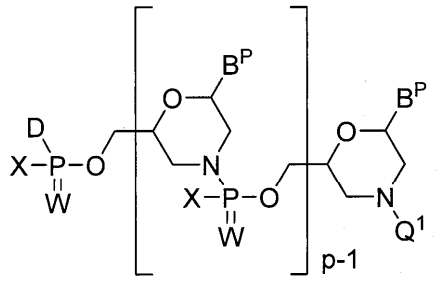
Claims

1. A method for producing a compound [C] by subjecting a compound [A] to a condensation reaction with a compound [B] in the presence of at least one reaction accelerator selected from the group consisting of a quaternary ammonium salt, a quaternary imidazolium salt, a quaternary morpholinium salt, a quaternary phosphonium salt, a quaternary piperidinium salt, a quaternary pyridinium salt, a quaternary pyrrolidinium salt and a quaternary sulfonium salt,
wherein

the compound [B] is a compound represented by the general formula [B-1]:



[B-1]

wherein

each B^P is the same or different and represents an optionally protected nucleic acid base,

D represents a halogen, 5- to 6-membered saturated cyclic amino, or di(C_{1-6} alkyl)amino,

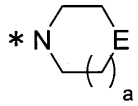
p represents an integer from 1 to 10,

Q^1 represents a removable group under an acidic condition,

each W is the same or different and represents an oxygen atom or a sulfur atom, and

each X is the same or different and represents a hydroxyl group substituted with a removable group under a neutral condition, 1,1,3,3-tetra(C_{1-6} alkyl)guanidyl, C_{1-6} alkoxy, di(C_{1-6} alkyl)amino, mono(amino-C_{1-6} alkyl substituted with a removable group under a basic condition)amino, di(amino-C_{1-6}

alkyl substituted with a removable group under a basic condition)amino, or a substituent represented by general formula [2]:



[2]

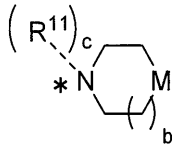
wherein

* represents a binding position with a phosphorus atom,

a represents an integer from 0 to 2,

E represents CH_2, $CH-A^1$, or $N-A^2$,

A^1 represents C_{1-6} alkyl, mono(C_{1-6} alkyl)amino-C_{1-6} alkyl substituted with a removable group under a basic condition, di(C_{1-6} alkyl)amino-C_{1-6} alkyl, tri(C_{1-6} alkyl)ammonio-C_{1-6} alkyl, amino substituted with a removable group under a basic condition, mono(C_{1-6} alkyl)amino substituted with a removable group under a basic condition, di(C_{1-6} alkyl)amino, tri(C_{1-6} alkyl)ammonio, amino substituted with amidino substituted with a removable group under a basic condition, or a substituent represented by the following general formula [3]:



[3]

wherein

* represents a binding position with E,

b represents an integer from 0 to 2,

c represents 0 or 1,

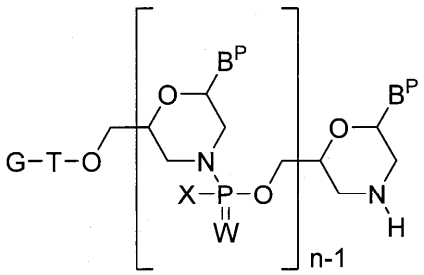
R^{11} represents C_{1-6} alkyl, and

M represents CH_2, an oxygen atom, a sulfur atom, or N-(a removable group under a basic condition), and

A^2 represents C_{1-6} alkyl, mono(C_{1-6} alkyl)amino-C_{1-6} alkyl substituted with a removable group under a basic condition, di(C_{1-6} alkyl)amino-C_{1-6} alkyl, tri(C_{1-6} alkyl)ammonio-C_{1-6}

alkyl, a removable group under a basic condition, aryl, or heteroaryl,

the compound [A] is a compound represented by the general formula [A-1]:



[A-1]

wherein

B^P, W and X are as defined above,

G represents

(1) a silyl substituent,

(2) long-chain alkyl-carbonyl,

(3) benzoyl substituted with 1 to 5 long-chain alkyloxy and/or long-chain alkenyloxy, or

(4) a substituent represented by the following general formula [7]:



[7]

wherein

* represents a binding position with T,

Z represents

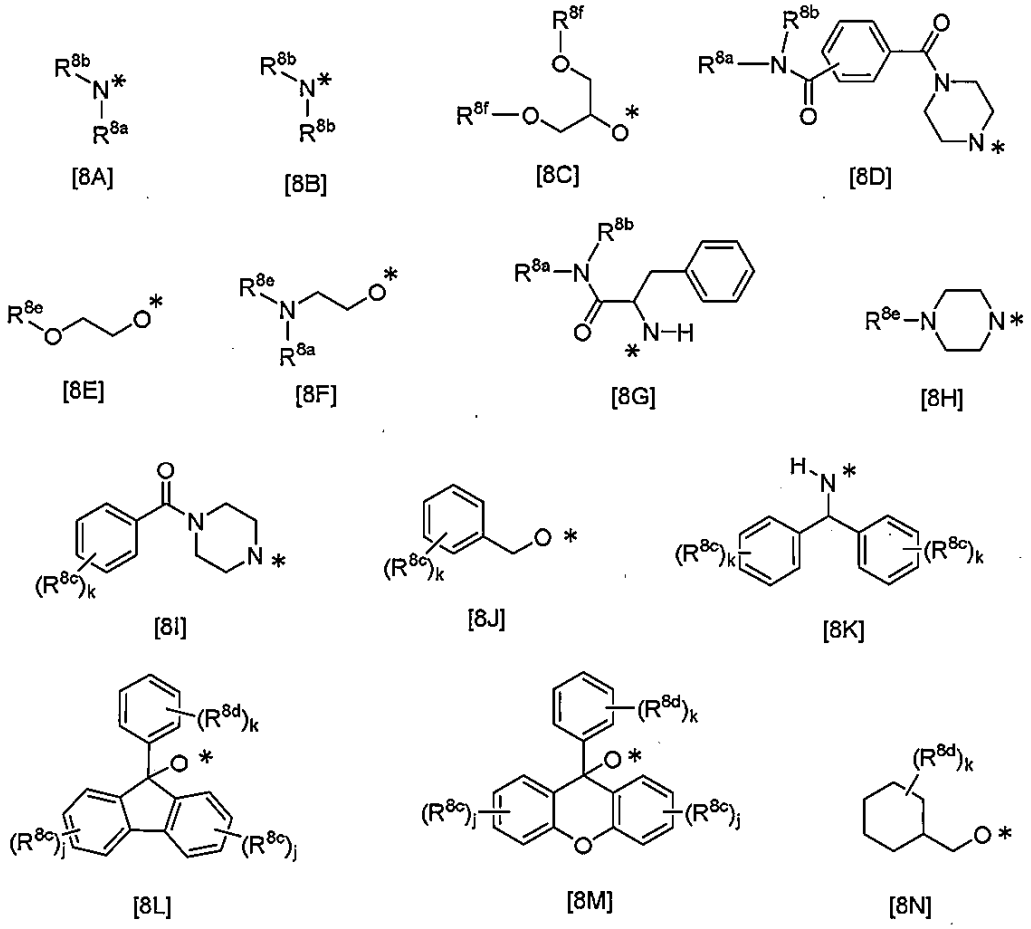
(1) (soluble polymer soluble in an organic solvent)-oxy,

(2) (soluble polymer soluble in an organic solvent)-amino,

(3) long-chain alkyloxy,

(4) a solid phase carrier, or

(5) a substituent represented by one of the following general formulae [8A] to [8N]:



wherein

* represents a binding position with L,

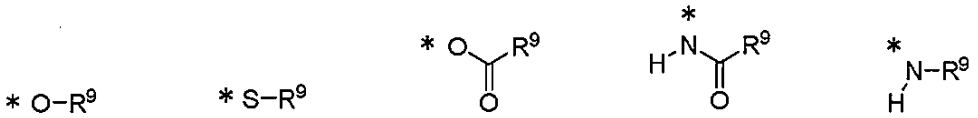
j represents an integer from 0 to 4,

k represents an integer from 0 to 5,

R^{8a} represents a hydrogen atom or C_{1-6} alkyl,

R^{8b} is the same or different and each represent long-chain alkyl,

R^{8c} is the same or different and each represent a substituent represented by one of the following general formulae [9A] to [9E]:



[9A] [9B] [9C] [9D] [9E]

wherein

* represents a binding position, and

R^9 represents long-chain alkyl and/or long-chain alkenyl,

R^{8d} is the same or different and each represent a hydrogen atom, a halogen, long-chain alkyl optionally substituted with 1 to 13 halogens, or long-chain alkyloxy optionally substituted with 1 to 13 halogens,

R^{8e} represents

(1) long-chain alkyl,

(2) long-chain alkyl-carbonyl, or

(3) benzoyl substituted with 1 to 5 long-chain alkyloxy and/or long-chain alkenyloxy, and

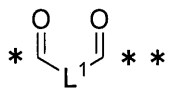
R^{8f} represents

(1) long-chain alkyl,

(2) long-chain alkyl-carbonyl, or

(3) long-chain alkenyl-carbonyl, and

L represents a substituent represented by general formula [10]:



[10]

wherein

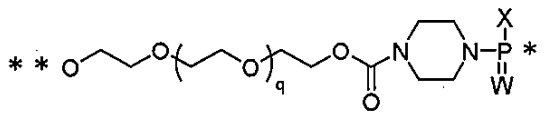
* represents a binding position with Z,

** represents a binding position with T, and

L^1 represents an optionally substituted C_{2-10} alkylene or an optionally substituted C_{6-10}

arylene, and

T represents a single bond or a substituent represented by general formula [11]:



[11]

wherein

X is as defined above,

W is as defined above,

* represents a binding position with O,

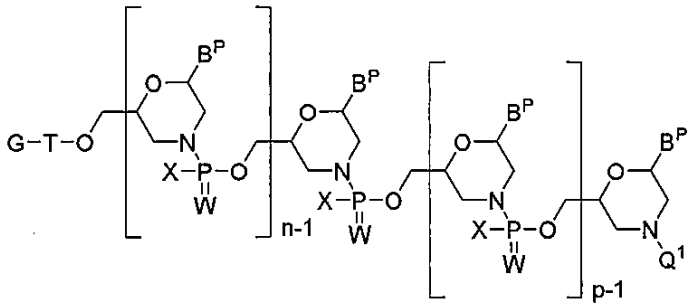
** represents a binding position with G, and

q represents an integer from 0 to 10,

provided that T is a single bond when G is a silyl substituent, and

n represents an integer from 1 to 50, and

the compound [C] is a compound represented by the general formula [C-1]:



[C-1]

wherein B^P, Q^1, W, X, G, T, n and p are as defined above. .

2. The method according to claim 1, wherein the reaction accelerator is at least one selected from the group consisting of a quaternary ammonium salt, a quaternary imidazolium salt, and a quaternary pyrrolidinium salt.

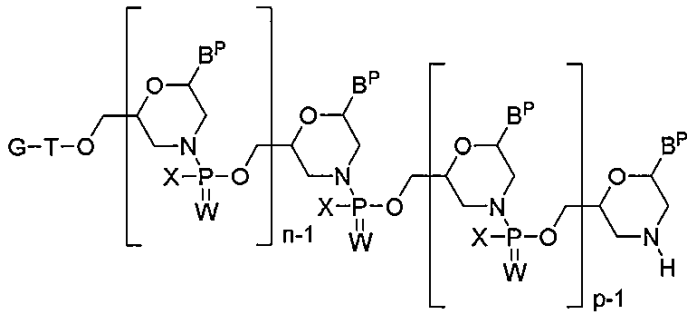
3. The method according to claim 1, wherein the reaction accelerator is at least one selected from the group consisting of tetra C_{1-18} alkyl ammonium chloride, 1-C_{1-18} alkyl-1-C_{1-18} alkylpyrrolidinium chloride, and 1-C_{1-18} alkyl-3-C_{1-18} alkylimidazolium chloride.

4. The method according to claim 1, wherein the reaction accelerator is at least one selected from the group consisting of:
tetrabutylammonium chloride,
tetrabutylammonium bromide,
dodecyltrimethylammonium chloride,
trioctylmethylammonium chloride,
choline chloride,
N,N,N-trimethylbutan-1-aminochloride,
1-ethylpyridinium bromide,
1-ethylpyridinium chloride,
1-butylpyridinium chloride,
1-ethyl-3-methylimidazolium chloride,
1-methyl-3-N-octylimidazolium chloride, and
1-butyl-1-methylpyrrolidinium chloride.

5. The method according to claim 1, wherein the reaction accelerator is at least one selected from the group consisting of tetrabutylammonium chloride, 1-butyl-1-methylpyrrolidinium chloride, and 1-methyl-3-N-octylimidazolium chloride.

6. The method according to any one of claims 1 to 5, wherein the method comprises further

removing Q^1 in situ subsequently by adding a solution containing an acid to a reaction mixture containing the compound [C-1] prepared by the method according to any one of claims 1 to 5, to form a compound represented by the general formula [E-1]:

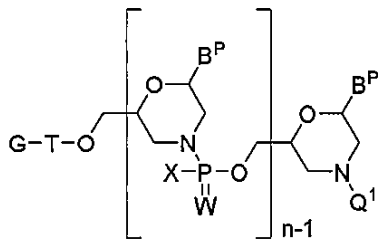


[E-1]

wherein n, p, B^P, G, T, W and X are as defined above.

7. The method according to any one of claims 1 to 6, wherein the method comprises

removing Q^1 from a compound of general formula [A-1-1]:



[A-1-1]

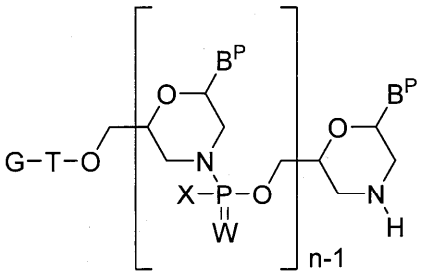
wherein

B^P, Q^1, W, X, G, T and n are as defined above, and

n represents an integer from 1 to 25,

in the presence of at least one reaction accelerator selected from the group consisting of a quaternary ammonium salt, a quaternary imidazolium salt, a quaternary morpholinium salt, a quaternary phosphonium salt, a quaternary piperidinium salt, a quaternary pyridinium salt, a quaternary pyrrolidinium salt and a

quaternary sulfonium salt, to form a compound of general formula [A-1]:

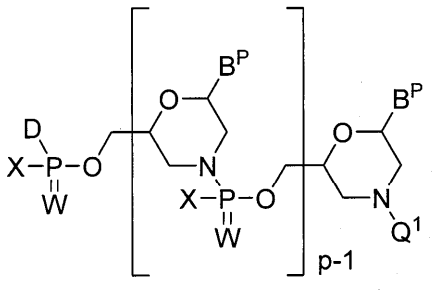


[A-1]

wherein

B^P, W, X, G, T and n are as defined above,

and then reacting the compound of general formula [A-1] with a compound of general formula [B-1]:



[B-1]

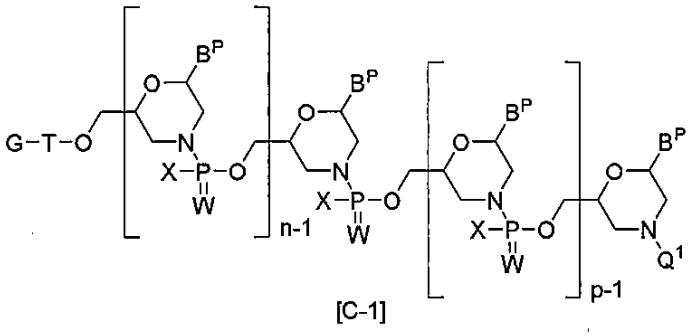
wherein

B^P, Q^1, W and X are as defined above,

D is a halogen, and

p is an integer from 1 to 10,

to obtain a compound of general formula [C-1]:



[C-1]

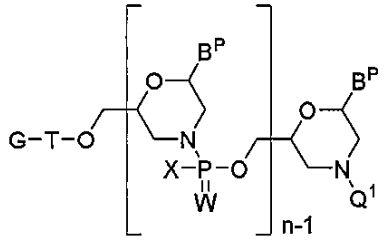
wherein n, p, B^P, Q^1, W, X, G and T are as defined above.

8. The method according to claim 7, wherein the reaction accelerator is at least one selected from the group consisting of:

tetramethylammonium chloride;
tetraethylammonium chloride;
tetrapropylammonium chloride;
tetrabutylammonium chloride;
tetrabutylammonium bromide;
dodecyltrimethylammonium chloride;
trioctylmethylammonium chloride;
N,N,N-trimethylbutan-1-aminochloride;
1-ethylpyridinium bromide;
1-ethylpyridinium chloride;
1-butylpyridinium chloride;
1-ethyl-3-methylimidazolium chloride;
1-methyl-3-N-octylimidazolium chloride; and
1-butyl-1-methylpyrrolidinium chloride, and

the amount of the reaction accelerator is in the range of 1 to 100 times, in molar ratio per 1 mol of the compound [A-1].

9. The method according to claim 7 or 8, wherein the method comprises removing Q^1 from a compound of general formula [A-1-1]:



[A-1-1]

wherein

Q^1 is trityl, monomethoxytrityl or dimethoxytrityl, and

n, B^P, W, X, G and T are as defined above,

in the presence of trifluoroacetic acid and 2,2,2-trifluoroethanol, and optionally triisopropylsilane or ethanol.

10. The method according to any one of claims 7 to 9, wherein the method comprises

supplying a solution containing a compound of general formula [A-1] and a solution containing a compound of general formula [B-1] to a flow reactor to form a compound of general formula [C-1], and

optionally, supplying a solution containing the compound of general formula [C-1] and a solution containing an acid to a flow reactor to remove Q^1 to form a compound of formula [E-1].

11. The method according to any one of claims 7 to 10, wherein the method comprises

supplying a solution containing a compound of general formula [A-1-1] and a solution containing an acid to a flow reactor to remove Q^1 to form a compound of general formula [A-1], and

supplying a solution containing the compound of general formula [A-1] and a solution containing a compound of general formula [B-1] to a subsequent flow reactor to form a compound of general formula [C-1].

12. The method according to any one of claims 1 to 11, wherein the protected nucleic acid base is a nucleic acid base wherein an amino group and/or a hydroxyl group of the nucleic acid base is protected with a protecting group, and

the protecting group of the amino group is independently selected from the group consisting of benzoyl, 4-methoxybenzoyl, acetyl, propionyl, butylyl, isobutylyl, phenylacetyl, phenoxyacetyl, 4-tert-butylphenoxyacetyl, 4-isopropylphenoxyacetyl, and (dimethylamino)methylene, and

the protecting group of the hydroxy group is independently selected from the group consisting of 2-cyanoethyl, 4-nitrophenethyl, phenylsulfonylethyl, methylsulfonylethyl, trimethylsilylethyl, phenyl optionally substituted with 1 to 5 electron-withdrawing groups at any substitutable positions, diphenylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, methylphenylcarbamoyl, 1-pyrolidinylcarbamoyl, morpholinocarbamoyl, 4-(tert-butylcarboxy)benzyl, 4-[(dimethylamino)carboxy]benzyl, and 4-(phenylcarboxy)benzyl.