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Chemoselective Synthesis of New Stable Phosphorus Ylides from the Reaction Between Triphenylphosphine and Activated Acetylenic Esters in the Presence of Heterocyclic Biological Bases

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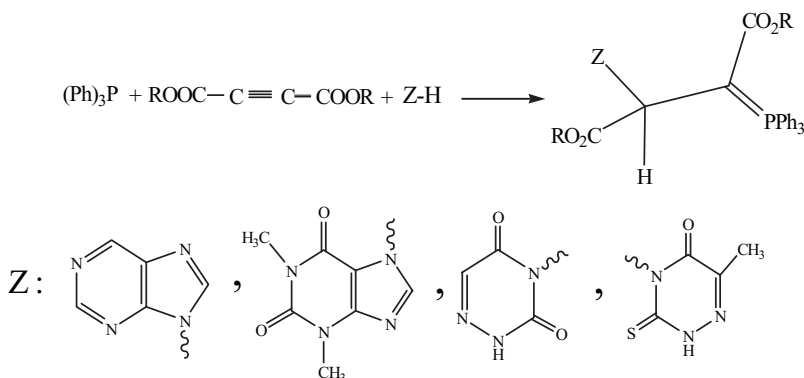
CHEMOSELECTIVE SYNTHESIS OF NEW STABLE PHOSPHORUS YLIDES FROM THE REACTION BETWEEN TRIPHENYLPHOSPHINE AND ACTIVATED ACETYLENIC ESTERS IN THE PRESENCE OF HETEROCYCLIC BIOLOGICAL BASES

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GRAPHICAL ABSTRACT



Abstract A facile and chemoselective one-pot synthesis of novel stable phosphorus ylides has been developed from the reaction between triphenylphosphine and dialkyl acetylenedicarboxylates in the presence of (heterocyclic) biological bases such as purine, theophylline, 6-azauracil, and 6-aza-2-thiothymine at ambient temperature.

Keywords 6-Aza-2-thiothymine; 6-azauracil; purine; stable phosphorus ylides; theophylline

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INTRODUCTION

Purine and pyrimidine ring systems form the backbone of many important biological molecules, such as nucleic acids, cofactors, and various toxins. The ability of these molecules to interact with proteins has been extensively exploited in the preparation of inhibitors that work specifically against certain conditions, such as Gleevec (cancer) or aronixil (atherosclerosis), for example. The privileged nature of the purine/pyrimidine structure in terms of their shape and hydrogen-bonding characteristics make them ideal starting points in the search for new chemical entities of biological significance.¹

The synthesis and chemistry of purine has attracted considerable attention due to its pharmaceutical and biological properties. Some purine derivatives such as theophylline have long been used as anti-inflammatory drugs.^{2–4} Phosphorus ylides are reactive systems, which take part in many reactions of value in organic synthesis.^{5–15} Several methods have been developed for the preparation of phosphorus ylides. These ylides are usually prepared by treatment of a phosphonium salt with a base, and phosphonium salts are usually obtained from the phosphine and an alkyl halide.^{5,9,10,12,13} In recent years, there have been some reports about the synthesis of stable phosphorus ylides.^{16–29} In this article, we describe an efficient synthetic route to new stable phosphorus ylides.

RESULTS AND DISCUSSION

The reaction between triphenylphosphine, electron-deficient acetylenic esters such as dialkyl acetylenedicarboxylates **1**, and biological bases **3** such as purine, theophylline, 6-azauracil, and 6-aza-2-thiothymine led to the corresponding stable phosphorus ylides (Figure 1). On the basis of the mechanism proposed in Figure 1, it is obvious that the reaction between acetylenic esters and PPh_3 produces the carbene–ylide intermediate **2**, which is sufficiently stabilized by resonance.^{26,27} Thus, compounds **4a–k** are apparently obtained from the initial addition of triphenylphosphine as a good nucleophile²⁸ to acetylenic esters as a

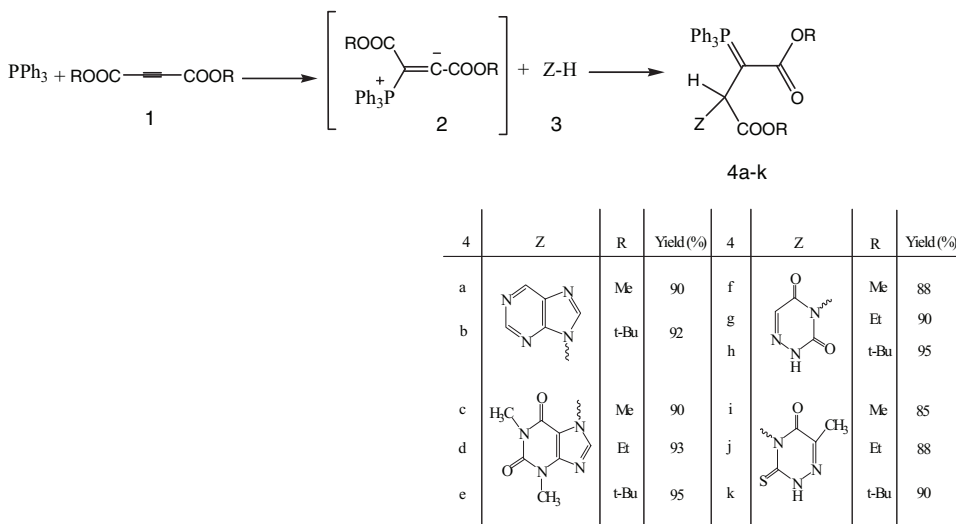


Figure 1 Synthesis of stable phosphorus ylides **4a–k**.

Michael acceptor,²⁹ and concomitant protonation of the carbene–ylide intermediate **2** by the heterocyclic biological bases **3**. Then the positively charged ion is attacked by the nitrogen of the conjugated base of **3** to form succinic esters containing several functional groups **4**.

The ¹H and ¹³C NMR spectra of the crude products clearly indicated the formation of phosphorus ylides **4**. No product other than **4** could be detected by NMR spectroscopy. The structures of compounds **4a–k** were characterized on the basis of elemental analyses, IR, mass, ¹H NMR, and ¹³C NMR spectra. The ¹H NMR spectrum of **4b** showed two singlet at $\delta = 1.01$, 1.54 for *tert*-butyl groups and a doublet at $\delta = 5.22$ ($J = 16.6$) arising from methine proton ($CH=C=P$ group). The aromatic protons of triphenylphosphine appeared as a multiplet at $\delta = 7.26$ – 7.69 and three singlets at $\delta = 8.56$, 8.98, and 9.02 for aromatic protons of purine. As can be seen in the Experimental section, the ¹³C NMR spectrum of **4b** displayed 23 distinct resonances, which are in a good agreement with only one isomer, presumably, because of the *tert*-butyl groups. Compounds **4e**, **4h**, and **4k** are similar to that of **4b**. The ¹H, ¹³C, and ³¹P NMR spectra of compounds **4a**, **4c**, **4d**, **4f**, **4g**, **4i**, and **4j** showed a mixture of two rotational isomers (Figure 2). Assignment of *E*-**4(a, c, d, f, g, i, j)** and *Z*-**4(a, c, d, f, g, i, j)** isomers as the major or minor form in phosphorus ylides have been previously reported in the literature.^{30–32} The ¹H NMR spectrum of **4a** exhibited two singlets at 3.23 and 3.74 ppm arising from two methoxy groups in the *Z* isomer and two singlets at 3.68 and 3.74 ppm for two methoxy groups in the *E* isomer. The shift at 3.23 ppm of the methoxy group in the *Z* isomer is shielded due to the anisotropic effect of a phenyl group of triphenylphosphine. This effect confirms why the *Z*-**4a** and *E*-**4a** isomers could appear as the major and minor forms, respectively, with respect to the experimental abundance percentage of both isomers (see the Experimental section). Also, signals for methine protons appeared as two doublets at $\delta = 5.37$ ($J = 16.7$ Hz) and $\delta = 5.41$ ($J = 16.7$ Hz), respectively, for the *E* and *Z* isomers. The carbonyl region of these compounds **4a–k** exhibited absorption bands for each compound in their IR spectra. Of special interest is the ester absorption at 1614–1755 cm^{−1}. Conjugation with the negative charge of the ylide moiety with the adjacent carbonyl group accounts for the reduction of the wave numbers of the carbonyl absorption bands. This phenomenon confirms why the equilibrium could appear between the *E* and *Z* isomers; this will be effective in the methodological study of synthesis of these compounds. The ylide moiety of these compounds is strongly conjugated with the adjacent carbonyl group, and rotation around the partial double bond *E*-**4(a, c, d, f, g, i, j)** and *Z*-**4(a, c, d, f, g, i, j)** isomers is slow on the NMR time scale at ambient temperature (Figure 2).

In continuation of our investigations, we found that from the reaction between triphenylphosphine, acetylenic esters, purine, or theophylline, a mixture of two products was obtained with different portions in the presence of acetone, ethyl acetate, and dichloromethane

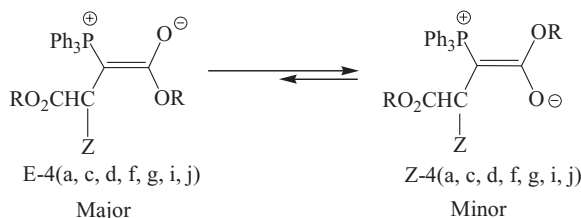


Figure 2 Equilibrium could appear between *E* and *Z* isomer.

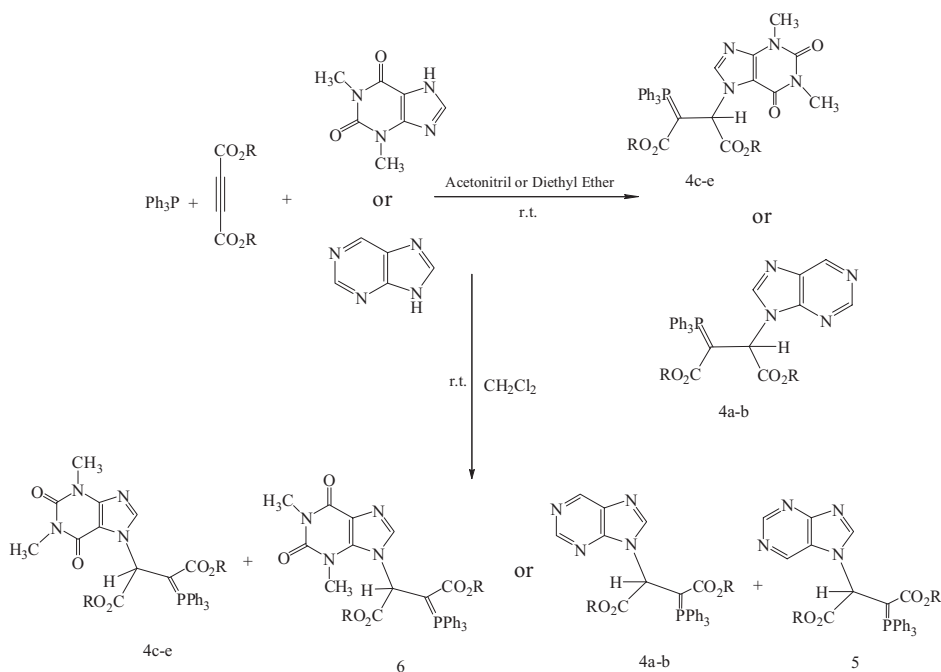


Figure 3 Synthesis of stable phosphorus ylide from purine and theophylline in different solvents.

solvents, respectively; our efforts to separate them were unsuccessful by chromatography, whereas they (purine or theophylline) produce only one product (**4a-b** or **4c-e**) in ether and acetonitrile solvents, respectively (Figure 3).

NMR spectroscopy was employed to distinguish **4** from the products **5** and **6**. For example, for the ylide containing a purine, the chemical shift of the ^{13}C NMR spectra for the carbon atom between two nitrogen atoms in the place of fused rings changes from 154.8 ppm (in the uncoordinated purine) to 151.6 ppm in product. This can be seen as a whole for bases with fused rings.³³ The structural assignments made for stable phosphorus ylides **4a-e** on the basis of the ^1H , ^{13}C , and ^{31}P NMR spectra were supported by their IR spectra.

CONCLUSIONS

In summary, we have demonstrated a one-pot, simple, and effective procedure for the preparation of stable phosphorus ylides from the reaction between triphenylphosphine and dialkyl acetylenedicarboxylates in the presence of biological bases such as purine, theophylline, 6-azauracil, and 6-aza-2-thiothymine at ambient temperature. The present method carries the advantage that, not only is the reaction performed under neutral conditions, but the substances can be mixed without any activation or modifications.^{12-23,31}

EXPERIMENTAL

Dialkyl acetylenedicarboxylate, purine, theophylline, 6-azauracil, 6-aza-2-thiothymine, and triphenylphosphine were purchased from Fluka (Buchs, Switzerland) and were used without further purification. Melting points and IR spectra were measured

on an Electrothermal 9100 apparatus and a Shimadzu IR-460 spectrometer, respectively. Also, the ^1H , ^{13}C , and ^{31}P NMR spectra were obtained from a Bruker DRX-500 Avance instrument using CDCl_3 as applied solvent at 500.1, 125.8, and 202.4 MHz, respectively. In addition, the mass spectra were recorded on a Shimadzu GC/MS QP 1100 EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer.

General Procedure for the Synthesis of Stable Phosphorus Ylides

To a magnetically stirred solution of triphenylphosphine (0.262 g, 1 mmol) and N-H acid (1 mmol) in diethyl ether (10 mL), a mixture of dialkyl acetylenedicarboxylate (1 mmol) in diethyl ether (2 mL) was added dropwise at -5°C over 10 min. The reaction mixture was then allowed to warm up to room temperature and stirred for 10 h. The solvent was then removed under reduced pressure, and the generated precipitate was filtered and washed with cold diethyl ether.

Dimethyl 2-(purine-1-yl)-3-(triphenylphosphoranylidene)-butanedioate (4a). Mp $160\text{--}162^\circ\text{C}$, yield 90%; IR (KBr) (ν_{max} , cm^{-1}): 1752 and 1630 ($\text{C}=\text{O}$).; MS, (m/z , %): 524 (M^+ , 8), 466 (42), 262 (85), 183 (100), 120 (76), 108 (42). Anal. Calcd. For $\text{C}_{29}\text{H}_{25}\text{N}_4\text{O}_4\text{P}$ (524): C, 66.41; H, 4.77; N, 10.68%. Found: C, 66.85; H, 4.73; N, 10.4%.

Major isomer 4a-(Z) (55%): ^1H NMR (500.1 MHz, CDCl_3): δ 3.23 and 3.74 (6H, 2s, 2OCH_3), 5.41 (1H, d, $^3J_{\text{PH}} = 16.7$ Hz, $\text{P}=\text{C}-\text{CH}$), 7.43–7.60 (15H, m, $3\text{C}_6\text{H}_5$), 8.58, 8.93 and 9.04 (3H, s, $\text{N}=\text{C}-\text{H}$). ^{13}C NMR (125.8 MHz, CDCl_3): δ 43.4 (d, $^1J_{\text{PC}} = 127.5$ Hz, $\text{P}=\text{C}$), 49.6 and 53.0 (2s, 2OCH_3), 56.7 (d, $^2J_{\text{PC}} = 17.2$ Hz, $\text{P}=\text{C}-\text{CH}$), 125.7 (d, $^1J_{\text{PC}} = 91.6$ Hz, C_{ipso}), 129.0 (d, $^3J_{\text{PC}} = 12.3$ Hz, C_{meta}), 129.3 ($\text{C}_5\text{H}_4\text{N}_4$), 132.5 (C_{para}), 133.4 (d, $^3J_{\text{PC}} = 9.9$ Hz, C_{ortho}), 146.1, 147.1, 151.6 and 155.1 ($\text{C}_5\text{H}_4\text{N}_4$), 165.5 (d, $^2J_{\text{PC}} = 15.9$ Hz, $\text{P}-\text{C}=\text{C}$), 171.0 (d, $^3J_{\text{PC}} = 12.4$, $\text{C}=\text{O}$). ^{31}P NMR (202.4 MHz, CDCl_3): δ 23.21 ($\text{Ph}_3\text{P}^+-\text{C}$).

Minor isomer 4a-(E) (45%): ^1H NMR (500.1 MHz, CDCl_3): δ 3.68 and 3.74 (6H, 2s, 2OCH_3), 5.37 (1H, d, $^3J_{\text{PH}} = 16.7$ Hz, $\text{P}=\text{C}-\text{CH}$), 7.43–7.60 (15H, m, $3\text{C}_6\text{H}_5$), 8.62, 8.71 and 9.06 (3H, s, $\text{N}=\text{C}-\text{H}$). ^{13}C NMR (125.8 MHz, CDCl_3): δ 43.2 (d, $^1J_{\text{PC}} = 131.0$ Hz, $\text{P}=\text{C}$), 52.3 and 53.1 (2OCH_3), 56.5 (d, $^2J_{\text{PC}} = 16.7$ Hz, $\text{P}=\text{C}-\text{CH}$), 125.1 (d, $^1J_{\text{PC}} = 92.7$ Hz, C_{ipso}), 128.5 (d, $^3J_{\text{PC}} = 11.2$ Hz, C_{meta}), 129.2 ($\text{C}_5\text{H}_4\text{N}_4$), 132.5 (C_{para}), 132.5 (d, $^2J_{\text{PC}} = 10.2$ Hz, C_{ortho}), 146.6, 147.3, 150.7 and 154.3 ($\text{C}_5\text{H}_4\text{N}_4$), 170.8 (d, $^2J_{\text{PC}} = 15.7$ Hz, $\text{P}-\text{C}=\text{C}$), 170.5 (d, $^3J_{\text{PC}} = 12.2$ Hz, $\text{C}=\text{O}$). ^{31}P NMR (202.4 MHz, CDCl_3): δ 24.40 ($\text{Ph}_3\text{P}^+-\text{C}$).

Di-tert-butyl 2-(purine-1-yl)-3-(triphenylphosphoranylidene)-butanedioate (4b). Mp $153\text{--}155^\circ\text{C}$, yield 92%; IR (KBr) (ν_{max} , cm^{-1}): 1742, 1628 ($\text{C}=\text{O}$). MS, m/z (%): 608 (M^+ , 11), 507 (63), 407 (96), 262 (98), 183 (73), 108 (39), 57 (44). Anal. Calcd. For $\text{C}_{35}\text{H}_{37}\text{N}_4\text{O}_4\text{P}$: C, 69.06; H, 6.13; N, 9.20%. Found: C, 69.10; H, 6.11; N, 9.14%.

Only isomer 4b-(Z) (92%): ^1H NMR (500.1 MHz, CDCl_3): δ 1.01 and 1.54 (18H, 2s, 2CMe_3), 5.22 (1H, d, $^3J_{\text{PH}} = 16.6$ Hz, $\text{P}=\text{C}-\text{CH}$), 7.27–7.69 (15H, m, $3\text{C}_6\text{H}_5$), 8.56, 8.98 and 9.02 (3H, 3s, $\text{N}=\text{C}-\text{H}$). ^{13}C NMR (125.8 MHz, CDCl_3): δ 28.1 and 28.3 (2CMe_3), 43.3 (d, $^1J_{\text{PC}} = 128.2$ Hz, $\text{P}=\text{C}$), 57.4 (d, $^2J_{\text{PC}} = 17.8$ Hz, $\text{P}=\text{C}-\text{CH}$), 78.2 and 82.0 (2OCMe_3), 126.9 (d, $^1J_{\text{PC}} = 91.8$ Hz, C_{ipso}), 128.8 (d, $^3J_{\text{PC}} = 12.3$ Hz, C_{meta}), 132.3 (C_{para}), 133.5 (d, $^2J_{\text{PC}} = 9.9$ Hz, C_{ortho}), 147.4, 150.7, 151.5 and 152.6 ($\text{C}_5\text{H}_4\text{N}_4$), 169.5 (d, $^2J_{\text{PC}} = 12.5$ Hz, $\text{P}-\text{C}=\text{C}$), 169.6 (d, $^3J_{\text{PC}} = 13.1$ Hz, $\text{C}=\text{O}$). ^{31}P NMR (202.4 MHz, CDCl_3): δ 22.83 ($\text{Ph}_3\text{P}^+-\text{C}^-$).

Dimethyl 2-(theophylline-1-yl)-3-(triphenylphosphoranylidene)-butane-dioate (4c). Mp 157–159°C. yield 90%; IR (KBr) ($\nu_{\max}$, cm^{-1}): 1755, 1707, 1663 and 1638 (C=O). MS, m/z (%): 584 (M^+ , 5), 262 (100), 183 (58), 180 (14), 108 (24), 77 (18). Anal. Calcd. For $\text{C}_{31}\text{H}_{29}\text{N}_4\text{O}_6\text{P}$: C, 63.69; H, 5.00; N, 9.58%. Found: C, 63.66; H, 5.08; N, 9.54%.

Major isomer 4c-(Z) (53%): ^1H NMR (500.1 MHz, CDCl_3): δ 3.18 and 3.61 (6H, 2s, 2CH_3), 3.46 and 3.74 (6H, 2s, 2OCH_3), 5.53 (1H, d, $^3J_{\text{PH}} = 17.6$ Hz, $\text{P}=\text{C}-\text{CH}$), 7.40–7.71 (15H, m, $3\text{C}_6\text{H}_5$), 8.28 (1H, s, $\text{N}=\text{C}-\text{H}$). ^{13}C NMR (125.8 MHz, CDCl_3): δ 27.5 and 29.6 (2CH_3), 43.0 (d, $^1J_{\text{PC}} = 130.7$ Hz, $\text{P}=\text{C}$), 49.6 and 52.9 (2OCH_3), 60.1 (d, $^2J_{\text{PC}} = 15.8$ Hz, $\text{P}-\text{C}-\text{CH}$), 106.9 ($\text{C}_7\text{H}_8\text{N}_4\text{O}_2$), 125.9 (d, $^1J_{\text{PC}} = 88.7$ Hz, C_{ipso}), 129.0 (d, $^3J_{\text{PC}} = 12.0$ Hz, C_{meta}), 132.5 (C_{para}), 133.4 (d, $^2J_{\text{PC}} = 8.8$ Hz, C_{ortho}), 139.9, 147.8, 151.7, 154.5 ($\text{C}_7\text{H}_8\text{N}_4\text{O}_2$), 170.3 (d, $^2J_{\text{PC}} = 12.6$ Hz, $\text{P}-\text{C}=\text{C}$), 170.9 (d, $^3J_{\text{PC}} = 12.8$ Hz, $\text{C}=\text{O}$). ^{31}P NMR (202.4 MHz, CDCl_3): δ 24.74 ($\text{Ph}_3\text{P}^+-\text{C}$).

Minor isomer 4c-(E) (47%): ^1H NMR (500.1 MHz, CDCl_3): δ 3.60 and 3.66 (6H, 2s, 2CH_3), 3.56 and 3.64 (6H, 2s, 2OCH_3), 5.50 (1H, d, $^3J_{\text{PH}} = 16.8$ Hz, $\text{P}=\text{C}-\text{CH}$), 7.40–7.71 (15H, m, $3\text{C}_6\text{H}_5$), 8.16 (1H, s, $\text{N}=\text{C}-\text{H}$). ^{13}C NMR (125.8 MHz, CDCl_3): δ 28.2 and 30.1 (2CH_3), 38.1 (d, $^1J_{\text{PC}} = 127.1$ Hz, $\text{P}=\text{C}$), 50.4 and 52.8 (2OCH_3), 60.1 (d, $^2J_{\text{PC}} = 15.8$ Hz, $\text{P}-\text{C}-\text{CH}$), 107.0 ($\text{C}_7\text{H}_8\text{N}_4\text{O}_2$), 125.2 (d, $^1J_{\text{PC}} = 91.0$ Hz, C_{ipso}), 129.0 (d, $^3J_{\text{PC}} = 12.0$ Hz, C_{meta}), 132.5 (C_{para}), 133.4 (d, $^2J_{\text{PC}} = 8.8$ Hz, C_{ortho}), 141.1, 148.63, 150.7, 155.5 ($\text{C}_7\text{H}_8\text{N}_4\text{O}_2$), 170.5 (d, $^2J_{\text{PC}} = 12.9$ Hz, $\text{P}-\text{C}=\text{C}$), 170.9 (d, $^3J_{\text{PC}} = 13.0$ Hz, $\text{C}=\text{O}$). ^{31}P NMR (202.4 MHz, CDCl_3): δ 25.80 ($\text{Ph}_3\text{P}^+-\text{C}$).

Diethyl 2-(theophylline-1-yl)-3-(triphenylphosphoranylidene)-butane-dioate (4d). Mp 185–186°C. yield 93%; IR (KBr) ($\nu_{\max}$, cm^{-1}): 1754, 1704, 1666 and 1637 (C=O). MS, m/z (%): 612 (M^+ , 6), 539 (4), 433 (100), 277 (4), 262 (95), 183 (40), 108 (22). Anal. Calcd. For $\text{C}_{33}\text{H}_{33}\text{N}_4\text{O}_6\text{P}$: C, 64.70; H, 5.43; N, 9.15%. Found: C, 64.77; H, 5.41; N, 9.10%.

Major isomer 4d-(Z) (54%): ^1H NMR (500.1 MHz, CDCl_3): δ 0.53 and 1.29 (6H, $2\text{OCH}_2\text{CH}_3$), 3.19 and 3.58 (6H, 2s, 2CH_3), 3.80 and 4.28 (4H, m, $2\text{OCH}_2\text{CH}_3$), 5.52 (1H, d, $^3J_{\text{PH}} = 17.2$ Hz, $\text{P}=\text{C}-\text{CH}$), 7.47–7.69 (15H, m, $3\text{C}_6\text{H}_5$), 8.30 (1H, s, $\text{N}=\text{C}-\text{H}$). ^{13}C NMR (125.8 MHz, CDCl_3): δ : 14.0 and 14.1 ($2\text{OCH}_2\text{CH}_3$), 27.5 and 29.6 (2CH_3), 42.8 (d, $^1J_{\text{PC}} = 127.0$ Hz, $\text{P}=\text{C}$), 58.3 and 60.0 ($2\text{OCH}_2\text{CH}_3$), 61.7 (d, $^2J_{\text{PC}} = 17.7$ Hz, $\text{P}=\text{C}-\text{CH}$), 107.0 ($\text{C}_7\text{H}_8\text{N}_4\text{O}_2$), 126.0 (d, $^1J_{\text{PC}} = 91.8$ Hz, C_{ipso}), 128.9 (d, $^3J_{\text{PC}} = 11.8$ Hz, C_{meta}), 132.0 (C_{para}), 133.4 (d, $^2J_{\text{PC}} = 9.6$ Hz, C_{ortho}), 141.8, 147.7, 151.7 and 154.4 ($\text{C}_7\text{H}_8\text{N}_4\text{O}_2$), 165.1 (d, $^2J_{\text{PC}} = 12.6$ Hz, $\text{P}-\text{C}=\text{C}$), 170.5 (d, $^3J_{\text{PC}} = 12.2$ Hz, $\text{C}=\text{O}$). ^{31}P NMR (202.4 MHz, CDCl_3): δ 23.56 ($\text{Ph}_3\text{P}^+-\text{C}$).

Minor isomer 4d-(E) (46%): ^1H NMR (500.1 MHz, CDCl_3): δ 1.26 and 1.31 (6H, $2\text{OCH}_2\text{CH}_3$), 3.22 and 3.58 (6H, 2s, 2CH_3), 4.08 and 4.16 (4H, m, $2\text{OCH}_2\text{CH}_3$), 5.46 (1H, d, $^3J_{\text{PH}} = 18.6$ Hz, $\text{P}=\text{C}-\text{CH}$), 7.47–7.69 (15H, m, $3\text{C}_6\text{H}_5$), 8.20 (1H, s, $\text{N}=\text{C}-\text{H}$). ^{13}C NMR (125.8 MHz, CDCl_3): δ : 14.1 and 14.8 ($2\text{OCH}_2\text{CH}_3$), 28.2 and 30.1 (2CH_3), 42.8 (d, $^1J_{\text{PC}} = 135.6$ Hz, $\text{P}=\text{C}$), 58.8 and 59.8 ($2\text{OCH}_2\text{CH}_3$), 61.8 (d, $^2J_{\text{PC}} = 17.2$ Hz, $\text{P}=\text{C}-\text{CH}$), 106.7 ($\text{C}_7\text{H}_8\text{N}_4\text{O}_2$), 125.4 (d, $^1J_{\text{PC}} = 91.6$ Hz, C_{ipso}), 128.5 (d, $^3J_{\text{PC}} = 12.0$ Hz, C_{meta}), 132.1 (C_{para}), 133.5 (d, $^2J_{\text{PC}} = 8.4$ Hz, C_{ortho}), 141.7, 148.4, 151.8 and 155.3 ($\text{C}_7\text{H}_8\text{N}_4\text{O}_2$), 169.7 (d, $^2J_{\text{PC}} = 12.0$ Hz, $\text{P}-\text{C}=\text{C}$), 170.3 (d, $^3J_{\text{PC}} = 12.0$ Hz, $\text{C}=\text{O}$). ^{31}P NMR (202.4 MHz, CDCl_3): δ 24.78 ($\text{Ph}_3\text{P}^+-\text{C}$).

Di-tert-butyl-2-(theophylline-1-yl)-3-(triphenylphosphoranylidene)-butanedioate (4e). Mp 136–137°C. yield 95%; IR (KBr) ($\nu_{\max}$, cm^{-1}): 1746, 1703, 1655 and 1630 (C=O). MS, m/z (%): 668 (M^+ , 8), 489 (4), 377 (8), 262 (100), 183 (38), 108 (93). Anal. Calcd. For $\text{C}_{37}\text{H}_{41}\text{N}_4\text{O}_6\text{P}$: C, 66.45; H, 6.18; N, 8.38%. Found: C, 66.40; H, 6.21; N, 8.34%.

Only isomer 4e-(Z) (95%): ^1H NMR (500.1 MHz, CDCl_3), δ 0.99 and 1.54 (18H, 2s, 2CMe_3), 3.17 and 3.56 (6H, 2s, 2CH_3), 5.40 (1H, d, $^3J_{\text{PH}} = 17.3$ Hz, $\text{P}=\text{C}-\text{CH}$), 7.27–7.71 (15H, m, $3\text{C}_6\text{H}_5$), 8.34 (1H, s, $\text{N}=\text{C}-\text{H}$). ^{13}C NMR (125.8 MHz, CDCl_3), δ 27.5 and 29.6 (2CH_3), 28.1 and 28.2 (2CMe_3), 43.0 (d, $^1J_{\text{PC}} = 127.1$ Hz, $\text{P}=\text{C}$), 60.7 (d, $^2J_{\text{PC}} = 17.5$ Hz, $\text{P}-\text{C}-\text{CH}$), 78.0 and 81.7 (2OCMe_3), 106.7 ($\text{C}_7\text{H}_8\text{N}_4\text{O}_2$), 126.4 (d, $^1J_{\text{PC}} = 91.5$ Hz, C_{ipso}), 128.8 (d, $^3J_{\text{PC}} = 12.0$ Hz, C_{meta}), 132.3 (C_{para}), 133.4 (d, $^2J_{\text{PC}} = 9.5$ Hz, C_{ortho}), 142.1 and 147.6 and 151.7 and 154.4 ($\text{C}_7\text{H}_8\text{N}_4\text{O}_2$), 169.2 (d, $^2J_{\text{PC}} = 12.3$ Hz, $\text{P}-\text{C}=\text{C}$), 169.7 (d, $^3J_{\text{PC}} = 11.7$ Hz, $\text{C}=\text{O}$). ^{31}P NMR (202.4 MHz, CDCl_3): δ 23.14 ($\text{Ph}_3\text{P}^+-\text{C}$).

Dimethyl 2-(6-azauracil-1-yl)-3-(triphenylphosphoranylidene)-butanedioate (4f). Mp 170–171°C, yield 88%; IR (KBr) (ν_{max} , cm^{-1}): 3449 (N–H) 1736, 1702, 1646 and 1618 ($\text{C}=\text{O}$). MS, m/z (%): 517 (M^+ , 11), 473 (3), 405 (3), 262 (100), 183 (53), 108 (29). Anal. Calcd. For $\text{C}_{27}\text{H}_{24}\text{N}_3\text{O}_6\text{P}$: C, 62.67; H, 4.67; N, 8.12%. Found: C, 62.70; H, 4.61; N, 8.18%.

Major isomer 4f-(Z) (60%): ^1H NMR (500.1 MHz, CDCl_3): δ 3.15 and 3.75 (6H, 2s, 2OCH_3), 5.26 (1H, d, $^3J_{\text{PH}} = 16.5$ Hz, $\text{P}=\text{C}-\text{CH}$), 7.27–7.69 (16H, m, $3\text{C}_6\text{H}_5$ and $\text{C}_3\text{H}_3\text{N}_3\text{O}_2$), 9.15 (1H, s, NH). ^{13}C NMR (125.8 MHz, CDCl_3): δ 38.6 (d, $^1J_{\text{PC}} = 129.6$ Hz, $\text{P}=\text{C}$), 49.2 and 52.9 (2OCH_3), 62.8 (d, $^2J_{\text{PC}} = 16.0$ Hz, $\text{P}=\text{C}-\text{CH}$), 126.4 (d, $^1J_{\text{PC}} = 91.5$ Hz, C_{ipso}), 128.9 (d, $^3J_{\text{PC}} = 12.0$ Hz, C_{meta}), 132.4 (C_{para}), 133.6 (d, $^2J_{\text{PC}} = 9.7$ Hz, C_{ortho}), 147.6, 156.4 and 165.4 ($\text{C}_3\text{H}_3\text{N}_3\text{O}_2$), 170.8 (d, $^2J_{\text{PC}} = 13.2$ Hz, $\text{P}-\text{C}=\text{C}$), 170.9 (d, $^3J_{\text{PC}} = 12.1$ Hz, $\text{C}=\text{O}$). ^{31}P NMR (202.4 MHz, CDCl_3): δ 23.03 ($\text{Ph}_3\text{P}^+-\text{C}$).

Minor isomer 4f-(E) (40%): ^1H NMR (500.1 MHz, CDCl_3): δ 3.56 and 3.70 (6H, 2s, 2OCH_3), 5.31 (1H, d, $^3J_{\text{PH}} = 17.9$, $\text{P}=\text{C}-\text{CH}$), 7.27–7.69 (16H, m, $3\text{C}_6\text{H}_5$ and $\text{C}_3\text{H}_3\text{N}_3\text{O}_2$), 9.15 (1H, s, NH). ^{13}C NMR (125.8 MHz, CDCl_3): δ 39.7 (d, $^1J_{\text{PC}} = 138.1$ Hz, $\text{P}=\text{C}$), 50.4 and 52.3 (2OCH_3), 62.2 (d, $^2J_{\text{PC}} = 16.0$ Hz, $\text{P}=\text{C}-\text{CH}$), 125.7 (d, $^1J_{\text{PC}} = 91.5$ Hz, C_{ipso}), 128.5 (d, $^3J_{\text{PC}} = 12.1$ Hz, C_{meta}), 132.4 (C_{para}), 133.6 (d, $^2J_{\text{PC}} = 9.1$ Hz, C_{ortho}), 148.7, 159.7 and 165.6 ($\text{C}_3\text{H}_3\text{N}_3\text{O}_2$), 169.9 (d, $^2J_{\text{PC}} = 12.9$ Hz, $\text{P}-\text{C}=\text{C}$), 171.1 (d, $^3J_{\text{PC}} = 17.3$ Hz, $\text{C}=\text{O}$). ^{31}P NMR (202.4 MHz, CDCl_3): δ 23.12 ($\text{Ph}_3\text{P}^+-\text{C}$).

Diethyl-2-(6-azauracil-1-yl)-3-(triphenylphosphoranylidene)-butanedioate (4g). Mp 165–166°C, yield 90%; IR (KBr) (ν_{max} , cm^{-1}): 3273 (N–H), 1730, 1702 and 1614 ($\text{C}=\text{O}$). MS, m/z (%): 545 (M^+ , 10), 409 (2), 380 (10), 283 (3), 262 (100), 183 (72), 113(5), 108 (28). Anal. Calcd. For $\text{C}_{29}\text{H}_{28}\text{N}_3\text{O}_6\text{P}$: C, 63.85; H, 5.17; N, 7.70%. Found: C, 63.894; H, 5.20; N, 7.74%.

Major isomer 4g-(Z) (55%): ^1H NMR (500.1 MHz, CDCl_3): δ 0.44 and 1.29 (6H, $2\text{OCH}_2\text{CH}_3$), 3.71 and 4.17 (4H, m, $2\text{OCH}_2\text{CH}_3$), 5.31 (1H, d, $^3J_{\text{PH}} = 17.3$ Hz, $\text{P}=\text{C}-\text{CH}$), 7.46–7.72 (16H, m, $3\text{C}_6\text{H}_5$ and $\text{C}_3\text{H}_3\text{N}_3\text{O}_2$), 8.76 (1H, s, NH). ^{13}C NMR (125.8 MHz, CDCl_3): δ 14.1 and 14.8 ($2\text{OCH}_2\text{CH}_3$), 38.4 (d, $^1J_{\text{PC}} = 129.9$ Hz, $\text{P}=\text{C}$), 57.8 and 61.3 ($2\text{OCH}_2\text{CH}_3$), 62.9 (d, $^2J_{\text{PC}} = 16.4$ Hz, $\text{P}=\text{C}-\text{CH}$), 126.7 (d, $^1J_{\text{PC}} = 91.4$ Hz, C_{ipso}), 128.5 (d, $^3J_{\text{PC}} = 12.1$ Hz, C_{meta}), 131.9 (C_{para}), 133.6 (d, $^2J_{\text{PC}} = 9.0$ Hz, C_{ortho}), 147.4, 156.3 and 165.0 ($\text{C}_3\text{H}_3\text{N}_3\text{O}_2$), 169.3 (d, $^2J_{\text{PC}} = 12.7$ Hz, $\text{P}-\text{C}=\text{C}$), 170.22 (d, $^3J_{\text{PC}} = 12.7$ Hz, $\text{C}=\text{O}$). ^{31}P NMR (202.4 MHz, CDCl_3): δ 23.03 ($\text{Ph}_3\text{P}^+-\text{C}$).

Minor isomer 4g-(E) (45%), ^1H NMR (500.1 MHz, CDCl_3): δ 1.15 and 1.31 (6H, $2\text{OCH}_2\text{CH}_3$), 4.01 and 4.23 (4H, m, $2\text{OCH}_2\text{CH}_3$), 5.21 (1H, d, $^3J_{\text{PH}} = 17.3$ Hz, $\text{P}=\text{C}-\text{CH}$), 7.46–7.72 (16H, m, $3\text{C}_6\text{H}_5$ and $\text{C}_3\text{H}_3\text{N}_3\text{O}_2$), 8.76 (1H, s, NH). ^{13}C NMR (125.8 MHz, CDCl_3): δ 13.8 and 14.0 ($2\text{OCH}_2\text{CH}_3$), 39.6 (d, $^1J_{\text{PC}} = 133.1$ Hz, $\text{P}=\text{C}$), 58.5 and 61.2 ($2\text{OCH}_2\text{CH}_3$), 62.3 (d, $^2J_{\text{PC}} = 17.2$ Hz, $\text{P}=\text{C}-\text{CH}$), 126.0 (d, $^1J_{\text{PC}} = 91.5$ Hz, C_{ipso}), 128.7 (d, $^3J_{\text{PC}} = 12.1$ Hz, C_{meta}), 131.9 (C_{para}), 132.1 (d, $^2J_{\text{PC}} = 9.8$ Hz, C_{ortho}), 147.5, 158.4 and 165.3 ($\text{C}_3\text{H}_3\text{N}_3\text{O}_2$), 170.3 (d, $^2J_{\text{PC}} = 11.3$ Hz, $\text{P}-\text{C}=\text{C}$), 170.9 (d, $^3J_{\text{PC}} = 15.1$ Hz, $\text{C}=\text{O}$). ^{31}P NMR (202.4 MHz, CDCl_3): δ 23.38 ($\text{Ph}_3\text{P}^+-\text{C}$).

Di-tert-butyl-2-(6-azauracil-1-yl)-3-(triphenylphosphoranylidene)-butanedioate (4h). Mp 186–188°C. yield 95%; IR (KBr) ($\nu_{\max}$, cm^{-1}): 3180 (N–H), 1750, 1714, 1681 and 1650 (C=O). MS, m/z (%): 601 (M^+ , 10), 262 (100), 183 (56), 108 (32), 57 (33). Anal. Calcd. For $\text{C}_{33}\text{H}_{36}\text{N}_3\text{O}_6\text{P}$: C, 65.88; H, 6.03; N, 6.98%. Found: C, 65.90; H, 6.01; N, 6.93%.

Only isomer 4h-(Z) (95%): ^1H NMR (500.1 MHz, CDCl_3): δ 0.93 and 1.54 (18H, 2s, 2CMe_3), 5.00 (1H, d, $^3J_{\text{PH}} = 16.8$ Hz, $\text{P}=\text{C}-\text{CH}$), 7.27–7.72 (16H, m, $3\text{C}_6\text{H}_5$ and $\text{C}_3\text{H}_3\text{N}_3\text{O}_2$), 9.15 (1H, s, NH). ^{13}C NMR (125.8 MHz, CDCl_3): δ 27.4 and 27.4 (2s, 2CMe_3), 39.5 (d, $^1J_{\text{PC}} = 125.4$ Hz, $\text{P}=\text{C}$), 62.3 (d, $^2J_{\text{PC}} = 17.4$ Hz, $\text{P}=\text{C}-\text{CH}$), 80.3 and 81.0 (2OCMe_3), 126.6 (d, $^1J_{\text{PC}} = 91.3$ Hz, C_{ipso}), 128.0 (d, $^3J_{\text{PC}} = 12.0$ Hz, C_{meta}), 131.3 (C_{para}), 133.9 (C_{ortho}), 147.3, 148.8 and 157.0 ($\text{C}_3\text{H}_3\text{N}_3\text{O}_2$), 167.7 (d, $^2J_{\text{PC}} = 12.2$ Hz, $\text{P}-\text{C}=\text{C}$), 168.8 (d, $^3J_{\text{PC}} = 13.6$ Hz, $\text{C}=\text{O}$). ^{31}P NMR (202.4 MHz, CDCl_3): δ 22.46 ($\text{Ph}_3\text{P}^+-\text{C}$).

Dimethyl-2-(6-aza-2-thiothymine-1-yl)-3-(triphenylphosphoranylidene)-butanedioate (4i). Mp 132–134°C. yield 85%; IR (KBr) ($\nu_{\max}$, cm^{-1}): 3423 (N–H), 1752, 1702 and 1628 (C=O). MS, m/z (%): 547 (M^+ , 11), 277 (12), 262 (100), 183 (100), 143 (13), 108 (35), 59 (23). Anal. Calcd. For $\text{C}_{28}\text{H}_{26}\text{N}_3\text{O}_5\text{PS}$: C, 61.42; H, 4.79; N, 7.67%. Found: C, 61.40; H, 4.075; N, 7.70%.

Major isomer 4i-(Z) (70%): ^1H NMR (500.1 MHz, CDCl_3): δ 2.26 (3H, s, CH_3), 3.15 and 3.81 (6H, 2s, 2OCH_3), 6.05 (1H, d, $^3J_{\text{PH}} = 19.1$ Hz, $\text{P}=\text{C}-\text{CH}$), 7.30–7.69 (15H, m, $3\text{C}_6\text{H}_5$), 9.39 (1H, s, N–H). ^{13}C NMR (125.8 MHz, CDCl_3): δ 16.6 (s, CH_3), 41.4 (d, $^1J_{\text{PC}} = 138.4$ Hz, $\text{P}=\text{C}$), 49.4 and 52.7 (2s, 2OCH_3), 68.8 (d, $^2J_{\text{PC}} = 15.5$ Hz, $\text{P}=\text{C}-\text{CH}$), 126.4 (d, $^1J_{\text{PC}} = 91.5$ Hz, C_{ipso}), 128.9 (d, $^3J_{\text{PC}} = 12.5$ Hz, C_{meta}), 132.2 (C_{para}), 133.6 (d, $^2J_{\text{PC}} = 9.7$ Hz, C_{ortho}), 147.1, 152.6 ($\text{C}_4\text{H}_5\text{N}_3\text{OS}$), 170.1 (d, $^2J_{\text{PC}} = 12.6$ Hz, $\text{P}-\text{C}=\text{C}$), 172.3 (d, $^3J_{\text{PC}} = 16.8$ Hz, $\text{C}=\text{O}$). 173.3 ($\text{C}_4\text{H}_5\text{N}_3\text{OS}$), ^{31}P NMR (202.4 MHz, CDCl_3): δ 24.05 ($\text{Ph}_3\text{P}^+-\text{C}$).

Minor isomer 4i-(E) (30%), ^1H NMR (500.1 MHz, CDCl_3): δ 2.29 (3H, s, CH_3), 3.56 and 3.70 (6H, 2s, 2OCH_3), 6.10 (1H, d, $^3J_{\text{PH}} = 18.6$ Hz, $\text{P}=\text{C}-\text{CH}$), 7.30–7.69 (15H, m, $3\text{C}_6\text{H}_5$), 9.39 (1H, s, N–H). ^{13}C NMR (125.8 MHz, CDCl_3): δ 16.1 (s, CH_3), 40.1 (d, $^1J_{\text{PC}} = 130.8$ Hz, $\text{P}=\text{C}$), 50.5 and 53.4 (2OCH_3), 67.9 (d, $^2J_{\text{PC}} = 15.8$ Hz, $\text{P}=\text{C}-\text{CH}$), 125.7 (d, $^1J_{\text{PC}} = 91.7$ Hz, C_{ipso}), 128.6 (d, $^3J_{\text{PC}} = 13.5$ Hz, C_{meta}), 132.2 (C_{para}), 132.0 (d, $^2J_{\text{PC}} = 7.3$ Hz, C_{ortho}), 148.2, 154.72, ($\text{C}_4\text{H}_5\text{N}_3\text{OS}$), 169.9 (d, $^2J_{\text{PC}} = 16.6$ Hz, $\text{P}-\text{C}=\text{C}$), 171.3 (d, $^3J_{\text{PC}} = 17.7$ Hz, $\text{C}=\text{O}$), 173.3 (s, $\text{C}_4\text{H}_5\text{N}_3\text{OS}$), ^{31}P NMR (202.4 MHz, CDCl_3): δ 24.09 ($\text{Ph}_3\text{P}^+-\text{C}$).

Diethyl-2-(6-aza-2-thiothymine-1-yl)-3-(triphenylphosphoranylidene)-butanedioate (4j). Mp 136–137°C. yield 88%; IR (KBr) ($\nu_{\max}$, cm^{-1}): 3423 3419 (N–H), 1740, 1698, 1616 and (C=O). MS, m/z (%): 575 (M^+ , 4), 491 (7), 277 (10), 262 (40), 183 (22), 108 (9). Anal. Calcd. For $\text{C}_{30}\text{H}_{30}\text{N}_3\text{O}_5\text{PS}$: C, 62.60; H, 5.25; N, 7.30%. Found: C, 62.65; H, 5.21; N, 7.33%.

Major isomer 4j-(Z) (70%): ^1H NMR (500.1 MHz, CDCl_3): δ 0.47 and 1.25 (6H, $2\text{OCH}_2\text{CH}_3$), 2.26 (3H, s, CH_3), 3.65 and 4.07 (4H, m, $2\text{OCH}_2\text{CH}_3$), 6.00 (1H, d, $^3J_{\text{PH}} = 17.1$ Hz, $\text{P}=\text{C}-\text{CH}$), 7.44–7.72 (15H, m, $3\text{C}_6\text{H}_5$), 9.60 (1H, s, N–H). ^{13}C NMR (125.8 MHz, CDCl_3): δ 13.9 and 14.1 ($2\text{OCH}_2\text{CH}_3$), 16.5 (s, CH_3), 40.0 (d, $^1J_{\text{PC}} = 130.4$ Hz, $\text{P}=\text{C}$), 57.9 and 61.5 ($2\text{OCH}_2\text{CH}_3$), 69.0 (d, $^2J_{\text{PC}} = 15.3$ Hz, $\text{P}=\text{C}-\text{CH}$), 126.7 (d, $^1J_{\text{PC}} = 91.5$ Hz, C_{ipso}), 128.7 (d, $^3J_{\text{PC}} = 11.8$ Hz, C_{meta}), 132.2 (C_{para}), 133.7 (d, $^2J_{\text{PC}} = 9.4$ Hz, C_{ortho}), 147.0, 152.6 ($\text{C}_4\text{H}_5\text{N}_3\text{OS}$), 169.4 (d, $^2J_{\text{PC}} = 11.5$ Hz, $\text{P}-\text{C}=\text{C}$), 172.5 (d, $^3J_{\text{PC}} = 12.2$ Hz, $\text{C}=\text{O}$), 172.2 ($\text{C}_4\text{H}_5\text{N}_3\text{OS}$). ^{31}P NMR (202.45 MHz, CDCl_3): δ 23.99 ($\text{Ph}_3\text{P}^+-\text{C}$).

Minor isomer 4j-(E) (30%), ^1H NMR (500.1 MHz, CDCl_3): δ 1.16 and 1.29 (6H, $2\text{OCH}_2\text{CH}_3$), 2.30 (3H, s, CH_3), 3.77 and 4.16 (4H, m, $2\text{OCH}_2\text{CH}_3$), 6.12 (1H, d, $^3J_{\text{PH}} = 17.5$ Hz, $\text{P}=\text{C}-\text{CH}$), 7.44–7.72 (15H, m, $3\text{C}_6\text{H}_5$), 9.60 (1H, s, $\text{N}-\text{H}$). ^{13}C NMR (125.8 MHz, CDCl_3): δ : 14.9 and 15.2 ($2\text{OCH}_2\text{CH}_3$), 16.4 (s, CH_3), 41.3 (d, $^1J_{\text{PC}} = 138.5$ Hz, $\text{P}=\text{C}$), 58.5 and 61.4 ($2\text{OCH}_2\text{CH}_3$), 67.9 (d, $^2J_{\text{PC}} = 16.2$ Hz, $\text{P}=\text{C}-\text{CH}$), 126.0 (d, $^1J_{\text{PC}} = 91.7$ Hz, C_{ipso}), 128.9 (d, $^3J_{\text{PC}} = 11.1$ Hz, C_{meta}), 132.1 (C_{para}), 133.5 (d, $^2J_{\text{PC}} = 8.4$ Hz, C_{ortho}), 146.8, 152.9 ($\text{C}_4\text{H}_5\text{N}_3\text{OS}$), 169.4 (d, $^2J_{\text{PC}} = 12.0$ Hz, $\text{P}-\text{C}=\text{C}$), 171.0 (d, $^3J_{\text{PC}} = 17.7$ Hz, $\text{C}=\text{O}$), 173.2 ($\text{C}_4\text{H}_5\text{N}_3\text{OS}$). ^{31}P NMR (202.4 MHz, CDCl_3): δ 24.31 ($\text{Ph}_3\text{P}^+-\text{C}$).

Di-tert-butyl-2-(6-aza-2-thiothymine-1-yl)-3-(triphenylphosphoranylidene)-butanedioate (4k). Mp 162–163°C. yield 90%; IR (KBr) (ν_{max} , cm^{-1}): 3420 ($\text{N}-\text{H}$), 1750, 1702 and 1653 ($\text{C}=\text{O}$). MS, m/z (%): 631 (M^+ , 45), 262 (48), 183 (45), 57 (43). Anal. Calcd. For $\text{C}_{34}\text{H}_{38}\text{N}_3\text{O}_5\text{PS}$: C, 64.64; H, 6.06; N, 6.65%. Found: C, 64.60; H, 6.01; N, 6.68%.

Only isomer 4k-(Z) (90%): ^1H NMR (500.1 MHz, CDCl_3), δ 0.94 and 1.54 (18H, 2s, 2CMe_3), 2.39 (3H, s, CH_3), 5.62 (1H, d, $^3J_{\text{PH}} = 17.2$ Hz, $\text{P}=\text{C}-\text{CH}$), 7.45–7.72 (15H, m, $3\text{C}_6\text{H}_5$), 9.11 (1H, s, $\text{N}-\text{H}$). ^{13}C NMR (125.8 MHz, CDCl_3), δ 16.9 (CH_3), 28.0 and 28.2 (2CMe_3), 39.5 (d, $^1J_{\text{PC}} = 131.7$ Hz, $\text{P}=\text{C}$), 69.5 (d, $^2J_{\text{PC}} = 18.0$ Hz, $\text{P}=\text{C}-\text{CH}$), 77.3 and 81.2 (2OCMe_3), 127.3 (d, $^1J_{\text{PC}} = 91.3$ Hz, C_{ipso}), 128.7 (d, $^3J_{\text{PC}} = 12.0$ Hz, C_{meta}), 132.1 (C_{para}), 133.6 (d, $^2J_{\text{PC}} = 9.2$ Hz, C_{ortho}), 146.9, 152.4 and 172.0 ($\text{C}_4\text{H}_5\text{N}_3\text{OS}$), 168.1 (d, $^2J_{\text{PC}} = 13.4$ Hz, $\text{P}-\text{C}=\text{C}$), 168.1 (d, $^3J_{\text{PC}} = 13.8$ Hz, $\text{C}=\text{O}$). ^{31}P NMR (202.4 MHz, CDCl_3): δ 23.64 ($\text{Ph}_3\text{P}^+-\text{C}$).

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