ABSOLUTE STEREOSTRUCTURES OF BETAVULGAROSIDES III AND IV, INHIBITORS OF GLUCOSE ABSORPTION, FROM THE ROOTS OF *BETA VULGARIS* L. (SUGAR BEET)

Masayuki YOSHIKAWA,* Toshiyuki MURAKAMI, Masahiro INADUKI, Kazuhiro HIRANO, Johji YAMAHARA, and Hisashi MATSUDA

Kyoto Pharmaceutical University, 5 Nakauchi-cho, Misasagi, Yamashina-ku, Kyoto 607, Japan

The absolute stereostructures of betavulgarosides III and IV, which were isolated from the roots of *Beta vulgaris* L. (sugar beet) and exhibited inhibitory activity on glucose absorption, were determined by the chemical correlation of betavulgaroside IV with a known saponin momordin I, which included the conversion from the α-L-arabinopyranosyl moiety of momordin I to the acidic acetal-type substituent of betavulgarosides III and IV *via* the α-L-ribopyranosyl derivative. Furthermore, four acidic acetal-type substituent analogues were synthesized from L- and D-arabinose.

KEY WORDS betavulgaroside; *Beta vulgaris*; absolute stereostructure; acidic acetal-type substituent synthesis; sugar beet; α-L-arabinopyranoside chemical correlation

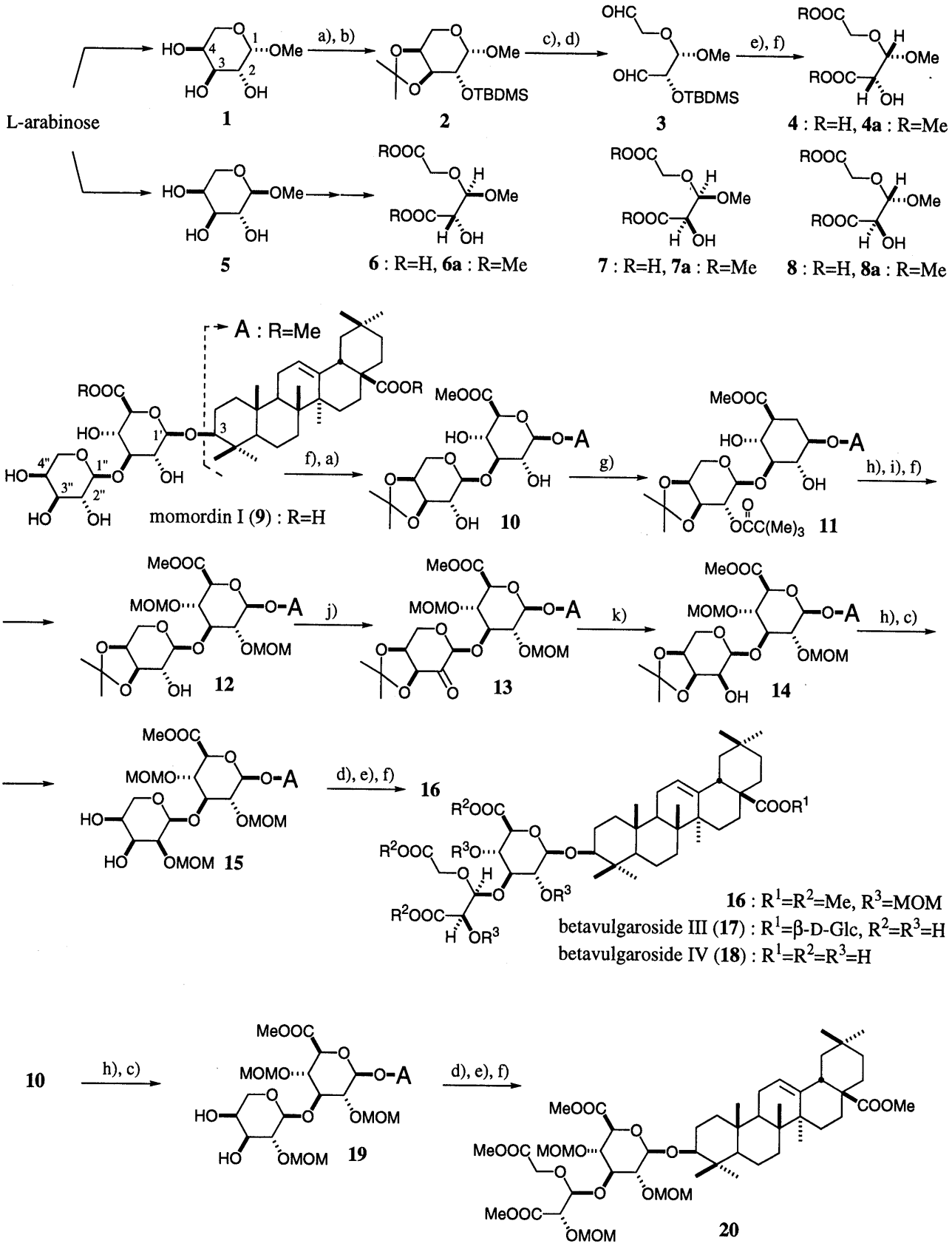
In the search for new biologically active constituents from medicinal foodstuffs,[1] we have isolated four oleanolic acid oligoglycosides called betavulgarosides I, II, III, and IV having a unique substituent from the roots of *Beta vulgaris* L. (sugar beet, Chenopodiaceae). Betavulgarosides II, III, and IV were found to show inhibitory activity on glucose absorption in the rat small intestine. The structures of betavulgarosides I, II, III, and IV were elucidated on the basis of chemical and physicochemical evidence, except for the stereostructure of the novel acidic acetal-type substituent in betavulgarosides III and IV.[2] Recently, we have reported several new saponins having the acidic acetal-type substituent, betavulgarosides V, VI, VII, VIII, and IX, from the roots and leaves of *Beta vulgaris*,[2a,3] but the stereostructure of their acidic acetal-type substituent was left uncharacterized. In this communication, we describe the elucidation of the absolute stereostructure of the acidic acetal-type substituent in betavulgarosides III (**17**) and IV (**18**) by means of chemical correlation with the known saponin momordin I (**9**).[4]

First, in order to confirm the plane structure of the acidic acetal-type substituent and the synthetic route from the arabinopyranosyl part of **9**, four acidic acetal-type substituent analogues were synthesized from L- and D-arabinose. That is, methyl α-L-arabinopyranoside (**1**), which was selectively obtained by methanolysis of L-arabinose with 9% HCl-dry MeOH, was treated with 2,2-dimethoxypropane in the presence of *p*-TsOH•H_2O, followed by silylation with *t*-butyldimethylsilyl (TBDMS) chloride and imidazole in DMF to give **2**[5] in 86% yield. The isopropylidene group of **2** was removed by treatment with 80% aqueous AcOH and subsequent oxidative cleavage of the 3,4-diol moiety with $Pb(OAc)_4$ in benzene furnished the dialdehyde derivative **3** in 60% yield. Oxidation of **3** with $NaClO_2$ and NH_2SO_3H in 75% aqueous 1,4-dioxane proceeded with desilylation of the 2-TBDMS group to provide the 1*S*,2*S*-analogue (**4**), which was converted to the dimethyl ester (**4a**)[6] by diazomethane methylation in 81% yield from **3**.

Methyl β-L-arabinopyranoside (**5**) was prepared by glycosidation of methanol with *O*-(2,3,4-tri-*O*-acetyl-α-L-arabinopyranosyl)trichloroacetimidate[7] in the presence of BF_3-etherate followed by deacetylation. By the same procedures to **4** and **4a** from **1**, **5** was transformed to the 1*R*,2*S*-analogue (**6**) and **6a**[8], while the 1*R*,2*R*-analogue (**7**), **7a**,[6] the 1*S*,2*R*-analogue (**8**), and **8a**[8] were synthesized from D-arabinose.

Next, we carried out the chemical correlation of betavulgaroside IV (**18**) with momordin I (**9**), whose component monosaccharides were determined to be D-glucuronic acid and L-arabinose by GLC analysis of their condensates with L-cysteine methyl ester.[9] Thus, momordin I (**9**) was subjected to methylation with diazomethane and subsequent acetonization of the 3" and 4"-diol moiety with 2,2-dimethoxypropane to give **10** quantitatively. Selective acylation of **10** with pivaloyl chloride in the presence of DMAP in pyridine at 0°C furnished the 2"-pivaloyl derivative (**11**)[9] in 78% yield. The 2"-position of the pivaloyl group in **11** was clarified by examination of its ^{1}H-NMR ($CDCl_3$) data [δ 4.31 (d, *J*=7.0Hz, 1'-H), 4.64 (d, *J*=6.1Hz, 1"-H), and 4.98 (t-like, *J*=*ca.* 6Hz, 2"-H)]. After protection of the 2'- and 4'-

* To whom correspondence should be addressed.



a) 2,2-dimethoxypropane, *p*-TsOH•H_2O/DMF; **b)** TBDMS-Cl, imidazole/DMF; **c)** 80% aqueous AcOH; **d)** $Pb(OAc)_4$/benzene; **e)** $NaClO_2$, NH_2SO_3H/75% aqueous 1,4-dioxane; **f)** CH_2N_2-etherate/MeOH; **g)** pivaloyl chloride, DMAP/pyridine, 0°C; **h)** MOM-Cl, *i*-Pr_2EtN/CH_2Cl_2; **i)** 5% NaOMe-MeOH; **j)** PCC/benzene; **k)** $NaBH_4$/MeOH

hydroxyl groups in **11** with chloromethyl methyl ether (MOM-Cl), the 2"-pivaloyl group was removed by treatment with 5% NaOMe-MeOH at 40°C to give **12**[11] in 60% yield. Oxidation of **12** with PCC in benzene provided an unstable ketone (**13**), which was immediately treated with $NaBH_4$ in MeOH to give the α-L-ribopyranosyl derivative (**14**)[12] in 53% yield. The stereostructure of the 2"-position was easy to determine by comparison of the ^{1}H-NMR ($CDCl_3$) data for **14** [δ 4.40 (d, *J*=7.6Hz, 1'-H) and 5.02 (d, *J*=3.9Hz, 1"-H)] with those for **12** [δ 4.38 (d, *J*=7.6Hz, 1'-H) and 4.46 (d, *J*=7.9Hz, 1"-H)]. The 2"-hydroxyl group of **14** was protected with the MOM group and then the isopropylidene group was removed with 80% aqueous AcOH to furnish **15** in 86% yield. Finally, **15** was converted to **16**[13] through the following successive reactions: 1) $Pb(OAc)_4$ cleavage of the 3"- and 4"-diol moiety; 2) oxidation of the aldehyde groups; and 3) diazomethane methylation. Compound **16** was found to be identical with 2',4',2"-tri-*O*-monomethoxymethylbetavulgaroside IV tetramethyl ester , which was easily derived from betavulgaroside IV (**18**). On the other hand, the treatment of **10** with MOMCl followed by removal of the isopropylidene group gave **19**, which was subjected to the same procedures as **15** to provide the 2"-epimer (**20**)[14] of **16**. On the basis of the above-mentioned evidence, the 1"*R* and 2"*R* configurations of the acidic acetal-type substituent were determined, so that the absolute stereostructures of betavulgaroside IV (**18**) and its 28-β-D-glucopyranosyl ester [betavulgaroside III (**17**)][2] were also characterized as shown. Furthermore, detailed comparison of the ^{1}H-NMR and ^{13}C-NMR spectra of **17** and **18** with those for betavulgarosides V-IX led us to confirm that the absolute stereostructure of the acidic acetal-type substituent in betavulgarosides V-IX was identical with that of betavulgarosides III (**17**) and IV (**18**).

REFERENCES AND NOTES : 1) Yoshikawa M., Murakami T., Komatsu H., Murakami N., Yamahara J., Matsuda H., *Chem. Pharm. Bull.*, **45**, 81-87 (1997) and the literatures cited in the paper.

2) a) Yoshikawa M., Murakami T., Kadoya M., Matsuda H., Yamahara J., Muraoka O., Murakami N., *Heterocycles*, **41**, 1621-1626 (1995); b) Yoshikawa M., Murakami T., Kadoya M., Matsuda H., Muraoka O., Yamahara J., Murakami N., *Chem. Pharm. Bull.*, **44**, 1212-1217 (1996).

3) Yoshikawa M., Murakami T., Kadoya M., Murakami N., Yamahara J., Matsuda H., *Chem. Pharm. Bull.*, in press.

4) Iwamoto M., Okabe H., Yamauchi T., *Chem. Pharm. Bull.*, **33**, 1-7 (1985).

5) All new compounds were characterized by physicochemical properties, and full characteristics will be presented in a full paper.

6) **4a** : colorless oil, $[\alpha]_D$ +6.0°, $C_8H_{14}O_7$, IR (KBr, cm^{-1}) : 3475, 1746. ^{1}H-NMR (pyridine-d_5) δ : 3.55, 3.62, 3.73 (all s, 1, 3, 4-OMe), 4.63 (s, 5-H_2), 4.81 (d, *J*=5.6, 2-H), 5.19 (d, *J*=5.6, 1-H). ^{13}C-NMR (pyridine-d_5) δc : 51.5, 51.8, 55.9 (3, 4, 1-OMe), 64.3, 73.5, 104.7, 172.4, 170.9 (5, 2, 1, 3, 4-C). FAB-MS (*m/z*) : 223 $(M+H)^+$; **7a** : colorless oil, $[\alpha]_D$ -7.6°, $C_8H_{14}O_7$.

7) a) Schmidt R. R., Stumpp M., *Justus Liebigs Ann. Chem.*, **1983**, 1249-1256; b) Yoshikawa M., Yoshizumi S., Murakami T., Matsuda H., Yamahara J., Murakami N., *Chem. Pharm. Bull.*, **44**, 492-499 (1996).

8) **6a** : colorless oil, $[\alpha]_D$ +10.4°, $C_8H_{14}O_7$, IR (KBr, cm^{-1}) : 3486, 1752, 1737. ^{1}H-NMR (pyridine-d_5) δ : 3.55, 3.62, 3.74 (all s, 1,3,4-OMe), 4.50, 4.60 (ABq, *J*=16.2, 5-H_2), 4.87 (d, *J*=5.3, 2-H), 5.24 (d, *J*=5.3, 1-H). ^{13}C-NMR (pyridine-d_5) δc : 51.6, 51.8, 54.8 (3, 4, 1-OMe), 64.4, 73.2, 104.0, 172.6, 170.7 (5, 2, 1, 3, 4-C). FAB-MS (*m/z*) : 223 $(M+H)^+$; **8a** : colorless oil, $[\alpha]_D$ -7.1°, $C_8H_{14}O_7$.

9) Hara S., Okabe H., Mihashi K., *Chem. Pharm. Bull.*, **34**, 1843-1845 (1986).

10) **11** : mp 208-210°C, $[\alpha]_D$ +21.3°, $C_{51}H_{80}O_{14}$, IR (KBr, cm^{-1}) : 3424, 1757, 1744, 1711, 1140. ^{1}H-NMR ($CDCl_3$) δ : 0.67, 0.77, 0.88, 0.95, 1.07 (all s, CH_3x5), 0.86 (s, CH_3x2), 1.19 (s, pivaloyl), 1.31, 1.52 (both s, isopropylidene), 2.81 (dd, *J*=4.2, 13.4, 18-H), 3.11 (dd, *J*=4.3, 11.3, 3-H), 3.58, 3.76 (both s, OCH_3x2), 4.31 (d, *J*=7.0, 1'-H), 4.64 (d, *J*=6.1, 1"-H), 4.98 (t-like, *J*=*ca.* 6, 2"-H), 5.23 (br s, 12-H). FAB-MS (*m/z*) : 939 $(M+Na)^+$.

11) **12** : mp 128-130°C, $[\alpha]_D$ +80.9°, $C_{50}H_{80}O_{15}$, IR (KBr, cm^{-1}) : 3459, 1754, 1730, 1125. ^{1}H-NMR ($CDCl_3$) δ : 0.72, 0.79, 0.92, 0.95, 1.11 (all s, CH_3x5), 0.90 (s, CH_3x2), 1.35, 1.52 (both s, isopropylidene), 2.85 (dd, *J*=3.3, 13.2, 18-H), 3.11 (dd, *J*=4.9, 10.8, 3-H), 3.28, 3.40 (both s, MOM-CH_3x2), 3.61, 3.78 (both s, OCH_3x2), 4.38 (d, *J*=7.6, 1'-H), 4.46 (d, *J*=7.9, 1"-H), 5.27 (1H, br s, 12-H). FAB-MS (*m/z*) : 943 $(M+Na)^+$.

12) **14** : mp 122-124°C, $[\alpha]_D$ +10.7°, $C_{50}H_{80}O_{15}$, IR (KBr, cm^{-1}) : 3467, 1754, 1734, 1078. ^{1}H-NMR ($CDCl_3$) δ : 0.72, 0.80, 0.93, 0.96, 1.11 (all s, CH_3x5), 0.90 (s, CH_3x2), 1.36, 1.51 (both s, isopropylidene), 2.85 (br d, 18-H), 3.11 (dd, *J*=5.0, 11.2, 3-H), 3.28, 3.43 (both s, MOM-CH_3x2), 3.61, 3.77 (both s, OCH_3x2), 4.40 (d, *J*=7.6, 1'-H), 5.02 (d, *J*=3.9, 1"-H), 5.27 (br s, 12-H). FAB-MS (*m/z*) : 943 $(M+Na)^+$.

13) **16** : mp 86-88°C, $[\alpha]_D$ +14.3°, $C_{51}H_{82}O_{18}$, IR (KBr, cm^{-1}) : 1755, 1732, 1156, 1030. ^{1}H-NMR ($CDCl_3$) δ : 0.71, 0.79, 0.92, 0.96, 1.11 (all s, CH_3x5), 0.90 (s, CH_3x2), 2.85 (br d, 18-H), 3.10 (dd, *J*=4.9, 11.2, 3-H), 3.29, 3.40, 3.44 (all s, MOM-CH_3x3), 3.62, 3.73, 3.76, 3.79 (all s, OCH_3x4), 4.38, 4.44 (ABq, *J*=16.5, 5"-H_2), 4.38 (d, *J*=6.6, 1'-H), 4.50 (d, *J*=3.3, 2"-H), 5.27 (br s, 12-H), 5.50 (d, *J*=3.3, 1"-H). FAB-MS (*m/z*) : 1005 $(M+Na)^+$.

14) **20** : mp 88-90°C, $[\alpha]_D$ +34.6°, $C_{51}H_{82}O_{18}$, IR (KBr, cm^{-1}) : 1754, 1736, 1157, 1032. ^{1}H-NMR ($CDCl_3$) δ : 0.70, 0.79, 0.92, 0.97, 1.11 (all s, CH_3x5), 0.89 (s, CH_3x2), 2.85 (br d, 18-H), 3.11 (dd, *J*=5.0, 11.2, 3-H), 3.28, 3.37, 3.40 (all s, MOM-CH_3x3), 3.62, 3.73, 3.75, 3.78 (all s, OCH_3x4), 4.31 (d, *J*=4.6, 2"-H), 4.33, 4.41 (ABq, *J*=16.1, 5"-H_2), 4.42 (d, *J*=7.9, 1'-H), 5.27 (br s, 12-H), 5.35 (d, *J*=4.6, 1"-H). FAB-MS (*m/z*) : 1005 $(M+Na)^+$.

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