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Studies on Synthesis of 3-*O*-Alkyl-D-glucose and 3-*O*-Alkyl-D-allose Derivatives and Their Biological Activities

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Twenty two 3-*O*-alkyl derivatives of D-glucose and D-allose, four 3-*O*-alkenyl derivatives of D-glucose having an end methylene group, and four 3-*O*-ω-hydroxyalkyl- or -methoxyalkyl derivatives of D-glucose were synthesized. Their cytotoxicity *in vitro* against the cultured leukemia L-5178Y cell line, antimicrobial activity and plant growth-inhibitory effect were determined.

Keywords——*O*-alkyl glucose; *O*-alkyl allose; antitumor activity; cytotoxicity; plant growth-inhibitory activity

We have studied the antitumor activity of polysaccharides isolated from *Basidiomycetes*[2] and found the antitumor activity of polysaccharides to be associated mainly with glucans. In order to elucidate the relationship between the structure and the activity, we investigated the antitumor activity of oligosaccharides composed of D-glucose and monosaccharide derivatives.[3–5] It was concluded from the studies on disaccharides that the *in vitro* cytotoxicity of sucrose derivatives was related to the values of hydrophile–lipophile-balance (HLB). Among trehalose-6,6′-diester derivatives the lauroyl ester had the highest activity.[3,5] Concerning monosaccharide derivatives, we reported previously on the antitumor activity of 1-*O*-, 3-*O*- and 6-*O*-acyl-D-glucopyranoses and determined their IC_{50} values by *in vitro* bioassay using a cultured L-5178Y cell line.[4]

In this study, we report on syntheses of 3-*O*-alkyl-D-glucose and -D-allose derivatives

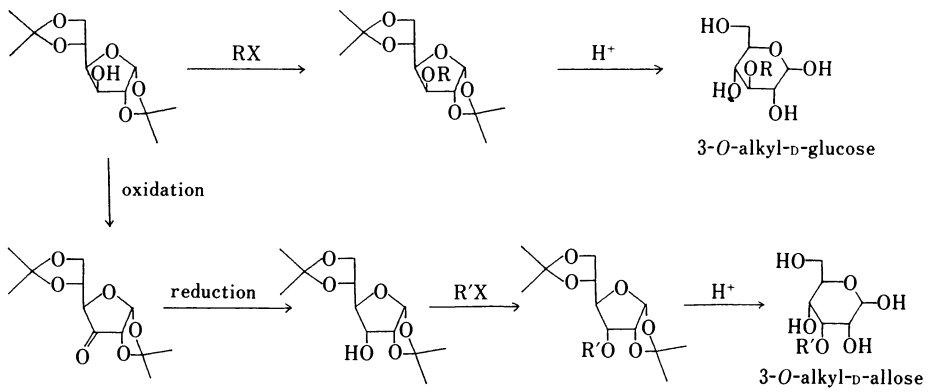

Chart 1. Synthesis of 3-*O*-Alkyl-D-glucose and -D-allose Derivatives

having substituents of various chain-length, and on the investigation of their *in vitro* cytotoxicity, antimicrobial activity and plant growth-inhibitory activity. Syntheses of 3-*O*-alkyl-D-glucose and -D-allose derivatives were carried out by the method shown in Chart 1. Among the compounds synthesized in this study, 3-*O*-allyl- and 3-*O*-lauryl-D-glucose and 3-*O*-alkyl-D-glucoses having an alkyl chain shorter than 4 carbon atoms, as well as 3-*O*-methyl-D-allose, have been previously prepared, but the antitumor activities have not been reported.

Materials and Methods

Physicochemical Properties——Melting points are not corrected. Measurement of infrared (IR) spectra was performed in KBr tablets with a Jasco A-102 infrared spectrophotometer. Nuclear magnetic resonance (NMR) spectra for solutions in dimethyl sulfoxide (DMSO)-d_6 or CD_3OD were measured using a Hitachi R-24B high resolution NMR spectrometer.

Preparation of 3-*O*-Alkyl-D-glucose Derivatives——DMSO (15 ml) containing 20 mmol of sodium hydride was slowly added, with stirring and cooling, to a solution of 1,2 : 5,6-di-*O*-isopropylidene-α-D-glucofuranose (10 mmol) in 15 ml of DMSO. With continued cooling, the mixture was stirred for 30 min and then 20 mmol of alkyl halide (RX) was added dropwise. The reaction mixture was stirred at room temperature for 2 h, the resulting solution was poured into ice water, and the product was extracted with ether. The ethereal extract was concentrated and the crude product was purified by silica gel column chromatography using chloroform as the eluant. A solution of the resulting 3-*O*-alkyl-1,2 : 5,6-di-*O*-isopropylidene-α-D-glucofuranose (1.0 g) in water (10 ml) was refluxed in the presence of Amberlite CG-120 (H^+ type, 1.0 g) for 4—20 h. After cooling, the crude product was extracted with ether and purified by silica gel column chromatography using chloroform–methanol (10 : 1) as the eluant, and the 3-*O*-alkyl-D-glucopyranose was recrystallized from ethanol. Yields: R = $C_{11}H_{23}$, 28.1%; R = $C_{12}H_{25}$, 22.1%; R = $C_{13}H_{27}$, 29.2% from 1,2 : 5,6-di-*O*-isopropylidene-α-D-glucofuranose. Melting points of the D-glucose series are: R = CH_3, 166—168 °C; C_2H_5, 143—145 °C; C_3H_7, 130—131 °C; C_4H_9, 139—143 °C; C_6H_{13}, 122—124 °C; C_8H_{17}, 128—130 °C; $C_{10}H_{21}$, 141—143 °C; $C_{11}H_{23}$, 137—139 °C; $C_{12}H_{25}$, 139—141 °C; $C_{13}H_{27}$, 138—140 °C; $C_{14}H_{29}$, 136—138 °C; $C_{16}H_{33}$, 134—135 °C; $C_{18}H_{37}$, 125—127 °C; $C_{20}H_{41}$, 110—113 °C; $C_{22}H_{45}$, 105—108 °C; CH_2=CH-CH_2, 131—132 °C; CH_2=CH-$(CH_2)_8$, 113—115 °C; CH_2=CH-$(CH_2)_9$, 134—136 °C; CH_2=CH-$(CH_2)_{10}$, 128—130 °C; HO$(CH_2)_{10}$, 108—110 °C; HO$(CH_2)_{16}$, 110—112 °C; $CH_3O(CH_2)_{10}$, 71—73 °C; $CH_3O(CH_2)_{12}$, 92—94 °C.

3-*O*-Alkyl-D-allose Derivatives[6]——1,2 : 5,6-Di-*O*-isopropylidene-α-D-glucofuranose (10 mmol) was dissolved in 40 ml of dichloromethane and oxidized with pyridinium chlorochromate[7] (40 mmol) in the presence of 3 Å molecular sieves (10 g). The resulting mixture was extracted with dichloromethane and, after evaporation of the solvent, the 3-keto compound thus obtained was dissolved in 15 ml of ethanol–water (3 : 7), and reduced with sodium borohydride (0.22 g). After extraction with dichloromethane and crystallization from cyclohexane, 1,2 : 5,6-di-*O*-isopropylidene-α-D-allofuranose (1.35 g) was obtained. 1,2 : 5,6-Di-*O*-isopropylidene-α-D-allofuranose (1.30 g) was dissolved in DMSO (20 ml) and 60% sodium hydride (0.40 g) was added. The mixture was stirred at room temperature for 1 h. Then, in the case of the lauryl derivative, lauryl bromide (1.37 g) was added under continuous stirring. Stirring was continued for 2 h at room temperature, then the resulting solution was poured into ice water and extracted with ether. The ethereal solution was concentrated and 3-*O*-lauryl-1,2 : 5,6-di-*O*-isopropylidene-α-D-allofuranose (1.70 g, 79%) was obtained. The foregoing compound (0.50 g) was suspended in water (15 ml), Amberlite CG-120 (H^+ type, 0.50 g) was added and the mixture was refluxed for 17 h. After cooling, the product was extracted with ether, and the ethereal phase was concentrated. The crude product was purified by elution from a silica gel column with chloroform–methanol (10 : 1) to give 3-*O*-lauryl-D-allopyranose (0.15 g) as colorless crystals. Yields: R = $C_{11}H_{23}$, 26.1%; R = $C_{12}H_{25}$, 29.2%; R = $C_{13}H_{27}$, 40.5% from 1,2 : 5,6-di-*O*-isopropylidene-α-D-allofuranose. Melting points of the D-allose series are: R = CH_3, 112—114 °C; C_6H_{13}, 52—54 °C; $C_{10}H_{21}$, 67—69 °C; $C_{11}H_{23}$, 69—70 °C; $C_{12}H_{25}$, 67—69 °C; $C_{13}H_{27}$, 67—68 °C; $C_{18}H_{37}$, 61—63 °C.

***In Vitro* Cytotoxic Activity**[3c]——The leukemia L-5178Y cell line maintained at this institute was cultured in RPMI-1640 medium supplemented with 10% calf serum, and the test sample was added at the desired concentration. The cells (1.0×10^5 cells/ml) were cultured in sealed tubes at 37 °C in a 5% CO_2 atmosphere in the presence or absence of the test sample. After a cultivation period of 48 h the cell growth-inhibitory effect was determined from the ratio of cell numbers counted visually with the aid of a microscope. The 50% inhibition concentration (IC_{50}) value was determined by a probit diagraming analysis.

Antimicrobial Activity——The first screening was performed by a paper disc assay using bacteria and fungi, that is, *Bacillus subtilis* ATCC 6633, *Escherichia coli* 0—1 and *Trichophyton mentagrophytes* QM 248. Active compounds selected by the first screening were subjected to a dilution assay and the minimum inhibition concentration (MIC) was determined by MIC determination assay, according to the procedure established by the Japanese Society of Chemotherapy.[8] The microorganisms used in this study were 8 gram-positive, 9 gram-negative bacteria and 20 fungi.

***In Vivo* Antitumor Activity**——Leukemia P-388 maintained in CDF_1 mice by weekly passage was used. P-388

(1.0×10^5 cells/mouse) was intraperitoneally (i.p.) inoculated into female CDF_1 mice, and the test sample was dissolved or suspended in an adequate vehicle, and administered i.p. once daily from day 1 to day 5. The increase in life-span was determined from the mean survival time by comparison with that of the control animals. The test samples were dissolved in 0.9% aqueous NaCl solution in the case of compounds containing less than 14 carbons, in 5% DMSO–saline for those containing 16—22 carbons, and in 30% DMSO–0.2% Tween 80–saline for the allyl derivatives.

***Avena* Coleoptile Straight Growth Test**——The method used in this study was identical with that reported in the previous paper.[9] Oat seeds (*Avena sativa* L.) were cultivated at 25 °C in darkness for 3 d after seeding, in the presence or absence of 3-indolylacetic acid (IAA). The test sample was dissolved in 0.1% ethanol solution. A section (6 mm long) was cut from the coleoptile about 2—3 mm below the tip, placed in a test tube containing 1 ml each of 10 mM KH_2PO_4–Na_2HPO_4 buffer solution (pH 5.2), 3 ppm IAA solution and 167 ppm test solution, and incubated at 25 °C for 18 h. For each sample 11 sections were used. After 18 h of incubation the section length was measured, and the growth was calculated as follows: Growth (%) $= \Delta T/\Delta C \times 100$, where ΔT is the average length (mm) after the incubation of the test group minus the initial length (6 mm), and ΔC is the corresponding value for the control group.

Results and Discussion

As reported in our previous paper,[4] monosaccharide esters did not show high *in vitro* cytotoxic activity. The *in vitro* cytotoxicity of ester derivatives of disaccharides, for example, sucrose monoester or trehalose diester derivatives,[5] was also not very high; at best, it was

TABLE I. Cell Growth-Inhibitory Effect on the Cultured L-5178Y Cell Line of Positional Isomers of *O*-Alkyl Monosaccharides

Compd.	IC_{50} (mcg/ml)
1-*O*-Lauryl-D-glucoside	21.8
3-*O*-Lauryl-D-glucose	0.6
6-*O*-Lauryl-D-glucose	31.0
6-*O*-Lauryl-D-galactose	100

TABLE II. Cell Growth-Inhibitory Effect on the Cultured L5178Y Cell Line of 3-*O*-Alkyl-D-glucose and -D-allose Derivatives

Compd.	R	IC_{50} (mcg/ml)	Compd.	R	IC_{50} (mcg/ml)
GC-1	CH_3–	7.0	GC-A3	$CH_2=CH$–CH_2–	100
GC-2	C_2H_5–	14.5	GC-A10	$CH_2=CH$–$(CH_2)_8$–	9.0
GC-3	C_3H_7–	20.0	GC-A11	$CH_2=CH$–$(CH_2)_9$–	1.3
GC-4	C_4H_9–	100	GC-A12	$CH_2=CH$–$(CH_2)_{10}$–	20.0
GC-6	C_6H_{13}–	4.4	GC-B10	$HO(CH_2)_{10}$–	100
GC-8	C_8H_{17}–	3.8	GC-B16	$HO(CH_2)_{16}$–	100
GC-10	$C_{10}H_{21}$–	6.5	GC-C10	$CH_3O(CH_2)_{10}$–	49
GC-11	$C_{11}H_{23}$–	7.6	GC-C12	$CH_3O(CH_2)_{12}$–	57
GC-12	$C_{12}H_{25}$–	0.6			
GC-13	$C_{13}H_{27}$–	5.0	AC-1	CH_3–	100
GC-14	$C_{14}H_{29}$–	4.4	AC-6	C_6H_{13}–	100
GC-16	$C_{16}H_{33}$–	1.6	AC-10	$C_{10}H_{21}$–	29
GC-18	$C_{18}H_{37}$–	1.1	AC-11	$C_{11}H_{23}$–	33
GC-20	$C_{20}H_{41}$–	3.4	AC-12	$C_{12}H_{25}$–	68
GC-22	$C_{22}H_{45}$–	100	AC-13	$C_{13}H_{27}$–	10.7
			AC-18	$C_{18}H_{37}$–	10.5

GC, 3-*O*-alkyl-D-glucose; GC-A, 3-*O*-ω-methylenealkyl-D-glucose; GC-B, 3-*O*-ω-hydroxyalkyl-D-glucose; GC-C, 3-*O*-ω-methoxyalkyl-D-glucose; AC, 3-*O*-alkyl-D-allose. Inoculum size, 1.0×10^5 cells/ml. Cell counting was performed 48 h after the inoculation.

50 mcg/ml (IC_{50}). Some structural relation to *in vitro* cytotoxicity[3,5] could, however, be found.

In this work we studied the biological activities of *O*-alkyl derivatives of D-glucose and D-allose, and the relationship between the structure and *in vitro* cytotoxicity. We also examined the difference in cytotoxic activity of the positional isomers of the *O*-alkyl derivatives of D-glucose. As shown in Table I, it was found that 3-*O*-alkyl-D-glucoses show high inhibitory activity on tumor cell growth, but the 1- or 6-*O*-alkyl derivatives do not. Therefore, we synthesized 3-*O*-alkyl derivatives of D-glucopyranose and D-allopyranose having various chain-length substituents, and found that it was essential for the carbon chain-length to be over 8 and below 20 in order for the derivatives to manifest cytotoxic activity. As shown in Table II, the IC_{50} values of compounds with carbon chain-lengths of C-8 to C-22 were less than 10 mcg/ml. The 3-*O*-lauryl derivative of D-glucose had the highest activity (IC_{50} below 1 mcg/ml). Among the tested alkenyl derivatives having an ω-methylene group the 11-carbon compound (GC-A11) showed a highly promising activity. Among the 6,6′-diester derivatives of, α,α-trehalose, the lauroyl ester showed the highest activity,[5] and in the D-glucose ester series the lauroyl derivative also showed the highest *in vitro* cytotoxicity[4] and plant growth-inhibitory effect.[9] Although it is not our intention to discuss here the reason why the lauryl or lauroyl derivatives of carbohydrates show such high biological activities, it may be suggested that the 12-carbon chain constitutes an important factor in some biological systems. As 3-*O*-lauryl-D-glucose showed the highest activity among the compounds synthesized in this study, we also tested by *in vivo* bioassay the antitumor activity of this and other structurally similar

TABLE III. Antitumor Activity of 3-*O*-Alkyl-D-glucose Derivatives

Compd.	Dose mg/kg × d	Mean survival (d)	ILS (%)	Result
Control		8.92		
GC-8	30 × 5	10.83	21	++
GC-10	30 × 5	10.83	16	++
Control		8.70		
GC-11	30 × 5	10.17	17	++
GC-12	30 × 5	10.67	23	++
GC-13	30 × 5	9.00	3	±

Tumor: P-388, 1.0×10^5 cells/mouse, i.p. Vehicle: 0.9% NaCl aq. solution. Animal: female BDF_1 mouse. Route: i.p. ILS: increase in life-span.

TABLE IV. Plant Growth-Inhibitory Activity on *Avena* Coleoptile Sections[a] of 3-*O*-Alkyl-D-glucose and -D-allose Derivatives

Compd.	Plant growth[b] (%)
GC-3	95.1 ± 4.9
GC-10	82.9 ± 4.9
GC-12	97.6 ± 2.4
GC-A3	97.6 ± 7.2
GC-A10	91.0 ± 3.0
GC-A11	46.3 ± 2.4
GC-A12	48.8 ± 7.2
AC-10	97.0 ± 3.0
AC-11	93.9 ± 0.0

a) 167 ppm. *b*) Mean ± S.E.

TABLE V. Spectral Data for 3-*O*-Alkyl-D-glucose and -D-allose Derivatives

Compd.	IR λ_{max}^{KBr} cm^{-1}	NMR[a] (δ ppm)
GC-1	2970, 1030	3.45 (s, 3H), 2.80—5.20 (m, 11H)
GC-2	2920, 1030	1.11 (t, 3H), 3.5 (q, 2H), 2.75—5.10 (m, 11H)
GC-3	2920, 1035	0.87 (t, 3H), 1.20—1.95 (m, 2H), 2.70—5.15 (m, 13H)
GC-4	2930, 1035	0.90 (t, 3H), 1.10—1.80 (m, 4H), 2.70—5.15 (m, 13H)
GC-6	2930, 1035	0.87 (t, 3H), 1.31 (br, 8H), 2.70—5.30 (m, 13H)
GC-8	2920, 1030	0.87 (t, 3H), 1.24 (br, 12H), 2.85—4.95 (m, 13H)
GC-10	2930, 1030	0.88 (t, 3H), 1.24 (br, 16H), 2.75—5.10 (m, 13H)
GC-11	2930, 1035	0.86 (t, 3H), 1.23 (br, 18H), 2.80—4.95 (m, 13H)
GC-12	2920, 1030	0.86 (t, 3H), 1.24 (br, 20H), 2.75—5.00 (m, 13H)
GC-13	2920, 1035	0.87 (t, 3H), 1.23 (br, 22H), 2.70—4.95 (m, 13H)
GC-14	2920, 1030	0.88 (t, 3H), 1.23 (br, 24H), 2.80—4.93 (m, 13H)
GC-16	2920, 1030	0.87 (t, 3H), 1.23 (br, 28H), 2.85—5.00 (m, 13H)
GC-18	2920, 1030	0.90 (t, 3H), 1.23 (br, 32H), 2.90—4.96 (m, 13H)
GC-20	2920, 1030	0.87 (t, 3H), 1.23 (br, 36H), 2.85—4.98 (m, 13H)
GC-22	2920, 1030	0.85 (t, 3H), 1.21 (br, 40H), 2.80—4.90 (m, 13H)
GC-A3	2920, 1030	2.70—5.50 (m, 15H), 5.60—6.30 (m, 1H)
GC-A10	2925, 1030	1.30 (br, 12H), 1.79—2.30 (m, 2H), 2.80—5.20 (m, 15H), 5.20—6.10 (m, 1H)
GC-A11	2925, 1035	1.25 (br, 14H), 1.74—2.20 (m, 2H), 2.80—5.20 (m, 15H), 5.20—6.10 (m, 1H)
GC-A12	2925, 1030	1.25 (br, 16H), 1.72—2.20 (m, 2H), 2.80—5.20 (m, 15H), 5.20—6.10 (m, 1H)
GC-B10	2935, 1035	1.25 (br, 16H), 2.70—5.20 (m, 16H)
GC-B16	2935, 1040	1.23 (br, 28H), 2.70—5.20 (m, 16H)
GC-C10	2930, 1035	1.27 (br, 16H), 3.21 (s, 3H), 2.70—5.20 (m, 15H)
GC-C12	2935, 1035	1.23 (br, 20H), 3.20 (s, 3H), 2.70—5.10 (m, 15H)
AC-1	2950, 1040	3.53 (s, 3H), 3.10—4.20 (m, 6H), 4.70—5.20 (m, 1H)
AC-6	2950, 1040	0.90 (t, 3H), 1.34 (br, 8H), 3.10—4.18 (m, 8H), 4.60—5.20 (m, 1H)
AC-10	2935, 1035	0.90 (t, 3H), 1.28 (br, 16H), 3.10—4.30 (m, 8H), 4.50—5.10 (m, 1H)
AC-11	2940, 1035	0.88 (t, 3H), 1.28 (br, 18H), 3.10—4.20 (m, 8H), 4.50—5.10 (m, 1H)
AC-12	2945, 1035	0.88 (t, 3H), 1.28 (br, 18H), 3.10—4.20 (m, 8H), 4.65—5.10 (m, 1H)
AC-13	2930, 1030	0.88 (t, 3H), 1.24 (br, 22H), 3.10—4.20 (m, 8H), 4.60—5.10 (m, 1H)
AC-18	2940, 1030	0.88 (t, 3H), 1.24 (br, 32H), 3.10—4.20 (m, 8H), 4.60—5.10 (m, 1H)

a) Glucose derivatives measured in DMSO-d_6; allose derivatives measured in CD_3OD.

compounds. The results correlate farily well with those of *in vitro* bioassay. Next, the antimicrobial activity of monosaccharide derivatives synthesized in this study was examined. The assay was done by a disc method using bacteria and fungi. Three compounds, namely 3-*O*-tridecyl-(GC-13), 3-*O*-myristyl-D-glucose (GC-14) and 3-*O*-lauryl-D-allose (AC-12), were selected by the preliminary disc assay. It is interesting to note that the alkyl chain-length in all these three compounds is close to 12. However, not all of the alkyl compounds tested showed high antimicrobial activity, and MIC was over 12.5 mcg/ml.

Plant growth-inhibition studies by the *Avena* coleoptile straight growth test[9] were also performed with these alkyl monosaccharides. In sugar ester derivatives, the chain-length and location of the acyl group are critical for the plant growth-inhibitory activity.[9] More specifically, only 1-*O*-lauroyl-D-glucose had a high plant growth-inhibitory activity. 3-*O*-Alkyl-D-glucose derivatives were less active. Among them, two 3-*O*-alkenyl derivatives having an ω-methylene group showed more than 50% plant growth-inhibitory activity, and the other compounds tested in this study were not active. As regards antitumor activity, the result of *in vitro* bioassay is rather well correlated with the *in vivo* data, but it is of interest that the inhibitory effects against animal tumor cells were quite different from those against plant growth or cell growth.

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