Homonojirimycin Isomers and Glycosides from *Aglaonema treubii*

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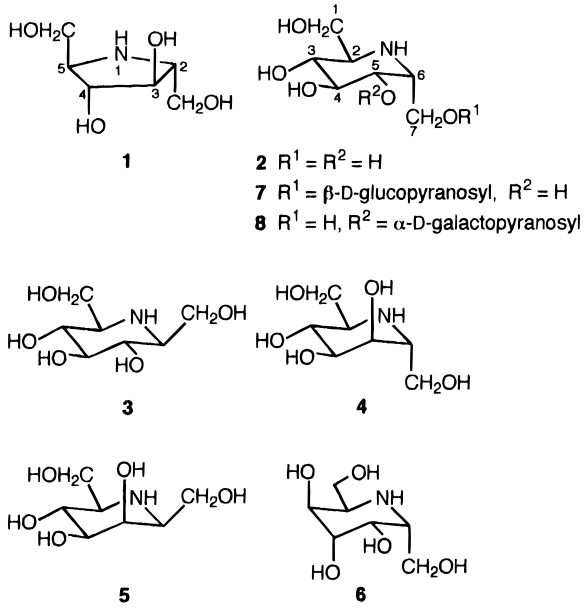
Received August 12, 1996[⊗]

A 50% aqueous EtOH extract of *Aglaonema treubii* found to potently inhibit α-glucosidase was subjected to various ion-exchange column chromatographic steps to give 2(*R*),5(*R*)-bis-(hydroxymethyl)-3(*R*),4(*R*)-dihydroxypyrrolidine (**1**), α-homonojirimycin (**2**), *β*-homonojirimycin (**3**), α-homomannojirimycin (**4**), *β*-homomannojirimycin (**5**), α-3,4-di-*epi*-homonojirimycin (**6**), 7-*O*-*β*-D-glucopyranosyl-α-homonojirimycin (**7**), and 5-*O*-α-D-galactopyranosyl-α-homonojirimycin (**8**). Compounds **1** and **2** are known inhibitors of various α-glucosidases. Compounds **6** and **8** are new natural products. Compounds **3**−**5** and **7** have been chemically synthesized previously, but this is the first report of their natural occurrence.

Glycosidases are involved in several important biological processes, such as intestinal digestion, the biosynthesis of glycoproteins, and the lysosomal catabolism of glycoconjugates. Glycosidase inhibitors are potentially useful as antidiabetic, antiviral, antimetastatic, and immunomodulatory agents.[1] In particular, α-glucosidase inhibitors have shown potential as therapeutic agents for diabetes type 2[2,3] and HIV-1 infection.[4−7]

As a result of a search for α-glucosidase inhibitors from plants using rice α-glucosidase as an assay enzyme, potent inhibitory activity ($IC_{50} = 0.07$ μg/mL) was exhibited by a 50% aqueous EtOH extract of *Aglaonema treubii* Engl. (Araceae) after preliminary purification by ion-exchange chromatography with Amberlite IR-120B [H^+ form] and Dowex 1 × 2 [OH^- form]. GC−MS analysis of the ion-exchange resin-treated sample showed the presence of many polyhydroxylated alkaloids in addition to the known 2(*R*),5(*R*)-bis(hydroxymethyl)-3(*R*),4(*R*)-dihydroxypyrrolidine (DMDP) (**1**) and α-homonojirimycin (**2**). In this paper, we describe the isolation of eight polyhydroxylated alkaloids (**1**−**8**) from *A. treubii* and their structural determination.



Results and Discussion

The ion-exchange resin treated extract was silylated for GC−MS with Sigma Sil-A, and the mass fragmentation pattern of the trimethylsilyl (TMSi) derivatives indicated that the NH group remained underivatized.[8] As seen in Figure 1, two major components, with retention times of 7.14 and 10.14 min, were identified as DMDP (**1**) and α-homonojirimycin (**2**), respectively. Compound **1** gave a tetra-TMSi derivative and a characteristic fragment ion at *m/z* 436, corresponding to loss of a CH_3 group, and a strong base peak with *m/z* 348, $[M - CH_2OTMSi]^+$, while **2** gave a penta-TMSi derivative and a characteristic fragment ion at *m/z* 538 $[M - CH_3]^+$ and a base peak at *m/z* 450 $[M - CH_2OTMSi]^+$. Compound **1** has been found in the leaves of the plant *Derris* spp.,[9,10] in the seeds of *Lonchocarpus sericeus*,[11] in the neotropical liana *Omphalea diandra*,[12] and recently in the cultured broth of *Streptomyces* spp.[13] Compound **2** was first chemically synthesized[14] and was later found in the leaves of *O. diandra*, together with **1**.[12]

Extraction of the whole plant of *A. treubii* (4.5 kg) with 50% aqueous EtOH, followed by ion-exchange chromatography on Amberlite IR-120B [H^+ form], gave a total alkaloid fraction. Subsequent chromatography on Dowex 1 × 2 [OH^- form] with H_2O as an eluent gave two pools, A and B. Each pool was chromatographed on a column of Amberlite CG-50 [NH_4^+ form] with H_2O or Dowex 1 × 2 [OH^- form] with H_2O, to give compounds **1** (1.21 g), **2** (460 mg), **3** (6 mg), **4** (20 mg), **5** (5 mg), **6** (112 mg), **7** (364 mg), and **8** (190 mg).

The optical rotations, FABMS, and NMR spectral data of DMDP (**1**) and α-homonojirimycin (**2**) obtained from *A. treubii* were in accord with those previously reported.[9,15] The FABMS and ^{13}C-NMR spectral data of compounds **3**−**5** showed that they were isomeric with α-homonojirimycin (**2**) and were consistent with those of the synthetic compounds, *β*-homonojirimycin, α-ho-

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⊗ Abstract published in *Advance ACS Abstracts,* January 15, 1997.

S0163-3864(96)00577-0 CCC: $14.00

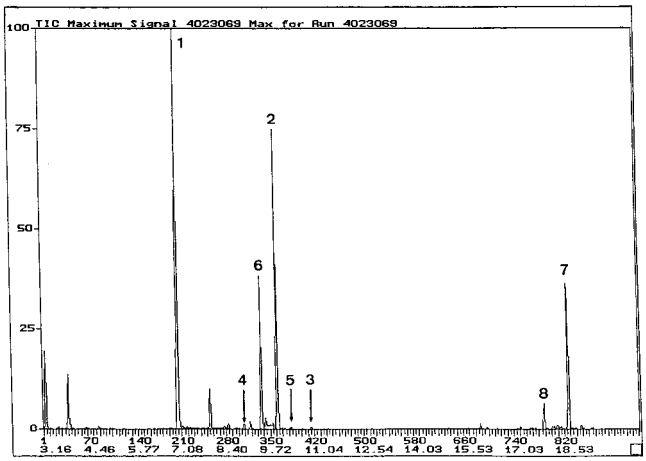

Figure 1. Gas chromatogram showing the trimethylsilylated alkaloids in an extract of the stem of *Aglaonema treubii* after ion-exchange chromatography. **1**, DMDP; **2**, α-homonojirimycin; **3**, β-homonojirimycin; **4**, α-homomannojirimycin; **5**, β-homomannojirimycin; **6**, α-3,4-di-*epi*-homonojirimycin; **7**, 7-*O*-β-D-glucopyranosyl-α-homonojirimycin (MDL 25,637); **8**, 5-*O*-α-D-galactopyranosyl-α-homonojirimycin.

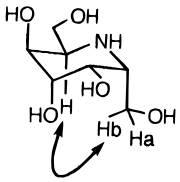

Figure 2. Selected NOE effect for α-3,4-di-*epi*-homonojirimycin (**6**).

momannojirimycin, and β-homomannojirimycin, respectively.[16−18] The present isolation of **3**−**5** is the first report of the natural occurrence of these compounds.

Compound **6** was also found to be an isomer of **2** from its HRFABMS (*m*/*z* 194.1024 $[M + H]^+$) and ^{13}C-NMR spectral data (δ 57.2, 58.1, 62.7, 63.5, 72.0, 72.1, 72.2). The ^{1}H-NMR spectral data, combined with extensive decoupling experiments and 2D ^{1}H−^{13}C COSY spectral data, defined the complete connectivity of the carbon and hydrogen atoms. Irradiation of H-2 of **6** enhanced the NOE intensity of H-7b (δ 4.61). This indicated that H-2 and the C-6 CH_2OH groups are in a 1,3-*trans*-diaxial orientation, as illustrated in Figure 2. The coupling pattern of H-3 (δ 4.26, dd, $J_{2,3} = 6.2$, $J_{3,4} = 3.3$ Hz) indicated an equatorial orientation of H-3. Furthermore, no significant NOE effects were observed between H-2 and H-4 and between H-5 and H-7a or H-7b, implying that H-4 and H-5 are equatorial and axial, respectively. Thus, compound **6** was determined to be α-3,4-di-*epi*-homonojirimycin.

The HRFABMS (*m*/*z* 356.1554 $[M + H]^+$) and 13 resonances in the ^{13}C-NMR spectrum of **7** established that the molecular formula was $C_{13}H_{25}O_{10}N$. The structure of **7** was determined as 7-*O*-β-D-glucopyranosyl-α-homonojirimycin on the basis of ^{1}H- and ^{13}C-NMR observations, including 2D ^{1}H−^{1}H and ^{1}H−^{13}C COSY and HMBC spectral data. This structure is the same as that of MDL 25,637,[15] which was chemically synthesized as an antidiabetic agent.[19] The specific rotation value (+24.6°) of **7** was also close to that (+27.5°) of the synthetic sample, and the ^{1}H-NMR data were completely in accord with those reported for MDL 25,637.[15] The isolation of **7** is the first report of the natural occurrence of this compound.

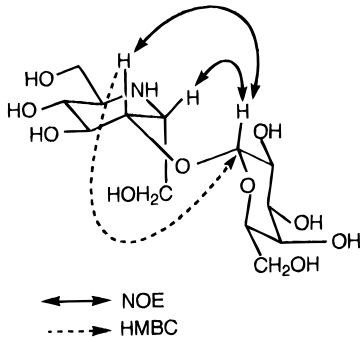

Figure 3. Selected NOE effects and an HMBC correlation for 5-*O*-α-D-galactopyranosyl-α-homonojirimycin (**8**).

Compound **8** was found to be a glycoside of α-homonojirimycin (**2**) or its isomer from its HRFABMS (*m*/*z* 356.1554 $[M + H]^+$) and ^{13}C-NMR spectral data. After acid hydrolysis of this glycoside using Dowex 50W × 2 [H^+ form], the aglycon part was eluted with 0.5-M NH_3 solution from the resin, concentrated to dryness, and confirmed as **2** by direct comparison of its optical rotation and ^{13}C-NMR spectrum with those of an authentic sample. The ^{1}H-NMR spectral data, together with information from extensive decoupling experiments, ^{13}C-NMR, and 2D ^{1}H−^{13}C COSY spectral data, defined the complete connectivity of the carbon and hydrogen atoms. The coupling constant of the anomeric proton (δ 5.13, δ, $J_{1',2'} = 3.7$ Hz) and the characteristic coupling patterns of H-4′ (δ 4.00, dd, $J_{3',4'} = 3.3$, $J_{4',5'} = 1.1$ Hz) and H-5′ (δ 4.17, dt, $J_{4',5'} = 1.1$, $J_{5',6'a} = J_{5',6'b} = 6.2$ Hz) suggested that this glycoside was the α-D-galactoside of **2**. The ^{13}C-NMR chemical shifts of the glycone part of **8** were consistent with those of 2-*O*-α-D-galactopyranosyl-1-deoxynojirimycin isolated from the leaves of *Morus bombycis*.[20] As illustrated in Figure 3, the HMBC spectrum showed a correlation peak between the anomeric proton of the glycone and the aglycon C-5 carbon, and, furthermore, a definite NOE effect between the anomeric proton and H-5 also defined the linkage site of the glycone as C-5 (Figure 3). Thus, the structure of **8** was determined to be 5-*O*-α-D-galactopyranosyl-α-homonojirimycin.

DMDP (**1**) is a inhibitor of invertase,[11] α- and β-glucosidase,[21,22] trehalase,[13] and human β-mannosidase.[11] Furthermore, **1** inhibits glycoprotein processing α-glucosidase I in cell culture, leading to the accumulation of glycoproteins with high-mannose structures that are mostly $Glc_3Man_{7-9}(GlcNAc)_2$ types,[23] but it is not an inhibitor of the glycoprotein processing α-glucosidase II.[10] α-Homonojirimycin (**2**) is a potent inhibitor of various α-glucosidases.[12,21,22,24] β-Homonojirimycin (**3**) and β-homomannojirimycin (**5**) are weak inhibitors of almond β-glucosidase and snail β-mannosidase, respectively.[16] 1-Deoxymannojirimycin is a potent inhibitor of glycoprotein processing α-mannosidase I[25,26] but is, in general, a much better inhibitor of α-fucosidase than of α-mannosidase,[11] while α-homomannojirimycin (**4**) is a very weak inhibitor of human liver α-mannosidases, but does not significantly inhibit other glycosidases.[18] MDL 25,637 (**7**) is an effective inhibitor of rat intestinal glucohydrolases in vitro and in vivo[19] and is more effective against glycoprotein processing α-glucosidase II than α-glucosidase I.[27] MDL 25,637 (**7**) is also a powerful competitive inhibitor of pig kidney trehalase.[28,29] A thorough investigation of a series of isomers of **2**,

including the *N*-alkylated derivatives and the glycosides of this compound on glycosidase inhibition, will be reported elsewhere.

Experimental Section

General Experimental Procedures. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra were recorded on a JEOL JNM-GX 400 spectrometer as indicated using sodium 3-(trimethylsilyl)propionate (TSP) in D_2O and Me_4Si in pyridine-d_5−D_2O (3:1) as internal standards. MS were measured on a JEOL JMS-SX 102A spectrometer. Alkaloids were chromatographed on HPTLC Si gel 60F_{254} (E. Merck) using the solvent system *n*-PrOH−AcOH−H_2O (4:1:1), and a chlorine-*o*-tolidine spray reagent[30] was used for detection.

Plant Material. Whole plants of *A. treubii* were collected in July 1995, at the Medicinal Plant Garden of Hokuriku University, Kanazawa, Japan. A voucher specimen representing this collection (NA9601) has been deposited at the herbarium of the Institute of Grassland and Environmental Research, Aberystwyth, U.K.

GC−MS Analysis. Samples were dried and silylated using 100 μL of Sigma Sil-A (Sigma Chemical Co.) per milligram of material. The column was a 25-m × 0.25-mm BPX5 capillary column (SGE) and the 25-min temperature program ran from 180 to 300 °C with an initial rate of increase of 10 °C/min and then held at 300 °C. The mass spectrometer was a QMASS 910 (Perkin-Elmer) set at 70 eV and a mass range of 100−650 amu.

Extraction and Isolation. The whole plant (4.5 kg fresh wt) of *A. treubii* was homogenized in 50% aqueous EtOH. The filtrate was applied to a column of Amberlite IR-120B [H^+ form, 500 mL] prepared in 50% aqueous EtOH. A 0.5-M NH_4OH eluate was concentrated to give a brown oil (7 g). This oil was chromatographed over a Dowex 1 × 2 column (2 × 97 cm, OH^- form) with H_2O as eluent (fraction size, 9 mL). The H_2O eluate was divided into two pools, A (fractions 51−72, 2.3 g) and B (fractions 73−115, 580 mg). Pool A was further chromatographed on an Amberlite CG-50 column [2 × 97 cm, NH_4^+ form] and eluted with H_2O to give **8** (190 mg), **3** (6 mg), **2** (460 mg), **5** (5 mg), **4** (20 mg), and **6** (112 mg), in order of elution. This column was further eluted with 0.1 M NH_4OH to give **1** (1.1 g). Pool B was rechromatographed on a Dowex 1 × 2 column (1.5 × 95 cm, OH^- form) to give **1** (110 mg) and **7** (364 mg) in order of elution.

2(*R*),5(*R*)-Bis(hydroxymethyl)-3(*R*),4(*R*)-dihydroxypyrrolidine (DMDP) (1): $[\alpha]_D$ + 56.9° (*c* 0.6, H_2O) [lit.[9] $[\alpha]_D$ + 56.4° (*c* 7, H_2O)]; ^{13}C NMR (100 MHz, D_2O) δ 64.4 (C-2,5), 64.9 (C-1,6), 80.7 (C-3,4); FABMS *m/z* 164 $[M + H]^+$.

α-Homonojirimycin (2): $[\alpha]_D$ +77.2° (*c* 0.57, H_2O); [lit.[15] $[\alpha]_D$ +79.1° (c 2.03, H_2O)]; ^{1}H NMR (400 MHz, D_2O) δ 2.87 (1H, ddd, *J* = 3.2, 7.1, 10.0 Hz, H-2), 3.21 (1H, dd, *J* = 9.0, 10.0 Hz, H-3), 3.29 (1H, ddd, *J* = 5.3, 6.1, 9.1 Hz, H-6), 3.50 (1H, dd, *J* = 9.0, 10.0 Hz, H-4), 3.57 (1H, dd, *J* = 7.1, 11.5 Hz, H-1a), 3.75 (1H, dd, *J* = 6.1, 10.0 Hz, H-5), 3.79−3.86 (2H, m, H-7a, H-7b), 3.90 (1H, dd, *J* = 3.2, 11.5 Hz, H-1b); ^{13}C-NMR data, see Table 1; HRFABMS *m/z* 194.1026 $[M + H]^+$ ($C_7H_{16}O_5N$ requires 194.1028).

Table 1. ^{13}C-NMR Data of Compounds **2**−**8** (in D_2O, 100 MHz)[a]

	compound						
carbon	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1	64.8	64.3	63.9	63.8	63.5	64.6	64.8
2	56.9	62.6	58.6	63.0	57.2	57.2	57.0
3	74.9	74.3	71.4	71.3	72.0	74.7	74.7
4	77.1	81.0	74.7	77.8	72.1	77.2	75.8
5	74.4	74.3	71.6	71.8	72.2	74.1	78.2
6	59.7	62.6	61.4	60.8	58.1	58.2	56.1
7	59.1	64.3	62.2	64.2	62.7	68.4	59.7
1′						105.8	98.2
2′						76.0	71.0
3′						78.5	72.0
4′						72.5	72.0
5′						78.8	73.6
6′						63.6	63.4

[a] Chemical shifts are expressed in ppm downfield from sodium 3-(trimethylsilyl)propionate.

β-Homonojirimycin (3): $[\alpha]_D$ −1.7° (*c* 0.35, H_2O); ^{1}H NMR (400 MHz, D_2O) δ 2.66 (2H, ddd, *J* = 2.9, 6.6, 9.9 Hz, H-2, H-6), 3.25 (2H, dd, *J* = 9.2, 9.9 Hz, H-3, H-5), 3.39 (1H, t, *J* = 9.2 Hz, H-4), 3.64 (2H, dd, *J* = 6.6, 11.5 Hz, H-1a, H-7a), 3.89 (2H, dd, *J* = 2.9, 11.5 Hz, H-1b, H-7b); ^{13}C-NMR data, see Table 1; HRFABMS *m/z* 194.1022 $[M + H]^+$ ($C_7H_{16}O_5N$ requires 194.1028).

α-Homomannojirimycin (4): $[\alpha]_D$ +4.3° (*c* 0.62, H_2O); [lit.[18] $[\alpha]_D$ +7.45° (*c* 0.55, H_2O)]; ^{1}H NMR (400 MHz, D_2O) δ 2.75 (1H, m, H-2), 3.15 (1H, ddd, *J* = 2.9, 6.8, 8.1 Hz, H-6), 3.65 (1H, t, *J* = 9.3 Hz, H-3), 3.68 (1H, dd, *J* = 2.9, 9.3 Hz, H-4), 3.69 (1H, dd, *J* = 6.8, 11.5 Hz, H-7a), 3.748 (1H, dd, *J* = 8.1, 11.5 Hz, H-7b), 3.751 (1H, dd, *J* = 5.8, 11.5 Hz, H-1a), 3.80 (1H, dd, *J* = 3.4, 11.5 Hz, H-1b), 4.02 (1H, t, *J* = 2.9 Hz, H-5); ^{13}C-NMR data, see Table 1; HRFABMS *m/z* 194.1026 $[M + H]^+$ ($C_7H_{16}O_5N$ requires 194.1028).

β-Homomannojirimycin (5): $[\alpha]_D$ + 12.0° (*c* 0.27, H_2O); ^{1}H NMR (400 MHz, D_2O) δ 2.59 (1H, ddd, *J* = 3.2, 5.4, 10.3 Hz, H-2), 2.87 (1H, dt, *J* = 1.7, 6.6 Hz, H-6), 3.56 (1H, dd, *J* = 2.5, 10.3 Hz, H-4), 3.59 (1H, t, *J* = 10.3 Hz, H-3), 3.62−3.71 (2H, H-7a, 7b), 3.74 (1H, dd, *J* = 5.4, 11.7 Hz, H-1a), 3.84 (1H, dd, *J* = 3.2, 11.7 Hz, H-1b), 4.01 (1H, dd, *J* = 1.7, 2.5 Hz, H-5); ^{13}C NMR in Table 1; HRFABMS *m/z* 194.1032 $[M + H]^+$ ($C_7H_{16}O_5N$ requires 194.1028).

α-3,4-Di-*epi*-homonojirimycin (6): $[\alpha]_D$ +39.1° (*c* 0.51, H_2O); ^{1}H NMR [400 MHz, pyridine-d_5−D_2O (3:1)] δ 3.65 (1H, ddd, *J* = 4.0, 4.8, 8.1 Hz, H-6), 3.87 (1H, ddd, *J* = 4.8, 6.2, 7.7 Hz, H-2), 4.21 (1H, dd, *J* = 7.7, 10.6 Hz, H-1a), 4.26 (1H, dd, H-3.3, 6.2 Hz, H-3), 4.30 (1H, dd, *J* = 4.8, 10.6 Hz, H-1b), 4.39 (1H, t, *J* = 3.3 Hz, H-4), 4.42 (1H, dd, *J* = 4.8, 11.0 Hz, H-7a), 4.48 (1H, dd, *J* = 3.3, 4.0 Hz, H-5), 4.61 (1H, dd, *J* = 8.1, 11.0 Hz, H-7b); ^{13}C-NMR data, see Table 1; HRFABMS *m/z* 194.1024 $[M + H]^+$ ($C_7H_{16}O_5N$ requires 194.1028).

7-*O*-β-D-Glucopyranosyl-α-homonojirimycin (MDL 25,637) (7): $[\alpha]_D$ +24.6° (*c* 0.70, H_2O); [lit.[15] $[\alpha]_D$ +27.5° (*c* 1, H_2O)]; ^{1}H NMR [400 MHz, D_2O] δ 2.90 (1H, ddd, *J* = 3.2, 6.9, 10.0 Hz, H-2), 3.24 (1H, dd, *J* = 9.0, 10.0 Hz, H-3), 3.32 (1H, dd, *J* = 7.8, 9.1 Hz, H-2′), 3.40 (1H, dd, *J* = 9.1, 9.8 Hz, H-4′), 3.44−3.50 (2H, H-6, H-5′), 3.51 (1H, t, *J* = 9.1 Hz, H-3′), 3.53 (1H, dd, *J* = 9.0, 10.0 Hz, H-4), 3.60 (1H, dd, *J* = 6.9, 11.4 Hz, H-1a), 3.74 (1H, dd, *J* = 5.9, 12.2 Hz, H-6′a), 3.75 (1H, dd, *J* = 6.1, 10.0 Hz, H-5), 3.88 (1H, dd, *J* = 3.2, 11.4 Hz, H-1b), 3.927 (1H, dd, *J* = 2.2, 12.2 Hz, H-6′b), 3.933 (1H, dd, *J* =

9.5, 10.7 Hz, H-7a), 4.13 (1H, dd, $J = 3.7$, 10.7 Hz, H-7b), 4.50 (1H, d, $J = 7.8$ Hz, H-1′); ^{13}C-NMR data, see Table 1; HRFABMS *m/z* 356.1554 $[M + H]^+$ ($C_{13}H_{26}O_{10}N$ requires 356.1557).

5-*O*-α-D-Galactopyranosyl-α-homonojirimycin (8): $[\alpha]_D$ +168.8° (*c* 0.54, H_2O); ^{1}H NMR (400 MHz, D_2O) δ 2.87 (1H, ddd, $J = 2.9$, 7.3, 9.9 Hz, H-2), 3.27 (1H, dd, $J = 9.2$, 9.9 Hz, H-3), 3.50 (1H, ddd, $J = 2.9$, 5.9, 9.1 Hz, H-6), 3.59 (1H, dd, $J = 7.3$, 11.4 Hz, H-1a), 3.64 (1H, dd, $J = 9.2$, 9.9 Hz, H-4), 3.75 (2H, d, H-6′a, H-6′b), 3.81 (1H, dd, $J = 5.9$, 9.9 Hz, H-5), 3.83 (1H, dd, $J = 9.1$, 11.4 Hz, H-7a), 3.87 (1H, dd, $J = 3.7$, 10.6 Hz, H-2′), 3.90 (1H, dd, $J = 2.9$, 11.4 Hz, H-1b), 3.91 (1H, dd, $J = 2.9$, 11.4 Hz, H-7b), 3.93 (1H, dd, $J = 3.3$, 10.6 Hz, H-3′), 4.00 (1H, dd, $J = 1.1$, 3.3 Hz, H-4′), 4.17 (1H, dt, $J = 1.1$, 6.2 Hz, H-5′), 5.13 (1H, d, $J = 3.7$ Hz, H-1′); ^{13}C-NMR data, see Table 1; HRFABMS *m/z* 356.1554 $[M + H]^+$ ($C_{13}H_{26}O_{10}N$ requires 356.1557).

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NP960577N