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Nucleoside Analogues: Synthesis from Strained Rings

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Dedication((optional))

Abstract: Nucleoside analogues are widely employed as bioactive compounds against cancer and viral infections. Consequently, it is important to develop efficient synthetic methods to access them with high efficiency and structural diversity. Herein, we present a full account of our work on the synthesis of nucleoside analogues via annulations of donor acceptor aminocyclopropanes and aminocyclobutanes. Thymine- and uracil- derived diester cyclopropanes were accessed from the corresponding nucleobases via vinylation and rhodium-catalyzed cyclopropanation, and were then used in (3+2) annulations with aldehydes, ketones and enol ethers. The obtained analogues could be transformed into important hydroxymethyl derivatives. Thymine and fluoro-uracil derived diester cyclobutanes obtained from the nucleobases via vinylation and (2+2) cycloaddition could also be used in a (4+2) annulation with aldehydes. Finally, purine-derived diester cyclopropanes could be accessed using the condensation of nucleobases with chloromethyl ethylidene malonates, but annulation reactions with this class of substrates was not successful.

Keywords: Nucleosides • Cyclopropanes • Annulations • Synthetic Method • Catalysis

1. Introduction

Nucleoside analogues are widely employed as bioactive compounds against a broad diversity of illnesses such as HIV and different types of cancer. Nevertheless, the emerging resistance towards nucleoside-based antiviral and anticancer agents is alarming.[1] Therefore, the development of new bioactive nucleoside analogues is urgently needed. Nucleosides exhibiting biological activity have structurally diverse cores, including the most common tetrahydrofuranyl amines such as the FDA approved drugs azidothymidine (**1**) and didanosine (**2**), and more rare six carbon based scaffolds such as the antiviral compounds anydrohexitol-g (**3**) and cyclohexenyl-g (**4**). Carbonucleoside analogues such as the antiviral compounds aristeromycin (**5**), abacavir (**6**) and cyclohexenyl-g (**4**) are also of great interest. In comparison with the corresponding tetrahydrofuranyl amine derivatives, they display increased metabolic stability.

Despite the fact that nucleoside analogues are of high interest and were extensively studied, there are only few methods for accessing them with high diversity and efficiency.[2] Nucleoside analogues are generally synthesized using the Vorbrüggen reaction.[2a] This transformation consists of the substitution of a leaving group on the ribose by a nucleobase, providing compounds derived from natural ribose. This method allows variation of the nucleobase. However, if unnatural modifications of the ribose core are desired, multi-step procedures are usually required.[3] A frequently used approach to access carbonucleoside analogues is to use the Vince lactam,[3a,b] which after opening delivers a cyclopentenylamine precursor for carbonucleoside derivatives.

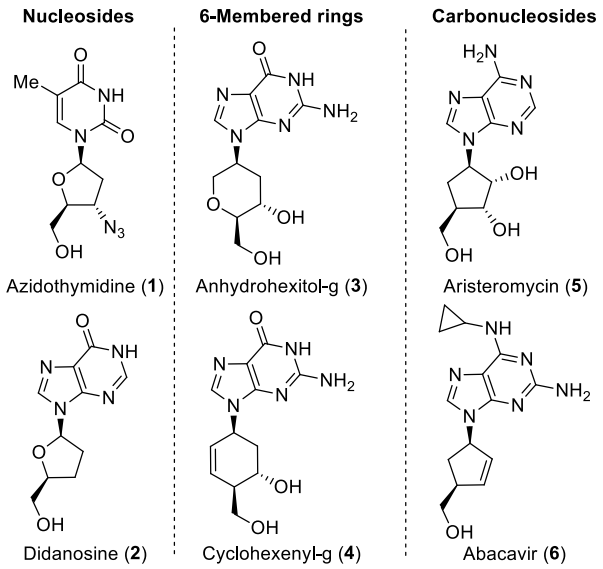

Figure 1. Bioactive nucleoside analogues.

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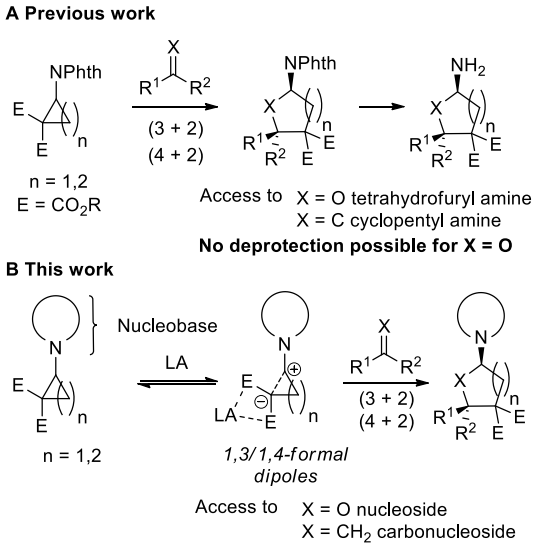
Further elegant work to access nucleoside analogues with a cyclopentyl core have been developed during the last years, proceeding via Pauson-Khand reaction,[3c] ring-closing methathesis[3d] or desymetrization of meso compounds such as cyclopentadiene or diols.[3e-g] Although these novel synthesis strategies increased the diversity of scaffolds accessible, they are often substrate specific and their scope is typically narrow.

Consequently, we decided to to develop a straightforward synthetic method for the synthesis of nucleoside analogues with broad structural diversity. Our goal was to take advantage of the strain release upon ring-opening of small rings such as cyclopropanes and cyclobutanes. Indeed 28 kcal/mol of energy is released during the ring opening of cyclopropane, which can be used to initiate chemical transformations. Donor-acceptor (DA) cyclopropanes and DA cyclobutanes in particular are versatile substrates as selective C-C bond cleavage is possible under mild conditions.[4] Thanks to the induced bond polarization, they can act as formal 1,3-dipoles and are suitable substrates for annulation with dipolarophiles providing an effective method for the synthesis of highly substituted five- or six-membered rings. Nitrogen-based DA cyclopropanes have been extensively studied in our group.[5] During these studies, we discovered that the protecting group on the nitrogen atom is key in the success of the annulation reactions. In particular, phthalimide-substituted DA cyclopropanes and cyclobutanes were excellent precursors for the synthesis of tetrahydrofuranyl and tetrahydropyranyl amines and cyclopentyl and cyclohexyl amines via formal (4+2) and (3+2) annulations (Scheme 1, **A**). In order to apply this methodology to the synthesis of nucleoside analogues, deprotection of the phthalimide group is required to introduce the nucleobase. Unfortunately, the removal of the phthalimide on tetrahydrofuranyl amines was not possible. Furthermore, even if the deprotection worked for cyclopentyl amines, the poor convergence of this strategy led us to design a new method for the synthesis of nucleoside analogues.

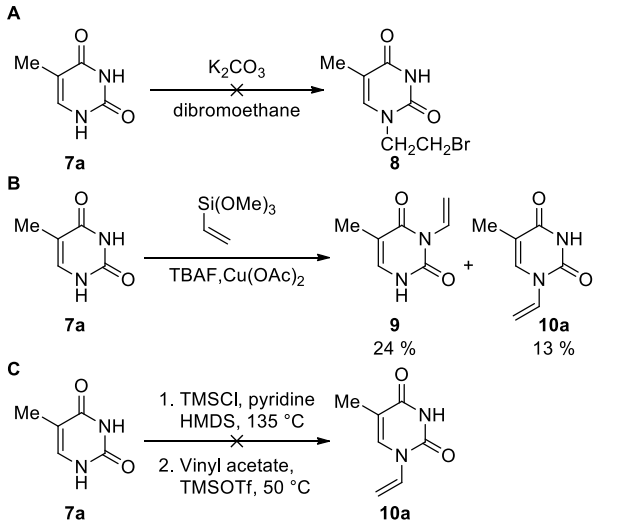
The new strategy consisted of having the nucleobase directly linked to the small ring, serving as the donor group (Scheme 1, **B**). With thymine and uracil-substituted DA cyclopropanes and cyclobutanes, five or six membered ring nucleoside analogues become accessible through (3+2) or (4+2) annulations with dipolarophiles such as ketones, aldehydes or enol ethers in a single step.[6] Herein, we would like to give a full account of this work, including details on the synthesis of the cyclopropanes, reaction optimization and scope of the annulation reactions. First attempts towards the synthesis of purine-based nucleoside analogues will be also described. At this stage, the nucleoside analogues are only obtained as racemic mixtures, but this could also be an advantage if both enantiomers are needed for biological testing.



Scheme 1. Strategy to access nucleoside analogues from nitrogen-substituted strained rings.

2. Synthesis of Nucleoside Analogues via Annulation reactions

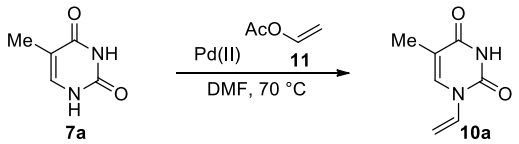
We planned to synthesize the required pyrimidine cyclopropanes via cyclopropanation of the corresponding enamides. Therefore, a robust synthesis of vinyl pyrimidines was needed. When we started our work there was only a few reports of vinylation methods applied to pyrimidine nucleobases: N(1) alkylation followed by elimination,[7] Chan-Lam coupling using trimethoxyvinyl silane as vinyl source along with tetrabutyl ammonium fluoride (TBAF) and stoichiometric amount of Cu(II),[8] and nucleophilic attack of TMS-protected thymine on vinyl acetate in presence of trimethylsilyl trifluoromethane sulfonate (TMSOTf).[9] In our hands the preparation of N(1) vinyl thymine **10a** following these reported procedures failed (Scheme 2). With dibromoethane, we were not able to isolate the desired product **8** (Scheme 2, **A**). This is in agreement with a later report of Nawrot and co-workers, who showed that alkylation of thymine under these conditions only led to bicyclic side products.[10] Even after intensive optimization, the desired products could be obtained only in 10% yield. Some conversion was observed in the Chan-Lam coupling leading to a mixture of N(3) and N(1) vinylated products **9** and **10a**, which were isolated in 24% and 13% yield respectively with N(3) vinylated thymine (**9**) as major product (Scheme 2, **B**). In addition to the low yield of the N(1) vinyl thymine (**10a**), the separation of the regioisomers was laborious, prohibiting the use of this reaction for the preparation of larger amounts of N(1) vinyl thymine (**10a**). In conclusion, the reported procedures were not suitable to prepare enough N(1) vinyl thymine (**10a**) for the further development of our methodology.



Scheme 2. Attempts for the preparation of N(1) vinyl thymine using reported procedures.

In a precedent report of our group, we described the preparation of vinyl phthalimide, maleimide and succinimide via palladium cross coupling.[5e] For this transformation, the palladium(II) sources used were sodium tetrachloropalladate or palladium dichloride with lithium chloride. However, these transformations were performed in vinylacetate (**11**) as solvent in which thymine (**7a**) is not soluble. Solubility experiments with different co-solvents were conducted with dichloromethane (DCM), dichloroethane (DCE), chloroform, methanol (MeOH), ethanol (EtOH), acetonitrile (ACN), tetrahydrofuran (THF), dioxane, dimethylformamide (DMF) and water. The solubility of thymine (**7a**) was highest in hot water and hot mixtures of alcohol (MeOH or EtOH) and water (60 °C), followed by dioxane and DMF (both at 60 °C) in which no complete dissolution was observed. Attempts at palladium coupling in dioxane were not successful, but better results were obtained in DMF. Na_2PdCl_4 or $PdCl_2$ with or without LiCl were not suitable catalysts for the vinylation of thymine (**7a**) (Table 1, entries 1 to 3): only traces of N(1) vinyl thymine (**10a**) were detected (a mixture of N(3) and N(1) vinyl thymine **9** and **10a** is observed with $PdCl_2$ (entry 1)). With $Pd(OAc)_2$ only 3% of conversion was observed, but selectively to N(1) vinylthymine (**10a**) (entry 4). No dependence on the equivalents of vinyl acetate (**11**) used was observed (entries 5 and 6). Further investigation with increased amount of $Pd(OAc)_2$ showed that higher loading in palladium led to better conversion (entries 7 and 8). Inspired by the work of Toti et al.[9] and Nawrot et al.,[10] who reported the alkylation or vinylation of thymine (**7a**) in presence of TMSOTf, we performed the reaction with a stoichiometric amount of TMSOTf. The conversion increased from 3% to 17% with 4% of $Pd(OAc)_2$ (entry 9). When the amount of TMSOTf was increased to 2.4 equivalents and the reaction time was extended to 24 h, the reaction conversion reached 32% and 51% respectively (entries 10 and 11).

Table 1. Screening of reaction conditions for N(1) vinylation of thymine (**7a**).

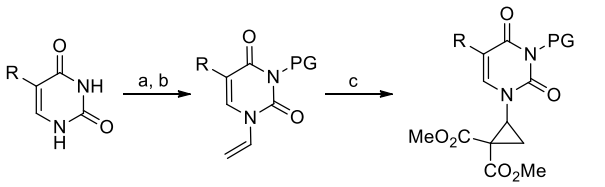


Entry	Catalyst	Loading[a]	Additive[b]	equiv **11**	Time	Ratio[c]
1	$PdCl_2$	4	-	1.2	10 h	<2%[d]
2	$Na_2Pd_2Cl_4$	4	-	1.2	10 h	<2%
3	$PdCl_2$	4	LiCl	1.2	24 h	<2%
4	$Pd(OAc)_2$	4	-	1.2	24 h	3%
5	$Pd(OAc)_2$	4	-	1.6	10 h	3%
6	$Pd(OAc)_2$	4	-	2	10 h	3%
7	$Pd(OAc)_2$	7	-	1.2	10 h	6%
8	$Pd(OAc)_2$	20	-	1.2	10 h	11%
9	$Pd(OAc)_2$	4	TMSOTf	1.2	10 h	17%
10	$Pd(OAc)_2$	4	TMSOTf[e]	1.2	10 h	32%
11	$Pd(OAc)_2$	4	TMSOTf[e]	1.2	24 h	51%
12	$Pd(OAc)_2$	4	TMSOTf[e] NEt_3[e]	1.2	24 h	83%

Reaction conditions: Thymine (**7a**) (0.1 g, 0.8 mmol), palladium catalyst and additives in DMF (2 mL) were stirred in a flame-dried flask under nitrogen and heated to 70 °C. [a] In mol%. [b] 1.2 equiv. [c] NMR ratio (**10a**/(**7a**+**10a**)) of the integration of the C=C-H thymine signals. [d] Mixture of N(1) and N(3) vinyl thymine. [e] 2.4 equiv additive was used.

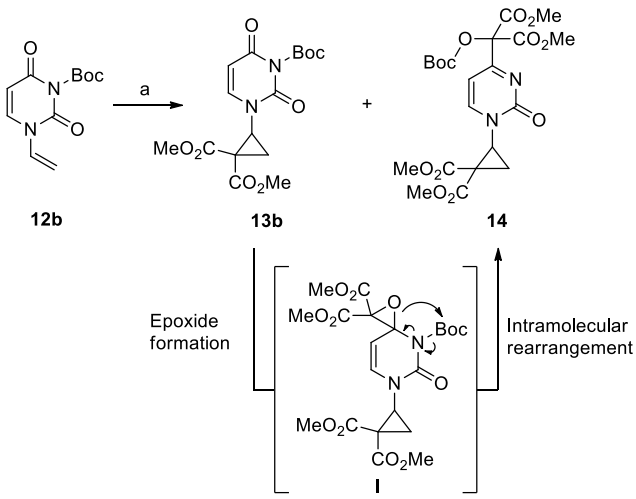
Finally after adding an additional base (triethylamine) the conversion went to 83% and the isolated yield reached 79% of the sole N(1) vinyl-thymine (**10a**) (entry 12). Fortunately, the vinylation worked well also on uracil (**7b**) and 5-fluoro-uracil (**7c**) with complete regioselectivity and respectively 69% and 57% isolated yield (products **10b** and **10c**).

To access the desired cyclopropanes, protection of the imide nitrogen was performed, followed by cyclopropanation using the corresponding diazomalonate and the rhodium Espino catalyst developed by Du Bois and co-workers (Scheme 3).[11] For thymine (**7a**) and uracil (**7b**), a *tert*-butoxycarbonyl protecting group was used. When protection of fluoro-uracil (**7c**) was attempted, a mixture of carbonates and carbamate was obtained in poor yield. In this case a benzoyl group could be installed selectively on the nitrogen. The three pyrimidine cyclopropanes **13a**, **13b** and **13c** were obtained in good overall yields.



Scheme 3. Synthesis of cyclopropanes **13**. Reaction conditions: a) 4 mol% $Pd(OAc)_2$, vinylacetate, TMSOTf, NEt_3, 70 °C, DMF. b) Boc_2O, DMAP, CH_2Cl_2 or BzCl DMAP, NEt_3. c) 0.02 mol% $Rh_2(esp)_2$, diazodimethylmalonate, CH_2Cl_2.

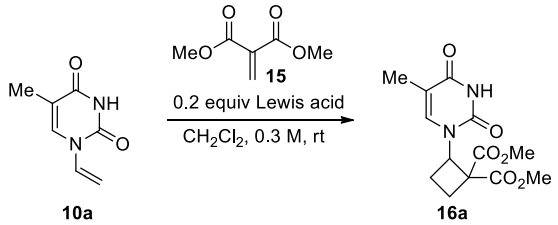
Surprisingly, when the cyclopropanation of vinyl-uracil **12b** was performed with 1.2 equivalents instead of an equimolar amount of the diazomalonate, a new pyrimidine cyclopropane was isolated containing two malonate moieties with an intact thymine double bond (Scheme 4). After extensive spectroscopic investigations, we identified this compound as **14**. The formation of cyclopropane **14** can be tentatively explained by the unusual formation of epoxide **I** instead of cyclopropanation of the thymine double bond through the reaction with one additional equivalent of diazomalonate mediated by the rhodium Espino catalyst. Then, an intramolecular rearrangement via opening of the epoxide, followed by the migration of the Boc group to the oxygen atom would afford pyridone cyclopropane **14**.



Scheme 4. Unexpected formation of pyridone cyclopropane **14** and tentative mechanism. Reaction conditions: a) 0.5 mol% $Rh_2(esp)_2$, 1.2 equiv diazodimethylmalonate, CH_2Cl_2. Yields: **13b** 28% and **14** 64%.[12]

Starting again from vinyl thymine **10a**, a [2+2] cycloaddition gave access to the thymine DA cyclobutane **16a**. As the reported procedure of our group to synthesize thymine cyclobutanes through [2+2] cycloaddition using $FeCl_3$ on aluminium oxide as catalyst[5i] gave low yield (Table 2, entry 1), other Lewis acids were screened. Low conversion was obtained with $Zn(OTf)_2$, $AuCl_3$, $Sn(OTf)_2$ and $Sc(OTf)_3$ (entries 2 to 5). Complete decomposition of the starting material was observed when $Hf(OTf)_4$ and $TiCl_4$ were used (entries 6 and 7). With $In(OTf)_3$, $Cu(OTf)_2$ and $Yb(OTf)_3$ as Lewis acid catalysts, the reaction exhibited low conversion (entries 8 to 10). Nevertheless, using $FeCl_3$ on aluminium oxide the conversion was increased from 13% after 14 hours to 35 % after 24 hours (entries 1 and 11). The reaction was shut down when other solvents were used such as MeOH, DMF, dioxane, CCl_4 or a mixture of DCM/MeOH. ACN allows the reaction to proceed, but with lower conversion. Using DCE as solvent gave roughly similar conversion to the DA cyclobutane **16a**.

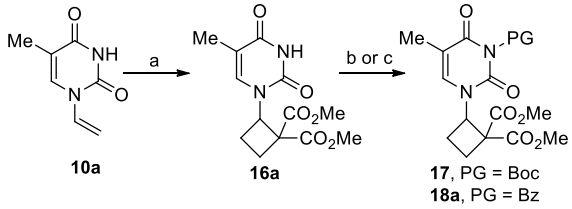
Table 2. Optimization of the [2+2] reaction.



Entry	LA	Ratio[a]	Entry	LA	Ratio[a]
1	$FeCl_3$•Al_2O_3	13%	7	$TiCl_4$	dec.
2	$Zn(OTf)_2$	<2%	8	$Cu(OTf)_2$	5%
3	$AuCl_3$	<2%	9	$Yb(OTf)_3$	5%
4	$Sc(OTf)_3$	<2%	10	$In(OTf)_3$	10%
5	$Sn(OTf)_2$	<2%	11	$FeCl_3$•Al_2O_3	35%[b]
6	$Hf(OTf)_4$	dec.			

Reaction conditions: Vinyl thymine **10a** (50 mg, 0.33 mmol), 2 equiv methylidene malonate **15**, dry CH_2Cl_2, 0.3 M, stirred under N_2. [a] NMR ratio (**16a**/(**10a**+**16a**)) of the integration of the C=C-H signals. [b] 24 hour reaction.

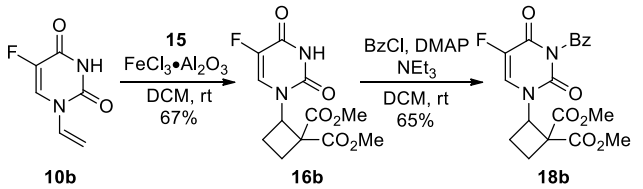
When the reaction is conducted with freshly prepared $FeCl_3$•Al_2O_3 and methylidene malonate on preparative scale, the isolated yield of **16a** reached 43% (Scheme 5). However, (4+2) cycloaddition was not successful with this substrate (*vide infra*). Thymine cyclobutane **16a** was therefore protected with a *tert*-butoxy carbonyl group to avoid side reactions. However, the Boc group exhibited high lability and was removed in presence of Lewis acids.



Scheme 5. Synthesis of thymine cyclobutanes. Reaction conditions: a) 0.2 equiv $FeCl_3$•Al_2O_3, methylidene dimethylmalonate (**15**), DCM, 43%. b) Boc_2O, DMAP, ACN, 81%. c) BzCl, DMAP, NEt_3, DCM, 86%.

Benzoyl as protecting group was then examined, as it was expected to be more stable than *tert*-butoxycarbonyl group. Benzoylation of **16a** gave protected cyclobutane **18a** in 86% yield. Using the same reaction sequence, fluoro-uracil

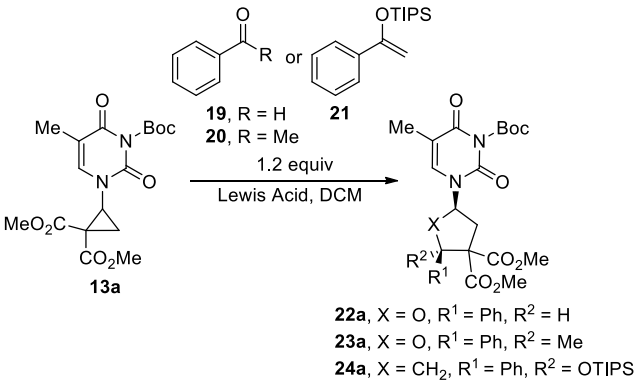
derived cyclobutane **18b** could be also obtained in good yield (Scheme 6).



Scheme 6. Preparation of 5-fluoro uracil cyclobutane **18b**.

Having the pyrimidine-based DA cyclopropanes **13a-c** and DA cyclobutanes **18a, b** in hand, we then examined the corresponding (3+2) and (4+2) formal cycloadditions catalyzed by Lewis acids with ketones, aldehydes and enol ethers as partners to access 5- and 6- membered nucleoside analogues. Using the conditions described for the (3+2) reaction with aldehydes and phthalimide-substituted DA cyclopropanes, the desired five-membered ring **22a** was isolated in low yield with the thymine-substituted DA cyclopropane **13a** (Table 3, entry 1).

Table 3. Optimization of the [3+2] annulation.

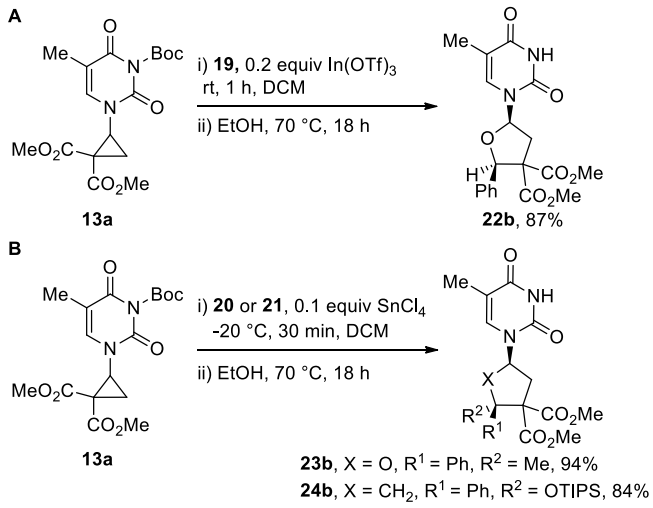


Entry	Partner[a]	LA	Loading[b]	T	Time	Yield[c]
1	**19**	$FeCl_3$•Al_2O_3	5	rt	3 days	27%
2	**19**	$In(OTf)_3$	20	rt	1 h	86%
3	**19**	$Hf(OTf)_4$	20	rt	1 h	49%[d]
4	**20**	$SnCl_4$	5	-78 °C	2 days	6%
5	**21**	$SnCl_4$	10	-78 °C	2 days	52%
6	**20**	$SnCl_4$	5	-20 °C	30 min	60%
7	**21**	$SnCl_4$	10	-20 °C	30 min	60%

[a] Reaction conditions: 1.2 equiv **19**, **20** or **21**, dry DCM, 0.3 M, stirred under N_2. [b] In mol%. [c] Isolated yield. [d] Yield of the nucleoside without the protecting group. Deprotection occurred under these conditions.

When the Lewis acid was changed from $FeCl_3$•Al_2O_3 to $In(OTf)_3$, the isolated yield increased to 86% (entry 2). Interestingly, with $Hf(OTf)_4$ as catalyst, the yield was moderate, but gave a direct access to the deprotected product **22b** (entry 3). However, this yield could not be improved. In our previous work, when ketones and enol ethers were used as dipolarophiles with phthalimide cyclopropanes, the best Lewis acid was $SnCl_4$ at low temperature.[5a-b] Using these conditions with thymine cyclopropane **13a** over two days led to low yield with acetophenone (**20**) and moderate yield with TIPS protected acetophenone (**21**) (entries 4 and 5). Increasing the temperature to -20 °C, resulted in complete conversion after 30 minutes (entries 6 and 7). The two desired nucleoside analogues **23a** and **24a**, synthesized from the ketone **20** and the enol ether **21**, respectively, were isolated in 60% yields.

As the Boc group on thymine is thermally labile, an efficient two step procedure, consisting in the Lewis acid-catalyzed (3+2) annulation, followed by filtration (to remove the Lewis acid catalyst) and *tert*-butoxycarbonyl removal at 70 °C for 18 h was developed (Scheme 7). When the two step procedure was applied to the (3+2) reaction with benzaldehyde (**19**), the unprotected nucleoside **22b** was isolated in 87% yield (Scheme 7, **A**). The two step protocol gave better yield of nucleoside analogues in the case of acetophenone (**20**): 94% yield of **23b** was obtained instead of 60% of **23a** without deprotection (Scheme 7, **B**). Carbonucleoside **24b** was isolated in 84% yield by using the two step procedure.

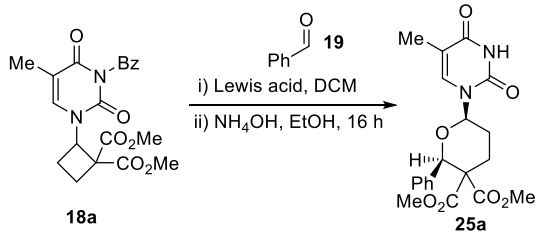


Scheme 7. Optimized conditions for annulation-deprotection.

The (4+2) reaction was then investigated using thymine cyclobutane **16a** with different Lewis acids ($Zn(OTf)_2$, $AuCl_3$, $Sn(OTf)_2$, $Sc(OTf)_3$ $TiCl_4$, $Hf(OTf)_4$, $In(OTf)_3$, $Cu(OTf)_2$, $FeCl_3$•Al_2O_3 and $Yb(OTf)_3$). No conversion was observed for most of the Lewis acids, except with $In(OTf)_3$ and $Hf(OTf)_4$: these catalysts gave access to tetrahydropyranyl amine in low yield due to degradation. A screening of Lewis acids was also conducted with Boc protected thymine cyclobutane **17**, including $Zn(OTf)_2$, $AuCl_3$, $Sn(OTf)_2$, $Sc(OTf)_3$, $TiCl_4$, $SnCl_4$, $Hf(OTf)_4$, $In(OTf)_3$, $Cu(OTf)_2$, $FeCl_3$•Al_2O_3 and $Yb(OTf)_3$. Encouraging results were obtained with $Hf(OTf)_4$ and $FeCl_3$•Al_2O_3: the desired nucleosides analogues were isolated in 59% and 56% yield respectively. However, partial loss of the Boc protecting group was again observed. Therefore, we focused our efforts on these two Lewis acids with benzoyl protected thymine cyclobutane **18a**. Even in this case, a partial benzoyl group removal was observed, thus deprotection using an ammonium hydroxide solution in ethanol was systematically performed directly after annulation.[13] As benzoyl deprotection was quantitative, the optimization focused on the conditions for the (3+2)

annulation (Table 4). With hafnium triflate, the two step procedure gave moderate yield after 14 hours (entry 1) due to partial decomposition of the product **25a**. When the reaction time was shortened to 30 min, the product **25a** was isolated in an increased 76% yield (entry 2). The optimum time was found to be 15 minutes (entry 3), as the conversion is complete and the degradation minimized. If the reaction time was shortened to 10 and 5 minutes (entries 4 and 5), the reaction was not complete and lower yields were obtained. The reaction with iron trichloride supported on alumina went to completion only after 14 hours, providing **25a** in moderate yield (entry 6). Therefore, a stoichiometric amount of $FeCl_3$•Al_2O_3 was used in order to shorten the reaction time. Complete conversion was reached after 30 min, but the yield was not improved (entry 7). The same observation was made when the reaction was performed at a 0.3 mmol scale. The reaction was stopped after completion (15 minutes in this case), after filtration and deprotection 60% yield was obtained (entry 8).

Table 4. Screening of conditions for the [4+2] annulation.



Entry	Lewis acid	Loading	Time	Yield[a]
1	$Hf(OTf)_4$	20 mol%	14 h	51%
2	$Hf(OTf)_4$	20 mol%	30 min	76%
3	$Hf(OTf)_4$	20 mol%	15 min	87%
4	$Hf(OTf)_4$	20 mol%	10 min	55%[b]
5	$Hf(OTf)_4$	20 mol%	5 min	44%[b]
6	$FeCl_3{\cdot}Al_2O_3$	20 mol%	14 h	59%
7	$FeCl_3{\cdot}Al_2O_3$	100 mol%	30 min	62%
8	$FeCl_3{\cdot}Al_2O_3$	100 mol%	15 min	60%[c]
9	$Hf(OTf)_4$	20 mol%	15 min	78%[c]

Reaction conditions: **18a** (20 mg, 0.050 mmol), 1.5 equiv benzaldehyde (**19**), 0.05 M in dry DCM, stirred under N_2. Then filtration, NH_4OH, EtOH, 16 hours. [a] NMR yields after isolation due to benzamide poisoning (not removable by column), all [4+2] annulations went to full conversion, otherwise stated. [b] [4+2] annulation not complete. [c] 0.3 mmol scale.

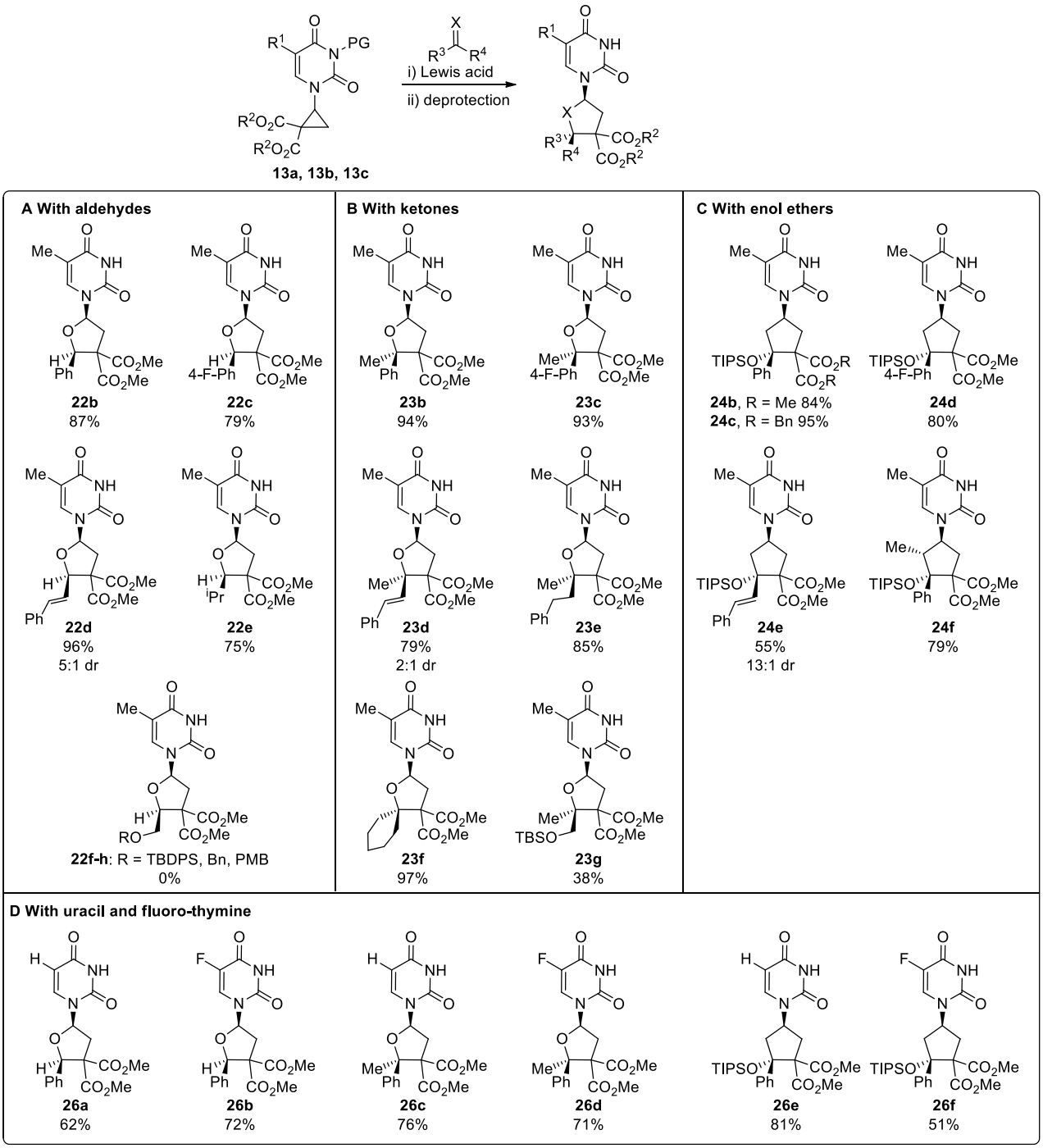
Finally, the (4+2) annulation was performed on larger scale with 0.3 mmol of cyclobutane **18a** with hafnium triflate, providing the nucleoside analogue **25a** in 78% isolated yield (entry 9). Unfortunately, the (4+2) annulation conducted with TIPS enol ether **21** gave only traces of product even after 24 hours. With acetophenone **20**, the desired benzoyl protected nucleoside was obtained in 54% yield after 24 hours, but the conversion was not complete.

Having the optimized conditions in hand for the (3+2) and the (4+2) annulations, we investigated the scope of the reaction and its limitations. The reaction was examined with aldehydes first (Scheme 8, **A**). The nucleoside **22c** synthesized from 4-fluoroacetophenone, was obtained in 79% yield and high diastereoselectivity. The diastereoselectivity was lower in the case of cinnamaldehyde, but product **22d** was still obtained in 96% yield. The (3+2) reaction worked also with the sterically hindered aliphatic isobutyraldehyde, providing **22e** in 75% yield and complete diastereoselectivity. We then examined the use of 2-hydroxy acetaldehyde derivatives in the reaction to provide nucleoside analogues **22f-h** with the hydroxymethyl group often required for the bioactivity of drugs. Unfortunately, this type of aldehydes was more prompt to polymerization and no conditions to obtain the nucleoside derivatives could be found.

We then turned to ketones as substrates (Scheme 8, **B**). Aromatic ketones (acetophenone (**20**) and 4-fluoro acetophenone) afforded the nucleoside analogues **23b** and **23c** in high yield and diastereoselectivity. In the case of an alkenyl ketone, the product **23d** was isolated in good yield and poor diastereoselectivity. Aliphatic ketones also worked well in the annulation reaction: the phenethyl substituted nucleoside derivative **23e** and the bicyclic nucleoside **23f** were obtained in 85% and 97% yield respectively. Using TBS protected 2-hydroxyacetacetone, nucleoside **23g** bearing a hydroxymethyl group could be accessed in 38% yield.

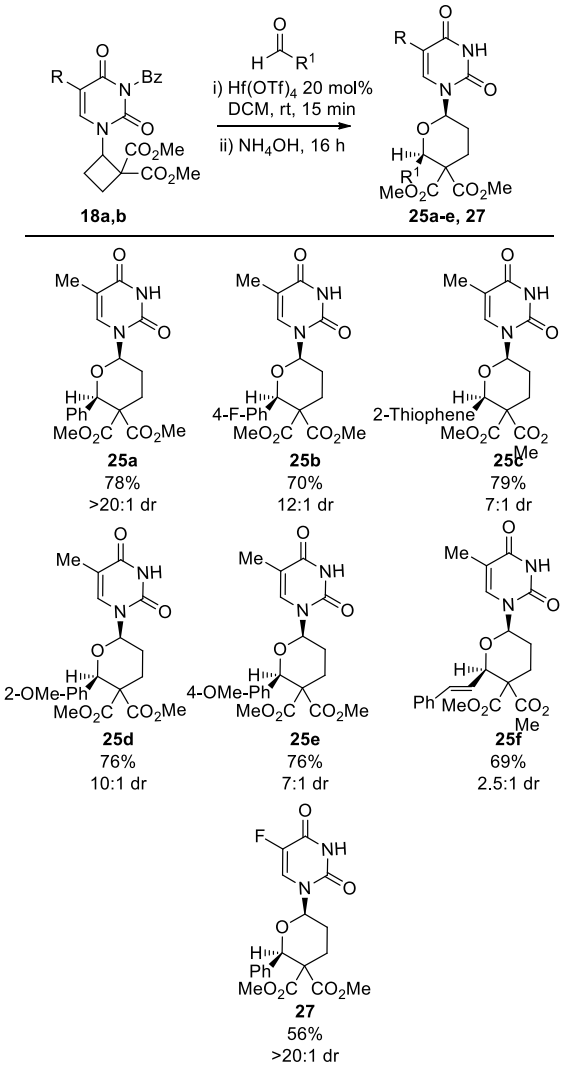
Carbonucleoside derivatives were then synthesized with enol ethers as dipolarophiles (Scheme 8, **C**). **24b-d** were obtained in high yield and diastereoselectivity with enol ethers substituted with aromatic groups. When a dibenzylester thymine cyclopropane was used with enol ether **21**, the yield reached 95% (product **24c**). The styrenyl carbonucleoside **24e** was isolated with 13:1 diastereoselectivity in 55% yield. One more stereocenter is formed using a tri-substituted enol ether and the highly substituted nucleoside analogue **24f** was obtained as a single diastereoisomer in 79% yield.

The annulation reaction was also conducted with 5-fluoro uracil cyclopropane **13c** and uracil cyclopropane **13b** under the conditions optimized for thymine cyclopropane **13a** (Scheme 8, **D**). For the deprotection of the benzoyl group on the 5-fluorouracil nucleoside, we used again NH_4OH in EtOH, and the mixture was stirred at room temperature for 18 hours. Nucleoside analogues synthesized from benzaldehyde bearing uracil and 5-fluoro-uracil nucleobases **26a** and **26b** were obtained in 62% and 72% yield. With acetophenone, the yields remain similar, 76% and 71% for **26c** and **26d**, respectively. Finally, carbonucleoside derivatives **26e** and **26f** were isolated in moderate to high yields (81% and 51% respectively).



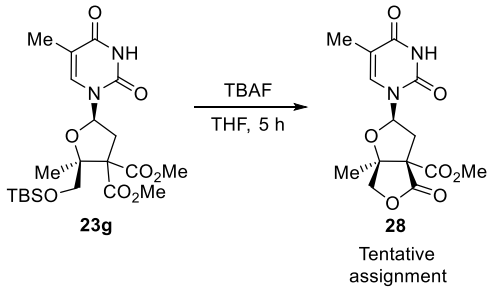
Scheme 8. Scope of the [3+2] annulation. The products were obtained as a single diastereoisomer, unless stated otherwise.

We then examined the scope of the (4+2) annulation with thymine and 5-fluoro uracil cyclobutanes **18a** and **18b** and aldehydes (Scheme 9). The (4+2) annulation worked with electron neutral, benzaldehyde, electron poor 4-fluoro-benzaldehyde and thiophene-2-carbaldehyde, providing pure compounds **25a**, **25b** and **25c** in 70 to 79% yield and 7:1 to >20:1 diastereoselectivity after column chromatography and recrystallization to remove the benzamide side product. Aldehydes bearing electron rich aromatic groups, such as *meta*-methoxy benzaldehyde and *para*-methoxy benzaldehyde, gave the corresponding nucleosides **25d** and **25e** in 76% yield. Styryl-substituted product **25f** could also be obtained, but with a loss of stereoselectivity as previously noticed in the [3+2] reaction. 5-Fluoro-uracil cyclobutane **18b**, efficiently provided the desired nucleoside analogue **27** with good diastereoselectivity.



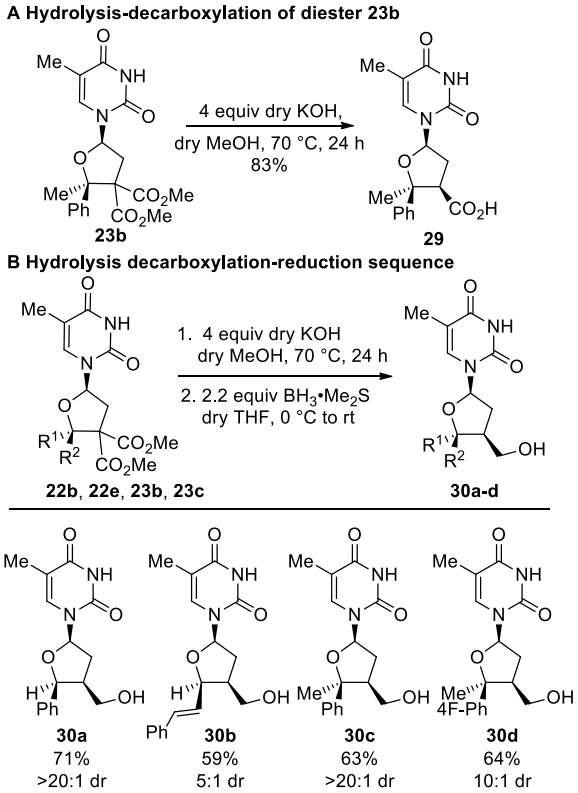
Scheme 9. Scope of the [4+2] annulation. Yield and diastereoselectivity are given after column chromatography and recrystallization.

In order to increase the diversity of our compounds and to provide potentially bioactive molecules, methods to access the hydroxymethyl substituted derivatives were examined. As discussed above, only α-hydroxylated ketones could be used directly in the annulation reaction. However, TBS deprotection of product **23g** led to a complex mixture containing a major compound tentatively identified as lactone **28**,[14] and the desired free alcohol could not be accessed (Scheme 10).



Scheme 10. Attempted deprotection of nucleoside analogue **23g**.

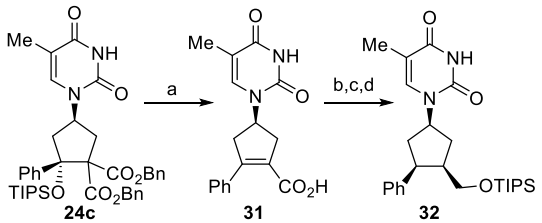
Consequently, we investigated modification of the esters to access the desired hydroxy methyl group. The Krapcho decarboxylation[15a,b] was first examined. With different salts (NaCl, LiCl, LiI and Li_2SO_4), and DMF or DMSO as solvent at high temperature (from 80 °C to 130 °C), no mono ester derivatives was isolated. Alternative methods for ester hydrolysis ($Ba(OH)_2$,[15c] Me_3SnOH[15d]) or reduction (DiBAl-H, $LiAlH_4$, $Me(EtO)_2SiH$ with $Zn(OAc)_2$[15e]) were then investigated. Unfortunately, either no reaction was observed or degradation occurred. However, in MeOH at 70 °C with an excess KOH, the compound **23b** underwent saponification of both dimethylesters, followed by a diastereoselective decarboxylation, providing cleanly the carboxylic acid derivative **29** in high yield and diastereoselectivity (Scheme 11, **A**).



Scheme 11. Synthesis of hydroxymethyl nucleoside analogues.

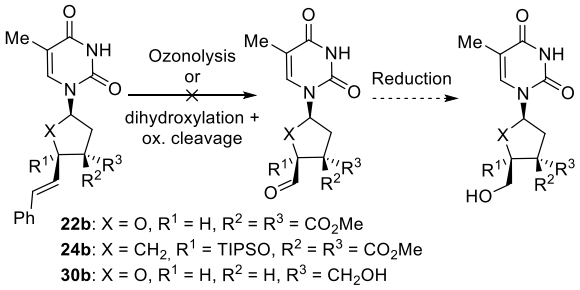
The use of four equivalents fine powdered and dry KOH in combination with dry MeOH was important to obtain reproducibly high yields and selectivity. Reduction of the carboxylic acid with boron dimethylsulfide complex gave then access to 4'-hydroxymethyl nucleoside derivatives. This efficient method was applied to the synthesis of nucleoside analogues **30a-d** in good yield, but with lower diastereoselectivity for **30b** and **30d** (Scheme 11, **B**).

When carbonucleoside derivatives were submitted to the saponification decarboxylation reaction, a mixture of unsaturated five membered rings was obtained due to silanol elimination. Consequently, we turned our attention to benzyl diester **24c**, which can be converted to the diacids under milder, non-basic conditions. The benzyl protecting groups were smoothly removed under hydrogenolysis conditions, then the diacid obtained was heated neat at 80 °C to allow decarboxylation to proceed providing the mono-acid **31** (Scheme 12). In this case, a controlled elimination of the silanol was observed. Finally, olefin hydrogenation followed by reduction of the carboxylic acid and protection of the corresponding alcohol afford the protected hydroxymethyl derivatives **32** in an efficient manner. Protection prior to isolation was preferred, as the free alcohol was unstable.



Scheme 12. Preparation of hydroxymethyl carbonucleoside derivative **32**. a) 10% Pd/C, 1 atm H_2, EtOH, 57 °C, then neat, 80°C, 64%. b) 5% Pd/C, 1 atm H_2, EtOH, 85%. c) BH_3•SMe_2, THF. d) TIPSCl, DMF, imidazole, 55% over two steps.

We were also interested in the synthesis of 4'-hydroxymethyl nucleoside analogues. Thus, we investigated the transformation of the styrene group of compounds **22b**, **24b**, and **30b** into the corresponding aldehyde, which could lead after reduction, to the targeted alcohol (Scheme 13). Ozonolysis generally led to degradation of the starting materials. Dihydroxylation followed by oxidative cleavage, using several reported procedures (cat. OsO_4 with $NaIO_4$ and lutidine, cat. OsO_4 with PIDA and lutidine,[16a] cat. OsO_4 with NMO and citric acid followed by $NaIO_4$[16b]) was also not successful, leading to inseparable mixtures of unidentified products along with decomposition of the starting materials.[17]

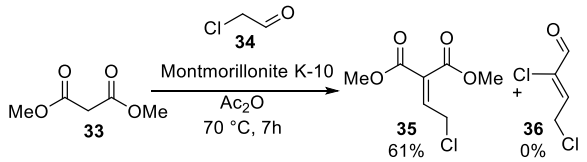


Scheme 13. Attempted synthesis of 4'-hydroxymethyl nucleoside analogues.

After the synthesis of pyrimidine nucleoside analogues had been achieved via annulation reactions of strained rings, we turned our attention to purine nucleoside analogues. As substituents on the cyclopropane, we chose adenine, 6-chloro-2-amino purine and 6-chloro purine. 6-Chloro-2-amino purine derivatives are interesting, as they can be used as precursors for both adenine and guanine derivatives.[18]

In order to synthesize purine cyclopropanes, we firstly thought about using the protocol developed for the pyrimidines. However, the palladium catalyzed vinylation was not successful with purines. As an alternative approach, a tandem Michael addition/cyclopropane formation of purines on chloromethyl-ethylidene malonates was envisaged. Indeed, Geen and co-workers had reported a single example of synthesis of a 6-chloro-2-amino purine derived diester cyclopropane using this approach.[19]

As described by Lehnert, chloromethyl-ethylidene malonates can be prepared via a Knoevenagel condensation of chloroacetaldehyde on malonate derivatives in presence of two equivalents of titanium tetrachloride and four of pyridine.[20] Unfortunately, in our hand this reaction turned out to give the product in highly fluctuating yields (from 60% to 0%), as polymerization of the starting material was often observed. Deshmuck and co-workers have described the condensation of trichloroacetaldehyde on diethylmalonate using Montmorillonite K-10 in Ac_2O at 150 °C for five hours.[21] These conditions were then examined with chloroacetaldehyde **34**, but after only 10 minutes of reaction, complete degradation was observed. When the temperature was lowered to 110 °C complete conversion was obtained after 1 h to the desired product **35**, together with the aldol dimer **36** of chloroacetaldehyde. As the two compounds were difficult to separate, the reaction conditions were optimized in order to avoid dimer formation. At 70 °C for 7 hours, the reaction was complete giving access to the desired ethylidene malonate **35** along with some remaining malonate **33**, which was easily removed by column chromatography (Scheme 14). The product was isolated up to 61% on a five gram scale reaction.

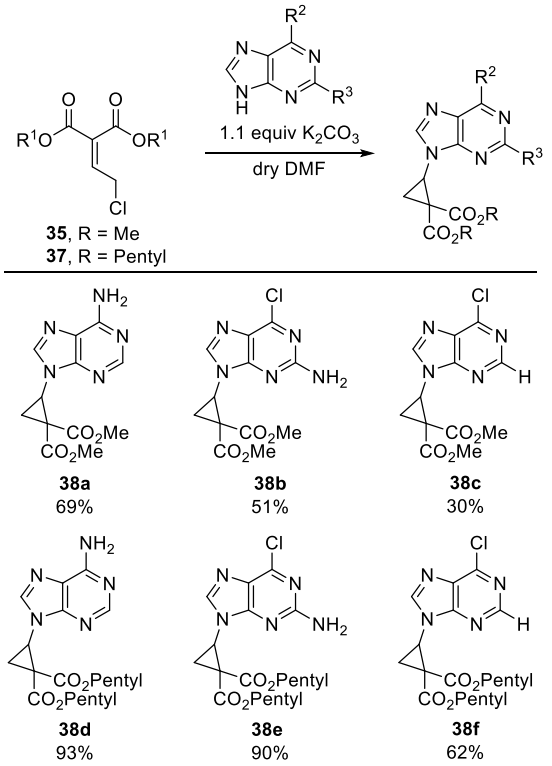


Scheme 14. Preparation of chloromethyl-ethylidene dimethylmalonate (**35**).

Furthermore, chloromethyl-ethylidene malonate **37** bearing pentyl esters was synthesized in order to increase the solubility of the purine cyclopropanes in organic solvents. It was obtained from the malonic acid through esterification with the corresponding pentyl

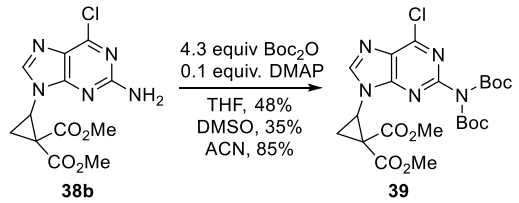
alcohol followed by the optimized Knoevenagel reaction.

The obtained alkylidene malonates **35** and **37** were then submitted to the previously reported conditions for cyclopropanation (Scheme 15).[19] Purine cyclopropanes were obtained in moderate to excellent yields, always with complete regioselectivity. Generally, cyclopropanes with geminal dimethyl ester **38a**, **38b** and **38c** were obtained in lower yields. Purification was a major issue due to their poor solubility in organic solvents and to their high polarity. The other three cyclopropanes **38d**, **38e** and **38f** with pentyl ester chains were isolated in higher yields (62 to 93%), as they were well soluble in organic solvents.



Scheme 15. Synthesis of purine cyclopropanes.

The solubility of dimethyl ester cyclopropanes **38a-c** was poor in all common organic solvents, even if the 6-chloropurine cyclopropane **38c** exhibited a slightly improved solubility. Only partial solubility in hot acetonitrile or DMF was observed. In contrast, the purine cyclopropanes **38d-f** bearing pentyl esters were completely soluble in dichloromethane at room temperature. In order to prevent any potential catalyst deactivation or side-reaction and also improve its solubility, the free amine of the 6-chloro-amino-purine cyclopropane **38b** was protected with two *tert*-butoxycarbonyl groups to give product **39** (Scheme 16). The yield of the protection step is highly dependent on the solvent: In THF or DMSO, the isolated yields were typically around 40%, whereas in acetonitrile the product was obtained in 85% yield.



Scheme 16. Preparation of the protected purine cyclopropane.

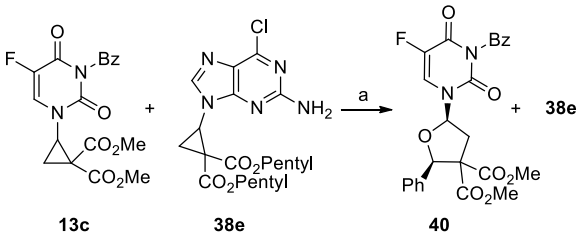
Attempts to protect the free amine with a benzyl group via a S_N^2 reaction using a phase transfer reagent[22] or through reductive amination[23] failed, as did protection with dimethylcarbonate.

Cyclopropanes **38a-f** were then examined in the (3+2) annulation with benzaldehyde (**19**) as partner and a broad range of Lewis acids. The first cyclopropane tested was the adenine cyclopropane **38a** bearing methyl esters. The screening was initially planned in dichloromethane, which had been the solvent of choice for the (3+2) annulation of thymine-substituted cyclopropanes. Unfortunately, adenine cyclopropane **38a** displayed extremely poor solubility in DCM, THF and ACN. Even with slightly more soluble purine cyclopropanes **38b** no reaction was observed using $In(OTf)_3$ as catalyst in several solvents (DCM, DCE, DCM/MeOH, CCl_4, THF, ACN, toluene, MeOH, benzene, DMF and DMSO). We hypothesized that the lack of reactivity of this cyclopropane may be the consequence of catalyst poisoning due to the coordination of the Lewis acid to the free amine of the substrate. Therefore, the annulation of **38c** was examined with different Lewis acids ($Zn(OTf)_2$, $AuCl_3$, $Sn(OTf)_2$, $Sc(OTf)_3$, $Hf(OTf)_4$, $In(OTf)_3$, stoichiometric $In(OTf)_3$, $Cu(OTf)_2$, $FeCl_3$•Al_2O_3 and $Yb(OTf)_3$). However, also in this case, no conversion to the desired nucleoside analogues was observed.

No reaction was observed with pentyl esters-substituted adenine cyclopropane **38d** as well as the other purines cyclopropane **38e** and **38f**, even though the solubility in DCM at room temperature was high and a wide range of Lewis acids were examined ($Zn(OTf)_2$, $FeCl_3$, $AuCl_3$, AuCl, $Sn(OTf)_2$, $Sc(OTf)_3$, $Hf(OTf)_4$, $In(OTf)_3$, $Cu(OTf)_2$, $Yb(OTf)_3$). Another possibility for the lack of reactivity observed, may be the hindrance created by the pentyl side chains around the esters avoiding the catalyst to chelate the malonate and therefore the reaction to proceed. However, when the soluble protected 6-chloro-2-amino purine dimethylester cyclopropane **39** was submitted to the conditions for (3+2) annulation with indium triflate as catalyst in either DCM or THF, only removal of the *tert*-butoxycarbonyl was observed.

To completely exclude catalyst poisoning by the substrate, we performed a competition experiment between pyrimidine cyclopropane **13c** and purine analogue **38e** under the conditions for (3+2) annulation (Scheme 17). After 45 minutes of reaction, complete

conversion of the pyrimidine cyclopropane **13c** into the corresponding nucleoside analogue **40** was observed, while the purine cyclopropane **38e** stayed untouched.



Scheme 17. Competition experiment. a) 0.2 equiv $In(OTf)_3$, 2.4 equiv benzaldehyde (**19**), DCM.

From this result, we can conclude that purine cyclopropanes **38a-f** do not coordinate too strongly to the Lewis acid. However, purine cyclopropanes **38a-f** are not suitable substrates for the (3+2) annulation, probably due to their different electronic properties leading to too low reactivity. In the future, further modulation of the DA cyclopropane structure will be required to extend the developed annulation processes to this important class of substrates.

3. Conclusions

A short synthesis of pyrimidine DA cyclopropanes and cyclobutanes was designed based on a regioselective vinylation followed by cyclopropanation or (2+2) cycloaddition. Purine DA cyclopropanes were prepared from chloromethyl-ethylidene malonates via a tandem Michael addition intramolecular substitution sequence. Pyrimidine nucleosides analogues were accessed from the DA cyclopropanes and DA cyclobutanes via (3+2) and (4+2) annulation reactions, opening a new chemical space for further biological investigations. Unfortunately, purine DA cyclopropanes remain unreactive in the (3+2) annulation reactions.

Acknowledgements

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[14] NMR data of compound **28** corresponded to the proposed structure, however this compound could not be purified for complete characterization.
[15] a) A. P. Krapcho, G. A. Glynn, B. J. Grenon, *Tetrahedron Lett.* **1967**, *8*, 215; b) A. P. Krapcho, E. G. E. Jahngen, A. J. Lovey, F. W. Short, *Tetrahedron Lett.* **1974**, *15*, 1091; c) N. Pérez-Hernández, M. Febles, C. Pérez, R. Pérez, M. L. Rodríguez, C. Foces-Foces, J. D. Martín, *J. Org. Chem.* **2006**, *71*, 1139; d) K. C. Nicolaou, A. A. Estrada, M. Zak, S. H. Lee, B. S. Safina, *Angew. Chem. Int. Ed.* **2005**, *44*, 1378; e) S. Das, K. Möller, K. Junge, M. Beller, *Chem. Eur. J.* **2011**, *17*, 7414.
[16] a) K. C. Nicolaou, V. A. Adsool, C. R. H. Hale, *Org. Lett.* **2010**, *12*, 1552; b) P. Dupau, R. Epple, A. Thomas, V. Fokin, K. Barr. Sharpless, *Adv. Synth. Catal.* **2002**, *344*, 421.
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[18] L. Beigelman, P. Haeberli, D. Sweedler, A. Karpeisky, *Tetrahedron* **2000**, *56*, 1047.
[19] G. R. Geen, P. M. Kincey, B. M. Choudary, *Tetrahedron Lett.* **1992**, *33*, 4609.
[20] W. Lehnert, *Tetrahedron* **1973**, *29*, 635.
[21] A. R. A. S. Deshmuck, D. G. Panse, B. M. Bhawal, *Synth. Commun.* **1999**, *10*, 1801.
[22] A. R. Maguire, W.-D. Meng, S. M. Roberts, A. J. Willetts, *J. Chem. Soc. Perkin 1* **1993**, 1795.
[23] BRISTOL-MYERS SQUIBB COMPANY, Patent: WO2003/99286 A1, 2003; Location in patent: P.89.

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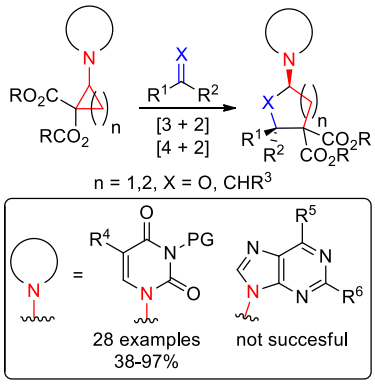

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1. General methods.

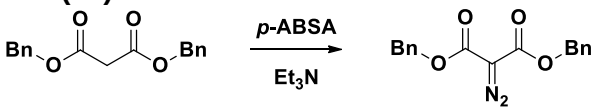
All reactions were carried out in flamed-dried glassware under an atmosphere of nitrogen, unless stated otherwise. HPLC grade solvents purchased from Sigma-Aldrich or freshly distilled solvents were used for flash chromatography. Reaction solvents were dried by passage over activated alumina under nitrogen atmosphere (H_2O 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. ^{1}H 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, qi = quintet, m = multiplet or unresolved, br = broad signal, coupling constant(s) in Hz, integration; interpretation). ^{13}C 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. All experimental procedures to synthesize the compounds described in the article are given. Only spectra of compounds which were not described in our previous publications are given. For compounds **10a-c**, **12a-c**, **13a-c**, **14**, **16a,b**, **17**, **18a,b**, **22a-f**, **23a-f**, **24a-f**, **25a-f**, **26a-f**, **27**, **29**, **30a-d**, **31** and **32**, please refer to the previous reports.[1]

[1] a) S. Racine, F. de Nanteuil, E. Serrano, J. Waser, *Angew. Chem. Int. Ed.* **2014**, *53*, 8484–8487. b) D. Perrotta, S. Racine, J. Vuilleumier, F. de Nanteuil, J. Waser, *Org. Lett.* **2015**, *17*, 1030–1033. c) F. de Nanteuil, J. Waser, *Angew. Chem. Int. Ed.* **2013**, *52*, 9009–9013.

2. Starting materials.

2.1 Diazomalonates.

Dibenzyl 2-diazomalonate (42).



41 42

In flame dried flask under nitrogen, 4-acetamidobenzenesulfonyl azide (1.27 g, 5.28 mmol, 1.5 equivuiv) was dissolved in acetonitrile (15 mL) and triethylamine (1.17 mL, 8.44 mmol, 2.4 equivuiv) and dibenzyl malonate (**41**) (0.88 mL, 3.5 mmol, 1equivuiv) 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% NEt_3 mixture to obtain the pure diazo-compound **42** (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)

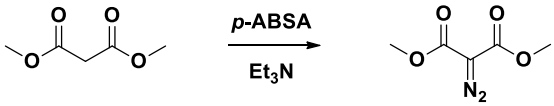
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39- 7.34 (m, 10H, Ar-H), 5.28 (s, 4H, CH_2).

^{13}C 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), 1689 (m), 1388 (s), 1271 (m), 1077 (s), 760 (s).

HRMS (ESI) calcd for $C_{17}H_{14}N_2NaO_4^+$ $[M+Na]^+$ 333.0846; found 333.0856.

Dimethyl 2-diazomalonate (44).



33 44

In a flame dried flask under nitrogen, 4-acetamidobenzenesulfonyl azide (6.82 g, 28.4 mmol, 1.5 equiv) was dissolved in acetonitrile (80 mL) and triethylamine (6.3 mL, 45 mmol, 2.4 equiv) and dimethyl malonate (**33**) (2.2 mL, 19 mmol, 1 equiv) 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% NEt_3 mixture to obtain the pure diazo-compound **44** (2.67 g, 16.9 mmol, 94%) as a slightly yellow oil (solid at 4 °C).

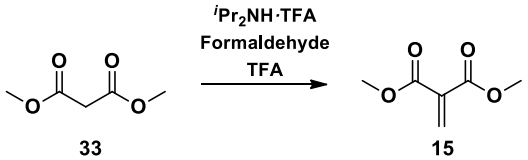
^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.84 (s, 4H, CH_2).

^{1}H NMR values correspond to the literature.[2]

2.2 Methylidene and ethylidene malonates.

Dimethyl 2-methylenemalonate (15).

[2] F. de Nanteuil, J. Waser, *Angew. Chem. Int. Ed.,***2011**, *50*, 12075–12079.

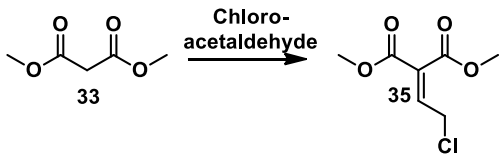


Following the described procedure of De Nanteuil et al.,[1c] paraformaldehyde (2.7 g, 90 mmol, 2.0 equiv) and diisopropylamine 2,2,2-trifluoroacetate (9.7 g, 45 mmol, 1.0 equiv) were added in a flame dried 250 mL round flask with a condenser. Then, tetrahydrofuran (65 mL), dimethyl malonate (**33**) (5.1 mL, 45 mmol, 1.0 equiv) and trifluoroacetic acid (0.35 mL, 4.5 mmol, 0.1 equiv) were added into the flask under nitrogen atmosphere and the suspension was stirred to reflux for 2 hours. Paraformaldehyde (2.7 g, 90 mmol, 2.0 equiv) was added to the reaction mixture and the reflux was restarted for 12 hours. The reaction mixture was cooled to room temperature and THF was removed under reduced pressure. The crude product was dissolved in diethyl ether (25 mL) and filtrated trough cotton. The organic layer was washed two times with 1 M HCl (25 mL), the aqueous layers were combined and washed three times with diethyl ether (50 mL). The combined organic layers were dry over magnesium sulfate, filtrated and concentrated under reduced pressure. The crude mixture was obtained as a colorless oil (**15**) (2.5 g).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.58 (s, 2H, CH_2), 3.83 (s, 6H, ester CH_3).

^{1}H NMR values correspond to the literature.[2]

Dimethyl 2-(2-chloroethylidene)malonate (**35**).



Following an adapted procedure from Deshmukh et al.,[3] Montmorillonite K-10 clay (0.50 g), Ac_2O (4.6 mL, 48 mmol, 1.3 equiv), 2-chloroacetaldehyde (3.1 mL, 45 mmol, 1.2 equiv), dimethyl malonate (**33**) (4.3 mL, 4.4 mmol, 1 equiv) were stirred under nitrogen atmosphere in flamed dried flask at 70 °C for 3 h 30. The reaction was cooled down to room temperature and saturated solution of $NaHCO_3$ (20 mL) was added, the mixture was extracted with ether (3x 20 mL). The combined organic layers were dry over magnesium sulfate, filtrated and concentrated under reduced pressure. The crude residue was purified by column chromatography using a mixture of pentane and ethyl acetate (100% pentane to 80:20% pentane/ ethyl acetate) affording the pure product **35** (4.33 g, 22.5 mmol, 61% yield) as a slightly yellow liquid.

RF (AcOEt/Pent (1:9) = 0.43.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.08 (t, *J* = 7.3 Hz, 1H, C=CH), 4.34 (d, *J* = 7.3 Hz, 2H, CH_2), 3.88 (s, 3H, Me ester), 3.85 (s, 3H, Me ester).

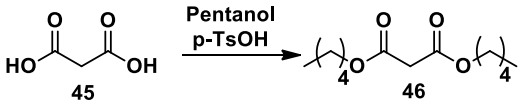
^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.3, 163.6, 144.2, 129.1, 52.8, 52.7, 39.2.

IR 2951 (w), 1732 (s), 1439 (m), 1282 (s), 1227 (s), 1058 (w), 769 (w).

HRMS (ESI) calcd for $C_7H_9ClNaO_4^+$ $[M+Na]^+$ 215.0082; found 215.0087.

[3] A. R. A. S. Deshmukh, D. G. Panse, B. M. Bhawal, *Synth. Commun.* 1999, *29*, 1801–1809.

Dipentyl malonate (46).



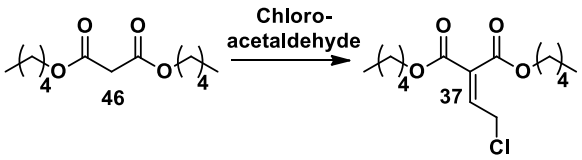
Following the procedure described by Tian et al.[4], 4-methylbenzenesulfonic acid monohydrate (0.033 g, 0.19 mmol, 0.01 equiv), pentan-1-ol (4,6 mL, 42 mmol, 2.2 equiv), malonic acid (**45**) (2.00 g, 19.2 mmol, 1 equiv) were stirred at 85 °C in a flame dried flask under nitrogen in benzene (40 mL) for 3 h. The mixture was cooled down to room temperature and a saturated solution of $NaHCO_3$ (20 mL) was added, the mixture was extracted with ethyl acetate (3x 20 mL). The combined organic layers were washed with saturated solution of Na_2CO_3 (20 mL), dry over magnesium sulfate, filtrated and concentrated under reduced pressure. The crude product **46** (3.4 g, 14 mmol, 73% yield) obtained as a yellow liquid after concentration under reduced pressure was clean enough to be used for the next step without further purification.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.17 (t, *J* = 6.8 Hz, 4H, pentyl CH_2), 3.40 (s, 2H, $C{=}OCH_2C{=}O$), 1.80 – 1.58 (m, 4H, pentyl CH_2), 1.36 (m, 8H, pentyl CH_2), 1.02 – 0.82 (m, 6H, pentyl CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 65.7, 41.7, 28.2, 27.9, 22.3, 14.0.

NMR value correspond to literature.[3]

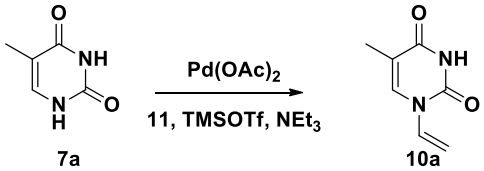
Dipentyl 2-(2-chloroethylidene)malonate (37).



Following an adapted procedure from Deshmukh et al.,[3] Montmorillonite K-10 clay (80 mg), Ac_2O (2.5 mL, 27 mmol, 1.3 equiv), 2-chloroacetaldehyde (1.7 mL, 25 mmol, 1.3 equiv), dipentyl malonate (**46**) (5.0 g, 20 mmol, 1 equiv) were stirred under nitrogen atmosphere in a flamed dried flask at 70 °C for 16 hours. The reaction was cooled down to room temperature and a saturated solution of $NaHCO_3$ (20 mL) was added, the mixture was extracted with ether (3x 20 mL). The combined organic layers were dried over magnesium sulfate, filtrated and concentrated under reduced pressure. The crude oil was used without any purification. In general, the crude contain a ratio 7:3 product **37** to product **46**.

2.3 Pyrimidine cyclopropanes.

1-Vinylthymine (10a).



Thymine (**7a**) (0.50 g, 3.9 mmol, 1.0 eq), diacetoxypalladium (0.036 g, 0.16 mmol, 0.04 eq) were suspended in DMF (10 mL) in a flame-dried sealed microwave vial under nitrogen atmosphere. Vinyl acetate (**11**) (0.82 g, 9.5 mmol, and 2.4 eq), triethylamine (1.3 mL, 9.5 mmol, 2.4 eq) and TMSOTf (1.7 mL, 9.5 mmol, and 2.4 eq) were added to the reaction mixture and stirred at 70 °C for 24 hours. The reaction mixture was cooled down to room temperature and the solvent was removed under reduced pressure. The crude mixture was purified by column

[4] Y. Tian, E. Akiyama, Y. Nagase, *J. Mater. Chem.* **2003**, *13*, 1253.

chromatography, eluting with a mixture of ethyl acetate/ pentane (7:3). The pure 1-vinylthymine (**10a**) (0.47 g, 3.1 mmol, 79% yield) was obtained as white solid.

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

Mp 208.0-209.1°C.

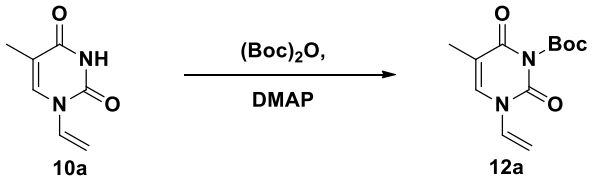
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.17 (s, 1 H, NH), 7.34 (s, 1 H, thymine C=C-H), 7.21 (dd, 1 H, *J* =16.0, 9.1 Hz, -vinyl-CH), 5.07 (dd, 1 H, *J* = 16.0, 2.1 Hz, vinyl-CH_2), 4.91 (dd, 1 H, *J* = 9.1, 2.1 Hz, vinyl-CH_2), 1.99 (s, 3 H, thymine-CH_3).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.6, 149.3, 134.5, 129.6, 112.1, 100.5, 12.6.

IR 3173 (w), 3048 (w), 1698 (s), 1644 (s), 1459 (w), 1381 (w), 1344 (m), 1278 (m), 1129 (w).

HRMS (ESI) calcd for $C_7H_9N_2O_2^+$ $[M+H]^+$ 153.0659; found 153.0653.

***Tert*-butyl 5-methyl-2,6-dioxo-3-vinyl-2,3-dihydropyrimidine-1(*6H*)-carboxylate (12a).**



1-Vinylthymine **10a** (0.92 g, 6.1 mmol, 1.0 equiv), di-*tert*-butyl dicarbonate (2.64 g, 12.1 mmol, 2.0 equiv) and dimethylaminopyridine (1.48 g, 12.1 mmol, 2.0 equiv) 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 **12a** (1.15 g, 4.56 mmol, 75% yield) was obtained as a white solid.

RF (Hex/AcOEt (9:1)) = 0.2.

Mp 109.9-111.2 °C.

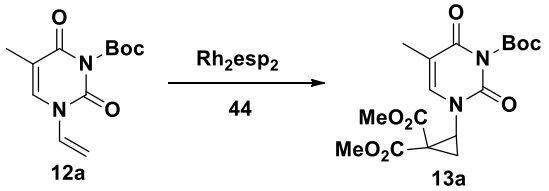
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 (m, 1H, thymine C=C-H), 7.15 (dd, *J* = 16.0, 9.1 Hz, 1H, -vinyl-CH), 5.09 (dd, *J* = 16.0, 2.2 Hz , 1H, vinyl-CH_2), 4.94 (dd, *J* = 9.1, 2.2 Hz , 1H, vinyl-CH_2), 1.99 (s, 3 H, thymine-CH_3), 1.60 (s, 9 H, Boc).

^{13}C NMR (400 MHz, Chloroform-*d*) δ 161.0, 147.6, 147.5, 134.0, 129.6, 111.8, 101.3, 87.1, 27.5, 12.7.

IR 2982 (w), 2937 (w), 1778 (s), 1721 (s), 1672 (s).

HRMS (ESI) calcd for $C_{12}H_{16}N_2NaO_4^+$ $[M+Na]^+$ 275.1002; found 275.1008.

Dimethyl 2-(3-(*tert*-butoxycarbonyl)-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(*2H*)-yl)cyclopropane-1,1-dicarboxylate (13a).



Diazomalonate **44** (1.80 g, 10.5 mmol, 1.2 equiv), $Rh_2(esp)_2$ (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 (**12a**) (2.2 g, 8.7 mmol, 1.0 equiv) 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 **13a** (3.30 g, 8.63 mmol, 99% yield) was obtained as a slightly yellow foamy oil. The cyclopropane **13a** was obtained in 64% yield over the three steps.

RF (hexane/AcOEt/1% NEt_3 (1:1)) = 0.26.

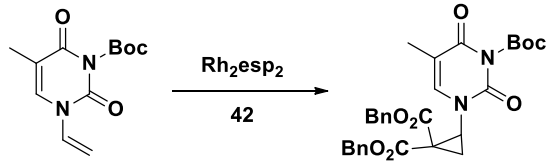
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.94 (m, 1H, thymine C=CH), 4.01 (dd, *J* = 8.3, 6.4 Hz, 1H, cyclopropane-CH), 3.79 (s, 3H, ester-CH_3), 3.71 (s, 3H, ester-CH_3), 2.27 (t, *J* = 6.5 Hz, 1H, cyclopropane-CH_2), 1.91 (m, 4H, thymine-CH_3 and cyclopropane-CH_2), 1.58 (s, 9H, Boc).

^{13}C 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 $C_{17}H_{22}N_2NaO_8^+$ $[M+Na]^+$ 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 (47).



12a **47**

Tert-butyl 5-methyl-2,6-dioxo-3-vinyl-2,3-dihydropyrimidine-1(6H)-carboxylate (**12a**) (0.30 g, 1.2 mmol, 1.0 equiv) and $Rh_2(esp)_2$ (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 **42** (0.45 g, 1.4 mmol, 1.2 equiv) 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% NEt_3 (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 (**47**) (0.60 g, 1.1 mmol, 93% yield) as a slightly yellow foam. The cyclopropane **47** was obtained in 60% yield over the three steps.

MP 76.9-82.1 °C.

RF (pent/AcOEt (7:3)) = 0.29.

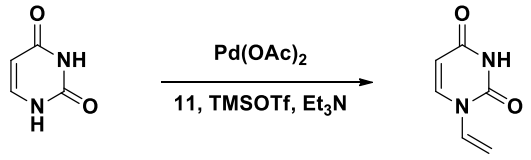
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 – 7.22 (m, 10 H, Ar-H), 6.83 (q, *J* = 1.1 Hz, 1H, thymine vinyl-CH), 5.27 – 5.10 (m, 4H, benzylic-CH_2), 4.05 (dd, *J* = 8.3, 6.5 Hz, 1H, cyclopropane-NCH), 2.31 (t, *J* = 6.6 Hz, 1H, cyclopropane -CH_2), 1.93 (dd, *J* = 8.3, 6.6 Hz, 1H, cyclopropane -CH_2), 1.78 (d, *J* = 1.3 Hz, 3H, thymine methyl), 1.59 (s, 9H, Boc).

^{13}C 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 carbone not resolved.

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

HRMS (ESI) calcd for $C_{29}H_{30}N_2NaO_8^+$ $[M+Na]^+$ 557.1894; found 557.1885.

1-Vinylpyrimidine-2,4(1H,3H)-dione (10b).



Palladium acetate (0.036 g, 0.040 mmol, 0.04 equiv), vinyl acetate (**11**) (0.87 mL, 10 mmol, 2.4 equiv), uracil (**7b**) (0.45 g, 4.0 mmol, 1.0 equiv), TMSOTf (1.7 mL, 9.5 mmol, 2.4 equiv) and triethylamine (1.4 mL, 9.5 mmol, 2.4 equiv) 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 **10b** (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.

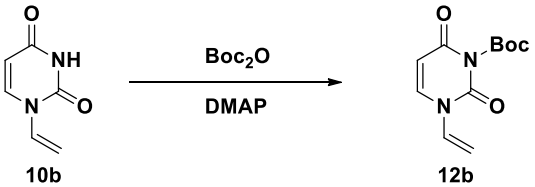
^{1}H NMR (400 MHz, Acetone) δ 9.21 (s, 1H, uracil N-H), 7.53 (d, *J* = 8.1 Hz, 1H, uracil CH), 7.23 (dd, *J* = 16.0, 9.0 Hz, 1H, vinyl-CH), 5.86 (dd, *J* = 8.1, 1.3 Hz, 1H, uracil CH), 5.13 (dd, *J* = 16.0, 2.3 Hz, 1H, vinyl-CH_2), 5.00 (dd, *J* = 9.0, 2.3 Hz, 1H, vinyl-CH_2).

^{13}C NMR (101 MHz, Acetone) δ 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 $C_6H_7N_2O_2^+$ $[M+H]^+$ 139.0502; found 139.0507.

***Tert*-butyl 2,6-dioxo-3-vinyl-3,6-dihydropyrimidine-1(2H)-carboxylate (12b).**



1-Vinyluracil (**10b**) (0.25 g, 1.8 mmol, 1.0 equiv), di-*tert*-butyl dicarbonate (0.78 g, 3.6 mmol, 2.0 equiv) and dimethylaminopyridine (0.44 g, 3.6 mmol, 2.0 equiv) 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 **12b** (0.43 g, 1.8 mmol, quantitative yield) was obtained as a yellow oil.

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

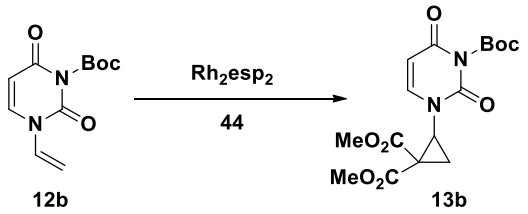
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.51 (d, *J* = 8.2 Hz, 1H, uracil CH), 7.15 – 7.02 (m, 1H, vinyl-CH), 5.80 (d, *J* = 8.2 Hz, 1H, uracil CH), 5.14 (dd, *J* = 16.0, 2.4 Hz, 1H, vinyl-CH_2), 4.96 (dd, *J* = 9.0, 2.5 Hz, 1H, vinyl-CH_2), 1.55 (s, 9H, Boc).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 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 (13b).



Diazomalonate **44** (0.28 g, 1.8 mmol, 1.0 equiv), $Rh_2(esp)_2$ (2.7 mg, 3.5 µmol, 0.02 mol%) and product **12b** (0.42 g, 1.8 mmol, 1.0 equiv) 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 **13b** (0.56 g, 1.5 mmol, 87% yield) was obtained as a colorless foam. The cyclopropane **13b** was obtained in 60% yield over the three steps.

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

MP 45.0-46.2°C.

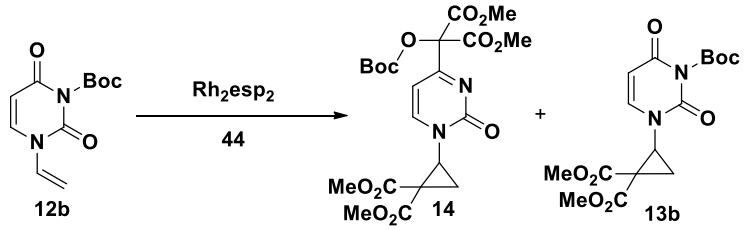
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.08 (d, *J* = 8.1 Hz, 1H, uracil CH), 5.64 (d, *J* = 8.2 Hz, 1H, uracil CH), 3.98 (dd, *J* = 8.2, 6.5 Hz, 1H, cyclopropane-CH), 3.73 (s, 3H, ester CH_3), 3.65 (s, 3H, ester CH_3), 2.19 (t, *J* = 6.6 Hz, 1H, cyclopropane-CH_2), 1.88 (dd, *J* = 8.5, 6.8 Hz, 1H, cyclopropane-CH_2), 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.

Dimethyl 2-(4-(2-((tert-butoxycarbonyl)oxy)-1,3-dimethoxy-1,3-dioxopropan-2-yl)-2-oxopyrimidin-1(2H)-yl)cyclopropane-1,1-dicarboxylate (14).



Dimethyl 2-diazomalonate (**44**) (0.51 g, 3.2 mmol, 1.2 equiv), $Rh_2(esp)_2$ (4 mg, 5 µmol, 0.02 mol%) and product **12b** (0.64 g, 2.7 mmol, 1.0 equiv) 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 product **14** (0.51 g, 1.0 mmol, 64% yield[5]) was obtained as white solid and the pure product **13b** (0.33 g, 0.90 mmol, 28% yield) as colorless foam.

RF (AcOEt/pentane (1:1)) = 0.18.

MP 159.1-160.3 °C.

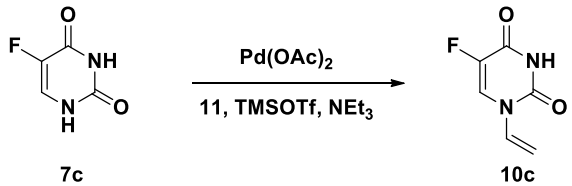
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47 (d, *J* = 7.4 Hz, 1H, uracil CH), 6.12 (d, *J* = 7.3 Hz, 1H, uracil CH), 4.22 (dd, *J* = 8.2, 6.7 Hz, 1H, cyclopropane-CH), 3.88 (m, 6H, ester CH_3), 3.83 (s, 3H, ester CH_3), 3.66 (s, 3H, ester CH_3), 2.31 (t, *J* = 6.7 Hz, 1H, cyclopropane-CH_2), 2.00 (dd, *J* = 8.2, 6.6 Hz, 1H, cyclopropane-CH_2), 1.52 (s, 9H, Boc).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 167.8, 166.0, 163.0, 160.6, 154.4, 146.6, 94.9, 85.0, 53.8, 53.1, 53.1, 44.4, 34.9, 27.6, 19.4. Two carbons are not resolved.

IR 3101 (w), 2956 (w), 1737 (s), 1678 (s), 1539 (s), 1455 (m), 1330 (s), 1119 (s), 798 (m).

HRMS (ESI) calcd for $C_{21}H_{27}N_2O_{12}^+$ $[M+H]^+$ 499.1559; found 499.1554.

5-Fluoro-1-vinylpyrimidine-2,4(1H,3H)-dione (10c).



Palladium acetate (0.013 g, 0.056 mmol, 0.04 equiv), vinyl acetate (**11**) (1.7 mL, 3.4 mmol, 2.4 equiv), fluoro-uracil **7c** (0.18 g, 1.4 mmol, 1.0 equiv), TMSOTf (0.60 mL, 3.4 mmol, 2.4 equiv) and triethylamine (0.47 mL, 3.4 mmol, 2.4 equiv) 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 **10c** (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).

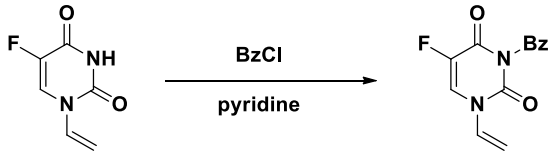
^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.1 (d, *J* = 27.3 Hz), 147.3, 141.1 (d, *J* = 241.8 Hz), 129.3, 123.1 (d, *J* = 34.2 Hz), 101.3.

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

HRMS (ESI) calcd for $C_6FH_6N_2O_2^+$ $[M+H]^+$ 157.0408; found 157.0414.

3-Benzoyl-5-fluoro-1-vinylpyrimidine-2,4(1H,3H)-dione (12c).

[5] Yield calculated from diazomalonate. If calculated with uracil as reference; **13b**: 33%, **14**: 38%.



10c 12c

In a flame-dried flask under nitrogen, 1-vinyl-fluorouracil (**10c**) (0.12 g, 0.79 mmol, 1.0 equiv) 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 equiv) 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 **12c** (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.

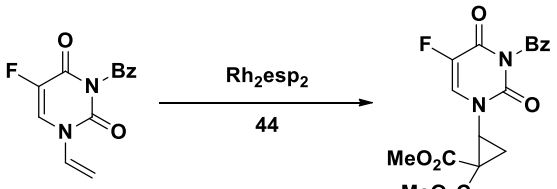
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.95 (dd, *J* = 8.3, 1.4 Hz, 2H, Ar-H), 7.75 – 7.64 (m, 2H, Ar-H and F-uracil vinyl-CH), 7.52 (t, *J* = 7.9 Hz, 2H, Ar-H), 7.12 (ddd, *J* = 15.9, 9.0, 1.8 Hz, 1H, vinyl-CH), 5.13 (dd, *J* = 15.8, 2.7 Hz, 1H, vinyl-CH_2), 4.99 (dd, *J* = 9.0, 2.8 Hz, 1H, vinyl-CH_2).

^{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 $C_{13}H_9FN_2NaO_3^+$ $[M+Na]^+$ 283.0489; found 283.0485.

Dimethyl 2-(3-benzoyl-5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)cyclopropane-1,1-dicarboxylate (13c).



12c 13c

Diazomalonate **44** (0.21 g, 1.3 mmol, 1.2 equiv), $Rh_2(esp)_2$ (0.002 g, 0.002 mmol, 0.02 mol%) and product **12c** (0.29 g, 0.11 mmol, 1.0 equiv) were stirred at room temperature in DCM (11 mL) in a flame-dried flask under nitrogen. After 1 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 **13c** (0.40 g, 1.0 mmol, 93% yield) was obtained as a white foamy solid. The cyclopropane was obtained in 39% yield over the three steps.

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

MP 62.7-64.4°C.

^{1}H 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 CH_3), 3.58 (s, 3H, ester CH_3), 2.09 (t, *J* = 6.5 Hz, 1H, cyclopropane-CH), 1.91 (dd, *J* = 8.1, 6.6 Hz, 1H, cyclopropane-CH).

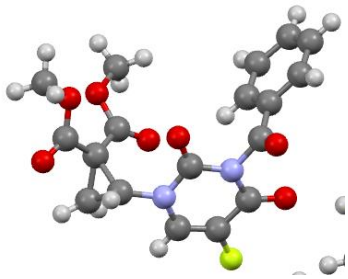
^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.1, 166.7, 156.0 (d, *J* = 27.2 Hz), 148.7, 139.7 (d, *J* = 240.3 Hz), 135.6, 130.8, 130.7, 129.2, 128.0 (d, *J* = 33.7 Hz), 53.3, 53.3, 42.9, 34.8, 20.3.

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).

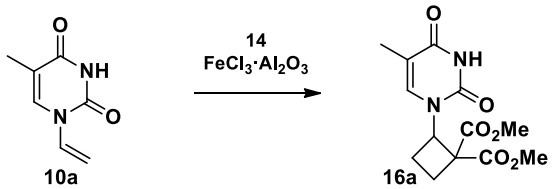
HRMS (ESI) calcd for $C_{18}H_{15}FN_2NaO_7^+$ $[M+Na]^+$ 413.0755; found 413.0763.

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



2.4 Pyrimidine cyclobutane.

Dimethyl 2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)cyclobutane-1,1-dicarboxylate (16a).



Following an adapted described procedure of De Nanteuil et al.,[1c] 5-methyl-1-vinylpyrimidine-2,4(1H,3H)-dione (**10a**) (0.43 g, 2.9 mmol, 1.0 equiv) and iron trichloride supported on alumina (1.0 mmol/g, 0.57 g, 0.57 mmol, 0.2 equiv) were added in a flame dried microwave vial under nitrogen atmosphere. Then, dry dichloromethane (7 mL) and a solution of crude freshly prepared dimethyl 2-methylenemalonate (**14**) (0.82 g, 5.7 mmol, 2.0 equiv) in dichloromethane (3 mL) were added into the vial and the reaction mixture was stirred at room temperature for 14 hours. The reaction mixture was filtrated over a pad of alumina eluting with ethyl acetate (25 mL) and concentrated under reduced pressure. The crude mixture was purified via column chromatography, eluting with a mixture of ethyl acetate/ pentane (6:4 to 9:1). The pure product **16a** (0.36 g, 1.2 mmol, 43% yield) was obtained as a white solid.

RF (Pent/AcOEt (2:8)) = 0.21.

Mp: 180.4- 182.1°C.

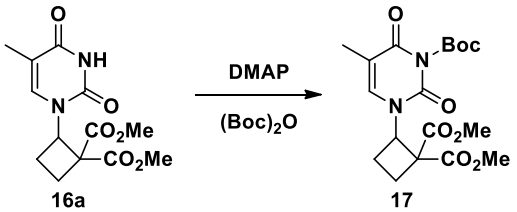
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.99 (s, 1H, NH), 7.05 (d, *J* = 1.3 Hz, 1H, thymine C=C-H), 5.33 (t, *J* = 9.2 Hz, 1H, cyclobutane-CH), 3.77 (s, 3H, ester CH_3), 3.69 (s, 3H, ester CH_3), 2.79 – 2.67 (m, 2H, cyclobutane-CH_2), 2.35 (q, *J* = 8.5 Hz, 1H, cyclobutane-CH_2), 2.27 – 2.16 (m, 1H, cyclobutane-CH_2), 1.93 (d, *J* = 1.2 Hz, 3H, thymine-CH_3).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.0, 168.8, 163.9, 151.0, 137.7, 110.3, 59.1, 55.0, 53.2, 53.1, 23.7, 22.8, 12.5.

IR: 3190 (w), 3034 (w), 2958 (w), 2361 (m), 1733 (s), 1690 (s), 1439 (w), 1278 (m), 1113 (w), 915 (w), 735 (w).

HRMS (ESI) calcd for $C_{13}H_{16}N_2NaO_6^+$ $[M+Na]^+$ 319.0901, found 319.0904.

Dimethyl 2-(3-(tert-butoxycarbonyl)-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)cyclobutane-1,1-dicarboxylate (17).



Cyclobutane **16a** (0.20 g, 0.68 mmol, 1.0 equiv) and dimethyl-4-aminopyridine (0.12 g, 1.0 mmol, 1.5 equiv) were dissolved in acetonitrile (3.0 mL) in a flame dried flask under nitrogen atmosphere. A solution of di-*tert*-butyl dicarbonate (0.29 g, 1.4 mmol, 2.0 equiv) in acetonitrile (0.5 mL) was added to the reaction mixture and it was stirred at room temperature for 14 hours. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography, eluting with a mixture of pentane/ ethyl acetate (8:2 to 6:4). The pure product **17** (0.22 g, 0.55 mmol, 81% yield) was obtained as slightly yellow oil.

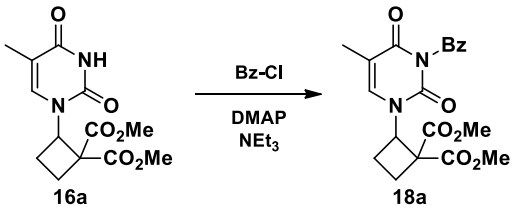
RF (Pent/AcOEt (4:6)) = 0.28.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.05 (d, *J* = 1.3 Hz, 1H, thymine C=C-H), 5.25 – 5.18 (m, 1H, cyclobutane-CH), 3.76 (s, 3H, ester CH_3), 3.69 (s, 3H, ester CH_3), 2.98 – 2.83 (m, 1H, cyclobutane-CH_2), 2.83 – 2.72 (m, 1H, cyclobutane-CH_2), 2.38 – 2.28 (m, 1H, cyclobutane-CH_2), 2.19 – 2.10 (m, 1H, cyclobutane-CH_2), 1.93 (d, *J* = 1.3 Hz, 3H, thymine-CH_3), 1.59 (s, 9H, Boc).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.2, 168.6, 161.4, 149.2, 147.9, 138.1, 110.1, 86.8, 59.2, 56.3, 53.3, 53.3, 27.6, 23.7, 23.0, 12.6.

NMR values correspond to the literature.[1c]

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



In a flame dried microwave vial under nitrogen atmosphere, cyclobutane **16a** (0.32 g, 1.1 mmol, 1.0 equiv) and dimethyl-4-aminopyridin (0.13 g, 1.1 mmol, 1.0 equiv) were dissolved in dry dichloromethane (10 mL). Then, triethylamine (0.60 mL, 4.3 mmol, 4.0 equiv) was added and the solution was cooled to 0°C. Benzoyl chloride (0.38 mL, 3.2 mmol, 3.0 equiv) was added dropwise and the reaction mixture was stirred at room temperature for 14 hours. A saturated solution of $NaHCO_3$ (8 mL) was added to the reaction mixture and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were washed with 1 M HCl (2 x 40 mL) and with water (30 mL), dried over $MgSO_4$ and concentrated under reduce pressure. The crude product was purified by column chromatography, eluting with a mixture of pentane/ ethyl acetate (4:6 to 2:8). The pure product **18a** (0.37 g, 0.93 mmol, 86% yield) was obtained as colorless foam.

RF (Pent/AcOEt (4:6)) = 0.32.

Mp: 153.8-155.4°C.

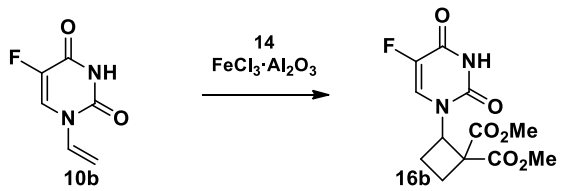
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.96 – 7.90 (m, 2H, Ar-H), 7.65 – 7.59 (m, 1H, Ar-H), 7.50 – 7.44 (m, 2H, Ar-H), 7.16 (d, *J* = 1.2 Hz, 1H, thymine C=C-H), 5.17 (t, *J* = 9.5 Hz, 1H, cyclobutane-CH), 3.69 (s, 3H, ester CH_3), 3.66 (s, 3H, ester CH_3), 2.94 – 2.82 (m, 1H, cyclobutane-CH_2), 2.74 (td, *J* = 11.0, 3.1 Hz, 1H, cyclobutane-CH_2), 2.35 (dtd, *J* = 11.6, 8.8, 3.1 Hz, 1H, cyclobutane-CH_2), 2.18 (dt, *J* = 11.7, 8.9 Hz, 1H, cyclobutane-CH_2), 1.95 (d, *J* = 1.2 Hz, 3H, thymine-CH_3).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.2, 168.9, 168.7, 162.8, 150.1, 138.7, 135.0, 131.6, 130.7, 129.1, 110.4, 58.8, 56.9, 53.3, 53.2, 23.9, 22.7, 12.6.

IR: 3006 (w), 2959 (w), 2358 (w), 2257 (w), 1737 (s), 1702 (m), 1655 (s), 1438 (m), 1266 (s), 1107 (m), 984 (w), 914 (w), 733 (s).

HRMS (ESI) calcd for $C_{20}H_{20}N_2NaO_7^+$ $[M+Na]^+$ 423.1163; found 423.1168.

Dimethyl 2-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)cyclobutane-1,1-dicarboxylate (16b).



5-Fluoro-1-vinylpyrimidine-2,4(1H,3H)-dione (**10b**) (0.60 g, 3.8 mmol, 1.0 equiv) and iron trichloride supported on alumina (1.0 mmol/g, 0.77 g, 0.77 mmol, 0.2 equiv) were added in a flame dried microwave vial under nitrogen atmosphere. Then, dry dichloromethane (8 mL) and a solution of crude freshly prepared dimethyl 2-methylenemalonate (**14**) (2.2 g, 15 mmol, 4.0 equiv) in dichloromethane (2 mL) were added into the vial and the reaction mixture was stirred at room temperature for 14 hours. The reaction mixture was filtrated over a pad of alumina eluting with ethyl acetate (50 mL) and concentrated under reduced pressure. The crude mixture was purified via column chromatography, eluting with a mixture of ethyl acetate/ pentane (5:5 to 2:8). The pure product **16b** (0.78 g, 2.6 mmol, 67% yield) was obtained as a

colorless oil.

RF (Pent/AcOEt (4:6)) = 0.28.

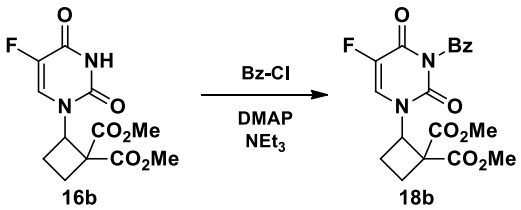
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.54 (s, 1H, NH), 7.36 (d, *J* = 6.1 Hz, 1H, F-uracil C=C-H), 5.28 (t, *J* = 9.0 Hz, 1H, cyclobutane-CH), 3.78 (s, 3H, ester CH_3), 3.73 (s, 3H, ester CH_3), 2.68 – 2.61 (m, 2H, cyclobutane-CH_2), 2.41 – 2.32 (m, 1H, cyclobutane-CH_2), 2.32 – 2.25 (m, 1H, cyclobutane-CH_2).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.7, 168.8, 156.8 (d, *J* = 26.7 Hz), 149.7, 140.2 (d, *J* = 237.5 Hz), 126.3 (d, *J* = 33.7 Hz), 59.0, 55.2, 53.3, 53.3, 23.7, 23.0.

IR: 3211 (w), 3085 (w), 2960 (w), 2362 (w), 2336 (w), 1726 (s), 1439 (w), 1361 (w), 1273 (m), 1110 (w), 915 (w), 735 (m).

HRMS (ESI) calcd for $C_{12}H_{13}FN_2NaO_6^+$ $[M+Na]^+$ 323.0650; found 323.0654.

Dimethyl 2-(3-benzoyl-5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)cyclobutane-1,1-dicarboxylate (18b).



In a flame dried microwave vial under nitrogen atmosphere, **16b** (0.70 g, 2.3 mmol, 1.0 equiv) and dimethyl-4-aminopyridin (0.28 g, 2.3 mmol, 1.0 equiv) were dissolved in dry dichloromethane (12 mL). Triethylamine (1.3 mL, 9.3 mmol, 4.0 equiv) was added and the solution was cooled to 0°C. Then, benzoyl chloride (0.81 mL, 6.9 mmol, 3.0 equiv) was added dropwise and the reaction mixture was stirred at room temperature for 16 hours. A saturated solution of $NaHCO_3$ (8 mL) was added to the reaction mixture and the layer were separated. The aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were washed with 1 M HCl (2 x 40 mL) and with water (30 mL), dried over $MgSO_4$ and concentrated under reduce pressure. The pure product **18b** (0.61 g, 1.5 mmol, 65%) was obtained as colorless foam.

RF (Pent/AcOEt (4:6)) = 0.55.

Mp: 60.9- 62.5°C.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93 – 7.89 (m, 2H, Ar-H), 7.66 – 7.59 (m, 1H, Ar-H), 7.50 – 7.43 (m, 3H, Ar-H and F-uracil C=C-H), 5.12 (t, *J* = 9.4 Hz, 1H, cyclobutane-CH), 3.69 (s, 3H, ester CH_3), 3.64 (s, 3H, ester CH_3), 2.73 (q, *J* = 10.0 Hz, 1H, cyclobutane-CH_2), 2.66 – 2.58 (m, 1H, cyclobutane-CH_2), 2.33 (dtd, *J* = 10.6, 8.4, 2.4 Hz, 1H, cyclobutane-CH_2), 2.23 (dt, *J* = 11.6, 8.9 Hz, 1H, cyclobutane-CH_2).

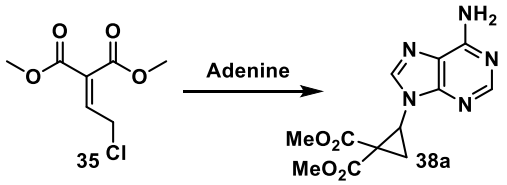
^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.8, 168.7, 167.1, 156.3 (d, *J* = 27.1 Hz), 148.6, 139.8 (d, *J* = 239.4 Hz), 135.5, 131.0, 130.9, 129.3, 127.1 (d, *J* = 33.6 Hz), 58.7, 56.8, 53.4, 53.3, 23.9, 22.8.

IR: 3090 (w), 3009 (w), 2958 (w), 2361 (w), 2262 (w), 1723 (s), 1668 (s), 1598 (w), 1445 (m), 1357 (w), 1266 (s), 1106 (m), 982 (w), 912 (m), 851 (w), 732 (s).

HRMS (ESI) calcd for $C_{19}H_{17}N_2FNaO_7^+$ $[M+Na]^+$ 427.0917; found 427.0920.

2.5 Purine cyclopropanes.

Dimethyl 2-(6-amino-9H-purin-9-yl)cyclopropane-1,1-dicarboxylate (38a).



Following the procedure described by Geen et al.,[6] dry K_2CO_3 (2.0 g, 14 mmol, 1.5 equiv), dimethyl 2-(2-chloroethylidene)malonate (**35**) (2.0 g, 10.5 mmol, 1.1 equiv), adenine (1.3 g, 9.5 mmol, 1 equiv) were stirred in a flame dried flask under nitrogen in dry DMF (25 mL) for 16 h. The reaction mixture was filtered on cotton with DMF (10 mL) and concentrated under high vacuo. The residue was purified by column chromatography using a mixture of pentane AcOEt (from 1:1 to 7:3 AcOEt/pentane) to afford the pure cyclopropane **38a** (2.2 g, 7.3 mmol, 69% yield) as a white powder.

RF (MeOH/DCM (0.5:9.5) = 0.39.

Mp 199.2-202.1 °C. (Decomposition)

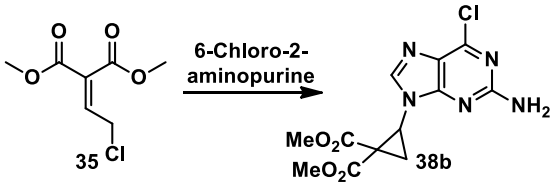
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (s, 1H, Adenine CH), 8.15 (s, 1H, Adenine CH), 7.27 (s, 2H, NH_2), 4.48 (dd, *J* = 8.5, 6.3 Hz, 1H cyclopropane NCH), 3.77 (s, 3H, Me ester), 3.31 (s, 3H, Me ester), 2.85 (t, *J* = 6.5 Hz, 1H, cyclopropane CH_2), 2.19 – 2.05 (m, 1H, cyclopropane CH_2).

^{13}C NMR (101 MHz, DMSO) δ 168.2, 165.9, 156.4, 152.9, 150.9, 140.9, 119.1, 53.4, 52.9, 37.9, 35.2, 18.4.

IR 3434 (w), 3083 (w), 3001 (w), 1719 (s), 1602 (s), 1431 (m), 1299 (s), 1200 (s), 893 (w), 768 (w).

HRMS (ESI) calcd for $C_{12}H_{14}N_5O_4^+$ $[M+H]^+$ 292.1040; found 292.1045

Dimethyl 2-(2-amino-6-chloro-9H-purin-9-yl)cyclopropane-1,1-dicarboxylate (38b).



Following the procedure described by Geen et al.[6], dry K_2CO_3 (3.42 g, 24.8 mmol, 1.5 equiv), dimethyl 2-(2-chloroethylidene)malonate (**35**) (3.50 g, 18.2 mmol, 1.1 equiv) and 6-chloro-7H-

[6] G. R. Geen, P. M. Kincey, B. M. Choudary, *Tetrahedron Lett.* 1992, *33*, 4609–4612.

purin-2-amine (2.80 g, 1.5 mmol, 1 equiv) were stirred in a flame dried flask under nitrogen in dry DMF (28 mL) for 16 h. The reaction mixture was filtered on cotton with DMF (10 mL) and concentrated under high vacuo. The residue was purified by column chromatography using a mixture of dichloromethane methanol (from pure dichloromethane to 8:2 dichloromethane/methanol) to afford the pure cyclopropane **38b** (4.30 g, 13.2 mmol, 51% yield) as a white powder.

RF (MeOH/DCM (1:9) = 0.56.

MP 215.3-218.6 °C. (Decomposition)

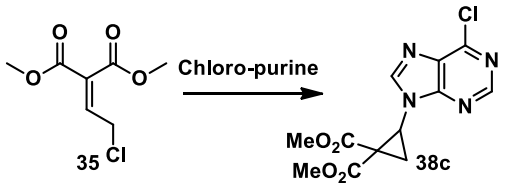
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H, purine CH), 7.05 (s, 2H, NH_2), 4.41 (dd, J = 8.6, 6.3 Hz, 1H, cyclopropane NCH), 3.38 (s, 3H, Me ester), 3.34 (s, 3H, Me ester), 2.82 (t, J = 6.5 Hz, 1H, cyclopropane CH_2), 2.10 (dd, J = 8.6, 6.7 Hz, 1H, cyclopropane CH_2).

^{13}C NMR (101 MHz, DMSO) δ 168.1, 165.8, 160.4, 155.4, 149.8, 143.0, 123.6, 53.5, 53.1, 37.8, 35.2, 18.5.

IR 3436 (w), 3163 (w), 1725 (s), 1563 (s), 1288 (s), 1210 (s), 1108 (s), 911 (s), 787 (w), 716 (m).

HRMS (ESI) calcd for $C_{12}H_{13}ClN_5O_4^+$ $[M+H]^+$ 326.0651; found 326.0654.

Dimethyl 2-(6-chloro-9H-purin-9-yl)cyclopropane-1,1-dicarboxylate (38c).



Following the procedure described by Geen et al.,[6] dry K_2CO_3 (5.7 g, 41 mmol, 1.5 equiv), dimethyl 2-(2-chloroethylidene)malonate (**35**) (5.8 g, 30 mmol, 1.1 equiv) and 6-chloro-purine (4.22 g, 27.3 mmol, 1 equiv) were stirred in a flame dried flask under nitrogen in dry DMF (55 mL) for 16 h. The reaction mixture was filtered on cotton with DMF (10 mL) and concentrated under high vacuo. The residue was purified by column chromatography using a mixture of dichloromethane methanol (from pure dichloromethane to 8:2 dichloromethane/methanol) to afford the pure cyclopropane **38c** (2.5g, 8.1 mmol, 30% yield) as foam.

RF (AcOEt/pentane (7:3) = 0.31

MP 120.1-123.6 °C.

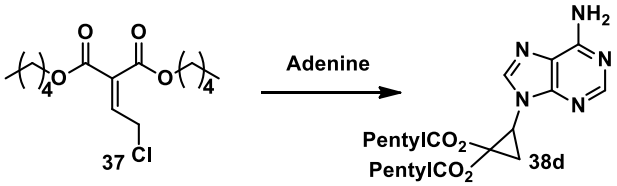
^{1}H NMR (400 MHz, Chloroform-d) δ 8.77 (s, 1H, purine CH), 8.10 (s, 1H, purine CH), 4.49 (dd, J = 8.4, 6.2 Hz, 1H, cyclopropane NCH), 3.87 (s, 3H, Me ester), 3.47 (s, 3H, Me ester), 2.82 (t, J = 6.4 Hz, 1H, cyclopropane CH_2), 2.18 (dd, J = 8.4, 6.7 Hz, 1H, cyclopropane CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 165.4, 152.6, 152.5, 151.4, 145.1, 131.5, 53.5, 53.3, 37.7, 35.0, 19.2.

IR 2938.34 (w), 1729 (s), 1603 (w), 1333 (s), 1230 (s), 1204 (s), 1142 (s), 941 (m).

HRMS (ESI) calcd for $C_{12}H_{12}ClN_4O_4^+$ $[M+H]^+$ 311.0542; found 311.0542.

Dimethyl 2-(6-amino-9H-purin-9-yl)cyclopropane-1,1-dicarboxylate (38d).



Following the procedure described by Geen et al.[6], dry K_2CO_3 (1.2 g, 8.9 mmol, 1.5 equiv), dimethyl 2-(2-chloroethylidene)pentylmalonate (**37**) (3.0 g, 6.5 mmol, 1.1 equiv, 66% Wt) and adenine (0.80 g, 5.9 mmol, 1 equiv) were stirred in a flame dried flask under nitrogen in dry DMF (11 mL) for 16 h. The reaction mixture was filtered on cotton with DMF (5 mL) and concentrated under high vacuo. The residue was purified by column chromatography using a mixture of dichloromethane methanol (from pure dichloromethane to 9.8:0.2 dichloromethane/methanol) to afford the pure cyclopropane **38d** (2.22 g, 5.49 mmol, 93% yield) as a white sticky powder.

RF (MeOH/DCM (0.2:9.8) = 0.51.

Mp 68.2-70.0 °C.

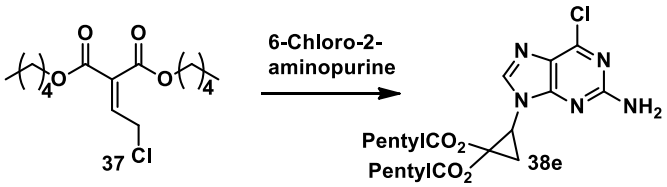
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 2H, adenine CH), 7.26 (s, 2H, adenine NH_2), 4.46 (dd, J = 8.6, 6.3 Hz, 1H, cyclopropane NCH), 4.27 – 4.18 (m, 2H, pentyl CH_2), 3.70 (td, J = 6.4, 4.6 Hz, 2H, pentyl CH_2), 2.86 (t, J = 6.5 Hz, 2H, cyclopropane CH_2), 2.05 (dd, J = 8.7, 6.7 Hz, 2H, cyclopropane CH_2), 1.71 – 1.49 (m, 2H, pentyl CH_2), 1.31 (ddt, J = 18.8, 7.9, 4.0 Hz, 4H, pentyl CH_2), 1.02 – 0.81 (m, 5H, pentyl CH_2 and pentyl CH_3), 0.78 (t, J = 7.3 Hz, 3H, pentyl CH_3).

^{13}C NMR (101 MHz, DMSO) δ 167.9, 165.4, 156.4, 153.1, 151.0, 140.6, 119.2, 66.0, 65.7, 37.8, 35.7, 28.1, 27.9, 27.7, 27.5, 22.2, 22.0, 18.0, 14.3, 14.1.

IR 3312 (w), 3135 (w), 2958 (m), 1726 (s), 1601 (m), 1471 (m), 1294 (s), 1197 (s), 967 (m), 735 (m).

HRMS (ESI) calcd for $C_{20}H_{30}N_5O_4^+$ $[M+H]^+$ 404.2292; found 404.2300.

Dipentyl 2-(2-amino-6-chloro-9H-purin-9-yl)cyclopropane-1,1-dicarboxylate (38e).



Following the procedure described by Geen et al.[6], dry K_2CO_3 (0.71 g, 5.1 mmol, 1.5 equiv), dimethyl 2-(2-chloroethylidene)pentylmalonate (**37**) (2.87 g, 3.77 mmol, 1.1 equiv, 40% Wt) and 6-chloro-7H-purin-2-amine (0.58 g, 3.4 mmol, 1 equiv) were stirred in a flame dried flask under nitrogen in dry DMF (7 mL) for 16 h. The reaction mixture was filtered on cotton with DMF (2 mL) and concentrated under high vacuo. The residue was purified by column chromatography using a mixture of dichloromethane methanol (from pure dichloromethane to 9.8:0.2 dichloromethane/methanol) to afford the pure cyclopropane **38e** (1.35 g, 3.08 mmol, 90% yield) as a white powder.

RF (MeOH/DCM (0.5:9.5) = 0.47.

Mp 127.1-128.3 °C. (Decomposition)

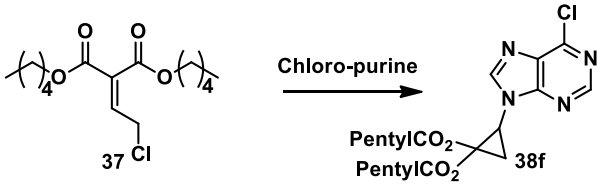
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.13 (s, 1H, purine CH), 7.04 (s, 2H, purine NH_2), 4.37 (dd, *J* = 8.6, 6.3 Hz, 1H, cyclopropane NCH), 4.26 – 3.99 (m, 2H, pentyl CH_2), 3.75 (td, *J* = 6.5, 2.5 Hz, 2H, pentyl CH_2), 2.82 (t, *J* = 6.5 Hz, 1H, cyclopropane CH_2), 2.01 (dd, *J* = 8.6, 6.8 Hz, 1H, cyclopropane CH_2), 1.61 (dd, *J* = 9.2, 4.9 Hz, 2H, pentyl CH_2), 1.31 (h, *J* = 3.7 Hz, 4H, pentyl CH_2), 1.10 (dq, *J* = 14.3, 7.3, 6.6 Hz, 4H, pentyl CH_2), 0.99 – 0.81 (m, 5H, pentyl CH_2 and pentyl CH_3), 0.77 (t, *J* = 7.3 Hz, 3H, pentyl CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 170.1, 165.1, 160.2, 154.6, 147.4, 128.5, 70.9, 70.6, 42.4, 40.5, 32.8, 32.7, 32.5, 32.3, 26.9, 26.8, 22.7, 19.0, 18.8.

IR 3441 (w), 3305 (w), 3201 (w), 2955 (w), 1699 (m), 1641 (s), 1560 (m), 1479 (w), 1309 (s), 1222 (s), 1186 (m), 959 (m), 912 (m), 785 (w).

HRMS (ESI) calcd for $C_{20}H_{28}ClN_5NaO_4$ [M+Na] 460.1727; found 460.1727.

Dipentyl 2-(6-chloro-9H-purin-9-yl)cyclopropane-1,1-dicarboxylate (38f).



Following the procedure described by Geen et al.[6], dry K_2CO_3 (1.99 g, 14.4 mmol, 1.5 equiv), dimethyl 2-(2-chloroethylidene)pentylmalonate (**37**) (6.5 g, 11 mmol, 1.1 equiv, 50% Wt) and 6-chloro-purine (1.5 g, 9.6 mmol, 1 equiv) were stirred in a flame dried flask under nitrogen in dry DMF (20 mL) for 16 h. The reaction mixture was filtered on cotton with DMF (10 mL) and concentrated under high vacuo. The residue was purified by column chromatography using a mixture of AcOEt pentane (from 1:1 to 7:3 AcOEt/pentane) to afford the pure cyclopropane **38f** (2.5 g, 5.9 mmol, 62% yield) as a yellow oil.

RF (pentane/AcOEt (8:2) = 0.18.

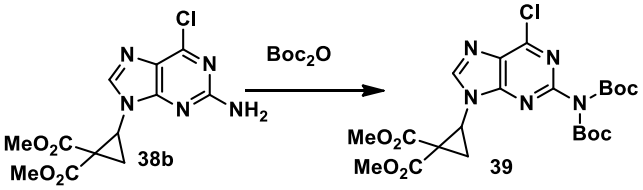
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.80 (s, 1H, purine CH), 8.12 (s, 1H, purine CH), 4.52 (dd, *J* = 8.4, 6.2 Hz, 1H, cyclopropane NCH), 4.32 (dt, *J* = 10.8, 6.8 Hz, 1H, pentyl CH_2), 4.25 (dt, *J* = 10.7, 6.7 Hz, 1H, pentyl CH_2), 3.87 (ddt, *J* = 33.9, 10.8, 6.7 Hz, 2H, pentyl CH_2), 2.84 (t, *J* = 6.4 Hz, 1H, cyclopropane CH_2), 2.17 (dd, *J* = 8.4, 6.6 Hz, 1H, cyclopropane CH_2), 1.44 – 1.26 (m, 4H, pentyl CH_2), 1.26 – 1.17 (m, 2H, pentyl CH_2), 1.14 – 1.04 (m, 2H, pentyl CH_2), 0.99 – 0.90 (m, 5H, pentyl CH_2 and pentyl CH_3), 0.85 (t, *J* = 7.3 Hz, 3H, pentyl CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 165.0, 152.7, 152.4, 151.3, 145.0, 131.5, 66.7, 66.5, 37.5, 35.52, 28.1, 27.9, 27.8, 27.6, 22.2, 22.1, 18.8, 13.9, 13.8.

IR 2953 (w), 2866 (w), 1723 (s), 1587 (w), 1563 (m), 1284 (s), 1201 (s), 1134 (s), 958 (m).

HRMS (ESI) calcd for $C_{20}H_{28}ClN_4O_4^+$ $[M+H]^+$ 423.1794; found 423.1794.

Dimethyl 2-(2-di^{t}Butylcarboxylate-amino-6-chloro-9H-purin-9-yl)cyclopropane-1,1-dicarboxylate (39).



Cyclopropane **38b** (0.050 g, 0.15 mmol, 1.0 equiv), di-*tert*-butyl dicarbonate (0.14 g, 0.66 mmol, 4.3 equiv) and dimethylaminopyridine (1.8 mg, 0.015 mmol, 0.1 equiv) were stirred in acetonitrile (2.5 mL) for 5 h in a flame-dried flask under nitrogen. After removal of the solvent, EtOAc (10 mL) was added and the solution was washed with 1 N HCl (3 mL) and then with brine (3 x 10 mL). Then the mixture was dried over anhydrous $MgSO_4$, filtered and concentrated. Then the crude residue was purified by column chromatography using a mixture of pentane and ethyl acetate (from 90:10 to 70:30 pentane/ ethyl acetate) affording the pure product **39** (0.069 g, 0.13 mmol, 85% yield, 90% purity) as a slightly yellow sticky oil.

RF (Pent/AcOEt (7:3) = 0.41.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 (s, 1H, purine CH), 4.38 (dd, *J* = 8.4, 6.1 Hz, 1H, cyclopropane NCH), 3.78 (s , 3H, Me ester), 3.43 (s, 3H, Me ester), 2.73 (t, *J* = 6.4 Hz, 1H, cyclopropane CH_2), 2.10 (m, 1H, cyclopropane CH_2), 1.39 (m, 18H, Boc).

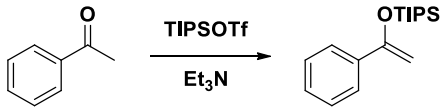
^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 165.2, 153.4, 152.3, 151.4, 150.4, 145.8, 129.7, 83.7, 53.4, 53.2, 37.6, 35.0, 27.8, 19.1.
Boc carbon peaks are superposed (Methyls, quaternary carbons and C=O.)

IR 3546 (w), 3117 (w), 2981 (w), 1792 (m), 1730 (s), 1568 (m), 1280 (s), 1103 (s), 856 (m), 779 (m).

HRMS (ESI) calcd for $C_{22}H_{28}ClN_5NaO_8^+$ $[M+Na]^+$ 548.1519; found 548.1515.

2.5 Dipolarophiles.

Triisopropyl((1-phenylvinyl)oxy)silane (21).



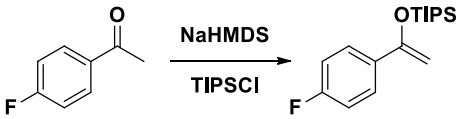
20 **21**

Acetophenone (**20**) (1.0 g, 8.3 mmol, 1 equiv) was solubilized in DCM (8 mL) and triethylamine (1.73 mL, 12.5 mmol, 1.5 equiv) was added at room temperature. Then at 0 °C tri*iso*propylsilyl trifluoromethanesulfonate (2.7 mL, 10 mmol, 1.2 equiv) 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 1% NEt_3 to obtain the pure enol-ether **21** (2.0 g, 7.2 mmol, 86% yield) as a colorless oil.

^{1}H 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, $C=CH_2$), 4.44 (d, *J* = 1.9 Hz, 1H, $C=CH_2$), 1.33 (m, 3H, TIPS-CH), 1.16 (m, 18H, TIPS-CH_3).

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

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



48 **49**

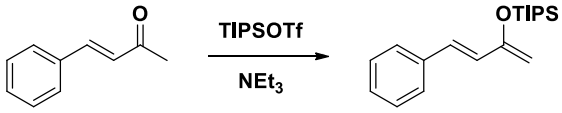
(4-Fluorophenyl)ethanone (**48**) (0.44 mL, 3.6 mmol, 1equiv) was solubilized in THF (15 mL) at -78 °C and NaHMDS (2M solution in THF, 2.1 mL, 4.1 mmol, 1.1 equiv) was added dropwise. The mixture was stirred 1 hour at room temperature and cooled down to -78 °C. TIPS-Cl (0.86 mL, 4.1 mmol, 1.1 equiv) 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 1% NEt_3 to obtain the pure enol-ether **49** (0.62 g, 2.1 mmol, 58% yield) as a slightly yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 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), 1.34-1.12 (m, 18H, TIPS-CH_3).

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

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



50 **51**

(*E*)-4-Phenylbut-3-en-2-one (**50**) (0.42 g, 2.9 mmol, 1 equiv) was solubilized in DCM (3 mL) and triethylamine (0.60 mL, 4.3 mmol, 1.5 equiv) was added at room temperature. Then triisopropylsilyl trifluoromethanesulfonate (0.93 mL, 3.4 mmol, 1.2 equiv) 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 1% NEt_3 to obtain the pure enol ether **51** (0.87 g, 2.9 mmol, quantitative yield) as a colorless oil.

RF (pentane) = 0.88.

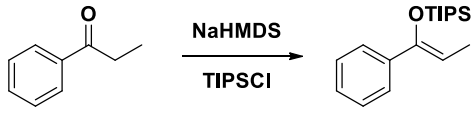
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64 – 7.54 (m, 2H, Ar-H), 7.45 (m, 2H, Ar-H), 7.40 – 7.32 (m, 1H, Ar-H), 7.15 (d, *J* = 15.6 Hz, 1H, C=CH), 6.74 (d, *J* = 15.7 Hz, 1H, C=CH), 4.61 – 4.59 (s, 1H, C=CH_2), 4.58 (s, 1H, C=CH_2), 1.54 – 1.42 (m, 3H, TIPS-CH), 1.34 (d, *J* = 7.8 Hz, 18H, TIPS-CH_3).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 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.

(Z)-Triisopropyl((1-phenylprop-1-en-1-yl)oxy)silane (53).



52 **53**

Propiophenone (**52**) (0.50 mL, 3.7 mmol, 1 equiv) was solubilized in THF (15 mL) at -78 °C and NaHMDS (2 M solution in THF, 2.1 mL, 4.1 mmol, 1.1 equiv) 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 equiv) 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 1% NEt_3 to obtain the pure enol-ether **53** (0.46 g, 1.6 mmol, 43% yield) as a slightly yellow oil.

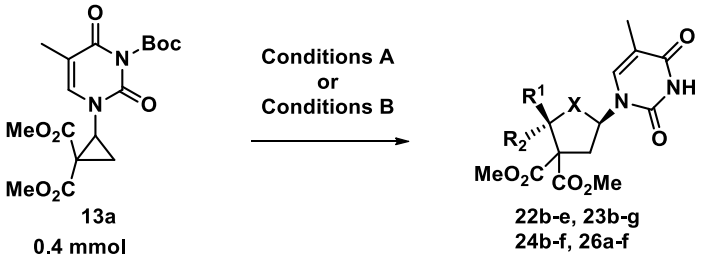
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 – 7.38 (m, 2H, Ar-H), 7.33 – 7.18 (m, 3H, Ar-H), 5.06 (q, *J* = 6.8 Hz, 1H, C=C), 1.77 (d, *J* = 6.9 Hz, 3H, CH_3), 1.15 – 0.97 (m, 21H, TIPS).

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

3. Scope of the reaction [3+2] reaction.

3.1 From thymine cyclopropanes.

General procedures for annulation reaction



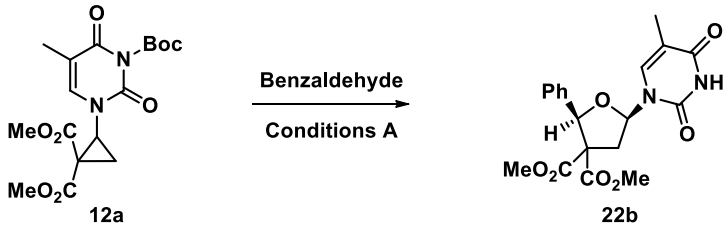
a) Conditions A

Dimethyl 2-(3-(*tert*-butoxycarbonyl)-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(*2H*)-yl)cyclopropane-1,1-dicarboxylate (**13a**) (0.15 g, 0.40 mmol 1.0 equiv), aldehyde (0.48 mmol, 1.2 equiv) and $In(OTf)_3$ (0.045 g, 0.080 mmol, 0.2 equiv) 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_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 (**13a**) (0.15 g, 0.40 mmol 1.0 equiv) and the ketone or sillylenol ether (0.48 mmol, 1.2 equiv) 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 equiv) 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 (22b).



Following the conditions A, using benzaldehyde (**19**) (0.051 g, 0.48 mmol, 1.2 equiv), the pure product **22b** (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.

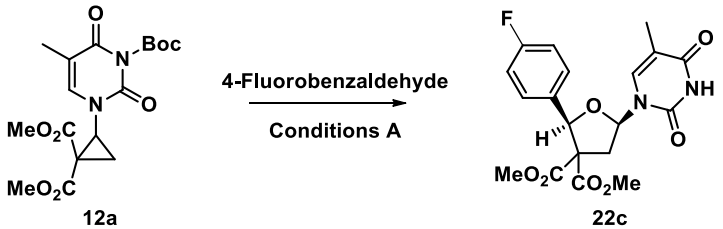
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.47 (s, 1H, thymine NH), 7.94 (d, *J* = 1.6 Hz, 1H, thymine vinyl-CH), 7.48 – 7.40 (m, 2H, Ar-H), 7.40 – 7.27 (m, 3H, Ar-H), 6.37 (t, *J* = 7.6 Hz, 1H, tetrahydrofuran-NCH), 5.61 (s, 1H, tetrahydrofuran-CH), 3.81 (s, 3H, ester methyl), 3.13 (s, 3H, ester methyl), 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 $C_{19}H_{20}N_2NaO_7^+$ $[M+Na]^+$ 411.1163; found 411.1168.

Dimethyl-2-(4-fluorophenyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)dihydrofuran-3,3(2H)-dicarboxylate (22c).



Following the conditions A, using 4-fluorobenzaldehyde (0.060 g, 0.48 mmol, 1.2 equiv), the pure product **22c** (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.

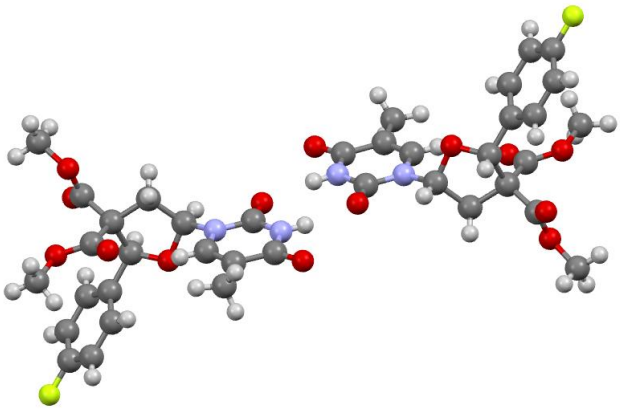
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.54 – 8.46 (m, 1H, thymine NH), 7.93 (d, *J* = 1.5 Hz, 1H, thymine vinyl-CH), 7.49 – 7.39 (m, 2H, Ar-H), 7.10 – 6.99 (m, 2H, Ar-H), 6.37 (t, *J* = 7.6 Hz, 1H, tetrahydrofuran-NCH), 5.56 (s, 1H, tetrahydrofuran-CH), 3.81 (s, 3H, ester methyl), 3.20 (s, 3H, ester 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.

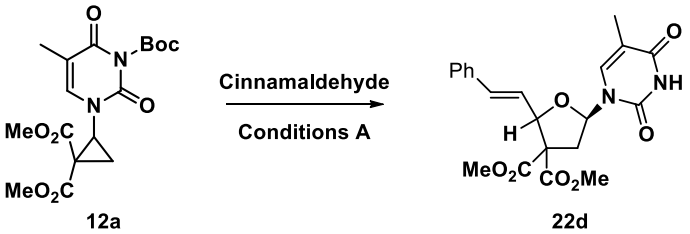
IR 3192 (w), 3069 (w), 1729 (s), 1695 (s), 1512 (m), 1281 (s), 1225 (m), 1094 (m), 1054 (m), 915 (m).

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-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(*2H*)-yl)-2-((*E*)-styryl)dihydrofuran-3,3(*2H*)-dicarboxylate. (22d)



Following the conditions A, using cinnamaldehyde (0.063 g, 0.48 mmol, 1.2 equiv), a mixture of diastereoisomers (5:1 by integration of methyl esters at 3.76 ppm and 3.71 ppm) **22d** (0.16 g, 0.28 mmol, 96% yield) was obtained as a colorless foam.

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

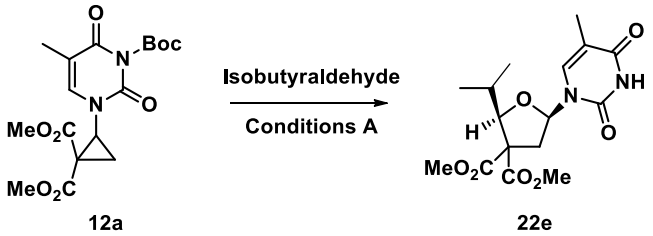
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.82 (s, 1H, NH), 7.70 (d, *J* = 1.3 Hz, 1H, thymine vinyl-CH, major diastereoisomer), 7.35 – 7.17 (m, 10H, Ar-H, both diastereoisomers), 7.14 (d, *J* = 1.3 Hz, 1H, thymine vinyl-CH, minor diastereoisomer), 6.72 (dd, *J* = 16.0, 1.3 Hz, 1H vinyl C-H, major and minor diastereoisomers), 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, 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), 1468 (m), 1435 (m), 1284 (s), 1085 (s), 972 (m), 913 (m), 734 (s).

HRMS (ESI) calcd for $C_{21}H_{23}N_2O_7^+$ $[M+H]^+$ 415.1500; found 415.1502.

Dimethyl 2-isopropyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(*2H*)-yl)dihydrofuran-3,3(*2H*)-dicarboxylate (22e).



Following the conditions A, using isobutyraldehyde (0.035 g, 0.48 mmol, 1.2 equiv), the pure product **22e** (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.

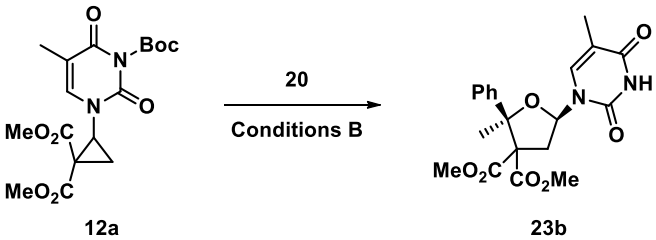
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.45 (s, 1H, N-H), 7.62 (d, *J* = 1.5 Hz, 1H, thymine vinyl-CH), 6.12 (t, *J* = 7.1 Hz, 1H, tetrahydrofuran-NCH), 4.14 (d, *J* = 7.8 Hz, 1H, tetrahydrofuran-OCH), 3.80 (s, 3H, ester methyl), 3.78 (s, 3H, ester methyl), 2.70 (dd, *J* = 14.5, 6.5 Hz, 1H, tetrahydrofuran-CH_2), 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*) δ 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 $C_{16}H_{23}N_2O_7^+$ $[M+H]^+$ 355.1500; found 355.1502.

Dimethyl-2-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(*2H*)-yl)-2-phenyldihydrofuran-3,3(2H)-dicarboxylate (23b).



Following the conditions B, using acetophenone (**20**) (0.058 g, 0.48 mmol, 1.2 equiv), the pure product **23b** (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,

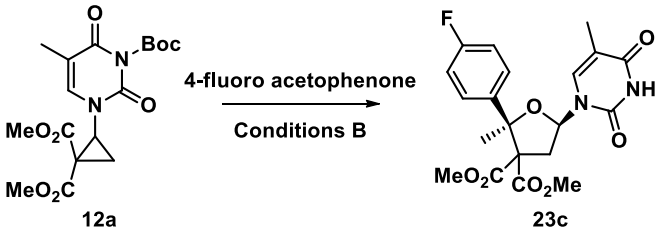
8.2 Hz, 1H, tetrahydrofuran-CH_2) 2.77 (dd, *J* = 14.9, 5.5 Hz, 1H, tetrahydrofuran-CH_2) 2.04 (d, *J* = 1.3 Hz, 3H, thymine methyl), 1.86 (s, 3H, tetrahydrofuran methyl).

^{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), 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)-2-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)dihydrofuran-3,3(2H)-dicarboxylate (23c).



Following the conditions B, using 4-fluoroacetophenone (0.067 g, 0.48 mmol, 1.2 equiv), the pure product **23c** (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.

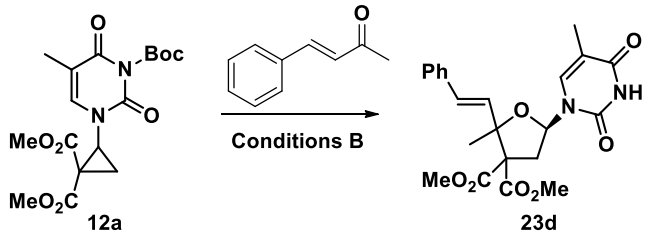
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.47 (s, 1H, thymine NH), 8.07 (d, *J* = 1.5 Hz, 1H, thymine vinyl-CH), 7.70 – 7.60 (m, 2H, Ar-H), 7.20 (t, *J* = 8.9 Hz, 2H, Ar-H), 6.36 (dd, *J* = 8.3, 5.5 Hz, 1H, tetrahydrofuran-NCH), 3.75 (s, 3H, ester methyl), 3.26 (dd, *J* = 14.9, 8.3 Hz, 1H, , tetrahydrofuran-CH_2), 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 $C_{20}FH_{22}N_2O_7^+$ $[M+H]^+$ 421.1406; found 421.1405.

Dimethyl 2-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(*2H*)-yl)-2-((*E*)-styryl)dihydrofuran-3,3(2H)-dicarboxylate. (23d)



Following the conditions B, using (*E*)-4-phenylbut-3-en-2-one (0.070 g, 0.48 mmol, 1.2 equiv), a mixture of unseparable diastereoisomers (ratio 2:1 obtained by integration of methyl esters at 3.64 ppm and 3.55 ppm) **23d** (0.14 g, 0.34 mmol, 79% yield) was obtained as a colorless foam.

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

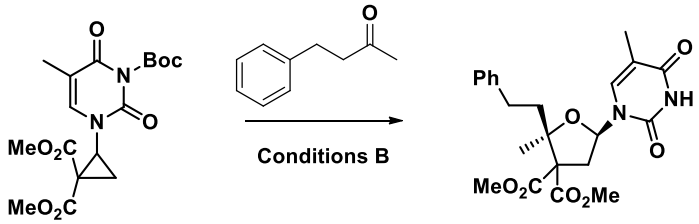
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.19 (br.s, 1H, N-H), 7.84 (d, *J* = 1.3 Hz, 1H, , thymine vinyl-CH, major diastereoisomer), 7.59 (d, *J* = 1.3 Hz, 1H, , thymine vinyl-CH, minor diastereoisomer), 7.36 – 7.16 (m, 5H, Ar-H), 6.69 (d, *J* = 15.9 Hz, 1H, vinyl C-H, minor diastereomer), 6.65 (d, *J* = 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, minor diastereoisomer), 1.89 (d, *J* = 1.2 Hz, 3H, thymine methyl, major diastereoisomer), 1.61 (s, 3H, tetrahydrofuran methyl, minor diastereoisomer), 1.52 (s, 3H, tetrahydrofuran methyl, major diastereoisomer).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 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, 128.7, 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 $C_{22}H_{25}N_2O_7^+$ $[M+H]^+$ 429.1656; found 429.1660.

Dimethyl-2-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenethyldihydrofuran-3,3(2H)-dicarboxylate (23e).



Following the conditions B, using 4-phenylbutan-2-one (0.071 g, 0.48 mmol, 1.2 equiv), the pure product **23e** (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.

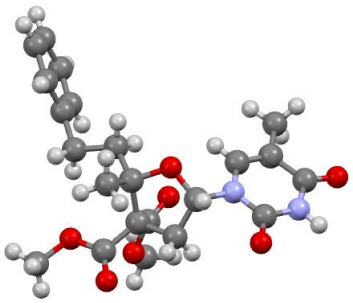
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.07 (s, 1H, thymine NH), 7.74 (q, *J* = 1.2 Hz, 1H, thymine vinyl-CH), 7.30 (dd, *J* = 8.5, 6.6 Hz, 2H, Ar-H), 7.24 – 7.17 (m, 3H, Ar-H), 6.18 (dd, *J* = 7.7, 5.3 Hz, 1H, tetrahydrofuran-NCH), 3.78 (s, 3H, ester methyl), 3.72 (s, 3H, ester methyl), 3.23 – 3.05 (m, 1H, tetrahydrofuran-CH_2), 2.92 – 2.69 (m, 2H, benzylic-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.

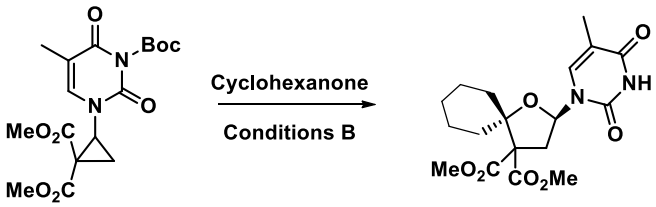
IR 3193 (w), 3060 (w), 2957 (w), 1735 (s), 1692 (s), 1468 (m), 1266 (s), 1097 (m), 914 (m).

HRMS (ESI) calcd for $C_{22}H_{27}N_2O_7^+$ $[M+H]^+$ 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. (23f)



12a 23f

Following the conditions B, using cyclohexanone (0.047 g, 0.48 mmol, 1.2 equiv), the pure product **23f** (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.

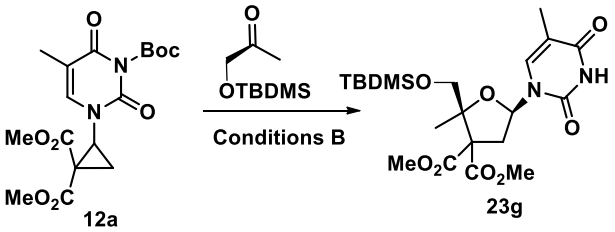
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.25 – 8.08 (br s, 1H, thymine NH), 7.70 (d, *J* = 1.5 Hz, 1H, thymine vinyl-CH), 6.03 (dd, *J* = 7.6, 5.2 Hz, 1H, tetrahydrofuran-NCH), 3.71 (s, 3H, ester methyl), 3.68 (s, 3H, ester methyl), 3.11 (dd, *J* = 14.9, 7.6 Hz, 1H, tetrahydrofuran-CH_2), 2.39 (dd, *J* = 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 $C_{18}H_{24}N_2NaO_7$ [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. (23g)



Following the conditions B, using 1-((*tert*-butyldimethylsilyl)oxy)propan-2-one (0.075 g, 0.48 mmol, 1.2 equiv), a single diasteroisomer **23g** (0.072 g, 0.15 mmol, 38% yield) was obtained as a colorless oil.

RF (pent/AcOET (1:1)) = 0.53.

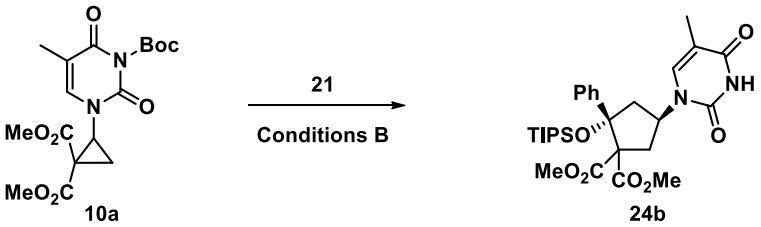
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.35 (s, 1H, N-H), 7.61 (d, *J* = 1.3 Hz, 1H, thymine vinyl-CH), 6.25 (dd, *J* = 8.0, 5.8 Hz, 1H, tetrahydrofuran-NCH), 4.09 (d, *J* = 10.9 Hz, 1H, CH_2O), 3.80 (s, 3H, ester methyl), 3.72 (s, 3H, ester methyl), 3.68 (d, *J* = 10.9 Hz, 1H, CH_2O), 3.05 (dd, *J* = 13.3, 5.8 Hz, 1H, tetrahydrofuran-CH_2), 2.72 (dd, *J* = 13.3, 8.1 Hz, 1H, tetrahydrofuran-CH_2), 1.92 (d, *J* = 1.1 Hz, 3H, thymine methyl), 1.31 (s, 3H, tetrahydrofuran methyl), 0.82 (s, 9H, TBDMS), 0.05 (s, 6H, TBDMS).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 168.2, 163.7, 150.1, 135.9, 109.3, 88.0, 85.6, 69.1, 64.2, 53.1, 52.6, 40.9, 25.6, 21.1, 18.0, 12.8, -5.7, -6.0.

IR 3180 (w), 3126 (w), 2909 (w), 1684 (s), 1443 (s), 1096 (w), 848 (s).

HRMS (ESI) calcd for $C_{21}H_{34}N_2NaO_8Si^+$ $[M+Na]^+$ 493.1977; found 493.1982.

Dimethyl-4-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(*2H*)-yl)-2-phenyl-2-((triisopropylsilyl)oxy)cyclopentane-1,1-dicarboxylate. (24b)



Following the conditions B, using TIPS protected acetophenone (**21**) (0.17 g, 0.60 mmol, 1.5 equiv), the pure product **24b** (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.

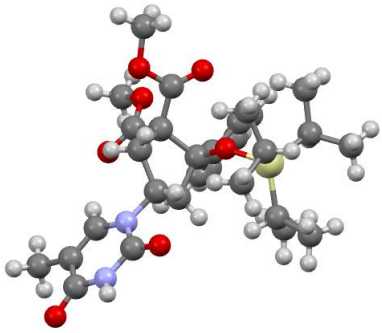
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.40 (s, 1H, thymine N-H), 7.86 (d, *J* = 1.6 Hz, 1H, thymine vinyl-CH), 7.82 – 7.74 (m, 2H, Ar-H), 7.34 – 7.27 (m, 3H, Ar-H), 5.70 (ddd, *J* = 11.4, 9.3, 5.7 Hz, 1H, cyclopentane-NCH), 3.76 (s, 3H, ester methyl), 3.29 (m, 4H, ester methyl and cyclopentane-CH_2), 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*) δ 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.

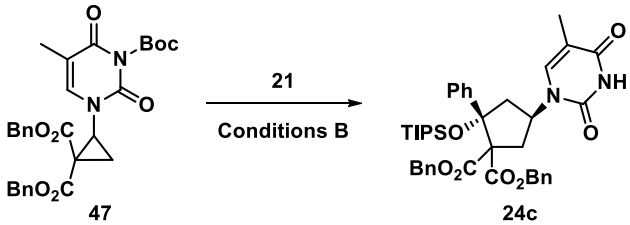
IR 2950 (w), 2868 (w), 1681 (s), 1467 (m), 1434 (w), 1392 (w), 1259 (s), 1135 (m), 1090 (m).

HRMS (ESI) calcd for $C_{29}H_{42}N_2NaO_7Si^+$ $[M+Na]^+$ 581.2653; found 581.2660.

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



Dibenzyl 4-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenyl-2-((triisopropylsilyl)oxy)cyclopentane-1,1-dicarboxylate. (24c)



Following the conditions B, using TIPS protected acetophenone **21** (0.17 g, 0.60 mmol, 1.5 equiv) and the corresponding cyclopropane 37 (0.21 g, 0.40 mmol, 1 equiv), the pure product **24c** (0.27 g, 0.38 mmol, 95% yield) was obtained as a white crystalline solid.

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

MP 69.4-73.1°C.

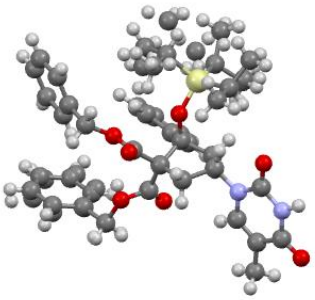
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.35 (s, 1H, thymine N-H), 7.84 (d, *J* = 1.6 Hz, 1H, thymine vinyl-CH), 7.77 (dd, *J* = 7.3, 1.8 Hz, 2H, Ar-H), 7.31 – 7.11 (m, 11H, Ar-H), 6.91 – 6.84 (m, 2H, Ar-H), 5.72 (tt, *J* = 11.5, 6.9 Hz, 1H, cyclopentane-NCH), 5.19 – 5.03 (m, 2H, benzylic-CH_2), 4.76 (d, *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), 2.38 (dd, *J* = 15.2, 7.0 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.

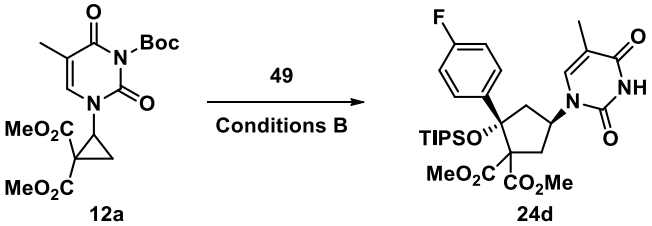
IR 3434 (w), 3160 (w), 3035 (w), 2872 (w), 1682 (s), 1456 (w), 1374 (w), 1136 (w), 1025 (m).

HRMS (ESI) calcd for $C_{41}H_{50}N_2NaO_7S^+$ $[M+Na]^+$ 733.3279; found 733.3271.

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



Dimethyl-2-(4-fluorophenyl)-4-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(*2H*)-yl)-2-((triisopropylsilyl)oxy)cyclopentane-1,1-dicarboxylate. (24d)



Following the conditions B, using ((1-(4-fluorophenyl)vinyl)oxy)triisopropylsilane (**49**) (0.14 g, 0.48 mmol, 1.2 equiv), the pure product **24d** (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.

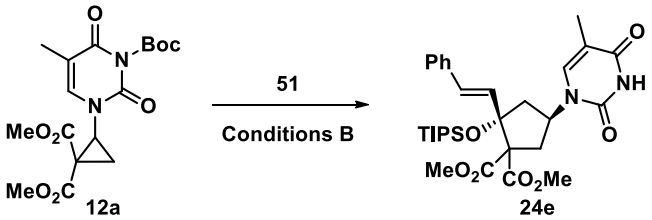
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.14 (d, *J* = 3.8 Hz, 1H, thymine-NH), 7.89 – 7.78 (m, 3H, Ar-H and thymine vinyl-CH), 7.03 (t, *J* = 8.7 Hz, 2H, Ar-H), 5.71 (tt, *J* = 11.4, 7.0 Hz, 1H, cyclopentane-NCH), 3.79 (s, 3H, methyl ester), 3.37 (s, 3H, ester methyl), 3.36 – 3.31 (m, 1H, cyclopentane-CH_2). 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*) δ 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 $C_{29}FH_{42}N_2O_7Si^+$ $[M+H]^+$ 577.2740; found 577.2719.

Dimethyl 4-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(*2H*)-yl)-2-((*E*)-styryl)-2-((tri*iso*propylsilyl)oxy)cyclopentane-1,1-dicarboxylate. (24e)



Following the conditions B, using (*E*)-triisopropyl((4-phenylbuta-1,3-dien-2-yl)oxy)silane (**51**) (0.15 g, 0.48 mmol, 1.2 equiv), a mixture of unseparable diastereoisomers (ratio 13:1 by integration of the NC-H proton at 5.64 ppm and 4.88 ppm) **24e** (0.13 g, 0.22 mmol, 55% yield) was obtained as a colorless foam.

RF (pent/AcOET (1:1)) = 0.54

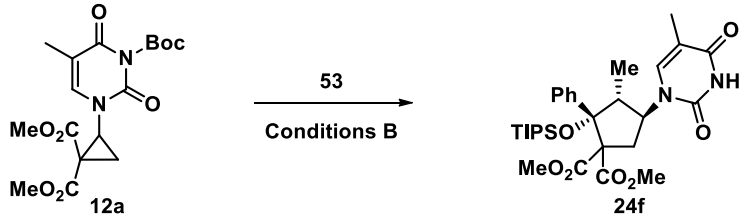
^{1}H NMR (400 MHz, Chloroform-*d,* Major diastereoisomer) δ 8.58 (s, 1H, N-H), 7.77 (d, *J* = 1.1 Hz, 1H, thymine vinyl-CH), 7.34 – 7.21 (m, 5H, Ar-H), 6.85 (d, *J* = 16.6 Hz, 1H, vinyl C-H), 6.43 (d, *J* = 16.5 Hz, 1H, vinyl C-H), 5.64 (tt, *J* = 11.5, 6.8 Hz, 1H, cyclopentane-NCH), 3.74 (s, 3H, ester 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), 2.30 (dd, *J* = 12.5, 7.0 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) δ 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 differents signals(18.2 and 18.0).

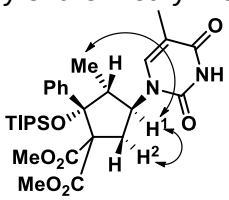
IR 2947 (w), 2868 (w), 1689 (m), 1465 (w), 1435 (w), 1260 (m), 1088 (w), 1017 (w), 976 (w), 911 (m), 732 (s).

HRMS (ESI) calcd for $C_{31}H_{45}N_2O_7Si^+$ $[M+H]^+$ 585.2991; found 585.3015.

Dimethyl-3-methyl-4-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenyl-2-((triisopropylsilyl)oxy)cyclopentane-1,1-dicarboxylate. (24f)



Following the conditions B, using triisopropyl((1-phenylprop-1-en-1-yl)oxy)silane (**53**) (0.14 g, 0.48 mmol, 1.2 equiv), the pure product **24f** (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 cyclopentane -NCH), 3.70 (s, 3H, ester methyl), 3.35 (dq, *J* = 13.6, 6.8 Hz, 1H, tetrahydrofuran-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 3175 (w), 2963 (w), 2870 (w), 1679 (m), 1468 (w), 1257 (m), 1079 (m), 1026 (m), 910 (m), 731 (s).

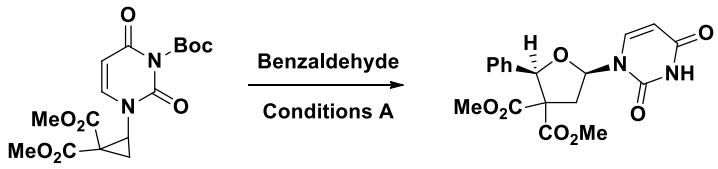
HRMS (ESI) calcd for $C_{30}H_{45}N_2O_7Si^+$ $[M+H]^+$ 573.2991; found 573.2992.

3.2 From uracil and 5-fluoro uracil cyclopropanes.

General procedure for Benzoyl removal.

The crude product was dissolved in EtOH (2 mL) and stirred at room temperature for 2 hours with NH_4OH (0.6 mL, 40 equiv, 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-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenyldihydrofuran-3,3(2H)-dicarboxylate (26a).



12b **26a**

Following the conditions A, using benzaldehyde (0.051 g, 0.48 mmol, 1.2 equiv) and the corresponding cyclopropane **12b** (0.15 g, 0.40 mmol, 1 equiv), the pure product **26a** (0.093 g, 0.25 mmol, 62% yield) was obtained as a white powder.

RF (AcOEt) = 0.65.

MP 209.0-210.7°C.

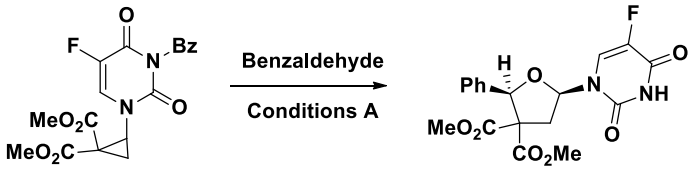
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.07 (s, 1H, NH), 8.05 (d, *J* = 8.2 Hz, 1H, uracil CH), 7.42 – 7.29 (m, 2H, Ar-H), 7.24 (m, 3H, Ar-H), 6.29 (t, *J* = 7.4 Hz, 1H, tetrahydrofuran N-CH), 5.84 (d, *J* = 8.1 Hz, 1H, uracil CH), 5.52 (s, 1H, tetrahydrofuran-CH), 3.72 (s, 3H, ester CH_3), 3.03 (s, 3H, 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*) δ 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 $C_{18}H_{18}N_2NaO_7^+$ $[M+Na]^+$ 397.1006; found 397.1004.

Dimethyl -5-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenyldihydrofuran-3,3(2H)-dicarboxylate (26b).



12c 26b

Following the conditions A, using benzaldehyde (0.051 g, 0.48 mmol, 1.2 equiv), and the corresponding cyclopropane **12c** (0.16 g, 0.40 mmol, 1 equiv), followed by the benzoyl deprotection, the pure product **26b** (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.

^{1}H 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 CH_3), 3.08 (s, 3H, ester CH_3), 2.80 (qd, *J* = 14.8, 7.4 Hz, 2H, tetrahydrofuran CH_2).

^{13}C 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), 1723 (s), 1668 (m), 1436 (w), 1273 (s), 1211 (m), 1094 (m), 1053 (m), 914 (m), 735 (m).

HRMS (ESI) calcd for $C_{18}H_{17}FN_2NaO_7$ [M+Na] 415.0917; found 415.0918.

Dimethyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methyl-2-phenyldihydrofuran-3,3(2H)-dicarboxylate (26c).

12b 26c

Following the conditions B, using acetophenone (**20**) (0.058 g, 0.48 mmol, 1.2 equiv) and the cyclopropane **41** (0.16 g, 0.40 mmol, 1 equiv), the pure product **26c** (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, tetrahydrofurane 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, tetrahydrofurane-CH_2), 3.03 (s, 3H, ester CH_3), 2.67 (dd, *J* = 14.8, 5.2 Hz, 1H, tetrahydrofurane-CH_2), 1.80 (s, 3H, tetrahydrofurane-CH_3).

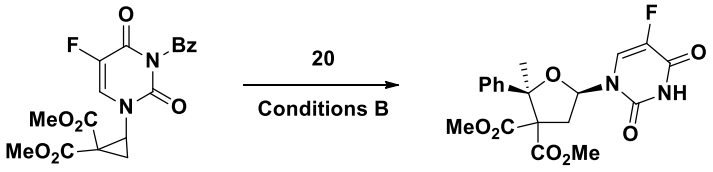
^{13}C NMR (101 MHz, DMSO-d_6) δ 170.6, 168.8, 163.6, 151.1, 141.1, 141.1, 128.2, 126.0, 102.3, 87.9, 81.2, 67.0, 53.2, 52.9, 25.8.

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) calcd for $C_{19}H_{20}N_2NaO_7^+$ $[M+Na]^+$ 411.1163; found 411.1168.

Dimethyl -5-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methyl-2-phenyldihydrofuran-3,3(2H)-dicarboxylate (26d).



12c 26d

Following the conditions B, using acetophenone (**20**) (0.058 g, 0.48 mmol, 1.2 equiv) and the corresponding cyclopropane **12c** (0.16 g, 0.40 mmol, 1 equiv) at -40 °C, followed by the benzoyl deprotection, the pure product **26d** (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.

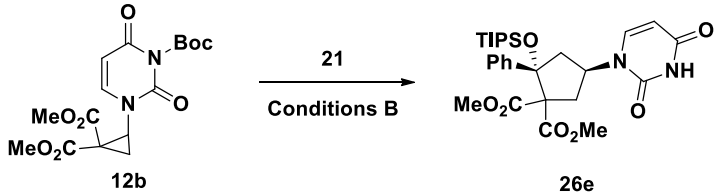
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.98 (d, *J* = 4.6 Hz, 1H, NH), 8.50 (d, *J* = 6.5 Hz, 1H, F-uracil CH), 7.77 – 7.65 (m, 2H, ArH), 7.51 – 7.16 (m, 3H, ArH), 6.42 (ddd, *J* = 8.2, 5.1, 1.7 Hz, 1H, tetrahydrofuran N-CH), 3.80 (s, 3H, ester CH_3), 3.18 (dd, *J* = 15.1, 8.2 Hz, 1H, tetrahydrofuran CH_2), 3.10 (s, 3H, ester CH_3), 2.78 (dd, *J* = 15.1, 5.1 Hz, 1H, tetrahydrofuran CH_2), 1.88 (s, 3H, CH_3).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 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), 1262 (s), 1205 (m), 1076 (s), 914 (m), 768 (m).

HRMS (ESI) calcd for $C_{19}H_{19}FN_2NaO_7$ [M+Na] 429.1074; found 429.1080.

Dimethyl-4-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenyl-2-((triisopropylsilyl)oxy)cyclopentane-1,1-dicarboxylate (26e).



12b 26e

Following the conditions B, using TIPS protected acetophenone **21** (0.17 g, 0.60 mmol, 1.5 equiv) and the cyclopropane **12b** (0.16 g, 0.40 mmol, 1 equiv), the pure product **26e** (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.

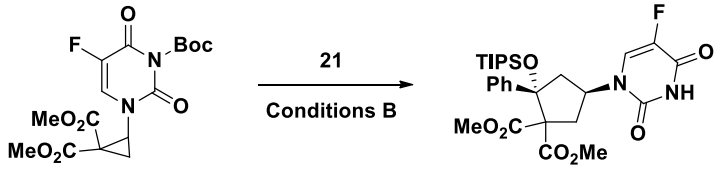
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.92 (s, 1H, NH), 8.11 (d, *J* = 8.1 Hz, 1H, uracil CH), 7.85 – 7.65 (m, 2H, ArH), 7.30 (m, 3H, ArH), 5.86 (dd, *J* = 8.1, 2.2 Hz, 1H, uracil CH), 5.74 (tt, *J* = 11.3, 7.0 Hz, 1H, cyclopentane N-CH), 3.76 (s, 3H ester methyl), 3.34 (dd, *J* = 15.1, 11.1 Hz, 1H, cyclopentane CH_2), 3.29 (s, 3H, ester methyl), 3.18 (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).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.7, 168.1, 163.7, 151.4, 141.7, 139.8, 128.4, 128.0, 127.4, 103.2, 88.3, 70.3, 52.8, 52.3, 51.5, 43.5, 38.2, 18.2, 18.2, 13.8.

IR 3183 (w), 3060 (w), 2950 (w), 1686 (s), 1462 (m), 1261 (m), 1113 (w), 990 (w), 885 (w).

HRMS (ESI) calcd for $C_{28}H_{40}N_2NaO_7Si^+$ $[M+Na]^+$ 567.2497; found 567.2496.

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



12c **26f**

Following the conditions B, using TIPS protected acetophenone **21** (0.17 g, 0.60 mmol, 1.5 equiv) and the corresponding cyclopropane **12c** (0.16 g, 0.40 mmol, 1 equiv) at -40 °C, followed by the benzoyl deprotection, the pure product **26f** (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*) δ 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).

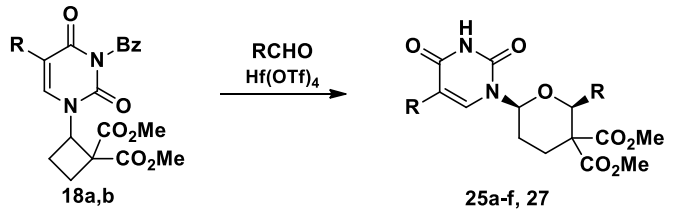
^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.8, 168.0, 157.0 (d, *J* = 26.5 Hz), 150.2, 141.0 (d, *J* = 237.5 Hz), 139.6, 128.5, 127.9, 127.4, 125.9 (d, *J* = 33.4 Hz), 88.4, 70.3, 52.9, 52.4, 52.0, 43.4, 38.0, 18.2, 18.2, 13.9.

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

HRMS (ESI) calcd for $C_{28}H_{39}FN_2NaO_7Si^+$ $[M+Na]^+$ 585.2403; found 585.2386.

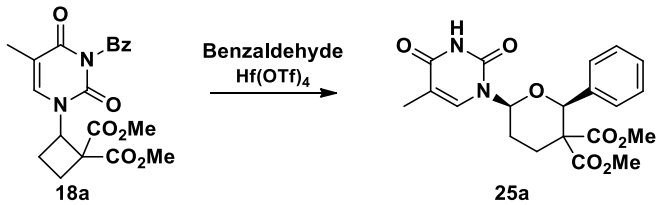
4. Scope of the reaction [4+2] reaction.

c) General conditions the [4+2] annulation



$Hf(OTf)_4$ (21 mg, 0.030 mmol, 0.1 equiv) was added in a flame dried 25 mL flask and under nitrogen atmosphere. Then, dry dichloromethane (4.5 mL) and aldehyde **5** (0.45 mmol, 1.5 equiv) were added into the flask. A solution of cyclobutane **18a** or **18b** (0.30 mmol, 1.0 equiv) in dry dichloromethane (1.5 mL) was added dropwise to the reaction mixture and stirred at room temperature for 15 minutes. The reaction mixture was filtrated on a pad of silica eluting with a mixture of ethyl acetate/ pentane (8:2) and concentrated under reduced pressure. The crude product was dissolved in ethanol (6 mL) and ammonium hydroxide solution (1.8 mL, 60 equiv, 25 %) was added. The resulting solution was stirred for 16 hours. The solvent was removed under reduced pressure and the crude product was dissolved in ethyl acetate (25 mL) and extracted with water (3 x 50 mL). The organic layer was dried over magnesium sulfate, filtrated and concentrated under reduced pressure. The crude mixture was purified by column chromatography eluting with a mixture of ethyl acetate/ pentane (5:5 to 9:1). The product was recrystallized in ethanol (2 mL).

Dimethyl (5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (25a).



Following the general procedure, using benzaldehyde (**5a**) (46 µL, 0.45 mmol, 1.5 equiv) cyclobutane **18a** (120 mg, 0.300 mmol, 1.0 equiv), a mixture of diastereoisomers (20:1 by integration of methyl esters at 3.52 ppm and 3.49 ppm) **25a** (102 mg, 0.255 mmol, 85% NMR yield)[7] was obtained after column chromatography as a colorless foam. After recrystallization in ethanol, the pure product **25a** (94 mg, 0.23 mmol, 78% isolated yield) was obtained as a colorless foam and as a mixture of diastereoisomers (> 20:1 by integration of methyl esters at 3.52 ppm and 3.49 ppm).

RF (Pentane/Ethyl acetate (3:7)) =.0.27.

MP 226.2- 227.9 °C.

^{1}H NMR (400 MHz, Chloroform-*d*, major diastereoisomer) δ 8.38 (s, 1 H, NH), 7.40 - 7.35 (m, 2 H, Ar-H), 7.34 – 7.27 (m, 4 H, Ar-H and thymine C=C-H), 5.96 (dd, *J* = 11.1, 2.9 Hz, 1 H, tetrahydropyran-NCH), 5.23 (s, 1 H, tetrahydropyran-CH), 3.68 (s, 3 H, ester CH_3), 3.52 (s, 3 H, ester CH_3), 2.74 – 2.64 (m, 1 H, tetrahydropyran-CH_2), 2.38 (tdd, *J* = 12.6, 11.0, 4.1 Hz, 1 H, tetrahydropyran-CH_2), 2.25 (td, *J* = 13.4, 4.1 Hz, 1 H, tetrahydropyran-CH_2), 1.99 (d, *J* = 1.2 Hz, 3 H, thymine-CH_3), 1.97 – 1.90 (m, 1 H, tetrahydropyran-CH_2).

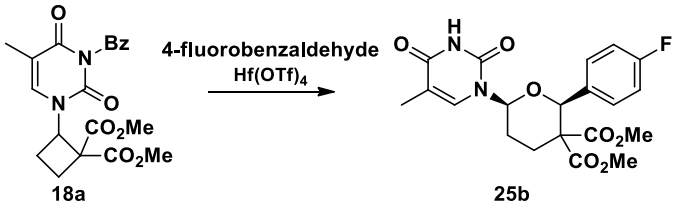
[7] Benzamide as impurity which is not possible to separate by column chromatography.

^{13}C NMR (101 MHz, Chloroform-*d*, major diastereoisomer) δ 170.3, 169.2, 163.4, 149.9, 137.5, 135.4, 128.5, 127.7, 127.5, 111.6, 82.3, 82.1, 57.1, 52.8, 52.0, 31.6, 26.6, 12.8.

IR 3191 (w), 3041 (w), 2954 (w), 2361 (w), 1725 (s), 1693 (s), 1461 (w), 1271 (s), 1096 (w), 1043 (w), 915 (w), 735 (m).

HRMS (ESI) calcd for $C_{20}H_{22}N_2NaO_7^+$ $[M+Na]^+$ 425.1319, found 425.1324.

Dimethyl 2-(4-fluorophenyl)-6-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (25b).



Following the general procedure, using 4-fluorobenzaldehyde (**5f**) (48 µL, 0.45 mmol, 1.5 equiv) cyclobutane **18a** (120 mg, 0.300 mmol, 1.0 equiv), a mixture of diastereoisomers (12:1 by integration of methyl esters at 3.54 ppm and 3.49 ppm) **25b** (99 mg, 0.24 mmol, 79% NMR yield)[7] was obtained after column chromatography as a colorless foam. After recrystallization in ethanol, the pure product **25b** (88 mg, 0.21 mmol, 70% isolated yield) was obtained as a colorless foam and as a mixture of diastereoisomers (12:1 by integration of methyl esters at 3.54 ppm and 3.49 ppm).

RF (Pentane/Ethyl acetate (3:7)) = 0.30.

MP 94.8- 96.9°C.

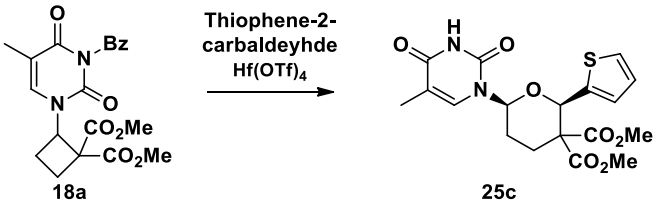
^{1}H NMR (400 MHz, Chloroform-*d*, major diastereoisomer) δ 8.06 (s, 1 H, NH), 7.40 – 7.33 (m, 2 H, Ar-H), 7.29 (d, *J* = 1.3 Hz, 1 H, thymine C=C-H), 7.03 – 6.95 (m, 2 H, Ar-H), 5.95 (dd, *J* = 11.3, 2.9 Hz, 1 H, tetrahydropyran-NCH), 5.21 (s, 1 H, tetrahydropyran-CH), 3.69 (s, 3 H, ester CH_3), 3.54 (s, 3 H, ester CH_3), 2.74 – 2.63 (m, 1 H, tetrahydropyran-CH_2), 2.48 – 2.32 (m, 1 H, tetrahydropyran-CH_2), 2.32 – 2.20 (m, 1 H, tetrahydropyran-CH_2), 1.99 (d, *J* = 1.2 Hz, 3 H, thymine-CH_3), 1.93 (dq, *J* = 9.3, 3.3 Hz, 1 H, tetrahydropyran-CH_2).

^{13}C NMR (101 MHz, Chloroform-*d*, major diastereoisomer) δ 170.3, 169.1, 163.6, 162.5 (d, *J* = 225.5 Hz), 150.2, 135.2, 133.4 (d, *J* = 3.3 Hz), 129.3 (d, J = 8.1 Hz), 114.6 (d, *J* = 21.4 Hz), 111.8, 82.0, 81.6, 57.0, 52.8, 52.1, 31.4, 26.5, 12.8.

IR 3203 (w), 3055 (w), 2961 (w), 2361 (w), 2255 (w), 1724 (s), 1691 (s), 1515 (w), 1464 (w), 1267 (s), 1229 (m), 1100 (m), 1050 (m), 913 (m), 735 (m).

HRMS (ESI) calcd for $C^{20}H^{21}FN^{2}NaO^{7+}$ $[M+Na]^+$ 443.1225; found 443.1224.

Dimethyl 6-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-(thiophen-2-yl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (25c).



Following the general procedure, using thiophene-2-carbaldehyde (42 µL, .45 mmol, 1.5 equiv) cyclobutane **18a** (120 mg, 0.300 mmol, 1.0 equiv), a mixture of diastereoisomers (12:1 by integration of methyl esters at 3.56 ppm and 3.54 ppm) **25c** (111 mg, 0.270 mmol, 90% NMR yield)[7] was obtained after column chromatography as a white foam. After recrystallization in

ethanol, the pure product **25c** (97 mg, 0.24 mmol, 79% isolated yield) was obtained as white foam and as a mixture of diastereoisomers (7:1 by integration of methyl esters at 3.56 ppm and 3.54 ppm).

RF (Pentane/Ethyl acetate (4:6)) = 0.24.

MpP186.4-188.3°C.

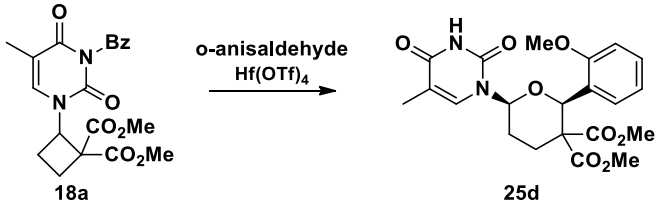
^{1}H NMR (400 MHz, Chloroform-d, major diastereoisomer) δ 9.74 (s, 1 H, NH), 7.27 (d, *J* = 1.4 Hz, 1 H, , thymine C=C-H), 7.23 (dd, *J* = 5.1, 1.2 Hz, 1 H, thiophene-H), 7.04 (dd, *J* = 3.5, 1.1 Hz, 1 H, thiophene -H), 6.92 (dd, *J* = 5.1, 3.6 Hz, 1 H, thiophene -H), 5.95 (dd, *J* = 10.9, 2.8 Hz, 1 H, tetrahydropyran-NCH), 5.48 (d, *J* = 0.8 Hz, 1 H, tetrahydropyran-CH), 3.71 (s, 3 H, ester CH_3), 3.56 (s, 3 H, ester CH_3), 2.70 – 2.61 (m, 1 H, tetrahydropyran-CH_2), 2.32 – 2.24 (m, 1 H, tetrahydropyran-CH_2), 2.23 – 2.14 (m, 1 H, tetrahydropyran-CH_2), 1.95 (d, *J* = 1.3 Hz, 3 H, thymine-CH_3), 1.92 (dd, *J* = 7.9, 2.3 Hz, 1 H, tetrahydropyran-CH_2).

^{13}C NMR (101 MHz, Chloroform-d, major diastereoisomer) δ 170.2, 168.9, 163.6, 150.1, 139.8, 135.2, 126.2, 126.2, 125.5, 111.7, 82.1, 79.1, 57.4, 52.9, 52.5, 31.1, 26.5, 12.8.

IR 3195 (w), 3042 (w), 2954 (w), 2832 (w), 2362 (w), 2252 (w), 2252 (w), 1690 (s), 1441 (w), 1375 (w), 1271 (s), 1103 (m), 1050 (w), 913 (m), 734 (m).

HRMS (ESI) calcd for $C_{18}H_{20}N_2NaO_7S^+$ $[M+Na]^+$ 431.0883; found 431.0879.

Dimethyl 2-(2-methoxyphenyl)-6-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (25d).



Following the general procedure, using o-anisaldehyde (61 mg, 0.45 mmol, 1.5 equiv) and cyclobutane **18a** (120 mg, 0.300 mmol, 1.0 equiv), a mixture of diastereoisomers (10:1 by integration of methyl esters at 3.54 ppm and 3.40 ppm) **25d** (108 mg, 0.252 mmol, 84% NMR yield)[7] was obtained after column chromatography as a white solid. After recrystallization in ethanol, the pure product **25d** (98 mg, 0.23 mmol, 76% isolated yield) was obtained as white solid and as a mixture of diastereoisomers (10:1 by integration of methyl esters at 3.54 ppm and 3.40 ppm).

RF (Pentane/Ethyl acetate (3:7)) = 0.29.

MP 193.9- 196.2 °C.

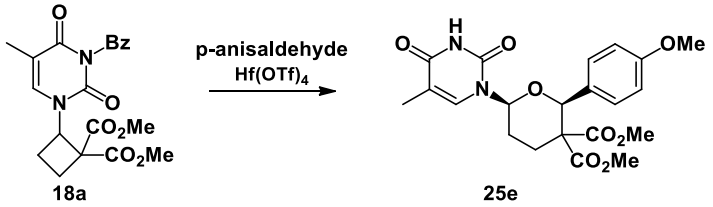
^{1}H NMR (400 MHz, Chloroform-*d*, major diastereoisomer) δ 8.05 (s, 1 H, NH), 7.77 (dd, *J* = 7.8, 1.7 Hz, 1 H, Ar-H), 7.39 (d, *J* = 1.4 Hz, 1 H, thymine C=C-H), 7.31 – 7.27 (m, 1 H, Ar-H), 7.01 (td, *J* = 7.6, 1.1 Hz, 1 H, Ar-H), 6.80 (dd, *J* = 8.3, 1.1 Hz, 1 H, Ar-H), 5.92 (dd, *J* = 11.0, 3.0 Hz, 1 H, tetrahydropyran-NCH), 5.29 (s, 1 H, tetrahydropyran-CH), 3.77 (s, 3 H, O-Me CH_3), 3.69 (s, 3 H, ester CH_3), 3.54 (s, 3 H, ester CH_3), 2.63 – 2.55 (m, 2 H, tetrahydropyran-CH_2), 2.05 – 2.01 (m, 1 H, tetrahydropyran-CH_2), 1.99 (d, *J* = 1.3 Hz, 3 H, thymine-CH_3), 1.85 – 1.74 (m, 1 H, tetrahydropyran-CH_2).

^{13}C NMR (101 MHz, Chloroform-*d*, major diastereoisomer) δ 169.0, 168.9, 163.8, 156.2, 150.0, 135.7, 129.9, 129.4, 125.6, 120.3, 111.5, 109.4, 82.2, 76.4, 56.9, 55.5, 52.5, 52.3, 31.1, 27.3, 12.9.

IR 3191 (w), 3045 (w), 2955 (w), 2841 (w), 2361 (w), 2338 (w), 2253 (w), 1731 (s), 1690 (s), 1464 (m), 1377 (w), 1259 (s), 1104 (m), 1047 (m), 914 (m), 733 (s).

HRMS (ESI) calcd for $C_{21}H_{24}N_2NaO_8^+$ $[M+Na]^+$ 455.1425; found 455.1429.

Dimethyl 2-(4-methoxyphenyl)-6-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (25e).



Following the general procedure, using *p*-anisaldehyde (55 µL, 0.45 mmol, 1.5 equiv) and cyclobutane **18a** (120 mg, 0.300 mmol, 1.0 equiv), a mixture of diastereoisomers (5:1 by integration of methyl esters at 3.55 ppm and 3.49 ppm) **25e** (115 mg, 0.264 mmol, 88% NMR yield)[7] was obtained after column chromatography as a slightly yellow foam. After recrystallization in ethanol, the pure product **25e** (99 mg, 0.22 mmol, 76% isolated yield) was obtained as a slightly yellow foam and as a mixture of diastereoisomers (7:1 by integration of methyl esters at 3.55 ppm and 3.49 ppm).

RF (Pentane/Ethyl acetate (3:7)) = 0.26.

MP 97.4- 99.5 °C.

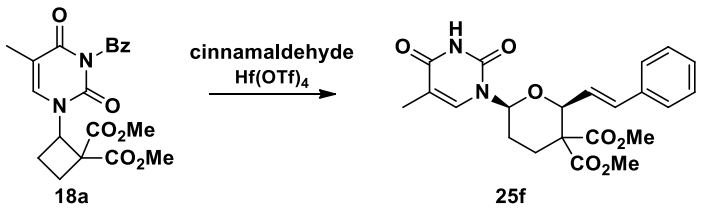
^{1}H NMR (400 MHz, Chloroform-*d*, major diastereoisomer) 9.03 (s, 1 H, NH), 7.31 (d, *J* = 1.3 Hz, 1 H, thymine C=C-H), 7.30 – 7.27 (m, 2 H, Ar-H), 6.86 – 6.78 (m, 2 H, Ar-H), 5.95 (dd, *J* = 11.1, 2.9 Hz, 1H, tetrahydropyran-NCH), 5.16 (s, 1 H, tetrahydropyran-CH), 3.78 (s, 3 H, O-Me CH_3), 3.67 (s, 3 H, ester CH_3), 3.55 (s, 3 H, ester CH_3), 2.74 – 2.61 (m, 1 H, tetrahydropyran-CH_2), 2.35 (tdd, *J* = 12.6, 11.0, 4.1 Hz, 1 H, tetrahydropyran-CH_2), 2.22 (td, *J* = 13.4, 4.1 Hz, 1 H, tetrahydropyran-CH_2), 1.97 (d, *J* = 1.3 Hz, 3 H, thymine-CH_3), 1.95 – 1.88 (m, 1 H, tetrahydropyran-CH_2).

^{13}C NMR (101 MHz, Chloroform-*d*, major diastereoisomer) δ 170.3, 169.3, 163.7, 159.5, 150.2, 135.4, 129.6, 128.8, 113.0, 111.6, 82.0, 82.0, 57.0, 55.3, 52.7, 52.1, 31.4, 26.6, 12.8.

IR 3191 (w), 3049 (w), 2954 (w), 2839 (w), 2360 (w), 2257 (w), 1687 (s), 1517 (w), 1461 (m), 1255 (s), 1109 (m), 1044 (m), 910 (m), 817 (w), 730 (s).

HRMS (ESI) calcd for for $C_{21}H_{24}N_2NaO_8^+$ $[M+Na]^+$ 455.1425; found 455.1428.

(*E*)-dimethyl 6-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-styryldihydro-2H-pyran-3,3(4H)-dicarboxylate (25f).



Following the general procedure, using cinnamaldehyde (57 µL, 0.45 mmol, 1.5 equiv) cyclobutane **18a** (120 mg, 0.300 mmol, 1.0 equiv), a mixture of diastereoisomers (2.5:1 by integration of methyl esters at 3.72 ppm and 3.67 ppm) **25f** (104 mg, 0.243 mmol, 81% NMR yield)[7] was obtained after column chromatography as a yellow foam. After recrystallization in ethanol, the pure product **25f** (89 mg, 0.21 mmol, 69% isolated yield) was obtained as yellow foam and as a mixture of diastereoisomers (2.5:1 by integration of methyl esters at 3.72 ppm and 3.67 ppm).

RF (Pentane/Ethyl acetate (3:7)) = 0.37.

MP 73.7-75-5 °C.

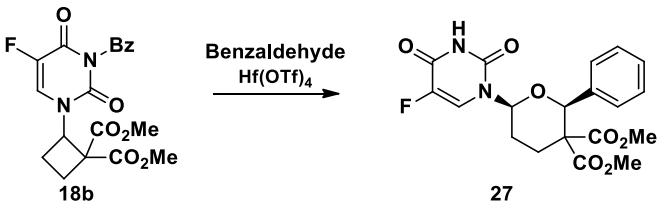
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.03 (s, 1H, N H, major diastereoisomer), 8.91 (s, 1 H, NH, minor diastereoisomer), 7.39 – 7.21 (m, 10 H, Ar-H, major and minor diastereoisomers), 7.18 (dd, *J* = 3.4, 2.0 Hz, 2 H, thymine C=C-H, , major and minor diastereoisomers), 6.79 (dd, *J* = 15.7, 1.1 Hz, 1 H, vinyl CH, minor diastereoisomer), 6.61 – 6.49 (m, 2 H, vinyl CH, major diastereoisomer), 6.31 (dd, *J* = 15.7, 8.0 Hz, 1 H, , vinyl CH, minor diastereoisomer), 6.02 (dd, *J* = 11.2, 2.8 Hz, 1 H, tetrahydropyran-NCH, minor diastereoisomer), 5.91 (dd, *J* = 11.0, 3.0 Hz, 1 H, tetrahydropyran-NCH, major diastereoisomer), 5.40 (d, *J* = 8.0 Hz, 1 H, tetrahydropyran-CH, minor diastereoisomer), 4.68 (d, J = 5.3 Hz, 1 H, tetrahydropyran-CH, major diastereoisomer), 3.87 (s, 3 H, ester CH_3, minor diastereoisomer), 3.78 (s, 3 H, ester CH_3, major diastereoisomer), 3.71 (s, 3 H, ester CH_3, major diastereoisomer), 3.66 (s, 3 H, ester CH_3, minor diastereoisomer), 2.65 (ddd, *J* = 13.6, 4.2, 2.7 Hz, 1 H, tetrahydropyran-CH_2, major diastereoisomer), 2.58 – 2.35 (m, 2 H, tetrahydropyran-CH_2, minor diastereoisomer), 2.26 – 2.15 (m, 1 H, tetrahydropyran-CH_2, major diastereoisomer), 2.15 – 1.98 (m, 2 H, tetrahydropyran-CH_2, major diastereoisomer and minor diastereoisomer), 1.95 (d, *J* = 1.2 Hz, 3 H, thymine-CH_3, major diastereoisomer), 1.93 (d, *J* = 1.3 Hz, 3 H, thymine-CH_3, minor diastereoisomer), 1.92 – 1.87 (m, 1 H, tetrahydropyran-CH_2, major diastereoisomer), 1.56 – 1.43 (m, 1 H, tetrahydropyran-CH_2, minor diastereoisomer).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.0, 169.6, 169.0, 168.3, 163.7, 163.7, 150.2, 150.1, 137.8, 136.5, 135.3, 135.3, 132.7, 128.8, 128.8, 128.6, 128.1, 127.1, 126.8, 125.2, 120.4, 111.6, 111.4, 81.8, 81.7, 76.1, 57.0, 56.6, 53.4, 53.2, 53.0, 52.6, 30.7, 27.5, 26.8, 24.1, 12.8.[8]

IR 3730 (w), 2955 (w), 2361 (s), 2336 (s), 1744 (m), 1699 (s), 1666 (m), 1442 (w), 1275 (m), 1099 (w), 976 (w), 914 (w), 736 (m).

HRMS (ESI) calcd for $C_{22}H_{24}N_2NaO_7^+$ $[M+Na]^+$ 451.1476; found 451.1474.

Dimethyl (5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenyldihydro-2H-pyran-3,3(4H)-dicarboxylate (27).



Following the general procedure, using benzaldehyde (46 µL, 0.45 mmol, 1.5 equiv) and cyclobutane **18b** (121 mg, 0.300 mmol, 1.0 equiv), a mixture of diastereoisomers (13:1 by integration of methyl esters at 3.52 ppm and 3.48 ppm) **27** (78 mg, 0.19 mmol, 64% NMR yield)[7] was obtained after column chromatography as a white foam. After recrystallization in ethanol, the pure product **27** (68 mg, 0.17 mmol, 56% yield) was obtained as white foam and as a mixture of diastereoisomers (>20:1 by integration of methyl esters at 3.52 ppm and 3.48 ppm).

RF (Pentane/Ethyl acetate (1:1)) = 0.32.

MP 80.1- 81.7°C.

^{1}H NMR (400 MHz, Chloroform-d, major diastereoisomer) δ 9.95 (s, 1 H, NH), 7.63 (d, *J* = 5.8 Hz, 1 H, Ar-H), 7.39 – 7.34 (m, 2 H, Ar-H), 7.33 – 7.27 (m, 3 H, Ar-H and F-uracil C=C-H), 6.01 – 5.93 (m, 1 H, tetrahydropyran-NCH), 5.23 (s, 1H, tetrahydropyran-CH), 3.67 (s, 3 H, ester CH_3), 3.52 (s, 3 H, ester CH_3), 2.71 – 2.62 (m, 1 H, tetrahydropyran-CH_2), 2.40 – 2.19 (m, 2 H, tetrahydropyran-CH_2), 2.02 – 1.95 (m, 1 H, tetrahydropyran-CH_2).

[8] 3 carbons of the minor diastereoisomer are not resolved.

^{13}C NMR (101 MHz, Chloroform-d, major diastereoisomer) δ 170.1, 169.1, 156.98 (d, *J* = 26.6 Hz), 148.9, 140.93 (d, *J* = 238.5 Hz), 137.2, 128.5, 127.7, 127.4, 124.12 (d, *J* = 33.6 Hz), 82.2, 82.1, 56.9, 52.8, 52.1, 31.2, 26.5.

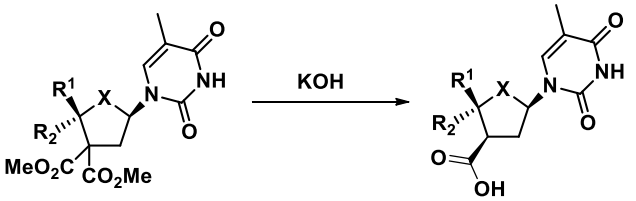
IR 3204 (w), 3064 (w), 2955 (w), 2361 (m), 2257 (w), 1717 (s), 1457 (w), 1368 (w), 1265 (s), 1103 (m), 1043 (w), 912 (s), 731 (s).

HRMS (ESI) calcd for $C_{19}H_{19}FN_2NaO_7^+$ $[M+Na]^+$ 429.1068; found 429.1065.

6. Thymine based nucleoside analogues derivatizations.

6.1 Acids.

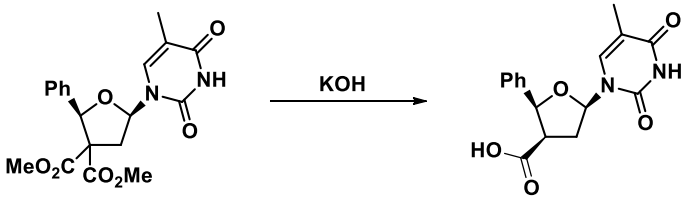
General procedure for hydrolysis and decarboxylation reaction



22b, 22e, 23b, 23c **54, 55, 29, 56**

Compound **22b**, **22e**, **23b**, and **23c** (1 equiv) and KOH (4 equiv) 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 $MgSO_4$ 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 (54).



22b **54**

Following the general procedure for hydrolysis and decarboxylation reaction, using compound **22b** (0.050 g, 0.13 mmol, 1 equiv) and KOH (29 mg, 0.52 mmol, 4 equiv) in dry MeOH (0.3 mL), the pure monoacid **54** (0.034 g, 0.10 mmol, 83% yield) was obtained as a white solid.

RF (AcOEt) = 0.23.

MP 123.2-125.3°C.

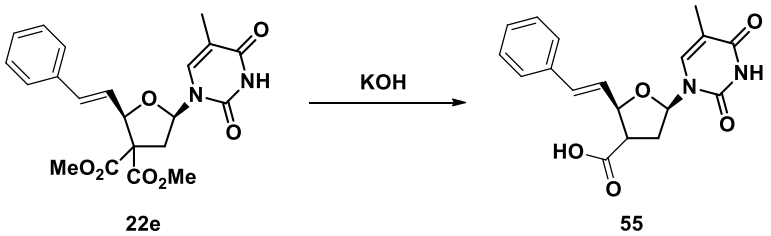
^{1}H NMR (400 MHz, Methanol-d_4) δ 7.37 (d, *J* = 8.6 Hz, 3H, Ar-H and thymine vinyl-CH), 7.32 – 7.22 (m, 3H, Ar-H), 6.20 – 6.08 (m, 1H, tetrahydrofuran-NCH), 5.01 (d, *J* = 8.7 Hz, 1H, tetrahydrofuran-CH), 3.35 – 3.24 (m, 1H, tetrahydrofuran-CH), 2.68 (dt, *J* = 13.1, 8.1 Hz, 1H tetrahydrofuran-CH_2), 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) δ 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 $C_{16}H_{16}N_2NaO_5^+$ $[M+Na]^+$ 339.0951; found 339.0944.

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



Following the general procedure for hydrolysis and decarboxylation reaction, using compound **22e** (0.14 g, 0.34 mmol, 1 equiv) and KOH (0.080 g, 1.4 mmol, 4.0 equiv) 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) **55** (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.

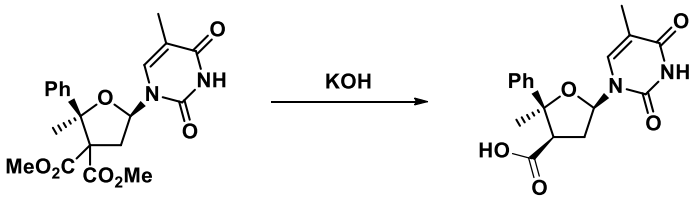
^{1}H NMR (400 MHz, Methanol-d_4) δ 7.65 (s, 1H, thymine vinyl-CH, minor diastereoisomer), 7.55 (s, 1H, thymine vinyl-CH, major diastereoisomer), 7.49 (d, *J* = 7.8 Hz, 4H, Ar-H, major and minor diastereoisomers), 7.40 – 7.25 (m, 6H, Ar-H, major and minor diastereoisomers), 6.76 (d, *J* = 15.9 Hz, 2H, 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), 2.47 (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 define and an aromatic one neither.
One carbon is missing for the minor diastereoisomer.

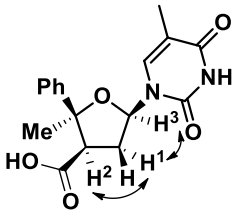
IR 3442 (w), 3184 (w), 3031 (w), 2531 (w), 1684 (s), 1485 (w), 1407 (w), 1369 (w), 1271 (m), 1204 (w), 1115 (w), 1072 (m), 980 (w), 751 (w), 695 (m).

HRMS (ESI) calcd for $C_{18}H_{19}N_2O_5^+$ $[M+H]^+$ 343.1288; found 343.1294.

.**2-Methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenyltetrahydrofuran-3-carboxylic acid (29).**



Following the general procedure for hydrolysis and decarboxylation reaction, using compound **23b** (0.020 g, 0.050 mmol, 1 equiv) and KOH (6 mg, 0.1 mmol, 4 equiv), the pure monoacid **29** (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.

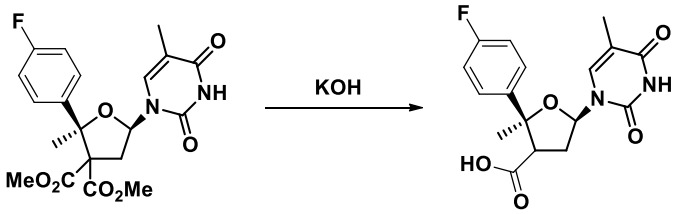
^{1}H NMR (400 MHz, Acetone-d_6) δ 11.39 (br s, 1H, COOH), 10.01 (s, 1H, thymine NH), 7.70 – 7.62 (m, 2H, Ar-H), 7.48 – 7.28 (m, 3H, Ar-H), 7.25 (q, *J* = 1.1 Hz, 1H, thymine vinyl-CH), 6.46 (dd, *J* = 7.5, 4.2 Hz, 1H, tetrahydrofuran-NCH), 3.75 (t, *J* = 8.7 Hz, 1H, tetrahydrofuran-CH), 2.99 (ddd, *J* = 14.1, 8.9, 7.6 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) δ 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 $C_{17}H_{19}N_2O_5^+$ $[M+H]^+$ 331.1288; found 331.1281.

2-(4-Fluorophenyl)-2-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3-carboxylic acid (56).



Following the general procedure for hydrolysis and decarboxylation reaction, using compound **23c** (0.040 g, 0.095 mmol, 1 equiv) and KOH (21 mg, 0.38 mmol, 4 equiv) 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) **56** (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) δ 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).

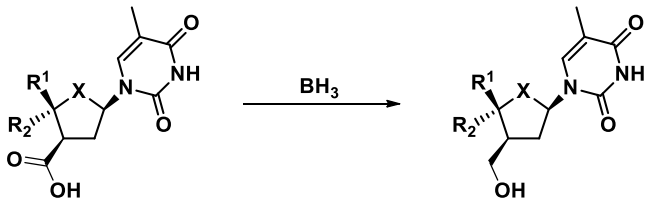
^{13}C NMR (101 MHz, Acetone-d_6) δ 174.7, 164.3, 164.2, 164.0, 162.8 (d, *J* = 244.1 Hz), 162.7 (d, *J* = 244.1 Hz). 151.4, 151.3, 142.7 (d, *J* = 3.0 Hz), 139.6 (d, *J* = 2.9 Hz), 137.8, 137.5, 128.5 (d, *J* = 8.1 Hz), 128.4 (d, *J* = 8.2 Hz), 115.5 (d, *J* = 21.4 Hz), 115.1 (d, *J* = 21.4 Hz), 111.0, 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 $C_{17}FH_{18}N_2O_5^+$ $[M+H]^+$ 349.1194; found 349.1194.

6.2 Alcohols.

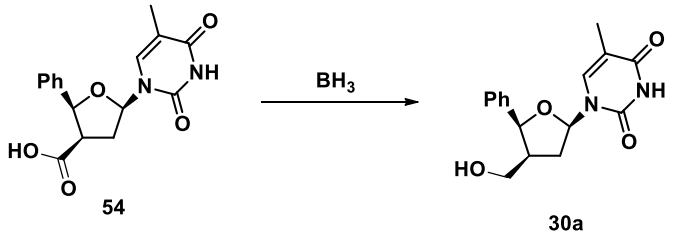
General procedure for reduction of carboxylic acids.



54, 55, 29, 56 **30a-d**

The carboxylic acid (1 equiv) 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 equiv) 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_2CO_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 (30a).



Following the general procedure for reduction of carboxylic acids, using compound **54** (0.012 g, 0.038 mmol, 1 equiv) and DMS solution (0.042 mL, 0.083 mmol, 2.2 equiv) in dry THF (0.35 mL), the alcohol **30a** (0.0095 g, 0.031 mmol, 86% yield, 71% over the two steps) was obtained as a colorless oil.

RF (AcOEt) = 0.34.

MP 68.1-69.4°C.

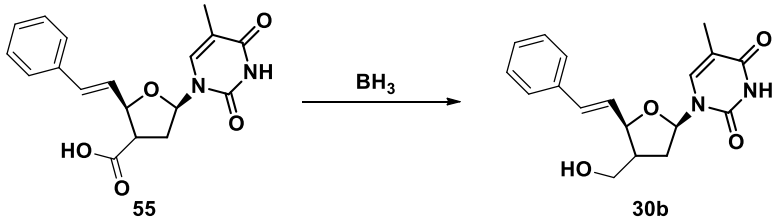
^{1}H NMR (400 MHz, Methanol-d_4) δ 7.53 – 7.47 (m, 1H, thymine vinyl-CH), 7.49 – 7.28 (m, 5H, Ar-H), 6.29 – 6.09 (m, 1H, tetrahydrofuran-NCH), 4.78 (d, *J* = 8.6 Hz, 1H , tetrahydrofuran-CH), 3.68 (dd, *J* = 11.2, 4.4 Hz, 1H , -C*H*$_2$OH), 3.64 – 3.53 (dd, *J* = 11.2, 5.6 Hz, 1H , -C*H*$_2$OH), 2.61 (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) δ 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 $C_{16}H_{18}N_2NaO_4^+$ $[M+Na]^+$ 325.1159; found 325.1159.

4-(Hydroxymethyl)-5-((E)-styryl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (30b).



Following the general procedure for reduction of carboxylic acids, using the mixture of diastereoisomers **55** (0.020 g, 0.058 mmol, 1 equiv) and DMS solution (0.063 mL, 0.13 mmol, 2.2 equiv) 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) **30b** (0.016 g, 0.049 mmol, 83% yield, 56% over the two steps) was obtained as colorless oil.

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

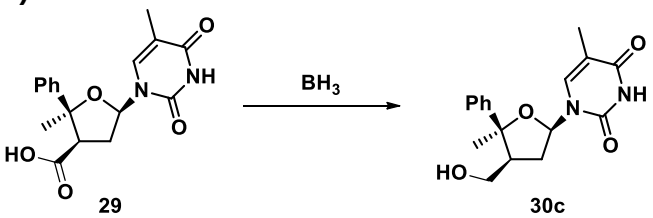
^{1}H NMR (400 MHz, Chloroform-*d*, major diastereoisomer) δ 8.24 (br.s, 1H, thymine-NH), 7.40 – 7.20 (m, 6H, Ar-H and thymine vinyl-CH), 6.67 (d, *J* = 16.0 Hz, 1H, vinyl-CH), 6.24 (dd, *J* = 15.8, 7.1 Hz, 1H, vinyl-CH), 6.07 (dd, *J* = 6.7, 3.6 Hz, 1H, tetrahydrofuran-NCH), 4.42 (t, *J* = 7.5 Hz, 1H, tetrahydrofuran-CH), 3.74 (dd, *J* = 10.7, 5.0 Hz, 1H, -C*H*$_2$OH), 3.68 (dd, *J* = 10.7, 5.1 Hz, 1H, -C*H*$_2$OH), 2.46 – 2.26 (m, 2H, tetrahydrofuran-CH$_2$), 2.16 (ddd, *J* = 12.1, 7.1, 3.5 Hz, 1H, tetrahydrofuran-CH), 1.86 (d, *J* = 1.2 Hz, 3H, thymine methyl).

^{13}C 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 $C_{18}H_{20}N_2NaO_4^+$ $[M+Na]^+$ 351.1315; found 351.1319.

4-(Hydroxymethyl)-5-methyl-5-phenyltetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (30c).



Following the general procedure for reduction of carboxylic acids, using compound **29** (0.018 g, 0.054 mmol, 1 equiv) and DMS solution (0.060 mL, 0.12 mmol, 2.2 equiv) in dry THF (0.5 mL), the alcohol **30c** (0.013 g, 0.041 mmol, 75% yield, 63% over the two steps) was obtained as a colorless foam.

RF (AcOEt) = 0.13.

MP 79.4-83.4°C.

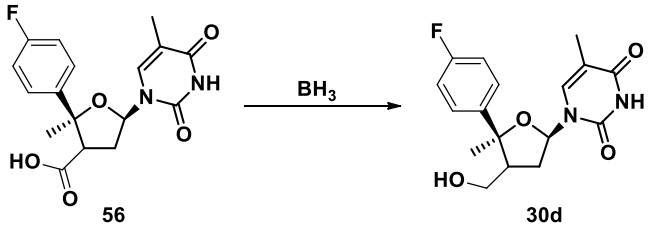
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.60 (s, 1H, thymine-NH), 7.46 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.39 – 7.22 (m, 3H, Ar-H), 6.82 (s, 1H, thymine vinyl-CH), 6.21 (d, *J* = 3.6 Hz, 1H, tetrahydrofuran-NCH), 3.96 (dd, *J* = 10.5, 5.4 Hz, 1H, -C*H*$_2$OH), 3.74 (dd, *J* = 10.7, 7.9 Hz, 1H, -C*H*$_2$OH), 2.75 (dd, *J* = 11.0, 4.6 Hz, 1H, tetrahydrofuran-CH), 2.44 – 2.25 (m, 2H, tetrahydrofuran-CH_2), 2.04 (br.s, 1H, OH), 1.60 (s, 3H, thymine methyl), 1.42 (s, 3H, tetrahydrofuran methyl).

^{13}C 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).

HRMS (ESI) calcd for $C_{17}H_{20}N_2NaO_4^+$ $[M+Na]^+$ 339.1315; found 339.1317.

5-(4-Fluorophenyl)-4-(hydroxymethyl)-5-methyltetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (30d).



Following the general procedure for reduction of carboxylic acids, using the mixture of diastereoisomers **56** (0.027 g, 0.078 mmol, 1 equiv) and DMS solution (0.085 mL, 0.17 mmol, 2.2 equiv) 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) **30d** (0.020 g, 0.059 mmol, 76% yield, 64% over the two steps) was obtained as colorless oil.

RF (AcOEt) = 0.53.

MP 192.3-193.8°C (decomp.).

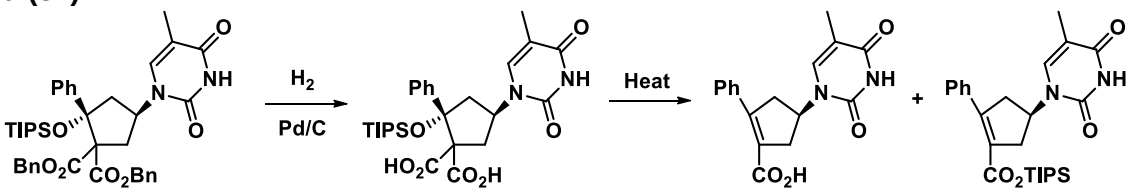
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.40 (s, 1H, thymine-NH, minor and major diastereoisomers), 7.58 (d, *J* = 1.3 Hz, 1H, thymine vinyl-CH, minor diastereoisomer), 7.46 (dd, *J* = 8.9, 5.2 Hz, 2H, Ar-H, major diastereoisomer), 7.33 (dd, *J* = 8.9, 5.2 Hz, 2H, Ar-H, minor diastereoisomer), 7.01 (t, *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_2OH, major diastereoisomer), 3.75 (dd, *J* = 10.6, 7.5 Hz, 1H, -CH_2OH, major diastereoisomer), 3.31 (dd, *J* = 11.2, 5.1 Hz, 0H, -CH_2OH, minor diastereoisomer), 3.23 (dd, *J* = 11.2, 6.0 Hz, 0H, -CH_2OH, 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 $C_{17}H_{19}FN_2NaO_4^+$ $[M+Na]^+$ 357.1221; found 357.1231.

6.3 Carbonucleoside alcohol. 5-Methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl-2-phenylcyclopent-1-ene-1-carboxylic acid (31).



24c 57 31 58

Compound **24c** (0.10 g, 0.14 mmol, 1.0 equiv) and Pd-C (0.030 g, 0.014 mmol, 0.1 equiv) 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 **57** 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 **31** (28 mg, 0.090 mmol, 64% yield) was obtained as a colorless oil. The corresponding TIPS protected carboxylic acid **58** (14 mg, 0.030 mmol, 20% yield) was also isolated as a colorless oil.

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

RF 31 (DCM/MeOH (9:1)) = 0.21.

MP 114.1-115.6 °C.

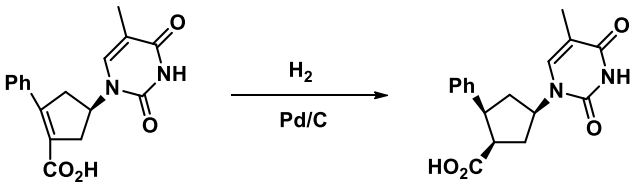
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.20 (d, *J* = 9.1 Hz, 1H, thymine-NH), 7.37 (s, 5H, Ar-H), 7.08 (d, *J* = 1.6 Hz, 1H, , thymine vinyl-CH), 5.37 (tt, *J* = 8.8, 4.3 Hz, 1H, cyclopentane-NCH), 3.60 – 3.25 (m, 2H, cyclopentane-CH_2), 2.96 (dddd, *J* = 18.9, 8.2, 3.7, 1.9 Hz, 2H, cyclopentane-CH_2), 1.92 (d, *J* = 1.2 Hz, 3H, thymine methyl).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 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 3169 (w), 3026 (w), 2929 (w), 1675 (s), 1472 (w), 1393 (w), 1270 (m), 1221 (w), 909 (m), 735 (s), 636 (w).

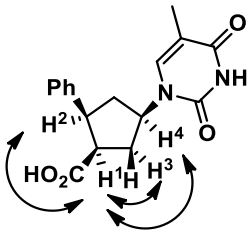
HRMS (ESI) calcd for $C_{17}H_{15}[^{2}H]_2N_2O_4^+$ $[M+H]^+$ 315.1306; found 315.1300.

5-Methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl-2-phenylcyclopentane-1-carboxylic acid (59).



31 59

Carboxylic acid **31** (0.021 g, 0.067 mmol, 1.0 equiv) and Pd-C (0.01 g, 0.007 mmol, 5 % wt, 0.1 equiv) 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 **59** (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.

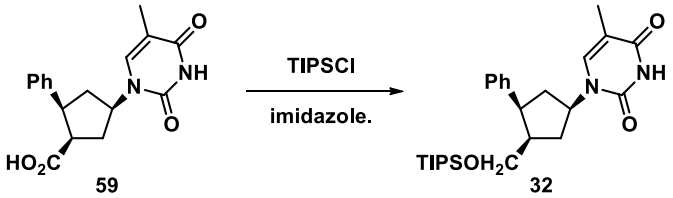
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H, -COOH), 11.20 (s, 1H, -NH), 7.80 (d, *J* = 1.4 Hz, 1H, , thymine vinyl-CH), 7.29 – 7.10 (m, 5H, Ar-H), 4.97 (dtd, *J* = 11.3, 9.1, 6.8 Hz, 1H, cyclopentane-NCH), 3.48 (ddd, *J* = 12.3, 9.1, 6.2 Hz, 1H, cyclopentane-CH), 3.19 – 3.00 (m, 1H), 2.36 – 2.21 (m, 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) δ 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 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 $C_{17}H_{19}N_2O_4^+$ $[M+H]^+$ 315.1339; found 315.1344.

5-Methyl-1-(3-phenyl-4-(((tri*iso*propylsilyl)oxy)methyl)cyclopentyl)pyrimidine-2,4(*1H,3H*)-dione (32).



Carboxylic acid **59** (0.019 g, 0.060 mmol, 1 equiv) 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 equiv) 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 equiv) and TIPSCl (14 mg, 0.072 mmol, 1.2 equiv) 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_2CO_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 **32** (15 mg, 0.033 mmol, 55%) as a colorless oil.

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

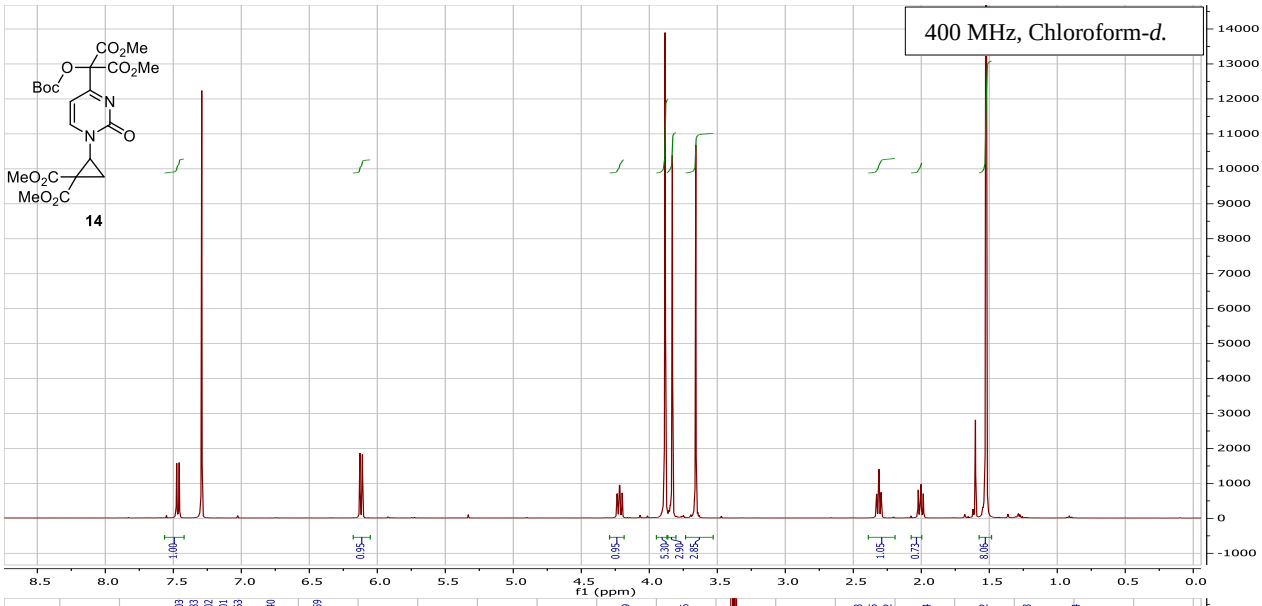
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.54 (s, 1H, -NH), 7.32 – 7.09 (m, 6H, Ar-H and thymine vinyl-CH), 5.05 (dtd, *J* = 11.6, 9.4, 6.5 Hz, 1H, cyclopentane-NCH), 3.42 – 3.21 (m, 3H, CH_2O and cyclopentane-CH), 2.46 (td, *J* = 9.0, 4.7 Hz, 1H, cyclopentane-CH), 2.39 – 2.27 (m, 1H cyclopentane-CH), 2.27 – 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).

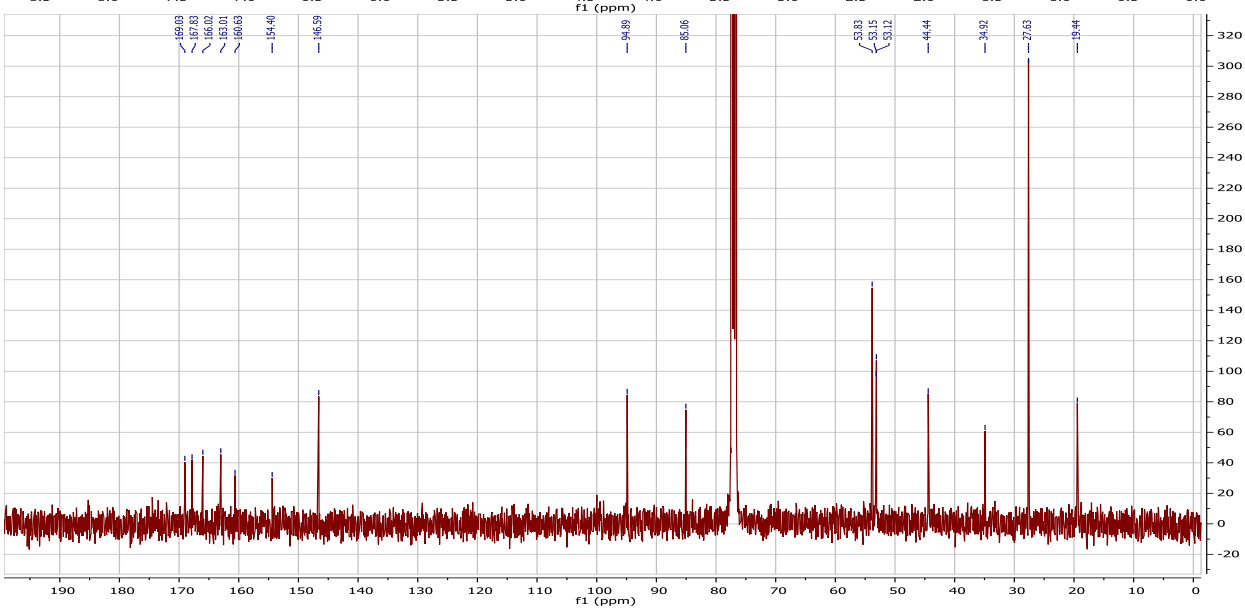
^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.5, 151.2, 139.9, 136.6, 128.3, 128.0, 126.4, 111.0, 64.0, 54.6, 44.8, 42.1, 35.3, 32.1, 18.0, 18.0, 12.4, 11.8.

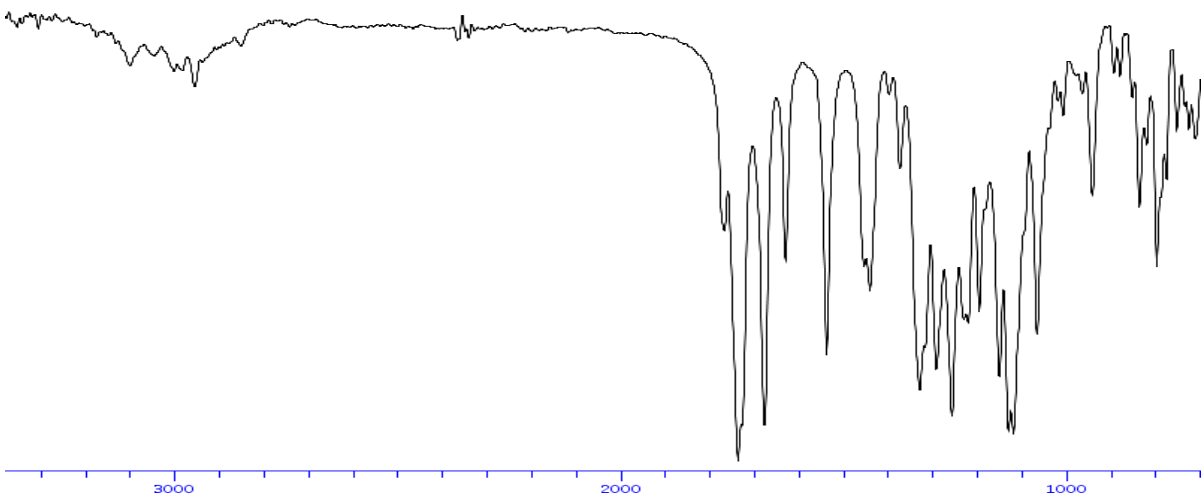
IR 3170 (w), 2945 (w), 1687 (s), 1469 (m), 1385 (w), 1272 (w), 1126 (w), 884 (w).

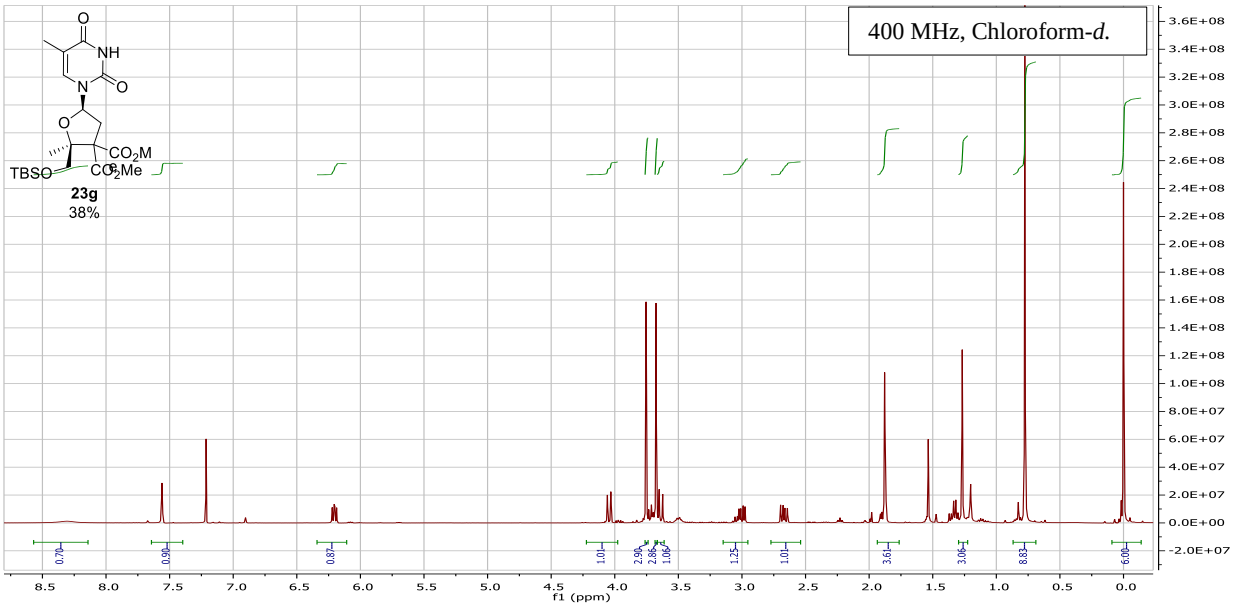
HRMS (ESI) calcd for $C_{26}H_{41}N_2O_3Si^+$ $[M+H]^+$ 457.2881; found 457.2881.

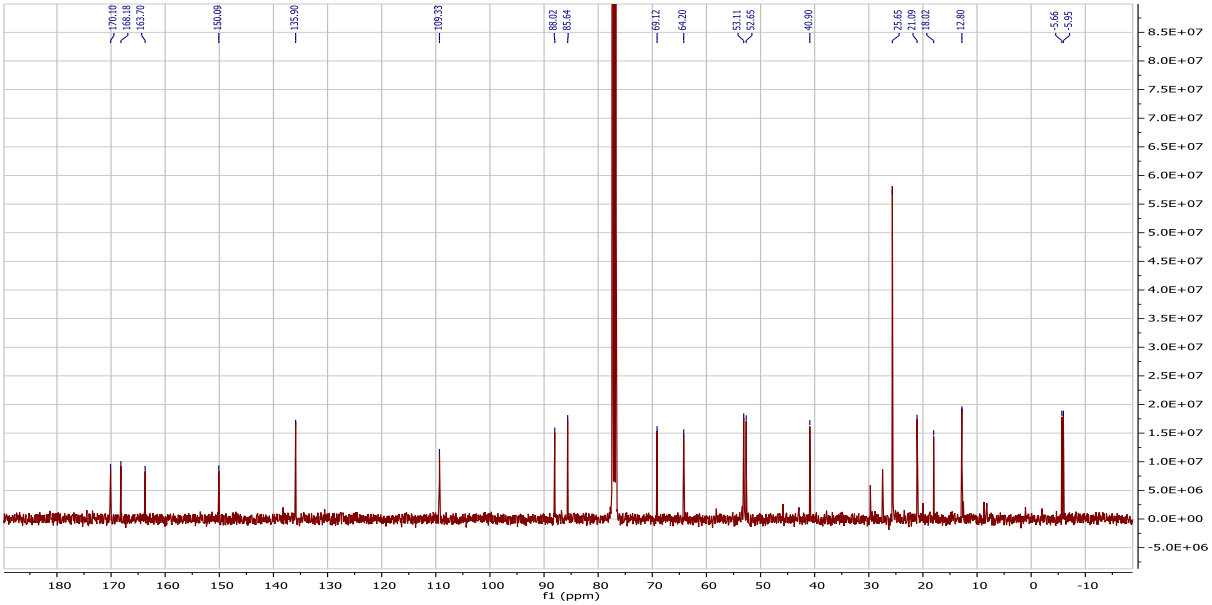
7. Spectra of new compounds

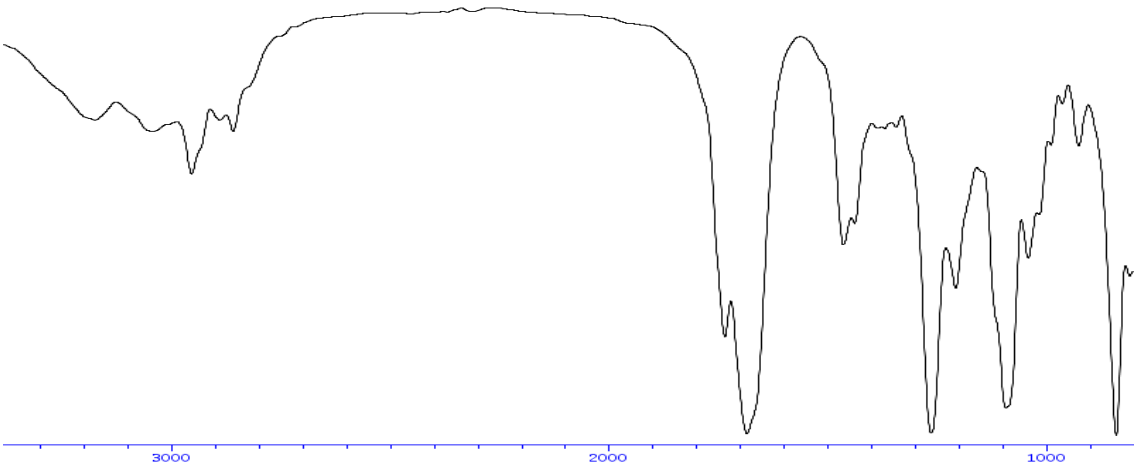

400 MHz, Chloroform-*d*.
14
f1 (ppm)

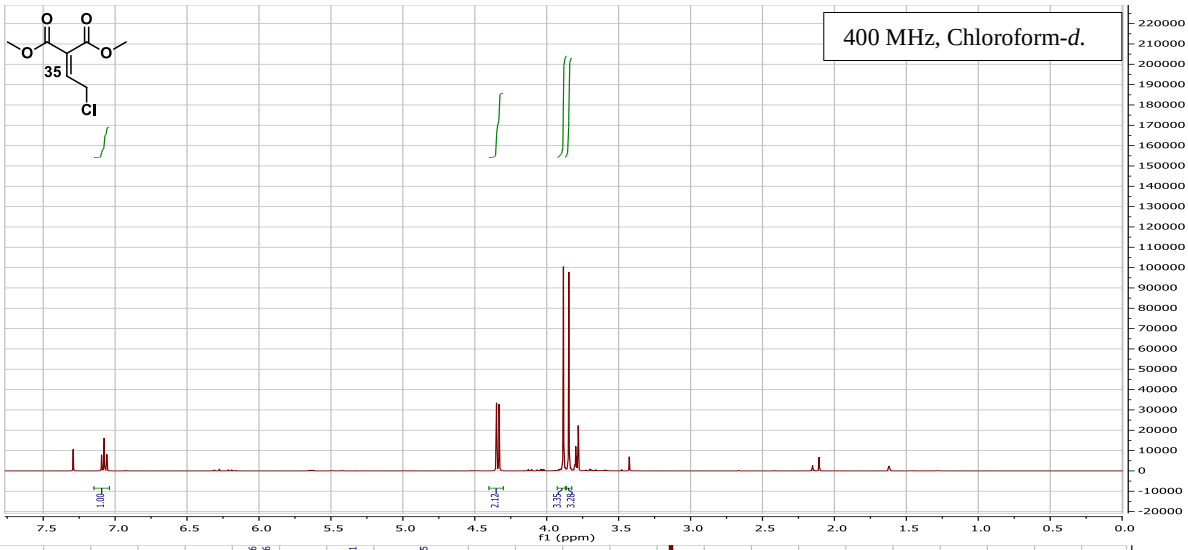

f1 (ppm)

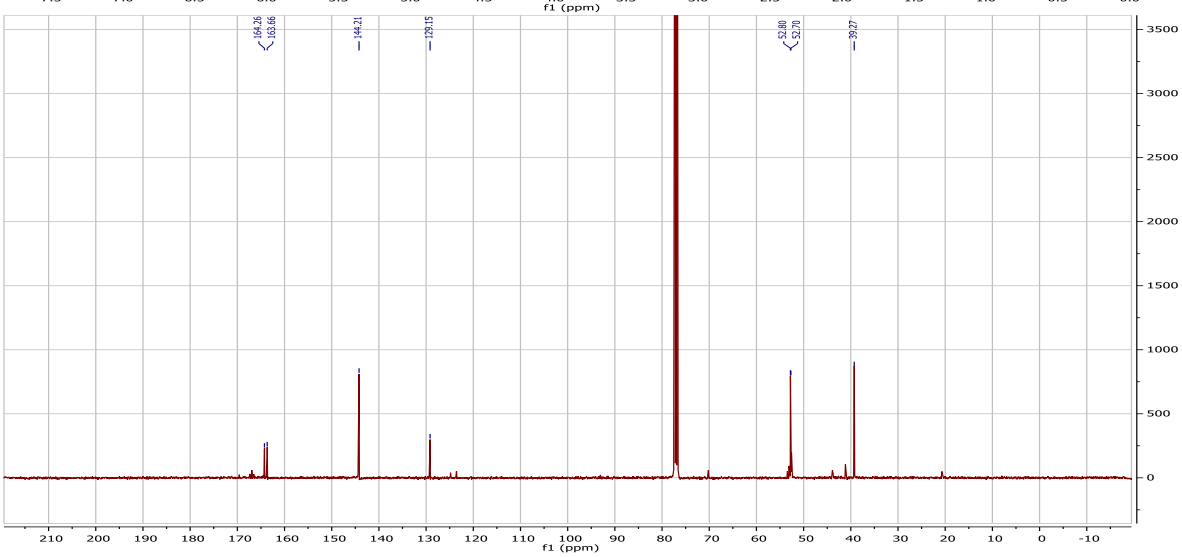


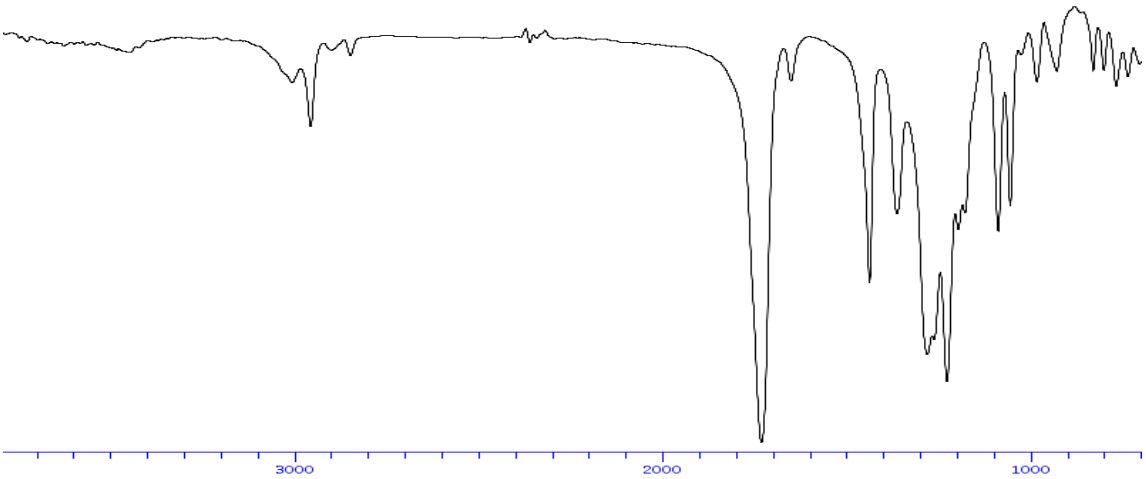

400 MHz, Chloroform-*d*.
TBSO
CO2M
CO2Me
23g
38%
f1 (ppm)

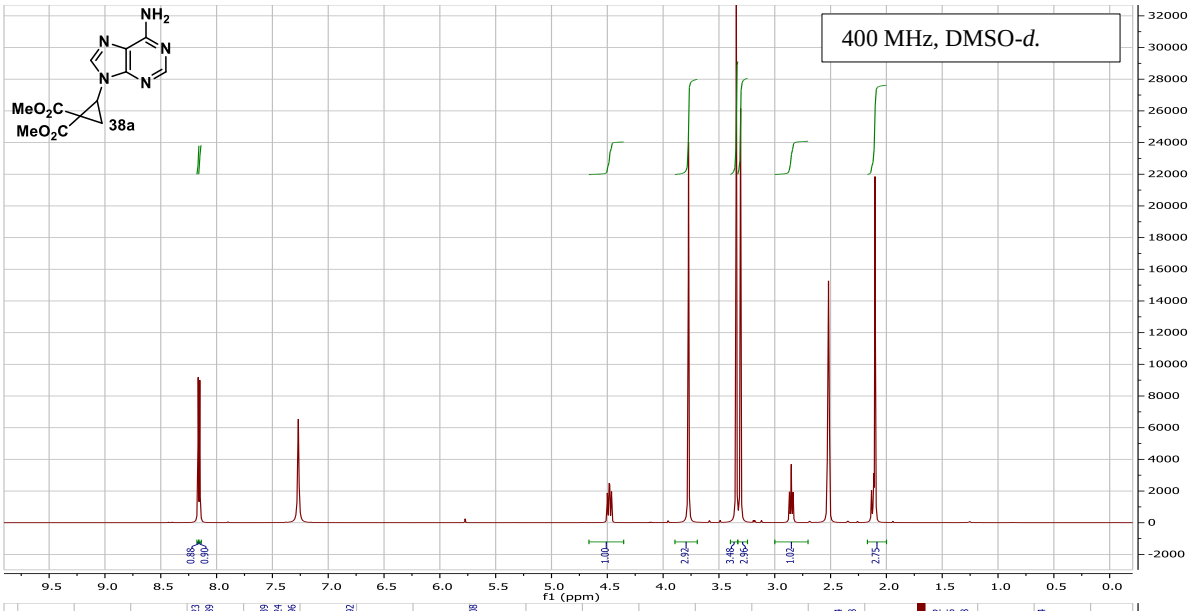

170.10
168.18
163.70
150.09
135.90
109.33
88.02
85.64
69.12
64.20
53.11
52.65
40.90
25.65
21.09
18.02
12.80
-5.66
-5.95
f1 (ppm)

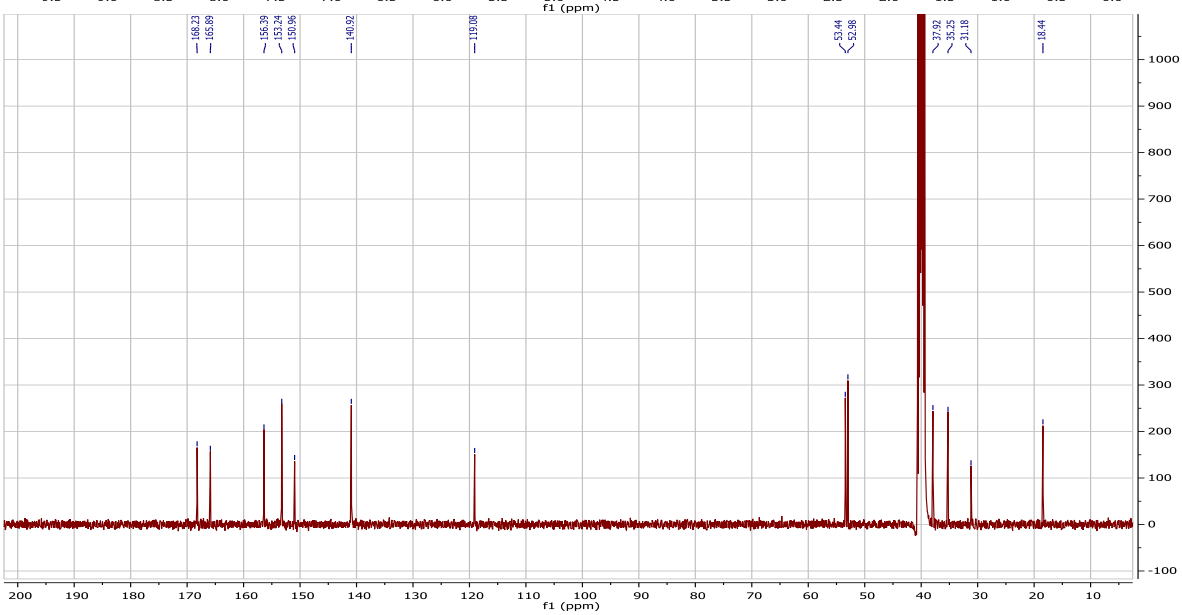

3000
2000
1000

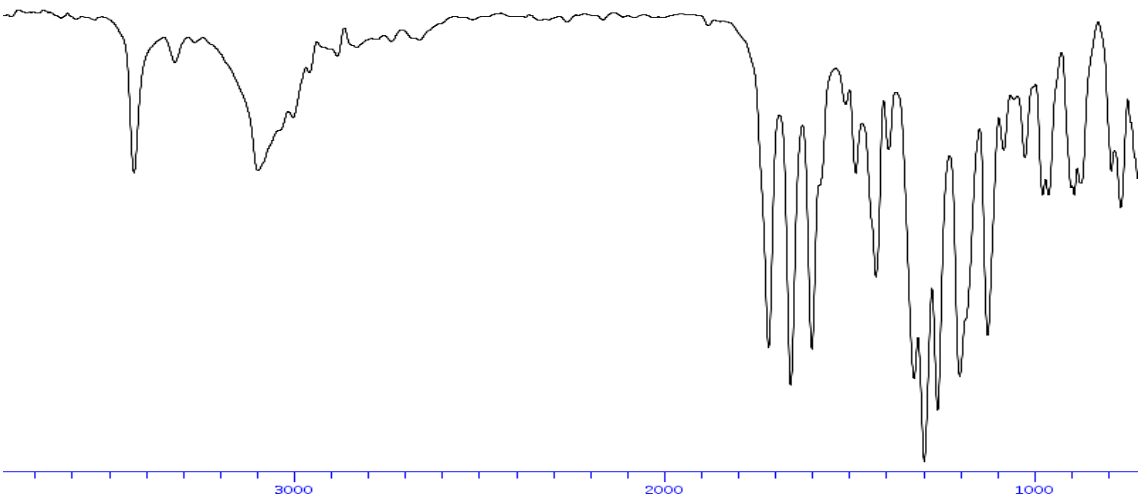

400 MHz, Chloroform-*d*.
35
Cl
f1 (ppm)

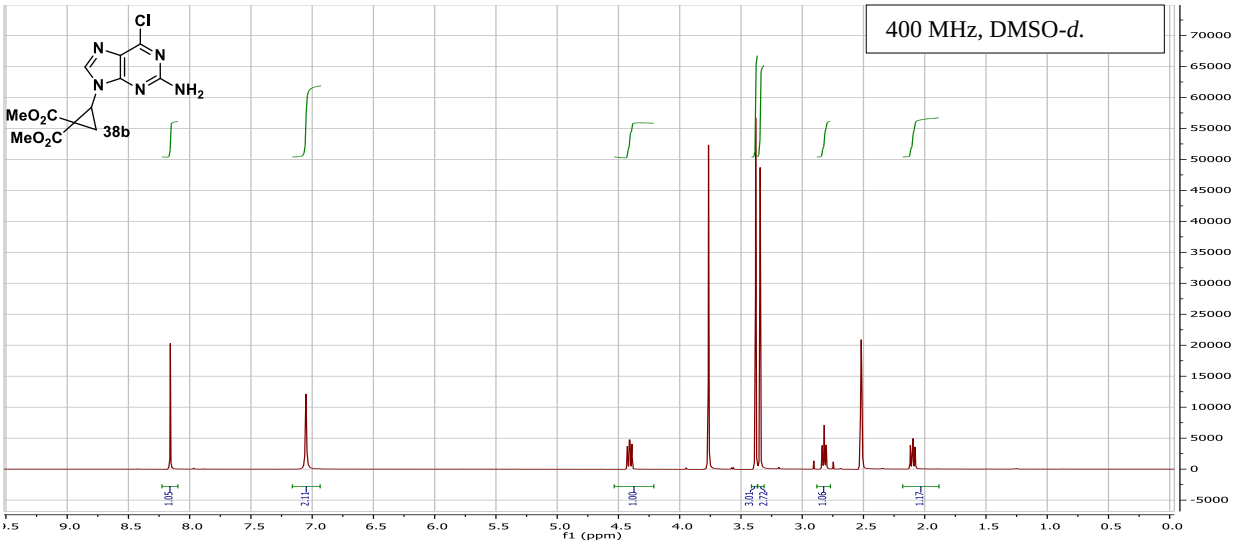

164.26
163.66
144.21
129.15
52.80
52.70
39.27
f1 (ppm)

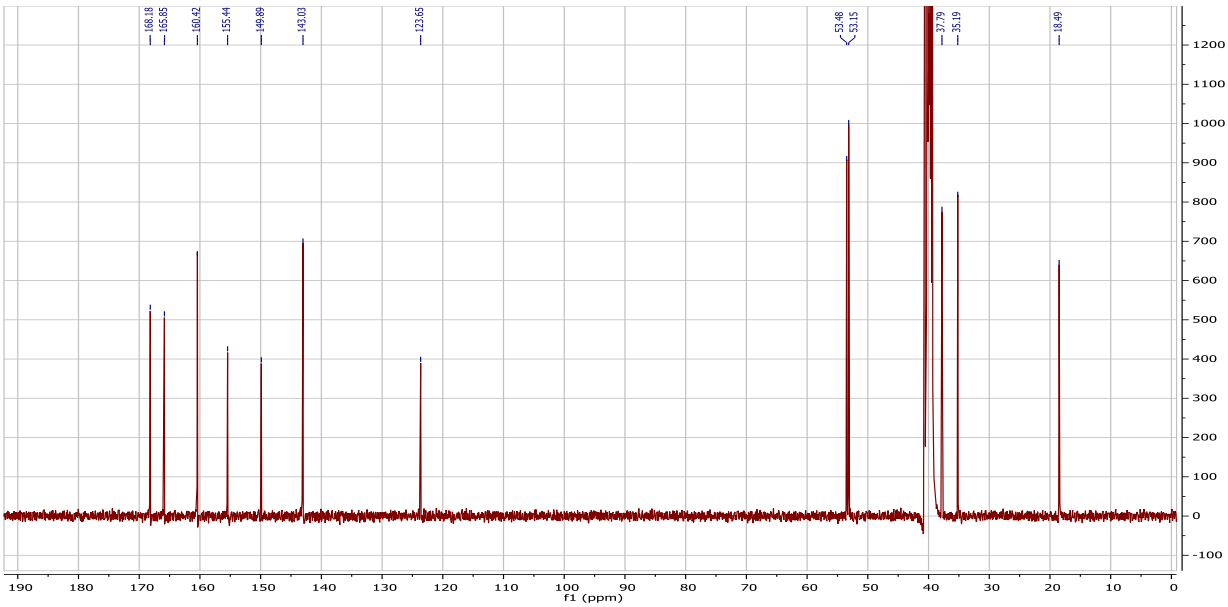

3000
2000
1000

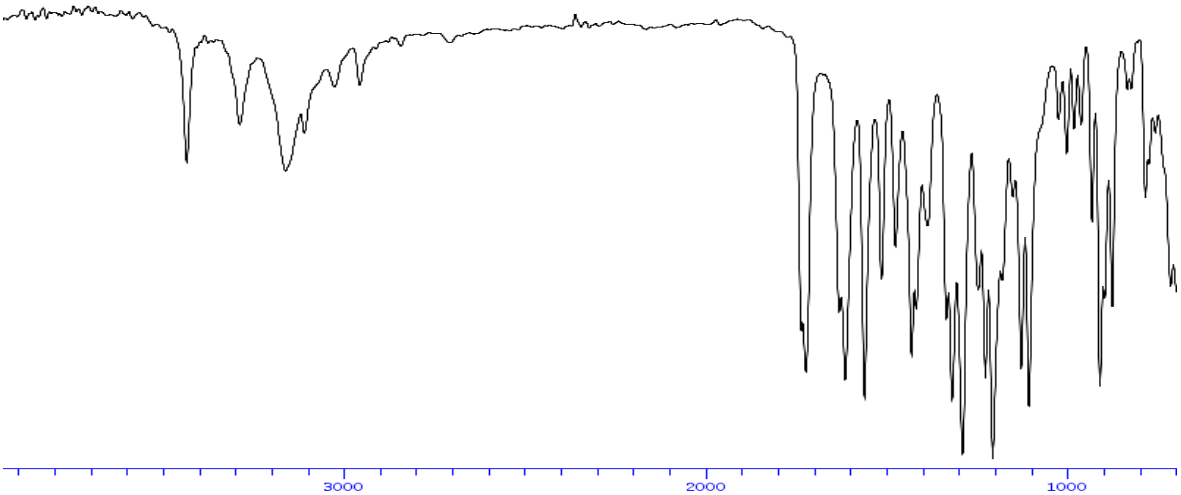

400 MHz, DMSO-*d*.
38a
f1 (ppm)

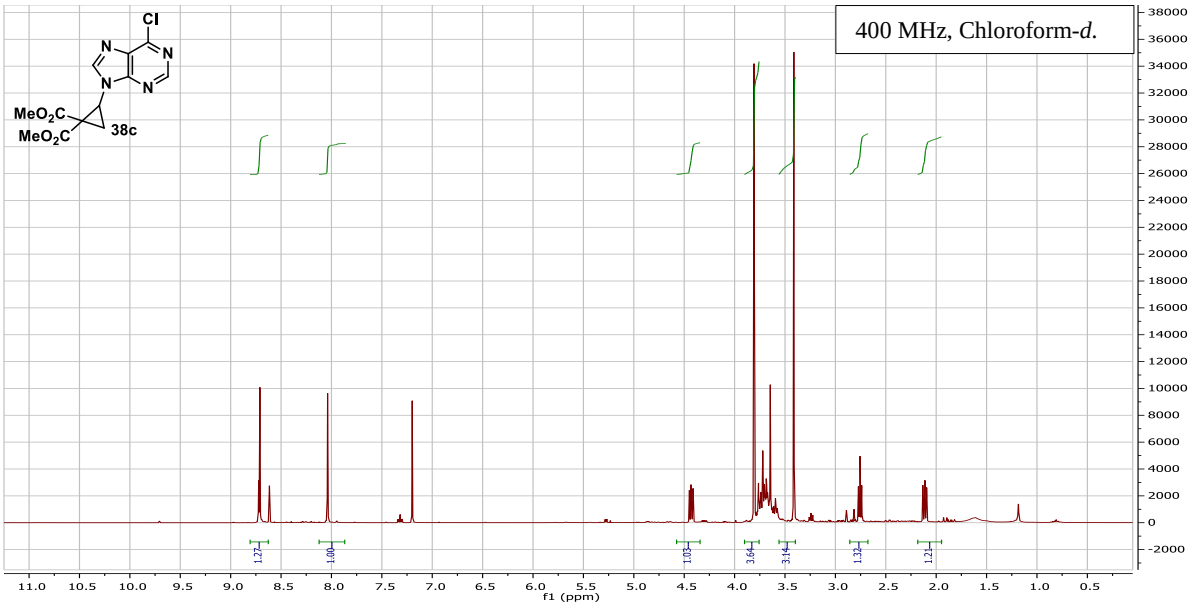

168.23
165.89
156.39
153.24
150.96
140.92
119.08
53.44
52.98
37.92
35.25
31.18
18.44
f1 (ppm)

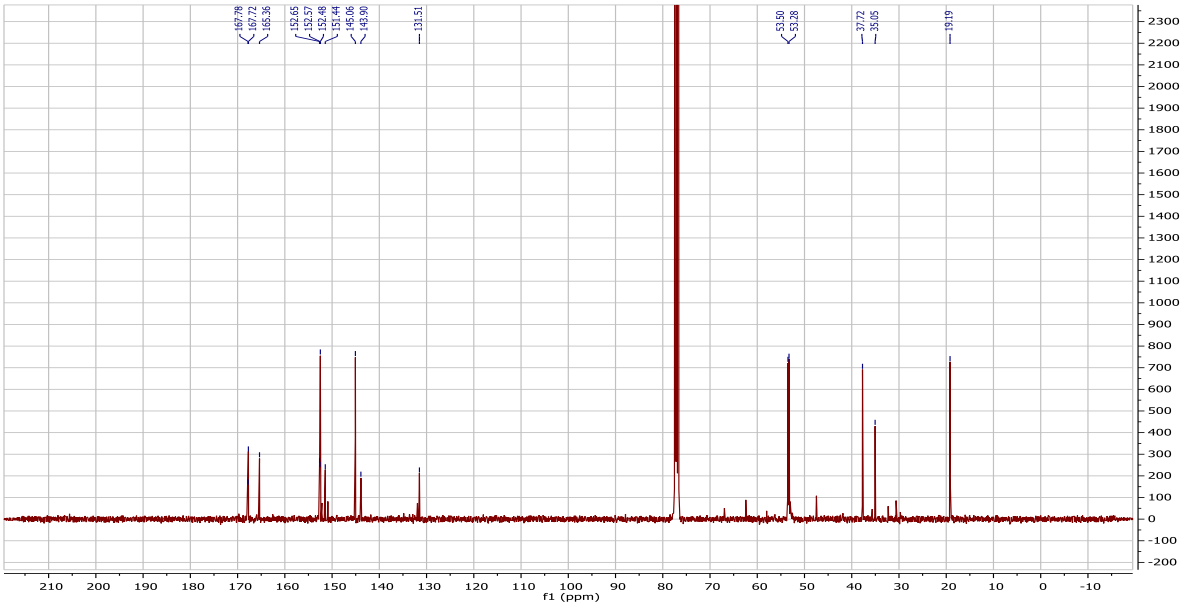

3000
2000
1000

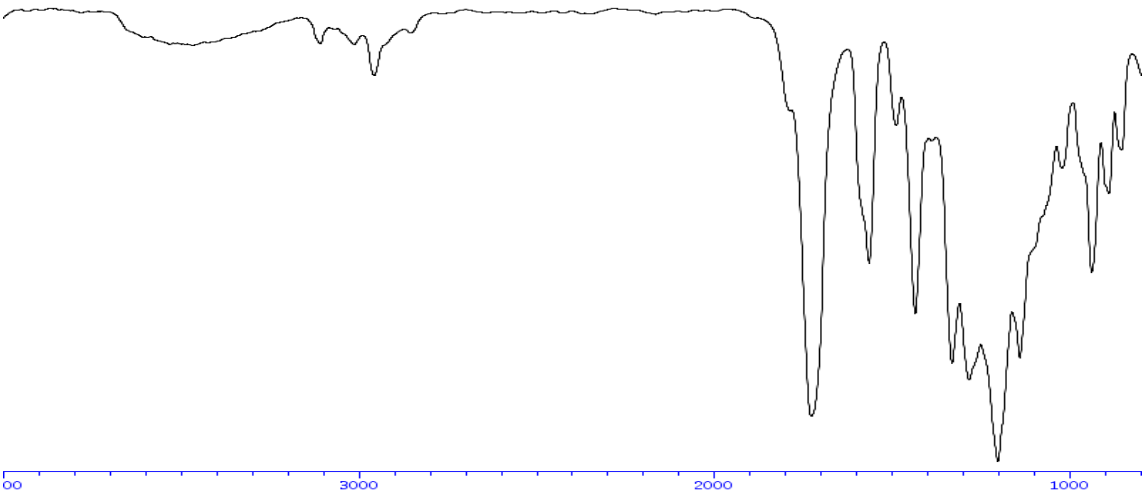

400 MHz, DMSO-*d*.
Cl
N
N
N
N
NH2
MeO2C
MeO2C
38b
f1 (ppm)

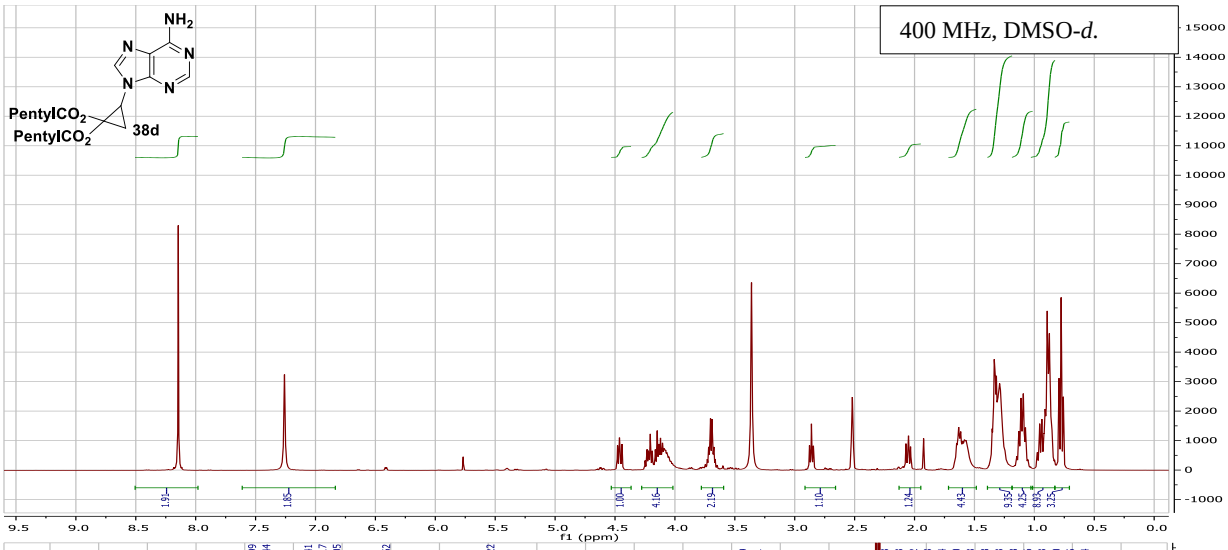

168.18
165.85
160.42
155.44
149.89
143.03
123.65
53.48
53.15
37.79
35.19
18.49
f1 (ppm)

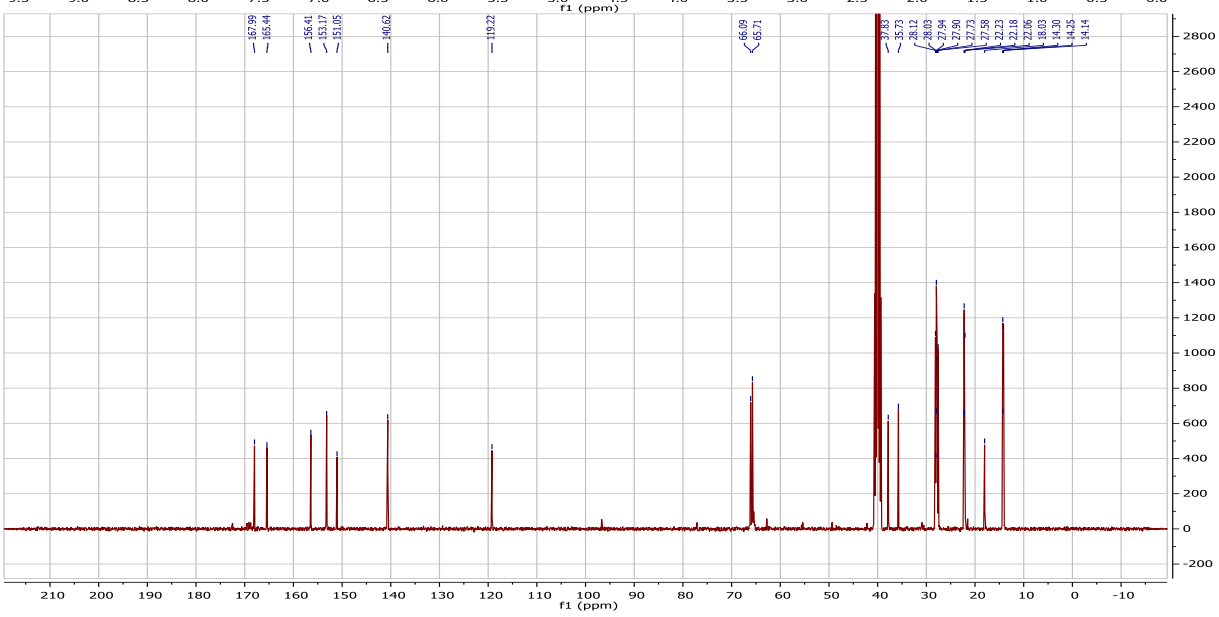

3000
2000
1000

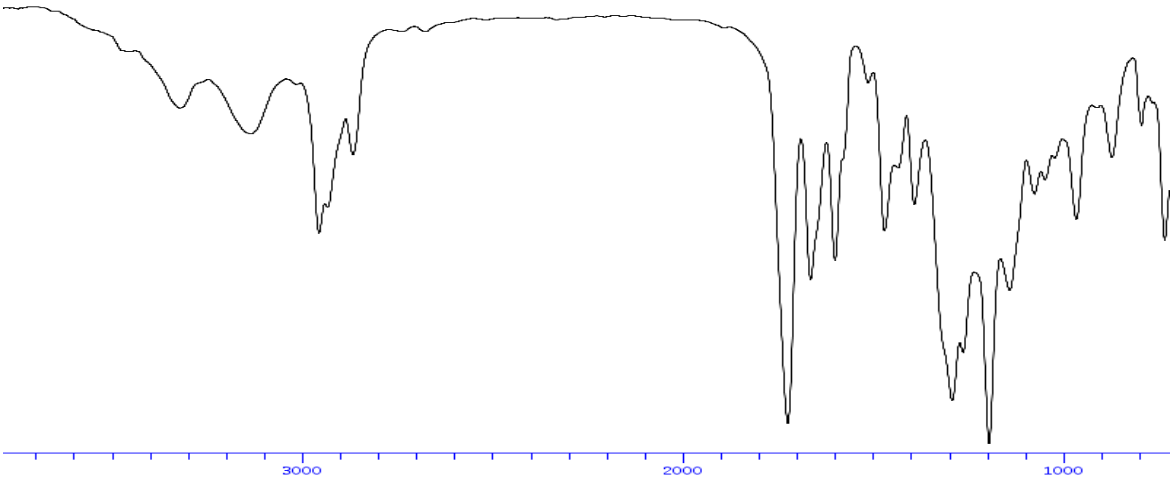

400 MHz, Chloroform-*d*.
Cl
N
N
N
N
MeO2C
MeO2C
38c
1.27
1.00
1.03
3.64
3.14
1.32
1.21
f1 (ppm)

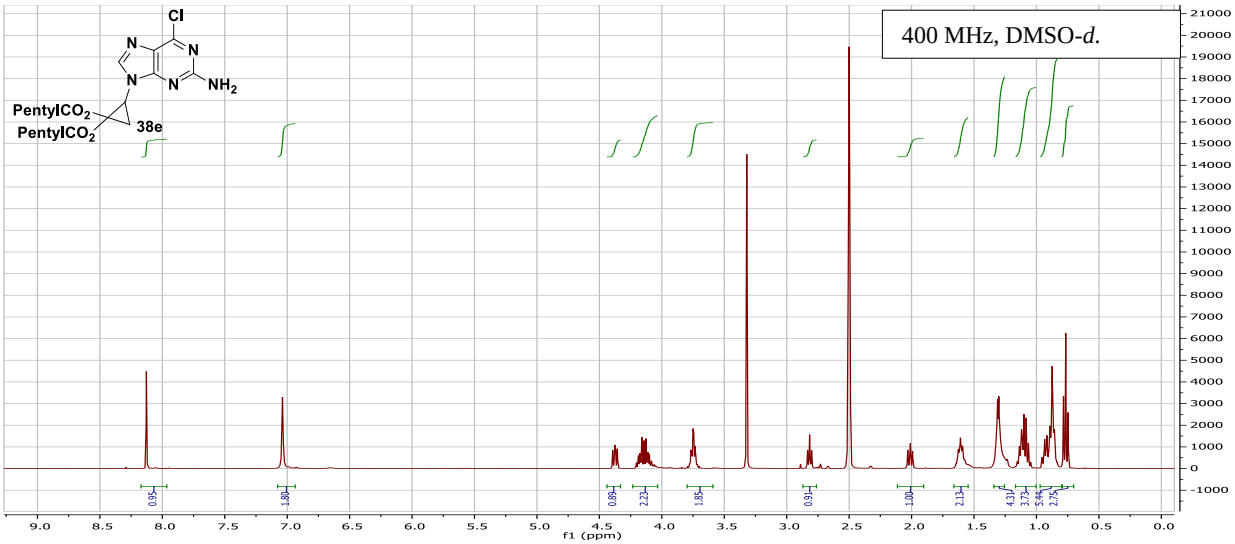

167.78
167.72
165.36
152.65
152.57
152.48
151.44
145.06
142.90
131.51
53.50
53.28
37.72
35.05
19.19
f1 (ppm)

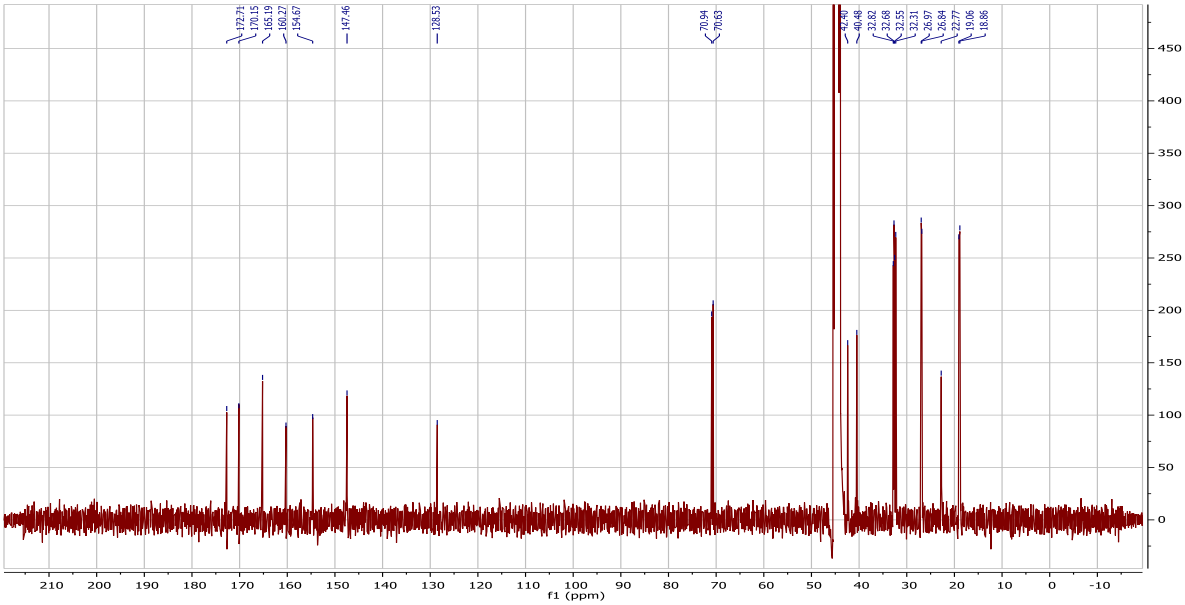

3000
2000
1000

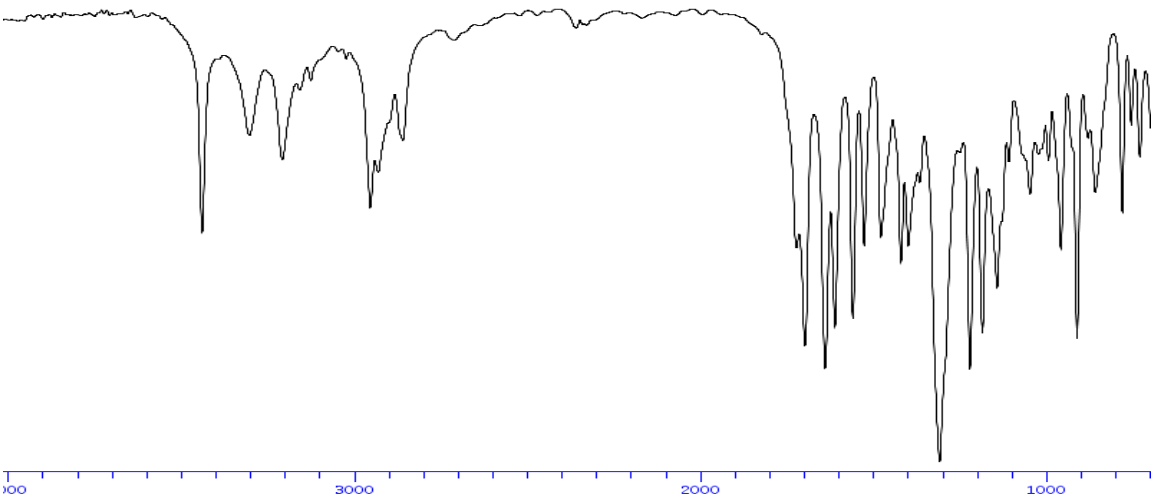

400 MHz, DMSO-*d*.
NH2
N
N
N
N
PentylCO2
PentylCO2
38d
f1 (ppm)

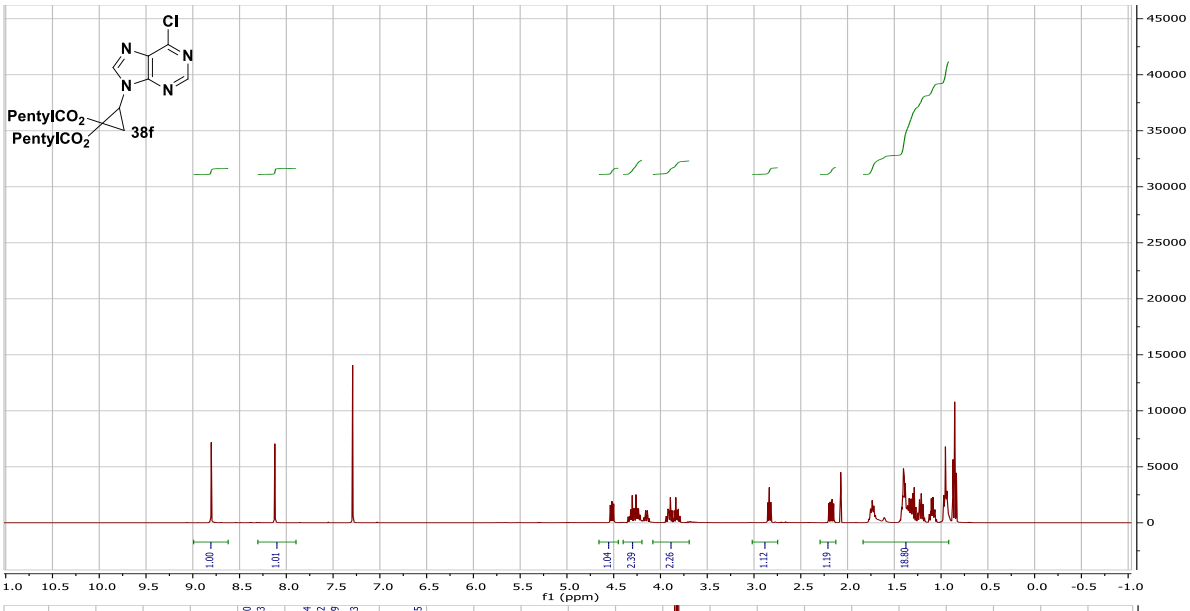

167.99
165.44
156.41
153.17
151.05
140.62
119.22
66.09
65.71
37.83
35.73
28.12
28.03
27.94
27.90
27.73
27.58
22.23
22.18
22.06
18.03
14.30
14.25
14.14
f1 (ppm)

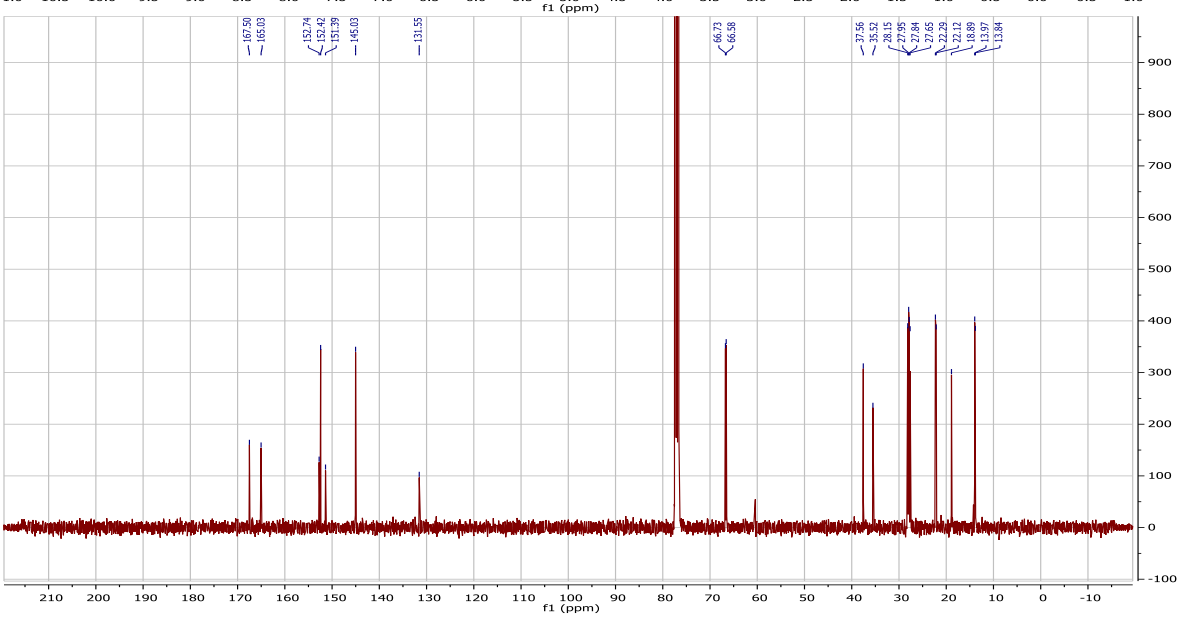

3000
2000
1000

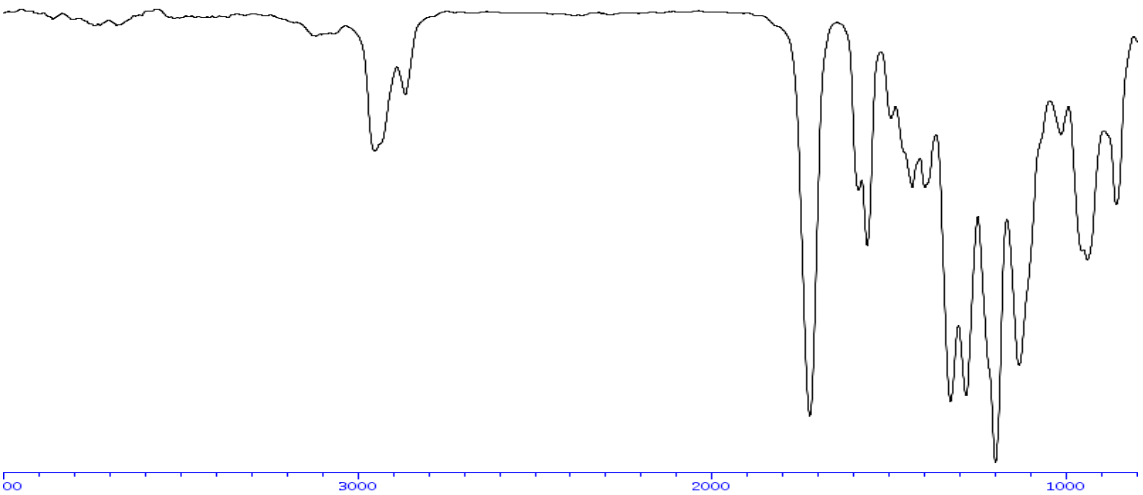

400 MHz, DMSO-*d*.
Cl
N
N
N
N
NH2
PentylCO2
PentylCO2
38e
f1 (ppm)

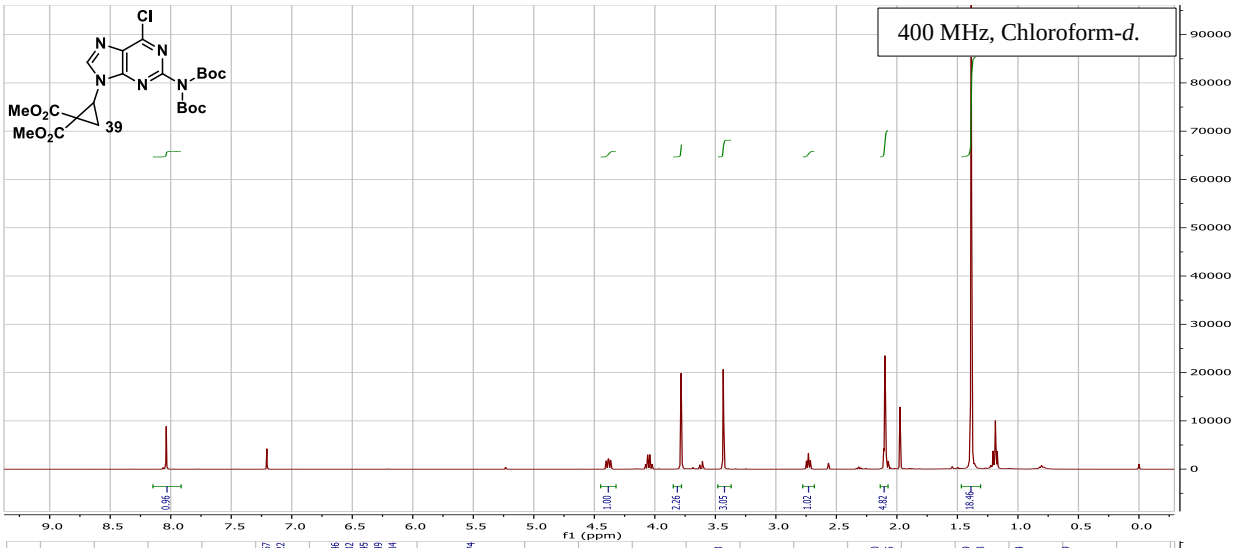

172.71
170.15
165.19
160.27
154.67
147.46
128.53
70.94
70.63
42.40
40.48
32.82
32.68
32.55
32.31
26.97
26.84
22.77
19.06
18.86
f1 (ppm)

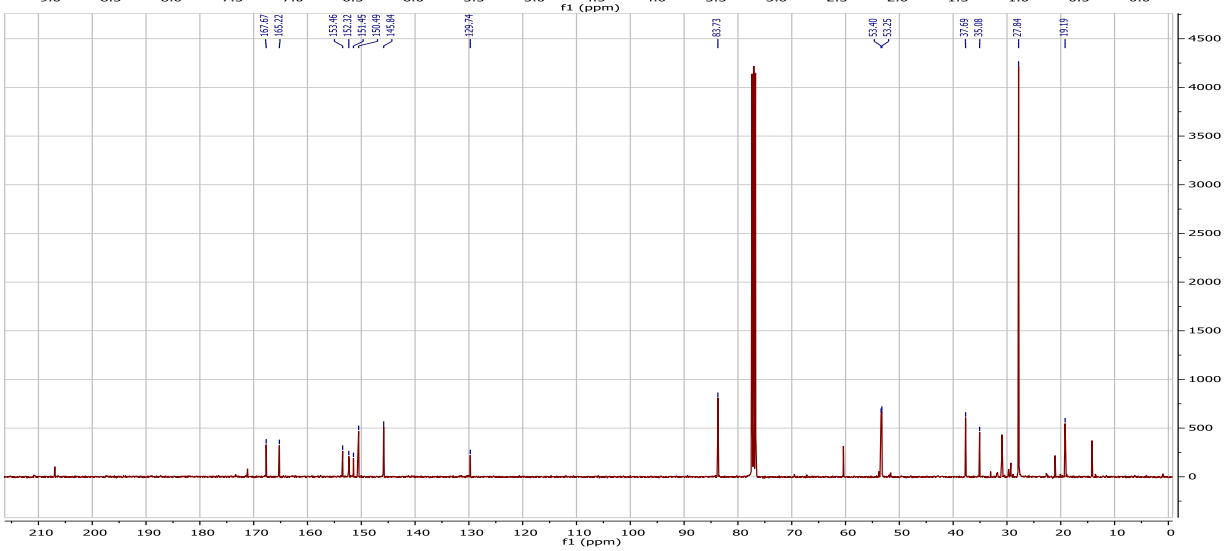

3000
2000
1000

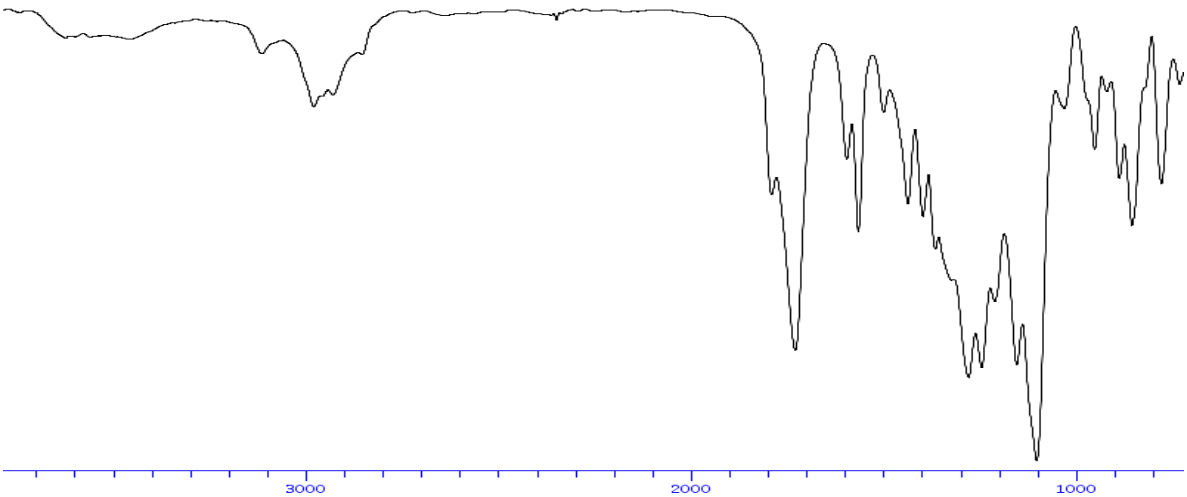

Cl
N
N
N
N
PentylCO2
PentylCO2
38f
1.00
1.01
1.04
2.39
2.26
1.12
1.19
18.80
f1 (ppm)


167.50
165.03
152.74
152.42
151.39
145.03
131.55
66.73
66.58
37.56
35.52
28.15
27.95
27.84
27.65
22.29
22.12
18.89
13.97
13.84
f1 (ppm)


3000
2000
1000


400 MHz, Chloroform-*d*.
Cl
N
N
N
N
N
Boc
Boc
MeO2C
MeO2C
39
0.96
1.00
2.26
3.05
1.02
4.62
18.46
f1 (ppm)


167.67
165.22
153.46
152.32
151.45
150.49
145.84
129.74
83.73
53.40
53.25
37.69
35.08
27.84
19.19
f1 (ppm)


3000
2000
1000