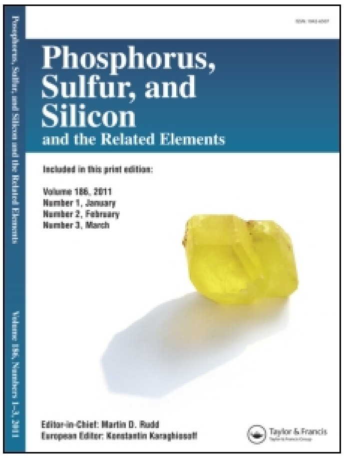

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The Synthesis of Amino Acid Methyl Ester 5'-Phosphoamidates of Protected Uridine

W. Z. Chen[ab]; Y. F. Zhao[ac]
[a] Department of Chemistry and Key Laboratory for Chemical Biology of Fujian Province, Xiamen University, Xiamen, China [b] The Third Institute of Oceanography of the State Oceanic Administration, Xiamen, China [c] Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing, China

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THE SYNTHESIS OF AMINO ACID METHYL ESTER 5′-PHOSPHOAMIDATES OF PROTECTED URIDINE

W. Z. Chen[1,2] and Y. F. Zhao[1,3]
[1]*Department of Chemistry and Key Laboratory for Chemical Biology of Fujian Province, Xiamen University, Xiamen, China*
[2]*The Third Institute of Oceanography of the State Oceanic Administration, Xiamen, China*
[3]*Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing, China*

In this article, we used the Atherton–Todd reaction to synthesize amino acid methyl ester 5′-phosphoamidates of uridine as prodrugs. Their structures were confirmed by ^{1}H NMR, ^{31}P NMR, ^{13}C NMR, IR, and mass spectrometry.

Supplemental materials are available for this article. Go to the publisher's online edition of **Phosphorus, Sulfur, and Silicon and the Related Elements** ***to view the free supplemental file.***

Keywords Amino acid methyl ester 5′-phosphoamidates of protected uridine; Atherton–Todd; spectra characterization; synthesis

INTRODUCTION

Nucleosides and their analogues as potential anticancer and antivirus agents have been studied extensively in recent years.[1–3] For example, several purine and pyridine bases and nucleoside analogs were used as a chemotherapeutic arsenal. However, the biological activity of most analogs requires intracellular metabolism to 5′-mononucleotides by kinase.[4] In order to overcome the problem of drug resistance and improve membrane penetration, a series of amino acid phosphoramidate di- and tri-esters of nucleotides have been developed to deliver phosphorylated nucleoside analogues as neutral derivatives into the cell.[5] These types of compounds exhibit enhancing antiviral activity and reducing cytotoxicity as compared to the corresponding parent nucleosides.[6,7] For the purpose of developing new types of prodrugs, a new type of amino acid methyl ester 5′-phosphoamidates of nucleoside was synthesized, and is reported in this article.

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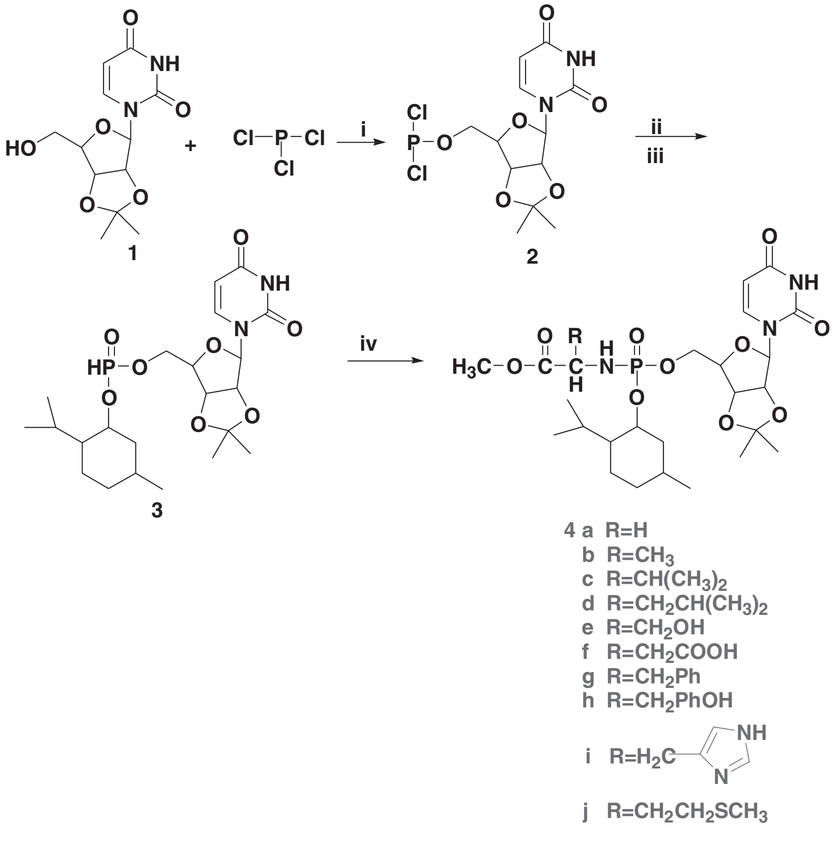
Address correspondence to Y. F. Zhao, Department of Chemistry and Key Laboratory for Chemical Biology of Fujian Province, Xiamen University, Xiamen 361005, China. E-mail: yfzhao@xmu.edu.cn

RESULTS AND DISCUSSION

Synthesis

The reported synthesis of O-nucleoside N-phosphoryl amino acid methyl esters involved the coupling of amino acid methyl esters with nucleoside monophosphates in the presence of condensing reagents such as dicyclohexylcarbodiimide (DCC) and 2,4,6-triisopropylbenzenesulfonyl chloride,[8] or with nucleoside phosphite triesters in the presence of iodine.[9] Phosphorochloridate approach was also reported in the preparation of aryl phosphate derivative of nucleoside analogs.[10] The amino acids chosen, however, were usually the nonpolar ones without active side chains. In the present article, we report the application of the Atherton–Todd[11] reaction in the synthesis of O-alkyl O-2′,3′-isopropylideneuridine N-phosphoryl amino acid methyl ester (Scheme 1). The present methodology was applicable to amino acid methyl esters with different side chains and with either of the nucleosid-3′ (or 5′)-yl H-phosphonates. Owing to the low nucleophilic reactivity of amino groups on the nucleobases and the hydroxyl on both the amino acid and the nucleoside compared with the α-amino group, it was unnecessary to protect them in the coupling reaction.



Scheme 1 Synthetic route of amino acid methyl ester 5′-phosphoamidates of protected uridine. Reagents and conditions: (i) NEt_3, dry CH_2Cl_2, 0°C for 0.5 h, then room temperature for 3 h; (ii) dry CH_2Cl_2, menthol, *tert*-butyl alcohol, 0°C, then room temperature for 0.5 h; (iii) NEt_3, dry CH_2Cl_2, 0°C, then room temperature for 10 min; (iv) CCl_4, NEt_3, H_2O, CH_3CN, amino acid methyl ester, room temperature.

^{31}P NMR Spectra

The ^{31}P nucleus is a very sensitive probe for structural studies of organophosphorus compounds. The ^{31}P NMR spectra of 2′,3′-isopropylidenenucleoside-5′-O-yl-H-phosphonate and O-alkyl O-2′,3′-isopropylideneuridine N-phosphoryl amino acid methyl ester are in the range of 5 to about 10 ppm. Due to the chirality at the phosphorus center, they both exhibit two different chemical shift values in the ^{31}P NMR spectra (Figures 1a and 1b), and the integral areas of ^{31}P NMR are basically the same if protons are decoupled.

But if the protons are not decoupled, nucleoside-5′-O-yl-H-phosphonate (Figure 1a) has a distinct different chemical shift value from uridine N-phosphoryl amino acid methyl ester (Figure 2a). It exhibits four different chemical shift values in the ^{31}P NMR spectra. This is because the phosphorus in nucleoside-5′-O-yl-H-phosphonate was coupled by the hydrogen on the phosphorus. The coupling constant $^1J_{PH}$ is about 700 Hz in nucleoside-5′-O-yl-H-phosphonate. For example, the coupling constant $^1J_{PH}$ is 703 Hz in menthyl 2′,3′-isopropylideneuridin-5′-yl-H-phosphonate (**3**). But in O-alkyl O-2′,3′-isopropylideneuridine N-phosphoryl amino acid methyl ester, although the hydrogen on the nitrogen has a coupling effect on the phosphorus, $^2J_{PH}$ is much smaller than $^1J_{PH}$, and the coupling splitting is not distinct. This is the difference between ^{31}P NMR spectra of nucleoside-5′-O-yl-H-phosphonate and O-alkyl O-2′,3′-isopropylideneuridine N-phosphoryl amino acid methyl ester.

^{1}H NMR Spectra

2′,3′-Isopropylideneuridine-5′-O-yl-H-phosphonate and O-alkyl O-2′,3′-isopropyli deneuridine N-phosphoryl amino acids methyl esters are a pair of diastereoisomers due to the chirality at the phosphorus center. Their ^{1}H NMR spectra are all pairs of peaks,

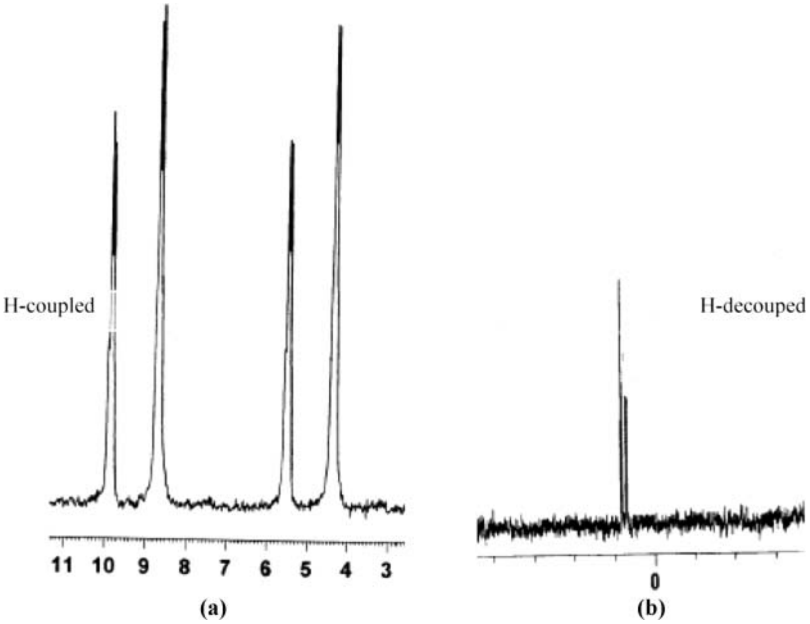


Figure 1 The ^{31}P NMR spectrum of menthyl 2′,3′-isopropylideneuridin-5′-yl-H-phosphonate (**3**).

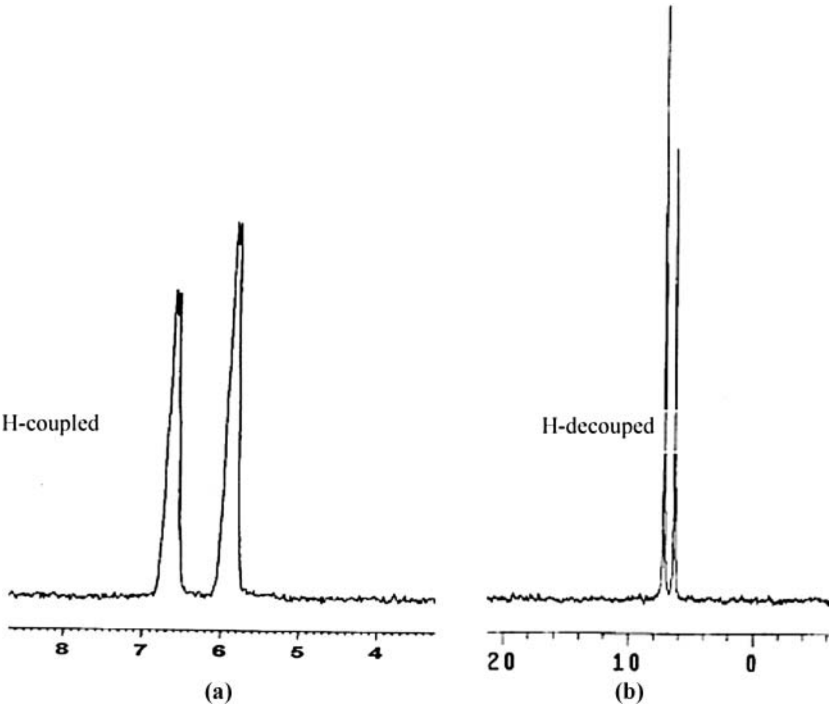


Figure 2 The ^{31}P NMR spectrum of O-nucleoside N-phosphoryl amino acids methyl esters (**4a**).

especially the H-6 of the nucleoside and methyl ester of the amino acid. For example, OCH_3 on the compound **4h** exhibits two single peaks. Their chemical shift values are 3.71 and 3.70.

^{13}C NMR Spectra

Due to the chirality at the phosphorus center, 2′,3′-isopropylideneuridine-5′-O-yl-H-phosphonate and O-alkyl O-2′,3′-isopropylideneuridine N-phosphoryl amino acids methyl esters are a pair of diastereoisomer, so some carbon atoms exhibit double peaks in the ^{13}C NMR spectra. For example, C-6 on the compound **4h** exhibits two single peaks. Their chemical shift values are 141.69 and 142.00.

Mass Spectra

Positive-ion mode electrospray ionization (ESI) mass spectral fragmentation pathways of 2′,3′-isopropylideneuridine phosphates were analyzed by multistage tandem mass spectrometry. Tables S1 and S2 (Supplemental Materials, available online) list the fragment ions observed in multistage tandem mass spectra of the protonated and sodium ion adducts of **4a–j**, respectively.

Because these compounds displayed very similar fragmentation patterns in positive-ion mode ESI multistage tandem mass spectrometry, the mass spectral fragmentation pathways of compound **4h** were discussed as a typical example (Scheme S1, Supplemental Materials). The protonated molecule has richer fragmentation pathways than the sodium ion adduct. The abundant characteristic fragment ions were observed by loss of uracil (112), amino acid methyl ester (195), menthene (138), and acetone (58), corresponding to the cleavage of glycosyl C-N between uracil and sugar, P-N, and C-O bonds. The fragment ions almost always contained a phosphoryl group. In addition, it was interesting that the fragmentation pathways of the sodium ion adduct showed some differences from that of the protonated molecule. The methoxy group of amino acid methyl ester could migrate from the carbonyl group to the phosphoryl group only for the sodium ion adduct, but not for the protonated molecule $[M + H]^+$. The ion at *m/z* 252 in the sodium ion adduct of **4h** might yield in this way.[12] The reason is that metal ions such as the sodium ion could coordinate with both carbonyl oxygen and phosphoryl oxygen to form a seven-membered ring, which might help the attack of the methoxy group on phosphorus. In contrast, with the smaller size, a proton could only attach to either the phosphoryl oxygen or the carbonyl oxygen. These characteristic ions in ESI mass spectra and the rearrangement mechanism are useful for the structural determination of amino acid methyl ester 5′-phosphoramidate of nucleosides.

CONCLUSION

In summary, we use a convenient and efficient approach to synthesize a series of amino acid methyl ester 5′-phosphoamidates of protected uridine under mild conditions. The reaction process was traced by ^{31}P NMR. In addition, the structures of these compounds were verified and fragmentation pathways were analyzed by positive-ion mode ESI-MS^n.

EXPERIMENTAL

Material and Methods

All glassware was dried in an oven for at least 3 h at 140 °C prior to use. Air-sensitive materials were transferred under a nitrogen atmosphere. CH_2Cl_2 and NEt_3 were dried over $CaCl_2$ and KOH, respectively. PCl_3 was distilled. ^{1}H NMR and ^{13}C NMR spectra were recorded in a Bruker AM 500 spectrometer. TMS ($\delta = 0.0$) and $CDCl_3$ ($\delta = 7.24$ ppm) were references for ^{1}H and ^{13}C NMR spectra, respectively. ^{13}C NMR spectra were all taken under ^{1}H-decoupled and ^{31}P-coupled conditions. ^{31}P NMR spectra were taken on a Bruker AM 500 spectrometer under ^{1}H decoupled conditions. ^{31}P NMR chemical shifts are reported in ppm downfield (+) or upfield (−) from external 85% H_3PO_4 as reference. ESI were determined with a Bruker ESQYIRE 3000 plus. Operating conditions for ESI in the positive ion mode were as follows: spray voltage, 4000 V; capillary temperature, 300°C; dry gas (N_2), 10 L/min; nebulizer (N_2), 30 psi. HRMS was recorded on a Micromass-LCT Premier Time of Flight (TOF) mass spectrometer (Waters, USA).

Synthesis of Amino Acid Methyl Ester Hydrochloride and Protected Nucleoside (1)

The preparations of amino acid methyl ester hydrochloride and protected nucleoside were carried out according to the literature.[13,14] All physical constants and spectroscopic data of the products synthesized were in agreement with the literature.

General Procedure for Synthesis of Aryl Phosphoramidate Derivatives of Nucleosides[15]

To a solution of PCl_3 (10 mmol) in anhydrous dichloromethane (10 mL), 2′,3′-isopropylideneuridine (**1**) was added (1 mmol) at −30°C under a nitrogen atmosphere, and the solution was stirred for 30 min at this temperature and then for 3 h at room temperature. The solvent and excess of PCl_3 were removed under reduced pressure. The residue was dissolved in anhydrous dichloromethane (10 mL). Menthol and tert-butyl alcohol (2.5 mmol, 1:1) in anhydrous dichloromethane (5 mL) was then added dropwise to the solution at 0°C, and the reaction was completed within 30 min. A solution of triethylamine (2 mmol) in anhydrous dichloromethane (5 mL) was added to the resulting solution. After 10 min, the solvent was removed by rotary evaporation, and the product was purified by chromatography on silica gel using CH_2Cl_2–MeOH (50:1) as eluent. The final product 2′,3′-isopropylideneuridine-5′-O-yl-H-phosphonate (**3**) was obtained in 90% yield.

To a solution of amino acid ester (1.2 mmol), water (0.5 mL), tetrachloromethane (0.5 mL), triethylamine (0.5 mL), and acetonitrile (5 mL), a solution of 2′,3′-Isopropylideneuridine-5′-O-yl-H-phosphonate (**3**) (1 mmol) in acetonitrile (5 mL) was added dropwise with an ice-bath. The solution was then stirred at room temperature for 10 min. The solvent was removed by rotary evaporation to a gum below 40 °C. The residual syrup was subjected to silica gel column chromatography by elution with 5% methanol in chloroform. Pooling and evaporation of appropriate fractions gave amino acid methyl ester 5′-phosphoamidates of protected uridine **4a–j** in 81–94% yields.

Menthyl 2′,3′-osopropylideneuridin-5′-yl H-phosphonate (3). Yield 4.37 g (90%). IR (film) ν: 3193, 3058, 2431, 1695, 1624, 1249, 1063, 954 cm^{-1}. ^{31}P NMR ($CDCl_3$, 202 MHz): δ 8.89, 8.04. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.40 (br, 1H, H-3), 7.52, 6.12 (d, d, 1H, $J_{PH} = 703.0$ Hz, P-H), 7.27, 7.26 (d, d, 1H, J = 8.0 Hz, H-6), 5.65–5.67 (m, 2H, H-1′, H-5), 4.86–4.87 (m, 1H, H-2′), 4.75–4.82 (m, 1H, H-3′), 4.19–4.26 (m, 4H, H-4′, H-5′, $OC\underline{H}R$), 2.06–2.13 (1H, m, $H_{menthyl}$), 1.92–2.01 (1H, m, $H_{menthyl}$), 1.81–1.90 (1H, m, $H_{menthyl}$), 1.58–1.60 (2H, m, $H_{menthyl}$), 1.49 (s, 3H, $>CCH_3$), 1.36–1.40 (1H, m, $H_{menthyl}$), 1.27 (s, 3H, $>CCH_3$), 1.12–1.19 (2H, m, $H_{menthyl}$), 0.87–1.00 (1H, m, $H_{menthyl}$), 0.84 (d, 6H, J = 7.0 Hz, $2CH_3$), 0.72 (d, 3H, J = 7.0 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.63 (C-4), 150.18 (C-2), 142.12 (C-6), 114.70 ($>\underline{C}Me_2$), 102.79, 102.69 (C-5), 94.27, 94.17 (C-1′), 85.63, 85.53, 85.47 (C-4′), 84.35 (C-2′), 80.73, 80.65 (C-3′), 78.95, 78.89 ($O\underline{C}HR$), 64.82 (C-5′), 48.24 ($C_{menthyl}$), 43.28, 42.79 ($C_{menthyl}$), 33.82 ($C_{menthyl}$), 31.52($C_{menthyl}$), 27.08 ($C_{menthyl}$), 25.87, 25.69, 25.22 (CH_3), 22.86 ($C_{menthyl}$), 21.87, 21.85 (CH_3), 20.84, 20.81 (CH_3), 15.65 (CH_3); HRMS (ESI) calcd for $C_{22}H_{36}N_2O_8P$: 567.2621, found 567.2616.

Glycine ester menthyl phosphoramidates of 2′,3′-isopropylideneuridine (4a). Yield 496 mg (86.6%). IR (film) ν: 3231, 1751, 1696, 1618, 1217, 1068, 990 cm^{-1}. ^{31}P NMR ($CDCl_3$, 202 MHz): δ 8.12, 7.32. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.46, 9.40 (br, br, 1H, H-3), 7.38, 7.34 (d, d, 1H, J = 8.0 Hz, H-6), 5.72–5.76 (m, 1H, H-1′), 5.66 (d, J = 8.0 Hz, 1H, H-5), 4.79–4.86 (m, 2H, H-2′, H-3′), 4.24–4.32 (m, 1H, $OC\underline{H}R$), 4.06–4.23 (m, 3H, H-4′, H-5′), 3.68, 3.67 (s, s, 3H, OCH_3), 3.39–3.65 (m, 3H, P-$N\underline{H}$, H-α,), 2.13–2.20 (m, 1H, $H_{menthyl}$), 1.92–1.98 (m, 2H, $H_{menthyl}$), 1.58–1.60 (m, 2H, $H_{menthyl}$), 1.51 (s, 3H, $>CCH_3$), 1.33–1.44 (m, 1H, $H_{menthyl}$), 1.28 (s, 3H, $>CCH_3$), 1.16–1.25 (m, 2H, $H_{menthyl}$), 0.89–1.01 (m, 1H, $H_{menthyl}$), 0.84 (d, 6H, J = 6.5 Hz, $2CH_3$), 0.74 (t, 3H, J = 7.0 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.16 (COOMe), 163.59 (C-4), 150.11 (C-2), 141.69, 141.33 (C-6), 114.09 ($>\underline{C}Me_2$), 102.27 (C-5), 92.64, 93.15 (C-1′), 85.45, 84.66 (C-4′), 84.03 (C-2′), 80.52 (C-3′), 78.38 ($O\underline{C}HR$), 65.45, 65.22 (C-5′), 51.97 (OCH_3), 48.16, 48.09

($\mathrm{C_{menthyl}}$), 42.44, 42.14 (C-α, $\mathrm{C_{menthyl}}$), 33.66 ($\mathrm{C_{menthyl}}$), 31.13 ($\mathrm{C_{menthyl}}$), 26.79 ($>\mathrm{C\underline{C}H_3}$), 25.31 ($>\mathrm{C\underline{C}H_3}$), 24.92 ($\mathrm{C_{menthyl}}$), 22.45 ($\mathrm{C_{menthyl}}$), 21.67 ($\mathrm{CH_3}$), 20.68 ($\mathrm{CH_3}$), 15.33, 15.27 ($\mathrm{CH_3}$). HRMS (ESI) calcd for $\mathrm{C_{25}H_{40}N_3O_{10}PNa}$ [M +Na]: 596.2349, found 596.2350.

Alanine ester menthyl phosphoramidates of 2′,3′-isopropylideneuridine (4b). Yield 450 mg (76.7%). IR (film) v: 3224, 1742, 1698, 1630, 1213, 1066, 1004 $\mathrm{cm^{-1}}$.^{31}P NMR ($\mathrm{CDCl_3}$, 202 MHz): δ 7.05, 6.39. ^{1}H NMR ($\mathrm{CDCl_3}$, 500 MHz): δ 8.98, 8.92 (br, br, 1H, H-3), 7.44, 7.39 (d, d, 1H, J = 8.0 Hz, H-6), 5.82, 5.76 (br, br, 1H, H-1′), 5.74 (d, 1H, J = 7.0 Hz, H-5), 4.86~4.91 (m, 2H, H-2′, H-3′), 4.22~4.35 (m, 1H, OCHR), 4.16~4.25 (m, 3H, H-5′, H-4′), 3.90~3.98 (m, 1H, H-α), 3.74, 3.73 (s, 3H, $\mathrm{OCH_3}$)7~3.51 (m, 1H, P-NH), 2.19~2.24 (m, 1H, $\mathrm{H_{menthyl}}$), 2.01~2.12 (m, 1H, $\mathrm{H_{menthyl}}$), 1.73~1.78 (m, 2H, $\mathrm{H_{menthyl}}$), 1.64~1.67 (m, 2H, $\mathrm{H_{menthyl}}$), 1.58 (s, 3H, $\mathrm{CH_3}$), 1.40~1.48 (m, 1H, $\mathrm{H_{menthyl}}$), 1.39, 1.38 (d, d, 3H, J = 4.0 Hz, H-β), 1.35 (s, 3H, $>\mathrm{CCH_3}$), 1.23-1.33 (m, 1H, $\mathrm{H_{menthyl}}$), 0.96~1.15 (m, 1H, $\mathrm{H_{menthyl}}$), 0.91 (t, 6H, J = 6.0 Hz, 2$\mathrm{CH_3}$), 0.81 (d, 3H, J = 7.0 Hz, $\mathrm{CH_3}$).^{13}C NMR ($\mathrm{CDCl_3}$, 125 MHz): δ 174.19 (COOMe), 163.57 (C-4), 150.13 (C-2), 141.71 (C-6), 114.35 ($>\mathrm{CMe_2}$), 102.49-5), 93.35 (C-1′), 85.45 (C-4′), 84.18 (C-2′), 80.64 (C-3′), 78.75 (OCHR), 65.41 (C-5′), 52.19 ($\mathrm{OCH_3}$), 49.28, 48.88 ($\mathrm{C_{menthyl}}$), 42.34 (C-α), 33.78 ($\mathrm{C_{menthyl}}$), 31.28 ($\mathrm{C_{menthyl}}$), 26.91 ($>\mathrm{CCH_3}$), 25.46 ($>\mathrm{CCH_3}$), 25.04 ($\mathrm{C_{menthyl}}$), 22.60 ($\mathrm{C_{menthyl}}$), 21.79 ($\mathrm{CH_3}$),20.80 ($\mathrm{CH_3}$), 15.49 ($\mathrm{CH_3}$). HRMS (ESI) calcd for $\mathrm{C_{26}H_{43}N_3O_{10}P}$: 588.2686, found 588.2688.

Valine ester menthyl phosphoramidates of 2′,3′-isopropylideneuridine (4c). Yield 364 mg (59.2%). IR (film) *v*: 3237, 1734, 1694, 1622, 1214, 1063, 998 $\mathrm{cm^{-1}}$. ^{31}P NMR ($\mathrm{CDCl_3}$, 202 MHz): δ 8.02, 7.78. ^{1}H NMR ($\mathrm{CDCl_3}$, 500 MHz): δ 9.02, 8.42 (br, br, 1H, H-3), 7.45, 7.38 (d, d, 1H, J = 8.0 Hz, H-6), 5.84, 5.77 (d, d, 1H, J = 3.0 Hz, H-1′), 5.76, 5.73 (d, d, 1H, J = 8.0 Hz, H-5), 4.81–4.90 (m, 2H, H-2′, H-3′), 4.31–4.34 (m, 1H, $\mathrm{OC\underline{H}R}$), 4.12–4.25 (m, 3H, H-4′, H-5′), 3.72 (s, 4H, H-α, $\mathrm{OCH_3}$), 3.31, 3.37 (t, t, 1H, J = 10.0 Hz, P-NH), 2.19–2.24 (m, 1H, H-β), 1.99–2.11 (m, 2H, $\mathrm{H_{menthyl}}$), 1.71–1.81 (m, 1H, $\mathrm{H_{menthyl}}$), 1.64–1.66 (m, 2H, $\mathrm{H_{menthyl}}$), 1.58 (s, 3H, $>\mathrm{CCH_3}$), 1.38–1.45 (m, 1H, $\mathrm{H_{menthyl}}$), 1.35 (s, 3H, $>\mathrm{CCH_3}$), 1.24–1.33 (m, 1H, $\mathrm{H_{menthyl}}$), 0.97–1.15 (m, 2H, $\mathrm{H_{menthyl}}$), 0.95 (t, 3H, J = 7.0 Hz, $\mathrm{CH_3}$), 0.91, 0.88 (d, d, 9H, J = 7.0 Hz, 3$\mathrm{CH_3}$), 0.81 (d, 3H, J = 7.0 Hz, $\mathrm{CH_3}$). ^{13}C NMR ($\mathrm{CDCl_3}$, 125 MHz): δ 173.34 (COOMe), 163.50 (C-4), 150.03 (C-2), 141.59, 141.18 (C-6), 114.38 ($>\mathrm{\underline{C}Me_2}$), 102.49 (C-5), 93.28, 92.62 (C-1′), 85.08 (C-4′), 84.62, 84.13 (C-2′), 80.69, 80.44 (C-3′), 78.65 ($\mathrm{O\underline{C}HR}$), 65.45 (C-5′), 59.71, 59.44 ($\mathrm{OCH_3}$), 51.85 (C-α), 48.31 ($\mathrm{C_{menthyl}}$), 42.46 ($\mathrm{C_{menthyl}}$), 33.80 ($\mathrm{C_{menthyl}}$), 32.10 (C-β), 31.25 ($\mathrm{C_{menthyl}}$), 26.91 ($>\mathrm{C\underline{C}H_3}$), 25.38 ($>\mathrm{C\underline{C}H_3}$), 25.02 ($\mathrm{C_{menthyl}}$), 22.57 ($\mathrm{C_{menthyl}}$), 21.79 ($\mathrm{CH_3}$), 20.82 ($\mathrm{CH_3}$), 18.79 (C-$\gamma$), 17.38 (C-$\gamma'$), 15.44 ($\mathrm{CH_3}$). HRMS (ESI) calcd for $\mathrm{C_{28}H_{47}N_3O_{10}P}$: 616.2999, found 616.2997.

Leucine ester menthyl phosphoramidates of 2′,3′-isopropylideneuridine (4d). Yield 562.4 mg (89.41%). IR (film) *v*: 3226, 1730, 1697, 1626, 1213, 1060, 999 $\mathrm{cm^{-1}}$. ^{31}P NMR ($\mathrm{CDCl_3}$, 202 MHz): δ 7.41, 6.80. ^{1}H NMR ($\mathrm{CDCl_3}$, 500 MHz): δ 9.00, 8.98 (br, br, 1H, H-3), 7.46, 7.38 (d, d, 1H, J = 8.0 Hz, H-6), 5.85, 576 (d, d, 1H, J = 2.5 Hz, H-1′), 5.75, 5.73 (d, d, 1H, J = 8.0 Hz, H-5), 4.82–4.91 (m, 2H, H-3′, H-4′), 4.30–4.35 (m, 1H, $\mathrm{OC\underline{H}R}$), 4.16–4.23 (m, 3H, H-4′, H-5′), 3.82–3.90 (m, 1H, H-α), 3.72 (s, 3H, $\mathrm{OCH_3}$), 3.44, 3.33 (t, t, 1H, J = 10.0 Hz, P-NH), 2.05–2.22 (m, 2H, H-β), 1.693–1.771 (m, 1H, H-γ, $\mathrm{H_{menthyl}}$), 1.66, 1.64 (br, 2H, $\mathrm{H_{menthyl}}$), 1.58, 1.57 (s, s, 3H, $>\mathrm{CCH_3}$), 1.40–1.51 (m, 1H, $\mathrm{H_{menthyl}}$), 1.35 (s, 3H, $>\mathrm{CCH_3}$), 1.26–1.32 (m, 2H, $\mathrm{H_{menthyl}}$), 1.04–1.14 (m, 1H, $\mathrm{H_{menthyl}}$), 0.98–1.16 (m, 4H, $\mathrm{H_{menthyl}}$), 0.89–0.98 (m, 12H, 4$\mathrm{CH_3}$), 0.81 (t, 3H, J = 7.0 Hz, $\mathrm{CH_3}$). ^{13}C NMR ($\mathrm{CDCl_3}$, 125 MHz): δ 174.41 (COOMe), 163.08 (C-4), 150.03 (C-2), 141.62 (C-6), 114.62 ($>\mathrm{\underline{C}Me_2}$), 102.71 (C-5), 93.52 (C-1′), 85.17 (C-4′), 84.32 (C-2′), 80.78 (C-3′), 78.96

(O$\underline{\text{C}}$HR), 65.48 (C-5′), 52.87, 52.16 (OCH$_3$), 48.50 (C$_{\text{menthyl}}$), 43.94 (C-α), 42.70 (C$_{\text{menthyl}}$, C-β), 33.95 (C$_{\text{menthyl}}$), 31.47 (C$_{\text{menthyl}}$), 27.11 (>C$\underline{\text{C}}$H$_3$), 25.63 (>C$\underline{\text{C}}$H$_3$), 25.19 (C$_{\text{menthyl}}$), 24.46 (C-γ), 22.74 (C$_{\text{menthyl}}$, CH$_3$), 21.96 (CH$_3$), 20.99 (CH$_3$), 15.61 (CH$_3$). HRMS (ESI) calcd for $C_{29}H_{49}N_3O_{10}P$: 630.3156, found 630.3160.

Serine ester menthyl phosphoramidates of 2′,3′-isopropylideneuridine (4e). Yield 384 mg (63.7%). IR (film) ν: 3256, 1750, 1693, 1630, 1216, 1070, 1012 cm^{-1}. ^{31}P NMR (CDCl$_3$, 202 MHz): δ 7.75, 6.72. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 9.34 (br, 1H, H-3), 7.31, 7.27 (d, d, 1H, J = 8.0 Hz, H-6), 5.70, 5.69 (d, d, 1H, J = 8.0 Hz, H-5), 5.60, 5.56 (d, d, 1H, J = 2.0 Hz, H-1′), 5.04, 5.00 (dd, dd, 1H, J = 6.5, 2.0 Hz, H-2′), 4.90 (dd, 1H, J = 6.5, 3.5 Hz, H-3′), 4.06–4.33 (m, 5H, H-4′, H-5′, H-β), 4.10 (q, 1H, J = 7.0 Hz, H-α), 3.89–3.98 (br, 2H, P-NH, OC$\underline{\text{H}}$R), 3.73 (s, 3H, OCH$_3$), 3.46 (br, 1H, -OH), 2.18–2.20 (m, 1H, H$_{\text{menthyl}}$), 1.99–2.04 (m, 1H, H$_{\text{menthyl}}$), 1.70–1.80 (m, 2H, H$_{\text{menthyl}}$), 1.61–1.64 (m, 2H, H$_{\text{menthyl}}$), 1.54 (s, 3H, >CCH$_3$), 1.37–1.44 (m, 1H, H$_{\text{menthyl}}$), 1.33 (s, 3H, >CCH$_3$), 1.21–1.26 (m, 1H, H$_{\text{menthyl}}$), 1.02–1.12 (m, 1H, H$_{\text{menthyl}}$), 0.88, 0.87 (d, d, 6H, J = 6.0 Hz, 2CH$_3$), 0.78 (d, 3H, J = 7.0 Hz, CH$_3$). ^{13}C NMR (CDCl$_3$, 125 MHz): δ 171.89 (COOMe), 163.71 (C-4), 150.35 (C-2), 142.34 (C-6), 114.23 (>$\underline{\text{C}}$Me$_2$), 102.54 (C-5), 94.46 (C-1′), 85.42 (C-4′), 84.20 (C-2′), 80.95 (C-3′), 78.99 (O$\underline{\text{C}}$HR), 65.48 (C-5′), 64.07 (C-β), 56.50 (OCH$_3$), 52.38 (C-α), 48.35 (C$_{\text{menthyl}}$), 42.34 (C$_{\text{menthyl}}$), 33.85 (C$_{\text{menthyl}}$), 31.33 (C$_{\text{menthyl}}$), 26.96 (>C$\underline{\text{C}}$H$_3$), 25.46 (>C$\underline{\text{C}}$H$_3$), 25.09 (C$_{\text{menthyl}}$), 22.62 (C$_{\text{menthyl}}$), 21.87 (CH$_3$), 20.87 (CH$_3$), 15.49 (CH$_3$). ESI-MS: 604 (M+H)$^+$, 626 (M+Na)$^+$. HRMS (ESI) calcd for $C_{26}H_{43}N_3O_{11}P$: 604.2635, found 604.2632.

Aspartic acid ester menthyl phosphoramidates of 2′,3′-isopropylideneuridine (4f). Yield 440 mg (68.2%). IR (film) ν: 3430, 1693, 1216, 1069, 1011 cm^{-1}. ^{31}P NMR (CDCl$_3$, 202 MHz): δ 7.60, 6.89; ^{1}H NMR (CDCl$_3$, 500 MHz): δ 9.31, 9.24 (br, br, 1H, H-3), 7.41, 7.37 (d, d, 1H, J = 7.5 Hz, H-6), 5.59–5.76 (m, 2H, H-1′, H-5), 4.85–5.06 (m, 2H, H-2′, H-3′), 4.28–4.34 (m, 1H, H-4′), 4.13–4.26 (m, 2H, H-5′), 3.78–3.94 (m, 3H, H-α, P-NH, OC$\underline{\text{H}}$R), 3.75 (s, 3H, OCH$_3$), 3.68 (s, 3H, OCH$_3$), 2.72–3.12 (m, 2H, H-β), 2.21–2.27 (m, 1H, H$_{\text{menthyl}}$), 2.01–2.13 (m, 1H, H$_{\text{menthyl}}$), 1.651–1.676 (m, 2H, H$_{\text{menthyl}}$), 1.58, 1.57 (s, 3H, CH$_3$), 1.40–1.48 (m, 1H, H$_{\text{menthyl}}$), 1.37, 1.35 (s, 3H, CH$_3$), 1.22–1.29 (m, 2H, H$_{\text{menthyl}}$), 0.96–1.15 (m, 2H, H$_{\text{menthyl}}$), 0.92 (d, 6H, J = 6.5 Hz, 2CH$_3$), 0.82 (d, 3H, J = 7.0 Hz, CH$_3$); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 171.06 (2COOMe), 163.08 (C-4), 150.01 (C-2), 141.61 (C-6), 114.34 (>$\underline{\text{C}}$Me$_2$), 102.54 (C-5), 93.54 (C-1′), 85.34 (C-4′), 84.56 (C-2′), 80.39 (C-3′), 72.13 (O$\underline{\text{C}}$HMe$_2$), 65.53 (C-5′), 52.79, 52.04 (OCH$_3$), 50.97 (C-α), 48.23 (C$_{\text{menthyl}}$), 42.60 (C$_{\text{menthyl}}$), 38.46 (C-β), 34.00 (C$_{\text{menthyl}}$), 31.48 (C$_{\text{menthyl}}$), 25.66, 25.31 (C$_{\text{menthyl}}$), 22.47 (C$_{\text{menthyl}}$), 21.75 (CH$_3$), 20.75 (CH$_3$), 15.37 (CH$_3$). HRMS (ESI) calcd for $C_{28}H_{44}N_3O_{12}PNa$ [M+Na]: 668.2560, found 668.2556.

Phenylalanine ester menthyl phosphoramidates of 2′,3′-isopropylideneuridine (4g). Yield 503.8 mg (75.9%). IR (film) ν: 3222, 1742, 1693, 1630, 1455, 1214, 1063, 998 cm^{-1}. ^{31}P NMR (CDCl$_3$, 202 MHz): δ 7.50, 6.81. ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.81, 8.68 (br, br, 1H, H-3), 7.40, 7.33 (d, d, 1H, J = 7.5 Hz, H-6), 7.22–7.31 (m, 5H, H$_{\text{Ph}}$), 5.80, 5.75 (br, br, 1H, H-1′), 5.686 (d, 1H, J = 7.0 Hz, H-5), 4.767–4.861 (m, 2H, H-2′, H-3′), 4.284–3.947 (m, 5H, H-4′, H-5′, H-α, OC$\underline{\text{H}}$R), 3.70, 3.67 (s, s, 3H, OCH$_3$), 3.03 (d, 2H, J = 6.0 Hz, H-β), 3.31 (t, 1H, J = 10.0 Hz, P-NH), 1.98–2.24 (m, 2H, H$_{\text{menthyl}}$), 1.70–1.79 (m, 2H, H$_{\text{menthyl}}$), 1.64–1.66 (m, 2H, H$_{\text{menthyl}}$), 1.57 (s, 3H, >CCH$_3$), 1.36–1.47 (m, 1H, H$_{\text{menthyl}}$),1.35 (s, 3H, >CCH$_3$), 1.22–1.30 (m, 1H, H$_{\text{menthyl}}$), 1.07–1.15 (m, 1H, H$_{\text{menthyl}}$), 0.905 (d, 6H, J = 6.0 Hz, 2CH$_3$), 0.784 (d, 3H, J = 7.0 Hz, CH$_3$). ^{13}C NMR (CDCl$_3$, 125 MHz): δ 172.93 (COOMe), 163.37 (C-4), 150.03 (C-2), 141.52 (C-6), 135.77 (C$_{\text{Ph}}$), 129.32 (C$_{\text{Ph}}$), 128.40 (C$_{\text{Ph}}$), 126.94 (C$_{\text{Ph}}$), 114.48 (>$\underline{\text{C}}$Me$_2$), 102.56

(C-5), 93.23 (C-1′), 84.96 (C-4′), 84.20 (C-2′), 80.64 (C-3′), 78.84 (O$\underline{C}$HR), 65.33 (C-5′), 55.36 (OCH$_3$), 52.09 (C-α), 48.35 (C$_{\text{menthyl}}$), 42.58 (C$_{\text{menthyl}}$), 40.45 (C-β), 33.87 (C$_{\text{menthyl}}$), 31.33 (C$_{\text{menthyl}}$), 27.01 (>C$\underline{C}$H$_3$), 25.53 (>C$\underline{C}$H$_3$), 25.17 (C$_{\text{menthyl}}$), 22.67 (C$_{\text{menthyl}}$), 21.87 (CH$_3$), 20.92 (CH$_3$), 15.56 (CH$_3$); HRMS (ESI) calcd for $C_{32}H_{47}N_3O_{10}P$: 664.2999, found 664.3004.

Tyrosine ester menthyl phosphoramidates of 2′,3′-isopropylideneuridine (4h). Yield 442.1 mg (65.1%). IR (film) *v*: 3253, 1710, 1692, 1615, 1517, 1455, 1216, 1067, 1017 cm^{-1}.^{31}P NMR (CDCl$_3$, 202 MHz): δ 7.56, 6.60; ^{1}H NMR (CDCl$_3$, 500 MHz): δ 9.79, 9.64 (br, br, 1H, H-3), 7.89–7.73 (br, 1H, -OH), 7.34, 7.30 (d, d, 1H, J = 8.0 Hz, H-6), 6.94–6.97 (m, 2H, H$_{\text{Ph}}$), 6.75–6.78 (m, 2H, H$_{\text{Ph}}$), 5.72, 5.67 (d, 1H, J = 2.0 Hz, H-1′), 5.66, 5.65 (d, d, 1H, J = 8.0 Hz, H-5), 4.917–4.96 (m, 2H, H-2′, H-3′), 4.87–4.88 (m, 1H, H-4′), 4.69–4.78 (m, 3H, H-5′, OC$\underline{H}$R), 3.90–3.99 (m, 1H, H-α), 3.71, 3.70 (s, s, 3H, OCH$_3$), 3.57 (t, 1H, J = 10.5 Hz, P-NH), 2.92–2.96 (m, 2H, H-β), 2.01–2.21 (m, 2H, H$_{\text{menthyl}}$), 1.69–1.78 (m, 2H, H$_{\text{menthyl}}$), 1.61–1.69 (m, 2H, H$_{\text{menthyl}}$), 1.55 (s, 3H, CH$_3$), 1.39–1.47 (m, 1H, H$_{\text{menthyl}}$), 1.34, 1.33 (s, s, 3H, CH$_3$), 1.22–1.30 (m, 1H, H$_{\text{menthyl}}$), 0.95–1.14 (m, 1H, H$_{\text{menthyl}}$), 0.90 (d, 3H, J = 7.0 Hz, CH$_3$), 0.87 (d, 3H, J = 7.0 Hz, CH$_3$), 0.79, 0.78 (d, d, 3H, J = 7.0 Hz, CH$_3$); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 173.42 (COOMe), 163.88 (C-4), 155.88 (PhOH), 150.79 (C-2), 142.00, 141.69 (C-6), 130.41 (C$_{\text{Ph}}$), 126.82 (C$_{\text{Ph}}$), 126.43 (C$_{\text{Ph}}$), 115.66 (C$_{\text{Ph}}$), 114.45 (>$\underline{C}$Me$_2$), 102.44 (C-5), 93.96, 93.44 (C-1′), 85.03 (C-4′), 84.23 (C-2′), 80.69 (C-3′), 79.28 (O$\underline{C}$HR), 65.38 (C-5′), 55.97 (OCH$_3$), 52.21 (C-α), 48.38 (C$_{\text{menthyl}}$), 42.51 (C$_{\text{menthyl}}$), 39.52 (C-β), 33.87 (C$_{\text{menthyl}}$), 31.33 (C$_{\text{menthyl}}$), 27.01 (>C$\underline{C}$H$_3$), 25.50 (>C$\underline{C}$H$_3$), 25.12 (C$_{\text{menthyl}}$), 22.64 (C$_{\text{menthyl}}$), 21.87 (CH$_3$), 20.92 (CH$_3$), 15.56 (CH$_3$). HRMS (ESI) calcd for $C_{32}H_{47}N_3O_{11}P$: 680.2948, found 680.2942.

Histidine ester menthyl phosphoramidates of 2′,3′-isopropylideneuridine (4i). Yield 465.6 mg (71.3%). IR (film) *v*: 3246, 1705, 1693, 1610, 1217, 1054, 999 cm^{-1}. ^{31}P NMR (CDCl$_3$, 202 MHz): δ 7.25, 6.40; ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.58 (s, 1H, H$_{\text{imidazole}}$), 7.41 (d, 1H, J = 8.0 Hz, H-6), 6.81, 6.77 (s, s, 1H, H$_{\text{imidazole}}$), 5.70 (br, 1H, H-1′), 5.65 (d, 1H, J = 8.0 Hz, H-5), 4.86–4.93 (m, 2H, H-2′, H-3′), 4.25–4.31 (m, 2H, H-4′, OC$\underline{H}$R), 4.14 (br, 3H, H-5′, P-NH), 4.05 (t, 1H, J = 5.5 Hz, H-α), 3.69 (s, 3H, OCH$_3$), 3.11, 3.06 (d, d, 2H, J = 3.5 Hz, H-β), 2.15-2.18 (m, 1H, H$_{\text{menthyl}}$), 2.03–2.12 (m, 1H, H$_{\text{menthyl}}$), 1.62–1.64 (m, 2H, H$_{\text{menthyl}}$), 1.56 (s, 3H, >CCH$_3$), 1.37–1.47 (m, 1H, H$_{\text{menthyl}}$), 1.34 (s, 3H, >CCH$_3$), 1.26–1.30 (m, 2H, H$_{\text{menthyl}}$), 0.93–1.09 (m, 2H, H$_{\text{menthyl}}$), 0.88, 0.87 (d, d, 6H, J = 6.5 Hz, 2CH$_3$), 0.78 (d, 3H, J = 7.0 Hz, CH$_3$); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 173.25 (COOMe), 164.08 (C-4), 150.54 (C-2), 141.93 (C-6), 135.41 (C$_{\text{imidazole}}$), 133.16 (C$_{\text{imidazole}}$), 119.58 (C$_{\text{imidazole}}$), 114.18 (>$\underline{C}$Me$_2$), 102.49 (C-5), 93.88 (C-1′), 85.25 (C-4′), 84.35 (C-2′), 80.90 (C-3′), 78.96 (O$\underline{C}$HR), 65.33 (C-5′), 54.83 (OCH$_3$), 52.19 (C-α), 48.43 (C$_{\text{menthyl}}$), 42.41 (C$_{\text{menthyl}}$), 35.82 (C$_{\text{menthyl}}$), 31.33 (C-β, C$_{\text{menthyl}}$), 27.01 (>C$\underline{C}$H$_3$), 25.46 (>C$\underline{C}$H$_3$), 25.12 (C$_{\text{menthyl}}$), 22.62 (C$_{\text{menthyl}}$), 21.87 (CH$_3$), 20.90 (CH$_3$), 15.51 (CH$_3$). HRMS (ESI) calcd for $C_{29}H_{45}N_5O_{10}P$: 654.2904, found 654.2899.

Methionine ester menthyl phosphoramidates of 2′,3′-isopropylideneuridine (4j). Yield 472.3 mg (73.1%). IR (film) *v*: 3216, 1722, 1694, 1625, 1216, 1063, 1011 cm^{-1}.^{31}P NMR (CDCl$_3$, 202 MHz): δ 7.49, 6.68; ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.91 (br, 1H, H-3), 7.36, 7.28 (d, d, 1H, J = 8.0 Hz, H-6), 5.63–5.74 (m, 2H, H-1′, H-5), 4.77–4.89 (m, 2H, H-2′, H-3′), 4.24–4.27 (m, 1H, H-4′), 4.06–4.21 (m, 3H, H-5′, OC$\underline{H}$R), 3.91–4.00 (m, 1H, H-α), 3.67 (s, 3H, OCH$_3$), 3.46–3.55 (m, 1H, P-NH), 2.49, 2.48 (d, 2H, J = 3.0 Hz, H-γ), 2.22, 2.15 (d, 2H, J = 10.5 Hz, H-β), 2.02 (s, 3H, SCH$_3$), 1.94–2.00 (m, 1H, H$_{\text{menthyl}}$), 1.80–1.91 (m, 1H, H$_{\text{menthyl}}$), 1.67–1.77 (m, 2H, H$_{\text{menthyl}}$), 1.54–1.63 (m, 2H, H$_{\text{menthyl}}$), 1.51 (s, 3H, >CCH$_3$), 1.33–1.43 (m, 1H, H$_{\text{menthyl}}$), 1.28 (s, 3H, >CCH$_3$), 1.19–1.23 (m, 1H, $H_{menthyl}$), 1.01–1.06 (m, 1H, $H_{menthyl}$), 0.84 (s, 6H, $2CH_3$), 0.74 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.32 (COOMe), 163.50 (C-4), 150.11 (C-2), 141.70, 141.38 (C-6), 114.26 ($>\underline{C}Me_2$), 102.44 (C-5), 93.44, 92.94 (C-1′), 85.01, 84.74 (C-4′), 84.11 (C-2′), 80.69, 80.47 (C-3′), 78.72 ($O\underline{C}HR$), 65.41 (C-5′), 53.20 (C-α), 52.19 (OCH_3), 48.23 ($C_{menthyl}$), 42.36 ($C_{menthyl}$), 33.68, 33.44 (C-β), 31.20 ($C_{menthyl}$), 29.44 (C-γ), 26.86 ($>\underline{C}CH_3$), 25.31 ($>\underline{C}CH_3$), 25.00 ($C_{menthyl}$), 22.47 ($C_{menthyl}$), 21.75 (CH_3), 20.75 (CH_3), 15.37 (CH_3), 15.08 ($S\underline{C}H_3$). HRMS (ESI) calcd for $C_{28}H_{47}N_3O_{10}PS$: 648.2720, found 648.2717.

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