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Synthesis of sulfated octadecyl ribo-oligosaccharides with potent anti-AIDS virus activity by ring-opening polymerization of a 1,4-anhydroribose derivative

YoonSoung Choi [a], Takashi Yoshida [b,*], Toru Mimura [c], Yutaro Kaneko [c], Hideki Nakashima [d], Naoki Yamamoto [e], Toshiyuki Uryu [a,1]

[a] *Institute of Industrial Science, University of Tokyo, Roppongi, Minato-ku, Tokyo 106, Japan*
[b] *Division of Biological Sciences, Graduate School of Science, Hokkaido University, Kita-ku, Sapporo 060, Japan*
[c] *Ajinomoto Company, Inc., Chuo-ku, Tokyo 108, Japan*
[d] *Yamanashi Medical University School of Medicine, Yamanashi 409-38, Japan*
[e] *Tokyo Medical and Dental University School of Medicine, Bunkyo-ku, Tokyo 113, Japan*

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Abstract

The synthesis and anti-AIDS virus activity of sulfated octadecyl ribofuranans with medium-range molecular weights have been investigated. Selective ring-opening polymerization of 1,4-anhydro-2,3-di-*O*-benzyl-α-D-ribopyranose with 10–20 mol% of boron trifluoride etherate as a catalyst in a large amount of dichloromethane gave 2,3-di-*O*-benzyl-(1 → 5)-α-D-ribofuranan in good yield. The molecular weight of the benzylated ribofuranan was in the range of 9×10^3 to 10×10^3. Debenzylation of the polymer followed by acetylation gave peracetylated (1 → 5)-α-D-ribofuranans. The peracetylated ribofuranans were treated with octadecyl alcohol and a stannic chloride catalyst to afford acetylated ribofuranans having octadecyl groups at the reducing terminal. The molecular weights of the resulting acetylated octadecyl ribofuranans were below 9×10^3. Sulfation of the deacetylated octadecyl ribofuranans by piperidine-*N*-sulfonic acid in dry Me_2SO gave sulfated octadecyl ribofuranans with molecular weights of 3×10^3 to 9×10^3 and sulfur contents of 13.0–16.2%. The sulfated octadecyl ribofuranans had potent anti-AIDS virus

* Corresponding author.
[1] Also corresponding author.

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activity, EC_{50} = 0.6–2.5 μg/mL (a standard curdlan sulfate showed EC_{50} = 0.43 μg/mL), and low anticoagulant activity, 4–17 units/mg (a standard dextran sulfate, 22.7 unit/mg). Structural analysis of the ribofuranans was performed by NMR at 400 and 600 MHz.

Keywords: Ring-opening polymerization; Oligosaccharide; Sulfated alkyl ribofuranan; Anti-AIDS virus activity; High resolution NMR

1. Introduction

We have reported that sulfated polysaccharides obtained by sulfation of synthetic and natural polysaccharides show potent inhibitory effects against the AIDS virus (human immunodeficiency virus, HIV) infection [1]. Among them, sulfated (1 → 5)-α-D-ribofuranan [2] and (1 → 4)-β-D-ribopyranan [3] completely inhibited the infection of AIDS virus to T-lymphocytes in concentrations as low as 3.3 μg/mL. However, they also displayed high anticoagulant activity, a deleterious side effect. We also found that curdlan sulfates exhibited high anti-HIV activity and low side effects [4,5]. The phase I/II testing, i.e., toxicity testing, of the curdlan sulfate as a potential AIDS drug has been carried out for AIDS virus carriers in the USA since December 1992. Recently, it was reported that intravenous injection of curdlan sulfate in HIV-infected patients induced short-term, dose-related increases in CD4 lymphocytes [6]. The anti-AIDS virus activity of sulfated polysaccharides was first discovered with dextran sulfate [7]. In contrast to curdlan sulfate, dextran sulfate was found to cause severe side effects and no remedial effects after both intravenous and oral administrations to AIDS virus carriers [8].

Recently, we reported that sulfated alkyl oligosaccharides had high anti-HIV activity [9–11]. For example, a sulfated dodecyl laminarapentaoside showed high anti-AIDS virus activity, EC_{50} = 0.2 μg/mL, a value nearly equal to that of curdlan sulfate. Although sulfated oligosaccharides lacking alkyl groups showed low anti-AIDS virus activites, sulfated alkyl oligosaccharides obtained by bonding a long alkyl group at the reducing terminal of a sulfated oligosaccharide exhibited high anti-HIV activity. These sulfated alkyl oligosaccharide have structures and properties similar to surface-active agents.

Various kinds of high-molecular-weight stereoregular polysaccharides have been prepared by selective ring-opening polymerization of anhydro sugars [12].

In this study, we report the synthesis of anti-AIDS virus-active sulfated octadecyl (1 → 5)-α-D-ribofuranans with molecular weights of ~ 4000–5000, employing an extension of the ring-opening polymerization method. First, (1 → 5)-α-D-ribofuranans with medium-range molecular weights were synthesized by the selective ring-opening polymerization of 1,4-anhydro-2,3-di-*O*-benzyl-α-D-ribopyranose, followed by debenzylation. Peracetylated (1 → 5)-α-D-ribofuranans were treated with octadecyl alcohol to provide octadecyl peracetylated ribofuranans. After deacetylation, octadecyl ribofuranans were sulfated to give sulfated octadecyl ribofuranans. We report high anti-AIDS virus activities and low blood anticoagulant activties of the sulfated octadecylribofuranans.

2. Experimental

Monomer.—1,4-Anhydro-2,3-di-*O*-benzyl-α-D-ribopyranose (**1**) was synthesized by pyrolysis of D-ribose followed by benzylation according to the previously described method [13].

Polymerization.—1,4-Anhydro-2,3-di-*O*-benzyl-α-D-ribopyranose (**1**, 1.0 g) was polymerized by $BF_3 \cdot OEt_2$ (10–20 mol%) in dichloromethane (10 mL) under high vacuum in the temperature range of −20 to −60 °C. After termination of the reaction by the addition of MeOH, the polymer solution in $CHCl_3$ was successively washed with 10% $NaHCO_3$ solution and water several times, dried (Na_2SO_4), and finally concentrated to a syrup. The syrupy polymer was purified by reprecipitation using the MeOH–$CHCl_3$ system three times and then freeze-dried from benzene. A white powdery polymer, 2,3-di-*O*-benzyl-(1 → 5)-α-D-ribofuranan, was obtained; yield 0.76–0.90 g.

Debenzylation.—To 80 mL of liquid NH_3 containing 0.7 g of Na was dropwise added a solution of poly-**1** (0.88 g) in 10 mL of dimethoxyethane at −78 °C under N_2. After 1 h of stirring at −78 °C, anhyd NH_4Cl was added until the dark blue color disappeared, and then a small amount of MeOH was added. After evaporation of the NH_3, water was added. The aqueous solution was washed with $CHCl_3$ and dialyzed with deionized water for 1 day. Finally (1 → 5)-α-D-ribofuranan was isolated by freeze-drying from water; yield 0.24 g.

Acetylation.—(1 → 5)-α-D-Ribofuranan (0.21 g) was added to a hot (120 °C) and vigorously stirred solution of NaOAc (1.8 g) in Ac_2O (80 mL). The solution was stirred for 1.5 h at 120 °C, and then cooled to room temperature. After evaporation off the excess of Ac_2O, the acetylated polymer was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water several times and dried (Na_2SO_4). Acetylated ribofuranan was isolated by freeze-drying from benzene; yield 0.21 g.

Glycosylation.—Peracetylated (1 → 5)-α-D-ribofuranan (0.2 g) was treated with dry octadecyl alcohol (0.3 g) and 20 mol% of stannic chloride as catalyst in CH_2Cl_2 (5 mL) for 2 h at 50 °C under high vacuum, according to the same technique as the polymerization already described. The mixture was extracted with $CHCl_3$–water. The $CHCl_3$ layer was washed with deionized water several times, dried (Na_2SO_4), and evaporated. The resulting product was purified by reprecipitation using $CHCl_3$ and hexane at least three times and then freeze-dried from benzene; yield 0.15 g; degree of alkylation 88%.

Deacetylation.—To a saturated solution of NH_3 in MeOH (40 mL) was added the peracetylated octadecyl (1 → 5)-α-D-ribofuranan (0.14 g). The mixture was stirred for 48 h at room temperature to provide octadecyl (1 → 5)-α-D-ribofuranan, which was purified by dissolving in MeOH followed by precipitation from acetone. A white solid polymer was obtained; yield 0.09 g.

Sulfation.—A solution of octadecyl (1 → 5)-α-D-ribofuranan (0.09 g) in Me_2SO (20 mL) was stirred for 2 h at 80 °C with pyridine-*N*-sulfonic acid (0.76 g). The mixture was cooled to room temperature, and then neutralized with suitable amounts of $NaHCO_3$, and then the mixture was dialyzed with deionized water at room temperature for more

than 24 h. Nacali Cellulose Dialyzer Tubing VT-801 was used for dialysis. The sulfated octadecyl ribofuranan was then obtained by freeze-drying from water; yield 0.09 g.

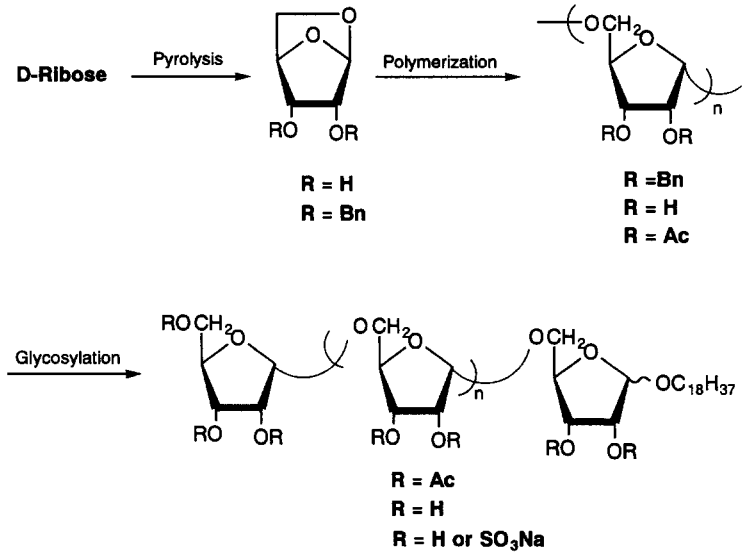
Anti-HIV assay.—The anti-AIDS virus activity of sulfated octadecyl ribofuranan was determined by the MTT method using MT-4 cells and $HIV_{HTLV\text{-}IIIB}$ virus [14]. MT-4 cells were infected with HIV at a multiplicity of 0.01. Next the HIV- or mock-infected MT-4 cells (1.5×10^5 cells/mL, respectively) were incubated for 5 days at 37 °C in the presence of various concentrations of the sulfated octadecyl ribofuranan. The cell viability was measured spectrophotometrically, and monitored the ability of viable cells to reduce 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) to a blue-colored formazan product. The activity was represented as EC_{50}, namely the concentration of the test compound that protected 50% of the HIV infection. The cytotoxicity is denoted as CC_{50}, which corresponds to the 50% cytotoxic concentration of the sulfated octadecyl ribofuranan against MT-4 cells.

Anticoagulant activity.—Anticoagulant activity was determined by the modified method of the United States Pharmacopoeia using bovine plasma [15]. Dextran sulfate (Meito Sangyo Co. Ltd, H-039) was used as a reference compound with an anticoagulant activity of 22.7 units/mg.

Characterization.—^{1}H NMR (600 or 400 MHz) spectra were recorded for solutions in D_2O or $CDCl_3$ by means of a Jeol EX-600 or -400 spectrometer. Me_4Si or DSS was used as the internal standard. The number-average molecular weight of water-soluble or THF-soluble polymers was estimated by gel-permeation chromatography (column: TOSOH TSK-gel, G2500PW, G3000PW, 7.5×600 mm$^2 \times 2$; eluent, 66.7 mmol of phosphate buffer, pH 6.86, or TOSOH TSK-gel, G3000HXL, G4000HXL, G5000HXL, 7.5×600 mm$^2 \times 3$) with standard pullulan (Shodex Standard P-82) or standard polystyrene (Shodex Standard SM-105) as a reference. Specific rotations were measured in $CHCl_3$ or water at 25 °C by a Perkin–Elmer 241 polarimeter in a 1-dm cell (10-cm length).

3. Results and discussion

Synthesis of octadecyl (1 → 5)-α-D-ribofuranan having medium-range molecular weight.—For this study, a low-molecular-weight benzylated ribofuranan is necessary for synthesizing medium-sized alkyl ribofuranan. Thus, the polymerization of **1** was carried out by changing molecular weight-controlling factors such as concentration of catalyst, the amount of solvent, polymerization temperature, and time. The synthetic route for the sulfated octadecyl (1 → 5)-α-D-ribofuranan is illustrated in Scheme 1. It was reported previously that the selective ring-opening polymerization of 1,4-anhydro-2,3-di-*O*-benzyl-α-D-ribopyranose (**1**) takes place rapidly through 1,5-scission to provide high-molecular-weight 2,3-di-*O*-benzyl-(1 → 5)-α-D-ribofuranan [13,17]. The result of polymerizations and the properties of the polymers are summarized in Table 1. When the polymerization was carried out with a large quantity (10–20 mol%) of $BF_3 \cdot OEt_2$ as catalyst in 10–20 mol% of monomer concentration at −20 °C, polymers were obtained in high yields (> 76%). The molecular weight was relatively low, in the range of 0.9×10^4 to 2.6×10^4. However, polymerizations at low temperatures produced poly-



Scheme 1. Synthesis of sulfated octadecyl ribofuranan with medium-range molecular weight.

mers of considerably higher molecular weight (Nos. 4 and 6). It was also found that the polymerization conditions, such as low monomer concentration, high catalyst concentration, and long polymerization time, caused the formation of low-molecular-weight polymers because the ring-opening polymerization has the nature of an equilibrium polymerization. The specific rotations of the polymers obtained by $BF_3 \cdot OEt_2$ ranged from +101 to +145°. From the results of NMR measurements, those polymers having high positive specific rotations had a stereoregular $(1 \rightarrow 5)$-α furanosidic structure. However, those polymers having somewhat lower specific rotations (below +128°) had

Table 1
Ring-opening polymerization of 1,4-anhydro-2,3-di-*O*-benzyl-α-D-ribopyranose (**1**) [a]

No.	Catalyst (mol%)	Temp (°C)	CH_2Cl_2 (mL)	Time (h)	Yield (%)	$\bar{M}_n$ [b] ($\times 10^4$)	$[\alpha]_D^{25}$ [c] (deg)	α-content [d] (%)
1	$BF_3 \cdot OEt_2$ (10)	−20	5	15	89	2.6	+101	90
2	$BF_3 \cdot OEt_2$ (10)	−20	10	24	88	1.0	+128	100
3	$BF_3 \cdot OEt_2$ (15)	−20	10	24	76	0.9	+110	95
4	$BF_3 \cdot OEt_2$ (15)	−40	10	24	93	5.1	+138	100
5	$BF_3 \cdot OEt_2$ (20)	−20	10	24	90	0.9	+125	99
6	$BF_3 \cdot OEt_2$ (20)	−60	10	3	82	14.0	+145	100
7	PF_5 (5)	−40	1	0.5	88	4.6	+121	99
8	PF_5 (10)	−40	1	1	82	4.0	+111	95

[a] Monomer: 1.0 g.
[b] Determined by GPC.
[c] Measured in $CHCl_3$ (*c* 1%).
[d] Calculated from ^{13}C NMR spectrum.

Table 2
Deprotection of 2,3-di-*O*-benzyl-(1 → 5)-α-D-ribofuranans [a]

No.	Poly-**1**		Free-OH ribofuranan			
	(g)	$\overline{M}_n$ ($\times 10^3$)	yield		$\overline{M}_n$ [b] ($\times 10^3$)	$[\alpha]_D^{25}$ [c] (deg)
			(g)	(%)		
1	0.90	7	0.23	64	6	+128
2	0.87	11	0.29	80	10	+127
3	0.82	9	0.22	63	5	+122
4	0.88	10	0.24	65	5	+125

[a] Conditions: liq. NH_3, 70–80 mL; Na, 0.7–0.8 g; temp, −78 °C; time, 1 h.
[b] Determined by GPC.
[c] Measured in water (*c* 1%).

not exclusively the (1 → 5)-α configuration, but had mixed structures composed of (1 → 5)-α furanosidic and small proportions (5–10%) of (1 → 4)-β-pyranosidic or (1 → 5)-β-furanosidic units. Those polymers of lower molecular weights tended to show lower specific rotations.

Since the purpose of the polymerization was to prepare polymers of molecular weight around 1.0×10^4, we anticipated degradation of the polymers during polymerization by large amounts of $BF_3 \cdot OEt_2$ catalyst and solvent at higher temperatures. Under the polymerization conditions used here, it was difficult to obtain completely (1 → 5)-α furanosidic stereoregular polymers having low molecular weights.

On the other hand, the polymerization of **1** by phosphorus pentafluoride catalyst at −40 °C gave polymers with relatively higher molecular weights (4.0×10^4 and 4.6×10^4). However, their specific rotations ranged from +111 to +121°, indicating that the polymers had mixed structures containing a small proportion of β units and a high proportion of (1 → 5)-α units. Accordingly, the polymers prepared by $BF_3 \cdot OEt_2$ catalysis were adopted for the following reaction steps.

Removal of the benzyl groups from benzylated ribofuranans with the molecular weights of 7×10^3 to 11×10^3 was carried out by sodium in liquid ammonia. The results are summarized in Table 2. Water-soluble, free (1 → 5)-α-D-ribofuranans with molecular weights of 5×10^3 to 10×10^3 were obtained in good yields.

The ribofuranans with relatively low molecular weights had somewhat lower specific rotations, +122 to +128°. Conditions forming a ribofuranan with the target molecular weight (below 10×10^3) were thus established. The 600 MHz ^1H NMR spectrum of unsubstituted (1 → 5)-α-D-ribofuranan (No. 1 in Table 2) is shown in Fig. 1A, small signals appeared at 3.6 and 5.2 ppm probably correspond to H-5 and H-1 peaks of the β anomer. The assignment of the absorptions was performed by H–H and C–H COSY measurements.

In order to bind a long-chain alkyl group to the reducing end of peracetylated ribofuranan, the medium-range molecular weight ribofuranan was acetylated with acetic anhydride–sodium acetate. This acetylation method should produce acetylated ribofuranans with a relatively higher proportion of the β anomer at the reducing end, as required for the next step. In glycosylation with an alcohol having a long alkyl chain the

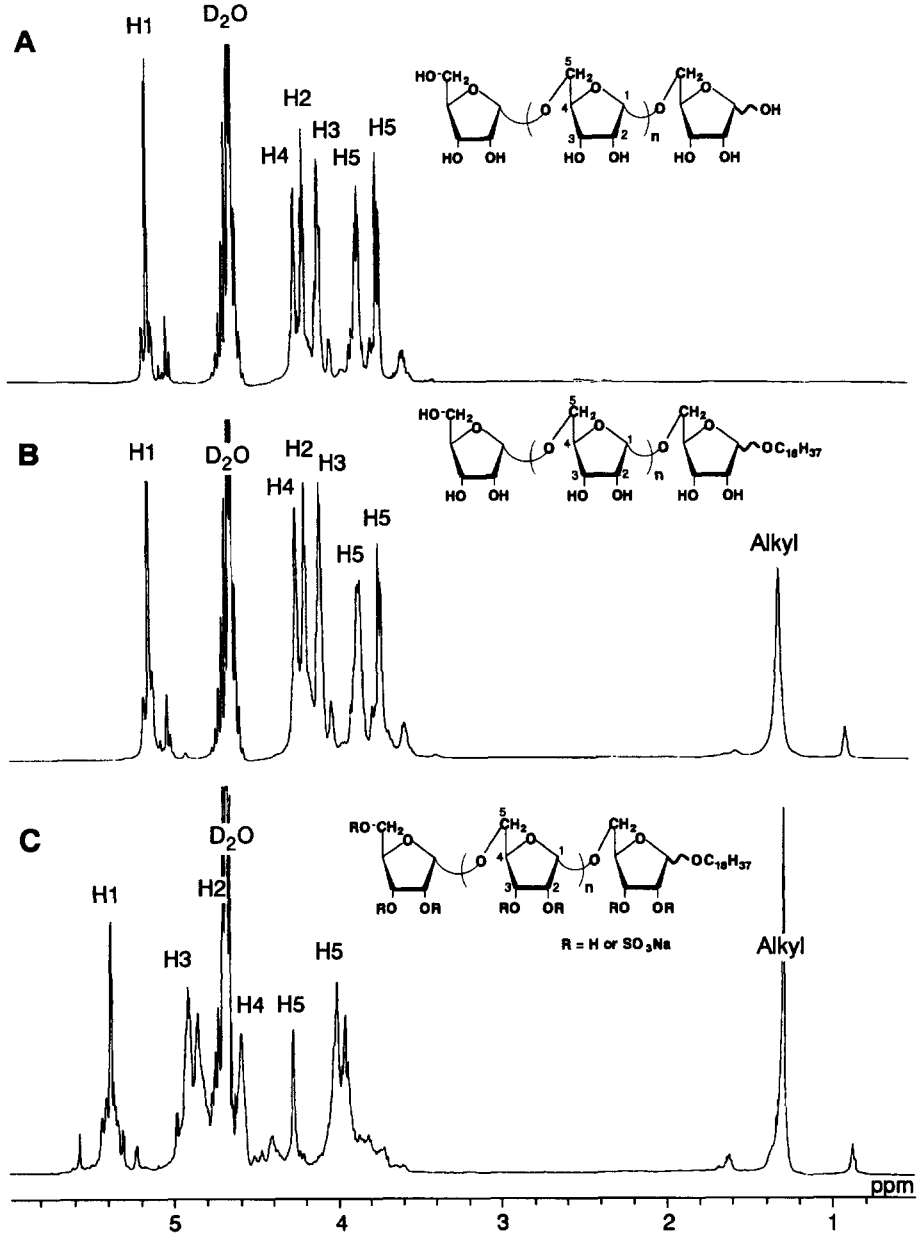


Fig. 1. 600 MHz ^{1}H NMR spectra of (A) free-OH ribofuranan ($\overline{M}_n = 0.5\times10^4$, $[\alpha]_D^{25}$ +125° (*c* 1, H_2O)), (B) octadecyl ribofuranan ($\overline{M}_n = 0.5\times10^4$, $[\alpha]_D^{25}$ +122° (*c* 1, H_2O); degree of alkylation 88%), and (C) sulfated octadecyl ribofuranan ($\overline{M}_n = 0.6\times10^4$, $[\alpha]_D^{25}$ +123° (*c* 1, H_2O); S 15.6%) (D_2O as solvent at 40 °C).

Table 3
Glycosylation of acetylated ribofuranan with *n*-octadecyl alcohol [a]

No.	Acetylated ribofuranan		Octadecyl alcohol	Catalyst (mol%)	Yield	$\overline{M}_n$ [b]	$[\alpha]_D^{25}$ [c]	Degree of glycosylation [d]
	(g)	$\overline{M}_n$ ($\times 10^3$)	(g (mmol))	to sugar unit	(g)	($\times 10^3$)	(deg)	(%)
1	0.12	8	0.11 (0.41)	20	0.07	5	+127	91
2	0.14	8	0.21 (0.78)	20	0.09	7	+121	73
3	0.20	7	0.30 (1.11)	20	0.15	5	+123	99
4	0.20	6	0.30 (1.11)	15	0.08	4	+121	83
5	0.20	6	0.30 (1.11)	15	0.07	3	+119	99
6	0.20	7	0.30 (1.11)	10	0.06	4	+127	78
7	0.25	13	0.37 (1.37)	20	0.08	9	+133	68
8	0.30	9	0.45 (1.66)	20	0.07	6	+135	88
9	0.32	10	0.50 (1.85)	20	0.08	6	+138	81

[a] Conditions: CH_2Cl_2, 5 mL; temp, 50 °C; $SnCl_4$, 10–20 mol%.
[b] Determined by GPC.
[c] Measured in $CHCl_3$.
[d] Calculated from ^1H NMR spectrum.

β-glycoside is much more reactive than the α anomer [10,11]. The peracetylated ribofuranans had molecular weights of 6×10^3 to 13×10^3 and specific rotations of +127 to +141°.

The acetylated ribofuranan was treated with octadecyl alcohol and stannic chloride catalyst to give acetylated octadecyl ribofuranan having the octadecyl group at the reducing terminal in good yields. The results are summarized in Table 3. It was found that main-chain scission of the acetylated ribofuranan occurred during the reaction, and the desired molecular weights of 3×10^3 to 9×10^3 were attained. As shown in Fig. 2, the 400 MHz ^1H NMR spectrum of acetylated octadecyl ribofuranan exhibits the presence of a small CH_3 absorption at 0.9 ppm and a large CH_2 absorption at 1.25 ppm, indicating attachment of the octadecyl group to the ribofuranan. The degree of glycosylation was estimated by comparing the integrated values of H-1 of the ribofuranan and the methylene groups (32 H) in the alkyl chain as the following equation:

$$\text{degree of glycosylation}\,(\%) = \frac{\text{integration value of methylene group}}{(\text{integration value of H-1}/\overline{\text{dp}}_n) \times 32} \times 100$$

where the average degree of polymerization ($\overline{\text{dp}}_n$) was calculated from the molecular weight of the acetylated octadecyl ribofuranans.

Deacetylation of the acetylated octadecyl ribofuranans with ammonia-saturated methanol gave octadecyl ribofuranans in 71–83% yields. The ^1H NMR spectrum exhibited the disappearance of the acetyl group at 2.1 ppm and the presence of the alkyl group, as shown in Fig. 1B.

Preparation of sulfated octadecyl ribofuranans.—Octadecyl ribofuranans were sulfated with piperidine-*N*-sulfonic acid in dry Me_2SO to give sulfated octadecyl ribofuranans with high degrees of sulfation in good yields (Table 4). The molecular weight of sulfated octadecyl ribofuranans was in the range of 3×10^3 to 9×10^3 which was near

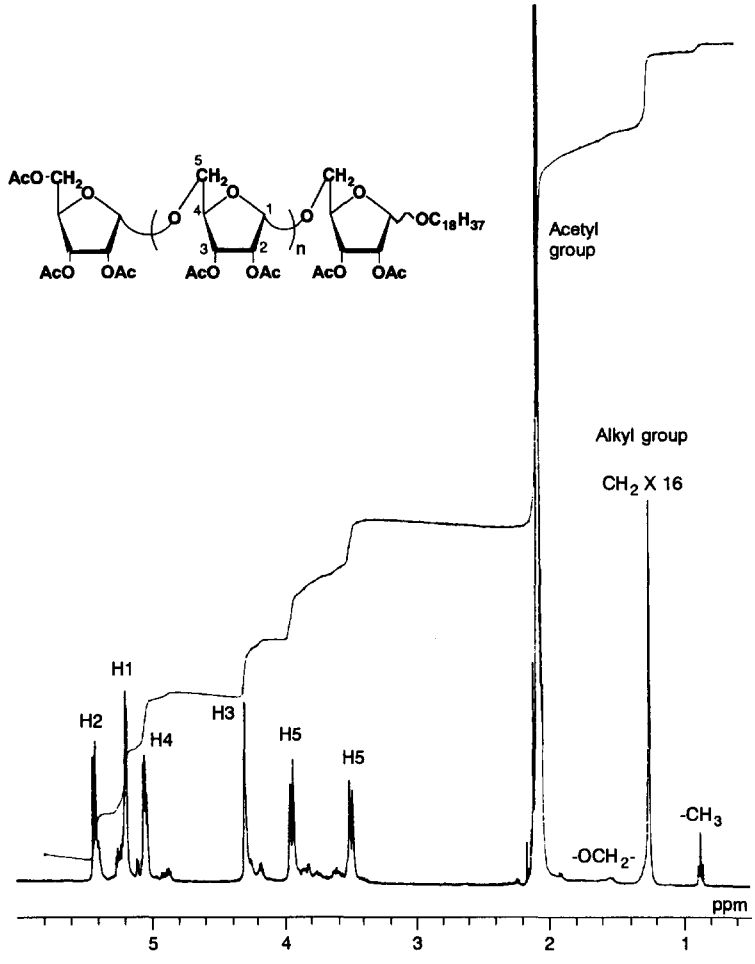


Fig. 2. 400 MHz ^{1}H NMR spectrum of acetylated octadecyl ribofuranan ($CDCl_3$ as solvent) ($\overline{M}_n = 0.6 \times 10^4$, $\overline{dp}_n = 26.7$, $[\alpha]_D^{25} +135°$ (*c* 1, $CHCl_3$); degree of alkylation 88%).

the target molecular weight (4×10^3 to 5×10^3). No degradation by the sulfating reagent occurred during sulfation. NMR measurements (Fig. 1C) and elementary analysis indicated that no cleavage of the alkyl chain occurred in the sulfated octadecyl ribofuranans, and the degree of sulfation was high (1.4 to 1.7). When the sulfur trioxide–pyridine complex was used as the sulfating reagent, the resulting polysaccharide sulfate decomposed, and the degree of sulfation was low.

Anti-AIDS virus and anticoagulant activities of sulfated alkyl ribofuranans.—Anti-AIDS virus activity of the sulfated octadecyl ribofuranans was measured by using MT-4 cells and $HIV_{HTLV\text{-}IIIB}$ virus, as described previously [14]. As shown in Table 5, the anti-AIDS virus activities of the sulfated octadecyl ribofuranans were high. For Nos. 1 and 3 having a molecular weight of 6×10^3, the EC_{50} value was 0.6 μg/mL, almost

Table 4
Sulfation of alkyl ribofuranan [a]

No.	Alkyl ribofuranan		PSA [b] (g)	Sulfated octadecyl ribofuranan					
	(g (mmol))	$\overline{M}_n$ ($\times 10^3$)		yield (g)	$\overline{M}_n$ ($\times 10^3$)	elemental analysis (%)			DS [c]
						C	H	S	
1	0.07 (0.49)	8	1.0	0.11	9	21.5	3.5	15.8	1.5
2	0.04 (0.30)	8	0.8	0.07	8	20.3	3.6	15.5	1.6
3	0.10 (0.76)	5	0.8	0.18	9	22.6	3.6	16.2	1.5
4	0.13 (0.98)	8	1.0	0.13	7	20.3	3.8	15.7	1.7
5	0.10 (0.76)	5	0.7	0.10	6	22.4	3.0	15.6	1.5
6	0.09 (0.68)	2	0.7	0.09	3	21.6	3.2	15.2	1.7
7	0.04 (0.30)	4	0.4	0.05	6	23.8	3.5	13.0	1.4

[a] Conditions: solvent, Me_2SO 20 mL; temp, 80 °C; time, 1.5 h.
[b] Piperidine-*N*-sulfonic acid.
[c] Degree of sulfation (DS).

comparable to the activity of highly active curdlan sulfate, i.e., $EC_{50} = 0.43$ μg/mL. The enhancement effect by the alkyl group was confirmed in the case of No. 5, which has a degree of alkylation of 21% and shows a low activity, EC_{50} 13.0 μg/mL. On the other hand, a non-alkylated sulfated ribofuranan with molecular weight 9×10^3 (No. 7) exhibited the same EC_{50} of 0.6 μg/mL. Therefore, the attachment of the octadecyl

Table 5
Anti-HIV and anticoagulant activities of sulfated octadecyl ribofuranan

No.	Sulfated alkyl ribofuranan				EC_{50} [a] (μg/mL)	CC_{50} [b] (μg/mL)	Anticoagulant activity [c] (unit/mg)
	$\overline{M}_n$ ($\times 10^3$)	$\overline{dp}_n$ [d]	S content (%)	Degree of alkylation (%)			
1	6	20	15.7	98	0.6	> 1000	11
2	8	27	15.5	90	1.9	> 1000	13
3	6	20	15.6	88	0.6	> 1000	4
4	3	10	15.2	85	2.5	> 1000	7
5	7	24	15.6	21	13.0	> 1000	12
6	6	20	13.0	0	68.6	> 1000	14
7	9	30	14.7	0	0.6	> 1000	17
RS [e]	17		17.6	0	3.3 [f]	> 1000	56
CS [g]	79 [h]		14.1	0	0.43	> 1000	

[a] 50% Effective concentration.
[b] 50% Cytotoxic concentration.
[c] Dextran sulfate H-039, 22.7 units/mg.
[d] Degree of polymerization calculated by the $\overline{M}_w$/molecular weight of sugar unit.
[e] Sulfated ribofuranan.
[f] Minimum effective concentration for 100% inhibition of the AIDS virus infection.
[g] Standard curdlan sulfate.
[h] Weight-average molecular weight.

group to the sulfated ribofuranan with a low molecular weight of 6×10^3 caused an increase in the anti-AIDS virus activity to the level of activity of a relatively high-molecular-weight (9×10^3) sulfated ribofuranan without the alkyl group.

In general, such sulfated polysaccharides as dextran sulfate demonstrate blood anticoagulant activities, which is a severe and undesirable side effect in an anti-AIDS virus drug [16]. We assayed the anticoagulant activity in vitro by using bovine plasma according to a modified procedure of the United States Pharmacopoeia [15]. Table 5, which summarizes the result of anticoagulant activity measurements, shows that the anticoagulant activity of sulfated octadecyl ribofuranans was low, 4–13 unit/mg, whereas that of sulfated ribofuranan with high molecular weight was 56 unit/mg.

In conclusion, sulfated octadecyl oligoribofuranans with high anti-AIDS virus activity and low anticoagulant activity have been synthesized. We found that an alkyl chain at the reducing end of the ribofuranan is important for the high anti-AIDS virus activity. This is the first report on the synthesis of an oligosaccharide derivative with a high anti-AIDS virus activity by the ring-opening polymerization of an anhydro sugar derivative.

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