

FGF RECEPTOR-ACTIVATING N-ACYL OCTASACCHARIDES,
PREPARATION THEREOF, AND THERAPEUTIC USE THEREOF

The present invention relates to N-acyl octasaccharides that are agonists of the
5 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 has been shown *in*
10 *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 migration and the
15 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.

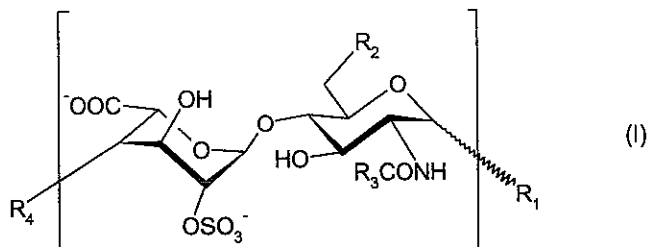
20 It is known that cell surface receptors with tyrosine kinase activity associate in
dimeric form with a complex formed from two ligand molecules and one heparan sulfate
molecule. The formation of this complex triggers a cascade of intracellular signals
resulting in activation of cell proliferation 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 interactions
30 with the FGF receptors (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
facilitating the formation of the FGF/FGFR complex and of thus promoting the *in vitro*
35 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 octasaccharide compounds corresponding to formula (I):



5 in which:

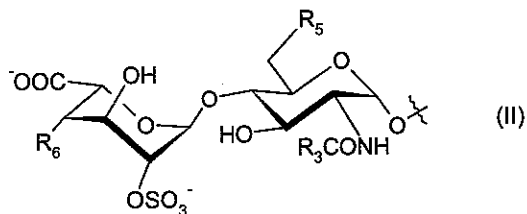
- the wavy line denotes a bond located either below or above the plane of the pyranose ring of the glucosamine unit,

- R_1 represents a group O-alkyl, in which the said alkyl group comprises from 1 to 16 carbon atoms and is optionally substituted with one or more (for example 1 or 2) groups, which may be identical or different, chosen from aryl and cycloalkyl groups,

- R_2 represents either a group OSO_3^- or a hydroxyl group,

- R_3 represents an alkyl, cycloalkyl or alkyl-cycloalkyl group, and

- R_4 represents a disaccharide of formula (II):

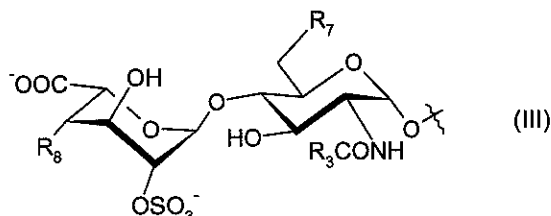


15 in which:

- R_3 is as defined above,

- R_5 represents either a group OSO_3^- or a hydroxyl group, and

- R_6 represents a disaccharide of formula (III):



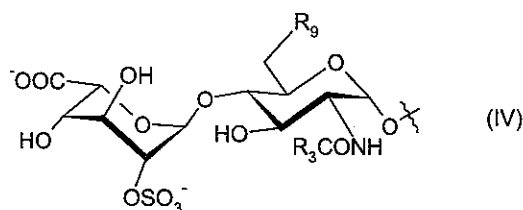
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in which:

- R_3 is as defined above,

- R_7 represents either a group OSO_3^- or a hydroxyl group, and

- R_8 represents a disaccharide of formula (IV):



in which:

- R_3 is as defined above,
- R_9 represents either a group OSO_3^- or a hydroxyl group.

In the context of the present invention, and unless otherwise mentioned in the text, the following definitions apply:

- alkyl group: a linear or branched saturated aliphatic group. Unless otherwise indicated in the text, such an alkyl group advantageously comprises between 1 and 6 carbon atoms. Examples that may be mentioned include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl, pentyl, etc. groups;
- cycloalkyl group: a cyclic alkyl group comprising from 3 to 6 carbon atoms, for example a cyclopentyl or cyclohexyl group;
- alkyl-cycloalkyl group: an alkyl group which is itself substituted with a cycloalkyl group, the said alkyl and cycloalkyl groups being as defined above; and
- aryl group: a cyclic aromatic group comprising between 5 and 10 carbon atoms, such as a phenyl group. Such an aryl group is optionally substituted with one or more groups such as halogen atoms and alkyl, alkoxy, thioalkyl, trifluoromethyl and phenyl groups.

The octasaccharides according to the invention are synthetic octasaccharides, 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 octasaccharides, i.e. they are free of other octasaccharide 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 $-\text{COO}^-$ and $-\text{SO}_3^-$ are, respectively, in $-\text{COOH}$ and $-\text{SO}_3\text{H}$ form.

5 The term "pharmaceutically acceptable salt of the compounds of the invention" means a compound in which one or more of the functions $-\text{COO}^-$ and/or $-\text{SO}_3^-$ 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.

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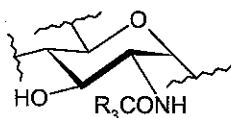
The compounds of formula (I) according to the invention also comprise those in which one or more hydrogen or carbon atoms have been replaced with a radioactive isotope, for example tritium or carbon ^{14}C . Such labelled compounds are useful in research, metabolism or pharmacokinetic studies, as ligands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

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

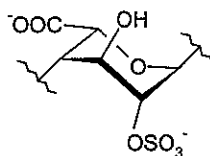
- the disaccharide of formula (II) is linked to the disaccharide unit represented in formula (I) via the oxygen atom located in position 1 of its glucosamine unit,
- 20 - similarly, the disaccharide of formula (III) is linked to the disaccharide of formula (II) via the oxygen atom located in position 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.

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



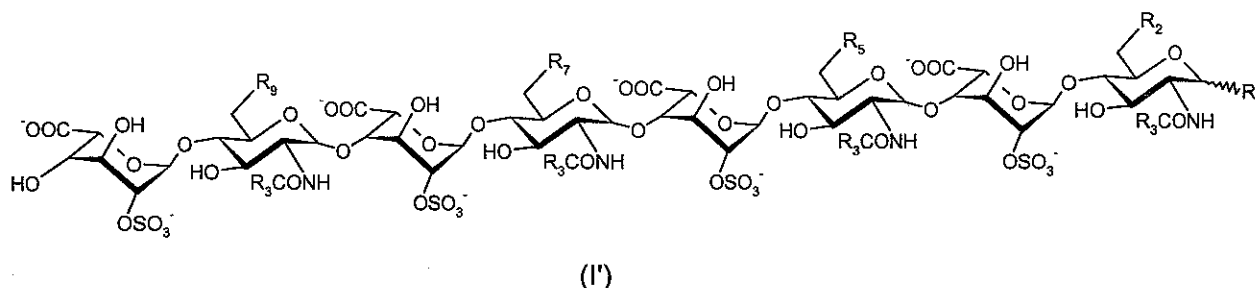
The other type of saccharide unit present in the compounds according to the invention is a uronic acid, more specifically an iduronic acid, corresponding to the following formula:

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Thus, the compounds of formula (I) according to the invention, which are octasaccharides, 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 ,

5 R_3 , R_5 , R_7 and R_9 are as defined previously:



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_1 represents:

- 10 - either a group O-alkyl, in which the said alkyl group comprises from 5 to 16 carbon atoms and advantageously from 5 to 12 carbon atoms (for example a group -O-pentyl, -O-undecyl or 2-propylpentyl),
- or a group O-alkyl, in which the said alkyl group comprises from 1 to 8 carbon atoms and advantageously from 3 to 6 carbon atoms (for example a group -O-propyl or
- 15 -O-pentyl), and is substituted with 1 or 2 groups, which may be identical or different, chosen from aryl and cycloalkyl groups (for example phenyl and cycloalkyl groups, such as cyclohexyl).

20 Among the compounds of formula (I)/(I') that are subjects of the invention, mention may be made of another subgroup of compounds, in which R_3 represents either an alkyl group comprising from 2 to 6 carbon atoms (for example a propyl or pentyl group) or a cycloalkyl group (for example a cyclopentyl group).

25 Among the compounds of formula (I)/(I') that are subjects of the invention, mention may be made of another subgroup of compounds, in which at least one of the groups R_2 , R_5 , R_7 and R_9 represents a hydroxyl group.

30 Another subgroup of compounds that are subjects of the invention is such that at least one of the groups R_2 , R_5 , R_7 and R_9 represents a hydroxyl group and at least one of the groups R_2 , R_5 , R_7 and R_9 represents a group OSO_3^- .

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

Mention may be made in particular of the subgroup of compounds of formula (I)

5 in which:

- R_1 represents:

. either a group O-alkyl, in which the said alkyl group comprises from 5 to 16 carbon atoms and advantageously from 5 to 12 carbon atoms (for example a group -O-pentyl, -O-undecyl or 2-propylpentyl),

10 . or a group O-alkyl, in which the said alkyl group comprises from 1 to 8 carbon atoms and advantageously from 3 to 6 carbon atoms (for example a group -O-propyl or -O-pentyl), and is substituted with 1 or 2 groups, which may be identical or different, chosen from aryl and cycloalkyl groups (for example phenyl and cycloalkyl groups, such as cyclohexyl),

15 - R_3 represents either an alkyl group comprising from 2 to 6 carbon atoms (for example a propyl or pentyl group) or a cycloalkyl group (for example a cyclopentyl group), and

- at least one of the groups R_2 , R_5 , R_7 and R_9 represents a hydroxyl group.

20 Among the compounds of the invention, mention may be made especially of the following octasaccharides:

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

30 - Pentyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- α -D-

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

- Pentyl (sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-2-(1-oxohexyl)amino-6-O-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-2-(1-oxohexyl)amino-6-O-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-2-(1-oxohexyl)amino-6-O-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-2-deoxy-2-(1-oxohexyl)amino-6-O-sodium sulfonato-β-D-glucopyranoside (**No. 3**);

- Pentyl (sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-[(cyclopentylcarbonyl)amino]-2-deoxy-6-O-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-[(cyclopentylcarbonyl)amino]-2-deoxy-6-O-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-[(cyclopentylcarbonyl)amino]-2-deoxy-6-O-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-2-[(cyclopentylcarbonyl)amino]-2-deoxy-6-O-sodium sulfonato-β-D-glucopyranoside (**No. 4**);

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- Undecyl (sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-2-acetamido-2-deoxy-6-O-sodium sulfonato-β-D-glucopyranoside (**No. 5**);

- 5-phenylpentyl (sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-2-acetamido-2-

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deoxy-6-O-sodium sulfonato- β -D-glucopyranoside (**No. 6**);

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

10 - Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranoside (**No. 8**);

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- Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranoside (**No. 9**);

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25 - Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy- α -D-glucopyranoside (**No. 10**);

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- Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-

acetamido-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranoside (**No. 11**);

- Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy- α -D-glucopyranoside (**No. 12**);

- Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranoside (**No. 13**);

- 5-phenylpentyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-2-(1-oxobutyl)amino- β -D-glucopyranoside (**No. 14**);

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

oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-2-(1-oxobutyl)amino- β -D-glucopyranoside **(No. 15)**;

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- 3-cyclohexylpropyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-acetamido-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-acetamido-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-acetamido- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-2-acetamido- β -D-glucopyranoside **(No. 16)**;

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- 3-cyclohexylpropyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-2-(1-oxobutyl)amino- β -D-glucopyranoside **(No. 17)**;

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- 3,3-diphenylpropyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-2-(1-oxobutyl)amino- β -D-glucopyranoside **(No. 18)**; and

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- 5-phenylpentyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(3-methyl-1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(3-methyl-1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(3-methyl-1-

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oxobutyl)amino- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-2-(3-methyl-1-oxobutyl)amino- β -D-glucopyranoside (**No. 19**).

5 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.*,
10 1993, 32, 1671-1690. These synthons are then coupled together so as to give an entirely protected equivalent of an octasaccharide 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
15 hydroxyl.

The specific synthetic schemes will be described in the detailed examples that follow.

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

- in a first phase, a fully protected equivalent of the desired octasaccharide (I) is synthesized,
- in a second phase, the positions that are to bear sulfonate groups on the final
25 molecule are deprotected and then O-sulfated,
- in a third phase, the whole compound is deprotected, and
- in a fourth phase, the N-acyl groups are introduced (introduction of groups the R₃-CO-).

30 The synthesis of the fully protected equivalent of the desired octasaccharide (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 oligosaccharide is coupled with a
35 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) is obtained, optionally in protected form. The nature and profile of the charge of the final desired compound determine the nature of the chemical 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
5 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.

The compounds of the invention may naturally be prepared using various
10 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
15 *Tetrahedron* (1996), 52, 1095-1121.

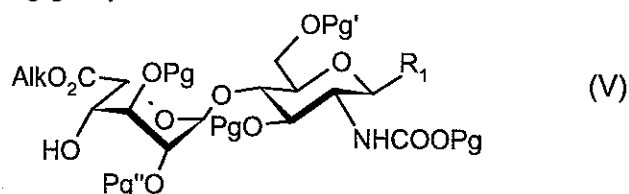
The protecting groups used in the process for preparing the compounds of formula (I)/(I') are those that make it possible firstly to protect a reactive function such as a hydroxyl or an amine during a synthesis, and secondly to regenerate the intact
20 reactive function at the end of the synthesis. The 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, methyl, pentenyl, benzoyl, levulinyl, benzyl, substituted benzyl,
25 azide, benzyl carbamate, *tert*-butyldimethylsilyl (tBDMS) and *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-
30 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
35 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.

- 5 A subject of the invention is also the compounds of formula (V) below, in which Alk represents an alkyl group, R_1 is as defined previously in relation with the compounds of formula (I)/(I'), and Pg, Pg' and Pg'', which may be identical or different, represent protecting groups:

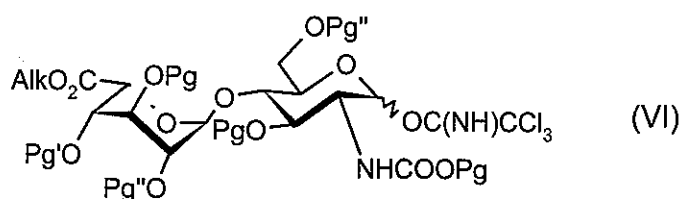


- 10 Such compounds are useful as intermediates in the synthesis of the compounds of formula (I)/(I').

- 15 In particular, a subject of the invention is the compounds (V) in which Alk represents a methyl group and Pg, Pg' and Pg'' represent, respectively, benzyl, tBDPS and acetyl groups. More particularly, among these compounds of formula (V), the invention is directed towards those in which R_1 is chosen from the following groups: -O-methyl, -O-(CH₂)₅-phenyl, -O-CH₂-CH(C₃H₇)₂, -O-(CH₂)₃-C₆H₁₁ and -O-(CH₂)₂-CH(phenyl)₂.

- 20 Such compounds correspond to disaccharides 58, 131, 132, 133 and 134 illustrated in the synthetic schemes below, which are useful for the synthesis of compounds 10, 11 and 14 to 19 according to the invention, as will be detailed hereinbelow.

- 25 A subject of the invention is also the compounds of formula (VI) below, in which Alk represents an alkyl group and 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 compound (VI) in which Alk represents a methyl group and Pg, Pg' and Pg'' represent, respectively, benzyl, levuliny and acetyl groups. Such a compound corresponds to disaccharide 24 illustrated in the synthetic schemes below, which is useful for the synthesis of compounds 1 to 4 according to the invention, as will be detailed hereinbelow.

10 The examples that follow describe the preparation of certain compounds 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
15 therein or that are known to those skilled in the art.

The following abbreviations are used:

[α]_D: optical rotation

Ac: acetyl

20 Bn: benzyl

TLC: thin-layer chromatography

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

ESI: Electron-Spray Ionization

h: hours

25 LC-MS (*): liquid chromatography coupled to mass spectrometry

Lev: levuliny

min: minutes

Me: methyl

PMB: para-methoxybenzyl

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

tBDMS: *tert*-butyldimethylsilyl

tBDPS: *tert*-butyldiphenylsilyl

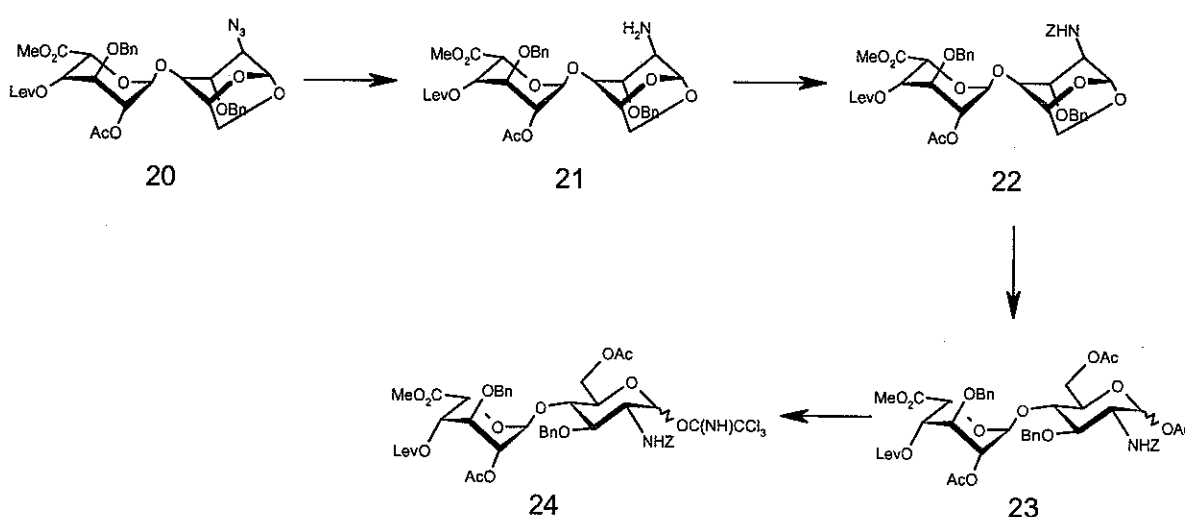
TFA: trifluoroacetic acid

35 T_R: retention time measured by LC-MS*

Z: benzyloxycarbonyl

*The LC-MS are acquired on a Waters brand ZQ4000 machine. The column used is a Symmetry C18 3.5 μm (2.1x50 mm). Eluent A is formed from H_2O + 0.005% TFA, pH 3.15. Eluent B is formed from acetonitrile + 0.005% TFA. The gradient ranges from 0 to 90% of eluent B over 10 (or 30) minutes + 5 minutes at 90% of eluent B. The flow rate is 0.4 mL/min.

Preparation of the synthetic intermediates:



Preparation of (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl-α-L-idopyranosyluronate)-(1→4)-2-amino-1,6-anhydro-3-O-benzyl-2-deoxy-β-D-glucopyranose (No. 21)

To a solution of compound **20** (21.6 g, 31 mmol) (C.A.A. Van Boeckel et al., J. Carbohydr. Chem., 4 (1985) 293-321) in *N,N*-dimethylformamide (155 mL) is added triethylamine (Et_3N) (65 mL, 15 molar equivalents), followed by addition of 1,3-propanedithiol (47 mL, 15 molar equivalents). After 17 hours of magnetic stirring, the reaction mixture is diluted with ethyl acetate, washed with water, dried (Na_2SO_4), filtered and concentrated, and then purified on silica gel (acetone - cyclohexane) to give **21** (15.8 g, 76%).

LC-MS m/z 672.2 $[(M + H)^+]$. T_R = 0.94 min

Preparation of (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl-α-L-idopyranosyluronate)-(1→4)-1,6-anhydro-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino-β-D-glucopyranose (No. 22)

To a solution of compound **21** (128.12 g, 190.7 mmol) in dichloromethane (240 mL) is added saturated aqueous sodium hydrogen carbonate solution (240 mL), followed by addition, at 0°C , of benzyloxycarbonyl chloride (35.5 mL, 1.3 molar

equivalents). After 15 minutes of vigorous magnetic stirring at 0°C, the reaction mixture is diluted with dichloromethane, washed with water to neutrality, dried (Na₂SO₄), filtered and concentrated. The crude product is used in the following step without purification.

LC-MS *m/z* 806.2 [(M + H)⁺]. T_R = 1.55 min

5

Preparation of (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-1,6-di-O-acetyl-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- α , β -D-glucopyranose (No. 23)

The residue obtained in the preceding step is dissolved in acetic anhydride (1.05 L), followed by addition, at 0°C and over 15 min, of trifluoroacetic acid (TFA) (105 mL). The reaction mixture is stirred for 10 minutes at 0°C and for 18 hours at room temperature, and is then concentrated, co-evaporated with toluene, and purified on silica gel (cyclohexane - acetone), to give compound **23** (138.9 g, 80%, 2 steps).

LC-MS *m/z* 930.3 [(M + Na)⁺]. T_R = 21.68/21.84 min

15

Preparation of (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-acetyl-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- α , β -D-glucopyranose trichloroacetimidate (No. 24)

To a solution of compound **23** (25 g, 27.5 mmol) in diethyl ether (1.1 L) is added, at 0°C, benzylamine (BnNH₂) (109 mL, 36 molar equivalents). After stirring for 1 hour at 0°C, and then for 4.5 hours at room temperature, the reaction mixture is diluted with ethyl acetate, and then neutralized with cold 1N HCl (0-4°C), washed with water, dried (Na₂SO₄), filtered and concentrated, and purified on silica gel (acetone - cyclohexane) to give (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-acetyl-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- α , β -D-glucopyranose (18.5 g, 78%).

LC-MS *m/z* 888.3 [(M + Na)⁺]. T_R = 19.95/20.60 min

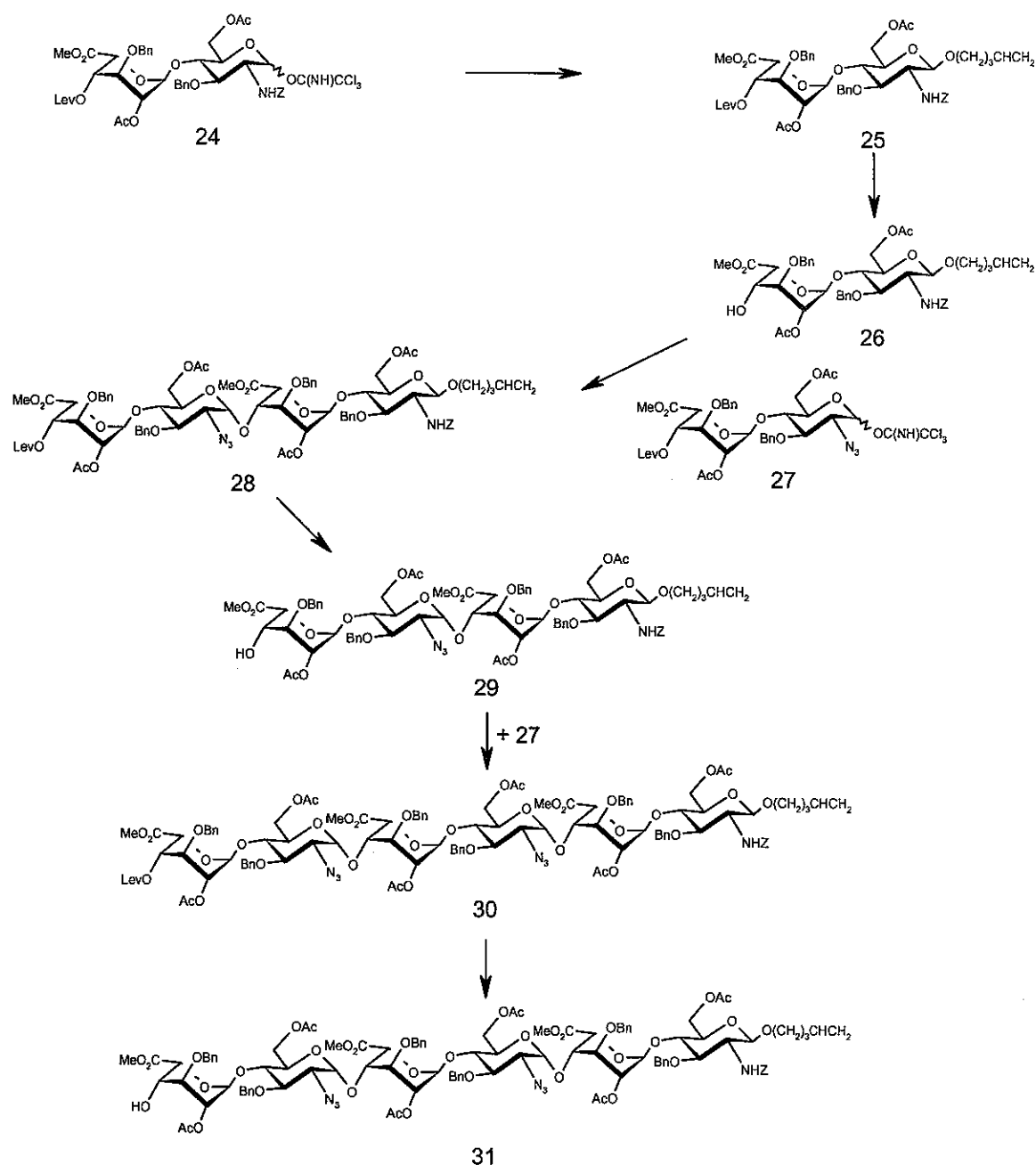
To a solution of the compound thus obtained (18.5 g, 21.4 mmol) in dichloromethane (405 mL) is added, under argon and at 0°C, caesium carbonate (Cs₂CO₃) (11.1 g, 1.6 molar equivalents) and trichloroacetonitrile (CCl₃CN) (14.8 mL, 5.0 molar equivalents). After stirring for 1 hour at room temperature, the reaction mixture is filtered and then concentrated. The residue is purified on silica gel (acetone - cyclohexane + 0.1% triethylamine) to give **24** (17.2 g, 80%).

R_f = 0.47 (7/3 ethyl acetate/cyclohexane).

Chemical shifts of anomeric protons (500 MHz, CDCl₃) δ 5.17 IdoUA^{II}, 6.28 Glc^I α

LC-MS *m/z* 866.3 [(M + Na)⁺]. T_{R1} = 19.91 min

35



Preparation of 4-pentenyl (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-acetyl-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]-amino- β -D-glucopyranoside (No. 25)

- 5 A solution of *tert*-butyldimethylsilyl triflate in dichloromethane (1M, 0.2 mol per mole of imidate) is added, under argon and at -20°C, to a solution of the imidate **24** (13.7 g, 13.56 mmol) and of allyl alcohol (6.8 mL, 5 molar equivalents) in dichloromethane (590 mL) in the presence of 4 Å molecular sieves (17.6 g). After 20 minutes of stirring (TLC), saturated aqueous sodium hydrogen carbonate solution is
- 10 added. After filtering, washing with water, drying (Na₂SO₄), filtering and evaporating to dryness, the mixture is purified on silica gel to give compound **25** (10.7 g, 85%).

LC-MS m/z 934.5 $[(M + H)^+]$. T_R = 24.00 min

Preparation of 4-pentenyl (methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-acetyl-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 26)

To a solution of compound **25** (10.6 g, 11.35 mmol) in a 1:2 mixture of toluene/ethanol (1.2 L) is added hydrazine acetate (5.2 g, 5 molar equivalents). After 2.5 hours of magnetic stirring, the mixture is concentrated under vacuum and then purified on silica gel to give compound **26** (6.98 g, 74%).

LC-MS m/z 858.4 $[(M + Na)^+]$. T_R = 22.62 min

Preparation of 4-pentenyl (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)-(methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-acetyl-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 28)

A solution of *tert*-butyldimethylsilyl triflate in dichloromethane (1M, 0.15 mol per mole of imidate) is added, under argon and at -20°C, to a solution of the imidate **27** (9.0 g, 9.98 mmol) (C. Tabeur et al., BioOrg. Med. Chem. (1999) 7, 2003-2012) and of the glycosyl acceptor **26** (6.95 g, 8.32 mmol) in dichloromethane (350 mL) in the presence of 4 Å molecular sieves (7.5 g). After 18 hours at -20°C (TLC), solid sodium hydrogen carbonate is added. After filtering, washing with aqueous 2% sodium hydrogen carbonate solution, with water, drying (Na_2SO_4), filtering and evaporating to dryness, the residue is purified on silica gel to give **28** (9.04 g, 69%).

R_f = 0.38 (1/4 acetone/toluene).

Preparation of 4-pentenyl (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-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 29)

To a solution of compound **28** (9.0 g, 5.7 mmol) in a 1:2 mixture of toluene/ethanol (570 mL) is added hydrazine acetate (2.6 g, 5 molar equivalents). After 1 hour of magnetic stirring, the mixture is concentrated under vacuum and then purified on silica gel to give compound **29** (7.15 g, 85%).

R_f = 0.29 (1/4 acetone/toluene).

Preparation of 4-pentenyl (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)-(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-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 30)

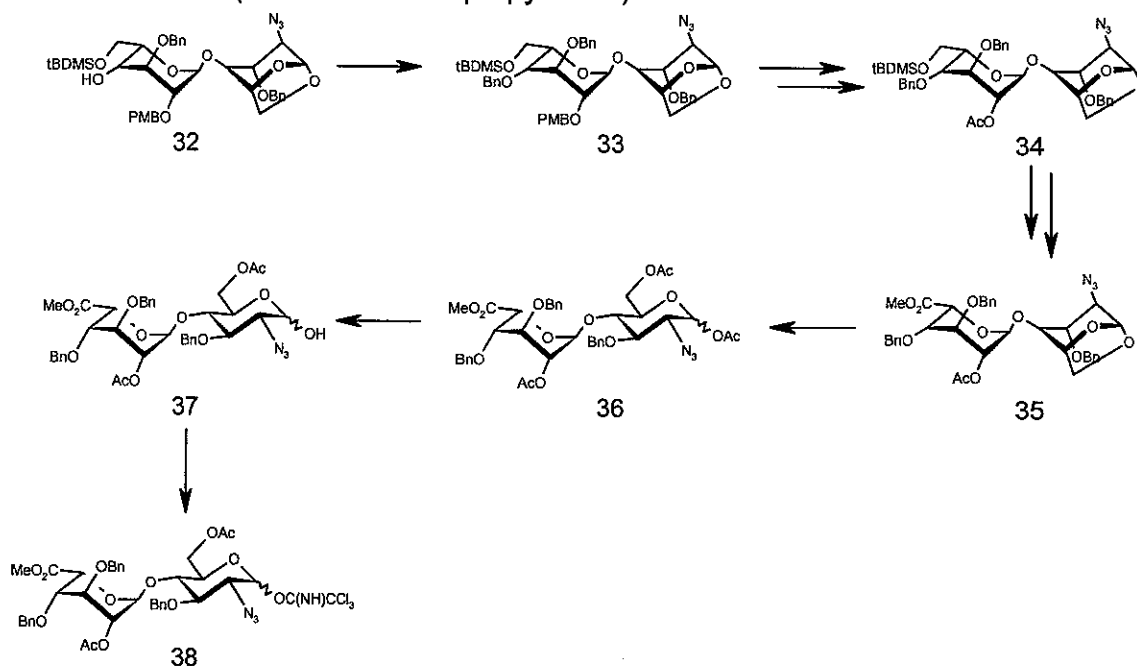
A solution of *tert*-butyldimethylsilyl triflate in dichloromethane (1M, 0.15 mol per mole of imidate) is added, under argon and at -20°C, to a solution of the imidate **27** (4.80 g, 5.32 mmol) and of the glycosyl acceptor **29** (7.15 g, 4.84 mmol) in dichloromethane (180 mL) in the presence of 4 Å molecular sieves (3.99 g). After 18 hours at -20°C (TLC), solid sodium hydrogen carbonate is added. After magnetic stirring at room temperature (30 minutes), filtering, washing with aqueous 2% sodium hydrogen carbonate solution, and then with water, drying (Na₂SO₄) and evaporating to dryness, the residue is purified on silica gel to give **30** (5.23 g, 49%).

R_f = 0.18 (1/4 acetone/diisopropyl ether).

Preparation of 4-pentenyl (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)-(methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-acetyl-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 31)

To a solution of compound **30** (5.21 g, 2.35 mmol) in a 1:2 mixture of toluene/ethanol (180 mL) is added hydrazine acetate (1.08 g, 5 molar equivalents). After 1 hour 10 minutes of magnetic stirring, the mixture is concentrated under vacuum and then purified on silica gel to give compound **31** (4.78 g, 96%).

R_f = 0.47 (1/3 acetone/diisopropyl ether).



Preparation of (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 (No. 33)

To a solution of compound **32** (32.3 g, 42.2 mmol) (WO 2006/021 653) in *N,N*-dimethylformamide (210 mL) is added, at 0°C and under argon, benzyl bromide (25 mL, 5 molar equivalents), followed by addition of 55% NaH (3 g, 1.5 molar equivalents). 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

Preparation of (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 (No. 34)

To a solution of crude **33** (38.6 g) in dichloromethane (1.6 L) is added water (80 mL), followed by addition, at 0°C, of DDQ (14.2 g, 1.5 molar equivalents). After 4 hours 45 minutes of stirring at 0°C, the medium is diluted with dichloromethane and 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), followed by addition of triethylamine (13 mL), 4-dimethylaminopyridine (2 g) and acetic anhydride (60 mL). 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 and water, and the organic phase is then dried (Na₂SO₄), filtered and concentrated.

The residue obtained is purified on silica (ethyl acetate – cyclohexane) to give **34** (26.8 g, 83%, 3 steps).

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

Preparation of (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 (No. 35)

To a solution of **34** (26.3 g, 33.9 mmol) in acetone (1.4 L) is added, at 0°C, a solution of CrO₃ (10.5 g, 3.1 molar equivalents) in aqueous 3.5 M H₂SO₄ (47 mL). After mechanical stirring for 4 hours at 0°C, the reaction medium is diluted with dichloromethane, washed with water to neutrality, 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), and potassium hydrogen carbonate (17 g, 5 molar equivalents) and methyl iodide (21 mL, 10 molar equivalents) 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 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

Preparation of (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 (No. 36)

The crude residue obtained in the preceding step is dissolved in acetic anhydride (177 mL), followed by addition of trifluoroacetic acid (TFA) (17.7 mL). 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 **36** (17.4 g, 65%, 3 steps).

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

Preparation of (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 (No. 37)

To a solution of compound **36** (7 g, 8.84 mmol) in diethyl ether (303 mL) is added, at 0°C and under argon, benzylamine (BnNH₂) (29.7 mL, 36 molar equivalents). After 1 hour of magnetic stirring at 0°C and then 6 hours at room temperature, the reaction mixture is neutralized with cold (0-4°C) 1N HCl, washed with water, dried (Na₂SO₄), filtered and concentrated, and purified on silica gel (ethyl acetate - cyclohexane) to give **37** (5.95 g, 90%).

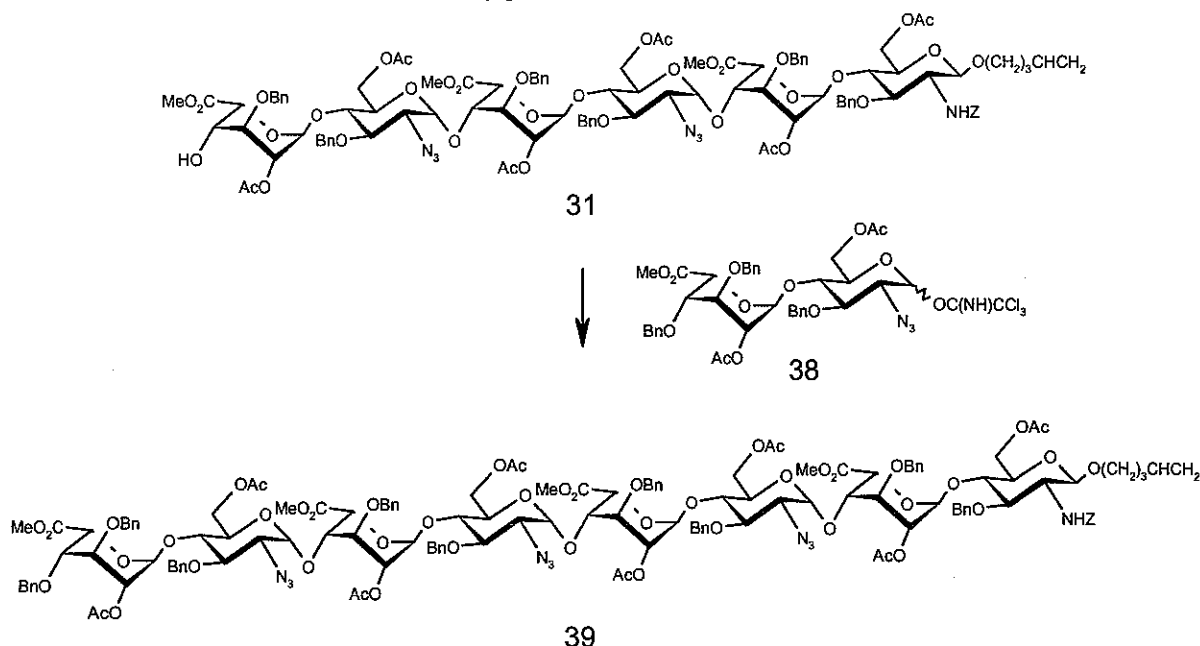
LC-MS *m/z* 767.7 [(M + NH₄)⁺]. T_R = 1.64 min

Preparation of (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 (No. 38)

To a solution of compound **37** (5.94 g, 7.9 mmol) in dichloromethane (150 mL) is added, under argon, caesium carbonate (Cs₂CO₃) (4.1 g, 1.6 molar equivalents), followed by addition of trichloroacetonitrile (CCl₃CN) (3.9 mL, 5.0 molar equivalents). 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 **38** (5.7 g, 81%).

LC-MS m/z 912.0 $[(M + NH_4)^+]$. $T_R = 1.81$ min

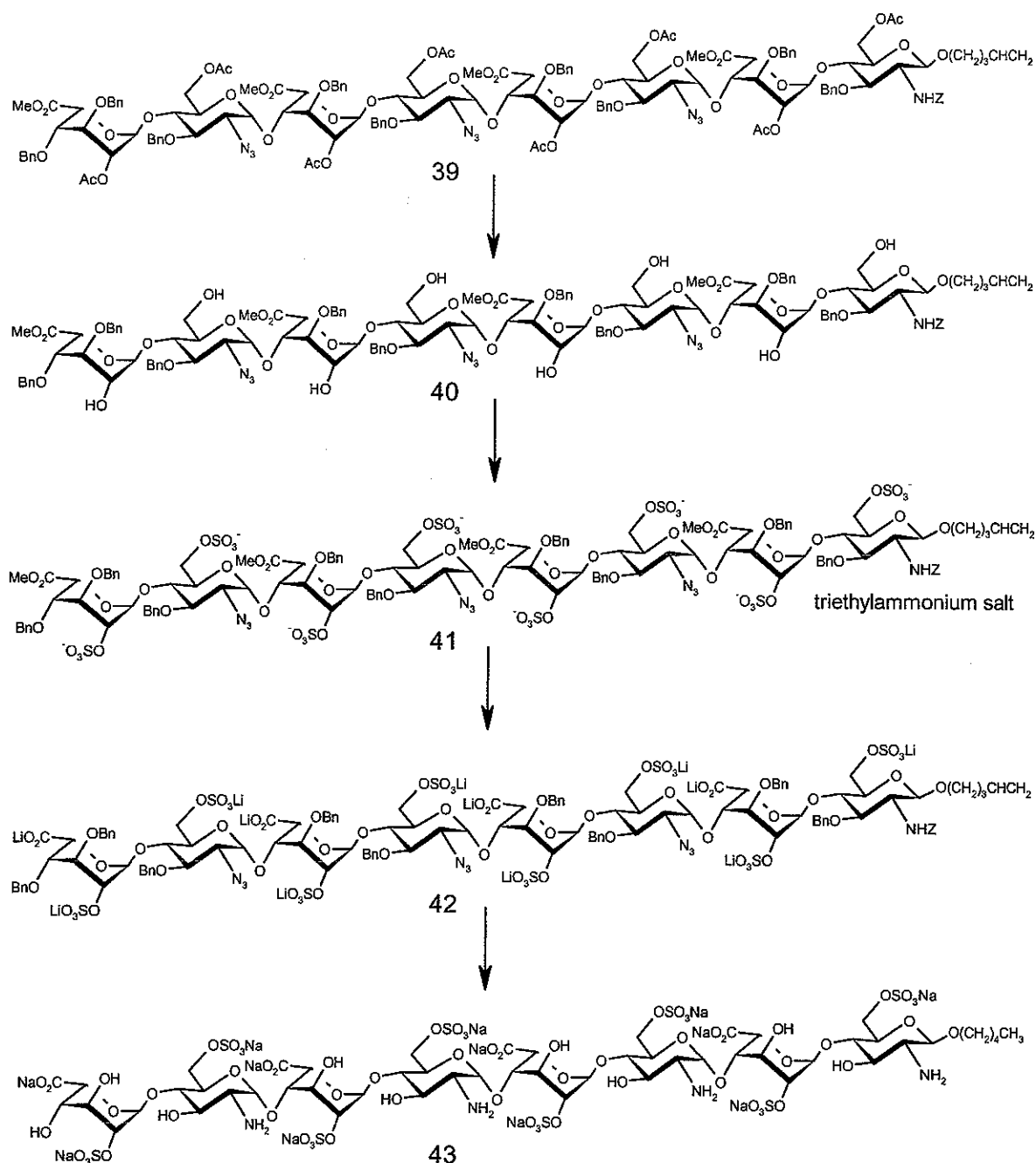


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Preparation of 4-pentenyl (methyl 2-O-acetyl-3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(6-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(6-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(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-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 39)

A solution of *tert*-butyldimethylsilyl triflate in dichloromethane (1M, 0.1 mol per mole of imide) is added, under argon and at -15°C, to a solution of the imide **38** (2.61 g, 2.92 mmol) and of the glycosyl acceptor **31** (4.78 g, 2.25 mmol) in dichloromethane (146 mL) in the presence of 4 Å molecular sieves (1.99 g). After 2 hours of magnetic stirring at -15°C (TLC), imide **38** is again added at time intervals of between 15 and 30 minutes, to maximum consumption of the acceptor **31**. At the end of the reaction (TLC), solid sodium hydrogen carbonate is added to neutralize, and after magnetic stirring at room temperature (15 minutes), filtering, washing with aqueous 2% sodium hydrogen carbonate solution, and then with water, drying (Na₂SO₄) and evaporating to dryness, the residue is purified on silica gel to give **39** (3.71 g, 58%).

Rf = 0.21 (15/85 acetone/toluene).



Preparation of 4-pentenyl (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-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonylamino]- β -D-glucopyranoside (No. 40)

To a solution of **39** (300 mg, 0.105 mmol) in a 3/2 mixture of methanol/dichloromethane (31 mL) is added, at 0°C, a 1M methanolic solution of sodium methoxide (0.31 mL), in the presence of 3 Å molecular sieves. After stirring at

0°C for 1 hour and at room temperature for 15 hours, the mixture is neutralized with H⁺ Dowex 50WX4 resin. After filtering and partially concentrating, the reaction mixture is purified on an LH-20 exclusion column using a 1:1 methanol/dichloromethane mixture as eluent, and, after pooling the fractions containing the product and concentrating under vacuum, the residue is purified on silica gel with a dichloromethane/ethyl acetate/ethanol mixture to give compound **40** (185 mg, 69%).

Rf = 0.22 (9/1/0.3 CH₂Cl₂/EtOAc/EtOH).

Preparation of 4-pentenyl (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)-(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- β -D-glucopyranoside (No. 41)

Triethylamine/sulfur trioxide complex (513 mg, 5 mol per hydroxyl function) is added to a solution in *N,N*-dimethylformamide (6.3 mL, 90 L/mol) of compound **40** (178 mg, 70.8 μ mol). After 17 hours of magnetic stirring at 55°C sheltered from light, methanol is added at 0°C and, after stirring for 30 minutes at 0°C and then for 30 minutes at room temperature, the reaction medium is purified by means of an LH-20 column, using a 9:1 mixture of methanol/*N,N*-dimethylformamide as eluent. The fractions containing the product are then concentrated under high vacuum to give the desired compound **41** (241 mg, 87%).

Rf = 0.33 (11/7/1.6/4 EtOAc/pyridine/AcOH/H₂O).

Preparation of 4-pentenyl (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)-(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- β -D-glucopyranoside (No. 42)

To a solution of compound **41** (238 mg, 60 μ mol) in a 1/1 mixture of methanol/tetrahydrofuran (9.6 mL) is added, at 0°C, a molar aqueous LiOH solution.

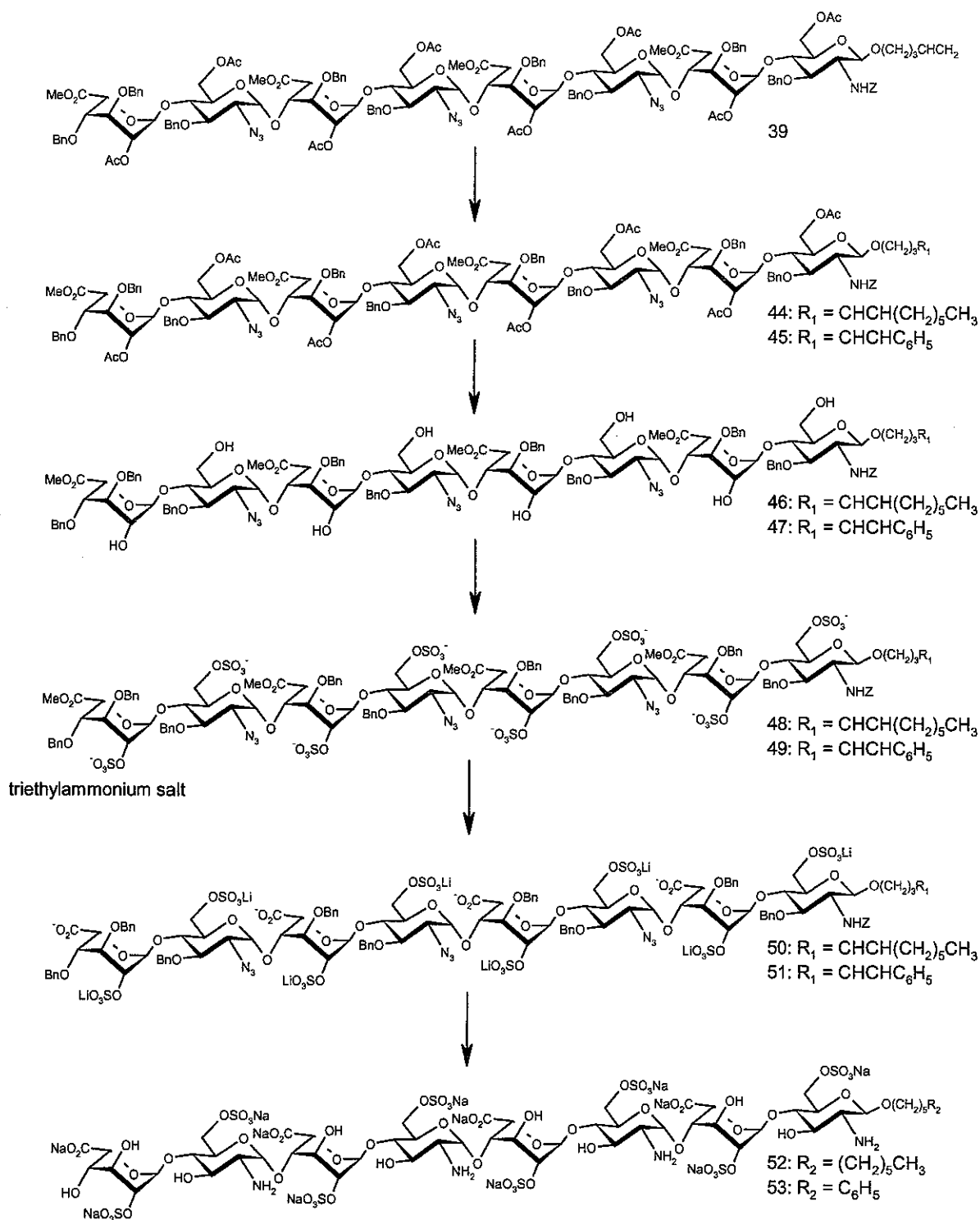
After stirring for 1 hour at 0°C and then for 16 hours at room temperature, the reaction medium is purified by means of an LH-20 column, using a 9:1 mixture of methanol/*N,N*-dimethylformamide as eluent. The fractions containing the product are then concentrated under high vacuum to give the desired compound **42**.

5 R_f = 0.42 (11/7/1.6/4 EtOAc/pyridine/AcOH/H₂O).

Preparation of pentyl (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)-(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- β -D-glucopyranoside (No. 43)

To a solution in a 1/1 mixture of *tert*-butanol/water (14 mL) of compound **42** obtained previously are successively added ammonium formate (617 mg, 9.8 mmol) and then 10% Pd/C (1.55 g). After stirring vigorously for 4 hours at room temperature, the reaction medium is filtered and partially concentrated under vacuum, and the solution is then applied to a Sephadex[®] G-25 column eluted with 0.2 M sodium chloride. The fractions containing the product are concentrated and desalified using the same column eluted with water. The fractions containing the product are then concentrated under high vacuum to give the desired compound **43** (123 mg, 61% (2 steps)).

Chemical shifts of the anomeric protons (600 MHz, D₂O) δ 5.11 IdoUA^{VIII}, 5.38 Glc^{VII}, 5.19 IdoUA^{VI}, 5.38 Glc^V, 5.19 IdoUA^{IV}, 5.38 Glc^{III}, 5.21 IdoUA^{II}, 4.70 Glc^I



- 5 Preparation of (Z/E) undec-4-enyl (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)-(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→4)-(methyl 2-O-acetyl-3-O-benzyl-α-L-idopyranosyluronate)-(1→4)-6-O-acetyl-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino-β-D-glucopyranoside (No. 44)

To a solution of compound **39** (610 mg, 214 μmol) in dichloromethane (10.7 mL) are added 1-octene (67 μL, 2 molar equivalents) and first-generation Grubbs catalyst (C₄₄H₇₄Cl₂P₂Ru) (18 mg, 0.1 molar equivalent). After refluxing for 6 hours and then stirring overnight at room temperature, the mixture is concentrated under high vacuum and may be used under the same conditions in the case of an incomplete reaction. The crude reaction product is purified by chromatography on silica gel (toluene-acetone) to give the desired product **44** (131 mg, 20%).

R_f = 0.18 (85/15 toluene/acetone).

Preparation of (Z/E) 5-phenyl-4-pentenyl (methyl 2-O-acetyl-3,4-di-O-benzyl-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)-(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)-(methyl 2-O-acetyl-3-O-benzyl-α-L-idopyranosyluronate)-(1→4)-6-O-acetyl-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino-β-D-glucopyranoside (No. 45)

To a solution of compound **39** (100 mg, 35 μmol) in dichloromethane (1 mL) are added styrene (16 μL, 4 molar equivalents) and second-generation Grubbs catalyst (C₄₆H₆₅Cl₂N₂PRu) (1.8 mg, 0.06 molar equivalent). After refluxing for 8 hours and then stirring overnight at 35°C, the reagents are optionally added, if necessary. The mixture is then concentrated under high vacuum and then purified by chromatography on silica gel (toluene-ethyl acetate) to give the desired product **45** (38 mg, 37%).

R_f = 0.25 (toluene-EtOAc 7/3).

Preparation of (Z/E) undec-4-enyl (methyl 3,4-di-O-benzyl-α-L-idopyranosyluronate)-(1→4)-(2-azido-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-(methyl 3-O-benzyl-α-L-idopyranosyluronate)-(1→4)-(2-azido-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-(methyl 3-O-benzyl-α-L-idopyranosyluronate)-(1→4)-(2-azido-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-(methyl 3-O-benzyl-α-L-idopyranosyluronate)-(1→4)-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino-β-D-glucopyranoside (No. 46)

To a solution of **44** (152 mg, 0.052 mmol) in a 3/2 mixture of methanol/dichloromethane (15 mL) is added, at 0°C, a 1M methanolic solution of sodium methoxide (154 μL), in the presence of 3 Å molecular sieves. After stirring at

0°C for 1 hour and at room temperature for 15 hours, the mixture is neutralized with H⁺ Dowex 50WX4 resin. After filtering and partially concentrating, the reaction mixture is purified on an LH-20 exclusion column using a 1/1 mixture of methanol/dichloromethane as eluent, and, after pooling the fractions containing the product and concentrating under vacuum, the residue is purified on silica gel with a toluene/acetone/ethyl acetate/ethanol mixture to give compound **46** (83 mg, 61%).

R_f = 0.25 (7/3/0.1 toluene/acetone/EtOH).

Preparation of (Z/E) 5-phenyl-4-pentenyl (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-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 47)

To a solution of **45** (229 mg, 0.078 mmol) in a 3/2 mixture of methanol/dichloromethane (23 mL) is added, at 0°C, a 1M methanolic solution of sodium methoxide (232 μ L), in the presence of 3 Å molecular sieves. After stirring at 0°C for 1 hour and at room temperature for 15 hours, the mixture is neutralized with H⁺ Dowex 50WX4 resin. After filtering and partially concentrating, the reaction mixture is purified on an LH-20 exclusion column using a 1/1 mixture of methanol/dichloromethane as eluent, and, after pooling the fractions containing the product and concentrating under vacuum, the residue is purified on silica gel with a dichloromethane/ethyl acetate/ethanol mixture to give compound **47** (141 mg, 69%).

R_f = 0.15 (7/3/0.1 toluene/acetone/EtOH).

Preparation of (Z/E) undec-4-enyl (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)-(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- β -D-glucopyranoside (No. 48)

Triethylamine/sulfur trioxide complex (225 mg, 5 mol per hydroxyl function) is added to a solution in *N,N*-dimethylformamide (2.8 mL, 90 L/mol) of compound **46**

(81 mg, 31 μ mol). After 16 hours of magnetic stirring at 50°C sheltered from light, methanol is added at 0°C (0.2 mL) and after 35 minutes of stirring at 0°C and then 2.5 hours at room temperature, the reaction medium is purified by means of an LH-20 column, using a 1/1/0.1 mixture of methanol/dichloromethane/*N,N*-dimethylformamide as eluent. The fractions containing the product are then concentrated under high vacuum to give the desired compound **48** (122 mg, 99%).

R_f = 0.36 (11/7/1.6/4 EtOAc/pyridine/AcOH/H₂O).

Preparation of (Z/E) 5-phenyl-4-pentenyl (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)-(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- β -D-glucopyranoside (No. 49)

Triethylamine/sulfur trioxide complex (385 mg, 5 mol per hydroxyl function) is added to a solution in *N,N*-dimethylformamide (4.7 mL, 90 L/mol) of compound **47** (138 mg, 53 μ mol). After 16 hours of magnetic stirring at 50°C sheltered from light, methanol is added at 0°C (0.35 mL) and after 30 minutes of stirring at 0°C and then 1 hour at room temperature, the reaction medium is purified by means of an LH-20 column, using a 1/1/0.1 mixture of methanol/dichloromethane/*N,N*-dimethylformamide as eluent. The fractions containing the product are then concentrated under high vacuum to give the desired compound **49** (194 mg, 92%).

R_f = 0.35 (11/7/1.6/4 EtOAc/pyridine/AcOH/H₂O).

Preparation of (Z/E) undec-4-enyl (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)-(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- β -D-glucopyranoside (No. 50)

To a solution of compound **48** (119 mg, 29 μ mol) in a 1/1 mixture of methanol/tetrahydrofuran (4.7 mL) is added, at 0°C, a molar aqueous LiOH solution

(1.18 mL). After stirring for 1 hour at 0°C and then for 19.5 hours at room temperature, the reaction medium is purified by means of an LH-20 column, using a 4:1 mixture of methanol/*N,N*-dimethylformamide as eluent. The fractions containing the product are then concentrated under high vacuum to give the desired compound **50**.

5 R_f = 0.40 (11/7/1.6/4 EtOAc/pyridine/AcOH/H₂O).

Preparation of (Z/E) 5-phenyl-4-pentenyl (lithium 3,4-di-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)-(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)-(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-deoxy-2-[(benzyloxy)carbonyl]amino-6-O-lithium sulfonato-β-D-glucopyranoside (No. 51)

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To a solution of compound **49** (190 mg, 47 μmol) in a 1/1 mixture of methanol/tetrahydrofuran (7.4 mL) is added, at 0°C, a molar aqueous LiOH solution (1.88 mL). After stirring for 1 hour at 0°C and then for 16 hours at room temperature, the reaction medium is purified by means of an LH-20 column, using a 9:1 mixture of methanol/*N,N*-dimethylformamide as eluent. The fractions containing the product are then concentrated under high vacuum to give the desired compound **51**.

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R_f = 0.44 (11/7/1.6/4 EtOAc/pyridine/AcOH/H₂O).

Preparation of undecyl (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-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)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-2-amino-2-deoxy-6-O-sodium sulfonato-β-D-glucopyranoside (No. 52)

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To a solution in a 1/1 mixture of *tert*-butanol/water (6 mL) of compound **50** obtained previously are successively added ammonium formate (260 mg, 4.1 mmol) and then 10% Pd/C (672 mg). After 4 hours 5 minutes of vigorous stirring at room temperature, the reaction medium is filtered and partially concentrated under vacuum, and the solution is then applied to a Sephadex[®] G-25 column eluted with 0.2 M sodium chloride. The fractions containing the product are concentrated and desalified using the same column eluted with water. The fractions containing the product are then concentrated under high vacuum to give the desired compound **52** (34 mg, 49%

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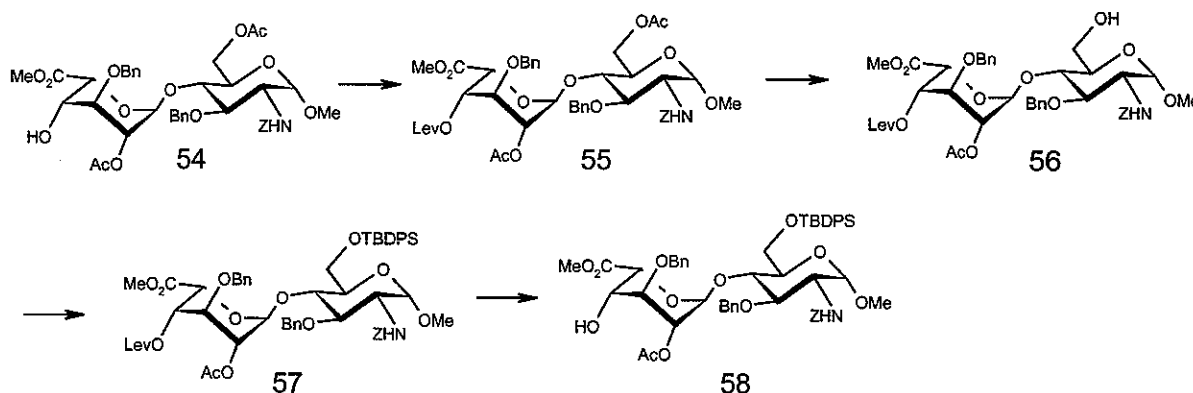
(2 steps)).

Mass: "ESI" method, negative mode: theoretical mass = 2337.81; experimental mass: 2337.27 ± 0.06 a.m.u. $[M-4Na+4H]$.

- 5 Preparation of 5-phenylpentyl (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)-(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- β -D-glucopyranoside (No. 53)

To a solution in a 1/1 mixture of *tert*-butanol/water (9.2 mL) of compound **51** obtained previously are successively added ammonium formate (407 mg, 6.47 mmol) and then 10% Pd/C (1.05 g). After 4 hours 5 minutes of vigorous stirring at room temperature, the reaction medium is filtered and partially concentrated under vacuum, and the solution is then applied to a Sephadex[®] G-25 column eluted with 0.2 M sodium chloride. The fractions containing the product are concentrated and desalified using the same column eluted with water. The fractions containing the product are then concentrated under high vacuum to give the desired compound **53** (79 mg, 72% (2 steps)).

"ESI" method, negative mode: multicharged ion detected m/z 537.0713 $[M-4H]^{4-}$ (acid form).



- 25 Preparation of methyl (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-acetyl-3-O-benzyl-2-benzyloxycarbonylamino-2-deoxy- α -D-glucopyranoside (No. 55)

To a solution of compound **54** (23.5 g, 30 mmol; *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 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 compound **55** (22.6 g).

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

10 Preparation of methyl (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-benzoyloxycarbonylamino-2-deoxy- α -D-glucopyranoside (No. 56)

To a solution of compound **55** (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 35°C. After concentrating, the residue (20.8 g) is used without purification in the following step.

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

20 Preparation of methyl (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-benzoyloxycarbonylamino-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranoside (No. 57)

To a solution of the crude compound **56** (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*-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 sodium chloride solution and then with water, dried over sodium sulfate, filtered and then evaporated. The residue is purified by flash chromatography on a column of silica gel (2/1 cyclohexane/ethyl acetate) to give compound **57** (24.4 g).

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

35 Preparation of methyl (methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-benzoyloxycarbonylamino-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-

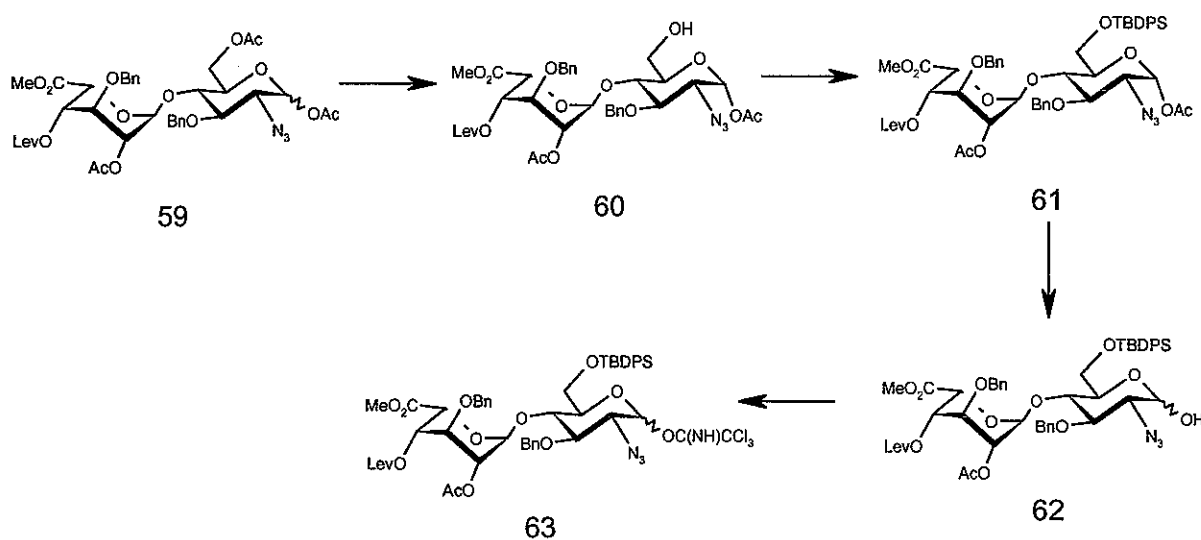
glucopyranoside (No. 58)

To a solution of compound **57** (22.6 g, 20.0 mmol) in a 1/2 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 **58**.

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

Chemical shifts of anomeric protons (500 MHz, $CDCl_3$) δ 5.19 IdoUA^{II}, 4.63 Glc^I

LC-MS m/z 978.5 $[(M + H)^+]$. T_R = 12.29 min



Preparation of (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyl-uronate)-(1 $\rightarrow$ 4)-1-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranose (No. 60)

To a solution of **59** (11 g, 13.7 mmol) (C. Tabour, et al., Carbohydr. Res., 281 (1996) 253-276) in a 1/1 mixture of methanol/tetrahydrofuran (80 mL) is added [tBu₂SnCl(OH)]₂ (0.55 g, 0.14 molar equivalent) prepared according to A. Orita et al., Chem. Eur. J. (2001) 7, 3321. After stirring at 35°C for 5.5 hours, 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 **60** (5.97 g, 57%).

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

Preparation of (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyl-uronate)-(1 $\rightarrow$ 4)-1-O-acetyl-2-azido-3-O-benzyl-6-O-tert-butylidiphenylsilyl-2-deoxy- α -D-glucopyranose (No. 61)

Compound **60** (5.97 g, 7.88 mmol) is dissolved in dichloromethane (63 mL). 4-Dimethylaminopyridine (0.481 g, 0.5 molar equivalent), triethylamine (2.7 mL, 2.5 molar

equivalents), and *tert*-butyldiphenylsilyl chloride (4 mL, 2 molar equivalents) are successively added at 0°C under argon. After magnetic stirring for 4 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 – heptane) to give **61** (7 g, 90%).

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

Preparation of (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 (No. 62)

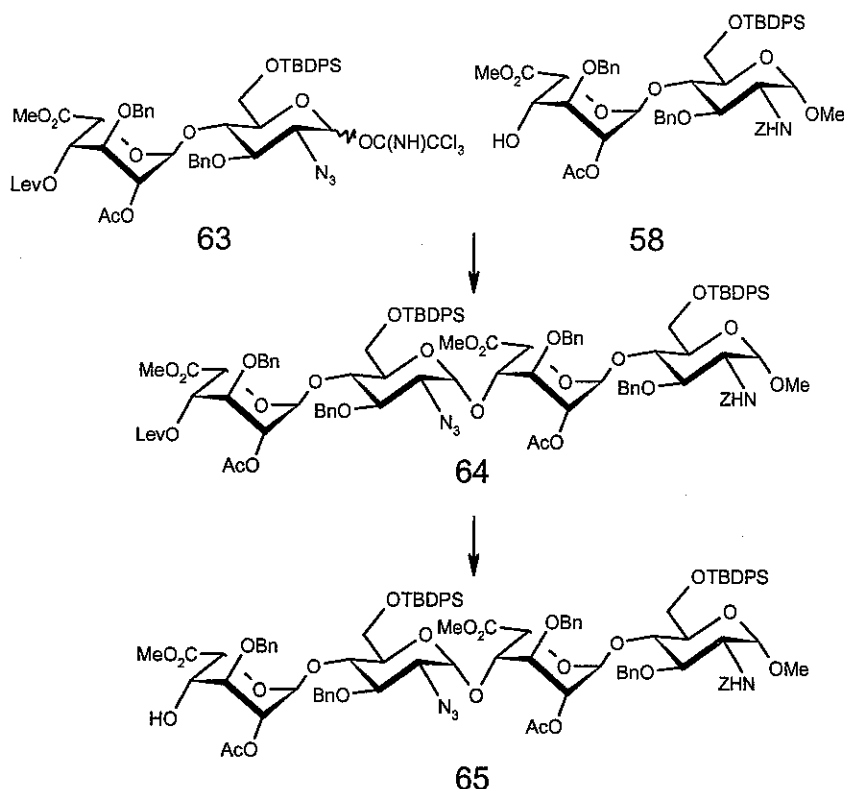
To a solution of compound **61** (7 g, 7.03 mmol) in diethyl ether (70 mL) is added, at 0°C, benzylamine (BnNH₂) (29 mL, 38 molar equivalents). After 15 minutes of stirring at 0°C and then 6 hours at room temperature, the reaction mixture is diluted with ethyl acetate, and then neutralized with cold 1N HCl (0-4°C), washed with water, dried (Na₂SO₄), filtered and concentrated, and purified on silica gel (ethyl acetate - toluene) to give **62** (5.86 g, 87%).

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

Preparation of (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 (No. 63)

To a solution of compound **62** (6.5 g, 6.81 mmol) in dichloromethane (140 mL) and in the presence of powdered 4 Å molecular sieves (7 g), is added, under argon, caesium carbonate (Cs₂CO₃) (3.5 g, 1.6 molar equivalents), followed by addition, at 0°C, of trichloroacetonitrile (CCl₃CN) (3.4 mL, 5.0 molar equivalents). After stirring for 15 minutes 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 **63** (6.33 g, 85%).

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



Preparation of 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-benzyloxycarbonylamino-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranoside (No. 64)

A mixture of the glycosyl acceptor **58** (8.80 g, 9.00 mmol), imidate **63** (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® LH-20 column (190 x 3.2 cm, 1/1 dichloromethane/ethanol) to give 8.26 g of compound **64**.

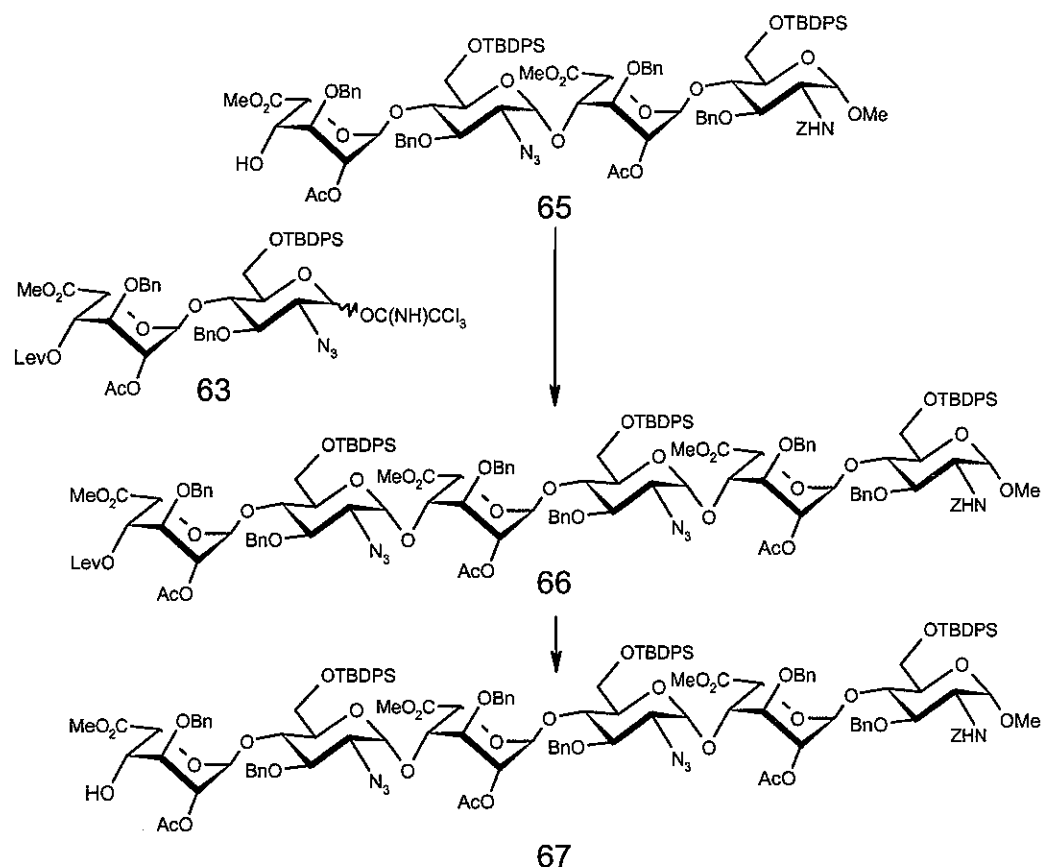
Rf = 0.30, silica gel, 2/1 cyclohexane/ethyl acetate

Preparation of 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)-3-O-benzyl-2-

benzyloxycarbonylamino-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranoside (No. 65)

Compound **64** (8.26 g, 4.31 mmol) is converted into compound **65** (6.41 g) according to the same procedure as that described for the synthesis of **58**.

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



Preparation of 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 (No. 66)

15 A mixture of the glycosyl acceptor **65** (7.42 g, 4.09 mmol), imidate **63** (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

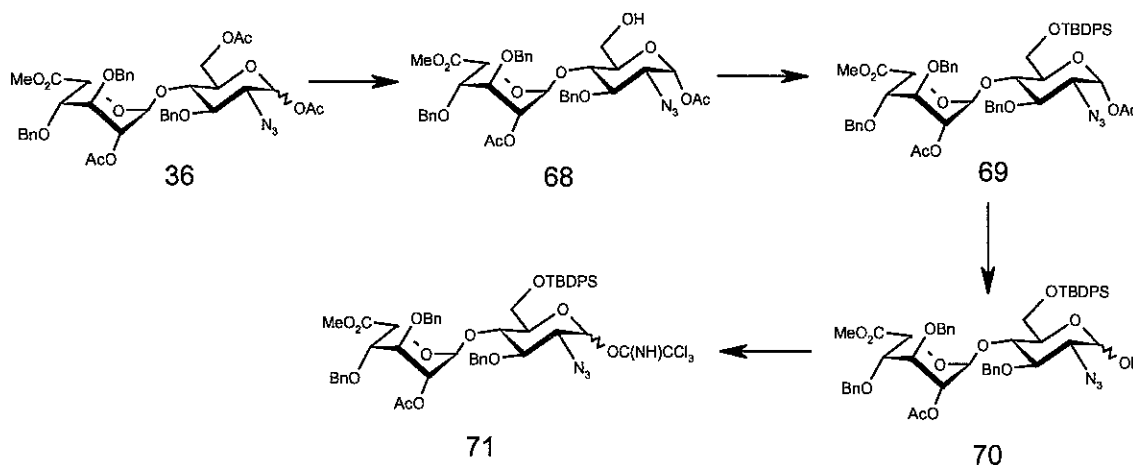
sodium hydrogen carbonate. After filtering through Celite®, the reaction medium is diluted with dichloromethane (800 mL). The organic phase is washed successively with 2% sodium hydrogen carbonate solution, with water and then dried over sodium sulfate, filtered and evaporated to dryness. The residue obtained is purified by chromatography on a Sephadex® LH-20 column (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 **66**.

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

- 10 Preparation of 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-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-benzoyloxycarbonyl-amino-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranoside (No. 67)

Compound **66** (7.14 g, 2.59 mmol) is converted into compound **67** (6.07 g) according to the same procedure as that described for the preparation of compound **58**.

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



- 20 Preparation of (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 (No. 68)

To a solution of **36** (5.05 g, 6.3 mmol) in a 1/1 mixture of methanol/tetrahydrofuran (76 mL) is added [tBu₂SnCl(OH)]₂ (0.25 g, 0.14 molar equivalent) 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 **68** (2.89 g, 64%).

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

Preparation of (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 (No. 69)

Compound **68** (2.89 g, 3.86 mmol) is dissolved in dichloromethane (31 mL).
5 Triethylamine (1.3 mL, 2.5 molar equivalents), 4-dimethylaminopyridine (0.235 g, 0.5 molar equivalent), and *tert*-butyldiphenylsilyl chloride (2 mL, 2 molar equivalents) are successively added at 0°C under argon. 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
10 residue obtained is purified on silica (ethyl acetate/cyclohexane) to give **69** (3.4 g, 90%).

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

Preparation of (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 (No.

15 **70)**

To a solution of compound **69** (3.44 g, 3.48 mmol) in diethyl ether (35 mL) is added, at 0°C, benzylamine (BnNH₂) (14.5 mL, 38 molar equivalents). 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
20 acetate, and then neutralized with cold 1N HCl (0-4°C), washed with water, dried (Na₂SO₄), filtered and concentrated, and purified on silica gel (ethyl acetate/cyclohexane 15/85) to give **70** (3.83 g, 91%).

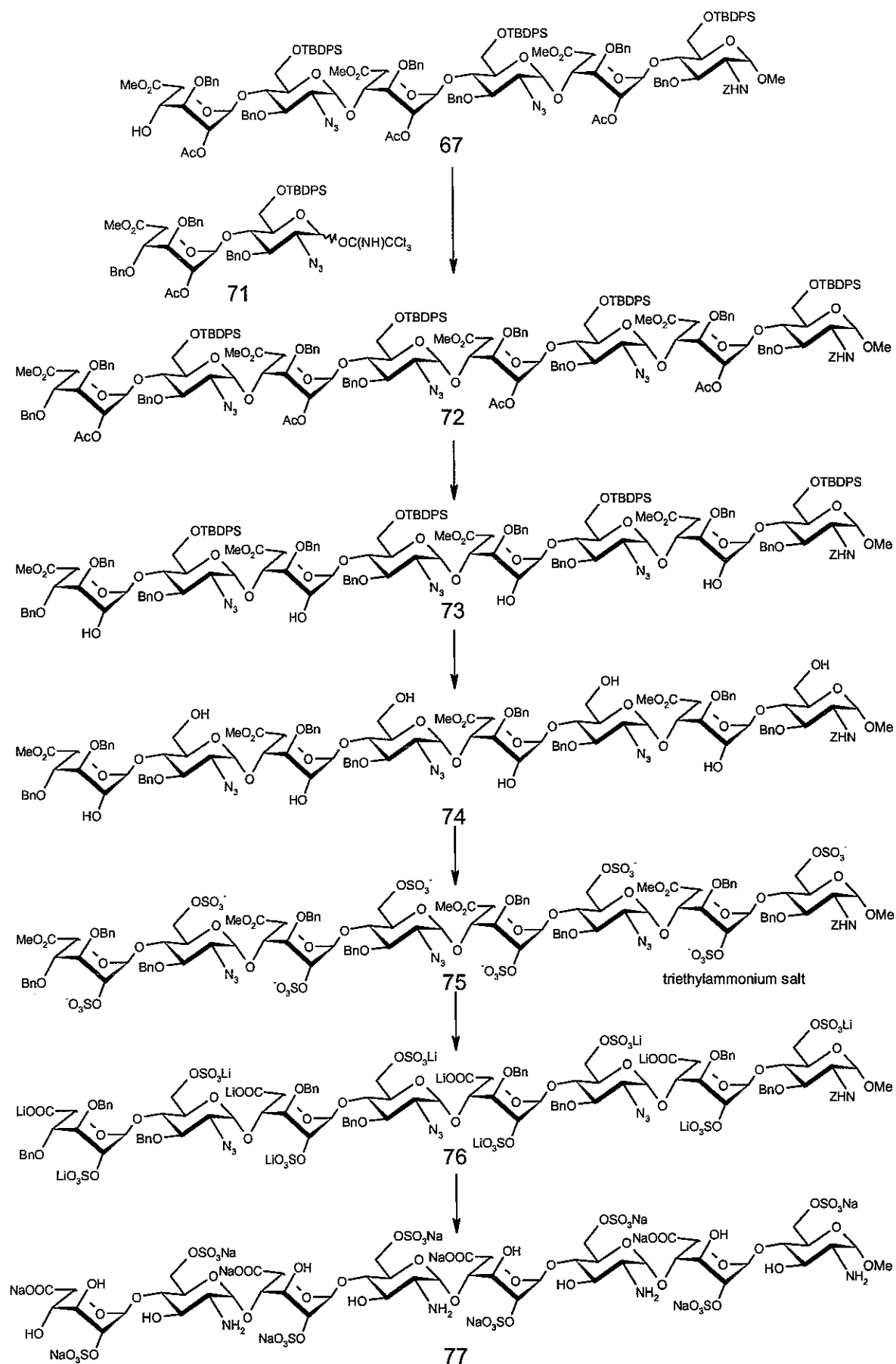
LC-MS *m/z* 963.6 [(M + NH₄)⁺]. T_R = 12.37, 12.47 min

Preparation of (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 trichloroacetimidate (No. 71)

To a solution of compound **70** (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
30 argon, caesium carbonate (Cs₂CO₃) (1.6 g, 1.6 molar equivalents) and then trichloroacetonitrile (CCl₃CN) (1.6 mL, 5.0 molar equivalents). After 20 minutes of stirring at 0°C, and 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
35 and then concentrated. The residue is purified on silica gel (15/85 ethyl acetate/cyclohexane + 0.1% triethylamine) to give **71** (2.69 g, 78%).

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

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Preparation of 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-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-benzyl-oxy-carbonylamino-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranoside (No. 72)

A mixture of the glycosyl acceptor **67** (3.50 g, 1.32 mmol), imidate **71** (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 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 Sephadex® LH-20 column (190 x 3.2 cm, 1/1 dichloromethane/ethanol), followed by chromatography on a column of silica gel (cyclohexane/ethyl acetate 4/1) to give 3.04 g of compound **72**.

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

Preparation of 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-benzyl-oxy-carbonylamino-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranoside (No. 73)

To a solution of compound **72** (2.23 g, 0.623 mmol) in a 2/3 dichloromethane/methanol mixture (187 mL) containing 3 Å 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 Sephadex® LH-20 column (120 x 3 cm, 1/1 dichloromethane/ethanol), followed by flash chromatography on a column of silica gel (1/0 $\rightarrow$ 66/34 cyclohexane/ethyl acetate) to give 1.80 g of compound **73**.

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

Preparation of 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-benzoyloxycarbonyl-amino-2-deoxy- α -D-glucopyranoside (No. 74)

To a solution of compound **73** (44.0 mg, 0.013 mmol) in methanol (1.7 mL) is added ammonium fluoride (38.0 mg, 1.03 mmol). After 140 hours of stirring at room temperature, the reaction mixture is applied to a Sephadex[®] LH-20 column (95 x 2 cm, 1/1 dichloromethane/ethanol), followed by flash chromatography on a column of silica gel (3/2 toluene/acetone) to give compound **74** (24.2 mg).

R_f = 0.46, silica gel, 3/2 toluene/acetone

Preparation of 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-O-triethylammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-benzoyloxycarbonyl-amino-2-deoxy-6-O-triethylammonium sulfonato- α -D-glucopyranoside (No. 75)

Compound **74** (24.2 mg, 9.96 μ mol) is dried by codistillation of *N,N*-dimethylformamide (3 x 1.0 mL) and is then dissolved in *N,N*-dimethylformamide (1.0 mL). To this solution is added triethylamine-sulfur trioxide complex (72.2 mg, 0.4 mmol). The mixture is stirred for 16 hours at 55°C sheltered from light and the excess reagent is then destroyed with methanol (16.2 μ L). The reaction medium is applied to a Sephadex[®] LH-20 column (120 x 3 cm) eluted with a 1/1 mixture of dichloromethane/ethanol to give compound **75** (29.0 mg).

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

Preparation of 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→4)-3-O-benzyl-2-benzyloxycarbonylamino-2-deoxy-6-O-lithium sulfonato-α-D-glucopyranoside (No. 76)

To a solution of compound **75** (78.5 mg, 30.1 μmol) in a 1/1 tetrahydrofuran/methanol mixture (3.2 mL) is added, at 0°C, a 0.7 M solution of lithium hydroxide in water (440 μL). After 1 hour at 0°C and then 16 hours at room temperature, the solution is applied to a Sephadex[®] LH-20 column (3 x 120 cm) eluted with a 50/50/1 dichloromethane/ethanol/water mixture to give compound **76** (60.3 mg).

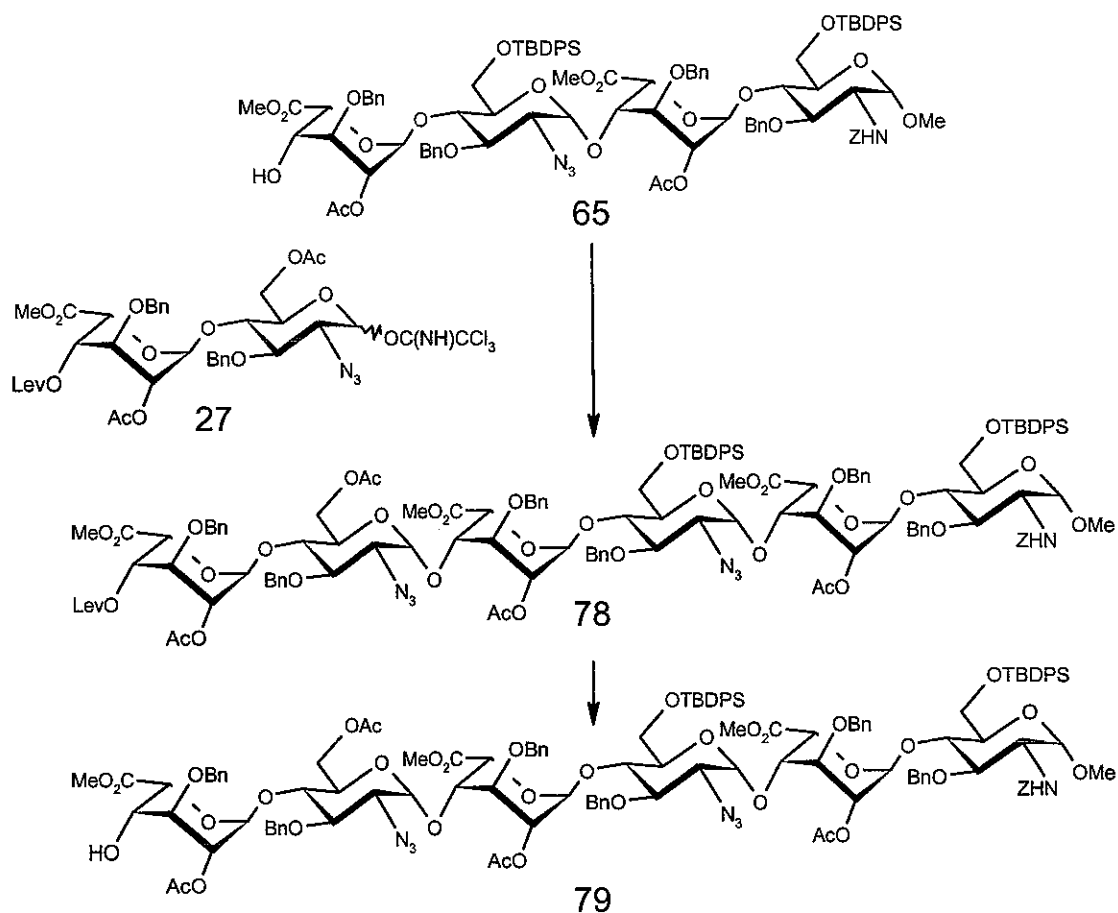
$[\alpha]_D^{25}$ 13.1° (c 1.0; MeOH)

10 Preparation of methyl (sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-amino-2-deoxy-6-O-sodium sulfonato-α-D-glucopyranosyl)-[1-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-amino-2-deoxy-6-O-sodium sulfonato-α-D-glucopyranosyl)]₂-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-2-amino-2-deoxy-6-O-sodium sulfonato-α-D-glucopyranoside (No. 77)

15 To a solution of compound **76** (19.3 mg, 6.16 μmol) in a 1/1 *tert*-butanol/water mixture (1.2 mL) are successively added ammonium formate (50.8 mg) and Pd/C 10% (125 mg). After 4 hours at room temperature, the reaction mixture is filtered (Millipore[®] LSWP 5 μm filter) and then applied to a column of fine Sephadex[®] G-25 gel (95 x 2 cm) eluted with aqueous 0.2 M NaCl solution. The fractions containing the expected product
20 are pooled and applied to a column of fine Sephadex[®] G-25 (95 x 2 cm) eluted with water, to give 11.2 mg of compound **77**.

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

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- Preparation of 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)-(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-benzyloxy-carbonylamino-6-O-*tert*-butyldiphenylsilyl-2-deoxy-α-D-glucopyranoside (No. 78)
- 5 A mixture of the glycosyl acceptor **65** (1.82 g, 1.00 mmol), imidate **27** (1.35 g, 1.50 mmol) and powdered 4 Å molecular sieves (1.12 g) in dichloromethane (52 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 (224 μL) is then added. After 50 minutes, the reaction medium is neutralized by addition of solid sodium hydrogen carbonate. After filtering through Celite®, the reaction medium is diluted with dichloromethane (500 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
- 10
- 15

chromatographed on a column (Sephadex[®] LH-20, 190 x 3.2 cm, 1/1 dichloromethane/ethanol), followed by flash chromatography on a column of silica gel (1/0→3/1 toluene/acetone) to give 1.57 g of compound **78**.

R_f = 0.47, silica gel, 3/1 toluene/acetone

5

Preparation of 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)-(methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1→4)-(2-azido-3-O-benzyl-6-O-*tert*-butyl-diphenylsilyl-2-deoxy- α -D-glucopyranosyl)-(1→4)-(methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1→4)-3-O-benzyl-2-benzyloxycarbonylamino-6-O-*tert*-butyl-diphenylsilyl-2-deoxy- α -D-glucopyranoside (No. 79)

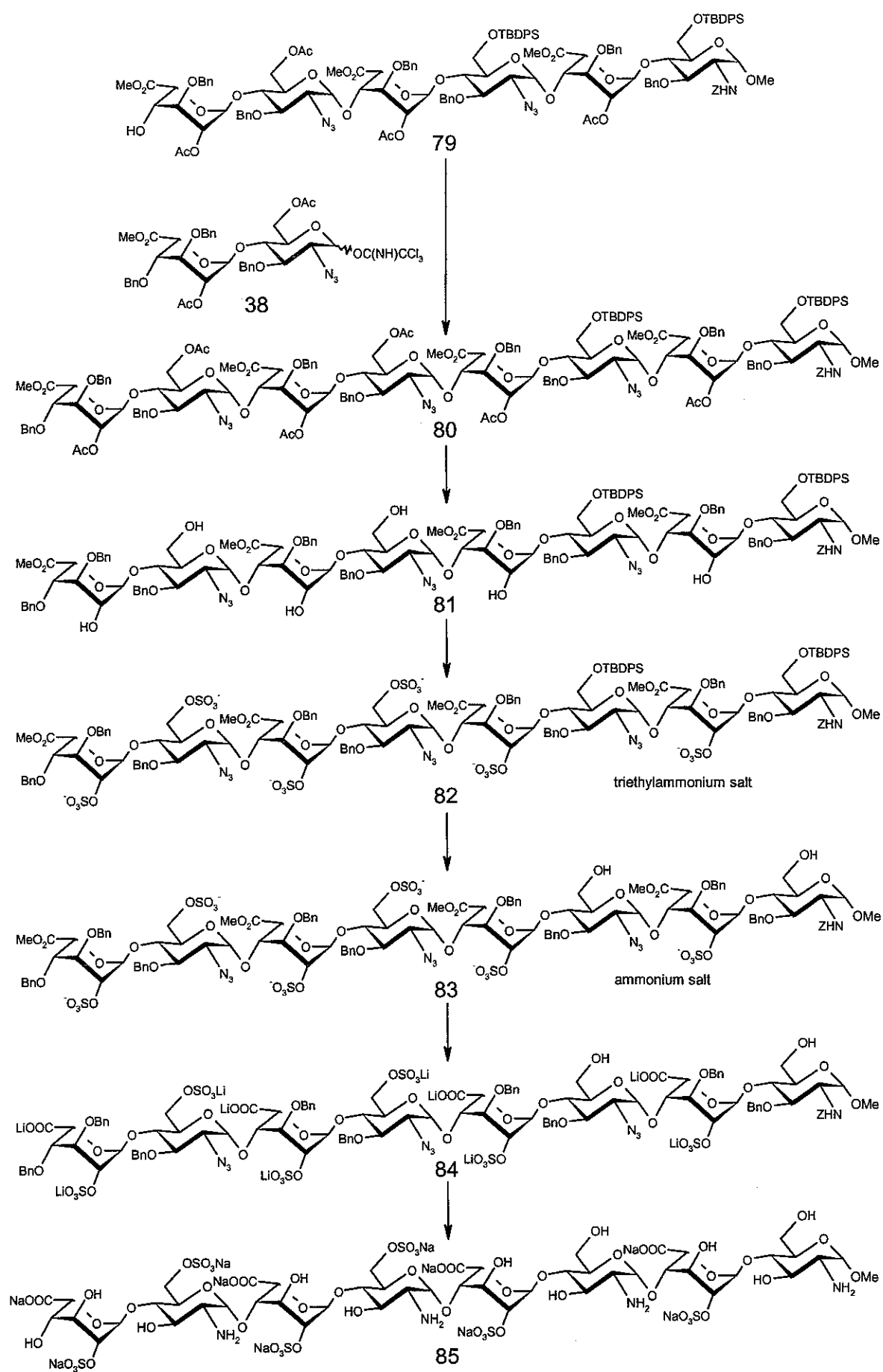
10

Compound **78** (1.56 g, 0.61 mmol) is converted into compound **79** (1.44 g) according to the same procedure as that described for the preparation of compound **58**.

R_f = 0.52, silica gel, 1/1 toluene/acetone

15

45



Preparation of 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)-(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-benzoyloxycarbonylamino-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranoside (No. 80)

A mixture of the glycosyl acceptor **79** (1.0 g, 0.41 mmol), imidate **38** (543 mg, 0.61 mmol) and powdered 4 Å molecular sieves (455 mg) in dichloromethane (21 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 (91.0 μ L) is added. After 1 hour 10 minutes, the reaction medium is neutralized by addition of solid sodium hydrogen carbonate. After filtering through Celite®, the reaction medium is diluted with dichloromethane (250 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 Sephadex® LH-20 column (190 x 3.2 cm, 1/1 dichloromethane/ethanol), followed by flash chromatography on a column of silica gel (1/0 $\rightarrow$ 0/1 toluene/ethyl acetate) to give compound **80** (822.4 mg).

R_f = 0.44, silica gel, 3/1 toluene/ethyl acetate

Preparation of 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-benzoyloxycarbonylamino-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranoside (No. 81)

Compound **80** (820 mg, 0.257 mmol) is saponified according to the method used for the preparation of compound **73**, to give the octasaccharide **81** (593.8 mg) after flash chromatography on a column of silica gel (1/0 $\rightarrow$ 0/1 toluene/acetone).

R_f = 0.57, silica gel, 2/1 toluene/acetone

Preparation of 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-triethyl-
 5 ammonium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl-2-O-triethyl-
 ammonium 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-triethyl-
 ammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-benzyloxycarbonyl-
 amino-6-O-*tert*-butyldiphenylsilyl-2-deoxy- α -D-glucopyranoside (No. 82)

10 Compound **81** (130 mg, 44.3 μ mol) is converted into compound **82** (164.1 mg) according to the same procedure as that described for the preparation of compound **75**.

Mass: "ESI" method, negative mode: theoretical mass = 4024.90; experimental mass: 4024

15 Preparation of 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)-(6-O-ammonium sulfonato- α -2-azido-3-O-benzyl-2-deoxy-
 20 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)-3-O-benzyl-2-benzyloxycarbonylamino-2-deoxy- α -D-glucopyranoside (No. 83)

To a solution of compound **82** (91.8 mg, 22.8 μ mol) in methanol (3.0 mL) is added ammonium fluoride (67.6 mg, 1.82 mmol). After 48 hours of stirring at 55°C, the
 25 reaction mixture is applied to a Sephadex[®] LH-20 column (120 x 3 cm, 1/1 dichloromethane/ethanol), followed by flash chromatography on a column of silica gel (95/5 methanol/water) to give compound **83** (62.7 mg).

R_f = 0.32, silica gel, 17/9/2.2/5 ethyl acetate/pyridine/acetic acid/water.

30 Preparation of 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)-(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-benzyloxycarbonylamino-2-deoxy- α -D-glucopyranoside (No. 84)

To a solution of compound **83** (86 mg, 24.2 μ mol) in a 1/1
5 tetrahydrofuran/methanol mixture (3.9 mL) is added, at 0°C, a 1 M solution of lithium hydroxide in water (780 μ L). After 1 hour at 0°C and then 16 hours at room temperature, the solution is applied to a column of Sephadex® LH-20 gel (95 x 2 cm) eluted with a 95/5 methanol/water mixture to give compound **84** (65.3 mg).

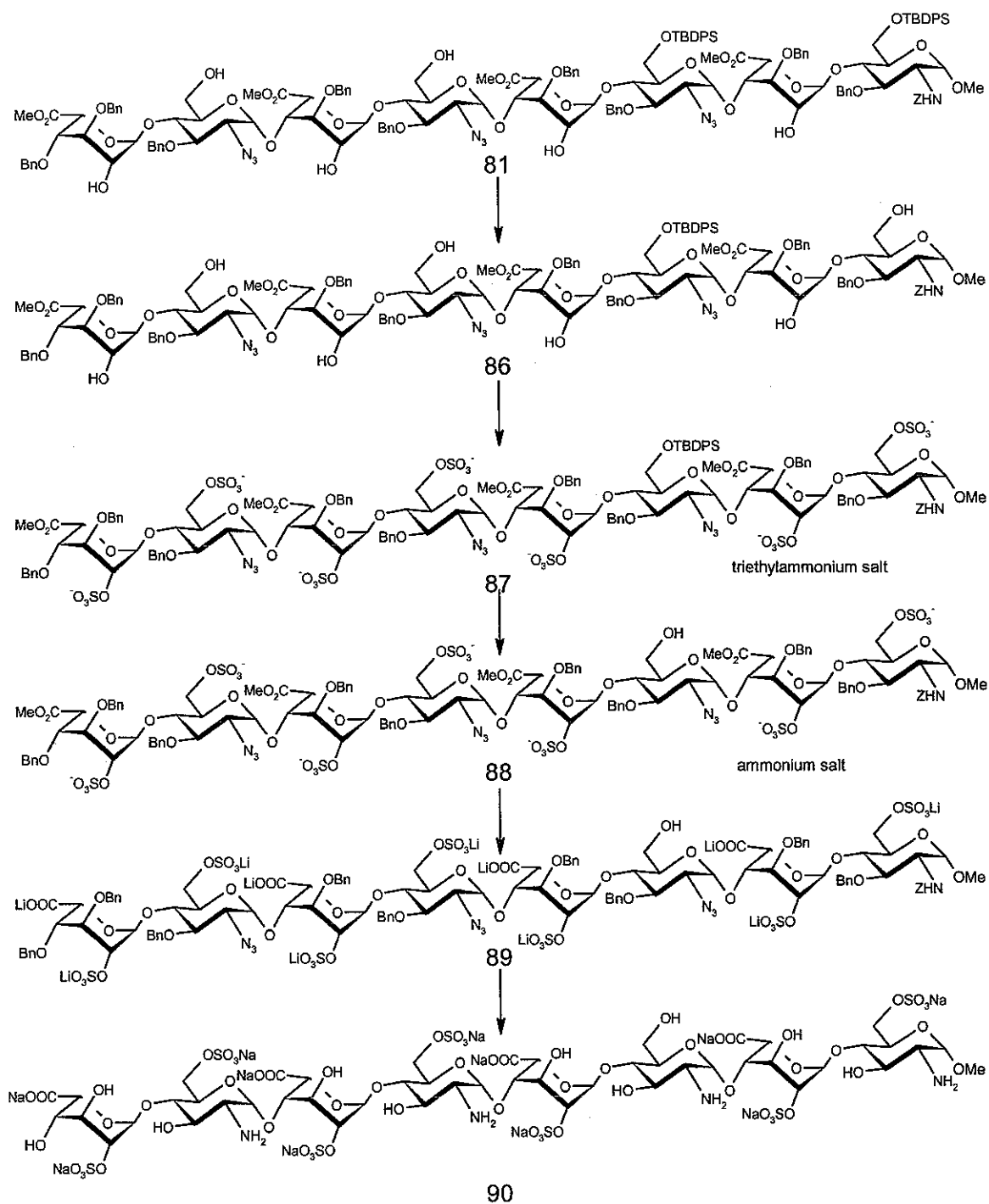
R_f = 0.27, silica gel, 17/9/2.2/5 ethyl acetate/pyridine/acetic acid/water.

10

Preparation of 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)-(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-glucopyranoside (No. 85)

Compound **84** (95.0 mg, 32.3 μ mol) is treated according to the same procedure
20 as that described for the preparation of compound **77**, to give compound **85** (47.3 mg).

Mass: "ESI" method, negative mode: theoretical mass = 2081.38; experimental mass: 1993.15 $\pm$ 0.11 a.m.u. (iduronic acids observed in COOH form).



- Preparation of 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-
 5 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-benzoyloxycarbonylamino-2-deoxy- α -D-gluco-
 pyranoside (No. 86)

To a solution of compound **81** (50 mg, 0.017 mmol) in methanol (2.2 mL) is added ammonium fluoride (25 mg, 0.68 mmol). After 7 hours of stirring at room temperature and then 16 hours at 20°C, the reaction mixture is diluted with dichloromethane. The organic phase is washed 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 (100/0→82/18 toluene/methanol) to give 27.7 mg of compound **86**.

R_f = 0.16, silica gel, 85/15 toluene/methanol

10 Preparation of methyl (methyl 3,4-di-O-benzyl-2-O-triethylammonium sulfonato-
α-L-idopyranosyluronate)-(1→4)-(2-azido-3-O-benzyl-2-deoxy-6-O-triethylammonium
sulfonato-α-D-glucopyranosyl)-(1→4)-(methyl 3-O-benzyl-2-O-triethylammonium
sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-azido-3-O-benzyl-2-deoxy-6-O-triethyl-
ammonium sulfonato-α-D-glucopyranosyl)-(1→4)-(methyl 3-O-benzyl-2-O-triethyl-
15 ammonium sulfonato-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-2-O-triethyl-
ammonium sulfonato-α-L-idopyranosyluronate)-(1→4)-3-O-benzyl-2-benzoyloxycarbonyl-
amino-2-deoxy-6-O-triethylammonium sulfonato-α-D-glucopyranoside (No. 87)

Compound **86** (94 mg, 34.8 μmol) is treated according to the same procedure as that described for the preparation of compound **75**, to give compound **87** (131.9 mg).

R_f = 0.37, silica gel, 17/9/2.2/5 ethyl acetate/pyridine/acetic acid/water.

25 Preparation of methyl (methyl 2-O-ammonium sulfonato-3,4-di-O-benzyl-α-L-
idopyranosyluronate)-(1→4)-(6-O-ammonium sulfonato-2-azido-3-O-benzyl-2-deoxy-α-
D-glucopyranosyl)-(1→4)-(methyl 2-O-ammonium sulfonato-3-O-benzyl-α-L-
idopyranosyluronate)-(1→4)-(2-azido-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-
(methyl 2-O-ammonium sulfonato-3-O-benzyl-α-L-idopyranosyluronate)-(1→4)-(2-azido-
3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-(methyl 3-O-benzyl-α-L-idopyranosyl-
uronate)-(1→4)-6-O-ammonium sulfonato-3-O-benzyl-2-benzoyloxycarbonylamino-2-
30 deoxy-α-D-glucopyranoside (No. 88)

Compound **87** (130 mg, 32.8 μmol) is treated according to the same procedure as that described for the preparation of compound **74**, to give compound **88** (102.0 mg).

R_f = 0.33, silica gel, 17/9/2.2/5 ethyl acetate/pyridine/acetic acid/water.

35 Preparation of methyl (lithium 3,4-di-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)-(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)-(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)-3-O-benzyl-2-benzoyloxycarbonylamino-2-deoxy-6-O-lithium sulfonato-α-D-glucopyranoside (**No. 89**)

Compound **88** (100 mg, 26.8 μmol) is treated according to the same procedure as that described for the preparation of compound **76**, to give crude compound **89**, which is used without further purification in the following step.

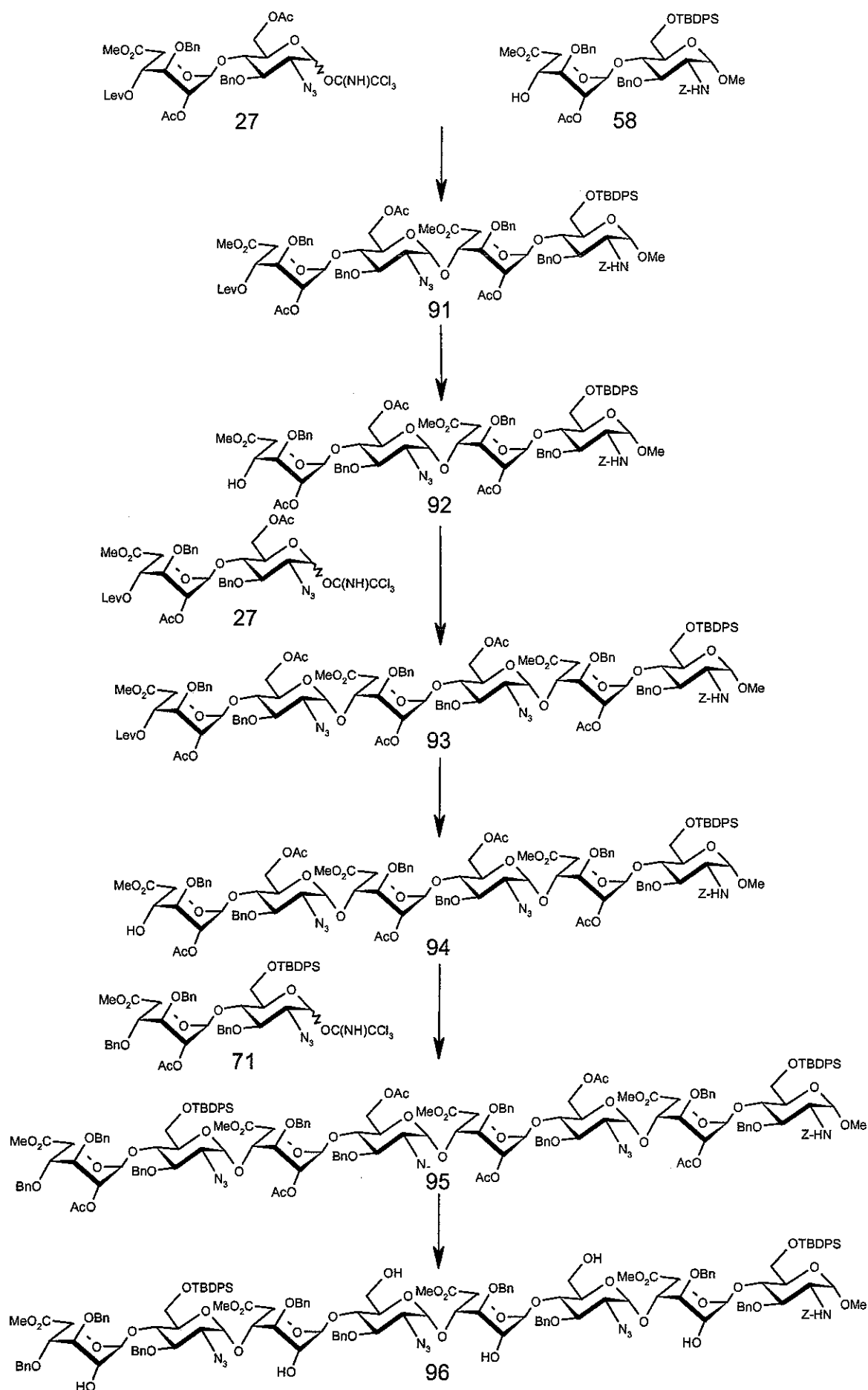
R_f = 0.25, silica gel, 17/9/2.2/5 ethyl acetate/pyridine/acetic acid/water.

Preparation of 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-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-glucopyranoside (**No. 90**)

Crude compound **89** (75 mg, 24.8 μmol) is treated according to the same procedure as that described for the preparation of compound **77** to give compound **90** (48.2 mg).

Mass: "ESI" method, negative mode: theoretical mass = 2183.42; experimental mass: 2095.07 ± 0.24 a.m.u. (iduronic acids observed in COOH form)

52



Preparation of 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)-(methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- α -D-glucopyranoside (No. 91)

A solution of *tert*-butyldimethylsilyl triflate in dichloromethane (1M, 0.15 mol per mole of imidate) is added, under argon and at -20°C, to a solution of the imidate **27** (3.26 g, 3.62 mmol) and of the glycosyl acceptor **58** (3.22 g, 3.29 mmol) in dichloromethane (115 mL) in the presence of 4 Å molecular sieves (2.5 g). After 1 hour 40 minutes at -20°C (TLC), solid sodium hydrogen carbonate is added. After filtering, washing with aqueous 2% sodium hydrogen carbonate solution, with aqueous sodium chloride solution, followed by drying (Na₂SO₄) and evaporating to dryness, the residue is purified on silica gel (toluene-acetone) to give **91** (4.66 g, 83%).

R_f = 0.49 (7/3 toluene/acetone).

Preparation of 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)-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- α -D-glucopyranoside (No. 92)

To a solution of compound **91** (4.66 g, 2.71 mmol) in a 1/2 mixture of toluene/ethanol (542 mL) is added hydrazine acetate (1.2 g, 5 molar equivalents). After magnetic stirring for 2 hours, the same amount of reagent is added and after 2 hours, the mixture is concentrated under vacuum and then purified on silica gel (toluene-acetone) to give compound **92** (3.83 g, 87%).

R_f = 0.42 (3/1 toluene-acetone).

Preparation of 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)-(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)-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- α -D-glucopyranoside (No. 93)

A solution of *tert*-butyldimethylsilyl triflate in dichloromethane (1M, 0.15 mol per mole of imidate) is added, under argon and at -20°C, to a solution of the imidate **27** (3.2 g, 3.55 mmol) and of the glycosyl acceptor **92** (3.83 g, 2.36 mmol) in dichloromethane (106 mL) in the presence of 4 Å molecular sieves (1.8 g). After 2.5 hours at -20°C (TLC), solid sodium hydrogen carbonate is added. After filtering, washing with aqueous 2% sodium hydrogen carbonate solution, with aqueous sodium

chloride solution, drying (Na₂SO₄) and evaporating to dryness, the residue is purified on silica gel (ethyl acetate/toluene) to give **93** (3.36 g, 61%).

R_f = 0.47 (1/1 toluene/ethyl acetate).

5 Preparation of 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)-(methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]-
 10 amino- α -D-glucopyranoside (No. 94)

To a solution of compound **93** (3.36 g, 1.42 mmol) in a 1/2 mixture of toluene/ethanol (280 mL) is added hydrazine hydrate (0.645 g, 4.93 molar equivalents). After 2.5 hours of magnetic stirring, the mixture is concentrated under vacuum and then purified on silica gel to give compound **94** (3.01 g, 96%).

15 R_f = 0.43 (4/1 toluene/acetone).

Preparation of 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)-(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)-(methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- α -D-glucopyranoside (No. 95)

25 A 0.1 M solution of *tert*-butyldimethylsilyl triflate in dichloromethane (1 mL) is added, under argon and at -20°C, to a solution of the imidate **71** (0.29 g, 0.3 mmol) and of the glycosyl acceptor **94** (3.01 g, 1.33 mmol) in dichloromethane (60 mL) in the presence of 4 Å molecular sieves (0.93 g). After magnetic stirring for 10 minutes at -20°C (TLC), imidate **71** is again added at time intervals of between 10 minutes and
 30 2.5 hours, up to a total amount of 3.19 g. After 20 hours at -20°C (TLC), solid sodium hydrogen carbonate is added to neutralize, and after filtering, washing with aqueous 2% sodium hydrogen carbonate solution, with aqueous sodium chloride solution, drying (Na₂SO₄) and evaporating to dryness, the residue is purified on silica gel to give **95** (2.58 g, 61%).

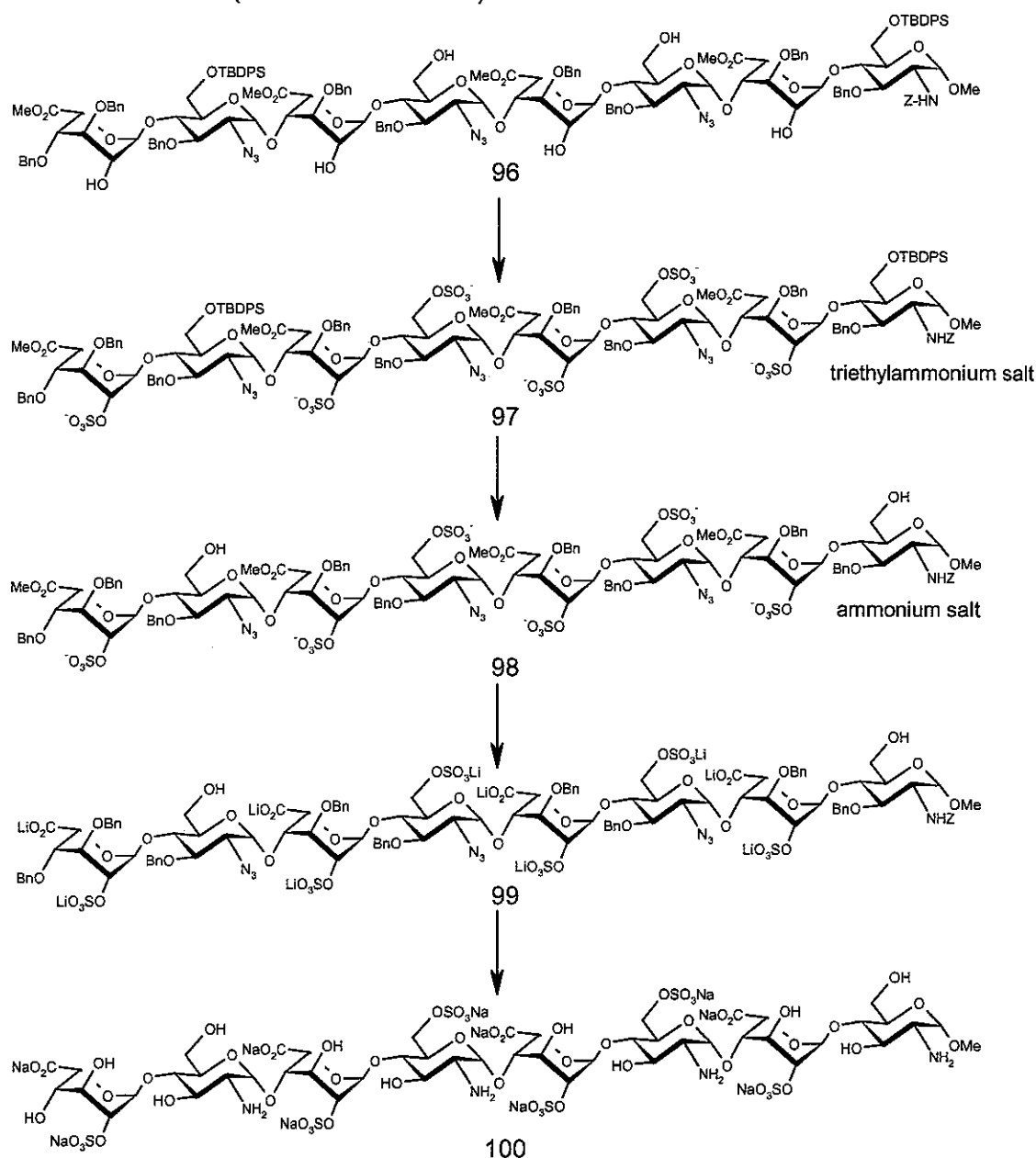
35 R_f = 0.45 (4/1 toluene/acetone).

Preparation of 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-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]-amino- α -D-glucopyranoside (No. 96)

- 5 To a solution of **95** (1.18 g, 0.37 mmol) in a 3/2 mixture of methanol/dichloromethane (111 mL) is added a 1M methanolic solution of sodium methoxide (1.1 mL), in the presence of 3 Å molecular sieves (463 mg). After stirring for 20 hours at room temperature, the mixture is neutralized with H⁺ Dowex 50WX4 resin.
- 10 After filtering and concentrating, the residue is purified on silica gel with a toluene/acetone mixture to give compound **96** (773 mg, 77%).

R_f = 0.51 (4/1 toluene/acetone).



Preparation of 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)-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- α -D-glucopyranoside (No. 97)

Triethylamine/sulfur trioxide complex (761 mg, 5 mol per hydroxyl function) is added to a solution in *N,N*-dimethylformamide (11 mL, 90 L/mol) of compound **96** (324 mg, 120 μ mol). After 17 hours of magnetic stirring at 55°C sheltered from light, methanol is added at 0°C and, after stirring for 30 minutes at 0°C and then for 30 minutes at room temperature, the reaction medium is diluted with methanol and then purified by means of an LH-20 column, using a 1/1 mixture of methanol/dichloromethane as eluent. The fractions containing the product are then concentrated under high vacuum and, if necessary, reacted again under the same conditions. Compound **97** obtained is then used directly in the following step.

R_f = 0.5 (11/7/1.6/4 EtOAc/pyridine/AcOH/H₂O).

20

Preparation of 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)-(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)-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- α -D-glucopyranoside (No. 98)

To a solution of compound **97** obtained previously in methanol (16 mL) is added ammonium fluoride (361 mg, 80 molar equivalents). After magnetic stirring at 55°C for 48 hours, the reaction mixture is purified with the aid of an LH-20 column, using a 75/20/5 mixture of methanol/*N,N*-dimethylformamide/water as eluent. The fractions containing the product are then concentrated under high vacuum to give compound **98** (410 mg, 95%, 2 steps).

R_f = 0.28 (57/29/7.2/16 EtOAc/pyridine/AcOH/H₂O).

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Preparation of 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)-(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- α -D-glucopyranoside (No. 99)

To a solution of compound **98** (202 mg, 57 μ mol) in a 1/1 mixture of methanol/tetrahydrofuran (9 mL) is added, dropwise and at 0°C, aqueous 1N LiOH solution (1.8 mL, 7.9 equivalents/methyl ester function). After stirring for 1 hour at 0°C, and then for 16 hours at room temperature, the reaction medium is purified by means of an LH-20 column, using a 75/20/5 mixture of methanol/*N,N*-dimethylformamide/water as eluent. The fractions containing the product are then concentrated under high vacuum to give the desired compound **99**, which is used directly in the following step.

R_f = 0.41 (57/29/7.2/16 EtOAc/pyridine/AcOH/H₂O)

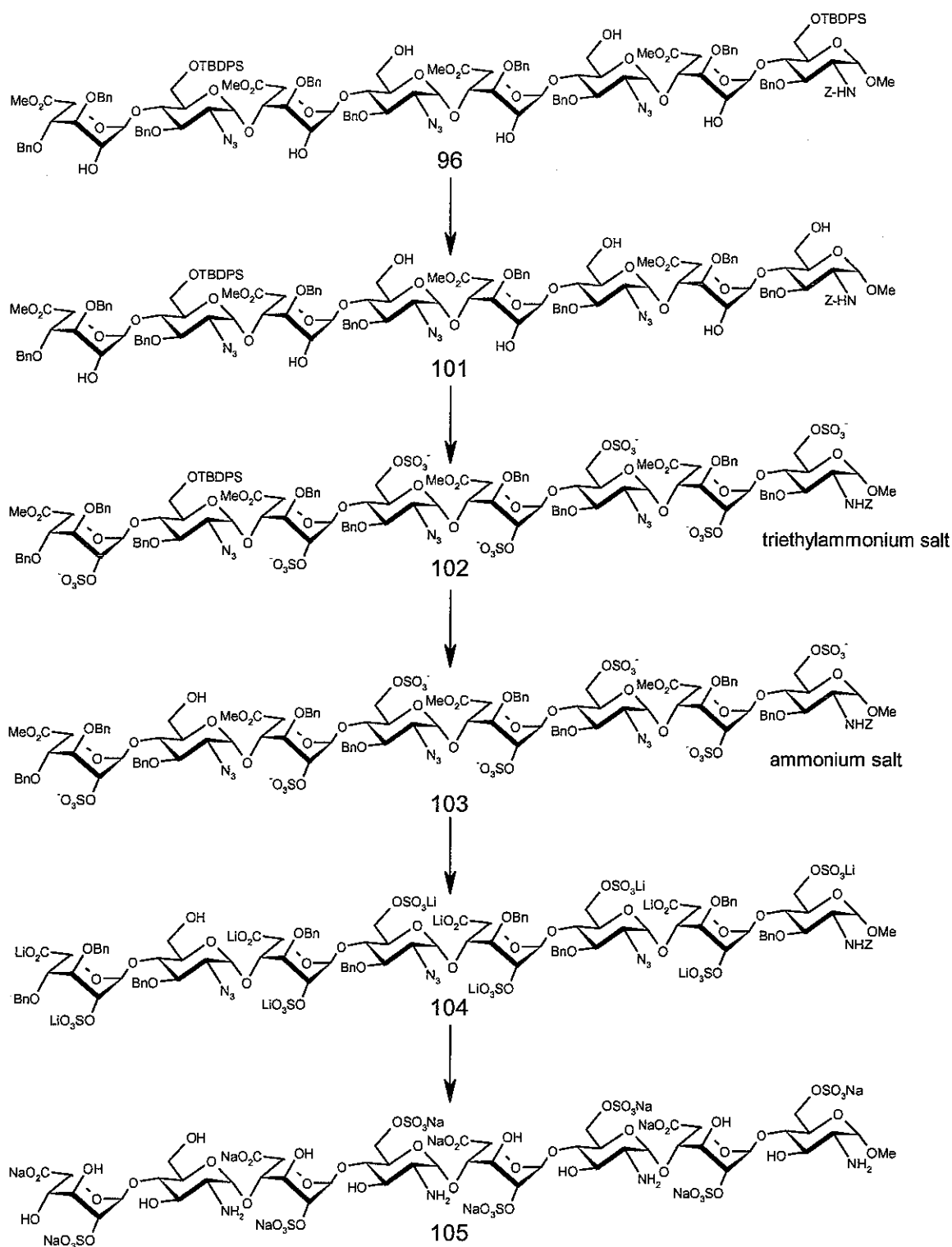
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Preparation of methyl (lithium 2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-amino-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(lithium 2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-amino-2-deoxy-6-O-lithium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(lithium 2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-amino-2-deoxy-6-O-lithium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(lithium 2-O-lithium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-amino-2-deoxy- α -D-glucopyranoside (No. 100)

To a solution in a 1/1 mixture of *tert*-butanol/water (13 mL) of compound **99** obtained previously are successively added ammonium formate (529 mg, 8.4 mmol) and then 10% Pd/C (1.24 g). After 4 hours 15 minutes of vigorous stirring at room temperature, the reaction medium is filtered and partially concentrated under vacuum, and the solution is then applied to a Sephadex[®] G-25 column eluted with 0.2 M sodium chloride. The fractions containing the product are concentrated and desalified using the same column eluted with water. The fractions containing the product are then concentrated under high vacuum to give the desired compound **100** (78 mg, 66%, 2 steps).

Mass: "ESI" method, negative mode: theoretical mass = 1992.8; experimental mass [M – Na – H]: 1971.03 $\pm$ 0.10 a.m.u. (iduronic acids observed in COOH form).

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Preparation of 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)-
 5 (methyl 3-O-benzyl-α-L-idopyranosyluronate)-(1→4)-(2-azido-3-O-benzyl-2-deoxy-α-D-
 glucopyranosyl)-(1→4)-(methyl 3-O-benzyl-α-L-idopyranosyluronate)-(1→4)-(2-azido-3-
 O-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-(methyl 3-O-benzyl-α-L-idopyranosyl-

uronate)-(1→4)-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino-α-D-glucopyranoside
(No. 101)

To a solution of compound **96** (570 mg, 194 μmol) in methanol (66 mL) is added ammonium fluoride (575 mg, 80 molar equivalents). After magnetic stirring at room temperature for 14 hours, the reaction mixture is concentrated under vacuum and then purified on a column of silica (toluene/acetone) to give compound **101** (282 mg, 54%).

R_f = 0.37 (7/3 toluene/acetone).

Preparation of methyl (methyl 3,4-di-O-benzyl-2-O-triethylammonium sulfonato-
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-2-O-triethylammonium sulfonato-
α-L-idopyranosyluronate)-(1→4)-(2-azido-3-O-benzyl-2-deoxy-6-O-triethylammonium
sulfonato-α-D-glucopyranosyl)-(1→4)-(methyl 3-O-benzyl-2-O-triethylammonium
sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-azido-3-O-benzyl-2-deoxy-6-O-triethyl-
ammonium sulfonato-α-D-glucopyranosyl)-(1→4)-(methyl 3-O-benzyl-2-O-triethyl-
ammonium sulfonato-α-L-idopyranosyluronate)-(1→4)-3-O-benzyl-2-deoxy-2-[(benzyl-
oxy)carbonyl]amino-6-O-triethylammonium sulfonato-α-D-glucopyranoside (No. 102)

Triethylamine/sulfur trioxide complex (376 mg, 5 mol per hydroxyl function) is added to a solution in *N,N*-dimethylformamide (5.3 mL, 90 L/mol) of compound **101** (160 mg, 59 μmol). After 17 hours of magnetic stirring at 55°C sheltered from light, methanol is added at 0°C and, after stirring for 30 minutes at 0°C and then for 30 minutes at room temperature, the reaction medium is diluted with methanol and then purified by means of an LH-20 column, using a 1/1 mixture of ethanol/dichloromethane as eluent. The fractions containing the product are then concentrated under high vacuum. The compound obtained is then used directly in the following step.

R_f = 0.52 (11/7/1.6/4 EtOAc/pyridine/AcOH/H₂O).

Preparation of methyl (methyl 2-O-ammonium sulfonato-3,4-di-O-benzyl-α-L-
idopyranosyluronate)-(1→4)-(2-azido-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-
(methyl 2-O-ammonium sulfonato-3-O-benzyl-α-L-idopyranosyluronate)-(1→4)-(6-O-
ammonium sulfonato-2-azido-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-(methyl 2-
O-ammonium sulfonato-3-O-benzyl-α-L-idopyranosyluronate)-(1→4)-(6-O-ammonium
sulfonato-2-azido-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-(methyl 2-O-
ammonium sulfonato-3-O-benzyl-α-L-idopyranosyluronate)-(1→4)-6-O-ammonium
sulfonato-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino-α-D-glucopyranoside (No.
103)

To a solution of compound **102** obtained previously in methanol (2.5 mL) is added ammonium fluoride (42 mg, 60 molar equivalents). After magnetic stirring at

room temperature for 3 hours, at 45°C for 18 hours, and then at 55°C for 4 hours, ammonium fluoride (14 mg, 20 molar equivalents) is again added, and the reaction mixture is stirred for 24 hours at 55°C and then at room temperature for 60 hours. The reaction mixture is then purified by means of an LH-20 column, using a 75/20/5 mixture of methanol/*N,N*-dimethylformamide/water as eluent. The fractions containing the product are then concentrated under high vacuum to give compound **103** (35 mg, 54%).

R_f = 0.54 (11/7/1.6/4 EtOAc/pyridine/AcOH/H₂O).

Preparation of 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-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 (No. 104)

To a solution of compound **103** (155 mg, 41.6 μ mol) in a 1/1 mixture of methanol/tetrahydrofuran (7 mL) is added, dropwise and at 0°C, aqueous 1N LiOH solution (1.4 mL, 8.4 equivalents/methyl ester function). After stirring for 1 hour at 0°C and then for 15 hours at room temperature, the reaction medium is purified by means of an LH-20 column, using a 95/5 methanol/water mixture as eluent. The fractions containing the product are then concentrated under high vacuum to give the desired compound **104** (114 mg, 90%).

R_f = 0.25 (11/7/1.6/4 EtOAc/pyridine/AcOH/H₂O).

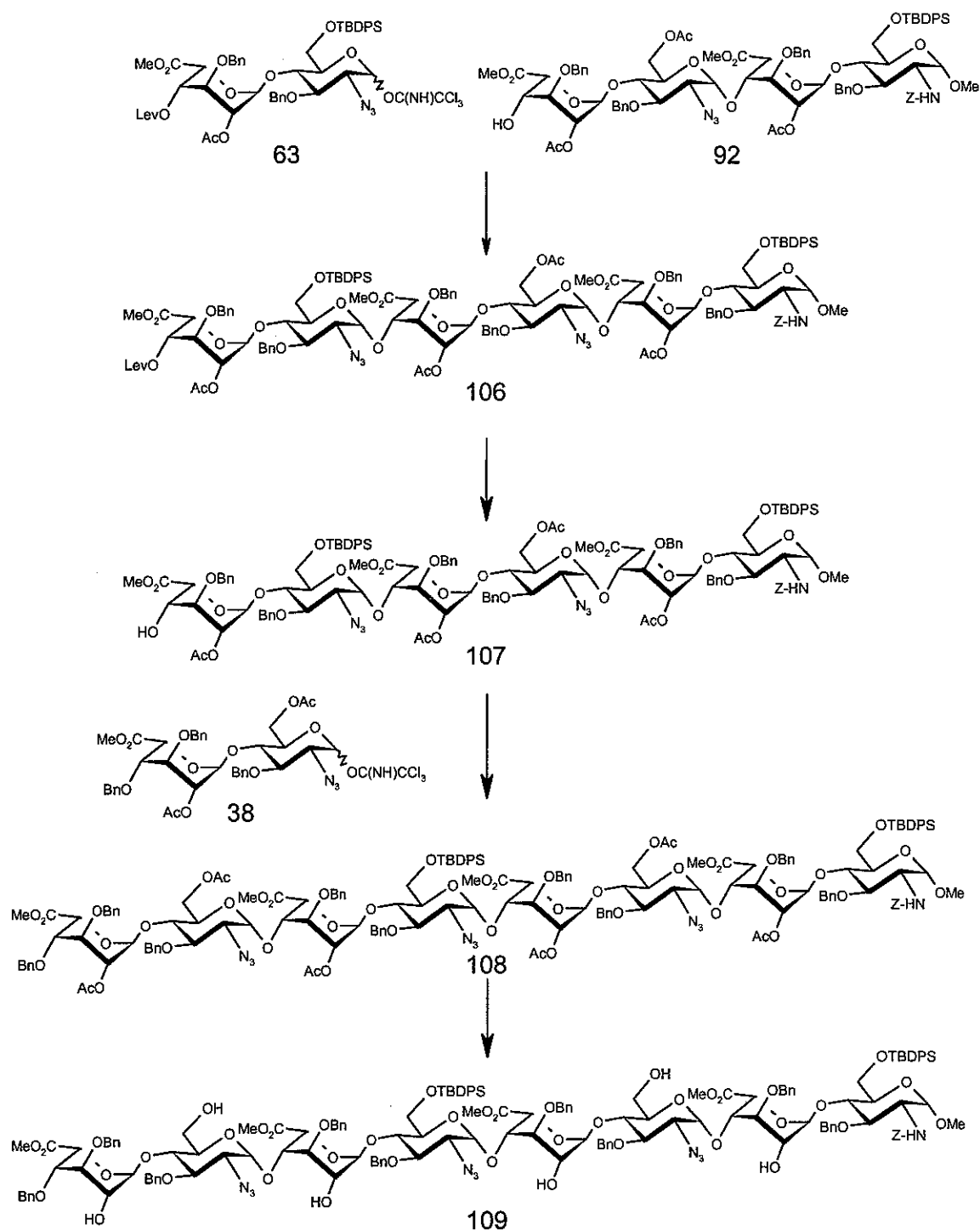
Preparation of methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-amino-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-amino-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-amino-2-deoxy-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 (No. 105)

To a solution in a 1/1 mixture of *tert*-butanol/water (8 mL) of compound **104** (110 mg, 36 μ mol) are successively added ammonium formate (298 mg, 4.72 mmol) and then 10% Pd/C (715 mg). After 4 hours 15 minutes of vigorous stirring at room temperature, the reaction medium is filtered and partially concentrated under vacuum, and the solution is then applied to a Sephadex[®] G-25 column eluted with 0.2 M sodium chloride. The fractions containing the product are concentrated and desalified using the

same column eluted with water. The fractions containing the product are then concentrated under high vacuum to give the desired compound **105** (63 mg, 80%).

Chemical shifts of the anomeric protons (600 MHz, D₂O) δ 5.08 IdoUA^{VIII}, 5.23* Glc^{VII}, 5.14 IdoUA^{VI}, 5.24* Glc^V, 5.14 IdoUA^{IV}, 5.24* Glc^{III}, 5.14 IdoUA^{II}, 4.73 Glc^I

5 *: The signals may be interchanged.



Preparation of methyl (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-*tert*-butyldiphenylsilyl- 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)-(methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- α -D-glucopyranoside (No. 106)

A solution of *tert*-butyldimethylsilyl triflate (1M, 0.2 mol per mole of imidate) in dichloromethane is added, under argon and at -15°C, to a solution of the imidate **63** (0.59 g, 0.54 mmol) and of the glycosyl acceptor **92** (0.58 g, 0.36 mmol) in dichloromethane (25 mL) in the presence of 4 Å molecular sieves (0.4 g). After 45 minutes at -15°C (TLC), further imidate **63** (0.39 g, 0.35 mmol) is added, followed by addition of *tert*-butyldimethylsilyl triflate in dichloromethane (1M, 1.1 mL). After 1 hour 10 minutes at -15°C (TLC), solid sodium hydrogen carbonate is added to neutralize. After filtering, washing with aqueous 2% sodium hydrogen carbonate solution, drying (Na₂SO₄) and evaporating to dryness, the residue is purified by means of an LH-20 column, using a 1/1 ethanol/dichloromethane mixture as eluent. The fractions containing the product are then concentrated under high vacuum and the residue is then purified on silica gel (ethyl acetate/toluene) to give **106** (0.69 g, 75%).

R_f = 0.16 (9/1 toluene/acetone).

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Preparation of methyl (methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-*tert*-butyldiphenylsilyl- 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)-(methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- α -D-glucopyranoside (No. 107)

To a solution of compound **106** (1.41 g, 0.552 mmol) in a 1/2 mixture of toluene/ethanol (110 mL) is added hydrazine acetate (0.254 g, 2.76 molar equivalents). After 2 hours 40 minutes of magnetic stirring, the mixture is concentrated under vacuum and then purified on silica gel to give compound **107** (1.15 g, 85%).

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R_f = 0.16 (9/1 toluene/acetone).

Preparation of 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)-(2-azido-3-O-benzyl-2-deoxy-6-O-*tert*-butyldiphenylsilyl- 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)-(methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-

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3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- α -D-glucopyranoside (No. 108)

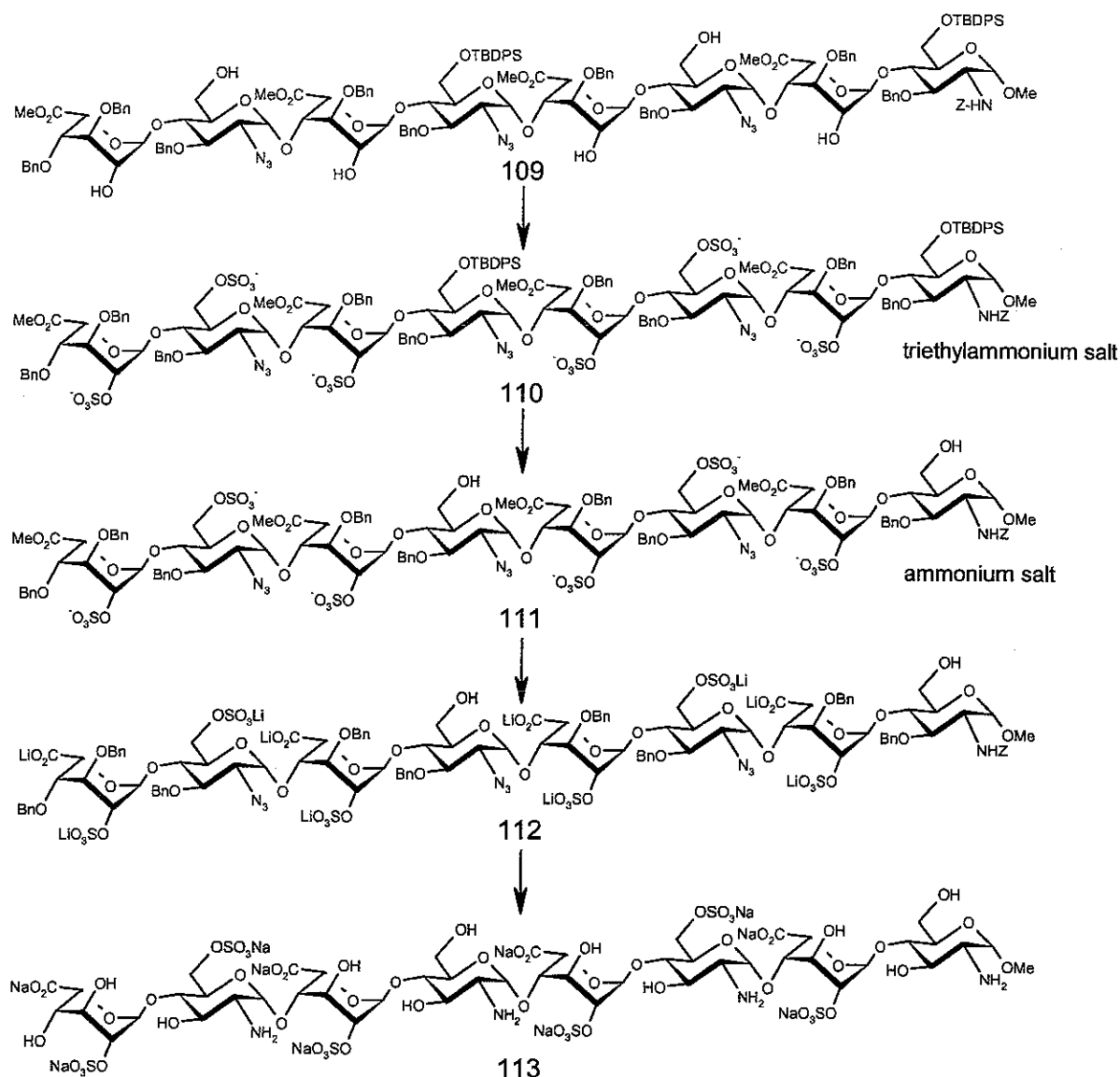
A 0.1 M solution of *tert*-butyldimethylsilyl triflate in dichloromethane (1.1 mL) is added, under argon and at -20°C, to a solution of the imidate **38** (0.67 g, 0.75 mmol) and of the glycosyl acceptor **107** (1.23 g, 0.49 mmol) in dichloromethane (32 mL) in the presence of 4 Å molecular sieves (0.55 g). After 1.5 hours at -20°C (TLC), solid sodium hydrogen carbonate is added to neutralize, and after filtering, washing with aqueous 2% sodium hydrogen carbonate solution, drying (Na₂SO₄) and evaporating to dryness, the residue is purified by means of an LH-20 column, using a 1/1 ethanol/dichloromethane mixture as eluent. The fractions containing the product are then concentrated under high vacuum and the residue is then purified on silica gel to give **108** (0.93 g, 59%).

R_f = 0.24 (7/3 cyclohexane/acetone).

Preparation of methyl (methyl 3,4-di-O-benzyl- α -L-idopyranosyluronate)-(1→4)-(2-azido-3-O-benzyl-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)-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1→4)-(2-azido-3-O-benzyl-2-deoxy- α -D-glucopyranosyl)-(1→4)-(methyl 3-O-benzyl- α -L-idopyranosyluronate)-(1→4)-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]-amino- α -D-glucopyranoside (No. 109)

To a solution of **108** (1.17 g, 0.36 mmol) in a 3/2 mixture of methanol/dichloromethane (109 mL) is added a 1M methanolic solution of sodium methoxide (1.6 mL), in the presence of 3 Å molecular sieves (458 mg). After stirring for 18 hours at room temperature, the mixture is neutralized with H⁺ Dowex 50WX4 resin. After filtering and concentrating, the residue is purified on silica gel with a cyclohexane/ethyl acetate mixture to give compound **109** (680 mg, 69%).

R_f = 0.34 (7/3 toluene/acetone).



- Preparation of methyl (methyl 3,4-di-O-benzyl-2-O-triethylammonium sulfonato-
 5 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*-butyldiphenyl-
silyl- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl-2-O-triethylammonium sulfonato- α -
 10 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-*tert*-butyldiphenylsilyl- α -D-glucopyranoside (No. 110)

Triethylamine/sulfur trioxide complex (267 mg, 5 mol per hydroxyl function) is added to a solution in *N,N*-dimethylformamide (4.4 mL, 90 L/mol) of compound **109**
 15 (144 mg, 49 μ mol). After 16 hours of magnetic stirring at 55°C sheltered from light,

methanol is added at 0°C and, after stirring for 30 minutes at 0°C and then for 30 minutes at room temperature, the reaction medium is diluted with methanol and then purified by means of an LH-20 column, using a 1/1 mixture of methanol/dichloromethane as eluent. The fractions containing the product are then concentrated under high vacuum. The compound obtained is then used directly in the following step.

R_f = 0.42 (57/29/7.2/16 EtOAc/pyridine/AcOH/H₂O).

Preparation of methyl (methyl 3,4-di-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)-(2-azido-3-O-benzyl- 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-deoxy-2-[(benzyloxy)carbonyl]amino- α -D-glucopyranoside (No. 111)

To a solution of compound **110** obtained previously in methanol (5 mL) is added ammonium fluoride (133 mg, 80 molar equivalents). After magnetic stirring at 55°C for 48 hours, the reaction mixture is purified with the aid of an LH-20 column using a 95/5 methanol/water mixture as eluent. The fractions containing the product are then concentrated under high vacuum. If necessary, the crude reaction product is used and treated again under the same conditions to give compound **111** (117 mg, 85%, 2 steps).

R_f = 0.31 (57/29/7.2/16 EtOAc/pyridine/AcOH/H₂O).

Preparation of methyl (lithium 3,4-di-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)-(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-deoxy-2-[(benzyloxy)carbonyl]amino- α -D-glucopyranoside (No. 112)

To a solution of compound **111** (80 mg, 22.3 μ mol) in a 1/1 mixture of methanol/tetrahydrofuran (3.6 mL) is added, dropwise and at 0°C, aqueous 1N LiOH solution (0.7 mL, 7.8 equivalents/methyl ester function). After 2 hours 45 minutes of stirring at 0°C, and then 17.5 hours at room temperature, the reaction medium is purified by means of an LH-20 column, using a 75/20/5 mixture of methanol/*N,N*-dimethylformamide/water as eluent. The fractions containing the product are then

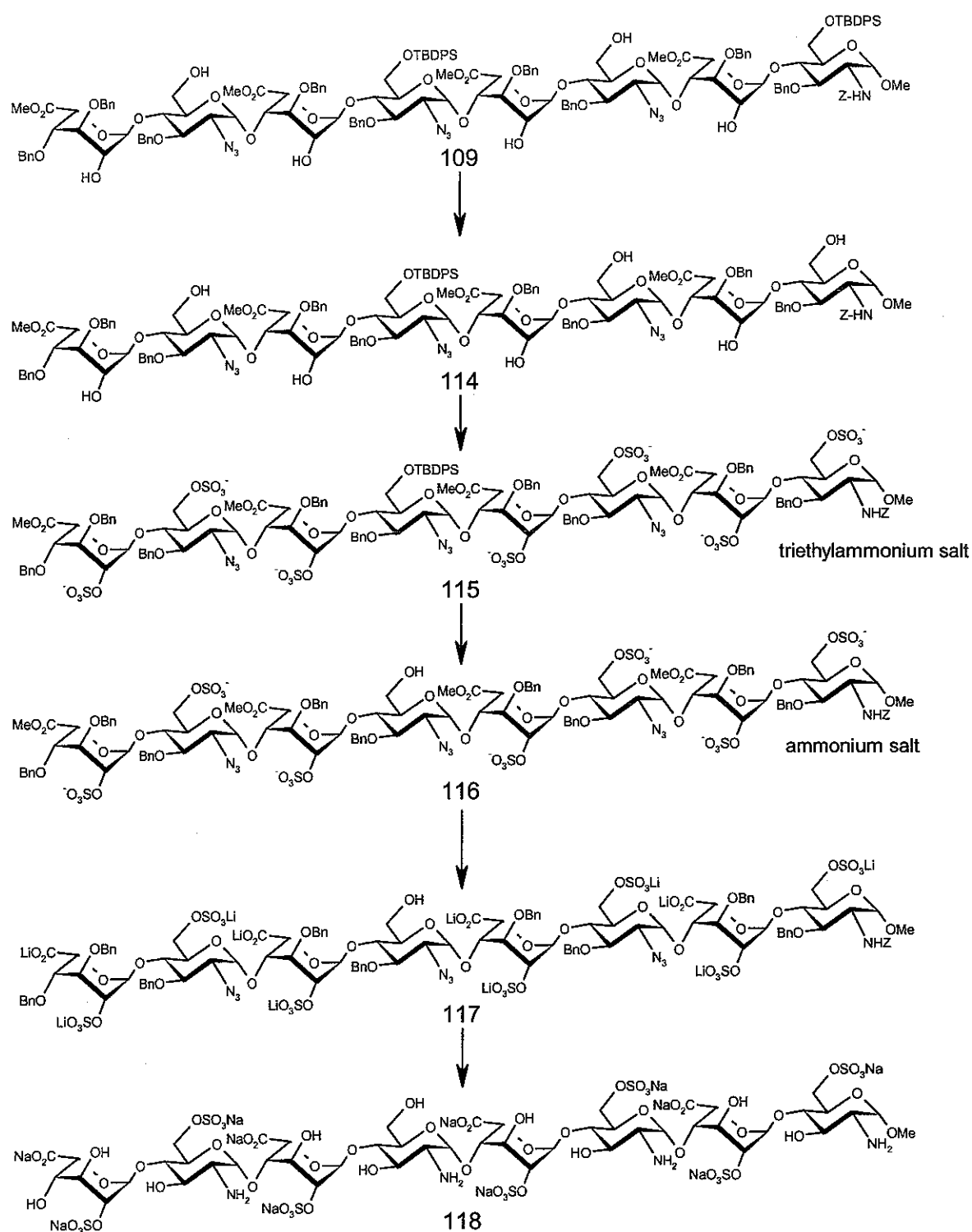
concentrated under high vacuum to give the desired compound **112** (64 mg, 98%).

$R_f = 0.25$ (56/32/7.6/18 EtOAc/pyridine/AcOH/H₂O).

Preparation of methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-
 5 (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-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-amino-2-deoxy- α -D-glucopyranoside (No.
 10 **113**)

To a solution in a 1/1 mixture of *tert*-butanol/water (4.3 mL) of compound **112** (64 mg, 21.7 μ mol) are successively added ammonium formate (178 mg, 2.8 mmol) and then 10% Pd/C (0.42 g). After 4 hours 30 minutes of vigorous stirring at room temperature, the reaction medium is filtered and partially concentrated under vacuum,
 15 and the solution is then applied to a Sephadex[®] G-25 column eluted with 0.2 M sodium chloride. The fractions containing the product are concentrated and desalified using the same column eluted with water. The fractions containing the product are then concentrated under high vacuum to give the desired compound **113** (29.5 mg, 65%).

Chemical shifts of the anomeric protons (600 MHz, D₂O) δ 5.18 IdoUA^{VIII}, 5.43
 20 Glc^{VII}, 5.24 IdoUA^{VI}, 5.45 Glc^V, 5.25 IdoUA^{IV}, 5.43 Glc^{III}, 5.26 IdoUA^{II}, 5.01 Glc^I



- 5 Preparation of 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-deoxy-2-[(benzyloxy)carbonyl]amino- α -D-glucopyranoside (No. 114)

To a solution of compound **109** (135 mg, 46 μ mol) in methanol (16 mL) is added ammonium fluoride (136 mg, 80 molar equivalents). After magnetic stirring at room temperature for 9 hours, and then at -25°C for 15 hours, the reaction mixture is concentrated under vacuum and then purified on a column of silica (toluene/acetone) to give compound **114** (57 mg, 46%).

R_f = 0.30 (toluene-methanol 85/15).

Preparation of 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-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 (No. 115)

Triethylamine/sulfur trioxide complex (317 mg, 5 mol per hydroxyl function) is added to a solution in *N,N*-dimethylformamide (4.5 mL, 90 L/mol) of compound **114** (135 mg, 50 μ mol). After 16 hours of magnetic stirring at 55°C sheltered from light, methanol is added at 0°C and, after stirring for 30 minutes at 0°C and then for 30 minutes at room temperature, the reaction medium is diluted with methanol and then purified by means of an LH-20 column, using a 1/1 mixture of ethanol/dichloromethane as eluent. The fractions containing the product are then concentrated under high vacuum. Compound **115** (168 mg, 86%) is then obtained.

R_f = 0.29 (56/32/7.6/18 EtOAc/pyridine/AcOH/H₂O).

Preparation of 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-deoxy-2-[(benzyloxy)carbonyl]amino- α -D-glucopyranoside (No. 116)

To a solution of compound **115** (168 mg, 43 μ mol) in methanol (5.6 mL) is added ammonium fluoride (128 mg, 80 molar equivalents). After magnetic stirring at 55°C for 48 hours, the reaction mixture is purified with the aid of an LH-20 column using a 95/5 methanol/water mixture as eluent. If necessary, the residue may be used under the same conditions, while monitoring the reaction progress (TLC), and may be purified in the same manner. The fractions containing the product are then concentrated under high vacuum to give compound **116** (109 mg, 81%).

R_f = 0.21 (56/32/7.6/18 EtOAc/pyridine/AcOH/H₂O).

Preparation of 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 (**No. 117**)

To a solution of compound **116** (89 mg, 28.5 μ mol) in a 1/1 mixture of methanol/tetrahydrofuran (3.8 mL) is added, dropwise and at 0°C, aqueous 1N LiOH solution (0.7 mL). After stirring for 3 hours at 0°C, and then for 19 hours at room temperature, the reaction medium is purified by means of an LH-20 column, using a 75/20/5 mixture of methanol/*N,N*-dimethylformamide/water as eluent. The fractions containing the product are then concentrated under high vacuum and if necessary, the reaction is repeated and then worked up in the same manner to give the desired compound **117** (70 mg, 81%).

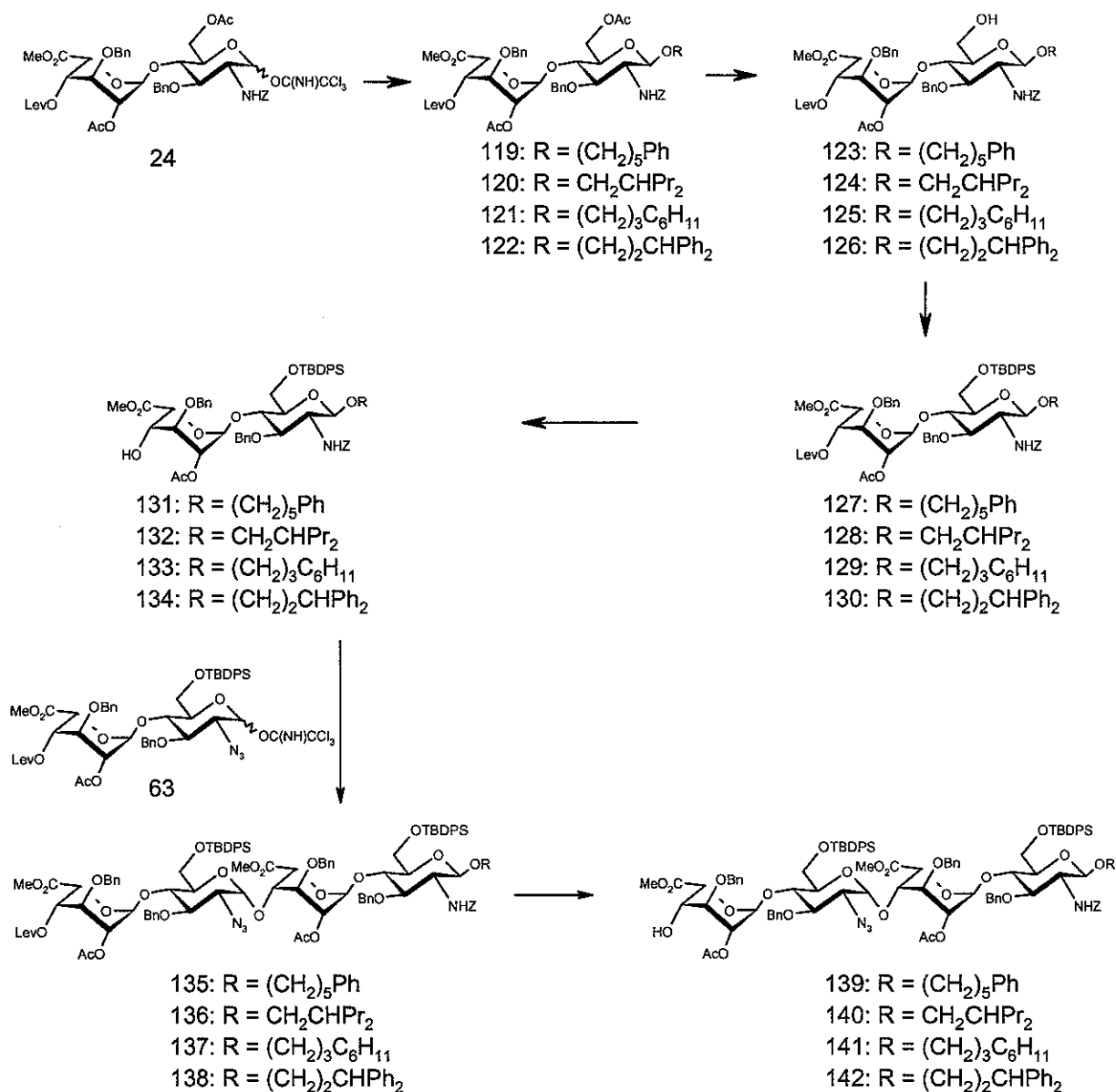
R_f = 0.12 (56/32/7.6/18 EtOAc/pyridine/AcOH/H₂O).

Preparation of 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- 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 (**No. 118**)

To a solution in a 1/1 mixture of *tert*-butanol/water (2.3 mL) of compound **117** (35 mg, 11.6 μ mol) are successively added ammonium formate (95 mg, 1.51 mmol) and then 10% Pd/C (229 mg). After 4 hours 30 minutes of vigorous stirring at room temperature, the reaction medium is filtered and partially concentrated under vacuum,

and the solution is then applied to a Sephadex[®] G-25 column eluted with 0.2 M sodium chloride. The fractions containing the product are concentrated and desalified using the same column eluted with water. The fractions containing the product are then concentrated under high vacuum to give the desired compound **118** (11.1 mg, 45%).

- 5 Chemical shifts of the anomeric protons (600 MHz, D₂O) δ 5.17 IdoUA^{VIII}, 5.42 Glc^{VII}, 5.25 IdoUA^{VI}, 5.45 Glc^V, 5.24 IdoUA^{IV}, 5.44 Glc^{III}, 5.26 IdoUA^{II}, 5.03 Glc^I



Preparation of 5-phenylpentyl (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-6-O-acetyl-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]-amino- β -D-glucopyranoside (No. 119)

tert-Butyldimethylsilyl triflate (1.13 mL, 0.2 mol per mole of imidate) in

dichloromethane is added, under argon and at -20°C, to a solution of the imidate **24** (24.9 g, 24.6 mmol) and 5-phenylpentanol (8.3 mL, 2 molar equivalents) in dichloromethane (1.1 L) in the presence of 4 Å molecular sieves (31 g). After 10 minutes (TLC), saturated aqueous sodium hydrogen carbonate solution at 0°C is added, and stirring is continued for 1 hour. The solution is filtered, washed with aqueous 2% sodium hydrogen carbonate solution, with saturated aqueous sodium chloride solution, dried (Na₂SO₄) and evaporated to dryness. Purification on silica gel gives **119** (21.9 g, 88%).

LC-MS *m/z* 1034.3 [(M + Na)⁺]. T_R = 1.80 min

Preparation of 2-propylpentyl (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1→4)-6-O-acetyl-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]-amino- β -D-glucopyranoside (No. 120)

A 0.1 M solution of *tert*-butyldimethylsilyl triflate (2.78 mL, 0.2 mol per mole of imidate) in dichloromethane is added, under argon, at -20°C, to a solution of the imidate **24** (1.2 g, 1.19 mmol) and 2-propylpentanol (1 mL, 5 molar equivalents) in dichloromethane (63 mL) in the presence of 4 Å molecular sieves (1.8 g). After 10 minutes (TLC), saturated aqueous sodium hydrogen carbonate solution is added at 0°C. The solution is filtered, washed with water, dried (Na₂SO₄) and evaporated to dryness. Purification on silica gel gives **120** (0.91 g, 76%).

LC-MS *m/z* 1000.3 [(M + Na)⁺]. T_R = 1.86 min

Preparation of 3-cyclohexylpropyl (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1→4)-6-O-acetyl-3-O-benzyl-2-deoxy-2-[(benzyloxy)-carbonyl]amino- β -D-glucopyranoside (No. 121)

Compound **24** (1.2 g, 1.19 mmol) is treated according to a protocol similar to that described for the synthesis of **120** to give compound **121** (1.09 g, 91%).

LC-MS *m/z* 1012.3 [(M + Na)⁺]. T_R = 1.88 min

Preparation of 3,3-diphenylpropyl (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1→4)-6-O-acetyl-3-O-benzyl-2-deoxy-2-[(benzyloxy)-carbonyl]amino- β -D-glucopyranoside (No. 122)

Compound **24** (1.2 g, 1.19 mmol) is treated according to a protocol similar to that described for the synthesis of **120** to give compound **122** (1.02 g, 82%).

R_f = 0.34 (7/3 cyclohexane/acetone).

Preparation of 5-phenylpentyl (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1→4)-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-

glucopyranoside (No. 123)

To a solution of **119** (21.9 g, 21.6 mmol) in a 1/1 mixture of methanol/tetrahydrofuran (260 mL) is added $[\text{tBu}_2\text{SnCl}(\text{OH})]_2$ (0.926 g, 0.15 molar equivalent) prepared according to A. Orita et al., *Chem. Eur. J.* (2001) 7, 3321. After stirring at 35°C for 7.5 hours and then at room temperature for 17 hours, the reaction mixture is concentrated under vacuum and then used directly in the following step.

LC-MS m/z 992.3 $[(\text{M} + \text{Na})^+]$. $T_R = 1.74$ min

10 Preparation of 2-propylpentyl (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 124)

To a solution of **120** (0.9 g, 0.93 mmol) in a 1/1 mixture of methanol/tetrahydrofuran (12 mL) is added $[\text{tBu}_2\text{SnCl}(\text{OH})]_2$ (0.037 g, 0.14 molar equivalent) prepared according to A. Orita et al., *Chem. Eur. J.* (2001) 7, 3321. After stirring at room temperature for 16 hours and then at 35°C for 4 hours, the reaction mixture is concentrated under vacuum and then used directly in the following step.

LC-MS m/z 959.2 $[(\text{M} + \text{Na})^+]$. $T_R = 1.79$ min

20 Preparation of 3-cyclohexylpropyl (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 125)

Compound **121** (1.09 g, 1.10 mmol) is treated according to a protocol similar to that described for the synthesis of **124** to give compound **125**, which is used directly in the following step.

25 LC-MS m/z 970.3 $[(\text{M} + \text{Na})^+]$. $T_R = 10.75$ min

30 Preparation of 3,3-diphenylpropyl (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 126)

Compound **122** (0.844 g, 0.80 mmol) is treated according to a protocol similar to that described for the synthesis of **124**. In the event of the reaction being incomplete, the same amount of reagent may optionally be added again. After workup, compound **126** is used directly in the following step.

$R_f = 0.41$ (3/2 cyclohexane/acetone).

35

Preparation of 5-phenylpentyl (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-6-O-tert-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 127)

Compound **123** obtained previously is dissolved in dichloromethane (173 mL). Triethylamine (7.6 mL, 2.5 molar equivalents), 4-dimethylaminopyridine (1.3 g, 0.5 molar equivalent), and *tert*-butyldiphenylsilyl chloride (11.2 mL, 2 molar equivalents) are successively added at 0°C under argon. After 5.5 hours of magnetic stirring, the reaction medium is diluted with dichloromethane, washed with aqueous 10% potassium hydrogen sulfate solution, with saturated aqueous sodium chloride solution, dried (Na₂SO₄), filtered and concentrated. The residue obtained is partially purified on silica (acetone – toluene) which is used in the following step.

LC-MS *m/z* 1231.2 [(M + Na)⁺]. T_R = 2.13 min

Preparation of 2-propylpentyl (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 128)

Compound **124** obtained previously is dissolved in dichloromethane (7.4 mL). 4-Dimethylaminopyridine (57 mg, 0.5 molar equivalent), triethylamine (0.32 mL, 2.5 molar equivalents), and *tert*-butyldiphenylsilyl chloride (0.48 mL, 2.0 molar equivalents) are successively added at 0°C under argon. After 18 hours of magnetic stirring, the reaction medium is diluted with dichloromethane, washed with aqueous 10% potassium hydrogen sulfate solution, with aqueous 2% sodium hydrogen carbonate solution and then with saturated aqueous sodium chloride solution, dried (Na₂SO₄), filtered and concentrated. The residue obtained is purified on silica (acetone – cyclohexane) to give **128** (962 mg, 88% (2 steps)).

R_f = 0.46 (3/2 cyclohexane/acetone).

Preparation of 3-cyclohexylpropyl (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 129)

Compound **125** obtained previously is treated according to a protocol similar to that described for the synthesis of **128**, to give compound **129** (1.12 g, 86% (2 steps)).

LC-MS *m/z* 1208.4 [(M + Na)⁺]. T_R = 13.01 min

Preparation of 3,3-diphenylpropyl (methyl 2-O-acetyl-3-O-benzyl-4-O-levulinoyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 130)

Compound **126** obtained previously is treated according to a protocol similar to that described for the synthesis of **128**, to give compound **130** (0.97 g, 81% (2 steps)).

LC-MS *m/z* 1278.3 [(M + Na)⁺]. T_R = 12.72 min

Preparation of 5-phenylpentyl (methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]-amino- β -D-glucopyranoside (No. 131)

To a solution of compound **127** obtained previously in a 1/2 mixture of
5 toluene/ethanol (1.01 L) is added hydrazine acetate (9.3 g, 5 molar equivalents). After
1 hour 10 minutes of magnetic stirring, the mixture is concentrated under vacuum and
then purified on silica gel to give compound **131** (16.7 g, 70% (3 steps)).

LC-MS m/z 1133.3 [(M + Na)⁺]. T_R = 2.12 min

Chemical shifts of the anomeric protons (500 MHz, CDCl₃) δ

10 5.19 IdoUA^{II}, 4.63 Glc^I

Preparation of 2-propylpentyl (methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]-amino- β -D-glucopyranoside (No. 132)

15 To a solution of compound **128** (0.96 g, 0.82 mmol) in a 1/2 mixture of
toluene/ethanol (164 mL) is added hydrazine acetate (0.38 g, 5 molar equivalents). After
1 hour of magnetic stirring, the mixture is concentrated under vacuum and then purified
on silica gel to give compound **132** (0.84 g, 96%).

R_f = 0.42 (7/3 cyclohexane/acetone).

20 Mass: "ESI" method, positive mode: theoretical mass = 1076.3326; experimental
mass: 1098.5109 [M+Na]⁺.

Chemical shifts of the anomeric protons (500 MHz, CDCl₃) δ

5.15 IdoUA^{II}, 4.61 Glc^I

25 Preparation of 3-cyclohexylpropyl (methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 133)

Compound **129** (1.12 g, 0.94 mmol) is treated according to a protocol similar to
that described for the synthesis of **132**, to give compound **133** (1.03 g, 98%).

30 LC-MS m/z 1110.4 [(M + Na)⁺]. T_R = 13.05 min

Chemical shifts of the anomeric protons (500 MHz, CDCl₃) δ

5.22 IdoUA^{II}, 4.64 Glc^I

35 Preparation of 3,3-diphenylpropyl (methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 134)

Compound **130** (0.96 g, 0.77 mmol) is treated according to a protocol similar to
that described for the synthesis of **132**, to give compound **134** (833 mg, 94%).

LC-MS m/z 1180.5 $[(M + Na)^+]$. $T_R = 12.22$ min

Chemical shifts of the anomeric protons (500 MHz, $CDCl_3$) δ

5.21 IdoUA^{II}, 4.54 Glc^I

5 Preparation of 5-phenylpentyl (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-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 135)

10 *tert*-Butyldimethylsilyl triflate (0.51 mL, 0.15 mol per mole of imidate) in dichloromethane is added, under argon and at -20°C, to a solution of the imidate **63** (24.7 g, 22.5 mmol) and of the glycosyl acceptor **131** (16.7 g, 15 mmol) in dichloromethane (788 mL) in the presence of 4 Å molecular sieves (16.9 g). After 2 hours 45 minutes at -20°C (TLC), solid sodium hydrogen carbonate is added. After
15 filtering, washing with aqueous 2% sodium hydrogen carbonate solution and with saturated aqueous sodium chloride solution, followed by drying (Na_2SO_4) and evaporating to dryness, the residue is purified on silica gel to give **135** (20.6 g, 67%).

Chemical shifts of the anomeric protons (500 MHz, $CDCl_3$) δ 5.35 IdoUA^{IV}, 4.77 Glc^{III}, 5.30 IdoUA^{II}, 4.61 Glc^I

20 $R_f = 0.41$ (9/1 toluene/acetone).

Preparation of 2-propylpentyl (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-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 136)

A 0.1 M solution of *tert*-butyldimethylsilyl triflate in dichloromethane (1.1 mL, 0.15 mol per mole of imidate) is added, under argon and at -20°C, to a solution of the imidate **63** (0.81 g, 0.73 mmol) and of the glycosyl acceptor **132** (0.84 g, 0.78 mmol) in
30 dichloromethane (26 mL) in the presence of 4 Å molecular sieves (0.55 g). After 2 hours 30 minutes at -20°C (TLC), solid sodium hydrogen carbonate is added. After filtering, washing with aqueous 2% sodium hydrogen carbonate solution and with saturated aqueous sodium chloride solution, followed by drying (Na_2SO_4) and evaporating to dryness, the residue is purified on silica gel to give **136** (0.66 g, 47%).

35 $R_f = 0.23$ (4/1 cyclohexane/acetone).

Preparation of 3-cyclohexylpropyl (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-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]-amino- β -D-glucopyranoside (No. 137)

5 The glycosyl donor **63** (0.63 g, 0.57 mmol) and the glycosyl acceptor **133** (1.03 g, 0.95 mmol) are treated according to a protocol similar to that described for the synthesis of **136** to give compound **137** (716 mg, 62%).

R_f = 0.20 (3/1 cyclohexane/acetone).

10 Preparation of 3,3-diphenylpropyl (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-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]-amino- β -D-glucopyranoside (No. 138)

15 The glycosyl donor **63** (0.63 g, 0.57 mmol) and the glycosyl acceptor **134** (0.83 g, 0.72 mmol) are treated according to a protocol similar to that described for the synthesis of **136**, to give compound **138**.

R_f = 0.34 (7/3 cyclohexane/acetone).

20 Preparation of 5-phenylpentyl (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-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 139)

25 To a solution of compound **135** (20.6 g, 10.0 mmol) in a 1/2 mixture of toluene/ethanol (500 mL) is added hydrazine acetate (4.6 g, 5 molar equivalents). After 1 hour 20 minutes of magnetic stirring, the mixture is concentrated under vacuum and then purified on silica gel to give compound **139** (16.8 g, 86%).

R_f = 0.37 (9/1 toluene/acetone).

30 Preparation of 2-propylpentyl (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-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 140)

35 To a solution of compound **136** (20.6 g, 10.0 mmol) in a 1/2 mixture of toluene/ethanol (500 mL) is added hydrazine acetate (4.6 g, 5 molar equivalents). After 1 hour 20 minutes of magnetic stirring, the mixture is concentrated under vacuum and then purified on silica gel to give compound **140** (16.8 g, 86%).

R_f = 0.36 (95/5 toluene/methanol).

Preparation of 3-cyclohexylpropyl (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-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 141)

Compound **137** (0.71 g, 0.35 mmol) is treated according to a protocol similar to that described for the synthesis of **140**, to give compound **141** (0.65 g, 96%).

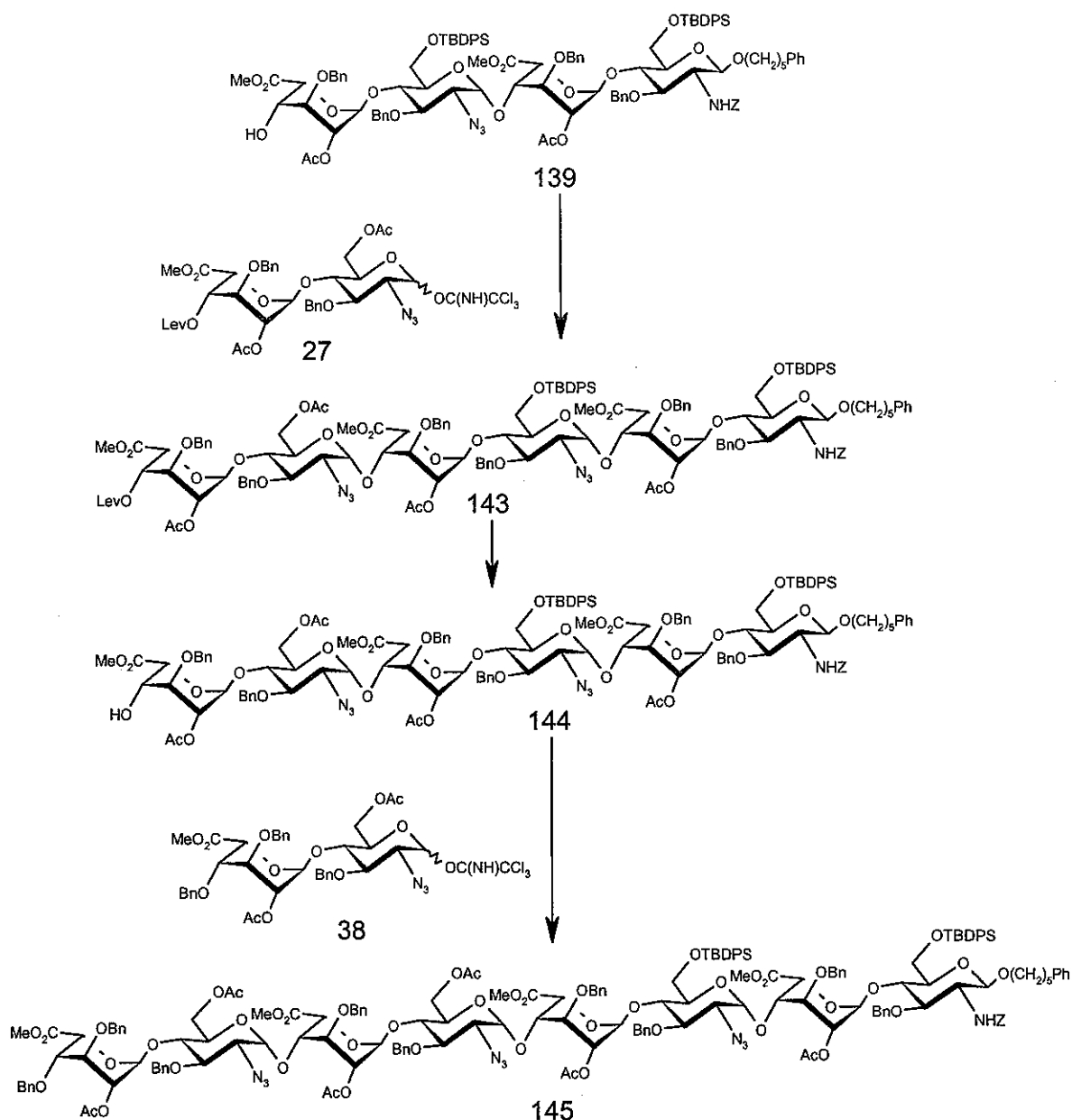
R_f = 0.37 (7/3 cyclohexane/acetone).

Preparation of 3,3-diphenylpropyl (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-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 142)

Compound **138** obtained in the preceding step is treated according to a protocol similar to that described for the synthesis of **140**, to give compound **142** (0.518 g, 45% (2 steps)).

R_f = 0.37 (9/1 toluene/acetone).

78



Preparation of 5-phenylpentyl (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)-(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-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 143)

tert-Butyldimethylsilyl triflate (0.42 mL, 0.15 mol per mole of imidate) in dichloromethane is added, under argon and at -20°C, to a solution of the imidate 27 (11.1 g, 12.3 mmol) and of the glycosyl acceptor 139 (16.8 g, 8.6 mmol) in dichloromethane (430 mL) in the presence of 4 Å molecular sieves (10.4 g). After 3 hours of magnetic stirring at -20°C (TLC), solid sodium hydrogen carbonate is added.

After filtering, washing with aqueous 2% sodium hydrogen carbonate solution and with saturated aqueous sodium chloride solution, followed by drying (Na_2SO_4) and evaporating to dryness, the residue is purified on silica gel to give **143** (14.71 g, 64%).

$R_f = 0.31$ (85/15 toluene/acetone).

5

Preparation of 5-phenylpentyl (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)-(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-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. **144**)

To a solution of compound **143** (13.51 g, 5.0 mmol) in a 1/2 mixture of toluene/ethanol (252 mL) is added hydrazine hydrate (2.31 g, 5 molar equivalents). After 30 minutes of magnetic stirring, the mixture is concentrated under vacuum and then purified on silica gel to give compound **144** (9.41 g, 72%).

15

$R_f = 0.18$ (85/15 toluene/acetone).

Preparation of 5-phenylpentyl (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)-(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-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. **145**)

25

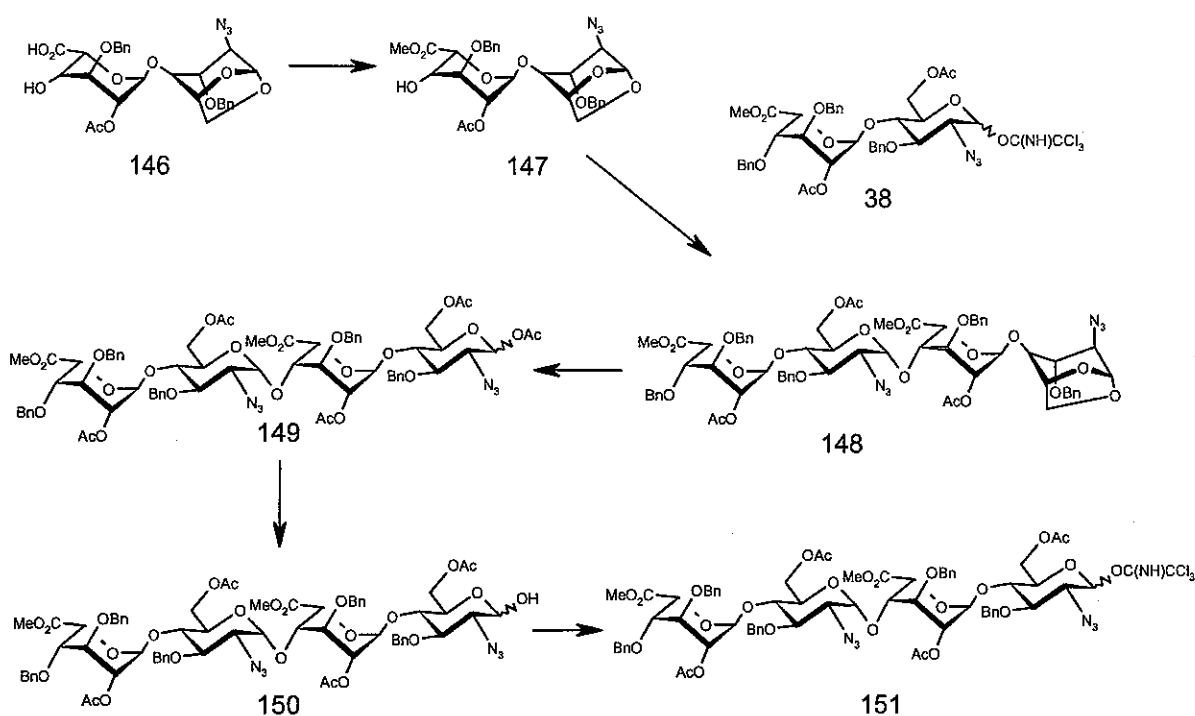
A 0.1 M solution of *tert*-butyldimethylsilyl triflate (7.2 mL, 0.15 mol per mole of imidate) in dichloromethane is added, under argon, at -20°C , to a solution of the imidate **38** (4.29 g, 4.8 mmol) and of the glycosyl acceptor **144** (10.33 g, 4.0 mmol) in dichloromethane (170 mL) in the presence of 4 Å molecular sieves (3.7 g). After 19 hours 45 minutes at -20°C (TLC), solid sodium hydrogen carbonate is added. After filtering, washing with aqueous 2% sodium hydrogen carbonate solution, with saturated aqueous sodium chloride solution, followed by drying (Na_2SO_4) and evaporating to dryness, the residue is purified on silica gel to give **145** (7.74 g, 58%).

30

$R_f = 0.4$ (85/15 toluene/acetone).

35

80



Preparation of (methyl 2-O-acetyl-3-O-benzyl- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-1,6-anhydro-2-azido-3-O-benzyl-2-deoxy- β -D-glucopyranose (No. 147)

- 5 To a solution of compound **146** (11.1 mmol) (WO 2006/021 653) in *N,N*-dimethylformamide (78 mL) is added, at 0°C and under argon, potassium hydrogen carbonate (5.56 g, 5 molar equivalents), followed by addition of methyl iodide (6.9 mL, 10 molar equivalents). After 17 hours of magnetic stirring, the reagents may be added once again, if necessary. Once the reaction is complete (TLC), the reaction medium is
- 10 concentrated under vacuum, the crude reaction product is diluted with ethyl acetate, washed with water and then with saturated aqueous sodium thiosulfate solution, dried (Na_2SO_4), filtered and concentrated. The residue obtained is used in the following step without purification.

LC-MS m/z 465.3 $[(M + \text{NH}_4)^+]$. $T_R = 0.8$ min

15

Preparation of (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)-1,6-anhydro-2-azido-3-O-benzyl-2-deoxy- β -D-glucopyranose (No. 148)

- 20 A 1 M solution of *tert*-butyldimethylsilyl triflate (0.95 mL, 0.15 mol per mole of imidate) in dichloromethane is added, under argon and at -20°C, to a solution of the imidate **38** (5.68 g, 6.35 mmol) and of the glycosyl acceptor **147** (4.2 g, 7 mmol) in dichloromethane (222 mL) in the presence of 4 Å molecular sieves (4.8 g). After 1.5 hours at -20°C (TLC), catalyst is optionally added until the reaction is complete

(TLC), and then solid sodium hydrogen carbonate is added. After filtering, washing with aqueous 2% sodium hydrogen carbonate solution and with saturated sodium chloride solution, drying (Na_2SO_4), filtering and evaporating to dryness, the residue is purified on silica gel to give **148** (3.15 g, 38%).

5 $R_f = 0.41$ (3/2 cyclohexane/ethyl acetate).

Preparation of (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)-1,6-di-O-acetyl-2-azido-3-O-benzyl-2-deoxy- α,β -D-glucopyranose (**No. 149**)

The residue obtained in the preceding step is dissolved in acetic anhydride (13 mL), followed by addition, at 0°C over 15 minutes, of trifluoroacetic acid (TFA) (1.3 mL). The reaction mixture is stirred for 10 minutes at 0°C and for 18 hours at room temperature, and is then concentrated, co-evaporated with toluene, and purified on silica gel (heptane/ethyl acetate), to give compound **149** (2.99 g, 88%).

LC-MS m/z 1456.0 [$(M + Na)^+$]. $T_R = 1.96$ min

Preparation of (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,β -D-glucopyranose (**No. 150**)

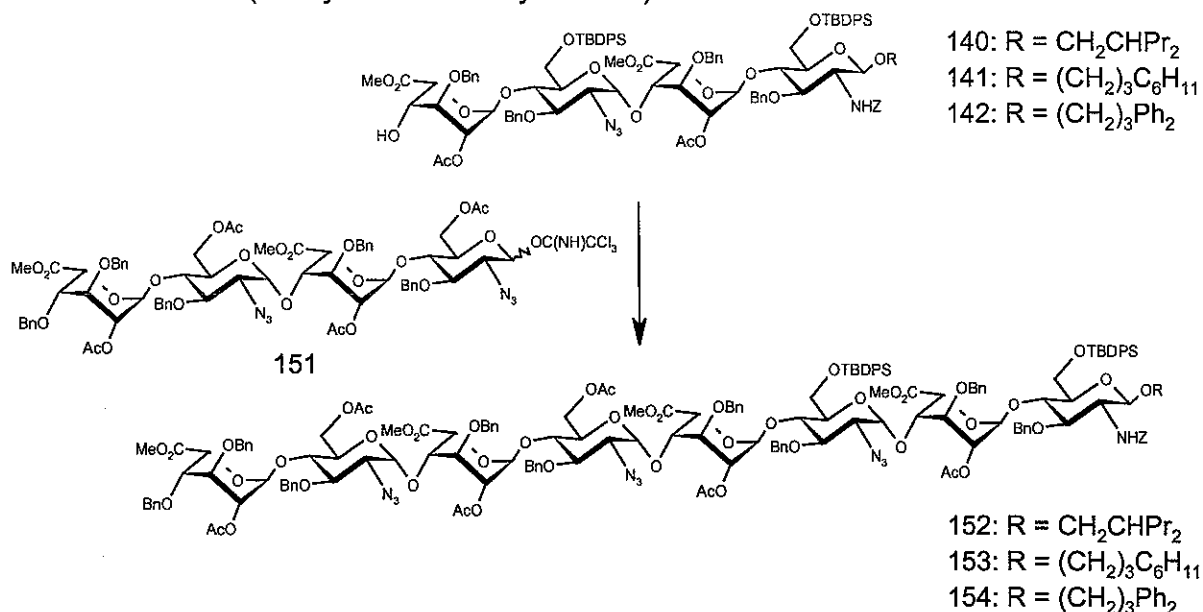
To a solution of compound **149** (2.99 g, 2.09 mmol) in diethyl ether (42 mL) is added, at 0°C, benzylamine (BnNH_2) (8.2 mL, 36 molar equivalents). After 1.5 hours of stirring at 0°C, and then 4.5 hours at room temperature, the reaction mixture is neutralized with cold (0-4°C) 1N HCl, washed with water, dried (Na_2SO_4), filtered and concentrated, and purified on silica gel (heptane/ethyl acetate) to give **150** (2.6 g, 90%).

$R_f = 0.21$ (3/2 cyclohexane/ethyl acetate).

Preparation of (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,β -D-glucopyranose trichloroacetimidate (**No. 151**)

To a solution of compound **150** (2.6 g, 1.9 mmol) in dichloromethane (36 mL) is added, under argon and at 0°C, caesium carbonate (Cs_2CO_3) (0.97 g, 1.6 molar equivalents), followed by addition of trichloroacetonitrile (CCl_3CN) (0.94 mL, 5.0 molar equivalents). After stirring for 1 hour 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 **151** (2.25 g, 80%).

R_f = 0.38 (3/2 cyclohexane/ethyl acetate).



Preparation of 2-propylpentyl (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)-(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-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 152)

A 0.1 M solution of *tert*-butyldimethylsilyl triflate (0.46 mL, 0.15 mol per mole of imidate) in dichloromethane is added, under argon and at -20°C, to a solution of the imidate **151** (0.56 g, 0.36 mmol) and of the glycosyl acceptor **140** (0.59 g, 0.31 mmol) in dichloromethane (11 mL) in the presence of 4 Å molecular sieves (0.27 g). After 5 hours at -20°C (TLC), solid sodium hydrogen carbonate is added. After filtering, washing with aqueous 2% sodium hydrogen carbonate solution and with saturated aqueous sodium chloride solution, followed by drying (Na₂SO₄) and evaporating to dryness, the residue is purified on silica gel to give **152** (0.82 g, 82%).

R_f = 0.32 (7/3 cyclohexane/acetone).

Preparation of 3-cyclohexylpropyl (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)-(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-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]-amino- β -D-glucopyranoside (No. 153)

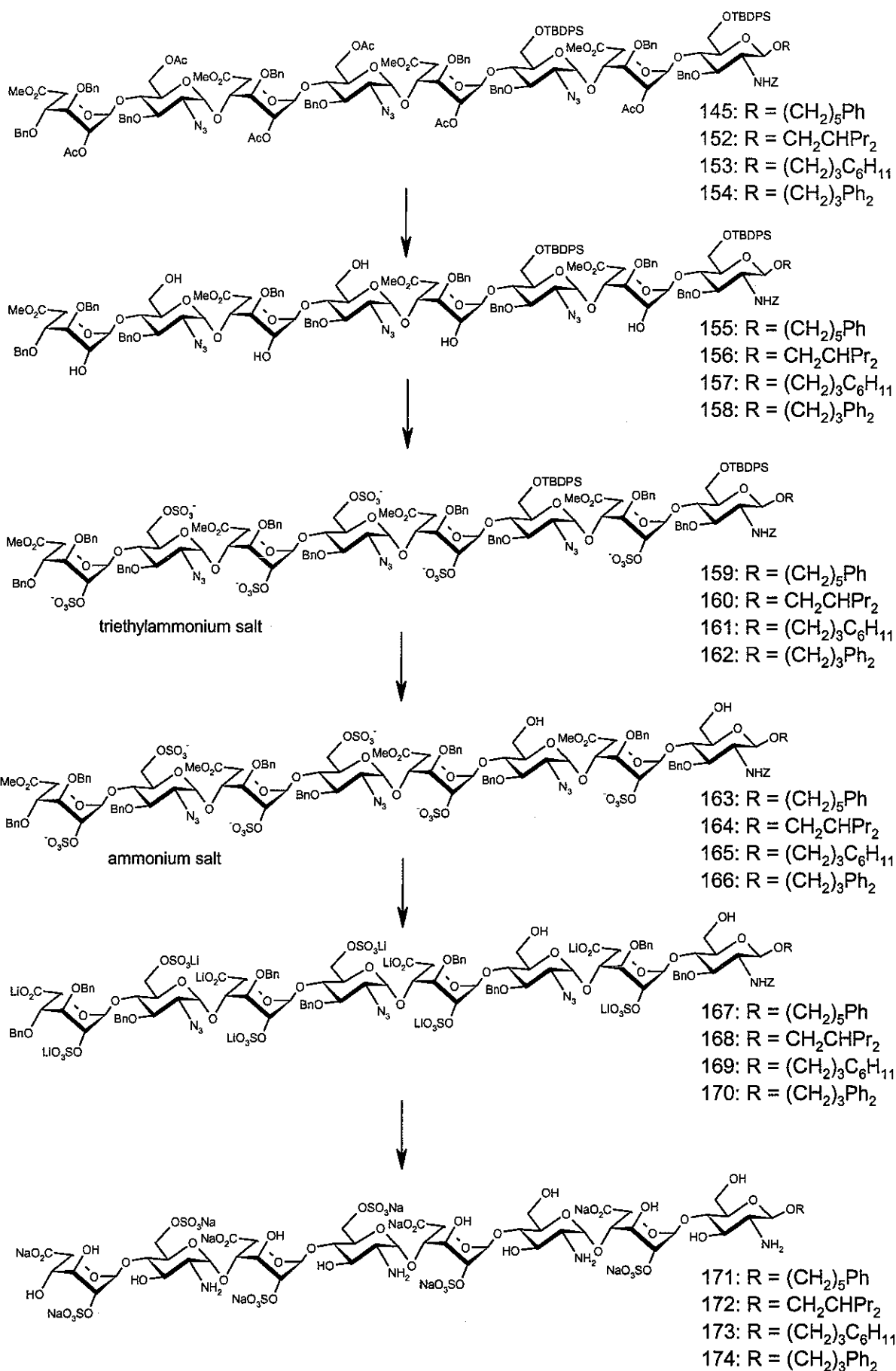
5 The glycosyl donor **151** (0.56 g, 0.36 mmol) and the glycosyl acceptor **141** (0.65 g, 0.34 mmol) are treated according to a protocol similar to that described for the synthesis of **152**, to give compound **153** (808 mg, 73%).

R_f = 0.36 (3/2 cyclohexane/acetone).

10 Preparation of 3,3-diphenylpropyl (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)-(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-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]-amino- β -D-glucopyranoside (No. 154)

15 The glycosyl donor **151** (0.51 g, 0.33 mmol) and the glycosyl acceptor **142** (0.52 g, 0.26 mmol) are treated according to a protocol similar to that described for the synthesis of **152**, to give compound **154** (635 mg, 73%).

20 R_f = 0.25 (7/3 cyclohexane/acetone).



Preparation of 5-phenylpentyl (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)-
 5 (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-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]-amino- β -D-glucopyranoside (**No. 155**)

To a solution of **145** (639 mg, 0.192 mmol) in a 3/2 mixture of
 10 methanol/dichloromethane (57 mL) in the presence of 3 Å molecular sieves (230 mg) is added, at 0°C, a 1M methanolic solution of sodium methoxide (0.427 mL). After stirring at 0°C for 3 hours and at room temperature for 15 hours, the mixture is neutralized at 0°C with H⁺ Dowex 50WX4 resin. After filtering and concentrating, the residue is purified on silica gel with a toluene/ethyl acetate/ethanol mixture to give compound **155**
 15 (444 mg, 80%).

R_f = 0.28 (7/3/0.3 toluene/ethyl acetate/ethanol).

Preparation of 2-propylpentyl (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)-
 20 (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-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]-amino- β -D-glucopyranoside (**No. 156**)

Compound **152** (420 mg, 0.128 mmol) is treated according to a protocol similar to that described for the synthesis of **155**, to give compound **156** (178 mg, 46%).

R_f = 0.20 (7/3 cyclohexane/acetone).

Preparation of 3-cyclohexylpropyl (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-6-O-*tert*-butyldiphenylsilyl-2-deoxy-
 30 2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (**No. 157**)

Compound **153** (402 mg, 0.122 mmol) is treated according to a protocol similar to that described for the synthesis of **155**, to give compound **157** (276 mg, 75%).

R_f = 0.40 (7/3 cyclohexane/acetone).

Preparation of 3,3-diphenylpropyl (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-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 158)

Compound **154** (315 mg, 0.093 mmol) is treated according to a protocol similar to that described for the synthesis of **155**, to give compound **158** (244 mg, 84%).

R_f = 0.13 (7/3 cyclohexane/acetone).

Preparation of 5-phenylpentyl (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)-(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)-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 159)

Triethylamine/sulfur trioxide complex (775 mg, 5 mol per hydroxyl function) is added to a solution in *N,N*-dimethylformamide (12.8 mL, 90 L/mol) of compound **155** (438 mg, 142 μ mol). After 17 hours of magnetic stirring at 50°C sheltered from light, methanol is added at 0°C and, after stirring for 30 minutes at 0°C and then 1 hour at room temperature, the reaction medium is diluted with methanol and then purified by means of an LH-20 column, using a 9/1 mixture of methanol/*N,N*-dimethylformamide as eluent. The fractions containing the product are then concentrated under high vacuum to give the desired compound **159** (571 mg, 96%).

R_f = 0.48 (29/13/3.4/7 EtOAc/pyridine/AcOH/H₂O).

Preparation of 2-propylpentyl (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)-(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)-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 160)

Compound **156** (178 mg, 0.054 mmol) is treated according to a protocol similar to that described for the synthesis of **159**, to give compound **160** (196 mg, 75%).

5 Rf = 0.48 (57/29/7.2/16 EtOAc/pyridine/AcOH/H₂O).

Preparation of 3-cyclohexylpropyl (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)-(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)-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 161)

Compound **157** (345 mg, 0.113 mmol) is treated according to a protocol similar to that described for the synthesis of **159**, to give compound **161** (332 mg, 70%).

Rf = 0.48 (57/29/7.2/16 EtOAc/pyridine/AcOH/H₂O).

Preparation of 3,3-diphenylpropyl (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)-(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)-3-O-benzyl-6-O-*tert*-butyldiphenylsilyl-2-deoxy-2-[(benzyloxy)carbonyl]amino- β -D-glucopyranoside (No. 162)

Compound **158** (300 mg, 0.096 mmol) is treated according to a protocol similar to that described for the synthesis of **159**. If necessary, the mixture obtained may be purified on an RP-18 reverse-phase column using a methanol/water mixture as eluent, to give compound **162** (211 mg, 52%).

Rf = 0.47 (29/13/3.4/7 EtOAc/pyridine/AcOH/H₂O).

Preparation of 5-phenylpentyl (methyl 3,4-di-O-benzyl-2-O-ammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-azido-3-O-benzyl-2-deoxy-6-O-ammonium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(methyl 3-O-benzyl-2-O-ammonium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 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)-(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)-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino-β-D-glucopyranoside (No. 163)

- 5 To a solution of compound **159** (520 mg, 125 μmol) in methanol (16 mL) is added ammonium fluoride (370 mg, 80 molar equivalents). After magnetic stirring at 55°C for 24 hours and then at room temperature for 16 hours, the reaction mixture is purified with the aid of an LH-20 column using a 9/1 mixture of methanol/*N,N*-dimethylformamide as eluent. The fractions containing the product are then concentrated under high vacuum and the residue is purified on silica gel with an ethyl acetate/pyridine/acetic acid/water mixture as eluent. The fractions containing the product are then partially concentrated and the residue is purified by means of an LH-20 column, using a 9/1 mixture of methanol/*N,N*-dimethylformamide as eluent. The fractions containing the product are then concentrated under high vacuum to give compound **163** (295 mg, 74%).

R_f = 0.45 (29/13/3.4/7 EtOAc/pyridine/AcOH/H₂O).

- Preparation of 2-propylpentyl (methyl 3,4-di-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)-(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)-(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)-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino-β-D-glucopyranoside (No. 164)

- Compound **160** (196 mg, 0.048 mmol) is treated according to a protocol similar to that described for the synthesis of **163**. The reaction time may optionally be shortened according to the TLC monitoring. Moreover, reverse-phase purification may prove to be necessary in order to obtain compound **164** (104 mg, 59%).

- 30 R_f = 0.32 (57/29/7.2/16 EtOAc/pyridine/AcOH/H₂O).

- Preparation of 3-cyclohexylpropyl (methyl 3,4-di-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)-(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)-(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)-3-O-

benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino-β-D-glucopyranoside (No. 165)

Compound **161** (230 mg, 0.055 mmol) is treated according to a protocol similar to that described for the synthesis of **164**, to give compound **165** (115 mg, 56%).

R_f = 0.57 (57/29/7.2/16 EtOAc/pyridine/AcOH/H₂O).

5

Preparation of 3,3-diphenylpropyl (methyl 3,4-di-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)-(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)-(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)-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino-β-D-glucopyranoside (No. 166)

10

Compound **162** (43 mg, 10.2 μmol) is treated according to a protocol similar to that described for the synthesis of **163**, to give compound **166**.

15

R_f = 0.32 (29/13/3.4/7 EtOAc/pyridine/AcOH/H₂O).

Preparation of 5-phenylpentyl (lithium 3,4-di-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)-(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)-(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)-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]amino-β-D-glucopyranoside (No. 167)

20

25

To a solution of compound **163** (289 mg, 91 μmol) in methanol (3.59 mL) are added, at 0°C, aqueous 30% hydrogen peroxide solution (2.23 mL), followed by dropwise addition of aqueous 5N LiOH solution (1.46 mL). After stirring for 3 hours at 0°C, for 16 hours at room temperature and then for 27 hours at 45°C, the reaction medium is neutralized at 0°C by addition of 3N hydrochloric acid, and then purified by means of an LH-20 column, using a 9/1 mixture of methanol/*N,N*-dimethylformamide as eluent. The fractions containing the product are then concentrated under high vacuum to give the desired compound **167** (267 mg, 95%).

30

R_f = 0.25 (57/29/7.2/16 EtOAc/pyridine/AcOH/H₂O).

35

Preparation of 2-propylpentyl (lithium 3,4-di-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-idopyranosyl-

uronate)-(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)-(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)-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]-
 5 amino-β-D-glucopyranoside (**No. 168**)

Compound **164** (104 mg, 0.029 mmol) is treated according to a protocol similar to that described for the synthesis of **167**, to give compound **168**.

R_f = 0.28 (57/29/7.2/16 EtOAc/pyridine/AcOH/H₂O).

10 Preparation of 3-cyclohexylpropyl (lithium 3,4-di-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-idopyranosyl-
 uronate)-(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)-(2-
 15 azido-3-O-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-(lithium 3-O-benzyl-2-O-lithium
 sulfonato-α-L-idopyranosyluronate)-(1→4)-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]-
 amino-β-D-glucopyranoside (**No. 169**)

Compound **165** (110 mg, 0.030 mmol) is treated according to a protocol similar to that described for the synthesis of **167**, to give compound **169** (76 mg, 83%).

20 R_f = 0.20 (57/29/7.2/16 EtOAc/pyridine/AcOH/H₂O).

Preparation of 3,3-diphenylpropyl (lithium 3,4-di-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-idopyranosyl-
 25 uronate)-(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)-(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)-3-O-benzyl-2-deoxy-2-[(benzyloxy)carbonyl]-
 amino-β-D-glucopyranoside (**No. 170**)

30 Compound **166** is treated according to a protocol similar to that described for the synthesis of **167**. If necessary, the residue obtained may be used under the same conditions to give compound **170** (27 mg, 87% (2 steps)).

R_f = 0.39 (57/29/7.2/16 EtOAc/pyridine/AcOH/H₂O).

35 Preparation of 5-phenylpentyl (sodium 2-O-sodium sulfonato-α-L-idopyranosyl-
 uronate)-(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)-(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-β-D-glucopyranoside (No. 171)

To a solution in a 1/1 mixture of *tert*-butanol/water (16.1 mL) of compound **167** obtained previously are successively added ammonium formate (658 mg, 10.4 mmol) and then 10% Pd/C (1.61 g). After stirring vigorously for 4 hours at room temperature, the reaction medium is filtered and partially concentrated under vacuum, and the solution is then applied to a Sephadex[®] G-25 column eluted with 0.2 M sodium chloride. The fractions containing the product are concentrated and desalified using the same column eluted with water. The fractions containing the product are then concentrated under high vacuum to give the desired compound **171** (109 mg, 62%).

"ESI" method, negative mode: multicharged ion detected m/z 663.08 $[M-3H]^{3-}$ (acid form).

Preparation of 2-propylpentyl (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-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-β-D-glucopyranoside (No. 172)

Compound **168** is treated according to a protocol similar to that described for the synthesis of **171**, to give compound **172** (47 mg, 74% (2 steps)).

Chemical shifts of the anomeric protons (500 MHz, D₂O) δ 5.29* IdoUA^{VIII}, 5.50** Glc^{VII}, 5.29* IdoUA^{VI}, 5.48** Glc^V, 5.29* IdoUA^{IV}, 5.48** Glc^{III}, 5.22* IdoUA^{II}, 4.78** Glc^I

* and **: The signals may be interchanged.

Preparation of 3-cyclohexylpentyl (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-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-β-D-glucopyranoside (No. 173)

Compound **169** (88 mg, 29 μmol) is treated according to a protocol similar to that described for the synthesis of **171**, to give compound **173** (63 mg, 99%).

Chemical shifts of the anomeric protons (500 MHz, D₂O) δ 5.29* IdoUA^{VIII}, 5.50** Glc^{VII}, 5.29* IdoUA^{VI}, 5.48** Glc^V, 5.29* IdoUA^{IV}, 5.48** Glc^{III}, 5.22* IdoUA^{II}, 4.78** Glc^I

* and **: The signals may be interchanged.

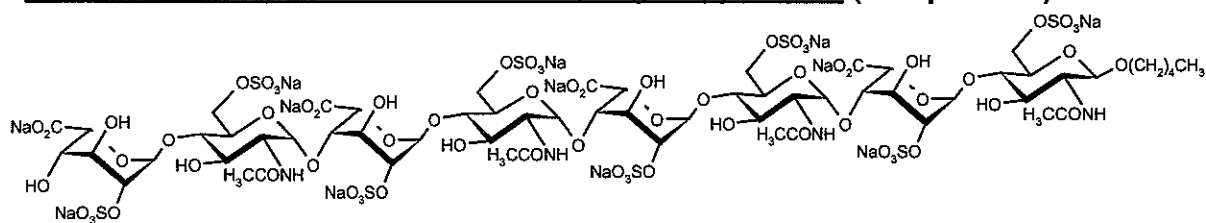
Preparation of 3,3-diphenylpentyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-amino-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-amino-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(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- β -D-glucopyranoside (**No. 174**)

Compound **170** (17.4 mg, 5.6 μ mol) is treated according to a protocol similar to that described for the synthesis of **171**, to give compound **174** (5.5 mg, 44%).

Chemical shifts of the anomeric protons (600 MHz, D₂O) δ 5.15 IdoUA^{VIII}, 5.42 Glc^{VII}, 5.23 IdoUA^{VI}, 5.40 Glc^V, 5.23 IdoUA^{IV}, 5.38 Glc^{III}, 5.19 IdoUA^{II}, 4.39 Glc^I

Examples of compounds according to the invention:

EXAMPLE 1: Pentyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy-6-O-sodium sulfonato- β -D-glucopyranoside (**Compound 1**)



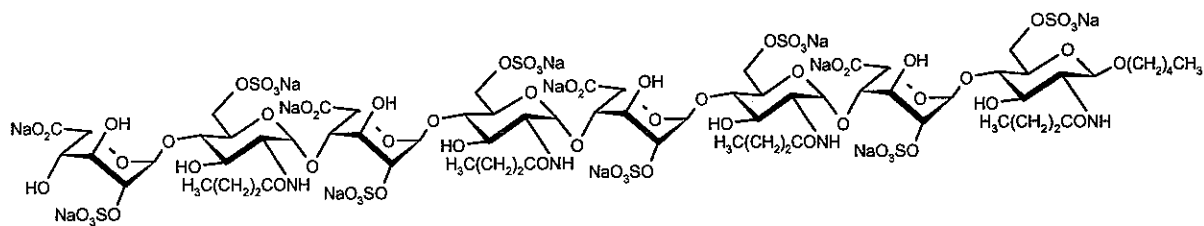
To a saturated aqueous sodium hydrogen carbonate solution (2.1 mL) of compound **43** (39 mg, 16.6 μ mol) is added sodium hydrogen carbonate (223 mg, 2.66 mmol), followed by dropwise addition, at 0°C, of acetic anhydride (126 μ L, 1.33 mmol). After stirring vigorously for 3 hours at 0°C and then for 15 hours at room temperature, the reaction medium is applied to a Sephadex[®] G-25 column eluted with 0.2 M sodium chloride. The fractions containing the product are concentrated and desalified using the same column eluted with water. The fractions containing the product are then concentrated under high vacuum to give the desired compound **1**

(30 mg, 73%).

Chemical shifts of the anomeric protons (500 MHz, D₂O) δ 5.14 IdoUA^{VIII}, 5.13 Glc^{VII}, 5.16 IdoUA^{VI}, 5.13 Glc^V, 5.15 IdoUA^{IV}, 5.14 Glc^{III}, 5.17 IdoUA^{II}, 4.51 Glc^I

Mass: "ESI" method, negative mode: theoretical mass = 2509.72; experimental mass: 2508.82 $\pm$ 0.34 a.m.u.

EXAMPLE 2: Pentyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- β -D-glucopyranoside (Compound 2)



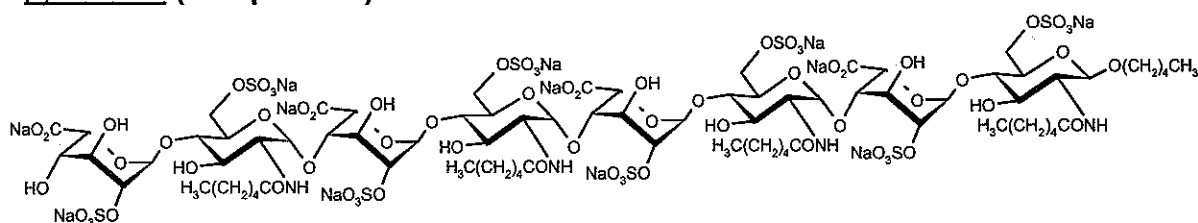
To a solution of compound **43** (26 mg, 11.1 μ mol) in a 7/3 mixture of *N,N*-dimethylformamide/water (2.9 mL) are added dropwise, at 0°C, diisopropylethylamine (33 μ L, 17 molar equivalents) dissolved in *N,N*-dimethylformamide (100 μ L) and *N*-hydroxysuccinimide butyrate (27.4 mg, 13 molar equivalents) dissolved in *N,N*-dimethylformamide (100 μ L). Stirring is continued at room temperature for 4 hours, and the same amount of reagent is then added twice more under the same conditions. After a total of 18 hours of stirring at room temperature, the reaction medium is applied to a Sephadex[®] G-25 column eluted with 0.2 M sodium chloride. The fractions containing the product are concentrated and desalified using the same column eluted with water. The fractions containing the product are then concentrated under high vacuum to give the desired compound **2** (26 mg, 89%).

Chemical shifts of the anomeric protons (600 MHz, D₂O) δ 5.14 IdoUA^{VIII}, 5.12* Glc^{VII}, 5.14 IdoUA^{VI}, 5.11* Glc^V, 5.14 IdoUA^{IV}, 5.10* Glc^{III}, 5.15 IdoUA^{II}, 4.50 Glc^I

*: The signals may be interchanged.

"ESI" method, negative mode: multicharged ion detected m/z 588.1095 [M-4H]⁴⁻ (acid form).

EXAMPLE 3: Pentyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxohexyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxohexyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxohexyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-2-(1-oxohexyl)amino-6-O-sodium sulfonato- β -D-glucopyranoside (Compound 3)

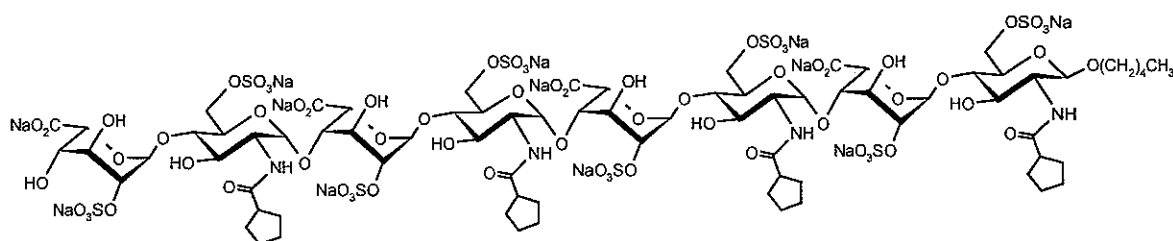


To a solution of compound **43** (10 mg, 4.27 μ mol) in water (0.3 mL) are added dropwise, at 0°C, diisopropylethylamine (20 μ L, 26.8 molar equivalents) dissolved in *N,N*-dimethylformamide (200 μ L) and *N*-hydroxysuccinimide hexanoate (18.2 mg, 20 molar equivalents) dissolved in *N,N*-dimethylformamide (500 μ L). Stirring is continued at 0°C for 15 minutes and then at room temperature for 16 hours. The reaction medium is then applied to a Sephadex® G-25 column eluted with 0.2 M sodium chloride. The fractions containing the product are concentrated and desalified using the same column eluted with water. The fractions containing the product are then concentrated under high vacuum to give the desired compound **3** (4 mg, 34%).

Chemical shifts of the anomeric protons (600 MHz, D₂O) δ 5.11 IdoUA^{VIII}, 5.08 Glc^{VII}, 5.14 IdoUA^{VI}, 5.09 Glc^V, 5.13 IdoUA^{IV}, 5.10 Glc^{III}, 5.14 IdoUA^{II}, 4.47 Glc^I

"ESI" method, negative mode: multicharged ion detected m/z 627.6120 [M-4H]⁴⁻ (acid form).

EXAMPLE 4: Pentyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-[(cyclopentylcarbonyl)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-[(cyclopentylcarbonyl)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-[(cyclopentylcarbonyl)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-[(cyclopentylcarbonyl)amino]-2-deoxy-6-O-sodium sulfonato- β -D-glucopyranoside (Compound 4)



To a solution of compound **43** (9 mg, 3.84 μmol) in water (0.3 mL) are added dropwise, at 0°C, *N,N*-dimethylformamide (0.5 mL), diisopropylethylamine (7 μL , 2.6 molar equivalents per free amine) dissolved in *N,N*-dimethylformamide (50 μL) and

5 2,6 molar equivalents per free amine) dissolved in *N,N*-dimethylformamide (50 μL) and *N*-hydroxysuccinimide cyclopentanecarboxylate (6.6 mg, 2 molar equivalents per free amine) dissolved in *N,N*-dimethylformamide (50 μL). Stirring is continued at room temperature for 2 hours, and the same amount of reagent is then added four more times under the same conditions. After a total of 18 hours of stirring at room

10 temperature, the reaction medium is applied to a Sephadex® G-25 column eluted with 0.2 M sodium chloride. The fractions containing the product are concentrated and desalified using the same column eluted with water. The fractions containing the product are then concentrated under high vacuum to give the desired compound **4** (5.6 mg, 55%). In the event of an incomplete reaction, the product obtained may be

15 reused under the same conditions. If necessary, it may be purified by ion-exchange chromatography using a semi-preparative Dionex CarboPac® PA100 column (9 x 250 mm) with a gradient starting from an eluent A to an eluent B, eluent A consisting of a water/acetonitrile mixture (4/1) + 0.01% of dimethyl sulfoxide, and eluent B consisting of a mixture of a 2N sodium chloride solution and acetonitrile (4/1). The fractions

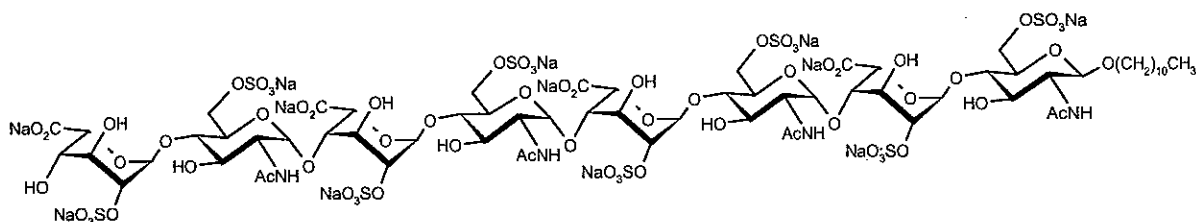
20 containing the product are then concentrated and desalified using a Sephadex® G-25 column eluted with water. The fractions containing the product are then concentrated under high vacuum to give the desired compound **4**.

Chemical shifts of the anomeric protons (600 MHz, D_2O) δ 5.06* IdoUA^{VIII}, 5.05** Glc^{VII}, 5.08* IdoUA^{VI}, 5.03** Glc^V, 5.06* IdoUA^{IV}, 5.05** Glc^{III}, 5.08* IdoUA^{II}, 4.44** Glc^I

25 * and **: The signals may be interchanged.
 $[\alpha]_{\text{D}} 15.4^\circ$ (c 0.25; H_2O).

EXAMPLE 5: Undecyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy-6-O-sodium sulfonato- β -D-glucopyranoside (Compound 5)

30



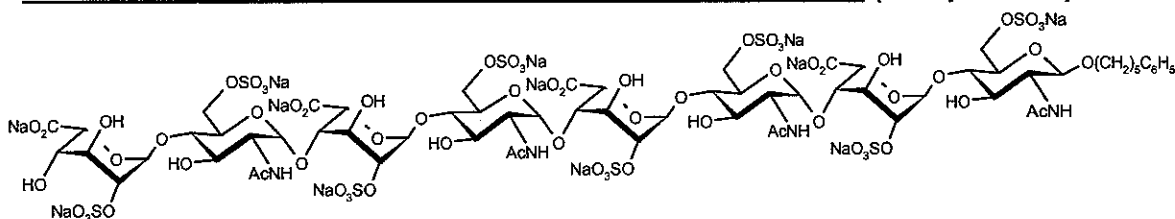
To a saturated aqueous sodium hydrogen carbonate solution (2.3 mL) of compound **52** (32 mg, 13.2 μmol) is added sodium hydrogen carbonate (174 mg, 2.08 mmol), followed by dropwise addition, at 0°C, of acetic anhydride (100 μL, 1.05 mmol). After stirring vigorously for 2.5 hours at 0°C and then for 15 hours at room temperature, the reaction medium is applied to a Sephadex® G-25 column eluted with 0.2 M sodium chloride. The fractions containing the product are concentrated and desalified using the same column eluted with water. The fractions containing the product are then concentrated under high vacuum to give the desired compound **5** (31 mg, 91%).

Chemical shifts of the anomeric protons (500 MHz, D₂O) δ 5.14 IdoUA^{VIII}, 5.13* Glc^{VII}, 5.14** IdoUA^{VI}, 5.13* Glc^V, 5.15** IdoUA^{IV}, 5.13* Glc^{III}, 5.16 IdoUA^{II}, 4.50 Glc^I

* and **: The signals may be interchanged.

[α]_D 18.6° (c 1; H₂O).

EXAMPLE 6: 5-phenylpentyl (sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato-β-D-glucopyranoside (Compound 6)



25

To a saturated aqueous sodium hydrogen carbonate solution (2.7 mL) of compound **53** (36 mg, 14.8 μmol) is added sodium hydrogen carbonate (199 mg, 2.38 mmol), followed by dropwise addition, at 0°C, of acetic anhydride (112 μL, 1.19 mmol). After stirring vigorously for 2.5 hours at 0°C and then for 15 hours at room temperature, the reaction medium is applied to a Sephadex® G-25 column eluted with

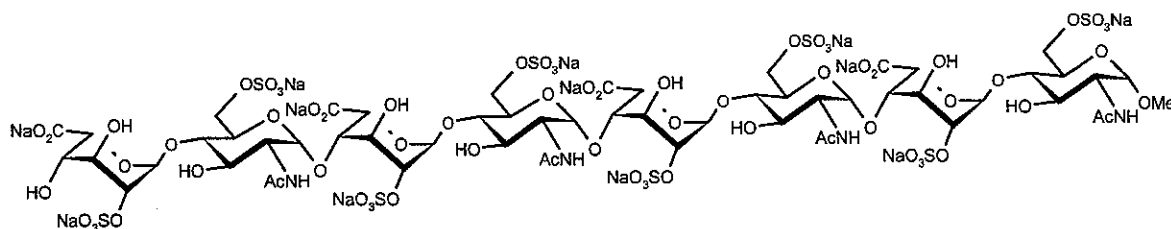
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0.2 M sodium chloride. The fractions containing the product are concentrated and desalified using the same column eluted with water. The fractions containing the product are then concentrated under high vacuum to give the desired compound **6** (25.6 mg, 68%). If necessary, it may be purified by ion-exchange chromatography using a semi-preparative Dionex CarboPac® PA100 column (9 x 250 mm) with a gradient starting from an eluent A to an eluent B, eluent A consisting of a water/acetonitrile mixture (4/1) + 0.01% of dimethyl sulfoxide, and eluent B consisting of a mixture of a 2N sodium chloride solution and acetonitrile (4/1). The fractions containing the product are then concentrated and desalified using a Sephadex® G-25 column eluted with water. The fractions containing the product are then concentrated under high vacuum to give the desired compound **6**.

Chemical shifts of the anomeric protons (500 MHz, D₂O) δ 5.14 IdoUA^{VIII}, 5.12 Glc^{VII}, 5.16 IdoUA^{VI}, 5.12 Glc^V, 5.16 IdoUA^{IV}, 5.12 Glc^{III}, 5.17 IdoUA^{II}, 4.48 Glc^I

"ESI" method, negative mode: multicharged ion detected m/z 579.0867 [M-4H]⁴⁻ (acid form).

EXAMPLE 7: Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-[(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-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-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranoside (Compound 7)



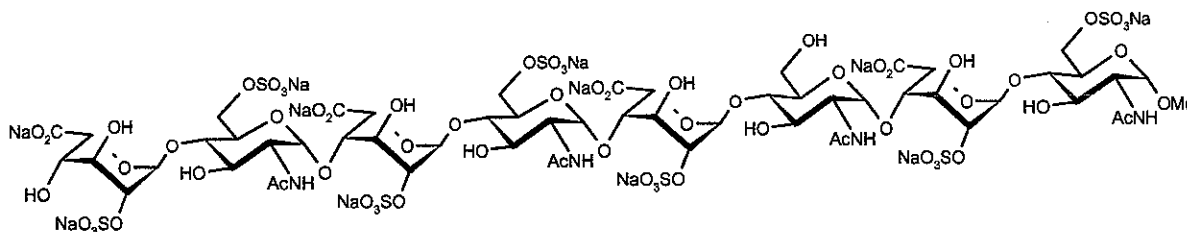
To a solution of compound **77** (10.8 mg, 4.73 μ mol) in saturated sodium hydrogen carbonate solution (472 μ L) are successively added, at 0°C and under an inert atmosphere, solid sodium hydrogen carbonate (64 mg) and acetic anhydride (36 μ L). After stirring for 18 hours at room temperature, the reaction mixture is filtered (Millipore® LSWP 5 μ m filter) and then applied to a column of fine Sephadex® G-25 gel eluted with aqueous 0.2 M NaCl solution. The fractions containing the expected product are pooled and applied to a column of fine Sephadex® G-25 (95 x 2 cm) eluted with water, to give 6.7 mg of compound **7**.

^1H NMR (D_2O) δ of the anomeric protons: 5.20; 5.18 (2 H); 5.17 (2H); 5.16; 5.15; 4.78 ppm.

Mass: "ESI" method, negative mode: theoretical mass = 2453.62; experimental mass: 2453.22 ± 0.17 a.m.u..

5

EXAMPLE 8: Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranoside (**Compound 8**)

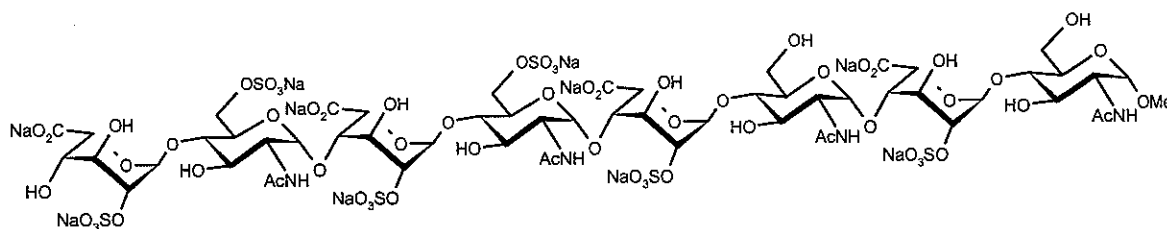


15 Compound **85** (23.0 mg, 11.1 μmol) is treated according to the same procedure as that described for the preparation of compound **7**, to give compound **8** (25.2 mg).

^1H NMR (D_2O) δ of the anomeric protons: 5.45; 5.42 (2 H); 5.22; 5.21; 5.20; 5.18; 5.03 ppm.

20 Mass: "ESI" method, negative mode: theoretical mass = 2249.53; experimental mass: 2249.19 ± 0.18 a.m.u..

EXAMPLE 9: Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy- α -D-glucopyranoside (**Compound 9**)

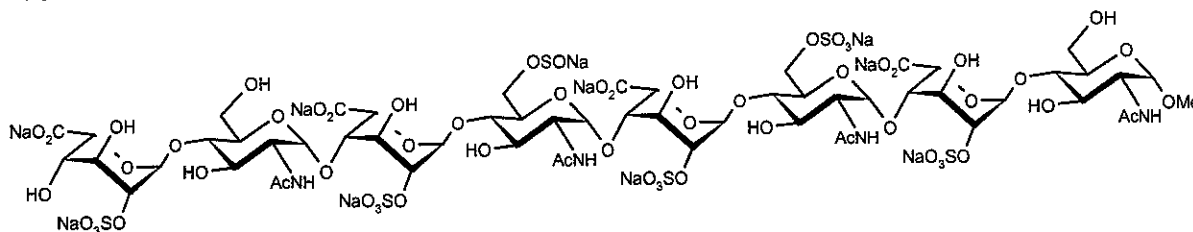


Compound **90** (52.1 mg, 23.9 μmol) is treated according to the same procedure as that described for the preparation of Example 7, to give compound **9** (50.7 mg).

- 5 ^1H NMR (D_2O) δ of the anomeric protons: 5.18; 5.16 (2H); 5.14; 5.15; 5.13; 5.09; 4.75 ppm.

Mass: "ESI" method, negative mode: theoretical mass = 2351.57; experimental mass: 2350.88 ± 0.10 a.m.u.

- 10 **EXAMPLE 10: Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy- α -D-glucopyranoside (Compound 10)**

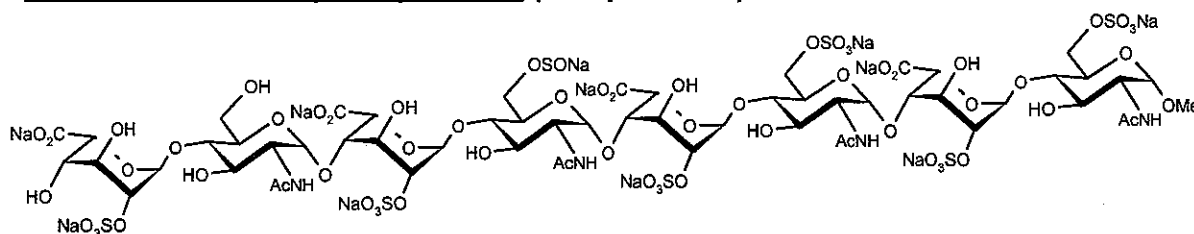


- 20 To a saturated aqueous sodium hydrogen carbonate solution (3.7 mL) of compound **100** (76 mg, 37 μmol) is added sodium hydrogen carbonate (497 mg, 5.92 mmol), followed by dropwise addition, at 0°C , of acetic anhydride (283 μL , 3.0 mmol). After stirring vigorously for 3 hours at 0°C and then for 15 hours at room temperature, the reaction medium is applied to a Sephadex[®] G-25 column eluted with 0.2 M sodium chloride. The fractions containing the product are concentrated and
- 25 desalified using the same column eluted with water. The fractions containing the product are then concentrated under high vacuum to give the desired compound **10** (61 mg, 73%).

Chemical shifts of the anomeric protons (600 MHz, D_2O) δ 5.13 IdoUA^{VIII}, 5.13 Glc^{VII}, 5.15 IdoUA^{VI}, 5.13 Glc^V, 5.16 IdoUA^{IV}, 5.10 Glc^{III}, 5.16 IdoUA^{II}, 4.75 Glc^I

Mass: "ESI" method, negative mode: theoretical mass = 2249.53; experimental mass: 2249.02 ± 0.35 a.m.u.

EXAMPLE 11: Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranoside (**Compound 11**)

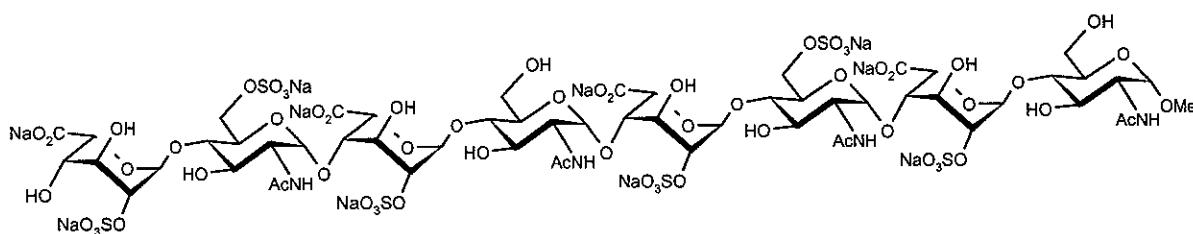


To a saturated aqueous sodium hydrogen carbonate solution (2.6 mL) of compound 105 (56 mg, 26 μ mol) is added sodium hydrogen carbonate (349 mg, 4.16 mmol), followed by dropwise addition, at 0°C, of acetic anhydride (194 μ L, 2.05 mmol). After stirring vigorously for 3 hours at 0°C and then for 15 hours at room temperature, the reaction medium is applied to a Sephadex[®] G-25 column eluted with 0.2 M sodium chloride. The fractions containing the product are concentrated and desalified using the same column eluted with water. The fractions containing the product are then concentrated under high vacuum to give the desired compound 11 (45 mg, 74%).

Chemical shifts of the anomeric protons (600 MHz, D₂O) δ 5.13 IdoUA^{VIII}, 5.12 Glc^{VII}, 5.16 IdoUA^{VI}, 5.12 Glc^V, 5.15 IdoUA^{IV}, 5.13 Glc^{III}, 5.17 IdoUA^{II}, 4.72 Glc^I

Mass: "ESI" method, negative mode: theoretical mass = 2351.57; experimental mass: 2351.13 ± 0.06 a.m.u.

EXAMPLE 12: Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy- α -D-glucopyranoside (**Compound 12**)

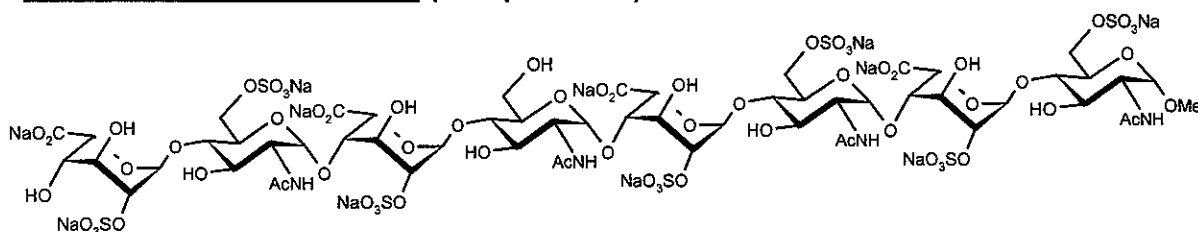


To a saturated aqueous sodium hydrogen carbonate solution (1.4 mL) of compound **113** (29.5 mg, 14 μ mol) is added sodium hydrogen carbonate (188 mg, 2.24 mmol), followed by dropwise addition, at 0°C, of acetic anhydride (105 μ L, 1.12 mmol). After stirring vigorously for 3 hours at 0°C and then for 15 hours at room temperature, the reaction medium is applied to a Sephadex® G-25 column eluted with 0.2 M sodium chloride. The fractions containing the product are concentrated and desalified using the same column eluted with water. The fractions containing the product are then concentrated under high vacuum to give the desired compound **12** (29 mg, 92%).

Chemical shifts of the anomeric protons (600 MHz, D₂O) δ 5.12 IdoUA^{VIII}, 5.06 Glc^{VII}, 5.14 IdoUA^{VI}, 5.11 Glc^V, 5.13 IdoUA^{IV}, 5.09 Glc^{III}, 5.14 IdoUA^{II}, 4.73 Glc^I
 $[\alpha]_D^{25} 115.3^\circ$ (c 0.3; H₂O).

15

EXAMPLE 13: Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranoside (Compound 13)



To a saturated aqueous sodium hydrogen carbonate solution (1.26 mL) of compound **118** (27 mg, 12.6 μ mol) is added sodium hydrogen carbonate (169 mg, 2.02 mmol), followed by dropwise addition, at 0°C, of acetic anhydride (95 μ L, 1.01 mmol). After stirring vigorously for 3 hours at 0°C and then for 16 hours at room temperature, the reaction medium is applied to a Sephadex® G-25 column eluted with 0.2 M sodium chloride. The fractions containing the product are concentrated and

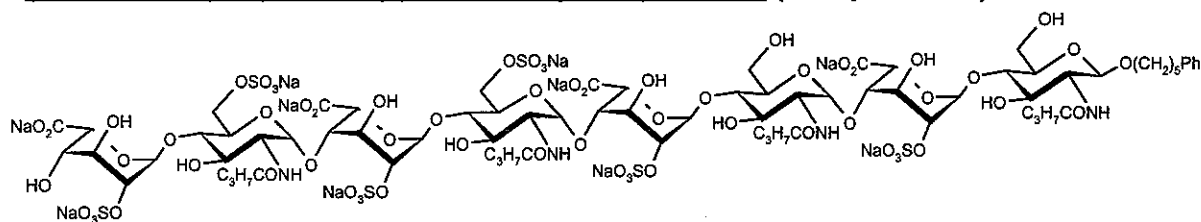
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desalified using the same column eluted with water. The fractions containing the product are then concentrated under high vacuum to give the desired compound **13** (26.5 mg, 89%).

Chemical shifts of the anomeric protons (600 MHz, D₂O) δ 5.12 IdoUA^{VIII}, 5.05 Glc^{VII}, 5.13 IdoUA^{VI}, 5.10 Glc^V, 5.13 IdoUA^{IV}, 5.10 Glc^{III}, 5.14 IdoUA^{II}, 4.72 Glc^I

Mass: "ESI" method, negative mode: theoretical mass = 2351.57; experimental mass: 2350.96 $\pm$ 0.20 a.m.u.

EXAMPLE 14: 5-phenylpentyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-2-(1-oxobutyl)amino- β -D-glucopyranoside (**Compound 14**)



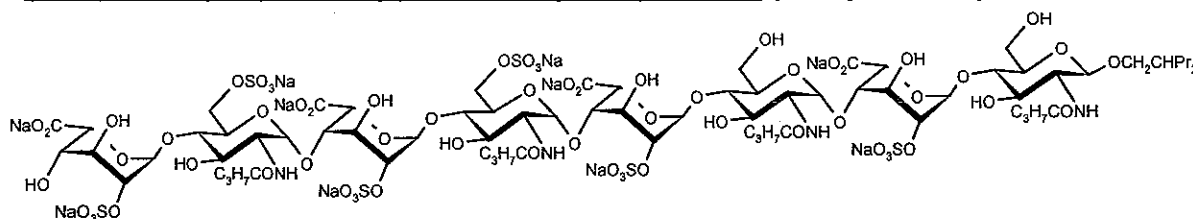
To a solution of compound **171** (126 mg, 56.9 μ mol) in a 7/3 mixture of *N,N*-dimethylformamide/water (12.6 mL) are added dropwise, at 0°C, diisopropylethylamine (148 μ L, 14.9 molar equivalents) dissolved in *N,N*-dimethylformamide (100 μ L), and *N*-hydroxysuccinimide butyrate (116 mg, 11 molar equivalents) dissolved in *N,N*-dimethylformamide (100 μ L). Stirring is continued at room temperature for 3 hours, and the same amount of reagent is then added three times under the same conditions. After a total of 23 hours of stirring at room temperature, the reaction medium is applied to a Sephadex[®] G-25 column eluted with 0.2 M sodium chloride. The fractions containing the product are concentrated and desalified using the same column eluted with water. The fractions containing the product are then concentrated under high vacuum to give the desired compound **14** (133 mg, 93%).

Chemical shifts of the anomeric protons (600 MHz, D₂O) δ 5.07 IdoUA^{VIII}, 4.99 Glc^{VII}, 5.09 IdoUA^{VI}, 5.04 Glc^V, 5.10 IdoUA^{IV}, 5.01 Glc^{III}, 5.06 IdoUA^{II}, 4.38 Glc^I

$[\alpha]_D^{25}$ 50.5° (c 1; H₂O).

EXAMPLE 15: 2-propylpentyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-2-(1-oxobutyl)amino- β -D-glucopyranoside (**Compound 15**)

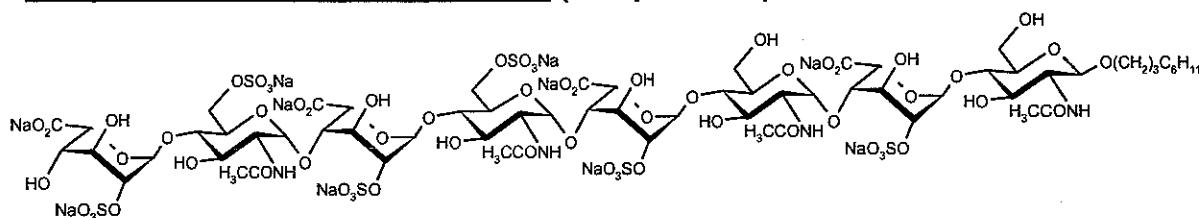
- pyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-2-(1-oxobutyl)amino-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-2-deoxy-2-(1-oxobutyl)amino-β-D-glucopyranoside (**Compound 15**)



Compound **172** (47 mg, 22 μmol) is treated according to a protocol similar to that described for the synthesis of **14**, to give compound **15** (46 mg, 85%).

- Chemical shifts of the anomeric protons (600 MHz, D₂O) δ 5.33 IdoUA^{VIII}, 5.30 Glc^{VII}, 5.35 IdoUA^{VI}, 5.24 Glc^V, 5.36 IdoUA^{IV}, 5.27 Glc^{III}, 5.32 IdoUA^{II}, 4.63 Glc^I [α]_D 60° (c 1; H₂O).

- EXAMPLE 16:** 3-cyclohexylpropyl (sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-2-acetamido-6-O-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-2-acetamido-6-O-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-2-acetamido-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-2-deoxy-2-acetamido-β-D-glucopyranoside (**Compound 16**)

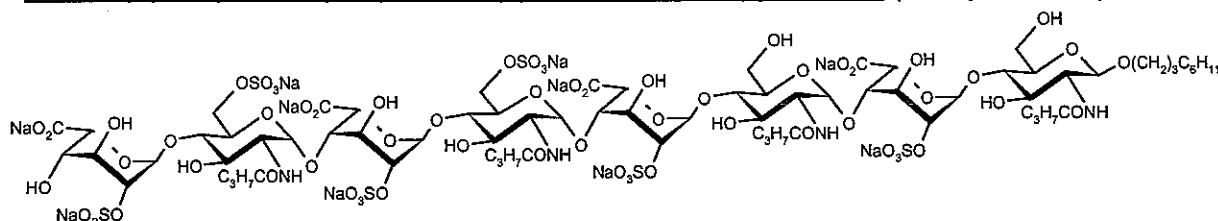


Compound **172** (10 mg, 4.56 μmol) is treated according to a protocol similar to that described for the synthesis of **13**, to give compound **16** (8.8 mg, 82%).

- Chemical shifts of the anomeric protons (600 MHz, D₂O) δ 5.15 IdoUA^{VIII}, 5.08 Glc^{VII}, 5.17 IdoUA^{VI}, 5.13 Glc^V, 5.17 IdoUA^{IV}, 5.11 Glc^{III}, 5.16 IdoUA^{II}, 4.50 Glc^I [α]_D +40.9° (c 0.88; H₂O).

- EXAMPLE 17:** 3-cyclohexylpropyl (sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-2-deoxy-2-(1-oxobutyl)amino-β-D-glucopyranoside (**Compound 17**)

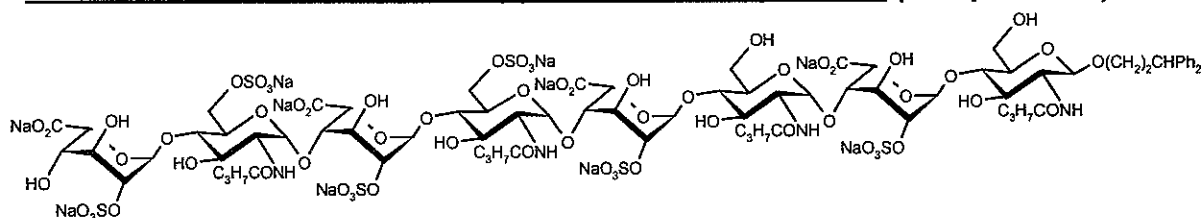
- glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-
 (2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-
 (sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-2-(1-oxobutyl)-
 amino-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyl-
 uronate)-(1→4)-2-deoxy-2-(1-oxobutyl)amino-β-D-glucopyranoside (**Compound 17**)



Compound **173** (10 mg, 4.56 μmol) is treated according to a protocol similar to that described for the synthesis of **14**, to give compound **17** (7.7 mg, 69%).

- Chemical shifts of the anomeric protons (600 MHz, D₂O) δ 5.23 IdoUA^{VIII}, 5.20 Glc^{VII}, 5.25 IdoUA^{VI}, 5.15 Glc^V, 5.26 IdoUA^{IV}, 5.17 Glc^{III}, 5.22 IdoUA^{II}, 4.57 Glc^I
 [α]_D +53.8° (c 0.77; H₂O).

- EXAMPLE 18:** 3,3-diphenylpropyl (sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-(2-deoxy-2-(1-oxobutyl)amino-α-D-glucopyranosyl)-(1→4)-(sodium 2-O-sodium sulfonato-α-L-idopyranosyluronate)-(1→4)-2-deoxy-2-(1-oxobutyl)amino-β-D-glucopyranoside (**Compound 18**)

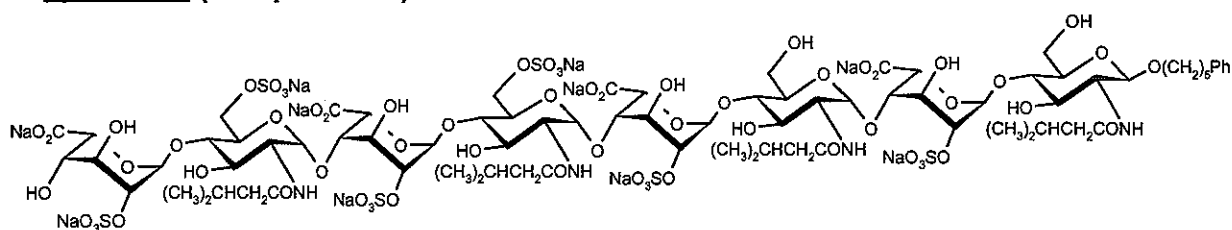


- To a solution of compound **174** (5.5 mg, 2.4 μmol) in a 2/1 mixture of *N,N*-dimethylformamide/water (4.8 mL) are added dropwise, at 0°C, diisopropylethylamine (63 μL, 15 molar equivalents) dissolved in *N,N*-dimethylformamide (43 μL), and *N*-hydroxysuccinimide butyrate (49 mg, 11 molar equivalents) dissolved in *N,N*-dimethylformamide (43 μL). Stirring is continued at room temperature for 3 hours, and the same amount of reagent is then added three times under the same conditions. After a total of 24 hours of stirring at room temperature, the reaction medium is applied to a Sephadex[®] G-25 column eluted with 0.2 M sodium chloride. The fractions containing

the product are concentrated and desalified using the same column eluted with water. The fractions containing the product are then concentrated under high vacuum to give the desired compound **18** (6 mg, 98%).

- Chemical shifts of the anomeric protons (600 MHz, D₂O) δ 5.22 IdoUA^{VIII}, 5.19 Glc^{VII}, 5.23 IdoUA^{VI}, 5.13 Glc^V, 5.23 IdoUA^{IV}, 5.17 Glc^{III}, 5.20 IdoUA^{II}, 4.48 Glc^I
 5 [α]_D +24° (c 0.48, H₂O).

EXAMPLE 19: 5-phenylpentyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(3-methyl-1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(3-methyl-1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(3-methyl-1-oxobutyl)amino- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-2-(3-methyl-1-oxobutyl)amino- β -D-glucopyranoside (Compound 19)



- A solution of compound **171** (84 mg, 37.8 μ mol) in a 7/3 mixture of *N,N*-dimethylformamide/water (8.4 mL) is treated with 1-[(3-methylbutanoyl)oxy] pyrrolidine-2,5-dione according to a process similar to the synthesis of compound **14**, to give the desired compound **19** (41.8 mg, 43%). If necessary, it may be purified by ion-exchange chromatography using a semi-preparative Dionex CarboPac[®] PA100 column (9 x 250 mm) with a gradient starting from an eluent A to an eluent B, eluent A consisting of a water/acetonitrile mixture (4/1) + 0.01% of dimethyl sulfoxide, and eluent B consisting of a mixture of a 2N sodium chloride solution and acetonitrile (4/1). The fractions containing the product are then concentrated and desalified using a Sephadex[®] G-25 column eluted with water. The fractions containing the product are then concentrated under high vacuum to give the desired pure compound **19**.

- Chemical shifts of the anomeric protons (600 MHz, D₂O) δ 5.23 IdoUA^{VIII}, 5.19 Glc^{VII}, 5.24 IdoUA^{VI}, 5.13 Glc^V, 5.25 IdoUA^{IV}, 5.17 Glc^{III}, 5.22 IdoUA^{II}, 4.55 Glc^I

"ESI" method, negative mode: multicharged ion detected m/z 581.3517 [M-4H]⁴⁻ (acid form).

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.

5 **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 µl 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
10 at 37°C.

Human venous endothelial cells (HUVEC ref: C-12200 - Promocell) are seeded onto the biological matrix at 7800 cells/well in 120 µl of EBM® medium (Endothelial Basal Medium, Lonza C3121) + 2% FCS (foetal calf serum - Lonza) + hEGF
15 (Recombinant Human Epidermal Growth Factor - Lonza) 10 µg/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
20 software).

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 2 are active at 10⁻¹¹ M.

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
30 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 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, Cellspon® ref. 0501)

impregnated with 50 µl of sterile solution containing the test product. The incision is then sutured and cleaned with Hexomedine®.

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
5 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 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
10 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). 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
15 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 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
20 value (± sem) for each group. The differences between the groups are tested with an ANOVA followed by a Dunnett test on the square 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. For example, compounds 1 and 2 are active at 45 ng/site, and compound 7 is active at 15 ng/site.

25 For comparative purposes relative to a compound analogous to compound 7 according to the invention, but in which all the -NH-acyl groups are replaced with -NH-SO₃- groups, compound 7 according to the invention has in this test an activity of greater than 21% relative to the said fully sulfated analogue, which shows the importance of the N-acyl groups in the compounds according to the invention.

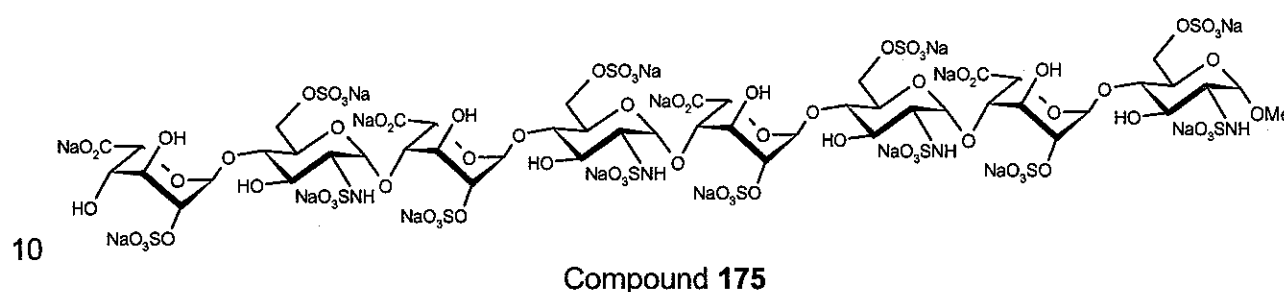
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Pharmacokinetics

The pharmacokinetic profile of the compounds according to the invention is evaluated after cutaneous administration, to OF1 or C57/BL6 mice, at a concentration of 30 mg/kg. The systemic exposure of the compounds is evaluated after a single
35 administration to the animal anaesthetized beforehand with pentobarbital. The blood is

collected from the vena cava and then transferred into plastic tubes containing lithium heparin. After centrifugation (2000×g for 10 minutes at 8°C), the concentration of the compounds in the plasma is quantified by LC/MS-MS.

In general, the test compounds have an improved pharmacokinetic profile (especially higher AUC and plasmatic concentration, and longer half-lives) relative to fully sulfated analogous compounds (replacement of the N-acyl groups with –NH–SO₃– groups). By way of example, the pharmacokinetic parameters of compounds **1**, **6** and **7** according to the invention are described in the table that follows, in comparison with a fully sulfated analogue No. **175** having the following formula:



Compound	AUC (0-tlast) (ng.h/mL)	T _{1/2} (h)	Plasma conc., t = 4h (ng/mL)
No. 1	18 000	1	924
No. 6	95 000	0.46	5740
No. 7	22 000	0.40	425
No. 175	15 000	0.33	20

. AUC (0-tlast): Area under the curve between time 0 (compound administration start time) and tlast (the time of the last measurement).

15 . T_{1/2} (h): half-life time

. Plasma conc., t = 4h: Plasmatic concentration at 4 hours

20 These results show the importance of the N-acyl groups in the compounds according to the invention, which make them particularly suitable for use as medicaments.

It emerges from the foregoing that the compounds according to the invention have agonist activity on the FGF receptors and activity on angiogenesis, and also on post-ischaemic revascularization. The compounds according to the invention 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

25

are useful in pathologies requiring activation of angiogenesis post-ischaemic revascularization.

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

These medicaments find their use in therapy, especially in the treatment of ischaemia (cardiac ischaemia, arterial ischaemia of the lower limbs), the treatment of
10 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 endoarterectomy, the treatment of cicatrization, muscle regeneration treatment, treatment for the survival of myoblasts, the treatment of peripheral neuropathy, the
15 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
20 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 cartilage repairing, treatment for repairing and protecting bones, treatment for repairing and protecting hair follicles and for protecting and regulating hair growth.

25

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
30 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 cardiology using
35 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 growth factor for advanced arteriosclerotic disease. Trends Cardiovasc. Med. 13, 116-22, 2003).

5 One of the applications of the compounds of the invention is post-ischaemic treatment after heart occlusion or occlusion of the peripheral arteries. 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
10 patients undergoing coronary bypass surgery: results of a phase I randomized, double-blind, placebo-controlled trial. 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
15 two patients required vascular surgery. Interestingly, the therapeutic benefit 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
20 performed during treatment of narrowing of the coronary arteries (Laham, R. J. 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,
25 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 intracoronary 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
30 the treatment of diseases associated with narrowing of the coronary arteries and especially in the treatment of angina pectoris.

 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
35 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
5 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.

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
10 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.

Peripheral neuropathy is an axonal or demyelinating attack of the motor and/or
15 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
20 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.

25

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
30 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
35 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.

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.

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.

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 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, 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.

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 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 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, 1-13, 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 fetus. 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.

20

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

30

According to another of its aspects, the present invention relates to pharmaceutical compositions comprising, as active principle, a compound according to the invention. These pharmaceutical compositions contain an effective dose of at least one compound according to the invention, or a pharmaceutically acceptable salt of the said compound, and also at least one pharmaceutically acceptable excipient. The said

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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.

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 of formula (I)/(I') 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 prevention or treatment of the above disorders or diseases.

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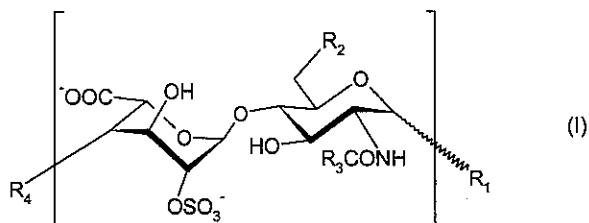
The appropriate unit administration forms include oral forms such as tablets, soft or hard gel capsules, powders, granules and oral solutions or suspensions, sublingual, buccal, intratracheal, intraocular, intranasal or inhalation administration forms, topical, transdermal, subcutaneous, intramuscular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

The injectable administration forms are particularly advantageous, conventionally comprising the active compound dissolved in water for injection, in the presence of
20 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.

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

CLAIMS

1. Octasaccharide compounds corresponding to formula (I):



5 in which:

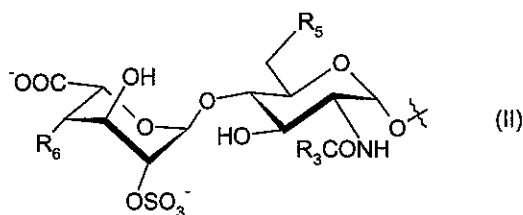
- the wavy line denotes a bond located either below or above the plane of the pyranose ring of the glucosamine unit,

- R_1 represents a group O-alkyl, in which the said alkyl group comprises from 1 to 16 carbon atoms and is optionally substituted with one or more groups, which may be identical or different, chosen from aryl and cycloalkyl groups,

- R_2 represents either a group OSO_3^- or a hydroxyl group,

- R_3 represents an alkyl, cycloalkyl or alkyl-cycloalkyl group, and

- R_4 represents a disaccharide of formula (II):

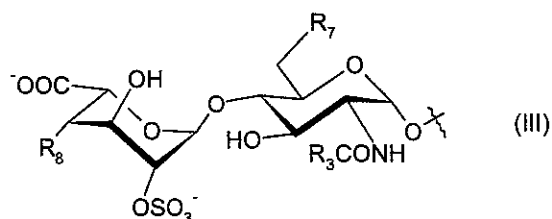


15 in which:

- R_3 is as defined above,

- R_5 represents either a group OSO_3^- or a hydroxyl group, and

- R_6 represents a disaccharide of formula (III):

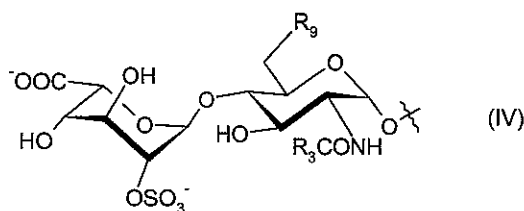


20 in which:

- R_3 is as defined above,

- R_7 represents either a group OSO_3^- or a hydroxyl group, and

- R_8 represents a disaccharide of formula (IV):



in which:

- R_3 is as defined above,
- R_9 represents either a group OSO_3^- or a hydroxyl group,

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

2. Compounds according to Claim 1, in which R_1 represents:

- either a group O-alkyl, in which the said alkyl group comprises from 5 to 16 carbon atoms,
- 10 - or a group O-alkyl, in which the said alkyl group comprises from 1 to 8 carbon atoms and is substituted with 1 or 2 groups, which may be identical or different, chosen from aryl and cycloalkyl groups.

3. Compounds according to Claim 1 or Claim 2, in which R_1 represents a group
15 O-alkyl, in which the said alkyl group comprises from 5 to 12 carbon atoms.

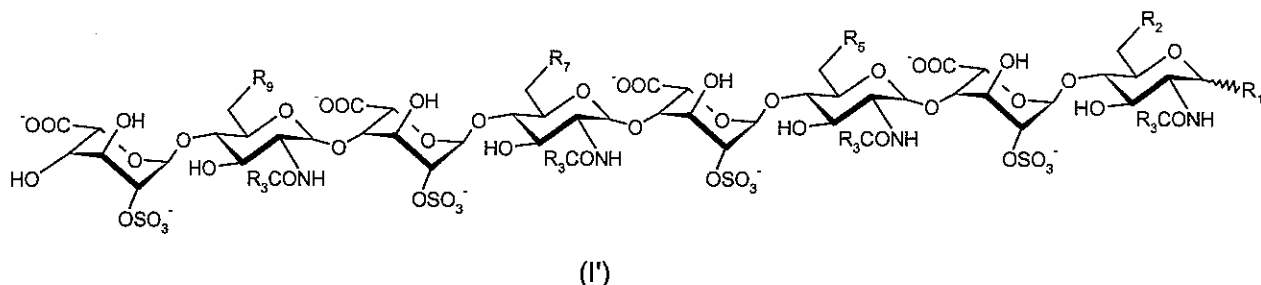
4. Compounds according to any one of Claims 1 to 3, in which R_1 represents a group O-alkyl, in which the said alkyl group comprises from 3 to 6 carbon atoms and is substituted with 1 or 2 groups, which may be identical or different, chosen from phenyl
20 and cycloalkyl groups.

5. Compounds according to any one of Claims 1 to 4, in which R_3 represents either an alkyl group comprising from 2 to 6 carbon atoms, or a cycloalkyl group.

25 6. Compounds according to any one of Claims 1 to 5, in which at least one of the groups R_2 , R_5 , R_7 and R_9 represents a hydroxyl group.

7. Compounds according to any one of Claims 1 to 6, in which at least one of the groups R_2 , R_5 , R_7 and R_9 represents a hydroxyl group and at least one of the groups R_2 ,
30 R_5 , R_7 and R_9 represents a group OSO_3^- .

8. Compounds according to any one of Claims 1 to 7, characterized in that they correspond to formula (I'), in which R₁, R₂, R₃, R₅, R₇ and R₉ are as defined in any one of Claims 1 to 7:



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9. Compounds according to any one of Claims 1 to 8, chosen from the following compounds:

- Pentyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy-6-O-sodium sulfonato- β -D-glucopyranoside (**No. 1**);
- Pentyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- β -D-glucopyranoside (**No. 2**);
- Pentyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxohexyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxohexyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxohexyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-2-(1-oxohexyl)amino-6-O-sodium sulfonato- β -D-glucopyranoside (**No. 3**);
- Pentyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-

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[(cyclopentylcarbonyl)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-[(cyclopentylcarbonyl)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-[(cyclopentylcarbonyl)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-[(cyclopentylcarbonyl)amino]-2-deoxy-6-O-sodium sulfonato- β -D-glucopyranoside (**No. 4**);

- Undecyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy-6-O-sodium sulfonato- β -D-glucopyranoside (**No. 5**);

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

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

- Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranoside (**No. 8**);

- Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranoside (**No. 9**);

- Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy- α -D-glucopyranoside (**No. 10**);

15 - Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-
acetamido-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-
idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-
acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-
20 sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranoside (**No. 11**);

25 - Methyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy- α -D-glucopyranoside (**No. 12**);

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

sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy-6-O-sodium sulfonato- α -D-glucopyranoside (**No. 13**);

- 5-phenylpentyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-
 5 (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-2-(1-oxobutyl)amino- β -D-glucopyranoside (**No. 14**);

10 - 2-propylpentyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-
 (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-2-(1-oxobutyl)amino- β -D-glucopyranoside (**No. 15**);

- 3-cyclohexylpropyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-acetamido-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-acetamido-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-acetamido- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-2-acetamido- β -D-glucopyranoside (**No. 16**);

- 3-cyclohexylpropyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-
 25 (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-2-(1-oxobutyl)amino- β -D-glucopyranoside (**No. 17**);

- 3,3-diphenylpropyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-
 (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-

oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(1-oxobutyl)amino- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-2-(1-oxobutyl)amino- β -D-glucopyranoside (**No. 18**); and

- 5 - 5-phenylpentyl (sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(3-methyl-1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(3-methyl-1-oxobutyl)amino-6-O-sodium sulfonato- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-(2-deoxy-2-(3-methyl-1-oxobutyl)amino- α -D-glucopyranosyl)-(1 $\rightarrow$ 4)-(sodium 2-O-sodium sulfonato- α -L-idopyranosyluronate)-(1 $\rightarrow$ 4)-2-deoxy-2-(3-methyl-1-oxobutyl)amino- β -D-glucopyranoside (**No. 19**).

- 10 10. Medicament, characterized in that it comprises a compound according to any one of Claims 1 to 9, or a pharmaceutically acceptable salt thereof.

- 20 11. Pharmaceutical composition, characterized in that it comprises a compound according to any one of Claims 1 to 9, or a pharmaceutically acceptable salt thereof, and also at least one pharmaceutically acceptable excipient.

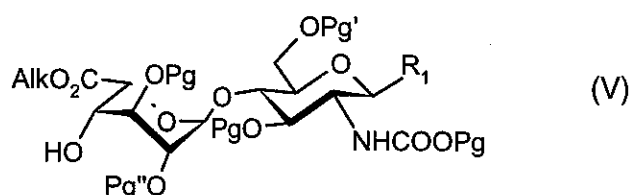
12. Compound according to any one of Claims 1 to 9, for its use in the treatment of pathologies requiring activation of the FGF receptors.

- 25 13. Compound according to Claim 12, for its use in the treatment of pathologies requiring angiogenesis activation and post-ischaemic revascularization.

- 30 14. Compound according to Claim 12 or Claim 13, 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 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 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.

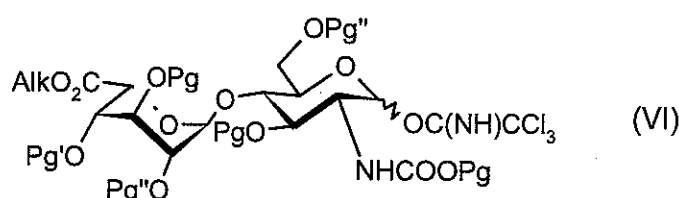
15. Compound of formula (V), in which Alk represents an alkyl group, R_1 is as defined in any one of Claims 1 to 4, and Pg, Pg' and Pg'', which may be identical or different, represent protecting groups:



16. Compound according to Claim 15, in which Pg, Pg' and Pg'' represent, respectively, benzyl, tBDPS and acetyl groups, Alk represents a methyl group and R_1 is as defined in any one of Claims 1 to 4.

17. Compound according to Claim 15 or 16, in which Pg, Pg' and Pg'' represent, respectively, benzyl, tBDPS and acetyl groups, Alk represents a methyl group and R_1 is chosen from the following groups: -O-methyl, -O-(CH₂)₅-phenyl, -O-CH₂-CH(C₃H₇)₂, -O-(CH₂)₃-C₆H₁₁ and -O-(CH₂)₂-CH(phenyl)₂.

18. Compound of formula (VI), in which Alk represents an alkyl group and Pg, Pg' and Pg'', which may be identical or different, represent protecting groups:



19. Compound according to Claim 18, in which Alk represents a methyl group and Pg, Pg' and Pg'' represent, respectively, benzyl, levulinyl and acetyl groups.