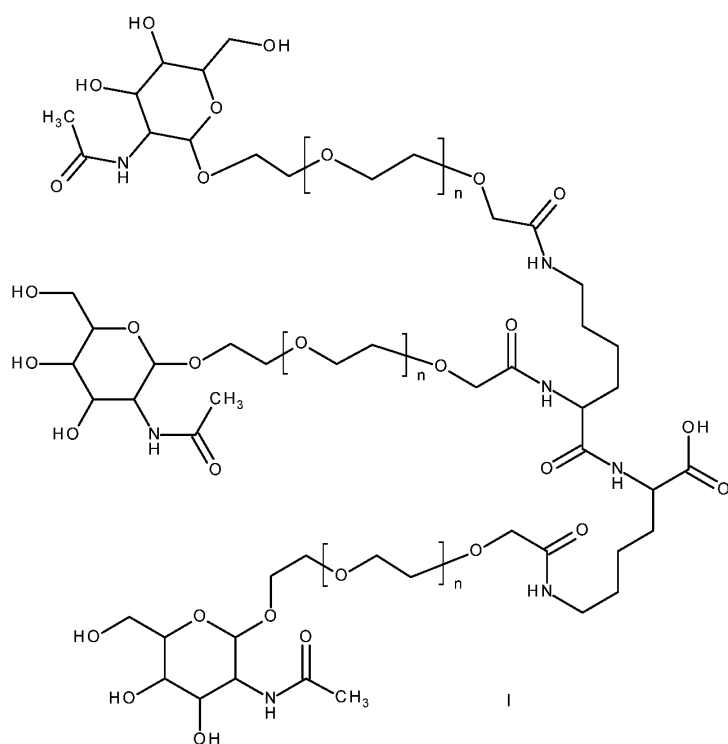


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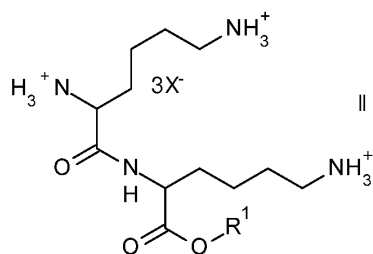
Claims:

1. Process for the preparation of GalNAc acid derivatives of the formula I

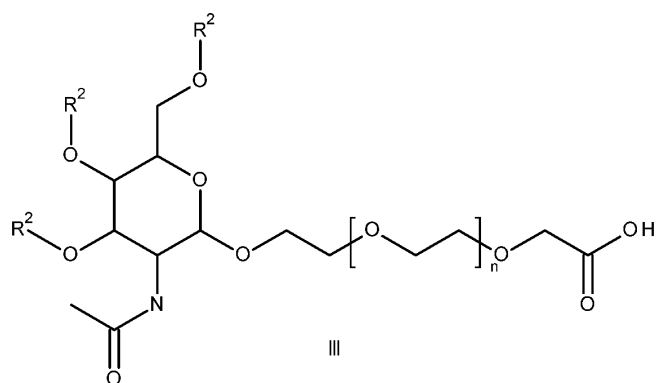


5 wherein n is an integer between 0 and 10 and its salts, corresponding enantiomers and/ or optical isomers thereof, comprising

a) the coupling of a triamine salt of formula II

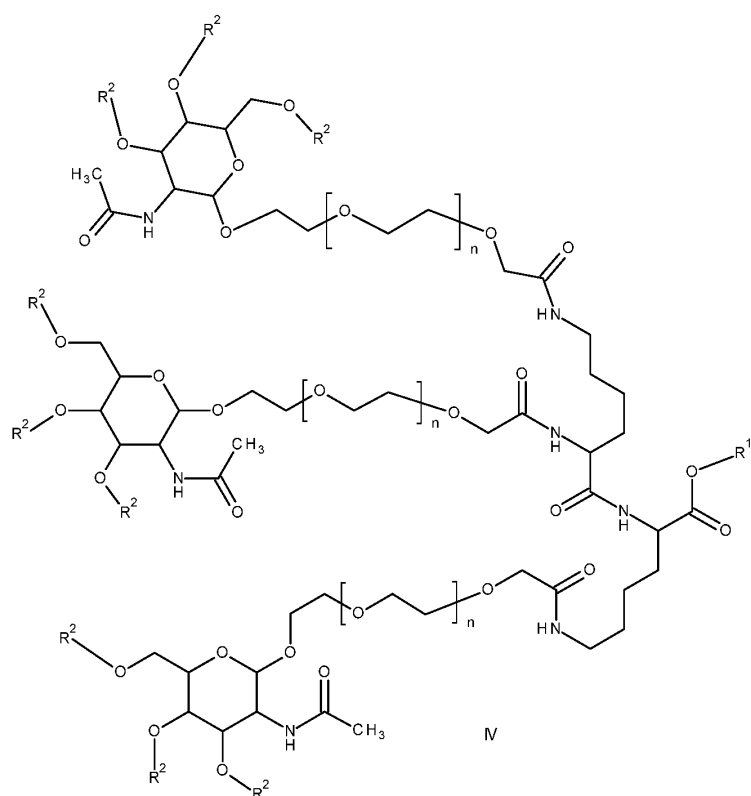


wherein R¹ is an ester protecting group and X is an anion of an acid with a tetrahydropyran acid of formula III



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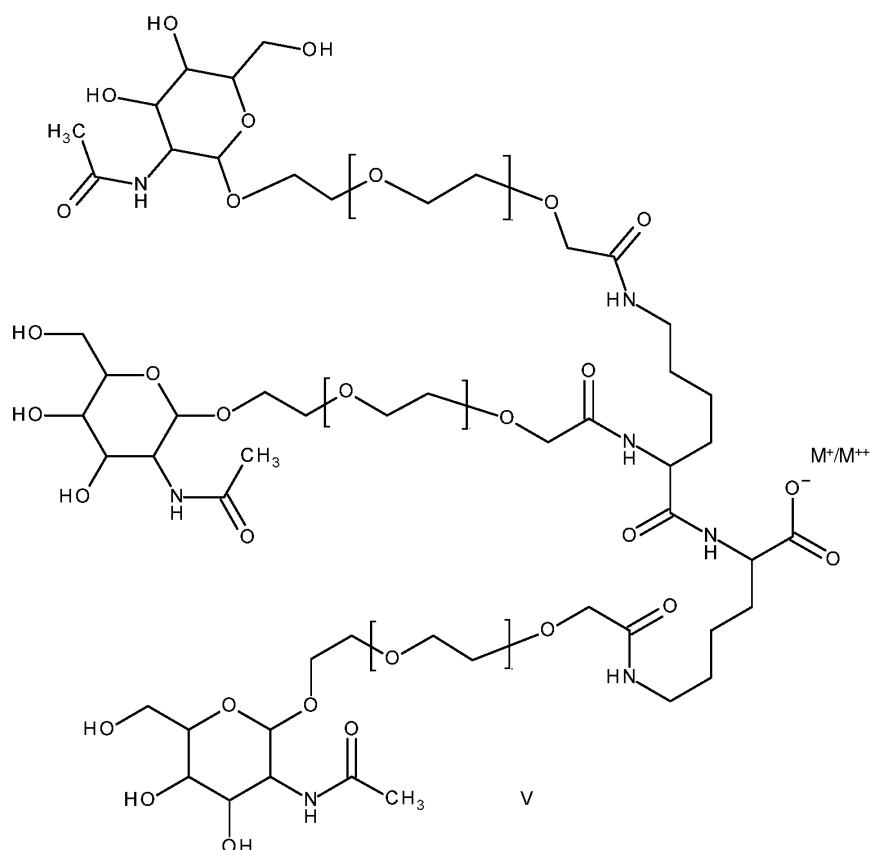
wherein R² is a hydroxy protecting group and n is as above in the presence of a peptide coupling agent, an amine base and an organic solvent to form the GalNAc ester of formula IV



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wherein R^1 and R^2 and n are as above;

b) the removal of the ester protecting group R^1 and of the hydroxy protecting groups R^2 in the presence of a mineral base to form the GalNAc acid salt of formula V



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wherein n is as above and M is a metal kation;

and

c) optionally to transform GalNAc acid salt of formula V into the GalNAc acid derivative
10 of formula I.

2. Process of claim 1, wherein n is an integer between 0 and 5 and the ester protecting group R^1 is C_{1-7} -alkyl or phenyl- C_{1-7} -alkyl, wherein the phenyl group is optionally substituted with

halogen or C₁₋₇-alkyl, the hydroxy protecting group R² is acetyl and X is selected from the anion of a sulfonic acid.

3. Process of any one of claims 1 or 2, wherein the peptide coupling agent is n-propylphosphonic acid anhydride and the amine base is a tertiary amine.

5 4. Process of any one of claim 1 to 3, wherein the coupling in step a) takes place in an organic solvent is a polar aprotic solvent at a reaction temperature from 20°C to 70°C.

5. Process of any one of claims 1 to 4, wherein the mineral base for the removal of the ester protecting group R¹ in step b) is an alkali hydroxide.

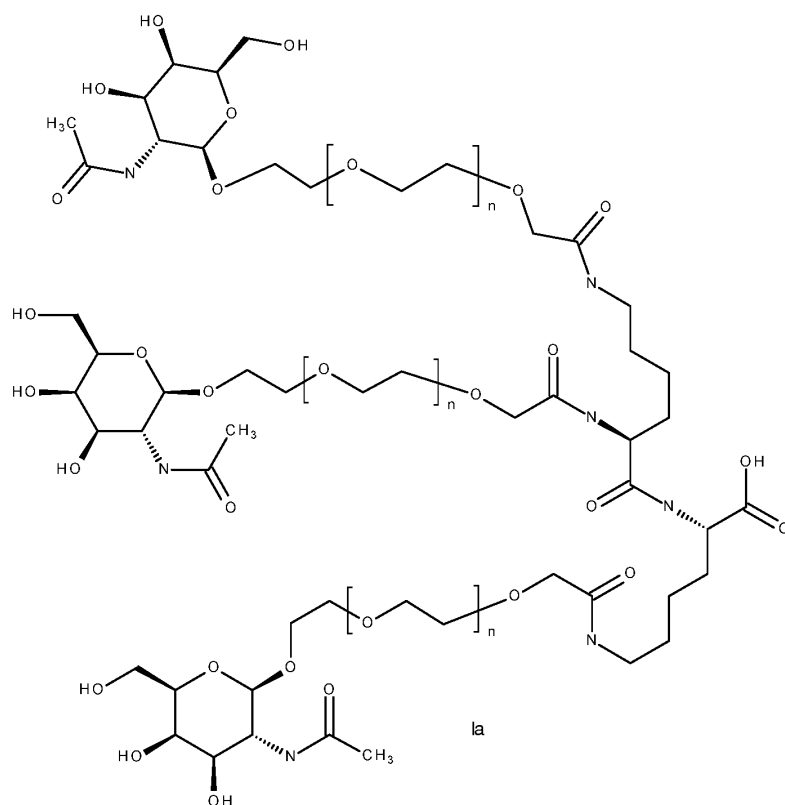
10 6. Process of any one of claims 1 to 5, wherein the step a) and b) are combined and performed in one step without isolating the GalNAc ester of formula V.

7. Process of any one of claims 1 to 6, wherein the optional transformation of the GalNAc acid salt of formula V into the GalNAc acid derivative of formula I is performed via kation exchange or via treatment with an acid.

15 8. Process of any one of claims 1 to 7, wherein the GalNAc acid derivative of formula I is an enantiomer of the formula Ia

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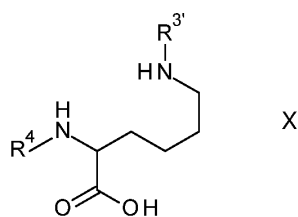
AND Enantiomer



wherein n is as above or a salt, a corresponding enantiomer and/or optical isomer thereof.

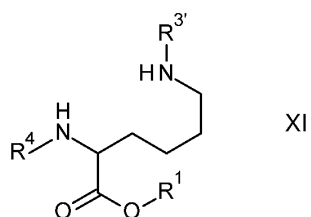
9. Process of claim 1 wherein the process for producing the triamine of formula II comprises the steps

5 a1) transforming the carboxylic acid of formula X



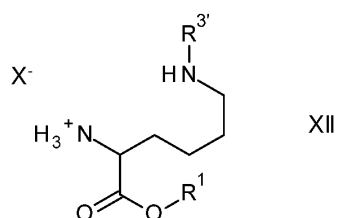
wherein $R^{3'}$ and R^4 are different and independent of each other are amino protecting groups into an ester of formula XI

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wherein R^1 is an ester protecting group and $R^{3'}$ and R^4 are as above;

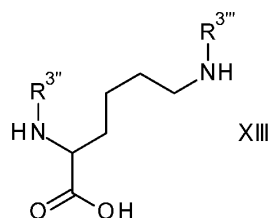
b1) removing the amino protecting group R^4 and subsequent forming an amine salt of formula XII



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wherein R^1 and $R^{3'}$ are as above and X^- is an acid anion;

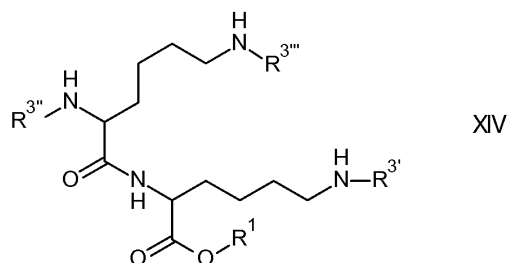
c1) coupling the amine salt of formula XII with a hexanoic acid derivative of formula XIII



wherein $R^{3''}$ and $R^{3'''}$ are amino protecting groups to form the protected triamine of formula XIV

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wherein $R^{3'}$, $R^{3''}$, $R^{3'''}$ and R^1 are as above;

d1) converting the protected triamine of formula XIV with an acid into the triamine salt of formula II.

5 10. Process of claim 9, wherein $R^{3'}$, $R^{3''}$ and $R^{3'''}$ are the same and protecting groups which are cleavable under acidic conditions and R^4 is a protecting group which is cleavable under basic conditions or by way of hydrogenolysis.

11. Process of claim 10, wherein $R^{3'}$, $R^{3''}$ and $R^{3'''}$ are Boc and R^4 is Fmoc.

10 12. Process of any one of claims 9 to 11, wherein the transformation in step a1) takes place with benzyl alcohol in the presence of an activating agent, an amine catalyst and an aprotic organic solvent at a reaction temperature of 20°C to 50°C.

13. Process of any one of claims 9 to 11, wherein the amino protecting group R^4 is Fmoc and its removal in step b1) is performed with a secondary aliphatic amine in a polar aprotic solvent at a reaction temperature of 20°C to 50°C.

15 14. Process of any one of claims 9 to 11, wherein the subsequent formation of the amine salt of formula XII in step b1) is effected with a sulfonic acid.

15. Process of any one of claims 9 to 11, wherein the coupling in step c1) is performed with n-propylphosphonic acid anhydride as coupling agent in the presence of a tertiary amine and a polar aprotic solvent at a reaction temperature from 20°C to 50°C.

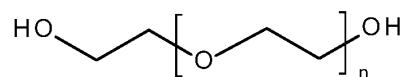
20 16. Process of any one of claims 9 to 11, wherein in step d1) the triamine salt of formula II is formed with a sulfonic acid in a polar aprotic solvent at a reaction temperature of 20°C to 80°C.

17. Process of claim 16, wherein a polar aprotic solvent is selected which prevents the triamine salt of formula II to crystallize.

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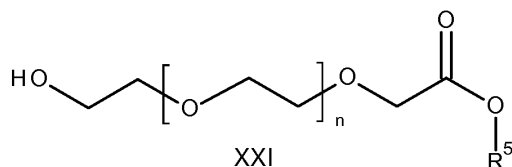
18. Process of claim 1, wherein the process for producing the tetrahydropyran acid of formula III comprises

a2) the transformation of the diol of formula XX



XX

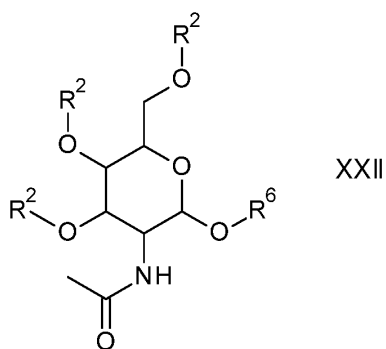
5 wherein n is as above into the alcohol ester of formula XXI



XXI

wherein n is as above and R⁵ is an ester protecting group;

b2) the coupling of the alcohol ester of formula XXI with a tetrahydropyran derivative of formula XXII

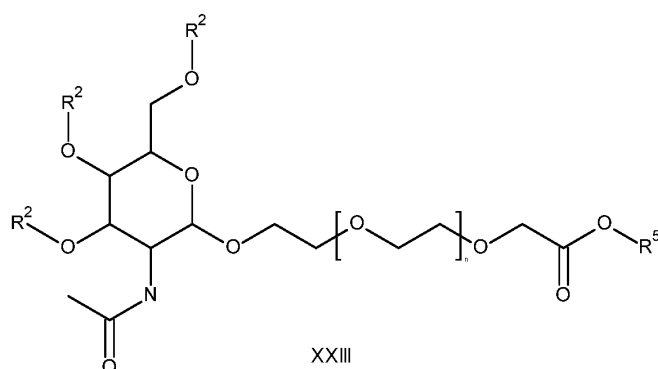


XXII

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wherein R² and R⁶ independent of each other are hydroxy protecting groups to form a tetrahydropyran ester of formula XXIII

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wherein n, R² and R⁵ are as above ;

c2) the removal of the ester group to form the tetrahydropyran acid of formula III.

- 5 19. Process of claim 18, wherein the hydroxy protecting group R² is acetyl, the ester protecting group R⁵ is benzyl and the hydroxy protecting group R⁶ is acetyl.

20. Process of claims 18 or 19, wherein in a first step of step a2) the diol of formula XX is deprotonated with an alkali metal alcoholate in the presence of a polar protic or polar aprotic solvent at a reaction temperature from 50°C to 120°C.

- 10 21. Process of claims 18 or 19, wherein in a second step of step a2) an acetic acid moiety is introduced with a halogen acetic acid or with a salt thereof in the presence of a polar protic or polar aprotic solvent at a reaction temperature from 50°C to 120°C.

22. Process of claims 18 or 19, wherein in a third step of step a2) the alcohol ester of formula XXI wherein R⁵ is benzyl is formed with a benzyl halogenide or a benzyl sulfonylester in a polar aprotic solvent at a reaction temperature from 20°C to 120°C.
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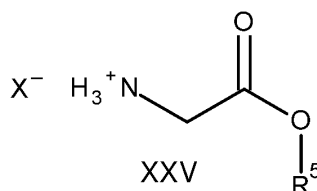
23. Process of claim 18 or 19, wherein in step b2) the alcohol ester of formula XXI is coupled with the tetrahydropyran derivative of formula XXII in the presence of a halogenated sulfonic acid in the presence of a polar aprotic solvent at a reaction temperature from 0°C to 140°C.

- 20 24. Process of claim 18 or 19, wherein in step c2) the benzylester group is removed by a catalytic hydrogenation with hydrogen in the presence of a hydrogenation catalyst.

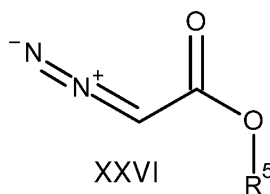
25. Process of claim 18, wherein the formation of the alcohol ester of formula XXI comprises

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a3) the diazotization of an 2-amino acetate of formula XXV



wherein R^5 is as above and X is a halogen atom with a nitrite salt to form the 2-diazo compound of formula XXVI



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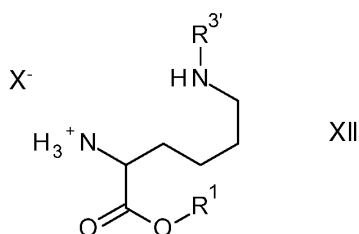
wherein R^5 is as above; and

b3) the transformation of the 2-diazo compound of formula XXVI with the diol of formula XX.

26. Process of claim 25, wherein the diazotization in step a3) is performed with an alkali nitrite in the presence of a solvent mixture of water and a non-polar aprotic solvent at a reaction temperature of -10°C to 10°C .

27. Process of claim 25 or 26, wherein the transformation of the 2-diazo compound with the diol of formula XX in step b3) is performed in the presence of a Lewis acid and a non-polar aprotic solvent at a reaction temperature of -10°C to 10°C .

28. Amine salt of formula XII



wherein R^1 and $R^{3'}$ are amine protecting groups and X^- is anion of an acid.

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29. Amine salt of claim 28, wherein R¹ is benzyl, R^{3'} is Boc and X is the anion of methanesulfonic acid.

30. Use of the process of claims 1 to 27 in a process for the preparation of GalNAc oligonucleotide conjugates.

5 31. Process for the preparation of GalNAc oligonucleotide conjugates comprising the steps

a3) preparing the GalNAc acid derivative of formula I or the GalNAc acid salt of formula V according to any one of claims 1 to 27 and

b3) conjugating the GalNAc acid derivative of formula I or the GalNAc acid salt of formula V under peptide coupling conditions with an oligonucleotide.

10 32. Process of claim 31, wherein the GalNAc acid salt of formula V is used.