Universitat Autònoma de Barcelona

Stereoselective Synthesis of Cyclobutane Nucleoside Analogues

PhD Thesis

Antoni Figueras Sorinas

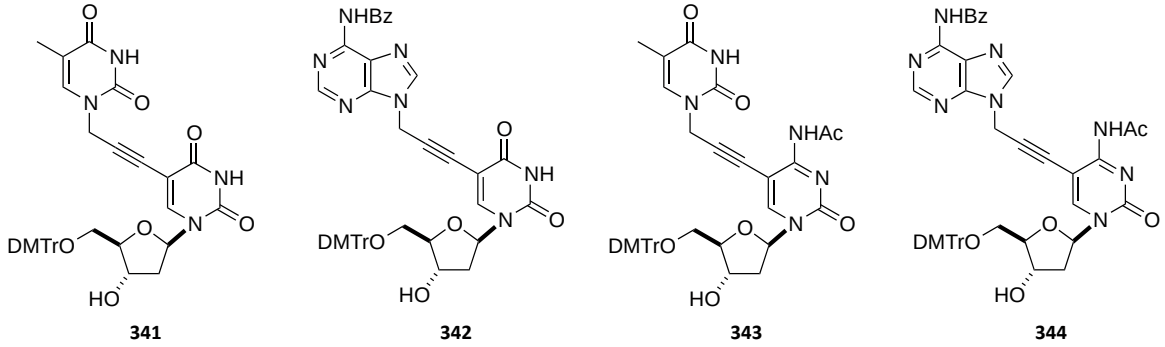
2012

Supervised by:
Dr. Ramon Alibés Arqués
Dr. Félix Busqué Sánchez

Programa de doctorat en Química
Departament de Química
Facultat de Ciències

1. INTRODUCTION

The goal of my three-month stay at the *Nucleic Acid Center* in the University of Southern Denmark (Odense) under the supervision of Prof. Poul Nielsen was the synthesis of the four nucleoside analogues **341**-**344** (Figure 73). These nucleosides would then be transformed into the corresponding phosphoramidites and incorporated into oligonucleotides. Eventually, the thermal stability of these oligonucleotides would be evaluated.



341 **342** **343** **344**

Figure 73. Targeted double-headed nucleosides.

1.1 Introduction to nucleic acid structure

Nucleotides are the constituents of DNA and RNA, biopolymers in which the genetic information is stored. A nucleotide consists of a nucleoside and a phosphate group (Figure 74). DNA and RNA are long sequences of nucleotides linked through the phosphate groups, where the 5'-phosphate group of one nucleotide is linked to the 3'-hydroxyl group of the next nucleotide, creating a phosphodiester bond. In DNA and double stranded RNA (dsRNA) two complementary antiparallel polynucleotide chains stack together forming a double helix. While hydrogen bonds

between parallel bases keep both strands together, base-stacking interactions help to stabilize the three-dimensional structure.[178]

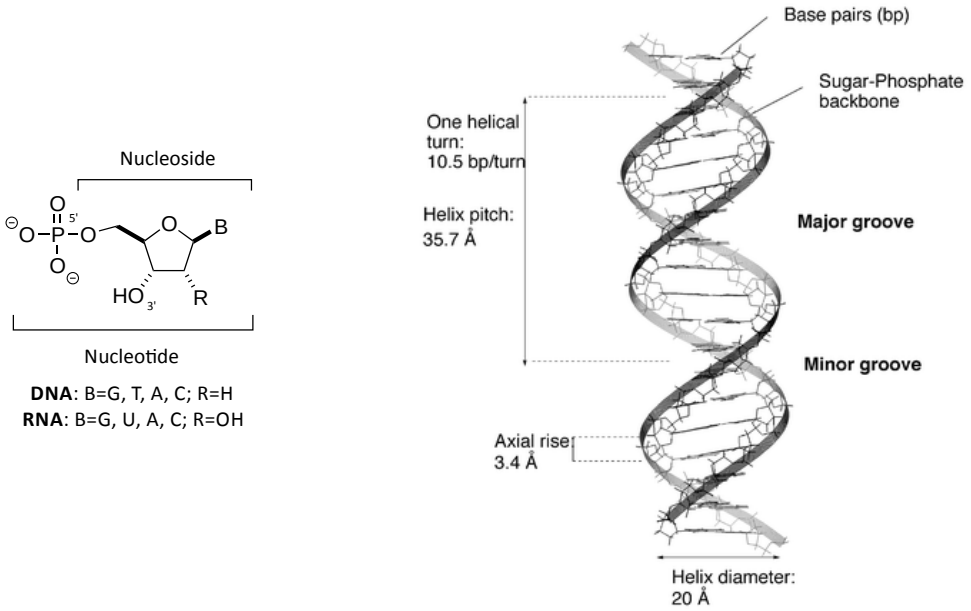


Figure 74. Structure of nucleotides and three-dimensional structure of DNA.[179]

1.1.1 Secondary structure

Double helical DNA can be found in different conformations, with the most important being the A- and B-forms (Figure 75). The A helix is favoured in dehydrated media, features 11 base pairs per turn and the base plane is tilted 20º with respect to the helix axis. The B form is the most stable for DNA:DNA duplexes under physiological conditions, features 10.5 bp per helical turn and the base plane is almost perpendicular to the helix axis. RNA:RNA duplexes exhibit A-type helixes, while DNA:RNA hybrids adopt helixes somewhere in between the two types.

[178] Nelson, D. L.; Cox, M. M. *Lehninger Principles of Biochemistry* 5th ed, W. H. Freeman and Company: New York, 2008.

[179] Belmont, P.; Constant, J.-F.; Demeunynck, M. *Chem. Soc. Rev.* **2001**, *30*, 70-81.

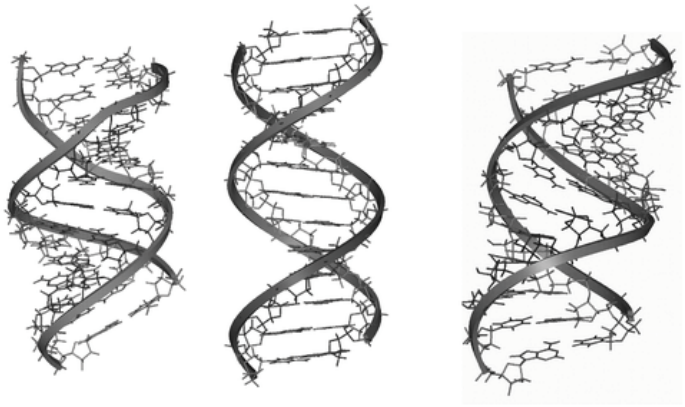


Figure 75. Representation of the main structural conformations of nucleic acids.[180]

Nucleic acids can also exhibit other secondary structures such as internal loops, bulges, hairpins, and three- and four-way junctions (Figure 76). Bulges, hairpins and internal loops are formed due to the presence of unpaired nucleotides, whereas three- and four-way junctions play important roles in replication and catalytic processes.[180]

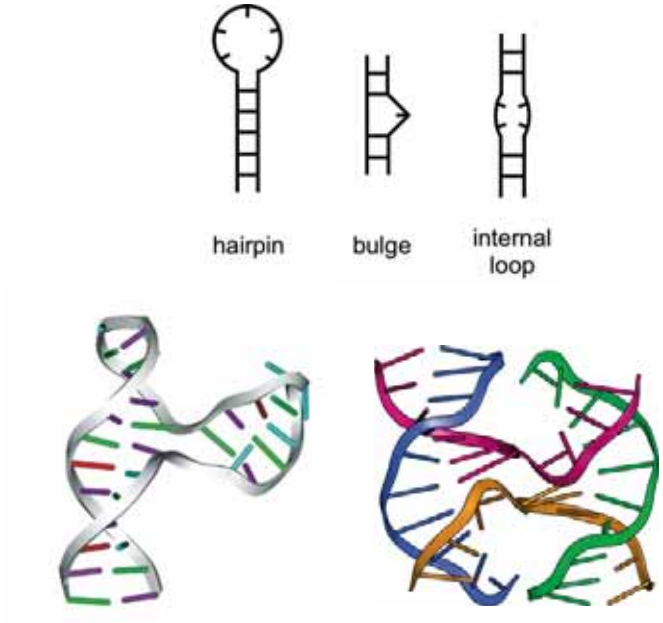


Figure 76. Examples of secondary structures of nucleic acids. Three-way junction (bottom left).[181] Four-way junction (bottom right).[182]

[180] (a) Pearson, C. E.; Zorbas, H.; Price, G. B.; Zannis-Hadjopoulos, M. *J. Cell. Biochem.* **1996**, *63*, 1-22. (b) Batey, R. T.; Rambo, R. P.; Doudna, J. A. *Angew. Chem. Int. Ed.* **1999**, *38*, 2326-2343.

[181] Wu, B.; Girard, F.; Van Buuren, B.; Schleucher, J.; Tessari, M.; Wijmenga, S. *Nucleic Acids Res.* **2004**, *32*, 3228-3239,

[182] Biertumpfel, C.; Yang, W.; Suck, D. *Nature* **2007**, *449*, 616-621.

1.2 Oligonucleotide synthesis

Oligonucleotides are short sequences of up to 50 nucleotides. Over the last 50 years, several methodologies have been developed to synthesize these short polynucleotides.[183] These methodologies differ in the phosphorous oxidation degree and/or substitution at this atom. Currently, the most used strategy for oligonucleotide synthesis is the phosphoramidite approach,[184] which was developed by Beaucage and Caruthers[185] and was later improved by Köster and co-workers.[186] Their findings established the bases of modern automated DNA synthesis.

Oligonucleotide synthesis follows the four-step cycle depicted in Figure 77.[187] The first step is the cleavage of the 5'-protecting group, which is usually a dimethoxytrityl group. The deprotection is carried out by treatment with a mild acid such as trichloroacetic acid (TCA). The DMTr cation (which is bright orange) released in the process is used to monitor the efficiency of the previous coupling step.

In the coupling stage 1*H*-tetrazole acts as a weak acid and nucleophile, activating the phosphorous to be attacked by the supported nucleoside. Although the coupling efficiency is very high (>98%), some supported nucleosides fail to react with the activated monomer. If these unreacted nucleosides were ignored, a mixture of truncated *n*-1 sequences would accumulate, leading to purification problems. This issue is prevented in the capping step, in which unreacted sites are acetylated and thereby rendered inert.

Finally, the reactive phosphite triester group resulting from the coupling step is oxidized to the corresponding phosphate triester, which is stable to the reaction conditions of the synthesizer. This reaction is carried out by mild oxidizing agents, usually iodine. At this point, the oligonucleotide can undertake a new cycle or it can be hydrolysed from the solid support by treatment with ammonia. The obtained oligonucleotide is purified (usually by reverse phase HPLC), detritylated and precipitated by treatment with sodium cations, rendering the oligonucleotide as a white solid.

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[183] Reese, C. B. *Org. Biomol. Chem.* **2005**, *3*, 3851-3868 and references cited therein.

[184] Beaucage, S. L.; Caruthers, M. H. In *Current Protocols in Nucleic Acid Chemistry*, Wiley: New York, 2000, unit 3.3, 1-20.

[185] Beaucage, S. L.; Caruthers, M. H. *Tetrahedron Lett.* **1981**, *22*, 1859-1862.

[186] Sinha, N. D.; Biernat, J.; Köster, H. *Tetrahedron Lett.* **1983**, *24*, 5843-5846.

[187] (a) Brown, T.; Brown, D. J. S. In *Oligonucleotides and Analogues: A Practical Approach*, Oxford University Press: New York, 1991, chapter 1, 1-24. (b) Somoza, A. *Chem. Soc. Rev.* **2008**, *37*, 2668-2775. (c) Jensen, M. D. *MSc Thesis*, Syddansk Universitet, **2010**.

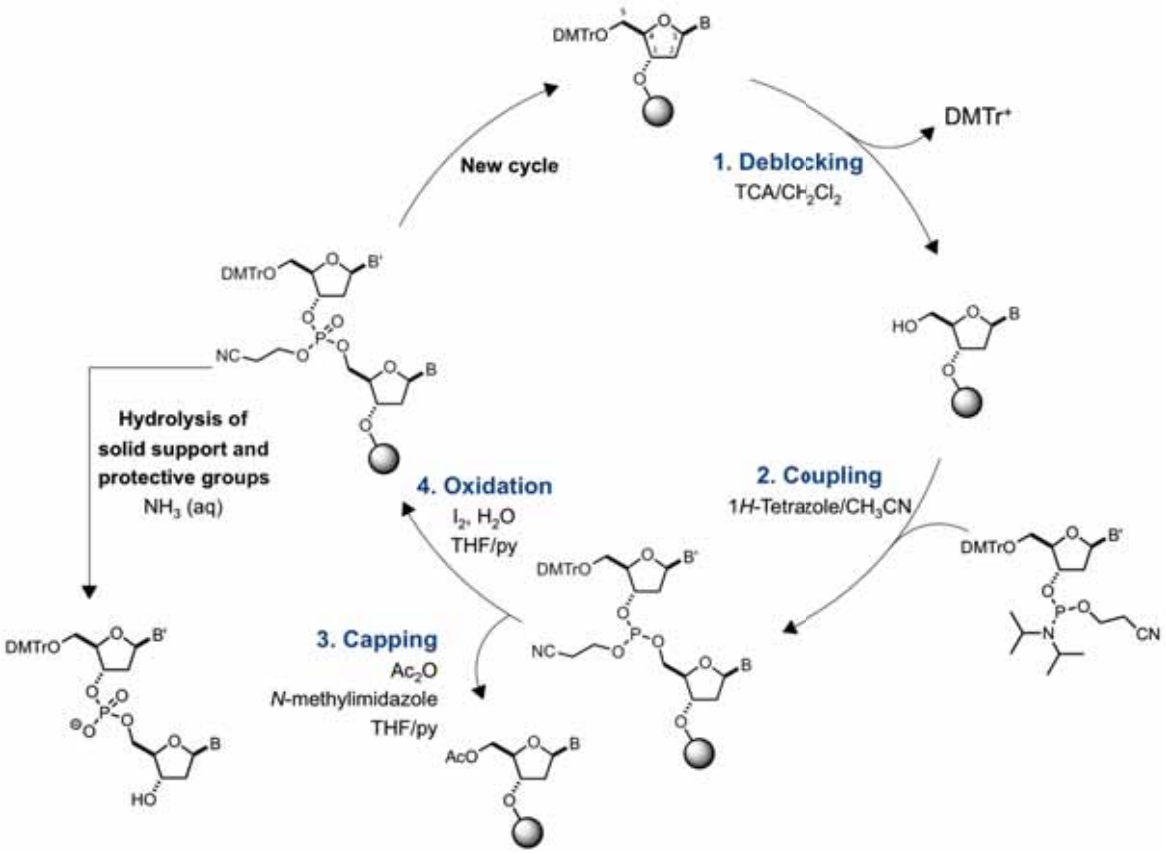

Figure 77. Oligonucleotide synthesis cycle.

1.2.1 Thermal denaturation

Thermal denaturation studies are a standard method to evaluate the stability of a newly synthesized oligonucleotide. They are based in the reversible denaturation and annealing of double-helical DNA; when a DNA double helix is subjected to extremes of pH or high temperatures, hydrogen bond interactions that keep both strands together are disrupted (DNA denaturation, melting). Cease of interaction between nucleobases causes an increase in light absorption (hyperchromic effect). Thus, this process is easily monitored by UV-spectroscopy. Plotting of a temperature vs. absorbance graph results in a sigmoidal curve (Figure 78). The temperature at the mid-point of the transition is called melting point (t_m) and represents the temperature at which half of the DNA is present as a single strand.

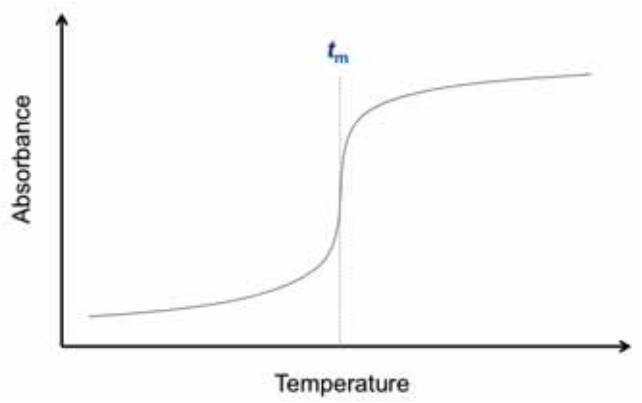

Figure 78. DNA melting curve.

1.3 Nucleic acids as therapeutic agents

In recent years, chemically modified nucleic acids have arisen as potential therapeutic agents due to the development of strategies based on the utilization of antisense oligonucleotides and aptamers. Antisense oligonucleotides are short and specific sequences of DNA or RNA that bind to a target mRNA inhibiting its translation (Figure 79). Currently, some of these oligonucleotides directed to the treatment of cancer,[188] HCV, HIV and other diseases are on different phases of clinical trials.[189]

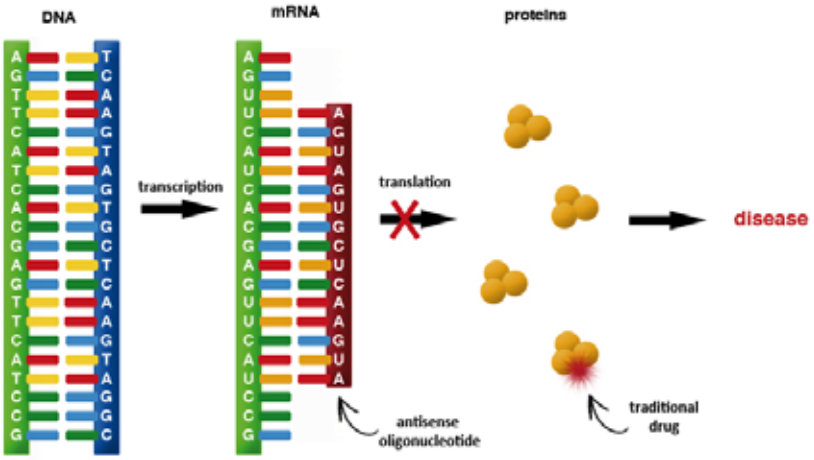

Figure 79. Mechanism of action of an antisense oligonucleotide.

On the other hand, aptamers are single-stranded nucleic acid molecules that bind to a specific target not because of its sequence complementarity but because their ability to fold into certain three-dimensional structures.[190]

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[188] Rayburn, E. R.; Wang, H.; Zhang, R. *Expert Opin. Emerg. Dr.* **2006**, *11*, 337-352.

[189] Rayburn, E. R.; Zhang, R. *Drug Discov. Today,* **2008**, *13*, 513-521.

[190] (a) Rimmele, M. *ChemBioChem* **2003**, *4*, 963-971. (b) Famulok, M.; Hartig, J. S.; Mayer, G. *Chem. Rev.* **2007**, *107*, 3715-3743.

2. SYNTHESIS OF DOUBLE-HEADED NUCLEOSIDES

2.1 Precedents

Double-headed nucleosides are synthetic nucleoside analogues featuring an additional nucleobase. The sense in introducing this additional nucleobase is to provide supplementary stabilizing interactions by base pairing or stacking.

The first double-headed nucleoside synthesized **345**, was described by Switzer and co-workers in 1996.[191] Since then, several analogues have been reported, mainly by Prof. Poul Nielsen's research group (Figure 80).[192]

Remarkably, nucleosides **347** and **349** have been found to exhibit interesting stabilizing interactions. While the first one showed stabilization of a three-way junction,[192b] the second one unveiled strong duplex stabilization when built in a (-3)-zipper[††] structure due to stacking between the two additional thymines.[192d]

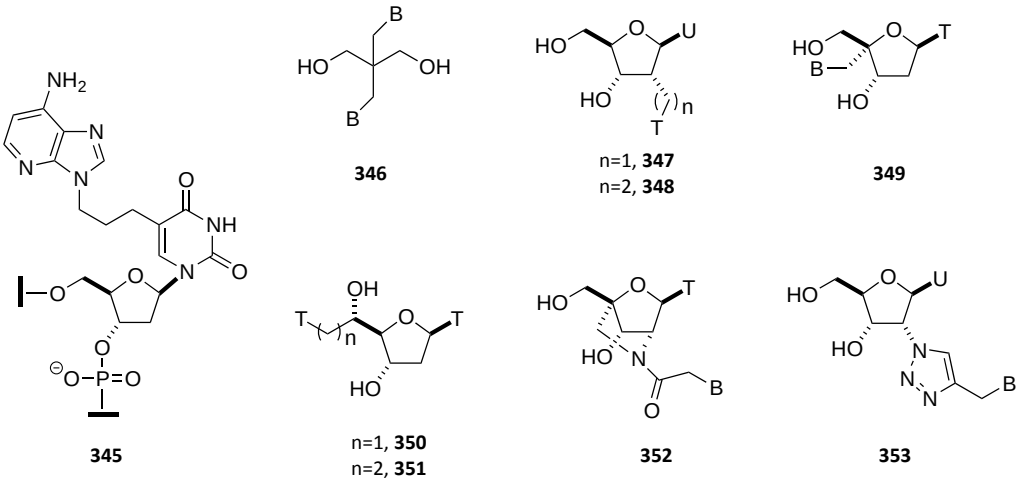


Figure 80. Examples of double-headed nucleosides.

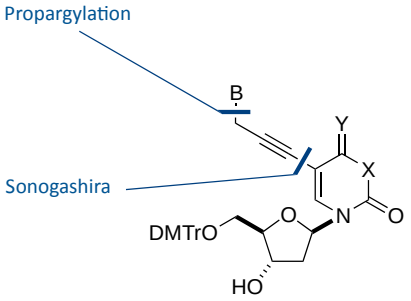
[191] Switzer, C.; Prakash, T. P.; Ahn, Y. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 815-818.

[192] (a) Wu, T.; Froeyen, M.; Schepers, G.; Mullens, K.; Rozenski, J.; Busson, R.; Van Aerschot, A.; Herdewijn, P. *Org. Lett.* **2004**, *6*, 51-54. (b) Pedersen, S. L.; Nielsen, P. *Org. Biomol. Chem.* **2005**, *3*, 3570-3575. (c) Wu, T.; Nauwelaerts, K.; Van Aerschot, A.; Froeyen, M.; Lescrinier, E.; Herdewijn, P. *J. Org. Chem.* **2006**, *71*, 5423-5431. (d) Christensen, M. S.; Madsen, C. M.; Nielsen, P. *Org. Biomol. Chem.* **2007**, *5*, 1586-1594. (e) Andersen, C.; Pedersen, S. L.; Nielsen, P. *Nucleosides, Nucleotides & Nucleic Acids* **2007**, *26*, 1435-1438. (f) Andersen, C.; Sharma, P. K.; Christensen, M. S.; Steffansen, S. I.; Madsen, C. M.; Nielsen, P. *Org. Biomol. Chem.* **2008**, *6*, 3983-3988. (g) Umemoto, T.; Wengel, J.; Madsen, A. S. *Org. Biomol. Chem.* **2009**, *7*, 1793-1797. (h) Jørgensen, A. S.; Shaikh, K. I.; Enderlin, G.; Ivarsen, E.; Kumar, S.; Nielsen, P. *Org. Biomol. Chem.* **2011**, *9*, 1381-1388.

[††] A zipper is a duplex containing modifications in both strands. The number indicates the relative disposition of the two nucleotides of interest, each one on opposite strands of the duplex. A positive value indicates that the modification is shifted towards the 5'-end, whereas a negative value indicates that it is shifted towards the 3'-end. For instance, the two nucleotides **X** in 5'-GTG T**X**T ACA:3'-CAC AAA **X**GT would exemplify a (+2)-zipper construct.

2.2 Synthetic strategy overview

Preparation of the targeted double-headed nucleosides **341**-**344** was planned by means of a propargylation reaction to install the additional three-carbon chain attached to the secondary nucleobase, and a Sonogashira reaction to assemble both fragments (Figure 81).



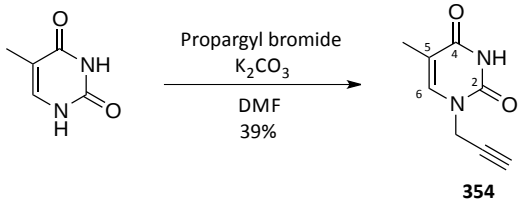
X=NH; Y=O; B=T, **341**
X=NH; Y=O; B=N^6-benzoyladenine, **342**
X=N; Y=NHAc; B=T, **343**
X=N; Y=NHAc; B=N^6-benzoyladenine, **344**

Figure 81. Planned synthetic strategy towards the double-headed nucleoside analogues **341-344**.

2.3 Synthesis of the building blocks

2.3.1 Propargylation of thymine and adenine

Propargylation of thymine and adenine was accomplished by reaction of the nucleobase with propargyl bromide and potassium carbonate in DMF.[193] In the cae of thymine, these conditions delivered a mixture of the N^1-mono and N^1,N^3-dialkylated compounds, which could be separated by column chromatography to afford the monoalkylated product **354** in 39% yield (Scheme 89).



354

Scheme 89. Propargylation of thymine.

The presence of the triple bond is readily observed by ^{1}H- and ^{13}C-NMR. Thus, in the proton spectrum two new signals appear at δ 4.47 and δ 3.38 corresponding to the methylene and

[193] Lazrek, H. B.; Taourirte, M.; Oulih, T.; Barascut, J. L.; Imbach, J. L.; Pannecouque, C.; Witrouw, M.; De Clercq, E. *Nucleosides, Nucleotides & Nucleic Acids* **2001**, *20*, 1949-1960.

ethynyl protons, respectively (Figure 82). The ethynyl signals are also clearly observed in the carbon spectrum, where two signals corresponding to C2' and C3' appear at δ 75.0-80.0.

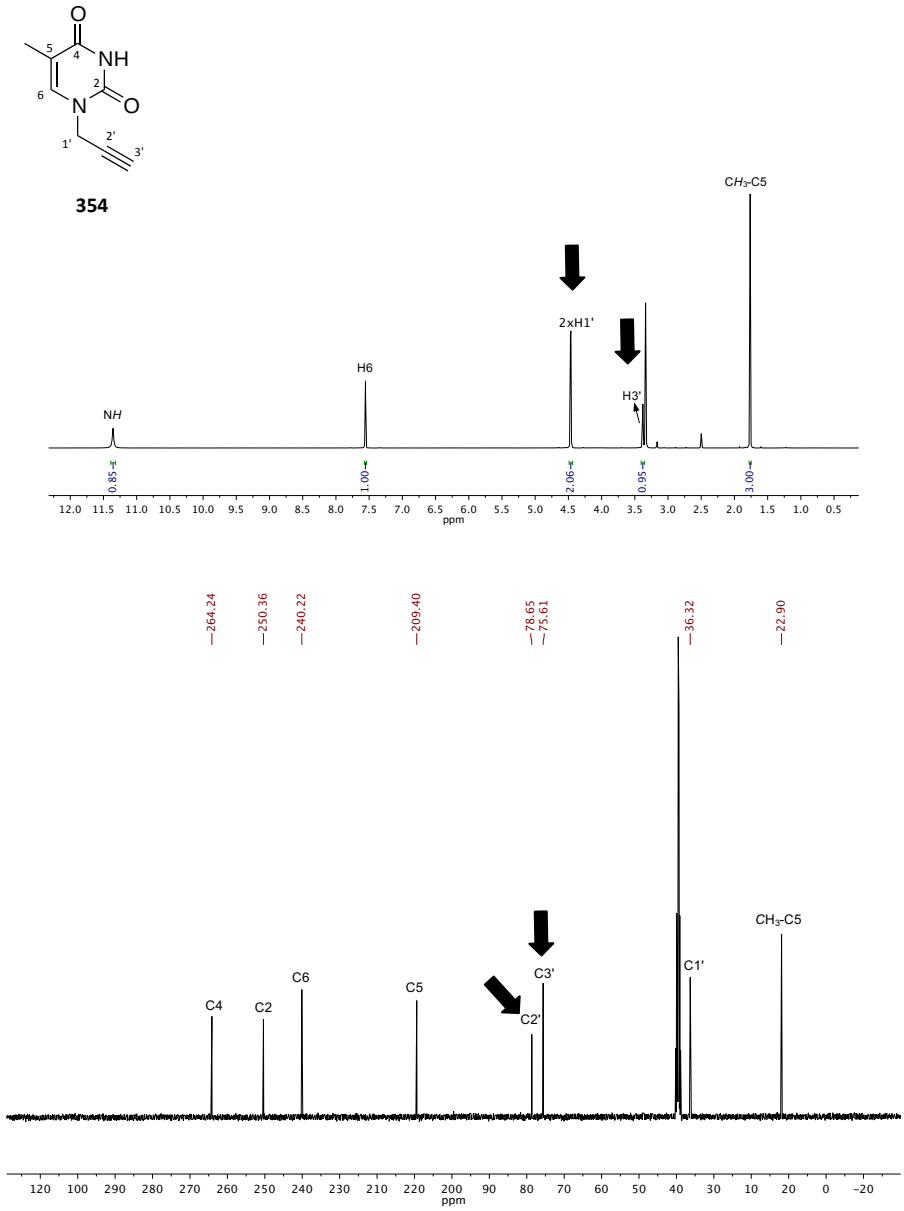
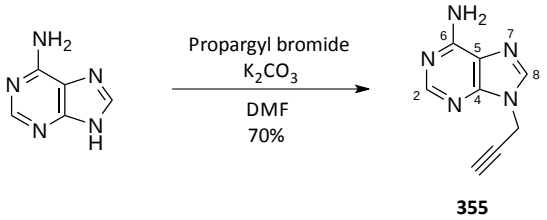


Figure 82. ^{1}H-NMR (400 MHz, DMSO) and ^{13}C-NMR (100 MHz, DMSO) spectra of **354** .

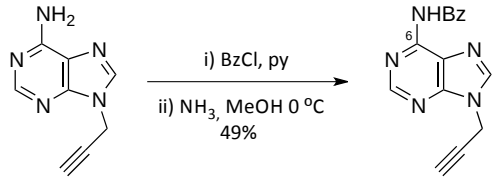
On the other hand, when adenine was submitted to the same conditions, only the desired alkylation at the *N*9 position was observed, affording **355** in 70% yield (Scheme 90).



355

Scheme 90. Propargylation of adenine.

Since the presence of adenine's free amino group could interfere with the process of oligonucleotide synthesis, it was protected as the monobenzoyl derivative. This task was accomplished by dibenzoylation of the *N*6-amino group using benzoyl chloride in pyridine followed by selective cleavage of one of the two benzoyl groups with ice-cooled methanolic ammonia (Scheme 91).[192a] This procedure rendered **356** in 49% yield for the two steps.



355 **356**

Scheme 91. Protection of **355** as the monobenzoyl derivative.

Evidence of the monobenzoylated derivative can be found on the ^{1}H-NMR spectrum, where six protons appear in the aromatic region and a broad -NH signal integrating for one proton appears at δ 11.23 (Figure 83).

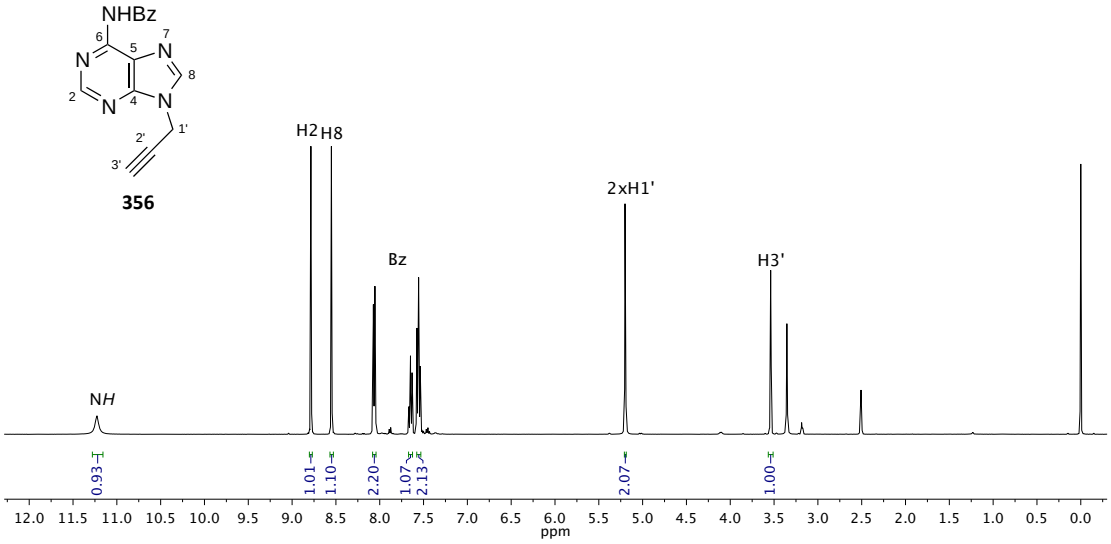


Figure 83. ^{1}H-NMR spectrum(400 MHz, DMSO) of **356**.

The aromatic and carbonyl peaks are also clearly identified in the ^{13}C-NMR spectrum (Figure 84).

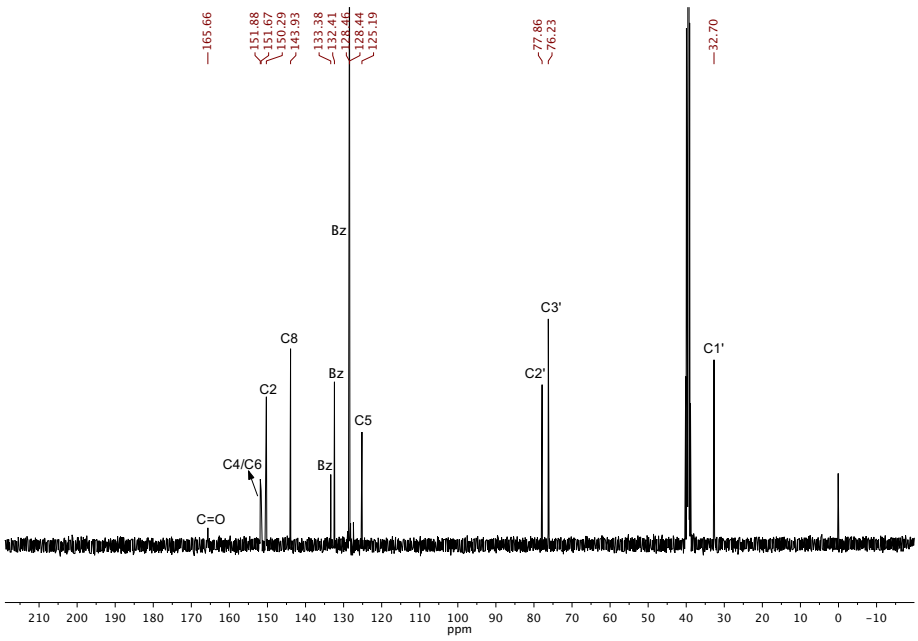
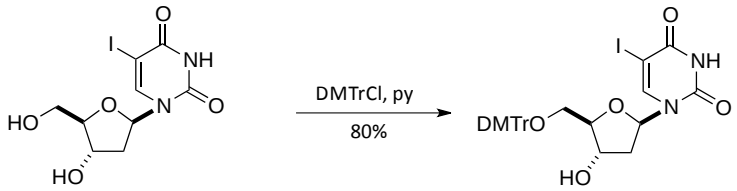


Figure 84. ^{13}C-NMR spectrum (100 MHz, DMSO) of **356**.

2.3.2 Tritylation of 5-iodo-2'-deoxyuridine

Standard oligonucleotide synthesis procedures require the 5'-hydroxyl group to be protected. As it has been pointed out, usually dimethoxytrityl is employed for this task. In consequence, commercial 5-iodo-2'deoxyuridine was treated with dimethoxytrityl chloride in pyridine giving regioselectively the mono-protected nucleoside **358** in 80% yield (Scheme 92).



357 **358**

Scheme 92. Protection of the 5'-hydroxyl group as the DMT derivative.

Proton spectrum of **358** shows the appearance of the DMT signals around 7.00-7.50 ppm and the two methoxy groups at 3.74 ppm (Figure 85).

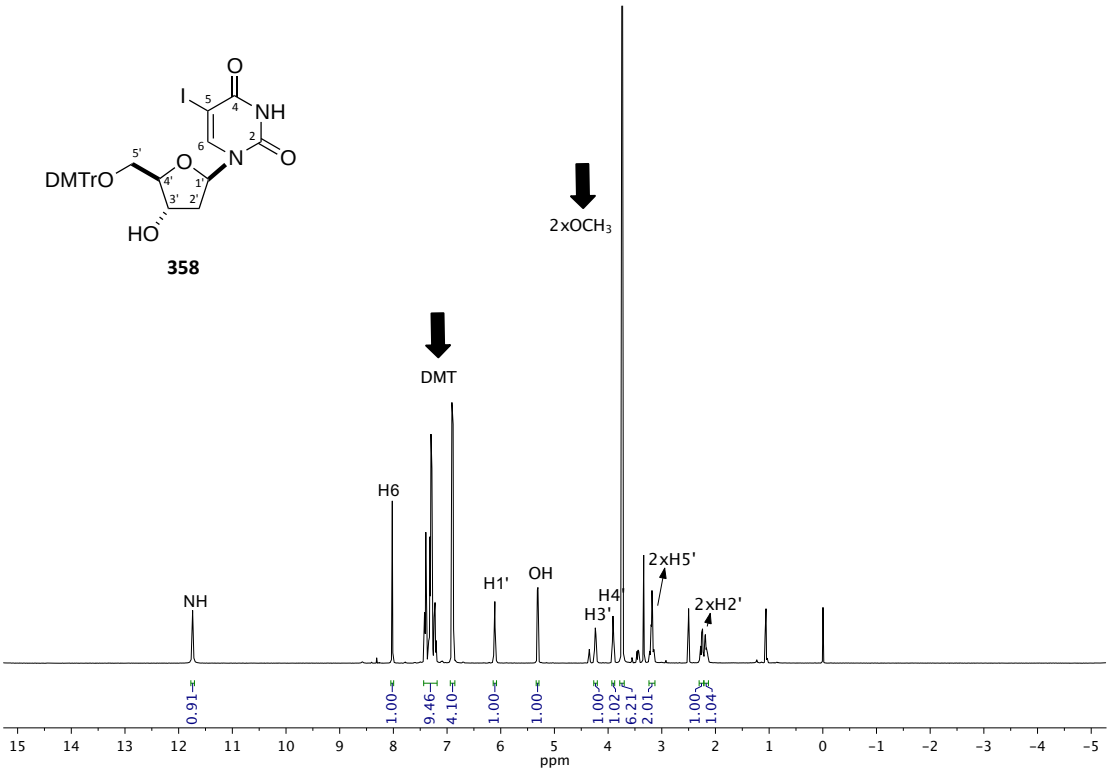
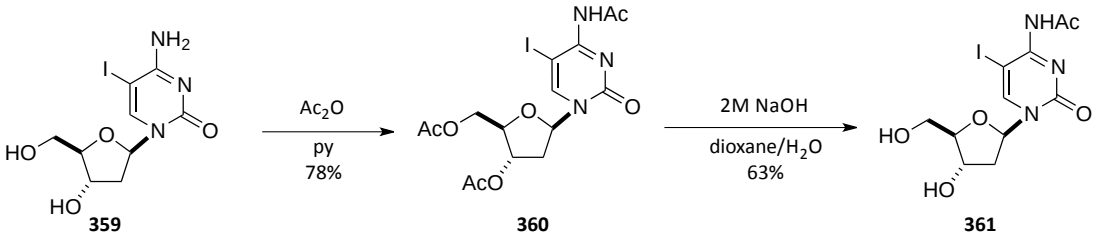


Figure 85. ^{1}H-NMR spectrum (400 MHz, DMSO) of **358**.

2.3.3 Synthesis and tritylation of 5-iodo-*N*^{4}-acetyl-2'-deoxycytidine

Monoprotection of the amino group of cytidine was accomplished in a two-step sequence involving triacetylation of 5-iodo-2'-deoxycytidine (commercially available) and selective hydrolysis of the *O*-acetyl groups. This procedure delivered nucleoside **361** in 49% yield for the two steps (Scheme 93). Comparison of the ^{1}H-NMR spectra of **360** and **361** reveals the disappearance of the *O*-acetyl groups and appearance of the two hydroxyl signals (Figure 86).



Scheme 93. Preparation of nucleoside **361**.

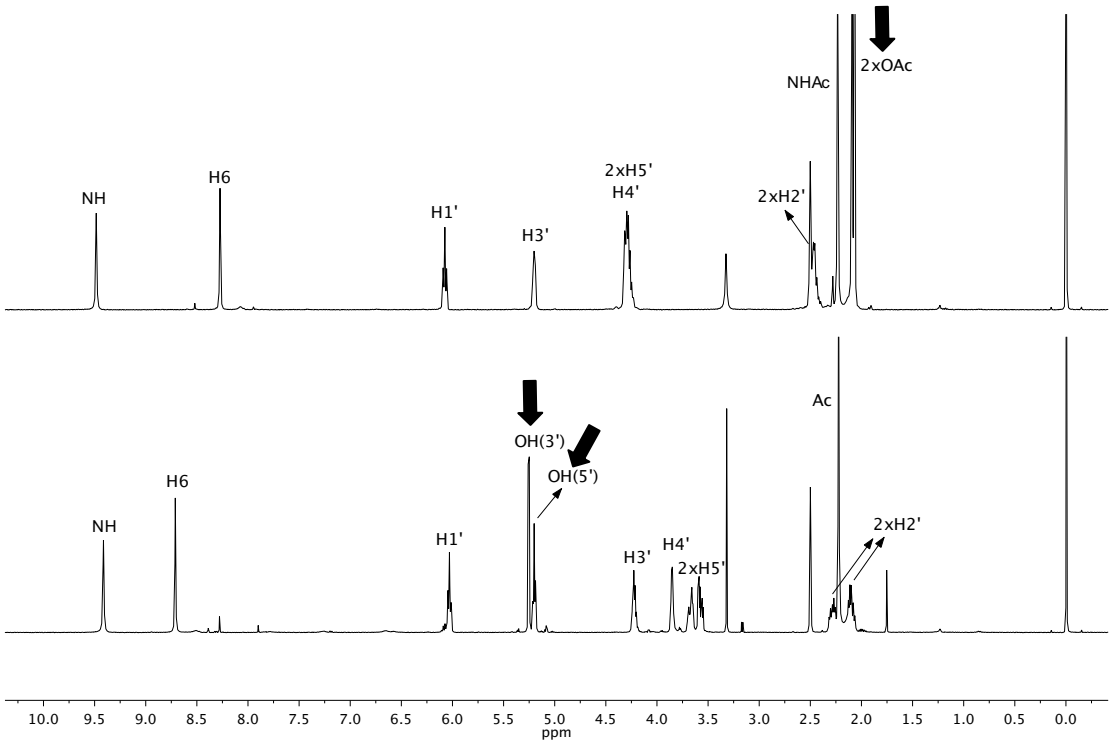
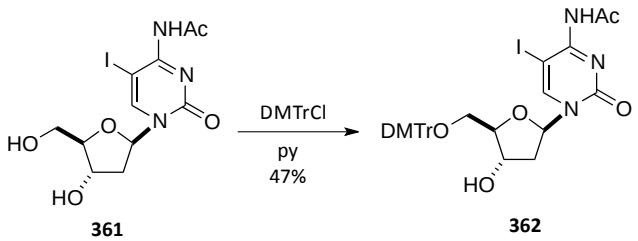


Figure 86. Comparison between ^{1}H-NMR spectra (400 MHz, DMSO) of **360** (top) and **361** (bottom).

Following the same procedure described above, compound **361** was regioselectively tritylated delivering **362** in 47% yield (Scheme 94). It should be pointed out that the cytidine derivatives were found to be rather unstable compared to their uridine counterparts, resulting in lower yields throughout the synthetic sequence.



361 **362**

Scheme 94. Protection of the 5'-hydroxyl group as the DMT derivative.

2.4 Synthesis of the double-headed nucleosides 341-344

2.4.1 The Sonogashira reaction

With the four building blocks in hand (**354**, **356**, **358** and **362**), the next step was their assembly by the Sonogashira reaction.

In general terms, the Sonogashira reaction is a coupling reaction of alkynes to aryl or vinyl halides. Tipically, two catalysts are required; a Pd(0) complex and a Cu(I) salt (although copper-free versions of the reaction have also been reported).[194,195] The reaction mechanism is believed to occur through two independent catalytic cycles (Figure 87).[195] The currently accepted mechanism for the palladium cycle is based on the oxidative addition of halide **II** to the catalytic 14-electron species **I** to form **III**. The next step connects the Pd-cycle with the Cu-cycle, in a usually rate-determining transmetalation, generating **IV**. This intermediate would evolve to the final product **V** after *trans*/*cis* isomerization and reductive elimination. Regarding the copper cycle, it should be remarked that the generally used amines are not basic enough to deprotonate the alkyne to generate the nucleophilic alkyne species. Therefore, it is believed that formation of a Cu-alkyne complex **VI** makes the proton more acidic for easier abstraction.

[194] Komáromi, A.; Tolnai, G. L.; Novák, Z. *Tetrahedron Lett.* **2008**, *49*, 7294-7298 and references cited therein.

[195] For a recent review see: Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874-922.

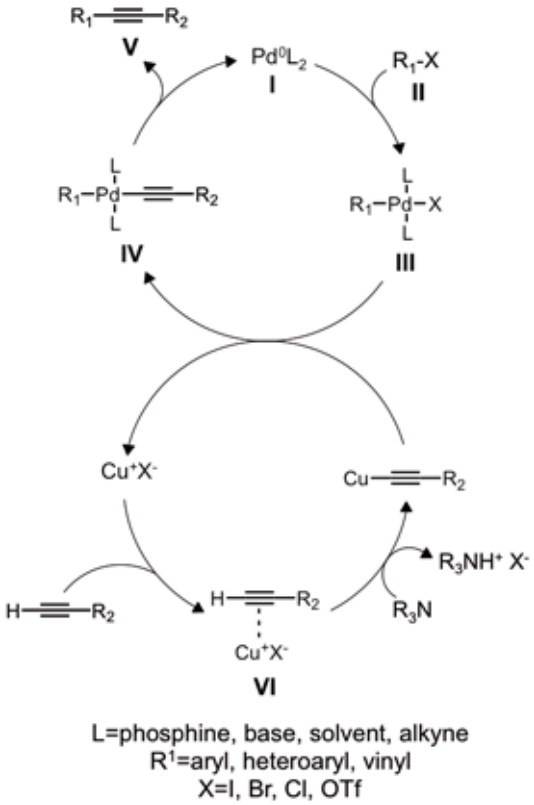
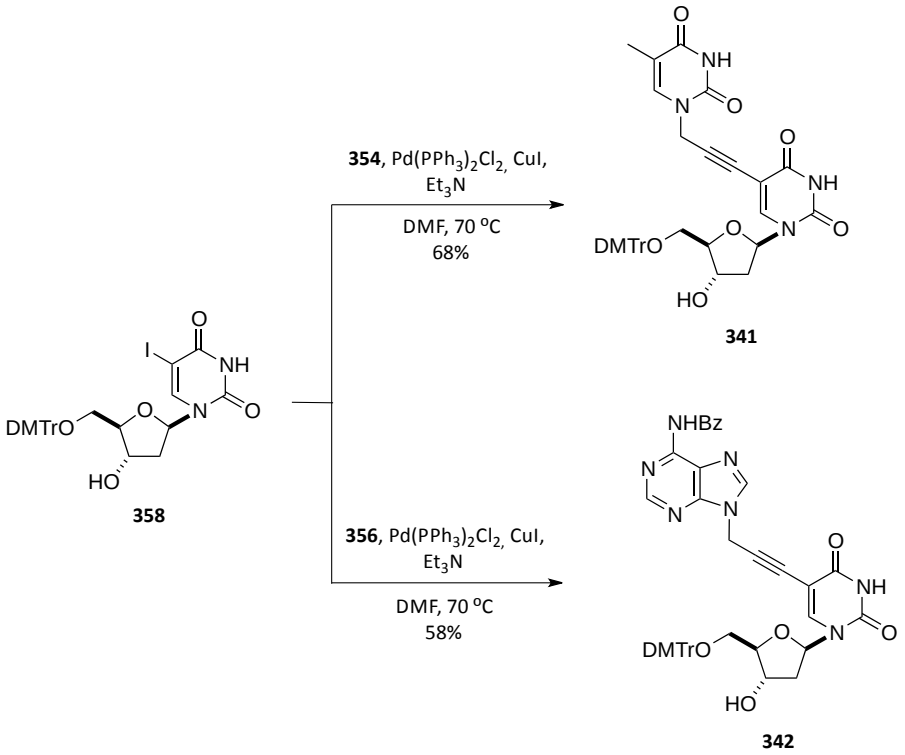


Figure 87. Mechanism of the Sonogashira reaction.

2.4.2 Synthesis of 341-344

Initially, the Sonogashira coupling was performed using the 5-iodouracil derivative **358**. Thus, treatment of this nucleoside with alkynes **354** and **356** using 4 mol % of $Pd(PPh_3)Cl_2$ and CuI in a 2:1 mixture of DMF/Et_3N delivered the double-headed nucleosides **341** and **342** in 68% and 58% yield, respectively (Scheme 95).



Scheme 95. Synthesis of double-headed nucleosides **341** and **342**.

The ^{1}H-NMR spectrum of both compounds shows the appearance of the signals of the additional nucleobase as well as the H3''' methylene signal at δ 4.50 for the thymine derivative **341** and at δ 5.19 for the adenine analogue **342**. ^{13}C-NMR spectra of these nucleosides show the presence of the two carbons of the triple bond at around 77.0 and 85.0 ppm (Figure 88) as well as the appearance of the signals corresponding to the additional nucleobases.

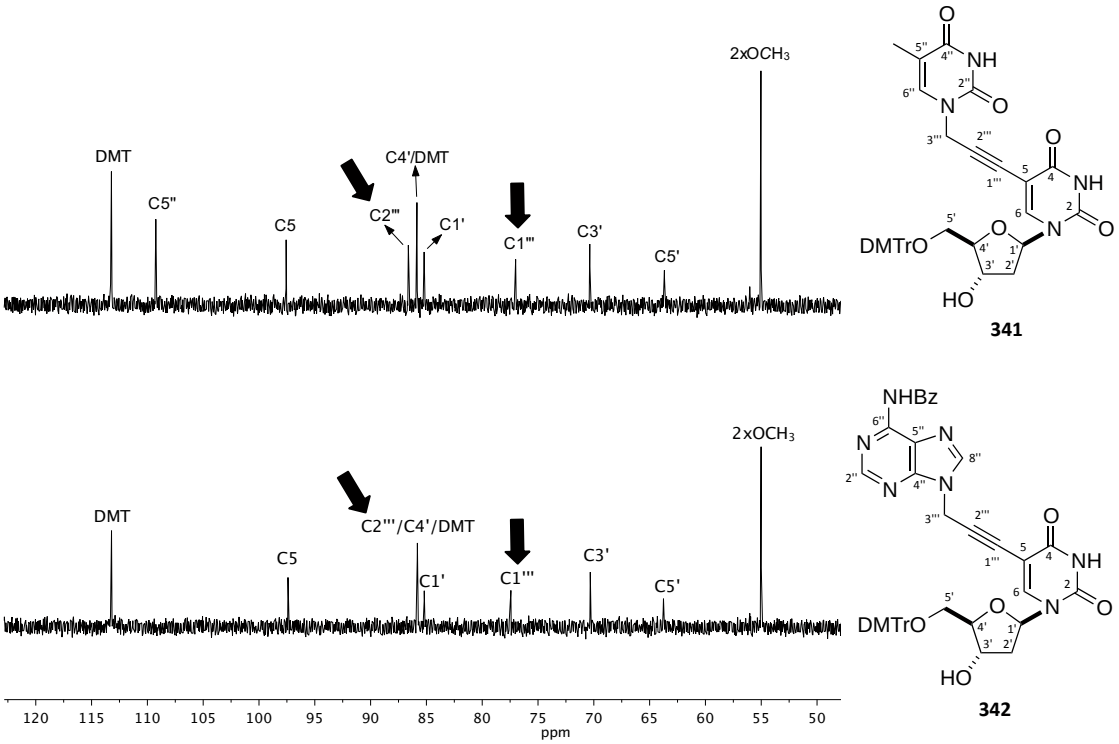


Figure 88. ^{13}C-NMR spectra (100 MHz, DMSO) of **341** and **342**.

Further evidence of the coupling of the two units is provided by the HMBC spectra of these compounds, where cross peaks between C5 and H3''' and between C1''' and H6 are observed. As an example, Figure 89 shows the HMBC spectrum of **341**.

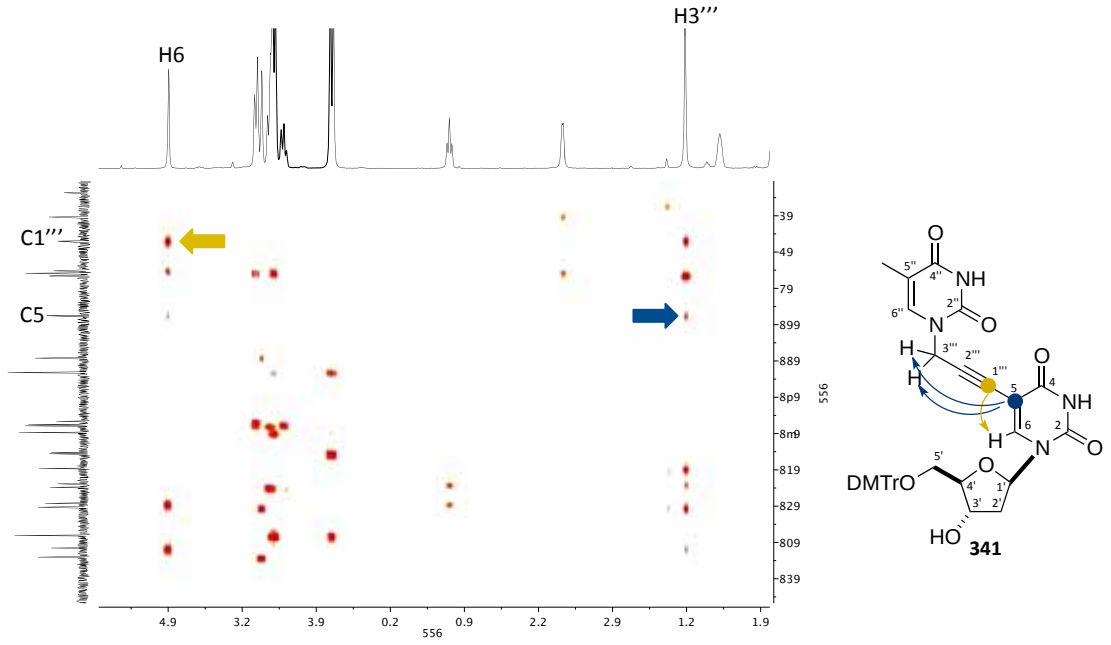
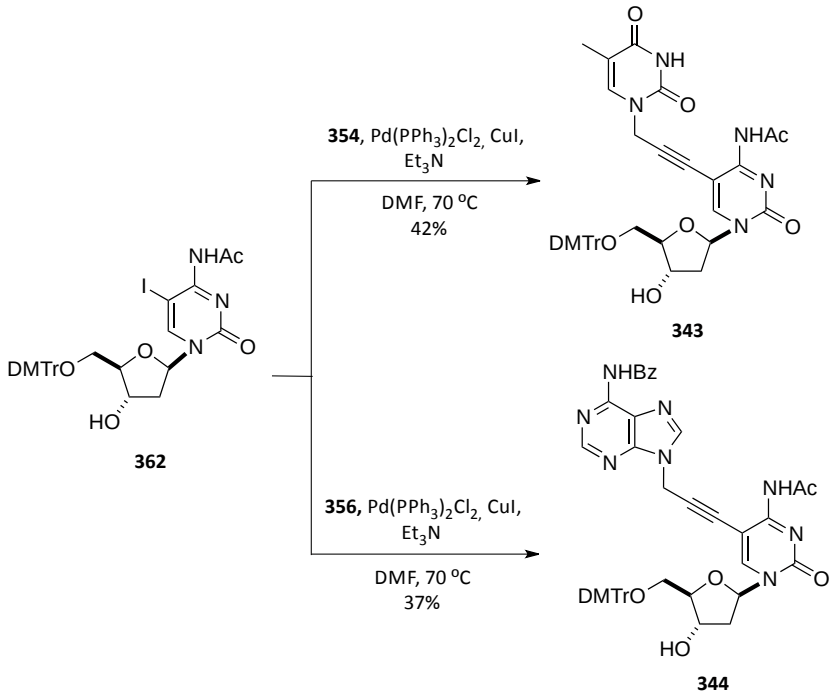


Figure 89. HMBC spectrum of **341** (400 MHz, DMSO).

Having completed the synthesis of nucleosides **341** and **342**, we focused on the synthesis of the cytidine derivatives **343** and **344**. Thus, following the same procedure described above, the 5-iodocytidine nucleoside **362** was reacted with alkynes **354** and **356** using 4 mol % of $Pd(PPh_3)Cl_2$ and CuI in a 2:1 mixture of DMF/Et_3N delivering the double-headed nucleosides **343** and **344** in 42% and 37% yield, respectively (Scheme 96). Figures 90 and 91 show the ^{1}H-NMR spectra of both nucleosides where, as before, signals corresponding to the additional nucleobase and the propargyl linker can be observed.



Scheme 96. Synthesis of the double-headed nucleosides **343** and **344**.

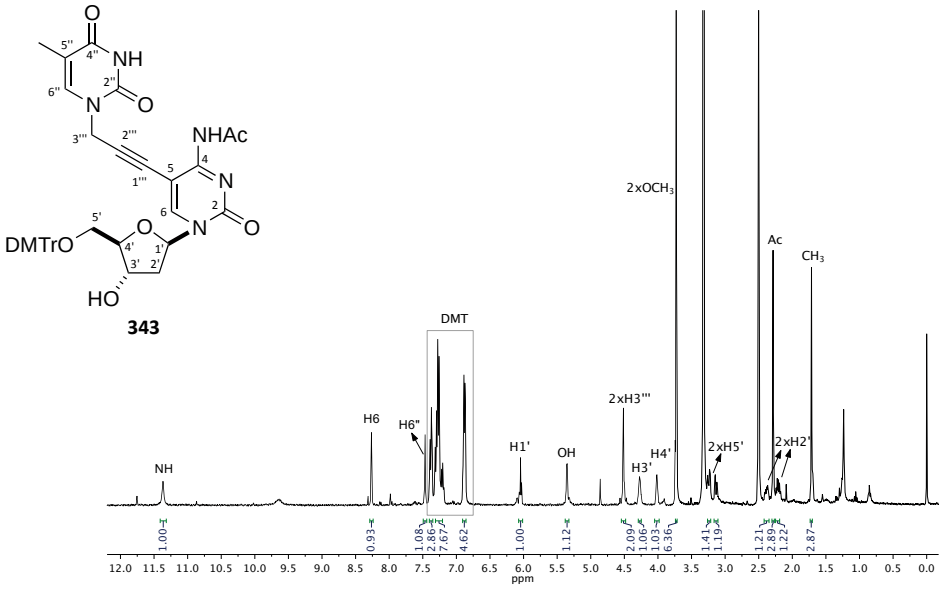


Figure 90. ^{1}H-NMR spectrum (400 MHz, DMSO) of **343**.

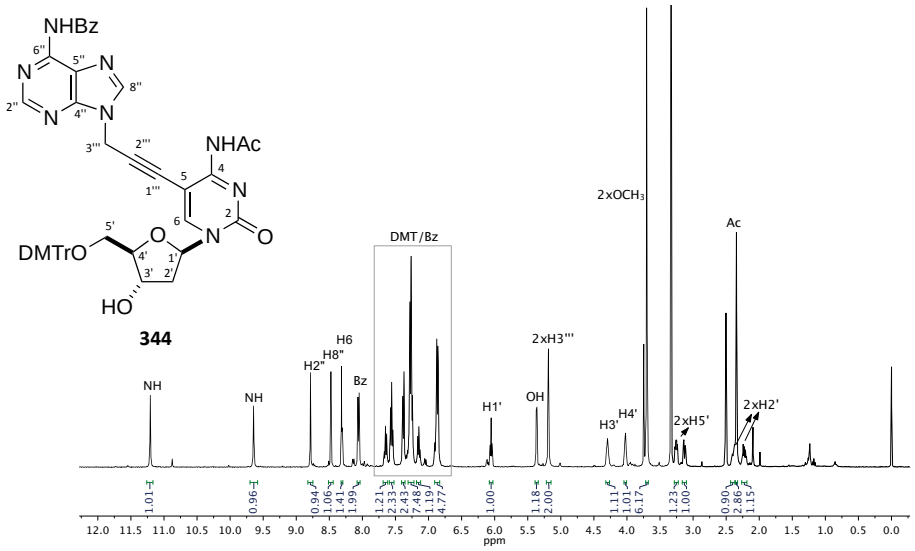


Figure 91. ^{1}H-NMR spectrum (400 MHz, DMSO) of **344**.

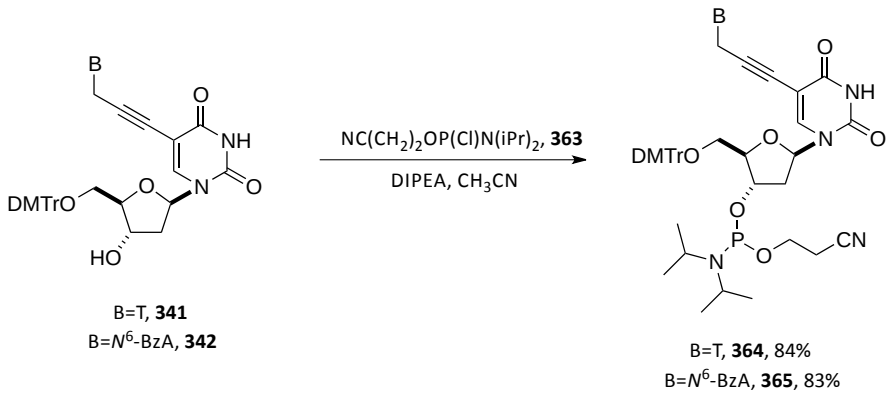
2.5 Oligonucleotide synthesis

2.5.1 Phosphoramidite synthesis

Due to the limited time, from this point onwards we centered our efforts in the synthesis of oligonucleotides bearing the double-headed thymine derivatives **341** and **342**.

In order to incorporate these nucleosides into oligonucleotides, it is necessary to introduce the 3'-phosphate group that will form the phosphodiester bond with the preceding 5'-nucleotide. In the phosphoramidite approach, the phosphorous atom is attached by reaction of the corresponding nucleoside with *N*,*N*-diisopropylamino-β-cyanoethylphosphinochloridite (commercially available), **363**, giving a stable P(III) derivative. At the same time, these species can be easily activated to participate in solid-phase automated synthesis.

Accordingly, nucleosides **341** and **342** were reacted with **363** and DIPEA in acetonitrile to deliver phosphoramidites **364** and **365** in 84% and 83%, respectively (Scheme 97).



B=T, **341**
B=N^6-BzA, **342**

B=T, **364**, 84%
B=N^6-BzA, **365**, 83%

Scheme 97. Preparation of **364** and **365**.

Since the introduction of the phosphorous unit produces two diastereomers, analysis of the ^{1}H- and ^{13}C-NMR data is intricate and not useful at all. In such cases, ^{31}P-NMR spectroscopy proves to be helpful. Thus, analysis of the ^{31}P spectra of compounds **364** and **365** showed two signals corresponding to the two diastereomers of each compound (Figure 92).

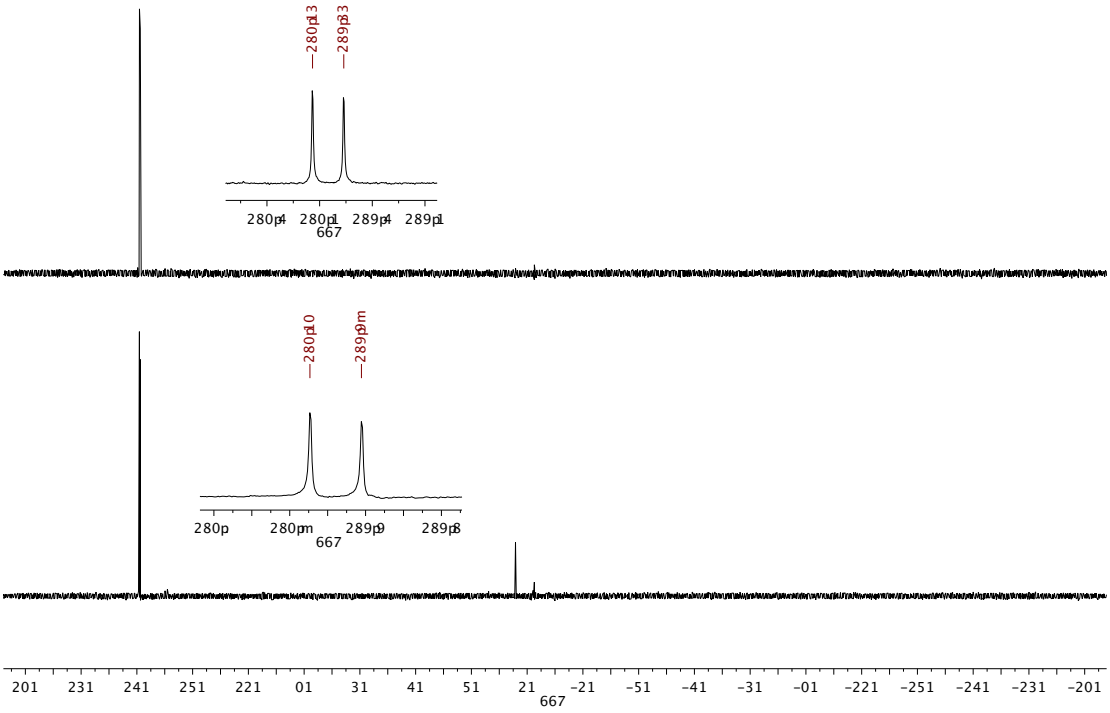


Figure 92. ^{31}P-NMR spectra (162 MHz, $CDCl_3$) of phosphoramidites **364** (top) and **365** (bottom).

2.5.2 Oligonucleotide synthesis and thermal denaturation studies

The newly synthesized phosphoramidites **364** and **365** were introduced into two different sequences of nine nucleotides each (a so-called 9-*mer*); **5'-GTG-TXT-TGC-3'**, presenting one incorporation of our modified nucleotides (denoted as X), and **5'-GTG-XXX-TGC-3'**, with three consecutive modifications.

Once these four 9-mers were synthesized and purified, the stabilizing/destabilizing capacity of these modifications in front of unmodified DNA and RNA complementary sequences was evaluated. The obtained results are summarized in the following table:

Entry	Name	Modification	Incorporations	Mean t_m	Δt_m
1	ADN/ADN	-[a]	-[a]	33.5	-
2	ADN/ARN	-[a]	-[a]	30.0	-
3	1x341/ADN	**341**	1	36.0	**+2.5**
4	3x341/ADN	**341**	3	37.0	**+3.5**
5	1x341/ARN	**341**	1	32.0	**+2.0**
6	3x341/ARN	**341**	3	37.0	**+7.0**
7	1x342/ADN	**342**	1	30.0	**-3.5**
8	3x342/ADN	**342**	3	34.0	**+0.5**
9	1x342/ARN	**342**	1	26.5	**-3.5**
10	3x342/ARN	**342**	3	36.5	**+6.5**

[a] Reference sequence.

Table 20. Thermal denaturation studies of duplexes featuring one or multiple incorporations of analogues **341** and **342**.

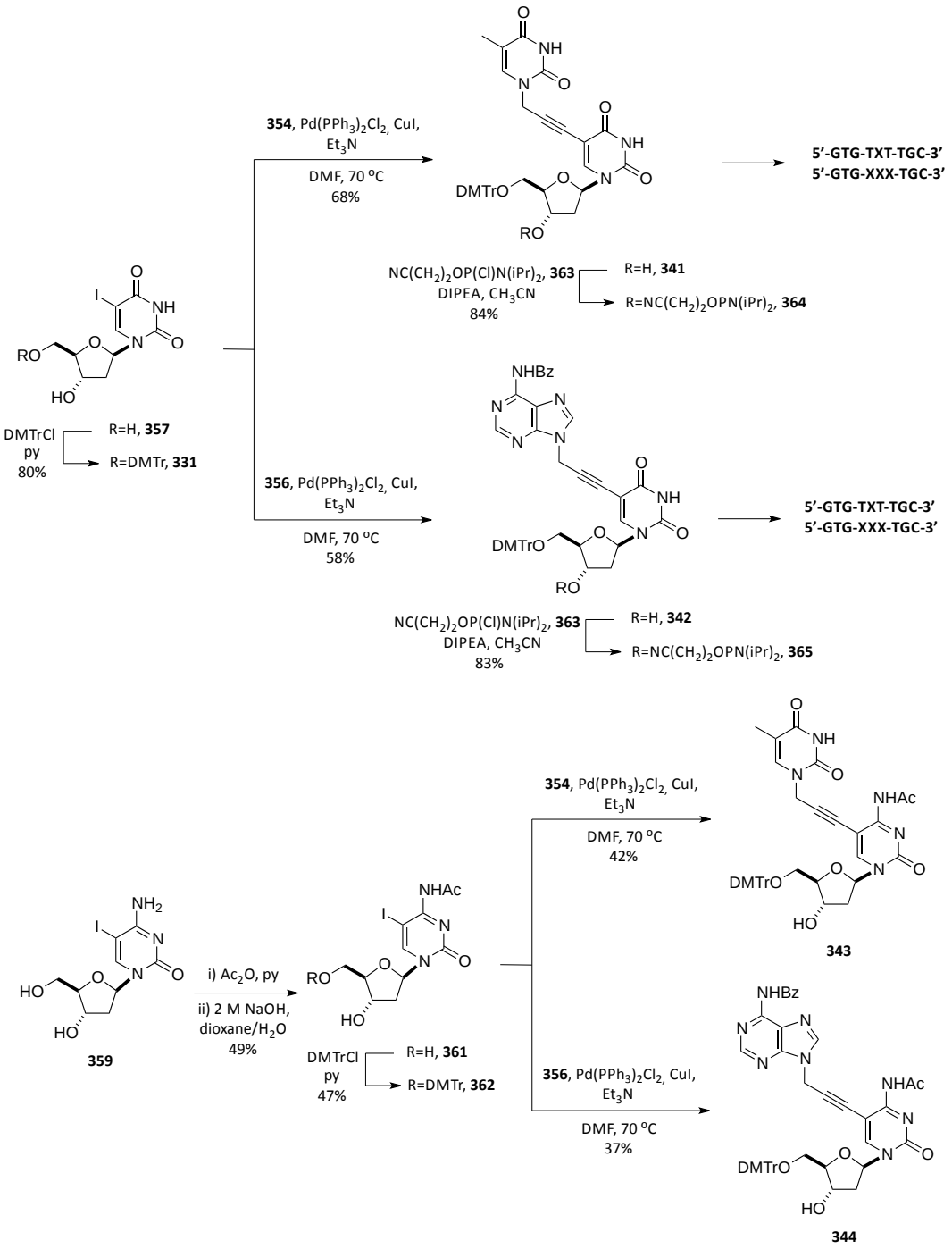
The data in Table 20 show that incorporation of one or three units of nucleotide **341** stabilizes notably the duplex formed whether being a DNA:DNA or a hybrid DNA:RNA. Remarkably, the introduction of one single incorporation stabilizes the duplex formed (the introduction of one modification usually destabilizes the duplex) in up to 2.5 degrees (entries 3 and 5). Successive incorporations stabilize even more the duplex (entries 4 and 6), probably by formation of base stacking interactions. This effect is clearly visible for the DNA:RNA duplex, acquiring an extra stabilization of 7 degrees (entry 6).

The much more usual destabilization produced by the introduction of a modification is observed for nucleoside **342**, destabilizing the duplexes formed in 3.5 degrees independently of the type of nucleic acid of the complementary strand (entries 7 and 9). However, the presence of three consecutive incorporations compensates this destabilization, leading to a neat stability gain of 6.5 degrees in the case of the DNA:RNA duplex (entry 10).

3. CHAPTER V OUTLINE

In this chapter, the synthesis of the four double-headed nucleosides **341**-**344** is described (Scheme 98). The synthetic sequence starts from the commercial 5-iodo-2'-deoxynucleosides **357** and **359** and features a Sonogashira coupling as the key step.

The thymidine analogues **341** and **342** have been converted into the corresponding phosphoramidites and incorporated into oligonucleotides upon which thermal denaturation studies have been carried out.

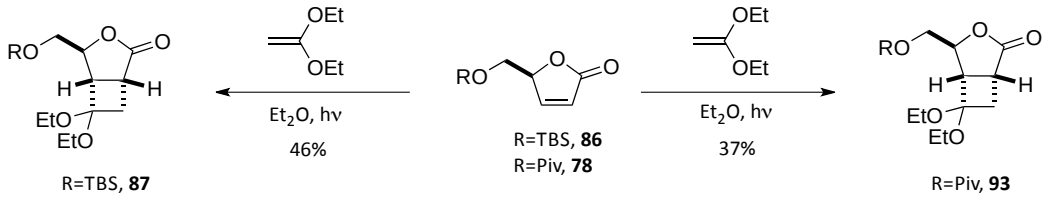


Scheme 98. Chapter V summary.

VI. Summary

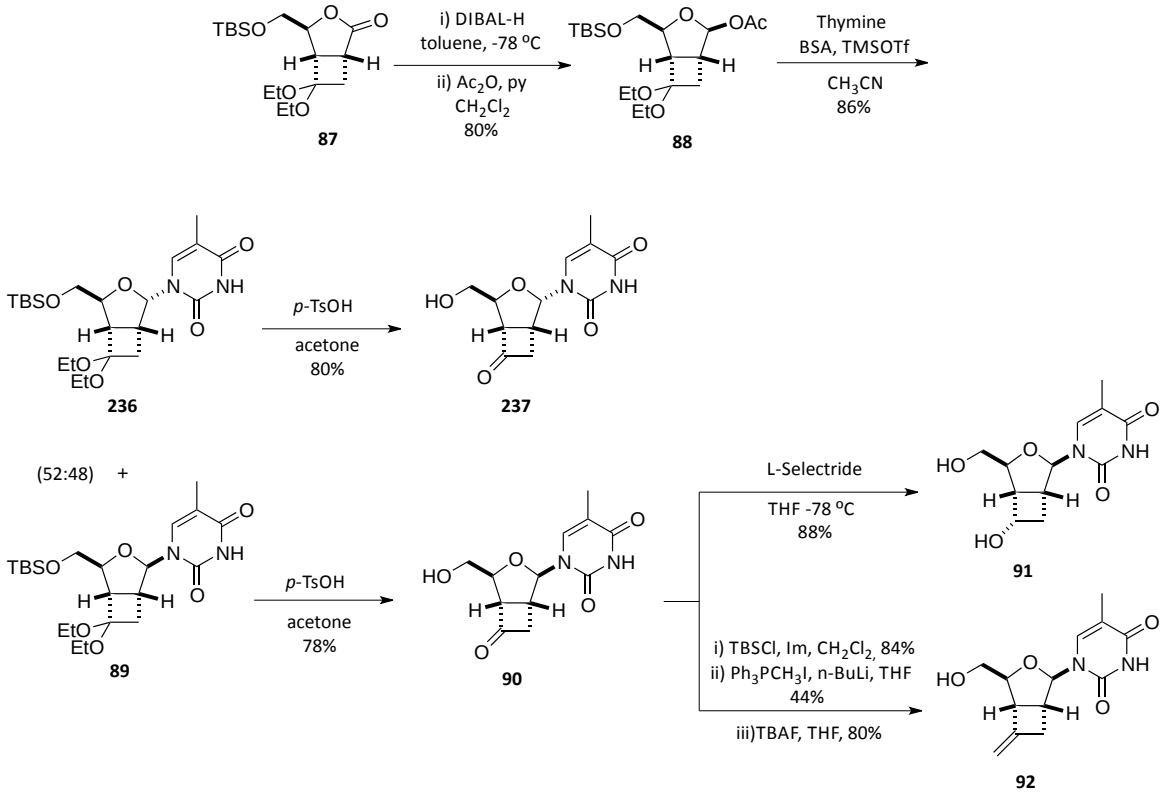
SUMMARY

i) The photochemical reactivity of the 2(5*H*)-furanones **86** and **78** with 1,1-diethoxyethylene has been investigated (Scheme 99). The effect of solvent polarity in the regio- and diastereoselectivity of the process has been evaluated. These photochemical reactions have been scaled up to 2 g of the starting 2(5*H*)-furanone, allowing the synthesis of the targeted HT-*anti* cycloadducts **87** and **93** in 46% and 37% yield, respectively. The two cycloadducts **87** and **93** have been used as starting material for the preparation of conformationally restricted and cyclobutane L-nucleoside analogues.



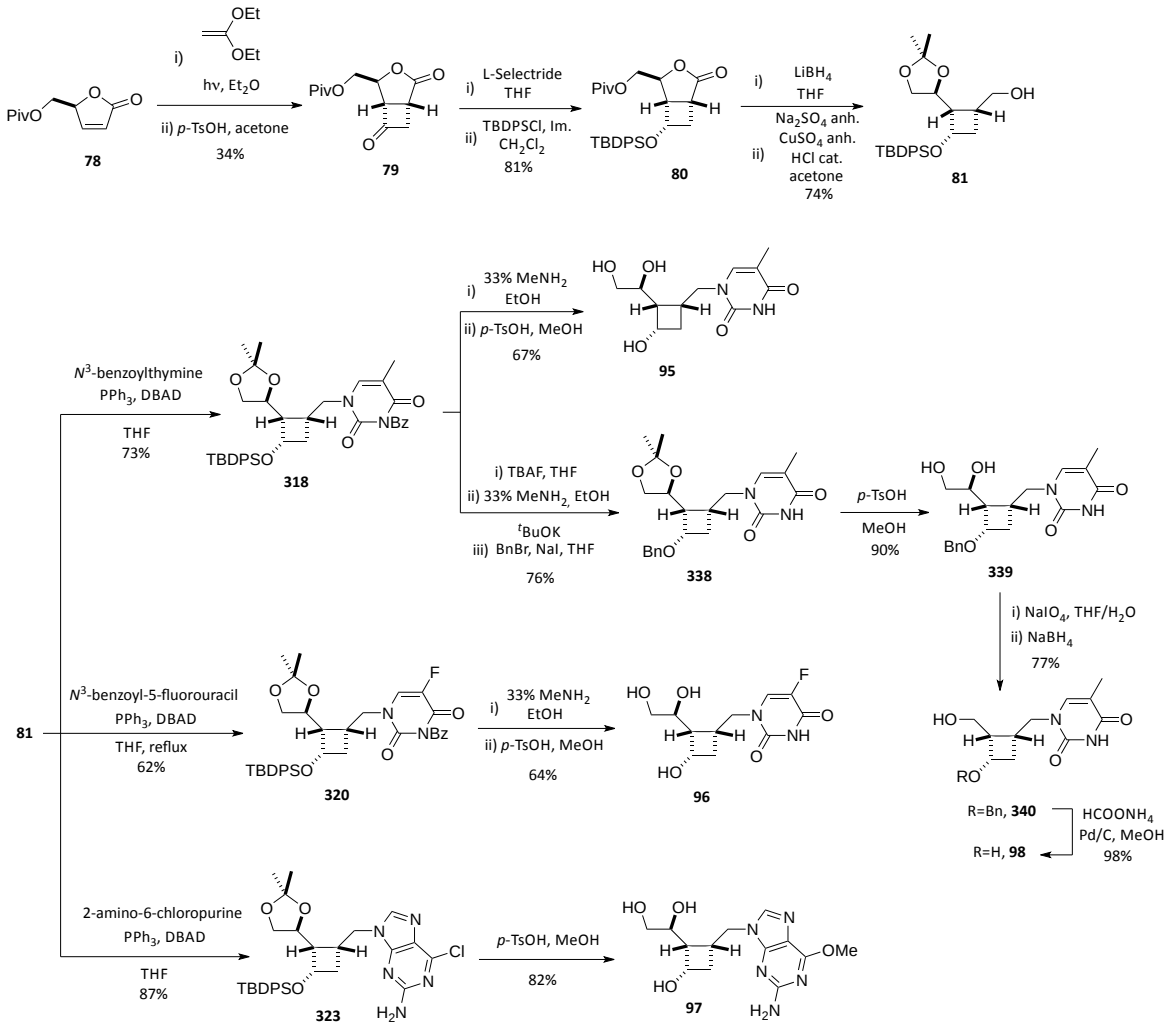
Scheme 99. [2+2] Photocycloaddition of 2(5*H*)-furanones to 1,1-diethoxyethylene.

ii) A new family of nucleosides conformationally restricted by the presence of a functionalized cyclobutane ring has been synthesized (Scheme 100). The cyclobutanone nucleosides **237** and **90** have been obtained in 5 steps and 13% and 12% yield, respectively. Nucleoside **91** has been achieved in 6 steps and 10% yield. Finally, nucleoside **92** has been obtained in 8 steps and 4% global yield. The biological activity of these analogues against several viruses has been evaluated, although none of them showed significant activity. Specifically, the lack of anti-HIV activity prompted a docking study to shed light on the activation process of these nucleosides and their binding with HIV-RT. Finally, a conformational study has revealed a C4'-exo conformation for the β-nucleosides **90**-**92** and a O4'-endo conformation for the α-nucleoside **237**.



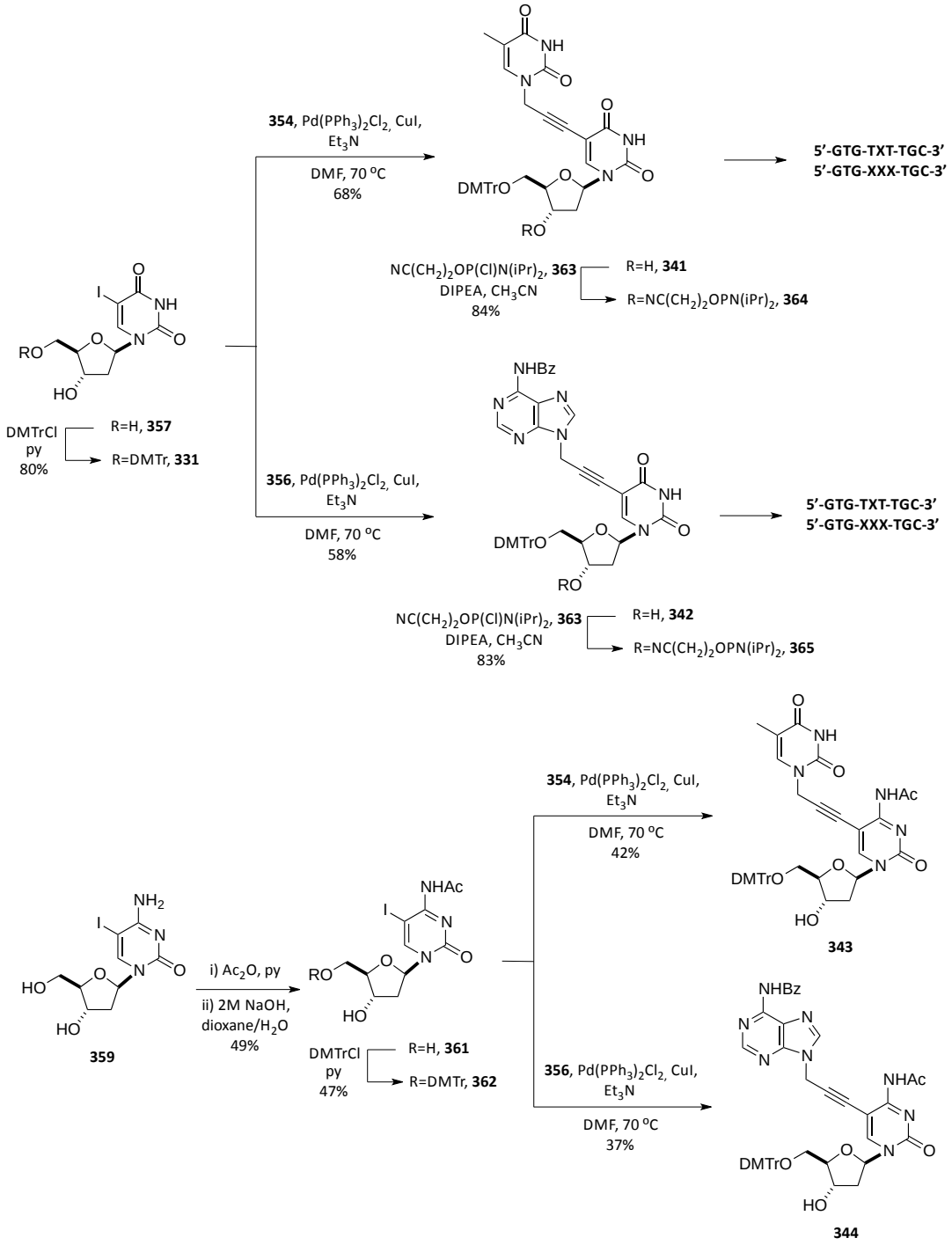
Scheme 100. Synthesis of nucleosides conformationally restricted by the presence of a functionalized cyclobutane ring.

iii) A new synthetic strategy for the synthesis of cyclobutane L-nucleoside analogues has been established. This approach has allowed the preparation of the four novel analogues **95**-**98** in yields comprised between 8-15% (Scheme 101). Among them, nucleoside **98** has been crystallized and analyzed by X-ray diffraction, showing a slightly puckered cyclobutane ring. The thymine, 5-fluorouracil and O^6-methylguanine nucleosides **95**-**97** have been screened for antiviral activity, although only the thymine analogue **95** showed weak activity and considerable cytotoxicity against influenza viruses.



Scheme 101. Synthesis of cyclobutane L-nucleoside analogues.

iv) During a three-month stay at the *Nucleic Acid Center* in the University of Southern Denmark (Odense) under the supervision of Prof. Poul Nielsen, the double-headed nucleosides **341**-**344** have been synthesized (Scheme 102). Nucleosides **341** and **342** have been successfully incorporated into oligonucleotide sequences upon which stability studies have been carried out.



Scheme 102. Synthesis of double-headed nucleosides.

VII. Experimental Section

1. GENERAL METHODS

Commercially available reagents were used as received. The solvents were dried by distillation over the appropriate drying agents. Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F254 pre-coated aluminium plates (0.25 mm thickness). Column chromatography was performed using silica gel 60 Å, particle size 35-70 µm. Solutions were concentrated using an evaporator at 15-20 Torr. Melting points were determined on hot stage and are uncorrected. ^{1}H-NMR at 250 or 360 or 400 MHz, ^{13}C-NMR at 62.5 or 90 or 100 MHz, ^{19}F-NMR at 235 or 376 MHz, ^{31}P-NMR at 162 MHz, were recorded at the *Servei de Ressonància Magnètica Nuclear de la Universitat Autònoma de Barcelona* or at the NMR service of the *Syddansk Universitet*. NMR signals were assigned with the help of DEPT, COSY, HMBC, HSQC, HMQC and NOESY experiments. Infrared spectra were recorded on a Sapphire-ATR Spectrophotometer. High resolution mass spectra (HRMS) were recorded at the *Servei d'Anàlisi Química de la Universitat Autònoma de Barcelona* or at the Mass Spectrometry service of the *Syddansk Universitet*. Microanalyses were performed at the *Servei d'Anàlisi Elemental de la Universitat Autònoma de Barcelona*. Optical rotations were measured at 22 ± 2 ^{o}C.

The photochemical reactions were conducted with a 125 W high pressure mercury lamp (Cathodeon HPK125) (Figure 93) or a 400 W medium pressure mercury lamp (Photochemical reactors, Model 3040). The photochemical reactor used was equipped with a quartz refrigeration jacket (Figure 95).

Figure 93. 125 W high pressure mercury lamp.

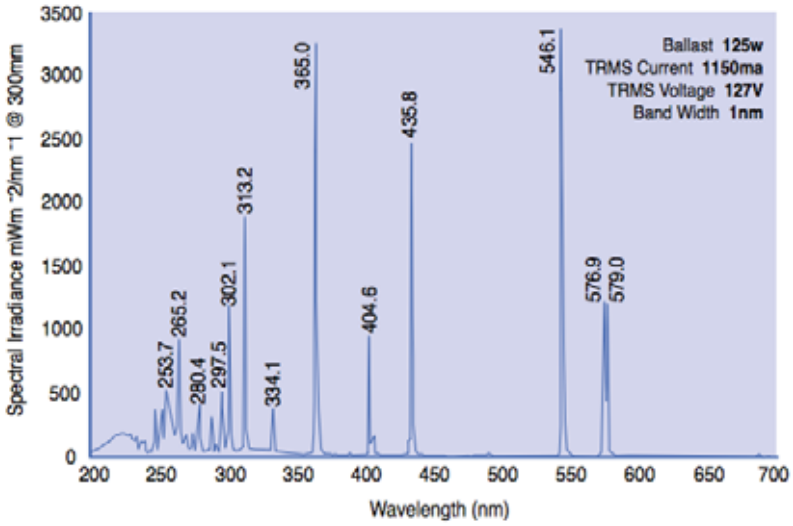


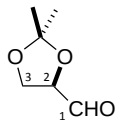
Figure 94. Spectral irradiance of the Cathodeon HPK125 lamp.

Figure 95. Photochemical reactor and refrigeration jacket.

2. [2+2] PHOTOCYCLOADDITION OF 2(5*H*)-FURANONES TO KETENE DIETHYL ACETAL

2.1 Synthesis of (*S*)-5-hydroxymethyl-2(5*H*)-furanone, **53**

2.1.1 Synthesis of 2,3-*O*-isopropylidene-D-gliceraldehyde, **163**

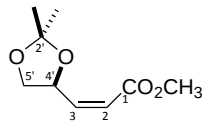


163

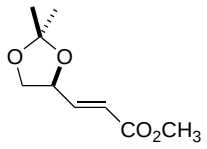
To a solution of 1,2:5,6-di-*O*-isopropylidene-D-mannitol, **162**, (12.00 g, 45.7 mmol) in THF (100 mL), a suspension of sodium periodate (10.80 g, 50.5 mmol) in a mixture of THF (37 mL) and H_2O (17 mL) was slowly added. The resulting white suspension was stirred at room temperature for 2 h. Then, diethyl ether (170 mL) was added and the mixture was stirred for 15 min prior to filtration of the white solid formed. The solvent was removed under reduced pressure and extracted with CH_2Cl_2 (3x25 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was carefully removed under reduced pressure to avoid the loss of aldehyde. A colorless oil (10.80 g, 83.0 mmol, 90% yield) was obtained and used in the next reaction without further purification. Variable amounts of hydrated aldehyde were observed by NMR and IR.

^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.70 (d, $J_{1,2}$=1.8 Hz, 1H, CHO) , 4.37 (ddd, $J_{2,3}$=7.4 Hz, $J_{2,3}$=4.8 Hz, $J_{2,1}$=1.8 Hz, 1H, H2), 4.15 (dd, J_{gem}=8.9 Hz, $J_{3,2}$=7.4 Hz, 1H, H3), 4.08 (dd, J_{gem}=8.9 Hz, $J_{3,2}$=4.8 Hz, 1H, H3), 1.46 (s, 3H, CH_3), 1.39 (s, 3H, CH_3).

2.1.2 Synthesis of methyl (2*Z*)- and (2*E*)-3-[(4*S*)-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)]-2-propenoate, (*Z*)-**164** and (*E*)-**164**



(*Z*)-**164**



(*E*)-**164**

To an ice-cooled solution of aldehyde **163** (10.60 g, 81.4 mmol) in MeOH (75 mL), methoxycarbonylmethylene(triphenyl)phosphorane (27.21 g, 81.4 mmol) was carefully added in small portions. The mixture was allowed to warm to room temperature and stirred for 2 h. Then, the solvent was removed under reduced pressure and the resulting white solid was extracted with hot hexane. The solution was cooled to 0 ºC and the excess of triphenyl phosphine oxide was filtered off. Evaporation of the solvent to dryness and purification by column chromatography (hexane-diethyl ether 3:1) afforded (*Z*)-**164** (10.72 g, 57.6 mmol, 71% yield) as an oil and (*E*)-**164** (2.23 g, 12.0 mmol, 15% yield) as an oil.

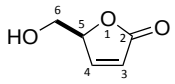
(*Z*)-**164**: **IR** (ATR) 2989, 2952, 2875, 1723, 1646, 1440, 1208, 1155 cm^{-1}.

^{1}H-NMR (250 MHz, $CDCl_3$) δ: 6.35 (dd, $J_{3,2}$=11.7 Hz, $J_{3,4'}$=6.9 Hz, 1H, H3), 5.84 (dd, $J_{2,3}$=11.7 Hz, $J_{2,4'}$=1.5 Hz, 1H, H2), 5.48 (dddd, $J_{4',5'}$=6.9 Hz, $J_{4',5'}$=6.9 Hz, $J_{4',3}$=6.9 Hz, $J_{4',2}$=1.5 Hz, 1H, H4'), 4.36 (dd, J_{gem}=8.4 Hz, $J_{5',4'}$=6.9 Hz, 1H, H5'), 3.70 (s, 3H, OCH_3), 3.60 (dd, J_{gem}=8.4 Hz, $J_{5',4'}$=6.9 Hz, 1H, H5'), 1.44 (s, 3H, CH_3), 1.39 (s, 3H, CH_3).

(*E*)-**164**: **IR** (ATR) 2989, 2950, 2880, 1727, 1663, 1438, 1264, 1217, 1125 cm^{-1}.

^{1}H-NMR (250 MHz, $CDCl_3$) δ: 6.87 (dd, $J_{3,2}$=15.9 Hz, $J_{3,4'}$=5.3 Hz, 1H, H3), 6.09 (dd, $J_{2,3}$=15.9 Hz, $J_{2,4'}$=1.5 Hz, 1H, H2), 4.65 (dddd, $J_{4',5'}$=7.0 Hz, $J_{4',5'}$=6.6 Hz, $J_{4',3}$=5.3 Hz, $J_{4',2}$=1.5 Hz, 1H, H4'), 4.16 (dd, J_{gem}=8.5 Hz, $J_{5',4'}$=6.6 Hz, 1H, H5'), 3.73 (s, 3H, OCH_3), 3.66 (dd, J_{gem}=8.5 Hz, $J_{5',4}$=7.0 Hz, 1H, H5'), 1.43 (s, 3H, CH_3), 1.40 (s, 3H, CH_3).

2.1.3 Synthesis of (*S*)-5-hydroxymethyl-2(5*H*)-furanone, **53**



53

To a solution of (*Z*)-**164** (10.72 g, 57.6 mmol) in MeOH (30 mL) a 30% aqueous solution of H_2SO_4 (260 µl) was added. The reaction mixture was stirred for 3 h at room temperature and the solvent was removed under reduced pressure. Purification of the crude by column chromatography (EtOAc) gave lactone **53** (6.23 g, 54.6 mmol, 95% yield) as a white solid.

mp: 40-41 ºC (pentane-EtOAc).

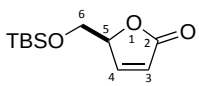
$[\alpha]_D$: -151.9 (*c* 2.4, H_2O).

IR (KBr) 3680-3200, 3107, 2930, 2880, 1743, 1602, 1170 cm^{-1}.

^{1}H-NMR (250 MHz, $CDCl_3$) δ: 7.46 (dd, $J_{4,3}$=5.8 Hz, $J_{4,5}$=1.5 Hz, 1H, H4), 6.19 (dd, $J_{3,4}$=5.8 Hz, $J_{3,5}$=2.2 Hz, 1H, H3), 5.13 (dddd, $J_{5,6}$=5.1 Hz, $J_{5,6}$=3.6 Hz, $J_{5,3}$=2.2 Hz, $J_{5,4}$=1.5 Hz, 1H, H5), 3.98 (ddd, J_{gem}=12.4 Hz, $J_{6,OH}$=6.9 Hz, $J_{6,5}$=3.6 Hz, 1H, H6), 3.77 (ddd, J_{gem}=12.4 Hz, $J_{6,OH}$=6.9 Hz, $J_{6,5}$=5.1 Hz, 1H, H6), 2.13 (dd, $J_{OH,6}$=6.9 Hz, $J_{OH,6}$=6.9 Hz, 1H, OH).

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ: 173.0 (C=O, C2), 153.5 (CH, C4), 123.0 (CH, C3), 84.0 (CH, C5), 62.4 (CH_2, C6).

2.2 Synthesis of (*S*)-5-*tert*-butyldimethylsilyloxymethyl-2(5*H*)-furanone, **86**



86

To a solution of **53** (1.00 g, mmol) in CH_2Cl_2 (10 mL) at 0 ºC, imidazole (834 mg, 13.7 mmol) and *tert*-butyldimethylsilyl chloride (1.72 g, 12.6 mmol) were successively added. The mixture was allowed to warm to room temperature and stirred for 16 h. Then it was diluted with CH_2Cl_2 (20 mL) and water (20 mL) was added. The mixture was separated and the organic layer was washed with two more portions of water (15

mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent to dryness gave a reaction crude which was purified by column chromatography (hexane-EtOAc 6:1) to afford **86** (1.83 g, 8.01 mmol, 91% yield) as a white solid.

mp: 32-34 ºC (pentane-EtOAc).

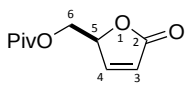
$[\alpha]_D$: -127 (*c* 4.8, $CHCl_3$).

IR (ATR) 1747, 1605, 1331 cm^{-1}.

^{1}H-NMR (250 MHz, $CDCl_3$) δ: 7.49 (dd, $J_{4,3}$=5.8 Hz, $J_{4,5}$=1.6 Hz, 1H, H4), 6.15 (dd, $J_{3,4}$=5.8 Hz, $J_{3,5}$=2.0 Hz, 1H, H3), 5.05 (dddd, $J_{5,6}$=5.4 Hz, $J_{5,6}$=4.5 Hz, $J_{5,3}$=2.0 Hz, $J_{5,4}$=1.6 Hz, 1H, H5), 3.93 (dd, J_{gem}=10.8 Hz, $J_{6,5}$=4.5 Hz, 1H, H6), 3.79 (dd, J_{gem}=10.8 Hz, $J_{6,5}$=5.4 Hz, 1H, H6), 0.86 (s, 9H, $(CH_3)_3C$), 0.07 (s, 3H, CH_3Si), 0.06 (s, 3H, CH_3Si).

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ: 172.9 (C=O, C2), 154.3 (CH, C4), 122.5 (CH, C3), 83.3 (CH, C5), 62.9 (CH_2, C6), 25.7 (3xCH_3, $(CH_3)_3C$), 18.2 (C, $(CH_3)_3C$), -5.5 (CH_3, CH_3Si), -5.6 (CH_3, CH_3Si).

2.3 Synthesis of (*S*)-5-pivaloyloxymethyl-2(5*H*)-furanone, **78**



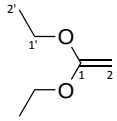
78

To a solution of **53** (3.63 g, 31.8 mmol) in dry CH_2Cl_2 (65 mL), pyridine (5.2 mL, 64.3 mmol) was added and the solution was cooled to 0 ºC. Then, pivaloyl chloride (8 mL, 63.7 mmol) was added dropwise and the mixture was allowed to stir at room temperature overnight. Afterwards, water (13 mL) was added and the layers were separated. The organic layer was successively washed with 5% HCl solution (2x28 mL), saturated $NaHCO_3$ solution (2x28 mL) and brine (1x28 mL). Then, it was dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude was purified by column chromatography (hexane-EtOAc 2:1) to give **78** (5.74 g, 29.0 mmol, 91% yield) as a colorless oil.

^{1}H-NMR (250 MHz, $CDCl_3$) δ: 7.41 (dd, $J_{4,3}$=5.7 Hz, $J_{4,5}$=1.6 Hz, 1H, H4) 6.17 (dd, $J_{3,4}$=5.7 Hz, $J_{3,5}$=2.0 Hz, 1H, H3), 5.24-5.19 (m, 1H, H5), 4.35 (d, $J_{6,5}$=3.8 Hz, 2H, H6), 1.14 (s, 9H, $(CH_3)_3C$).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 178.1 (C=O, C2), 172.3 (C=O, Piv), 152.5 (CH, C4), 123.3 (CH, C3), 81.1 (CH, C5), 62.1 (CH_2, C6), 39.0 (C, $(CH_3)_3C$) 27.1 (3xCH_3, $(CH_3)_3C$).

2.4 Synthesis of 1,1-diethoxyethylene, **138**



138

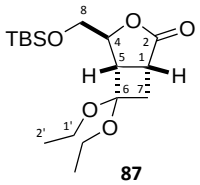
A two-necked round-bottom flask was charged with ^{t}BuOK (74.6 g, 631.5 mmol) and equipped with an addition funnel and a mechanical stirrer. Bromoacetaldehyde diethyl acetal (95 mL, 631.5 mmol) was added to the addition funnel and the reaction flask was cooled in an ice bath. Then, bromoacetaldehyde diethyl acetal was added and a white smoke formed immediately. After the reaction appeared to be complete, a brown

slurry remained. Next, the flask was equipped with a distillation apparatus and was heated to 120-130 ºC to distillate the ^{t}BuOH (83 ºC/760 mmHg) generated from the reaction. The system was then allowed to cool to 70-75 ºC and attached to a water vaccum pump. Distillation of the reaction mixture afforded 1,1-diethoxyethylene (28-30 ºC/12 mmHg) (34.2 g, 294.2 mmol, 48% yield), **138**, as a colorless liquid.

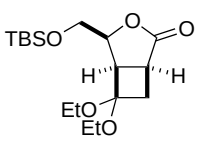
^{1}H-NMR (250 MHz, $CDCl_3$) δ: 3.82 (q, $J_{1',2'}$=7.1 Hz, 4H, 4xH1'), 3.09, (s, 2H, 2xH2), 1.32 (t, $J_{2',1'}$=7.1 Hz, 6H, 6xH2').

2.5 [2+2] Photocycloaddition of (*S*)-5-*tert*-butyldimethylsilyloxymethyl-2(5*H*)-furanone, **86**, to 1,1-diethoxyethylene

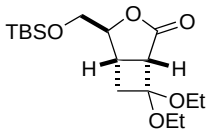
2.5.1 Synthesis of (1*R*,4*S*,5*S*)- and (1*S*,4*S*,5*R*)-4-*tert*-butyldimethylsilyloxymethyl-6,6-diethoxy-3-oxabicyclo[3.2.0]heptan-2-one (**87** and **166**) and (1*R*,4*S*,5*S*)- and (1*S*,4*S*,5*R*)-4-*tert*-butyldimethylsilyloxymethyl-7,7-diethoxy-3-oxabicyclo[3.2.0]heptan-2-one (**167** and **168**)



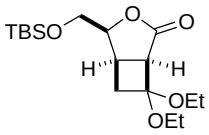
87



166



167



168

A solution of lactone **86** (2.08 g, 9.12 mmol) and 1,1-diethoxyethylene (12.7 mL, 96.3 mmol), **138**, in diethyl ether (800 mL) was placed in a photochemical reactor (two-necked vessel fitted with a Quartz immersion type cooling jacket). The reactor was immersed in a cooling bath at -40 ºC and a stream of MeOH at -15 ºC was circulated throughout the refrigeration jacket. The reaction mixture was irradiated using a medium pressure 400W mercury lamp for 5 h. Evaporation of the solvent and column chromatography (from hexane-EtOAc 35:1 to hexane-EtOAc 5:1) afforded a 64:29:5:2 mixture of **87**, **166**, **167** and **168** (2.61 g, 7.58 mmol, 83% yield). Repeated column chromatography (from hexane-EtOAc 25:1 to hexane-EtOAc 15:1) provided pure **87** (1.45 g, 4.21 mmol, 46% yield), pure **166** (565 mg, 1.64 mmol, 18% yield) and enriched fractions of compounds **167** and **168**.

87: $[\alpha]_D$: -30.4 (*c* 1.58, $CHCl_3$).

IR (ATR) ν 2929, 1773, 1250, 1112, 1043, 835, 779 cm^{-1}.

^{1}H-NMR (250 MHz, $CDCl_3$) δ: 4.81 (ddd, $J_{4,8}$=3.7 Hz, $J_{4,8}$=2.7 Hz, $J_{4,5}$=2.0 Hz, 1H, H4), 3.80 (dd, J_{gem}=11.0 Hz, $J_{8,4}$=3.7 Hz, 1H, H8), 3.66 (dd, J_{gem}=11.0 Hz, $J_{8,4}$=2.7 Hz, 1H, H8), 3.46-3.30 (m, 4H, 4xH1'), 3.11 (dddd, $J_{5,1}$=8.2 Hz, $J_{5,4}$=2.0 Hz, $J_{5,7}$=1.7 Hz, $J_{5,7}$=0.9 Hz, 1H, H5), 2.96 (ddd, $J_{1,7}$=9.9 Hz, $J_{1,5}$=8.2 Hz, $J_{1,7}$=4.4 Hz, 1H, H1), 2.58 (ddd, J_{gem}=13.1 Hz, $J_{7,1}$=9.9 Hz, $J_{7,5}$=1.7 Hz, 1H, H7),

2.41 (ddd, J_{gem}=13.1 Hz, $J_{7,1}$=4.4 Hz, $J_{7,5}$=0.9 Hz, 1H, H7), 1.24-1.14 (m, 6H, 6xH2'), 0.87 (s, 9H, (CH_3)$_3$C), 0.06 (s, 3H, CH_3Si), 0.05 (s, 3H, CH_3Si).

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ: 179.5 (C=O, C2), 99.4 (C, C6), 78.9 (CH, C4), 64.7 (CH_2, C8), 56.9 (CH_2, C1'), 56.6 (CH_2, C1'), 47.2 (CH, C5), 36.7 (CH_2, C7), 31.7 (CH, C1), 25.9 (3xCH_3, (CH_3)$_3$C), 18.3 (C, (CH$_3$)$_3$*C*), 15.2 (CH_3, C2'), 15.1 (CH_3, C2'), -5.4 (CH_3, *C*H$_3$Si), -5.5 (CH_3, *C*H$_3$Si).

HRMS (ESI+) calcd for ([$C_{17}H_{32}O_5Si$+Na]$^+$) 367.1911, found 367.1905.

COSY, HMBC, HMQC and **NOESY** experiments have been recorded.

166: $[\alpha]_D$: +22.5 (*c* 1.16, $CHCl_3$).

IR (ATR) ν 2930, 1772, 1250, 1042, 835, 778 cm^{-1}.

^{1}H-NMR (250 MHz, $CDCl_3$) δ: 4.54 (ddd, $J_{4,8}$=7.1 Hz, $J_{4,5}$=5.8 Hz, $J_{4,8}$=4.6 Hz, 1H, H4), 4.29 (dd, J_{gem}=11.3 Hz, $J_{8,4}$=7.1 Hz, 1H, H8), 4.01 (dd, J_{gem}=11.3 Hz, $J_{8,4}$=4.6 Hz, 1H, H8), 3.43-3.33 (m, 4H, 4xH1'), 3.12 (dd, $J_{5,1}$=8.2 Hz, $J_{5,4}$=5.8 Hz, 1H, H5), 3.03 (ddd, $J_{1,5}$=8.2 Hz, $J_{1,7}$=4.0 Hz, $J_{1,7}$=1.2 Hz, 1H, H1), 2.48 (dd, J_{gem}=7.8 Hz, $J_{7,1}$=4.0, 1H, H7), 2.44 (dd, J_{gem}=7.8 Hz, $J_{7,1}$=1.2 Hz, 1H, H7), 1.22-1.12 (m, 6H, 6xH2'), 0.90 (s, 9H, (CH_3)$_3$C), 0.09 (s, 3H, CH_3Si), 0.08 (s, 3H, CH_3Si).

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ: 179.1 (C=O, C2), 102.7 (C, C6), 83.0 (CH, C4), 63.3 (CH_2, C8), 57.1 (CH_2, C1'), 56.8 (CH_2, C1'), 47.3 (CH, C5), 35.8 (CH_2, C7), 32.7 (CH, C1), 26.0 (3xCH_3, (CH_3)$_3$C), 18.5 (C, (CH$_3$)$_3$*C*), 15.3 (CH_3, C2'), 15.1 (CH_3, C2'), -5.1 (CH_3, *C*H$_3$Si), -5.3 (CH_3, *C*H$_3$Si).

HRMS (ESI+) calcd for ([$C_{17}H_{32}O_5Si$+Na]$^+$) 367.1911, found 367.1907.

COSY, HMBC, HMQC and **NOESY** experiments have been recorded.

167: **^{1}H-NMR** (250 MHz, $CDCl_3$) δ: 4.40 (m, 1H, H4), 4.00-3.30 (m, 7H, 2xH8/4xH1'/H1), 2.82 (m, 1H, H5), 2.63 (ddd, J_{gem}=8.9 Hz, $J_{6,5}$=6.1 Hz, $J_{6,4}$=3.3 Hz, 1H, H6), 2.36 (m, 1H, H6), 1.20 (m, 6H, H2'), 0.88 (s, 9H, (CH_3)$_3$C), 0.07 (s, 3H, CH_3Si), 0.06 (s, 3H, CH_3Si).

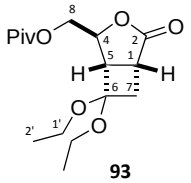
^{13}C-NMR (62.5 MHz, $CDCl_3$) δ: 174.6 (C=O, C2), 99.9 (C, C7), 85.3 (CH, C4), 65.3 (CH_2, C8), 58.0 (CH_2, C1'), 57.4 (CH_2, C1'), 51.9 (CH, C1), 38.0 (CH_2, C6), 29.5 (CH, C5), 26.2 (3xCH_3, (CH_3)$_3$C), 18.6 (C, (CH$_3$)$_3$*C*), 15.5 (CH_3, C2'), 15.4 (CH_3, C2'), -5.15 (CH_3, *C*H$_3$Si), -5.25 (CH_3, *C*H$_3$Si).

168: **^{1}H-NMR** (250 MHz, $CDCl_3$) δ: 4.54 (ddd, $J_{4,8}$=9.3 Hz, $J_{4,8}$=6.4 Hz, $J_{4,5}$=4.9 Hz, 1H, H4), 4.00-3.30 (m, 7H, 2xH8/4xH1'/H1), 2.99 (m, 1H, H5), 2.29 (m, 1H, H6), 2.18 (dd, J_{gem}=13.4 Hz, $J_{6,5}$=6.4 Hz, 1H, H6), 1.20 (m, 6H, H2'), 0.90 (s, 9H, (CH_3)$_3$C), 0.08 (s, 3H, *C*H$_3$Si), 0.08 (s, 3H, *C*H$_3$Si).

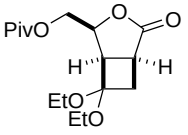
^{13}C-NMR (62.5 MHz, $CDCl_3$) δ: 177.6 (C=O, C2), 99.2 (C, C7), 80.8 (CH, C4), 64.9 (CH_2, C8), 58.1 (CH_2, C1'), 57.5 (CH_2, C1'), 51.4 (CH, C1), 32.2 (CH_2, C6), 29.3 (CH, C5), 26.2 (3xCH_3, (CH_3)$_3$C), 17.3 (C, (CH$_3$)$_3$*C*), 15.8 (CH_3, C2'), 15.4 (CH_3, C2'), -4.99 (CH_3, *C*H$_3$Si), -5.08 (CH_3, *C*H$_3$Si).

2.6 [2+2] Photocycloaddition of (*S*)-5-pivaloyloxymethyl-2(5*H*)-furanone, **78**, to 1,1-diethoxyethylene

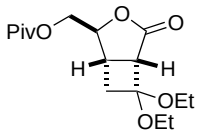
2.6.1 Synthesis of (1*R*,4*S*,5*S*)- and (1*S*,4*S*,5*R*)-4-pivaloyloxymethyl-6,6-diethoxy-3-oxabicyclo[3.2.0]heptan-2-one (**93** and **159c**) and (1*R*,4*S*,5*S*)- and (1*S*,4*S*,5*R*)-4-pivaloyloxymethyl-7,7-diethoxy-3-oxabicyclo[3.2.0]heptan-2-one (**160c** and **161c**)



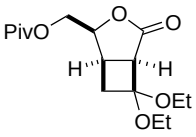
93



159c



160c



161c

A solution of lactone **78** (2.01 g, 10.14 mmol) and 1,1-diethoxyethylene (10.7 mL, 81.31 mmol) in diethyl ether (800 mL) was placed in a photochemical reactor (two-necked vessel fitted with a Quartz immersion type cooling jacket). The reactor was immersed in a cooling bath at -40 ºC and a stream of MeOH at -15 ºC was circulated throughout the refrigeration jacket. The reaction mixture was irradiated using a medium pressure 400W mercury lamp for 5 h. Evaporation of the solvent and column chromatography (from hexane-EtOAc 35:1 to hexane-EtOAc 5:1) afforded a 60:35:3:2 mixture of **93**, **159c**, **160c** and **161c** (2.17 g, 6.90 mmol, 68% yield). Repeated column chromatography (from hexane-EtOAc 25:1 to hexane-EtOAc 15:1) provided pure **93** (1.18 g, 3.75 mmol, 37% yield), pure **159c** (638 mg, 2.03 mmol, 20% yield) and enriched fractions of compounds **160c** and **161c**.

93: **^{1}H-NMR** (400 MHz, $CDCl_3$) δ: 4.99 (ddd, $J_{4,8}$=3.2 Hz, $J_{4,8}$=3.2 Hz, $J_{4,5}$=1.8 Hz, 1H, H4), 4.23 (dd, J_{gem}=12.0 Hz, $J_{8,4}$=3.2 Hz, 1H, H8), 4.09 (dd, J_{gem}=12.0 Hz, $J_{8,4}$=3.5 Hz, 1H, H8), 3.45-3.25 (m, 4H, H1'), 3.05-2.95 (m, 2H, H1/H5), 2.58 (ddd, J_{gem}=13.0 Hz, $J_{7,1}$=8.5 Hz, $J_{7,5}$=3.2 Hz, 1H, H7), 2.42 (dd, J_{gem}=13.0 Hz, $J_{7,1}$=2.9 Hz, 1H, H7), 1.28-1.05 (m, 15H, 5xCH_3).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 178.5 (C=O, C2), 177.9 (C=O, Piv), 98.8 (C, C6), 75.9 (CH, C4), 65.3 (CH_2, C8), 56.8 (CH_2, C1'), 56.5 (CH_2, C1'), 46.8 (CH, C5), 38.6 (C, $(CH_3)_3C$), 36.5 (CH_2, C7), 31.1 (CH, C1), 27.1 (CH_3, $(CH_3)_3C$), 14.9 (CH_3, C2'), 14.8 (CH_3, C2').

159c: **^{1}H-NMR** (250 MHz, $CDCl_3$) δ: 4.70-4.53 (m, 2H, H4/H8), 4.46 (dd, J_{gem}=11.2 Hz, $J_{8,4}$=1.1 Hz, 1H, H8), 3.48-3.28 (m, 4H, H1'), 3.16 (dd, $J_{5,1}$=8.2 Hz, $J_{5,4}$=5.7 Hz, 1H, H5), 3.01 (ddd, $J_{1,5}$=8.2 Hz, $J_{1,7}$=7.7 Hz, $J_{1,7}$=5.0 Hz, 1H, H1), 2.47-2.41 (m, 2H, H7), 1.22-1.10 (m, 15H, 5xCH_3).

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ: 178.4 (2xC=O, C2/Piv), 102.0 (C, C6), 79.8 (CH, C4), 64.7 (CH_2, C8), 56.9 (CH_2, C1'), 56.8 (CH_2, C1'), 47.3 (CH, C5), 38.6 (C, $(CH_3)_3C$), 35.5 (CH_2, C7), 32.1 (CH, C1), 27.0 (CH_3, $(CH_3)_3C$), 15.0 (CH_3, C2'), 14.8 (CH_3, C2').

160c: **^{1}H-NMR** (250 MHz, $CDCl_3$) δ: 4.55 (m, 1H, H4), 4.18 (dd, J_{gem}=12.0 Hz, $J_{8,4}$=3.2 Hz, 1H, H8), 4.04 (dd, J_{gem}=12.0 Hz, $J_{8,4}$=3.7 Hz, 1H, H8), 3.60-3.30 (m, 5H, 4xH1'/H1), 2.69 (m, 1H, H5), 2.58 (m, 1H, H6), 2.18 (m, 1H, H6), 1.19 (s, 15H, 5xCH_3).

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ: 177.9 (C=O, C2), 173.4 (C=O, Piv), 99.2 (C, C7), 82.3 (CH, C4), 65.4 (CH_2, C8), 57.5 (CH_2, C1'), 57.0 (CH_2, C1'), 51.0 (CH, C1), 38.0 (CH_2, C6), 36.5 (C, $(CH_3)_3C$), 28.9 (CH, C5), 27.0 (CH_3, (CH_3)$_3$C), 14.9 (CH_3, 2xC2').

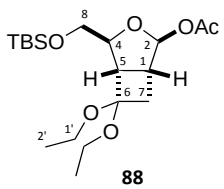
161c: **^{1}H-NMR** (250 MHz, $CDCl_3$) δ: 4.64 (ddd, $J_{4,8}$=6.6 Hz, $J_{4,8}$=6.6 Hz, $J_{4,5}$=5.7 Hz, 1H, H4), 4.20 (m, 2H, H8), 3.70-3.20 (m, 5H, 4xH1'/H1), 2.95 (m, 1H, H5), 2.33 (m, 2H, H6), 1.19 (s, 15H, 5xCH_3).

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ: 178.0 (2xC=O, C2/Piv), 98.5 (C, C7), 77.9 (CH, C4), 62.8 (CH_2, C8), 57.7 (CH_2, C1'), 57.1 (CH_2, C1'), 51.0 (CH, C1), 38.7 (C, $(CH_3)_3C$), 32.0 (CH_2, C6), 28.7 (CH, C5), 27.1 (CH_3, (CH_3)$_3$C), 14.9 (CH_3, C2'), 14.8 (CH_3, C2').

3. SYNTHESIS OF CYCLOBUTANE-FUSED NUCLEOSIDES

3.1 Synthesis of the keto α- and β-nucleosides **237** and **90**

3.1.1 Synthesis of (1*R*,2*S*,4*S*,5*S*)-2-acetyloxy-4-*tert*-butyldimethylsilyloxymethyl-6,6-diethoxy-3-oxabicyclo[3.2.0]heptane, **88**



88

To a solution of **87** (346 mg, 1.00 mmol) in dry toluene (38 mL) at -78 ºC, a 1.0 M of DIBAL-H in toluene (2.0 mL, 2.00 mmol) was added dropwise over a period of 30 min. After 50 min of stirring at -78 ºC, the reaction mixture was quenched by the slow addition of methanol and allowed to warm to room temperature. EtOAc (1.70 mL) and a saturated solution of $NaHCO_3$ (0.40 mL) were added. After 20 min of vigorous stirring, anhydrous Na_2SO_4 (2.90 g) was added. The suspension was stirred vigorously overnight, filtered through Celite and concentrated to dryness affording a reaction crude, which was used in the next reaction without further purification. To an ice-cooled solution of this crude and pyridine (1.0 mL) in CH_2Cl_2 (9 mL), acetic anhydride (1.0 mL) was added dropwise. The reaction mixture was stirred at room temperature overnight. Then, the reaction was washed with a 5% solution of HCl (2x4.5 mL), saturated $NaHCO_3$ solution (3x4.5 mL) and brine (4.5 mL). The organic layer was dried with anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude residue was purified by column chromatography (hexane-EtOAc 15:1) to give **88** (311 mg, 0.80 mmol, 80% yield for the 2 steps) as a colorless oil.

$[\alpha]_D$: -55.2 (*c* 1.20, $CHCl_3$).

IR (ATR) ν 2929, 2857, 2360, 1742, 1234, 1101, 1051, 835, 778 cm^{-1}.

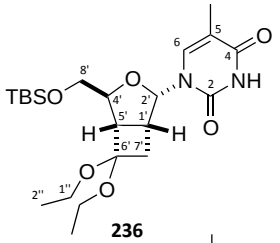
^{1}H-NMR (250 MHz, $CDCl_3$) δ: 6.10 (s, 1H, H2), 4.46 (ddd, $J_{4,8}$=8.4 Hz, $J_{4,8}$=5.8 Hz, $J_{4,5}$=2.3 Hz, 1H, H4), 3.70 (dd, J_{gem}=9.7 Hz, $J_{8,4}$=5.8 Hz, 1H, H8), 3.49-3.28 (m, 5H, H8/4xH1'), 3.01-2.94 (m, 1H, H5), 2.75 (dt, $J_{1,7}$=8.8 Hz, $J_{1,5}$=7.3 Hz, $J_{1,7}$=7.3 Hz, 1H, H1), 2.33 (ddd, J_{gem}= 12.8 Hz, $J_{7,1}$=8.8 Hz, $J_{7,5}$=4.0 Hz, 1H, H7), 1.99 (s, 3H, CH_3CO), 1.86 (ddd, J_{gem}=12.8 Hz, $J_{7,1}$=7.3 Hz, $J_{7,5}$=0.9 Hz 1H, H7), 1.19 (t, $J_{2',1'}$=7.1 Hz, 3H, H2'), 1.15 (t, $J_{2',1'}$=7.1 Hz, 3H, H2'), 0.88 (s, 9H, (CH_3)$_3$C), 0.07 (s, 6H, CH_3Si).

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ: 170.2 (C=O, CH_3*C*O), 102.3 (CH, C2), 98.7 (C, C6), 82.7 (CH, C4), 65.5 (CH_2, C8), 56.5 (CH_2, C1'), 56.4 (CH_2, C1'), 50.0 (CH, C5), 37.8 (CH, C1), 34.1 (CH_2, C7), 26.0 (3xCH_3, (*C*H_3)$_3$C), 21.6 (CH_3, *C*H_3CO), 18.4 (C, (CH$_3$)$_3$*C*), 15.5 (CH_3, C2'), 15.0 (CH_3, C2'), -5.2 (CH_3, *C*H_3Si), -5.3 (CH_3, *C*H_3Si).

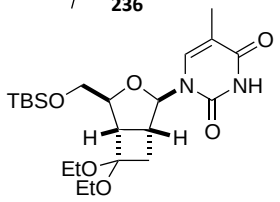
HRMS (ESI+) calcd for ([$C_{19}H_{36}O_6Si$+Na]$^+$) 411.2173, found 411.2162.

COSY, HMBC, HMQC and **NOESY** experiments have been recorded.

3.1.2 Synthesis of (1*S*,2*S*,4*S*,5*R*)- and (1*S*,2*R*,4*S*,5*R*)-1-(4-*tert*-butyldimethylsilyloxymethyl-6,6-diethoxy-3-oxabicyclo[3.2.0]hept-2-yl)thymine, **236** and **89**



236



89

N,*O*-Bis(trimethylsilyl)acetamide (BSA) (162 µl, 0.63 mmol) was added to a suspension of thymine (32 mg, 0.25 mmol) in dry acetonitrile (2 mL) under argon atmosphere. The reaction was allowed to stir for 20 min and cooled to 0 ºC. Then, a solution of **88** (80 mg, 0.21 mmol) in dry acetonitrile (1 mL) and TMSOTf (58 µL, 0.32 mmol) were successively added and the reaction mixture was stirred at room temperature for 0.5 h. CH_2Cl_2 (12 mL) was added and the reaction was quenched with aqueous saturated solution of $NaHCO_3$ (2 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x2 mL). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated to dryness. The crude residue was purified by column chromatography (hexane-EtOAc 3:1) to afford the α-anomer **236** (42 mg, 0.09 mmol, 45% yield) as a yellow oil and the β-anomer **89** (39 mg, 0.09 mmol, 41% yield) as a yellow oil.

236: $[\alpha]_D$: -103.4 (*c* 2.06, $CHCl_3$).

IR (ATR) ν 2928, 1686, 1462, 1250, 1096, 1049, 834, 776 cm^{-1}.

^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.27 (br s, 1H, NH), 7.57 (q, J_{6,CH_3}=1.0 Hz, 1H, H6), 5.96 (d, $J_{2',1'}$=5.7 Hz, 1H, H2'), 4.58 (ddd, $J_{4',8'}$=4.4 Hz, $J_{4',8'}$=3.7 Hz, $J_{4',5'}$=2.3 Hz, 1H, H4'), 3.67 (dd, J_{gem}=10.6 Hz,

$J_{8',4'}$=4.4 Hz, 1H, H8'), 3.60 (dd, J_{gem}=10.6 Hz, $J_{8',4'}$=3.7 Hz, 1H, H8'), 3.42-3.20 (m, 5H, H1'/4xH1''), 3.03 (d, $J_{5',1'}$=8.1 Hz, 1H, H5'), 2.09 (ddd, J_{gem}=13.5 Hz, $J_{7',1'}$=9.2 Hz, $J_{7',5'}$=2.6 Hz, 1H, H7'), 1.95 (d, $J_{CH_3,6}$=1.0 Hz, 3H, CH_3-C5), 1.73 (dd, J_{gem}=13.5 Hz, $J_{7',1'}$=5.8 Hz, 1H, H7'), 1.18 (t, $J_{2'',1''}$=7.1 Hz, $J_{2'',1''}$=7.1 Hz, 6H, 6xH2''), 0.90 (s, 9H, (CH_3)$_3$C), 0.08 (s, 6H, 2xCH_3Si).

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ: 164.2 (C=O, C4), 150.0 (C=O, C2), 136.6 (CH, C6), 109.0 (C, C5), 98.4 (C, C6'), 88.6 (CH, C2'), 80.2 (CH, C4'), 65.9 (CH_2, C8'), 56.6 (CH_2, C1''), 56.2 (CH_2, C1''), 50.5 (CH, C5'), 35.5 (CH, C1'), 30.7 (CH_2, C7'), 26.0 (3xCH_3, (CH_3)$_3$C), 18.3 (C, (CH_3)$_3$*C*), 15.3 (CH_3, C2''), 15.2 (CH_3, C2''), 12.7 (CH_3, *C*H_3-C5), -5.3 (CH_3, *C*H_3Si), -5.4 (CH_3, *C*H_3Si).

HRMS (ESI+) calcd for ([$C_{22}H_{38}N_2O_6Si$+Na]$^+$) 477.2391, found 477.2391.

COSY, HMBC, HMQC and **NOESY** experiments have been recorded.

89: $[\alpha]_D$: -29.4 (*c* 1.02, $CHCl_3$).

IR (ATR) ν 2928, 1686, 1463, 1253, 1049, 835, 777 cm^{-1}.

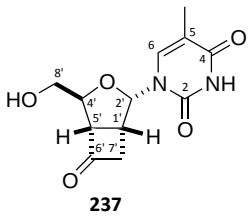
^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.39 (br s, 1H, NH), 7.32 (q, J_{6,CH_3}=1.2 Hz, 1H, H6), 5.92 (d, $J_{2',1'}$=2.1 Hz, 1H, H2'), 4.52 (q, $J_{4',5'}$=4.2 Hz, $J_{4',8'}$=4.2 Hz, $J_{4',8'}$=4.2 Hz, 1H, H4'), 3.80 (dd, J_{gem}=11.1 Hz, $J_{8',4'}$=4.2 Hz, 1H, H8'), 3.68 (dd, J_{gem}=11.1 Hz, $J_{8',4'}$=4.2 Hz, 1H, H8'), 3.48-3.32 (m, 4H, 4xH1''), 3.09 (ddd, $J_{5',1'}$=7.8 Hz, $J_{5',4'}$=4.2 Hz, $J_{5',7'}$=3.6 Hz, 1H, H5'), 2.75 (dddd, $J_{1',7'}$=8.7 Hz, $J_{1',5'}$=7.8 Hz, $J_{1',7'}$=6.4 Hz, $J_{1',2'}$=2.1 Hz, 1H, H1'), 2.51 (ddd, J_{gem}=12.6 Hz, $J_{7',1'}$=8.7 Hz, $J_{7',5'}$=3.6 Hz, 1H, H7'), 2.21 (dd, J_{gem}=12.6 Hz, $J_{7',1'}$=6.4 Hz, 1H, H7'), 1.90 (d, $J_{CH_3,6}$=1.2 Hz, 3H, CH_3-C5), 1.23-1.15 (m, 6H, 6xH2''), 0.89 (s, 9H, (CH_3)$_3$C), 0.07 (br s, 6H, 2xCH_3Si).

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ: 163.8 (C=O, C4), 150.4 (C=O, C2), 136.0 (CH, C6), 110.3 (C, C5), 99.1 (C, C6'), 91.4 (CH, C2'), 82.1 (CH, C4'), 64.7 (CH_2, C8'), 56.7 (2xCH_2, C1''), 50.6 (CH, C5'), 39.2 (CH, C1'), 35.9 (CH_2, C7'), 26.0 (3xCH_3, (CH_3)$_3$C), 18.5 (C, (CH_3)$_3$*C*), 15.3 (CH_3, C2''), 15.0 (CH_3, C2''), 12.3 (CH_3, *C*H_3-C5), -5.31 (CH_3, *C*H_3Si), -5.34 (CH_3, *C*H_3Si).

HRMS (ESI+) calcd for ([$C_{22}H_{38}N_2O_6Si$+Na]$^+$) 477.2391, found 477.2383.

COSY, HMBC, HMQC and **NOESY** experiments have been recorded.

3.1.3 Synthesis of (1*S*,2*S*,4*S*,5*R*)-1-(4-hydroxymethyl-6-oxo-3-oxabicyclo[3.2.0]hept-2-yl)thymine, **237**



237

To a solution of **236** (42 mg, 0.09 mmol) in acetone (2.5 mL), *p*-toluensulfonic acid (5 mg, 0.02 mmol) was added and the reaction was allowed to stir for 24 h. Evaporation of the solvent and purification by column chromatography (EtOAc) afforded **237** (20 mg, 0.08 mmol, 80% yield) as a white solid.

mp: 84-86 ºC (EtOAc).

$[\alpha]_D$: -198.6 (*c* 1.48, H_2O).

IR (ATR) ν 3100-3500, 2928, 1779, 1655, 1466, 1270, 1099, 1051, 767 cm^{-1}.

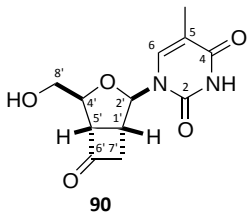
^{1}H-NMR (360 MHz, D_2O) δ: 7.80 (d, J_{6,CH_3}=1.1 Hz, 1H, H6), 6.21 (d, $J_{2',1'}$=5.6 Hz, 1H, H2'), 4.75-4.68 (m, 1H, H4'), 3.95-3.87 (m, 1H, H5'), 3.80-3.72 (m, 1H, H1'), 3.71-3.66 (m, 2H, H8'), 3.20 (ddd, J_{gem}=19.2 Hz, $J_{7',1'}$=9.2 Hz, $J_{7',5'}$=4.7 Hz, 1H, H7'), 2.81 (ddd, J_{gem}=19.2 Hz, $J_{7',1'}$=5.1 Hz, $J_{7',5'}$=3.0 Hz, 1H, H7'), 1.91 (d, $J_{CH_3,6}$=1.1 Hz, 3H, CH_3, CH_3-C5).

^{13}C-NMR (90 MHz, D_2O) δ: 211.3 (C=O, C6'), 166.9 (C=O, C4), 151.5 (C=O, C2), 137.6 (CH, C6), 110.8 (C, C5), 88.4 (CH, C2'), 81.3 (CH, C4'), 65.4 (CH, C5'), 63.5 (CH_2, C8'), 46.3 (CH_2, C7'), 34.3 (CH, C1'), 12.0 (CH_3, CH_3-C5).

HRMS (ESI+) calcd for ($[C_{12}H_{14}N_2O_5+Na]^+$) 289.0795, found 289.0784.

COSY, HMBC, HSQC and **NOESY** experiments have been recorded.

3.1.4 Synthesis of (1*S*,2*R*,4*S*,5*R*)-1-(4-hydroxymethyl-6-oxo-3-oxabicyclo[3.2.0]hept-2-yl)thymine, **90**



90

To a solution of **89** (224 mg, 0.49 mmol) in acetone (15 mL), *p*-toluensulfonic acid (27 mg, 0.14 mmol) was added and the reaction was allowed to stir for 24 h. Evaporation of the solvent and purification by column chromatography (EtOAc) afforded **90** (102 mg, 0.38 mmol, 78% yield) as a white solid.

mp: 94-96 ºC (EtOAc).

$[\alpha]_D$: -92.0 (*c* 1.00, H_2O).

IR (ATR) ν 3100-3500, 2928, 1780, 1655, 1468, 1260, 1087, 1044, 771 cm^{-1}.

^{1}H-NMR (360 MHz, D_2O) δ: 7.60 (d, J_{6,CH_3}=1.2 Hz, 1H, H6), 6.24 (d, $J_{2',1'}$=1.0 Hz, 1H, H2'), 4.61 (ddd, $J_{4',8'}$=5.9 Hz, $J_{4',5'}$=3.9 Hz, $J_{4',8'}$=3.9 Hz, 1H, H4'), 4.03-3.95 (m, 1H, H5'), 3.72 (dd, J_{gem}=12.4, $J_{8',4'}$=3.9 Hz, 1H, H8'), 3.62 (dd, J_{gem}=12.4 Hz, $J_{8',4'}$=5.9 Hz, 1H, H8'), 3.56-3.46 (m, 1H, H1'), 3.49 (dd, J_{gem}=8.9 Hz, $J_{7',1'}$=5.4 Hz, 1H, H7'), 3.35 (ddd, J_{gem}=8.9 Hz, $J_{7',1'}$=8.9 Hz, $J_{7',5'}$=2.0 Hz, 1H, H7'), 1.91 (d, $J_{CH_3,6}$=1.2 Hz, 3H, CH_3-C5).

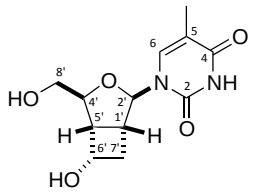
^{13}C-NMR (90 MHz, D_2O) δ: 209.6 (C=O, C6'), 166.6 (C=O, C4), 151.9 (C=O, C2), 138.2 (CH, C6), 110.9 (C, C5), 92.2 (CH, C2'), 83.6 (CH, C4'), 65.8 (CH, C5'), 63.0 (CH_2, C8'), 50.9 (CH_2, C7'), 35.6 (CH, C1'), 11.4 (CH_3, CH$_3$-C5).

HRMS (ESI+) calcd for ($[C_{12}H_{14}N_2O_5+Na]^+$) 289.0795, found 289.0787.

COSY, HMBC, HSQC and **NOESY** experiments have been recorded.

3.2 Synthesis of the hydroxyl nucleoside **91**

3.2.1 Synthesis of (1*S*,2*R*,4*S*,5*R*,6*S*)-1-(4-hydroxymethyl-6-hydroxy-3-oxabicyclo[3.2.0]hept-2-yl)thymine, **91**



91

To a solution of **90** (17 mg, 0.05 mmol) in dry THF (0.5 mL) at -78 ºC, a 1.0 M solution of L-Selectride® in THF (77 µL, 0.08 mmol) was added dropwise. After 1 h of stirring at -78 ºC, the reaction was quenched by the slow addition of saturated NH_4Cl solution, and allowed to warm to room temperature. The two layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and evaporated to dryness to afford nucleoside **91** (15 mg, 0.06 mmol, 88% yield) as a white solid.

mp: 124-126 ºC (EtOAc).

$[\alpha]_D$: +1.4 (*c* 1.45, MeOH).

IR (ATR) ν 3100-3500, 2925, 1687, 1658, 1469, 1255, 1118, 1093, 1034 cm^{-1}.

^{1}H-NMR (360 MHz, MeOD) δ: 7.60 (q, J_{6,CH_3}=1.2 Hz, 1H, H6), 5.89 (s, 1H, H2'), 4.76 (ddd, $J_{4',5'}$=5.9 Hz, $J_{4',8'}$=5.0 Hz, $J_{4',8'}$=3.1 Hz, 1H, H4'), 4.38-4.31 (m, 1H, H6'), 3.80 (dd, J_{gem}=12.1 Hz, $J_{8',4'}$=3.1 Hz, 1H, H8'), 3.59 (dd, J_{gem}=12.1 Hz, $J_{8',4'}$=5.0 Hz, 1H, H8'), 3.23-3.15 (m, 1H, H5'), 2.73-2.63 (m, 2H, H1'/H7'), 2.03-1.95 (m, 1H, H7'), 1.86 (d, $J_{CH_3,6}$=1.2 Hz, 3H, CH_3-C5).

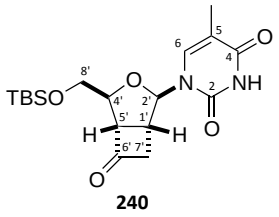
^{13}C-NMR (100 MHz, MeOD) δ: 166.6 (C=O, C4), 152.5 (C=O, C2), 138.9 (CH, C6), 110.9 (C, C5), 92.2 (CH, C2'), 83.0 (CH, C4'), 64.7 (CH_2, C8'), 62.7 (CH, C6'), 48.9 (CH, C5'), 39.3 (CH, C1'), 36.3 (CH_2, C7'), 12.4 (CH_3, CH$_3$-C5).

HRMS (ESI+) calcd for ($[C_{12}H_{16}N_2O_5+Na]^+$) 291.0951, found 291.0952.

COSY, HMBC, HSQC and **NOESY** experiments have been recorded.

3.3 Synthesis of the methylene nucleoside **92**

3.3.1 Synthesis of (1*S*,2*R*,4*S*,5*R*)-1-(4-*tert*-butyldimethylsilyloxymethyl-6-oxo-3-oxabicyclo[3.2.0]hept-2-yl)thymine, **240**



240

To an ice-cooled solution of **90** (390 mg, 1.46 mmol and imidazole (175 mg, 2.55 mmol) in CH_2Cl_2 (6 mL), TBSCl (303 mg, 1.95 mmol) was added slowly. The reaction was allowed to stir for 24 h at room temperature. The reaction crude was diluted with CH_2Cl_2 (2 mL) and washed with water (5 mL). The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated to dryness. The crude was purified by column chromatography (hexane-EtOAc 1:1) to give **240** (468 mg, 1.23 mmol, 84% yield) as a white solid.

mp: 34-36 ºC (hexane-EtOAc).

$[\alpha]_D$: -43.3 (*c* 1.20, $CHCl_3$).

IR (ATR) ν 2928, 2856, 1785, 1682, 1463, 1256, 1085, 1007, 834, 777 cm^{-1}.

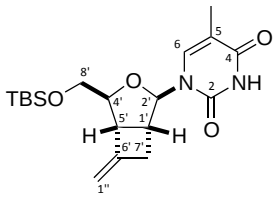
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.78 (s, 1H, NH), 7.45 (q, J_{6,CH_3}=1.1 Hz, 1H, H6), 5.97 (d, $J_{2',1'}$=2.1 Hz, 1H, H2'), 4.52 (dt, $J_{4',8'}$=4.1 Hz, $J_{4',5'}$=4.1 Hz, $J_{4',8'}$=2.8 Hz, 1H, H4'), 3.88 (ddd, $J_{5',1'}$=7.2 Hz, $J_{5',4'}$=4.1 Hz, $J_{5',7'}$=2.8 Hz, 1H, H5') 3.86 (dd, J_{gem}=11.5 Hz, $J_{8',4'}$=2.8 Hz, 1H, H8'), 3.64 (dd, J_{gem}=11.5 Hz, $J_{8',4'}$=4.1 Hz, 1H, H8'), 3.45 (ddd, J_{gem}=14.4 Hz, $J_{7',1'}$=10.4 Hz, $J_{7',5'}$=2.8 Hz, 1H, H7'), 3.26-3.18 (m, 2H, H1'/H7'), 1.90 (d, $J_{CH_3,6}$=1.1 Hz, 3H, CH_3-C5), 0.87 (s, 9H, (CH_3)$_3$C), 0.05 (s, 6H, 2xCH_3Si).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 204.9 (C=O, C6'), 164.4 (C=O, C4), 150.8 (C=O, C2), 135.7 (CH, C6), 110.5 (C, C5), 93.3 (CH, C2'), 83.8 (CH, C4'), 65.9 (CH, C5'), 64.4 (CH_2, C8'), 51.8 (CH_2, C7'), 38.4 (CH, C1'), 25.9 (3xCH_3, (*C*H$_3$)$_3$C), 18.4 (C, (CH$_3$)$_3$*C*), 12.7 (CH_3, *C*H$_3$-C5), -5.2 (CH_3, *C*H$_3$Si), -5.3 (CH_3, *C*H$_3$Si).

HRMS (ESI+) calcd for ($[C_{18}H_{28}N_2O_5Si+Na]^+$) 403.1660, found 403.1656.

COSY, HMBC, HSQC and **NOESY** experiments have been recorded.

3.3.2 Synthesis of (1*S*,2*R*,4*S*,5*R*)-1-(4-*tert*-butyldimethylsilyloxymethyl-6-methylene-3-oxabicyclo[3.2.0]hept-2-yl)thymine, **241**



241

A 1.6 M solution of *n*-butyllithium in hexane (105 µL, 0.17 mmol) was added dropwise to a solution of methyltriphenylphosphonium iodide (71 mg, 0.17 mmol) in dry THF at 0 ºC under argon atmosphere and the reaction was allowed to stir for 1 h. Then, a solution of **240** (54 mg, 0.14 mmol) in dry THF (1 mL) was added dropwise and the reaction mixture was allowed to stir for 3 h. After evaporation of the solvent, the resulting crude was purified by column chromatography (hexane-EtOAc 3:1) to give **241** (24 mg, 0.06 mmol, 44% yield) as a colorless oil.

$[\alpha]_D$: -38.9 (*c* 1.08, $CHCl_3$).

IR (ATR) 3045, 2927, 2856, 1681, 1463, 1255, 1109, 1084, 834, 777 cm^{-1}.

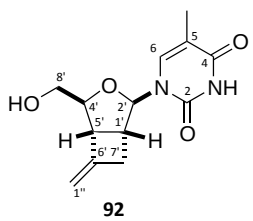
^{1}H-NMR (360 MHz, $CDCl_3$) δ: 8.46 (s, 1H, NH), 7.39 (q, J_{6,CH_3}=1.1 Hz, 1H, H6), 6.00 (d, $J_{2',1'}$=2.8 Hz, 1H, H2'), 4.91 (m, 2H, 2xH1''), 4.28 (q, $J_{4',5'}$=3.9 Hz, $J_{4',8'}$=3.9 Hz, $J_{4',8'}$=3.9 Hz, 1H, H4'), 3.85 (dd, J_{gem}=11.2 Hz, $J_{8',4'}$=3.9 Hz, 1H, H8'), 3.70 (dd, J_{gem}=11.2 Hz, $J_{8',4'}$=3.9 Hz, 1H, H8'), 3.56-3.49 (m, 1H, H5'), 2.90-3.08 (m, 2H, H1'/H7'), 2.79 (ddt, J_{gem}=15.5 Hz, $J_{7',1'}$=4.4 Hz, $J_{7',9'}$=2.3 Hz, $J_{7',9'}$=2.3 Hz, 1H, H7'), 1.91 (d, $J_{CH_3,6}$=1.1 Hz, 3H, CH_3-C5), 0.91 (s, 9H, (CH_3)$_3$C), 0.09 (s, 6H, 2xCH_3Si).

^{13}C-NMR (90 MHz, $CDCl_3$) δ: 163.8 (C=O, C4), 150.4 (C=O, C2), 147.0 (C, C6'), 136.1 (CH, C6), 110.4 (C, C5), 108.6 (CH_2, C1''), 92.5 (CH, C2'), 87.3 (CH, C4'), 64.6 (CH_2, C8'), 50.5 (CH, C5'), 43.3 (CH, C1'), 35.0 (CH_2, C7'), 26.0 (3xCH_3, (*C*H$_3$)$_3$C), 18.5 (C, (CH$_3$)$_3$*C*), 12.8 (CH_3, *C*H$_3$-C5), -5.2 (CH_3, 2x*C*H$_3$Si).

HRMS (ESI+) calcd for ([$C_{19}H_{30}N_2O_4Si$+Na]$^+$) 401.1867, found 401.1875.

COSY, HMBC, HSQC and **NOESY** experiments have been recorded.

3.3.3 Synthesis of (1*S*,2*R*,4*S*,5*R*)-1-(4-hydroxymethyl-6-methylene-3-oxabicyclo[3.2.0]hept-2-yl)thymine, **92**



92

To a solution of **241** (14 mg, 0.04 mmol) in THF (0.5 mL), a 1.0 M solution of TBAF in THF (70 µL, 0.07 mmol) was added. The reaction was allowed to stir for 1 h and the solvent was removed. The residue was purified by column chromatography (hexane-EtOAc 1:1) to give **92** (8 mg, 0.03 mmol, 80% yield) as a white solid.

mp: 150-152 ºC (hexane-EtOAc).

$[\alpha]_D$: -72.5 (*c* 0.91, $CHCl_3$).

IR (ATR) ν 3424, 2926, 1681, 1467, 1260, 1063, 876 cm^{-1}.

^{1}H-NMR (360 MHz, $CDCl_3$) δ: 8.60 (s, 1H, NH), 7.27 (d, J_{6,CH_3}=0.7 Hz, 1H, H6), 6.01 (d, $J_{2',1'}$=2.3 Hz, 1H, H2'), 4.92 (d, J_{gem}=1.9 Hz, 1H, H1''), 4.89 (dd, J_{gem}=1.9 Hz, 1H, H1''), 4.32 (td, $J_{4',8'}$=4.5 Hz, $J_{4',5'}$=4.5 Hz, $J_{4',8'}$=2.8 Hz, 1H, H4'), 3.92 (dd, J_{gem}=12.0 Hz, $J_{8',4'}$=2.8 Hz, 1H, H8'), 3.70 (dd, J_{gem}=12.0 Hz, $J_{8',4'}$=4.5 Hz, 1H, H8'), 3.64-3.57 (m, 1H, H5'), 3.13-3.04 (m, 1H, H1'), 3.04-2.97 (m, 1H, H7'), 2.85-2.76 (m, 1H, H7'), 1.90 (d, $J_{CH_3,6}$=0.7 Hz, 3H, CH_3-C5).

^{13}C-NMR (90 MHz, $CDCl_3$) δ: 163.8 (C=O, C4), 150.5 (C=O, C2), 146.2 (C, C6'), 137.0 (CH, C6), 111.1 (C, C5), 108.6 (CH_2, C1''), 92.9 (CH, C2'), 87.4 (CH, C4'), 63.9 (CH_2, C8'), 50.5 (CH, C5'), 42.4 (CH, C1'), 35.2 (CH_2, C7'), 12.6 (CH_3, *C*H_3-C5).

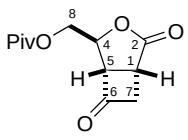
HRMS (ESI+) calcd for ($[C_{13}H_{16}N_2O_4+Na]^+$) 287.1002, found 287.1006.

COSY, HMBC, HSQC and **NOESY** experiments have been recorded.

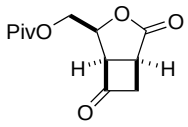
4. SYNTHESIS OF CYCLOBUTANE L-NUCLEOSIDES

4.1 Synthesis of the common intermediate **81**

4.1.1 Synthesis of (1*R*,4*S*,5*S*)- and (1*S*,4*S*,5*R*)-4-pivaloyloxymethyl-3-oxabicyclo[3.2.0]heptan-2,6-dione (**79** and **366**)



79



366

A solution of lactone **78** (2.01 g, 10.14 mmol) and 1,1-diethoxyethylene **138** (10.7 mL, 81.31 mmol) in diethyl ether (800 mL) was placed in a photochemical reactor (two-necked vessel fitted with a Quartz immersion type cooling jacket). The reactor was immersed in a cooling bath at -40 ºC and a stream of MeOH at -15 ºC was circulated throughout the refrigeration jacket. The reaction mixture was irradiated using a medium pressure 400W mercury lamp for 5 h. Evaporation of the solvent and column chromatography (from hexane-EtOAc 20:1 to hexane-EtOAc 15:1) afforded a 60:35:3:2 mixture of **93**, **159c**, **160c** and **161c**. This mixture of isomers was diluted in acetone (300 mL) and *p*-toluenesulfonic acid (550 mg, 2.89 mmol) was added. The mixture was stirred overnight at reflux temperature. Evaporation of the solvent and purification by column chromatography (from hexane-EtOAc 4:1 to hexane-EtOAc 3:1) afforded the *anti* isomer **79** (830 mg, 3.45 mmol, 34% yield) as a colorless oil and the *syn* isomer **366** (439 mg, 1.83 mmol, 18% yield) as a yellow oil.

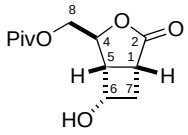
79: **^{1}H-NMR** (250 MHz, $CDCl_3$) δ: 4.93 (ddd, $J_{4,8}$=2.9 Hz, $J_{4,8}$=2.9 Hz, $J_{4,5}$=1.5 Hz, 1H, H4), 4.32 (dd, J_{gem}=12.2 Hz, $J_{8,4}$=2.9 Hz, 1H, H8), 4.14 (dd, J_{gem}=12.2 Hz, $J_{8.4}$=2.9 Hz, 1H, H8), 3.93 (dddd, $J_{5,1}$=7.4 Hz, $J_{5,7}$=3.0 Hz, $J_{5,7}$=3.0 Hz, $J_{5,4}$=1.5 Hz, 1H, H5), 3.75 (ddd, J_{gem}=18.0 Hz, $J_{7,1}$=10.0 Hz, $J_{7,5}$=3.0 Hz, 1H, H7), 3.49 (ddd, $J_{1,7}$=10.0 Hz, $J_{1,5}$=7.5 Hz, $J_{1,7}$=3.7 Hz, 1H, H1), 3.35 (ddd, J_{gem}=18.0 Hz, $J_{7,1}$=3.7 Hz, $J_{7,5}$=3.0 Hz, 1H, H7), 1.22 (s, 9H, $(CH_3)_3C$).

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ: 202.4 (C=O, C6), 177.8 (C=O, Piv), 176.2 (C=O, C2), 76.4 (CH, C4), 65.4 (CH_2, C8), 62.7 (CH, C5), 54.1 (CH_2, C7), 39.0 (C, $(CH_3)_3C$), 31.0 (CH, C1), 27.3 (CH_3, $(CH_3)_3C$).

366: **^{1}H-NMR** (250 MHz, $CDCl_3$) δ: 4.80 (ddd, $J_{4,5}$=9.0 Hz, $J_{4,8}$=5.8 Hz, $J_{4,8}$=3.5 Hz, 1H, H4), 4.53 (dd, J_{gem}=12.6 Hz, $J_{8,4}$=3.5 Hz, 1H, H8), 4.18 (dd, J_{gem}=12.6 Hz, $J_{8,4}$=5.8 Hz, 1H, H8), 4.12-4.05 (m, 1H, H5), 3.68 (ddd, J_{gem}=17.7 Hz, $J_{7,1}$=9.4 Hz, $J_{7,5}$=3.5 Hz, 1H, H7), 3.52 (ddd, $J_{1,7}$=9.4 Hz, $J_{1,5}$=7.7 Hz, $J_{1,7}$=3.9 Hz, 1H, H1), 3.40 (ddd, J_{gem}=17.7 Hz, $J_{7,1}$=3.9 Hz, $J_{7,5}$=3.5 Hz, 1H, H7), 1.20 (s, 9H, $(CH_3)_3C$).

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ: 200.6 (C=O, C6), 177.6 (C=O, Piv), 176.0 (C=O, C2), 76.8 (CH, C4), 62.6 (CH_2, C8), 61.6 (CH, C5), 53.7 (CH_2, C7), 38.7 (C, $(CH_3)_3C$), 30.8 (CH, C1), 27.0 (CH_3, $(CH_3)_3C$).

4.1.2 Synthesis of (1*R*,4*S*,5*R*,6*S*)-6-hydroxy-4-pivaloyloxymethyl-3-oxabicyclo[3.2.0]heptan-2-one, **238**



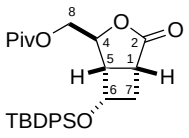
238

To a solution of **79** (477 mg, 1.99 mmol) in dry THF (30 mL) at -78 ºC, a 1.0 M solution of L-Selectride® in THF (1.53 mL, 1.53 mmol) was added dropwise. After 2 h of stirring at -78 ºC, the reaction was quenched by the slow addition of saturated NH_4Cl solution and allowed to warm to room temperature. The two layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered and evaporated to dryness. The crude residue was purified by column chromatography (hexane-EtOAc 1:1) to afford alcohol **238** (441 mg, 1.82 mmol, 92% yield) as a white solid.

^{1}H-NMR (250 MHz, $CDCl_3$) δ: 5.25 (ddd, $J_{4,8}$=4.0 Hz, $J_{4,5}$=3.0 Hz, $J_{4,8}$=3.0 Hz, 1H, H4), 4.65-4.53 (m, 1H, H6), 4.33 (dd, J_{gem}=12.1 Hz, $J_{8,4}$=2.9 Hz, 1H, H8), 4.13 (dd, J_{gem}=12.1 Hz, $J_{8,4}$=4.1 Hz, 1H, H8), 3.16-3.05 (m, 1H, H5), 3.00-2.87 (m, 2H, H1/H7), 2.30-2.15 (m, 1H, H7), 1.20 (s, 9H, $(CH_3)_3C$).

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ: 178.9 (C=O, Piv), 178.4 (C=O, C2), 75.6 (CH, C4), 66.0 (CH_2, C8), 63.6 (CH, C6), 42.7 (CH, C5), 39.0 (C, $(CH_3)_3C$), 35.9 (CH_2, C7), 33.0 (CH, C1), 27.3 (3xCH_3, $(CH_3)_3C$).

4.1.3 Synthesis of (1*R*,4*S*,5*R*,6*S*)-6-*tert*-butyldiphenylsilyloxy-4-pivaloyloxymethyl-3-oxabicyclo[3.2.0]heptan-2-one, **80**



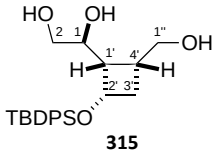
80

To an ice-cooled solution of **238** (162 mg, 0.67 mmol) in CH_2Cl_2 (15 mL), imidazole (118 mg, 1.73 mmol) and *tert*-butyldiphenylsilyl chloride (0.41 mL, 1.58 mmol) were added. The mixture was allowed to stir overnight at room temperature and then was diluted with CH_2Cl_2 (15 mL). Water (7.5 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3x3 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated to dryness. The crude was purified by column chromatography (from hexane-EtOAc 15:1 to hexane-EtOAc 8:1) to give **80** (281 mg, 0.58 mmol, 88% yield) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.61-7.54 (m, 4H, Ph), 7.48-7.35 (m, 6H, Ph), 5.34-5.31 (m, 1H, H4), 4.54-4.48 (m, 1H, H6), 4.22 (dd, J_{gem}=12.2 Hz, $J_{8,4}$=2.7 Hz, 1H, H8), 3.91 (dd, J_{gem}=12.2 Hz, $J_{8,4}$=4.1 Hz, 1H, H8), 2.93-2.86 (m, 1H, H1), 2.82-2.68 (m, 2H, H7/H5), 2.33-2.26 (m, 1H, H7), 1.18 (s, 9H, $(CH_3)_3C$), 1.07 (s, 9H, $(CH_3)_3C$).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 178.6 (C=O, Piv), 178.1 (C=O, C2), 135.6 (2xCH, Ph), 135.4 (2xCH, Ph), 133.2 (C, Ph), 133.0 (C, Ph), 130.3 (CH, Ph), 130.2 (CH, Ph), 128.1 (2xCH, Ph), 128.0 (2xCH, Ph), 75.9 (CH, C4), 65.9 (CH_2, C8), 64.4 (CH, C6), 43.3 (CH, C1), 39.0 (C, $(CH_3)_3C$), 36.7 (CH_2, C7), 32.6 (CH, C5), 27.3 (CH_3, $(CH_3)_3C$), 26.9 (CH_3, $(CH_3)_3C$), 19.2 (C, $(CH_3)_3C$).

4.1.4 Synthesis of (1*S*)-1-[(1*S*,2*S*,4*R*)-2-(*tert*-butyldiphenylsilyloxy)-4-(hydroxymethyl)cyclobutyl]-1,2-ethanediol, **315**



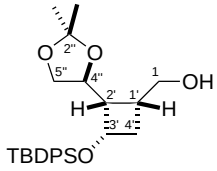
315

A 2.0 M solution of $LiBH_4$ in THF (1.0 mL, 2.00 mmol) was added dropwise to a solution of **80** (203 mg, 0.42 mmol) in dry THF (8 mL). Then, the mixture was heated to reflux temperature. After 5 h, the reaction was allowed to cool to room temperature and was quenched by the slow addition of a saturated solution of NH_4Cl. The crude was diluted with EtOAc, the layers were separated and the aqueous layer was extracted with EtOAc (3x4 mL). The organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness. The crude was purified by column chromatography (EtOAc) to afford **315** (149 mg, 0.37 mmol, 88% yield) as a colorless oil.

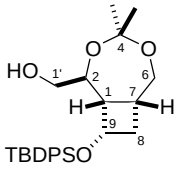
^{1}H-NMR (250 MHz, $CDCl_3$) δ: 7.66-7.55 (m, 4H, Ph), 7.48-7.32 (m, 6H, Ph), 4.40 (ddd, $J_{1,1'}$=10.0 Hz, $J_{1,2}$=7.2 Hz, $J_{1,2}$=3.1 Hz, 1H, H1), 4.33 (q, $J_{2',1'}$=7.2 Hz, $J_{2',3'}$=7.2 Hz, $J_{2',3'}$=7.2 Hz, 1H, H2'), 3.99 (dd, J_{gem}=10.9 Hz, $J_{2,1}$=3.1 Hz, 1H, H2), 3.81 (dd, J_{gem}=11.5 Hz, $J_{1'',4'}$=9.7 Hz, 1H, H1''), 3.60 (dd, J_{gem}=11.5 Hz, $J_{1'',4'}$=4.2 Hz, 1H, H1''), 3.54 (dd, J_{gem}=10.9 Hz, $J_{2,1}$=7.2 Hz, 1H, H2), 3.18 (s, 3H, O*H*), 2.69-2.56 (m, 1H, H1'), 2.28-2.10 (m, 1H, H4'), 2.00-1.86 (m, 1H, H3'), 1.82-1.68 (m, 1H, H3'), 1.06 (s, 9H, $(CH_3)_3C$).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 135.8 (2xCH, Ph), 135.6 (2xCH, Ph), 133.7 (C, Ph), 133.4 (C, Ph), 130.1 (CH, Ph), 130.0 (CH, Ph), 127.9 (2xCH, Ph), 127.8 (2xCH, Ph), 69.8 (CH, C1), 66.4 (CH, C2'), 66.1 (CH_2, C2), 63.5 (CH_2, C1''), 45.9 (CH, C4'), 34.0 (CH, C1'), 32.3 (CH_2, C3'), 27.1 (CH_3, $(CH_3)_3C$), 19.2 (C, $(CH_3)_3C$).

4.1.5 Synthesis of {(1*R*,2*S*,3*S*)-3-*tert*-butyldiphenylsilyloxy-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclobutyl}methanol, **81**, and (1*S*,2*S*,7*R*,9*S*)-9-*tert*-butyldiphenylsilyloxy-4,4-dimethyl-2-hydroxymethyl-3,6-dioxabicyclo[5.2.0]nonane, **316**



81



316

To a solution of triol **315** (235 mg, 0.59 mmol) in freshly distilled acetone (12 mL), was added anhydrous sodium sulphate (1.7 g), anhydrous copper sulphate (937 mg, 5.87 mmol) and a catalytic amount of concentrated HCl were added. After being stirred for 12 h, the reaction was quenched by the slow addition of 30% NH_3 and filtered through a Celite pad. Evaporation of the solvent gave a crude residue that was purified by column chromatography (hexane-EtOAc 6:1) affording **81** (217 mg, 0.49 mmol, 84% yield) as a colorless oil and **316** (23 mg, 0.05 mmol, 9% yield) as a colorless oil.

81: ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 7.65-7.55 (m, 4H, Ph), 7.47-7.31 (m, 6H, Ph), 4.74 (dt, $J_{4'',2'}$=11.0 Hz, $J_{4'',5''}$=6.4 Hz, $J_{4'',5''}$=6.4 Hz, 1H, H4''), 4.38 (dd, J_{gem}=8.4 Hz, $J_{5'',4''}$=6.4 Hz, 1H, H5''), 4.28 (dt, $J_{3',4'}$=8.4 Hz, $J_{3',2'}$=7.4 Hz, $J_{3',4'}$=7.4 Hz, 1H, H3'), 3.69 (dd, J_{gem}=8.4 Hz, $J_{5'',4''}$=6.4 Hz, 1H, H5''), 3.68-3.61 (m, 1H, H1), 3.49 (dd, J_{gem}=11.9 Hz, $J_{1,1'}$=4.6 Hz, 1H, H1), 2.68 (dddd, $J_{2',4''}$=11.0 Hz, $J_{2',1'}$=7.5 Hz, $J_{2',3'}$=7.4, $J_{2',4'}$=3.4 Hz, 1H, H2'), 2.18-1.99 (m, 1H, H1'), 1.89-1.65 (m, 2H, 2xH4'), 1.42 (s, 6H, 2xCH_3-C2''), 1.06 (s, 9H, $(CH_3)_3C$).

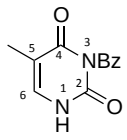
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 135.8 (2xCH, Ph), 135.6 (2xCH, Ph), 133.8 (C, Ph), 133.4 (C, Ph), 130.0 (CH, Ph), 130.0 (CH, Ph), 127.9 (2xCH, Ph), 127.8 (2xCH, Ph), 108.3 (C, C2''), 73.3 (CH, C4''), 70.5 (CH_2, C5''), 65.0 (CH, C3'), 63.6 (CH_2, C1), 48.9 (CH, C2'), 34.0 (CH_2, C4'), 31.1 (CH, C1'), 27.1 (3xCH_3, $(CH_3)_3C$), 26.9 (CH_3, CH_3-C2''), 25.6 (CH_3, CH_3-C2''), 19.0 (C, $(CH_3)_3C$).

316: **^{1}H-NMR** (250 MHz, $CDCl_3$) δ: 7.69-7.57 (m, 4H, Ph), 7.47-7.32 (m, 6H, Ph), 4.60 (ddd, $J_{2,1}$=10.9 Hz, $J_{2,1'}$=7.4 Hz, $J_{2,1'}$=3.5 Hz, 1H, H2), 4.28-4.18 (m, 1H, H9), 3.95 (dd, J_{gem}=13.1 Hz, $J_{6,7}$=1.7 Hz, 1H, H6), 4.00-3.83 (m, 1H, H1'), 3.50 (ddd, J_{gem}=10.7 Hz, $J_{1',2}$=7.4 Hz, $J_{1',OH}$=3.0 Hz, 1H, H1'), 3.29 (dd, J_{gem}=13.1 Hz, $J_{6,7}$=1.0 Hz, 1H, H6), 2.53-2.39 (m, 1H, H1), 2.38-2.28 (m, 1H, H8), 2.14-2.10 (m, 1H, OH), 1.81-1.64 (m, 2H, H8/H7), 1.49 (s, 3H, CH_3-C4), 1.38 (s, 3H, CH_3-C4), 1.07 (s, 9H, (CH_3)$_3$C).

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ: 135.7 (2xCH, Ph), 135.4 (2xCH, Ph), 133.8 (C, Ph), 133.4 (C, Ph), 129.7 (CH, Ph), 129.7 (CH, Ph), 127.7 (2xCH, Ph), 127.6 (2xCH, Ph), 102.2 (C, C4), 69.4 (CH, C2), 66.1 (CH_2, C1'), 65.6 (CH, C9), 61.5 (CH_2, C6), 46.4 (CH, C1), 33.5 (CH_2, C8), 29.8 (CH, C7), 26.8 (CH_3, (CH_3)$_3$C), 25.5 (CH_3-C4), 24.5 (CH_3-C4), 19.0 (C, (CH_3)$_3$C).

4.2 Nucleobase introduction. Preparation of **318, 320** and **323**

4.2.1 Synthesis of N^3-benzoylthymine, **317**

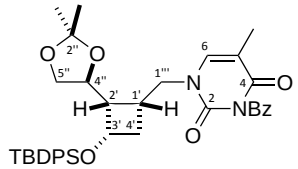


317

To a solution of thymine (3.00 g, 23.79 mmol) in dry acetonitrile (24 mL), anhydrous pyridine (9.5 mL) was added and the mixture was cooled to 0 ºC in an ice bath. Then, benzoyl chloride (6.2 mL, 52.57 mmol) was added dropwise. The solution was allowed to stir overnight at room temperature. After that, the products were concentrated under reduced pressure and the residue was partitioned between CH_2Cl_2 (120 mL) and H_2O (120 mL). The organic layer was separated and evaporated under reduced pressure. The residue was dissolved in a mixture of dioxane (50 mL) and a 0.5 M solution of K_2CO_3 (25 mL) and stirred for 30 min at room temperature. Then, the suspension was acidified to pH 5 by the addition of glacial acetic acid. The products were concentrated under reduced pressure and the residue was stirred with a saturated $NaHCO_3$ solution. After 1 h, the residue was filtered and washed with cold H_2O (3x12 mL). Finally, the product obtained was crystallized from aqueous CH_3CN to give **317** (1.95 g, 8.47 mmol, 65% yield) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.01 (br s, 1H, NH), 7.75 (dd, J_{Ar}=8.0 Hz, J_{Ar}=1.2 Hz, 2H, Bz), 7.68 (q, J_{6,CH_3}=1.3 Hz, 1H, H6), 7.63 (m, 1H, Bz), 7.48 (t, J_{Ar}=8.0 Hz, 2H, Bz), 2.03 (d, $J_{CH_3,6}$=1.3 Hz, 3H, CH_3-C5).

4.2.2 Synthesis of 3-benzoyl-1-({(1*R*,2*S*,3*S*)-3-*tert*-butyldiphenylsilyloxy-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclobutyl}methyl)-thymine, **318**



318

To a solution of PPh_3 (243 mg, 0.88 mmol) in dry THF (5.5 mL), di-*tert*-butyl azodicarboxylate (203 mg, 0.88 mmol) was added and the solution was allowed to stir at room temperature for 30 min. Then, a suspension of **81** (193 mg, 0.44 mmol) and N^3-benzoylthymine (202 mg, 0.88 mmol) in dry THF (5.5 mL) was added over the initial solution and the mixture was heated to reflux temperature. After 2 h, the mixture was allowed to cool to room temperature. Evaporation of the solvent and purification by column chromatography (from hexane-diethyl ether 2:1 to hexane-diethyl ether 1:1) afforded **318** (208 mg, 0.32 mmol, 73% yield) as a white foam.

$[\alpha]_D$: +37.0 (*c* 0.87, $CHCl_3$)

IR (ATR) 2931, 1746, 1698, 1653, 1429, 1368, 1239, 1154, 1109, 1051, 856, 702 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.90-7.84 (m, 2H, Ar), 7.65-7.54 (m, 5H, Ar), 7.49-7.32 (m, 9H, Ar/H6), 4.67 (dt, $J_{4'',2'}$=10.8 Hz, $J_{4'',5''}$=6.8 Hz, $J_{4'',5''}$=6.8 Hz, 1H, H4''), 4.39 (dd, J_{gem}=8.4 Hz, $J_{5'',4''}$=6.5 Hz, 1H, H5''), 4.18 (q, $J_{3',4'}$=7.5 Hz, $J_{3',4'}$=7.5 Hz, $J_{3',2'}$=7.5 Hz, 1H, H3'), 3.95 (dd, J_{gem}=14.2 Hz, $J_{1''',1'}$=6.8 Hz, 1H, H1'''), 3.82 (dd, J_{gem}=14.2 Hz, $J_{1''',1'}$=7.0 Hz, 1H, H1'''), 3.67 (dd, J_{gem}=8.4 Hz, $J_{5'',4''}$=6.8 Hz, 1H, H5''), 2.66 (dddd, $J_{2',4''}$=10.8 Hz, $J_{2',1'}$=7.5 Hz, $J_{2',3'}$=7.5 Hz, $J_{2',4'}$=3.4 Hz, 1H, H2'), 2.19-2.07 (m, 1H, H1'), 2.00-1.86 (m, 2H, H4'), 1.91 (d, $J_{CH_3,6}$=1.0 Hz, 3H, CH_3-C5), 1.42 (s, 3H, CH_3-C2''), 1.40 (s, 3H, CH_3-C2''), 1.04 (s, 9H, (CH_3)$_3$C).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.2 (C=O, Bz), 163.3 (C=O, C4), 150.1 (C=O, C2), 141.1 (CH, C6), 135.7 (2xCH, Ph), 135.5 (2xCH, Ph), 134.9 (C, Bz), 133.5 (C, Ph), 133.1 (C, Ph), 131.9 (CH, Bz), 130.4 (2xCH, Bz), 130.1 (CH, Ph), 130.0 (CH, Ph), 129.2 (2xCH, Bz), 127.9 (2xCH, Ph), 127.8 (2xCH, Ph), 109.7 (C, C5), 108.2 (C, C2''), 73.0 (CH, C4''), 70.4 (CH_2, C5''), 64.8 (CH, C3'), 50.0 (CH, C2'), 49.9 (CH_2, C1'''), 36.5 (CH_2, C4'), 28.7 (CH, C1'), 27.0 (4xCH_3, (*C*H$_3$)$_3$C/*C*H$_3$-C2''), 25.7 (CH_3, *C*H$_3$-C2''), 19.0 (C, (CH$_3$)$_3$*C*), 12.4 (CH_3, *C*H$_3$-C5).

HRMS (ESI+) calcd for ($[C_{38}H_{44}N_2O_6Si+Na]^+$) 675.2861, found 675.2860.

COSY, HMBC, HSQC and **NOESY** experiments have been recorded.

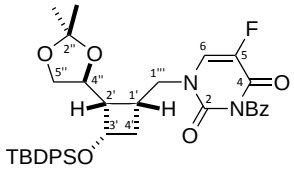
4.2.3 Synthesis of N^3-benzoyl-5-fluorouracil, **319**

319

To a solution of 5-fluorouracil (3.00 g, 23.09 mmol) in dry acetonitrile (30 mL), anhydrous pyridine (9.25 mL) was added and the mixture was cooled to 0 ºC in an ice bath. Then, benzoyl chloride (6.0 mL, 51.04 mmol) was added dropwise. The solution was allowed to stir overnight at room temperature. After that, the products were concentrated under reduced pressure and the residue was partitioned between CH_2Cl_2 (120 mL) and H_2O (120 mL). The organic layer was separated and evaporated under reduced pressure. The residue was dissolved in a mixture of dioxane (50 mL) and a 0.5 M solution of K_2CO_3 (25 mL) and stirred for 30 min at room temperature. Then, the suspension was acidified to pH 5 by the addition of glacial acetic acid. The products were concentrated under reduced pressure and the residue was stirred with a saturated $NaHCO_3$ solution. After 1 h, the residue was filtered and washed with cold H_2O (3x12 mL). Finally, the product obtained was crystallized from aqueous CH_3CN to give **319** (1.95 g, 8.47 mmol, 65% yield) as a white solid.

^{1}H-NMR (250 MHz, DMSO) δ: 8.09 (d, $J_{6,F}$=6.1 Hz, 1H, H6), 8.05 (dd, J_{Ar}=7.9 Hz, J_{Ar}=1.3 Hz, 2H, Bz), 7.81 (m, 1H, Bz), 7.62 (t, J_{Ar}=7.9 Hz, 2H, Bz).

4.2.4 Synthesis of 3-benzoyl-1-({(1*R*,2*S*,3*S*)-3-{[*tert*-butyl(diphenyl)silyl]oxy}-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclobutyl}methyl)-5-fluoro-thymine, **320**



320

To a solution of PPh_3 (97 mg, 0.37 mmol) in dry THF (2.5 mL), di-*tert*-butyl azodicarboxylate (85 mg, 0.37 mmol) was added and the solution was allowed to stir at room temperature for 30 min. Then, a suspension of **81** (82 mg, 0.19 mmol) and N^3-benzoyl-5-fluorouracil (87 mg, 0.37 mmol) in dry THF (2.5 mL) was added over the initial solution and the mixture was heated to reflux temperature. After 5h, the mixture was allowed to cool to room temperature. Evaporation of the solvent and purification by column chromatography (from hexane-diethyl ether 5:1 to hexane-diethyl ether 1:1) afforded **320** (76 mg, 0.12 mmol, 62% yield) as a white foam.

$[\alpha]_D$: +43.7 (*c* 0.93, $CHCl_3$).

IR (ATR) ν 2929, 1751, 1712, 1666, 1449, 1369, 1237, 1156, 1110, 702 cm^{-1}.

^{1}H-NMR (250 MHz, $CDCl_3$) δ: 7.91-7.79 (m, 2H, Ar), 7.83 (d, $J_{6,F}$=6.1 Hz, 1H, H6), 7.69-7.52 (m, 5H, Ar), 7.52-7.30 (m, 8H, Ar), 4.67 (dt, $J_{4'',2'}$=10.9 Hz, $J_{4'',5''}$=6.5 Hz, $J_{4'',5''}$=6.5 Hz, 1H, H4''), 4.42 (dd, J_{gem}=8.5 Hz, $J_{5'',4''}$=6.5 Hz, 1H, H5''), 4.18 (q, $J_{3',2'}$=7.5 Hz, $J_{3',4'}$=7.5 Hz, $J_{3',4'}$=7.5 Hz, 1H, H3'), 3.97 (dd, J_{gem}=14.0 Hz, $J_{1''',1'}$=5.2 Hz, 1H, H1'''), 3.75 (dd, J_{gem}=14.0 Hz, $J_{1''',1'}$=7.4 Hz, 1H, H1'''), 3.71 (dd, J_{gem}=8.5 Hz, $J_{5'',4''}$=6.5 Hz, 1H, H5''), 2.69 (dtd, $J_{2',4''}$=10.9 Hz, $J_{2',3'}$=7.5 Hz, $J_{2',1'}$=7.5 Hz, $J_{2',4'}$=3.7 Hz, 1H, H2'), 2.18-2.02 (m, 1H, H1'), 1.99-1.79 (m, 2H, H4'), 1.43 (s, 6H, 2xCH_3-C2''), 1.05 (s, 9H, $(CH_3)_3C$).

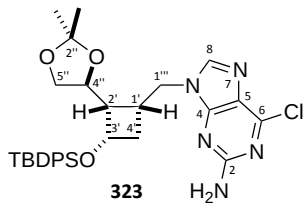
^{13}C-NMR (62.5 MHz, $CDCl_3$) δ: 167.5 (s, C=O, Bz), 156.4 (d, $J_{C,F}$=27.0 Hz, C=O, C4), 148.6 (s, C=O, C2), 139.5 (d, $J_{C,F}$=237.3 Hz, C, C5), 135.7 (s, 2xCH, Ph), 135.5 (s, 2xCH, Ph), 135.4 (s, C, Bz), 133.4 (s, C, Ph), 133.0 (s, C, Ph), 131.3 (s, CH, Bz), 130.6 (s, 2xCH, Bz), 130.2 (s, CH, Ph), 130.1 (s, CH, Ph), 129.8 (d, $J_{C,F}$=33.5 Hz, CH, C6), 129.3 (s, 2xCH, Bz), 128.0 (s, 2xCH, Ph), 127.9 (s, 2xCH, Ph), 108.5 (s, C, C2''), 72.9 (s, CH, C4''), 70.4 (s, CH_2, C5''), 64.7 (s, CH, C3'), 50.1 (s, CH_2, C1'''), 50.0 (s, CH, C2'), 36.3 (s, CH_2, C4'), 28.5 (s, CH, C1'), 27.0 (s, 3xCH_3, $(CH_3)_3C$), 26.9 (s, CH_3, CH_3-C2''), 25.7 (s, CH_3, CH_3-C2''), 19.0 (s, C, $(CH_3)_3C$).

^{19}F-NMR (235 MHz, $CDCl_3$) δ: -167.3 (d, $J_{F,6}$=6.1 Hz).

HRMS (ESI+) calcd for ($[C_{37}H_{41}FN_2O_6Si+Na]^+$) 679.2610, found 679.2616.

COSY, DEPT-135, HMBC, HSQC and **NOESY** experiments have been recorded.

4.2.5 Synthesis of 9-({(1*R*,2*S*,3*S*)-3-{[*tert*-butyl(diphenyl)silyl]oxy}-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclobutyl}methyl)-6-chloro-9*H*-purin-2-amine, **323**



323

To a solution of PPh_3 (113 mg, 0.41 mmol) in dry THF (3 mL), di-*tert*-butyl azodicarboxylate (94 mg, 0.41 mmol) was added and the solution was allowed to stir at room temperature for 30 min. Then, a suspension of **81** (91 mg, 0.21 mmol) and 2-amino-6-chloropurine (70 mg, 0.41 mmol) in dry THF (3 mL) was added over the initial solution and the mixture was allowed to stir overnight at room temperature. After that, the mixture was allowed to cool to room temperature. Evaporation of the solvent and purification by column chromatography (hexane-diethyl ether 2:1) afforded **323** (106 mg, 0.18 mmol, 87% yield) as a brownish oil.

$[\alpha]_D$: +27.9 (*c* 0.98, $CHCl_3$).

IR (ATR) ν 3322, 2931, 1610, 1561, 1460, 1151, 1110, 1052, 854, 822, 731, 701 cm^{-1}.

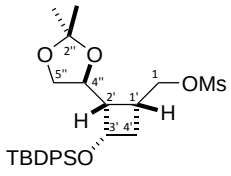
^{1}H-NMR (250 MHz, $CDCl_3$) δ: 7.86 (s, 1H, H8), 7.62-7.52 (m, 4H, Ph), 7.47-7.31 (m, 6H, Ph), 5.13 (br s, 2H, NH_2), 4.74 (dt, $J_{4'',2'}$=10.9 Hz, $J_{4'',5''}$=6.4 Hz, $J_{4'',5''}$=6.4 Hz, 1H, H4''), 4.40 (dd, J_{gem}=8.4 Hz, $J_{5'',4''}$=6.4 Hz, 1H, H5''), 4.32 (dd, J_{gem}=14.2 Hz, $J_{1''',1'}$=7.7 Hz, 1H, H1'''), 4.20 (q, $J_{3',2'}$=7.5 Hz, $J_{3',4'}$=7.5 Hz, $J_{3',4'}$=7.5 Hz, 1H, H3'), 4.08 (dd, J_{gem}=14.2 Hz, $J_{1''',1'}$=7.0 Hz, 1H, H1'''), 3.67 (dd, J_{gem}=8.4 Hz, $J_{5'',4''}$=6.4 Hz, 1H, H5''), 2.66 (dt, $J_{2',4''}$=10.9 Hz, $J_{2',1'}$=7.5 Hz, $J_{2',3'}$=7.5 Hz, 1H, H2'), 2.41-2.23 (m, 1H, H1'), 1.97-1.87 (m, 2H, 2xH4'), 1.42 (s, 3H, CH_3-C2''), 1.38 (s, 3H, CH_3-C2''), 1.05 (s, 9H, (CH_3)$_3$C).

^{13}C-NMR (62.5 MHz, $CDCl_3$) δ: 159.0 (C, C2), 153.9 (C, C4), 151.1 (C, C6), 143.3 (CH, C8), 135.8 (2xCH, Ph), 135.5 (2xCH, Ph), 133.5 (C, Ph), 133.1 (C, Ph), 130.1 (CH, Ph), 130.1 (CH, Ph), 128.0 (2xCH, Ph), 127.9 (2xCH, Ph), 125.4 (C, C5), 108.4 (C, C2''), 73.0 (CH, C4''), 70.4 (CH_2, C5''), 64.7 (CH, C3'), 49.6 (CH, C2'), 45.5 (CH_2, C1'''), 36.5 (CH_2, C4'), 29.1 (CH, C1'), 27.0 (3xCH_3, (*C*H_3)$_3$C), 27.0 (CH_3, *C*H_3-C2''), 25.8 (CH_3, *C*H_3-C2''), 19.0 (C, (CH_3)$_3$*C*).

HRMS (ESI+) calcd for ([$C_{31}H_{38}ClN_5O_3Si$+Na]$^+$) 614.2325, found 614.2330.

COSY, DEPT-135, HMBC, HSQC and **NOESY** experiments have been recorded.

4.2.6 Synthesis of {(1*R*,2*S*,3*S*)-3-{[*tert*-butyldiphenylsilyloxy}-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclobutyl}methyl methanesulfonate, **324**



324

To a solution of **81** (285 mg, 0.65 mmol) in dry CH_2Cl_2 (7 mL), anhydrous triethylamine (182 µL, 1.29 mmol) and methanesulfonyl chloride (85 µL, 1.10 mmol) were added. After 1h, the solution was evaporated to dryness and the crude was purified by column chromatography (hexane-diethyl ether 1:1) to give **324** (320 mg, 0.62 mmol, 95% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.65-7.57 (m, 4H, Ph), 7.48-7.34 (m, 6H, Ph), 4.65 (ddd, $J_{4'',2'}$=10.8 Hz, $J_{4'',5''}$=6.7 Hz, $J_{4'',5''}$=5.4 Hz, 1H, H4''), 4.47 (dd, J_{gem}=10.4 Hz, $J_{1,1'}$=5.2 Hz, 1H, H1), 4.35-4.22 (m, 3H, H5''/H3'/H1), 3.65 (dd, J_{gem}=8.3 Hz, $J_{5'',4''}$=6.7 Hz, 1H, H5''), 2.97 (s, 3H, Ms), 2.66 (dddd, $J_{2',4''}$=10.8 Hz, $J_{2',1'}$=7.2 Hz, $J_{2',3'}$=7.2, $J_{2',4'}$=3.6 Hz, 1H, H2'), 2.24-2.13 (m, 1H, H1'), 2.11-1.94 (m, 2H, 2xH4'), 1.38 (s, 6H, 2xCH_3-C2''), 1.06 (s, 9H, (CH_3)$_3$C).

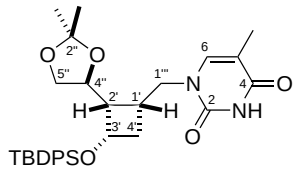
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 135.7 (2xCH, Ph), 135.5 (2xCH, Ph), 133.5 (C, Ph), 133.1 (C, Ph), 130.0 (CH, Ph), 130.0 (CH, Ph), 127.9 (2xCH, Ph), 127.8 (2xCH, Ph), 108.2 (C, C2''), 73.0 (CH, C4''), 72.0 (CH_2, C1), 70.2 (CH_2, C5''), 65.0 (CH, C3'), 49.0 (CH, C2'), 37.3 (CH_3, Ms), 36.0 (CH_2, C4'), 28.4 (CH, C1'), 27.1 (CH_3, *C*H_3-C2''), 27.0 (3xCH_3, (*C*H_3)$_3$C), 25.6 (CH_3, *C*H_3-C2''), 19.0 (C, (CH_3)$_3$*C*).

HRMS (ESI+) calcd for ([$C_{27}H_{38}O_6SSi$+Na]$^+$) 541.2051, found 541.2042.

COSY, HMBC, HSQC and **NOESY** experiments have been recorded.

4.3 Synthesis of the thymine nucleoside **95**

4.3.1 Synthesis of 1-({(1*R*,2*S*,3*S*)-3-{[*tert*-butyldiphenylsilyloxy}-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclobutyl}methyl)-thymine, **325**



325

Compound **318** (116 mg, 0.18 mmol) was dissolved in 3 mL of a 33% $MeNH_2$ solution in EtOH. The solution was stirred for 30 min at room temperature. Afterwards, the solvent was evaporated under reduced pressure and the crude was purified by column chromatography (hexane-EtOAc 1:1) to provide **325** (78 mg, 0.14 mmol, 80% yield) as a white foam.

$[\alpha]_D$: +40.6 (*c* 0.42, $CHCl_3$)

IR (ATR) ν 2930, 2857, 1672, 1462, 1427, 1369, 1154, 1107, 1052, 856, 701 cm^{-1}.

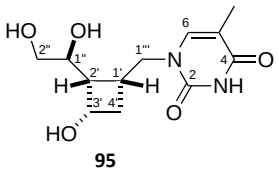
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.97 (br s, 1H, NH), 7.61-7.55 (m, 4H, Ph), 7.47-7.33 (m, 6H, Ph), 7.23 (q, J_{6,CH_3}=1.0 Hz, 1H, H6), 4.67 (dt, $J_{4'',2'}$=10.8 Hz, $J_{4'',5''}$=6.5 Hz, $J_{4'',5''}$=6.5 Hz, 1H, H4''), 4.39 (dd, J_{gem}=8.4 Hz, $J_{5'',4''}$=6.5 Hz, 1H, H5''), 4.17 (q, $J_{3',2'}$=7.3 Hz, $J_{3',4'}$=7.3 Hz, $J_{3',4'}$=7.3 Hz, 1H, H3'), 3.89 (dd, J_{gem}=14.2 Hz, $J_{1''',1'}$=7.0 Hz, 1H, H1'''), 3.78 (dd, J_{gem}=14.2 Hz, $J_{1''',1'}$=6.8 Hz, 1H, H1'''), 3.65 (dd, J_{gem}=8.4 Hz, $J_{5'',4''}$=6.5 Hz, 1H, H5''), 2.63 (dddd, $J_{2',4''}$=10.8 Hz, $J_{2',3'}$=7.3 Hz, $J_{2',1'}$=7.3 Hz, $J_{2',4'}$=3.6 Hz, 1H, H2'), 2.17-2.06 (m, 1H, H1'), 2.00-1.88 (m, 2H, H4'), 1.87 (d, $J_{CH_3,6}$=1.0 Hz, 3H, CH_3-C5), 1.41 (s, 3H, CH_3-C2''), 1.38 (s, 3H, CH_3-C2''), 1.05 (s, 9H, (CH_3)$_3$C).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 164.5 (C=O, C4), 151.1 (C=O, C2), 141.5 (CH, C6), 135.8 (2xCH, Ph), 135.5 (2xCH, Ph), 133.5 (C, Ph), 133.2 (C, Ph), 130.1 (CH, Ph), 130.0 (CH, Ph), 127.9 (2xCH, Ph), 127.8 (2xCH, Ph), 109.7 (C, C5), 108.2 (C, C2''), 73.0 (CH, C4''), 70.4 (CH_2, C5''), 64.8 (CH, C3'), 49.9 (CH, C2'), 49.8 (CH_2, C1'''), 36.5 (CH_2, C4'), 28.6 (CH, C1'), 27.0 (3xCH_3, (CH_3)$_3$C), 27.0 (CH_3, CH_3-C2''), 25.7 (CH_3, CH_3-C2''), 19.0 (C, (CH$_3$)$_3$*C*), 12.4 (CH_3, CH_3-C5).

HRMS (ESI+) calcd for ($[C_{31}H_{40}N_2O_5Si+Na]^+$) 571.2599, found 571.2602.

COSY, DEPT-135, HMBC, HSQC and **NOESY** experiments have been recorded.

4.3.2 Synthesis of 1-({(1*R*,2*R*,3*S*)-2-[(1*S*)-1,2-dihydroxyethyl]-3-hydroxycyclobutyl}methyl)-thymine, **95**



95

Compound **325** (77 mg, 0.14 mmol) was dissolved in MeOH (5 mL) and *p*-toluenesulfonic acid (27 mg, 0.14 mmol) was added. The solution was heated to reflux temperature and it was allowed to stir for 5 h. Then, the solution was allowed to cool to room temperature and the solvent was evaporated. The crude was purified by filtration through DOWEX 1x8 resin and column chromatography (from EtOAc to EtOAc-MeOH 9:1) to give **95** (32 mg, 0.12 mmol, 84% yield) as a white solid.

mp: 45-47 ºC (MeOH).

$[\alpha]_D$: -49.1 (*c* 1.06, MeOH).

IR (ATR) ν 3100-3500, 2963, 1655, 1260, 1021, 792 cm^{-1}.

^{1}H-NMR (400 MHz, MeOD) δ: 7.48 (d, J_{6,CH_3}=1.2 Hz, 1H, H6), 4.24 (q, $J_{3',4'}$=6.5 Hz, $J_{3',4'}$=6.5 Hz, $J_{3',2'}$=6.5 Hz, 1H, H3'), 4.15 (dd, J_{gem}=13.7 Hz, $J_{1''',1'}$=5.2 Hz, 1H, H1'''), 4.12-4.15 (m, 1H, H1''), 4.05 (dd, J_{gem}=13.7 Hz, $J_{1''',1'}$=10.4 Hz, 1H, H1'''), 3.78 (dd, J_{gem}=11.1 Hz, $J_{2'',1''}$=3.7 Hz, 1H, H2''), 3.46 (dd, J_{gem}=11.1 Hz, $J_{2'',1''}$=6.4 Hz, 1H, H2''), 2.65-2.55 (m, 1H, H2'), 2.55-2.45 (m, 1H, H1'), 2.33 (dtd, J_{gem}=11.4 Hz, $J_{4',3'}$=6.5 Hz, $J_{4',1'}$=6.5 Hz, $J_{4',2'}$=2.5 Hz, 1H, H4'), 1.90 (ddd, J_{gem}=11.4 Hz, $J_{4',1'}$=7.8 Hz, $J_{4',3'}$=6.5 Hz, 1H, H4'), 1.86 (d, $J_{CH_3,6}$=1.2 Hz, 3H, CH_3-C5).

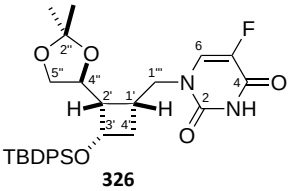
^{13}C-NMR (100 MHz, MeOD) δ: 166.9 (C=O, C4), 153.1 (C=O, C2), 143.6 (CH, C6), 110.7 (C, C5), 70.1 (CH, C1''), 67.1 (CH_2, C2''), 66.1 (CH, C3'), 51.7 (CH_2, C1'''), 46.9 (CH, C2'), 35.2 (CH_2, C4'), 31.4 (CH, C1'), 12.2 (CH_3, *C*H_3-C5).

HRMS (ESI+) calcd for ($[C_{12}H_{18}N_2O_5+Na]^+$) 293.1108, found 293.1106.

COSY, HMBC, HSQC and **NOESY** experiments have been recorded.

4.4 Synthesis of the 5-fluorouracil nucleoside **96**

4.4.1 Synthesis of 1-({(1*R*,2*S*,3*S*)-3-{[*tert*-butyl(diphenyl)silyl]oxy}-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclobutyl}methyl)-5-fluoro-thymine, **326**



326

Compound **320** (78 mg, 0.12 mmol) was dissolved in 2.5 mL of a 33% $MeNH_2$ solution in EtOH. The solution was stirred for 30 min at room temperature. Afterwards, the solvent was evaporated under reduced pressure and the crude was purified by column chromatography (hexane-EtOAc 1:1) to provide **326** (63 mg, 0.11 mmol, 95% yield) as a yellow foam.

$[\alpha]_D$: +52.0 (*c* 1.23, $CHCl_3$).

IR (ATR) ν 3070, 2931, 2857, 1688, 1662, 1372, 1238, 1155, 1109, 1051, 856, 701 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.47 (d, $J_{NH,F}$=5.2 Hz, 1H, NH), 7.70 (d, $J_{6,F}$=5.2 Hz, 1H, H6), 7.60-7.55 (m, 4H, Ph), 7.47-7.34 (m, 6H, Ph), 4.66 (dt, $J_{4'',2'}$=10.9 Hz, $J_{4'',5''}$=6.5 Hz, $J_{4'',5''}$=6.5 Hz, 1H, H4''), 4.41 (dd, J_{gem}=8.6 Hz, $J_{5'',4''}$=6.5, 1H, H5''), 4.18 (dt, $J_{3',4'}$=8.5 Hz, $J_{3',4'}$=7.3 Hz, $J_{3',2'}$=7.3 Hz, 1H, H3'), 3.92 (dd, J_{gem}=14.0 Hz, $J_{1''',1'}$=5.5 Hz, 1H, H1'''), 3.71 (dd, J_{gem}=14.0 Hz, $J_{1''',1'}$=8.0 Hz, 1H, H1'''), 3.69 (dd, J_{gem}=8.6 Hz, $J_{5'',4''}$=6.5 Hz, 1H, H5''), 2.65 (dtd, $J_{2',4''}$=10.9 Hz, $J_{2',3'}$=7.3 Hz, $J_{2',1'}$=7.3 Hz, $J_{2',4'}$=3.7 Hz, 1H, H2'), 2.16-2.04 (m, 1H, H1'), 1.97 (dtd, J_{gem}=10.8 Hz, $J_{4',3'}$=7.3 Hz, $J_{4',1'}$=7.3 Hz, $J_{4',2'}$=3.7 Hz, 1H, H4'), 1.87 (dt, J_{gem}=10.8 Hz, $J_{4',1'}$=10.8 Hz, $J_{4',3'}$=8.5 Hz, 1H, H4'), 1.42 (s, 3H, CH_3-C2''), 1.40 (s, 3H, CH_3-C2''), 1.05 (s, 9H, (CH_3)$_3$C).

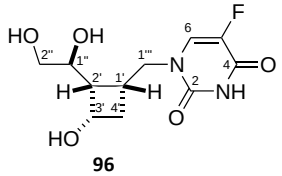
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 157.4 (d, $J_{C,F}$=26.0 Hz, C=O, C4), 149.8 (s, C=O, C2), 139.9 (d, $J_{C,F}$=235.5 Hz, C, C5), 135.7 (s, 2xCH, Ph), 135.5 (s, 2xCH, Ph), 133.4 (s, C, Ph), 133.0 (s, C, Ph), 130.2 (s, CH, Ph), 130.1 (s, CH, Ph), 129.9 (d, $J_{C,F}$=31.5 Hz, CH, C6), 128.0 (s, 2xCH, Ph), 127.9 (s, 2xCH, Ph), 108.4 (s, C, C2''), 72.8 (s, CH, C4''), 70.4 (s, CH_2, C5''), 64.7 (s, CH, C3'), 49.9 (s, CH_2, C1'''), 49.9 (s, CH, C2'), 36.3 (s, CH_2, C4'), 28.4 (s, CH, C1'), 27.0 (s, 3xCH_3, (*C*H_3)$_3$C), 26.8 (s, CH_3, *C*H_3-C2''), 25.7 (s, CH_3, *C*H_3-C2''), 19.0 (s, C, (CH$_3$)$_3$*C*).

^{19}F-NMR (376 MHz, $CDCl_3$) δ: -167.7 (t, $J_{F,NH}$=5.2 Hz, $J_{F,6}$=5.2 Hz).

HRMS (ESI+) calcd for ($[C_{30}H_{37}FN_2O_5Si+Na]^+$) 575.2348, found 575.2353.

COSY, HMBC, HSQC and **NOESY** experiments have been recorded.

4.4.2 Synthesis of 1-({(1*R*,2*R*,3*S*)-2-[(1*S*)-1,2-dihydroxyethyl]-3-hydroxycyclobutyl}methyl)-5-fluoro-thymine, **96**



96

Compound **326** (62 mg, 0.11 mmol) was dissolved in MeOH (4 mL) and *p*-toluenesulfonic acid (21 mg, 0.11 mmol) was added. The solution was heated to reflux temperature and it was allowed to stir overnight. Then, the solution was allowed to cool to room temperature and the solvent was evaporated. The crude was purified by filtration through DOWEX 1x8 resin and column chromatography (from EtOAc to EtOAc-MeOH 9:1) to give **96** (20 mg, 0.07 mmol, 67% yield) as a yellow oil.

$[\alpha]_D$: -36.2 (*c* 0.85, MeOH).

IR (ATR) ν 3500-3100, 2939, 1657, 1371, 1237,1020 cm^{-1}.

^{1}H-NMR (400 MHz, MeOD) δ: 7.89 (d, $J_{6,F}$=6.3 Hz, 1H, H6), 4.23 (q, $J_{3',2'}$=6.6 Hz, $J_{3',4'}$=6.6 Hz, $J_{3',4'}$=6.6 Hz, 1H, H3'), 4.13 (dd, J_{gem}=13.9 Hz, $J_{1''',1'}$=5.6 Hz, 1H, H1'''), 4.14-4.07 (m, 1H, H1''), 4.03 (dd, J_{gem}=13.9 Hz, $J_{1''',1'}$=9.8 Hz, 1H, H1'''), 3.78 (dd, J_{gem}=11.1 Hz, $J_{2'',1''}$=3.7 Hz, 1H, H2''), 3.45 (dd, J_{gem}=11.1 Hz, $J_{2'',1''}$=6.3 Hz, 1H, H2''), 2.59 (dddd, $J_{2',1''}$=11.0 Hz, $J_{2',1'}$=8.8 Hz, $J_{2',3'}$=6.6 Hz, $J_{2',4'}$=2.4 Hz, 1H, H2'), 2.55-2.45 (m, 1H, H1'), 2.37 (dtd, J_{gem}=11.4 Hz, $J_{4',1'}$=6.6 Hz, $J_{4',3'}$=6.6 Hz, $J_{4',2'}$=2.4 Hz, 1H, H4'), 1.89 (ddd, J_{gem}=11.4 Hz, $J_{4',1'}$=8.4 Hz, $J_{4',3'}$=6.6 Hz, 1H, H4').

^{13}C-NMR (100 MHz, MeOD) δ: 159.9 (d, $J_{C,F}$=25.7 Hz, C=O, C4), 151.6 (s, C=O, C2), 141.4 (d, $J_{C,F}$=231.5 Hz, C, C5), 131.6 (d, $J_{C,F}$=33.1 Hz, CH, C6), 70.0 (s, CH, C1''), 67.2 (s, CH_2, C2''), 65.9 (s, CH, C3'), 52.0 (s, CH_2, C1'''), 47.0 (s, CH, C2'), 35.2 (s, CH_2, C4'), 31.1 (s, CH, C1').

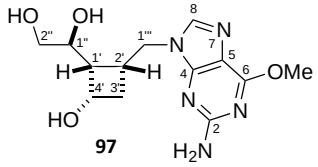
^{19}F-NMR (376 MHz, MeOD) δ: -171.0 (d, $J_{F,6}$=6.3 Hz).

HRMS (ESI+) calcd for ($[C_{11}H_{15}FN_2O_5+Na]^+$) 297.0857, found 297.0854.

COSY, HMBC, HSQC and **NOESY** experiments have been recorded.

4.5 Synthesis of the *O*^{6}-methylguanine nucleoside **97**

4.5.1 Synthesis of (1*S*)-1-{(1*R*,2*R*,4*S*)-2-[(2-amino-6-methoxy-9*H*-purin-9-yl)methyl]-4-hydroxycyclobutyl}-1,2-ethanediol, **97**



97

Compound **324** (106 mg, 0.18 mmol) was dissolved in MeOH (6 mL) and *p*-toluenesulfonic acid (34 mg, 0.18 mmol) was added. The solution was heated to reflux temperature and it was allowed to stir overnight. Then, the solution was allowed to cool to room temperature and the solvent was evaporated. The crude was purified by filtration through DOWEX 1x8 resin and column chromatography (from EtOAc to EtOAc-MeOH 9:1) to give **97** (45 mg, 0.15 mmol, 82% yield) as a white solid.

mp: 155-157 ºC (MeOH).

$[\alpha]_D$: -12.0 (*c* 0.81, MeOH).

IR (ATR) ν 3500-3000, 2922, 2852, 2361, 1641, 1606, 1587, 1483, 1398, 1248, 1066 cm^{-1}.

^{1}H-NMR (400 MHz, MeOD) δ: 7.85 (s, 1H, H8), 4.53 (dd, J_{gem}=13.9 Hz, $J_{1''',2'}$=5.2 Hz, 1H, H1'''), 4.38 (dd, J_{gem}=13.9 Hz, $J_{1''',2'}$=9.8 Hz, 1H, H1'''), 4.24 (dt, $J_{4',1'}$=6.7 Hz, $J_{4',3'}$=6.7 Hz, $J_{4',3'}$=1.3 Hz, 1H, H4'), 4.19 (ddd, $J_{1'',1'}$=10.0 Hz, $J_{1'',2''}$=6.3 Hz, $J_{1'',2''}$=3.8 Hz, 1H, H1''), 4.04 (s, 3H, CH_3O-C6), 3.80 (dd, J_{gem}=11.1 Hz, $J_{2'',1''}$=3.8 Hz, 1H, H2''), 3.49 (dd, J_{gem}=11.1 Hz, $J_{2'',1''}$=6.3 Hz, 1H, H2''), 2.73-2.59 (m, 2H, H1'/H2'), 2.28-2.20 (m, 1H, H3'), 1.86 (ddd, J_{gem}=11.7 Hz, $J_{3',2'}$=7.3 Hz, $J_{3',4'}$=6.7 Hz, 1H, H3').

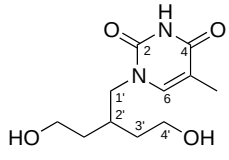
^{13}C-NMR (100 MHz, MeOD) δ: 162.7 (C, C6), 161.7 (C, C2), 155.0 (C, C4), 141.3 (CH, C8), 115.2 (C, C5), 70.0 (CH, C1''), 67.2 (CH_2, C2''), 66.1 (CH, C4'), 54.1 (CH_3, CH_3O-C6), 47.1 (CH_2, C1'''), 46.7 (CH, C1'), 35.4 (CH_2, C3'), 32.2 (CH, C2').

HRMS (ESI+) calcd for ($[C_{13}H_{19}N_5O_4$+Na]$^+$) 332.1329, found 332.1329.

COSY, DEPT-135, HMBC, HSQC and **NOESY** experiments have been recorded.

4.6 Synthesis of the thymine nucleoside **98**

4.6.1 Synthesis of 1-[4-hydroxy-2-(2-hydroxyethyl)butyl]-thymine, **329**



329

Compound **95** (25 mg, 0.09 mmol) was dissolved in a 1:1 mixture of THF/H_2O (2 mL). The solution was cooled to 0 ºC in an ice bath and $NaIO_4$ (26 mg, 0.12 mmol) was added. After 15 min, the bath was removed and the mixture was allowed to stir at room temperature. After about 30 min, THF (2 mL) was added and the solution was cooled to 0 ºC. The white precipitate formed was filtered off and the filtrate was cooled to 0 ºC. Then, $NaBH_4$ (17 mg, 0.44 mmol) was added and the reaction was allowed to stir for 2 h, when it was quenched by the addition of saturated NH_4Cl solution. When the bubbling ceased, some drops of concentrated NH_3 were added and the mixture was evaporated to dryness and purified by column chromatography (from EtOAc to EtOAc-MeOH 9:1) to give **329** (16 mg, 0.07 mmol, 73% yield) as a white solid.

mp: 96-98 ºC (MeOH).

IR (ATR) ν 3461, 3354, 2915, 1668, 1470, 1348, 1226, 1034, 1008, 850, 713 cm^{-1}.

^{1}H-NMR (360 MHz, MeOD) δ: 7.45 (q, J_{6,CH_3}=1.2 Hz, 1H, H6), 3.71 (d, $J_{1',2'}$=10.5 Hz, 2H, H1'), 3.69-3.57 (m, 4H, H4'), 2.10 (dquint, $J_{2',1'}$=10.5 Hz, $J_{2',3'}$=6.7 Hz, 1H, H2'), 1.88 (d, $J_{CH_3,6}$=1.2 Hz, 3H, CH_3-C5), 1.55 (q, $J_{3',2'}$=6.7 Hz, $J_{3',4'}$=6.7 Hz, 2H, H3'), 1.56 (q, $J_{3',2'}$=6.7 Hz, $J_{3',4'}$=6.7 Hz, 2H, H3').

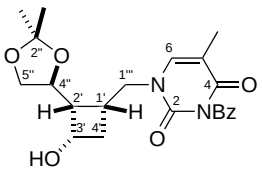
^{13}C-NMR (90 MHz, MeOD) δ: 166.9 (C=O, C4), 153.3 (C=O, C2), 143.5 (CH, C6), 111.0 (C, C5), 60.4 (2xCH_2, C4'), 53.1 (CH_2, C1'), 35.1 (2xCH_2, C3'), 33.3 (CH, C2'), 12.2 (CH_3, *C*H_3-C5).

HRMS (ESI+) calcd for ($[C_{11}H_{18}N_2O_4+Na]^+$) 265.1159, found 265.1159.

COSY, HMBC, HSQC and **NOESY** experiments have been recorded.

4.6.2 Approximation A. *p*-Methoxybenzyl as the 3' protecting group

4.6.2.1 Synthesis of 3-benzoyl-1-({(1*R*,2*R*,3*S*)-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxycyclobutyl}methyl)-thymine, **336**

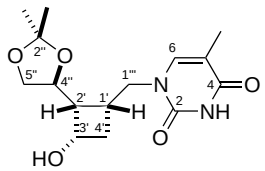


336

To a solution of **319** (205 mg, 0.31 mmol) in THF (5.5 mL), a 1 M solution of TBAF in THF (630 µL, 0.63 mmol) was added. After 2 h, the mixture was evaporated to dryness and the crude was purified by column chromatography (from hexane-EtOAc 1:1 to EtOAc) to afford **336** (129 mg, 0.31 mmol, 99% yield) as a yellow foam.

^{1}H-NMR (250 MHz, $CDCl_3$) δ: 7.91-7.86 (m, 2H, Ph), 7.65-7.59 (m, 1H, Ph), 7.50-7.44 (m, 2H, Ph), 7.38 (q, J_{6,CH_3}=1.2 Hz, 1H, H6), 4.53 (ddd, $J_{4'',2'}$=10.5 Hz, $J_{4'',5''}$=7.0 Hz, $J_{4'',5''}$=6.3 Hz, 1H, H4''), 4.25 (dd, J_{gem}=8.4 Hz, $J_{5'',4''}$=6.3 Hz, 1H, H5''), 4.21 (q, $J_{3',2'}$=7.7 Hz, $J_{3',4'}$=7.7 Hz, $J_{3',4'}$=7.7 Hz, 1H, H3'), 4.00 (dd, J_{gem}=14.1 Hz, $J_{1''',1'}$=7.0 Hz, 1H, H1'''), 3.86 (dd, J_{gem}=14.1 Hz, $J_{1''',1'}$=6.8 Hz, 1H, H1'''), 3.58 (J_{gem}=8.4 Hz, $J_{5'',4''}$=7.0 Hz, 1H, H5''), 2.64 (dddd, $J_{2',4''}$=10.8 Hz, $J_{2',1'}$=7.2 Hz, $J_{2',3'}$=7.2 Hz, $J_{2',4'}$=3.7 Hz, 1H, H2'), 2.48-2.39 (m, 1H, H1'), 2.39-2.30 (m, 1H, H4'), 1.96-1.87 (m, 1H, H4'), 1.92 (d, $J_{CH_3,6}$=1.2 Hz, 3H, C*H*$_3$-C5), 1.40 (s, 3H, C*H*$_3$-C2''), 1.37 (s, 3H, C*H*$_3$-C2'').

4.6.2.2 Synthesis of 1-({(1*R*,2*R*,3*S*)-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxycyclobutyl}methyl)-thymine, **337**

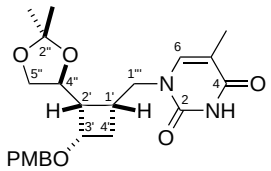


337

Compound **336** (129 mg, 0.31 mmol) was dissolved in a 33% $MeNH_2$ solution in EtOH (6.5 mL). The solution was stirred for 2 h at room temperature. Afterwards, the solvent was evaporated under reduced pressure and the crude was purified by column chromatography (from hexane-EtOAc 1:1 to EtOAc) to give **337** (96 mg, 0.31 mmol, 99% yield) as a white foam.

^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.38-9.25 (m, 1H, NH), 7.25 (q, J_{6,CH_3}=0.9 Hz, 1H, H6), 4.58 (ddd, $J_{4'',2'}$=10.6 Hz, $J_{4'',5''}$=6.8 Hz, $J_{4'',5''}$=6.6 Hz, 1H, H4''), 4.32-4.19 (m, 2H, H5''/H3'), 4.02 (dd, J_{gem}=14.0, $J_{1''',1'}$=7.3 Hz, 1H, H1'''), 3.81 (dd, J_{gem}=14.0, $J_{1''',1'}$=6.5 Hz, 1H, H1'''), 3.60 (dd, J_{gem}=8.2 Hz, $J_{5'',4''}$=7.2 Hz, 1H, H5''), 2.65 (dddd, $J_{2',4''}$=10.6 Hz, $J_{2',1'}$=7.2 Hz, $J_{2',3'}$=7.2 Hz, $J_{2',4'}$=3.6 Hz, 1H, H2'), 2.52-2.26 (m, 3H, H1'/H4'/OH), 1.97 (q, J_{gem}=8.6 Hz, $J_{4',1'}$=8.6 Hz, $J_{4',3'}$=8.6 Hz, 1H, H4'), 1.88 (d, $J_{CH_3,6}$=0.9 Hz, 3H, CH_3-C5), 1.39 (s, 3H, CH_3-C2''), 1.37 (s, 3H, CH_3-C2'').

4.6.2.3 1-({(1*R*,2*R*,3*S*)-3-(4-methoxybenzyl)oxy-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclobutyl}methyl)-thymine, **333**



333

PMBOC(=NH)CCl_3 (810 µL, 3.87 mmol) was added to a solution of **337** (120 mg, 0.39 mmol) in dry THF (5.0 mL) and the solution was cooled to 0 ºC in an ice bath. Afterwards, $BF_3{\cdot}OEt_2$ (20 µL, 0.16 mmol) was added, the ice bath was removed and the mixture was allowed to stir overnight at room temperature. Then, the reaction was quenched by the addition of saturated $NaHCO_3$ solution. Layers were separated and the aqueous one was extracted with EtOAc (3x2 mL). The organic extracts were washed with brine, dried over Na_2SO_4 and evaporated to dryness. The crude was purified by column chromatography (hexane-EtOAc 1:1) to give **333** (124 mg, 0.29 mmol, 75% yield) as an ochre solid.

mp: 157-159 ºC (hexane-EtOAc).

$[\alpha]_D$: +46.0 (*c* 1.83, $CHCl_3$).

IR (ATR) ν 3200, 3074, 2925, 1681, 1511, 1459, 1371, 1244, 1157, 1049, 819 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.28 (s, 1H, H6), 7.18 (d, J_{Ar}=8.4 Hz, 2H, Ar), 6.86 (d, J_{Ar}=8.4 Hz, 2H, Ar), 4.55 (dt, $J_{4'',2'}$=11.3 Hz, $J_{4'',5''}$=6.8 Hz, $J_{4'',5''}$=6.8 Hz, 1H, H4''), 4.35 (d, J_{gem}=11.4 Hz, 1H, CH_2-Ar), 4.27-4.22 (m, 1H, H5''), 4.23 (d, J_{gem}=11.4 Hz, 1H, CH_2-Ar), 3.99-3.88 (m, 2H, H1'''/H3'), 3.87-3.80 (m, 1H, H1'''), 3.58 (dd, J_{gem}=8.4 Hz, $J_{5'',4''}$=6.8 Hz, 1H, H5''), 2.74-2.65 (m, 1H, H2'), 2.45-2.30 (m, 2H, H1'/H4'), 1.96-1.90 (m, 1H, H4'), 1.89 (s, 3H, CH_3-C5), 1.37 (s, 6H, 2xCH_3-C2'').

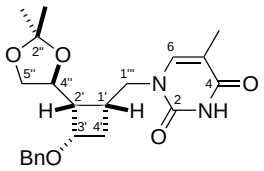
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 164.1 (C=O, C4), 159.4 (C, Ar), 151.0 (C=O, C2), 141.6 (CH, C6), 130.1 (C, Ar), 129.1 (2xCH, Ar), 114.0 (2xCH, Ar), 109.7 (C, C5), 108.3 (C, C2''), 72.8 (CH, C4''), 70.2 (2xCH_2, C5''/*C*H_2-Ar), 69.1 (CH, C3'), 55.4 (CH_3, O*C*H_3), 50.1 (CH_2, C1'''), 48.2 (CH, C2'), 33.5 (CH_2, C4'), 29.0 (CH, C1'), 27.0 (CH_3, *C*H_3-C2''), 25.8 (CH_3, *C*H_3-C2''), 12.4 (CH_3, *C*H_3-C5).

HRMS (ESI+) calcd for ($[C_{23}H_{30}N_2O_6+Na]^+$) 453.1996, found 453.2005.

COSY, HMBC, HSQC and **NOESY** experiments have been recorded.

4.6.3 Approximation B. Benzyl as the 3' protecting group

4.6.3.1 Synthesis of 1-({(1*R*,2*R*,3*S*)-3-(benzyloxy)-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclobutyl}methyl)-thymine, **338**



338

A suspension of ^{t}BuOK (111 mg, 0.94 mmol) in dry THF (3 mL) was stirred for 15 min at room temperature. Afterwards, a solution of **337** (97 mg, 0.31 mmol) in dry THF (3 mL) was added dropwise over the ^{t}BuOK suspension. The mixture was allowed to stir for 30 min at room temperature. At the same time, BnBr (114 µL, 0.94 mmol) was added dropwise over a suspension of NaI (142 mg, 0.94 mmol) in dry THF (2 mL) and the mixture was allowed to stir for 30 min at room temperature. At this point, the BnI solution was added dropwise over the initial solution and the mixture was allowed to stir for 30 min. The reaction was quenched by the addition of saturated solution of NH_4Cl. The crude was diluted with EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc, and the organic extracts were washed with saturated solution of $NaHCO_3$ and brine. The organic layer was then dried over $MgSO_4$ and evaporated to dryness. Purification of the crude by column chromatography (hexane-EtOAc 1:1) provided **338** (97 mg, 0.24 mmol, 78% yield) as a white solid.

mp: 156-158 ºC (hexane-EtOAc).

$[\alpha]_D$: +52.4 (*c* 0.96, $CHCl_3$).

IR (ATR) ν 3205, 2930, 1681, 1456, 1373, 1323, 1255, 1158, 1111, 1050, 907, 849, 762, cm^{-1}.

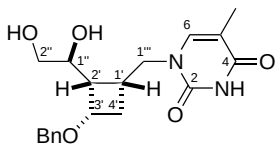
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.99 (br s, 1H, NH), 7.36-7.24 (m, 6H, H6/Ph), 4.58 (dt, $J_{4'',2'}$=10.7 Hz, $J_{4'',5''}$=6.8 Hz, $J_{4'',5''}$=6.8 Hz, 1H, H4''), 4.43 (d, J_{gem}=12.0 Hz, 1H, CH_2-Ph), 4.31 (d, J_{gem}=12.0 Hz, 1H, CH_2-Ph), 4.27 (dd, J_{gem}=7.9 Hz, $J_{5'',4''}$=6.8 Hz, 1H, H5''), 3.97 (dd, J_{gem}=14.0 Hz, $J_{1''',1'}$=6.8 Hz, 1H, H1'''), 3.95 (q, $J_{3',2'}$=7.1 Hz, $J_{3',4'}$=7.1 Hz, $J_{3',4'}$=7.1 Hz, 1H, H3'), 3.85 (dd, J_{gem}=14.0 Hz, $J_{1''',1'}$=6.8 Hz, 1H, H1'''), 3.61 (dd, J_{gem}=7.9 Hz, $J_{5'',4''}$=6.8 Hz, 1H, H5''), 2.72 (dddd, $J_{2',4''}$=10.7 Hz, $J_{2',1'}$=7.4 Hz, $J_{2',3'}$=7.1 Hz, $J_{2',4'}$=3.2 Hz, 1H, H2'), 2.47-2.32 (m, 2H, H1'/H4'), 1.98-1.89 (m, 1H, H4'), 1.90 (d, $J_{CH_3,6}$=1.2 Hz, 3H, CH_3-C5), 1.38 (s, 6H, 2xCH_3-C2'').

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 164.0 (C=O, C4), 151.0 (C=O, C2), 141.5 (CH, C6), 138.1 (C, Ph), 128.6 (2xCH, Ph), 127.9 (CH, Ph), 127.5 (2xCH, Ph), 109.8 (C, C5), 108.4 (C, C2''), 72.9 (CH, C4''), 70.6 (CH_2, *C*H_2-Ph), 70.2 (CH_2, C5''), 69.6 (CH, C3'), 50.1 (CH_2, C1'''), 48.3 (CH, C2'), 33.5 (CH_2, C4'), 29.1 (CH, C1'), 27.1 (CH_3, *C*H_3-C2''), 25.8 (CH_3, *C*H_3-C2''), 12.4 (CH_3, *C*H_3-C5).

HRMS (ESI+) calcd for ($[C_{22}H_{28}N_2O_5+Na]^+$) 423.1890, found 423.1886.

COSY, HMBC, HSQC and **NOESY** experiments have been recorded.

4.6.3.2 Synthesis of 1-({(1*R*,2*S*,3*S*)-3-(benzyloxy)-2-[(1*S*)-1,2-dihydroxyethyl]cyclobutyl}methyl)-thymine, **339**



339

To a solution of **338** (78 mg, 0.19 mmol) in MeOH (8 mL), *p*-toluenesulfonic acid (36 mg, 0.19 mmol) was added. The solution was allowed to stir for 4 h at room temperature. Then, the crude was evaporated to dryness, filtered through DOWEX 1x8 resin and purified by column chromatography (from EtOAc to EtOAc-MeOH 9:1) to afford **339** (63 mg, 0.17 mmol, 90% yield) as a white solid.

mp: 66-68 ºC (MeOH).

$[\alpha]_D$: -36.4 (*c* 1.21, MeOH).

IR (ATR) ν 3500-3100, 2923, 1660, 1454, 1347, 1209, 1139, 1060, 1026, 740 cm^{-1}.

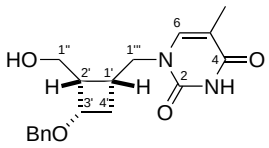
^{1}H-NMR (400 MHz, MeOD) δ: 7.39 (q, J_{6,CH_3}=1.0 Hz, 1H, H6), 7.36-7.22 (m, 5H, Ph), 4.52 (d, J_{gem}=11.8 Hz, 1H, CH_2-Ph), 4.31 (d, J_{gem}=11.8 Hz, 1H, CH_2-Ph), 4.19-4.10 (m, 3H, 2xH1'''/H1''), 4.06 (ddd, $J_{3',4'}$=11.8 Hz, $J_{3',2'}$=7.4 Hz, $J_{3',4'}$=2.6 Hz, 1H, H3'), 3.81 (dd, J_{gem}=11.3 Hz, $J_{2'',1''}$=3.0 Hz, 1H, H2''), 3.43 (dd, J_{gem}=11.3 Hz, $J_{2'',1''}$=6.5 Hz, 1H, H2''), 2.74 (ddddd, $J_{2',1''}$=10.5 Hz, $J_{2',3'}$=7.4 Hz, $J_{2',1'}$=7.2 Hz, $J_{2',4'}$=2.2 Hz, $J_{2',4'}$=1.2 Hz, 1H, H2'), 2.62-2.50 (m, 1H, H1'), 2.29-2.20 (m, 1H, H4'), 1.98 (dddd, J_{gem}=7.5 Hz, $J_{4',1'}$=6.3 Hz, $J_{4',3'}$=2.6, $J_{4',2'}$=1.2 Hz, 1H, H4'), 1.85 (d, $J_{CH_3,6}$=1.0 Hz, 1H, H6).

^{13}C-NMR (100 MHz, MeOD) δ: 166.9 (C=O, C4), 153.2 (C=O, C2), 143.4 (CH, C6), 139.7 (C, Ph), 129.4 (2xCH, Ph), 128.8 (2xCH, Ph), 128.6 (CH, Ph), 110.8 (C, C5), 73.4 (CH, C3'), 71.1 (CH_2, CH_2-Ph), 69.9 (CH, C1''), 67.0 (CH_2, C2''), 51.4 (CH_2, C1'''), 45.2 (CH, C2'), 32.4 (CH, C1'), 32.2 (CH_2, C4'), 12.2 (CH_3, CH_3-C5).

HRMS (ESI+) calcd for ($[C_{19}H_{24}N_2O_5+Na]^+$) 383.1577, found 383.1585.

COSY, HMBC, HSQC and **NOESY** experiments have been recorded.

4.6.3.3 Synthesis of 1-{[(1*R*,2*S*,3*S*)-3-(benzyloxy)-2-(hydroxymethyl)cyclobutyl]methyl}-thymine, **340**



340

Compound **339** (80 mg, 0.22 mmol) was dissolved in 9 mL of a 1:1 mixture of THF/H_2O. The solution was cooled to 0 ºC in an ice bath and $NaIO_4$ (59 mg, 0.28 mmol) was added. After 15 min, the bath was removed and the mixture was allowed to stir at room temperature. After about 30 min, THF (4.5 mL) was added and the solution was cooled to 0 ºC. The white precipitate formed was filtered off and the filtrate was cooled to 0 ºC. Then, $NaBH_4$ (41 mg, 1.08 mmol) was added and the reaction was allowed to stir for 2 h, when it was quenched by the addition of saturated NH_4Cl solution. When the bubbling ceased, some drops of concentrated NH_3 were added and the mixture was evaporated to dryness and purified by column chromatography (from EtOAc to EtOAc-MeOH 9:1) to give **340** (56 mg, 0.17 mmol, 77% yield) as a white foam.

$[\alpha]_D$: -57.9 (*c* 1.21, MeOH).

IR (ATR) ν 3500-3000, 2930, 2361, 1661, 1468, 1352, 1252, 1206, 1016, 738 cm^{-1}.

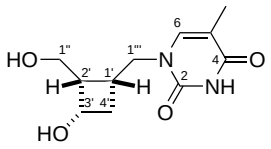
^{1}H-NMR (400 MHz, MeOD) δ: 7.47 (q, J_{6,CH_3}=0.8 Hz, 1H, H6), 7.34-7.23 (m, 5H, Ph), 4.43 (s, 2H, CH_2-Ph), 4.06 (q, $J_{3',2'}$=7.3 Hz, $J_{3',4'}$=7.3 Hz, $J_{3',4'}$=7.3 Hz, 1H, H3'), 4.00-3.91 (m, 3H, 2xH1''/H1'''), 3.85 (dd, J_{gem}=13.8 Hz, $J_{1''',1'}$=9.1 Hz, 1H, H1'''), 2.86-2.74 (m, 1H, H2'), 2.45-2.35 (m, 1H, H1'), 2.35-2.25 (m, 1H, H4'), 2.00 (dt, J_{gem}=10.2 Hz, $J_{4',1'}$=10.0 Hz, $J_{4',3'}$=7.5 Hz, 1H, H4'), 1.85 (d, $J_{CH_3,6}$=0.8 Hz, 3H, CH_3-C5).

^{13}C-NMR (100 MHz, MeOD) δ: 166.9 (C=O, C4), 153.0 (C=O, C2), 143.4 (CH, C6), 139.6 (C, Ph), 129.4 (2xCH, Ph), 128.9 (2xCH, Ph), 128.7 (CH, Ph), 110.8 (C, C5), 71.8 (CH_2/CH, *C*H_2-Ph/C3'), 59.0 (CH_2, C1''), 50.3 (CH_2, C1'''), 45.6 (CH, C2'), 34.0 (CH_2, C4'), 30.0 (CH, C1'), 12.2 (CH_3, *C*H_3-C5).

HRMS (ESI+) calcd for ($[C_{18}H_{22}N_2O_4+Na]^+$) 353.1472, found 353.1470.

COSY, HMBC, HSQC and **NOESY** experiments have been recorded.

4.6.3.4 Synthesis of 1-{[(1*R*,2*S*,3*S*)-3-hydroxy-2-(hydroxymethyl)cyclobutyl]methyl}-thymine, **98**



98

To a solution of **340** (55 mg, 0.17 mmol) in MeOH (2 mL), Pd/C (9 mg) was added. The mixture was heated to reflux temperature and ammonium formate (129 mg, 2.04 mmol) was added in portions throughout the course of the reaction. After 6 h, the mixture was allowed to cool to room temperature and filtered through Celite. Evaporation of the solvent afforded **98** (39 mg, 0.16 mmol, 98% yield) as a white solid.

mp: 164-166 ºC (MeOH).

$[\alpha]_D$: -50.8 (*c* 1.22, MeOH).

IR (ATR) ν 3500-3000, 2926, 1705, 1664, 1432, 1351, 1236, 1055 cm^{-1}.

^{1}H-NMR (400 MHz, MeOD) δ: 7.48 (q, J_{6,CH_3}=1.0 Hz, 1H, H6), 4.26 (q, $J_{3',2'}$=7.6 Hz, $J_{3',4'}$=7.6 Hz, $J_{3',4'}$=7.6 Hz, 1H, H3'), 3.97 (d, $J_{1'',2'}$=7.4 Hz, 2H, 2xH1''), 3.95 (dd, J_{gem}=13.8 Hz, $J_{1''',1'}$=5.7 Hz, 1H, H1'''), 3.85 (dd, J_{gem}=13.8 Hz, $J_{1''',1'}$=8.8 Hz, 1H, H1'''), 2.74-2.65 (m, 1H, H2'), 2.42-2.30 (m, 2H, H1'/H4'), 2.01-1.90 (m, 1H, H4'), 1.86 (d, $J_{CH_3,6}$=1.0 Hz, 3H, C*H*$_3$-C5).

^{13}C-NMR (100 MHz, MeOD) δ: 166.8 (C=O, C4), 153.0 (C=O, C2), 143.3 (CH, C6), 110.9 (C, C5), 65.2 (CH, C3'), 59.3 (CH_2, C1''), 50.3 (CH_2, C1'''), 46.5 (CH, C2'), 36.1 (CH_2, C4'), 29.8 (CH, C1'), 12.2 (CH_3, *C*H_3-C5).

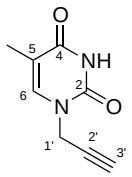
HRMS (ESI+) calcd for ($[C_{11}H_{16}N_2O_4+Na]^+$) 263.1002, found 263.1001.

COSY, HMBC, HSQC and **NOESY** experiments have been recorded.

5. SYNTHESIS OF DOUBLE-HEADED NUCLEOSIDES

5.1 Synthesis of the building blocks

5.1.1 Synthesis of 1-(prop-2-yn-1-yl)thymine, **354**



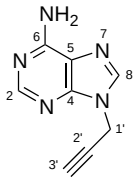
354

To a solution of thymine (1.01 g, 8.01 mmol) in anhydrous DMF (75 mL), K_2CO_3 (1.16 g, 8.39 mmol) was added. Then, propargyl bromide (2.68 ml, 24.0 mmol) was added dropwise over a period of 30 min and the solution was stirred at room temperature for 3 h. Evaporation of the solvent and purification by column chromatography (CH_2Cl_2-MeOH 9:1) afforded **354** (513 mg, 3.13 mmol, 39% yield) as a white solid.

^{1}H-NMR (400 MHz, DMSO) δ: 11.36 (br s, 1H, N*H*), 7.56 (d, J_{6,CH_3}=1.2 Hz, 1H, H6), 4.47 (d, $J_{1',3'}$=2.5 Hz, 2H, 2xH1'), 3.38 (t, $J_{3',1'}$=2.5 Hz, $J_{3',1'}$=2.5 Hz, 1H, H3'), 1.76 (d, $J_{CH_3,6}$=1.2 Hz, 3H, C*H*$_3$-C5).

^{13}C-NMR (100 MHz, DMSO) δ: 164.1 (C=O, C4), 150.4 (C=O, C2), 140.1 (CH, C6), 109.4 (C, C5), 78.7 (C, C2'), 75.6 (CH, C3'), 36.3 (CH_2, C1'), 11.9 (CH_3, *C*H_3-C5).

5.1.2 Synthesis of 9-(prop-2-yn-1-yl)adenine, **355**



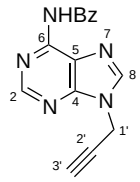
355

To a solution of adenine (502 mg, 3.71 mmol) in anhydrous DMF (50 mL), K_2CO_3 (513 mg, 3.71 mmol) was added. Then, propargyl bromide (1.25 mL, 11.1 mmol) was added and the solution was allowed to stir overnight at room temperature. Evaporation of the solvent and purification by column chromatography (from 5 to 7% MeOH in CH_2Cl_2) afforded **355** (448 mg, 2.59 mmol, 70% yield) as a white solid.

^{1}H-NMR (400 MHz, DMSO) δ: 8.19 (s, 1H, H2), 8.18 (s, 1H, H8), 7.30 (br s, 2H, NH_2), 5.03 (d, $J_{1',3'}$=2.5 Hz, 2H, 2xH1'), 3.45 (t, $J_{3',1'}$=2.5 Hz, $J_{3',1'}$=2.5 Hz, 1H, H3').

^{13}C-NMR (100 MHz, DMSO) δ: 156.0 (C, C6), 152.7 (CH, C2), 149.1 (C, C4), 140.1 (CH, C8), 118.5 (C, C5), 78.3 (C, C2'), 75.8 (CH, C3'), 32.3 (CH_2, C1').

5.1.3 Synthesis of *N*-(9-(prop-2-yn-1-yl)-9*H*-purin-6-yl)benzamide, **356**



356

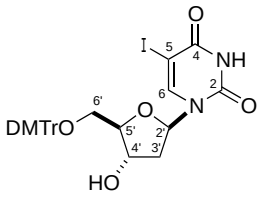
Benzoyl chloride (0.54 mL, 4.61 mmol) was added dropwise to an ice-cooled suspension of **355** (363 mg, 2.10 mmol) in anhydrous pyridine (8 mL). The solution was allowed to warm to room temperature and stirred overnight. Methanol (1 mL) was added and the mixture was evaporated to dryness *in vacuo*. The crude obtained was redissolved in an ice-cooled saturated solution of NH_3 in MeOH (70 mL) and stirred for 30 min. Then, the mixture was concentrated, diluted with EtOAc and water was added. The layers were separated and the aqueous phase was washed with EtOAc (3x10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness to afford **356** (283 mg, 1.02 mmol, 49% yield) as a white solid.

^{1}H-NMR (400 MHz, DMSO) δ: 11.23 (br s, 1H, NH), 8.79 (s, 1H, H2), 8.55 (s, 1H, H8), 8.08-8.04 (m, 2H, Bz), 7.67-7.62 (m, 1H, Bz), 7.58-7.53 (m, 2H, Bz), 5.20 (d, $J_{1',3'}$=2.5 Hz, 2H, 2xH1'), 3.54 (t, $J_{3',1'}$=2.5 Hz, $J_{3',1'}$=2.5 Hz, 1H, H3').

^{13}C-NMR (100 MHz, DMSO) δ: 165.7 (C=O, Bz), 151.9/151.7 (2xC, C4/C6), 150.3 (CH, C2), 143.9 (CH, C8), 133.4 (C, Bz), 132.4 (CH, Bz), 128.5 (2xCH, Bz), 128.4 (2xCH, Bz), 125.2 (C, C5), 77.9 (C, C2'), 76.2 (CH, C3'), 32.7 (CH_2, C1').

HMBC and **HSQC** spectra have been registered.

5.1.4 Synthesis of 1-((2*R*,4*S*,5*R*)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)-5-iodouracil, **358**



358

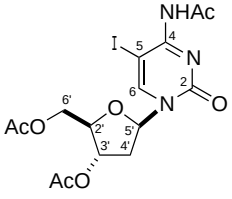
5-Iodo-2'-deoxyuridine (1.03 g, 2.91 mmol) was dissolved in anhydrous pyridine (28 mL). DMTrCl (1.18 g, 3.48 mmol) was added and the solution was allowed to stir 3 h at room temperature. After that time, EtOH (2 mL) was added, the solution was diluted with EtOAc (100 mL) and washed with a saturated solution of $NaHCO_3$ (50 mL). Layers were separated and the aqueous layer was extracted with EtOAc (3x15 mL). The organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness. The crude was purified by column chromatography (from 0 to 5% MeOH in CH_2Cl_2, containing 1% of pyridine) to give **358** (1.52 g, 2.32 mmol, 80% yield) as a yellow foam.

^{1}H-NMR (400 MHz, DMSO) δ: 11.73 (br s, 1H, NH), 8.01 (s, 1H, H6), 7.43-7.14 (m, 9H, DMT), 6.91 (s, 2H, DMT), 6.88 (s, 2H, DMT), 6.10 (t, $J_{2',3'}$=6.8 Hz, $J_{2',3'}$=6.8 Hz, 1H, H2'), 5.30 (d, $J_{OH,4'}$=4.5 Hz, 1H, OH), 4.23 (m, 1H, H4'), 3.90 (m, 1H, H5'), 3.74 (s, 6H, 2xOCH_3), 3.18 (m, 2H, 2xH6'), 2.24 (dd, J_{gem}=13.5 Hz, $J_{3',2'}$=6.8 Hz, 1H, H3'), 2.16 (ddd, J_{gem}=13.5 Hz, $J_{3',2'}$=6.8 Hz, $J_{3',4'}$=3.4 Hz, 1H, H3').

^{13}C-NMR (100 MHz, DMSO) δ: 160.5 (C=O, C4), 158.1 (C, DMT), 158.1 (C, DMT), 150.0 (C=O, C2), 144.7 (C, DMT), 144.2 (CH, C6), 135.5 (C, DMT), 135.4 (C, DMT), 129.7 (4xCH, DMT), 127.9 (2xCH, DMT), 127.7 (2xCH, DMT), 126.7 (CH, DMT), 113.3 (4xCH, DMT), 85.8 (CH, C5'), 85.8 (C, DMT), 84.9 (CH, C2'), 70.5 (CH, C4'), 69.8 (C, C5), 63.7 (CH_2, C6'), 55.1 (2xCH_3, OCH_3), 39.9 (CH, C3').

HSQC spectrum has been registered.

5.1.5 Synthesis of (2*R*,3*S*,5*R*)-5-(4-acetamido-5-iodo-2-oxopyrimidin-1(2*H*)-yl)-2-(acetoxymethyl)tetrahydrofuran-3-yl acetate, **360**



360

To an ice-cooled solution of 5-iodo-2'-deoxycytidine (500 mg, 1.42 mmol) in anhydrous pyridine (14 mL), Ac_2O (441 µL, 4.67 mmol) was added dropwise. After the addition, cooling was removed and the reaction was allowed to stir at room temperature overnight. Then, the solution was diluted with CH_2Cl_2 (15 mL) and washed with a saturated solution of $NaHCO_3$ (15 mL). Layers were separated and the aqueous phase was extracted with CH_2Cl_2 (4x8 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness.

Purification of the crude by column chromatography (from 0 to 5% MeOH in CH_2Cl_2) led to **360** (533 mg, 1.11 mmol, 78% yield) as a white foam.

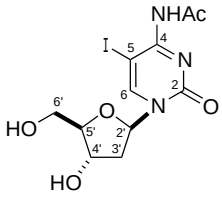
^{1}H-NMR (400 MHz, DMSO) δ: 9.48 (br s, 1H, NH), 8.27 (br s, 1H, H6), 6.07 (t, $J_{5',4'}$=6.8 Hz, $J_{5',4'}$=6.8 Hz, 1H, H5'), 5.20 (br s, 1H, H3'), 4.27 (m, 3H, 2xH6'/H2'), 2.44 (m, 2H, 2xH4'), 2.23 (s, 3H, NHCOCH_3), 2.09 (s, 3H, OCOCH_3), 2.07 (s, 3H, OCOCH_3).

^{13}C-NMR (100 MHz, DMSO) δ: 170.0 (C=O, O*C*OCH$_3$), 170.0 (C=O, O*C*OCH$_3$), 169.8 (C=O, NH*C*OCH$_3$), 161.8 (C, C4), 152.9 (C=O, C2), 150.2 (CH, C6), 87.1 (CH, C5'), 82.3 (CH, C2'), 74.0 (CH, C3'), 63.5 (CH_2, C6'), 61.2 (C, C5), 37.3 (CH_2, C4'), 24.5 (CH_3, NHCO*C*H$_3$), 20.7 (2xCH_3, OCO*C*H$_3$).

HRMS (ESI+) calcd for ([$C_{15}H_{18}IN_3O_7$+Na]$^+$) 502.0082, found 502.0084.

HMBC and **HSQC** spectra have been registered.

5.1.6 Synthesis of *N*-(1-((2*R*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-iodo-2-oxo-1,2-dihydropyrimidin-4-yl)acetamide, **361**



361

A 2 M solution of NaOH (1.44 mL, 2.87 mmol) was added dropwise to an ice-cooled solution of **360** (344 mg, 0.72 mmol) in a 2:1 mixture of 1,4-dioxane and H_2O (22.5 mL). After 30 min, a saturated solution of NH_4Cl (11 mL) was added and the solvent was removed under reduced pressure. The crude was purified by column chromatography (from 0 to 10% MeOH in CH_2Cl_2) affording **361** (178 mg, 0.45 mmol, 63% yield) as a pale yellow foam.

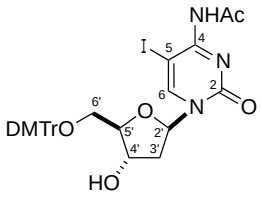
^{1}H-NMR (400 MHz, DMSO) δ: 9.43 (br s, 1H, NH), 8.71 (s, 1H, H6), 6.03 (t, $J_{2',3'}$=5.9 Hz, $J_{2',3'}$=5.9 Hz, 1H, H2'), 5.26 (d, $J_{OH,4'}$=4.5 Hz, 1H, OH), 5.21 (t, $J_{OH,6'}$=4.6 Hz, $J_{OH,6'}$=4.6 Hz, 1H, OH), 4.23 (m, 1H, H4'), 3.85 (q, $J_{5',6'}$=3.3 Hz, $J_{5',6'}$=3.3 Hz, $J_{5',4'}$=3.3 Hz, 1H, H5'), 3.68 (ddd, J_{gem}=12.1 Hz, $J_{6',OH}$=4.6 Hz, $J_{6',5'}$=3.3 Hz, 1H, H6'), 3.57 (ddd, J_{gem}=12.1 Hz, $J_{6',OH}$=4.6 Hz, $J_{6',5'}$=3.3 Hz, 1H, H6'), 2.29 (m, 1H, H3'), 2.22 (s, 3H, NHCOCH_3), 2.10 (m, 1H, H3').

^{13}C-NMR (100 MHz, DMSO) δ: 169.8 (C=O, NH*C*OCH$_3$), 161.6 (C, C4), 153.0 (C=O, C2), 150.6 (CH, C6), 87.9 (CH, C5'), 86.5 (CH, C2'), 69.2 (CH, C4'), 60.8 (C, C5), 60.3 (CH_2, C6'), 41.0 (CH_2, C3'), 24.4 (CH_3, NHCO*C*H$_3$).

HRMS (ESI+) calcd for ([$C_{11}H_{14}IN_3O_5$+Na]$^+$) 417.9871, found 417.9875.

COSY, HMBC and **HSQC** spectra have been registered.

5.1.7 Synthesis of *N*-(1-((2*R*,4*S*,5*R*)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)-5-iodo-2-oxo-1,2-dihydropyrimidin-4-yl)acetamide, **362**



362

DMTrCl (218 mg, 0.64 mmol) was added to a solution of **361** (212 mg, 0.54 mmol) in anhydrous pyridine (6 mL) and the mixture was allowed to stir for 3 h. EtOH (0.5 mL) was added, the solution was diluted with EtOAc (20 mL) and washed with a saturated solution of $NaHCO_3$ (10 mL). Layers were separated and the aqueous phase was extracted with EtOAc (3x3 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The crude was purified by column chromatography (from 0 to 5% MeOH in CH_2Cl_2, containing 1% of pyridine) to give **362** (176 mg, 0.25 mmol, 47% yield) as a white foam.

^{1}H-NMR (400 MHz, DMSO) δ: 9.42 (br s, 1H, NH), 8.30 (s, 1H, H6), 7.42-7.20 (m, 9H, DMT), 6.91 (s, 2H, DMT), 6.89 (s, 2H, DMT), 6.06 (t, $J_{2',3'}$=6.4 Hz, $J_{2',3'}$=6.4 Hz, 1H, H2'), 5.33 (br s, 1H, OH), 4.20 (m, 1H, H4'), 3.99 (m, 1H, H5'), 3.74 (s, 6H, 2xOCH_3), 3.21 (m, 2H, H6'), 2.36 (m, 1H, H3'), 2.24 (s, 3H, NHCOCH_3), 2.17 (m, 1H, H3').

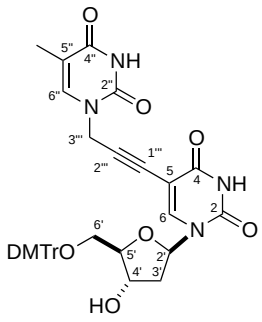
^{13}C-NMR (100 MHz, DMSO) δ: 169.8 (C=O, NH*C*OCH_3), 161.7 (C, C4), 158.1 (2xC, DMT), 152.9 (C=O, C2), 149.5 (CH, C6), 144.7 (C, DMT), 135.4 (C, DMT), 135.4 (C, DMT), 129.7 (4xCH, DMT), 128.0 (2xCH, DMT), 127.6 (2xCH, DMT), 126.7 (CH, DMT), 113.3 (2xCH, DMT), 86.9 (CH, C2'), 86.4 (CH, C5'), 85.9 (C, DMT), 70.4 (CH, C4'), 63.4 (CH_2, C6'), 61.1 (C, C5), 55.0 (2xCH_3, O*C*H_3), 40.9 (CH_2, C3'), 24.5 (CH_3, NHCO*C*H_3).

HRMS (ESI+) calcd for ([$C_{32}H_{32}IN_3O_7$+Na]$^+$) 720.1178, found 720.1157.

HMBC and **HSQC** spectra have been registered.

5.2 Synthesis of the double-headed nucleosides **341**-**344**

5.2.1 Synthesis of 1-((2*R*,4*S*,5*R*)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)-5-(3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)prop-1-yn-1-yl)pyrimidine-2,4(1*H*,3*H*)-dione, **341**



341

A solution of **358** (146 mg, 0.22 mmol) and **354** (40 mg, 0.24 mmol) in a mixture of DMF (2.4 mL) and Et_3N (1.2 mL) was added over $Pd(PPh_3)_2Cl_2$ (4 mol%) and CuI (4 mol%). The solution was stirred for 45 min at 70 ºC, and after that time, it was diluted with EtOAc (15 mL) and washed with a saturated solution of NaCl (15 mL). Layers were separated and the aqueous phase was extracted with EtOAc (4x4 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness. The crude was purified by column chromatography (from 0 to 5% MeOH in CH_2Cl_2, containing 1% of pyridine) affording **341** (105 mg, 0.15 mmol, 68% yield) as a white foam.

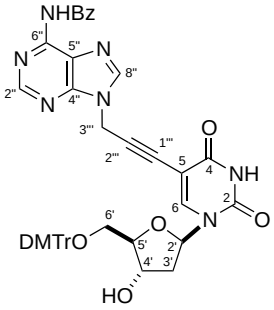
^{1}H-NMR (400 MHz, DMSO) δ: 11.72 (br s, 1H, NH), 11.37 (br s, 1H, NH), 7.99 (s, 1H, H6), 7.43-7.18 (m, 10H, DMT/H6''), 6.90 (s, 2H, DMT), 6.88 (s, 2H, DMT), 6.09 (t, $J_{2',3'}$=6.4 Hz, $J_{2',3'}$=6.4 Hz, 1H, H2'), 5.33 (d, $J_{OH,4'}$=3.3 Hz, 1H, OH), 4.50 (s, 2H, 2xH3'''), 4.27 (br s, 1H, H4'), 3.91 (br s, 1H, H5'), 3.73 (s, 6H, 2xOCH_3), 3.24 (dd, J_{gem}=10.1 Hz, $J_{6',5'}$=4.9 Hz, 1H, H6'), 3.10 (d, J_{gem}=10.1 Hz, 1H, H6'), 2.29 (m, 1H, H3'), 2.19 (m, 1H, H3'), 1.70 (s, 3H, CH_3-C5'').

^{13}C-NMR (100 MHz, DMSO) δ: 164.1 (C=O, C4''), 161.6 (C=O, C4), 158.1 (2xC, DMT), 150.3 (C=O, C2''), 149.3 (C=O, C2), 144.8 (C, DMT), 143.9 (CH, C6), 139.6 (CH, C6''), 135.6 (C, DMT), 135.3 (C, DMT), 129.7 (2xCH, DMT), 129.7 (2xCH, DMT), 127.9 (2xCH, DMT), 127.5 (2xCH, DMT), 126.7 (CH, DMT), 113.3 (2xCH, DMT), 113.2 (2xCH, DMT), 109.2 (C, C5''), 97.6 (C, C5), 86.6 (C, C2'''), 85.9 (C, DMT), 85.9 (CH, C5'), 85.2 (CH, C2'), 77.0 (C, C1'''), 70.4 (CH, C4'), 63.7 (CH_2, C6'), 55.0 (2xCH_3, OCH_3), 39.9 (CH_2, C3'), 36.9 (CH_2, C3'''), 11.9 (CH_3, CH_3-C5).

HRMS (ESI+) calcd for ($[C_{38}H_{36}N_4O_9+Na]^+$) 715.2375, found 715.2367.

COSY, HMBC and **HSQC** spectra have been registered.

5.2.2 Synthesis of *N*-(9-(3-(1-((2*R*,4*S*,5*R*)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)prop-2-yn-1-yl)-9*H*-purin-6-yl)benzamide, **342**



342

A solution of **358** (211 mg, 0.32 mmol) and **356** (98 mg, 0.35 mmol) in a mixture of DMF (3.2 mL) and Et_3N (1.6 mL) was added over $Pd(PPh_3)_2Cl_2$ (4 mol%) and CuI (4 mol%). The solution was stirred for 1.5 h at 70 ºC, and after that time, it was diluted with EtOAc (20 mL) and washed with a saturated solution of NaCl (20 mL). Layers were separated and the aqueous phase was extracted with EtOAc (4x5 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness. The crude was purified by column chromatography (from 0 to 5% MeOH in CH_2Cl_2, containing 1% of pyridine) affording **342** (151 mg, 0.19 mmol, 58% yield) as a pale yellow foam.

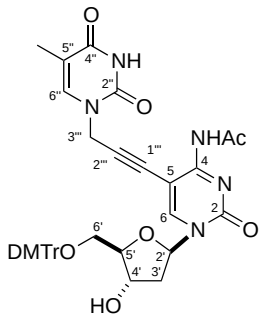
^{1}H-NMR (400 MHz, DMSO) δ: 11.73 (br s, 1H, NH), 11.20 (br s, 1H, NH), 8.76 (s, 1H, H2''), 8.40 (s, 1H, H8''), 8.07 (s, 1H, Bz), 8.05 (s, 1H, Bz), 8.01 (s, 1H, H6), 7.68-7.13 (m, 12H, DMT/Bz), 6.89 (s, 2H, DMT), 6.87 (s, 2H, DMT), 6.10 (t, $J_{2',3'}$=6.5 Hz, $J_{2',3'}$=6.5 Hz, 1H, H2'), 5.33 (d, $J_{OH,4'}$=4.3 Hz, 1H, OH), 5.19 (s, 2H, H3'''), 4.26 (m, 1H, H4'), 3.91 (m, 1H, H5'), 3.71 (s, 6H, 2xOCH_3), 3.25 (dd, J_{gem}=9.9 Hz, $J_{6',5'}$=5.4 Hz, 1H, H6'), 3.08 (d, J_{gem}=9.9 Hz, 1H, H6'), 2.30 (m, 1H, H3'), 2.20 (m, 1H, H3').

^{13}C-NMR (100 MHz, DMSO) δ: 165.6 (C=O, Bz), 161.5 (C=O, C4), 158.1 (2xC, DMT), 151.9 (C, C4''), 151.7 (CH, C2''), 150.3 (C, C6''), 149.3 (C=O, C2), 144.8 (C, DMT), 144.1 (CH, C8''), 143.6 (CH, C6), 135.6 (C, DMT), 135.3 (C, DMT), 133.4 (C, Bz), 132.4 (CH, Bz), 129.7 (2xCH, DMT), 129.7 (2xCH, DMT), 128.5 (4xCH, Bz), 127.9 (2xCH, DMT), 127.5 (2xCH, DMT), 126.6 (CH, DMT), 125.2 (C, C5''), 113.2 (2xCH, DMT), 113.2 (2xCH, DMT), 97.4 (C, C5), 85.8 (C, C2'''), 85.8 (CH, C5'), 85.8 (C, DMT), 85.2 (CH, C2'), 77.4 (C, C1'''), 70.3 (CH, C4'), 63.8 (CH_2, C6'), 55.0 (2xCH_3, OCH_3), 39.8 (CH_2, C3'), 33.5 (CH_2, C3''').

HRMS (ESI+) calcd for ($[C_{45}H_{39}N_7O_8$+Na$]^+$) 828.2753, found 828.2747.

HMBC and **HSQC** spectra have been registered.

5.2.3 Synthesis of *N*-(1-((2*R*,4*S*,5*R*)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)-5-(3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)prop-1-yn-1-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)acetamide, **343**



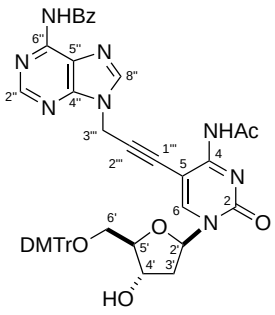
343

A solution of **362** (183 mg, 0.26 mmol) and **354** (53 mg, 0.32 mmol) in a mixture of DMF (3 mL) and Et_3N (1.5 mL) was added over $Pd(PPh_3)_2Cl_2$ (4 mol%) and CuI (4 mol%). The solution was stirred for 30 min at 70 ºC, and after that time, it was diluted with EtOAc (15 mL) and washed with a saturated solution of NaCl (15 mL). Layers were separated and the aqueous phase was extracted with EtOAc (4x4 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness. The crude was purified by column chromatography (from 0 to 5% MeOH in CH_2Cl_2, containing 1% of pyridine) affording **343** (81 mg, 0.11 mmol, 42% yield) as a white foam.

^{1}H-NMR (400 MHz, DMSO) δ: 11.36 (br s, 1H, NH), 8.26 (s, 1H, H6), 7.46 (s, 1H, H6''), 7.41-7.17 (m, 9H, DMT), 6.88 (m, 4H, DMT), 6.04 (t, $J_{2',3'}$=6.3 Hz, $J_{2',3'}$=6.3 Hz, 1H, H2'), 5.35 (d, $J_{OH,4'}$=4.0 Hz, 1H, OH), 4.51 (s, 2H, 2xH3'''), 4.27 (m, 1H, H4'), 4.01 (m, 1H, H5'), 3.73 (s, 6H, 2xOCH_3), 3.24 (dd, J_{gem}=10.8 Hz, $J_{6',5'}$=5.0 Hz, 1H, H6'), 3.13 (dd, J_{gem}=10.8 Hz, $J_{6',5'}$=2.3 Hz, 1H, H6'), 2.38 (m, 1H, H3'), 2.28 (s, 3H, NHCOCH_3), 2.21 (m, 1H, H3'), 1.71 (s, 3H, CH_3-C5'').

HRMS (ESI+) calcd for ($[C_{40}H_{39}N_5O_9+H]^+$) 734.2821, found 734.2799.

5.2.4 Synthesis of *N*-(9-(3-(4-acetamido-1-((2*R*,4*S*,5*R*)-5-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-4-hydroxytetrahydrofuran-2-yl)-2-oxo-1,2-dihydropyrimidin-5-yl)prop-2-yn-1-yl)-9*H*-purin-6-yl)benzamide, **344**



344

A solution of **362** (148 mg, 0.21 mmol) and **356** (65 mg, 0.23 mmol) in a mixture of DMF (2.5 mL) and Et_3N (1.25 mL) was added over $Pd(PPh_3)_2Cl_2$ (4 mol%) and CuI (4 mol%). The solution was stirred for 1.5 h at 70 ºC, and after that time, it was diluted with EtOAc (12 mL) and washed with a saturated solution of NaCl (12 mL). Layers were separated and the aqueous phase was extracted with EtOAc (4x3 mL). The combined organic extracts were dried over $MgSO_4$, filtered and evaporated to dryness. The crude was purified by column chromatography (from 0 to 5% MeOH in CH_2Cl_2, containing 1% of pyridine) affording **344** (66 mg, 0.08 mmol, 37% yield) as a yellow foam.

^{1}H-NMR (400 MHz, DMSO) δ: 11.20 (br s, 1H, NH), 9.64 (br s, 1H, NH), 8.78 (s, 1H, H2''), 8.47 (s, 1H, H8''), 8.31 (s, 1H, H6), 8.06 (s, 1H, Bz), 8.05 (s, 1H, Bz), 7.68-7.11 (m, 12H, DMT/Bz), 6.87 (m, 2H, DMT), 6.85 (m, 2H, DMT), 6.05 (t, $J_{2',3'}$=6.1 Hz, $J_{2',3'}$=6.1 Hz, 1H, H2'), 5.36 (d, $J_{OH,4'}$=4.5 Hz, 1H, OH), 5.18 (s, 2H, 2xH3'''), 4.29 (m, 1H, H4'), 4.02 (m, 1H, H5'), 3.70 (s, 6H, 2xOCH_3), 3.25 (dd, J_{gem}=10.4 Hz, $J_{6',5'}$=4.8 Hz, 1H, H6'), 3.13 (dd, J_{gem}=10.4 Hz, $J_{6',5'}$=2.1 Hz, 1H, H6'), 2.38 (m, 1H, H3'), 2.34 (s, 3H, NHCOCH_3), 2.23 (m, 1H, H3').

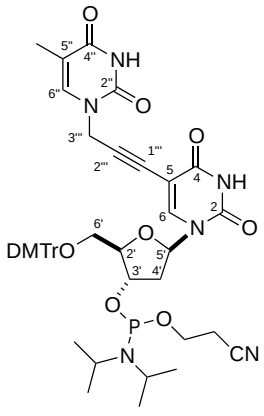
^{13}C-NMR (100 MHz, DMSO) δ: 170.6 (C=O, Ac), 165.6 (C=O, Bz), 161.2 (C=O, C4), 158.1 (2xC, DMT), 152.3 (C=O, C2), 152.0 (C, C4'')), 151.8 (CH, C2''), 150.3 (C, C6''), 147.3 (CH, C6), 144.7 (C, DMT), 143.8 (CH, C8''), 135.5 (C, DMT), 135.2 (C, DMT), 133.4 (C, Bz), 132.4 (CH, Bz), 129.7 (2xCH, DMT), 129.6 (2xCH, DMT), 128.5 (2xCH, Bz), 128.5 (2xCH, Bz), 127.9 (2xCH, DMT), 127.5 (2xCH, DMT), 126.6 (CH, DMT), 125.3 (C, C5''), 113.3 (2xCH, DMT), 113.2 (2xCH, DMT), 91.8 (C, C5), 89.3(C, C2'''), 87.1 (CH, C2'), 86.3 (CH, C5'), 85.9 (C, DMT), 76.2 (C, C1'''), 70.1 (CH, C4'), 63.4 (CH_2, C6'), 55.0 (2xCH_3, OCH_3), 40.9 (CH_2, C3'), 33.9 (CH_2, C3'''), 25.4 (CH_3, NHCOCH_3).

HRMS (ESI+) calcd for ([$C_{47}H_{42}N_8O_8$+H]$^+$) 847.3199, found 847.3199.

HMBC and **HSQC** spectra have been registered.

5.3 Synthesis of phosphoramidites **364** and **365**

5.3.1 Synthesis of (2*R*,3*S*,5*R*)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-5-(5-(3-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)prop-1-yn-1-yl)-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite, **364**



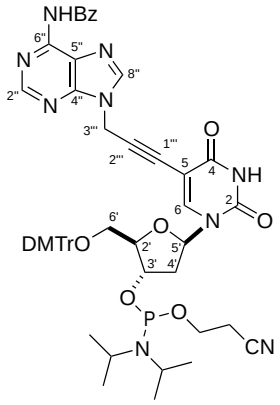
364

Compound **341** (100 mg, 0.14 mmol) was co-evaporated with CH_3CN (2x4 mL) and redissolved in anhydrous CH_3CN (1.8 mL). DIPEA (500 µL, 2.87 mmol) and *N*,*N*-diisopropylamino-β-cyanoethylphosphinochloridite (64 µL, 0.29 mmol) were added and the mixture was stirred at room temperature for 1 h. EtOH (1 mL) was added and the solvent was removed under reduced pressure. Purification of the crude by column chromatography (from 0 to 3% MeOH in CH_2Cl_2, containing 1% of pyridine) gave **364** (108 mg, 0.12 mmol, 84% yield) as a white foam.

^{31}P-NMR (162 MHz, $CDCl_3$) δ: 149.07, 148.77.

HRMS (ESI+) calcd for ([$C_{47}H_{53}N_6O_{10}P$+Na]$^+$) 915.3453, found 915.3455.

5.3.2 Synthesis of (2*R*,3*S*,5*R*)-5-(5-(3-(6-benzamido-9*H*-purin-9-yl)prop-1-yn-1-yl)-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)tetrahydrofuran-3-yl (2-cyanoethyl) diisopropylphosphoramidite, **365**



365

Compound **342** (110 mg, 0.14 mmol) was co-evaporated with CH_3CN (2x4 mL) and redissolved in anhydrous CH_3CN (2 mL). DIPEA (476 µL, 2.73 mmol) and *N*,*N*-diisopropylamino-β-cyanoethylphosphinochloridite (60 µL, 0.27 mmol) were added and the mixture was stirred at room temperature for 1 h. EtOH (1 mL) was added and the solvent was removed under reduced pressure. Purification of the crude by column chromatography (from 0 to 5% MeOH in CH_2Cl_2, containing 1% of pyridine) gave **365** (114 mg, 0.11 mmol, 83% yield) as a pale yellow foam.

^{31}P-NMR (162 MHz, $CDCl_3$) δ: 149.09, 148.82.

HRMS (ESI+) calcd for ($[C_{54}H_{56}N_9O_9P+Na]^+$) 1028.3832, found 1028.3802.

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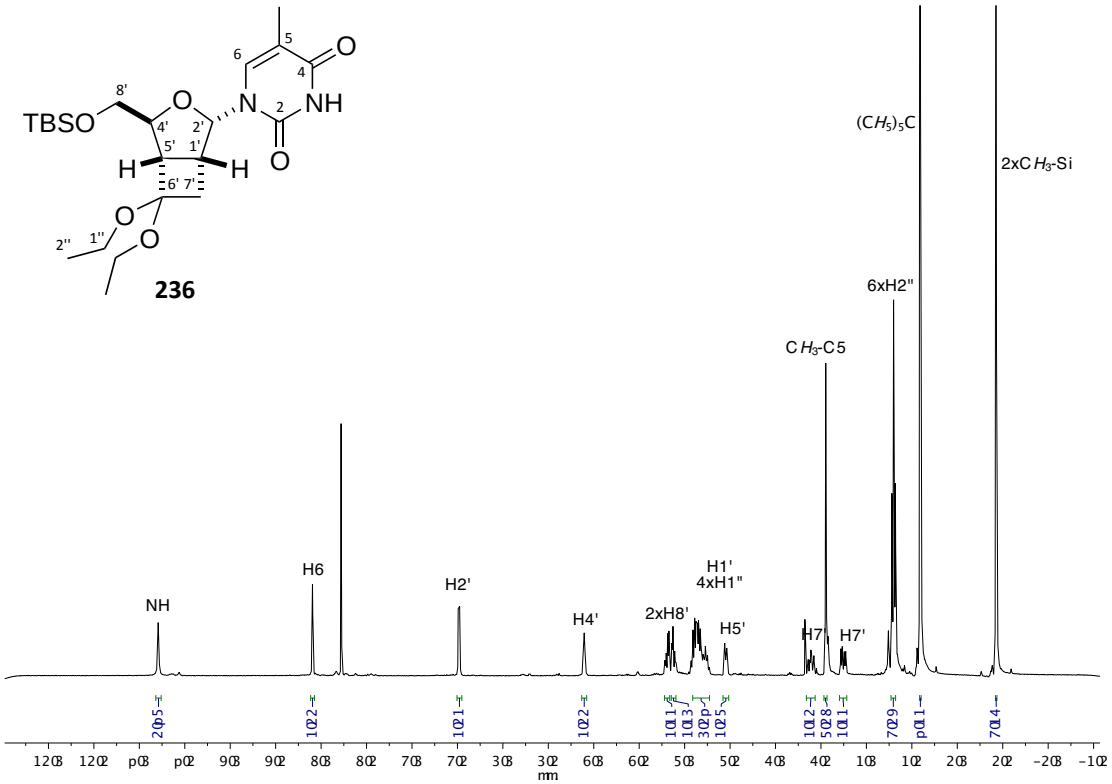
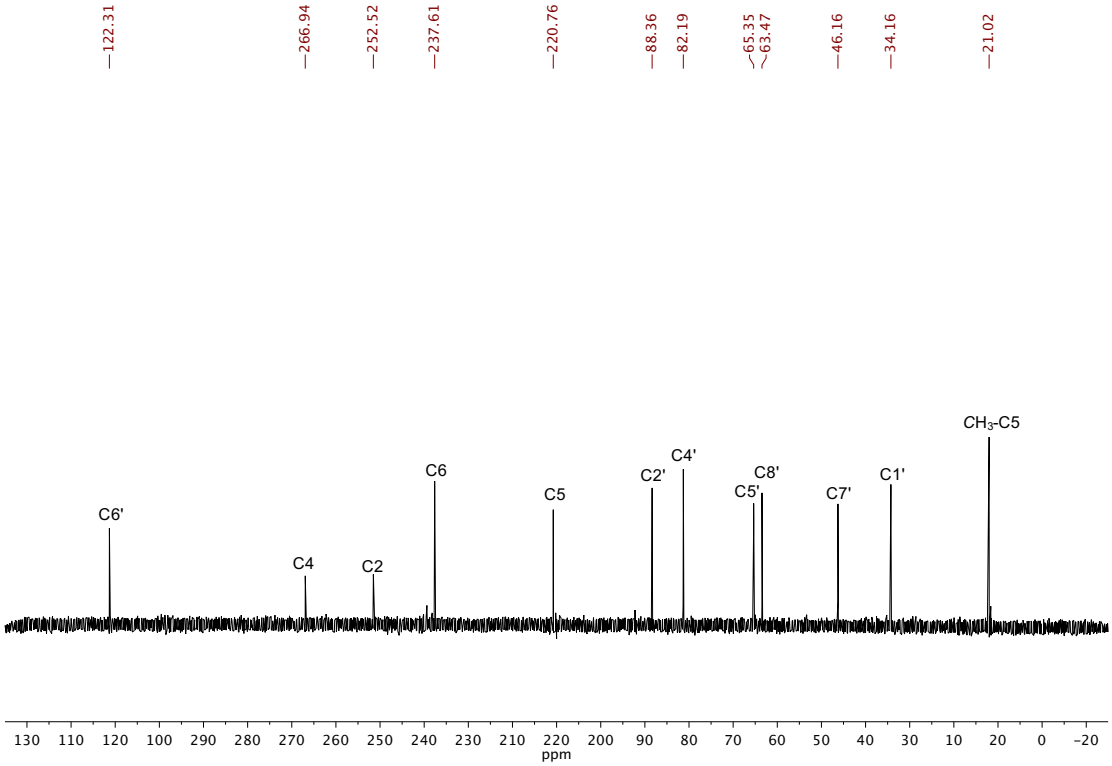
IX. ^{1}H- and ^{13}C-NMR of selected compounds



^{1}H-NMR (250 MHz, $CDCl_3$)



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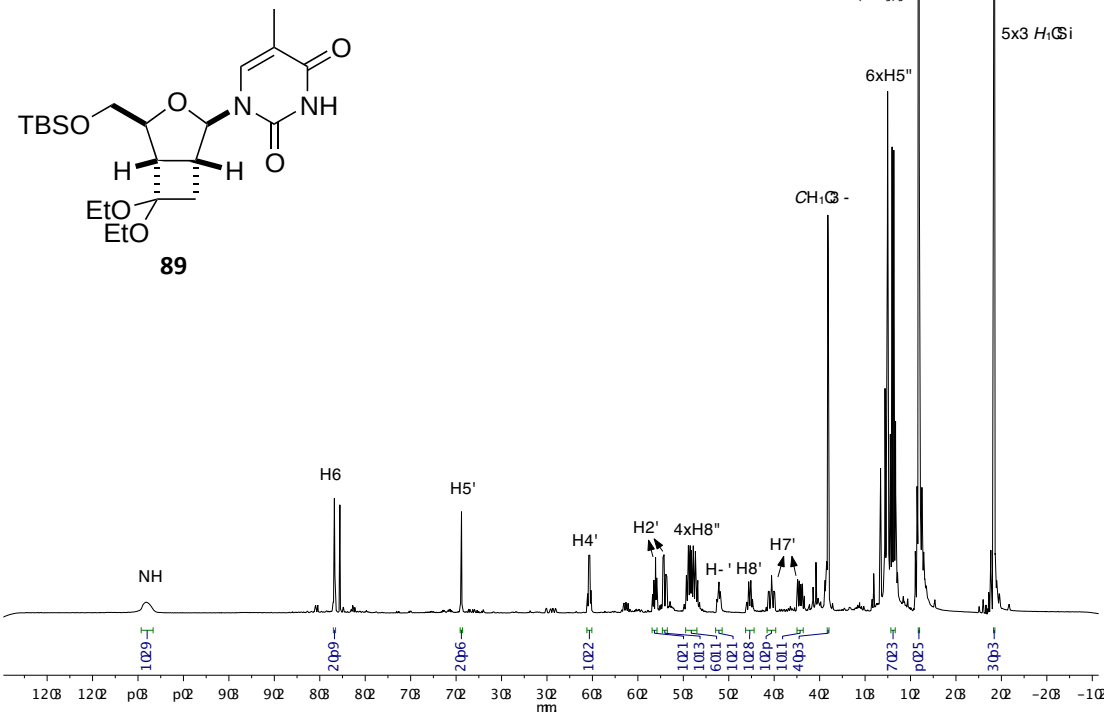

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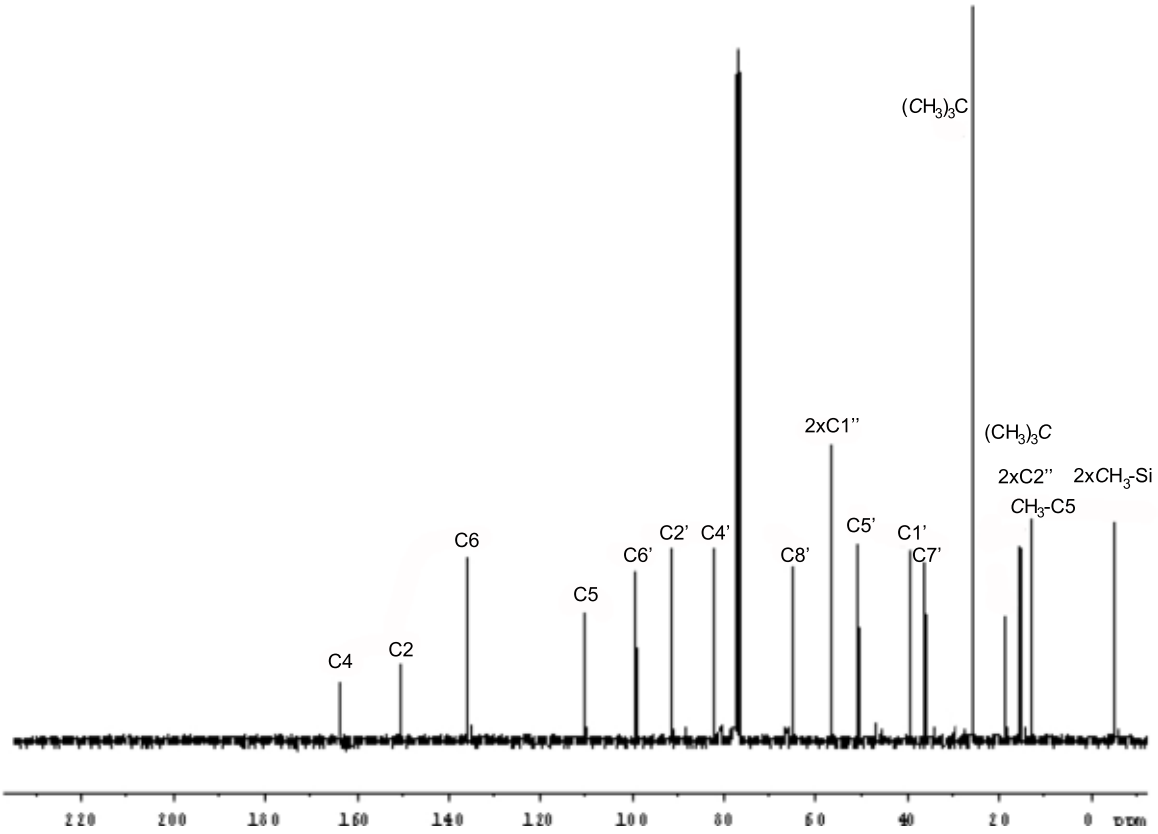

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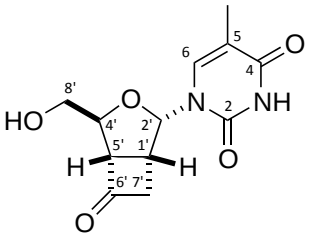

237

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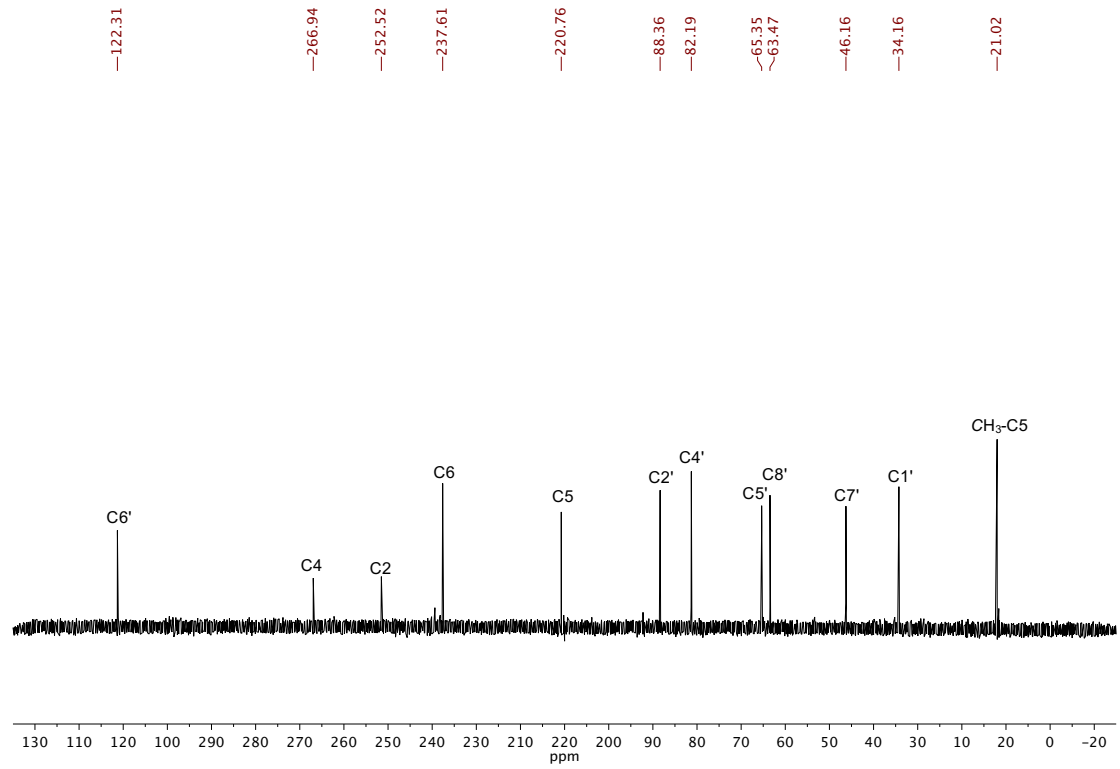

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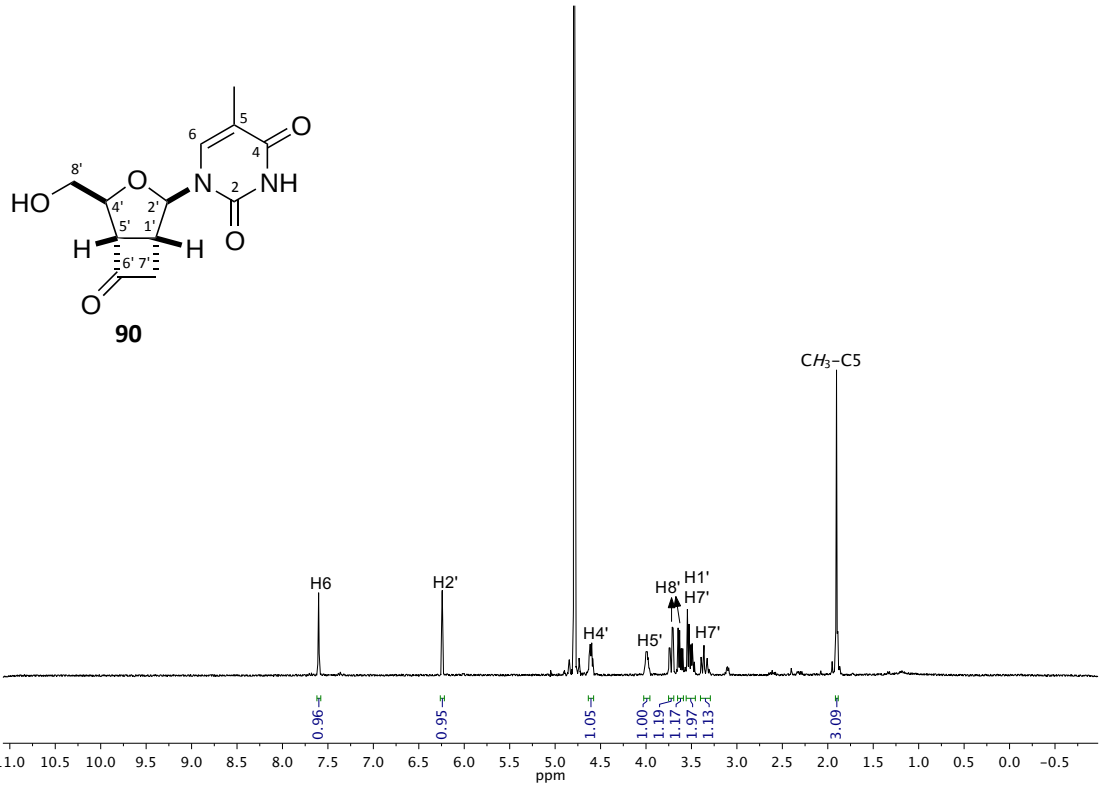

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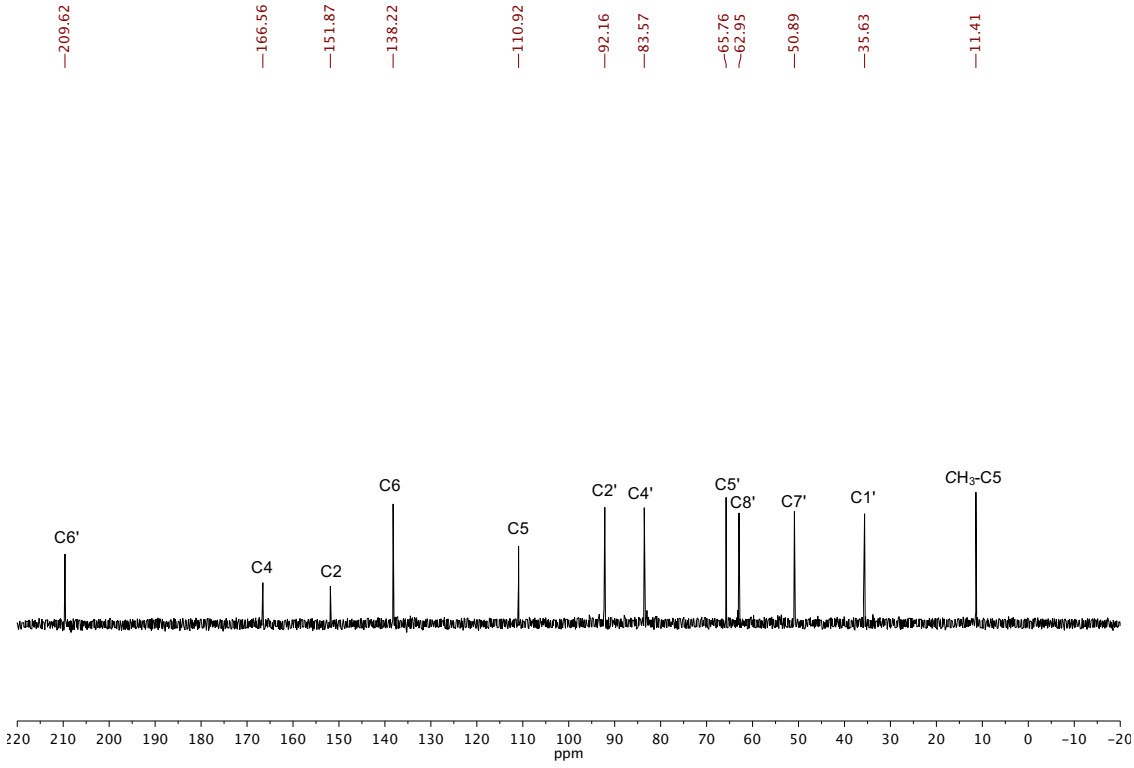

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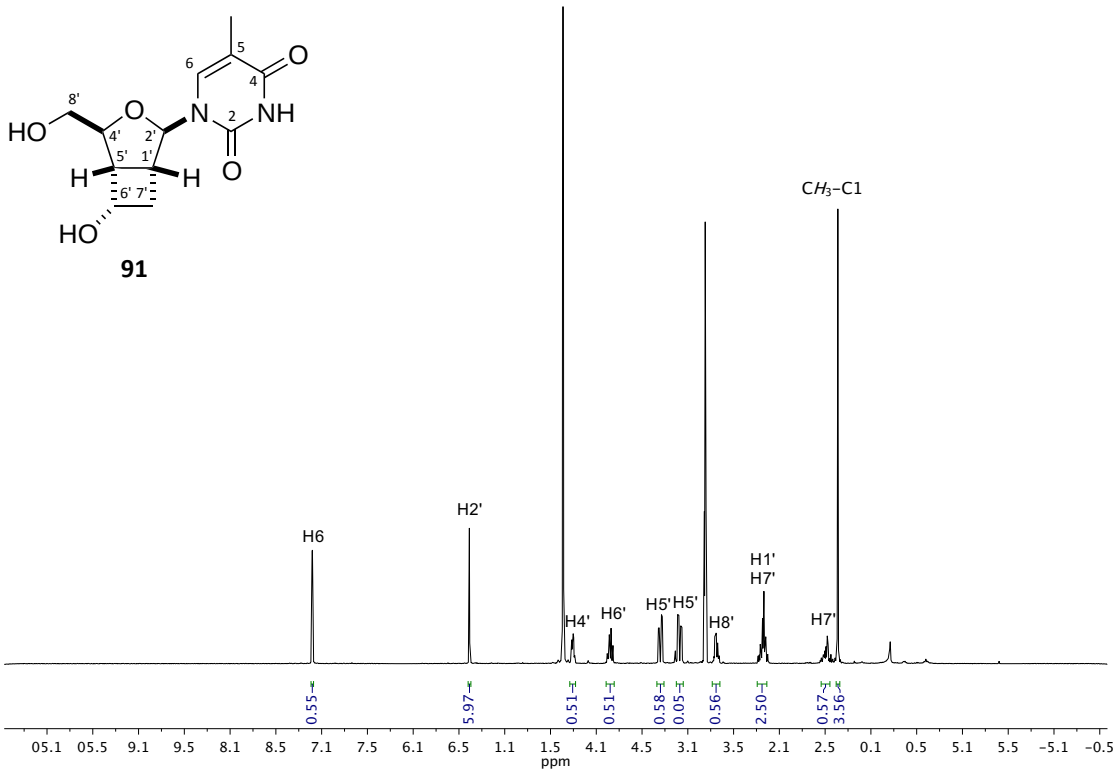

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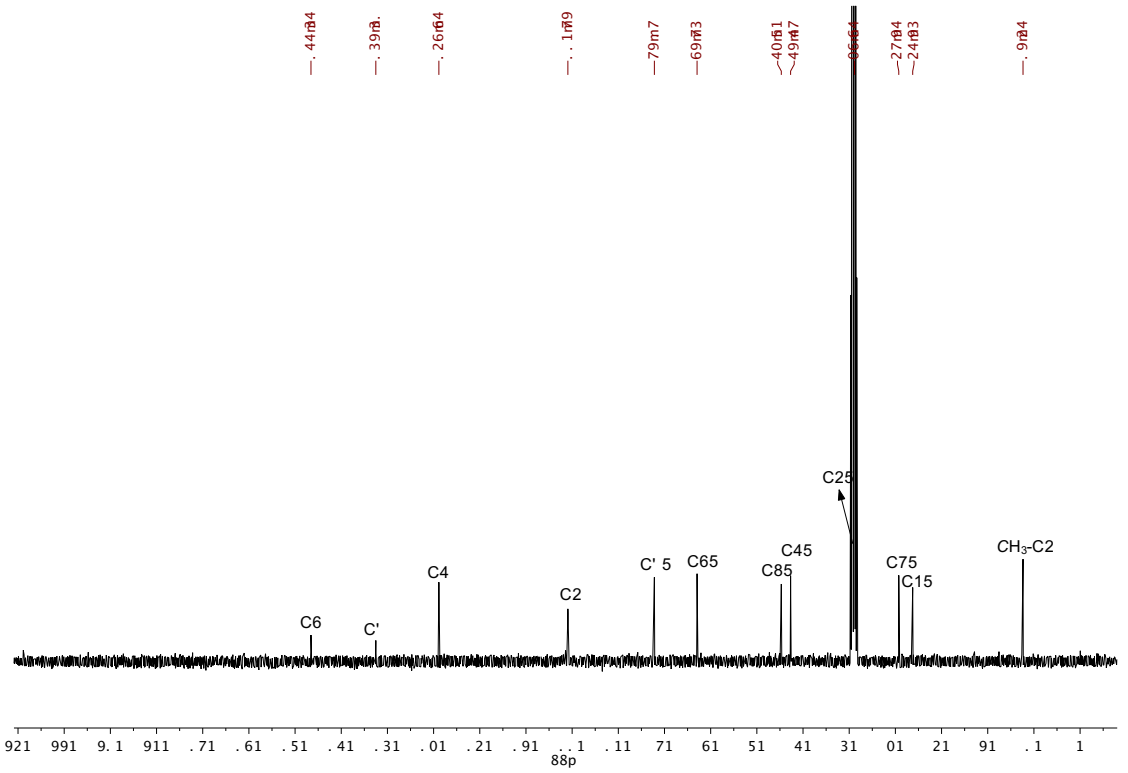

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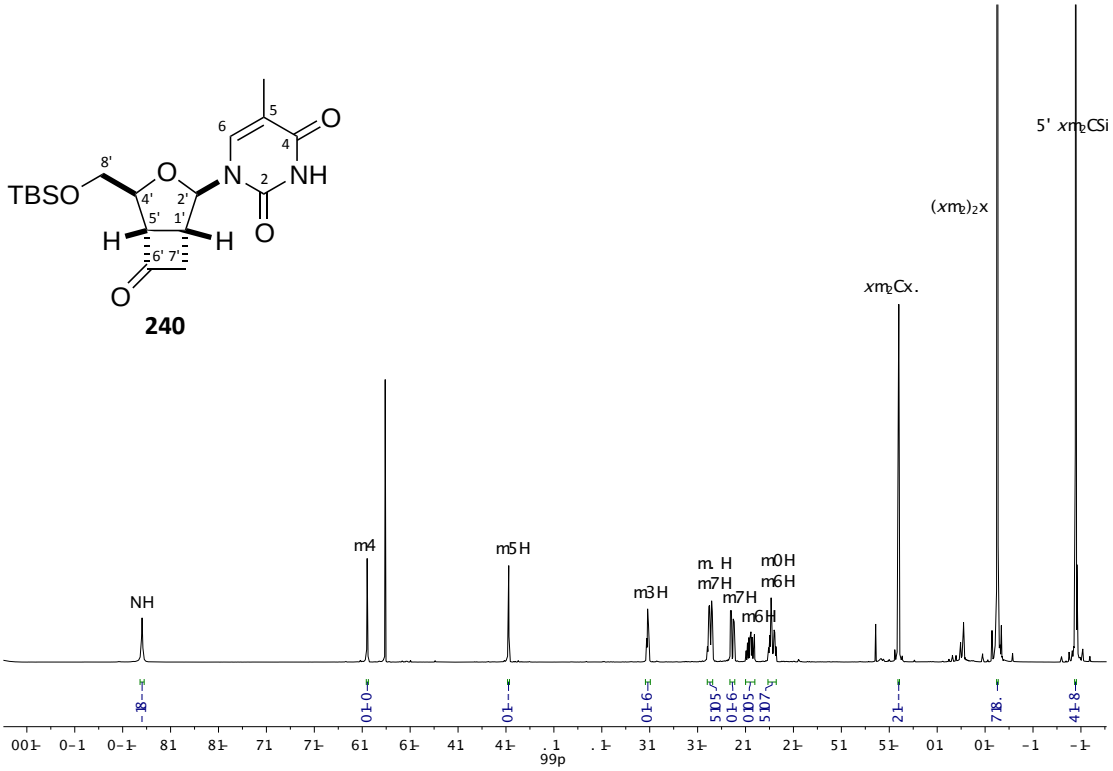

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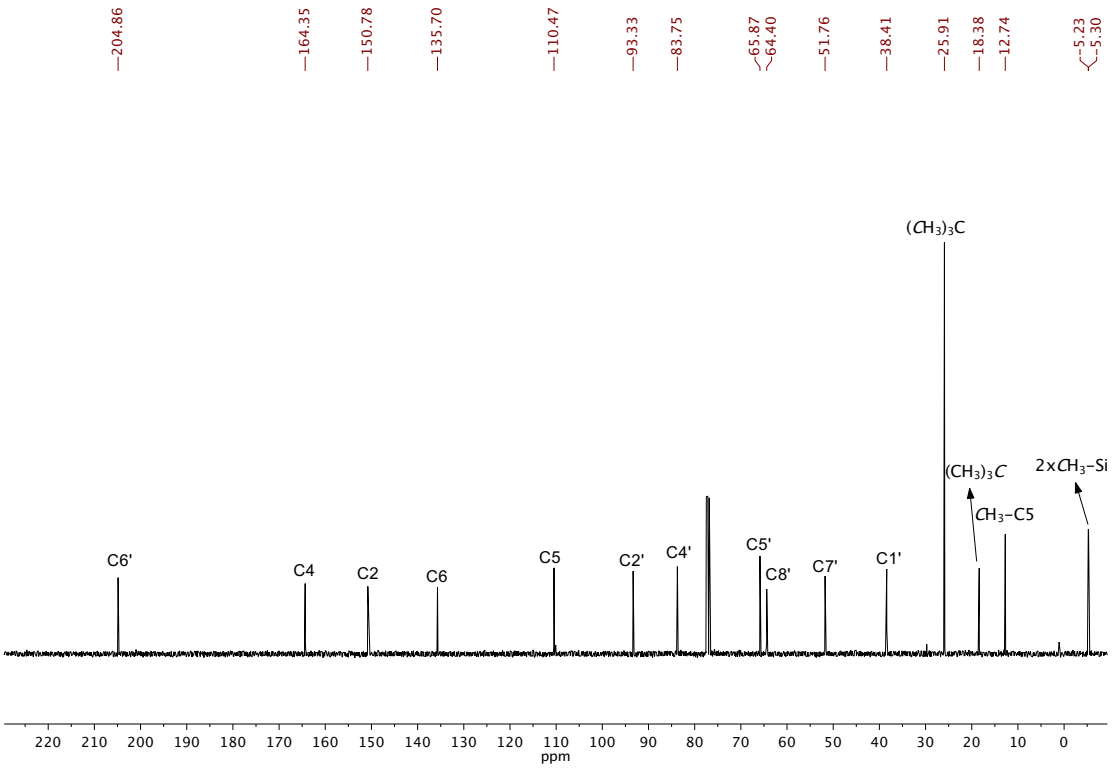

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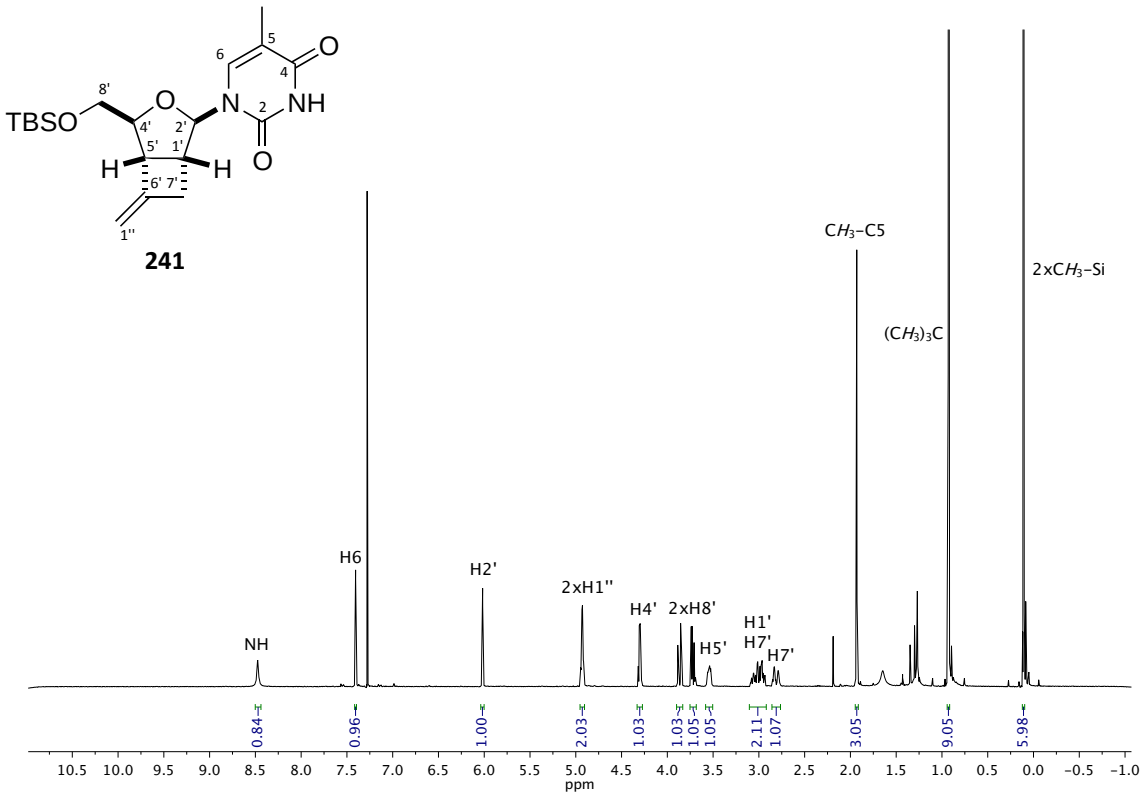

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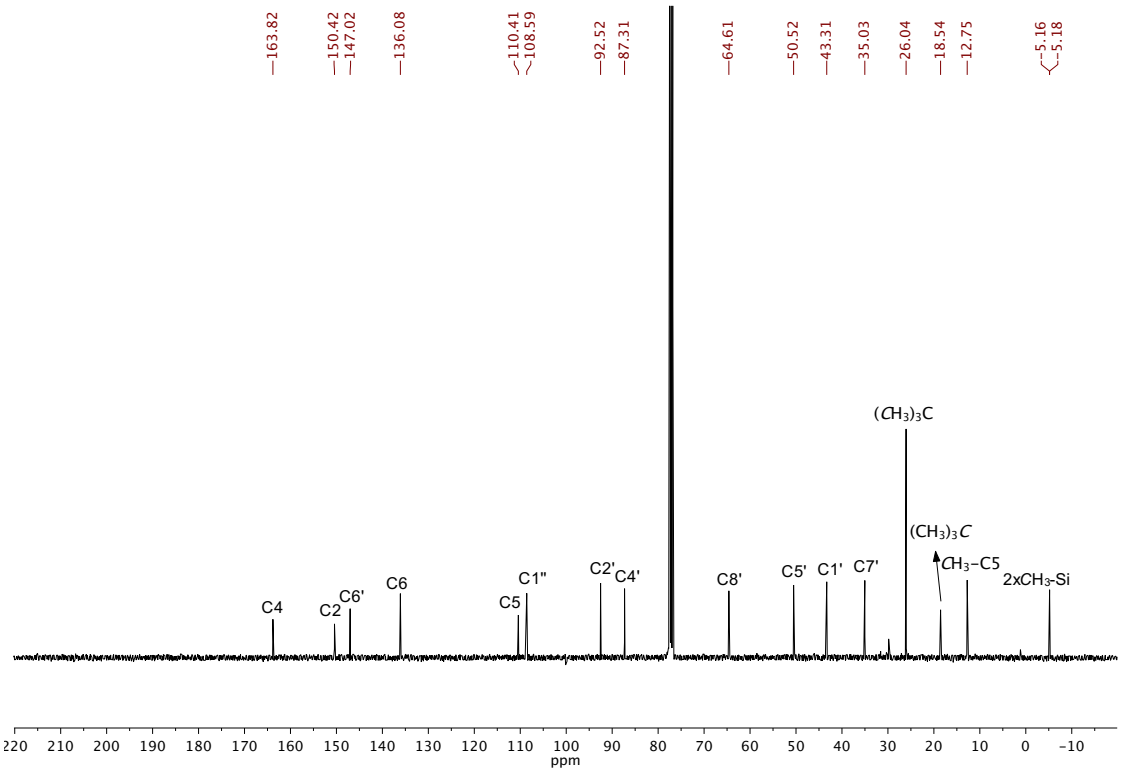

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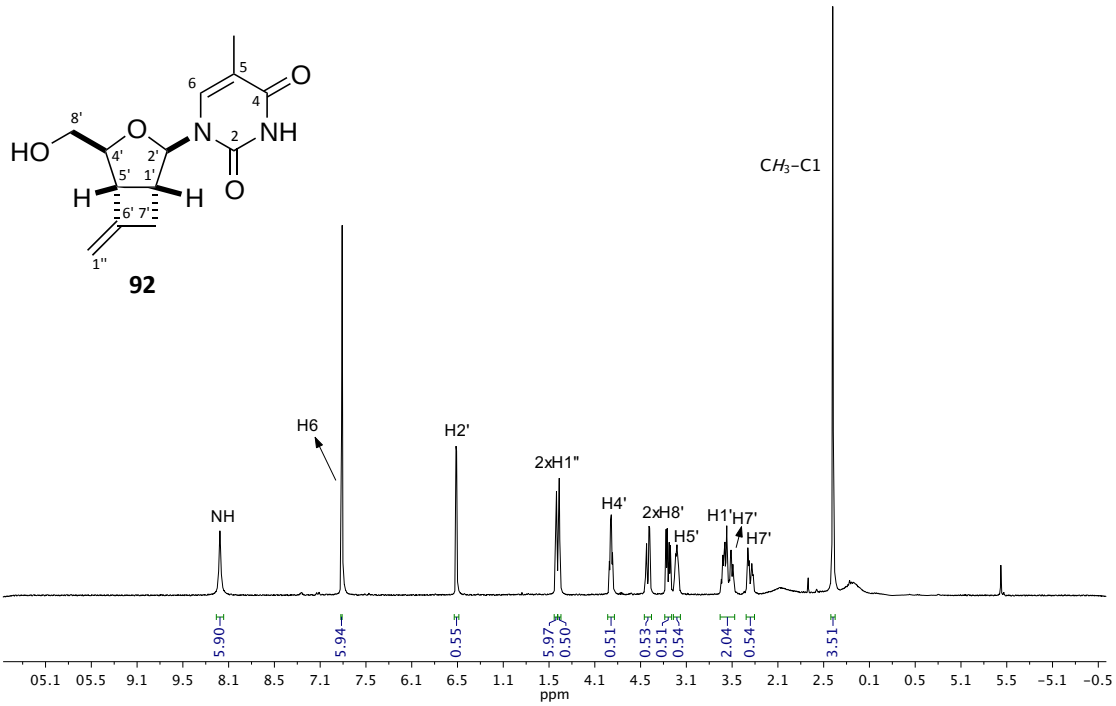

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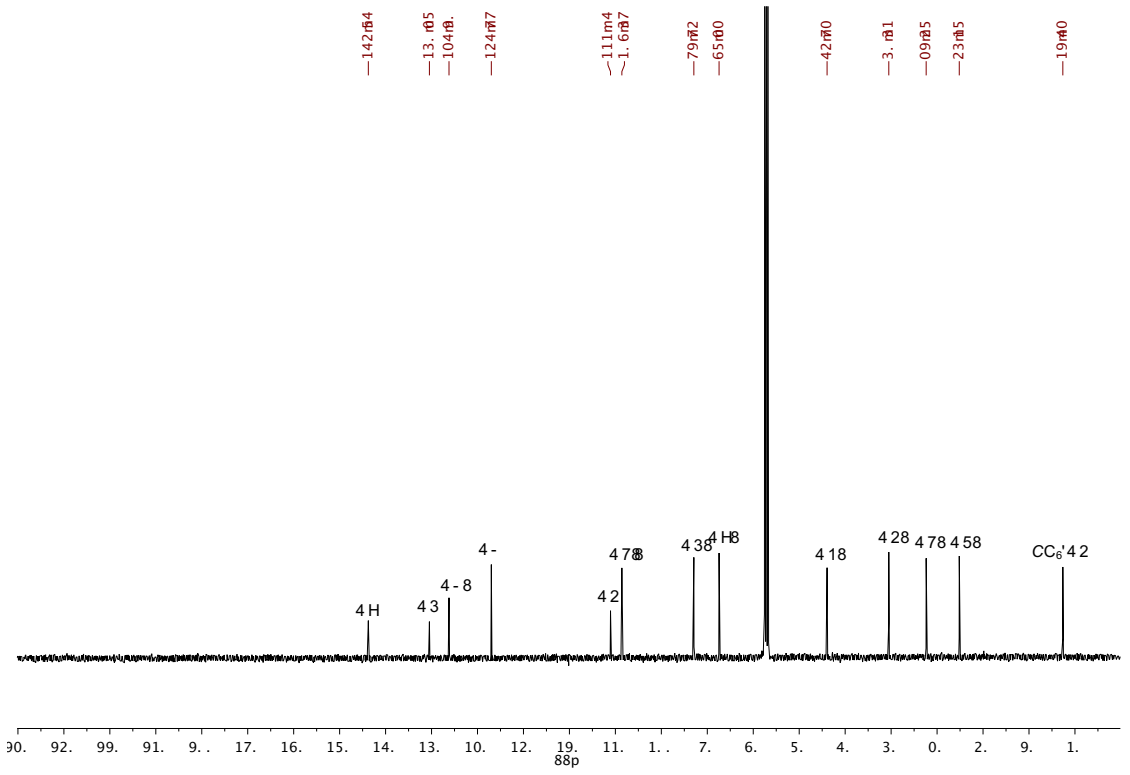

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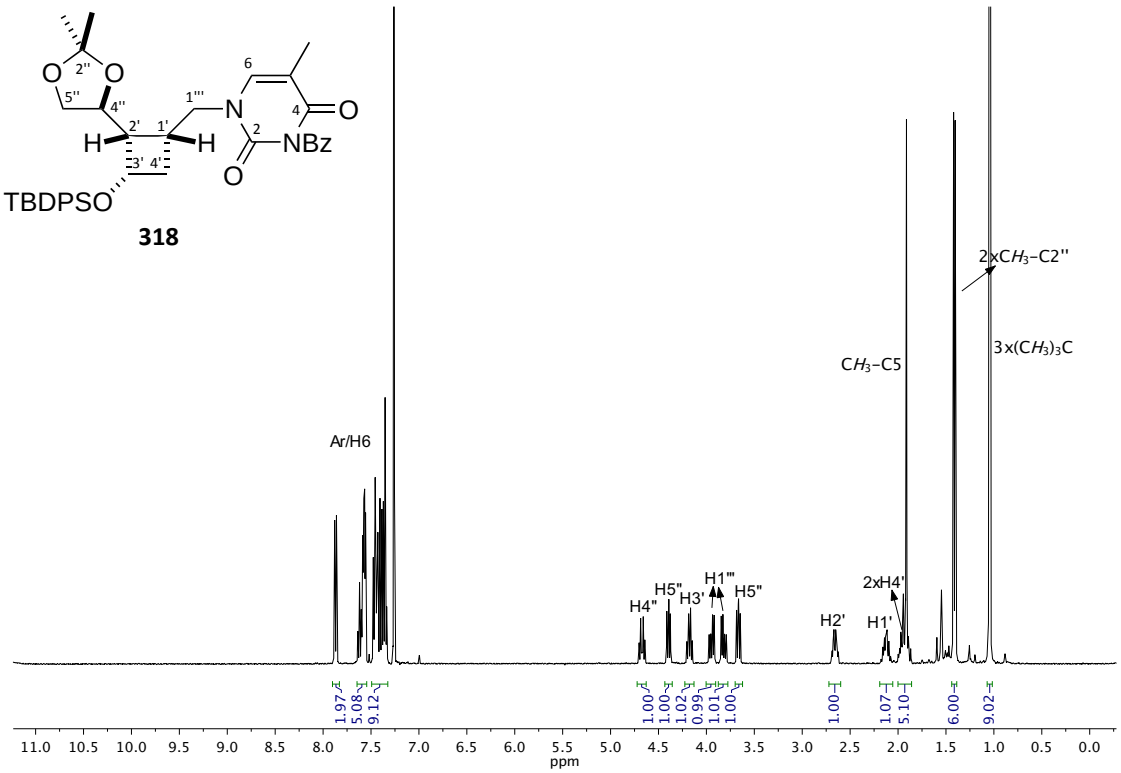

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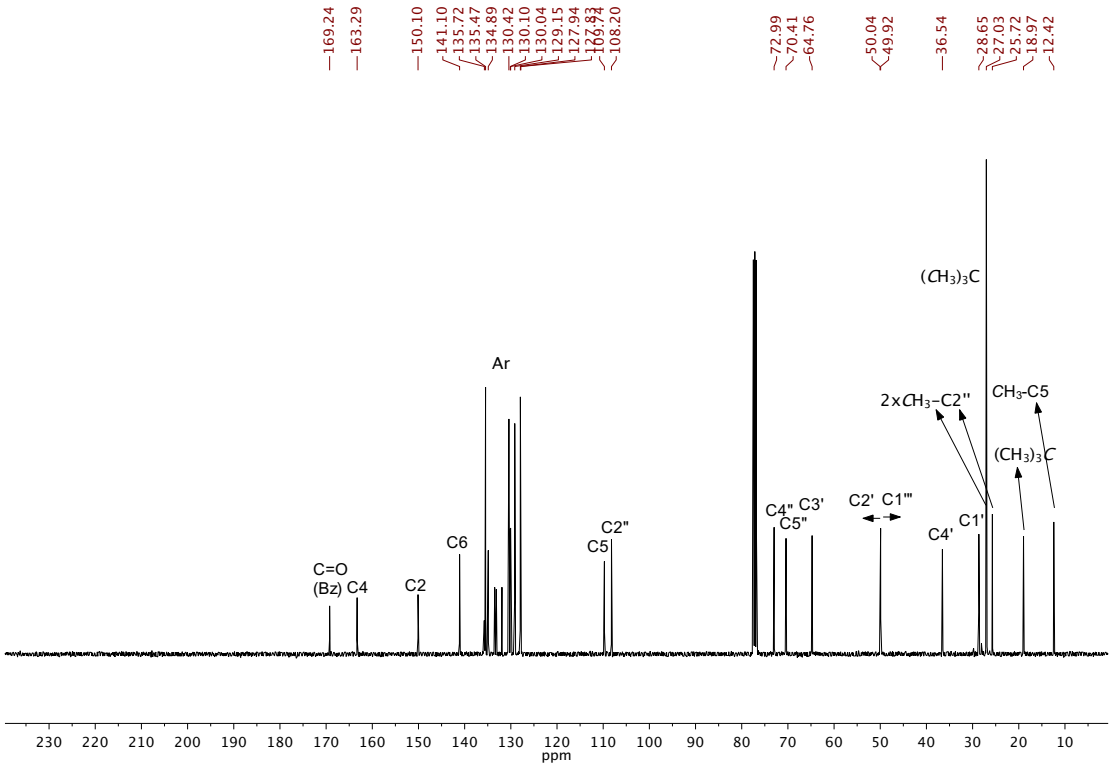

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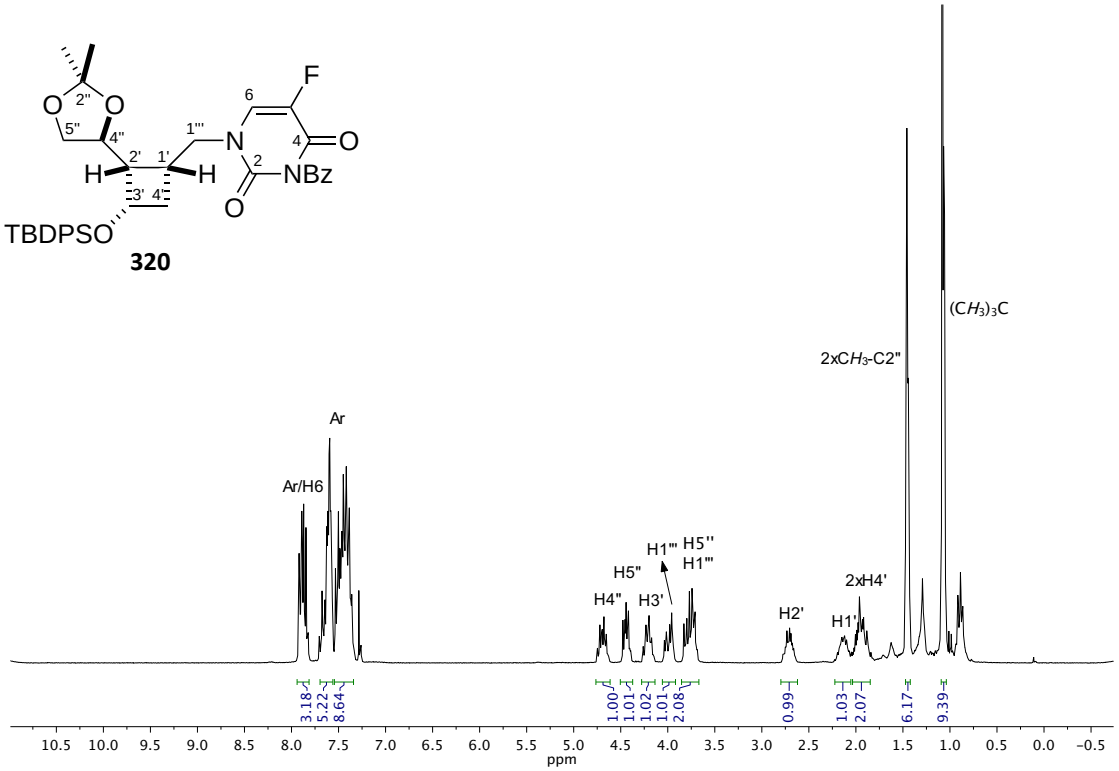

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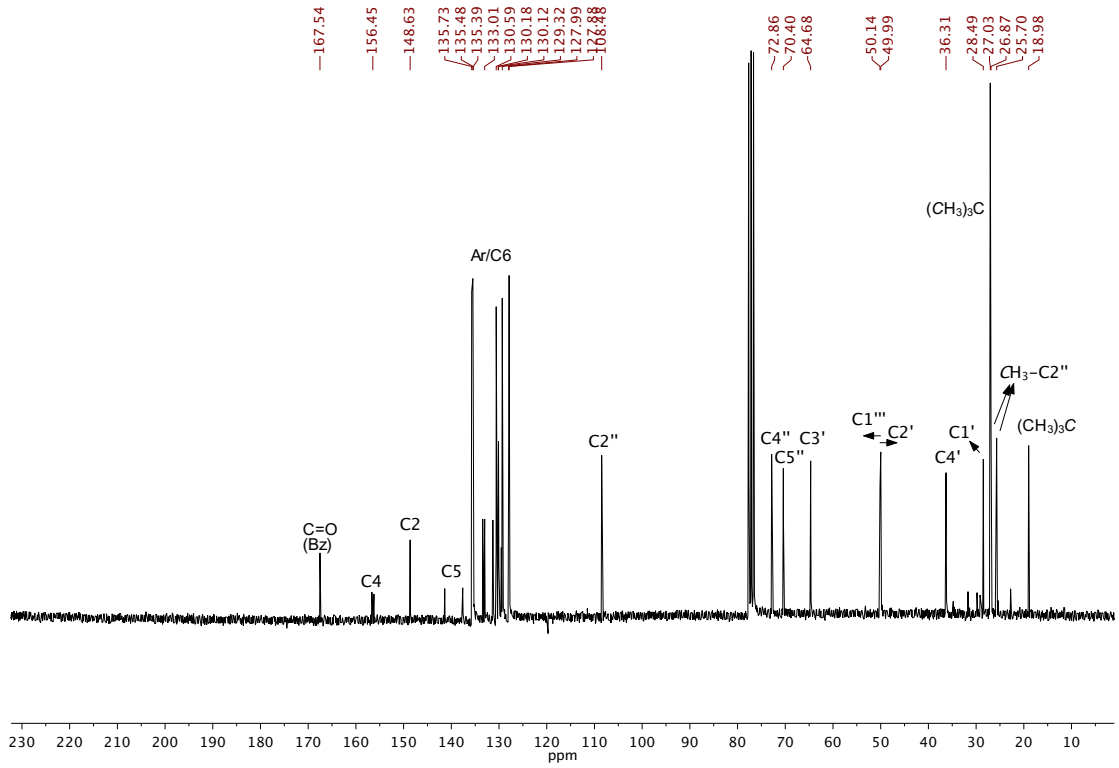

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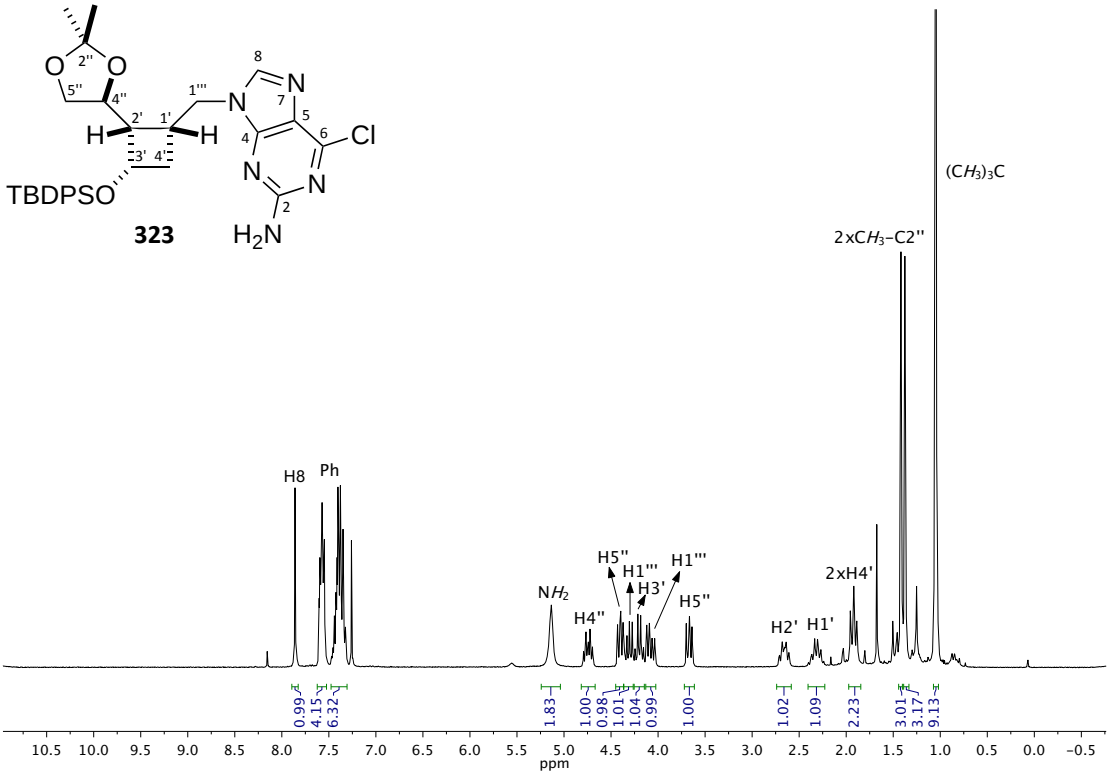
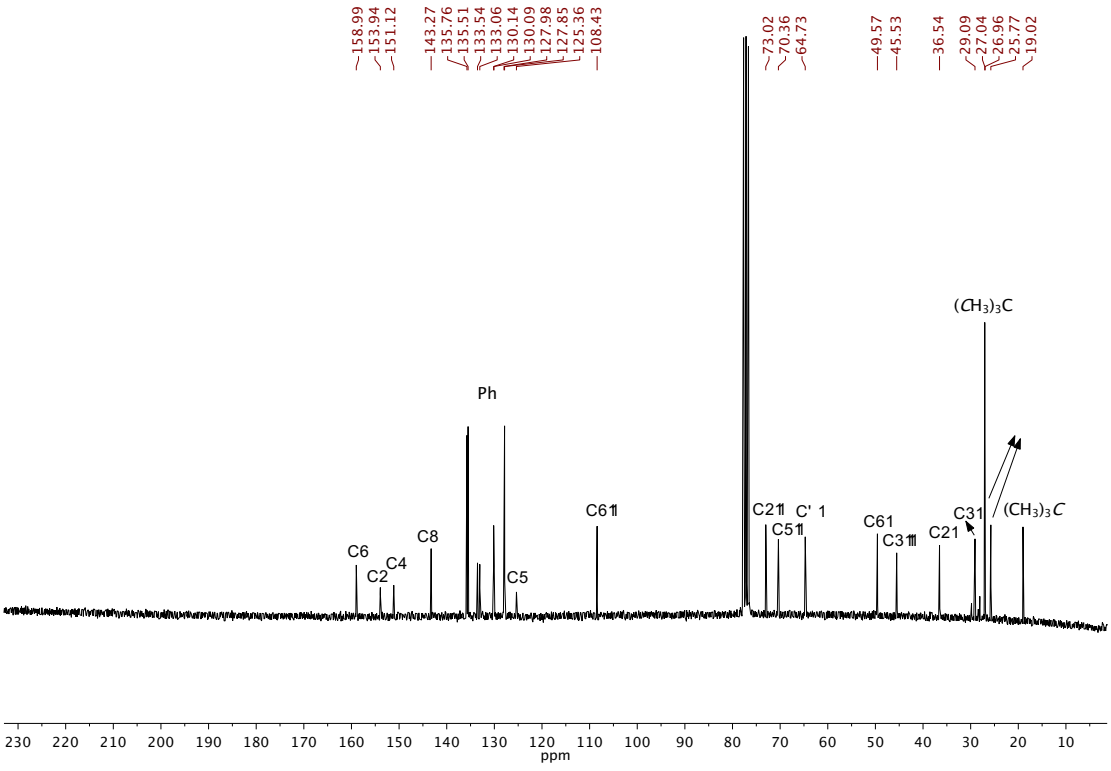
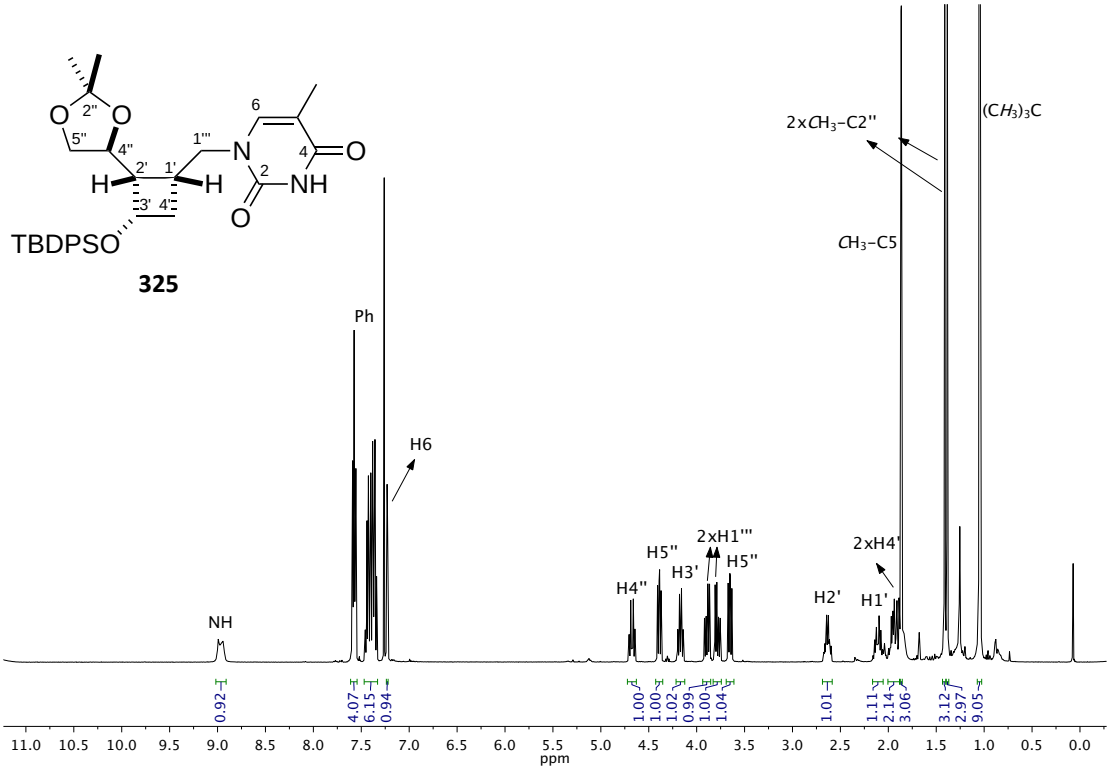


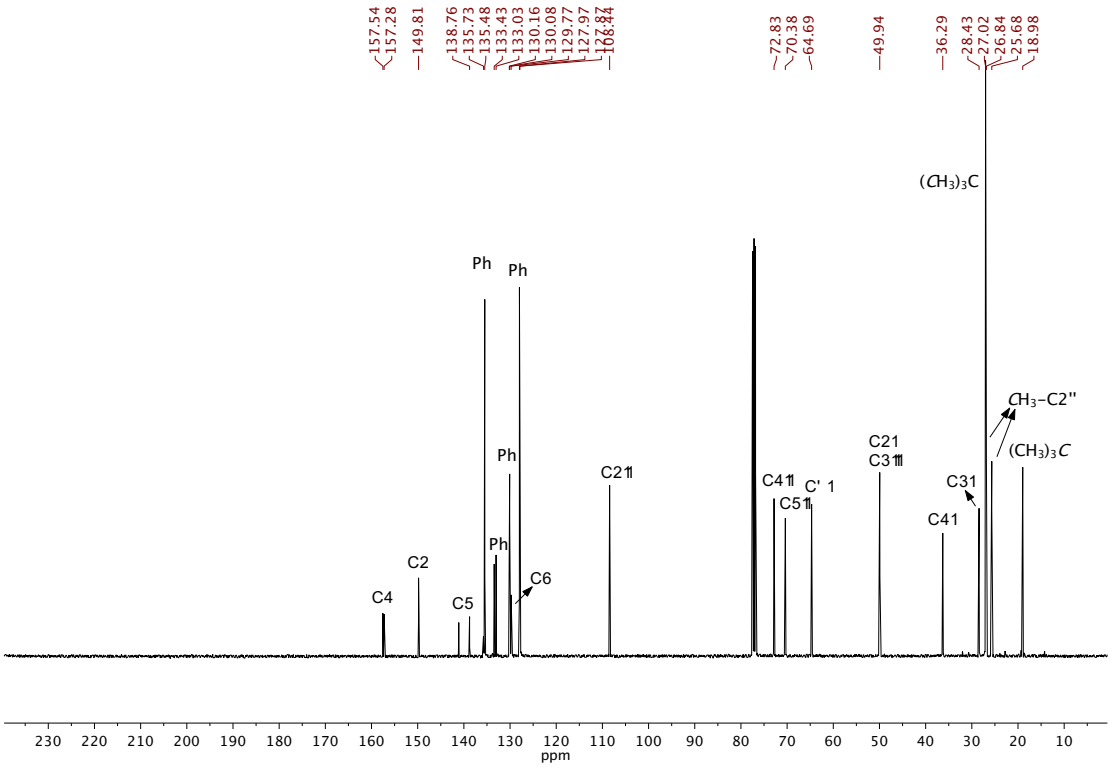
^{1}H-NMR (250 MHz, $CDCl_3$)



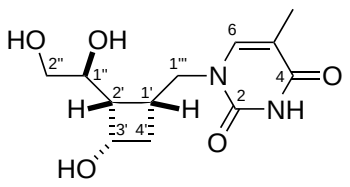
^{13}C-NMR (62.5 MHz, $CDCl_3$)



^{1}H-NMR (400 MHz, $CDCl_3$)

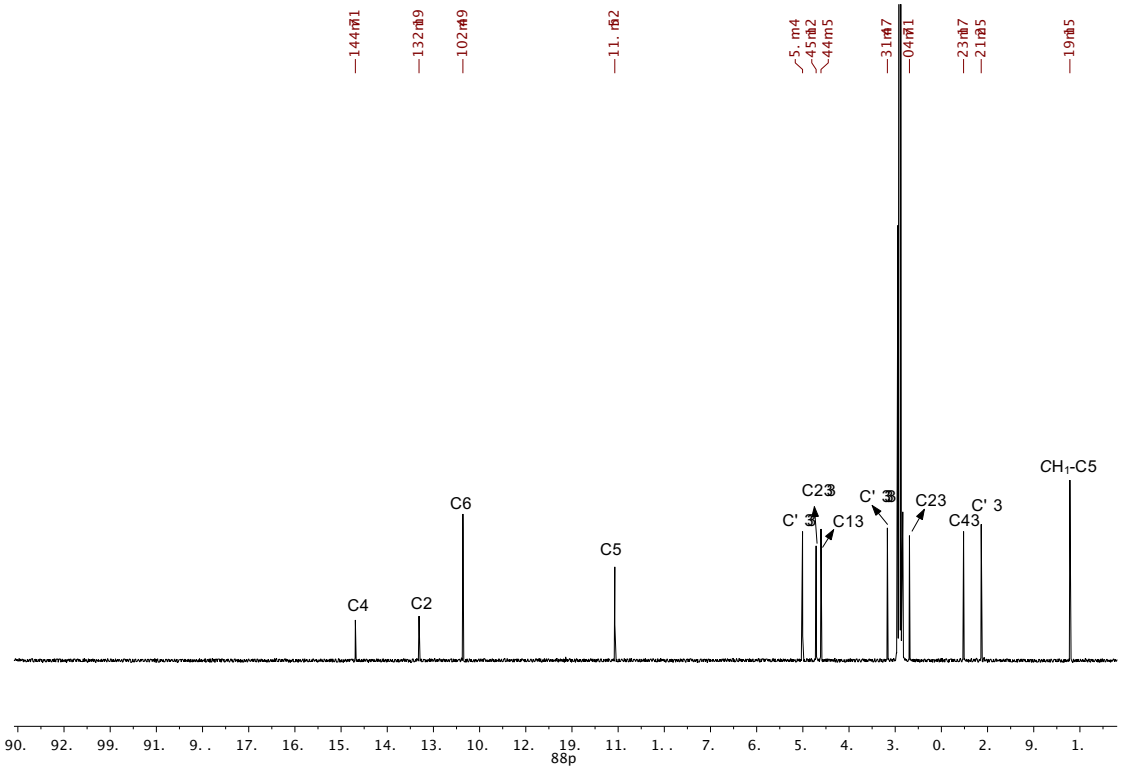


^{13}C-NMR (100 MHz, $CDCl_3$)

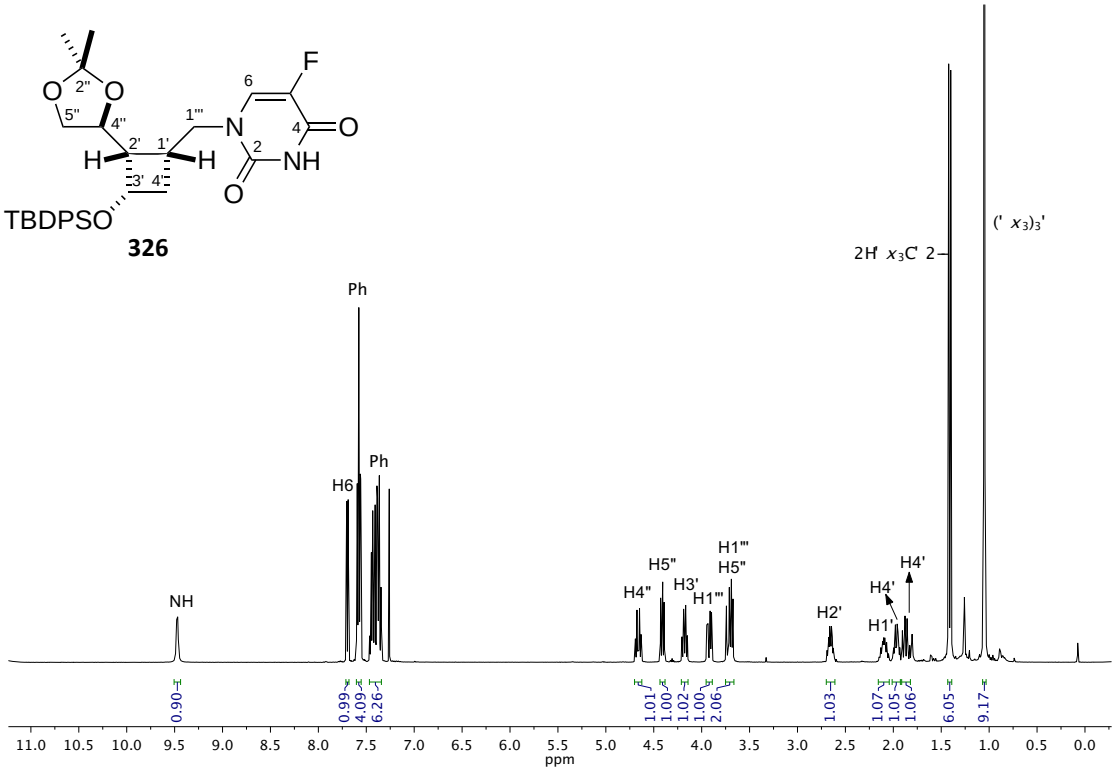


95

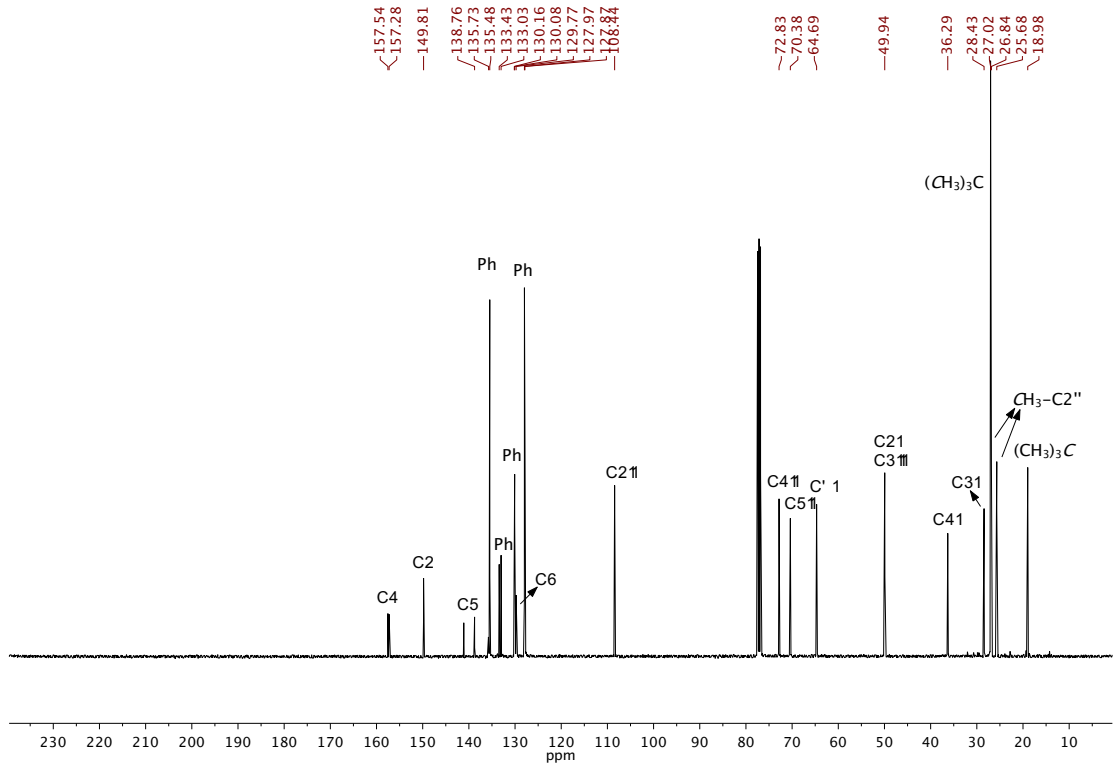
^{1}H-NMR (400 MHz, MeOD)



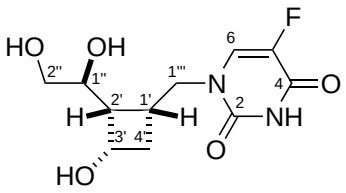
^{13}C-NMR (100 MHz, MeOD)



^{1}H-NMR (400 MHz, $CDCl_3$)



^{13}C-NMR (100 MHz, $CDCl_3$)



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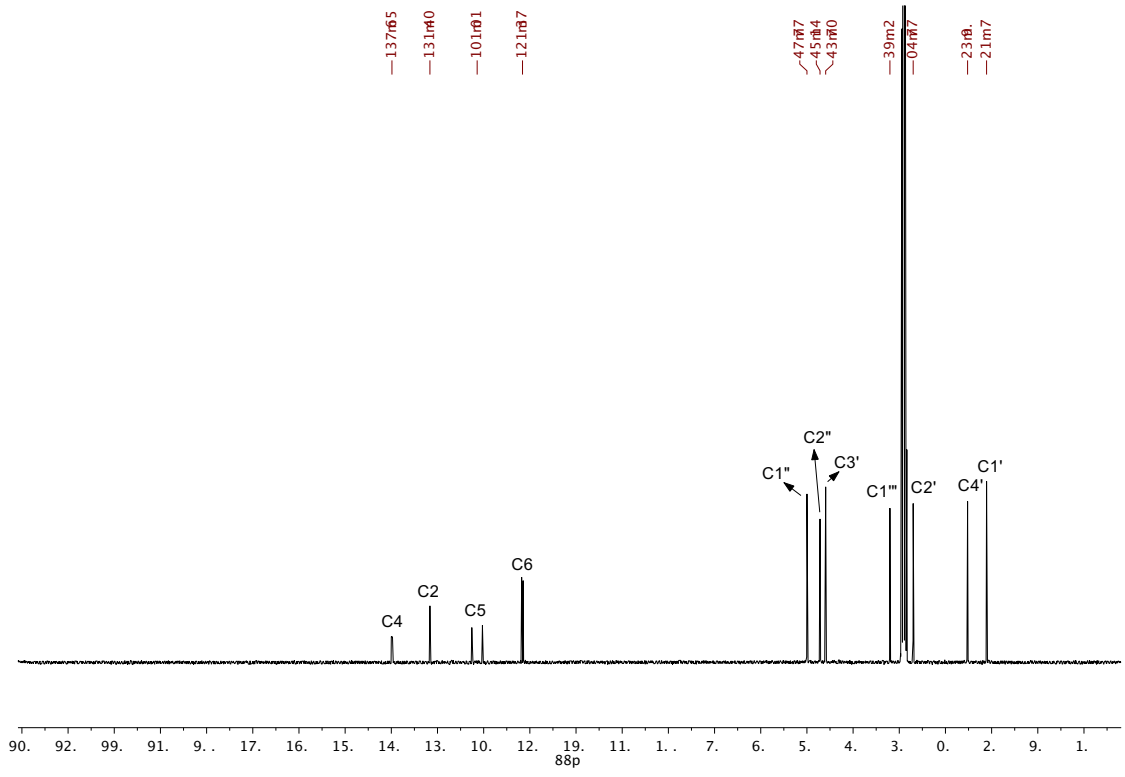
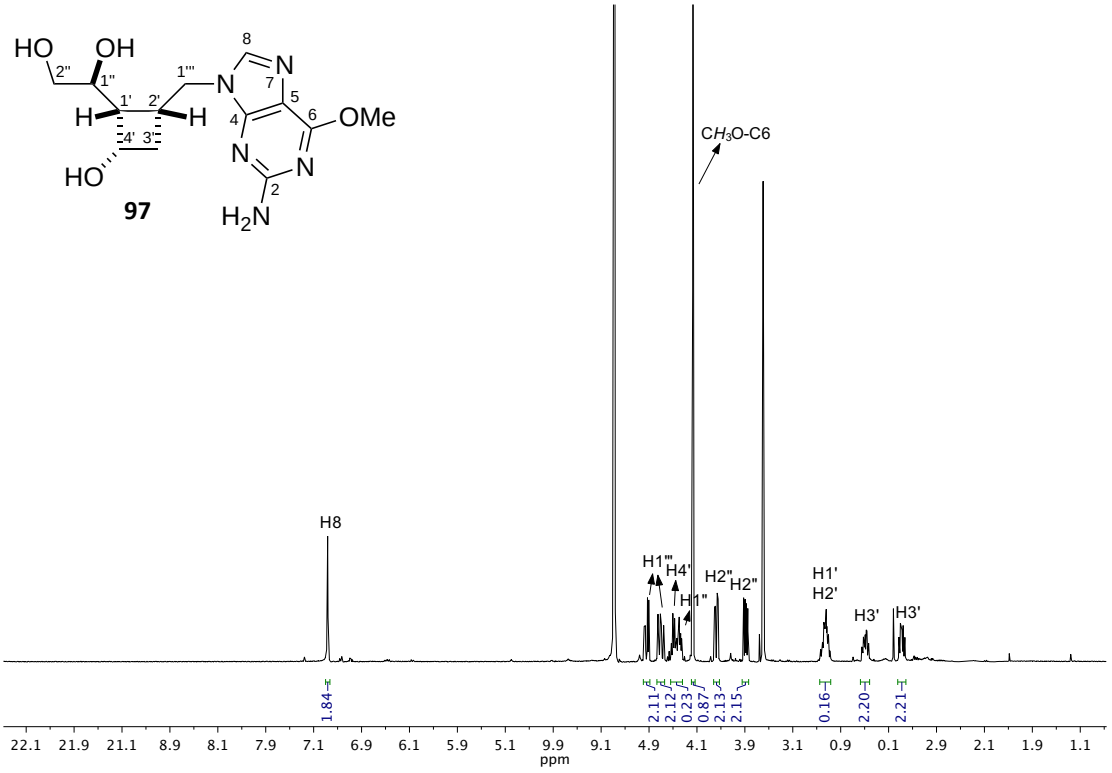
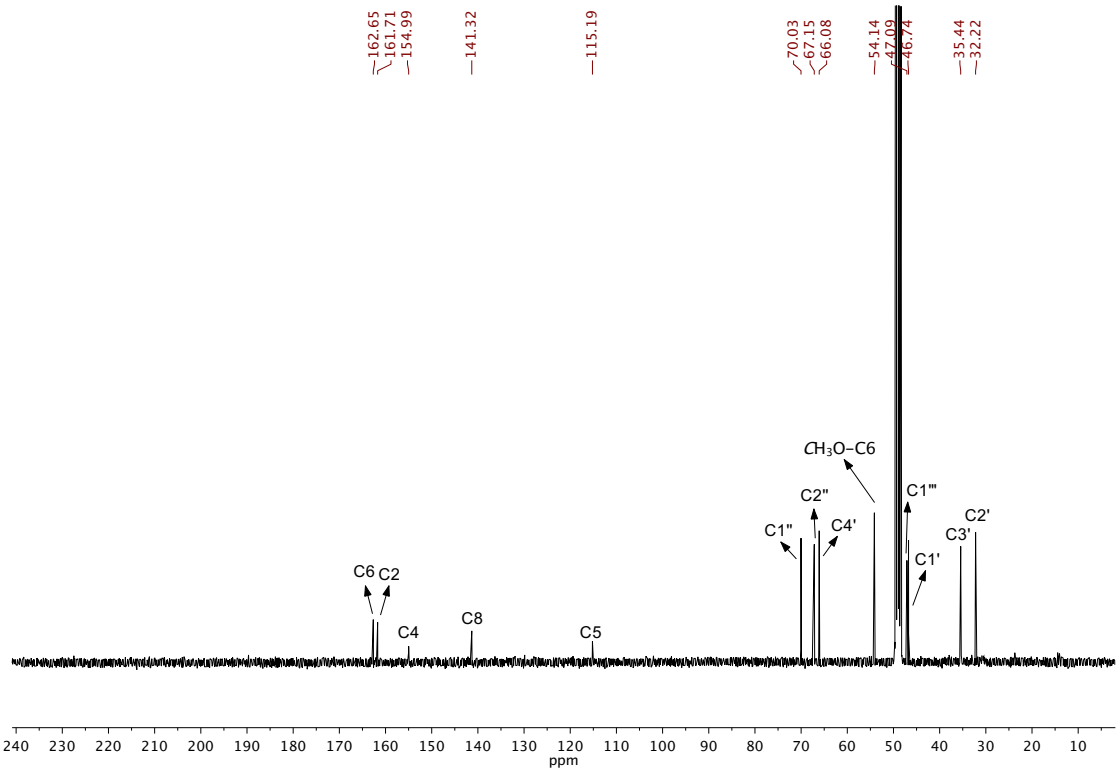
^{1}H-NMR (400 MHz, MeOD)



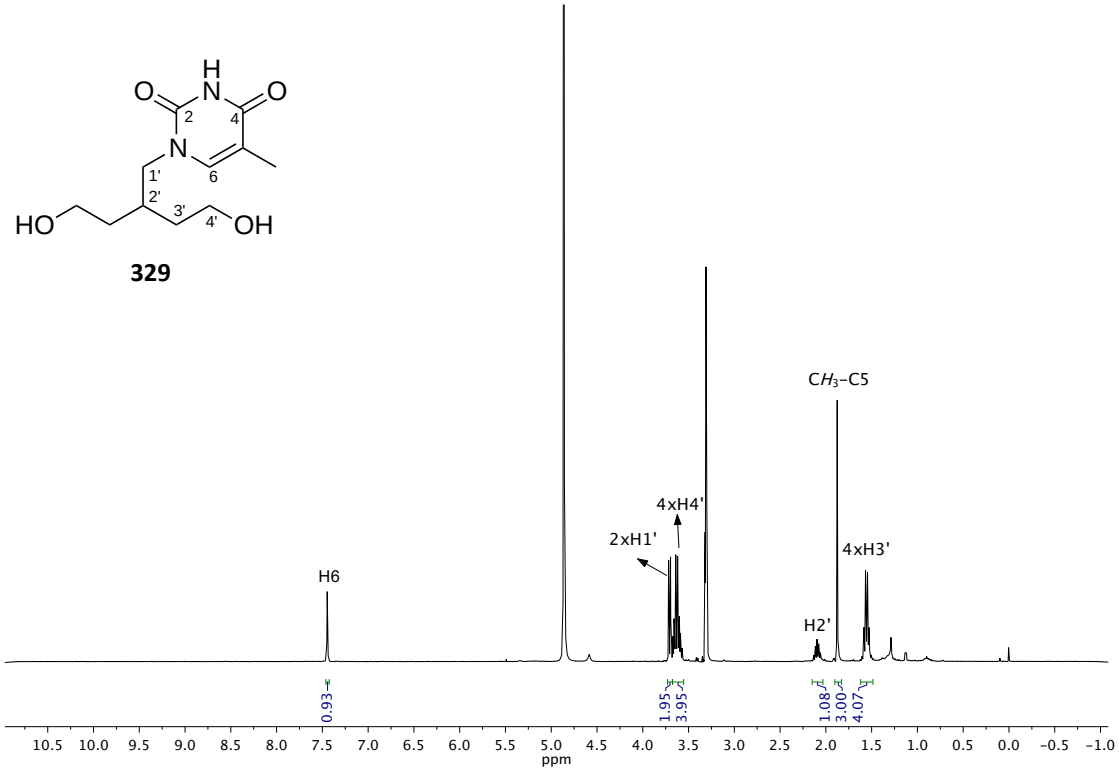
^{13}C-NMR (100 MHz, MeOD)



^{1}H-NMR (400 MHz, MeOD)



^{13}C-NMR (100 MHz, MeOD)



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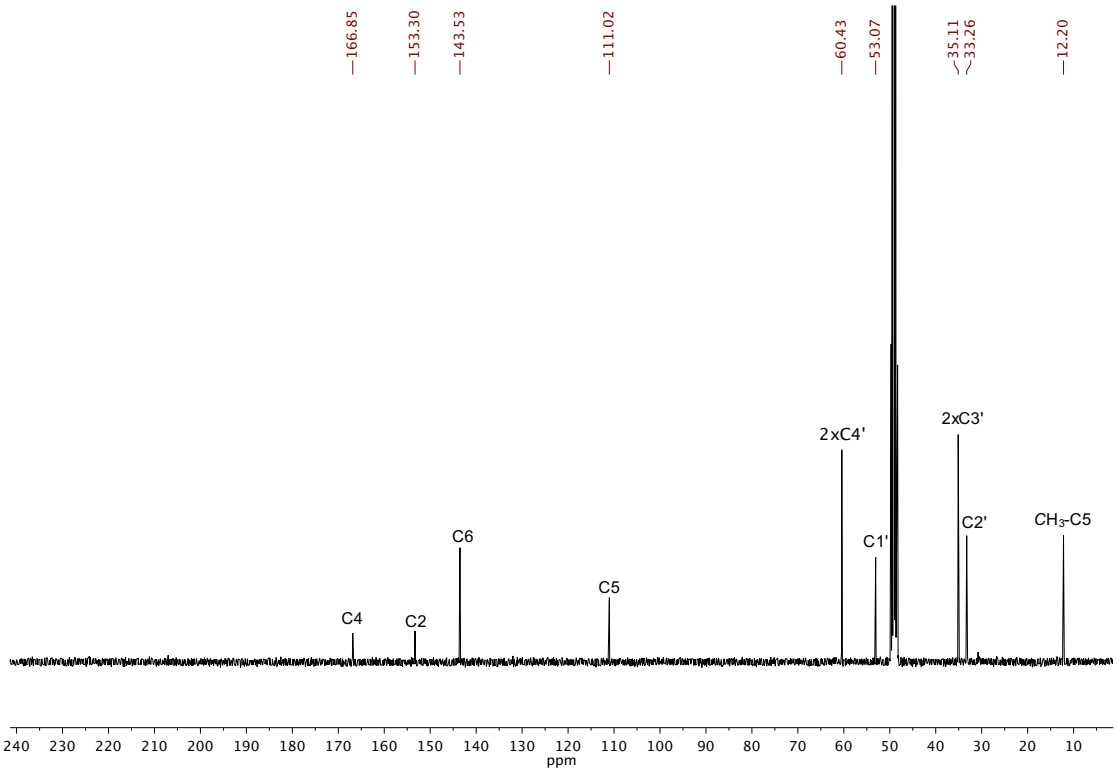
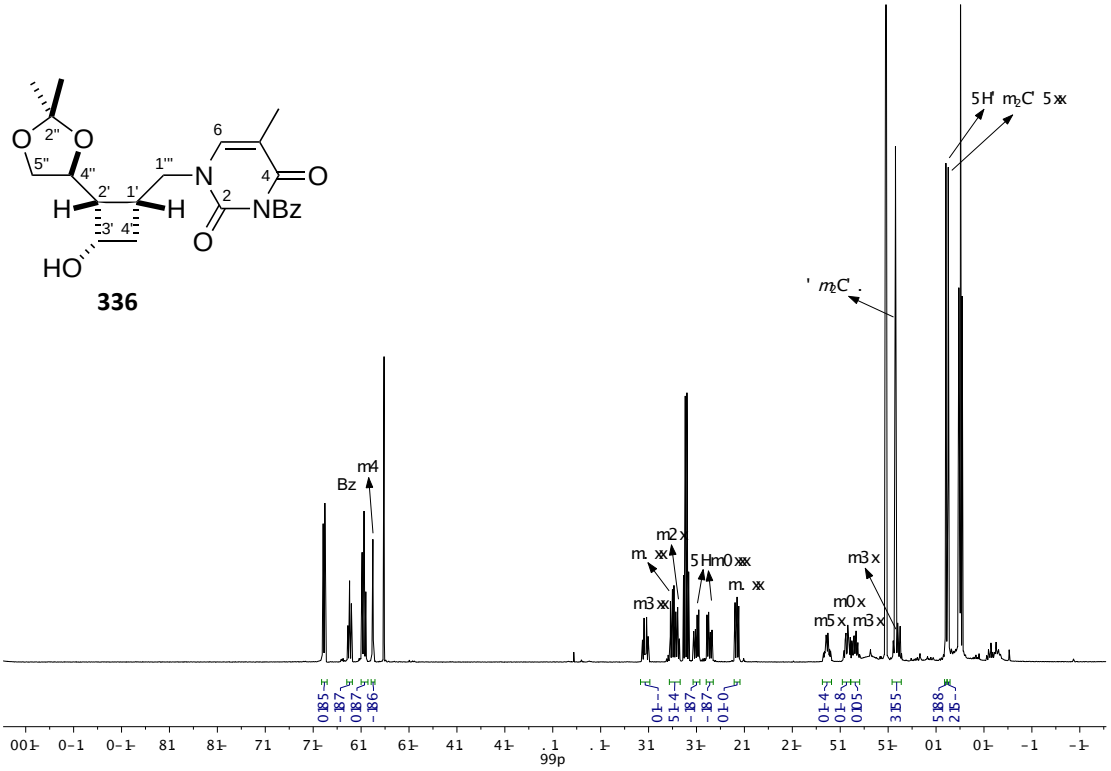
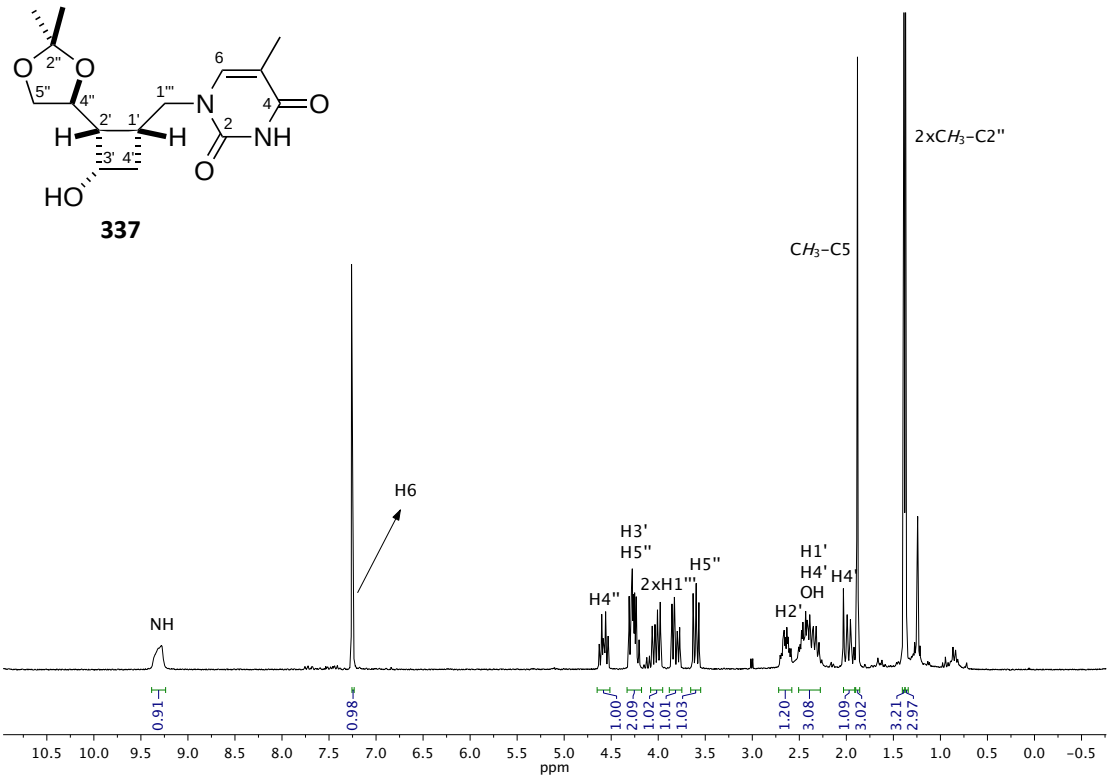
^{1}H-NMR (360 MHz, MeOD)



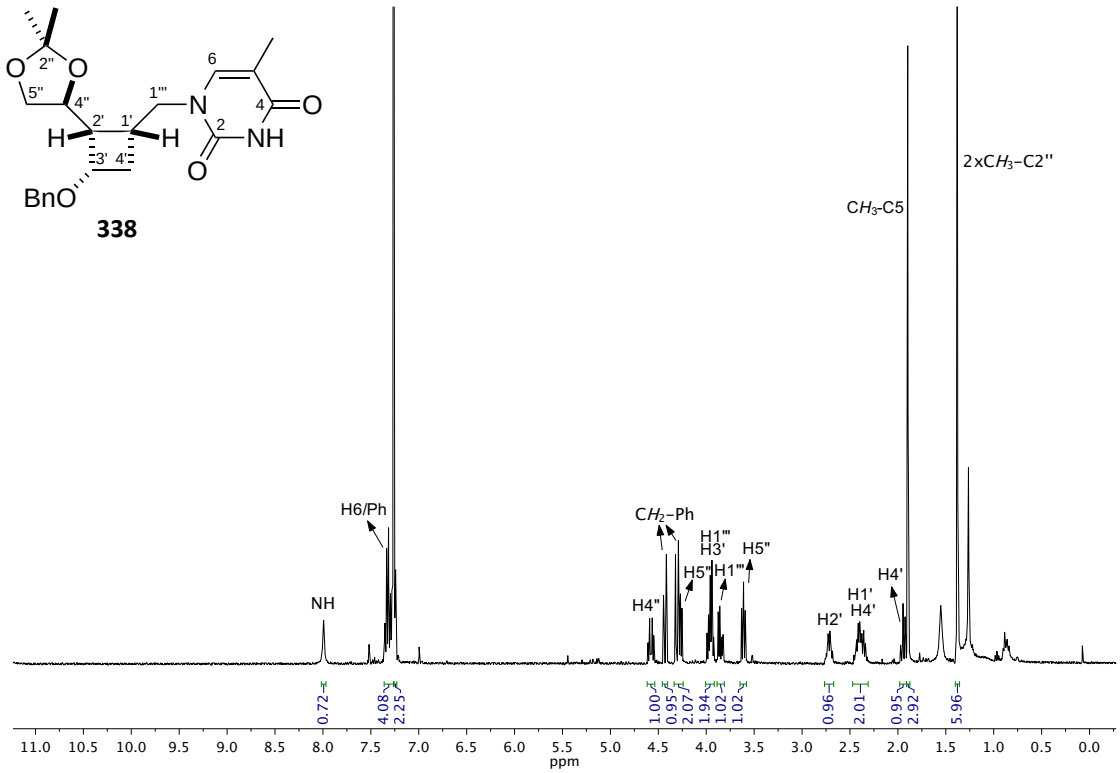
^{13}C-NMR (90 MHz, MeOD)



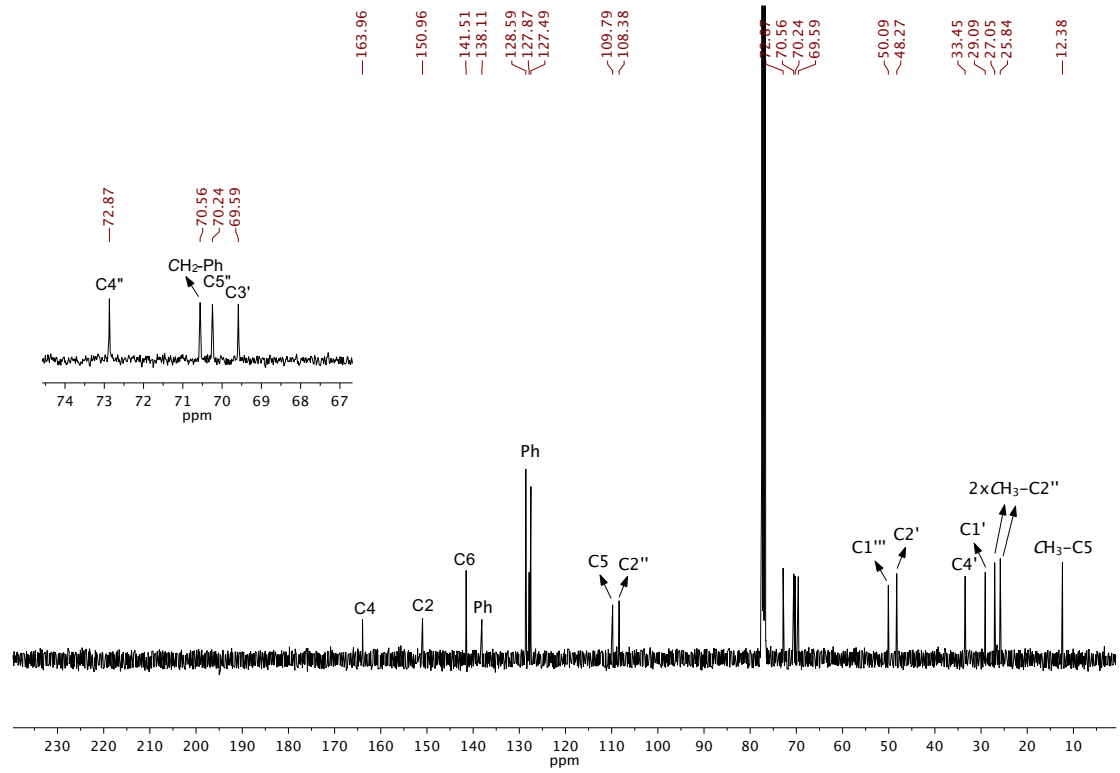
^{1}H-NMR (250 MHz, $CDCl_3$)



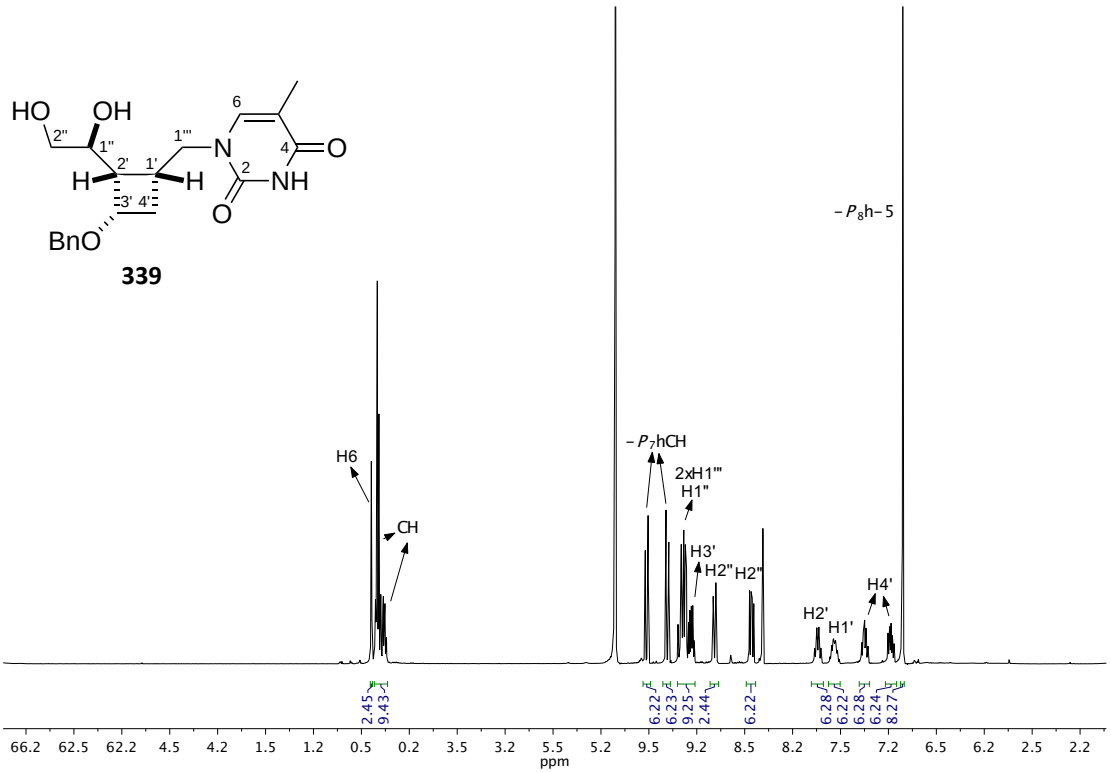
^{1}H-NMR (250 MHz, $CDCl_3$)



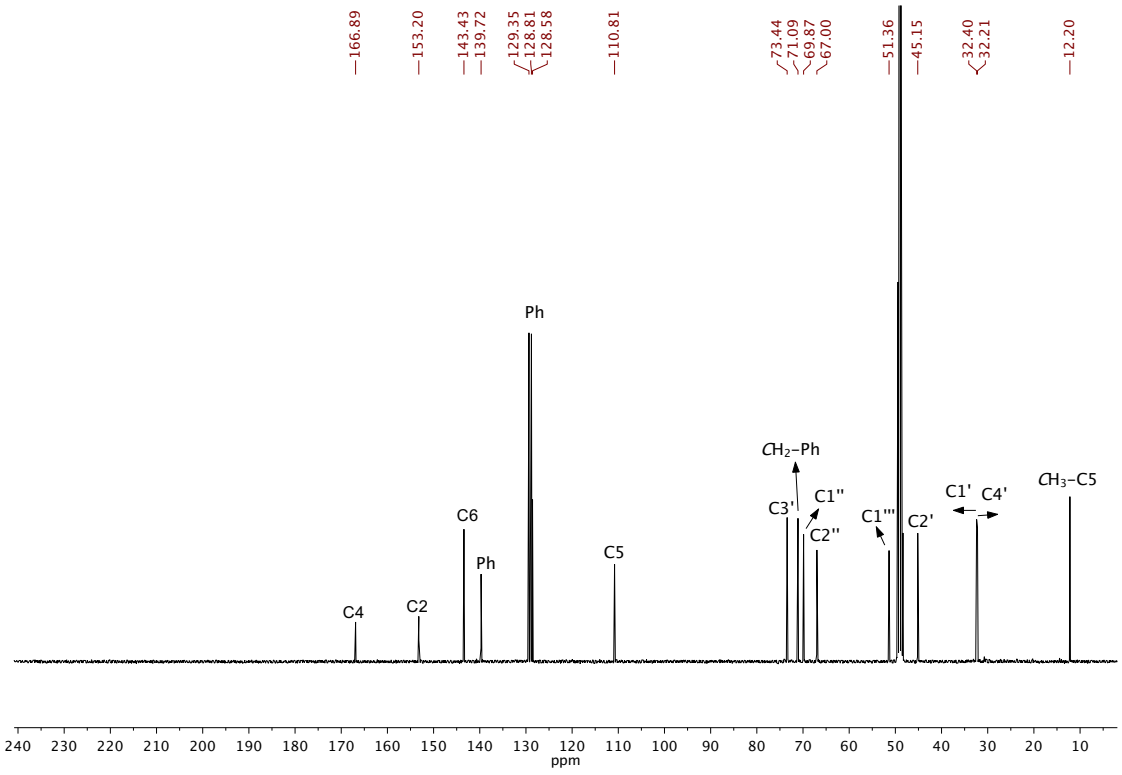
^{1}H-NMR (400 MHz, $CDCl_3$)



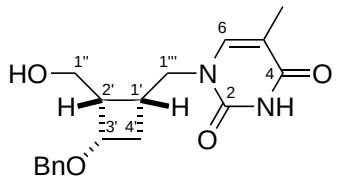
^{13}C-NMR (100 MHz, $CDCl_3$)



^{1}H-NMR (400 MHz, MeOD)

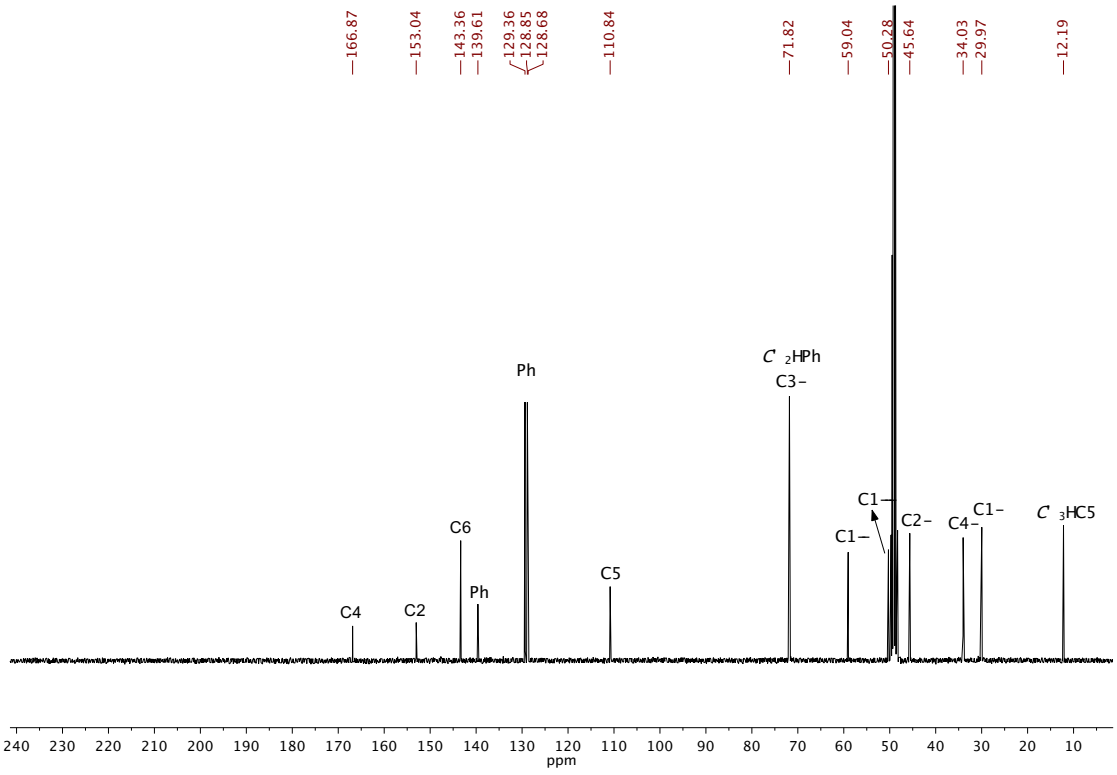


^{13}C-NMR (100 MHz, MeOD)

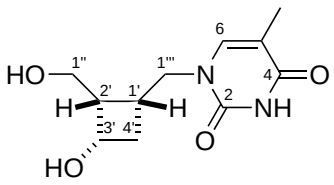


340

^{1}H-NMR (400 MHz, MeOD)



^{13}C-NMR (100 MHz, MeOD)



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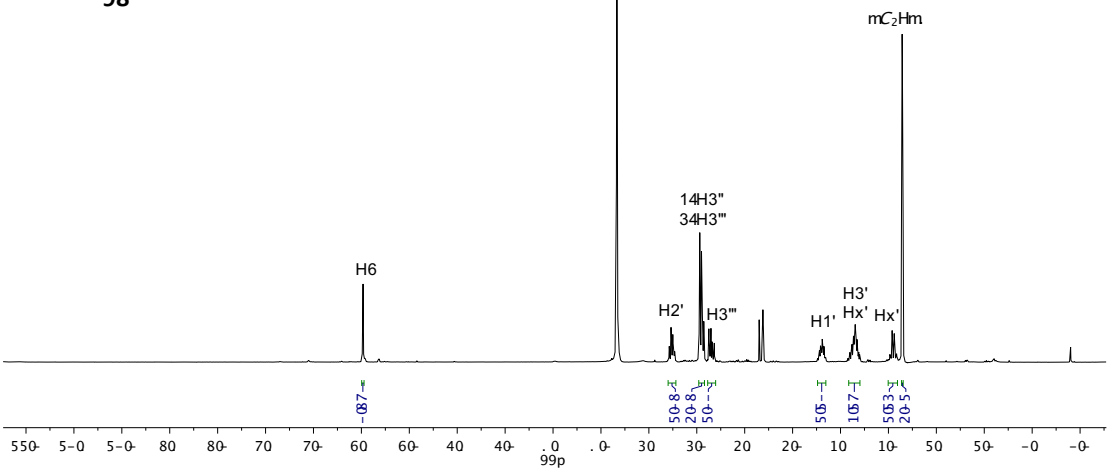
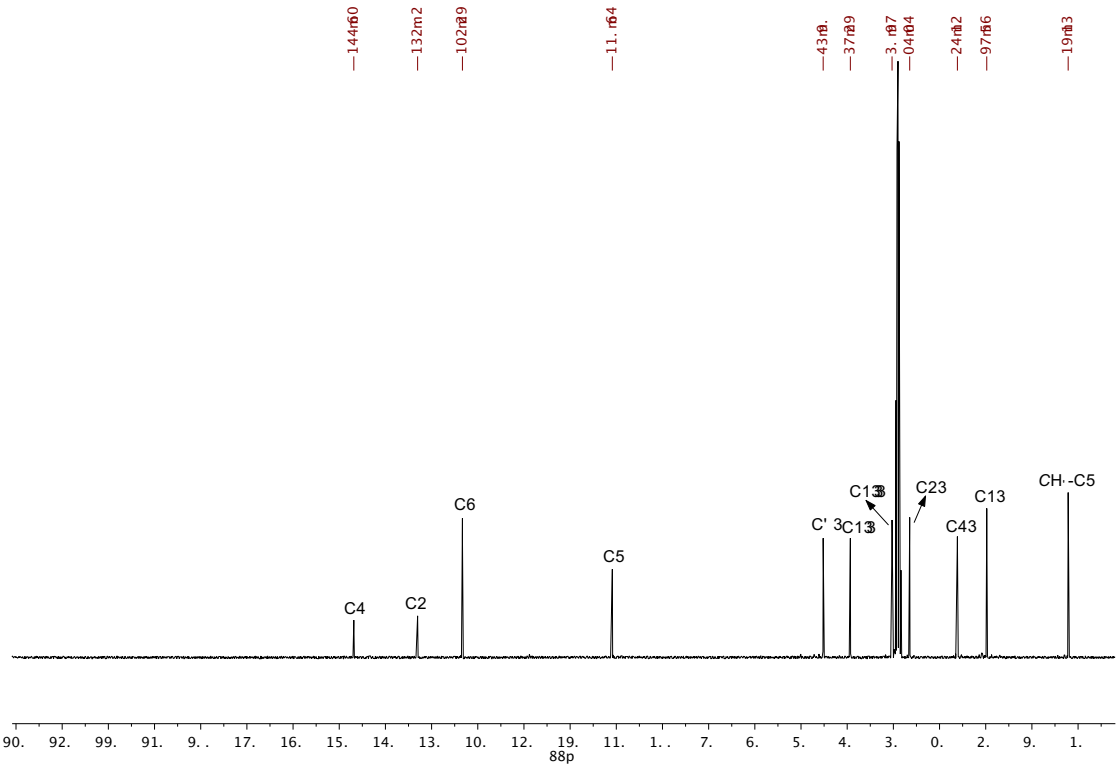


^{1}H-NMR (400 MHz, MeOD)



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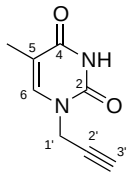

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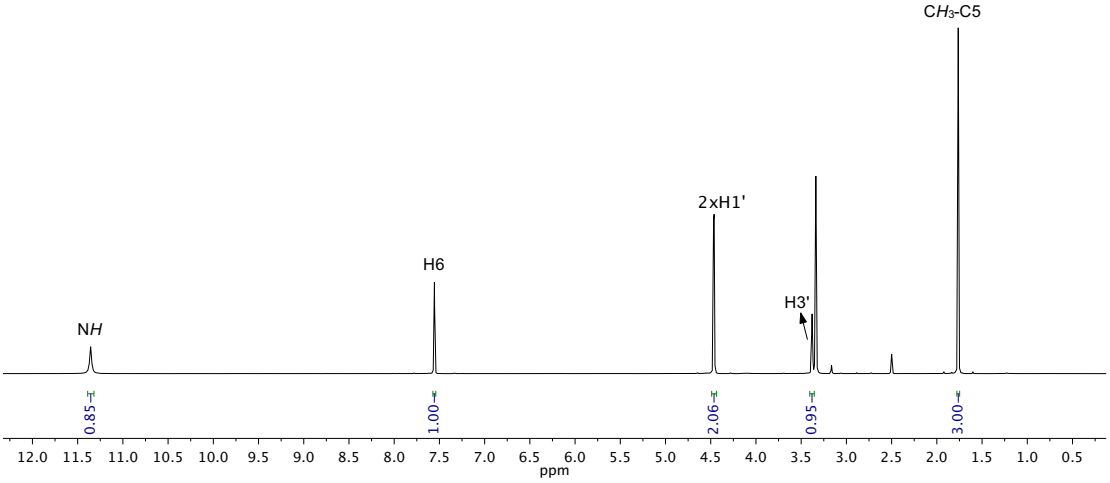
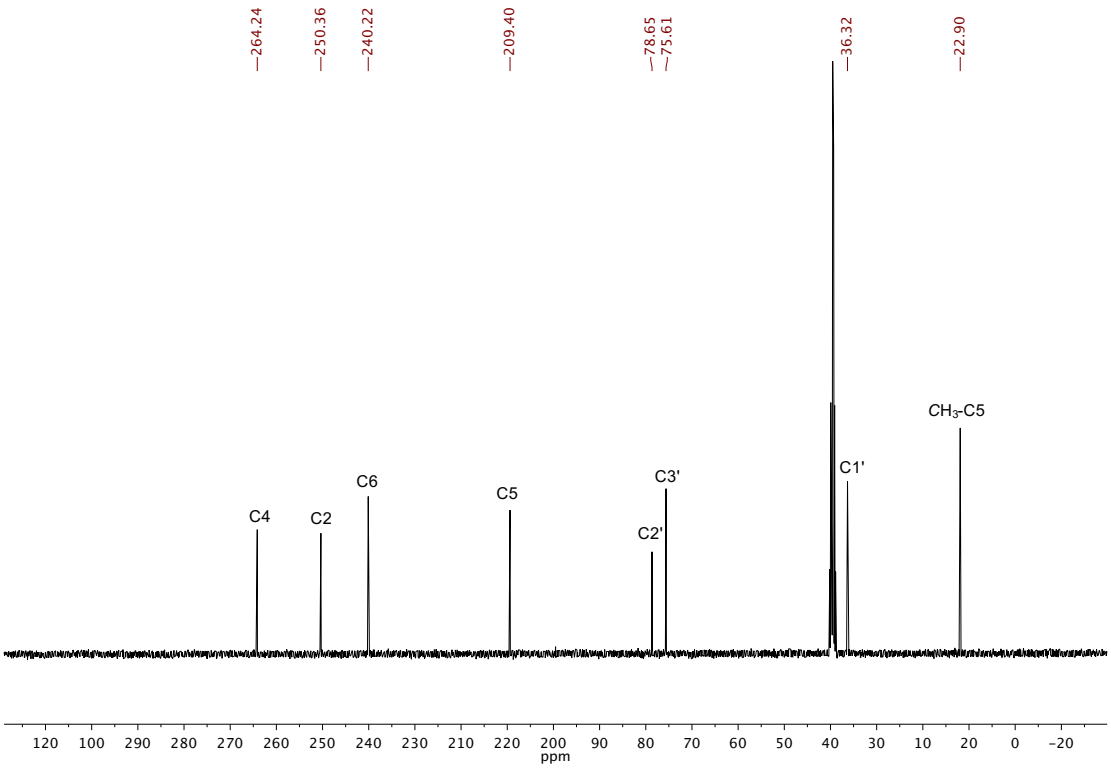
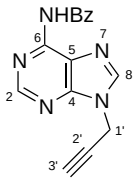


^{1}H-NMR (400 MHz, DMSO)



^{13}C-NMR (100 MHz, DMSO)



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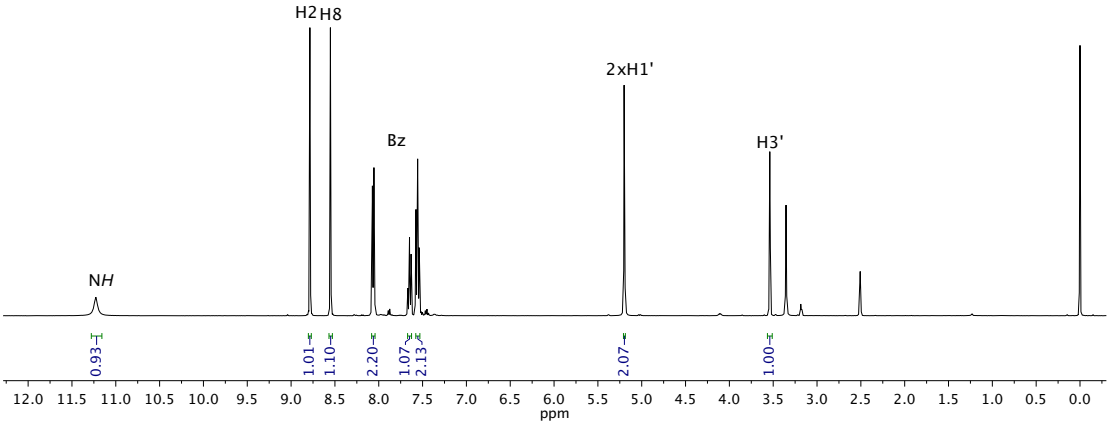
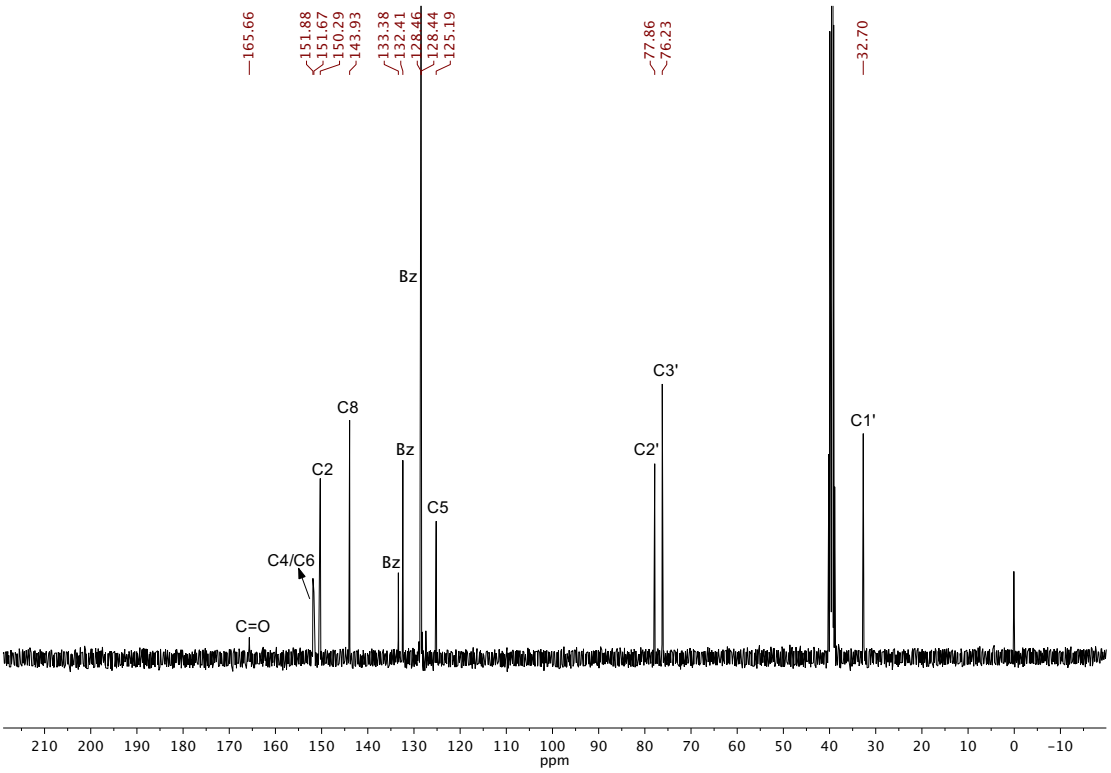
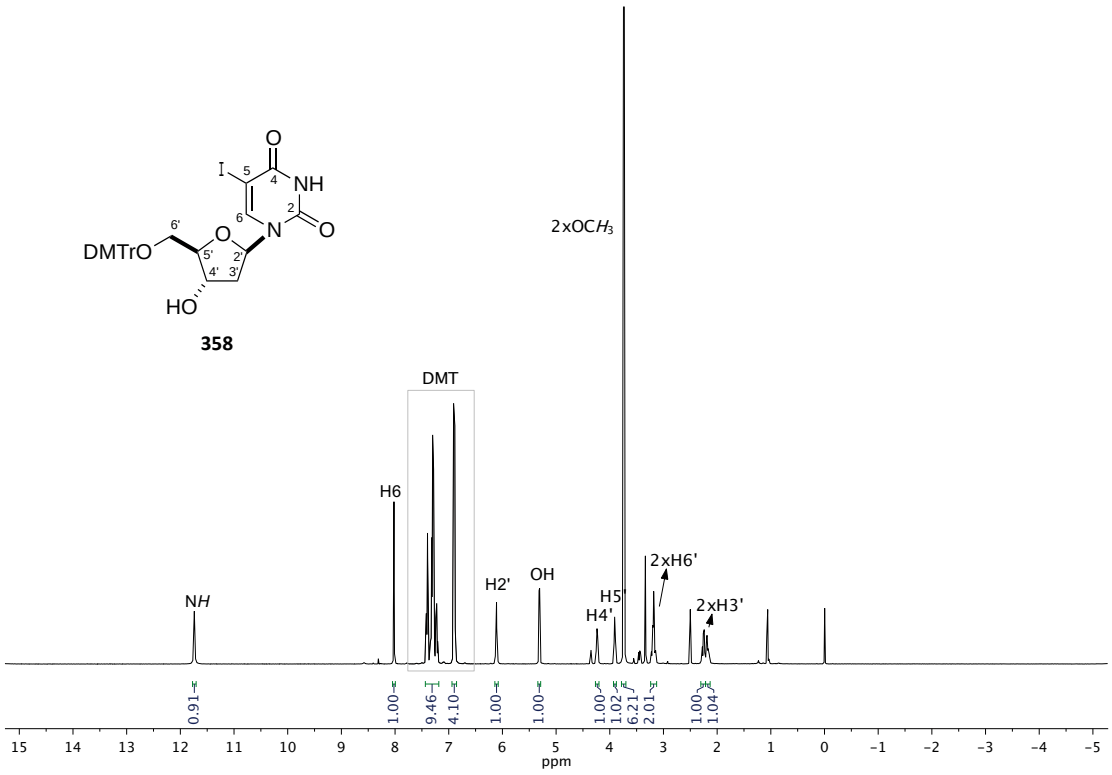


^{1}H-NMR (400 MHz, DMSO)



^{13}C-NMR (100 MHz, DMSO)



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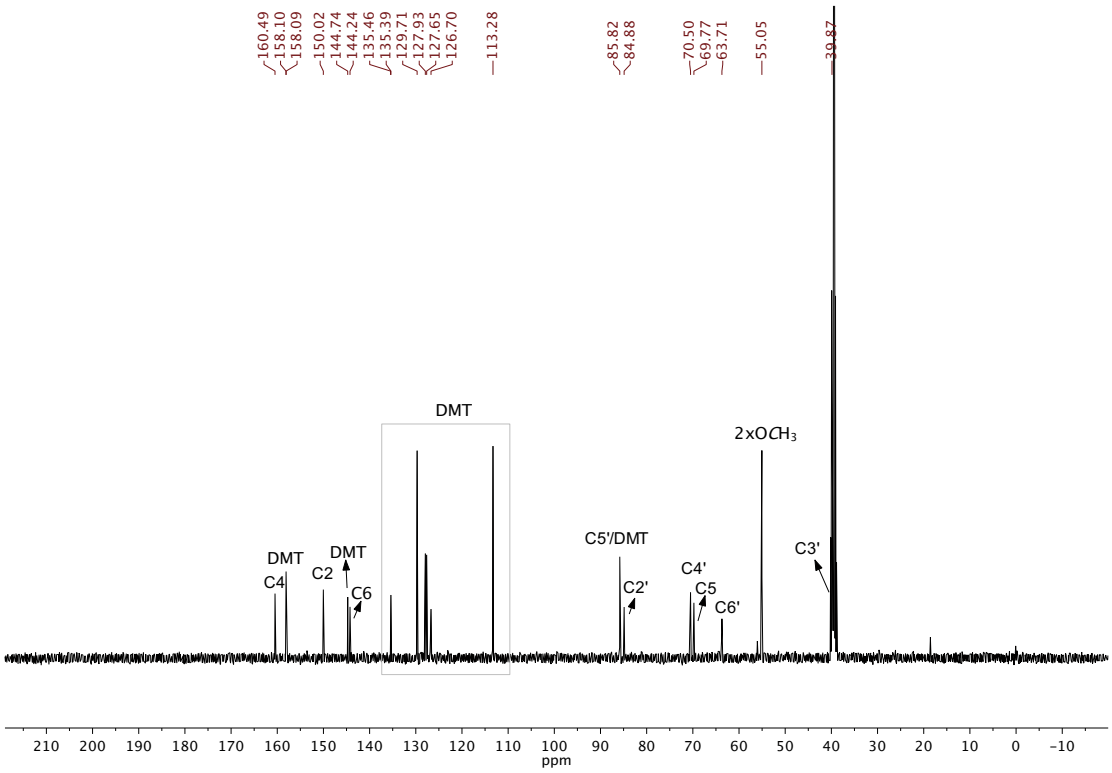
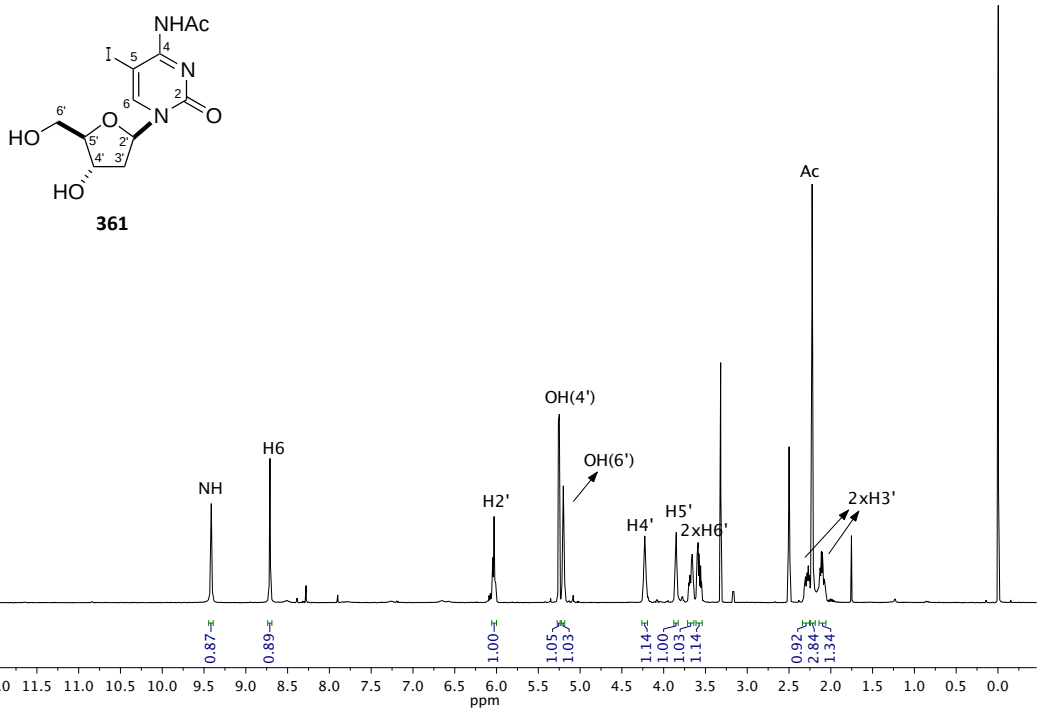
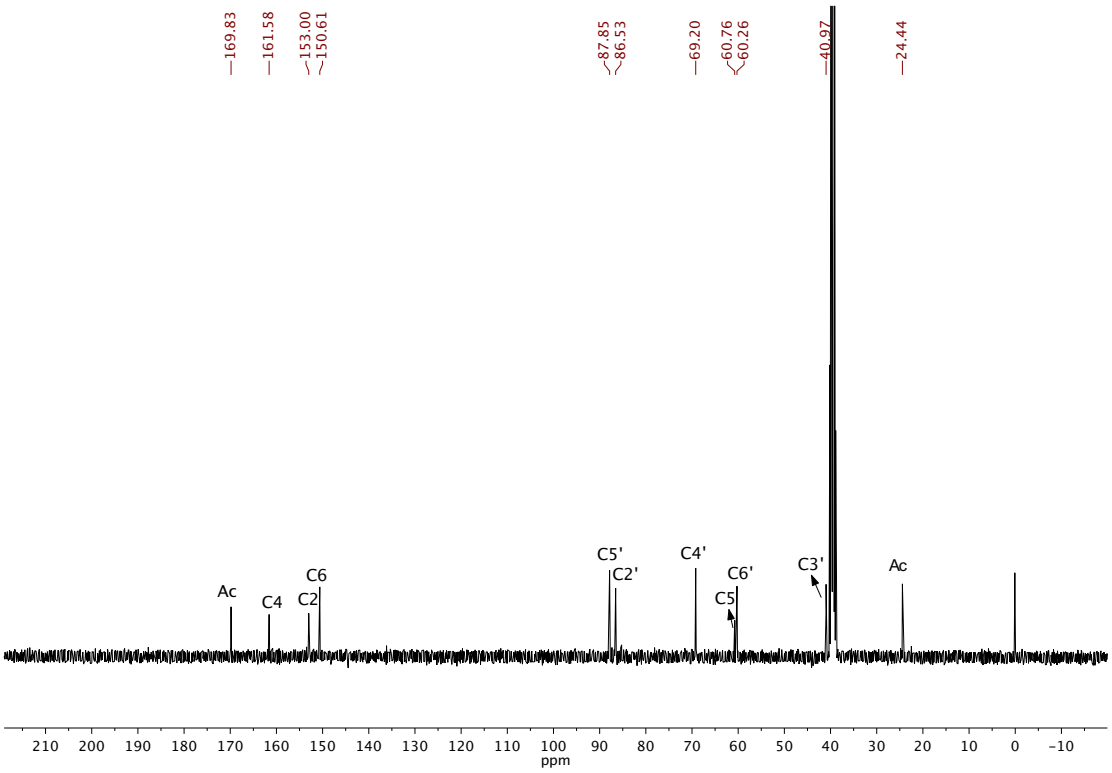
^{1}H-NMR (400 MHz, DMSO)



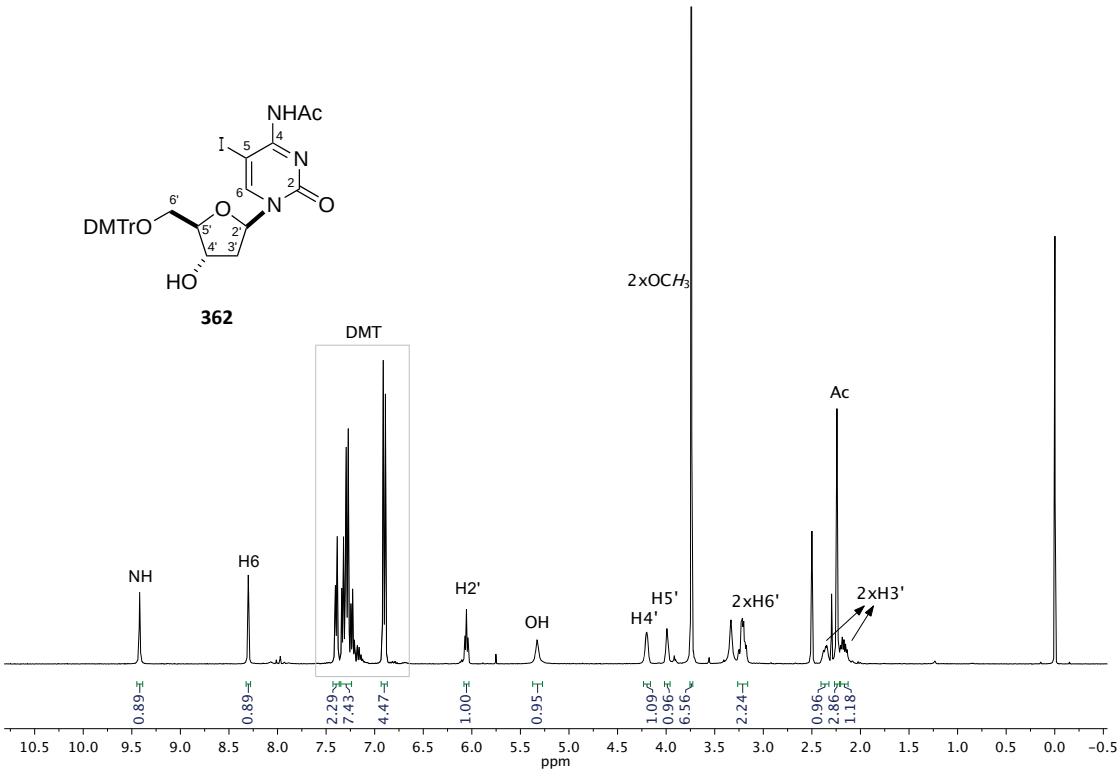
^{13}C-NMR (100 MHz, DMSO)



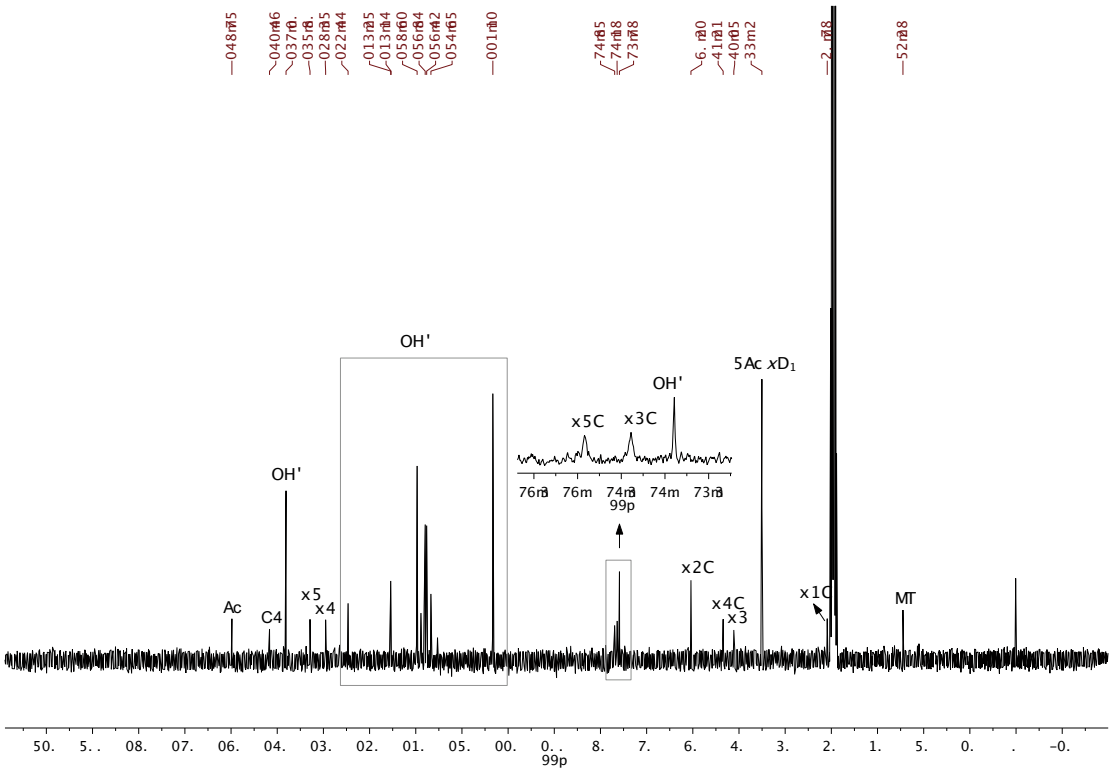
^{1}H-NMR (400 MHz, DMSO)



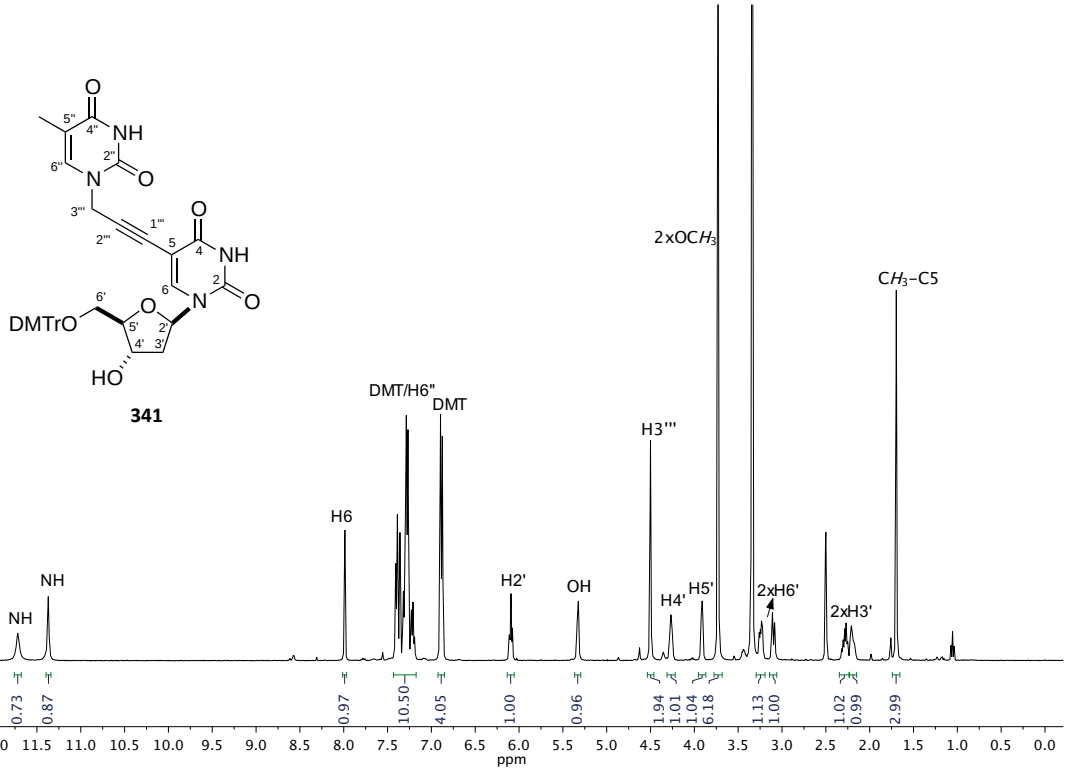
^{13}C-NMR (100 MHz, DMSO)



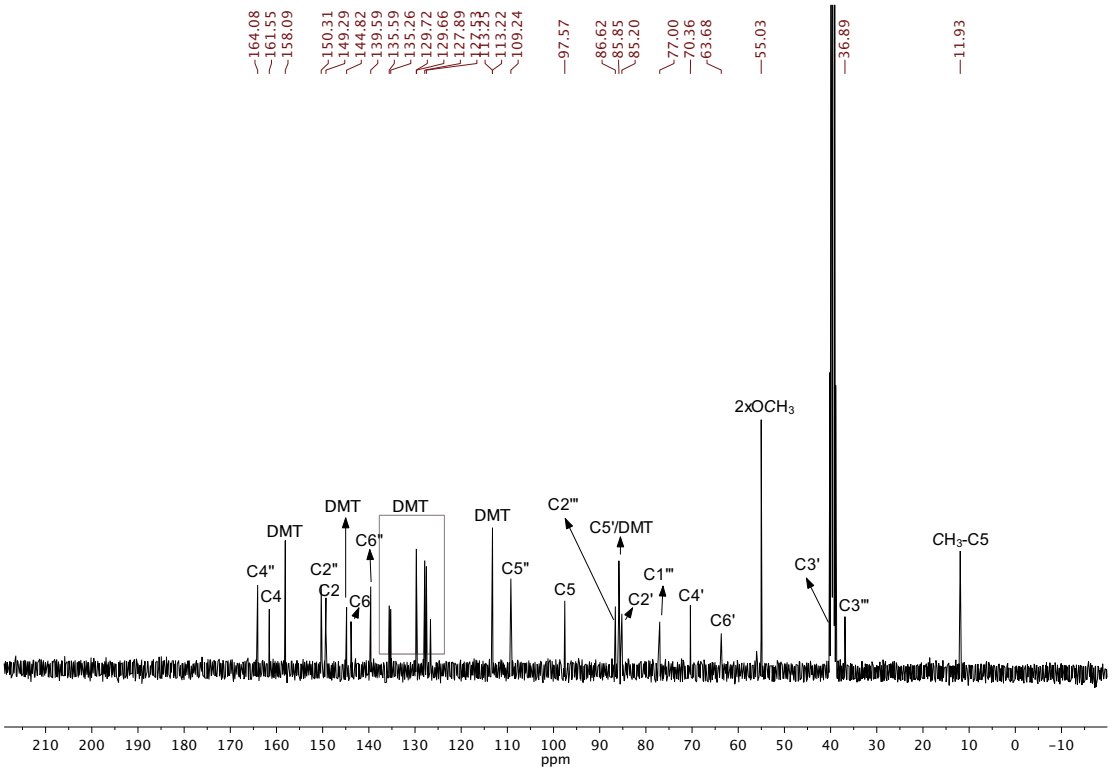
^{1}H-NMR (400 MHz, DMSO)



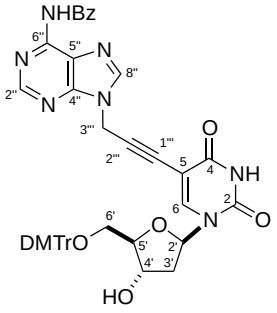
^{13}C-NMR (100 MHz, DMSO)



^{1}H-NMR (400 MHz, DMSO)



^{13}C-NMR (100 MHz, DMSO)



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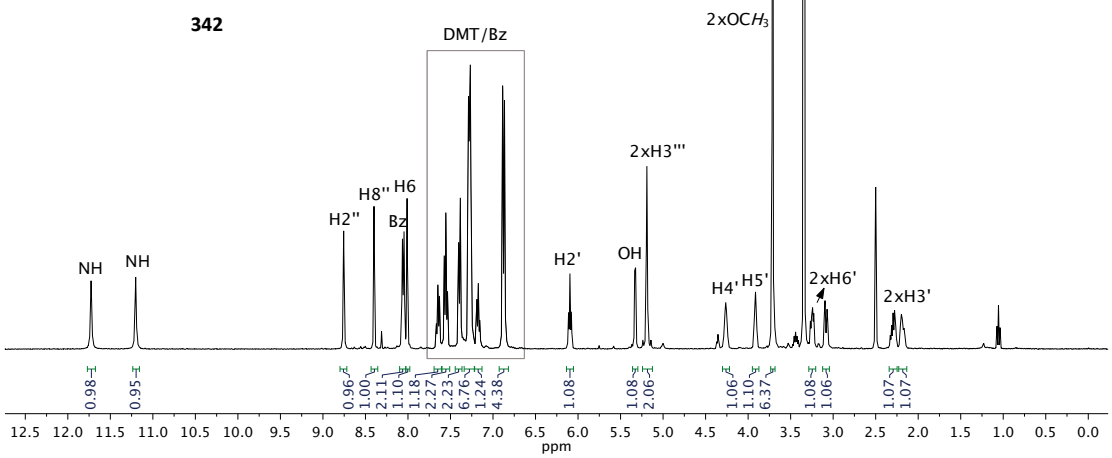
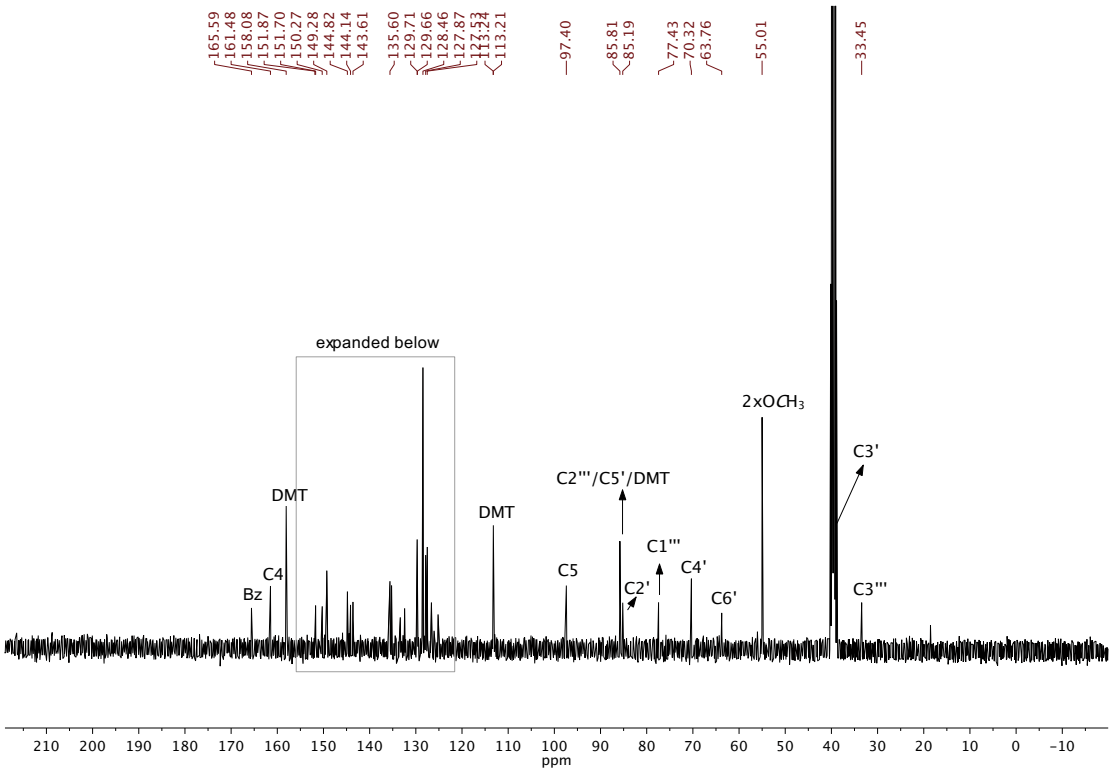
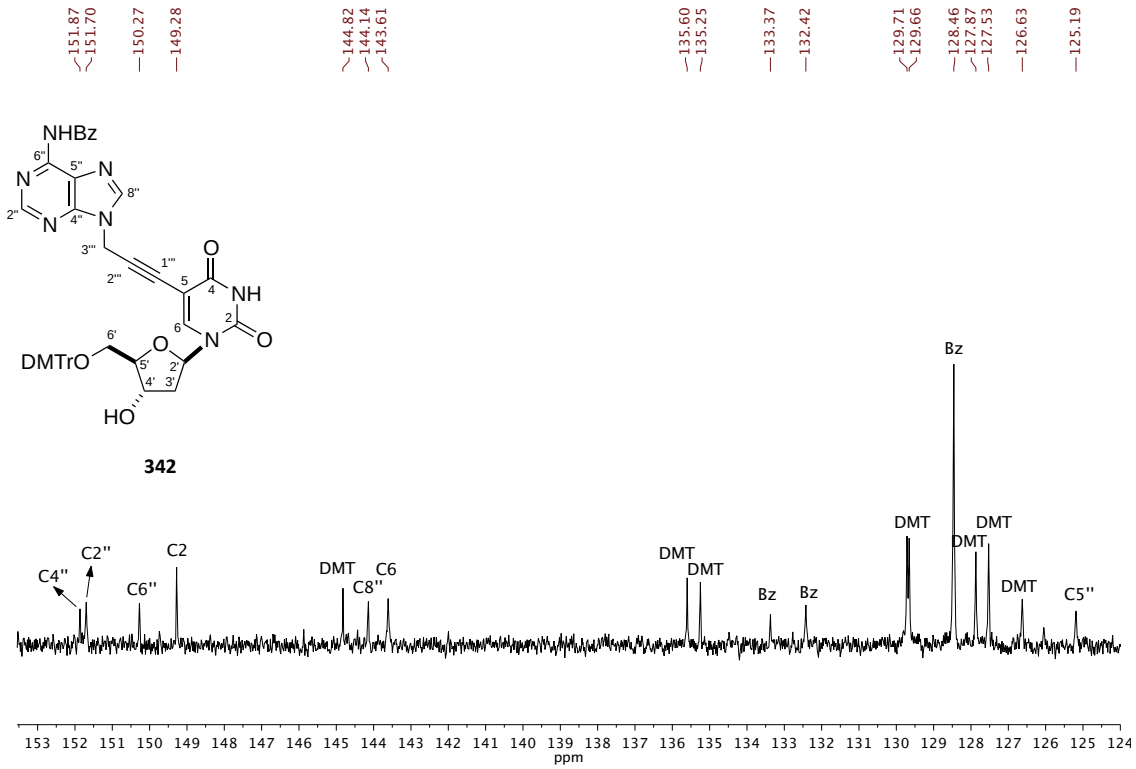


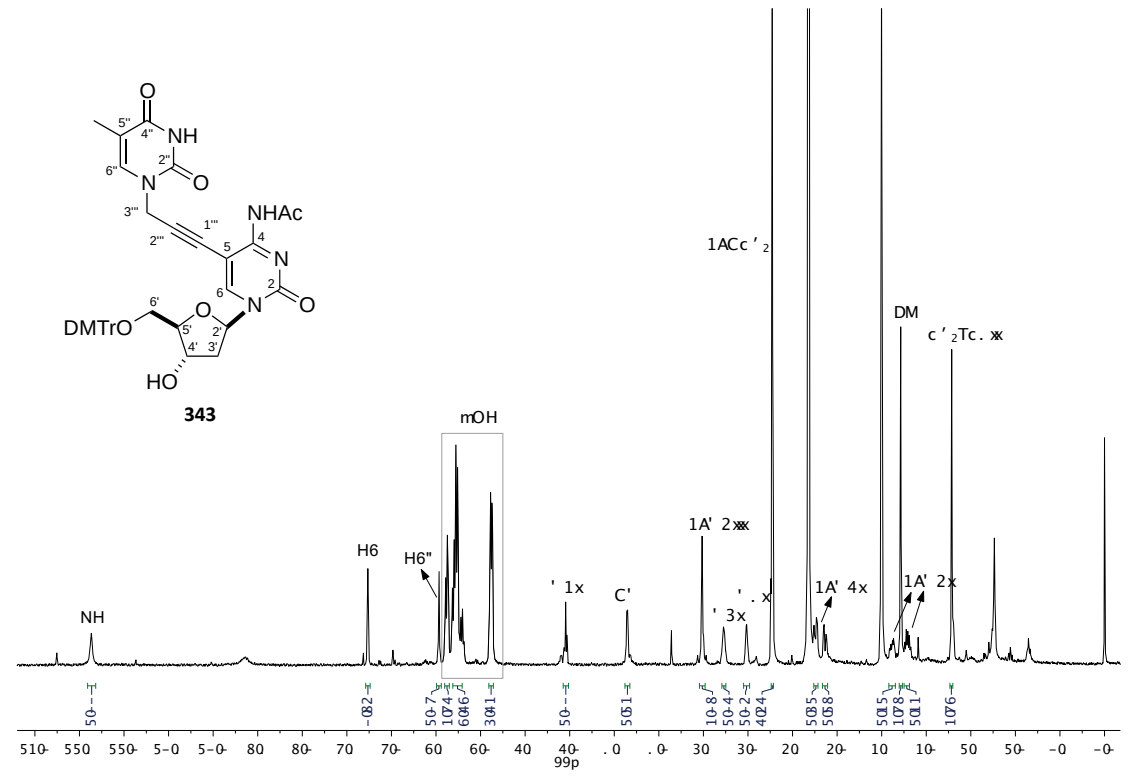
^{1}H-NMR (400 MHz, DMSO)



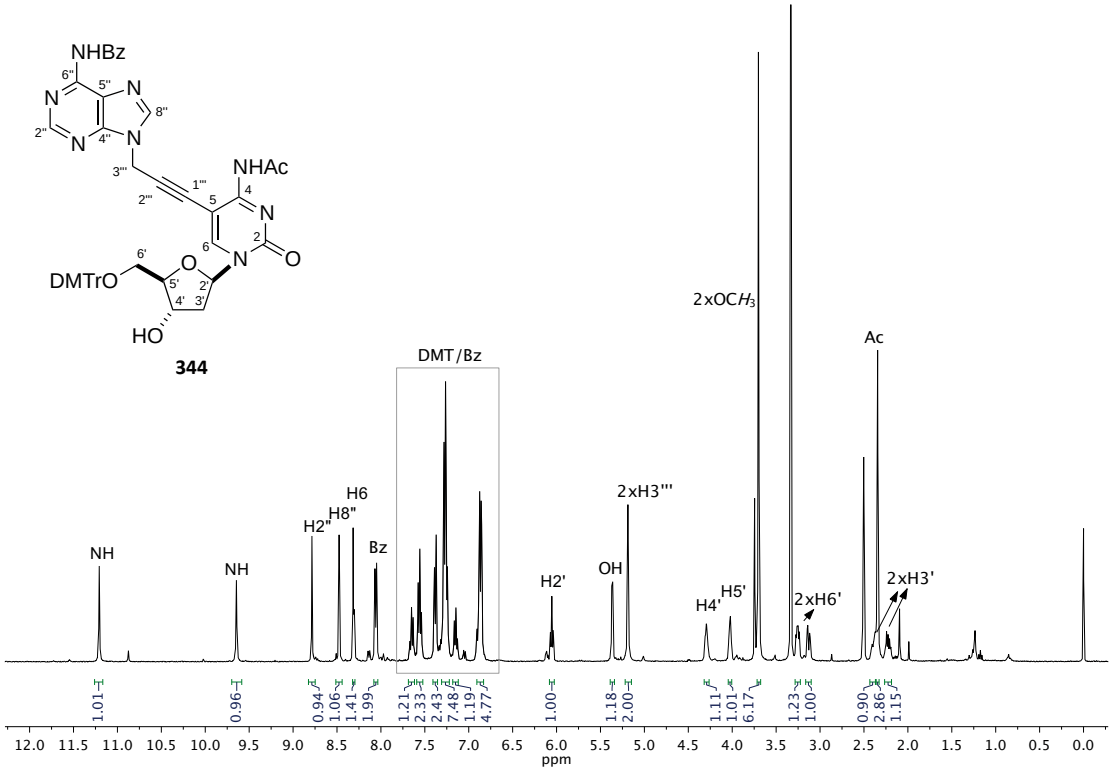
^{13}C-NMR (100 MHz, DMSO)



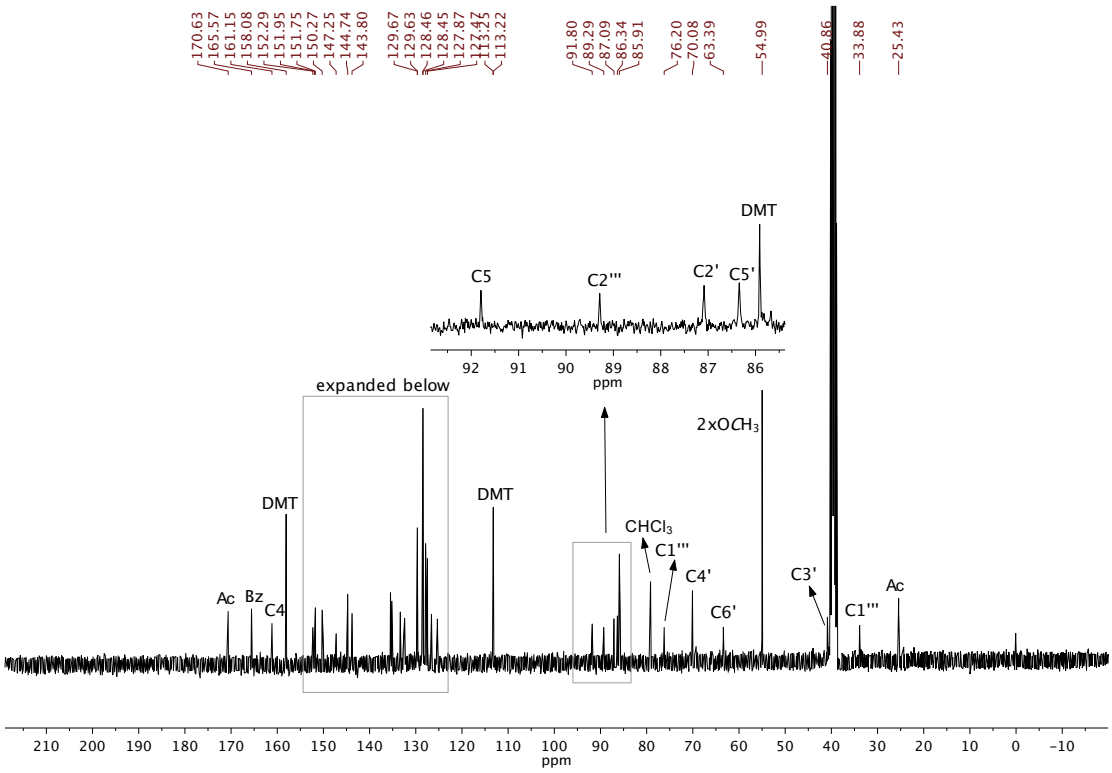
^{13}C-NMR (100 MHz, DMSO)



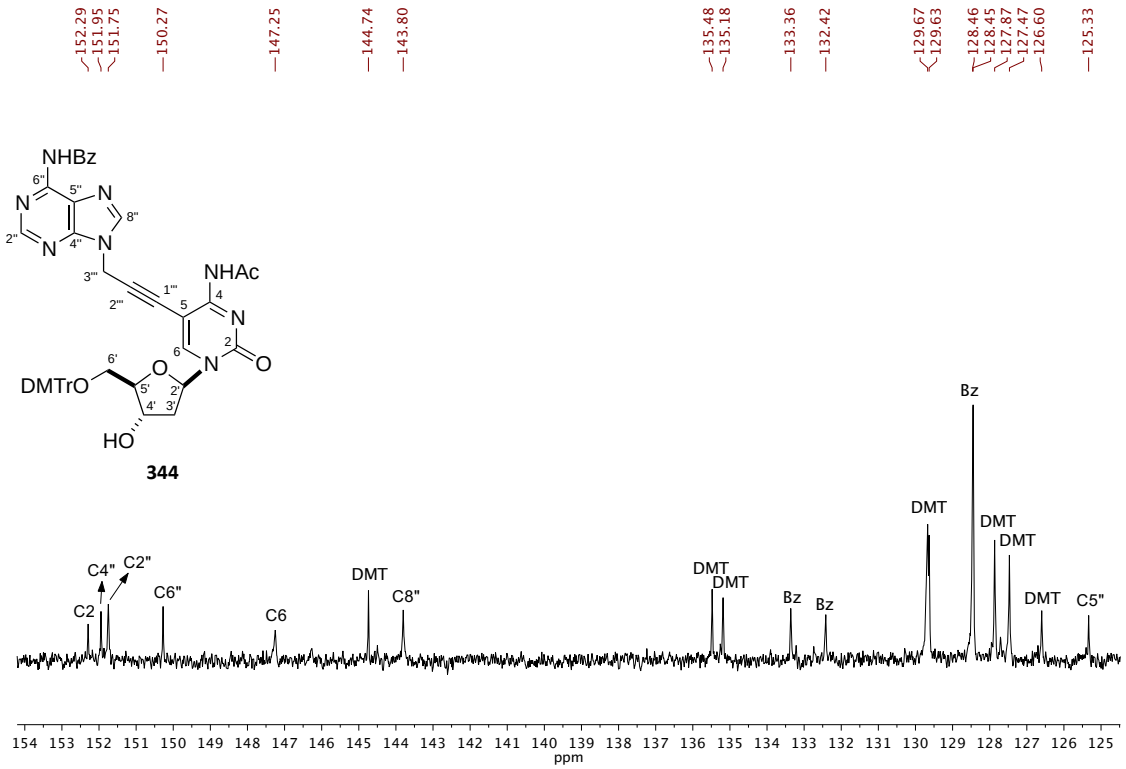
^{1}H-NMR (400 MHz, DMSO)



^{1}H-NMR (400 MHz, DMSO)



^{13}C-NMR (100 MHz, DMSO)



^{13}C-NMR (100 MHz, DMSO)

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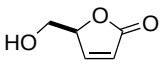
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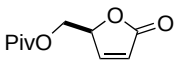
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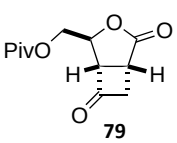
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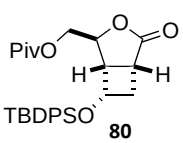
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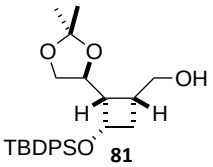
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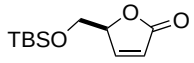
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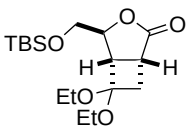
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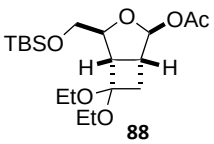
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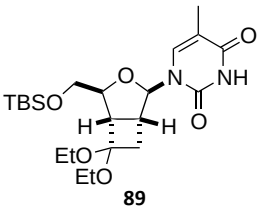
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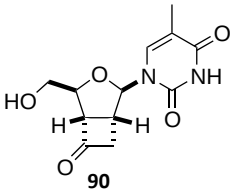
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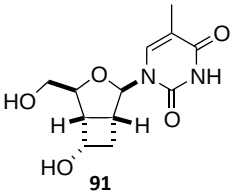
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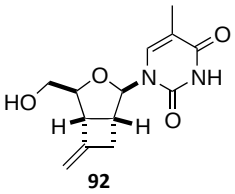
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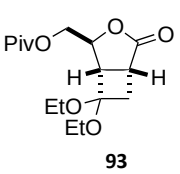
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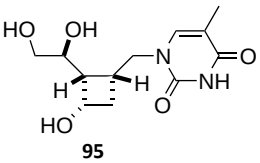
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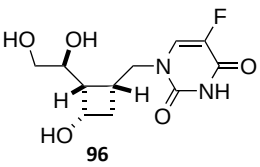
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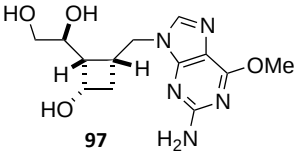
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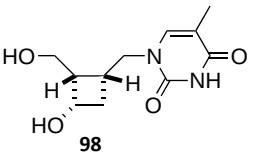
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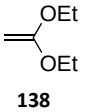
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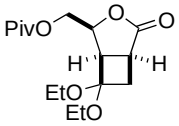
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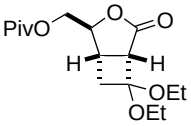
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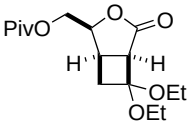
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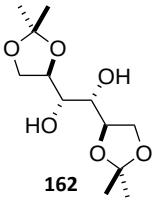
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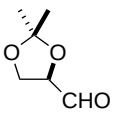
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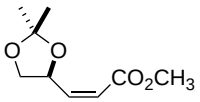
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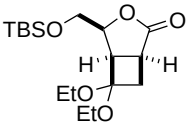
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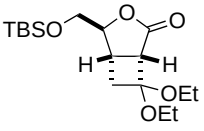
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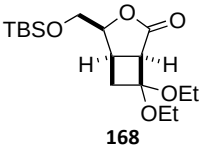
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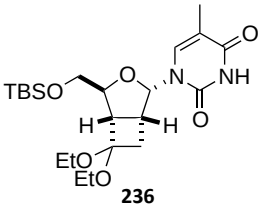
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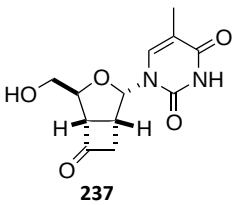
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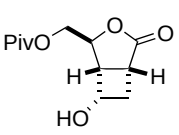
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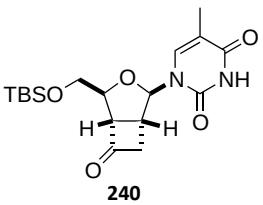
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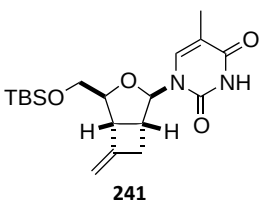
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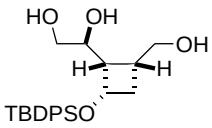
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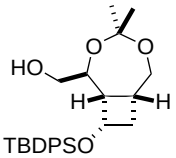
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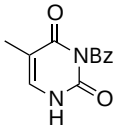
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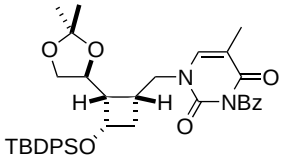
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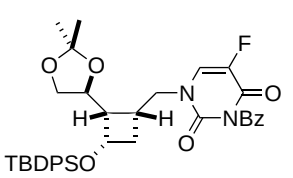

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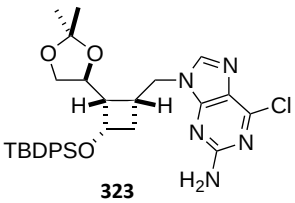

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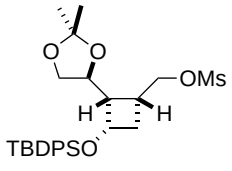

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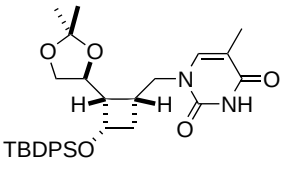

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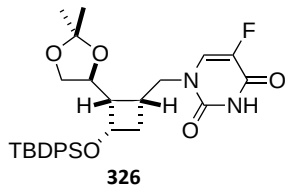

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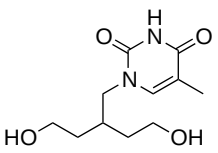

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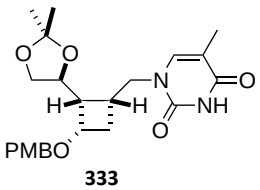

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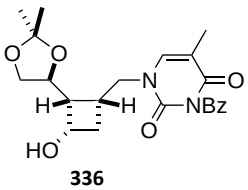

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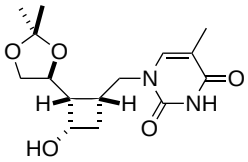

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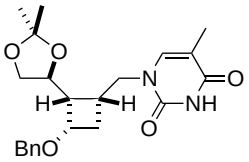

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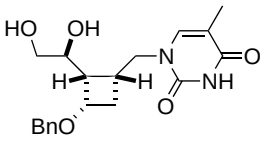

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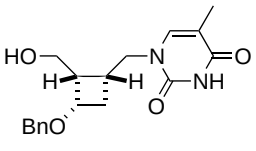

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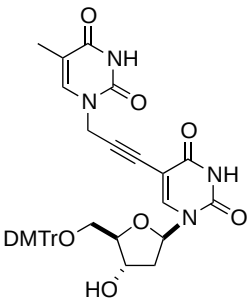

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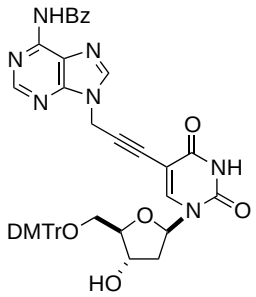

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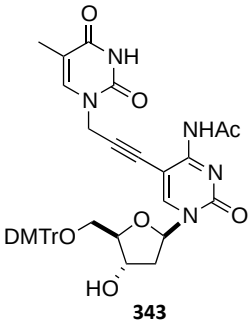

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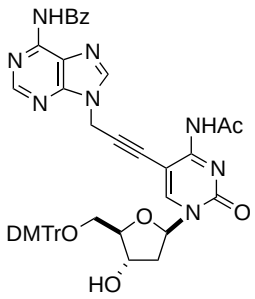

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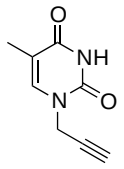

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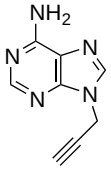

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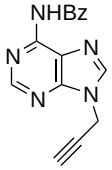

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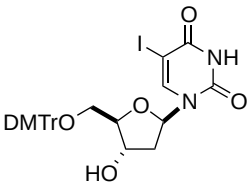

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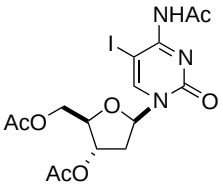

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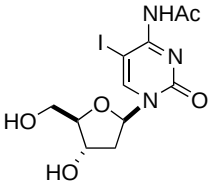

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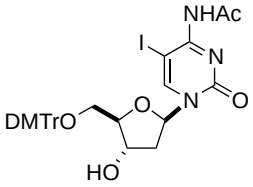

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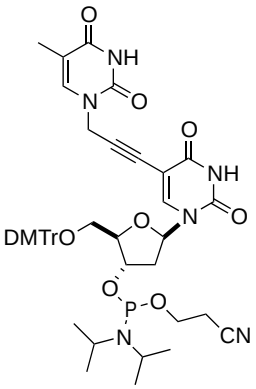

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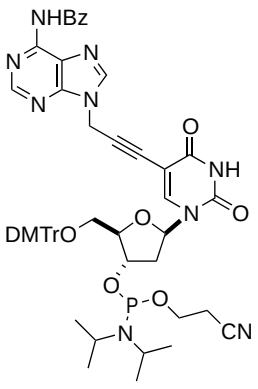

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