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Synthesis of Poly-1-{3-O-[1-(benzyl-L-alanyl Carboxylate)ethyl]-D-glucos-6-O-carbonyl}-1-methylethylene

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ABSTRACT

Poly-1-{3-O-[1-(benzyl-L-alanyl carboxylate)ethyl]-D-glucos-6-O-carbonyl}-1-methylethylene was synthesized as the lipophilic and polymeric models of N-acetylmuramyl-L-alanyl-D-isoglutamine corresponding to the minimal structure required for the immunoadjuvant activity of bacterial cell wall. N-[2-(1,2-O-isopropylidene-6-O-methacryloyl-α-D-glucofuranos-3-O-yl)propionyl]-L-alanine benzyl ester was prepared from D-glucose through eight steps as a key monomer in the synthesis. The polymerization of that monomer was carried out in benzene at 50°C by using 2,2'-azobisisobutyronitrile as a radical initiator to give poly-1-{1,2-O-isopropylidene-3-O-[1-(benzyl-L-alanyl carboxylate)ethyl]-α-D-glucofuranos-6-O-carbonyl}-1-methylethylene. The removal of isopropylidene groups in this polymer was carried out by treatment with trifluoroacetic acid-water (6:1 v/v) to give the intended polymer. Characterizations of the polymers obtained were carried out.

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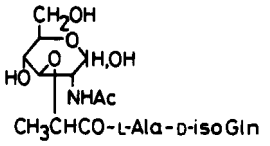
INTRODUCTION

Recently, Ellouz et al. [1] and Kotani et al. [2] reported independently that N-acetylmuramyl-L-alanyl-D-isoglutamine (MDP) was the minimal structure responsible for the immunoadjuvant activity elicited by peptidoglycan of the bacterial cell wall.



(MDP)

MDP can be used instead of mycobacterial cells in Freund's complete adjuvant which is the most used adjuvant consisting of heat-killed mycobacterial cells in mineral oil [3] to potentiate both B cell- and T cell-mediated immune responses [4, 5]. Although mycobacterium bovis Bacille de Calmette-Guerin (BCG) cell wall is highly effective in tumor immunotherapy, MDP has no effect which can suppress the growth of tumor [4]. One of the remarkable differences between such a cell wall and MDP is seen in the lack of lipophilicity in the latter, since the BCG cell wall is covered with a long-chain fatty acid (i.e., mycolic acid) on the surface [6]. Actually, it is clear by chemical modification of the primary hydroxy group of MDP that the antitumor effect of the cell wall might be attributed to the lipophilic character of the mycolic acid moiety connected with the adjuvant activity of muramyl peptide moiety [7]. Another marked difference of MDP from the cell wall can be recognized in the lack of polymeric character in the former because the main chain of the cell wall consists of such polymeric materials as peptidoglycan [6]. Several lipophilic or polymeric models have been designed from these standpoints in order to generate the antitumor ability of MDP [8-16]. As a new means of introducing both lipophilicity and polymeric character to the MDP molecule, it occurred to us that a lipophilic synthetic polymer containing the MDP units might be synthesized for this purpose. The investigation using pharmacologically active macromolecular compounds as drugs is a new area in polymer chemistry. The specific properties of polymeric materials in this field have been investigated [17, 18]. However, little attempt has been made to discuss the syntheses and the bioactivities of immunologically active polymers.

As the first stage of our work on the syntheses of a variety of polymeric and lipophilic models of MDP, we prepared the lipophilic vinyl-type polymer containing the simple analog of MDP instead of MDP itself and selected N-[2-(D-glucos-3-O-yl) propionyl]-L-alanine

(GPA) benzyl ester [10] and poly-(1-methylethylene) chain as a simple D-glucose analog of MDP and a lipophilic polymer backbone, respectively. For the present paper we synthesized poly-1-{3-O-[1-(benzyl-L-alanyl carboxylate)ethyl]-D-glucos-6-O-carbonyl}-1-methylethylene, in which GPA units and the poly-(1-methylethylene) chain are combined with ester bondings. The basic strategy of the synthesis was first adopted to prepare poly-1-{1,2-O-isopropylidene-3-O-[1-(benzyl-L-alanyl carboxylate)ethyl]-α-D-glucofuranos-6-O-carbonyl}-1-methylethylene by the polymerization of N-[2-(1,2-O-isopropylidene-6-O-methacryloyl-α-D-glucofuranos-3-O-yl)propionyl]-L-alanine benzyl ester and then to remove the isopropylidene groups by means of polymer reaction.

EXPERIMENTAL

Materials

Ethyl-2-bromopropionate, benzyl alcohol, triethylamine (TEA), methacrylic acid, and thionyl chloride were purified by distillation. 2,2'-Azobisisobutyronitrile (AIBN) was recrystallized three times from methanol. D-Glucose, sodium hydride (fine powder dispersed in mineral oil at 50% concentration), L-α-alanine, p-toluenesulfonic acid, dicyclohexylcarbodiimide (DCC), N-hydroxysuccinimide, hydroquinone, and trifluoroacetic acid (TFA) were of reagent commercial grade and used without further purification.

1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose (I) was prepared by the sulfuric acid catalyzed condensation of D-glucose with acetone according to Schmidt's method [20], mp 109.5-110.5°C (Ref. 20, mp 110°C).

L-Alanine benzyl ester tosyrate was prepared by the reaction of L-α-alanine with benzyl alcohol in the presence of p-toluenesulfonic acid according to the method of Izumiya et al. [22], mp 116.5-117.5°C, $[\alpha]_D^{22}$ -6.6° (c 1.0, water) (Ref. 21, mp 114°C, $[\alpha]_D^{18}$ -6.8° (c 2.0, water)).

Methacrylic anhydride was prepared by the reaction of methacrylic acid with thionyl chloride in the presence of TEA and hydroquinone according to the method of Brotherton et al. [23].

Other reagents were commercially supplied and purified by the usual methods.

Chromatography

The reactions were monitored by thin-layer chromatography (TLC) with Merck F_{254} silica gel plates which were developed with petroleum ether-1-buthanol (9:1 v/v) for Compounds I-IV and VIII and with 1-buthanol-ethanol-water (4:1:1 v/v) for Compounds V-VII.

The silica gel used for column chromatography was Wakogel C-300 supplied by Wako Pure Chemical Industries, Ltd.

Spectroscopic Measurements

Optical rotations were determined with a Union Digital PM-101 polarimeter. IR spectra were recorded on a JASCO A-202 spectrophotometer. Mass spectra were obtained on a JEOL JMS-01SG double-focusing mass spectrometer at 75 eV. ^{1}H-NMR spectra were measured with a JEOL JNM-PMX-60 spectrometer at 60 MHz using TMS as the internal reference. ^{13}C-NMR spectra were obtained on a JEOL JNM-PS-100 spectrometer equipped with a JNM-PFT-100 Fourier transform accessory. The molecular weight of the polymer was determined by light-scattering photometry with a Union LS-601 light-scattering photometer.

1, 2:5, 6-Di-O-isopropylidene-3-O-[1-(ethoxycarbonyl)ethyl]-α-D-glucofuranose (III)

Sodium hydride (1.6 g, 34 mmol, fine powder dispersed in mineral oil at 50% concentration) was added in portions to a solution of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (I) (6.0 g, 23 mmol) in dry tetrahydrofuran (THF; 40 mL) under dry nitrogen. After the initial vigorous reaction had subsided, the mixture was refluxed for 30 min with stirring. After ethyl 2-bromopropionate (15 mL, 120 mmol) was added to the solution cooled to room temperature, the reaction mixture was again refluxed for 6 h. Methanol was added dropwise onto the reaction mixture to decompose the excess sodium hydride, and then THF and methanol were evaporated under reduced pressure. The residual suspension was washed thoroughly with water and the organic layer was distilled to give an oily product, 7.9 g (95%), bp 154.0-154.5°C/2.0 mmHg.

IR (neat) showed absorption at 1742 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$) showed δ 1.28-1.4 (m, $6CH_3$, 18H); 4.67 (d, 1H, J = 4 Hz); and 5.77 ppm (t, H-1, 1H).

Analysis: Calculated for $C_{17}H_{28}O_8$: C, 56.65; H, 7.83%. Found: C, 56.48; H, 7.91%.

1, 2:5, 6-Di-O-isopropylidene-3-O-(1-carboxyethyl)-α-D-glucofuranose (IV)

1,2:5,6-Di-O-isopropylidene-3-O-[1-(ethoxycarbonyl)ethyl]-α-D-glucofuranose (III) (2.1 g, 5.7 mmol) was dispersed in 0.5 N sodium hydroxide solution (21 mL). The clear solution obtained by refluxing for 30 min was acidified to pH 1.5 by the careful addition of 1 N hydrochloric acid with stirring under ice-water cooling. The aqueous

solution was extracted with chloroform and the chloroform extract was dried over anhydrous sodium sulfate. The drying agent was filtered off and the filtrate was evaporated under reduced pressure. The residue was lyophilized to give the crude product as a heavy syrup, 1.8 g (95%). This compound was sufficiently pure to use in the next synthesis step.

IR (neat) showed absorption at 1735 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$) showed δ 1.28-1.41 (m, $5CH_3$, 15H); 4.69 (d, 1H, J = 4 Hz); 5.80 (t, H-1, 1H); and 8.90 ppm (s, COOH, 1H).

N-[2-(1,2:5,6-Di-O-isopropylidene-α-D-glucofuranos-3-O-yl)propionyl]-L-alanine Benzyl Ester (VI)

DCC (0.92 g, 4.5 mmol) was added to an ice-cooled solution of 1,2:5,6-di-O-isopropylidene-3-O-(1-carboxyethyl)-α-D-glucofuranose (IV) (1.5 g, 4.5 mmol) and N-hydroxysuccinimide (0.64 g, 5.6 mmol) in THF (45 mL). The reaction mixture was stirred in an ice bath for 3 h and at room temperature for 1 h. The N,N'-dicyclohexylurea formed was filtered off and washed with THF. Benzyl L-alaninate tosyrate (1.76 g, 5.0 mmol) and TEA (0.70 mL, 5.0 mmol) were added to the combined filtrate and the washings cooled in an ice bath. The mixture was stirred for 15 h at room temperature. The insoluble materials was filtered off and the solvent was evaporated under reduced pressure. The residual syrup was extracted with diethyl ether (70 mL) and the insoluble material was decanted off. After evaporation of ether, the syrupy residue was subjected to column chromatography on silica gel. Elution with n-hexane-benzene-methanol (24:16:1 v/v) afforded a product as a syrup. This product was dissolved in a minimum quantity of n-hexane and cooled to crystallize in needles, 1.0 g (45%), mp 92.5-93.0°C.

IR (KBr) showed the absorptions at 3300 (NH); 1730 (ester C=O); and 1656 cm^{-1} (amide C=O).

^{1}H-NMR ($CDCl_3$) showed δ 1.25-1.49 (m, $6CH_3$, 18H); 4.43 (d, 1H, J = 4 Hz); 5.13 (s, CH_2Ph, 2H); 5.74 (d, H-1, 1H, J = 4 Hz); and 7.83 ppm (s, Ph, 5H).

MS: m/e 493 (M^+); $[\alpha]_D^{30}$ -16.4° (c 0.50, methanol).

Analysis: Calculated for $C_{25}H_{35}NO_9$: C, 60.84; H, 7.15; N, 2.84%. Found: C, 60.43; H, 7.08; N, 2.87%.

N-[2-(1,2-O-Isopropylidene-α-D-glucofuranos-3-O-yl)propionyl]-L-alanine Benzyl Ester (VII)

0.2 N Sulfuric acid (100 mL) was added with stirring to the solution of N-[2-(1,2:5,6-di-O-isopropylidene-α-D-glucofuranos-3-O-yl)-propionyl]-L-alanine benzyl ester (VI) (8.0 g, 16 mmol) in 1-buthanol (60 mL) and the mixture was stirred at room temperature for 70 h.

The reaction mixture was neutralized sufficiently with barium carbonate and filtered. The filtrate was allowed to stand in a refrigerator overnight. The colorless needles formed were collected by filtration and washed thoroughly with water to give pure product (3.5 g). The combined filtrate and washings were evaporated under reduced pressure. The residual crystals were recrystallized from ethyl acetate-petroleum ether to give needles of product (2.5 g), total yield 6.1 g (82%), mp 144.5-145.5°C.

IR (KBr) showed the absorptions at 3500 (OH); 3350 (NH); 1720 (ester C=O); and 1640 cm^{-1} (amide C=O).

^{1}H-NMR ($CDCl_3$) showed δ 1.30-1.48 (m, $4CH_3$, 12H); 2.70 (s, OH, 1H); 5.17 (s, CH_2Ph, 2H); 5.87 (d, 1-H, 1H, J = 4 Hz); and 7.32 ppm (s, Ph, 5H).

MS: m/e 453 (M^+); $[\alpha]_D^{26}$ -16.0° (c 0.1, methanol).

Analysis: Calculated for $C_{22}H_{31}NO_9$: C, 58.27; H, 6.89; N, 3.09%. Found: C 58.09; H, 6.97; N, 3.18%.

N-[2-(1,2-O-Isopropylidene-6-O-methacryloyl-α-D-glucofuranos-3-O-yl)propionyl]-L-alanine Benzyl Ester (VIII)

Methacrylic anhydride (8.8 g, 57 mmol) was added to the solution of N-[2-(1,2-O-isopropylidene-α-D-glucofuranos-3-O-yl)propionyl]-L-alanine benzyl ester (VII) (5.2 g, 11 mmol) in dry pyridine, keeping the temperature at -20°C and then stirred at the same temperature for 1 h. The reaction mixture was allowed to warm to room temperature and continued to be stirred for 72 h. After a large amount of water was added onto the mixture to decompose the excess methacrylic anhydride, the mixture was extracted with chloroform and then the chloroform extract was washed thoroughly with water, 0.8% sulfuric acid solution, saturated sodium hydrogen carbonate solution, and water, and dried over anhydrous sodium sulfate. After the drying agents were filtered off, the filtrate was evaporated under reduced pressure in the presence of CuO as an inhibitor of polymerization. The last trace of pyridine was removed by repeated evaporations with diethyl ether and then the residue was subjected to column chromatography on silica gel. Elution with n-hexane-benzene-methanol (24:16:1 v/v) afforded a product as a syrup. Further purification of the syrup was carried out with silica gel column chromatography. Fractions containing only the main product (monitored with TLC) were collected and evaporated under reduced pressure to afford a colorless syrup, 5.2 g (87%).

IR (neat) showed the absorptions at 3400 (NH); 1720 (ester C=O); and 1660 cm^{-1} (amide C=O).

^{1}H-NMR ($CDCl_3$) showed δ 1.30-1.50 (m, $4CH_3$, 12H); 1.97 (s, $=CCH_3-$, 3H); 5.18 (s, CH_2Ph, 2H); 5.60 (s, $-CH=$, 1H); 5.92 (d, H-1, 1H, J = 4 Hz); 6.20 (s, $-CH=$, 1H); 7.09 (d, NH, 1H, J = 8 Hz); and 7.33 ppm (s, Ph, 5H).

$[\alpha]_D^{18}$ - 19.8° (c 1.0, chloroform).

Analysis: Calculated for $C_{26}H_{35}NO_{10}$: C, 59.88; H, 6.76; N, 2.68%. Found: C, 58.88; H, 6.79; N, 2.62%.

Polymerization of N-[2-(1,2-O-Isopropylidene-6-O-methacryloyl-α-D-glucofuranos-3-O-yl)propionyl]-L-alanine Benzyl Ester (VIII)

N-[2-(1,2-O-Isopropylidene-6-O-methacryloyl-α-D-glucofuranos-3-O-yl)propionyl]-L-alanine benzyl ester (VIII) was polymerized in benzene by using AIBN as an initiator. A solution of VIII (3.1 g, 6.0 mmol) in benzene (30 mL) and AIBN (4.9 mg, 3.0×10^{-2} mmol) were mixed in a glass tube. The tube was sealed in vacuo after thawing with nitrogen and kept at 50°C in a water bath. After 4 h the contents of the tube were poured into a large amount of n-hexane to precipitate the polymer. The polymer obtained was purified by reprecipitation from chloroform solution with n-hexane, 2.8 g (91%). The white powdery polymer obtained was soluble in benzene, chloroform, THF, and N,N'-dimethylformamide (DMF) but insoluble in n-hexane.

IR (KBr) showed the absorptions at 3400 (NH and OH); 1730 (ester C=O); and 1660 cm^{-1} (amide C=O).

^{1}H-NMR ($CDCl_3$) showed δ 0.60-1.83 (m, $5CH_3$, 15H); 5.17 (s, CH_2Ph, 2H); 5.90 (broad, H-1, 1H); and 7.33 ppm (s, Ph, 5H).

Weight-averaged molecular weight ($\overline{M}_w$) measured in THF by light-scattering photometry: 2.35×10^7.

$[\alpha]_D^{25}$ -12.2° (c 1.0, chloroform).

Analysis: Calculated for $(C_{26}H_{35}NO_{10})_n$: C, 59.88; H, 6.76; N, 2.68%. Found: C, 58.64; H, 6.68; N, 2.63%.

Acidic Removal of the Isopropylidene Groups in Poly-1-{1,2-O-isopropylidene-3-O-[1-(benzyl-L-alanyl Carboxylate)ethyl]-α-D-glucofuranos-6-O-carbonyl}-1-methylethylene (IX)

Polymer IX was dissolved in TFA-water (6:1 v/v) (3 mL) with stirring. After being stirred at room temperature for 30 min, TFA and water were removed in vacuo under ice-cooling. The resulting syrup dissolved in a small amount of acetone was poured into a large amount of benzene to precipitate the polymer as a white powder. The purification of the polymer was carried out by reprecipitation from acetone solution with benzene. Polymer X was soluble in acetone and DMF but insoluble in chloroform, benzene, methanol, and water.

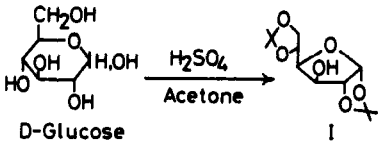
In its ^{1}H-NMR spectrum, the signal assigned to H-1 proton in

glucofuranoid structure at 5.90 ppm disappeared and the signal assigned to H-1 proton in glucopyranoid structure appeared at 5.00 ppm. Furthermore, the signals assigned to the protons in glucofuranoid frame were seen at 2.73-3.70 ppm.

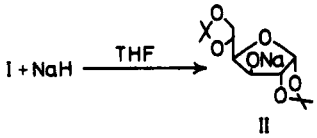
$[\alpha]_D^{25}$ +39.5° (c 0.4, acetone, after 24 h).

RESULTS AND DISCUSSION

The synthesis of N-[2-(1,2-O-isopropylidene-6-O-methacryloyl-α-D-glucofuranos-3-O-yl)propionyl]-L-alanine benzyl ester (VIII) was performed through the reaction steps shown in Eqs. (1)-(8).



(1)



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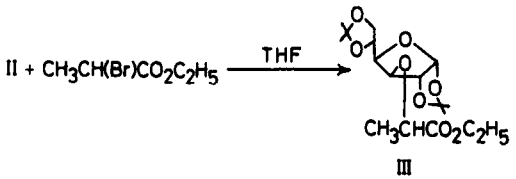

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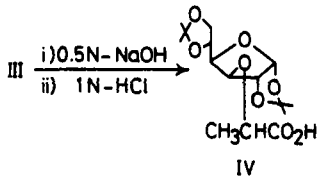
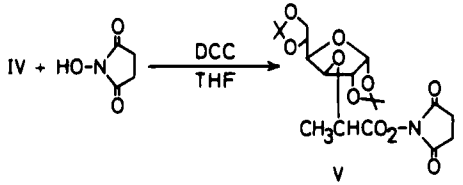


(4)

The starting material (I) was prepared by a conventional method [20]. The isopropylidene group was selected as the protection group of D-glucose to be able to remove simultaneously under mild acidic condition at the final synthetic step. The treatment of I with sodium



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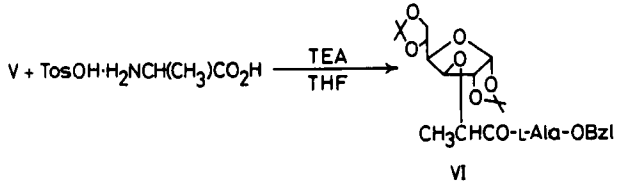

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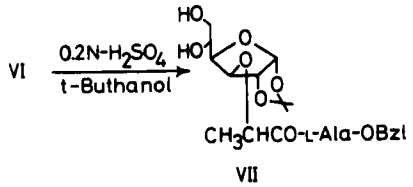

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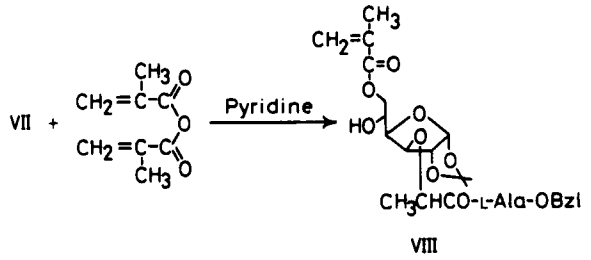


(8)

hydride in dry THF afforded a corresponding alcoholate (II). Alkylation of II with ethyl 2-bromopropionate gave the ester compound (III) in good yield as an oily liquid with high boiling point, which was hydrolyzed by 0.5 N sodium hydroxide solution to give the corresponding acid (IV) in 95% yield.

Coupling of IV with benzyl L-alaninate was conducted by the active ester method which was first examined for coupling of muramic acid with peptides by Shiba et al. [24]. The 1-succinimidyl ester (V) obtained by using DCC as a condensing agent was allowed to react with benzyl L-alaninate to give VI in 45% yield. Its structure was confirmed by elemental analysis, ^{1}H-, and ^{13}C-NMR spectra, in

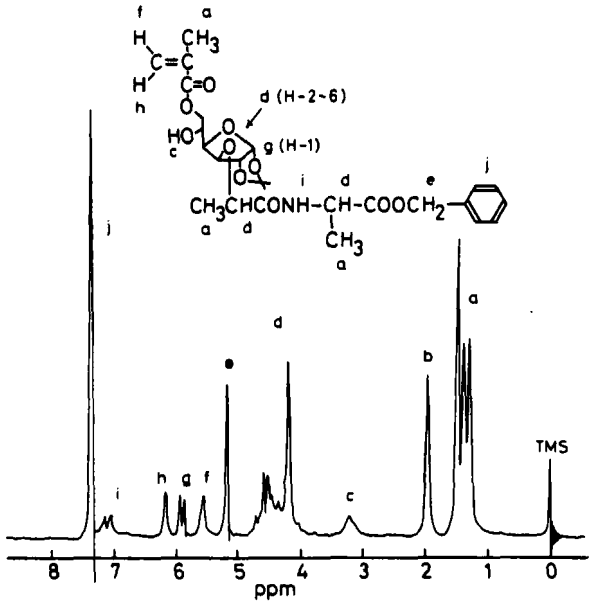


FIG. 1. ^{1}H-NMR spectrum of Monomer VIII. Reference: TMS. Solvent: $CDCl_3$.

which signals attributed to the alanine and the glucose residues were clearly observed. The acidic removal of the 5,6-isopropylidene group in VI was carried out with 0.2 N sulfuric acid in 1-buthanol. Although other kinds of alcohol instead of 1-buthanol could be used, they caused ester exchanged products to form. Thus, their removal required a laborious process. We have also found that the treatment of VI with 0.2 N sulfuric acid in the absence of alcohol afforded N-[2-(D-glucos-3-O-yl)propionyl]-L-alanine benzyl ester which has a pyranoid structure due to the complete deprotection of glucose residue in VI [19]. Thus, VI was treated with 0.2 N sulfuric acid in 1-buthanol at room temperature to afford VII in good yield.

Methacryloylation of VII was carried out by reaction with methacrylic anhydride in pyridine at -20°C-room temperature. Methacryloylation of the primary hydroxyl group occurred almost exclusively, so that 6-O-monomethacrylate (VIII) was isolated by the chromatographic technique in 87% yield as a colorless heavy syrup which was freely soluble in many organic solvents such as chloroform, benzene, methanol, and DMF, but insoluble in water. When VII was treated with methacryloyl chloride under similar conditions, the required product was obtained in low yield. Its structure was identified by means of IR, ^{1}H-NMR (Fig. 1), ^{13}C-NMR (Fig. 2) spectra,

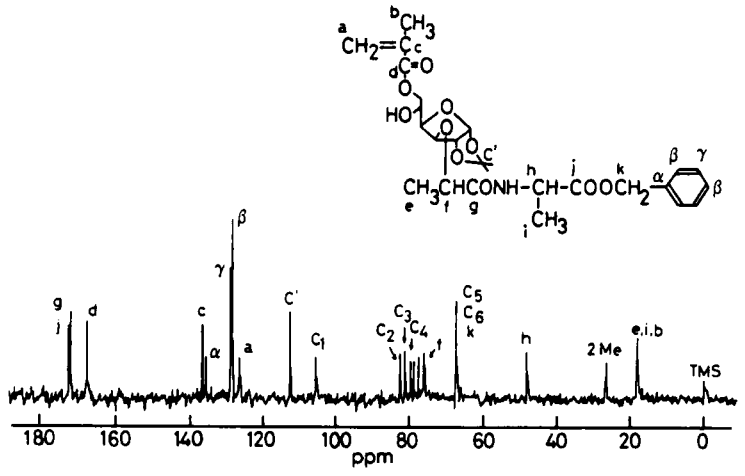
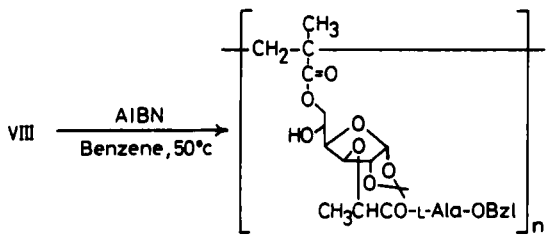


FIG. 2. ^{13}C-NMR spectrum of Monomer VIII. Reference: TMS. Solvent $CDCl_3$.

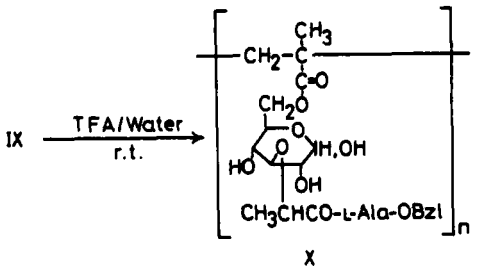
and elemental analysis. These spectral and analytical data were entirely consistent with the proposed structure.

The reaction route from VIII to poly-1-{3-O-[1-(benzyl-L-alanyl carboxylate)ethyl]-D-glucos-6-O-carbonyl}-1-methylethylene (X) is expressed in Eqs. (9) and (10).



(9)

The polymerization of VIII was carried out in benzene at 50° C for 4 h by using AIBN as an initiator to give a white polymer in good yield. The signals at 5.60 and 6.20 ppm, assigned to two kinds of proton of the vinyl group and recognized in the ^{1}H-NMR spectrum of the monomer, disappear clearly in that of the polymer (Fig. 3). In spite of the very bulky pendant group of VIII, a polymer of very high molecular weight was obtained. Polymer IX was soluble in chloroform, benzene, THF, and DMF, but insoluble in water and n-hexane.



(10)

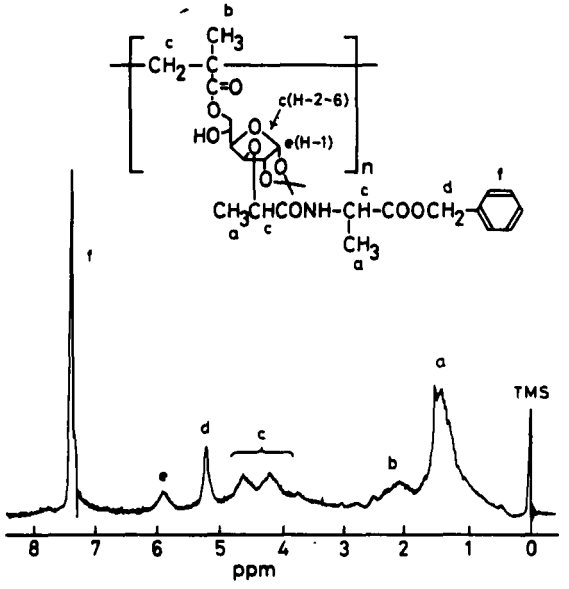


FIG. 3. ^{1}H-NMR spectrum of Polymer IX. Reference: TMS. Solvent: $CDCl_3$.

Acidic removal of the isopropylidene groups in Polymer IX was performed with TFA-water (6:1-3:1 v/v) to convert the glucofuranoid structure into the glucopyranoid structure. For the removal of the isopropylidene groups, the sulfuric acid method was not applicable because of degradation at pendant moiety.

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REFERENCES

[1] F. Ellouz, A. Adam, R. Ciorbaru, and E. Lederer, Biochem. Biophys. Res. Commun., 59, 1317 (1974)
[2] S. Kotani, Y. Watanabe, F. Kinoshita, T. Shimono, I. Morisaki, T. Shiba, S. Kusumoto, Y. Tarumi, and K. Ikenaka, Biken J., 18, 105 (1975).
[3] J. Freund, Adv. Tuber. Res., 7, 130 (1956).
[4] I. Azuma, K. Sugimura, T. Taniyama, M. Yamawaki, Y. Yamamura, S. Kusumoto, S. Okada, and T. Shiba, Infect. Immun., 14, 18 (1976).
[5] F. Audibrrt, L. Chedid, P. Lefracier, and J. Choay, Cell. Immunol., 21, 243 (1976).
[6] I. Azuma, Y. Yamamura, and K. Fukushi, J. Bacteriol., 96, 1885 (1968).
[7] T. Shiba, S. Okada, S. Kusumoto, I. Azuma, and Y. Yamamura, Bull. Chem. Soc. Jpn., 51, 3307 (1978).
[8] A. Hasegawa, H. Okumura, M. Kiso, I. Azuma, and Y. Yamamura, Agric. Biol. Chem., 44, 1309 (1980).
[9] Y. Yamamura, I. Azuma, K. Sugimura, M. Yamawaki, M. Uemiya, S. Kusumoto, S. Okada, and T. Shiba, Proc. Jpn. Acad., 53, 63 (1977).
[10] S. Kobayashi, T. Fukuda, and Y. Yukimasa, Bull. Chem. Soc. Jpn., 53, 2917 (1980).
[11] S. Kobayashi, T. Fukuda, I. Imada, M. Fujino, I. Azuma, and Y. Yamamura, Chem. Pharm. Bull., 21, 3193 (1979).
[12] M. Inage, M. Imoto, Y. Kambayashi, S. Kusumoto, and T. Shiba, Tetrahedron Lett., p. 3767 (1980).
[13] S. Kusumoto, K. Yamamoto, and T. Shiba, Ibid., p. 4407 (1978).
[14] P. L. Durette, E. P. Meitzner, and T. Y. Shen, Carbohydr. Res., 77, C1 (1979).
[15] M. Kiso, Y. Kaneda, R. Shimizu, and A. Hasegawa, Ibid., 83, C8 (1980).
[16] P. L. Durette, E. P. Meitzner, and T. Y. Shen, Tetrahedron Lett., p. 4013 (1979).
[17] H. Ringsdorf, J. Polym. Sci., Polym. Symp. Ed., 51, 135 (1975).
[18] L. G. Donaruma and O. Vogl (eds.), Polymeric Drugs, Academic, New York, 1978.
[19] H. Chikashita and T. Ouchi, J. Heterocycl. Chem., 19, 981 (1982).
[20] O. T. Schmidt, Methods Carbohydr. Chem., 2, 318 (1963).
[21] N. Izumiya and S. Sakazumi, Nippon Kagaku Zasshi, 78, 662 (1957).
[22] N. Izumiya and S. Sakazumi, Ibid., 78, 1768 (1957).
[23] T. K. Brotherton, J. Smith, and J. W. Lynn, J. Org. Chem., 26, 1283 (1961).
[24] S. Kusumoto, Y. Tarumi, K. Ikenaka, and T. Shiba, Bull. Chem. Soc. Jpn., 49, 533 (1976).

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