

FGF RECEPTOR-ACTIVATING N-SULFATE OLIGOSACCHARIDES,
PREPARATION THEREOF, AND THERAPEUTIC USE THEREOF

The present invention relates to N-sulfate oligosaccharides that are
5 agonists of the FGF/FGFR system, and to their preparation and therapeutic use.

Angiogenesis is a process of generation of new blood capillaries. During
the blockage of a blood vessel, angiogenesis, combined with arteriogenesis
(dilation of the capillaries), improves the revascularization of the blocked area. It
10 has been shown *in vitro* and *in vivo* that several growth factors, such as
Fibroblast Growth Factors (FGFs), stimulate the neovascularization process.

FGFs are a family of 23 members. FGF2 (or basic FGF) is an 18 kDa
protein. FGF2 induces, in endothelial cells in culture, their proliferation and
15 migration and the production of proteases. *in vivo*, FGF2 promotes
neovascularization. FGF2 interacts with endothelial cells via two classes of
receptors, the high-affinity receptors with tyrosine kinase activity (FGFRs) and
the low-affinity receptors of heparan sulfate proteoglycan (HSPG) type.

20 It is known that cell surface receptors with tyrosine kinase activity
associate in dimeric form with a complex formed from two ligand molecules and
one heparan sulfate molecule. The formation of this complex triggers a cascade
of intracellular signals resulting in activation of cell proliferation and migration,
which are two key processes involved in angiogenesis.

25

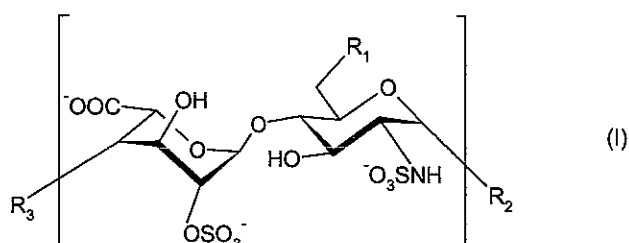
Thus, FGF2 and its receptors represent very pertinent targets for
therapies directed towards activating or inhibiting angiogenesis processes.

Synthetic oligosaccharides have also been the subject of studies of
30 interactions with the FGF receptors and have shown their inhibitory effects on
the binding of FGF-2 to its receptor on smooth muscle cells, with an IC₅₀ of
16 µg/mL, and also an inhibition of proliferation of these cells induced with

FGF-2, with an IC₅₀ of about 23 µg/mL (C. Tabeur et al., *Bioorg. & Med. Chem.*, 1999, 7, 2003-2012; C. Noti et al., *Chem. Eur. J.*, 2006, 12, 8664-8686).

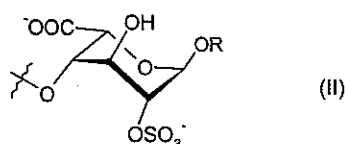
We have now found novel synthetic oligosaccharides that are capable of
 5 facilitating the formation of the FGF/FGFR complex and of thus promoting the *in vitro* survival of endothelial cells and of increasing the *in vitro* and *in vivo* formation of new blood vessels.

One subject of the present invention is novel oligosaccharide compounds
 10 corresponding to formula (I):

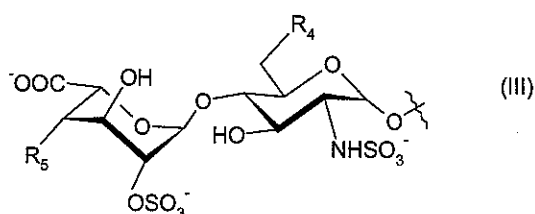


in which:

- R₁ represents a group -OSO₃⁻ or a hydroxyl group,
- R₂ represents either a group -O-alkyl, or a monosaccharide of formula
 15 (II), in which R represents an alkyl group:



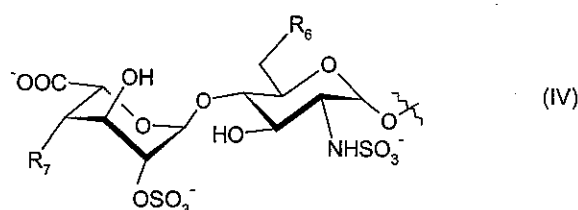
- R₃ represents a disaccharide of formula (III):



20 in which:

- R₄ represents a group -OSO₃⁻ or a hydroxyl group,
- R₅ represents a disaccharide of formula (IV):

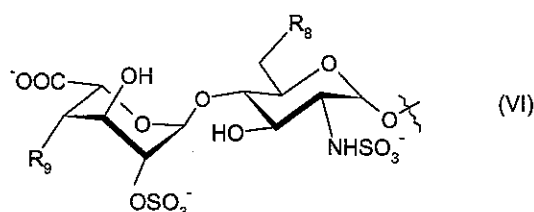
3



in which:

- R_6 represents a group $-\text{OSO}_3^-$ or a hydroxyl group,
- R_7 represents either a hydroxyl group or a disaccharide of formula (VI):

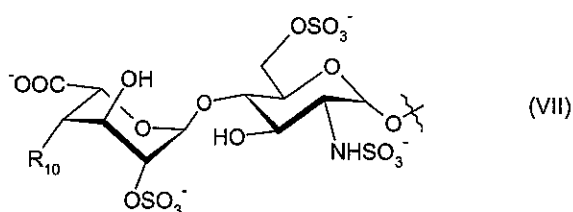
5



in which:

- R_8 represents a group $-\text{OSO}_3^-$ or a hydroxyl group,
- R_9 represents either a hydroxyl group or a group $-\text{O-alkyl}$, or a disaccharide of formula (VII):

10



- 15 in which R_{10} represents a group $-\text{O-alkyl}$,

on condition that: R_9 represents a hydroxyl group or a group $-\text{O-alkyl}$ when R_2 represents a monosaccharide of formula (II) as defined above; R_7 represents a disaccharide of formula (VI) as defined above when R_2 represents a group $-\text{O-alkyl}$; and R_1 , R_4 , R_6 and R_8 do not simultaneously represent hydroxyl groups.

20

In the context of the present invention, and unless otherwise mentioned in the text, the term "alkyl group" is understood to mean a linear or branched saturated aliphatic group comprising 1 to 4 carbon atoms. Examples that may be

mentioned include methyl, ethyl, propyl, isopropyl, butyl, isobutyl and *tert*-butyl groups. In the compounds according to the invention, including each of the subgroups of compounds that will be defined hereinbelow, the alkyl groups advantageously represent methyl groups, except for the substituents R₉ and R₁₀ in which the alkyl radicals of the groups -O-alkyl advantageously represent propyl groups.

The compounds according to the invention are synthetic oligosaccharides, i.e. they are compounds obtained by total synthesis starting from intermediate synthons, as will be described in detail in the text hereinbelow. In this respect, they differ from oligosaccharides obtained by depolymerization or isolation from complex mixtures of polysaccharides, such as heparins or low molecular weight heparins. In particular, the compounds according to the invention have a well-defined structure resulting from their chemical synthesis and are in the form of pure oligosaccharides, i.e. they are free of other oligosaccharide species.

The invention encompasses the compounds of formula (I) in acid form or in the form of any pharmaceutically acceptable salt thereof. In the acid form, the functions -COO⁻ and -SO₃⁻ are, respectively, in -COOH and -SO₃H form.

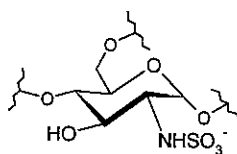
The term "pharmaceutically acceptable salt of the compounds of the invention" means a compound in which one or more of the functions -COO⁻ and/or -SO₃⁻ are ionically linked to a pharmaceutically acceptable cation. The preferred salts according to the invention are those in which the cation is chosen from alkali metal cations, especially the Na⁺ cation.

The compounds of formula (I) according to the invention also comprise those in which one or more hydrogen or carbon atoms have been replaced with a radioactive isotope, for example tritium or carbon ¹⁴C. Such labelled compounds are useful in research, metabolism or pharmacokinetic studies, as ligands in biochemical tests.

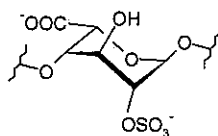
In formula (I) of the compounds according to the present invention, it is understood that:

- the monosaccharide of formula (II) is linked to the disaccharide unit represented in formula (I) via the oxygen atom located in position 4 of its uronic acid unit,
- the disaccharide of formula (III) is linked to the disaccharide unit represented in formula (I) via the oxygen atom located in position 1 of its glucosamine unit,
- similarly, the disaccharide of formula (IV) is linked to the disaccharide of formula (III) via the oxygen atom located in position 1 of its glucosamine unit,
- similarly, the disaccharide of formula (VI) is linked to the disaccharide of formula (IV) via the oxygen atom located in position 1 of its glucosamine unit,
- similarly, the disaccharide of formula (VII) is linked to the disaccharide of formula (VI) via the oxygen atom located in position 1 of its glucosamine unit.

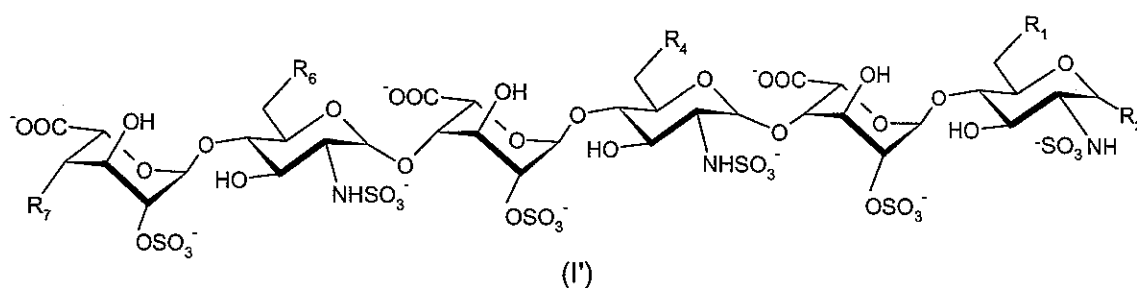
The term "glucosamine unit" means the monosaccharide unit having the following formula:



The other type of saccharide unit present in the compounds according to the invention is a uronic acid, more specifically an iduronic acid, corresponding to the following formula:



Thus, the compounds of formula (I) according to the invention may also be represented according to formula (I') as follows, in which the iduronic units and the glucosamine units succeed each other and in which R_1 , R_2 , R_4 , R_6 and R_7 are as defined previously:



Depending on the meanings of R_2 and R_7 , the oligosaccharides according to the invention may thus comprise from 7 to 10 saccharide units.

5

Among the compounds of formula (I)/(I') that are subjects of the invention, mention may be made of those in which:

- R_1 , R_3 , R_4 , R_5 and R_6 are as defined previously,
- R_2 represents a monosaccharide of formula (II) as defined previously,

10 and

- R_7 represents a hydroxyl group.

Such compounds are heptasaccharides. They correspond to formula (I-1) below, in which R_7 represents a hydroxyl group and R , R_1 , R_4 and R_6 are as defined previously, and are in acid form or in the form of any pharmaceutically acceptable salt thereof.

15

Among the compounds of formula (I)/(I') that are subjects of the invention, mention may be made of a subgroup of compounds in which R_2 represents a group -O-alkyl.

20

Such compounds are octasaccharides or decasaccharides. They correspond to formula (I-2) below in which R_1 , R_4 , R_6 , R_8 and R_9 are as defined previously and R_2 represents a group -O-alkyl, and are in acid form or in the form of any pharmaceutically acceptable salt thereof.

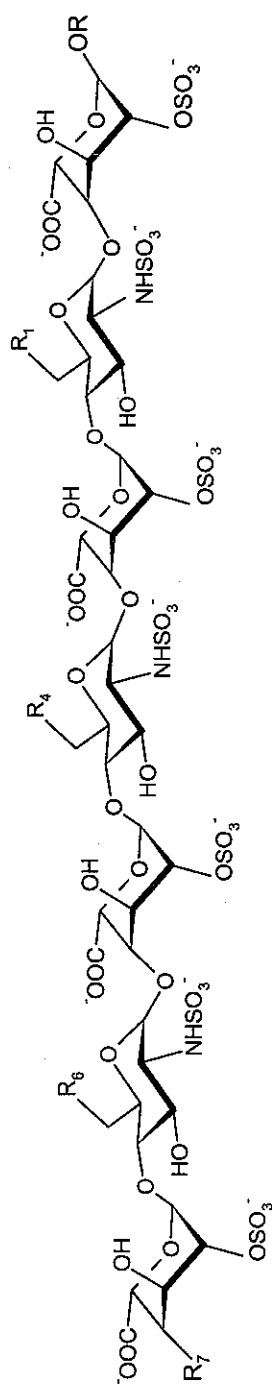
25

Among the compounds of formula (I)/(I') that are subjects of the invention, mention may be made of a subgroup of compounds in which:

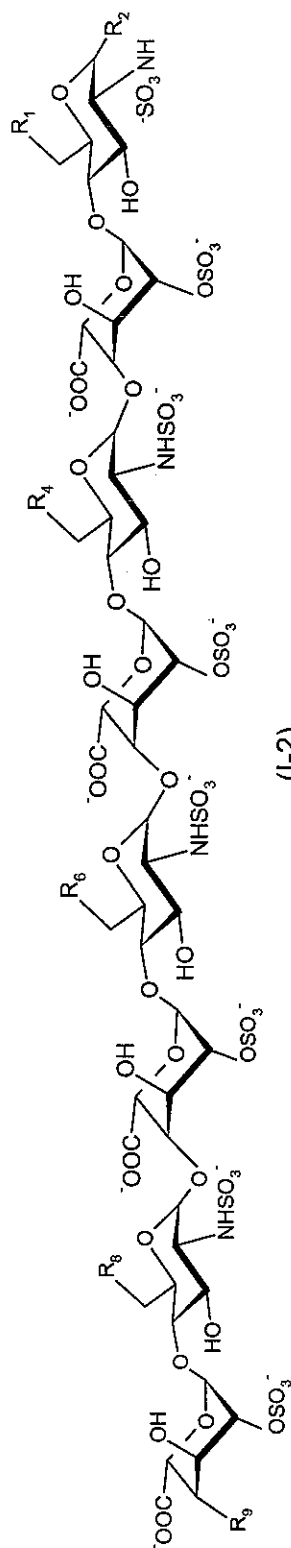
- R_2 represents a group -O-alkyl, and

- R₇ represents a disaccharide of formula (VI) as defined above, in which R₉ represents a disaccharide of formula (VII) as defined above.

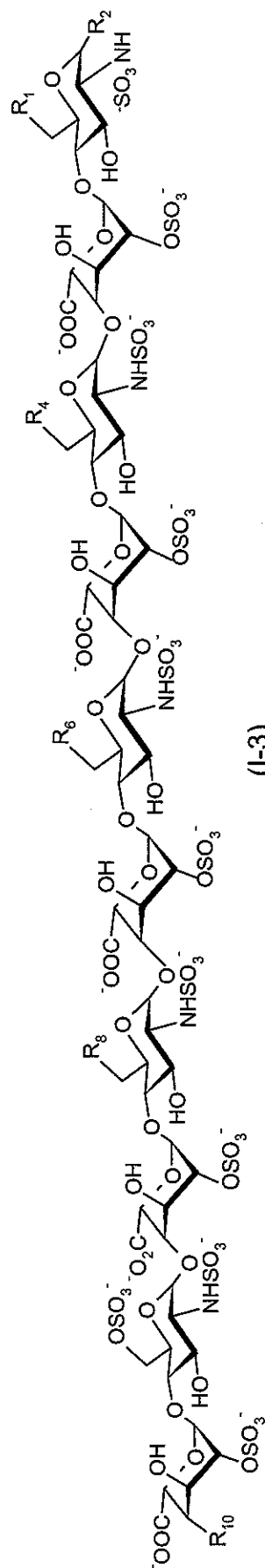
5 Such compounds are decasaccharides. They correspond to formula (I-3) below, in which R₁, R₄, R₆, R₈ and R₁₀ are as defined previously, and are in acid form or in the form of any pharmaceutically acceptable salt thereof.



(I-1)



(I-2)



(I-3)

Among the compounds of formula (I) that are subjects of the invention, mention may be made of a subgroup of compounds in which:

- R₂ represents a group -O-alkyl, and
 - R₇ represents a disaccharide of formula (VI) as defined above, in which
- 5 R₉ represents either a hydroxyl group or a group -O-alkyl.

Such compounds are octasaccharides and correspond to formula (I-2) above in which R₁, R₄, R₆ and R₈ are as defined previously, R₂ represents a group -O-alkyl and R₉ represents either a hydroxyl group or a group -O-alkyl.

10

Advantageously, the octasaccharides according to the invention are such that R₉ represents a group -O-alkyl.

Other subgroups of compounds according to the invention may have
15 several of the characteristics listed above for each of the subgroups defined previously.

The invention relates especially to the following oligosaccharides:

- 20 - methyl (sodium 4-O-propyl-2-O-sodium sulfonato- α -L-idopyranosyl-uronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl-(1 $\rightarrow$ 4)]₂-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-
25 (1 $\rightarrow$ 4)-2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranoside (**No. 1**);

- methyl (sodium 4-O-propyl-2-O-sodium sulfonato- α -L-idopyranosyl-uronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl-(1 $\rightarrow$ 4)]₃-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-
- 30

(1→4)-2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)-α-D-glucopyranoside (**No. 2**);

- sodium [methyl (sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)-α-D-glucopyranosyl)-(1→4)-[(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)-α-D-glucopyranosyl)-(1→4)]₂-2-O-sodium sulfonato-α-L-idopyranoside]-uronate (**No. 3**);

10

- methyl (sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-2-sodium (sulfonatoamino)-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-2-sodium (sulfonatoamino)-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)-α-D-glucopyranoside (**No. 4**);

20 - methyl (sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-2-sodium (sulfonatoamino)-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-2-sodium (sulfonatoamino)-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)-α-D-glucopyranoside (**No. 5**);

25 - methyl (sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-

30

2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranoside (**No. 6**);

- methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranoside (**No. 7**);

- methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium(sulfonatoamino)- α -D-glucopyranosyl)-[(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)]₂-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-6-O-sodium sulfonato-2-(sulfonato)amino- α -D-glucopyranoside (**No. 8**);

- methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonato)amino- α -D-glucopyranosyl)-[(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)]₂-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-2-sodium (sulfonatoamino)- α -D-glucopyranoside (**No. 9**).

In its principle, the process for preparing the compounds according to the invention uses di- or oligosaccharide synthons prepared as reported previously

in the literature. Reference will be made especially to the patents or patent applications EP 0 300 099, EP 0 529 715, EP 0 621 282 and EP 0 649 854, and also to the publication by C. Van Boeckel and M. Petitou published in *Angew. Chem. Int. Ed. Engl.*, 1993, 32, 1671-1690. These synthons are then coupled
5 together so as to give an entirely protected equivalent of a compound according to the invention. This protected equivalent is then converted into a compound according to the invention. In the coupling reactions mentioned above, a "donor" di- or oligosaccharide, activated on its anomeric carbon, reacts with an "acceptor" di- or oligosaccharide, bearing a free hydroxyl.

10

The present invention thus relates to a process for preparing compounds of formula (I)/(I'), characterized in that:

- in a first phase, a fully protected equivalent of the desired compound (I) is synthesized,

- in a second phase, the groups -COO^- and -OSO_3^- are introduced and/or unmasked,

- in a third phase, the whole compound is deprotected, and

- in a fourth phase, the N-sulfate groups are introduced.

20 The synthesis of the fully protected equivalent of the desired compound (I) is performed according to reactions that are well known to those skilled in the art, and using methods for the synthesis of oligosaccharides (for example G.J. Boons, *Tetrahedron* (1996), 52, 1095-1121 and patent applications WO 98/03554 and WO 99/36443), in which a glycoside bond-donating
25 oligosaccharide is coupled with a glycoside bond-accepting oligosaccharide to give another oligosaccharide whose size is equal to the sum of the sizes of the two reactive species. This sequence is repeated until the compound of formula (I)/(I') is obtained, optionally in protected form. The nature and profile of the charge of the final desired compound determine the nature of the chemical
30 species used in the various synthetic steps, according to the rules well known to those skilled in the art. Reference may be made, for example, to C. Van Boeckel and M. Petitou, *Angew. Chem. Int. Ed. Engl.* (1993), 32, 1671-1690 or alternatively to H. Paulsen, "Advances in selective chemical syntheses of complex oligosaccharides", *Angew. Chem. Int. Ed. Engl.* (1982), 21, 155-173.

35

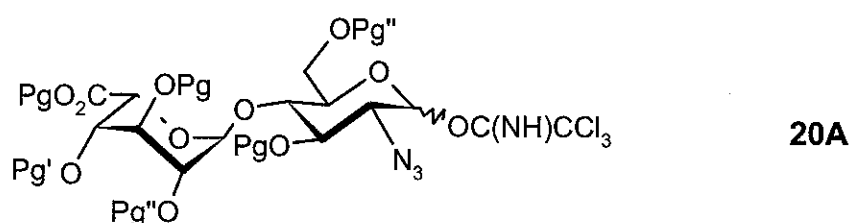
The compounds of the invention may naturally be prepared using various strategies known to those skilled in the art of oligosaccharide synthesis. The process described above is the preferred process of the invention. However, the compounds of formula (I)/(I') may be prepared via other well-known methods of sugar chemistry, described, for example, in "Monosaccharides, their chemistry and their roles in natural products", P.M. Collins and R.J. Ferrier, J. Wiley & Sons (1995) and by G.J. Boons in *Tetrahedron* (1996), 52, 1095-1121.

The protecting groups used in the process for preparing the compounds of formula (I)/(I') are those that make it possible firstly to protect a reactive function such as a hydroxyl or an amine during a synthesis, and secondly to regenerate the intact reactive function at the end of the synthesis. The protecting groups commonly used in sugar chemistry, as described, for example, in "Protective Groups in Organic Synthesis", Greene et al., 3rd edition (John Wiley & Sons, Inc., New York) are used to perform the process according to the invention. The protecting groups are chosen, for example, from acetyl, halomethyl, benzoyl, levuliny, benzyl, allyl, *tert*-butyldiphenylsilyl (tBDPS) groups.

Activating groups may also be used; these are the groups conventionally used in sugar chemistry, for example according to G.J. Boons, *Tetrahedron* (1996), 52, 1095-1121. These activating groups are chosen, for example, from imidates and thioglycosides.

The process described above allows the compounds of the invention to be obtained in the form of salts, advantageously in the form of the sodium salt. To obtain the corresponding acids, the compounds of the invention in salt form may be placed in contact with a cation-exchange resin in acidic form. The compounds of the invention in acid form may then be neutralized with a base to obtain the desired salt. For the preparation of the salts of the compounds of formula (I)/(I'), any mineral or organic base that gives pharmaceutically acceptable salts with the compounds of formula (I)/(I') may be used.

A subject of the invention is also the compounds of formula 20A below, in which Pg, Pg' and Pg'', which may be identical or different, represent protecting groups:

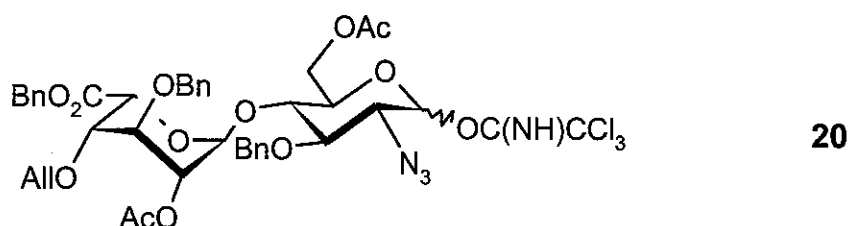


Such compounds are useful as intermediates in the synthesis of the compounds of formula (I)/(I').

5

In particular, a subject of the invention is the compounds 20A in which Pg, Pg' and Pg'' represent, respectively, benzyl, allyl and acetyl groups. Such a compound corresponds to disaccharide 20 illustrated in scheme 2 below, useful for the synthesis of compounds 1 and 2 according to the invention, as will be detailed hereinbelow:

10



The examples that follow describe the preparation of certain compounds and synthetic intermediates in accordance with the invention. These compounds are not limiting, but serve merely to illustrate the present invention. The starting compounds and the reagents, when their mode of preparation is not expressly described, are commercially available or described in the literature, or else may be prepared according to methods that are described therein or that are known to those skilled in the art.

20

The following abbreviations are used:

[α]_D: optical rotation

Ac: acetyl

25

All: allyl

Bn: benzyl

Bz: benzoyl

TLC: thin-layer chromatography

CrO₃: chromium trioxide

DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

5 ESI: Electron-Spray Ionization

h: hours

H₂SO₄: sulfuric acid

Lev: levuliny

Me: methyl

10 min: minutes

Rf: Retardation factor (retention time measured on TLC relative to the solvent migration front)

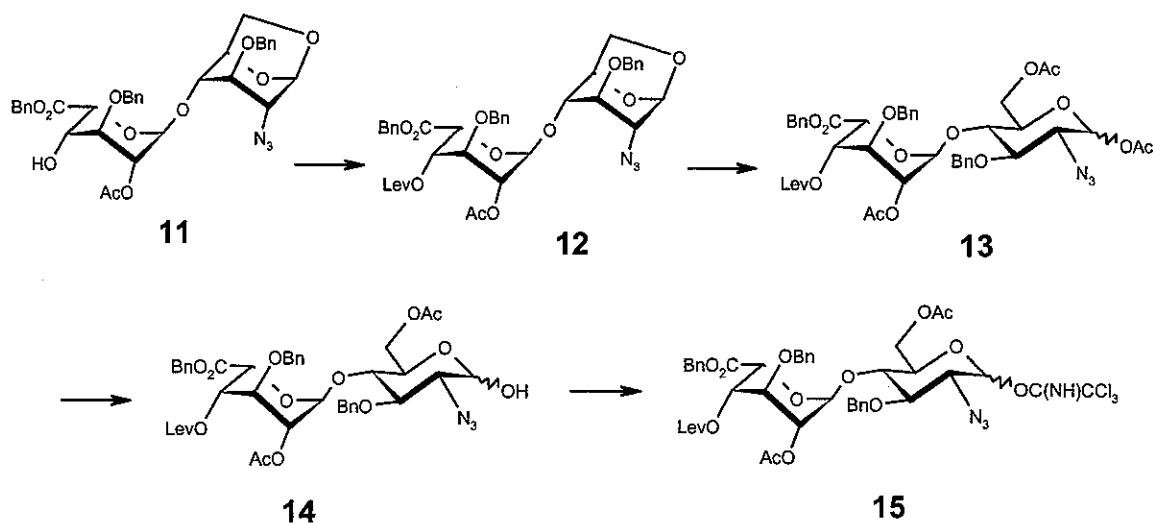
tBDPS: *tert*-butyldiphenylsilyl

Z: benzyloxycarbonyl

15

Preparation of the synthetic intermediates:

SCHEME 1: Preparation of the donor disaccharide **15**



20

(Benzyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-
(1 $\rightarrow$ 4)-1,6-anhydro-2-azido-3-O-benzyl-2-deoxy- β -D-glucopyranose (12)

To a solution of compound **11** (11.6 g, 16.2 mmol) (described in the preparation of compound 8 of patent application WO 2006/021653) in anhydrous
5 dioxane (340 mL) are successively added 4-dimethylaminopyridine (2.12 g, 17.3 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (6.5 g, 34.3 mmol) and levulinic acid (3.6 mL; 34.3 mmol). After stirring for 4 hours 30 minutes, the mixture is diluted with dichloromethane (1800 mL). The organic phase is washed successively with aqueous 10% potassium hydrogen sulfate
10 solution, with saturated sodium chloride solution, with saturated aqueous sodium hydrogen carbonate solution and then with water, dried over sodium sulfate, filtered and then evaporated to dryness. The residue is purified by chromatography on a column of silica gel (5/1 v/v toluene/acetone) to give 12.7 g of compound **12**.

15 TLC: R_f = 0.42, silica gel, 3/1 v/v toluene/acetone

(Benzyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-
(1 $\rightarrow$ 4)-1,6-di-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α,β -D-glucopyranose (13)

To a solution of compound **12** (12.76 g, 16.2 mmol) in acetic anhydride
20 (160 mL) is added, at 0°C, trifluoroacetic acid (14.1 mL, 183 mmol). The reaction medium is stirred for 16 hours at room temperature. After concentrating, the mixture is co-evaporated with toluene. Purification of the residue by chromatography on a column of silica gel (4/1 v/v toluene/acetone) gives 10.5 g of compound **13**.

25 TLC: R_f = 0.49, silica gel, (4/1 v/v toluene/acetone)

(Benzyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-
(1 $\rightarrow$ 4)-6-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α,β -D-glucopyranose (14)

A solution of compound **13** (10.5 g, 12.0 mmol) and benzylamine (50 mL,
30 457 mmol) in diethyl ether (360 mL) is stirred at room temperature for 2 hours. The reaction mixture is diluted with diethyl ether (2000 mL). The organic phase is washed with cold aqueous 1 M hydrochloric acid solution and then with water,

dried over sodium sulfate, filtered and then concentrated to dryness. The residue is chromatographed on a column of silica gel (3/1 v/v toluene/acetone) to give 7.14 g of compound **14**.

TLC: R_f = 0.40, silica gel, 3/1 v/v toluene/acetone

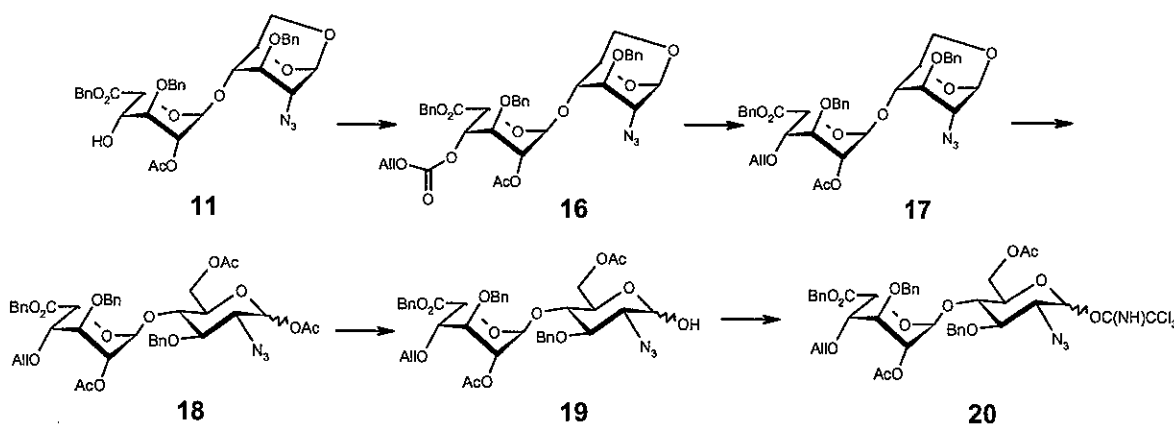
5

(Benzyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α,β -D-glucopyranose trichloroacetimidate (**15**)

Trichloroacetonitrile (4.3 mL, 42.8 mmol) and caesium carbonate (1.89 g, 13.7 mmol) are added to a solution of compound **14** (7.14 g, 8.56 mmol) in dichloromethane (160 mL). After stirring for 30 minutes, the reaction medium is filtered and then concentrated. The residue is purified by chromatography on a column of silica gel (2/1 v/v toluene/acetone + 0.1% triethylamine) to give 7.0 g of compound **15**.

15 TLC: R_f = 0.37 and 0.28, silica gel, 2/1 v/v toluene/acetone

SCHEME 2: Preparation of the glycosyl donor **20**



(Benzyl 2-O-acetyl-4-O-(allyloxy)carbonyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-1,6-anhydro-2-azido-3-O-benzyl-2-deoxy- β -D-glucopyranose (**16**)

25 To a solution of compound **11** (11.7 g, 17.3 mmol) (described in the preparation of compound 8 of patent application WO 2006/021653) in anhydrous

tetrahydrofuran are successively added, at 0°C, pyridine (14 mL; 173 mmol), 4-dimethylaminopyridine (2.12 g, 17.3 mmol) and allyl chloroformate (18.3 mL, 173 mmol). After stirring for 16 hours at room temperature, water (47 mL) is added at 0°C. After stirring for 30 minutes, the mixture is diluted with ethyl acetate (800 mL). The organic phase is washed successively with aqueous 10% potassium hydrogen sulfate solution and water and then with saturated aqueous sodium hydrogen carbonate solution and water, dried over sodium sulfate, filtered and then evaporated to dryness. The residue is purified by chromatography on a column of silica gel (2/1 v/v cyclohexane/ethyl acetate) to give 11.4 g of compound **16**.

TLC: R_f = 0.37, silica gel, 2/1 v/v cyclohexane/ethyl acetate.

(Benzyl 2-O-acetyl-4-O-allyl-3-O-benzyl- α -L-idopyranosyluronate)-(1→4)-1,6-anhydro-2-azido-3-O-benzyl-2-deoxy- β -D-glucopyranose (**17**)

Compound **16** (11.44 g, 15.1 mmol) is dissolved in tetrahydrofuran (100 mL). Palladium acetate (67.6 mg, 0.30 mmol) and triphenylphosphine (395 mg, 1.5 mmol) are added. After stirring for 2 hours at reflux, the reaction medium is concentrated to dryness. The residue is purified by chromatography on a column of silica gel (3/1 v/v cyclohexane/ethyl acetate) to give 8.0 g of compound **17**.

TLC: R_f = 0.33, silica gel, 2/1 v/v cyclohexane/ethyl acetate.

(Benzyl 2-O-acetyl-4-O-allyl-3-O-benzyl- α -L-idopyranosyluronate)-(1→4)-1,6-di-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α,β -D-glucopyranose (**18**)

To a solution of compound **16** (7.96 g, 11.1 mmol) in acetic anhydride (105 mL) cooled to 0°C is added trifluoroacetic acid (9.4 mL). The reaction medium is stirred for 16 hours at room temperature. After concentrating, the mixture is coevaporated with toluene (5 x 200 mL). Purification of the residue by chromatography on a column of silica gel (2/1 v/v cyclohexane/ethyl acetate) gives 7.72 g of compound **18**.

TLC: R_f = 0.40, silica gel, 2/1 v/v cyclohexane/ethyl acetate

(Benzyl 2-O-acetyl-4-O-allyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α,β -D-glucopyranose (19)

A solution of compound **18** (7.72 g, 9.44 mmol) and benzylamine (3.9 mL, 35.2 mmol) in diethyl ether (280 mL) is stirred at room temperature for 6 hours.

- 5 The reaction mixture is diluted with diethyl ether (800 mL). The organic phase is washed with aqueous 1 M hydrochloric acid solution and then with water, dried over sodium sulfate, filtered and then concentrated to dryness. The residue is purified by chromatography on a column of silica gel (5/2 v/v toluene/ethyl acetate) to give 6.14 g of compound **19**.

10 TLC: R_f = 0.45, silica gel, 5/3 v/v toluene/ethyl acetate

(Benzyl 2-O-acetyl-4-O-allyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α,β -D-glucopyranose trichloroacetimidate (20)

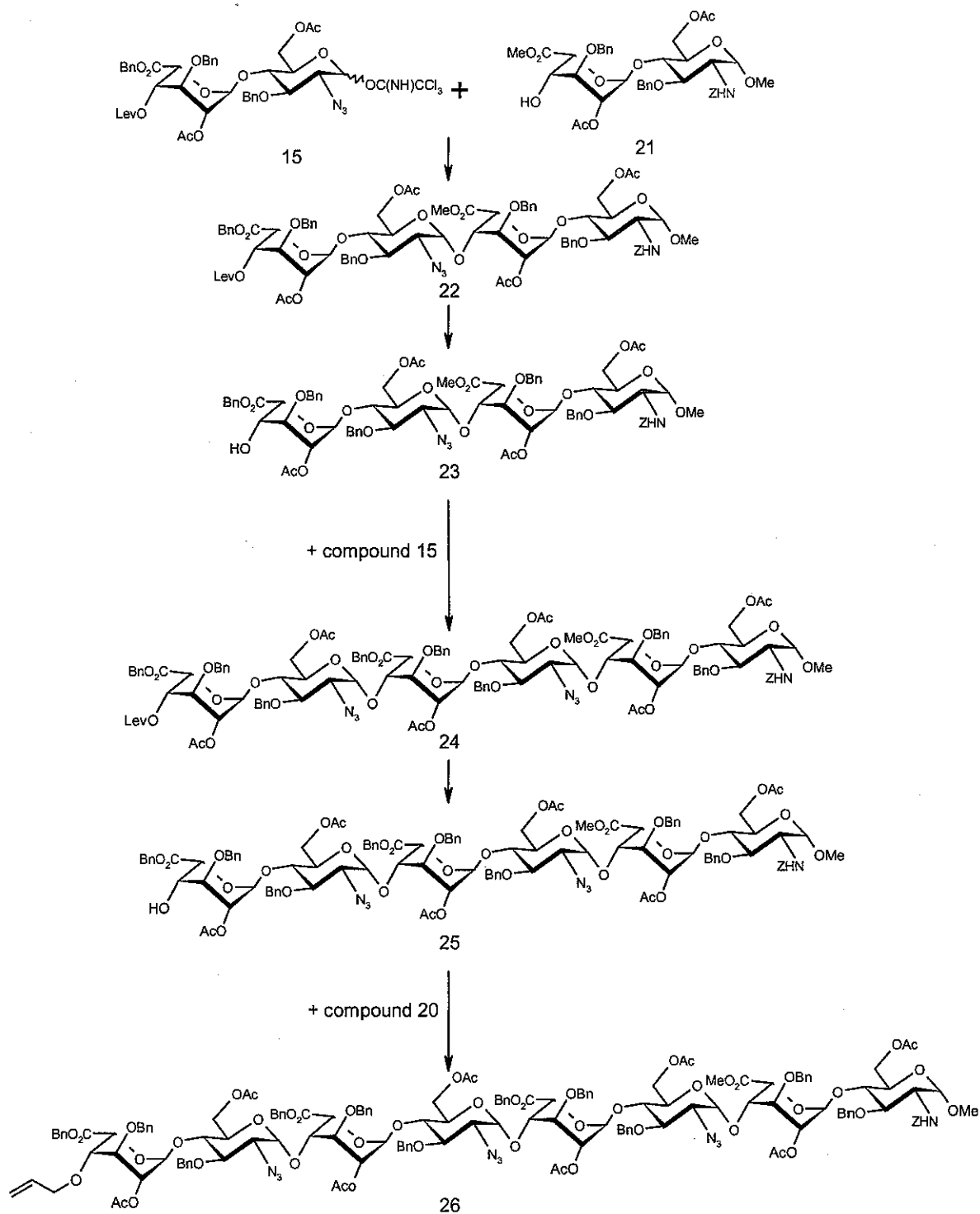
- 15 Trichloroacetonitrile (4 mL, 39.6 mmol) and caesium carbonate (4.13 g, 12.7 mmol) are added to a solution of compound **19** (6.14 g, 7.9 mmol) in dichloromethane (150 mL). After stirring for 30 minutes, the reaction medium is filtered and then concentrated. The residue is purified by chromatography on a column of silica gel (4/1 v/v toluene/ethyl acetate) to give 6.5 g of compound **20**.

20 TLC: R_f = 0.50, silica gel, 3/1 v/v toluene/ethyl acetate

Chemical shifts of the anomeric protons (500 MHz, CDCl₃) δ 5.27 IdoUA^{II}, 5.57 Glc^I β and 5.28 IdoUA^{II}, 6.36 Glc^I α

LC-MS *m/z* 798.2 [(M + Na)⁺]. T_{R1} = 13.59 min and T_{R2} = 13.75 min

SCHEME 3: Preparation of the octasaccharide 26



Methyl (benzyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(6-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-acetyl-3-O-benzyl-2-[(benzyloxy)carbonylamino]-2-deoxy- α -D-glucopyranoside (22)

A mixture of the imidate **15** (541 mg, 0.553 mmol), the glycosyl acceptor **21** (650 mg, 0.83 mmol) (prepared according to the method described in *Carbohydrate Research* (1987), 167 67-75) and powdered 4 Å molecular sieves (412 mg) in a toluene/dichloromethane mixture (23 mL, 20/3 v/v) is stirred under an argon atmosphere for 1 hour at 25°C. The reaction mixture is cooled to -25°C and a 1 M solution of *tert*-butyldimethylsilyl triflate in dichloromethane (82.5 μ L) is added to the reaction medium. After 15 minutes, the reaction medium is neutralized by addition of solid sodium hydrogen carbonate. After filtering and concentrating, the residue obtained is purified by size exclusion chromatography (Sephadex[®] LH20, 120 x 3 cm, 1/1 v/v dichloromethane/ethanol) to give 746 mg of compound **22**.

TLC: R_f = 0.37, silica gel, 5/6 v/v cyclohexane/ethyl acetate.

Methyl (benzyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(6-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-acetyl-3-O-benzyl-2-[(benzyloxy)carbonylamino]-2-deoxy- α -D-glucopyranoside (23)

To a solution of compound **22** (2.3 g, 1.44 mmol) in a 1/2 v/v toluene/ethanol mixture (290 mL) is added hydrazine acetate (662.3 mg, 7.2 mmol). The reaction medium is stirred for 2 hours at room temperature. After concentrating, the residue is purified by flash chromatography on a column of silica gel (5/6 v/v cyclohexane/ethyl acetate) to give 1.84 g of compound **23**.

TLC: R_f = 0.48, silica gel, 5/6 v/v cyclohexane/ethyl acetate.

Methyl (benzyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(6-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(benzyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(6-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-acetyl-3-O-benzyl-2-[[benzyloxy]carbonyl]amino}-2-deoxy- α -D-glucopyranoside (24)

A mixture of the glycosyl acceptor **23** (1.97 g, 1.12 mmol), the imidate **15** (1.63 g, 1.66 mmol) and powdered 4 Å molecular sieves (2.6 g) in a 1/1 v/v dichloromethane/toluene mixture (75 mL) is stirred under an argon atmosphere for 1 hour at 25°C. The reaction mixture is cooled to -20°C and a 1 M solution of *tert*-butyldimethylsilyl triflate in dichloromethane (250 μ L) is added to the reaction medium. After 10 minutes, the reaction medium is neutralized by addition of solid sodium hydrogen carbonate. After filtering and concentrating, the residue obtained is purified by size exclusion chromatography (Sephadex[®] LH20, 190 x 3.2 cm, 1/1 v/v dichloromethane/ethanol) to give 1.63 g of compound **24**.

TLC: R_f = 0.33, silica gel, 3/1 v/v toluene/acetone.

Methyl (benzyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(6-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(benzyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(6-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-acetyl-3-O-benzyl-2-[[benzyloxy]carbonyl]amino}-2-deoxy- α -D-glucopyranoside (25)

To a solution of compound **24** (1.7 g, 0.73 mmol) in a 1/2 v/v toluene/ethanol mixture (145 mL) is added hydrazine acetate (338 mg, 3.67 mmol). The reaction medium is stirred for 2 hours at room temperature. After concentrating, the residue is purified by flash chromatography on a column of silica gel (1/1 v/v cyclohexane/ethyl acetate) to give compound **25** (1.41 g).

TLC: R_f = 0.47, silica gel, 1/1 v/v cyclohexane/ethyl acetate.

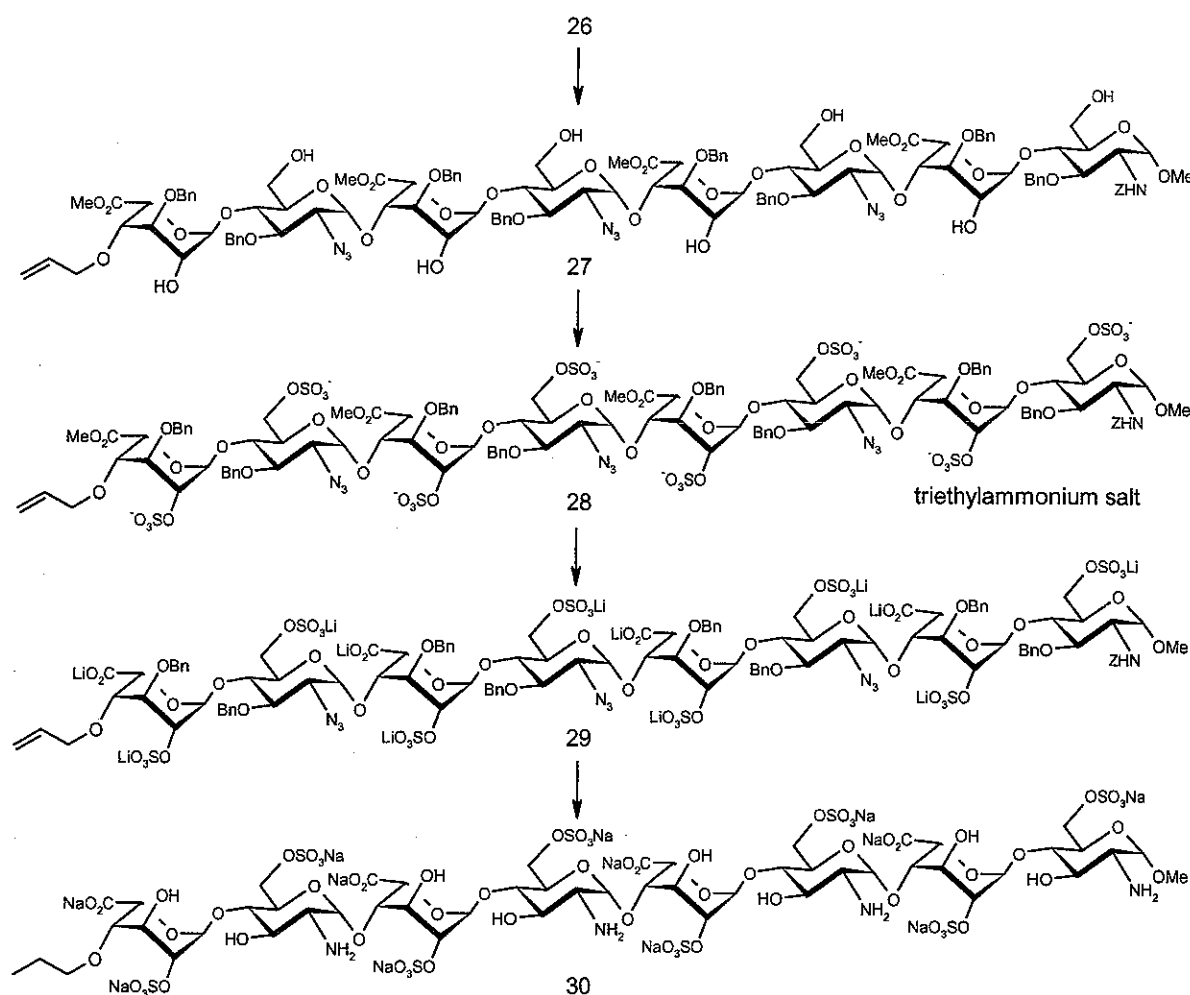
Methyl (benzyl 2-O-acetyl-4-O-allyl-3-O-benzyl- α -L-idopyranosyluronate)-
(1 $\rightarrow$ 4)-(6-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-
[(benzyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(6-O-acetyl-2-
azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl-(1 $\rightarrow$ 4)]₂-(methyl 2-O-acetyl-3-O-
 5 benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-acetyl-3-O-benzyl-2-
{[(benzyloxy)carbonyl]amino}-2-deoxy- α -D-glucopyranoside (26)

A mixture of the imidate **20** (0.681 mg, 0.74 mmol), the glycosyl acceptor **25** (1.10 g, 0.5 mmol), and powdered 4 Å molecular sieves (0.555 g) in a 1/1 v/v dichloromethane/toluene mixture (26 mL) is stirred under an argon atmosphere
 10 for 1 hour at 25°C. The reaction mixture is cooled to -20°C and a 1 M solution of *tert*-butyldimethylsilyl triflate in dichloromethane (111 μ L) is added. After 20 minutes, the reaction medium is neutralized by addition of solid sodium hydrogen carbonate. After filtering through Celite® and concentrating, the residue obtained is chromatographed on a size exclusion column (Sephadex®
 15 LH20, 190 x 3.2 cm, 1/1 v/v dichloromethane/ethanol) to give successively 468 mg of octasaccharide **26** and 842 mg of a mixture containing the hexasaccharide **25** and the octasaccharide **26**.

This mixture (842 mg) is treated under the above conditions to give compound **26** (513.6 mg) after treatment and column chromatography
 20 (Sephadex® LH20, 190 x 3.2 cm, 1/1 v/v dichloromethane/ethanol).

The two fractions (468 mg and 513.6 mg) are combined and purified by preparative HPLC chromatography on a column of silica gel (2/1 v/v toluene/ethyl acetate) to give compound **26** (1.03 g).

TLC: R_f = 0.44, silica gel, 2/1 v/v toluene/ethyl acetate.

SCHEME 4: Preparation of the octasaccharide **30**

5

Methyl (methyl 4-O-allyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)]₂-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-[(benzyloxy)carbonylamino]-2-deoxy- α -D-glucopyranoside (27)

10

To a solution of compound **26** (819 mg, 0.27 mmol) in a 2/3 v/v dichloromethane/methanol mixture (83 mL) containing 3 Å molecular sieves (10.3 g) is added, at 0°C, under an argon atmosphere a 1 M solution of sodium methoxide in methanol (1.65 mL). After 16 hours at -18°C, the reaction medium is neutralized with Dowex® 50WX4 H⁺ resin. After filtering and concentrating, the residue is purified by size exclusion chromatography (Sephadex® LH20, 120 x

15

3 cm, 1/1 v/v dichloromethane/ethanol) followed by chromatography on a column of silica gel (4/3 v/v toluene/acetone) to give 605 mg of compound **27**.

TLC: R_f = 0.41, silica gel, 4/3 v/v toluene/acetone.

5 Methyl (methyl 4-O-allyl-3-O-benzyl-2-O-triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-triethylammonium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(methyl 3-O-benzyl-2-O-triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-triethylammonium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)]₂-(methyl 3-O-benzyl-2-O-
 10 triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-[[benzyloxy]carbonyl]amino}-2-deoxy-6-O-triethylammonium sulfonato- α -D-glucopyranoside (**28**)

Compound **27** (300 mg, 0.12 mmol) is dried by co-distillation of *N,N*-dimethylformamide (3 x 10 mL) and is then dissolved in *N,N*-dimethylformamide
 15 (11 mL). To this solution is added the sulfur trioxide-triethylamine complex (902 mg; 4.98 mmol). The mixture is stirred for 16 hours at 55°C protected from light and then neutralized with methanol (202 μ L, 4.98 mmol). The reaction medium is deposited on a column of Sephadex[®] LH20 gel (95 x 2 cm) eluted with a 1/1 v/v dichloromethane/ethanol mixture to give compound **28** (426 mg).

20 TLC: R_f = 0.32, silica gel, 11/7/1.6/4 v/v/v/v ethyl acetate/pyridine/acetic acid/water.

Methyl (lithium 4-O-allyl-3-O-benzyl-2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-lithium sulfonato-
 25 α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(lithium 3-O-benzyl-2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-lithium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)]₂-(lithium 3-O-benzyl-2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-[[benzyloxy]carbonyl]amino}-2-deoxy-6-O-lithium sulfonato- α -D-glucopyranoside (**29**)

30 To a solution of compound **28** (459 mg, 0.12 mmol) in a 1/1 v/v tetrahydrofuran/methanol mixture (19 mL) is added, at 0°C, a 0.7 M solution of lithium hydroxide in water (7.6 mL; qs final concentration of 0.2 M). After 1 hour

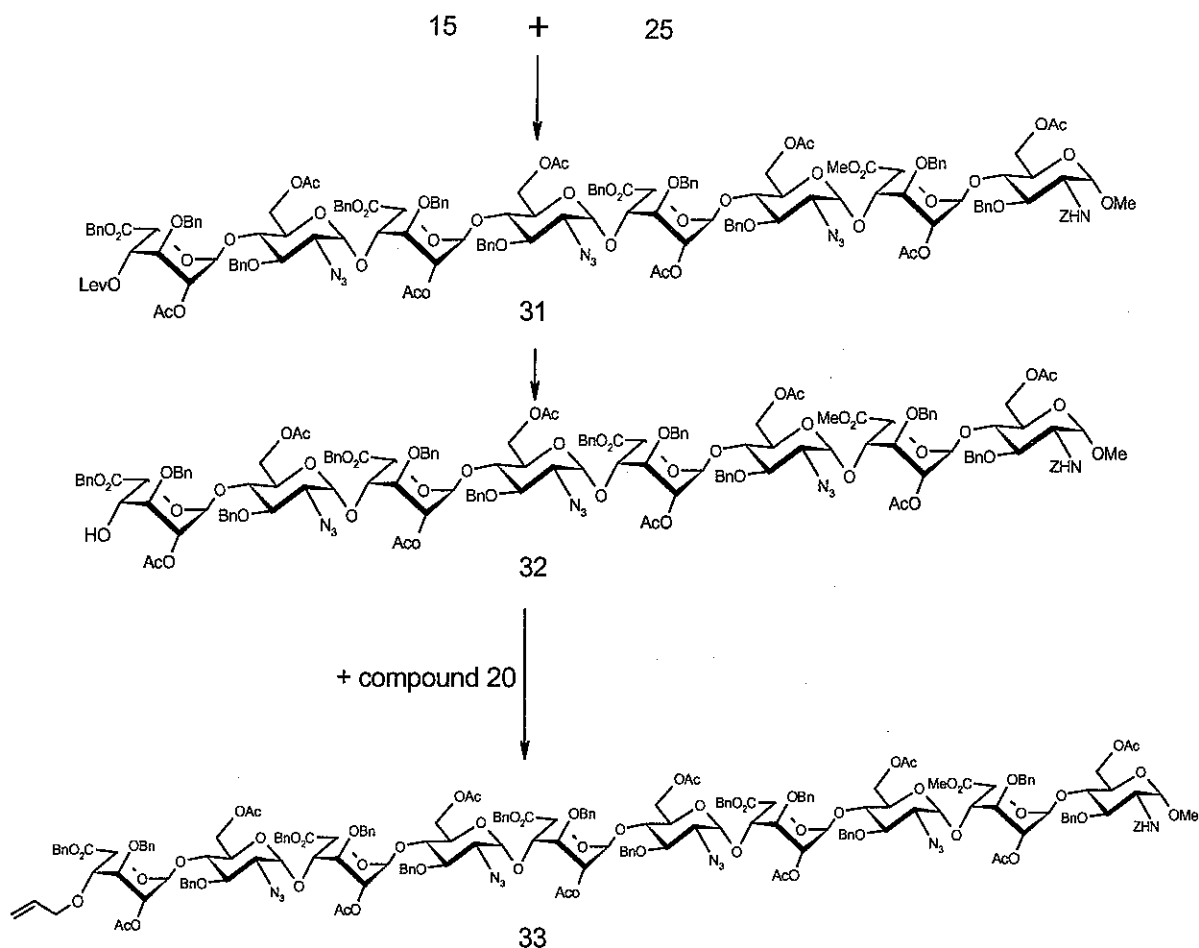
at 0°C and then 16 hours at room temperature, the reaction medium is cooled to 0°C, neutralized with acetic acid (305 µL) and then deposited on a Sephadex® LH20 column (95 x 2 cm) eluted with a 4/1 v/v methanol/water mixture to give compound **29** (368 mg).

- 5 TLC: R_f = 0.25, silica gel, 27/19/4.2/11 v/v/v/v ethyl acetate/pyridine/acetic acid/water.

Methyl (sodium 4-O-*n*propyl-2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-amino-2-deoxy-6-O-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-[sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-amino-2-deoxy-6-O-sodium sulfonato-α-D-glucopyranosyl-(1→4)]₂-(sodium 2-O-sulfonato-α-L-idopyranosyluronate)-(1→4)-2-amino-2-deoxy-6-O-sodium sulfonato-α-D-glucopyranoside (30)

- 15 A solution of compound **29** (170 mg) in a 2/3 v/v *tert*-butanol/water mixture (27 mL) is treated under pressure of hydrogen (1 bar) in the presence of 10% palladium-on-charcoal (340 mg) at 30°C for 24 hours. After filtration (Millipore® LSWP 5 µm filter), the reaction mixture is deposited on a column of Sephadex® G25-fine (90 x 3 cm) eluted with aqueous 0.2 M sodium chloride solution. The fractions containing the product are concentrated and desalified
- 20 using the same column eluted with water. After concentrating to dryness, compound **30** (205 mg) is obtained.

Mass: "ESI" method, negative mode: theoretical mass = 2327.55; experimental mass: 2239 a.m.u. (iduronic acids observed in COOH form).

SCHEME 5: Preparation of the decasaccharide **33**

5

Methyl (benzyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(6-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(benzyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(6-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)]₂-(methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-acetyl-3-O-benzyl-2-[(benzyloxy)carbonylamino]-2-deoxy- α -D-glucopyranoside (**31**)

A mixture of the imidate **15** (250 mg, 0.255 mmol), the glycosyl acceptor **25** (376 mg, 0.169 mmol) and powdered 4 Å molecular sieves (396 mg) in a 1/1 v/v dichloromethane/toluene mixture (11.4 mL) is stirred under an argon atmosphere for 1 hour at 25°C. The reaction mixture is cooled to -20°C and a 0.1 M solution of *tert*-butyldimethylsilyl triflate in dichloromethane (381 μ L) is

15

added. After 12 minutes, the reaction medium is neutralized by addition of solid sodium hydrogen carbonate. After filtering and concentrating, the residue obtained is chromatographed on a Sephadex[®] LH20 column (120 x 3 cm, 1/1 v/v dichloromethane/ethanol) to give successively 150 mg of crude compound 31 and 318 mg of a mixture containing the hexasaccharide 25 and the octasaccharide 31.

The mixture containing the hexasaccharide 25 and the octasaccharide 33 is treated under the above conditions to give after size exclusion chromatography (Sephadex[®] LH20) 151 mg of crude compound 31 and 191 mg of a mixture containing the hexasaccharide 25 and the octasaccharide 31. This operation is repeated twice to the point of depletion of the hexasaccharide 25.

The fractions containing the crude octasaccharide 31 are combined and purified by flash chromatography on a column of silica gel (7/3 v/v toluene/ethyl acetate) to give compound 31 (351 mg).

TLC: R_f = 0.37, silica gel, 7/5 v/v toluene/ethyl acetate.

Methyl (benzyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(6-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(benzyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(6-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)]₂-(methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-acetyl-3-O-benzyl-2-[(benzyloxy)carbonyl]amino-2-deoxy- α -D-glucopyranoside (32)

To a solution of compound 31 (335 mg, 0.11 mmol) in a 1/2 v/v toluene/ethanol mixture (22 mL) is added hydrazine acetate (51 mg, 0.55 mmol). The reaction medium is stirred for 2 hours at room temperature. The reaction mixture is diluted with dichloromethane (50 mL). The organic phase is washed with aqueous 2% potassium hydrogen sulfate solution, and then with water, dried over sodium sulfate, filtered and then concentrated to dryness. The residue is purified by chromatography on a column of silica gel (7/3 v/v toluene/acetone) to give compound 32 (238 mg).

TLC: R_f = 0.50, silica gel, 5/6 v/v cyclohexane/ethyl acetate.

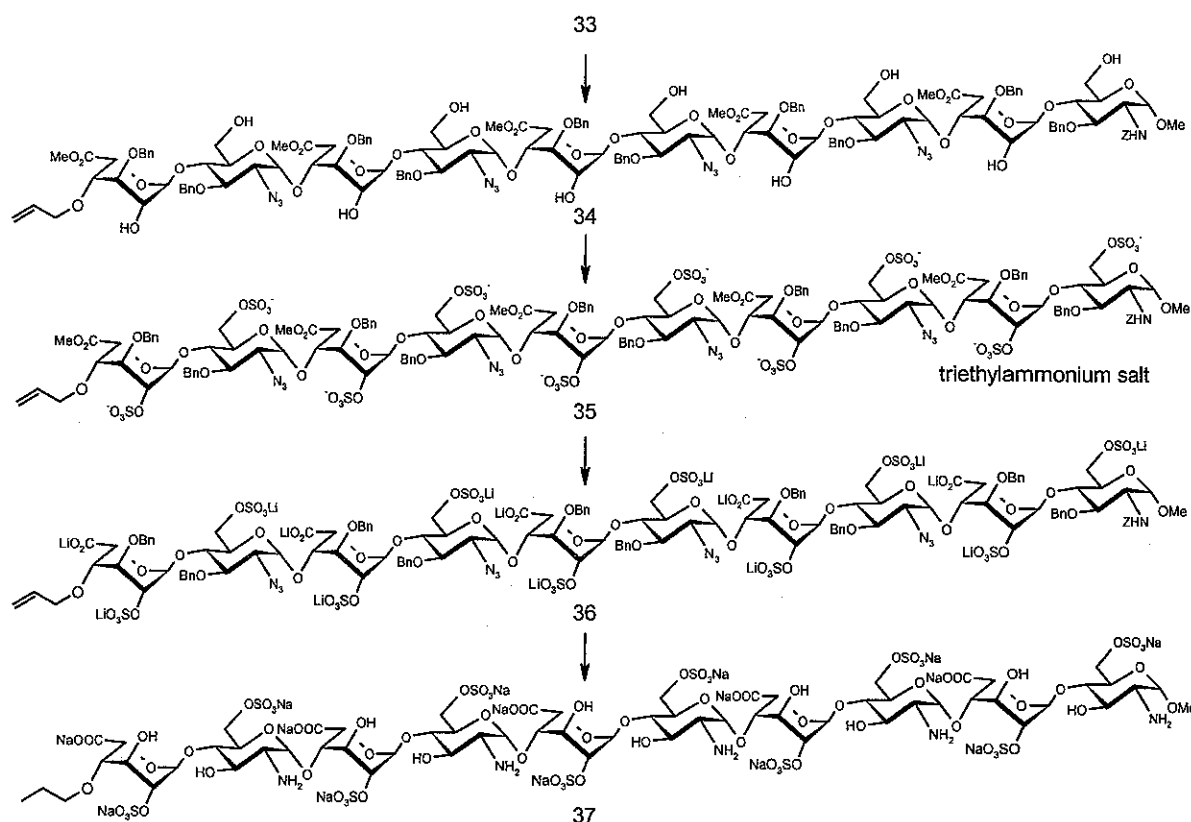
Methyl (benzyl 2-O-acetyl-4-O-allyl-3-O-benzyl- α -L-idopyranosyluronate)-
(1 $\rightarrow$ 4)-(6-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-
[(benzyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(6-O-acetyl-2-
azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl-(1 $\rightarrow$ 4)]₃-(methyl 2-O-acetyl-3-O-
 5 benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-acetyl-3-O-benzyl-2-
{[(benzyloxy)carbonyl]amino}-2-deoxy- α -D-glucopyranoside (33)

A mixture of the imidate **20** (64 mg, 0.066 mmol), the glycosyl acceptor **32** (130 mg, 0.044 mmol) and powdered 4 Å molecular sieves (49 mg) in a 1/1 v/v dichloromethane/toluene mixture (2.2 mL) is stirred under an argon atmosphere
 10 for 1 hour at 25°C. The reaction mixture is cooled to -20°C and a 0.1 M solution of *tert*-butyldimethylsilyl triflate in dichloromethane (100 μ L) is added. After 10 minutes, the reaction medium is neutralized by addition of solid sodium hydrogen carbonate. After filtering and concentrating, the residue obtained is chromatographed on a Sephadex® LH20 column (120 x 3 cm, 1/1 v/v
 15 dichloromethane/ethanol) to give successively 61 mg of crude compound **33** and 87.7 mg of a mixture containing the octasaccharide **32** and the decasaccharide **33**.

The above mixture (87.7 mg) is treated under the above conditions to give crude compound **33** (120 mg) after chromatography on a Sephadex® LH20
 20 column (120 x 3 cm, 1/1 v/v dichloromethane/ethanol).

The two fractions containing the crude compound are combined and purified by flash chromatography on a column of silica gel (7/2 v/v toluene/ethyl acetate) to give compound **33** (120 mg).

TLC: R_f = 0.52, silica gel, 1/1 v/v cyclohexane/ethyl acetate

SCHEME 6: Preparation of the decasaccharide **37**

5

Methyl (methyl 4-O-allyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)]₃-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-

10 [[[(benzyloxy)carbonyl]amino]-2-deoxy- α -D-glucopyranoside (**34**)

To a solution, cooled to 0°C, of compound **33** (51.8 mg, 0.014 mmol) in a 2/3 v/v dichloromethane/methanol mixture (982 μ L) containing 3 Å molecular sieves (125 mg) is added under an argon atmosphere a 1 M solution of sodium methoxide in methanol (21.0 μ L). After 5 hours at room temperature, the reaction medium is neutralized with Dowex® 50WX4 H⁺ resin. After filtering and concentrating, the residue is purified by size exclusion chromatography (Sephadex® LH20, 95 x 2 cm, 1/1 v/v dichloromethane/ethanol) to give compound **34** (31.4 mg).

15

TLC: R_f = 0.47, silica gel, 7/3 v/v dichloromethane/acetone

Methyl (methyl 4-O-allyl-3-O-benzyl-2-O-triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-triethylammonium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(methyl 3-O-benzyl-2-O-triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-triethylammonium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)]₃-(methyl 3-O-benzyl-2-O-triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-[[benzyloxy]carbonyl]amino}-2-deoxy-6-O-triethylammonium sulfonato- α -D-glucopyranoside (35)

Compound **34** (31.5 mg, 10.6 μ mol) is treated as in the preparation of compound **28** to give compound **35** (47.0 mg) after size exclusion chromatography (Sephadex[®] LH20, 100 x 1.2 cm, 1/1 v/v dichloromethane/methanol).

TLC: R_f = 0.55, silica gel, 16/11/2.6/7 v/v/v/v ethyl acetate/pyridine/acetic acid/water.

Methyl (lithium 4-O-allyl-3-O-benzyl-2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-lithium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(lithium 3-O-benzyl-2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-lithium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)]₃-(lithium 3-O-benzyl-2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-[[benzyloxy]carbonyl]amino}-2-deoxy-6-O-lithium sulfonato- α -D-glucopyranoside (36)

To a solution of compound **35** (47 mg, 12.5 μ mol) in a 1/1 v/v tetrahydrofuran/methanol mixture (2.0 mL) is added, at 0°C, a 1 M solution of lithium hydroxide in water (500 μ L; qs a final concentration of 0.2 M). After 1 hour at 0°C and then 4 hours at room temperature, the reaction medium is neutralized with acetic acid and then left at -20°C for 16 hours. The reaction mixture is deposited on a column of Sephadex[®] LH20 gel eluted with a 4/1 v/v methanol/water mixture to give compound **36** (38.9 mg).

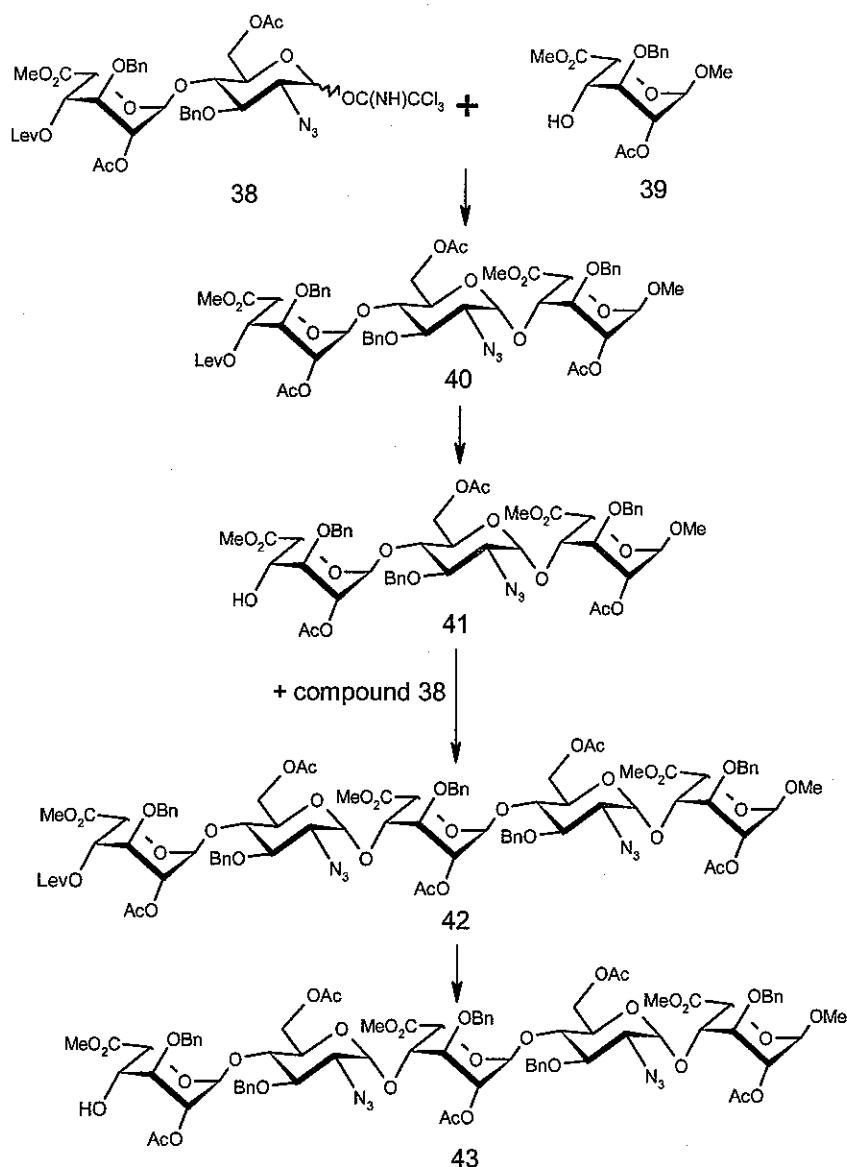
- Methyl (sodium 4-O-propyl-2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-amino-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-amino-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)]₃-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-amino-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranoside (37)
- 5

A solution of compound **36** (40 mg, 10.8 μ mol) in a 6/9 v/v *tert*-butanol/water mixture (1 mL) is treated under pressure of hydrogen (11 bar) in the presence of 10% palladium-on-charcoal (80 mg, 2 x amount of compound to be reduced) at 40°C for 4 hours. After filtration (Millipore[®] LSWP 5 μ m filter), the solution is deposited on a column of Chelex[®] 100 resin (1 mL) eluted with water and then concentrated to dryness. The crude compound thus obtained (27 mg) is used without further purification in the following step.

10

Mass: "ESI" method, negative mode: theoretical mass = 2781.10; experimental mass: 2782.05 $\pm$ 0.30 a.m.u.

15

SCHEME 7: Preparation of the heptasaccharide **43**

5

Methyl [methyl (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(6-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-2-O-acetyl-3-O-benzyl- α -L-idopyranoside]uronate (**40**)

A mixture of the imidate **38** (1.1 g, 1.22 mmol), prepared according to the method described by C. Tabeur *et al.*, *BioOrg. Med. Chem.* (1999) 7, 2003-2012, the glycosyl acceptor **39** (864 mg, 2.44 mmol), prepared according to the method described by Koshida, S. *et al.*, *Tetrahedron Lett.*, 1999, 40, 5725-5728,

and powdered 4 Å molecular sieves (914 mg) in toluene (43 mL) is stirred under an argon atmosphere for 1 hour at 25°C. The reaction mixture is cooled to -20°C and a 1 M solution of *tert*-butyldimethylsilyl triflate in dichloromethane (183 µL) is added. After stirring for 1 hour, the reaction medium is neutralized by addition of solid sodium hydrogen carbonate. After filtering through Celite® and concentrating, the residue obtained is chromatographed on a Sephadex® LH20 column (120 x 3 cm, 1/1 v/v dichloromethane/ethanol) followed by chromatography on a column of silica gel (1/1 v/v toluene/ethyl acetate) to give compound **40** (936 mg).

TLC: R_f = 0.38, silica gel, 1/1 v/v toluene/ethyl acetate

Methyl [methyl (methyl 2-O-acetyl-3-O-benzyl-α-L-idopyranosyluronate)-(1→4)-(6-O-acetyl-2-azido-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-2-O-acetyl-3-O-benzyl-α-L-idopyranoside]uronate (**41**)

Compound **40** (2.56 g, 2.34 mmol) is treated according to the same procedure as that described for the preparation of compound **23** to give compound **41** (2.17 g) after flash chromatography on a column of silica gel (1/1 v/v toluene/ethyl acetate).

TLC: R_f = 0.35, silica gel, 1/1 v/v toluene/ethyl acetate

20

Methyl [methyl (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl-α-L-idopyranosyluronate)-(1→4)-(6-O-acetyl-2-azido-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-(methyl 2-O-acetyl-3-O-benzyl-α-L-idopyranosyluronate)-(1→4)-(6-O-acetyl-2-azido-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-2-O-acetyl-3-O-benzyl-α-L-idopyranoside]uronate (**42**)

25

A mixture of the imidate **38** (1.1 g, 1.22 mmol), the glycosyl acceptor **41** (1.2 g, 1.20 mmol) and powdered 4 Å molecular sieves (903 mg) in dichloromethane (42 mL) is stirred under an argon atmosphere for 1 hour at 25°C. The reaction mixture is cooled to -20°C and a 1 M solution of *tert*-butyldimethylsilyl triflate in dichloromethane (181 µL) is added. After 15 minutes, the reaction medium is neutralized by addition of solid sodium hydrogen carbonate. After filtering and concentrating, the residue obtained is purified by

30

chromatography on a size exclusion column (Sephadex[®] LH20, 190 x 3.2 cm, 1/1 v/v dichloromethane/ethanol) followed by chromatography on a column of silica gel (1/1 v/v toluene/ethyl acetate) to give 1.63 g of compound **42**.

TLC: R_f = 0.30, silica gel, 1/1 v/v toluene/ethyl acetate

5

Methyl [methyl (methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(6-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(6-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-2-O-acetyl-3-O-benzyl- α -L-idopyranoside]uronate (**43**)

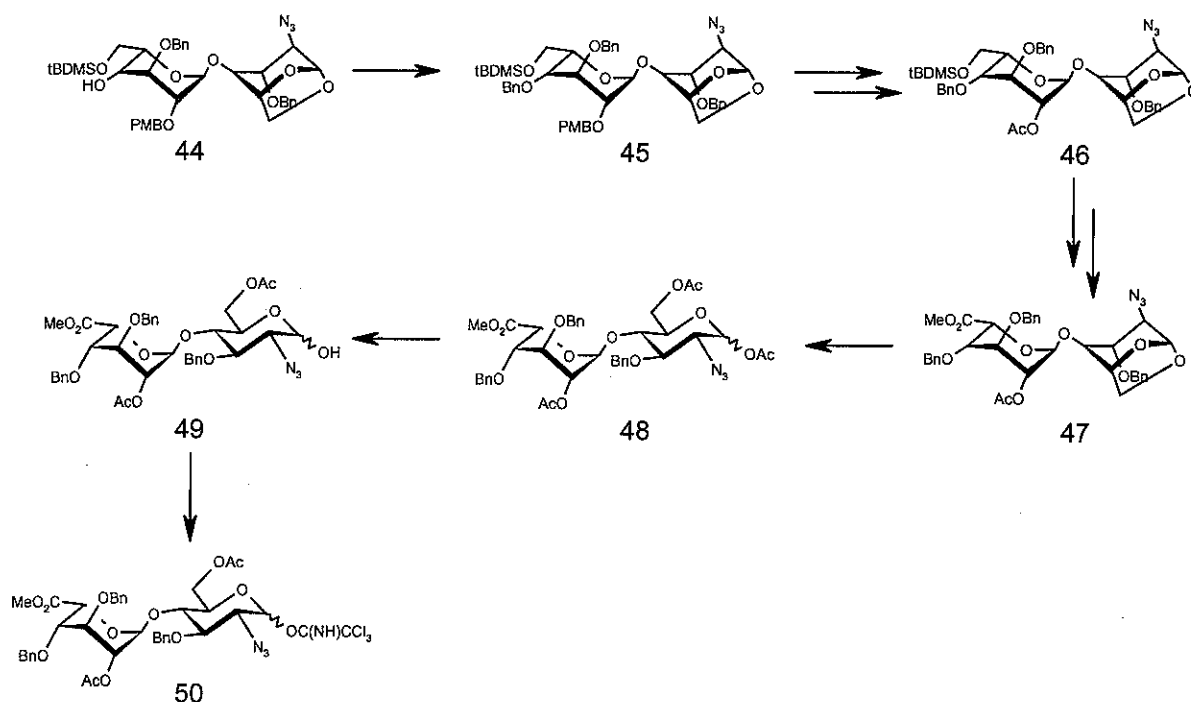
10

Compound **42** (3.90 g, 2.25 mmol) is treated according to the same procedure as that described for the preparation of compound **23**. Chromatography on a column of silica gel (1/1 v/v toluene/ethyl acetate) gives compound **43** (3.39 g).

15

TLC: R_f = 0.33, silica gel, 1/1 v/v toluene/ethyl acetate

SCHEME 8: Preparation of the disaccharide 50



(3,4-di-O-benzyl-2-O-(4-methoxy)benzyl-6-O-*tert*-butyldimethylsilyl- α -L-idopyranosyl)-(1 $\rightarrow$ 4)-1,6-anhydro-2-azido-3-O-benzyl-2-deoxy- β -D-glucopyranose (45)

To a solution of compound **44** (32.3 g, 42.2 mmol) (described in the preparation of compound 108 of patent application WO 2006/021653) in *N,N*-dimethylformamide (210 mL) is added, at 0°C and under argon, benzyl bromide (25 mL, 211 mmol) and then 55% NaH (3 g, 126 mmol). After 20 minutes of magnetic stirring, methanol is added (30 mL), the reaction medium is concentrated under vacuum, and the crude reaction product is diluted with ethyl acetate, washed with water and then with saturated aqueous sodium chloride solution, dried (Na₂SO₄), filtered and concentrated. The residue obtained is used in the following step without purification.

LC-MS *m/z* 871.7 [(M + NH₄)⁺]. T_R = 13.86 min

(2-O-acetyl-3,4-di-O-benzyl-6-O-*tert*-butyldimethylsilyl- α -L-idopyranosyl)-(1 $\rightarrow$ 4)-1,6-anhydro-2-azido-3-O-benzyl-2-deoxy- β -D-glucopyranose (46)

To a solution of crude compound **45** (38.6 g) in dichloromethane (1.6 L) are added water (80 mL) and then, at 0°C, DDQ (14.2 g). After stirring for 4 hours 45 minutes at 0°C, the medium is diluted with dichloromethane and aqueous sodium hydrogen carbonate solution is added. The organic phase is then washed with water, dried (Na₂SO₄), filtered and concentrated. The compound obtained is used in the following step without purification.

The residue obtained is dissolved in dichloromethane (350 mL), and triethylamine (13 mL), 4-dimethylaminopyridine (2 g) and acetic anhydride (60 mL) are added. After magnetic stirring for 10 minutes at 0°C, and then 1 hour 45 minutes at room temperature, the reaction mixture is diluted with dichloromethane, and then washed successively with aqueous 10% potassium hydrogen sulfate solution, water, and the organic phase is then dried (Na₂SO₄), filtered and concentrated.

The residue obtained is purified on silica (ethyl acetate/cyclohexane) to give compound **46** (26.8 g).

LC-MS *m/z* 798.3 [(M + Na)⁺]. T_R = 12.97 min

(Methyl 2-O-acetyl-3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-1,6-anhydro-2-azido-3-O-benzyl-2-deoxy- β -D-glucopyranose (47)

To a solution of compound **46** (26.3 g, 33.9 mmol) in acetone (1.4 L) is added, at 0°C, a solution of CrO₃ (10.5 g) in aqueous 3.5 M H₂SO₄ (47 mL).
5 After mechanical stirring for 4 hours at 0°C, the reaction medium is diluted with dichloromethane, washed with water until neutral, and the organic phase is then dried (Na₂SO₄), filtered and concentrated. The compound obtained is used in the following step without purification.

The residue obtained is dissolved in *N,N*-dimethylformamide (210 mL),
10 and potassium hydrogen carbonate (17 g) and methyl iodide (21 mL) are added. The reaction mixture is stirred at room temperature for 16 hours, and then concentrated under vacuum. The residue is diluted with ethyl acetate and then washed with water, with saturated aqueous sodium thiosulfate solution, with saturated aqueous sodium chloride solution, and then dried (Na₂SO₄), filtered
15 and concentrated. The compound obtained is used in the following step without purification.

LC-MS *m/z* 707.3 [(M + NH₄)⁺]. T_R = 10.37 min

(Methyl 2-O-acetyl-3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-1,6-di-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α,β -D-glucopyranose (48)

The crude residue obtained in the preceding step is dissolved in acetic anhydride (177 mL) and trifluoroacetic acid (TFA) (17.7 mL) is then added. The reaction mixture is stirred for 16 hours, and is then concentrated, co-evaporated with toluene and purified on silica gel (cyclohexane/ethyl acetate), to give
25 compound **48** (17.4 g).

LC-MS *m/z* 809.3 [(M + NH₄)⁺]. T_R = 10.81 min

(Methyl 2-O-acetyl-3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α,β -D-glucopyranose (49)

To a solution of compound **48** (7 g, 8.84 mmol) in diethyl ether (303 mL) is added, at 0°C and under argon, benzylamine (BnNH₂) (29.7 mL). After magnetic stirring for 1 hour at 0°C and then for 6 hours at room temperature, the

reaction mixture is neutralized with cold aqueous 1N HCl solution, washed with water, dried (Na_2SO_4), filtered and concentrated, and purified on silica gel (ethyl acetate/cyclohexane) to give compound **49** (5.95 g).

LC-MS m/z 767.7 $[(M + \text{NH}_4)^+]$. $T_R = 1.64$ min

5

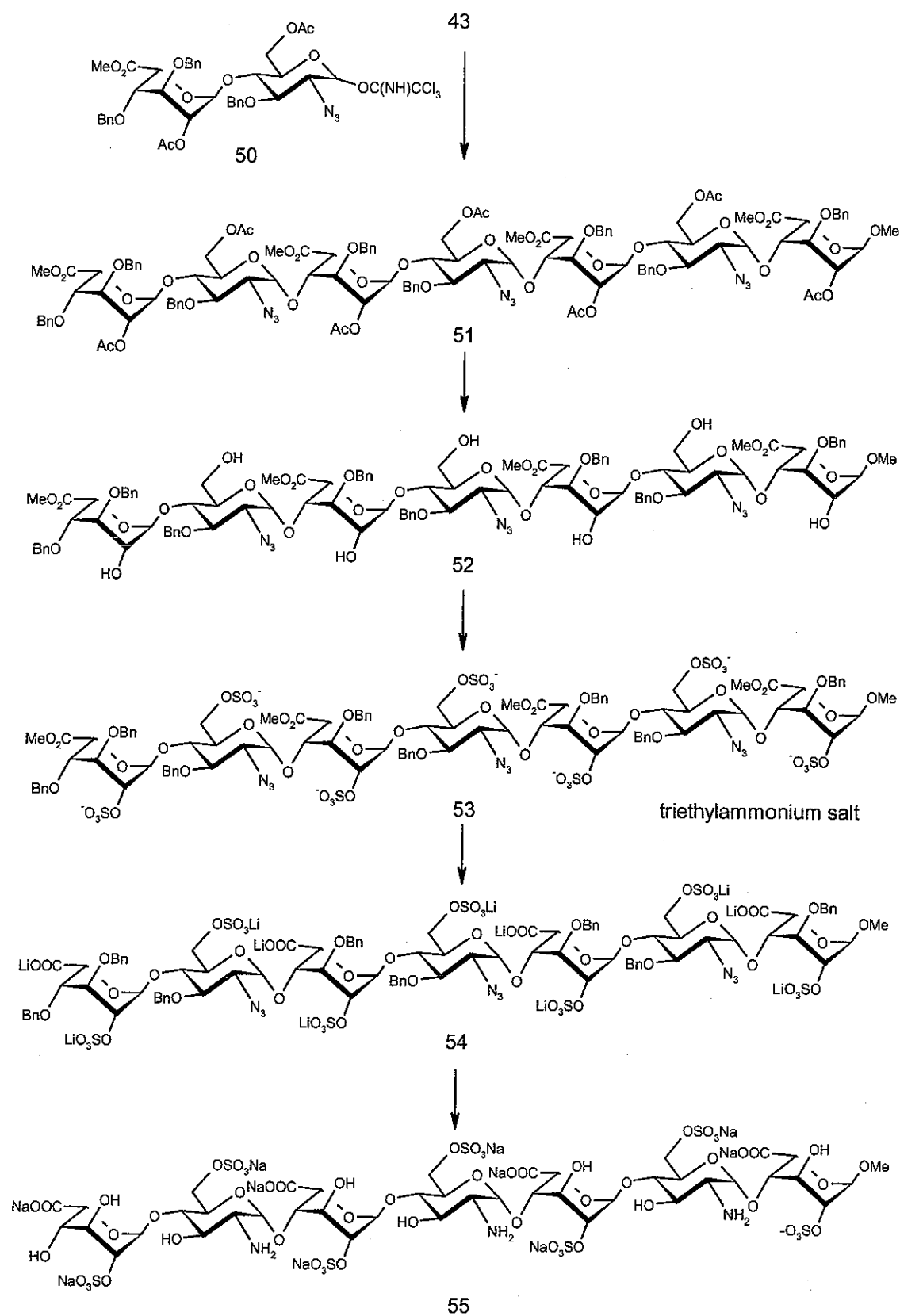
(Methyl 2-O-acetyl-3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α,β -D-glucopyranose trichloroacetimidate (**50**)

To a solution of compound **49** (5.94 g, 7.9 mmol) in dichloromethane (150 mL) are added, under argon, caesium carbonate (Cs_2CO_3) (4.1 g) and then
10 trichloroacetonitrile (CCl_3CN) (3.9 mL). After stirring for 45 minutes at room temperature, the reaction mixture is filtered and then concentrated. The residue is purified on silica gel (ethyl acetate/cyclohexane + 0.1% triethylamine) to give compound **50** (5.7 g).

LC-MS m/z 912.0 $[(M + \text{NH}_4)^+]$. $T_R = 1.81$ min

15

SCHEME 9: Preparation of the heptasaccharide 55



Methyl {methyl (methyl 2-O-acetyl-3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(6-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(6-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)]₂-2-O-acetyl-3-O-benzyl- α -L-idopyranoside}uronate (51)

A mixture of the glycosyl acceptor **43** (200 mg, 0.12 mmol), the imidate **50** (163 mg, 0.18 mmol) and powdered 4 Å molecular sieves (137 mg) in dichloromethane (6.5 mL) is stirred under an argon atmosphere for 1 hour at 25°C. The reaction mixture is cooled to -20°C and a 1 M solution of *tert*-butyldimethylsilyl triflate in dichloromethane (27 μ L) is added. After 1 hour, the reaction medium is neutralized by addition of solid sodium hydrogen carbonate. After filtering and concentrating, the residue obtained is purified by chromatography on a size exclusion column (Sephadex® LH20, 90 x 3 cm, 1/1 v/v dichloromethane/ethanol) followed by chromatography on a column of silica gel (2/1 v/v toluene/ethyl acetate) to give compound **51** (212 mg).

TLC: R_f = 0.38, silica gel, 1/1 v/v toluene/ethyl acetate.

Methyl {methyl (methyl 3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)]₂-3-O-benzyl- α -L-idopyranoside}uronate (52)

Compound **51** (271 mg, 0.11 mmol) is treated according to the same procedure as that described for the preparation of compound **27** to give compound **52** (186 mg) after chromatography on a size exclusion column (Sephadex® LH20, 120 x 3 cm, 1/1 v/v dichloromethane/ethanol) followed by chromatography on a column of silica gel (5/3 v/v toluene/acetone).

TLC: R_f = 0.65, silica gel, 4/3 v/v toluene/ethyl acetate

Methyl {methyl (methyl 3,4-di-O-benzyl-2-O-triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-triethylammonium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(methyl 3-O-benzyl-2-O-triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-triethylammonium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)]₂-3-O-benzyl-2-O-triethylammonium sulfonato- α -L-idopyranoside}uronate (53)

Compound **52** (172 mg, 0.08 mmol) is treated according to the same procedure as that described for the preparation of compound **28** to give compound **53** (196 mg) after size exclusion chromatography (Sephadex[®] LH20, 120 x 3 cm, 1/1 v/v dichloromethane/ethanol).

¹H NMR (D₂O) δ of the main anomeric protons: 5.41; 5.38; 5.34; 5.15; 5.14; 5.05; 5.15; 5.02 ppm.

Lithium {methyl (lithium 3,4-di-O-benzyl-2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-lithium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(lithium 3-O-benzyl-2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-lithium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)]₂-3-O-benzyl-2-O-lithium sulfonato- α -L-idopyranoside}uronate (54)

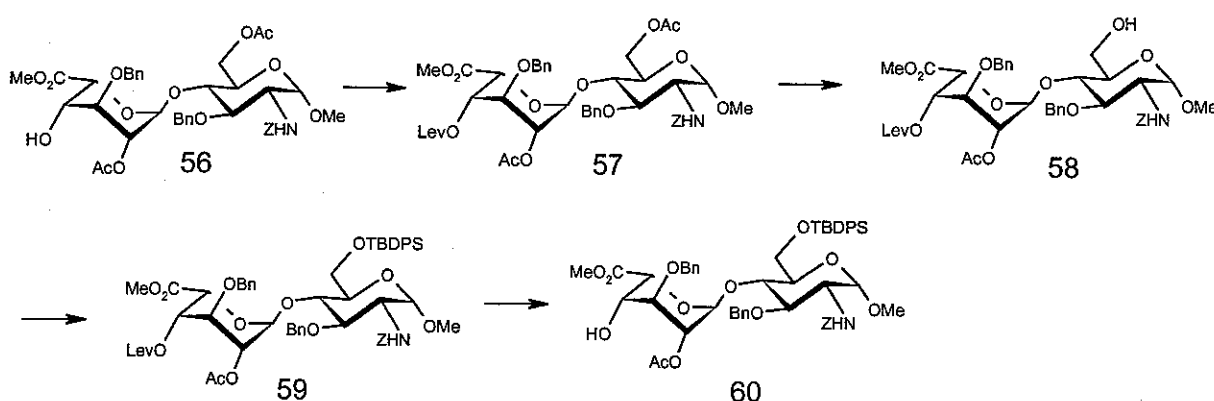
Compound **53** (186 mg, 70.7 μ mol) is treated according to the same procedure as that described for the preparation of compound **29** to give compound **54** (141 mg) after size exclusion chromatography (Sephadex[®] LH20, 120 x 3 cm, 50/50/1 v/v/v dichloromethane/ethanol/water).

TLC: R_f = 0.24, silica gel, 27/19/4.2/11 v/v/v/v ethyl acetate/pyridine/acetic acid/water

Sodium {methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-amino-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-amino-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)]₂-2-O-sodium sulfonato- α -L-idopyranoside}uronate (**55**)

A solution of compound **54** (60.0 mg, 0.022 mmol) in a 1/1 v/v *tert*-butanol/water mixture (6 mL) is treated under pressure of hydrogen (< 200 mbar) in the presence of 10% palladium-on-charcoal (60 mg) at room temperature. After stirring for 24 hours, the reaction medium is filtered (Millipore® LSWP 5 μ m filter) and then concentrated to dryness. The crude product **55** thus obtained (48.7 mg) is used without further purification in the following step.

SCHEME 10: Preparation of the glycoside acceptor 60



15

Methyl (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-acetyl-3-O-benzyl-2-benzoyloxycarbonylamino-2-deoxy- α -D-glucopyranoside (**57**)

To a solution of compound **56** (23.5 g, 30 mmol; prepared according to the method described in *Carbohydrate Research* (1987), 167, 67-75) in dichloromethane (600 mL) are added, at 0°C and under an inert atmosphere, 4-dimethylaminopyridine (733 mg, 6 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (11.5 g, 60 mmol) and levulinic acid (6.2 mL, 60 mmol). After stirring for 16 hours at room temperature, the mixture is diluted with dichloromethane (1.5 L). The organic phase is washed successively with

25

aqueous 10% potassium hydrogen sulfate solution, with water, with saturated sodium hydrogen carbonate solution and then with water, dried over sodium sulfate, filtered and then evaporated to dryness. The residue is purified by flash chromatography on a column of silica gel (1/3 cyclohexane/ethyl acetate) to give
5 compound **57** (22.6 g).

R_f = 0.37, silica gel, 1/3 v/v cyclohexane/ethyl acetate

Methyl (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-
idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-benzyloxycarbonylamino-2-deoxy- α -D-
10 glucopyranoside (**58**)

To a solution of compound **57** (20.2 g, 23 mmol) in a 1/1 tetrahydrofuran/methanol mixture (140 mL) is added, under an inert atmosphere, [tBu₂SnCl(OH)]₂ (226 mg, 0.79 mmol) prepared according to A. Orita *et al.*, *Chem. Eur. J.* (2001) 7, 3321. The reaction medium is stirred for 38 hours at
15 35°C. After concentrating, the residue (20.8 g) is used in the following step without purification.

R_f = 0.23, silica gel, 1/3 v/v cyclohexane/ethyl acetate

Methyl (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-
20 idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-benzyloxycarbonylamino-6-O-*tert*-
butyldiphenylsilyl-2-deoxy- α -D-glucopyranoside (**59**)

To a solution of crude compound **58** (23 mmol) in dichloromethane (190 mL) are added, at 0°C and under an inert atmosphere, triethylamine (8 mL, 57.5 mmol), 4-dimethylaminopyridine (1.4 g, 11.5 mmol) and *tert*-
25 butyldiphenylsilyl chloride (12 mL, 46.0 mmol). The reaction medium is stirred for 16 hours at room temperature. The reaction mixture is diluted with dichloromethane. The organic phase is washed successively with saturated aqueous sodium chloride solution and then with water, dried over sodium sulfate, filtered and then evaporated. The residue is purified by flash
30 chromatography on a column of silica gel (2/1 cyclohexane/ethyl acetate) to give compound **59** (24.4 g).

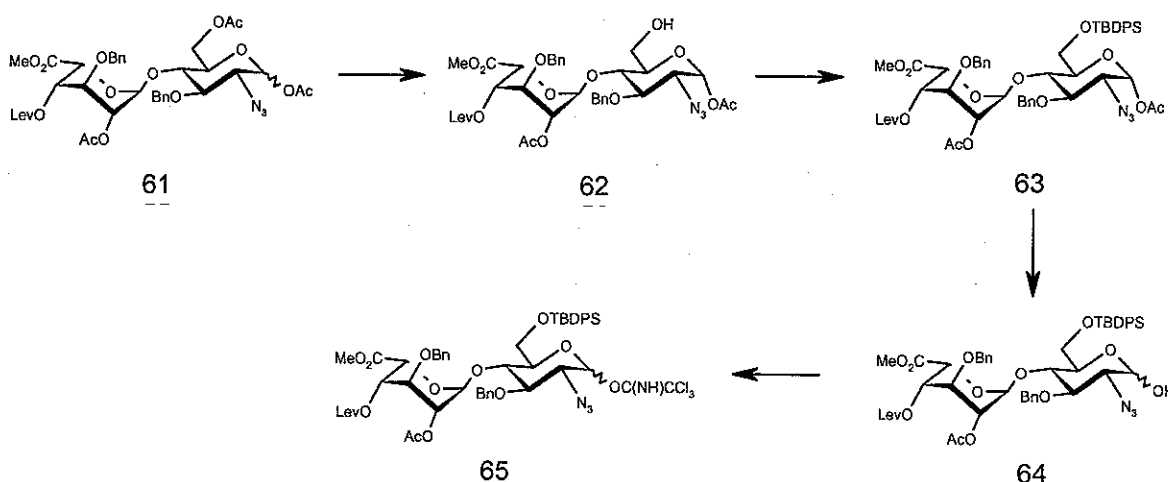
R_f = 0.42, silica gel, 2/1 v/v cyclohexane/ethyl acetate

Methyl (methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-benzylloxycarbonylamino-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranoside (60)

To a solution of compound **59** (22.6 g, 20.0 mmol) in a 1/2
5 toluene/ethanol mixture (2.5 L) is added hydrazine acetate (9.21 g, 100.0 mmol). The reaction medium is stirred for 30 minutes at room temperature. After concentrating, the residue is purified by flash chromatography on a column of silica gel (2/1 cyclohexane/ethyl acetate) to give 17.6 g of compound **60**.

R_f = 0.40, silica gel, 2/1 v/v cyclohexane/ethyl acetate

SCHEME 11: Preparation of the glycoside donor **65**



(Methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-1-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranose (62)

To a solution of **61** (11 g, 13.7 mmol) (prepared according to the method described by C. Tabeur *et al.*, Carbohydr. Res., 281 (1996) 253-276) in a 1/1
20 methanol/tetrahydrofuran mixture (80 mL) is added [tBu₂SnCl(OH)]₂ (0.55 g) prepared according to A. Orita *et al.*, Chem. Eur. J. (2001) 7, 3321. After stirring at 35°C for 5.5 hours, and then at room temperature for 16 hours, and then again at 35°C for 4 hours, the reaction mixture is concentrated under vacuum and then purified by chromatography to give compound **62** (5.97 g).

25 LC-MS *m/z* 780.2 [(M + Na)⁺]. T_R = 9.14 min

(Methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-
(1 $\rightarrow$ 4)-1-O-acetyl-2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-
glucopyranose (63)

- 5 Compound **62** (5.97 g, 7.88 mmol) is dissolved in dichloromethane (63 mL). At 0°C and under argon, 4-dimethylaminopyridine (0.481 g), triethylamine (2.7 mL), and *tert*-butyldiphenylsilyl chloride (4 mL) are successively added. After magnetic stirring for 4 hours, the reaction medium is diluted with dichloromethane, washed with aqueous 10% potassium hydrogen
10 sulfate solution, with water, dried (Na₂SO₄), filtered and concentrated. The residue obtained is purified on silica (ethyl acetate/heptane) to give compound **63** (7 g).

LC-MS *m/z* 1018.3 [(M + Na)⁺]. T_R = 12.33 min

- 15 (Methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-
(1 $\rightarrow$ 4)-2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α,β -D-
glucopyranose (64)

- To a solution of compound **63** (7 g, 7.03 mmol) in diethyl ether (70 mL), is added, at 0°C, benzylamine (BnNH₂) (29 mL). After stirring for 15 minutes at
20 0°C, and then for 6 hours at room temperature, the reaction mixture is diluted with ethyl acetate, and then neutralized with cold 1N HCl, washed with water, dried (Na₂SO₄), filtered and concentrated, and purified on silica gel (ethyl acetate/toluene) to give compound **64** (5.86 g).

LC-MS *m/z* 976.3 [(M + Na)⁺]. T_R = 27.6/27.8 min

25

(Methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-
(1 $\rightarrow$ 4)-2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α,β -D-
glucopyranose trichloroacetimidate (65)

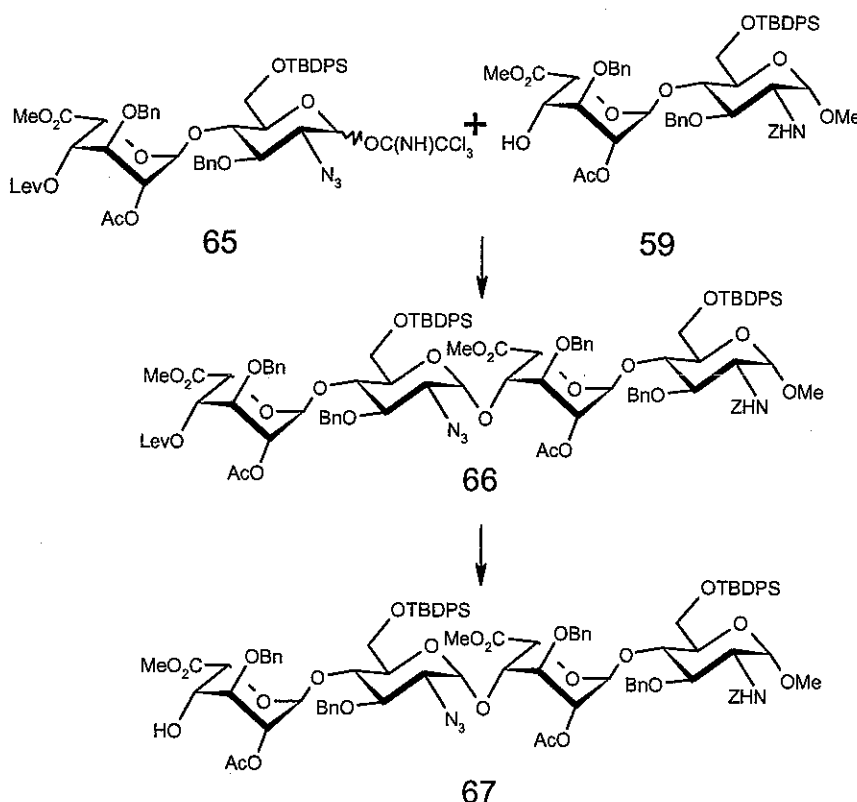
- To a solution of compound **64** (6.5 g, 6.81 mmol) in dichloromethane
30 (140 mL) and in the presence of powdered 4 Å molecular sieves (7 g) is added, under argon, caesium carbonate (Cs₂CO₃) (3.5 g) and then, at 0°C, trichloroacetonitrile (CCl₃CN) (3.4 mL). After stirring for 15 minutes at 0°C, and

then for 5 hours at room temperature, the reaction mixture is filtered and then concentrated. The residue is purified on silica gel (1/4 ethyl acetate/toluene + 0.1% triethylamine) to give compound **65** (6.33 g).

LC-MS m/z 1119.1 $[(M + Na)^+]$. $T_R = 31.2$

5

SCHEME 12: Preparation of the tetrasaccharide **67**



Methyl (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-benzylloxycarbonylamino-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranoside (**66**)

A mixture of the glycosyl acceptor **59** (8.80 g, 9.00 mmol), the imidate **65** (6.58 g, 6.00 mmol) and powdered 4 Å molecular sieves (4.50 g) in dichloromethane (210 mL) is stirred under an argon atmosphere for 1 hour at 25°C. The reaction mixture is cooled to -20°C and a 1 M solution of *tert*-butyldimethylsilyl triflate in dichloromethane (900 μ L) is added. After 1 hour 20 minutes, the reaction medium is neutralized by addition of solid sodium

hydrogen carbonate. After filtering through Celite® and concentrating, the residue obtained is chromatographed on a Sephadex® LH20 column (190 x 3.2 cm, 1/1 dichloromethane/ethanol) to give 8.26 g of compound **66**.

R_f = 0.30, silica gel, 2/1 cyclohexane/ethyl acetate

5

Methyl (methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1→4)-(2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranosyl)-(1→4)-(methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1→4)-3-O-benzyl-2-benzoyloxycarbonylamino-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranoside

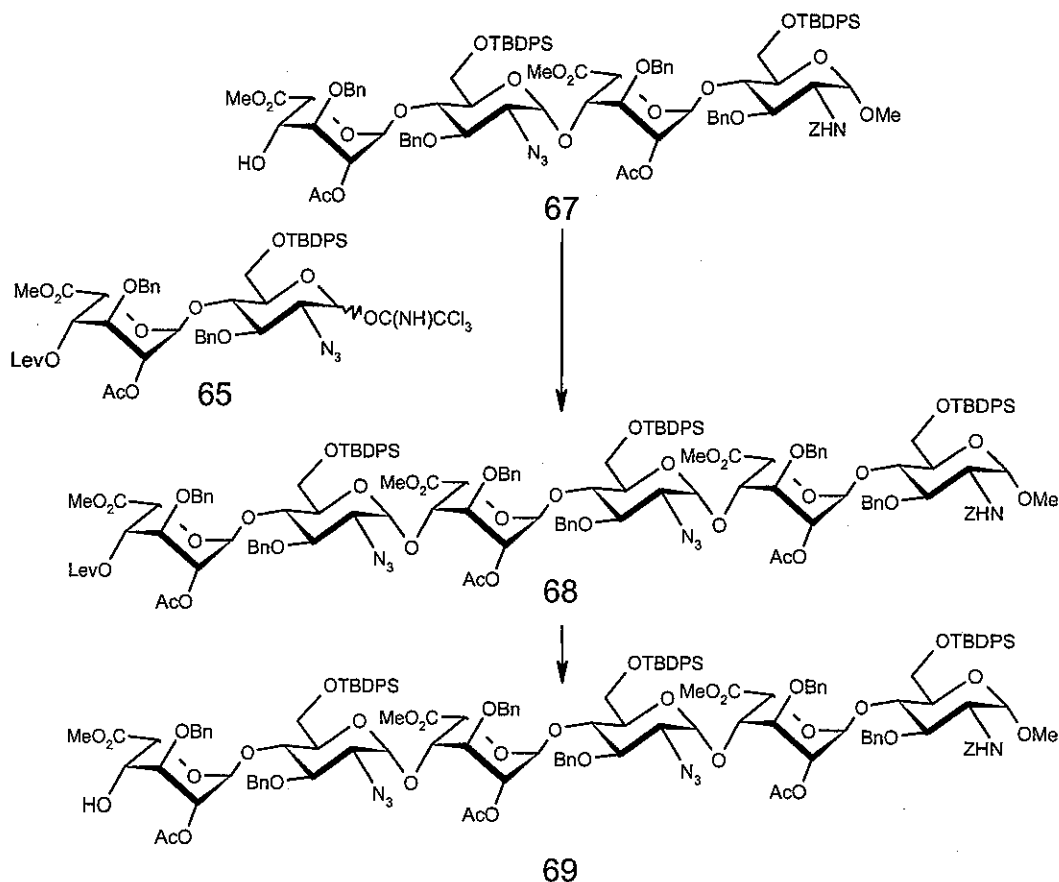
10 (67)

Compound **66** (8.26 g, 4.31 mmol) is transformed into compound **67** (6.41 g) according to the same procedure as that described for the synthesis of compound **23**.

R_f = 0.34, silica gel, 2/1 cyclohexane/ethyl acetate

15

SCHEME 13: Preparation of the hexasaccharide **69**



Methyl (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-benzyloxycarbonylamino-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranoside (68)

A mixture of the glycosyl acceptor **67** (7.42 g, 4.09 mmol), the imidate **65** (6.73 g, 6.1 mmol), and powdered 4 Å molecular sieves (4.60 g) in dichloromethane (215 mL) is stirred under an argon atmosphere for 1 hour at 25°C. The reaction mixture is cooled to -20°C and a 1 M solution of *tert*-butyldimethylsilyl triflate in dichloromethane (920 μ L) is added. After 1 hour 30 minutes, the reaction medium is neutralized by addition of solid sodium hydrogen carbonate. After filtering through Celite®, the reaction medium is diluted with dichloromethane (800 mL). The organic phase is washed successively with aqueous 2% sodium hydrogen carbonate solution, with water and then dried over sodium sulfate, filtered and then evaporated to dryness. The residue obtained is purified by chromatography on a column of Sephadex® LH20 (190 x 3.2 cm, 1/1 dichloromethane/ethanol) followed by chromatography on a column of silica gel (6/1 toluene/ethyl acetate) to give 6.13 g of compound **68**.

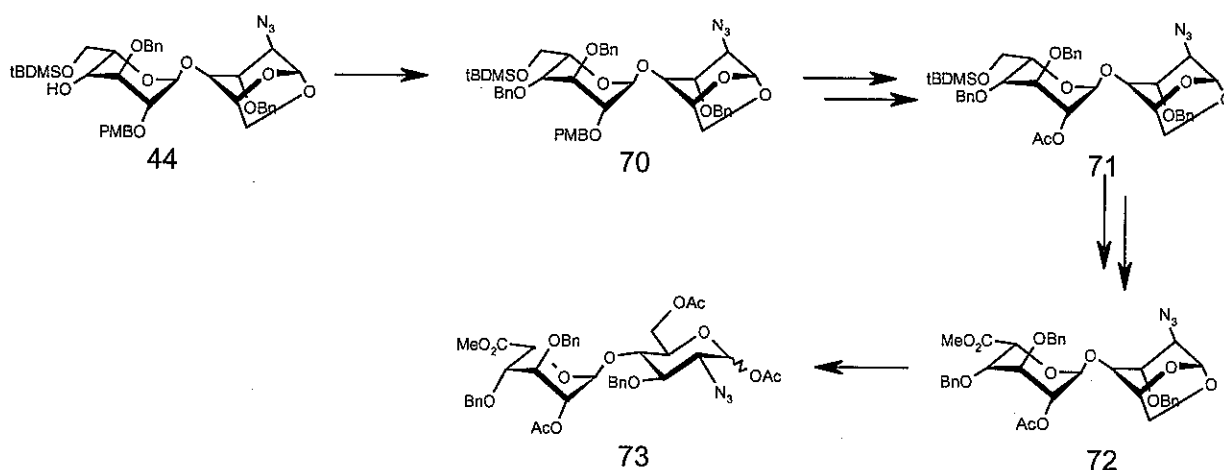
R_f = 0.46, silica gel, 4/1 v/v toluene/ethyl acetate

Methyl (methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranosyl)- (1 $\rightarrow$ 4)-
(methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-
benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 2-
 5 O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-
benzyloxycarbonylamino-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranoside
 (69)

Compound **68** (7.14 g, 2.59 mmol) is transformed into compound **69** (6.07 g) according to the same procedure as that described for the preparation
 10 of compound **23**.

R_f = 0.37, silica gel, 2/1 v/v cyclohexane/ethyl acetate

SCHEME 14: Preparation of the disaccharide **73**



15

(3,4-di-O-benzyl-2-O-(4-methoxy)benzyl-6-O-*tert*-butyldimethylsilyl- α -L-
idopyranosyl)-(1 $\rightarrow$ 4)-1,6-anhydro-2-azido-3-O-benzyl-2-deoxy- β -D-
 20 glucopyranose (70)

To a solution of compound **44** (32.3 g, 42.2 mmol) (described in the preparation of compound 108 of patent application WO 2006/021653) in *N,N*-dimethylformamide (210 mL) is added, at 0°C and under argon, benzyl bromide (25 mL) and then 55% NaH (3 g). After 20 minutes of magnetic stirring, methanol
 25 is added (30 mL), the reaction medium is concentrated under vacuum, and the

crude reaction product is diluted with ethyl acetate, washed with water and then with saturated aqueous sodium chloride solution, dried (Na_2SO_4), filtered and concentrated. The residue obtained (38.6 g) is used in the following step without purification.

5 LC-MS m/z 871.7 $[(M + \text{NH}_4)^+]$. T_R = 13.86 min

(2-O-acetyl-3,4-di-O-benzyl-6-O-*tert*-butyldimethylsilyl- α -L-idopyranosyl)-(1 $\rightarrow$ 4)-1,6-anhydro-2-azido-3-O-benzyl-2-deoxy- β -D-glucopyranose (71)

To a solution of crude compound **70** (38.6 g) in dichloromethane (1.6 L) are added water (80 mL) and then, at 0°C, DDQ (14.2 g). After stirring for 4 hours 45 minutes at 0°C, the medium is diluted with dichloromethane and aqueous sodium hydrogen carbonate solution is added. The organic phase is then washed with water, dried (Na_2SO_4), filtered and concentrated. The compound obtained is used in the following step without purification.

15 The residue obtained is dissolved in dichloromethane (350 mL), and then triethylamine (13 mL), 4-dimethylaminopyridine (2 g), and acetic anhydride (60 mL) are added. After magnetic stirring for 10 minutes at 0°C, and then for 1 hour 45 minutes at room temperature, the reaction mixture is diluted with dichloromethane, and then washed successively with aqueous 10% potassium hydrogen sulfate solution, water, and the organic phase is then dried (Na_2SO_4), filtered and concentrated. The residue obtained is purified on silica (ethyl acetate/cyclohexane) to give compound **71** (26.8 g).

LC-MS m/z 798.3 $[(M + \text{Na})^+]$. T_R = 12.97 min

25 (Methyl 2-O-acetyl-3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-1,6-anhydro-2-azido-3-O-benzyl-2-deoxy- β -D-glucopyranose (72)

To a solution of compound **71** (26.3 g, 33.9 mmol) in acetone (1.4 L) is added, at 0°C, a solution of CrO_3 (10.5 g) in aqueous 3.5 M H_2SO_4 (47 mL). After mechanical stirring for 4 hours at 0°C, the reaction medium is diluted with dichloromethane, washed with water until neutral, and then the organic phase is dried (Na_2SO_4), filtered and concentrated. The compound obtained is used in the following step without purification.

The residue obtained is dissolved in *N,N*-dimethylformamide (210 mL), and potassium hydrogen carbonate (17 g) and methyl iodide (21 mL) are added. The reaction mixture is stirred at room temperature for 16 hours, and then concentrated under vacuum. The residue is diluted with ethyl acetate and then washed with water, with saturated aqueous sodium thiosulfate solution, with saturated aqueous sodium chloride solution, and then dried (Na_2SO_4), filtered and concentrated. The compound obtained is used in the following step without purification.

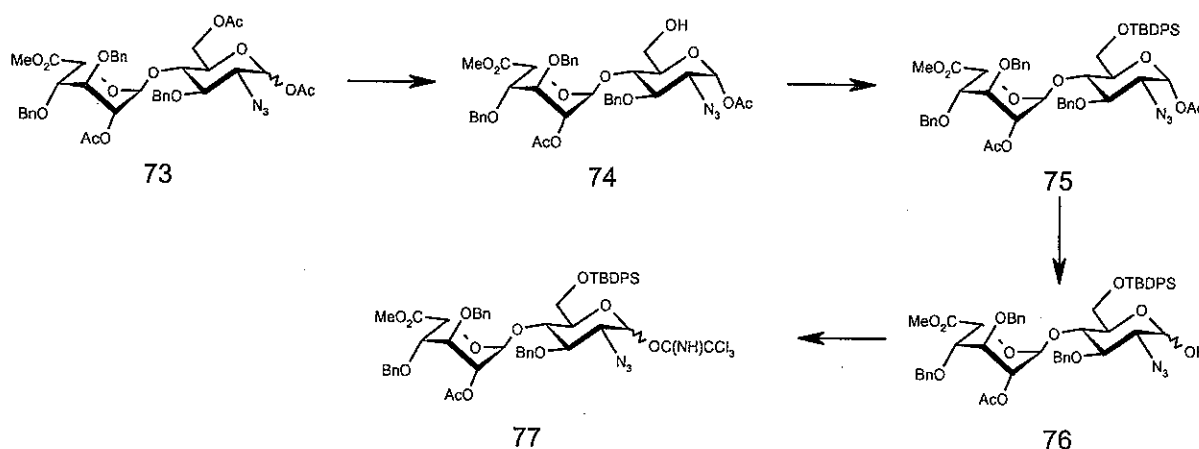
LC-MS m/z 707.3 $[(M + \text{NH}_4)^+]$. $T_R = 10.37$ min

(Methyl 2-O-acetyl-3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-1,6-di-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α,β -D-glucopyranose (73)

The crude residue obtained in the preceding step is dissolved in acetic anhydride (177 mL), and trifluoroacetic acid (TFA) (17.7 mL) is then added. The reaction mixture is stirred for 16 hours, and is then concentrated, co-evaporated with toluene, and purified on silica gel (cyclohexane/ethyl acetate), to give compound **73** (17.4g).

LC-MS m/z 809.3 $[(M + \text{NH}_4)^+]$. $T_R = 10.81$ min

SCHEME 15: Preparation of the glycosyl donor **77**



(Methyl 2-O-acetyl-3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-1-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranose (74)

To a solution of compound **73** (5.05 g, 6.3 mmol) in a 1/1 methanol/tetrahydrofuran mixture (76 mL) is added [tBu₂SnCl(OH)]₂ (0.25 g, 0.88 mmol), prepared according to A. Orita *et al.*, *Chem. Eur. J.* (2001) 7, 3321. After stirring at room temperature for 72 hours, the reaction mixture is concentrated under vacuum and then purified by chromatography to give compound **74** (2.89 g).

LC-MS *m/z* 772.4 [(M + Na)⁺]. T_R = 10.23 min

(Methyl 2-O-acetyl-3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-1-O-acetyl-2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranose (75)

Compound **74** (2.89 g, 3.86 mmol) is dissolved in dichloromethane (31 mL). At 0°C and under argon, triethylamine (1.3 mL), 4-dimethylaminopyridine (0.235 g) and *tert*-butyldiphenylsilyl chloride (2 mL) are successively added. After magnetic stirring for 3 hours, the reaction medium is diluted with dichloromethane, washed with aqueous 10% potassium hydrogen sulfate solution, with water, dried (Na₂SO₄), filtered and concentrated. The residue obtained is purified on silica (ethyl acetate/cyclohexane) to give compound **75** (3.4 g).

LC-MS *m/z* 1010.6 [(M + Na)⁺]. T_R = 13.10 min

(Methyl 2-O-acetyl-3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α,β -D-glucopyranose (76)

To a solution of compound **75** (3.44 g, 3.48 mmol) in diethyl ether (35 mL) is added, at 0°C, benzylamine (BnNH₂) (14.5 mL). After stirring for 8 hours at room temperature, the reaction mixture is placed at -18°C for 16 hours, and then again for 2.5 hours at room temperature. The medium is then diluted with ethyl acetate, and then neutralized with cold 1N HCl, washed with water, dried (Na₂SO₄), filtered and concentrated, and purified on silica gel (ethyl acetate/cyclohexane 15/85) to give **76** (3.83 g).

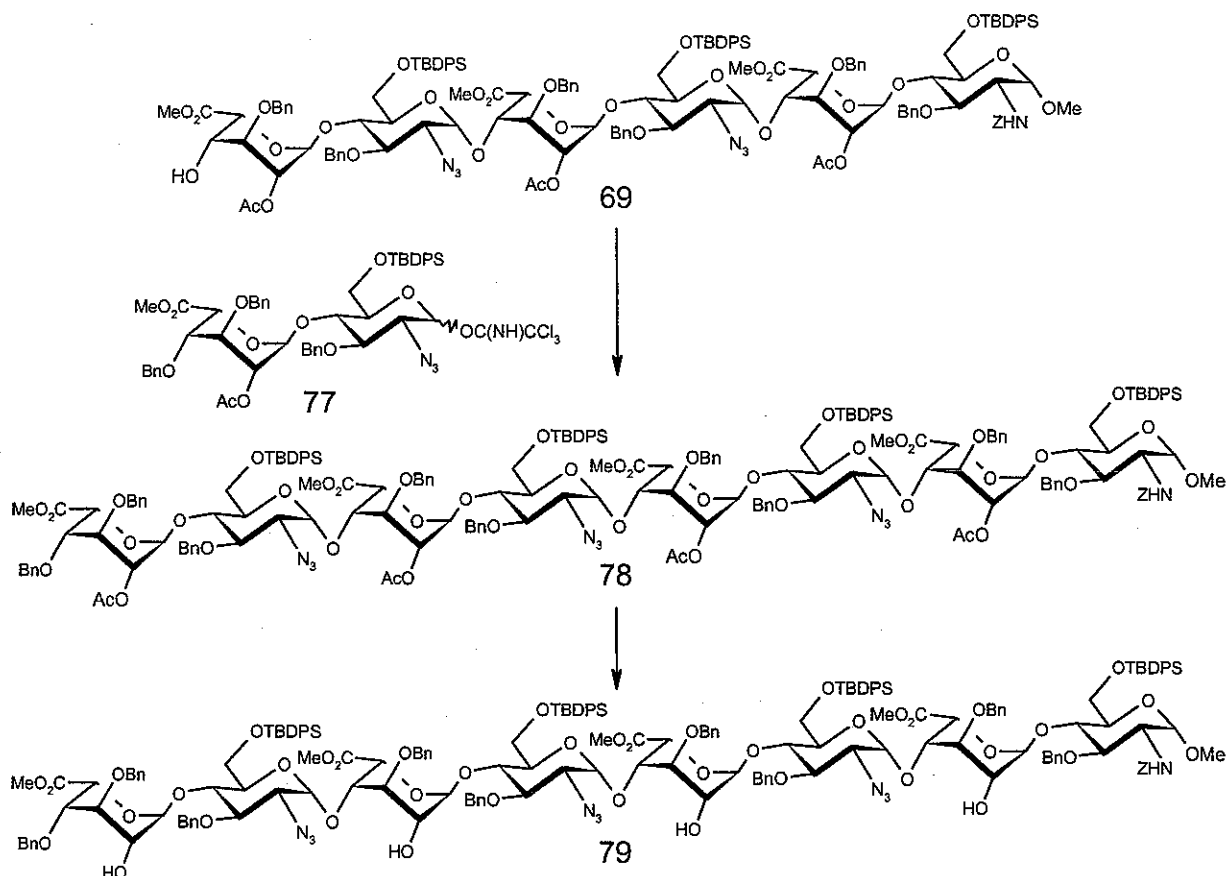
LC-MS m/z 963.6 $[(M + NH_4)^+]$. T_R = 12.37, 12.47 min

(Methyl 2-O-acetyl-3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α,β -D-glucopyranose

5 trichloroacetimidate (77)

To a solution of compound **76** (2.99 g, 3.16 mmol) in dichloromethane (60 mL) and in the presence of powdered 4 Å molecular sieves (3 g) are added, at 0°C under argon, caesium carbonate (Cs_2CO_3) (1.6 g), and then trichloroacetonitrile (CCl_3CN) (1.6 mL). After stirring for 20 minutes at 0°C, for 10 7 hours at room temperature, storing at -18°C for 16 hours, and then magnetic stirring for 8 hours at room temperature, storing at -18°C for 16 hours, and finally magnetic stirring for 1 hour at room temperature, the reaction mixture is filtered and then concentrated. The residue is purified on silica gel (15/85 ethyl acetate/cyclohexane + 0.1% triethylamine) to give compound **77** (2.69 g).

15 LC-MS m/z 1113.4 $[(M + Na)^+]$. T_R = 14.58 min

SCHEME 16: Preparation of the octasaccharide **79**

- 5 Methyl (methyl 2-O-acetyl-3,4-di-O-benzyl- α -L-idopyranosyluronate)-
(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-
glucopyranosyl)-(1 $\rightarrow$ 4)-[(methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-
(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-
glucopyranosyl)-(1 $\rightarrow$ 4)]2-(methyl 2-O-acetyl-3-O-benzyl- α -L-
10 idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-benzyloxycarbonylamino-6-O-*tert*-
butyldiphenylsilyl-2-deoxy- α -D-glucopyranoside (**78**)

A mixture of the glycosyl acceptor **69** (3.50 g, 1.32 mmol), the imidate **77** (2.16 g, 1.98 mmol) and powdered 4 Å molecular sieves (1.48 g) in dichloromethane (69 mL) is stirred under an argon atmosphere for 1 hour at room temperature. The reaction mixture is cooled to -20°C and a 1 M solution of *tert*-butyldimethylsilyl triflate in dichloromethane (297 μ L) is added. After 2 hours 30 minutes, the reaction medium is neutralized by addition of solid sodium

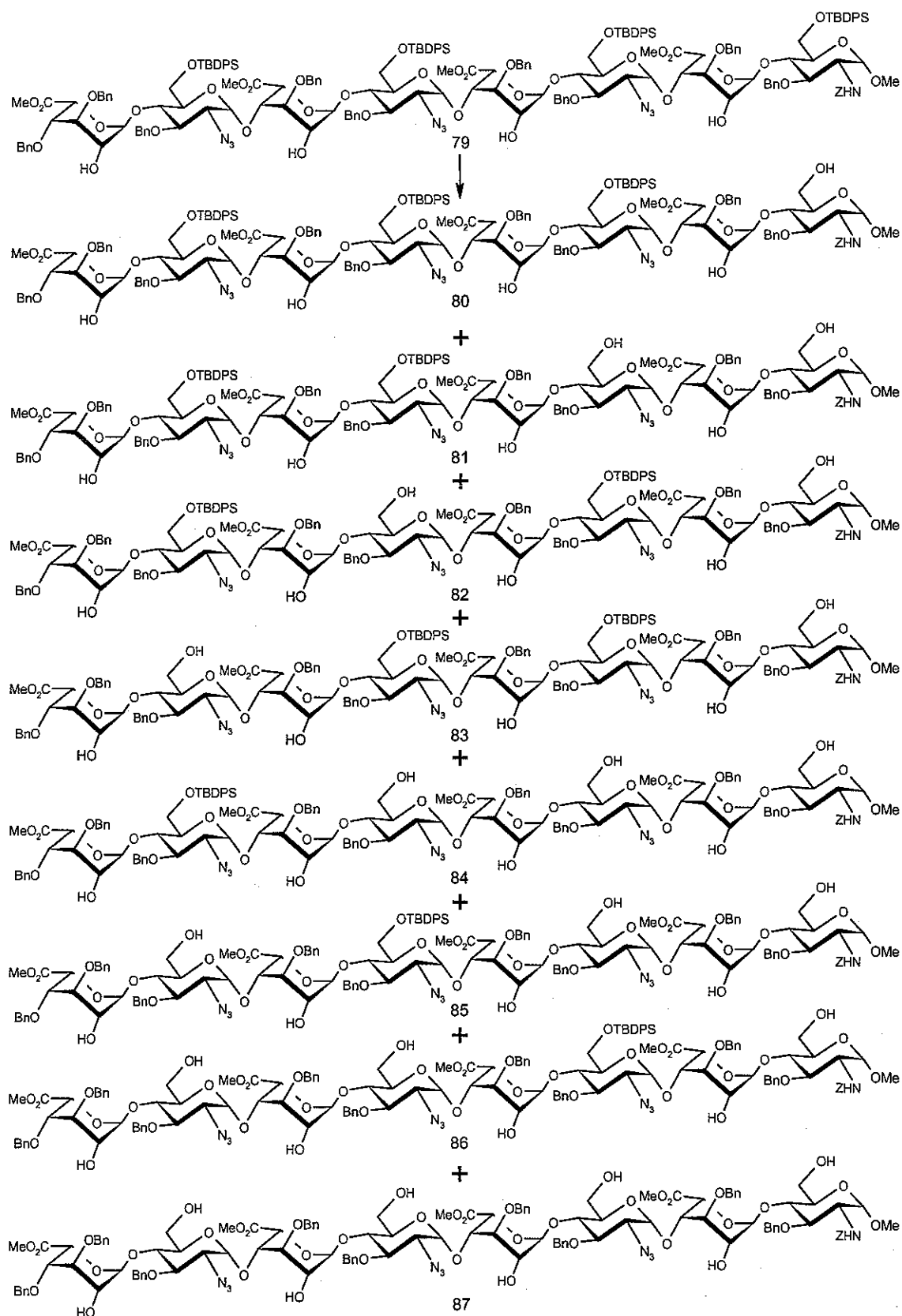
hydrogen carbonate. After filtering through Celite®, the reaction medium is diluted with dichloromethane (400 mL). The organic phase is washed successively with aqueous 2% sodium hydrogen carbonate solution, with water and then dried over sodium sulfate, filtered and then evaporated to dryness. The residue obtained is purified by chromatography on a column of Sephadex® LH20 (190 x 3.2 cm, 1/1 dichloromethane/ethanol) followed by chromatography on a column of silica gel (4/1 cyclohexane/ethyl acetate) to give 3.04 g of compound **78**.

R_f = 0.30, silica gel, 3/1 cyclohexane/ethyl acetate

Methyl (methyl 3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1→4)-(2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranosyl)-(1→4)-[(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1→4)-(2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranosyl)-(1→4)]₂-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1→4)-3-O-benzyl-2-benzyloxycarbonylamino-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranoside (**79**)

To a solution of compound **78** (2.23 g, 0.623 mmol) in a 2/3 dichloromethane/methanol mixture (187 mL) containing 3 Å molecular sieves (78 mg) is added, under an argon atmosphere and at 0°C, a 1 M solution of sodium methoxide in methanol (99.7 μ L). After 24 hours at room temperature, the reaction medium is neutralized with Dowex AG 50 WX4 H⁺ resin. After filtering and concentrating, the residue is chromatographed on a column of Sephadex® LH20 (120 x 3 cm, 1/1 dichloromethane/ethanol) followed by flash chromatography on a column of silica gel (100/0→66/34 cyclohexane/ethyl acetate) to give 1.80 g of compound **79**.

R_f = 0.38, silica gel, 3/1 v/v cyclohexane/ethyl acetate

SCHEME 17: Preparation of the octasaccharides **80**, **81**, **82**, **83**, **84**, **85**, **86** and **87**

Methyl (methyl 3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)]₂-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-[[*(benzyloxy)carbonyl*]amino]-2-deoxy- α -D-glucopyranoside (80)

Methyl (methyl 3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-[[*(benzyloxy)carbonyl*]amino]-2-deoxy- α -D-glucopyranoside (81)

Methyl (methyl 3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-[[*(benzyloxy)carbonyl*]amino]-2-deoxy- α -D-glucopyranoside (82)

Methyl (methyl 3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)]₂-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-[[*(benzyloxy)carbonyl*]amino]-2-deoxy- α -D-glucopyranoside (87)

To a solution of compound **79** (373 mg, 0.11 mmol) in methanol (14 mL) is added ammonium fluoride (324 mg, 8.74 mmol). After stirring for 20 hours at room temperature, the reaction mixture is deposited on a column of Sephadex® LH20 gel (120 x 3 cm, 1/1 v/v dichloromethane/ethanol) followed by flash chromatography on a column of silica gel (1/0 $\rightarrow$ 7/3 v/v toluene/acetone) to give successively:

- Compound **80** (58.8 mg)
TLC: R_f = 0.63, silica gel, 65/35 v/v toluene/acetone
- Compound **81** (44.4 mg)
TLC: R_f = 0.53, silica gel, 65/35 v/v toluene/acetone
- 5 - Compound **82** (37.7 mg)
TLC: R_f = 0.45, silica gel, 65/35 v/v toluene/acetone
- A mixture of compound **83** and of compound **84** (54.0 mg)
- A mixture of compound **85** and of compound **86** (48.3 mg)
- Compound **87** (26.6 mg)
- 10 TLC: R_f = 0.14, silica gel, 65/35 v/v toluene/acetone

Methyl (methyl 3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-[[*(benzyloxy)carbonyl*]amino]-2-deoxy- α -D-glucopyranoside (**83**))

Methyl (methyl 3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[[methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)]₂-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-[[*(benzyloxy)carbonyl*]amino]-2-deoxy- α -D-glucopyranoside (**84**))

25 The mixture of compounds **83** and **84** (260 mg) is purified by flash chromatography on a column of silica gel (100/0 $\rightarrow$ 85/15 v/v toluene/methanol) to give compound **83** (27.8 mg).

TLC: R_f = 0.22, silica gel, 85/15 v/v toluene/methanol

30 The remaining fractions are repurified by flash chromatography on a column of silica gel (100/0 $\rightarrow$ 97/3 v/v dichloromethane/methanol) to give compound **84** (45.3 mg).

TLC: R_f = 0.13, silica gel, 85/15 v/v toluene/methanol

5 Methyl (methyl 3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-[(benzyloxy)carbonyl]-amino}-2-deoxy- α -D-glucopyranoside (85)

10 Methyl (methyl 3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-[(benzyloxy)carbonyl]-amino}-2-deoxy- α -D-glucopyranoside (86)

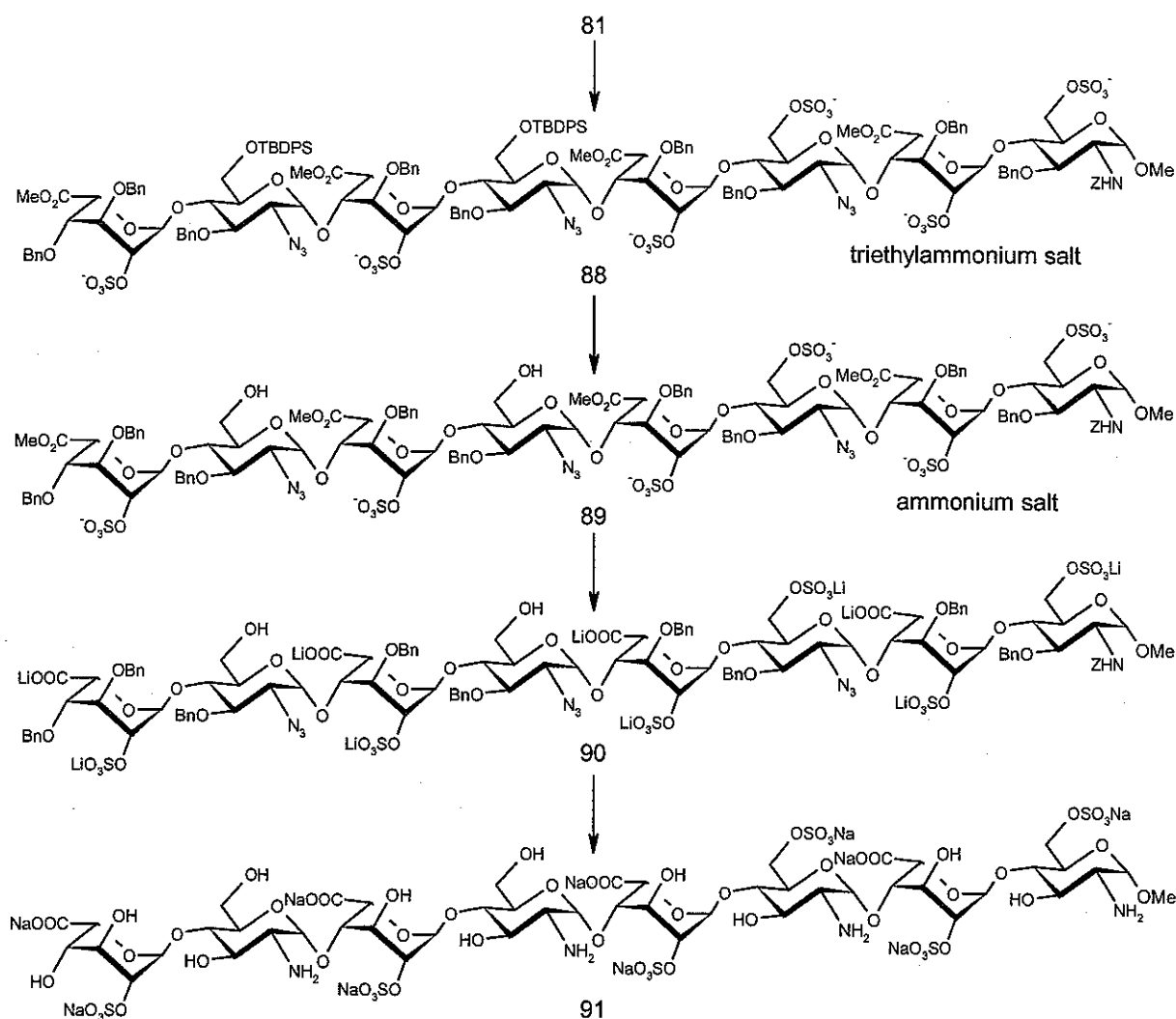
The mixture of compounds **85** and **86** (135 mg) is purified by HPLC chromatography on a column of C18 silica gel (Waters® Sunfire, 5 μ m, 150 x 19 mm, 9/1 acetonitrile/water + 0.1% trifluoroacetic acid) to give successively:

20 - Compound **85** (32.6 mg), after size exclusion chromatography (Sephadex® LH20, 120 x 3 cm, 1/1 v/v dichloromethane/ethanol)

Mass: "ESI" method, negative mode: theoretical mass = 2698.96; experimental mass: 2698.55 $\pm$ 0.65 a.m.u.

- Compound **86** (26.5 mg), after size exclusion chromatography (Sephadex® LH20, 120 x 3 cm, 1/1 v/v dichloromethane/ethanol)

25 Mass: "ESI" method, negative mode: theoretical mass = 2698.96; experimental mass: 2698.95 $\pm$ 1.05 a.m.u.

SCHEME 18: Preparation of the octasaccharide **91**

5

Methyl (methyl 3,4-di-O-benzyl-2-O-triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl-2-O-triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-6-O-*tert*-butyl-

10 diphenylsilyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl-2-O-triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-triethylammonium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl-2-O-triethylammonium sulfonato- α -L-idopyranosyluronate)-

(1→4)-3-O-benzyl-2-[[benzyloxy]carbonyl]amino}-2-deoxy-6-O-triethylammonium sulfonato-α-D-glucopyranoside (88)

Compound **81** (69 mg, 23.5 μmol) is treated according to the same procedure as that described for the preparation of compound **28** to give
 5 compound **88** (85.1 mg) after size exclusion chromatography (Sephadex® LH20, 120 x 3 cm, 1/1 v/v dichloromethane/ethanol).

TLC: R_f = 0.62, silica gel, 17/9/2.2/5 v/v/v/v ethyl acetate/pyridine/acetic acid/water.

10 Methyl (methyl 3,4-di-O-benzyl-2-O-ammonium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-azido-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-(methyl 3-O-benzyl-2-O-ammonium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-azido-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-(methyl 3-O-benzyl-2-O-ammonium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-azido-3-O-benzyl-2-deoxy-6-O-ammonium sulfonato-α-D-glucopyranosyl)-(1→4)-(methyl 3-O-benzyl-2-O-ammonium sulfonato-α-L-idopyranosyluronate)-(1→4)-3-O-benzyl-2-[[benzyloxy]carbonyl]amino}-2-deoxy-6-O-ammonium sulfonato-α-D-glucopyranoside (89)

To a solution of compound **88** (85.1 mg, 21.1 μmol) in methanol (2.7 mL)
 20 is added ammonium fluoride (31.3 mg, 0.846 mmol). After 48 hours at 55°C, the reaction mixture is deposited on a column of Sephadex® LH20 gel (95 x 2 cm) eluted with *N,N*-dimethylformamide to give compound **89** (64 mg).

[α]_D 19.4° (c 1.0; MeOH)

25 Methyl (lithium 3,4-di-O-benzyl-2-O-lithium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-azido-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-(lithium 3-O-benzyl-2-O-lithium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-azido-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-(lithium 3-O-benzyl-2-O-lithium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-azido-3-O-benzyl-2-deoxy-6-O-lithium sulfonato-α-D-glucopyranosyl)-(1→4)-(lithium 3-O-benzyl-2-O-lithium sulfonato-α-L-idopyranosyluronate)-(1→4)-3-O-benzyl-2-

30

{[(benzyloxy)carbonyl]amino}-2-deoxy-6-O-lithium sulfonato- α -D-glucopyranoside (90)

Compound **89** (63.3 mg; 17.8 μ mol) is treated according to the same procedure as that described for the preparation of compound **29**.

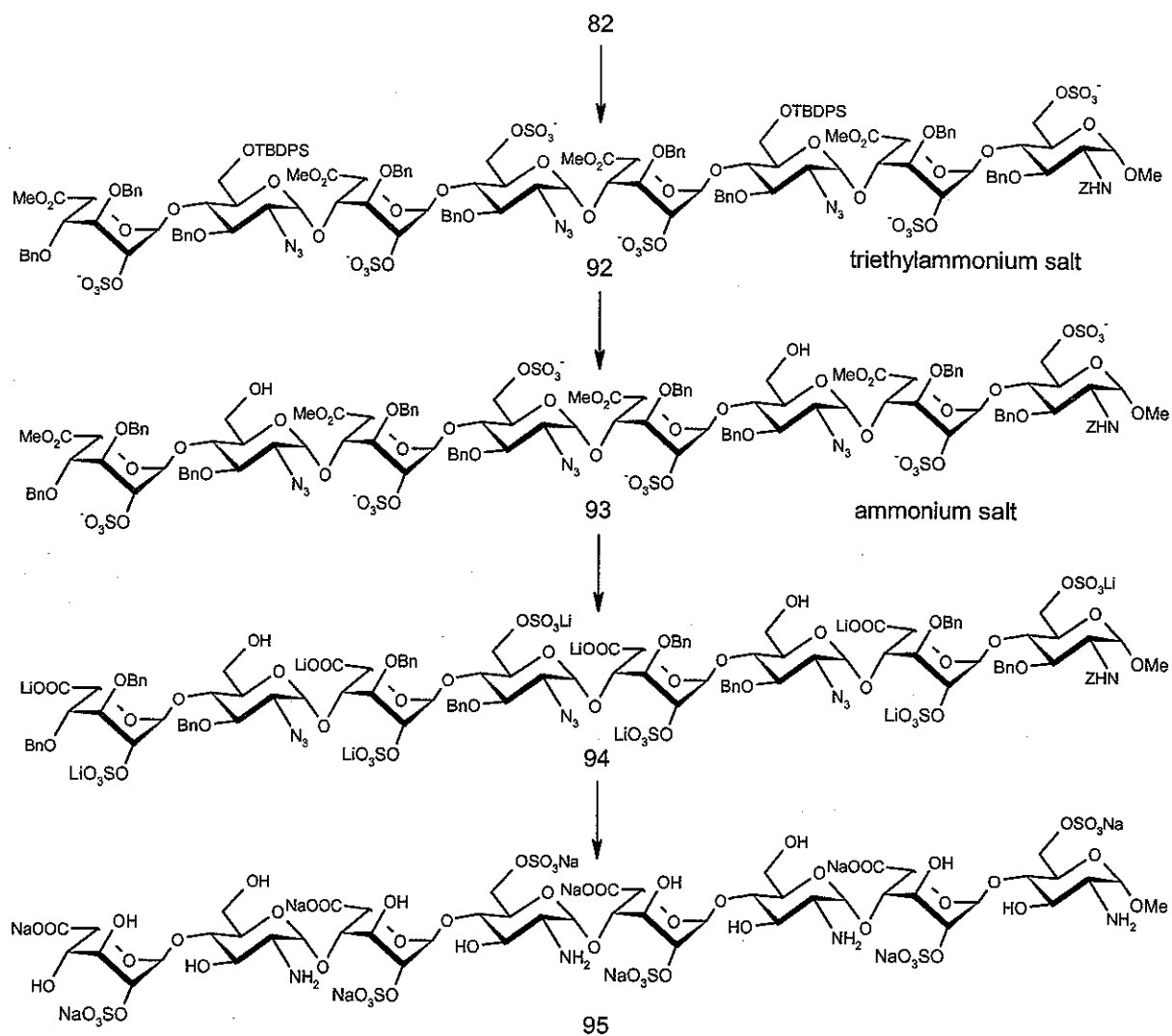
- 5 Chromatography on a column of Sephadex[®] LH20 gel (120 x 3 cm, 50/50/1 v/v/v dichloromethane/ethanol/water) gives compound **90** (49.8 mg).

$[\alpha]_D$ 14.6° (c 1.0; MeOH)

- Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-amino-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-amino-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-amino-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-amino-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranoside (**91**)
- 10
15

To a solution of compound **90** (7.6 mg; 2.6 μ mol) in a 1/1 v/v *tert*-butanol/water mixture (516 μ L) are successively added, at room temperature, ammonium formate (21.2 mg; 0.33 μ mol) and 10% palladium-on-charcoal (49.4 mg). After stirring for 4 hours, the reaction medium is filtered (Millipore[®] LSWP 5 μ m filter) and deposited on a column of Sephadex[®] G25-fine gel (95 x 2 cm) eluted with aqueous 0.2 M NaCl solution. The fractions containing the expected compound are combined and deposited on a column of Sephadex[®] G25-fine gel (95 x 2 cm) eluted with water. The crude product **91** thus obtained (5.5 mg) is used without further purification in the following step.

SCHEME 19: preparation of the octasaccharide 95



Methyl (methyl 3,4-di-O-benzyl-2-O-triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl-2-O-triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-triethylammonium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl-2-O-triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-*tert*-butyldiphenylsilyl- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl-2-O-triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-[[*(benzyloxy)carbonyl*]amino]-2-deoxy-6-O-triethylammonium sulfonato- α -D-glucopyranoside (92)

Compound **82** (16.5 mg, 5.6 μ mol) is treated according to the same procedure as that described for the preparation of compound **28** to give compound **92** (21.5 mg) after chromatography on a column of Sephadex[®] LH20 gel (120 x 3 cm, 1/1 v/v dichloromethane/ethanol).

TLC: R_f = 0.73, silica gel, 28/16/3.8/9 v/v/v/v ethyl acetate/pyridine/acetic acid/water.

Methyl (methyl 2-O-ammonium sulfonato-3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 2-O-ammonium sulfonato-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(6-O-ammonium sulfonato 2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 2-O-ammonium sulfonato-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 2-O-ammonium sulfonato-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-ammonium sulfonato-3-O-benzyl-2-[[*(benzyloxy)carbonyl*]amino]-2-deoxy- α -D-glucopyranoside (93)

Compound **92** (21.5 mg, 5.3 μ mol) is treated according to the same procedure as that described for the preparation of compound **89** to give compound **93** (21.5 mg) after size exclusion chromatography (Sephadex[®] LH20, 95 x 2 cm, *N,N*-dimethylformamide).

TLC: R_f = 0.63, silica gel, 11/7/1.6/4 v/v/v/v ethyl acetate/pyridine/acetic acid/water.

Methyl (lithium 3,4-di-O-benzyl-2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(lithium 3-O-benzyl-2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-lithium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(lithium 3-O-benzyl-2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(lithium 3-O-benzyl-2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-[[benzyloxy]carbonyl]amino-2-deoxy-6-O-lithium sulfonato- α -D-glucopyranoside
(94)

Compound **93** (14.7 mg, 4.1 μ mol) is treated according to the same procedure as that described for the preparation of compound **31** to give compound **94** (13.0 mg) after size exclusion chromatography (Sephadex[®] LH20, 95 x 2 cm, 50/50/1 v/v/v dichloromethane/ethanol/water).

TLC: R_f = 0.56, silica gel, 28/16/3.8/9 v/v/v/v ethyl acetate/pyridine/acetic acid/water

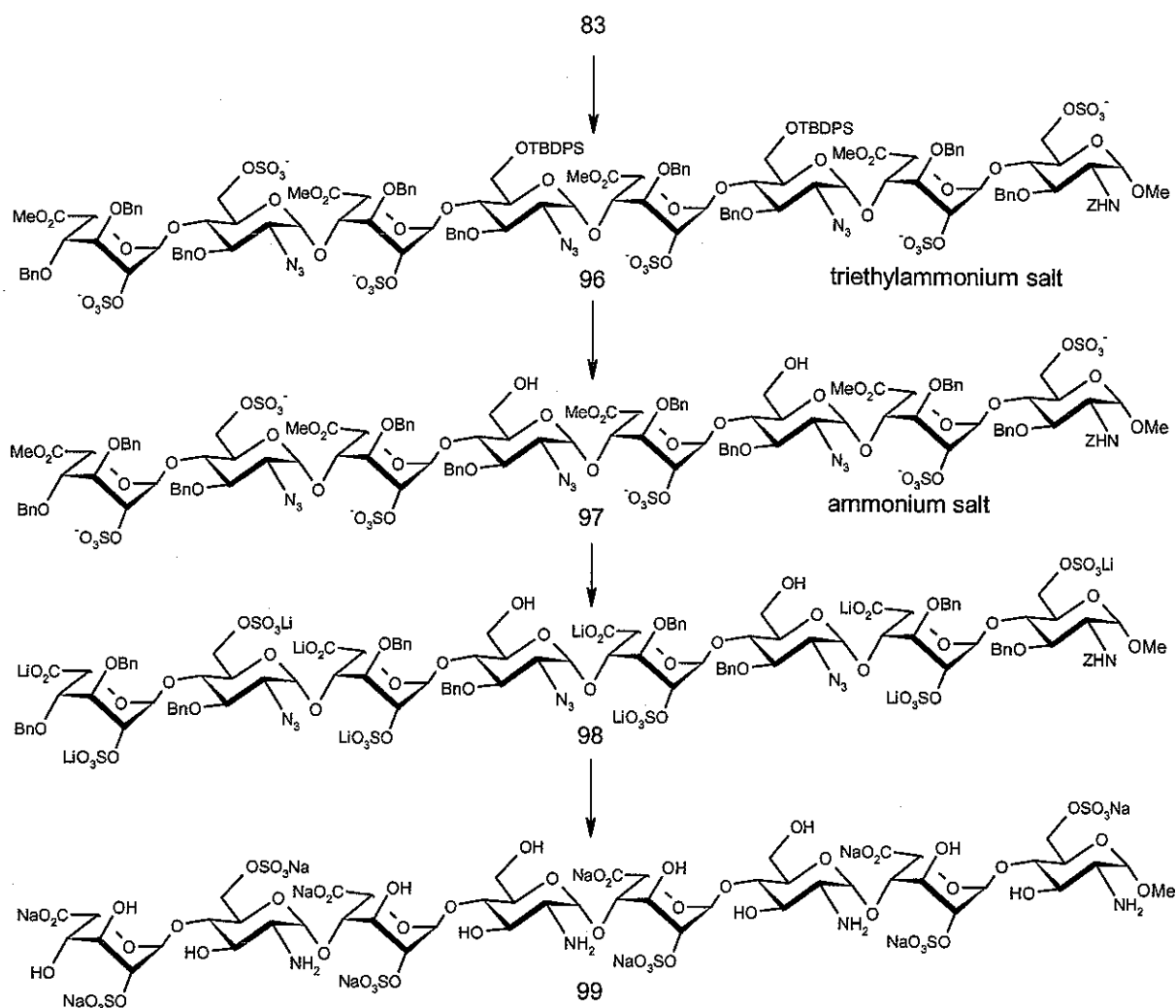
Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-amino-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-amino-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-amino-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-amino-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranoside (95)

To a solution of compound **94** (13 mg, 4.4 μ mol) in a 1/1 v/v *tert*-butanol/water mixture (883 μ L) are added ammonium formate (36 mg, 0.57 mmol) and 10% palladium-on-charcoal (34 mg). After stirring for 4 hours at room temperature, the reaction medium is filtered (Millipore[®] LSWP 5 μ m filter) and concentrated to dryness. The residue is deposited on a column of Sephadex[®] G25-fine gel (95 x 2 cm) eluted with aqueous 0.2 M NaCl solution. The fractions containing the expected compound are combined and deposited on a column of Sephadex[®] G25-fine gel (95 x 2 cm) eluted with water. The crude

product **95** thus obtained (2.5 mg) is used without further purification in the following step.

SCHEME 20: preparation of the octasaccharide **99**

5



10 Methyl (methyl 3,4-di-O-benzyl-2-O-triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-triethylammonium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(methyl 3-O-benzyl-2-O-triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl-2-O-triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)]₂-3-O-benzyl-2-

{[(benzyloxy)carbonyl]amino}-2-deoxy-6-O-triethylammonium sulfonato- α -D-glucopyranoside (96)

Compound **83** (35.1 mg, 12.0 μ mol) is treated according to the same procedure as that described for the preparation of compound **28** to give
 5 compound **96** (46.3 mg) after chromatography on a column of Sephadex[®] LH20 gel (120 x 3 cm, 1/1 v/v dichloromethane/ethanol).

$[\alpha]_D^{111}$ (c 0.95; CH₂Cl₂)

Methyl (methyl 2-O-ammonium sulfonato-3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(6-O-ammonium sulfonato-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 2-O-ammonium sulfonato 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 2-O-ammonium sulfonato-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-
 10 (1 $\rightarrow$ 4)-(methyl 2-O-ammonium sulfonato-3-O-benzyl- α -L-idopyranosyluronate)-
 15 (1 $\rightarrow$ 4)-6-O-ammonium sulfonato-3-O-benzyl-2-{[(benzyloxy)carbonyl]amino}-2-deoxy- α -D-glucopyranoside (97)

Compound **96** (45.0 mg, 11.2 μ mol) is treated according to the same procedure as that described for the preparation of compound **89** to give
 20 compound **97** (30.8 mg) after chromatography on a column of Sephadex[®] LH20 gel (95 x 2 cm, *N,N*-dimethylformamide).

$[\alpha]_D^{14.7}$ (c 0.95; MeOH)

Methyl (lithium 3,4-di-O-benzyl-2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-lithium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(lithium 3-O-benzyl-2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-
 25 (1 $\rightarrow$ 4)]₂-(lithium methyl 3-O-benzyl-2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-{[(benzyloxy)carbonyl]amino}-2-
 30 deoxy-6-O-lithium sulfonato- α -D-glucopyranoside (98)

Compound **97** (27.1 mg, 7.6 μ mol) is treated according to the same procedure as that described for the preparation of compound **29** to give

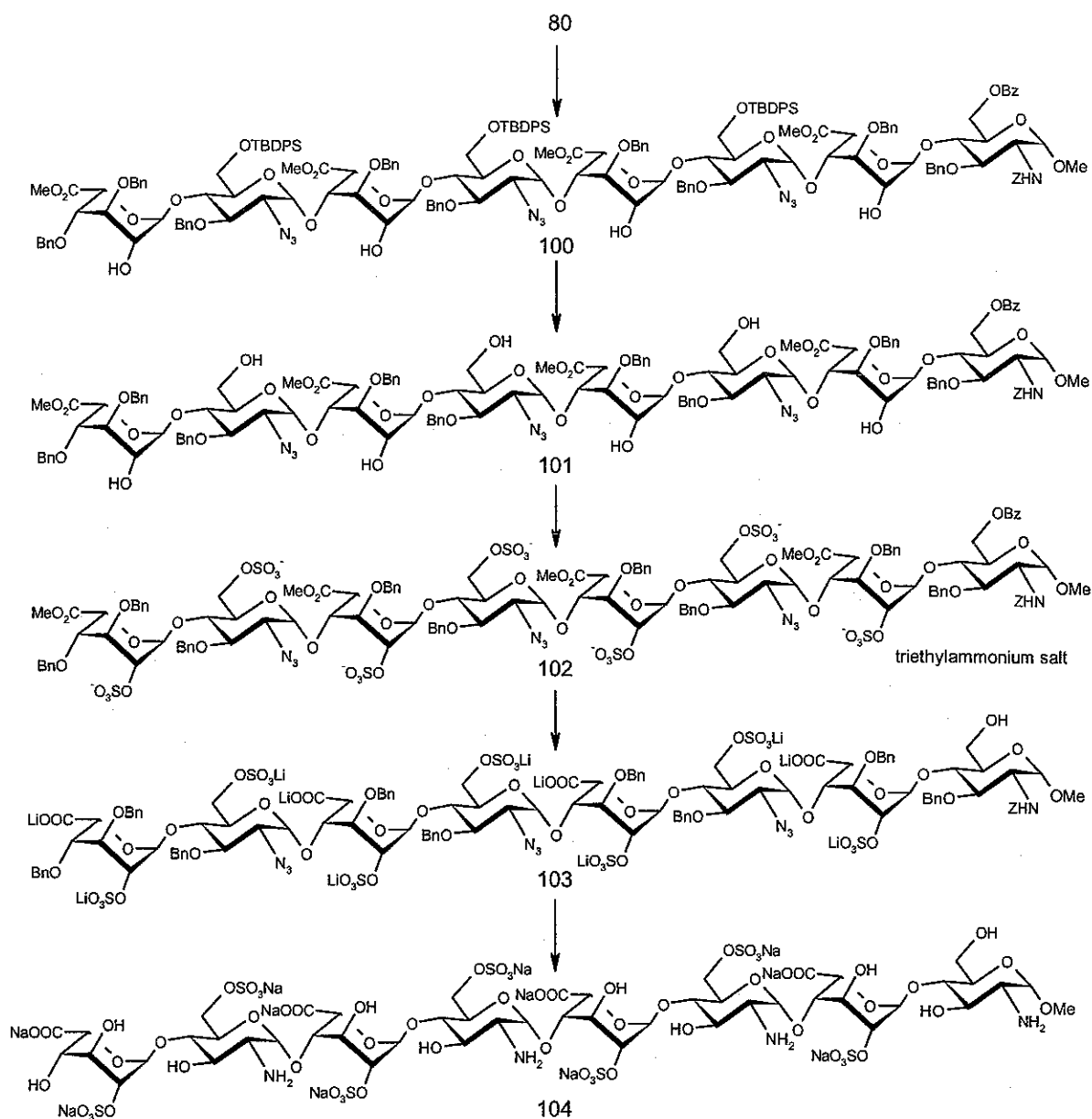
compound **98** (20.7 mg) after chromatography on a column of Sephadex[®] LH20 gel (95 x 2 cm, 50/50/1 v/v/v dichloromethane/ethanol/water).

$[\alpha]_D$ 14.4° (c 1.01; MeOH)

- 5 Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1→4)-(2-amino-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1→4)-[(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1→4)-(2-amino-2-deoxy- α -D-glucopyranosyl)-(1→4)]₂-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1→4)-2-amino-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranoside (**99**)
- 10

Compound **98** (17.5 mg, 5.9 μ mol) is treated according to the same procedure as that described for the preparation of compound **91** to give compound **99** (9.5 mg).

- Mass: "ESI" method, negative mode: theoretical mass = 2081.38;
15 experimental mass: 1993.28 $\pm$ 0.14 a.m.u. (iduronic acids observed in COOH form).

SCHEME 21: preparation of the octasaccharide **104**

Methyl (methyl 3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)]₂-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-benzoyl-3-O-benzyl-2-[[benzyloxy]-carbonyl]amino}-2-deoxy- α -D-glucopyranoside (100)

A solution of compound **80** (355 mg, 0.117 mmol), benzoic anhydride (75.8 mg, 0.335 mmol) and triethylamine (47.3 μ L, 0.335 mmol) in 1,2-dichloroethane (5.6 mL) is stirred at 60°C for 24 hours and then for 64 hours at room temperature. The reaction mixture is deposited on a column of Sephadex[®] LH20 gel (120 x 3 cm) eluted with a 1/1 v/v dichloromethane/ethanol mixture, followed by flash chromatography on a column of silica gel (100/0 $\rightarrow$ 85/15 v/v toluene/acetone) to give compound **100** (193.2 mg).

TLC: R_f = 0.38, silica gel, 2/1 v/v cyclohexane/ethyl acetate

Methyl (methyl 3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)]₂-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-benzoyl 3-O-benzyl-2-[[benzyloxy]carbonyl]amino}-2-deoxy- α -D-glucopyranoside (101)

Compound **100** (60.0 mg, 0.018 mmol) is treated according to the same procedure as that described for the preparation of compound **89** to give compound **101** (46.1 mg) after chromatography on a column of Sephadex[®] LH20 gel (120 x 3 cm, 1/1 v/v dichloromethane/ethanol).

Mass: "ESI" method, negative mode: theoretical mass = 2564.66; experimental mass: 2563.66 $\pm$ 0.19 a.m.u.

Methyl (methyl 3,4-di-O-benzyl-2-O-triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-triethylammonium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(methyl 3-O-benzyl-2-O-triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-triethylammonium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)]₂-(methyl 3-O-benzyl-2-

O-triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-benzoyl-3-O-benzyl-2-[[benzyloxy]carbonyl]amino}-2-deoxy- α -D-glucopyranoside (102)

Compound **101** (42.9 mg, 0.016 mmol) is treated according to the same procedure as that described for the preparation of compound **28** to give
 5 compound **102** (28.7 mg) after chromatography on a column of Sephadex[®] LH20 gel (120 x 3 cm, 1/1 v/v dichloromethane/ethanol) and then flash chromatography on a column of C₁₈ silica gel (40-60 μ m; A: methanol, 5% water, 23 mM ammonium acetate; B: acetonitrile, 45% methanol, 5% water, 17 mM ammonium acetate; A $\rightarrow$ B 100/0 $\rightarrow$ 70/30) followed by desalting on a Sephadex[®]
 10 LH20 column (95 x 2 cm, 50/50/1 v/v/v dichloromethane/ethanol/water).

Methyl (lithium 3,4-di-O-benzyl-2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-lithium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(lithium 3-O-benzyl-2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-lithium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)]₂-(lithium 3-O-benzyl-2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-[[benzyloxy]carbonyl]amino}-2-deoxy- α -D-glucopyranoside (103)

Compound **102** (28.7 mg, 7.5 μ mol) is treated according to the same
 20 procedure as that described for the preparation of compound **29** to give crude compound **103** (17.3 mg).

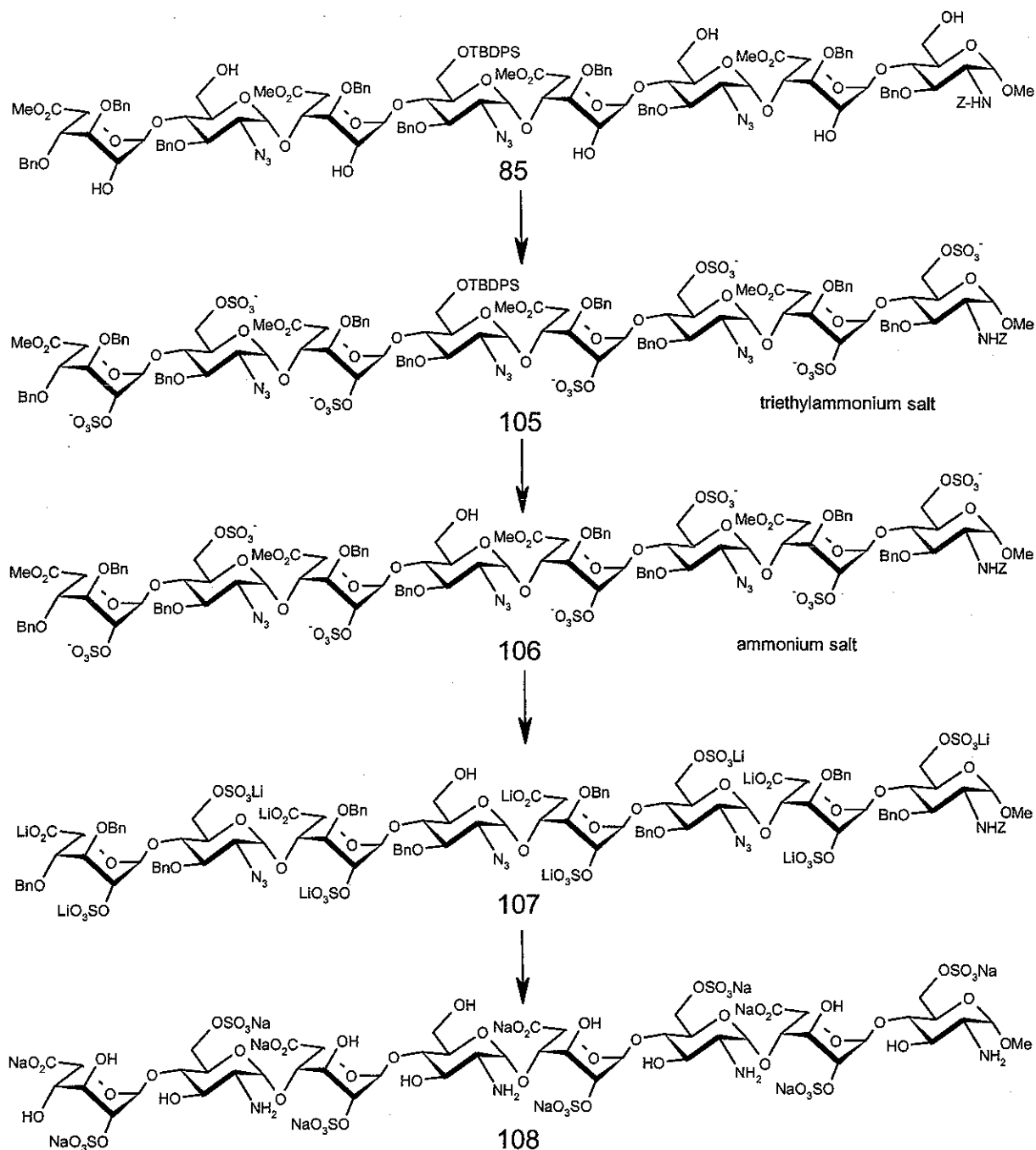
Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-amino-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-amino-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)]₂-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-amino-2-deoxy- α -D-glucopyranoside (104)

Compound **103** (17.3 mg, 5.7 μ mol) is treated according to the same procedure as that described for the preparation of compound **91**. The crude
 30 compound **104** thus obtained is again saponified. To a solution of crude compound **104** in a 1/1 v/v tetrahydrofuran/methanol mixture (506 μ L) is added, at 0°C, a 0.7 M solution of lithium hydroxide in water (202 μ L, qs a final

concentration of 0.2 M). After 1 hour at 0°C and then 16 hours at room temperature, the reaction medium is chromatographed on an exclusion column (Sephadex[®] G25-fine, 95 x 2 cm, 0.2 M NaCl and then Sephadex[®] G25-fine, 95 x 2 cm, water) to give compound **104** (6.5 mg).

- 5 ¹H NMR [600 MHz] (D₂O) δ of the anomeric protons: 5.45; 5.44; 5.43; 5.26; 5.25; 5.24; 5.18; 4.98 ppm

SCHEME 22: preparation of the octasaccharide 108



5

Methyl (methyl 3,4-di-O-benzyl-2-O-triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-triethylammonium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl-2-O-triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-6-O-tert-butylidiphenylsilyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl-2-O-

triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-triethylammonium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl-2-O-triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino-6-O-triethylammonium sulfonato- α -D-glucopyranoside (105)

Compound **85** (31.4 mg, 11.6 μ mol) is treated according to the same procedure as that described for the preparation of compound **28** to give compound **105** (40.2 mg) after chromatography on a column of Sephadex[®] LH20 gel (120 x 3 cm, 50/50/1 v/v/v dichloromethane/ethanol/water).

Methyl (methyl 2-O-ammonium sulfonato-3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(6-O-ammonium sulfonato-2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 2-O-ammonium sulfonato-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 2-O-ammonium sulfonato-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(6-O-ammonium sulfonato-2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 2-O-ammonium sulfonato-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-ammonium sulfonato-3-O-benzyl-2-[(benzyloxy)carbonyl]amino-2-deoxy- α -D-glucopyranoside (106)

Compound **105** (38.4 mg, 9.68 μ mol) is treated according to the same procedure as that described for the preparation of compound **89** to give compound **106** (28.4 mg) after chromatography on a column of Sephadex[®] LH20 gel (95 x 2 cm, *N,N*-dimethylformamide).

R_f = 0.21 (28/16/3.8/9 EtOAc/pyridine/AcOH/H₂O).

Methyl (lithium 3,4-di-O-benzyl-2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-lithium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(lithium 3-O-benzyl-2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(lithium 3-O-benzyl-2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-lithium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(lithium 3-O-benzyl-2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-

benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino-6-O-lithium sulfonato- α -D-glucopyranoside (107)

Compound **106** (28.4 mg, 7.62 μ mol) is treated according to the same procedure as that described for the preparation of compound **89** to give
5 compound **107** (28.0 mg) after chromatography on a column of Sephadex[®] LH20 gel (95 x 2 cm, 50/50/1 v/v/v dichloromethane/ethanol/water).

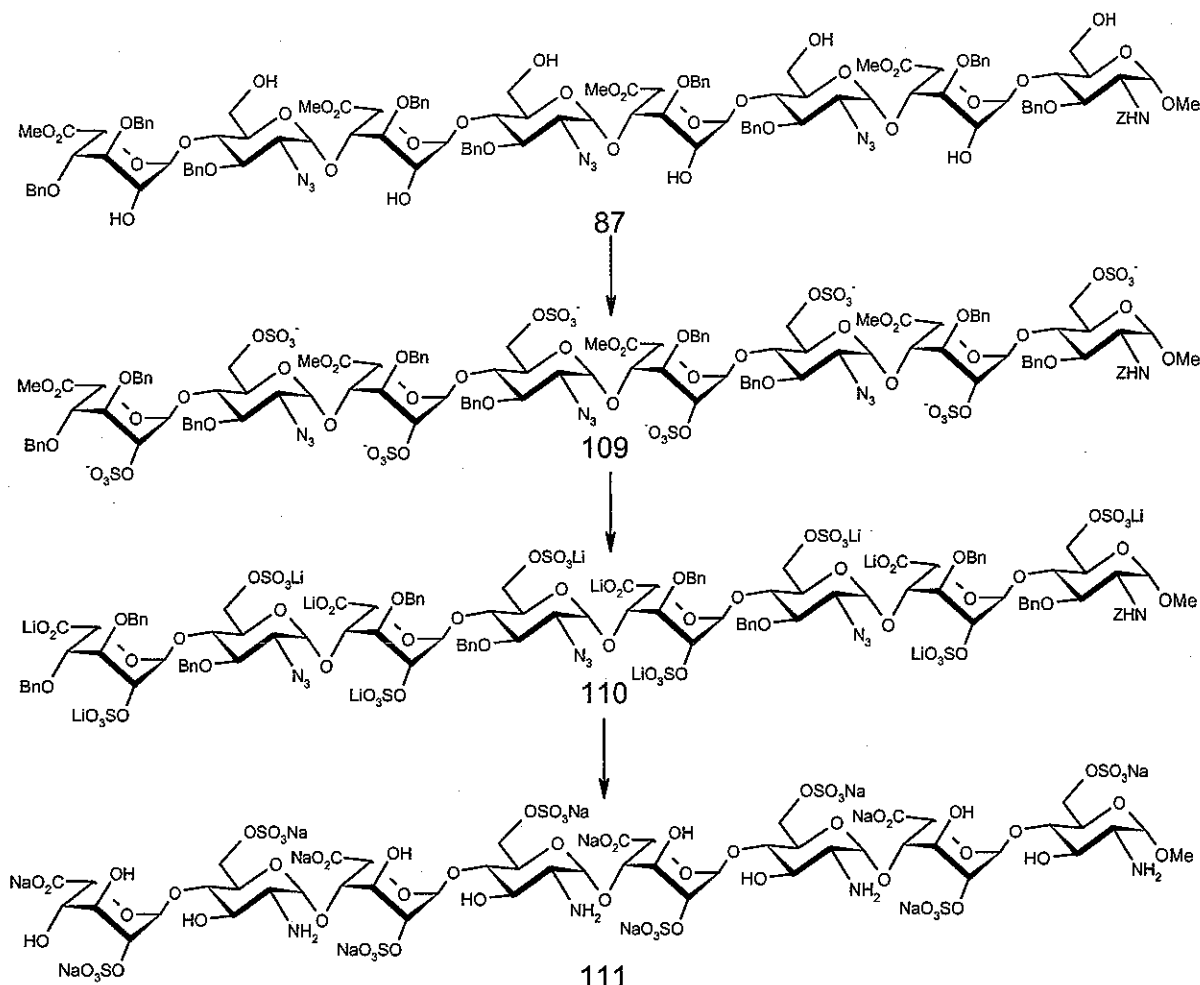
R_f = 0.12 (28/16/3.8/9 EtOAc/pyridine/AcOH/H₂O).

Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1-4)-(2-amino-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1-4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1-4)-(2-amino-2-deoxy- α -D-glucopyranosyl)-(1-4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1-4)-(2-amino-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1-4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1-4)-2-amino-2-deoxy-6-O-
15 sodium sulfonato- α -D-glucopyranoside (108)

Compound **107** (5.8 mg, 2.85 μ mol) is treated according to the same procedure as that described for the preparation of compound **91** to give compound **108** (2.5 mg), which is used without further purification in the following step.

20 ¹H NMR [600 MHz] (D₂O) δ of the anomeric protons: 5.45; 5.44; 5.42; 5.26; 5.25; 5.24; 5.17; 5.03 ppm

SCHEME 23: preparation of the octasaccharide 111



- 5 Methyl (methyl 3,4-di-O-benzyl-2-O-triethylammonium sulfonato- α -L-
idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-triethylammonium
sulfonato- α -D-glucopyranosyl)-[(1 $\rightarrow$ 4)-(methyl 3-O-benzyl-2-O-triethylammonium
sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-
triethylammonium sulfonato- α -D-glucopyranosyl)]₂-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl-2-
 10 O-triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-
benzyloxycarbonylamino-2-deoxy-6-O-triethylammonium sulfonato- α -D-
glucopyranoside (109)

Compound **87** (37.0 mg, 0.15 mmol) is dried by co-distillation of *N,N*-dimethylformamide (3 x 1.4 mL) and is then dissolved in *N,N*-dimethylformamide (1.4 mL). To this solution is added the sulfur trioxide-triethylamine complex (109 mg; 6.01 mmol). The mixture is stirred for 16 hours at 55°C protected from

light and the excess reagent is then destroyed with methanol (25 μ L). The reaction medium is deposited on a column of Sephadex[®] LH20 (120 x 3 cm) eluted with a 1/1 dichloromethane/ethanol mixture to give compound **109** (59.8 mg).

5 R_f = 0.26, silica gel, 28/16/3.8/9 ethyl acetate/pyridine/acetic acid/water.

Methyl (lithium 3,4-di-O-benzyl-2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-lithium sulfonato- α -D-glucopyranosyl)-[(1 $\rightarrow$ 4)-(lithium 3-O-benzyl-2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-lithium sulfonato- α -D-glucopyranosyl)]₂-(1 $\rightarrow$ 4)-(lithium 3-O-benzyl-2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-benzyloxycarbonylamino-2-deoxy-6-O-lithium sulfonato- α -D-glucopyranoside (**110**)

To a solution of compound **109** (57.3 mg, 13.7 μ mol) in a 1/1 v/v tetrahydrofuran/methanol mixture (2.2 mL) is added, at 0°C, a 0.7 M solution of lithium hydroxide in water (0.88 mL; qs final concentration of 0.2 M). After 1 hour at 0°C and then 16 hours at room temperature, the reaction medium is deposited on a column of Sephadex[®] LH20 (120 x 3 cm) eluted with a 50/50/1 v/v/v dichloromethane/ethanol/water mixture to give compound **110** (38.1 mg).

20 $[\alpha]_D$ 13.1° (c 1.0; MeOH)

Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-amino-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-[(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-amino-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)]₂-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-amino-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranoside (**111**)

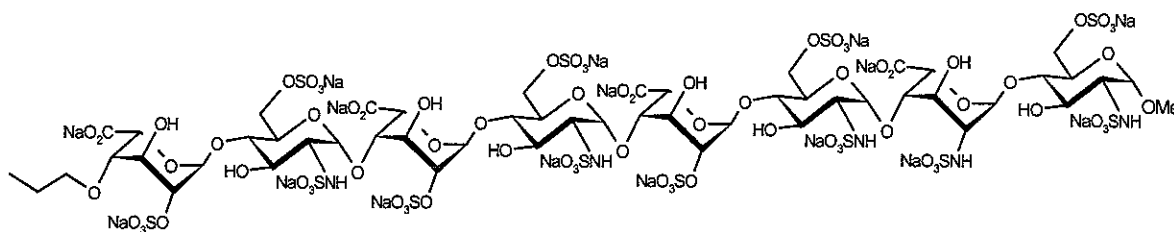
To a solution of compound **110** (40 mg, 12.8 μ mol) in a 1/1 v/v *tert*-butanol/water mixture (2.6 mL) are added ammonium formate (105 mg, 1.67 mmol) and 10% palladium-on-charcoal (260 mg). After stirring for 4 hours at room temperature, the reaction medium is filtered (Millipore[®] LSWP 5 μ m filter) and concentrated to dryness. The residue is deposited on a column of

Sephadex[®] G25-fine gel (95 x 2 cm) eluted with aqueous 0.2 M NaCl solution. The fractions containing the expected compound are combined and deposited on a column of Sephadex[®] G25-fine gel (95 x 2 cm) eluted with water. The crude product **111** thus obtained (14.7 mg) is used without further purification in the following step.

Mass: "ESI" method, negative mode: theoretical mass = 2285.47; experimental mass: 2197.20 ± 0.34 a.m.u. (iduronic acids observed in COOH form).

Examples of compounds according to the invention:

EXAMPLE 1: Methyl (sodium 4-O-propyl-2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1→4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1→4)-[(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1→4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl-(1→4)]₂-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1→4)-2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranoside (compound 1)



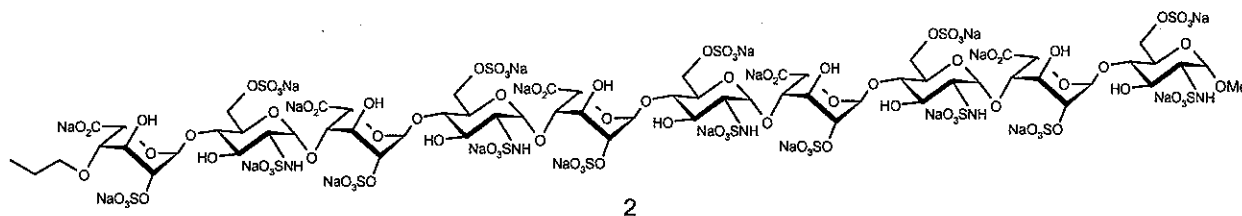
To a freshly prepared solution of compound **30** (180 mg, 0.077 mmol) in saturated aqueous sodium hydrogen carbonate solution (15 mL, 100 mL/mmol) are added, at 0°C and under an argon atmosphere, solid sodium hydrogen carbonate (1.17 g, 13.9 mmol) and then the pyridine-sulfur trioxide complex (985 mg, 6.19 mmol) portionwise over 30 minutes. After 16 hours at room temperature, the reaction mixture is deposited on a column of Sephadex[®] G25-fine gel (90 x 3 cm) eluted with aqueous 0.2 M NaCl solution. The fractions containing the expected compound are combined and deposited on a column of

Sephadex[®] G25-fine gel (90 x 3 cm) eluted with water. After concentrating the fractions containing the expected compound, 200 mg of compound **1** are obtained.

¹H NMR [600 MHz] (D₂O) δ of the anomeric protons: 5.45; 5.42 (2 H);
5.22; 5.21; 5.20; 5.18; 5.03 ppm.

Mass: "ESI" method, negative mode: theoretical mass = 2735.72; experimental mass: 2734 a.m.u.

EXAMPLE 2: Methyl (sodium 4-O-propyl-2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)-α-D-glucopyranosyl)-(1→4)-[(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)-α-D-glucopyranosyl-(1→4)]₃-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)-α-D-glucopyranoside (compound 2)

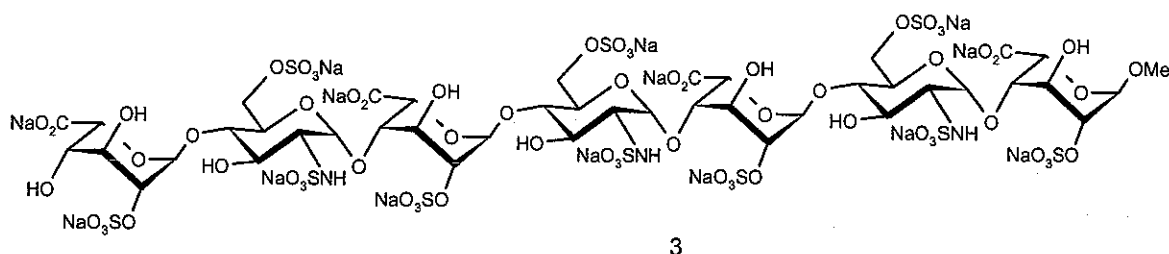


Compound **37** (29.5 mg, 11.56 μmol) is treated according to the same procedure as that described for the preparation of Example 1 to give compound **2** (7.4 mg) after purification by ion-exchange chromatography (SAX column, conditions: 0.5 mL/min, A: H₂O, B: 2 M NaCl, gradient 30% of B to 90% over 30 min) followed by chromatography on a column of Sephadex[®] G25-fine gel (54 x 1.7 cm, water).

¹H NMR [600 MHz] (D₂O) δ of the anomeric protons: 5.45; 5.42; 5.41 (2 H); 5.22; 5.21 (2H); 5.20; 5.18; 5.03 ppm.

Mass: "ESI" method, negative mode: theoretical mass = 3401.12; experimental mass: 3400.40 ± 0.76 a.m.u.

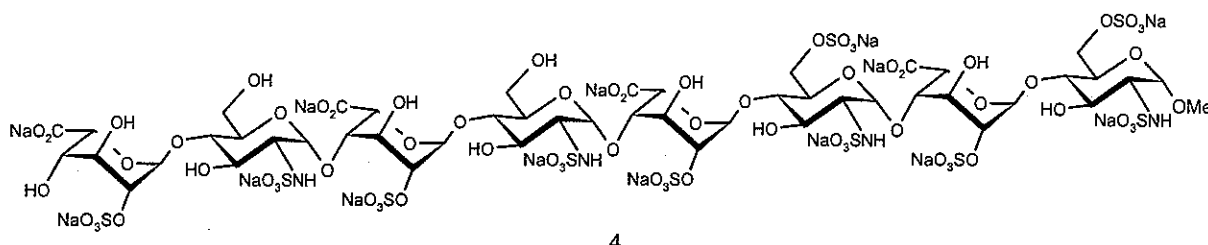
EXAMPLE 3: Sodium [methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)]₂-2-O-sodium sulfonato- α -L-idopyranoside]uronate (**compound 3**)



Crude compound **55** (48.7 mg) is treated according to the same procedure as that described for the preparation of Example 1 to give compound **3** (37.6 mg).

¹H NMR [600 MHz] (D₂O) δ of the anomeric protons: 5.43 (2H); 5.35; 5.25; 5.24; 5.19; 5.18; 5.09 ppm.

EXAMPLE 4: Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranoside (**compound 4**)

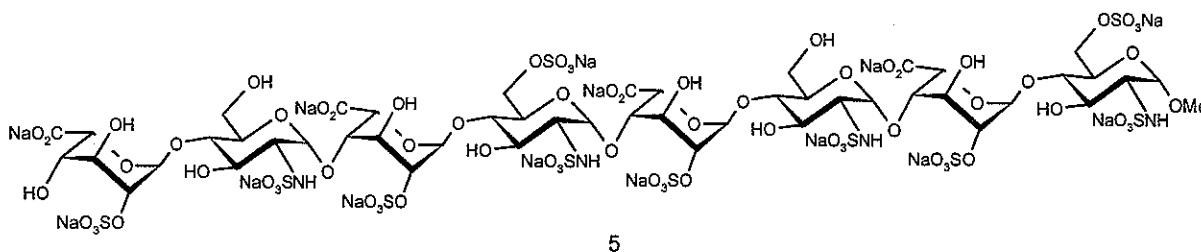


Compound **91** (5.5 mg, 2.64 μ mol) is treated according to the same procedure as that described for the preparation of Example 1 to give compound **4** (4.5 mg).

^1H NMR [600 MHz] (D_2O) δ of the anomeric protons: 5.44; 5.40; 5.31; 5.25; 5.24; 5.22; 5.16; 5.03 ppm.

Mass: "ESI" method, negative mode: theoretical mass = 2489.55; experimental mass: 2465.63 ± 0.64 a.m.u.

EXAMPLE 5: Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranoside (**compound 5**)

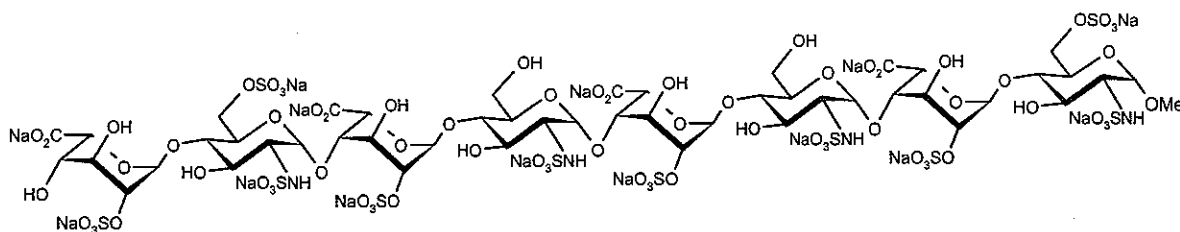


Compound **95** (2.5 mg, 1.2 μ mol) is treated according to the same procedure as that described for the preparation of Example 1 to give compound **5** (1.9 mg).

^1H NMR [600 MHz] (D_2O) δ of the anomeric protons: 5.45; 5.43; 5.33; 5.25; 5.23; 5.21; 5.16; 5.05 ppm.

EXAMPLE 6: Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-sodium (sulfonatoamino)- α -D-

glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-
(1→4)-(2-deoxy-2-sodium (sulfonatoamino)-α-D-glucopyranosyl)-(1→4)-(sodium
2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-2-deoxy-6-O-sodium
sulfonato-2-sodium (sulfonatoamino)-α-D-glucopyranoside (compound 6)



5

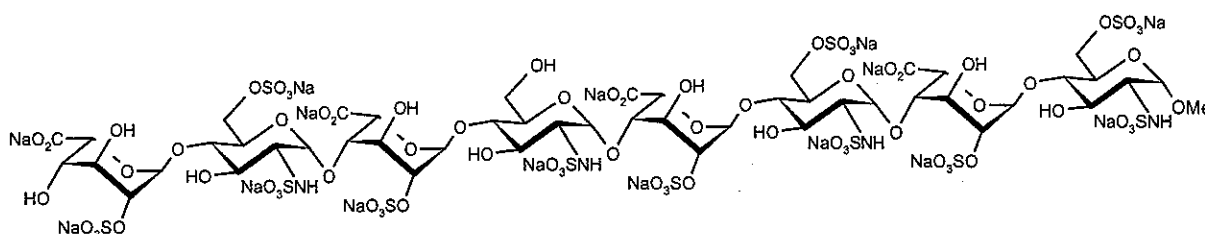
6

Compound **99** (8.9 mg, 4.28 μmol) is treated according to the same procedure as that described for the preparation of Example 1 to give compound **6** (7.3 mg).

¹H NMR [600 MHz] (D₂O) δ of the anomeric protons: 5.46; 5.32 (2 H); 5.26; 5.25; 5.21; 5.20; 5.05 ppm.

Mass: "ESI" method, negative mode: theoretical mass = 2489.55; experimental mass: 2488.00 ± 1.5 a.m.u.

EXAMPLE 7: Methyl (sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-2-sodium (sulfonatoamino)-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)-α-D-glucopyranoside (**compound 7**)



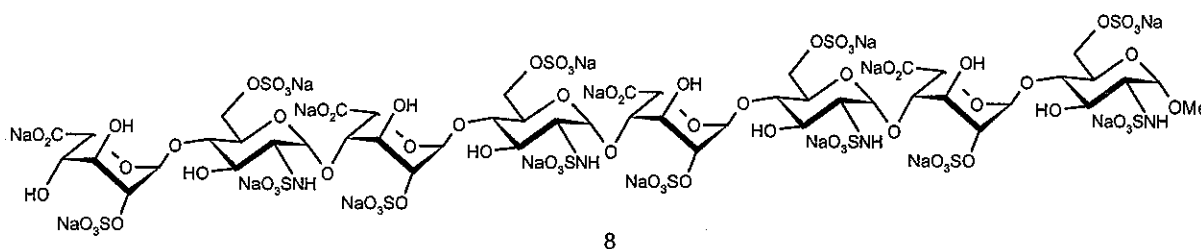
7

25

Compound **108** (3.7 mg, 1.42 μ mol) is treated according to the same procedure as that described for the preparation of Example 1 to give compound **7** (1.8 mg).

^1H NMR [600 MHz] (D_2O) δ of the anomeric protons: 5.46; 5.42; 5.31; 5.26; 5.24; 5.22; 5.18; 5.03 ppm.

EXAMPLE 8: Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-[(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)]₂-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-6-O-sodium sulfonato-2-(sulfonato)amino- α -D-glucopyranoside (**compound 8**)



15

Compound **111** (42 mg, 18.4 μ mol) is treated according to the same procedure as that described for the preparation of Example 1 to give compound **8** (44.1 mg).

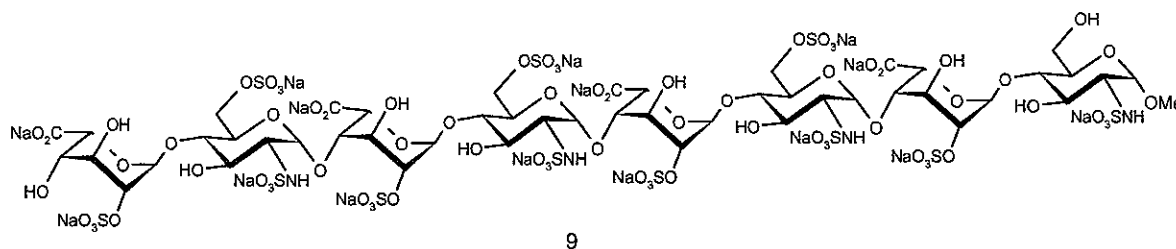
^1H NMR [600 MHz] (D_2O) δ of the anomeric protons: 5.45; 5.44; 5.25; 5.24 (2H); 5.20; 5.04 ppm.

Mass: "ESI" method, negative mode: theoretical mass = 2693.84; experimental mass: 2692.97 $\pm$ 0.18 a.m.u.

EXAMPLE 9: Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonato)amino- α -D-glucopyranosyl)-[(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)]₂-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -

25

L-idopyranosyluronate)-(1→4)-2-deoxy-2-sodium (sulfonatoamino)- α -D-glucopyranoside (**compound 9**)



5

Compound **104** (6.5 mg, 2.98 μ mol) is treated according to the same procedure as that described for the preparation of Example 1 to give compound **9** (6.0 mg).

^1H NMR [600 MHz] (D_2O) δ of the anomeric protons: 5.44 (2H); 5.43; 5.22 (2H); 5.19; 5.18; 5.05 ppm.

Mass: "ESI" method, negative mode: theoretical mass = 2591.60; experimental mass: 2591.80 ± 0.33 a.m.u.

The compounds according to the invention underwent pharmacological trials to determine their agonist effect on the FGF receptors and their activity on angiogenesis and also on post-ischaemic revascularization.

Model of *in vitro* angiogenesis: specific activity towards FGF2

The *in vitro* angiogenesis model corresponds to a rearrangement of human venous endothelial cells on a biological matrix. The matrix is made by dispensing, into each well of a 96-well plate (Becton Dickinson 353872), 60 μ l of Matrigel[®] diluted to 1/3 (Growth factor reduced Matrigel[®]: Becton Dickinson 356230) in collagen (rat tail collagen, type I: Becton Dickinson 354249). The biological matrix hardens after 1 hour at 37°C.

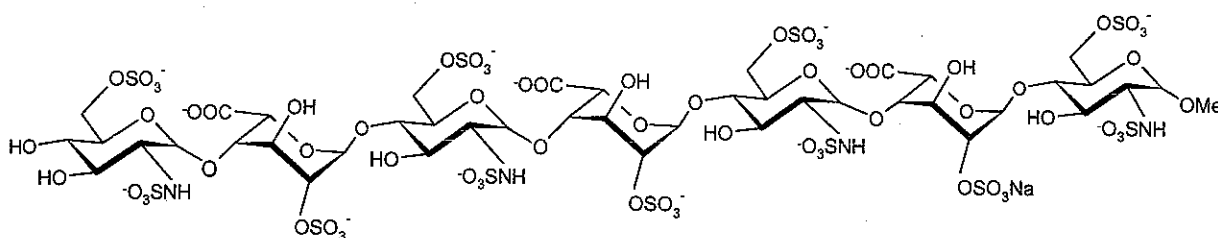
Human venous endothelial cells (HUVEC ref: C-12200 - Promocell) are seeded onto the biological matrix at 7800 cells/well in 120 μ l of EBM[®] medium (Endothelial Basal Medium, Lonza C3121) + 2% FCS (foetal calf serum - Lonza) + hEGF (Recombinant Human Epidermal Growth Factor - Lonza) 10 μ g/ml. The cells are stimulated with FGF2 (R&D Systems / 234 - FSE - 0 50) 10 ng/ml or

with the products of the invention for 18 hours at 37°C in the presence of 5% CO₂. After 24 hours, the cells are observed under a microscope (X4 objective lens) and analysis of the length of the pseudo-tubules is performed with the aid of image software (Biocom VisioLab 2000 software).

- 5 In this test of *in vitro* angiogenesis, the compounds of the invention have a specific activity of between 10⁻⁶ M and 10⁻¹² M. For example, compounds **1** and **7** are active at 10⁻⁶ M.

Compound **10** having the following formula:

10



10

- 15 tested in sodium salt form, also demonstrated activity in this *in vitro* angiogenesis test.

Moreover, it was demonstrated in an *in vitro* cellular test that the octasaccharide No. **8** according to the invention, the heptasaccharide No. **3** and the decasaccharide No. **2** are better FGF-2 activators than the hexasaccharide analogue thereof (compound described by C. Tabeur *et al.* in Bioorg. & Med. Chem., 1999, 7, 2003-2012). Furthermore, the majority of the other octasaccharide compounds according to the invention, for instance compound No. **7**, have the same activity as the octasaccharide No. **8** on *in vitro* models.

25 Model of cellulose implant in mice

This model is an adaptation of the model described by Andrade *et al.* (Microvascular Research, 1997, 54, 253-61) for testing pharmacological products capable of activating the onset of angiogenesis.

The animals (white consanguineous BALB/c J mice) are anaesthetized with a xylazine (Rompun[®], 10 mg/kg)/ketamine (Imalgene[®] 1000, 100 mg/kg) mixture intraperitoneally. The animal's back is shaved and disinfected with Hexomedine[®]. An air pocket is created subcutaneously on the mouse's back by
5 injecting 5 ml of sterile air. An incision of about 2 cm at the top of the animal's back is made in order to introduce a sterile cellulose implant (disk 1 cm in diameter, 2 mm thick, Cellspan[®] ref. 0501) impregnated with 50 µl of sterile solution containing the test product. The incision is then sutured and cleaned with Hexomedine[®].

10 On the days following the insertion of the implant, the mice can receive the product into the implant via an injection through the skin (50 µl/implant/day) under gaseous anaesthesia (5% isoflurane (Aerrane[®], Baxter)).

Seven days after inserting the sponge, the mice are sacrificed by means of a lethal dose of pentobarbital sodium (CEVA Santé Animale), administered
15 intraperitoneally. The skin is then excised, about 1 cm around the sponge, while avoiding the scar, so as to release the skin and the sponge. The sponge is then cut into several pieces and placed in a Ribolyser[®] containing 1 ml of lysis buffer (Cell Death Detection ELISA, Roche). The tubes are shaken four times consecutively, for 20 seconds, at force 4, using a cell mill (FastPrep[®] FP 120).
20 The tubes are then centrifuged for 10 minutes at 2000×g at 20°C and the supernatants are frozen at -20°C until the time of the haemoglobin assay. On the day of the assay, the tubes are again centrifuged after thawing and the haemoglobin concentration is measured with the Drabkin reagent (Sigma, volume for volume) by reading on a spectrophotometer at 405 nm against a
25 standard range of bovine haemoglobin (Sigma).

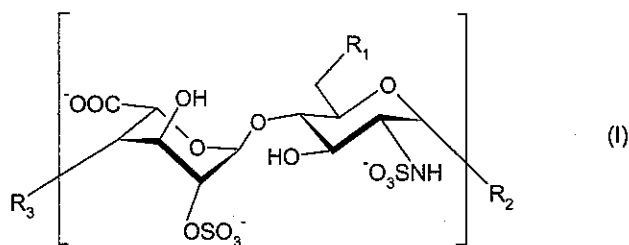
The haemoglobin concentration in each sample is expressed in mg/ml from the polynomial regression produced from the range. The results are expressed as a mean value (± sem) for each group. The differences between the groups are tested with an ANOVA followed by a Dunnett test on the square
30 root of the values.

In this *in vivo* test, the compounds of the invention revealed a specific activity of between 5 and 45 ng/site. Thus, compounds **1** and **7** are active at a concentration of 45 ng/site.

5 It therefore appears that the compounds according to the invention have agonist activity on the FGF receptors and activity on angiogenesis, and also on post-ischaemic revascularization. These compounds may thus be used for the preparation of medicaments, especially medicaments that are useful for treating diseases that require activation of the FGF receptors, or of medicaments that are
 10 useful in pathologies requiring activation of angiogenesis post-ischaemic revascularization.

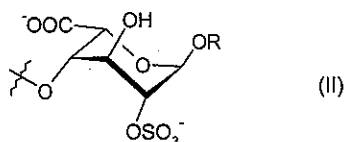
Thus, according to another of its aspects, a subject of the invention is thus medicaments that comprise a compound of formula (I)/(I') or compound **10**,
 15 or a pharmaceutically acceptable salt thereof.

One subject of the invention is, more generally, medicaments comprising a compound of formula (I):



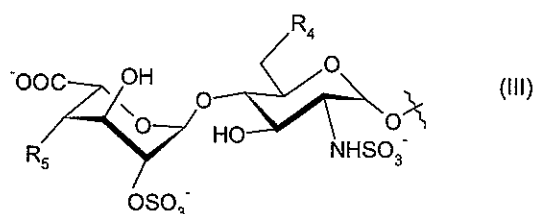
in which:

- R_1 represents a group $-\text{OSO}_3^-$ or a hydroxyl group,
- R_2 represents either a group $-\text{O-alkyl}$, or a monosaccharide of formula (II), in which R represents an alkyl group:



- R_3 represents a disaccharide of formula (III):

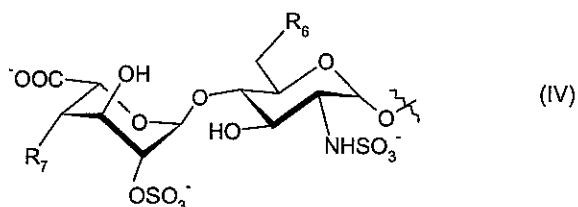
88



in which:

- R_4 represents a group $-\text{OSO}_3^-$ or a hydroxyl group,
- R_5 represents a disaccharide of formula (IV):

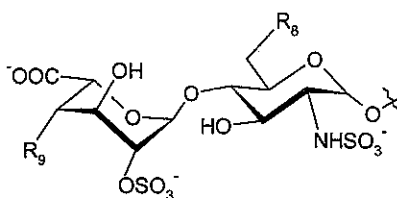
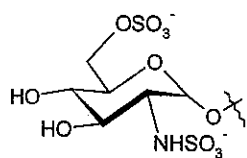
5



in which:

- R_6 represents a group $-\text{OSO}_3^-$ or a hydroxyl group,
- R_7 represents either a hydroxyl group or a monosaccharide of formula (V) below, or a disaccharide of formula (VI):

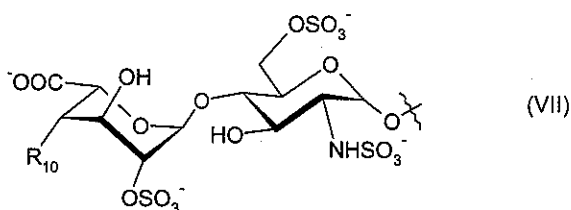
10



in which:

- R_8 represents a group $-\text{OSO}_3^-$ or a hydroxyl group,
- R_9 represents either a hydroxyl group or a group $-\text{O-alkyl}$, or a disaccharide of formula (VII):

15



20

in which R_{10} represents a group $-\text{O-alkyl}$,

on condition that: R₉ represents a hydroxyl group or a group -O-alkyl when R₂ represents a monosaccharide of formula (II) as defined above; R₇ represents a disaccharide of formula (VI) as defined above when R₂ represents a group -O-alkyl; and R₁, R₄, R₆ and R₈ do not simultaneously represent hydroxyl groups.

5

Such compounds include those of formula (I)/(I') defined above, and also the heptasaccharide **10** defined previously, described in patent application US 2006/0079483 A1.

10 These medicaments find their use in therapy, especially in the treatment of ischaemia (cardiac ischaemia, arterial ischaemia of the lower limbs), the treatment of diseases associated with narrowing or obstruction of the arteries or arterites, the treatment of angina pectoris, the treatment of thromboangitis obliterans, the treatment of atherosclerosis, the treatment of inhibition of
15 restenosis after angioplasty or endoarterectomy, the treatment of cicatrization, muscle regeneration treatment, treatment for the survival of myoblasts, the treatment of peripheral neuropathy, the treatment of post-operative nerve damage, the treatment of nerve deficiencies such as Parkinson's disease, Alzheimer's disease, prion disease and neuronal degeneration in alcoholics, the
20 treatment of dementias, treatment for improving the survival of a bioartificial pancreas graft in the case of diabetics, treatment for improving the revascularization of grafts and the survival of grafts, the treatment of retinal degeneration, the treatment of pigmentary retinitis, the treatment of osteoarthritis, the treatment of pre-eclampsia or the treatment of vascular lesions
25 and of acute respiratory distress syndrome, treatment for cartilage repairing, treatment for repairing and protecting bones, treatment for repairing and protecting hair follicles and for protecting and regulating hair growth.

30 Ischaemia is a decrease in arterial circulation in an organ, leading to a decrease in oxygen concentration in the damaged tissues. In the mechanisms of post-ischaemic revascularization, two main mechanisms are involved: angiogenesis and arteriogenesis. Angiogenesis is the process of generating new blood capillaries from pre-existing vessels. Arteriogenesis contributes towards

the development (increase in size and calibre) of the collateral vessels around the ischaemic or avascular area.

Among the growth factors involved in these revascularization processes, the FGF family and especially FGF-2 has been the most widely described (Post, M. J., Laham, R., Sellke, F. W. & Simons, M. Therapeutic angiogenesis in
5 cardiology using protein formulations. *Cardiovasc. Res.* 49, 522-31, 2001).

Thus, FGF2 and its receptors represent very pertinent targets for therapies directed towards inducing angiogenesis and arteriogenesis processes (Khurana, R. & Simons, M. Insights from angiogenesis trials using fibroblast
10 growth factor for advanced arteriosclerotic disease. *Trends Cardiovasc. Med.* 13, 116-22, 2003).

One of the applications of the compounds of the invention is post-ischaemic treatment after heart occlusion or occlusion of the peripheral arteries.
15 As regards the treatment of cardiac ischaemia, one of the most promising clinical tests is a clinical test in which FGF-2 was sequestered in alginate microspheres in the presence of heparin (Laham, R. J. et al. Local perivascular delivery of basic fibroblast growth factor in patients undergoing coronary bypass surgery: results of a phase I randomized, double-blind, placebo-controlled trial.
20 *Circulation* 100, 1865-71, 1999). These microspheres were implanted close to the ischaemic locus in the myocardium. After 90 days, all the patients treated with FGF2 showed no ischaemic cardiac symptoms. In comparison, in the control group, three of the seven patients had persistent symptoms at 90 days and two patients required vascular surgery. Interestingly, the therapeutic benefit
25 was maintained after 3 years of monitoring. These observations suggest that compounds that mimic FGF2 may represent a therapy of choice for treating the consequences of cardiac ischaemia.

Three clinical tests on the injection of FGF2 into the coronary artery were performed during treatment of narrowing of the coronary arteries (Laham, R. J.
30 et al. Intracoronary basic fibroblast growth factor (FGF-2) in patients with severe ischemic heart disease: results of a phase I open-label dose escalation study. *J. Am. Coll. Cardiol.* 36, 2132-9, 2000; Simons, M. et al. Pharmacological treatment of coronary artery disease with recombinant fibroblast growth factor-2:

double-blind, randomized, controlled clinical trial. *Circulation* 105, 788-93, 2002; Unger, E. F. et al. Effects of a single intracoronary injection of basic fibroblast growth factor in stable angina pectoris. *Am. J. Cardiol.* 85, 1414-9, 2000). The result of these three tests shows that intra-coronary infusions of FGF2 are well tolerated and significantly improve the condition of the patients. Thus, the compounds described in the invention may find an application in the treatment of diseases associated with narrowing of the coronary arteries and especially in the treatment of angina pectoris.

10 Diseases of the distal arteries and especially arteritis of the lower limbs are caused by chronic obstruction of the arterioles that irrigate the extremities. These pathologies mainly affect the lower limbs. In a phase I clinical trial, patients with peripheral artery pathologies leading to claudication received injections of FGF2 (Lazarous, D. F. et al., Basic fibroblast growth factor in patients with intermittent claudication: results of a phase I trial. *J. Am. Coll. Cardiol.* 36, 1239-44, 2000). In this context, FGF2 was well tolerated in these patients and the clinical data suggest a beneficial effect of FGF2 and especially on improving walking. These clinical data suggest that the compounds of the invention represent a therapeutic tool of choice for the treatment of diseases associated with obstruction of the distal arteries.

25 Buerger's disease or thromboangitis obliterans affects the distal vascular structures and is characterized by distal arteritis of the legs, with pain and ulceration. In this context, an induction of angiogenesis and of vasculogenesis would represent a therapy for this pathology. The compounds of the said invention represent a therapy of choice for thromboangitis obliterans.

30 Peripheral neuropathy is an axonal or demyelinating attack of the motor and/or sensory peripheral nerve which leads to desensitization of the distal limbs. One of the major secondary complications of diabetes is the chronic development of peripheral neuropathy. In this context, it has been demonstrated that FGF2 induces axonal regeneration, which might be a therapy of choice in the treatment of peripheral nerve lesion and thus in peripheral neuropathy (Basic

fibroblast growth factor isoforms promote axonal elongation and branching of adult sensory neurons *in vitro*. Klimaschewski L, Nindl W, Feurle J, Kavakebi P, Kostron H. Neuroscience. 2004;126(2):347-53). By virtue of the agonist activity on the FGF receptors, the compounds of the said invention would represent a treatment of choice in peripheral neuropathy in the case of healthy or diabetic patients.

It is clearly established that FGF2 is an activator of nerve cells during development. Recent results suggest that FGF2 is also a pivotal factor for promoting the regeneration of neurons in adults (Sapieha PS, Peltier M, Rendahl KG, Manning WC, Di Polo A., Fibroblast growth factor-2 gene delivery stimulates axon growth by adult retinal ganglion cells after acute optic nerve injury. Mol. Cell. Neurosci. 2003 Nov.; 24(3):656-72.). By virtue of their agonist activities on the FGF receptors, the compounds of the said invention would represent a treatment of choice in repairing post-operative nerve damage, in repairing nerve deficiencies such as Parkinson's disease, Alzheimer's disease, prion disease and neuronal degeneration in alcoholics or in the case of dementia.

The proliferation and migration of vascular smooth muscle cells contributes towards intimal hypertrophy of the arteries and thus plays a predominant role in atherosclerosis and in restenosis after angioplasty and endoarterectomy. It has been demonstrated that an angiogenic factor, VEGF, significantly reduces the thickening of the intima by accelerating re-endothelialization (Van Belle, E., Maillard, L., Tio, F. O. & Isner, J. M. Accelerated endothelialization by local delivery of recombinant human vascular endothelial growth factor reduces in-stent intimal formation. Biochem. Biophys. Res. Commun. 235, 311-6, 1997). Thus, the compounds of the present invention, with pro-angiogenic activity, may be useful in treatment of atherosclerosis and in inhibiting restenosis after angioplasty or endoarterectomy.

30

The vascular network is essential to the development and maintenance of tissues. By promoting the delivery of nutrients, oxygen and cells, the blood vessels help to maintain the functional and structural integrity of tissues. In this

context, angiogenesis and vasculogenesis make it possible to preserve and to perfuse tissues after ischaemia. The angiogenic growth factors such as VEGF and FGF2 thus promote revascularization for tissue regeneration. The compounds presented in the invention could represent a treatment of choice in muscle regeneration treatment.

The processes of muscle regeneration on dystrophic or normal muscles depend on the supply of cytokines and of angiogenic growth factors at the local level (Fibbi, G., D'Alessio, S., Pucci, M., Cerletti, M. & Del Rosso, M. Growth factor-dependent proliferation and invasion of muscle satellite cells require the cell-associated fibrinolytic system. *Biol. Chem.* 383, 127-36, 2002). It has been proposed that the FGF system is a critical system of muscle regeneration and of myoblast survival and proliferation (Neuhaus, P. et al. Reduced mobility of fibroblast growth factor (FGF)-deficient myoblasts might contribute to dystrophic changes in the musculature of FGF2/FGF6/mdx triple-mutant mice. *Mol. Cell. Biol.* 23, 6037-48, 2003). FGF2 and the compounds of the said invention could be exploited in order to promote cardiac regeneration. They would thus improve the perfusion of the myocardium after ischaemia (Hendel, R. C. et al. Effect of intracoronary recombinant human vascular endothelial growth factor on myocardial perfusion: evidence for a dose-dependent effect. *Circulation* 101, 118-21, 2000) and also the survival and progress of transplanted myoblasts, especially in Duchenne's muscular dystrophy.

Angiogenesis is an essential phenomenon during cutaneous cicatrization. The new vessels formed supply the oxygen and nutrients required for tissue repair. In the case of diabetics, cicatrization is a slow and difficult process presenting angiogenesis defects. FGFs are among the growth factors that are the most involved in angiogenesis processes during the cicatrization phase. Certain FGFs are highly overregulated in dermal cells after a cutaneous injury. On account of their agonist activity on the FGF receptors, the compounds of the said invention would represent a therapy of choice for the treatment of cicatrization in healthy or diabetic patients.

Bioartificial pancreas transplantation is a very promising technique for the treatment of certain types of diabetes. It has been demonstrated, in diabetic rats, that vascularisation in bioartificial pancreases is much greater when the pancreases are impregnated with microspheres bearing FGF2 (Sakurai, Tomonori; Satake, Akira, Sumi, Shoichiro, Inoue, Kazutomo, Nagata, Natsuki, Tabata, Yasuhiko. The Efficient Prevascularization Induced by Fibroblast Growth Factor 2 With a Collagen-Coated Device Improves the Cell Survival of a Bioartificial Pancreas. *Pancreas*. 28(3):e70-e79, April 2004). This revascularization thus improves the survival of implanted bioartificial pancreases and consequently the survival of the graft. By virtue of their agonist activities on the FGF receptors, the compounds of the said invention would represent a therapy of choice in improving the survival of bioartificial pancreas grafts in diabetics and more generally in improving the revascularization of grafts and consequently the survival of the grafts.

15

Pigmentary retinitis is a pathology involving progressive degeneration of the retina characterized by degeneration of the photoreceptors and obliteration of the retinal vessels. Lahdenranta et al. (An anti-angiogenic state in mice and humans with retinal photoreceptor cell degeneration. *Proc. Natl. Acad. Sci. USA* 98, 10368-73, 2001) have proposed that angiogenic growth factors regulate the neural coordination and the associated vascularization of the retina by simultaneously functioning as photoreceptor survival factors and as endothelial cell regulators. In this context, the intra-vitreous injection of FGF2 retards the degeneration of the photoreceptors by acting on retinal survival and retinal angiogenesis (Faktorovich, E. G., Steinberg, R. H., Yasumura, D., Matthes, M. T. & LaVail, M. M. Basic fibroblast growth factor and local injury protect photoreceptors from light damage in the rat. *J. Neurosci.* 12, 3554-67, 1992). These observations demonstrate the interest of the compounds described in the invention as a therapy in retinal degeneration and especially in pigmentary retinitis.

30

In the field of osteoarthritis, many studies have been performed for restoring destroyed articular cartilage. In this context, it has been reported that

the proliferation and differentiation of chondrocytes were stimulated by FGF2 *in vitro* (Kato Y, Gospodarowicz D. Sulfated proteoglycan synthesis by confluent cultures of rabbit costal chondrocytes grown in the presence of fibroblast growth factor. J. Cell Biol. 1985 Feb.; 100(2):477-85). Furthermore, Cuevas et al. have
5 shown that FGF2 induces cartilage repair *in vivo* (Cuevas P, Burgos J, Baird A. Basic fibroblast growth factor (FGF) promotes cartilage repair *in vivo*. Biochem. Biophys. Res. Commun. 1988 Oct. 31;156(2):611-8). Takafuji et al. have also shown that FGF2 implants significantly improve temporo-mandibular cartilage in rabbits suffering from osteoarthritis (Takafuji H, Suzuki T, Okubo Y, Fujimura K,
10 Bessho K Regeneration of articular cartilage defects in the temporomandibular joint of rabbits by fibroblast growth factor-2: a pilot study. Int. J. Oral Maxillofac. Surg. 2007 Oct.; 36(10):934-7). These observations demonstrate the interest the compounds described in the invention as a therapy in treatment of osteoarthritis and cartilage repair.

15

In the field of bone repair, one of the essential needs is to find agents that stimulate bone formation. Among the main growth factors, it is established that the systemic administration of FGF2 facilitates bone repair (Acceleration of fracture healing in nonhuman primates by fibroblast growth factor-2. Kawaguchi
20 H, Nakamura K, Tabata Y, Ikada Y, Aoyama I, Anzai J, Nakamura T, Hiyama Y, Tamura M. J. Clin. Endocrinol. Metab. 2001 Feb.; 86(2), 875-880). The local application of FGF2 in gelatin matrices accelerates bone repair in primates, suggesting the clinical utility of FGF2 in the treatment of fractures. By virtue of their agonist properties for the FGF receptors, the compounds of the said
25 invention would represent a treatment of choice in bone repair.

Pre-eclampsia is a pathology of the placenta associated with a vascularization defect (Sherer, D. M. & Abulafia, O. Angiogenesis during implantation, and placental and early embryonic development. Placenta 22, 1-
30 13, 2001). These vascularization defects are thought to be due to an angiogenesis defect and lead to placental disruptions that may result in the death of the foetus. The compounds of the invention may be a treatment of choice for overcoming an angiogenesis defect in pre-eclamptic placentas.

In addition to angiogenesis-inducing effects, growth factors such as VEGF or FGF2 protect endothelial cells against intrinsic and extrinsic apoptosis inducers. The intrinsic signalling pathway is activated by the mitochondria in response to a stress such as deprivation or DNA damage, whereas the extrinsic signalling pathway is induced by the binding of pro-apoptotic factors such as TNF- α or Fas. It is now clearly described that VEGF and FGF2 are two factors of endothelial cell survival (Role of Raf in Vascular Protection from Distinct Apoptotic Stimuli: A Alavi, J.D. Hood, R. Frausto, D. G. Stupack, D.A. Cheresh: Science 4 July 2003: Vol. 301. No. 5629, pp. 94-96). Acute respiratory distress syndrome (ARDS) is characterized by cardiovascular and neuropsychiatric problems. In the context of the cardiovascular problems, the patients present major vascular lesions and especially a high induction of apoptosis of endothelial cells. Recently, Hamacher et al. have demonstrated that the bronchoalveolar lavage fluids of patients suffering from ARDS showed pro-apoptotic activity against lung microvascular endothelial cells (Tumor necrosis factor-alpha and angiostatin are mediators of endothelial cytotoxicity in bronchoalveolar lavages of patients with acute respiratory distress syndrome. Am. J. Respir. Crit. Care Med. 2002 Sep. 1;166(5):651-6: Hamacher J., Lucas R., Lijnen H.R., Buschke S., Dunant Y., Wendel A., Grau G.E., Suter P.M., Ricou B.). By virtue of their activity on endothelial cell survival, the products of the invention might be a treatment of choice in the vascular improvement of patients suffering from vascular lesions and especially patients suffering from ARDS.

25

The endogenous overregulation of FGF7 (or KGF) and of FGF18 appears to be an important mechanism for promoting the proliferation, migration and protection of hair follicles in pathological cases or after a tumoral treatment (Comprehensive Analysis of FGF and FGFR Expression in Skin: FGF18 Is Highly Expressed in Hair Follicles and Capable of Inducing Anagen from Telogen Stage Hair Follicles. Mitsuko Kawano, Akiko Komi-Kuramochi, Masahiro Asada, Masashi Suzuki, Junko Oki, Ju Jiang and Toru Imamura). By virtue of their agonist activity on the FGF receptors, the compounds of the said

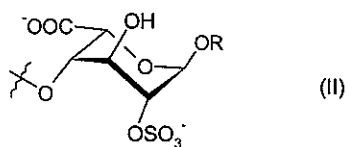
30

invention might be a treatment of choice for repairing and protecting hair follicles and for protecting and regulating hair growth.

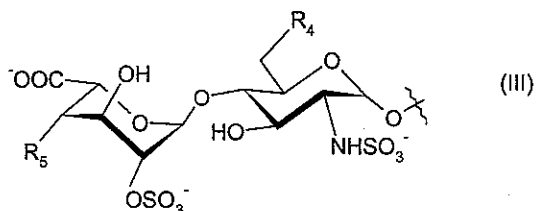
According to another of its aspects, the present invention relates to
 5 pharmaceutical compositions comprising, as active principle, a compound according to the invention or a compound **10**. These pharmaceutical compositions contain an effective dose of at least one compound according to the invention or of compound **10**, or a pharmaceutically acceptable salt of the said compound, and also at least one pharmaceutically acceptable excipient.
 10 The said excipients are chosen, according to the pharmaceutical form and the desired mode of administration, from the usual excipients known to those skilled in the art.

Thus, one subject of the invention is a pharmaceutical composition
 15 comprising, as active principle, at least one compound of formula (I) in which:

- R_1 represents a group $-\text{OSO}_3^-$ or a hydroxyl group,
- R_2 represents either a group $-\text{O-alkyl}$, or a monosaccharide of formula (II), in which R represents an alkyl group:



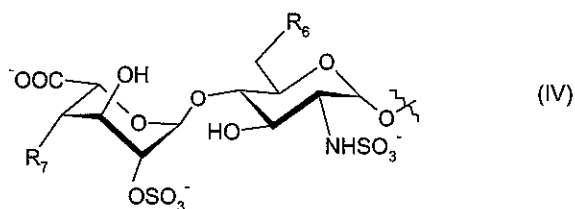
- R_3 represents a disaccharide of formula (III):



in which:

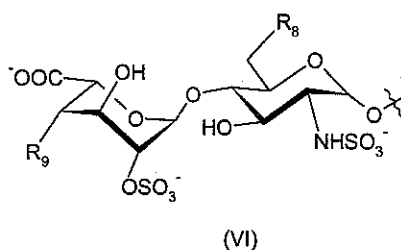
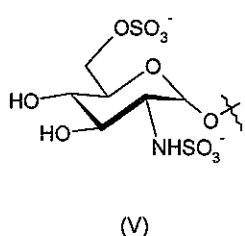
- R_4 represents a group $-\text{OSO}_3^-$ or a hydroxyl group,
- R_5 represents a disaccharide of formula (IV):

98



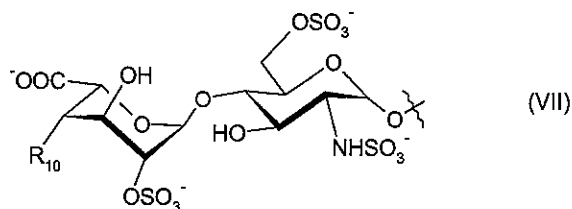
in which:

- R_6 represents a group $-\text{OSO}_3^-$ or a hydroxyl group,
 - R_7 represents either a hydroxyl group or a monosaccharide of
- 5 formula (V) below, or a disaccharide of formula (VI):



in which:

- R_8 represents a group $-\text{OSO}_3^-$ or a hydroxyl group,
 - R_9 represents either a hydroxyl group or a group $-\text{O-alkyl}$, or a
- 10 disaccharide of formula (VII):



- 15 in which R_{10} represents a group $-\text{O-alkyl}$,
 on condition that: R_9 represents a hydroxyl group or a group $-\text{O-alkyl}$ when
 R_2 represents a monosaccharide of formula (II) as defined above; R_7 represents
 a disaccharide of formula (VI) as defined above when R_2 represents a group
 $-\text{O-alkyl}$; and R_1 , R_4 , R_6 and R_8 do not simultaneously represent hydroxyl groups,
 20 or a pharmaceutically acceptable salt of the said compound, and also at
 least one pharmaceutically acceptable excipient.

Compounds of this kind encompass those of formula (I)/(I') defined above, as well as heptasaccharide **10** defined above, which has been described in patent application US 2006/0079483 A1.

5 In the pharmaceutical compositions of the present invention for oral, sublingual, subcutaneous, intramuscular, intravenous, topical, local, intratracheal, intranasal, transdermal or rectal administration, the active principle above or the salt thereof may be administered in a unit administration form, as a mixture with standard pharmaceutical excipients, to man and animals for the
10 prevention or treatment of the above disorders or diseases.

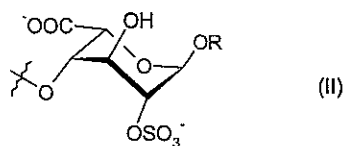
 The appropriate unit administration forms include oral forms such as tablets, soft or hard gel capsules, powders, granules and oral solutions or suspensions, sublingual, buccal, intratracheal, intraocular, intranasal or
15 inhalation administration forms, topical, transdermal, subcutaneous, intramuscular or intravenous administration forms, rectal administration forms and implants. For topical application, the compounds according to the invention may be used in creams, gels, ointments or lotions.

20 The injectable administration forms are particularly advantageous, conventionally comprising the active compound dissolved in water for injection, in the presence of sodium chloride. The unit dose of active compound should be suited to the desired therapeutic effect; it may be, for example, between 0.1 and 100 mg of active principle.

25 According to another of its aspects, the present invention also relates to the use of a compound according to the invention or of a compound **10**, or a pharmaceutically acceptable salt thereof, for treating the pathologies indicated above.

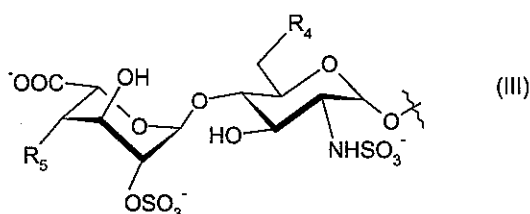
30 Thus, one subject of the invention is a compound of formula (I) in which:
- R₁ represents a group -OSO₃⁻ or a hydroxyl group,

- R_2 represents either a group $-O\text{-alkyl}$, or a monosaccharide of formula (II), in which R represents an alkyl group:



- R_3 represents a disaccharide of formula (III):

5

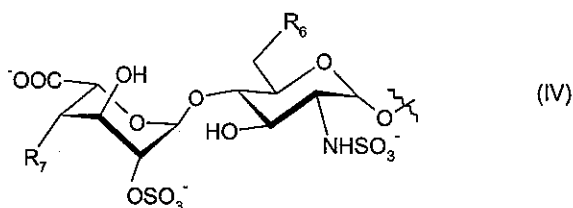


in which:

- R_4 represents a group $-\text{OSO}_3^-$ or a hydroxyl group, and

- R_5 represents a disaccharide of formula (IV):

10

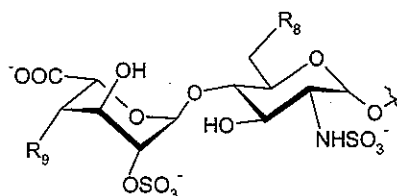
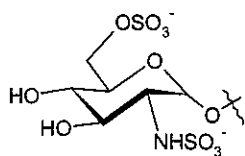


in which:

- R_6 represents a group $-\text{OSO}_3^-$ or a hydroxyl group,

- R_7 represents either a hydroxyl group or a monosaccharide of

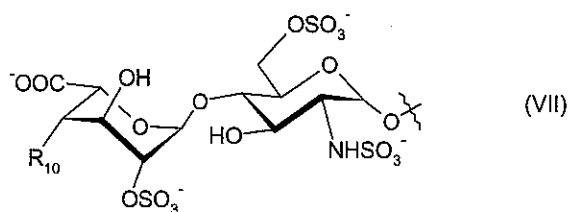
15 formula (V) below, or a disaccharide of formula (VI):



in which:

- R_8 represents a group $-\text{OSO}_3^-$ or a hydroxyl group,

20 - R_9 represents either a hydroxyl group or a group $-O\text{-alkyl}$, or a disaccharide of formula (VII):



in which R_{10} represents a group -O-alkyl,

- 5 on condition that: R_9 represents a hydroxyl group or a group -O-alkyl when R_2 represents a monosaccharide of formula (II) as defined above; R_7 represents a disaccharide of formula (VI) as defined above when R_2 represents a group -O-alkyl; and R_1 , R_4 , R_6 and R_8 do not simultaneously represent hydroxyl groups, or a pharmaceutically acceptable salt of the said compound,
- 10 for treating the pathologies indicated above.

Compounds of this kind encompass those of formula (I)/(I') defined above, as well as heptasaccharide **10** defined above, which has been described in patent application US 2006/0079483 A1.

15

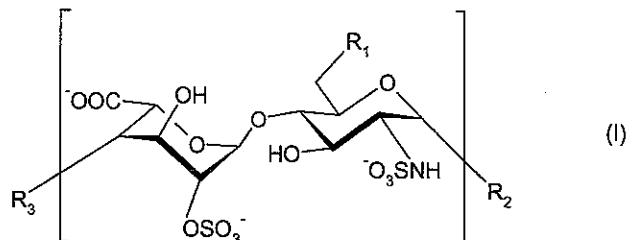
According to another of its aspects, the present invention also relates to a method for treating the pathologies indicated above, which comprises the administration to patients of an effective dose of a compound according to the invention or of a compound **10** or a pharmaceutically acceptable salt thereof.

20

The medicaments, pharmaceutical compositions and treatment method according to the invention may also concern any of the subgroups of compounds defined previously.

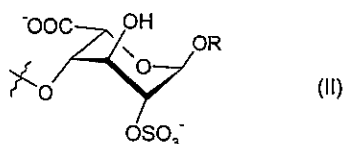
CLAIMS

1. Oligosaccharide compounds corresponding to formula (I):



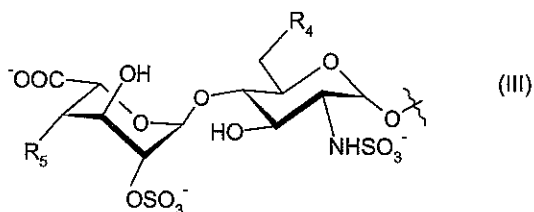
5 in which:

- R₁ represents a group -OSO₃⁻ or a hydroxyl group,
- R₂ represents either a group -O-alkyl, or a monosaccharide of formula (II), in which R represents an alkyl group:



10

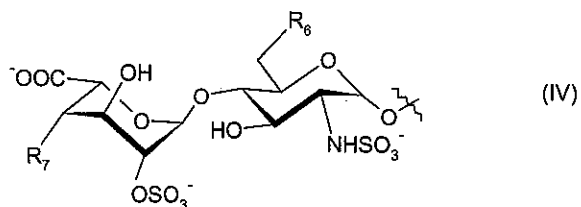
- R₃ represents a disaccharide of formula (III):



in which:

- R₄ represents a group -OSO₃⁻ or a hydroxyl group,
- R₅ represents a disaccharide of formula (IV):

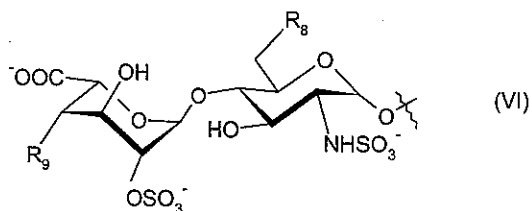
15



in which:

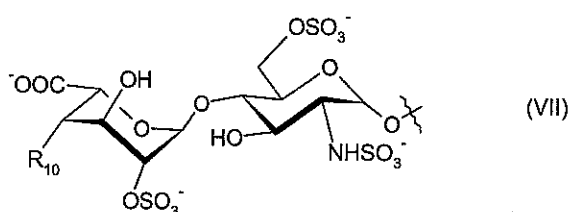
- R₆ represents a group -OSO₃⁻ or a hydroxyl group,
- R₇ represents either a hydroxyl group or a disaccharide of formula (VI):

20



in which:

- 5 - R₈ represents a group -OSO₃⁻ or a hydroxyl group,
 - R₉ represents either a hydroxyl group or a group -O-alkyl, or a
 disaccharide of formula (VII):



10

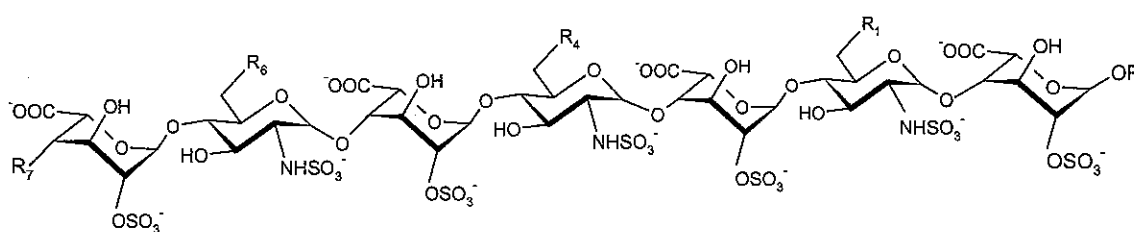
in which R₁₀ represents a group -O-alkyl,

- on condition that: R₉ represents a hydroxyl group or a group -O-alkyl when
 R₂ represents a monosaccharide of formula (II) as defined above; R₇ represents
 a disaccharide of formula (VI) as defined above when R₂ represents a group
 15 -O-alkyl; and R₁, R₄, R₆ and R₈ do not simultaneously represent hydroxyl groups;
 in acid form or in the form of any pharmaceutically acceptable salt thereof.

20

2. Compounds according to Claim 1, in which R₂ represents a
 monosaccharide of formula (II) and R₇ represents a hydroxyl group.

3. Compounds according to Claim 1 or Claim 2, corresponding to
 formula (I-1) below, in which R₇ represents a hydroxyl group and R, R₁, R₄ and
 R₆ are as defined in Claim 1:

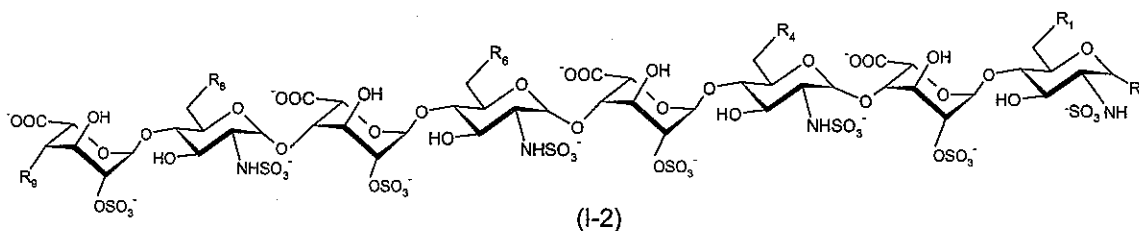


(I-1)

in acid form or in the form of any pharmaceutically acceptable salt thereof.

4. Compounds according to Claim 1, in which R_2 represents a group
5 -O-alkyl.

5. Compounds according to Claim 1 or Claim 4, corresponding to formula (I-2) below, in which R_2 represents a group -O-alkyl and R_1 , R_4 , R_6 , R_8 and R_9 are as defined in Claim 1:



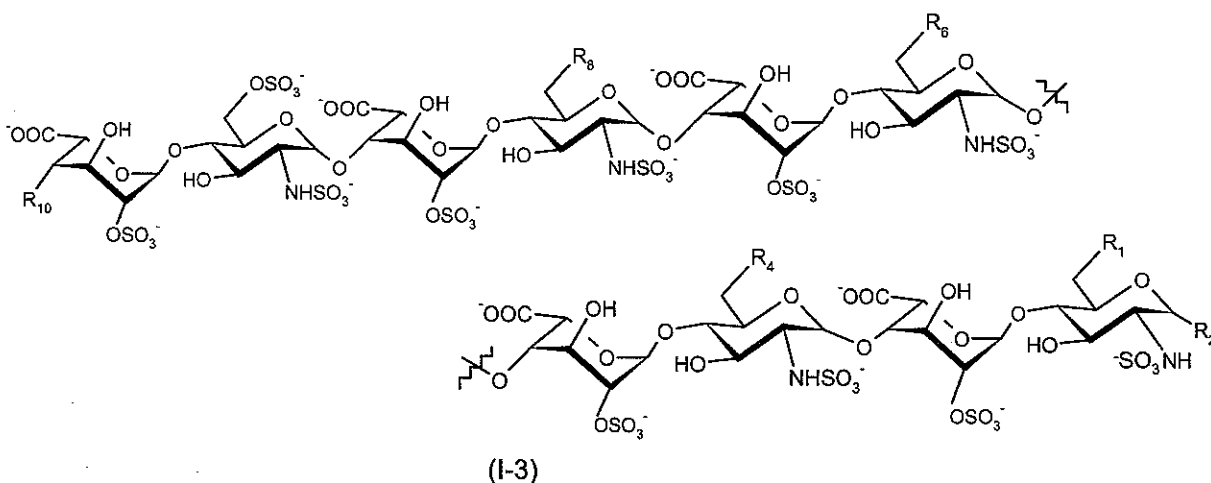
10

(I-2)

in acid form or in the form of any pharmaceutically acceptable salt thereof.

6. Compounds according to Claim 1, in which:
- R_2 represents a group -O-alkyl, and
 - 15 - R_7 represents a disaccharide of formula (VI) as defined in Claim 1, in which R_9 represents a disaccharide of formula (VII) as defined in Claim 1.

7. Compounds according to Claim 1 or Claim 6, corresponding to formula (I-3) below, in which R_2 and R_9 are as defined in Claim 6 and R_1 , R_4 , R_6 ,
20 R_8 and R_{10} are as defined in Claim 1:



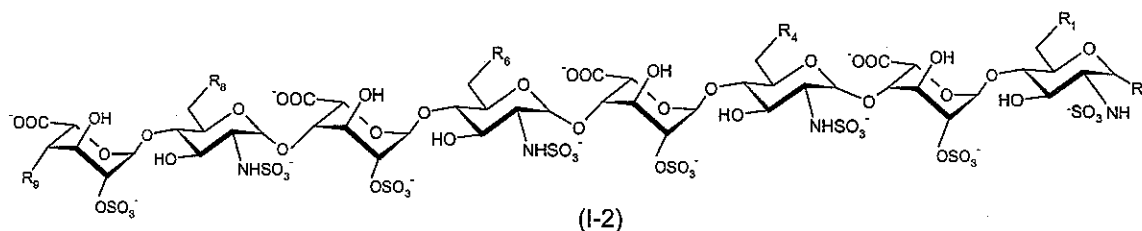
in acid form or in the form of any pharmaceutically acceptable salt thereof.

5 8. Compounds according to Claim 1, in which:

- R_2 represents a group -O-alkyl, and

- R_7 represents a disaccharide of formula (VI) as defined in Claim 1, in which R_9 represents either a hydroxyl group or a group -O-alkyl.

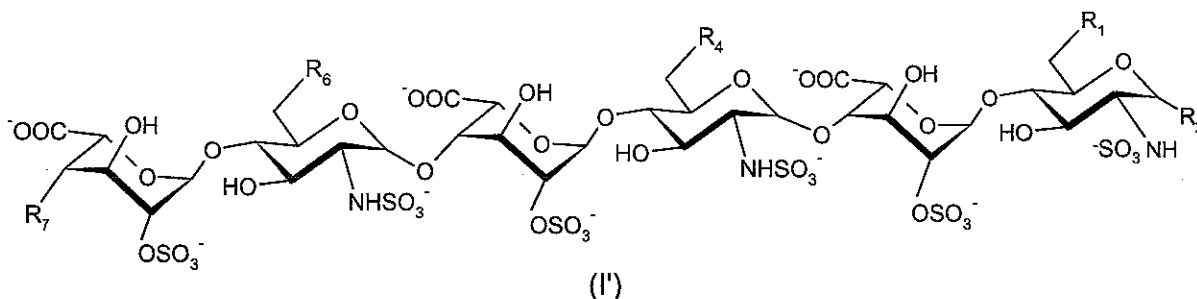
10 9. Compounds according to Claim 1 or Claim 8, corresponding to formula (I-2) below, in which R_1 , R_4 , R_6 and R_8 are as defined in Claim 1, R_2 represents a group -O-alkyl and R_9 represents either a hydroxyl group or a group -O-alkyl:



15 in acid form or in the form of any pharmaceutically acceptable salt thereof.

10. Compounds according to Claim 8 or Claim 9, in which R_9 represents a group -O-alkyl.

11. Compounds according to any one of Claims 1 to 10, characterized in that they correspond to the formula (I'), in which R₁, R₂, R₄, R₆ and R₇ are as defined in any one of Claims 1 to 9:



5

12. Compounds according to any one of Claims 1 to 11, chosen from the following compounds:

- methyl (sodium 4-O-propyl-2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl-(1 $\rightarrow$ 4)]₂-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranoside (**No. 1**);

15 - methyl (sodium 4-O-propyl-2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl-(1 $\rightarrow$ 4)]₃-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranoside (**No. 2**);

20 - sodium [methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-[(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)]₂-2-O-sodium sulfonato- α -L-idopyranoside]-uronate (**No. 3**);

25

- methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-
(2-deoxy-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-
sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-sodium (sulfonato-
amino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-
5 idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium
(sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-
idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-6-O-sodium sulfonato-2-sodium
(sulfonatoamino)- α -D-glucopyranoside **(No. 4)**;
- methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-
10 (2-deoxy-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-
sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium
sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-
sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-sodium
(sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-
15 idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-6-O-sodium sulfonato-2-sodium
(sulfonatoamino)- α -D-glucopyranoside **(No. 5)**;
- methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-
(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-
(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-
20 2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium
sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-sodium (sulfonatoamino)-
 α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyl-
uronate)-(1 $\rightarrow$ 4)-2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-
glucopyranoside **(No. 6)**;
- 25 - methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-
(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-
(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-
2-sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium
sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-
30 sodium (sulfonatoamino)- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium

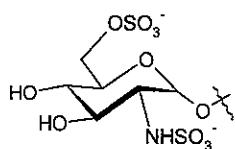
sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranoside (**No. 7**);

- methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium(sulfonatoamino)- α -D-glucopyranosyl)-
 5 [(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)]₂-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-6-O-sodium sulfonato-2- (sulfonato)amino- α -D-glucopyranoside (**No. 8**); and

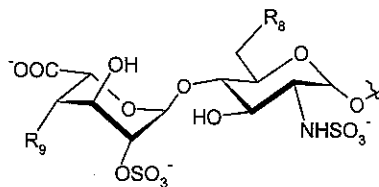
- methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonato)amino- α -D-glucopyranosyl)-
 10 [(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-6-O-sodium sulfonato-2-sodium (sulfonatoamino)- α -D-glucopyranosyl)]₂-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-2-sodium (sulfonatoamino)- α -D-glucopyranoside (**No. 9**).

15

13. Medicament, characterized in that it comprises a compound according to any one of Claims 1 to 12 and in which R₇ represents either a hydroxyl group or a monosaccharide of formula (V) below, or a disaccharide of formula (VI), in which R₈ and R₉ are as defined in any one of Claims 1 to 10:



(V)



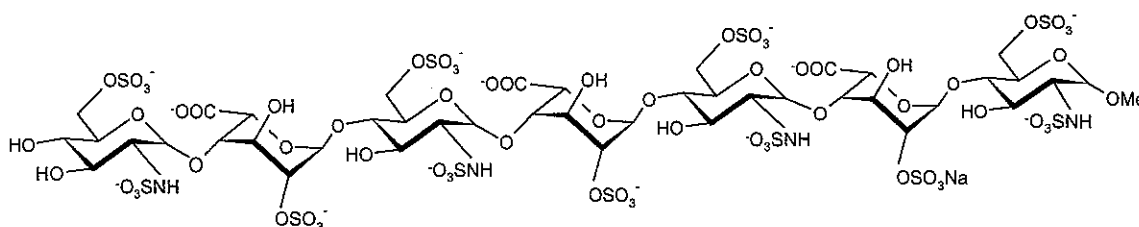
(VI)

20

or a pharmaceutically acceptable salt thereof.

14. Medicament according to Claim 13, characterized in that it comprises a compound according to any one of Claims 1 to 12, or a pharmaceutically
 25 acceptable salt thereof.

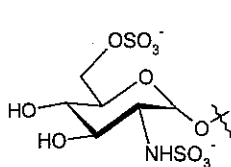
15. Medicament according to Claim 13, characterized in that it comprises compound **10**:



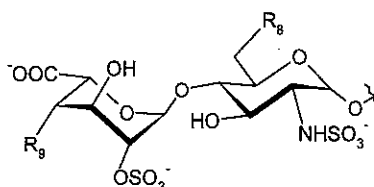
10

or a pharmaceutically acceptable salt thereof.

16. Pharmaceutical composition, characterized in that it comprises a compound according to any one of Claims 1 to 12, and in which R_7 represents either a hydroxyl group or a monosaccharide of formula (V) below, or a disaccharide of formula (VI), in which R_8 and R_9 are as defined in any one of Claims 1 to 10:



(V)

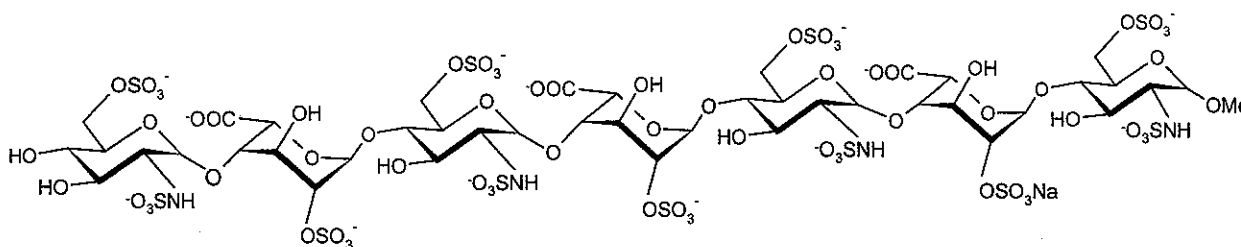


(VI)

- or a pharmaceutically acceptable salt thereof, and also at least one pharmaceutically acceptable excipient.

17. Pharmaceutical composition, characterized in that it comprises a compound according to any one of Claims 1 to 12, or a pharmaceutically acceptable salt thereof, and also at least one pharmaceutically acceptable excipient.

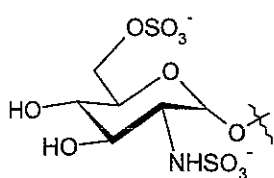
18. Pharmaceutical composition, characterized in that it comprises compound 10:



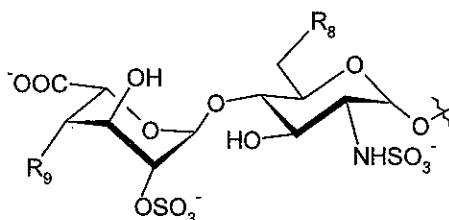
10

or a pharmaceutically acceptable salt thereof, and also at least one pharmaceutically acceptable excipient.

19. Compound according to any one of Claims 1 to 12, in which R_7 represents either a hydroxyl group or a monosaccharide of formula (V) below, or a disaccharide of formula (VI), in which R_8 and R_9 are as defined in any one of Claims 1 to 10:



(V)

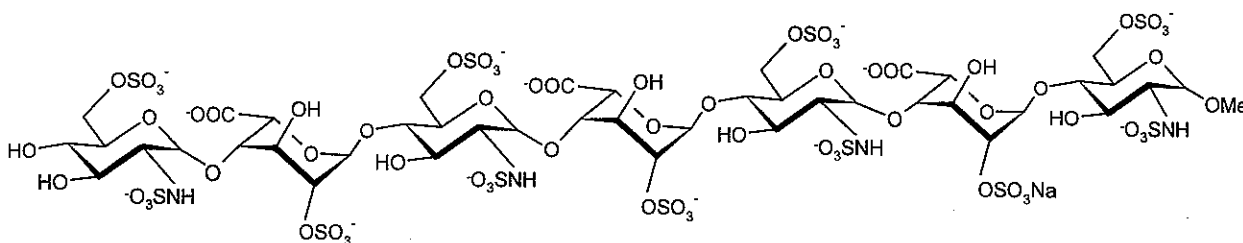


(VI)

- for its use in the treatment of pathologies requiring activation of the FGF receptors.

20. Compound according to any one of Claims 1 to 12, or pharmaceutically acceptable salt thereof, for its use in the treatment of pathologies requiring activation of the FGF receptors.

21. Compound **10**, or a pharmaceutically acceptable salt thereof:

**10**

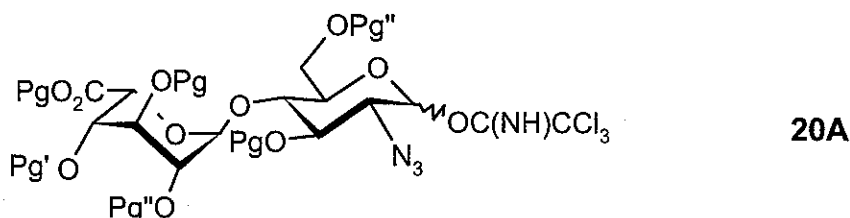
20

for its use in the treatment of pathologies requiring activation of the FGF receptors.

22. Compound according to any one of Claims 19 to 21, for its use in the treatment of pathologies requiring angiogenesis activation and post-ischaemic revascularization.

23. Compound according to any one of Claims 19 to 22, for its use in the treatment of ischaemia, such as cardiac ischaemia and arterial ischaemia of the lower limbs, the treatment of diseases associated with narrowing or obstruction of the arteries or arterites, the treatment of angina pectoris, the treatment of thromboangitis obliterans, the treatment of atherosclerosis, the treatment of inhibition of restenosis after angioplasty or endarterectomy, the treatment of cicatrization, muscle regeneration treatment, treatment for the survival of myoblasts, the treatment of peripheral neuropathy, the treatment of post-operative nerve damage, the treatment of nerve deficiencies such as Parkinson's disease, Alzheimer's disease, prion disease and neuronal degeneration in alcoholics, the treatment of dementias, treatment for improving the survival of a bioartificial pancreas graft in the case of diabetics, treatment for improving the revascularization of grafts and the survival of grafts, the treatment of retinal degeneration, the treatment of pigmentary retinitis, the treatment of osteoarthritis, the treatment of pre-eclampsia or the treatment of vascular lesions and of acute respiratory distress syndrome, treatment for repairing cartilage, treatment for repairing and protecting bones, treatment for repairing and protecting hair follicles and for protecting and regulating hair growth.

24. Compound of formula 20A, in which Pg, Pg' and Pg'', which may be identical or different, represent protecting groups:



25. Compound according to Claim 24, in which Pg, Pg' and Pg'' represent, respectively, benzyl, allyl and acetyl groups.