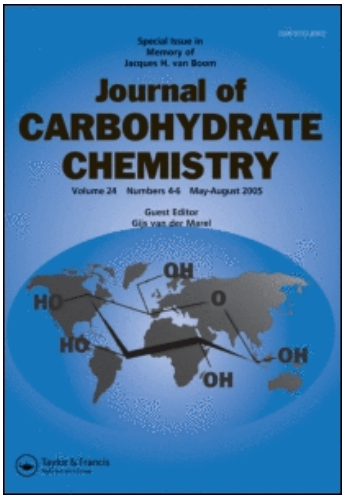


Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

An Efficient Synthesis of Sulfo Lewis X Analog Containing 1-Deoxynojirimycin

Hirotsugu Ogawa[a]; Yasunari Harada[a]; Yohsuke Kyotani[a]; Toshihiro Ueda[a]; Satoru Kitazawa[a]; Kazuhisa Kandori[a]; Takashi Seto[a]; Kohichi Ishiyama[a]; Masahiko Kojima[a]; Tadaaki Ohgi[a]; Yohji Ezure[a]; Masahiro Kise[a]

[a] Discovery Research Lab. II, Nippon Shinyaku Co., Ltd., Kyoto, Japan

To cite this Article Ogawa, Hirotsugu , Harada, Yasunari , Kyotani, Yohsuke , Ueda, Toshihiro , Kitazawa, Satoru , Kandori, Kazuhisa , Seto, Takashi , Ishiyama, Kohichi , Kojima, Masahiko , Ohgi, Tadaaki , Ezure, Yohji and Kise, Masahiro(1998) 'An Efficient Synthesis of Sulfo Lewis X Analog Containing 1-Deoxynojirimycin', Journal of Carbohydrate Chemistry, 17: 4, 729 — 738

To link to this Article: DOI: 10.1080/07328309808002348

URL: http://dx.doi.org/10.1080/07328309808002348

J. CARBOHYDRATE CHEMISTRY, 17(4&5), 729-738 (1998)

AN EFFICIENT SYNTHESIS OF SULFO LEWIS X ANALOG CONTAINING 1-DEOXYNOJIRIMYCIN[1]

Hirotsugu Ogawa,* Yasunari Harada, Yohsuke Kyotani, Toshihiro Ueda, Satoru Kitazawa, Kazuhisa Kandori, Takashi Seto, Kohichi Ishiyama, Masahiko Kojima, Tadaaki Ohgi, Yohji Ezure and Masahiro Kise

Discovery Research Lab. II, Nippon Shinyaku Co., Ltd., Nishioji-hachijyo, Minami-ku, Kyoto 601-8550, Japan

Final Form March 2, 1998

ABSTRACT

Sulfo Lewis[x] analog containing 1-deoxynojirimycin (**13**) has been efficiently synthesized. Glycosidation of ethyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-fucopyranoside (**5**) with *O*-(2,6-di-*O*-benzoyl-3,4-isopropylidene-β-D-galactopyranosyl)-(1→4)-2,6-di-*O*-benzoyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-glucitol (**4**), prepared from *O*-β-D-galactopyranosyl-(1→4)-1,5-dideoxy-1,5-imino-D-glucitol (**1**) *via* 3 steps, and subsequent acid hydrolysis of the isopropylidene group gave the desired trisaccharide diol derivative (**7**) in good yield. Compound **7** was easily converted into 3'-*O*-sulfo Lewis[x] analog (**13**) *via* 6 steps in high yield.

INTRODUCTION

The selectins are a family of cell adhesion molecules and play important roles in the adhesion and migration of leukocyte to the site of inflammation. The natural ligand recognized by selectins was identified as the sialyl Lewis[x] (sLe^x)[2-4] tetrasaccaride. And it was shown that 3'-*O*-sulfo Lewis[x] (sulfo Le^x)[5] was also recognized by selectins. SLe^x related compounds are considered to have a potency inhibiting leukocytes' adhe-

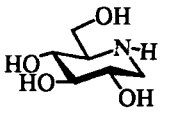
sion to selectins and to be candidates as anti-inflammatory agents.[6-9] Many groups have been developing the synthesis of sLe^x and sulfo Le^x derivatives.[10-13]

Hasegawa et al.[14,15] reported the syntheses of sLe^x, sLe^a, sulfo Le^x and sulfo Le^a analogs, containing *N*-alkylated-1-deoxynojirimycin, as novel carbohydrate inhibitors of selectin binding. These compounds are of great interest for their biological activities, and *N*-substituents of 1-deoxynojirimycin (DNJ) part are considered to be important to the strength of activity.

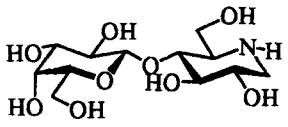
For the synthesis of sulfo Le^x derivatives with various *N*-substituents, it is considered that free sulfo Le^x analog containing DNJ (**13**) is a key compound. We have recently reported the enzymatic synthesis of *O*-β-D-galactopyranosyl-(1→4)-1-deoxynojirimycin (**1**) and its positional isomers.[16] A transgalactosylation from lactose to 1-deoxynojirimycin was accomplished by using β-galactosidase from *Bacillus circulans*. We describe herein an efficient synthesis of sulfo Le^x analog containing 1-deoxynojirimycin (**13**) using **1** as a starting compound.

RESULTS AND DISCUSSION

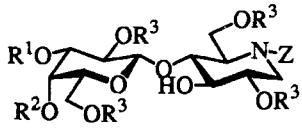
Treatment of *O*-β-D-galactopyranosyl-(1→4)-1,5-dideoxy-1,5-imino-D-glucitol[16] (**1**) with benzyloxycarbonyl chloride in the presence of sodium hydrogen carbonate in chloroform and water afforded the *N*-benzyloxycarbonyl derivative **2**. 3',4'-*O*-Isopropylidenation of **2** was done using 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid monohydrate in *N*,*N*-dimethylformamide (DMF) to give **3** in 60.8 % yield. Treatment of **3** with benzoyl chloride (5 equiv) in pyridine for 2 h at -40 ℃ gave the desired product **4** in 68.8 % yield. The structure of **4** was confirmed from 2D ^{1}H NMR spectra. The significant signals of the compound **4** were as follows. Twenty five aromatic protons at δ 7.03-8.12 showed that four Bz groups were introduced. Two CH protons were downshifted at δ 5.06 (m) and δ 5.37 (t, J = 7.8 Hz), which were identified as H-2 and H-2', respectively. The signal of H-3 was found at δ 4.10, indicating that the C-3 hydroxyl group was not benzoylated. These results showed that C-2,6,2',6' hydroxyl groups of **3** were selectively benzoylated. Nashed et al.[17] have reported the regioselective benzoylation of 3',4'-*O*-isopropylidene lactoside derivatives. Our result was in good agreement with Nashed's. The reactivity



1-Deoxynojirimycin (DNJ)

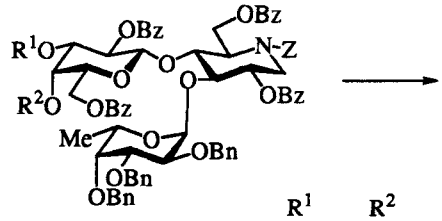


1

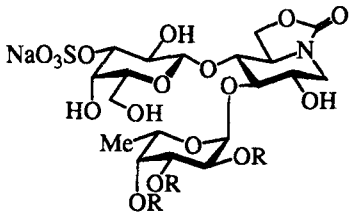


	R^1	R^2	R^3
2	H	H	H
3	isopropylidene		H
4	isopropylidene		Bz

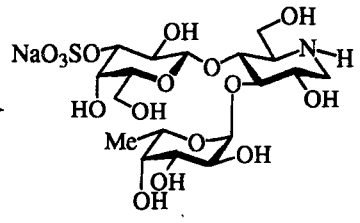
5



	R^1	R^2
6	isopropylidene	
7	H	H
8	$=CCH_3(OCH_3)$	
9	H	Ac
10	SO_3H•Pyr	Ac



11 R = Bn
12 R = H



13

Z = benzyloxycarbonyl
Bz = benzoyl
Bn = benzyl

Scheme

* Compound **1** is efficiently synthesized by β-galactosidase from *Bacillus circulans*.[16]

of the C-3 hydroxyl group of **3** may be low due to steric hindrance or to formation of an intramolecular hydrogen bond between the C-3 hydroxyl group and ring oxygen (C-5) of the galactose residue.

The glycosylation of **4** with ethyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-fucopyranoside[18] (**5**) in dichloromethane for 30 min at -40 ℃ in the presence of *N*-iodosuccinimide (NIS),[19] trimethylsilyl trifluoromethanesulfonate (TMSOTf) and powdered molecular sieves 4Å gave a crude fully protected trisaccharide derivative **6**, which was directly used in the next reaction without purification. The isopropylidene group of **6** was removed by treatment with aq HCl in 1,4-dioxan at 60 ℃, to give the desired trisaccharide diol derivative **7** in 74.9 % yield. This compound (**7**) could be easily isolated by crystallization from ethyl acetate-hexane without chromatography. Significant signals in the ^{1}H NMR of **7** (DMSO-d_6, at 60 ℃) were at δ 0.97 (d, 3H, $J_{5,6}$ = 5.1 Hz, H-6 of Fuc), 5.09 (d, 1H, $J_{1,2}$ = 3.3 Hz, H-1 of Fuc), 5.21 (dd, 1H, $J_{1,2}$ = 8.1 Hz, $J_{2,3}$ = 9.6 Hz, H-2 of Gal) and 6.91-7.96 (m, 40H, 8Ph), indicating the structure assigned. When the ^{1}H NMR of **7** was recorded at room temperature in $CDCl_3$ or DMSO-d_6, the peaks were broad and it was difficult to assign the signals.

The diol derivative **7** was converted into **11** *via* four steps. Treatment of **7** with i) trimethyl orthoacetate (exess) and D,L-camphor-10-sulfonic acid (0.2 equiv to **7**) in benzene [3',4'-*O*-(1-methoxy)ethylidene formation (compound **8**)], ii) aq acetic acid in tetrahydrofuran [acid hydrolysis of 3',4'-*O*-(1-methoxy)ethylidene into monoacetate derivative **9**], iii) sulfur trioxide pyridine complex (6.5 equiv to **7**) in pyridine [sulfation of compound **9** into compound **10**] and iv) sodium methoxide in methanol gave **11** in 90.3 % yield from **7**. In each of the steps i)-iii), the reaction proceeded almost quantitatively, and the obtained crude products were used in the next reaction. In step iv), *O*-acyl protecting groups were removed, the pyridinium salt of the sulfo group was exchanged into a sodium salt, and cyclic carbamate was formed between the C-6 hydroxyl group and *N*-benzyloxycarbonyl group of DNJ, accompanied by the elimination of benzyl alcohol under basic conditions. Significant signals in the ^{1}H NMR of **11** were δ 1.15 (d, 3H, $J_{5,6}$ = 6.6 Hz,H-6 of Fuc), 4.22 (m, 2H, H-3,4 of Gal), 4.45 (d, 1H, $J_{1,2}$ = 7.4 Hz, H-1 of Gal), 5.58 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1 of Fuc), 7.23-7.44 (m, 15H, 3Ph). In the FAB-MS spectra, the molecular ion peak was observed at *m/z* 846 $(M-Na)^-$. These data supported the structure of **11**.

Catalytic hydrogenolysis (10% Pd-C) of the benzyl groups of **11** in aq methanol and subsequent ring opening of cyclic carbamate with aq NaOH in methanol at 100 ℃ gave the desired sulfo Le^x analog containing DNJ (**13**) in 94.9 % yield. Significant signals in the ^1H NMR of **13** were δ 1.20 (d, 3H, $J_{5,6}$ = 6.6 Hz, H-6 of Fuc), 2.84 (dd, 1H, $J_{1ax,1eq}$ = 12.6 Hz, $J_{1ax,2}$ = 10.8 Hz, H-1*ax* of DNJ), 3.35 (dd, 1H, $J_{1eq,2}$ = 4.8 Hz, H-1*eq* of DNJ), 4.33 (dd, 1H, $J_{2,3}$ = 9.9 Hz, $J_{3,4}$ = 3.3 Hz, H-3 of Gal), 4.58 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1 of Gal), 5.43 (d, 1H, $J_{1,2}$ = 3.9 Hz, H-1 of Fuc). In the FAB-MS spectra, the $(M-Na)^-$ ion peak was observed at *m/z* 550. These data supported the structure of **13**.

In conclusion, we efficiently synthesized the desired sulfo Le^x analog containing DNJ (**13**) from **1** in 11 steps in 26.8% overall yield (average yield in each step ca. 88 %). In this synthetic route, column chromatography was performed only three times. We consider a large scale production of sulfo Le^x analog containing DNJ is possible by this method.

EXPERIMENTAL

General methods. Melting points were determined with a Buchi 510 apparatus and are uncorrected. Specific rotations were measured at 20 ℃ using a HORIBA SEPA polarimeter. ^1H NMR spectra were recorded with Varian Unity plus 300 or Varian Gemini 2000 spectrometer. The FAB-mass spectra were recorded with a JEOL JMS-SX 102. Elemental analyses were performed on Yanako CHN coda MT-5 instrument. Electrodialysis was done using a Micro Acilyzer S1 (Asahi Chemical Industry Co. Ltd.) with a separating membrane in an Aciplex cartridge AC-110-20. Column chromatography was performed using Wakogel C-300 (Wako chemical Co. Ltd.) with the solvent system specified. Concentrations were carried out below 40 ℃ under reduced pressure.

***O*-(3,4-*O*-Isopropylidene-β-D-galactopyranosyl)-(1 → 4)-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-glucitol (3).** To a suspension of *O*-β-D-galactopyranosyl-(1→4)-1,5-dideoxy-1,5-imino-D-glucitol[16] (**1**, 15.0 g, 46.1 mmol) and $NaHCO_3$ (4.92 g, 60 mmol) in H_2O (150 mL) and chloroform (150 mL) was added dropwise benzyloxycarbonyl chloride (Z-Cl, 16.5 mL, 115 mmol) at 0 ℃. The

mixture was stirred vigorously overnight at room temperature, and then neutralized with 2N HCl. The water layer was washed twice with chloroform (150 mL x 2) and concentrated to dryness. *N*,*N*-Dimethylformamide (DMF) was added to the residue, and the insoluble mass was filltered. The filtrate was concentrated to give a crude syrup of *O*-β-D-galactopyranosyl-(1→4)-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-glucitol (**2**), which was used for the next reaction without purification. To a solution of crude **2** in DMF (150 mL) were added 2,2-dimethoxypropane (11.34 mL, 92.2 mmol) and *p*-toluenesulfonic acid monohydrate (1.75 g, 9.2 mmol), and the mixture was stirried for 2 h at 60 ℃. The reaction mixture was neutralized with triethylamine while cooling, and then concentrated. Column chromatography (ethyl acetate:methanol = 20:1) on silica gel (500 g) gave **3** (14.0 g, 60.8 %) as an amorphous mass: $[\alpha]_D$ -6.4° (*c* 1.0, H_2O); ^1H NMR (200 MHz, DMSO-d_6 + D_2O) δ 1.37, 1.23 (2s, 6H, Me_2C), 4.22 (d, 1H, $J_{1',2'}$ = 7.8 Hz, H-1'), 5.04 (dd, 2H, CO_2CH_2), 7.27-7.41 (m, 5H, Ph).

Anal. Calcd for $C_{23}H_{33}NO_{11}\cdot 0.5\ H_2O$: C, 54.32; H, 6.74; N, 2.75. Found: C, 54.33; H, 6.97; N, 2.81.

***O*-(2, 6-Di-*O*-benzoyl-3, 4-*O*-isopropylidene-β-D-galactopyranosyl)-(1→4)-2, 6-di-*O*-benzoyl-*N*-benzyloxycarbonyl-1, 5-dideoxy-1, 5-imino-D-glucitol (4).** To a solution of **3** (5.0 g, 10 mmol) in pyridine (50 mL) was added dropwise benzoyl chloride (5.88 mL, 50.7 mmol) at -40 ℃, and the mixture was stirred for 2 h at -40 ℃. Methanol (10 mL) was added to the mixture, and the reaction mixture was concentrated. The resulting residue was extracted with dichloromethane, and the extract was successively washed with aq HCl, aq $NaHCO_3$, and H_2O, then dried over Na_2SO_4 and concentrated. Column chromatography (ethyl acetate:hexane = 1:2) on silica gel (250 g) gave **4** (6.31 g, 68.8 %) as an amorphous mass: $[\alpha]_D$ -11.9° (*c* 0.54, chloroform); ^1H NMR (300 MHz, $CDCl_3$) δ 1.36, 1.64 (2s, 6H, Me_2C), 3.34 (dd, 1H, $J_{1,2}$ = 3.6 Hz, $J_{1ax,1eq}$ = 15.6 Hz, H-1*ax*), 3.81 (t, 1H, $J_{3,4} = J_{4,5}$ = 9.0 Hz, H-4), 4.10 (m, 2H, H-3,5), 4.28 (m, 4H, H-1*eq*,4',5',6a), 4.45 (dd, 1H, H-3'), 4.49 (m, 2H, H-6b,6'a), 4.73 (d, 1H, $J_{1',2'}$ = 7.8 Hz, H-1'), 4.82 (dd, 1H, $J_{5',6b'}$ = 3.0 Hz, $J_{6a',6b'}$ = 12.0 Hz, H-6'b), 4.97 (t, 1H, CO_2CH_2), 5.06 (m, 1H, H-2), 5.37 (t, 1H, $J_{2',3'}$ = 7.8 Hz, H-2'), 7.03-8.12 (m, 25H, 5Ph).

Anal. Calcd for $C_{51}H_{49}NO_{15}$: C, 66.88; H, 5.39; N, 1.53. Found: C, 66.44; H, 5.27; N,1.59.

***O*-(2,6-Di-*O*-benzoyl-β-D-galactopyranosyl)-(1 → 4)-[*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-(1→3)]-2,6-di-*O*-benzoyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-glucitol (7).** To a solution of **4** (30.0 g, 32.8 mmol) and ethyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside[18] (**5**, 23.5 g, 49.1 mmol) in dichloromethane (300 mL) was added molecular sieves 4Å (60 g). The mixture was stirred for 2 h at room temperature under argon gas and then cooled to -40 ℃. *N*-Iodosuccinimide (12.2 g, 54.2 mmol) and trimethylsilyl trifluoromethanesulfonate (0.95 mL, 4.92 mmol) were added to the mixture, and the mixture was stirred for 30 min at -40 ℃, filtered, and then washed with dichloromethane. The combined filtrate and washings were successively washed with aq $NaHCO_3$ and aq $Na_2S_2O_3$, then dried over Na_2SO_4 and concentrated, to give crude trisaccharide **6**. To a solution of crude **6** in 1,4-dioxan (500 mL) was added 2N HCl (100 mL), and the mixture was stirred for 2 h at 60 ℃. The reaction mixture was concentrated to about one-third volume and extracted with ethyl acetate. The extract was successively washed with aq $NaHCO_3$ and H_2O, then dried over Na_2SO_4 and concentrated. Crystallization from ethyl acetate and hexane gave **7** (31.7 g, 74.9 % based on **4**): mp 182-183 ℃; $[\alpha]_D$ -58° (*c* 1.0, chloroform); ^1H NMR (300 MHz, DMSO-d_6, at 60 ℃) δ 0.97 (d, 3H, $J_{5,6}$ = 5.1Hz, H-6 of Fuc), 4.94 (m, 3H, H-1 of Gal and CO_2CH_2), 5.09 (d, 1H, $J_{1,2}$ = 3.3 Hz, H-1 of Fuc), 5.21 (dd, 1H, $J_{1,2}$ = 8.1 Hz, $J_{2,3}$ = 9.6 Hz, H-2 of Gal), 6.91-7.96 (m, 40H, 8Ph).

Anal. Calcd for $C_{75}H_{73}NO_{19}$: C, 69.59; H, 5.84; N, 1.08. Found: C, 69.44; H, 5.71; N, 1.42.

***O*-(3-*O*-Sulfo-β-D-galactopyranosyl)-(1 → 4)-[*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-(1 → 3)]-*N*,6-*O*-carbonyl-1,5-dideoxy-1,5-imino-D-glucitol, sodium salt (11).** To a suspension of **7** (20.0 g, 15.5 mmol) in benzene (750 mL) were added trimethyl orthoacetate (35 mL) and D,L-camphor-10-sulfonic acid (0.36 g, 1.55 mmol), and the mixture was stirred for 2 h at room temperature. The reaction mixture was successively washed with aq $NaHCO_3$ and H_2O, then dried over Na_2SO_4 and concentrated to give crude orthoester derivative **8**. To a solution of crude **8** in tetrahydrofuran (450 mL) was added aq 80% acetic acid (300 mL), and the mixture was stirred for 1.5 h at room temperature. The reaction mixture was concentrated and the remaining trace of acetic acid was removed by coevaporation with

toluene, to give a crude monoacetate derivative **9**. To a solution of crude **9** in pyridine (400 mL) was added sulfur trioxide pyridine complex (16.0 g, 101 mmol), and the mixture was stirred for 15 h at room temperature. Methanol (150 mL) was added, and the mixture was concentrated. Ethyl acetate was added to the residue, and the precipitate was filtered off and washed with ethyl acetate. The combined filtrate and washings were washed with brine, dried over Na_2SO_4 and then concentrated, to give a crude sulfo derivative **10**. To a solution of crude **10** in methanol (300 mL) was added 28% sodium methoxide / methanol (40 mL), and the mixture was stirred for 15 h at room temperature. After cooling the reaction mixture to 0 ℃ and adjusting the pH to 8 with 2N HCl, the reaction mixture was concentrated. Column chromatography (dichloromethane:methanol = 10:1) on silica gel (400 g) gave **11** (12.2 g, 90.3 %) as an amorphous mass: $[\alpha]_D$ -56° (*c* 1.1, methanol); ^{1}H NMR (200 MHz, CD_3OD) δ 1.15 (d, 3H, $J_{5,6}$ = 6.6 Hz, H-6 of Fuc), 2.79 (dd, 1H, $J_{1ax,1eq}$ = 12.4 Hz, $J_{1ax,2}$ = 9.8 Hz, H-1*ax* of DNJ), 4.22 (m, 2H, H-3,4 of Gal), 4.45 (d, 1H, $J_{1,2}$ = 7.4 Hz, H-1 of Gal), 5.58 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1 of Fuc), 7.23-7.44 (m, 15H, 3Ph); FAB-MS *m/z* 846 $(M\text{-}Na)^-$.

Anal. Calcd for $C_{40}H_{48}NO_{17}SNa{\cdot}2H_2O$: C, 53.03; H, 5.79; N, 1.55. Found: C, 53.10; H, 5.92; N, 1.75.

***O*-(3-*O*-Sulfo-β-D-galactopyranosyl)-(1→4)-[*O*-α-L-fucopyranosyl-(1→3)]-1,5-dideoxy-1,5-imino-D-glucitol, sodium salt (13).** A solution of **11** (2.70 g, 3.10 mmol) in methanol (80 mL) and H_2O (8 mL) was stirred for 15 h at 35 ℃ under H_2 gas in the presence of 10% Pd/C (2.0 g). The precipitate was filtered off and washed with methanol. The combined filtrate and washings were concentrated. The residue was dissolved in methanol (30 mL) and H_2O (30 mL), and 2N NaOH (7.8 mL) was added to the mixture. The mixture was refluxed (at 100 ℃) for 3 h under argon gas. After cooling the reaction mixture to 0 ℃ and adjusting the pH to 8 with 2N HCl, the reaction mixture was concentrated. Methanol was added to the residue, and the precipitate was filtered off and washed with methanol. The combined filtrate and washings were concentrated. The residue was dissolved in H_2O, electrodialyzed, and then lyophilized to give **13** (1.69 g, 94.9 %) as an amorphous powder: $[\alpha]_D$ -36° (*c* 0.5, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 1.20 (d, 3H, $J_{5,6}$ = 6.6 Hz, H-6 of Fuc), 2.84 (dd, 1H, $J_{1ax,1eq}$ = 12.6 Hz, $J_{1ax,2}$ = 10.8Hz, H-1*ax* of DNJ), 3.35 (dd, 1H, $J_{1eq,2}$ =

4.8Hz, H-1*eq* of DNJ), 3.65 (dd, 1H, $J_{1,2}$ = 7.8Hz, $J_{2,3}$ = 9.9Hz, H-2 of Gal), 4.28 (d, 1H, H-4 of Gal), 4.33 (dd, 1H, $J_{3,4}$ = 3.3Hz, H-3 of Gal), 4.58 (d, 1H, H-1 of Gal), 4.75 (m, 1H, H-5 of Fuc), 5.43 (d, 1H, $J_{1,2}$ = 3.9Hz, H-1 of Fuc); FAB-MS *m/z* 550 $(M-Na)^-$.

Anal. Calcd for $C_{18}H_{32}NO_{16}SNa \cdot 1.5H_2O$: C, 36.00; H, 5.87; N, 2.33. Found : C, 36.29; H, 6.10; N, 2.50.

REFERENCES AND NOTES

1. Dedicated to the memory of Professor Akira Hasegawa.
2. D. Tyrrell, P. James, N. Rao, C.Foxall, S. Abbas, F. Dasgupta, M. Nashed, A. Hasegawa, M. Kiso, D. Asa, J. Kidd and B. K. Brandley, *Proc. Natl. Acad. Sci. USA*, **88**, 10372 (1991).
3. C. Foxall, S. R. Watson, D. Dowbenko, C. Fennie, L. A. Lasky, M. Kiso, A. Hasegawa, D. Asa and B. K. Brandley, *J. Cell Biol.*, **117**, 895 (1992).
4. M. J. Polley, M. L. Phillips, E. Wayner, E. Nudelman, A. K. Singhal, S. Hakomori and J. C. Paulson, *Proc. Natl. Acad. Sci. USA*, **88**, 6224 (1991).
5. C. -T. Yuen, A. M. Lawson, W. Chai, M. Larkin, M. S. Stoll, A. C. Stuart, F. X. Sullivan, T. J. Ahern and T. Feizi, *Biochemistry*, **31**, 9126 (1992).
6. Y. Wada, T. Saito, N. Matsuda, H. Ohmoto, K. Yoshino, M. Ohashi, H. Kondo, H. Ishida, M. Kiso and A. Hasegawa, *J. Med. Chem.*, **39**, 2055 (1996).
7. M. S. Mulligan, J. B. Lowe, R. D. Larsen, J. Paulson, Z.-L. Zheng, S. DeFrees, K. Maemura, M. Fukuda and P. A. Ward, *J. Exp. Med.*, **178**, 623 (1993).
8. M. S. Mulligan, J. C. Paulson, S. D. Frees, Z.-L. Zheng, J. B. Lowe and P. A. Ward, *Nature*, **364**, 149 (1993).
9. M. Buerke, A. S. Weyrich, Z. -L. Zheng, F. C. A. Gaeta, M. J. Forrest and A. M. Lefer, *J. Clin. Invest.*, **93**. 1140 (1994).
10. U. Sprengard, H. Kunz, C. Hüls, W. Schmidt, D. Seiffge and G. Kretzschmar, *Bioorg. Med. Chem. Lett.*, **6**, 509 (1996).
11. J. Y. Ramphal, M. Hiroshige, B. Lou, J. J. Gaudino, M. Hayashi, S. M. Chen, L. C. Chiang, F.C. A. Gaeta and S. A. DeFres, *J. Med. Chem.*, **39**, 1357 (1996).
12. S. A. DeFrees, W. Kosch, W. Way, J. C. Paulson, S. Sabesan, R. L. Hacomb, D. -H. Huang, Y. Ichikawa and C. -H Wong, *J. Am. Chem. Soc.* **117**, 66 (1995).
13. A. Hasegawa, K. Ito, H. Ishida and M. Kiso, *J. Carbohydr. Chem.*, **14**, 353 (1995).
14. M. Kiso, H. Furui, K. Ando, H. Ishida and A. Hasegawa, *Bioorg. Med. Chem.*, **2**, 1295 (1994).
15. A. Hasegawa, Presented at the *International Bio Symposium*, Nagoya, Japan, January 26-27, 1995. Program & abstracts p 232-238.

16. M. Kojima, T. Seto, Y. Kyotani, H. Ogawa, S. Kitazawa, K. Mori, S. Maruo, T. Ohgi and Y. Ezure, *Biosci., Biotechnol., Biochem.*, **60**, 694 (1996).
17. M. A. Nashed and J. H. Musser, *Carbohydr. Res.*, **250**, C1 (1993).
18. H. Lönn, *Carbohydr. Res.*, **139**, 105 (1985).
19. G. H. Veeneman, S. H. van Leeuen and J. H. van Boom, *Tetrahedron Lett.*, **31**, 1331 (1990).