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Synthesis and α-Glucosidase-Inhibiting Activity of a New α-Glucosidase Inhibitor, 4-*O*-α-D-Glucopyranosylmoranoline and Its N-Substituted Derivatives

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Various N-substituted derivatives of 4-*O*-α-D-glucopyranosylmoranoline have been synthesized, and their inhibitory activities against rabbit sucrase and maltase have been measured, as well as their effects on postprandial hyperglycemia in the sucrose-loaded rat, 4-*O*-α-D-Glucopyranosylmoranoline was also shown to have potent hypoglycemic activity in starch-loaded dogs.

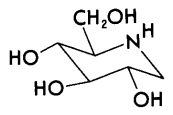
Keywords glucosyl moranoline; 4-*O*-α-D-glucopyranosylmoranoline; 4-*O*-α-D-glucopyranosyl-N-substituted moranoline; α-glucosidase inhibitor; sucrase inhibitor; hypoglycemic agent; anti-diabetic

Studies have been reported on α-glucosidase inhibitors as potent oral antidiabetic agents.[1-3] In the course of screening for inhibitors of mammalian intestinal α-glucosidase, an inhibitor was isolated from the root bark of a *Morus* species and named moranoline (**1**) [1-deoxynojirimycin, Chart 1] by Yagi *et al.*[4] Compound **1** was also produced in the fermentation broth of some strains of *Streptomyces lavendulae* as reported previously.[5,6]

The enzymatic synthesis of 4-*O*-α-D-glucopyranosyl moranoline (**2**) with **1** as the starting material, was described in the previous paper.[7] This paper deals with the α-glucosidase-inhibiting activity of the new α-glucosidase inhibitor, **2**, and its N-substituted derivatives, which may be potent oral antidiabetic agents.

Chemistry

N-Substituted derivatives were prepared by the reaction of **2** with alkyl, aralkyl and aralkenyl bromide in the presence of anhydrous potassium carbonate in *N*,*N*-dimethylformamide (DMF). The general method of isolating the product was as follows. After removal of the precipitate by filtration, the solvent was evaporated off under reduced pressure. The residue was suspended in water, and the chloroform-soluble substances were removed by extraction with chloroform. The water layer was then passed through a column of strong cation exchange resin [Dowex 50 W × 2(H^+)]. The column was washed with water, and the product was eluted with 1 N aqueous ammonia. Further purification was conducted as follows. a) If the product was easy to crystallize in water, methanol or ethanol, the eluate was evaporated, and the product was purified by recrystallization from the appropriate solvent. b) If the product was not easy to crystallize in water, methanol, ethanol, *etc.*, it was purified as the *p*-toluenesulfonate, because the *p*-toluenesulfonates of N-substituted derivatives generally produce good crystals. c) For the N-(β-phenylethyl) derivative, silica gel column chromatography was used for purification.



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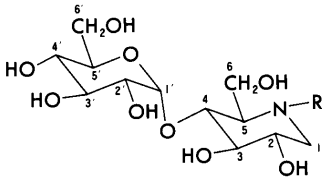

Compound	R	Compound	R	Compound	R
2	H	**7**	Br-C$_6$H$_4$-CH$_2$-	**12**	C$_6$H$_5$-O-CH$_2$-CH$_2$-
3	CH$_3$-	**8**	CH$_3$-C$_6$H$_4$-CH$_2$-	**13**	C$_6$H$_5$-O-CH$_2$-CH$_2$-CH$_2$-
4	C$_2$H$_5$-	**9**	C$_6$H$_5$-CH$_2$-	**14**	C$_6$H$_5$-O-CH$_2$-CH$_2$-CH$_2$-CH$_2$-
5	C$_3$H$_7$-	**10**	C$_6$H$_5$-CH$_2$-CH$_2$-	**15**	C$_6$H$_5$-CH=CH-CH$_2$-
6	C$_4$H$_9$-	**11**	C$_6$H$_5$-CH$_2$-CH$_2$-CH$_2$-		

Chart 1

Biological Results and Discussion

The IC_{50} values *in vitro* (50% inhibitory molar concentration) toward rabbit sucrase and maltase are shown in Table I. As reported previously,[8,9] **1** and its N-substituted derivatives strongly inhibited both rabbit sucrase and rabbit maltase. It is interesting that **2** and its N-substituted derivatives had strong inhibitory activity against rabbit sucrase but only weak activity against rabbit maltase.

The IC_{50} values for sucrase inhibition ranged from 10 to 72 μM. Lengthening the chain moiety of alkyl derivatives (**3**—**6**) aralkyl derivatives (**9**—**11**) or phenoxyalkyl derivatives (**12**—**14**) did not greatly change the inhibitory activity. The introduction of a bromo atom or methyl group into the *para* position of **9** did not change the inhibitory activity, as seen in **7** or **8**.

The introduction of an unsaturated bond into **11** did not affect the activity as shown by **15**.

The IC_{50} values for maltase inhibition varied much more than those for sucrase inhibition (Table I). The inhibitory activity against maltase of **3**, **5**, or **7** was more potent than that of the other derivatives. A clear structure–activity correlation was not apparent.

The inhibitory activity against maltase of N-substituted derivatives of glucosyl moranoline was much less than that of N-substituted derivatives of moranoline.[8,9] The ratio (IC_{50} for maltase)/(IC_{50} for sucrase) of some glucosyl moranoline derivatives was high.

The ratio for compound **2** (27.7) was more than 10 times the corresponding ratio for compound **1**.[8] In comparison with the ratios for acarbose[1] and AO-128,[3] advanced intestinal α-glucosidase inhibitors which have been evaluated in clinical trials, the high value of **2** is noteworthy: the ratios calculated from the published data are 0.20[1] and 3.3[3] for acarbose and AO-128, respectively. The K_i values of **2** for rabbit maltase and sucrase (competitive inhibition) were 2.6×10^{-5} and 3.8×10^{-6} M (Lineweaver–Burk plot), respectively. The K_m values for maltase and sucrase were 2.1×10^{-3} and 1.2×10^{-2} M, respectively. Highly selective sucrase inhibition by **2** was again confirmed.

TABLE I. Inhibition of Intestinal α-Glucosidase and Postprandial Hyperglycemia by N-Substituted Derivatives of Glucosylmoranoline

Compd.	Sucrase IC_{50} (μM)	Maltase		M/S[b]	Sucrose load[a] % inhibition[d]
		% inhibition[c]	IC_{50} (mM)		
1	0.41[e]		0.001[e]	2.4	84
2	22		0.61	27.7	93
3	23		0.17	7.4	82
4[f]	64	48	>0.95	>14.8	81
5[f]	22		0.072	3.3	78
6[f]	49	38	>0.90	>18.4	60
7	20		0.069	3.5	61
8[f]	24	48	>0.83	>34.6	73
9[f]	23	34	>0.85	>37.0	56
10	72		0.45	6.3	70
11	16	48	>1.00	>62.5	84
12	14		0.50	35.7	65
13[f]	31	44	>0.79	25.5	70
14[f]	10		0.37	37.0	83
15[f]	16		0.46	28.8	77

a) Inhibition of increment of area under blood glucose curve up to 180 min after sucrose (2 g/kg) administration to rats. *b*) (IC_{50} for maltase)/(IC_{50} for sucrase). *c*) 500 μg/ml. *d*) 30 mg/kg. *e*) Data are taken from reference 9. *f*) Tosylate.

The hypoglycemic activity of N-substituted derivatives of glucosyl moranoline at the dose of 30 mg/kg was evaluated in sucrose-loaded rats. All compounds had potent hypoglycemic activity (Table I).

The ED_{50} values (doses that suppressed the postprandial blood glucose increase by 50%) were 5.8 mg/kg in sucrose-loaded (2 g/kg) and 145 mg/kg in starch-loaded (2 g/kg) rats given **2** together with the corresponding carbohydrate. The ratio (ED_{50} for starch load)/(ED_{50} for sucrose load) was 25, almost the same as the ratio for IC_{50} of **2** and much higher than that of **1** (0.76[8]), acarbose (1.4[1]) or AO-128 (5.0[3]). This higher selectivity of **2** for inhibiting sucrase and postprandial hyperglycemia after a sucrose load is expected to result in a different clinical effect from that of acarbose or AO-128. Namely, **2** may reduce sucrose absorption without affecting severely the absorption of maltose digested from starch, which sometimes causes diarrhea when it accumulates in the intestinal tract.

The hypoglycemic activity of **2** was also tested in dogs together given 2 g/kg of starch. The ED_{50} value, obtained by a similar method to the used in the rat model, was 3.9 mg/kg. Thus, **2** had very potent hypoglycemic activity against postprandial hyperglycemic in starch-loaded dogs. Although it would be very interesting to know the potency of **2** in sucrose-loaded dogs, the ED_{50} value could not be measured because of the very poor hyperglycemic response of dogs to a sucrose load.

The details of the animal experiments on the efficacy and safety of **2** will be reported elsewhere.

Experimental

Melting points were determined with a Yanaco MP-21 apparatus and are uncorrected. Optical rotations were determined with a Horiba SEPA-200 polarimeter. ^{1}H-NMR spectra were determined with a Varian XL-200 spectrometer at 200 MHz, with dioctyl sodium sulfosuccinate (DSS) as the internal standard in D_2O.

4-*O*-α-D-Glucopyranosylmoranoline (2) Compound **2** was prepared enzymatically, as described previously.[7]

4-*O*-α-D-Glucopyranosyl-*N*-methylmoranoline (3) The synthesis of compound **3** was described previously.[10]

4-*O*-α-D-Glucopyranosyl-*N*-ethylmoranoline·*p*-Toluenesulfonate (4) A mixture of **2** (5 g, 0.015 mol), anhydrous potassium carbonate (7.4 g, 0.054 mol) and ethyl bromide (5 g, 0.046 mol) in DMF (50 ml) was stirred at room temperature for 2 d. The filtrate of the mixture was evaporated, and the residue was dissolved in water. The water solution was then passed through a column of Dowex 50 W × 2(H^+) (100 ml). The column was washed with distilled water, and the product was eluted with 1 N aqueous ammonia. The eluate was evaporated under reduced pressure and dried *in vacuo*. The residue (5.1 g) was dissolved in ethanol (10 ml).

To this solution, *p*-toluenesulfonic acid (monohydrate, 4.1 g) was added, and the mixture was kept at room temperature overnight. The resulting crystals were collected by filtration and redissolved in water. The water solution was passed through a column of strong anion exchange resin [Diaion SA-11A (OH^-)] to remove *p*-toluenesulfonic acid, and the product was eluted with distilled water. The eluate was evaporated under reduced pressure, and dried *in vacuo*. Recrystallization by *p*-toluenesulfonate formation was repeated, as described above; 7.1 g of **4** was obtained (87.8%) as colorless crystals: mp 198—200 °C, $[\alpha]_D^{24}$ +64.0 °(c=1, H_2O). ^{1}H-NMR δ: 1.33 (3H, t, J=7.3 Hz, CH_3–CH_2–), 2.39 (3H, s, CH_3–C_6H_4–SO_3H), 3.09 (1H, t, J=11.2 Hz, H-1a), 3.24—4.12 [15H, m, 4H (–CH_2OH), 5H (–CHOH), H-4, H-5, H-5′, H-1e, 2H (CH_3–CH_2–)] 5.37 (1H, d, J=3.5 Hz, H-1′), 7.34, 7.67 (2H × 2, d × 2, J=8.5 Hz, CH_3–C_6H_4–SO_3H). *Anal.* Calcd for $C_{21}H_{35}NO_{12}S$: C, 47.99; H, 6.71; N, 2.67. Found: C, 47.91; H, 6.85; N, 2.64.

4-*O*-α-D-Glucopyranosyl-*N*-(*n*-propyl)moranoline·*p*-Toluenesulfonate (5) Compound **5** (5.1 g, 61.5%) was prepared from a reaction mixture of **2** (5 g, 0.015 mol), anhydrous potassium carbonate (7.4 g, 0.054 mol) and *n*-propyl bromide (6.4 g, 0.052 mol) in DMF (50 ml) at 105—110 °C for 7 h,

by a procedure similar to that described for **4**, except that **5** was recrystallized from methanol as colorless crystals: mp 167—170 °C, $[\alpha]_D^{24}$ +60.0° ($c=1$, H_2O). ^{1}H-NMR δ: 0.98 (3H, t, $J=7.2$ Hz, CH_3–CH_2–CH_2–), 1.62—1.87 (2H, m, CH_3–CH_2–CH_2), 2.39 (3H, s, CH_3–C_6H_4–SO_3H), 3.00—4.16 ([16H, m, 4H (–CH_2OH), 5H (–CHOH), H-4, H-5, H-5′, H-1a, H-1e, 2H (CH_3–CH_2–CH_2–)], 5.37 (1H, d, $J=3.7$ Hz, H-1′), 7.36 7.68 (2H×2, d×2, $J=8.3$ Hz, CH_3–C_6H_4–SO_3H). *Anal.* Calcd for $C_{22}H_{37}NO_{12}S$: C, 48.97; H, 6.91; N, 2.60. Found: C, 48.37; H, 6.87; N, 2.42.

4-*O*-α-D-Glucopyranosyl-*N*-(*n*-butyl)moranoline·*p*-Toluenesulfonate (6) Compound **6** (7.2 g, 60.4%) was prepared from a reaction mixture of **2** (7 g, 0.022 mmol), anhydrous potassium carbonate (10.4 g, 0.075 mol) and *n*-butyl bromide (8.8 g, 0.064 mol) in DMF (100 ml) at 100—105 °C for 5 h, by a procedure similar to that described for **4**: colorless crystals, mp 198—200 °C, $[\alpha]_D^{24}$ +56.0° ($c=1$, H_2O). ^{1}H-NMR δ: 0.94 (3H, t, $J=7.1$ Hz, CH_3–CH_2–CH_2–CH_2–), 1.28—1.50 (2H, m, CH_3–CH_2–CH_2–CH_2–), 1.62—1.83 (2H, m, CH_3–CH_2–CH_2–CH_2–), 2.39 (3H, s, CH_3–C_6H_4–SO_3H), 2.84—4.16 [16H, m, 4H (–CH_2OH), 5H (–CHOH), H-4, H-5, H-5′, H-1a, H-1e, 2H (CH_3–CH_2–CH_2–CH_2–)], 5.37 (1H, d, $J=3.4$ Hz, H-1′), 7.36, 7.68 (2H×2, d×2, $J=8.3$ Hz, CH_3–C_6H_4–SO_3H). *Anal.* Calcd for $C_{23}H_{39}NO_{12}S$: C, 49.90; H, 7.10; N, 2.53. Found: C, 49.63; H, 7.10; N, 2.54.

4-*O*-α-D-Glucopyranosyl-*N*-(4-bromobenzyl)moranoline (7) A mixture of **2** (5 g, 0.015 mol), anhydrous potassium carbonate (6.4 g, 0.046 mol) and *p*-bromobenzyl bromide (9.6 g, 0.038 mol) in DMF (50 ml) was stirred at room temperature for 4 h. The filtrate of the mixture was evaporated, and the residue was suspended in water and partitioned between chloroform and water. The aqueous layer was passed through a column of Dowex 50 W×2(H^+) (50 ml), washed with water and then eluted with 1 N aqueous ammonia. The eluate was concentrated, treated with active carbon, evaporated and dried *in vacuo*. Compound **7** was recrystallized from methanol to give 4.7 g (61.8%) of colorless crystals: mp 210—212 °C, $[\alpha]_D^{24}$ +55.5° ($c=1$, H_2O). ^{1}H-NMR δ: 1.96—2.11 (1H, m, H-1a), 2.37—2.43 (1H, m, H-5), 2.82—2.91 (1H, m, H-1e), 3.33—4.20 [13H, m, 4H (–CH_2OH), 5H (–CHOH), H-4, H-5′, 2H (Br–C_6H_4–CH_2–)], 5.33 (1H, d, $J=3.7$ Hz, H-1′), 7.28 7.56 (2H×2, d×2, $J=8.5$ Hz, Br–C_6H_4–CH_2–). *Anal.* Calcd for $C_{19}H_{28}BrNO_9$: C, 46.16; H, 5.71; N, 2.83. Found: C, 46.03, H, 5.87; N, 2.88.

4-*O*-α-D-Glucopyranosyl-*N*-(4-methylbenzyl)moranoline·*p*-Toluene sulfonate (8) A mixture of **2** (5 g, 0.015 mol), anhydrous potassium carbonate (6.4 g, 0.046 mol) and 4-methylbenzyl bromide (7.1 g, 0.038 mol) in DMF (50 ml) was stirred at 100—105 °C for 5 h. The filtrate of the mixture was evaporated, and the residue was suspended in water and partitioned between chloroform and water. The aqueous layer was passed through a column of Dowex 50 W×2(H^+) (50 ml), washed with water, and then eluted with 1 N aqueous ammonia. The eluate was evaporated and dried *in vacuo*. The residue (5.8 g) was dissolved in ethanol (100 ml). To this solution, *p*-toluenesulfonic acid (monohydrate, 3.9 g) was added, and the mixture was kept at room temperature overnight. The resulting crystals were collected by filtration. The crystals were dissolved again in water. The water solution was passed through a column of Diaion SA-11A (OH^-), and the product was eluted with distilled water. The eluate was evaporated and dried *in vacuo*, and recrystallization by *p*-toluenesulfonate formation was repeated, as described above; 7.2 g of **8** was obtained (71.4%) as colorless crystals: mp 214—216 °C, $[\alpha]_D^{24}$ +47.7° ($c=1$, H_2O). ^{1}H-NMR δ: 2.39 (6H, s, CH_3–C_6H_4–SO_3H, CH_3–C_6H_4–CH_2–), 2.82—2.98 (1H, m, H-1a), 3.22—4.00 [13H, m, 4H (–CH_2OH), 5H (–CHOH), H-4, H-5, H-5′, H-1e], 4.10—4.35 (2H, m, CH_3–C_6H_4–CH_2–), 5.40 (1H, d, $J=3.4$ Hz, H-1′), 7.38 (4H, s, CH_3–C_6H_4–CH_2–), 7.35, 7.68 (2H×2, d×2, $J=8.2$ Hz, CH_3–C_6H_4–SO_3H). *Anal.* Calcd for $C_{27}H_{39}NO_{12}S\cdot 3H_2O$: C,49.46; H, 6.92; N, 2.14. Found: C, 49.60; H, 6.84; N, 2.20.

4-*O*-α-D-Glucopyranosyl-*N*-benzylmoranoline·*p*-Toluenesulfonate (9) Compound **9** (9.8 g, 77.5%) was prepared from a reaction mixture of **2** (7 g, 0.022 mol), anhydrous potassium carbonate (10.4 g, 0.075 mol) and benzyl bromide (11.0 g, 0.064 mol) and DMF (50 ml) at 100—105 °C, by a procedure similar to that described for **8**: colorless crystals, mp 218—220 °C, $[\alpha]_D^{24}$ +55.6° ($c=1$, H_2O). ^{1}H-NMR δ: 2.38 (3H, s, CH_3–C_6H_4–SO_3H), 2.84—3.00 (1H, m, H-1a), 3.24—4.38 [15H, m, 4H (–CH_2OH), 5H (–CHOH), H-4, H-5, H-5′, H-1e, C_6H_5–CH_2–], 5.39 (1H, d, $J=3.5$ Hz, H-1), 7.35, 7.67 (2H×2, d×2, $J=8.3$ Hz, CH_3–C_6H_4–SO_3H), 7.52 (5H, s, C_6H_5–CH_2–). *Anal.* Calcd for $C_{26}H_{37}NO_{12}S$: C, 53.14; H, 6.35; N, 2.38. Found: C, 52.93; H, 6.32; N, 2.55.

4-*O*-α-D-Glucopyranosyl-*N*-(β-phenylethyl)moranoline (10) A reaction mixture of **2** (5 g, 0.015 mol), anhydrous potassium carbonate (6.4 g, 0.046 mol) and (2-bromoethyl)benzene (7.1 g, 0.038 mol) in DMF (50 ml) was stirred at 90—100 °C for 5 h. The filtrate of the mixture was evaporated, and the residue was suspended in water and partitioned between chloroform and water. The aqueous layer was passed through a column of Dowex 50 W×2(H^+) (50 ml), washed with water, and then eluted with 1 N aqueous ammonia. The eluate was evaporated, and the residue was chromatographed on a column of silica gel (40 g) with chloroform–methanol (1 : 1). The eluate was evaporated and dried *in vacuo* to give **10** (3.7 g, 56.1%) as a white powder: it did not show a sharp melting point; incomplete melting began at 87—89 °C and ended at 103—106 °C. $[\alpha]_D^{24}$ +71.2° ($c=1$, H_2O). ^{1}H-NMR δ: 2.42—2.56 (2H, m, H-1a, H-5), 2.78—3.09 (4H, m, C_6H_5–CH_2–CH_2–), 3.06—3.15 (1H, m, H-1e), 3.34—4.01 [11H, m, 4H (–CH_2OH), 5H (–CHOH), H-4, H-5′], 5.31 (1H, d, $J=3.7$ Hz, H-1′), 7.22—7.42 (5H, m, C_6H_5–). *Anal.* Calcd for $C_{20}H_{31}NO_9$: C, 55.94; H, 7.28; N, 3.26, Found: C, 55.64; H, 7.25; N, 3.55.

4-*O*-α-D-Glucopyranosyl-*N*-(3-phenylpropyl)moranoline (11) Compound **11** (7.3 g, 70.5%) was prepared from a reaction mixture of **2** (7 g, 0.022 mol), anhydrous potassium carbonate (10.4 g, 0.075 mol) and 1-bromo-3-phenylpropane (12.8 g, 0.064 mol) in DMF (100 ml) at 105—110 °C for 7 h, by a procedure similar to that described for **7**, except that **11** was recrystallized from distilled water as colorless crystals: mp 93—95 °C, $[\alpha]_D^{24}$ +63.9° ($c=1$, H_2O). ^{1}H-NMR δ: 1.70—1.94 (2H, m, C_6H_5–CH_2–CH_2–CH_2–), 2.25—2.46 (2H, m, H-1a, H-5), 2.54—2.84 (4H, m, C_6H_5–CH_2–CH_2–CH_2–), 2.92—3.06 (1H, m, H-1e), 3.34—3.88 [11H, m, 4H (–CH_2OH), 5H (–CHOH), H-4, H-5′], 5.29 (1H, d, $J=3.7$ Hz, H-1′), 7.20—7.42 (5H, m, C_6H_5–). *Anal.* Calcd for $C_{21}H_{33}NO_9\cdot 2H_2O$: C, 52.60; H, 7.78; N, 2.92. Found: C, 52.27; H, 7.88; N, 2.96.

4-*O*-α-D-Glucopyranosyl-*N*-(β-phenoxyethyl)moranoline (12) Compound **12** (4.3 g, 62.7%) was prepared from a reaction mixture of **2** (5 g, 0.015 mol), anhydrous potassium carbonate (6.4 g, 0.046 mol) and β-bromophenetole (7.7 g, 0.038 mol) in DMF (50 ml) at 105—110 °C for 3 h, by a procedure similar to that described for **7**, except that **12** was recrystallized from ethanol as colorless crystals: mp 162—164 °C, $[\alpha]_D^{24}$ +65.9° ($c=1$, H_2O). ^{1}H-NMR δ: 2.40—2.62 (2H, m, H-1a, H-5), 3.00—3.30 (3H, m, C_6H_5–O–CH_2–CH_2–, H-1e), 3.34—4.06 [11H, m, 4H (–CH_2OH), 5H (–CHOH), H-4, H-5′], 4.23 (2H, t, $J=5.2$ Hz, C_6H_5–O–CH_2–CH_2–), 5.32 (1H, d, $J=3.6$ Hz, H-1′), 6.97—7.44 (5H, m, C_6H_5–O–). *Anal.* Calcd for $C_{20}H_{31}NO_{10}$: C, 53.93; H, 7.01; N, 3.14. Found: C, 53.44; H, 7.07; N, 3.05.

4-*O*-α-D-Glucopyranosyl-*N*-(3-phenoxypropyl)moranoline·*p*-Toluenesulfonate (13) Compound **13** (5.9 g, 60.8%) was prepared from a reaction mixture of **2** (5 g, 0.015 mol), anhydrous potassium carbonate (7.5 g, 0.054 mol) and 3-phenoxypropyl bromide (9.9 g, 0.046 mol) in DMF (100 ml) at 105—110 °C for 8 h, by a procedure similar to that described for **8**, except that **13** was recrystallized from methanol as colorless crystals: mp 198—200 °C, $[\alpha]_D^{24}$ +50.0° ($c=1$, H_2O). ^{1}H-NMR δ: 2.14—2.35 (2H, m, C_6H_5–O–CH_2–CH_2–CH_2–), 2.38 (3H, s, CH_3–C_6H_4–SO_3H), 3.14 (1H, t, $J=11.3$ Hz, H-1a), 3.34—4.09 [15H, m, 4H (–CH_2OH), 5H (–CHOH), H-1e, H-4, H-5, H-5′, C_6H_5–O–CH_2–CH_2–CH_2–], 4.18 (2H, t, $J=5.5$ Hz, C_6H_5–O–CH_2–), 5.37 (1H, d, $J=3.3$ Hz, H-1′), 6.96—7.44 (5H, m, C_6H_5–O–), 7.33, 7.66 (2H×2, d×2, $J=8.2$ Hz, CH_3–C_6H_4–SO_3H). *Anal.* Calcd for $C_{28}H_{41}NO_{13}S$: C, 53.24; H, 6.54; N, 2.22. Found: C, 52.97; H, 6.45; N, 2.26.

4-*O*-α-D-Glucopyranosyl-*N*-(4-phenoxybutyl)moranoline·*p*-Toluenesulfonate (14) Compound **14** (5.7 g, 57.4%) was prepared from a reaction mixture of **2** (5 g, 0.015 mol), anhydrous potassium carbonate (6.4 g, 0.046 mol) and 4-phenoxybutyl bromide (8.8 g, 0.038 mol) in DMF (50 ml) at 105—110 °C for 5 h, by a procedure similar to that described for **13**: colorless crystals, mp 152—155 °C (dec.), $[\alpha]_D^{24}$ +36.6° ($c=1$, H_2O), ^{1}H-NMR δ: 1.72—2.06 (4H, br s, C_6H_5–O–CH_2–CH_2–CH_2–CH_2–), 2.37 (3H, s, CH_3–C_6H_4–SO_3H), 3.10 (1H, t, $J=11.2$ Hz, H-1a), 3.02—4.06 [15H, m, 4H (–CH_2OH), 5H (–CHOH), H-1e, H-4, H-5, H-5′, C_6H_5–O–CH_2–CH_2–CH_2–CH_2–], 4.09 (2H, t, $J=5.6$ Hz, C_6H_5–O–CH_2–), 5.37 (1H, d, $J=3.6$ Hz, H-1′), 6.96—7.44 (5H, m, C_6H_5–O–), 7.33, 7.66 (2H×2, d×2, $J=8.2$ Hz, CH_3–C_6H_4–SO_3H). *Anal.* Calcd for $C_{29}H_{43}NO_{13}S$: C, 53.94; H, 6.71; N, 2.17. Found: C, 53.49; H, 6.80; N, 2.37.

4-*O*-α-D-Glucopyranosyl-*N*-cinnamylmoranoline·*p*-Toluenesulfonate (15) Compound **15** (1.3 g, 13.8%) was prepared from a reaction mixture of **2** (5 g, 0.015 mol), anhydrous potassium carbonate (6.4 g, 0.046 mol) and cinnamyl bromide (7.6 g, 0.039 mol) in DMF (50 ml) at room temperature for 1 h, without stirring, by a procedure similar to that described for **13**: colorless crystals, mp 212—214 °C, $[\alpha]_D^{24}$ +35.2° ($c=1$, H_2O), ^{1}H-NMR δ: 2.38 (3H, s, CH_3–C_6H_4–SO_3H), 3.12 (1H, t, $J=11.4$ Hz, H-1a), 3.36—3.54 (2H, m, C_6H_5–CH=CH–CH_2–), 3.56—4.24 [13H, m, 4H (–CH_2OH), 5H (–CHOH), H-1e, H-4, H-5, H-5′], 5.40 (1H, d, $J=3.3$ Hz, H-1′), 6.22—6.41 (1H, m, C_6H_5—CH=CH–CH_2–), 6.98 (1H, d, $J=15.8$ Hz,

C_6H_5–C<u>H</u>=CH–CH_2–), 7.35, 7.68 (2H × 2, d × 2, J=8.2 Hz, CH_3–C_6<u>H_4</u>–SO_3H), 77.38—7.60 (5H, m, C_6<u>H_5</u>–CH=CH–CH_2–). *Anal.* Calcd for $C_{28}H_{39}NO_{12}S$: C, 54.80; H, 6.41; N, 2.28. Found: C, 54.12; H, 6.59; N, 2.11.

***In Vitro* Assays of α-Glucosidase-Inhibiting Activity** α-Glucosidase-inhibiting activities against rabbit sucrase and maltase were assayed *in vitro*, as reported previously.[8]

Inhibition of Postprandial Hyperglycemia after Sucrose or Starch Administration in Rats The method and results were described in the previous paper.[8]

Inhibition of Postprandial Hyperglycemia after Starch Administration in Dogs Compound **2** and 2 g/kg of soluble starch (Kanto Chemical Co., Inc., Tokyo, Japan) were given simultaneously through a rubber stomach tube to 7-month-old male beagles after an overnight fast, and blood was withdrawn from the forelimb vein without anesthesia 15, 30, 45, 60, 90, 120 and 180 min later. Whole blood glucose levels were measured enzymatically with a kit (Boehringer Mannheim–Yamanouchi, Tokyo, Japan). The dose required to suppress the increment of the area under the blood glucose curve by 50% (ED_{50}) was calculated in the same way as in the rat model.[8]

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