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New Synthesis of Sugar, Nucleoside and α-Amino Acid Phosphonates.

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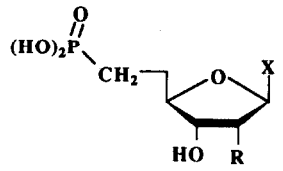
Abstract: *Photolysis of N-hydroxy-2-thiopyridone esters derived from uronic acids or α-amino acids in presence of vinyl phosphonate affords the corresponding phosphonate derivatives. A convenient route for the synthesis of the isostere of AZT-5' monophosphate is described .*

Résumé: *La photolyse des esters thiohydroxamiques des acides uroniques dérivés du D-ribose, des nucléosides ou des acides aminés en présence de diéthylvinyl phosphonate fournit les dérivés phosphonates correspondants. La synthèse de l'isostère de l'AZT-5' monophosphonate est décrite.*

The replacement of the *O*-phosphate group in a biologically active molecule by a phosphonic acid or methylenephosphonic acid might be expected to have interesting biological effects[1,2]. This modification can confer to these isosteres a greater stability since the carbon-phosphorus bond cannot be hydrolyzed by the enzymes involved in O-phosphate ester cleavage. It was presumed that the isosteric phosphonic acid analogues in which a methylene replaces the oxygen atom of the phosphate, would be better substrates than the nonisosteric compounds due to their similarity in size and shape with natural phosphates[1] (Fig. 1) .



(1) X= OCH_3, R= OH

(2) X= Adenine, R= OH

(3) X= Uracil, R= OH

(4) X: Thymine, R= H

Figure 1

Several approaches to the preparation of isosteric or nonisosteric phosphonate analogues of carbohydrate and nucleoside phosphates have been reported. The most used methods are those involving a stabilized Wittig reagent or the Arbuzov reaction on the halogen derivative. The isosteric analogue[3] of ribose 5-phosphate **1** was prepared by treatment of a suitably protected *β-D*-ribose-5-aldehyde with the stable ylide [Ph_3P=CHPO(OPh)$_2$]. This approach was used for the synthesis of many other sugars and also for the preparation of isosteric phosphonic analogues of nucleosides, such as, the isosteric phosphonic analogues of adenosine[4] **2**, uridine[4] **3** and thymidine[5] **4**. The second method (Arbuzov reaction) was used to prepare the phosphonate nucleosides[6] **2** and **3**.

Several methods[7,8] for the racemic synthesis of phosphonate analogues of amino acids have been described but only a few examples of their asymmetric synthesis have been reported. Minowa and coll.[9] described the asymmetric synthesis of *(D)*-2-amino-4-phosphonobutyric acid which possesses herbicidal and antiviral activities. Ornstein[10] reported the enantioselective synthesis of *(D)*-2-amino-5-phosphonovaleric acid which is a potent antagonist of the excitatory amino acid receptors[8].

We decided to develop an alternative, more efficient, route for the introduction of the carbon-phosphorus bond. For this objective, radical chemistry[11] appeared to us as a suitable method. We have recently reported[12] that radicals, derived from isopropylidene uronic esters of *N*-hydroxy-2-thiopyridone, add to activated olefins, giving the elongated furanosides at C-4' with good stereoselectivity (retention of configuration at C-4'). The high stereoselectivity was attributed to the steric bulk of the dimethylketal function [12,13]. Using these type of radicals in the presence of the commercially available vinyl phosphonate **5** and trimethyl-2-phosphonoacrylate **6**, we report in this paper the synthesis of the phosphonates of sugars, nucleosides and α-amino acids[2,17] (Fig. 2 and 3).

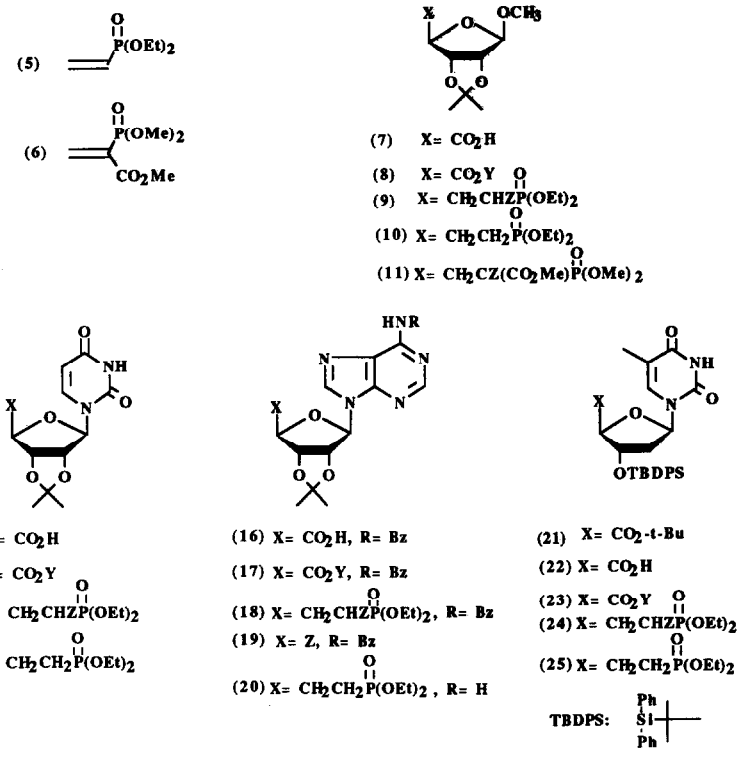


Figure 2

The known riburonic acid[14] **7** was converted to its 2-thiopyridone ester **8** using the mixed anhydride method[15] and the latter was irradiated with tungsten light in the presence of diethylvinyl phosphonate **5** to give the addition product **9** as a mixture of two diastereoisomers (65%). The thiopyridyl group of **9** was reduced with tributyltin hydride to afford the monophosphonate derivative **10**. The radical C-C bond formation was stereoselective with retention of configuration at C-4' ($J_{3',4'}$= 0). The same thiohydroxamic ester **8** was irradiated with the more reactive olefin **6** to give the derivative **11** in a satisfactory yield (70%).

We have also applied this radical chemistry for the preparation of isosteres of protected nucleoside monophosphates using the uronic acids[12] **12**, **16** and **22** prepared from uridine, adenosine and thymidine, respectively. With phosphonate **5**, the thiohydroxamic ester **13** gave the crystalline adduct **14** (60%) which afforded the stereochemically pure **15** on reduction with tributyltin hydride. Similarly, the uronic acid **16** derived from adenosine was transformed to ester **17** and on photolysis with phosphonate **5** gave the crystalline addition adduct **18** (45%) as well as the rearrangement product **19** (20%). The reduction of **18** with Raney-

nickel under reflux in ethanol afforded the reduced and debenzoylated derivative **20** as a single stereoisomer (70%).

We have also examined the stereoselectivity of the radical reaction in the biologically important 2'-deoxy-nucleosides. We expected to obtain a good stereoselectivity for the C-C bond formation at C-4' by introducing a bulky group in position 3'. The known[16] 3'-*O*-*t*-butyldiphenylsilyl derivative of thymidine was converted via the crystalline *t*-butylester **21** into the crystalline protected uronic acid[12] **22** in a good overall yield (72%) (fig. 4). The thiohydroxamic ester **23** of acid **22** was photolysed in presence of diethyvinyl phosphonate **5** to give the addition product **24** (57%) and the reduced compound **25** (13%). Reduction of the thiopyridyl function of **24** by tributyltin hydride afforded the crystalline **25** in 92% yield. This result shows the importance of the bulky silyl group in controlling radical stereoselectivity.

We have applied this chemistry to the synthesis of a phosphonate isostere[17] **30** which mimics 3'-azido-3'-deoxy-thymidine-5'-monophosphate (AZT-5'-monophosphate) (fig. 4). 3'-Azido-3'-deoxythymidine (AZT) is the only clinically useful drug for the treatment of acquired immunodeficiency syndrome (AIDS).

For this purpose, the silyl group of the derivative **25** was cleaved using tetrabutylammonium fluoride in THF and the alcohol thus obtained was mesylated to give **26** with 85% overall yield. Treatment of **26** with alkali gave the cyclic imino-ether[18] **27**, which on base catalysed hydrolysis, afforded the inverted alcohol and by mesylation the mesylate **28** (40% from mesylate **26**). Azidolysis of **28** with lithium azide in *N,N'*-dimethylformamide furnished the azide **29** (68%). Phosphonate ester cleavage of **29** with trimethylsilyl bromide in *N,N'*-dimethylformamide afforded the crystalline azido phosphonic acid **30** (90%).

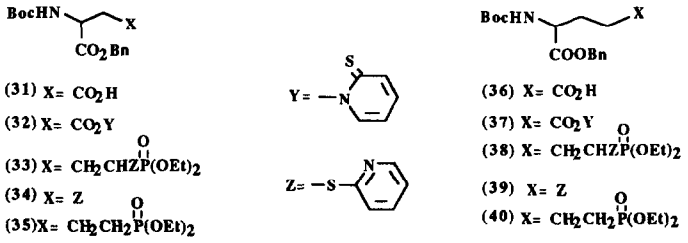


Figure 3

The *N*-hydroxy-2-thiopyridone derivatives of protected amino acids are also a good source of radicals[19]. We report here the synthesis of two phosphonate analogues of protected amino acids **35** and **40** (Fig. 3). The *N*-hydroxy-2-thiopyridone **32**, derived from aspartic acid[20] **31**, was photolysed in the presence of alkene **5** to give the addition product **33** as a mixture of two diastereoisomers at C-5 and the rearrangement product[20] **34** in 43% and 36% yields, respectively. Removal of thiopyridyl group of **33** using tributyltin hydride afforded the phosphonic analogue of 2-aminoadipic acid **35** (76%). In a similar way, the glutamic acid derivative **36** was transformed to **37**. This gave on photolysis the major product **38** (56%) and the rearrangement product **39** (24%). Reduction of **38** afforded the phosphonic analogue of 2-aminopimelic acid **40** (88%).

All these examples show that this method should be applicable to the synthesis of a great variety of phosphonate isosters of natural phosphates.

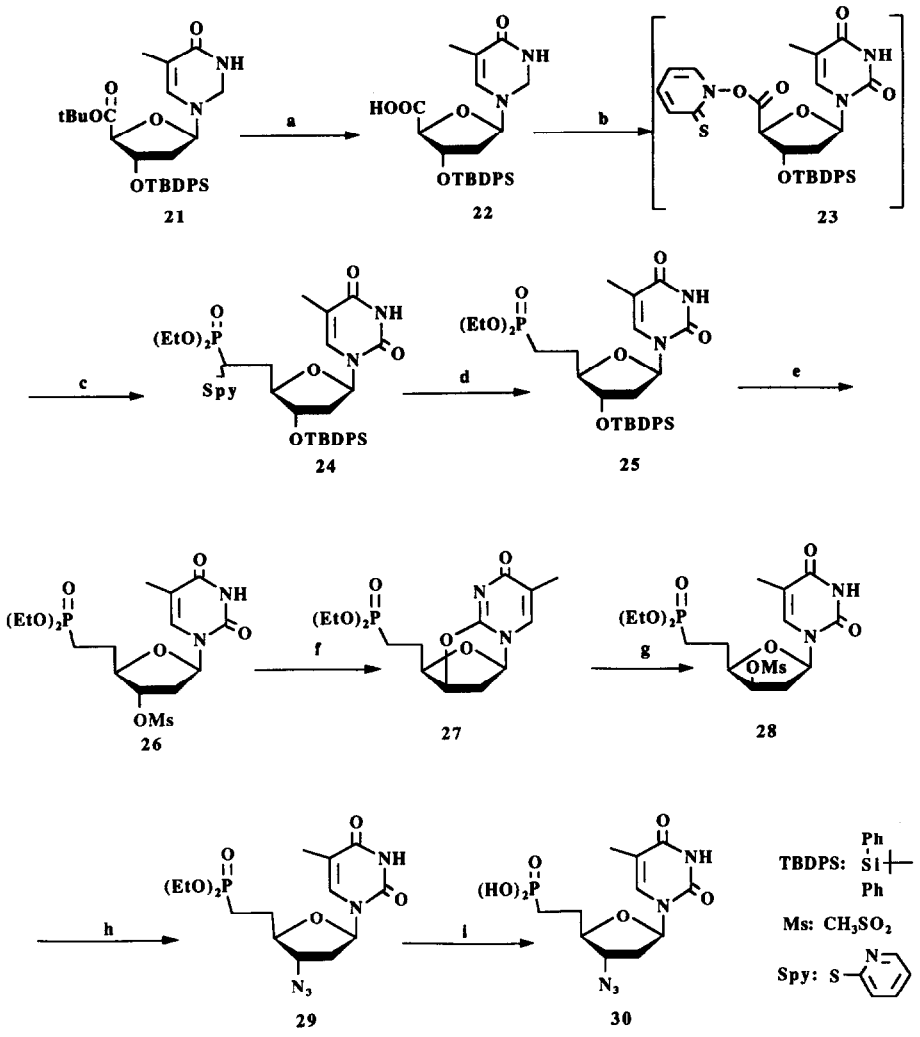


Figure 4

a: Trifluoro-acetic acid, CH_2Cl_2, RT; b: isobutyl chloroformate, *N*-methylmorpholine, THF, 0°C- *N*-hydroxy-2-thiopyridone sodium salt; c: diethylvinyl phosphonate-hν-0°C; d: Bu_3SnH, AIBN, benzene under reflux; e: 1) $Bu_4N^+ F^-$, THF, RT. 2) MsCl, pyridine; f: NaOH (1eq.), EtOH, H_2O, under reflux; g: 1) NaOH (1eq.), EtOH, H_2O under reflux. 2) MsCl, pyridine; h: LiN_3, DMF, 90°C; i: Me_3SiBr, DMF, RT.

Experimental Section

General. Column chromatography was carried out on silica gel 60 (0.040 - 0.060 μm). TLC analysis was performed on thin layer analytical plates $60F_{254}$ (Merck). ^1H and ^{13}C NMR spectra were recorded on a Bruker WP200 SY (200 MHz) or on a AM 400 (400 MHz). Chemical shifts (δ) are expressed in ppm from Me_4Si as internal standard. Coupling constants *J* are in Hz. Most spectra were taken in $CDCl_3$. In other cases the solvent is specified. Infra-red spectra were recorded on a Perkin-Elmer 297. Melting points were taken on a Reicher apparatus and are uncorrected. Routine mass spectra were recorded on an AEI MS50, AEI MS9 and Kratos MS80 (for FAB spectra). Elementary analyses were carried out at the Institut de Chimie des Substances Naturelles.

General procedure for radical addition to vinylphosphonate.

To the acid (1 mmol) in anhydrous tetrahydrofuran (10 ml) was added *N*-methylmorpholine (0.11 mL, 1 mmol) and isobutyl chloroformate (0.14 mL, 1 mmol). After stirring for 15 min. at 0° under argon the sodium salt of *N*-hydroxy-2-thiopyridone (0.178 g, 1.2 mmol) was added. The reaction mixture was stirred under argon at 0°C for 1h with exclusion of light (aluminium foil) to form the thiohydroxamic ester. Then the olefin (6 mmol. of diethylvinylphosphonate or 5 mmol. of trimethyl 2-phosphonoacrylate) was added and the yellow solution was irradiated with a tungsten lamp (250 watts) at 0° for 30 minutes. The reaction mixture was evaporated under reduced pressure to remove the excess of vinylphosphonate and the residue was diluted with $CHCl_3$ (50 ml) and washed with saturated sodium hydrogen carbonate solution (50 ml) and with water (50 ml). The organic phase was dried over $MgSO_4$ and, after filtration, was evaporated under reduced pressure. The residue thus obtained was chromatographed on a silica gel column using gradient elution.

General procedure for reduction of thiopyriridyl group.

The above addition product (1 mmol.) in dry and degased benzene (5 mL) was treated under reflux with tributyltin hydride (0.806 mL, 4 mmol.) and α,α'-azoisobutyronitrile (0.016 g, 0.1 mmol) for 24 h under argon. The reaction mixture was cooled and the solvent was evaporated under reduced pressure. The residue was chromatographed on a silica gel column.

Methyl 5,6-dideoxy-6-diethoxyphosphonate-2,3-*O*-isopropylidene-6-thio-(2'-pyridyl)-β-*D*-*ribo*-hexofuranoside 9.

Acid[14] **7** (0.218 g, 1 mmol) was treated with diethylvinylphosphonate according to the general procedure to give, after purification on a silica gel column (ethyl acetate-hexane, 6-4), the oily addition product **9** (0.291 g, 65%). MS: (C.I., m/z): 448 $(MH)^+$, 339 $(MH\text{-}Spy+H)^+$. IR: ν_{max} (film): 1580, 1240, 1100, 1040, 960 cm^{-1}. Anal.Calcd. for $C_{19}H_{30}NO_7PS$, C(51.00); H(6.71); N(3.13); P(6.93); S(7.15), Found: C(51.23); H(6.64); N(3.15), P(6.87); S(7.18).

Methyl 5,6-dideoxy-6-diethoxyphosphonate-2,3-*O*-isopropylidene-β-*D*-*ribo*-hexofuranoside 10.

The thiopyridyl group of adduct **9** (0.160 g, 0.357 mmol) was reduced with tributyltin hydride according to the general procedure to yield after chromatography on a silica gel column (ethyl acetate-hexane, 7-3) derivative **10** (0.115 g, 95%) as colorless oil. Anal.Calcd. for $C_{14}H_{27}O_7P$, C(49.70); H(7.98); P(9.17), Found: C(49.49); H(7.86); P(8.90). $[\alpha]_D^{20}$ = -2.6° (c=20.8, $CHCl_3$). MS: (C.I., m/z): 339 $(MH)^+$. IR: ν_{max} (film): 1246, 1216, 1106, 1036, 960 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δppm: 4.96 (s, 1H, H_1); 4.61 (d, 1H, H_2, $J_{2,3}$= 6 Hz); 4.53 (d, 1H, H_3); 4.10 (m, 5H, H_4, $[CH_3CH_2]_2PO$, J_{CH2CH3}= 7 Hz); 3.33 (s, 3H, OCH_3); 1.86 (m, 4H, H_5, H_6); 1.5, 1.32 (s, 6H, CMe_2); 1.33 (t, 6H, $[CH_3CH_2]_2PO$).

Methyl 5,6-dideoxy-6-dimethoxyphosphonate-2,3-*O*-isopropylidene-6-thio-(2'-pyridyl)-β-*D*-*ribo*-heptofuranosiduronate 11.

Acid **7** (0.218 g, 1 mmol) was treated with trimethyl-2-phosphonoacrylate (5 mmol.) according to the general procedure to give after purification on a silica gel column (ethyl acetate-hexane, 8-2) the oily addition product **11** (0.334 g, 70%). Anal.Calcd. for $C_{19}H_{28}NO_9PS$, C(47.79); H(5.87); N(2.93); P(6.49); S(6.70),

Found: C(47.97); H(6.05); N(2.84), P(6.76); S(6.45). MS: (C.I., m/z): 478 $(MH)^+$, 446 $(MH\text{-}MeOH)^+$, 369 $(MH\text{-}Spy+H)^+$. IR: ν_{max} (film):1730, 1580, 1236, 1060, 970, 870, 770 cm^{-1}.

(5',6'-Dideoxy-6'-diethoxyphosphonate-2',3'-*O*-isopropylidene-6'-thio-(2'-pyridyl)-β-*D*-*ribo*-hexofuranosyl)-1-uracil 14.

The acid[12] **12** (0.745 g, 2.5 mmol) was treated with diethylvinylphosphonate according the general procedure to give after purification on a silica gel column (ethyl acetate-methanol, 9.8-0.2) the crystalline adduct **14** (0.8 g, 61%). Anal.Calcd. for $C_{22}H_{30}N_3O_8PS$, C(50.09); H(5.69); N(7.96); P(5.88), S(6.07) Found: C(50.24); H(5.89); N(7.84), P(6.05), S(5.96). Mp: 75-85°C (ether-hexane). MS: (F.A.B., m/z): 528 $(MH)^+$, 112 $(base+H)^+$. IR: ν_{max} ($CHCl_3$): 1690, 1060, 970 cm^{-1}.

(5',6'-Dideoxy-6'-diethoxyphosphonate-2',3'-O-isopropylidene-β-*D*-*ribo*-hexofuranosyl)-1-uracil 15

The thiopyridyl group of adduct **14** (0.527 g, 1 mmol) was reduced with tributyltin hydride according to the general procedure to yield after chromatography on a silica gel column (ethyl acetate-methanol, 9.5-0.5) derivative **15** (0.372 g, 89%) as colorless oil. Anal.Calcd. for $C_{17}H_{27}N_2O_8P$, C(48.80); H(6.45); N(6.69); P(7.41), Found: C(49.01); H(6.60); N(6.50); P(7.17). $[\alpha]_D^{20}$ = +2.3° (c=30.33; $CHCl_3$). MS: (C.I., m/z): 419 $(MH)^+$. IR: ν_{max} ($CHCl_3$): 3337, 1690, 1060, 1590, 970 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ ppm: 7.28 (d, 1H, H_6, $J_{6,5}$= 8 Hz); 5.80 (d, 1H, H_5); 5.66 (d, 1H, $H_{1'}$, $J_{1',2'}$= 2 Hz); 5.00 (dd, 1H, $H_{2'}$, $J_{2',3'}$= 6.5 Hz); 4.65 (dd, 1H, $H_{3'}$, $J_{3',4'}$= 5 Hz); 4.13 (m, 5H, $H_{4'}$, $[CH_3CH_2]_2PO$, J_{CH2CH3}= 7 Hz); 2.05-1.83 (m, 4H, $H_{6'}$, $H_{6''}$, $H_{5'}$, $H_{5''}$); 1.56, 1.35 (2s, 6H, CMe_2); 1.33 (t, 6H, $[CH_3CH_2]_2PO$, J= 7 Hz).

(5',6'-Dideoxy-6'-diethoxyphosphonate-2',3'-*O*-isopropylidene-6'-thio-(2'-pyridyl)-β-*D*-*ribo*-hexofuranosyl)-9-N^6-benzoyl-adenine 18

The acid **16** (0.425 g, 1 mmol)[21] was treated with diethylvinylphosphonate according to the general procedure to give after purification on a silica gel column the crystalline adduct **18** (ethyl acetate-methanol, 9.5-0.5) (0.295 g, 45%) as well as the rearrangement product **19** (ethyl acetate-hexane, 7-3) (0.098 g, 20%).
Derivative 18: Anal.Calcd. for $C_{30}H_{35}N_6O_7PS$. 1/2H_2O, C(54.29); H(5.42); N(12.66); P(4.67), Found: C(54.34); H(5.34); N(12.65), P(4.48). Mp: 86-88°C (ether-hexane). MS: (F.A.B., m/z): 655 $(MH)^+$, 416 $(MH\text{-}base)^+$, 240 $(base+H)^+$. IR: ν_{max} ($CHCl_3$): 1700, 1610, 1580, 1060, 960 cm^{-1}.

Rearrangement product 19: $[\alpha]_D^{20}$ = +167° (c=0.5 $CHCl_3$). Mp: 100-105°C (CH_2Cl_2-pentane). MS: (C.I., m/z): 491 $(MH)^+$, 382 $(MH\text{-}Spy+H)^+$, 240 $(Base+H)^+$, 112 $(Spy+H)^+$. IR: ν_{max} ($CHCl_3$): 1710, 1610, 1580, 1080 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δppm: 8.95 (s, 1H, H_2); 8.26 (s, 1H, H_8); 8.55, 8.08, 7.58, 7.38, 7.13 (m, 9H, COPh, Spy); 6.71 (d, 1H, $H_{1'}$, $J_{1',2'}$= 1.5 Hz); 6.40 (s, 1H, $H_{4'}$); 5.83 (d, 1H, $H_{3'}$, $J_{3',2'}$= 6 Hz); 5.45 (dd, 1H, $H_{2'}$); 1.68, 1.64 (s, 6H, CMe_2).

(5',6'-Dideoxy-6'-diethoxyphosphonate-2',3'-O-isopropylidene-β-*D*-*ribo*-hexofuranosyl)-9-adenine 20.

To a solution of **18** (0.392 g, 0.6 mmol) in ethanol (5 mL) was added Raney-nickel under argon. The reaction mixture was heated under reflux for 24 h, then cooled and filtered on a pad of celite. The solvent was evaporated under reduced pressure and the residue was chromatographed on a silica gel column (ethyl acetate-methanol, 9-1) to give the reduced and debenzoylated product **20** as a colorless oil (0.188 g, 71%). Anal.Calcd. for $C_{18}H_{28}N_5O_6P$. 1/2H_2O, C(48.00); H(6.44), Found: C(48.14); H (6.32), $[\alpha]_D^{20}$ = +1,05 (c=12,16; $CHCl_3$). MS: (F.A.B., m/z): 442 $(MH)^+$, 307 $(MH\text{-}base)^+$, 136 $(base+H)^+$. IR: ν_{max} ($CHCl_3$): 3530, 3420, 1630, 1590, 1060, 970 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δppm: 8.40 (s, 1H, H_2); 7.98 (s, 1H, H_8); 6.15 (br s, 2H, NH_2); 6.10 (d, 1H, $H_{1'}$, $J_{1',2'}$= 2 Hz); 5.55 (dd, 1H, $H_{2'}$, $J_{2',3'}$= 6.5 Hz); 4.95 (dd, 1H, $H_{3'}$, $J_{3',4'}$= 4 Hz); 4.25 (td, 1H, $H_{4'}$, $J_{4',5'}$= 7 Hz); 4.06 (m, 4H, $[CH_3CH_2]_2PO$, J_{CH2CH3}= 7 Hz); 2.01 (m, 2H, $H_{6'}$, $H_{6''}$); 1.81 (m, 2H, $H_{5'}$, $H_{5''}$); 1.61, 1.40 (s, 6H, CMe_2); 1.28 (t, 6H, $[CH_3CH_2]_2PO$, J_{CH2CH3}= 7 Hz).

[6'-Diethoxyphosphonate-3'-*O-tert*-butyldiphenylsilyl-6'-thio-(2'-pyridyl)-2',5',6'-trideoxy-*β-D-ribo*-hexofuranosyl]-1-thymine 24.

The acid **22** (2.97 g, 6 mmol) was treated with diethylvinylphosphonate according to the general procedure to give after purification on a silica gel column with gradient elution (ethyl acetate-heptane, 1-1, ethyl acetate) the adduct **24** as a white foam (2.473 g, 57%) and the reduced crystalline product **25** (0.479, 13%). Anal.Calcd. for $C_{36}H_{46}N_3O_7PSSi$, C(59.75); H(6.36); N(5.80); P(4.28); S(4.42), Found: C(59.49); H(6.18); N(5.54); P(4.35); S(4.62).

(6'-Diethoxyphosphonate-3'-*O-tert*-butyldiphenylsilyl-2',5',6'-trideoxy-*β-D-ribo*-hexofura-nosyl)-1-thymine 25.

The thiopyridyl group of adduct **24** (2.89 g, 4 mmol) was reduced with tributyltin hydride according to the general procedure to yield after chromatography on a silica gel column with gradient elution (ethyl acetate-heptane, 1-1, ethyl acetate) derivative **25** (2.235 g, 91%) as a white foam. Anal.Calcd. for $C_{31}H_{43}N_2O_7PSi$, C(60.58); H(7.00); N(4.56); P(5.04), Found: C(60.84); H(7.19); N(4.47); P(4.87). Mp: 150-154°C (ether-pentane), $[\alpha]_D^{20}$ = +33° (c= 0.5, $CHCl_3$). MS: (F.A.B., m/z): 615 $(MH)^+$. IR: ν_{max} (nujol): 1715, 1693, 1275, 1248, 1239, 1125, 1104, 1060, 1046, 1018, 1008, 967, 709 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ ppm: 9.03 (s, 1H, NH); 7.66, 7.45 (m, 10H, Ph); 6.98 (s, 1H, H_6); 6.38 (t, 1H, $H_{1'}$, $J_{1',2'}$= $J_{1',2''}$= 7 Hz); 4.06 (m, 5H, $H_{3'}$, $[CH_3CH_2O]_2PO$); 3.38 (m, 1H, $H_{4'}$); 2.33 (m, 1H, $H_{2'}$); 1.9 (s, 3H, CH_3); 1.83-1.36 (m, 5H, $H_{2''}$, $H_{5'}$, $H_{5''}$, $H_{6'}$, $H_{6''}$); 1.26 (t, 6H, $[CH_3CH_2O]_2PO$); 1.1 (s, 9H, $[CH_3]_3CSi$).

6'-Diethoxyphosphonate-3'-O-methanesulphonyl-2',5',6'-trideoxy-*β-D-ribo*-hexofuranosyl)-1-thymine 26.

To a solution of derivative **25** (1.85 g, 3 mmol) in dry tetrahydrofuran (25 mL) was added tetrabutylammonium fluoride 1M in THF (4.5 mL, 1.5 eq.). The reaction mixture was stirred at room temperature for 1 h and evaporated to dryness under reduced pressure. The residue was chromatographed on a silica gel column (chloroform-ethanol, 9.5-0.5) to yield the corresponding alcohol as a colorless oil (1.11 g, 98%). The latter (1.11g, 2.95 mmol) was dissolved in pyridine (15 mL) and treated with mesyl chloride (0.32 mL, 4.13 mmol). The mixture was stirred at room temperature for 24 h and water (1 mL) was added at 0°C. The solution was evaporated to dryness under reduced pressure and the residue thus obtained was chromatographed on a silica gel column ($CHCl_3$-EtOH, 9.5-0.5) to give the mesylate **26** as a white foam (1.1 g, 82%). Anal.Calcd. for $C_{16}H_{27}O_9PS$, C(42.29); H(5.94); N(6.16); P(6.82); S(7.04), Found: C(42.57); H(6.18); N(5.86); P(7.02); S(7.30). $[\alpha]_D^{20}$ = +21° (c=0.83, $CHCl_3$). MS: (C.I., m/z): 455 $(MH)^+$, 359 $(MH-CH_3SO_3H)^+$, 127 (base+H)$^+$. ^1H NMR (200 MHz, $CDCl_3$): δ ppm: 9.53 (s, 1H, NH); 7.10 (s, 1H, H_6); 6.20 (t, 1H, $H_{1'}$, $J_{1',2'}$= $J_{1',2''}$= 7 Hz); 5.06 (m, 1H, $H_{3'}$, $J_{3',4'}$= $J_{3',2''}$= 3 Hz, $J_{3',2'}$= 6 Hz); 4.11 (m, 5H, $H_{4'}$, $[CH_3CH_2]_2PO$); 3.11 (s, H, CH_3SO_2); 2.63 (m, 1H, $H_{2'}$, $J_{2',2''}$= 15 Hz); 2.36 (m, 1H, $H_{2''}$); 2.15-1,.6 (m, 4H, $H_{5'}$, $H_{5''}$, $H_{6'}$, $H_{6''}$); 1.95 (s, 3H, CH_3); 1.33 (t, 6H, $[CH_3CH_2]_2PO$).

(6'-Diethoxyphosphonate-3'-O-methanesulphonyl-2',5',6'-trideoxy-*β-D-lyxo*-hexofurano-syl)-1-thymine 28.

To a solution of mesylate **26** (0.59 g, 1.3 mmol) in ethanol (100 mL) was added a solution of sodium hydroxide 0.1N (14 mL, 1 eq.). The reaction mixture was heated under reflux for 15 min. Then, was added sodium hydroxide 0.1N (14 mL, 1eq).The solution was stirred under reflux for 30 min and brought to pH 3 with a solution of HCl 1N. The solvent was evaporated under reduced pressure and the residue thus obtained was chromatographed on a silica gel column (chloroform-ethanol, 9.5-0.5) to give the alcohol (0.244 g, 50%) which was transformed directly to the mesylate derivative **28**. To a solution of the alcohol thus obtained (0.452 g, 0.917 mmol) in dry pyridine (5 mL) was added at 0°C mesyl chloride (0.107 mL, 1.5 eq.). The reaction mixture was stirred at room temperature for 24 h and water (1 mL) was added at 0°C. The solution was evaporated to dryness under reduced pressure and the residue thus obtained was chromatographed on a silica gel column ($CHCl_3$-EtOH, 9.5-0.5) to give the mesylate **28** as a white foam (0.436 g, 80%). Anal.Calcd. for $C_{16}H_{27}N_2O_9PS.1/2H_2O$, C(41.46); H(6.04); N(6.04); P(6.69); S(6.91), Found: C(41.65); H(6.13); N(6.29); P(6.95); S(6.84). $[\alpha]_D^{20}$ = -14,4° (c= 1, $CHCl_3$). MS: (F.A.B., m/z, NaCl): 455 $(MH)^+$, 127 (base+H)$^+$. IR: ν_{max} ($CHCl_3$): 3400, 1700 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ ppm: 9.56 (s, 1H, NH); 7.31 (s, 1H, H_6); 6.21 (dd, 1H, $H_{1'}$, $J_{1',2'}$= 8 Hz, $J_{1',2''}$= 2.5 Hz); 5.18 (dd, 1H, $H_{3'}$, $J_{3'2'}$= 5 Hz, $J_{3',4'}$= 2 Hz); 4.11 (m, 5H, $H_{4'}$, $[CH_3CH_2O]_2PO$); 3.1 (s, 3H, CH_3SO_3); 2.85 (m, 1H, $H_{2'}$, $J_{2',3'}$= 5 Hz, $J_{2',2''}$= 16 Hz); 2.17 (dd, 1H, $H_{2''}$); 2.02-1.86 (m, 4H, $H_{5'}$, $H_{5''}$, $H_{6'}$, $H_{6''}$); 1.95 (s, 3H, CH_3); 1.33 (t, 6H, $[CH_3CH_2O]_2PO$).

(3'-Azido-6'-diethoxyphosphonate-2',5',6'-trideoxy-β-*D*-*ribo*-hexofuranosyl)-1-thymine 29.

To a solution of mesylate **28** (0.3 g, 0.66 mmol.) in dry *N,N* dimethylformamide (3 mL) was added lithium azide (0.097 g, 3 eq.). The reaction mixture was heated at 90°C for 4 h and evaporated to dryness under reduced pressure. The residue thus obtained was chromatographed on a silica gel column ($CHCl_3$-EtOH, 9.5-0.5) to give the oily azide **29** (0.18 g, 68%). Anal.Calcd. for $C_{15}H_{24}N_5O_6P$, C(44.88); H(5.98); N(17.45); P(7.73); Found: C(45.02); H(6.06); N(17.61); P(7.48); $[\alpha]_D^{20}$ = +44° (c= 0.5, $CHCl_3$). MS: (C.I., m/z): 402 $(MH)^+$. IR: ν_{max} ($CHCl_3$): 2100, 1690, 1260, 1060, 960 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ ppm: 9.08 (s, 1H, NH); 7,18 (s, 1H, H_6); 6.15 (t, 1H, $H_{1'}$, $J_{1',2'}$= $J_{1',2''}$= 6.5 Hz); 4.18 (m, 4H, $[CH_3CH_2O]_2PO$); 4.01 (dd, 1H, $H_{3'}$, $J_{3',4'}$= $J_{3',2'}$= 6 Hz); 3.85 (m, 1H, $H_{4'}$); 2.43 (m, 2H, $H_{2'}$, $H_{2''}$); 2.1-1.83 (m, 4H, $H_{5'}$, $H_{5''}$, $H_{6'}$, $H_{6''}$); 1.98 (s, 3H, CH_3); 1.36 (t, 6H, $[CH_3CH_2O]_2PO$).

6'[3'-Azido-2',3',5',6'-tetradeoxy-β-*D*-*ribo*-hexofuranosyl)-1-thymine]-phosphonic acid 30.

To a solution of **29** (0.121 g, 0.3 mmol.) in dry *N,N*-dimethylformamide (3 mL) was added at room temperature bromotrimethylsilane (0.4 mL, 10 eq.). The reaction mixture was stirred at room temperature for 16 h and then evaporated to dryness under reduced pressure. The residue thus obtained was diluted with water (3 mL) and stirred for 15 min. The water was evaporated and the residue was chromatographed on an RP silica gel column (H_2O-CH_3CN, 9.5-0.5) to give the crystalline product **30** (0.094 g, 90%). Anal. Calcd. for $C_{11}H_{16}N_5O_6P$. $2H_2O$, C(34.65); H(5.29); N(18.37); Found: C(34.90); H(5.41); N(18.39). Mp: 46-50°C (methanol-ether). $[\alpha]_D^{20}$ = +22° (c= 0.75, H_2O). MS: (F.A.B., m/z): 390 $(MH+2Na-2)^+$. IR: ν_{max} (nujol): 2106, 1700, 1686, 1655, 1095, 988 cm^{-1}. ^1H NMR (400 MHz, D_2O): δ ppm: 7.1 (s, 1H, H_6); 5.98 (t, 1H, $H_{1'}$, $J_{1',2'}$= $J_{1',2''}$= 6 Hz); 4.05 (m, 1H, $H_{3'}$), 3.75 (m, 1H, $H_{4'}$); 2.65, 2.28 (m, 2H, $H_{2'}$, $H_{2''}$); 1.7 (s, 3H, CH_3); 1.61 (m, 4H, $H_{5'}$, $H_{5''}$, $H_{6'}$, $H_{6''}$).

Benzyl *N*-*tert*-butoxycarbonyl-2-amino-5-diethoxyphosphonate-(2'-pyridyl)-5-*L*-valeric ester 33.

The acid[20] **31** (0.969 g, 3 mmol) was treated with diethylvinylphosphonate (5 equiv.) according to the general procedure to give after purification on a silica gel column (ethyl acetate-hexane, 6-4) the colorless oily addition product **33** (0,712 g, 43%) as well as the rearrangement product **34** (ethyl acetate-hexane, 2-8) for which the physical data are identical to the literature[20] values (0.428 g, 36%).

Derivative 33: Anal. Calcd. for $C_{26}H_{37}N_2O_7PS$, C(56.52); H(6.70); N(5.07); P(5.61); S(7.79), Found: C(56.49); H(6.67); N(4.84), P(5.70); S(5.60). MS: (C.I., m/z): 553 $(MH)^+$, 442 $(MH-Spy+H)^+$. IR: ν_{max} (film): 1705, 1580, 1240, 11,60, 1040, 970 cm^{-1}

Benzyl *N*-*tert*-butoxycarbonyl-2-amino-5-diethoxyphosphonate-5-*L*-valeric ester 35

The thiopyridyl group of adduct **33** (0.552 g, 1mmol) was reduced with tributyltin hydride according to the general procedure to yield after chromatography on a silica gel column (ethyl acetate-hexane, 7-3) derivative **35** (0.39 g, 88%) as colorless oil. Anal.Calcd. for $C_{21}H_{34}NO_7P$, C(56.88); H(7.67); N(3.16); P(6.99), Found: C(56.83); H(7.39); N(3.11); P(6.75). $[\alpha]_D^{20}$ = -0,1° (c=49, $CHCl_3$). MS: (C.I., m/z): 444 $(MH)^+$, 344 $(MH-Boc+H)^+$. IR: ν_{max} (film): 1700, 1240, 1160, 1040, 970 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δppm: 7.35 (s, 5H, Ph); 5.16 (s, 2H, OCH_2Ph); 5.10 (d, 1H, *NH*Boc); 4.35 (m, 1H, H_2); 4.06 (m, 4H, $[CH_3CH_2]_2PO$, J_{CH2CH3}= 7 Hz); 1.90-1.66 (m, 6H, H_3, $H_{3'}$, H_4, $H_{4'}$, H_5, $H_{5'}$); 1.41 (s, 9H, Boc); 1.28 (t, 6H, $[CH_3CH_2]_2PO$, J= 7 Hz).

Benzyl *N*-*tert*-butoxycarbonyl-2-amino-6-diethoxyphosphonate-(2'-pyridyl)-6-*L*-pimelic ester 38

The acid[20] **36** (0.337 g, 1 mmol) was treated with diethylvinylphosphonate according to the general procedure to give after purification on a silica gel column (ethyl acetate-hexane, 6-4) the colorless oily addition product **38** (0,317 g, 56%) as well as the rearrangement product **39** (ethyl acetate-hexane, 2-8) for which the physical data are identical to the literature[20] (0.096 g, 24%).

Derivative 38: Anal.Calcd. for $C_{27}H_{39}N_2O_7PS$, C(57.24); H(6.89); N(4.94); P(5.47); S(5.65), Found: C(57.40); H(7.13); N(4.77), P(5.36); S(5.62). MS: (C.I., m/z): 567 $(MH)^+$, 458 $(MH-Spy+H)^+$. IR: ν_{max} (film): 1700, 1240,11,60, 1040, 970 cm^{-1}.

Benzyl N-tert-butoxycarbonyl-2-amino-6-diethoxyphosphonate-6-L-pimelic ester 40

The thiopyridyl group of adduct **38** (0.283 g, 0.5 mmol) was reduced with tributyltin hydride according to the general procedure to yield after chromatography on a silica gel column (ethyl acetate-hexane, 8-2) derivative **40** (0.176 g, 76%) as colorless oil. Anal.Calcd. for $C_{22}H_{36}NO_7P$, C(57.76); H(7.87); N(3.06); P(6.78), Found: C(57.70); H(8.04); N(3.04); P(6.65). $[\alpha]_D^{20}$ = -0,17° (c=24.6 $CHCl_3$). MS: (C.I., m/z): 458 $(MH)^+$, 358 $(MH\text{-}Boc+H)^+$. IR: ν_{max} (film): 1710, 1240, 1160, 1040, 970 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δppm: 7.43 (s, 5H, Ph); 5.21 (d, 2H, OCH_2Ph); 5.10 (d, 1H, *NH*Boc); 4.36 (m, 1H, H_2); 4.11 (m, 4H, $[CH_3CH_2]_2PO$, J_{CH2CH3}= 7 Hz); 1.93-1.63 (m, 8H, H_3, $H_{3'}$, H_4, $H_{4'}$, H_5, $H_{5'}$, H_6, $H_{6'}$); 1.45 (s, 9H, Boc); 1.33 (t, 6H, $[CH_3CH_2]_2PO$, J= 7 Hz).

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