycosides with biological activities.[11] From the roots of *W. japonica*, six new thioglycosides (**1**−**6**) and one known analogue (**7**) were identified including three rare derivatives (**1**−**3**) possessing a disulfide bond connecting the carbohydrate motif and the aglycone. Their structures were elucidated by conventional NMR and HRMS data analyses and computational methods coupled with advanced statistics (DP4 and CP3). The isolated compounds (**1**−**7**) were also tested for their anti-inflammatory, neuroprotective, and cytotoxic activities.



Wasulfiside A (**1**) was isolated as a colorless gum. The molecular formula of **1** was established as $C_{10}H_{16}O_6S_2$ based on the $[M + H]^+$ ion peak at m/z 297.0456 (calcd for

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$C_{10}H_{17}O_6S_2^+$, *m/z* 297.0461). The ^{1}H NMR spectrum of **1** showed the presence of a methyl group [δ_H 1.18 (1H, d, *J* = 7.4 Hz)] and methylene [δ_H 2.58 (1H, dd, *J* = 15.0, 13.7 Hz) and 2.86 (1H, dd, *J* = 15.0, 3.7 Hz)] and methine [δ_H 3.82 (1H, dqd, *J* = 13.7, 7.4, 3.7 Hz)] protons, along with a 1-thio-*β*-glucopyranosyl moiety [δ_H 5.22 (1H, d, *J* = 9.6 Hz), 5.83 (1H, brt, *J* = 9.5 Hz), 4.37 (1H, brt, *J* = 9.1 Hz), 4.26 (1H, brt, *J* = 9.3 Hz), 4.10 (1H, ddd, *J* = 9.7, 5.2, 2.0 Hz), 4.51 (1H, dd, *J* = 12.2, 2.0 Hz), and 4.31(1H, dd, *J* = 12.2, 5.2 Hz)]. The ^{13}C NMR spectrum of **1** exhibited 10 resonances including an ester carbonyl carbon (δ_C 168.8). Analysis of the COSY and HSQC spectra of **1** confirmed two partial structures, a 1-thio-*β*-glucopyranosyl moiety and a four-carbon aliphatic fragment. These two fragments were connected through the ester carbonyl carbon (δ_C 168.8) based on the HMBC cross-peaks from H-3, H-4, and H-2′ to C-1 (Figure 1). The other

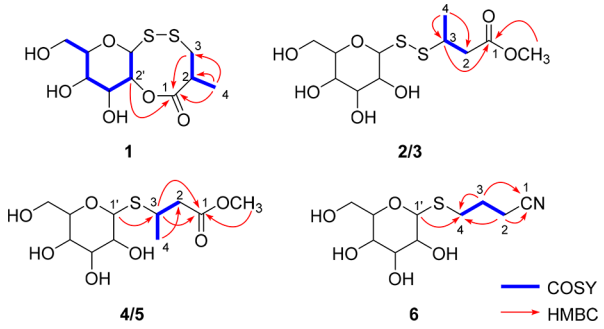

Figure 1. Key COSY and HMBC correlations of **1**−**6**.

connectivity between C-3 and C-1′ through a disulfide bridge was confirmed through the characteristic ^{13}C NMR chemical shift values of C-3 and C-1′; the anomeric carbon (C-1′) chemical shift values of **4**−**6** possessing a monosulfide bridge were δ_C 86.3−87.4, which were less downfield than that of **1** (δ_C 92.3). The ^{13}C NMR chemical shift difference for the anomeric carbons, depending on the numbers of sulfur atoms that were connected, was also consistent with the ^{13}C NMR chemical shift values (δ_C 83.6 and 91.6) of the anomeric carbons of desulfo-4-(*β*-D-glucopyranosyldisulfanyl)-butylglucosinolate,[8] connected to both mono- and disulfide bridges, respectively. In addition, the ^{13}C NMR chemical shift value of C-3 in **1** (δ_C 45.7) was more downfield than those in **4**−**6** (δ_C 30.1−37.5), which were similar to those of the *β* carbons of cysteine (δ_C 25.1−32.0) and cystine (δ_C 39.0−44.1), a dimer of cysteine with a disulfide bond.[12] Collectively, the 2D structure of **1** was established and incorporated 1,4,5-oxadithiocane, an unusual eight-membered ring with a disulfide bridge. The D-configuration of the 1-thio-*β*-glucopyranosyl moiety was confirmed by acid hydrolysis and chiral derivatization of **1** analyzed by LC/MS.[13,14] To assign the absolute configuration at C-2, the NOESY spectrum of **1** was acquired, but no cross-peak was observed between the protons of the 1-thio-*β*-glucopyranosyl moiety and those occurring in the aglycone (H-2, H-3, or H-4). Instead, the coupling constants between H-2 and H-3a, H-3b of **1** were compared with calculated values of 2*R* and 2*S* isomers. As shown in Figure 2, the calculated coupling constants of the 2*S* isomer [4.2 ($^3J_{H\text{-}2/H\text{-}3a}$) and 10.8 ($^3J_{H\text{-}2/H\text{-}3b}$) Hz] were more similar to those of the experimental values [3.7 ($^3J_{H\text{-}2/H\text{-}3a}$) and 13.7 ($^3J_{H\text{-}2/H\text{-}3b}$) Hz] than of the 2*R* isomer [2.4 ($^3J_{H\text{-}2/H\text{-}3a}$) and 4.8 ($^3J_{H\text{-}2/H\text{-}3b}$) Hz]. To corroborate this 2*S* configurational assignment, the ^{1}H and ^{13}C NMR data of the 2*R* and 2*S* isomers were calculated and applied to DP4 probability analysis with the experimental values.[15] The results showed that the more likely configuration of C-2 among the two epimers is *S* with 100% probability (Figures 3A and S26, Supporting Information). Therefore, the structure of **1** was elucidated as 3-(*β*-D-glucopyranosyldisulfanyl)isobutyric acid 1,2′-lactone.

Wasulfiside B (**2**) and 3-epiwasulfiside B (**3**) were isolated as a mixture in a 1:1 ratio. Their molecular formulas were determined as $C_{11}H_{20}O_7S_2$ based on the HRESIMS data. The ^{13}C NMR spectrum of **2**/**3** showed duplicated resonances at δ_C 93.2/91.8, 82.7/82.6, 79.7/79.7, 73.2/72.7, 71.5/71.4, 63.1/63.0, 43.8/43.3, 42.0/41.9, and 20.7/20.6, suggesting the potential presence of two diastereomers. The ^{1}H and ^{13}C

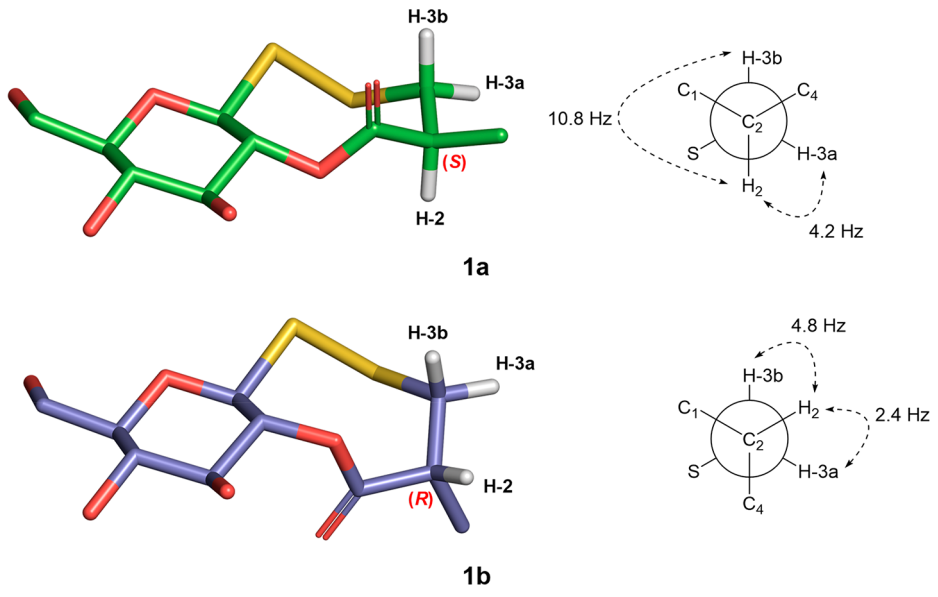

Figure 2. 3D structures of the major conformers of **1a** and **1b** minimized at the MMFF94 force field (left) and their Newman projections from C-2 to C-3 with the calculated coupling constants between H-2 and H-3a, H-3b (right).

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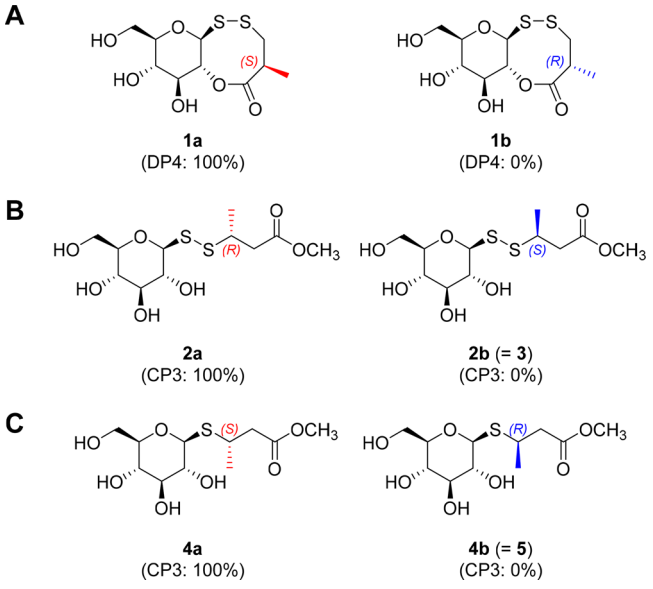

Figure 3. DP4 and CP3 analysis results: (A) **1**, (B) **2**/**3**, (C) **4**/**5**.

NMR data of **2**/**3** were similar to those of **1** except for the presence of resonances of a methoxy group [δ_H 3.71 (3H, s); δ_C 52.4] and a carbonyl group more deshielded than that in **1** (δ_C 174.5, **2**/**3**; δ_C 168.8, **1**). This indicated that **2**/**3** possess a methyl ester carbonyl functionality instead of a lactone in **1**. The related COSY and HMBC cross-peaks confirmed the partial structure of a 3-substituted methyl butyrate moiety (Figure 1). This acyl chain was connected to the 1-thio-β-glucopyranosyl unit through a disulfide bridge based on the relatively large ^{13}C NMR chemical shift values of the anomeric carbons (δ_C 93.2/91.8) as in **1** (δ_C 92.3).[8] Compounds **2** and **3** are C-3 epimers given that acid hydrolysis and chemical derivatization validating the presence of D-glucopyranoses[13,14] and the 2D NMR spectrum obtained displayed the presence of only one stereogenic center at C-3 in the side chain. The assignment of the absolute configuration of C-3 of **2**/**3** was challenging because the stereogenic center C-3 is in the middle of an acyl chain without any other adjacent stereogenic center(s), in which case conventional NOESY data analysis and *J*-based configurational analysis are ineffective. Accordingly, the CP3 probability method[16,17] was employed using the entire experimental and calculated ^{1}H and ^{13}C NMR chemical shifts to assign the absolute configuration of C-3 in **2**/**3**. The C-3 configurations of **2** and **3** are *R* and *S*, respectively, with 100% CP3 probability (Figures 3B and S27, Supporting Information). Thus, the structures of **2** and **3** were established as 3*R*- and 3*S*-(β-D-glucopyranosyldisulfanyl)butyric acid methyl ester, respectively.

Wasulfiside C (**4**) and 3-epiwasulfiside C (**5**) were obtained as a mixture in a ratio of 3:1. The ^{1}H and ^{13}C NMR data of **4**/**5** were reminiscent of those of **2**/**3**, with major differences in the ^{13}C NMR chemical shifts of the anomeric (δ_C 86.3/87.1, **4**/**5**; δ_C 93.2/91.8, **2**/**3**) and sulfur-bound methine (δ_C 37.0/37.5, **4**/**5**; δ_C 43.8/43.3, **2**/**3**) carbons, which suggested that **4**/**5** possesses a monosulfide bridge, rather than a disulfide bridge as found in **2**/**3**.[8,12] This inference was confirmed by the HMBC cross-peak of H-1′/C-3 (Figure 1) and the HRESIMS data (see Experimental Section). The absolute configurations of C-3 in **4** and **5** were assigned as *S* and *R*, respectively, using the aforementioned methods utilized for **2**/**3** (Figures 3C and S28, Supporting Information). Consequently, the structures of **4** and **5** were established as 3*S*- and 3*R*-(β-D-glucopyranosylsulfanyl)butyric acid methyl ester, respectively.

Wasulfiside D (**6**) gave the molecular formula $C_{10}H_{17}NO_5S$, requiring three degrees of unsaturation. Inspection of the ^{1}H and ^{13}C NMR data of **6** suggested that this compound has the same 1-thio-β-D-glucopyranosyl unit with a monosulfide bond as in **4**/**5**. The COSY correlations of H-3/H-2 and H-4 and the HMBC cross-peaks of H-1′/C-4 and H-2 and H-3/C-1 confirmed the structure of the aglycone to be a linear four-carbon unit connected to the 1-thio-β-D-glucopyranosyl moiety through C-4. A cyano functional group at C-1 was determined by the typical ^{13}C NMR chemical shift (δ_C 121.1),[18] IR band at 2248 cm^{-1}, and the remaining two degrees of unsaturation. Thus, the structure of **6** was elucidated as 4-(β-D-glucopyranosylsulfanyl)butyronitrile.

Compound **7** was identified as indole-3-acetonitrile-4-methoxy-2-*S*-β-D-glucopyranoside by comparison of its NMR and MS data with the reported values.[3]

All the isolated compounds (**1**−**7**) were tested for their potential anti-inflammatory activity by measuring nitric oxide (NO) production levels in lipopolysaccharide (LPS)-stimu-

Table 1. ^{1}H [ppm, mult. (*J* in Hz)] and ^{13}C NMR Data of Compounds 1−3

	1[a]		**2**[b]		**3**[b]	
position	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
1	168.8		174.5		174.5	
2a	52.1	3.82, dqd (13.7, 7.4, 3.7)	42.0	2.95, dd (15.8, 6.6)	41.9	3.01, dd (15.9, 6.7)
2b				2.55, dd (15.8, 7.6)		2.53, dd (15.9, 6.7)
3a	45.7	2.86, dd (15.0, 3.7)	43.8	3.45, overlap	43.3	3.42, overlap
3b		2.58, dd (15.0, 13.7)				
4	22.9	1.18, d (7.4)	20.7	1.38, d (6.9)	20.6	1.36, d (6.9)
1′	92.3	5.22, d (9.6)	93.2	4.34, d (9.1)	91.8	4.32, d (9.5)
2′	79.3	5.83, brt (9.5)	73.2	3.42, overlap	72.7	3.50, brt (9.2)
3′	77.2	4.37, brt (9.1)	79.7	3.40, overlap	79.7	3.41, overlap
4′	71.3	4.26, brt (9.3)	71.4	3.34, overlap	71.5	3.33, overlap
5′	85.0	4.10, ddd (9.7, 5.2, 2.0)	82.6	3.32, overlap	82.7	3.32, overlap
6′a	62.6	4.51, dd (12.2, 2.0)	63.0	3.89, overlap	63.1	3.89, overlap
6′b		4.31, dd (12.2, 5.2)		3.69, overlap		3.69, overlap
OCH_3			52.4	3.71, s	52.4	3.72, s

[a]Measured in pyridine-d_5. [b]Measured in methanol-d_4.

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Table 2. ^{1}H [ppm, mult. (J in Hz)] and ^{13}C NMR Data of Compounds 4−6 in Methanol-d_4

	4		5		6	
position	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
1	174.0		174.0		121.1	
2a	43.9	2.81, dd (15.7, 6.6)	43.8	2.83, dd (15.9, 5.9)	16.3	2.66, t (7.2)
2b		2.59, dd (15.7, 6.6)		2.58, overlap		
3	37.0	3.50, m	37.5	3.50, m	27.3	2.01, m
4a	22.3	1.40, d (6.8)	22.2	1.38, d (6.8)	30.1	2.93, dt (13.7, 6.9)
4b						2.79, dt (13.7, 6.9)
1′	86.3	4.50, d (9.7)	87.1	4.51, d (9.7)	87.4	4.38, d (9.7)
2′	74.6	3.19, dd (9.7, 8.5)	74.6	3.18, overlap	74.5	3.22, dd (9.7, 8.7)
3′	79.8	3.37, overlap	79.8	3.37, overlap	79.8	3.37, overlap
4′	71.6	3.32, overlap	71.6	3.32, overlap	71.6	3.33, overlap
5′	82.1	3.31, overlap	82.0	3.31, overlap	82.2	3.31, overlap
6′a	63.1	3.89, overlap	63.1	3.89, overlap	63.0	3.89, dd (12.0, 1.9)
6′b		3.67, overlap		3.67, overlap		3.67, dd (12.0, 5.5)
OCH_3	52.3	3.71, s	52.3	3.71, s		

lated murine microglia. Compound **1** showed moderate activity with an IC_{50} value of 41.2 μM without significant cell toxicity (IC_{50} 21.4 μM for L-NMMA, positive control).

In summary, six new thioglycosides (**1**−**6**) were identified along with one known analogue (**7**) from the roots of *W. japonica*. These phytochemicals were structurally interesting since compounds **1**−**3** feature a glucose unit with a disulfide bond, which is rare in Nature. Among them compound **1**, exhibiting moderate anti-inflammatory activity, possesses an unusual 1,4,5-oxadithiocane ring system.

EXPERIMENTAL SECTION

General Experimental Procedures and Plant Material. As described in previous communications.[19,20]

Extraction and Isolation. The roots (3.3 kg) of *W. japonica* were extracted and partitioned through the same method as described in a previous communication.[20] The EtOAc-soluble fraction (5.8 g) was separated by passage over Diaion HP-20 resin by elution with MeOH−H_2O (0:1, 1:4, 2:3, 3:2, 4:1, and 1:0), to give six fractions (E1−E6). Fraction E2 (300 mg) was separated by a Lobar-A RP-C_{18} column with 20% aqueous MeOH and further purified by semipreparative HPLC (EtOAc−MeOH−H_2O, 3:1:0.15) to give **6** (t_R: 13.2 min, 3 mg). Fraction E4 (200 mg) was separated over a silica gel column ($CHCl_3$−MeOH−H_2O, 3:1:0.15) to give nine fractions (E41−E49), and a mixture of **2** and **3** (t_R: 25.8 min, 2 mg) was obtained by semipreparative HPLC (25% aqueous CH_3CN) from fraction E43 (25 mg). Fraction E5 (160 mg) was chromatographed on a silica gel column ($CHCl_3$−MeOH−H_2O, 3:1:0.15) to yield five fractions (E51−E55), and fraction E53 (30 mg) and E54 (15 mg) were purified by semipreparative HPLC (50% aqueous MeOH) to yield **1** (t_R: 15.4 min, 2 mg) and **7** (t_R: 12.9 min, 2 mg), respectively. The *n*-BuOH-soluble fraction (2.7 g) was separated over Diaion HP-20 resin with MeOH−H_2O (0:1 and 1:0) and further purified over a silica gel column ($CHCl_3$−MeOH−H_2O, 3:1:0.1) to yield 10 fractions (B1−B10). Fraction B3 (250 mg) was separated by a Lobar-A RP-C_{18} column (20% aqueous MeOH) and further purified by semipreparative HPLC (EtOAc−MeOH−H_2O, 10:1:0.1) to yield a mixture of **4** and **5** (t_R: 30.1 min, 4 mg).

*Wasulfiside A (**1**):* colorless gum; $[\alpha]_D^{25}$ +6 (*c* 0.1, MeOH); IR (KBr) ν_{max} 3411, 2930, 2864, 1744 cm^{-1}; ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR data in pyridine-d_5, see Table 1; HRESIMS (positive-ion mode) m/z 297.0456 $[M + H]^+$ (calcd for $C_{10}H_{17}O_6S_2^+$, m/z 297.0461).

*Mixture of wasulfiside B (**2**) and 3-epiwasulfiside B (**3**):* colorless gum; IR (KBr) ν_{max} 3430, 2913, 2855, 1738 cm^{-1}; ^{1}H (700 MHz) and ^{13}C (175 MHz) NMR data in methanol-d_4, see Table 1; HRESIMS (positive-ion mode) m/z 351.0555 $[M + Na]^+$ (calcd for $C_{11}H_{20}O_7S_2Na^+$, m/z 351.0543).

*Mixture of wasulfiside C (**4**) and 3-epiwasulfiside C (**5**):* colorless gum; IR (KBr) ν_{max} 3422, 2911, 2860, 1737 cm^{-1}; ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR data in methanol-d_4, see Table 2; HRESIMS (positive-ion mode) m/z 319.0824 $[M + Na]^+$ (calcd for $C_{11}H_{20}O_7SNa^+$, m/z 319.0822).

*Wasulfiside D (**6**):* colorless gum; $[\alpha]_D^{25}$ +7 (*c* 0.2, MeOH); IR (KBr) ν_{max} 3423, 2907, 2866, 2248 cm^{-1}; ^{1}H (700 MHz) and ^{13}C (175 MHz) NMR data in methanol-d_4, see Table 2; HRESIMS (positive-ion mode) m/z 264.0904 $[M + H]^+$ (calcd for $C_{10}H_{18}NO_5S^+$, m/z 264.0900).

Acid Hydrolysis of 1−6 and Sugar Analysis. As described in a previous communication.[14]

Computational Analysis. All conformers addressed in the study were evaluated using the same method described in a previous communication.[19] Conformers within 10 kJ/mol of each global minimum were Boltzmann-averaged based on their respective Boltzmann populations at the MMFF94 force field. Conformers of **1** (more than 5% population at the MMFF94 force field) were subjected to coupling constant calculations using the Gaussian 09 package (Gaussian Inc.) at the #mPW1PW91/6-31+G(d,p) level (gas phase). The calculated coupling constants were averaged based upon their respective Boltzmann populations. The gauge-invariant atomic orbital (GIAO) shielding constants were calculated for the conformers with more than 5% population (MMFF94 force field) using the polarizable continuum model (PCM) mode with a dielectric constant representing pyridine for **1** and methanol for **3**−**6** at the B3LYP/6-31+G(d,p) level. The calculated NMR properties were averaged as described above and used for calculations of DP4 and CP3 probability analysis for **1** and **3**−**6**, respectively, facilitated by the applets available at http://www-jmg.ch.cam.ac.uk/tools/nmr.

NO Production and Viability in LPS-Stressed BV-2 Cells, NGF and Cell Viability Assays, and Cytotoxicity Assessment. As described in previous communications.[17,20−22]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.8b00570.

HRESIMS and 1D and 2D NMR spectra of **1**−**6** and computational data of **1**−**5** (PDF)

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AUTHOR INFORMATION

Corresponding Author

*Tel: +82-31-290-7710. Fax: +82-31-290-7730. E-mail: krlee@skku.edu.

ORCID

Chung Sub Kim: 0000-0001-9961-4093

Kang Ro Lee: 0000-0002-3725-5192

Notes

The authors declare no competing financial interest.

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