Synthesis of C-6-substituted uridine phosphonates through aerobic ligand-free Suzuki–Miyaura cross-coupling†‡

Radim Nencka,[a,b] Davy Sinnaeve,[c] Izet Karalic,[a] José C. Martins[c] and Serge Van Calenbergh*[a]

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An efficient protocol for the construction of C-6-(hetero)aryl-substituted uridine phosphonate analogues utilizing an aerobic, ligand-free Suzuki–Miyaura cross-coupling reaction of a 6-iodo-precursor in aqueous media has been established. The method presents a modular approach toward the target compounds as demonstrated by the synthesis of a small library comprising 14 novel nucleoside phosphonates.

Introduction

Nucleoside phosphonates (NPs) have received considerable attention due to their interesting pharmacological properties and the synthesis of novel nucleotides containing a phosphonate moiety as bioisostere of a phosphate group has been extensively attracting the focus of medicinal chemists during last years.[1] Acyclic NPs, such as cidofovir **1**, tenofovir **2** and adefovir **3**, represent efficient agents that are clinically used against various viral diseases.[2] Several cyclic NPs also express promising activity profiles. GS-9148 (**4**), for example, combines favorable activity against multiple NRTI-resistant HIV-1 strains with a low potential for mitochondrial toxicity and minimal nephrotoxicity.[3] Besides antiviral activity, NPs may exert a broad spectrum of other activities including antiparasitic, cytostatic and immunomodulatory activity.[4] Recently, we have identified uridine 5′-methylenephosphonate **5** as an agonist of the $P2Y_2$ receptor, which contrasted with lack of such activity displayed by the analogous uridine monophosphate.[5] Since **5** probably activates the $P2Y_2$ receptor through binding to a yet unknown allosteric site, further derivatization may strengthen the binding affinity of **5** (Fig. 1).

Although extensive synthetic efforts have been devoted towards modifications of all nucleobases and several methodologies based on palladium catalyzed cross-couplings[6] or C–H activations[7] have been invented, the 6-position of uridine has been largely overlooked and only a few 6-aryl derivatives of uridine have been reported so far. The Stille cross coupling[8] and photochemical synthesis[9] have been recently presented as possible synthetic routes towards these derivatives. However, both methods suffer from known drawbacks such as the toxicity of the organotin reagents used in the Stille coupling and the limited control of regioselectivity in the case of photochemical derivatization.

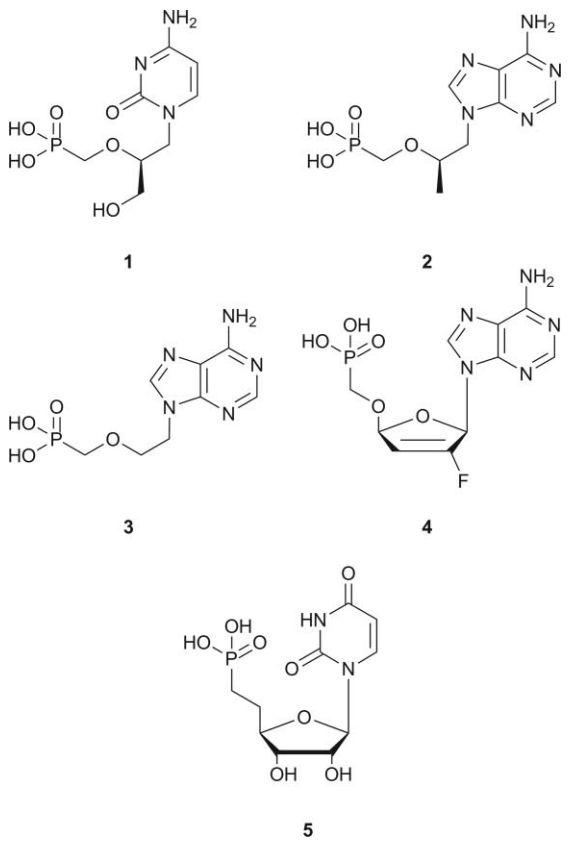


Fig. 1 Biologically active nucleoside phosphonates.

We decided to explore the Suzuki–Miyaura cross-coupling for the introduction of aryl groups at position 6 of **5**. Although the Suzuki reaction is one of the most efficient methods for carbon–carbon bond formation[10] and has been adopted in the chemistry of nucleic acid components,[11] most examples used for the synthesis of nucleoside and nucleotide analogues have been performed in the presence of (often complicated and/or sensitive) phosphine

[a]*Laboratory for Medicinal Chemistry, Faculty of Pharmaceutical Sciences (FFW), Ghent University, Harelbekestraat 72, B-9000, Ghent, Belgium. E-mail: serge.vancalenbergh@ugent.be; Fax: +32 9 2648146; Tel: +32 9 2648124*

[b]*Centre for New Antivirals and Antineoplastics, Institute of Organic Chemistry and Biochemistry Academy of Sciences of the Czech Republic, v.v.i.(IOCB), Gilead & IOCB Research Center, 166 10, Prague 6, Czech Republic. E-mail: nencka@uochb.cas.cz; Fax: +420 220183560; Tel: +420 220183323*

[c]*NMR and Structure Analysis Unit, Department of Organic Chemistry, Ghent University, Krijgslaan 281 S4, B-9000, Ghent, Belgium. E-mail: jose.martins@ugent.be; Fax: +32 9 2644972*

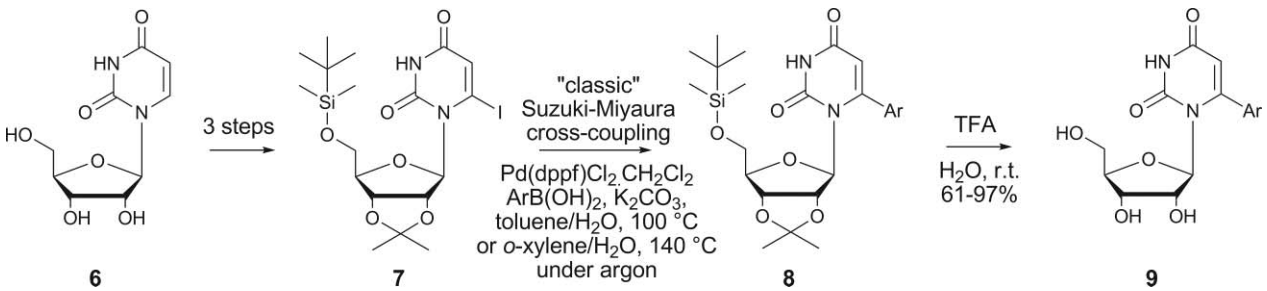
† Electronic supplementary information (ESI) available: Tables depicting cross-coupling optimization and spectral data of compounds **8a–e**, **9a–d**, **11**, **12**, **16**, copies of ^{1}H NMR spectra (700 MHz) of **5**, **22a** and **9b**, measured scalar couplings [Hz] for compounds **5**, **22a** and **9b**, and oberved nOe contacts for compounds **5**, **22a** and **9b**. See DOI: 10.1039/c0ob00061b

‡ Abbreviations: NPs nucleoside phosphonates; IBX 2-iodoxybenzoic acid; dppf 1,1′-bis(diphenylphosphino)ferrocene; TPPTS tris(3-sulfonatophenyl)phosphine trisodium salt; TFA triflouroacetic acid.

Table 1 Suzuki–Miyaura cross coupling of protected 6-iodouridine

Entry	$ArB(OH)_2$	Product	Ar	Time/min	T/°C	Solvent	Yield (%)[a]
1.	**10a**	**8a**		120	100	Toluene : H_2O	83
2.	**10b**	**8b**		120	100	Toluene : H_2O	81
3.	**10c**	**8c**		45	100	Toluene : H_2O	82
4.	**10d**	**8d**		360	100	Toluene : H_2O	17
5.	**10d**	**8d**		60	140	*o*-Xylene : H_2O	66
6.	**10e**	**8e**		45	100	Toluene : H_2O	0
7.	**10e**	**8e**		60	140	*o*-Xylene : H_2O	10

[a] Isolated yield.



Scheme 1 Synthesis of C-6 substituted uridines *via* "classical" Suzuki–Miyaura cross coupling procedure.

ligands. Recently, a great deal of effort was invested into the research of the Suzuki–Miyaura cross-coupling under ligand-free conditions, usually in aqueous media, thereby better complying with economical and green chemistry concepts.[12]

Recent papers also describe protocols to perform this coupling reaction under aerobic conditions.[12d] However, most reports on the ligandless Suzuki–Miyaura coupling, only involve simple aromatic or heteroaromatic systems.

The main goal of the current study was to investigate possible routes towards analogues of **5**, with aryl substituents at position 6 of the uracil moiety.

Results and discussion

In order to synthesize the desired C-6 substituted derivatives, we explored two distinct pathways. Both routes started from derivative **7**, which was easily accessible in 3 steps from uridine by a known procedure[13] that was modified to meet the requirements of a large-scale synthesis, *i.e.* most of the chromatographic steps were replaced by crystallizations. Next, we turned our attention to the Suzuki–Miyaura cross coupling of protected 6-iodouridine **7**. Unfortunately, the substrate appeared to be quite unstable and degradation was observed under most experimental conditions tested (ESI Table S1†). The only satisfactory results were obtained employing $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ as the catalyst and mixture of toluene and water as solvent. Under these conditions, we were able to obtain a number of the desired coupling products (Scheme 1, Table 1).

However, heterocyclic boronic acids such as **10d** and **10l** (Table 2) afforded only poor yields or failed to react. This inconvenience could be partially overcome by using *o*-xylene instead of toluene, which allowed to rise the temperature up to 140 °C. Furthermore, we found that the resulting C-6 substituted nucleosides can be readily deprotected by simple treatment with trifluoroacetic acid (TFA) in water to afford the appropriate uridine derivatives. However, the synthesis of such uridine derivatives was not our main interest and only a limited number of such derivatives was prepared for illustrative purposes (Table 3).

Intermediate **8a** could be converted to phosphonate **13a** by subsequent desilylation, IBX-mediated oxidation,[14] and Horner–Wadsworth–Emmons reaction of the resulting aldehyde **12** with the sodium salt of bisphosphonate **14** (Scheme 2, Fig. 2).[15]

However, we felt that incorporation of the phosphonate moiety after C-6 derivatization is rather impractical due to the number of subsequent reaction steps. Therefore, we decided to investigate the use of intermediate **18** towards a more divergent synthesis of the target NP. Selective deprotection of the 5′-position of **7** with ammonium fluoride afforded **16**. However, the introduction of

Table 2 Derivatives and boronic acids used in the study

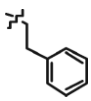
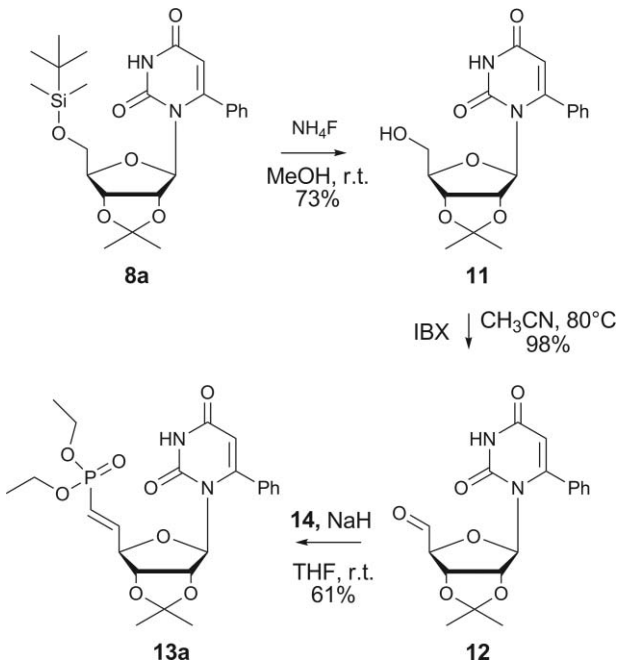
Entry	Derivative	$ArB(OH)_2$	Ar
1.	**a**	**10a**	
2.	**b**	**10b**	
3.	**c**	**10c**	
4.	**d**	**10d**	
5.	**e**	**10e**	
6.	**f**	**10f**	
7.	**g**	**10g**	
8.	**h**	**10h**	
9.	**i**	**10i**	
10.	**j**	**10j**	
11.	**k**	**10k**	
12.	**l**	**10l**	
13.	**m**	**10m**	
14.	**n**	—	

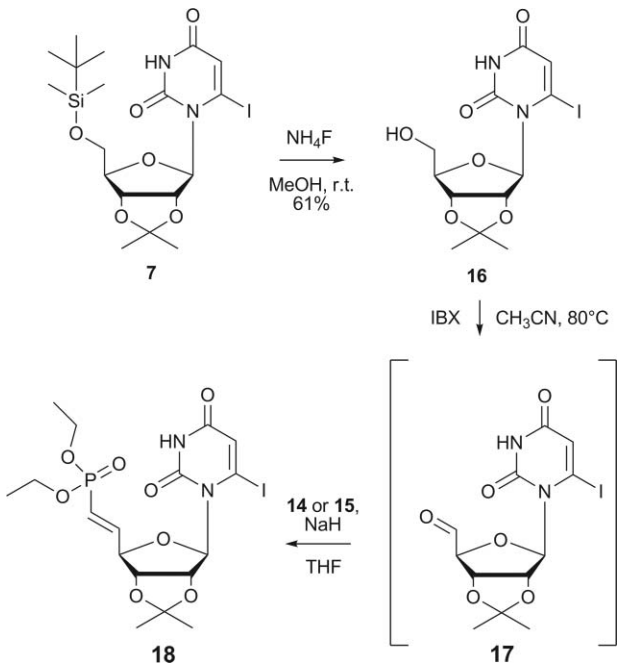
Table 3 Deprotection of C-6 substituted uridines

Entry	Substrate	Product	Yield (%)[a]
1.	**8a**	**9a**	93
2.	**8b**	**9b**	61
3.	**8c**	**9c**	91
4.	**8d**	**9d**	98

[a] Isolated yield.



Scheme 2 Introduction of the phosphonate moiety through Horner–Wadsworth–Emmons reaction.



Scheme 3 Synthesis of strategic intermediate **18**.

the phosphonate moiety presented a serious synthetic challenge (Scheme 3).

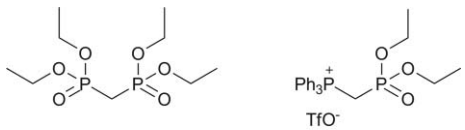
First, intermediate **17**, prepared by the oxidation of alcohol **16** by IBX, usualy contained some impurities that were hardly separable from the desired compound due to its inherent instability. Extractions or column chromatography were found to be highly inefficient. The best way to remove most of the impurities was to cool down the acetonitrile solution in an ice bath and to remove the insoluble material by filtration. Further difficulties were faced during the olefination step (Table 4), but optimization of the reaction conditions allowed to obtain **18** in 43% yield (over the oxidation and olefination step).

Having the protected 6-iodouridine phosphonate precursor in hand, the Suzuki–Miyaura cross coupling with diverse boronic acids was investigated. Remarkably, the conditions optimized for the cross coupling of the protected 6-iodouridine **7** failed when applied to **18**. Many other conditions and catalysts were tested and mostly found unsatisfactory (ESI Table S2†).

Table 4 Oxidation-olefination sequence

Entry	Reagent	Ratio	Time/h	Temp.	Yield (%)[a]
1.	**15**	3eq.	16	r.t.	0
2.	**14**	1eq.	16	r.t.	8
3.	**14**	3eq.	1.5	r.t.	21
4.	**14**	3eq.	2.75	0 °C	31
5.	**14**	5eq.	4	0 °C	32
6.[b]	**14**	2.4eq.	2.5	0 °C	29
7.[b]	**14**	3eq.	2.5	0 °C	43

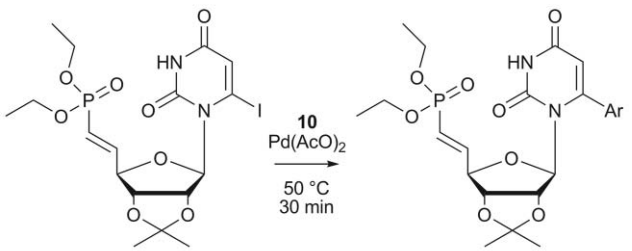
[a] Isolated yield based on **16** (two steps). [b] Large scale.



14 **15**

Fig. 2 Reagents for olefination reactions.

In search for suitable reaction conditions, we experienced that the phosphine ligands presented no actual advantage for the reaction. In addition, the use of inert atmosphere could be omitted and reactions could be performed open to air. Further optimization of the $Pd(OAc)_2$-catalyzed reaction led to proper conditions for this ligandless coupling reaction (Scheme 4, Table 5).



11 **12**

Scheme 4 Cross-coupling reaction of nucleoside phosphonates.

All test reactions were carried out in presence of 10 mol% $Pd(AcO)_2$ at 50 °C for 30 min. The best results were obtained for the reaction performed using K_3PO_4 as a base in the 1 : 1 mixture of n-propanol and water. These conditions were applied with a reduced amount of catalyst (5%) for the synthesis of various 6-aryl substituted nucleoside phosphonates **13** (Table 6). As a notable benefit, the conversion could be conveniently monitored by ^{31}P-NMR.

Table 5 Optimization of the aerobic ligand-free Suzuki cross coupling[a]

Entry	$ArB(OH)_2$	Product	Solvent	Base	Yield(%)
1.	**10b**	**13b**	$CH_3CN–H_2O$	Cs_2CO_3	43
2.	**10b**	**13b**	H_2O	Cs_2CO_3	2
3.	**10b**	**13b**	$EtOH–H_2O$	Cs_2CO_3	52
4.	**10b**	**13b**	$MeOH–H_2O$	Cs_2CO_3	61
5.	**10b**	**13b**	$iPrOH/H_2O$	Cs_2CO_3	58
6.	**10b**	**13b**	$tBuOH/H_2O$	Cs_2CO_3	50
7.	**10b**	**13b**	$Dioxane/H_2O$	Cs_2CO_3	43
8.	**10b**	**13b**	$PrOH/H_2O$	Cs_2CO_3	63
9.	**10b**	**13b**	$PrOH/H_2O$	CsF	57
10.	**10b**	**13b**	$PrOH/H_2O$	K_3PO_4	72
11.	**10b**	**13b**	$PrOH/H_2O$	$NaHCO_3$	41
12.	**10b**	**13b**	$PrOH/H_2O$	NaOH	0
13.	**10b**	**13b**	$PrOH/H_2O$	KOAc	30
14.	**10b**	**13b**	$PrOH/H_2O$	Et_3N	55
15.	**10b**	**13b**	$PrOH/H_2O$	K_2CO_3	54

[a] Yield determined by quantitative ^{31}P NMR.

Table 6 Synthesis of C-6 substituted nucleoside phosphonates *via* Suzuki–Miyaura cross-coupling[a]

Entry	$ArB(OH)_2$	Product	Ar	Yield (%)[b]
1.	**10a**	**13a**		45
2.	**10b**	**13b**		64
3.	**10c**	**13c**		trace
4.	**10d**	**13d**		24
5.	**10f**	**13f**		53
6.	**10g**	**13g**		63
7.	**10h**	**13h**		51
8.	**10i**	**13i**		45
9.	**10j**	**13j**		trace
10.	**10k**	**13k**		52
11.	**10l**	**13l**		64
12.	**10m**	**13m**		80

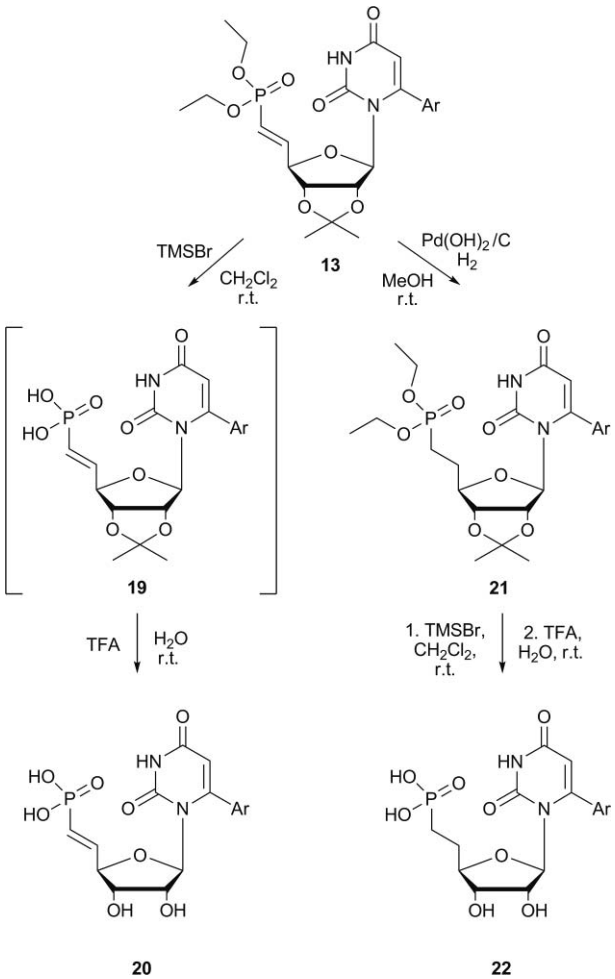
[a] *Reaction conditions*: compound **18** (1 mmol), 5% $Pd(AcO)_2$, K_3PO_4, $PrOH/H_2O$ (1 : 1), 50 °C, 30 min. [b] Isolated yield.

The reaction is remarkably fast and in most cases the conversion was quantitative within 30 min. Although the moderate yields of this cross-coupling reaction can be ascribed partly to the reductive dehalogention, our preliminary experiments also showed that the cleavage of the N-glycosidic bond could be one of important side reactions.

Seven C-6 substituted products (*i.e.*, **13a,b,f,g,h,k** and **m**) were used for subsequent transformations. For the synthesis of the unsaturated NPs, compounds **13** were first treated with TMSBr in dichloromethane. In the case of compound **13a**, it was possible to isolate the product of the partial deprotection **19a** (^{1}H-NMR and HR-MS), which, however, underwent spontaneous decomposition during the ^{13}C-NMR measurement in D_2O overnight. The isopropylidene group of **19a** could be removed by treatment with aqueous trifluoroacetic acid (TFA) to give the desired

phosphonate **20a**. For the other examples, the isolation of the intermediate **19** was omitted and the reaction with TMSBr was directly followed by hydrolysis of the acetonide with TFA.

The saturated analogues were obtained by catalytic hydrogenation of the coupling products **13** on $Pd(OH)_2/C$. This step afforded excellent yields of intermediates **21** that were subsequently deprotected by identical procedure as used above. Both double bonds of the compounds **13m** were hydrogenated to give product **21n**, which was further converted to the free phosphonate **22n**. The purity of the final products **20** and **22** was determined by LC-MS. Compounds that did not meet 95% purity were purified by reversed-phase HPLC. The yields of compounds **20**, **21** and **22** (see Scheme 5) are summarized in Table 7.



Scheme 5 Deprotection and hydrogenation-deprotection steps.

For nucleotides, it is known that the five membered ring structure can be in equilibrium between two favored puckering conformations, labeled the North (N) and South (S) state.[16] Davies *et al.*[17] have derived a simple set of equations that relate the fraction of the Northern conformer X_N with the values of the three vicinal scalar couplings that can be measured between the protons of the ring:

$$J_{H1',H2'} = 9.3(1 - X_N)$$
$$J_{H2',H3'} = 4.6X_N + 5.3\,(1 - X_N)$$
$$J_{H3',H4'} = 9.3X_N$$

Table 7 The yields of saturated compounds **21** and final NPs **20** and **22**

	Yields of compounds (%)[a]		
Derivative	**20**	**21**	**22**
a	40%	90%	21%
b	91%	88%	81%
f	87%	88%	30%
g	96%	97%	94%
h	77%	82%	49%
k	46%	95%	71%
m	95%	—	—
n	—	99%	93%

[a] Isolated yield.

Table 8 ^{1}H-NMR derived mole fraction of the N-type conformer of **5**, **22a** and **9b** at different temperatures

	% N		
T/°C	**5**	**22a**	**9b**
20	55.5	74.7	—
27	54.8	74.2	64.3
35	54.4	73.6	65.3
42	54.1	73.0	60.5
50	54.0	73.0	58.5
60	—	—	58.7

To assess the impact of the presence of a substituent at the C-6 position of the uracil base on the relative proportions of Northern and Southern conformers, these scalar couplings were measured at five different temperatures for the 6-naphthyl substituted uridine (**9b**) and the 6-phenyl substituted uridine phosphonate (**22a**), while the same was done for the non-C-6 substituted uridine phosphonate (**5**). The fraction of the N-type conformer was obtained by minimizing the sum of square difference between the experimental couplings and those calculated from the above equations. The results are shown in Table 8.

For **5**, the Northern and Southern conformers are nearly equally present, with a small preference for the Northern. For both C-6 substituted nucleotides, this preference increases significantly, while an increase in temperature makes it decrease.

A second aspect of the conformation is the orientation of the base relative to the ring structure, which is here assumed to be either *syn* (with the substituent pointing away from the ring) or *anti* (with the substituent pointing towards the ring). For all three nucleotides, 2D NOESY spectra were recorded to study the nOe contacts between the base protons and the ribofuranse protons. In the case of **5**, the H6 proton can only come close enough to the H3′ and the H5′ protons to provide a nOe contact when the *anti* rotamer is adopted. The NOESY spectrum indeed shows clear cross-peaks from the H6 proton to the H3′ and both H5′ protons, indeed confirming that the anti rotamer can be adopted. The NOESY spectrum indeed shows clear cross′peaks with the H3′ and both H5′ protons, indeed confirming that the *anti* rotamer can be adopted. In the case of **22a**, the *anti* rotamer is expected to lead to strong nOe contacts with protons of the phenyl group, while in the *syn* rotamer the fenyl group will be oriented too far away from the H3′ and certainly the H5′ protons. Only nOe contacts from the *ortho* and *meta* protons to H1′ and from the *ortho* protons to H2′ are observed in the NOESY, demonstrating that in this case

only the *syn* rotamer is available. This demonstrates that bulky substituents at the C-6 position of the base strongly limit the rotational freedom of the C1′–N1 bond. Similar results are found for **9b**, where only nOe contacts are detected between H1′ and both the H2″ and H10″ protons of the naphthyl group, and a weak contact between H2′ and H2″. ESI Fig. S4† gives an overview of all observed nOe contacts.

Conclusions

Two synthetic procedures are described for the preparation of C-6 substituted NPs as derivatives of lead compound **5**. In a first approach a Suzuki–Miyaura cross coupling of protected nucleoside analogue **7** was performed under classical conditions using $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ as the catalyst and a mixture of toluene or *o*-xylene with water as solvent. This method mostly afforded good yields of the C-6 arylated products **8**, which could be further converted to the desired NPs as demonstrated for **8a**, or deprotected to the free C-6 substituted nucleosides **9**. This approach offers one of the rare alternatives to Stille coupling for the synthesis of C-6 substituted derivatives of uridine and its phosphonate analogues. Since it was desirable to realize the C-6 derivatisation in the later stage of the synthesis, however, a more divergent synthetic route was developed for the NPs **20** and **22**. Towards this end, we first optimized the preparation of the key intermediate **18**, which was then used in the subsequent Suzuki–Miyaura coupling. Intriguingly, carrying out this reaction under aerobic and ligand-free conditions proved to be the most convenient in this case. Seven C-6 substituted products were further converted to the desired unsaturated and saturated NPs **20** and **22**, respectively. This way, 14 new analogues of lead compound **5** were obtained. As far as we know, this is the first example of an aerobic, ligand-free Suzuki–Miyaura cross coupling reaction applied for the preparation of molecules with this level of complexity.

Experimental

Chemical Synthesis

Chemicals were obtained from commercial sources (Acros Organics, Sigma-Aldrich and Alfa Aesar) or prepared according to published procedures. NMR spectra were recorded at room temperature on a Varian Mercury 300 spectrometer. Chemical shifts are quoted in ppm relative to residual solvent peaks as appropriate. Exact mass measurements were performed on a Waters LCT Premier XETM Time of flight (TOF) mass spectrometer equipped with a standard electrospray ionization and modular LockSpray TM interface. Samples were infused in a CH_3CN–water (1 : 1) mixture at 10 μL min^{-1}. The purity of the final phosphonic acids was assessed by HPLC and PDA detection (190–400 nm) using a reverse phase column (Phenomenex Luna 2.5 μm C18(2)-HST, 100 × 2.00 mm) with a linear gradient of 10–100% B over 9 min, where A is 0.1% formic acid in H_2O and B is 0.1% formic acid in CH_3CN at a flow rate of 0.4 mL min^{-1}).

Synthesis of compounds 8a–e: General procedure

Compound **4** (100 mg, 0.19 mmol), boronic acid (0.30 mmol), K_2CO_3 (38.5 mg, 0.28 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (5.6 mg, 0.068 mmol) were suspended in toluene or *o*-xylene (4 cm^3) and added to a bath preheated to 100 °C or 140 °C (see Table 1). After 2 min., degassed water (0.9 cm^3) was added and the mixture was heated for an additional 45 min. Then, the reaction mixture was poured onto saturated aqueous NH_4Cl (7 cm^3) and extracted with EtOAc (3 × 15 cm^3). The organic layers were combined and dried over $MgSO_4$. Evaporation afforded the crude product that was purified on a silica gel column (EtOAc : Hexanes, 1 : 1).

Synthesis of unprotected nucleosides 9a–d: General procedure

The protected nucleoside **8** (0.3 mmol) was suspended in a mixture of water (1 cm^3) and TFA (1.5 cm^3) at 0 °C and the resulting mixture was stirred at rt in the dark for 3 h. The solvents were evaporated and co-distilled with water (2 × 5 cm^3) and EtOH (2 × 5 cm^3). Column chromatography (EtOAc : Acetone : EtOH : water, 20 : 3 : 1 : 1) of the crude product afforded the desired nucleoside **9**.

Synthesis of partially unprotected nucleosides 11 and 16: General procedure

The silylated compound **7** or **8a** (4 mmol) was dissolved in methanol (25 cm^3) and treated with NH_4F (1.48 g, 40 mmol) for 48 h. The solvent was evaporated and the residue was partioned between EtOAc (100 cm^3) and water (60 cm^3). The water phase was extracted with EtOAc (4 × 100 cm^3). The organic phases were combined, dried over Mg_2SO_4 and evaporated. The residue was chromatographed on a silica gel column (EtOAc : Toluene, 10 : 1) to give the desired alcohols **11** (form **8a**, white solid, 1.05 g, 73%) and **16** (from **7**, white foam, 1.16 g, 71%).

1-((3a*R*,4*R*,6*R*,6a*R*)-6-(Hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-6-phenylpyrimidine-2,4(1*H*,3*H*)-dione 12

IBX (2.15 g, 7.7 mmol) was added to the stirred solution of the 6-phenyluridine derivative **11** (920 mg, 2.6 mmol) in CH_3CN (22 cm^3) and the resulting slurry was heated at 80 °C for 4 h. The reaction mixture was cooled to 0 °C for 30 min, solids were filtered off and the filtrate cake was washed several times with cold CH_3CN. Then, the collected filtrates were evaporated and the residue was purified by column chromatography (EtOAc : Toluene, 10 : 1) to afford aldehyde **12** (0.9 g, 98%) as slightly opalescent colorless oil.

Diethyl (*E*)-2-((3a*R*,4*R*,6*R*,6a*R*)-6-(2,4-dioxo-6-phenyl-3,4-dihydropyrimidin-1(2*H*)-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)vinylphosphonate 13a

A solution of aldehyde **12** (0.9 g, 2.5 mmol) in THF (10 cm^3) was added to the stirred solution of freshly prepared sodium salt of bisphosphonate **14** (prepared by addition of bisphosphonate **14** (1.35 cm^3, 5.5 mmol) to the stirred suspension of NaH (60% dispersion in mineral oil, 211 mg, 5.3 mmol) and stirring of the resulting suspension for 30 min) under argon atmosphere. The mixture was stirred overnight and subsequently evaporated to half its volume, diluted with EtOH (3 cm^3) and adsorbed onto silica gel. Column chromatography (EtOAc : Acetone : EtOH : water, 42 : 6 : 1 : 1) afforded the desired phosphonate **13a** (765 mg, 61%) as colorless oil.

Diethyl (*E*)-2-((3a*R*,4R,6R,6aR)-6-(6-iodo-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)vinylphosphonate 18

IBX (2.94 g, 10.5 mmol) was added to a solution of **16** (1.43 g, 3.5 mmol) in CH_3CN and the resulting suspension was stirred at 85 °C for 4 h. After cooling in an ice bath (15 min), the solid was removed by filtration and washed with cold CH_3CN (2 × 15 cm^3). The solvent was evaporated and the residue was co-distilled with toluene (2 × 30 cm^3). The obtained crude aldehyde was dissolved in dry THF (25 cm^3) under argon. The salt of bisphosphonate **14** was freshly prepared by addition of the latter (2.6 cm^3, 10.5 mmol) to a suspension NaH (417 mg, 10.5 mmol) in THF (25 cm^3) and stirring for 30 min. The solution of the aldehyde was added to the resulting mixture at 0 °C and stirring was continued for another 2.5 h at the 0 °C. Then, a solution of NH_4Cl (100 cm^3) was added and the mixture was extracted with EtOAc (3 × 200 cm^3). The combined organic layers were washed with saturated solution of $NaHCO_3$ (100 cm^3), dried over $MgSO_4$ and evaporated to dryness. Chromatography on a silica gel column (EtOAc : Hexanes, 20 : 1) afforded the desired phosphonate **18** (818 mg, 43%). δ_H(300 MHz; DMSO-d_6; Me_4Si) 1.22 (6 H, t, *J* 7.0, 2×OCH_2CH_3), 1.30 (3 H, s, CH_3), 1.51 (3 H, s, CH_3), 3.92 (4 H, m, 2 × CH_2), 4.64 (1 H, m, 4′-H), 4.84 (1 H, dd, $J_{3',2'}$ 6.2, $J_{3',4'}$ 3.8, 3′-H), 5.28 (1 H, d, $J_{2',3'}$ 6.7, 2′-H), 5.96 (1 H, ddd, $J_{6',4'}$ 1.2, $J_{6',5'}$ 17.0, $J_{6',P}$ 19.9, 6′-H), 6.05 (1 H, s, 1′-H), 6.37 (1 H, d, *J* 2.1, 5-H), 6.66 (1 H, ddd, $J_{5',4'}$ 6.5, $J_{5',6'}$ 17.0, $J_{H5',P}$ 21.7, 5′-H), 11.66 (1 H, d, *J* 1.8, NH); δ_C(75 MHz; DMSO-d_6; DMSO) 16.15 (s), 16.23 (s), 25.08 (s), 26.92 (s), 61.34 (d, *J* 4.5), 61.35 (d, *J* 4.5), 84.45 (2C, s), 88.84 (d, *J* 24.1), 100.72 (s), 112.96 (s), 115.45 (s), 116.51(s), 118.82 (d, *J* 183.0), 147.76 (s), 148.82 (d, *J* 5.3), 161.50 (s); δ_P(121 MHz; DMSO-d_6; H_3PO_4) 17.47 (s); *m*/*z* 543.0399 (ESI) (M+H^+. $C_{17}H_{25}IN_2O_8P^+$ requires 543.0388).

Synthesis of nucleoside phosphonates 13 by ligandless Suzuki cross-coupling: General procedure

In a test tube opened to air, a mixture of iodophosphonate **18** (100 mg, 0.18 mmol), K_3PO_4 (78 mg, 0.36 mmol), boronic acid (0.27 mmol) and $Pd(AcO)_2$ (2 mg, 9 μmol) in *n*-PrOH (1 cm^3) and H_2O (1 cm^3) was stirred at 50 °C for 30 min. Brine was added (5 cm^3) and the mixture was extracted with EtOAc (3×15 cm^3). The organic layers were combined, dried over $MgSO_4$ and evaporated. The crude product was purified by column chromatography (EtOAc : Acetone : EtOH : H_2O, 42 : 6 : 1 : 1), dissolved in MeOH (5 cm^3), treated with activated charcoal (10 mg) overnight, and filtered through a silica gel pad yielding the cross coupling products **13**.

Diethyl (*E*)-2-((3a*R*,4*R*,6*R*,6a*R*)-6-(2,4-dioxo-6-phenyl-3,4-dihydropyrimidin-1(2*H*)-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)vinylphosphonate 13a

The title compound was obtained as a colorless oil (41 mg, 45%) δ_H(300 MHz; DMSO-d_6; Me_4Si) 1.24 (6 H, t, *J* 6.9, 2×OCH_2CH_3), 1.24 (3 H, s, CH_3), 1.32 (3 H, s, CH_3), 3.97 (4 H, m, 2 × CH_2), 4.51 (1 H, m, 4′-H), 4.83 (1 H, dd, $J_{3',2'}$ 6.1, $J_{3',4'}$ 4.0, 3′-H), 5.28 (1 H, d, $J_{2',3'}$ 6.4, 2′-H), 5.32 (1 H, s, 1′-H), 5.54 (1 H, s, 5-H), 6.01 (1 H, ddd, $J_{6',4'}$ 1.3, $J_{6',5'}$ 17.3, $J_{6',P}$ 20.3, 6′-H), 6.72 (1 H, ddd, $J_{5',4'}$ 6.7, $J_{5',6'}$ 17.0, $J_{H5',P}$ 21.6, 5′-H), 7.48–7.51 (2 H, m, Ar), 7.55–7.58 (3 H, m, Ar), 11.62 (1 H, s, NH); δ_C(75 MHz; DMSO-d_6; DMSO) 16.18, 16.25, 24.99, 26.79, 61.31 (d, *J* 5.4), 61.36 (d, *J* 5.4), 84.33, 84.51, 88.64 (d, *J* 24.3), 92.52, 103.63, 112.75, 118.87 (d, *J* 182.4), 128.16, 129.04 (2C, s), 130.37, 132.69, 149.02 (d, *J* 5.5), 150.78, 155.04, 162.26; δ_P(121 MHz; DMSO-d_6; H_3PO_4) 17.59; *m*/*z* 493.1740 (ESI) (M+H^+. $C_{23}H_{30}N_2O_8P^+$ requires 493.1734).

Diethyl (*E*)-2-((3a*R*,4*R*,6*R*,6a*R*)-2,2-dimethyl-6-(6-(naphtha-len-2-yl)-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetra-hydrofuro[3,4-*d*][1,3]dioxol-4-yl)vinylphosphonate 13b

Phosphonate **13b** was obtained as a colorless oil (64 mg, 64%) δ_H(300 MHz; DMSO-d_6; Me_4Si) 1.20–1.30 (12 H, m, 2×OCH_2CH_3+ 2×CH_3), 3.99 (4 H, m, 2 × CH_2), 4.51 (1 H, m, 4′-H), 4.85 (1 H, dd, $J_{3',2'}$ 6.2, $J_{3',4'}$ 4.0, 3′-H), 5.32 (1 H, br d, $J_{2',3'}$ 5.5, 2′-H), 5.38 (1 H, s, 1′-H), 5.68 (1 H, d, $J_{5,NH}$ 2.1, 5-H), 6.03 (1 H, ddd, $J_{6',4'}$ < 1, $J_{6',5'}$ 17.4, $J_{6',P}$ 19.3, 6′-H), 6.74 (1 H, ddd, $J_{5',4'}$ 6.4, $J_{5',6'}$ 17.2, $J_{H5',P}$ 23.3, 5′-H), 7.57–7.69 (3 H, m, Ar), 8.02–8.12 (4 H, m, Ar), 11.67 (1 H, d, $J_{2',3'}$ 2.0,NH); δ_C(75 MHz; DMSO-d_6; DMSO) 16.18, 16.25, 24.95, 26.73, 61.32 (d, *J* 5.5), 61.37 (d, *J* 5.5), 84.40, 84.50, 88.68 (d, *J* 24.9), 92.64, 103.99, 112.77, 118.87 (d, *J* 183.0), 127.27, 127.80, 128.09, 128.48, 128.52, 130.07, 132.38, 133.18, 149.01 (d, *J* 5.5), 150.77, 155.05, 162.23; δ_P(121 MHz; DMSO-d_6; H_3PO_4) 17.60 (s); *m*/*z* 543.1892 (ESI) (M+H^+. $C_{27}H_{32}N_2O_8P^+$ requires 543.1891).

Diethyl (*E*)-2-((3a*R*,4*R*,6*R*,6a*R*)-6-(6-(furan-2-yl)-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,2-dimethyltetrahydrofuro [3,4-*d*][1,3]dioxol-4-yl)vinylphosphonate 13d

Phosphonate **13d** was obtained as a colorless oil (21 mg, 24%) δ_H(300 MHz; DMSO-d_6; Me_4Si) 1.22 (6 H, t, *J* 7.0, 2×OCH_2CH_3), 1.28 (3 H, s, CH_3), 1.43 (3 H, s, CH_3), 3.96 (4 H, m, 2 × CH_2), 4.63 (1 H, m, 4′-H), 4.88 (1 H, dd, $J_{3',2'}$ 6.2, $J_{3',4'}$ 3.8, 3′-H), 5.30 (1 H, d, $J_{2',3'}$ 6.6, 2′-H), 5.65 (1 H, s, 1′-H), 5.84 (1 H, d, $J_{2',3'}$ 2.2, 5-H), 5.99 (1 H, ddd, $J_{6',4'}$ 1.3, $J_{6',5'}$ 17.1, $J_{6',P}$ 20.1, 6′-H), 6.72 (1 H, ddd, $J_{5',4'}$ 6.5, $J_{5',6'}$ 17.1, $J_{H5',P}$ 21.7, 5′-H), 6.76 (1 H, dd, *J* 3.5, *J* 1.8, Ar), 7.09 (1H, dd, *J* 3.5, *J* 0.7, Ar), 8.03 (1H, dd, *J* 1.8, *J* 0.7,Ar), 11.64 (1 H, d, *J* 1.8, NH); δ_C(75 MHz; DMSO-d_6; DMSO) 16.14, 16.23, 25.04, 26.85, 61.30 (d, *J* 5.8), 61.35 (d, *J* 5.7), 84.55, 88.90 (d, *J* 24.2), 93.09, 102.59, 112.40, 112.73, 114.94, 118.72 (d, *J* 183.3), 144.05, 144.16, 149.09 (d, *J* 5.5), 150.64, 162.23; δ_P(121 MHz; DMSO-d_6; H_3PO_4) 17.48; *m*/*z* 483.1516 (ESI) (M+H^+. $C_{21}H_{28}N_2O_9P^+$ requires 483.1526).

Diethyl (*E*)-2-((3aR,4R,6R,6aR)-6-(2,4-dioxo-6-m-tolyl-3,4-dihydropyrimidin-1(2*H*)-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)vinylphosphonate 13f

Phosphonate **13f** was obtained as a colorless oil (49.5 mg, 53%) δ_H(300 MHz; DMSO-d_6; Me_4Si) 1.21 (6 H, t, *J* 7.1, 2×OCH_2CH_3), 1.22 (3 H, s, CH_3), 1.32 (3 H, s, CH_3), 3.97 (4 H, m, 2×CH_2), 4.51 (1 H, m, 4′-H), 4.83 (1H, dd, $J_{3',2'}$ 6.2, $J_{3',4'}$ 3.8, 3′-H), 5.28 (1H, d, $J_{2',3'}$ 6.2, 2′-H), 5.36 (1H, s, 1′-H), 5.53 (1H, s, 5-H), 6.00 (1H, ddd, $J_{6',4'}$ 1.2, $J_{6',5'}$ 17.0, $J_{6',P}$ 20.1, 6′-H), 6.72 (1H, ddd, $J_{5',4'}$ 6.6, $J_{5',6'}$ 17.0, $J_{5',P}$ 22.0, 5′-H), 7.33–7.45 (4H, m, Ar), 11.61 (1H, s, NH); δ_C(75 MHz; DMSO-d_6; DMSO) 16.16, 16.24, 24.96, 26.76, 61.31 (d, *J* 5.3), 61.38 (d, *J* 5.4), 84.33, 84.50, 88.58 (d, *J* 14.3), 90.51,103.46, 112.76, 118.86 (d, *J* 183.0), 125.17, 128.82, 130.98, 132.58,

138.55, 148.99 (d, *J* 5.0), 150.73, 155.18, 162.19; δ_P(121 MHz; DMSO-d_6; H_3PO_4) 17.58; *m/z* (ESI) 507.1901 (M+H$^+$. $C_{24}H_{32}N_2O_8P^+$ requires 507.1891).

Diethyl (*E*)-2-((3aR,4R,6R,6aR)-6-(6-(3-methoxyphenyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)vinylphosphonate 13g

Phosphonate **13g** was obtained as a colorless oil (61 mg, 63%) δ_H(300 MHz; DMSO-d_6; Me_4Si) 1.23 (6 H, t, *J* 7.1, 2×OCH$_2$CH_3), 1.25 (3 H, s, CH$_3$), 1.34 (3 H, s, CH$_3$), 3.81 (3 H, s, OCH$_3$), 3.94 (4 H, m, 2×CH$_2$), 4.52 (1 H, m, 4′-H), 4.83 (1H, dd, $J_{3',2'}$ 6.2, $J_{3',4'}$ 3.8, 3′-H), 5.29 (1H, d, $J_{2',3'}$ 6.6, 2′-H), 5.36 (1H, s, 1′-H), 5.58 (1H, s, 5-H), 6.00 (1H, ddd, $J_{6',4'}$ 1.2, $J_{6',5'}$ 17.2, $J_{6',P}$ 20.2, 6′-H), 6.72 (1H, ddd, $J_{5',4'}$ 6.5, $J_{5',6'}$ 17.0, $J_{5',P}$ 21.7, 5′-H), 7.02–7.16 (3H, m, Ar), 7.47 (1H, dd, *J* 8.2, *J* 7.9, Ar), 11.61 (1H, s, NH); δ_C(75 MHz; DMSO-d_6; DMSO) 16.16, 16.24, 24.99, 26.79, 55.30, 61.30 (d, *J* 6.1), 61.36 (d, *J* 5.8), 84.34, 84.44, 88.54 (d, *J* 24.6), 92.51, 103.46, 112.79, 113.67, 118.86 (d, *J* 183.2), 120.06, 130.27, 133.83, 148.97 (d, *J* 5.3), 150.71, 154.82, 159.24, 162.22; δ_P(121 MHz; DMSO-d_6; H_3PO_4) 17.52; *m/z* (ESI) 523.1845 (M+H$^+$. $C_{24}H_{32}N_2O_9P^+$ requires 523.1840).

Diethyl (*E*)-2-((3a*R*,4*R*,6*R*,6a*R*)-6-(6-(4-fluorophenyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,2-dimethyltetra-hydrofuro[3,4-*d*][1,3]dioxol-4-yl)vinylphosphonate 13h

Phosphonate **13h** was obtained as a colorless oil (48 mg, 51%) δ_H(300 MHz; DMSO-d_6; Me_4Si) 1.24 (6 H, t, *J* 7.0, 2×OCH$_2$CH_3), 1.25 (3 H, s, CH$_3$), 1.33 (3 H, s, CH$_3$), 3.98 (4 H, m, 2 × CH$_2$), 4.53 (1 H, m, 4′-H), 4.84 (1 H, dd, $J_{3',2'}$ 6.2, $J_{3',4'}$ 4.1, 3′-H), 5.28 (1 H, d, $J_{2',3'}$ 6.2, 2′-H), 5.29 (1 H, s, 1′-H), 5.57 (1 H, d, $J_{5,NH}$ 2.1 Hz, 5-H), 6.02 (1 H, ddd, $J_{6',4'}$ 1.2, $J_{6',5'}$ 17.0, $J_{6',P}$ 20.2, 6′-H), 6.73 (1 H, ddd, $J_{5',4'}$ 6.4, $J_{5',6'}$ 17.0, $J_{H5',P}$ 23.4, 5′-H), 7.42 (2 H, t, *J* 9.0, Ar), 7.58 (2 H, m, Ar), 11.61 (1 H, d, *J* 1.5, NH); δ_C(75 MHz; DMSO-d_6; DMSO) 16.16, 16.24, 24.94, 26.78, 61.31 (d, *J* 5.3), 61.36 (d, *J* 5.2), 84.30, 84.50, 88.68 (d, *J* 24.3), 92.56, 103.92, 112.75, 116.14 (2C, d, *J* 22.1), 118.81 (d, *J* 182.4), 129.07 (d, *J* 3.3), 130.76 (d, *J* 8.8), 149.00 (d, *J* 5.5), 150.71, 154.09, 162.15, 163.01 (d, *J* 248.2); δ_P(121 MHz; DMSO-d_6; H_3PO_4) 17.56; δ_F(282 MHz; DMSO-d_6; CCl_3F) 90.18 (s); *m/z* (ESI) 511.1644 (M+H$^+$. $C_{25}H_{32}N_2O_8P^+$ requires 511.1640).

Diethyl (*E*)-2-((3a*R*,4*R*,6*R*,6a*R*)-6-(2,4-dioxo-6-(1-phenyl-vinyl)-3,4-dihydropyrimidin-1(2*H*)-yl)-2,2-dimethyltetra-hydrofuro[3,4-*d*][1,3]dioxol-4-yl)vinylphosphonate 13i

Phosphonate **13i** was obtained as a colorless oil (43 mg, 45%) δ_H(300 MHz; DMSO-d_6; Me_4Si) 1.17 (3 H, s, CH$_3$), 1.22 (6 H, t, *J* 7.0, 2×OCH$_2$CH_3), 1.28 (3 H, s, CH$_3$), 3.95 (4 H, m, 2 × CH$_2$), 4.40 (1 H, m, 4′-H), 4.77 (1 H, dd, $J_{3',2'}$ 6.2, $J_{3',4'}$ 4.0, 3′-H), 5.12 (1 H, d, $J_{2',3'}$ 6.2, 2′-H), 5.41 (1 H, s, 1′-H), 5.60 (2 H, m, 5-H+C=CH_a), 5.92 (1 H, ddd, $J_{6',4'}$ 1.0, $J_{6',5'}$ 17.2, $J_{6',P}$ 20.1, 6′-H), 6,15 (1 H, s, C=CH_b), 6.66 (1 H, ddd, $J_{5',4'}$ 6.6, $J_{5',6'}$ 17.2, $J_{H5',P}$ 21.7, 5′-H), 7.37–7.45 (3 H, m, Ar), 7.49 –7.56 (2H, m, Ar), 11.64 (1 H, d, *J* 1.8, NH); δ_C(75 MHz; DMSO-d_6; DMSO) 16.15 (s), 16.23 (s), 25.04 (s), 26.75 (s), 61.28 (d, *J* 3.7), 61.35 (d, *J* 3.7), 84.35 (2C, s), 88.49 (d, *J* 24.4), 92.76 (s), 103.55 (s), 112.63 (s), 118.80 (d, *J* 182.9), 125.92(2C, s), 129.01 (2C, s), 135.24 (s), 140.49 (s), 149.03 (d, *J* 5.4), 150.55 (s), 154.45 (s), 162.56 (s); δ_P(121 MHz; DMSO-d_6; H_3PO_4) 17.54 (s); *m/z* 517.1747 (negESI) (M – H$^+$. $C_{25}H_{30}N_2O_8P^+$ requires 517.1745).

Diethyl (*E*)-2-((3aR,4R,6R,6aR)-6-(2,4-dioxo-6-p-tolyl-3,4-dihydropyrimidin-1(2*H*)-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)vinylphosphonate 13k

Phosphonate **13k** was obtained as a colorless oil (48.5 mg, 52%) δ_H(300 MHz; DMSO-d_6; Me_4Si) 1.22 (6H, t, *J* 7.1, 2×OCH$_2$CH_3), 1.26 (3H, s, CH$_3$), 1.31 (3 H, s, CH$_3$), 3.97 (4H, m, 2×CH$_2$), 4.49 (1 H, m, H4′), 4.81 (1H, dd, $J_{3',2'}$ 6.2, $J_{3',4'}$ 4.1 Hz, 3′-H), 5.25 (1H, d, $J_{2',3'}$ 6.2, 2′-H), 5.35 (1H, s, 1′-H), 5.50 (1H, d, $J_{5,NH}$ 2.0, 5-H), 6.01 (1H, ddd, $J_{6',4'}$ 1.2, $J_{6',5'}$ 17.2, $J_{6',P}$ 20.2 Hz, 6′-H), 6.72 (1H, ddd, $J_{5',4'}$ 6.5, $J_{5',6'}$ 17.2, $J_{5',P}$ 21.7, 5′-H), 7.37 (4H, br d, *J* 1.3, Ar), 11.57 (1H, d, $J_{NH,5}$ 1.3, NH); δ_C(75 MHz; DMSO-d_6; DMSO) 16.16, 16.24, 20.89, 24.94, 26.80, 61.30 (d, *J* 3.9), 61.38 (d, *J* 3.9), 84.40, 84.51, 88.66 (d, *J* 23.8), 92.40, 103.44, 112.76, 118.84 (d, *J* 182.4), 128.05, 129.56, 129.78, 140.24, 149.03 (d, *J* 5.5), 150.79, 155.20, 162.21; δ_P(121 MHz; DMSO-d_6; H_3PO_4) 17.60; *m/z* (ESI) 507.1887 (M+H$^+$. $C_{24}H_{32}N_2O_8P^+$ requires 507.1891).

Diethyl (*E*)-2-((3aR,4R,6R,6aR)-6-(6-(1*H*-indol-5-yl)-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,2-dimethyltetra-hydrofuro[3,4-d][1,3]dioxol-4-yl)vinylphosphonate 13l

Phosphonate **13l** was obtained as a colorless oil (63 mg, 64%) δ_H(300 MHz; DMSO-d_6; Me_4Si) 1.21–1.27 (9 H, m, 2×OCH$_2$CH_3+CH$_3$), 1.28 (3 H, s, CH$_3$), 3.98 (4 H, m, 2 × CH$_2$), 4.49 (1 H, m, 4′-H), 4.83 (1 H, dd, $J_{3',2'}$ 5.9, $J_{3',4'}$ 4.1, 3′-H), 5.27 (1 H, d, $J_{2',3'}$ 6.1, 2′-H), 5.35 (1 H, s, 1′-H), 5.52 (1 H, d, $J_{5,NH}$ 2.3 Hz, 5-H), 6.02 (1 H, ddd, $J_{6',4'} < 1$, $J_{6',5'}$ 17.6, $J_{6',P}$ 19.4, 6′-H), 6.56 (1 H, br s, Ar), 6.74 (1 H, ddd, $J_{5',4'}$ 6.7, $J_{5',6'}$ 17.3, $J_{5',P}$ 22.0, 5′-H), 7.17 (1 H, br d, *J* 8.2, Ar), 7.50 (1 H, t, *J* 2.6, Ar), 7.50 (1 H, t, *J* 2.6, Ar), 7.55 (1 H, d, *J* 8.5, Ar), 7.69 (1 H, s, Ar), 11.45 (1 H, s, NH), 11.55 (1 H, s, NH); δ_C(75 MHz; DMSO-d_6; DMSO) 16.20 (d, *J* 6.1), 24.93, 26.77, 61.31 (d, *J* 5.1), 61.36 (d, *J* 5.2), 84.50, 84.59, 88.63 (d, *J* 23.2), 92.37, 101.89, 103.39, 104.30, 111.91, 112.72, 118.83 (d, *J* 182.4), 123.25, 127.22, 127.39, 149.20 (d, *J* 5.4), 150.95, 156.87, 162.26; δ_P(121 MHz; DMSO-d_6; H_3PO_4) 17.62 (s); *m/z* (ESI) 532.1837 (M+H$^+$. $C_{25}H_{31}N_3O_8P^+$ requires 532.1843).

Diethyl (*E*)-2-((3a*R*,4*R*,6*R*,6a*R*)-6-(2,4-dioxo-6-styryl-3,4-dihydropyrimidin-1(2*H*)-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)vinylphosphonate 13m

Phosphonate **13m** was obtained as a colorless oil (76.5 mg, 80%) δ_H(300 MHz; DMSO-d_6; Me_4Si) 1.22 (6 H, t, *J* 7.0, 2×OCH$_2$CH_3), 1.28 (3 H, s, CH$_3$), 1.46 (3 H, s, CH$_3$), 3.96 (4 H, m, 2 × CH$_2$), 4.63 (1 H, m, 4′-H), 4.86 (1 H, dd, $J_{3',2'}$ 6.2, $J_{3',4'}$ 4.1, 3′-H), 5.29 (1 H, d, $J_{2',3'}$ 6.4, 2′-H), 5.79 (1 H, s, 1′-H), 5.85 (1 H, d, $J_{5,NH}$ 2.3 Hz, 5-H), 5.99 (1 H, ddd, $J_{6',4'}$ 1.5, $J_{6',5'}$ 17.3, $J_{6',P}$ 19.7, 6′-H), 6.71 (1 H, ddd, $J_{5',4'}$ 6.2, $J_{5',6'}$ 17.0, $J_{H5',P}$ 23.1, 5′-H), 7.09 (1 H, d, *J* 15.8, CH=CH–Ph), 7.30 (1 H, d, *J* 16.1, CH=CH–Ph), 7.39–7.47 (3 H, m, Ar), 7.68 (2 H, m, Ar), 11.49 (1 H, s, NH); δ_C(75 MHz; DMSO-d_6; DMSO) 16.15, 16.23, 25.01, 26.90, 61.30 (d, *J* 5.3), 61.36 (d, *J* 5.2), 84.24, 84.35, 88.31 (d, *J* 24.3), 91.81, 100.67, 112.94, 118.56 (d, *J* 183.6), 118.88, 127.81, 128.88, 129.59, 134.99, 138.42, 148.89 (d, *J* 5.0), 150.62, 153.00, 162.56; δ_P(121 MHz; DMSO-d_6; H_3PO_4) 17.53 (s); *m/z* 519.1889 (ESI) (M+H$^+$. $C_{25}H_{32}N_2O_8P^+$ requires 519.1891).

Preparation of saturated nucleoside phosphonates 21: General procedure

The vinyl phosphonates **13** (0.2 mmol) were dissolved in MeOH (5 cm^3) and $Pd(OH)_2/C$ (12 mg) was added. The resulting suspension was stirred under hydrogen atmosphere for 48 h. The catalyst was filtered off, and the filtrate was evaporated to dryness and purified by column chromatography (EtOAc : Acetone : EtOH : H_2O, 42 : 6 : 1 : 1) to give the desired products **21**.

Diethyl 2-((3a*R*,4*R*,6*R*,6a*R*)-6-(2,4-dioxo-6-phenyl-3,4-dihydropyrimidin-1(2*H*)-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)ethylphosphonate 21a

The title compound was obtained from **13a** (423 mg, 0.86 mmol) as a colorless oil (383 mg, 90%) δ_H(300 MHz; DMSO-d_6; Me_4Si) 1.22 (6 H, t, *J* 7.1, 2×OCH_2CH_3), 1.23 (3 H, s, CH_3), 1.28 (3 H, s, CH_3), 1.80 (4H, m, 5′-H+6′-H), 3.88 (1 H, m, 4′-H), 3.95 (4 H, m, 2 × CH_2), 4.65 (1 H, dd, $J_{3',2'}$ 1.0, $J_{3',4'}$ 5.5, 3′-H), 5.22 (1 H, d, $J_{2',3'}$ 1.0, 2′-H), 5.24 (1 H, s, 1′-H), 5.53 (1 H, s, 5-H), 7.47–7.57 (5 H, m, Ar), 11.58 (1 H, br s, NH); δ_C(75 MHz; DMSO-d_6; DMSO) 16.23, 16.31, 20.87(d, *J* 140.4), 25.18, 25.80(d, *J* 4.4), 27.00, 60.89 (d, *J* 2.7), 60.97 (d, *J* 2.7), 83.34, 83.84, 87.18 (d, *J* 18.0), 93.09, 102.59, 112.73, 128.09, 128.99, 130.34, 132.74, 150.54, 155.18, 162.18; δ_P(121 MHz; DMSO-d_6; H_3PO_4) 31.81; *m/z* 495.1891 (ESI) (M+H^+. $C_{23}H_{30}N_2O_8P^+$ requires 495.1891).

Diethyl 2-((3a*R*,4*R*,6*R*,6a*R*)-2,2-dimethyl-6-(6-(naphthalen-2-yl)-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydro-furo[3,4-*d*][1,3]dioxol-4-yl)ethylphosphonate 21b

The title compound was obtained from **13b** (126 mg, 0.23 mmol) as a colorless oil (111 mg, 88%) δ_H(300 MHz; DMSO-d_6; Me_4Si) 1.22 (12 H, m, 2×OCH_2CH_3 + 2×CH_3), 1.75–1.90 (4H, m, 5′-H+6′-H), 3.82 (1 H, m, 4′-H), 3.98 (4 H, m, 2 × CH_2), 4.66 (1 H, dd, $J_{3',2'}$ 4.7, $J_{3',4'}$ 5.8, 3′-H), 5.23 (2 H, br s, 2′-H+1′-H), 5.66 (1 H, s, 5-H), 7.55–7.69 (3 H, m, Ar), 8.01–8.11 (4 H, m, Ar), 11.62 (1 H, br s, NH); δ_C(75 MHz; DMSO-d_6; DMSO) 16.23, 16.31, 20.86(d, *J* 140.4), 25.15, 25.77, 26.95, 60.88 (d, *J* 2.5), 60.97 (d, *J* 2.4), 83.34, 83.91, 87.17 (d, *J* 17.1), 91.76 (s), 103.88 (s), 112.69 (s), 127.24 (s), 127.78 (2C, s), 128.44 (2C, s), 128.44 (2C, s), 130.15 (s), 132.35 (s), 133.16 (s), 150.58 (s), 155.16 (s), 162.22 (s); δ_P(121 MHz; DMSO-d_6; H_3PO_4) 31.75 (s); *m/z* 545.2045 (ESI) (M+H^+. $C_{27}H_{34}N_2O_8P^+$ requires 545.2047).

Diethyl 2-((3aR,4R,6R,6aR)-6-(2,4-dioxo-6-*m*-tolyl-3,4-dihydropyrimidin-1(2H)-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)ethylphosphonate 21f

The title compound was obtained from **13f** (71 mg, 0.14 mmol) as a colorless oil (63 mg, 88%) δ_H(300 MHz; DMSO-d_6; Me_4Si) 1.22 (6 H, t, *J* 7.0, 2×OCH_2CH_3), 1.24 (3 H, s, CH_3), 1.29 (3 H, s, CH_3), 1.67–1.90 (4 H, m, 5′-H+6′-H), 2.37 (3 H, s, CH_3), 3.83 (1 H,dd, $J_{4',3'}$5.9, $J_{4',3'}$ 10.5, 4′-H), 3.97 (4 H, m, 2 × CH_2), 4.64 (1 H, dd, $J_{3',2'}$ 6.2 Hz, $J_{3',4'}$ 4.8, 3′-H), 5.24 (1 H, d, $J_{2',3'}$ 6.2, 2′-H), 5.27 (1 H, s, 1′-H), 5.51 (1 H, d, $J_{5,NH}$ 2.1, 5-H), 7.35–7.50 (4 H, m, Ar), 11.56 (1 H, d, $J_{NH,\,H5}$ 1.2, NH); δ_C(75 MHz; DMSO-d_6; DMSO) 16.23, 16.30, 20.85(d, *J* 140.4), 20.88, 25.18, 25.76 (d, *J* 4.4), 26.98, 60.88 (d, *J* 2.9), 60.96 (d, *J* 2.9), 83.30, 83.80, 87.03 (d, *J* 18.2), 91.63, 103.35, 112.70, 128.78, 130.94, 132.66, 138.48, 150.53, 155.31, 162.19; δ_P(121 MHz; DMSO-d_6; H_3PO_4) 31.80; *m/z* 509.2052 (ESI) (M+H^+. $C_{24}H_{34}N_2O_8P^+$ requires 509.2047).

Diethyl 2-((3a*R*,4*R*,6*R*,6a*R*)-6-(6-(3-methoxyphenyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,2-dimethyltetra-hydrofuro[3,4-*d*][1,3]dioxol-4-yl)ethylphosphonate 21g

The title compound was obtained from **13g** (98 mg, 0.19 mmol) as a colorless oil (96 mg, 97%) δ_H(300 MHz; DMSO-d_6; Me_4Si) 1.22 (6 H, t, *J* 7.2, 2×OCH_2CH_3), 1.24 (3 H, s, CH_3), 1.30 (3 H, s, CH_3), 1.71–1.87 (4 H, m, 5′-H+6′-H), 3.81 (4 H, m, 4′-H + OCH_3), 3.97 (4 H, m, 2 × CH_2), 4.64 (1 H, dd, $J_{3',2'}$ 1.2, $J_{3',4'}$ 6.4, 3′-H), 5.25 (1 H, d, $J_{2',3'}$ 1.2, 2′-H), 5.27 (1 H, s, 1′-H), 5.53 (1 H, s, 5-H), 7.04–7.46 (5 H, m, Ar), 7.49 (5 H, t, *J* 8.2, Ar), 11.57 (1 H, br s, NH); δ_C(75 MHz; DMSO-d_6; DMSO) 16.22, 16.31, 20.87(d, *J* 140.8), 25.19, 25.74(d, *J* 4.9), 27.01, 55.27, 60.88 (d, *J* 2.9), 60.96 (d, *J* 2.9), 83.30, 83.87, 87.07 (d, *J* 17.4), 91.65, 103.36, 112.78, 113.48, 116.20, 120.18, 130.25, 133.92, 150.53, 154.96, 159.19, 162.23; δ_P(121 MHz; DMSO-d_6; H_3PO_4) 31.80; *m/z* 525.2001 (ESI) (M+H^+. $C_{24}H_{34}N_2O_9P^+$ requires 525.1996).

Diethyl 2-((3aR,4R,6R,6aR)-6-(6-(4-fluorophenyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2,2-dimethyltetrahydro-furo[3,4-d][1,3]dioxol-4-yl)ethylphosphonate 13h

The title compound was obtained from **21h** (55 mg, 0.11 mmol) as a colorless oil (45 mg, 82%) δ_H(300 MHz; DMSO-d_6; Me_4Si) 1.22 (6 H, t, *J* 7.0, 2×OCH_2CH_3), 1.23 (3 H, s, CH_3), 1.29 (3 H, s, CH_3), 1.72–1.88 (4 H, m, 5′-H+6′-H), 3.84 (1 H,dd, *J* 6.8, *J* 11.4, 4′-H), 3.97 (4 H, m, 2 × CH_2), 4.65 (1 H, dd, $J_{3',2'}$ 6.2 Hz, $J_{3',4'}$ 4.7, 3′-H), 5.19 (1 H, d, $J_{1',2'}$ 1.2, 1′-H), 5.24 (1 H, dd, $J_{2',1'}$ 1.2, $J_{2',3'}$ 6.4, 2′-H), 5.54 (1 H, s, 5-H), 7.36–7.45 (2 H, m, Ar), 7.53–7.58 (2 H, m, Ar), 11.59 (1 H, s, NH); δ_C(75 MHz; DMSO-d_6; DMSO) 16.23, 16.30, 20.88 (d, *J* 140.4), 25.18, 25.83 (d, *J* 4.5), 27.00, 60.88 (d, *J* 2.5), 60.96 (d, *J* 2.5), 83.35, 83.80, 87.25 (d, *J* 18.3), 91.70, 103.83, 112. 67, 116.10 (2C, d, *J* 21.8), 129.16 (2C, d, *J* 3.3), 130.76 (d, *J* 7.7), 150.53, 154.17, 162.17, 162.98 (2C, d, *J* 248.2); δ_P(121 MHz; DMSO-d_6; H_3PO_4) 31.82; δ_P(282 MHz; DMSO-d_6; CCl_3F) 90.13; *m/z* 513.1797 (ESI) (M+H^+. $C_{23}H_{31}FN_2O_8P^+$ requires 513.1797).

Diethyl 2-((3a*R*,4*R*,6*R*,6a*R*)-6-(2,4-dioxo-6-p-tolyl-3,4-dihydropyrimidin-1(2*H*)-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)ethylphosphonate 21k

The title compound was obtained from **13k** (98 mg, 0.19 mmol) as a colorless oil (93 mg, 95%) δ_H(300 MHz; DMSO-d_6; Me_4Si) 1.22 (6 H, t, *J* 7.0, 2×OCH_2CH_3), 1.23 (3 H, s, CH_3), 1.30 (3 H, s, CH_3), 1.72–1.85 (4 H, m, 5′-H+6′-H), 2.38 (3 H, s, CH_3), 3.56 (1 H,dd, $J_{4',3'}$5.9, $J_{4',3'}$ 10.5, 4′-H), 3.97 (4 H, m, 2 × CH_2), 4.65 (1 H, dd, $J_{3',2'}$ 6.4 Hz, $J_{3',4'}$ 5.9, 3′-H), 5.22 (1 H, d, $J_{2',3'}$ 6.4, 2′-H), 5.28 (1 H, s, 1′-H), 5.49 (1 H, d, $J_{5,NH}$ 2.3, 5-H), 7.36 (4 H, m, Ar), 11.55 (1 H, d, $J_{NH,\,H5}$ 2.3, NH); δ_C(75 MHz; DMSO-d_6; DMSO) 16.22, 16.30, 20.86 (d, *J* 140.4), 20.87, 25.15, 25.76 (d, *J* 4.5), 27.02, 60.88 (d, *J* 2.6), 60.96 (d, *J* 2.6), 83.94, 84.32, 87.20 (d, *J* 18.3), 91.51, 103.33, 112.67, 127.99, 129.51, 129.86, 140.20, 150.59, 155.31, 162.19; δ_P(121 MHz; DMSO-d_6; H_3PO_4) 31.74; *m/z* 509.2053 (ESI) (M+H^+. $C_{24}H_{34}N_2O_8P^+$ requires 509.2047).

Diethyl 2-((3a*R*,4*R*,6*R*,6a*R*)-6-(2,4-dioxo-6-phenethyl-3,4-dihydropyrimidin-1(2*H*)-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)ethylphosphonate 21n

The title compound **21n** was obtained from **13m** (124 mg, 0.24 mmol) as a colorless oil (124 mg, 99%) δ_H(300 MHz; DMSO-d_6; Me_4Si) 1.21 (6 H, t, J 7.0, 2×OCH_2CH_3), 1.23 (3 H, s, CH_3), 1.30 (3 H, s, CH_3), 1.70–1.90 (4 H, m, 5′-H+6′-H), 2.88 (4 H, s, 2×CH_2), 3.96 (4 H, m, 2 × CH_2), 4.01 (1 H, m, 4′-H), 4.70 (1 H, dd, $J_{3',2'}$ 4.7, $J_{3',4'}$ 6.3, 3′-H), 5.25 (1 H, dd, $J_{2',1'}$ 0.8, $J_{2',3'}$ 6.5, 2′-H), 5.45 (1 H, s, 1′-H), 5.70 (1 H, s, 5-H), 7.19–7.33 (5 H, m, Ar), 11.35 (1 H, br s, NH); δ_C(75 MHz; DMSO-d_6; DMSO) 16.22 (s), 16.30 (s), 20.87(d, J 141.0), 25.30 (s), 25.81(d, J 4.4), 27.17 (s), 32.92 (s), 33.60 (s), 60.90 (d, J 3.3), 60.94 (d, J 3.3), 83.39 (s), 84.14 (s), 87.47 (d, J 17.6), 90.29 (s), 101.98 (s), 113.06 (s), 126.38 (s), 128.35 (2C, s), 128.43 (2C, s), 139.61 (s), 150.66 (s), 154.93 (s), 162.41 (s); δ_P(121 MHz; DMSO-d_6; H_3PO_4) 31.74 (s); m/z 523.2204 (ESI) ($M+H^+$. $C_{23}H_{30}N_2O_8P^+$ requires 523.2201).

(*E*)-2-((3a*R*,4*R*,6*R*,6a*R*)-6-(2,4-dioxo-6-phenyl-3,4-dihydropyrimidin-1(2*H*)-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)vinylphosphonic acid 19a

TMSBr (0.86 cm^3, 6.5 mmol) was added to a solution of **13a** (320 mg, 0.65 mmol) in CH_2Cl_2 (15 cm^3) under argon and the resulting mixture was stirred for 24 h at rt. After evaporation of the solvents and co-distillation with toluene (3 × 25 cm^3), the residue was dissolved in water (35 cm^3) and washed with Et_2O (2 × 25 cm^3). The water phase was immediately frozen and lyophilized to afford the compound **19a** (276 cm^3, 97%) as a white hygroscopic powder. δ_H(300 MHz; D_2O; dioxane) 1.34 (3 H, s, CH_3), 1.39 (3 H, s, CH_3), 4.57 (1 H, dddd, $J_{4',5'}$ 5.8, $J_{4',3'}$ 4.4, $J_{4',P}$ 2.9, $J_{4',6'}$ 1.5, 4′-H), 4.98 (1 H, dd, $J_{3',2'}$ 6.3, $J_{3',4'}$ 4.4, 3′-H), 5.43 (1 H, dd, $J_{2',1'}$ 1.1, $J_{2',3'}$ 6.3, 2′-H), 5.58 (1 H, d, $J_{1',2'}$ 1.2, 1′-H), 5.78 (1 H, s, 5-H), 6.07 (1 H, ddd, $J_{6',4'}$ 1.5, $J_{6',5'}$ 17.2, $J_{H6',P}$ 18.8, 6′-H), 6.63 (1 H, ddd, $J_{5',4'}$ 5.8, $J_{5',6'}$ 17.2, $J_{H5',P}$ 21.4, 5′-H), 7.46–7.63 (5 H, s, Ar); δ_P(121 MHz; D_2O; H_3PO_4) 13.78; m/z 435.0969 (negESI) ($M - H^+$. $C_{19}H_{22}N_2O_8P^+$requires 435.0963).

(*E*)-2-((2*R*,3*S*,4*R*,5*R*)-5-(2,4-dioxo-6-phenyl-3,4-dihydropyrimidin-1(2*H*)-yl)-3,4-dihydroxytetrahydrofuran-2-yl)vinylphosphonic acid 20a

To an ice-cooled solution of phosphonic acid **19a** (246 mg, 0.56 mmol) in water (6 cm^3), TFA (50%, 6 cm^3) was added. After removal of the ice bath, the mixture was stirred under exclusion of light for 2 h at rt. Evaporation of the solvent and multiple co-distillation with water (5 × 15 cm^3) afforded the crude product, which was crystallized from an EtOH–Et_2O mixture to give extremely hygroscopic crystals (95 mg, 40%), which according to ^{1}H NMR contain EtOH (3.9%) and Et_2O (1.9%). δ_H(300 MHz; DMSO-d_6; Me_4Si) 4.12–4.19 (1 H, m, 4′-H), 4.31 (1 H, dd, $J_{3',2'}$ 6.4, $J_{3',4'}$ 7.9, 3′-H), 4.73 (1 H, dd, $J_{2',1'}$ 2.7, $J_{2',3'}$ 6.3, 2′-H), 5.33 (1 H, d, $J_{1',2'}$ 2.7, 1′-H), 5.75 (1 H, s, 5-H), 6.15 (1 H, ddd, $J_{6',4'}$ 1.2, $J_{6',5'}$ 17.2, $J_{H6',P}$ 19.4, 6′-H), 6.61 (1 H, ddd, $J_{5',4'}$ 6.0, $J_{5',6'}$ 17.2, $J_{H5',P}$ 21.7, 5′-H), 7.46–7.63 (5 H, s, Ar); δ_C(75 MHz; D_2O; EtOH) 72.47, 73.60, 83.24 (d, J 23.2), 94.40, 104.44, 123.72 (d, J 179.1), 128.66, 129.67, 131.48, 132.54, 144.17 (d, J 5.2), 152.08, 158.45, 165.70; δ_P(121 MHz; D_2O; H_3PO_4) 14.19; m/z 397.0799 (ESI) ($M+H^+$. $C_{16}H_{18}N_2O_8P^+$ requires 397,0795).

Deprotection of final nucleoside phosphonates 20 and 22: General procedure

The phosphonic diester (0.2 mmol) was dissolved in CH_2Cl_2 (4 cm^3) under argon. TMSBr (0.528 cm^3, 4 mmol) was added and the resulting solution was stirred for 18 h. The solvents were evaporated and the residue was co-distilled with toluene (2 × 10 cm^3). Then, water (2 cm^3) was added followed by TFA (50%, 4 cm^3) and the mixture was stirred for 2 h. The solvent was evaporated, the residue was co-distilled with water (5 × 10 cm^3) and subsequently partioned between EtOAc–Et_2O (1 : 1, 10 cm^3) and water (25 cm^3). The organic phase was washed with water (15 cm^3) and the water layers were combined and evaporated to afford the final product. The purity of all final compounds (>95%) was confirmed by LC-MS, the substances that did not meet this standard were further purified by C_{18} (Phenomenex Luna 250 × 21.20 mm 5 µm) RP-HPLC with an elution gradient of 10–100% B over 18 min, where A is 0.1% formic acid in H_2O and B is 0.1% formic acid in CH_3CN.

2-((2*R*,3*S*,4*R*,5*R*)-5-(2,4-dioxo-6-phenyl-3,4-dihydropyri-midin-1(2*H*)-yl)-3,4-dihydroxytetrahydrofuran-2-yl)ethyl-phosphonic acid 22a

Phosphonic acid **22a** was obtained from **21a** (335 mg, 0.68 mmol) as a white foam (58 mg, 21%) after HPLC purification. δ_H(300 MHz; DMSO-d_6; Me_4Si) 1.37–1.94 (4H, m, 5′-H+6′-H), 3.42 (1 H, dd, $J_{4',3'}$ 6.9, $J_{4',5'}$ 12.1, 4′-H), 4.01 (1 H, dd, $J_{3',2'}$ 6.8, $J_{3',4'}$ 7.1, 3′-H), 4.46 (1 H, dd, $J_{2',1'}$ 2.5, $J_{2',3'}$ 6.3, 2′-H), 5.00 (1 H, d, $J_{1',2'}$ 2.5, 1′-H), 5.50 (1 H, s, 5-H), 7.44–7.59 (5 H, m, Ar), 11.45 (1 H, s, NH); δ_C(75 MHz; D_2O, EtOH) 23.52 (d, J 135.6), 26.17 (d, J 3.7), 58.05, 72.33, 72.74, 83.03 (d, J 17.8), 93.93, 104.39; 128.71, 129.64, 131.42, 132.62, 152.09, 158.62, 165.84; δ_P(121 MHz; D_2O; H_3PO_4) 28.30; m/z 399.0948 (ESI) ($M+H^+$. $C_{16}H_{20}N_2O_8P^+$ requires 399.0952).

(*E*)-2-((2*R*,3*S*,4*R*,5*R*)-3,4-dihydroxy-5-(6-(naphthalen-2-yl)-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-2-yl)vinylphosphonic acid 20b

The unsaturated phosphonic acid **20b** was obtained from **13b** (60 mg,0.11 mmol) as a white foam (45 mg, 91%) δ_H(300 MHz; D_2O, dioxane) 4.51 (1 H, ddd app t, J 7.0, 4′-H), 4.28 (1 H, dd, $J_{3',2'}$ 6.5, $J_{3',4'}$ 7.9, 3′-H), 4.71 (1 H, dd, $J_{2',1'}$ 2.6, $J_{2',3'}$ 6.5, 2′-H), 5.32 (1 H, d, $J_{1',2'}$ 2.6, 1′-H), 5.65 (1 H, s, 5-H), 6.12 (1 H, ddd app t, J 18.5, 6′-H), 6.55 (1 H, ddd, $J_{5',4'}$ 6.2, $J_{5',6'}$ 17.3, $J_{H5',P}$ 21.7, 5′-H), 7.44–7.47 (1 H, m, Ar), 7.62–7.68 (2 H, m, Ar), 7.93–8.00 (4 H, m, Ar); δ_C(75 MHz; DMSO-d_6; DMSO) 71.98, 73.34, 82.91 (d, J 22.7), 94.31, 103.92, 123.95 (d, J 179.6), 127.45, 127.72, 128.30, 128.47, 130.47, 132.35, 133.18, 143.42 (d, J 5.0), 150.43, 155.83, 162.22; δ_P(121 MHz; D_2O; H_3PO_4) 13.71; m/z 543.1892 (ESI) ($M+H^+$. $C_{27}H_{32}N_2O_8P^+$ requires 543.1891).

2-((2*R*,3*S*,4*R*,5*R*)-3,4-dihydroxy-5-(6-(naphthalen-2-yl)-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-2-yl)ethylphosphonic acid 22b

Phosphonic acid **22b** was obtained from **21b** (99 mg, 0.18 mmol) as a pale beige foam (66 mg, 81%) δ_H(300 MHz; DMSO-d_6; Me_4Si) 1.55–1.91(4H, m, 5′-H+6′-H), 3.42 (1 H, dd, $J_{4',3'}$ 6.1, $J_{4',5'}$ 11.39,

4′-H), 4.02 (1 H, dd, $J_{3',2'} = J_{3',4'}$ 7.1, 3′-H), 4.50 (1 H, dd, $J_{2',1'}$ 2.1, $J_{2',3'}$ 5.9, 2′-H), 5.05 (1 H, d, J 2.1, 1′-H), 5.64(1 H, d, J 2.1, 5-H), 7.57–7.69 (3 H, m, Ar), 7.99–8.13 (4 H, m, Ar), 11.51 (1 H, d, J 1.9, NH); δ_C(75 MHz; DMSO-d_6; DMSO) 23.61(d, J 137.7), 25.95 (d, J 3.3), 71.95, 72.09, 82.36 (d, J 18.0), 93.98, 103.84, 127.13, 127.66, 128.24, 128.47, 130.54, 132.33, 133.18, 150.38, 155.91, 162.23; δ_P(121 MHz; DMSO-d_6; H_3PO_4) 27.03; m/z 447.0970 (negESI) ($M - H^+$. $C_{20}H_{20}N_2O_8P^+$ requires 447.0963).

(*E*)-2-((2*R*,3*S*,4*R*,5*R*)-5-(2,4-dioxo-6-m-tolyl-3,4-dihydropyri-midin-1(2*H*)-yl)-3,4-dihydroxytetrahydrofuran-2-yl)vinyl-phosphonic acid 20f

The unsaturated phosphonic acid **20f** was obtained from **13f** (71 mg, 0.14 mmol) as a pale beige foam (50 mg, 87%) δ_H(300 MHz; DMSO-d_6; Me_4Si) 2.37 (3H, s, CH_3), 3.97 (1 H, ddd, J 1.8, J 6.2, J 7.6, 4′-H), 4.12 (1 H, dd, $J_{3',2'}$ 6.4, $J_{3',4'}$ 7.3, 3′-H), 4.49 (1 H, dd, $J_{2',1'}$ 2.3, $J_{2',3'}$ 5.9, 2′-H), 5.01 (1 H, d, $J_{1',2'}$ 2.3, 1′-H), 5.50 (1 H, d, $J_{5,NH}$ 2.1, 5-H), 5.92 (1 H, ddd, J 1.2, J 17.3, J 18.7, 6′-H), 6.43 (1 H, ddd, $J_{5',4'}$ 6.2, $J_{5',6'}$ 17.3, $J_{H5',P}$ 21.4, 5′-H), 7.27–7.43 (4 H, m, Ar), 11.48 (1H, d, $J_{NH,5}$ 2.1, NH); δ_C(75 MHz; DMSO-d_6; DMSO) 20.93, 72.04, 73.33, 82.52 (d, J 22.7), 94.14, 103.41, 123.91 (d, J 179.7), 128.67, 130.84, 132.96, 138.33, 143.48 (d, J 5.0), 150.43, 154.94, 162.19; δ_P(121 MHz; D_2O; H_3PO_4) 12.36; m/z 411.0952 (ESI) ($M+H^+$. $C_{17}H_{20}N_2O_8P^+$ requires 411.0952).

2-((2*R*,3*S*,4*R*,5*R*)-5-(2,4-dioxo-6-m-tolyl-3,4-dihydropyri-midin-1(2H)-yl)-3,4-dihydroxytetrahydrofuran-2-yl)ethyl-phosphonic acid 22f

Phosphonic acid **22f** was obtained from **21f** (59 mg, 0.12 mmol) as a white foam (15 mg, 30%) after HPLC purification. δ_H(300 MHz; DMSO-d_6; Me_4Si) 1.45–1.90 (4H, m, 5′-H+6′-H), 1.83 (3H, s, CH_3), 2.36 (3H, s, CH_3), 3.42 (1 H, dd, $J_{4',3'}$ 7.0, $J_{4',5'}$ 12.0, 4′-H), 3.99 (1 H, dd, $J_{3',2'}$ 6.7, $J_{3',4'}$ 7.0, 3′-H), 4.44 (1 H, dd, $J_{2',1'}$ 2.6, $J_{2',3'}$ 6.4, 2′-H), 5.01 (1 H, d, $J_{1',2'}$ 2.6, 1′-H), 5.48 (1 H, s, 5-H), 7.27–7.54 (2 H, m, Ar), 7.54–7.58 (2 H, m, Ar), 11.43 (1 H, s, NH); δ_C(75 MHz; D_2O, dioxane) 21.06, 24.08 (d, J 134.9), 26.61 (d, J 3.8), 72.36, 72.75, 83.26 (d, J 17.7), 93.91, 104.16; 129.52, 132.01, 132.58, 140.04, 152.07, 158.76, 165.83; δ_P(121 MHz; D_2O; H_3PO_4) 26.15; m/z 413.1110 (ESI) ($M+H^+$. $C_{20}H_{20}N_2O_8P^+$ requires 413.1108).

(*E*)-2-((2*R*,3*S*,4*R*,5*R*)-3,4-dihydroxy-5-(6-(3-methoxyphenyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-2-yl)vinylphosphonic acid 20g

The unsaturated phosphonic acid **20g** was obtained from **13g** (51 mg, 0.10 mmol) as a white foam (40 mg, 96%) δ_H(300 MHz; DMSO-d_6; Me_4Si) 3.81 (3H, s, CH_3), 3.98 (1 H, app t, J 6.5, 4′-H), 4.16 (1 H, dd, $J_{3',2'}$ 6.4, $J_{3',4'}$ 7.2, 3′-H), 4.51 (1 H, dd, $J_{2-,1-}$ 2.5, $J_{2-,3-}$ 6.1, 2—H), 5.09 (1 H, d, $J_{1',2'}$ 2.5, 1′-H), 5.55 (1 H, d, $J_{5,NH}$ 2.2, 5-H), 5.92 (1 H, ddd, $J_{6',4'}$ 1.2, $J_{6',5'}$ 17.4, $J_{H6',P}$ 18.8, 6′-H), 6.43 (1 H, ddd, $J_{5',4'}$ 6.1, $J_{5',6'}$ 17.1, $J_{H5',P}$ 21.2, 5′-H), 7.01–7.13 (3 H, m, Ar), 7.43 (1H, dd, J 8.8 and 4.1 Hz), 11.49 (1H, d, $J_{NH,5}$ 2.0, NH); δ_C(75 MHz; D_2O; EtOH) 56.17, 72.42, 73.63, 83.46 (d, J 22.7), 94.39, 104.32, 117.32, 125.16 (d, J 177.2), 131.12, 133.82, 143.00 (d, J 5.2), 152.08, 158.07, 159.69, 165.83; δ_P(121 MHz; D_2O; H_3PO_4) 13.11; m/z 427.0901 (ESI) ($M+H^+$. $C_{17}H_{20}N_2O_9P^+$ requires 427.0901).

2-((2*R*,3*S*,4*R*,5*R*)-3,4-dihydroxy-5-(6-(3-methoxyphenyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-2-yl)ethylphosphonic acid 22g

Phosphonic acid **22g** was obtained from **21g** (66 mg, 0.13 mmol) as a white foam (51 mg, 94%) δ_H(300 MHz; DMSO-d_6; Me_4Si) 1.47–1.93 (4H, m, 5′-H+6′-H), 3.81 (3H, s, CH_3), 3.43 (1 H, dt, $J_{4',3'}$ 7.6, $J_{4',5'}$ 15.7, 4′-H), 4.02 (1 H, dd, $J_{3',2'}$ 6.6, $J_{3',4'}$ 7.2, 3′-H), 4.47 (1 H, dd, $J_{2',1'}$ 2.5, $J_{2',3'}$ 6.2, 2′-H), 5.02 (1 H, d, $J_{1',2'}$ 2.5, 1′-H), 5.48 (1 H, d, $J_{5,NH}$ 2.2, 5-H), 7.03–7.14 (2 H, m, Ar), 7.39–7.50 (2 H, m, Ar), 11.45 (1 H, d, $J_{NH,5}$ 2.0, NH); δ_C(75 MHz; D_2O, EtOH) 23.27 (d, J 134.9), 26.61 (br s), 56.17, 72.31, 72.75, 82.90 (d, J 18.0), 93.98, 104.26, 117.34, 131.09, 133.88, 152.05, 158.17, 159.64, 165.84; δ_P(121 MHz; D_2O; H_3PO_4) 26.77; m/z 429.1057 (ESI) ($M+H^+$. $C_{17}H_{22}N_2O_9P^+$ requires 429.1059).

(*E*)-2-((2*R*,3*S*,4*R*,5*R*)-5-(6-(4-fluorophenyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-3,4-dihydroxytetrahydrofuran-2-yl)vinylphosphonic acid 20h

The unsaturated phosphonic acid **20h** was obtained from **13h** (40 mg, 0.078 mmol) as a white foam (25 mg, 77%) after HPLC purification. δ_H(300 MHz; DMSO-d_6; Me_4Si) 3.99 (1 H, ddd app t, J 7.0, 4′-H), 4.14 (1 H, dd, $J_{3',2'}$ 6.4, $J_{3',4'}$ 7.3, 3′-H), 4.49 (1 H, dd, $J_{2',1'}$ 2.6, $J_{2',3'}$ 6.2, 2′-H), 5.02 (1 H, d, $J_{1',2'}$ 2.6, 1′-H), 5.54 (1 H, d, $J_{5,NH}$ 2.1, 5-H), 5.93 (1 H, ddd, J 0.9, J 18.5, J 18.6, 6′-H), 6.43 (1 H, ddd, $J_{5',4'}$ 6.2, $J_{5',6'}$ 17.3, $J_{H5',P}$ 21.4, 5′-H), 7.35–7.41 (2 H, m, Ar), 7.54–7.59 (2 H, m, Ar), 11.51 (1H, d, $J_{NH,5}$ 2.1, NH); δ_C(75 MHz; DMSO-d_6; DMSO) 71.91, 73.33, 82.82 (d, J 22.7), 94.11, 103.87, 115.93 (2 C, d, J 22.1), 123.94 (d, J 179.7), 129.41 (2C, d, J 3.3), 130.55 (d, J 9.9), 143.34 (d, J 4.7), 150.37, 154.77, 162.11, 162.97 (d, J 248.0); δ_P(121 MHz; D_2O; H_3PO_4) 12.33; δ_P(282 MHz; DMSO-d_6; CCl_3F) 89.87; m/z 415.0701 (ESI) ($M+H^+$. $C_{16}H_{17}FN_2O_8P^+$ requires 415.0701).

2-((2*R*,3*S*,4*R*,5*R*)-5-(6-(4-fluorophenyl)-2,4-dioxo-3,4-dihydro-pyrimidin-1(2*H*)-yl)-3,4-dihydroxytetrahydrofuran-2-yl)-ethylphosphonic acid 22h

Phosphonic acid **22h** was obtained from **21h** (40 mg, 0.078 mmol) as a white foam (16 mg, 49%) after HPLC purification. δ_H(300 MHz; DMSO-d_6; Me_4Si) 1.45–1.91 (4H, m, 5′-H+6′-H), 3.45 (1 H, dd, $J_{4',3'}$ 6.9, $J_{4',5'}$ 9.8, 4′-H), 4.00 (1 H, dd, $J_{3',2'} = J_{3',4'}$ 7.1, 3′-H), 4.46 (1 H, dd, $J_{2',1'}$ 2.6, $J_{2',3'}$ 6.3, 2′-H), 4.95 (1 H, d, $J_{1',2'}$ 2.6, 1′-H), 5.52 (1 H, d, J 2.1, 5-H), 7.35–7.54 (2 H, m, Ar), 7.54–7.58 (2 H, m, Ar), 11.47 (1 H, d, J 1.8, NH); δ_C(75 MHz; DMSO-d_6; DMSO) 23.59 (d, J 137.9), 25.98 (d, J 3.9), 71.88, 72.13, 82.37 (d, J 17.4), 93.77, 103.77, 115.89 (2 C, d, J 22.1), 129.49 (2C, d, J 3.3), 130.58 (br s), 150.32, 154.85, 162.12, 162.96 (d, J 248.2); δ_P(121 MHz; D_2O; H_3PO_4) 26.86; δ_P(282 MHz; DMSO-d_6; CCl_3F) 89.89; m/z 447.0970 (negESI) ($M - H^+$. $C_{20}H_{20}N_2O_8P^+$ requires 447.0963).

(*E*)-2-((2*R*,3*S*,4*R*,5*R*)-5-(2,4-dioxo-6-p-tolyl-3,4-dihydropyri-midin-1(2*H*)-yl)-3,4-dihydroxytetrahydrofuran-2-yl)vinyl-phosphonic acid 20k

The unsaturated phosphonic acid **20k** was obtained from **13k** (48 mg, 0.094 mmol) as a white foam (18 mg, 46%) after HPLC purification. δ_H(300 MHz; D_2O; HCOOH) 2.40 (3H, s, CH_3), 4.16

(1 H, ddd app t, *J* 6.2, *J* 7.0, 4′-H), 4.31 (1 H, dd, $J_{3',2'}$ 6.5, $J_{3',4'}$ 7.6, 3′-H), 4.73 (1 H, dd, $J_{2',1'}$ 2.6, $J_{2',3'}$ 6.5, 2′-H), 5.37 (1 H, d, $J_{1',2'}$ 2.6, 1′-H), 5.70 (1 H, s, 5-H), 6.15 (1 H, ddd, *J* 18.7, *J* 19.6, 6′-H), 6.60 (1 H, ddd, $J_{5',4'}$ 5.9, $J_{5',6'}$ 17.3, $J_{H5',P}$ 21.7, 5′-H), 7.37 (4 H, s, Ar); δ_C(75 MHz; D_2O; HCOOH) 21.14, 72.48, 73.63, 83.23 (d, *J* 22.9), 94.40, 104.21, 124.07 (d, *J* 179.9), 128.63, 129.59, 130.19, 142.38, 143.88 (d, *J* 5.0), 152.16, 158.65, 165.73; δ_P(121 MHz; D_2O; H_3PO_4) 13.92; *m/z* 411.0953 (ESI) (M+H$^+$. $C_{17}H_{20}N_2O_8P^+$ requires 411.0952).

2-((2*R*,3*S*,4*R*,5*R*)-5-(2,4-Dioxo-6-p-tolyl-3,4-dihydropyri-midin-1(2H)-yl)-3,4-dihydroxytetrahydrofuran-2-yl)ethyl-phosphonic acid 22k

Phosphonic acid **22k** was obtained from **21k** (88 mg, 0.17 mmol) as a white foam (22 mg, 30%) after HPLC purification. δ_H(300 MHz; D_2O, dioxane) 1.76–2.08 (4H, m, 5′-H+6′-H), 2.40 (3H, s, CH_3), 3.66 (1 H, dd, $J_{4',3'}$ 7.1, $J_{4',5'}$ 11.7, 4′-H), 4.19 (1 H, dd, $J_{3',2'}$ 6.4, $J_{3',4'}$ 7.1, 3′-H), 5.22 (1 H, dd, $J_{2',1'}$ 3.2, $J_{2',3'}$ 6.4, 2′-H), 5.28 (1 H, d, $J_{1',2'}$ 3.2, 1′-H), 5.74 (1 H, s, 5-H), 7.38 (4 H, s, Ar); δ_C(75 MHz; DMSO-d_6, DMSO) 21.13, 23.22 (d, *J* 136.0), 25.98 (d, *J* 3.6), 72.35, 72.76, 82.84 (d, *J* 18.0), 93.95, 104.20; 128.67, 129.70, 130.17, 142.32, 152.16, 158.82, 165.85; δ_P(121 MHz; D_2O; H_3PO_4) 29.77; *m/z* 411.0963 (negESI) (M − H$^+$. $C_{17}H_{20}N_2O_8P^-$requires 411.0963).

(E)-2-((2*R*,3*S*,4*R*,5*R*)-5-(2,4-dioxo-6-styryl-3,4-dihydropyri-midin-1(2H)-yl)-3,4-dihydroxytetrahydrofuran-2-yl)vinyl-phosphonic acid 20m

The unsaturated phosphonic acid **20m** was obtained from **13m** (48 mg, 0.092 mmol) as a yellow foam (37 mg, 95%). δ_H(300 MHz; D_2O, dioxane) 4.18 (1 H, dd, $J_{3',2'}$ 6.3, $J_{3',4'}$ 7.9, 3′-H), 4.42 (1 H, ddd app t, *J* 6.8, 4′-H), 4.44 (1 H, dd, $J_{2',1'}$ 2.4, $J_{2',3'}$ 6.2, 2′-H), 5.54 (1 H, d, $J_{1',2'}$ 2.3, 1′-H), 5.69 (1 H, s, 5-H), 6.07 (1 H, ddd, $J_{6',4'}$ 0.6, $J_{6',5'}$ 17.1, $J_{H6',P}$ 18.1, 6′-H), 6.54 (1 H, ddd, $J_{5',4'}$ 5.6, $J_{5',6'}$ 17.3, $J_{H5',P}$ 22.0, 5′-H), 6.68 (1H, d, *J* 15.8, CH═CH), 7.02 (1H, d, *J* 15.8, CH═CH), 7.21–7.26 (3 H, m, Ar), 7.30–7.37 (2 H, m, Ar); δ_C(75 MHz; D_2O, dioxane) 72.59, 73.85, 83.01 (d, *J* 23.6), 93.46, 100.81, 118.09, 123.27 (d, *J* 180.2), 128.17, 129.57, 130.89, 135.02, 140.60, 144.83 (d, *J* 5.1), 151.48, 155.73, 165.83; δ_P(121 MHz; D_2O; H_3PO_4) 14.54; *m/z* 421.0803 (negESI) (M+H$^+$. $C_{18}H_{20}N_2O_8P^+$ requires 421.0806).

2-((2*R*,3*S*,4*R*,5*R*)-5-(2,4-dioxo-6-phenethyl-3,4-dihydropyri-midin-1(2*H*)-yl)-3,4-dihydroxytetrahydrofuran-2-yl)ethyl-phosphonic acid 22n

Phosphonic acid **22n** was obtained from **21n** (88 mg, 0.17 mmol) as a white hygroscopic solid (67 mg, 93%) δ_H(300 MHz; DMSO-d_6; Me_4Si) 1.47–2.00 (4H, m, 5′-H+6′-H), 2.78–2.98 (4H, m, CH_2CH_2), 3.66 (1 H, m, 4′-H), 4.08 (1 H, dd app t, *J* 7.0, 3′-H), 4.50 (1 H, dd, $J_{2',1'}$ 2.4, $J_{2',3'}$ 6.2, 2′-H), 5.06–5.55 (~4H, br s, OH), 5.41 (1 H, d, $J_{1',2'}$ 2.5, 1′-H), 5.46 (1 H, d, $J_{5,NH}$ 1.9, 5-H), 7.17–7.36 (5 H, m, Ar), 11.23 (1 H, d, $J_{NH,5}$ 1.4, NH); δ_C(75 MHz; DMSO-d_6; DMSO) 26.03 (br s), 33.17, 34.11, 72.01, 72.17, 82.44 (br s), 92.22, 101.92; 126.35, 128.37, 128.44, 139.79, 150.40, 155.53, 162.44; δ_P(121 MHz; D_2O; H_3PO_4) 26.87; *m/z* 427.1272 (ESI) (M+H$^+$. $C_{18}H_{24}N_2O_8P^+$ requires 427.1265).

Conformational analysis

Approximately 5.0 mg of **5** and **22a** were dissolved in 600 µl D_2O. Due to solubility issues, we were forced to dissolve **9b** in DMSO-d6 (3.0 mg in 600 µl). The 1D ^{1}H spectra of each compound are shown in the ESI.†

All NMR spectra were measured on an Avance II Bruker Spectrometer operating at a ^{1}H frequency of 700 MHz and equipped with a ^{1}H/^{13}C/^{15}N TXI-z probe. The $^3J_{H1'H2'}$, $^3J_{H2'H3'}$, $^3J_{H3'H4'}$ scalar couplings were measured for each compound at five different temperatures, *i.e.* 20 °C, 27 °C, 35 °C, 42 °C and 50 °C for **5** and **22a**, and 27 °C, 35 °C, 42 °C, 50 °C and 60 °C for **9b**. The $^3J_{H1'H2'}$ scalar couplings could be measured directly from the H1′ doublet in a Gaussian resolution enhanced 1D ^{1}H spectrum. When the resonance line width was too broad, the multiplets overlapped with other multiplets or showed too complex patterns, the scalar coupling constants were determined by selectively irradiating both involved resonances during a SERF experiment.[18] This was the case for **5** and **9b**.

The 2D NOESY spectra were measured at 20 °C (27 °C in the case of **9b**), with 2048 time domain points in the direct dimension and 256 time domain points in the indirect dimension (except for **9b**, where 450 indirect time domain points were sampled). The mixing time was 600 ms for each compound. Before Fourier transform, both dimensions were multiplied with a squared cosine bell window function and zero filled until a 1024 × 1024 real data matrix was obtained. The spectra were baseline corrected using a fifth order polynomial.

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