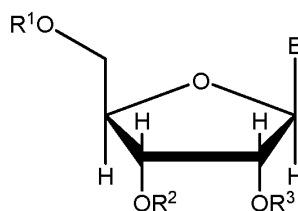


CLAIMS

What is claimed is:

1. A method for synthesizing oligonucleotides having at least one nucleoside with a 3'-OH group, the method comprising:
 - (i) coupling a free hydroxyl group on a nucleoside or oligonucleotide with a nucleoside phosphoramidite monomer having a triisopropylsilylether (TIPS) protected 3'-hydroxyl group to form a phosphite triester intermediate; and
 - (ii) oxidizing or sulfurizing said phosphite triester intermediate to form a protected intermediate.
2. The method of claim 1, wherein all synthetic steps are performed on an automated oligonucleotide synthesizer.
3. The method of claim 1, wherein oligonucleotide is synthesized at a large scale.
4. The method of claim 1, wherein said oxidizing is in presence of a weak base.
5. The method of claim 4, wherein said weak base is pyridine, lutidine, picoline or collidine.
6. The method of claim 1, wherein said oxidizing is in presence of I₂/H₂O.
7. The method of claim 1, wherein said sulfurizing is in presence of a sulfur transfer reagent.
8. The method of claim 7, wherein said sulfur transfer reagent is 3-(dimethylaminomethylidene)amino-3H-1,2,4-dithiazole-3-thione (DDTT) or 3H-1,2-benzodithiol-3-one 1,1-dioxide.
9. The method of claim 1, further comprising a step of deprotecting the protected intermediate with a base.
10. The method of claim 9, wherein said base is ammonium hydroxide, methylamine, or a mixture of ammonium hydroxide and methylamine.
11. The method of claim 9, wherein said treating with the base is at room temperature or an elevated temperature.
12. The method of claim 11, wherein said treating with the base is at a temperature of 30°C or higher.
13. The method of claim 9, wherein said treating with the base is for at least 30 minutes.
14. The method of claim 13, wherein said treating with the base is for at least 4 hours.

15. The method of claim 9, further comprising treating the base treated intermediate with a deprotecting reagent effective to convert the TIPS-protected hydroxyl group to a free hydroxyl group
16. The method of claim 15, wherein the deprotecting reagent comprises fluoride anions.
17. The method of claim 15, wherein the deprotecting reagent is HF.pyridine.
18. The method of claim 15, wherein said treating with the deprotecting reagent is at temperature of 30°C or higher.
19. The method of claim 1, wherein the oligonucleotide comprises from about 6 to about 50 nucleotides.
20. The method of claim 10, wherein the oligonucleotide comprises from about 10 to about 30 nucleotides.
21. A nucleoside monomer having the structure of Formula (I):



FORMULA (I)

wherein:

B is a modified or unmodified nucleobase;

R¹ is a hydroxyl protecting group;

R² is -Si(R⁴)₃;

R³ is H or -P(NR⁵R⁶)OR⁷;

each R⁴ is independently optionally substituted alkyl, aryl, aralkyl, alkaryl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl or cycloalkynyl;

R⁵ and R⁶ are independently optionally substituted alkyl, aryl, aralkyl, alkaryl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl or cycloalkynyl, or wherein R⁵ and R⁶ are linked to form a heterocyclyl; and

R⁷ is optionally substituted alkyl, aryl, aralkyl, alkaryl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl or cycloalkynyl.

22. The nucleoside monomer of claim 21, wherein the hydroxyl protecting group is selected from the group consisting of 4,4'-dimethoxytrityl (DMT), monomethoxytrityl (MMT), 9-fluorenylmethylcarbonate (Fmoc), o-nitrophenylcarbonyl, p-

phenylazophenylcarbonyl, phenylcarbonyl, p-chlorophenylcarbonyl, and 5'-(α -methyl-2-nitropiperonyl)oxycarbonyl (MeNPOC).

23. The nucleoside monomer of claim 21, wherein each R^4 is independently an optionally substituted C_1 - C_6 alkyl.
24. The nucleoside monomer of claim 21, wherein each R^4 is isopropyl.
25. The nucleoside monomer of claim 21, wherein R^5 and R^6 are independently optionally substituted C_1 - C_6 alkyl.
26. The nucleoside monomer of claim 21, wherein R^5 and R^6 are isopropyl.
27. The nucleoside monomer of claim 6, wherein R^7 is an optionally substituted C_1 - C_6 alkyl.
28. The nucleoside monomer of claim 21, wherein R^7 is methyl or β -cyanoethyl.
29. The nucleoside monomer of claim 6, wherein B is adenine, guanine, cytosine, thymine or uracil; R^1 is monomethoxytrityl or dimethoxytrityl; R^4 are independently optionally substituted C_1 - C_6 alkyl; R^5 and R^6 are independently optionally substituted C_1 - C_6 alkyl or R^5 and R^5 are linked to form a 4-8 membered heterocyclyl; and R^7 is an optionally substituted C_1 - C_6 alkyl.
30. The nucleoside monomer of claim 29, wherein B is adenine, guanine, cytosine or uracil; R^1 is dimethoxytrityl; R^4 , R^5 and R^6 are isopropyl; and R^7 is β -cyanoethyl.