DOI: 10.1002/anie.201((will be filled in by the editorial staff))

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

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

Dedication((optional))

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

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

The synthesis of nucleoside analogues has been the focus of intensive effort since several decades.[2] Nevertheless, most methods are based on a linear approach involving first the synthesis of a ribose analogue followed by introduction of the nucleobase, either via formation of the C-N bond using a substitution reaction from an acetate **I** (Vorbrüggen reaction)[2b] or a condensation reaction from an aminoglycoside **II**[2a] (Scheme 1, **A**). This approach is efficient if the targeted analogue is similar to a natural ribose derivative, but can involve a long multi-step sequence if a more elaborate scaffold is desired.[3] This is particularly true for carbonucleoside analogues, for which elegant synthetic approaches involving ring-closing metathesis,[3a] Pauson-Khand[3b] or desymmetrization starting from cyclopentadiene and proceeding via diols, [3c-e] Vince's lactam[3f-g] or nitroso cycloaddition reactions[3h] have been developed.

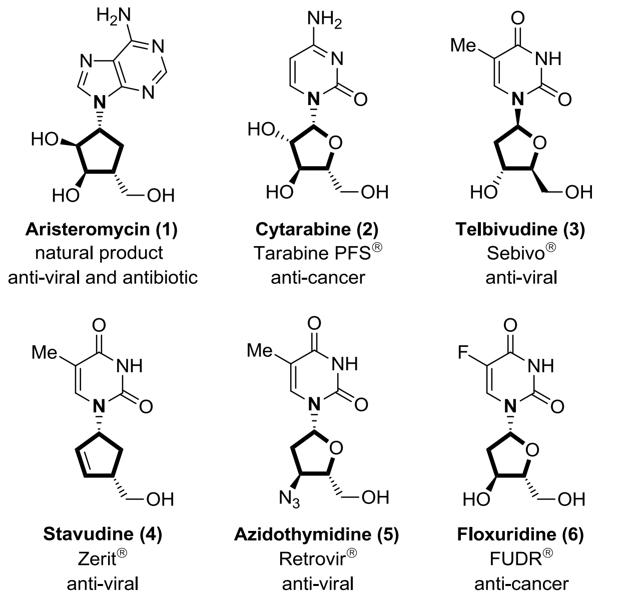


Figure 1. Natural and synthetic bioactive nucleoside analogues.

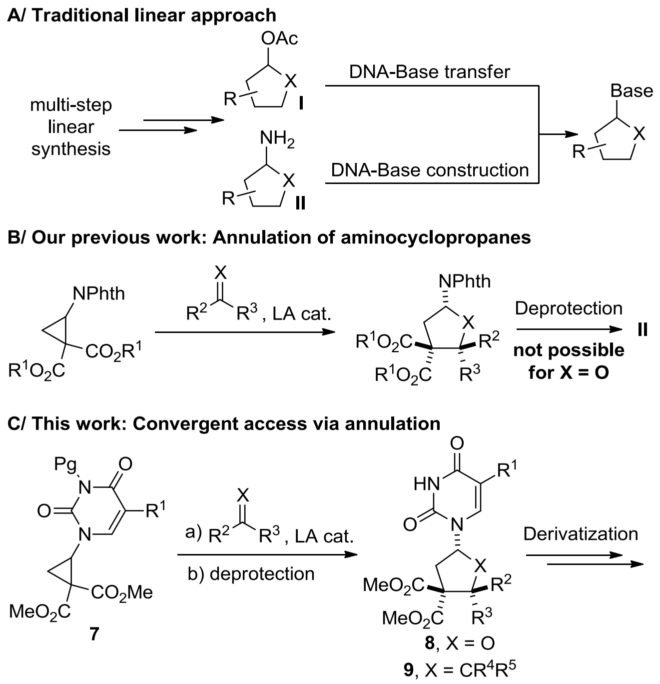
Our group has introduced the use of imide-substituted diester cyclopropanes in [3+2] annulation reactions.[4] With this new class of donor-acceptor cyclopropanes,[5] access to intermediates of type **II** became possible (Scheme 2, **B**). Nevertheless, the efficiency of the annulation process was mitigated by the necessary removal of the phthalimide group followed by DNA-base construction, which would add several steps to the synthetic sequence. Furthermore, the deprotection of the pththalimide group could not be achieved on the tetrahydrofurylamines.

If a DNA-base could be used as amino substituent on the cyclopropane, a more efficient synthesis would become possible (Scheme 1, **C**). Herein, we would like to report the successful

[*] Sophie Racine, F. de Nanteuil, Eloisa Serrano and Prof. Dr. J. Waser
Laboratory of Catalysis and Organic Synthesis
Ecole Polytechnique Fédérale de Lausanne
EPFL SB ISIC LCSO, BCH 4306, 1015 Lausanne (CH)
Fax: (+)41 21 693 97 00
E-mail: jerome.waser@epfl.ch
Homepage: http://lcso.epfl.ch/

[**] EPFL, F. Hoffmann-La Roche Ltd, SNF (grant number 200021_129874) and the NCCR chemical biology are acknowledged for financial support. Dr. Rosario Scopelliti (EPFL) is acknowledged for the X-ray studies.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201xxxxxx implementation of this strategy, including: (1) the first efficient three-step synthesis of thymine/uracil donor-acceptor cyclopropanes, (2) their successful [3+2] cycloaddition with enol ethers, aldehydes and ketones and (3) their further derivatization to access hydroxylated analogues.

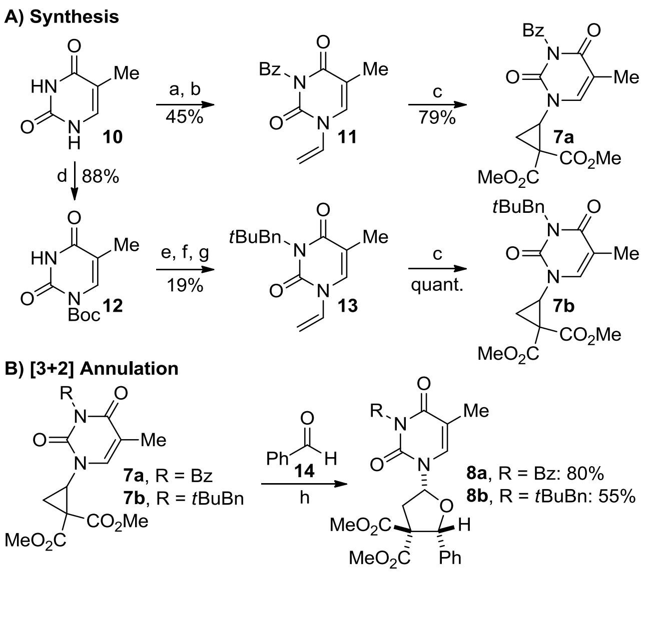


Scheme 1. Traditional approach (**A**), our previous work (**B**) and new strategy (**C**) to access (carbo)nucleoside analogues. Phth = Phthalimido, Pg = protecting group, LA = Lewis Acid.

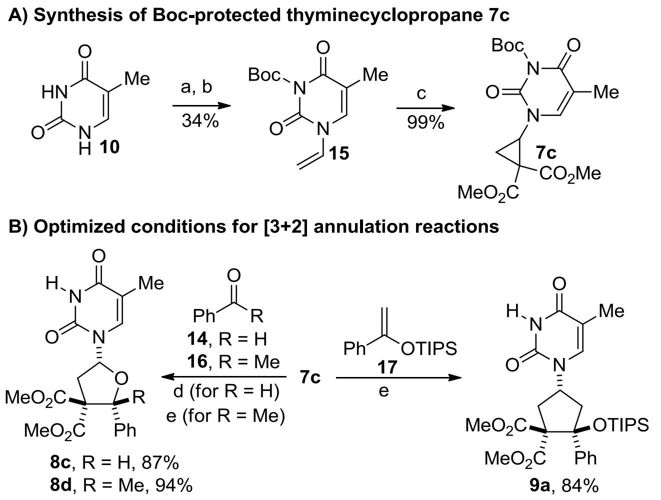
In our work with phthalimide-substituted cyclopropanes, modulating the electronic density on the nitrogen was essential for a successful annulation reaction. Based on the fact that thymine and phthalimide have similar pKa values (8.3 and 9.9 respectively), we started our investigations with thymine-substituted cyclopropanes (Scheme 2, **A**). Cyclopropane **7a** was easily accessed by selective mono benzoylation of thymine (**10**),[6] followed by Pd-catalyzed vinylation under slightly modified reported conditions[7] and cyclopropanation using Du Bois' Rhodium-espino complex.[8] As N3-selective *tert*-butylbenzylation was not possible, a longer sequence involving temporary Boc protection of the N1 nitrogen was necessary in the case of cyclopropane **7b**.[9]

With aminocyclopropanes **7a** and **7b** in hand, we first examined the iron-catalyzed [3+2] annulation reaction with benzaldehyde (**14**) (Scheme 2, **B**).[4c] The reaction was successful for both substrates **7a** and **7b**. Nevertheless, we were never able to remove either of the protecting groups on the nitrogen of thymine. We decided consequently to turn to the easily removable *tert*-butoxy carbonyl (Boc) protecting group.

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



Scheme 2. Synthesis of aminocyclopropanes **7a** and **7b** (**A**) and first attempts of [3+2] annulation (**B**). Reaction conditions: a) BzCl, pyridine, CH_3CN, 69%. b) 4 mol% Na_2PdCl_4, vinylacetate, 80 °C, 65%. c) 0.2 mol% $Rh_2(esp)_2$, diazodimethylmalonate, CH_2Cl_2. d) Boc_2O, DMAP, CH_3CN. e) *t*BuBnBr, NaH, DMF, 0 °C, quant. f) K_2CO_3, MeOH, 81%. g) 4 mol% Na_2PdCl_4, vinylacetate, 80 °C, 23%, h) 5 mol% Fe_2O_3•Al_2O_3, CH_2Cl_2.

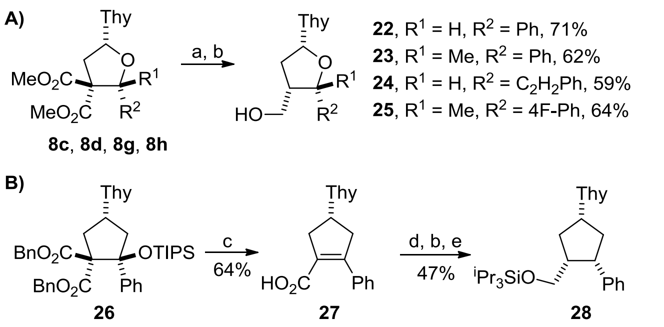


Scheme 3. Synthesis of aminocyclopropanes **7c** (**A**) and optimized conditions for [3+2] annulation reactions (**B**). Reaction conditions: a) 4 mol% $Pd(OAc)_2$, vinylacetate, TMSOTf, 70 °C, DMF, 45%. b) Boc_2O, DMAP, CH_2Cl_2, 75%. c) 0.02 mol% $Rh_2(esp)_2$, diazodimethylmalonate, CH_2Cl_2. d) 20 mol% $In(OTf)_3$, CH_2Cl_2; then EtOH, 70 °C. e) 10 mol% $SnCl_4$, CH_2Cl_2, -20 °C; then EtOH, 70 °C.

First attempts towards the annulation of **7c** with benzaldehyde (**14**) using an iron catalyst gave the desired product only in low yield (<27%). This was due to loss of the Boc protecting group during both reaction and purification. Changing to $In(OTf)_3$ as catalyst[12] and direct Boc deprotection of the crude product by heating in ethanol at 70 °C afforded the desired NH-free product **8c** in 87% yield (Scheme 3, **B**). Aminocyclopropane **7c** could also be used in other [3+2] annulation processes involving either ketones[4b] or silyl enol ethers[4a] to give tetrahydrofuryl amine **8d** and cyclopentyl amine **9a** in 94% and 84% yield respectively. In this case, the lower reactivity of **7c** compared with phthalimide-substituted cyclopropanes required the use of a higher temperature (-20 instead of -78 °C) in the tin-catalyzed process.

We then turned to the investigation of the scope of the [3+2] annulation (Figure 2).[13] The reaction was successful in the case of aromatic (products **8c** and **8e**), aliphatic (products **8f**) and vinylic aldehydes product **8g**). Excellent diastereoselectivity (> 20:1) was observed, except for product **8g** (5:1). The same was also true for ketones (products **8d** and **8h-k**), although the diastereoselectivity was lower for vinylic ketones (product **8k**). With enol ethers, more substituted derivatives, such as tetrasubstituted cyclopentane **9c**, could also be accessed. The [3+2] annulation product was obtained in 55% yield with a dienol ether as partner (product **9d**). Finally, modification of the thymine substituent was also examined. Both cyclopropanes derived from uracil and 5-fluoro-uracil could also be used in the annulation reaction with aldehydes, ketones and enol ethers (products **18**-**21**).[14]

For most nucleoside drugs enzymatic phosphorylation of a hydroxy group is an important step in the mode of action.[1] Modification of the obtained products to include hydroxy group(s) would be consequently highly rewarding in the quest of new bioactive compounds. To reach this goal, saponification followed by decarboxylation of diester **8c** gave access to a single isomer of the corresponding carboxylic acid,[15] which could be reduced to primary alcohol **22** in 71% overall yield (Scheme 4, **A**). The same sequence was also successful for styrene derivative **8g**, giving the corresponding alcohol **24** in 59% yield. Products **8d** and **8h** could also be converted into the desired alcohols **23** and **25** in 62 and 64% yield respectively. In the case of the carbonucleoside analogues, dibenzylester cyclopentylamine **26** could be converted into the corresponding diacid by hydrogenation.[16] Heating the neat crude diacid to 80 °C led then to decarboxylation and silyl ether elimination to give acid **27** (Scheme 4, **B**). Pd-catalyzed hydrogenation followed by acid reduction gave the corresponding unstable saturated alcohol, which was isolated as silyl ether **28**.



Scheme 4. Modification of the tetrahydrofuran (**A**) and cyclopentane (**B**) products. Reaction conditions: a) KOH, MeOH. b) BH_3•SMe_2, THF. c) 10% Pd/C, 1 atm H_2, EtOH, 57 °C, then neat, 80°C. d) 5% Pd/C, 1 atm H_2, EtOH, 85%. e) $^iPr_3SiCl$, DMF, imidazole, 55% over two steps.

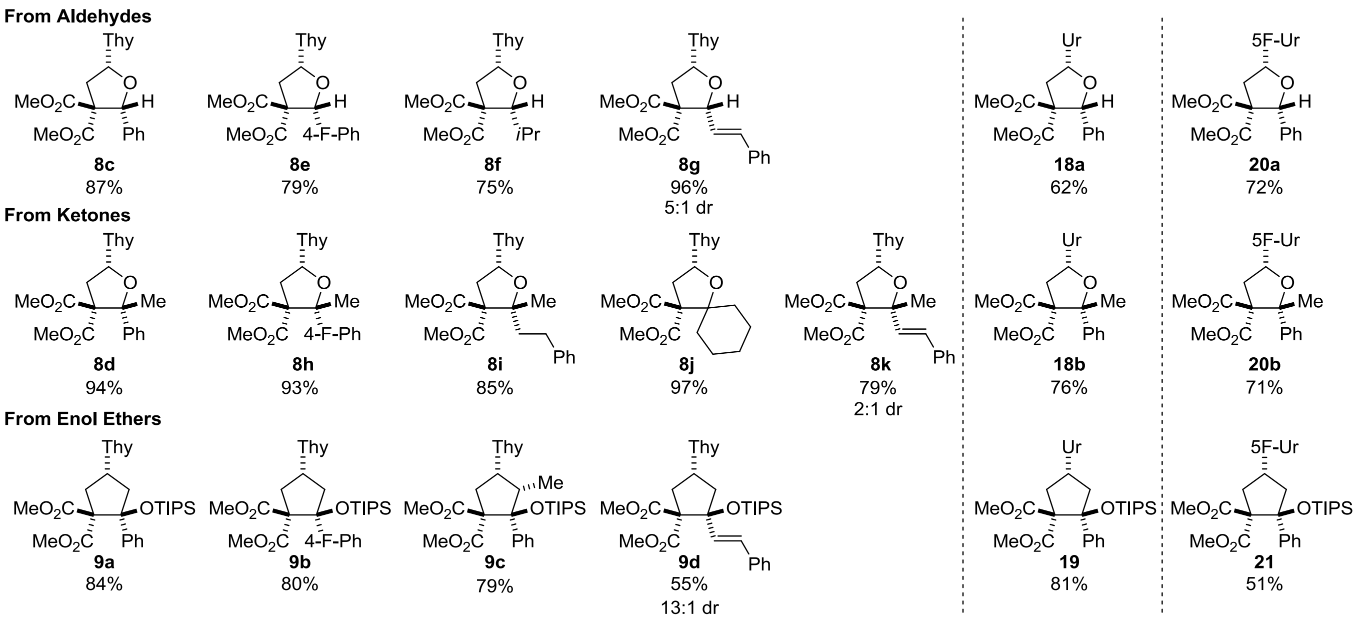


Figure 2. Scope of the [3+2] annulation reaction. The reactions were run on 0.40 mmol scale using the conditions of Scheme 3 and isolated yields after column chromatography are given. See Supporting Information for full experimental details. Thy = Thymine, Ur = Uracil, 5F-Ur = 5-Fluro-Uracil.

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

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

[1] a) *Modified Nucleosides in Biochemistry, Biotechnology and Medicine*, P. Herdewijn ed., Wiley-VCH, Weinheim, **2008**. b) S. Broder, *Antiviral Res.* **2010**, *85*, 1. c) J. C. Martin, M. J. M. Hitchcock, E. De Clercq, W. H. Prusoff, *Antiviral Res.* **2010**, *85*, 34. d) T. Cihlar, A. S. Ray, *Antiviral Res.* **2010**, *85*, 39. e) G. Antonelli, O. Turriziani, *Int. J.*

Antimicrob. Agents **2012**, *40*, 95. f) L. P. Jordheim, D. Durantel, F. Zoulim, C. Dumontet, *Nat. Rev. Drug Discovery* **2013**, *12*, 447.

[2] a) G. Shaw, R. N. Warrener, M. H. Maguire, R. K. Ralph, *J. Chem. Soc.* **1958**, 2294. b) U. Niedball, H. Vorbrüggen, *Angew. Chem., Int. Ed.* **1970**, *9*, 461.Reviews: g) M. T. Crimmins, *Tetrahedron* **1998**, *54*, 9229. h) H. Vorbrüggen, C. Ruh-Polenz, *Handbook of Nucleoside Synthesis*, John Wiley & Sons, **2001**. i) *Antiviral Nucleosides: Chiral Synthesis and Chemotherapy*, C. K. Chu ed., Elsevier, Amsterdam, **2003**. j) C. Mathe, C. Perigaud, *Eur. J. Org. Chem.* **2008**, 1489. k) G. Romeo, U. Chiacchio, A. Corsaro, P. Merino, *Chem. Rev* **2010**, *110*, 3337. l) *Chemical Synthesis of Nucleoside Analogues*, P. Merino ed., John Wiley & Sons, Hoboken, New Jersey, **2013**. m) O. Boutureira, M. I. Matheu, Y. Diaz, S. Castillon, *Chem. Soc. Rev.* **2013**, *42*, 5056. n) L. Scagnelli, M. G. Memeo, S. Carosso, B. Bovio, P. Quadrelli, *Eur. J. Org. Chem.* **2013**, 3835.

[3] a) W. J. Choi, J. G. Park, S. J. Yoo, H. O. Kim, H. R. Moon, M. W. Chun, Y. H. Jung, L. S. Jeong, *J. Org. Chem* **2001**, *66*, 6490. b) J. Velcicky, A. Lanver, J. Lex, A. Prokop, T. Wieder, H. G. Schmalz, *Chem. Eur. J.* **2004**, *10*, 5087. c) B. M. Trost, G. H. Kuo, T. Benneche, *J. Am. Chem. Soc.* **1988**, *110*, 621. d) B. M. Trost, L. S. Kallander, *J. Org. Chem.* **1999**, *64*, 5427. e) L. F. Tietze, C. Stadler, N. Böhnke, G. Brasche, A. Grube, *Synlett* **2007**, 485. f) S. Daluge, R. Vince, *Tetrahedron Lett.* **1976**, *17*, 3005. g) R. Singh, R. Vince, *Chem. Rev* **2012**, *112*, 4642. h) M. J. Mulvihill, J. L. Gage, M. J. Miller, *J. Org. Chem* **1998**, *63*, 3357. i) G. A. Boyle, C. D. Edlin, Y. F. Li, D. C. Liotta, G. L. Morgans, C. C. Musonda, *Org. Biomol. Chem.* **2012**, *10*, 1870.

[4] [3+2] annulation with imido-cyclopropanes: a) F. de Nanteuil, J. Waser, *Angew. Chem., Int. Ed.* **2011**, *50*, 12075. b) F. Benfatti, F. de Nanteuil, J. Waser, *Chem. Eur. J.* **2012**, *18*, 4844. c) F. Benfatti, F. de Nanteuil, J. Waser, *Org. Lett.* **2012**, *14*, 386. d) F. de Nanteuil, E. Serrano, D. Perrotta, J. Waser, *J. Am. Chem. Soc.* **2014**, *136*, 6239. Other reactions with imido-cyclopropanes: e) F. de Nanteuil, J. Loup, J. Waser, *Org. Lett.* **2013**, *15*, 3738. f) R. Tejero, A. Ponce, J. Adrio, J. C. Carretero, *Chem. Comm.* **2013**, *49*, 10406. g) A. R. Rivero, I. Fernandez, M. A. Sierra, *Org. Lett.* **2013**, *15*, 4928.

[5] Reviews on donor-acceptor cyclopropanes: a) H. U. Reissig, R. Zimmer, *Chem. Rev* **2003**, *103*, 1151. b) M. Yu, B. L. Pagenkopf, *Tetrahedron* **2005**, *61*, 321. c) C. A. Carson, M. A. Kerr, *Chem. Soc. Rev.* **2009**, *38*, 3051. d) F. De Simone, J. Waser, *Synthesis* **2009**, 3353. e) T. P. Lebold, M. A. Kerr, *Pure Appl. Chem.* **2010**, *82*, 1797. f) M. Y. Mel'nikov, E. M. Budynina, O. A. Ivanova, I. V. Trushkov, *Mendeleev Commun.* **2011**, *21*, 293. g) P. Tang, Y. Qin, *Synthesis* **2012**, *44*, 2969. h) M. A. Cavitt, L. H. Phun, S. France, *Chem. Soc. Rev.* **2014**, *43*, 804. i) T. F. Schneider, J. Kaschel, D. B. Werz, *Angew. Chem., Int. Ed.* **2014**, *53*, 5504. Theoretical investigation on the ring-opening of donor-acceptor cyclopropanes: j) T. F. Schneider, D. B. Werz, *Org. Lett.* **2011**, *13*, 1848.

[6] J. L. Zhou, P. B. Shevlin, *Synth. Commun.* **1997**, *27*, 3591.

[6] a) E. Bayer, K. Geckeler, *Angew. Chem., Int. Ed.* **1979**, *18*, 533. b) N. Baret, J. P. Dulcere, J. Rodriguez, J. M. Pons, R. Faure, *Eur. J. Org. Chem.* **2000**, 1507.

[8] a) C. G. Espino, K. W. Fiori, M. Kim, J. Du Bois, *J. Am. Chem. Soc.* **2004**, *126*, 15378. b) F. Gonzalez-Bobes, M. D. B. Fenster, S. Kiau, L. Kolla, S. Kolotuchin, M. Soumeillant, *Adv. Synth. Catal.* **2008**, *350*, 813.

[9] S. Jaime-Figueroa, A. Zamilpa, A. Guzman, D. J. Morgans, *Synth. Commun.* **2001**, *31*, 3739.

[10] a) H. J. Gi, Y. J. Xiang, R. F. Schinazi, K. Zhao, *J. Org. Chem.* **1997**, *62*, 88. b) P. Ciapetti, M. Taddei, *Tetrahedron* **1998**, *54*, 11305. c) P. Arsenyan, A. Petrenko, E. Paegle, S. Belyakov, *Mendeleev Commun.* **2011**, *21*, 326. d) K. S. Toti, M. Derudas, C. McGuigan, J. Balzarini, S. Van Calenbergh, *Eur. J. Med. Chem.* **2011**, *46*, 3704.

[11] Cyclopropanation in absence of the Boc protecting group was not successful.

[12] R. Ghosh, S. Maiti, *J. Mol. Catal. A: Chem.* **2007**, *264*, 1-8.

[13] The stereochemistry of compounds **8e**, **8i**, and **9a** has been determined by X-ray crystallography. The data is available at the Cambridge Crystallographic Data Centre with the numbers CCDC 995573, CCDC 994735 and CCDC 994948 respectively. The stereochemistry of the other compounds has been assigned by analogy or NMR experiments. See Supporting Information for further details.

[14] The uracil and 5-fluoro-uracil substituted cyclopropanes were obtained using a similar synthetic sequence. In the case of the 5-fluoro uracil derivatives, it was necessary to use a more stable benzoyl protecting group. See Supporting Information for further details.

[15] The diastereoselectivity in the decarboxylation step was usually high (>5:1, >20:1 for 8c). The products are obtained under kinetic control, but the rationalization of the high selectivity will require further investigations.

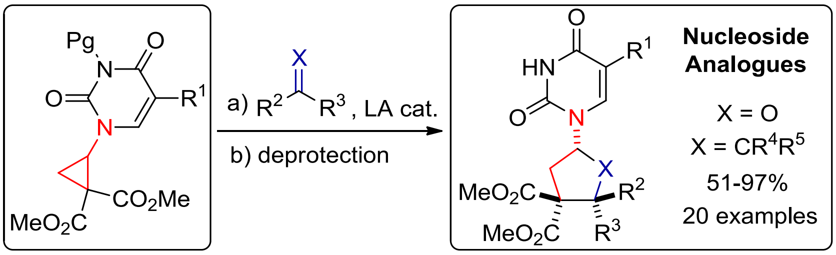
[16] Cyclopentylamine **26** was obtained in 94% yield from the [3+2] annulation of the corresponding dibenzylester-substituted cyclopropane with enol ether **17**.

Synthetic Method

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

__________ **Page – Page**

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



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

Contents

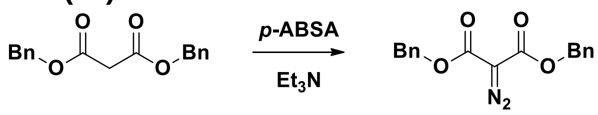
1. General methods.

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.

2. Starting materials.

2.1 Diazomalonates.

Dibenzyl 2-diazomalonate (30).



29 **30**

In flame dried flask under nitrogen, 4-acetamidobenzenesulfonyl azide (1.27 g, 5.28 mmol, 1.5 eq) was dissolved in acetonitrile (15 mL) and triethylamine (1.17 mL, 8.44 mmol, 2.4 eq) and dibenzyl malonate (**29**) (0.88 ml, 3.5 mmol, 1eq) 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 **30** (1.02 g, 3.29 mmol, 93%) as a slightly yellow solid.

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

Mp 54.8-55.4°C. (Decomposition)

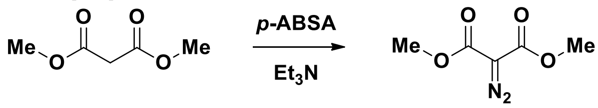
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39- 7.34 (m, 10H, Ar-H), 5.28 (s, 4H, CH_2).

^{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 (32).



31 **32**

In flame dried flask under nitrogen, 4-acetamidobenzenesulfonyl azide (6.82 g, 28.4 mmol, 1.5 eq) was dissolved in acetonitrile (80 mL) and triethylamine (6.3 mL, 45 mmol, 2.4 eq) and dimethyl malonate (**31**) (2.2 mL, 19 mmol, 1eq) 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 **32** (2.67 g, 16.9 mmol, 94%) as a slightly yellow oil (solid at 4 °C).

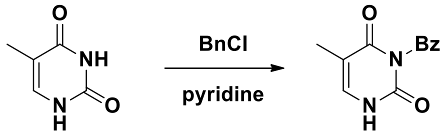
^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.84 (s, 4H, CH_2).

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

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

2.2 Thymine cyclopropanes.

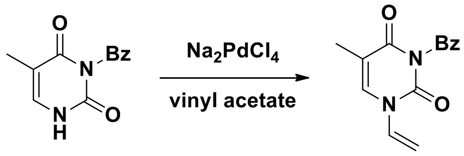
3-Benzoyl-5-methylpyrimidine-2,4(1H,3H)-dione (33).



Following the procedure of Zhou and co-workers.[2], benzoyl chloride (1.01 mL, 8.72 mmol, 2.2 eq) and thymine (**10**) (0.050 g, 4.0 mmol, 1.0 eq) were suspended in a mixture of acetonitrile (4 mL) and pyridine (1.6 mL, 4.0 mmol, 1.0 eq) in a flame-dried flask under nitrogen. The reaction was stirred under nitrogen atmosphere at room temperature for 12 h. Then, the reaction was partitioned between DCM and water. The aqueous layer was extracted three times with DCM and the combined organic layers were dried over anhydrous K_2CO_3. The solvent was removed under reduced pressure. The residue was dissolved in dioxane (8 mL) and K_2CO_3 (0.3 g) in 4 mL water was added and the reaction mixture was stirred for 1h30. AcOH was added to reach pH 5. The crude residue was concentrated under vacuo and suspended in 20 mL of a saturated solution of $NaHCO_3$ for 1 h and filtered with cold water. The pure product **33** (0.63 g, 2.7 mmol, 69% yield) was obtained after recrystallization in acetone (10 mL) as colorless needles.

^{1}H NMR (400 MHz, DMSO) δ 11.37 (s, 1H, N-H), 7.94 (m, 2H, Ar-H), 7.79 (m, 1H, Ar-H), 7.61 (m, 2H, Ar-H), 7.54 (d, *J* = 1.2 Hz, 1H, C=C-H), 1.83 (d, *J* = 1.1 Hz, 3H, CH_3).
NMR values correspond to the literature.[2]

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



Following an adapted procedure of Baret and co-workers.[3], 3-benzoyl-5-methylpyrimidine-2,4(1H,3H)-dione (**33**) (0.061 g, 0.27 mmol, 1.0 eq) and Na_2PdCl_4 (8 mg, 0.03 mmol, 10 mol%) were heated in vinyl acetate (5 mL) at 80 °C for 6 h in a flamed dried flask under nitrogen. The reaction mixture was allowed to cool down and was filtered on a syringe filter. Then, the crude residue was concentrated under reduced pressure and purified by column chromatography using a mixture of DCM/AcOEt (9.5:0.5) as eluting solvent. The pure product **11** (0.40 g, 0.16 mmol, 65% yield) was obtained as a white solid.

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

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.02 – 7.93 (m, 2H, Ar-H), 7.68 (ddt, *J* = 8.7, 7.1, 1.3 Hz, 1H, Ar-H), 7.59 – 7.43 (m, 3H, Ar-H and C=CH), 7.21 (dd, *J* = 16.0, 9.1 Hz, 1H, vinyl-C-H), 5.17 (dd, *J* = 16.0, 2.3 Hz, 1H, vinyl-CH_2), 5.00 (dd, *J* = 9.1, 2.3 Hz, 1H, vinyl-CH_2), 2.05 (d, *J* = 1.3 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.4, 162.5, 148.3, 135.1, 134.3, 131.4, 130.5, 129.5, 129.2, 112.1, 101.2, 12.7.

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

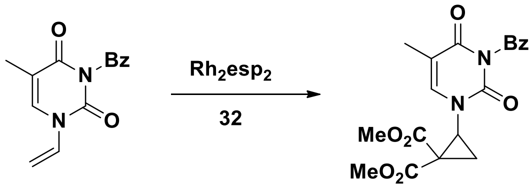
HRMS (ESI) calcd for $C_{14}H_{13}N_2O_3^+$ $[M+H]^+$ 257.0921; found 257.0913.

---

[2] J. Zhou, P. B. Shevlin, *Synth. Commun.,* **1997**, *27*, 3591–3597.
[3] N. Baret, J.-P. Dulcere, J. Rodriguez, J.-M. Pons, R. Faure, *Eu. J. Org. Chem.*, **2000**, *2000*, 1507–1516.

NMR values correspond to the literature[3]

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



11 7a

Dimethyl 2-diazomalonate (0.078 g, 0.40 mmol, 1.5 eq) was added to a solution of 3-benzoyl-1-vinylpyrimidine-2,4(1H,3H)-dione (**11**) (0.064 g, 0.26 mmol, 1.0 eq) and $Rh_2(esp)_2$ (0.4 mg, 0.5 µmol, 5% mol). The reaction mixture was stirred in anhydrous DCM (1 mL) at room temperature for 4 h in a flamed dried flask under nitrogen. Then, the crude residue was concentrated under reduced pressure and purified by column chromatography using a mixture of AcOEt/PET (7:3, 1% NEt_3) affording the pure product **7a** (0.083 g, 0.20 mmol, 79% yield) as a colorless foam.

RF (AcOEt/PET (7:3, 1% NEt_3)) = 0.23.

Mp 61.2-63.0°C.

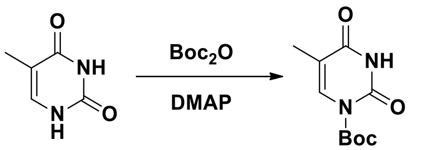
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 – 7.88 (m, 2H, Ar-H), 7.70 – 7.60 (m, 1H, Ar-H), 7.54 – 7.45 (m, 2H, Ar-H), 7.11 (q, *J* = 1.2 Hz, 1H, thymine C=CH), 4.00 (dd, *J* = 8.1, 6.4 Hz, 1H, cyclopropane-CH), 3.79 (s, 3H, ester-CH_3), 3.68 (s, 3H, ester-CH_3), 2.26 (t, *J* = 6.4 Hz, 1H, cyclopropane-CH_2), 2.05 – 1.95 (m, 4H, cyclopropane-CH_2 and thymine-CH_3).

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

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

HRMS (ESI) calcd for $C_{19}H_{19}N_2O_7^+$ $[M+H]^+$ 387.1192; found 387.1194.

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



10 12 4

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

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

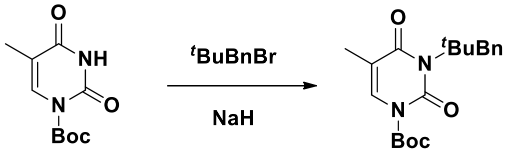
^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.41 (br. s, 1H, N-H), 7.72 (s, 1H, C=C-H), 1.81 (s 3H, CH_3), 1.46 (s, 9H, BOC).

[4] S. Jaime-Figueroa, A. Zamilpa, A. Guzmán, D. J. Morgans, *Synth. Commun.,* **2001**, *31*, 3739–3746.

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

HRMS (ESI) calcd for $C_{10}H_{15}N_2O_4^+$ $[M+H]^+$ 227.1026; found 227.1030.
NMR values correspond to the literature.[4]

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



12 34

Following a procedure described by Jacobsen and co-workers.[5], *tert*-butyl 5-methyl-2,4-dioxo-3,4-dihydropyrimidine-1(2H)-carboxylate (**12**) (0.75 g, 3.3 mmol, 1.0 eq) and NaH (0.159 g, 3.98 mmol, 1.2 eq) were stirred 30 min at room temperature in DMF (20 mL) in a flame-dried flask under nitrogen. Then 1-(bromomethyl)-4-(*tert*-butyl)benzene (0.731 mL, 3.98 mmol, 1.2 eq). was added at 0 °C. The reaction mixture was stirred at room temperature for 45 min and was partitioned between AcOEt and water. The aqueous layer was extracted three times with AcOEt and the organic layers were washed once with a sat. NH_4Cl solution and dried over anhydrous K_2CO_3. The solvent was removed under reduced pressure. The pure product **34** (1.24 g, 3.32 mmol, quantitative yield) was obtained after column chromatography using DCM as eluting solvent as white powder.

RF (DCM) = 0.24.

Mp 145.6-146.7°C.

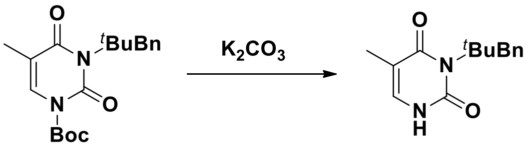
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.62 (q, *J* = 1.3 Hz, 1H, thymine C=C-H), 7.47 – 7.39 (m, 2H, Ar-H), 7.36 – 7.27 (m, 2H, Ar-H), 5.09 (s, 2H, benzylic-CH_2), 1.96 (d, *J* = 1.4 Hz, 3H, thymine methyl), 1.60 (s, 9H, Boc), 1.29 (s, 9H, ^{t}Bu).

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

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

HRMS (ESI) calcd for $C_{21}H_{29}N_2O_4^+$ $[M+H]^+$ 373.2122; found 373.2135.

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



34 35

Following a procedure described by Jacobsen and co-workers.[5], 3-(4-(*tert*-butyl)benzyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**34**) (1.4 g, 3.8 mmol, 1.0 eq), K_2CO_3 (0.26 g, 3.8 mmol, 1.0 eq) were stirred in MeOH (40 mL) at room temperature for 4 h. Afterwards, the reaction mixture was partitioned between DCM and water. The aqueous layer was extracted three times with DCM and the organic layers were washed once with a sat. NH_4Cl solution and dried over anhydrous K_2CO_3. The solvent was removed under reduced pressure affording pure **35** (0.83 g, 3.1 mmol, 81% yield) as a white solid.

[5] M. F. Jacobsen, M. M. Knudsen, K. V. Gothelf, *J. Org. Chem.,* **2006**, *71*, 9183–9190.

Mp 198.2-200.0°C.

^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.34 (s, 1H, thymine vinyl-C-H), 7.30 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.21 (d, *J* = 8.2 Hz, 2H, Ar-H), 4.93 (s, 2H, benzylic-CH_2), 1.79 (s, 3H, thymine-CH_3), 1.23 (s, 9H, ^{t}Bu).

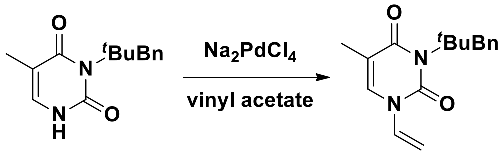
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.94 – 9.87 (m, 1H, thymine N-H), 7.48 – 7.38 (m, 2H, Ar-H), 7.38 – 7.31 (m, 2H, Ar-H), 7.02 (dt, *J* = 5.3, 1.2 Hz, 1H, thymine vinyl-C-H), 5.11 (s, 2H, benzylic-CH_2), 1.95 (d, *J* = 1.2 Hz, 3H, thymine-CH_3), 1.31 (s, 9H, ^{t}Bu).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.0, 153.2, 150.5, 134.4, 133.7, 128.7, 125.3, 110.3, 43.6, 34.5, 31.4, 13.0.

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

HRMS (ESI) calcd for $C_{16}H_{21}N_2O_2^+$ $[M+H]^+$ 273.1598; found 273.1599.
^{1}H NMR values are in accordance with the spectra performed in DMSO in the literature[5]

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



Following an adapted procedure described by Baret and co-workers.[3] 3-(4-(*tert*-butyl)benzyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**35**) (0.825 g, 3.03 mmol, 1 eq) and Na_2PdCl_4 (37 mg, 0.13 mmol, 0.05 eq) were heated at 80°C in vinylacetate (10 mL) for 6 h in a flame-dried flask under nitrogen. The reaction mixture was cooled down and filtered on a syringe filter. The pure product **13** (0.21 g, 0.70 mmol, 23% yield) was obtained after column chromatography using a mixture of DCM/AcOEt (9.5/0.5) as a white solid.

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

Mp 107.6-108.9°C.

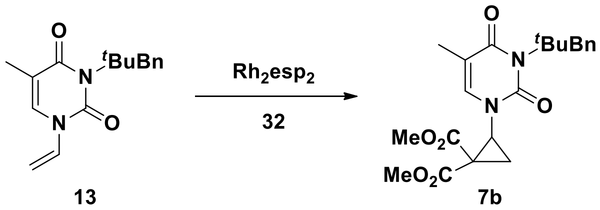
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 – 7.42 (m, 2H, Ar-H), 7.39 – 7.22 (m, 4H, Ar-H, thymine-H and vinyl-CH), 5.14 (s, 2H, benzyl-CH_2), 5.05 (dd, *J* = 16.1, 2.1 Hz, 1H, thymine vinyl-CH_2), 4.90 (dd, *J* = 9.1, 2.2 Hz, 1H, thymine vinyl-CH_2), 2.02 (d, *J* = 1.3 Hz, 3H, thymine-CH_3), 1.31 (s, 9H, ^{t}Bu).

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

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

HRMS (ESI) calcd for $C_{18}H_{23}N_2O_2^+$ $[M+H]^+$ 299.1754; found 299.1747.

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



3-(4-(*Tert*-butyl)benzyl)-5-methyl-1-vinylpyrimidine-2,4(1H,3H)-dione **13** (0.10 g, 0.34 mmol, 1.0 eq), $Rh_2(esp)_2$ (0.51 mg, 0.67 µmol, 0.2 mol%) and dimethyl 2-diazomalonate (0.10 g, 0.50 mmol, 1.5 eq) were stirred in a flame-dried flask under nitrogen with anhydrous DCM (4 mL) at room temperature for 5 h. Then, the crude residue was concentrated under reduced pressure and purified by column chromatography with DCM and 1% NEt_3, affording the pure product **7b** (0.14 g, 0.34 mmol, quantitative yield) as a slightly yellow oil.

RF (DCM) = 0.31.

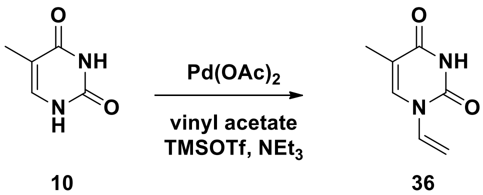
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.21 (m, 4H, Ar-H), 6.93 (app. d, *J* = 1.4 Hz, 1H, thymine C=CH), 5.08 (d, *J* = 13.7 Hz, 1H, benzylic-CH_2), 5.01 – 4.91 (m, 1H, benzylic-CH_2), 4.00 (dd, *J* = 8.2, 6.5 Hz, 1H, cyclopropane-CH), 3.75 (s, 3H, ester-CH_3), 3.36 (s, 3H, ester-CH_3), 2.19 (t, *J* = 6.5 Hz, 1H, cyclopropane-CH_2), 1.93 – 1.89 (m, 1H, cyclopropane-CH_2), 1.92 (s, 3H, thymine-CH_3), 1.22 (s, 9H, ^{t}Bu).

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

IR 4436 (w), 3625 (w), 2958 (m), 2860 (w), 1732 (s), 1668 (s), 1448 (m), 1441 (s), 1337 (s), 1294 (s), 1219 (s), 1131 (m).

HRMS (ESI) calcd for $C_{23}H_{29}N_2O_6^+$ $[M+H]^+$ 429.2020; found 429.2022.

1-Vinylthymine (36).



Palladium acetate (0.11 g, 0.48 mmol, 0.04 eq), vinyl acetate (8.8 mL, 9.5 mmol, 2.4 eq), thymine (**10**) (1.5 g, 12 mmol, 1.0 eq) and TMSOTf (5.2 mL, 12 mmol, 2.4 eq) were stirred in DMF (30.0 mL) for 16 hours at 70 °C in a flame-dried sealed flask under nitrogen atmosphere. Then the reaction mixture was cooled down to room temperature and partitioned between water (25 mL) and AcOEt (30 mL). The aqueous layer was extracted three times with ethyl acetate (30 mL), the organic layers were combined and washed three times with water (30 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography, eluting with hex/AcOEt/NEt_3 (7:3:0.01) to obtain the pure 1-vinylthymine **36** (0.81 g, 5.3 mmol, 45% yield) as a white solid.

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

Mp 208.0-209.1°C.

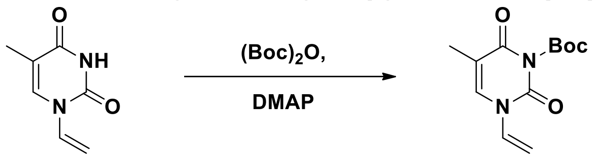
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.17 (s, 1 H, NH), 7.34 (s, 1 H, thymine C=C-H), 7.21 (dd, 1 H, *J* =16.0, 9.1 Hz, -vinyl-CH), 5.07 (dd, 1 H, *J* = 16.0, 2.1 Hz, vinyl-CH_2), 4.91 (dd, 1 H, *J* = 9.1, 2.1 Hz, vinyl-CH_2), 1.99 (s, 3 H, thymine-CH_3).

^{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 (15).**



36 15

1-Vinylthymine **36** (0.92 g, 6.1 mmol, 1.0 eq), di-*tert*-butyl dicarbonate (2.64 g, 12.1 mmol, 2.0 eq) and dimethylaminopyridine (1.48 g, 12.1 mmol, 2.0 eq) were stirred in acetonitrile (25.0 mL) for 12 h in a flame-dried flask under nitrogen. Silica and triethylamine (0.5 mL) were added to the reaction and the solvent was removed under reduced pressure. The dry residue was purified by column chromatography using a mixture of hexane/ethyl acetate/1% NEt_3 (95:5 to 80:20) as eluting solvent. The pure product **15** (1.15 g, 4.56 mmol, 75% yield) was obtained as a white solid.

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

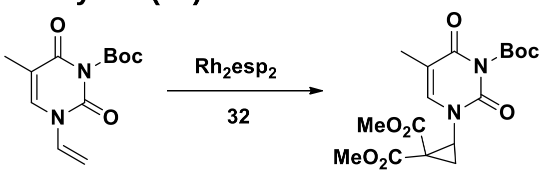
Mp 109.9-111.2 °C.

^{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 (7c).



15 7c

Diazomalonate **32** (1.80 g, 10.5 mmol, 1.2 eq), $Rh_2(esp)_2$ (0.013 g, 0.017 mmol, 0.02 mol%) and *tert*-butyl 5-methyl-2,6-dioxo-3-vinyl-2,3-dihydropyrimidine-1(6H)-carboxylate (**15**) (2.2 g, 8.7 mmol, 1.0 eq) were stirred at room temperature in DCM (18 mL) in a flame-dried flask under nitrogen. After 40 min. NEt_3 (0.4 mL) and silica were added and the solvent was removed under reduced pressure. The dried residue was purified by column chromatography using a mixture of pentane/ethyl acetate/1% NEt_3 (1:1) as solvent gradient. The pure product **7c** (3.30 g, 8.63 mmol, 99% yield) was obtained as a slightly yellow foamy oil.

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

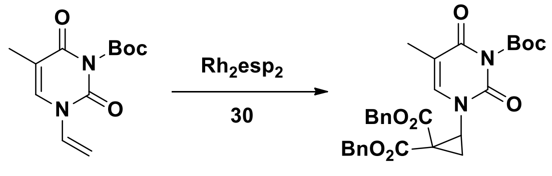
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.94 (m, 1H, thymine C=CH), 4.01 (dd, *J* = 8.3, 6.4 Hz, 1H, cyclopropane-CH), 3.79 (s, 3H, ester-CH_3), 3.71 (s, 3H, ester-CH_3), 2.27 (t, *J* = 6.5 Hz, 1H, cyclopropane-CH_2), 1.91 (m, 4H, thymine-CH_3 and cyclopropane-CH_2), 1.58 (s, 9H, Boc).

^{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 (37).



15 37

Tert-butyl 5-methyl-2,6-dioxo-3-vinyl-2,3-dihydropyrimidine-1(6H)-carboxylate (**15**) (0.30 g, 1.2 mmol, 1.0 eq) and $Rh_2(esp)_2$ (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 **30** (0.45 g, 1.4 mmol, 1.2 eq) was added at 0 °C. Then, the reaction mixture was allowed to warm up to room temperature and stirred for 14 h. Silica and triethylamine (0.5 mL) were added and the solvent was removed under reduced pressure. The dried residue was purified by column chromatography using a mixture of pentane/ethyl acetate/1% 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 (**37**) (0.60 g, 1.1 mmol, 93% yield) as a slightly yellow foam.

MP 76.9-82.1 °C.

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

^{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).

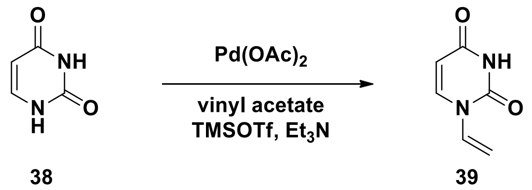
^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.2, 165.4, 161.1, 149.2, 147.5, 138.0, 135.0, 134.8, 128.6, 128.6, 128.5, 128.4, 128.2, 110.5, 86.8, 68.3, 68.0, 43.1, 35.3, 27.5, 20.3, 12.4.
One carbone not resolved.

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.

2.3 Uracil cyclopropane.

1-Vinylpyrimidine-2,4(1H,3H)-dione (39).



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

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

MP 175.2-176.7°C.

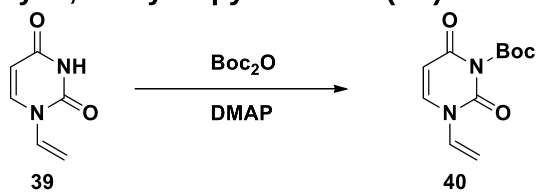
^{1}H NMR (400 MHz, Acetone) δ 9.21 (s, 1H, uracil N-H), 7.53 (d, *J* = 8.1 Hz, 1H, uracil CH), 7.23 (dd, *J* = 16.0, 9.0 Hz, 1H, vinyl-CH), 5.86 (dd, *J* = 8.1, 1.3 Hz, 1H, uracil CH), 5.13 (dd, *J* = 16.0, 2.3 Hz, 1H, vinyl-CH_2), 5.00 (dd, *J* = 9.0, 2.3 Hz, 1H, vinyl-CH_2).

^{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 (40).**



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

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

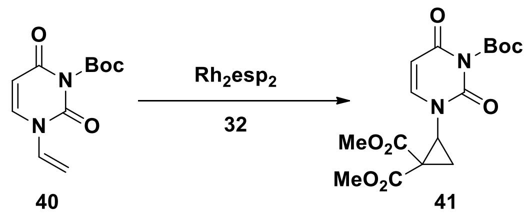
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.51 (d, *J* = 8.2 Hz, 1H, uracil CH), 7.15 – 7.02 (m, 1H, vinyl-CH), 5.80 (d, *J* = 8.2 Hz, 1H, uracil CH), 5.14 (dd, *J* = 16.0, 2.4 Hz, 1H, vinyl-CH_2), 4.96 (dd, *J* = 9.0, 2.5 Hz, 1H, vinyl-CH_2), 1.55 (s, 9H, Boc).

^{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 (41).



Diazomalonate **32** (0.28 g, 1.8 mmol, 1.0 eq), $Rh_2(esp)_2$ (2.7 mg, 3.5 µmol, 0.02 mol%) and product **40** (0.42 g, 1.8 mmol, 1.0 eq) were stirred at room temperature in DCM (18 mL) in a flame-dried flask under nitrogen. After 2 hour. NEt_3 (0.1 mL) and silica were added and the solvent was removed under reduced pressure. The dried residue was purified by column chromatography using a mixture of pentane/AcOEt (3:7) as eluting solvent. The pure cyclopropane **41** (0.56 g, 1.5 mmol, 87% yield) was obtained as a colorless foam.

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

MP 45.0-46.2°C.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.08 (d, *J* = 8.1 Hz, 1H, uracil CH), 5.64 (d, *J* = 8.2 Hz, 1H, uracil CH), 3.98 (dd, *J* = 8.2, 6.5 Hz, 1H, cyclopropane-CH), 3.73 (s, 3H, ester CH_3), 3.65 (s, 3H, ester CH_3), 2.19 (t, *J* = 6.6 Hz, 1H, cyclopropane-CH_2), 1.88 (dd, *J* = 8.5, 6.8 Hz, 1H, cyclopropane-CH_2), 1.51 (s, 9H, Boc).

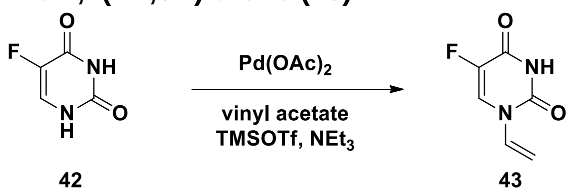
^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.5, 166.1, 160.2, 149.1, 147.2, 142.4, 101.9, 87.0, 53.3, 53.2, 43.0, 34.9, 27.4, 19.8.

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

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

2.4 5-Fluoro-uracil cyclopropane.

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



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

RF (AcOEt/pentane (6:4)) = 0.51.

MP 135.1-137.0°C.

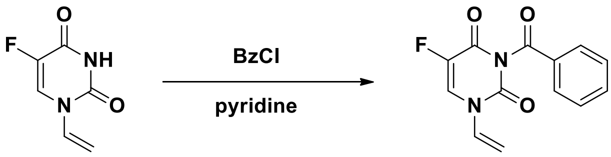
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.52 (d, *J* = 5.8 Hz, 1H, F-uracil vinyl-CH), 7.12 (ddd, *J* = 15.9, 9.1, 1.8 Hz, 1H, vinyl-CH), 5.11 – 4.79 (m, 2H, vinyl-CH_2).

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

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

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

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



43 44

In a flame-dried flask under nitrogen, 1-vinyl-fluorouracil (**43**) (0.12 g, 0.79 mmol, 1.0 eq) was stirred with pyridine (2 mL), and added dropwise over 10 min to a solution of benzoyl chloride (0.34 g, 2.4 mmol, 3 eq) in pyridine (0.7 mL) and stirred for 2 h at room temperature. Then the crude mixture was partitioned between water (10 mL) and AcOEt (10 mL). The aqueous layer was extracted three times with AcOEt (10 mL) and the organic layers were dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the dry residue was purified by column chromatography using a mixture of pentane/AcOEt (7:3 to 1:1) as eluting solvent. The pure product **44** (0.15 g, 0.58 mmol, 73% yield) was obtained as a white solid.

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

MP 128.6-129.3°C.

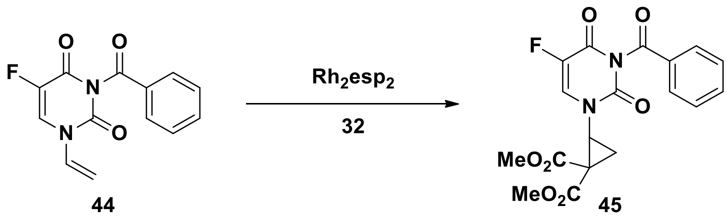
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.95 (dd, *J* = 8.3, 1.4 Hz, 2H, Ar-H), 7.75 – 7.64 (m, 2H, Ar-H and F-uracil vinyl-CH), 7.52 (t, *J* = 7.9 Hz, 2H, Ar-H), 7.12 (ddd, *J* = 15.9, 9.0, 1.8 Hz, 1H, vinyl-CH), 5.13 (dd, *J* = 15.8, 2.7 Hz, 1H, vinyl-CH_2), 4.99 (dd, *J* = 9.0, 2.8 Hz, 1H, vinyl-CH_2).

^{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 (45).



44 45

Diazomalonate **32** (0.21 g, 1.3 mmol, 1.2 eq), $Rh_2(esp)_2$ (0.002 g, 0.002 mmol, 0.02 mol%) and product **44** (0.29 g, 0.11 mmol, 1.0 eq) were stirred at room temperature in DCM (11 mL) in a flame-dried flask under nitrogen. After 1 hour, 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 **45** (0.40 g, 1.0 mmol, 93% yield) was obtained as a white foamy solid.

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

MP 62.7-64.4°C.

^{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).

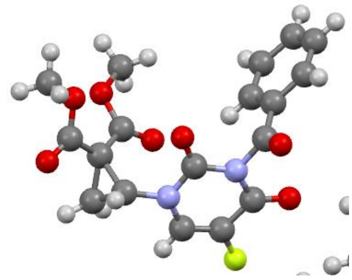
^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.1, 166.7, 156.0 (d, *J* = 27.2 Hz), 148.7, 139.7 (d, *J* = 240.3 Hz), 135.6, 130.8, 130.7, 129.2, 128.0 (d, *J* = 33.7 Hz), 53.3, 53.3, 42.9, 34.8, 20.3.

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).

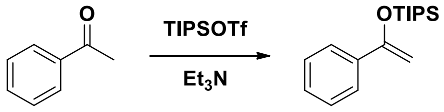
HRMS (ESI) calcd for $C_{18}H_{15}FN_2NaO_7^+$ $[M+Na]^+$ 413.0755; found 413.0763.

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



2.5 Dipolarophiles.

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



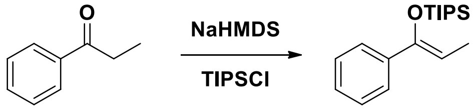
16 17

Following the reported procedure of Waser et al.,[1] acetophenone (**16**) (1.0 g, 8.3 mmol, 1 eq) was solubilized in DCM (8 mL) and triethylamine (1,73 mL, 12,5 mmol, 1.5 eq) was added at room temperature. Then at 0 °C tri*iso*propylsilyl trifluoromethanesulfonate (2,7 ml, 10 mmol, 1.2 eq) was added dropwise and the reaction mixture was stirred at room temperature for 8 h. The solvent was evaporated under a flow of nitrogen. The crude product was purified by column chromatography, eluting with pentane and NEt_3 1% to obtain the pure enol-ether **17** (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]

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



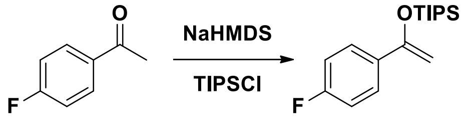
46 47

Following the reported procedure of Waser et al,[1] propiophenone (**46**) (0.50 mL, 3.7 mmol, 1eq) was solubilized in THF (15 mL) at -78°C and NaHMDS (2M solution in THF, 2.1 mL, 4.1 mmol, 1.1 eq) was added dropwise. The mixture was stirred 1 hour at room temperature and cooled down to -78 °C. TIPS-Cl (0.86 mL, 4.1 mmol, 1.1 eq) was added dropwise and the reaction mixture was stirred at room temperature for 8 h. The solvent was evaporated and the crude product was purified by column chromatography, eluting with pentane and NEt_3 1% to obtain the pure enol-ether **47** (0.46 g, 1.6 mmol, 43% yield) as a slightly yellow oil.

^{1}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]

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



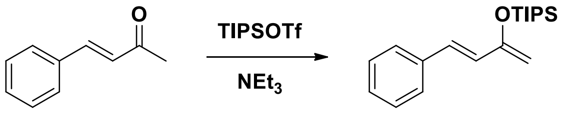
48 49

Following the reported procedure of Waser et al,[1] (4-fluorophenyl)ethanone (**48**) (0.44 mL, 3.6 mmol, 1eq) was solubilized in THF (15 mL) at -78°C and NaHMDS (2M solution in THF, 2.1 mL, 4.1 mmol, 1.1 eq) was added dropwise. The mixture was stirred 1 hour at room temperature and cooled down to -78°C. TIPS-Cl (0.86 mL, 4.1 mmol, 1.1 eq) was added dropwise and the reaction mixture was stirred at room temperature for 8 h. The solvent was evaporated and the crude product was purified by column chromatography, eluting with pentane and NEt_3 1% to obtain the pure enol-ether **49** (0.62 g, 2.1 mmol, 58% yield) as a slightly yellow oil.

^{1}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

Following the reported procedure of Waser et al.,[1] (*E*)-4-phenylbut-3-en-2-one (**50**) (0.42 g, 2.9 mmol, 1 eq) was solubilized in DCM (3 mL) and triethylamine (0.60 mL, 4.3 mmol, 1.5 eq) was added at room temperature. Then triisopropylsilyl trifluoromethanesulfonate (0.93 mL, 3.4 mmol, 1.2 eq) was added at 0 °C dropwise and the reaction mixture was stirred at room temperature for 8 h. The solvent was evaporated under a flow of nitrogen. The crude product was purified by column chromatography, eluting with pentane and NEt_3 1% to obtain the pure enol ether **51** (0.87 g, 2.9 mmol, quantitative yield) as a colorless oil.

RF (pentane) = 0.88.

^{1}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.

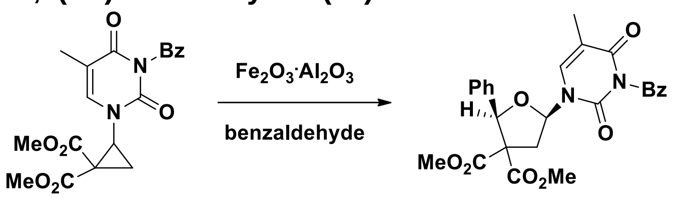
IR 4319 (w), 4056 (w), 2945 (m), 2867 (m), 1638 (w), 1464 (m), 1327 (s), 1026 (s), 883 (s).

HRMS (ESI) calcd for $C_{19}H_{31}OSi^+$ $[M+H]^+$ 303.2139; found 303.2140.

3. Scope of the reaction.

3.1 From thymine cyclopropanes.

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



7a 8a

Following the described procedure of Benfatti et al.[6] a flame-dried microwave vial was loaded under nitrogen with $FeCl_3$-Al_2O_3 (26 mg, 0.020 mmol, 5 mol %) and dimethyl 2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)cyclopropane-1,1-dicarboxylate (**7a**) (0.15 g, 0.39 mmol, 1.0 eq). Then, anhydrous DCM (1 mL) was added followed by benzaldehyde (0.059 mL, 0.58 mmol, 1.2 eq). The reaction mixture was stirred for 2 h at room temperature. After solvent removal under reduced pressure, the crude product was purified by column chromatography using a mixture of AcOEt/hexane (7:3) with 1% NEt_3 as eluting solvent. The pure product **8a** (0.15 g, 0.31 mmol, 80% yield) was obtained as a white solid.

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

MP 93.2-95.1 °C.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.07 (d, *J* = 1.4 Hz, 1H, thymine vinyl-CH), 7.95 (dd, *J* = 8.4, 1.4 Hz, 2H, Ar-H), 7.69 – 7.59 (m, 1H, Ar-H), 7.54 – 7.43 (m, 4H, Ar-H), 7.40 – 7.33 (m, 3H, Ar-H), 6.36 (t, *J* = 7.5 Hz, 1H, tetrahydrofuran-NCH), 5.61 (s, 1H, tetrahydrofuran-CH), 3.80 (s, 3H, ester methyl), 3.15 (s, 3H, ester methyl), 2.99 (dd, *J* = 14.5, 7.4 Hz, 1H, tetrahydrofuran-CH_2), 2.80 (dd, *J* = 14.6, 7.7 Hz, 1H, tetrahydrofuran-CH_2), 2.10 (d, *J* = 1.2 Hz, 3H, thymine methyl).

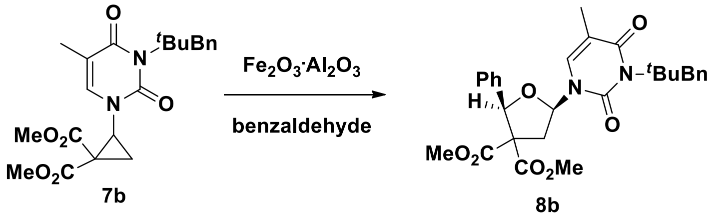
^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.8, 169.7, 168.8, 162.7, 149.5, 135.8, 135.2, 135.1, 131.5, 130.5, 129.1, 128.8, 128.2, 126.5, 112.1, 82.5, 81.5, 63.8, 53.2, 52.8, 39.1, 13.0.

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

[7] F. Benfatti, F. de Nanteuil, J. Waser, *Org. Lett.* **2012**, *14*, 386–389.

HRMS (ESI) calcd for $C_{26}H_{24}N_2NaO_8^+$ [M+Na]$^+$ 515.1425; found 515.1435.

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



Following the described procedure of Benfatti et al.[7] a flame-dried microwave vial under nitrogen was loaded with $FeCl_3$-Al_2O_3 (3.5 mg, 0.0035 mmol, 5 mol %) and dimethyl 2-(3-(4-(*tert*-butyl)benzyl)-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)cyclopropane-1,1-dicarboxylate (**7b**) (0.03 g, 0.07 mmol, 1.0 eq). Then, anhydrous dichloromethane (1 mL) followed by benzaldehyde (10 µl, 0.10 mmol, 1.5 eq) were added. The mixture was stirred for 2 h at room temperature. Afterwards, it was concentrated under reduced pressure with silica and NEt_3 (0.3 mL). The dried residue was purified by column chromatography using a mixture of hexane/ethylacetate (7:3) with 1% NEt_3 as eluting solvent. The pure product **8b** (20 mg, 0.040 mmol, 55% yield) was obtained as a white solid.

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

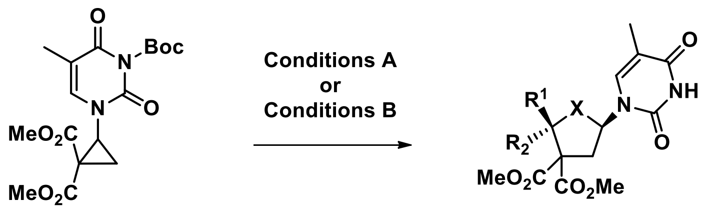
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 (d, *J* = 1.6 Hz, 1H, thymine vinyl-CH), 7.47 – 7.39 (m, 4H, Ar-H), 7.37 – 7.28 (m, 5H, Ar-H), 6.40 (t, *J* = 7.6 Hz, 1H, tetrahydrofuran-NCH), 5.60 (s, 1H, tetrahydrofuran-OCH), 5.11 (s, 2H, benzylic-CH_2), 3.80 (s, 3H, ester-methyl), 3.12 (s, 3H, ester methyl), 2.92 (dd, *J* = 14.5, 7.6 Hz, 1H, tetrahydrofuran-CH_2), 2.76 (dd, *J* = 14.5, 7.5 Hz, 1H, tetrahydrofuran-CH_2), 2.06 (d, *J* = 1.2 Hz, 3H,thymine-CH_3), 1.28 (s, 9H, ^{t}Bu).

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

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

HRMS (ESI) calcd for $C_{30}H_{34}N_2NaO_7^+$ [M+Na]$^+$ 557.2258; found 557.2266.

General procedures for annulation reaction



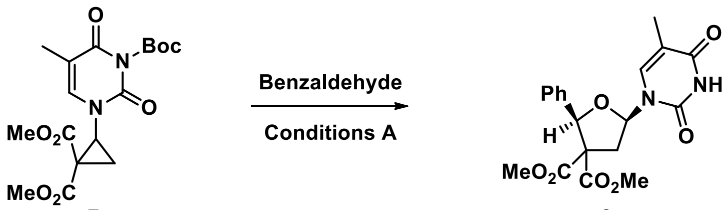
a) Conditions A

Dimethyl 2-(3-(*tert*-butoxycarbonyl)-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(*2H*)-yl)cyclopropane-1,1-dicarboxylate (**7c**) (0.15 g, 0.40 mmol 1.0 eq), aldehyde (0.48 mmol, 1.2 eq) and $In(OTf)_3$ (0.045 g, 0.080 mmol, 0.2 eq) were stirred under nitrogen in a flame-dried sealed microwave vial with anhydrous DCM (2.0 mL) at room temperature for 2 h. Then, NEt_3 (0.9 mL) was added to quench the reaction and the crude mixture was concentrated under reduced pressure. After a rapid filtration on a silica plug with AcOEt and removal of the solvent, the crude product was heated at 70 °C in EtOH (3 mL) in a sealed microwave vial for 18 h. The mixture was concentrated under reduced pressure and purified by column chromatography with a gradient mixture of pentane/AcOEt from 7:3 up to 1:1 and the column was washed with straight AcOEt.

b) Conditions B

Dimethyl 2-(3-(*tert*-butoxycarbonyl)-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)cyclopropane-1,1-dicarboxylate (**7c**) (0.15 g, 0.40 mmol 1.0 eq) and the ketone or sillylenol ether (0.48 mmol, 1.2 eq) were stirred under nitrogen in a flame-dried sealed microwave vial with anhydrous DCM (2.0 mL) and cooled down to -20 °C. Then, a 0.43 M tin(IV) chloride solution (0.09 mL, 0.04 mmol, 0.1 eq) was added and the reaction mixture was stirred for 2 h at -20 °C. NEt_3 (0.9 mL) was added at -20 °C to quench the reaction and the reaction mixture was allowed to reach room temperature. The crude mixture was concentrated under reduced pressure. After a rapid filtration on a silica plug with AcOEt and removal of the solvent, the crude product was heated at 70 °C in EtOH (3 mL) in a sealed microwave vial for 18 h. The mixture was concentrated under reduced pressure and purified by column chromatography with a gradient mixture of pentane/AcOEt from 7:3 up to 1:1 and the column was washed with straight AcOEt.

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



7c 8c

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

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

MP 206.9-208.1 °C.

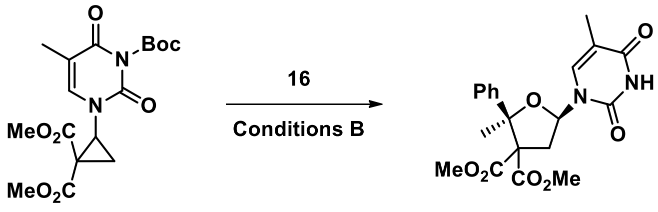
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.47 (s, 1H, thymine NH), 7.94 (d, *J* = 1.6 Hz, 1H, thymine vinyl-CH), 7.48 – 7.40 (m, 2H, Ar-H), 7.40 – 7.27 (m, 3H, Ar-H), 6.37 (t, *J* = 7.6 Hz, 1H, tetrahydrofuran-NCH), 5.61 (s, 1H, tetrahydrofuran-CH), 3.81 (s, 3H, ester methyl), 3.13 (s, 3H, ester methyl), 2.95 (dd, *J* = 14.5, 7.6 Hz, 1H, tetrahydrofuran-CH_2), 2.78 (dd, *J* = 14.5, 7.7 Hz, 1H, tetrahydrofuran-CH_2), 2.06 (d, *J* = 1.3 Hz, 3H, thymine methyl).

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

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

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

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



7c **8d**

Following the conditions B, using acetophenone (**16**) (0.058 g, 0.48 mmol, 1.2 eq), the pure product **8d** (0.15 g, 0.38 mmol, 94% yield) was obtained as a white solid.

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

MP 246.8-247.3°C.

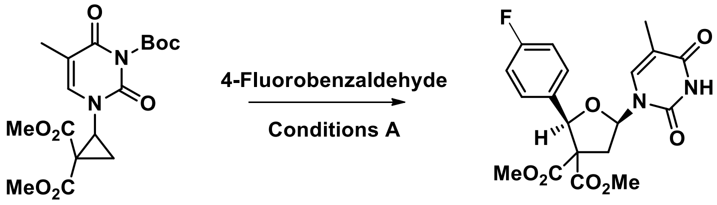
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.59 (s, 1H, thymine NH), 8.18 (d, *J* = 1.7 Hz, 1H, thymine vinyl-CH), 7.72 – 7.65 (m, 2H, Ar-H), 7.38 – 7.24 (m, 3H, Ar-H), 6.43 (dd, *J* = 8.2, 5.6 Hz, 1H, tetrahydrofuran-NCH), 3.79 (s, 3H, ester methyl), 3.16 (s, 3H, ester methyl), 3.11 (dd, *J* = 15.0, 8.2 Hz, 1H, tetrahydrofuran-CH_2) 2.77 (dd, *J* = 14.9, 5.5 Hz, 1H, tetrahydrofuran-CH_2) 2.04 (d, *J* = 1.3 Hz, 3H, thymine methyl), 1.86 (s, 3H, tetrahydrofuran methyl).

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

IR 1733 (m), 1706 (m), 1663 (m), 1272 (s), 1207 (w), 1126 (w), 1077 (w).

HRMS (ESI) calcd for $C_{20}H_{22}NNaO_7^+$ $[M+Na]^+$ 425.1319; found 425.1320.

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



7c **8e**

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

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

MP 218.8-220.3 °C.

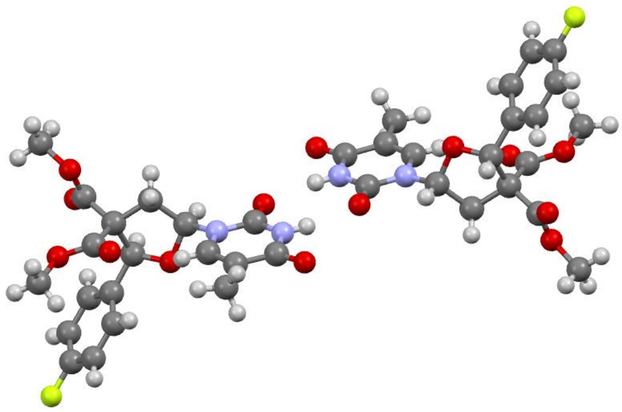
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.54 – 8.46 (m, 1H, thymine NH), 7.93 (d, *J* = 1.5 Hz, 1H, thymine vinyl-CH), 7.49 – 7.39 (m, 2H, Ar-H), 7.10 – 6.99 (m, 2H, Ar-H), 6.37 (t, *J* = 7.6 Hz, 1H, tetrahydrofuran-NCH), 5.56 (s, 1H, tetrahydrofuran-CH), 3.81 (s, 3H, ester methyl), 3.20 (s, 3H, ester methyl), 2.93 (dd, *J* = 14.6, 7.5 Hz, 1H, tetrahydrofuran-CH_2), 2.77 (dd, *J* = 14.6, 7.8 Hz, 1H, tetrahydrofuran-CH_2), 2.05 (d, *J* = 1.2 Hz, 3H, thymine methyl).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.8, 162.9 (d, *J* = 249 Hz), 150.4, 135.8, 131.0 (d, *J* = 3.2 Hz), 128.5 (d, *J* = 8.2 Hz), 128.4, 115.2 (d, *J* = 21.6 Hz), 115,0, 112.2, 81.7, 81.2, 63.6, 53.2, 52.9, 38.8, 12.8.

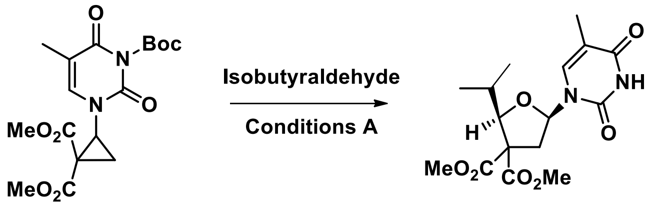
IR 3192 (w), 3069 (w), 1729 (s), 1695 (s), 1512 (m), 1281 (s), 1225 (m), 1094 (m), 1054 (m), 915 (m).

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

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



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



7c 8f

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

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

MP 157.7-160.8 °C.

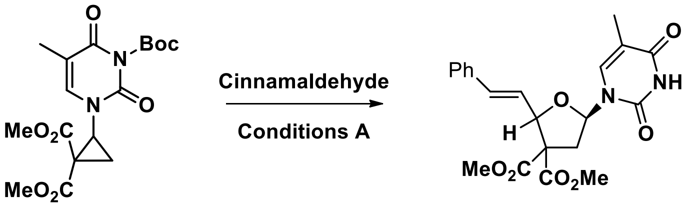
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.45 (s, 1H, N-H), 7.62 (d, *J* = 1.5 Hz, 1H, thymine vinyl-CH), 6.12 (t, *J* = 7.1 Hz, 1H, tetrahydrofuran-NCH), 4.14 (d, *J* = 7.8 Hz, 1H, tetrahydrofuran-OCH), 3.80 (s, 3H, ester methyl), 3.78 (s, 3H, ester methyl), 2.70 (dd, *J* = 14.5, 6.5 Hz, 1H, tetrahydrofuran-CH_2), 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-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(*2H*)-yl)-2-((*E*)-styryl)dihydrofuran-3,3(*2H*)-dicarboxylate. (8g)



7c 8g

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

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

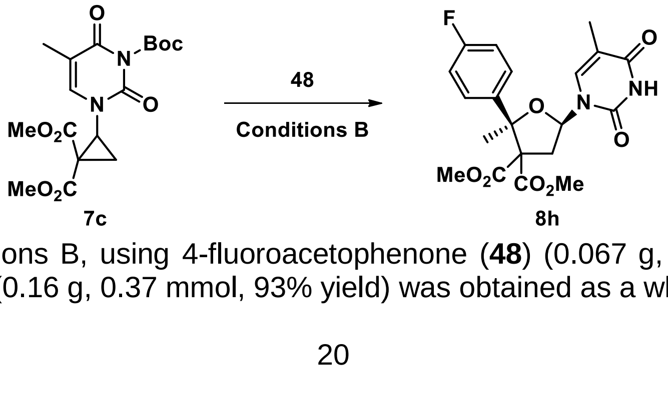
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.82 (s, 1H, NH), 7.70 (d, *J* = 1.3 Hz, 1H, thymine vinyl-CH, major diastereoisomer), 7.35 – 7.17 (m, 10H, Ar-H, both diastereoisomers), 7.14 (d, *J* = 1.3 Hz, 1H, thymine vinyl-CH, minor diastereoisomer), 6.72 (dd, *J* = 16.0, 1.3 Hz, 1H vinyl C-H, major and minor 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-(4-fluorophenyl)-2-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)dihydrofuran-3,3(2H)-dicarboxylate (8h).



7c 8h

Following the conditions B, using 4-fluoroacetophenone (**48**) (0.067 g, 0.48 mmol, 1.2 eq), the pure product **8h** (0.16 g, 0.37 mmol, 93% yield) was obtained as a white solid.

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

MP 248.8-250.2 °C.

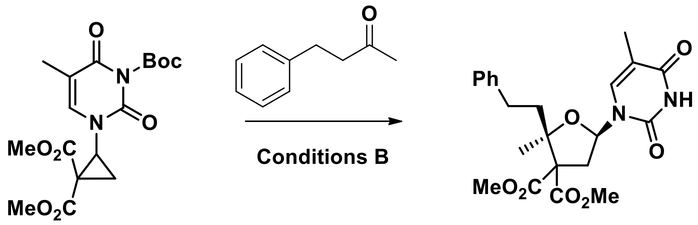
^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.47 (s, 1H, thymine NH), 8.07 (d, *J* = 1.5 Hz, 1H, thymine vinyl-CH), 7.70 – 7.60 (m, 2H, Ar-H), 7.20 (t, *J* = 8.9 Hz, 2H, Ar-H), 6.36 (dd, *J* = 8.3, 5.5 Hz, 1H, tetrahydrofuran-NCH), 3.75 (s, 3H, ester methyl), 3.26 (dd, *J* = 14.9, 8.3 Hz, 1H, , tetrahydrofuran-CH_2), 3.13 (s, 3H, ester methyl), 2.71 (dd, *J* = 14.9, 5.6 Hz, 1H, , tetrahydrofuran-CH_2), 1.87 (d, *J* = 1.2 Hz, 3H, thymine methyl), 1.79 (s, 3H, tetrahydrofuran methyl).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 170.6, 168.9, 164.1, 161.9 (d, *J* = 243.9 Hz), 151.1, 137.4 (d, *J* = 3.0 Hz), 136.7, 128.4 (d, *J* = 8.2 Hz), 114.9 (d, *J* = 21.3 Hz), 109.9, 87.1, 80.6, 67.2, 53.3, 53.0, 38.5, 25.9, 13.2.

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

HRMS (ESI) calcd for $C_{20}FH_{22}N_2O_7^+$ $[M+H]^+$ 421.1406; found 421.1405.

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



7c 8i

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

MP 167.9-168.7 °C.

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

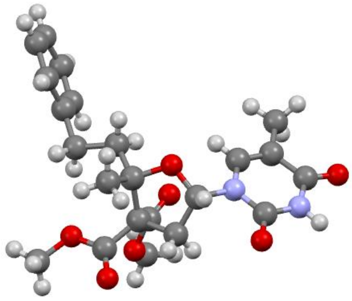
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.07 (s, 1H, thymine NH), 7.74 (q, *J* = 1.2 Hz, 1H, thymine vinyl-CH), 7.30 (dd, *J* = 8.5, 6.6 Hz, 2H, Ar-H), 7.24 – 7.17 (m, 3H, Ar-H), 6.18 (dd, *J* = 7.7, 5.3 Hz, 1H, tetrahydrofuran-NCH), 3.78 (s, 3H, ester methyl), 3.72 (s, 3H, ester methyl), 3.23 – 3.05 (m,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

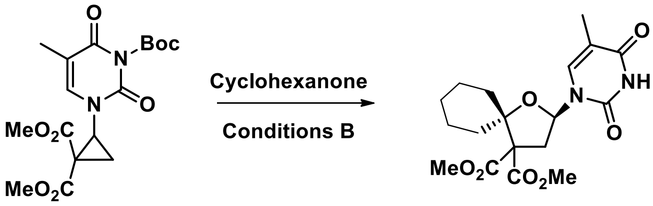
IR 3193 (w), 3060 (w), 2957 (w), 1735 (s), 1692 (s), 1468 (m), 1266 (s), 1097 (m), 914 (m).

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. (8j)



7c 8j

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

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

MP 184.1-185.6 °C.

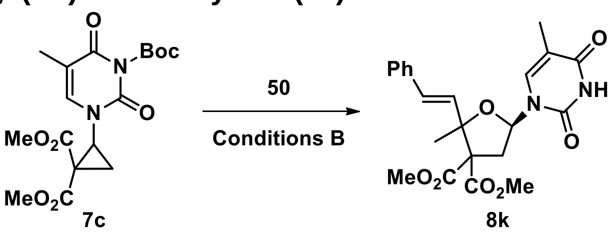
^{1}**H NMR** (400 MHz, Chloroform-*d*) δ 8.25 – 8.08 (br s, 1H, thymine NH), 7.70 (d, *J* = 1.5 Hz, 1H, thymine vinyl-CH), 6.03 (dd, *J* = 7.6, 5.2 Hz, 1H, tetrahydrofuran-NCH), 3.71 (s, 3H, ester methyl), 3.68 (s, 3H, ester methyl), 3.11 (dd, *J* = 14.9, 7.6 Hz, 1H, tetrahydrofuran-CH_2), 2.39 (dd, *J* = 14.9, 5.3 Hz, 1H, tetrahydrofuran-CH_2), 1.91 (d, *J* = 1.2 Hz, 3H, thymine methyl), 1.75 – 1.47 (m, 8H, cyclohexane C-H), 1.22 – 1.12 (m, 2H, cyclohexane C-H).

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

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

HRMS (ESI) calcd for $C_{18}H_{24}N_2NaO_7$ [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. (8k)



7c 8k

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

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

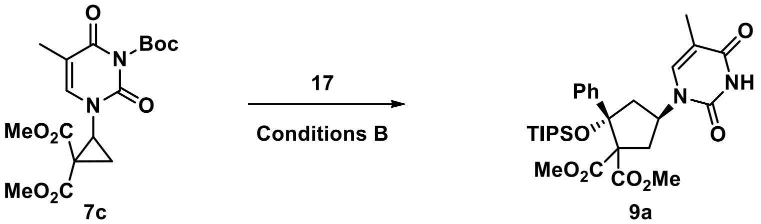
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.19 (br.s, 1H, N-H), 7.84 (d, *J* = 1.3 Hz, 1H, , thymine vinyl-CH, major diastereoisomer), 7.59 (d, *J* = 1.3 Hz, 1H, , thymine vinyl-CH, minor diastereoisomer), 7.36 – 7.16 (m, 5H, Ar-H), 6.69 (d, *J* = 15.9 Hz, 1H, vinyl C-H, minor diastereomer), 6.65 (d, *J* = 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-4-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(*2H*)-yl)-2-phenyl-2-((triisopropylsilyl)oxy)cyclopentane-1,1-dicarboxylate. (9a)



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

RF (pent/AcOEt (1:1)) = 0.56.

MP 81.8-83.2 °C.

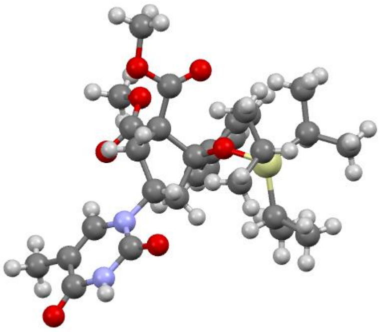
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.40 (s, 1H, thymine N-H), 7.86 (d, *J* = 1.6 Hz, 1H, thymine vinyl-CH), 7.82 – 7.74 (m, 2H, Ar-H), 7.34 – 7.27 (m, 3H, Ar-H), 5.70 (ddd, *J* = 11.4, 9.3, 5.7 Hz, 1H, cyclopentane-NCH), 3.76 (s, 3H, ester methyl), 3.29 (m, 4H, ester methyl and cyclopentane-CH_2),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

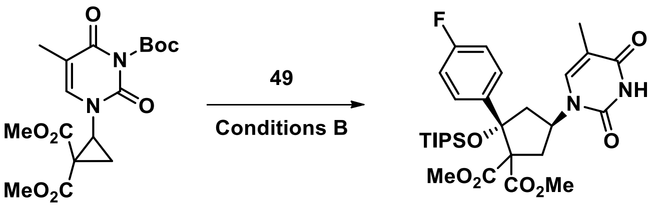
IR 2950 (w), 2868 (w), 1681 (s), 1467 (m), 1434 (w), 1392 (w), 1259 (s), 1135 (m), 1090 (m).

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**



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



7c 9b

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

MP 105.6-106.7 °C.

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

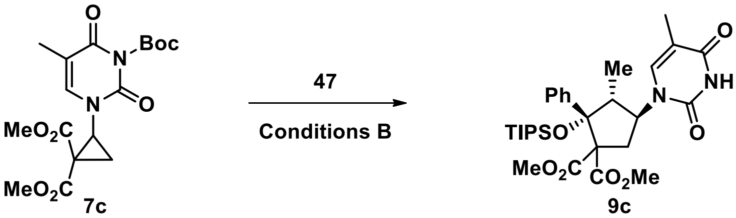
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.14 (d, *J* = 3.8 Hz, 1H, thymine-NH), 7.89 – 7.78 (m, 3H, Ar-H and thymine vinyl-CH), 7.03 (t, *J* = 8.7 Hz, 2H, Ar-H), 5.71 (tt, *J* = 11.4, 7.0 Hz, 1H, cyclopentane-NCH), 3.79 (s, 3H, methyl ester), 3.37 (s, 3H, ester methyl), 3.36 – 3.31 (m, 1H, cyclopentane-CH_2). 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.

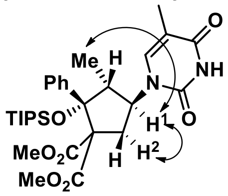
IR 3196 (w), 2951 (w), 2869 (w), 1681 (s), 1513 (w), 1466 (w), 1260 (m), 1098 (m), 911 (m), 731 (s).

HRMS (ESI) calcd for $C_{29}FH_{42}N_2O_7Si^+$ $[M+H]^+$ 577.2740; found 577.2719.

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



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



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

MP 127.4-128.3 °C.

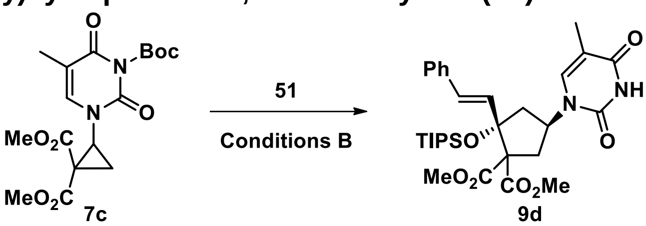
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06 (s, 1H, thymine NH), 8.01 (d, *J* = 1.5 Hz, 1H, thymine vinyl-CH), 7.73 – 7.66 (m, 2H, Ar-H), 7.39 – 7.25 (m, 3H, Ar-H), 5.36 (td, *J* = 11.4, 6.8 Hz, 1H cyclopentane -NCH), 3.70 (s, 3H, ester methyl), 3.35 (dq, *J* = 13.6, 6.8 Hz, 1H, tetrahydrofuran-CH), 3.20 (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.

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. (9d)



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

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

^{1}H NMR (400 MHz, Chloroform-*d,* Major diastereoisomer) 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).

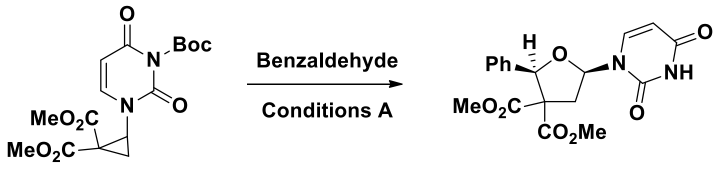
^{13}C NMR (101 MHz, Chloroform-*d*, Major diastereoisomer) δ 172.4, 168.8, 163.7, 151.1, 137.6, 136.1, 130.7, 128.8, 128.8, 128.2, 126.7, 111.5, 86.7, 69.9, 53.1, 52.6, 51.4, 41.1, 37.1, 29.7, 18.2, 18.0, 13.1, 12.8.
TIPS methyls are giving 2 differents signals(18.2 and 18.0).

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.

3.2 From uracil cyclopropane.

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



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

RF (AcOEt) = 0.65.

MP 209.0-210.7°C.

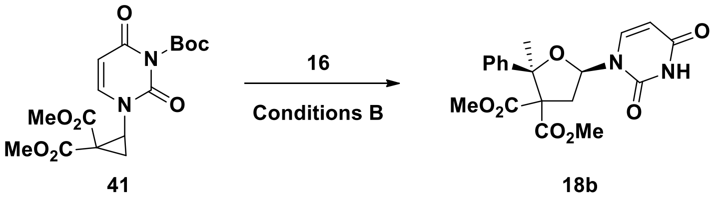
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.07 (s, 1H, NH), 8.05 (d, *J* = 8.2 Hz, 1H, uracil CH), 7.42 – 7.29 (m, 2H, Ar-H), 7.24 (m, 3H, Ar-H), 6.29 (t, *J* = 7.4 Hz, 1H, tetrahydrofuran N-CH), 5.84 (d, *J* = 8.1 Hz, 1H, uracil CH), 5.52 (s, 1H, tetrahydrofuran-CH), 3.72 (s, 3H, ester CH_3), 3.03 (s, 3H, 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-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methyl-2-phenyldihydrofuran-3,3(2H)-dicarboxylate (18b).



Following the conditions B, using acetophenone (**16**) (0.058 g, 0.48 mmol, 1.2 eq) and the cyclopropane **41** (0.16 g, 0.40 mmol, 1 eq), the pure product **18b** (0.12 g, 0.30 mmol, 76% yield) was obtained as a white powder.

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

MP 235.8-238.4°C.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.44 (s, 1H, NH), 8.18 (d, *J* = 8.2 Hz, 1H, uracil CH), 7.71 – 7.51 (m, 2H, ArH), 7.46 – 7.23 (m, 3H, ArH), 6.29 (dd, *J* = 8.2, 5.1 Hz, 1H, 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).

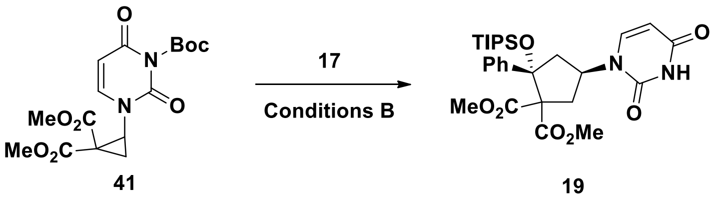
^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 170.6, 168.8, 163.6, 151.1, 141.1, 141.1, 128.2, 126.0, 102.3, 87.9, 81.2, 67.0, 53.2, 52.9, 25.8.

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



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

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

MP 67.7-77.0°C.

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

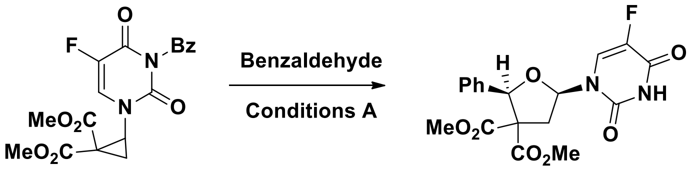
HRMS (ESI) calcd for $C_{28}H_{40}N_2NaO_7Si^+$ $[M+Na]^+$ 567.2497; found 567.2496.

3.3 From 5-fluoro-uracil cyclopropane.

General procedure for Benzoyl removal.

The crude product was dissolved in EtOH (2 mL) and stirred at room temperature for 2 hours with NH_4OH (0.6 mL, 40 eq, 25%). The mixture was evaporated to dryness and directly submitted to the column chromatography using a gradient of solvent from pentane/AcOEt (7:3) up to (3:7).

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



45 20a

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

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

MP 227.9-228.5°C.

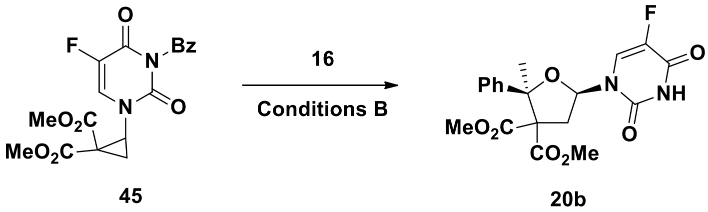
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.22 (s, 1H, NH), 8.25 (d, *J* = 6.1 Hz, 1H, F-uracil CH), 7.47 – 7.34 (m, 2H, ArH), 7.34 – 7.22 (m, 3H, ArH), 6.31 (ddd, *J* = 7.8, 6.9, 1.7 Hz, 1H, tetrahydrofuran N-CH), 5.53 (s, 1H, tetrahydrofuran CH), 3.74 (s, 3H, ester CH_3), 3.08 (s, 3H, ester CH_3), 2.80 (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-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-methyl-2-phenyldihydrofuran-3,3(2H)-dicarboxylate (20b).



Following the conditions B, using acetophenone (**16**) (0.058 g, 0.48 mmol, 1.2 eq) and the corresponding cyclopropane **45** (0.16 g, 0.40 mmol, 1 eq) at -40 °C, followed by the benzoyl deprotection, the pure product **20b** (0.12 g, 0.28 mmol, 71% yield) was obtained as a white powder.

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

MP 209.3-210.2°C.

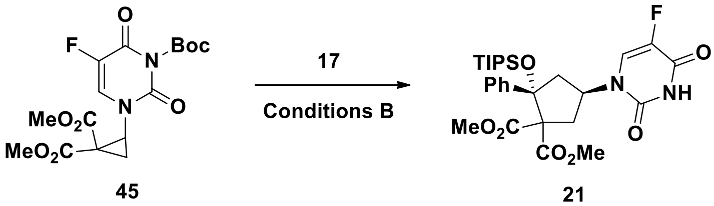
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.98 (d, *J* = 4.6 Hz, 1H, NH), 8.50 (d, *J* = 6.5 Hz, 1H, F-uracil CH), 7.77 – 7.65 (m, 2H, ArH), 7.51 – 7.16 (m, 3H, ArH), 6.42 (ddd, *J* = 8.2, 5.1, 1.7 Hz, 1H, tetrahydrofuran N-CH), 3.80 (s, 3H, ester CH_3), 3.18 (dd, *J* = 15.1, 8.2 Hz, 1H, tetrahydrofuran 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-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenyl-2-((triisopropylsilyl)oxy)cyclopentane-1,1-dicarboxylate (21).



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

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

^{1}H NMR (400 MHz, Chloroform-*d*) 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.

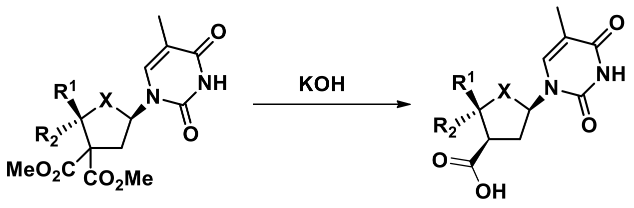
IR 3194 (w), 3067 (w), 2951 (w), 2855 (w), 1718 (s), 1466 (w), 1256 (s), 1134 (m), 991 (m), 788 (m), 740 (m).

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

4. Thymine based nucleoside analogues derivatizations.

4.1 Acids.

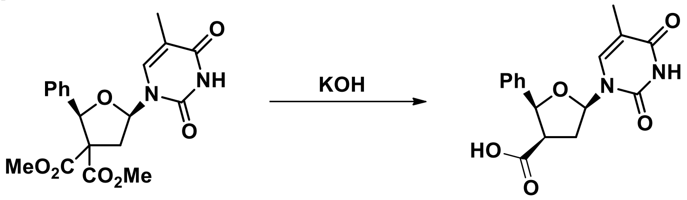
General procedure for hydrolysis and decarboxylation reaction



8c, 8d, 8g, 8h. **52-55**

Compound **8** (1 eq) and KOH (4 eq) were stirred under nitrogen in a dried and sealed microwave vial with dry methanol (0.06 mL) for 2 days at 70 °C. The thick yellow mixture was cooled down to room temperature and acidified with a 0.1 M HCl solution (0.5 mL). The mixture was extracted 3 times with AcOEt (2 mL), the organic layers were dried over anhydrous $MgSO_4$ 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 (52).



8c **52**

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

RF (AcOEt) = 0.23.

MP 123.2-125.3°C.

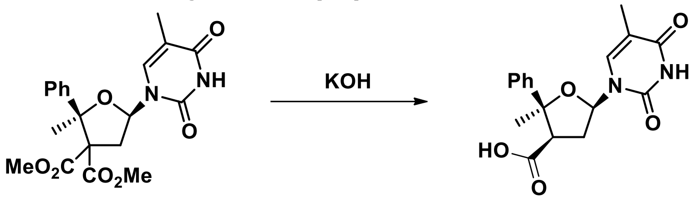
^{1}**H NMR** (400 MHz, Methanol-*d*$_4$) δ 7.37 (d, *J* = 8.6 Hz, 3H, Ar-H and thymine vinyl-CH), 7.32 – 7.22 (m, 3H, Ar-H), 6.20 – 6.08 (m, 1H, tetrahydrofuran-NCH), 5.01 (d, *J* = 8.7 Hz, 1H, tetrahydrofuran-CH), 3.35 – 3.24 (m, 1H, tetrahydrofuran-CH), 2.68 (dt, *J* = 13.1, 8.1 Hz, 1H tetrahydrofuran-CH_2), 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).

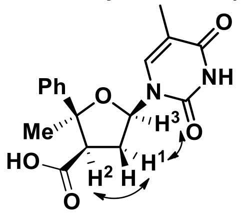
HRMS (ESI) calcd for $C_{16}H_{16}N_2NaO_5^+$ [M+Na]$^+$ 339.0951; found 339.0944.

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



8d 53

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



RF (AcOEt) = 0.18.

MP 236.2-236.7 °C.

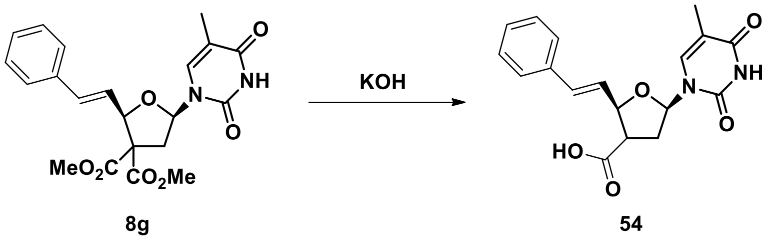
^{1}H NMR (400 MHz, Acetone-d_6) δ 11.39 (br s, 1H, COOH), 10.01 (s, 1H, thymine NH), 7.70 – 7.62 (m, 2H, Ar-H), 7.48 – 7.28 (m, 3H, Ar-H), 7.25 (q, J = 1.1 Hz, 1H, thymine vinyl-CH), 6.46 (dd, J = 7.5, 4.2 Hz, 1H, tetrahydrofuran-NCH), 3.75 (t, J = 8.7 Hz, 1H, tetrahydrofuran-CH), 2.99 (ddd, J = 14.1, 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.

5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-((E)-styryl)tetrahydrofuran-3-carboxylic acid (54).



Following the general procedure for hydrolysis and decarboxylation reaction, using compound **8g** (0.14 g, 0.34 mmol, 1 eq) and KOH (0.080 g, 1.4 mmol, 4.0 eq) in dry MeOH (1.4 mL). A mixture of unseparable monoacids (ratio 5:1 obtained by integration of the proton at 5.17 ppm and 4.76 ppm) **54** (82 mg, 0.24 mmol, 71% yield) was obtained as a white solid.

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

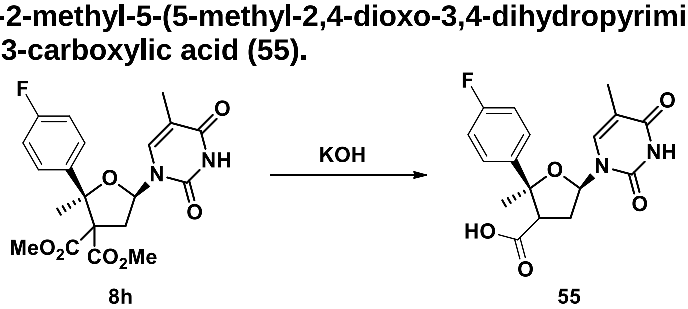
^{1}H NMR (400 MHz, Methanol-d_4) δ 7.65 (s, 1H, thymine vinyl-CH, minor diastereoisomer), 7.55 (s, 1H, thymine vinyl-CH, major diastereoisomer), 7.49 (d, J = 7.8 Hz, 4H, Ar-H, major and minor diastereoisomers), 7.40 – 7.25 (m, 6H, Ar-H, major and minor diastereoisomers), 6.76 (d, J = 15.9 Hz, 2H, vinyl-CH, major and minor diastereoisomers), 6.48 (ddd, J = 16.1, 7.2, 1.7 Hz, 1H, vinyl-CH, major diastereoisomer), 6.34 (ddd, J = 16.0, 6.7, 1.7 Hz, 1H, vinyl-CH, minor diastereoisomers), 6.26 – 6.17 (m, 2H, tetrahydrofuran-NCH, major and minor diastereoisomers), 5.17 (t, J = 7.0 Hz, 1H, tetrahydrofuran-CH, minor diastereoisomer), 4.76 (t, J = 7.7 Hz, 1H, tetrahydrofuran-CH, major diastereoisomer), 3.25 (q, J = 8.9 Hz, 1H, tetrahydrofuran-CH, major diastereoisomer), 3.18 (q, J = 8.9 Hz, , tetrahydrofuran-CH, major diastereoisomer), 2.86 – 2.71 (m, 2H, , tetrahydrofuran-CH_2, major and minor diastereoisomers), 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-(4-Fluorophenyl)-2-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3-carboxylic acid (55).



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

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

MP 193.4-194.2 °C.

^{1}H NMR (400 MHz, Acetone-*d*$_6$) 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).

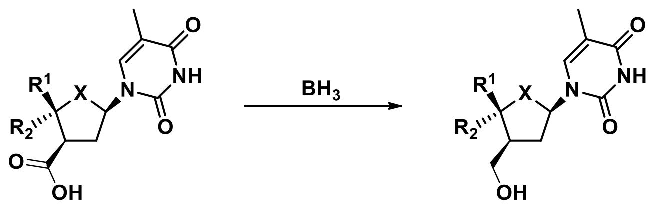
^{13}C NMR (101 MHz, Acetone-*d*$_6$) δ 174.7, 164.3, 164.2, 164.0, 162.8 (d, *J* = 244.1 Hz), 162.7 (d, *J* = 244.1 Hz). 151.4, 151.3, 142.7 (d, *J* = 3.0 Hz), 139.6 (d, *J* = 2.9 Hz), 137.8, 137.5, 128.5 (d, *J* = 8.1 Hz), 128.4 (d, *J* = 8.2 Hz), 115.5 (d, *J* = 21.4 Hz), 115.1 (d, *J* = 21.4 Hz), 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.

4.2 Alcohols.

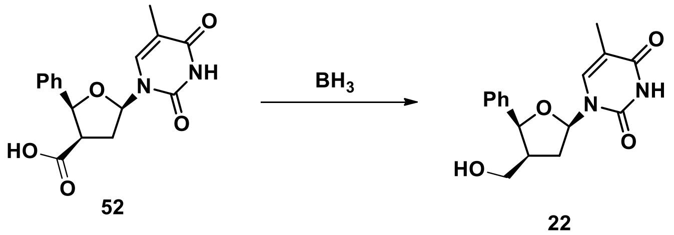
General procedure for reduction of carboxylic acids.



52-55 22-25

The carboxylic acid (1 eq) was solubilized in dry THF in a dried round bottom flask under nitrogen. The reaction mixture under nitrogen was cooled to 0 °C and dimethylsulfide borane solution (2 M in THF, 0,042 mL, 0.083 mmol, 2.2 eq) was added dropwise. The reaction was allowed to slowly warm up and was stirred under nitrogen for 16 h. The reaction mixture was quenched by addition of a saturated solution of Na_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 (22).



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

RF (AcOEt) = 0.34.

MP 68.1-69.4°C.

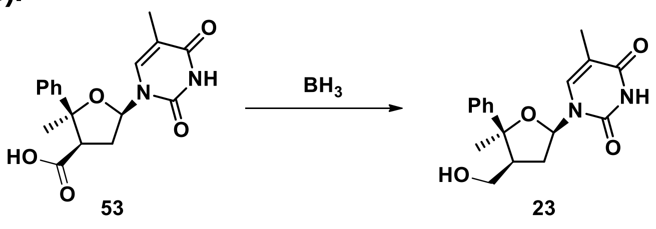
^{1}H NMR (400 MHz, Methanol-d_4) δ 7.53 – 7.47 (m, 1H, thymine vinyl-CH), 7.49 – 7.28 (m, 5H, Ar-H), 6.29 – 6.09 (m, 1H, tetrahydrofuran-NCH), 4.78 (d, *J* = 8.6 Hz, 1H , tetrahydrofuran-CH), 3.68 (dd, *J* = 11.2, 4.4 Hz, 1H , -C*H*$_2$OH), 3.64 – 3.53 (dd, *J* = 11.2, 5.6 Hz, 1H , -C*H*$_2$OH), 2.61 (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-methyl-5-phenyltetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (23).



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

RF (AcOEt) = 0.13.

MP 79.4-83.4°C.

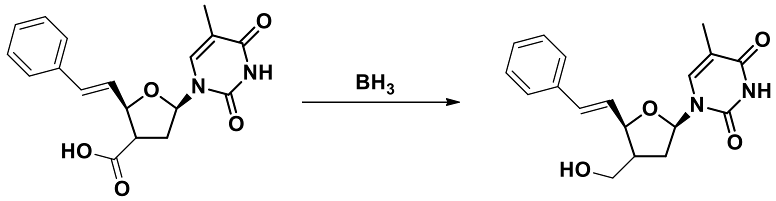
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.60 (s, 1H, thymine-NH), 7.46 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.39 – 7.22 (m, 3H, Ar-H), 6.82 (s, 1H, thymine vinyl-CH), 6.21 (d, *J* = 3.6 Hz, 1H, tetrahydrofuran-NCH), 3.96 (dd, *J* = 10.5, 5.4 Hz, 1H, -C*H*$_2$OH), 3.74 (dd, *J* = 10.7, 7.9 Hz, 1H, -C*H*$_2$OH),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

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



54 24

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

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

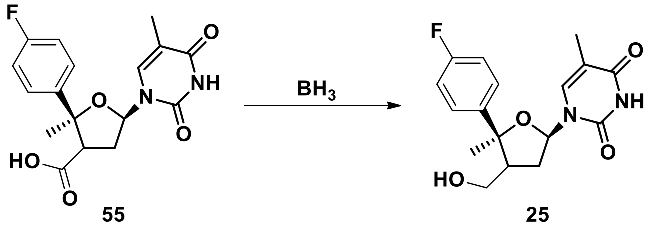
^{1}H NMR (400 MHz, Chloroform-*d*, major diastereoisomer) δ 8.24 (br.s, 1H, thymine-NH), 7.40 – 7.20 (m, 6H, Ar-H and thymine vinyl-CH), 6.67 (d, *J* = 16.0 Hz, 1H, vinyl-CH), 6.24 (dd, *J* = 15.8, 7.1 Hz, 1H, vinyl-CH), 6.07 (dd, *J* = 6.7, 3.6 Hz, 1H, tetrahydrofuran-NCH), 4.42 (t, *J* = 7.5 Hz, 1H, tetrahydrofuran-CH), 3.74 (dd, *J* = 10.7, 5.0 Hz, 1H, -CH_2OH), 3.68 (dd, *J* = 10.7, 5.1 Hz, 1H, -CH_2OH), 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.

5-(4-Fluorophenyl)-4-(hydroxymethyl)-5-methyltetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (25).



55 25

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

RF (AcOEt) = 0.53.

MP 192.3-193.8°C (decomp.).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.40 (s, 1H, thymine-NH, minor and major 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).

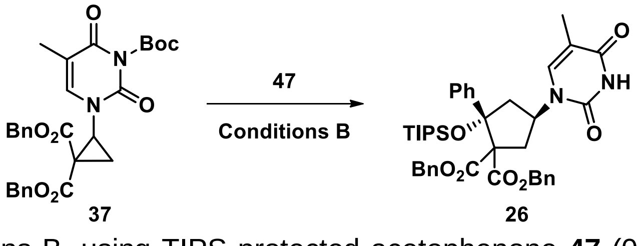
^{13}C NMR (101 MHz, Chloroform-*d*, Major diastereoisomer) δ 163.5, 162.1 (d, *J* = 247.3 Hz), 150.3, 141.5 (d, *J* = 3.6 Hz), 136.0, 127.0 (d, *J* = 8.0 Hz), 115.3 (d, *J* = 21.3 Hz), 110.5, 87.3, 84.9, 62.5, 47.8, 36.5, 24.3, 12.6.

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.

4.3 Carbonucleoside alcohol.

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



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

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

MP 69.4-73.1°C.

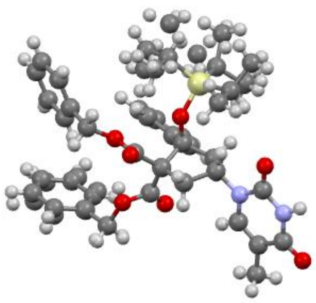
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.35 (s, 1H, thymine N-H), 7.84 (d, *J* = 1.6 Hz, 1H, thymine vinyl-CH), 7.77 (dd, *J* = 7.3, 1.8 Hz, 2H, Ar-H), 7.31 – 7.11 (m, 11H, Ar-H), 6.91 – 6.84 (m, 2H, Ar-H), 5.72 (tt, *J* = 11.5, 6.9 Hz, 1H, cyclopentane-NCH), 5.19 – 5.03 (m, 2H, benzylic-CH_2), 4.76 (d, *J* = 12.3 Hz, 1H, benzylic-CH_2), 4.56 (d, *J* = 12.2 Hz, 1H, benzylic-CH_2), 3.35 (dd, *J* = 15.1, 11.1 Hz, 1H, cyclopentane-CH_2), 3.21 (t, *J* = 12.4 Hz, 1H, cyclopentane-CH_2), 2.53 (dd, *J* = 12.9, 6.9 Hz, 1H, cyclopentane-CH_2), 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.

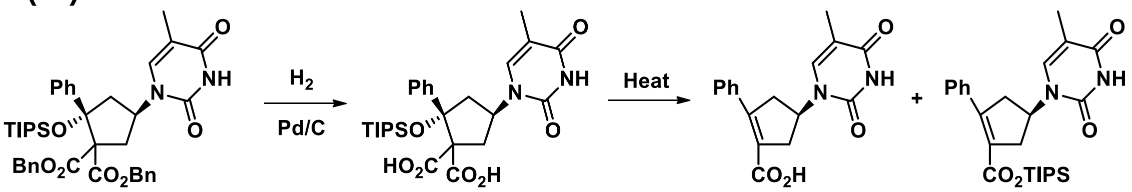
IR 3434 (w), 3160 (w), 3035 (w), 2872 (w), 1682 (s), 1456 (w), 1374 (w), 1136 (w), 1025 (m).

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.**



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



26 56 27 57

Compound **136** (0.10 g, 0.14 mmol, 1.0 eq) and Pd-C (0.030 g, 0.014 mmol, 0.1 eq) were stirred in a flame-dried flask under H_2 at 57 °C with ethanol (10 mL) 5 min to solubilize the starting material, then the reaction was let for 10 min to cool down. The reaction mixture was filtered on a pore 5 filter with hot ethanol (50 mL) to afford after solvent evaporation, the pure diacid **56** as colorless needles. Then the crude product was heated neat at 80 °C for 16 h. After column chromatography using DCM to a mixture of DCM/MeOH (9:1) with 1% AcOH as solvent, the pure product **27** (28 mg, 0.090 mmol, 64% yield) was obtained as a colorless oil. The corresponding TIPS protected carboxylic acid **57** (14 mg, 0.030 mmol, 20% yield) was also isolated as a colorless oil.

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

RF 27 (DCM/MeOH (9:1)) = 0.21.

MP 114.1-115.6 °C.

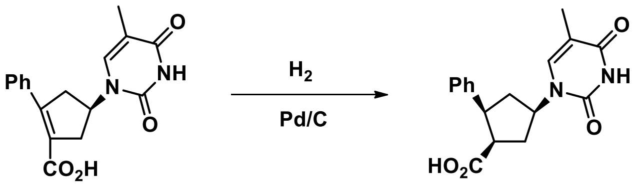
^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.20 (d, *J* = 9.1 Hz, 1H, thymine-NH), 7.37 (s, 5H, Ar-H), 7.08 (d, *J* = 1.6 Hz, 1H, , thymine vinyl-CH), 5.37 (tt, *J* = 8.8, 4.3 Hz, 1H, cyclopentane-NCH), 3.60 – 3.25 (m, 2H, cyclopentane-CH_2), 2.96 (dddd, *J* = 18.9, 8.2, 3.7, 1.9 Hz, 2H, cyclopentane-CH_2),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

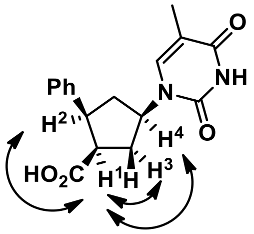
HRMS (ESI) calcd for $C_{17}H_{15}[^2H]_2N_2O_4^+$ $[M+H]^+$ 315.1306; found 315.1300.

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



27 58

Carboxylic acid **27** (0.021 g, 0.067 mmol, 1.0 eq) and Pd-C (0.01 g, 0.007 mmol, 5 % wt, 0.1 eq) were stirred in a flame dried flask under H_2 at room temperature with ethanol (1 mL). TLC shows that the reaction was accomplished after 10 minutes and filtered on pore 5 filter. The residue was washed several times with hot ethanol. The pure product **58** (0.018 g, 0.057 mmol, 85% yield) precipitated directly as white spheres. The stereochemistry was assigned by NOE experiment.



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

MP 227.8-236.9°C.

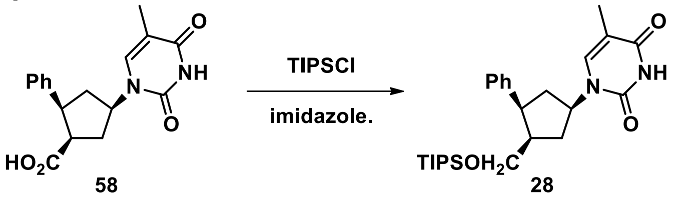
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H, -COOH), 11.20 (s, 1H, -NH), 7.80 (d, *J* = 1.4 Hz, 1H, , thymine vinyl-CH), 7.29 – 7.10 (m, 5H, Ar-H), 4.97 (dtd, *J* = 11.3, 9.1, 6.8 Hz, 1H, cyclopentane-NCH), 3.48 (ddd, *J* = 12.3, 9.1, 6.2 Hz, 1H, cyclopentane-CH), 3.19 – 3.00 (m, 1H), 2.36 – 2.21 (m, 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 (28).



Carboxylic acid **58** (0.019 g, 0.060 mmol, 1 eq) was solubilized in dry THF (0.35 mL) in a dried round bottom flask. The reaction mixture was cooled under nitrogen to 0°C and a 2 M dimethylsulfide borane solution in THF (0.076 mL, 0.15 mmol, 2.2 eq) was added dropwise. The reaction was stirred at 0 °C for 5 hours, then it was quenched by addition of a 1 M HCl solution (1 mL). The mixture was extracted three times with AcOEt (3 mL) and the organic layers were dried over anhydrous $MgSO_4$. The crude was directly solubilized into dry and degassed DMF (0.7 mL), imidazole (6 mg, 0.09 mmol, 1.5 eq) and TIPSCl (14 mg, 0.072 mmol, 1.2 eq) were added. The mixture was stirred at room temperature for 6 hours. The solvent was removed under reduced pressure and the mixture was partitioned between water (2 mL) and AcOEt (2 mL). The aqueous layer was extracted 3 times with AcOEt and the organic layers were dried over anhydrous Na_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 **28** (15 mg, 0.033 mmol, 55%) as a colorless oil.

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

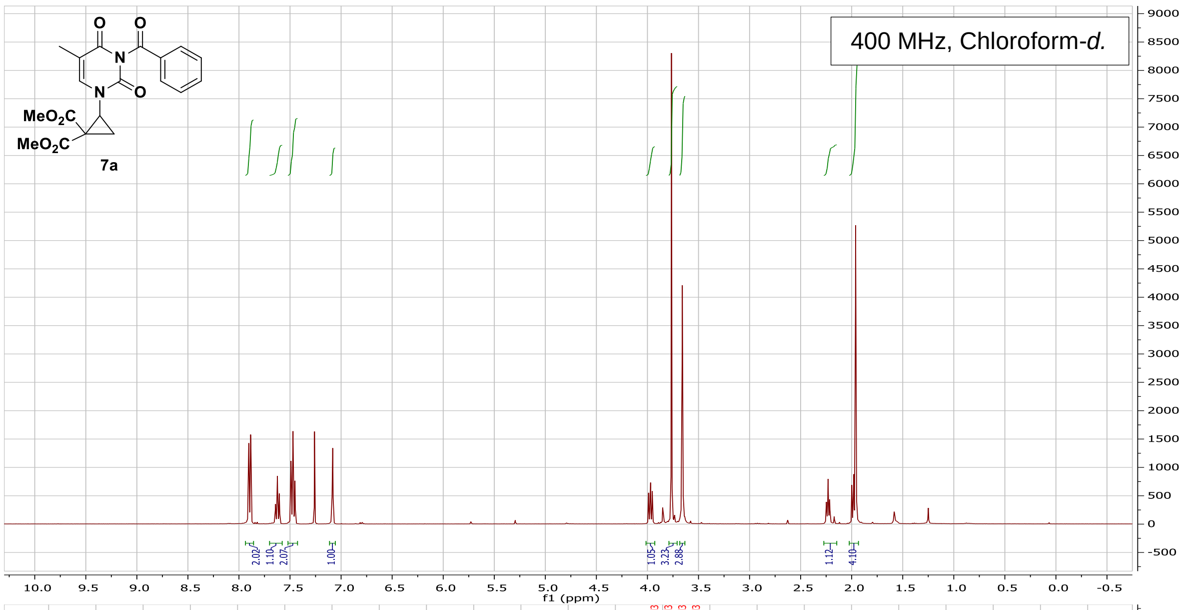
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.54 (s, 1H, -NH), 7.32 – 7.09 (m, 6H, Ar-H and thymine vinyl-CH), 5.05 (dtd, *J* = 11.6, 9.4, 6.5 Hz, 1H, cyclopentane-NCH), 3.42 – 3.21 (m, 3H, CH_2O and cyclopentane-CH), 2.46 (td, *J* = 9.0, 4.7 Hz, 1H, cyclopentane-CH), 2.39 – 2.27 (m, 1H cyclopentane-CH), 2.27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

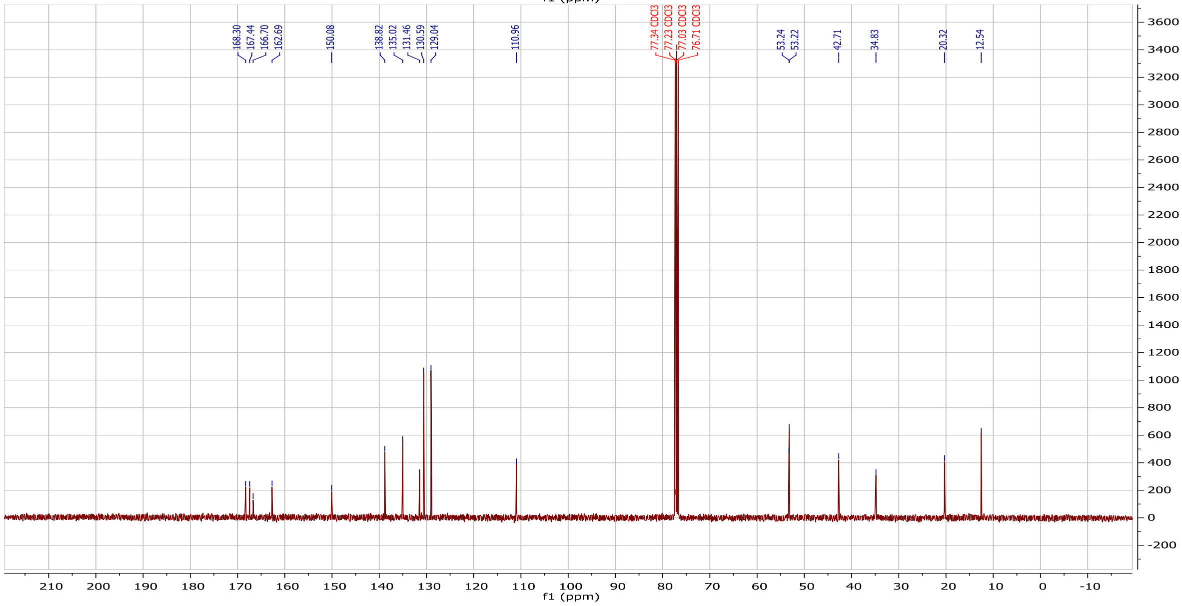
^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.5, 151.2, 139.9, 136.6, 128.3, 128.0, 126.4, 111.0, 64.0, 54.6, 44.8, 42.1, 35.3, 32.1, 18.0, 18.0, 12.4, 11.8.

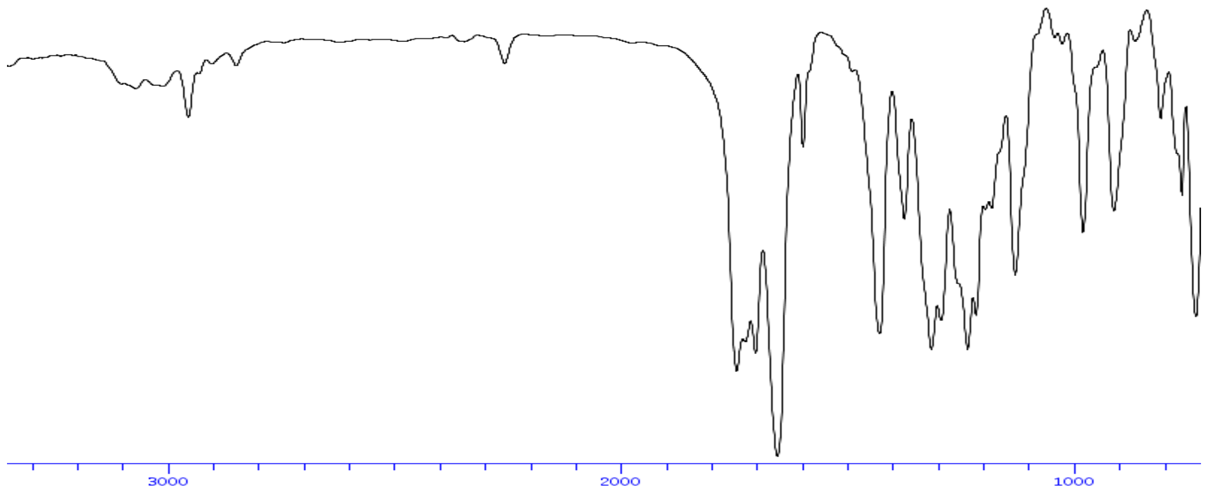
IR 3170 (w), 2945 (w), 1687 (s), 1469 (m), 1385 (w), 1272 (w), 1126 (w), 884 (w).

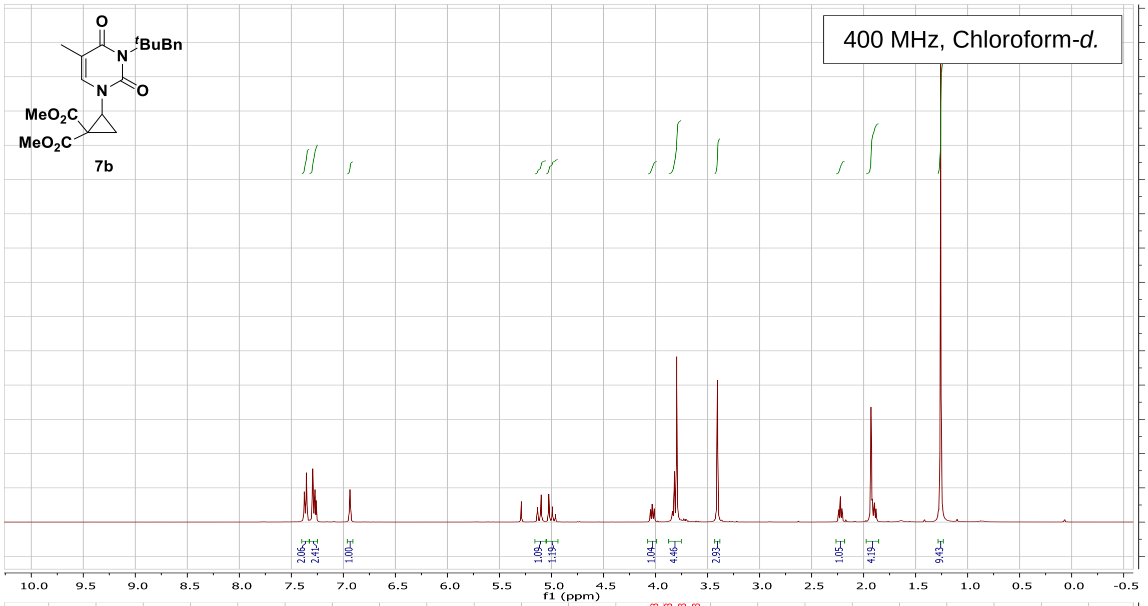
HRMS (ESI) calcd for $C_{26}H_{41}N_2O_3Si^+$ $[M+H]^+$ 457.2881; found 457.2881.

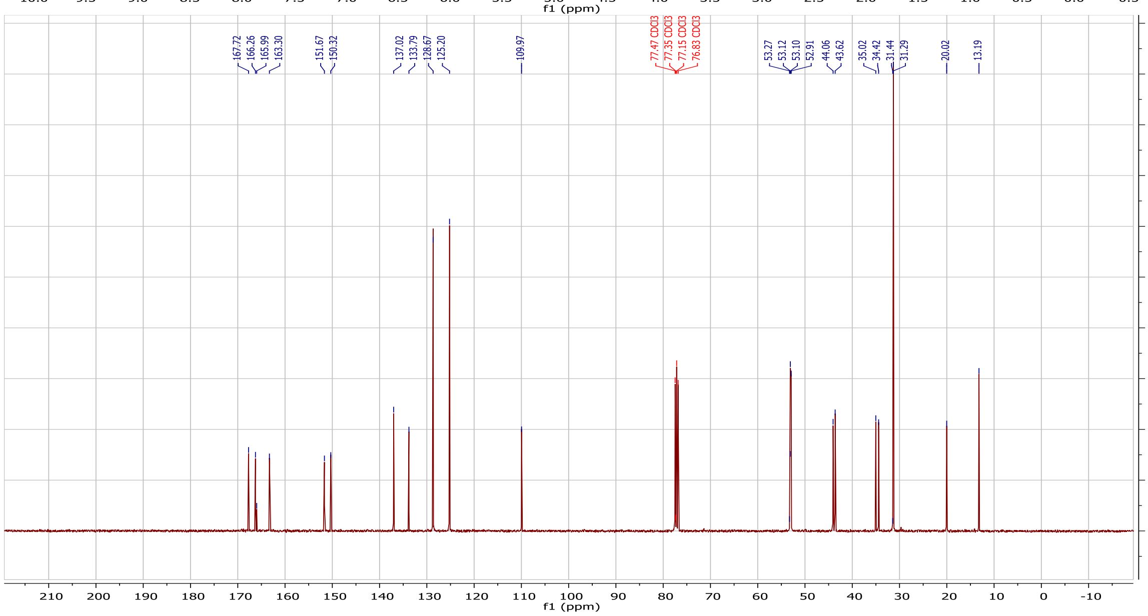
5. Spectra of new compounds

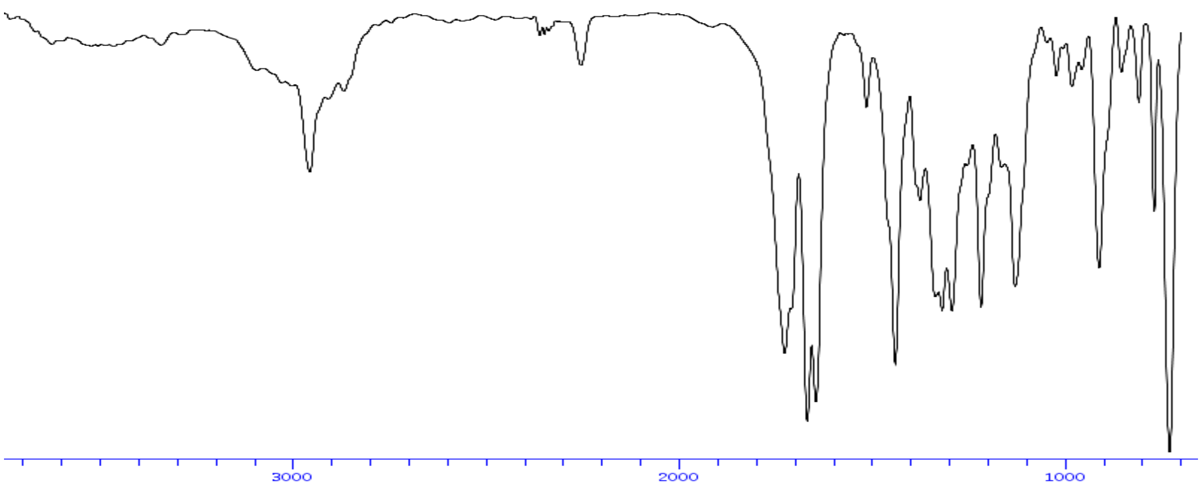

400 MHz, Chloroform-d.
MeO2C
MeO2C
7a
f1 (ppm)

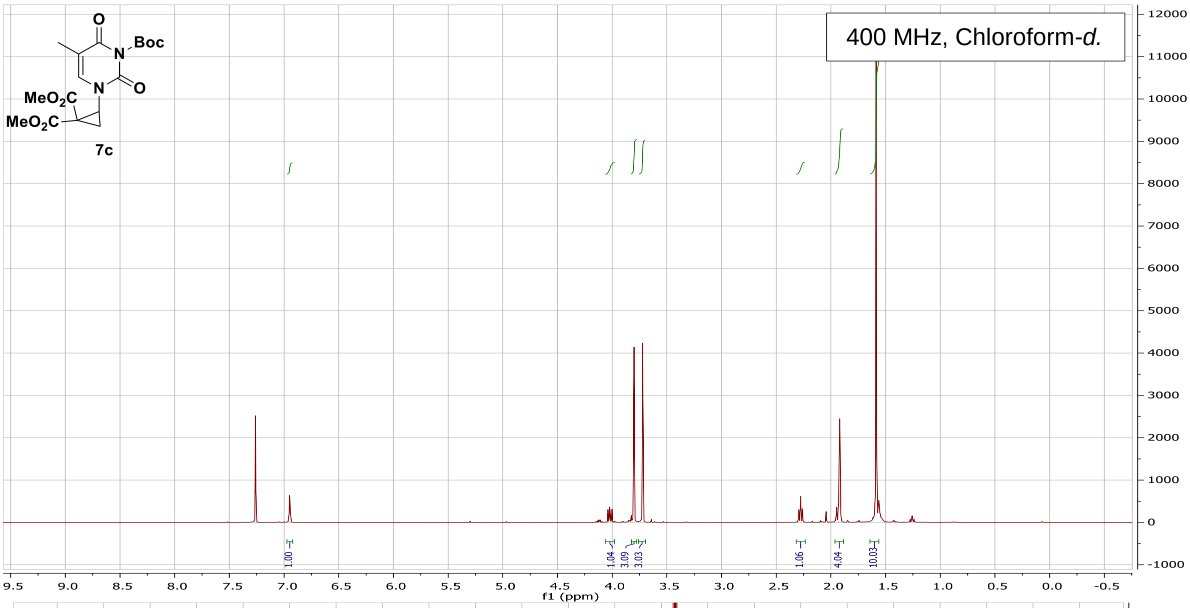

168.30
167.44
166.70
162.69
150.08
138.82
135.02
131.46
130.59
129.04
110.96
77.34 CDCl3
77.23 CDCl3
77.03 CDCl3
76.71 CDCl3
53.24
53.22
42.71
34.83
20.32
12.54
f1 (ppm)


3000
2000
1000

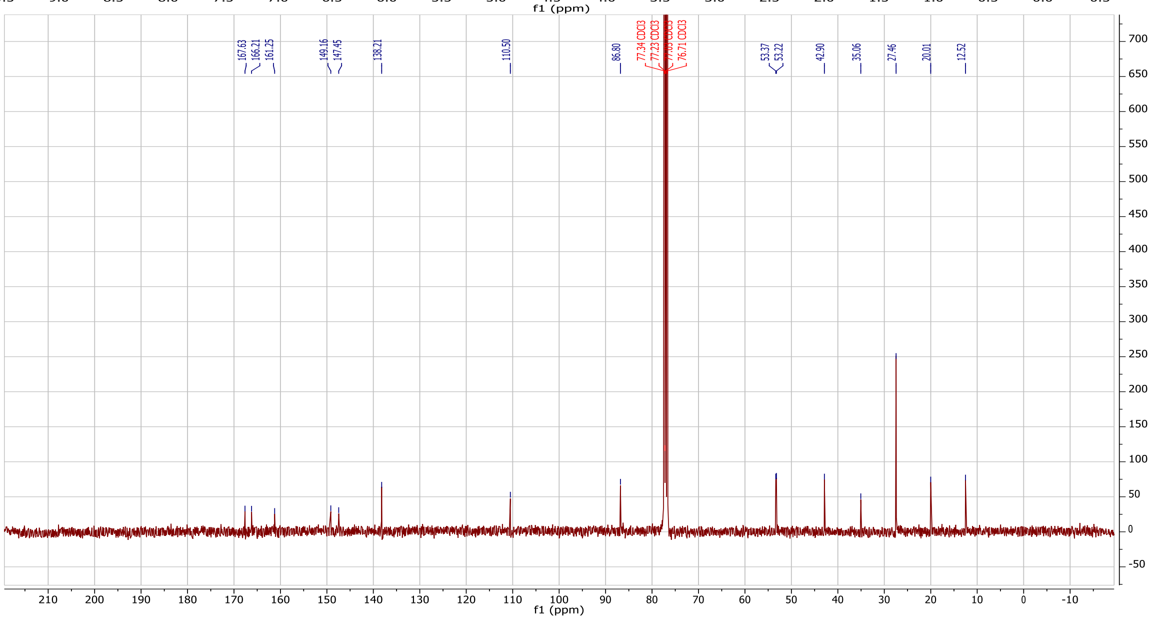

7b
400 MHz, Chloroform-d.
f1 (ppm)


f1 (ppm)

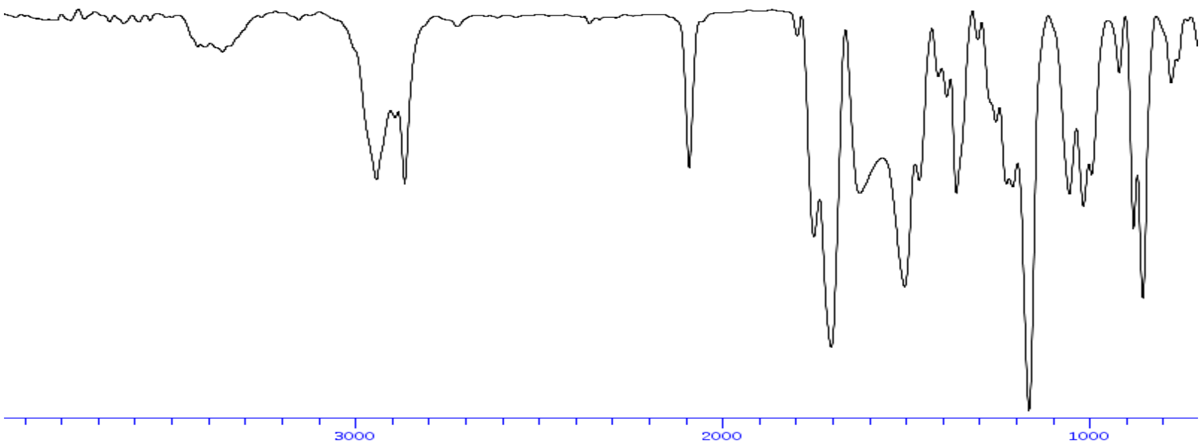




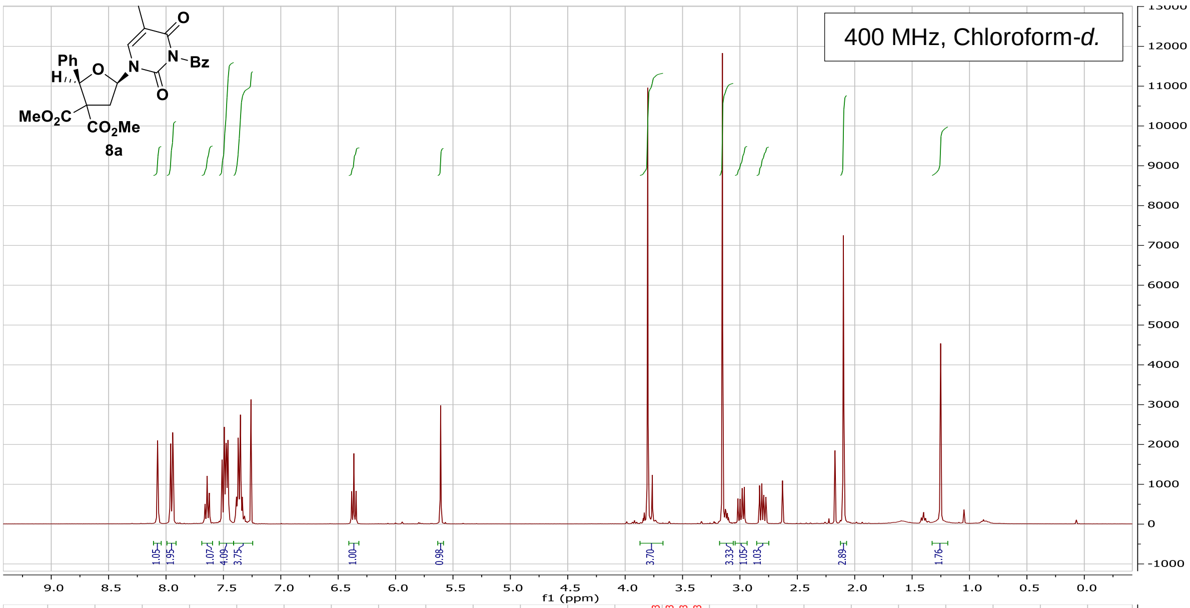
Boc
MeO2C
MeO2C
7c
400 MHz, Chloroform-d.
f1 (ppm)
1.00
1.04
3.09
3.03
1.06
4.04
10.03

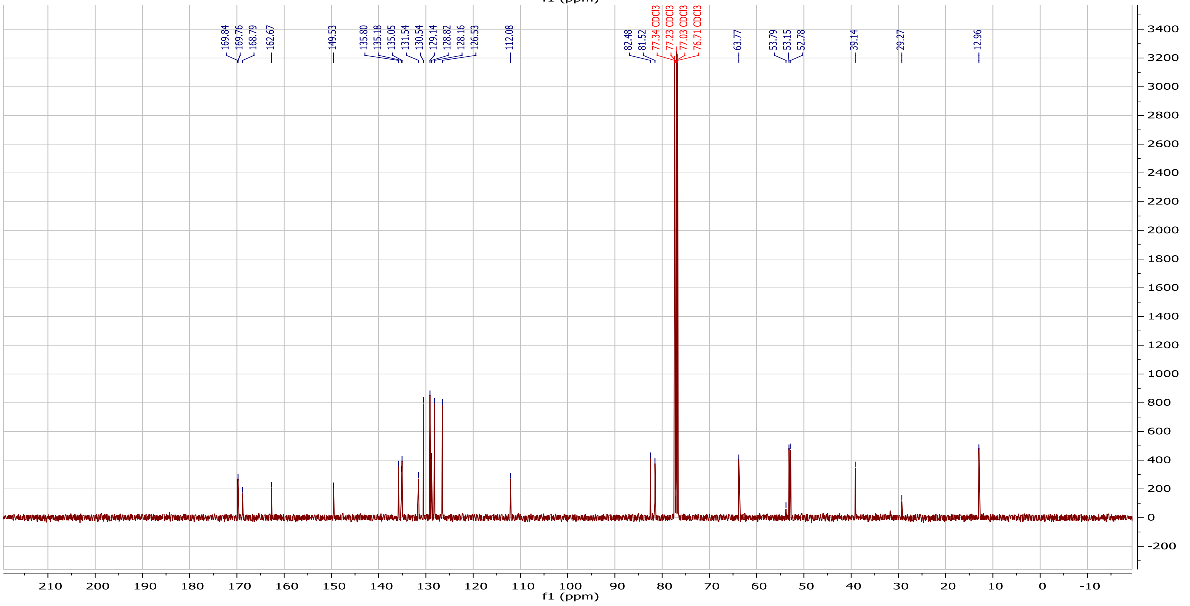


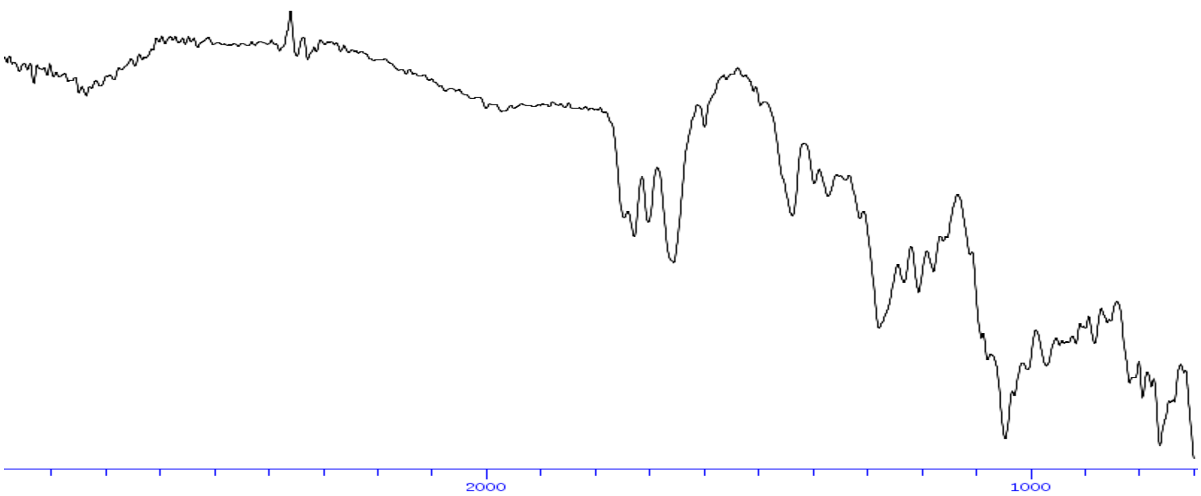
167.63
166.21
161.25
149.16
147.45
138.21
110.50
86.80
77.34 CDCl3
77.23 CDCl3
77.03 CDCl3
76.71 CDCl3
53.37
53.22
42.90
35.06
27.46
20.01
12.52
f1 (ppm)

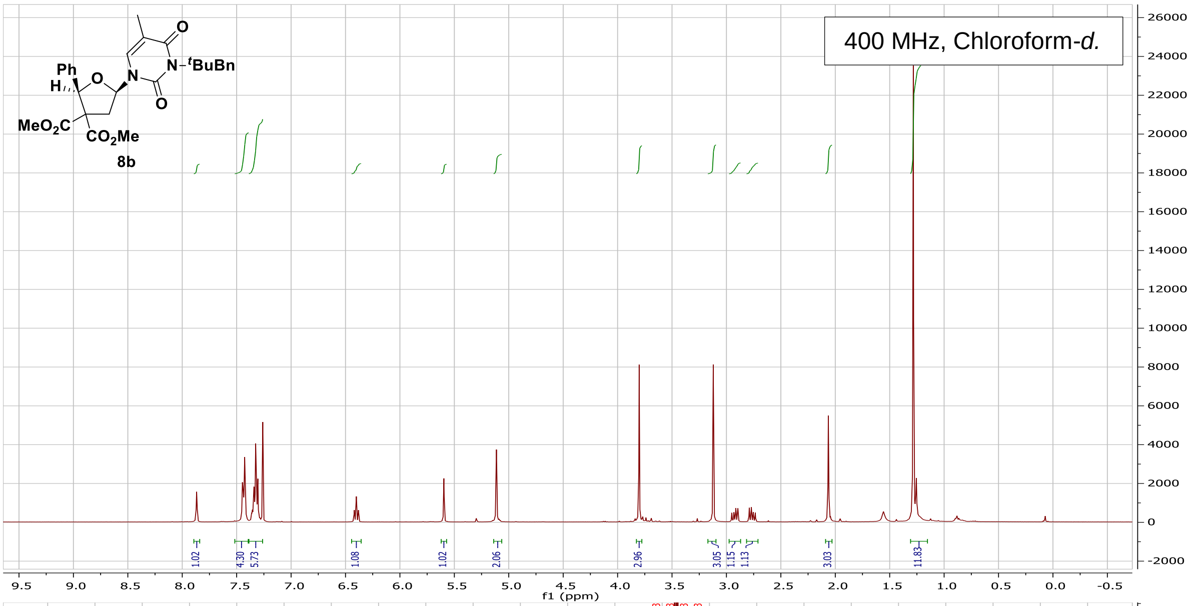


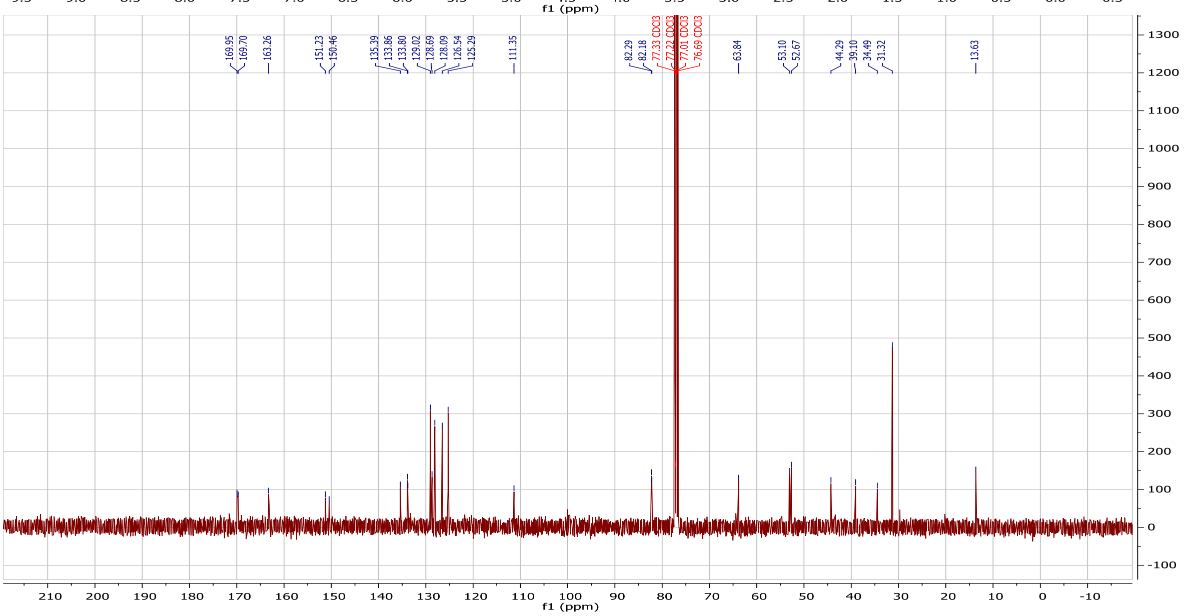
3000
2000
1000

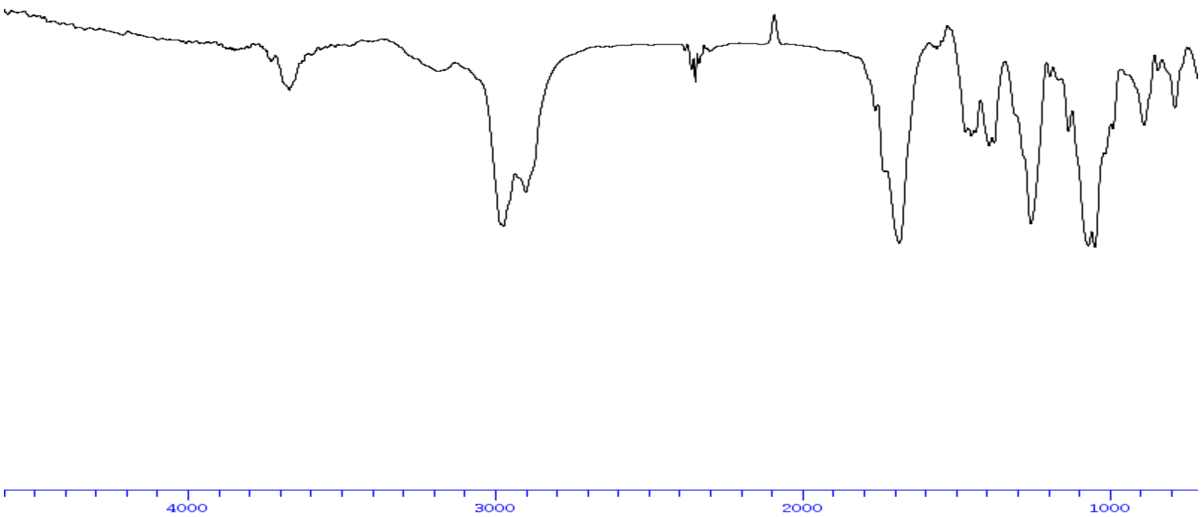

400 MHz, Chloroform-d.
Ph
H
O
N
N–Bz
O
O
MeO2C
CO2Me
8a
1.05
1.95
1.07
4.09
3.75
1.00
0.98
3.70
3.33
1.05
1.03
2.89
1.76
f1 (ppm)

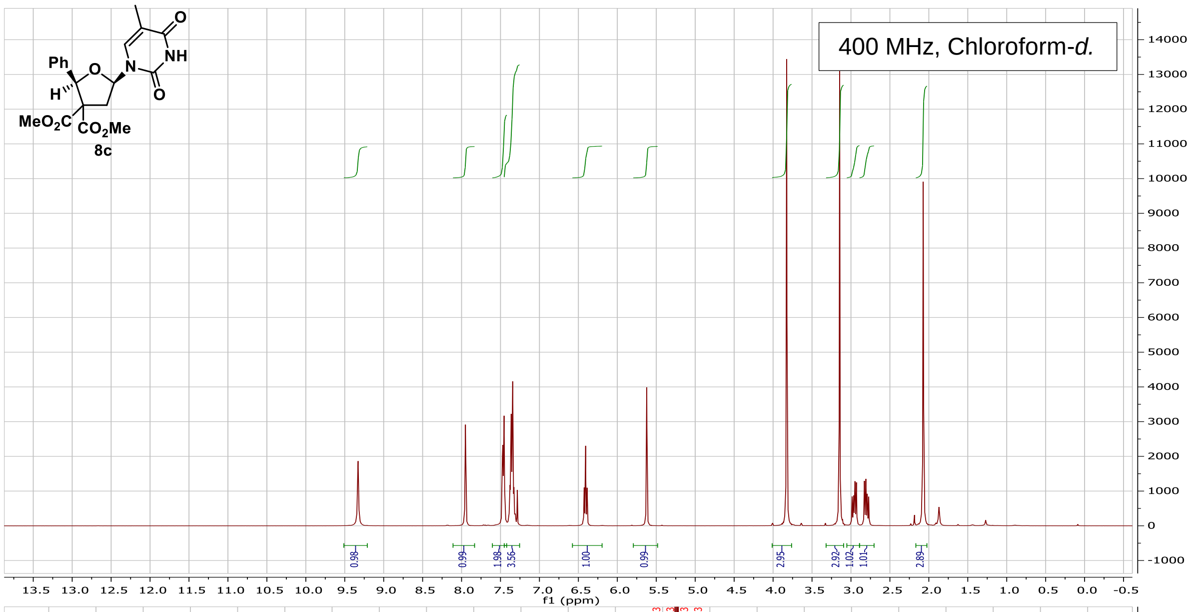

169.84
169.76
168.79
162.67
149.53
135.80
135.18
135.05
131.54
130.54
129.14
128.82
128.16
126.53
112.08
82.48
81.52
77.34 CDCl3
77.23 CDCl3
77.03 CDCl3
76.71 CDCl3
63.77
53.79
53.15
52.78
39.14
29.27
12.96
f1 (ppm)

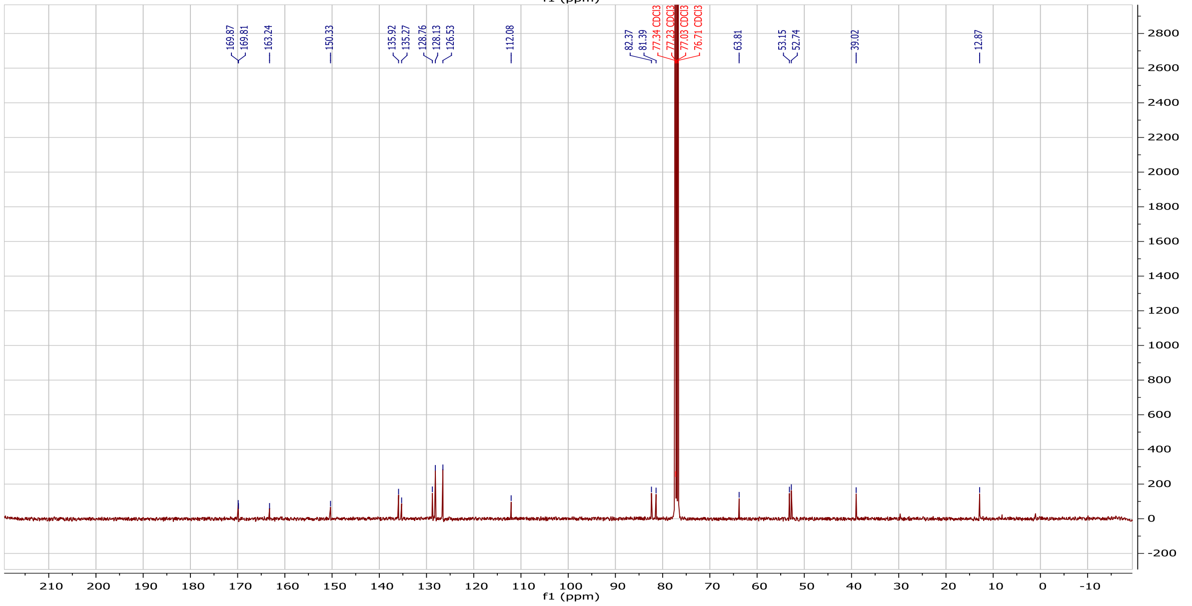

2000
1000

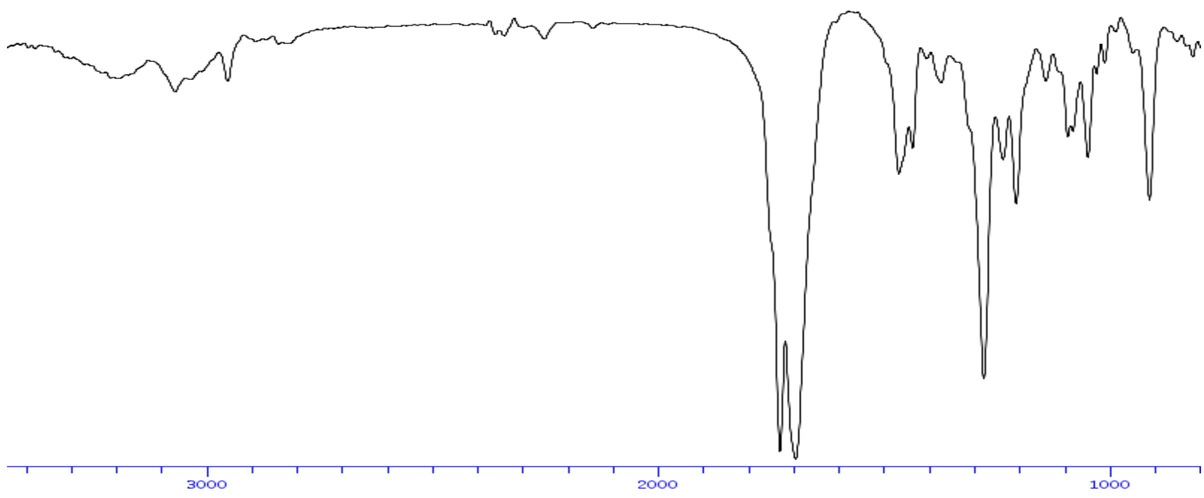

400 MHz, Chloroform-d.
8b
f1 (ppm)

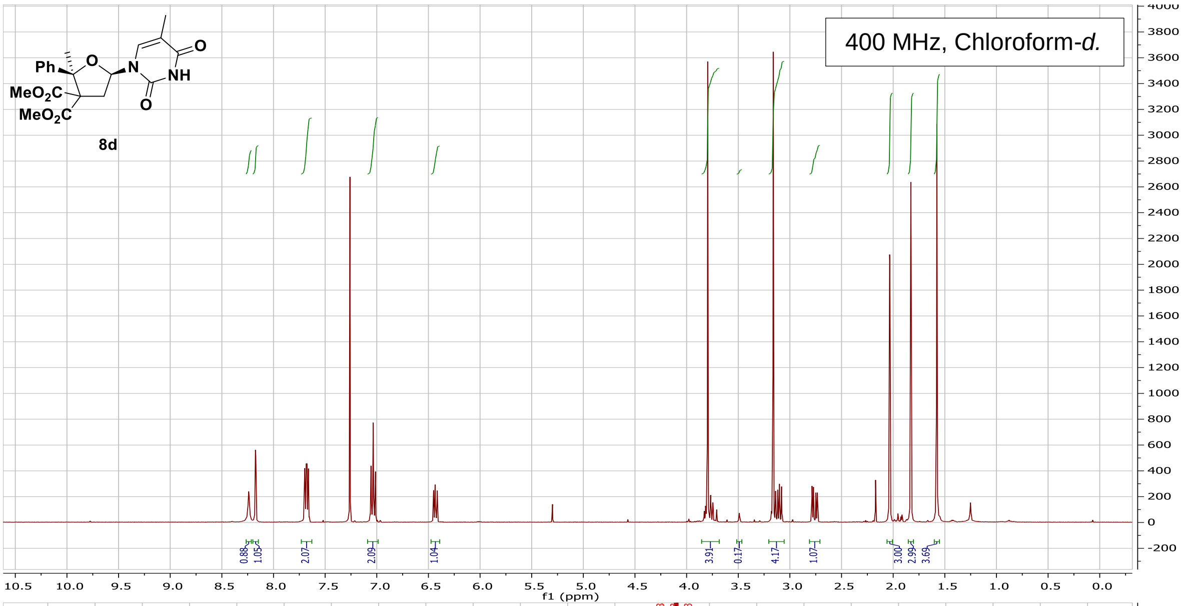

f1 (ppm)

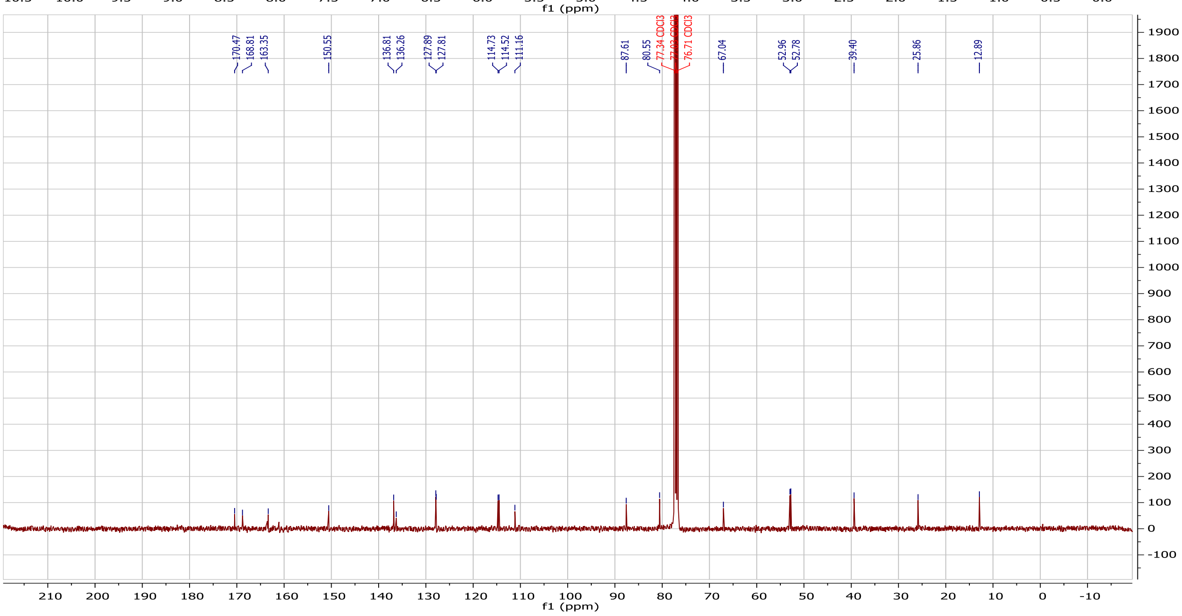


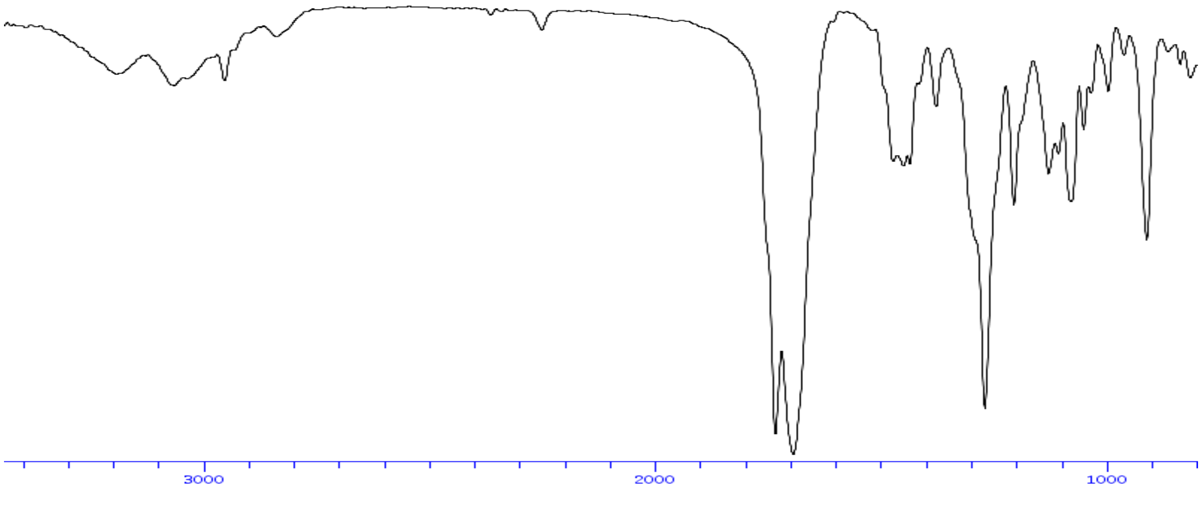

400 MHz, Chloroform-*d.*
Ph
H
O
N
NH
O
O
MeO2C
CO2Me
8c
0.98
0.99
1.98
3.56
1.00
0.99
2.95
2.92
1.02
1.01
2.89
f1 (ppm)

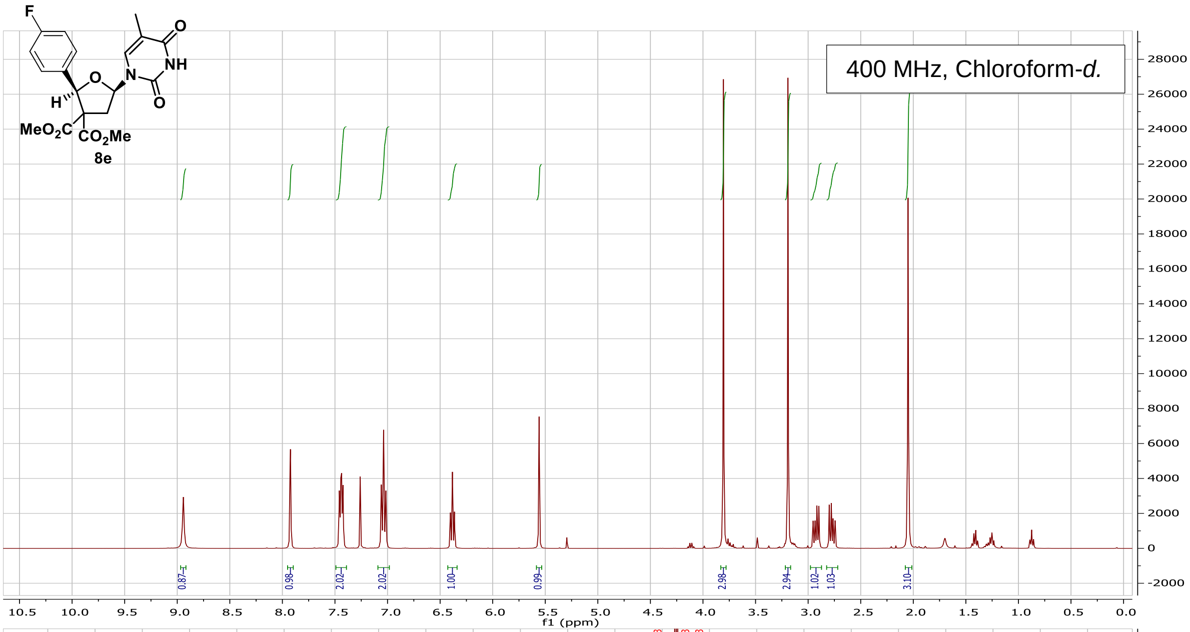

169.87
169.81
163.24
150.33
135.92
135.27
128.76
128.13
126.53
112.08
82.37
81.39
77.34 CDCl3
77.23 CDCl3
77.03 CDCl3
76.71 CDCl3
63.81
53.15
52.74
39.02
12.87
f1 (ppm)

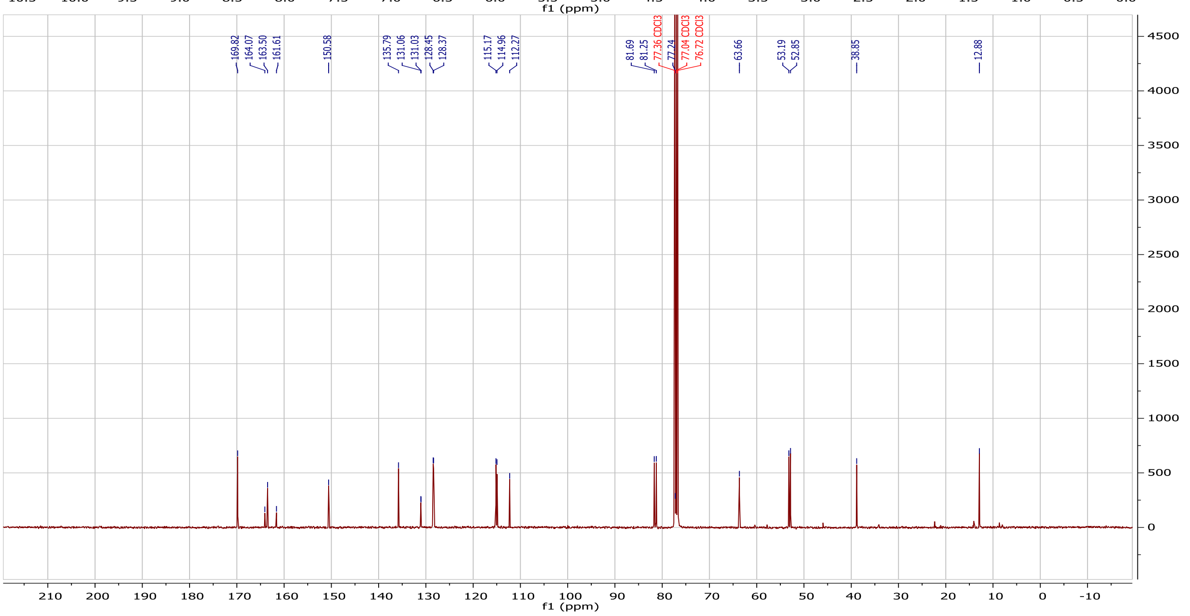

3000
2000
1000

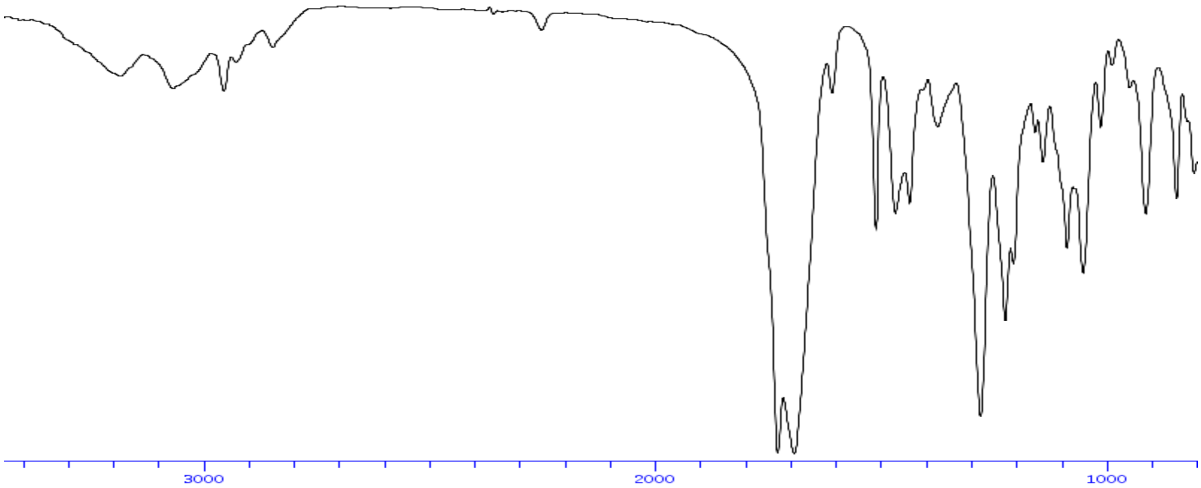

400 MHz, Chloroform-d.
8d
Ph
MeO2C
MeO2C
O
N
NH
O
O
0.88
1.05
2.07
2.09
1.04
3.91
0.17
4.17
1.07
3.00
2.99
3.69
f1 (ppm)

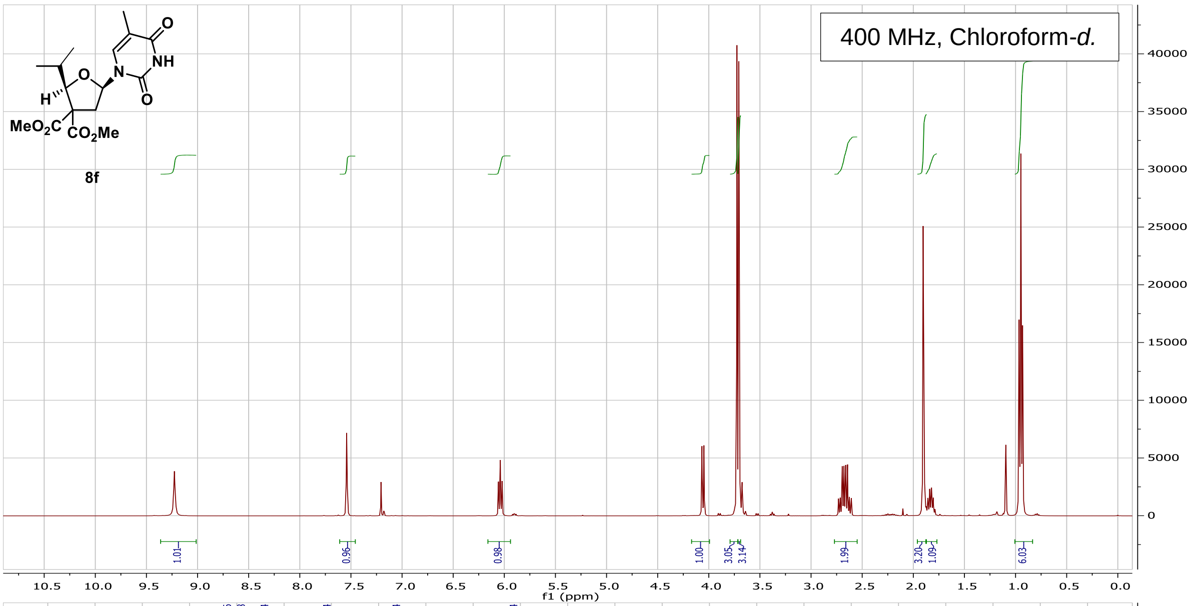

170.47
168.81
163.35
150.55
136.81
136.26
127.89
127.81
114.73
114.52
111.16
87.61
80.55
77.34 CDCl3
76.71 CDCl3
67.04
52.96
52.78
39.40
25.86
12.89
f1 (ppm)

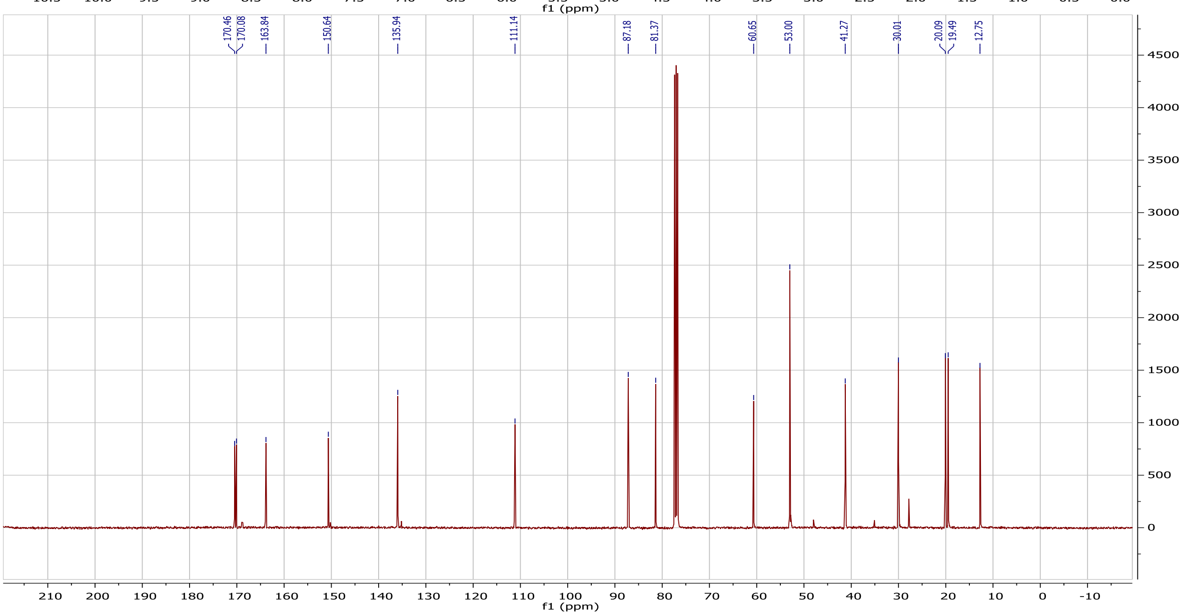

3000
2000
1000

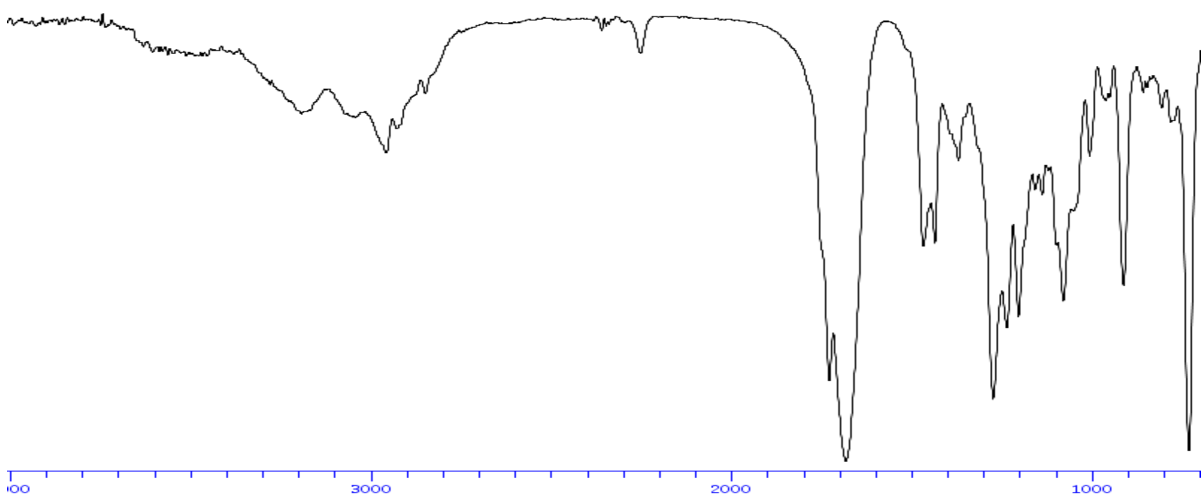

F
O
N
NH
O
O
H
MeO2C
CO2Me
8e
400 MHz, Chloroform-d.
f1 (ppm)
0.87
0.98
2.02
2.02
1.00
0.99
2.98
2.94
1.02
1.03
3.10


169.82
164.07
163.50
161.61
150.58
135.79
131.06
131.03
128.45
128.37
115.17
114.96
112.27
81.69
81.25
77.36 CDCl3
77.24
77.04 CDCl3
76.72 CDCl3
63.66
53.19
52.85
38.85
12.88
f1 (ppm)

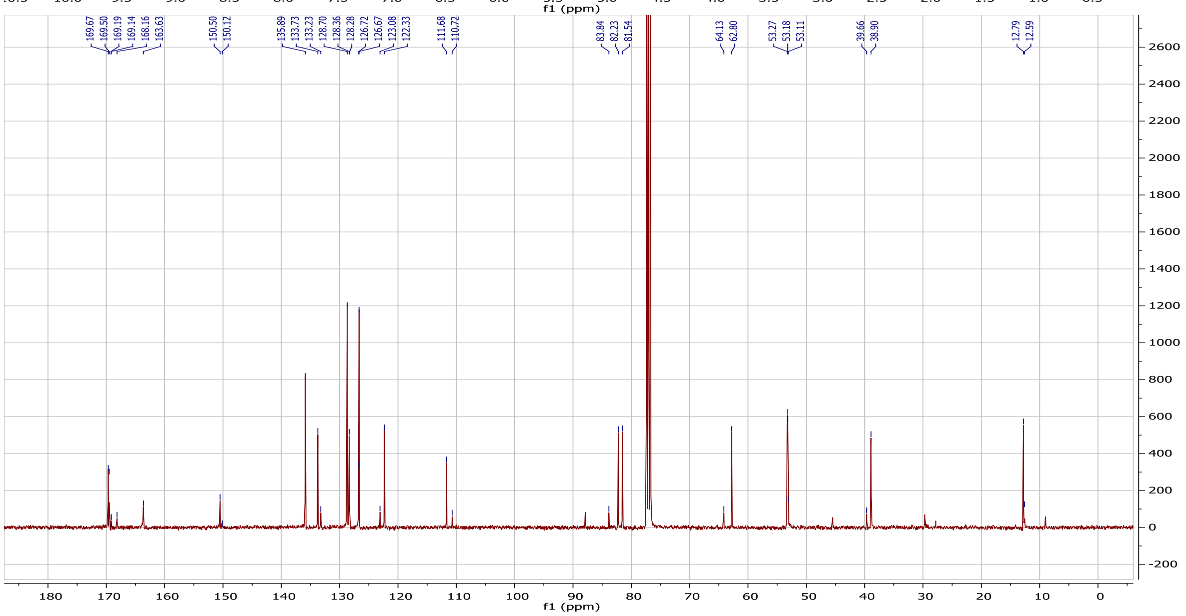

3000
2000
1000

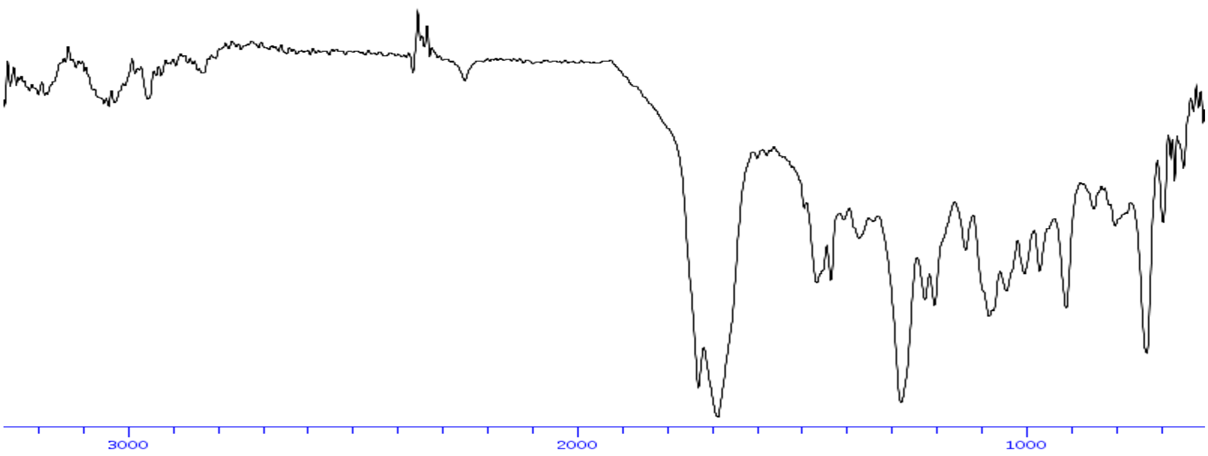

400 MHz, Chloroform-d.
MeO2C
CO2Me
NH
8f
1.01
0.96
0.98
1.00
3.05
3.14
1.99
3.20
1.09
6.03
f1 (ppm)

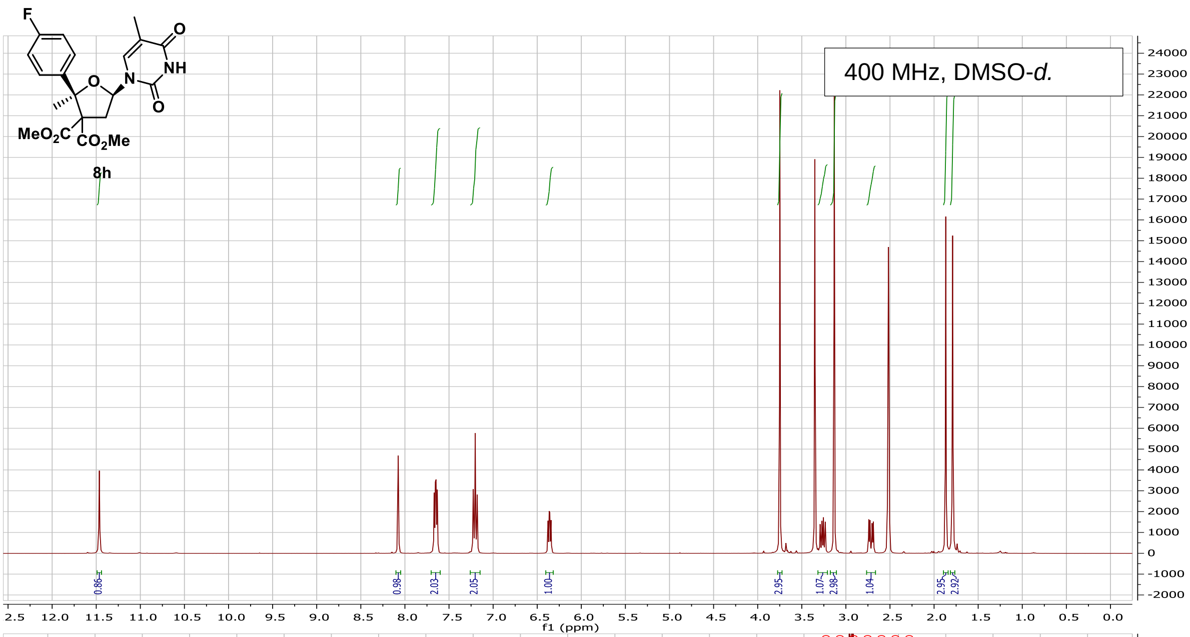

170.46
170.08
163.84
150.64
135.94
111.14
87.18
81.37
60.65
53.00
41.27
30.01
20.09
19.49
12.75
f1 (ppm)

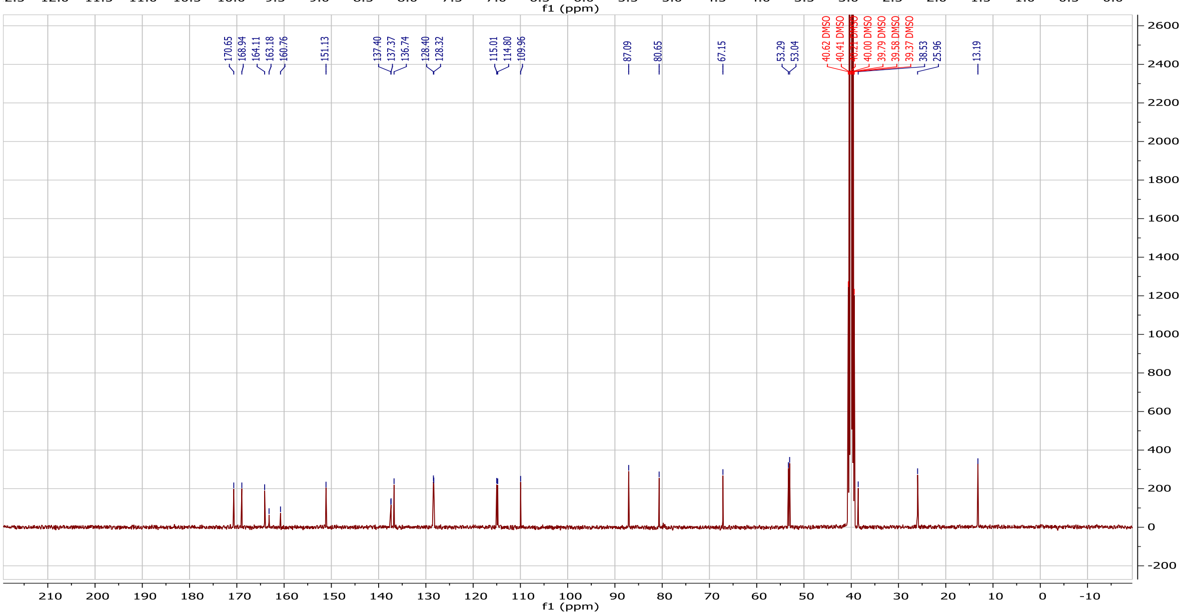

3000
2000
1000

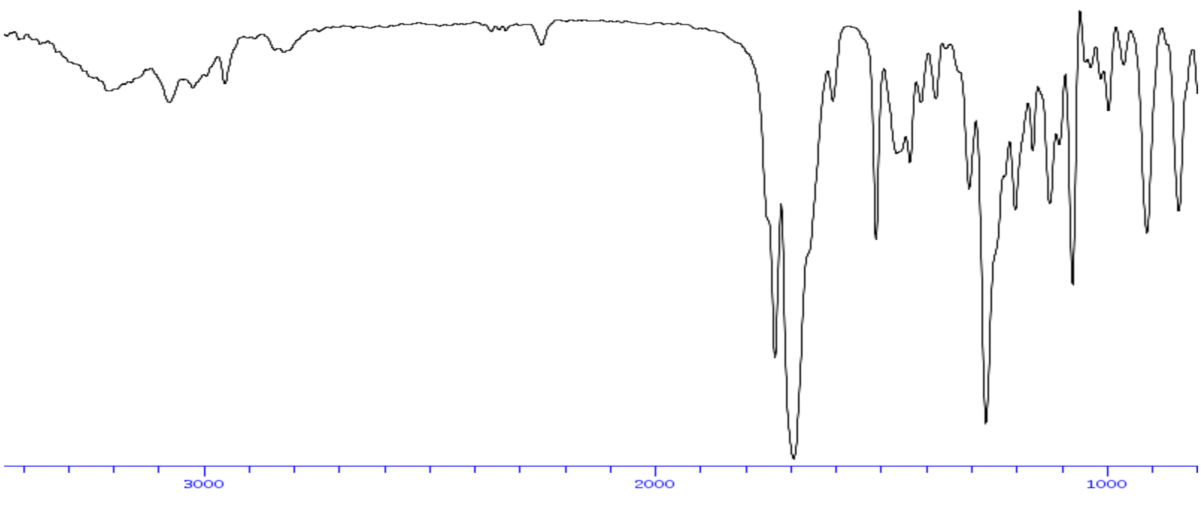

400 MHz, Chloroform-d.
Ph
H
MeO2C
CO2Me
NH
8g
f1 (ppm)

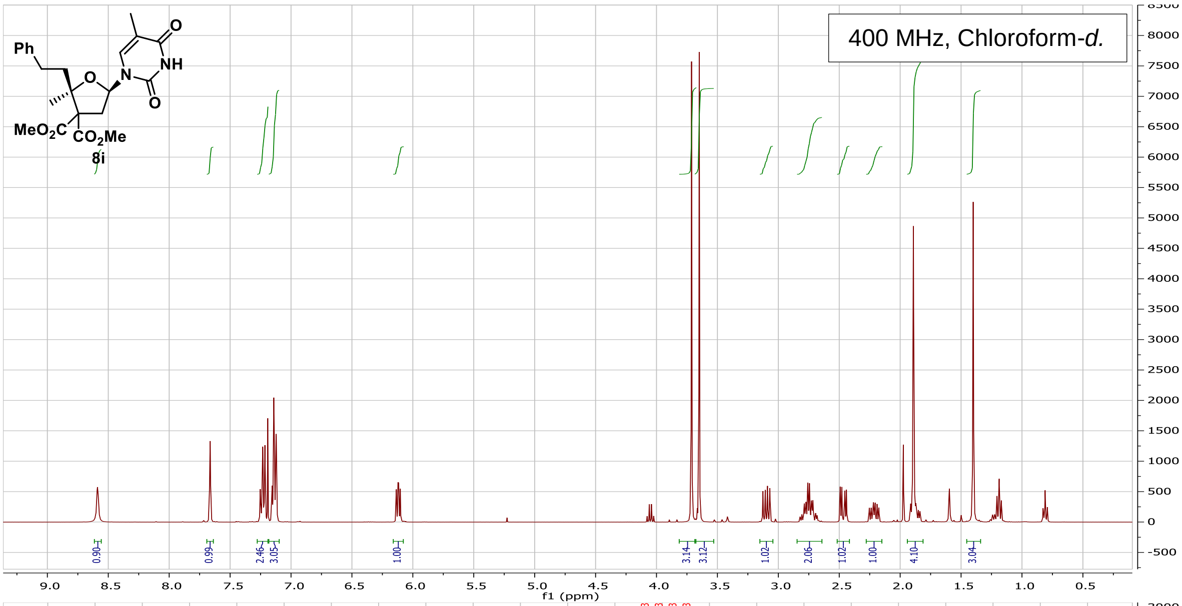

169.67
169.50
169.19
169.14
168.16
163.63
150.50
150.12
135.89
133.73
133.23
128.70
128.36
128.28
126.72
126.67
123.08
122.33
111.68
110.72
83.84
82.23
81.54
64.13
62.80
53.27
53.18
53.11
39.66
38.90
12.79
12.59
f1 (ppm)

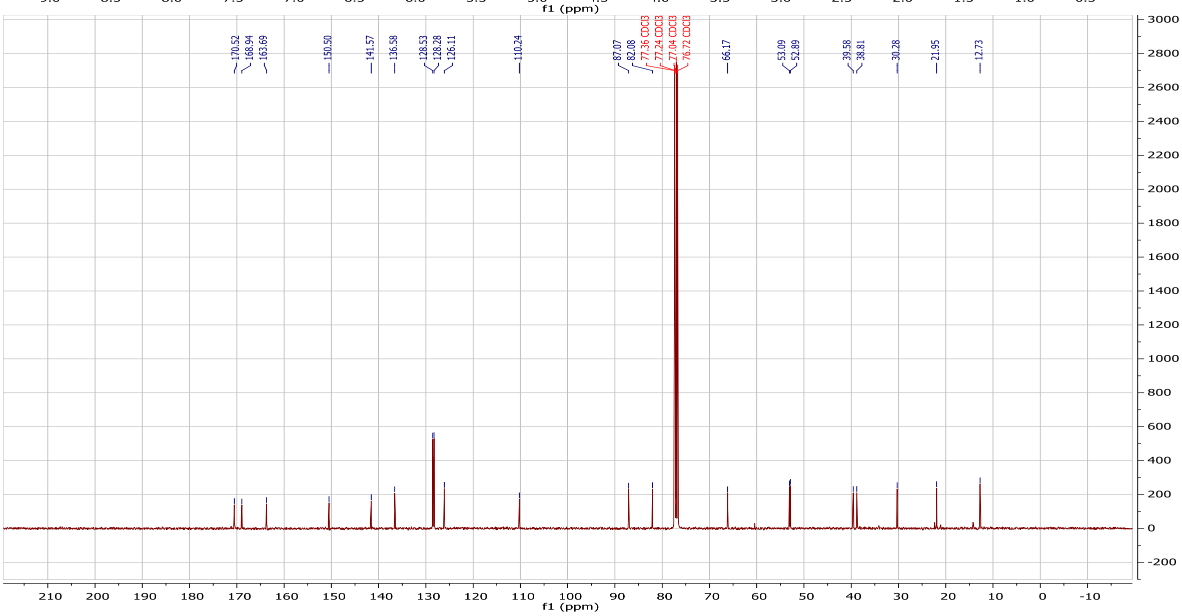

3000
2000
1000

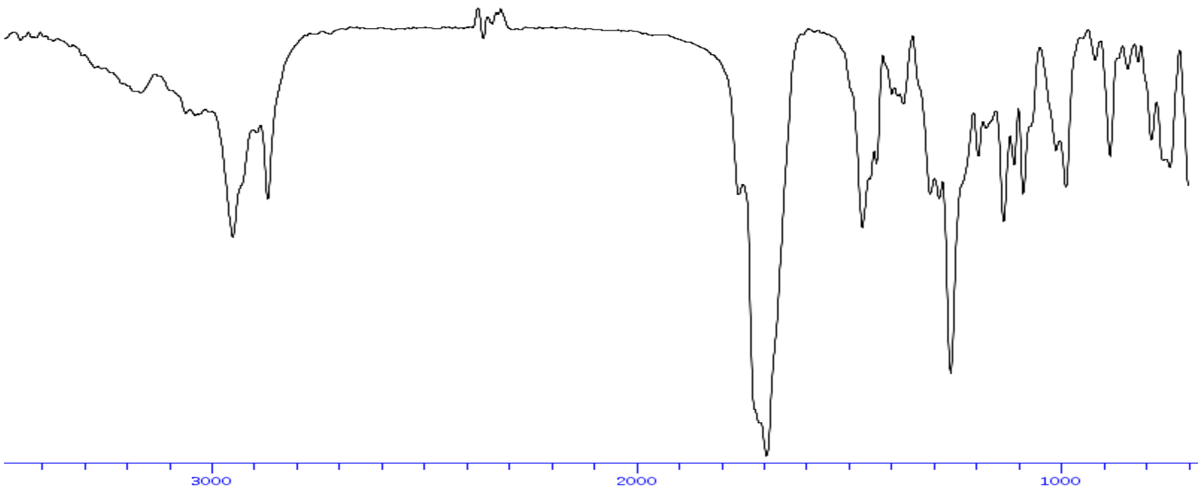

8h
400 MHz, DMSO-d.
f1 (ppm)

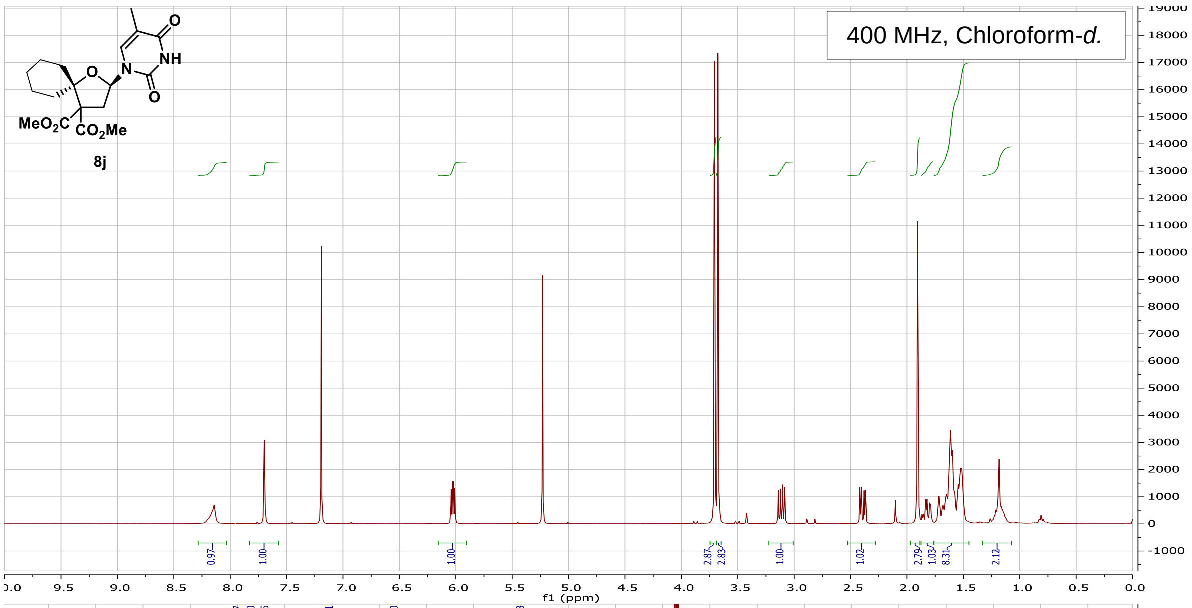

170.65
168.94
164.11
163.18
160.76
151.13
137.40
137.37
136.74
128.40
128.32
115.01
114.80
109.96
87.09
80.65
67.15
53.29
53.04
38.53
25.96
13.19
f1 (ppm)

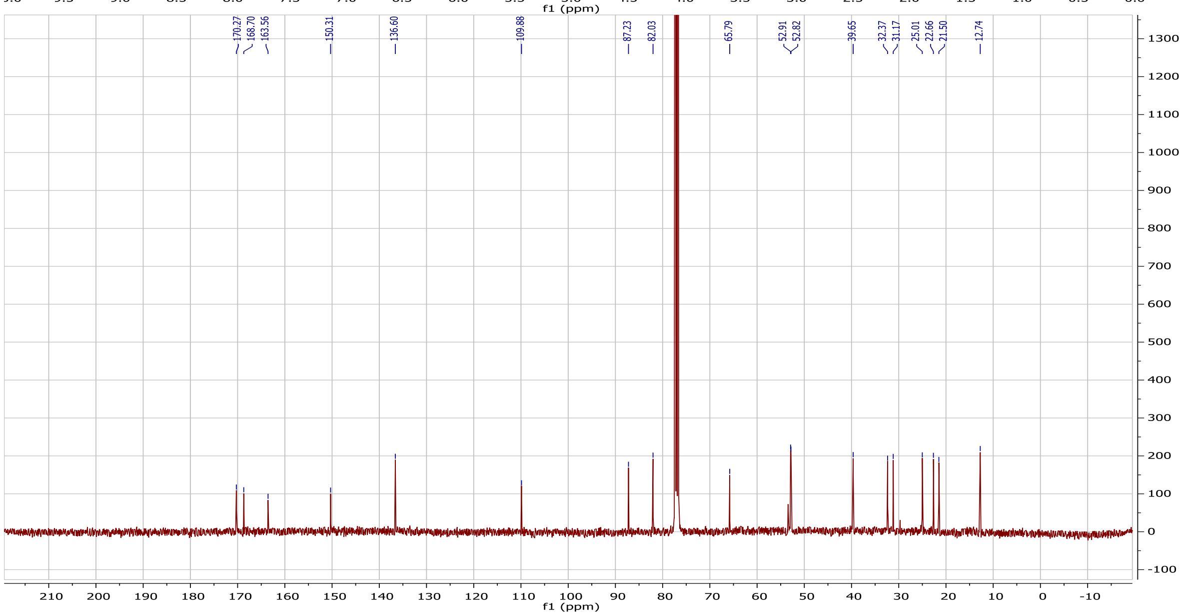

3000
2000
1000

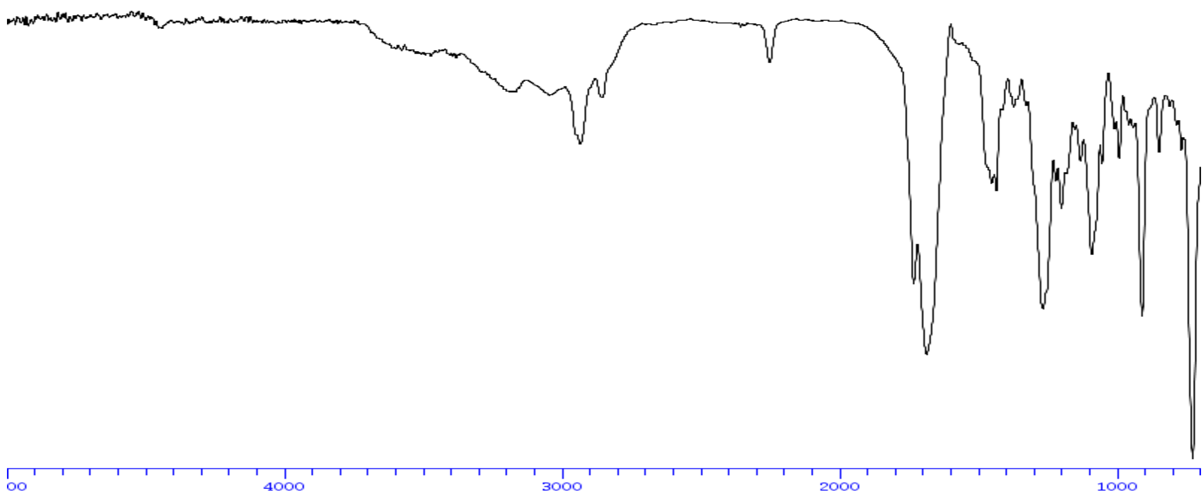

400 MHz, Chloroform-d.
Ph
NH
MeO2C
CO2Me
8i
f1 (ppm)

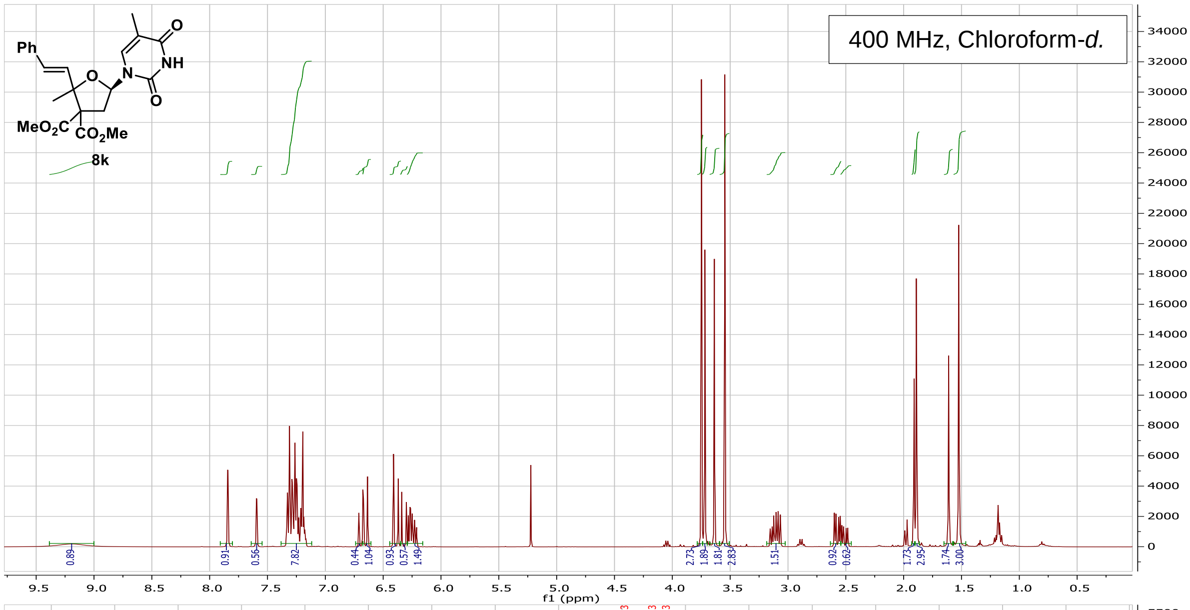

170.52
168.94
163.69
150.50
141.57
136.58
128.53
128.28
126.11
110.24
87.07
82.08
77.36 CDCl3
77.24 CDCl3
77.04 CDCl3
76.72 CDCl3
66.17
53.09
52.89
39.58
38.81
30.28
21.95
12.73
f1 (ppm)

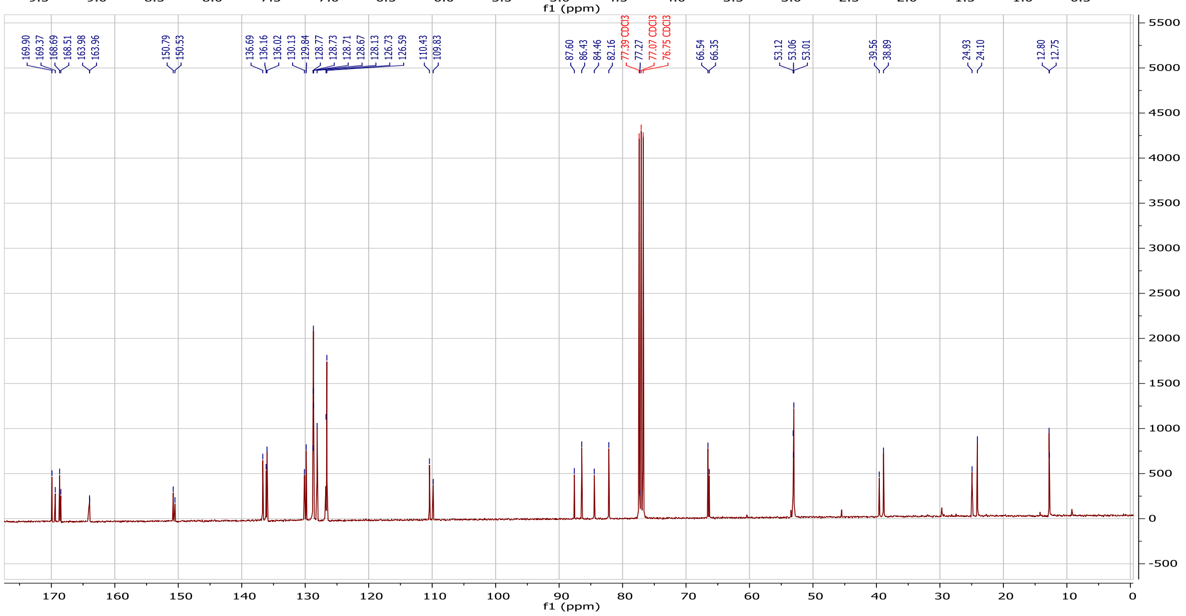

3000
2000
1000

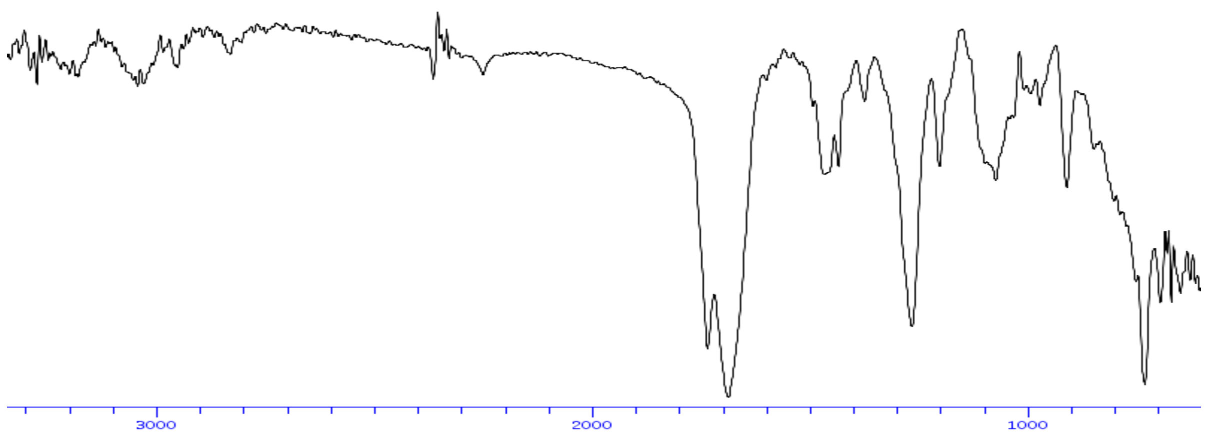

MeO2C
CO2Me
NH
8j
400 MHz, Chloroform-d.
0.97 1.00 1.00 2.87 2.83 1.00 1.02 2.79 1.03 8.31 2.12
f1 (ppm)

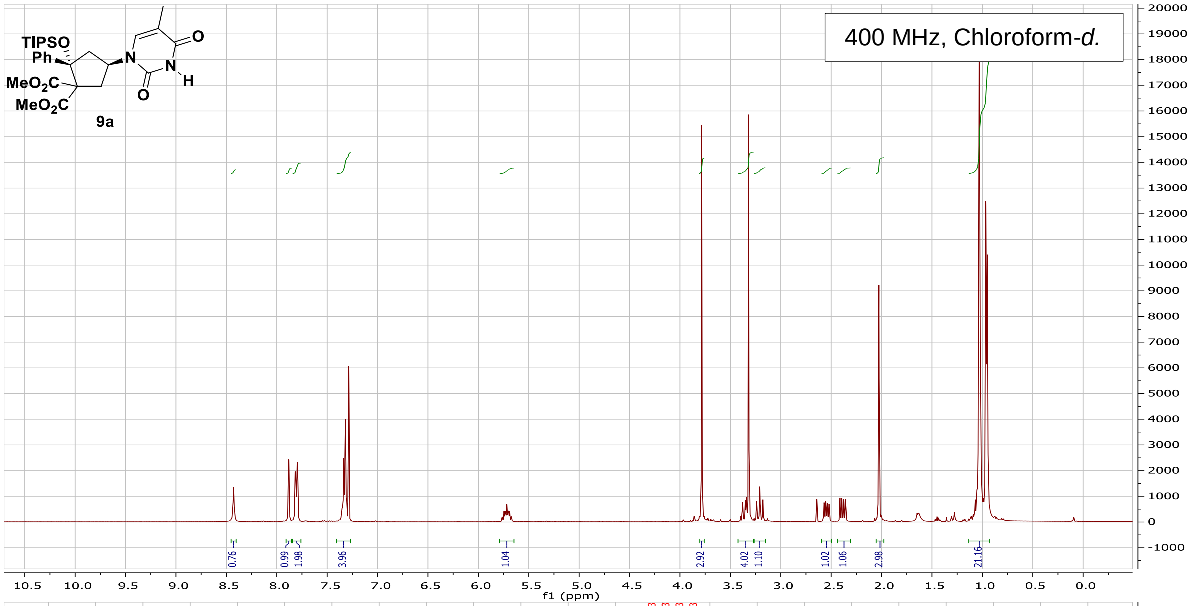

170.27
168.70
163.56
150.31
136.60
109.88
87.23
82.03
65.79
52.91
52.82
39.65
32.37
31.17
25.01
22.66
21.50
12.74
f1 (ppm)

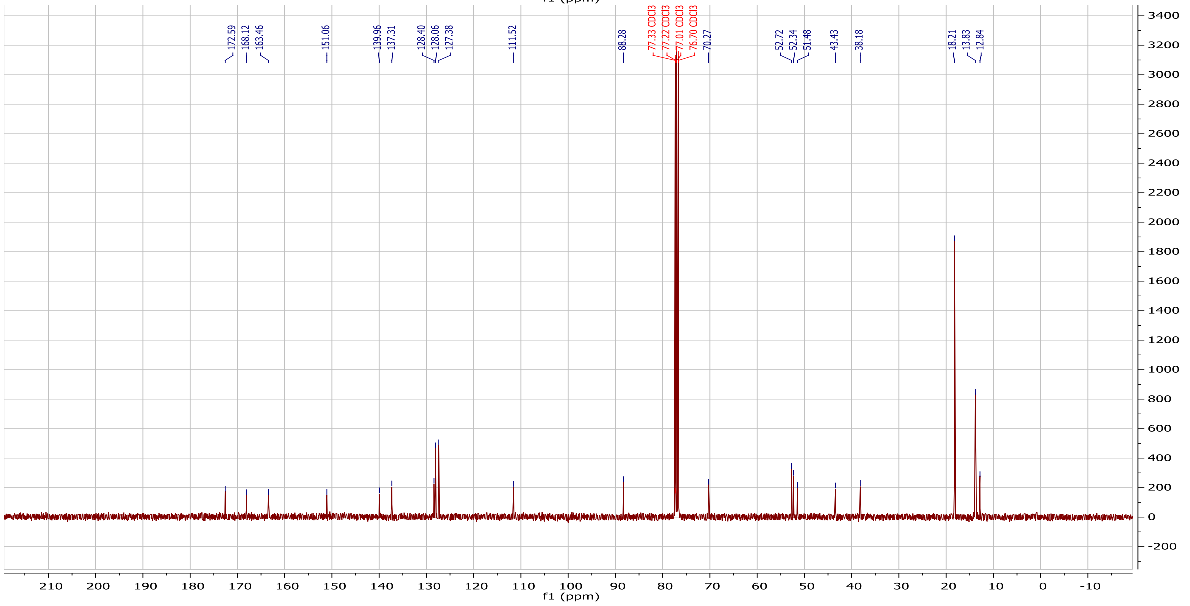

4000
3000
2000
1000

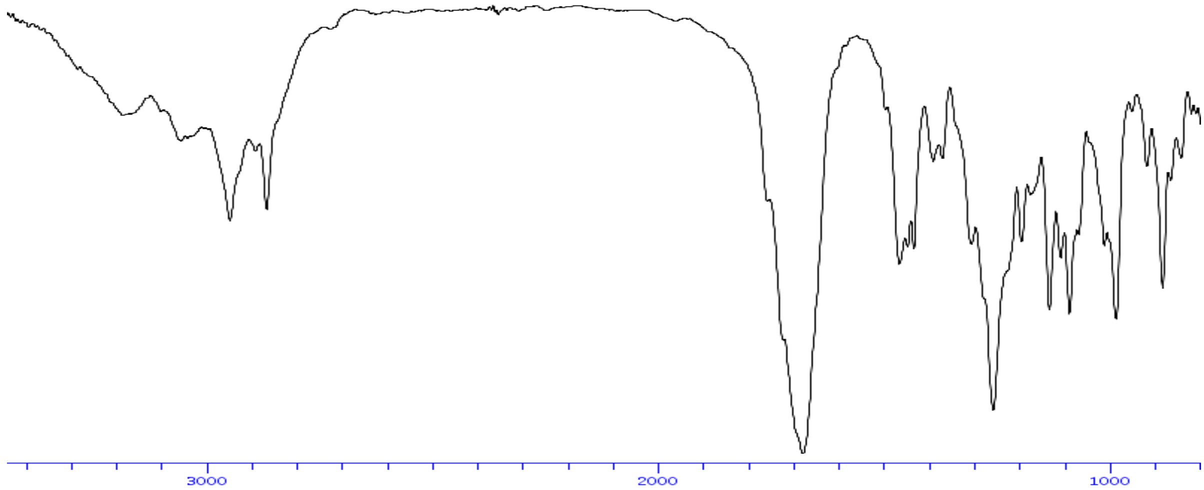

Ph
O
N
O
NH
O
MeO2C
CO2Me
8k
400 MHz, Chloroform-d.
f1 (ppm)

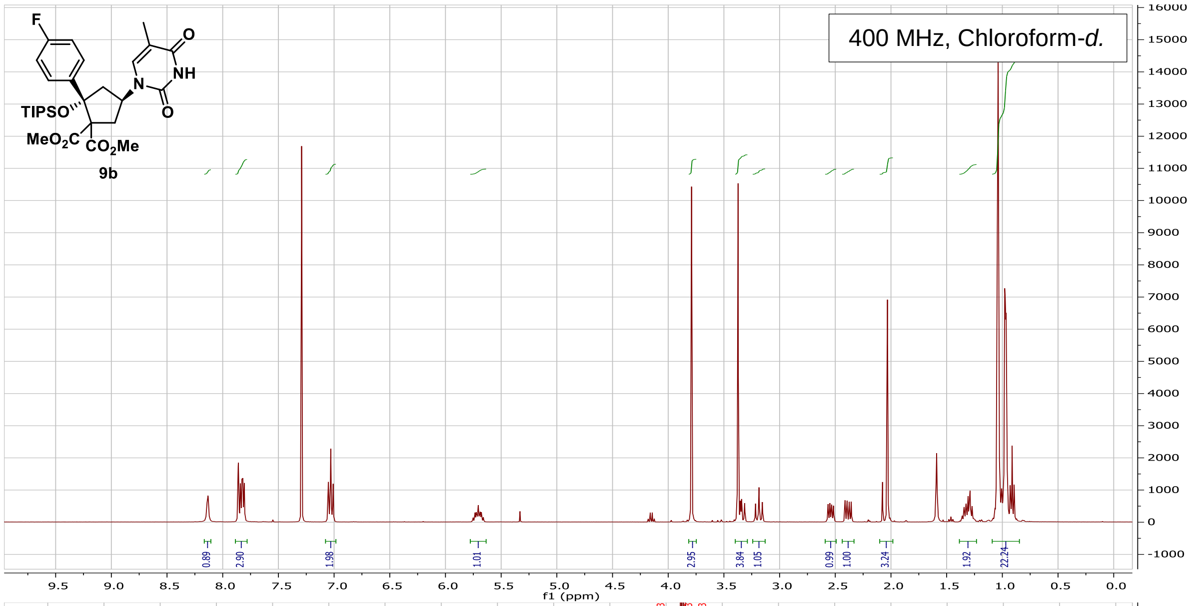

f1 (ppm)

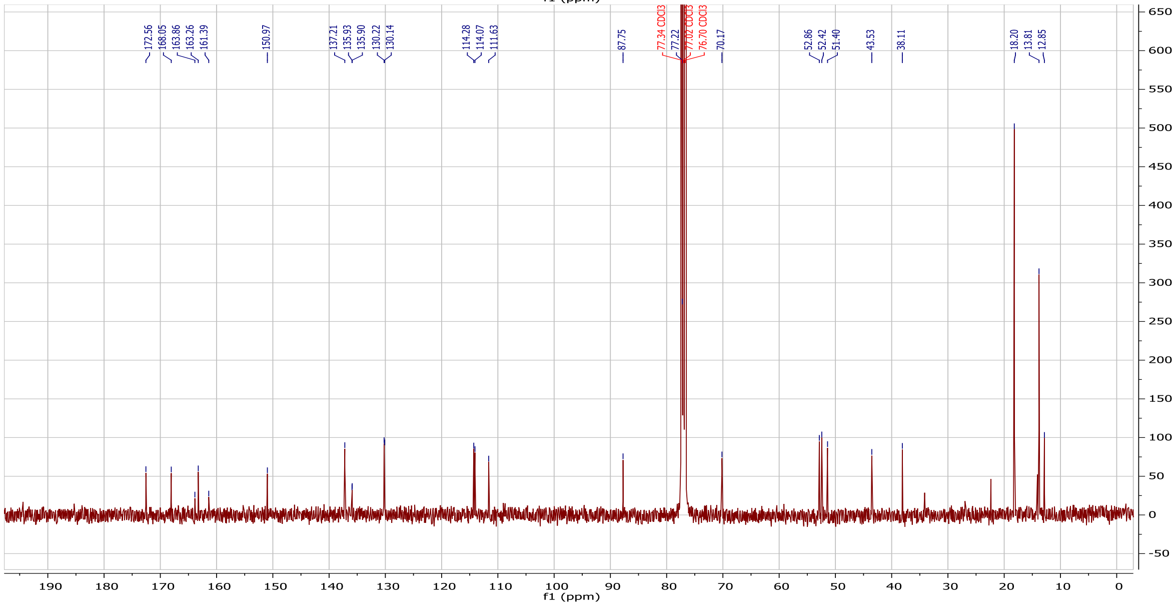

3000
2000
1000

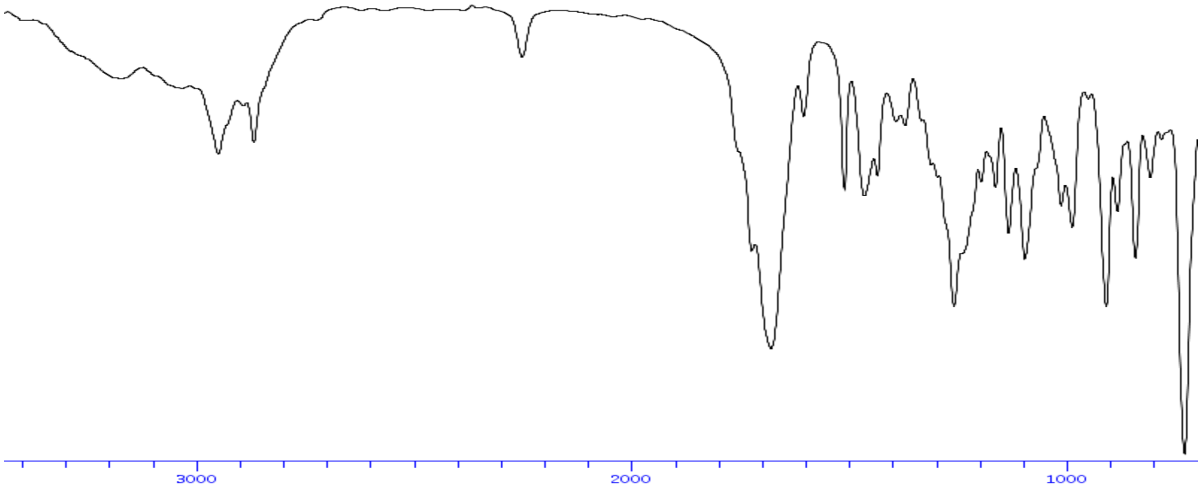

TIPSO
Ph
MeO2C
MeO2C
9a
400 MHz, Chloroform-d.
f1 (ppm)

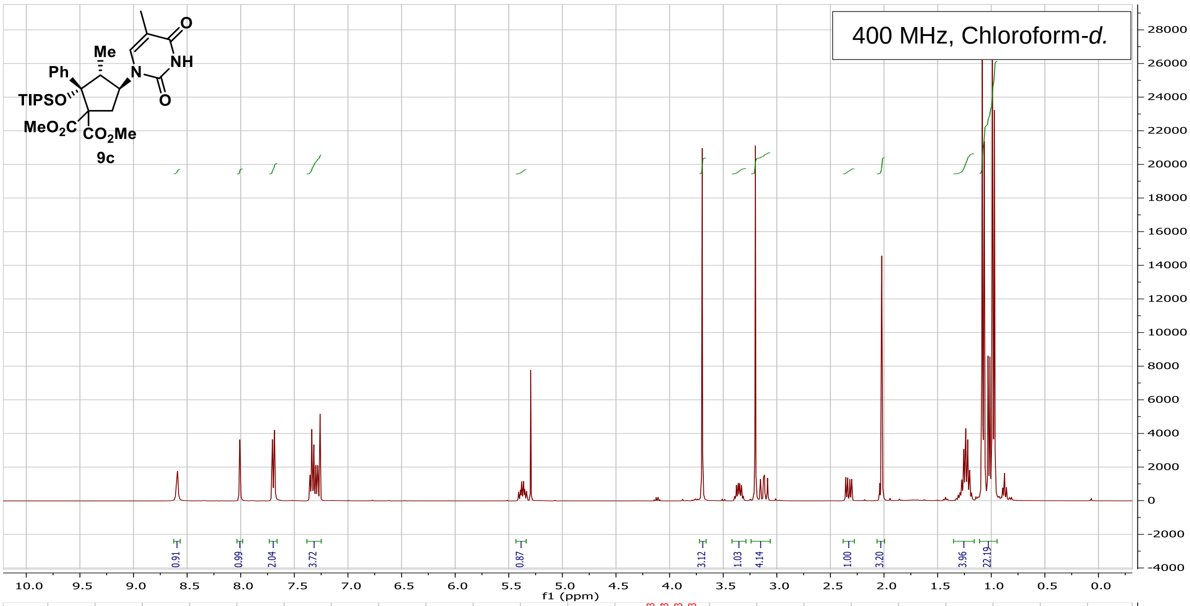

f1 (ppm)

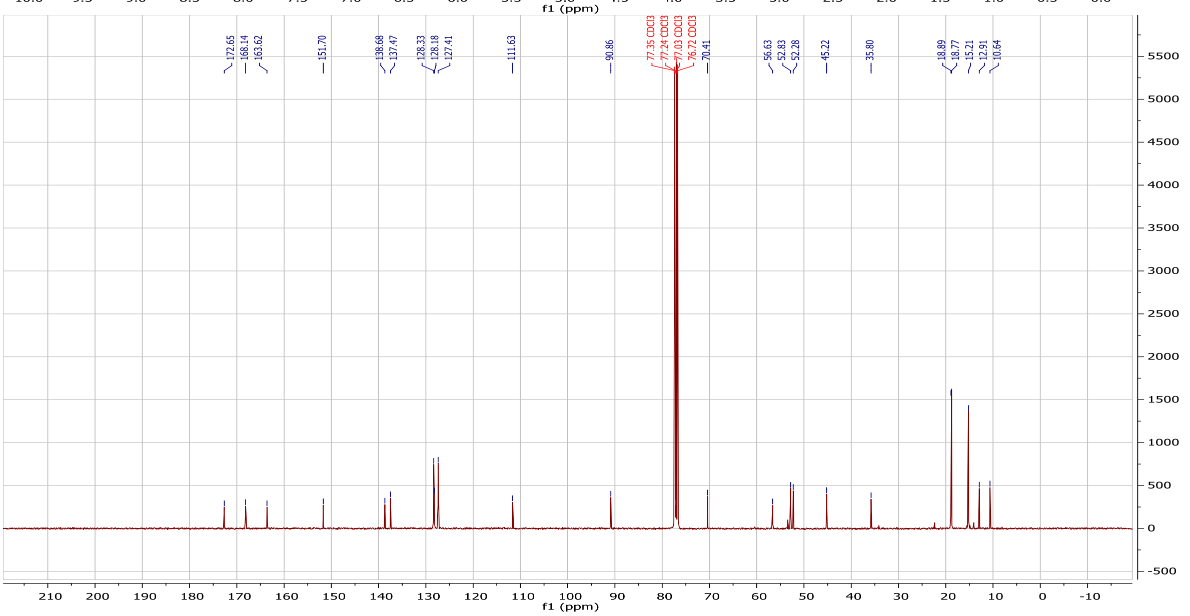

3000
2000
1000

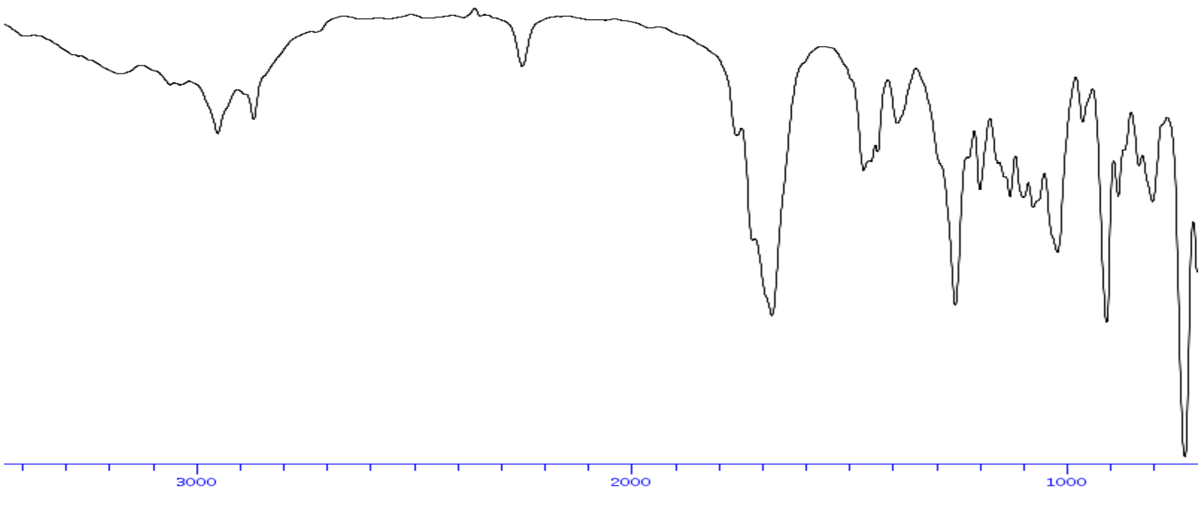

400 MHz, Chloroform-d.
F
TIPSO
MeO2C
CO2Me
N
NH
O
O
9b
f1 (ppm)


172.56
168.05
163.86
163.26
161.39
150.97
137.21
135.93
135.90
130.22
130.14
114.28
114.07
111.63
87.75
77.34 CDCl3
77.22
77.02 CDCl3
76.70 CDCl3
70.17
52.86
52.42
51.40
43.53
38.11
18.20
13.81
12.85
f1 (ppm)

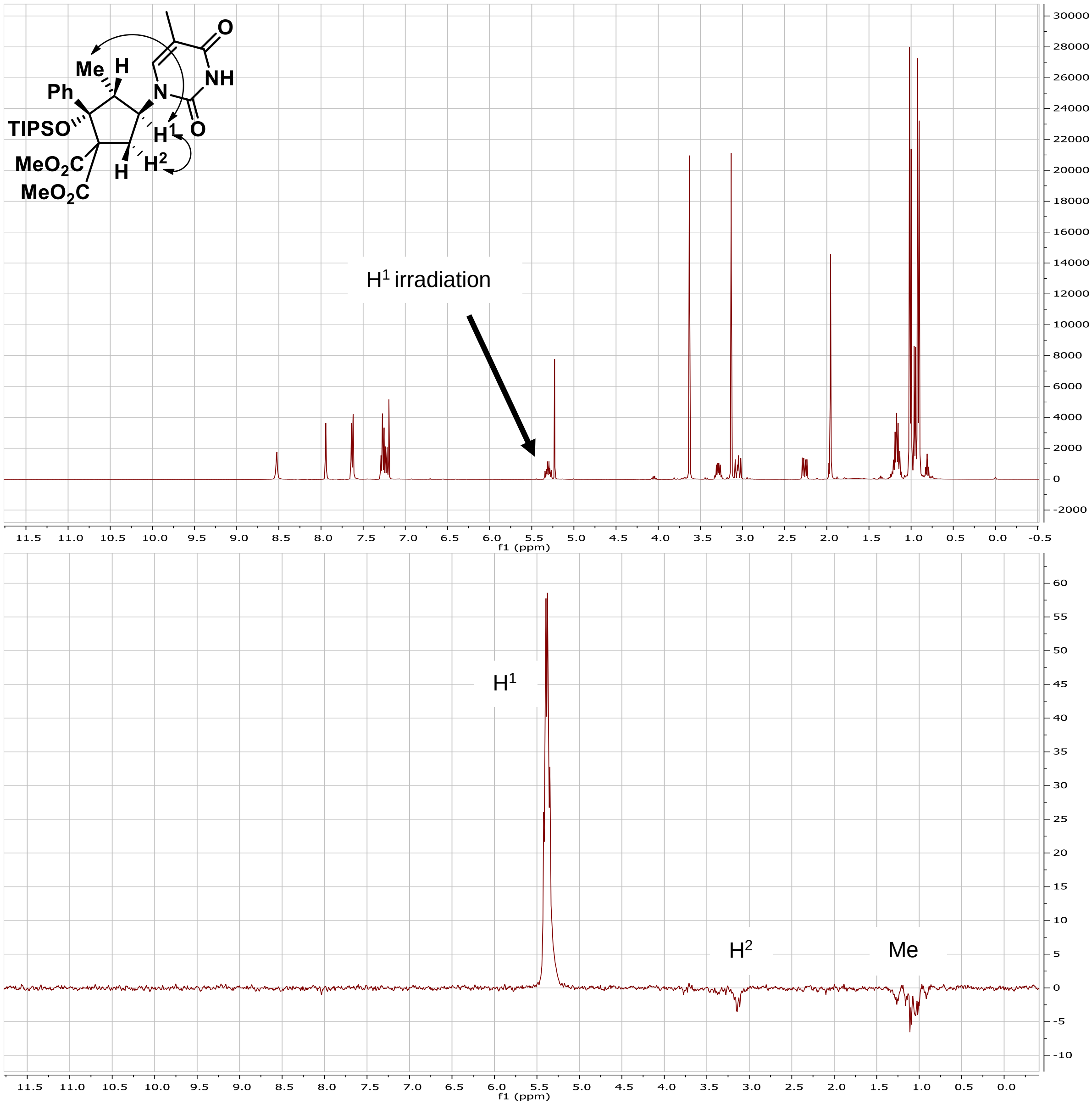

3000
2000
1000


Me
NH
O
Ph
TIPSO
N
O
MeO2C
CO2Me
9c
400 MHz, Chloroform-d.
0.91
0.99
2.04
3.72
0.87
3.12
1.03
4.14
1.00
3.20
3.96
22.19
f1 (ppm)

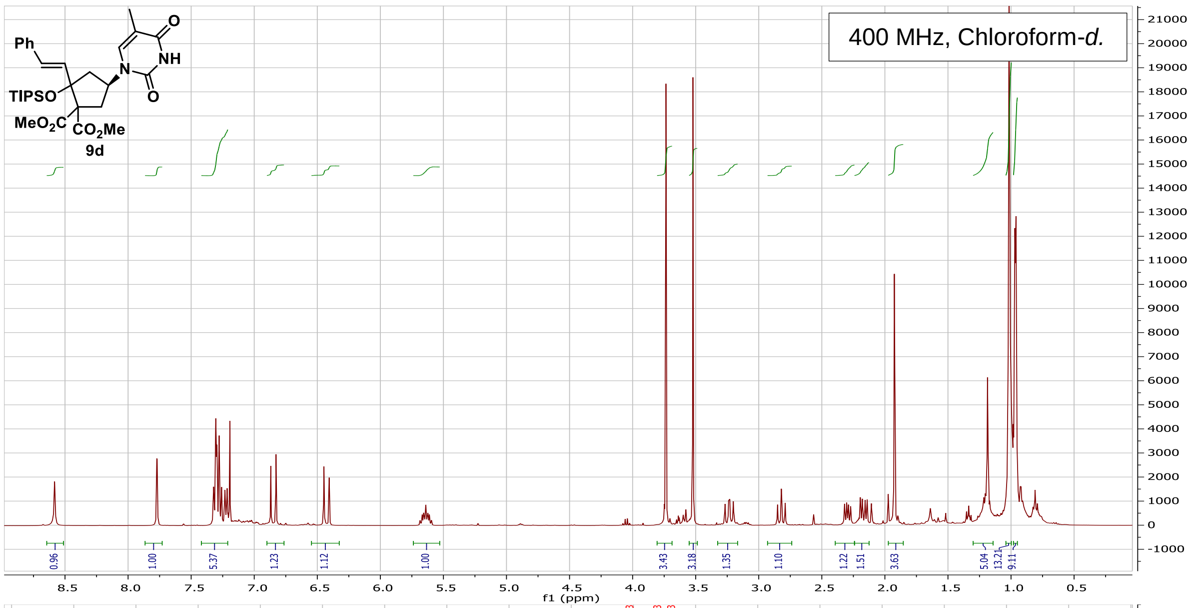

172.65
168.14
163.62
151.70
138.68
137.47
128.33
128.18
127.41
111.63
90.86
77.35 CDCl3
77.24 CDCl3
77.03 CDCl3
76.72 CDCl3
70.41
56.63
52.83
52.28
45.22
35.80
18.89
18.77
15.21
12.91
10.64
f1 (ppm)

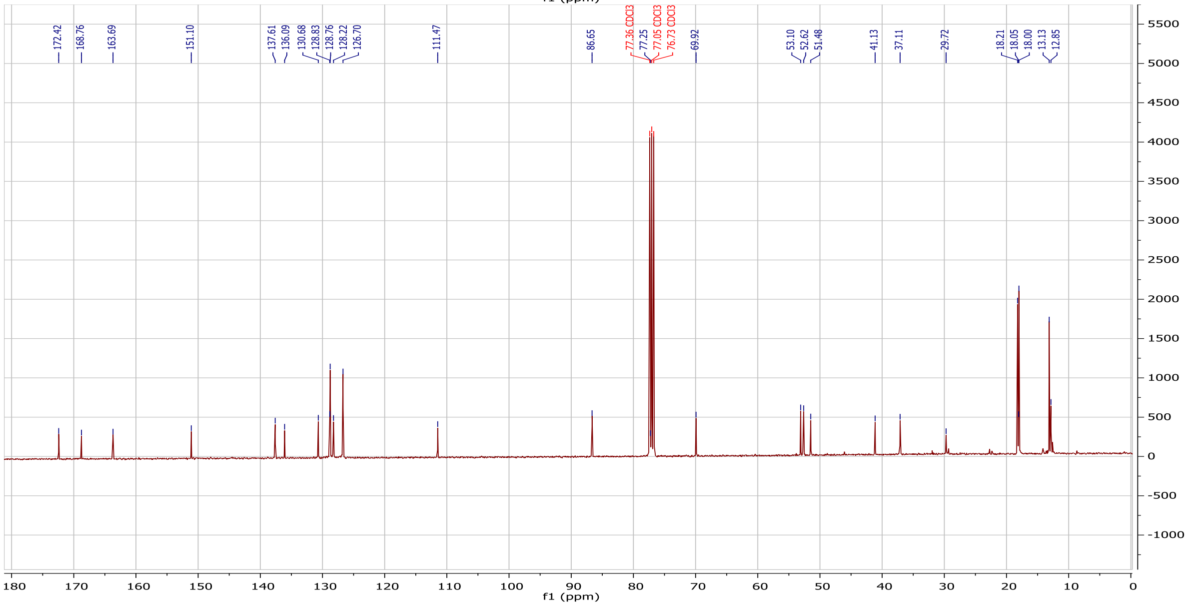

3000
2000
1000

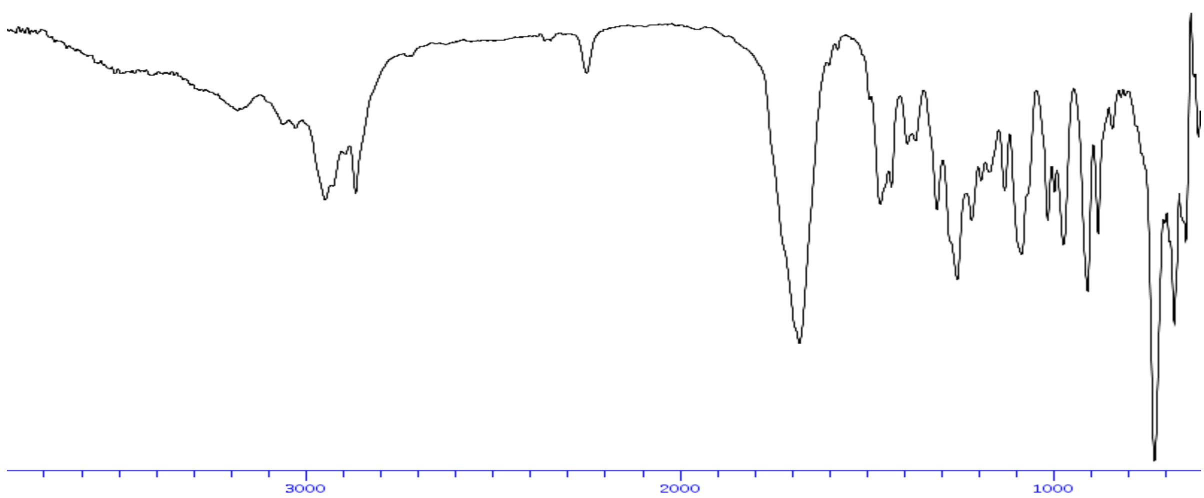
H1

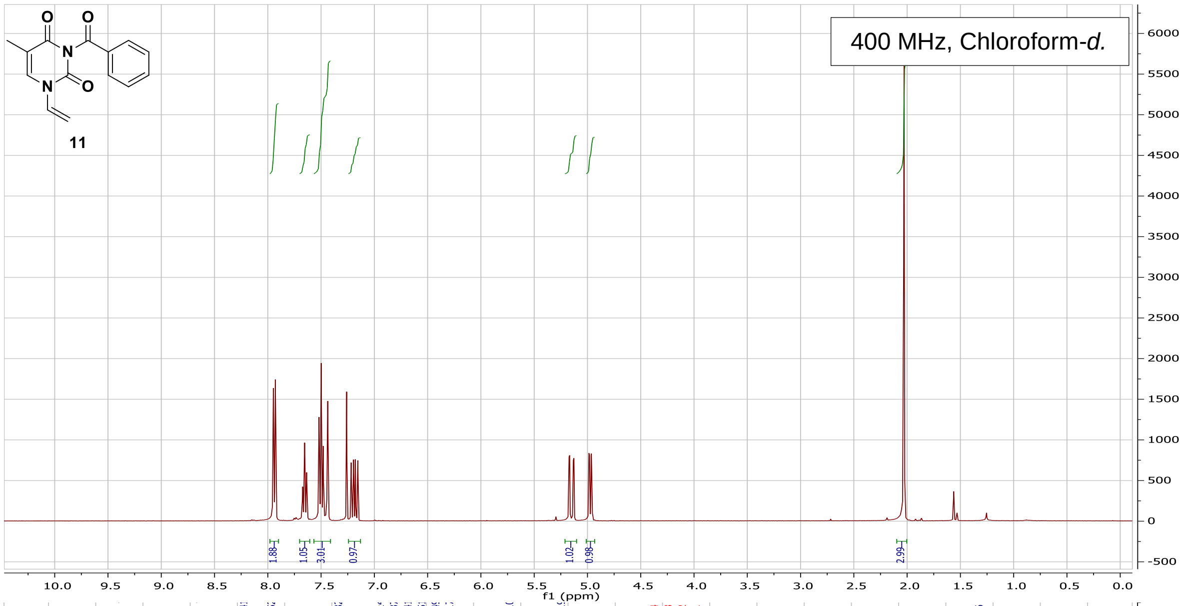


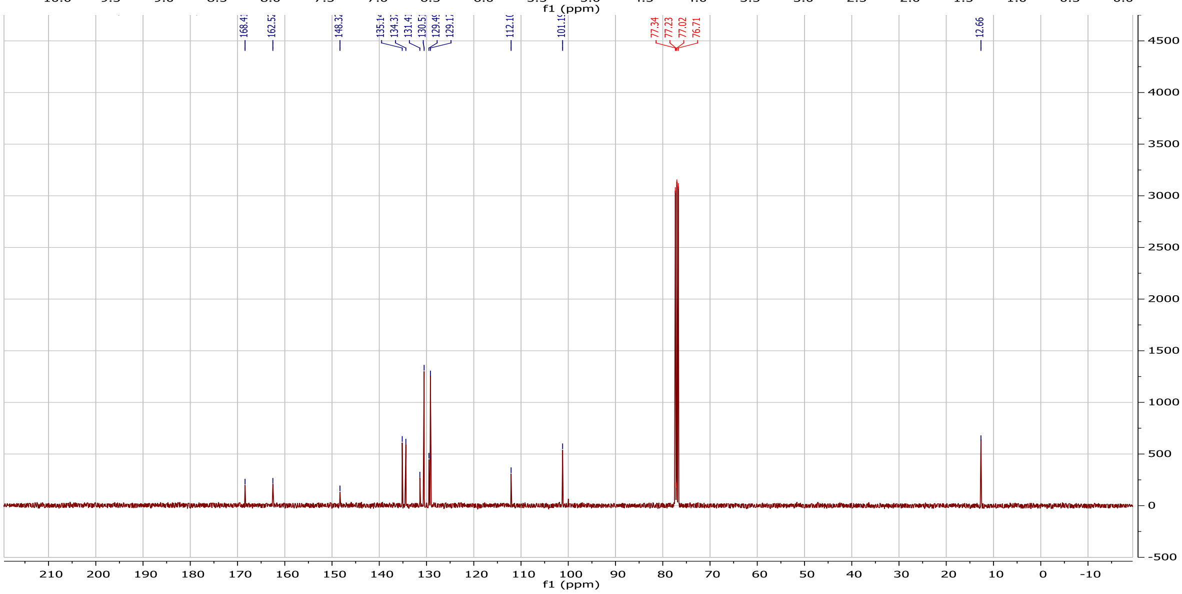
NOESY 1D experiment permitted to define the stereochemistry of the new stereocenter. In fact, we were able to see the NOE interaction between the thymine NCH proton (**H¹**) and the cyclopentane methyl (**Me**) and the cyclopentane CH (**H²**). The absence of coupling between thymine NCH proton (**H¹**) and the cyclopentane CH (3.37 ppm) one is also supporting this assignment.

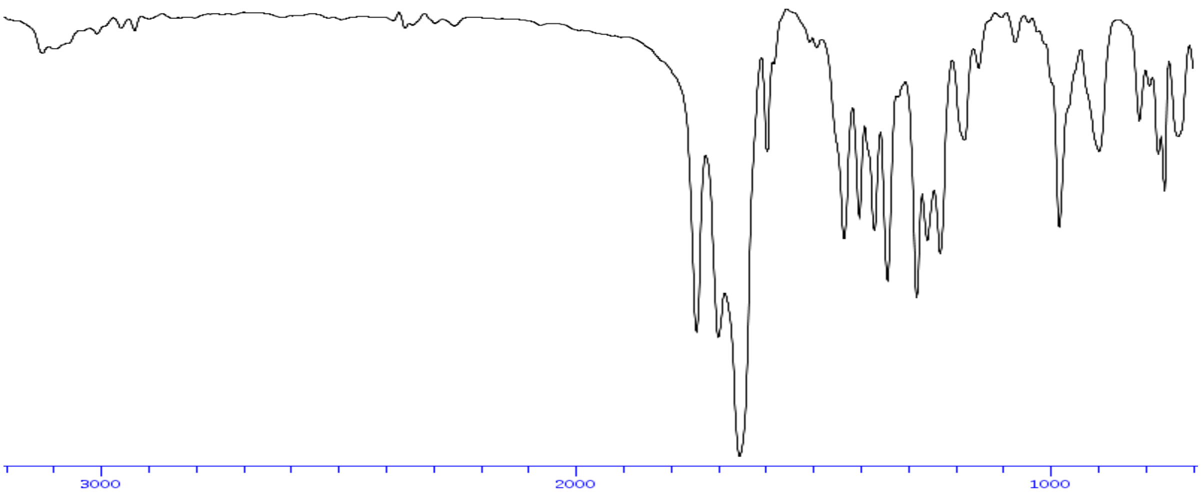

Ph
TIPSO
MeO2C
CO2Me
9d
400 MHz, Chloroform-d.
f1 (ppm)

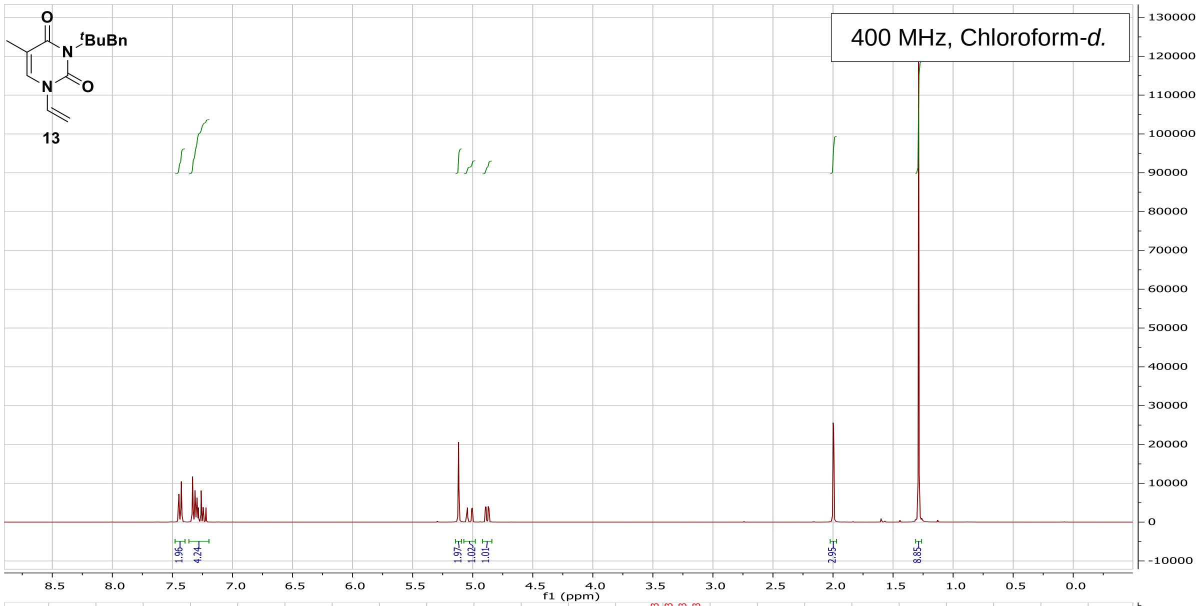

f1 (ppm)



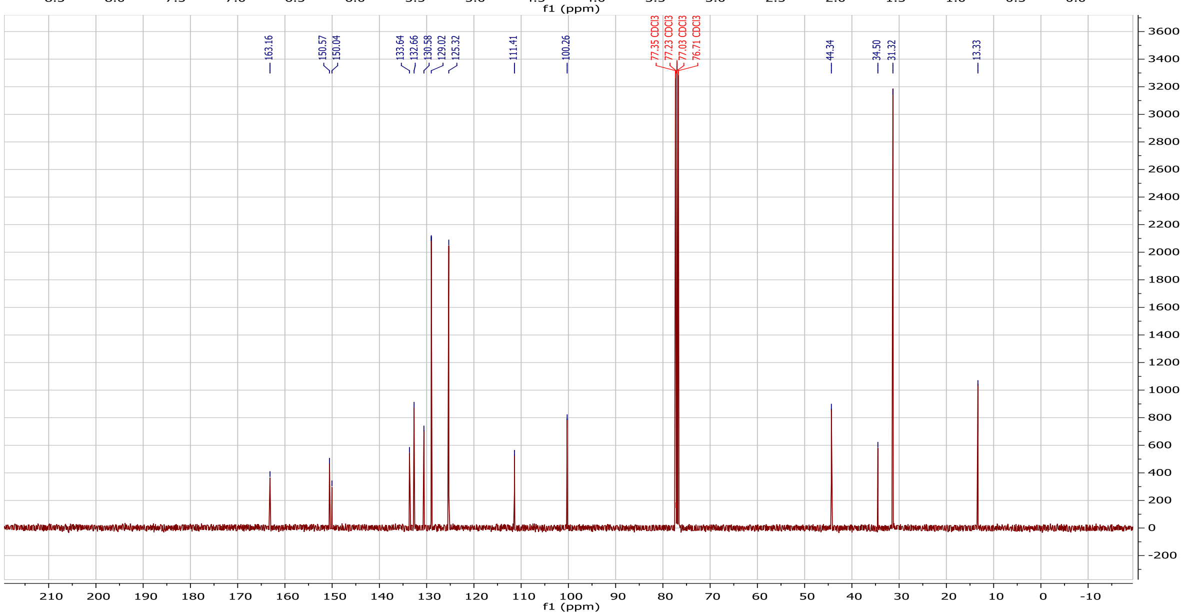

400 MHz, Chloroform-d.
11
f1 (ppm)


f1 (ppm)

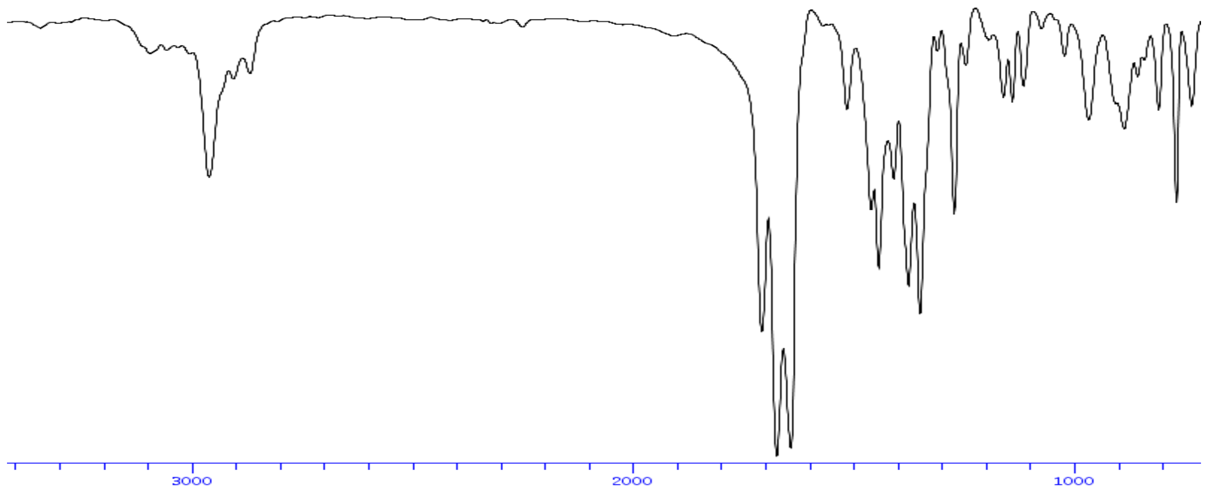

3000
2000
1000



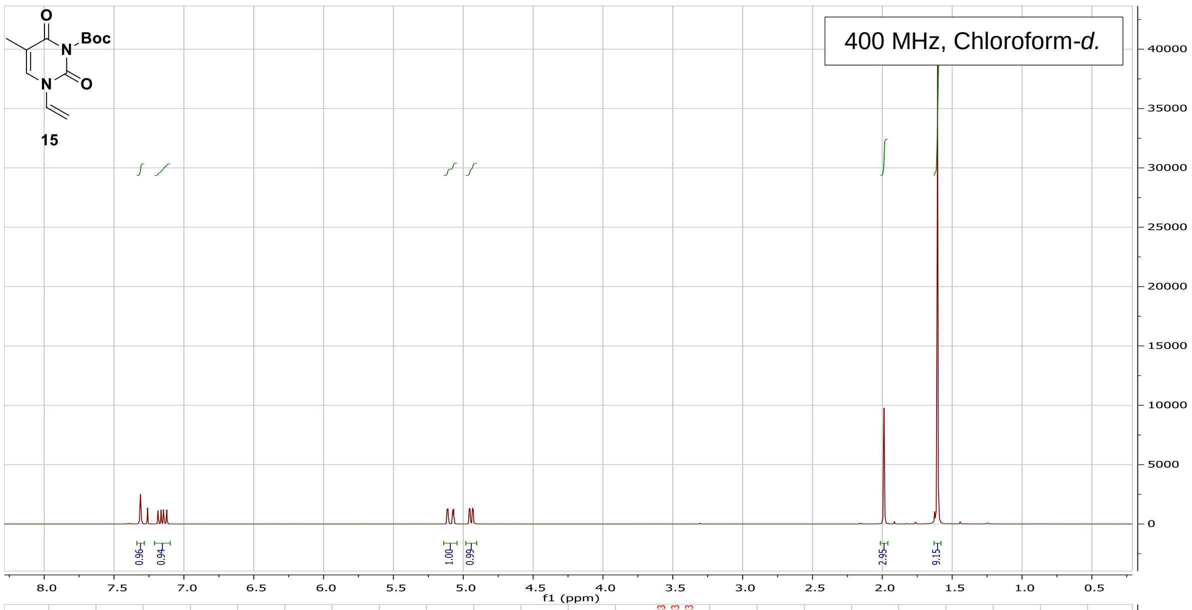
13
400 MHz, Chloroform-d.
f1 (ppm)

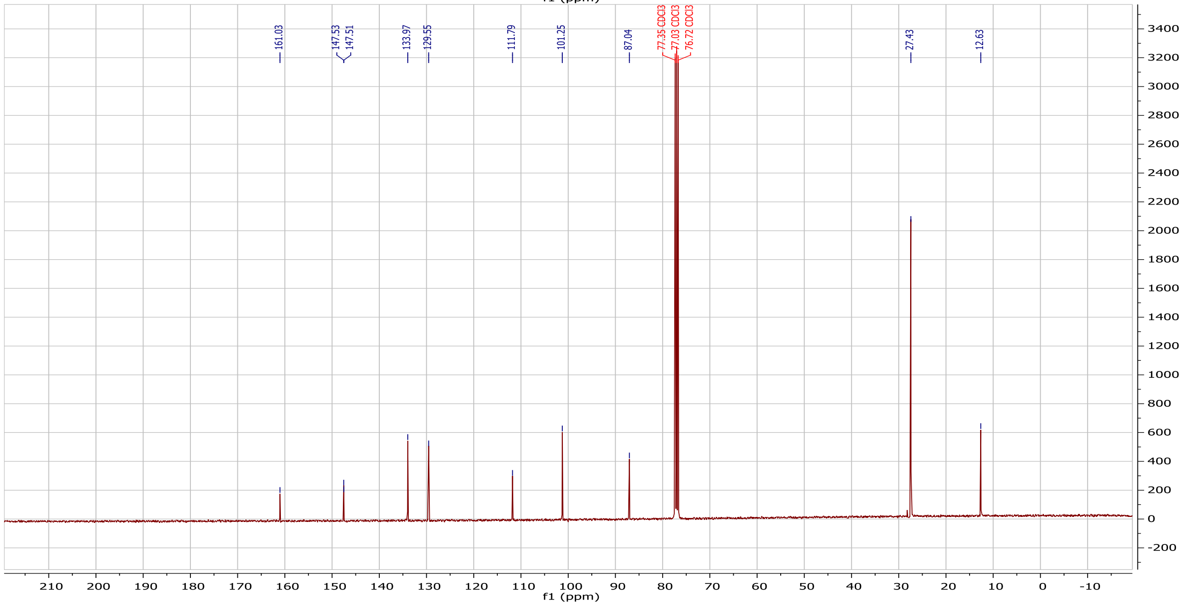


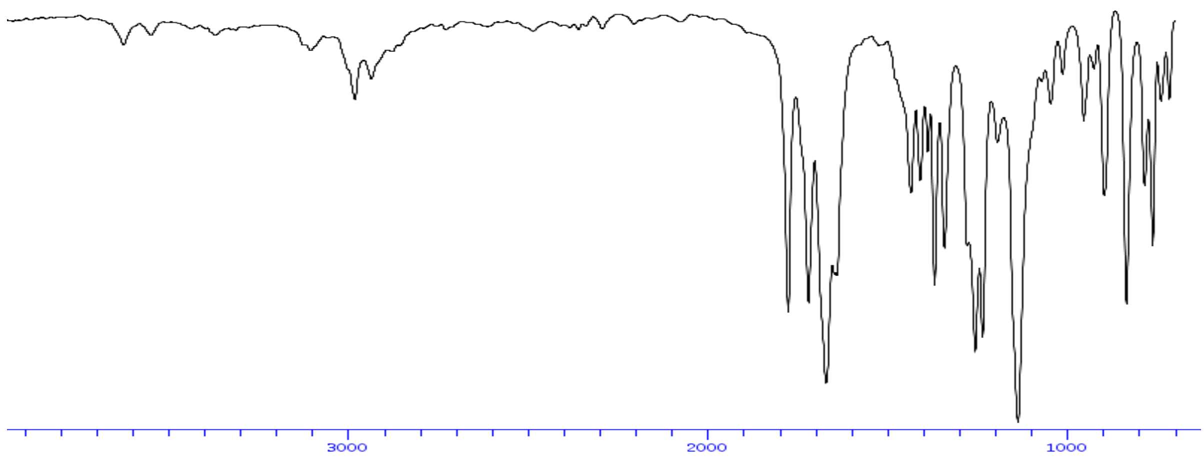
f1 (ppm)

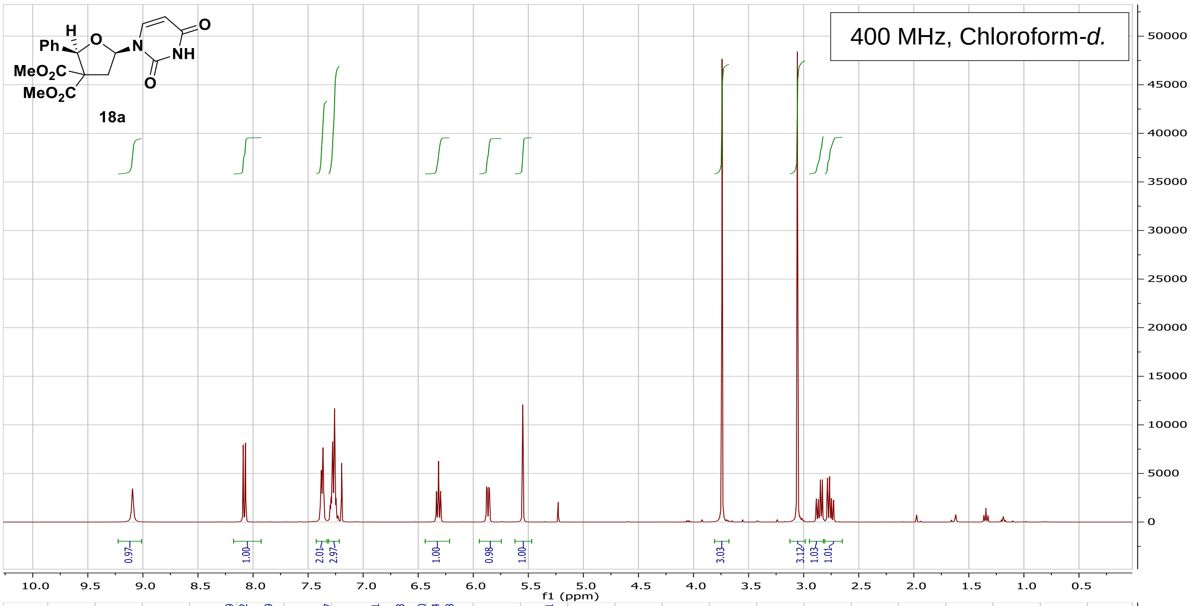


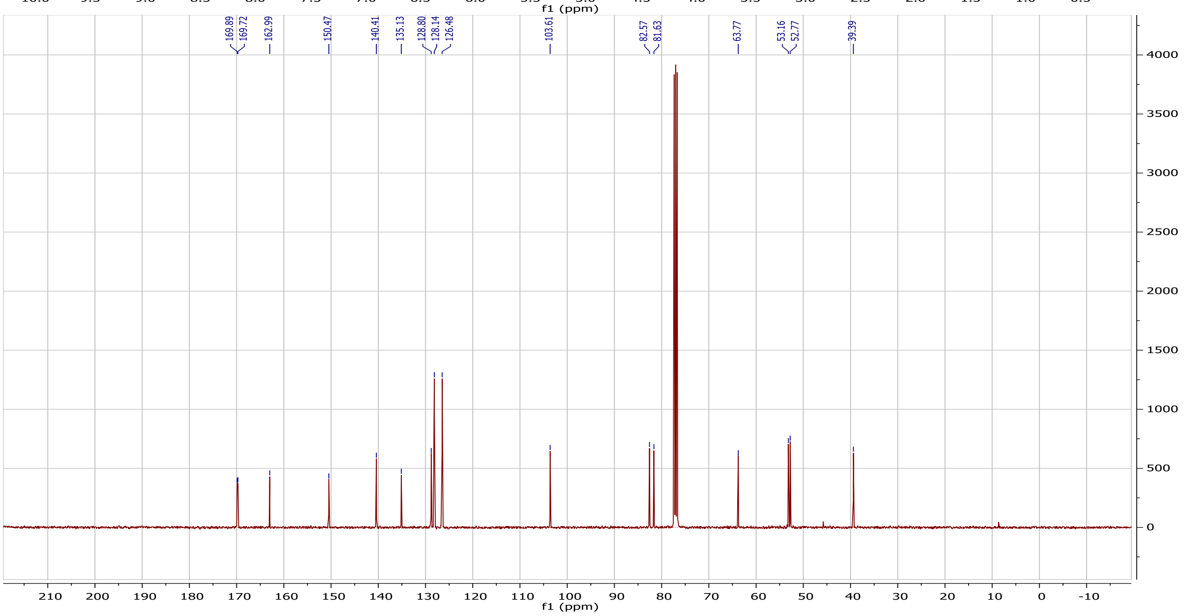
3000
2000
1000

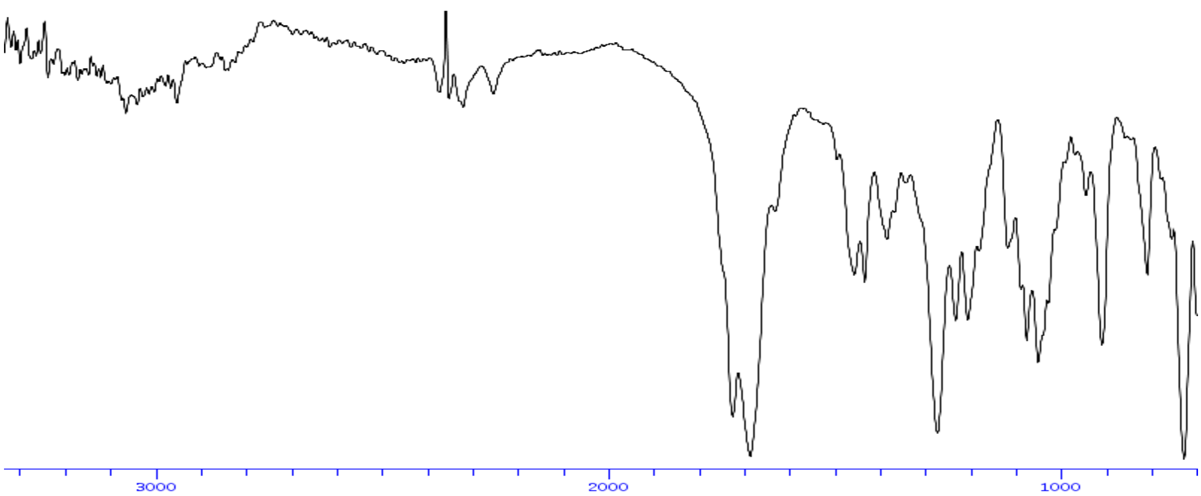

O
N
Boc
O
N
15
400 MHz, Chloroform-d.
0.96
0.94
1.00
0.99
2.95
9.15
f1 (ppm)

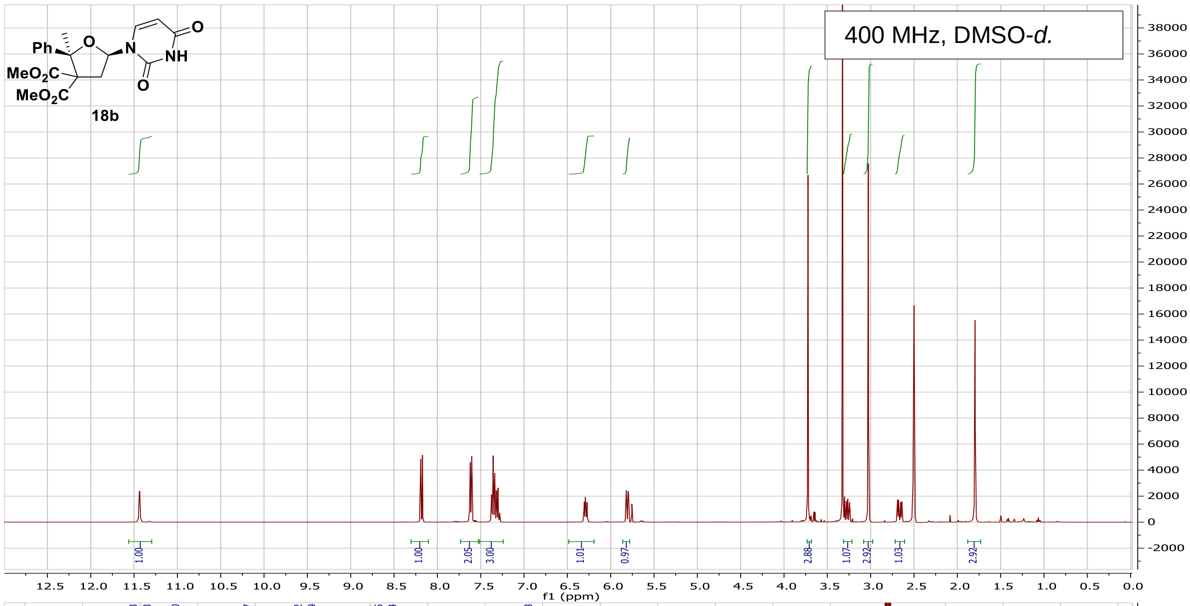

161.03
147.53
147.51
133.97
129.55
111.79
101.25
87.04
77.35 CDCl3
77.03 CDCl3
76.72 CDCl3
27.43
12.63
f1 (ppm)

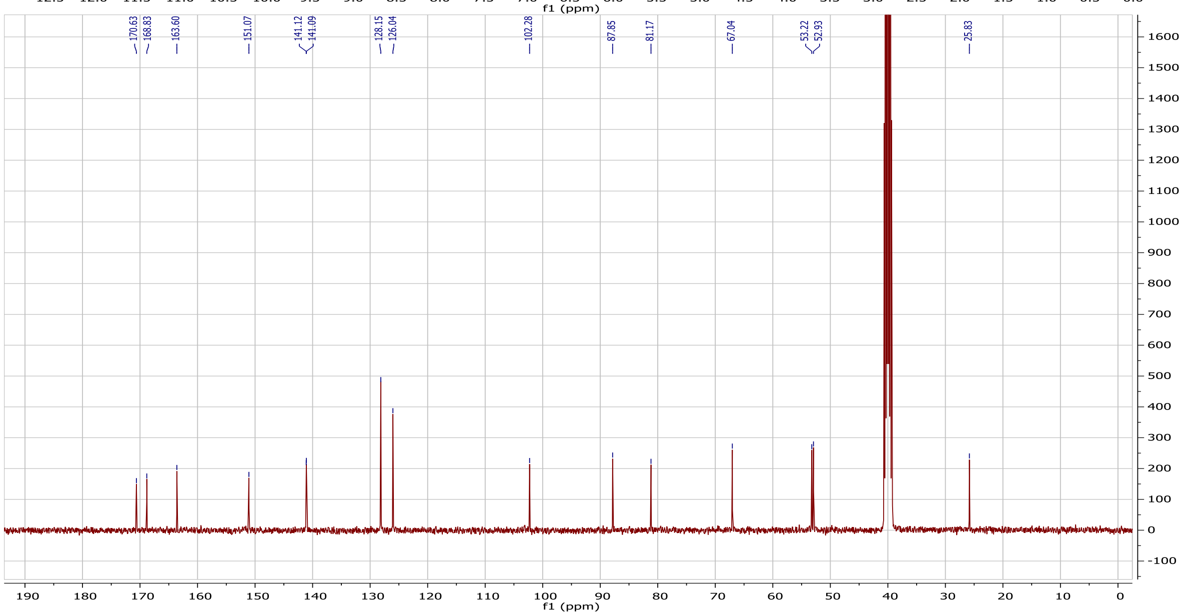

3000
2000
1000

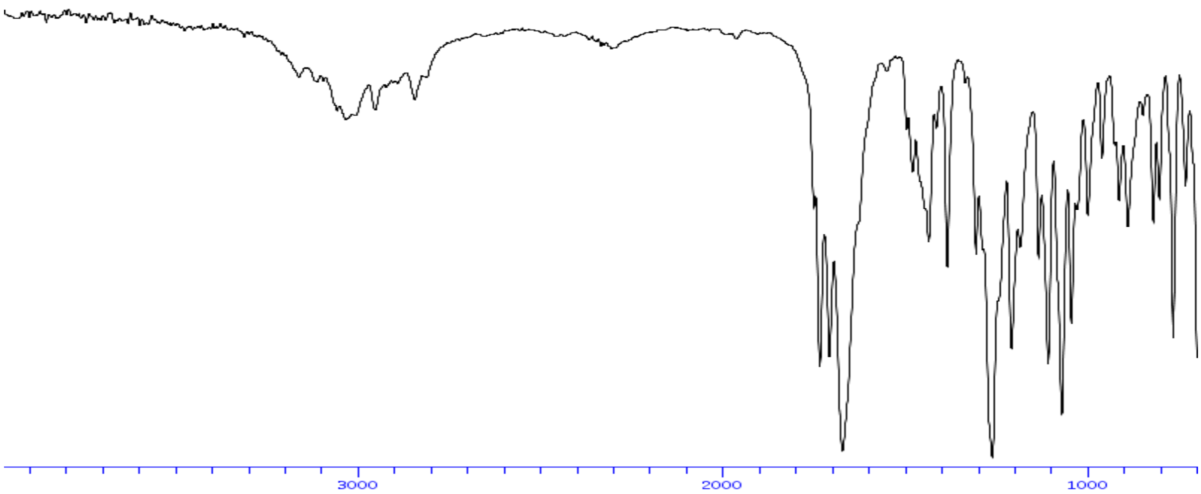

400 MHz, Chloroform-*d.*
18a
f1 (ppm)

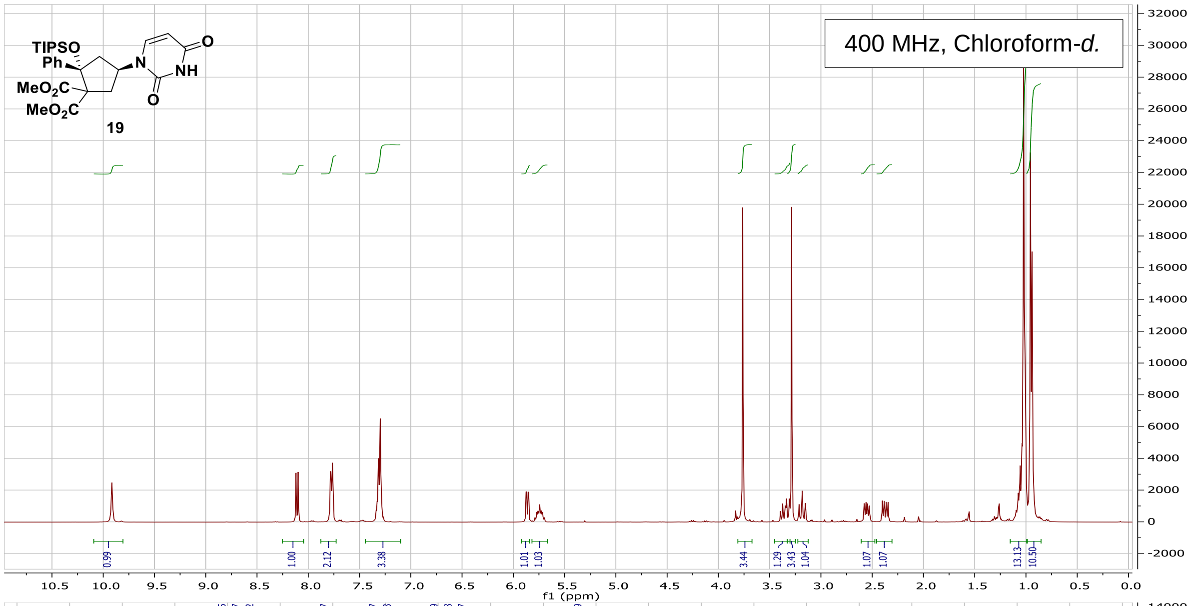

169.89
169.72
162.99
150.47
140.41
135.13
128.80
128.14
126.48
103.61
82.57
81.63
63.77
53.16
52.77
39.39
f1 (ppm)

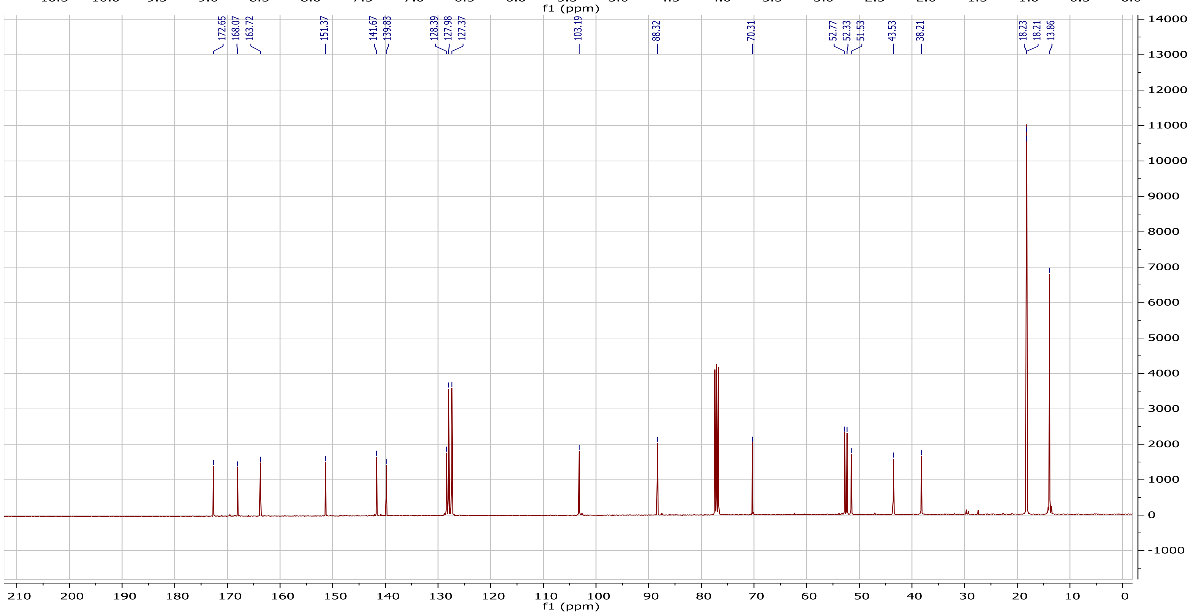

3000
2000
1000

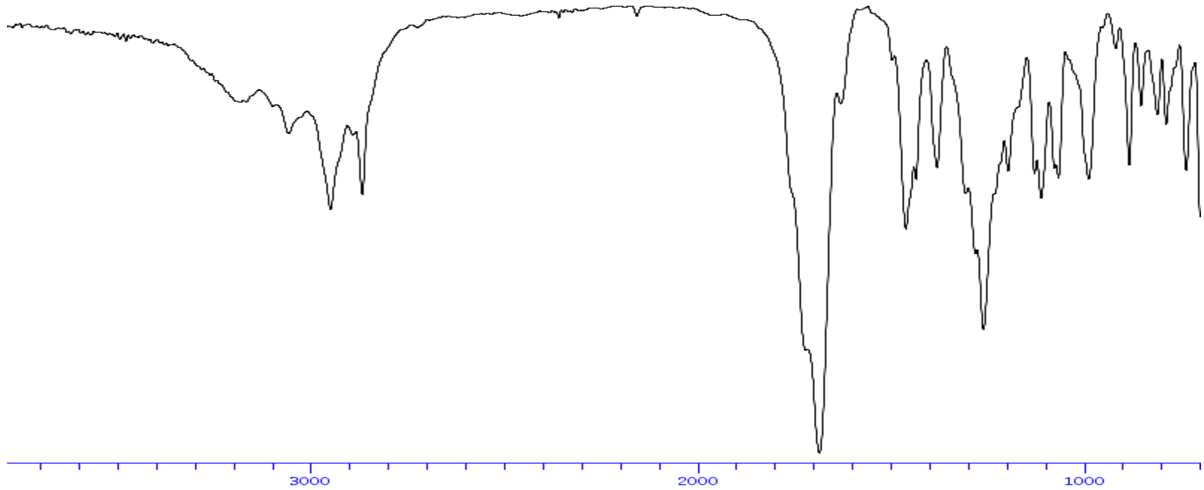

400 MHz, DMSO-d.
Ph
MeO2C
MeO2C
O
N
NH
O
O
18b
f1 (ppm)

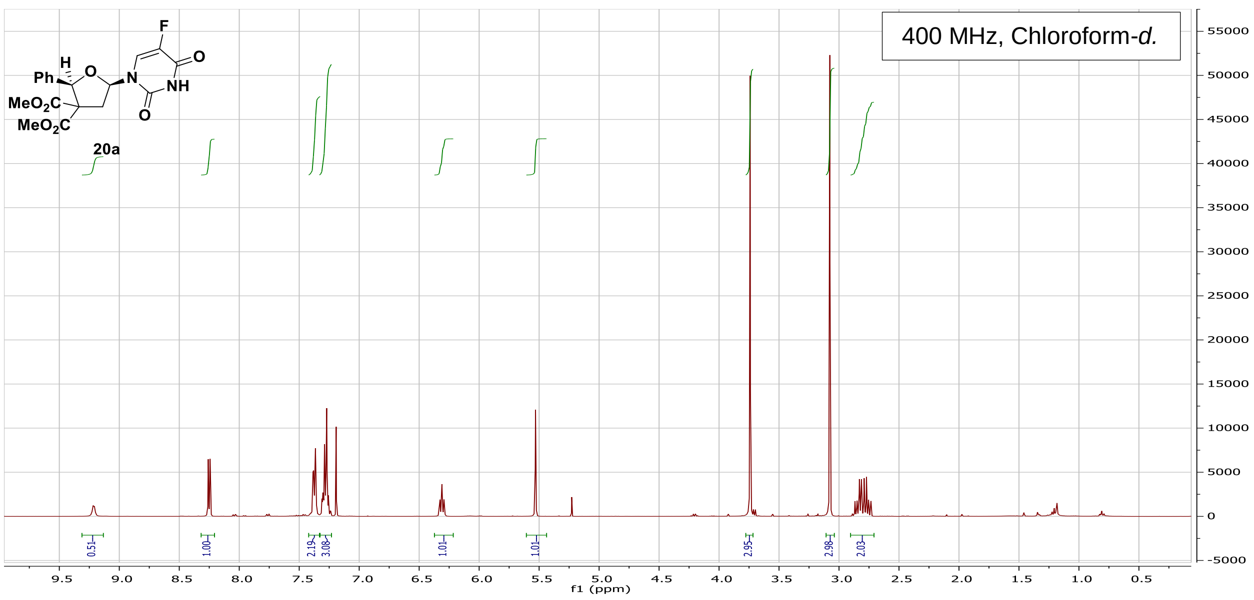

170.63
168.83
163.60
151.07
141.12
141.09
128.15
126.04
102.28
87.85
81.17
67.04
53.22
52.93
25.83
f1 (ppm)

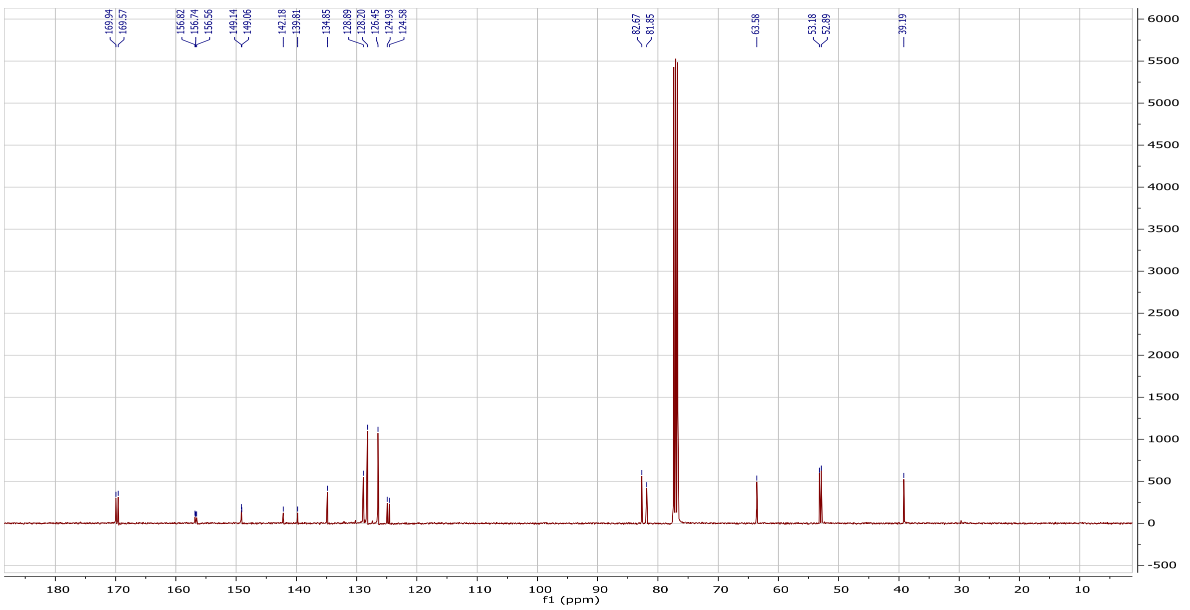

3000
2000
1000

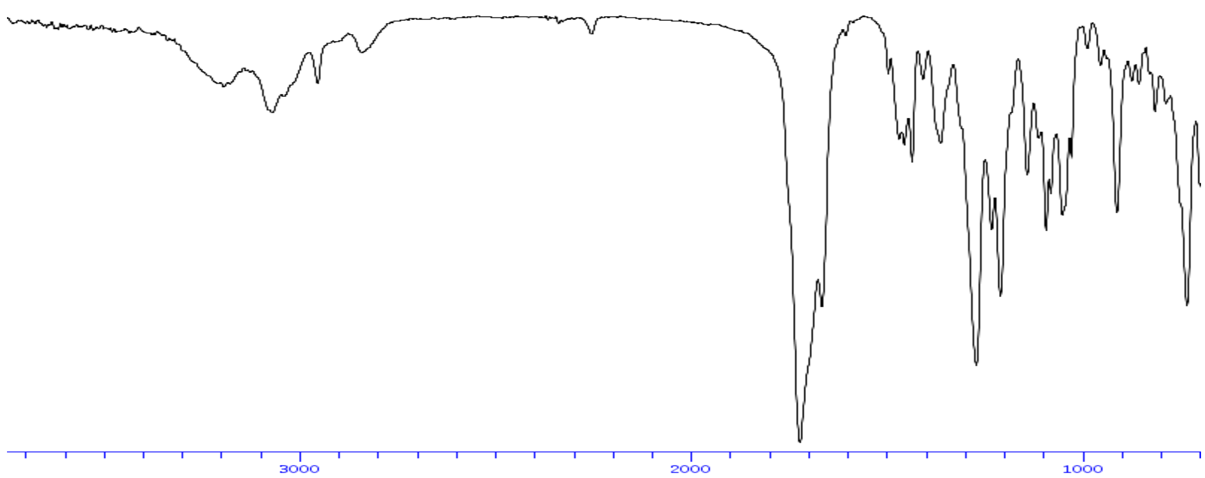

TIPSO
Ph
MeO2C
MeO2C
N
NH
O
O
19
400 MHz, Chloroform-d.
0.99
1.00
2.12
3.38
1.01
1.03
3.44
1.29
3.43
1.04
1.07
1.07
13.13
10.50
f1 (ppm)

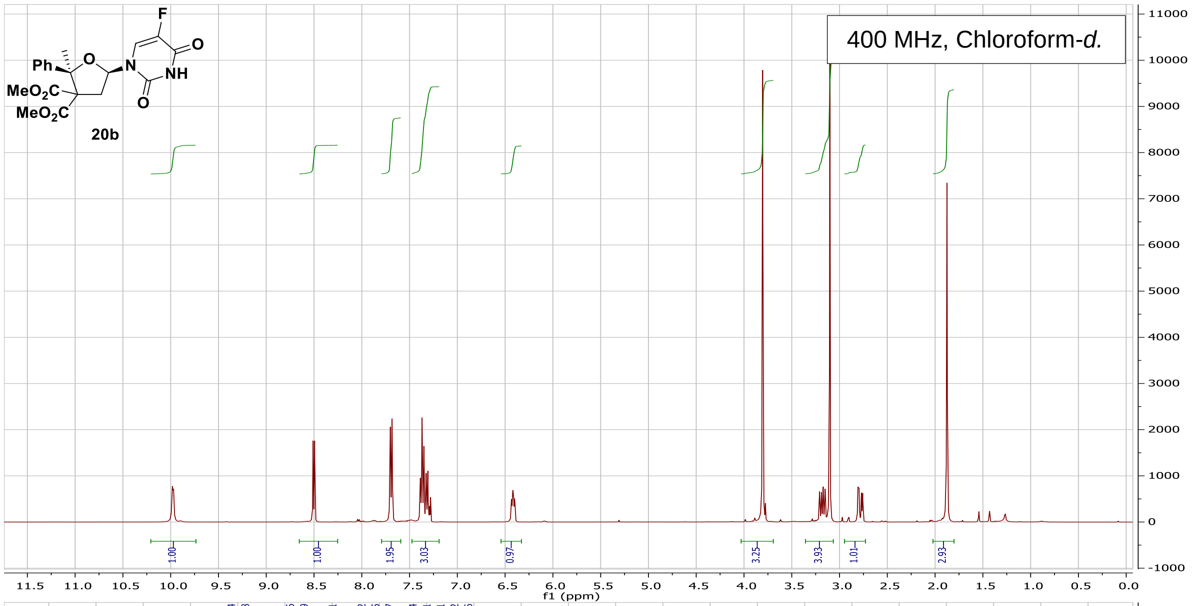

172.65
168.07
163.72
151.37
141.67
139.83
128.39
127.98
127.37
103.19
88.32
70.31
52.77
52.33
51.53
43.53
38.21
18.23
18.21
13.86
f1 (ppm)

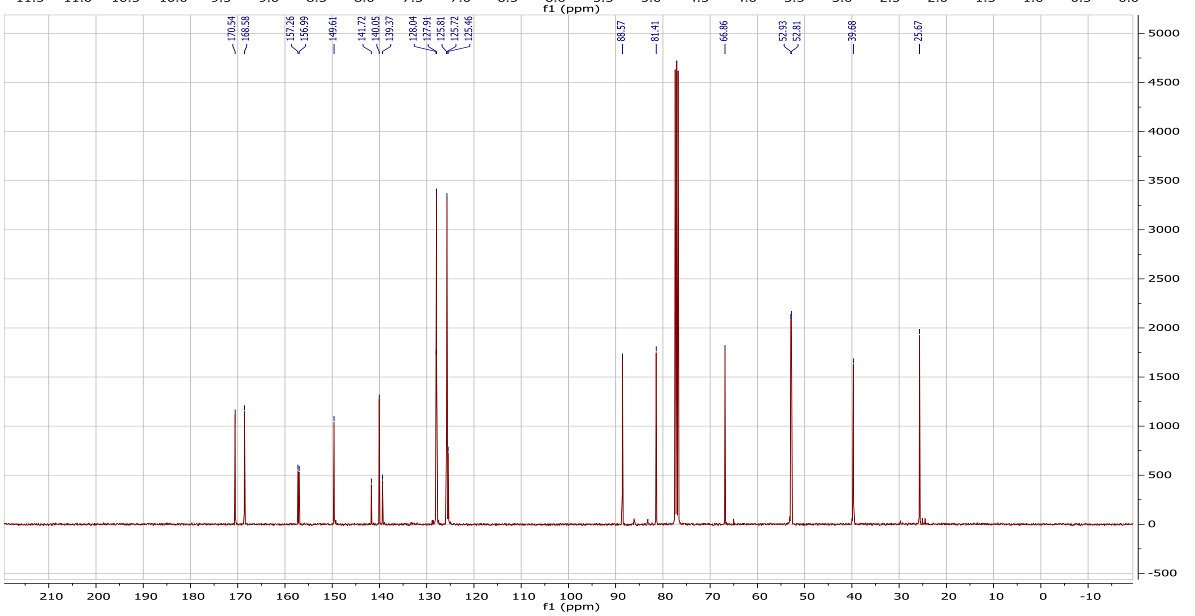

3000
2000
1000

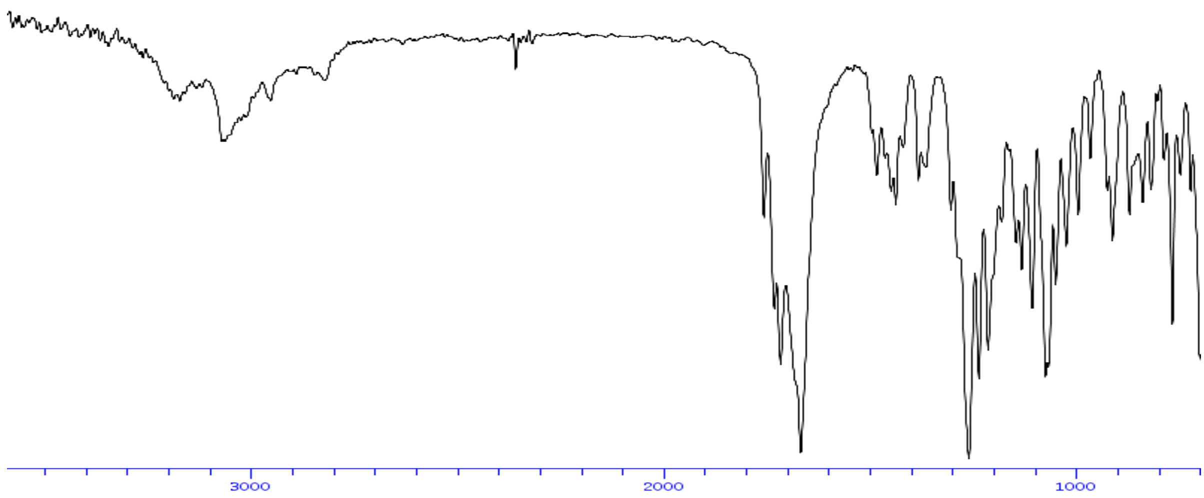

400 MHz, Chloroform-d.
20a
0.51
1.00
2.19
3.08
1.01
1.01
2.95
2.98
2.03
f1 (ppm)

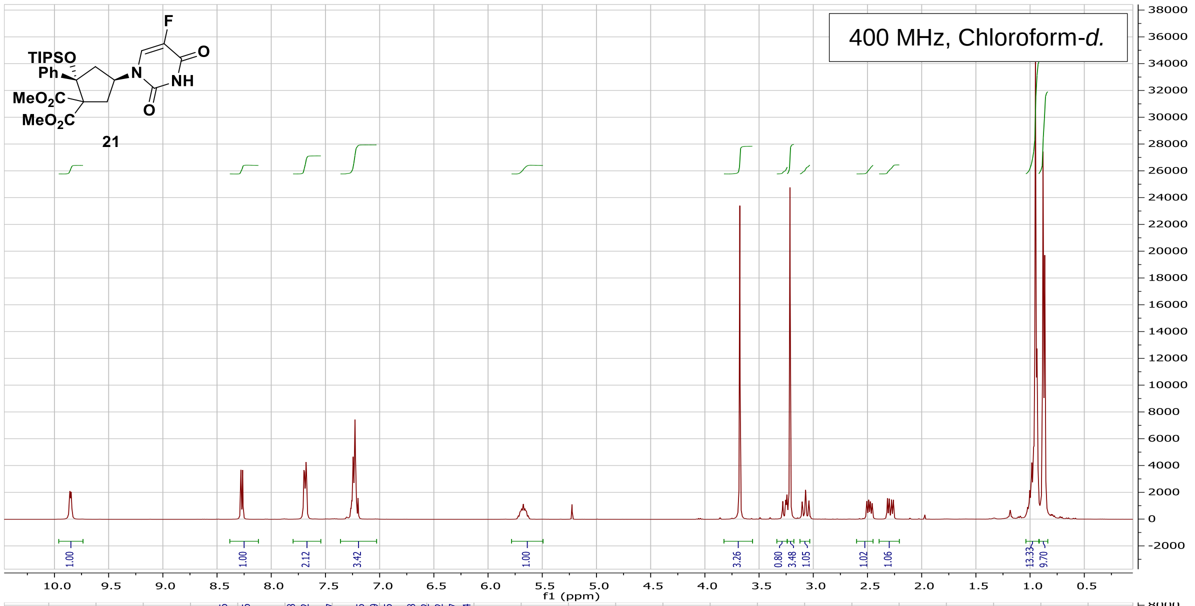

169.94
169.57
156.82
156.74
156.56
149.14
149.06
142.18
139.81
134.85
128.89
128.20
126.45
124.93
124.58
82.67
81.85
63.58
53.18
52.89
39.19
f1 (ppm)

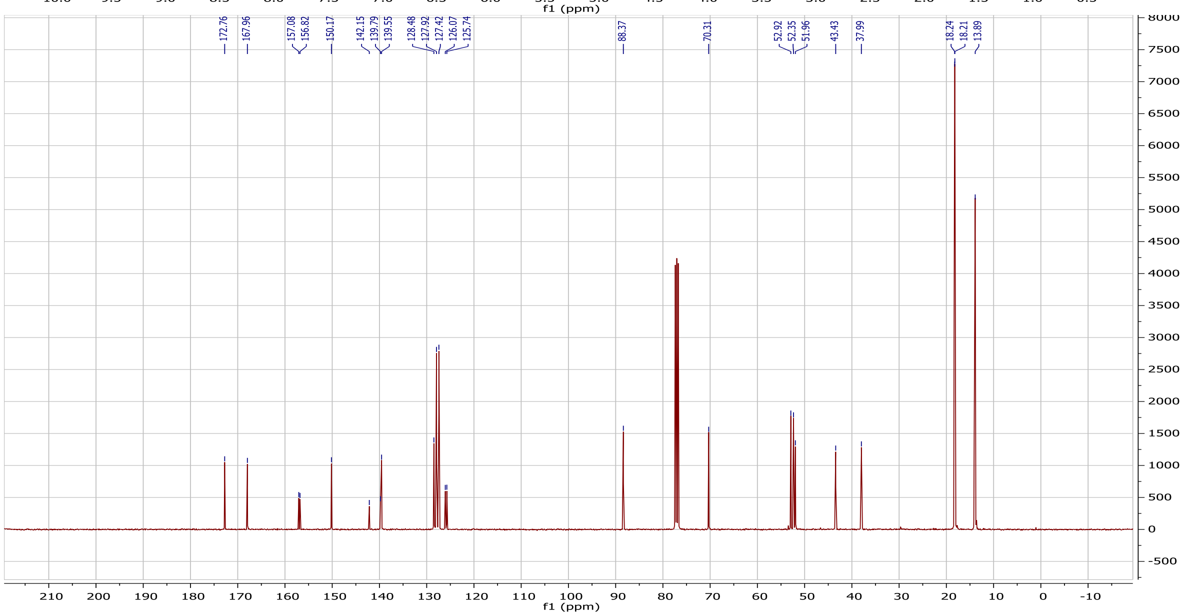


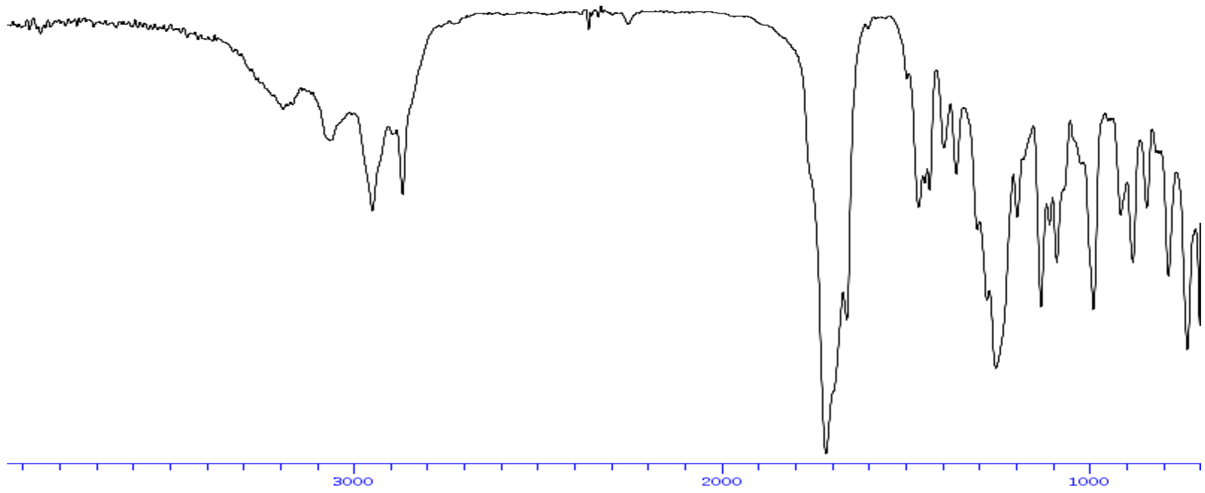

400 MHz, Chloroform-d.
Ph
MeO2C
MeO2C
F
O
N
NH
20b
1.00
1.00
1.95
3.03
0.97
3.25
3.93
1.01
2.93
f1 (ppm)

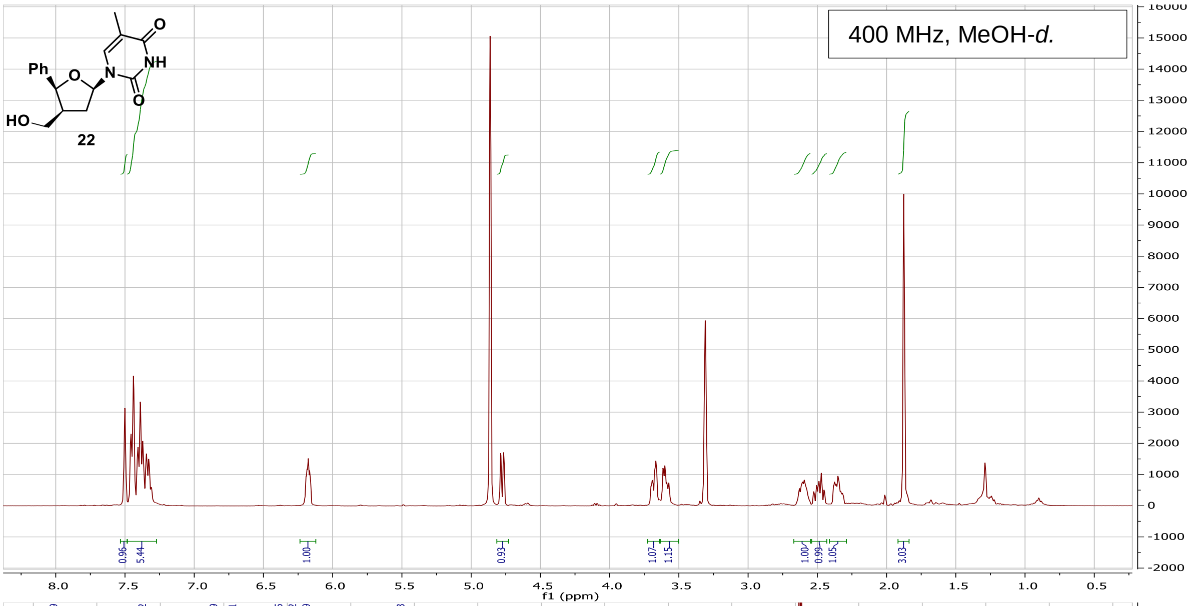

170.54
168.58
157.26
156.99
149.61
141.72
140.05
139.37
128.04
127.91
125.81
125.72
125.46
88.57
81.41
66.86
52.93
52.81
39.68
25.67
f1 (ppm)


3000
2000
1000

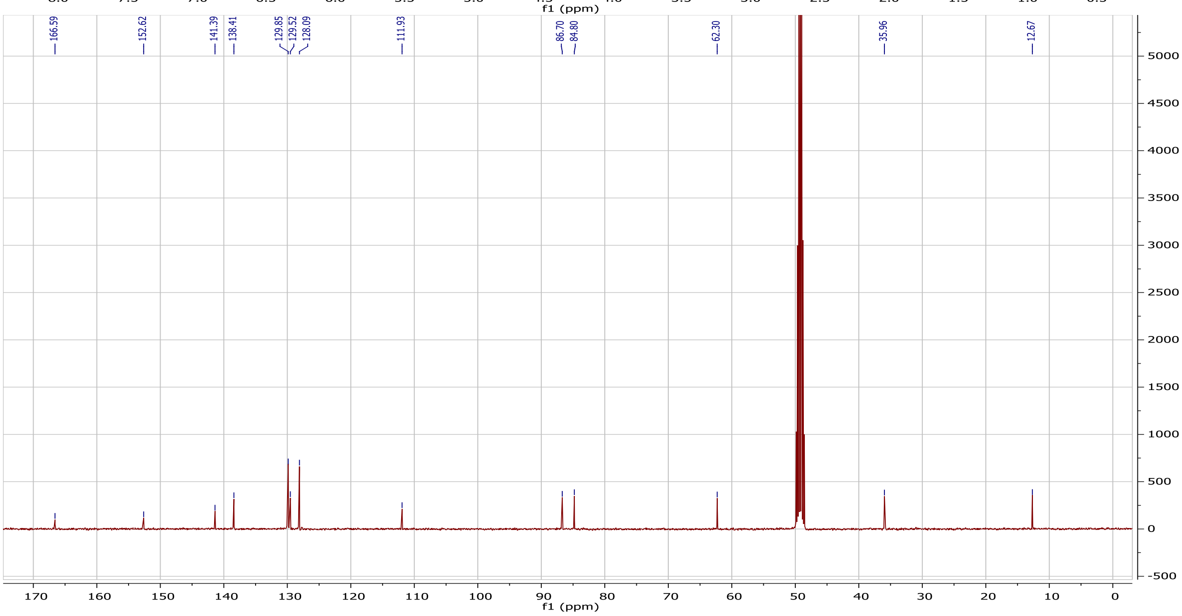

400 MHz, Chloroform-d.
TIPSO
Ph
MeO2C
MeO2C
F
O
N
NH
O
21
1.00
1.00
2.12
3.42
1.00
3.26
0.80
3.48
1.05
1.02
1.06
13.33
9.70
f1 (ppm)


172.76
167.96
157.08
156.82
150.17
142.15
139.79
139.55
128.48
127.92
127.42
126.07
125.74
88.37
70.31
52.92
52.35
51.96
43.43
37.99
18.24
18.21
13.89
f1 (ppm)

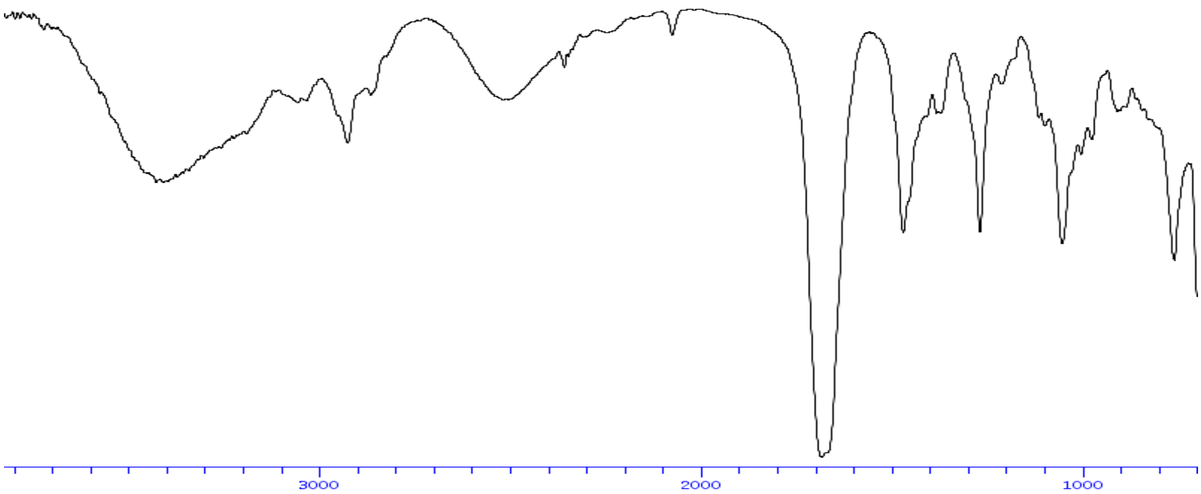

3000
2000
1000

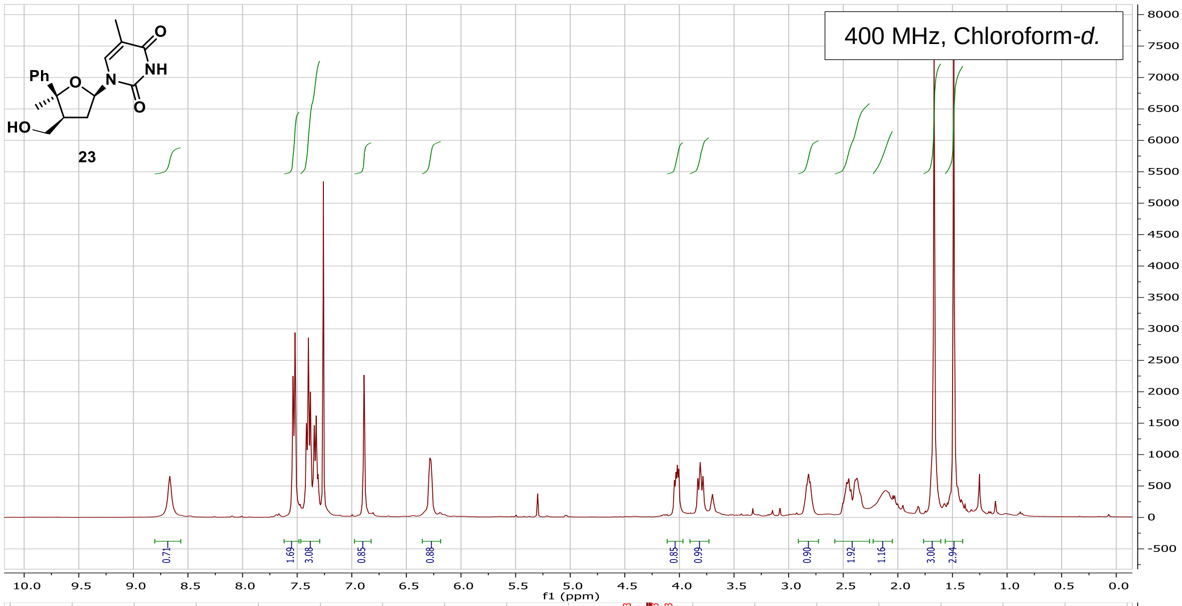


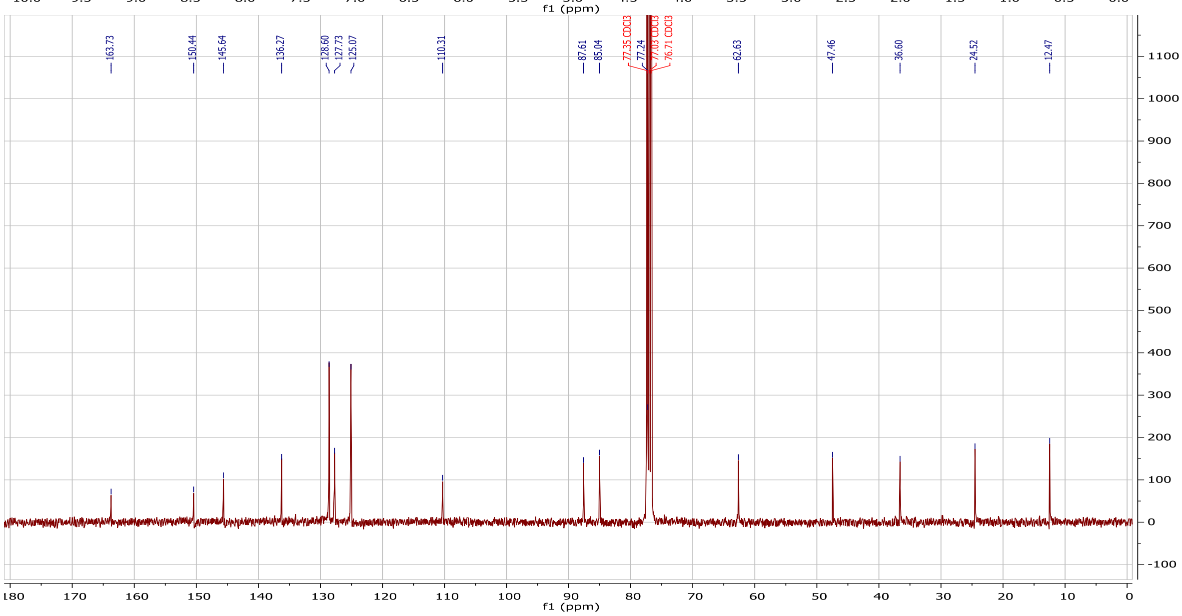
400 MHz, MeOH-*d.*
22
f1 (ppm)

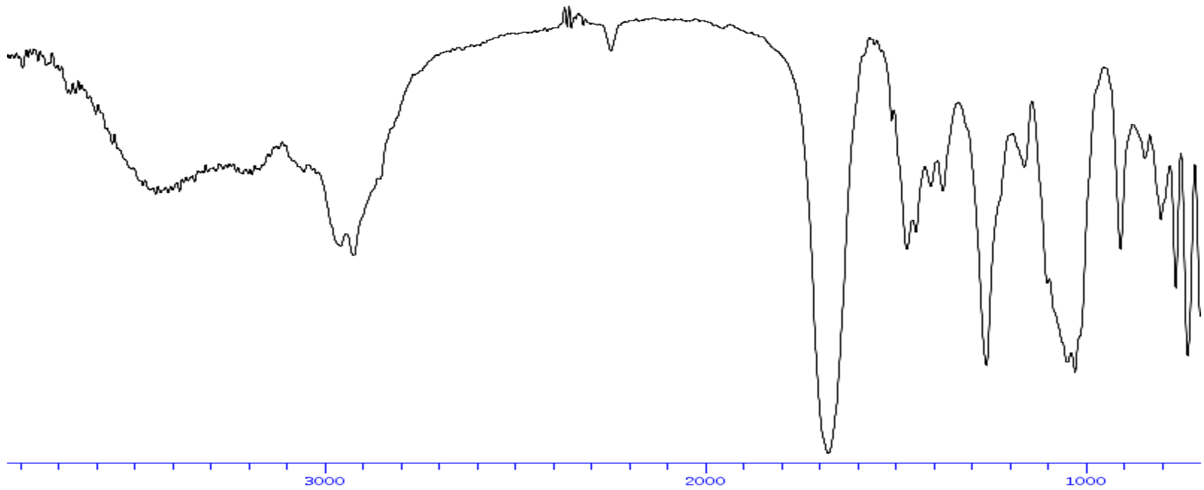


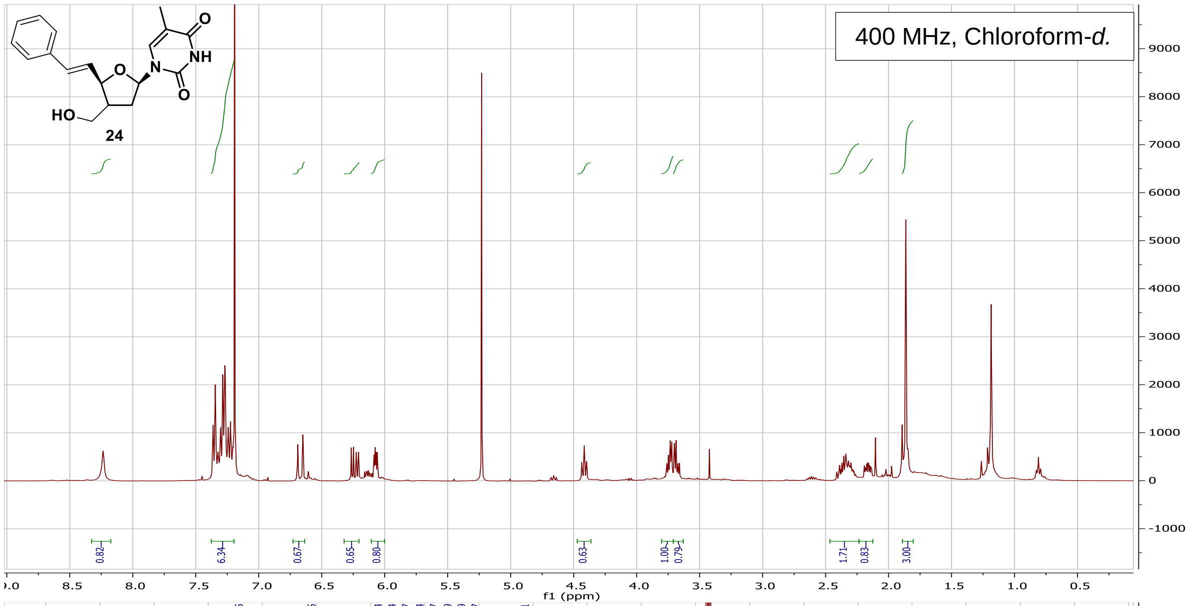
f1 (ppm)

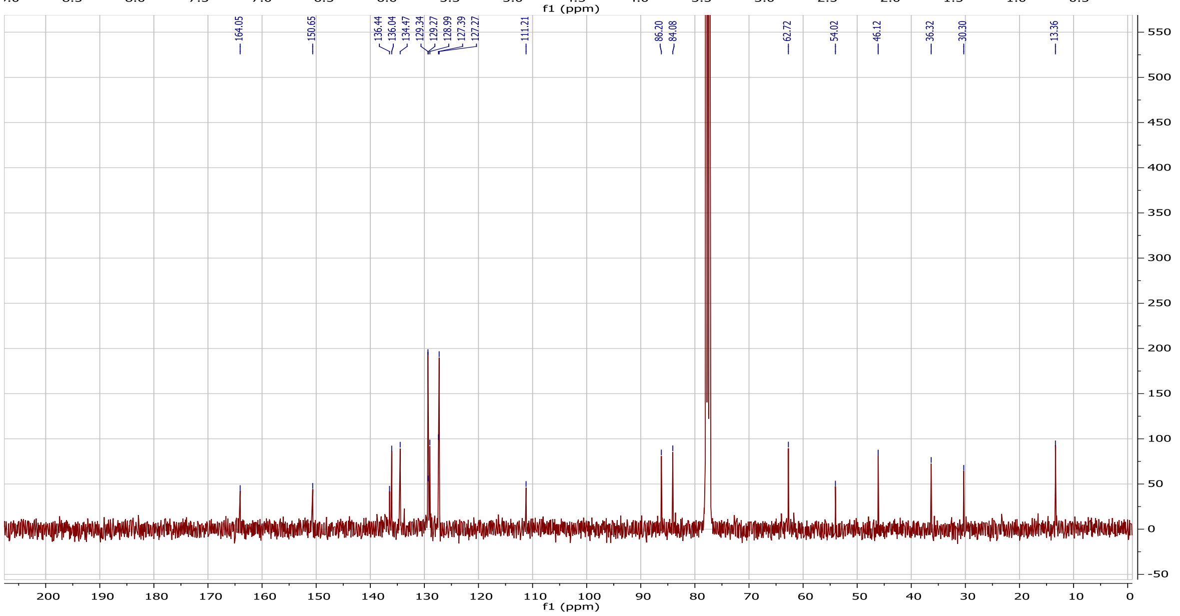


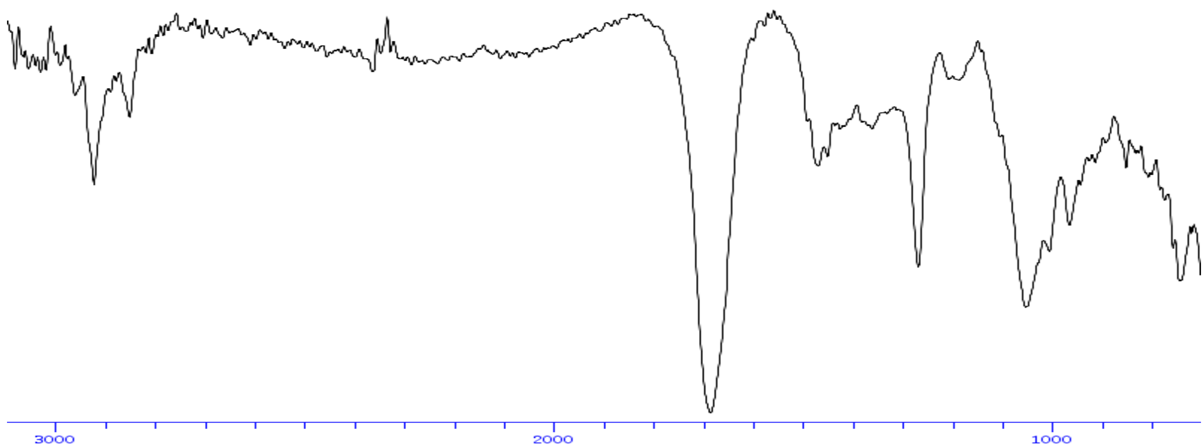

Ph
O
N
NH
O
O
HO
23
400 MHz, Chloroform-d.
0.71
1.69
3.08
0.85
0.88
0.85
0.99
0.90
1.92
1.16
3.00
2.94
f1 (ppm)

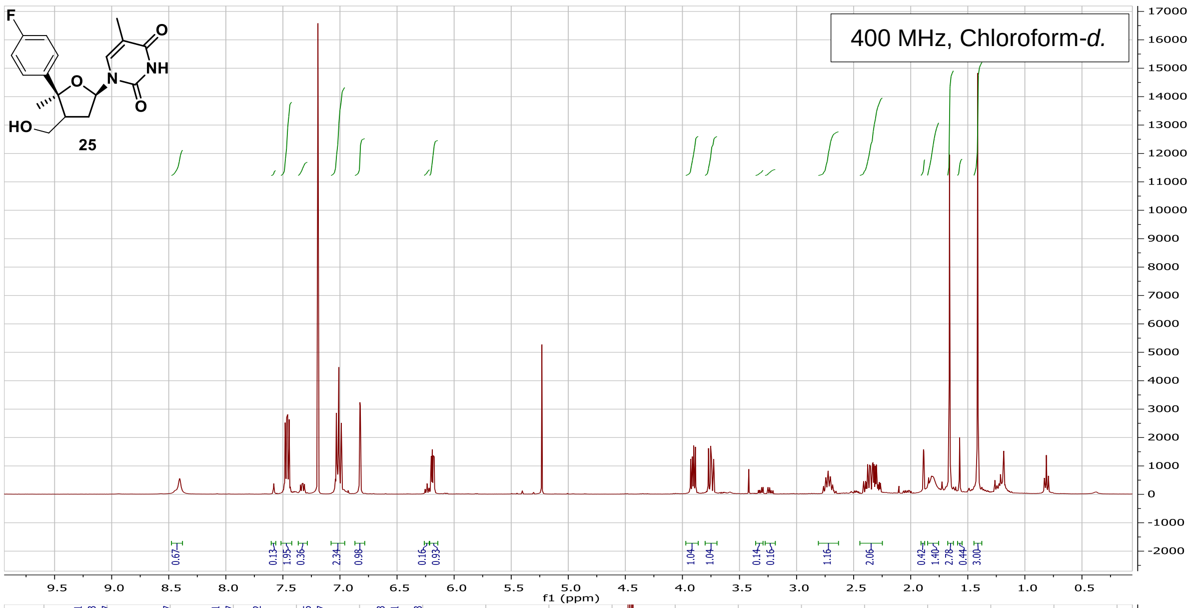

163.73
150.44
145.64
136.27
128.60
127.73
125.07
110.31
87.61
85.04
77.35 CDCl3
77.24
77.03 CDCl3
76.71 CDCl3
62.63
47.46
36.60
24.52
12.47
f1 (ppm)

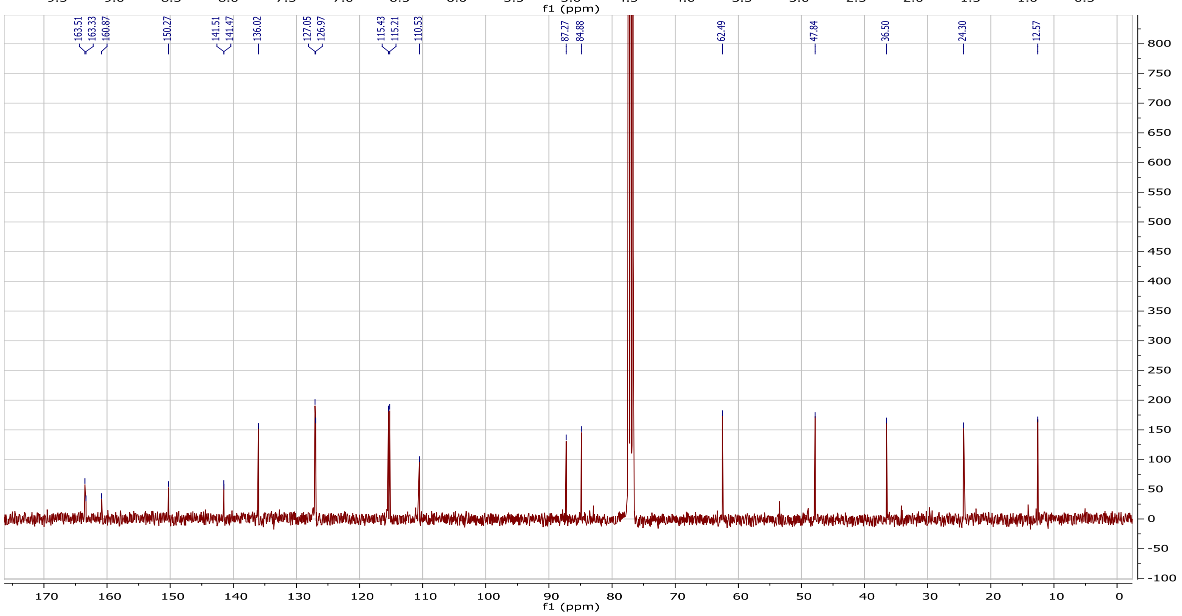

3000
2000
1000

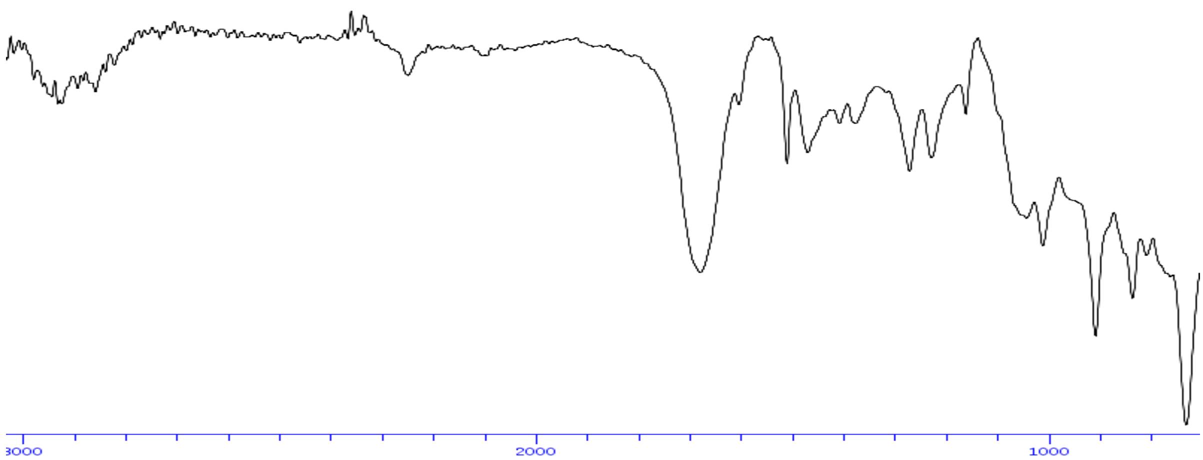

HO
24
400 MHz, Chloroform-d.
f1 (ppm)

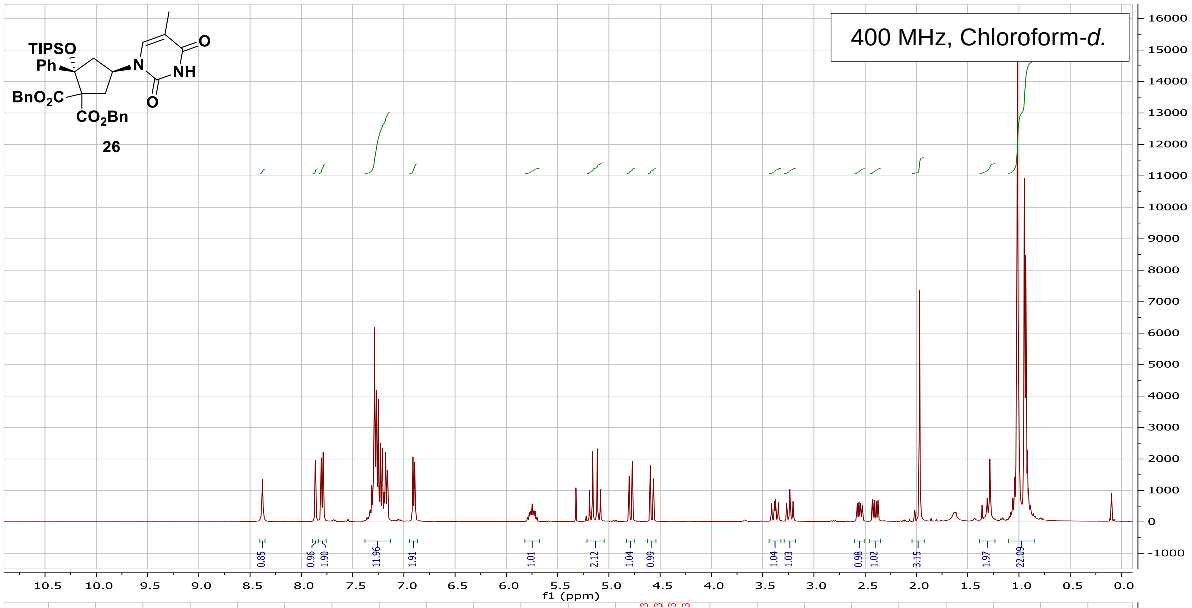

164.05
150.65
136.44
136.04
134.47
129.34
129.27
128.99
127.39
127.27
111.21
86.20
84.08
62.72
54.02
46.12
36.32
30.30
13.36
f1 (ppm)

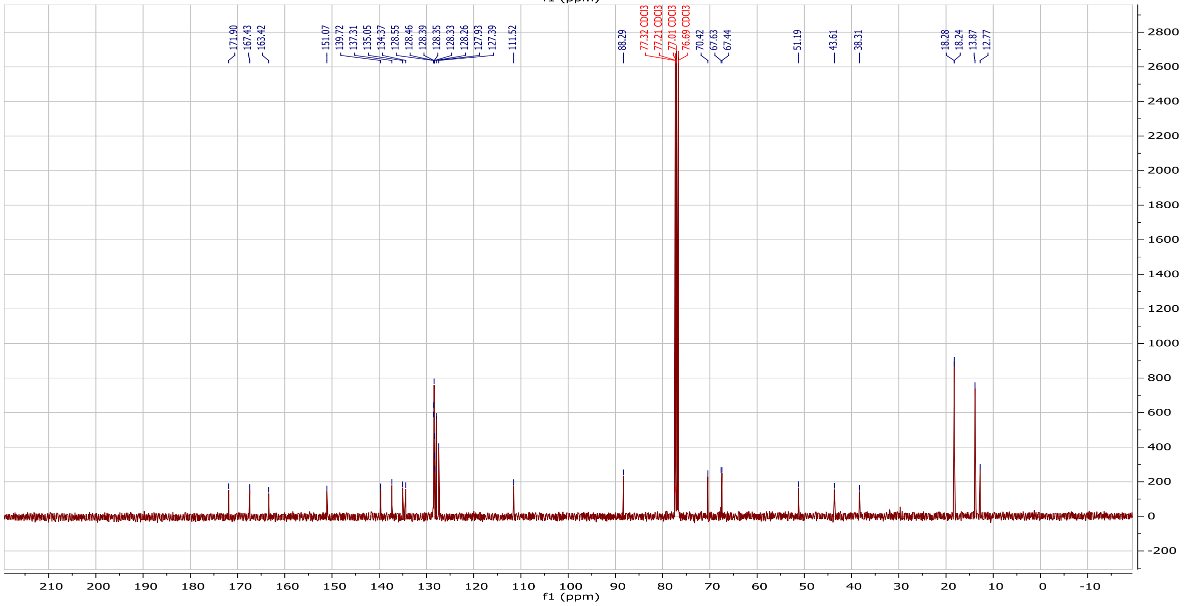

3000
2000
1000

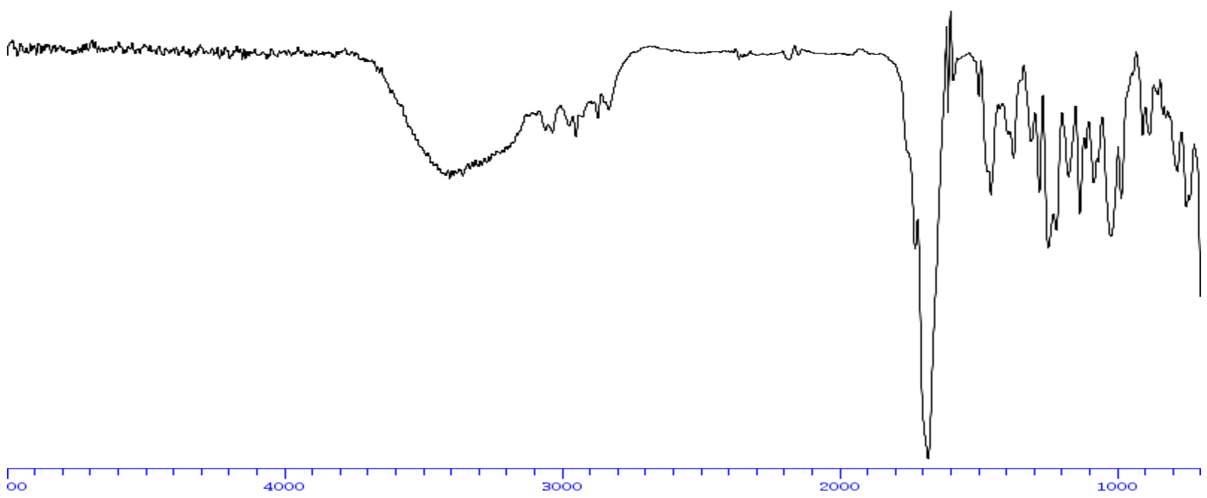

F
O
NH
N
O
HO
25
400 MHz, Chloroform-d.
0.67
0.13
1.95
0.36
2.34
0.98
0.16
0.93
1.04
1.04
0.14
0.16
1.16
2.06
0.42
1.40
2.78
0.44
3.00
f1 (ppm)

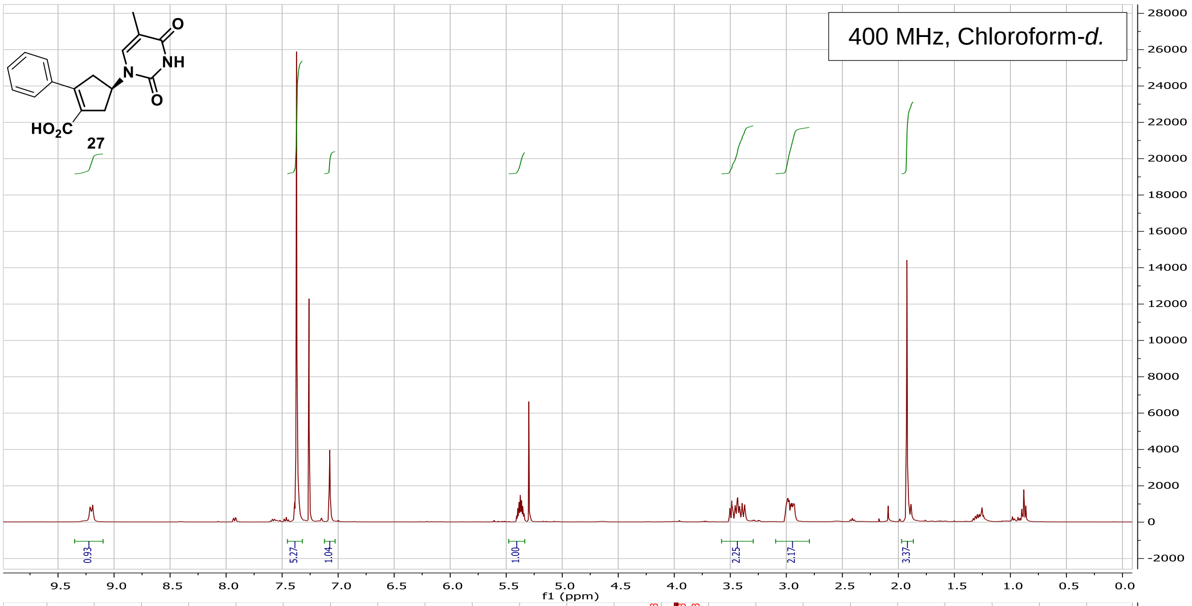

163.51
163.33
160.87
150.27
141.51
141.47
136.02
127.05
126.97
115.43
115.21
110.53
87.27
84.88
62.49
47.84
36.50
24.30
12.57
f1 (ppm)

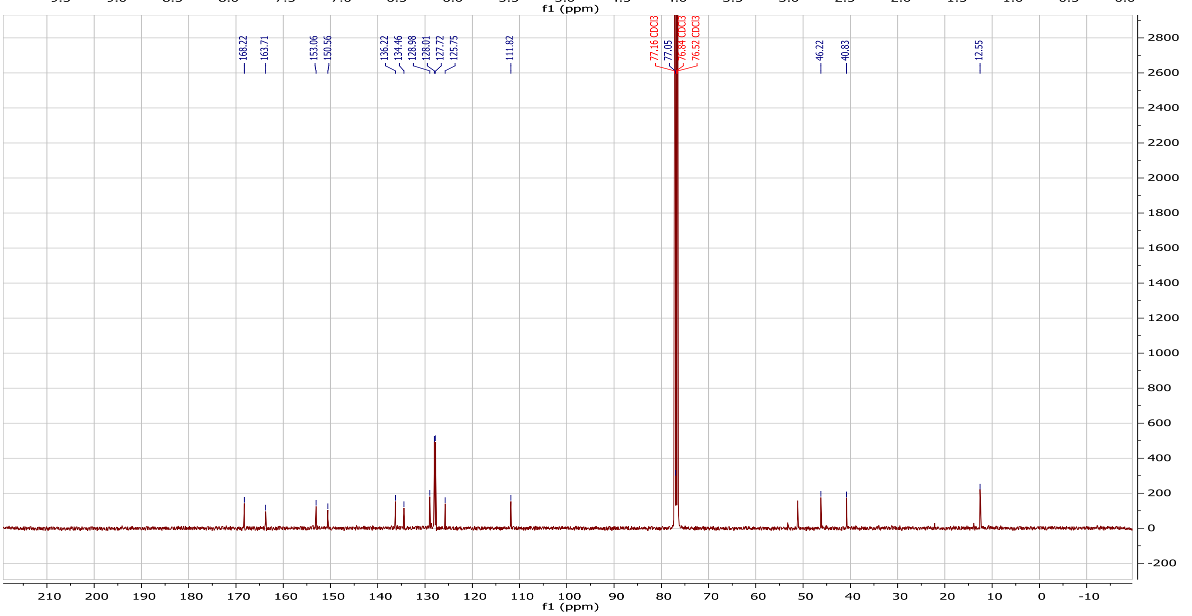

3000
2000
1000

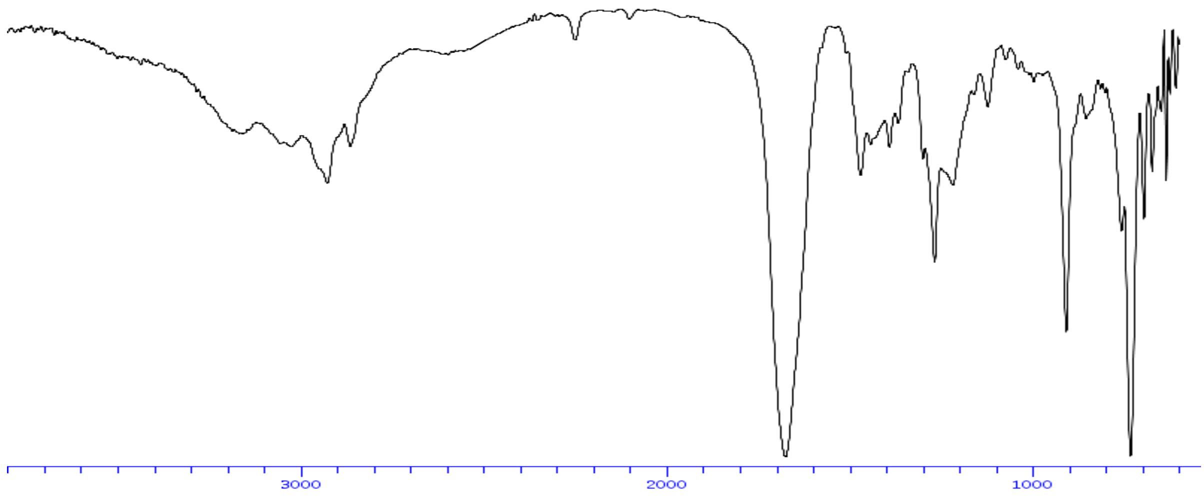

TIPSO
Ph
BnO2C
CO2Bn
N
NH
O
O
O
26
400 MHz, Chloroform-d.
0.85
0.96
1.90
11.96
1.91
1.01
2.12
1.04
0.99
1.04
1.03
0.98
1.02
3.15
1.97
22.09
f1 (ppm)

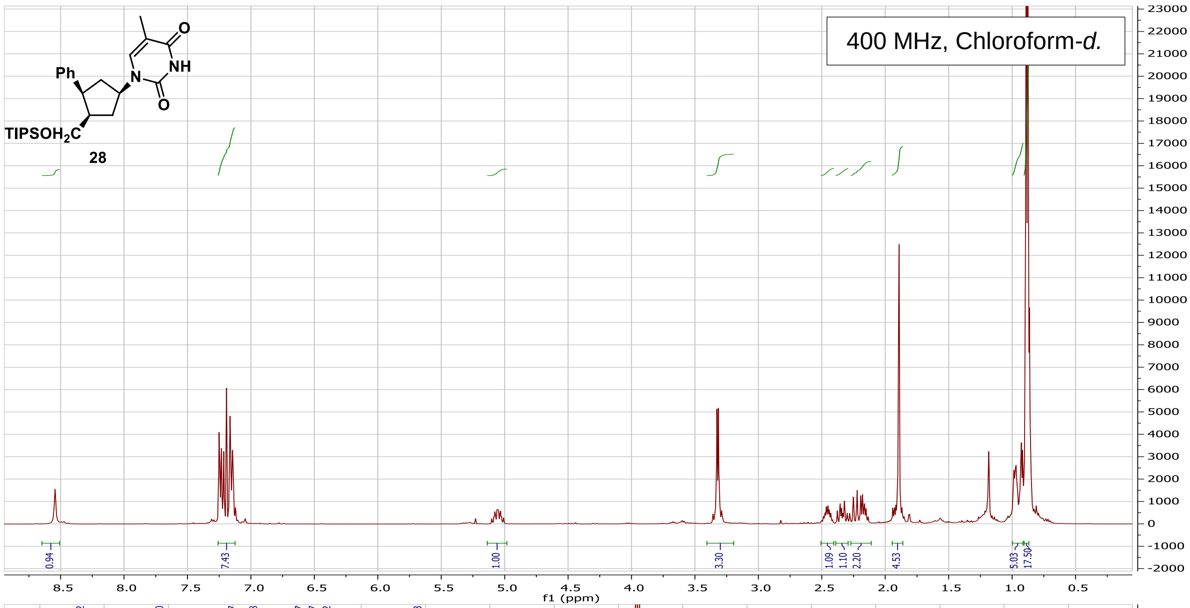

171.90
167.43
163.42
151.07
139.72
137.31
135.05
134.37
128.55
128.46
128.39
128.35
128.33
128.26
127.93
127.39
111.52
88.29
77.32 CDCl3
77.21 CDCl3
77.01 CDCl3
76.69 CDCl3
70.42
67.63
67.44
51.19
43.61
38.31
18.28
18.24
13.87
12.77
f1 (ppm)

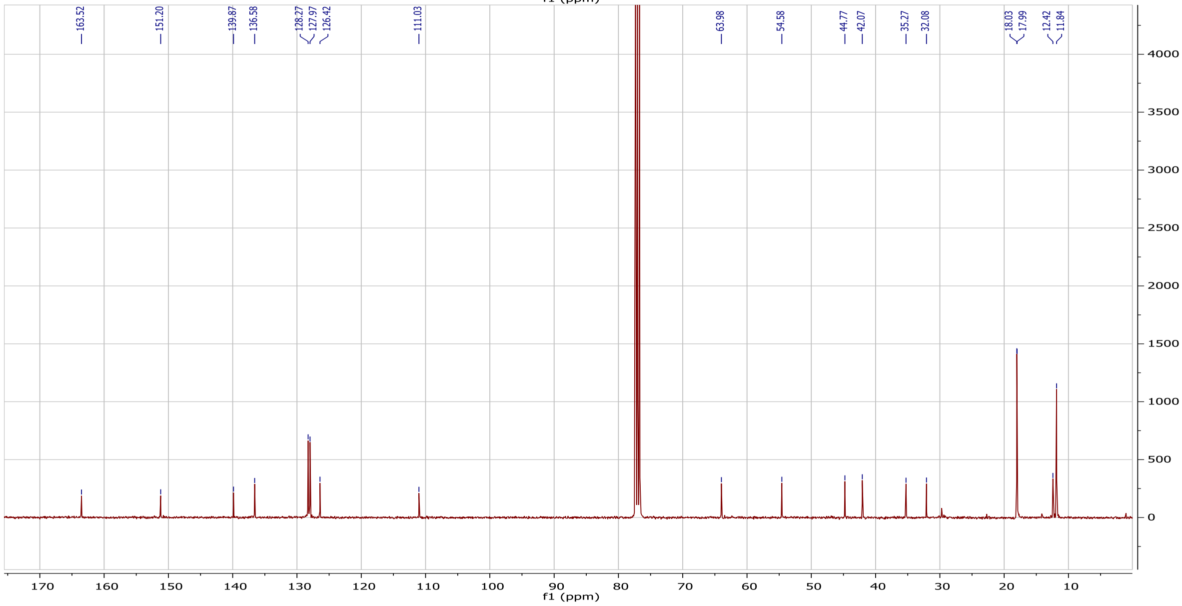


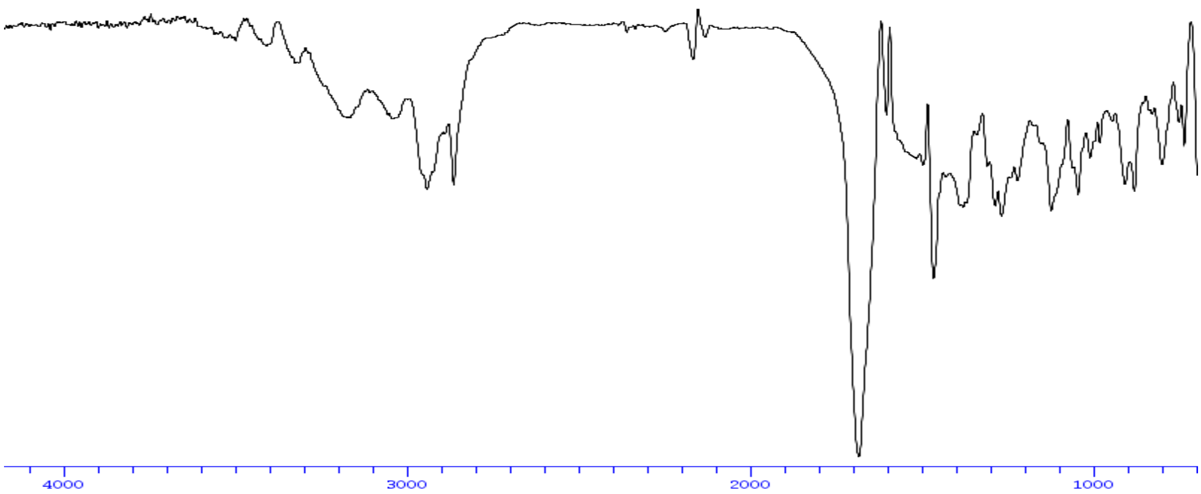

400 MHz, Chloroform-d.
HO2C
27
NH
N
O
0.93
5.27
1.04
1.00
2.25
2.17
3.37
f1 (ppm)

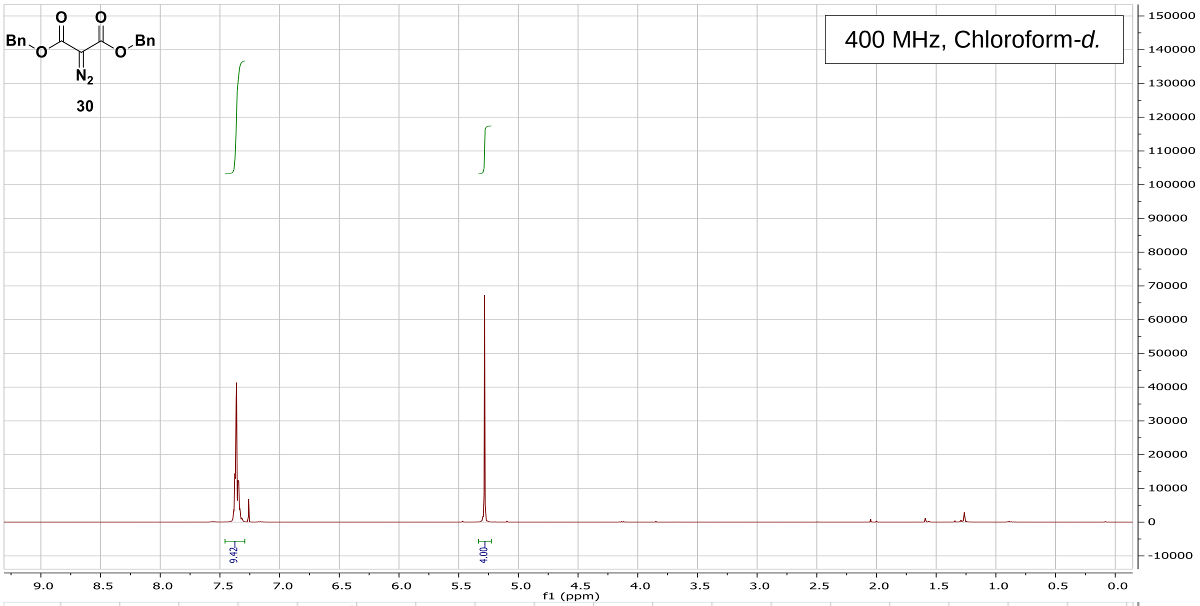

168.22
163.71
153.06
150.56
136.22
134.46
128.98
128.01
127.72
125.75
111.82
77.16 CDCl3
77.05
76.84 CDCl3
76.52 CDCl3
46.22
40.83
12.55
f1 (ppm)


3000
2000
1000

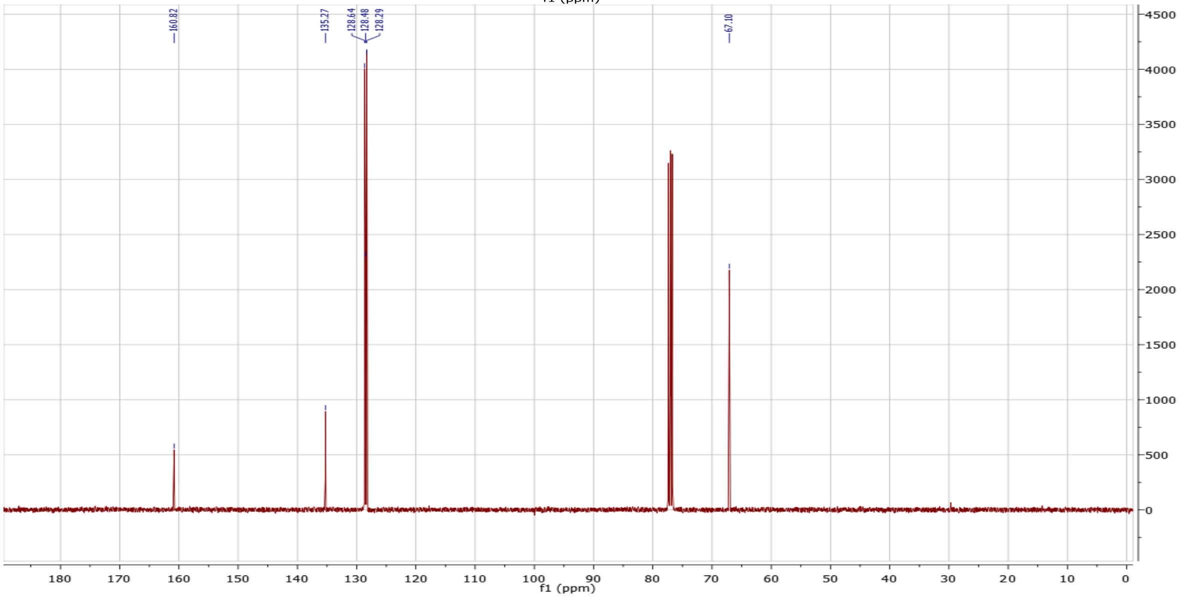

400 MHz, Chloroform-d.
Ph
NH
O
N
TIPSOH2C
28
0.94
7.43
1.00
3.30
1.09
1.10
2.20
4.53
5.03
17.50
f1 (ppm)


163.52
151.20
139.87
136.58
128.27
127.97
126.42
111.03
63.98
54.58
44.77
42.07
35.27
32.08
18.03
17.99
12.42
11.84
f1 (ppm)

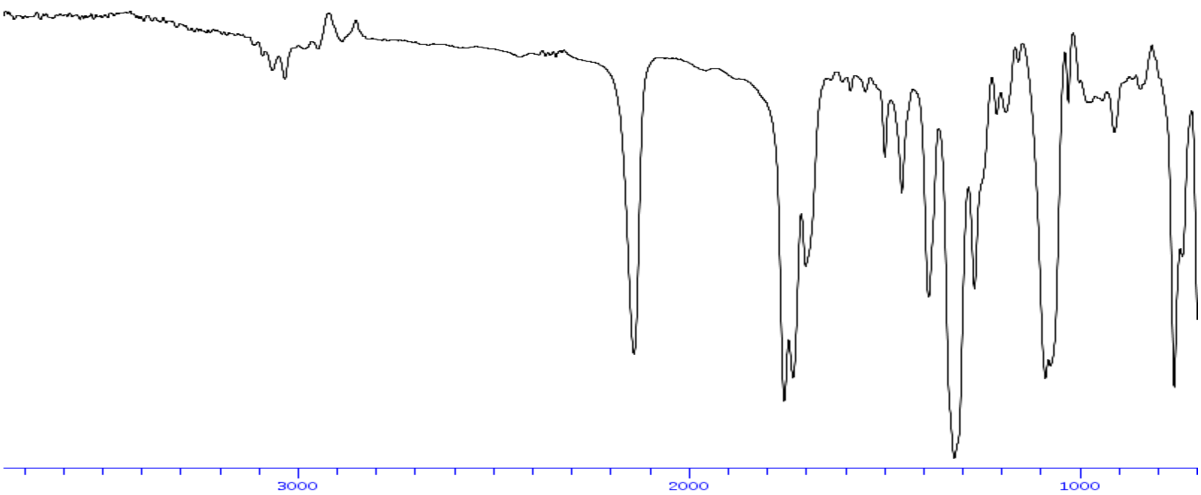

4000
3000
2000
1000



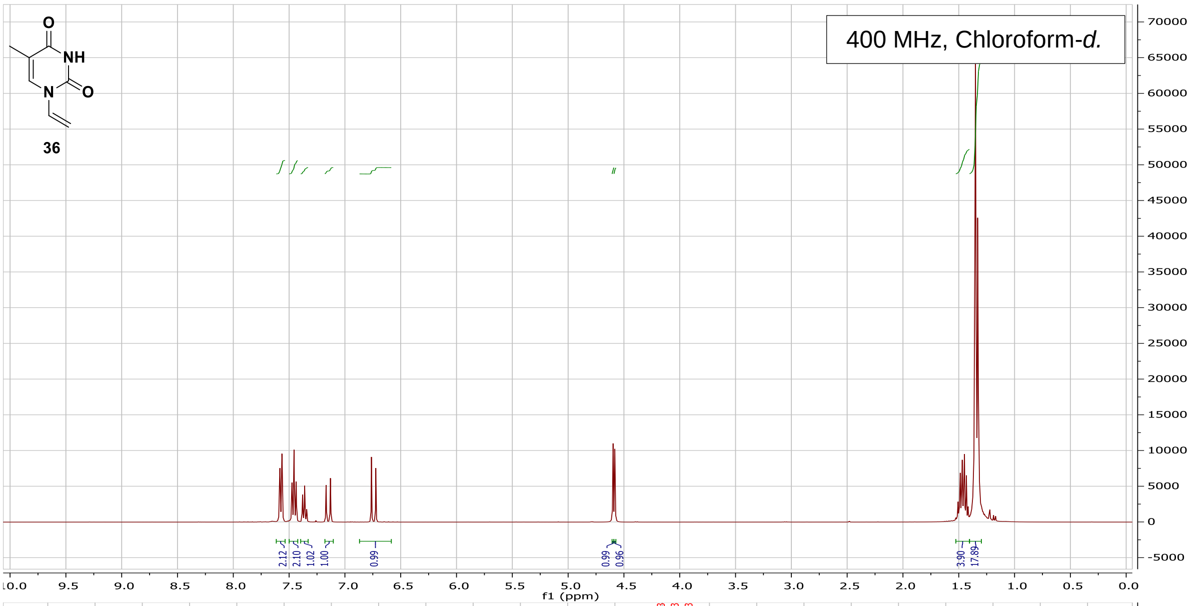
Bn O O Bn
N2
30
400 MHz, Chloroform-d.
9.42
4.00
f1 (ppm)

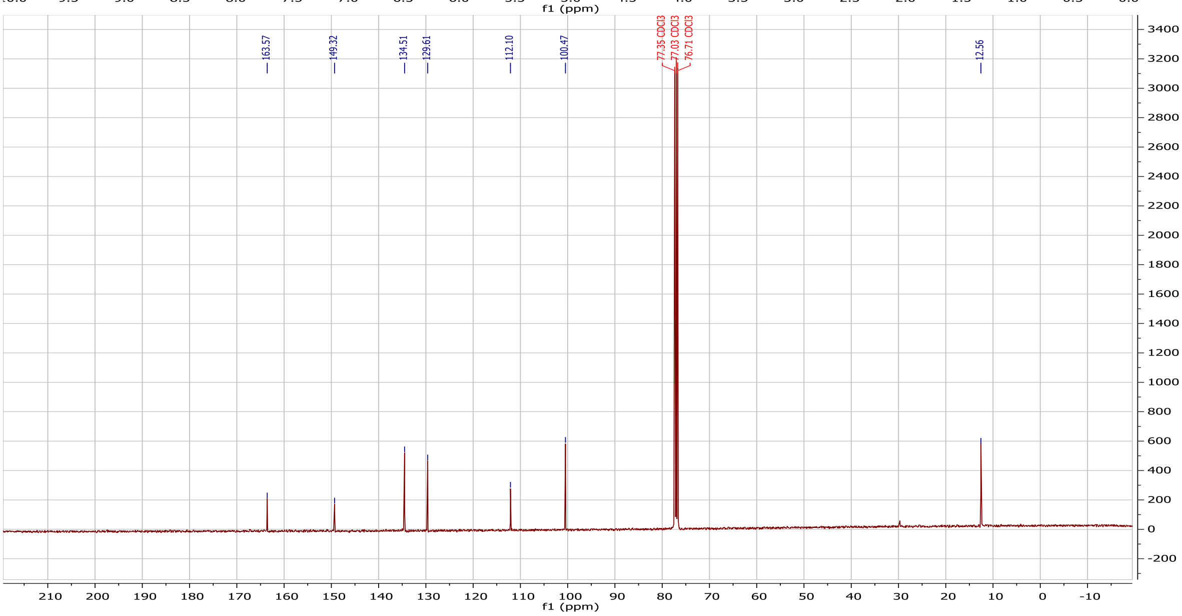


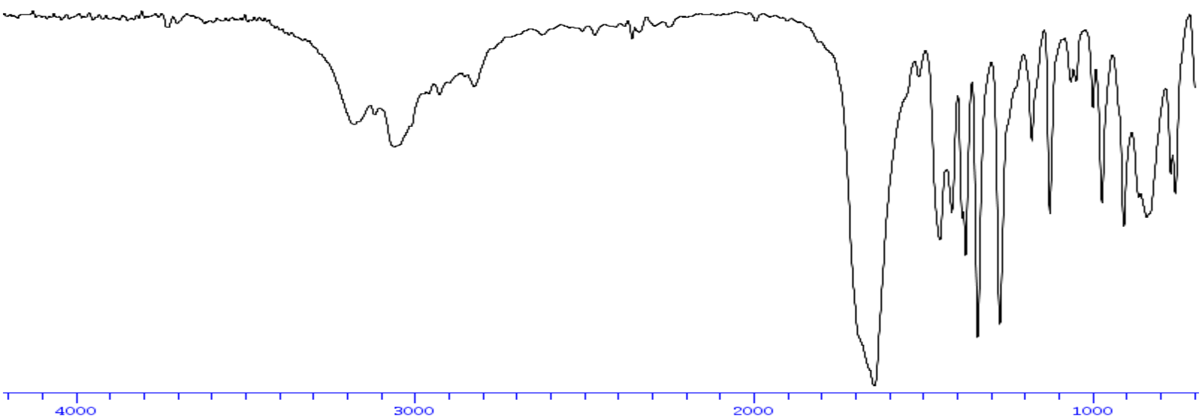
160.82
135.27
128.64
128.48
128.29
67.10
f1 (ppm)

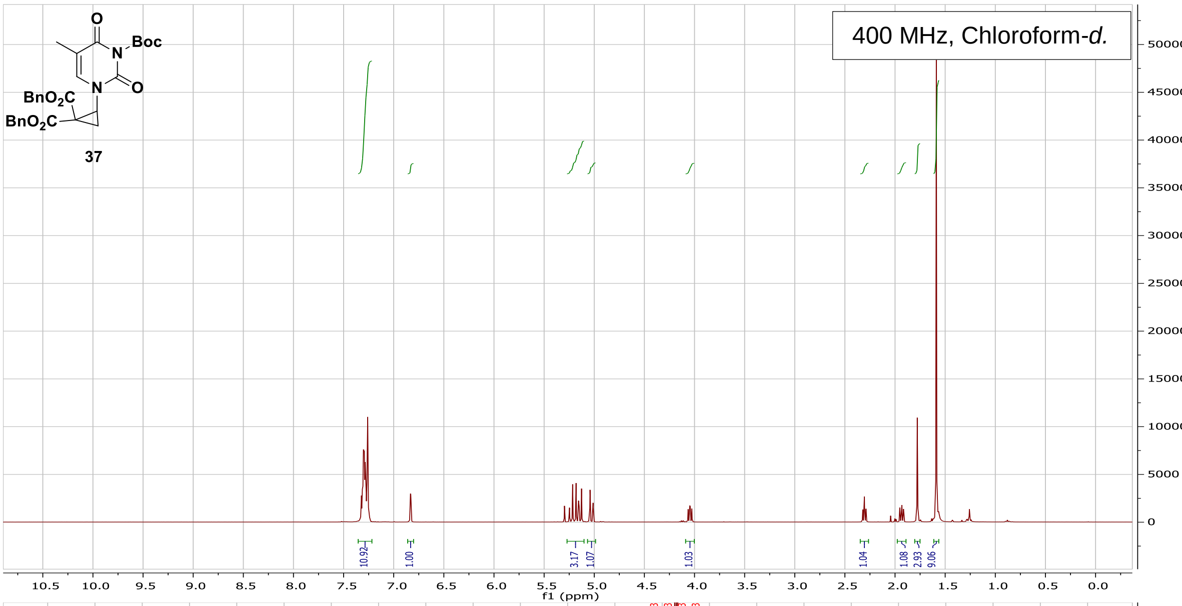


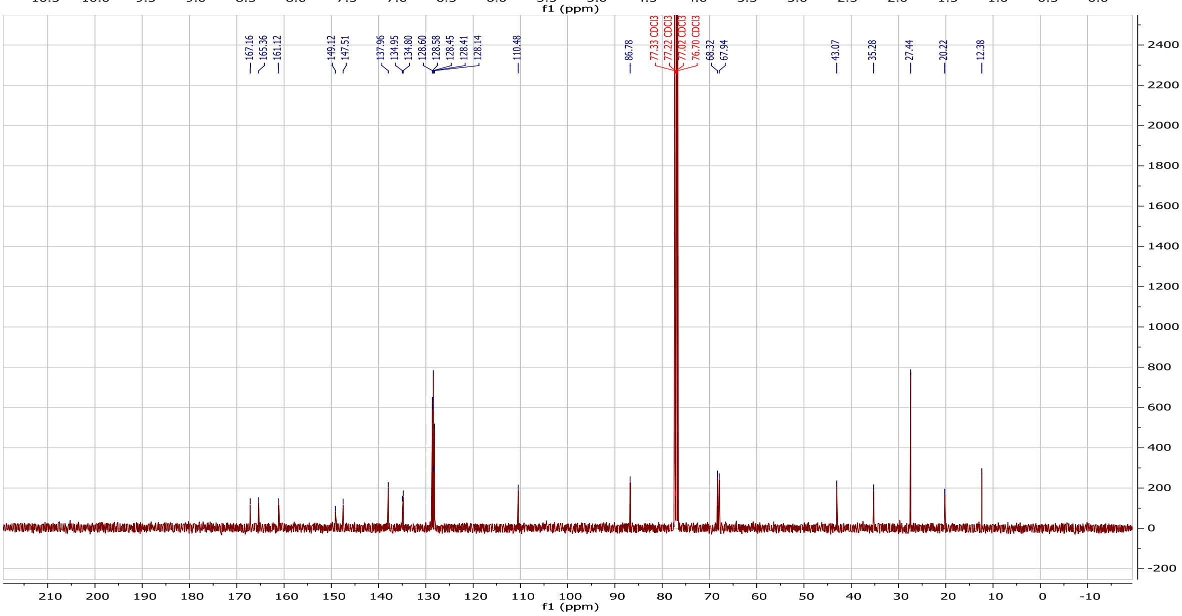
3000
2000
1000

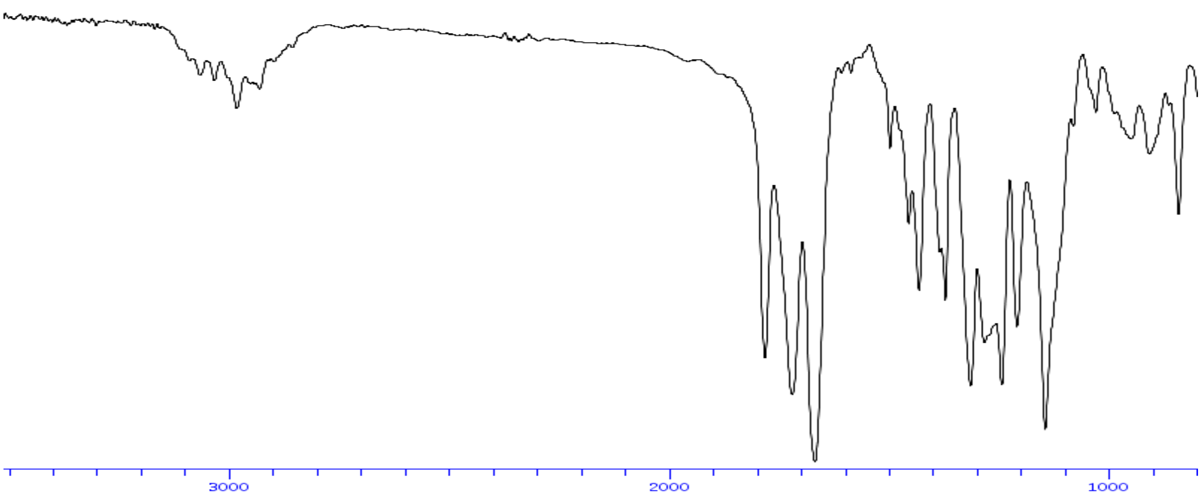

400 MHz, Chloroform-d.
36
2.12
2.10
1.02
1.00
0.99
0.99
0.96
3.90
17.89
f1 (ppm)

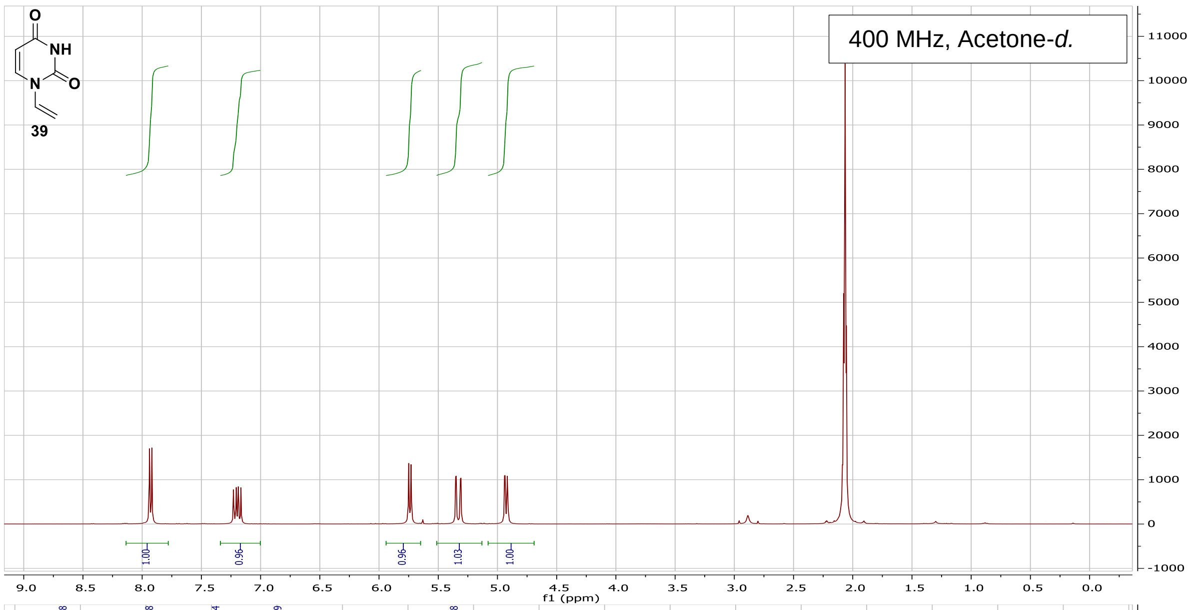

163.57
149.32
134.51
129.61
112.10
100.47
77.35 CDCl3
77.03 CDCl3
76.71 CDCl3
12.56
f1 (ppm)

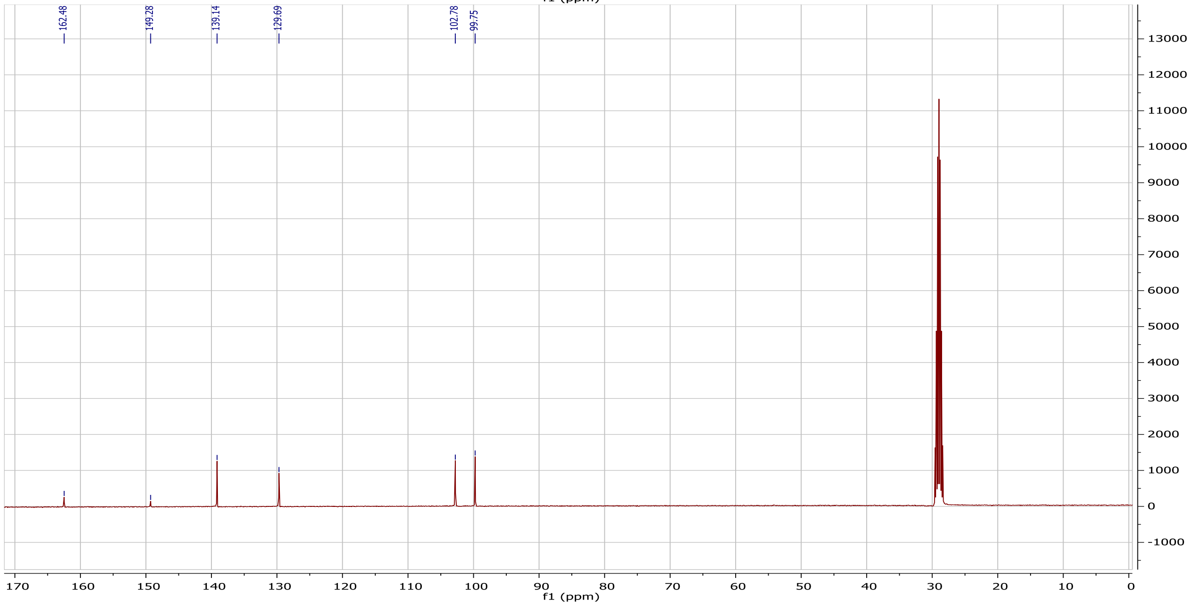

4000
3000
2000
1000

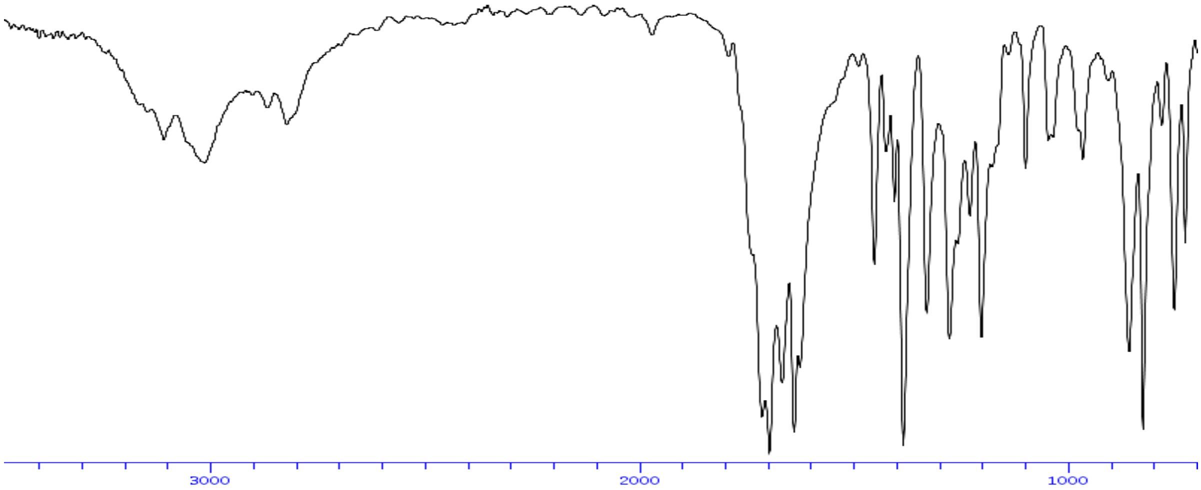

O
N
Boc
N
O
BnO2C
BnO2C
37
400 MHz, Chloroform-d.
f1 (ppm)

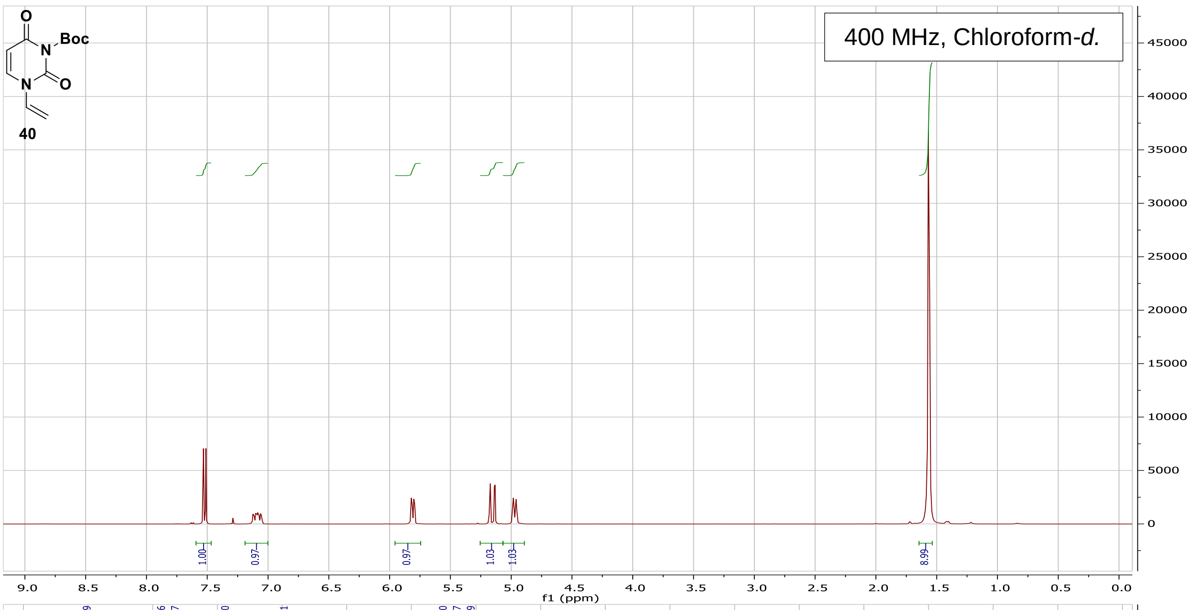

f1 (ppm)

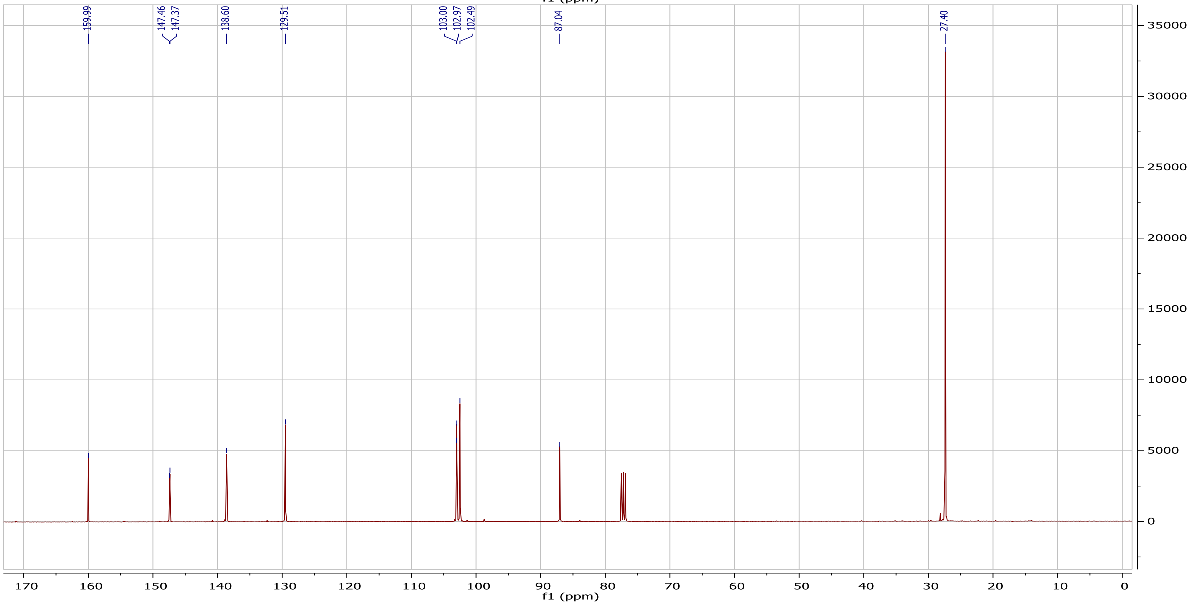


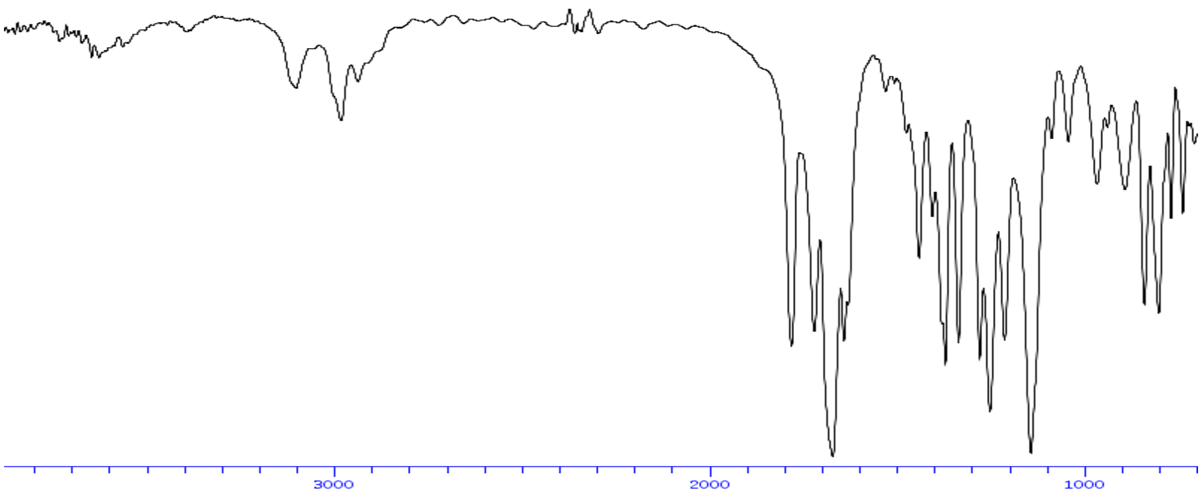

O
NH
N
O
39
400 MHz, Acetone-d.
1.00
0.96
0.96
1.03
1.00
f1 (ppm)

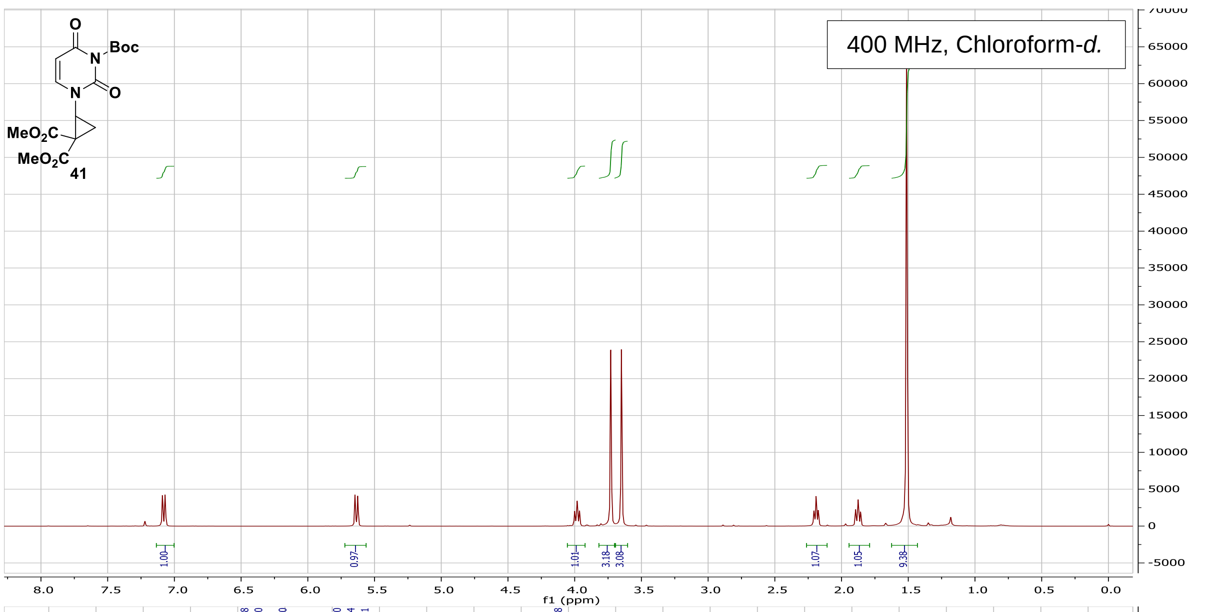

162.48
149.28
139.14
129.69
102.78
99.75
f1 (ppm)

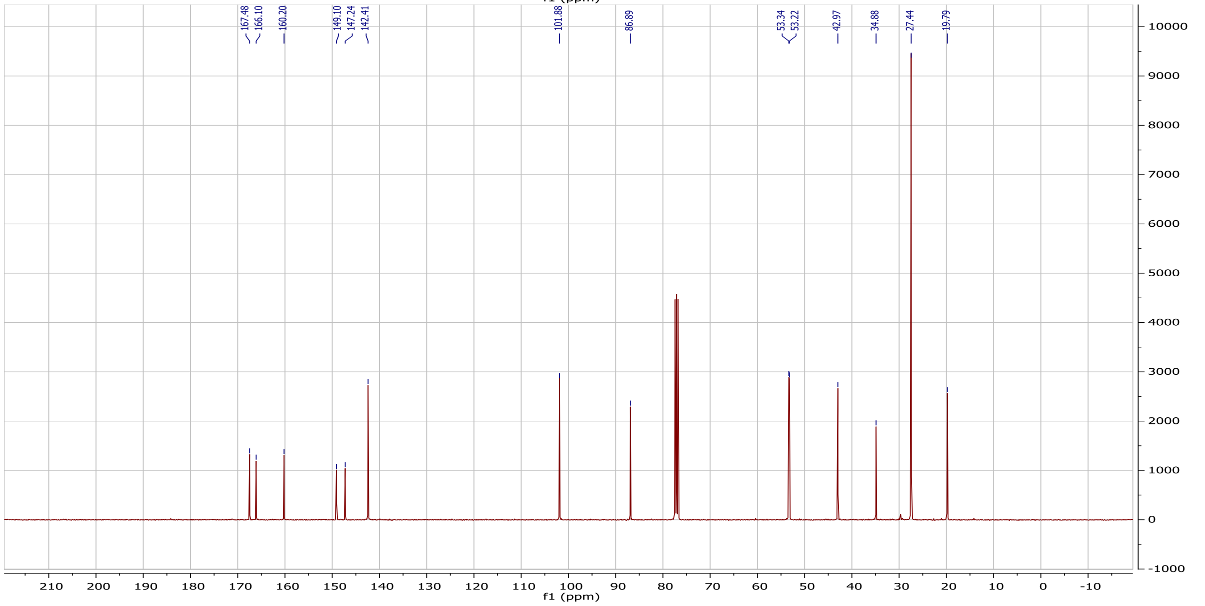

3000
2000
1000

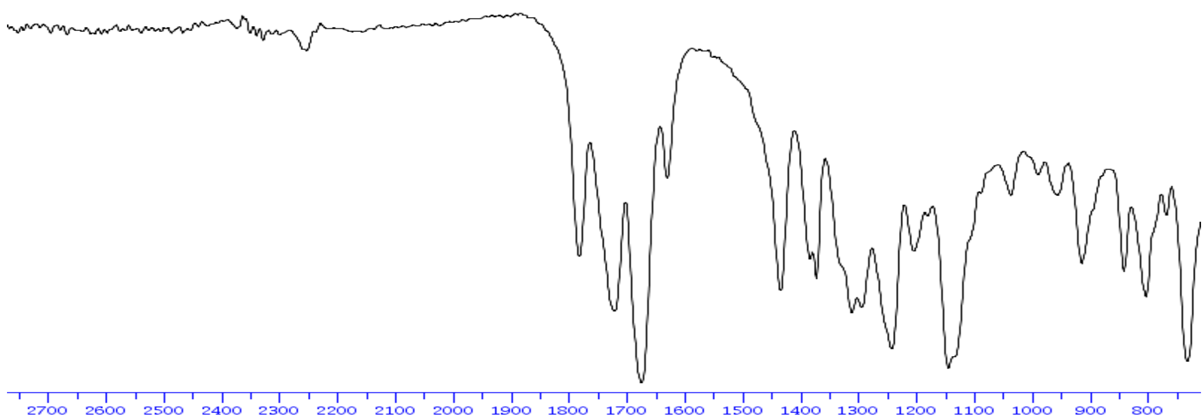

Boc
40
400 MHz, Chloroform-d.
1.00
0.97
0.97
1.03
1.03
8.99
f1 (ppm)

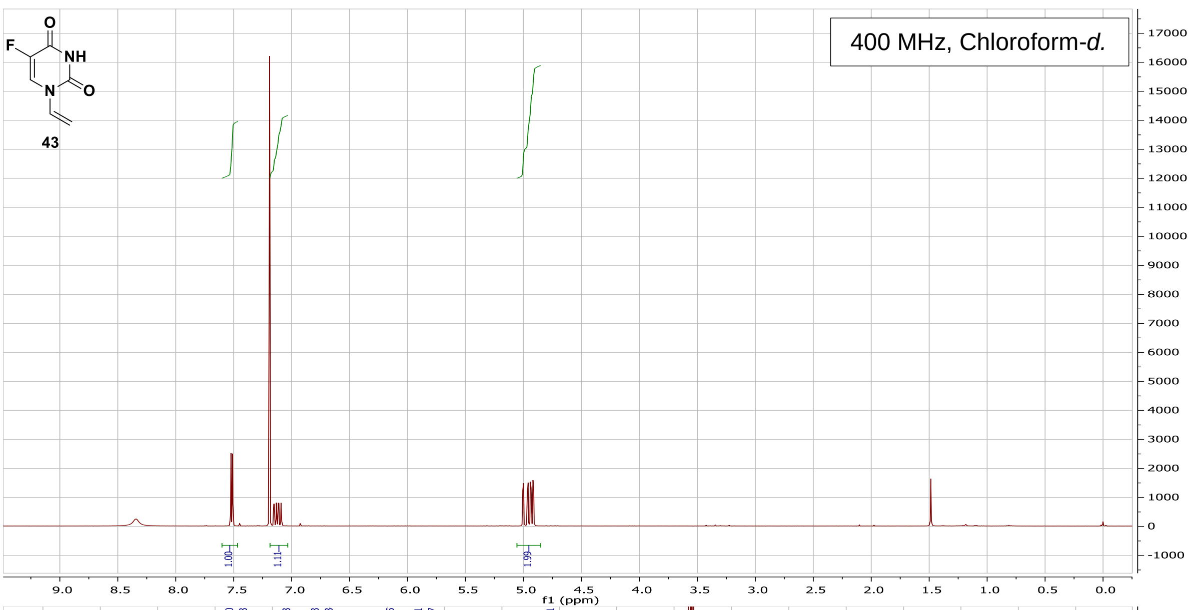

159.99
147.46
147.37
138.60
129.51
103.00
102.97
102.49
87.04
27.40
f1 (ppm)

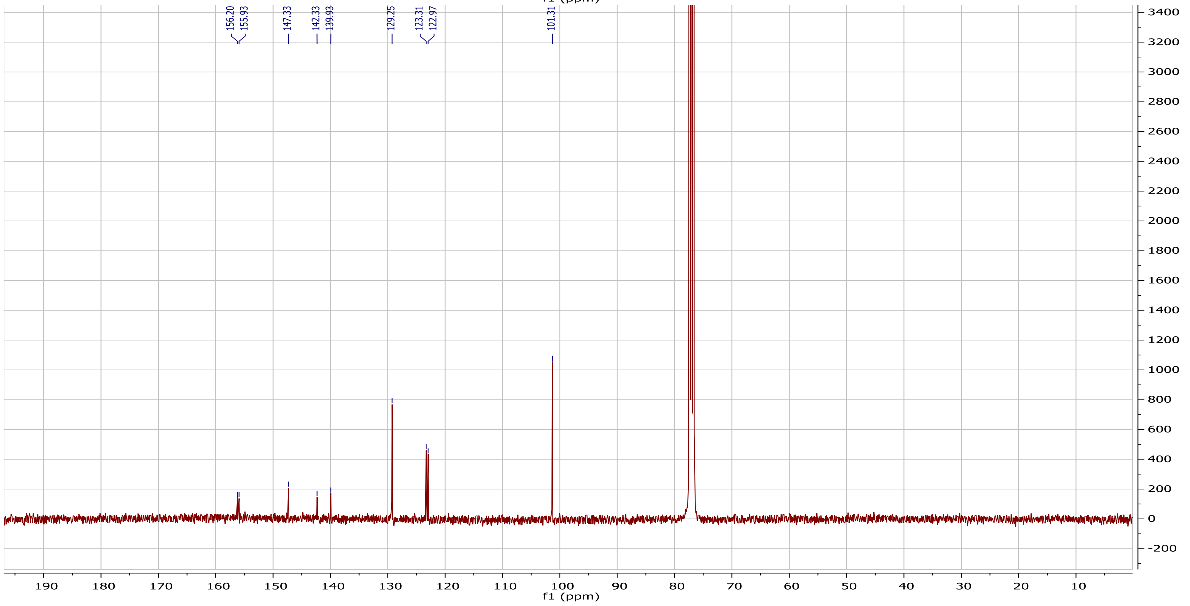

3000
2000
1000

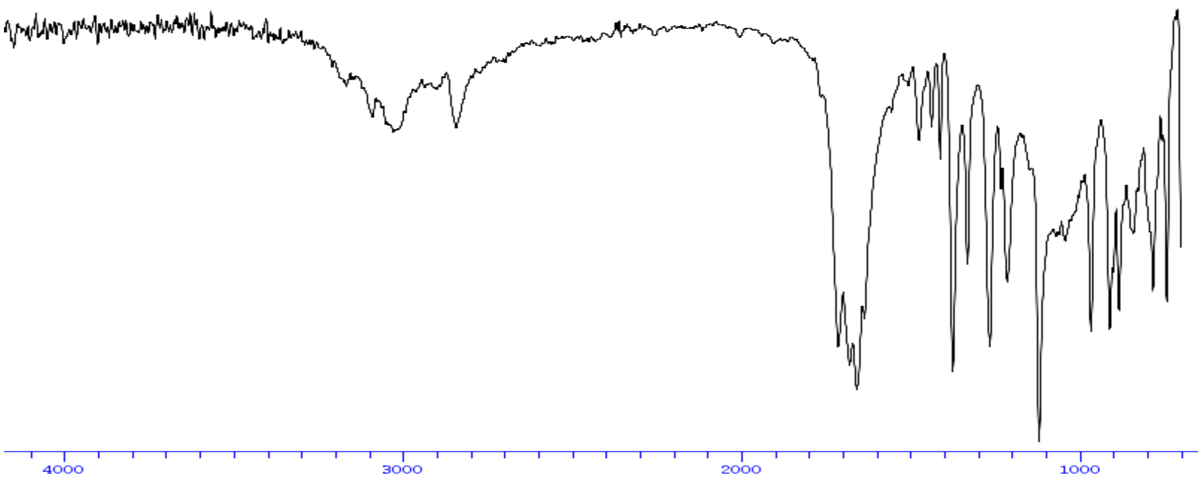

400 MHz, Chloroform-d.
Boc
MeO2C
MeO2C
41
1.00
0.97
1.01
3.18
3.08
1.07
1.05
9.38
f1 (ppm)

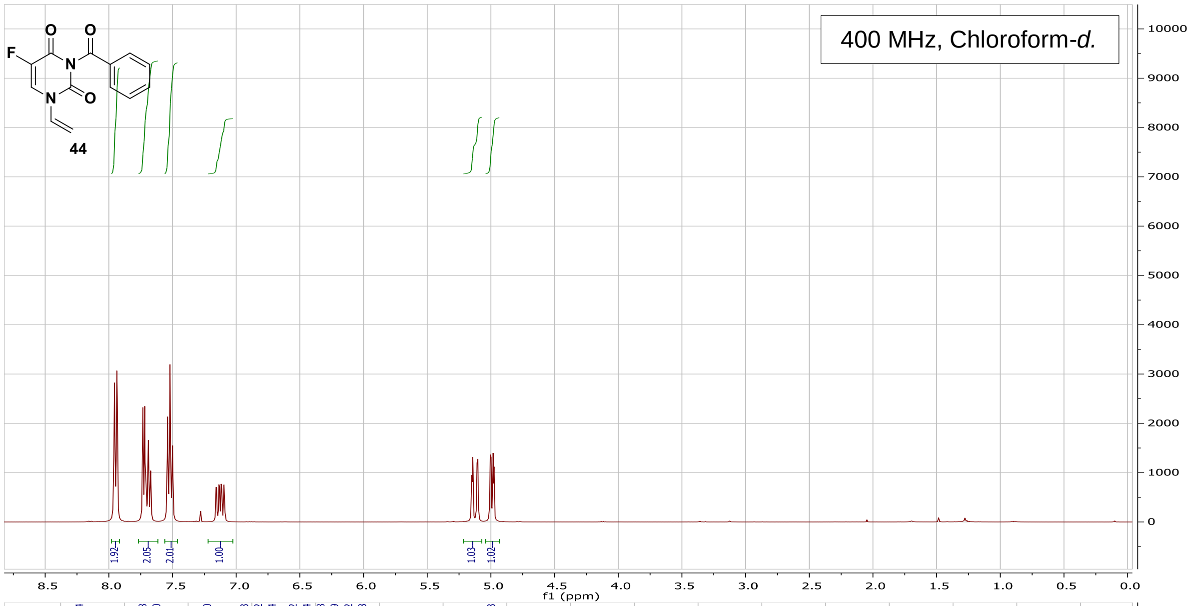

167.48
166.10
160.20
149.10
147.24
142.41
101.88
86.89
53.34
53.22
42.97
34.88
27.44
19.79
f1 (ppm)

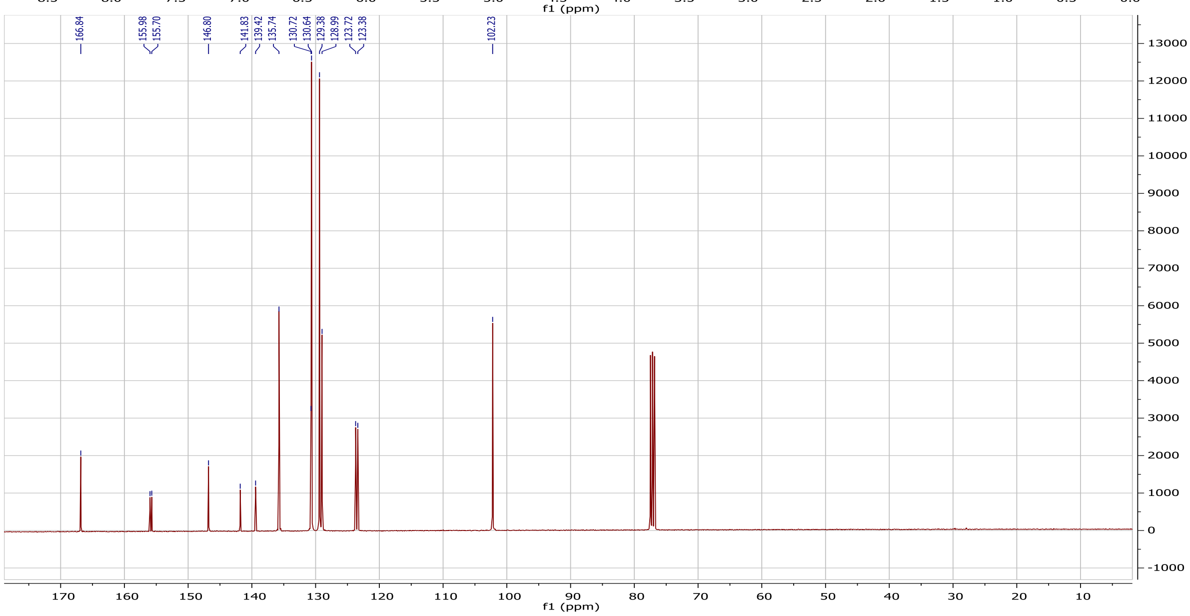


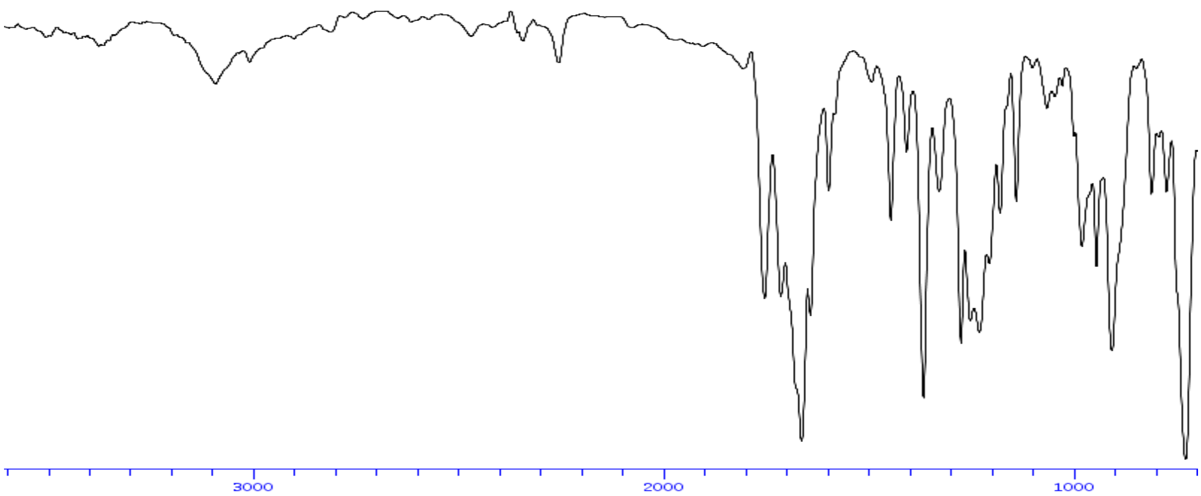

400 MHz, Chloroform-d.
43
1.00
1.11
1.99
f1 (ppm)

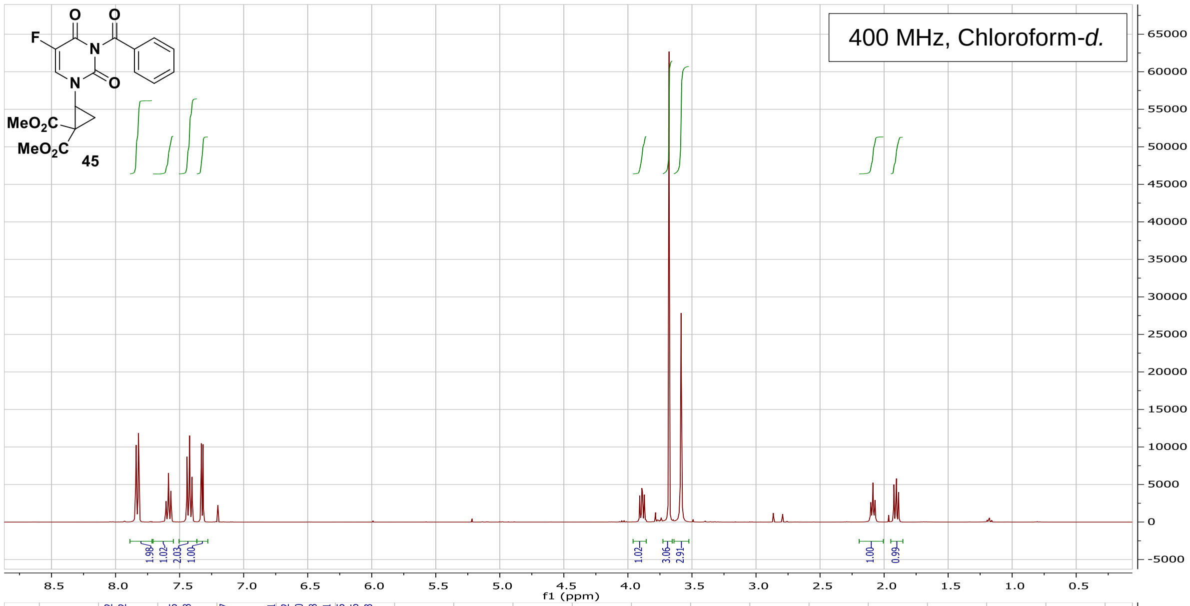

156.20
155.93
147.33
142.33
139.93
129.25
123.31
122.97
101.31
f1 (ppm)

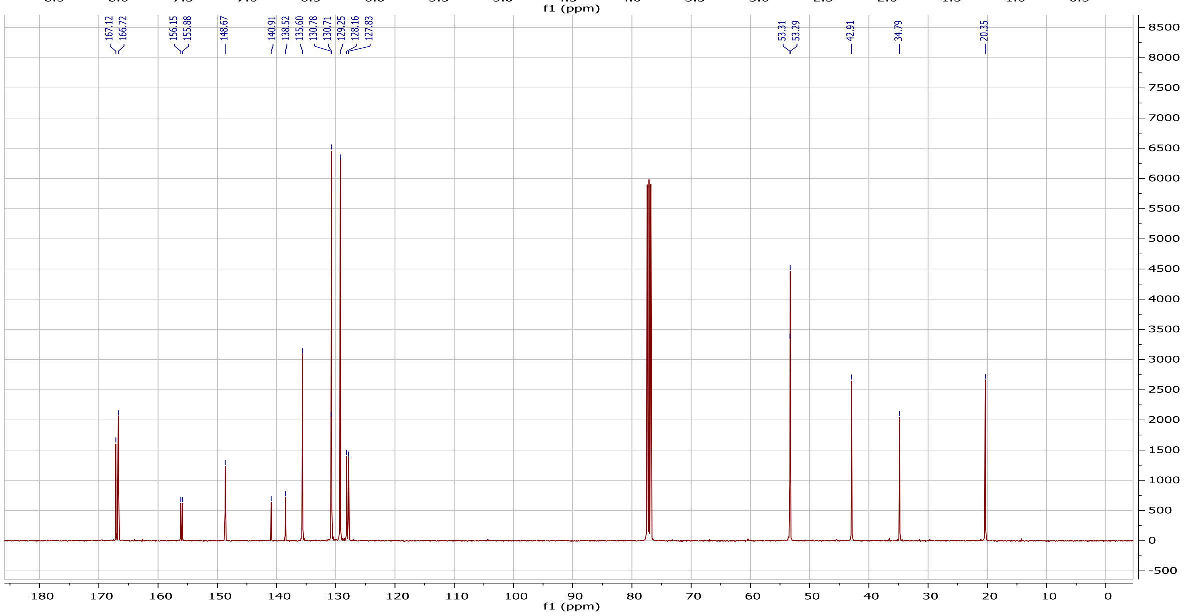


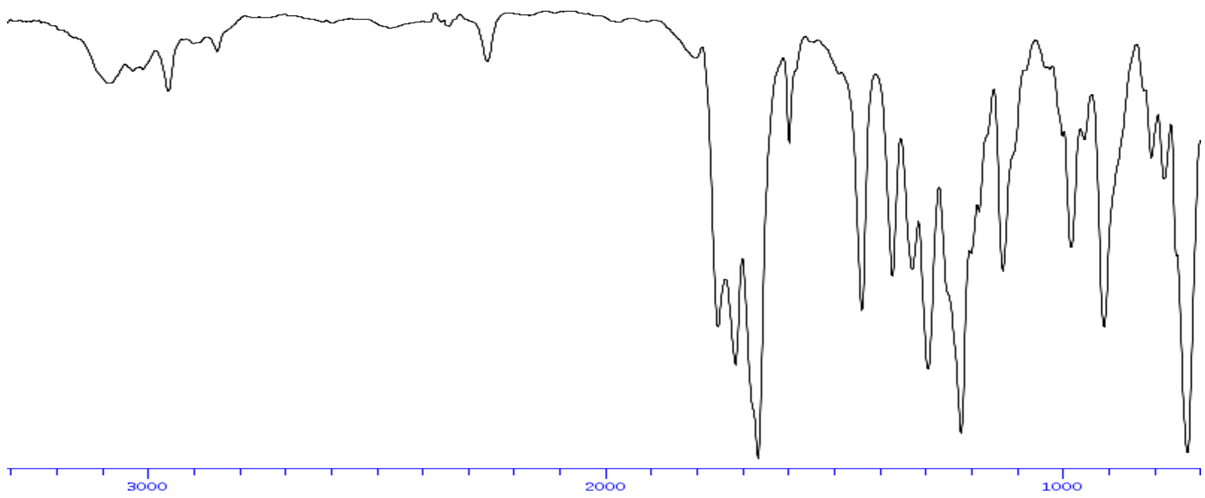

44
400 MHz, Chloroform-d.
1.92
2.05
2.01
1.00
1.03
1.02
f1 (ppm)

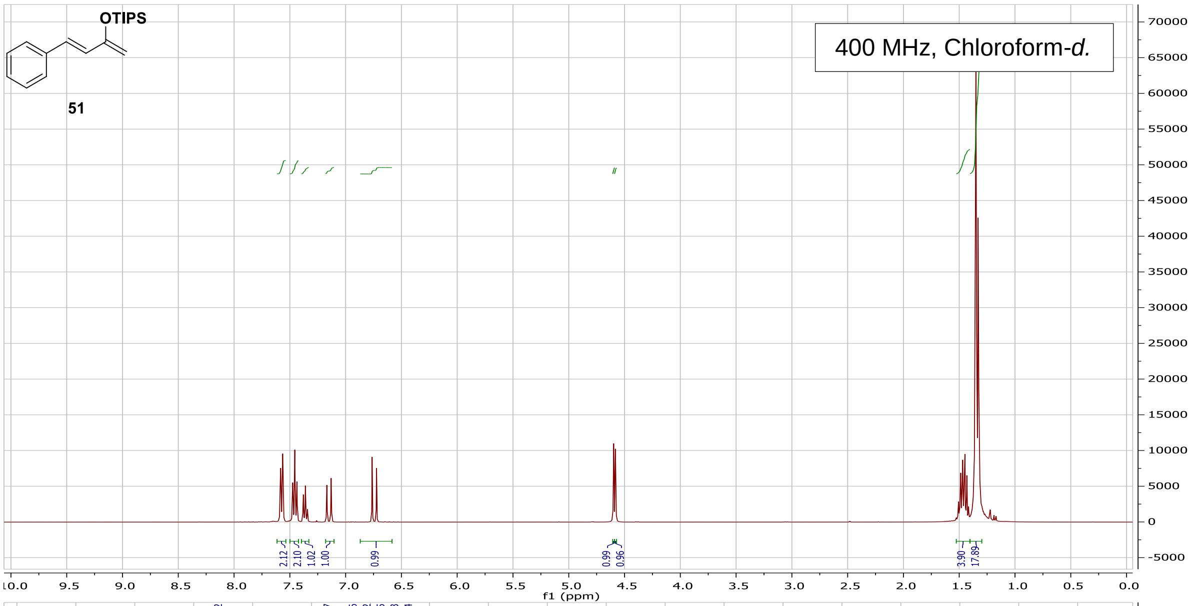

166.84
155.98
155.70
146.80
141.83
139.42
135.74
130.72
130.64
129.38
128.99
123.72
123.38
102.23
f1 (ppm)

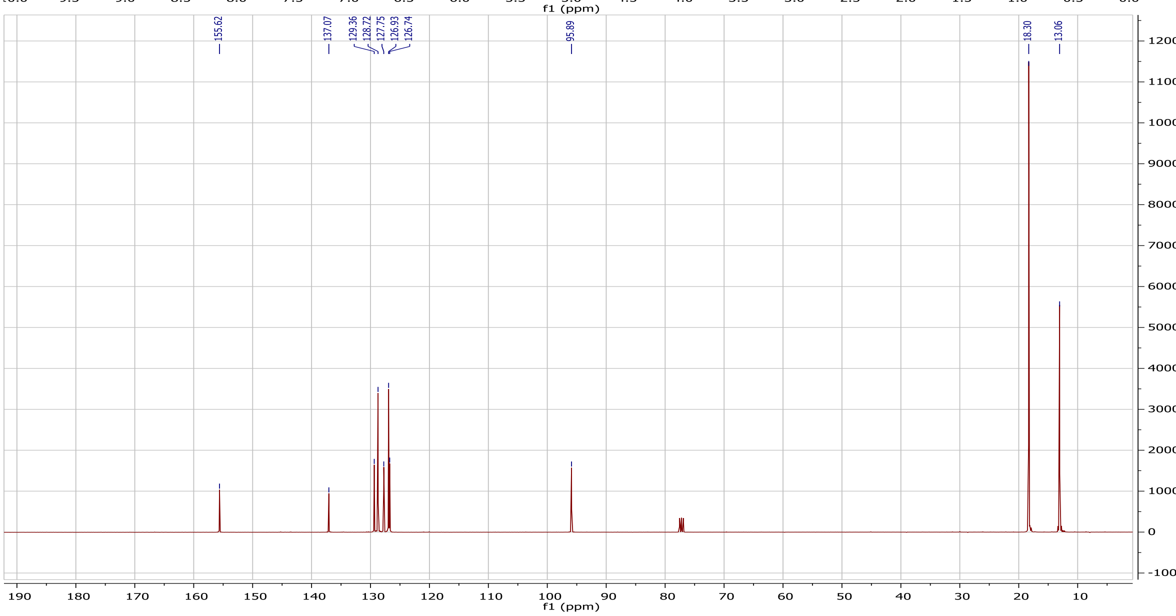

3000
2000
1000

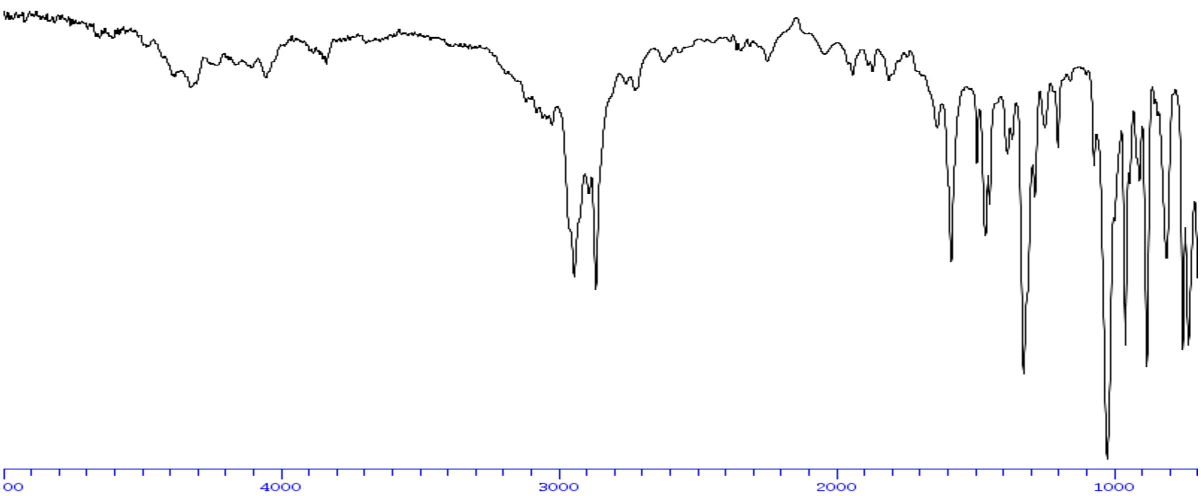

F
O
O
N
N
O
MeO2C
MeO2C
45
400 MHz, Chloroform-d.
f1 (ppm)

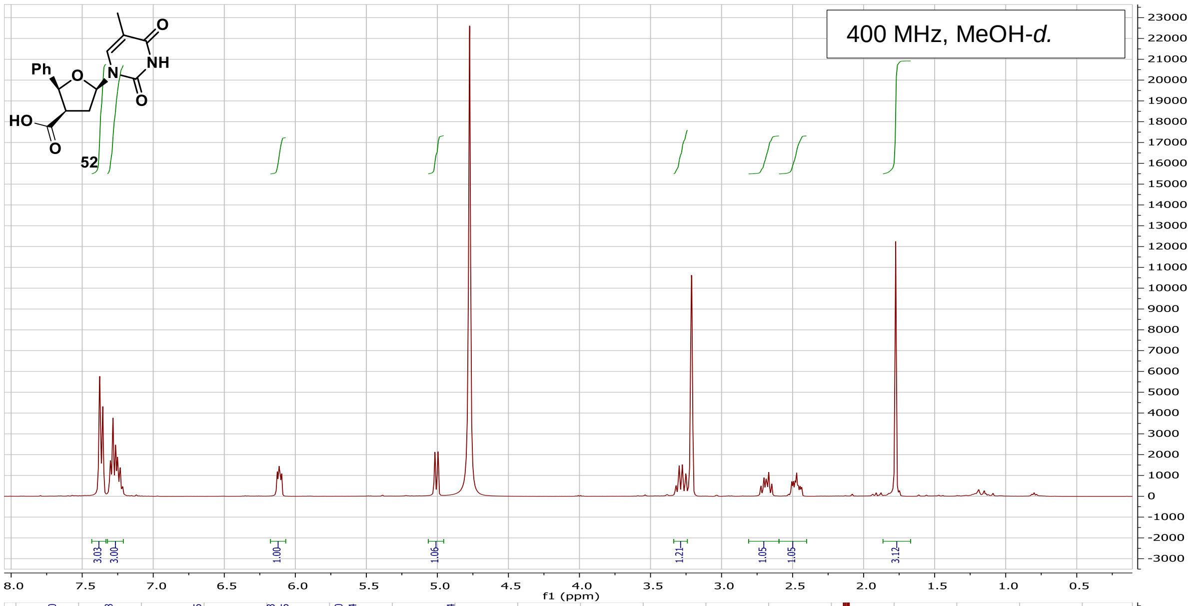

167.12
166.72
156.15
155.88
148.67
140.91
138.52
135.60
130.78
130.71
129.25
128.16
127.83
53.31
53.29
42.91
34.79
20.35
f1 (ppm)

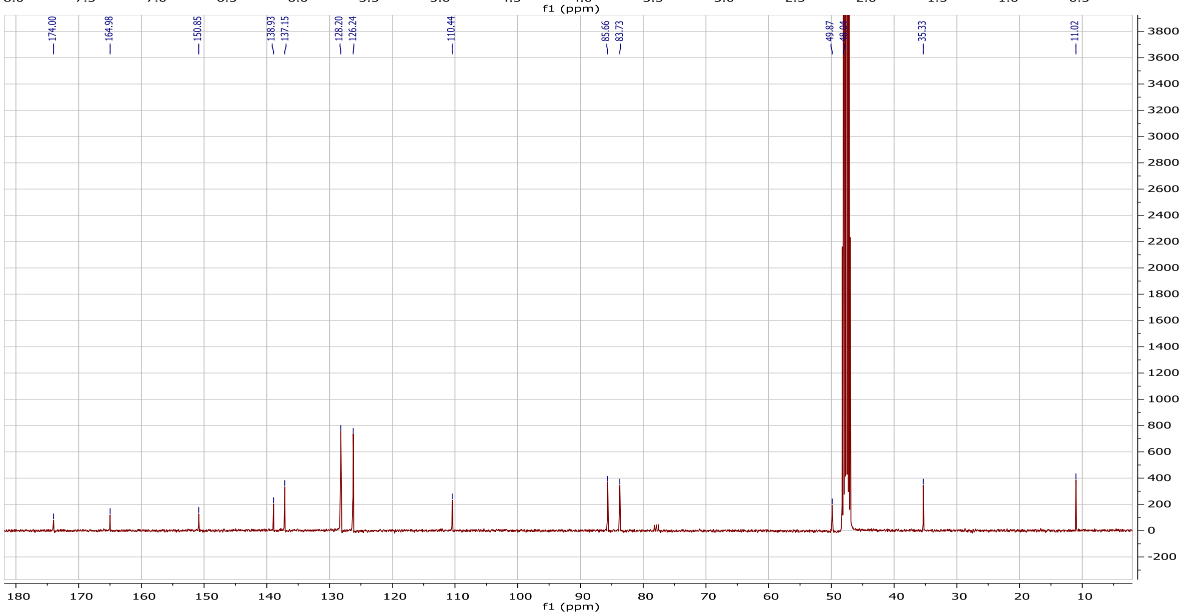

3000
2000
1000

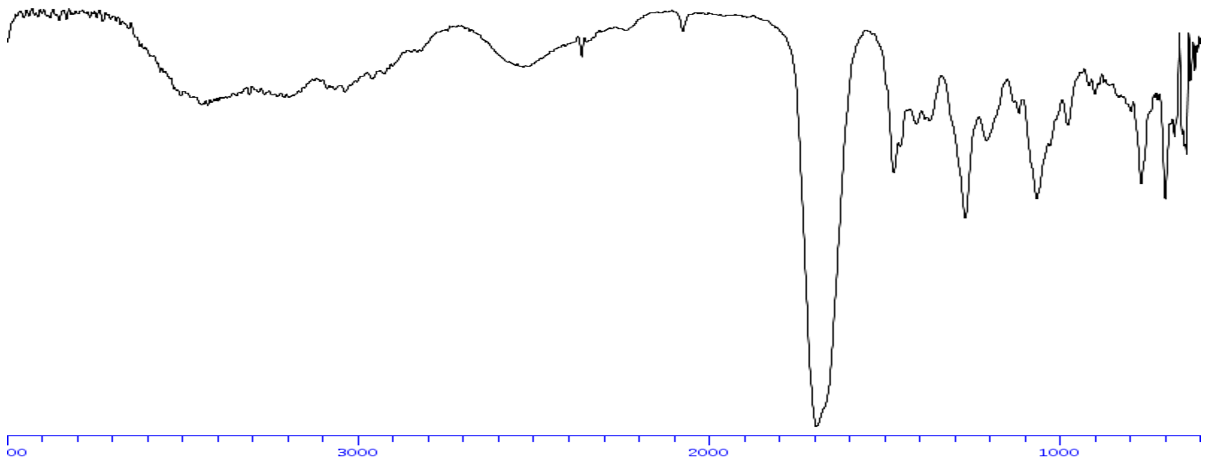

OTIPS
51
400 MHz, Chloroform-d.
2.12
2.10
1.02
1.00
0.99
0.99
0.96
3.90
17.89
f1 (ppm)

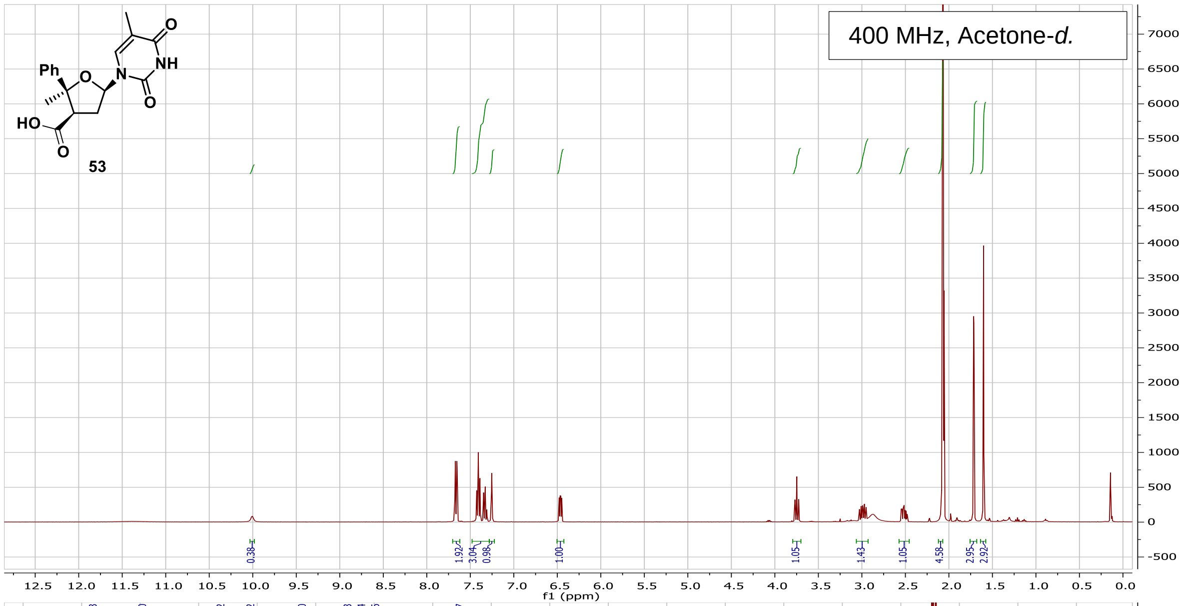

155.62
137.07
129.36
128.72
127.75
126.93
126.74
95.89
18.30
13.06
f1 (ppm)

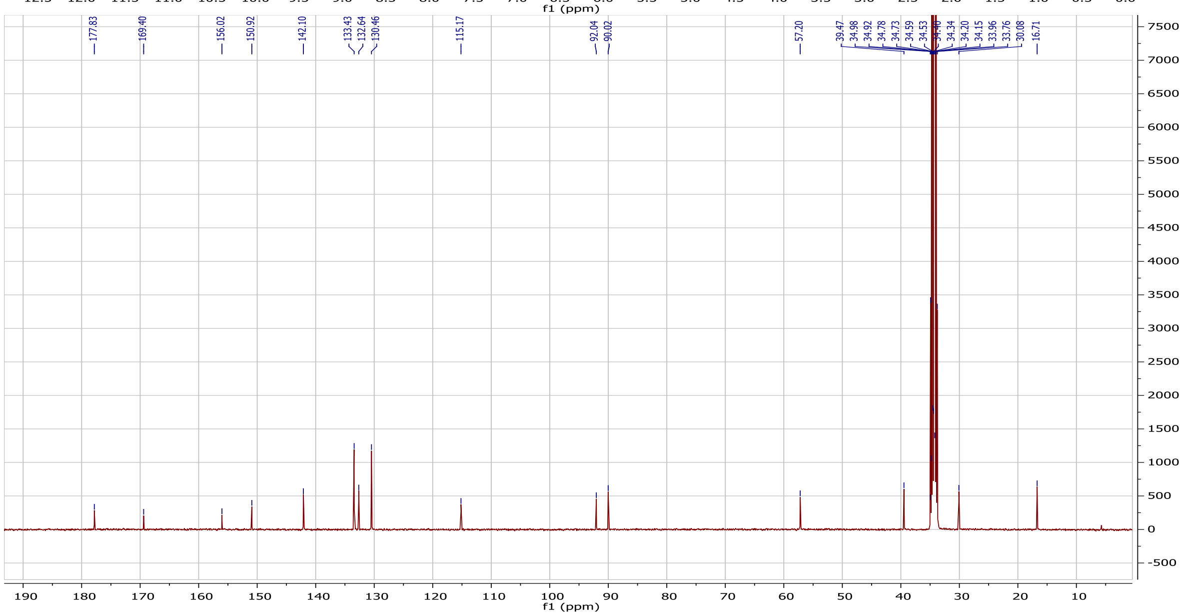

4000
3000
2000
1000

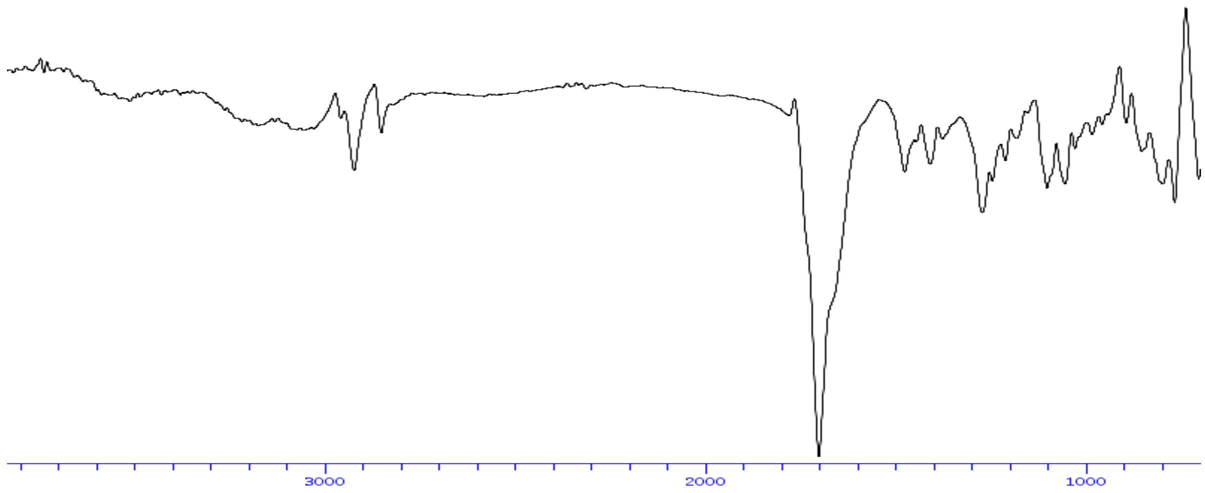

400 MHz, MeOH-d.
Ph
O
N
NH
O
O
HO
O
52
3.03
3.00
1.00
1.06
1.21
1.05
1.05
3.12
f1 (ppm)

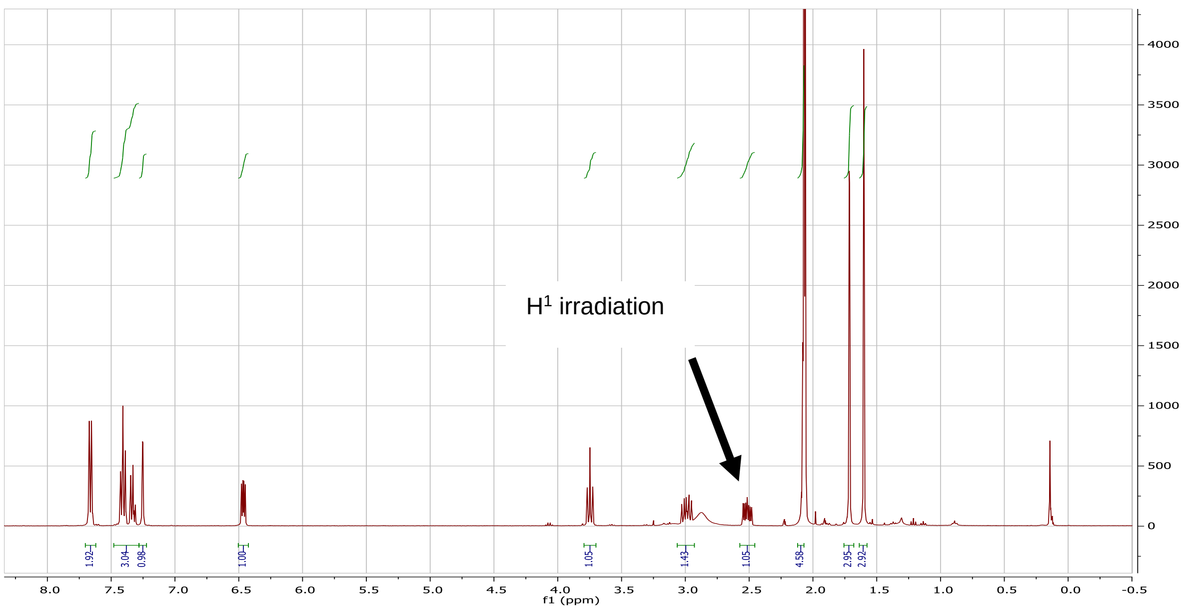

174.00
164.98
150.85
138.93
137.15
128.20
126.24
110.44
85.66
83.73
49.87
35.33
11.02
f1 (ppm)

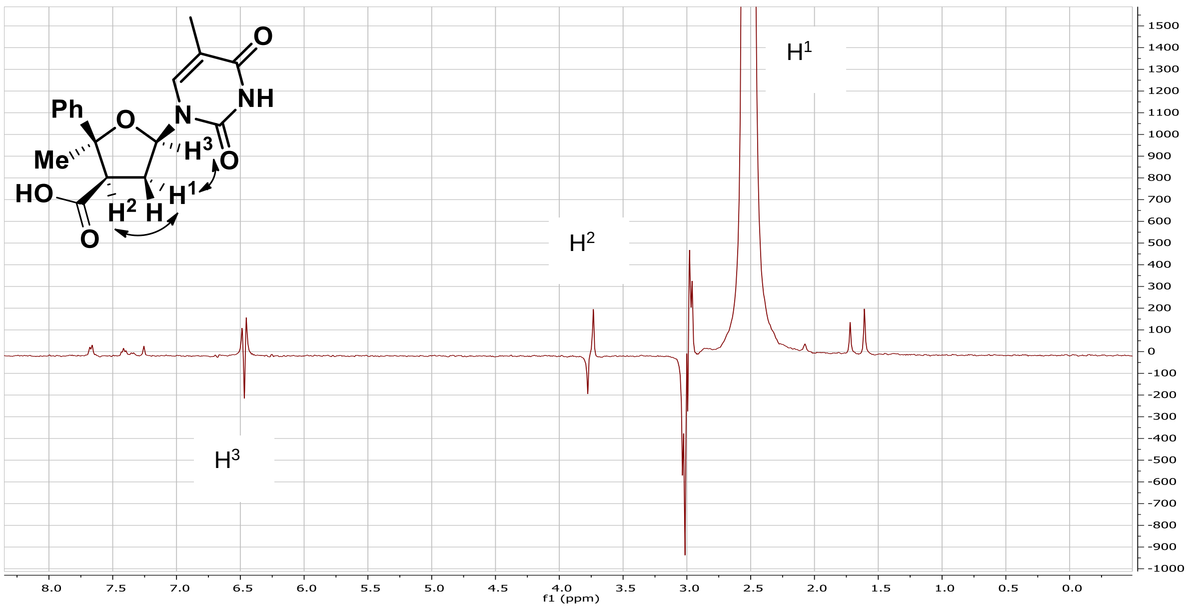

3000
2000
1000


400 MHz, Acetone-*d.*
Ph
HO
NH
53
f1 (ppm)

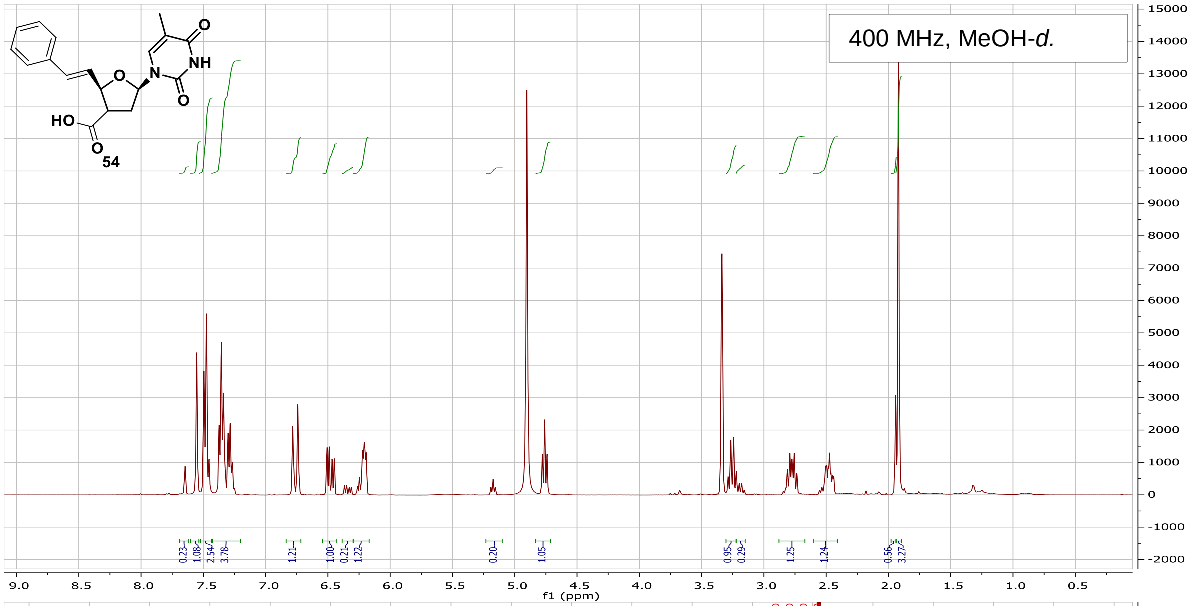

177.83
169.40
156.02
150.92
142.10
133.43
132.64
130.46
115.17
92.04
90.02
57.20
39.47
16.71
f1 (ppm)

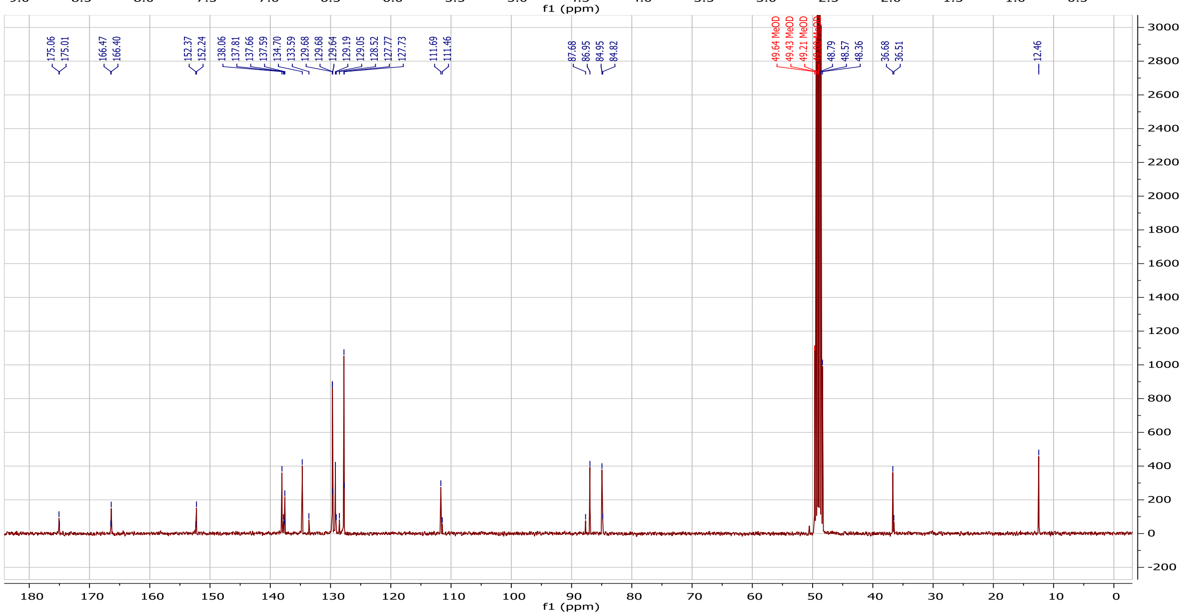

3000
2000
1000

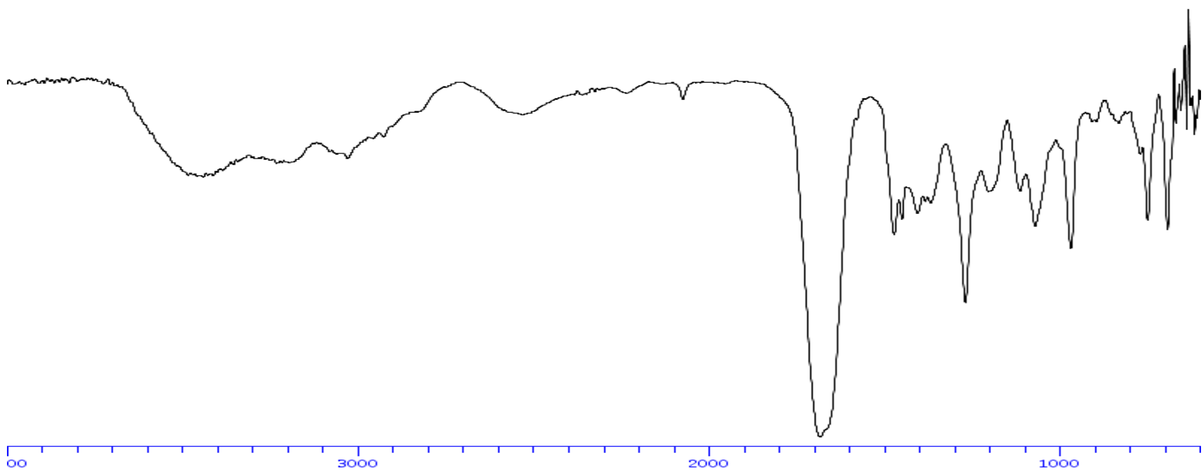


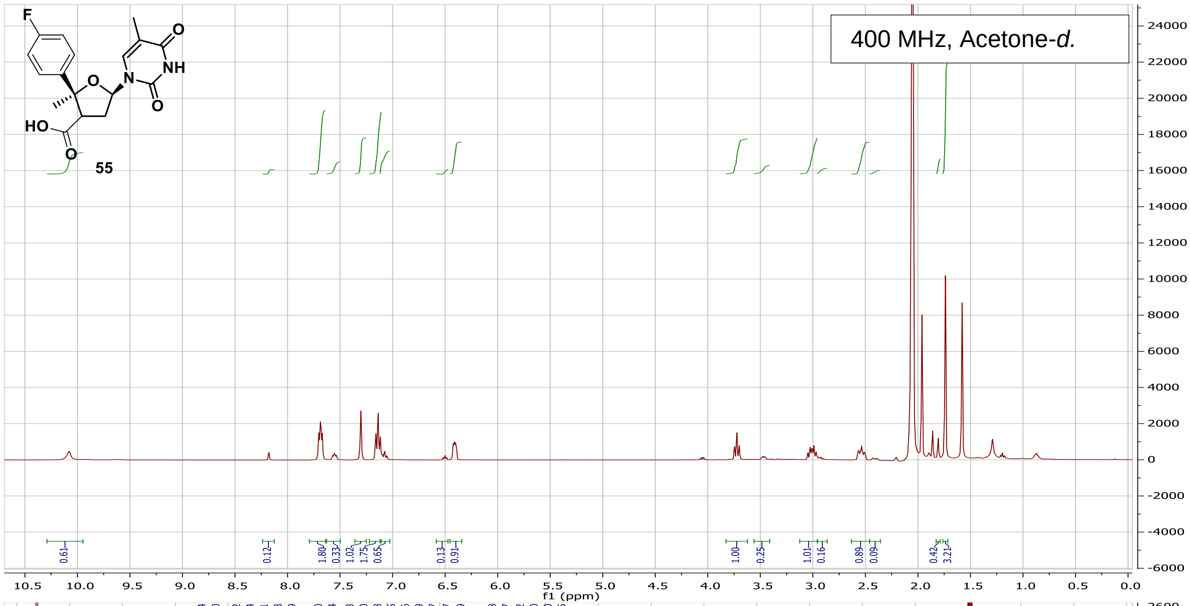


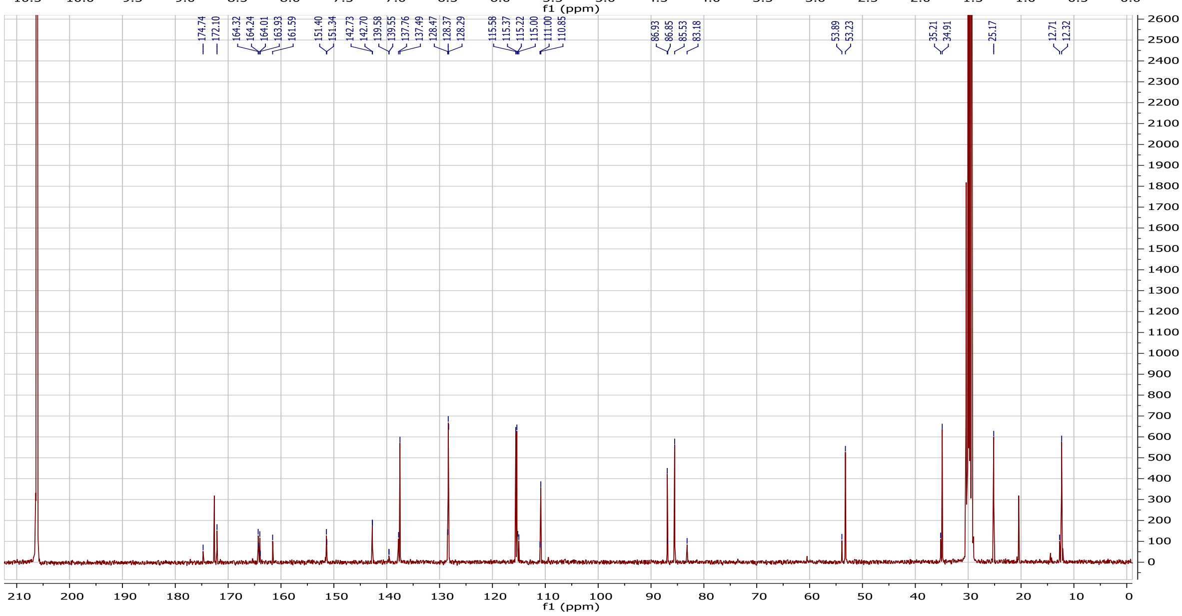
NOESY 1D experiment permitted to define the stereochemistry of the new stereocenter. In fact, we were able to see the NOE interaction between the cyclopentane proton (**H^1**) and the thymine NCH proton (**H^3**) and the proton (**H^2**).

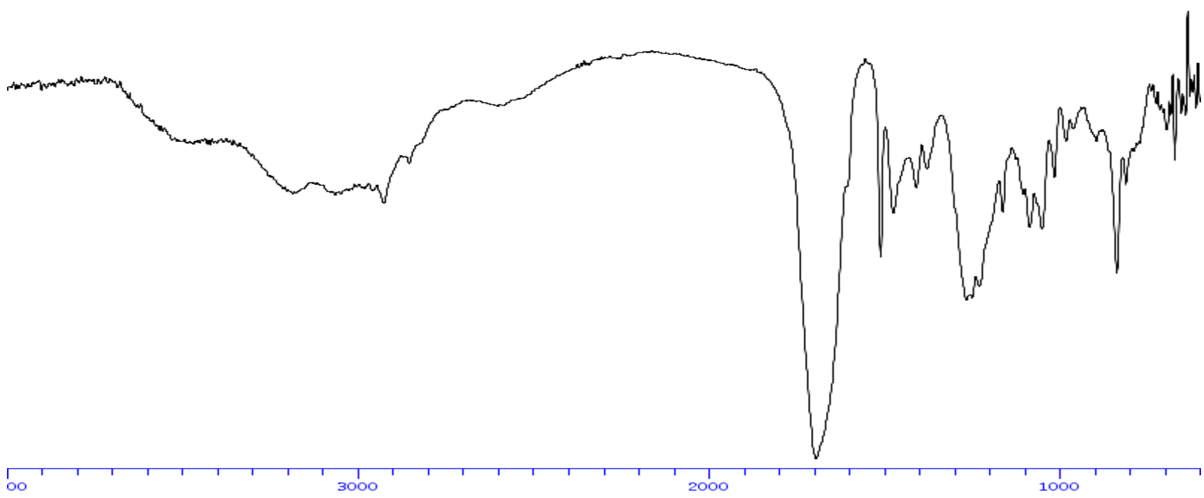

400 MHz, MeOH-d.
HO
O
O
N
NH
O
O
54
f1 (ppm)

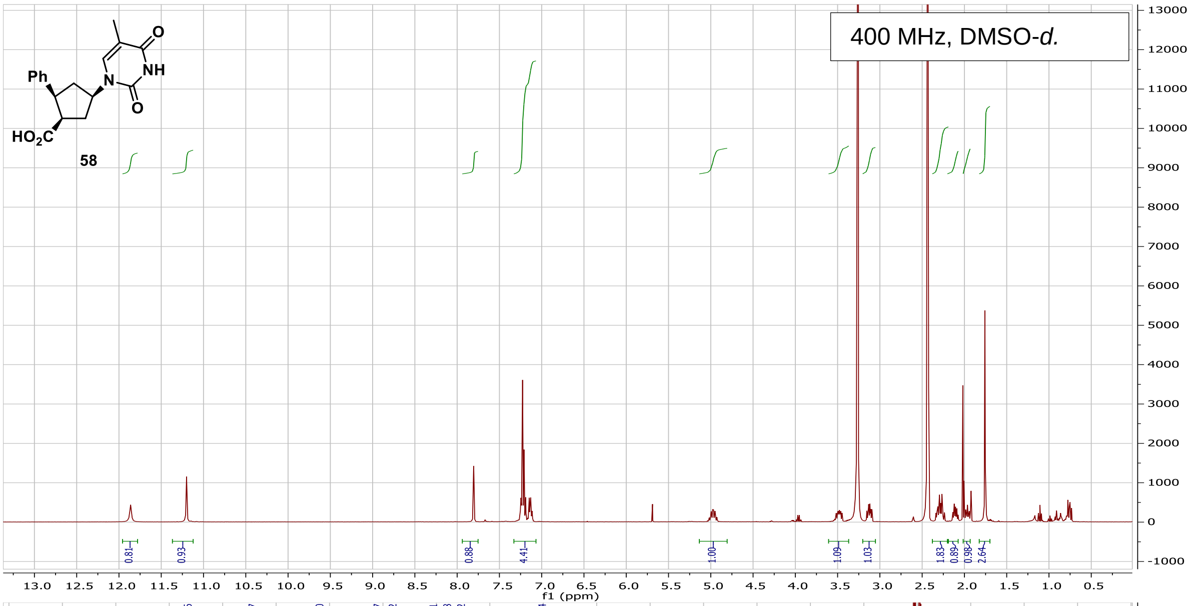

f1 (ppm)

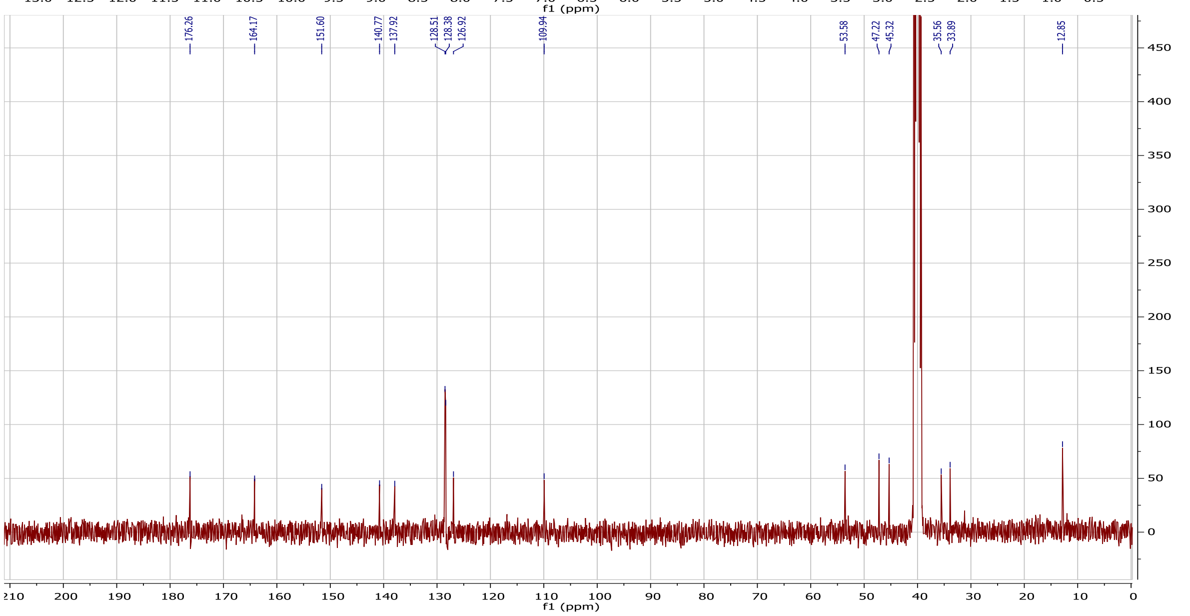


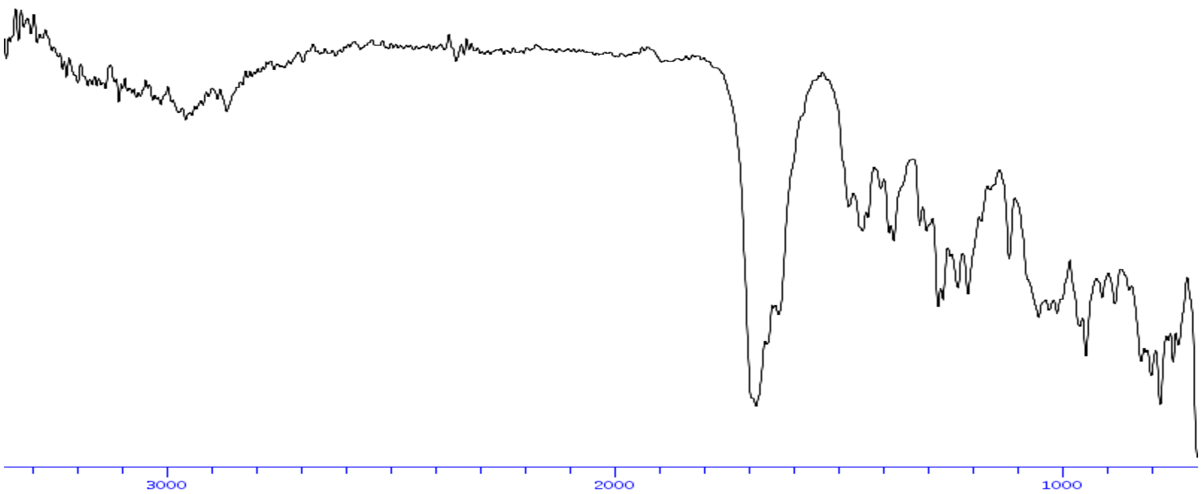

400 MHz, Acetone-*d.*
55
f1 (ppm)

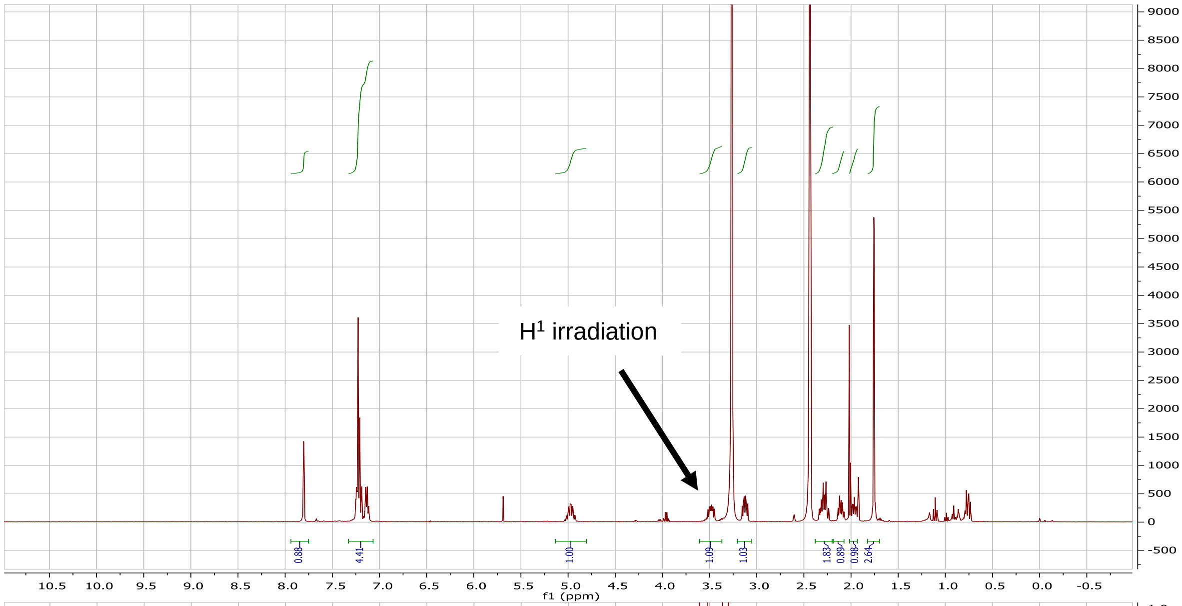

f1 (ppm)

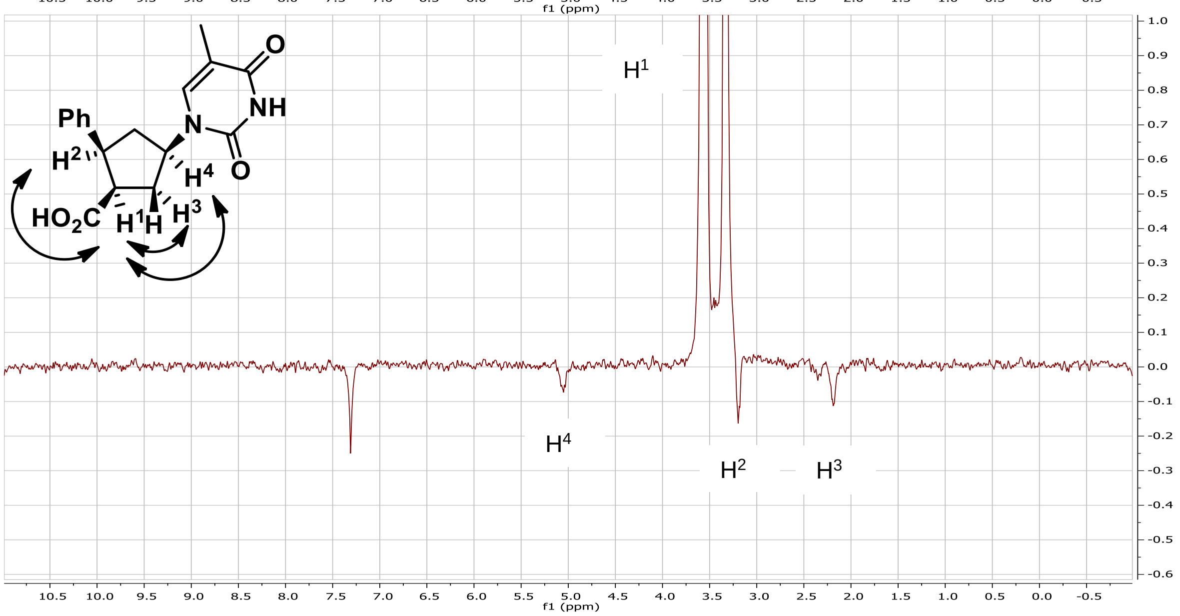



400 MHz, DMSO-d.
Ph
HO2C
N
NH
O
O
58
0.81
0.93
0.88
4.41
1.00
1.09
1.03
1.83
0.89
0.98
2.64
f1 (ppm)


176.26
164.17
151.60
140.77
137.92
128.51
128.38
126.92
109.94
53.58
47.22
45.32
35.56
33.89
12.85
f1 (ppm)







NOESY 1D experiment permitted to define the stereochemistry of the new stereocenter. In fact, we were able to highlight see the NOE interaction between the cyclopentane proton (**H**[3]) and the three other protons **H**[2], **H**[1] and **H**[4].