Biosci. Biotechnol. Biochem., **74** (4), 741–745, 2010

Methyl Caffeate as an α-Glucosidase Inhibitor from *Solanum torvum* Fruits and the Activity of Related Compounds

Keisuke TAKAHASHI,[1] Yasuyuki YOSHIOKA,[1] Eisuke KATO,[1] Shigeki KATSUKI,[2] Osamu IIDA,[2] Keizo HOSOKAWA,[3] and Jun KAWABATA[1,†]

[1]*Laboratory of Food Biochemistry, Division of Applied Bioscience, Graduate School of Agriculture, Hokkaido University, Kita-ku, Sapporo 060-8589, Japan*
[2]*Tanegashima Division, Research Center for Medicinal Plant Resources, National Institute of Biomedical Innovation, Nakatane-cho, Kumage-gun, Kagoshima 891-3604, Japan*
[3]*Department of Nutritional Management, Faculty of Health Sciences, Hyogo University, Kakogawa 675-0195, Japan*

Received October 27, 2009; Accepted December 29, 2009; Online Publication, April 7, 2010
[doi:10.1271/bbb.90789]

In screening experiments for rat intestinal α-glucosidase (sucrase and maltase) inhibitors in 325 plants cultivated in Japan's southern island, of Tanegashima, marked inhibition against both sucrase and maltase was found in the extract of the fruit of *Solanum torvum*. Enzyme-assay guided fractionation of the extract led to the isolation of methyl caffeate (1) as a rat intestinal sucrase and maltase inhibitor. We examined 13 caffeoyl derivatives for sucrase- and maltase-inhibitory activities. The results showed that methyl caffeate (1) had a most favorable structure for both sucrase and maltase inhibition, except for a higher activity of methyl 3,4,5-trihydroxycinnamate (14) against sucrase. Its moderate inhibitory action against α-glucosidase provides a prospect for antidiabetic usage of *S. torvum* fruit.

Key words: *Solanum torvum*; α-glucosidase inhibitor; methyl caffeate; Tanegashima

Diabetes mellitus is one of the most serious chronic diseases. It is caused by continual hyperglycemia and develops along with increases in obesity and aging in the general population.[1)] One of the therapeutic approaches to decreasing postprandial hyperglycemia is to retard absorption of glucose by inhibition of carbohydrate hydrolyzing enzymes α-amylase and α-glucosidase in the digestive organs.[2)] In recent years, many efforts have been made to search for effective α-glucosidase inhibitors from natural sources in order to develop a physiological functional food or to discover lead compounds for medicinal usage against diabetes.[3)] In the course of our search for rat intestinal α-glucosidase-inhibiting principles from various plants, we have isolated and identified several active compounds from plants grown in Asian regions, including Japan,[4–7)] Thailand,[8,9)] China,[10,11)] and Nepal.[12)] In this paper, we present the results of a screening of plants cultivated in Tanegashima, a southern island of Japan, for rat intestinal α-glucosidase inhibition. In the screening experiments for rat intestinal sucrase and/or maltase inhibitors in 325 plants, potent sucrase and maltase inhibiting activity was found in extract of the fruit of *Solanum torvum* (Solanaceae), an edible herbaceous perennial plant. There have been several reports on the chemical constituents of this plant, which include well-documented steroidal compounds[13–15)] and antiviral activities,[16)] but no other biologically active compounds from this plant have been reported to date. Hence, the promising screening result prompted us to isolate and elucidate the structures of active compounds in this plant. Separation of *S. torvum* fruit extract using various column chromatographic techniques lead to the isolation of methyl caffeate (**1**) as one of active principles. Some α-glucosidase inhibitors previously isolated from plants contain the caffeoyl moiety as the part of their structure and have been found to be important in exerting inhibitory activity,[3,7)] but the contribution of an ester part to the α-glucosidase-inhibitory activity of caffeic esters has not been studied. Hence we also present comparative results for α-glucosidase inhibition of various synthetic caffeic esters and related compounds.

Materials and Methods

Materials. Three hundred and twenty-five species of temperate Japanese plants were cultivated and collected in an experimental field in Tanegashima, Japan. All voucher specimens are deposited at the Tanegashima Division, Research Center for Medicinal Plant Resources, National Institute for Biomedical Innovation, Tanegashima, Japan. All chemicals used were of reagent grade, and were purchased from Wako Pure Chemicals (Osaka, Japan), unless otherwise stated. All solvents were distilled before use.

Apparatus. NMR spectra were recorded on a Bruker AMX500 instrument (^{1}H, 500 MHz). Chemical shifts (ppm) were calculated from the residual solvent signals of δ_H 2.04 in acetone-d_6, δ_H 2.49 in dimethyl sulfoxide (DMSO)-d_6, δ_H 3.30 in methanol-d_4, or δ_H 7.24 in chloroform-d. Field desorption (FD), FD-high resolution (HR), and electron ionization (EI) mass spectra were obtained on a JMS-SX102A instrument (Jeol, Tokyo).

Intestinal α-glucosidase-inhibitory activity determination. Sucrase- and maltase-inhibitory activities indicating inhibition of sucrase- and maltase-hydrolyzing activities respectively in rat intestinal glucosidase complexes were measured as described previously.[7)] Briefly, a crude enzyme solution prepared from rat intestinal acetone powder (Sigma-Aldrich Japan, Tokyo) was used as the small intestinal α-glucosidase. A reaction mixture consisting of crude enzyme solution (0.05 ml of maltase or 0.2 ml of sucrase), substrate solution (0.35 ml of 3.5 mM

† To whom correspondence should be addressed. Tel/Fax: +81-11-706-2496; E-mail: junk@chem.agr.hokudai.ac.jp

maltose or 0.2 ml of 56 mM sucrose) in 0.1 M potassium phosphate buffer (pH 6.3), and the test sample in 50% aqueous DMSO (0.1 ml) was incubated for 15 min at 37 °C. The reaction was stopped by adding 0.75 ml of 2 M Tris–HCl buffer (pH 7.0), and then this was passed through a short column of basic alumina (Merck Japan, Tokyo) to remove phenolic compounds, which might have interfered with enzymatic glucose quantification at the following step. The amount of liberated glucose was measured by the glucose oxidase method using a commercial test kit (Glucose CII-test Wako, Wako, Osaka, Japan).

Screening experiments. Screening experiments for rat intestinal maltase and sucrase inhibition were carried out with extracts of 524 plant parts from 325 species. Dried plant parts were extracted with 50% aqueous methanol. The extracts were evaporated to dryness, redissolved in 50% aqueous DMSO, and used as test samples to assess rat intestinal α-glucosidase inhibitory activity. Extractable constituents obtained from 100 mg of plant material dissolved in 1 ml of test solution were used as the final concentration in the experiments.

*Isolation of methyl caffeate (**1**) from* S. torvum *fruit.* Dried fruits (50 g) of *S. torvum* were extracted with 50% aqueous methanol. The extracts were concentrated and charged onto a hydrophobic resin column (Diaion HP-20, Mitsubishi chemical, Tokyo). The column was washed with water to remove sugars that would have disturbed the α-glucosidase-inhibitory assay and then eluted with methanol. The methanol eluate was concentrated and partitioned between ethyl acetate and water. The ethyl acetate fraction showed activities for both sucrase (29%) and maltase (47%). In contrast, the water fraction showed higher inhibitory activity against maltase (62%), whereas the sucrase-inhibitory activity was low (13%). Hence further fractionation was carried out to isolate sucrase and maltase inhibitors from the ethyl acetate fraction. The ethyl acetate fraction was fractionated by silica gel column chromatography with gradient elution by chloroform and methanol. Sucrase inhibitory activity was eluted in chloroform-methanol (4:1) eluate, while maltase inhibitory activity was dispersed throughout the fractions. The chloroform-methanol (4:1) fraction was further purified by preparative HPLC (column, Inertsil PREP-ODS, $\phi 20 \times 250$ mm, GL-Science, Tokyo; mobile phase, 15–30% MeCN in water (0–60 min), 30% MeCN in water (60–90 min); flow rate, 5.0 ml/min; detection, UV 254 nm). A peak eluted at $t_R = 64.8$ min showing the highest sucrase and maltase inhibitory activities was collected to give **1** (16 mg). The analytical data were closely consistent with those of the authentic specimen. **1**: FD-MS m/z: 194 (M^+); ^{1}H NMR (DMSO-d_6) δ (ppm): 3.67 (3H, *s*, OCH_3), 6.25 (1H, *d*, $J = 16.0$ Hz, H-8), 6.74 (1H, *d*, $J = 8.2$ Hz, H-5), 6.99 (1H, *br d*, $J = 8.2$ Hz, H-6), 7.04 (1H, *br s*, H-2), 7.47 (1H, *d*, $J = 16.0$ Hz, H-7).

*General procedure for the preparation of **2**–**7** and **10**–**14**.* Compounds **2**–**7**,[17] **10**,[18] **11**,[19] and **12**[20] were prepared as described below and spectral properties were matched with the reported data. Compounds **8** and **9** are commercially available. Compounds **13** and **14** were prepared as described below.

*Preparation of **2**–**5**, and **12**.* To a stirred solution of the corresponding cinnamic or benzoic acid (10 mmol) in each alcohol (50 ml) was added dropwise conc. H_2SO_4 (2.5 ml). The reaction mixture was heated to reflux for 6–24 h. After cooling, the resulting mixture was concentrated, diluted with water, and extracted with ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane-ethyl acetate) to give the desired esters.

Preparation of tert*-butyl caffeate (**6**).* To a stirred solution of triphenylphosphine (6.0 g, 23 mmol) in toluene (20 ml) was added *tert*-butyl bromoacetate (3.8 ml, 26 mmol, 1.1 eq). The reaction mixture was heated to reflux overnight. The mixture was cooled to room temperature and the resulting precipitate was filtered, washed successively with toluene and hexane, and dried to give a phosphonium salt (86%). The obtained phosphonium salt (2.35 g, 5 mmol) in chloroform (10 ml) was added to a stirred solution of 3,4-dihydroxybenzaldehyde (690 mg, 5 mmol) in dioxane (10 ml) and then $KHCO_3$ (2.5 g, 25 mmol, 5 eq) was added to the mixture. The mixture was refluxed for 6 h and cooled to room temperature, and the resulting insoluble salt was filtered off. The filtrate was concentrated and purified by silica gel column chromatography (hexane-ethyl acetate (3:2)) to give **6** (76%).

*Preparation of phenyl caffeate (**7**).* To a stirred solution of malonic acid (4.16 g, 40 mmol) in acetic anhydride (4.8 ml) was added conc. H_2SO_4 (0.16 ml). After 20 min, acetone (4 ml) was added to the solution and this was stirred for 6 h. The resulting precipitate was collected to give Meldrum's acid (66%). Meldrum's acid (268 mg, 1.86 mmol) was then dissolved in toluene (10 ml), and phenol (188 mg, 2 mmol, 1.1 eq) was added. The mixture was heated to reflux for 5 h. After cooling of the mixture to room temperature, 3,4-dihydroxybenzaldehyde (276 mg, 2 mmol, 1.1 eq), pyridine (0.5 ml), and piperidine (0.05 ml) were added. The mixture was stirred further 12 h at room temperature. After removal of the solvent, the mixture was diluted with 1 M HCl and extracted with ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane-ethyl acetate 3:2) to give **7** (10%).

Preparation of (E)*-4-(3,4-dihydroxyphenyl)but-3-en-2-one (**10**).* To a stirred solution of 3,4-dihydroxybenzaldehyde (1.38 g, 10 mmol) in DMF (50 ml) were added ethyldiisopropylamine (6.45 g, 50 mmol, 5 eq) and methoxymethyl chloride (1.9 ml, 25 mmol, 2.5 eq). The mixture was stirred for 6 h at room temperature, diluted with water and extracted with ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane-ethyl acetate 4:1) to give 3,4-bis(methoxymethoxy)benzladehyde (**10a**, 48%). The obtained **10a** (1.08 g, 4.8 mmol) was dissolved in methanol (25 ml) and acetone (1 ml), and KOH (2.8 g, 50 mmol, 10.4 eq) in water (5 ml) was added to the solution. The mixture was stirred at room temperature for 24 h. Then the mixture was poured into ice water (50 ml), neutralized with 1 M HCl, and extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane-ethyl acetate 4:1) to give (*E*)-4-[3,4-bis(methoxymethoxy)phenyl]but-3-en-2-one (**10b**, 42%). To a stirred solution of **10b** (50 mg, 0.19 mmol) in methanol (3 ml), 6 M HCl (3 ml) was added dropwise. The mixture was stirred for 1 h, then diluted with water and extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane-ethyl acetate 3:2) to give **10** (65%).

*Preparation of methyl 3-(3,4-dihydroxyphenyl)propanoate (**11**).* A stirred solution of **1** (1.94 g, 10 mmol) in methanol (30 ml) was hydrogenated using a balloon filled with H_2 for 24 h in the presence of 10% Pd-C (106 mg). After filtering of the catalyst, the solvent was removed and the residue was purified by silica gel column chromatography (hexane-ethyl acetate 3:2) to give **11** (63%).

*Preparation of methyl 2,3,4-trihydroxycinnamate (**13**).* To a stirred solution of 2,3,4-tris(methoxymethoxy)benzaldehyde[21] (1.43 g, 5 mmol) in dioxane (10 ml) were added (methoxycarbonylmethyl)triphenylphosphonium chloride (1.85 g, 5 mmol, 1 eq) in chloroform (10 ml) and $KHCO_3$ (2.5 g, 25 mmol, 5 eq). The mixture was refluxed for 6 h, and cooled to room temperature, and the resulting insoluble salt was filtered off. The filtrate was concentrated and purified by silica gel column chromatography (hexane-ethyl acetate 4:1) to give methyl 2,3,4-tris(methoxymethoxy)cinnamate (**13a**, 80%). **13a**: FD-HR-MS m/z (M^+): Calcd. for $C_{16}H_{22}O_8$: 342.1315, Found: 342.1317; ^{1}H NMR (chloroform-*d*) δ (ppm): 3.50 (3H, *s*, OCH_3), 3.60 (6H, *s*, $2 \times OCH_3$), 3.79 (3H, *s*, OCH_3), 5.13, 5.18, and 5.23 (each 2H, *s*, $3 \times OCH_2$), 6.38 (1H, *d*, $J = 16.1$ Hz, H-8), 6.96 (1H, *d*, $J = 8.9$ Hz, H-5), 7.28 (1H, *d*, $J = 8.9$ Hz, H-6), 8.02 (1H, *d*, $J = 16.1$ Hz, H-7). To a stirred solution of **13a** (50 mg, 0.19 mmol) in methanol (3 ml), 6 M HCl (3 ml) was added dropwise. The mixture was stirred for 1 h, then diluted with water and extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by silica gel column chromatog-

raphy (hexane-ethyl acetate 3:2) to give **13** (35%). **13**: FD-HR-MS m/z (M^+): Calcd. for $C_{10}H_{10}O_5$: 210.0528, Found: 210.0536; ^{1}H NMR (DMSO-d_6) δ (ppm): 3.66 (3H, *s*, OCH_3), 6.34 (1H, *d*, $J = 8.5$ Hz, H-6), 6.38 (1H, *d*, $J = 16.1$ Hz, H-8), 6.93 (1H, *d*, $J = 8.5$ Hz, H-5), 7.77 (1H, *d*, $J = 16.1$ Hz, H-7).

*Preparation of methyl 3,4,5-trihydroxycinnamate (**14**).* Following the method of preparing **13a**, 3,4,5-tris(methoxymethoxy)benzaldehyde[22] and (methoxycarbonylmethyl)triphenylphosphonium chloride were reacted to give methyl 3,4,5-tris(methoxymethoxy)cinnamate (**14a**) (76%). **14a**: FD-HR-MS m/z (M^+): Calcd. for $C_{16}H_{22}O_8$: 342.1315, Found: 342.1308; ^{1}H NMR (chloroform-*d*) δ (ppm): 3.51 (6H, *s*, 2 × OCH_3), 3.61 (3H, *s*, OCH_3), 3.80 (3H, *s*, OCH_3), 5.18, (2H, *s*, OCH_2), 5.21 (4H, *s*, 2 × OCH_2), 6.34 (1H, *d*, $J = 15.9$ Hz, H-8), 7.04 (2H, *s*, H-2, 6), 7.58 (1H, *d*, $J = 15.9$ Hz, H-7). Following the method of preparing **13**, **14a** was deprotected to give **14** (73%). **14**: FD-HR-MS m/z (M^+): Calcd. for $C_{10}H_{10}O_5$: 210.0528, Found: 210.0524; ^{1}H NMR (DMSO-d_6) δ (ppm): 3.67 (3H, *s*, OCH_3), 6.16 (1H, *d*, $J = 15.9$ Hz, H-8), 6.58 (2H, *s*, H-2, 6), 7.38 (1H, *d*, $J = 15.9$ Hz, H-7).

Results and Discussion

In the screening experiment, 109 samples showed more than 50% sucrase inhibitory activity and 222 samples showed more than 50% maltase inhibitory activity out of 524 samples from 325 plant species (Supplemental Table 1; see *Biosci. Biotechnol. Biochem.* Web site). Among these, notable inhibitory active species (>90%) against rat intestinal sucrase or maltase are shown in Table 1. Of these promising species, *Solanum torvum* fruit was chosen, as it had not been studied before as to glucosidase inhibitory activity and was available in large quantities. Also, *S. torvum* fruit is edible and might easily be applied in antidiabetic treatment. Therefore, we started an identification of the active principles of *S. torvum* fruit.

Table 1. Plant Species Showing Notable Inhibitory Activity against Rat Intestinal Sucrase or Maltase

Scientific name	Part	Inhibitory activity (%)	
		Sucrase	Maltase
Aleurites fordii	stem	33	100
Averrhoa bilimbi	leaf	30	100
Averrhoa carambola	leaf	30	96
Camellia japonica	stem	55	100
Cassia angustifolia	leaf	82	92
Citrus aurantium	fruit	100	100
Citrus depressa	fruit	99	89
Citrus hanayu	fruit	100	95
Derris elliptica	leaf	100	98
Derris elliptica	stem	100	97
Elaeocarpus sylvestris	leaf	61	90
Eugenia uniflora	leaf	92	88
Glochidion obovatum	leaf	42	90
Hibiscus acetosella	leaf	99	86
Ipomoea batatas (*hanaimo*)	stem	100	100
Ipomoea batatas (*Shimon 1 gou*)	stem	98	100
Liquidambar styraciflua	leaf	61	100
Morinda citrifolia	fruit	99	109
Morus australis	leaf	98	100
Morus australis	branch	95	100
Pittosporum tobira	leaf	100	100
Quassia amara	leaf	62	99
Solanum torvum	fruit	100	100
Styrax japonica	leaf	100	92
Swietenia macrophylla	leaf	36	91
Zanthoxylum schinifolium	stem	100	100

Dried fruits of *S. torvum* were extracted with 50% aqueous methanol. After evaporation, the crude extract was fractionated successively by hydrophobic resin column chromatography, solvent partition, silica gel column chromatography, and preparative HPLC to yield methyl caffeate (**1**) as an inhibitor against rat intestinal sucrase and maltase.

Methyl caffeate (**1**) showed moderate inhibitory activity, with IC_{50} values of 1.5 mM and 2.0 mM, against rat intestinal sucrase and maltase respectively. These activities are comparable to or stronger than those of ordinary flavonoid inhibitors.[23] A number of caffeoyl esters have been isolated from plants as α-glucosidase inhibitors.[3,7,24] Although caffeic acid is assumed to be the critical component in α-glucosidase inhibition, an ester moiety appeared to affect α-glucosidase inhibition also. Hence, to investigate the effects of the ester moiety together with the caffeoyl moiety against α-glucosidase inhibition, we synthesized or purchased a series of caffeoyl ester **2**–**8** and methyl caffeate analogs **9**–**14**, and tested for sucrase and maltase inhibitory activities. The compounds tested included four linear alkyl caffeates (**2**–**4**), two branched-chain alkyl caffeates (**5**, **6**), phenyl caffeate (**7**), a ketone analog (**10**), methyl dihydrocaffeate (**11**), and two trihydroxycinnamates (**13**, **14**), and chlorogenic acid (**8**), caffeic acid (**9**), and methyl protocatechuate (**12**) (Fig. 1).

The results are summarized in Table 2 and Supplemental Figs. 1–10 (see *Biosci. Biotechnol. Biochem.* Web site). In contrast to the moderate activities of methyl caffeate (**1**) against sucrase and maltase, compounds **2**, **3**, and **4**, possessing longer alkyl chains than **1**, showed slight decreases in sucrase inhibition. In branched-chain esters **5** and **6**, sterically hindered *tert*-butyl ester **6** showed less sucrase inhibitory activity than smaller isopropyl ester **5**. In contrast, the maltase inhibitory activity of compounds **2**–**6** remained unchanged compared to that of **1**. These data suggest that a larger alkyl group in the ester moiety was unfavorable to sucrase inhibition in caffeoyl esters regardless of linear or branched chains, and that maltase-inhibitory activity was not influenced by changes in the size or shape of the alkyl group. The sucrase inhibitory activity of phenyl ester **7** remained unchanged as compared to **1**. So the presence of an aromatic ring in the ester moiety is probably effective for sucrase inhibition even though it is sterically bulky. Maybe the electronic effect of the aromatic ring affects its conjugated caffeoyl moiety or interaction with the enzyme, but the details were not clear. A naturally abundant caffeic ester, chlorogenic acid (**8**), showed decreased inhibitory activity against both sucrase and maltase as compared to **1**. This result also confirms the disadvantage of a sterically hindered ester for sucrase inhibition. On the other hand, the decreased maltase inhibitory activity of **8** might have been due to the hydrophilicity of the quinic ester moiety, as the steric effect does not alter maltase inhibition, as suggested by results for compounds **2**–**6**. Caffeic acid (**9**) and (*E*)-4-(3,4-dihydroxyphenyl)but-3-en-2-one (**10**) also showed decreases in the maltase inhibitory activity, but the decrease in the sucrase inhibitory activity was not very large. The presence of a hydrophobic ester group appeared to be important to maltase inhibition regardless of its size. These caffeoyl

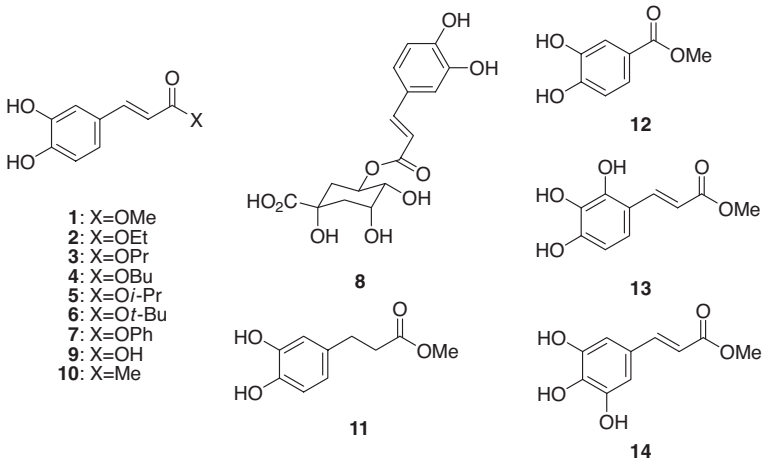

Fig. 1. Structures of Methyl Caffeate (**1**) and Related Compounds.

Table 2. Inhibitory Activity of **1**–**14** against Rat Intestinal Sucrase and Maltase

Compound	IC_{50} (mM)	
	Sucrase	Maltase
1	1.5	2.0
2	1.8	1.9
3	3.1	2.2
4	3.2	1.8
5	2.0	1.9
6	2.7	2.2
7	1.3	2.1
8	7.6	6.3
9	2.9	5.2
10	2.7	7.2
11	7.5	12.2
12	6.5	16.9
13	5.1	4.9
14	1.0	2.8

derivatives showed some variance in inhibitory activity, in spite of their low activity as compared to reported caffeoyl inhibitors having a multi caffeoyl or flavonol structure within the molecule.[3,7,24] Therefore caffeoyl ester itself showed some inhibitory activity, while the number of inhibitory active structures within the molecule might be influential.

In view of the results for **11** and **12**, the omission of a double bond in **1** led to a decrease in activity. Finally, an effect of the additional hydroxyl group in **1** was examined. Although the addition of a hydroxyl group to the C-5 position did not alter inhibitory activity much, the addition of a hydroxyl group to the C-2 position decreased its activity, as seen in the results for methyl 2,3,4-trihydroxycinnamate (**13**) and methyl 3,4,5-trihydroxycinnamate (**14**). Methyl 3,4,5-trihydroxycinnamate (**14**) is a C_2 symmetrical compound, and hence 3-OH and 5-OH are equivalent. This might be the reason **14** retained inhibitory activity. In contrast, an additional hydroxyl group of 2-OH might be sterically unfavorable or might have an detrimental electron-donating effect against the neighboring double bond, which was found to contribute to the inhibitory effect, resulting in a decrease in inhibitory activity.

In conclusion, methyl caffeate (**1**) was isolated as the active component in the α-glucosidase inhibitory activity of *S. torvum*. Methyl caffeate (**1**) and several derivatives (**2**–**14**) were tested for α-glucosidase inhibitory activity, and it was determined that **1** had a favorable structure for both sucrase and maltase inhibition, except for the slightly higher activity of **14** against sucrase. Its moderate α-glucosidase inhibitory action provides a promising application of *Solanum torvum* fruit as an antidiabetic agent.

Acknowledgments

We are grateful to Mr. Kenji Watanabe and Dr. Eri Fukushi of the GC-MS and NMR Laboratory, Graduate School of Agriculture, Hokkaido University, for measuring mass spectra.

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