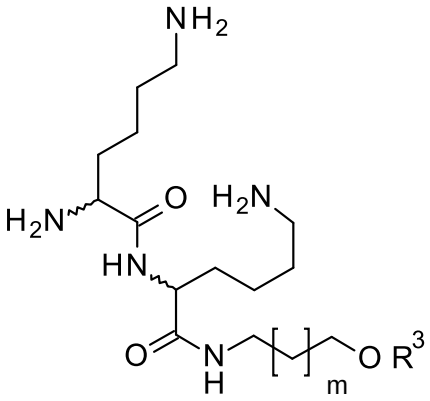
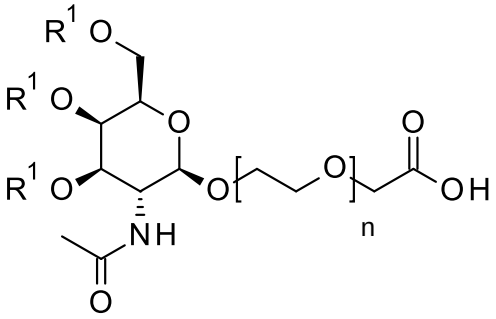
a) coupling an epimerically pure compound of formula II,



II

wherein R^3 is a hydroxy protecting groups and m is as above, or a salt thereof with a GalNAc moiety of the formula III

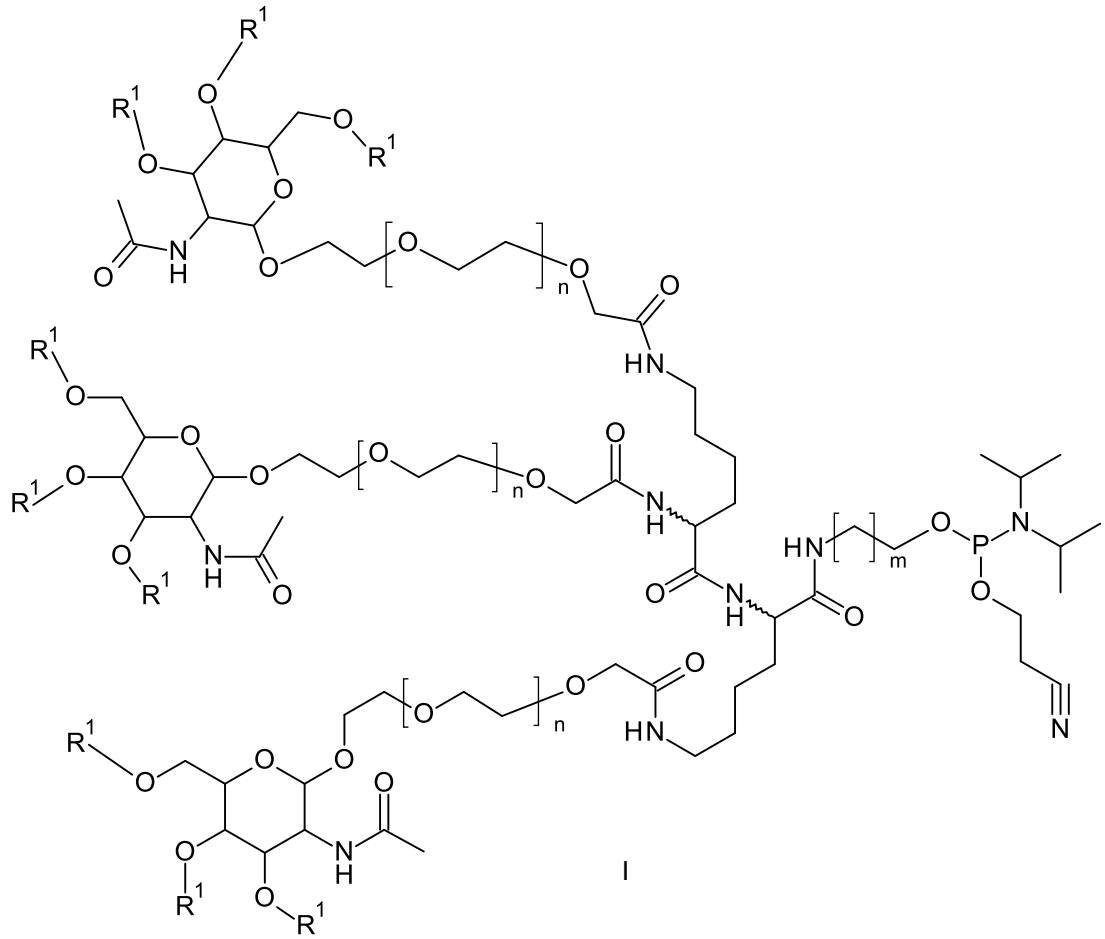


III

wherein R^1 and n is as above to form the GalNAc amide of formula IV

Claims:

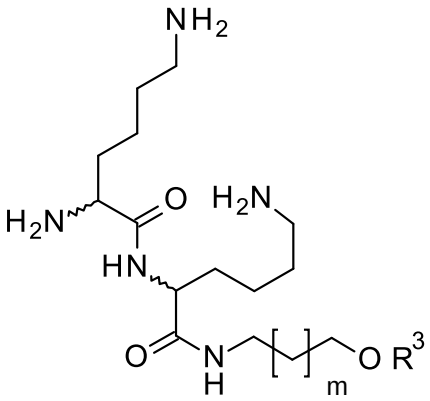
1. Process for the preparation of epimerically pure GalNAc phosphoramidite epimers of the formula I,



I

wherein R^1 is a hydroxy protecting group, n is an integer from 0 to 10 and m is an integer from 0 to 20, corresponding enantiomers and/ or optical isomers thereof comprising

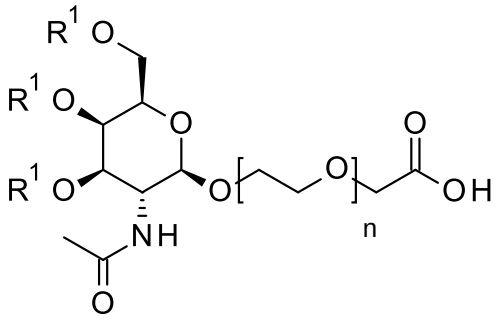
a) coupling an epimerically pure compound of formula II,



II

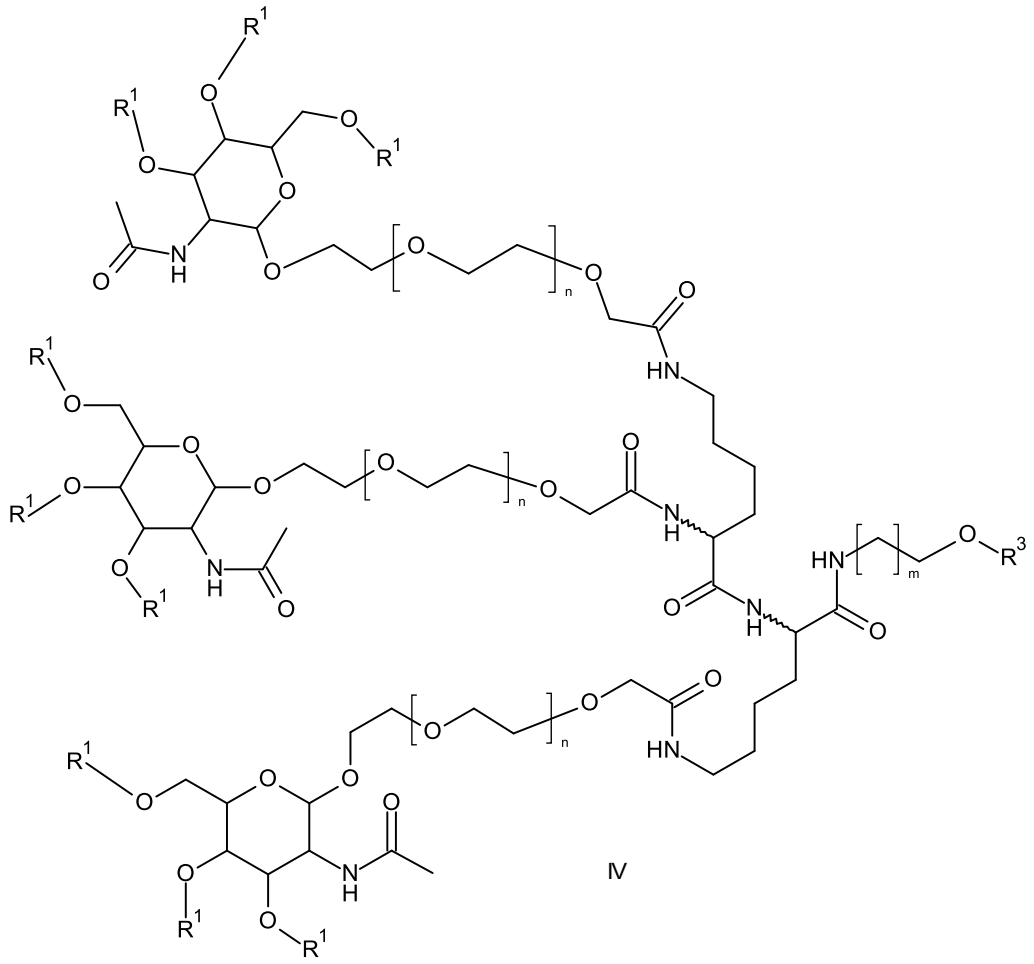
wherein R^3 is a hydroxy protecting groups and m is as above, or a salt thereof

with a GalNAc moiety of the formula III



III

wherein R^1 and n is as above to form the GalNAc amide of formula IV



IV

wherein R^1, R^3, n and m are as above; and

b) removing the hydroxyl protecting group R^3 to form the free alcohol of the GalNAc amide of formula IV and

c) reacting the free alcohol of the GalNAc amide of formula IV with a phosphoroamidating agent to form the GalNAc phosphoramidite epimer of the formula I.

2. Process of claim 1, wherein R^1 is an acyl group.

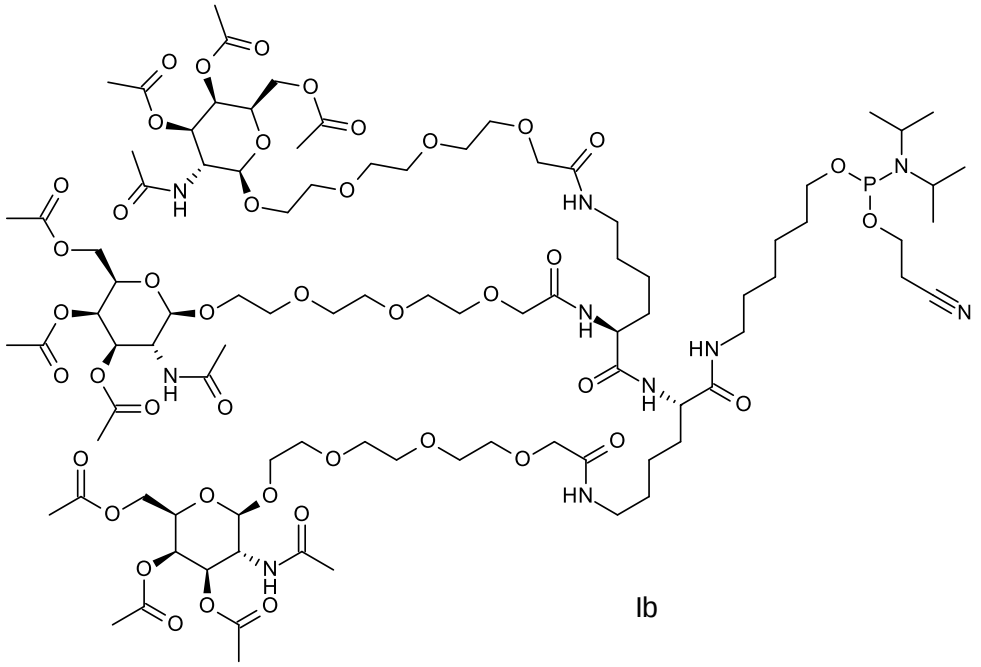
3. Process of claim 1 or 2, wherein R^1 is a C_{1-6}-alkylcarbonyl group which is optionally substituted by C_{1-6}-alkyl or phenyl.

4. Process of any one of claims 1 to 3, wherein n is an integer from 0 to 5 and m is an integer from 0 to 10.

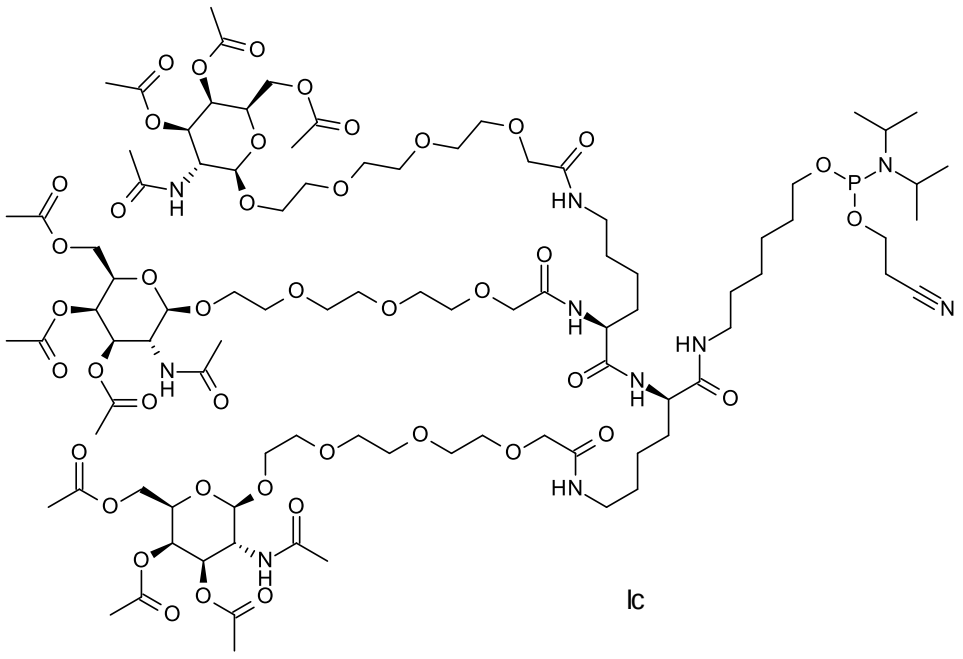
5. Process of any one of claims 1 to 4, wherein R^1 is acetyl, n is 2 and m is 5.

6. Process of anyone of claims 1 to 5, wherein R^3 is benzyl.

7. Process of any one of claims 1 to 6, wherein the formula I comprises GalNAc phosphoramidite epimers of the formulas Ib to Ie.

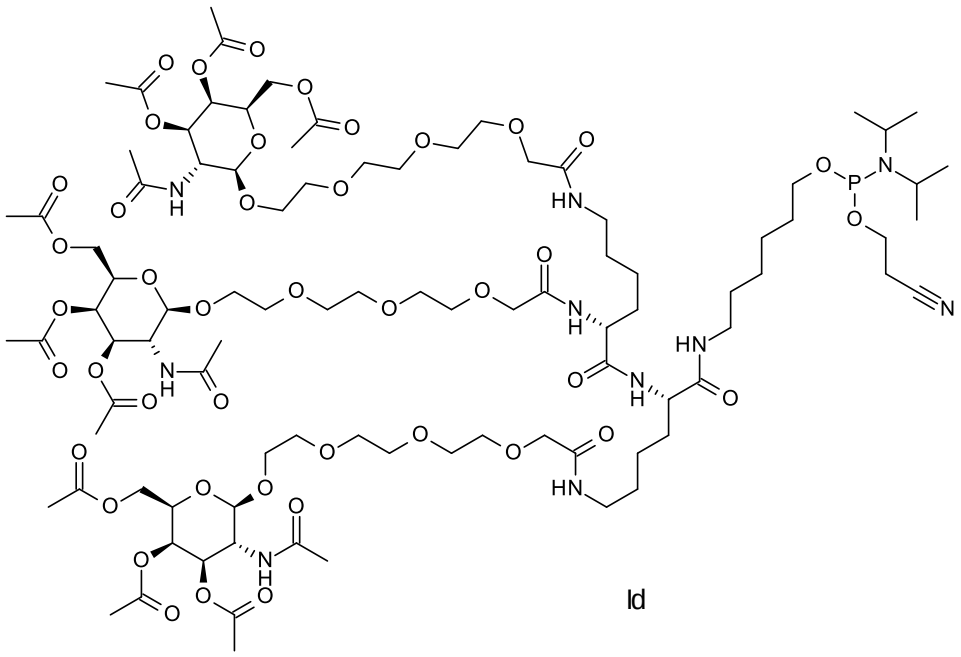


Ib

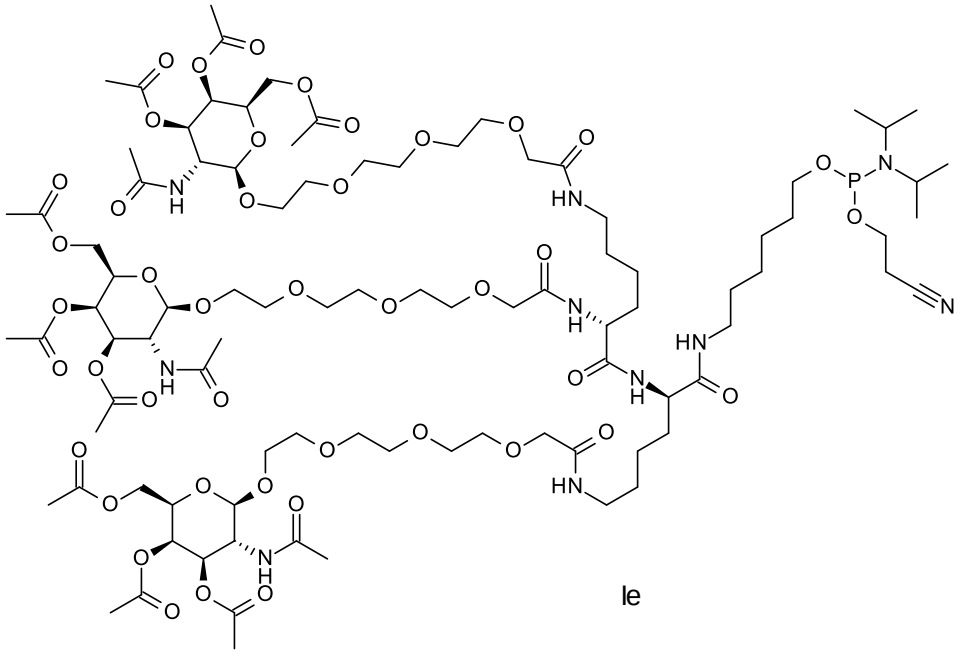


Ic

5



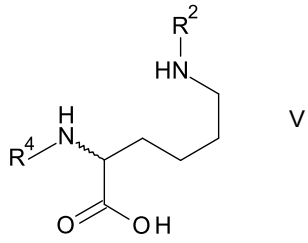
Id



Ie

8. Process of any one of claims 1 to 7, wherein the epimerically pure compound of formula II is prepared by

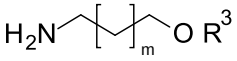
a1) coupling a lysine compound of formula V



V

wherein R^2 and R^4 are amino protecting groups

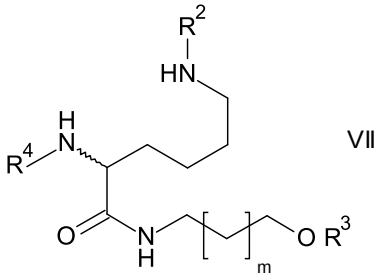
with an amine of the formula VI



VI

wherein R^3 and m are as above

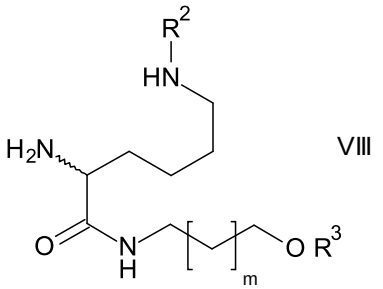
to form the carboxamide of formula VII;



VII

wherein R^2, R^3, R^4 and m are as above and

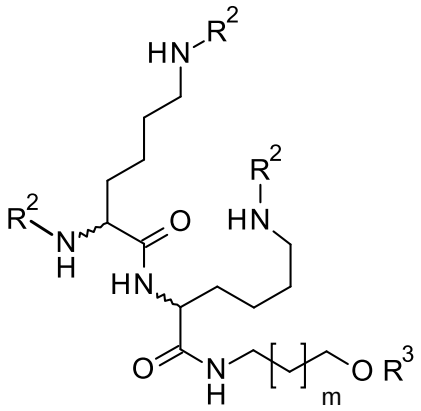
b1) removing the amino protecting R^4 to form the amine of formula VIII



VIII

wherein R^2, R^3 and m are as above;

c1) coupling the amine of formula VIII with an amino group protected lysine to form the dipeptide of formula IX



IX

wherein R^2 and R^3 and m are as above; and

d1) removing the amino protecting groups R^2 to form the epimerically pure compound of formula II.

9. Process of claim 8, wherein the coupling steps a1) and c1) are performed in the presence of a peptide coupling agent, an amine base and an organic solvent.

10. Process of claims 8 or 9, wherein the peptide coupling agent is n-propylphosphonic acid anhydride, the amine base is a tertiary amine, the organic solvent is a polar aprotic solvent and the reaction temperature is selected from 20°C to 70°C.

11. Process of claim 8 to 10, wherein R^4 is an amino protecting group cleavable under basic conditions, preferably FMOC.

12. Process of claim 11, wherein the basic conditions involve the treatment with a secondary aliphatic amine, preferably diethyl amine in the presence of an organic solvent.

13. Process of anyone of claims 8 to 12, wherein the amino protecting group R^2 is tert-butyloxycarbonyl.

14. Process of claim 8, wherein in step d1) the amino protecting group R^2 is removed under acidic conditions and a tri-ammonium salt of the dipeptide of formula IX with the respective acid is formed.

15. Process of claim 14, wherein the acid is a sulfonic acid, preferably methanesulfonic acid.

16. Process of claim 1 to 7, wherein the coupling of the epimerically pure compound of formula II with the GalNAc moiety of the formula III in step a) is performed in the presence of a peptide coupling agent, an amine base and an organic solvent.

17. Process of claim 16, wherein the peptide coupling agent is n-propylphosphonic acid anhydride, the amine base is a tertiary amine, the organic solvent is a polar aprotic solvent and the reaction temperature is selected from 20°C to 70°C.

18. Process of claim 1 to 7, wherein the removing the hydroxyl protecting group R^3 to form the free alcohol in step b) is performed by way of a catalytic hydrogenation with hydrogen in the presence of a hydrogenation catalyst.

19. Process of claim 1 to 7, wherein the phosphoroamidating agent in step c) is selected from 2-cyanoethyl-N,N-di-(2-propyl)chlorophosphoroamidite or from 2-Cyanoethyl-N,N,N',N'-tetra (2-propyl)phosphorodiamidite.

20. Process of claim 19, wherein the reaction in step c) is performed with 2-Cyanoethyl-N,N,N',N'-tetra (2-propyl)phosphorodiamidite in the presence of an acidic ammonium salt of a secondary amine and a polar aprotic solvent at a reaction temperature between -20°C and 50°C.

21. Use of the process of claims 1 to 20 in a process for the preparation of GalNAc-cluster oligonucleotide conjugates comprising the GalNAc moiety as single epimer.

22. Use of claim 21, wherein the preparation of GalNAc-cluster oligonucleotide conjugates comprises

a) the preparation of the GalNAc phosphoramidite epimer of the formula I according to claims 1 to 20;

b) the employment of the GalNAc phosphoramidite epimer of the formula I in a solid phase oligonucleotide synthesis together with a desired nucleoside building block in a desired sequence to form a desired GalNAc-cluster oligonucleotide conjugate bound to the solid support and finally the

c) cleavage of the GalNAc-cluster oligonucleotide conjugate from the solid phase support and full deprotection and purification