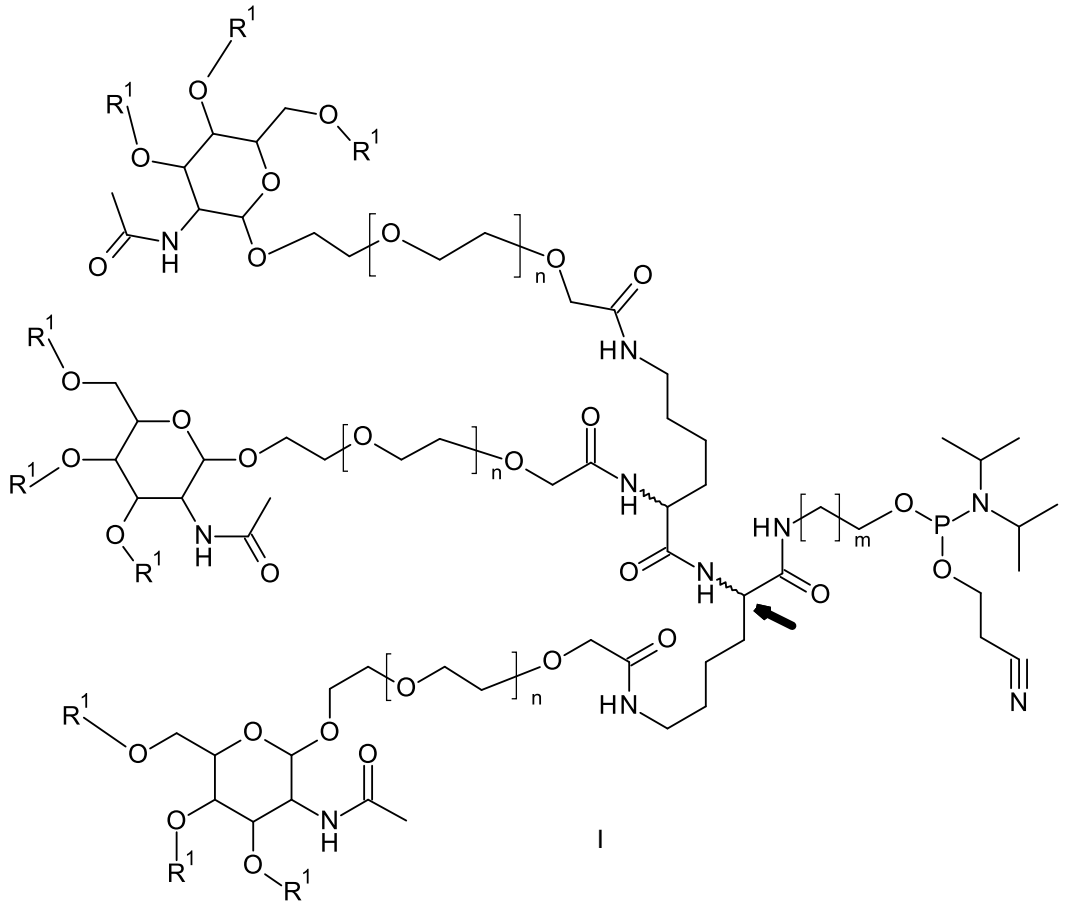
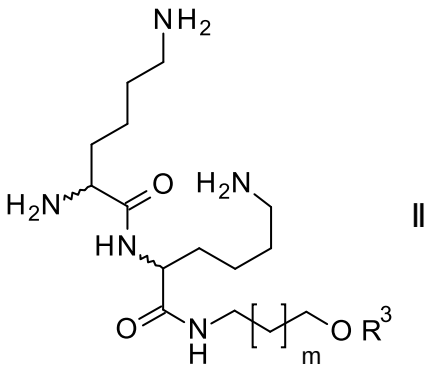


I

The object of the disclosure therefore was to provide a novel process to produce the building block in epimerically pure form.

The object could be achieved with the novel process for the preparation of epimerically pure GalNAc phosphoramidite epimers of the formula I which comprises

a) coupling a compound of formula II,

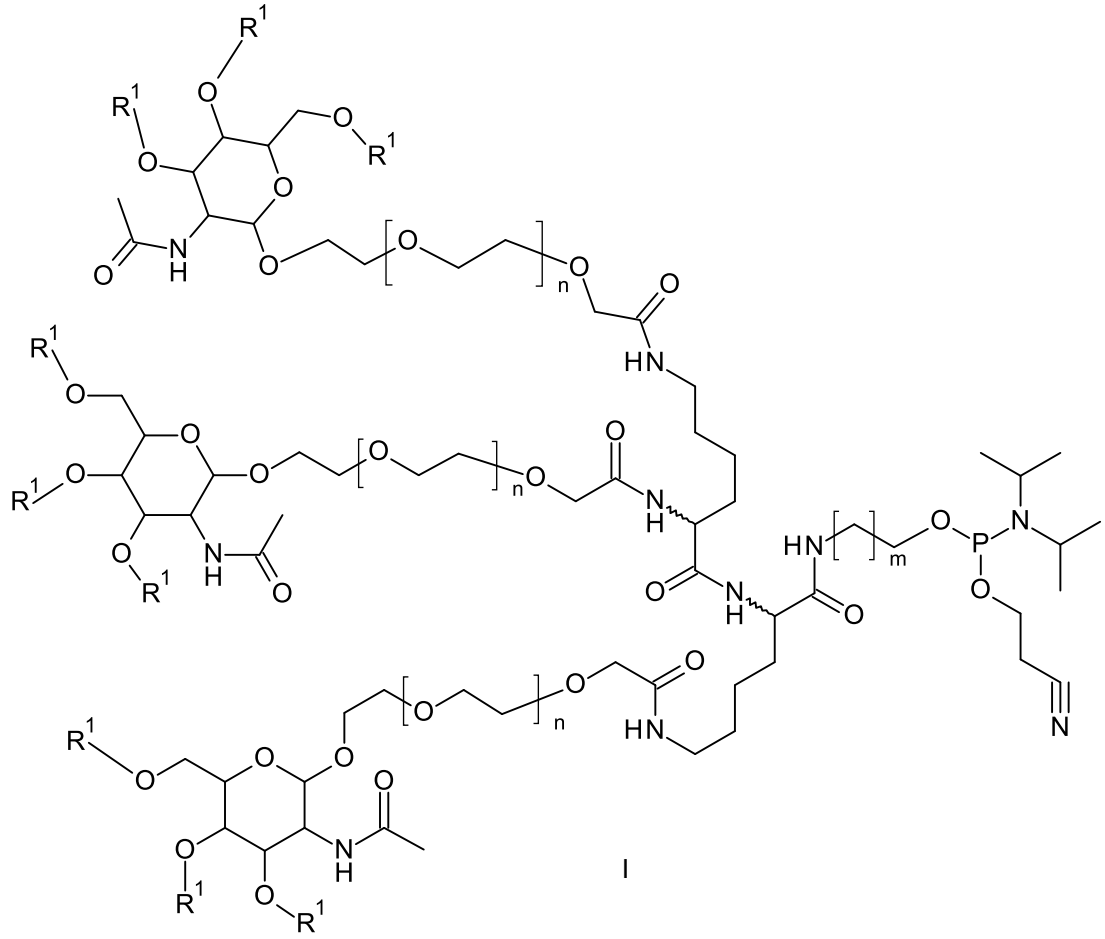


II

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

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.

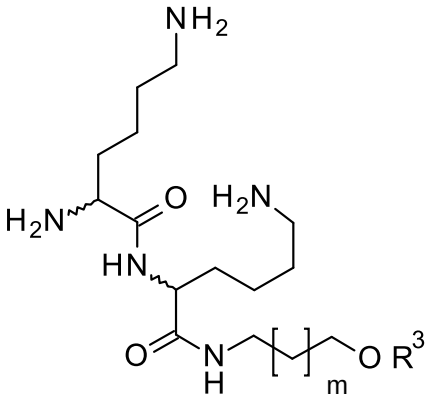
In one aspect, the present disclosure provides a process for the preparation of epimerically pure GalNAc phosphoramidite epimers of the formula I,



I

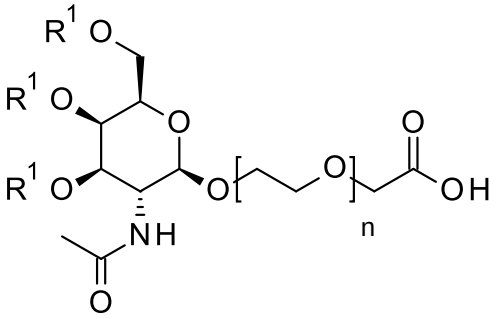
wherein R^1 is a hydroxy protecting group, n is an integer from 0 to 10 and m is an integer from 0 to 20, corresponding enantiomers and/ or optical isomers thereof comprising

a) coupling a compound of formula II,



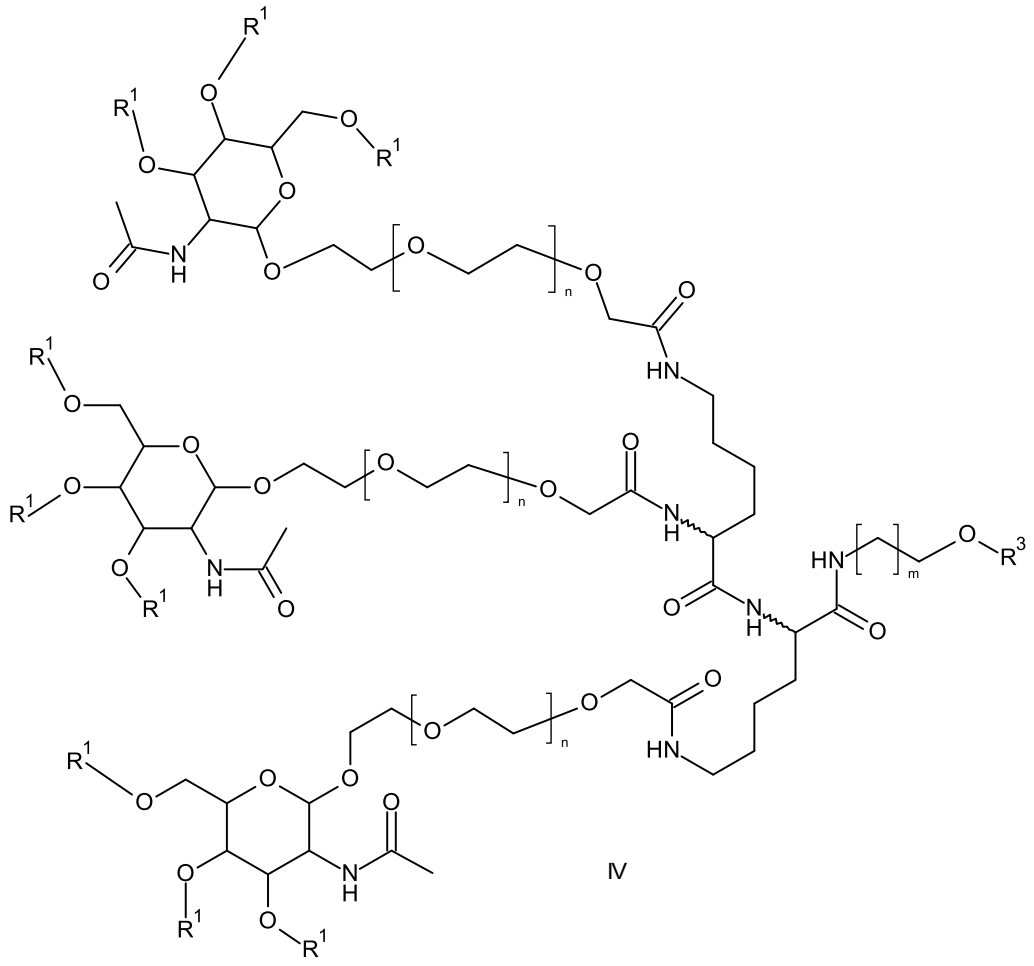
II

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.

In another aspect, the present disclosure provides use of the process of the disclosure in a process for the preparation of GalNAc-cluster oligonucleotide conjugates comprising the GalNAc moiety as single epimer.

The following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

Whenever a chiral carbon is present in a chemical structure, it is intended that all stereoisomers associated with that chiral carbon are encompassed by the structure as pure stereoisomers as well as mixtures thereof.

The term epimer denotes one of a pair of stereoisomers, wherein the isomers differ in configuration at only one stereogenic center and wherein all other stereocenters in the molecules are the same.

The term "C_{1-12}-alkyl" denotes a monovalent linear or branched saturated hydrocarbon group of 1 to 12 carbon atoms and the term "C_{1-6}-alkyl" a monovalent linear or branched saturated hydrocarbon group of 1 to 6 carbon atoms.

Examples of "C_{1-12}–alkyl" or "C_{1-6}–alkyl" include methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, and pentyl and hexyl with its isomers.

The term "acyl" denotes a carbonyl group which is linked to an alkyl group. The term particularly stands for a C_{1-12}-alkylcarbonyl group, more particularly a C_{1-6}-alkylcarbonyl group which is optionally substituted by C_{1-6}-alkyl or optionally substituted by phenyl. Examples for acyl groups are acetyl, pivaloyl or benzoyl. Optional substitutions for phenyl are halogen such as chlorine, bromine or iodine or a C_{1-6}-alkyl group as defined above. Acyl preferably stands for acetyl.

The term "hydroxy-protecting group" denote groups which are intended to protect a hydroxy group and include ester- and ether-forming groups, in particular tetrahydropyranyl, acyl (e.g. benzoyl, acetyl, carbamoyl), benzyl and silylethers (e.g. TBS, TBDPS) groups. Further examples of these groups are found in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", 2nd ed., John Wiley & Sons, Inc., New York, NY, 1991, chapters 2-3; E. Haslam, "Protective Groups in Organic Chemistry", J. G. W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapter 5, and T.W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, NY, 1981.

The term "amino-protecting group" denotes groups intended to protect an amino group and includes benzoyl, benzyloxycarbonyl, carbobenzyloxy (CBZ or Z), 9-fluorenylmethyloxycarbonyl