Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 4, pp. 973-984, 1995

0957-4166/95 $9.50+0.00

0957-4166(95)00108-5

Stereocontrolled Synthesis of Phosphonate Derivatives of Tetrahydro- and Dihydro-2*H*-Pyranyl Nucleosides : The Selectivity of the Ferrier Rearrangement

María-Jesús Pérez-Pérez, Bogdan Doboszewski, Jef Rozenski and Piet Herdewijn*

Laboratory of Medicinal Chemistry, Rega Institute for Medical Research, Minderbroedersstraat 10, B-3000 Leuven, Belgium.

Abstract : Phosphonate derivatives of 2,5-*cis* substituted tetrahydro- and dihydro-2*H*-pyranyl nucleosides have been synthesized following a stereocontrolled approach. The key step in the synthetic pathway is the introduction of the phosphonomethoxy moiety on pentopyranosyl glycals through a Ferrier-type rearrangement, yielding the 1,4-*trans* phosphonomethyl glycosides as the major isomers. The heterocyclic base has then been incorporated following a Mitsunobu-type condensation reaction, to obtain the 2,5-*cis*-dihydro-2*H*-pyranyl nucleosides. The tetrahydro-pyranyl analogues have been prepared through hydrogenation of 2,5-*cis*-dihydro-2*H*-pyranyl nucleosides.

INTRODUCTION

2',3'-Dideoxynucleosides (ddN) are potent inhibitors of HIV replication[1] and several members of this class of compounds such as AZT, ddI, ddC and d4T are the only approved drugs for the treatment of AIDS. However, their toxicity and, in some cases, their low stability (i.e. the adenine analogue ddA[2]) has encouraged the design and synthesis of new dideoxynucleoside analogues. A particular interesting strategy is the transposition of the heterocyclic base from the 1' or anomeric position to another carbon of the sugar ring affording the so called isomeric dideoxynucleosides[3-5]. The resulting regioisomeric nucleosides have been reported to present important advantages compared to their natural analogues, such as their greater stability towards chemical or enzymatic degradation[3,4]. Also a reduced toxicity is expected based on the less discriminatory capacity of the viral enzymes compared to the host enzymes[5].

It should be mentioned that a prerequisite for the anti-HIV activity of any ddN or modified analogue is their recognition by the cellular kinases to generate the triphosphate, the real active drug[6]. In this respect, the

phosphonomethoxy moiety has been described as being isosteric and isoelectronic to the monophosphate function[7], and it has been proven that its incorporation in acyclic[8,9] and furanosyl[10] nucleosides circumvent the first phosphorylation step, which is the limiting step in the activation of many nucleoside analogues.

As part of our programme on the synthesis and antiviral evaluation of di- and tri-deoxy six membered ring nucleosides[11,12], we have recently reported on the synthesis of compounds represented by the general formulae **I** and **II** (Figure 1), both series having a phosphonomethoxy moiety in a 1,4-*cis* relationship with the heterocyclic base[13,14]. We now report on the synthesis of compounds **1a**, **2a** and their enantiomers **1b**, **2b**, where the heterocyclic base and the phosphonomethoxy moiety have been transposed compared to the natural series **I**. The synthesis of this new family of compounds is further supported by our findings that the transposition of the heterocyclic base from the 1' to the 2' position in six-membered ring nucleosides, in the so called 1,5-anhydrohexitol nucleosides (**III**), has led to antiviral activity[15]. In these compounds the relationship between the heterocyclic base and the OH to be phosphorylated is also 1,4-*cis*.

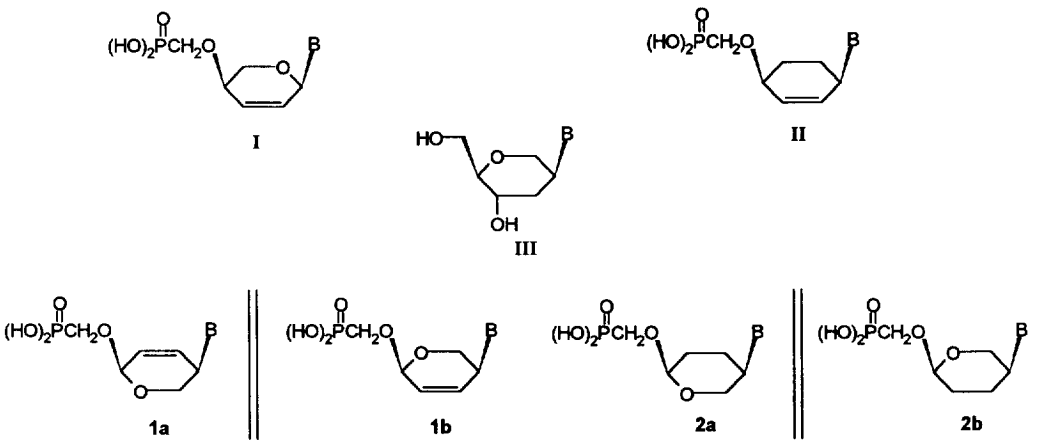
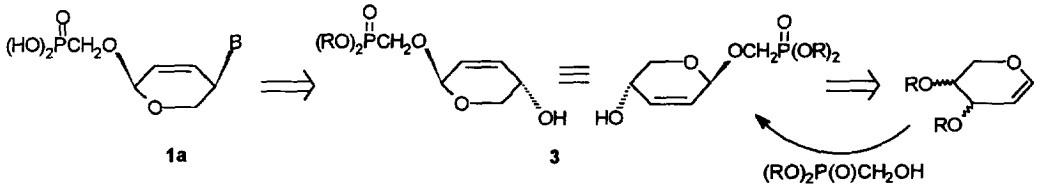


Figure 1

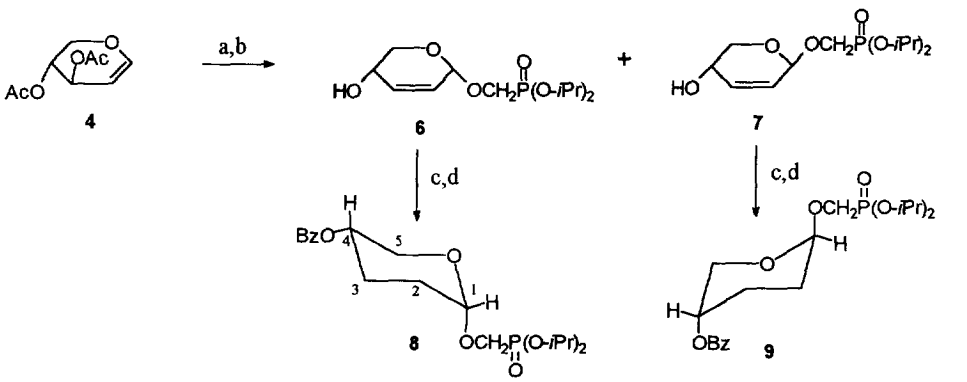
Our approach for the synthesis of the isomeric nucleosides **1** (Scheme 1) has been based on the obtention of the appropriate sugar synthon carrying the phosphonomethoxy moiety so that incorporation of the heterocyclic base should occur in the latest step. The introduction of the phosphonomethoxy moiety prior to the base allows the use of the same synthon for the synthesis of the different nucleoside derivatives and also avoids protection or undesired alkylation of the base moiety during the introduction of the phosphonomethyl function. The heterocyclic base could be introduced in such an alcohol (**3**) under Mitsunobu conditions[16,17] to yield the desired *cis* nucleoside. The allylic nature of the alcohol **3** should favour the success of this reaction[14]. For the synthesis of the key synthon **3**, we have focussed our attention on the allylic rearrangement initally described by Ferrier and coworkers on treatment of glycals with alcohols in the presence of acids[18]. Our results concerning this strategy on pentopyranosyl glycals and its utility for the synthesis of nucleoside derivatives is described and discussed in this paper. We have focussed on guanine derivatives which are, from a biological point of view, probably the most interesting compounds.



Scheme 1

RESULTS AND DISCUSSION

3,4-Di-*O*-acetyl-D-xylal (**4**) was synthesized according to a recently described procedure[19]. The diisopropyl ester of hydroxymethylphosphonic acid[20] (**5**) was chosen for the introduction of the phosphonomethoxy moiety. When the glycal **4** (Scheme 2) was reacted with the alcohol **5** in acetonitrile in the presence of trimethylsilyl triflate (TMSTf) as catalyst, two isomeric glycosides were obtained in a relation 1:3, that were resolved after deprotection of the 4-OAc-function (**6** and **7**, global yield from **4** : 72%). The determination of the stereochemistry as α-D for **6** and β-D for **7** was made from their respective derivatives **8** and **9**, obtained after hydrogenation of the double bond and benzoylation of the OH-4 function (carbohydrate nomenclature and numbering is used for compounds **4-12**). The ^{1}H NMR spectrum of compound **8**, obtained from the minor isomer **6**, showed small coupling constants for the anomeric proton (δ 4.55) and a wide multiplet for the signal corresponding to H-4 (δ 4.92-5.05), indicating an equatorial orientation for H-1 and an axial disposition for H-4. On the other hand, compound **9** obtained from the major isomer (**7**), showed small coupling constants for both H-1 and H-4, this meaning that both protons are equatorial. In both isomers **8** and **9**, the diisopropyl phosphonylmethoxy moiety is axially oriented, therefore the conformation of **8** and **9** is clearly determined by the anomeric effect. The 4-benzoyloxy moiety is axially oriented in **9** and equatorially oriented in **8**. So it can be concluded that **8**, and therefore **6**, have an α-D configuration, while **9** and thus **7** are the β-D isomers.

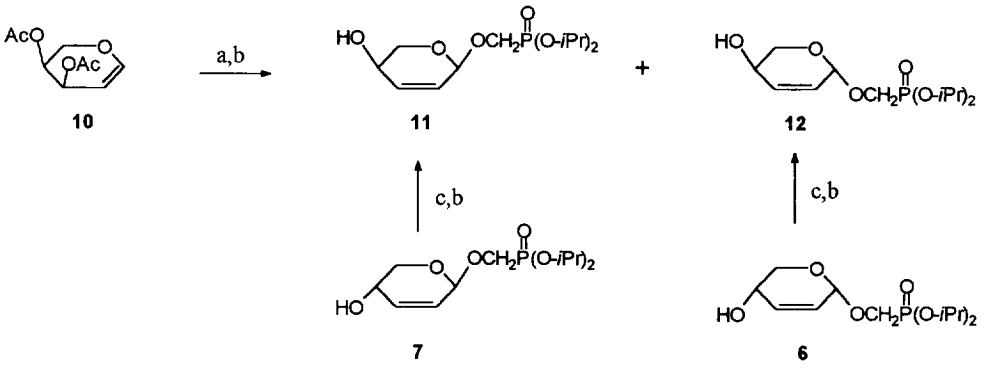


(a) (*i*-PrO)$_2$P(O)CH$_2$OH (**5**), TMStriflate, CH$_3$CN; (b) NH$_3$/MeOH; (c) H$_2$, 10%Pd/C, EtOH; (d) BzCl, pyridine

Scheme 2

The obtention of the β-D isomer as the major compound contrasts with previous reports of Ferrier rearrangement on hexopyranosid D-glycals, where the α-D-anomer is obtained as the major isomer[18,21-23]. To determine whether these results were due to the nature of the catalyst (TMS triflate), the reaction was carried out in the presence of different catalysts that have also been used in the Ferrier rearrangement and related reactions such as $BF_3.OEt_2$[22], trityl perchlorate[24], $PdCl_2$[25] or, more recently, I_2[23], but in every case the α-D-anomer (**6**) was obtained as the minor isomer.

On the other hand, starting from 3,4-di-*O*-acetyl-L-arabinal (**10**)[26,19] (Scheme 3) and performing the reaction in the same conditions as initially described (**5**, TMSTf, CH_3CN, rt), two compounds were obtained in a 1:3 ratio, that were resolved after deprotection with methanolic ammonia (global yield from **10** : 65%). These isomers (**11** as the minor and **12** as the major) showed identical NMR values and TLC mobilities to **6** and **7**, respectively, but had opposite $[\alpha]_D$ values as should correspond to enantiomers. This was further confirmed by inverting the configuration of the OH-4 center in the D-alcohols **6** and **7** under Mitsunobu conditions to afford derivatives with NMR and $[\alpha]_D$ values identical to **12** and **11**, respectively. Therefore, starting either from 3,4-di-O-acetyl-D-xylal or 3,4-di-O-acetyl-L-arabinal, the 1,4-*trans*-substituted compounds (**7** and **12**) are formed predominantly.

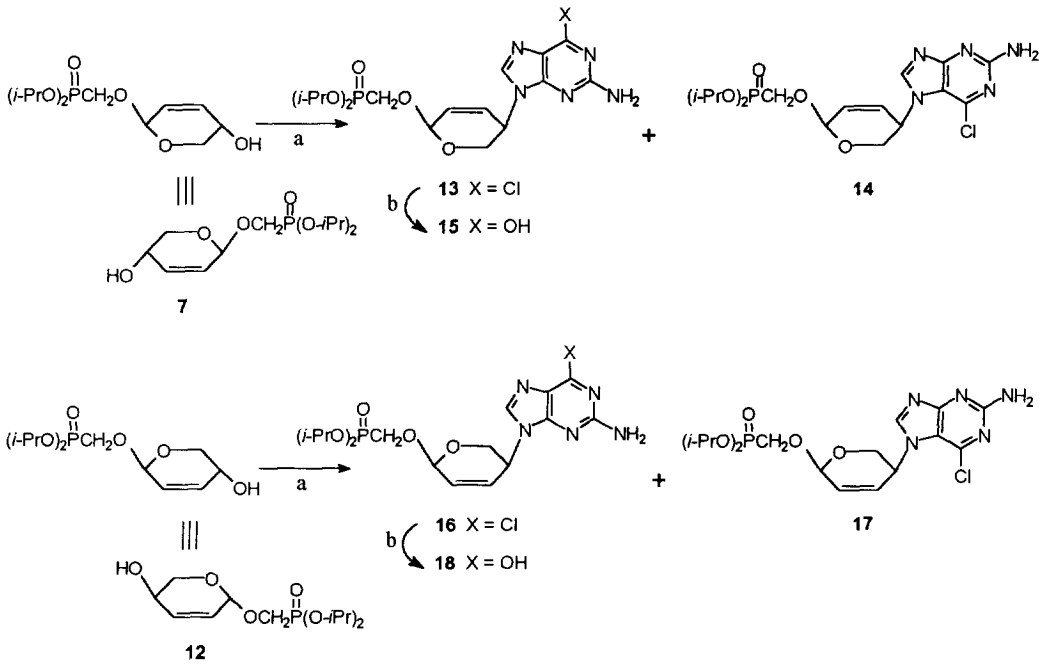


(a) $(i\text{-PrO})_2P(O)CH_2OH$ (**5**), TMStriflate, CH_3CN; (b) NH_3/MeOH; (c) Ph_3P, DEAD, benzoic acid, dioxane

Scheme 3

Following our synthetic strategy, the *trans* alcohols **7** and **12** were used for the synthesis of the *cis* substituted nucleosides, the heterocyclic base being introduced under Mitsunobu conditions. So, reaction of **7** (Scheme 4) with 2-amino-6-chloropurine in the presence of Ph_3P and DEAD in dioxane afforded the N-9-alkylated derivative **13** in 35% yield together with 16% of the N-7 isomer (**14**). The structural determination of both isomers was based on their NMR spectra (^1H and ^{13}C) and on the λ_{max} value of their UV spectra, and by comparison with data reported in the literature[27,28]. Similarly, and starting from the enantiomeric alcohol **12**, the N-9 and N-7 derivatives of 2-amino-6-chloropurine were obtained [**16** (42%) and **17** (18%), respectively]. The transformation of the N-9 derivatives (**13** and **16**) into their corresponding guanine analogues (**15** and **18**) was accomplished by treatment with 35% aqueous trimethylamine, followed by reaction with DBU to complete

the transformation of the trimethylammonium salt into guanine, following a slight modification of described procedures[29,30].

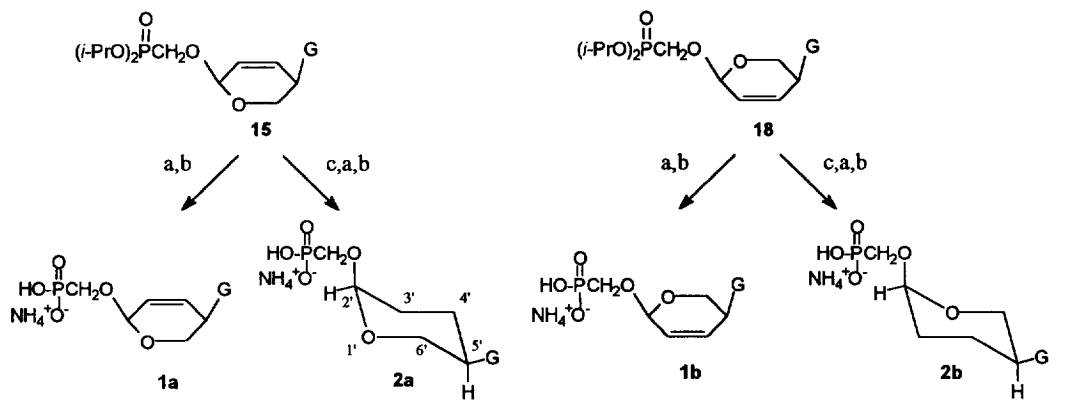


(a) 2-Amino-6-chloropurine, Ph_3P, DEAD, dioxane; (b) 35% Me_3N, and then DBU

Scheme 4

The diisopropyl ester functions in **15** and **18** were removed by reaction with trimethylsilyl bromide in DMF and in the presence of 2,6-lutidine, followed by hydrolysis with aqueous ammonia, to afford **1a** and **1b** as their ammonium salts in yields of 59% and 53%, respectively (Scheme 5). On the other hand, the saturated derivatives **2a** and **2b** were obtained from **15** and **18** by catalytic hydrogenation followed by deprotection of the phosphonate moiety as described above (**2a** 39%; **2b** 35% yield).

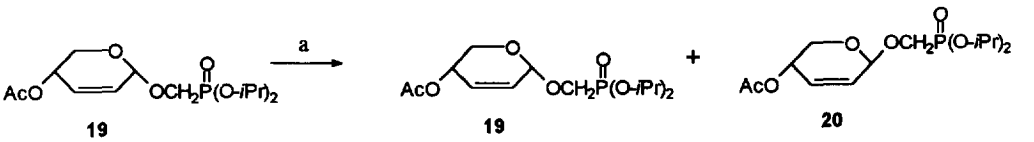
The *cis* substitution pattern for all the nucleosides was confirmed from the coupling constants measured in the ^1H NMR spectra of the saturated compounds **2a** and **2b**. The signal corresponding to H-5' in the tetrahydropyran moiety, that is, the proton attached to the carbon carrying the heterocyclic base, appears as a wide multiplet (δ 4.23-4.39) with large diaxial couplings, indicating its axial orientation (pyrane nomenclature and numbering is used for compounds **1-2** and **13-18**). On the other hand, the signal assigned to the proton attached to the carbon carrying the phosphonomethoxy moiety (H-2') is a narrow multiplet, as should correspond to its equatorial orientation. As we already mentioned, the phosponomethoxy moiety will be axial because of the anomeric effect. So, H-5' being axial and H-2' being equatorial, both substituents (the base and the phosphonomethoxy moiety) have to be *cis*. This also indicates an equatorial orientation of the guanine base in **2a**, **2b**. If both substituents were *trans*, probably both axially oriented, no diaxial coupling should be observed in the signal of H-5'.



(a) TMSBr, 2,6-lutidine, DMF; (b) NH_4OH; (c) H_2, 10% Pd/C, MeOH

Scheme 5

To the best of our knowledge, the mechanism of Ferrier-type rearrangement has not been fully established[23]. In his early works, Ferrier proposed a mechanism which involves isomerization by an initial 1,2 to 2,3-rearrangement of the double bond, probably anchimerically assisted by the 4-acetoxy group, followed by alkoxylation at C-1. The importance of the *trans* relationship between the 4-OAc and the leaving group at C-3 was stressed[18]. Later reports by other authors exclude the importance of this anchimeric assistance[21,31] and propose that the initial step implies formation of a complex between the leaving group at C-3 and a molecule of the acid catalyst. Elimination of this complex should generate an allylic carbonium ion that then reacts with a molecule of the alcohol present in the medium[21]. From our data and under our experimental conditions, it is clear that the configuration of the leaving group at C-3 has no effect on the stereochemical outcome of the reaction. There is also almost no energy difference between the most stable conformations of the starting materials (**4** and **10**). However, it seems that the substituent at the 4-position is involved in determining the stereochemistry of the anomeric center, the attack of the alcohol being predominantly "anti", starting from either 3,4-di-*O*-acetyl-D-xylal (**4**) or 3,4-di-*O*-acetyl-L-arabinal (**10**). It cannot be excluded that the participating effects of the AcO-4 group in the above mentioned carbonium intermediate may be involved in the specificity of the attack of the incoming nucleophile (preferentially onto the face opposite to this group, resulting in 1,4-*trans* substitution). However, it should be mentioned that anomeric equilibrium is attained during acid-catalyzed Ferrier reaction of glycals with alcohols.[32] Actually, when the acetylated derivative of the minor isomer **6**, that is **19** (Scheme 6), was treated with the alcohol **5** in the presence of the catalyst (TMS triflate), an anomeric mixture (**19**:**20**) in a ratio of 1:3 was obtained. Minimum energy calculations (in these calculations, the phosphonomethoxy moiety has been replaced by a methoxy group) revealed that the energy of the most stable conformation of the *trans* isomer (**20**) is 4.7 KJ/mol lower than the energy of the most stable conformation of the *cis* isomer (**19**). So, under the reaction circumstances, it can be considered that the energetically favoured 1,4-*trans*-isomers are predominant over the 1,4-*cis* isomers, and this energy difference further determines the diastereoselectivity of the reaction.



(a) $(i\text{-PrO})_2P(O)CH_2OH$ (5), TMStriflate, CH_3CN

Scheme 6

CONCLUSIONS

A novel family of phosphonate derivatives of six membered ring nucleosides has been synthesized according to a new strategy based on introduction of the phosphonomethoxy moiety by Ferrier rearrangement, followed by condensation of the resulting allylic alcohols with the heterocyclic base under Mitsunobu conditions. In the present article, guanine derivatives have been prepared, but, according to our previous results[14], N-9 purine and N-1 pyrimidine derivatives could be synthesized following the same strategy.

The diastereoselectivity of the Ferrier rearrangement has given us direct access to both series of enantiomeric nucleosides: starting from 3,4-di-*O*-acetyl-D-xylal, the (2*S*,5*R*)-dihydro-2*H*-pyranyl nucleosides are available, while from 3,4-di-*O*-acetyl-L-arabinal, the enantiomeric series (2*R*,5*S*) have been synthesized. In this rearrangement, and under our experimental conditions, the 1,4-*trans*-isomers are obtained as the major compounds, which also correspond to the energetically more favoured isomers.

EXPERIMENTAL SECTION

Ultraviolet spectra were recorded with a Philips PU 8700 UV/VIS spectrophotometer. The NMR spectra were determined with a Varian Gemini-200 spectrometer. Liquid secondary ion mass spectra (LSIMS) were obtained on a Kratos Concept 1H mass spectrometer, using glycerol (GLY) or thioglycerol (THGLY) as matrix. Column chromatography was performed on silica gel (0.060-0.200 nm and 0.030-0.075 nm). Preparative centrifugal circular thin layer was performed on a Chromatotron^R (Silicagel 60 PF_{254} containig gypsum-Merck). DEAE-Sephadex A-25 (HCO_3^--form) was used for ion-exchange chromatography. Conformations were calculated using MacroModel V.3.0.

Reaction of 3,4-di-*O*-acetyl-D-xylal (4) with diisopropyl hydroxymethyl phosphonate (5). To a solution of **4** (1 g, 5 mmol) in dry acetonitrile (15 mL) and the alcohol **5** (1.27 g, 6.5 mmol) at room temperature, TMS triflate (0.27 mL, 1 mmol) was added. After 20 min, 200 mL of CH_2Cl_2 and 50 ml of $NaHCO_3$ were added. The organic phase was washed with water, brine, dried on $MgSO_4$, and evaporated. The crude mixture was passed through a silica gel column (hexane:EtOAc 1:2) and the residue obtained was treated with methanolic ammonia overnight. This mixture was purified by column chromatography on silica gel [hexane:EtOAc 9:1, (2) EtOAc-MeOH (100:1)] to afford **(Diisopropylphosphonyl)methyl 2,3-dideoxy-α-D-**

***glycero*-pent-2-eno pyranoside (6)** (260 mg) and its β-D-isomer **7** (790 mg). (global yield from **4** : 72 %). For **6** : $[\alpha]_D$ + 52.0 (*c* 1, chloroform). LSIMS (THGLY) 295 $(M+H)^+$, 197. HRMS calcd. for $C_{12}H_{24}O_6P$ $(M+H)^+$ 295.1310, found 295.1315. ^1H NMR ($CDCl_3$) δ 3.61-3.86 (m, 2H, H-5), 3.90 (m, 2H, J = 9.4, 13.9, OCH_2P), 4.25 (m, 1H, H-4), 4.76 [m, 2H, $(CH_3)_2\underline{C}H\underline{O}$], 5.00 (m, 1H, H-1), 5.77, 6.03 (2m, 2H, $J_{2,3}$ = 10.5 Hz, H-2, H-3). ^{13}C NMR ($CDCl_3$) δ 23.95, 24.06 [$(\underline{C}H_3)_2CHO$], 61.94 ($J_{C,P}$ = 165 Hz, OCH_2P), 62.98 (C-4), 65.59 (C-5), 71.20 [$J_{C,P}$ = 7.5 Hz, $(CH_3)_2\underline{C}HO$], 95.09 ($J_{C,P}$ = 12 Hz, C-1), 126.53, 133.92 (C-2, C-3). For **7** : $[\alpha]_D$ + 46.5 (*c* 1, chloroform). LSIMS (THGLY) 295 $(M+H)^+$, 197, 155. HRMS calcd. for $C_{12}H_{24}O_6P$ $(M+H)^+$ 295.1310, found 295.1305. ^1H NMR ($CDCl_3$) δ 3.72 (dd, 1H, J = 13.8, 8.4 Hz, OCH_2P), 3.91 (dd, 1H, J = 9.3, 13.7 Hz, OCH_2P), 3.73-4.10 (m, 3H, H-4, H-5), 4.73 [m, 2H, $(CH_3)_2\underline{C}H\underline{O}$], 4.99 (m, 1H, H-1), 5.87 (dd, 1H, $J_{2,3}$ = 9.9, $J_{1,2}$ = 2.9 Hz, H-2), 6.12 (m, H-3). ^{13}C NMR ($CDCl_3$) δ 23.91, 24.03 [$(\underline{C}H_3)_2CHO$], 61.76 ($J_{C,P}$ = 170 Hz, OCH_2P), 61.21 (C-4), 64.55 (C-5), 71.14 [$J_{C,P}$ = 3.5 Hz, $(CH_3)_2\underline{C}HO$], 94.05 ($J_{C,P}$ = 11.4 Hz, C-1), 127.61, 129.55 (C-2, C-3).

(Diisopropylphosphonyl)methyl 4-*O*-benzoyl-2,3-dideoxy-α-D-glycero-pentopyranoside (8).
A solution of **6** (300 mg, 1.02 mol) in EtOH (15 mL) was hydrogenated in the presence of 10 % Pd/C (130 mg) at 30 psi for 5 h. The mixture was filtered, evaporated and coevaporated first with toluene and then with pyridine. The residue was dissolved in pyridine (4 mL) and benzoyl chloride (0.4 mL) was added. The mixture was stirred at room temperature for 1 h. The reaction was taken in CH_2Cl_2 (150 mL) and washed with 1N-HCl, water, brine, and dried on $MgSO_4$. After evaporation, the residue was purified by column chromatography [hexane:EtOAc (1:2)] to give **8** (224 mg, 55%) as a syrup. $[\alpha]_D$ + 63.0 (*c* 1, chloroform) LRMS (THGLY) 401 $(M+H)^+$. HRMS calcd. for $C_{19}H_{30}O_7P$ $(M+H)^+$ 401.1729, found 401.1743. ^1H NMR (C_6D_6) δ 1.42 (m, 1H, H-2eq), 1.65 (m, 2H, H-2ax, H-3eq), 1.90 (m, 1H, H-3ax), 3.60 (m, 1H, H-5eq), 3.65 (dd, 1H, J = 8.7, J = 14.2 Hz, OCH_2P), 3.82 (dd, 1H, J = 10.8, 8.5 Hz, H-5ax), 3.94 (m, 1H, J = 9.5, 13.9 Hz, OCH_2P), 4.55 (pseud t, 1H, J = 2.9 Hz, H-1), 4.73 [m, 2H, $(CH_3)_2\underline{C}H\underline{O}$], 4.92-5.05 (m, 1H, H-4), 6.97-7.01 [m, 3H, C_6H_5 (m, p)], 8.03-8.08 [m, 2H, C_6H_5 (o)]. ^{13}C NMR (C_6D_6) δ 24.78, 28.28 (C-2, C-3), 61.79 ($J_{C,P}$ = 170 Hz, OCH_2P), 62.73 (C-5), 68.31 (C-4), 70.59 [$J_{C,P}$ = 7 Hz, $(CH_3)_2\underline{C}HO$], 98.07 ($J_{C,P}$ = 10 Hz, C-1).

(Diisopropylphosphonyl)methyl 4-*O*-benzoyl-2,3-dideoxy-β-D-*glycero*-pentopyranoside (9).
Compound **7** (250 mg, 0.85 mmol) was hydrogenated and benzoylated as described for **6** to yield **9** (174 mg, 51%) as a syrup. $[\alpha]_D$ -72.0 (*c* 1, chloroform). LRMS (THGLY) 401 $(M+H)^+$, 197. HRMS calcd. for $C_{19}H_{30}O_7P$ $(M+H)^+$ 401.1729, found 401.1737. ^1H NMR ($CDCl_3$) δ 1.71 (m, 1H), 1.89 (m, 1H), 2.18 (m, 2H), 3.73 (dd, 1H, J = 13.7, 8.8 Hz, OCH_2P), 3.78 (m, 1H, J = 12.8, 2.1 Hz, H-5eq), 3.97 (dd, 1H, J = 13.7, 9.6 Hz, OCH_2P), 4.05 (dd, 1H, J = 12.5, 1.8 Hz, H-5ax), 4.80 [m, 2H, $(CH_3)_2\underline{C}H\underline{O}$], 4.91 (m, 1H, H-1), 5.05-5.13 (m, 1H, H-4), 7.42-7.58 [m, 3H, C_6H_5 (m, p)], 8.07-8.11 [m, 2H, C_6H_5(o)]. ^{13}C NMR ($CDCl_3$) δ 21.99, 24.76 (C-2, C-3), 61.28 (J = 170 Hz, OCH_2P), 61.84 (C-5), 67.74 (C-4), 71.01 [J = 6.7 Hz, $(CH_3)_2\underline{C}HO$], 97.80 (J = 11.6 Hz, C-1).

Reaction of 3,4-di-*O*-acetyl-L-arabinal (10) with diisopropyl hydroxymethyl phosphonate (5).
Compound **10** (1 g, 5 mmol) was made to react with **5** (1.27 g, 6.5 mmol) in the presence of TMS triflate (0.72 mL, 1 mol) as described for **4** during 20 min. After deprotection and column chromatography purification [(1)

hexane:EtOAc 9:1, (2) EtOAc:MeOH (100:1)] **(Diisopropylphosphonyl)methyl 2,3-dideoxy-α-L-*glycero*-pent-2-eno pyranoside (11)** (240 mg) and its β-L-isomer **12** (720 mg) were obtained with a global yield of 65% from **10**. For **11**: $[\alpha]_D$ - 53.0 (*c* 1, chloroform). LRMS (THGLY) : 295 $(M+H)^+$ 197, 155. HRMS calc. for $C_{12}H_{24}O_6P$ $[M+H]^+$ 295.1310, found 295.1287. ^1H and ^{13}C NMR as described for **6**. For **12** $[\alpha]_D$ - 47.0 (*c* 1, chloroform). LRMS (THGLY) : 295 $(M+H)^+$ 197. HRMS calc. for $C_{12}H_{24}O_6P$ $[M+H]^+$ 295.1310, found 295.1294. ^1H and ^{13}C NMR as described for **7**.

Conversion of 6 (7) to 12 (11). To a solution of **6** (7) (300 mg, 1.02 mmol) and Ph_3P (400 mg, 1.52 mmol) in dry dioxane (8 mL), a preformed solution of benzoic acid (187 mg, 1.53 mol) and DEAD (0.24 mL, 1.53 mol) in dioxane (3 mL) was slowly added. After two hours, volatiles were removed and the resulting residue was passed through a silica gel column [hexane:EtOAc (1:1)]. Fractions containing the desired compound were evaporated and treated with methanolic ammonia overnight. After evaporation, the residue was purified by column chromatography [EtOAc:MeOH (100:1)] to yield **11** (220 mg, 73% from **7**) or **12** (230 mg, 76% from **6**) as syrups.

Condensation of 7 with 2-amino-6-chloropurine. To a suspension containing the alcohol **7** (300 mg, 1 mmol), triphenylphosphine (525 mg, 2 mol) and 2-amino-6-chloropurine (340 mg, 2 mmol) in dry dioxane (10 mL), a solution of DEAD (0.31 mL, 2 mol) in dioxane (3 mL) was slowly added. The mixture was stirred at room temperature for 2 hours. Volatiles were removed and the residue was taken up into EtOAc (200 mL), filtered through celite and evaporated. Flash column chromatography [(1) CH_2Cl_2:MeOH (99:1), (2) CH_2Cl_2:MeOH (98:2), (3) CH_2Cl_2:MeOH (96:4)] afforded **13** (156 mg, 35%) as a syrup and its N-7 isomer **14** (71 mg, 16%). A sample of this lattest was obtained after purification on Chromatotron^R [CH_2Cl_2:MeOH (95:5)]. For **9-[(*2S,5R*)-2*H*-5,6-Dihydro-2-[(diisopropylphosphonyl)methoxy]-5-pyranyl]-2-amino-6-chloropurine (13)** : LRMS (THGLY) 446 $[M+H]^+$, 250. HRMS calc. for $C_{17}H_{26}N_5O_5ClP$ $(M+H)^+$ 446.1360, found 446.1354. UV λ_{max} (MeOH) : 249, 311 nm. ^1H NMR ($CDCl_3$) δ 3.74-4.04 (m, 4H, H-6', OCH_2P), 4.73 [m, 2H, $(CH_3)_2C\underline{H}O$], 5.12 (m, 2H, H-2', H-5'), 5.63 (br s, 2H, NH_2), 6.06 (m, 2H, H-3', H-4'), 7.75 (s, 1H, H-8). ^{13}C NMR ($CDCl_3$) δ 47.27 (C-5'), 62.20 ($J_{C,P}$ = 169 Hz, OCH_2P), 61.61 (C-6'), 71.08 [$J_{C,P}$ = 6.8 Hz, $(CH_3)\underline{C}HO$], 94.76 ($J_{C,P}$ = 11.4 Hz, C-2'), 124.78 (C-5), 127.74, 130.15 (C-3', C-4'), 140.11 (C-8), 151.25 (C-6), 153.45 (C-4), 159.26 (C-2). For **7-[(*2S,5R*)-2H-5,6-Dihydro-2-[(diisopropylphosphonyl)methoxy]-5-pyranyl]-2-amino-6-chloropurine (14)** : LRMS (THGLY) 446 $[M+H]^+$, 250, 170. HRMS calc. for $C_{17}H_{26}N_5O_5ClP$ $(M+H)^+$ 446.1360, found 446.1366. UV λ_{max} (MeOH) : 324 nm. ^1H NMR ($CDCl_3$) δ 3.84 (dd, 1H, J = 13.8, 8.1 Hz, OCH_2P), 3.92 (dd, 1H, J = 11.3, 7.6 Hz, H-6'), 4.04 (dd, 1H, J = 13.8, 9.5 Hz, OCH_2P), 4.13 (dd, 1H, J = 11.2, 5.1 Hz, H-6'), 4.78 [m, 2H, $(CH_3)_2C\underline{H}O$], 5.23 (d, 1H, H-2'), 5.32 (br s, 2H, NH_2), 5.56 (m, 1H, H-5'), 6.22 (m, 2H, H-3', H-4'), 8.08 (s, 1H, H-8). ^{13}C NMR ($CDCl_3$) δ 49.93 (C-5'), 62.33 ($J_{C,P}$ = 120 Hz, OCH_2P), 63.33 (C-6'), 71.15 [$J_{C,P}$ = 7.4 Hz, $(CH_3)\underline{C}HO$], 94.94 ($J_{C,P}$ = 10.8 Hz, C-2'), 115.93 (C-5), 126.95, 131.08 (C-3', C-4'), 142.91 (C-6), 146.45 (C-8), 159.45 (C-2), 164.16 (C-4).

9-[(2*S*,5*R*)-2*H*-5,6-Dihydro-2-[(diisopropylphosphonyl)methoxy]-5-pyranyl]guanine (15). Compound **13** (400 mg, 0.9 mol) was treated with 35% aqueous trimethylamine (40 mL) for 1 hour at room temperature. DBU (0.15 mL) was added and the reaction was stirred for aditional 30 min. Then, 0.2 mL of

AcOH were added and volatiles were removed. The residue was passed through a silica gel column [CH_2Cl_2:MeOH:NH_4OH (90:10:0.1)] and the product obtained (285 mg, 74%) was used as such in the next step. LRMS (THGLY) : 450 $[M+Na]^+$, 428 $[M+H]^+$, 152. UV λ_{max} (MeOH) : 256 nm.

9-[(2*S*,5*R*)-2*H*-5,6-Dihydro-2-(phosphonomethoxy)-5-pyranyl]guanine Ammonium Salt (1a). Compound **15** (100 mg, 0.24 mmol) was dissolved in dry DMF (3 mL) and 2,6-lutidine (0.42 mL, 3.6 mmol) and treated with trimethylsilyl bromide (0.31 mL, 2.4 mmol) for 24 h. The reaction was cooled and treated with NH_4OH (4 mL) for 6 h. Then, CH_2Cl_2 (30 mL) and H_2O (30 mL) were added and the aqueous phase was evaporated. The residue was applied on a XAD-column and eluted with H_2O and H_2O:MeOH (70:30). The UV positive fractions were collected, evaporated and purified by DEAE-Sephadex-A25 ($HCO3^-$ form) eluting with a gradient H_2O-0.1 M NH_4HCO_3. Appropriate fractions were evaporated, coevaporated with water and lyophilised to yield 51 mg (59%) of **1a**. LSIMS (THGLY) 342 $(M-H)^-$. HRMS calc. for $C_{11}H_{13}N_5O_6P$ $(M-H)^-$ 342.0603, found 342.0602. UV λ_{max} (H_2O) 253 nm (ε = 14800). ^1H NMR (D_2O) δ 3.65 (dd, 1H, J = 9.0, 13.3 Hz, OCH_2P), 3.85 (dd, 1H, J = 9.1, 13.3 Hz, OCH_2P), 3.94 (m, 2H, H-6'), 4.93-5.06 (m, 1H, H-5'), 5.19 (br s, 1H, H-2'), 6.11 (m, 2H, H-3', H-4'), 7.82 (br s, 1H, H-8). ^{13}C NMR (D_2O) δ 48.06 (C-5'), 61.94 (C-6'), 64.49 ($J_{C,P}$ = 157 Hz, OCH_2P), 95.81 ($J_{C,P}$ = 11.4 Hz, C-2'), 115.96 (C-5), 128.33, 130.01 (C-3', C-4'), 138.58 (br s, C-8), 151.64 (C-4), 154.18 (C-2), 159.05 (C-6).

9-[(2*S*,5*R*)-Tetrahydro-2-(phosphonomethoxy)-5-pyranyl]guanine Ammonium Salt (2a) Compound **15** (180 mg, 0.43 mmol) was dissolved in EtOH (15 mL) and hydrogenated in the presence of 10% Pd/C (100 mg) at 30 psi for 5 h. The mixture was filtered and passed through a short silica gel column eluting with CH_2Cl_2:MeOH:NH_4OH (100:10:0.1). The residue obtained after evaporation of the appropriate fractions (110 mg) was dissolved in DMF (3 mL) and deprotected and purified as described above for **1a**, affording 60 mg (39%) of **2a** as a white lyophiliate. LSIMS (THGLY) 344 $(M-H)^-$. HRMS calc. for $C_{11}H_{15}N_5O_6P$ $(M-H)^-$ 344.0759, found 344.0744. UV λ_{max} (H_2O) 254 nm (ε = 12300). ^1H NMR (D_2O) δ 1.80-2.38 (m, 4H, H-3', H-4'), 3.54 (dd, 1H, J = 13.2, 9.3 Hz, OCH_2P), 3.78 (dd, 1H, J = 13.2, 9.2 Hz, OCH_2P), 3.80 (m, 2H, H-6'eq), 3.95 (pseudt, 1H, J = 9.8 Hz, H-6'ax), 4.33-4.39 (m, 1H, H-5'), 4.86 (d, J = 4.1 Hz, H-2'), 7.88 (br s, 1H, H-8). ^{13}C NMR (D_2O) δ 24.05, 28.52 (C-3', C-4'), 50.10 (C-5'), 62.52 (C-6'), 63.48 ($J_{C,P}$ = 158.4 Hz, OCH_2P), 98.34 ($J_{C,P}$ = 11.1 Hz, C-2'), 116.11 (C-5), 138.26 (C-8), 151.62 (C-4), 153.98 (C-2), 159.16 (C-6).

Condensation of 12 with 2-amino-6-chloropurine. Following a procedure analogous to the one described for **7**, the alcohol derivative **12** (300 mg, 1 mol) reacted with 2-amino-6-chloropurine under Mitsunobu conditions. Flash column chromatography of the final residue afforded **16** (190 mg, 42%) and its N-7 isomer **17** (80 mg, 18%), the lattest being purified by Chromatotron^R [CH_2Cl_2:MeOH (95:5)]. For **9-[(2*R*,5*S*)-2H-5,6-Dihydro-2-[(diisopropylphosphonyl)methoxy]-5-pyranyl]-2-amino-6-chloropurine (16):** LRMS (THGLY) 446 $(M+H)^+$, 250. HRMS calcd. for $C_{17}H_{26}N_5O_5ClP$ $(M+H)^+$ 446.1360, found 446.1365. UV λ_{max} (MeOH) : 249, 331 nm. ^1H NMR and ^{13}C NMR as descibed for **13**. For **7-[(2*R*,5*S*)-2H-5,6-Dihydro-2-[(diisopropylphosphonyl)methoxy]-5-pyranyl]-2-amino-6-chloropurine (17) :** LRMS (THGLY) 446 $(M+H)^+$, 250, 170. HRMS calcd. for $C_{17}H_{26}N_5O_5ClP$ $(M+H)^+$ 446.1360, found 446.1347. UV λ_{max} (MeOH) : 324 nm. ^1H NMR and ^{13}C NMR as descibed for **14**.

9-[(2*R*,5*S*)-2*H*-5,6-Dihydro-2-[(diisopropylphosphonyl)methoxy]-5-pyranyl]guanine (18). Compound **16** (445 mg, 1.0 mmol) reacted with aqueous 35% trimethylamine as described for the synthesis of **15**. The residue obtained after column chromatography (330 mg, 78% yield) was used as such in the next step. LRMS (THGLY) 450 $(M+Na)^+$, 428 $(M+H)^+$, 152. UV λ_{max} (MeOH) : 256 nm.

9-[(2*R*,5*S*)-2*H*-5,6-Dihydro-2-(phosphonomethoxy)-5-pyranyl]guanine Ammonium Salt (1b). Compound **18** (100 mg, 0.24 mol) was deprotected and purified as described for **1a**, to afford 46 mg (53%) of **1b** as a white lyophiliate. LSIMS (THGLY) 342 $(M-H)^-$. HRMS calcd. for $C_{11}H_{15}N_5O_6P$ $(M-H)^-$ 342.0603, found 342.0608. UV λ_{max} (H_2O) : 253 nm (ε = 16000). ^1H NMR and ^{13}C NMR as described for **1a**.

9-[(2*R*,5*S*)-Tetrahydro-2-(phosphonomethoxy)-5-pyranyl]guanine Ammonium Salt (2b) Compound **18** (200 mg, 0.48 mol) was hydrogenated, deprotected and purified as described for **2a**, affording 60 mg (35%) of **2b** as a white lyophiliate. LSIMS (THGLY) 344 $(M-H)^-$ HRMS calcd. for $C_{11}H_{15}N_5O_6P$ $(M-H)^-$ 344.0759, found ,344.0745. UV λ_{max} (H_2O) : 252 nm (ε = 16000). ^1H NMR and ^{13}C NMR as described for **2a**.

ACKNOWLEDGEMENTS

We are gratefull to Prof. Dr. P. De Clercq for energy calculations and the Biomedical and Health Programme of the European Community. (BMH1-CT-93-6600) for financial support. We also thank MiekeVandekinderen for excellent editorial service.

REFERENCES

1. Herdewijn, P.; Balzarini, J.; De Clercq, E. "Dideoxynucleoside Analogues as Anti-HIV agents" in *Advances in Antiviral Drug Design*, JAI Press, **1993**, Vol. 1, pp. 233-318.
2. York, J.L. *J. Org. Chem.* **1981**, *46*, 2171-2173.
3. a) Huryn, D.M.; Sluboski, B.C.; Tam, S.Y.; Todaro, L.J.; Weigele, M. *Tetrahedron Lett.* **1989**, *30*, 6259-6262.
   b) Huryn, D.M.; Sluboski, B.C.; Tam, S.Y.; Weigele, M.; Sim, I.; Anderson, B.D.; Mitsuya, H.; Broder, S. *J. Med. Chem.* **1992**, *35*, 2347-2354.
4. a) Nair, V.; Nuesca, Z.M. *J. Am. Chem. Soc.* **1992**, *114*, 7951-7953.
   b) Sells, T.B.; Nair, V. *Tetrahedron Lett.* **1993**, *34*, 3527-3530.
   c) Sells, T.B.; Nair, V. *Tetrahedron* **1994**, *50*, 117-138.
5. Tino, J.A.; Clarck, J.M.; Field, A.K. et al. *J. Med. Chem.* **1993**, *36*, 1221-1229.
6. Balzarini, J.; Herdewijn, P.; De Clercq, E. *J. Biol. Chem.* **1989**, *264*, 6127-6133.
7. Holý, A. "Isopolar Phosphorus-Modified Nucleotide Analogues" in *Advances in Antiviral Drug Design*, JAI Press, **1993**, Vol. 1, pp. 179-231.
8. De Clercq, E.; Holy, A.; Rosenberg, I.; Sakuma, T.; Balzarini, J.; Maudgol, P.C. *Nature* **1986**, *323*, 464-467 .
9. Balzarini, J.; Zoo, Z.; Herdewijn, P.; Johns, D.G.; De Clercq, E. *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 1499-1503.

10. Kim, C.V.; Luh, B.Y.; Martin, J.C. *J. Org. Chem.* **1991**, *56*, 2642-2647.
11. a) Herdewijn, P.; Van Aerschot, A. *Bull. Soc. Chim. Belg.* **1990**, *99*, 895-901 .
    b) Herdewijn, P.; Van Aerschot, A.; Balzarini, J.; De Clercq, E. *Nucleosides & Nucleotides* **1991**, *10*, 119-127 .
12. Augustyns, K.; Rozenski, J.; Van Aerschot, A.; Janssen, G.; Herdewijn, P. *J. Org. Chem.* **1993**, *58*, 2977-2982 .
13. a) Pérez-Pérez, M.J.; Rozenski, J.; Herdewijn, P. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1199-1202.
    b) Pérez-Pérez, M.J.; Doboszewski, B.; De Clercq, E.; Herdewijn, P. *Nucleosides & Nucleotides* (in press).
14. Pérez-Pérez, M.J.; Rozenski, J.; Busson, R.; Herdewijn, P. *J. Org. Chem.* (in press).
15. Verheggen, I.; Van Aerschot, A.; Toppet, S.; Snoeck, R.; Janssen, G.; Claes, P.; Balzarini, J.; De Clercq, E.; Herdewijn, P. *J. Med. Chem.* **1993**, *36*, 2033-2040.
16. Mitsunobu, O. *Synthesis* **1981**, 1-28.
17. For recent reports on the application of Mitsunobu-type condensation to the synthesis of cyclopentyl nucleosides see:
    a) Jenny, T.F., Previsani, N.; Benner, S.A. *Tetrahedron Lett.* **1991**, *48*, 7029-7032.
    b) Toyota, A.; Katagiri, N.; Kaneko, C. *Synth. Commun.* **1993**, *23*, 1295-1305.
    c) Rodriguez, J.B.; Marquez, V.E.; Nicklaus, M.C.; Mitsuya, H.; Barchi Jr., J.J. *J. Med. Chem.* **1994**, *37*, 3389-3399.
    d) Bonnal, C.; Chavis, C.; Lucas, M. *J. Chem. Soc. Perkin Trans I* **1994**, 1401-1410.
18. a) Ferrier, R.J.; Prasad, N. *J. Chem. Soc. (C)* **1969**, 570-575.
    b) Ferrier, R.J. *Adv. Carbohydr. Chem. Biochem.* **1969**, *24*, 199-265.
19. Somsák, L.; Németh, I. *J. Carbohydr. Chem.* **1993**, *12*, 679-684.
20. Phillion, D.P.; Andrews, J.J. *Tetrahedron Lett.* **1986**, *27*, 1477-1480.
21. Grynkiewicz, G.; Priebe, W.; Zamojski, A. *Carbohydr. Res.* **1979**, *68*, 33-41.
22. Wattman, M.D.; Halcomb, R.K.; Danishefsky, S.J. *J. Org. Chem.* **1990**, *55*, 1979-1981.
23. Banik, B.K.; Manhas, M.S.; Bose, A.K. *J. Org. Chem.* **1994**, *59*, 4174-4176.
24. Herscovici, J.; Montserret, R.; Antonakis, K. *Carbohydr. Res.* **1988**, *176*, 219-229.
25. Dunkerton, L.V.; Brady, K.T.; Mohamed, F.; McKillican, B.P. *J. Carbohydr. Chem.* **1988**, *7*, 49-65.
26. Kartha, K.P.R.; Jennings, H. *J. Carbohydr. Chem.* **1990**, *9*, 777-781.
27. Toyota, A.; Katagiri, N.; Kaneko, C. *Heterocycles* **1993**, *36*, 1625-1630.
28. Choudary, B.M.; Geen, G.R.; Grinter, T.J.; MacBeth, F.S.; Parrat, M.J. *Nucleosides & Nucleotides* **1994**, *13*, 979-996.
29. Gaffney, B.L.; Jones, R.A. *Tetrahedron Lett.* **1982**, *23*, 2253-2256.
30. Ashwell, M.; Bleasdale, C.; Golding, B.T.; O'Neill, I.K. *J. Chem. Soc. Chem. Commun.* **1990**, 995-956.
31. Descotes, G.; Martin, J.C. *Carbohydr. Res.* **1977**, *56*, 168-172.
32. Bhaté, P.; Horton, D;; Priebe, W. *Carbohydr. Res.* **1985**, *144*, 331-337.

(*Received in UK 27 February* 1995)