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Development of O–H insertion for the attachment of phosphonates to nucleosides; synthesis of α-carboxy phosphononucleosides

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ABSTRACT

Development of rhodium catalysed O–H insertion reactions employing α-diazophosphonates with appropriately protected adenosine, uridine and thymidine derivatives is described. This synthetic methodology leads, following deprotection, to novel phosphononucleoside derivatives bearing a carboxylic acid moiety adjacent to the phosphonate. Protection strategies are critical to the success of the key O–H insertion. There are two important aspects: avoiding competing insertion pathways or catalyst poisoning, and being able to achieve deprotection without degradation of the phosphononucleosides.

1. Introduction

The search for novel antiviral agents has attracted enormous attention over the past 25 years, especially in the drive for novel compounds active against HIV and other viruses.[1] Among the strategies explored is the use of non-natural nucleoside analogues envisaged to act as mimics of the natural nucleosides. To exert their antiviral activities through inhibition of HIV reverse transcriptase, these nucleosides analogues must be triphosphorylated by cellular kinases. The first phosphorylation can be rate limiting with the non-natural nucleosides as the substrate.[2] Use of phosphate analogues of the nucleosides as antiviral agents is not feasible in part due to their potential for hydrolysis of the O–P link. To circumvent the problematic first phosphorylation with non-natural nucleosides, one strategy, which has proven successful is the use of isosteric phosphonate analogues as phosphate mimics providing pronucleotides or nucleotide analogues.[3,4] In the phosphonate analogues, the key P–C bond cannot be cleaved by phosphatases or by hydrolysis, and therefore the phosphononucleosides offer a distinct advantage over use of monophosphates as drugs. As part of our ongoing drug discovery program, we have been investigating the synthesis of phosphononucleoside analogues bearing an α-carboxylic acid substituent (Fig. 1).[5]

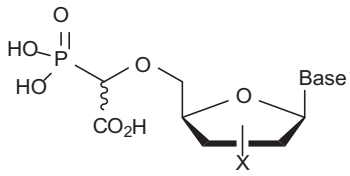

Fig. 1.

It was envisaged that the novel phosphononucleosides illustrated in Fig. 1 bearing a carboxylic acid moiety could potentially act as analogues of a nucleoside diphosphate. Previously Gilbert and co-workers explored the citrate derivatives of nucleosides as potential triphosphate isosteres, but found that they were inactive.[6] In 2007, Vederas reported the synthesis of nucleoside dicarboxylates as potential mimics of nucleoside diphosphates, which were also found to be inactive.[7]

Considering both phosphonoacetic and phosphonoformic acids have antiviral activity,[8] our strategy combines these simple

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antiviral agents with the phosphononucleoside approach leading to potentially interesting compounds for evaluation, which can be envisaged as nucleoside diphosphate mimics.

The most commonly employed method for the attachment of phosphonate moieties to nucleoside derivatives involves nucleophilic displacement of precursors such as $(RO)_2OPCH_2OTs$ with an alkoxide anion under strongly basic conditions.[9] However, the harsh conditions associated with this method are limiting in terms of the substrate range, which can tolerate the high pH. In the context of our ongoing program of research in rhodium and copper catalysed transformation of α-diazocarbonyl derivatives,[10] we devised an alternative attractive synthetic strategy. We envisaged that O–H insertion reactions with α-diazophosphonate derivatives could be employed to attach phosphonate moieties to nucleoside derivatives under mild conditions, at neutral pH. The O–H insertion reactions can occur thermally, photochemically, by acid catalysis or most commonly by transition metal catalysis.[11,12] In 1984, Paquet and Sinai reported the functionalisation of the primary alcohol group of a protected glucose derivative by an O–H insertion reaction catalysed by rhodium acetate using trimethyl diazophosphonoacetate.[13] Related functionalisations were carried out independently by Berchtold and co-workers in 1987,[14] and by Ganem and co-workers in 1992 on the synthesis of chorismic acid.[15]

In 1986, Moody and co-workers began an extensive program focused on the applications of the O–H insertion reaction catalysed by rhodium carbenoids, particularly for the synthesis of seven- and eight-membered ring ethers obtained in an intramolecular fashion.[16] In 1991, they carried out the cyclisation with α-diazo-β-ketophosphonates.[17] This reaction was later applied to the synthesis of the pyranooxepane and oxepanooxepane subunits of marine polyether toxins.[18]

Moody and co-workers also investigated intermolecular O–H insertion reactions of α-diazophosphonate derivatives,[11,19,20] and some examples of O–H insertion reactions with more highly functionalised alcohols have been reported.[21] In 2000, Kim and co-workers demonstrated that insertion reactions of α-diazocarbonyl compounds are possible in presence of heterocyclic bases.[22] However, to the best of our knowledge, previous to our recent work,[5] we are not aware of any reports of transition metal catalysed O–H insertion reactions of α-diazophosphonates with nucleosides, or carbocyclic analogues.

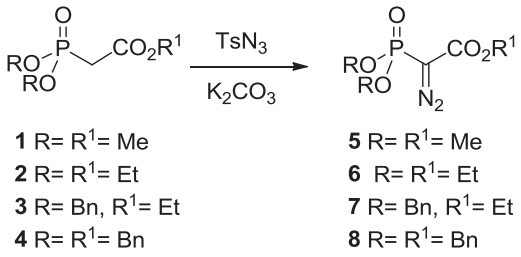
At the outset of the project, catalyst inhibition through coordination with the heterocyclic bases was envisaged as a potential complication; however, this did not prove to be a significant problem in practice, as judicious protecting group selection can be used to avoid catalyst poisoning. Selecting rhodium(II) as the catalyst system we focused on optimising conditions for the O–H insertion reactions using α-diazophosphonates with a range of unprotected and protected nucleosides. In the screening process for the O–H insertion, solvents, catalyst loading, reaction temperature and other parameters were explored. Herein, we report the protection strategies investigated for the nucleosides, and the development of the O–H insertion reaction for the synthesis of a series of phosphononucleosides bearing an α-carboxylic acid moiety, envisaged as potential diphosphate mimics. The strategies for deprotection and purification of the fully deprotected phosphononucleosides, following the key O–H insertion step leading to the phosphonate attachment, are also discussed.

2. Results and discussion

Commercially available uridine, thymidine, adenosine and 2′,3′-*O*-isopropylidene adenosine were employed as starting materials for the development of the methodology, allowing exploration of the impact of purine and pyrimidine bases and both ribose and 2′-deoxyribose systems on the O–H insertion reaction and subsequent deprotection.

2.1. Synthesis of α-diazophosphonate precursors

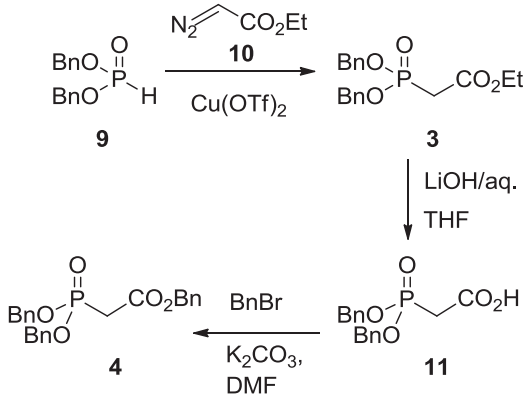
Use of the α-diazophosphonate precursors **5**–**8** was explored (Scheme 1). The trimethyl and triethyl derivatives **5**[23] and **6**[24] are known and were prepared by diazo transfer to the commercially available trimethyl phosphonoacetate **1** and triethyl phosphonoacetate **2**. The conditions chosen in this case are those reported by Koskinen for the synthesis of a range of diazophosphonate derivatives,[25] using tosyl azide and potassium carbonate in acetonitrile.



Scheme 1. Conversion of phosophonoacetates to diazophosphonoacetates.

Use of benzyl derivatives **7** and **8** was of interest due to the potential to deprotect later in the reaction sequence under neutral conditions via hydrogenolysis, if hydrolysis of the carboxylic and phosphonate esters under acidic or basic conditions proved problematic once attached to the nucleoside units.

A number of approaches to prepare tribenzyl phosphonoacetate **4** were explored including esterification of phosphonoacetic acid, transesterification of triethyl phosphonoacetate, Michaelis–Becker type reactions or treatment of dibenzyl phosphite **9** with bases followed by bromoacetate esters. However, the most successful approach involved P–H insertion into dibenzyl phosphite. The reaction of phosphites with diazo compounds under the influence of copper catalysts has appeared a number of times in the literature.[26] The most efficient catalyst is reported to be copper acetylacetonate, and the reactions were generally conducted in benzene at reflux. While $Cu(acac)_2$ proved to be ineffective in our hands as a catalyst for the reaction between dibenzyl phosphite and ethyl diazoacetate, better results were observed with copper(II) triflate, and the desired P–H insertion product **3** was obtained (Scheme 2).



Scheme 2. Synthesis of tribenzyl phosphonoacetate **4**.

The optimum conditions for this process were found to be addition over 30 min of a fivefold excess of neat ethyl diazoacetate to dibenzyl phosphite in CH_2Cl_2 in the presence of 5 mol % $Cu(OTf)_2$ at room temperature followed by stirring overnight, which affords the desired compound **3** as the predominant product in good yield (up to 84%). A critical part of the optimisation was the identification of a suitable method of purification; chromatography over silica gel leads to poor recovery, but use of alumina (activity III) gives good, reproducible results.

While extension of the P–H insertion process to the synthesis of the tribenzyl phosphono ester **4** through reaction with benzyl diazoacetate in place of ethyl diazoacetate can be envisaged, use of a large excess of benzyl diazoacetate, which is not commercially available, is not an attractive strategy. Instead conversion of the ethyl dibenzyl phosphono ester **3** prepared above to the tribenzyl derivative **4** proceeds efficiently as summarised in Scheme 2.

Hydrolysis of the ethyl ester **3** with excess lithium hydroxide in 50% aqueous THF affords the acid **11** in good yield and purity (Scheme 2); the acid **11** has been previously prepared by the carbonation of the anion derived from dibenzyl methylphosphonate by treatment with methyllithium.[27] The present method compares favourably in terms of efficiency and overall cost with this previously reported method.

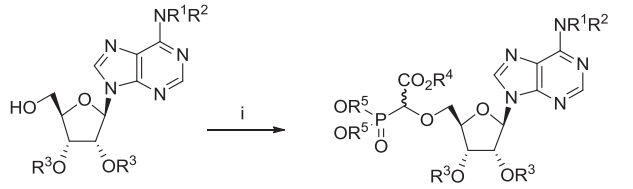
The esterification reaction of the acid **11** with benzyl bromide in the presence of potassium carbonate in DMF proves to be highly satisfactory (Scheme 2). This is significant since it means that tribenzyl phosphonoacetate **4** can be prepared in three steps from dibenzyl phosphite in 45% typical overall yield following the reaction sequence outlined in Scheme 2 with only one chromatographic purification.

Diazo transfer to the two benzyl phosphono esters **3** and **4** was achieved using the conditions described by McKenna,[28] leading to the novel α-diazophosphonates **7** and **8** in 66 and 68% yields, respectively. These diazo precursors were readily handled, stored and characterised.

2.2. O–H insertion reactions

A range of unprotected and selectively protected nucleosides were evaluated as substrates for O–H insertion reactions catalysed by rhodium carboxylate and carboxamide catalysts. The key objectives were to establish firstly if the O–H insertion could be effected in the presence of purine and pyrimidine bases without protection, and secondly, if base protection is required, which protecting groups are compatible with the O–H insertion process.

2.2.1. Investigation of O–H insertion reactions with adenosine derivatives. The first substrate explored for the O–H insertion was 2′,3′-*O*-isopropylidene adenosine **12**. As summarised in Scheme 3 and Table 1, initial investigation of the O–H insertion reaction with **12** and triethyl diazophosphonoacetate **6** was carried out in presence of rhodium(II) acetate as catalyst in refluxing benzene or dichloromethane and in all cases no insertion was found in the presence of the unprotected purine base; only the unreacted starting material **12** was recovered after 12 h. Accordingly, suitable protecting groups for the adenine base were sought. The *N*-monobenzoyl adenosine derivative **13**[29] was then prepared as the electron-withdrawing benzoyl group would be expected to deactivate the adenine base towards interaction with the rhodium complex. When the O–H insertion reaction was attempted with this *N*-monoprotected derivative **13** in the presence of rhodium(II) acetate in refluxing benzene for 12 h, again there was no evidence of the insertion product. This suggested that even with partial protection, complexation of the nucleoside base to the rhodium catalyst was resulting in catalyst poisoning.



Unprotected base
12 R^1= R^2 = H, R^3= $C(CH_3)_2$

Protected base
13 R^1= H, R^2= Bz, R^3= $C(CH_3)_2$
14 R^1= R^2= Bz, R^3= $C(CH_3)_2$
15 R^1R^2= $CHNBn_2$, R^3= $C(CH_3)_2$
16 R^1= R^2= R^3= Bz

17 R^1= R^2= Bz, R^3= $C(CH_3)_2$, R^4= R^5= Et
18 R^1R^2= $CHNBn_2$, R^3= $C(CH_3)_2$, R^4= R^5= Et
19 R^1= R^2= R^3= Bz, R^4= R^5= Me

Scheme 3. Investigation of the O–H insertion reaction with adenosine derivatives. Reaction conditions: (i) **5** or **6**, $Rh_2(OAc)_4$ or $Rh_2(NHCOCF_3)_4$, CH_2Cl_2, THF or C_6H_6, reflux.

Table 1
O–H insertion of trimethyl and triethyl diazophosphonoacetate **5** and **6** with adenosine derivatives **14**–**16**

Entry	Substrate	Diazo compound (mol equiv)	Solvent	Catalyst (1 mol %)	Time (h)	Product (% yield)[a]
1	**12**	**6** (2)	C_6H_6 or CH_2Cl_2	$Rh_2(OAc)_4$	12	—
2	**13**	**6** (2)	C_6H_6	$Rh_2(OAc)_4$	12	—
3	**14**	**6** (2)	CH_2Cl_2	$Rh_2(OAc)_4$	12	—
4	**14**	**6** (2)	C_6H_6	$Rh_2(OAc)_4$	12	**17** (11)
5	**14**	**6** (2)	THF	$Rh_2(NHCOCF_3)_4$	12	**17** (10)
6	**14**	**6** (2)	C_6H_6	$Rh_2(NHCOCF_3)_4$	12	**17** (39)
7	**14**	**6** (2)	C_6H_6	$Rh_2(NHCOCF_3)_4$	24	**17** (45)
8	**15**	**6** (2)	C_6H_6	$Rh_2(NHCOCF_3)_4$	24	**18** (55)
9	**16**	**5** (1.2)	C_6H_6	$Rh_2(OAc)_4$	12	**19** (66)

[a] After chromatography.

Further protection of **12** as N^6,N^6-dibenzoyl-2′,3′-*O*-isopropylidene adenosine **14**, following a literature procedure,[30] was then undertaken to reduce the reactivity of the adenine moiety. As summarised in Table 1, O–H insertion reaction with the dibenzoylated precursor **14** bearing a free 5′-hydroxyl group with triethyl diazophosphonoacetate **6** was achieved using either rhodium(II) acetate or rhodium(II) trifluoroacetamide as catalyst in a range of solvents to form the desired product **17**, which was readily purified by chromatography on silica gel. Notably use of the lower boiling dichloromethane as solvent (entry 3) does not result in any O–H insertion indicating the increased stability of α-diazophosphonates compared to α-diazocarbonyl derivatives, in agreement with Moody's work.[11,16–20] With the triethyl diazophosphonate precursor **6**, optimum yields were obtained using rhodium trifluoroacetamide as catalyst; in agreement with the observations made by Moody (entries 6, and 7).[20b]

Investigation of other protecting groups was also carried out. The *N*,*N*-dibenzyl formamidine protecting group described by Mioskowski,[31] which can be cleaved by hydrogenolysis, was explored to enable subsequent deprotection under neutral conditions. Thus, 2′,3′-*O*-isopropylidene adenosine **12** was treated in refluxing acetonitrile with *N*,*N*-dibenzylformamide dimethyl acetal, formed in situ by transamidation between dibenzylamine and *N*,*N*-dimethylformamide dimethyl acetal, to give the novel protected adenosine derivative **15** in 94% yield. Employing the most efficient conditions for the O–H insertion observed with **14**, i.e., rhodium(II) trifluoroacetamide in refluxing benzene for 24 h, compound **15** afforded the phosphonate derivative **18** in 55% yield.

Use of the tetrabenzoyl adenosine derivative **16**,[32] which offers practical advantages in terms of subsequent deprotection, together with just a small excess of trimethyl diazophosphonate **5** led to effective transformation using rhodium acetate as catalyst (entry 9) in refluxing benzene for 12 h.[5]

Throughout this work the products of O–H insertion were isolated as an essentially equimolar mixture of diastereoisomers readily identified spectroscopically from the characteristic signals in the ^{1}H and ^{13}C NMR spectra for the CH adjacent to the phosphonate, for instance, for compound **17**: δ_C 76.8 (d, J_{PC} 156.6 Hz) and δ_P 15.09 (54%), 15.00 (46%) or for compound **19**: δ_C 76.4, 76.1 (d, J_{PC} 156.6, 156.7 Hz, PCH) and δ_P 16.08 (two epimers).[5] On occasion a slight excess of one diastereoisomer can be observed but the ratio was never greater than 60:40, indicating very low diastereoselection in the insertion as described in Moody's O–H insertion with other systems.[11,19–23] Interestingly, the NMR signals for the bases adenine, thymine and uracil were frequently quite well distinguished in the two diastereomers, possibly due to different conformations. Phosphorus NMR spectra proved to be very useful in identifying and quantifying diastereoisomeric mixtures.

Thus the O–H insertion process cannot be carried out in the presence of unprotected or monoprotected adenine, presumably due to complexation of the catalyst to the base, but the reaction is compatible with both *N*,*N*-dibenzoyl and *N*,*N*-dibenzyl formamidine protection. Protection of the secondary 2′,3′-OH groups either as isopropylidene acetals **14** and **15** or as benzoate esters **16**, to ensure selective insertion at the primary 5′-OH, is equally effective in terms of O–H insertion efficiency. The O–H insertion proceeds equally efficiently with both the trimethyl and triethyl diazophosphonoacetates **5** and **6**.

2.2.2. Exploration of O–H insertion with uridine derivatives. 2.2.2.1. Without protection of the pyrimidine base. Uridine was first converted to the 2′,3′-*O*-isopropylidene derivative **20** as described in the literature,[33] to block insertion at the 2′ and 3′ hydroxy functions, and also to determine whether catalyst poisoning occurs in the presence of the unprotected pyrimidine base. In this case, reaction with the triethyl diazophosphonoacetate **6** in the presence of rhodium(II) trifluoroacetamide in refluxing benzene gave two phosphononucleoside derivatives (Scheme 4 and Table 2), which indicates that catalyst poisoning is not a problem with the uracil base. Unsurprisingly, products derived from both O–H and N–H insertion are formed. The major product **22** (26%) was clearly formed through N–H insertion at the *N*-3 position of the uracil base, while a small amount of the 5′-OH insertion product **21** (9%) was also isolated from the reaction. Evidently the N–H insertion is favoured over the O–H insertion.[34] The two O–H and N–H insertion products are readily characterised spectroscopically. The characteristic pair of doublets in the ^{13}C NMR spectra for the carbon adjacent to the phosphonate was particularly useful in identifying the products: δc 76.6, 74.5 (J_{PC} 158.0 Hz) for **21** and δ_C 71.1, 69.1 (J_{PC} 160.0 Hz) for **22**.

Table 2
Rhodium catalysed reaction with **6** and 2′,3′-*O*-isopropylidene uridine **20**[a]

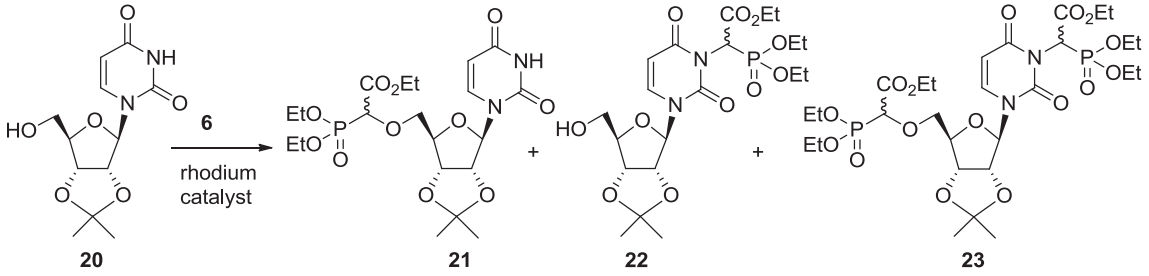
Entry	Catalyst	**6** (eq.)	**21** (%)	**22** (%)	**23** (%)
1	$Rh_2(NHCOCF_3)_4$	1.2	9	26	—
2	$Rh_2(OAc)_4$	1.0	—	27	—
3	$Rh_2(OAc)_4$	4.0	—	—	39

[a] Reaction conditions: (entry 1) 1.2 equiv **6**, $Rh_2(NHCOCF_3)_4$ cat, benzene, reflux, 36 h; (entry 2) 1.0 equiv **6**, $Rh_2(OAc)_4$ cat, benzene, reflux, overnight; (entry 3) 4.0 equiv **6**, $Rh_2(OAc)_4$ cat, benzene, reflux, overnight.

The selectivity for N–H insertion is increased when rhodium(II) acetate is employed as catalyst—the product of insertion at *N*-3 **22** was isolated exclusively in 27% yield when an equimolar amount of the triethyl diazophosphonoacetate **6** was employed (Scheme 4). Use of 4 equiv of **6** resulted in exclusive isolation of the double insertion product **23** in 39% yield as an essentially equimolar mixture of four diastereoisomers.

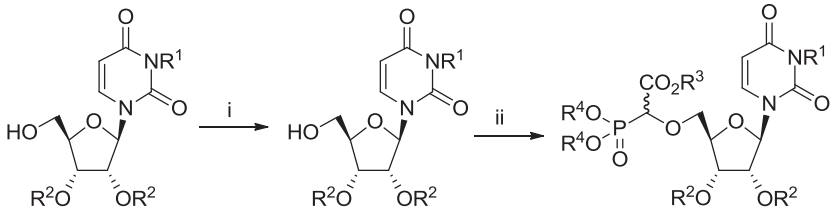
2.2.2.2. Use of protection to achieve selective 5′-OH insertion. In order to obtain **21** in significant amounts, protection of the *N*-3 position on the uracil base in compound **20** is necessary. Single-step N^3-benzoylation of compound **20** can be effected using benzoyl chloride and triethylamine in dichloromethane as shown in Scheme 5.[35] Treatment of N^3-benzoyl-2′,3′-*O*-isopropylidene uridine **25** with the triethyl diazophosphonoacetate **6** in the presence of rhodium(II) acetate afforded the phosphononucleoside **29** in 60% yield. The use of the benzoyl protecting group is again very effective, resulting in a relatively high yield of the O–H insertion product.

Use of the methoxyethoxymethyl (MEM) group as a protecting group for the uracil moiety was also explored as illustrated in Scheme 5, as Takaku and co-workers showed that this group can be removed under mild conditions using triphenylmethyl fluoroborate.[36] We describe here the synthesis of the novel MEM protected uridine derivative **26** under phase transfer conditions. Conversion of 2′,3′-*O*-isopropylidene uridine **20** into the 5′-benzoylated derivative using standard conditions,[37] then treatment with MEMCl under phase transfer catalysis using benzyltriethylammonium chloride (BTEAC)[38] (KOH/BTEAC/CH_2Cl_2) gave 5′-benzoyl-3-methoxyethoxymethyl-2′,3′-*O*-isopropylidene uridine. This compound was treated with aqueous methanolic ammonia to give the novel *N*-protected derivative, 3-methoxyethoxymethyl-2′,3′-*O*-isopropylidene uridine **26** in 51% yield. The use of phase transfer catalysis was found to be preferable to the more usual method for protection using MEMCl and diisopropylethylamine,[39] which did not afford the desired MEM ether derivative **26** in this case. On treatment with triethyl diazophosphonoacetate **6** in the presence of rhodium(II) acetate, the uridine derivative **26** was transformed to the desired phosphononucleoside derivative **30** in 32% yield (Scheme 5, Table 3). The MEM group does not result in any significant complication in the key



Scheme 4. Rhodium catalysed reaction with triethyl diazophosphonoacetate **6** and 2′,3′-*O*-isopropylidene uridine **20**.

O–H insertion step, despite the possibility of side reactions such as oxonium ylide formation.



20 R^1= H, R^2= $C(CH_3)_2$

24 R^1= R^2= H

25 R^1= Bz, R^2= $C(CH_3)_2$
26 R^1= MEM, R^2= $C(CH_3)_2$
27 R^1= Bn, R^2= $C(CH_3)_2$
28 R^1= R^2= Bz

29 R^1= Bz, R^2= $C(CH_3)_2$, R^3= R^4= Et
30 R^1= MEM, R^2= $C(CH_3)_2$, R^3= R^4= Et
31 R^1= Bn, R^2= $C(CH_3)_2$, R^3= R^4= Et
32 R^1= R^2= Bz, R^3= R^4= Me

Scheme 5. Strategy for the exclusive 5′-OH insertion reaction. Reaction conditions: (i) selective protection, see Experimental section for details; (ii) **5** or **6**, rhodium catalyst, C_6H_6, reflux.

Table 3
O–H insertion of trimethyl and triethyl diazophosphonoacetate **5** and **6** with uridine derivatives **25**–**28**

Entry	Substrate	Diazo compound (mol equiv)	Solvent	Catalyst (1 mol %)	Time	Product (% yield)[a]
1	**25**	**6** (2)	C_6H_6	$Rh_2(OAc)_4$	12 h	**29** (60)
2	**26**	**6** (2)	C_6H_6	$Rh_2(OAc)_4$	12 h	**30** (32)
3	**27**	**6** (2)	C_6H_6	$Rh_2(NHCOCF_3)_4$	12 h	**31** (42)
4	**28**	**5** (1.2)	C_6H_6	$Rh_2(OAc)_4$	12 h	**32** (72)

[a] After chromatography.

The benzyl protected uridine derivative **27**[40] was also subjected to the O–H insertion reaction affording **31** in 42% yield, highlighting the fact that the insertion reaction proceeds well in the presence of the less electron-withdrawing benzyl protecting group on the pyrimidine base.

As observed in the adenosine series the isopropylidene protecting group can be replaced with benzoyl protection for the 2′- and 3′-OH groups without detrimental effect on the key O–H insertion step. In fact the most efficient O–H insertion in the uridine series was obtained using the tribenzoyl uridine derivative **28** with rhodium acetate (1 mol %) and just 1.2 equiv of the trimethyl diazophosphonate **5** in benzene at reflux overnight.[5]

Thus in the uridine series, the unprotected base does not lead to catalyst poisoning and O–H insertion can be effected without base protection, but with competing N–H insertion at the base. Use of *N*-benzoyl, MEM or benzyl protection on the uracil base leads efficiently to 5′-OH insertion with either the triethyl or trimethyl diazophosphonate **6** or **5**.

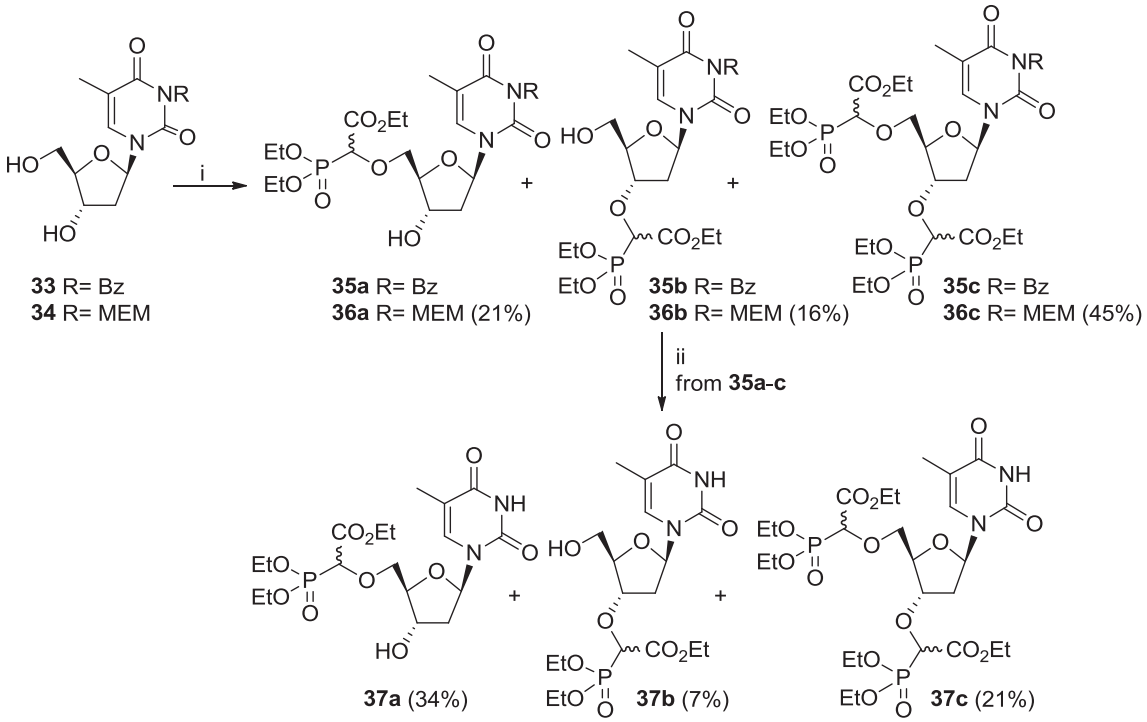
2.2.3. Exploration of O–H insertion with thymidine derivatives. Investigation of insertion reactions with thymidine was also undertaken (Scheme 6); in this case we decided to focus on O–H insertion with N-protection to enable investigation of competition between the 5′ and 3′ O–H insertion. Thus, N^3-benzoylthymidine **33** was prepared from thymidine in two steps following the procedure we have previously described.[35] Rhodium(II) acetate catalysed reaction of the diazophosphonate **6** (2.0 equiv) with **33** gave three products: the products of insertion at the 5′-OH, 3′-OH and bis-insertion at both sites **35a**, **35b** and **35c** were each recovered. These were purified as a mixture but not separated. Instead, the mixture was directly heated in benzyl alcohol to give the analogous deprotected derivatives **37a**, **37b** and **37c**. Separation was achieved by careful chromatography, affording compounds **37a** (34%), **37b** (7%) and **37c** (21%). Clearly insertion at the primary hydroxyl group is preferred. Notably the overall yields of the insertion products were again quite respectable in the presence of the benzoyl protecting group, as had been observed with the uridine derivatives **25** and **28**.

Use of the MEM protecting group in the thymidine series was also investigated (Scheme 6). The MEM protection of *N*-3 of the thymine base was accomplished in a similar manner to that used to protect the uracil base. Both hydroxy groups of thymidine were protected by benzoylation,[36] and the MEM group was then introduced at *N*-3 under phase transfer conditions as described above. Removal of the benzoyl groups using aqueous methanolic ammonia gave the novel *N*-protected derivative, 3-methoxyethoxymethyl thymidine **34** in 56% yield. Again while O–H insertion at the 3′- and 5′-OH groups can be envisaged it was expected that insertion at the primary hydroxyl group would be preferred. Investigation of the O–H insertion reactions of **34** with the diazophosphonate **6** in the presence of rhodium(II) acetate is summarised in Scheme 6. The reaction employing 2.0 equiv of **6** yielded the products derived from insertion at the 5′- and 3′-hydroxyl groups **36a** and **36b**, respectively, and the bis-insertion product **36c**, which was isolated as the major product. From the product ratios recovered it appears that there is a slight preference for reaction at the primary 5′-hydroxyl group as expected. Chromatographic separation of the three products **36a**, **36b** and **36c** was carried out for characterisation.

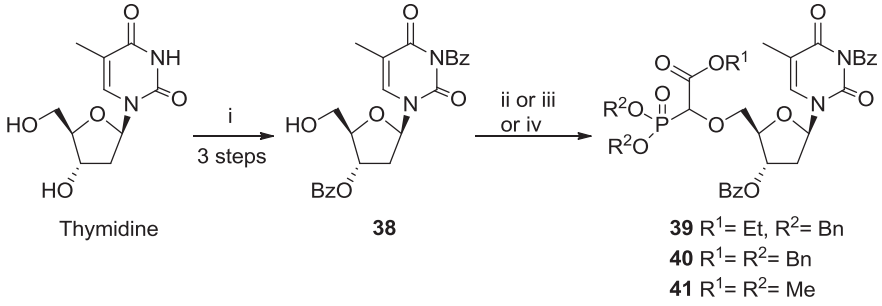
Thus O–H insertion at the 5′-OH is readily achieved in the thymidine series but blocking of the 3′-OH is necessary as the selectivity for insertion at the 5′-position is not particularly high. Accordingly the dibenzoyl thymidine derivative **38** where both the N–H and 3′-OH groups are blocked was synthesised as a key substrate for the O–H insertion process (Scheme 7).[5]

It is well known that 2′-deoxy nucleoside derivatives are more easily hydrolysed under acidic conditions than the other nucleosides[4j] and therefore the potential to effect deprotection under neutral conditions could be very significant. Thus, investigation of O–H insertion using dibenzyl ethyl diazophosphonate **7** and tribenzyl diazophosphonate **8** with the 3′-*O*,3-*N*-dibenzoylated thymidine **38** was carried out (Scheme 7, Table 4).

The reaction of **38** with dibenzyl ethyl diazophosphonate **7** proceeds with modest efficiency in benzene at reflux in the presence of 1 mol % rhodium acetate to afford compound **39** in approximately 60% yield. The reaction with the tribenzyl diazo compound **8** was very sluggish under the same conditions, probably due to the bulky nature of **8**. Even using a large excess of **8** added in portions, the reaction was not driven to completion. Furthermore, O–H insertion with the tribenzyl diazo precursor **8** was not very reproducible and yields of **40** varied from 30 to 40%.



Scheme 6. O–H insertion reaction with N^3-protected thymidine derivatives **33** and **34b**. Reaction conditions: (i) **6** (2.0 equiv), $Rh_2(OAc)_4$, benzene, reflux, overnight; (ii) when R=Bz, BnOH, 90 °C, 24 h.



Scheme 7. Synthesis of compounds **39**–**41**. Reaction conditions: (i) selective protection, see Experimental section for details; (ii) dibenzyl ethyl diazophosphonoacetate **7** (2 equiv), $Rh_2(OAc)_4$ (0.01 equiv), molecular sieves, benzene, reflux, 12 h; (iii) tribenzyl diazophosphonoacetate **8** (2 equiv), $Rh_2(OAc)_4$ (0.01 equiv), molecular sieves, benzene, reflux, 12 h; (iv) trimethyl diazophosphonoacetate **5** (1.2 equiv), $Rh_2(OAc)_4$ (0.01 equiv), molecular sieves, benzene, reflux, 12 h.

Table 4
O–H Insertion of α-diazophosphonoacetates **5**, **7** and **8** with thymidine derivative **38**

Entry	Substrate	Diazo compound (mol equiv)	Solvent	Catalyst (1 mol %)	Time	Product (% yield)[a]
1	**38**	**7** (2)	C_6H_6	$Rh_2(OAc)_4$	12 h	**39** (~60%)
2	**38**	**8** (2)	C_6H_6	$Rh_2(OAc)_4$	12 h	**40** (30–40%)
3	**38**	**5** (1.2)	C_6H_6	$Rh_2(OAc)_4$	12 h	**41** (86%)

[a] After chromatography.

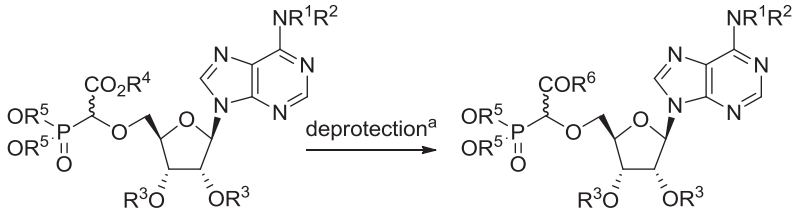
Reaction of **38** with **7** and **8** was attempted in toluene at 90 °C and using $Rh_2(NHCOCF_3)_4$ as catalyst; while the O–H insertion products **39** and **40** were isolated, the yields were lower than those obtained using $Rh_2(OAc)_4$ and benzene.

In contrast, treatment of **38** with trimethyl diazophosphonoacetate **5** led very efficiently to the O–H insertion product **41** (Scheme 7, Table 4). This process was employed as the synthetic route to the fully deprotected phosphononucleoside.[5] Thus, O–H insertion with the di- and tribenzyl diazophosphonate precursors **7** and **8**, while possible, is less favourable than with the analogous methyl and ethyl derivatives **5** and **6**.

2.3. Investigation of complete deprotection of the phosphononucleosides subsequent to O–H insertion

2.3.1. Exploration of deprotection with adenosine derivatives. Deprotection of N^6,N^6-dibenzoylated adenosine derivatives is generally accomplished with aqueous methanolic ammonia.[41] Treatment of **17** under these conditions afforded the partially deprotected α-amide phosphono adenosine **42** in 37% yield, resulting from debenzoylation accompanied by conversion of the carboxylic ester to the primary amide (Scheme 8, Table 5). Formation of the primary amide adjacent to the phosphonate was of interest, as this substituent can also be envisaged as a potential diphosphate mimic once the phosphonate is deprotected. Deprotection was also attempted using NaOH in MeOH at room temperature;[42] while the ester was efficiently hydrolysed, only one of the benzoyl groups on the adenine was cleaved under these conditions to afford compound **43**. By conducting the base hydrolysis at reflux overnight, efficient cleavage of the two benzoyl groups from the adenine base in **19** was achieved.[5]

Having prepared the phosphonate derivative **42**, complete deprotection was attempted using the McKenna procedure.[43] It was

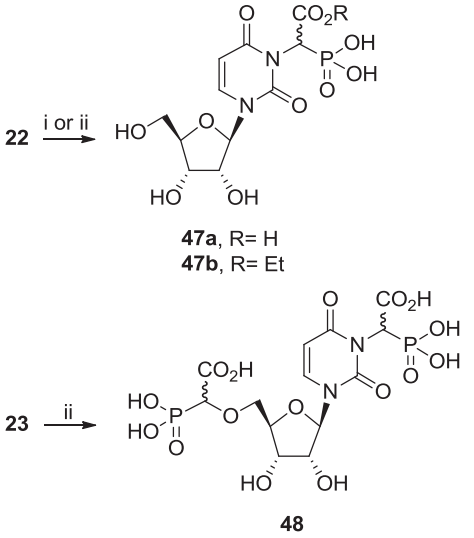


17 R^1= R^2= Bz, R^3= $C(CH_3)_2$, R^4= R^5= Et

18 R^1R^2= $CHNBn_2$, R^3= $C(CH_3)_2$, R^4= R^5= Et
19 R^1= R^2= R^3= Bz, R^4= R^5= Me

42 R^1= R^2= H, R^3= $C(CH_3)_2$, R^5= Et, R^6= NH_2
43 R^1= H, R^2= Bz, R^3= $C(CH_3)_2$, R^5= Et, R^6= OH
44 R^1= R^2= H, R^3= $C(CH_3)_2$, R^5= Et, R^6= OEt
45 R^1= H, R^2= Bz, R^3= R^5=H, R^6= OH
46 R^1= R^2= R^3= R^5=H, R^6= OH

Scheme 8. Partial deprotections of **17** and **18** and partial and full deprotection of **19**. [a]See Table 5 for conditions and yields.



Scheme 9. Deprotection reaction of compounds **22** and **23**. Reaction conditions: (i) (1) TMSBr (10 equiv), CH_3CN, rt, overnight, (2) H_2O, rt, 1 h; (ii) (1) TMSBr (10 equiv), CH_3CN, rt, overnight, (2) H_2O, rt, 1 h, (3) H_2O, 90 °C, overnight.

aqueous methanol for 8 h to provide the deprotected derivative **44** in 58% yield (Scheme 8, Table 5). However, all attempts to deprotect the ester derivative **44** using the McKenna procedure proved unsuccessful leading only to complex mixtures of unidentifiable products, as had been previously observed with the analogous amide **42**.

Given the challenges in effecting deprotection of the O–H insertion products derived from isopropylidene adenosine, it was decided to focus attention instead on the tetrabenzoyl derivative **19** with the expectation that all four benzoyl groups and the carboxylate ester could be cleaved in a single-step. As mentioned earlier, O–H insertion proceeded efficiently with the trimethyl diazophosphonoacetate **5** and the selectively protected nucleoside **16** to form **19**. Complete deprotection of **19** to reveal **46** in a remarkable 61% overall yield can be conveniently effected in a one-pot reaction using first excess TMSBr in dichloromethane at reflux for 2 h, to cleave the phosphonate esters, followed by basic hydrolysis of the remaining carboxylate methyl ester and benzoyl groups by addition of a solution of NaOH (1 M, excess) and heating the biphasic mixture at reflux overnight (Scheme 8, Table 5).[5] When the TMSBr deprotection was conducted at room temperature in CH_2Cl_2 or in CH_3CN the reaction was much less efficient. Interestingly when the

Table 5
Deprotection reactions of compounds **17**–**19**

Entry	Substrate	Deprotection step 1	Partial deprotection (% yield)	Deprotection step 2	Full deprotection (% yield)[a]
1	**17**	NH_4OH/MeOH	**42** (37)	TMSBr[b] then H_2O	—
2	**17**	NaOH/MeOH	**43**	—	—
3	**18**	$Pd(OH)_2$/C	**44** (58)	TMSBr[b] then H_2O	—
4[c]	**19**	TMSBr[d] then H_2O	Not isolated	NaOH (1 M) room temperature	**45** (53)
5[c]	**19**	TMSBr[d] then H_2O	Not isolated	NaOH (1 M) reflux	**46** (61)

[a] After charcoal chromatography.
[b] TMSBr, CH_3CN, rt, 12 h.
[c] Data from Ref. 5.
[d] TMSBr, CH_2Cl_2, reflux, 2 h.

envisaged that in the case of the O–H insertion products such as **17**, once the acidic phosphonic acid was revealed following the addition of water, then under the aqueous acidic conditions hydrolysis of both the ester and acetonide moieties would ensue. Accordingly deprotection of **42** was investigated using TMSBr in acetonitrile at room temperature overnight, followed by addition of water; while the starting material was completely consumed in these conditions, no identifiable products could be identified in the complex mixture formed, presumably indicating decomposition of the nucleoside derivative under the acidic conditions.

As anticipated the formamidine was cleanly removed from **18** by hydrogenolysis in the presence of the Pearlman catalyst in 50%

basic hydrolysis of the adenosine derivative **19** is conducted at room temperature, one benzoyl group remains attached to the 6-amino group of the adenine base to afford the partially deprotected compound **45** (Scheme 8, Table 5).

Purification of the highly polar phosphononucleosides **45** and **46** was readily effected by chromatography on a charcoal column by elution with a solution of 20% NH_4OH,[44] affording the desired compounds as ammonium salts, which were characterised by NMR (^1H, ^{13}C, ^{31}P) and MS. Thus, use of O–H insertion is feasible as a method of attachment of the phosphonoacetic acid moiety in the presence of adenine provided suitable protection/deprotection strategies are employed.

2.3.2. Deprotection reactions with uridine derivatives. Deprotection of each of the insertion products **22** and **23** was achieved using a large excess of trimethylsilyl bromide in acetonitrile at room temperature overnight followed by hydrolysis of the resulting silyl ester by addition of water (Scheme 9). Efficient deprotection of the phosphonic acid and the acetonide groups occurs readily under these conditions affording compound **47b**; for complete hydrolysis to **48** it was necessary to heat the reaction mixture with water at 90 °C overnight. Interestingly in some of the deprotected phosphonic acid derivatives the signals for the CHP carbon were not detected in the ^{13}C NMR; it is believed that this is due to deuterium exchange in either D_2O or CD_3OD.

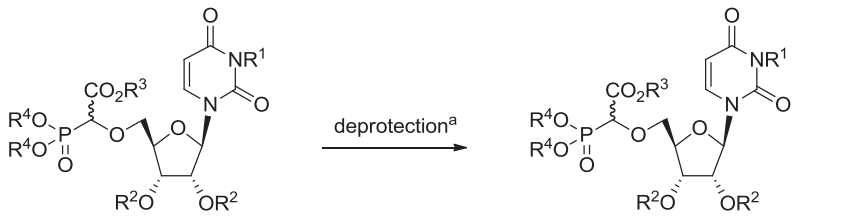
The product **29** was deprotected in two sequences (Scheme 10). In the first instance N-debenzoylation was effected by treatment in benzyl alcohol at 90 °C to give **49** in 77% yield,[35,45] which was subsequently treated with TMSBr in acetonitrile at room temperature overnight followed by reaction with water at room temperature for 1 h to reveal the phosphonic acid. The NMR spectra of the product indicated that while the phosphonate esters and the isopropylidene group were efficiently hydrolysed, only partial cleavage of the carboxylic ester had taken place. Purification by charcoal chromatography gave the phosphonate derivatives as the corresponding ammonium salts **50a**/**50b** (Scheme 10). To effect complete deprotection, the mixture was re-exposed to TMSBr followed by heating with water at 90 °C, which afforded **50b** in 23% overall yield from **29**. When TMSBr deprotection was applied to isolated **49**, followed by heating in water at 90 °C for 17 h, **50b** was isolated in 77% yield (59% overall from **29**).

Use of benzyl alcohol as described above to deprotect the *N*-benzoyl group is significant as these neutral conditions are compatible with the presence of the ester group.[35] Alternatively, when standard conditions for removal of a benzoyl group were employed involving treatment of the insertion product **29** with methanolic ammonia, the *N*-benzoyl group was removed and in addition the ester was transformed to the corresponding primary amide **51** (Scheme 10). Then, the phosphonate esters were deprotected by using TMSBr in acetonitrile at room temperature overnight to form the phosphonate **52** bearing an amide group adjacent to the phosphonate substituent. This amide derivative can be considered as a potential diphosphate mimic and therefore is of interest for biological evaluation for comparison to the analogous carboxylic acid phosphonate **50b**.

Attempted deprotection of the MEM protecting group in compound **30** using the conditions described by Takaku and co-workers[36] proved particularly intractable. We therefore investigated other agents such as titanium(IV) chloride[46] or iodotrimethylsilane[47] and an alternative method described by Takaku and co-workers (concd ammonia/pyridine 9:1 at 50 °C).[48] None of these deprotection conditions proved effective. The NMR spectra of the products revealed that the MEM group was still present in each case. While the MEM protecting group is readily introduced and proved compatible with the O–H insertion conditions, its resistance to cleavage makes it unsuitable for this sequence.

The benzyl protecting group in compound **31** also proved impossible to remove; literature precedent suggests that conventional deprotection does not work,[49] while attempted transfer hydrogenolysis with excess HCO_2NH_4, Pd/C, aqueous MeOH for 6 days at 65 °C failed to afford the desired product.

As observed with the adenosine series, the best conditions for the full deprotection of **32** were found to be using the McKenna



29 R^1= Bz, R^2= $C(CH_3)_2$, R^3= R^4= Et

30 R^1= MEM, R^2= $C(CH_3)_2$, R^3= R^4= Et
31 R^1= Bn, R^2= $C(CH_3)_2$, R^3= R^4= Et
32 R^1= R^2= Bz, R^3= R^4= Me

49 R^1= H, R^2= $C(CH_3)_2$, R^3= R^4= Et
50a R^1= R^2= R^4= H, R^3= Et
50b R^1= R^2= R^3= R^4= H
51 R^1= H, R^2= $C(CH_3)_2$, R^3= NH_2, R^4= Et
52 R^1= R^2= R^4= H, R^3= NH_2

50b R^1= R^2= R^3= R^4= H

Scheme 10. Deprotection of compounds **29** and **32**. [a]See Table 6 for conditions and yields.

Table 6
Deprotection reactions of compounds **29** and **32**

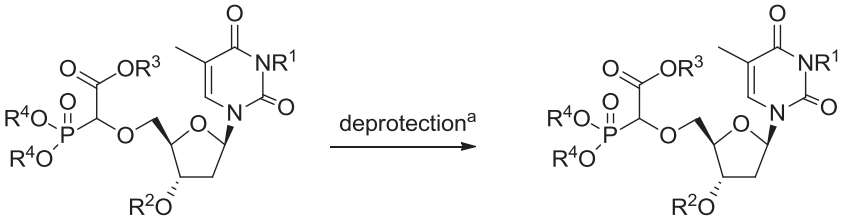
Entry	Substrate	Deprotection step 1	Partial deprotection (% yield)	Deprotection step 2	Full deprotection (% yield)[a]
1	**29**	BnOH	**49** (77)	TMSBr[b] then H_2O	**50a**/**50b**
2	**29**	BnOH	**49** (77)	TMSBr[b] then H_2O at reflux	**50b** (59)
3	**29**	NH_4OH/MeOH	**51**	TMSBr[b] then H_2O	**52**
4	**30**	Triphenylmethylfluoroborate	—		—
5	**31**	HCO_2NH_4, Pd/C	—		—
6[c]	**32**	TMSBr[d] then H_2O	Not isolated	NaOH (1 M)	**50b** (56)

[a] After charcoal chromatography.
[b] TMSBr, CH_3CN, rt, 12 h.
[c] Data from Ref. 5.
[d] TMSBr CH_2Cl_2, reflux, 2 h.

procedure with TMSBr in dichloromethane at reflux for 2 h to cleave the phosphonate esters, followed by basic hydrolysis of the remaining carboxylate methyl ester and benzoyl groups using a solution of NaOH (1 M, excess) at room temperature (Scheme 10) to afford compound **50b**.[5]

2.3.3. Deprotection reactions with thymidine derivatives. Deprotection of compound **37a** using excess of TMSBr in acetonitrile at room temperature overnight followed by hydrolysis gave extensive decomposition of the compound and none of the desired product was observed. This result is to be compared with the deprotection of uridine derivative **49** highlighting the lability of 2′-deoxynucleosides compared to nucleosides. As described above for the uridine derivative all attempts to remove the MEM group in compounds **36a**–**c** proved unsuccessful.

Under atmospheric pressure of hydrogen, both the dibenzyl and tribenzyl esters **39** and **40** are cleaved in the presence of 10% w/w of 5% Pd/C. In the case of **39** the carboxylic ester is obviously unaffected (Scheme 11, Table 7). Due to the easier synthesis of compound **41** followed by its full deprotection in a one-pot reaction using first the McKenna procedure, followed by basic hydrolysis at room temperature (Scheme 11, Table 7) to afford compound **55**,[5] the deprotection of compounds **53** and **54** was not pursued further.



39 R^1= R^2= Bz, R^3= Et, R^4= Bn
40 R^1= R^2= Bz, R^3= R^4= Bn
41 R^1= R^2= Bz, R^3= R^4= Me

53 R^1= R^2= Bz, R^3= Et, R^4= H
54 R^1= R^2= Bz, R^3= R^4= H
55 R^1= R^2= R^3= R^4= H

Scheme 11. Deprotection of compounds **39**–**41**. [a]See Table 7 for conditions and yields.

Table 7
Deprotection reactions of compounds **39**–**41**

Entry	Substrate	Deprotection step 1	Partial deprotection (% yield)	Deprotection step 2	Full deprotection (% yield)[a]
1	**30**	H_2, Pd/C, 1 bar	**53** (quantitative)	—	—
2	**40**	H_2, Pd/C, 1 bar	**54** (quantitative)	—	—
3	**41**	TMSBr[b] then H_2O	Not isolated	NaOH (1 M)	**55** (57)

[a] After charcoal chromatography.
[b] TMSBr, CH_2Cl_2, reflux, 2 h.

3. Conclusions

In conclusion, rhodium(II) acetate or rhodium(II) trifluoroacetamide catalysed reactions of the α-diazophosphonates **5**–**8** can be employed to attach the phosphonate moiety bearing an α-carboxylic ester substituent to nucleosides, via an O–H insertion process. In the case of adenosine, protection of the base was required to enable the O–H insertion process; however, with the pyrimidine derivatives, reaction is possible in the presence of the unprotected uracil base, albeit with competing N–H insertion at the base. Protection at this site results in exclusive O–H insertion. When both 3′- and 5′-hydroxyl groups are available in thymidine, insertion at each group occurs although insertion at the 5′-position is favoured. Deprotection of the phosphonates using TMSBr was successfully achieved to provide phosphononucleosides.

4. Experimental

4.1. General

Proton and ^{13}C NMR were recorded on a Jeol GSX FT (270 MHz) or a Bruker Avance DPX (300 MHz) spectrometer. Chemical shifts are expressed in parts per million relative to tetramethylsilane, *J* values are reported in hertz. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrometer as thin films or KBr discs as appropriate. Elemental analyses were performed on a Perkin–Elmer 240 elemental analyser. Mass spectra were recorded on a Kratos Profile HV-4 double focussing high resolution mass spectrometer (E.I.). Thin layer chromatography was performed on DC-Alufoilen Kieselgel $60F_{254}$ 0.2 mm plates (Merck) and visualised under UV light and stained with phosphomolybdic acid/aqueous sulfuric acid solution. Flash chromatography was performed on Kieselgel 60 (Merck) 60–200 mesh. All solvents were distilled before use: hexane from calcium chloride, dichloromethane and ethyl acetate from phosphorous pentoxide. Dry solvents were prepared by refluxing over a drying agent under an inert atmosphere: THF was dried over sodium/benzophenone while ether, benzene and toluene were dried over $LiAlH_4$, and DMF was distilled from calcium hydride under reduced pressure (ca. 15 mmHg) then stored over 4 Å molecular sieves.

Rhodium(II) acetate was obtained from Johnson Matthey. Rhodium(II) trifluoroacetamide,[50] diazophosphonoacetates **6** and **8**,[25] N^3-benzyl-2′,3′-*O*-isopropylidene uridine **29**[40] were synthesised using the procedures described in the literature. The synthesis and characterisation of compounds **32**, **41**, **45**, **46** and **55** are described elsewhere.[5]

4.2. Ethyl dibenzylphosphonoacetate 3

Copper(II) triflate (0.34 g, 0.94 mmol) was added to a solution of dibenzyl phosphite (5.0 g, 19.0 mmol) in CH_2Cl_2 (100 mL) and the mixture was stirred for 15 min to give a slightly pinkish solution. This was degassed by several cycles of evacuate/backfill and immersed in a large water bath at 19 °C, then neat ethyl diazoacetate (10 mL, 10.85 g, 95.0 mmol) was added dropwise for 30 min by means of a syringe pump. After the addition, the mixture was allowed to stir for a further 30 min at room temperature then concentrated and purified by flash chromatography over alumina (150 mL activity II/III Al_2O_3, hexane/EtOAc 4:1 then hexane/EtOAc 1:1). Yield typically 3.30–5.60 g (50–86%). δ_H ($CDCl_3$) 7.45–7.25 (m, 10H, ArH), 5.15–5.00 (m, 4H, $PhCH_2$), 4.15 (q, *J* 7, 2H, CH_2CH_3), 2.99 (d, J_{PH} 21, 2H, PCH_2), 1.22 (t, *J* 7, 3H, CH_2CH_3); δ_C 165.6 (J_{PC} 6.3), 135.9 (J_{PC} 6.3), 128.6, 128.5, 128.0, 68.0 (J_{PC} 6.3), 61.7, 34.7 (J_{PC} 135.6), 14.0; δ_P 22.1; ν_{max}/cm^{-1} (thin film) 3065 w, 2980 w (C–H), 1735 s (C=O),

1500 m, 1455 m, 1370 m (C–C), 1270 s (P=O), 998 s (P–O), 737 s, 700 s (C–H); HRMS (ESI) $[M+H]^+$: calculated for $C_{18}H_{22}O_5P$: 349.1205, found: 349.1190.

4.3. Dibenzylphosphonoacetic acid 11

A solution of LiOH (1.65 g, 68.9 mmol) in water (80 mL) was added to the ethyl ester **3** (20.0 g, 57.4 mmol) in THF (80 mL). The resulting mixture was stirred overnight at room temperature then diluted with ether and 1 M NaOH. The aqueous phase was separated, washed with ether and made acidic by dropwise addition of concd HCl. The acidic solution was extracted with ether, the combined organic phases were dried over $MgSO_4$ and concentrated to afford the acid **11** as a pale, viscous oil (15.0 g, 82%) with spectroscopic characteristics in accordance with the literature.[27] δ_H ($CDCl_3$) 9.88 (1H, br s, CO_2H), 7.40–7.25 (10H, m, ArH), 3.02 (2H, d, J_{PH} 22, PCH_2); δ_C 168.3 (d, *J* 5.2), 136.0 (d, *J* 6.3), 129.02, 129.0, 128.5, 69.0 (d, *J* 6.3), 34.9 (d, *J* 136.2); δ_P 23.5; ν_{max} (thin film) 3035 w, 2945 w (C–H), 1730 s (C=O), 1498, 1456, 1381 (C–C), 1217 s (P=O), 998 s (P–O), 737 s, 697 s (C–H).

4.4. Tribenzyl phosphonoacetate 4

The acid **11** (15.0 g, 46.8 mmol) was dissolved in undistilled DMF (ca. 100 mL) and K_2CO_3 (7.10 g, 51.40 mmol) was added. Benzyl bromide (5.40 mL, 7.76 g, 45.40 mmol) was added and the resulting mixture was stirred at room temperature overnight. The mixture was diluted with water, acidified by dropwise addition of concd HCl and extracted three times with Et_2O. The combined organic layers were washed three times with 2 M HCl, once with brine, dried over $MgSO_4$ and concentrated to afford the product **4** as a viscous oil (15.4 g, 83.%), which could be used without purification. Spectroscopic data were in agreement with the literature.[51] δ_H ($CDCl_3$) 7.45–7.25 (15H, m, ArH), 5.13 (2H, s, CH_2Ph), 5.10–4.97 (4H, m, $PhCH_2$), 3.04 (2H, d, J_{PH} 21, PCH_2); δ_C 165.4 (d, *J* 6.3), 135.9 (d, *J* 6.3), 135.1, 128.58, 128.56, 128.50, 128.4, 128.0, 68.0 (d, *J* 6.3), 67.4, 34.7 (d, *J* 135.6); δ_P 21.8;ν_{max} (thin film) 3034 w, 2954 w (C–H), 1738 s (C=O), 1498, 1456, 1378 (C–C), 1271 s (P=O), 998 s (P–O), 737 s, 697 s (C–H).

4.5. Ethyl dibenzylphosphonodiazoacetate 7

A solution of ethyl dibenzylphosphonoacetate **3** (1.21 g, 3.47 mmol) in toluene (10 mL) was added dropwise to a cooled (0 °C) suspension of *t*-BuOK (0.47 g, 4.17 mmol) in toluene (10 mL). After 25 min stirring at 0 °C, a solution of 2-naphthalenesulfonyl azide (0.81 g, 3.47 mmol) in toluene (5 mL) was added, and the mixture was stirred and allowed to warm to room temperature overnight. The mixture was filtered and concentrated to afford a yellow oil, which was further purified by flash chromatography (hexanes/EtOAc 4:1) to afford the title product **7** as a pale, viscous oil (0.85 g, 66%). δ_H ($CDCl_3$) 7.43–7.25 (m, 10H, ArH), 5.22–5.08 (m, 4H, CH_2Ph), 4.15 (q, *J* 7.1, 2H, CH_2CH_3), 1.22 (t, *J* 7.1, 3H, CH_2CH_3); δ_C 163.2, 135.5, 128.7, 128.6, 128.0, 69.1, 61.7; δ_P 12.2; ν_{max} (thin film) 3035 w, 2955 w (C–H), 2130 m (C=N), 1704 s (C=O), 1499, 1457, 1381 (C–C), 1280 s (P=O), 998 s (P–O), 740 m, 700 m (C–H); HRMS (ESI) $[M+H]^+$: calculated for $C_{18}H_{20}N_2O_5P$: 357.1110, found: 357.1095.

4.6. Tribenzyl phosphonodiazoacetate 8

This was prepared using the same procedure as described above for ethyl dibenzylphosphonodiazoacetate **7** starting from the tribenzyl ester **4** (2.50 g, 6.09 mmol), *t*-BuOK (0.82 g, 7.31 mmol) and 2-naphthalenesulfonyl azide (1.42 g, 6.09 mmol). Purification by flash chromatography (hexanes/EtOAc 2:1) afforded the title product **8** as a viscous yellow oil (1.80 g, 68%). δ_H ($CDCl_3$) 7.40–723 (m, 15H, ArH), 5.15–5.00 (m, 6H, CH_2Ph); δ_C 162.0, 134.2, 134.1, 127.62, 127.56, 127.4, 127.2, 127.0, 68.1, 66.2; δ_P 11.8; ν_{max} (thin film) 3034 w, 2957 w (C–H), 2132 m (C=N), 1704 s (C=O), 1498, 1456, 1379 (C–C), 1282 s (P=O), 998 s (P–O), 740 m, 697 m (C–H); HRMS (ESI) $[M+H]^+$: calculated for $C_{23}H_{22}N_2O_5P$: 437.1266, found: 437.1251,.

4.7. N^6,N^6-Dibenzylformamidine-2′,3′-*O*-isopropylidene adenosine 15

A mixture of freshly distilled dibenzylamine (9.62 g, 48.7 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (1.95 g, 16.2 mmol) in acetonitrile (15 mL) was heated at reflux temperature for 24 h. Anhydrous toluene (15 mL) was added and the solution was concentrated in vacuo. The crude residue was dissolved in acetonitrile (15 mL) and added dropwise to a stirring solution of 2′,3′-*O*-isopropylidene adenosine **12** (2.0 g, 6.5 mmol) in acetonitrile (10 mL). The reaction mixture was stirred for 24 h at 45 °C then concentrated in vacuo. Flash chromatography (hexane/EtOAc 1:1) afforded **15** as a white solid (3.19 g, 94%) with spectroscopic characteristics in accordance with the literature.[31] δ_H (270 MHz, $CDCl_3$) 9.4 (1H, s, CH=N), 8.57 (1H, s, H-2), 8.00 (1H, s, H-8), 7.42–7.18 (10H, m, 2Ph), 5.93 (1H, d, $J_{1'2'}$ 4.6, H-1′), 5.30–5.21 (1H, m, H-2′), 5.15–5.08 (1H, m, H-3′), 4.88 (2H, s, CH_2Ph), 4.60–4.53 (1H, m, H-4′), 4.45 (2H, s, CH_2Ph), 4.05–3.77 (2H, m, 2H-5′), 1.64, 1.37 (6H, 2s, $2CH_3$); δ_C (67.8 MHz, $CDCl_3$) 160.4 (C-6), 159.0 (CH=N), 152.0 (C-2), 150.4 (C-4, C-5), 141.5 (C-8), 135.5, 135.1, 129.1, 128.8, 128.6, 128.4, 127.9, 127.6 (C–Ar), 113.8 [$C(CH_3)_2$], 93.9 (C-1′), 86.1 (C-2′), 83.1 (C-3′), 81.6 (C-4′), 63.2 (C-5′), 54.6, 47.8 ($2CH_2$), 27.5, 25.1 ($2CH_3$).

4.8. N^6,N^6-Dibenzoyl-5′-*O*-[diethyl(ethoxycarbonyl) phosphonomethyl]-2′,3′-*O*-isopropylidene adenosine 17

A mixture of N^6,N^6-dibenzoyl-2′,3′-*O*-isopropylidene adenosine[30] **14** (1.0 g, 19.4 mmol), triethyl diazophosphonoacetate **6** (0.97 g, 38.8 mmol) and rhodium(II) trifluoroacetamide (~1 mol %) in benzene (15 mL) was heated at 80 °C for 12 h under nitrogen atmosphere. The solution was concentrated in vacuo and the crude mixture purified by flash chromatography (EtOAc/hexane 1:1) affording compound **17** as a clear yellow oil (0.56 g, 39%), which was an essentially equimolar mixture of diastereoisomers. Found: C, 56.59; H, 6.13; N, 9.55. $C_{35}H_{40}N_5O_{11}P$ requires C, 56.99; H, 5.47; N, 9.49. δ_H (270 MHz, $CDCl_3$) 8.67, 8.66, 8.64, 8.60 (2H, 4s, H-2, H-8, 2 isomers), 7.86–7.29 (10H, m, 2Ph), 6.30–6.21 (1H, m, H-1′), 5.35–5.05 (2H, m, H-2′, H-3′), 4.55–4.41 (1H, m, H-4′), 4.40–3.80 (9H, m, $2CH_2OP$, CH_2ester, CHP, 2H-5′), 1.65, 1.39 (6H, 2s, $2CH_3$), 1.30–1.20 (9H, m, $3CH_3$); δ_C (67.8 MHz, $CDCl_3$) 172.1 (2COPh), 166.8, 166.4 (COester), 152.9, 152.7, 152.1 and 151.7 (C-6, C-2, C-4 and C-5), 143.9 (C-8), 134.2, 132.7, 129.4, 128.7 (C–Ar), 114.5, 114.3 ($C(CH_3)_2$), 91.5, 90.3 (C-1′), 84.9, 84.8, 84.7, 84.4 (C-2′, C-3′), 81.4, 81.2 (C-4′), 76.8 (d, J_{PC} 156.6, CHP), 72.2, 72.1 (2d, J_{PC} 11.2, 11.2, C-5′), 63.7–63.5 (m, $2CH_2OP$), 61.9 (CH_2ester), 27.2, 25.3 ($2CH_3$), 16.2, 16.3 ($2CH_3$phosphonate), 14.0 (CH_3ester); δ_P (121.5 MHz, $CDCl_3$) +15.09 (54%), 15.00 (46%); ν_{max} (film)/cm^{-1}: 1750 (C=Oester), 1715 [C=O(Bz)], 1600, 1238 and 1026 [$PO(OEt)_2$]; *m*/*z* (%): 77 (100), 198 (50), 371 (21), 472 (2). When this reaction was repeated with a reaction time of 24 h an increased yield (45%) was obtained.

4.9. N^6,N^6-Dibenzylformamidine-5′-*O*-[diethyl(ethoxycarbonyl)phosphonomethyl]-2′,3′-*O*-isopropylidene adenosine 18

A solution of N^6,N^6-dibenzylformamidine-2′,3′-*O*-isopropylidene adenosine **15** (0.5 g, 0.97 mmol), triethyl diazophosphonoacetate **6** (0.48 g, 1.94 mmol) and rhodium(II)

trifluoroacetamide (~1 mol %) in benzene (15 mL) was heated at reflux temperature for 24 h under nitrogen atmosphere. The solution was concentrated in vacuo and the crude mixture purified by flash chromatography (EtOAc/hexane 7:3) affording the insertion product **18** as a yellow oil (0.39 g, 55%) and an essentially equimolar mixture of diastereoisomers. Found: 56.95; H, 6.28; N, 11.04. $C_{36}H_{45}N_6O_9P.H_2O$ requires C, 57.29; H, 6.28; N, 11.13. δ_H (270 MHz, $CDCl_3$) 9.43, 9.42 (1H, 2s, CH=N), 8.64, 8.63 (1H, 2s, H-2), 8.34, 8.29 (1H, 2s, H-8), 7.46–7.21 (10H, m, 2Ph), 6.25 (1H, d, $J_{1',2'}$ 3.0, H-1′), 5.44–5.34 (1H, m, H-2′), 5.24–5.13 (1H, m, H-3′), 4.99–4.81 (2H, m, CH_2Ph), 4.60–4.10 (10H, m, H-4′, $2CH_2OP$, CH_2ester, CH_2Ph, CHP), 4.08–3.77 (2H, m, 2H-5′), 1.60, 1.41 (6H, 2s, $2CH_3$), 1.40–1.18 (9H, m, $3CH_3$); δ_C (67.8 MHz, $CDCl_3$) 166.7, 166.5 (COester), 159.6 (C-6), 158.9 (CH=N), 152.6 (C-2), 151.4, 151.2 (C-4, C-5), 140.8 (C-8), 135.6, 135.2, 128.7, 128.5, 128.0, 127.9, 127.8, 127.6 (C–Ar), 114.2, 114.0 [$C(CH_3)_2$], 90.9, 90.0 (C-1′), 85.2, 84.7 (C-2′), 84.3, 84.0 (C-3′), 81.7, 81.2 (C-4′), 76.8, 76.7 (2d, J_{PC} 156.2, 156.2, CHP), 72.0, 71.9 (2d, J_{PC} 11.2, 11.2, C-5′), 63.8–63.1 (m, $2CH_2OP$), 61.7, 61.6 (CH_2ester), 54.4, 47.5 ($2CH_2Ph$), 27.1, 25.2 ($2CH_3$), 16.2, 16.1 ($2CH_3$phosphonate), 13.8 (CH_3ester); δ_P (121.5 MHz, $CDCl_3$) +15.06; ν_{max} (film)/cm^{-1}: 1744 (C=Oester), 1556 (C=N), 1265 (P=O); *m*/*z* (%): 43 (100), 91 (69), 197 (41), 285 (4).

4.10. 5′-*O*-[Diethyl(ethoxycarbonyl)phosphonomethyl]-2′,3′-*O*-isopropylidene uridine 21 and N^3-[diethyl(ethoxycarbonyl) phosphonomethyl]-2′,3′-*O*-isopropylidene uridine 22

A solution of 2′,3′-*O*-isopropylidene uridine **20** (0.66 g, 2.3 mmol), triethyl diazophosphonoacetate **6** (0.7 g, 2.7 mmol) and a catalytic amount of rhodium(II) trifluoroacetamide (~1 mol %) in benzene (10 mL) was heated at 80 °C for 36 h under nitrogen atmosphere. The solution was concentrated in vacuo and the crude mixture purified by flash chromatography (EtOAc/hexane 2:8) to afford a mixture of **21** and **22** each as a pair of diastereoisomers. Separation was achieved on preparative TLC plates (ether/EtOAc 4:6) and gave the less polar product **21** (0.106 g, 9%) and the more polar product **22** (0.305 g, 26%) each as a colourless oil, which was an essentially equimolar mixture of diastereoisomers. *Compound* ***21***: Found: C, 47.61; H, 5.99; N, 5.27. $C_{20}H_{31}N_2O_{11}P$ requires C, 47.43; H, 6.17; N, 5.53. δ_H (300 MHz, $CDCl_3$) 7.99, 7.89 (1H, 2d, $J_{5,6}$ 8.1, 8.1, H-6), 6.08, 6.14 (1H, 2d, $J_{1',2'}$ 3.6, 3.6, H-1′), 5.82, 5.76 (1H, 2d, $J_{5,6}$ 8.1, 8.1, H-5), 5.08–5.00, 4.95–4.88 (1H, 2m, H-2′), 4.79–4.69 (1H, m, H-3′), 4.43–4.09 (7H, m, $2CH_2OP$, CH_2ester, PCHO), 4.01–3.78 (2H, m, 2H-5′), 1.50 (3H, s, CH_3), 1.35–1.20 (12H, m, $4CH_3$); δ_C (75.4 MHz, $CDCl_3$) 165.8, 165.1 (COester), 162.4, 162.3 (C-4), 149.2 (C-2), 140.7, 140.5 (C-6), 113.9, 113.8 ($C(CH_3)_2$), 102.1, 101.5 (C-5), 90.9, 89.8 (C-1′), 83.6, 83.4, 83.2, 83.1 (C-2′, C-3′), 79.8, 79.3 (C-4′), 76.6, 74.5 (2d, J_{PC} 158.0, PCHO), 71.3, 71.1 (2d, J_{PC} 9.2, 12.0, C-5′), 63.2–62.3 (m, $2CH_2OP$), 61.1 (CH_2ester), 26.3, 24.4 ($2CH_3$), 15.4, 15.3 ($2CH_3$phosphonate), 13.1 (CH_3ester); δ_P (121.5 MHz, $CDCl_3$) +15.37 (55%), +15.10 (45%); ν_{max} (film)/cm^{-1}: 3020 (CH), 1716 (C=Oester), 1695, 1265 (P=O); *m*/*z* (%): 43 (100), 224 (18).

Compound ***22***: Found: C, 47.09; H, 6.31; N, 5.43. $C_{20}H_{31}N_2O_{11}P$ requires C, 47.43; H, 6.17; N, 5.53. δ_H (270 MHz, $CDCl_3$) 7.95, 7.87 (1H, 2d, $J_{5,6}$ 8.1, 8.1, H-6), 6.17–6.15, 6.14–6.12, 6.02–5.95 (2H, 3m, H-5, H-1′), 5.67, 5.62 (1H, 2d, $J_{2',3'}$ 2.4, H-2′), 5.11–5.07, 5.06–4.96 (2H, 2m, H-3′, H-4′), 4.38–4.12 (7H, m, $2CH_2OP$, CH_2ester, PCHN), 3.96–3.74 (2H, m, 2H-5′), 1.60 (3H, s, CH_3), 1.42–1.18 (12H, m, $4CH_3$); δ_C (67.8 MHz, $CDCl_3$) 170.4, 170.1 (COester), 164.8, 164.7 (C-4), 154.9 (C-2), 147.3, 147.0 (C-6), 114.0 [$C(CH_3)_2$], 97.7, 97.2 (C-5), 95.5, 95.4 (C-1′), 88.0, 87.8 (C-2′), 84.2, 84.0 (C-3′), 80.4, 80.3 (C-4′), 71.1, 69.1 (2d, J_{PC} 160.0, 160.0, PCHN), 64.2–64.1 (m, $2CH_2OP$), 62.6, 62.5 (CH_2ester, C-5′), 27.2, 25.2 ($2CH_3$), 16.3 ($2CH_3$phosphonate), 14.0 (CH_3ester); δ_P (121.5 MHz, $CDCl_3$) +13.82 (56%), +13.79 (44%); ν_{max} (film)/cm^{-1}: 3091 (CH), 1751 (C=Oester), 1671, 1265 (P=O), 1218; *m*/*z* (%): 43 (95), 224 (100), 464 (20).

4.11. N^3-[Diethyl(ethoxycarbonyl)phosphonomethyl]-2′,3′-*O*-isopropylidene uridine 22

A solution of 2′,3′-*O*-isopropylidene uridine **20** (0.50 g, 1.75 mmol), triethyl diazophosphonoacetate **6** (0.44 g, 1.75 mmol) and rhodium(II) acetate (~1 mol %) in benzene (10 mL) was heated at 80 °C overnight under nitrogen atmosphere. The solution was concentrated in vacuo and flash chromatography (EtOAc) afforded **22** as a colourless oil, which was an essentially equimolar mixture of diastereoisomers (0.250 g, 27%). Spectroscopic data were identical to that described above.

4.12. N^3,5′-*O*-[Bis-diethyl(ethoxycarbonyl) phosphonomethyl]-2′,3′-*O*-isopropylidene uridine 23

A solution of 2′,3′-*O*-isopropylidene uridine **20** (0.50 g, 1.80 mmol), triethyl diazophosphonoacetate **6** (1.75 g, 7.5 mmol) and rhodium(II) acetate (~1 mol %) in benzene (25 mL) was heated at reflux temperature overnight under nitrogen atmosphere. The solution was concentrated in vacuo and purification by flash chromatography (EtOAc) then (EtOAc/MeOH 95:5) afforded **23** as a yellow oil (0.528 g, 39%), which was an essentially equimolar mixture of diastereoisomers. Found: C, 46.38; H, 6.31; N, 3.83. $C_{28}H_{46}N_2O_{16}P_2$ requires C, 46.16; H, 6.36; N, 3.83. δ_H (270 MHz, $CDCl_3$) 8.29, 8.19, 8.18, 8.13 (1H, 4d, $J_{5,6}$ 7.4, 7.4, 7.4, 7.4, H-6), 6.20–6.11 (1H, m, H-5), 6.10–6.00 (1H, m, H-1′), 5.99–5.86 (1H, m, H-2′), 5.00–4.90, 4.89–4.78 (1H, 2m, H-3′), 4.77–4.60 (1H, m, H-4′), 4.40–3.70 (16H, m, PCHO, PCHN, $4CH_2OP$, $2CH_2$ester, 2H-5′), 1.50 (3H, s, CH_3), 1.32–1.10 (21H, m, $7CH_3$); δ_C (67.8 MHz, $CDCl_3$) 170.5, 170.4 (COester), 167.1, 166.9 (COester), 165.2, 165.1 (C-4), 155.2, 155.1 (C-2), 146.5, 146.3, 146.1 (C-6), 114.6, 114.4 ($C(CH_3)_2$), 96.1, 95.7, 95.6, 95.5 (C-5), 94.4, 93.9, 93.3, 92.8 (C-1′), 86.4, 86.2, 86.1, 85.9, 85.8, 85.7 (C-2′, C-3′), 80.9, 80.8, 80.7, 80.6 (C-4′), 77.7, 76.4, 75.6, 74.2 (4d, J_{PC} 159.5, J_{PC} 157.6, 157.6, 158.1, 158.1, PCHO), 71.4, 71.3, 70.7, 69.1, 69.0, 68.6 (6d, J_{PC} 159.5, 159.5, 160.2, 160.2, 9.1, 9.1, 12.1, 12.1, PCHN, C-5′), 64.3–63.8 (m, $4CH_2OP$), 63.0, 61.2 ($2CH_2$ester), 27.6, 27.5, 25.8, 25.7 ($2CH_3$), 16.8, 16.6, 16.5 ($2CH_3$phosphonate), 14.6, 14.5, 14.4 (CH_3ester); δ_P (121.5 MHz, $CDCl_3$) +15.23 (11%), 15.16 (10%), 15.05 (10%), 15.02 (14%), 14.00 (16%), 13.97 (17%), 13.95 (10%), 13.91 (11%); ν_{max} (film)/cm^{-1}: 1750 (C=Oester), 1670, 1265 (P=O); *m*/*z* (%): 228 (100), 286 (83), 514 (60), 571 (8).

4.13. N^3-Methoxyethoxymethyl-2′,3′-*O*-isopropylidene uridine 26

A mixture of methoxyethoxymethyl chloride (0.16 mL, 1.4 mmol), KOH (0.08 g, 1.4 mmol), benzyltriethylammonium chloride (20 mg, 0.09 mmol) and 5′-*O*-benzoyl-2′,3′-*O*-isopropylidene uridine[37] (0.46 g, 1.2 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 8 h, then washed with water (20 mL). The organic layer was dried, concentrated, redissolved in MeOH (10 mL) and treated with concd ammonia (10 mL). The solution was stirred at room temperature for 8 h, concentrated and purified by flash chromatography (CH_2Cl_2/EtOH 95:5) to afford **26** as a colourless oil (0.23 g, 51%). Found: C, 50.87; H, 6.48; N, 7.42. $C_{16}H_{24}N_2O_8$+0.3H_2O requires C, 50.87; H, 6.56; N, 7.42. δ_H (300 MHz, $CDCl_3$) 7.55 (1H, d, $J_{5,6}$ 8.1, H-6), 5.75 (1H, d, $J_{5,6}$ 8.1, H-5), 5.74–5.65 (1H, m, H-1′), 5.50–5.38 (2H, m, CH_2 of MEM), 5.00–4.88 (2H, m, H-2′, H-3′), 4.35–4.25 (1H, m, H-4′), 3.98–3.88, 3.87–3.75 (4H, 2m, 2H-5′, CH_2 of MEM), 3.58–3.51 (2H, m, CH_2 of MEM), 3.35 (3H, s, CH_3 of MEM), 1.60, 1.38 (6H, 2s, $2CH_3$); δ_C (75.4 MHz, $CDCl_3$) 162.7 (C-4), 151.1 (C-2), 141.1 (C-6), 114.2 ($C(CH_3)_2$), 101.9 (C-5), 95.6 (C-1′), 86.9 (C-2′), 84.3 (C-3′), 80.4 (C-4′), 71.7, 71.0, 69.9 ($3CH_2$ of MEM), 62.5 (C-5′), 58.9 (CH_3 of MEM), 27.2, 25.2 ($2CH_3$); ν_{max} (film)/

cm^{-1}: 1718, 1670; *m*/*z* (%): 59 (100), 69 (61), 89 (54), 113 (62), 173 (56), 372 (1, M^+).

4.14. N^3-Benzoyl-5′-*O*-[diethyl(ethoxycarbonyl) phosphonomethyl]-2′,3′-*O*-isopropylidene uridine 29

A solution of N^3-benzoyl-2′,3′-*O*-isopropylidene uridine **25**[35] (0.31 g, 8 mmol), triethyl diazophosphonoacetate **6** (0.40 g, 16 mmol) and rhodium(II) acetate (~1 mol %) in benzene (10 mL) was heated at reflux temperature overnight under nitrogen atmosphere. The solution was concentrated in vacuo and purification by flash chromatography (EtOAc) afforded the insertion product **29** as a colourless oil (0.29 g, 60%), which was an essentially equimolar mixture of diastereoisomers. Found: C, 52.13; H, 5.92; N, 4.33. $C_{27}H_{35}N_2O_{12}P+0.5H_2O$ requires C, 52.34; H, 5.86; N, 4.52. δ_H (300 MHz, $CDCl_3$) 8.10, 8.00 (1H, 2d, $J_{5,6}$ 8.2, 8.2, H-6), 8.05–7.90, 7.75–7.40 (5H, 2m, H–Ar), 6.07, 6.01 (1H, 2d, $J_{5,6}$ 3.6, 3.3, H-1′), 5.94, 5.88 (1H, 2d, $J_{5,6}$ 8.2, 8.2, H-5), 5.10–5.00, 4.96–4.88 (1H, 2m, H-2′), 4.86–4.75 (1H, m, H-3′), 4.50–4.05 (8H, m, $2CH_2OP$, CH_2ester, CHP, H-4′), 4.02–3.72 (2H, m, 2H-5′), 1.55 (3H, s, CH_3), 1.44–1.16 (12H, m, $4CH_3$); δ_C (75.4 MHz, $CDCl_3$) 167.7 (COPh), 165.7, 165.4 (COester), 162.3, 162.2 (C-4), 149.4 (C-2), 141.5, 141.3 (C-6), 135.1, 131.5, 130.5, 129.1 (C–Ar), 114.3, 114.0 [$C(CH_3)_2$], 103.0, 102.3 (C-5), 92.7, 91.4 (C-1′), 84.9, 84.6, 84.3, 84.2 (C-2′, C-3′), 81.1, 80.6 (C-4′), 76.5, 76.4 (2d, J_{PC} 157.5, 157.0, CHP), 72.3, 72.2 (2d, J_{PC} 9.4, 12.1, C-5′), 63.8–63.5 (m, $2CH_2OP$), 62.2 (CH_2ester), 27.3, 27.2, 25.4, 25.3 ($2CH_3$), 16.5, 16.4 ($2CH_3$phosphonate), 14.1 (CH_3ester); δ_P (121.5 MHz, $CDCl_3$) +15.14 (42%), +15.05 (58%); ν_{max} (film)/cm^{-1}: 1749 (C=Oester), 1709, 1673, 1269 (P=O); *m*/*z* (%): 77 (66), 105 (100, Ph^+), 137 (80), 241 (35), 395 (66), 610 (1, M^+).

4.15. N^3-Methoxyethoxymethyl-5′-*O*-[diethyl(ethoxycarbonyl) phosphonomethyl]-2′,3′-*O*-isopropylidene uridine 30

A solution of N^3-methoxyethoxymethyl-2′,3′-*O*-isopropylidene uridine **26** (0.29 g, 1.09 mmol), triethyl diazophosphonoacetate **6** (0.54 g, 2.18 mmol) and rhodium(II) acetate (~1 mol %) in benzene (10 mL) was heated at 80 °C overnight under nitrogen atmosphere. The solution was concentrated in vacuo and flash chromatography (EtOAc) afforded the insertion product **30** as a yellow oil (0.15 g, 32%), which was an essentially equimolar mixture of diastereoisomers. Found: C, 48.62; H, 6.87; N, 4.96. $C_{24}H_{39}N_2O_{13}P$ requires C, 48.48; H, 6.61; N, 4.71. δ_H (300 MHz, $CDCl_3$) 7.88, 7.78 (1H, 2d, $J_{5,6}$ 8.1, 8.1, H-6), 6.05–6.00, 5.99–5.92 (1H, 2m, H-1′), 5.78, 5.73 (1H, 2d, $J_{5,6}$ 8.1, 8.1, H-5), 5.48–5.32 (2H, m, CH_2 of MEM), 5.00–4.91, 4.86–4.77 (1H, 2m, H-2′), 4.73–4.62 (1H, m, H-3′), 4.40–4.02 (8H, m, $2CH_2OP$, CH_2ester, CHP, H-4′), 3.99–3.80, 3.79–3.60 (4H, 2m, 2H-5′, CH_2 of MEM), 3.50–3.45 (2H, m, CH_2 of MEM), 3.25 (3H, s, CH_3 of MEM), 1.48 (3H, s, CH_3), 1.35–1.10 (12H, m, $4CH_3$); δ_C (75.4 MHz, $CDCl_3$) 165.7, 165.4 (COester), 161.8, 161.7 (C-4), 150.2 (C-2), 139.2, 139.2 (C-6), 113.4, 113.1 [$C(CH_3)_2$], 101.6, 101.0 (C-5), 91.9, 90.7 (C-1′), 83.9, 83.5, 83.4, 83.1 (C-2′, C-3′), 79.9, 79.4 (C-4′), 75.5 (d, J_{PC} 157.2, CHP), 71.3, 71.2 (2d, J_{PC} 9.2, 12.3, C-5′), 70.7, 70.0, 68.7 ($3CH_2$ of MEM), 63.2–61.7 (m, $2CH_2OP$), 61.2 (CH_2ester), 57.9 (CH_3 of MEM), 26.3, 24.3 ($2CH_3$), 15.5, 15.3 ($2CH_3$phosphonate), 13.1 (CH_3ester); δ_P (121.5 MHz, $CDCl_3$) +15.20 (45%), +15.05 (55%); ν_{max} (film)/cm^{-1}: 1741 (C=Oester), 1671, 1265 (P=O), 1217; *m*/*z* (%): 137 (100), 224 (29), 395 (26), 594 (1, M^+).

4.16. N^3-Benzyl-5′-*O*-[diethyl(ethoxycarbonyl) phosphonomethyl]-2′,3′-*O*-isopropylidene uridine 31

A solution of N^3-benzyl-2′,3′-*O*-isopropylidene uridine **27** (0.47 g, 1.2 mmol), triethyl diazophosphonoacetate **6** (0.62 g, 2.4 mmol) and rhodium(II) trifluoroacetamide (~1 mol %) in benzene (10 mL) was heated at 80 °C for 36 h under nitrogen atmosphere. The solution was concentrated in vacuo and purified by flash chromatography (EtOAc/hexane 2:8) to afford **31** (0.32 g, 42%). Found: C, 50.58; H, 6.47; N, 4.50. $C_{27}H_{35}N_2O_{12}P+2.5H_2O$ requires C, 50.54; H, 6.60; N, 4.37. δ_H 7.88–7.81 (m, 1H, H-6), 7.48–7.21 (m, 5H, Ph), 6.08–6.00 (dd, 1H, H-1′), 5.87–5.82 (m, 1H, H-5), 5.18–5.00 (m, 2H, CH_2Ph), 4.91–4.81 (m, 1H, H-2′), 4.78–4.69 (m, 1H, H-3′), 4.35–4.10 (m, 8H, $2CH_2OP$, CH_2ester, CHPO, H-4′), 4.03–3.74 (m, 2H, 2H-5′), 1.59 (s, 3H, CH_3), 1.37–1.30 (m, 12H, $4CH_3$); δ_C 166.4, 166.2 (COester, two isomers), 162.3, 162.2 (C-4), 150.6, 150.4 (C-2), 139.2, 139.0 (C-6), 136.7, 129.1, 129.1, 128.4, 128.3, 127.6 (C–Ar), 113.8, 113.5 ($C(CH_3)_2$, two isomers), 102.0, 101.4 (C-5), 93.3, 91.7 (C-1′), 84.6–84.4 (C-2′ and C-3′), 80.8, 80.1 (C-4′), 77.0, 72.1 (d, J_{PC} 157.2, P–CH), 71.9–69.7 (m, C-5′), 63.8–63.6 (m, $2CH_2OP$), 62.1 (CH_2ester), 43.7 (CH_2Ph), 27.8, 24.9 ($2CH_3$), 15.9 ($2CH_3$phosphonate), 13.8 (CH_3ester); δ_P +15.24 (45%), +15.04 (55%); ν_{max} (film)/cm^{-1}: 3054–2986, 1746 (COester), 1670, 1265 (PO); *m*/*z* (%): 43 (86), 99 (100), 167 (67), 596 (3) [M^+].

4.17. N^3-Methoxyethoxymethyl thymidine 34

A mixture of methoxyethoxymethyl chloride (0.05 mL, 0.43 mmol), KOH (24 mg, 0.43 mmol), benzyltriethylammonium chloride (10 mg, 0.05 mmol) and 3′,5′-*O*-dibenzoyl thymidine[37] (0.16 g, 0.36 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 8 h then washed with water (20 mL). The organic layer was dried, concentrated, redissolved in MeOH (10 mL) and treated with concd ammonia (10 mL). The solution was stirred at room temperature for 8 h, concentrated in vacuo and purified by flash chromatography (CH_2Cl_2/EtOH 20:1) to afford **34** as a colourless oil (66 mg, 56%). Found: C, 50.12; H, 6.66; N, 8.17. $C_{14}H_{22}N_2O_7+0.25H_2O$ requires C, 50.22; H, 6.77; N, 8.37. δ_H (300 MHz, $CDCl_3$) 7.50 (1H, s, H-6), 6.18 (1H, t, $J_{1',2'}$ 6.7, H-1′), 5.41–5.32 (2H, m, CH_2 of MEM), 4.51–4.40 (1H, m, H-3′), 3.97–3.90 (1H, m, H-4′), 3.82–3.75 (2H, m, 2H-5′), 3.74–3.67 (2H, m, CH_2 of MEM), 3.51–3.40 (2H, m, CH_2 of MEM), 3.28 (3H, s, CH_3 of MEM), 2.40–2.15 (2H, m, 2H-2′), 1.83 (3H, 1s, CH_3); δ_C (75.4 MHz, $CDCl_3$) 162.6 (C-4), 150.1 (C-2), 134.5 (C-6), 109.3 (C-5), 86.1 (C-4′), 85.4 (C-1′), 70.6 (CH_2 of MEM), 70.2 (C-3′), 70.0, 68.5 ($2CH_2$ of MEM), 61.0 (C-5′), 57.8 (CH_3 of MEM), 39.1 (C-2′), 12.2 (CH_3) ; ν_{max} (film)/cm^{-1}: 1706, 1653, 1265, 1092; *m*/*z* (%): 73 (69), 99 (56), 117 (100), 139 (46), 214 (21), 330 (1).

4.18. N^3-Methoxyethoxymethyl-5′-*O*-[diethyl(ethoxycarbonyl) phosphonomethyl]thymidine 36a and N^3-methoxyethoxymethyl-3′-*O*-[diethyl(ethoxycarbonyl) phosphonomethyl]thymidine 36b

A solution of N^3-methoxyethoxymethyl thymidine **34** (0.263 g, 0.8 mmol), triethyl diazophosphonoacetate **6** (0.44 g, 1.6 mmol) and rhodium(II) trifluoroacetamide (~1 mol %) in benzene (10 mL) was heated at reflux temperature overnight under nitrogen atmosphere. The solution was concentrated in vacuo and purified by flash chromatography (EtOAc) to afford two compounds: the more polar 5′-OH insertion product **36a** (98 mg, 22%), and the less polar 3′-OH insertion product **36b** (72 mg, 16%) each as a colourless oil, which was an essentially equimolar mixture of diastereoisomers. *Compound* ***36a***: Found: C, 47.70; H, 6.80; N, 4.50. $C_{22}H_{37}NO_{12}P$ requires C, 47.83; H, 6.75; N, 5.07. δ_H (300 MHz, $CDCl_3$) 7.70, 7.50 (1H, 2s, H-6), 6.35 (1H, t, $J_{1',2'}$ 7.0, H-1′), 5.50–5.35 (2H, m, CH_2 of MEM), 4.65–4.50 (1H, m, H-3′), 4.40–3.80 (10H, m, $2CH_2PO$, CH_2ester, CHP, H-4′, 2H-5′), 3.78–3.69 (2H, m, CH_2 of MEM), 3.52–3.42 (2H, m, CH_2 of MEM), 3.30 (3H, s, CH_3 of MEM), 2.38–2.05 (2H, m, 2H-2′), 2.00 (3H, s, CH_3), 1.40–1.10 (9H, m, $3CH_3$); δ_C (75.4 MHz, $CDCl_3$) 166.7, 166.5 (COester), 162.3 (C-4), 151.1 (C-2), 135.0, 134.8 (C-6), 110.5, 110.3 (C-5), 84.5, 84.1, 84.0, 83.9 (C-4′, C-1′), 75.3, 75.1 (2d, J_{PC} 158.8, 158.6, CHP), 71.2, 71.1 (2d, J_{PC} 9.8, 10.9, C-5′), 70.7 (CH_2O of

MEM), 70.5, 70.4 (C-3′), 70.2, 70.1, 68.6, 68.7 ($2CH_2$ of MEM), 62.9–62.5 (m, $2CH_2PO$), 61.1 (CH_2ester), 57.9 (CH_3 of MEM), 39.7, 39.6 (C-2′), 15.5, 15.4 ($2CH_3$phosphonate), 13.1 (CH_3ester), 11.9, 11.8 (CH_3); δ_P (121.5 MHz, $CDCl_3$) +15.68 (54%), +15.29 (46%); ν_{max} (film)/cm^{-1}: 1747 (C=Oester), 1706, 1215 (P=O); *m*/*z* (%): 81 (100), 99 (58), 139 (70), 224 (73), 552 (1). *Compound* ***36b***: Found: C, 47.71; H, 6.72; N, 5.17. $C_{22}H_{37}N_2O_{12}P$ requires C, 47.83; H, 6.75; N, 5.07. δ_H (300 MHz, $CDCl_3$) 7.49, 7.40 (1H, 2s, H-6), 6.13, 6.10 (1H, 2t, $J_{1',2'}$ 6.3, 6.3, H-1′), 5.53–5.41 (2H, s, CH_2 of MEM), 4.53–4.07 (9H, m, $2CH_2PO$, CH_2ester, CHP, H-4′, H-3′), 4.00–3.82 (2H, m, 2H-5′), 3.81–3.74 (2H, m, CH_2 of MEM), 3.61–3.49 (2H, m, CH_2 of MEM), 3.38 (3H, s, CH_3 of MEM), 2.56–2.30 (2H, m, 2H-2′), 1.95 (3H, s, CH_3), 1.47–1.22 (9H, m, $3CH_3$); δ_C (75.4 MHz, $CDCl_3$) 167.2, 166.7 (COester), 163.5, 163.4 (C-4), 150.9 (C-2), 135.7, 135.4 (C-6), 110.4, 110.3 (C-5), 87.6, 87.0 (C-4′), 84.9, 84.5 (C-1′), 81.0–80.8 (m, C-3′), 75.2, 74.6 (2d, J_{PC} 158.0, 158.0, CHP), 71.7, 71.2, 71.1, 69.8, 69.7 ($3CH_2$ of MEM), 64.3–63.7 (m, $2CH_2PO$), 62.3, 62.2 (CH_2ester), 61.8 (C-5′), 59.0 (CH_3 of MEM), 37.5, 36.8 (C-2′), 16.4, 16.3 ($2CH_3$phosphonate), 14.2, 14.1 (CH_3ester), 13.2 (CH_3); δ_P (121.5 MHz, $CDCl_3$) +15.37 (44%), +14.68 (56%); ν_{max} (film)/cm^{-1}: 1747 (C=Oester), 1709, 1215 (P=O); *m*/*z* (%): 81 (100), 99 (71), 139 (82), 241 (86), 552 (1).

4.19. N^3-Methoxyethoxymethyl-5′-*O*-[diethyl(ethoxycarbonyl) phosphonomethyl]thymidine 36a, N^3-methoxyethoxymethyl-3′-*O*-[diethyl(ethoxycarbonyl)-phosphonomethyl]thymidine 36b and N^3-methoxyethoxymethyl-3′,5′-bis-*O*-[diethyl(ethoxycarbonyl)phosphonomethyl]thymidine 36c

A solution of N^3-methoxyethoxymethyl thymidine **34** (0.19 g, 0.58 mmol), triethyl diazophosphonoacetate **6** (0.29 g, 1.15 mmol) and rhodium(II) acetate (~1 mol %) in benzene (10 mL) was heated at reflux temperature overnight under nitrogen atmosphere. The solution was concentrated in vacuo and flash chromatography (EtOAc) afforded three compounds: the most polar 5′-OH insertion product **36a** (68 mg, 21%), the 3′-OH insertion product **36b** (52 mg, 16%) and the least polar 3′,5′-bis-OH insertion product **36c** (120 mg, 45%) each as a colourless oil and an essentially equimolar mixture of diastereoisomers. The spectral data for **36a** and **36b** were identical to those described above. *Compound* ***36c***: Found: C, 46.51; H, 7.00; N, 3.69. $C_{30}H_{52}N_2O_{17}P_2$ requires C, 46.51; H, 6.77; N, 3.62. δ_H (300 MHz, $CDCl_3$) 7.76, 7.75, 7.57, 7.56 (1H, 4s, H-6), 6.45–6.30 (1H, m, H-1′), 5.50–5.35 (2H, s, CH_2 of MEM), 4.52–4.00 (16H, m, $4CH_2PO$, $2CH_2$ester, 2CHP, H-4′, H-3′), 3.95–3.82 (1H, m, 1H-5′), 3.81–3.62 (3H, m, 1H-5′, CH_2 of MEM), 3.58–3.40 (2H, m, CH_2 of MEM), 3.20 (3H, s, CH_3 of MEM), 2.50–2.00 (2H, m, 2H-2′), 1.92, 1.88 (3H, 2s, CH_3), 1.40–1.20 (18H, m, $6CH_3$); δ_C (75.4 MHz, $CDCl_3$) 166.1, 166.0, 165.9, 165.8, 165.6, 165.5 (COester), 162.7, 162.6 (C-4), 150.2, 150.1 (C-2), 134.1, 133.7 (C-6), 109.9, 109.6 (C-5), 84.6, 84.4, 84.0, 83.8 (C-4′), 82.6, 82.5, 82.1, 82.0 (C-1′), 82.2, 81.5, 81.4, 80.8 (4d, J_{PC} 9.8, 10.9, 12.6, 12.6, C-3′), 76.8–72.9 (16 line m, 2CHP), 71.6, 70.9 (2t, J_{PC} 12.6, 12.6, C-5′), 70.7, 70.2, 70.1, 68.6, 68.7 ($3CH_2$ of MEM), 63.2–62.4 (m, $2CH_2PO$), 61.2, 61.1, 60.0 ($2CH_2$ester), 57.9 (CH_3 of MEM), 36.8, 36.5, 36.0, 35.8 (C-2′), 15.4, 15.3 ($2CH_3$phosphonate), 13.1 (CH_3ester), 11.8, 11.7 (CH_3); δ_P (121.5 MHz, $CDCl_3$) +15.47 (13%), +15.38 (16%), +15.26 (11%), +15.12 (10%), +14.96 (11%), +14.89 (10%), +14.63 (14%), +14.61 (15%); ν_{max} (film)/cm^{-1}: 1749 (C=Oester), 1709, 1669, 1266 (P=O); *m*/*z* (%): 45 (70), 81 (100), 139 (56), 224 (50).

4.20. 5′-*O*-[Diethyl(ethoxycarbonyl)phosphonomethyl] thymidine 37a, 3′-*O*-[diethyl(ethoxycarbonyl) phosphonomethyl]thymidine 37b and 3′,5′-*O*-bis [diethyl(ethoxycarbonyl)phosphonomethyl]thymidine 37c

A solution of N^3-benzoylthymidine **33**[35] (0.338 g, 0.98 mmol), triethyl diazophosphonoacetate **6** (0.49 g, 1.95 mmol) and rhodium(II) acetate (~1 mol %) in benzene (10 mL) was heated at 80 °C overnight under nitrogen atmosphere. The solution was concentrated in vacuo and subjected to flash chromatography (EtOAc/MeOH 95:5) to afford a mixture of the intermediate products **35a**–**c**, which was then heated at 90 °C in benzyl alcohol (4 mL) for 12 h. The solvent was evaporated in vacuo and the crude products were separated by preparative TLC (MeOH/EtOAc 1:9) to afford compounds **37a** (154 mg, 34%, most polar), **37b** (31 mg, 7%) and **37c** (140 mg, 21%, least polar) each as a colourless oil, which was an essentially equimolar mixture of diastereoisomers. *Compound* ***47a***: Found: C, 46.05; H, 6.22; N, 5.22. $C_{18}H_{29}N_2O_{10}P+0.2H_2O$ requires C, 46.19; H, 6.22; N, 5.99. δ_H (300 MHz, $CDCl_3$) 9.65–9.55 (1H, m, NH), 7.75, 7.55 (1H, s, H-6), 6.42–6.25 (1H, m, H-1′), 4.62–4.48 (1H, m, H-3′), 4.46–3.95 (9H, m, H-4′, CHP, $2CH_2OP$, CH_2ester), 3.93–3.65 (2H, m, 2H-5′), 2.45–2.08 (2H, m, 2H-2′), 1.86, 1.85 (3H, 2s, CH_3), 1.40–1.07 (9H, m, $3CH_3$); δ_C (75.4 MHz, $CDCl_3$) 166.1, 165.6 (COester,), 163.3, 163.2 (C-4), 149.8 (C-2), 135.6, 135.4 (C-6), 110.5, 110.3 (C-5), 84.4, 84.2, 83.9, 83.4 (C-4′, C-1′), 75.8, 75.5 (2d, J_{PC} 158.6, 157.6, CHP), 71.3, 71.1 (2d, J_{PC} 9.2, 11.5, C-5′), 70.7 (C-3′), 62.9–62.5 (m, $2CH_2OP$), 61.2, 61.1 (CH_2ester), 39.3, 39.0 (C-2′), 15.4, 15.3 ($2CH_3$phosphonate), 13.1 (CH_3ester), 11.2, 11.1 (CH_3); δ_P (121.5 MHz, $CDCl_3$) +15.67 (58%), +15.30 (42%); ν_{max} (film)/cm^{-1}: 1749 (C=Oester), 1688, 1264 (PO); *m*/*z* (%): 49 (84), 81 (100), 111 (29), 321 (44), 464 (3, M^+). *Compound* ***37b***: Found: C, 46.52; H, 5.92; N, 6.58. $C_{18}H_{29}N_2O_{10}P$ requires C, 46.55; H, 6.29; N, 6.03. δ_H (300 MHz, $CDCl_3$) 9.40, 9.35 (1H, 2s, NH), 7.43, 7.37 (1H, s, H-6), 6.15–6.00 (1H, m, H-1′), 4.50–4.00 (9H, m, H-3′, H-4′, CHP, J_{PH} 18.4, $2CH_2OP$, CH_2ester), 3.90–3.72 (2H, m, 2H-5′), 2.50–2.18 (2H, m, 2H-2′), 1.80 (3H, s, CH_3), 1.35–1.04 (9H, m, $3CH_3$); δ_C (75.4 MHz, $CDCl_3$) 166.2, 165.9 (COester), 163.1, 163.0 (C-4), 149.5 (C-2), 136.1, 135.9 (C-6), 110.0, 109.8 (C-5), 85.9, 85.5 (C-4′), 84.1, 83.7 (C-1′), 80.4–80.2 (m, C-3′), 74.6, 74.3 (2d, J_{PC} 158.6, 159.2, CHP), 63.3–62.8 (m, $2CH_2OP$), 61.2 (CH_2ester), 60.9 (C-5′), 36.4, 35.8 (C-2′), 15.4, 15.3 ($2CH_3$phosphonate), 13.1 (CH_3ester), 11.5, 11.4 (CH_3); δ_P (121.5 MHz, $CDCl_3$) +15.34 (47%), +14.84 (53%); ν_{max} (film)/cm^{-1}:1749 (C=Oester), 1689, 1266 (PO); *m*/*z* (%): 49 (100), 71 (18), 84 (92), 99 (18), 149 (20), 256 (3), 430 (1). *Compound* ***37c***: Found: C, 45.61; H, 6.29; N, 4.37. $C_{26}H_{44}N_2O_{15}P_2$ requires C, 45.48; H, 6.46; N, 4.08. δ_H (300 MHz, $CDCl_3$) 9.35–9.14 (1H, m, NH), 7.80, 7.76, 7.60, 7.56 (1H, s, H-6), 6.43–6.25 (1H, m, H-1′), 4.52–4.00 (16H, m, H-3′, H-4′, 2CHP, $4CH_2OP$, $2CH_2$ester), 3.98–3.68 (2H, m, 2H-5′), 2.48–2.00 (2H, m, 2H-2′), 1.90, 1.88 (3H, s, CH_3), 1.40–1.10 (18H, m, $6CH_3$); δ_C (75.4 MHz, $CDCl_3$) 166.1, 165.9, 165.6, 165.5 (COester), 163.2, 163.1 (C-4), 149.5 (C-2), 135.3, 134.9 (C-6), 110.6, 110.4 (C-5), 84.0, 83.8, 83.3, 83.1 (C-4′), 82.4, 82.3, 82.1, 82.0 (C-1′), 82.3, 81.6, 81.5, 80.9 (4d, J_{PC} 9.9, 9.1, 12.6, 12.6, C-3′), 76.8–72.9 (16 line m, 2CHP), 71.8, 70.9 (2t, J_{PC} 12.6, 12.6, C-5′), 63.1–62.4 (m, $2CH_2PO$), 61.2, 61.1, 60.9 ($2CH_2$ester), 36.8, 36.5, 36.0, 35.8 (C-2′), 15.4, 15.3 ($2CH_3$phosphonate), 13.1 (CH_3ester), 11.8, 11.7 (CH_3); δ_P (121.5 MHz, $CDCl_3$) +15.45 (14%), +15.43 (19%), +15.28 (13%), +15.16 (12%), +15.04 (11%), +14.98 (20%), +14.67 (17%); ν_{max} (film)/cm^{-1}: 1747 (C=Oester), 1688, 1265 (P=O); *m*/*z* (%): 43 (100), 91 (98), 167 (45), 196 (84), 300 (66), 386 (13), 647 (4).

4.21. N^3,3′-*O*-Dibenzoyl-5′-*O*-[dibenzyl(ethoxycarbonyl) phosphonomethyl]thymidine 39

Rhodium acetate (4.9 mg, 11 μmol) was added to a degassed solution of **38** (250 mg, 0.55 mmol) and the diazo compound **7** (415 mg, 1.1 mmol) in PhMe (20 mL) and the mixture was placed in a pre-equilibrated bath at 90 °C for 18 h. The volatiles were removed after which flash chromatography (EtOAc/hexane 1:1) afforded 207 mg (53%) of **39** as a mixture of diastereomers. δ_H ($CDCl_3$) 8.03–7.97 (m, 2H, ArH), 7.96–7.85 (m, 2H, ArH), 7.93 (s with unresolved splitting, 1H, H-6), 7.67–7.53 (m, 2H, ArH), 7.52–7.39 (m, 4H, ArH), 7.37–7.28 (m, 10H, ArH), 6.66–6.48 (m, 1H, H-1′),

5.73–5.68 (m, 0.5H, H-4′ one diastereomer), 5.48–5.44 (m, 1H, H-4′ one diastereomer), 5.19–5.08 (m, 4H, $PhCH_2O$), 4.58 (d, 0.5H, *J* 15.6, PCH one diastereomer), 4.41 (d, 0.5H, *J* 17.9, PCH one diastereomer), 4.28–4.22 (m, 3H, CH_3CH_2O, H-3′), 4.01–3.77 (m, 2H, 2×H-5′), 2.44–2.21 (m, 2H, 2×H-2′), 1.98, 1.93 (2×s, 3H, CH_3 both diastereomers), 1.27 (t, 3H, CH_3CH_2O); δ_C 169.0, 169.1, 166.7, 166.4, 166.1, 163.0, 162.9, 149.8, 149.7, 135.6 (d, *J* 5.8), 135.4 (d, *J* 6.3), 135.3 (d, *J* 5.7), 134.9, 133.6, 131.8, 131.7, 130.5, 129.7, 129.3, 129.2, 129.14, 129.12, 128.9, 128.8, 128.78, 128.76, 128.6, 128.5, 128.17, 128.16, 112.2, 111.9, 85.0, 84.5, 83.8, 83.7, 77.0 (d, *J* 158), 76.6, 76.5 (d, *J* 158), 76,3, 72.7 (d, *J* 12.1), 72.3 (d, *J* 10.9), 69.1 (d, *J* 6.3), 69.0 (d, *J* 6.3), 68.9 (d, *J* 6.3), 68.7 (d, *J* 6.3), 62.5, 37.4, 37.0, 14.2, 14.1, 12.2, 12.0; δ_P 17.52, 16.06.

4.22. N^3,3′-*O*-Dibenzoyl-5′-*O*-[dibenzyl(benzyloxycarbonyl) phosphonomethyl]thymidine 40

Rhodium acetate (6 mg, 12.5 μmol) was added to a degassed mixture of 3-*N*,3′-*O*-dibenzoyl thymidine **38** (0.40 g, 0.89 mmol), tribenzyl phosphonodiazoacetate **8** (0.50 g, 1.15 mmol) and activated molecular sieve beads (a small spoonful, ca. 0.8 g undried weight) in benzene (10 mL). The mixture was placed in a pre-equilibrated bath at 85 °C and stirred at this temperature for 48 h. After filtration the volatiles were removed in vacuo and the residue was purified by flash chromatography (EtOAc/hexane 1:1) to afford 0.35 g (45%) of colourless, slightly oily foam, shown by ^{1}H NMR to be a roughly 1.66:1 mixture of diastereomers. δ_H ($CDCl_3$) 8.05–7.92 (m, 4H, ArH), 7.82 (d, 0.4H, *J* 1.0, H-6 minor diastereomer), 7.66–7.55 (m, 2.6H, H-6 major diastereomer, ArH), 7.52–7.40 (m, 4H, ArH), 7.37–7.20 (m, 15H, ArH), 6.53–4.46 (m, 1H, H-1′), 5.67–5.62 (m, 0.4H, H-4′ minor diastereomer), 5.47–5.43 (m, 0.6H, H-4′ major diastereomer), 5.32–5.15 (m, 2H, carboxyl $PhCH_2O$), 5.10–4.95 (m, 4H, phosphonate $PhCH_2O$), 4.45 (d, 0.4H, *J* 18, PCH minor diastereomer), 4.31 (d, 0.6H, *J* 19, PCH major diastereomer), 4.26–4.22 (m, 1H, H-3′), 4.00–3.78 (m, 2H, H-5′), 2.39–2.16 (m, 2H, H-2′), 1.95 (d, 1.2H, *J* 1.0, CH_3 minor diastereomer), 1.85 (d, 1.8H, *J* 0.9, CH_3 major diastereomer).

4.23. 5′-*O*-[Diethyl(amido)phosphonomethyl]-2′,3′-*O*-isopropylidene adenosine 42

A solution of concd aqueous ammonia (4 mL) was added to a stirring solution of compound **17** (0.1 g, 0.13 mmol) in methanol (4 mL). The mixture was stirred at room temperature for 12 h then concentrated in vacuo. Flash chromatography (EtOAc) afforded **42** as a yellow oil (22 mg, 37%), which was an essentially equimolar mixture of diastereoisomers. Found: C, 45.76; H, 6.10; N, 14.98. $C_{19}H_{29}N_6O_8P$ requires C, 45.60; H, 5.84; N, 16.79. δ_H (270 MHz, $CDCl_3$) 8.25, 8.22, 8.14 and 8.10 (2H, 4 s, H-2, H-8), 7.40–6.60 (4H, m, $2NH_2$), 6.16–6.11, 6.07–6.01 (1H, 2m, H-1′), 5.46–5.37 (1H, m, H-2′), 5.19–5.11, 5.09–5.02 (1H, 2m, H-3′), 4.51–4.38 (1H, m, H-4′), 4.29–3.81 (7H, m, $2CH_2OP$, CHP, 2H-5′), 1.60, 1.37 (6H, 2s, $2CH_3$), 1.35–1.25 (6H, m, 2CH3); δ_C (67.8 MHz, $CDCl_3$) 168.9, 168.8 ($CONH_2$), 156.0, 153.2, 149.4, 149.2 (C-6, C-2, C-4, C-5), 140.0 (C-8), 114.6, 114.5 [$C(CH_3)_2$], 90.6 (C-1′), 85.5, 84.7 (C-2′), 84.0, 83.7 (C-3′), 81.3, 81.0 (C-4′), 78.0, 77.9 (2d, J_{PC} 156.6, 156.4, CHP), 72.8, 72.7 (2d, J_{PC} 8.7, 7.4, C-5′), 63.8–63.7 (m, $2CH_2OP$), 27.2, 25.3 ($2CH_3$), 16.3, 16.2 ($2CH_3$phosphonate); δ_P (121.5 MHz, $CDCl_3$) +17.3 (56%), +16.8 (44%); ν_{max} (film)/cm^{-1}: 3334–2936, 1693 (C=Oamide), 1644, 1265 and 1024 [$PO(OEt)_2$]; *m*/*z* (%): 43 (100), 306 (4), 368 (2).

4.24. N^6-Benzoyl-5′-*O*-[diethyl(carboxyl)phosphonomethyl]-2′,3′-*O*-isopropylidene adenosine 43

A solution of NaOH (0.2 M, 14 mL, 2.8 mmol) was added to a solution of compound **17** (0.1 g, 0.13 mmol) in methanol (10 mL). The mixture was stirred at room temperature for 12 h, then concentrated in vacuo to afford compound **43**, which was characterised only by NMR spectroscopy. Yield 63 mg, 77%. δ_H (270 MHz, $CDCl_3$) 8.58, 8.47, 8.2 (3×s, 3H, H-2, H-8, NH), 8.10–7.43 (m, 5H, ArH), 6.20 (m, 1H, H-1′), 5.35 (m, 1H, H-2′), 5.12 (m, 1H, H-3′), 4.55 (m, 1H, H-4′), 4.30–4.00 (m, 5H, $2\times CH_2PO$, CHPO), 3.7 (m, 2H, 2×H-5′), 1.63, 1.40 (2×s, 6H, $2\times CH_3$); δ_C (67.8 MHz, $CDCl_3$) 173.1 (CO_2H), 169.5 (COPh), 155.6–143.5 (C-6, C-2, C-4, C-5), 143.3 (C-8), 135.7–130.1 (CAr), 116.9 ($C(CH_3)_2$), 93.6–93.1, 88.4–88.1, 87.5 (C-1′, C-2′, C 4′), 87.5–84.8 (d, J_{PC} 158.3, CHP), 75.1–75.0 (m, C-5′), 66.1–66.0 (m, $2\times CH_2OP$), 29.1, 27.3 ($2\times CH_3$), 18.3, 18.2 ($2\times CH_3$).

4.25. 5′-*O*-[Diethyl(ethoxycarbonyl)phosphonomethyl]-2′,3′-*O*-isopropylidene adenosine 44

Compound **18** (0.17 g, 0.23 mmol) and $Pd(OH)_2$/C (20% Pd, 50% water, 0.3 g, ca. 1.8 equiv w/w) were placed in 50% aqueous methanol (10 mL) and stirred under a hydrogen atmosphere (50 psi) for 5 h. The mixture was filtered, concentrated and purified by flash chromatography (EtOAc/EtOH 9:1) to afford **44** as a colourless oil (71 mg, 58%), which was an essentially equimolar mixture of diastereoisomers. Found: C, 47.60; H, 6.06; N, 13.00. $C_{21}H_{32}N_5O_9P$ requires C, 47.64; H, 6.09; N, 13.23. δ_H (300 MHz, $CDCl_3$) 8.37, 8.35, 8.34, 8.30 (2H, 4s, H-2, H-8), 6.80–6.55 (2H, m, NH_2), 6.28–6.18 (1H, m, H-1′), 5.28–5.16, 5.15–5.02 (2H, 2m, H-2′, H-3′), 4.60–4.52, 4.51–4.47 (1H, 2m, H-4′), 4.45–4.09 (7H, m, CHP, $2CH_2OP$, CH_2ester), 4.07–3.72 (2H, m, 2H-5′), 1.65, 1.40 (6H, 2s, $2CH_3$), 1.38–1.15 (9H, m, $3CH_3$); δ_C (75.4 MHz, $CDCl_3$) 165.9, 165.7 (COester), 154.4 (C-6), 151.9 (C-2), 148.6, 148.4 (C-4, C-5), 136.8 (C-8), 113.9, 113.2 ($C(CH_3)_2$), 90.0, 88.9 (C-1′), 84.1, 83.9, 83.7, 83.6 (C-2′, C-3′), 80.7, 80.2 (C-4′), 75.9, 75.8 (d, J_{PC} 188.0, CHP), 71.3, 71.2 (2d, J_{PC} 10.9, 11.5, C-5′), 62.8–61.5 (m, $2CH_2OP$), 61.1, 61.0 (CH_2ester), 26.6, 24.4 ($2CH_3$), 15.4, 15.3 ($2CH_3$phosphonate), 13.1 (CH_3ester); δ_P (121.5 MHz, $CDCl_3$) +15.15 (66%), +15.05 (34%); ν_{max} (film)/cm^{-1}: 1713 (C=Oester), 1223 (P=O); *m*/*z* (%): 44 (100), 112 (45), 285 (40).

4.26. N^3-[(Carboxyl)phosphonomethyl]uridine 47a

Trimethylsilyl bromide (0.62 mL, 4.7 mmol) was added via syringe to a solution of compound **22** (0.250 g, 0.47 mmol) in acetonitrile (10 mL) and the resulting mixture was stirred at room temperature overnight under a nitrogen atmosphere. Water (1 mL) was added and the mixture was stirred for a further 1 h then concentrated in vacuo. The residue was redissolved in water (2 mL) and the resulting mixture was heated at 90 °C overnight. The volatiles were evaporated to afford 55 mg (31%) of **47a**. δ_H (300 MHz, D_2O) 7.70 (1H, d, $J_{5,6}$ 7.32, H-6), 5.7–5.58 (2H, m, H-1′ and H-5), 4.50–3.80 (3H, m, H-2′, H-3′, H-4′), 3.79–3.50 (2H, m, 2H-5′); δ_C (75.4 MHz, D_2O) 173.3 (CO_2H), 166.3 (C-4), 151.82 (C-2), 142.1 (C-6), 102.6 (C-5), 89.5 (C-1′), 84.4 (C-2′), 73.9 (C-3′), 69.7 (C-4′), 61.1 (C-5′); PCHO not seen in ^{1}H and ^{13}C NMR spectra presumably due to D exchange; δ_P (121.5 MHz, D_2O) +14.86.

When the reaction was heated in water at 90 °C for only 1 h then a mixture of compounds **47a** and N^3-[(ethoxycarbonyl)-phosphonomethyl]uridine **47b** (3:1) was obtained as a brown oil. Signals due to compound **47b**: δ_H (300 MHz, MeOH-d_4) 7.45 (1H, d, $J_{5,6}$ 7.9, H-6), 4.61–4.50 (1H, m, H-2′), 4.34–4.12 (3H, m, H-3′, CH_2), 1.38–1.25 (CH_3); δ_C (75.4 MHz, MeOH-d_4) CO_2Et not seen, 166.3 (C-4), 101.7 (C-5), 62.8 (CH_2), 14.4 (CH_3); PCHO not seen in ^{1}H and ^{13}C NMR spectra presumably due to D exchange; δ_P (121.5 MHz, MeOH-d_4) +16.3. HRMS (ESI^+): exact mass calculated for $C_{11}H_{16}N_2O_{11}P$ $[M+H]^+$ 383.0492, found 383.0486; *m*/*z* (%): 383 (M+1, 56%), 377 (5), 245 (25), 242 (100), 180 (6), 139 (16), 74 (17), 46 (9).

4.27. N^3,5′-*O*-[Bis(carboxyl)phosphonomethyl]uridine 48

The deprotected compound **48** (47 mg, ~33% yield) was prepared from **23** (0.2 g, 0.27 mmol) following the procedure described for **47a** with trimethylsilyl bromide (0.36 mL, 2.7 mmol) and was obtained as a brown oil, which was an essentially equimolar mixture of diastereoisomers. δ_H (300 MHz, D_2O) 8.12, 7.91 (1H, 2d, $J_{5,6}$ 8.1, 8.1, H-6), 5.88–5.60 (2H, m, H-1′, H-5′), 4.50–4.35, 4.32–4.18, 4.15–3.95 (5H, 3m, H-2′, H-3′, H-4′, PCHO, PCHN), 3.90–3.40 (2H, m, 2H-5′); δ_C (75.4 MHz, D_2O) 173.14, 171.80 (CO_2H), 166.6, 166.5 (C-4), 151.98 (C-2), 142.85, 142.47 (C-6), 102.80, 102.53 (C-5), 88.91 (C-1′), 83.63, 83.42 (C-2′), 77.5, 77.4 (2d, J_{PC} 147.3, 147.3, PCHO), 74.27, 73.99 (C-3′), 71.37 (C-5′), 70.31, 70.19 (C-4′); δ_P (121.5 MHz, D_2O) +15.36, +12.21. HRMS (ESI^+): exact mass calculated for $C_{13}H_{19}N_2O_{16}P_2$ $[M+H]^+$ 521.0210; found 521.0203; *m*/*z* (%): 521 (M+1, <5%), 459 (3), 405 (22), 383 (45), 286 (4), 242 (10), 171 (6), 127 (11), 115 (62), 74 (88), 64 (100), 59 (40).

4.28. 5′-*O*-[Diethyl(ethoxycarbonyl)phosphonomethyl]-2′,3′-*O*-isopropylidene uridine 49

Compound **29** (0.29 g, 0.47 mmol) was dissolved in benzyl alcohol (1 mL) and heated at 90 °C for 24 h. The solvent was removed in vacuo and the residue was purified by flash chromatography (EtOAc/MeOH 95:5) to afford **49** as a colourless oil (0.18 g, 77%), which was an essentially equimolar mixture of diastereoisomers. Found: C, 47.61; H, 5.99; N, 5.27. $C_{20}H_{31}N_2O_{11}P$ requires C, 47.43; H, 6.17; N, 5.53. δ_H (300 MHz, $CDCl_3$) 7.99, 7.89 (1H, 2d, $J_{5,6}$ 8.1, 8.1, H-6), 6.08, 6.14 (1H, 2d, $J_{1',2'}$ 3.6, 3.6, H-1′), 5.82, 5.76 (1H, 2d, $J_{5,6}$ 8.1, 8.1, H-5), 5.08–5.00, 4.95–4.88 (1H, 2m, H-2′), 4.79–4.69 (1H, m, H-3′), 4.43–4.09 (7H, m, $2CH_2OP$, CH_2ester, PCHO), 4.01–3.78 (2H, m, 2H-5′), 1.50 (3H, s, CH_3), 1.35–1.20 (12H, m, $4CH_3$); δ_C (75.4 MHz, $CDCl_3$) 165.8, 165.1 (COester), 162.4, 162.3 (C-4), 149.2 (C-2), 140.7, 140.5 (C-6), 113.9, 113.8 ($C(CH_3)_2$), 102.1, 101.5 (C-5), 90.9, 89.8 (C-1′), 83.6, 83.4, 83.2, 83.1 (C-2′, C-3′), 79.8, 79.3 (C-4′), 75.5 (d, J_{PC} 158.0, PCHO), 71.3, 71.1 (2d, J_{PC} 9.2, 12.0, C-5′), 63.2–62.3 (m, $2CH_2OP$), 61.1 (CH_2ester), 26.3, 24.4 ($2CH_3$), 15.4, 15.3 ($2CH_3$phosphonate), 13.1 (CH_3ester); δ_P (121.5 MHz, $CDCl_3$) +15.37 (55%), +15.10 (45%); ν_{max} (film)/cm^{-1}: 3020 (CH), 1716 (C=Oester), 1695, 1265 (P=O); *m*/*z* (%): 43 (100), 224 (18).

4.29. 5′-*O*-[(Ethoxycarbonyl)phosphonomethyl]uridine 50a and 5′-*O*-[(carboxyl)phosphonomethyl]uridine 50b

Trimethylsilyl bromide (0.39 mL, 2.96 mmol) was added via syringe to a solution of compound **49** (0.15 g, 0.296 mmol) in acetonitrile (10 mL) and the resulting mixture was stirred overnight at room temperature under a nitrogen atmosphere. Water (1 mL) was introduced and the mixture was stirred for 1 h then concentrated in vacuo. The residue was purified by 'dry flash' charcoal chromatography using activated carbon Darco G-60, 100 Mesh (charcoal: sample ~20:1, 3 g). The column was pre-eluted with ethanol (30 mL) then water (30 mL) and the sample was applied to the column using water (2 mL). The column was eluted with water (30 mL) to remove inorganic impurities, with 10% aqueous ammonia (30 mL) and then with 25% aqueous ammonia (20 mL) to afford a mixture of **50a** and **50b** (4:1) (0.11 g, ~87% yield). *Compound **50a***: δ_H (300 MHz, D_2O) 8.31, 8.08 (1H, 2d, $J_{5,6}$ 8.1, 8.1, H-6), 5.98–5.80 (2H, m, H-5, H-1′), 4.45–4.10 (6H, m, H-2′, H-3′, H-4′, CH_2ester, CHP), 3.90–3.62 (2H, m, 2H-5′), 1.31–1.12 (3H, m, CH_3); δ_C (75.4 MHz, D_2O) 170.7, 170.6 (COester), 165.5, 165.4 (C-4), 150.9 (C-2), 142.8, 141.6 (C-6), 101.8, 101.5 (C-5), 87.8, 87.7 (C-1′), 82.6, 82.5 (C-2′), 78.1, 78.2 (2d, J_{PC} 140.8, 140.2, CHP), 73.1, 72.7 (C-3′), 70.2, 70.1 (2d, J_{PC} 11.5, 11.5, C-5′), 69.4, 69.3 (C-4′), 61.5 (CH_2ester), 12.5 (CH_3ester); δ_P (121.5 MHz, D_2O) +9.08. Signals attributed to the acid **50b** (~20%) were seen at δ_H 8.20, 8.10 and δ_C 72.9, 72.8.

4.30. 5′-*O*-[(Carboxyl)phosphonomethyl]uridine 50b

Compound **49** (0.072 g, 0.15 mmol) was dissolved in anhydrous acetonitrile (5 mL), cooled to 0 °C and treated dropwise with trimethylsilyl bromide (0.07 mL, 0.58 mmol). The resulting mixture was stirred at room temperature overnight after which water (1 mL) was added and the mixture was stirred for a further 1 h then evaporated under reduced pressure. The residue was redissolved in water (10 mL) and the resulting mixture was heated at 90 °C overnight then concentrated in vacuo. Compound **50b** was purified using charcoal chromatography as described above to afford the acid as its ammonium salt (0.044 g, 77%). δ_H (300 MHz, D_2O) 8.15, 8.03 (1H, 2d, $J_{5,6}$ 8.1, 8.1, H-6), 5.91–5.69 (2H, m, H-5, H-1′), 4.41–3.81 (3H, m, H-2′, H-3′, H-4′, CHP), 3.80–3.50 (2H, m, 2H-5′); δ_C (75.4 MHz, D_2O) 166.66 (C-4), 152.16 (C-2), 143.20, 142.86 (C-6), 103.02, 102.82 (C-5), 89.32, 89.00 (C-1′), 83.74, 83.59 (C-2′), 74.11, 74.04 (C-3′), 71.13 (C-5′), 70.50, 70.33 (C-4′); δ_P (121.5 MHz, D_2O) +12.89. HRMS (ESI^+): exact mass calculated for $C_{11}H_{16}N_2O_{11}P$ $[M+H]^+$ 383.0492, found 383.0488; *m*/*z* (%): 383 (M+1, 39%), 377 (5), 153 (5), 143 (38), 102 (41), 74 (42), 42 (100).

4.31. 5′-[Diethyl(amido)phosphonomethoxy]-2′,3′-*O*-isopropylidene uridine 51

A solution of concd aqueous ammonia (4 mL) was added to a solution of compound **29** (0.14 g, 0.27 mmol) in methanol (4 mL). The mixture was stirred at room temperature for 12 h, then concentrated in vacuo. Flash chromatography (EtOAc) afforded **51** (57 mg, 44%) as a yellow solid. Found: C, 44.55; H, 5.65; N, 8.21. $C_{18}H_{28}N_3O_{10}P+0.5H_2O$ requires C, 44.44; H, 6.01; N, 8.64. δ_H (300 MHz, $CDCl_3$) 7.40–7.30 (m, 1H, H-6), 6.98, 6.64 (2s, 2H, NH_2, two isomers), 5.68–5.65 (m, 1H, H-5), 5.60–5.50 (m, 1H, H-1′), 5.08–4.73 (m, 2H, H-2′, H-3′), 4.41–3.85 (m, 8H, $2CH_2OP$, CHPO, 2H-5′, H-4′), 1.50 (3H, s, CH_3), 1.30–1.15 (9H, m, $3CH_3$); δ_C (75.4 MHz, $CDCl_3$) 169.5, 167.8 ($CONH_2$), 162.8 (C-4), 149.9, 149.4 (C-2), 142.5, 141.7 (C-6), 113.4, 113.2 [$C(CH_3)_2$], 102.3, 101.8 (C-5), 95.6, 93.3 (C-1′), 86.1, 84.3, 83.3, 83.2 (C-2′, C-3′), 80.1, 79.4 (C-4′), 76.6, 76.4 (2d, J_{PC} 155.9, 157.0, PCH), 72.0, 71.8 (2d, J_{PC} 12.0, 7.5, C-5′), 62.8–62.7 (m, $2CH_2OP$), 26.2, 24.3 ($2CH_3$), 15.4 ($2CH_3$phosphonate); δ_P (121.5 MHz, $CDCl_3$) +17.45 (47%),+16.66 (53%); ν_{max} ($CHCl_3$)/cm^{-1}: 3054–2986 (NH), 1697 (C=Oamide), 1266 (P=O); *m*/*z* (%): 121 (43), 155 (56), 229 (26), 275 (75), 289 (100), 303 (16), 426 (3).

4.32. 5′-*O*-[(Amido)phosphonomethyl]uridine 52

Trimethylsilyl bromide (0.32 mL, 2.4 mmol) was added via syringe to a solution of compound **51** (0.153 g, 0.32 mmol) in acetonitrile (10 mL). The reaction mixture was stirred at room temperature overnight after which water (1 mL) was added and the mixture was stirred for 1 h then concentrated in vacuo. The residue was purified by charcoal chromatography as described above to give **52** (91 mg, 72% yield) as a yellow solid, which was an essentially equimolar mixture of diastereoisomers. δ_H (300 MHz, D_2O) 7.75–7.30 (1H, m, H-6), 5.85–5.68 (2H, m, H-5, H-1′), 4.35–4.00 (3H, m, H-2′, H-3′, H-4′), 3.92–3.55 (3H, m, CHP, 2d, J_{PH} 16.4, 16.7, 2H-5′); δ_C (300 MHz, D_2O) 175.4, 175.2 (COamide), 166.6, 166.5 (C-4), 152.0 (C-2), 142.8, 142.7 (C-6), 102.9, 102.8 (C-5), 89.7, 89.4 (C-1′), 83.1 (C-2′), 81.9, 81.7 (2d, J_{PC} 136.7, 137.2, CHP), 73.8, 73.7 (C-3′), 71.7, 71.3 (2d, J_{PC} 10.9, 9.9, C-5′), 70.1, 69.9 (C-4′); δ_P (121.5 MHz, D_2O) +10.18 (50%), +9.94 (50%).

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