Synthesis of (Carbo)nucleoside Analogues via [3+2] Annulation of Aminocyclopropanes**

Sophie Racine, Florian de Nanteuil, Eloisa Serrano and Jérôme Waser *

Abstract: (Carbo)nucleoside derivatives constitute an important class of pharmaceuticals, yet there are only few convergent methods to access new analogues. In this communication, we report the first synthesis of thymine, uracil and 5-fluorouracil substituted diester donor-acceptor cyclopropanes and their use in the indium- and tin-catalyzed [3+2] annulations with aldehydes, ketones and enol ethers. The obtained diester products could be easily decarboxylated and reduced to the corresponding alcohols. The method gives access to a broad range of new (carbo)nucleoside analogues in only four-five steps and will be highly useful for the synthesis of libraries of bioactive compounds.

The natural nucleosides constitute the building blocks of DNA and RNA. The interaction of enzymes and other biomolecules with nucleosides is essential for the regulation of genetic expression and cell replication. Therefore, the nucleoside scaffold constitutes a privileged structure in medicinal chemistry (Figure 1). [1] In addition to bioactive natural products, such as the antiviral and antibiotic aristeromycin (1), more than 45 FDA approved drugs are nucleoside analogues. Besides only slightly modified analogues, such as cytarabine (2) and telbivudine (3), more elaborated compounds derived from thymine have been successful, such as the carbonucleoside stavudine (4), the anti-HIV front drug azidothymidine (5) or the fluorinated floxuridine (6). Nevertheless, resistances are emerging in viral infections, and less toxic anti-cancer agents would be highly desirable, asking for the development of new bioactive nucleoside analogues.

The synthesis of nucleoside analogues has been the focus of intensive effort since several decades. [12] Nevertheless, most methods are based on a linear approach involving first the synthesis of a ribose analogue followed by introduction of the nucleobase, either via formation of the C-N bond using a substitution reaction from an acetate (Vorbrüggen reaction) [3b] or a condensation reaction from an aminoglycoside (Scheme 1, A). This approach is efficient if the targeted analogue is similar to a natural ribose derivative, but can involve a long multi-step sequence if a more elaborate scaffold is desired. [3] This is particularly true for carbonucleoside analogues, for which elegant synthetic approaches involving ring-closing metathesis, [1a] Pauson-Khand [1b] or desymmetrization starting from cyclopentadiene and proceeding via diols, [1c,d] Vince’s lactam [1e] or nitroso cycloaddition reactions [1h] have been developed.

Figure 1. Natural and synthetic bioactive nucleoside analogues.

Our group has introduced the use of imide-substituted diester cyclopropanes in [3+2] annulation reactions. [4] With this new class of donor-acceptor cyclopropanes, [5] access to intermediates of type II became possible (Scheme 2, B). Nevertheless, the efficiency of the annulation process was mitigated by the necessary removal of the phthalimide group followed by DNA-base construction, which would add several steps to the synthetic sequence. Furthermore, the deprotection of the phthalimide group could not be achieved on the tetrahydrofurylamines. If a DNA-base could be used as amino substituent on the cyclopropane, a more efficient synthesis would become possible (Scheme 1, C). Herein, we would like to report the successful
implementation of this strategy, including: (1) the first efficient three-step synthesis of thymine/uracil donor-acceptor cyclopropanes, (2) their successful [3+2] cycloaddition with enol ethers, aldehydes and ketones and (3) their further derivatization to access hydroxylated analogues.

**A/ Traditional linear approach**

![Diagram of DNA-base transfer and construction steps]

**B/ Our previous work: Annulation of aminocyclopropanes**

![Scheme 1: Traditional approach (A) and new strategy (C) to access (carbo)nucleoside analogues. Phth = Phthalimido, Pg = protecting group, LA = Lewis Acid.]

In our work with phthalimide-substituted cyclopropanes, modulating the electronic density on the nitrogen was essential for a successful annulation reaction. Based on the fact that thymine and phthalimide have similar pKa values (8.3 and 9.9 respectively), we started our investigations with thymine-substituted cyclopropanes (Scheme 2, A). Cyclopropane 7a was easily accessed by selective mono benzoylation of thymine (10), followed by Pd-catalyzed vinylation under slightly modified reported conditions (7) and cyclopropanation using Du Bois’ Rhodium-espino complex. As N3-selective tert-butylenzylation was not possible, a longer sequence involving temporary Boc protection of the N1 nitrogen was necessary in the case of cyclopropane 7b.[9]

With aminocyclopropanes 7a and 7b in hand, we first examined the iron-catalyzed [3+2] annulation reaction with benzaldehyde (14) (Scheme 2, B).[44] The reaction was successful for both substrates 7a and 7b. Nevertheless, we were never able to remove either of the protecting groups on the nitrogen of thymine. We decided consequently to turn to the easily removable tert-butoxy carbonyl (Boc) protecting group.

Due to the incompatibility of the Boc group with the vinyl group in the vinylation conditions, a method to access selectively N1-vinyl thymine prior to introduction of the Boc group was required. All the reported methods to access this substrate proceeded with low yield and reproducibility in our hands.[10] Nevertheless, we discovered that N1-selective Pd-catalyzed vinylation was possible in 45% yield from thymine itself in presence of trimethylsilyl triflate (TMSOTf) as additive (Scheme 3, A). Boc-protectio[11] and cyclopropanation then proceeded in good yields, giving access to 7c in only three steps.

**Scheme 2: Synthesis of aminocyclopropanes 7a and 7b (A) and first attempts of [3+2] annulation (B). Reaction conditions: a) BzCl, pyridine, CH₂CN, 69%, b) 4 mol% Na₂PdCl₂, vinylacetate, 80 °C, 65%, c) 2 mol% R₈H(sph), diazodimethylmalonate, CH₂Cl₂, d) Boc₂O, DMAP, CH₂CN, e) BuBnBr, NaH, DMF, 0 °C, quant. f) K₂CO₃, MeOH, 81%, g) 4 mol% Na₂PdCl₂, vinylacetate, 80 °C, 23%, h) 5 mol% Fe₂O₂Al₂O₃, CH₂Cl₂.

**Scheme 3: Synthesis of aminocyclopropanes 7c (A) and optimized conditions for [3+2] annulation reactions (B). Reaction conditions: a) 4 mol% Pd(OAc)₂, vinylacetate, TMSOTf, 70 °C, DMF, 45%, b) Boc₂O, DMAP, CH₂CN, 75%, c) 0.02 mol% R₈H(sph), diazodimethylmalonate, CH₂Cl₂, 20 mol% LiOTf, CH₂Cl₂; then EtOH, 70 °C, e) 10 mol% SnCl₄, CH₂Cl₂, 20 °C; then EtOH, 70 °C.**

First attempts towards the annulation of 7c with benzaldehyde (14) using an iron catalyst gave the desired product only in low yield (+27%). This was due to the loss of the Boc protecting group during both reaction and purification. Changing to LiOTf₃ as catalyst[12] and direct Boc deprotection of the crude product by heating in ethanol at 70 °C afforded the desired NH-free product 8c in 87% yield (Scheme 3, B). Aminocyclopropane 7c could also be used in other [3+2] annulation processes involving either ketones[46] or silyl enol ethers[44] to give tetrahdrofuryl amine 8d and cyclopentyl amine 9a in 94% and 84% yield respectively. In this case, the lower reactivity of 7c compared with phthalimide-substituted...
cyclopropanes required the use of a higher temperature (-20 instead of -78 °C) in the tin-catalyzed process.

We then turned to the investigation of the scope of the [3+2] annulation (Figure 2).[15] The reaction was successful in the case of aromatic (products 8c and 8e), aliphatic (products 8f) and vinylic aldehydes product 8g). Excellent diastereoselectivity (> 20:1) was observed, except for product 8g (5:1). The same was also true for ketones (products 8d and 8h-k), although the diastereoselectivity was lower for vinylic ketones (product 8k). With enol ethers, more substituted derivatives, such as tetrasubstituted cyclopentane 9c, could also be accessed. The [3+2] annulation product was obtained in 55% yield with a dienol ether as partner (product 9d). Finally, modification of the thymine substituent was also examined. Both cyclopropanes derived from uracil and 5-fluoro-uracil could also be used in the annulation reaction with aldehydes, ketones and enol ethers (products 18-21).[14]

For most nucleoside drugs enzymatic phosphorylation of a hydroxy group is an important step in the mode of action.[11] Modification of the obtained products to include hydroxy group(s) would be consequently highly rewarding in the quest of new bioactive compounds. To reach this goal, saponification followed by decarboxylation of diester 8c gave access to a single isomer of the corresponding carboxylic acid,[15] which could be reduced to primary alcohol 22 in 71% overall yield (Scheme 4, A). The same sequence was also successful for styrene derivative 8g, giving the corresponding alcohol 24 in 59% yield. Products 8d and 8h could also be converted into the desired alcohols 23 and 25 in 62 and 64% yield respectively. In the case of the carbonucleoside analogues, dibenzyler cyclopentylamine 26 could be converted into the corresponding diacid by hydrogenation.[16] Heating the neat crude diacid to 80 °C led then to decarboxylation and silyl ether elimination to give acid 27 (Scheme 4, B). Pd-catalyzed hydrogenation followed by acid reduction gave the corresponding unsaturated alcohol, which was isolated as silyl ether 28.

In conclusion, we have reported the first synthesis of nucleobase-substituted diester cyclopropanes and their use in cycloaddition with aldehydes, ketones and enol ethers. This new transformation gave access in a few steps to important nucleoside derivatives analogues, which were easily modified to give hydroxylated derivatives. Future work will focus on the synthesis of a broader range of analogues to build up a chemical library for biological testing and extending the scope of the reaction to the purine class of nucleobases.

![Figure 2. Scope of the [3+2] annulation reaction. The reactions were run on 0.40 mmol scale using the conditions of Scheme 3 and isolated yields after column chromatography are given. See Supporting Information for full experimental details. Thy = Thymine, Ur = Uracil, 5F-Ur = 5-Fluo-Uracil.](image)

**Keywords:** Annulation • Cyclopropanes • Catalysis • Nucleosides • Stereoselective Synthesis

Synthetic Method

Sophie Racine, Florian de Nanteuil, Eloisa Serrano and Jérôme Waser*

Synthesis of (Carbo)nucleoside Analogues via [3+2] Annulation of Aminocyclopropanes

(Carbo)nucleoside derivatives constitute an important class of pharmaceuticals. We report the first synthesis of thymine, uracil and 5-fluorouracil substituted diester donor-acceptor cyclopropanes and their use in the indium- and tin-catalyzed [3+2] annulations with aldehydes, ketones and enol ethers. The method gave access to (carbo)nucleoside analogues in only few steps and will be highly useful for the synthesis of libraries of bioactive compounds.
Contents

1. General methods ................................................................. 1
2. Starting materials ............................................................ 2
   2.1 Diazomalonates .............................................................. 2
   2.2 Thymine cyclopropanes .................................................... 3
   2.3 Uracil cyclopropane .......................................................... 10
   2.4 5-Fluoro-uracil cyclopropane ............................................... 11
   2.5 Dipolarophiles ................................................................. 13
3. Scope of the reaction .......................................................... 15
   3.1 From thymine cyclopropanes ............................................... 15
      General procedures for annulation reaction ................................ 16
         a) Conditions A ................................................................. 16
         b) Conditions B ................................................................. 17
   3.2 From uracil cyclopropane ................................................... 26
   3.3 From 5-fluoro-uracil cyclopropane ........................................ 28
      General procedure for Benzoyl removal ..................................... 28
4. Thymine based nucleoside analogues derivatizations ..................... 30
   4.1 Acids .............................................................................. 30
      General procedure for hydrolysis and decarboxylation reaction ........ 30
   4.2 Alcohols ....................................................................... 33
      General procedure for reduction of carboxylic acids ...................... 33
   4.3 Carbonucleoside alcohol .................................................... 36
5. Spectra of new compounds ................................................ 39
1. General methods.

All reactions were carried out in flamed-dried glassware under an atmosphere of nitrogen, unless stated otherwise. HPLC grade solvents purchased from Sigma-Aldrich or freshly distilled solvents were used for flash chromatography. Reaction solvents were dried by passage over activated alumina under nitrogen atmosphere (H₂O content < 30 ppm, Karl-Fischer titration). Commercially available reagents were purchased from Acros, Aldrich, Fluka, VWR, Aplichem, Merck or TCI and used without any further purification. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40-63, 60 Å, using the solvents indicated as eluent with 0.1-0.5 bar pressure. TLC was performed on Merck silica gel 60 F254 TLC plates and visualized with UV light and permanganate stain. Melting points were measured on a calibrated Büchi B-540 melting point apparatus using open glass capillaries. ¹H NMR spectra were measured on a Brucker DPX-400, 400 MHz spectrometer, all signals are reported in ppm with the corresponding internal solvent peak or TMS as standard. The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, q = quintet, m = multiplet or unresolved, br = broad signal, coupling constant(s) in Hz, integration; interpretation). ¹³C NMR spectra were carried out with ¹H-decoupling on a Brucker DPX-400 100 MHz. All signals are reported in ppm with the corresponding internal solvent signal or TMS as standard. Infrared spectra were obtained on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prisma and are reported as cm⁻¹ (w = weak, m = medium, s = strong, sh = shoulder). High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API.
2. Starting materials.

2.1 Diazomalonates.

Dibenzyl 2-diazo-2,2-dimethoxyethene (30).

![Chemical Structure]

In flame dried flask under nitrogen, 4-acetamidobenzenesulfonyl azide (1.27 g, 5.28 mmol, 1.5 eq) was dissolved in acetonitrile (15 mL) and triethylamine (1.17 mL, 8.44 mmol, 2.4 eq) and dibenzyl malonate (29) (0.88 mL, 3.5 mmol, 1 eq) were added. The reaction mixture was stirred at room temperature for 2 days. The solvent was evaporated and the crude product was filtered on coton with acetonitrile (30 mL). The crude mixture was concentrated under reduced pressure and filtered on coton one more time with DCM (30 mL) and finally purified by column chromatography, eluting with pentane/AcOEt (9:1) and 1% NEt₃ mixture to obtain the pure diazo-compound 30 (1.02 g, 3.29 mmol, 93%) as a slightly yellow solid.

RF (AcOEt/Pent: 1:9) = 0.22.

Mp 54.8-55.4°C. (Decomposition)

[^1]H NMR (400 MHz, Chloroform-d) δ 7.39-7.34 (m, 10H, Ar-H), 5.28 (s, 4H, CH₂).

[^1]3C NMR (101 MHz, Chloroform-d) δ 160.8, 135.3, 128.7, 128.5, 128.3, 67.1.

One carbon is not resolved.

IR 3035 (w), 2141 (s), 1757 (s), 1388 (s), 1271 (m), 1077 (s), 760 (s).


Dimethyl 2-diazo-2,2-dimethoxyethene (32).

![Chemical Structure]

In flame dried flask under nitrogen, 4-acetamidobenzenesulfonyl azide (6.82 g, 28.4 mmol, 1.5 eq) was dissolved in acetonitrile (80 mL) and triethylamine (6.3 mL, 45 mmol, 2.4 eq) and dimethyl malonate (31) (2.2 mL, 19 mmol, 1 eq) were added. The reaction mixture was stirred at room temperature for 1 day. The solvent was evaporated and the crude product was filtered on coton with acetonitrile (30 mL). The crude mixture was concentrated under reduced pressure and filtered on coton one more time with DCM (30 mL) and finally purified by column chromatography, eluting with pentane/AcOEt (9:1) and 1% NEt₃ mixture to obtain the pure diazo-compound 32 (2.67 g, 16.9 mmol, 94%) as a slightly yellow oil (solid at 4 °C).

[^1]H NMR (400 MHz, Chloroform-d) δ 3.84 (s, 4H, CH₂).

[^1]H NMR values correspond to the literature.^[1]

2.2 Thymine cyclopropanes.

3-Benzoyl-5-methylpyrimidine-2,4(1H,3H)-dione (33).

Following the procedure of Zhou and co-workers,[2] benzoyl chloride (1.01 mL, 8.72 mmol, 2.2 eq) and thymine (10) (0.050 g, 4.0 mmol, 1.0 eq) were suspended in a mixture of acetonitrile (4 mL) and pyridine (1.6 mL, 4.0 mmol, 1.0 eq) in a flame-dried flask under nitrogen. The reaction was stirred under nitrogen atmosphere at room temperature for 12 h. Then, the reaction was partitioned between DCM and water. The aqueous layer was extracted three times with DCM and the combined organic layers were dried over anhydrous K$_2$CO$_3$. The solvent was removed under reduced pressure. The residue was dissolved in dioxane (8 mL) and K$_2$CO$_3$ (0.3 g) in 4 mL water was added and the reaction mixture was stirred for 1h30. AcOH was added to reach pH 5. The crude residue was concentrated under vacuo and suspended in 20 mL of a saturated solution of NaHCO$_3$ for 1 h and filtered with cold water. The pure product 33 (0.63 g, 2.7 mmol, 69% yield) was obtained after recrystallization in acetone (10 mL) as colorless needles.

$^1$H NMR (400 MHz, DMSO) δ 11.37 (s, 1H, N-H), 7.94 (m, 2H, Ar-H), 7.79 (m, 1H, Ar-H), 7.61 (m, 2H, Ar-H), 7.54 (d, $J = 1.2$ Hz, 1H, C=C-H), 1.83 (d, $J = 1.1$ Hz, 3H, CH$_3$).

NMR values correspond to the literature.[2]

3-Benzoyl-5-methyl-1-vinylpyrimidine-2,4(1H$_2$,3H)-dione (11).

Following an adapted procedure of Baret and co-workers,[3] 3-benzoyl-5-methylpyrimidine-2,4(1H,3H)-dione (33) (0.061 g, 0.27 mmol, 1.0 eq) and Na$_2$PdCl$_4$ (8 mg, 0.03 mmol, 10 mol%) were heated in vinyl acetate (5 mL) at 80 °C for 6 h in a flame dried flask under nitrogen. The reaction mixture was allowed to cool down and was filtered on a syringe filter. Then, the crude residue was concentrated under reduced pressure and purified by column chromatography using a mixture of DCM/AcOEt (9.5:0.5) as eluting solvent. The pure product 11 (0.40 g, 0.16 mmol, 65% yield) was obtained as a white solid.

RF (DCM/AcOEt (9.5:0.5)) = 0.73.

$^1$H NMR (400 MHz, Chloroform-d) δ 8.02 – 7.93 (m, 2H, Ar-H), 7.68 (ddt, $J = 8.7, 7.1, 1.3$ Hz, 1H, Ar-H), 7.59 – 7.43 (m, 3H, Ar-H and C=CH), 7.21 (dd, $J = 16.0, 9.1$ Hz, 1H, vinyl-C-H), 5.17 (dd, $J = 16.0, 2.3$ Hz, 1H, vinyl-CH$_2$), 5.00 (dd, $J = 9.1, 2.3$ Hz, 1H, vinyl-CH$_2$), 2.05 (d, $J = 1.3$ Hz, 3H, CH$_3$).

$^{13}$C NMR (101 MHz, Chloroform-d) δ 168.4, 162.5, 148.3, 135.1, 134.3, 131.4, 130.5, 129.5, 129.2, 101.2, 12.7.

IR 3125 (w), 1753 (m), 1701 (s), 1656 (s), 1439 (m), 1345 (m), 1233 (m).

HRMS (ESI) calcd for C$_{14}$H$_{13}$N$_2$O$_3$ $^{+}$ [M+H]$^+$ 257.0921; found 257.0913.

NMR values correspond to the literature[3]

**Dimethyl 2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)cyclopropane-1,1-dicarboxylate (7a).**

Dimethyl 2-diazomalonate (0.078 g, 0.40 mmol, 1.5 eq) was added to a solution of 3-benzoyl-1-vinylpyrimidine-2,4(1H,3H)-dione (11) (0.064 g, 0.26 mmol, 1.0 eq) and Rh₂(esp)₂ (0.4 mg, 0.5 µmol, 5% mol). The reaction mixture was stirred in anhydrous DCM (1 mL) at room temperature for 4 h in a flame dried flask under nitrogen. Then, the crude residue was concentrated under reduced pressure and purified by column chromatography using a mixture of AcOEt/PET (7:3, 1% NEt₃) affording the pure product 7a (0.083 g, 0.20 mmol, 79% yield) as a colorless foam.

RF (AcOEt/PET (7:3, 1% NEt₃)) = 0.23.

Mp 61.2-63.0°C.

**¹H NMR** (400 MHz, Chloroform-d) δ 7.98 – 7.88 (m, 2H, Ar-H), 7.70 – 7.60 (m, 1H, Ar-H), 7.54 – 7.45 (m, 2H, Ar-H), 7.11 (q, J = 1.2 Hz, 1H, thymine C=CH), 4.00 (dd, J = 8.1, 6.4 Hz, 1H, cyclopropane-CH), 3.79 (s, 3H, ester-CH₃), 3.68 (s, 3H, ester-CH₃), 2.26 (t, J = 6.4 Hz, 1H, cyclopropane-CH₂), 2.05 – 1.95 (m, 4H, cyclopropane-CH₂ and thymine-CH₃).

**¹³C NMR** (101 MHz, Chloroform-d) δ 168.3, 167.4, 166.7, 162.7, 150.1, 138.8, 135.0, 131.5, 130.6, 129.0, 111.0, 53.2, 53.2, 42.7, 34.8, 20.3, 12.5.

**IR** 3125 (w), 3067 (w), 1747 (s), 1656 (s), 1436 (m), 1283 (m), 1233 (m).

**HRMS (ESI)** calcd for C₁₉H₁₉N₂O₇ [M+H]⁺ 387.1192; found 387.1194.

**Tert-butyl 5-methyl-2,4-dioxo-3,4-dihydropyrimidine-1(2H)-carboxylate (12).**

Following the procedure described by Jaime-Figueroa and co-workers,[4] thymine (10) (1.0 g, 7.9 mmol, 1.0 eq), di-tert-butyl dicarbonate (1.7 g, 7.9 mmol, 1.0 eq) and DMAP (0.1 g, 0.8 mmol, 0.1 eq) were stirred in a flame-dried flask under nitrogen with acetonitrile (40 mL) for 4 h at room temperature. Then, the crude residue was concentrated under reduced pressure and purified by column chromatography using a mixture of DCM/AcOEt (9:1) as eluting solvent. The pure product 12 (1.6 g, 7.0 mmol, 88% yield) was obtained as a white solid.

RF (DCM/AcOEt (9:1)) = 0.18.

**¹H NMR** (400 MHz, DMSO-d6) δ 11.41 (br. s, 1H, N-H), 7.72 (s, 1H, C=H), 1.81 (s 3H, CH₃), 1.46 (s, 9H, BOC).

IR 3306 (w), 1743 (s), 1706 (s), 1359 (w), 1306 (m), 1152 (m).

HRMS (ESI) calcd for C$_{10}$H$_{15}$N$_2$O$_4$ $^+$ [M+H]$^+$ 227.1026; found 227.1030. NMR values correspond to the literature.$^{[4]}$

Tert-butyl 3-(4-(tert-butyl)benzyl)-5-methyl-2,4-dioxo-3,4-dihydropyrimidine-1(2H)-carboxylate (34).

Following a procedure described by Jacobsen and co-workers.$^{[5]}$, tert-butyl 5-methyl-2,4-dioxo-3,4-dihydropyrimidine-1(2H)-carboxylate (12) (0.75 g, 3.3 mmol, 1.0 eq) and NaH (0.159 g, 3.98 mmol, 1.2 eq) were stirred 30 min at room temperature in DMF (20 mL) in a flame-dried flask under nitrogen. Then 1-(bromomethyl)-4-(tert-butyl)benzene (0.731 mL, 3.98 mmol, 1.2 eq) was added at 0 °C. The reaction mixture was stirred at room temperature for 45 min and was partitioned between AcOEt and water. The aqueous layer was extracted three times with AcOEt and the organic layers were washed once with a sat. NH$_4$Cl solution and dried over anhydrous K$_2$CO$_3$. The solvent was removed under reduced pressure. The pure product 34 (1.24 g, 3.32 mmol, quantitative yield) was obtained after column chromatography using DCM as eluting solvent as white powder.

RF (DCM) = 0.24.

Mp 145.6-146.7°C.

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.62 (q, $J = 1.3$ Hz, 1H, thymine C=C-H), 7.47 – 7.39 (m, 2H, Ar-H), 7.36 – 7.27 (m, 2H, Ar-H), 5.09 (s, 2H, benzylic-CH$_2$), 1.96 (d, $J = 1.4$ Hz, 3H, thymine methyl), 1.60 (s, 9H, Boc), 1.29 (s, 9H, $^t$Bu).

$^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 163.0, 150.6, 148.8, 148.3, 133.5, 133.4, 129.1, 125.3, 111.4, 86.6, 44.3, 34.5, 31.3, 27.8, 13.3.

IR 2965 (w), 2907 (w), 1750 (s), 1681 (s), 1434 (m), 1282 (s), 1146 (s), 846 (m).

HRMS (ESI) calcd for C$_{21}$H$_{29}$N$_2$O$_4$ $^+$ [M+H]$^+$ 373.2122; found 373.2135.

3-(4-(Tert-butyl)benzyl)-5-methylpyrimidine-2,4(1H,3H)-dione (35).

Following a procedure described by Jacobsen and co-workers.$^{[6]}$, 3-(4-(tert-butyl)benzyl)-5-methylpyrimidine-2,4(1H,3H)-dione (34) (1.4 g, 3.8 mmol, 1.0 eq), K$_2$CO$_3$ (0.26 g, 3.8 mmol, 1.0 eq) were stirred in MeOH (40 mL) at room temperature for 4 h. Afterwards, the reaction mixture was partitioned between DCM and water. The aqueous layer was extracted three times with DCM and the organic layers were washed once with a sat. NH$_4$Cl solution and dried over anhydrous K$_2$CO$_3$. The solvent was removed under reduced pressure affording pure 35 (0.83 g, 3.1 mmol, 81% yield) as a white solid.


Mp 198.2-200.0°C.

\[^1\text{H NMR} (400 MHz, DMSO-d6) \delta 7.34 (s, 1H, thymine vinyl-C-H), 7.30 (d, J = 8.2 Hz, 2H, Ar-H), 7.21 (d, J = 8.2 Hz, 2H, Ar-H), 4.93 (s, 2H, benzylic-CH\_2), 1.79 (s, 3H, thymine-CH\_3), 1.23 (s, 9H, \text{^t}Bu).\]

\[^1\text{H NMR} (400 MHz, Chloroform-d) \delta 9.94 – 9.87 (m, 1H, thymine N-H), 7.48 – 7.38 (m, 2H, Ar-H), 7.38 – 7.31 (m, 2H, Ar-H), 7.02 (dt, J = 5.3, 1.2 Hz, 1H, thymine vinyl-C-H), 5.11 (s, 2H, benzylic-\text{CH\_2}), 1.95 (d, J = 1.2 Hz, 3H, thymine-\text{CH\_3}), 1.31 (s, 9H, \text{^t}Bu).\]

\[^{13}\text{C NMR} (101 MHz, Chloroform-d) \delta 164.0, 153.2, 150.5, 134.4, 133.7, 128.7, 125.3, 110.3, 43.6, 34.5, 31.4, 13.0.\]

IR 3235 (w), 2963 (w), 2869 (w), 1713 (m), 1643 (s), 1515 (w), 1443 (w), 1206 (w).

HRMS (ESI) calcd for C\_16H\_21N\_2O\_2\+[M+H] \^+ 273.1598; found 273.1599.

\[^1\text{H NMR values are in accordance with the spectra performed in DMSO in the literature}[^5].\]

3-(4-(Tert-butyl)benzyl)-5-methyl-1-vinylpyrimidine-2,4(1H,3H)-dione (13).

Following an adapted procedure described by Baret and co-workers[^3] 3-(4-(tert-butyl)benzyl)-5-methyl-1-vinylpyrimidine-2,4(1H,3H)-dione (35) (0.825 g, 3.03 mmol, 1 eq) and Na\_2PdCl\_4 (37 mg, 0.13 mmol, 0.05 eq) were heated at 80°C in vinylacetate (10 mL) for 6 h in a flame-dried flask under nitrogen. The reaction mixture was cooled down and filtered on a syringe filter. The pure product 13 (0.21 g, 0.70 mmol, 23% yield) was obtained after column chromatography using a mixture of DCM/AcOEt (9.5/0.5) as a white solid.

RF (DCM/AcOEt (9.5/0.5)) = 0.73.

Mp 107.6-108.9°C.

\[^1\text{H NMR} (400 MHz, Chloroform-d) \delta 7.50 – 7.42 (m, 2H, Ar-H ), 7.39 – 7.22 (m, 4H, Ar-H, thymine-H and vinyl-CH), 5.14 (s, 2H, benzylic-\text{CH\_2}), 5.05 (dd, J = 16.1, 2.1 Hz, 1H, thymine vinyl-\text{CH\_2}), 4.90 (dd, J = 9.1, 2.2 Hz, 1H, thymine vinyl-\text{CH\_2}), 2.02 (d, J = 1.3 Hz, 3H, thymine-\text{CH\_3}), 1.31 (s, 9H, \text{^t}Bu).\]

\[^{13}\text{C NMR} (101 MHz, Chloroform-d) \delta 163.2, 150.6, 150.0, 133.6, 132.7, 130.6, 129.0, 125.3, 111.4, 100.3, 44.3, 34.5, 31.3, 13.3.\]

IR 3097 (w), 2963 (w), 2907 (w), 1709 (s), 1676 (s), 1644 (s), 1444 (m), 1377 (m), 1351 (m), 1274 (m).

HRMS (ESI) calcd for C\_18H\_25N\_2O\_2\+[M+H] \^+ 299.1754; found 299.1747.

Dimethyl 2-(3-(4-(tert-butyl)benzyl)-5-methyl-2,4-dixo-3,4-dihydropyrimidin-1(2H)-yl)cyclopropane-1,1-dicarboxylate (7b).
3-(4-(Tert-butyl)benzyl)-5-methyl-1-vinylpyrimidine-2,4(1H,3H)-dione 13 (0.10 g, 0.34 mmol, 1.0 eq), Rh$_2$(esp)$_2$ (0.51 mg, 0.67 µmol, 0.2 mol%) and dimethyl 2-diazomalonate (0.10 g, 0.50 mmol, 1.5 eq) were stirred in a flame-dried flask under nitrogen with anhydrous DCM (4 mL) at room temperature for 5 h. Then, the crude residue was concentrated under reduced pressure and purified by column chromatography with DCM and 1% NEt$_3$, affording the pure product 7b (0.14 g, 0.34 mmol, quantitative yield) as a slightly yellow oil.

RF (DCM) = 0.31.

$^1$H NMR (400 MHz, Chloroform-$d$) δ 7.41 – 7.21 (m, 4H, Ar-H), 6.93 (app. d, $J$ = 1.4 Hz, 1H, thymine C=CH), 5.08 (d, $J$ = 13.7 Hz, 1H, benzylic-CH$_2$), 5.01 – 4.91 (m, 1H, benzylic-CH$_2$), 4.00 (dd, $J$ = 8.2, 6.5 Hz, 1H, cyclopropane-CH), 3.75 (s, 3H, ester-CH$_3$), 3.36 (s, 3H, ester-CH$_3$), 2.19 (t, $J$ = 6.5 Hz, 1H, cyclopropane-CH$_2$), 1.93 – 1.89 (m, 1H, cyclopropane-CH$_2$), 1.92 (s, 3H, thymine-CH$_3$), 1.22 (s, 9H, tBu).

$^{13}$C NMR (101 MHz, Chloroform-$d$) δ 167.7, 166.3, 163.3, 151.7, 150.3, 137.0, 133.8, 128.7, 125.2, 110.0, 53.1, 52.9, 44.1, 43.6, 35.0, 34.4, 31.3, 20.0, 13.2.

IR 4436 (w), 3625 (w), 2958 (m), 2860 (w), 1732 (s), 1668 (s), 1448 (s), 1294 (s), 1219 (s), 1131 (m).

HRMS (ESI) calcd for C$_{23}$H$_{29}$N$_2$O$_6$+ [M+H]$^+$ 429.2020; found 429.2022.

1-Vinylthymine (36).

Palladium acetate (0.11 g, 0.48 mmol, 0.04 eq), vinyl acetate (8.8 mL, 9.5 mmol, 2.4 eq), thymine (10) (1.5 g, 12 mmol, 1.0 eq) and TMSOTf (5.2 mL, 12 mmol, 2.4 eq) were stirred in DMF (30.0 mL) for 16 hours at 70°C in a flame-dried sealed flask under nitrogen atmosphere. Then the reaction mixture was cooled down to room temperature and partitioned between water (25 mL) and AcOEt (30 mL). The aqueous layer was extracted three times with ethyl acetate (30 mL), the organic layers were combined and washed three times with water (30 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography, eluting with hex/AcOEt/NEt$_3$ (7:3:0.01) to obtain the pure 1-vinylthymine 36 (0.81 g, 5.3 mmol, 45% yield) as a white solid.

RF (Hex/AcOEt (1:1)) = 0.5.

Mp 208.0-209.1°C.

$^1$H NMR (400 MHz, Chloroform-$d$) δ 9.17 (s, 1 H, NH), 7.34 (s, 1 H, thymine C=C-H), 7.21 (dd, 1 H, $J$ = 16.0, 9.1 Hz, -vinyl-CH), 5.07 (dd, 1 H, $J$ = 16.0, 2.1 Hz, vinyl-CH$_2$), 4.91 (dd, 1 H, $J$ = 9.1, 2.1 Hz, vinyl-CH$_2$), 1.99 (s, 3H, thymine-CH$_3$).
\[\delta_{13C} \text{ NMR} \ (101 \text{ MHz, Chloroform-}d) \ \delta \ 163.6, 149.3, 134.5, 129.6, 112.1, 100.5, 12.6.\]

\[\text{IR} \ 3173 \text{ (w), 3048 \text{ (w), 1698 \text{ (s), 1644 \text{ (s), 1459 \text{ (w), 1381 \text{ (w), 1344 \text{ (w, 1278 \text{ (m, 1129 \text{ (w.}}}}\]

\[\text{HRMS (ESI) calcd for } C_{7}H_{9}N_{2}O_{2}^{+} [M+H]^{+} 153.0659; \text{ found } 153.0653.\]

**Tert-butyl 5-methyl-2,6-dioxo-3-vinyl-2,3-dihydropyrimidine-1(6H)-carboxylate (15).**

1-Vinylthymine 36 (0.92 g, 6.1 mmol, 1.0 eq), di-tert-butyl dicarbonate (2.64 g, 12.1 mmol, 2.0 eq) and dimethylaminopyridine (1.48 g, 12.1 mmol, 2.0 eq) were stirred in acetonitrile (25.0 mL) for 12 h in a flame-dried flask under nitrogen. Silica and triethylamine (0.5 mL) were added to the reaction and the solvent was removed under reduced pressure. The dry residue was purified by column chromatography using a mixture of hexane/ethyl acetate/1% NEt\(_3\) (95:5 to 80:20) as eluting solvent. The pure product 15 (1.15 g, 4.56 mmol, 75% yield) was obtained as a white solid.

\[RF \ (\text{Hex/AcOEt (9:1)) = 0.2.}\]

\[\text{Mp} \ 109.9-111.2 \degree C.\]

\[\text{\textsuperscript{1}H NMR} \ (400 \text{ MHz, Chloroform-}d) \ \delta 7.31 \text{ (m, 1H, thymine } C=C-H), 7.15 \text{ (dd, } J = 16.0, 9.1 \text{ Hz, 1H, -vinyl-CH), 5.09 \text{ (dd, } J = 16.0, 2.2 \text{ Hz , 1H, vinyl-CH}\_2), 4.94 \text{ (dd, } J = 9.1, 2.2 \text{ Hz , 1H, vinyl-CH}\_2), 1.99 \text{ (s, 3 H, thymine-CH}\_3), 1.60 \text{ (s, 9 H, Boc).}\]

\[\text{\textsuperscript{13C NMR} \ (400 \text{ MHz, Chloroform-}d) \ \delta 161.0, 147.6, 147.5, 134.0, 129.6, 111.8, 101.3, 87.1, 27.5, 12.7.}\]

\[\text{IR} \ 2982 \text{ (w), 2937 \text{ (w), 1778 \text{ (s), 1721 \text{ (s), 1672 \text{ (s.}}}}\]

\[\text{HRMS (ESI) calcd for } C_{12}H_{16}N_{2}NaO_{4}^{+} [M+Na]^{+} 275.1002; \text{ found } 275.1008.\]

**Dimethyl 2-(3-(tert-butoxycarbonyl)-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)cyclopropane-1,1-dicarboxylate (7c).**

Diazomalonate 32 (1.80 g, 10.5 mmol, 1.2 eq), Rh\(_2\)(esp)\(_2\) (0.013 g, 0.017 mmol, 0.02 mol%) and tert-butyl 5-methyl-2,6-dioxo-3-vinyl-2,3-dihydropyrimidine-1(6H)-carboxylate (15) (2.2 g, 8.7 mmol, 1.0 eq) were stirred at room temperature in DCM (18 mL) in a flame-dried flask under nitrogen. After 40 min, NEt\(_3\) (0.4 mL) and silica were added and the solvent was removed under reduced pressure. The dried residue was purified by column chromatography using a mixture of pentane/ethyl acetate/1% NEt\(_3\) (1:1) as solvent gradient. The pure product 7c (3.30 g, 8.63 mmol, 99% yield) was obtained as a slightly yellow foamy oil.

\[RF \ (\text{hexane/AcOEt/1% NEt}_{3} (1:1)) = 0.26.\]
**H NMR** (400 MHz, Chloroform-d) δ 6.94 (m, 1H, thymine C=CH), 4.01 (dd, J = 8.3, 6.4 Hz, 1H, cyclopropane-CH), 3.79 (s, 3H, ester-CH3), 3.71 (s, 3H, ester-CH3), 2.27 (t, J = 6.5 Hz, 1H, cyclopropane-CH2), 1.91 (m, 4H, thymine-CH3 and cyclopropane-CH2), 1.58 (s, 9H, Boc).

**13C NMR** (101 MHz Chloroform-d) δ 167.6, 166.2, 161.2, 149.1, 147.4, 138.2, 110.5, 86.8, 53.3, 53.2, 42.9, 35.0, 27.5, 20.0, 12.5.

**IR** 3431 (w), 3364 (w), 2943 (m), 2866 (m), 2092 (w), 1705 (s), 1628 (m), 1505 (m), 1364 (m), 1167 (s).

**HRMS (ESI)** calcd for C17H22N2NaO8+ [M+Na]+ 405.1268; found 405.1271.

**Dibenzyl 2-(3-(tert-butoxycarbonyl)-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)cyclopropane-1,1-dicarboxylate (37).**

\[
\begin{align*}
\text{BnO}_2\text{C} & \quad \text{Rh}_{2}\text{esp}_2 \\
\text{BnO}_2\text{C} & \quad \text{Boc}
\end{align*}
\]

**Tert-butyl 5-methyl-2,6-dioxo-3-vinyl-2,3-dihydropyrimidine-1(6H)-carboxylate (15) (0.30 g, 1.2 mmol, 1.0 eq) and Rh2(esp)2 (1.8 mg, 2.4 µmol, 0.02 mol%) were stirred in a flame-dried flask under nitrogen atmosphere with anhydrous DCM (2.3 mL) and diazomalonate 30 (0.45 g, 1.4 mmol, 1.2 eq) was added at 0 °C. Then, the reaction mixture was allowed to warm up to room temperature and stirred for 14 h. Silica and triethylamine (0.5 mL) were added and the solvent was removed under reduced pressure. The dried residue was purified by column chromatography using a mixture of pentane/ethyl acetate/1% NEt3 (9:1) as eluting solvent to afford dibenzyl 2-(3-(tert-butoxycarbonyl)-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)cyclopropane-1,1-dicarboxylate (37) (0.60 g, 1.1 mmol, 93% yield) as a slightly yellow foam.

**MP** 76.9–82.1 °C.

**RF** (pent/ACOEt (7:3)) = 0.29.

**H NMR** (400 MHz, Chloroform-d) δ 7.35 – 7.22 (m, 10 H, Ar-H), 6.83 (q, J = 1.1 Hz, 1H, thymine vinyl-CH), 5.27 – 5.10 (m, 4H, benzylic-CH2), 4.05 (dd, J = 8.3, 6.5 Hz, 1H, cyclopropane-NCH), 2.31 (t, J = 6.6 Hz, 1H, cyclopropane -CH2), 1.93 (dd, J = 8.3, 6.6 Hz, 1H, cyclopropane -CH2), 1.78 (d, J = 1.3 Hz, 3H, thymine methyl), 1.59 (s, 9H, Boc).

**13C NMR** (101 MHz, Chloroform-d) δ 167.2, 165.4, 161.1, 149.2, 147.5, 138.0, 135.0, 134.8, 128.6, 128.6, 128.5, 128.4, 128.2, 110.5, 86.8, 68.3, 68.0, 43.1, 35.3, 27.5, 20.3, 12.4. One carbon not resolved.

**IR** 3066 (w), 2984 (w), 2932 (w), 1783 (s), 1725 (s), 1670 (s), 1433 (m), 1373 (m), 1316 (s), 1146 (s).

Palladium acetate (0.036 g, 0.040 mmol, 0.04 eq), vinyl acetate (0.87 mL, 10 mmol, 2.4 eq), uracil (38) (0.45 g, 4.0 mmol, 1.0 eq), TMSOTf (1.7 mL, 9.5 mmol, 2.4 eq) and triethylamine (1.4 mL, 9.5 mmol, 2.4 eq) were stirred in DMF (11.5 mL) for 16 hours at 70 °C in a flame-dried sealed flask under nitrogen atmosphere. Then the reaction mixture was cooled down to room temperature and filtered on celite with AcOEt (50 mL). The crude mixture was concentrated under reduced pressure and purified by column chromatography, eluting with pentane and AcOEt mixture (2:8) to obtain the pure product 39 (0.38 g, 2.7 mmol, 69% yield) as a white solid.

RF (AcOEt/pentane (1:1)) = 0.20.

MP 175.2-176.7°C.

\[ ^1H \text{ NMR (400 MHz, Acetone)} \delta 9.21 \text{ (s, 1H, uracil N-H)}, 7.53 \text{ (d, } J = 8.1 \text{ Hz, 1H, uracil CH)}, 7.23 \text{ (dd, } J = 16.0, 9.0 \text{ Hz, 1H, vinyl-CH)}, 5.86 \text{ (dd, } J = 8.1, 1.3 \text{ Hz, 1H, uracil CH)}, 5.13 \text{ (dd, } J = 16.0, 2.3 \text{ Hz, 1H, vinyl-CH}_2), 5.00 \text{ (dd, } J = 9.0, 2.3 \text{ Hz, 1H, vinyl-CH}_2). \]

\[ ^{13}C \text{ NMR (101 MHz, Acetone)} \delta 162.5, 149.3, 139.1, 129.7, 102.8, 99.7. \]

IR 3015 (w), 2823 (w), 1698 (s), 1640 (s), 1385 (s), 1278 (m), 1203 (m), 827 (s).

HRMS (ESI) calcd for C_{6}H_{7}N_{2}O_{2}^{+} [M+H]^+ 139.0502; found 139.0507.

**Tert-butyl 2,6-dioxo-3-vinyl-3,6-dihydropyrimidine-1(2H)-carboxylate (40).**

1-Vinyluracil (39) (0.25 g, 1.8 mmol, 1.0 eq), di-tert-butyl dicarbonate (0.78 g, 3.6 mmol, 2.0 eq) and dimethylaminopyridine (0.44 g, 3.6 mmol, 2.0 eq) were stirred in acetonitrile (8.5 mL) for 12 h in a flame-dried flask under nitrogen. Silica and triethylamine (0.5 mL) were added to the reaction and the solvent was removed under reduced pressure. The dry residue was purified by column chromatography eluting with pentane/AcOEt mixture (2:8) as solvent. The pure product 40 (0.43 g, 1.8 mmol, quantitative yield) was obtained as a yellow oil.

RF (AcOEt/pentane (1:1)) = 0.40.

\[ ^1H \text{ NMR (400 MHz, Chloroform-d)} \delta 7.51 \text{ (d, } J = 8.2 \text{ Hz, 1H, uracil CH)}, 7.15 – 7.02 \text{ (m, 1H, vinyl-CH)}, 5.80 \text{ (d, } J = 8.2 \text{ Hz, 1H, uracil CH)}, 5.14 \text{ (dd, } J = 16.0, 2.4 \text{ Hz, 1H, vinyl-CH}_2), 4.96 \text{ (dd, } J = 9.0, 2.5 \text{ Hz, 1H, vinyl-CH}_2), 1.55 \text{ (s, 9H, Boc).} \]

\[ ^{13}C \text{ NMR (101 MHz, Chloroform-d)} \delta 160.0, 147.5, 147.4, 138.6, 129.5, 103.0, 102.5, 87.0, 27.4. \]

IR 3104 (w), 2984 (w), 1783 (s), 1673 (s), 1440 (m), 1372 (s), 1280 (s), 1144 (s), 803 (m).
HRMS (ESI) calcd for $C_{11}H_{14}N_2NaO_4^+$ [M+Na]$^+$ 261.0846; found 261.0859.

Dimethyl 2-(3-(tert-butoxycarbonyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)cyclopropane-1,1-dicarboxylate (41).

\[
\begin{align*}
N & \quad \text{Boc} \\
\text{O} & \\
\text{O} & \\
& \quad \text{MeO}_2\text{C} \\
& \quad \text{MeO}_2\text{C}
\end{align*}
\]

Diazaomalinate 32 (0.28 g, 1.8 mmol, 1.0 eq), Rh$_2$(esp)$_2$ (2.7 mg, 3.5 µmol, 0.02 mol%) and product 40 (0.42 g, 1.8 mmol, 1.0 eq) were stirred at room temperature in DCM (18 mL) in a flame-dried flask under nitrogen. After 2 hour. NEt$_3$ (0.1 mL) and silica were added and the solvent was removed under reduced pressure. The dried residue was purified by column chromatography using a mixture of pentane/AcOEt (3:7) as eluting solvent. The pure cyclopropane 41 (0.56 g, 1.5 mmol, 87% yield) was obtained as a colorless foam.

RF (AcOEt/pentane (1:1)) = 0.20.

MP 45.0-46.2°C.

$^1$H NMR (400 MHz, Chloroform-$_d$) δ 7.08 (d, $J = 8.1$ Hz, 1H, uracil CH), 5.64 (d, $J = 8.2$ Hz, 1H, uracil CH), 3.98 (dd, $J = 8.2$, 6.5 Hz, 1H, cyclopropane-CH), 3.73 (s, 3H, ester CH$_3$), 3.65 (s, 3H, ester CH$_3$), 2.19 (t, $J = 6.6$ Hz, 1H, cyclopropane-CH$_2$), 1.88 (dd, $J = 8.5$, 6.8 Hz, 1H, cyclopropane-CH$_2$), 1.51 (s, 9H, Boc).

$^{13}$C NMR (101 MHz, Chloroform-$_d$) δ 167.5, 166.1, 160.2, 149.1, 147.2, 142.4, 101.9, 87.0, 53.3, 53.2, 43.0, 34.9, 27.4, 19.8.

IR 1780 (w), 1723 (m), 1676 (s), 1435 (w), 1312 (m), 1145 (s), 733 (s).

HRMS (ESI) calcd for $C_{16}H_{20}N_2NaO_8^+$ [M+Na]$^+$ 391.1112; found 391.1106.

2.4 5-Fluoro-uracil cyclopropane.

5-Fluoro-1-vinylpyrimidin-2,4(1H,3H)-dione (43).

Palladium acetate (0.013 g, 0.056 mmol, 0.04 eq), vinyl acetate (1.7 mL, 3.4 mmol, 2.4 eq), fluoro-uracil 42 (0.18 g, 1.4 mmol, 1.0 eq), TMSOTf (0.60 mL, 3.4 mmol, 2.4 eq) and triethylamine (0.47 mL, 3.4 mmol, 2.4 eq) were stirred in DMF (4 mL) for 16 hours at 70 °C in a flame-dried sealed flask under nitrogen atmosphere. Then the reaction mixture was cooled down to room temperature and filtered on celite with AcOEt (50 mL). The crude mixture was concentrated under reduced pressure and purified by column chromatography, eluting with pentane and AcOEt mixture (1:1) to obtain the pure product 43 (0.12 g, 0.58 mmol, 57% yield) as a white solid.

RF (AcOEt/pentane (6:4)) = 0.51.
MP 135.1-137.0°C.

$^1$H NMR (400 MHz, Chloroform-d) δ 7.52 (d, $J = 5.8$ Hz, 1H, F-uracil vinyl-CH), 7.12 (ddd, $J = 15.9$, 9.1, 1.8 Hz, 1H, vinyl-CH), 5.11 – 4.79 (m, 2H, vinyl-CH$_2$).

$^{13}$C NMR (101 MHz, Chloroform-d) δ 156.1 (d, $J = 27.3$ Hz), 147.3, 141.1 (d, $J = 241.8$ Hz), 129.3, 123.1 (d, $J = 34.2$ Hz), 101.3.

IR 3031 (w), 2844 (w), 1661 (s), 1377 (s), 1268 (s), 1122 (s), 970 (m), 913 (m).

HRMS (ESI) calcd for C$_6$H$_6$F$_6$N$_2$O$_2$ $\text{[M+H]}^+$ 157.0408; found 157.0414.

3-Benzoyl-5-fluoro-1-vinylpyrimidine-2,4(1H,3H)-dione (44).

![Chemical structure](image)

In a flame-dried flask under nitrogen, 1-vinyl-fluorouracil (43) (0.12 g, 0.79 mmol, 1.0 eq) was stirred with pyridine (2 mL), and added dropwise over 10 min to a solution of benzoyl chloride (0.34 g, 2.4 mmol, 3 eq) in pyridine (0.7 mL) and stirred for 2 h at room temperature. Then the crude mixture was partitioned between water (10 mL) and AcOEt (10 mL). The aqueous layer was extracted three times with AcOEt (10 mL) and the organic layers were dried over anhydrous MgSO$_4$. The solvent was removed under reduced pressure and the dry residue was purified by column chromatography using a mixture of pentane/AcOEt (7:3 to 1:1) as eluting solvent. The pure product 44 (0.15 g, 0.58 mmol, 73% yield) was obtained as a white solid.

RF (AcOEt/pentane (1:1)) = 0.54.

MP 128.6-129.3°C.

$^1$H NMR (400 MHz, Chloroform-d) δ 7.95 (dd, $J = 8.3$, 1.4 Hz, 2H, Ar-H), 7.75 – 7.64 (m, 2H, Ar-H and F-uracil vinyl-CH), 7.52 (t, $J = 7.9$ Hz, 2H, Ar-H), 7.12 (ddd, $J = 15.9$, 9.0, 1.8 Hz, 1H, vinyl-CH$_2$), 5.13 (dd, $J = 15.8$, 2.7 Hz, 1H, vinyl-CH$_2$), 4.99 (dd, $J = 9.0$, 2.8 Hz, 1H, vinyl-CH$_2$).

$^{13}$C NMR (101 MHz, Chloroform-d) δ 166.8, 155.8 (d, $J = 27.5$ Hz), 146.8, 140.6 (d, $J = 242.6$ Hz), 135.7, 130.7, 130.6, 129.4, 129.0, 123.6 (d, $J = 34.2$ Hz), 102.2.

IR 1756 (m), 1665 (s), 1448 (w), 1368 (s), 1276 (m), 1229 (m), 909 (m).

HRMS (ESI) calcd for C$_{13}$H$_9$FN$_2$NaO$_3$ $\text{[M+Na]}^+$ 283.0489; found 283.0485.

Dimethyl 2-(3-benzoyl-5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)cyclopropane-1,1-dicarboxylate (45).

![Chemical structure](image)
Diazomalonate 32 (0.21 g, 1.3 mmol, 1.2 eq), Rh₂(PPh₃)₂ (0.002 g, 0.002 mmol, 0.02 mol%) and product 44 (0.29 g, 0.11 mmol, 1.0 eq) were stirred at room temperature in DCM (11 mL) in a flame-dried flask under nitrogen. After 1 hour, NEt₃ (0.1 mL) and silica were added and the solvent was removed under reduced pressure. The dried residue was purified by column chromatography using a mixture of pentane/AcOEt (3:7) as eluting solvent. The pure cyclopropane 45 (0.40 g, 1.0 mmol, 93% yield) was obtained as a white foamy solid.

RF (AcOEt/pentane (3:7)) = 0.33.

MP 62.7-64.4°C.

¹H NMR (400 MHz, Chloroform-d) δ 7.85 – 7.78 (m, 2H, Ar-H), 7.62 – 7.55 (m, 1H, Ar-H), 7.45 – 7.39 (m, 2H, Ar-H), 7.32 (d, J = 5.6 Hz, 1H, F-uracil vinyl-CH), 3.89 (dd, J = 8.0, 6.3 Hz, 1H, cyclopropane-CH), 3.68 (s, 3H, ester CH₃), 3.58 (s, 3H, ester CH₃), 2.09 (t, J = 6.5 Hz, 1H, cyclopropane-CH).

¹³C NMR (101 MHz, Chloroform-d) δ 167.1, 166.7, 156.0 (d, J = 27.2 Hz), 148.7, 139.7 (d, J = 240.3 Hz), 135.6, 130.8, 130.7, 129.2, 128.0 (d, J = 33.7 Hz), 53.3, 53.3, 42.9, 34.8, 20.3.

One C=O of methyl-ester is not resolved.

IR 3084 (w), 2953 (w), 1755 (m), 1717 (s), 1440 (m), 1296 (s), 1227 (s), 911 (m), 729 (s).

HRMS (ESI) calcd for C₁₈H₁₅FN₂NaO₇ [M+Na]+ 413.0755; found 413.0763.

The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number: CCDC 99618.

2.5 Dipolarophiles.
Triisopropyl((1-phenylvinyl)oxy)silane (17).

Following the reported procedure of Waser et al.,¹¹ acetophenone (16) (1.0 g, 8.3 mmol, 1 eq) was solubilized in DCM (8 mL) and triethylamine (1.73 mL, 12.5 mmol, 1.5 eq) was added at room temperature. Then at 0 ºC triisopropylsilyl trifluoromethanesulfonate (2.7 ml, 10 mmol, 1.2 eq) was added dropwise and the reaction mixture was stirred at room temperature for 8 h. The solvent was evaporated under a flow of nitrogen. The crude product was purified by column chromatography, eluting with pentane and NEt₃ 1% to obtain the pure enol-ether 17 (2.0 g, 7.2 mmol, 86% yield) as a colorless oil.

¹H NMR (400 MHz, Chloroform-d) δ 7.70 – 7.64 (m, 2H, Ar-H), 7.41 – 7.27 (m, 3H, Ar-H), 4.87 (d, J = 1.8 Hz, 1H, C=CH₂), 4.44 (d, J = 1.9 Hz, 1H, C=CH₂), 1.33 (m, 3H, TIPS-CH), 1.16 (m, 18H, TIPS-CH₃).
\(^{1}\text{H} \) NMR values correspond to the literature.\(^{[1]} \)

(Z)-Triisopropyl((1-phenylprop-1-en-1-yl)oxy)silane (47).

Following the reported procedure of Waser et al.\(^{[1]} \) propiophenone (46) (0.50 mL, 3.7 mmol, 1 eq) was solubilized in THF (15 mL) at -78°C and NaHMDS (2M solution in THF, 2.1 mL, 4.1 mmol, 1.1 eq) was added dropwise. The mixture was stirred 1 hour at room temperature and cooled down to -78 °C. TIPS-Cl (0.86 mL, 4.1 mmol, 1.1 eq) was added dropwise and the reaction mixture was stirred at room temperature for 8 h. The solvent was evaporated and the crude product was purified by column chromatography, eluting with pentane and NEt\(_3\) 1% to obtain the pure enol-ether 47 (0.46 g, 1.6 mmol, 43% yield) as a slightly yellow oil.

\(^{1}\text{H} \) NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 7.50 – 7.38 (m, 2H, Ar-H), 7.33 – 7.18 (m, 3H, Ar-H), 5.06 (q, \(J = 6.8\) Hz, 1H, C=C), 1.77 (d, \(J = 6.9\) Hz, 3H, CH\(_3\)), 1.15 – 0.97 (m, 21H, TIPS-CH\(_3\)).

\(^{1}\text{H} \) NMR values correspond to the literature.\(^{[1]} \)

((1-(4-Fluorophenyl)vinyl)oxy)triisopropylsilane (49).

Following the reported procedure of Waser et al.\(^{[1]} \) (4-fluorophenyl)ethanone (48) (0.44 mL, 3.6 mmol, 1 eq) was solubilized in THF (15 mL) at -78°C and NaHMDS (2M solution in THF, 2.1 mL, 4.1 mmol, 1.1 eq) was added dropwise. The mixture was stirred 1 hour at room temperature and cooled down to -78°C. TIPS-Cl (0.86 mL, 4.1 mmol, 1.1 eq) was added dropwise and the reaction mixture was stirred at room temperature for 8 h. The solvent was evaporated and the crude product was purified by column chromatography, eluting with pentane and NEt\(_3\) 1% to obtain the pure enol-ether 49 (0.62 g, 2.1 mmol, 58% yield) as a slightly yellow oil.

\(^{1}\text{H} \) NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 7.61 (dd, \(J = 8.9, 5.4\) Hz, 2H, Ar-H), 7.00 (t, \(J = 8.8\) Hz, 2H, Ar-H), 4.77 (d, \(J = 1.9\) Hz, 1H, C=CH), 4.39 (d, \(J = 1.9\) Hz, 1H, C=CH), 1.39 – 1.20 (m, 3H, TIPS-CH\(_3\)), 1.34-1.12 (m, 18H, TIPS-CH\(_3\)).

\(^{1}\text{H} \) NMR values correspond to the literature.\(^{[1]} \)

(E)-Triisopropyl((4-phenylbuta-1,3-dien-2-yl)oxy)silane (51).

Following the reported procedure of Waser et al.\(^{[1]} \) (E)-4-phenylbut-3-en-2-one (50) (0.42 g, 2.9 mmol, 1 eq) was solubilized in DCM (3 mL) and triethylamine (0.60 mL, 4.3 mmol, 1.5 eq) was added at room temperature. Then triisopropylsilyl trifluoromethanesulfonate (0.93 mL, 3.4 mmol, 1.2 eq) was added at 0 °C dropwise and the reaction mixture was stirred at room temperature for 8 h. The solvent was evaporated under a flow of nitrogen. The crude product was purified by column chromatography, eluting with pentane and NEt\(_3\) 1% to obtain the pure enol ether 51 (0.87 g, 2.9 mmol, quantitative yield) as a colorless oil.

RF (pentane) = 0.88.
\[^{1}\text{H NMR}\] (400 MHz, Chloroform-\(d\)) \(\delta\) 7.64 – 7.54 (m, 2H, Ar-H), 7.45 (m, 2H, Ar-H), 7.40 – 7.32 (m, 1H, Ar-H), 7.15 (d, \(J = 15.6\) Hz, 1H, C=CH), 6.74 (d, \(J = 15.7\) Hz, 1H, C=CH), 4.61 – 4.59 (s, 1H, C=CH\(_2\)), 4.58 (s, 1H, C=CH\(_2\)), 1.54 – 1.42 (m, 3H, TIPS-CH), 1.34 (d, \(J = 7.8\) Hz, 18H, TIPS-CH\(_3\)).

\[^{13}\text{C NMR}\] (101 MHz, Chloroform-\(d\)) \(\delta\) 155.6, 137.1, 129.4, 128.7, 127.8, 126.9, 126.7, 95.9, 18.3, 13.1.

IR 4319 (w), 4056 (w), 2945 (m), 2867 (m), 1638 (w), 1464 (m), 1327 (s), 1026 (s), 883 (s).

HRMS (ESI) calcd for C\(_{19}\)H\(_{31}\)OSi\(^{+}\) [M+H\(^+\)] 303.2139; found 303.2140.

3. Scope of the reaction.

3.1 From thymine cyclopropanes.

\((\text{Cis})\)-dimethyl 5-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenyldihydrofuran-3,3(2H)-dicarboxylate (8a)

Following the described procedure of Benfatti et al.\(^{[6]}\) a flame-dried microwave vial was loaded under nitrogen with FeCl\(_3\)-Al\(_2\)O\(_3\) (26 mg, 0.020 mmol, 5 mol %) and dimethyl 2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)cyclopropane-1,1-dicarboxylate (7a) (0.15 g, 0.39 mmol, 1.0 eq). Then, anhydrous DCM (1 mL) was added followed by benzaldehyde (0.059 mL, 0.58 mmol, 1.2 eq). The reaction mixture was stirred for 2 h at room temperature. After solvent removal under reduced pressure, the crude product was purified by column chromatography using a mixture of AcOEt/hexane (7:3) with 1% NEt\(_3\) as eluting solvent. The pure product 8a (0.15 g, 0.31 mmol, 80% yield) was obtained as a white solid.

RF (AcOEt/hex (3:7)) = 0.27.

MP 93.2-95.1 °C.

\[^{1}\text{H NMR}\] (400 MHz, Chloroform-\(d\)) \(\delta\) 8.07 (d, \(J = 1.4\) Hz, 1H, thymine vinyl-CH), 7.95 (dd, \(J = 8.4, 1.4\) Hz, 2H, Ar-H), 7.69 – 7.59 (m, 1H, Ar-H), 7.54 – 7.43 (m, 4H, Ar-H), 7.40 – 7.33 (m, 3H, Ar-H), 6.36 (t, \(J = 7.5\) Hz, 1H, tetrahydrofuran-NCH), 5.61 (s, 1H, tetrahydrofuran-CH), 3.80 (s, 3H, ester methyl), 3.15 (s, 3H, ester methyl), 2.99 (dd, \(J = 14.5, 7.4\) Hz, 1H, tetrahydrofuran-CH\(_2\)), 2.80 (dd, \(J = 14.6, 7.7\) Hz, 1H, tetrahydrofuran-CH\(_2\)), 2.10 (d, \(J = 1.2\) Hz, 3H, thymine methyl).

\[^{13}\text{C NMR}\] (101 MHz, Chloroform-\(d\)) \(\delta\) 169.8, 169.7, 168.8, 162.7, 149.5, 135.8, 135.2, 131.5, 130.5, 129.1, 128.8, 128.2, 126.5, 112.1, 82.5, 81.5, 63.8, 53.2, 52.8, 39.1, 13.0.

IR 2736 (w), 1729 (m), 1673 (m), 1438 (m), 1278 (s), 1047 (s), 758 (s).

HRMS (ESI) calcd for C_{26}H_{24}N_{2}NaO_{8}^{+} [M+Na]^{+} 515.1425; found 515.1435.

(Cis)-Dimethyl 5-(3-(4-(tert-butyl)benzyl)-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenylidhydrofuran-3,3(2H)-dicarboxylate (8b)

Following the described procedure of Benfatti et al.\[7\] a flame-dried microwave vial under nitrogen was loaded with FeCl_{3}-Al_{2}O_{3} (3.5 mg, 0.0035 mmol, 5 mol %) and dimethyl 2-(3-(4-(tert-butyl)benzyl)-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)cyclopropane-1,1-dicarboxylate (7b) (0.03 g, 0.07 mmol, 1.0 eq). Then, anhydrous dichloromethane (1 mL) followed by benzaldehyde (10 µl, 0.10 mmol, 1.5 eq) were added. The mixture was stirred for 2 h at room temperature. Afterwards, it was concentrated under reduced pressure with silica and NEt_{3} (0.3 mL). The dried residue was purified by column chromatography using a mixture of hexane/ethylacetate (7:3) with 1% NEt_{3} as eluting solvent. The pure product 8b (20 mg, 0.040 mmol, 55% yield) was obtained as a white solid.

RF (AcOEt/hex (3:7)) = 0.37.

{1H NMR (400 MHz, Chloroform-d) δ 7.87 (d, J = 1.6 Hz, 1H, thymine vinyl-CH), 7.47 – 7.39 (m, 4H, Ar-H), 7.37 – 7.28 (m, 5H, Ar-H), 6.40 (t, J = 7.6 Hz, 1H, tetrahydrofuran-NCH), 5.60 (s, 1H, tetrahydrofuran-OCH), 5.11 (s, 2H, benzylic-CH\textsubscript{2}), 3.80 (s, 3H, ester-methyl), 3.12 (s, 3H, ester methyl), 2.92 (dd, J = 14.5, 7.6 Hz, 1H, tetrahydrofuran-CH\textsubscript{2}), 2.76 (dd, J = 14.5, 7.5 Hz, 1H, tetrahydrofuran-CH\textsubscript{2}), 2.06 (d, J = 1.2 Hz, 3H, thymine-CH\textsubscript{3}), 1.28 (s, 9H, tBu).

{13C NMR (101 MHz, Chloroform-d) δ 170.0, 169.7, 163.3, 151.2, 150.5, 135.4, 133.9, 133.8, 129.02, 128.7, 128.1, 126.5, 125.3, 111.4, 82.3, 82.2, 63.8, 53.1, 52.7, 44.3, 39.1, 34.5, 31.3, 13.6.

IR 3694 (w), 2975 (s), 2892 (m), 1687 (s), 1393 (m), 1258 (s), 1071 (s), 889 (w).

HRMS (ESI) calcd for C_{30}H_{34}N_{2}NaO_{7}^{+} [M+Na]^{+} 557.2258; found 557.2266.

General procedures for annulation reaction

a) Conditions A

Dimethyl 2-(3-(tert-butoxycarbonyl)-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)cyclopropane-1,1-dicarboxylate (7c) (0.15 g, 0.40 mmol, 1.0 eq), aldehyde (0.48 mmol, 1.2 eq) and In(OTf)\textsubscript{3} (0.045 g, 0.080 mmol, 0.2 eq) were stirred under nitrogen in a flame-dried sealed microwave vial with anhydrous DCM (2.0 mL) at room temperature for 2 h. Then, NEt\textsubscript{3} (0.9 mL) was added to quench the reaction and the crude mixture was concentrated under reduced pressure. After a rapid filtration on a silica plug with AcOEt and removal of the
solvent, the crude product was heated at 70 °C in EtOH (3 mL) in a sealed microwave vial for 18 h. The mixture was concentrated under reduced pressure and purified by column chromatography with a gradient mixture of pentane/AcOEt from 7:3 up to 1:1 and the column was washed with straight AcOEt.

b) Conditions B

**Dimethyl 2-(3-(tert-butoxycarbonyl)-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)cyclopropane-1,1-dicarboxylate (7c)** (0.15 g, 0.40 mmol 1.0 eq) and the ketone or silylenol ether (0.48 mmol, 1.2 eq) were stirred under nitrogen in a flame-dried sealed microwave vial with anhydrous DCM (2.0 mL) and cooled down to -20 °C. Then, a 0.43 M tin(IV) chloride solution (0.09 mL, 0.04 mmol, 0.1 eq) was added and the reaction mixture was stirred for 2 h at -20 °C. NEt$_3$ (0.9 mL) was added at -20 °C to quench the reaction and the reaction mixture was allowed to reach room temperature. The crude mixture was concentrated under reduced pressure. After a rapid filtration on a silica plug with AcOEt and removal of the solvent, the crude product was heated at 70 °C in EtOH (3 mL) in a sealed microwave vial for 18 h. The mixture was concentrated under reduced pressure and purified by column chromatography with a gradient mixture of pentane/AcOEt from 7:3 up to 1:1 and the column was washed with straight AcOEt.

**Dimethyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenyldihydrofuran-3,3(2H)-dicarboxylate (8c).**

Following the conditions A, using benzaldehyde (0.051 g, 0.48 mmol, 1.2 eq), the pure product 8c (0.14 g, 0.35 mmol, 87% yield) was obtained as a white foamy solid.

**RF (pent/AcOEt (1:1)) = 0.64.**

**MP 206.9-208.1 °C.**

$^1$H NMR (400 MHz, Chloroform-d) δ 8.47 (s, 1H, thymine NH), 7.94 (d, $J = 1.6$ Hz, 1H, thymine vinyl-CH), 7.48 – 7.40 (m, 2H, Ar-H), 7.40 – 7.27 (m, 3H, Ar-H), 6.37 (t, $J = 7.6$ Hz, 1H, tetrahydrofuran-NCH), 5.61 (s, 1H, tetrahydrofuran-CH), 3.81 (s, 3H, ester methyl), 3.13 (s, 3H, ester methyl), 2.95 (dd, $J = 14.5$, 7.6 Hz, 1H, tetrahydrofuran-CH$_2$), 2.78 (dd, $J = 14.5$, 7.7 Hz, 1H, tetrahydrofuran-CH$_2$), 2.06 (d, $J = 1.3$ Hz, 3H, thymine methyl).

$^{13}$C NMR (101 MHz, Chloroform-d) δ 169.9, 169.8, 163.3, 150.4, 135.9, 135.3, 128.7, 128.1, 126.5, 112.1, 82.4, 81.4, 63.8, 53.1, 52.7, 39.0, 12.8.

**IR** 3192 (w), 3069 (w), 1729 (s), 1695 (s), 1512 (m), 1281 (s), 1225 (m), 1094 (m), 1054 (m), 915 (m).

**HRMS (ESI)** calcd for C$_{19}$H$_{20}$N$_2$NaO$_7$ $^{[M+Na]^+}$ 411.1163; found 411.1168.

**Dimethyl-2-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenyldihydrofuran-3,3(2H)-dicarboxylate (8d).**
Following the conditions B, using acetophenone (16) (0.058 g, 0.48 mmol, 1.2 eq), the pure product 8d (0.15 g, 0.38 mmol, 94% yield) was obtained as a white solid.

RF (AcOEt/pent (1:1)) = 0.36.

MP 246.8-247.3°C.

$^1$H NMR (400 MHz, Chloroform-$d$) δ 8.59 (s, 1H, thymine NH), 8.18 (d, $J = 1.7$ Hz, 1H, thymine vinyl-CH), 7.72 – 7.65 (m, 2H, Ar-H), 7.38 – 7.24 (m, 3H, Ar-H), 6.43 (dd, $J = 8.2$, 5.6 Hz, 1H, tetrahydrofuran-NCH), 3.79 (s, 3H, ester methyl), 3.16 (s, 3H, ester methyl), 3.11 (dd, $J = 15.0$, 8.2 Hz, 1H, tetrahydrofuran-CH$_2$) 2.77 (dd, $J = 14.9$, 5.5 Hz, 1H, tetrahydrofuran-CH$_2$) 2.04 (d, $J = 1.3$ Hz, 3H, thymine methyl), 1.86 (s, 3H, tetrahydrofuran methyl).

$^{13}$C NMR (101 MHz, Chloroform-$d$) δ 170.4, 168.8, 163.6, 150.7, 140.5, 136.9, 127.9, 127.8, 125.8, 110.9, 88.0, 80.7, 67.1, 52.8, 52.6, 39.6, 25.7, 12.8.

IR 1733 (m), 1706 (m), 1663 (m), 1580 (m), 1512 (m), 1461 (m), 1452 (m), 1351 (w), 1272 (s), 1207 (w), 1126 (w), 1077 (w).

HRMS (ESI) calcd for C$_{20}$H$_{22}$NNaO$_7$ $^+$ [M+Na$^+$] 425.1319; found 425.1320.

Dimethyl-2-(4-fluorophenyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)dihydrofuran-3(2H)-dicarboxylate (8e).

Following the conditions A, using 4-fluorobenzaldehyde (0.060 g, 0.48 mmol, 1.2 eq), the pure product 8e (0.13 g, 0.32 mmol, 79% yield) was obtained as a slightly yellow solid.

RF (pent/AcOET (1:1)) = 0.63.

MP 218.8-220.3°C.

$^1$H NMR (400 MHz, Chloroform-$d$) δ 8.54 – 8.46 (m, 1H, thymine NH), 7.93 (d, $J = 1.5$ Hz, 1H, thymine vinyl-CH), 7.49 – 7.39 (m, 2H, Ar-H), 7.10 – 6.99 (m, 2H, Ar-H), 6.37 (t, $J = 7.6$ Hz, 1H, tetrahydrofuran-NCH), 5.56 (s, 1H, tetrahydrofuran-CH), 3.81 (s, 3H, ester methyl), 3.20 (s, 3H, ester methyl), 2.93 (dd, $J = 14.6$, 7.5 Hz, 1H, tetrahydrofuran-CH$_2$), 2.77 (dd, $J = 14.6$, 7.8 Hz, 1H, tetrahydrofuran-CH$_2$) 2.05 (d, $J = 1.2$ Hz, 3H, thymine methyl).

$^{13}$C NMR (101 MHz, Chloroform-$d$) δ 169.8, 162.9 (d, $J = 249$ Hz), 150.4, 135.8, 131.0 (d, $J = 3.2$ Hz), 128.5 (d, $J = 8.2$ Hz), 128.4, 115.2 (d, $J = 21.6$ Hz), 115.0, 112.2, 81.7, 81.2, 63.6, 53.2, 52.9, 38.8, 12.8.
IR 3192 (w), 3069 (w), 1729 (s), 1695 (s), 1512 (m), 1281 (s), 1225 (m), 1094 (m), 1054 (m), 915 (m).

HRMS (ESI) calcd for $C_{19}H_{19}FN_2NaO_7^+$ [M+Na]$^+$ 429.1068; found 429.1055.

The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number: CCDC 995573.

Dimethyl 2-isopropyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)dihydrofuran-3,3(2H)-dicarboxylate (8f).

Following the conditions A, using isobutyraldehyde (0.035 g, 0.48 mmol, 1.2 eq), the pure product 8f (0.11 g, 0.30 mmol, 75% yield) was obtained as a colorless foam.

RF (AcOEt/pent (1:1)) = 0.42.

MP 157.7-160.8 °C.

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 9.45 (s, 1H, N-H), 7.62 (d, $J = 1.5$ Hz, 1H, thymine vinyl-CH), 6.12 (t, $J = 7.1$ Hz, 1H, tetrahydrofuran-NCH), 4.14 (d, $J = 7.8$ Hz, 1H, tetrahydrofuran-OCH), 3.80 (s, 3H, ester methyl), 3.78 (s, 3H, ester methyl), 2.70 (dd, $J = 14.5$, 6.5 Hz, 1H, tetrahydrofuran-CH$_2$), 2.63 (dd, $J = 14.5$, 7.6 Hz, 1H, tetrahydrofuran-CH$_2$), 1.98 (d, $J = 1.3$ Hz, 3H, thymine methyl), 1.92 (dt, $J = 13.7$, 7.0 Hz, 1H, iso-propyl C-H), 1.03 (t, $J = 6.8$ Hz, 6H, iso-propyl CH$_3$).

$^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 170.5, 170.1, 163.9, 150.7, 135.9, 111.1, 87.2, 81.4, 60.6, 53.0, 41.3, 30.0, 20.1, 19.5, 12.7.

IR 3194 (w), 2960 (w), 2929 (w), 1730 (s), 1683 (s), 1468 (m), 1436 (m), 1275 (s), 1237 (m), 1205 (m), 1081 (m), 916 (m), 733 (s).

HRMS (ESI) calcd for $C_{16}H_{25}N_2O_7^+$ [M+H]$^+$ 355.1500; found 355.1502.
Dimethyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-((E)-styryl)dihydrofuran-3,3(2H)-dicarboxylate. (8g)

Following the conditions A, using cinnamaldehyde (0.063 g, 0.48 mmol, 1.2 eq), a mixture of diastereoisomers (5:1 by integration of methyl esters at 3.76 ppm and 3.71 ppm) 8g (0.16 g, 0.28 mmol, 96% yield) was obtained as a colorless foam.

RF (pent/AcOET (1:1)) = 0.67

$^1$H NMR (400 MHz, Chloroform-d) δ 8.82 (s, 1H, NH), 7.70 (d, $J = 1.3$ Hz, 1H, thymine vinyl-CH, major diastereoisomer), 7.35 – 7.17 (m, 10H, Ar-H, both diastereoisomers), 7.14 (d, $J = 1.3$ Hz, 1H, thymine vinyl-CH, minor diastereoisomer), 6.20 (t, $J = 7.3$ Hz, 1H, tetrahydrofuran-NCH, major diastereoisomer), 6.16-6.05 (m, 2H, vinyl C-H and tetrahydrofuran-NCH, minor diastereoisomer), 6.11(dd, $J = 16.0, 6.2$ Hz, 1H, vinyl C-H, major diastereoisomer), 5.49 (dd, $J = 6.2, 1.4$ Hz, 1H, tetrahydrofuran-CH$_2$, minor diastereoisomer), 5.04 (dd, $J = 6.3, 1.4$ Hz, 1H, tetrahydrofuran-CH$_2$, major diastereoisomer), 3.76 (s, 3H, ester methyl, major diastereoisomer), 3.71 (s, 3H, ester methyl, minor diastereoisomer), 3.59 (s, 6H, ester methyl, minor and major diastereoisomers), 3.24 (dd, $J = 14.3, 6.8$ Hz, 1H, tetrahydrofuran-CH$_2$, minor diastereoisomer), 2.82 – 2.69 (m, 2H, tetrahydrofuran-CH$_2$, major diastereoisomer), 2.58 (dd, $J = 14.3, 5.4$ Hz, 1H, tetrahydrofuran-CH$_2$, minor diastereoisomer), 1.93 (d, $J = 1.3$ Hz, 3H, thymine methyl, major diastereoisomer), 1.88 (d, $J = 1.2$ Hz, 3H, thymine methyl minor diastereoisomer).

$^{13}$C NMR (101 MHz, Chloroform-d) δ 169.6, 169.5, 169.1, 169.1, 168.1, 163.6, 150.5, 150.1, 135.9, 133.7, 133.2, 128.7, 128.4, 128.3, 126.7, 126.7, 123.1, 122.3, 111.7, 110.7, 83.8, 82.2, 81.5, 64.1, 62.8, 53.3, 53.2, 53.1, 39.7, 38.9, 12.8, 12.6.

One carbon of the major diastereoisomer in the aromatic region is unresolved. Six carbons of the minor diastereoisomer are unresolved.

IR 3201 (w), 3073 (w), 2953 (w), 1731 (s), 1688 (s), 1534 (m), 1468 (m), 1435 (m), 1284 (s), 1085 (s), 972 (m), 913 (m), 734 (s).

HRMS (ESI) calcd for C$_{21}$H$_{23}$N$_2$O$_7$ $[M+H]^+$ 415.1500; found 415.1502.

Dimethyl-2-(4-fluorophenyl)-2-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)dihydrofuran-3,3(2H)-dicarboxylate (8h).

Following the conditions B, using 4-fluoroacetophenone (48) (0.067 g, 0.48 mmol, 1.2 eq), the pure product 8h (0.16 g, 0.37 mmol, 93% yield) was obtained as a white solid.
RF (AcOEt/pent (1:1)) = 0.40.

MP 248.8-250.2 °C.

$^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.47 (s, 1H, thymine NH), 8.07 (d, $J = 1.5$ Hz, 1H, thymine vinyl-CH), 7.70 – 7.60 (m, 2H, Ar-H), 7.20 (t, $J = 8.9$ Hz, 2H, Ar-H), 6.36 (dd, $J = 8.3$, 5.5 Hz, 1H, tetrahydrofuran-NCH), 3.75 (s, 3H, ester methyl), 3.26 (dd, $J = 14.9$, 8.3 Hz, 1H, tetrahydrofuran-CH$_2$), 3.13 (s, 3H, ester methyl), 2.71 (dd, $J = 14.9$, 5.6 Hz, 1H, tetrahydrofuran-CH$_2$), 1.87 (d, $J = 1.2$ Hz, 3H, thymine methyl), 1.79 (s, 3H, tetrahydrofuran methyl).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 170.6, 168.9, 164.1, 161.9 (d, $J = 243.9$ Hz), 151.1, 137.4 (d, $J = 3.0$ Hz), 136.7, 128.4 (d, $J = 8.2$ Hz), 114.9 (d, $J = 21.3$ Hz), 109.9, 87.1, 80.6, 67.2, 53.3, 53.0, 38.5, 25.9, 13.2.

IR 3221 (w), 3072 (w), 2948 (w), 1513 (m), 1439 (w), 1269 (s), 1128 (m), 1077 (m), 964 (w), 913 (m), 842 (m).

HRMS (ESI) calcd for C$_{20}$H$_{22}$N$_2$O$_7$ $[M+H]^+$ 421.1406; found 421.1405.

Dimethyl-2-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenethylidihydrofuran-3,3(2H)-dicarboxylate (8i).

Following the conditions B, using 4-phenylbutan-2-one (0.071 g, 0.48 mmol, 1.2 eq), the pure product 8i (0.15 g, 0.34 mmol, 85% yield) was obtained as a slightly yellow solid.

MP 167.9-168.7 °C.

RF (pent/AcOET (1:1)) = 0.19.

$^1$H NMR (400 MHz, Chloroform-$d$) δ 8.07 (s, 1H, thymine NH), 7.74 (q, $J = 1.2$ Hz, 1H, thymine vinyl-CH), 7.30 (dd, $J = 8.5$, 6.6 Hz, 2H, Ar-H), 7.24 – 7.17 (m, 3H, Ar-H), 6.18 (dd, $J = 7.7$, 5.3 Hz, 1H, tetrahydrofuran-NCH), 3.78 (s, 3H, ester methyl), 3.72 (s, 3H, ester methyl), 3.23 – 3.05 (m, 1H, tetrahydrofuran-CH$_2$), 2.92 – 2.69 (m, 2H, benzylidene-CH$_2$), 2.54 (dd, $J = 15.0$, 5.4 Hz, 1H, tetrahydrofuran-CH$_2$), 2.28 (ddd, $J = 13.7$, 11.7, 6.0 Hz, 1H, CH$_2$), 2.00 – 1.90 (m, 4H, thymine methyl and CH$_2$), 1.47 (s, 3H, tetrahydrofuran methyl).

$^{13}$C NMR (101 MHz, Chloroform-$d$) δ 170.5, 168.9, 163.5, 150.3, 141.5, 136.6, 128.5, 128.3, 126.1, 110.2, 87.0, 82.0, 66.2, 53.1, 52.9, 4.5, 38.8, 30.3, 21.9, 12.7.

IR 3193 (w), 3060 (w), 2957 (w), 1735 (s), 1692 (s), 1468 (m), 1266 (s), 1097 (m), 914 (m).

HRMS (ESI) calcd for C$_{22}$H$_{27}$N$_2$O$_7^+ [M+H]^+$ 431.1813; found 431.1802.

The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number: CCDC 994735.
Dimethyl 2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-1-oxaspiro[4.5]decane-4,4-dicarboxylate. (8j)

Following the conditions B, using cyclohexanone (0.047 g, 0.48 mmol, 1.2 eq), the pure product 8j (0.15 g, 0.39 mmol, 97% yield) was obtained as a colorless foamy solid.

RF (AcOEt/pent (1:1)) = 0.3.

MP 184.1-185.6 °C.

$^1$H NMR (400 MHz, Chloroform-d) δ 8.25 – 8.08 (br s, 1H, thymine NH), 7.70 (d, J = 1.5 Hz, 1H, thymine vinyl-CH), 6.03 (dd, J = 7.6, 5.2 Hz, 1H, tetrahydrofuran-NCH), 3.71 (s, 3H, ester methyl), 3.68 (s, 3H, ester methyl), 3.11 (dd, J = 14.9, 7.6 Hz, 1H, tetrahydrofuran-CH$_2$), 2.39 (dd, J = 14.9, 5.3 Hz, 1H, tetrahydrofuran-CH$_2$), 1.91 (d, J = 1.2 Hz, 3H, thymine methyl), 1.75 – 1.47 (m, 8H, cyclohexane C-H), 1.22 – 1.12 (m, 2H, cyclohexane C-H).

$^{13}$C NMR (101 MHz, Chloroform-d) δ 170.3, 168.7, 163.6, 150.3, 136.6, 109.9, 87.2, 82.0, 65.8, 52.9, 52.8, 39.6, 32.4, 31.2, 25.0, 22.7, 21.5, 12.7.

IR 3210 (w), 2931 (w), 2856 (w), 1733 (m), 1687 (s), 1437 (w), 1268 (m), 1201 (w), 1095 (m), 911 (m), 729 (s).

HRMS (ESI) calcd for C$_{18}$H$_{26}$N$_2$NaO$_7$ [M+Na]$^+$ 403.1481; found 403.1488.

Dimethyl 2-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-((E)-styryl)dihydrofuran-3,3(2H)-dicarboxylate. (8k)

Following the conditions B, using (E)-4-phenylbut-3-en-2-one (50) (0.070 g, 0.48 mmol, 1.2 eq), a mixture of unseparable diastereoisomers (ratio 2:1 obtained by integration of methyl
esters at 3.64 ppm and 3.55 ppm \(8k\) (0.14 g, 0.34 mmol, 79% yield) was obtained as a colorless foam.

**RF** (pent/AcOET (1:1)) = 0.4

**\(^1\)H NMR** (400 MHz, Chloroform-\(d\)) \(\delta\) 9.19 (br.s, 1H, N-H), 7.84 (d, \(J = 1.3\) Hz, 1H, thymine vinyl-CH, major diastereoisomer), 7.59 (d, \(J = 1.3\) Hz, 1H, thymine vinyl-CH, minor diastereoisomer), 7.36 – 7.16 (m, 5H, Ar-H), 6.69 (d, \(J = 15.9\) Hz, 1H, vinyl C-H, minor diastereomer), 6.65 (d, \(J = 16.1\) Hz, 1H, vinyl C-H, major diastereomer), 6.39 (d, \(J = 16.1\) Hz, 1H, vinyl C-H, major diastereomer), 6.32 (d, \(J = 16.0\) Hz, 1H, vinyl C-H, minor diastereomer), 6.25 (m, 1H, tetrahydrofuran-NCH, major and minor diastereoisomers), 3.75 (s, 3H, ester methyl, major diastereoisomer), 3.72 (s, 3H, ester methyl, minor diastereoisomer), 3.64 (s, 3H, ester methyl, minor diastereoisomer), 3.55 (s, 3H, ester methyl, major diastereoisomer), 3.13 (dd, \(J = 14.7, 7.1\) Hz, 1H, tetrahydrofuran-CH\(_2\), minor diastereoisomer), 3.09 (dd, \(J = 14.9, 7.8\) Hz, 1H, tetrahydrofuran-CH\(_2\), major diastereoisomer), 2.57 (dd, \(J = 14.9, 5.5\) Hz, 1H, tetrahydrofuran-CH\(_2\), major diastereoisomer), 2.51 (dd, \(J = 14.8, 5.6\) Hz, 1H, tetrahydrofuran-CH\(_2\), minor diastereoisomer), 1.91 (d, \(J = 1.2\) Hz, 3H, thymine methyl, major diastereoisomer), 1.89 (d, \(J = 1.2\) Hz, 3H, thymine methyl, minor diastereoisomer), 1.61 (s, 3H, tetrahydrofuran methyl, minor diastereoisomer), 1.52 (s, 3H, tetrahydrofuran methyl, major diastereoisomer).

**\(^{13}\)C NMR** (101 MHz, Chloroform-\(d\)) \(\delta\) 169.9, 169.4, 168.7, 168.5, 164.1, 164.0, 150.8, 150.5, 136.7, 136.2, 136.0, 130.1, 129.8, 128.8, 128.7, 128.7, 128.1, 126.7, 126.6, 110.4, 109.8, 87.6, 86.4, 84.5, 82.2, 66.5, 66.4, 53.1, 53.1, 53.0, 39.6, 38.9, 24.9, 24.1, 12.8, 12.7. 3 carbons are unresolved.

**IR** 3180 (w), 3044 (w), 1736 (s), 1688 (s), 1458 (w), 1258 (s), 1076 (w), 733 (s).

**HRMS (ESI)** calcd for C\(_{22}\)H\(_{25}\)N\(_2\)O\(_7\) \([M+H]^+\) 429.1656; found 429.1660.

**Dimethyl-4-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenyl-2-((triisopropylsilyl)oxy)cyclopentane-1,1-dicarboxylate. \(9a\)**

Following the conditions B, using TIPS protected acetophenone \(17\) (0.17 g, 0.60 mmol, 1.5 eq), the pure product \(9a\) (0.19 g, 0.33 mmol, 84% yield) was obtained as a white crystalline solid.

**RF** (pent/AcOET (1:1)) = 0.56.

**MP** 81.8-83.2 °C.

**\(^1\)H NMR** (400 MHz, Chloroform-\(d\)) \(\delta\) 8.40 (s, 1H, thymine N-H), 7.86 (d, \(J = 1.6\) Hz, 1H, thymine vinyl-CH), 7.82 – 7.74 (m, 2H, Ar-H), 7.34 – 7.27 (m, 3H, Ar-H), 5.70 (ddd, \(J = 11.4, 9.3, 5.7\) Hz, 1H, cyclopentane-NCH), 3.76 (s, 3H, ester methyl), 3.29 (m, 4H, ester methyl and cyclopentane-CH\(_2\)), 3.18 (t, \(J = 12.4\) Hz, 1H, cyclopentane-CH\(_2\)), 2.52 (dd, \(J = 12.8, 6.8\) Hz, 1H, cyclopentane-CH\(_2\)), 2.36 (dd, \(J = 15.0, 7.3\) Hz, 1H, cyclopentane-CH\(_2\)), 2.00 (d, \(J = 1.2\) Hz, 3H, thymine methyl), 1.03 – 0.97 (m, 11H, TIPS), 0.97 – 0.90 (m, 10H, TIPS).

**\(^{13}\)C NMR** (101 MHz, Chloroform-\(d\)) \(\delta\) 172.6, 168.1, 163.5, 151.1, 139.9, 137.3, 128.4, 128.1, 127.4, 111.5, 88.3, 70.3, 52.7, 52.3, 51.5, 43.4, 38.2, 18.2, 13.8, 12.8.
IR 2950 (w), 2868 (w), 1681 (s), 1467 (m), 1434 (w), 1392 (w), 1259 (s), 1135 (m), 1090 (m).

HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{42}\text{N}_2\text{NaO}_7\text{Si}^+$ $[\text{M+Na}]^+$ 581.2653; found 581.2660.

The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number: **CCDC 994948**

Dimethyl-2-(4-fluorophenyl)-4-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-((triisopropylsilyl)oxy)cyclopentane-1,1-dicarboxylate. (9b)

Following the conditions B, using ((1-(4-fluorophenyl)vinyl)oxy)triisopropylsilane (49) (0.14 g, 0.48 mmol, 1.2 eq), the pure product 9b (0.18 g, 0.32 mmol, 80% yield) was obtained as a white foamy solid.

MP 105.6-106.7 °C.

RF (pent/AcOET (1:1)) = 0.45.

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.14 (d, $J = 3.8$ Hz, 1H, thymine-NH), 7.89 – 7.78 (m, 3H, Ar-H and thymine vinyl-CH), 7.03 (t, $J = 8.7$ Hz, 2H, Ar-H), 5.71 (tt, $J = 11.4$, 7.0 Hz, 1H, cyclopentane-NCH), 3.79 (s, 3H, methyl ester), 3.37 (s, 3H, ester methyl), 3.36 – 3.31 (m, 1H, cyclopentane-CH$_2$), 3.19 (t, $J = 12.3$ Hz, 1H, cyclopentane-CH$_2$), 2.54 (dd, $J = 12.8$, 6.8 Hz, 1H, cyclopentane-CH$_2$), 2.38 (dd, $J = 15.1$, 7.2 Hz, 1H, cyclopentane-CH$_2$), 2.03 (d, $J = 1.2$ Hz, 3H, thymine methyl), 1.39 – 1.23 (m, 3H, TIPS), 1.09 – 0.85 (m, 18H, TIPS).

$^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 172.6, 168.1, 162.7 (d, $J = 246.7$ Hz), 163.3, 151.0, 137.2, 135.9 (d, $J = 3.2$ Hz), 130.2 (d, $J = 8.1$ Hz), 114.2 (d, $J = 21.3$ Hz), 111.6, 87.7, 70.2, 52.8, 52.4, 51.4, 43.5, 38.1, 18.2, 13.8, 12.8.

IR 3196 (w), 2951 (w), 2869 (w), 1681 (s), 1513 (w), 1466 (w), 1260 (m), 1098 (m), 911 (m), 731 (s).

HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{42}\text{N}_2\text{O}_7\text{Si}^+$ $[\text{M+H}]^+$ 577.2740; found 577.2719.
Dimethyl-3-methyl-4-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenyl-2-((triisopropylsilyl)oxy)cyclopentane-1,1-dicarboxylate. (9c)

Following the conditions B, using triisopropyl((1-phenylprop-1-en-1-yl)oxy)silane (47) (0.14 g, 0.48 mmol, 1.2 eq), the pure product 9c (0.18 g, 0.32 mmol, 79% yield) was obtained as a shiny foamy solid. The stereochemistry of the methyl was determined by NOE experiments.

RF (pent/AcOET (1:1)) = 0.48.

MP 127.4-128.3 °C.

$^1$H NMR (400 MHz, Chloroform-d) δ 8.06 (s, 1H, thymine NH), 8.01 (d, $J = 1.5$ Hz, 1H, thymine vinyl-CH), 7.73 – 7.66 (m, 2H, Ar-H), 7.39 – 7.25 (m, 3H, Ar-H), 5.36 (td, $J = 11.4$, 6.8 Hz, 1H, tetrahydrofuran-CH), 3.70 (s, 3H, ester methyl), 3.35 (dq, $J = 13.6$, 6.8 Hz, 1H, cyclopentane-CH), 3.20 (s, 3H, ester methyl), 3.12 (dd, $J = 15.1$, 11.3 Hz, 1H, cyclopentane-CH$_2$), 2.33 (dd, $J = 15.1$, 6.8 Hz, 1H, cyclopentane-CH$_2$), 2.02 (d, $J = 1.2$ Hz, 3H, thymine methyl), 1.56 (s, 3H, cyclopentane methyl), 1.24 (hept, $J = 7.3$ Hz, 3H, TIPS), 1.12 – 0.94 (m, 18H, TIPS).

$^{13}$C NMR (101 MHz, Chloroform-d) δ 172.7, 168.1, 163.3, 151.5, 138.6, 137.5, 128.3, 128.2, 127.4, 111.6, 90.9, 70.4, 56.7, 52.8, 45.2, 35.8, 18.9, 18.8, 15.2, 12.9, 10.6.

IR (w), 3175 (w), 2963 (w), 2870 (w), 1679 (m), 1468 (w), 1257 (m), 1079 (m), 1026 (m), 910 (m), 731 (s).

HRMS (ESI) calcd for $C_{30}H_{45}N_2O_7Si^+ [M+H]^+$ 573.2991; found 573.2992.

Dimethyl 4-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-((E)-styryl)-2-((triisopropylsilyl)oxy)cyclopentane-1,1-dicarboxylate. (9d)

Following the conditions B, using (E)-triisopropyl((4-phenylbuta-1,3-dien-2-yl)oxy)silane (52) (0.15 g, 0.48 mmol, 1.2 eq), a mixture of unseparable diastereoisomers (ratio 13:1 by integration of the NC-H proton at 5.64 ppm and 4.88 ppm) 9d (0.13 g, 0.22 mmol, 55% yield) was obtained as a colorless foam.

RF (pent/AcOET (1:1)) = 0.54
$^1$H NMR (400 MHz, Chloroform-$d$, Major diastereoisomer) $\delta$ 8.58 (s, 1H, N-H), 7.77 (d, $J = 1.1$ Hz, 1H, thymine vinyl-CH), 7.34 – 7.21 (m, 5H, Ar-H), 6.85 (d, $J = 16.6$ Hz, 1H, vinyl C-H), 6.43 (d, $J = 16.5$ Hz, 1H, vinyl C-H), 5.64 (tt, $J = 11.5$, 6.8 Hz, 1H, cyclopentane-NCH), 3.74 (s, 3H, ester methyl), 3.52 (s, 3H, ester methyl), 3.23 (dd, $J = 15.1$, 11.3 Hz, 1H, cyclopentane-CH$_2$), 2.82 (t, $J = 12.1$ Hz, 1H cyclopentane -CH$_2$), 2.17 (dd, $J = 15.1$, 6.5 Hz, 1H, cyclopentane -CH$_2$), 1.92 (d, $J = 1.2$ Hz, 3H, thymine methyl), 1.18 (m, $J = 1.5$ Hz, 3H, TIPS), 1.01 (d, $J = 2.5$ Hz, 12H, TIPS), 0.96 (dd, $J = 3.4$, 1.8 Hz, 6H, TIPS).

$^{13}$C NMR (101 MHz, Chloroform-$d$, Major diastereoisomer) $\delta$ 172.4, 168.8, 163.7, 151.1, 137.6, 136.1, 130.7, 128.8, 128.8, 128.2, 126.7, 111.5, 86.7, 69.9, 53.1, 52.6, 51.4, 41.1, 37.1, 29.7, 18.2, 18.0, 13.1, 12.8.

TIPS methyls are giving 2 different signals (18.2 and 18.0).

IR 2947 (w), 2868 (w), 1689 (m), 1465 (w), 1435 (w), 1260 (m), 1088 (w), 911 (m), 732 (s).

HRMS (ESI) calcd for C$_{31}$H$_{45}$N$_2$O$_7$Si$^+$ [M+H]$^+$ 585.2991; found 585.3015.

3.2 From uracil cyclopropane.

Dimethyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenylidihydrofuran-3,3(2H)-dicarboxylate (18a).

Following the conditions A, using benzaldehyde (0.051 g, 0.48 mmol, 1.2 eq) and the corresponding cyclopropane 41 (0.15 g, 0.40 mmol, 1 eq), the pure product 18a (0.093 g, 0.25 mmol, 62% yield) was obtained as a white powder.

RF (AcOEt) = 0.65.

MP 209.0-210.7°C.

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 9.07 (s, 1H, NH), 8.05 (d, $J = 8.2$ Hz, 1H, uracil CH), 7.42 – 7.29 (m, 2H, Ar-H), 7.24 (m, 3H, Ar-H), 6.29 (t, $J = 7.4$ Hz, 1H, tetrahydrofuran N-CH), 5.84 (d, $J = 8.1$ Hz, 1H, uracil CH), 5.52 (s, 1H, tetrahydrofuran-CH), 3.72 (s, 3H, ester CH$_3$), 3.03 (s, 3H, ester CH$_3$), 2.83 (dd, $J = 14.7$, 7.2 Hz, 1H, tetrahydrofuran-CH$_2$), 2.73 (dd, $J = 14.7$, 7.8 Hz, 1H, tetrahydrofuran-CH$_2$).

$^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 170.0, 169.7, 163.0, 150.5, 140.4, 135.1, 128.8, 128.1, 126.5, 103.6, 82.6, 81.6, 63.8, 53.2, 52.8, 39.4.

IR 3100 (w), 2968 (w), 1727 (s), 1694 (s), 1459 (m), 1275 (s), 1077 (s), 1052 (s), 730 (s).

HRMS (ESI) calcd for C$_{18}$H$_{18}$N$_2$O$_7$Na$^+$ [M+Na]$^+$ 397.1006; found 397.1004.

Dimethyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methyl-2-phenylidihydrofuran-3,3(2H)-dicarboxylate (18b).
Following the conditions B, using acetophenone (16) (0.058 g, 0.48 mmol, 1.2 eq) and the cyclopropane 41 (0.16 g, 0.40 mmol, 1 eq), the pure product 18b (0.12 g, 0.30 mmol, 76% yield) was obtained as a white powder.

RF (AcOEt/pent (1:1)) = 0.2.

MP 235.8-238.4°C.

$^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.44 (s, 1H, NH), 8.18 (d, $J = 8.2$ Hz, 1H, uracil CH), 7.71 – 7.51 (m, 2H, ArH), 7.46 – 7.23 (m, 3H, ArH), 6.29 (dd, $J = 8.2, 5.1$ Hz, 1H, tetrahydrofuran N-CH), 5.81 (dd, $J = 8.2, 2.2$ Hz, 1H, uracil CH), 3.72 (s, 3H, ester CH$_3$), 3.27 (dd, $J = 14.8, 8.2$ Hz, 1H, tetrahydrofuran-CH$_2$), 3.03 (s, 3H, ester CH$_3$), 2.67 (dd, $J = 14.8, 5.2$ Hz, 1H, tetrahydrofuran-CH$_2$), 1.80 (s, 3H, tetrahydrofuran-CH$_3$).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 170.6, 168.8, 163.6, 151.1, 141.1, 141.1, 128.2, 126.0, 102.3, 87.9, 81.2, 67.0, 53.2, 52.9, 25.8.

Two carbons are unresolved.

IR 3163 (w), 3035 (w), 2953 (w), 2838 (w), 1735 (s), 1733 (s), 1673 (s), 1436 (m), 1385 (m), 1263 (s), 1210 (s), 1072 (s), 767 (s).

HRMS (ESI) calcld for C$_{19}$H$_{20}$N$_2$NaO$_7$+ [M+Na]$^+$ 411.1163; found 411.1168.

Dimethyl-4-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenyl-2-((triisopropylsilyl)oxy)cyclopentane-1,1-dicarboxylate (19).

Following the conditions B, using TIPS protected acetophenone 17 (0.17 g, 0.60 mmol, 1.5 eq) and the cyclopropane 41 (0.16 g, 0.40 mmol, 1 eq), the pure product 19 (0.18 g, 0.33 mmol, 81% yield) was obtained as a colorless foam.

RF (AcOEt/pent (1:1)) = 0.5.

MP 67.7-77.0°C.

$^1$H NMR (400 MHz, Chloroform-$d$) δ 9.92 (s, 1H, NH), 8.11 (d, $J = 8.1$ Hz, 1H, uracil CH), 7.85 – 7.65 (m, 2H, ArH), 7.30 (m, 3H, ArH), 5.86 (dd, $J = 8.1, 2.2$ Hz, 1H, uracil CH), 5.74 (tt, $J = 11.3, 7.0$ Hz, 1H, cyclopentane N-CH), 3.76 (s, 3H ester methyl), 3.34 (dd, $J = 15.1, 11.1$ Hz, 1H, cyclopentane CH$_2$), 3.29 (s, 3H, ester methyl), 3.17 (t, $J = 12.4$ Hz, 1H, cyclopentane CH$_2$), 2.55 (dd, $J = 12.9, 6.8$ Hz, 1H, cyclopentane CH$_2$), 2.37 (dd, $J = 15.1, 7.1$ Hz, 1H, cyclopentane CH$_2$), 1.02-0.95 (m, 21H, TIPS).
**3.3 From 5-fluoro-uracil cyclopropane.**

**General procedure for Benzoyl removal.**

The crude product was dissolved in EtOH (2 mL) and stirred at room temperature for 2 hours with NH₄OH (0.6 mL, 40 eq, 25%). The mixture was evaporated to dryness and directly submitted to the column chromatography using a gradient of solvent from pentane/AcOEt (7:3) up to (3:7).

**Dimethyl -5-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenyldihydrofuran-3,3(2H)-dicarboxylate (20a).**

Following the conditions A, using benzaldehyde (0.051 g, 0.48 mmol, 1.2 eq), and the corresponding cyclopropane 45 (0.16 g, 0.40 mmol, 1 eq), followed by the benzoyl deprotection, the pure product 20a (0.11 g, 0.29 mmol, 72% yield) was obtained as a white powder.

**RF (AcOEt/pentane (1:1)) = 0.60.**

**MP 227.9-228.5°C.**

**1H NMR (400 MHz, Chloroform-d) δ 9.22 (s, 1H, NH), 8.25 (d, J = 6.1 Hz, 1H, F-uracil CH), 7.47 – 7.34 (m, 2H, ArH), 7.34 – 7.22 (m, 3H, ArH), 6.31 (ddd, J = 7.8, 6.9, 1.7 Hz, 1H, tetrahydrofuran N-CH), 5.53 (s, 1H, tetrahydrofuran CH), 3.74 (s, 3H, ester CH₃), 3.08 (s, 3H, ester CH₃), 2.80 (qd, J = 14.8, 7.4 Hz, 2H, tetrahydrofuran CH₂).**

**13C NMR (101 MHz, Chloroform-d) δ 169.9, 169.6, 156.6 (dd, J = 27.1, 8.7 Hz), 149.1 (d, J = 7.7 Hz), 141.0 (d, J = 238.8 Hz), 134.8, 129.0, 128.2, 126.4, 124.7 (d, J = 34.8 Hz), 82.7, 81.8, 63.6, 53.2, 53.0, 39.2.**

**IR 3196 (w), 3071 (w), 2956 (w), 1728 (s), 1668 (m), 1436 (w), 1273 (s), 1121 (m), 1094 (m), 1053 (m), 914 (m), 735 (m).**

**HRMS (ESI) calcd for C₁₈H₁₇FN₂NaO₇ [M+Na]⁺ 415.0917; found 415.0918.**

**Dimethyl -5-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methyl-2-phenyldihydrofuran-3,3(2H)-dicarboxylate (20b).**
Following the conditions B, using acetophenone (16) (0.058 g, 0.48 mmol, 1.2 eq) and the corresponding cyclopropane 45 (0.16 g, 0.40 mmol, 1 eq) at -40 °C, followed by the benzoyl deprotection, the pure product 20b (0.12 g, 0.28 mmol, 71% yield) was obtained as a white powder.

RF (AcOEt/pentane (1:1)) = 0.42.

MP 209.3-210.2°C.

\(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 9.98 (d, \(J = 4.6\) Hz, 1H, NH), 8.50 (d, \(J = 6.5\) Hz, 1H, F-uracil CH), 7.77 – 7.65 (m, 2H, ArH), 7.51 – 7.16 (m, 3H, ArH), 6.42 (ddd, \(J = 8.2, 5.1, 1.7\) Hz, 1H, tetrahydrofuran N-CH). 3.80 (s, 3H, ester CH\(_3\)), 3.18 (dd, \(J = 15.1, 8.2\) Hz, 1H, tetrahydrofuran CH\(_2\)), 3.10 (s, 3H, ester CH\(_3\)), 2.78 (ddd, \(J = 15.1, 5.1\) Hz, 1H, tetrahydrofuran CH\(_2\)), 1.88 (s, 3H, CH\(_3\)).

\(^{13}\)C NMR (101 MHz, Chloroform-\(d\)) \(\delta\) 170.5, 168.6, 157.1 (d, \(J = 26.8\) Hz), 149.6, 140.5 (d, \(J = 236.4\) Hz), 140.0, 128.0, 127.9, 125.7, 125.6 (d, \(J = 35.1\) Hz), 88.6, 81.4, 66.9, 52.9, 52.8, 39.7, 25.7.

IR 3173 (w), 3065 (w), 2954 (w), 1758 (w), 1718 (s), 1669 (s), 1485 (w), 1421 (w), 1252 (s), 1076 (s), 914 (m), 768 (m).

HRMS (ESI) calcd for C\(_{19}\)H\(_{19}\)F\(_2\)N\(_2\)NaO\(_7\) [M+Na] 429.1074; found 429.1080.

Dimethyl -4-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenyl-2-((triisopropylsilyl)oxy)cyclopentane-1,1-dicarboxylate (21).

Following the conditions B, using TIPS protected acetophenone 17 (0.17 g, 0.60 mmol, 1.5 eq) and the corresponding cyclopropane 45 (0.16 g, 0.40 mmol, 1 eq) at -40 °C, followed by the benzoyl deprotection, the pure product 21 (0.12 g, 0.20 mmol, 51% yield) was obtained as a colorless oil.

RF (AcOEt/pentane (1:1)) = 0.75.

\(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 9.96 (br. m., 1H, NH), 8.33 (d, \(J = 6.5\) Hz, 1H, F-uracil CH), 7.76 (dd, \(J = 7.8, 2.0\) Hz, 2H, ArH), 7.39 – 7.21 (m, 3H, ArH), 5.74 (dddd, \(J = 8.6, 6.5, 4.6, 1.5\) Hz, 1H, tetrahydrofuran N-CH), 3.74 (s, 3H, ester CH\(_3\)), 3.39 – 3.29 (m, 1H, tetrahydrofuran CH\(_2\)), 3.28 (s, 3H, ester CH\(_3\)), 3.14 (dd, \(J = 13.0, 11.7\) Hz, 1H, tetrahydrofuran CH\(_2\)), 2.55 (dd, \(J = 12.9, 7.0\) Hz, 1H, tetrahydrofuran CH\(_2\)), 2.35 (dd, \(J = 15.2, 6.7\) Hz, 1H, tetrahydrofuran CH\(_2\)), 1.01-0.94 (m, 21H, TIPS).
13C NMR (101 MHz, Chloroform-d) δ 172.8, 168.0, 157.0 (d, J = 26.5 Hz), 150.2, 141.0 (d, J = 237.5 Hz), 139.6, 128.5, 127.9, 127.4, 125.9 (d, J = 33.4 Hz), 88.4, 70.3, 52.9, 52.4, 52.0, 43.4, 38.0, 18.2, 18.2, 13.9.

IR 3194 (w), 3067 (w), 2951 (w), 2855 (w), 1718 (s), 1466 (w), 1256 (s), 1134 (m), 991 (m), 788 (m), 740 (m).


4. Thymine based nucleoside analogues derivatizations.

4.1 Acids.

General procedure for hydrolysis and decarboxylation reaction

Compound 8 (1 eq) and KOH (4 eq) were stirred under nitrogen in a dried and sealed microwave vial with dry methanol (0.06 mL) for 2 days at 70 °C. The thick yellow mixture was cooled down to room temperature and acidified with a 0.1 M HCl solution (0.5 mL). The mixture was extracted 3 times with AcOEt (2 mL), the organic layers were dried over anhydrous MgSO4 and concentrated under reduced pressure. The corresponding monoacid was obtained after column chromatography with a gradient of DCM to a solvent mixture of DCM/MeOH 8:2 and 1% AcOH.

5-(5-Methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenyltetrahydrofuran-3-carboxylic acid (52).

Following the general procedure for hydrolysis and decarboxylation reaction, using compound 8c (0.050 g, 0.13 mmol, 1 eq) and KOH (29 mg, 0.52 mmol, 4 eq) in dry MeOH (0.3 mL), the pure monoacid 52 (0.034 g, 0.10 mmol, 83% yield) was obtained as a white solid.

RF (AcOEt) = 0.23.

MP 123.2-125.3°C.

1H NMR (400 MHz, Methanol-d4) δ 7.37 (d, J = 8.6 Hz, 3H, Ar-H and thymine vinyl-CH), 7.32 – 7.22 (m, 3H, Ar-H), 6.20 – 6.08 (m, 1H, tetrahydrofuran-NCH), 5.01 (d, J = 8.7 Hz, 1H, tetrahydrofuran-CH), 3.35 – 3.24 (m, 1H, tetrahydrofuran-CH), 2.68 (dt, J = 13.1, 8.1 Hz, 1H...
tetrahydrofuran-CH$_2$), 2.47 (ddd, $J = 13.8, 9.5, 4.5$ Hz, 1H, tetrahydrofuran-CH$_2$), 1.78 (s, 3H, thymine methyl).

$^{13}$C NMR (101 MHz, Methanol-$d_4$) $\delta$ 174.0, 165.0, 150.9, 138.9, 137.2, 128.2, 126.2, 110.4, 85.7, 83.7, 49.9, 35.3, 11.0.

The acid carbon is not defined.

IR 3429 (w), 3211 (w), 3039 (w), 2529 (w), 1695 (s), 1475 (w), 1272 (m), 1068 (m), 769 (w), 701 (m).

HRMS (ESI) calcd for C$_{16}$H$_{16}$N$_2$O$_5$ [M+Na]$^+$ 339.0951; found 339.0944.

$^{2}$-Methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenyltetrahydrofuran-3-carboxylic acid (53).

Following the general procedure for hydrolysis and decarboxylation reaction, using compound 8d (0.020 g, 0.050 mmol, 1 eq) and KOH (6 mg, 0.1 mmol, 4 eq), the pure monoacid 53 (0.014 g, 0.042 mmol, 83% yield) was obtained as a white solid. The stereochemistry of the acid was determined by NOE experiment.

RF (AcOEt) = 0.18.

MP 236.2-236.7 °C.

$^{1}$H NMR (400 MHz, Acetone-$d_6$) $\delta$ 11.39 (br s, 1H, COOH ), 10.01 (s, 1H, thymine NH), 7.70 – 7.62 (m, 2H, Ar-H), 7.48 – 7.28 (m, 3H, Ar-H), 7.25 (q, $J = 1.1$ Hz, 1H, thymine vinyl-CH), 6.46 (dd, $J = 7.5, 4.2$ Hz, 1H, tetrahydrofuran-NCH), 3.75 (t, $J = 8.7$ Hz, 1H, tetrahydrofuran-CH$_2$), 2.51 (ddd, $J = 14.0, 8.7, 4.2$ Hz, 1H, tetrahydrofuran-CH$_2$), 1.71 (d, $J = 1.3$ Hz, 3H, thymine methyl), 1.60 (s, 3H, tetrahydrofuran methyl).

$^{13}$C NMR (101 MHz, Acetone-$d_6$) $\delta$ 177.8, 169.4, 156.0, 150.9, 142.1, 133.4, 132.6, 130.5, 115.2, 92.0, 90.0, 57.2, 39.5, 30.0, 16.7.

IR 3220 (w), 3054 (w), 2925 (w), 2854 (w), 1704 (s), 1660 (m), 1478 (w), 1419 (w), 1271 (w), 1110 (w), 1058 (w), 855 (w), 800 (w), 769 (w).

HRMS (ESI) calcd for C$_{17}$H$_{18}$N$_2$O$_5$ [M+H]$^+$ 331.1288; found 331.1281.

5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-((E)-styryl)tetrahydrofuran-3-carboxylic acid (54).
Following the general procedure for hydrolysis and decarboxylation reaction, using compound 8g (0.14 g, 0.34 mmol, 1 eq) and KOH (0.080 g, 1.4 mmol, 4.0 eq) in dry MeOH (1.4 mL). A mixture of unseparable monoacids (ratio 5:1 obtained by integration of the proton at 5.17 ppm and 4.76 ppm) 54 (82 mg, 0.24 mmol, 71% yield) was obtained as a white solid.

**RF** diacid (DCM/MeOH (8:2) 1% AcOH) = 0.05.
**RF 56** (DCM/MeOH (8:2) 1% AcOH) = 0.2.

**$^{1}$H NMR** (400 MHz, Methanol-d$_4$) δ 7.65 (s, 1H, thymine vinyl-CH, minor diastereoisomer), 7.55 (s, 1H, thymine vinyl-CH, major diastereoisomer), 7.49 (d, $J$ = 7.8 Hz, 4H, Ar-H, major and minor diastereoisomers), 7.40 – 7.25 (m, 6H, Ar-H, major and minor diastereoisomers), 6.76 (d, $J$ = 15.9 Hz, 2H, vinyl-CH, major and minor diastereoisomers), 6.48 (ddd, $J$ = 16.1, 7.2, 1.7 Hz, 1H, vinyl-CH, major diastereoisomer), 6.34 (ddd, $J$ = 16.0, 6.7, 1.7 Hz, 1H, vinyl-CH, minor diastereoisomers), 6.26 – 6.17 (m, 2H, tetrahydrofuran-NCH, major and minor diastereoisomers), 5.17 (t, $J$ = 7.0 Hz, 1H, tetrahydrofuran-CH, minor diastereoisomer), 4.76 (t, $J$ = 7.7 Hz, 1H, tetrahydrofuran-CH, major diastereoisomer), 3.25 (q, $J$ = 8.9 Hz, 1H, tetrahydrofuran-CH, major diastereoisomer), 3.18 (q, $J$ = 8.9 Hz, tetrahydrofuran-CH, major diastereoisomer), 2.86 – 2.71 (m, 2H, tetrahydrofuran-CH$_2$, major and minor diastereoisomers), 1.94 (s, 3H, thymine methyl, minor diastereoisomer), 1.92 (s, 3H, thymine methyl, major diastereoisomer).

**$^{13}$C NMR** (101 MHz, Methanol-d$_4$) δ 175.1, 175.0, 166.5, 166.4, 152.4, 152.2, 138.1, 137.8, 137.7, 137.6, 134.7, 133.6, 129.7, 129.7, 129.6, 129.2, 129.0, 128.5, 127.8, 127.7, 111.7, 111.5, 87.7, 86.9, 84.9, 84.8, 49.6, 49.4, 49.2, 49.0, 48.8, 48.6, 48.4, 36.7, 36.5, 12.5.

For the major diastereoisomer, the acid carbon is not defined and an aromatic one neither. One carbon is missing for the minor diastereoisomer.

**IR** 3442 (w), 3184 (w), 3031 (w), 2531 (w), 1684 (s), 1485 (w), 1407 (w), 1369 (w), 1271 (m), 1204 (w), 1115 (w), 1072 (m), 980 (w), 751 (w), 695 (m).

**HRMS (ESI)** calcd for C$_{18}$H$_{19}$N$_2$O$_5^{-}$ [M+H]$^+$ 343.1288; found 343.1294.

2-(4-Fluorophenyl)-2-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3-carboxylic acid (55).

Following the general procedure for hydrolysis and decarboxylation reaction, using compound 8h (0.040 g, 0.095 mmol, 1 eq) and KOH (21 mg, 0.38 mmol, 4 eq) in a mixture of MeOH/water (0.1 mL/0.1 mL), a mixture of unseparable monoacids (ratio 10:1 obtained by
integration of the proton at 6.50 ppm and 6.40 ppm) 55 (0.028 g, 0.080 mmol, 84% yield) were obtained as a white solid.

RF (DCM/MeOH (9:1)) = 0.15.

MP 193.4-194.2 °C.

$^1$H NMR (400 MHz, Acetone-$d_6$) $\delta$ 10.08 (br.s, 1H, COOH), 8.17 (s, 1H, NH), 7.68 (dd, $J = 8.1$, 4.9 Hz, 2H, Ar-H, major diastereoisomer), 7.55 (dd, $J = 8.0$, 4.8 Hz, 2H, Ar-H, minor diastereoisomer), 7.30 (s, 1H, thymine vinyl-CH, major diastereoisomer), 7.13 (t, $J = 8.3$ Hz, 2H, Ar-H, major diastereoisomer), 7.07 (t, $J = 8.4$ Hz, 2H, Ar-H, minor diastereoisomer), 6.50 (t, $J = 7.0$ Hz, 1H, tetrahydrofuran-NCH, minor diastereoisomer), 6.40 (dd, $J = 8.0$, 3.9 Hz, 1H, tetrahydrofuran-NCH, major diastereoisomer), 3.72 (t, $J = 9.1$ Hz, 1H, tetrahydrofuran-CH, major diastereoisomer), 3.46 (dd, $J = 9.2$, 4.1 Hz, 1H, tetrahydrofuran-CH, minor diastereoisomer), 3.00 (dt, $J = 13.4$, 8.7 Hz, 1H, tetrahydrofuran-CH$_2$ major diastereoisomer), 2.93 (dd, $J = 15.4$, 7.9 Hz, 1H, tetrahydrofuran-CH$_2$ minor diastereoisomer), 2.53 (ddd, $J = 13.7$, 8.9, 3.9 Hz, 1H, tetrahydrofuran-CH$_2$ major diastereoisomer), 2.46 – 2.35 (m, 1H, tetrahydrofuran-CH$_2$ minor diastereoisomer), 1.80 (s, 3H, thymine methyl, minor diastereoisomer), 1.74 (s, 3H, thymine methyl, major diastereoisomer).

$^{13}$C NMR (101 MHz, Acetone-$d_6$) $\delta$ 174.7, 164.3, 164.2, 164.0, 162.8 (d, $J = 244.1$ Hz), 162.7 (d, $J = 244.1$ Hz), 151.4, 151.3, 142.7 (d, $J = 3.0$ Hz), 139.6 (d, $J = 2.9$ Hz), 137.8, 137.5, 128.5 (d, $J = 8.1$ Hz), 128.4 (d, $J = 8.2$ Hz), 115.5 (d, $J = 21.4$ Hz), 115.1 (d, $J = 21.4$ Hz), 111.0, 110.9, 86.9, 86.9, 85.5, 83.2, 53.9, 53.2, 35.2, 34.9, 12.7, 12.3.

IR 3530 (w), 3189 (w), 3065 (w), 2927 (w), 1697 (s), 1512 (m), 1268 (m), 1088 (w), 1052 (w), 839 (m).

HRMS (ESI) calcd for C$_{17}$H$_{18}$N$_2$O$_5$ $^+$ [M+H]$^+$ 349.1194; found 349.1194.

4.2 Alcohols.

General procedure for reduction of carboxylic acids.

The carboxylic acid (1 eq) was solubilized in dry THF in a dried round bottom flask under nitrogen. The reaction mixture under nitrogen was cooled to 0 °C and dimethylsulfide borane solution (2 M in THF, 0.042 mL, 0.083 mmol, 2.2 eq) was added dropwise. The reaction was allowed to slowly warm up and was stirred under nitrogen for 16 h. The reaction mixture was quenched by addition of a saturated solution of Na$_2$CO$_3$ (0.5 mL) and acidified by addition of a 1 M HCl solution (1 mL). Then the mixture was extracted three times with AcOEt (3 mL) and the organic layers were dried over anhydrous MgSO$_4$. The crude product was purified by column chromatography with a gradient of pure AcOEt to a mixture of AcOEt/MeOH (8:2), affording the pure alcohol, as a colorless foam.
4-(Hydroxymethyl)-5-phenyltetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (22).

Following the general procedure for reduction of carboxylic acids, using compound 52 (0.012 g, 0.038 mmol, 1 eq) and DMS solution (0.042 mL, 0.083 mmol, 2.2 eq) in dry THF (0.35 mL), the alcohol 22 (0.0095 g, 0.031 mmol, 86% yield) was obtained as a colorless oil.

RF (AcOEt) = 0.34.

MP 68.1-69.4°C.

$^1$H NMR (400 MHz, Methanol-\(d_4\)) $\delta$ 7.53 – 7.47 (m, 1H, thymine vinyl-CH), 7.49 – 7.28 (m, 5H, Ar-H), 6.29 – 6.09 (m, 1H, tetrahydrofuran-NCH), 4.78 (d, $J$ = 8.6 Hz, 1H, tetrahydrofuran-CH), 3.68 (dd, $J$ = 11.2, 4.4 Hz, 1H, -CH$_2$OH), 3.64 – 3.53 (dd, $J$ = 11.2, 5.6 Hz, 1H, -CH$_2$OH), 2.61 (ddd, $J$ = 14.2, 8.3, 2.8 Hz, 1H, tetrahydrofuran-CH), 2.49 (ddd, $J$ = 13.7, 8.7, 7.6 Hz, 1H, tetrahydrofuran-CH$_2$), 2.35 (ddd, $J$ = 13.6, 9.0, 4.5 Hz, 1H, tetrahydrofuran-CH$_2$), 1.88 (d, $J$ = 2.4 Hz, 3H, thymine methyl).

$^{13}$C NMR (101 MHz, Methanol-\(d_4\)) $\delta$ 166.5, 152.6, 141.4, 138.4, 129.85, 129.5, 128.1, 111.9, 86.7, 84.8, 62.3, 49.1, 35.9, 12.7.

IR 3410 (w), 3207 (w), 2927 (w), 2520 (w), 1686 (s), 1471 (m), 1271 (m), 1055 (m), 911 (w), 760 (m).

HRMS (ESI) calcd for C$_{16}$H$_{18}$N$_2$NaO$_4$ [M+Na]$^+$ 325.1159; found 325.1159.

Following the general procedure for reduction of carboxylic acids, using compound 53 (0.018 g, 0.054 mmol, 1 eq) and DMS solution (0.060 mL, 0.12 mmol, 2.2 eq) in dry THF (0.5 mL), the alcohol 23 (0.013 g, 0.041 mmol, 75% yield) was obtained as a colorless foam.

RF (AcOEt) = 0.13.

MP 79.4-83.4°C.

$^1$H NMR (400 MHz, Chloroform-d) $\delta$ 8.60 (s, 1H, thymine-NH), 7.46 (d, $J$ = 7.6 Hz, 2H, Ar-H), 7.39 – 7.22 (m, 3H, Ar-H), 6.82 (s, 1H, thymine vinyl-CH), 6.21 (d, $J$ = 3.6 Hz, 1H, tetrahydrofuran-NCH), 3.96 (dd, $J$ = 10.5, 5.4 Hz, 1H, -CH$_2$OH), 3.74 (dd, $J$ = 10.7, 7.9 Hz, 1H, -CH$_2$OH), 2.75 (dd, $J$ = 11.0, 4.6 Hz, 1H, tetrahydrofuran-CH), 2.44 – 2.25 (m, 2H,
tetrahydrofuran-CH₂), 2.04 (br.s, 1H, OH), 1.60 (s, 3H, thymine methyl), 1.42 (s, 3H, tetrahydrofuran methyl).

¹³C NMR (101 MHz, Chloroform-d) δ 163.7, 150.4, 145.6, 136.3, 128.6, 127.7, 125.1, 110.3, 87.6, 85.0, 62.6, 47.5, 36.6, 24.5, 12.5.

IR 3446 (w), 2959 (w), 1679 (s), 1473 (w), 1448 (w), 1265 (m), 1031 (s), 911 (w), 767 (m), 735 (m).


4-(Hydroxymethyl)-5-((E)-styryl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (24).

Following the general procedure for reduction of carboxylic acids, using the mixture of diastereoisomers 54 (0.020 g, 0.058 mmol, 1 eq) and DMS solution (0.063 mL, 0.13 mmol, 2.2 eq) in dry THF (0.53 mL), the mixture of diastereoisomeric alcohols (ratio 5:1 obtained by integration of the proton at 4.42 ppm and 4.65 ppm) 24 (0.016 g, 0.049 mmol, 83% yield) was obtained as colorless oil.

RF (DCM/MeOH (9.5:0.5)) = 0.25.

¹H NMR (400 MHz, Chloroform-d, major diastereoisomer) δ 8.24 (br.s, 1H, thymine-NH), 7.40 – 7.20 (m, 6H, Ar-H and thymine vinyl-CH), 6.67 (d, J = 16.0 Hz, 1H, vinyl-CH), 6.24 (dd, J = 15.8, 7.1 Hz, 1H, vinyl-CH), 6.07 (dd, J = 6.7, 3.6 Hz, 1H, tetrahydrofuran-NCH), 4.42 (t, J = 7.5 Hz, 1H, tetrahydrofuran-CH), 3.74 (dd, J = 10.7, 5.0 Hz, 1H, -CH₂OH), 3.68 (dd, J = 10.7, 5.1 Hz, 1H, -CH₂OH), 2.46 – 2.26 (m, 2H, tetrahydrofuran-CH₂), 2.16 (ddd, J = 12.1, 7.1, 3.5 Hz, 1H, tetrahydrofuran-CH₂), 1.86 (d, J = 1.2 Hz, 3H, thymine methyl).

¹³C NMR (101 MHz, Chloroform-d, major diastereoisomer) δ 164.1, 150.6, 136.4, 136.0, 134.5, 129.3, 129.0, 127.4, 127.3, 111.2, 86.2, 84.1, 62.7, 46.1, 36.3, 13.3.

IR 2962 (w), 2924 (w), 2853 (w), 1687 (s), 1471 (w), 1363 (w), 1268 (m), 1189 (w), 1055 (s), 967 (m), 744 (m).

HRMS (ESI) calcd for C₁₈H₂₂N₂NaO₄⁺ [M+Na]⁺ 351.1319; found 351.1319.

5-(4-Fluorophenyl)-4-(hydroxymethyl)-5-methyltetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (25).
Following the general procedure for reduction of carboxylic acids, using the mixture of diastereoisomers 55 (0.027 g, 0.078 mmol, 1 eq) and DMS solution (0.085 mL, 0.17 mmol, 2.2 eq) in dry THF (0.5 mL), the mixture of diastereoisomeric alcohols (ratio 10:1 obtained by integration of the proton at 3.31 ppm and 3.91 ppm) 25 (0.020 g, 0.059 mmol, 76% yield) was obtained as colorless oil.

RF (AcOEt) = 0.53.

MP 192.3-193.8°C (decomp.).

$^1$H NMR (400 MHz, Chloroform-d) δ 8.40 (s, 1H, thymine-NH, minor and major diastereoisomer), 7.58 (d, J = 1.3 Hz, 1H, thymine vinyl-CH, minor diastereoisomer), 7.33 (dd, J = 8.9, 5.2 Hz, 2H, Ar-H, major diastereoisomer), 7.01 (t, J = 8.7 Hz, 4H, Ar-H, minor and major diastereoisomers), 6.82 (d, J = 1.3 Hz, 1H, thymine vinyl-CH, major diastereoisomer), 6.23 (d, J = 7.0 Hz, 1H tetrahydrofuran-NCH, minor diastereoisomer), 6.19 (dd, J = 6.9, 3.4 Hz, 1H tetrahydrofuran-NCH, major diastereoisomer), 3.91 (dd, J = 10.6, 6.0 Hz, 1H CH$_2$OH, major diastereoisomer), 3.75 (dd, J = 10.6, 7.5 Hz, 1H, -CH$_2$OH, major diastereoisomer), 3.31 (dd, J = 11.1, 5.1 Hz, 0H, -CH$_2$OH, minor diastereoisomer), 2.72 (m, 2H, tetrahydrofuran-CH, minor and major diastereoisomers), 2.45 – 2.22 (m, 4H, tetrahydrofuran-CH$_2$, minor and major diastereoisomers), 1.89 (d, J = 1.2 Hz, 3H, thymine methyl, minor diastereoisomer), 1.81 (br.s, 1H, OH, minor and major diastereoisomer), 1.66 (d, J = 1.2 Hz, 3H, thymine methyl, major diastereoisomer), 1.57 (s, 3H, tetrahydrofuran methyl, minor diastereoisomer), 1.41 (s, 3H, tetrahydrofuran methyl, major diastereoisomer).

$^{13}$C NMR (101 MHz, Chloroform-d) Major diastereoisomer δ 163.5, 162.1 (d, J = 247.3 Hz), 150.3, 141.5 (d, J = 3.6 Hz), 136.0, 127.0 (d, J = 8.0 Hz), 115.3 (d, J = 21.3 Hz), 110.5, 87.3, 84.9, 62.5, 47.8, 36.5, 24.3, 12.6.

IR 2981 (w), 2925 (w), 2860 (w), 1680 (m), 1511 (w), 1473 (w), 1273 (w), 1230 (w), 1055 (m), 1013 (m), 909 (s), 733 (s).

HRMS (ESI) calcd for C$_{17}$H$_{19}$FN$_2$NaO$_4$ $^{\text{+}}$ [M+Na]$^{\text{+}}$ 357.1221; found 357.1231.

4.3 Carbonucleoside alcohol.

Dibenzyl 4-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenyl-2-((triisopropylsilyl)oxy)cyclopentane-1,1-dicarboxylate. (26)

Following the conditions B, using TIPS protected acetophenone 47 (0.17 g, 0.60 mmol, 1.5 eq) and the corresponding cyclopropane 37 (0.21 g, 0.40 mmol, 1 eq), the pure product 26 (0.27 g, 0.38 mmol, 94% yield) was obtained as a white crystalline solid.

RF (pent/AcOEt (1:1)) = 0.70.

MP 69.4-73.1°C.
$^1$H NMR (400 MHz, Chloroform-$d$) δ 8.35 (s, 1H, thymine N-H), 7.84 (d, $J = 1.6$ Hz, 1H, thymine vinyl-CH), 7.77 (dd, $J = 7.3$, 1.8 Hz, 2H, Ar-H), 7.31 – 7.11 (m, 11H, Ar-H), 6.91 – 6.84 (m, 2H, Ar-H), 5.72 (tt, $J = 11.5$, 6.9 Hz, 1H, cyclopentane-NCH), 5.19 – 5.03 (m, 2H, benzylic-CH$_2$), 4.76 (d, $J = 12.3$ Hz, 1H, benzylic-CH$_2$), 4.56 (d, $J = 12.2$ Hz, 1H, benzylic-CH$_2$), 3.35 (dd, $J = 15.1$, 11.1 Hz, 1H, cyclopentane-CH$_2$), 3.21 (t, $J = 12.4$ Hz, 1H, cyclopentane-CH$_2$), 2.53 (dd, $J = 12.9$, 6.9 Hz, 1H, cyclopentane-CH$_2$), 1.94 (d, $J = 1.2$ Hz, 3H, thymine methyl), 1.03 – 0.92 (m, 21H, TIPS).

$^{13}$C NMR (101 MHz, Chloroform-$d$) δ 171.9, 167.4, 163.4, 151.1, 139.7, 137.3, 135.1, 134.4, 128.6, 128.5, 128.4, 128.4, 128.4, 128.3, 128.0, 127.4, 111.5, 88.3, 70.4, 67.7, 67.5, 51.2, 43.6, 38.3, 18.3, 13.9, 12.8.

One carbone not resolved.

IR 3434 (w), 3160 (w), 3035 (w), 2872 (w), 1682 (s), 1456 (w), 1374 (w), 1136 (w), 1025 (m).

HRMS (ESI) calcd for C$_{41}$H$_{50}$N$_2$NaO$_7$S $^+\ [M+Na]^+$ 733.3279; found 733.3271.

The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number: CCDC 995131.

---

5-Methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl-2-phenylcyclopent-1-ene-1-carboxylic acid (27).

![Chemical Structure](image)

Compound 136 (0.10 g, 0.14 mmol, 1.0 eq) and Pd-C (0.030 g, 0.014 mmol, 0.1 eq) were stirred in a flame-dried flask under H$_2$ at 57 °C with ethanol (10 mL) 5 min to solubilize the starting material, then the reaction was let for 10 min to cool down. The reaction mixture was filtered on a pore 5 filter with hot ethanol (50 mL) to afford after solvent evaporation, the pure diacid 56 as colorless needles. Then the crude product was heated neat at 80 °C for 16 h. After column chromatography using DCM to a mixture of DCM/MeOH (9:1) with 1% AcOH as solvent, the pure product 27 (28 mg, 0.090 mmol, 64% yield) was obtained as a colorless oil. The corresponding TIPS protected carboxylic acid 57 (14 mg, 0.030 mmol, 20% yield) was also isolated as a colorless oil.

RF 57 (DCM/MeOH (9:1)) = 0.37.

RF 27 (DCM/MeOH (9:1)) = 0.21.
MP 114.1-115.6 °C.

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 9.20 (d, $J = 9.1$ Hz, 1H, thymine-NH), 7.37 (s, 5H, Ar-H), 7.08 (d, $J = 1.6$ Hz, 1H, thymine vinyl-CH), 5.37 (tt, $J = 8.8$, 4.3 Hz, 1H, cyclopentane-NCH), 3.60 – 3.25 (m, 2H, cyclopentane-CH$_2$), 2.96 (ddd, $J = 18.9$, 8.2, 3.7, 1.9 Hz, 2H, cyclopentane-CH$_2$), 1.92 (d, $J = 1.2$ Hz, 3H, thymine methyl).

$^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 168.2, 163.7, 153.1, 150.5, 136.2, 134.4, 128.8, 128.0, 127.7, 125.7, 111.8, 46.2, 40.8, 12.5.

IR (w), 3026 (w), 2929 (w), 1675 (s), 1472 (w), 1393 (w), 1270 (m), 1221 (w), 909 (m), 735 (s), 636 (w).

HRMS (ESI) calcd for C$_{17}$H$_{15}$N$_2$O$_4$ [M+H]$^+$ 315.1306; found 315.1300.

5-Methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl-2-phenylcyclopentane-1-carboxylic acid (60).

Carboxylic acid 27 (0.021 g, 0.067 mmol, 1.0 eq) and Pd-C (0.01 g, 0.007 mmol, 5 % wt, 0.1 eq) were stirred in a flame dried flask under H$_2$ at room temperature with ethanol (1 mL). TLC shows that the reaction was accomplished after 10 minutes and filtered on pore 5 filter. The residue was washed several times with hot ethanol. The pure product 58 (0.018 g, 0.057 mmol, 85% yield) precipitated directly as white spheres. The stereochemistry was assigned by NOE experiment.

RF (DCM/MeOH (8:2) 1% AcOH) = 0.49.

MP 227.8-236.9°C.

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.86 (s, 1H, -COOH), 11.20 (s, 1H, -NH), 7.80 (d, $J = 1.4$ Hz, 1H, thymine vinyl-CH), 7.29 – 7.10 (m, 5H, Ar-H), 4.97 (dtd, $J = 11.3$, 9.1, 6.8 Hz, 1H, cyclopentane-NCH), 3.48 (ddd, $J = 12.3$, 9.1, 6.2 Hz, 1H, cyclopentane-CH), 3.19 – 3.00 (m, 1H), 2.36 – 2.21 (m, 2H, cyclopentane-H), 2.11 (dt, $J = 12.3$, 6.5 Hz, 1H, cyclopentane-H), 1.96 (ddd, $J = 14.0$, 9.0, 5.5 Hz, 1H, cyclopentane-H), 1.76 (d, $J = 1.1$ Hz, 3H, thymine methyl).

$^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 176.3, 164.2, 151.6, 140.8, 137.9, 128.5, 128.4, 126.9, 109.9, 53.6, 47.2, 45.3, 35.6, 33.9, 12.8.

The carboxylic acid carbon is not resolved.

IR (w), 3225 (w), 2959 (w), 2860 (w), 1686 (s), 1636 (s), 1449 (m), 1380 (m), 1280 (s), 1213 (m), 1054 (s), 950 (s), 784 (s).
HRMS (ESI) calcd for C_{17}H_{19}N_{2}O_{4}^{+} [M+H]^{+} 315.1339; found 315.1344.

5-Methyl-1-(3-phenyl-4-(((triisopropylsilyl)oxy)methyl)cyclopentyl)pyrimidine-2,4(1H,3H)-dione (28).

Carboxylic acid 58 (0.019 g, 0.060 mmol, 1 eq) was solubilized in dry THF (0.35 mL) in a dried round bottom flask. The reaction mixture was cooled under nitrogen to 0°C and a 2 M dimethylsulfide borane solution in THF (0.076 mL, 0.15 mmol, 2.2 eq) was added dropwise. The reaction was stirred at 0°C for 5 hours, then it was quenched by addition of a 1 M HCl solution (1 mL). The mixture was extracted three times with AcOEt (3 mL) and the organic layers were dried over anhydrous MgSO_{4}. The crude was directly solubilized into dry and degassed DMF (0.7 mL), imidazole (6 mg, 0.09 mmol, 1.5 eq) and TIPSCI (14 mg, 0.072 mmol, 1.2 eq) were added. The mixture was stirred at room temperature for 6 hours. The solvent was removed under reduced pressure and the mixture was partitioned between water (2 mL) and AcOEt (2 mL). The aqueous layer was extracted 3 times with AcOEt and the organic layers were dried over anhydrous Na_{2}CO_{3} and concentrated under reduced pressure. The crude yellow oil was purified by column chromatography, starting with pure DCM and then changing gradually to a mixture of DCM/MeOH (9:1), affording the pure protected alcohol 28 (15 mg, 0.033 mmol, 55%) as a colorless oil.

RF (DCM/MeOH (9:1)) = 0.58.

{\textsuperscript{1}H} NMR (400 MHz, Chloroform-d) δ 8.54 (s, 1H, -NH), 7.32 – 7.09 (m, 6H, Ar-H and thymine vinyl-CH), 5.05 (dt, J = 11.6, 9.4, 6.5 Hz, 1H, cyclopentane-NCH), 3.42 – 3.21 (m, 3H, CH_{2}O and cyclopentane-CH), 2.46 (td, J = 9.0, 4.7 Hz, 1H, cyclopentane-CH), 2.39 – 2.27 (m, 1H cyclopentane-CH), 2.27 – 2.13 (m, 2H, cyclopentane-CH), 1.96 – 1.91 (m, 1H, cyclopentane-CH), 1.89 (d, J = 1.2 Hz, 3H, thymine methyl), 0.93 (m, 3H, TIPS), 0.88 (d, J = 4.9 Hz, 18H, TIPS).

{\textsuperscript{13}C} NMR (101 MHz, Chloroform-d) δ 163.5, 151.2, 139.9, 136.6, 128.3, 128.0, 126.4, 111.0, 64.0, 54.6, 44.8, 42.1, 35.3, 32.1, 18.0, 18.0, 12.4, 11.8.

IR 3170 (w), 2945 (w), 1687 (s), 1469 (m), 1385 (w), 1272 (w), 1126 (w), 884 (w).

HRMS (ESI) calcd for C_{26}H_{41}N_{2}O_{3}Si^{+} [M+H]^{+} 457.2881; found 457.2881.

5. Spectra of new compounds
400 MHz, Chloroform-d.
400 MHz, Chloroform-\(\text{d}_2\).
400 MHz, Chloroform-d.
400 MHz, Chloroform-d.
400 MHz, Chloroform-\textit{d}.
400 MHz, Chloroform-\textit{d}.
400 MHz, Chloroform-\text{d}.
400 MHz, Chloroform-d.
400 MHz, Chloroform-\textit{d}.
400 MHz, Chloroform-d.
H
NOESY 1D experiment permitted to define the stereochemistry of the new stereocenter. In fact, we were able to see the NOE interaction between the thymine NCH proton (H\textsuperscript{1}) and the cyclopentane methyl (Me) and the cyclopentane CH (H\textsuperscript{2}). The absence of coupling between thymine NCH proton (H\textsuperscript{1}) and the cyclopentane CH (3.37 ppm) one is also supporting this assignment.
400 MHz, Chloroform-d.
59 MHz, Chloroform-d.
400 MHz, Chloroform-d.
400 MHz, Chloroform-d.
400 MHz, Chloroform-d.
400 MHz, Chloroform-d.
400 MHz, Chloroform-d.
400 MHz, Chloroform-d.
400 MHz, MeOH-d.
400 MHz, Chloroform-d.
400 MHz, Chloroform-\textit{d}.
400 MHz, Chloroform-d.
400 MHz, Chloroform-d.
400 MHz, Chloroform-\textit{d}. \\

![Chemical Structure and Spectra](image-url)
400 MHz, Chloroform-\textit{d}.
400 MHz, Acetone-d.
400 MHz, Chloroform-\textit{d}.

[Chemical structure diagrams and spectra]

80
400 MHz, Chloroform-$d$. 

[Chemical Structure Image]
400 MHz, Chloroform-\textit{d}.
400 MHz, Chloroform-\textit{d}.
400 MHz, MeOH-d.
400 MHz, Acetone-\textit{d}.
NOESY 1D experiment permitted to define the stereochemistry of the new stereocenter. In fact, we were able to see the NOE interaction between the cyclopentane proton (H$^1$) and the thymine NCH proton (H$^3$) and the proton (H$^2$).
400 MHz, MeOH-d.
400 MHz, DMSO-d.
NOESY 1D experiment permitted to define the stereochemistry of the new stereocenter. In fact, we were able to highlight the NOE interaction between the cyclopentane proton ($H^3$) and the three other protons $H^2$, $H^1$ and $H^4$. 