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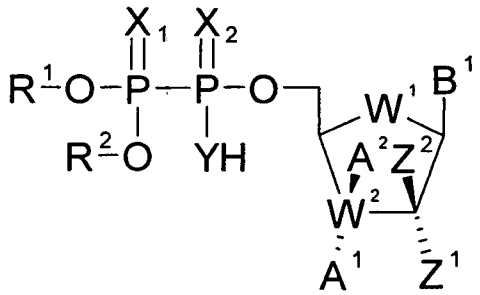


(1)

(57) Abstract: The subject of the invention includes derivatives of nucleoside-5'-*O*-hypophosphates and their mono- and dithiohypophosphate analogues, in particular 5'-*O*-[β,β-dialkyl-(α- thiohypophosphate)]-, 5'-*O*-[β,β-dialkyl-(α,α-dithiohypophosphate)]-, 5'-*O*-[β,β-dialkyl-(α,β-dithiohypophosphate)-, 5'-*O*-[β-alkyl-(α-thiohypophosphate)]-, 5'-*O*-[β-alkyl-(α,oc- dithiohypophosphate)]-, 5'-*O*-(α-thiohypophosphate)]- and 5'-*O*-(a,a- dithiohypophosphate)nucleosides of general formula 1, wherein A^1 is a fluorine atom, azide or hydroxyl group, A^2 is a hydrogen atom, B^1 is adenine, 2-chloroadenine, 2-bromoadenine, 2-fluoroadenine, 2-iodoadenine, hypoxantine, guanine, cytosine, 5-fluorocytosine, 5- bromocytosine, 5-iodocytosine, 5-chlorocytosine, azacytosine, thymine, 5-fluorouracil, 5- bromouracil, 5-iodouracil, 5-chlorouracil, 5-(2-bromovinyl)uracil, 2-pyrimidione residue, W^1 is an oxygen or carbon atom or a methylidene group, W^2 is a carbon atom or A^1, A^2, W^2 jointly represent a sulfur atom or an oxygen atom, Z^1 is a hydrogen or fluorine atom or a hydroxyl group or an alkoxyl group, Z^2 is a hydrogen or fluorine atom or a hydroxyl or methyl group or Z^1 and Z^2 jointly represent a fluoromethylene group or A^1, A^2, Z^1 and Z^2 jointly represent a carbon-carbon double bond, X^1, X^2 and Y represent an oxygen atom or a sulfur atom, R^1 and R^2 represent a simple alkyl, aryl or a hydrogen atom and the process for the manufacture thereof.

WO 2009/005382 A2

Derivatives of nucleoside-5'-*O*-hypophosphates and their mono- and dithiohypophosphate analogues and the process for the manufacture thereof

The subject of the invention includes derivatives of nucleoside-5'-*O*-hypophosphates and their mono- and dithiohypophosphate analogues, in particular 5'-*O*-[β,β-dialkyl-(α-thiohypophosphate)]- and 5'-*O*-[β,β-dialkyl-(α,α-dithiohypophosphate)]- and 5'-*O*-[β,β-dialkyl-(α,β-dithiohypophosphate)- and 5'-*O*-[β-alkyl-(α-thiohypophosphate)]- and 5'-*O*-[β-alkyl-(α,α-dithiohypophosphate)]- and 5'-*O*-(α-thiohypophosphate)]- and 5'-*O*-(α,α-dithiohypophosphate)-nucleosides of general formula **1**, wherein A^1 is a fluorine atom, azide or hydroxyl group, A^2 is a hydrogen atom, B^1 is adenine, 2-chloroadenine, 2-bromoadenine, 2-fluoroadenine, 2-iodoadenine, hypoxantine, guanine, cytosine, 5-fluorocytosine, 5-bromocytosine, 5-iodocytosine, 5-chlorocytosine, azacytosine, thymine, 5-fluorouracil, 5-bromouracil, 5-iodouracil, 5-chlorouracil, 5-(2-bromovinyl)uracil, 2-pyrimidione residue, W^1 is an oxygen or carbon atom or a methylidene group, W^2 is a carbon atom or W^2 with A^1 and A^2 represent a sulfur atom or an oxygen atom, Z^1 is a hydrogen or fluorine atom or a hydroxyl group or an alkoxyl group, Z^2 is a hydrogen or fluorine atom or a hydroxyl or methyl group or Z^1 and Z^2 jointly represent a fluoromethylene group or A^1, A^2, Z^1 and Z^2 jointly represent a carbon-carbon double bond, X_1, X_2 and Y represent an oxygen atom or a sulfur atom, R^1 and R^2 represent an alkyl, aryl or a hydrogen atom associated with amine, and the process for the manufacture of derivatives of nucleoside-5'-*O*-hypophosphates and their mono- and dithiohypophosphate analogues of general formula **1**, wherein A^1, A^2, B^1, W^1, W^2, Z^1, Z^2, R^1, R^2, X_1, X_2 and Y are as above.

Nucleoside polyphosphates whose structures contain a phosphorus-phosphorus bond between the phosphorus atoms at the alpha and beta positions of the polyphosphate chain may reveal inhibiting activity with respect to polymerases.

The derivatives of nucleoside-5'-*O*-hypophosphates and their mono- and dithiohypophosphate analogues, in particular 5'-*O*-[β,β-dialkyl-(α-thiohypophosphate)]- and 5'-*O*-[β,β-dialkyl-(α,α-dithiohypophosphate)]- and 5'-*O*-[β,β-dialkyl-(α,β-dithiohypophosphate)- 5'-*O*-[β-alkyl-(α-thiohypophosphate)]- and 5'-*O*-[β-alkyl-(β,β-dithiohypophosphate)]- and 5'-*O*-(α-thiohypophosphate)]- and 5'-*O*-(α,α-dithiohypophosphate)-nucleosides of the present invention are of general formula **1**, wherein A^1 is a fluorine atom, azide or hydroxyl group, A^2 is a hydrogen atom, B^1 is adenine, 2-chloroadenine, 2-bromoadenine, 2-fluoroadenine, 2-iodoadenine, hypoxantine, guanine, cytosine, 5-fluorocytosine, 5-bromocytosine, 5-iodocytosine, 5-chlorocytosine, azacytosine, thymine, 5-fluorouracil, 5-bromouracil, 5-iodouracil, 5-chlorouracil, 5-(2-bromovinyl)uracil, 2-pyrimidione residue, W^1 is an oxygen or carbon atom or a methylidene group, W^2 is a carbon atom or W^2, A^1 and A^2 jointly represent a sulfur atom or an oxygen atom, Z^1 is a hydrogen or fluorine atom or a hydroxyl group or an alkoxyl group, Z^2 is a hydrogen or fluorine atom or a hydroxyl or methyl group or Z^1 and Z^2 jointly represent a fluoromethylene group or A^1, A^2, Z^1 and Z^2 jointly represent a carbon-carbon double bond, X_1, X^2 and Y represent an oxygen atom or a sulfur atom, R^1 and R^2 represent an alkyl, aryl or a hydrogen atom associated with amine.

The process for the manufacture of derivatives of nucleoside-5'-*O*-hypophosphates and their mono- and dithiohypophosphate analogues of general formula **1**, wherein A^1, A^2, B^1, R^1, R^2, W^1, W^2, Z^1, Z^2, X_1, X_2 and Y are as above according to the present invention consists in that the nucleoside derivatives of general formula **2**, wherein R^3, R^4, R^5 and R^6 represent a hydrogen atom, simple alkyl or aryl with 1 to 6 carbon atoms, wherein A^2, W^1 are as above, A^3 is a fluorine atom, azide group or a protected hydroxyl group, W^2 is a carbon atom or A^2, A^3, W^2 jointly represent a sulfur atom or oxygen atom, B^2 is adenine, 2-chloroadenine, 2-bromoadenine, 2-fluoroadenine, 2-iodoadenine, hypoxantine, guanine or cytosine residue of formulae **3, 4, 5** wherein Z^5 is a hydrogen atom or a known exoamine protecting group, Z^6 is a hydrogen atom or a chlorine, fluorine, bromine or iodine atom, Z^7 is a hydrogen atom or a chlorine, fluorine, bromine or iodine atom or B^2 is a thymine residue or azacytosine residue or 5-fluorouracil, 5-bromouracil, 5-iodouracil, 5-chlorouracil, 5-(2-bromovinyl)uracil residue or 2-pyrimidione residue and Z^3 is a hydrogen, fluorine atom or a protected hydroxyl group, Z^4 is a hydrogen, fluorine atom or a protected hydroxyl group or a methyl group or Z^3 and Z^4

jointly represent a fluoromethyl group or A^2, A^3, Z^3, Z^4 jointly represent a carbon-carbon double bond undergo a condensation reaction with phosphorous acid diesters of general formula $(R^7O)(R^8O)POH$ or thiophosphorous acid diesters of general formula $(R^7O)(R^8O)PSH$, wherein R^7 and R^8 represent an alkyl or aryl, and the condensation is carried out in anhydrous organic solvents in the presence of condensation activators and after reaction completion the groups which protect 2′- and 3′-hydroxyl groups and the groups which protect nucleoside exoamine groups are removed according to known prior art.

The protective groups for the 2'- and 3'-hydroxyl groups preferably include known protecting groups selected from a group consisting of the acyl, benzoyl, 4,4′-dimethoxytriphenylmethyl, benzyl, trialkylsilyl, in particular a trimethylsilyl group.

The protective groups used for the exoamine groups include known protecting groups preferably selected from a group consisting of the phenoxyacetyl, isopropoxyacetyl, isobutyryl, benzoyl, (dialkylamino)methylidene and (dialkylamino)ethylidene group.

The condensation activators used include non-nucleophilic alcoholates, such as potassium *tert*-butanolate, or amines, such as imidazole, 1-methylimidazole, 4-dimethylaminopyridine, triethylamine and in particular 1,8-diazabicyclo[5.4]undec-7-ene (DBU).

The condensàtion reaction is preferably carried out in an anhydrous organic solvent selected from a group consisting of acetonitrile, methylene chloride, N,N-dimethylformamide, pyridine, dioxane and tetrahydrofuran.

In the process according to the present invention, compounds of formula **1**, wherein X_1, X_2 and Y represent an oxygen atom, are preferably obtained from previously prepared compounds of formula **1** wherein X_1=S or X_1=O, X_2=S, Y=S or Y=O in the oxidation reaction using oxidation reagents known in the art, particularly iodosobenzene and iodoxobenzene. The process according to the present invention is general and may be used in the direct synthesis of nucleoside-5′-*O*-hypophosphates of general formula **1**.

In the process according to the present invention, compounds of formula **1**, wherein R^1 represents a hydrogen atom associated with amine, are preferably obtained from previously prepared compounds of formula **1**, wherein R^1 is a methyl group and R^2 is an alkyl or aryl in the reaction with primary amines or ammonia, particularly with *tert*-butylamine. The process according to the present invention is general and may be used in the direct synthesis of 5′-*O*-[β-alkyl-(α-thiohypophosphate)]- and 5′-*O*-[β-alkyl-(α,α-dithiohypophosphate)]nucleosides of general formula **1**.

In the process according to the present invention, compounds of formula **1**, wherein R^1 and R^2 represent a hydrogen atom associated with amine, are preferably obtained from previously prepared compounds of formula **1**, wherein R^1 and R^2 represent an alkyl or R^1 is a hydrogen atom associated with amine and R^2 is an alkyl in the reaction with trimethylsilyl halide, particularly with bromotrimethylsilane. The process according to the present invention is general and may be used in the direct synthesis of 5'-*O*-(α-thiohypophosphate)- and 5'-*O*-(α, α-dithiohypophosphate)-nucleosides of general formula **1.**

The process of the invention may be utilised to manufacture 5'-*O*-[β,β-dialkyl-(α-thiohypophosphate)]- and 5'-*O*-[β,β-dialkyl-(α,α-dithiohypophosphate)]- and 5'-*O*-[β,β-dialkyl-(α,β-dithiohypophosphate)- and 5'-*O*-[β-alkyl-(α-thiohypophosphate)]- and 5'-*O*-[β-alkyl-(α,α-dithiohypophosphate)]- and 5'-*O*-(α-thiohypophosphate)]- and 5'-*O*-(α,α–dithiohypophosphate)-nucleosides of general formula **1**, wherein A^1 is a fluorine atom, azide or hydroxyl group, A^2 is a hydrogen atom, B^1 is adenine, 2-chloroadenine, 2-bromoadenine, 2-fluoroadenine, 2-iodoadenine, hypoxantine, guanine, cytosine, 5-fluorocytosine, 5-bromocytosine, 5-iodocytosine, 5-chlorocytosine, azacytosine, thymine, 5-fluorouracil, 5-bromouracil, 5-iodouracil, 5-chlorouracil, 5-(2-bromovinyl)uracil, 2-pyrimidione residue, W^1 is an oxygen or carbon atom or a methylidene group, W^2 is a carbon atom or A^1, A^2, W^2 jointly represent a sulfur atom or an oxygen atom, Z^1 is a hydrogen or fluorine atom or a hydroxyl group or an alkoxyl group , Z^2 is a hydrogen or fluorine atom or a hydroxyl or methyl group or Z^1 and Z^2 jointly represent a fluoromethylene group or A^1, A^2, Z^1 and Z^2 jointly represent a carbon-carbon double bond, X^1, X^2 and Y represent an oxygen atom or a sulfur atom, and X^1, X^2 and Y may independently represent an oxygen or sulfur atom, R^1 and R^2 represent an alkyl, aryl or a hydrogen atom associated with amine.

The process according to the present invention is illustrated in the examples which follow.

Example I

5'-*O*-[β,β-diethyl-(α-thiohypophosphate)]-uridine

To a solution of 0.05 mmol of 5'-(2-thio-[1,3,2]-oxathiaphospholanyl)-$O^{2'},O^{3'}$-diisopropoxyacetyluridine in 0.5 mL of acetonitrile 0.05 mmol of diethyl phosphite was added and subsequently 0.055 mmol of DBU was added dropwise. The reaction was carried out at ambient temperature for 2.5 hours (TLC and ^{31}P NMR analyses). The

reaction mixture was then concentrated under reduced pressure and aqueous saturated ammonia (3 mL) was added to the residue (ambient temperature, 1 hour). The ammonia was subsequently distilled off under reduced pressure. The product was isolated in a 19% yield using ion-exchange chromatography (DEAE-Sephadex A-25) with TEAB (0.10-0.80M; pH=7.5) as the eluent. *^{31}P NMR (D_2O)* δ: 55.790, 13.225 ppm, $^1J_{P-P}$ = 501Hz, *MALDI-TOF m/z*: (M-1) 459.2.

Example II

5'-*O*-[β,β-dimethyl-(α-thiohypophosphate)]-uridine

To a solution of 0.05 mmol of 5'-(2-thio-[1,3,2]-oxathiaphospholanyl)-*O*$^{2'}$,*O*$^{3'}$-diisopropoxyacetyluridine in 0.5 mL of acetonitrile 0.05 mmol of dimethyl phosphite was added and subsequently 0.055 mmol of DBU was added dropwise. The reaction was carried out at ambient temperature for 2.5 hours (TLC and ^{31}P NMR analyses). The reaction mixture was then concentrated under reduced pressure and aqueous saturated ammonia (3 mL) was added to the residue (ambient temperature, 1 hour). The ammonia was subsequently distilled off under reduced pressure. The product was isolated in a 26% yield using ion-exchange chromatography (DEAE-Sephadex A-25) with TEAB (0.10-0.60M; pH=7.5) as the eluent. *^{31}P NMR (D_2O)* δ: 55.177, 15.653 ppm, $^1J_{P-P}$ = 501Hz, *MALDI-TOF m/z*: (M-1) 431.0.

Example III

5'-*O*-[β-methyl-(α-thiohypophosphate)]-uridine

To 6 µmol of 5'-*O*-[β,β-dimethyl-(α-thiohypophosphate)]-uridine 0.5 ml of *t*-butylamine was added. The reaction was carried out at ambient temperature for 4 days (HPLC and ^{31}P NMR analyses) until the complete conversion of the substrate into the product. The reaction mixture was subsequently concentrated under reduced pressure with the final yield of 100%. *^{31}P NMR (D_2O)* δ: 65.107, 9.813 ppm, $^1J_{P-P}$ = 531Hz, *MALDI-TOF m/z*: (M-2) 416.9.

Example IV

5'-*O*-(α-thiohypophosphate)-uridine

To a solution of 0.05 mmol of 5'-(2-thio-[1,3,2]-oxathiaphospholanyl)-*O*$^{2'}$,*O*$^{3'}$-diisopropoxyacetyluridine in 0.5 mL of acetonitrile 0.05 mmol of dimethyl phosphite was added and subsequently 0.055 mmol of DBU was added dropwise. The reaction was carried out at ambient temperature for 2.5 hours (TLC and ^{31}P NMR analyses). The

reaction mixture was subsequently cooled to -40°C and 0.2 mmol of bromotrimethylsilane was added dropwise. The mixture was heated at a rate of 10°C per 0.5 hour. Once the mixture was heated to ambient temperature, the reaction was carried out for 12 hours. The reaction mixture was then concentrated under reduced pressure and aqueous saturated ammonia (3 mL) was added to the residue (ambient temperature, 1 hour). The ammonia was subsequently distilled off under reduced pressure. The product was isolated in a 18% yield using ion-exchange chromatography (DEAE-Sephadex A-25) with TEAB (0.10-0.60M; pH=7.5) as the eluent and gel filtration on Sephadex LH-20 using water as the eluent. *^{31}P NMR (D_2O) δ*: 66.366, 7.643 ppm, $^{1}J_{P-P}$ = 543Hz, *MALDI-TOF m/z*: (M-1) 403.0.

Example V

5'-*O*-[β,β-diethyl-(α,β-dithiohypophosphate)]-uridine

To a solution of 0.05 mmol of 5'-(2-thio-[1,3,2]-oxathiaphospholanyl)-*O*$^{2'}$,*O*$^{3'}$-diisopropoxyacetyluridine in 0.5 mL of acetonitrile 0.05 mmol of diethyl thiophosphite was added and subsequently 0.055 mmol of DBU was added dropwise. The reaction was carried out at ambient temperature for 16 hours (TLC and ^{31}P NMR analyses). The reaction mixture was then concentrated under reduced pressure and aqueous saturated ammonia (3 mL) was added to the residue (ambient temperature, 1 hour). The ammonia was subsequently distilled off under reduced pressure. The product was isolated in a 23% yield using ion-exchange chromatography (DEAE-Sephadex A-25) with TEAB (0.10-0.60M; pH=7.5) as the eluent. *^{31}P NMR (D_2O) δ*: 83.995, 83.804, 60.632, 60.467 ppm, $^{1}J_{P-P}$ = 384Hz, *MALDI-TOF m/z*: (M-1) 475.1.

Example VI

5'-*O*-β-methylhypophosphatecytidine

To a solution of 16 μmol of 5'-*O*-[β-methyl-(α-thiohypophosphate)]-cytidine in 2 ml of methanol 16 μmol of iodoxobenzene was added. The reaction was carried out at ambient temperature for 12 hours (HPLC and ^{31}P NMR analyses). The reaction mixture was subsequently concentrated under reduced pressure. The product was isolated in an 82% yield using ion-exchange chromatography (DEAE-Sephadex A-25) with TEAB (0.0-0.3M; pH=7.5) as the eluent. *^{31}P NMR (D_2O) δ*: 9.725 ppm, *MALDI-TOF m/z*: (M-1) 412.0.

Example VII

5'-*O*-β,β-dimethylhypophosphateuridine

To a solution of 15 μmol of 5'-O-[β,β-dimethyl-(α-thiohypophosphate)]-uridine in 0.5 ml of methanol 15 μmol of iodoxobenzene was added. The reaction was carried out at ambient temperature for 12 hours (HPLC and ^{31}P NMR analyses). The reaction mixture was subsequently concentrated under reduced pressure. The product was isolated in a 79% yield using ion-exchange chromatography (DEAE-Sephadex A-25) with TEAB (0.0-0.3M; pH=7.5) as the eluent. *^{31}P NMR (D_2O) δ*:19.488, -0.450 ppm, $^1J_{P-P}$=657Hz , *MALDI-TOF m/z*: (M-1) 415.0.

Example VIII

5'-*O*-[β-methyl-(α-thiohypophosphate)]-2'-*O*-methyl-guanosine

To a solution of 0.20 mmol of 5'-(2-thio-[1,3,2]-oxathiaphospholanyl)-*O*$^{3'}$-acety-2'-*O*-methyl-*N*-isobutyryl-guanosine in 1 mL of acetonitrile 0.20 mmol of dimethyl phosphite was added and subsequently 0.23 mmol of DBU was added dropwise. The reaction was carried out at ambient temperature for 2.5 hours (TLC and ^{31}P NMR analyses). The reaction mixture was then concentrated under reduced pressure and aqueous saturated ammonia (3 mL) was added to the residue (temperature 45°C, 4 hour). The ammonia was subsequently distilled off under reduced pressure. The product was isolated in a 16% yield using ion-exchange chromatography (DEAE-Sephadex A-25) with TEAB (0.10-0.60M; pH=7.5) as the eluent. *^{31}P NMR (D_2O) δ*: 60.79, 6.28 ppm, $^1J_{P-P}$ = 450Hz, *MALDI-TOF m/z*: (M-1) 470.1.

Patent claims

1. Derivatives of nucleoside-5′-*O*-hypophosphates and their mono- and dithiohypophosphate analogues of general formula **1**, wherein A^1 represents a fluorine atom or azide or hydroxyl group, A^2 represents a hydrogen atom, B^1 represents an adenine, 2-chloroadenine, 2-fluoroadenine, 2-bromoadenine, 2-iodoadenine, hypoxanthine, guanine, cytosine, 5-fluorocytosine, 5-bromocytosine, 5-iodocytosine, 5-chlorocytosine, azacytosine, thymine, 5-fluorouracil, 5-bromouracil, 5-iodouracil, 5-chlorouracil, 5-(2-bromovinyl)uracil or 2-pyrimidione residue, W^1 represents an oxygen or carbon atom or a methylidene group, W^2 represents a carbon atom or A^1, A^2, W^2 jointly represent a sulfur or oxygen atom, Z^1 represents a hydrogen or fluorine atom or hydroxyl group or an alkoxyl group, Z^2 represents a hydrogen or fluorine atom or hydroxyl or methyl group or Z^1 and Z^2 jointly represent a fluoromethylene group or A^1, A^2, Z^1 and Z^2 represent a carbon-carbon double bond, X_1, X_2 and Y represent an oxygen or sulfur atom, R^1 and R^2 represent an alkyl or aryl or a hydrogen atom.

2. A process for the manufacture of nucleoside-5′-*O*-hypophosphates and their mono- and dithiohypophosphate analogues, in particular 5′-*O*-[β,β-dialkyl-(α-thiohypophosphate)]-, 5′-*O*-[β,β-dialkyl-(α,α-dithiohypophosphate)]-, 5′-*O*-[β,β-dialkyl-(α,β-dithiohypophosphate)-, 5′-*O*-[β-alkyl-(α-thiohypophosphate)]-, 5′-*O*-[β-alkyl-(α,α-dithiohypophosphate)]-, 5′-*O*-(α-thiohypophosphate)]- and 5′-O-(α,α-dithiohypophosphate)-nucleosides of general formula **1**, wherein A^1 is a fluorine atom, azide or hydroxyl group, A^2 is a hydrogen atom, B^1 is adenine, 2-chloroadenine, 2-bromoadenine, 2-fluoroadenine, 2-iodoadenine, hypoxantine, guanine, cytosine, 5-fluorocytosine, 5-bromocytosine, 5-iodocytosine, 5-chlorocytosine, azacytosine, thymine, 5-fluorouracil, 5-bromouracil, 5-iodouracil, 5-chlorouracil, 5-(2-

bromovinyl)uracil, 2-pyrimidione residue, W^1 is an oxygen or carbon atom or a methylidene group, W^2 is a carbon atom or A^1, A^2, W^2 represent a sulfur atom or an oxygen atom, Z^1 is a hydrogen or fluorine atom or a hydroxyl group or an alkoxyl group, Z^2 is a hydrogen or fluorine atom or a hydroxyl or methyl group or Z^1 and Z^2 jointly represent a fluoromethylene group or A^1, A^2, Z^1 and Z^2 jointly represent a carbon-carbon double bond, X^1, X^2 and Y represent an oxygen atom or a sulfur atom, R^1 and R^2 represent an alkyl, aryl or a hydrogen atom associated with amine characterised in that the condensation involves phosphorous acid diesters of general formula $(R^7O)(R^8O)POH$ or thiophosphorous acid diesters of general formula $(R^7O)(R^8O)PSH$, wherein R^7 and R^8 represent an alkyl or aryl with the nucleoside derivatives of general formula **2**, wherein A^2, A^3, B^2, R^3, R^4, R^5, R^6, W^1, W^2, Z^3, Z^4 are as above, X_1, X_2 and Y represent an oxygen atom, and the condensation is carried out in anhydrous organic solvents in the presence of condensation activators and after reaction completion the groups which protect 2'- and 3'-hydroxyl groups and the groups which protect nucleoside exoamine groups are removed according to known prior art.

3. Process according to Claim 2 characterised in that the protective groups for 2'- and 3'-hydroxyl groups include known protecting groups selected from a group consisting of the acyl, aroyl, 4,4'-dimethoxytriphenylmethyl, arylalkyl, trialkylsilyl, and in particular trimethylsilyl group.

4. Process according to Claim 2 characterised in that the protective groups used for exoamine groups include known protecting groups selected from a group consisting of the phenoxyacetyl, isopropoxyacetyl, isobutyryl, benzoyl, (dialkylamino)methylidene and (dialkylamino)ethylidene group.

5. Process according to Claim 2 characterised in that the condensation activators used include non-nucleophilic alcoholates, such as potassium tert-butanolate, or amines, such as imidazole, 1-methylimidazole, 4-dimethylaminopyridine, triethylamine and in particular 1,8-diazabicyclo[5.4]undec-7-ene (DBU).

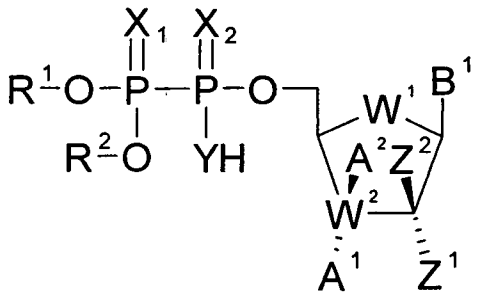
6. Process according to Claim 2 characterised in that the condensation reaction is carried out in an anhydrous organic solvent selected from a group consisting of acetonitrile, methylene chloride, N,N-dimethylformamide, pyridine, dioxane and tetrahydrofuran.

7. Process according to Claim 2 characterised in that a compound of formula **1**, wherein X_1, X_2 and Y represent an oxygen atom, is obtained from previously prepared compounds of formula **1**, wherein X_1=S or X_1=O, X_2=S, Y=S or Y=O in an oxidation reaction using oxidation reagents known in the art, particularly iodosobenzene and iodoxobenzene.

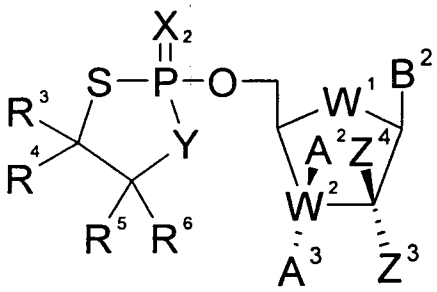
8. Process according to Claim 2 characterised in that a compound of formula **1**, wherein R^1 represents a hydrogen atom associated with amine, is preferably obtained from previously prepared compounds of formula **1**, wherein R^1 represents a methyl group and R^2 represents an alkyl or aryl in the reaction with primary amines or ammonia, particularly with *tert*-butylamine.

9. Process according to Claim 2 characterised in that a compound of formula **1**, wherein R^1 and R^2 represent a hydrogen atom associated with amine, is preferably obtained from previously prepared compounds of formula 1 wherein R^1 and R^2 represent an alkyl or R^1 is a hydrogen atom or a hydrogen atom associated with amine and R^2 is an alkyl in the reaction with trimethylsilyl halide, particularly with bromotrimethylsilane.

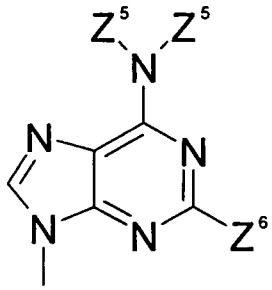
BPP/4079/CH5/2007



Formula 1



Formula 2



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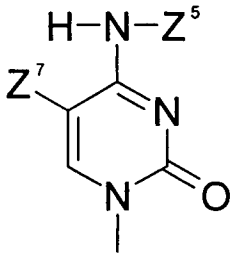

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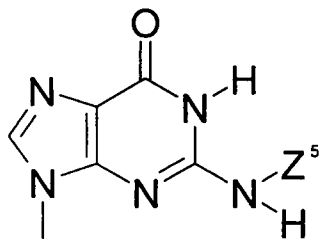

Formula 5