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Expeditious convergent procedure for the preparation of bis(POC) prodrugs of new (*E*)-4-phosphono-but-2-en-1-yl nucleosides

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ABSTRACT

A series of unsaturated acyclonucleoside bis(POC) prodrugs of *E* configuration were synthesized through an expeditious, highly efficient and stereoselective one-step procedure from corresponding bis(POC)allylphosphonate through Ru catalyzed cross-coupling metathesis reaction. The [$RuCl_2(PCy_3)$(SIPr)(Indenylidene)] and [$RuCl_2(PCy_3)$(IMes)(benzylidene)] catalysts were employed; the unsaturated ANP were used bore *C*5-halovinyl uracil, *C*5-dihalovinyluracil or furanopyrimidine motifs. The chemical cleavage of biolabile (POC) group is a useful pathway to acid phosphonate derivatives.

1. Introduction

Acyclonucleoside phosphonates (ANPs)[1] represent a unique and prominent class of antiviral drugs, which has attracted considerable attention. Among ANPs, 9-[2-(phosphonomethoxy)ethyladenine (PMEA, **1a**) and its prodrug bis(POM)PMEA (**1b**),[2] or (*R*)-[2-(phosphonomethoxy)-propyl]adenine (PMPA, **2a**) and its prodrug bis(POC) PMPA (**2b**)[3] are approved for the treatment of severe viral infections (Fig. 1). Their efficiency as drugs depends on several factors, such as their cell penetration and the ability of human/viral kinases to provide their triphosphate active forms at a high concentration at the right location. ANPs possess a phosphonomethyl ether moiety and bypass the limiting first phosphorylation step.

Our laboratory recently reported a new type of antiviral acyclic nucleoside phosphonates with the (*E*)-4-phosphono-but-2′-en-1′-yl moiety.[4,5] By X-ray studies of thymidylate kinase in complex with our thymine ANP analogue **3** (TbutP) and with the natural substrate dTMP (thymidine 5′-monophosphate), we have demonstrated that only this (*E*)-but-2-enyl side-chain moiety can mimic the conformation of the C1–O4–C4–C5 atoms from the 2-deoxyribose in TMP. However, contrary to PMEA and PMPA, which exhibit in vitro cellular antiviral activities, all free phosphonate analogues were not active and required their conversion to a phosphonodiester form of reduced polarity, to exhibit pronounced in vitro antiviral activity [e.g., for (**4**): EC_{50} 3.1 μM (HSV-1), 6.1 μM (HSV-2), 0.41 μM (VZV TK^+) and 0.19 μM (VZV TK^-)].

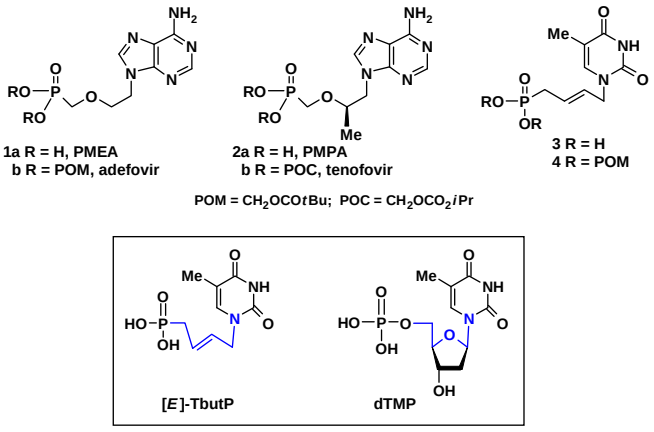

Fig. 1. Some ANPs and but-2′-enyl ANPs.

In this paper, we describe efficient convergent synthesis of effective bis(POC) prodrugs of new (*E*)-4-phosphono-but-2-en-1-yl nucleosides (**21a–f** and **23a–f**), (Fig. 2). However, due to low stability and easy hydrolysis of the disoproxil side-chain of POC moiety[6,7] compared to POM, we cannot follow the exact synthetic scheme and must design a new assembly.

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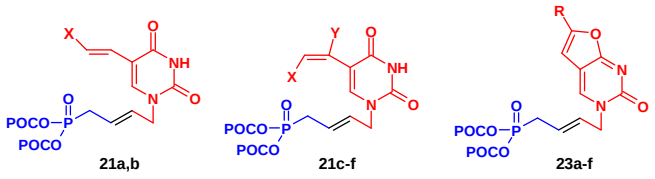
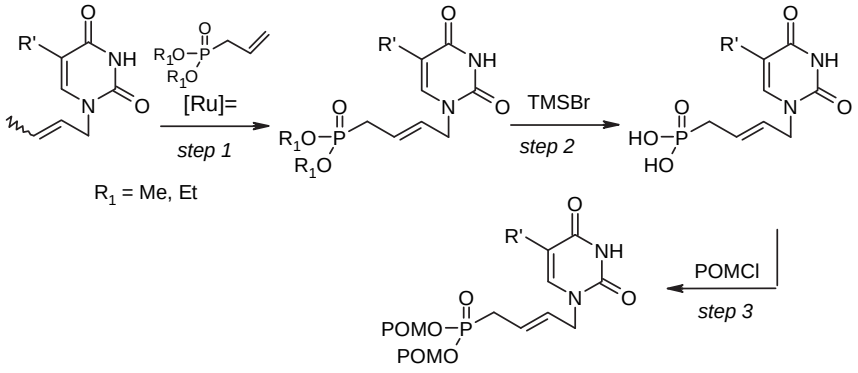


Fig. 2. Targeted new unsaturated ANP.

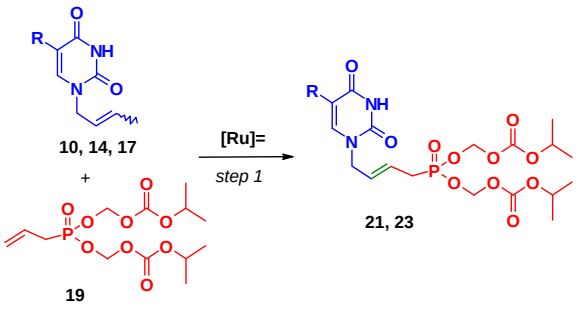
2. Results and discussion

Typically, the bis(POM)-ButP analogues of **4** were obtained in three steps[5] (Scheme 1): (step one), cross metathesis (ACM) with allylphosphonate; (step two), the hydrolysis of phosphonate diester via a Lewis acid-promoted nucleophilic dealkylation (typically, 6 equiv of TMSBr are needed). TMSBr is a strong Lewis acid which requires careful handling and anhydrous conditions. The obtained phosphonic acids are only soluble in DMF or DMSO; (step three), a base-promoted alkylation with excess of POMCl. This linear approach cannot be use for the synthesis of bis(POC) analogues.



Scheme 1. General approach to bis(POM) ANPs.

Our one-step synthetic strategy to hitherto unknown bis(POC)-*C*5-substituted-(*E*)-4-phosphono-but-2-en-1-yl acyclic nucleosides, shown in Scheme 2, directly introduces the bis(POC) phosphonate moiety through cross-coupling metathesis of the bulky bis(POC) allylphosphonate **19** with various *C*5-substituted crotylated uracils (**10a**,**b**, **14a**–**d** and **17a**–**f**). This step is the most critical point of this contribution as, based on Grubbs work,[8] generally diethyl- (or dimethyl) allylphosphonates are preferred partners for ACM.



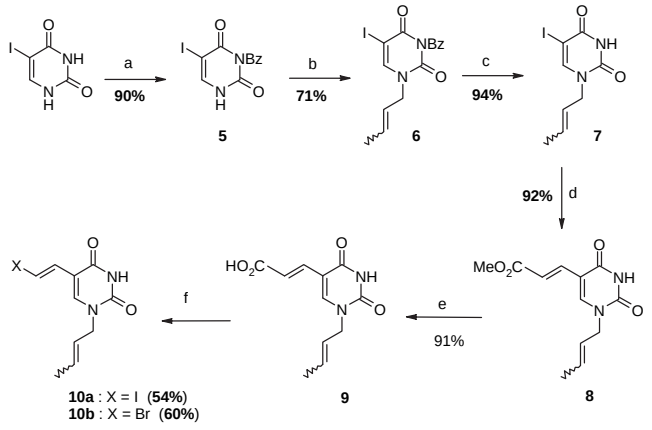
Scheme 2. General convergent approach to bis(POC) ANPs.

2.1. Preparation of N^1-crotyl-*C*5-halovinyluracil moiety

Compounds **10a**,**b** were obtained through the key intermediate N^1-crotyl-5-iodo-uracil (**7**). Thus, a regioselective N^3-benzoylation of the commercially available 5-iodo uracil afforded **5**, which was subsequently crotylated at N^1-position to **6**. A debenzoylation of **6** by treatment of ammonia in methanol solution afforded **7** in 60% overall yield (on three steps), (Scheme 3). *C*5-Acrylated uracil **8** was synthesized under conventional Pd-mediated Heck conditions in 92% yield. A saponification of **8** by NaOH (1 M) solution and subsequent acidification by HCl (6 N) afforded the pure carboxylic acid **9**. N^1-Crotyl-*C*5-iodovinyl-uracil **10a** and N^1-crotyl-*C*5-bromovinyl-uracil **10b** were prepared in moderate yield (54% and 60% yield, respectively), under Hunsdiecker–Borodin decarboxylation–halogenation reaction, by treatment with NIS or NBS, respectively, in the presence of $KHCO_3$ in DMF, insuring the vinyl functionality retention.[9] No side halogenation reaction of the crotyl double bond was observed as confirmed by ^1H and ^{13}C NMR.

2.2. Preparation of N^1-crotyl-*C*5-dihalovinyluracil moiety

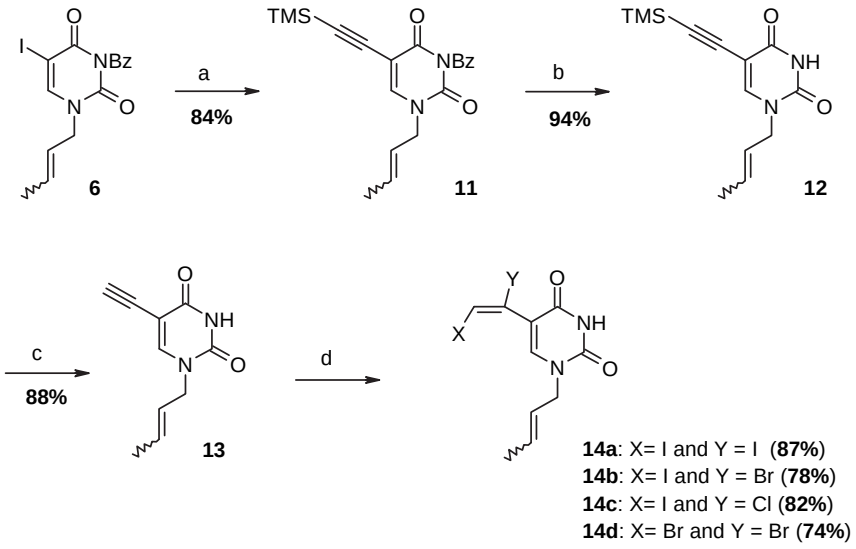
*C*5-Dihalovinyl base analogues were readily prepared following the procedure previously introduced by our team (Scheme 4). This synthesis proceeded on a Pd-catalysed coupling reaction under Sonogashira conditions.[10] Treatment of **6** with trimethylsilylacety-



Scheme 3. Reagent and conditions: (a) BzCl, MeCN/pyridine, rt, 15 h; (b) crotyl bromide, K_2CO_3, DMF, rt, 5 h; (c) NH_3/MeOH (7 N), 4 °C, 16 h; (d) PPh_3, $Pd(OAc)_2$, methyl acrylate, Et_3N, dioxane, 80 °C, 12 h; (e) NaOH 1 M, rt, 1 h, then HCl 6 N; (f) $KHCO_3$, NIS or NBS, DMF, rt, 2 h.

lene, $PdCl_2(PPh_3)_2$, Copper iodine, triethylamine in dimethylformamide afford **11** in good yield. Protected N^3-benzoyl-N^1-crotyl-*C*5-iodouracil was chosen as starting materiel because of unsuccess Sonogashira reaction[11] with N^3-H free uracil **7**. Deprotected compound **13** was obtained through successive N^3-debenzoylation followed by treatment with *n*-Bu_4NF in high efficiency.

Dihalogenation of ethynyl group was performed in MeCN at 0 °C with corresponding dihalogen I_2, IBr, ICl and Br_2 to give, respectively,

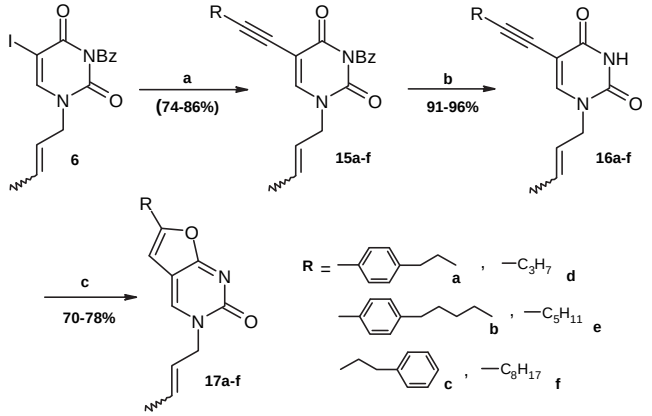


Scheme 4. Reagent and conditions: (a) $PdCl_2(PPh_3)_2$, trimethylsilyl acetylene, CuI, Et_3N, DMF, rt, 16 h; (b) NH_3/MeOH (7 N), 4 °C, 16 h; (c) *n*-Bu_4NF, rt, 2 h; (d) halogen (X–Y), MeCN, 0 °C, 3 h.

14a–**d** average 74% yield. In this case, the low temperature (0 °C) is critical to avoid halogenation of the crotyl group. For **14a**–**c**, the formation of vicinal halo-iodoalkenes occurred with exclusive *anti*-stereospecificity, through an iodonium intermediate. The regioselectivity of this dihalogenation is based on ^{13}C NMR and is in agreement with our previous publications[12] and the literature.[13]

2.3. Preparation of N^3-crotyl-6-substituted-furano-[2,3-*d*]-pyrimidin-2-one moiety

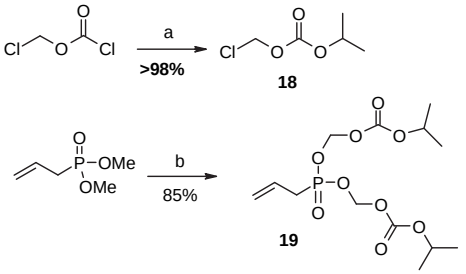
The N^3-crotyl-6-substituted-furano-[2,3-*d*]-pyrimidin-2-one was obtained from **7** through a first Sonogashira reaction yielding *C*5-substituted bases **15a**–**f** in 74–86%. After debenzoylation, the *C*5-alkynyl bases **16a**–**f** were employed in the synthesis of fused bicyclic pyrimidinone through copper-catalyzed 5-*endo*-*dig* cyclisation (Scheme 5). Compounds **16a**–**f** were then treated with CuI and Et_3N in MeOH at reflux,[14] to give the desired bicyclic derivatives **17a**–**f**, respectively, in 70% yield.



Scheme 5. Reagent and conditions: (a) $PdCl_2(PPh_3)_2$, ethynyl derivatives, CuI, NEt_3, DMF, rt, 16 h; (b) NH_3/MeOH (7 N), 4 °C, 16 h (c) CuI, Et_3N, MeOH, 70 °C, 5 h.

2.4. Preparation of bis(POC)-allylphosphonate synthon

Bis(POC)-allylphosphonate (**19**), the key compound for olefin cross metathesis with various alkenes, was obtained by reacting dimethyl allylphosphonate with freshly prepared chloromethyl isopropylcarbonate **18** in the presence of sodium iodine during 72 h (Scheme 6). Bis(POC)-allylphosphonate synthon was obtained in 85% yield without any purification but need to be stored over 3 Å molecular sieves.

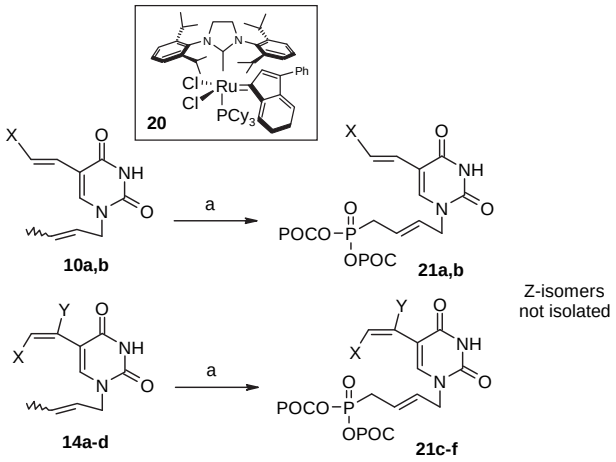


Scheme 6. Reagent and conditions: (a) *i*-PrOH, NEt_3, 0 °C; (b) NaI, **18**, MeOH, 70 °C, 72 h.

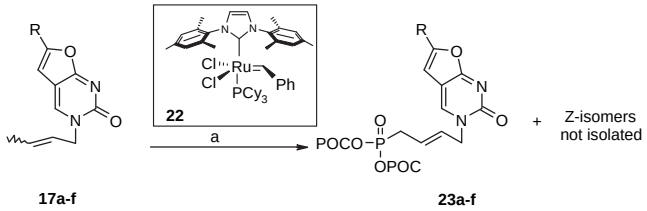
2.5. Olefin cross metathesis reaction

Since their discovery, second-generation Grubbs systems have evolved into a large family of catalysts.[15] Due to the potential instability of the *C*5-halovinyl-(**10a**,**b**) and *C*5-dihalovinyl (**14a**–**d**) moieties at solvent reflux, we have performed the olefin cross metathesis reaction at milder conditions using [$RuCl_2(PCy_3)$(SIPr)(indenylidene)] catalyst **20**,[16] which has been reported to be one of the most efficient catalyst working at room temperature. Thus, the *C*5-substituted N^1-crotylated uracil analogues **10a**,**b** and **14c**–**f**, unprotected at N^3 position, were then treated in anhydrous CH_2Cl_2 with a bis(POC) allylphosphonate **19** (1.3 equiv) and the [Ru]=catalyst **20** (5 mol%). The cross-metathesis products of major *E*- and minor *Z*-isomers (Scheme 7) were separated by column chromatography and pure **21a**–**f** (*E*-isomers) were obtained in moderate yields (40–53%). Due to the ^1H NMR signals superposition of olefinic protons, the *E*/*Z* stereochemistry at the double bond was assigned from the ^{13}C NMR by observing the signals of the allylic carbons NCH_2 at δ 49.4 ppm for the *E* isomer. This is in agreement with Goux et al.[17] and our previous work[4] (which reported a NCH_2 at $\delta \sim 48$ ppm and 44 ppm for the *E* and *Z* isomers of similar system, respectively).

For the cross metathesis of the thermally more stable N^1-crotylated analogues **17a**–**f** with bis(POC)allyl phosphonate **19** at reflux CH_2Cl_2, the thermally robust [$RuCl_2(PCy_3)$(IMes)(benzylidene)] catalyst **22**[18] was chosen (Scheme 8). The reactions gave, after purification, the *E*-isomers **23a**–**f** from 54 to 64% yields.



Scheme 7. Synthesis of *C*5-halovinyl- and *C*5-dihalovinyl-ANP derivatives. Reagent and conditions: (a) bis(POC) allylphosphonate (1.3 equiv), [Ru]=catalyst (5 mol%), CH_2Cl_2, rt.

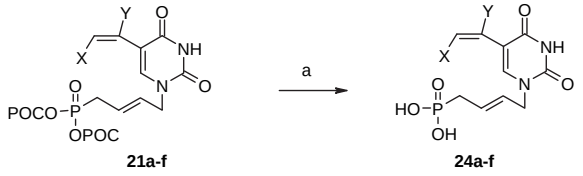


Scheme 8. Synthesis of furanopyrimidine ANP derivatives. Reagent and conditions: (a) bis(POC) allylphosphonate (1.3 equiv), [Ru]= catalyst (5 mol%), CH_2Cl_2, reflux.

For all those reactions, we did not observe any olefin isomerised by-product, which could hamper the metathesis efficiency as reported in the literature.[19]

2.6. Chemical cleavage of POC group

To study the enzymatic phosphorylation mechanism of unsaturated acyclonucleoside phosphonates by various human and viral kinases, it is necessary to have in hand those compounds under their acid form (and not the prodrug form). We thus run the cleavage of the POC moiety by carbonate saponification under soft basic conditions, in ultrapure water (Scheme 9). Among various tested basic conditions (sodium and potassium hydroxide, carbonates and hydrogenocarbonate), at different concentrations (1 M, 0.1 M, 0.05 M and 0.01 M), only hydrogenocarbonates failed to remove the POC moiety. pH measurement showed that the POC deprotection was initiated for pH ranging from 10.5 to 11.0. A 0.1 M Elga water solution of sodium hydroxide was finally chosen to achieve POC saponification at room temperature with the reaction monitored by TLC.



Scheme 9. Reagent and conditions: (a) NaOH (0.1 M Elga water), rt, 5 h then Dowex 50W8 resin (H^+ ion exchange).

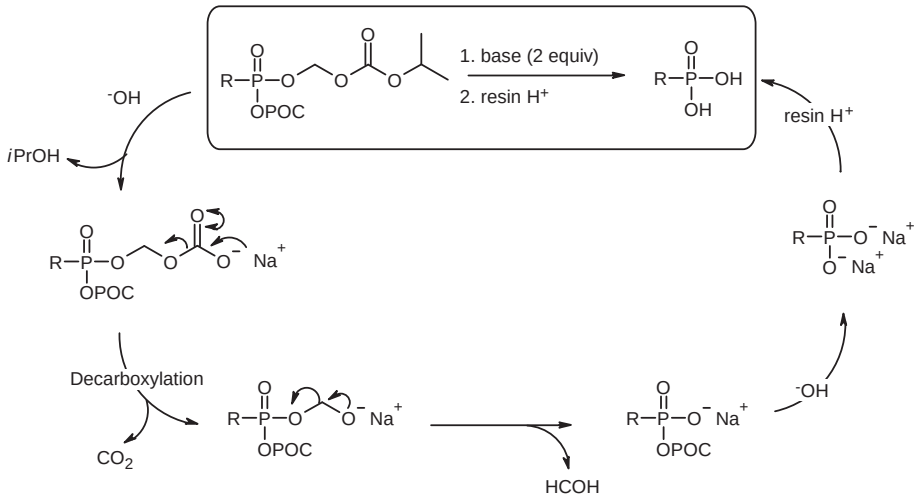
The solution containing ANP salt and an excess of base was then neutralized through a Dowex 50W8 acidic ion exchange resin cartridge to give after dichloromethane extraction and evaporation of all volatiles the pure desired acid ANPs **24a**–**f** in excellent yield (quantitative). No further purification is required.

This chemical deprotection mimics the intracellular enzymatic degradation of the POC moiety by an esterase as it leads to the desired phosphonate salt and isopropanol, CO_2 and formaldehyde as degradation products (Scheme 10).

This approach shortens the usual pathway to acid phosphonate, which is based on the harsh deprotection of a dialkylated allylphosphonate with trimethylsilylbromide (TMSBr). In our case, no by-product formation or partial deprotection was observed.

2.7. Biological activity screening

The title bis(POC) (*E*)-4-phosphono-but-2-en-1-yl acyclic nucleosides **21** and **23a**–**f** were subjected to a standard in vitro antiviral screening using a wide spectrum of viruses, in HEL and HeLa cell lines, for Vaccinia (VV), Herpes Simplex Virus-1(KOS) (HSV-1), Herpes Simplex virus-2(G) (HSV-2), Vesicular Stomatitis Virus (VSV), Varicella-Zoster Virus (VZV TK^+ and TK^-), Human Cytomegalovirus and (AD-169 strain and Davis strain) in HEL cells and Coxsackie B4, Respiratory syncytial in HeLa cells. None of the compounds exhibited



Scheme 10. Mechanism of chemical cleavage of POC group.

any significant antiviral activity or cytotoxicity in HEL and Vero cells. In order to estimate the influence of the prodrug moiety on those results, the biological activity and toxicity of acid phosphonates **24a**–**f** were also investigated but these compounds were devoid of antiviral activity. The nucleotide binding study of **24a**–**f** to (human) UMP-CMP kinase, TMP kinase and vaccinia virus TMP kinase was thus performed and no significant activities were observed.

Thus, the lack of activity of those compounds can likely be explained by the lack of an efficient phosphorylation.

3. Conclusion

In summary, an expeditious and convergent route to various bis(POC) (*E*)-4-phosphono-but-2′-en-1′-yl acyclic nucleosides based on an olefin cross metathesis has been achieved. A chemical cleavage of biolabile (POC) group was also successfully applied for the development of new ANPs. This method offers two pathways to biological interesting compounds: (1) an easy access to the bis(-POC) prodrugs for biological evaluation in which the polar character at physiological pH is masked; (2) an easy access to the free acid phosphonates for metabolic and pharmacokinetic evaluations, by a soft chemical decomposition of the bis(POC) moiety.

4. Experimental section

4.1. General

Commercially available chemicals were of reagent grade and used as received. Acetonitrile was distilled from CaH_2. The reactions were monitored by thin layer chromatography (TLC) analysis using silica gel plates (Kieselgel $60F_{254}$, E. Merck). Column chromatography was performed on Silica Gel 60 M (40–63 mm, E. Merck). Melting points are uncorrected and were measured on a Kofler apparatus. NMR spectra were recorded on a Varian InovaUnity 400 NMR spectrometer. Chemical shifts (δ) are given in parts per million relative to solvent: references for $CDCl_3$ were 7.26 ppm (^{1}H NMR) and 77.16 ppm (^{13}C NMR), for DMSO-d_6 2.50 ppm (^{1}H NMR) and 39.51 ppm (^{13}C NMR), for MeOD-d_4 3.31 ppm (^{1}H NMR) and 49.00 ppm (^{13}C NMR). For the ^{1}H and ^{13}C NMR spectra, TMS was used as the internal reference, while for the ^{31}P NMR spectra, H_3PO_4 was used as the external reference (inner-capillary method). The resonance assignments are based on peak integration, peak multiplicity and 2D correlation experiments. Multiplets were assigned as s (singlet), d (doublet), t (triplet), dd (doublet of doublet), m (multiplet), mc (centred multiplet) and br s (broad singlet). High Resolution Mass spectra were performed by the Mass Spectrometry Center of Blaise Pascal University (Program Masslynx 4.0) (Aubière, France).

4.2. N^3-Benzoyl-5-iodouracil (5)

To a solution of 5-iodouracil (1 g) in a 2/5 mixture of pyridine and acetonitrile (21 mL) was added benzoyl chloride (3 equiv). The reaction mixture was for stirred 24 h at room temperature. After evaporation of all the volatiles, the residue was purified by silica gel column chromatography (hexanes/EtOAc, 5/5 to 0/1) to give compound **5** (92%). ^{1}H NMR (250 MHz, acetone-d_6) δ 8.02 (m, 2H), 8.01 (s, 1H), 7.72 (t, J=7.5 Hz, 1H), 7.56 (t, J=7.5 Hz, 2H). ^{13}C NMR (100 MHz, acetone-d_6) δ 167.8, 159.1, 149.3, 147.9, 147.8, 135.1, 130.9, 130.4, 129.1, 67.2.

4.3. N^3-Benzoyl-N^1-crotyl-5-iodo-uracil (6)

To a DMF (12 mL) solution of N^3-benzoyl-5-iodouracil (1 g) were added K_2CO_3 (1.05 equiv) and crotyl bromide (1.05 equiv) under argon atmosphere. After 3 h stirring at room temperature, the reaction mixture was evaporated. The residue was diluted with EtOAc and then washed with an aqueous saturated NH_4Cl solution. The aqueous phase was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexanes, 3/7) to give compound **6** as colourless oil (95%) as mixture of *E*/*Z* isomers (8/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J=7.8 Hz, 2H), 7.71 (s, 1H), 7.70 (s, 1H), 7.64 (t, J=7.5, 1H), 7.48 (t, J=7.8 Hz, 2H), 5.94–5.77 (m, 1H), 5.56–5.41 (m, 1H), 4.41 (d, J=7.2 Hz, 2H), 4.29 (d, J=6.7 Hz, 2H), 1.74 (t, J=9.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 159.1, 149.3, 147.9, 147.8, 135.1, 133.4, 131.9, 130.9, 130.4, 129.1, 123.5, 122.3, 67.2, 50.1, 44.7, 17.7, 13.0. HRMS (M+H): found 397.0062 calculated for $C_{15}H_{14}N_2O_3I$ 397.0049.

4.4. N^1-Crotyl-5-iodo-uracil (7)

The debenzoylation of **6** (100 mg) was carried out at 0 °C overnight in a methanol solution 7 N of ammonia (5 mL). After evaporation of all the volatiles, the residue was purified by silica gel column chromatography (EtOAc/hexanes, 1/1) to yield the desired compound in 95% yield (*E*/*Z*, 8/2) as a white solid. Mp: 165 °C ($CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.23 (s, 1H), 7.60 (s, 1H), 5.88–5.74 (m, 2H), 5.56–5.44 (m, 2H), 4.42 (d, J=7.5 Hz, 2H), 4.30 (d, J=6.6 Hz, 2H), 1.80–1.75 (m, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 159.9, 150.1, 147.6, 132.4, 131.2, 123.3, 122.2, 67.3, 49.4, 43.9, 17.3, 12.6.

4.5. N^1-Crotyl-5-acrylicmethylester-uracil (8)

To a DMF solution (60 mL) of N^1-crotyl-5-iodo uracil **7** (850 mg, 2.91 mmol) were added triphenylphosphine (191 mg, 0.73 mmol), $Pd(OAc)_2$ (0.2 equiv) and triethylamine (1.18 *g*, 11.6 mmol). After 15 min stirring at 85 °C, methyl acrylate was added and the solution warmed at 85 °C for 12 h. The mixture was filtrated on Celite and the filtrate evaporated to dryness. Purification of residue by silica gel column chromatography (EtOAc/hexanes, 1/1) gave compound **8** (675 mg, 2.72 mmol, 92%) as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.41 (s, 1H), 7.40 (s, 1H), 7.28 (d, J=15.8 Hz, 1H), 7.00 (d, J=15.8 Hz, 1H), 5.98–5.78 (m, 1H), 5.57–5.44 (m, 1H), 4.46 (d, J=7.5 Hz, 2H), 4.34 (d, J=6.6 Hz, 2H), 3.77 (s, 3H), 1.78 (dd, J=6.5, 1.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 161.1, 149.4, 145.5, 135.9, 133.2, 123.7, 122.5, 119.3, 109.9, 51.7, 50.0, 44.4, 17.8, 13.2. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{12}H_{14}N_2NaO_4$: 273.0851, found: 273.0852.

4.6. N^1-Crotyl-5-acrylicacid-uracil (9)

To a 1 M aqueous solution of sodium hydroxide (2 mL) was added ester **8** (100 mg, 0.4 mmol). After 1 h stirring at room temperature, a 6 N aqueous solution of hydrochloric acid was added dropwise to precipitation. The mixture was filtrated and the solid washed with water to pH 7 giving pure compound **9** (86 mg, 0.36 mmol, 91%) as a white powder. ^{1}H NMR (400 MHz, CD_3OD) δ 7.95 (s, $1H_{minor}$), 7.94 (s, $1H_{major}$), 7.35 (d, J=15.8 Hz, 1H), 6.88 (d, J=15.8 Hz, 1H), 5.87–5.78 (m, 1H), 5.63–5.50 (m, 1H), 4.47 (d, J=6.9 Hz, 2H), 4.34 (d, J=6.3 Hz, 2H), 1.78 (d, J=6.9 Hz, 2H), 1.73 (dd, J=6.4, 1.0 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 171.0, 164.0, 151.6, 149.0, 138.7, 132.7, 125.7, 119.3, 110.4, 51.1, 49.7, 46.1, 17.9, 13.2. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{11}H_{12}N_2NaO_4$: 259.0695, found: 259.0699.

4.7. N^1-Crotyl-5-bromovinyl-uracil (10a)

A DMF solution (10 mL) of carboxylic acid **9** (120 mg, 0.51 mmol) and potassium hydrogenocarbonate (178 mg, 1.78 mmol) was stirred for 20 min at room temperature. To this mixture was added

N-bromosuccinimide (109 mg, 0.61 mmol). After 2 h stirring at room temperature, volatiles were removed under reduced pressure and residue diluted into water (10 mL). The solution was extracted three times by CH_2Cl_2 (10 mL), and the combined organic layers dried over $MgSO_4$, filtrated and evaporated to dryness. Purification of residue by silica gel column chromatography (EtOAc/hexanes, 1/3) gave compound **10a** (83 mg, 0.31 mmol, 60%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.42 (d, J=13.6 Hz, 1H), 7.14 (s, 1H$_{major}$), 7.13 (s, 1H$_{minor}$), 6.65 (d, J=13.6 Hz, 1H), 5.87–5.75 (m, 1H), 5.56–5.46 (m, 1H), 4.43 (d, J=7.2 Hz, 2H), 4.31 (d, J=6.5 Hz, 2H), 1.76 (d, J=6.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 149.8, 141.3, 132.5, 131.4, 128.0, 123.9, 122.8, 111.3, 109.9, 49.7, 44.3, 17.7, 13.1. HRMS (ESI): m/z [M+Na]$^+$ calcd for $C_{10}H_{11}N_2NaO_2Br$: 271.0082, found: 271.0084.

4.8. N^1-Crotyl-5-iodovinyl-uracil (10b)

A DMF solution (3 mL) of carboxylic acid **9** (100 mg, 0.42 mmol) and potassium hydrogenocarbonate (148 mg, 1.48 mmol) was stirred for 20 min at room temperature. To this mixture was added *N*-iodosuccinimide (191 mg, 0.85 mmol). After 24 h stirring at room temperature, volatiles were removed under reduced pressure and residue diluted into water (10 mL). The solution was extracted three times by CH_2Cl_2 (10 mL) and the combined organic layers dried over $MgSO_4$, filtrated and evaporated to dryness. Purification of residue by silica gel column chromatography (EtOAc/hexanes,1/3) gave compound **10b** (72 mg, 0.23 mmol, 54%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90 (s, 1H), 7.37 (d, J=14.5 Hz, 1H), 7.14 (s, 1H$_{major}$), 7.12 (s, 1H$_{minor}$), 6.96 (d, J=14.6 Hz, 1H), 5.84–5.73 (m, 1H), 5.54–5.43 (m, 1H), 4.41 (d, J=7.1 Hz, 2H$_{minor}$), 4.30 (t, J=6.5 Hz, 2H$_{major}$), 1.74 (dd, J=6.52, 0.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 149.8, 141.4, 135.4, 132.5, 131.4, 123.9, 122.8, 112.8, 80.5, 49.7, 44.3, 17.7, 13.1. HRMS (ESI): m/z [M+Na]$^+$ calcd for $C_{10}H_{12}N_2NaO_2I$: 318.9944, found: 318.9945.

4.9. N^3-Benzoyl-N^1-crotyl-5-[2-(trimethylsilyl)ethynyl]uracil (11)

A deoxygenated DMF solution (30 mL) of derivative **6** (1 equiv), Et_3N (3 mL), (trimethylsilyl)acetylene (1.2 equiv), $(PPh_3)_2PdCl_2$ (0.2 equiv) and CuI (0.2 equiv) was stirred at room temperature for 16 h under argon, then thoroughly evaporated until brown solid foam. The crude was purified by silica gel column chromatography with hexanes/ethyl acetate (8/2) to give **11** as a yellow solid (84%) as mixture of *E*/*Z* isomers. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.89 (d, J=1.4 Hz, 1H), 7.69–7.60 (m, 1H), 7.56 (s, 1H), 7.55–7.44 (m, 2H), 5.86 (dq, J=13.0, 6.5 Hz, 1H), 5.53 (dtd, J=15.1, 6.6, 1.6 Hz, 1H), 4.32 (d, J=7.0 Hz, 2H$_{minor}$), 4.27 (d, J=6.5Hz, 2H$_{major}$), 1.79 (dd, J=6.5, 1.2 Hz, 3H), 0.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 159.1, 149.3, 147.9, 147.8, 135.1, 133.4, 131.9, 130.9, 130.4, 129.1, 123.5, 122.3, 105.7, 59.7, 50.1, 44.7, 17.7, 13.0, 0.15, 0.14.

4.10. N^1-Crotyl-5-[2-(trimethylsilyl)ethynyl]uracil (12)

5-Substituted uracil analogue (100 mg) (**11**) was dissolved in methanol solution 7 N of ammonia (5 mL). The mixture is cooled at 4 °C for 16 h. After evaporation of solvents, the crude product was purified by silica gel column with CH_2Cl_2/MeOH; 98/2, to give pure debenzoylated product **12**. White solid (94%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.46 (s, 1H), 5.81 (dq, J=12.9, 6.4 Hz, 1H), 5.58–5.38 (m, 1H), 4.41 (d, J=7.1 Hz, 2H$_{minor}$), 4.34 (d, J=6.9 Hz, 2H$_{major}$), 1.76 (dd, J=6.4, 1.2 Hz, 3H), 0.23 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 159.1, 149.3, 147.9, 147.8, 133.4, 131.9, 123.5, 122.3, 105.7, 59.7, 50.1, 44.7, 17.7, 13.0, 0.15, 0.14. HRMS (M+H): found 263.3942 calculated for $C_{13}H_{18}N_2O_2Si$ 263.3948.

4.11. N^1-Crotyl-5-(ethynyl)uracil (13)

To a solution of **12** (2 mmol) in dry acetonitrile (24 mL) was added tetrabutylammonium fluoride (1 equiv). The mixture was stirred for 2 h at room temperature. Then acetonitrile is evaporated under reduced pressure and the obtained crude is purified on chromatography by using column silica packed in hexanes with hexanes/ethyl acetate (8:2) as the eluant to yield product **13** as white solid (74%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.50 (s, 1H, H$_{NH}$), 7.49 (s, 1H, H$_6$), 6.00–5.71 (m, 1H, H$_{3'}$), 5.60–5.38 (m, 1H, H$_{2'}$), 4.43 (d, J=7.2 Hz, 2H, H$_{1'minor}$), 4.40 (d, J=7.0 Hz, 2H, H$_{1'major}$), 3.20 (s, 1H, H$_{alcyne}$), 1.77 (dd, J=6.5, 1.6 Hz, 3H, H$_{4'}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 159.1, 149.3, 147.9, 147.8, 133.4, 131.9, 123.5, 122.3, 105.7, 94.8, 59.7, 50.1, 44.7, 17.7, 13.0. HRMS (M+Na): found 213.0634 calculated for $C_{10}H_{10}N_2O_2Na$ 213.0640.

4.12. General procedure 1 for dihalogenation of compound 13

5-Ethynyl-uracil derivatives **13** (0.5 mmol) was dissolved in 5 mL dry CH_3CN and the mixture was cooled in an ice bath. 0.6 mmol (1.2 equiv) of a solution of the halogenating reagent (i.e., I_2, IBr, ICl or Br_2) in 1 mL dry CH_3CN was added dropwise and the mixture was stirred at 0 °C until completion (typically 3 h, checked by TLC). The reaction mixture was quenched at 0 °C by a saturated $Na_2S_2O_3$ solution (2 mL) then extracted with AcOEt (3×10 mL). The organic layer was washed with water (2×5 mL) and brine (10 mL) then dried over $MgSO_4$ and concentrated in vacuo to give the desired di-halogenated compound. Pure analytical samples were obtained using flash chromatography (hexanes/AcOEt, 1/1).

*4.12.1. N^1-Crotyl-5-(1,2-diiodovinyl)uracil (**14a**).* Yellow crystals (87%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.17 (s, 1H), 7.35 (s, 1H), 7.30 (s, 1H), 5.83 (dq, J=12.9, 6.4 Hz, 1H), 5.62–5.42 (m, 1H), 4.45 (d, J=6.9 Hz, 2H$_{minor}$), 4.43(d, J=6.4 Hz, 2H$_{major}$), 1.76 (dd, J=6.5, 1.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 159.3, 149.5, 148.0, 147.9, 133.4, 132.0, 123.4, 122.2, 105.7, 94.8, 59.7, 50.1, 44.7, 18.1, 12.8. HRMS (M+Na): found 467.0129 calculated for $C_{10}H_{10}N_2O_2NaI$ 467.0122.

*4.12.2. N^1-Crotyl-5-(1-bromo-2-iodovinyl)uracil (**14b**).* Yellow crystals (81%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.35 (s, 1H), 7.11 (s, 1H), 5.86 (ddt, J=14.1, 12.9, 3.8 Hz, 1H), 5.64–5.41 (m, 1H), 4.42 (d, J=6.8 Hz, 2H$_{minor}$), 4.36 (d, J=6.0 Hz, 2H$_{major}$), 1.77 (dd, J=6.4, 1.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 159.1, 149.3, 147.9, 147.8, 133.4, 131.9, 123.5, 122.3, 105.7, 94.8, 59.7, 50.1, 44.7, 17.7, 13.0. HRMS (M+Na): found 420.0018 calculated for $C_{10}H_{10}N_2O_2NaIBr$ 420.0022.

*4.12.3. N^1-Crotyl-5-(1-chloro-2-iodovinyl)uracil (**14c**).* Yellow crystals (80%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.41 (s, 1H), 6.90 (s, 1H), 5.87 (dq, J=12.9, 6.5 Hz, 1H), 5.57 (dtd, J=7.9, 6.4, 1.6 Hz, 1H), 4.43 (d, J=6.9 Hz, 2H$_{minor}$), 4.39 (d, J=6.5 Hz, 2H$_{major}$), 1.80 (dd, J=9.2, 3.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 159.1, 149.3, 147.9, 147.8, 133.4, 131.9, 123.5, 122.3, 105.7, 94.8, 59.7, 50.1, 44.7, 17.7, 13.0. HRMS (M+H): found 352.9540 calculated for $C_{10}H_{11}N_2O_2ClI$ 352.9554.

*4.12.4. N^1-Crotyl-5-(1,2-dibromovinyl)uracil (**14d**).* Yellow crystals (74%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.37 (s, 1H), 6.86 (s, 1H), 5.84 (dd, J=15.2, 6.5 Hz, 1H), 5.63–5.42 (m, 1H), 4.33 (d, J=6.4 Hz, 2H$_{minor}$), 4.29 (d, J=6.0 Hz, 2H$_{major}$), 1.76 (dd, J=9.2, 3.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 159.0, 149.3, 147.9, 148.0, 133.4, 132.0, 123.4, 122.3, 105.6, 94.8, 59.9, 50.1, 44.7, 17.9, 12.8. HRMS (M+H): found 348.9195 calculated for $C_{10}H_{11}N_2O_2Br_2$ 253.0589.

4.13. General procedure 2 for Sonogashira reaction at *C*5 position of 6

To 300 mL of deoxygenated Et_3N was added **6** (1 equiv) followed by alkyne (1.2 equiv), $(PPh_3)_2PdCl_2$ (0.2 equiv) and CuI (0.2 equiv). The suspension was stirred at room temperature for 16 h under argon, evaporated thoroughly to brown foam. Chromatography was performed by using column silica gel packed in hexanes with hexanes/ethyl acetate (8:2) as eluant to give desired product.

*4.13.1. N^3-Benzoyl-N^1-crotyl-5-((4-propylphenyl)1-ethynyl)-uracil (**15a**).* White solid (78%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.02–7.92 (m, 2H), 7.72–7.58 (m, 2H), 7.56–7.39 (m, 4H), 7.15 (d, J=8.2 Hz, 2H), 5.85 (dq, J=12.9, 6.5 Hz, 1H), 5.62–5.45 (m, 1H), 4.38 (d, J=6.9 Hz, $2H_{minor}$), 4.32 (d, J=6.4 Hz, $2H_{minor}$), 2.59 (t, J=7.3 Hz, 2H), 1.77 (d, J=6.5 Hz, 3H), 1.64 (m, J=7.5 Hz, 2H), 0.94 (t, J=7.3 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.52, 163.88, 152.93, 148.95, 148.26, 134.99, 133.83, 133.43, 131.38, 128.82, 128.59, 127.31, 127.10, 127.00, 117.56, 97.62, 86.68, 71.97, 50.33, 38.12, 24.48, 17.03, 12.98. HRMS (M+H): found 413.1848 calculated for $C_{26}H_{25}N_2O_3$ 413.1865.

*4.13.2. N^3-Benzoyl-N^1-crotyl-5-((4-pentylphenyl)1-ethynyl)-uracil (**15b**).* White solid (86%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.04–7.90 (m, 2H), 7.73–7.59 (m, 2H), 7.56–7.39 (m, 4H), 7.14 (d, J=8.1 Hz, 2H), 5.87 (dq, J=12.9, 6.4 Hz, 1H), 5.63–5.47 (m, 1H, $H_{2'}$), 4.38 (d, J=6.9 Hz, $2H_{minor}$), 4.32 (d, J=6.6 Hz, $2H_{major}$), 2.60 (t, J=7.4 Hz, 2H), 1.79 (d, J=6.5 Hz, 3H), 1.37 (m, 4H), 1.20 (m, J=7.5 Hz, 2H), 0.94 (t, J=7.3 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.52, 163.88, 152.93, 148.22, 134.99, 133.75, 133.54, 131.38, 128.82, 128.59, 128.10, 127.70, 127.00, 118.09, 97.62, 86.68, 71.97, 50.33, 36.41, 30.64, 30.02, 22.07, 17.03, 14.02. HRMS (M+H): found 441.5556 calculated for $C_{28}H_{29}N_2O_3$ 441.5559.

*4.13.3. N^3-Benzoyl-N^1-crotyl-5-(4-phenyl-1-butynyl)uracil (**15c**).* White solid (80%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.01–7.89 (m, 2H), 7.67 (dd, J=10.5, 4.3 Hz, 1H), 7.52 (t, J=7.6 Hz, 2H), 7.44 (s, 1H), 7.36–7.15 (m, 5H), 6.03–5.77 (m, 1H), 5.63–5.42 (m, 1H), 4.38 (d, J=7.0 Hz, $2H_{minor}$), 4.34 (d, J=6.5 Hz, $2H_{major}$), 2.93 (t, J=8.1 Hz, 2H), 2.70 (t, J=7.4 Hz, 2H), 1.81 (d, J=6.7 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 168.15, 161.12, 148.86, 145.02, 140.40, 135.05, 133.77, 133.36, 132.04, 131.31, 130.70, 130.59, 129.13, 126.42, 123.61, 122.45, 100.55, 95.00, 71.38, 60.89, 50.21, 46.81, 34.81, 21.82, 21.22, 17.85. HRMS (M+Na): found 421.1519 calculated for $C_{25}H_{22}N_2O_3Na$ 421.1528.

*4.13.4. N^3-Benzoyl-N^1-crotyl-5-(1-pentynyl)uracil (**15d**).* White solid (81%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.08–7.95 (m, 2H), 7.63 (s, 1H), 7.42(t, J=8.7 Hz, 3H), 5.75 (m, 1H), 5.58 (m, 1H), 4.80 (d, J=7.1 Hz, $1H_{minor}$), 4.74 (d, J=6.5 Hz, $2H_{major}$), 2.37 (t, J=6.4 Hz, 2H), 1.64 (m, 2H), 1.07 (t, J=11.9 Hz, 3H). ^{13}C NMR (250 MHz, $CDCl_3$) δ 164.52, 163.88, 152.93, 151.02, 134.99, 131.38, 128.82, 128.59, 127.00, 104.91, 86.03, 83.83, 50.33, 22.71, 21.14, 17.03, 12.98. HRMS (M+Na): found 336.0901 calculated for $C_{20}H_{20}N_2O_3Na$ 336.0906.

*4.13.5. N^3-Benzoyl-N^1-crotyl-5-(1-heptynyl)uracil (**15e**).* White solid (81%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.05–7.95 (m, 2H), 7.65 (s, 1H), 7.46 (t, J=8.9 Hz, 3H), 5.76 (m, 1H), 5.58 (m, 1H), 4.82 (d, J=7.0 Hz, $1H_{minor}$), 4.75 (d, J=6.6 Hz, $2H_{major}$), 2.34 (t, J=6.5 Hz, 2H), 1.65 (m, 2H), 1.58–1.41 (m, 4H), 1.00 (t, J=12.1 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.52, 163.88, 152.93, 151.02, 134.99, 131.38, 128.82, 128.59, 127.00, 104.91, 86.23, 81.48, 50.33, 30.64, 28.21, 22.94, 18.79, 17.03, 14.02. HRMS (M+Na): found 364.4579 calculated for $C_{22}H_{24}N_2O_3Na$ 364.4582.

*4.13.6. N^3-Benzoyl-N^1-crotyl-5-(1-decynyl)-uracil (**15f**).* White solid (84%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.68–7.56 (m, 2H), 7.44 (s, 1H), 7.39–7.33 (m, 2H), 5.76 (m, 1H), 5.59 (s, 1H), 4.51 (d, J=6.9 Hz, $2H_{minor}$), 4.47 (d, J=6.5 Hz, $2H_{major}$), 2.34 (t, J=6.4 Hz, 2H), 1.65 (d, J=6.7 Hz, 3H), 1.39–1.35 (m, 4H), 1.35–1.17 (m, 8H), 0.99 (t, J=12.1 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.52, 163.88, 152.93, 151.02, 134.99, 131.38, 128.82, 128.59, 127.00, 104.91, 86.23, 81.48, 50.33, 31.65, 29.06, 28.87, 28.50, 22.94, 18.79, 17.03, 14.02. HRMS (M+H): found 407.2330 calculated for $C_{25}H_{31}N_2O_3$ 407.2335.

4.14. General procedure 3 for deprotection of benzoyl groups

The necessary amount of 5-substituted uracil derivatives is dissolved in a solution of ammonia in methanol. The mixture is cooled at 4 °C for 16 h. After evaporation of solvents, the crude product was purified by silica gel column with CH_2Cl_2/MeOH; 98/2 as eluant, to give pure debenzoyled product.

*4.14.1. N^1-Crotyl-5-(2(4-propylphenyl)-1-ethynyl)-uracil (**16a**).* White solid (95%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.93 (s, 1H), 8.02–7.92 (m, 2H), 7.62 (s, 1H), 7.15 (d, J=8.2 Hz, 2H), 5.85 (dq, J=12.9, 6.5 Hz, 1H), 5.62–5.45 (m, 1H), 4.38 (d, J=6.9 Hz, $2H_{minor}$), 4.34 (d, J=6.4 Hz, $2H_{major}$), 2.59 (t, J=7.3 Hz, 2H), 1.77 (d, J=6.5 Hz, 3H), 1.64 (m, J=7.5 Hz, 2H), 0.94 (t, J=7.3 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.18, 152.41, 149.51, 148.95, 133.83, 133.43, 127.31, 127.10, 127.00, 117.56, 103.59, 92.47, 72.97, 49.88, 38.12, 24.48, 17.03, 12.98. HRMS (M+H): found 309.1585 calculated for $C_{19}H_{21}N_2O_2$ 309.1603.

*4.14.2. N^1-Crotyl-5–((4-pentylphenyl)ethynyl)-uracil (**16b**).* White solid (97%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.51 (s, 1H), 7.43 (d, J=8.2 Hz, 2H), 7.14 (d, J=8.3 Hz, 2H), 5.81 (dq, J=12.9, 6.4 Hz, 1H), 5.59–5.41 (m, 1H), 4.34 (d, J=7.0 Hz, $2H_{minor}$), 4.31 (d, J=6.5 Hz, $2H_{major}$), 2.67–2.52 (m, 2H), 1.75 (dd, J=6.5, 1.4 Hz, 3H), 1.69–1.52 (m, 2H), 1.43–1.21 (m, 4H), 0.90 (t, J=6.8 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.18, 152.41, 149.51, 148.19, 133.75, 133.54, 128.10, 127.70, 127.00, 118.09, 103.59, 92.47, 72.97, 49.88, 36.41, 30.64, 30.02, 22.94, 17.03, 14.02. HRMS (M+Na): found 359.1742 calculated for $C_{21}H_{24}N_2O_2Na$ 359.1735.

*4.14.3. N^1-Crotyl-5-((4-phenyl)butynyl)-uracil (**16c**).* White solid (91%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.93 (s, 1H), 8.01–7.89 (m, 2H), 7.67 (dd, J=10.5, 4.3 Hz, 1H), 7.52 (t, J=7.6 Hz, 2H), 7.44 (s, 1H), 6.03–5.77 (m, 1H), 5.64–5.42 (m, 1H), 4.37 (d, J=7.0 Hz, $2H_{minor}$), 4.32 (d, J=6.5 Hz, $2H_{major}$), 2.93 (t, J=8.1 Hz, 2H), 2.70 (t, J=7.4 Hz, 2H), 1.80 (d, J=6.5 Hz, 3H). ^{13}C NMR (250 MHz, $CDCl_3$) δ 165.18, 153.51, 152.41, 141.00, 129.05, 128.65, 127.00, 126.53, 109.65, 96.48, 81.44, 49.88, 34.86, 19.95, 17.03. HRMS (M+Na): found 317.1277 calculated for $C_{18}H_{18}N_2O_2Na$ 317.1266.

*4.14.4. N^1-Crotyl-5-pentynyl-uracil (**16d**).* White solid (94%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.63 (s, 1H), 5.70 (m, 1H), 5.55 (m, 1H), 4.81 (d, J=7.1 Hz, $2H_{minor}$), 4.74 (d, 2H, J=6.4 Hz, $2H_{major}$), 2.38 (t, J=6.7 Hz, 2H), 1.64 (m, 2H), 0.95 (t, J=12.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.18, 153.51, 152.41, 127.00, 109.65, 92.49, 82.28, 49.88, 22.71, 21.14, 17.03, 12.98. HRMS (M+H): found 232.2789 calculated for $C_{13}H_{17}N_2O_2$ 232.2790.

*4.14.5. N^1-Crotyl-5-heptynyl-uracil (**16e**).* White solid (93%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.65 (s, 1H), 5.73 (m, 1H), 5.58 (m, 1H), 4.80 (d, J=7.0 Hz, $2H_{minor}$), 4.74 (d, 2H, J=6.5 Hz, $2H_{major}$), 2.34 (t, J=6.4 Hz, 2H), 1.65 (m, 2H), 1.60–1.40 (m, 4H), 0.97 (t, J=12.1 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.18, 153.51, 152.41, 127.00, 109.65, 93.12, 79.54, 49.88, 30.64, 28.21, 22.94, 18.79, 17.03, 14.02. HRMS (M+H): found 261.1585 calculated for $C_{15}H_{21}N_2O_2$ 261.1603.

*4.14.6. N^1-Crotyl-5-decynyl-uracil (**16f**).* White solid (94%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.44 (s, 1H), 5.76 (m, 1H), 5.59 (s, 1H), 4.51 (d, J=6.9 Hz, $2H_{minor}$), 4.47 (d, J=6.5 Hz, $2H_{major}$), 2.32

(t, *J*=6.4 Hz, 2H), 1.65 (d, *J*=6.7 Hz, 3H), 1.39–1.35 (m, 4H), 1.35–1.17 (m, 8H), 0.97 (t, *J*=12.1 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.18, 153.51, 152.41, 127.00, 109.65, 93.12, 79.54, 49.88, 31.65, 29.06, 28.87, 28.50, 22.94, 18.79, 17.03, 14.0. HRMS (M+H): found 303.2061 calculated for $C_{18}H_{27}N_2O_2$ 303.2073.

4.15. General procedure 4: bicyclic base synthesis

Linear compound **16** was solubilized in methanol and triethylamine mixture (7/3) with CuI (0.2 equiv). The solution was heated at 70 °C for 5 h. After completion of the reaction (monitored by TLC), solvents were removed under reduced pressure and the obtained crude product was purified on silica gel (hexanes/ethyl acetate, 4/6), to obtain a mixture of *E* (major) and *Z* (minor) isomers.

*4.15.1. N^1-Crotyl-6-(4-n-propylphenyl)-2,3-dihydrofuro[2,3-d]pyrimidin-2-one (**17a**).* White solid (77%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.67 (d, *J*=8.3 Hz, 2H), 7.25 (d, *J*=7.9 Hz, 2H), 6.63 (s, 1H), 5.84 (dq, *J*=12.9, 6.5 Hz, 1H), 5.71–5.55 (m, 1H), 4.64 (d, *J*=7.1 Hz, $2H_{minor}$), 4.59 (d, *J*=6.5 Hz, $2H_{major}$), 2.69–2.56 (m, 2H), 1.84–1.73 (m, 3H), 1.73–1.56 (m, 2H), 0.95 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 144.85, 138.47, 132.52, 129.07, 125.87, 124.95, 124.63, 108.43, 96.30, 52.79, 37.90, 24.33, 17.84, 13.75. HRMS (M+H): found 309.1605 calculated for $C_{19}H_{21}N_2O_2$ 309.1603.

*4.15.2. N^1-Crotyl-6-(4-n-pentylphenyl)-2,3-dihydrofuro[2,3-d]pyrimidin-2-one (**17b**).* White solid (72%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.67 (d, *J*=8.3 Hz, 2H), 7.25 (d, *J*=7.9 Hz, 2H), 6.63 (s, 1H), 5.84 (dq, *J*=12.9, 6.5 Hz, 1H), 5.71–5.55 (m, 1H), 4.65 (d, *J*=6.9 Hz, 2H),4.59 (d, *J*=6.5 Hz, 2H), 2.67–2.52 (m, 2H), 1.75 (dd, *J*=6.5, 1.4 Hz, 3H), 1.69–1.52 (m, 2H), 1.43–1.21 (m, 4H), 0.90 (t, *J*=6.8 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.44, 162.33, 151.54, 143.94, 143.62, 131.04, 128.08, 127.87, 127.00, 124.31, 124.10, 102.19, 50.95, 36.41, 30.64, 30.02, 22.94, 17.03, 14.02. HRMS (M+H): found 337.1928 calculated for $C_{21}H_{25}N_2O_2$ 337.1916.

*4.15.3. N^1-Crotyl-6-(2-phenyl-1-ethyl)-2,3-dihydrofuro[2,3-d]pyrimidin-2-one (**17c**).* White solid (70%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.01–7.89 (m, 2H), 7.67 (dd, *J*=10.5, 4.3 Hz, 1H), 7.52 (t, *J*=7.6 Hz, 2H), 7.44 (s, 1H), 6.60 (s, 1H), 6.03–5.77 (m, 1H), 5.64–5.42 (m, 1H), 4.37 (d, *J*=7.0 Hz, $2H_{minor}$) 4.32 (d, *J*=6.4 Hz, $2H_{major}$), 2.93 (t, *J*=8.1 Hz, 2H), 2.70 (t, *J*=7.4 Hz, 2H), 1.80 (d, *J*=6.5 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 163.72, 162.33, 148.01, 141.00, 138.22, 129.05, 128.65, 127.00, 126.53, 108.20, 103.63, 50.95, 32.83, 31.96, 17.03. HRMS (M+H): found 295.1436 calculated for $C_{18}H_{19}N_2O_2$ 295.1447.

*4.15.4. N^1-Crotyl-6-propyl-2,3-dihydrofuro[2,3-d]pyrimidin-2-one (**17d**).* White solid (71%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.80 (s, 1H), 6.05 (s, 1H), 5.74 (dq, *J*=21.9, 6.1 Hz, 1H), 5.69–5.46 (m, 1H), 4.57 (d, *J*=6.7 Hz, $2H_{minor}$), 4.50 (d, *J*=6.3 Hz, $2H_{minor}$), 2.32 (t, *J*=6.6 Hz, 2H), 1.64 (m, 2H), 1.04 (t, *J*=12.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.72, 162.33, 151.55, 138.22, 127.00, 109.96, 103.63, 50.95, 33.19, 20.39, 17.03, 13.57. HRMS (M+H): found 233.2809 calculated for $C_{13}H_{17}N_2O_2$ 233.2817.

*4.15.5. N^1-Crotyl-6-pentyl-2,3-dihydrofuro[2,3-d]pyrimidin-2-one (**17e**).* White solid (78%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.82 (s, 1H), 6.02 (s, 1H), 5.77 (dq, *J*=21.5, 6.3 Hz, 1H), 5.66–5.45 (m, 1H), 4.56 (d, *J*=6.9 Hz, $2H_{minor}$), 4.51 (d, *J*=6.3 Hz, $2H_{major}$), 2.34 (t, *J*=6.4 Hz, 2H), 1.65 (m, 2H), 1.60–1.40 (m, 4H), 0.99 (t, *J*=12.1 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 163.72, 162.33, 152.74, 138.22, 127.00, 111.39, 103.63, 50.95, 31.88, 30.83, 25.86, 22.94, 17.03, 14.02. HRMS (M+H): found 261.1601 calculated for $C_{15}H_{21}N_2O_2$ 261.1603.

*4.15.6. N^1-Crotyl-6-octyl-2,3-dihydrofuro[2,3-d]pyrimidin-2-one (**17f**).* White solid (75%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.84 (s, 1H), 6.07 (s, 1H), 5.77 (dq, *J*=21.5, 6.3 Hz, 1H), 5.66–5.45 (m, 1H), 4.57 (d, *J*=6.8 Hz, $2H_{minor}$), 4.51 (d, *J*=6.3 Hz, $2H_{major}$), 2.58 (t, *J*=7.3 Hz, 2H), 1.82–1.52 (m, 5H), 1.24 (d, *J*=12.3 Hz, 10H), 0.82 (t, *J*=6.6 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ 163.72, 162.33, 152.74, 138.22, 127.00, 111.39, 103.63, 50.95, 31.88, 31.65, 29.26, 28.82, 26.11, 22.94, 17.03, 14.02. HRMS (M+H): found 303.2063 calculated for $C_{18}H_{27}N_2O_2$ 303.2073.

4.16. Bis(POC)allylphosphonate (19)

To an acetonitrile (23 mL) solution of dimethyl allylphosphonate (3.4 g, 22.6 mmo1), anhydrous sodium iodide (6.8 g, 45.2 mmol), chloromethyl isopropylcarbonate (**18**) (8.50 g, 56.7 mmol) was added. This solution was stirred at reflux for 72 h under positive pressure of dry Ar. After cooling, this solution was added to 220 mL of diethyl ether and washed by 45 mL of water. The organic layer was dried over magnesium sulfate, evaporated and purified by silica gel column chromatography (EtOAc/hexanes, 1/4) to give 5.75 g (16.9 mmol, **75**%) of pure bis(POC) allylphosphonate as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82–5.71 (m, 1H), 5.68 (dd, *J*=11.6, 5.4 Hz, 2H), 5.65 (dd, *J*=11.6, 5.4 Hz, 2H), 5.30–5.22 (m, 2H), 4.94 (m, *J*=6.2 Hz, 2H), 2.74 (tdd, *J*=22.8, 7.4, 1.1 Hz, 2H), 1.33 (d, *J*=6.28 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 125.7, 125.6, 121.3, 121.2, 84.1, 84.0, 73.2, 32.9, 31.5, 21.6. ^{31}P NMR (162 MHz, $CDCl_3$) δ=27.99. HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{13}H_{23}NaO_9Pr$: 377.0977, found: 377.0990.

4.17. General procedure 5: cross metathesis between *N*^{3}-crotyl-*C*5-halo- and dihalovinyl-uracils and bis(POC)-allylphosphonate

To a CH_2Cl_2 (25 mL/mmol) solution of *N*^{1}-crotyl-*C*5-substituted uracil **16** (1 equiv), bis(POC) allylphosphonate **19** (1.3 equiv) under dry argon was added $[RuCl_2(PCy_3)(SIPr)(indenylidene)]$ catalyst **20** (0.05 equiv). After 3 h or 3.5 h stirring at room temperature, the solution was directly deposed on silica gel and purified (pure CH_2Cl_2 then MeOH/CH_2Cl_2 1:200) to afford pure *E* compounds (**21a**–**f**).

*4.17.1. (E)-N^1-(4′-Bis(POC)-phosphinyl-but-2′-enyl)-5-iodovinyl-uracil (**21a**).* Light yellow oil in 47% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.42 (d, *J*=14.6 Hz, 1H), 7.21 (s, 1H), 7.02 (d, *J*=14.6 Hz, 1H), 5.82–5.60 (m, 6H), 4.94 (m, *J*=6.3 Hz, 2H), 4.36 (t, *J*=4.5 Hz, 2H), 2.77 (dd, *J*=23.0, 5.6 Hz, 2H), 1.33 (d, *J*=6.3 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 153.1, 149.4, 141.1, 135.2, 129.5, 129.4, 124.3, 124.2, 113.2, 84.2, 84.1, 80.8, 73.5, 49.3, 31.3, 29.9, 21.6. ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.7. HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{20}H_{28}N_2NaO_{11}IP$: 653.0373, found: 653.0355.

*4.17.2. (E)-N^1-(4′-Bis(POC)-phosphinylbut-2′-enyl)-5-bromovinyl-uracil (**21b**).* Light yellow oil in 51% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.41 (d, *J*=13.6 Hz, 1H), 7.20 (s, 1H), 6.67 (d, *J*=13.6 Hz, 1H), 5.69 (m, 6H), 4.93 (m, *J*=6.2 Hz, 2H), 4.36 (t, *J*=4.5 Hz, 2H), 2.76 (dd, *J*=23.1, 5.5 Hz, 2H), 1.32 (d, *J*=6.3 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 153.1, 149.5, 141.1, 129.6, 129.4, 127, 124.3, 124.2, 111.6, 110.1, 84.2, 84.1, 73.5, 49.2, 31.3, 29.9, 21.6. ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.8. HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{20}H_{28}N_2NaO_{11}BrP$: 605.0512, found: 605.0495.

*4.17.3. (E)-N^1-(4′-Bis(POC)phosphinylbut-2′-enyl)-5-(1,2-diiodovinyl)uracil (**21c**).* Yellow oil (51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.38 (s, 1H), 7.33 (s, 1H), 5.79–5.61 (m, 6H), 4.95 (m, *J*=6.3 Hz, 2H), 4.38 (t, *J*=4.6 Hz, 2H), 2.78 (dd, *J*=23.1, 5.5 Hz, 2H), 1.33 (d, *J*=6.3 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 153.0, 149.7, 148.7, 140.4, 129.3, 129.2, 124.5, 124.4, 109.0, 116.58, 85.4,

84.2, 84.1, 73.4, 49.4, 31.3, 29.9, 21.6, 21.5. ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.70. HRMS (M+Na): found 778.9355 calculated for $C_{20}H_{27}N_2O_{11}PNa$ 778.9340.

*4.17.4. (E)-N^1-(4′-Bis(POC)-phosphinylbut-2′-enyl)-5-(1-iodo-2-bromovinyl)uracil (**21d**).* Light yellow oil (40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.42 (s, 1H), 7.15 (s, 1H), 5.85–5.61 (m, 6H), 4.95 (m, *J*=6.3 Hz, 2H), 4.42 (t, *J*=4.6 Hz, 2H), 2.76 (dd, *J*=23.1, 5.5 Hz, 2H), 1.36 (d, *J*=6.3 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 153.2, 149.7, 148.7, 140.4, 129.3, 129.2, 124.5, 124.4, 109.0, 116.58, 85.4, 84.2, 84.1, 73.4, 49.4, 31.3, 29.9, 21.6, 21.5. ^{31}P NMR (400 MHz, $CDCl_3$) δ 26.80. HRMS (M+Na): found 732.2228 calculated for $C_{20}H_{27}N_2O_{11}PNaIBr$ 732.2230.

*4.17.5. (E)-N^1-(4′-Bis(POC)-phosphinylbut-2′-enyl)-5-(1-iodo-2-chlorovinyl)uracil (**21e**).* Light yellow oil (45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.45 (s, 1H), 6.91 (s, 1H), 5.83–5.59 (m, 6H), 4.96 (m, *J*=6.3 Hz, 2H), 4.41 (t, *J*=4.6 Hz, 2H), 2.80 (dd, *J*=23.2, 5.5 Hz, 2H), 1.35 (d, *J*=6.3 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 152.9, 149.7, 148.9, 140.4, 129.3, 129.0, 124.5, 124.3, 109.0, 116.58, 85.5, 84.7, 84.1, 73.6, 49.4, 31.3, 29.9, 21.4, 21.3. ^{31}P NMR (163 MHz, $CDCl_3$) δ 26.70. HRMS (M+H): found 665.0179 calculated for $C_{20}H_{28}N_2O_{11}PClI$ 665.0164.

*4.17.6. (E)-N^1-(4′-Bis(POC)-phosphinylbuten-2′-yl)-5-(1,2-dibromovinyl)uracil (**21f**).* Light yellow oil (48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.40 (s, 1H), 6.86 (s, 1H), 5.79–5.61 (m, 6H), 4.93 (m, *J*=6.3 Hz, 2H), 4.39 (t, *J*=4.6 Hz, 2H), 2.77 (dd, *J*=23.0, 5.6 Hz, 2H), 1.32 (d, *J*=6.3 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 153.0, 149.7, 148.7, 140.4, 129.3, 129.2, 124.5, 124.4, 109.0, 116.58, 85.4, 84.2, 84.1, 73.4, 49.4, 31.3, 29.9, 21.6, 21.5. ^{31}P NMR (163 MHz, $CDCl_3$) δ 26.80. HRMS (M+Na): found 685.7984 calculated for $C_{20}H_{27}N_2O_{11}PNaBr_2$ 685.7988.

4.18. General procedure 6: cross metathesis between N^3-crotyl-bicyclic bases and bis(POC)-allylphosphonate

To a CH_2Cl_2 (25 mL/mmol) solution of N^1-crotyl-C5-substituted uracil **17** (1 equiv) and bis(POC) allylphosphonate (1.3 equiv) **19** under dry argon was added [$RuCl_2(PCy_3)$(IMes)(benzylidene)] catalyst **22** (0.05 equiv). After 16 h stirring at reflux, the solution was cooled and then directly deposed on silica gel chromatography and purified (pure CH_2Cl_2 then MeOH/CH_2Cl_2 1:200) to afford pure *E* compounds (**23a**–**f**).

*4.18.1. N^1-(4′-Bis(POC)-phosphinylbut-2′-enyl)-6-(4-n-propylphenyl)-2,3-dihydrofuro[2,3-d]pyrimidin-2-one (**23a**).* Yellow oil (52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.69 (d, *J*=8.2 Hz, 2H), 7.35–7.18 (m, 2H), 6.71 (s, 1H), 5.98–5.58 (m, 6H), 4.95 (m, *J*=6.3 Hz, 2H), 4.38 (t, *J*=4.6 Hz, 2H), 2.81 (dd, *J*=22.7, 6.6 Hz, 2H), 2.64 (t, *J*=7.6 Hz, 2H), 1.68 (dq, *J*=14.6, 7.3 Hz, 2H), 1.32 (d, *J*=6.3 Hz, 12H), 0.97 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.44, 162.33, 155.38, 154.95, 151.54, 144.56, 143.62, 131.59, 130.92, 127.57, 127.18, 124.39, 124.18, 122.27, 102.19, 85.18, 84.27, 72.53, 72.22, 51.10, 38.12, 32.31, 24.48, 22.65, 22.44, 12.98. ^{31}P NMR (400 MHz, $CDCl_3$) δ 27.00. HRMS (M+Na): found 643.2049 calculated for $C_{29}H_{37}N_2O_{11}NaP$ 643.2033.

*4.18.2. N^1-(4′-Bis(POC)-phosphinylbut-2′-enyl)-6-(4-n-pentylphenyl)-2,3-dihydrofuro[2,3-d]pyrimidin-2-one (**23b**).* Yellow oil (55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.69 (d, *J*=8.2 Hz, 2H), 7.27 (d, *J*=8.1 Hz, 2H), 6.70 (s, 1H), 5.97–5.61 (m, 6H), 4.93 (m, *J*=6.3 Hz, 2H), 4.72–4.62 (t, *J*=4.6 Hz), 2.81 (dd, *J*=22.7, 6.6 Hz, 2H), 2.71–2.59 (m, 2H), 1.65 (dt, *J*=15.1, 7.5 Hz, 2H), 1.41–1.24 (m, 16H), 0.92 (t, *J*=6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.44, 162.33, 155.38, 154.95, 151.54, 143.94, 143.62, 131.59, 131.04, 128.08, 127.87, 124.31, 124.10, 122.27, 102.19, 85.18, 84.27, 72.53, 72.22, 51.10, 36.41, 32.31, 30.64, 30.02, 22.94, 22.65, 22.44, 14.02. ^{31}P NMR (163 MHz, $CDCl_3$) δ 27.04. HRMS (M+Na): found 671.6524 calculated for $C_{31}H_{41}N_2O_{11}NaP$ 671.6533.

*4.18.3. N^1-(4′-Bis(POC)-phosphinylbut-2′-enyl)-6-(2-phenyl-1-ethyl)-2,3-dihydrofuro[2,3-d]pyrimidin-2-one (**23c**).* Yellow oil (58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.37–7.15 (m, 5H), 6.09 (s, 1H), 5.95–5.58 (m, 6H), 4.90 (hept, *J*=6.2 Hz, 2H), 4.67 (t, *J*=4.7 Hz, 2H), 3.10–2.93 (m, 4H), 2.80 (dd, *J*=22.7, 6.7 Hz, 2H), 1.34 (d, *J*=6.3 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.72, 162.33, 155.38, 154.95, 148.01, 141.00, 138.22, 131.59, 129.05, 128.65, 126.53, 122.27, 108.20, 103.63, 85.18, 84.27, 72.53, 72.22, 51.10, 33.25, 28.37, 22.65, 22.44. ^{31}P NMR (163 MHz, $CDCl_3$) δ 27.10. HRMS (M+Na): found 643.2049 calculated for $C_{29}H_{37}N_2O_{11}NaP$ 643.2033.

*4.18.4. N^1-(4′-Bis(POC)-phosphinylbut-2′-enyl)-6-propyl-2,3-dihydrofuro[2,3-d]pyrimidin-2-one (**23d**).* Yellow oil (51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 6.07 (s, 1H), 5.88–5.59(m, 6H), 4.92 (m, *J*=6.2 Hz, 2H), 4.65–4.55 (m, 2H), 2.71 (dd, *J*=22.5, 7.3 Hz, 2H), 2.60 (t, *J*=7.3 Hz, 2H), 1.62–1.54 (m, 2H), 1.40 (d, *J*=5.7 Hz, 12H), 1.05 (t, *J*=6.6 Hz, 3H), 0.87 (dd, *J*=8.5, 5.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.72, 162.33, 155.38, 154.95, 151.55, 138.22, 131.59, 122.27, 109.96, 103.63, 85.18, 84.27, 72.53, 72.22, 51.10, 32.75, 22.65, 22.44, 20.39, 13.57. ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.09. HRMS (M+H): found 540.5002 calculated for $C_{23}H_{34}N_2O_{11}P$ 540.4997.

*4.18.5. N^1-(4′-Bis(POC)-phosphinylbut-2′-enyl)-6-pentyl-2,3-dihydrofuro[2,3-d]pyrimidin-2-one (**23e**).* Yellow oil (49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 6.09 (s, 1H), 5.88–5.56 (m, 6H), 4.89 (sept, *J*=6.3 Hz, 2H), 4.63–4.55 (m, 2H), 2.74 (dd, *J*=22.7, 7.1 Hz, 2H), 2.61 (t, *J*=7.4 Hz, 2H), 1.71–1.60 (m, 2H), 1.37–1.24 (m, 16H), 0.87 (dd, *J*=8.5, 5.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.94, 160.04, 155.36, 153.09, 137.97, 130.27, 123.87, 108.21, 98.57, 84.11, 73.42, 52.00, 31.44, 31.13, 30.05, 28.21, 26.40, 22.26, 21.59, 13.88. ^{31}P NMR (163 MHz, $CDCl_3$) δ 27.06. HRMS (M+H): found 573.2208 calculated for $C_{25}H_{38}N_2O_{11}P$ 573.2213.

*4.18.6. N^1-(4′-Bis(POC)-phosphinylbuten-2′-yl)-6-octyl-2,3-dihydrofuro[2,3-d]pyrimidin-2-one (**23f**).* Yellow oil (51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 6.09 (s, 1H), 5.88–5.57 (m, 6H), 4.89 (m, *J*=6.3 Hz, 2H), 4.74 (t, *J*=4.5 Hz, 2H), 2.75 (dd, *J*=22.7, 7.2 Hz, 2H), 2.61 (t, *J*=7.4 Hz, 2H), 1.70–1.59 (m, 2H), 1.27 (m, 22H), 0.85 (t, *J*=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.95, 160.08, 155.36, 153.09, 137.92, 130.28, 123.88, 108.21, 98.54, 84.11, 73.43, 52.01, 31.77, 31.44, 30.05, 29.28, 28.82, 28.26, 26.73, 22.59, 21.60, 14.05. ^{31}P NMR (163 MHz, $CDCl_3$) δ 27.07. HRMS (M+H): found 615.2682 calculated for $C_{28}H_{44}N_2O_{11}P$ 615.2683.

4.19. General procedure 7: deprotection of POC biolabile group via chemical cleavage

To compounds **21a**–**f** (20 mg) was added a 0.1 M Elga water solution of sodium hydroxide (4 mL, 0.4 mmol). After 5 h stirring at room temperature, the solution was passed through a cartridge of acidic ion exchange DOWEX 50W8 resin. The neutral solution was washed two times with CH_2Cl_2 (2 mL) and evaporated to dryness to give pure compound **24a**–**f** (generally quantitative reaction).

*4.19.1. (E)-N^1-(4′-Dihydroxyphosphinylbut-2′-enyl)-5-iodovinyl-uracil (**24a**).* Amorphous solid (97%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.56 (s, 1H), 7.23 (d, *J*=14.6 Hz, 1H), 7.02 (d, *J*=14.6 Hz, 1H), 5.72–5.60 (m, 2H), 4.27 (t, *J*=4.6 Hz, 2H), 2.49 (dd, *J*=21.7, 6.9 Hz, 2H). ^{13}C NMR

(100 MHz, CD_3OD) δ 164.2, 151.8, 144.6, 137.6, 129.2, 129.1, 127.8, 127.7, 113.7, 78.6, 50.5 (2C, $C^{1'}$), 33.4, 32.0. ^{31}P NMR (163 MHz, CD_3OD) δ 23.8. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{10}H_{13}N2O_5IP$: 398.9607, found: 398.9620.

*4.19.2. (E)-N^1-(4′-Dihydroxyphosphinylbut-2′-enyl)-5-bromovinyluracil (**24b**).* Amorphous solid (quantitative). ^1H NMR (400 MHz, CD_3OD) δ 7.63 (s, 1H), 7.31 (d, J=13.6 Hz, 1H), 6.77 (d, J=13.6 Hz, 1H), 5.84–5.66 (m, 2H), 4.35 (t, J=4.5 Hz, 2H), 2.57 (dd, J=21.9, 6.6 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 164.1, 151.8, 144.5, 130.2, 129.3, 129.2, 127.6, 127.5, 112.1, 108.8, 50.5, 33.3, 31.9. ^{31}P NMR (163 MHz, CD_3OD) δ 24.1. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{10}H_{13}N_2O_5BrP$: 350.9745, found: 350.9760.

*4.19.3. (E)-N^1-(4′-Dihydroxyphosphinylbut-2′-enyl)-5-(1,2-diiodovinyl)uracil (**24c**).* Amorphous yellow solid (91%). ^1H NMR (400 MHz, CD_3OD) δ 7.28 (s, 1H), 7.23 (s, 1H), 5.70–5.57 (m, 2H), 4.30 (m, 2H), 2.49 (m, 2H), 1.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 152.9, 142.5, 129.7, 126.6, 111.4, 69.7, 50.1, 25.3, 12.2. ^{31}P NMR (163 MHz, $CDCl_3$) δ 23.58. HRMS (M+Na): found 546.9895 calculated for $C_{10}H_{11}N_2O_5PNaI_2$ 546.9897.

*4.19.4. (E)-N^1-(4′-Dihydroxyphosphinylbuten-2′-yl)-5-(1-bromo-2-iodo vinyl)uracil (**24d**).* Light yellow solid (97%). ^1H NMR (400 MHz, CD_3OD) δ 7.77 (d, J=6.3 Hz, 1H), 7.15 (s, 1H), 5.86–5.67 (m, 2H), 4.34–4.30 (m, 2H), 2.63 (dd, J=21.5, 6.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 151.3, 141.2, 130.5, 129.5, 127.1, 103.8, 69.7 50.4, 26.3. ^{31}P NMR (163 MHz, $CDCl_3$) δ 24.15. HRMS (M+Na): found 499.9999 calculated for $C_{10}H_{11}N_2O_5PNaIBr$ 499.9992.

*4.19.5. (E)-N^1-(4′-Dihydroxyphosphinylbut-2′-enyl)-5-(1-chloro-2-iodovinyl)uracil (**24e**).* Amorphous yellow solid (94%). ^1H NMR (400 MHz, CD_3OD) δ 7.87 (s, 1H), 6.91 (s, 1H), 5.84–5.68 (m, 2H), 4.44–4.35 (m, 2H), 2.70 (dd, J=22.6, 6.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 152.5, 144.5, 130.0, 128.1, 109.7, 103.8, 69.7, 52.1, 33.3. ^{31}P NMR (163 MHz, $CDCl_3$) δ 23.93. HRMS (M+Na): found 455.5412 calculated for $C_{10}H_{11}N_2O_5PNaICl$ 455.5415.

*4.19.6. (E)-N^1-(4′-Dihydroxyphosphinylbut-2′-enyl)-5-(1,2-dibromovinyl)uracil (**24f**).* Amorphous light yellow solid (99%). ^1H NMR (400 MHz, DMSO) δ 11.65 (s, 1H), 7.98 (s, 1H), 6.86 (s, 1H), 5.83–5.69 (m, 2H), 4.37 (m, 2H), 2.63 (dd, J=21.0, 6.3 Hz, 2H). ^{13}C NMR (100 MHz, DMSO) δ 162.0, 152.1, 146.1, 129.4, 127.1, 103.8, 69.7, 96.6, 50.6, 33.0. ^{31}P NMR (163 MHz, $CDCl_3$) δ 24.31. HRMS (M+Na): found 452.9987 calculated for $C_{10}H_{11}N_2O_5PNaBr_2$ 452.9981.

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