SUPPORTING INFORMATION

Inhibition and mechanism of *Plasmodium falciparum* hypoxanthine-guanine-xanthine phosphoribosyltransferase

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Table S1: Molecular weight analysis of bands on crosslinked SDS PAGE of different activation conditions of *Pf*HGXPRT

Figure 1D				Figure 1E			
(MW ladder)	Band No.	Mol. Wt. (kDa)	Relative Front	**(MW ladder)**	Band No.	Mol. Wt. (kDa)	Relative Front
	1	250	0.056		1	250	0.14
	2	150	0.15		2	150	0.21
	3	100	0.27		3	100	0.30
	4	75	0.33		4	75	0.36
	5	50	0.50		5	50	0.54
	6	37	0.67		6	37	0.67
	7	25	0.88		7	25	0.84
	8	20	0.94		8	20	0.95
Lane 1	Band No.	Mol. Wt. (kDa)	Relative Front	**Lane 1**	Band No.	Mol. Wt. (kDa)	Relative Front
	1	200	0.036		1	27	0.80
	2	139	0.17				
	3	102	0.29				
	4	53	0.55				
	5	23	0.86				
Lane 2	Band No.	Mol. Wt. (kDa)	Relative Front	**Lane 2**	Band No.	Mol. Wt. (kDa)	Relative Front
	1	198	0.040		1	139	0.23
	2	138	0.18		2	103	0.34
	3	99	0.30		3	53	0.57
	4	52	0.55		4	24	0.84
	5	23	0.87				
Lane 3	Band No.	Mol. Wt. (kDa)	Relative Front	**Lane 3**	Band No.	Mol. Wt. (kDa)	Relative Front
	1	186	0.063		1	158	0.18
	2	140	0.17		2	100	0.34
	3	99	0.30		3	54	0.56
	4	51	0.56		4	23	0.8
	5	23	0.86				
Lane 4	Band No.	Mol. Wt. (kDa)	Relative Front	**Lane 4**	Band No.	Mol. Wt. (kDa)	Relative Front
	1	196	0.045		1	168	0.16
	2	151	0.14		2	97	0.35
	3	97	0.31		3	52	0.57
	4	52	0.55		4	23	0.85
	5	23	0.86				

Bands are numbered from the top to bottom on the gel.

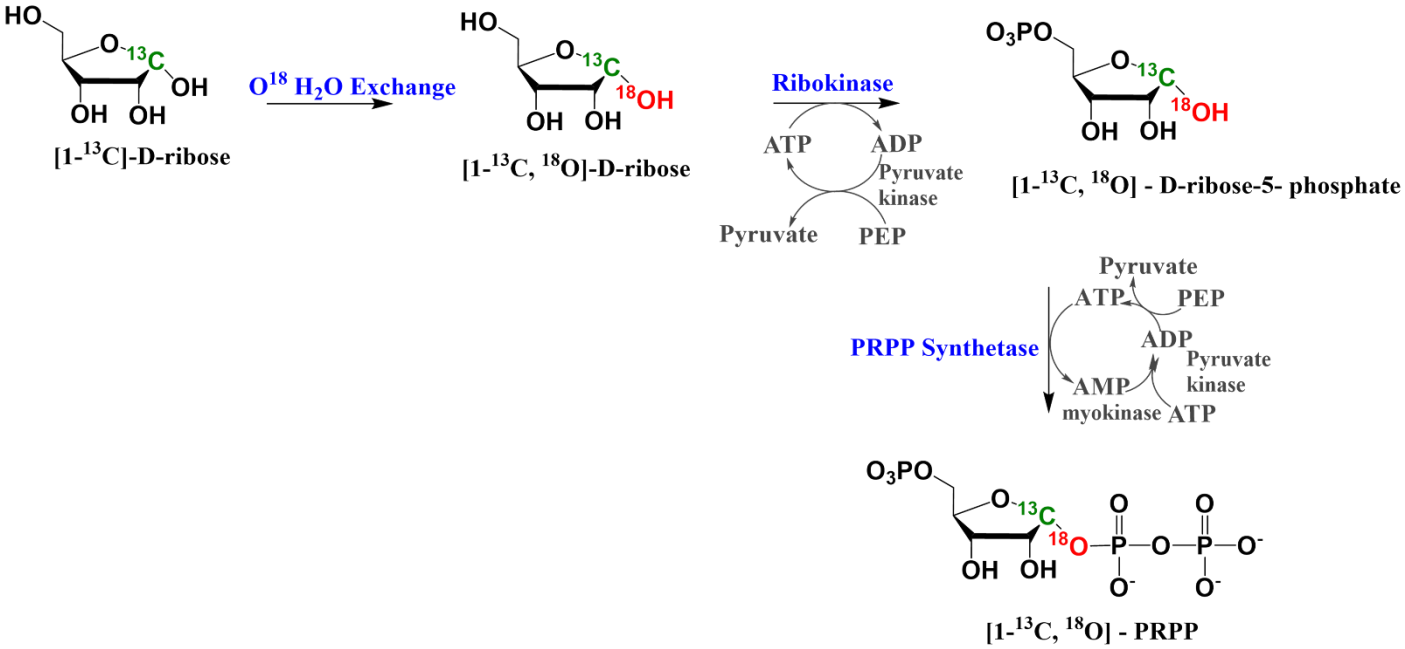


Figure S1: Enzymatic synthesis of [1-^{13}C,^{18}O]PRPP from [1-^{13}C]D-ribose. ^{18}O exchange was carried out at 61°C in 5 mM phosphate pH 7.0 overnight. [1-^{13}C,^{18}O]PRPP purity and concentration was determined by NMR.

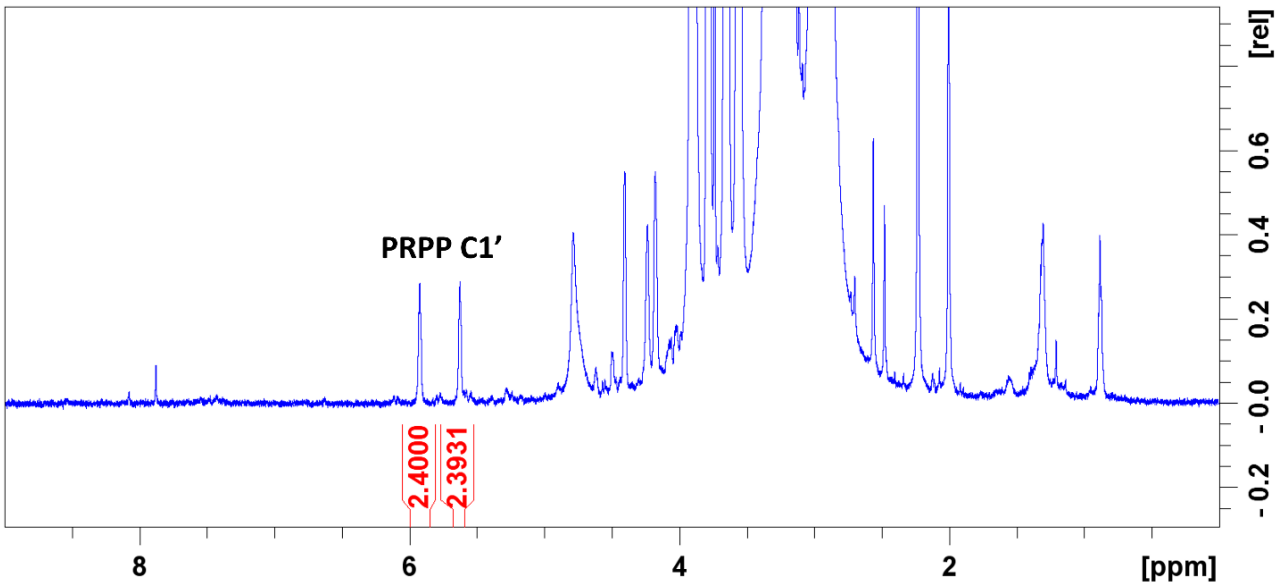


Figure S2: Quantitative ^{1}H-NMR of [1-^{13}C,^{18}O]PRPP. The doublet corresponding to the PRPP C1' proton was integrated and compared to a 15 mM benzoic acid standard to give a concentration of 4.8 mM.

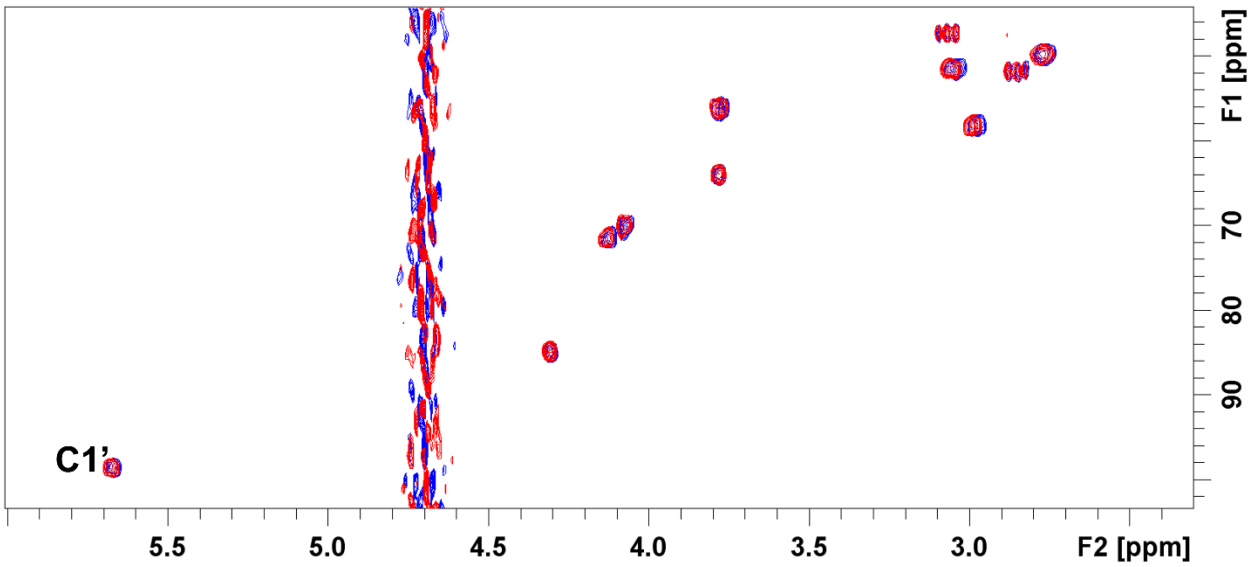


Figure S3: The presence of Mg^{2+} does not change the C1' peak and allows for continuous kinetic measurement of the PIX reaction using NMR**.**

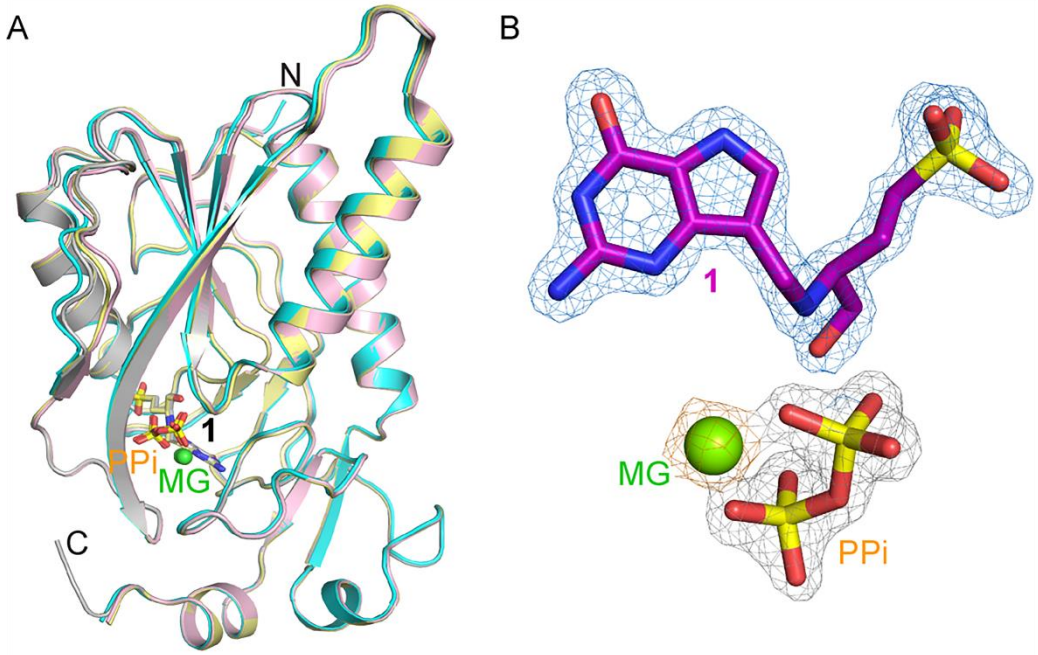


Figure S4: Subunit structure and omit maps at the active site. **A**, Superimposition of the four subunits of the *Pf*HGXPRT tetramer. Subunits are color coded as in Figure 6. **B,** Maps (σ= 4) corresponding to compound **1** (blue), pyrophosphate (grey), and magnesium (orange). Sticks (compound **1** and pyrophosphate) and sphere (magnesium) built into the maps.

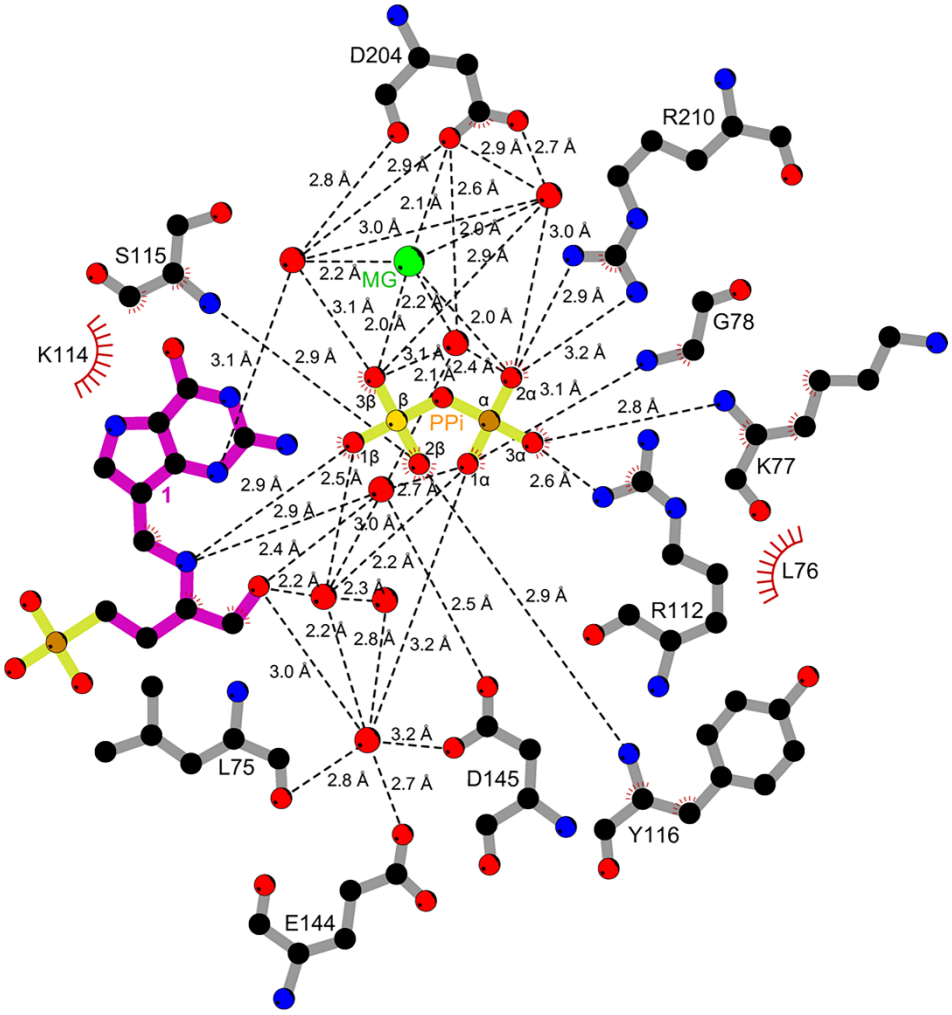
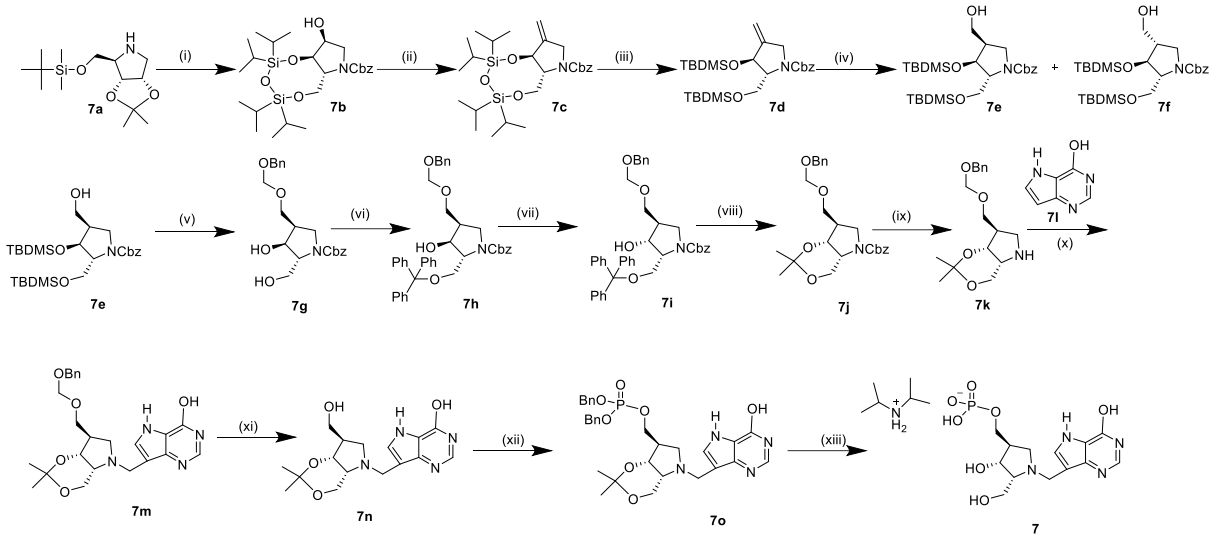


Figure S5. Interaction of pyrophosphate at the *Pf*HGXPRT active site. A 2-D ligand contact map depicts interactions of pyrophosphate and magnesium with the enzyme, compound **1** and waters (color coded as in Figure 5).

Organic synthesis - General Methods

Proton (^{1}H) and carbon (^{13}C{^{1}H}) NMR spectra were recorded on 500 MHz (^{1}H) spectrometers and their assignments were based 2D (^{1}H-^{1}H DQF-COSY, ^{1}H-^{13}C HSQC) and DEPT experiments where necessary. All chemical shifts (δ) are reported in parts per million (ppm) and referenced to residual protium or the carbon resonance of the NMR solvent, respectively. ^{31}P{^{1}H} NMR spectra were referenced to H_3PO_4 as an external standard. ^{1}H NMR data are recorded as follows: chemical shift (*δ*) [multiplicity, coupling constant(s) *J* (Hz), relative integral] where multiplicity is defined as b = broad; s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; or combinations of the above. Electrospray ionization (ESI, +ve or –ve) mass spectrometry (MS) experiments were performed on a Waters Q-TOF Premier™ Electrospray Mass Spectrometer under normal conditions. Sodium formate solution was used as calibrant for HRMS measurements. The analytical LCMS analysis was performed on an Agilent 1260 Infinity II Series LC System with an Agilent 6120B Single Quadrupole LC/MS (ESI), equipped with an Agilent 1100 Multi Wavelength Detector and an Agilent Infinity II 1290 Evaporative Light Scattering Detector using a C18 Kinetex column (50 × 3 mm, 2.6 µm) with a linear gradient system (solvent A: 0.1% (v/v) formic acid in water, solvent B: MeOH, 5% - 100% B over 6 min) at a flow rate of 1 mL min^{-1}. All reactions, unless otherwise stated, were conducted under an atmosphere of argon. Heating of reactions was performed using Radley Aluminium heating blocks. Anhydrous solvents were obtained commercially and used as received. All reactions were monitored by thin-layer chromatography (TLC) using 0.2 µm silica gel (60 F_{254}) pre-coated plates and visualised with a 254 nm ultraviolet lamp or stained with an appropriate dip followed by heating. Dips included cerium molybdate dip (400 mL 10% sulfuric acid/water, 20 g ammonium molybdate and 0.2 g cerium sulfate), potassium permanganate dip (100 mL water, 2 g Na_2CO_3, 1 g $KMnO_4$), dip of 0.1% ninhydrin in ethanol or Ehrich's solution. R_f, = retention factor. Flash column chromatography was performed on silica gel with a particle size of 0.040–0.063 mm or using a BÜCHI Pure system with continuous gradient facility using Flash Pure (50 µm) cartridges or SiliCycle® cartridges (25 µm). Petroleum Ether (PE) refers to the fraction boiling at 60–80 °C. Solvents for reactions and chromatography were analytical grade and were used as supplied unless otherwise stated.

Synthesis of compound 7:



Reagents and conditions: (i) (a) conc. aq hydrochloric acid, methanol, (b) triethylamine, benzyl chloroformate, 97%, (c) imidazole, 1,3-dichlorotetraisopropyldisiloxane, DMF, −20 °C, 90%; (ii) (a) DMSO, DCM, $(CF_3CO)_2O$, −70 °C, Et_3N to RT, (b) methyltriphenylphosphonium bromide, THF, 0 °C then *n*-BuLi, −70 °C, 66%; (iii) (a) TBAF, THF, RT, (b) imidazole, DMF, *tert*-butyldimethylsilyl chloride, RT, 91%; (iv)Borane methyl sulfide complex, THF, 0 °C to RT, 2M NaOH, H_2O_2, 57%; (v) (a) Diisopropylethylamine, benzyl chloromethyl ether, CH_3CN, RT, (b) TBAF, THF, 90%; (vi) py, TrCl, RT, 84%; (vii) (a) DCM, DMSO, trifluoroacetic anhydride, Et_3N, −70 °C, (b) 1M lithium tri-sec-butyl borohydride in THF, −70 °C , THF, H_2O, 2M NaOH, 30% H_2O_2, 94%; (viii) (a) AcOH, H_2O, (b) acetone, D,L-camphor-10-sulfonic acid, RT, 60%;(ix) KOH, IPA, 57%; (x) **7j**, HCHO, dioxane, water, 80 °C, 82%; (xi) Pd/C, H_2, EtOH, 7N NH_3/MeOH, 72%; (xii) Dibenzyl-*N,N*-diisopropylphosphoramidite, tetrazole, acetonitrile, *tert*-butyl hydroperoxide, 0 °C to RT, 31%; (xiii)(a) Pd/C, H_2, 7N ammonia in MeOH, (b) 4M HCl, MeOH, RT, 18% over 2 steps.

Compound 7b: Conc. aq hydrochloric acid (10 mL) was added to a solution of iminoribitol **7a**[1](4.18 g, 14.54 mmol) in methanol (30 mL) and the solution was, stirred for 1 h. The solution was evaporated and then ethanol was added and evaporated. Triethylamine (8.17 ml, 58.2 mmol) was added to this material in methanol (30 mL), and then benzyl chloroformate (3.11 mL, 21.81 mmol) was added and the solution was stirred at room temperature overnight. After evaporation the residue was purified by flash column chromatography (chloroform/ethyl acetate/methanol 5:2:1) to give Cbz protected iminoribitol (3.75 g, 97%). HRMS (ESI, +ve) $C_{13}H_{17}NNaO_5$ $(M + Na)^+$ calculated 290.1004; found 290.1003.
Imidazole (295 mg, 4.34 mmol) was added to a solution of this material (290 mg, 1.08 mmol) in dry dimethylformamide (8 mL) and then the solution was cooled to − 20 °C and 1,3-dichlorotetraisopropyldisiloxane (382 µl, 1.19 mmol) was added slowly. After 20 minutes more dichlorotetraisopropyldisiloxane was added, if necessary, until TLC showed complete consumption of starting material. The reaction was quenched with water, diluted with toluene,

and washed with water (x2), brine and dried over magnesium sulphate. The residue was purified by flash column chromatography (silica, ethyl acetate/hexane 1:3) to give compound **7b** as colourless syrup (497 mg, 90%).

Compound 7c: Dimethyl sulfoxide (2.25 mL, 31.8 mmol) was added into a solution of compound **7b** (5.4 g, 10.59 mmol) in dry dichloromethane (80 mL), and the solution was cooled to − 70 °C. Trifluoroacetic anhydride (3.68 mL, 26.5 mmol) was added and the solution was stirred in cold bath for ~ 20-30 minutes, then triethylamine (10.42 mL, 74.1 mmol) was added and the mixture was allowed to warm to room temperature. The reaction mixture was diluted with dichloromethane and washed with 1M hydrochloric acid, saturated sodium bicarbonate, brine and dried over magnesium sulphate, filtered, and concentrated. The crude product was co-evaporated with toluene and used in the next step without further purification. A suspension of dried methyltriphenylphosphonium bromide (8.32 g, 23.30 mmol) in dry tetrahydrofuran (120 mL) was cooled to 0 °C under argon. Butyllithium 2.2 M in hexanes (9.63 mL, 21.19 mmol) was added. The mixture was stirred for 10 minutes and then cooled to − 70 °C. A solution of the above material in dry tetrahydrofuran (20 mL) was added. A white precipitate formed. After 5 minutes, the reaction mixture was allowed to warm to room temperature and then diluted with ethyl acetate and washed water, brine and dried over magnesium sulphate, filtered, and concentrated. The residue was purified by flash column chromatography (silica, ethyl acetate/hexane 1:10) to give compound **7c** (3.56 g, 66%) as a syrup. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.59 – 7.29 (m, 5H), 5.43 – 5.19 (m, 1H), 5.20 – 5.07 (m, 3H), 4.89 – 4.79 (m, 1H), 4.40 – 4.16 (m, 2H), 4.14 – 3.88 (m, 2H), 3.85 – 3.66 (m, 1H), 1.37 – 0.52 (m, 24H); ^{13}C NMR (126 MHz, Chloroform-d) δ 155.1, 145.4, 136.4, 128.5, 128.3, 128.0, 108.5, 107.4, 75.2, 73.9, 66.9, 66.2, 63.7, 62.1, 58.3, 49.9, 29.7, 18.5, 17.4, 17.3, 17.2, 17.2, 17.2, 17.1, 17.0, 16.9, 13.6, 13.4, 13.2, 13.2, 13.0, 12.8, 12.7, 12.5; HRMS (ESI, +ve) $C_{26}H_{43}NNaO_5Si_2$ $(M + Na)^+$ calculated 528.2578; found 528.2582.

Compound 7d: Tetrabutylammonium fluoride in tetrahydrofuran (31.4 mL, 31.4 mmol, 1M) was added to a solution of compound **7c** (3.18 g, 6.29 mmol) in tetrahydrofuran (30 mL) and the solution was stirred at room temperature for 30 minutes. The solvent was evaporated, and the residue was purified by flash column chromatography (silica, ethyl acetate) to give a syrup. Imidazole (2.57 g, 37.7 mmol) was added to this material in dry dimethylformamide (15 mL), and then *tert*-butyldimethylsilyl chloride (3.79 g, 25.1 mmol) was added and the solution was stirred at room temperature for 2 h. The reaction mixture was quenched with water, then was added, and washed with water (x2), brine and dried over magnesium sulphate, filtered, and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:10) to give compound **7d** (2.8 g, 91%) as colourless syrup. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.45 – 7.27 (m, 5H), 5.26 – 5.00 (m, 4H), 4.53 (d, J = 24.7 Hz, 1H), 4.39 – 4.18 (m, 1H), 3.90 – 3.79 (m, 2H), 3.76 (dd, J = 10.2, 3.5 Hz, 0.5H), 3.65 (dd, J = 10.1, 3.8 Hz, 0.5H), 3.47 (dd, J = 10.2, 7.8 Hz, 0.5H), 3.25 (t, J = 9.5 Hz, 0.5H), 1.16 – 0.67 (m, 18H), 0.27 – -0.33 (m, 12H);

^{13}C NMR (126 MHz, Chloroform-d) δ 155.0, 154.8, 147.1, 146.3, 136.9, 136.8, 128.4, 127.9, 127.9, 127.7, 110.7, 109.9, 75.8, 74.9, 67.7, 67.6, 66.8, 66.7, 61.9, 61.0, 49.7, 25.8, 25.8, 18.2, 18.0, -4.4, -4.5, -4.6, -4.7, -5.5, -5.5, -5.6; HRMS (ESI, +ve) $C_{26}H_{45}NNaO_4Si_2$ $(M + Na)^+$ calculated 514.2785; found 514.2782.

Compound 7e: Borane methyl sulfide complex (0.94 mL, 9.84 mmol) was added to a solution of compound **7d** (2.20 g, 4.47 mmol) in tetrahydrofuran (35 mL) at 0 °C. The reaction mixture was then allowed to warm to room temperature. Then after 1 h, TLC showed complete consumption of starting material. The reaction mixture was re-cooled in an ice bath and water (7 mL) was added carefully followed by 2M aq sodium hydroxide (13.42 ml, 26.8 mmol) and hydrogen peroxide (8.22 ml, 81 mmol, 30%). The reaction mixture was warmed to 45 ºC and stirred for 5 h and then was diluted with ethyl acetate and washed with water, brine and dried over magnesium sulphate, filtered, and concentrated. The stereoisomers **7e** and **7f** (2.7:1) were separated by flash column chromatography (silica, ethyl acetate/hexane 1:4) to give desired stereoisomer **7e** (1.31 g, 57%). Compound **7e:** ^{1}H NMR (500 MHz, Chloroform-d) δ 7.45 – 7.28 (m, 5H), 5.24 – 5.03 (m, 2H), 4.51 – 4.36 (m, 1H), 3.92 – 3.65 (m, 4H), 3.59 – 3.43 (m, 2.5H), 3.41 – 3.23 (m, 0.5H), 2.51 – 2.37 (m, 1H), 2.25 – 1.97 (m, 1H), 1.77 (s, 1H); ^{13}C NMR (126 MHz, Chloroform-d) δ 155.1, 136.9, 136.7, 128.4, 128.4, 127.9, 127.9, 127.8, 127.6, 75.2, 75.2, 68.5, 68.1, 66.8, 66.6, 62.5, 61.7, 60.6, 60.4, 47.1, 46.8, 43.7, 42.9, 25.9, 25.9, 25.7, 25.7, 18.2, 17.9, -4.5, -4.6, -4.6, -5.0, -5.5, -5.6, -5.6, -5.6; HRMS (ESI, +ve) $C_{26}H_{48}NO_5Si_2$ $(M + H)^+$ calculated 510.3071; found 510.3070. Compound **7f**: ^{1}H NMR (500 MHz, Chloroform-d) δ 7.44 – 7.27 (m, 5H), 5.21 – 5.05 (m, 2H), 4.47 – 4.30 (m, 1H), 4.20 – 4.02 (m, 1H), 3.98 – 3.84 (m, 1H), 3.84 – 3.54 (m, 4H), 3.23 – 3.09 (m, 1H), 2.37 – 2.16 (m, 1H), 1.54 (s, 1H), 0.87 (d, *J* = 6.6 Hz, 18H), 0.17 – -0.34 (m, 12H); ^{13}C NMR (126 MHz, Chloroform-d) δ 154.5, 136.9, 128.4, 127.9, 74.9, 74.0, 67.4, 66.9, 66.6, 62.6, 61.6, 60.3, 48.7, 29.7, 25.9, 25.7, 18.2, 17.9, -4.4, -4.6, -5.5.

Compound 7g: Diisopropylethylamine (259 µl, 1.57mmol) and benzyl chloromethyl ether (60%) (182 µl, 785 µmol) were added to a solution of compound **7e** (80 mg, 157 µmol) in dry acetonitrile (3 mL) and the solution was stirred at room temperature for 2 h before being diluted with chloroform and washed with 1M hydrochloric acid, saturated sodium bicarbonate and brine. The organic layer was dried over magnesium sulphate, filtered, and concentrated. The crude material was dissolved in tetrahydrofuran (2 mL) and tetrabutylammonium fluoride 1.0 M in tetrahydrofuran (500 µl, 627 µmol) was added and the solution was stirred at room temperature until TLC showed complete conversion to product. The solution was evaporated, and the residue was purified by flash column chromatography (silica, ethyl acetate/hexane 3:1) to give compound **7g** (57 mg, 90%). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.44 – 7.27 (m, 10H), 5.20 – 5.05 (m, 2H), 4.75 (s, 2H), 4.59 (s, 2H), 4.31 – 4.15 (m, 1H), 4.04 – 3.88 (m, 1H), 3.88 – 3.78 (m, 1H), 3.78 – 3.60 (m, 3H), 3.60 – 3.52 (m, 1H), 3.48 – 3.32 (m, 1H), 3.11 – 2.99 (m, 1H), 2.69 – 2.42 (m, 1H), 1.90 (s, 1H); ^{13}C NMR (126 MHz, Chloroform-d) δ 156.6, 137.5,

136.3, 128.5, 128.5, 128.1, 127.9, 127.8, 95.0, 73.2, 69.9, 68.9, 67.3, 65.4, 63.8, 47.4, 41.8.

Compound 7h: Compound **7g** (0.627 g, 1.56 mmol) was dissolved in dry pyridine (10 mL), trityl chloride (0.653 g, 2.34 mmol) was added and the solution was stirred at room temperature for 36 h, TLC showed still plenty of starting material (at least 50%). More trityl chloride (0.653 g, 2.34 mmol) was added and continued stirring at room temperature for 2 days. Then TLC showed complete consumption of starting material. The reaction mixture was diluted with chloroform (30 mL), washed with water, 1M hydrochloric acid, saturated sodium bicarbonate and brine. The residue was purified by flash column chromatography (silica, ethyl acetate/hexane 1:2) to give compound **7h** (0.848 g, 84%) as colourless foam.

Compound 7i: Dimethylsulfoxide (0.549 mL, 7.74 mmol) was added to a solution of compound **7h** (0.83 g, 1.29 mmol) in dry dichloromethane (25 mL), then the solution was cooled to - 70 ºC and trifluoroacetic anhydride (0.538 mL, 3.87 mmol) was added. The reaction mixture was stirred for 30 minutes, then triethylamine (1.45 mL, 10.31 mmol) was added, and the reaction mixture was allowed to warm to room temperature, diluted with dichloromethane and washed with dilute hydrochloric acid, aqueous sodium bicarbonate and brine. The organic layer was dried over magnesium sulphate, filtered, and concentrated. Crude syrupy product in dry tetrahydrofuran (20 mL) was cooled to - 70 ºC under argon and lithium tri-sec-butylborohydride 1 M in tetrahydrofuran (2.58 mL, 2.58 mmol) was added slowly, then the solution was stirred in the cold bath for 20 minutes and then allowed to warm to ~ 0 ºC and quenched with water (1 mL). 2M aq sodium hydroxide (3.87 mL, 7.74 mmol) was added followed by 30% hydrogen peroxide (2.37 mL, 23.21 mmol) (exothermic). Then the solution was stirred at room temperature for 30 minutes. The reaction mixture was then diluted with chloroform and washed with water and brine. The organic layer was dried over magnesium sulphate, filtered, and evaporated. The residue was purified by flash chromatography (ethyl acetate/hexane 1:2) to give compound **7i** (780 mg, 94%) as colourless foam. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.53 – 7.08 (m, 25H), 5.25 – 4.87 (m, 2H), 4.77 (s, 2H), 4.60 (s, 2H), 4.35 – 4.19 (m, 1H), 4.18 – 3.96 (m, 1H), 3.87 – 3.54 (m, 3H), 3.49 – 3.24 (m, 3H), 2.89 – 2.76 (m, 1H), 2.74 – 2.54 (m, 1H); ^{13}C NMR (126 MHz, Chloroform-d) δ 154.8, 143.4, 137.7, 136.7, 136.4, 128.8, 128.4, 128.4, 128.1, 128.0, 127.9, 127.7, 127.6, 127.3, 94.8, 87.7, 87.7, 74.1, 73.3, 69.6, 69.5, 67.6, 67.0, 66.8, 62.3, 61.9, 59.2, 58.7, 47.3, 47.2, 45.8, 44.7. HRMS (ESI, +ve) $C_{41}H_{41}NNaO_6$ $(M + Na)^+$ calculated 666.2832; found 666.2825.

Compound 7j: Compound **7i** (92 mg, 143 µmol) was dissolved in acetic acid (4 mL), water (1 mL) was added, and the solution was stirred at room temperature for 3 h. The reaction mixture was diluted with chloroform and washed with water, saturated sodium bicarbonate and brine. The organic layer was dried over magnesium sulphate, filtered, and concentrated. The crude productwas dissolved in acetone (3 mL), D,L-camphor-10-sulfonic acid (9.96 mg, 42.9 µmol) was added and the solution was stirred at room temperature for 1 h before being diluted with

chloroform and washed with saturated sodium bicarbonate and brine. The organic layer was dried over magnesium sulphate, filtered, and concentrated. The residue was purified by flash column chromatography (silica, ethyl acetate/hexane 1:4, then 1:2) to give compound **7j** (38 mg, 60%) as a syrup. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.41 – 7.28 (m, 10H), 5.20 – 5.01 (m, 2H), 4.71 (d, *J* = 4.9 Hz, 2H), 4.56 (d, *J* = 9.7 Hz, 2H), 4.38 – 4.22 (m, 1H), 4.21 – 3.95 (m, 1H), 3.91 – 3.76 (m, 1H), 3.77 – 3.63 (m, 2H), 3.56 (d, *J* = 10.3 Hz, 1H), 3.53 – 3.34 (m, 2H), 2.51 – 2.30 (m, 1H), 1.57 – 1.16 (m, 6H); ^{13}C NMR (126 MHz, Chloroform-d) δ 155.3, 154.9, 137.7, 137.6, 136.7, 136.5, 128.5, 128.4, 128.0, 127.9, 127.8, 98.8, 98.3, 94.7, 73.2, 72.2, 69.6, 67.3, 67.1, 66.9, 60.9, 60.0, 55.9, 55.6, 48.4, 48.1, 44.1, 43.5, 26.8, 25.7, 22.1, 21.2. HRMS (ESI, +ve) $C_{25}H_{31}NNaO_6$ $(M + Na)^+$ calculated 464.2049; found 464.2040.
Compound 7k: Compound **7j** (0.10 g, 0.23 mmol) was dissolved in potassium hydroxide in isopropanol (3.40 mL, 6.79 mmol, 2M) and heated under reflux for 1.5 h. Then it was pre-absorbed on silica gel and purified by flash column chromatography (silica, 5% 7M ammonia in methanol in dichloromethane) to give compound **7k** (40 mg, 57%) as syrup. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.47 – 7.19 (m, 5H), 4.85 – 4.71 (m, 2H), 4.63 – 4.51 (m, 2H), 4.28 – 4.02 (m, 2H), 3.84 (dd, *J* = 12.5, 2.3 Hz, 1H), 3.56 – 3.42 (m, 2H), 3.36 (dd, *J* = 12.0, 8.3 Hz, 1H), 2.71 (q, *J* = 3.1 Hz, 1H), 2.56 (dd, *J* = 12.0, 5.3 Hz, 1H), 2.45 – 2.25 (m, 1H), 1.43 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-d) δ 137.8, 128.4, 127.7, 127.7, 127.4, 126.8, 97.9, 94.9, 74.8, 69.6, 68.4, 64.9, 60.1, 55.9, 48.6, 47.7, 28.9, 19.2.

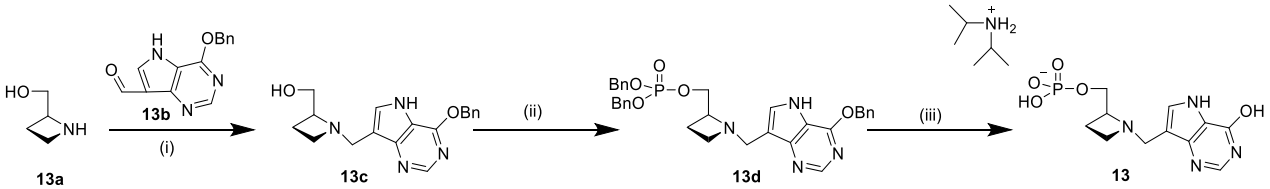
Compound 7m: 9-Deazahypoxanthine **7l** (0.101 g, 0.75 mmol) and formaldehyde solution 37% (0.087 mL, 1.12 mmol) were added to a solution of compound **7i** (0.115 g, 0.37 mmol) in dioxane (2 mL), and then water (0.5 mL) was added, and the mixture was heated at 80 °C over a weekend. After evaporation the residue was purified by flash column chromatography (7% 7N ammonia in methanol in dichloromethane) to give compound **7m** (140 mg, 82%) as a colourless foam. ^{1}H NMR (500 MHz, Chloroform-d) δ 11.53 (s, 1H), 7.88 (s, 1H), 7.36 – 7.27 (m, 5H), 7.22 (s, 1H), 5.70 – 5.48 (m, 2H), 4.59 – 4.45 (m, 2H), 4.15 – 4.05 (m, 1H), 4.01 – 3.80 (m, 3H), 3.75 – 3.68 (m, 1H), 3.64 – 3.50 (m, 2H), 3.48 – 3.32 (m, 1H), 2.63 – 2.42 (m, 2H), 2.28 – 2.11 (m, 1H), 1.45 – 1.29 (m, 6H); ^{13}C NMR (126 MHz, Chloroform-d) δ 141.5, 137.8, 130.4, 128.4, 127.8, 127.7, 117.1, 112.5, 99.0, 94.7, 74.7, 73.7, 72.5, 69.4, 68.2, 61.7, 60.8, 55.2, 45.9, 44.3, 29.6, 26.7, 21.6, 21.4.

Compound 7n: A solution of compound **7m** (0.78 g, 1.716 mmol) in ethanol (10 mL) and 7N ammonia in methanol (10 mL) was stirred with 10% palladium on carbon under hydrogen atmosphere overnight. The mixture was filtered and evaporated. The residue was purified by flash chromatography (20% 7N ammonia in methanol in dichloromethane) to give compound **7n** (0.415 mg, 72%) as white solid. ^{1}H NMR (500 MHz, Methanol-d4) δ 7.93 (s, 1H), 7.45 (s, 1H), 4.25 – 4.05 (m, 1H), 3.97 – 3.80 (m, 3H), 3.74 – 3.65 (m, 1H), 3.48 – 3.35 (m, 2H), 3.22 – 3.07 (m, 1H), 2.61 – 2.32 (m, 1H), 2.26 – 2.08 (m, 2H), 1.37 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (126 MHz, Methanol-d4) δ 156.0, 145.1, 143.0, 130.8, 118.1, 111.9, 100.4, 74.5, 62.6, 61.1,

60.2, 54.9, 46.7, 45.4, 27.4, 21.1.

Compound 7o: Compound **7n** (50 mg, 0.15 mmol) was dissolved in tetrahydrofuran (20 mL) and heated at 60 °C for 1 h. It was then cooled to room temperature. Dibenzyl *N,N*-diisopropylphosphoramidite (84 µL, 1.5 equiv., 0.22 mmol) and tetrazole in acetonitrile (1 mL, 3 equiv., 0.45 mmol, 0.45 mol/L) were added drop-wise. The reaction mixture was stirred overnight at room temperature. A milky solution was formed. *tert*-Butyl hydroperoxide in water (23 µL, 1.1 equiv., 0.16 mmol, 70 mass%) was added and the mixture was stirred for 1 h and then was evaporated and the residue was dissolved in methanol. This was pre-absorbed on silica and automated chromatography (0-20 % methanol/dichloromethane) afforded **7o** as syrup (22 mg with minor impurities). ^{1}H NMR (500 MHz, Methanol-d4) δ 7.88 (s, 1H), 7.56 (s, 1H), 7.48 – 7.19 (m, 10H), 5.07 – 4.90 (m, 4H), 4.35 (s, 2H), 4.28 (dd, *J* = 3.9, 1.6 Hz, 1H), 4.23 – 3.99 (m, 2H), 3.93 – 3.72 (m, 2H), 3.61 (dd, *J* = 11.8, 8.7 Hz, 1H), 3.09 – 2.95 (m, 2H), 2.50 – 2.37 (m, 1H), 1.39 (s, 3H), 1.35 (s, 3H); ^{31}P NMR (202 MHz, Methanol-d4) δ -1.38. This material **7o** (22 mg, 0.04 mmol) was dissolved in ammonia in methanol (10 mL, 70 mmol, 7.0 mol/L). Palladium on carbon (20 mg) was added and the mixture was stirred under a hydrogen atmosphere overnight. It was then filtered through celite and evaporated. The residue was dissolved in methanol and hydrochloric acid (1 mL, 4 mmol, 4 mol/L) was added slowly and the solution was stirred at room temperature for 3 h. Water was added, and the solution was evaporated (x3). Diisopropylamine was added and evaporated (0.2 mL x 2). The residue was triturated with methanol (2 x 2 mL). Then the non-soluble material was purified by C18 reverse phase column chromatography (water) to afford Compound **7** (13 mg, 18% over 2 steps as diisopropylamine salt ~0.7 equiv.) as a white solid. 1H NMR (500 MHz, Deuterium Oxide) δ 8.15 (s, 1H), 7.85 (s, 1H), 4.91-4.72 (m, 1H under D_2O peak), 4.66 – 4.47 (m, 2H), 4.20 – 4.07 (m, 2H), 4.02 – 3.89 (m, 2H), 3.88 – 3.73 (m, 2H), 3.65 – 3.48 (m, 1.5H), 3.41 – 3.16 (m, 1H), 2.68 – 2.46 (m, 1H), 1.38 – 1.34 (m, 9.5H); 31P NMR (202 MHz, Deuterium Oxide) δ 3.66. ^{13}C NMR (126 MHz, Deuterium Oxide) δ 155.2, 144.1, 143.2, 132.0, 117.9, 104.6, 72.0, 68.8, 63.1 (d, *J* = 5.1 Hz), 56.7, 52.7, 47.3, 47.0, 45.4 (d, *J* = 8.0 Hz), 18.3. HRMS (ESI, +ve) $C_{13}H_{20}N_4O_7P$ $(M+H)^+$ calculated 375.1070; found 375.1062; (ESI, −ve) $C_{13}H_{18}N_4O_7P$ $(M-H)^-$ calculated 373.0913; found 373.0926.

Synthesis of compound 13:

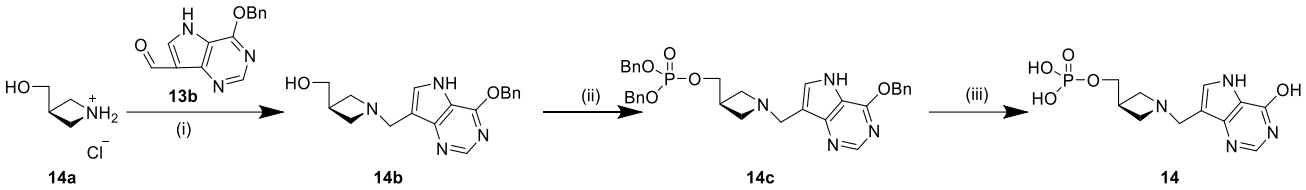


Reagents and conditions: (i) **13b**, Borane-2-picoline complex, MeOH, 60 °C 40%; (ii) Dibenzyl-*N,N*-diisopropylphosphoramidite, tetrazole, acetonitrile, *tert*-butyl hydroperoxide, 0 °C to RT; (iii) Pd/C, H_2, 23% over 2 steps.

Compound 13c: Aldehyde **13b**[2] (200 mg, 0.79 mmol) was dissolved in methanol (10 mL) and 4 mL chloroform. Azetidin-2-ylmethanol **13a**[3] (62 mg, 0.9 equiv., 0.71 mmol) was added and that solution was stirred for 30 minutes at 60 °C. Then borane-2-picoline complex (178 mg, 2 equiv., 1.58 mmol) was added and the solution was stirred at room temperature overnight (pH 6) and then concentrated in vacuo and the residue was purified by automated chromatography (silica, methanol/dichloromethane 0-30 %) to afford **13c** (102 mg, 40 %) as colourless oil. ^{1}H NMR (500 MHz, Methanol-d4) δ 8.44 (s, 1H), 7.70 – 7.46 (m, 3H), 7.49 – 7.08 (m, 3H), 5.63 (s, 2H), 4.04 (d, *J* = 13.3 Hz, 1H), 3.77 (d, *J* = 13.3 Hz, 1H), 3.53 – 3.41 (m, 3H), 3.26 – 3.16 (m, 1H), 3.12 – 3.00 (m, 1H), 2.03 – 1.82 (m, 2H).; ^{13}C NMR (126 MHz, Methanol-d4) δ 157.1, 150.2, 149.9, 137.9, 131.2, 129.5, 129.4, 129.3, 116.6, 112.4, 69.1, 67.9, 66.0, 51.4, 20.9; HRMS (ESI, +ve) $C_{18}H_{21}N_4O_2$ $(M + H)^+$ calculated 325.1665; found 325.1665.

Compound 13: Compound **13c** (102 mg, 0.31 mmol) was dissolved in acetonitrile (5 mL, 95 mmol). Dibenzyl *N,N*-diisopropylphosphoramidite (0.18 mL, 1.5 equiv., 0.47 mmol) and then tetrazole in acetonitrile (2.1 mL, 3 equiv., 0.94 mmol, 0.45 mol/L) were added drop-wise. The reaction mixture was stirred at room temperature for 2 h. Then the reaction mixture was cooled to 0 °C and tert-butyl hydroperoxide in water (48 µL, 1.1 equiv., 0.35 mmol, 70 %) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for another 2 h. The reaction was quenched with aqueous sodium bicarbonate and then was diluted with ethyl acetate (40 mL) and washed with water. The organic layer was dried over magnesium sulphate, filtered, and concentrated. The residue was purified by automated column chromatography (silica, methanol/dichloromethane 0-25 %) to afford compound **13d** as a syrup. HRMS (ESI, +ve) $C_{32}H_{34}N_4O_5P$ $(M + H)^+$ calculated 585.2267; found 585.2264. The partially purified **13d** (144 mg, 0.25 mmol) was dissolved in methanol (10 mL). Palladium on carbon (36 mg, 25 mass%) was added and the mixture was stirred at under hydrogen overnight. The mixture was filtered through celite and concentrated, and the residue was purified by reverse phase flash column chromatography (C18, 100 % water then 5% methanol) to afford compound **13** as a diisopropylamine salt (~0. equiv.) (30 mg, 23% over 2 steps). 1H NMR (500 MHz, Deuterium Oxide) δ 8.14 (s, 1H), 7.81 (s, 1H), 4.74 (m, 1H, under D_2O peak), 4.57 (d, *J* = 14.0 Hz, 2H), 4.14 – 3.82 (m, 4H), 3.56 (p, *J* = 6.5 Hz, 1H), 2.73 – 2.55 (m, 1H), 2.53 – 2.41 (m, 1H), 1.36 (d, *J* = 6.6 Hz, 5H).; 13C NMR (126 MHz, Deuterium Oxide) δ 155.2, 144.0, 143.1, 131.3, 117.9, 104.8, 67.3, 62.5, 50.0, 47.3, 46.7, 18.3, 17.4; 31P NMR (202 MHz, Deuterium Oxide) δ 1.89; HRMS (ESI, +ve) $C_{11}H_{16}N_4O_5P$ $(M + H)^+$ calculated 315.0858; found 315.0861; (ESI, −ve) $C_{11}H_{14}N_4O_5P$ $(M - H)^-$ calculated 313.0702; found 313.0706.

Synthesis of compound 14:

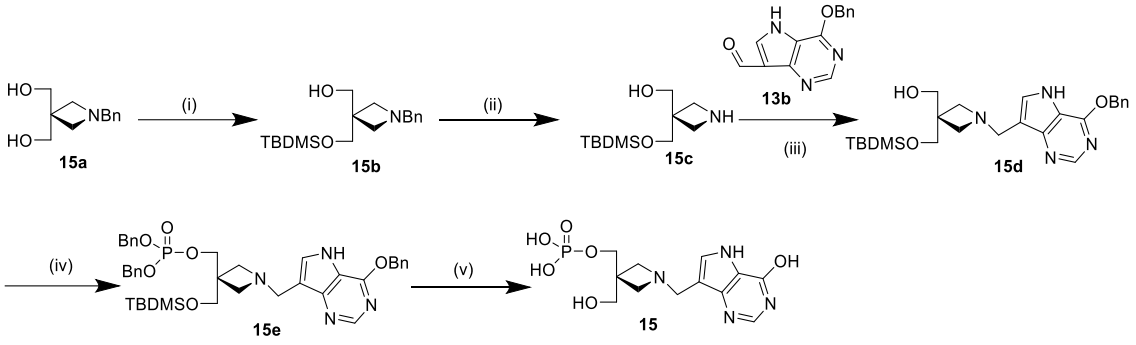


Reagents and conditions: (i) **13b**, Borane-2-picoline complex, MeOH, $CHCl_3$, 60 °C 63%; (ii) Dibenzyl-*N,N*-diisopropylphosphoramidite, tetrazole, acetonitrile, *tert*-butyl hydroperoxide, 0 °C to RT; (iii) Pd/C, H_2, 12% over 2 steps.

Compound 14b: Aldehyde **13b**[2](100 mg, 0.39 mmol) was dissolved in methanol and chloroform (35 mL, 5:2), azetidin-3-ylmethanol **14a**[3] (31 mg, 0.9 equiv., 0.36 mmol) and borane-2-picoline complex (89 mg, 4 equiv., 0.79 mmol) were added (pH 6) and stirred the reaction mixture at 60 °C for 1 h then at room temperature overnight. The reaction mixture was concentrated in vacuo and the residue was purified by flash column chromatography (silica, 7-15% methanol/dichloromethane) to afford compound **14b** (81 mg, 63 %) as colourless oil. 1H NMR (500 MHz, Methanol-d4) δ 8.53 (s, 1H), 7.81 (s, 1H), 7.65 – 7.47 (m, 2H), 7.47 – 7.29 (m, 3H), 5.66 (s, 2H), 4.53 (s, 2H), 4.27 – 4.15 (m, 2H), 4.15 – 4.00 (m, 2H), 3.63 (d, *J* = 4.4 Hz, 2H), 3.01 – 2.90 (m, 1H); 13C NMR (126 MHz, Methanol-d4) δ 157.4, 151.4, 149.8, 137.7, 133.3, 129.6, 129.5, 129.4, 117.0, 105.5, 69.3, 61.2, 56.1, 49.1, 32.2; HRMS (ESI, +ve) $C_{18}H_{21}N_4O_2$ $(M + H)^+$ calculated 325.1665, found 325.1672.

Compound 14: Compound **14b** (88 mg, 0.27 mmol) was dissolved in acetonitrile (5 mL, 95 mmol). Dibenzyl *N,N*-diisopropylphosphoramidite (0.21 mL, 1.5 equiv., 0.41 mmol) and then tetrazole in acetonitrile (2.5 ml, 3 equiv., 0.81 mmol, 0.45 mol/L) were added drop-wise. The reaction mixture was stirred at room temperature for 2 h. Then the reaction mixture was cooled to 0 °C and *tert*-butyl hydroperoxide (57 µL, 1.1 equiv., 0.41 mmol) was added slowly. The solution was warmed to room temperature and stirred for another 2 h. The reaction was quenched with aqueous sodium bicarbonate, and then evaporated. The residue was dissolved in ethyl acetate and washed with water and brine. The organic layer was dried, filtered, and concentrated. Purification by flash column chromatography (silica, 5-15% methanol/dichloromethane) afforded slightly impure compound **14c**. This material (90 mg, 0.15 mmol) was dissolved in methanol (5 mL). Palladium on carbon (22 mg, 25%) was added and the reaction mixture was stirred under hydrogen for 24 h. The reaction mixture was filtered through celite and concentrated *in vacuo*. Purification by reverse phase column chromatography (C18, 100% water) afforded compound **14** (11.6 mg, 12% over 2 steps) as white solid. 1H NMR (500 MHz, Deuterium Oxide) δ 8.14 (s, 1H), 7.72 (s, 1H), 4.40 (s, 2H), 4.28 – 4.10 (m, 2H), 4.10 – 3.99 (m, 2H), 3.99 – 3.81 (m, 2H), 3.11 – 2.88 (m, 1H); 13C NMR (126 MHz, Deuterium Oxide) δ 157.7, 145.5, 144.2, 130.2, 118.1, 105.6, 62.9, 55.0, 48.1, 29.8 (d, $^2J_{cp}$ = 8.3 Hz). 31P NMR (202 MHz, Deuterium Oxide) δ 4.10. HRMS (ESI, +ve) $C_{11}H_{16}N_4O_5P$ $(M + H)^+$ calculated 315.0858; found 315.0856; HRMS (ESI, −ve) $C_{11}H_{14}N_4O_5P$ $(M - H)^-$ calculated 313.0702; found 313.0702.

Synthesis of compound 15:



Reagents and conditions: (i) NaH, TBDMSCl, THF, 0 °C to RT, 40%; (ii) Pd/C, H_2, MeOH, quant. (iii) **13b**, Borane-2-picoline complex, MeOH, $CHCl_3$, 50 °C to RT 24%; (ii) Dibenzyl-*N,N*-diisopropylphosphoramidite, tetrazole, acetonitrile, *tert*-butyl hydroperoxide, 0 °C to RT, 39%; (iii) 6M HCl, MeOH, 100 °C, 86%.

Compound 15b: Compound **15a**[3](1.1 g, 5.3 mmol) was dissolved in tetrahydrofuran (10 mL). Sodium hydride (210 mg, 1 equiv., 5.3 mmol, 60 %) was added at 0 °C. The mixture was stirred for 30 minutes then *tert*-butyldimethylsilyl chloride (810 mg, 1 equiv., 5.3 mmol) was added and the reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched with methanol then evaporated. The residue was dissolved in ethyl acetate (30 mL) and washed with water (50 mL). The organic layer was separated and dried over magnesium sulphate, filtered, and evaporated. Purification by flash column chromatography (silica, 0-10% methanol/ethyl acetate) afforded compound **15b** (672 mg, 40 %) as white solid. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.45 – 6.99 (m, 5H), 3.81 (s, 2H), 3.78 (s, 2H), 3.64 (s, 2H), 3.16 – 2.98 (m, 4H), 0.91 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (126 MHz, Chloroform-d) δ 138.1, 128.3, 128.3, 126.9, 68.0, 67.9, 63.1, 58.4, 40.8, 25.8, 18.2, -5.6. HRMS (ESI, +ve) $C_{18}H_{32}NO_2Si$ $(M + H)^+$ calculated 322.2202; found 322.2198.

Compound 15c: Compound **15b** (272 mg, 0.85 mmol) was dissolved in methanol (3 mL). Palladium hydroxide on carbon (70 mg, 25% (w/w)) was added and the reaction mixture was stirred at room temperature under hydrogen for 2 days and then filtered through celite and evaporated, to afford compound **15c** (195 mg, quantitative). 1H NMR (500 MHz, Methanol-d4) δ 3.75 (s, 2H), 3.67 (s, 2H), 3.43 (s, 4H), 0.92 (s, 9H), 0.10 (s, 6H); 13C NMR (126 MHz, Methanol-d4) δ 65.9, 64.7, 50.7, 46.1, 26.4, 19.2, -5.4. HRMS (ESI, +ve) $C_{11}H_{26}NO_2Si$ $(M + H)^+$ calc. 232.1733; found 232.1728.

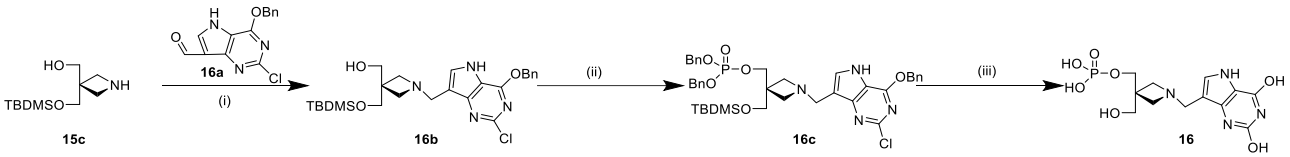
Compound 15d: Aldehyde **13b**[2] (149 mg, 0.59 mmol), azetidine **15c** (1.0 equiv., 0.59 mmol) and borane-2-picoline complex (86 mg, 1.3 equiv., 0.76 mmol) was dissolved in methanol (5 mL). The solution was heated at 50 °C for 20 minutes (pH 6). The reaction mixture was then

stirred at room temperature for 1 h and then concentrated to dryness. The residue was purified by flash column chromatography (silica, 0-10% methanol/dichloromethane) to afford compound **15d** (66 mg, 24 %). ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.43 (s, 1H), 7.61 – 7.24 (m, 6H), 5.63 (s, 2H), 3.90 (s, 2H), 3.67 (d, *J* = 13.2 Hz, 4H), 3.19 (s, 4H), 0.88 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (126 MHz, Methanol-d_4) δ 157.2, 150.3, 150.0, 137.9, 130.9, 129.6, 129.5, 129.3, 116.5, 112.2, 69.1, 66.1, 65.0, 57.6, 51.5, 42.0, 26.4, 19.2, -5.3. HRMS (ESI, +ve) $C_{25}H_{37}N_4O_3Si$ $(M + H)^+$ calculated 469.2635; found 469.2626.

Compound 15e: Compound **15d** (66 mg, 0.14 mmol) was dissolved in acetonitrile (5 mL, 95 mmol). Dibenzyl *N,N*-diisopropylphosphoramidite (79 µL, 1.5 equiv., 0.21 mmol) and then tetrazole in acetonitrile (0.94 mL, 3 equiv., 0.42 mmol, 0.45 mol/L) were added drop-wise and the reaction mixture was stirred at room temperature for 2 h. It was then cooled to 0 °C and *tert*-butyl hydroperoxide in water (21 µL, 1.1 equiv., 70 mass %) was added slowly. After warming to room temperature, the solution was stirred for 2 h and then quenched with aqueous sodium bicarbonate. The solvent was evaporated, and the residue dissolved in ethyl acetate. This was washed with water and brine. The organic layer was dried over magnesium sulphate, filtered, and then concentrated. Purification by flash column chromatography (silica, 5-15% methanol/dichloromethane) afforded compound **15e** (40 mg, 39%). 1H NMR (500 MHz, Methanol-d4) δ 8.45 (s, 1H), 7.56 (s, 1H), 7.54 – 7.48 (m, 2H), 7.40 – 7.28 (m, 13H), 5.63 (s, 2H), 5.13 – 4.95 (m, 4H), 4.18 – 4.01 (m, 4H), 3.61 (s, 2H), 3.42 (q, *J* = 9.3 Hz, 4H), 0.86 (s, 9H), 0.03 (s, 6H). 31P NMR (202 MHz, Methanol-d4) δ -1.25. 13C NMR (126 MHz, Methanol-d4) δ 157.2, 150.7, 150.0, 137.8, 137.1, 137.1, 131.8, 129.8, 129.7, 129.6, 129.5, 129.3, 129.2, 116.7, 109.6, 71.0 (d, *J* = 6.0 Hz), 69.7 (d, *J* = 5.6 Hz), 69.2, 64.9, 57.1, 50.6, 41.1 (d, *J* = 8.4 Hz), 26.4, 26.3, 19.2, -5.4. HRMS (ESI, +ve) $C_{39}H_{50}N_4O_6Psi$ $(M + H)^+$ calculated 729.3237; found 729.3230.

Compound 15: Compound **15e** (40 mg, 0.06 mmol) was dissolved in 6M hydrochloric acid in methanol (3 mL). It was refluxed at 100 °C for 2 h. After evaporation the residue was purified by flash column chromatography (silica, isopropyl alcohol:water:triethylamine 75:25:3) then by reverse phase chromatography (C18, 100% water) to afford compound **15** (21 mg, 86 %) as a triethylamine salt (~0.1 equiv.). ^{1}H NMR (600 MHz, Deuterium Oxide with NaOD) δ 7.93 (s, 1H), 7.23 (s, 1H), 3.71 (d, *J* = 5.4 Hz, 2H), 3.65 (s, 2H), 3.53 (s, 2H), 3.04 (d, *J* = 8.6 Hz, 2H), 2.98 (d, *J* = 8.6 Hz, 2H), 2.35 (q, *J* = 7.2 Hz, 1H), 0.84 (t, *J* = 7.2 Hz, 1H). 13C NMR (151 MHz, Deuterium Oxide with NaOD) δ 163.5, 151.7, 145.1, 127.0, 118.9, 109.6, 66.0, 64.1, 56.6, 50.2, 45.3, 39.9 (d, *J* = 8.0 Hz), 10.1. 31P NMR (202 MHz, Deuterium Oxide, with NaOD) δ 4.57. HRMS (ESI, −ve) $C_{12}H_{16}N_4O_6P$ $(M - H)^-$ calculated 343.0807; found 343.0797; HRMS (ESI, +ve) $C_{12}H_{18}N_4O_6P$ $(M + H)^+$ calculated 345.0964; found 345.0973.

Synthesis of compound 16:



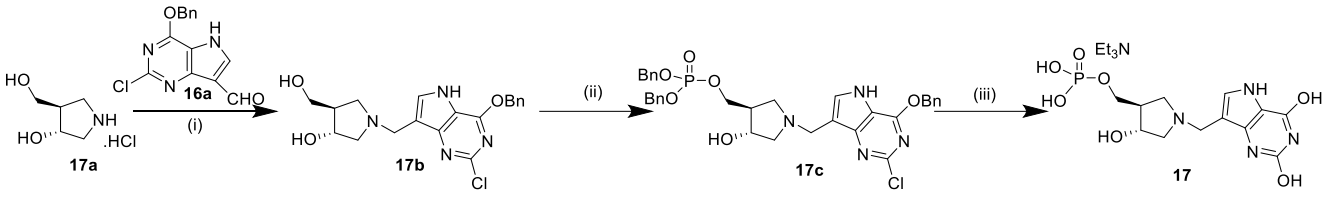
Reagents and conditions: (i) **16a**, Borane-2-picoline complex, MeOH, $CHCl_3$, 50 °C to RT 35%; (ii) Dibenzyl-*N,N*-diisopropylphosphoramidite, tetrazole, acetonitrile, *tert*-butyl hydroperoxide, 0 °C to RT, (iii) 6M HCl, MeOH, 100 °C, 43% over 2 steps.

Compound 16b: Aldehyde **16a**[4] (140 mg, 0.49 mmol) was dissolved in methanol (10 mL) and chloroform (3 mL). Compound **15c** (101 mg, 0.9 equiv., 0.44 mmol) and borane-2-picoline complex (219 mg, 4 equiv., 1.95 mmol) were added and the solution was stirred at 50 ˚C for 15 minutes and then overnight at room temperature (pH 6). After being concentrated to dryness, the residue was purified by flash column chromatography (silica, 7-20 % methanol/dichloromethane) to afford compound **16b** (85 mg, 35 %). 1H NMR (500 MHz, Chloroform-d) δ 7.56 – 7.32 (m, 5H), 7.17 (s, 1H), 5.54 (s, 2H), 3.82 (s, 2H), 3.71 (d, J = 3.6 Hz, 4H), 3.19 (d, J = 7.9 Hz, 2H), 3.11 (d, J = 7.9 Hz, 2H), 0.87 (s, 9H), 0.05 (s, 6H). 13C NMR (126 MHz, Chloroform-d) δ 156.0, 151.2, 150.4, 135.7, 129.5, 129.1, 128.8, 114.1, 112.7, 69.1, 68.1, 67.5, 58.1, 51.3, 40.5, 26.0, 18.3, -5.4; HRMS (ESI, +ve) $C_{25}H_{36}N_4O_3SiCl$ $(M + H)^+$ calculated 503.2245; found 503.2242.

Compound 16: Compound **16b** (85 mg, 0.17 mmol) was dissolved in acetonitrile (10 mL) and dibenzyl *N,N*-diisopropylphosphoramidite (95 µL, 1.5 equiv., 0.25 mmol) was added slowly followed by tetrazole in acetonitrile (0.49 mL, 1.3 equiv., 0.22 mmol, 0.45 mol/L). The reaction mixture was stirred for 2 h. *tert*-Butyl hydroperoxide in water (26 µL, 1.1 equiv., 0.19 mmol, 70 mass%) was added at 0 °C and the solution was stirred at room temperature for 2 h. The reaction was quenched with aqueous sodium bicarbonate and then diluted with excess ethyl acetate. The organic layer was separated, dried over magnesium sulphate, filtered, and concentrated. The residue was purified by flash column chromatography (silica, 7-15 % methanol/dichloromethane) to afford **16c** as syrup containing some impurities. This material (126 mg, 0.17 mmol) was dissolved in methanol (3 mL), 6M hydrochloric acid (2 mL, 18.3 mmol) was added and the solution was heated under reflux for 1 h. The solvent was evaporated, and the residue was dissolved in water containing 1 % triethylamine. It was pre-absorbed onto C18 reverse phase silica and purified by flash chromatography (C18, 100% water). Then the purified material was triturated with methanol (2 x 30 mL) and the methanol was removed to afford compound **16** as a triethylamine salt (~ 0.8 equiv.) (33.2 mg, 43% over 2 steps). 1H NMR (500 MHz, Deuterium Oxide) δ 7.58 (s, 1H), 4.38 (s, 2H), 4.19 (d, *J* = 11.0 Hz, 2H), 4.05 (d, *J* = 10.8 Hz, 2H), 3.80 (d, *J* = 4.5 Hz, 2H), 3.71 – 3.43 (m, 2H), 3.23 (q, *J* = 7.3 Hz, 5H), 1.31 (t, *J* = 7.3 Hz, 8H); 13C NMR (126 MHz, Deuterium Oxide, pH8-9) δ 160.5, 158.8, 142.8, 128.0, 111.7, 107.1, 65.9 (d, *J* = 4.4 Hz) , 63.9, 56.9, 50.5, 48.9, 45.6, 45.3, 39.2 (d, *J* = 7.3 Hz); 31P NMR (202 MHz, Deuterium Oxide, pH8-9) δ 4.39; HRMS (ESI, +ve)

$C_{12}H_{18}N_4O_7P$ $(M + H)^+$ calculated 361.0913, found 361.0922; (ESI, −ve) $C_{12}H_{16}N_4O_7P$ $(M - H)^-$ calculated 359.0757, found 359.0761.

Synthesis of compound 17:



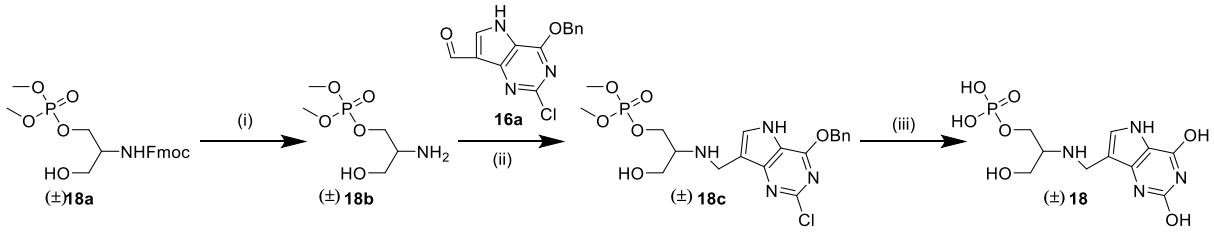
Reagents and conditions: (i) **16a**, Borane-2-picoline complex, MeOH, $CHCl_3$, 50 °C to RT 59%; (ii) Dibenzyl-*N,N*-diisopropylphosphoramidite, tetrazole, acetonitrile, *tert*-butyl hydroperoxide, 0 °C to RT, (iii) 6M HCl, MeOH, 100 °C, 16% over 2 steps.

Compound 17b: Amine **17a**[3] (128 mg, 0.83 mmol) and aldehyde **16a**[4] (240 mg, 1 equiv., 0.83 mmol) were dried under high vacuum and then dissolved in anhydrous methanol (10 mL) and anhydrous chloroform (5 mL). Borane-2-picoline complex (188 mg, 2 equiv., 1.67 mmol) was added (pH 6-7) and the reaction mixture was heated at 50 °C for 30 minutes and then stirred at room temperature overnight. The solvent was evaporated, and the residue was purified by automated chromatography (silica, 0-50 % methanol/dichloromethane) to afford compound **17b** (191 mg, 59 %). 1H NMR (500 MHz, Methanol-d4) δ 7.84 (s, 1H), 7.62 – 7.47 (m, 2H), 7.46 – 7.20 (m, 3H), 5.63 (s, 2H), 4.53 (s, 2H), 4.41 – 4.28 (m, 1H), 3.70 (dd, *J* = 11.8, 8.2 Hz, 1H), 3.60 (d, *J* = 5.2 Hz, 2H), 3.54 – 3.45 (m, 1H), 3.34 – 3.32 (m, 1H), 3.28 – 3.20 (m, 1H), 2.51 – 2.37 (m, 1H). 13C NMR (126 MHz, Methanol-d4) δ 157.9, 152.2, 151.8, 137.1, 135.0, 129.8, 129.6, 115.7, 105.9, 72.8, 70.3, 61.9, 61.5, 55.5, 49.9, 48.8 (under solvent peak). HRMS (ESI, +ve) $C_{19}H_{22}N_4O_3Cl$ $(M+ H)^+$ Calculated 389.1380; found 389.1382.

Compound 17: Compound **17b** (200 mg, 0.51 mmol) was dissolved in tetrahydrofuran (18 mL) by heating. Then the solution was cooled to 0 °C and dibenzyl *N,N*-diisopropylphosphoramidite (0.19 mL, 1 equiv., 0.51 mmol) and tetrazole in acetonitrile (2.3 ml, 2 equiv., 1.02 mmol, 0.45 mol/l) were added drop-wise and the reaction mixture was stirred for 2 h at 0 °C and overnight at room temperature. *tert*-Butyl hydroperoxide in water (78 µL, 1.1 equiv., 0.57 mmol, 70 mass%) was added and the solution was stirred for 1 h at room temperature. Aqueous sodium bicarbonate was added followed by extraction with ethyl acetate (20 mL x 2). The combined organic phases were dried over magnesium sulphate, filtered, and evaporated. Purification by automated chromatography (silica, 0-20% methanol/dichloromethane) afforded **17c** as a syrup with some impurities. 1H NMR (500 MHz, Methanol-d4) δ 7.56 (s, 1H), 7.55 – 7.50 (m, 2H), 7.42 – 7.28 (m, 13H), 5.58 (s, 2H), 5.10 – 4.93 (m, 4H), 4.05 – 3.91 (m, 3H), 3.92 – 3.79 (m, 2H), 2.97 (dd, *J* = 10.2, 8.1 Hz, 1H), 2.84 (dd, *J* = 10.4, 6.2 Hz, 1H), 2.68 (dd, *J* = 10.3, 4.1 Hz, 1H), 2.43 (dd, *J* = 10.2, 6.9 Hz, 1H), 2.35 – 2.23 (m, 1H); ^{31}P NMR (202 MHz, Methanol-d4) δ -1.51. This material (50 mg, 0.07703

mmol) was dissolved in methanol (1 mL). 6M hydrochloric acid (1 mL, 32.6 mmol, 6M) was added and the solution was heated under reflux for 1 hour and then evaporated to dryness. The residue was triturated with methanol (5 mL) (and the methanol discarded) and then a few drops of triethylamine were added with 1 mL methanol and evaporated. The solid was triturated with methanol (2 mL x 2). The residue was then purified by reverse phase flash column chromatography (C18, 100 % water) to afford compound **17** (29 mg, 16 % over 2 steps as a triethylamine salt ~ 1.5 equiv.) as white solid. ^{1}H NMR (500 MHz, Deuterium Oxide) δ 7.59 (s, 1H), 4.64 – 4.56 (m, 1H), 4.46 (s, 2H), 4.01 – 3.83 (m, 2H), 3.82 – 3.66 (m, 2H), 3.53 – 3.44 (m, 1H), 3.35 – 3.29 (m, 1H), 3.25 (q, *J* = 7.3 Hz, 9H), 2.65 (s, 1H), 1.33 (t, *J* = 7.3 Hz, 14H); ^{13}C NMR (126 MHz, Deuterium Oxide) δ 157.0, 153.1, 134.5, 131.0, 111.2, 99.2, 71.6, 63.7 (d, *J* = 4.4 Hz), 59.6, 53.8, 48.4, 46.8, 46.5 (d, *J* = 7.7 Hz), 8.3. ^{31}P NMR (202 MHz, Deuterium Oxide) δ 3.57. HRMS (ESI, +ve) $C_{12}H_{18}N_4O_7P$ $(M + H)^+$ Calculated 361.0913; found 361.0923; (ESI, −ve) $C_{12}H_{16}N_4O_7P$ $(M - H)^-$ Calculated 359.0757; found 359.0767.

Synthesis of compound 18:



Reagents and conditions: (i) 5% piperidine in DMF, 65%; (ii) **16a**, borane-2-picoline complex, MeOH, $CHCl_3$, 50 °C to RT 44%; (iii) aqHBr, 80 °C, 32%.

Compound 18b: Racemic carbamate **18a**[2] (0.55 g, 1.31 mmol) was stirred in 5% piperidine in dimethylformamide (10 ml) for 1 h. The solvent was evaporated (50 °C/0.1 mmHg) to leave a colourless solid. This residue was purified by automated Chromatography (silica, dichloromethane-methanol, 9:1 then 7:3) to give racemic compound **18b** (0.17 g, 65% yield) as a colourless gum. ^{1}H NMR (500 MHz, Chloroform-d) δ 4.11 – 3.90 (m, 2H), 3.77 (d, *J* = 0.8 Hz, 3H), 3.75 (d, *J* = 0.8 Hz, 3H), 3.64 – 3.48 (m, 2H), 3.09 (t, *J* = 5.4 Hz, 1H), 2.56 (bs, exchanged to D_2O, 3H); ^{13}C NMR (126 MHz, Chloroform-d) δ 69.2 (d, *J* = 5.9 Hz), 62.8, 54.4 (d, *J* = 6.1 Hz), 52.5 (d, *J* = 6.2 Hz); ^{31}P NMR (202 MHz, Chloroform-d) δ 1.79; HRMS (ESI, +ve) $C_5H_{15}NO_5P$ $(M + H)^+$ Calculated 200.0688; found 200.0688.

Compound 18: Aldehyde **16a**[4] (100 mg, 0.35 mmol) and amine **18b** (76 mg, 1.1 equiv., 0.38 mmol) were dissolved in ethanol (10 mL) and chloroform (3 mL). The solution was heated to 60 °C for 1 h and then cooled to 0 °C before the addition of sodium borohydride (2 equiv., 0.70 mmol). After stirring at room temperature for 30 minutes the reaction mixture was diluted with ethyl acetate and washed with water (x1). The organic phase was dried, filtered and

concentrated to dryness. The residue was purified by column chromatography (50-100% petroleum ether/ethyl acetate then dichloromethane/7N ammonia in methanol 9:1) to afford compound **18c** containing some impurities (72 mg, 44%). HRMS (ESI, +ve) $C_{19}H_{25}N_4O_6ClP$ $(M + H)^+$ Calculated 471.1200; found 471.1200. Hydrobromic acid (3 mL of a 48% w/v aqueous solution, 26.7 mmol) was added to this material (16 mg, 0.03 mmol) and the mixture was heated to 80 °C for 2 h. The solution was evaporated (50 °C/0.1 torr), water was added, and the mixture concentrated (x2). The residue was triturated with methanol (2 x 3 mL) and the residue was purified by reverse phase flash column chromatography (C18, 100% water) to afford compound **18** (4 mg, 32%). 1H NMR (500 MHz, Deuterium Oxide, pH 8) δ 7.42 (s, 1H), 4.06 – 3.87 (m, 4H), 3.82 – 3.65 (m, 2H), 3.08 – 2.97 (m, 1H); 13C NMR (126 MHz, Deuterium Oxide, pH 8) δ 159.0, 156.3, 138.8, 128.7, 111.3, 108.3, 64.9, 62.6, 62.5 (d, *J* = 4.7 Hz), 60.5, 57.9 (d, *J* = 7.0 Hz), 39.6; 31P NMR (202 MHz, Deuterium Oxide) δ 4.35; HRMS (ESI, +ve) $C_{10}H_{16}N_4O_7P$ $(M + H)^+$ calculated 335.0757; found 335.0757; (ESI, −ve) $C_{10}H_{14}N_4O_7P$ $(M - H)^-$ calculated 333.0600; found 333.0590.

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