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Preparation of acyclo nucleoside phosphonate analogues based on cross-metathesis

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Abstract

In our on-going program targeting anti-pox activity, we report here the synthesis of *hitherto unknown* acyclic nucleoside phosphonates using olefin cross-metathesis (CM) as a key assembly step. Modification at the C-5 position of the uracil moiety was performed under optimized Pd(0)-catalyzed Stille cross-coupling conditions. None of the obtained compounds were active against poxviruses, nor do they exhibit any toxicity.

1. Introduction

The cidofovir (CDV, HPMPC, 1-(*S*)-[3-hydroxy-2-(phosphonomethoxy)propyl]cytosine)[1] is an acyclo nucleoside phosphonate (ANP), which possesses a biologically stable carbon–phosphorus bond. It is a potent and selective anti-DNA virus agent, licensed against the treatment of human cytomegalovirus. It also exhibits in vitro and in vivo potent anti-pox activity (against smallpox virus and monkeypox virus—potential bioterrorism weapons). Because of therapeutic potential, several developments in the modification of cidofovir either on the pyrimidinone (5-aza analogue) or on the side chain (2-pentenyl) have been reported.[2]

As part of an on-going program on orthopox virus, we describe herein an efficient synthesis of several *hitherto unknown* acyclic nucleoside phosphonates. The key synthetic steps leading to these involve the olefin cross-metathesis reaction and the palladium-mediated C5-alkylation of the uracil moiety.

Thus, two series of vinyl ANP (**3**, **15a–f**) and their allyl analogues (**7**, **16a–f**) have been obtained from the same N^1-crotyl-5-phenylthiouracil (Fig. 1).

2. Results and discussion

Unsaturated phosphonates are primarily formed under the Michaelis–Arbuzov reaction,[3] or phosphonylation of unsaturated aldehydes,[4] palladium[5,6] catalyzed cross-coupling of hydrogen phosphonates to conjugated dienes, allenes or alkynes. Nevertheless, often those methods suffer from elimination and/or loss of olefin stereochemical integrity, due to high reaction temperatures and provide low regioselectivity in the case of highly substituted phosphonate products. Over the past decade, the olefin metathesis[7] reaction has become a most powerful tool for advanced organic synthesis, mainly due to the introduction of various ruthenium catalysts such as those developed by Grubbs,[8] Hoveyda,[9] Nolan.[10] The ring-closing metathesis reactions have been already utilized in the construction of a variety of phosphorus containing organic molecules.[11]

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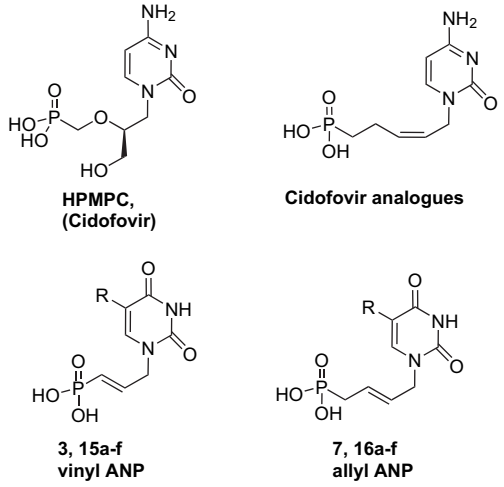
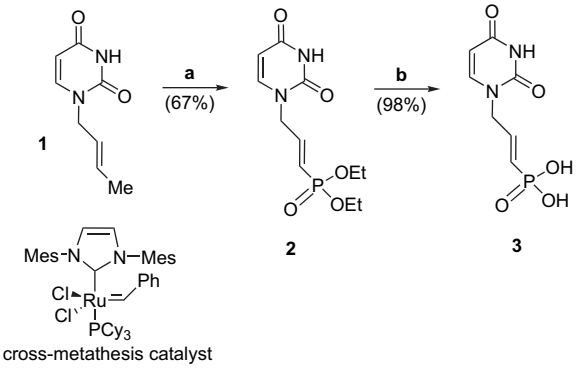


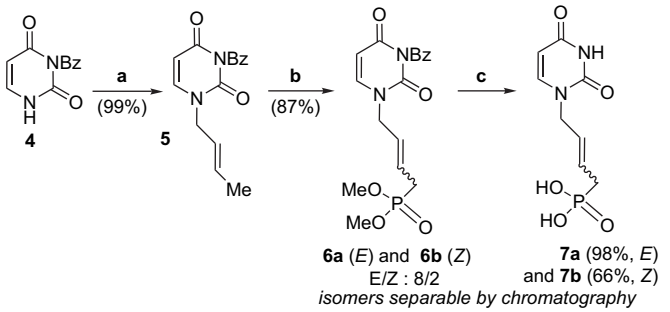
Figure 1. Some bioactive acyclic nucleoside phosphonates and our target compounds.

Recently, Grubbs et al.[12] reported on a general model for selectivity in cross-metathesis (CM), by ranking the olefin reactivity in CM by categorizing the olefins in their abilities to undergo homodimerization via CM and by the stability of those homodimers. Based on this model, we began to explore the cross-metathesis reaction of the reactive crotylated uracil (**1**) with vinyl diethylphosphonate, (Scheme 1). A mixture of the heterodimer (**2**) with the homodimer (**2′**) was obtained. The desired cross-coupling heterodimer (**2**) was obtained in 67% yield as the *E* isomer. It is important to note that the reaction proceeded without the protection at the N^3-position of the heterocycle. Compound **2** was deprotected with TMSBr to afford the desired ANP.



Scheme 1. Reagent and conditions: (a) diethylvinylphosphonate, [Ru]=catalyst (5 mol %), CH_2Cl_2, reflux.

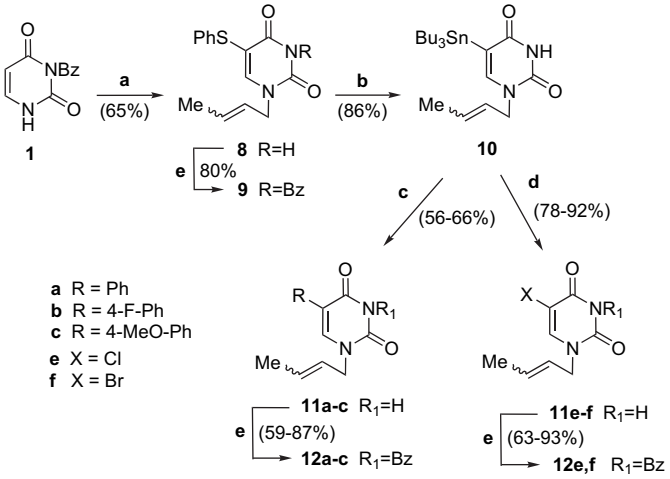
The same procedure was successfully applied to the cross-metathesis involving dimethyllallyl phosphonate. Our preliminary results indicated that the expected heterodimers were isolated in only low yields (20–30%). We thus hypothesized that the active N^3-proton of the pyrimidine would avoid for a metathesis reaction. Thus starting with the N^3-benzoylated crotylated uracil (**5**) prepared from N^3-benzoyluracil (**4**),[13] the CM reaction gave the desired allyl phosphonate (**6**), isolated as a mixture of major and thermodynamically stable *E*-isomer (**6a**, 72%) with the minor *Z*-isomer present in small amounts (**6b**, 15%) (Scheme 2). Both isomers can be separated by liquid chromatography on silica gel.



Scheme 2. Reagent and conditions: (a) crotyl bromide, K_2CO_3, DMF; (b) dimethyl allyl phosphonate (4 equiv), [Ru]=catalyst (5 mol %), CH_2Cl_2, reflux; (c) TMSBr (4.0 equiv), CH_2Cl_2.

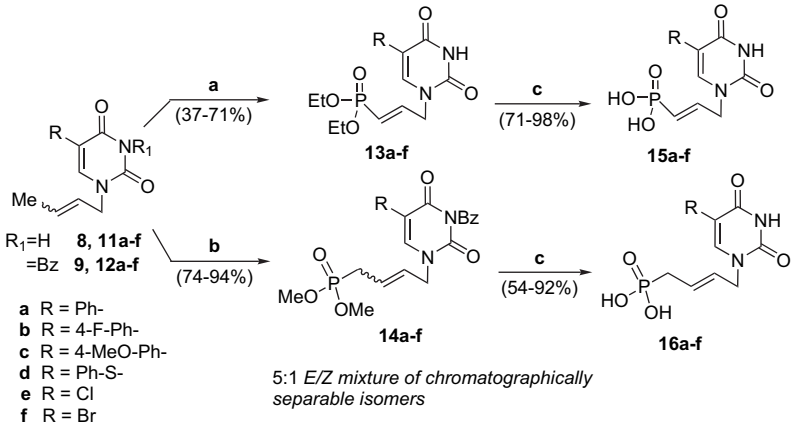
These results indicated that the allyl phosphonate would be more active metathesis partner than the vinyl analogue.

Based on those results, we next extended this approach to several 5-substituted uracil derivatives, which were obtained using the 5-phenylthiouracil derivative (**8**) as a synthetic common intermediate for the construction of either the C5-halogeno- (**11a–c**) or the C5-carbon-substituted (**11d–f**) uracil analogues as well as their N^3-protected analogues (**12a–f**) (Scheme 3).



Scheme 3. Reagent and conditions: (a) (i) PhSH, NCS, pyridine, MeCN, reflux, (ii) crotyl bromide, K_2CO_3, DMF, (iii) K_2CO_3, MeOH; (b) Bu_3SnH, AIBN, toluene, reflux; (c) RI, $PdCl_2(PPh_3)_2$ (10 mol %), CuI, DMF, rt; (d) NXS (for **11e** and **11f**); (e) BzCl, DMAP, *i*-Pr_2Net, MeCN.

Thus, the 5-phenylthio derivative (**8**) was prepared from **4** by (i) introduction of phenylthio group at the C5-position, (ii) crotylation of the N^1-position, and (iii) debenzoylation of N^3-position in 65% over three steps. By treating **8** with tributyltin radical, a sulfur-extrusive stannylation[14] occurred and the desired tin derivative **10** was obtained in high yields. On the one hand, the Pd(0)-mediated Stille-coupling reaction[15] involving **10** allowed for the isolation of the desired C5-carbon substituted derivatives (**11a–c**). On the other hand, compound



Scheme 4. Reagent and conditions: (a) diethyl vinyl phosphonate (4 equiv), [Ru]=catalyst **4** (5 mol %), CH_2Cl_2, reflux; (b) dimethyl allyl phosphonate (4.0 equiv), [Ru]=catalyst (5 mol %), CH_2Cl_2, reflux; (c) TMSBr (4.0 equiv), CH_2Cl_2.

10 was easily converted into the 5-chloro (**11e**), 5-bromo (**11f**) derivatives by simple treatment with NCS or NBS, respectively. A final benzoylation of **11a–f** afforded the desired protected analogues **12a–f**. The 5-phenylthiouracil analogue (**8**) was benzoylated into **9**.

The C5-substituted N^3-unprotected uracil derivatives (**8**, **11a–f**) were engaged in a cross-metathesis reaction with diethyl vinyl phosphonate. The desired cross-metathesis products (**13a–f**) were isolated in moderate to good yield. The stereochemistry of the olefin was confirmed ^{1}H NMR and ^{31}P NMR spectroscopy. The coupling constants of the olefinic protons (average of 17.0 Hz) and the coupling constants of phosphine oxide [average of $^2J_{H-P}$=25.0 Hz and $^3J_{Htrans-P}$=22.5 Hz gave a triplet ($^3J_{Hcis-P}$=41.5 Hz)] are in agreement with the exclusive formation of the thermodynamically stable (*E*)-isomer. A final deprotection by treatment with TMSBr in CH_2Cl_2 afforded the free phosphonates **15a–f** in good yields (Scheme 4).

The cross-metathesis of N^3-protected uracil analogues (**9, 12a–f**) with allyl diethylphosphonate was also performed and the cross products **14a–f** were isolated as a mixture of *E* and *Z* isomers (average *E*/*Z* ratio 8:2) separable by chromatography. The final deprotection of N^3-benzoyl and diethylphosphonate was similarly performed by treatment with TMSBr in CH_2Cl_2, and the free phosphonates (**16a–f**) were obtained in good yields, respectively.

3. Conclusion

In summary, the syntheses of various acyclic nucleoside phosphonates based on alkene cross-metathesis have been achieved. The reactivity and stereochemistry of the cross-coupling metathesis of various C5-substituted crotylated uracil with vinyl(and allyl) phosphonate have been established. The anti-vaccinia virus activity of all synthesized compounds were tested systematically in E_6SM or HEL cell cultures infected with vaccinia virus (Lederle strain ATCC VR-118), on Vero cells infected by vaccinia virus (Lister strain) or by cowpox virus (Brighton strain). No significant activities were observed; these compounds did not exhibit any significant toxicity at concentration up to 100 μM in HEL and Vero cells. The nucleotide binding of all those new acyclic phosphonate analogs to human UMP–CMP kinase or to TMK kinase was performed and results are reported elsewhere.[16]

4. Experimental section

4.1. General

Commercially available chemicals were reagent of grade and used as received. THF was distilled from sodium/benzophenone ketyl; CH_2Cl_2 from CaH_2 immediately prior use and benzene over Na. The reactions were monitored by thin layer chromatography (TLC), analysis using silica gel plates (Kieselgel 60 F_{254}, E. Merck). Compounds were visualized by UV irradiation, followed by charring at 150 °C. Column chromatography was performed on Silica Gel 60M (0.040–0.063 mm, E. Merck). The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 250 and Varian Inova Unity 400 spectrometer (^{1}H: 399.81 MHz, ^{13}C: 100.54 MHz) in $CDCl_3$ or DMSO-$d_6$shift values in parts per million relative to $SiMe_4$ as internal reference, and the ^{31}P spectra were reported using aq phosphoric acid as external reference (^{31}P: 161.97 MHz) in CD_3OD, unless otherwise stated; *J* in hertz. UV–visible spectra were recorded on Perkin–Elmer Lambda25. High Resolution Mass spectra (HRMS) were performed by the Centre Regional de Mesures Physiques de l'Ouest (University of Rennes, France), using FAB (Fast Atom Bombardment) or ESI (Electron Spray Ionization).

4.2. N^1-Crotyluracil (**1**)[17]

Registry number: 852998-43-7.

4.3. N^1-[(E)-3-Diethoxyphosphinyl-2-propenyl]uracil (**2**)

To a CH_2Cl_2 (10 mL) solution of N^1-crotyluracil (**1**) (300 mg, 1.80 mmol) and diethyl vinyl phosphonate (1.119 mL, 7.22 mmol), [Ru]=catalyst **4** (76 mg, 0.05 mmol) was added. This solution was refluxed for 22 h under positive

pressure of dry Ar. After evaporation of all volatiles, the residue was purified by chromatography on silica gel (AcOEt/MeOH: 15:1). Yield: 67% (347 mg) as a foam. ^{1}H NMR (CD_3OD) δ: 1.27 (t, 6H, J=6.9 Hz, $-OCH_2CH_3$), 3.99 (q, 2H, J=6.9 Hz, OCH_2CH_3), 4.02 (q, 2H, J=6.9 Hz, OCH_2CH_3), 4.58 (m, 2H, U−CH_2−), 5.73 (d, 1H, J=8.0 Hz, H5), 5.85 (t, 1H, J=16.8 Hz, CH=CH), 6.80 (ddt, 1H, J=4.4, 16.8, 21.9 Hz, CH=C*H*), 7.57 (d, 1H, J=8.0 Hz, H6), 9.55 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 16.9, 17.0, 62.0, 62.1, 102.3, 117.3, 120.2, 146.1, 147.3, 151.5, and 164.2.

4.4. N^1-[(E)-3-Dihydroxyphosphinyl-2-propenyl]uracil (**3**)

Compound (**2**) (74 mg, 0.26 mmol), was solubilized in CH_2Cl_2 (15 mL), and TMSBr (138 μL, 1.04 mmol) was added and stirred for 60 h at room temperature under positive pressure of dry Ar. MeOH (5 mL) was added and evaporated with heating (ca. 60 °C). MeOH (5 mL) was added again, and this procedure was repeated three times more. The residue was extracted with H_2O and CH_2Cl_2, and the inorganic phase was evaporated to dryness. The desired compound **3** (59 mg, 98%) was isolated as a foam. ^{1}H NMR (DMSO-d_6) δ: 4.40−4.41 (2H, m, U−CH_2−), 5.62 (d, 1H, J=6.6 Hz, H5), 5.69 (t, 1H, J=17.0 Hz, C*H*=CH), 6.60 (ddt, 1H, J=4.7, 17.0, 21.2 Hz, C*H*=CH), 7.60 (d, 1H, J=6.6 Hz, H6), 11.35 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 47.9, 100.7, 121.7, 124.6, 140.1, 140.2, 144.8, 150.0, and 163.0. HRMS: $C_7H_9N_2O_5P$ calcd for m/z 232.1322, found m/z 232.1325.

4.5. N^3-Benzoyl-N^1-crotyluracil (**5**)

A DMF (30 mL) solution of N^3-Benzoyluracil (**4**)[3] (2.19 g, 10.1 mmol) was stirred at room temperature where K_2CO_3 (2.1 g, 15.1 mmol) and crotyl bromide (1.55 mL, 15.15 mmol) were added. This mixture was stirred for 1 h at room temperature under positive pressure of dry Ar. The mixture was treated with EtOAc and aq saturated NH_4Cl, and the organic phase w extracted and dried over $MgSO_4$. After filtration and evaporation of the solution, the residue was purified by column chromatography (petroleum ether/EtOAc=1:2). This procedure provided **5** (2.7 g, 99%) as an oil. ^{1}H NMR ($CDCl_3$) δ: 1.75 (dd, 3H, J=6.6, 1.3 Hz, Me), 4.26−4.30 (m, 2H, U−$CH_{2\ major}$), 4.39−4.42 (m, 2H, U−$CH_{2\ minor}$), 5.46−5.58 (m, 1H, C*H*=CH), 5.74−5.92 (m, 1H, CH=C*H*), 5.75 (1H, d, J=7.9 Hz, H5), 7.27 (1H, d, J=7.9 Hz, H6), 7.40−7.52 (m, 2H, H_{arom}), 7.61−7.68 (m, 1H, H_{arom}), 7.91−7.94 (m, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ: 11.3, 16.0, 42.6, 48.3, 100.3, 100.4, 121.0, 122.1, 127.3, 127.4, 128.7, 128.9, 129.7, 131.0, 133.3, 141.7, 148.0, 148.1, 160.7, and 167.2. HRMS: $C_{15}H_{14}N_2O_3$ calcd for m/z 270.2872, found m/z 270.2881.

4.6. N^3-Benzoyl-N^1-[(3-methoxyphosphinyl-2-butenyl]-uracil (**6**)

A mixture of **5** (500 mg, 1.85 mmol), dimethyl allyl phosphonate (1.11 g, 7.4 mmol), and **5** (74 mg, 0.09 mmol) in CH_2Cl_2 (19 mL) was refluxed for 16 h under positive pressure of dry Ar. After evaporation of all volatiles, the residue was purified by chromatography on silica gel (EtOAc/MeOH=15:1 for **6b**, EtOAc/MeOH=10:1 for **6a**). This gave the major **6a** (504 mg, 72%) and the minor **6b** (107 mg, 15%) as oils, respectively. NMR data for **6a**: ^{1}H NMR ($CDCl_3$) δ: 2.65 (dd, 2H, J=21.4, 5.7 Hz, P(O)CH_2−), 3.75 (d, 6H, J=10.7 Hz, P(*OMe*)$_2$), 4.35−4.38 (2H, m, U−CH_2−), 5.75−5.79 (m, 2H, C*H*=C*H*), 5.83 (1H, d, J=8.2 Hz, H5), (d, 1H, J=8.2 Hz, H6), 7.47−7.53 (m, 2H, H_{arom}), 7.63−7.65 (m, 1H, H_{arom}), 7.92−7.95 (m, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ: 26.7, 28.9, 48.2, 51.4, 51.5, 101.0, 124.5, 124.7, 126.6, 126.9, 127.7, 129.0, 130.0, 133.7, 141.8, 148.2, 160.8, and 167.3. HRMS: $C_{17}H_{19}N_2O_6P$ calcd for m/z 378.3206, found m/z 378.3207. NMR data for **6b**: ^{1}H NMR ($CDCl_3$) δ: 2.75 (dd, 2H, J=22.9 and 7.3 Hz, P(O)CH_2−), 3.76 (d, 6H, J=11.0 Hz, P(*OMe*)$_2$), 4.46−4.50 (m, 2H, U−CH_2−), 5.70−5.81 (m, 2H, C*H*=C*H*), 5.83 (d, 1H, J=7.8 Hz, H5), 7.47−7.53 (m, 2H, H_{arom}), 7.60 (d, 1H, J=7.8 Hz, H6), 7.62−7.69 (m, 1H, H_{arom}), 7.92−7.95 (m, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ: 22.4, 24.6, 43.4, 51.4, 51.5, 101.0, 122.2, 122.4, 126.0, 126.2, 127.7, 129.0, 130.0, 133.6, 142.6, 148.5, 161.0, and 167.4.

4.7. N^1-[(E)-4-Dihydroxyphosphinyl-2-butenyl]uracil (**7a**)

To a CH_2Cl_2 (30 mL) solution of **6a** (254 mg, 0.67 mmol), TMSBr (360 μL, 2.69 mmol) was added and stirred for 60 h at room temperature under positive pressure of dry Ar. MeOH (5 mL) was added and evaporated with heating (ca. 60 °C). MeOH (5 mL) was added again, and this procedure was repeated three more times. The residue was extracted with H_2O and CH_2Cl_2 and the inorganic phase was evaporated. Compound **7a** was isolated as a foam (165 mg, >98%). ^{1}H NMR (DMSO-d_6) δ: 2.35−2.46 (m, 2H, P−CH_2−), 4.24−4.26 (m, 2H, U−CH_2−), 5.56 (d, 1H, J=8.2 Hz, H5), 5.61−5.69 (m, 2H, C*H*=C*H*), 7.57 (d, 1H, J=8.2 Hz, H6), 11.26 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 31.7, 33.8, 49.1, 101.8, 127.0, 127.1, 128.2, 128.4, 145.9, 151.5, and 164.4. HRMS: $C_8H_{11}N_2O_5P$ calcd for m/z 246.1590, found m/z 246.1592.

4.8. N^1-[(Z)-4-Dihydroxyphosphinyl-2-butenyl]uracil (**7b**)

Compound **7b** was prepared from **6b** (100 mg, 0.26 mmol) using the same procedure as mentioned above. Compound **7b** was isolated as a foam (43 mg, 66%). ^{1}H NMR (DMSO-d_6) δ: 2.52−2.65 (m, 2H, P−CH_2−), 4.25−4.36 (m, 2H, U−CH_2−), 5.48−5.70 (m, 3H, H5 and C*H*=C*H*), 7.69 (d, 1H, J=7.8 Hz, H6), 11.26 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 31.7, 33.8, 46.2, 103.3, 127.7, 127.9, 129.0, 147.6, 153.3, and 166.0. HRMS: $C_8H_{11}N_2O_5P$ calcd for m/z 246.1590, found m/z 246.1591.

4.9. N^1-Crotyl-5-phenylthiouracil (**8**)

A mixture of NCS (3.7 g, 27.8 mmol) in MeCN (60 mL) was cooled to 0 °C. PhSH (2.9 mL, 27.8 mmol) was added dropwise to the mixture and stirred. After 0.5 h, **1** (2.0 g,

9.25 mmol) was added at 0 °C and stirred for 0.5 h. Pyridine (2.28 mL, 27.8 mmol) was then added and the mixture was refluxed for 16 h under positive pressure of dry Argon. After evaporation of all volatiles, the residue was purified by chromatography on silica gel (petroleum ether/EtOAc=1:2). This gave crude 5-phenylthiouracil derivative (this included some of succinimide). This was used for the next reaction without further purification. A DMF (40 mL) solution of the crude 5-phenylthiouracil (4.03 g), K_2CO_3 (3.84 g, 27.8 mmol), and crotyl bromide (1.9 ml, 18.5 mmol) was stirred for 40 min at room temperature under positive pressure of dry Argon. After extraction of this reaction mixture with EtOAc and aq saturated NH_4Cl, the organic phase was separated and dried over $MgSO_4$, filtered, and evaporated to dryness. This was purified by chromatography on silica gel (petroleum ether/EtOAc=1:1). This gave crotylated product (2.61 g) as an oil. This product was used in the next step. A mixture of the above crotylated product (2.61 g) and NH_3/MeOH (0 °C, saturated, 50 mL) was kept below 0 °C for 22 h. After evaporation of all volatiles, the residue was purified by chromatography on silica gel (petroleum ether/EtOAc=1:2). This gave **8** (2.27 g, 65% over 3 steps) as a solid (1:3 of stereoisomeric mixture). ^{1}H NMR ($CDCl_3$) δ: 1.69–1.77 (m, 3H, CH_3), 4.30 (d, 2H, J=6.6 Hz, U–$CH_{2\ major}$), 4.41 (d, 2H, J=7.2 Hz, U–$CH_{2\ minor}$), 5.45–5.57 (m, 2H, C*H*=C*H*$_{major}$), 5.73–5.91 (m, 2H, C*H*=C*H*$_{minor}$), 7.17–7.32 (m, 5H, H_{arom}), 7.59 (s, 1H, H6), 9.16 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 18.2, 50.3, 107.5, 123.0, 124.2, 127.3, 129.2, 132.1, 133.4, 135.4, 148.4, 148.8, 150.8, and 161.8. HRMS: $C_{14}H_{14}N_2O_2S$ calcd for *m*/*z* 274.3428, found *m*/*z* 274.3431.

4.10. N^3-Benzoyl-N^1-crotyl-5-phenylthiouracil (**9**)

To a stirred MeCN (15 mL) solution of crotyluracil analogue (**8**) (400 mg, 1.46 mmol), *N*,*N*-dimethylaminopyridine (320 mg, 2.62 mmol) and *i*-Pr_2NEt (608 μL, 3.50 mmol), benzoyl chloride (302 mL, 2.62 mmol) was added and stirred for 1 h at room temperature under positive pressure of dry Ar. This mixture was then extracted with CH_2Cl_2 and aq saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on silica gel (petroleum ether/EtOAc=1:2) to yield the desired compound **9**. Yield: 80% (440 mg) as an oil (1:3 of stereoisomeric mixture). ^{1}H NMR ($CDCl_3$) δ: 1.77 (dd, 3H, J=0.6, 6.2 Hz, CH_3), 4.32 (d, 2H, J=6.6 Hz, U–$CH_{2\ major}$), 4.43 (d, 2H, J=7.2 Hz, U–$CH_{2\ minor}$), 5.46–5.57 (m, 1H, CH=C*H*), 5.79–5.88 (m, 1H, C*H*=CH), 7.09–7.26 (m, 5H, H_{arom}), 7.31–7.37 (m, 2H, H_{arom}), 7.56–7.66 (m, 1H, H_{arom}), 7.67 (s, 1H, H6), 7.87–7.90 (m, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ: 13.4, 18.1, 45.0, 50.6, 107.9, 108.2, 122.7, 123.8, 127.5, 128.4, 129.5, 129.9, 130.5, 130.7, 131.5, 132.4, 133.9, 134.0, 135.4, 142.4, 147.7, 149.8, 161.0, and 168.6.

4.11. N^1-Crotyl-5-(tributyl)stannyluracil (**10**)

A toluene (50 mL) solution of **8** (2.5 g, 9.11 mmol), tri-*n*-butyltin hydride (3.68 mL, 13.67 mmol), AIBN (448 mg, 2.73 mmol), and Et_3N (2.54 mL, 18.2 mmol) were refluxed for 2 h under positive pressure of dry Argon. After evaporation of all volatiles, this was purified by chromatography on silica gel (petroleum ether/EtOAc=2:1). The product **10** (3.56 g, 86%) was obtained as an oil (1:3 of stereoisomeric mixture). ^{1}H NMR ($CDCl_3$) δ: 0.82–1.55 (m, 27H, Sn*Bu*$_3$), 1.73–1.78 (m, 3H, CH_3), 4.27 (d, 2H, J=6.0 Hz, U–$CH_{2\ major}$), 4.39 (d, 2H, J=6.0 Hz, U–$CH_{2\ minor}$), 4.39 (d, 2H, J=7.2 Hz, U–CH_2), 5.46–5.55 (m, 2H, C*H*=C*H*), 5.68–5.82 (m, 2H, C*H*=C*H*), 6.91 (t, 1H, $J_{H,Sn}$=15.7 Hz, H6), 8.23 (br, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 8.7, 12.6, 16.7, 26.2, 27.9, 48.1, 111.1, 123.7, 130.1, 146.6, 150.2, and 165.5.

4.12. General procedure for the Stille reaction

A mixture of **9** (500 mg, 1.1 mmol), aryliodide (370 mL, 3.3 mmol), $PdCl_2(PPh_3)_2$ (77 mg, 0.11 mmol), and CuI (42 mg, 0.22 mmol) in DMF (2 mL) was stirred for 15 h at room temperature under positive pressure of dry Ar. This mixture was extracted with brine and EtOAc. The organic phase was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on silica gel (petroleum ether/EtOAc=1:1) and the desired compound was isolated.

4.12.1. N^1-Crotyl-5-phenyluracil (**11a**)

Yield: 66% (175 mg) as a solid (1:3 stereoisomeric mixture). ^{1}H NMR ($CDCl_3$) δ: 1.26–1.81 (m, 3H, CH_3), 4.36 (d, 2H, J=6.6 Hz, U–C$H_{2\ major}$), 4.48 (d, 2H, J=6.9 Hz, U–C$H_{2\ minor}$), 5.50–5.61 (m, 2H, C*H*=C*H*), 5.74–5.88 (m, 2H, C*H*=C*H*), 7.26–7.53 (m, 6H, H_{arom} and H6), 9.12 (br, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 18.1, 50.3, 115.7, 124.6, 128.3, 128.4, 128.8, 132.5, 141.4, 150.2, and 162.7. HRMS: $C_{14}H_{14}N_2O_2$ calcd for *m*/*z* 242.2768, found *m*/*z* 242.2773.

4.12.2. N^1-Crotyl-5-(4-fluorophenyl)-uracil (**11b**)

Yield: 66% (376 mg) as a solid (1:3 of stereoisomeric mixture). ^{1}H NMR ($CDCl_3$) δ: 1.73–1.80 (m, 3H, CH_3), 4.35 (d, 2H, J=6.3 Hz, U–C$H_{2\ major}$), 4.46 (d, 2H, J=7.2 Hz, U–C$H_{2\ minor}$), 5.49–5.61 (m, 2H, C*H*=C*H*), 5.75–5.86 (m, 2H, C*H*=C*H*), 7.02–7.11 (m, 2H, 4-F–Ph), 7.31 (s, 1H, H6), 7.45–7.53 (m, 2H, 4-F–Ph), 10.49 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 16.5, 48.5, 113.2, 113.1, 113.5, 123.0, 126.9, 128.6, 128.7, 131.0, 139.6, 148.9, 160.9, and 163.3. HRMS: $C_{14}H_{13}FN_2O_2$ calcd for *m*/*z* 260.2673, found *m*/*z* 260.2675.

4.12.3. N^1-Crotyl-5-(4-methoxyphenyl)-uracil (**11c**)

Yield: 56% (336 mg) as a solid (1:3 of stereoisomeric mixture). ^{1}H NMR ($CDCl_3$) δ: 1.73–1.80 (m, 3H, CH_3), 3.82 (s, 3H, CH_3–O–Ph), 4.35 (d, 2H, J=6.3 Hz, U–C$H_{2\ major}$), 4.47 (d, 2H, J=7.2 Hz, U–C$H_{2\ minor}$), 5.52–5.58 (m, 2H, C*H*=C*H*), 5.76–5.85 (m, 2H, C*H*=C*H*), 6.94 (d, 2H, J=9.0 Hz, H_{arom}), 7.24 (s, 1H, H6), 7.44 (d, 2H, J=9.0 Hz, H_{arom}), 8.93 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 17.0, 48.9, 54.6, 113.3, 114.4, 123.8, 128.6, 131.2, 139.4, 149.6, 158.8, and 163.8. HRMS: $C_{15}H_{16}N_2O_3$ calcd for *m*/*z* 272.3030, found *m*/*z* 272.3033.

*4.12.4. 5-Chloro-N^1-crotyluracil (**11e**)*

A THF (10 ml) solution of **9** (1.0 g, 2.2 mmol) and NCS (588 mg, 4.4 mmol) was refluxed for 24 h under positive pressure of dry Ar. After evaporation of all of volatiles, this was purified by chromatography on silica gel (petroleum ether/AcOEt=1:1). This gave **10e** (360 mg, 81%) as a solid (1:3 of stereoisomeric mixture). ^{1}H NMR ($CDCl_3$) δ: 1.74–1.79 (m, 3H, CH_3), 4.28 (d, 2H, J=7.5 Hz, U–C$H_{2\ major}$), 4.40 (d, 2H, J=7.5 Hz, U–C$H_{2\ minor}$), 5.28–5.56 (m, 2H, CH=CH), 5.73–5.93 (m, 2H, CH=CH), 7.39 (s, 1H, $H6_{minor}$), 7.49 (s, 1H, $H6_{major}$), 11.43 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 16.0, 50.6, 106.4, 121.4, 130.4, 138.8, 148.6 and 158.2. HRMS: $C_8H_9ClN_2O_2$ calcd for *m/z* 200.6240, found *m/z* 200.6242.

*4.12.5. 5-Bromo-N^1-crotyluracil (**11f**)*

A THF (10 mL) solution of **9** (1.0 g, 2.2 mmol) and NBS (508 mg, 2.86 mmol) was stirred for 1.5 h at room temperature under positive pressure of dry Ar. After extraction of that between CH_2Cl_2 and H_2O, the organic phase was dried with $MgSO_4$, filtrated, and evaporated. This was purified by chromatography on silica gel (petroleum ether/EtOAc=1:2). This gave **10f** (496 mg, 92%) as an oil (1:3 stereoisomeric mixture). ^{1}H NMR ($CDCl_3$) δ: 1.75–1.78 (m, 3H, CH_3), 4.30 (d, 2H, J=6.6 Hz, U–C$H_{2\ major}$), 4.42 (d, 1H, J=7.2 Hz, U–C$H_{2\ minor}$), 5.43–5.56 (m, 2H, CH=CH), 5.75–5.90 (m, 21H, CH=CH), 7.48 (s, 1H $H6_{minor}$), 7.51 (s, 1H $H6_{major}$), 8.96 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 19.4, 51.5, 98.0, 124.1, 125.3, 134.7, 144.6, 151.6, and 160.8. HRMS: $C_8H_9BrN_2O_2$ calcd for *m/z* 245.0753, found *m/z* 245.0757.

4.13. General procedure for N^3-benzoylation of uracil analogues

To a stirred MeCN (15 mL) solution of crotyluracil analogue (428 mg, 1.75 mmol), *N*,*N*-dimethylaminopyridine (320 mg, 2.62 mmol) and *i*-Pr_2NEt (608 μL, 3.50 mmol), benzoyl chloride (302 mL, 2.62 mmol) was added, and stirred for 1 h at room temperature under positive pressure of dry Ar. This was extracted with CH_2Cl_2 and aq saturated $NaHCO_3$. The organic layer was dried with $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on silica gel (petroleum ether/EtOAc=1:2) to yield the desired compound.

*4.13.1. N^3-Benzoyl -N^1-crotyl-5-phenyluracil (**12a**)*

Yield: 59% (279 mg) as an oil (1:3 stereoisomeric mixture). ^{1}H NMR ($CDCl_3$) δ: 1.77 (dd, 3H, J=1.2, 6.5 Hz, CH_3), 4.37 (d, 2H, J=6.4 Hz, U–C$H_{2\ major}$), 4.50 (d, 2H, J=6.9 Hz, U–C$H_{2\ minor}$), 5.49–5.63 (m, 1H, CH=CH), 5.78–5.80 (m, 1H, CH=CH), 7.29–7.41 (m, 4H, H_{arom} and H6), 7.49–7.54 (m, 4H, H_{arom}), 7.61–7.66 (m, 1H, H_{arom}), 7.95–7.99 (m, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ: 20.4, 52.6, 117.7, 125.4, 126.5, 130.7, 131.1, 131.7, 133.0, 134.2, 134.3, 135.4, 137.5, 143.1, 143.2, 151.9, 164.1, and 171.6.

*4.13.2. N^3-Benzoyl-N^1-crotyl-5-(4-fluorophenyl)-uracil (**12b**)*

Yield: 87% (282 mg) as an oil (1:3 stereoisomeric mixture). ^{1}H NMR ($CDCl_3$) δ: 1.77 (dd, 3H, J=1.2, 6.2 Hz, CH_3), 4.38 (d, 2H, J=6.6 Hz, U–C$H_{2\ major}$), 4.51 (d, 2H, J=7.2 Hz, U–C$H_{2\ minor}$), 5.49–5.64 (m, 1H, CH=CH), 5.79–5.94 (m, 1H, CH=CH), 7.03–7.11 (m, 2H, H_{arom}), 7.39 (s, 1H, H6), 7.45–7.52 (m, 2H, H_{arom}), 7.64 (m, 1H, H_{arom}), 7.94–7.98 (m, 2H, H_{arom}), 8.10–8.13 (m, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ: 18.2, 50.5, 114.7, 115.7, 116.1, 123.2, 124.3, 128.1, 128.2, 128.9, 129.5, 130.2, 130.3, 130.6, 130.8, 131.9, 132.0, 133.3, 134.1, 135.5, 140.7, 140.8, 149.7, 161.1, 161.9, 165.0, 169.2, and 172.2.

*4.13.3. N^3-Benzoyl-N^1-crotyl-5-(4-methoxyphenyl)-uracil (**12c**)*

Yield: 74% (314 mg) as an oil (1:3 stereoisomeric mixture). ^{1}H NMR ($CDCl_3$) δ: 1.76 (dd, 3H, J=0.9, 6.2 Hz, CH_3), 3.80 (s, 3H, OMe), 4.37 (d, 2H, J=6.6 Hz, U–C$H_{2\ major}$), 4.49 (d, 2H, J=6.9 Hz, U–C$H_{2\ minor}$), 5.52–5.63 (m, 1H, CH=CH), 5.78–5.87 (m, 1H, CH=CH), 6.88–6.94 (m, 2H, H_{arom}), 7.36 (s, 1H, H6), 7.44–7.52 (m, 4H, H_{arom}), 7.61–7.67 (m, 1H, H_{arom}), 7.95–7.98 (m, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ: 20.3, 52.5, 57.8, 116.5, 117.4, 125.4, 126.5, 131.6, 132.9, 133.9, 134.1, 135.1, 137.4, 142.0, 142.2, 151.8, 162.1, 164.2, and 171.5.

*4.13.4. N^3-Benzoyl-5-chloro-N^1-crotyluracil (**12e**)*

Yield: 93% (706 mg) as an oil (1:3 stereoisomeric mixture). ^{1}H NMR ($CDCl_3$) δ: 1.77 (dd, 3H, J=1.0, 6.6 Hz, CH_3), 4.31 (d, 2H, J=6.6 Hz, U–C$H_{2\ major}$), 4.44 (d, 2H, J=7.5 Hz, U–C$H_{2\ minor}$), 5.37–5.58 (m, 1H, CH=CH), 5.79–5.96 (m, 1H, CH=CH), 7.45–7.53 (m, 2H, H_{arom}), 7.50 (s, 1H, H6), 7.63–7.69 (m, 1H, H_{arom}), 7.89–7.93 (m, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ: 17.8, 50.3, 108.5, 119.5, 122.1, 123.4, 129.2, 130.5, 131.0, 132.3, 133.8, 135.3, 140.1, 140.2, 148.8, 158.3, and 167.6.

*4.13.5. N^3-Benzoyl-5-bromo-N^1-crotyluracil (**12f**)*

Yield: 63% (387 mg) as a solid (1:3 stereoisomeric mixture). ^{1}H NMR ($CDCl_3$) δ: 1.77 (dd, 3H, J=1.2, 6.5 Hz, CH_3), 4.30 (d, 2H, J=6.9 Hz, U–C$H_{2\ major}$), 4.44 (d, 2H, J=7.5 Hz, U–C$H_{2\ minor}$), 5.42–5.59 (m, 1H, CH=CH), 5.74–5.96 (m, 1H, CH=CH), 7.44–7.50 (m, 2H, H_{arom}), 7.52–7.63 (m, 1H, H_{arom}), 7.62 (s, 1H, H6), 7.75–7.78 (m, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ: 17.4, 17.5, 49.5, 49.9, 95.8, 95.9, 121.8, 122.2, 123.0, 123.3, 128.8, 130.1, 130.6, 131.4, 131.9, 132.6, 133.4, 134.9, 142.4, 142.5, 148.7, 149.6, 157.9, 158.8, and 167.3.

4.14. General procedure for cross-metathesis with diethyl vinyl phosphonate

To a CH_2Cl_2 (10 mL) solution of N^1-crotyl-5-substituted uracil (300 mg, 1.03 mmol) and diethyl vinyl phosphonate (635 μL, 4.1 mmol), (**4**) (42 mg, 0.05 mmol) was added. This solution was refluxed for 22 h under positive pressure of dry Ar. After evaporation of all volatiles, the residue was purified by chromatography on silica gel (EtOAc/MeOH=15:1).

*4.14.1. N^1-[(E)-3-Diethoxyphosphinyl-2-propenyl]-5-phenyluracil (**13a**)*

Yield: 67% (222 mg) as a solid. ^{1}H NMR ($CDCl_3$) δ: 1.31 (t, 6H, J=7.3 Hz, $-OCH_2CH_3$), 4.07 (q, 2H, J=7.3 Hz, OCH_2CH_3), 4.12 (q, 2H, J=7.3 Hz, OCH_2CH_3), 4.55–4.59 (m, 2H, U–CH_2–), 5.85 (t, 1H, J=16.9 Hz, C*H*=CH), 6.78 (ddt, 1H, J=5.0, 16.9, 21.9 Hz, CH=C*H*), 7.23–7.50 (m, 6H, H6 and H_{arom}), 8.68 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 15.2, 15.3, 48.9, 61.2, 61.4, 115.2, 118.4, 121.4, 127.1, 127.3, 127.6, 130.6, 139.7, 143.1, 143.2, 148.8, and 160.8. HRMS: $C_{17}H_{21}N_2O_5P$ calcd for *m/z* 364.3370, found *m/z* 364.3372.

*4.14.2. N^1-[(E)-3-Diethoxyphosphinyl-2-propenyl]-5-(4-fluorophenyl)uracil (**13b**)*

Yield: 71% (198 mg) as a foam. ^{1}H NMR ($CDCl_3$) δ: 1.25 (t, 6H, J=6.9 Hz, $-OCH_2CH_3$), 4.13 (m, 4H, $-OCH_2CH_3$), 4.54–4.58 (m, 2H, U–CH_2–), 5.85 (t, 1H, J=17.2 Hz, C*H*=CH), 6.78 (ddt, 1H, J=5.0, 17.2, 21.3 Hz, CH=C*H*),7.03–7.12 (m, 2H, 4-F–*Ph*), 7.23 (s, 1H, H6), 7.43–7.49 (m, 2H, 4-F–*Ph*), 9.55 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 15.4, 15.5, 48.7, 61.3, 61.4, 114.9, 118.5, 121.5, 126.8, 126.9, 129.0, 139.8, 143.4, 143.5, 149.2, 159.8, 161.4, and 163.8. HRMS: $C_{17}H_{20}FN_2O_5P$ calcd for *m/z* 382.3275, found *m/z* 382.3276.

*4.14.3. N^1-[(E)-3-Diethoxyphosphinyl-2-propenyl]-5-(4-methoxyphenyl)uracil (**13c**)*

Yield: 52% (135 mg) as a foam. ^{1}H NMR ($CDCl_3$) δ: 1.32 (t, 6H, J=7.2 Hz, $-OCH_2CH_3$), 3.83 (s, 3H, MeO), 4.08 (q, 2H, J=7.2 Hz, OCH_2CH_3), 4.11 (q, 2H, J=7.2 Hz, OCH_2CH_3), 4.55 (m, 2H, U–CH_2–), 5.84 (t, 1H, J=17.3 Hz, C*H*=CH), 6.77 (ddt, 1H, J=5.0, 17.3, 22.0 Hz, CH=C*H*), 6.92 (d, 2H, J=8.8 Hz, H_{arom}), 7.17 (1H, s, H6), 7.42 (d, 2H, J=8.8 Hz, H_{arom}), 8.80 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 17.9, 18.0, 57.0, 63.8, 63.9, 115.7, 117.6, 120.9, 123.9, 125.5, 127.5, 131.0, 141.5, 145.9, 146.0, 151.5, 161.3, and 163.8. HRMS: $C_{18}H_{23}N_2O_6P$ calcd for *m/z* 394.3632, found *m/z* 394.3634.

*4.14.4. N^1-[(E)-3-Diethoxyphosphinyl-2-propenyl]-5-phenylthiouracil (**13d**)*

Yield: 42% (111 mg) as a solid. ^{1}H NMR ($CDCl_3$) δ: 1.33 (t, 6H, J=7.2 Hz, $-OCH_2CH_3$), 4.06 (q, 2H, J=7.2 Hz, OCH_2CH_3), 4.09 (q, 2H, J=7.2 Hz, OCH_2CH_3), 4.51–4.55 (m, 2H, U–CH_2–), 5.80 (t, 1H, J=17.3 Hz, C*H*=CH), 6.73 (ddt, 1H, J=4.7, 17.3, 22.2 Hz, CH=C*H*), 7.15–7.28 (m, 5H, H_{arom}), 7.63 (s, 1H, H6), 11.20 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 17.2, 17.3, 41.0, 62.9, 63.0, 108.3, 120.0, 127.6, 129.2, 130.0, 145.4, 149.5, 151.4, and 163.0. HRMS: $C_{17}H_{21}N_2O_5PS$ calcd for *m/z* 396.403, found *m/z* 396.4032.

*4.14.5. 5-Chloro-N^1-[(E)-3-diethoxyphosphinyl-2-propenyl]uracil (**13e**)*

Yield: 63% (260 mg) as a solid. ^{1}H NMR ($CDCl_3$) δ: 1.34 (t, 6H, J=7.1 Hz, $-OCH_2CH_3$), 4.08 (q, 2H, J=7.1 Hz, OCH_2CH_3), 4.12 (q, 2H, J=7.1 Hz, OCH_2CH_3), 4.50–4.52 (m, 2H, U–CH_2–), 5.83 (t, 1H, J=17.1 Hz, C*H*=CH), 6.73 (ddt, 1H, J=4.7, 17.1, 21.6 Hz, CH=C*H*), 7.35 (s, 1H, H6), 9.44 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 17.9, 18.0, 51.7, 63.9, 64.1, 111.2, 121.4, 124.4, 141.9, 145.3, 151.1, and 160.5. HRMS: $C_{11}H_{16}ClN_2O_5P$ calcd for *m/z* 322.6842, found *m/z* 322.6839.

*4.14.6. 5-Bromo-N^1-[(E)-3-diethoxyphosphinyl-2-propenyl]uracil (**13f**)*

Yield: 37% (302 mg) as a foam. ^{1}H NMR ($CDCl_3$) δ: 1.33 (t, 6H, J=7.2 Hz, $-OCH_2CH_3$), 4.09 (q, 2H, J=7.2 Hz, OCH_2CH_3), 4.12 (q, 2H, J=7.2 Hz, OCH_2CH_3), 4.49–4.53 (m, 2H, U–CH_2–), 5.84 (t, 1H, J=17.0 Hz, C*H*=CH), 6.77 (ddt, 1H, J=4.7, 17.0, 21.9 Hz, CH=C*H*), 7.46 (s, 1H, H6), 9.44 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 18.6, 18.7, 52.0, 52.4, 64.4, 64.6, 99.6, 122.0, 125.0, 145.2, 152.0, and 161.4. HRMS: $C_{11}H_{16}BrN_2O_5P$ calcd for *m/z* 367.1355, found *m/z* 367.1357.

4.15. General procedure for cross-metathesis with dimethyl allyl phosphonate

A mixture of protected N^1-crotyl-5-substituted uracil (332 mg, 0.95 mmol), dimethyl allyl phosphonate (572 mg, 3.8 mmol), and (**4**) (41 mg, 0.05 mmol) in CH_2Cl_2 (10 mL) was refluxed for 16 h under positive pressure of dry Ar. After evaporation of all volatiles, the residue was purified by chromatography on silica gel (EtOAc/MeOH=20:1) to yield the desired compound.

*4.15.1. N^3-Benzoyl-N^1-(4-dimethoxyphosphinyl-2-butenyl)-5-phenyluracil (**14a**)*

Yield: 94% (270 mg), as an oil. ^{1}H NMR ($CDCl_3$) δ: 2.57–2.83 (m, 2H, P–CH_2–), 3.66–3.78 (m, 6H, P(*OMe*)$_2$), 4.42–4.46 (m, 2H, U–CH_2), 5.72–5.85 (m, 2H, C*H*=C*H*), 7.27–7.69 (m, 8H, H_{arom}), 7.43 (s, 1H, H6), 7.95–7.99 (m, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ: 28.6, 30.8, 50.0, 53.1, 53.2, 115.8, 120.5, 126.5, 126.7, 128.5, 128.7, 128.8, 128.9, 129.0, 129.6, 131.9, 132.0, 135.5, 140.9, 141.5, 149.7, 161.9, and 169.3. HRMS: $C_{23}H_{23}N_2O_6P$ calcd for *m/z* 454.4182, found *m/z* 454.4179.

*4.15.2. N^3-Benzoyl-N^1-(4-dimethoxyphosphinyl-2-butenyl)-5-(4-fluorophenyl)uracil (**14b**)*

Yield: 81% (199 mg) as an oil. ^{1}H NMR ($CDCl_3$) δ: 2.61–2.85 (m, 2H, P–CH_2–), 3.67–3.77 (m, 6H, P(*OMe*)$_2$), 4.43–4.47 (m, 2H, U–CH_2), 5.70–5.81 (m, 2H, C*H*=C*H*), 7.03–7.11 (m, 2H, H_{arom}), 7.41 (s, 1H, H6), 7.47–7.68 (m, 4H, H_{arom}), 7.68–7.76 (m, 1H, H_{arom}), 7.94–7.96 (2H, m, Ph). ^{13}C NMR ($CDCl_3$) δ: 29.3, 31.6, 50.9, 53.9, 54.0, 115.7, 116.5, 127.0, 127.4, 127.6, 128.8, 129.3, 129.5, 129.7, 130.4, 131.0, 131.2, 131.6, 132.6, 141.4, 150.4, 161.9, 162.6, and 169.9. HRMS: $C_{23}H_{22}FN_2O_6P$ calcd for *m/z* 472.4086, found *m/z* 472.4088.

*4.15.3. N^3-Benzoyl-N^1-(4-dimethoxyphosphinyl-2-butenyl)-5-(4-methoxyphenyl)uracil (**14c**)*

Yield: 92% (320 mg) as an oil. ^{1}H NMR ($CDCl_3$) δ: 2.58–2.76 (m, 2H, P–CH_2–), 3.67–3.74 (m, 6H, P(*OMe*)$_2$), 3.80 (s,

3H, *Me*O), 4.42–4.45 (m, 2H, U–CH_2), 5.70–5.88 (m, 2H, C*H*=C*H*), 6.89–6.92 (m, 2H, H_{arom}), 7.37 (s, 1H, H6), 7.44–7.68 (m, 6H, H_{arom}), 7.61–7.68 (m, 1H, H_{arom}), 7.95–7.98 (m, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ: 29.5, 31.7, 50.9, 54.0, 54.1, 56.7, 115.3, 116.5, 121.5, 125.2, 127.3, 127.5, 128.3, 129.6, 129.8, 130.5, 130.7, 131.8, 132.9, 136.3, 140.8, 150.6, 161.0, 163.0, and 170.3. HRMS: $C_{24}H_{25}N_2O_7P$ calcd for *m/z* 484.4444, found *m/z* 484.4449.

*4.15.4. N^3-Benzoyl-N^1-(4-dimethoxyphosphinyl-2-butenyl)-5-phenylthiouracil (**14d**)*

Yield: 74% (357 mg, oil) ^{1}H NMR ($CDCl_3$) δ: 2.58–2.80 (m, 2H, P–CH_2–), 3.73–3.79 (m, 6H, P(*OMe*)$_2$), 4.37–4.41 (m, 2H, U–CH_2), 5.66–5.88 (m, 2H, C*H*=C*H*), 7.19–7.32 (m, 5H, H_{arom}), 7.45–7.51 (m, 2H, H_{arom}), 7.61–7.64 (m, 1H, H_{arom}), 7.70 (s, 1H, H6), 7.87–7.94 (m, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ: 26.6, 28.9, 48.3, 51.2, 51.3, 106.5, 125.3, 125.5, 125.8, 126.1, 126.3, 127.6, 127.7, 127.9, 128.0, 128.9, 129.6, 132.7, 133.6, 145.7, 147.9, 159.0, and 166.5. HRMS: $C_{23}H_{23}N_2O_6PS$ calcd for *m/z* 486.4842, found *m/z* 486.4843.

*4.15.5. N^3-Benzoyl-5-chloro-N^1-(4-dimethoxyphosphinyl-2-butenyl)uracil (**14e**)*

Yield: 87% (668 mg) as an oil. ^{1}H NMR ($CDCl_3$) δ: 2.58–2.80 (m, 2H, P–CH_2–), 3.69–3.81 (m, 6H, P(*OMe*)$_2$), 4.35–4.39 (m, 2H, U–CH_2), 5.65–5.92 (m, 2H, C*H*=C*H*), 7.48–7.54 (m, 2H, H_{arom}), 7.55 (s, 1H, H6), 7.64–7.70 (m, 1H, H_{arom}), 7.90–7.94 (m, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ: 28.7, 31.0, 50.4, 53.4, 53.6, 109.3, 125.1, 127.4, 127.9, 128.3, 129.8, 131.1, 131.5, 135.9, 140.7, 149.4, 158.7, and 168.1. HRMS: $C_{17}H_{18}ClN_2O_6P$ calcd for *m/z* 412.7654, found *m/z* 412.7657.

*4.15.6. N^3-Benzoyl-5-bromo-N^1-(4-dimethoxyphosphinyl-2-butenyl)uracil (**14f**)*

Yield: 74% (323 mg) as an oil. ^{1}H NMR ($CDCl_3$) δ: 2.62–2.80 (m, 2H, P–CH_2–), 37.6–38.1 (m, 6H, P(*OMe*)$_2$), 4.37–4.41 (m, 2H, U–CH_2), 5.66–5.93 (m, 2H, C*H*=C*H*), 7.48–7.54 (m, 2H, H_{arom}), 7.64 (s, 1H, H6), 7.64–7.70 (m, 1H, H_{arom}), 7.90–8.00 (m, 2H, H_{arom}). ^{13}C NMR ($CDCl_3$) δ: 26.4, 28.6, 48.1, 51.0, 51.1, 94.7, 125.4, 125.6, 125.7, 125.9, 127.4, 128.8, 129.1, 133.5, 140.7, 147.2, 156.4, and 165.7. HRMS: $C_{17}H_{18}BrN_2O_6P$ calcd for *m/z* 452.2167, found *m/z* 452.2169.

4.16. General procedure for the deprotection of phosphonate diesters

To a CH_2Cl_2 (15 mL) solution of phosphonate diester (153 mg, 0.42 mmol), TMSBr (222 μL, 1.67 mmol) was added and stirred for 60 h at room temperature under positive pressure of dry Ar. MeOH (5 mL) was added and evaporated with heating (ca. 60 °C). MeOH (5 mL) was added again, and this procedure was repeated three times. The residue was extracted with deionized H_2O (ELGA® Water) and CH_2Cl_2, then the aqueous phase was evaporated to yield the expected compound.

*4.16.1. N^1-[(E)-3-Dihydroxyphosphinyl-2-propenyl]5-phenyluracil (**15a**)*

Yield: 97% (162 mg) as a foam. ^{31}P NMR (CD_3OD) δ: 15.60 (t, J=19.8 Hz). ^{1}H NMR (DMSO-d_6) δ: 4.50–4.52 (m, 2H, U–CH_2–), 5.86 (t, 1H, J=17.4 Hz, C*H*=CH), 6.53 (ddt, 1H, J=4.4, 17.4, 22.9 Hz, CH=C*H*), 7.27–7.58 (m, 5H, H_{arom}), 7.94 (s, 1H, H6), 11.56 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 47.9, 115.3, 124.7, 127.6, 129.4, 130.1, 130.2, 135.1, 145.2, 152.4 and 164.7. HRMS: $C_{13}H_{13}N_2O_5P$ calcd for *m/z* 308.2298, found *m/z* 308.2296.

*4.16.2. N^1-[(E)-3-Dihydroxyphosphinyl-2-propenyl]5-(4-fluorophenyl)uracil (**15b**)*

Yield: 97% (113 mg) as a foam. ^{31}P NMR (CD_3OD) δ: 13.89 (t, J=19.4 Hz). ^{1}H NMR (DMSO-d_6) δ: 4.49–4.50 (m, 2H, U–CH_2–), 5.79 (t, 1H, J=17.2 Hz, C*H*=CH), 6.45 (ddt, 1H, J=5.9, 17.2, 22.9 Hz, CH=C*H*), 7.19–7.26 (m, 2H, H_{arom}), 7.58–7.64 (m, 2H, H_{arom}), 7.95 (s, 1H, H6), 11.59 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 47.3, 110.8, 113.5, 113.8, 121.3, 124.1, 128.0, 128.6, 128.7, 139.5, 141.8, 148.9, and 161.3. HRMS: $C_{13}H_{12}FN_2O_5P$ calcd for *m/z* 326.2203, found *m/z* 326.2205.

*4.16.3. N^1-[(E)-3-Dihydroxyphosphinyl-2-propenyl]5-(4-methoxyphenyl)uracil (**15c**)*

Yield: 95% (101 mg) as a foam. ^{31}P NMR (CD_3OD) δ: 13.95 (t, J=19.2 Hz). ^{1}H NMR (DMSO-d_6) δ: 3.77 (s, 3H, MeO), 4.48–4.49 (m, 2H, U–CH_2–), 5.78 (t, 1H, J=17.0 Hz, C*H*=CH), 6.47 (ddt, 1H, J=4.7, 17.0, 21.6 Hz, CH=C*H*), 6.96 (d, 2H, J=8.8 Hz, H_{arom}), 7.50 (d, 2H, J=8.8 Hz, H_{arom}), 7.84 (s, 1H, H6), 11.51 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 47.9, 53.9, 111.7, 112.4, 121.4, 124.3, 127.9, 139.6, 139.7, 140.8, 149.0, 157.4, and 161.5. HRMS: $C_{14}H_{15}N_2O_6P$ calcd for *m/z* 338.2560, found *m/z* 338.2561.

*4.16.4. N^1-[(E)-3-Dihydroxyphosphinyl-2-propenyl]5-phenylthiouracil (**15d**)*

Yield: 88% (75 mg) as a foam. ^{31}P NMR (CD_3OD) δ: 13.92 (t, J=19.6 Hz). ^{1}H NMR (DMSO-d_6) δ: 4.34–4.35 (m, 2H, U–CH_2–), 5.66 (t, 1H, J=17.2 Hz, C*H*=CH), 6.29 (ddt, 1H, J=4.7, 17.2, 21.6 Hz, CH=C*H*), 7.00–7.19 (m, 5H, H_{arom}), 8.11 (s, 1H, H6), 11.58 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 47.9, 103.2, 123.1, 126.0, 126.6, 129.4, 136.8, 140.8, 140.9, 151.0, 152.4, and 162.3. HRMS: $C_{13}H_{13}N_2O_5PS$ calcd for *m/z* 340.2958, found *m/z* 340.2963.

*4.16.5. 5-Chloro-N^1-[(E)-3-dihydroxyphosphinyl-2-propenyl]uracil (**15e**)*

Yield: 71% (275 mg) as a foam. ^{31}P NMR (CD_3OD) δ: 13.83 (t, J=18.6 Hz). ^{1}H NMR (DMSO-d_6) δ: 4.40–4.41 (m, 2H, U–CH_2–), 5.77 (t, 1H, J=17.2 Hz, C*H*=CH), 6.39 (ddt, 1H, J=4.7, 17.2, 21.9 Hz, CH=C*H*), 8.14 (s, 1H, H6), 11.87 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 47.9, 109.6, 128.6, 140.0, 145.7, 152.9, and 162.5. HRMS: $C_7H_8ClN_2O_5P$ calcd for *m/z* 266.5770, found *m/z* 266.5771.

*4.16.6. 5-Bromo-N^1-[(E)-3-dihydroxyphosphinyl-2-propenyl]uracil (**15f**)*

Yield: >95% (130 mg) as a foam. ^{31}P NMR (CD_3OD) δ: 13.77 (t, J=18.6 Hz). ^{1}H NMR (DMSO-d_6) δ: 4.40–4.41 (m, 2H, U–CH_2–), 5.83 (t, 1H, J=17.0 Hz, CH=CH), 6.40 (ddt, 1H, J=4.4, 17.0, 21.0 Hz, CH=CH), 8.19 (s, 1H, H6), 11.80 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 49.7, 96.0, 126.2, 141.4, 146.3, 151.5, and 160.5. HRMS: $C_7H_8BrN_2O_5P$ calcd for m/z 231.1243, found m/z 231.1246.

*4.16.7. N^1-(4-Dihydroxyphosphinyl-2-butenyl)-5-phenyluracil (**16a**)*

Yield: 81% (68 mg) as an oil. ^{31}P NMR (CD_3OD) δ: 24.12. ^{1}H NMR (DMSO-d_6) δ: 2.36–2.41 (m, 2H, P–CH_2–), 4.35 (br s, 2H, U–CH_2–), 5.65–5.76 (m, 2H, CH=CH), 7.29 (m, 1H, H_{arom}),7.38 (m, 2H, H_{arom}), 7.57 (m, 2H, H_{arom}), 7.88 (s, 1H, H6), 11.48 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 30.9, 49.7, 114.8, 126.64, 128.0, 128.9, 129.3, 129.5, 134.1, and 143.0. HRMS: $C_{14}H_{15}N_2O_5P$ calcd for m/z 340.2471, found m/z 340.2473.

*4.16.8. N^1-(4-Dihydroxyphosphinyl-2-butenyl)-5-(4-fluorophenyl)uracil (**16b**)*

Yield: 63% (79 mg) as an oil. ^{31}P NMR (CD_3OD) δ: 24.26. ^{1}H NMR (DMSO-d_6) δ: 2.51–2.82 (m, 2H, P–CH_2–), 4.47–4.48 (m, 2H, U–CH_2–), 4.56–4.57 (m, 2H, U–CH_2–), 5.78–5.84 (m, 2H, CH=CH), 7.30–7.38 (m, 2H, H_{arom}), 7.71–7.79 (m, 2H, H_{arom}), 8.15 (s, 1H, H6), 11.65 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 31.0, 33.2, 50.8, 114.1, 116.9, 117.3, 128.7, 128.9, 129.6, 130.8, 132.0, 132.2, 145.0, 152.4, and 164.7. HRMS: $C_{14}H_{14}FN_2O_5P$ calcd for m/z 340.2471, found m/z 340.2473.

*4.16.9. N^1-(4-Dihydroxyphosphinyl-2-butenyl)-5-(4-methoxyphenyl)uracil (**16c**)*

Yield: 70% (144 mg) as a foam. ^{31}P NMR (CD_3OD) δ: 23.82. ^{1}H NMR (CD_3OD) δ: 2.55–2.64 (m, 2H, P–CH_2), 3.79 (s, 3H, OMe), 4.40–4.51 (m, 2H, U–CH_2), 5.77–5.78 (m, 2H, CH=CH), 6.89–6.93 (m, 2H, H_{arom}), 7.43–7.46 (m, 2H, H_{arom}), 7.62 (s, 1H, H6). ^{13}C NMR (CD_3OD) δ: 25.1, 48.9, 56.6, 115.6, 116.8, 127.0, 130.4, 130.5, 131.5, 143.9, 153.2, and 166.0. HRMS: $C_{15}H_{17}N_2O_6P$ calcd for m/z 352.2828, found m/z 352.2830.

*4.16.10. N^1-(4-Dihydroxyphosphinyl-2-butenyl)-5-phenylthiouracil (**16d**)*

Yield: 54% (135 mg) as a foam. ^{31}P NMR (CD_3OD) δ: 23.98 (t, J=22.9 Hz). ^{1}H NMR (DMSO-d_6) δ: 2.34–2.51 (m, 2H, P–CH_2–), 4.32–4.33 (m, 2H, U–CH_2–), 4.41–4.42 (m, 2H, U–CH_2–), 5.58–5.75 (m, 2H, CH=CH), 7.13–7.37 (m, 5H, H_{arom}), 8.21 (s, 1H, H6), 11.65 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 33.3, 33.6, 51.2, 105.1, 128.0, 128.2, 129.2, 129.4, 129.9, 130.1, 131.6, 139.1, 153.2, 154.4, and 164.4. HRMS: $C_{14}H_{15}N_2O_5PS$ calcd for m/z 354.3226, found m/z 354.3229.

*4.16.11. 5-Chloro-N^1-(4-dihydroxyphosphinyl-2-butenyl)-uracil (**16e**)*

Yield: 96% (351 mg) as a foam. ^{31}P NMR (CD_3OD) δ: 23.93. ^{1}H NMR (CD_3OD) δ: 2.56–5.84 (m, 2H, P–CH_2), 4.35–4.44 (m, 2H, U–CH_2), 5.68–5.84 (m, 2H, CH=CH), 7.87 (s, 1H, H6). ^{13}C NMR (CD_3OD) δ: 27.9, 30.1, 32.2, 34.4, 51.5, 52.0, 109.5, 109.7, 128.1, 128.3, 128.6, 128.8, 129.5, 129.7, 130.0, 130.2, 144.5, 144.6, 152.7, and 162.7. HRMS: $C_8H_{10}ClN_2O_5P$ calcd for m/z 280.6038, found m/z 280.6032.

*4.16.12. 5-Bromo-N^1-(4-dihydroxyphosphinyl-2-butenyl)-uracil (**16f**)*

Yield: 92% (161 mg) as a foam. ^{31}P NMR (CD_3OD) δ: 24.31 (t, J=21.0 Hz). ^{1}H NMR (CD_3OD) δ: 2.59–2.66 (m, 2H, P–CH_2), 4.37 (m, 2H, U–CH_2), 5.69–5.83 (m, 2H, CH=CH), 7.98 (s, 1H, H6), 11.65 (br s, 1H, NH). ^{13}C NMR (CD_3OD) δ: 33.0, 50.6, 96.6, 127.1, 129.4, 146.1, 152.1, 162.0. HRMS: $C_8H_{10}BrN_2O_5P$ calcd for m/z 280.6038, found m/z 280.6032.

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