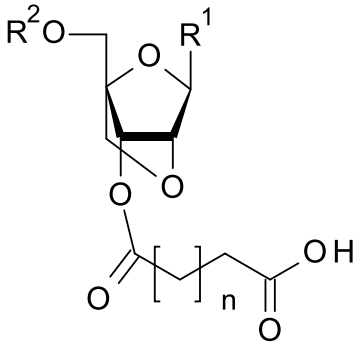
and the oligonucleotide is then synthesized by sequentially coupling monomers to the solid support-bound synthon. This iterative elongation eventually results in a final oligonucleotide compound which it is cleaved from the support and, if necessary further worked up to produce the final oligonucleotide compound.

In a further development linker molecules attached to the solid support have been introduced for carrying out the oligonucleotide synthesis more efficiently, particularly on the automated process synthesizers nowadays used. For instance the Int. Patent Publication WO 2005/049621 or WO 2006/029023 discloses such linker compounds. Oligonucleotide elongation usually starts from an O-dimethoxytrityl (O-DMT) on the linker molecule.

However, in the synthesis of LNA oligonucleotides, it was found in that to a certain extent the first coupling on the linker molecule failed, resulting in final oligonucleotides with a substantial amount of (N-1) impurities, i.e. oligonucleotides with one lacking nucleoside at the 3'-end.

Object of the present disclosure therefore was to reduce the amount of 3`-end (N-1) impurities to a great extent, as such impurities can hardly be removed by state-of-the-art chromatographic purification methods and cause thereof a substantial loss in yield, e.g. by tight fraction pooling in the preparative chromatography step and/or an unsatisfying impurity profile in the isolated LNA oligonucleotide.

In one aspect, there is provided LNA-dicarboxylic acid derivatives of the formula I



I

or salts thereof,

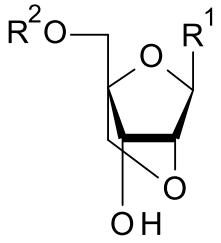
wherein

R^1 is an optionally modified and / or an amino group protected adenine (A), cytosine (C), guanine (G) or thymine (T);

R^2 is a hydroxy protecting group; and

n is an integer from 1 to 5.

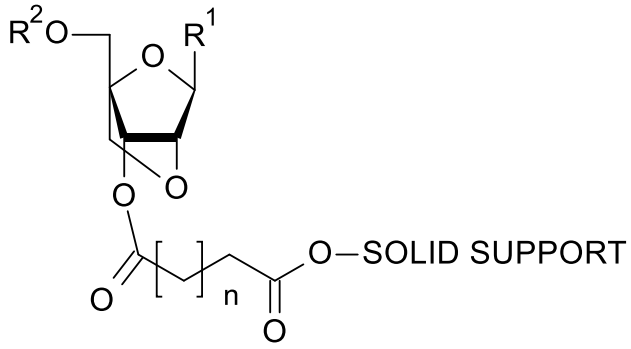
In another aspect, there is provided a process for the preparation of LNA-dicarboxylic acid derivatives of formula I comprising the reaction of an LNA alcohol of formula II



II

wherein R^1 and R^2 are as above, with a C_{2-6}-dicarboxylic acid anhydride, in the presence of a base and an organic solvent to form the LNA-dicarboxylic acid derivatives of formula I.

In another aspect, there is provided use of the LNA-dicarboxylic acid derivatives of the formula I as defined herein, for the preparation of a preloaded solid support of the formula III

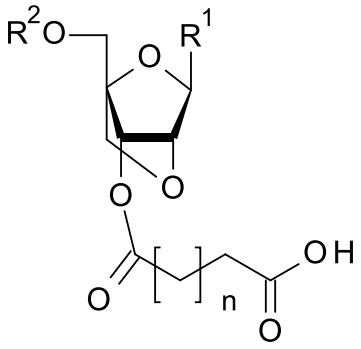


III

wherein R^1, R^2 and n are as above and SOLID SUPPORT is a solid support material suitable for oligonucleotide synthesis.

Claims:

1. LNA-dicarboxylic acid derivatives of the formula I



I

or salts thereof,

wherein

R^1 is an optionally modified and / or an amino group protected adenine (A), cytosine (C), guanine (G) or thymine (T);

R^2 is a hydroxy protecting group; and

n is an integer from 1 to 5.

2. LNA-dicarboxylic acid derivatives of claim 1, wherein R^1 is an amino group protected adenine (A), an amino group protected cytosine (C), an amino group protected 5-methyl cytosine (5-MeC) , an amino group protected guanine (G) or is thymine.

3. LNA-dicarboxylic acid derivatives of claim 2, wherein the amino protecting group is selected from C_{1-6}-alkanoyl, benzoyl (bz) or dimethylformamidine (dmf).

4. LNA-dicarboxylic acid derivatives of anyone of claims 1 to 3, wherein R^2 is an acid sensitive hydroxyl protecting group selected from an alkoxy-modified trityl group, preferably from 4,4`-dimethoxytrityl.

5. LNA-dicarboxylic acid derivatives of anyone of claims 1 to 4, wherein n is 1.

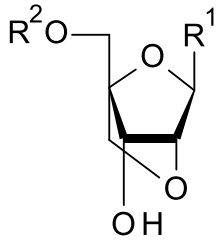
6. LNA-dicarboxylic acid derivatives of any one of claims 1 to 5, in the form of a salt from an inorganic or organic base.

7. LNA-dicarboxylic acid derivatives of any one of claims 1 to 6, in the form of an ammonium salt of an organic amine.

8. LNA-dicarboxylic acid derivatives of claim 7, in the form of an ammonium salt of a tertiary amine, preferably a tri-C_{1-4}-alkylamine or pyridine, more preferably triethylamine or pyridine.

9. LNA-dicarboxylic acid derivatives of any one of claims 1 to 8, in the form of any mixture of the free acid and the salt from the inorganic or organic base.

10. Process for the preparation of LNA-dicarboxylic acid derivatives of formula I comprising the reaction of an LNA alcohol of formula II



II

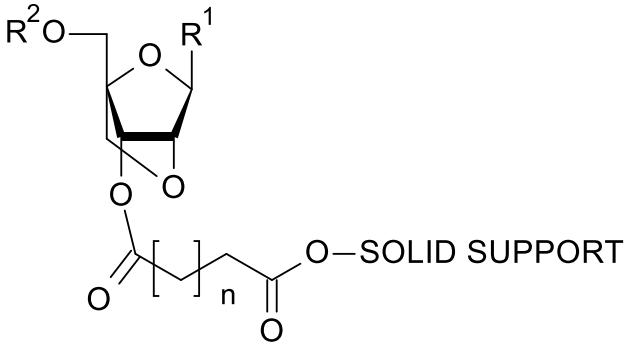
wherein R^1 and R^2 are as above, with a C_{2-6}-dicarboxylic acid anhydride, in the presence of a base and an organic solvent to form the LNA-dicarboxylic acid derivatives of formula I.

11. Process of claim 10, wherein the C_{2-6}-dicarboxylic acid anhydride is succinic anhydride.

12. Process of claims 10 or 11, wherein the base is an organic amine, preferably a tertiary amine, more preferably a tri-C_{1-4}-alkylamine or pyridine even more preferably triethylamine or pyridine.

13. Process of any one of claims 10 to 12, wherein the organic solvent is a halogenated hydrocarbon.

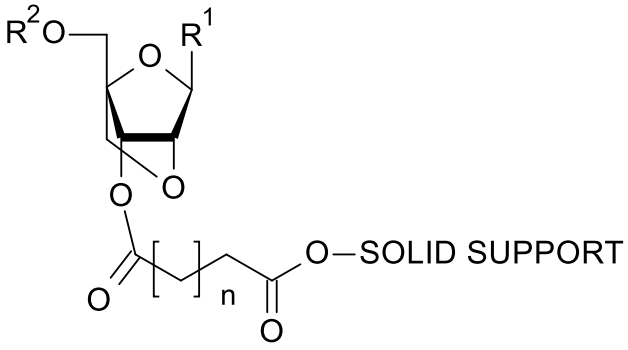
14. Use of the LNA-dicarboxylic acid derivatives of the formula I of claims 1 to 9, for the preparation of a preloaded solid support of the formula III



III

wherein R^1, R^2 and n are as above and SOLID SUPPORT is a solid support material suitable for oligonucleotide synthesis.

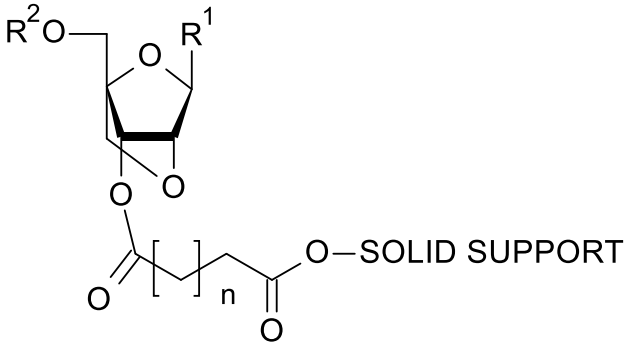
15. Preloaded solid support of the formula III



III

wherein R^1, R^2 and n are as above and SOLID SUPPORT is a solid support material suitable for oligonucleotide synthesis.

16. Use of the preloaded solid support of the formula III



III

wherein R^1, R^2 and n are as above and SOLID SUPPORT is a solid support material suitable for oligonucleotide synthesis as start material in oligonucleotide synthesis.