STUDIES ON THE SYNTHESIS OF NEW HEXOPYRANOSYL THYMINES

Thesis

Submitted to the

UNIVERSITY OF PUNE

for the degree of

DOCTOR OF PHILOSOPHY

in

CHEMISTRY

By

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in memories of my father and my elder brother
…..Nitin

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CERTIFICATE

This is to certify that the thesis entitled **"Studies on the Synthesis of New Hexopyranosyl Thymines"** submitted for Ph. D. degree to the University of Pune by **Mr. Sachin G. Deshpande** was carried out under the joint supervision of Dr. M. S. Shashidhar of the Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune - 411008 and myself. This work has been carried out in the Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune - 411008. Materials obtained from other sources have been duly acknowledged in the thesis.

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M. S. Shashidhar
August 24, 2006

DECLARATION

I hereby declare that the thesis entitled “Studies on the Synthesis of New Hexopyranosyl Thymines” submitted for Ph. D. degree to the University of Pune has not been submitted by me for a degree to any other University.

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Sachin G. Deshpande

CONTENTS

Abbreviations

A	*: Adenine*
Ac	*: Acetyl*
Ac_2O	*: Acetic anhydride*
AIBN	*: Azobisisobutyronitrile*
AZT	*: 2'-Azido 2',3'-dideoxy thymidine*
Bn	*: Benzyl*
Bz	*: Benzoyl*
C	*: Cyatosine*
C-n	*: Carbon atom numbered 'n'*
COSY	*: Correlation Spectroscopy*
DAST	*: Diethylaminosulphur trifluoride*
DBU	*: 1,8-Diazabicyclo [5.4.0] undec-7-ene*
DCM	*: Dichloromethane*
DEPT	*: Distortionless Enhancement by Polarization Transfer*
ddC	*: 2',3'-Dideoxycytidine*
ddI	*: 2',3'-Dideoxyinosine*
d4T	*: 2',3'-Dehydro 2',3'-dideoxythymidine*
DMAP	*: 4-Dimethylaminopyridine*
DMF	*: N,N-Dimethylformamide*
DMSO	*: Dimethyl sulfoxide*
DNA	*: Deoxyribo Nucleic Acid*
ddN	*: 2',3'-Dideoxynucleoside*
EDC	*: Ethylenedichloride*
EtOAc	*: Ethylacetate*
FddAra	*: 9-(2,3-Dideoxy-2-fluoro-ß-D-threo-pentofuranosyl)adenine*
G	*: Guanine*
H	*: Hypoxanthine*
Halo	*: Halogeno*
HIV	*: Human Immunodeficiency Virus*
HMBC	*: Heteronuclear Multiple Bond Correlation*
Hn	*: Hydrogen atom located on 'C-n'*
HSQC	*: Heteronuclear Single-Quantum Coherence*
Hz	*: Hertz*
IR	*: Infrared*
LAH	*: Lithium Aluminum Hydride*
LAD	*: Lithium Aluminum Deuteride*

mCPBA	*: m-Chloroperoxybenzoic acid*
MHz	*: Megahertz*
Ms	*: Methanesulfonyl*
MMTr	*: 4-Monomethoxytriphenylmethyl*
MMPP	*: Magnesium monoperoxypthalate*
Mp	*: Melting point*
Nu	*: Nucleophile*
NMR	*: Nuclear magnetic resonance*
ORTEP	*: Oak Ridge Thermal-Ellipsoid Plot Program*
PNB	*: 4-Nitrobenzoate*
ppm	*: Parts per million*
rt	*: Room temperature*
S_N1	*: Unimolecular nucleophilic substitution*
S_N2	*: Biomolecular nucleophilic substitution*
T	*: Thymine*
TEA	*: Triethylamine*
TFA	*: Trifluroacetic acid*
Th	*: Theophylline*
3TC	*: 2',3'-Dideoxy-3'-thiocytidine(L)*
TLC	*: Thin layer chromatography*
TolSH	*: Toluenethiol*
Ts	*: p-Toluenesulfonyl*
Tr	*: Triphenylmethyl*
U	*: Uracil*
X	*: Xanthine*

Synopsis of the Thesis

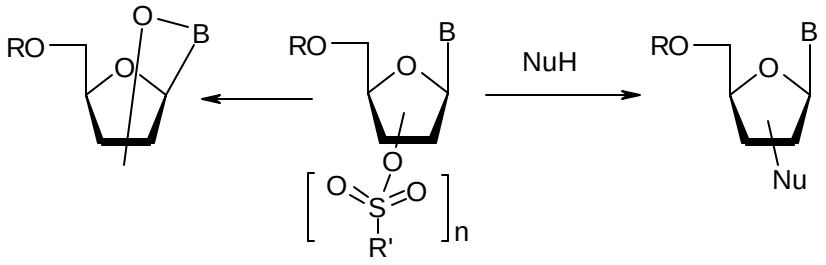
CHAPTER 1

Selected Methods for the Functionalization at the 2'- and /or 3'- sites of Pentofuranosyl Nucleosides

Dideoxynucleosides (ddNs), such as 2′,3′-dideoxyinosine (ddI), 2′,3′-didexoycytidine (ddC), 3′-azido-3′-deoxythymidine (AZT) etc appear to be the most successful anti-HIV prodrugs.[1] The chemotherapeutic properties of the ddNs triggered significant level of interest in the synthesis and biological properties of pentofuranosyl nucleosides over the years.[1] The modifications at the 2' and/or 3' positions are carried out using nucleoside intermediates such as, 2'-and /or 3'-*O*-sulfoates,[2a] 2,2'- and 2,3'-*O*-anhydro-,[2b] 2',3'-*O*-anhydro nucleosides etc.[2c] The reactions of these intermediates have been reviewed in this chapter.

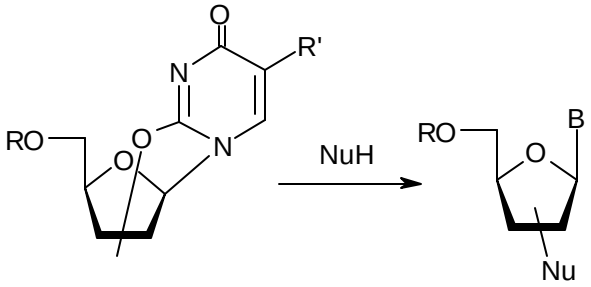
i) Displacement of the sulfonate groups: Nucleophilic substitution reactions on sulfonated nucleosides are the simplest and the direct methods for the incorporation of nitrogen, sulfur, and halogen or oxygen nucleophiles at the 2'- and / or 3'- sites (**Scheme 1.1**).

Scheme 1.1



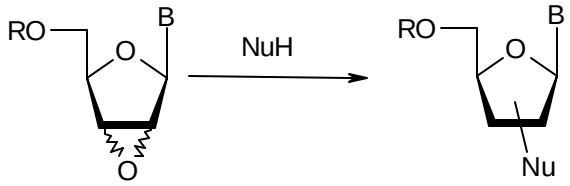
ii) Reactions of 2,2'- and 2,3'-*O*-anhydro nucleosides: In general, 2,2'- or 2,3'-*O*-anhydro pyrimidine nucleosides react with soft nucleophiles to afford 2'- or 3'-modified pyrimidine nucleosides (**Scheme 1.2**).

Scheme 1.2



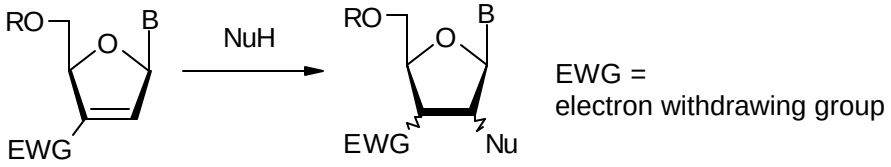
iii) Opening of 2',3'-*O*-anhydro nucleosides: 2',3'-*O*-Anhydro nucleosides are versatile intermediates and react with almost all nucleophiles including carbon nucleophiles (**Scheme 1.3**).

Scheme 1.3



iv) Reactions of unsaturated nucleosides: Activated unsaturated nucleosides are useful intermediates for the functionalization of the 2' and 3'-sites (**Scheme 1.4**).[3]

Scheme 1.4

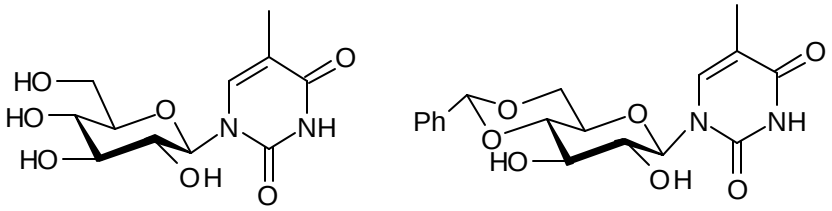


CHAPTER 2

A Systematic Approach towards the Functionlization of Hexopyranosyl Thymines

The biological properties of several unnatural hexopyranosyl nucleosides were also recognized quite early.[4] Although the functionalization of hexopyranosyl nucleosides at the 2', 3', or 4' positions poses major synthetic challenges, reported methodologies are narrowly focused to prepare only special classes of compounds.[5] Surprisingly, no serious effort has been made so far to develop general methodologies for the synthesis of modified hexopyranosyl nucleosides from common intermediates as was the case for the pentofuranosyl nucleosides.[6] It is, therefore, necessary to develop general strategies for the synthesis of a wide range of hexopyranosyl nucleosides. We envisaged that the synthesis of tosyl-, epoxy-, or 2,2'-O-anhydronucleosides of the hexopyranosyl type would pave the way for generating a wide range of unnatural nucleosides. However, it is important to note that the accessibility to important intermediates, such as 2,2'-*O*-anhydro-*altro*- and 2',3'-*O*-anhydrohexopyranosyl pyrimidine nucleosides is crucially dependent on the selective tosylation of the 3'-hydroxy group of tetrol **1** or the partially protected diol **2** (**Figure 2.1**).

Figure 2.1

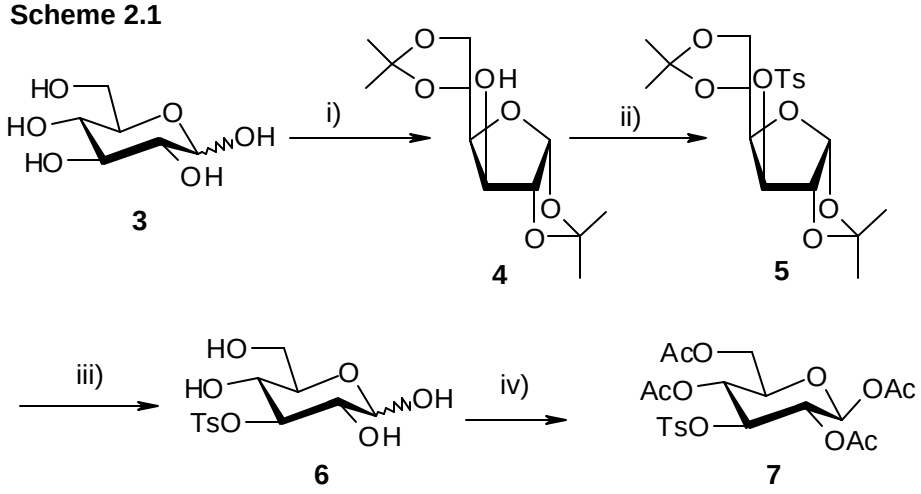


1 **2**

SECTION A

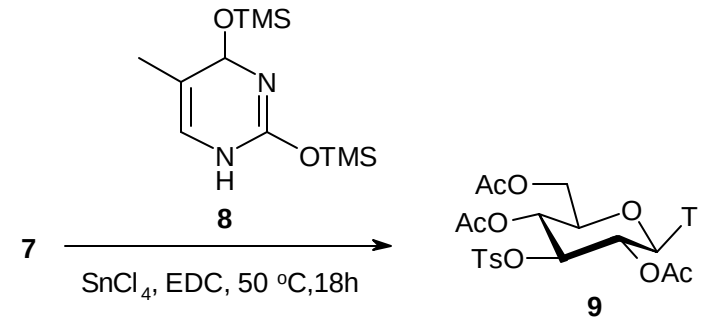
i) Synthesis of 1-(2,4,6-tri-*O*-acetyl-3-*O*-tosyl-*ß*-D-*gluco*pyranosyl) thymine 9: In the absence of any suitable methodology for the selective tosylation of the 3'-hydroxyl group of **1** or **2** we decided to incorporate the tosyl group in the sugar moiety prior to the synthesis of the nucleoside. For this purpose, 1,2,4,6-tetra-*O*-acetyl-3-*O*-tosyl-*b*-D-*gluco*pyranose **7**[7] was prepared in large scale from from D-glucose **3** via 1,2:5,6-di-*O*-isopropylidene-3-*O*-*p*-toluenesulfonyl-*a*-D-glucofuranose **5**[8] following a literature procedure used for the synthesis of *b*-D-pentaacetate glucose (**Scheme 2.1**).[9] Compound **7** was then coupled with bistrimethylsilylated thymine **8** in the presence of $SnCl_4$ to produce a single nucleoside **9** (**Scheme 2.2**).[10]

Scheme 2.1



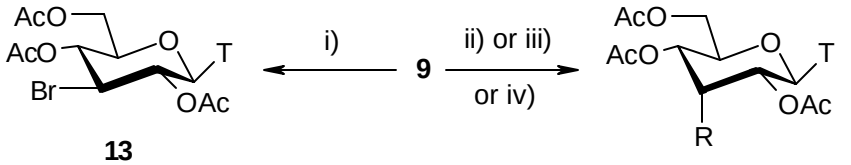
i) $FeCl_3$, acetone, reflux, 5h. ii) TsCl, pyridine, rt, 2.5 days. iii) 0.5 N H_2SO_4, dioxane, 100 ^oC, 5h. iv) NaOAc, Ac_2O, heat.

Scheme 2.2



ii) Reactions of 1-(2,4,6-*O*-triacetyl-3-*O*-tosyl-*ß*-D-*gluco*pyranosyl) thymine 9: 3'-functionalization of the carbohydrate moiety of hexopyranosyl thymine was achieved with ease *via* nucleophilic displacement reactions of 3'-*O*-tosyl *ß*-D-*gluco* nucleoside **9** with nitrogen, sulfur, oxygen and halogen nucleophiles yielding 3'-deoxy-3'-substitued-*ß*-D-*allo*pyranosyl thymines **10**-**12** and 3'-bromo-3'-deoxy-*ß*-D-*gluco*pyranosyl thymine **13** respectively (**Scheme 2.3**).

Scheme 2.3



10 R = N_3
11 R = p-TolS
12 R = AcO

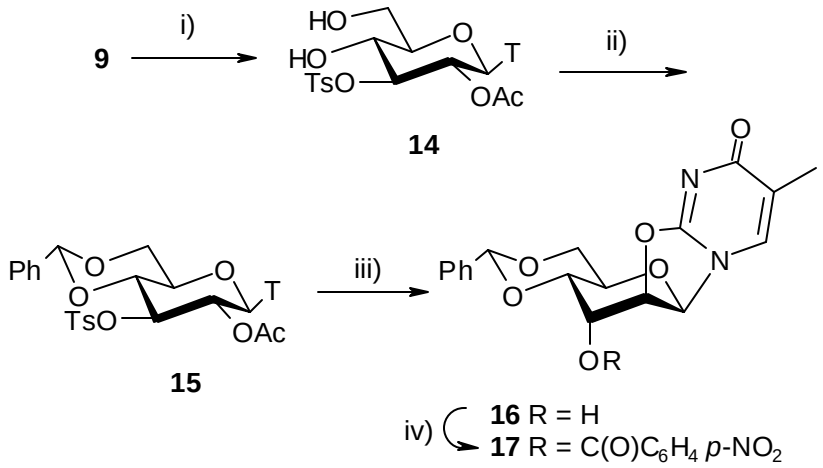
i) LiBr, DMF, 110 °C, 10h, 85%. ii) a. LiN_3, DMF, 120 °C, 20h. b. Ac_2O, pyridine, 61%. iii) a. NaOAc, DMF, 150 °C, 20h. b. Ac_2O, pyridine, 70%. iv) a. p-TolSH, NaOMe, DMF, 90°C, 10h. b. Ac_2O, pyridine, 70%.

SECTION B

i) Synthesis of 2,2'-*O*-anhydro-1-(4,6-*O*-phenylmethylene-*ß*-D-*altro*-pyranosyl) thymine 16: The attempted deacetylation of **9**, with NaOMe in MeOH furnished mixture of products whereas treatment with *iso*propylamine in MeOH afforded clean monoacetyl derivative **14**. Compound **14** was benzylidenated and identified as fully-protected 1-(2-*O*-acetyl-4,6-*O*-phenylmethylene-3-*O*-tosyl-*ß*-D-*gluco*-pyranosyl) thymine **15** in overall (from **9**) 70 % Yield. Treatment of **15** with NaOMe in MeOH, gave highly hygroscopic, 2,2'-*O*-anhydro compound **16**. Compound **16** was identified as its *p*-nitrobenzoate derivative **17** in 64 % yield (**Scheme 2.4**). The *altrose*-configuation of compound **16** reveals the *in situ*

formation of 2',3'-*O*-anhydro-*allo*-pyranosyl epoxide, followed by intramolecular attack of O-2 at C-2'.

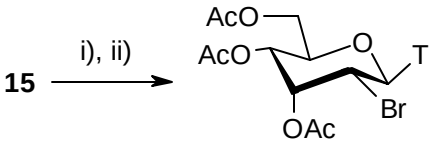
Scheme 2.4



i) isopropylamine, MeOH, 5h, rt. ii) $PhCH(OCH_3)_2$, TsOH, DMF, 1h, 100 °C. iii) NaOMe, MeOH, 30h, rt. iv) *p*-$NO_2C_6H_4COCl$, pyridine, 0 °C to rt, overnight, 64% (from **15**).

ii) Reactions of 2,2'-*O*-anhydro *altro*pyranosyl thymine 16: To establish the usefulness of the 2,2'-*O*-anhydro *ß*-D-*altro* pyranosyl thymine, we decided to react **16** with nucleophiles. However, only the bromide nucleophile in the presence of the catalytic amount of trifluroacetic acid could successfully open the 2,2'-*O*-bridge to afford 2'-bromo compound. The de-benzylidenated product was acetylated with acetic anhydride and pyridine at room temperature for overnight to afford the tri-O-acetyled *ß*-D-*allo* nucleoside **18** in 30 % overall yield from compound **15** (**Scheme 2.5**).

Scheme 2.5

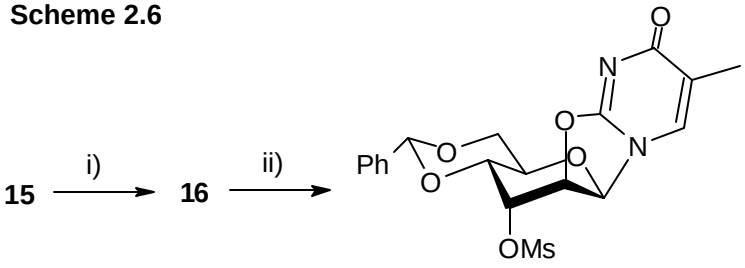


i) NaOMe, MeOH, 30h, rt. ii) a. LiBr, TFA, DMF, 90 °C, 24h. b. Ac_2O, pyridine, rt, overnight.

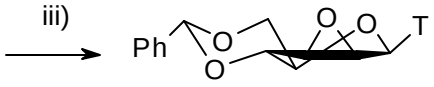
SECTION C

i) Synthesis of 1-(2',3'-*O*-anhydro-4,6-*O*-phenylmethylene)-ß-D-*manno*-pyranosyl thymine 20: Compound **16** was mesylated with mesyl chloride in pyridine at 0 ^{o}C to afford, 2,2'-*O*-anhydro-1-(4,6-*O*-phenylmethylene-3-deoxy-3-*O*-mesyl-ß-D-*altro*-pyranosyl) thymine **19**. On reaction with aqueous NaOH, the crude mesylated product **19** was converted directly to the targeted 2',3'-*O*-anhydro-ß-D-*manno*-pyranosyl thymine **20** (**Scheme 2.6**). The overall yield of product **20** starting from compound **15** was 30-34%.

Scheme 2.6



19



20

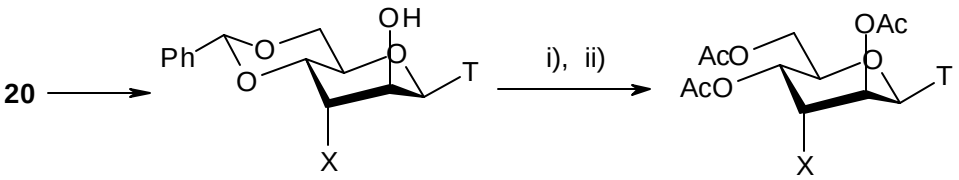
i) NaOMe, MeOH, 30h, rt. ii) MsCl, pyridine, 0-4 ^{o}C, overnight. ii) aq. NaOH, dixoane, rt, 0.5h.

ii) Reactions of *manno*-epoxide 20: To exploit the synthetic utility of epoxide nucleoside **20**, a range of nucleophiles was selected for opening the epoxide ring for producing a series of 3'-deoxy-3'-substitued-ß-D-*altro*pyranosyl thymines **21a-i** (**Scheme 2.7**). The nitrogen nucleophiles such as azide, isobutylamine, pyrrolidine, 1-acetyl piperidine and morpholine, a planar heterocylcle imidazole reacted smoothly with the epoxy-nucleoside. On the other hand, two sulphur nucleophiles, namely SCN and p-TolS and one carbon nucleophile CN also reacted with **20** and established the general pattern of addition of a range of nucleophiles to this epoxy-nucleoside. All compounds were isolated and characterized as the triacetyl derivatives **22a-i** (**Scheme 2.7**).

SECTION D

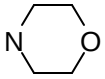
i) Attempted synthesis of 1-(2,3-dideoxy-(3-*C*-*p*-toluenesulfonyl)-4,6-*O*-phenylmethylene-ß-D-hex-2-*eno*pyranosyl) thymine 25: The synthesis of compound **25** was attempted, starting from the partially protected thio-nucleoside **23**. Thus, the displacement of the tosyl group from **9** with p-TolSNa in DMF, followed by deprotection

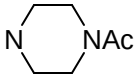
Scheme 2.7



21a LiN_3, NH_4Cl, EtOH, reflux, 10h, 83%.
21b isobutylamine, DMSO, 70 °C, 22h, 79%.
21c pyrrolidine, DMSO, 90 °C, 24h, 84%.
21d morpholine, DMSO, 90 °C, 25h, 80%.
21e 1-acetylpiperazine, 90 °C, 30h, 56%.
21f imidazole, TMG, DMSO, 70 °C, 20h, 86%.
21g TolSH, NaOMe, DMF, 70 °C, 10h, 66%.
21h NH_4SCN, DMF, 70 °C, 10h, 71%.
21i NaCN, DMF, 70 °C, 10h, 68%.

22a (65%). **22b** (70%). **22c** (85%).
22d (75%). **22e** (75%). **22f** (65%).
22g (55%). **22h** (56%). **22i** (65%).

X = a) N_3 b) $HNCH_2CH(CH_3)_2$ c)  d) 

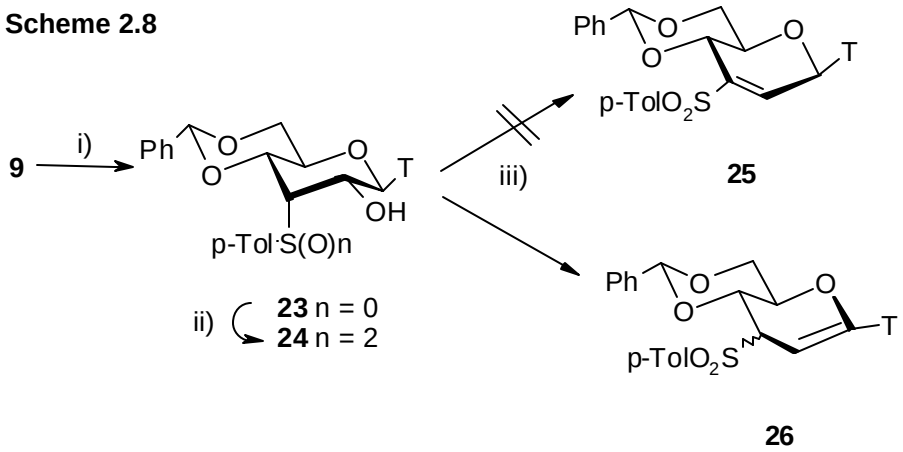
e)  f)  g) p-TolS h) SCN i) CN

i) TFA, water, rt, 10-20 min. ii) Ac_2O, pyridine, rt, overnight.

and benzylidenation gave partially protected nucleoside **23**. Compound **23** was oxidized using MMPP (magnesium monoperoxy perphthalate) in MeOH to produce the corresponding sulfone **24**. The crude sulfone product was mesylated under standard condition. However, on treatment with DBU (1,8-diazabicyclo [5.4.0] undec-7-ene) the mesyl derivative did not produce the desired vinyl sulfone **25**; instead, the unwanted hex-1-enopyranosyl nucleoside **26** was obtained (**Scheme 2.8**).

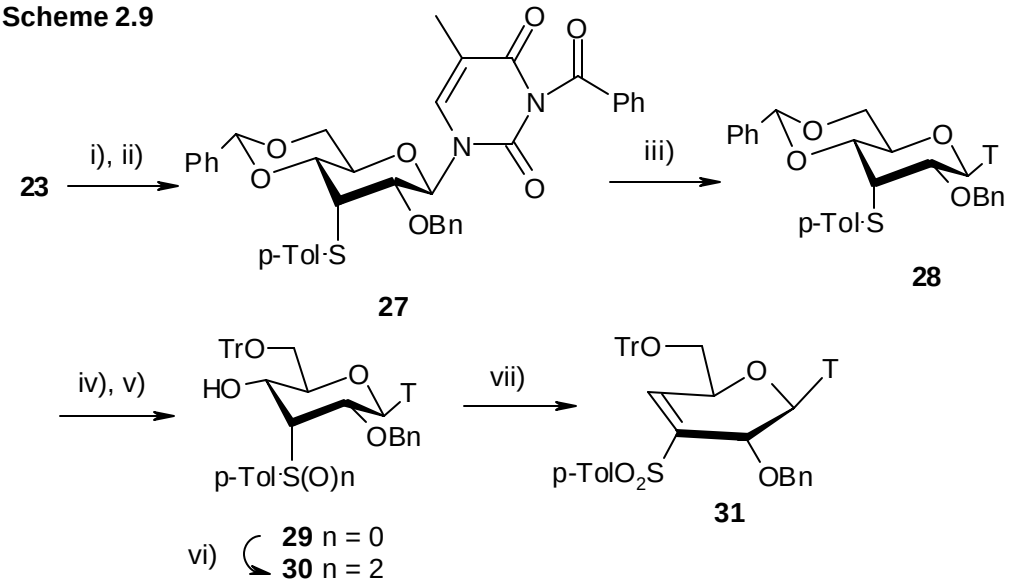
ii) Synthesis and reactions of 1-[2-*O*-benzyl-3,4-dideoxy-(3-*C*-*p*-toluenesulfonyl)-6-*O*-trityl-*erythro*-ß-D-hex-3-*eno*-pyranosyl] thymine 31: For the generation of a C3'—C4' double bond, it was necessary to block the 2'-hydroxyl group with a protecting group stable towards nucleophiles like amines. Therefore, we decided to synthesize the 2'-*O*-benzyl ether **28**. Thus, the thio nucleoside **23** was benzoylated and the product was benzylated to produce **27**. Compound **27** on treatment with NaOMe in MeOH afforded **28**. The benzylidiene group of **28** was removed using 80 % TFA: water; the C-6' hydroxyl group of the product was tritylated selectively with trityl chloride in pyridine at an elevated temperature to give **29**. Compound **29** was oxidized using MMPP in MeOH, to produce sulfone **30**. Compound **30** was mesylated at C-4' with mesyl chloride in pyridine at 0-4 °C to produce the elimination product 3'-*eno* pyranosyl nucleoside **31** (**Scheme 2.9**).

Scheme 2.8



i) a. p-TolSH, NaOMe, DMF, 90 °C, 10h. b. NaOMe, MeOH, rt, 6h. c. $PhCH(OCH_3)_2$, TsOH, DMF, 100 °C, 1.5h, 65% (from **9**).
ii) MMPP, MeOH, rt, 3-3.5h. iii) a. MsCl, pyridine, 0-4 °C, overnight. b. DBU, DCM, rt, 5h, 52% (from **23**).

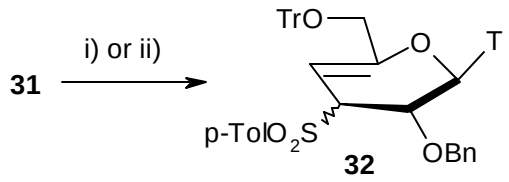
Scheme 2.9



i) a.TMSCl, pyridine, 30 min., BzCl, pyridine, rt, overnight. b. 0.05%TFA, $CHCl_3$, MeOH, 30 min. ii) BnBr, NaH, DMF, rt, overnight. iii) NaOMe, MeOH, rt, 3h. iv) aq.TFA (80%), rt, 30 min. v) TrCl, pyridine, reflux, 2h. vi) MMPP, MeOH, rt, 3h. vii) MsCl, pyridine, 0-4 °C, overnight.

Reactions of compound **31** with several amines and carbon nucleophiles did not produce any stable Michael adducts. However, the reactions of primary amine such as benzyl amine and the secondary amine, piperidine in the non-polar solvent such as ethylenedichloride (EDC) caused the isomerization of the C3'—C4' double boned to give the more stable product, namely 1-[2-*O*-benzyl-3,4-deoxy-(3-C-*p*-toluenesulfonyl)-6-*O*-trityl-*erythro*-*ß*-D-hex-4-*eno*-pyranosyl] thymine **32** in 50-55% yield (**Scheme 2.10**).

Scheme 2.10



i) benzylamine, EDC, rt, 48h, 55%.
ii) piperadine, EDC, rt, 5h, 50%.

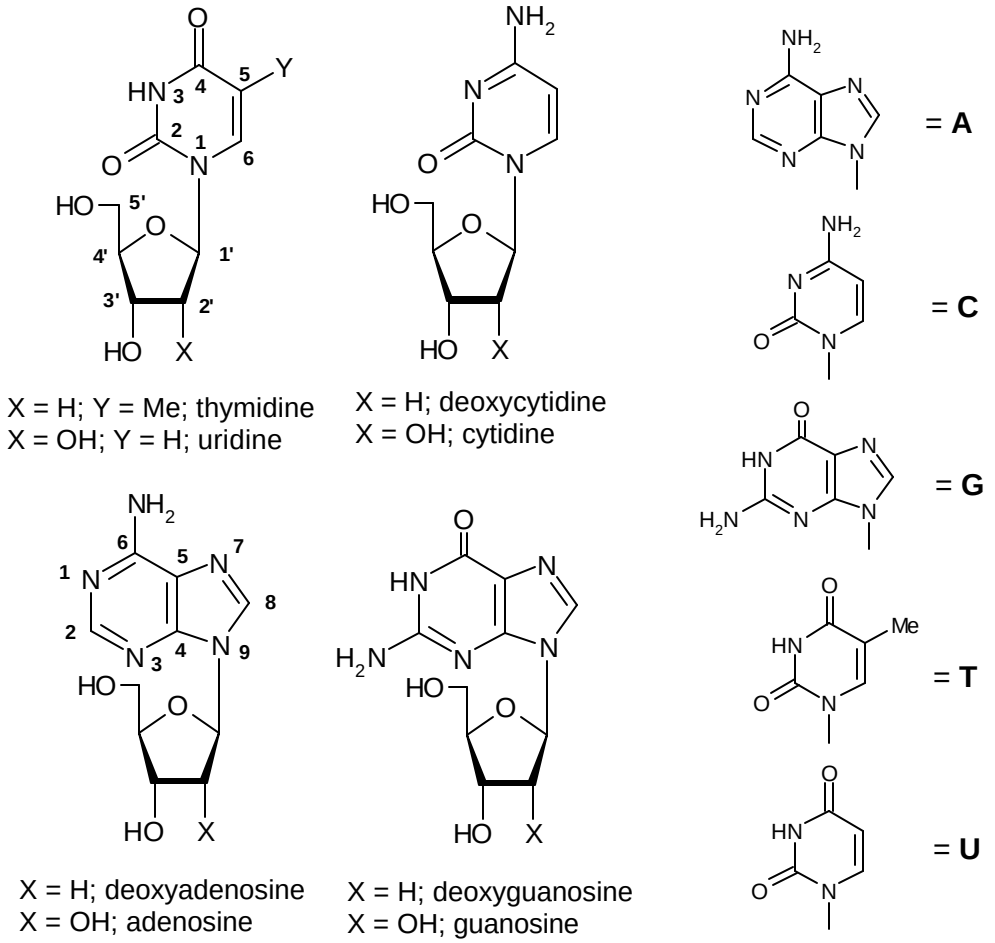
CHAPTER ONE

Selected Methods for the Functionalization of the 2'- and /or 3'- sites of Pentofuranosyl Nucleosides

1.1 Introduction

The term 'nucleoside' was introduced in 1909 to describe carbohydrate derivatives of the purine and pyrimidine bases. Nucleic acids, building blocks of DNA and RNA contain nucleosides of two types: derivatives of D-ribose (ribonucleosides) and those of 2 -deoxy-D-ribose (deoxyribonucleosides). In nucleosides which are constituents of DNA or RNA, the pyrimidine or purine ring is joined from a ring nitrogen to the anomeric carbon of a pentose sugar (**Figure 1.1.1**).[1]

Figure 1.1.1



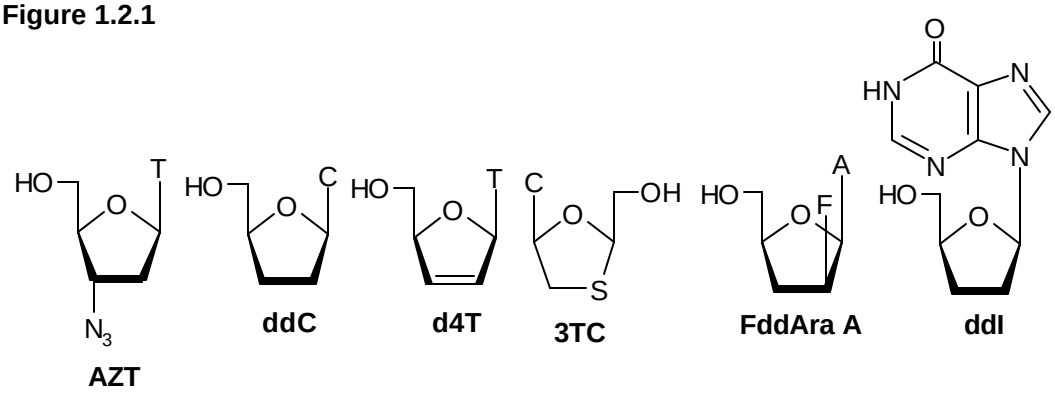
Although the synthesis of modified nucleosides has been of interest for over four decades, the finding that 3'-azido-3'-deoxythymidine or AZT is a therapeutic agent for the treatment of acquired immunodeficiency syndrome (AIDS), has triggered explosive new developments in the synthetic chemistry of nucleosides.[2] Therefore, today the term "nucleoside" describes a broad class of naturally occurring and synthetic compounds that are essentially various combinations of nitrogen heterocycles, aromatic ring systems and

carbohydrates and their cyclic or acyclic derivatives as well as systems where the ring oxygen of sugar has been replaced by *S*-, *N*- and even a methylene group.[2]

1.2 Sugar modified nucleosides

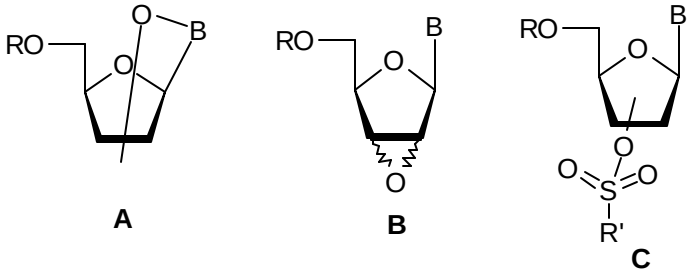
Modification of the sugar moiety of nucleosides produced marked change in their spectrum of biological activity and degree of selectivity, toxicity as well as their chemical and physical properties. In the context of antiviral compounds in particular, modification of 2'- and/or 3'-positions have resulted in compounds with broad range of biological activities (**Figure 1.2.1**).[2]

Figure 1.2.1



Modification of the sugar moiety at 2'-and/ or 3'- positions with either reversal or retention of the configuration is readily achieved via nucleophilic opening of anhydro -pyrimidines (**A**), epoxides of pyrimidine and purine nucleosides (**B**) or by simple nucleophillic displacement at 2'- and/or 3'- sites using sulfonates (**C**) as leaving groups (**Figure 1.2.2**).

Figure 1.2.2



Such functional modifications at 2'- and 3'-positions, occurring have been reviewed in this chapter. Syntheses of modified nucleosides using these intermediates from the early years to the mid-1970s have been reviewed.[3] The developments that have taken place over the last three decades in this area will be discussed in this review. We have also

included a discussion on unsaturated nucleosides which is relevant to our work. In this chapter starting materials have been compiled in figure **1.XA** and products in figure **1.XB** or **C**.

1.3 2'-*O*-Sulfonated pyrimidine nucleosides (Figures 1.3A and 1.3B)

The *azido group* was introduced at the 2'-position of the sugar moiety of pentofuranosyl nucleosides by sulfonate displacement reactions. Displacement of the 2'-*O*-triflate group of **1.001a** by azide followed by deprotection gave 2'-azido-2'-deoxyarabinoadenosine **1.007a**. Compound **1.007a** was reduced to 2'-amino-2'-deoxy nucleoside **1.007b**.[4a] Diazido **1.008a** and monoazido uridine **1.008b** derivatives were synthesized from **1.002a** and **1.002b** respectively via intra-molecular neighboring group assistance.[4b] Compounds **1.001b** and **1.001c** were converted to 2'-amino-2'-deoxy-ß-D-arabinofuranosyl purine nucleosides **1.007b** and **1.007c** and their biological properties were reported.[4c] A method for the synthesis an antibiotic 2'-amino-2'-deoxyguanosine **1.008c** from **1.003a** was reported.[5] 2'-Deoxy-2'-*N*-phthaloyl nucleosides **1.008d-f** were prepared from arabinonucleosides **1.003b-d** by triflate displacement with phthalimide in the presence of DBU. Compounds **1.008d-f** were subsequently converted to 2'-deoxy-2'-aminonucleosides and their phosphoramidites.[6] Compound **1.009a** and **1.009b** were synthesized by reacting 8-bromo-2'-*O*-toluene-*p*-sulfonyladenosine **1.001h** hydrazine and methylhydrazine respectively.[7]

Oxygen nucleophiles are also known to react with the sulfonated nucleoside derivatives. A synthesis of the L-enantiomer of nelarabine **1.010** is described; using appropriately protected 2'-*O*-sulfonated nucleoside **1.004**.[8] The reaction of 2'-*O*-tosyl-3',5'-di-*O*-benzoyl-1-ß-D-xylofuranosylthymine **1.005** with BzONa followed by deprotection with MeONa-MeOH afforded 2,2'-*O*-anhydro-1-ß-D-lyxofuranosylthymine **1.011**.[9] Similarly, the synthesis of 8,2'-*O*-cyclonucleoside **1.012a** and **1.013a** from 8-bromo nucleosides **1.001h** and **1.001i** was reported.[10]

9-(2-deoxy-2-*alkyldithio*-ß-D-arabinofuranosyl) purine nucleoside **1.007e** was synthesized from **1.007d** which was a displacement product of **1.001a**.[11] Compounds **1.001a** and **1.003e** were reacted with 9-(4-methoxyphenyl) xanthene-9-thiol (AXT) in the presence of TMG for accessing 2'-thio arabinoadenosine **1.007f** and its ribo-analogue **1.008h** respectively.[12] Suitably protected 2'-deoxy-2'-(*t*-butylthio)-ß-D-purines **1.008i** and **1.008j** were synthesized from 2'-*O*-triflate derivatives **1.003d** and **1.003f**.[13] 8,2'-*S*-cyclonucleosides **1.012b** and **1.013b** were synthesized efficiently from 2'-*O*-tosyl-8-bromopurine nucleosides **1.001h** and **1.001i** respectively.[14]

2'-Haloeno-derivatives of base modified arabinofuranosyl adenosines **1.007g** and **1.007h** were synthesized from **1.001j**.[15] 9-(2-Deoxy-2-fluoro-ß-D-arabinofuranosyl) hypoxanthine **1.007i** was obtained by the displacement of the 2'-*O*-triflate group **1.001k** by fluoride.[16] Analogues of antibiotics toyocamycin and sangivamycin, **1.007j-k**, were synthesized

Figure 1.3A: 2'-*O*-Sulfonylated nucleosides

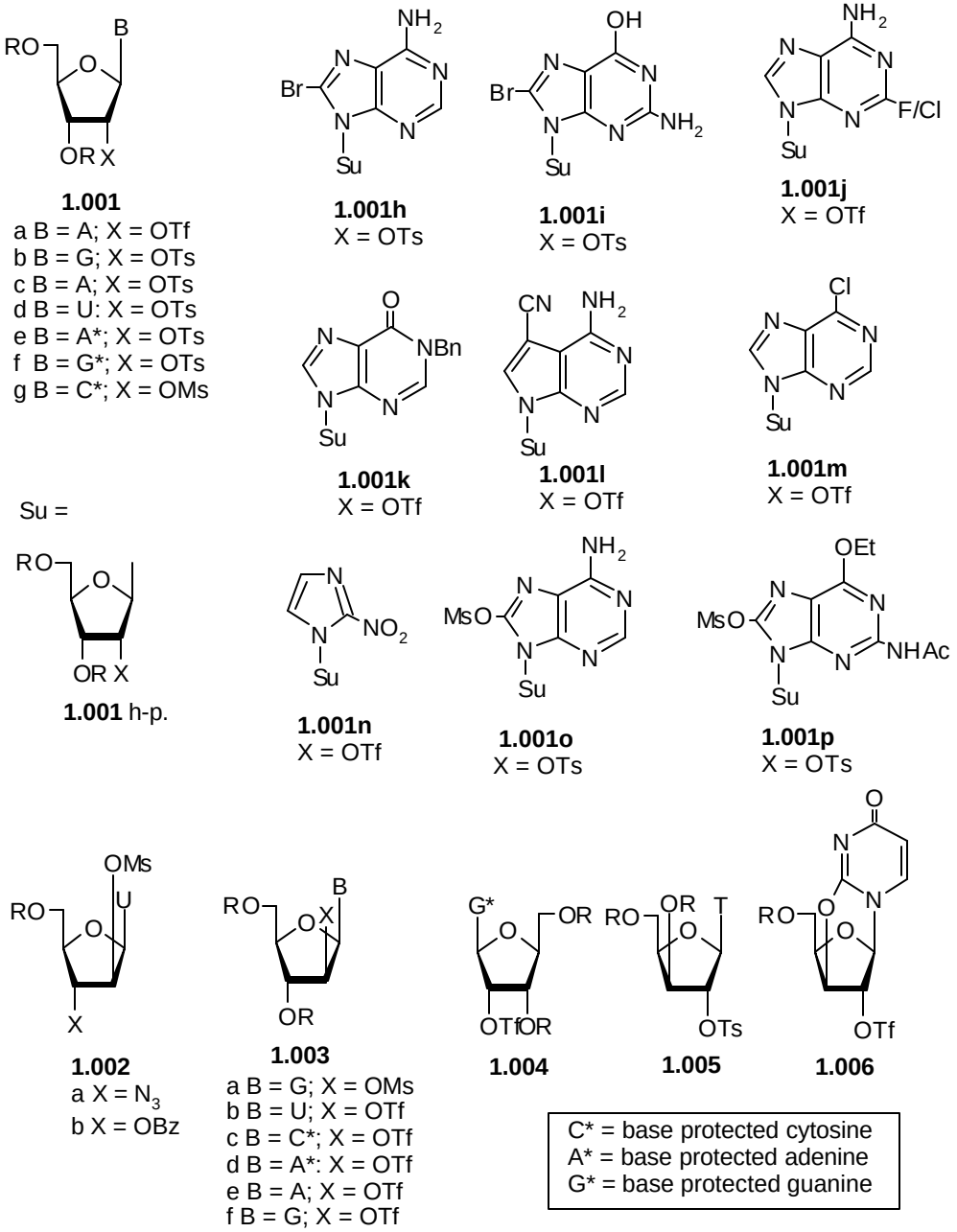
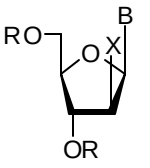
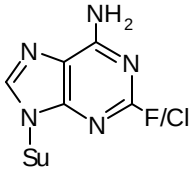


Figure 1.3B: Products of the reactions of 2'-*O*-sulfonylated nucleosides with various nucleophiles



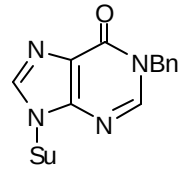
1.007

a B = A; X = N_3
b B = A; X = NH_2
c B = G; X = NH_2
d B = A; X = SAc
e B = A; X = SSPr
f B = A; X = SH

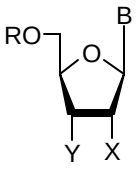


1.007

g X = Halo
h X = N_3



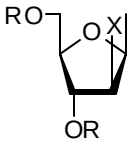
1.007i X = F



1.008

a B = U; X = Y = N_3
b B = U; X = N_3; Y = OBz
c B = G; X = NH_2; Y = OR
d B = U; X = Nptha; Y = OR
e B = C*; X = Nptha; Y = OR
f B = A*; X = Nptha; Y = OR
g B = G*; X = H; Y = N_3
h B = A; X = SH; Y = OR
i B = A*; X = $SCMe_3$; Y = OR
j B = G; X = $SCMe_3$; Y = OR

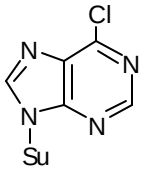
Su =



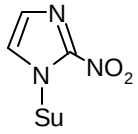
1.007g-m

1.007

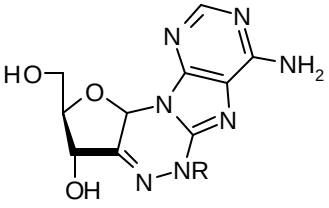
j X = Halo
k X = N_3



1.007l X = F

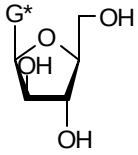


1.007m X = I

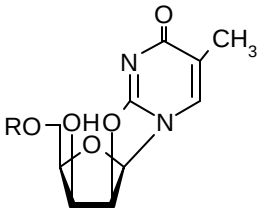


1.009

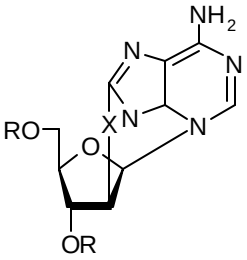
a R = H
b R = Me



1.010

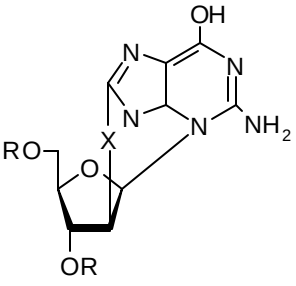


1.011



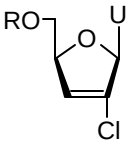
1.012

a X = O
b X = S
c X = CH_2

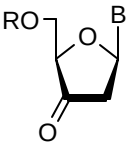


1.013

a X = O
b X = S
c X = CH_2

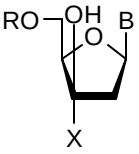


1.014



1.015

a B = A*
b B = U
c B = G*



1.016

a B = A*; X = CH_3
b B = U; X = CH_3
c B = G*; X = H

A* = base protected adenine
G* = base protected guanine

from **1.001l**.[17] The synthesis of 2'-chloro-2',3'-dideoxyuridinene **1.014**, from 2'-*O*-triflyl-2,3'-*O*-anhydroxylosyluracil **1.006** was reported.[18] An improved synthesis of 9-(2,3-dideoxy-2-fluoro-ß-D-threo-pentofuranosyl) adenine (FddA) involved synthesis of **1.007l** from **1.001m** using triethylamine trihydrofluoride ($Et_3N.3HF$) was reported.[19] The synthesis of 1-(ß-D-2-iodo-2-deoxyarabinofuranosyl)-2-nitroimidazole (2-IAZA) **1.007m** was achieved via the nucleophilic displacement of the 2'-*O*-triflate of **1.001n**.[20]

Suitably protected 8-methanesulfonyl-2'-*O*-*p*-toluenesulfonyl purines **1.001o** and **1.001p** were treated with $NaCH(CO_2Et)_2$ to afford 2'-deoxy-8,2'-methylenecyclopurine nucleosides **1.012c** and **1.013c** respectively.[21]

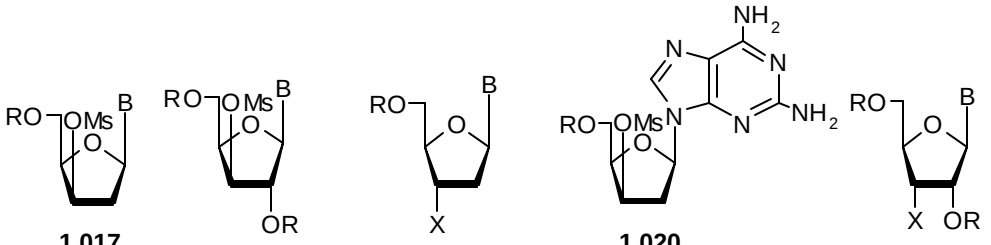
A deoxygenative [1,2]-hydride shift rearrangement was an important source for 2'-deoxy 3'-ulosyl intermediate **1.015a-c**. Thus, 3'-*C*-methyl nucleoside **1.016a** was synthesized from **1.001e** on reaction with Grignard reagent.[22] Similarly reaction of **1.001d** with methylmagnesium iodide gave 3'-*C*-methyl-2'-deoxyribonuridine **1.016b**.[23] Protected 2'-*O*-sulfonyl guanosine **1.001f** (3'-OR = OH) was converted to 9-(2-deoxythreo-pentofuranosyl) guanine **1.016c**.[24]

1.4 3'-*O*-Sulfonated pyrimidine nucleosides (Figures 1.4A and 1.4B)

3'-Azido 2',3'-dideoxy uridine **1.022a** were prepared from 3'-mesyl derivative **1.017a**.[25] The synthesis of 3'-azido-2',3'-dideoxyguanosine **1.022b** and 2-amino-9-(3-azido-2,3-dideoxy-ß-D-erythro-pentofuranosyl)-6-methoxy-9H-purine **1.022c** was described involving the displacement on **1.018a** and **1.018b** respectively.[26] 5'-*O*-trityl-3'-*O*-mesylthymidine **1.019a** on treatment with NaN_3 in DMF at elevated temperature gave 5'-*O*-trityl-3'-azido-3'-deoxythymidine **1.022d** and 6,3'-imino-1-(5-*O*-trityl-3-deoxy-ß-D-*threo*-pento furanosyl) thymine **1.023**. The mechanism of formation of the imino-bridge nucleoside has been proposed.[27] 3'-Azido-2',3'-dideoxy-2,6-diaminopurine riboside **1.024** was synthesized from **1.020**.[28] Attempted displacement of the 3'-*O*-mesyl group of 2'-deoxypyrimidine nucleoside **1.017b** with amines produced the elimination product **1.025a** in most of the cases. However, reactions with benzylamine and morpholine gave 3'-amino-substituted products **1.026a** and **1.026b** respectively.[29]

The reactions of 3'-*O*-tosyl adenosine **1.019b** with R'SH (R' = Et, Me_2CH, Pr) gave xylo nucleoside **1.027a** and ribo nucleoside **1.026c** in approximately 6:1 ratio.[30] 3'-Thio subtituted-2',3'-dideoxythymidines **1.026d** and **1.026e** were synthesized from 3'-*O*-mesyl-2'-deoxy thymidines **1.017b**.[31] Synthesis of 3'-thiothymidylyl (3'-5') thymidine, was reported using

Figure 1.4A: 3'-*O*-Sulfonylated nucleosides



1.017
a B = U
b B = T

1.018
a B = G*
b B = G
c B = U

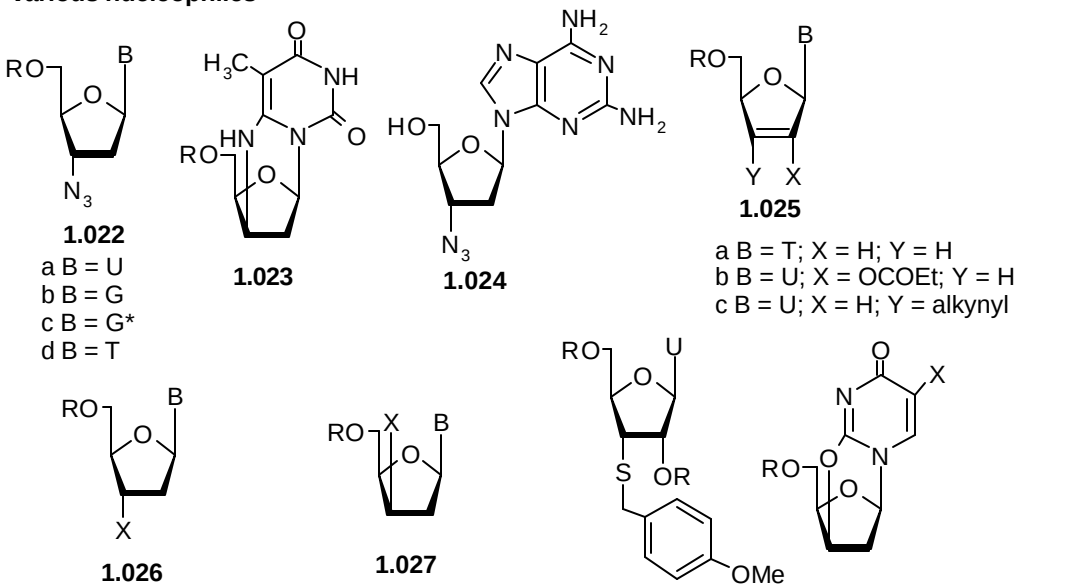
A* = base protected adenine
G* = base protected guanine

1.019
a B = T; X = OMs
b B = A; X = OTs
c B = U; X = OMs
d B = U; X = OTs
e B = U(5-Fl); X = OTs

1.020

1.021
a B = A*; B = OTf
b B = G*; B = OTf
c B = U; X = OMs
d B = B; X = OMs
e B = U; X = OTs

Figure 1.4B: Products of the reactions of 3'-*O*-sulfonylated nucleosides with various nucleophiles



1.022
a B = U
b B = G
c B = G*
d B = T

1.023

1.024

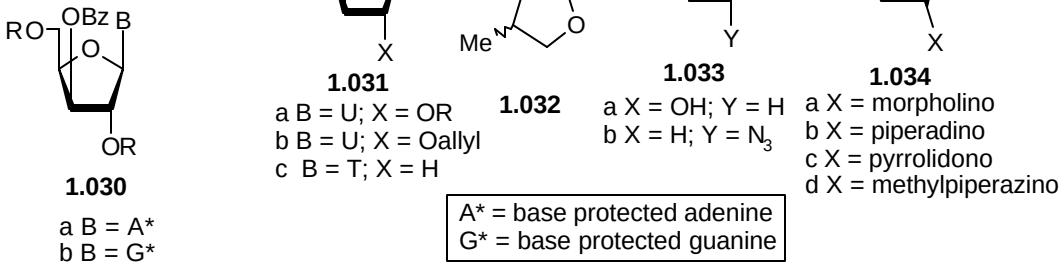
1.025
a B = T; X = H; Y = H
b B = U; X = OCOEt; Y = H
c B = U; X = H; Y = alkynyl

1.026
a B = T; X = bezylamino
b B = T; X = morpholino
c B = A; X = SR'
d B = T; X = STol
e B = T; X = SAc
f B = T; X = SBz
g B = T; X = SH

1.027
a B = A; X = SR'
b B = U; X = Me
c B = U(5-Fl); X = Me

1.028

1.029
a X = Me
b X = H



1.030
a B = A*
b B = G*

1.031
a B = U; X = OR
b B = U; X = Oallyl
c B = T; X = H

1.032

1.033
a X = OH; Y = H
b X = H; Y = N_3

1.034
a X = morpholino
b X = piperadino
c X = pyrrolidono
d X = methylpiperazino

A* = base protected adenine
G* = base protected guanine

1.026g. Whereas displacement reaction on **1.017b** gave **1.026f**.[32] Similar synthesis of 3'-thiouridylyl-(3'-5')-uridine [(Us)pU], was reported; in this case 3'-*S*-(4-methoxybenzyl)-3'-thiouridine **1.028**, was prepared from 2',5'-*O*-dityrityl-3'-*O*-mesyl uridine **1.018c** (R = Tr).[33]

Treatment of an appropriately protected 3'-*O*-sulfonate nucleosides **1.019a** and **1.019c** with DBU was reported to be a convenient procedure for the formation of thymine and uracil anhydronucleosides **1.029a-b**.[34] Compounds **1.030a** and **1.030b** which were obtained from the reactions of **1.021a** and **1.021b** with oxygen nudeophiles such as potassium benzoate and sodium acetate were used as intermediates for the preparation of 3'-fluro 3'-deoxy purine nucleoside.[35]

3'-Phenylseleno derivative **1.031a** prepared from **1.021c**, was used to obtain enol ester nucleoside **1.025b**.[36] similarly, synthesis of **1.025c** from 3'-phenylseleno derivatives **1.031a**, prepared from **1.021c** have been reported.[37]

Stereo selective intramolecular free-radical addition-cyclization reactions of protected 3'-deoxy-3'-phenylseleno-2'-*O*-allyl-ß-D-arabinofuranosyl uracil **1.031b** produced **1.032**.[38] A high yield synthesis of 1-(2,3-dideoxy-ß-D-glycero-pent-2-*eno* furanosyl) thymine d4T **1.025a** was reported from the key intermediate 3'-deoxy-3'(R)-phenylseleno derivative **1.031c**.[39]

Compounds **1.027b** and **1.027c** were obtained by the substitution reactions of the *p*-toluenesulfonyloxy group of **1.019d** and **1.019e** by an alkyl group generated from Gilman reagent R_2CuLi.[40]

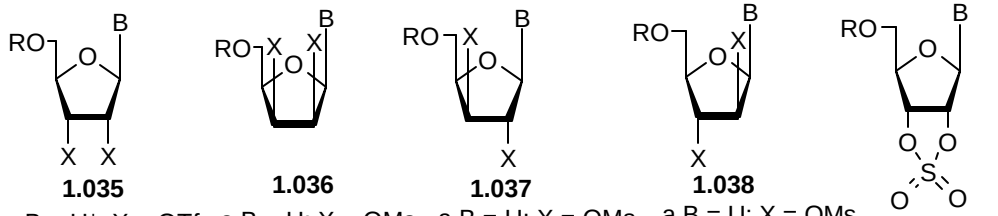
A method for the synthesis of 2'-azido-2',3'-dideoxynucleosides (B = U, C*, A*, G*, H, X) **1.033b** from **1.033a** was reported. In this case [1,2]-hydride shift was used as a key step on sulfonated nucleoside **1.021d** [R = C(O)butyl].[41] One-pot deoxygenative conversion of a ribonucleoside **1.021e** to enaminonucleosides **1.034a-d** involving 1,2-hydride shift rearrangement was reported.[42]

1.5 2',3'-Di-*O*-sulfonated pyrimidine nucleosides (Figures 1.5A and 1.5B)

2',3'-Disubstituted 2',3'-dideoxy xylo nucleosides **1.040a** was obtained by reacting the 2',3'-ditriflate uridine **1.035a** with azide. Compound **1.040a** was converted to diamino derivative **1.040b**; the salen-type ligands derived from **1.040b** was used for the synthesis of copper(II) complex.[43] Reactions of **1.036a** with secondary amines afforded enamino nucleosides **1.042a-d** via intermediacy of 2'-ketouridine **1.041a**.[44] Reactions of

methylamine with sulfonated nucleoside **1.035b** (R = Ms) gave 2,3'-(substituted-imino)-lyxofuranosyl uracils **1.043**, which was converted to piperidine nucleosides **1.044a-b**.[45]

Figure 1.5A: 2',3'-*O*-Disulfonylated nucleosides



1.035
a B = U*; X = OTf
b B = U; X = OMs
c B = A; X = OTs
d B = T; X = OMs
e B = A; X = OMs
f B = C*; X = OMs

1.036
a B = U; X = OMs
b B = C; X = OMs
c B = A; X = OTs

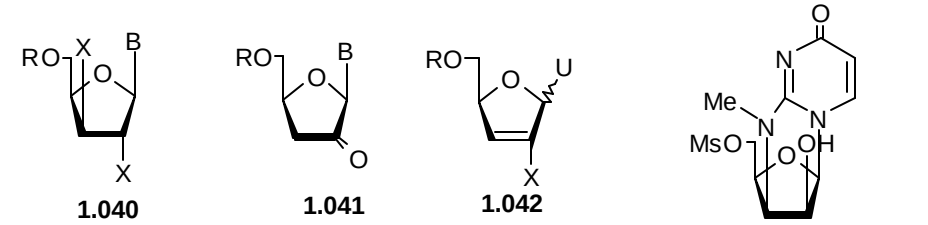
1.037
a B = U; X = OMs
b B = A; X = OTs

1.038
a B = U; X = OMs
b B = A; X = OTs

1.039
a B = A
b B = G*

U* = base protected uracil
C* = base protected cytosine
G* = base protected guanine

Figure 1.5B: Products of the reactions of 2',3'-*O*-disulfonylated nucleosides with various nucleophiles

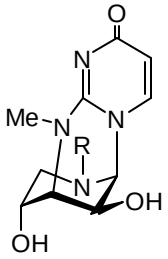


1.040
a B = U*; X = N_3
b B = U*; X = NH_2

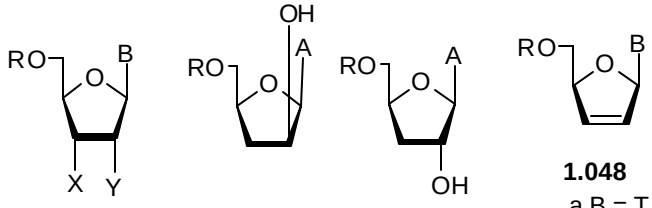
1.041
a B = U
b B = C
c B = A

1.042
a X = pyrrolidino
b X = piperadino
c X = morpholino
d X = acetyl piperazino

1.043



1.044
a R = Me
b R = Bn



1.045
a B = U; X = Y = STol
b B = T; X = OMs; Y = Br

1.046

1.047

1.048
a B = T
b B = A
c B = U
d B = C*
e B = G*

U* = base protected uracil
C* = base protected cyatosine
G* = base protected guanine

2',3'-*O*-Dimesyl uridine derivative **1.037a** or **1.038a** on reactions with NaSTol*(p)* produced the 2',3'-dithiotolyl-2',3'-dideoxy ribouridine **1.045a** via the intermediacy of 2,2'- and 2,3'-*O*-anhydro uridines.[46]

The selective elimination reaction of 1-(5-*O*-trityl-2,3-*O*-dimesyl-ß-D-lyxofuranosyl) cytosine **1.036b** with NaOBz in DMF followed by the detritylation of the product with 80% HOAc produced 1-(3-deoxy-ß-D-glyceropentofuran-2-ulosyl) cytosine **1.041b** (R = H).[47]

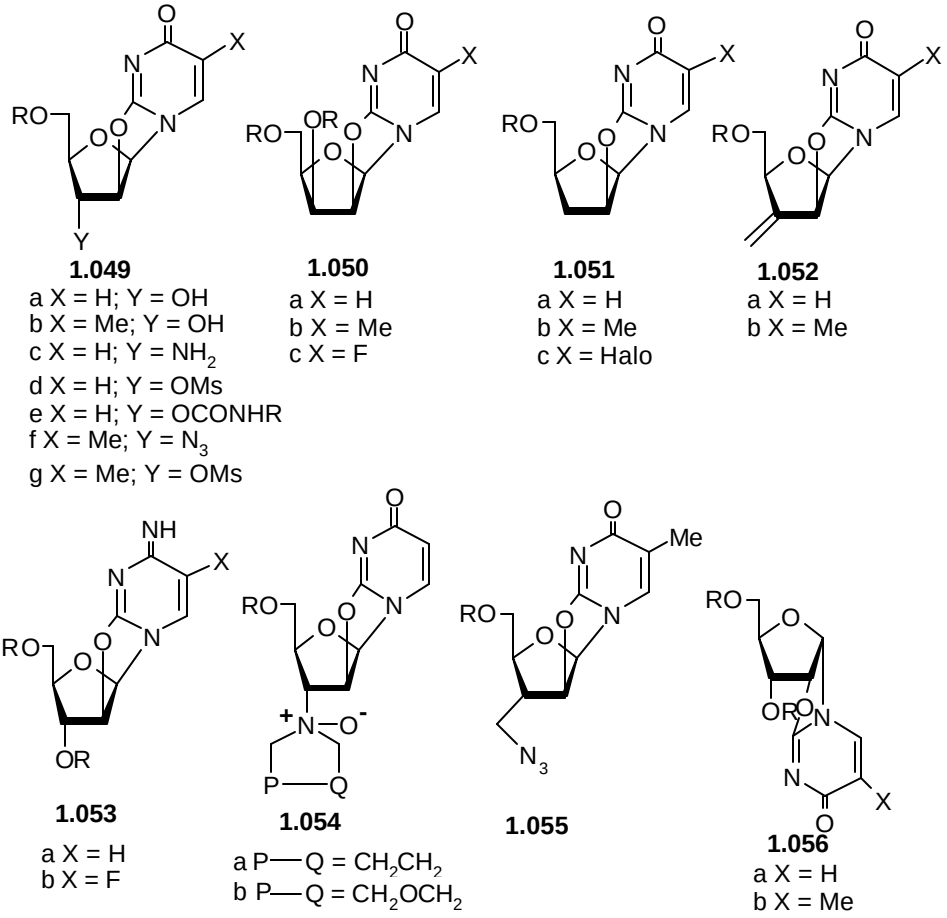
2',3'-Di-*O*-tosylated derivatives **1.035c** and **1.036c** on reactions with $LiEt_3BH$ produced 9-(3-deoxy-ß-D-erythro-pentofuranosyl) adenine **1.046** via the combination of elimination, detosylation and the stereo selective reduction of 3'-deoxy-2'-ketoadenosine intermediate **1.041c**. Under similar conditions xylo analogue **1.037b** and arabino analogue **1.038b** produced **1.046** and **1.047** respectively.[48]

Compound **1.035d** was converted to the bromo derivative **1.045b** *via* 2,2'-*O*-anhydro derivative. On reaction with Zn, compound **1.045b** afforded the anti-AIDS drug 2',3'-didehydro-2',3'-dideoxy thymidine (d4T) **1.048a**.[49] 2',3'-Di-*O*-mesylates of various nucleosides **1.035b,d-e** reacted with Na_2Te or Li_2Te to produce the corresponding 2',3'-didehydro-2',3'-dideoxy compounds **1.048a-d**.[50] Cyclic 2',3'-sulfates **1.039a-b** underwent reductive elimination with sodium naphthalenide to afford **1.048b,e**.[51]

1.6 2,2'-*O*-Anhydro pyrimidine nucleosides (Figures 1.6A and 1.6B)

A 'soft' nucleophile, such as azide ions attacked the C-2' site of 2,2'-*O*-anhydro nucleosides **1.049a** and **1.050a-c** to give C-2'-substituted derivatives 2'-azido 2'-deoxy ribo **1.057a**[52] and xylo **1.058a-c**[53] uridines respectively. Compound **1.057a** was reduced to amino derivative **1.057b** which was converted to nucleosides **1.057c-d** containing two nucleobases.[54] Compound **1.057e** synthesized from 2,2'-*O*-anhydro nucleoside **1.049b** was evaluated as inhibitors of *mycobacterium tuberculosis*.[55] The synthesis and biological application of a labeled analogue of **1.057e** was reported.[56] 2'-Azido-2'-deoxythymidine and it's C-5-substituted analogues **1.059a-c** were synthesized from **1.051a-c** respectively.[57] 3'-Azidomethyl-2',3'-dehydro-2',3'-dideoxy pyrimidines **1.060a-b** were synthesized from **1.052a-b** respectively and evaluated for their anti-viral properties.[58] The direct introduction of amines to the carbohydrate moiety of pyrimidine nucleosides via opening 2,2'-*O*-anhdro bridge did not occur; the reactions of amines with 2,2'-*O*-anhydropyrimidines gave only C-2 substituted nucleosides.[59-61] However, the reactions of secondary amines with 2,2'-*O*-anhydrouridine **1.049d** gave a new class of isocytidines **1.061a-d**.[62] However, intramolecular opening of the 2,2'-*O*-anhydro ring by the 3'-tethered alkyl or alkoxy carbamates **1.049e** led to the formation of oxazolidinone **1.062**. Deprotection of **1.062** afforded 2'-alkylamino-2'-deoxy[63] and 2'-alkoxyamino-2'-deoxy[64] nucleosides **1.057f** (R' = OBn, OTHF, H, Me etc). 2'-*N*-alkyluridine nucleosides

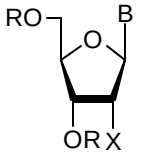
Figure 1.6A: Various 2,2'-*O*-anhydro nucleosides used in reactions



were synthesized via intramolecular reaction of alkyl isocyanates with 5'-*O*-protected-2,2'-anhydrouridine.[65] Excess amines converted **1.049d** to **1.063**, which on hydrolysis produced a mixture of **1.064** (R' = NHMe, Me, Et, Ph, *p*-methoxyphenyl) and **1.065** (R"= Ph, *p*-methoxyphenyl).[66]

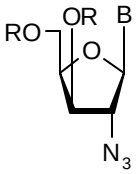
A 'hard' nucleophile such as hydroxide ion, attacked irreversibly at C-2 of 2,2'-*O*-anhydro pyrimidine nucleosides. However, 2-*O*-alkyl derivatives was never isolated, the only stable products isolated was *C*-2'-*O*-alkyl carbohydrate modified pyrimidine nucleosides.[67] Opening of the 2,2'-*O*-anhydro bridge of **1.049a** by $Mg(OMe)_2$ yielded **1.057i**, which was used for the synthesis of 2',3'-*O*-methyleneadenos-5'-yl bis (2',5'-di-*O*-methylurid-3'-yl) phosphate, a sugar-*O*-alkylated trinucleoside 3',3',5'-monophosphate.[68] Similarly, **1.057j** was obtained from **1.049b**.[69] Compounds **1.049b** was also converted to a 2'-*O*-modified nucleoside **1.057k** using ethylene glycol.[70] The synthesis of 3'-amino-3'-deoxyuridine

Figure 1.6B: Products of the reactions of 2,2'-*O*-anhydro nucleosides with various nucleophiles



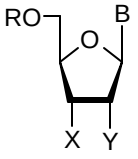
1.057

a B = U; X = N_3
b B = U; X = NH_2
c B = U; X = U
d B = U; X = T
e B = T; X = N_3
f B = U; X = NHR'
g B = C; X = OH
h B = C(5-Fl); X = OH
i B = U; X = OMe
j B = T; X = OMe
k B = T; X = OCH_2CH_2OH
l B = U; X = SCH_2CH_2TMS
m B = U; X = SSMe
n B = U; X = SR'
o B = U; X = Cl
p B = T; X = Br
q B = U; X = Br
r B = U; X = I
s B = U; X = CH=C=CH_2
t B = U; X = CH_2=CH_2
u B = U; X = CH_2CHO
v B = U; X = CHO



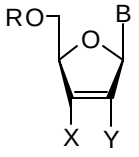
1.058

a B = U
b B = T
c B = U(5-Fl)



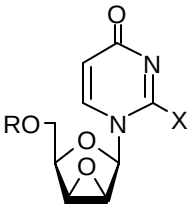
1.059

a B = U; X = H; Y = N_3
b B = T; X = H; Y = N_3
c B = U(5-Halo); X = H; Y = N_3
d B = U; X = NH_2; Y = OH
e B = T; X = N_3; Y = Cl
f B = T; X = NH_2; Y = Cl
g B = T; X = OMs; Y = Br
h B = T; X = OH; Y = H



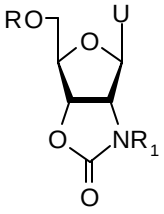
1.060

a B = U; X = CH_2N_3; Y = H
b B = T; X = CH_2N_3; Y = H
c B = U; X = Y = H
d B = U; X = H; Y = Cl
e B = T; X = Y = H

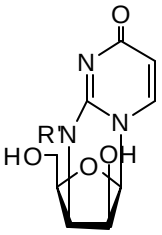


1.061

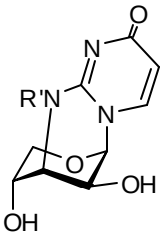
a X = pyrrolidino
b X = piperadino
c X = piperazino
d X = ethyl isonipecotatyl



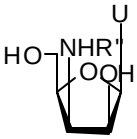
1.062



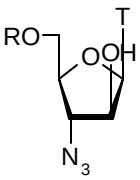
1.063



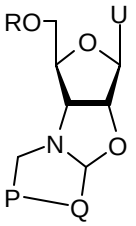
1.064



1.065

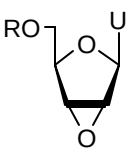


1.066

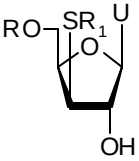


1.067

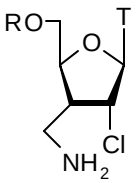
a P— Q = CH_2CH_2
b P—Q = CH_2OCH_2



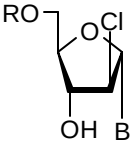
1.068



1.069



1.070



1.071

a B = U
b B = T

1.059d involved the opening of 2,2'-*O*-anhydro bridge of **1.049c** by the benzoate anion followed by debezoylation,[71] while the aqueous NaOH treatment of the anhydronucleoside **1.049f** yielded the arabinonucleoside **1.066**.[72]

Opening of the 2,2'-*O*-bridge of **1.053a-b** by $NaHCO_3$ led to the formation of ribonucleosides **1.057g-h**.[73] A thermal reaction of *N*-oxides derived from 3'-deoxy-3'-*N*-pyrrolidino- and 3'-deoxy-3'-*N*-morpholino-2,2'-*O*-anhydrouridines **1.054a** and **1.054b** yielded the oxazolidine derivatives **1.067a** and **1.067b** respectively.[74]

Using sodium hydride or potassium *tert*-butoxide in DMSO the 2,2'-*O*-anhydronucleoside **1.049a** was converted into the isomeric 2',3'-*O*-riboepoxide **1.068**.[75]

Conjugate bases of alkyl- and aryl thiols converted 2,2'-*O*-anydro-ß-D-arabinofuranosyl uracil to the corresponding 2'-deoxy-2'-mercapto-uridines.[76,77] 2-(Trimethylsilyl) ethanethiol on reaction with **1.049a** gave **1.057l** which was converted to dithio derivative **1.057m**.[78] Compound **1.057n**, obtained from **1.049a**, was utilized for the synthesis of 2'-[alkyl(or aryl)sulfonyl]-2'-deoxy-2'-fluorouridines.[79] It was observed that the 2,2'-*O*-anhydronucleoside **1.049a** on reactions with excess NaSR' yielded 2'-*S*-thio-2'-deoxyuridine **1.057n**, whereas the treatment of **1.049a** first with NaH followed by a treatment of R'SH gave 3'-*S*-thio-3'-deoxy xylouridine **1.069** in high yields.[80]

3'-Azido-3'-deoxy derivative **1.049f**, on reaction with HCl afforded **1.059e**, which was reduced to **1.059f**.[72] 3'-*C*-aminomethyl-3'-deoxy derivative **1.070** was synthesized from **1.055**.[81] Synthesis of biologically important labeled ^{14}C-2 analogues of 5-Chloro- and 5-fluoro-1-(2-fluoro-2-deoxy-ß-D-ribofuranosyl) uracil was reported.[82] The conversion of *a*-D-arabinofuranosyl pyrimidines **1.056a-b** to 2'-chloro-2'-deoxy-*a*-D-ribofuranosides **1.071a-b** was discussed.[83] 2'-Chloro-2',3'-dideoxy-2',3'-didehydro nucleosides **1.060d** was synthesized from **1.049a** via **1.057o**.[84] 2'-Halogeno-2'-deoxy pyrimidines **1.059g** and **1.057p** served as synthetic intermediates for d4T **1.060e**[49] and 2'-dehydro- **1.059h**;[85] compounds **1.059g** and **1.057p** were obtained from **1.049g** and **1.049b** respectively.

2'-Bromo-2'-deoxy- and 2'-deoxy-2'-iodouridines **1.057q** and **1.057r** were synthesized by treating **1.049a** with LiBr and NaI respectively; free radical reactions of **1.057q** and **1.057r** afforded 2'-*a*-*C*-allenyl-2'-deoxyuridine **1.057s**.[86] The iodo derivative **1.057r** was used further in the synthesis of 2'-deoxy-2'-*C*-vinyl-and 2'-deoxy-2'-*C*-hydroxymethyluridines **1.057t-v** using the radical cyclization as the key step.[87]

1.7 2,3'-*O*-Anhydro pyrimidine nucleosides (Figures 1.7A and 1.7B)

Azido group attacked the 3' position of 2,3'-*O*-anhydro compound **1.072a** to produce 3'-azido-3'-deoxythymidine (AZT) **1.077a**.[2a] Azidonucleosides **1.077a-c** have been synthesized also for accessing the corresponding amino compounds.[88] Activation of 2,3'-*O*-anhydrohymidine **1.072a** via N^3-alkylation followed by the nucleophilic opening at the 3'-position generated a series of 3'-deoxy-3'-modified nucleosides **1.078a-g**.[89] Azoles like tetrazole reacted with **1.072a** to afford **1.077d**.[90] 2,3'-*O*-anhydro-5'-*O*-mesylnucleosides **1.073a-b** underwent displacements at 3'- and 5'-sites simultaneously by azide ion to afford **1.079c-d**.[91] Compound **1.073b** reacted with potassium pthalimide to yield **1.079e.**[92] Compounds **1.079c-e** were converted to diamino compounds **1.079f-g**.[91,92] Amines *were* incapable of attacking the C-3' site of 2,3'-*O*-anhydronucleosides.[60,93]

A group of 3'-*O*-nitro-2'-deoxynucleosides **1.080a-e** were synthesized from 2,3'-*O*-anhydrohpyrimidines **1.072a-c** and evaluated for their biological properties.[94]

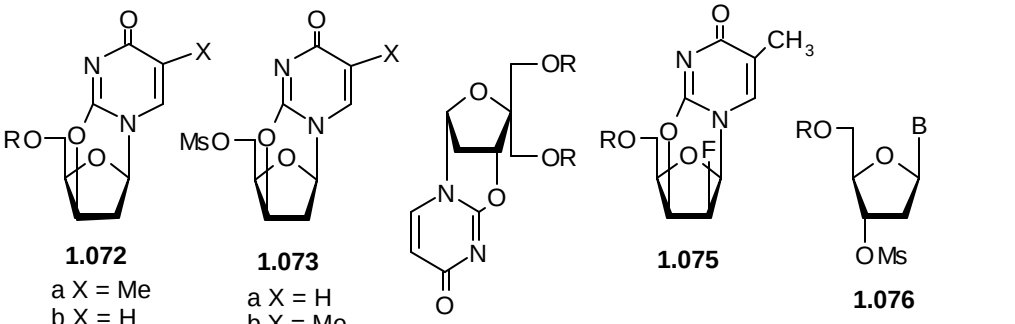
Synthesis of 3'-deoxythymidin-3'-yl methyl disulfide from 2,3'-*O*-anhydrothymidine **1.072a** reacted with 2-(trimethylsilyl) ethanethiol to afford **1.080f** which was converted to the disulfide **1.080g**.[78] Synthesis of 3',5'-dithio derivatives **1.079a-b** from **1.073b** was described.[95] X-ray crystal structure and the complexation behaviors of 3',5'-dithiothymidine **1.079b** with Au(I) was also reported.[92] Compound **1.072a** reacted with *S*-(O,O-dialkyl) phosphorodithioate to afford the corresponding thiolate, which reacted with 1,2-dichloroethane in the presence of fluoride ion to afford **1.080h**.[96]

Preparation and the biological properties of chloro and sulfanyl derivatives of 1-(2-deoxy-4-*C*-hydroxymethyl-*α*-L-threo-pentofuranosyl) uracil **1.083a-b** from **1.074** was reported.[97] Compound **1.072a** was converted to 3'-(methylthio)-3'-deoxythymidine[98] **1.080i** and the latter was used as an intermediate for the synthesis of **1.080j-k**.[99] 3'-Chloro- and 3'-thiocyanato-2',3'-dideoxythymidine were prepared from 2,3'-anhydro-2'-deoxythymidine with NH_4Cl and LiSCN, respectively. The 5'-triphosphates of the nucleoside analogs were tested as termination substrates of DNA polymerases.[100]

Fluorination of **1.072a-b** was carried out using the AlF_3-HF[101] or HF-DMF[102] to produce the 3'–fluorinated nucleosides **1.080l-m**. Difluoropyrimidines **1.081a-b** and olefinic compound **1.082** were synthesized from **1.075**.[101] The base modified nucleoside **1.080o** was synthesized from **1.072c**.[103] Compound **1.072a** was converted to the iodo derivative

1.080n, which was used as an intermediate for the synthesis of 3'-*a*-*C*-allenyl-2',3'-dideoxythymidine **1.080p** via free radical reactions.[104]

Figure 1.7A: 2,3'-*O*-Anhydro nucleosides



1.072
a X = Me
b X = H
c X = F
d X = Halo

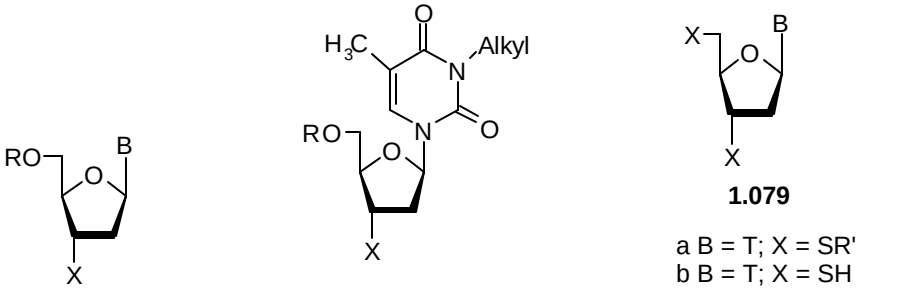
1.073
a X = H
b X = Me

1.074

1.075

1.076
a B = U
b B = T
c B = U(5-Halo)

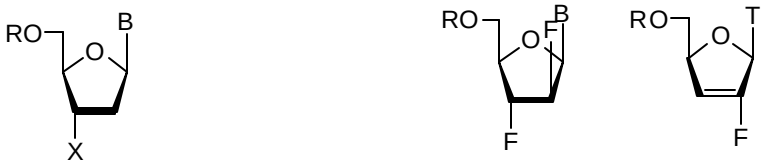
Figure 1.7B: Products of the reactions of 2,3'-*O*-anhydro nucleosides with various nucleophiles



1.077
a B = T; X = N_3
b B = U; X = N_3
c B = U(5-Halo); X = N_3
d B = T; X = tetrazolyl

1.078
a X = N_3
b X = OH
c X = Br
d X = I
e X = SCN
f X = CN
g X = CH(COOMe)

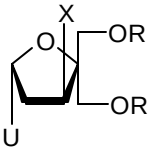
1.079
a B = T; X = SR'
b B = T; X = SH
c B = U; X = N_3
d B = T; X = N_3
e B = T; X = NPtha
f B = T; X = NH_2
g B = U; X = NH_2



1.080
a B = U; X = ONO_2
b B = T; X = ONO_2
c B = U(5-Halo); X = ONO_2
d B = C; X = ONO_2
e B = C(5-Halo); X = ONO_2
f B = T; X = SCH_2CH_2TMS
g B = T; X = SSMe
h B = T; X = SCH_2CH_2Cl
i B = T; X = SMe
j B = T; X = $SOCH_2F$
k B = T; X = SO_2CH_2F
l B = T; X = F
m B = U; X = F
n B = T; X =I
o B = U(5-Fl); X = F
p B = T; X = $CH=C=CH_2$

1.081
a B = T
b B = C

1.082



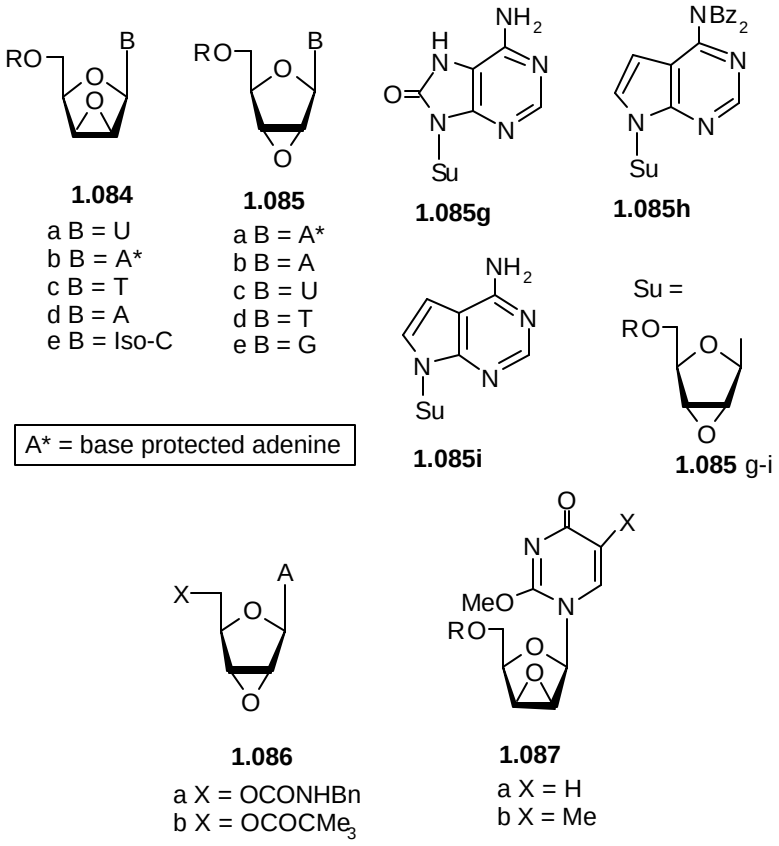
1.083
a X = Cl
b X = SAc

1.8 2',3'-*O*-Anhydro pyrimidine nucleosides (Figures 1.8A, 1.8B and 1.8C)

NH_4N_3 in ethanol reacted with 5'-*O*-benzyl 2',3'-*O*-anhydrolyxouracil **1.084a** in a regioselective fashion to afford the 3'-azido derivative **1.088a**.[105] Base-protected epoxide **1.084b** was converted to **1.088b** which was used as a synthetic intermediate for the preparation of the 2'-deoxy-2'-fluro-analogue of natural antibiotic puramycin **1.089**.[106] A new class of adeonsine A1 receptor antagonist, N^6-cyclopentyl 3'-substituted xylofuranosyladenosines **1.090a-b** were synthesized involving the oxirane ring cleavage of the riboepoxide **1.085a**.[107] Azidonucleosides **1.088c** and **1.091a** obtained from **1.084c** was converted to fluoronucleosides **1.094a-b**.[101] Epoxides **1.084a** and **1.084c** were opened with various azoles to obtain ara-derivatives **1.088d-i** and xylo-derivatives **1.091b-g**.[108] An acetamido group was introduced directly into the sugar moiety of nucleoside epoxide **1.084a** and **1.084d** by using $BF_3.Et_2O$ and acetonitrile to afford **1.088j** and **1.088k** respectively.[109] The ring opening reactions of appropriately protected 2',3'-*O*-anhydro lyxoadenosine afforded the desired product but the reaction of 2',3'-*O*-anhydro-lyxouridine with pyrrolidine failed as it led only to cleavage of the glycosidic bond.[29] 2',3'-*O*-anhydro lyxofuanosyluridine **1.084a** with different primary and secondary amines produce the arabino- **1.088l-s** and xylo- **1.091h-o** derivatives in good yields.[110] The regiospecific synthesis of 3'-aminoxylonucleosides **1.090c** involved an intramolecular attack of the partially protected amino nucleophile from the 5'-position to the 3'-position of the sugar epoxide **1.086a**.[111]

Alkali metal alkoxides[112,113], acetates[114] and hydroxides[115] have been extensively used for the opening of the 2',3'-epoxides. Opening of epoxide **1.084c** with allyl alcohol generated compounds **1.092a** and **1.093a**, which were converted to spironucleosides **1.095** and **1.096** via the formation of *N*-methylnitrones followed by tandem intramolecular 1,3-dipolar cycloadditions.[116] A new technique for the phosphorylation has been devised, in which the epoxide ring of **1.084a** was opened by phosphate to get **1.092b** and **1.093b**; the same strategy was used for the opening of the epoxide ring by 5'-phosphorylated uridine for accessing dinucleotides.[117a] Similarly, 3'-phosphate derivative of arabinoadenine was prepared by opening a lyxo epoxide with H_2PO_4 in $(Me_2N)_3PO$.[117b] A theoretical study on the regioselectivity of the opening of nucleoside epoxides by phosphates was reported.[118] Intramolecular attack by the acyloxonium ion generated from the ribo-epoxide **1.086b** in the presence of KBH_4 provided the intermediate **1.097** which was synthetically manipulated further to yield lyxoepoxide **1.084d**.[119]

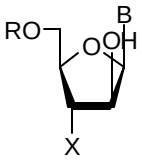
Figure 1.8A: 2',3'-*O*-Anhydro nucleosides



The interconversion between 2',3'-*O*-anhydro riboepoxide **1.085g** and 8,2'-*O*-anhydro arabinopurine **1.098** was reported;[120] a similar interconversion between **1.085c** and **1.099a** was also known.[80]

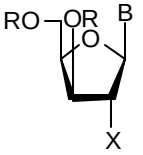
Alkylthiols,[80,121] arylthiols[122,123] was incorporated to the sugar moieties of nucleosides via opening of 'up' and 'down' epoxides under basic conditions. For example 2', 3'-*O*-anhydro**u**bercidin **1.085h** on treatment with sodium benzylthiolate yielded 3'-benzylthionucleoside **1.100** exclusively.[121] Similarly, ribo epoxide **1.085b** produced **1.090d**.[122] Thionucleosides **1.093c-d** generated from epoxide **1.084a** were oxidized to the corresponding sulfones and the sulfones were converted to vinylsulfone **1.101a**[124] and bisvinylsulfone **1.102**;[125] the latter compounds were used as Michael acceptors for the synthesis of modified nucleosides (see later). The 3'-sulfonic acid analogue **1.093e** was readily obtained from **1.084d**.[126] 3'-Deoxy-3'-halo arabino- **1.093f-h** and xylo-analogues **1.090e-g** were synthesized form the lyxoepoxide **1.084d** and riboepoxide **1.085b** respectively.[127] Base-modified lyxoepoxides **1.087a-b** reacted with

Figure 1.8B: Products of the reactions of 2',3'-*O*-anhydro nucleosides with various nucleophiles



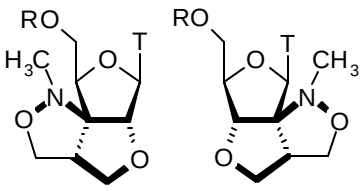
1.088

a B = U; X = N_3
b B = A*; X = N_3
c B = T; X = N_3
d B = U; X = pyrazol-1-yl
e B = U; X = imidazol-1-yll
f B = U; X = triazol-1-yl
g B = T; X = pyrazol-1-y
h B = T; X = imidazol-1-yl
i B = T; X = triazol-1-yl
j B = U; X = NHAc
k B = A; X = NHAc
l B = U; X = isobutylamino
m B = U; X = benzylamino
n B = U; X = cyclohexylamino
o B = U; X = pyrrolidino
p B = U; X = piperadino
q B = U; X = morpholino
r B = U; X = isonepicotatyl
s B = U; X = anilino

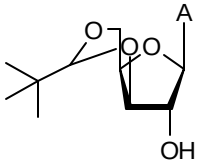


1.092

a B = T; X = Oallyl
b B = U; X = OPO_3H
c B = T; X = F
d B = T; X = Br
e B = U; X = SePh

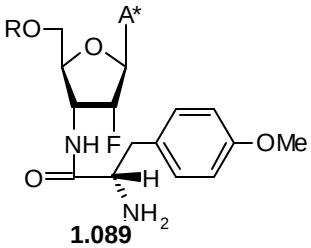


1.095 **1.096**

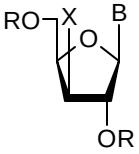


1.097

A* = base protected adenine

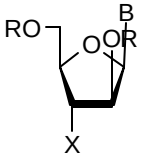


1.089



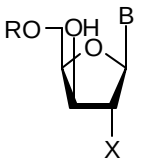
1.090

a B = A*; X = N_3
b B = A*; X = NH_2
c B = A; X = NH_2
d B = A; X = SBz
e B = A; X = Br
f B = A; X = Cl
g B = A; X = I
h B = A*; X = I
i B = A*; X = H
j B = G; X = H
k B = A*; X = Me
l B = A; X = SePh



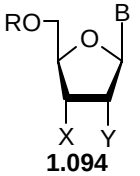
1.093

a B = T; X = Oallyl
b B = U; X = OPO_3H
c B = U; X = STol
d B = U; X = SCH_2CH_2OH
e B = A; X = SO_3H
f B = A; X = Br
g B = A; X = Cl
h B = A; X = I
i B = T; X = F
j B = T; X = Br
k B = A*; X = H
l B = A*; X = D
m B = U; X = H
n B = T; X = H
o B = U; X = Me
p B = T; X = Me
q B = U; X = CN
r B = T; X = CN
s B = A; X = CN
t B = Iso-C; X = CN
u B = U; X = CCH
v B = T; X = dithiazinyl
w B = U; X = SePh
x B = T; X = SePh



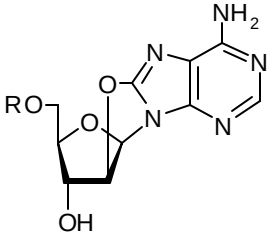
1.091

a B = T; X = N_3
b B = U; X = pyrazol-1-yl
c B = U; X = imidazol-1-yl
d B = U; X = triazol-1-yl
e B = T; X = pyrazol-1-yl
f B = T; X = imidazol-1-yl
g B = T; X = triazol-1-yl
h B = U; X = isobutylamino
i B = U; X = benzylamino
j B = U; X = cyclohexyl amino
k B = U; X = pyrrolidino
l B = U; X = piperadine
m B = U; X = morpholino
n B = U; X = isonepicotatyl
o B = U; X = anilino

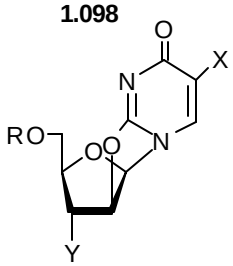


1.094

a B = T; X = N_3; Y = F
b B = T; X = F; Y = N_3
c B = T; X = Y = F
d B = A; X = NH_2; Y = OH
e B = T; X = CN; Y = H
f B = T; X = CHO; Y = H



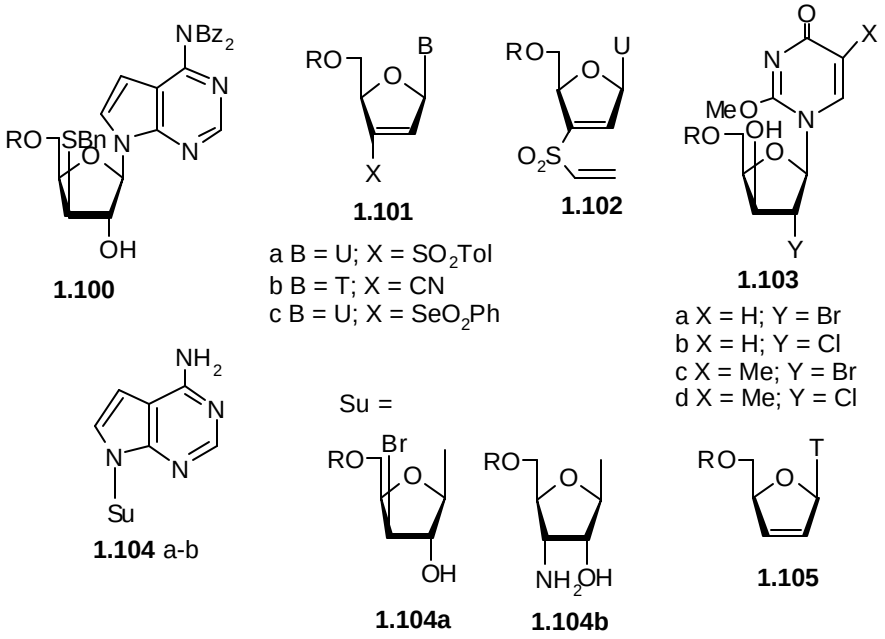
1.098



1.099

a X = H; Y = OH
b X = H; Y = Br
c X = H; Y = Cl
d X = Me; Y = Br
e X = Me; Y = Cl

Figure 1.8C: Products of the reactions of 2',3'-*O*-anhydro nucleosides with various nucleophiles



Li_2CuBr_4 or Li_2CuCl_4 to yield 2,2'-*O*-anhydro-3'-halo nucleosides **1.099b-e** and xylo derivatives **1.103a-d**.[128] Cleavage of the oxirane ring of **1.084c** by KHF_2 generated a mixture of fluorinated nucleosides **1.092c** and **1.093i** which were further transformed into difluoro compound and **1.094c**.[101] *S*yntheses of puromycin[129] and 7-deazapuromycin,[130] involved the opening of the epoxide rings of **1.085b** and **1.085i** with Me_2BBr to get 3'-bromo-3'-deoxy derivatives **1.090e** and **1.104a**. Further synthetic manipulations of the bromo compounds afforded **1.094d** and **1.104b**. Regio- and stereo selective cleavage of 2',3'-*O*-anhydropurine nucleosides was achieved with SmI_2 and ethyl bromoacetate to produce the corresponding 3'-iodopurine nucleosides; thus **1.085a** was converted to **1.090h**, which was reduced to a cordycepin analogue **1.090i**.[131] Lyxoepoxide **1.084c** on reactions with AcBr generated a mixture of trans-bromoacetates **1.092d** (3'-OR = 3'-OAc) and **1.093j** (2'-OR = 2'-OAc) which under reductive conditions afforded the anti-AIDS drug d4T **1.105**.[132]

Reductive opening of the base protected lyxoepoxide **1.084b** with LAH and LAD afforded 3'-deoxy derivatives **1.093k-l**;[133] similar reduction of riboepoxide **1.085a** gave cordycepin **1.090i**.[134] Opening of the oxirane ring with $LiEt_3BH$ of lyxoepoxides **1.084a, 1.084c** yielded **1.093m-n**.[135] Similarly, 3'-deoxyguanosine **1.090j** was synthesized by opening the epoxide ring of the guanosine derivative **1.085e** with $LiHEt_3BH$.[136] The stereo specific synthesis of 3'-*C*-methyl analogue of cordycepin **1.090k**, was achieved by the reaction of

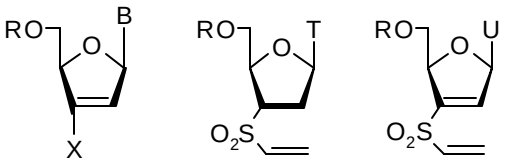
MeMgI in the presence of CuI with base-protected riboepoxide **1.085a**.[137] MeMgCl and CuCN reacted with lyxoepoxides **1.084a, 1.084c** to afford **1.093o-p**.[135b] Me_3Al was also used as a reagent for opening the epoxide rings of pyrimidine nucleosides.[138] Compound **1.084a** was reacted with a number of carbon nucleophiles, such as LiC≡CH, NaCN and 1,3-diathane for the synthesis of branched-chain nucleosides.[139] 3'-Cyno-3'-deoxy-ß-D-arabino nucleosides **1.093q-t** were obtained by the regioselective opening of the lyxoepoxides **1.084a,c,d,e** with Et_2AlCN.[140] Epoxide **1.084c** was reacted with LiCN followed, by the treatment of thiocarbonyldiimidazole to get vinyl nitrile derivative **1.101b,** which was converted to **1.094e**.[141,142] Opening of the epoxide ring of **1.084a** with LiC=CH afforded **1.093u**, which was further converted to a self-polymerizable 2'-deoxyribonucleoside analogue, 3',4'-diethylnyl-2',3',5'-trideoxy-5'-noruridine.[143] Reactions of epoxide **1.084c** with diathiazine afforded **1.093v**, which was hydrolyzed to **1.094f**.[144]

Epoxides derived from nucleosides **1.084a,c** and **1.085b** were easily opened by $(PhSe)_2$ in the presence of LAH to afford **1.093w,x** and **1.090l** respectively.[145,147,148] An efficient Michael acceptor, vinyl selenone-modified nucleoside **1.101c** was prepared from **1.093w**.[145] A selenoxide derived from **1.090l** was subjected to elimination reactions.[123,146,147] Oxidative elimination of phenyl selenium from **1.093x** and further synthetic manipulations of the product afforded 4'-cyano-2',3'-didehydro-3'-deoxythymidine.[148]

1.9 Reactions of unsaturated nucleosides (Figures 1.9A and 1.9B)

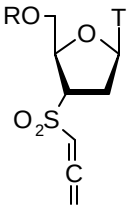
Michael addition reactions to 3'-ene sulfone nucleoside **1.106a** with ammonia, primary amines such as methylamine, benzylamine, glycine methyl ester; secondary amines dimethyl amine, pyrrolidine, piperidene, morpholine and carbon nucleophiles yielded a range of new 2',3'-dideoxy-2',3'-disubstituted **1.110** (Nu = nucleophihes).[124] Primary amines such as ammonia, methylamine, benzylamine and glycine methyl ester underwent conjugate additions at C-2' of vinyl selenone-modified nucleoside **1.106b** followed by a direct intramolecular S_N2 type displacement at C-3' to give various 2',3' dideoxy-ribo-aziridino uridines **1.111**. Secondary amines such as dimethylamine, pyrrolidine and morpholine gave 2,2'-*O*-anhydro-3'-doexy-3'-substitutedaminouridines **1.112**. Carbon nucleophiles yielded 2',3'-didexoy-2',3'- cyclopropyl derivatives of uridine **1.113a**.[145] Exocyclic vinyl sulfone group-modified nucleoside **1.107** reacted with a series of nucleophiles to yield various thymidine analogues **1.114**.[149] Divinyl sulfone moiety was incorporated to the carbohydrate part of a pentofuranosyl nucleoside **1.108** which served

Figure 1.9A: Unsaturted nucleosides



1.106 **1.107** **1.108**

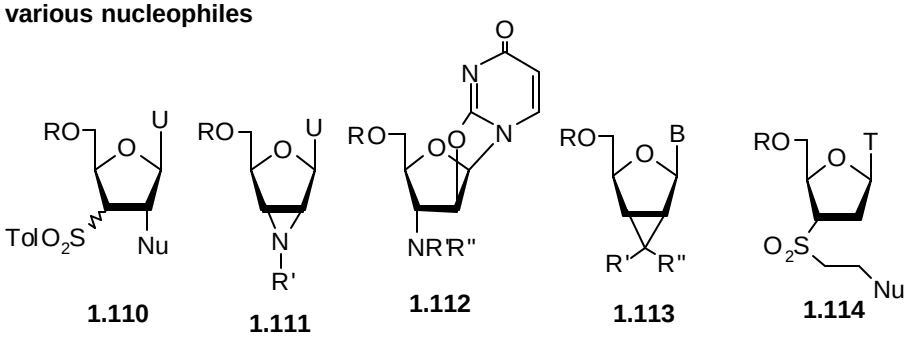
a B = U; X = SO_2Tol
b B = U; X = SeO_2Ph
c B = T; X = SeO_2Ph
d B = T; X = CN
e B = T; X = NO_2
f B = T; X = CH_2OH
g B = T; X = CH_2CH_2CN
h B = T; X = $CH_2CH_2COCH_3$



1.109

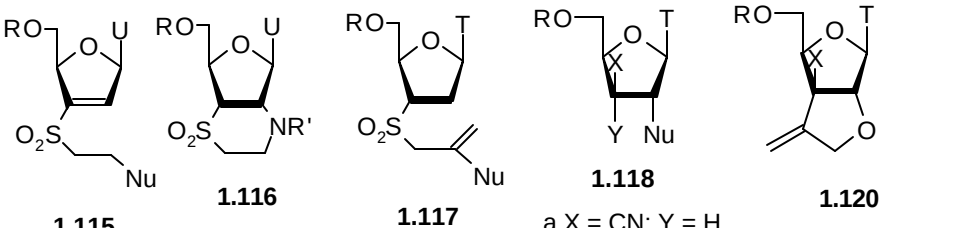
as a bifunctionalized nucleoside Michael acceptor. Secondary amines and carbon nucleophiles gave a series of mono substituted nucleosides **1.115** and primary amines produced a new class of bicyclic *S*,*S*-dioxidethiazine derivatives **1.116**.[125] Exocyclic allenic sulfone-modified nucleoside **1.109** reacted very efficiently with a wide array of nucleophiles to afford compounds **1.117**.[150] Compound **1.06c** was reacted with CH_3NO_2 in presence of *t*-BuOK and reduced to **1.113b**, which was coupled with a nucleoside derived carboxylic acid to afford an amide linked dimmer.[151] Protected 3'-enenitrile of thymidine **1.106d** underwent Michael addition reactions with ammonia, primary amines, secondary amines and carbon-nucleophiles to yield addition products **1.118a**; ammonia gave the cis-isomer **1.118b** as the major product.[152] Vinyl nitro compound **1.106e** was also synthesized and reacted with a range of nucleophiles to afford **1.118c-d**.[153] Michael addition of the phenylthiolate to nitroolefin gave mixture of **1.119a-b**, which was subjected to Henry reaction with formaldehyde, methylvinyl ketone and acrylonitrile to produce diasteriomeric mixtures **1.119e-h**. Subsequent, free-radical induced elimination of phenylthio and nitro groups of **1.119c,e,g** gave 2',3'-dideoxy-2',3'-didehydro-3'-*C*-substituted thymidines **1.106f-g**.[154] A similar manipulation using propargyl alcohol on **1.106e** gave **1.119i-j**. Reactions of **1.119i-j** with electron deficient agents such as formaldehyde and acrylonitrile produced mixtures of diasteriomers **1.119k-n**. Compounds **1.119k,m** upon treatment with $BuSn_3H$ and AIBN afforded 3'-bis-*C*-substituted [3.3.0]-cis-fused nucleosides **1.120a-b**.[155]

Figure 1.9B: Products of the reactions of unsatutared nucleosides with various nucleophiles



1.110 **1.111** **1.112** **1.113** **1.114**

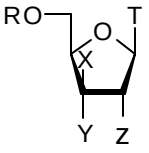
a B = U; R', R'' = H, alkyl
b B = T; R' = H; R'' = NH_2



1.115 **1.116** **1.117** **1.118** **1.120**

a X = CN; Y = H
b X = H; Y = CN
c X = NO_2; Y = H
d X = H; Y = NO_2

a X = CH_2OH
b X = CH_2CH_2CN



1.119

a X = H; Y = NO_2; Z = SPh
b X = NO_2; Y = H; Z = SPh
c X = CH_2OH; Y = NO_2; Z = SPh
d X = NO_2; Y = CH_2OH; Z = SPh
e X = CH_2CH_2CN; Y = NO_2; Z = SPh
f X = NO_2; Y = CH_2CH_2CN; Z = SPh
g X = $CH_2CH_2COCH_3$; Y = NO_2; Z = SPh
h X = NO_2; Y = $CH_2CH_2COCH_3$; Z = SPh
i X = H; Y = NO_2; Z = OCH_2CCH
j X = NO_2; Y = H; Z = OCH_2CCH
k X = CH_2OH; Y = NO_2; Z = OCH_2CCH
l X = NO_2; Y = CH_2OH; Z = OCH_2CCH
m X = CH_2CH_2CN; Y = NO_2; Z = OCH_2CCH
n X = NO_2; Y = CH_2CH_2CN; Z = OCH_2CCH

1.10 Conclusion

It is clear from the above discussion and compilation of strategies for the modification of the sugar moieties of carbohydrates that in the case of pentofuranosyl nucleosides, sulfonylated nucleosides (Sections **1.3**, **1.4** and **1.5**), several different *O*-anhydronucleosides (Sections **1.6** and **1.7**) and epoxy nucleosides (Section **1.8**) played significant roles in the synthesis of a large number of modified nucleosides. Moreover, in recent times electron deficient nucleosides (Section **1.9**) also generated new approaches towards the modification of the carbohydrate moieties of nucleosides. Information

gathered from this deliberation is useful for designing strategies for the synthesis of hexopyranosyl nucleosides described in the next chapter.

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155. Garg, N.; Hossain, N.; Chattopadhyaya, J. *Tetrahedron* **1994**, *50*, 5273-5278.

CHAPTER TWO

A Systematic Approach towards the Functionalization of Hexopyranosyl Thymines

2.1 Introduction

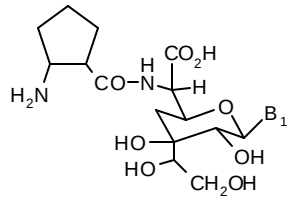
Although a greater level of interest has been generated in the synthesis and biological properties of pentofuranosyl nucleosides over the years (**Chapter 1**), the very first nucleoside ever synthesized, namely 9-ß-D-glucopyranosyladenine was a hexopyranosyl derivative.[1] 1-(2-Deoxy-ß-D-arabinohexopyranosyl) thymine was recognized to be an inhibitor of a pyrimidine nucleoside phosphorylase.[2] Hexopyranosyl nucleosides derived from allose, altrose, gulose, talose, and mannose were synthesized and tested against various microorganisms.[3] 1-(2-Deoxy-6-*O*-phosphono-ß-D-ribohexopyranosyl)-2,4-pyrimidinedione demonstrated antiviral and antileukemic activities.[4] Synthetic studies of the pyranosyl nucleoside-based naturally occurring antibiotics have been documented.[5] The synthesis and biological properties of a large number of pyranosyl azidonucleosides have been reviewed.[6] The obvious but intriguing question-'why pentose- and not hexose-nucleic acids?', led investigators to study hexopyraonsyl-oligonucleotide systems in great depth.[7] A number of pyranosyl nucleosides with a variety of biological activities occur in nature. Representative examples, such as amipurimycin, blasticidin, gougerotin, hikizimycin, mildiomycin, miharamycin, pentopyranine and amicetin are listed in (**Figure 2.1.1**).[8]

More recently, the synthesis and biological properties of a new class of sugar-modified nucleosides derived from 1, 5-anhydrohexitols have been reported. Studies on structural requirement of nucleosides with six-member carbohydrate moiety, led to the identification of the 1,5-anhydrohexitols (**Figure 2.1.2**) as therapeutically most promising sugar components; these nucleoside achieved optimal binding with the enzyme active site.[9]

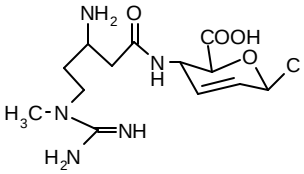
2.2 Reported methods of syntheses of hexopyranosyl nucleoside

A perusal of the literature revealed that there are mainly three ways of synthesizing pyranosyl nucleosides. The first method involves the coupling of a functionalized sugar with appropriately protected nucleobases. For example, modified sugars with acetyl,[10a] halogeno,[10b] methoxy[10c] groups at C-1' center (**Figure 2.2.1**) or glycals[10d] (**Figure 2.2.2**) were coupled with appropriately protected nucleobases to obtain different hexopyranosyl nucleosides. An alternative method, made use of the oxidative cleavage of the 5'-*O*-protected uridine with sodium metaperiodate and the resulting dialdehyde was condensed with nitromethane. The hexopyranosyl nucleoside, thus generated, was exploited for the synthesis of a variety of functionalized hexopyranosyl nucleosides (**Figure 2.2.3**).[11,12]

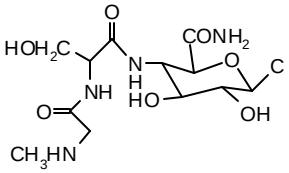
Figure 2.1.1



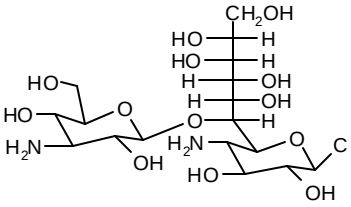
amipurimycin



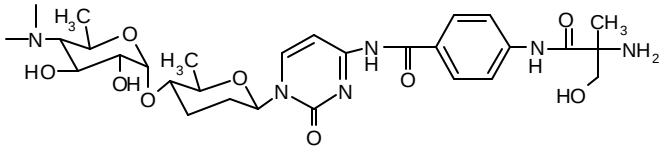
blasticidin S



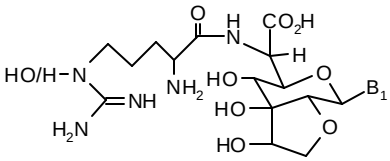
gougerotin



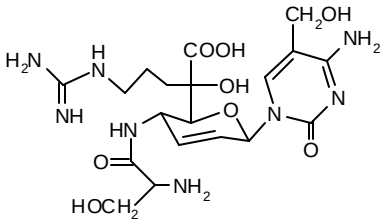
hikizimycin



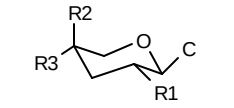
amicetin



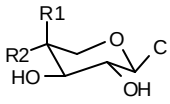
miharamycin



mildiomycin

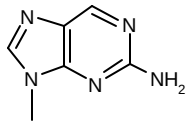


R1 = R3 = H, R2 = OH; A
R1 = R2 = H, R3 = OH; B
R1 = R2 = OH, R3 = H; C
R1 = R3 = OH, R2 = H; D



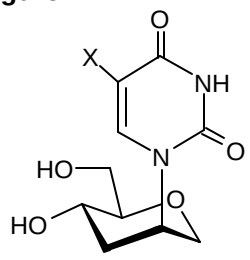
R1 = OH, R2 = H; E
R1 = H, R2 = OH; F

B_1 =

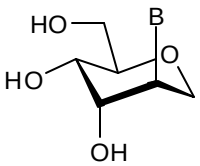


Pentopyranine

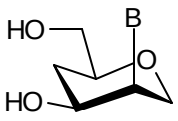
Figure 2.1.2



X = I, Cl, CF_3, Et, Me



B = A, G, C, U



B = A, U

Figure 2.2.1

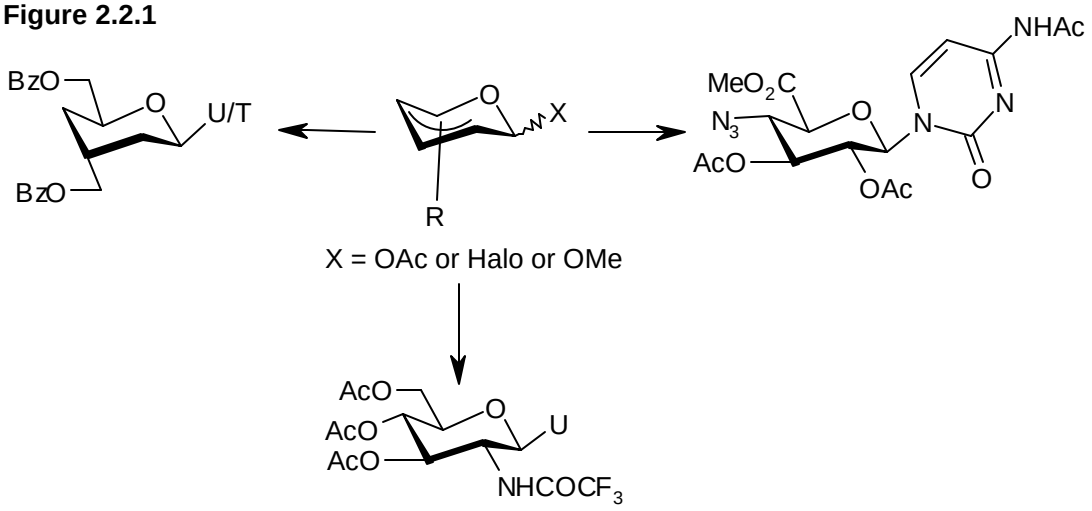


Figure 2.2.2

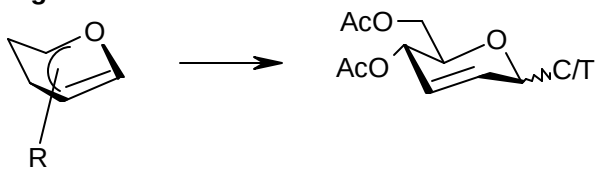
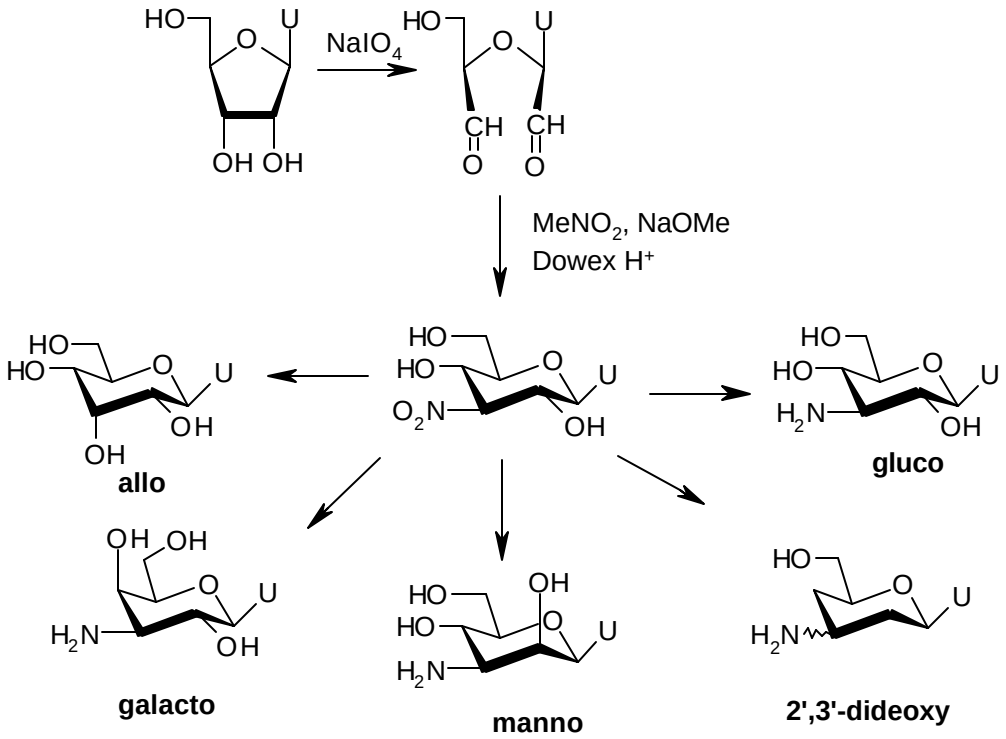


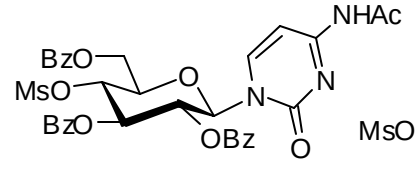
Figure 2.2.3



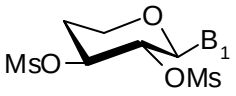
Although it is possible to couple a modified monosaccharide with a nucleobase for the synthesis of a particular hexopyranosyl nucleoside, it would also be useful to develop methodologies applicable directly on easily accessible hexopyranosyl nucleosides as was the case for pentofuranosyl nucleosides (**Chapter 1**). Surprisingly this strategy is understudied and underutilized in the case of hexopyranosyl nucleosides. Nevertheless, it will be pertinent to review the information reported in the literature.

i) Sulfonate displacement reactions on pyranosyl nucleosides

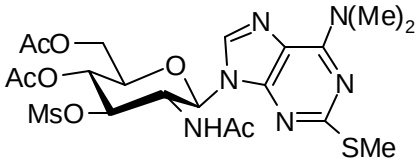
Reactions of sulfonylated hexopyranosyl nucleosides **2.01-2.05** were reported. Thus, azidolysis of **2.01** followed by reduction afforded 4'-amino-4'-deoxy-*ß*-D-*galacto*-pyranosylcytosine **2.06**.[13] Similarly, **2.02** yielded **2.07b** via **2.07a**.[14] 3'-*O*-mesyl displacement reaction of **2.03** generated allo-derivative **2.08**.[8] Similarly, 2'-amino-2'-deoxy-*ß*-D-allopyranosyl azauracil derivative **2.09** was obtained from **2.04**.[15] Synthesis of 3'-azido-2',3'-dideoxy-4'-keto-hexopyranoid **2.10** involved the introduction of an axial azido group at 3'-position, via tosyl dipalcement of **2.05a-c**.[16]



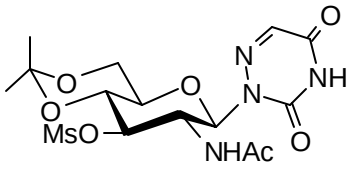
2.01



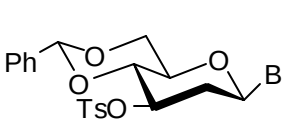
2.02



2.03

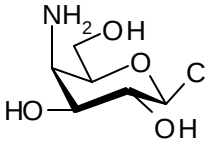


2.04

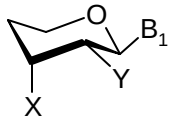


2.05

a B = T
b B = 5-FU
c B = 5-ClU

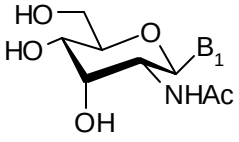


2.06

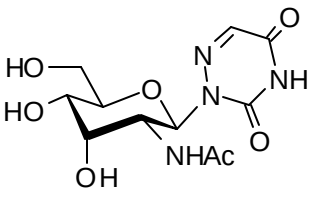


2.07

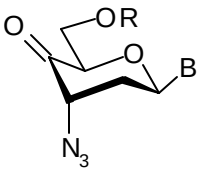
a X = N_3; Y = OMs
b X = NH_2; Y = OH



2.08

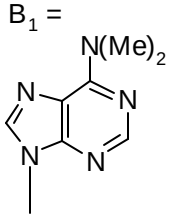


2.09



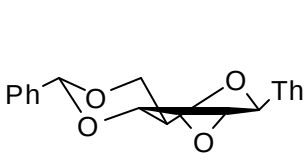
2.10

a B = T
b B = 5-FU
c B = 5-ClU

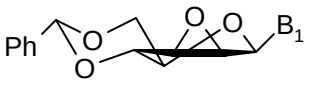


ii) 2',3'-Epoxide opening reactions

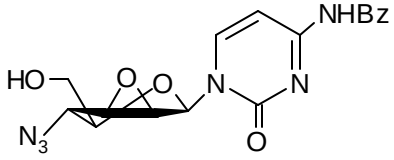
1-(2,3-*O*-anhydro-4,6-*O*-phenylmethylene-ß-D-allopyranosyl) theophylline **2.11** was subjected to phosphorylation to yield **2.16**.[17] An unidentified "monotosyl monoacetate" obtained from 1-(4,6-*O*-phenylmethylene-ß-D-glucopyranosy) 4-ethoxy-2(1H)pyrimidone, was converted to the ß-D-mannopyranosyl epoxide **2.12**.; the latter compound was converted to **2.18** via **2.17**, a component of the antibiotic amicetin.[18] 1-(4-Amino-2,3,4-trideoxy-ß-D-2-enopyranosyl) cytosine **2.19** and its derivatives, related to natural antibiotic blasticidin S and gougerotin was synthesized from the manno-epoxide **2.13**.[19] Pentopyranine A was synthesized via opening of epoxide ring of **2.14** followed by conversion of the intermediate to **2.20** and reduction of **2.20** to **2.21**.[20] 2,2'-*O*-anhydro compound **2.22** was synthesized from the allo-epoxide **2.15** via the intramolecular attack of O-2 at C-2'.[10a]



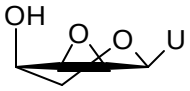
2.11



2.12



2.13



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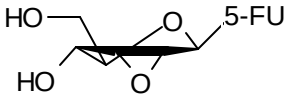
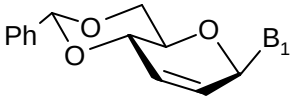


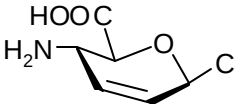
2.15

2.16



2.17

2.18



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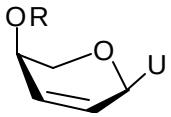
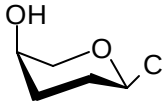


2.20



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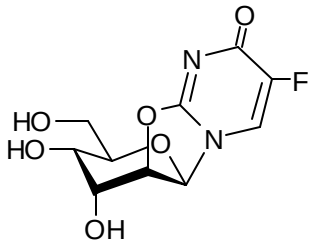
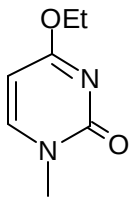
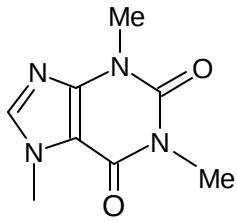


2.22

B_1 =

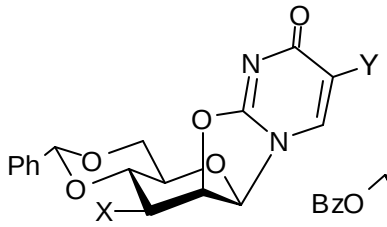


Th =

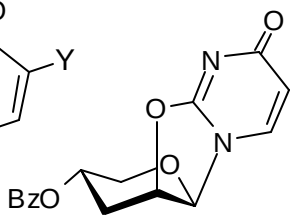


iii) The 2,2'-*O*-anhydro pyranosyl nucleoside intermediates

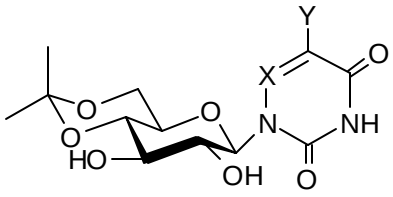
Treatment of 2,2'-*O*-anhydro-derivative **2.23** with dilute NaOH, and liquid NH_3 afforded the *ß*-D-mannopyranosyl uracil **2.27a** and isocyatosine **2.27b** respectively.[11b] The olefinic nucleoside **2.28** was synthesized by reacting **2.24** with NaI in boiling DMF.[21] Pentopyranine B **2.29b**, was synthesized by opening 2,2'-*O*-anhydro bridge of **2.25** with bromine followed by the reduction of **2.29a**.[22] Compound **2.26 a-d** was reacted with two equivalents of DAST to afford the fluoro derivatives **2.30a-d**.[23]



2.23 X = NHAc; Y = H
2.24 X = OMs; Y = CH_3

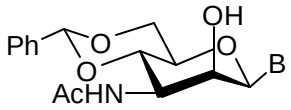


2.25



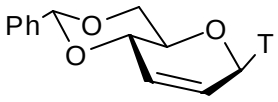
2.26

a. X = CH; Y = H c. X = CH; Y = Me
b. X = N; Y = H d. X = N; Y = Me

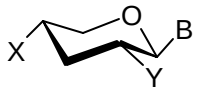


2.27

a B = U
b B = isoC

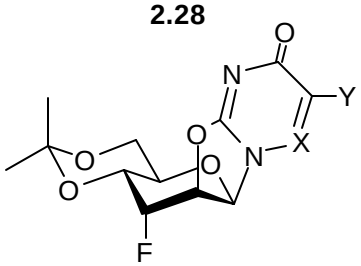


2.28



2.29

a B = U; X = OBz; Y = Br
b B = C; X = OH; Y = H

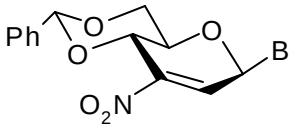


2.30

a. X = CH; Y = H c. X = CH; Y = Me
b. X = N; Y = H d. X = N; Y = Me

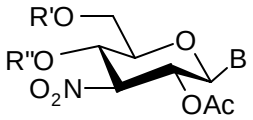
iv) Unsaturated hexopyranosyl nucleosides

Vinyl nitro-modified hexopyranosyl nucleosides **2.31a-b** on reactions with various nucleophiles such as primary amines, secondary amines, sulfur and carbon nucleophiles afforded a series of hexopyranosyl derivatives **2.33a-b**.[24] Nitrosugar derived nucleosides **2.32a-b** generated the vinyl nitro group *in situ* and the product underwent Michael addition reactions to produce **2.33c** and **2.34a** respectively.[25,26] Compound **2.34a**, derived from **2.32b** was reduced to prepare a triamino derivative **2.34b**.[27]



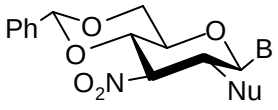
2.31

a B = U
b B = A



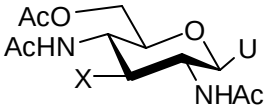
2.32

a B = Hx; R',R" = HCPh
b B = U; R' = R" = Ac



2.33

a B = U
b B = A
c B = Hx



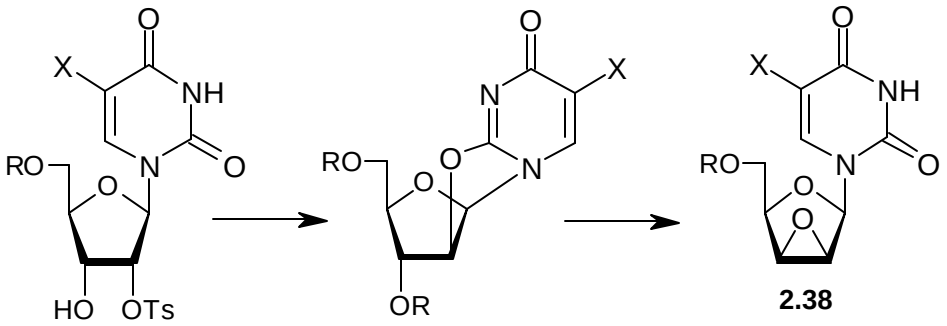
2.34

a X = NO_2
b X = NHAc

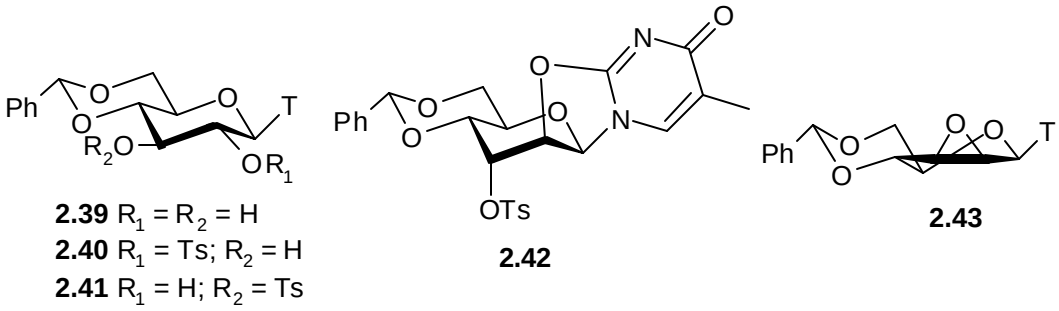
2.3 Present Work

Although the functionalization of hexopyranosyl nucleosides at the 2', 3' or 4' positions poses major synthetic challenges, reported methodologies are narrowly focused to prepare only special classes of compounds.[1-5,8] Surprisingly, no genuine effort has been made so far to develop general methodologies for the synthesis of modified hexopyranosyl nucleosides from common intermediates as was the case for the pentofuranosyl nucleosides (see **Chapter 1**). It is, therefore necessary to develop general strategies for the synthesis of wide range of hexopyranosyl nucleosides.

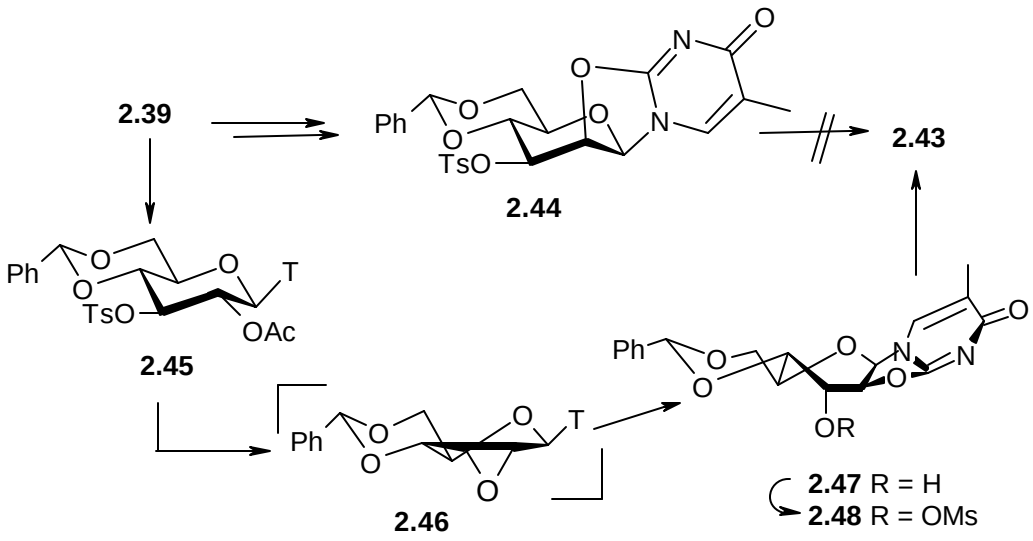
It was clear from the discussion in the first chapter that in the case of pentofuranosyl nucleosides, sulfonylated nucleosides (Sections **1.3**, **1.4** and **1.5**), several different *O*-anhydronucleosides (Sections **1.6** and **1.7**) and epoxy nucleosides (Section **1.8**) played significant roles in deciding the routes for the synthesis of modified nucleosides. Moreover, in recent times electron deficient nucleosides (Section **1.9**) also generated new approaches towards the modification of the carbohydrate moieties of nucleosides. It was also evident from the information available from this chapter that the synthesis of the first three groups was interrelated to a major extent especially in the case of pyrimidine nucleosides. Thus the monotosylate **2.35** was easily converted to the 2,2'-*O*-anhydro derivative **2.36**. The anhydro derivative **2.36** after mesylation followed by a base treatment generated the epoxide **2.38**. On the other hand compounds **2.35**-**2.38** individually reacted with a range of nucleophiles to generate hundreds of products reported in chapter 1. The access to the unsaturated nucleosides was, therefore natural fallout of the successful reactions of any of these three compounds with appropriate



nucleophiles. We envisaged that these three types of compounds, such as selectively sulfonylated-, epoxy-, 2,2'-*O*-anhydro-nucleosides of hexopyranosyl variety would also act as general intermediates and would pave the way for generating a wide range of unnatural nucleosides modified at 2'-, 3'- and even at 4'-positions. So far there are only a few and scattered examples of synthesis and use of such intermediates (Section **2.2**). However, if we started our synthesis from one of the most easily available glucopyranosyl nucleosides **2.39**, [21] then we needed to develop a methodology for the selective tosylation of the nucleoside to get monotosylates **2.40** or **2.41**. It was obvious that 2'-*O*-tosyl derivative **2.40** would not have produced **2.42** and without **2.42** we would not have produced **2.43**. Therefore, **2.40** was not the desired starting material for accessing two other functionalized nucleosides **2.42** and **2.43**.



It was also clear that **2.40** would produce **2.44** and the latter would not have produced epoxide **2.43**. On the other hand, we presumed that allo-epoxide **2.46** easily obtainable from the acetyl derivative **2.45** (prepared from **2.41**) would undergo an intramolecular (see later) attack to produce 2,2'-*O*-anhydro derivative **2.47**. Mesylation of **2.47** would produce **2.48** which would undergo ring-opening under basic conditions to generate the desired epoxide **2.43**.



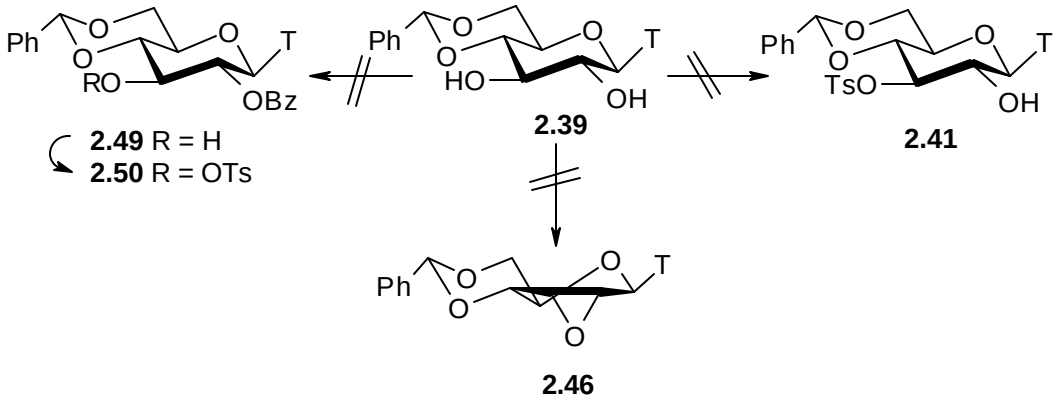
SECTION A

Synthesis and reactions of 1-(2,4,6-*O*-triacetyl-3-*O*-tosyl-ß-D-glucopyranosyl) thymine (2.57)

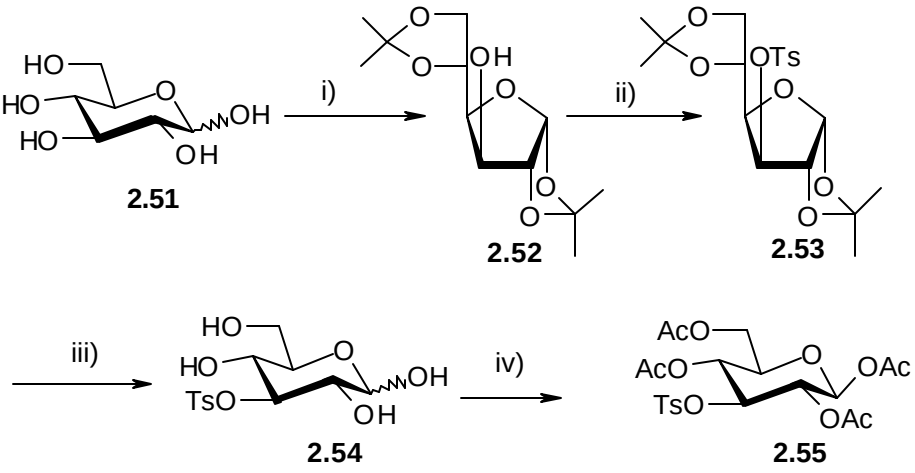
i) Synthesis

The accessibility to intermediates, such as 2,2'-*O*- anhydro- **2.42** and 2',3'-*O*-anhydrohexopyranosyl pyrimidine **2.43** was crucially dependent on the selective sulfonylation of the partially protected diol **2.39**. The literature reports indicated that the tosylation of the dibutylstannylene derivatives of methyl ß-D-glucopyranoside or benzylidene derivative of methyl ß-D-glucopyranoside produced 6-*O*-tosyl pyranoside or a mixture of 2-/ 3-*O*-tosyl pyranoside with the marginal selectivity, respectively.[28,29] The failure of this method with methyl ß-D-glucopyranoside was attributed to the lack of coordination between tin and the ß-methoxy group.[28] In another report, dibutyltin oxide mediated tosylation in the presence of 4-dimethylaminopyridine (DMAP), methyl 4,6-*O*-phenylmethylene ß-D-glucopyranoside, gave high regio-selectivity.[30]

We wanted to establish whether a partially protected diol **2.39** could be sulfonylated selectively. Compound **2.39**, was subjected to selective alkylation or esterification reaction following literature procudures.[28-31] However, none of the reported methods yielded the desired products **2.41**, **2.46** or **2.50**. The failure prompted us to functionalize the sugar component before coupling it with the thymine.



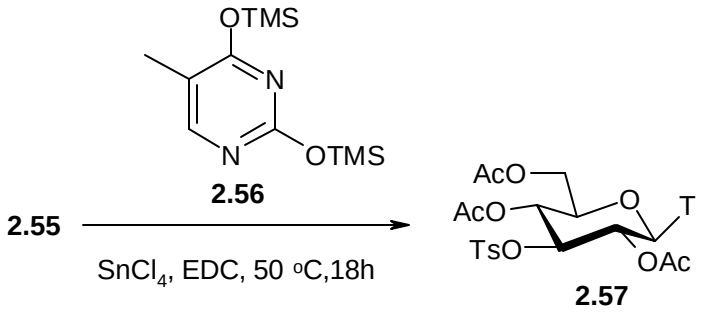
Since we have already proposed that 3'-*O*-tosylated compound **2.41** would afford the desired epoxide, we identified 1,2:5,6-di-*O*-isopropylidene-3-*O*-tosyl-*a*-D-glucofuranoside **2.53** as the most useful starting material because a) it was easily accessible from D-glucose in large scale and b) during glycosylation, the "down" 2-*O*-acetyl group (in **2.55**) would direct the in-coming nucleobase to attack the anomeric centre from the ß side, via neighboring group-participation. Thus, D-glucose **2.51** on reactions with dry acetone in the presence of $FeCl_3$ produced 1,2:5,6-di-*O*-isopropylidene-*a*-D-glucofuranose **2.52**.[32] The diacetone glucose was tosylated with tosyl chloride and pyridine.[33] The hydrolysis with dilute H_2SO_4 in dioxane,[34] gave 3-*O*-tosyl-*ß*-D-glucopyranose **2.54**, which was acetylated with the procedure described for *ß*-D-pentaacetate glucose **2.55**.[35]



i) $FeCl_3$, acetone, reflux, 5h. ii) TsCl, pyridine, rt, 2.5 days. iii) 0.5 N H_2SO_4, dioxane, 100 °C, 5h. iv) NaOAc, Ac_2O, heat.

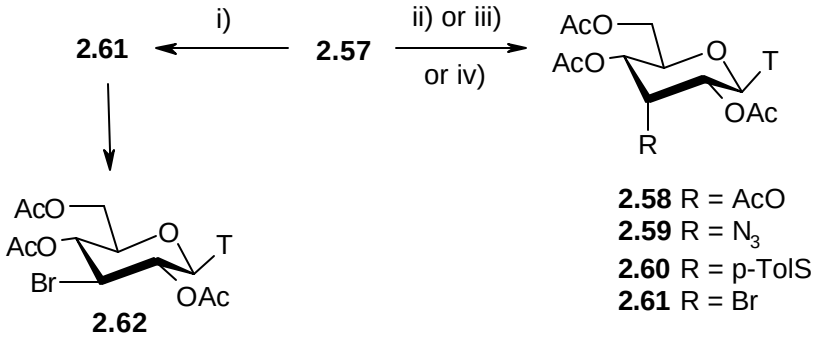
Compound **2.55** was coupled with bistrimethylsilylated thymine **2.56** in the presence of $SnCl_4$ to produce a single nucleoside **2.57** in 75% yield. A large coupling constant for

H1'-H2' (*J1',2' = 9.3 Hz*) indicated that H1' and H2' were *trans* to each other, and hence the *ß*-configuration of the base thymine.[36]



ii) Reactions

In order to establish the usefulness of the new hexopyranosyl nucleoside, **2.57** was subjected to nucleophilic displacement. Problems associated with any loss of acetyl groups were circumvented by reacetylating the product mixture. Thus, a DMF solution of **2.57** was treated with NaOAc at 150 ^{o}C for 20h and the resulting mixture of products was acetylated. A typical work-up and purification yielded 1-(2,3,4,6-tetra-*O*-acetyl-*ß*-D-allopyranosyl) thymine **2.58** in 70% yield. Although the synthesis of allopyranosyl thymine had been reported earlier,[37] the present work is the first report on the conversion of a versatile intermediate such as **2.57** into an allopyranosyl nucleoside.



i) LiBr, DMF, 110 ^{o}C, 10h, 85%. ii) a. NaOAc, DMF, 150 ^{o}C, 20h. b. Ac_2O, pyridine, 70%. iii) a. LiN_3, DMF, 120 ^{o}C, 20h. b. Ac_2O, pyridine, 61%.
iv) a. p-TolSH, NaOMe, DMF, 90^{o}C, 10h. b. Ac_2O, pyridine, 70%.

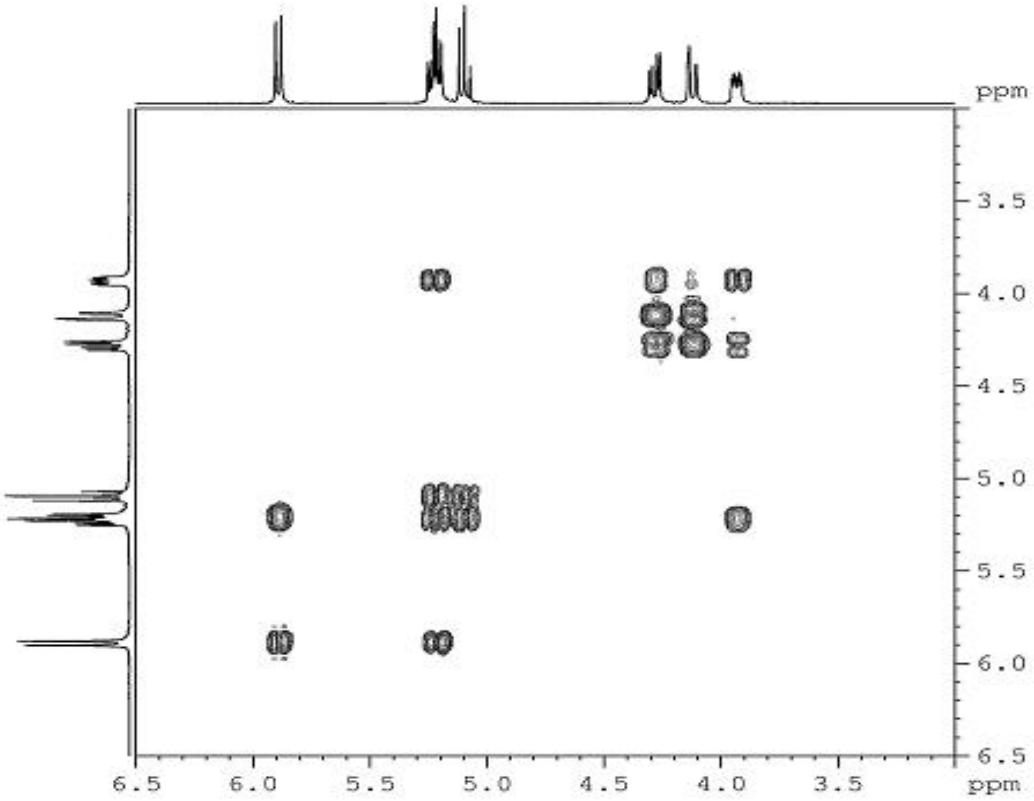
Since this route to allopyranosyl thymine derivatives is expected to be general in nature, treatment of compound **2.57** with LiN_3 in DMF at 120 ^{o}C for 20h followed by reacetylation gave 1-(2,4,6-tri-*O*-acetyl-3-azido-3-deoxy-*ß*-D-allopyranosyl) thymine **2.59** in 61% yield. Compound **2.59** is the first of its kind to be reported. Similarly, treatment of **2.57** with

NaSTol(p) in DMF at 90 °C for 10h followed by acetylation afforded 1-(2,4,6-tri-*O*-acetyl-3-deoxy-3-*S*-tolyl-*ß*-D-allopyranosyl) thymine **2.60** in 70% yield. On the other hand, reaction of LiBr under similar conditions, gave 3'-deoxy 3'-bromo D-gluco nucleoside **2.62** where no deacetylation was observed. However, attempted amination at 3'-postion, using amines for the reaction with nucleoside **2.57**, did not produce the desired products.

iii) Structural assignments

Chemical shift values of the protons of **2.57** were assigned with the help of its ^{1}H-^{1}H COSY spectrum (**Figure 2.3.1**). The connectivities of the protons were established considering the peak at δ 5.88 arising out of the anomeric proton. The only neighboring

Figure 2.3.1: ^{1}H-^{1}H COSY spectrum for **2.57**



proton H2'-signal at δ 5.18-5.24 overlapped with that of H4'. Both these protons correlated with H3'-signal at δ 5.08 which appeared as a triplet with large coupling constant (*J* = 9.3 Hz) establishing the axial relationships between coupling protons. The signal of H5' at δ 3.92 showed a complicated splitting pattern, because of its couplings with H4' and both protons H6' and H6'' (**Table 2.3.1**). The larger values of *J1',2'* = 9.5

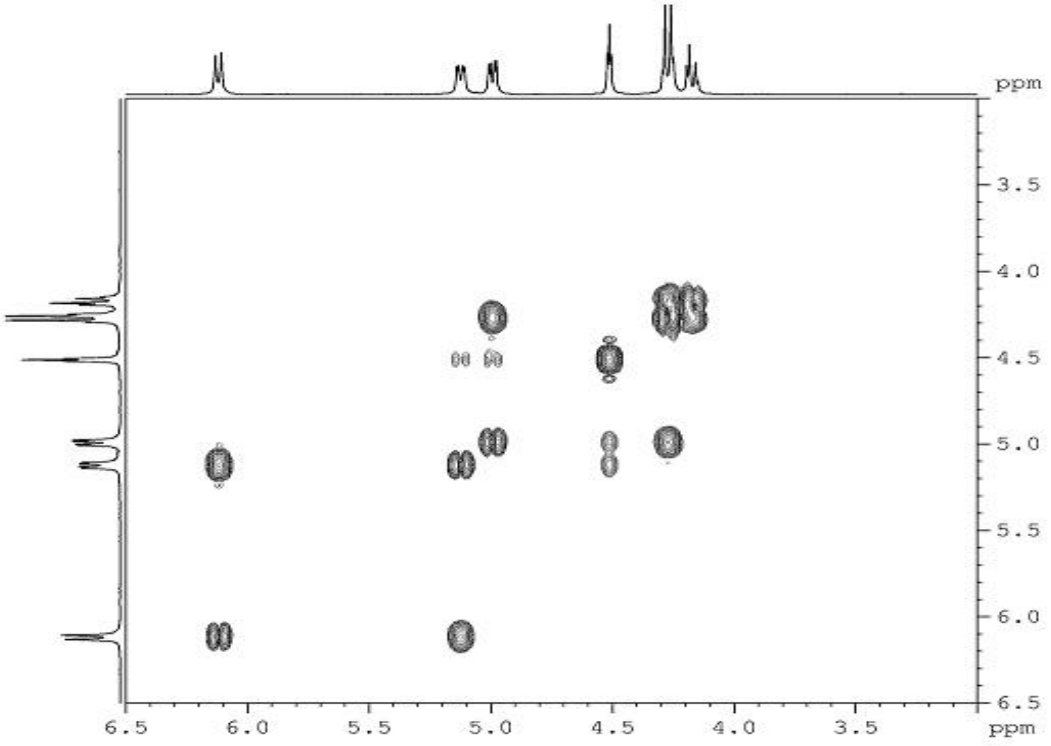
Hz; *J2',3'* = *J3',4'* = 9.3 Hz; were indicative of the *ß*-configuration and $^4C_1$ ring conformation.[38]

Table 2.3.1: Assignment of ^{1}H-NMR spectrum of **2.57**

Chemical shift (d) Coupling constant (Hz)	**H1'** *J1',2'*	**H2'** *J2',3'*	**H3'** *J3',4'*	**H4'** *J4',5'*	**H5'** *J5',6'*	**H6'** *J6'6"*	**H6''** *J5',6"*
	5.88 9.5	5.18-5.24 9.3	5.08 9.3	5.18-5.24 _____	3.92 2.0	4.11 12.8	4.27 5.0

Similarly the allo-configuration of the representative compound 3'-azido-*ß*-D allopyranosyl thymine **2.59**, was established using the ^{1}H-^{1}H COSY spectrum (**Figure 2.3.2**). The

Figure 2.3.2: ^{1}H-^{1}H COSY spectrum for **2.59**



anomeric proton appeared as a doublet at δ 6.11 (*J = 9.5 Hz*). The subsequent correlations have been tabulated below (**Table 2.3.2**). Notably the H3'-signal appeared as a triplet with *J* = 3.3 Hz showed axial-equatorial correlations of the coupling protons H2', H3' and H4'. The two large coupling constants *J1',2'* = *J4',5'* = 9.5 Hz indicates $^4C_1$-conformation of an *ß*-D allopyranose sugar moiety.[38]

Table 2.3.2: Assignment of ^{1}H-NMR spectrum of **2.59**

Chemical shift (d) Coupling constant (Hz)	**H1'** *J1',2'*	**H2'** *J2',3'*	**H3'** *J3',4'*	**H4'** *J4',5'*	**H5'** *J5',6'*	**H6'** *J6'6"*	**H6"** J5',6"
	6.11 9.5	4.99 3.3	4.50 3.3	5.11 9.5	4.27		4.16

The coupling constants *J1',2'* of the anomeric proton for compounds **2.57**, **2.62** (gluco-type) and **2.58-2.60** (allo-type) type have showed consistently high coupling constants ranging from 9-9.8 Hz. However, the orientations of the C-3' substitutions in compounds **2.57** and **2.59** was concluded by comparing the coupling constants of H3' protons (**Table 2.3.3**). In the case of the gluco compound **2.57**, the triplet signal due to H3' proton appeared at δ 5.08 with large coupling constant J = 9.3 Hz due to axial orientations of coupling protons, thus indicating the equatorial orientation C-3'-OTs. Whereas H3' for allo compound **2.59** appears at δ 4.50 with J = 3.3 Hz indicating the axial-equatorial orientations of coupling protons indicating the axial C-3'-N_3.

Table 2.3.3: Comparison of *J2',3'* and *J3',4'* of **2.57** and **2.59**

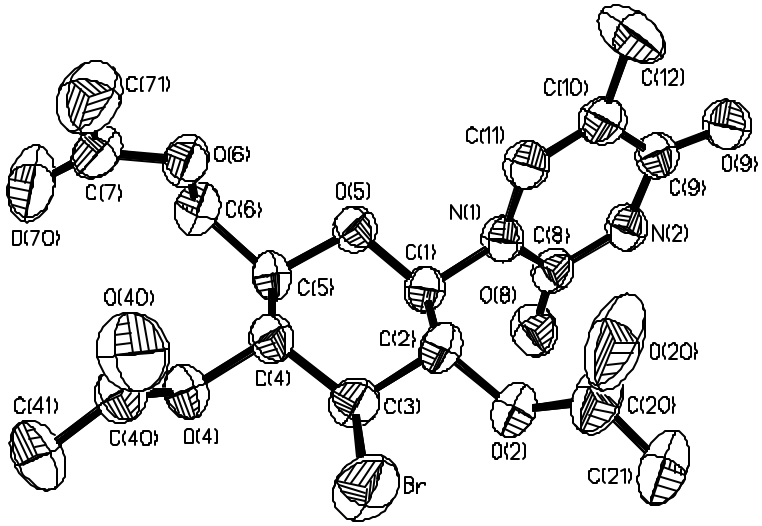
Coupling constant (Hz)	*J2',3'*	*J3',4'*
Compound **2.57**	9.3	9.3
Compound **2.59**	3.3	3.3

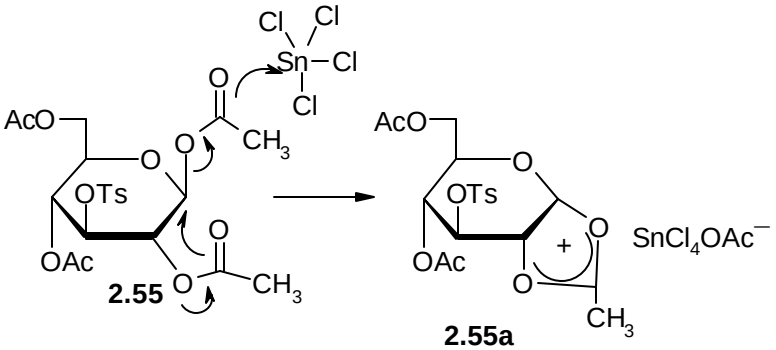
Nevertheless, the structure of compound **2.62** was established unambiguously with the help of the X-ray of its single crystal (**Figure 2.3.3**).

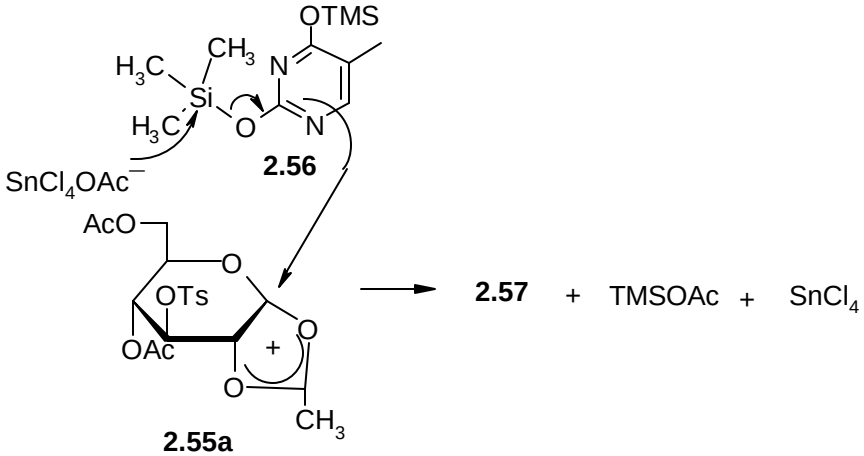
iv) Discussion

The exclusive formation of 3'-*O*-tosyl-*ß*-D-gluco thymine **2.57** at C-1' in the of presence 3'-*O*-tosyl leaving group can be easily explained. Reaction of $SnCl_4$ with the acetylated sugar **2.55** first leads to formation of a stable cyclic 1,2-acyloxonium cation **2.55a** and $SnCl_4OAc^-$ ion.[39,40] The silylated pyrimidine **2.56** reacted with the $SnCl_4OAc^-$ ion to generate TMSOAc and $SnCl_4$ with the simultaneous attack to electrophile sugar cation to give the nucleoside **2.57**. It was note worthy that irrespective of C-1' configuration of the acetyled sugar, the trans nucleoside was produced via the carbonium ion intermediate. With the *a*-face of the sugar blocked, the attack by the nucleobase was from the top face resulting in the formation of the trans *ß*-nucleoside.

Figure 2.3.3: ORTEP for compound **2.61**







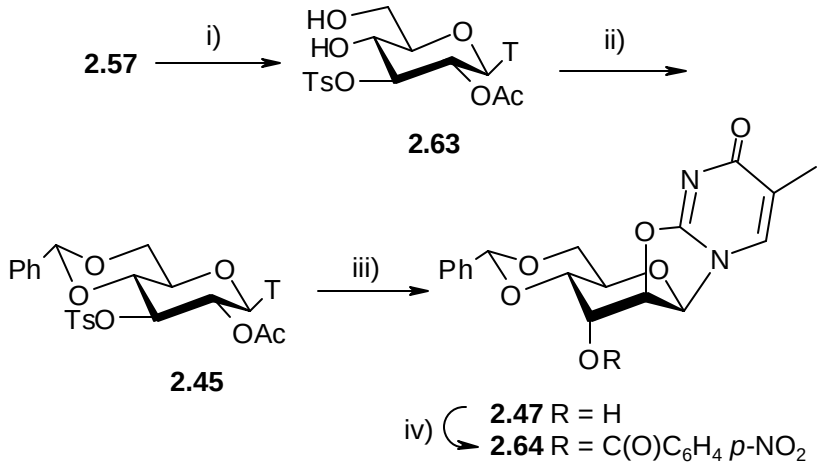
The nucleophilic displacement reactions of **2.57** produced the expected **2.58, 2.59** and **2.60**. Clearly, these products were formed due to the inversion of configuration at C-3', and produced the *ß*-D-allo nucleoside isomers. The formation of the unexpected gluco isomer **2.62**, with the retention of configuration was attributed to the thermodynamic stability of the 2',3'-diequatorial isomer formed.[41] Since bromide was a good leaving group, the allo-isomer **2.61** was attacked by another bromide ion to produce the gluco-derivative **2.62**.

SECTION B

Synthesis and Reactions of 2,2'-*O*-anhydro-(4,6-*O*-phenylmethylene-*ß*-D-altro-pyranosyl) thymine (2.47)

i) Synthesis

At this stage we were looking for an efficient method for the deacetylation of 4'- and 6'-*O*-acetyl groups of **2.57** retaining the 2'-*O*-acetyl protection. This was necessary because we did not want the deacetylated 2'-OH to attack intramolecularly the C-3' position. Attempted deprotection using MeOH-NH_3 or MeOH-NaOMe produced an inseparable mixture of compounds. After several experimentations, we identified MeOH-*i*PrNH_2 as the best combination for the selective deacetylation of 4'- and 6'-*O*-acetyl groups to afford the diol **2.63**. To establish the sites of deacetylation unambiguously, we directly converted crude **2.63** to the benzylidene protected nucleoside **2.45** in overall 70 % yield in two steps.

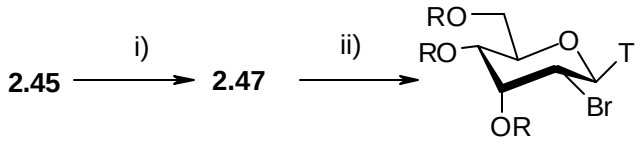


i) isopropylamine, MeOH, 5h, rt. ii) $PhCH(OCH_3)_2$, TsOH, DMF, 1h, 100 °C. iii) NaOMe, MeOH, 30h, rt. iv) *p*-$NO_2C_6H_4COCl$, pyridine, 0 °C to rt, overnight, 64% (from **2.45**).

This protecting group blocked the 4' and 6'-hydroxyl groups and established the absence of any acetyl group on those two sites. Treatment of **2.45** with MeOH-NaOMe, gave highly hygroscopic, 2,2'-*O*-anhydro compound **2.47**, which was identified as its *p*-nitrobenzoate derivative **2.64**. The overall yield of compound **2.64** in three steps from **2.45** was 64 %.

ii) Reactions

In order to study the reactivities of the 2,2'-*O*-anhydro-bridge we wanted to react **2.47** with various nucleophiles. However, because of the hygroscopic nature of **2.47**, compound **2.45** was converted to **2.47** and the crude **2.47** was directly subjected to the nucleophilic displacement reactions. Unlike its pentofuranosyl counterpart, compound **2.47** was found to be inert towards a wide range of nucleophiles (**Table 2.3.4**). Only LiBr in the presence of a catalytic amount of TFA could open the bridge. Because of the acidic reaction conditions debenzylidenation occurred and the triol **2.65** generated *in situ* was acetylated with acetic anhydride in pyridine and isolated as the tri-acetylated ß-D-allo nucleoside **2.66** in 30 % overall yield from **2.45**.



2.65 R = H
2.66 R = Ac

i) NaOMe, MeOH, 30h, rt. ii) a. LiBr, TFA, DMF, 90 °C, 24h.
b. Ac_2O, pyridine, rt, overnight.

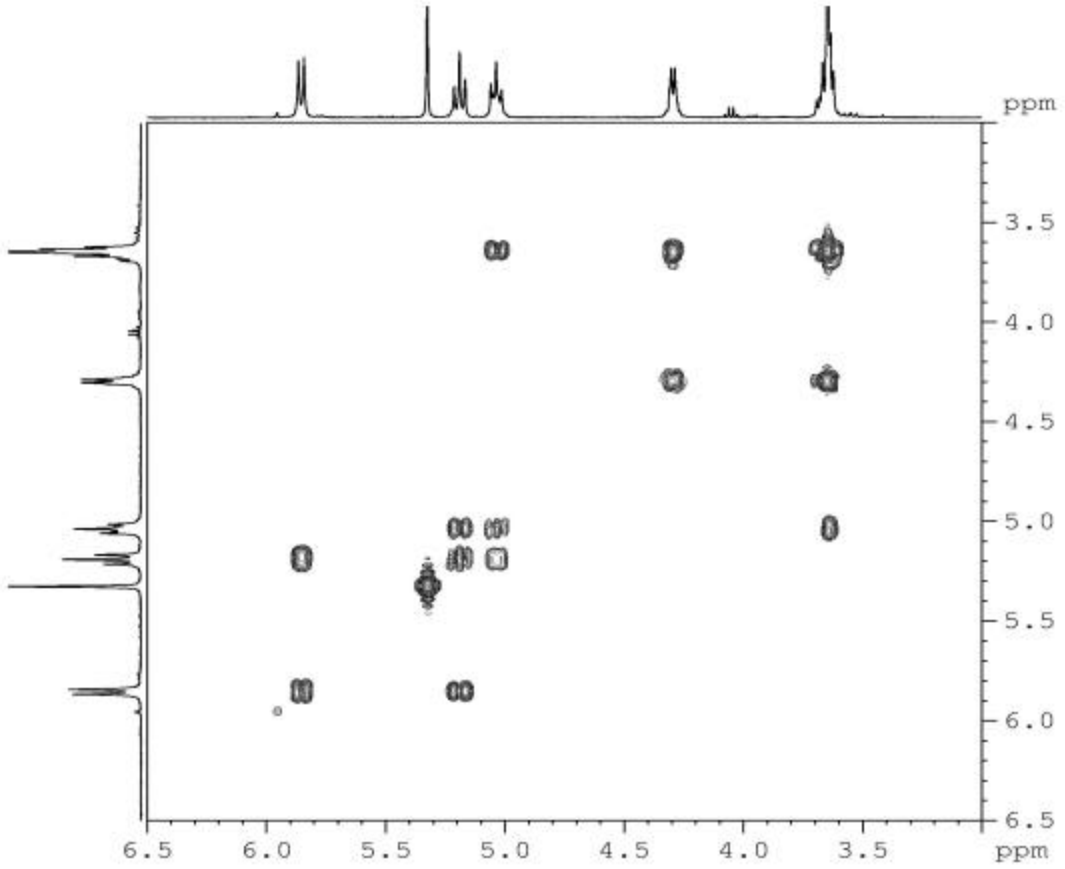
Table 2.3.4: Reactivity of **2.47**

SL No.	Reaction Conditions	Result
1.	LiN_3, TFA, DMF, 90-110 °C, 24-30h.	Inseparable mixture of products
2.	BzONa, BzOH, DMF, 90-110 °C, 24-30h.	Inseparable mixture of products
3.	LiBr, TFA, DMF, 90 °C, 24h.	Compound **2.66**; 30 % from **2.45**
4.	Thiocresol, NaOMe, DMF, 90-110 °C, 24h.	Unreacted starting material recovered

iii) Structural assignments

In this section, the fully protected **2.45**, the protected 2,2'-*O*-anhydro nucleoside **2.47** and the bromo compound **2.66** were synthesized and characterized. It was important to establish the structure of compound **2.45**, since it formed the basis for the synthesis of 2,2'-*O*-anhydro nucleoside **2.47**. The interpretations of ^{1}H-^{1}H COSY spectrum (**Figure 2.3.4**) for compound **2.45** was conveniently started from the anomeric proton at δ 5.93

Figure 2.3.4: ^{1}H-^{1}H COSY spectrum for compound **2.45**



with *J1',2' = 9.5 Hz*. Notably the higher coupling constant values *J1',2'* (9.5 Hz) and *J2',3'* (9.3 Hz) (**Table 2.3.5**) indicated the axial orientations of coupling protons H1', H2' and H3'.

The anomeric proton for the 2,2'-*O*-anhydro derivative **2.64** appears as a doublet at δ 5.83 with *J1',2'* as 3.6 Hz, indicating the axial/equitorial relationship of the couping protons H1' and H2' and compound is expected to have *ß*-D altro configuration. Whereas the anomeric proton for compound **2.66** appeared at δ 6.22 as a broad doublet signal

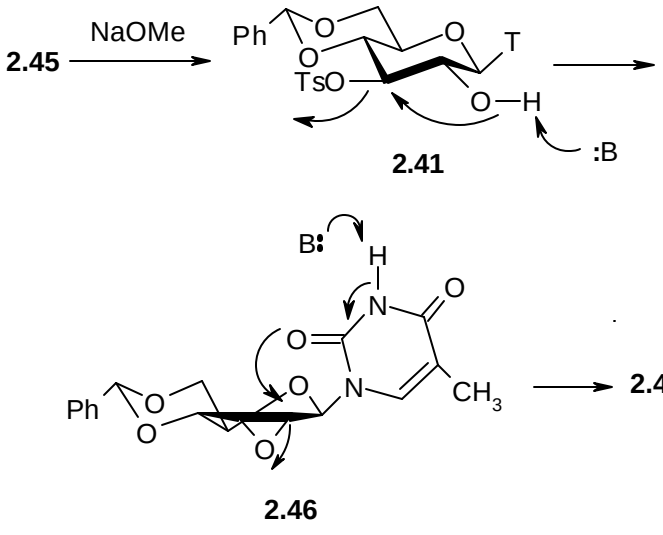
Table 2.3.5: Assignment of ^{1}H-NMR spectrum of **2.45**

Chemical shift (d**)** Coupling constant (Hz)	**H1'** *J1',2'*	**H2'** *J2',3'*	**H3'** *J3',4'*	**H4'** *J4',5'*	**H5'** *J5',6'*	**H6'** *J6',6"*	**H6"** *J5',6"*
	5.93 9.5	5.26 9.3	5.11 —	3.69-3.76 ———			4.37 —

with *J1',2'* as 9.4 Hz which indiactes the diaxially placed coupling protons H1' and H2'. The opening of 2,2'-*O*-anhydro nucleoside **2.47** with the nucleophile allowed it to have only the ß-D allo configuration (see Discusson). The coupling constant for the anomeric proton at δ 6.22, *J1',2'* = 9.4 Hz of **2.66** clearly suggested that H1' and H2' were diaxially oriented.

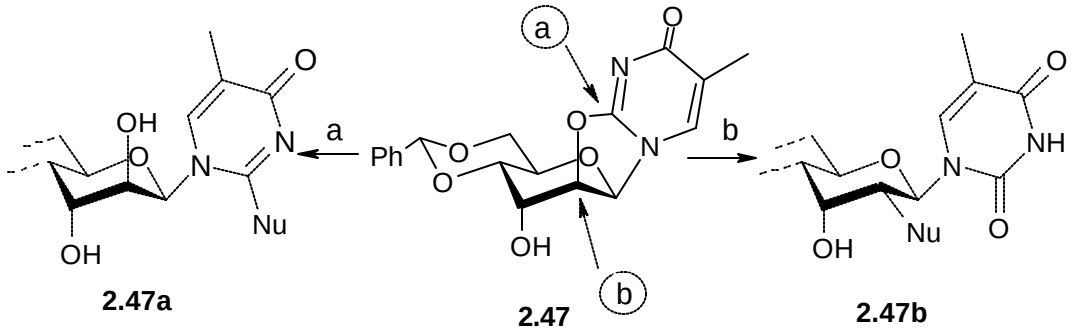
iv) Discussion

Although the exact reason for the selective deacetylation of **2.57** was not clear to us, we argued that the presence of a controlled amount of amine (**2.57** : *iso*propylamine = 1:10) instead of a large excess of amine (for example, in saturated MeOH-NH_3) in the reaction mixture might have contributed to the selectivity. The formation of **2.47** under basic conditions could be explained as follows. Compound **2.45** underwent deacetylation and the free hydroxyl group intramolecularly attacked the C-3' position to afford the allo-epoxide **2.46**. A concomitant attack of O2-oxo group of the thymine base opened the allo epoxide **2.46** trans-diaxially to produced the 2,2'-*O*-anhydro derivative **2.47**.[42]



The 2,2'-*O*-bridge of **2.47** could be opened from two directions. It is known in the case of pentofuranosyl analogues that "hard" nucleophiles tend to attack the nucleobase (path a)

and "soft" nucleophiles attack the carbohydrate moiety (path b).[43] In the present case, the former would lead to the formation of 2-substited ß-D altropyranosyl pyrimidines **2.47a** and the latter would produce the 2'-substitiend-2'-deoxy-ß-D-allopyranosyl thymine **2.47b**. The formation of the bromo compound **2.65** was therefore easily understood and was consistent with the known results for similar reactions with halides.[44]



2.47a **2.47** **2.47b**

On the other hand, a hard nucleophile $^{-}$OH did indeed attack the nucleobase; the reaction has been utilized in the synthesis of the epoxy nucleoside **2.43** (see later). The resistance of the 2,2'-*O*-anhydro-bridge towards S_N2 type reactions with a series of nucleophiles may be explained by imagining a stereoelectronic repulsion faced by the incoming nucleophiles (path b producing **2.47b**) of the axially oriented 3'-hydroxyl group of the rigid molecule **2.47**. This repulsion was absent in the corresponding pentofuranosyl systems (compound **2.36**) because of the pseudo-axial nature of the C-3'-OH bond. It was highly probable that the sole successful reaction of **2.47**, which led to the formation of **2.65** was in fact an S_N1 reaction; protonation of the anhydro-bridge of **2.47** generated a carbenium ion at C-2' and then the C-Br bond formation took place.

SECTION C

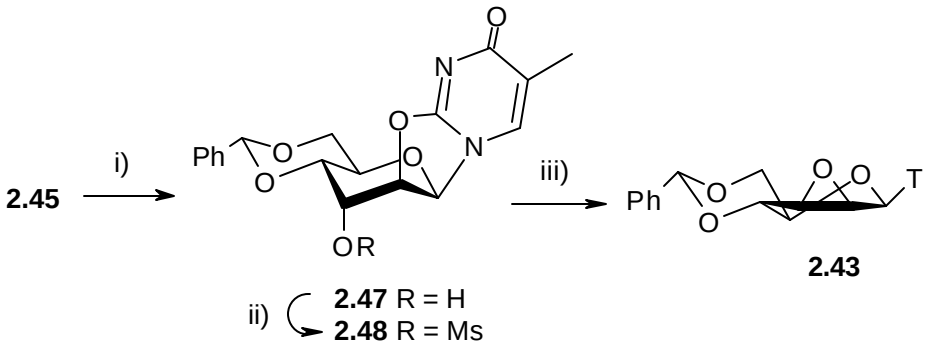
Synthesis and reactions of 2',3'-*O*-anhydro ß-D-hexopyranosyl thymine (2.43)

i) Synthesis

Nucleophilic ring opening of 2',3'-*O*-anhydro-uridine/lyxo-uridine and ribo-/lyxo-thymidine **1.085c** /**1.084a** and **1.085d** /**1.084c** in general is one of the most important strategies for the synthesis of sugar-modified nucleosides (**Chapter 1**). Considering the importance of hexopyranosyl nucleosides as "new chemical entities", we envisaged that a functionalized compound like 2',3'-*O*-anydrohexopyranosyl pyrimidine has the high potential to act as a versatile and general intermediate for the synthesis of modified hexopyranosyl pyrimidines. The selection of epoxy nucleoside was also important because of the fact that 1-(2,4,6-tri-*O*-acetyl-3-*O*-tosyl-ß-D-glucopyranosyl) thymine

(compound **2.57**, Section **2.3, A**) although useful in producing various 3'-deoxy-3'-substituted allopyranosyl nucleosides was incapable of reacting with a number of nucleophiles including amines and carbon nucleophiles because of the sluggish reactivity of C-3' position having a secondary carbon.

Our synthesis started with compound **2.47** which was easily accessible from **2.45**. Thus, compound **2.47** was mesylated with mesyl chloride in pyridine at 0 °C to afford, 2,2'-*O*-anhydro-(4,6-*O*-phenylmethylene-3-deoxy-3-*O*-mesyl-ß-D-altropyranosyl) thymine **19**, The crude mesylated product **2.48**, on reaction with aqueous NaOH, was converted directly to the targeted 2',3'-*O*-anhydro-ß-D-mannopyranosyl thymine **2.43**. The overall yield for the reaction sequence starting from compound **2.45** to compound **2.43** was 30-34 %.

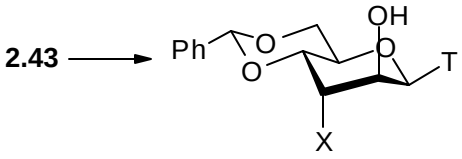


i) NaOMe, MeOH, 30h, rt. ii) MsCl, pyridine,
0-4 °C, overnight. ii) aq. NaOH, dixoane, rt, 0.5h.

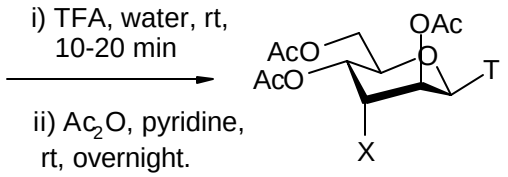
ii) Reactions

To establish the synthetic utility of epoxide **2.43**, a range of nucleophiles was selected for opening the epoxide ring. Thus, keeping in mind the importance of azido nucleosides,[6] **2.43** was reacted with a mixture of LiN_3 and NH_4Cl at an elevated temperature in anhydrous ethanol to afford a single product **2.67a** containing the azido group. The product after purification was treated with TFA: water mixture (4:1) for a brief period to remove the phenylmethylene protecting group. However, for the convenience of isolation and purification the deprotected compound was acetylated to obtain **2.68a** in 65%. This strategy of acetylation after deprotection was followed in all subsequent reactions with other nucleophiles. Since 2'-amino-2'-deoxythymidine was identified for its anti-HIV property in certain cell-lines,[6] and some of the 3'-*N*-alkylamino-3'-deoxy-ara-uridines[45] were identified as potential inhibitors of ribonuclease A and angiogenin,[46] we reacted **2.43** with a series of amines. Thus, *iso*butylamine (70 °C for 24 h), pyrrolidine (90 °C for

24 h), morpholine (90 °C for 25 h) and 1-acetylpiperazine (90 °C for 30 h) opened the epoxide ring of **2.43** in DMSO to generate aminonucleosides **2.67b-e** respectively. A planar heterocycle imidazole also reacted with **2.43** at an elevated temperature to afford **2.67f**. The methodology was equally useful for the formation of C-S bond at the C-3' position. Thus, two thio-nucleophiles such as *p*-tolylthiol and NH_4SCN also opened the epoxide ring of **2.43** to generate thionucleosides **2.67g** and **2.67h** respectively. To expand the scope of the methodology further, an important transformation was achieved by opening the epoxide ring of **2.43** with NaCN in DMF at an elevated temperature to get **2.67i**.[47] Compounds **2.67b-i** were deprotected with acid and triols were converted to their triacetylated derivatives **2.68b-i** respectively. As expected,[48] all epoxide opening

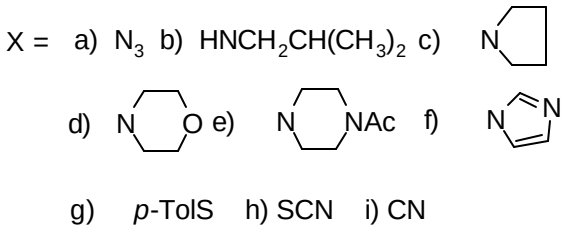


2.67a LiN_3, NH_4Cl, EtOH, reflux, 10h (83%)
2.67b *iso*butylamine, DMSO 70 °C, 22h (79%)
2.67c pyrrolidine, DMSO, 90 °C, 24h (84%)
2.67d morpholine, DMSO, 90 °C, 25h (80%)
2.67e 1-acetylpiperazine, 90 °C, 30h (56%)
2.67f imidazole, TMG, DMSO, 70 °C, 20h (86%)
2.67g TolSH, NaOMe, DMF, 70 °C, 10h (66%)
2.67h NH_4SCN, DMF, 70 °C, 10h (71%)
2.67i NaCN, DMF, 70 °C, 10h (68%)



2.68a-2.68i

2.68a (65%); **2.68b** (70%); **2.68c** (85%)
2.68d (75%); **2.68e** (75%); **2.68f** (65%)
2.68g (55%); **2.68h** (56%); **2.68i** (65%)

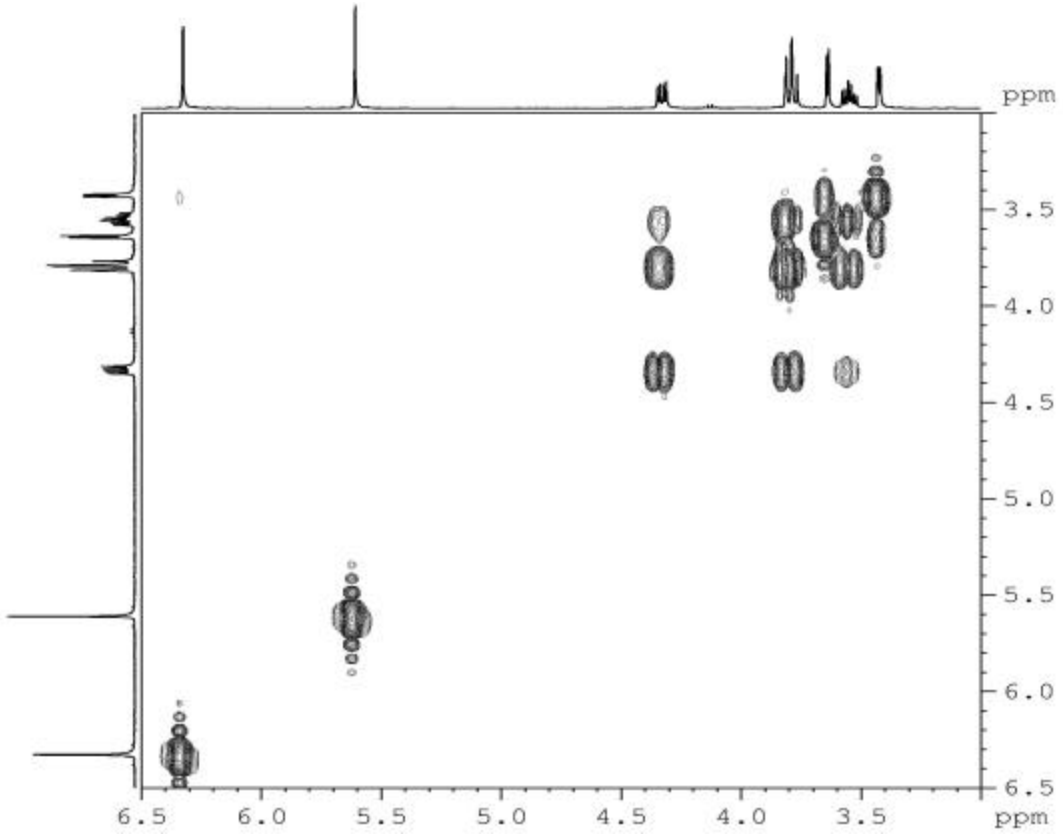


reactions reported here generated single products. All products were identified as their triacetylated derivatives **2.68a-i**.

iii) Structural assignments

The anomeric proton of compound **2.43** appeared at δ 6.32 as a doublet with small *J 1',2'.* This signal showed a small coupling correlation with the doublet signal at δ 3.42, which was assigned for H2' with *J2',3'* = 3.8 *Hz*. Evidently, H3' proton appeared as a doublet at δ 3.63 with *J3',2'* = 3.7 Hz. The connectivities of other proton signals for compound **2.43** was established using ^{1}H-^{1}H COSY spectrum (**Figure 2.3.5**) and are tabulated below (**Table 2.3.6**).

Figure 2.3.5: ^{1}H-^{1}H COSY spectrum of epoxide **2.43**



The chemical shifts and *J1',2'* values of the anomeric protons for the *ß*-D altrose series **2.68a-2.68i** have been tabulated below (**Table 2.3.7**). The low *J1',2'* values ranging from 0-3.2 Hz of **2.68a-2.68i** indicated *axial-equatorial* orientation of coupling protons H1', H2' in the *ß*-D altrose series of nucleosides. The interpretations of ^{1}H-^{1}H COSY spectra (**Figure 2.3.6** and **2.3.7**) starting from the anomeric protons δ 6.22 and δ 5.87 for compounds **2.68e** and **2.68i** (**Table 2.3.8**) respectively have been tabulated below. Notably the lower *J2',3'* values, for both the compounds **2.68e** and **2.68i** (**Table 2.3.8**) are indicative of the diequatorial orientations of coupling protons H2' and H3'.

Table 2.3.6: Assignment of ^{1}H-NMR spectrum of **2.43**

Chemical shift (d) Coupling constant (Hz)	**H1'** *J1',2'*	**H2'** *J2',3'*	**H3'** *J3',4'*	**H4'** *J4',5'*	**H5'** *J5',6'*	**H6'** *J6'6"*	**H6''** *J5,6"*
	6.32 ___	3.42 3.7 -3.8	3.63 ___	3.78 ___	3.51-3.57 ____	3.78 ___	4.32 ___

Table 2.3.7: Chemical shifts and *J1',2'* of anomeric protons of **2.68a-i**

Compound Number	**2.68a**	**2.68b**	**2.68c**	**2.68d**	**2.68e**	**2.68f**	**2.68g**	**2.68h**	**2.68i**
d **H1'**	6.02	6.35	6.25	6.23	6.22	6.25	6.49	6.01	5.87
J1',2' Hz	---	---	---	---	2.3	3.2	1.6	1.5	1.3

Figure 2.3.6: ^{1}H-^{1}H COSY spectrum for **2.68e**

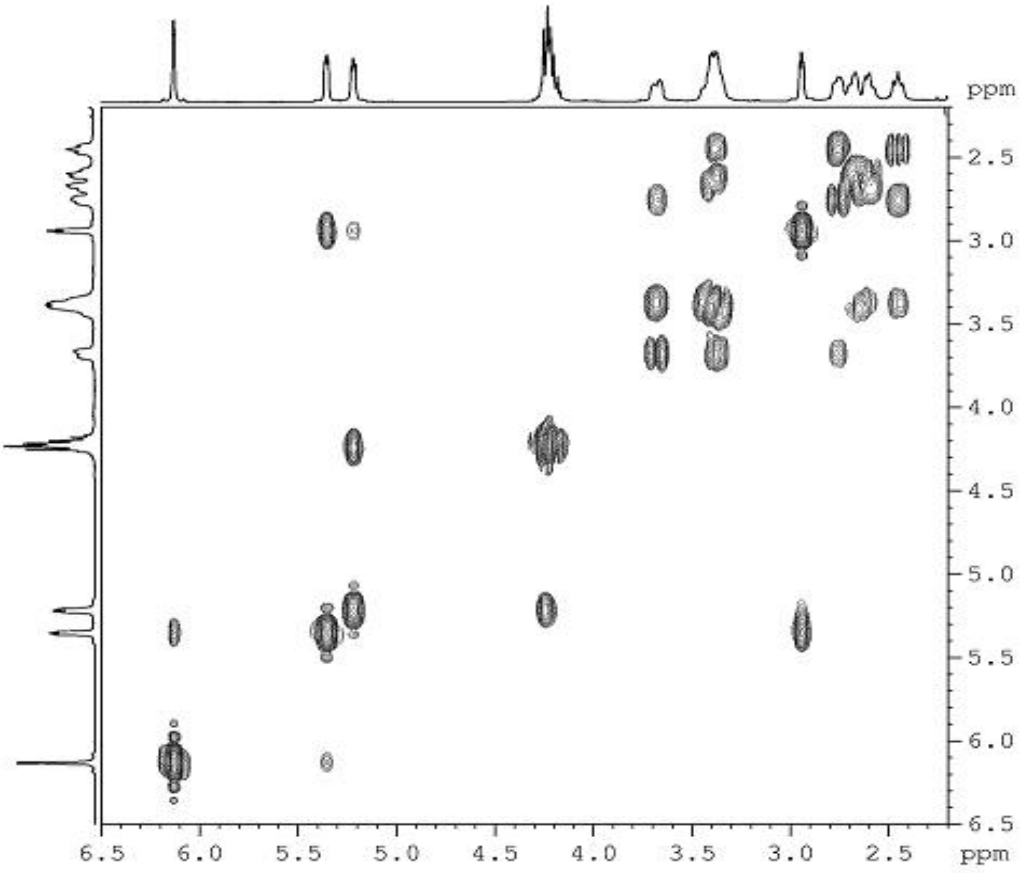


Figure 2.3.7: ^{1}H-^{1}H COSY spectrum for **2.68i**

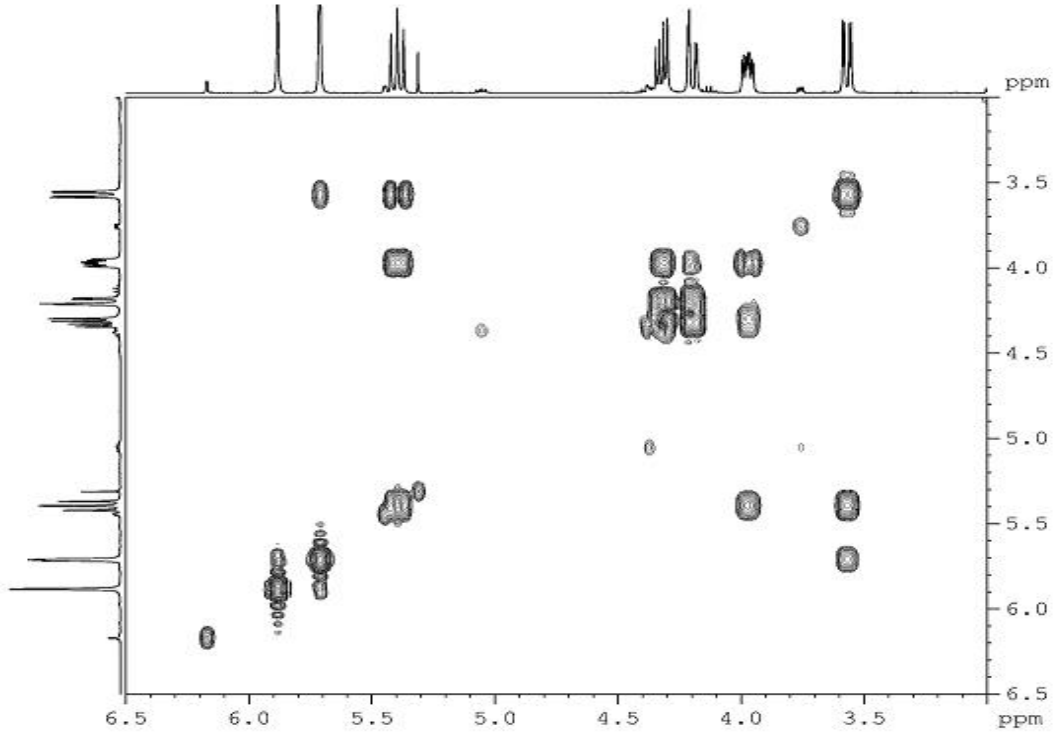
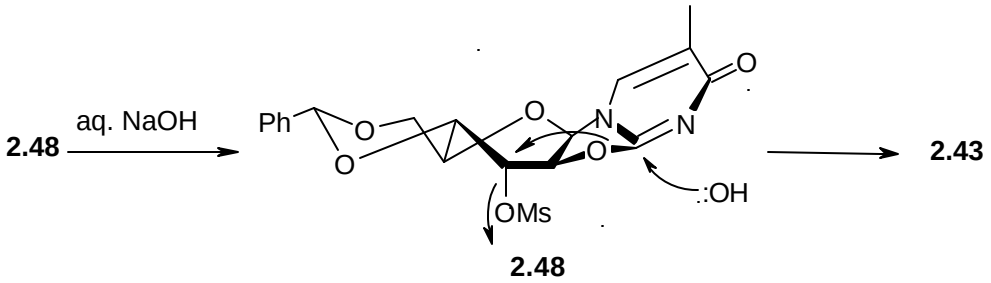


Table 2.3.8: Assignment of ^{1}H-NMR spectra of **2.68e** and **2.68i**

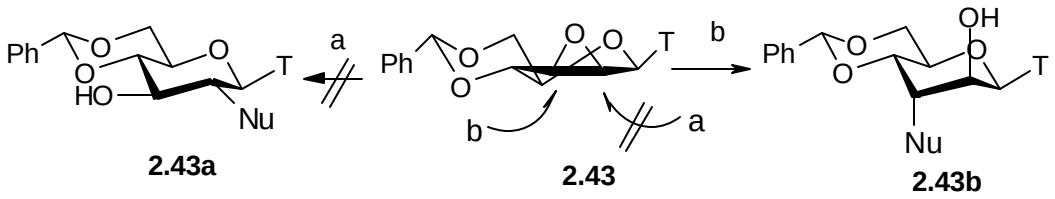
Chemical shift (d) Coupling constant (Hz)	**H1'** *J1',2'*	**H2'** *J2',3'*	**H3'** *J3',4'*	**H4'** *J4',5'*	**H5'** *J5',6'*	**H6'** *J6',6"*	**H6"** *J5',6"*
Compound 2.68e	6.22 2.3	5.44 5.1	3.02 3.3	5.30 5.5	4.26-4.35		
Compound 2.68i	5.87 1.3	5.70 2.8	3.56 11.1	5.39 10.1	3.97 2.5	4.19 12.6	4.32 6.0

iv) Discussion

Although the epoxide ring opening of nucleosides may appear to be an obvious strategy for the synthesis of modified hexopyranosyl nucleosides we were surprised to note that compounds such as **2.43** have not been exploited for the modification of sugar residues of these nucleosides. We have already discussed the synthetic strategy for accessing the desired epoxide **2.43**. The most plausible mechanism for the formation of 2',3'-*O*-anhydro-mannopyranosyl nucleoside **2.43** was as follows. The hard nucleophile hydroxide ion in an aqueous medium attacked the C-2 of nucleobase of **2.48**. The newly generated C-2' oxygen nucleophile attacked the C-3' position intramolecularly and displaced the mesyl group forming the 2',3'-*O*-anhydro ring of **2.43**.

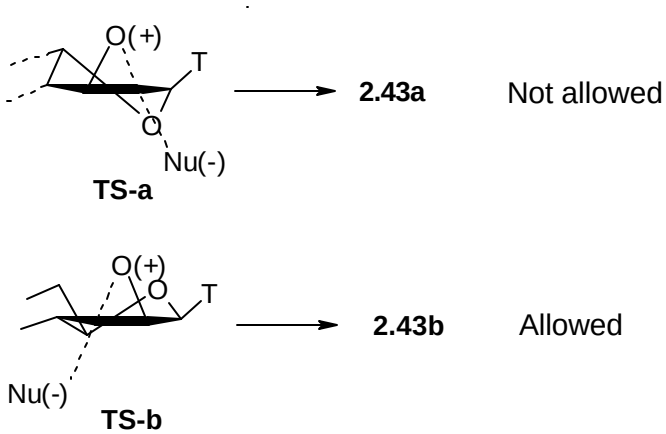


It should be noted that we planned to synthesize the benzylidene protected manno epoxide **2.43** because such compounds were known to undergo trans-diaxial type of attack of nucleophiles at C-3' affording only altropyranosyl derivatives.[48] Bimolecular trans-opening of the general cyclohexane epoxide of a conformationally rigid system had discussed in detail.[48c] In our case also, the S_N2 attack of nucleophiles on compound **2.43**



2.43a **2.43** **2.43b**

involved the formation of a transition state, and thus was conformational control during formation of the products. It was proposed[49] that the co-planarity of three member oxide ring with the incoming nucleophile could only be achieved in a half-chair conformation in the transition state (like in **TS-b**). In this case possibility of alternate half chair conformation (^1H_o) **TS-a** was prevented by the *trans* junction between benzylidene ring and pyranose portion in a transition state.[48b,48c] Thus the attack of a nucleophile was only possible through path b, leading to the transition state **TS-b**.



SECTION D

Synthesis and properties of vinyl sulfone-modified ß-D-hexopyranosyl thymines

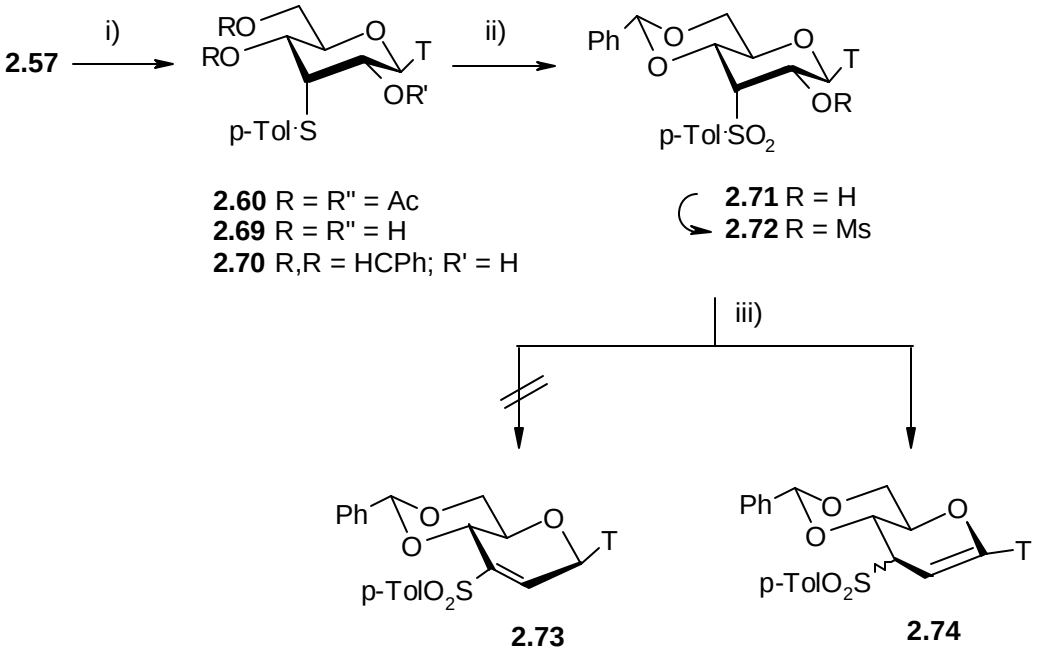
Vinyl sulfone- and bisvinyl sulfone-modified pentofuranosyl nucleosides were exploited for the synthesis of several 2', /3'-modified nucleosides (**Chapter 1,** Section **1.9**). Michael addition reactions of nitrogen and carbon nucleophiles to vinyl sulfone-modified hex-2-enopyranosides were used efficiently for the synthesis of amino- and branched chain carbohydrates.[50,51] Since we could easily synthesize different thionucleosides such as the allo-derivative **2.60** or the altro-derivative **2.68g**, we decided to synthesize and study the reactivities of these important modified nucleosides.

i) Attempted synthesis of 1-[2,3-deoxy-(4,6-*O*-phenylmethylene)-(3-*C*-*p*-toluenesulfonyl)-*erythro*-ß-D-hex-2-*eno*-pyranosyl] thymine (2.73)

1-(2,4,6-Tri-*O*-acetyl-3-*O*-tosyl-ß-D-glucopyranosyl) thymine **2.57** was converted to a mixture of **2.60** and partially deacetylated compounds in the usual way. Complete deacetylation of the mixture was achieved by NaOMe in methanol. The triol **2.69**, thus obtained was bezylidenated yielding the partially protected alcohol **2.70**. Compound **2.70** was oxidized with MMPP in MeOH to produce the sulfonylated nucleoside **2.71**. Crude **2.71** was mesylated using the standard conditions and the product **2.72** was subsequently treated with DBU. Although oxidation-mesylation-base treatment was a standard route which was used earlier for the synthesis of vinyl sulfone-modified carbohydrates and nucleosides, in this case the desired compound **2.73** was not produced. The isolated product was identified as the hex-1-enopyranosyl nucleoside, 1-[2,3-deoxy-(4,6-*O*-phenylmethylene)-(3-*C*-*p*-toluenesulfonyl)-*erythro*-ß-D-hex-1-*eno*-pyranosyl] thymine **2.74**. Since **2.74** was not the desired product, no attempt was made further to unambiguously establish the configuration of the C-3' center of this compound.

ii) Synthesis and reactions of 1-[2-*O*-benzyl-3,4-deoxy-(3-*C*-*p*-toluenesulfonyl)-6-*O*-trityl-erythro-ß-D-hex-3-eno-pyranosyl] thymine (2.82)

Some of the naturally occurring and biologically important hexopyranosyl nucleosides having functional groups at the 4'-positins were reported in the literature. (**Figure 2.1.1, Sec 2.1**). This class of compounds has been synthesized so far either by coupling the modified carbohydrates with the suitable nucleobases,[5] or by displacing the sulfonate group attached to C-4'.[13] We envisaged that by designing a compound like **2.82** and studying its reactivities we would be able to access C-4' modified hexopyranosyl nucleosides through a new route.

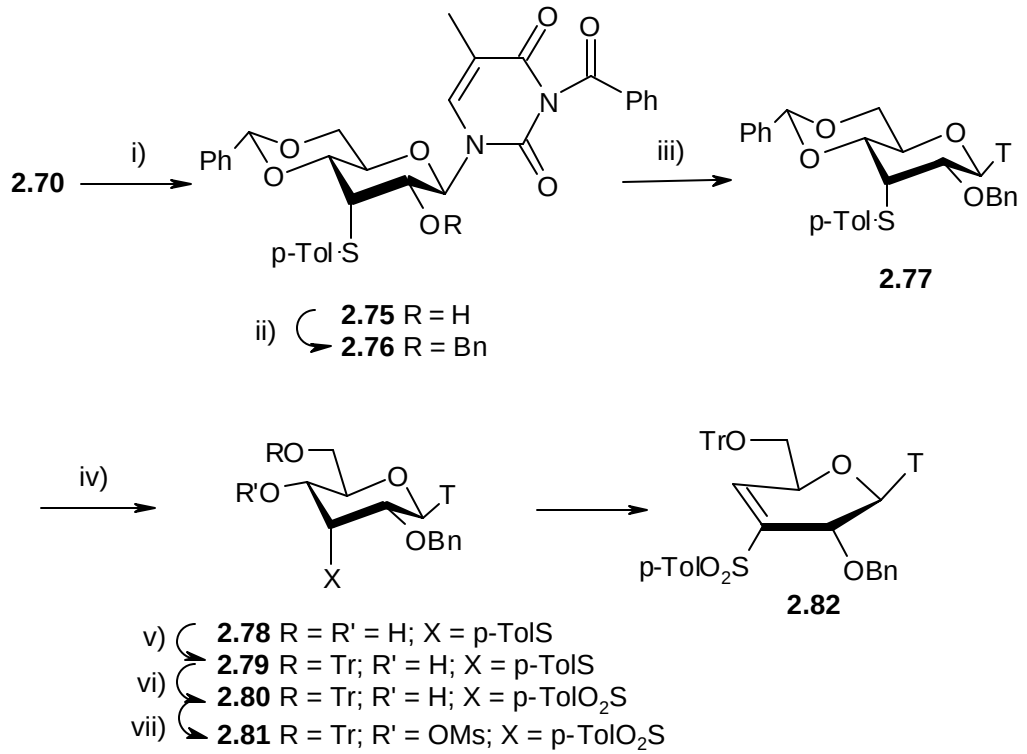


i) a. p-TolSH, NaOMe, DMF, 90 °C, 10h. b. NaOMe, MeOH, rt, 6h. c. $PhCH(OCH_3)_2$, TsOH, DMF, 100 °C, 1.5h, 65% (from **2.57**). ii) MMPP, MeOH, rt, 3-3.5h. iii) a. MsCl, pyridine, 0-4 °C, overnight. b. DBU, DCM, rt, 5h, 52% (from **2.71**).

iia) Synthesis of 2.82

Because of its easy accessibility, we started our synthesis with thio nucleoside **2.70**. Our intention was to deprotect **2.70**, protect the primary alcohol selectively and then mesylate C-4'-OH group. However, for this strategy it was necessary to protect the C-2'-OH group. Instability of ester groups under nucleophilic reaction conditions to be used later, prompted us to select benzyl group for the protection of the C-2'-OH group. It was therefore necessary to protect the nucleobase prior to the protection of the C-2'-OH group to avoid any alkylation of the nucleobase. Thus, alcohol **2.70** was treated with trimethylsilyl chloride in pyridine at 0 °C followed by benzoyl chloride in one-pot fashion. The product after usual work-up, was treated with 0.05 % TFA in the mixture of solvents MeOH:$CHCl_3$ for few minutes to produce the N^3-benzoylated derivative **2.75**. Compound **2.75** was benzylated using excess of benzyl bromide and NaH in anhydrous DMF. After purification, compound **2.76** was treated with NaOMe in MeOH to afford nucleoside **2.77**. Compound **2.77** was treated with TFA:water mixture (4:1) for a brief period to remove the phenylmethylene-protecting group. The primary C-6'-OH of **2.78**, thus obtained, was protected with trityl group to produce **2.79**. Compound **2.79** was oxidized to sulfone nucleoside **2.80**. The sulfone **2.80** was mesylated in pyridine and the reaction condition was basic enough to initiate an elimination reaction to afford the vinyl sulfone-modified

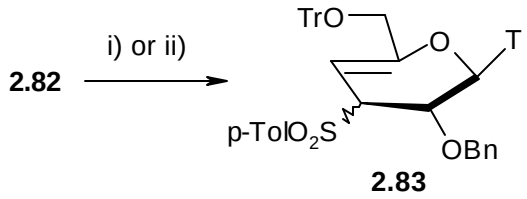
nucleoside **2.82**. The final product was identified as the desired 1-[2-*O*-benzyl-3,4-deoxy-(3-*C*-*p*-toluenesulfonyl)-6-*O*-trityl-*erythro*-ß-D-hex-3-*eno*-pyranosyl] thymine **2.82** and its structure was established unambiguously with the help of X-ray of single crystal (see later).



i) a.TMSCl, pyridine, 30 min., BzCl, pyridine, rt, overnight. b. 0.05%TFA, $CHCl_3$, MeOH, 30 min. ii) BnBr, NaH, DMF, rt, overnight. iii) NaOMe, MeOH, rt, 3h. iv) aq.TFA (80%), rt, 30 min. v) TrCl, pyridine, reflux, 2h. vi) MMPP, MeOH, rt, 3h. vii) MsCl, pyridine, 0-4 ^oC, overnight.

iib) Reactions of 2.82

Michael acceptor **2.82** was treated with several amines and carbon nucleophiles generated from nitromethane or dimethylmalonate. Almost all reactions produced inseparable mixture of products (**Table 2.3.9**). Only benzylamine and piperidine in a non-polar solvent like (EDC) afforded an isomerized product **2.83,** which was identified as having C4'-C5' double bond to give the more stable product, namely 1-[2-*O*-benzyl-3,4-deoxy-(3-*C*-*p*-toluenesulfonyl)-6-*O*-trityl-*erythro*-ß-D-hex-4-*eno*-pyranosyl] thymine **2.83** in 50-55% yield.



i) benzylamine, EDC, rt, 48h, 55%.
ii) piperadine, EDC, rt, 5h, 50%.

Table 2.3.9: Reactions of **2.82** under various conditions

Sl. No.	**Reaction conditions**	**Products**
1.	benzylamine (5 eqv.) in EDC; rt; 48h	55 % of **2.83**
2.	piperidine (5 eqv.) in EDC; rt; 5h.	50 % of **2.83**
3.	*iso*butylamine (neat); rt; 8-10h.	Inseparable mixture
4.	$EtNH_2$ aq. (70 %, excess) in dioxane; rt; 1h.	Inseparable mixture
5.	NH_3 aq. (excess) in dioxane; rt; 1h	Inseparable mixture
6.	nitromethane-NaOMe in MeOH; rt; 10-12h	Inseparable mixture
7.	dimethyl malonate -NaH in THF; rt; 24h	Inseparable mixture

iii) Structural assignment

The presence of peaks at δ 5.40 (1H), 4.48 (1H), 4.20 (2H), 4.09 (1H), 3.84 (1H) in the ^{1}H-NMR of **2.74** established the absence of one proton from the carbohydrate ring which was also supported by the elemental analysis data of compound **2.74**. Moreover, it was established in the case of compound **2.87** (see Discussion later) that H2 olefinic proton appeared at δ 6.94 (1H, m) and for nucleoside **1.106a** (**Chapter 1**, Section **1.9**) the peak due to H2' appeared at δ 6.56; the absence of any such peak around that region a for

2.74 indicated the absence of a vinyl sulfone group in this compound. The signal of H2' alkene proton for **2.74** was identified (^{1}H-^{1}H COSY; **Figure 2.3.8**) as a doublet appearing at δ 5.40. All other sugar protons were assigned using correlation spectrum (**Table 2.3.10**). ^{13}C-signals were assigned on the basis of their direct coupling correlation through single bond with the assigned protons in ^{1}H-^{13}C HSQC spectrum (**Figure 2.3.9**).

The peak position of quaternary C-1' was established to be δ 149.0 on the basis of its correlations with two ß protons, H3' (δ 4.20) and H6 (δ 7.13) in HMBC spectrum **(Figure**

2.3.10). The identification of C-1' as a quaternary carbon and the presence of the olefinic proton at a higher field (δ 5.40 as opposed to > δ 6.50) established the position of the double bond between C-1' and C-2'.

The structure of compound **2.82** was easily established with the help of its ^{1}H-^{1}H COSY spectrum (**Figure 2.3.11**). The characteristic peak of the vinyl proton of the vinyl sulfone group was identified at δ 7.10-7.43. The positions of other peaks have been presented in tabular form (**Table 2.3.11**). However the structure of this compound was established unambiguously with the help of X-ray data of single crystal (**Figure 2.3.12**). Notably the C3'-C4' bond length was 1.31 ^{o}A, which was less than the average carbon? carbon single bond length. This confirmed the existence of a double bond between C-3' and C-4' (**Table 2.3.12A and 2.3.12B**).

Figure 2.3.8: ^{1}H-^{1}H COSY spectrum for **2.74**

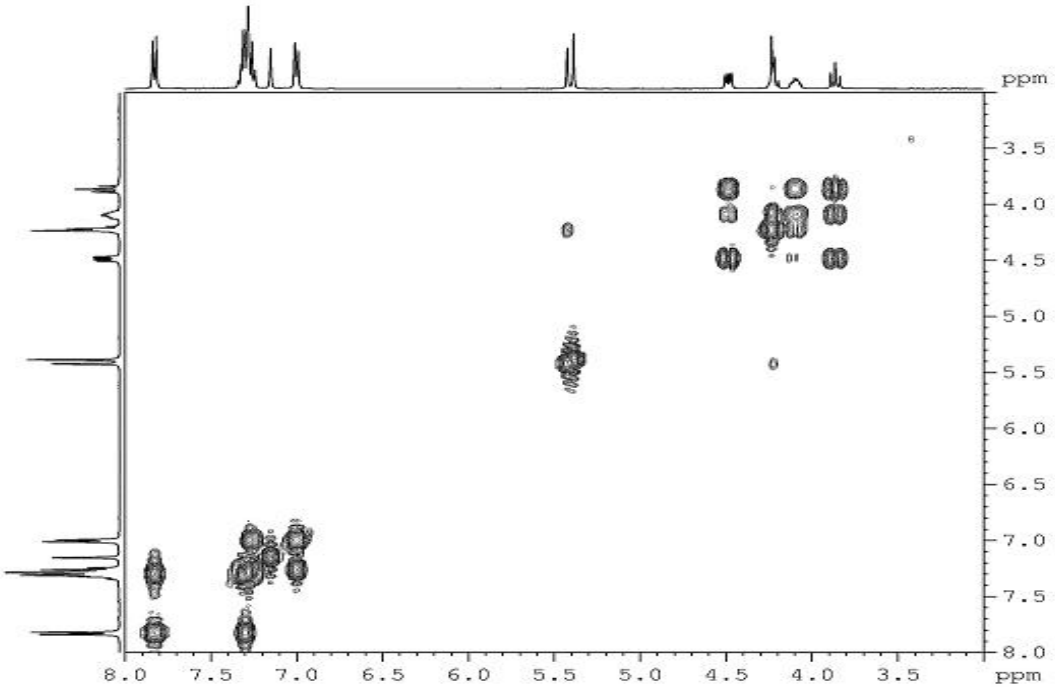


Table 2.3.10: Assignment of ^{1}H-NMR and ^{13}C-NMR spectra of **2.74**

Carbon (proton)	**C-2' (H-2')**	**C-3' (H-3')**	**C-4' (H-4')**	**C-5' (H-5')**	**C-6' (H6',6")**	**PhC (PhCH)**	**C-6 (H6)**
Chemical shifts (d)	90.4 (5.40)	63.1 (4.20)	73.4 (4.20)	69.4 (4.09)	67.6 (4.48, 3.48)	100.9 (5.37)	138.7 (7.13)

Figure 2.3.9: ^{1}H-^{13}C HSQC spectrum for **2.74**

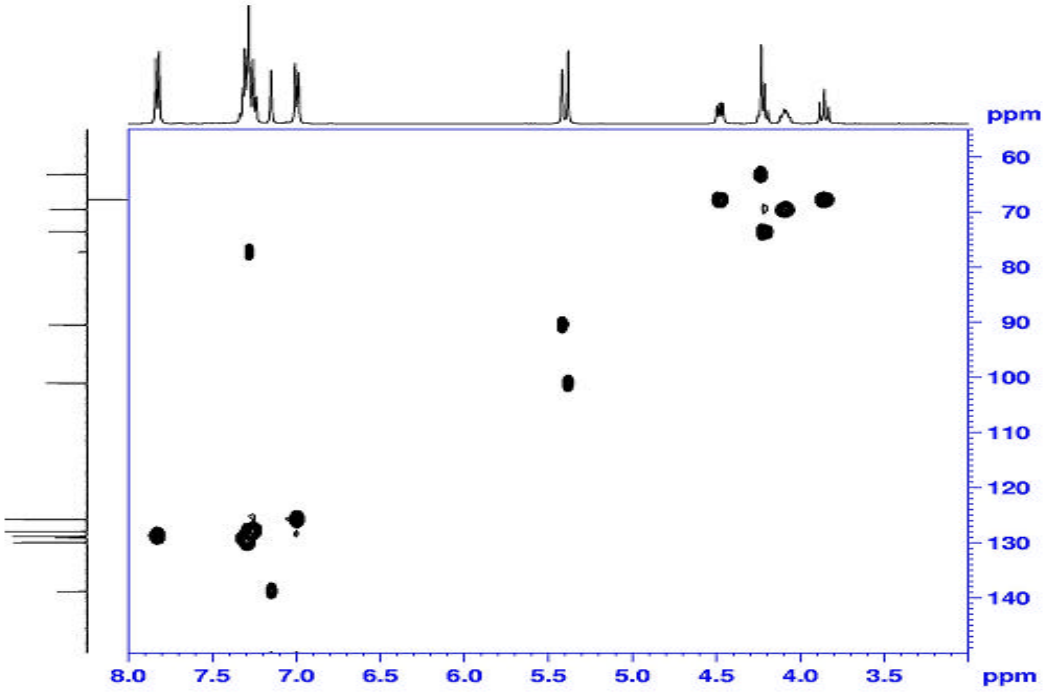
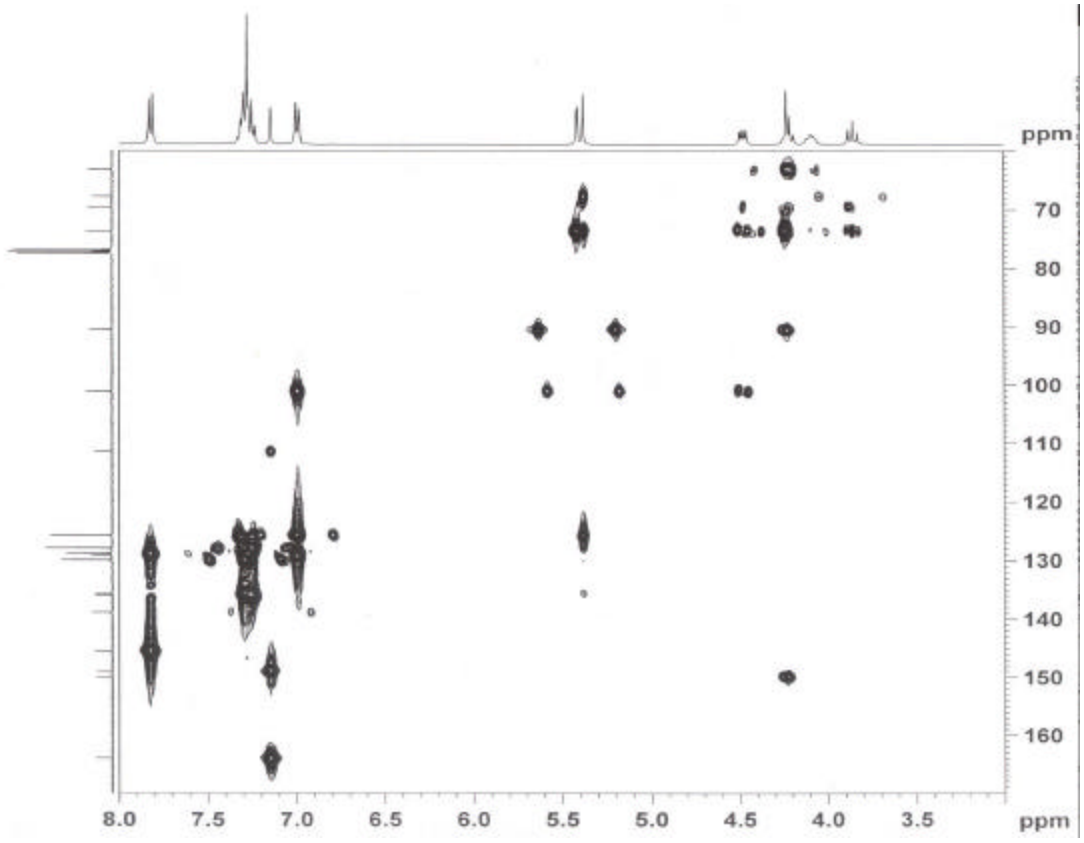


Figure 2.3 .10: HMBC spectrum for **2.74**



The structure of compound **2.83** was established on the basis of its ^{1}H-^{1}H COSY-, the ^{1}H-^{13}C HSQC- and HMBC spectra. The peak at δ 5.84 was identified as the H1' proton and the rest of the protons were assigned by using the correlation spectrum (**Figure 2.3.13**).The corresponding carbon peaks were identified using the ^{1}H-^{13}C correlation spectrum (**Figure 2.3.14**). Table 2.3.13 represents the assignment of the proton as well as carbon signals for compound **2.83**. Notably the absence of H5'-proton, simplified the splitting patterns of H6'and H6" protons which appeared at δ 3.44-3.55 (**Table 2.3.11**). The peak position of quaternary C-5' was established to be δ 156.1 on the basis of its correlations with two *a* protons, H4' (δ 5.10) and H6', H6" (δ 3.50) in HMBC spectrum **(Figure 2.3.15)**. The identification of C-5' as a quaternary carbon and the presence of the olefinic proton H4' at a higher field (δ 5.10 as opposed to >δ 6.50 for vinyl sulfones **2.87** and **1.106a**) devoid of any coupling with H5', established the position of the double bond between C-4' and C-5'.

Figure 2.3.11: ^{1}H-^{1}H COSY spectrum for **2.82**

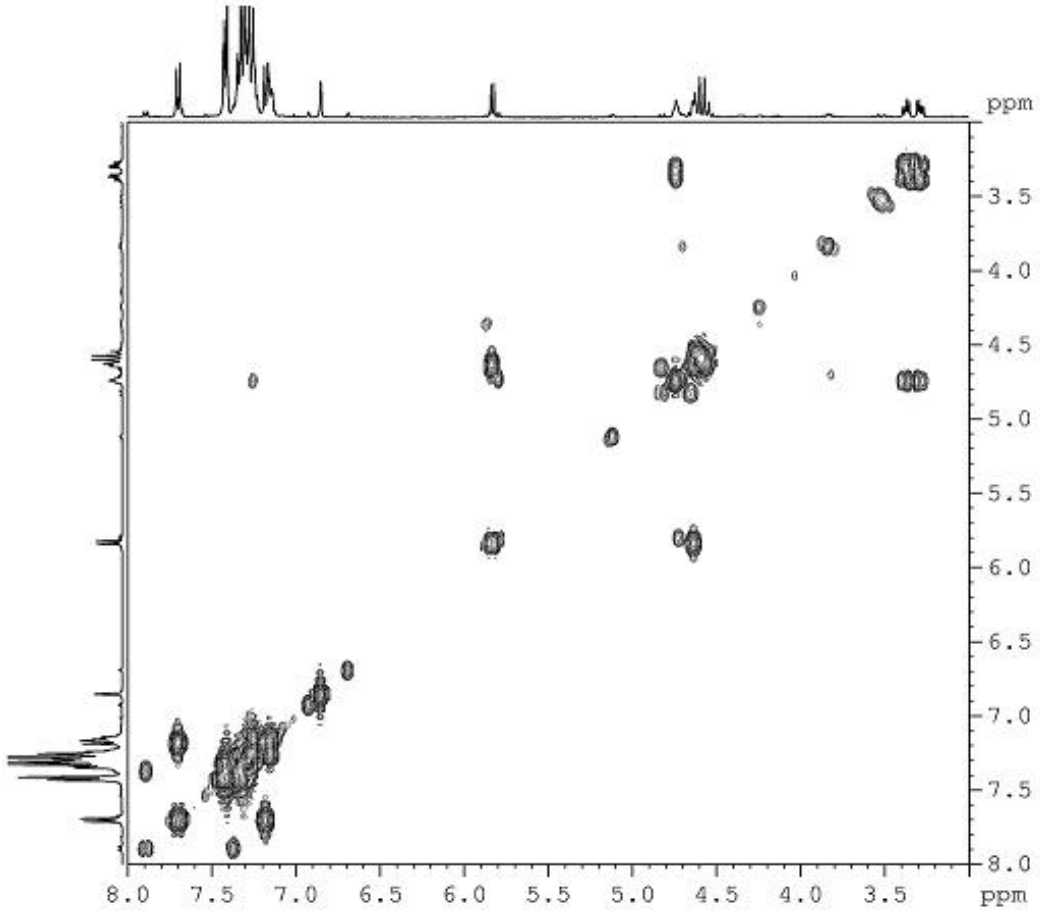


Table 2.3.11: Assignment of ^{1}H-NMR spectrum of **2.82**

Chemical shift (d) Coupling constant (Hz)	**H1'** *J1',2'*	**H2'** *J2',3'*	**H4'** *J4',5'*	**H5'** *J5',6'*	**H6'** *J6'6"*	**H6''** *J5',6"*
	5.83 7.4	4.54-4.63 ———	7.10-7.43 ———	4.73 ———	3.28 ———	3.36 ———

Figure 2.3.12: ORTEP for compound **2.82**

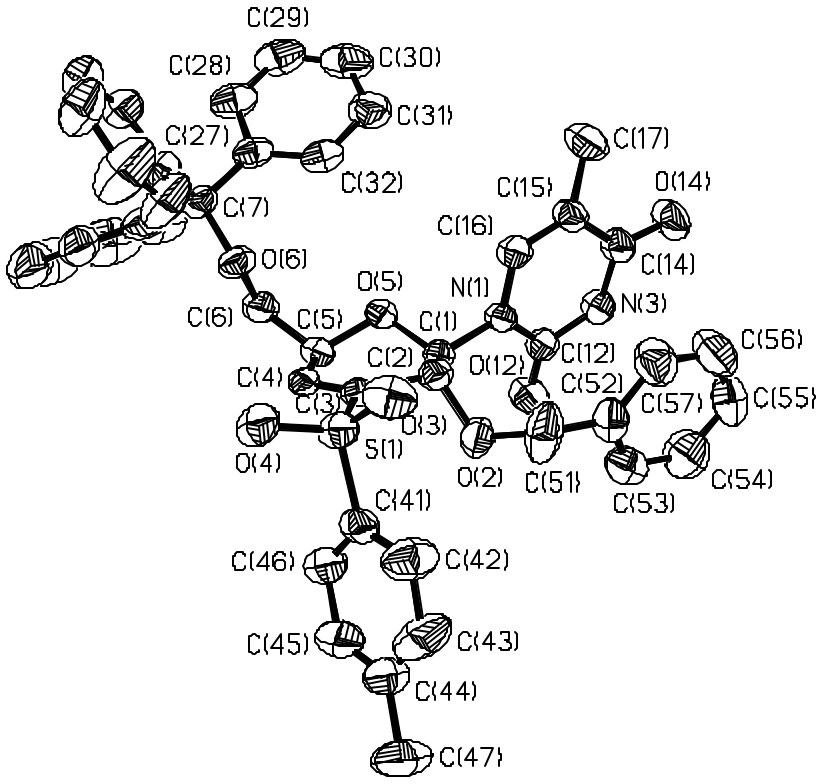


Table 2.3.12A: Bond lengths (standard deviation) for **2.82**

Bond	O5-C1	O5-C5	C1-C2	C1-N1	C2-O2	C'-C3	C3-C4	C3-S1
Bond length (^{o}A)	1.41(7)	1.43(6)	1.52(6)	1.45(6)	1.42(6)	1.50(7)	1.31(6)	1.77(7)

Table 2.3.12B: Bond lengths (standard deviation) for **2.82**

Bond	C4-C5	C5-C6	C6-O6	O6-C7
Bond length in ^{o}A	1.49(6)	1.51(7)	1.42(6)	1.44(7)

Figure 2.3.13: ^{1}H-^{1}H COSY spectrum for **2.83**

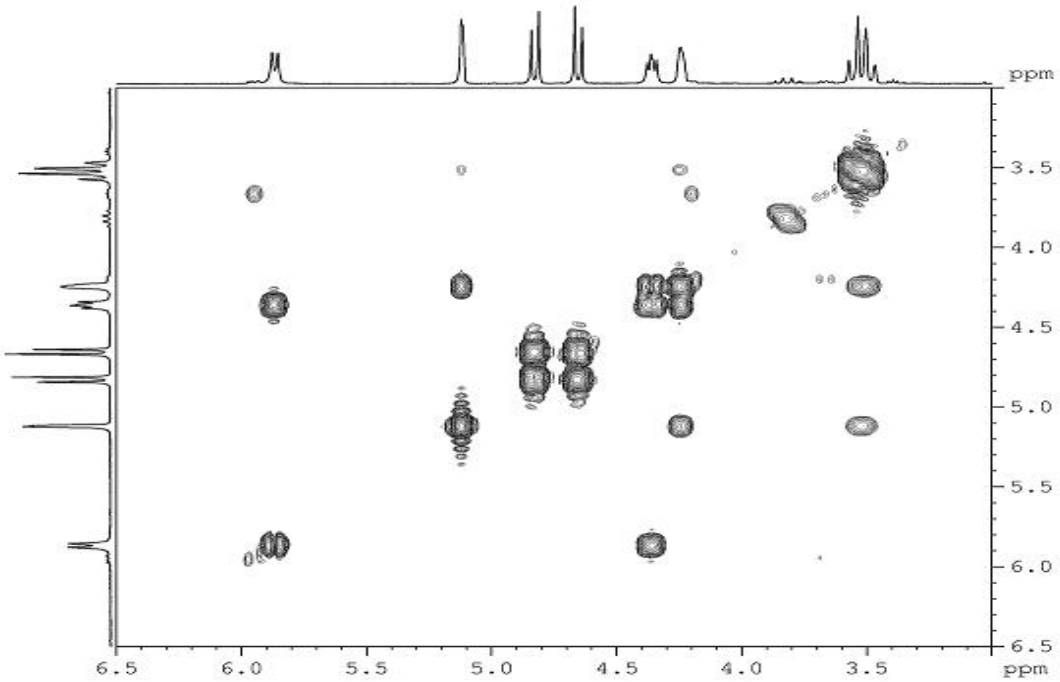


Figure 2.3.14: ^{1}H-^{13}C HSQC spectrum for **2.83**

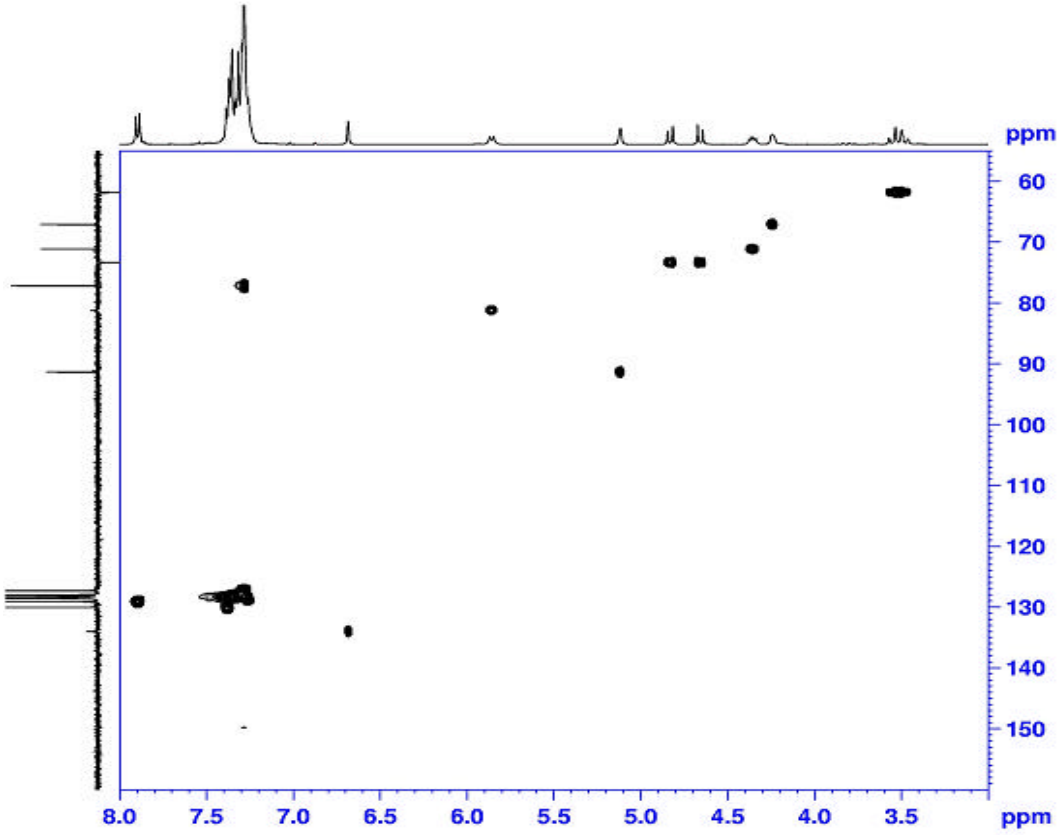
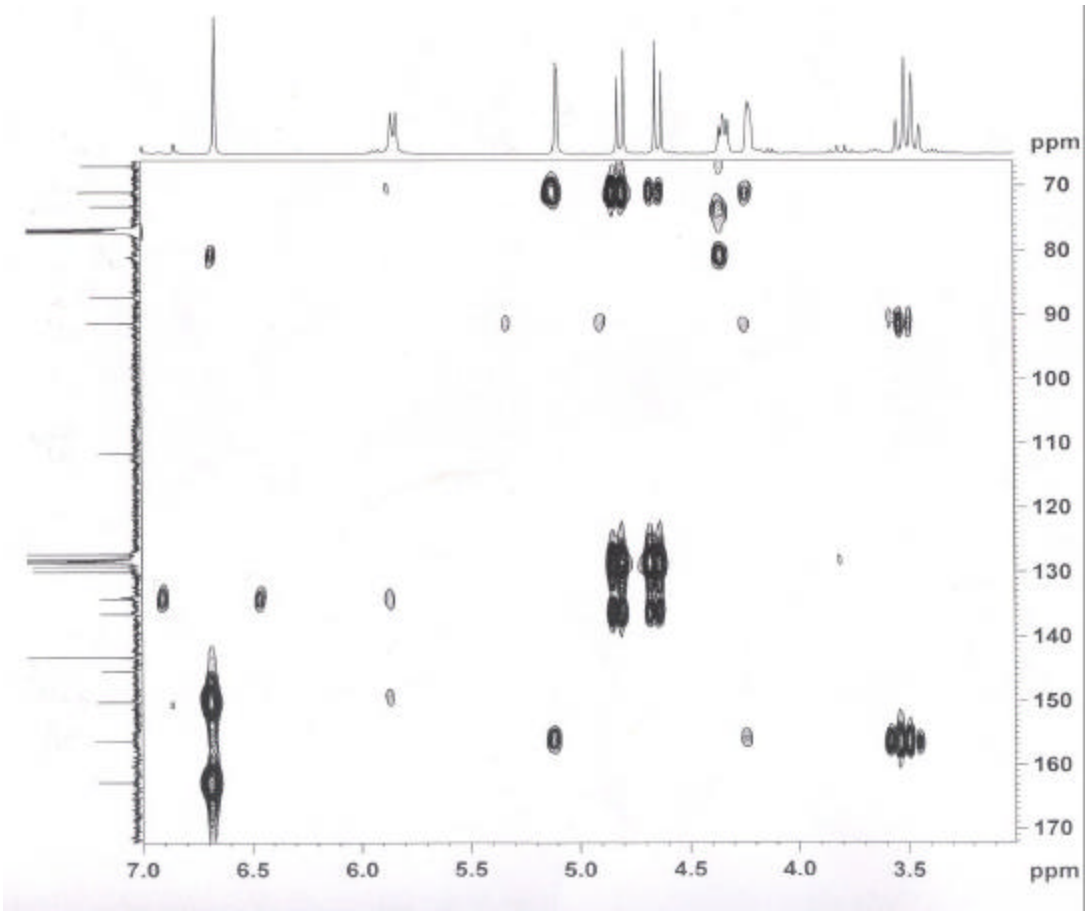


Table 2.3.13: Assignment of ^{1}H-NMR and ^{13}C-NMR spectra of **2.83**

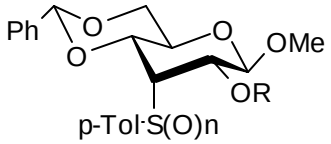
Carbon (proton)	**C-1' (H-1')**	**C-2' (H-2')**	**C-3' (H-3')**	**C-4' (H-4')**	**C-6' (H6',6")**	**BenzylicC (Benzylic -CH_2)**	**TritylC**	**C-6 (H6)**
Chemical shifts ()	81.0 (5.84)	71.0 (4.34)	66.9 (4.22)	91.2 (5.10)	61.7 (3.44-3.55)	73.2 (4.63,4.81)	87.2	136.4 (6.66)

Figure 2.3.15: HMBC spectrum for **2.83**

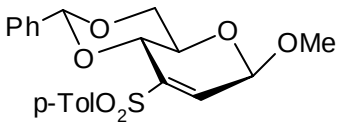


iv) Discussion

Although methyl 2,3-dideoxy-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfonyl-*ß*-D-erythro-hex-2-enopyranoside **2.87** was easily synthesized from **2.84** and **2.85**,[50,51] the failure of the same reaction sequence to afford the vinyl sulfone-modified hexopyranosyl nucleosides **2.74** was a surprising result.[51] The unexpected result may be partially explained by considering the fact that the presence of a better electron-withdrawing and

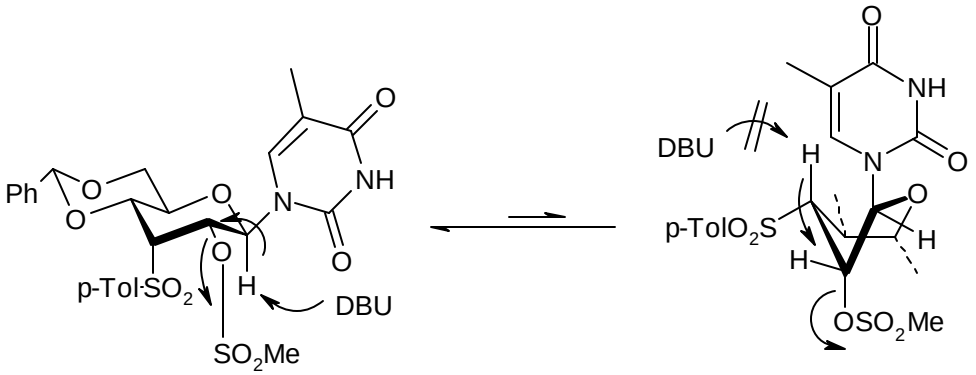


2.84 X = p-TolS; R = H
2.85 X = p-TolSO_2; R = H
2.86 X = p-TolSO_2; R = OMs



2.87

sterically bulkier nucleobase at the anomeric position of **2.72** as opposed to the methoxy group of **2.86** tripped the balance in favor of the C1'-C2' eliminated product **2.74** instead of the desired **2.73**. However, it should be noted that the pentofuranosyl vinyl sulfone **1.106a** was easily synthesized following the same route.[52] Therefore, to settle the anomaly, it may be argued that for the *trans*-elimination required for the bond-formation between C-2' and C-3', the H3' and C-4'-OMs should be antiperiplanar (diaxial). In that case the mesylated compound **2.72** needed to flip to a twist-boat conformation **2.72a**, which would create severe 1,3-diaxial interaction between the bulky nucleobase and H3' proton.[53] Under the circumstances, acidity of H1', as well as the stability of C1'-C2' olefin via conjugation of the ring oxygen would favor the formation of compound **2.74**.

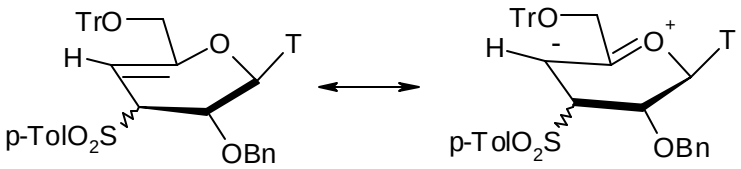


2.72 **2.72a**

2.74 **2.73**

It should be noted that the steric hindrance mentioned in scheme below would be minimum in the case of carbohydrate derived mesylate **2.86** because of much smaller bulk of OMe and also because of the fact that the methyl group attached to oxygen was "removed somewhat"[54] from the ring.

On the other hand compound **2.82** was easily synthesized from **2.81** because, in this case the six-membered ring could easily flip to the required conformation to place the H3' and C-4'-OMs in antiperiplanar positions. It is important to note that even a strong base like DBU could not facilitate the formation of vinyl sulfone **2.73** from **2.72** whereas under the conditions employed for mesylation, **2.81** was transformed to **2.82** by pyridine at +4 ^{o}C. The expected Michael-addition reactions to compound **2.82** did not yield the addition product. Instead a stable isomer **2.83** was obtained. The formation of compound **2.83** may be considered as a simple migration of a double bond which was facilitated by the abstraction of the C-5' proton followed by the stability imparted by the delocalization of the lone pairs of the ring oxygen.



2.83 **2.83a**

2.4 Conclusion

In this thesis, we reported the first systematic study on the synthesis and reactions of 1-(2,4,6-*O*-triacetyl-3-*O*-tosyl-*ß*-D-glucopyranosyl) thymine **2.57**, 2,2'-*O*-anhydro-(4,6-*O*-phenylmethylene-*ß*-D-altro-pyranosyl) thymine **2.47**, 2',3'-*O*-anhydrohexopyranosyl thymine **2.43** and two vinyl sulfone-modified hexopyranosyl nucleosides, namely 1-[2,3-deoxy-(4,6-*O*-phenylmethylene)-(3-*C*-*p*-toluenesulfonyl)-*erythro*-*ß*-D-hex-2-*eno*-pyranosyl] thymine **2.73** and 1-[2-*O*-benzyl-3,4-deoxy-(3-*C*-*p*-toluenesulfonyl)-6-*O*-trityl-erythro-β-D-hex-3-eno-pyranosyl] thymine **2.82**. The accessibility of **2.47**, **2.43** and **2.82** crucially depended on the easy availability of the 3'-*O*-tosyl derivative **2.57**. At the same time compound **2.57** was also useful for the synthesis of a series of allopyranosyl nucleosides **2.58-2.60** and the glucopyranosyl nucleoside **2.62**. The 2,2'-*O*-anhydro-derivative **2.47** was found to be unusually stable and produced only a allopyranosyl bromo derivative **2.66**. This epoxy nucleoside **2.43** reacted with azide, amines, sulfur nucleophiles as well as a carbon nucleophile paving the way for the synthesis of a great number and wide variety of hitherto unknown 3'-deoxy-3'-substituted-altropyranosyl thymines **2.68a-i**. It should be noted that these altropyranosyl nucleosides could not have been accessed by any other synthetic strategy. In the case of vinyl sulfone modified hex-2-enopyranosyl nucleoside, the desired product **2.73** could not be obtained for reasons delineated above. On the other hand, vinyl sulfone modified hex-3-

enopyranosyl nucleoside **2.82** was synthesized easily from **2.70**. However, compound **2.82** did not react with nucleophiles according to our expectations and underwent isomerization to **2.83** instead.

In a nut shell, the studies reported in this thesis opens up several routes for the synthesis of hitherto unknown hexopyranosyl nucleosides. A perusal of the literature compiled in chapter 1 indicates that compounds **2.43**, **2.47** and **2.57** remain to be subjected to a large number of reaction conditions and reagent systems for accessing hexopyranosyl structure based new chemical entities. On the other hand, approaches to and reactions of vinyl nitro-modified hexopyranosyl nucleosides[24-27] should be studied in depth for the successful synthesis and reactions of vinyl sulfone-modified hexopyranosyl nucleosides.

2.5 Experimental

General methods: All fine chemicals were obtained from commercial-suppliers and were used without purification. Solvents were dried and distilled following standard procedures. Melting points were determined in open-end capillary tubes using a Büchi B-540 electro-thermal melting point apparatus and were uncorrected. Analytical TLC was carried out on pre-coated aluminum plates (E-Merck silica gel 60, F_{254}) and spots were visualized with UV light or by charring the plate dipped in 5 % H_2SO_4-MeOH solution or ninhydrine solution in EtOH. Column chromatography was performed on silica gel (60-120 or 230-400 mesh). IR spectra were recorded as nujol mull, or in solution (conc. 1 µM) on a Shimadzu FTIR-8400 spectrophotometer. ^{1}H NMR were recorded at 200 MHz using AC 200 MHz, at 300 MHz using MSL 300 MHz, or 500 MHz using DRX 500 MHz in $CDCl_3$ using trimethylsilane as internal standard. Special experiments such as ^{1}H-^{1}H COSY was carried-out on 400 MHz at AV 400 MHz. ^{13}C-spectra and DEPT were recorded at 50.3, 75.5 or 125.8 MHz using the triplet centered as at δ 77.0 as the standard. Specific rotations were determined using Bellingham ADP220 polarimeter or a JASCO P-1030 polarimeter at 589 nm. Micro analytical data were obtained using a Carlo-Erba CHNS-0 EA 1108 Elemental analyzer.

Attempted synthesis of 2.41:[30] A mixture of **2.39** (0.38 g, 1.0 mmol) and Bu_2SnO (0.25 g, 1 mmol) in dry MeOH (15 mL) was heated under reflux for 2-3h. The reaction mixture was cooled to rt, and all the volatile matters was evaporated under reduced pressure. The dried tin complex was dissolved in dioxane (10 mL). *p*-Toluenesulfonyl chloride (0.22 g, 1.1 mmol) and DMAP (15 mg, 0.12 mmol) was added to the reaction mixture. The reaction mixture was heted under reflux until the entire starting compound

disappeared (TLC). All the volatile matters were evaporated under reduced pressure. The reaction produced an inseparable mixture of products.

Attempted synthesis 2.49:[28] A mixture of **2.39** (0.38 g, 1.0 mmol) and Bu_2SnO (0.25 g, 1 mmol) in dry MeOH (15 mL) was heated under reflux for 2-3h. The reaction mixture was cooled to rt, and all the volatile matters was evaporated under reduced pressure. Triethylamine (0.15 mL) was added to a solution of tin complex (0.51 g, 1 mmol) in dioxane (20 mL). The reaction mixture was cooled 5 ^oC, benzoyl chloride (0.12 mL, 1 mmol) in dioxane (5 mL) was slowly added. The solution was stirred for 6h at rt. The solid residue was filtered and the filtrate was collected. All volatile matters were evaporated under reduced pressure. The residue was purified over silica gel column to remove the tin compounds. The reaction produced an inseparable mixture of products.

Attempted synthesis of alloepoxide 2.46:[31] A mixture of **2.39** (0.38 g, 1.0 mmol), diethylcarbonate (1.3 mL), anhydrous K_2CO_3 (4 mg, 0.22 mmol) and tetrabutylammonium bromide (2 mg) in DMF (5 mL) was heated at 130-135 ^oC under vacuum. The reaction mixture was cooled to rt, and all volatile matters were evaporated under reduced pressure. The reaction produced an inseparable mixture of products.

1-(2,4,6-tri-*O*-acetyl-3-*O*-tosyl-ß-D-glucopyranosyl) thymine 2.57: A mixture of thymine (2.52 g, 20 mmol) hexamethyldisilazane (15 mL), few drops of trimethylsilyl chloride and few crystals of $NH_4(SO_4)_2$ was heated under reflux for 3-5h to get a clear solution. The moisture sensitive reaction mixture was evaporated under reduced pressure to remove all the liquid. A solution of 1,2,4,6-tetra-*O*-acetyl-3-*O*-tosyl-ß-D-glucopyranose **2.55** (5.03 g, 10 mmol) in anhydrous 1, 2-dichloroethane (60 mL) was added to the flask. Tin (IV) chloride (1.64 mL, 14 mmol) was injected in the flask with care. The reaction was allowed to stir at 50 ^oC. After 18h the reaction mixture was cooled to rt. The reaction mixture was carefully added to sat. $NaHCO_3$ solution (150 mL) and the products were extracted with $CHCl_3$ (3x75 mL). Any emulsion formed was filtered over celite bed and the bed was washed several times with chloroform. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The crude product was purified over silica gel column to afford **2.57**.

Eluent: EtOAc/petroleum ether (2:3)
Yield : 4.25 g, 75 %.
Mp.: 123-125 ^oC.
$[\alpha]_D^{27}$: +16.7 ^{o} (*c* 1.0, $CHCl_3$).

IR (Nujol): 1749, 1693 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) (^{1}H-^{1}H COSY): δ 1.87 (s, 3H, CH_3), 1.94 (s, 3H, thymine CH_3), 2.01 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.92 (m, 1H, H5'), 4.11 (dd, *J* = 2.0, 12.8 Hz, 1H, H6"), 4.27 (dd, *J* = 5.0, 12.8 Hz, 1H, H6'), 5.08 (t, *J* = 9.3 Hz, 1H, H3'), 5.18-5.24 (m, 2H, H2',H4'), 5.88 (d, *J1',2'* = 9.5 Hz, 1H, H1'), 7.11 (s, 1H, H6), 7.33 (d, *J* = 8.3 Hz, 2H, aromatic), 7.71 (d, *J* = 8.3 Hz, 2H, aromatic), 8.84 (bs, 1H, NH).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ 12.2, 20.0, 20.3, 20.4, 21.3, 61.6 (CH_2), 67.2, 68.8, 74.3, 79.4, 79.8, 112.0, 127.3, 129.7, 133.7, 134.4, 145.0, 150.5, 163.3, 169.2, and 170.2.

Analysis: Calcd for $C_{24}H_{28}N_2O_{12}S.{}^1/_2H_2O$: C, 49.91; H, 5.06. Found: C, 50.00; H, 5.28.

MS: EI m/z 568 (4 M^+), 443 (100 M^+-Thy), 396 (29 M^+-*O*-Tosyl).

1-(2,3,4,6-tetra-*O*-acetyl-ß-D-allopyranosyl) thymine 2.58: Compound **2.57** (0.28 g, 0.5 mmol) was added to a suspended solution of NaOAc (0.41 g, 5 mmol) in DMF (5 mL). The reaction mixture was heated at 150 °C for 20h. After cooling to rt, DMF was evaporated under reduced pressure. To a solution of reaction mixture in dry pyridine (5 mL), acetic anhydride (0.47 mL, 5 mmol) was added. The reaction mixture was stirred at rt for overnight. The reaction mixture was concentrated and the residue was dissolved in EtOAc (50 mL). The solution was washed with sat. $NaHCO_3$ solution (2x25 mL), water (20 mL), and brine (5 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated. The crude product was purified over silica gel column to afford **2.58**. Foamy solid.

Eluent: EtOAc/ petroleum ether (1:1).
Yield : 0.16 g, 70 %.
Mp.: 117-120 °C.
[α]$_D^{25}$: +3.8° (*c* 1.0, $CHCl_3$).
IR (Nujol): 1749, 1693 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.95 (s, 3H), 2.00 (s, 3H), 2.05 (s, 3H), 2.11 (s, 3H), 2.23 (s, 3H), 4.21-4.34 (m, 3H), 5.03 (dd, *J* = 3.0, 10.3 Hz, 1H), 5.15 (dd, *J* = 2.9, 9.8 Hz, 1H), 5.76 (t, *J* = 3 Hz, 1H), 6.18 (d, *J* = 9.8 Hz, 1H), 7.13 (s, 1H), 9.33 (bs, 1H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ 12.3, 20.3, 20.5, 62.0 (CH_2), 65.7, 66.7, 67.9, 72.4, 77.7, 111.9, 134.4, 150.7, 159.6, 163.5, 169.1, 169.6, and 170.4.

Analysis: Calcd for $C_{19}H_{24}N_2O_{11}.{}^1/_2H_2O$. C, 49.02; H, 5.41. Found: C, 49.38; H, 5.25.

MS: EI m/z 456 (5 M^+), 331 (88 M^+-Thy).

1-(2,4,6-tri-*O*-acetyl-3-azido-3-deoxy-ß-D-allopyranosyl) thymine 2.59: A solution of compound **2.57** (0.28 g, 0.5 mmol) and LiN_3 (0.25 g, 5 mmol) in DMF (5 mL) was heated at 120 °C for 20h. After cooling to rt, DMF was evaporated under reduced pressure. The reaction mixture was acetylated using acetic anhydride (0.47 mL, 5 mmol) in dry pyridine (5 mL). The reaction mixture was concentrated and the residue was diluted with EtOAc (50 mL). The organic layer was washed with sat. $NaHCO_3$ solution (2x25 mL), water (5 mL) and brine (5 mL). The crude product was purified over silica gel column to afford **2.59**. White solid.

Eluent: EtOAc/ petroleum ether (2:3).
Yield : 0.14 g, 61 %.
Mp.: 105-107 °C.
[α**]**$_D^{27}$: +39.6 ° (*c* 1.0, $CHCl_3$).
IR (Nujol): 2110 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) (^{1}H-^{1}H COSY): δ 1.94 (s, 3H, Thymine CH_3), 2.10 (s, 6H, 2xCH_3), 2.16 (s, 3H, CH_3), 4.16 (dd, 1H, H6"), 4.27 (dd, 2H, H5', H6'), 4.50 (t, *J* = 3.3 Hz, 1H, H3'), 4.98 (dd, *J* = 3.3, 9.5 Hz, 1H, H2'), 5.11 (dd, *J* = 3.3, 9.5 Hz, 1H, H4'), 6.11 (d, *J1', 2'* = 9.5 Hz, 1H, H1'), 7.08 (d, 1H, H6), 9.00 (s, 1H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ 12.1, 19.9, 20.1, 20.3, 60.5, 61.9 (CH_2), 66.7, 67.8, 71.9, 77.2, 111.6, 134.5, 150.4, 159.5, 163.4, 169.2, and 170.2.

Analysis: Calcd for $C_{17}H_{21}N_5O_9$. C, 46.47; H, 4.82. Found: C, 46.55; H, 4.62.

MS: EI m/z 439 (13 M^+), 314 (53 M^+-Thy).

1-(2,4,6-tri-*O*-acetyl-3-deoxy-3-*S*-tolyl-ß-D-allopyranosyl) thymine 2.60: To a solution of 4-methylbenzenethiol (0.44 g, 0.5 mmol) in DMF (5 mL), NaOMe (0.14 g, 2.5 mmol)

was added. The reaction mixture was stirred at rt for 0.5h. Compound **2.57** (0.28 g, 0.5 mmol) was added to the reaction mixture. The reaction mixture was heated at 90 ^{o}C for 10h. Acetylation of the reaction mixture under ususal conditions afforded **2.60**. White solid.

Eluent: EtOAc/ petroleum ether (1:3).
Yield : 0.18 g, 70%.
Mp.: 196-198 ^{o}C.
[a]$_{D}^{27}$: +72.9 ^{o} (*c* 1.20, $CHCl_3$).
IR (Nujol): 1747, 1737, 1694 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.76 (s, 3H), 1.91 (s, 3H), 1.94 (s, 3H), 2.10 (s, 3H), 2.31 (s, 3H), 4.25-4.35 (m, 3H), 4.47 (t, *J* = 4.4 Hz, 1H), 5.03 (dd, *J* = 4.4, 10.2 Hz, 1H), 5.17 (dd, *J* = 4.4, 9.8 Hz, 1H), 6.28 (d, *J* = 9.8 Hz, 1H), 7.09 (d, *J* = 7.8 Hz, 3H), 7.31 (d, *J* = 8.3 Hz, 2H), 9.41 (bs, 1H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ 12.4, 20.1, 20.3, 20.4, 20.9, 52.4, 62.3 (CH_2), 67.6, 68.9, 73.4, 78.5, 111.8, 129.8, 130.6, 132.7, 134.6, 137.7, 150.5, 159.6, 163.5, 169.5, 170.5.

Analysis: Calcd for $C_{24}H_{28}N_2O_9S$. C, 55.37; H, 5.42. Found: C, 55.60; H, 5.67.

MS: EI m/z 520 (3 M^{+}).

1-(2,4,6-tri-*O*-acetyl-3-bromo-ß-D-glucopyranosyl) thymine 2.62: A mixture of **2.57** (0.57 g, 1 mmol), and LiBr (0.44 g, 5 mmol) in DMF (5 mL) was heated at 110 ^{o}C for 10h. The reaction mixture was cooled to rt. DMF was evaporated under reduced pressure, and the reaction mixture was diluted with EtOAc (50 mL). The solution was washed with brine (5 mL), sat. K_2CO_3 solution (5 mL), water (5 mL) and brine (2 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated. The crude product was purified over silica gel column to afford **2.62**. The compound was crystallized from EtOAc/ petroleum ether mixture. White crystals.

Eluent: EtOAc/ petroleum ether (1:3).
Yield : 0.40 g, 84 %.
Mp.: 199.4-200.4 ^{o}C.
[a]$_{D}^{28}$: +26.0 ^{o} (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$): 1751, 1697 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ 1.97 (s, 3H), 2.08 (s, 3H), 2.11 (s, 3H), 2.16 (s, 3H), 3.85 (m, 1H), 4.09-4.30 (m, 3H), 5.31 (m, 2H), 5.80 (d, *J* = 9.0 Hz, 1H), 7.19 (s, 1H), 9.04 (s, 1H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ 12.4, 20.2, 20.5, 20.6, 50.4, 61.8 (CH_2), 69.2, 71.0, 76.5, 80.7, 112.1, 134.6, 150.6, 163.5, 169.0, 170.4.

Analysis: Calcd for $C_{17}H_{21}BrN_2O_9.1CHCl_3$. C, 36.23; H, 3.72. Found: C, 36.44; H, 3.74.

1-(2-*O*-acetyl-4,6-*O*-(phenylmethylene)-3-*O*-tosyl-*ß*-D-glucopyranosyl) thymine 2.45: To a solution of compound **2.57** (4.0 g, 7.04 mmol) in anhydrous MeOH (75 mL), was added *iso*propylamine (4.15 g, 70.4 mmol). The reaction mixture was stirred at rt for 5h. All the volatile matters were evaporated under the reduced pressure. Crude 1-(2-*O*-acetyl-3-*O*-tosyl-*ß*-D-gulcopyranosyl) thymine **2.63** was taken directly to the next step. To the solution of crude **2.63** in anhydrous in DMF (35 mL), benzaldehyde dimethyl acetal (1.42 mL, 10 mmol) was added. A catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) was added to the reaction mixture. The reaction mixture was heated at 100 °C under vacuum for 1h. DMF was evaporated under reduce pressure. The residue was diluted with EtOAc (150 mL) and washed with sat. $NaHCO_3$ solution (2x25 mL). The volatile matters were evaporated under reduced pressure. The crude product was purified over silica gel column to afford **2.45**. The compound was crystallized from EtOAc/petroleum ether mixture.

Eluent: EtOAc/petroleum ether (1:1).
Yield : 3.0 g, 70 %.
Mp.: 168-170 °C.
[α]$_D^{26}$: −42.2 ° (*c* 1.52, $CHCl_3$).
IR (Nujol): 1755, 1711, 1697 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) (^1H-^1H COSY): δ 1.94 (s, 3H), 2.05 (s, 3H), 2.31 (s, 3H), 3.69-3.76 (m, 3H, H4', H5', H6'), 4.37 (m, 1H, H6"), 5.11 (m, 1H, H3'), 5.26 (t, *J2',3'* = 9.3 Hz, 1H, H2'), 5.40 (s, 1H), 5.93 (d, *J1',2'* = 9.5 Hz, 1H, H1'), 7.00 (d, *J* = 8.3 Hz, 2H), 7.11 (s, 1H), 7.31-7.40 (m, 5H, aromatic), 7.67 (d, *J* = 8.3 Hz, 2H), 8.61 (s, 1H).

^{13}C NMR (50.3 MHz, DMSO-D_6): δ 12.3, 20.2, 21.3, 67.3, 67.6 (CH_2), 69.9, 76.8, 79.8, 100.6, 110.3, 126.2, 127.6, 128.1, 129.1, 129.9, 133.9, 136.5, 137.0, 144.9, 150.6, 154.7, 163.7, 169.2.

Analysis: Calcd for $C_{27}H_{28}N_2O_{10}S.{}^1/_4H_2O$: C, 56.19; H, 4.98. Found: C, 56.20; H, 5.25.

MS: EI m/z 447 (47 M^+-Thy), 275 (9 M^+- (Thy + O-Ts)).

2,2'-*O*-Anhydro-1-(4,6-*O*-phenylmethylene-ß-D-altropyranosyl) thymine 2.47: A solution of compound **2.45** (1.9 g, 3.32 mmol) in anhydrous MeOH (60 mL) was treated with NaOMe (0.91 g, 16.5 mmol) at rt. After 30h the solution was neutralized with Dowex (50x8) H^+ resin. The reaction mixture was filtered and the filtrate was concentrated. Hygroscopic 2,2'-*O*-Anhydro-1-(4,6-*O*-phenylmethylene-ß-D-altropyranosyl) thymine **2.47** was dried by co-evaporation with pyridine and taken directly for the next reactions.

2,2'-*O*-Anhydro-1-(3-*O*-4-nitrobenzoyl-4,6-*O*-phenylmethylene-ß-D-altropyranosyl) thymine 2.64: To a solution of compound **2.47** (0.13 g, 0.36 mmol) in pyridine (7 mL) was added 4-nitrobenzoyl chloride (0.34 g, 1.85 mmol) at rt. The reaction mixture was stirred for overnight. The reaction mixture was diluted with DCM (75 mL) and washed sat. $NaHCO_3$ solution (2x15 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated to obtain a polar compound. The crude product was purified over silica gel column to afford **2.64**. Pale yellow solid.

Eluent: EtOAc/petroleum ether (4:1).
Yield : 0.12 g, 64 % (from **2.45**).
Mp.: 300 °C and above.
[α**]**$_D^{26}$: –32.6 ° (*c* 0.35, DMF).
IR (Nujol): 1742, 1676 cm^{-1}.

^{1}H NMR (300 MHz, CD_2Cl_2): δ 1.91 (s, 3H), 3.69 (t, *J* = 10.3 Hz, 1H), 4.08-4.19 (m, 2H), 4.36 (dd, *J* = 3.7, 9.5 Hz, 1H), 4.83 (s, 1H), 5.58 (s, 1H), 5.83 (d, *J* = 3.6 Hz, 1H), 6.08 (s, 1H), 7.23-7.31 (m, 6H, aromatic), 8.23 (d, *J*= 8.8 Hz, 2H), 8.30 (d, *J*= 8.8 Hz, 2H).

^{13}C NMR (75.5 MHz, CD_2Cl_2): δ 14.2, 62.7, 66.6, 69.0 (CH_2), 74.0, 78.2, 82.8, 102.7, 120.5, 124.4, 126.6, 128.8, 129.8, 131.1, 131.6, 134.8, 137.3, 151.8, 160.3, 180.6.

Analysis: Calcd for $C_{25}H_{21}N_3O_9$: C, 59.17; H, 4.17. Found: C, 58.95; H, 4.09.

MS: EI m/z 507 (100 M^+).

1-(3,4,6-tri-*O*-acetyl-2-bromo-ß-D-allopyranosyl) thymine 2.66 : 2,2'-*O*-anhydro nucleoside **2.47** was generated *in situ* from **2.45** (0.44 g, 0.75 mmol) by the treatment of NaOMe (0.21 g, 3.75 mmol) in MeOH (15 mL). A solution of crude **2.47** in anhydrous DMF (2 mL) was added LiBr (0.22 g, 2.5 mmol) and catalytic amount of TFA (0.04 mL, 0.5 mmol). The reaction mixture was heated at 90 ^oC for 24h. The reaction mixture was cooled to rt and all the volatile matters were evaporated under reduced pressure. The residue **2.65** was dissolved in dry pyridine (5 mL), and acetic anhydride (2 mL) was added. The reaction mixture was stirred at rt for overnight. All volatile matters were evaporated under reduced pressure. The residue was diluted with EtOAc (75 mL). The organic layer was washed with sat. $NaHCO_3$ solution (3x10 mL), water (10 mL) and brine (5 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was evaporated under reduced pressure. The crude product was purified over silica gel column to afford **2.66**. Foamy solid.

Eluent: EtOAc/ petroleum ether (1:3).
Yield : 0.10 g, 30 % (from **2.45**)
Mp.: 97-99 ^oC.
[a]$_D^{27.7}$: +68.8^o (*c* 1.25, $CHCl_3$).
IR ($CHCl_3$): 1697, 1715, 1755 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.98 (s, 3H), 2.03 (s, 3H), 2.09 (s, 3H), 2.25 (s, 3H), 4.20-4.35 (m, 4H), 5.01 (m, 1H), 5.83 (m, 1H), 6.22 (bd, *J* = 9.4 Hz, 1H), 7.04 (s, 1H), 9.07 (1H, s).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ 12.6, 20.4, 20.5, 20.7, 45.2, 62.1 (CH_2), 66.6, 69.3, 72.8, 79.6, 112.7, 133.2, 150.4, 160.2, 163.1, 169.5, 170.5.

Analysis: Calcd for $C_{17}H_{21}$ Br N_2O_9. C, 42.75; H, 4.44. Found: C, 43.02; H, 4.35.

1-(2,3-*O*-anhydro-4,6-*O*-phenylmethylene-ß-D-mannopyranosyl) thymine 2.43: To a solution of **2.47** (obtained from 1.9 g/3.32 mmol of **2.45** as described above) in anhydrous pyridine (60 mL) was added methanesulfonyl chloride (1.70 mL, 21 mmol) at

0 ^{O}C. The reaction mixture was kept overnight at +4 ^{o}C. The solution was partitioned between saturated $NaHCO_3$ solution (30 mL) and $CHCl_3$ (3x30 mL). The combine organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to obtain 2,2'-*O*-anhydro-1-(4,6-*O*-phenylmethylene-3-*O*-methylsulfonyl-*ß*-D-altropyranosyl) thymine **2.48**. An aqueous solution of NaOH (2N, 4.1 mL) was added drop-wise to a solution of **2.48** (1.8 g, 4.1 mmol) in dioxane (20 mL). The reaction mixture was stirred for 2h at rt. The reaction mixture was diluted with EtOAc (50 mL) and washed with sat. $NaHCO_3$ solution (2x15 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The crude product was purified over silica gel column to afford **2.43**. The compound was crystallized from $CHCl_3$. White crystals.

Eluent: EtOAc/petroleum ether (2:3).
Yield : 0.4 g, 34 % (from **2.45**).
Mp.: 255-257 ^{o}C.
[α**]**$_D^{29}$: +43.9 ^{o} (*c* 1.10, $CHCl_3$).
IR (Nujol): 1714, 1682 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.96 (s, 3H), 3.42 (d, *J* = 3.8 Hz, 1H, H2'), 3.51-3.57 (m, 1H, H5'), 3.63 (d, *J* = 3.7 Hz, 1H, H3'), 3.78 (m, 2H, H4', H6'), 4.32 (dd, 1H, H6"), 5.60 (s, 1H), 6.32 (s, 1H, H_1'), 7.40 (m, 3H), 7.44 (s, 1H), 7.51 (m, 2H), 8.79 (s, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.4, 50.5, 55.0, 68.8 (CH_2), 70.3, 74.1, 78.1, 102.6, 111.5, 126.1, 128.3, 129.3, 136.6, 150.6, 163.5.

Analysis: Calcd for $C_{18}H_{18}N_2O_6$.1$CHCl_3$: C, 47.77; H, 4.01. Found: C, 47.91; H, 4.18.

MS: EI m/z 358 (26 M^+), 233 (4 M^+-Thy).

1-(2,4,6-Tri-*O*-acetyl-3-azido-*ß*-D-altropyranosyl) thymine 2.68a: A mixture the epoxide **2.43** (0.36 g, 1 mmol), LiN_3 (0.49 g, 10 mmol) and NH_4Cl (0.27 g, 5 mmol) was heated under reflux in anhydrous EtOH (10 mL) for 10h. The solvent was evaporated under reduced pressure. The residue was diluted with EtOAc (75 mL). The solution was successively washed with sat. $NaHCO_3$ (2x15 mL), water (10 mL), and brine (5 mL). The organic layer was dried over anhydrous Na_2SO_4, and filtered. All the volatile matters were evaporated under reduced pressure. The crude product was purified over silica gel

column to afford **2.67a** (0.33 g, 83 %). The product was treated with TFA: water mixture (4:1, 1 mL) at rt for 20 min. The solvents were evaporated under reuced pressure and the residue was dried under vacuuo. The residue was acetylated with acetic anhydride in dry pyridine at rt. All the volatile matters were evaporated under reuced pressure, and the residue was diluted with EtOAc (150 mL). The organic layer was washed with aqueous satd. $NaHCO_3$ (3x20 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure. The crude product was purified over silica gel column to afford **2.68a**. Foamy solid.

Eluent: EtOAc/petroleum ether (2:3).
Yield : 0.25 g , 65%
Mp.: 85-87 ^{o}C.
[a]$_D^{29}$: +55.1 ^{o} (*c* 1.0, $CHCl_3$).
IR ($CHCl_3$): 2115.8 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.93 (s, 3H), 2.09 (s, 3H), 2.12 (s, 3H), 2.17 (s, 3H), 4.23-4.37 (m, 4H), 5.14 (m, 2H), 6.02 (s, 1H), 7.23 (s, 1H), 9.27 (s, 1H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 12.5, 20.5, 20.6, 20.7, 59.0, 62.6 (CH_2), 66.0, 68.8, 73.0, 77.9, 110.3, 135.5, 149.5, 163.4, 168.8, 169.6, 170.6.

Analysis: Calcd for $C_{17}H_{21}N_5O_9$: C, 46.47; H, 4.82. Found: C, 46.34; H, 5.30.

1-(2,4,6-Tri-*O*-acetyl-3-*N*-isobutylamino-*ß*-D-altropyranosyl) thymine 2.68b: A mixture of epoxide **2.43** (0.36 g, 1 mmol) and *iso*butylamine (0.51 g, 7 mmol) in DMSO (5 mL) was heated at 70 ^{o}C for 24h. Excess amine was removed under reduced pressure. The residue was diluted with EtOAc (75 mL). The solution was washed with brine (2x15 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure. The crude product was purified over silica gel column to afford **2.67b** (0.35 g, 79 %). The product was deprotected and acetylated following the procedure described for **2.68a** to obtain **2.68b**.

Eluent: EtOAc/petroleum ether (3:2).
Yield : 0.26 g, 70%.
Mp.: 76-78 ^{o}C.
[a]$_D^{29}$: +78.9 ^{o} (*c* 1.10, $CHCl_3$).

IR ($CHCl_3$): 2958.6, 1745.5, 1691.5 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.93 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 1.74 (m, 1H), 1.93 (s, 3H), 2.07 (s, 3H), 2.11 (s, 3H), 2.12 (s, 3H), 2.51 (m, 2H), 3.26 (bs, 1H), 4.18-4.26 (m, 2H), 4.44 (m, 1H), 5.18 (m, 1H), 5.23 (s, 1H), 6.35 (s, 1H), 7.30 (s, 1H), 8.32 (bs, 1H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 12.4, 20.3, 20.4, 20.6, 20.7, 20.8, 28.5, 55.5 (CH_2), 56.7, 63.2 (CH_2), 66.5, 68.4, 72.8, 78.2, 109.8, 136.1, 149.5, 163.3, 169.2, 170.6.

Analysis: Calcd for $C_{21}H_{29}N_3O_9.1H_2O$: C, 51.95; H, 6.44. Found: C, 51.94; H, 6.41.

1-(2,4,6-tri-*O*-acetyl-3-*N*-pyrrolidino-*ß*-D-altropyranosyl) thymine 2.68c: A mixture of epoxide **2.43** (0.36 g, 1 mmol), and pyrrolidine (0.36 g, 5 mmol) in DMSO (3 mL) was heated at 90 °C for 24h. Excess amine was removed under reduced pressure. The residue was diluted with EtOAc (75 mL). The solution was washed with brine (2x15 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure. The crude product was purified over silica gel column to afford **2.67b** (0.36 g, 84 %). The product was deprotected and acetylated following the procedure described for **2.68a** to obtain **2.68c**. White foam solid.

Eluent: EtOAc/petroleum ether (3:2).
Yield : 0.33 g, 85%.
Mp.: 89-92 °C.
[a]$_D^{27}$: +68.3 ° (*c* 1.18 $CHCl_3$).
IR ($CHCl_3$): 1743.5,1687.6 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.78 (m, 4H), 1.93 (s, 3H), 2.07 (s, 3H), 2.09 (s, 3H), 2.11 (s, 3H), 2.73 (m, 2H), 2.80 (m, 2H), 2.92 (m, 1H), 4.25 (m, 1H), 4.32 (m, 1H), 4.61 (m, 1H), 5.27 (dd, *J* = 2.8, 10.3 Hz, 1H), 5.46 (m, 1H), 6.25 (s, 1H), 7.31 (s, 1H), 8.38 (s, 1H).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 12.5, 20.7, 21.1, 23.4 (CH_2), 52.7 (CH_2), 62.2, 63.1 (CH_2), 68.3, 69.6, 72.6, 78.2, 109.8, 136.0, 149.7, 163.5, 169.2, 169.5, 170.7.

Analysis: Calcd for $C_{21}H_{29}N_3O_9.1/2H_2O$: C, 52.94; H, 6.35. Found: C, 53.22; H, 6.48.

1-(2,4,6-tri-*O*-acetyl-3-*N*-morphino-*ß*-D-altropyranosyl) thymine 2.68d: A mixture of epoxide **2.43** (0.36 g, 1 mmol), and morpholine (0.44 g, 5 mmol) in DMSO (4 mL) was heated at 90 °C for 25h. The reaction mixture was diluted with EtOAc (75 mL) and the EtOAc solution was washed with brine (2x15 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure. The crude product was purified over silica gel column to afford **2.67d** (0.36 g, 80 %). The product was deprotected and acetylated following the procedure described for **2.68a** to obtain **2.68d**. White foam.

Eluent: EtOAc/petroleum ether (3:2).
Yield: 0.29 g, 75%.
Mp.: 97-99 °C.
[a]$_D^{29}$: +37.1 ° (*c* 1.30, $CHCl_3$).
IR ($CHCl_3$): 1745.5, 1689.5 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.94 (s, 3H), 2.06 (s, 3H), 2.13 (s, 6H), 2.68 (m, 2H), 2.76 (m, 2H), 2.98 (m, 1H), 3.73 (m, 4H), 4.27 (m, 1H), 4.32 (m, 1H), 4.40 (m, 1H), 5.33 (m, 1H), 5.46 (bs, 1H), 6.23 (s, 1H), 7.27 (s, 1H), 8.80 (bs, 1H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ 12.4, 20.7, 21.1, 51.6 (CH_2), 62.0, 63.0 (CH_2), 67.1 (CH_2), 67.7, 74.9, 78.6, 109.9, 136.0, 149.7, 163.5, 169.2, 169.5, 170.6.

Analysis: Calcd for $C_{21}H_{29}N_3O_{10}.1/2H_2O$: C, 51.21; H, 6.14. Found: C, 51.09; H, 5.83.

1-(2,4,6-tri-*O*-acetyl-3-*N*-(1-acetylpiperazino)-*ß*-D-altropyranosyl) thymine 2.68e: A mixture of epoxide **2.43** (0.36 g, 1 mmol), and 1-acetylpiperazine (0.64 g, 5 mmol) in DMSO (5 mL) was heated at 90 °C for 30h. The reaction mixture was diluted with EtOAc (75 mL) and the EtOAc solution was washed with brine (2x15 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure. The crude product was purified over silica gel column to afford **2.67e** (0.279 g, 56 %). The product was deprotected and acetylated following the procedure described for **2.68a** to obtain **2.68e**. White foam; Hygroscopic.

Eluent: EtOAc/petroleum ether (3:2).
Yield: 0.22 g, 75%.
Mp.: 105-107 °C.

[a]$_D^{29}$: +38.2 ^{o} (*c* 0.60, $CHCl_3$).
IR ($CHCl_3$): 1745.5, 1689.5, 1637.5 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): (**^{1}H -^{1}H COSY)**: δ 1.94 (s, 3H, thymine CH_3), 2.04 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.13 (s, 6H, 2xCH_3), 2.53 (m, 1H, piperazine), 2.68 (m, 1H, piperazine), 2.75 (m, 1H, piperazine), 2.85 (m, 1H, piperazine), 3.02 (dd, 1H, H3'), 3.46 (m, 3H, piperazine), 3.78 (m, 1H, piperazine), 4.32 (m, 3H, H5', H6', H6"), 5.30 (dd, 1H, H4'), 5.44 (dd, 1H, H2'), 6.22 (d, *J1',2'*= 2.3 Hz, 1H, H1'), 7.27 (s, 1H, H6), 9.28 (bs, 1H, NH).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ 12.4, 20.6, 20.7, 21.1, 41.6 (CH_2), 46.5 (CH_2), 50.9 (CH_2), 61.8, 63.0 (CH_2), 67.6, 67.8, 75.6, 78.7, 110.0, 135.9, 149.8, 163.5, 168.9, 169.2, 169.4, 170.5.

Analysis: Calcd for $C_{23}H_{32}N_4O_{10}.1H_2O$: C, 50.92; H, 6.35. Found: C, 50.76; H, 6.55.

1-(2,4,6-tri-*O*-acetyl-3-*N*-imidazoline-*ß*-D-altropyranosyl) thymine 2.68f: 1,1,3,3-Tetramethylguanidine (0.17 g, 1.5 mmol) was added to a solution of imidazole (0.17 g, 2.5 mmol) in DMSO (2 mL). After 15 min. at rt, the epoxide **2.43** (0.18 g, 0.5 mmol) was added to the solution. The reaction mixture was heated at 70 ^{o}C for 20h. The reaction mixture was cooled to rt and DCM (75 mL) was added. The organic layer was washed with brine (3x5 mL) and separated. The organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was evaporated under reduced pressure. The crude product was purified over silica gel column to afford **2.67f** (0.18 g, 86 %). The product was deprotected and acetylated following the procedure described for **2.68a** to obtain **2.68f**. White solid.

Eluent: EtOAc/petroleum ether (4:1).
Yield : 0.12 g, 65%.
Mp.: 108-110 ^{o}C.
[a]$_D^{27}$: +20.4 ^{o} (*c* 1.47, $CHCl_3$).
IR ($CHCl_3$): 1753.2, 1691.5 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.95 (s, 3H), 2.00 (s, 3H), 2.13 (s, 3H), 2.16 (s, 3H), 4.22-4.47 (m, 3H), 4.76 (dd, *J* = 4.3, 5.8 Hz, 1H), 5.22 (dd, *J* = 4.3, 5.9 Hz, 1H), 5.64 (dd, *J* = 3.1, 5.5 Hz, 1H), 6.25 (d, *J* = 3.2 Hz, 1H), 7.15 (m , 2H), 7.23 (s, 1H), 7.70 (s ,1H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ 12.4, 20.3, 20.7, 55.8, 62.9 (CH_2), 68.0, 69.1, 76.1, 78.8, 110.5, 118.5, 130.2, 135.2, 137.3, 149.7, 163.4, 168.7, 169.6, 170.4.

Analysis: Calcd for $C_{20}H_{24}N_4O_9.1/4H_2O$: C, 51.23; H, 5.27. Found: C, 51.31; H, 5.46.

1-(2,4,6-tri-*O*-acetyl-3-*S*-thio-(p)tolyl-ß-D-altropyranosyl) thymine 2.68g: NaOMe (0.138 g, 2.5 mmol) was added to a solution of 4-methylbenzenethiol (0.44 g, 3.5 mmol) in DMF (5 mL). After 15 min. at rt, epoxide **2.43** (0.18 g, 0.5 mmol) was added in the solution. The reaction mixture was heated at 70 °C for 10h. The reaction mixture was cooled to rt, and diluted with EtOAc (50 mL). The organic layer was washed with brine (2x10 mL), separated and dried over anhydrous Na_2SO_4. The liquid was filtered and evaporated under reduced pressure. The crude product was purified over silica gel column to afford **2.67g** (0.16 g, 66 %). The product was deprotected and acetylated following the procedure described for **2.68a** to obtain **2.68g**. The compound was crystallized from $CHCl_3$. White crystals.

Eluent: EtOAc/petroleum ether (3:2).
Yield: 0.12 g, 55%
Mp.: 77-82 °C.
[a]$_D^{25}$: +99.2 ° (*c* 1.29, $CHCl_3$).
IR ($CHCl_3$): 1745.5, 1689.5 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.93 (s, 3H), 2.01 (s, 3H), 2.03 (s, 3H), 2.13 (s, 3H), 2.33 (s, 3H), 4.03 (m, 1H), 4.29-4.44 (m, 3H), 5.11-5.18 (m, 2H), 6.49 (d, *J* = 1.6 Hz, 1H), 7.15 (d, 2H, *J* = 7.8 Hz), 7.27 (s, 1H), 7.44 (d, 2H, *J* = 8.2 Hz), 8.72 (s, 1H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ 12.5, 20.7, 20.8, 21.1, 49.5, 62.9 (CH_2), 65.9, 70.1, 73.8, 78.0, 110.0, 127.5, 130.2, 134.0, 135.9, 138.9, 149.5, 163.5, 168.9, 169.7, 170.7.

Analysis: Calcd for $C_{24}H_{28}N_2O_9S.1/4H_2O$: C, 54.90; H, 5.47. Found: C, 54.77; H, 5.40.

1-(2,4,6-tri-*O*-acetyl-3-*S*-thionitrilo-ß-D-altropyranosyl) thymine 2.68h: A mixture of epoxide **2.43** (0.36 g, 1 mmol) and NH_4SCN (0.36 g, 5 mmol) in DMF (3 mL) was heated at 70 °C for 5h. The reaction mixture was cooled to rt, and diluted with EtOAc (50 mL). The organic layer was washed with brine (2x10 mL), separated and dried over

anhydrous Na_2SO_4. The liquid was filtered and evaporated under reduced pressure. The crude product was purified over silica gel column to afford **2.67h** (0.30 g, 71 %). The product was deprotected and acetylated following the procedure described for **2.68a** to obtain **2.68h**. White foam.

Eluent: EtOAc/petroleum ether (1:1).
Yield: 0.18 g, 56%.
Mp.: 89-90 °C.
[a]$_D^{25}$: +65.0 ° (*c* 1.40, $CHCl_3$).
IR ($CHCl_3$): 2164 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.94 (s, 3H), 2.11 (s, 3H), 2.14 (s, 3H), 2.20 (s, 3H), 4.23-4.42 (m, 4H), 5.30 (dd, 1H, *J* = 4.4, 9.1 Hz,), 5.44 (m, 1H), 6.01 (d, *J* = 1.5 Hz, 1H), 7.21 (s, 1H), 8.93 (s, 1H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ 12.4, 20.3, 20.4, 20.6, 48.5, 62.2 (CH_2), 64.5, 68.8, 73.9, 77.8, 108.8, 110.5, 135.0, 149.6, 163.5, 168.5, 169.3, 170.4.

Analysis: Calcd for $C_{18}H_{21}N_3O_9S$: C, 47.47; H, 4.65. Found: C, 47.77; H, 4.64.

1-(2,4,6-tri-*O*-acetyl-3-cyano-*ß*-D-altropyranosyl) thymine 2.68i: A mixture of epoxide **2.43** (0.179 g, 0.5 mmol), and NaCN (0.123 g, 2.5 mmol) in DMSO (2 mL) was heated at 70 °C for 10h. The reaction mixture was diluted in EtOAc (75 mL). The solution was washed with brine (2x10 mL). The EtOAc part was dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure. The crude product was purified over silica gel column to afford **2.67i** (0.14 g, 68 %). The product was deprotected and acetylated following the procedure described for **2.68a** to obtain **2.68i**. White solid.

Eluent: EtOAc/petroleum ether (2:3).
Yield: 0.10 g, 65%.
Mp.: 99 °C.
[a]$_D^{25}$: +64.5 ° (*c* 0.78, $CHCl_3$).
IR ($CHCl_3$): 2254.6 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) (^{1}H-^{1}H COSY): δ 1.93 (s, 3H, thymine CH_3), 2.12 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 3.56 (dd, *J* = 2.8, 11.1 Hz, 1H, H3'), 3.97 (m, 1H, H5'), 4.19 (dd, *J* = 2.5, 12.5 Hz, 1H, H6'), 4.32 (dd, *J* = 6.0, 12.5 Hz, 1H, H6"), 5.39 (t, *J* = 10.1 Hz, 1H, H4'), 5.70 (m, 1H, H2'), 5.87 (d, *J1',2'* = 1.3 Hz, 1H, H1'), 7.19 (s, 1H, H6), 9.77 (bs, 1H, NH).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ 12.5, 20.3, 20.5, 20.7, 36.6, 62.1 (CH_2), 63.5, 66.1, 77.3, 80.5, 111.0, 115.0, 134.4, 149.9, 163.3, 168.9, 169.2, 170.5.

Analysis: Calcd for $C_{18}H_{21}N_3O_9.1/2H_2O$: C, 50.00; H, 5.13. Found: C, 50.23; H, 5.20.

1-(4,6-*O*-phenylmethylene-3-deoxy-3-*S*-tolyl-ß-D-allopyranosyl) thymine 2.70 : To a solution of 4-methylbenzenethiol (0.87 g, 7 mmol) in DMF (5 mL), NaOMe (0.27 g, 5 mmol) was added. The reaction mixture was stirred at rt for 0.5 h. Compound **2.57** (0.57 g, 1.0 mmol) was added and the reaction mixture was heated at 90 °C for 10h. The reaction mixture was allowed to cool to rt and DMF was evaporated under reduced pressure. To a methanolic solution (10 mL) of the reaction mixture, NaOMe (0.17 g, 3 mmol) was added. After 6h at rt, the reaction mixture was neutralized with Dowex H^+ (50x8), filtered. All volatile matters were removed under reduced pressure and crude residue was purified over silica gel to get **2.69**. To a mixture of the unprotected thio nucleoside **2.69** (0.32 g, 0.81 mmol) and benzaldehyde dimethyl acetal (0.18 g, 1.21 mmol) in DMF (25 mL), a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) was added. The reaction mixture was heated at 100 °C under vacuum for 1h. After cooling the mixture at rt, DMF was evaporated under reduced pressure. The residue was diluted with EtOAc (50 mL) and the solution was washed with sat. $NaHCO_3$ solution (2x25 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated. The crude product was purified over silica gel column to afford **2.70**. The compound was crystallized from $CHCl_3$, petroleum ether mixture. White crystals.

Eluent: EtOAc/ petroleum ether (3:2).
Yield : 0.32 g, 66% (from **2.57**)
Mp.: 220 °C.
[α**]**$_D^{25}$: – 73.0 ° (*c* 1.20, $CHCl_3$).
IR (Nujol): 1686 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.94 (s, 3H), 2.29 (s, 3H), 3.71-4.10 (m, 5H), 4.37 (dd, *J* = 4.8, 10.2 Hz, 1H), 5.62 (s, 1H), 5.69 (d, *J* = 8.8 Hz, 1H), 7.03 (d, *J* = 7.9 Hz, 2H), 7.12 (s, 1H), 7.37-7.51 (m, 7H, aromatic), 9.26 (s, 1H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ 12.3, 20.8, 59.0, 67.6, 68.5 (CH_2), 69.0, 78.0, 82.3, 101.4, 111.5, 126.2, 128.1, 129.0, 129.7, 131.2, 133.3, 135.0, 136.9, 137.8, 151.0, and 163.5.

Analysis: Calcd for $C_{25}H_{26}N_2O_6S.1/2H_2O$: C, 61.09; H, 5.54. Found: C, 61.35; H, 5.44.

1-[2,3-deoxy-(4,6-*O*-phenylmethylene)-(3-C-*p*-toluenesulfonyl)-*erythro*-ß-D-hex-1-*eno*-pyranosyl] thymine 2.74 : A mixture of compound **2.70** (0.96 g, 2 mmol) and MMPP (4.94 g, 10 mmol) in MeOH (150 mL) was stirred vigorously at rt for 3-3.5h. The reaction mixture was passed through a basic alumina column. Filtrate was evaporated under reduced pressure. A pyridine solution (25 mL) of the resulting product **2.71** (1.0 g, 1.94 mmol) was cooled to 0 ^oC in ice bath. Methanesulfonyl chloride (0.9 mL, 10 mmol) was added drop-wise to the reaction mixture. The reaction mixture was kept at +4 ^oC overnight. The reaction mixture was quenched with ice. Pyridine was evaporated under reduced pressure, and co-evaporated with toluene. The residue was diluted with DCM (75 mL). The organic layer was washed with sat. $NaHCO_3$ solution (2x10 mL), water (5 mL) and brine (5 mL). The organic layer was dried over anhydrous Na_2SO_4, and filtered. The filtrate was evaporated under reduced pressure. A solution of the crude mesylated sulfone nucleoside **2.72** in DCM (40 mL) was cooled to 0 ^oC in ice bath. To the reaction mixture was added DBU (0.61 g, 4 mmol), drop-wise with constant stirring. The mixture was stirred at rt for 5 h. The volume of the reaction mixture was reduced to one-fifth by evaporation. The solution, thus obtained was loaded directly on a silica-gel column. Purification afforded compound **2.74**. The product **2.74** was crystallized from EtOAc/ petroleum ether mixture. White crystals.

Eluent: EtOAc/ petroleum ether (3:2).
Yield : 0.46 g, 52 % (overall form **2.70)**
Mp.: 204 ^oC (Decomp.)
[a]$_D^{27.7}$: +14.6^o (*c* 1.60, $CHCl_3$).
IR ($CHCl_3$): 1732, 1697.2.

^{1}H NMR (400 MHz, $CDCl_3$) (^{1}H -^{1}H COSY): δ 1.95 (s, 3H, CH_3 Thymine), 2.36 (s, 3H, CH_3), 3.84 (t, *J* = 10.3 Hz, 1H, H6"), 4.09 (m, 1H, H5'), 4.20 (m, 2H, H3', H4'), 4.48 (dd, *J* = 5.0, 10.3 Hz, 1H, H6'), 5.37 (s, 1H, PhCH), 5.40 (d, 1H, H2'), 6.98 (m, 2H, aromatic), 7.13 (s, 1H, H6), 7.24-7.32 (m, 5H, aromatic), 7.82 (d, *J* = 8.3 Hz, 2H, aromatic), 9.00 (s, 1H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$) (^{1}H-^{13}C COSY; HSQC): δ 12.0 (C-methyl Thymine), 21.5 (C-methyl), 63.1 (C-3'), 67.6 (CH_2, C-6'), 69.4 (C-5'), 73.4 (C-4'), 90.3 (C-2'), 100.9 (PhC), 111.2, 125.6, 127.8, 128.7, 129.0, 129.8, 135.3, 135.8, 138.7 (C-6 Thymine), 145.3, 149.0, 149.7, 164.0.

Analysis: Calcd for $C_{25}H_{24}N_2O_7S$. C, 60.47; H, 4.87 Found: C, 60.38; H, 4.49.

1-[2-*O*-benzyl-3-deoxy-(4,6-*O*-phenylmethylene)-3-*S*-(*p*)-tolyl-*b*-D-*allo*pyranosyl] N^3-benzoyl thymine 2.75: To a solution of **2.70** (0.96 g, 2 mmol) in dry pyridine (10 mL) were added triethylamine (1.01 mL, 10 mmol) and chlorotrimethylsilane (0.4 mL, 3 mmol) under cold conditions. After stirring the reaction mixture for 1h it was cooled using an ice-bath. Benzoyl chloride (0.35 mL, 3 mmol) was added drop-wise and the reaction mixture was stirred at rt for an additional 1h. The reaction was quenched with a few drops of sat. $NaHCO_3$ solution. Pyridine was evaporated under reduced pressure, and co-evaporated with toluene. The residue was diluted with EtOAc (50 mL) and the organic layer was washed with sat. $NaHCO_3$ solution (3x10 mL), water (5 mL) and brine (5 mL). The organic layer was dried on Na_2SO_4 and filtered. The filtrate was evaporated, under reduced pressure. TFA (0.5 mL) was added to a solution of the crude product in a 1:1 mixture of DCM and MeOH (20 mL) and the solution was left at rt for 20 min. All volatile matters were removed under reduced pressure and crude product was purified over silica gel column to afford **2.75** (0.82 g; 70 %).

1-[2-*O*-benzyl-3-deoxy-(4,6-*O*-phenylmethylene)-3-*S*-(*p*)-tolyl-*b*-D-*allo*pyranosyl] thymine 2.77: A mixture of compound **2.75** (1.23 g, 2.1 mmol) and benzyl bromide (2.5 mL, 21 mmol) in DMF (10 mL) was cooled to 0 ^oC in a ice bath. To the reaction mixture was added NaH (0.092 g, 2.25 mmol, 60 % dispersion in oil) in portions with constant stirring. The reaction mixture was stirred at rt for overnight. The reaction mixture was diluted with EtOAc (250 mL). The organic layer was washed with brine (3x15 mL). The volatile matters were evaporated under reduced pressure. Purification over silica-gel column gave benzyl bromide free compound **2.76**. A solution of **2.76** in MeOH (40 mL),

and sodium methoxide (0.33 g, 6 mmol) was stirred at rt for 3-5h. Dowex H^+ (50x8) resin was used to neutralize the solution. Silica-gel column purification gave the desired compound **2.77**. Foamy solid.

Eluent: EtOAc/ petroleum ether (1:1).
Yield : 0.80 g, 66 % (from **2.70**).
Mp.: 108-110 ^{o}C.
[a]$_D^{27.1}$: –92.9^{o} (*c* 1.40, $CHCl_3$).
IR ($CHCl_3$): 1718.5 1685.7 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.78 (s, 3H), 2.31 (s, 2H), 3.62-3.80 (m, 3H), 4.17 (m, 3H), 4.30-4.35 (m, 1H), 4.50 (d, *J* = 12.6 Hz, 1H), 5.55 (s, 1H), 6.09 (bs, 1H), 6.64 (bs, 1H), 7.03-7.56 (m, 14H, aromatic), 8.38 (d, *J* = 8.6 Hz, 1H).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ 12.3, 20.9, 53.1, 67.0, 68.4 (CH_2), 69.4 (CH_2), 73.5, 77.8, 79.5, 101.3, 110.9, 126.1, 128.0, 128.2, 128.4, 128.9, 129.4, 131.5, 133.8, 136.0, 136.7, 137.5, 150.5, 163.6.

Analysis: Calcd for $C_{32}H_{32}N_2O_6S.1/4H_2O$. C, 66.59; H, 5.65 Found: C, 66.74; H, 5.54.

1-[2-*O*-benzyl-3,4-deoxy-(3-C-*p*-toluenesulfonyl)-6-*O*-trityl-*erythro*-ß-D-hex-3-*eno*-pyranosyl] thymine 2.82: Compound **2.77** (2.84 g, 5 mmol) was treated with TFA: water (4 : 1) mixture (3 mL) at rt for 30-45 min. All the volatile matters were evaporated under reduced pressure. A solution of crude product **2.78** (2.34 g, 5 mmol) in dry pyridine (20 mL) was reacted with trityl chloride (1.68 g, 6 mmol). The reaction mixture was heated under reflux for 3h. The reaction mixture was cooled to rt. Pyridine was evaporated under reduced pressure. The reaction mixture was diluted with EtOAc (150 mL), washed with water (10 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4, filtered. The filtrate was concentrated. The crude product was purified over neutral alumina column to afford **2.79** (3.2 g, 90%). A mixture of **2.79** (3.4 g, 4.78 mmol) and MMPP (11.8 g, 23.9 mmol) in MeOH (150 mL) was stirred vigorously at rt for 3-3.5h. The solvent was concentrated to a small volume and the filtration column over basic alumina afforded a polar compound **2.80**. A solution of the trityl protected sulfone nucleoside **2.80** (3.28 g, 4.42 mmol) in dry pyridine (30 mL) was cooled to 0 ^{o}C in ice bath. Methanesulfonyl chloride (1.8 mL, 22.1 mmol) was added drop-wise to the reaction mixture. The reaction mixture was kept at +4 ^{o}C overnight. The reaction was quenched with ice. Pyridine was

evaporated under reduced pressure and co-evaporated with toluene. The residue was diluted with DCM (75 mL), the organic layer was washed with sat. $NaHCO_3$ solution (2x10 mL), water (5 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated. The product was purified over neutral alumina column to yield compound **2.82**. The product was crystallized from a mixture of $CHCl_3$ and petroleum ether. Colorless crystals.

Eluent: EtOAc/ petroleum ether (1:3).
Yield : 2 g, 61 % (from **2.77**).
Mp.: 225-229 °C (Decomp.).
[a]$_D^{28}$: –87.8 ° (*c* 1.98, $CHCl_3$).
IR ($CHCl_3$): 1695 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) (^{1}H -^{1}H COSY): δ 1.69 (s, 3H, CH_3 Thymine), 2.37 (s, 3H, CH_3), 3.28 (dd, 1H, H6'), 3.36 (dd, 1H, H6''), 4.54-4.63 (m, 3H, H2', benzylic CH_2), 4.73 (m, 1H, H5'), 5.83 (d, *J1',2'* = 7.4 Hz, 1H, H1'), 6.85 (s, 1H, H6), 7.10-7.43 (m, 23H, aromatic, H4'), 7.69 (d, *J* = 8.3 Hz, 2H, aromatic), 8.49 (s, 1H, NH).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ 12.4, 21.5, 64.7 (CH_2), 71.2, 74.2, 74.8 (CH_2), 81.2, 87.0, 111.5, 127.3, 127.9, 128.6, 129.5, 134.1, 136.4, 137.3, 140.6, 141.3, 143.1, 144.4, 150.3, 163.1.

Analysis: Calcd for $C_{44}H_{40}N_2O_7S.1/4H_2O$ C, 70.90; H, 5.47. Found: C, 70.89; H, 5.37.

1-[2-*O*-benzyl-3,4-deoxy-(3-*C*-*p*-toluenesulfonyl)-6-*O*-trityl-*erythro*-ß-D-hex-4-*eno*-pyranosyl] thymine 2.83. Reaction A: A mixture of **2.82** (0.20 g, 0.27 mmol), benzylamine (0.14 g, 1.35 mmol) in EDC (5 mL) was stirred at rt for 48h. The reaction mixture was directly loaded over a silica gel column. The column purification afforded the amine free compound **2.83**. Reaction B: A mixture of compound **2.82** (0.20 g, 0.27 mmol) and piperidine (0.115 g, 1.35 mmol) in EDC (5 mL) was stirred at rt for 5h. Purification as above, afforded **2.83** (0.1 g, 50 %). White solid.

Eluent: EtOAc/ petroleum ether (1:3).
Yield : 0.14 g, 55 %.
Mp.: 118-120 °C (Decomp.).

[a]$_D^{28}$: +22.1 ^{o} (*c* 1.40, $CHCl_3$).
IR ($CHCl_3$): 1765, 1716.5 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) (^{1}H -^{1}H COSY): δ 1.73 (s, 3H, CH_3, Thymine), 2.46 (s, 3H, CH_3), 3.44-3.55 (m, 2H, H6', H6"), 4.22 (m, 1H, H3'), 4.34 (m, 1H, H2'), 4.63 (d, *J* = 11.7 Hz, 1H, benzylic CH_2), 4.81 (d, *J* = 11.7 Hz, 1H, benzylic CH), 5.10 (bs, 1H, H4'), 5.84 (d, *J1',2'* = 9.0 Hz, 1H, H1'), 6.66 (s, 1H, H6), 7.23-7.35 (m, 22H, aromatic), 7.87 (d, *J* = 8.1 Hz, 2H, aromatic), 8.35 (s, 1H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$) (^{1}H-^{13}C COSY; HSQC): δ 12.4 (C-methyl Thymine), 21.7 (C-methyl), 61.7 (CH_2, C-6'), 66.9 (C-3'), 71.0 (C-2'), 73.2 (benzylic C), 81.0 (C-1'), 87.2 (Trityl C), 91.2 (C-4'), 111.7, 127.2, 127.9, 128.1, 128.3, 128.4, 128.5, 129.0, 129.9, 133.9, 134.1, 136.4 (C-6), 143.2, 145.3, 150.5, 156.1, 163.2.

Analysis: Calcd for $C_{44}H_{40}N_2O_7S.1H_2O$. C, 69.63; H, 5.58. Found: C, 69.25; H, 5.70.

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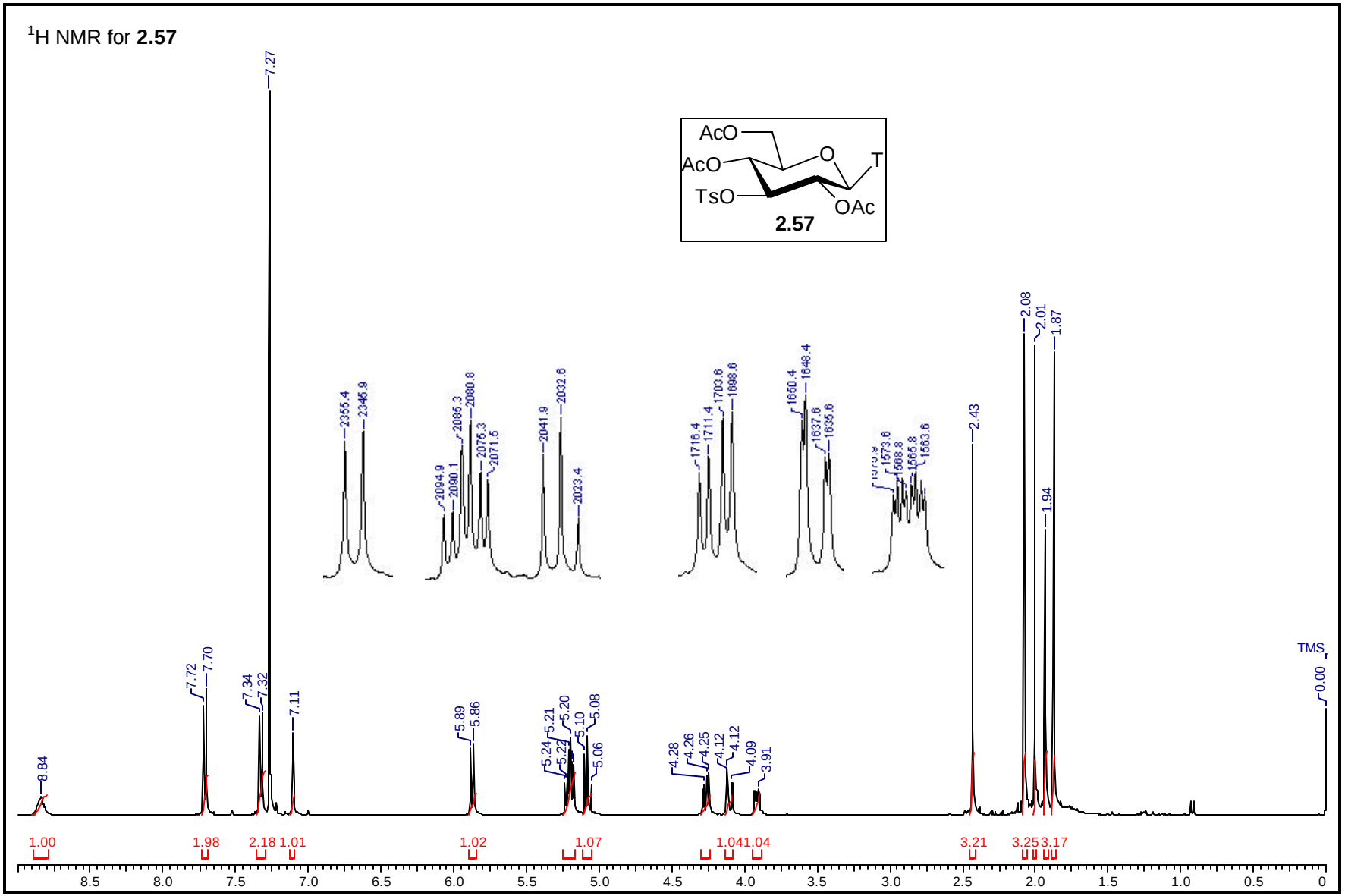
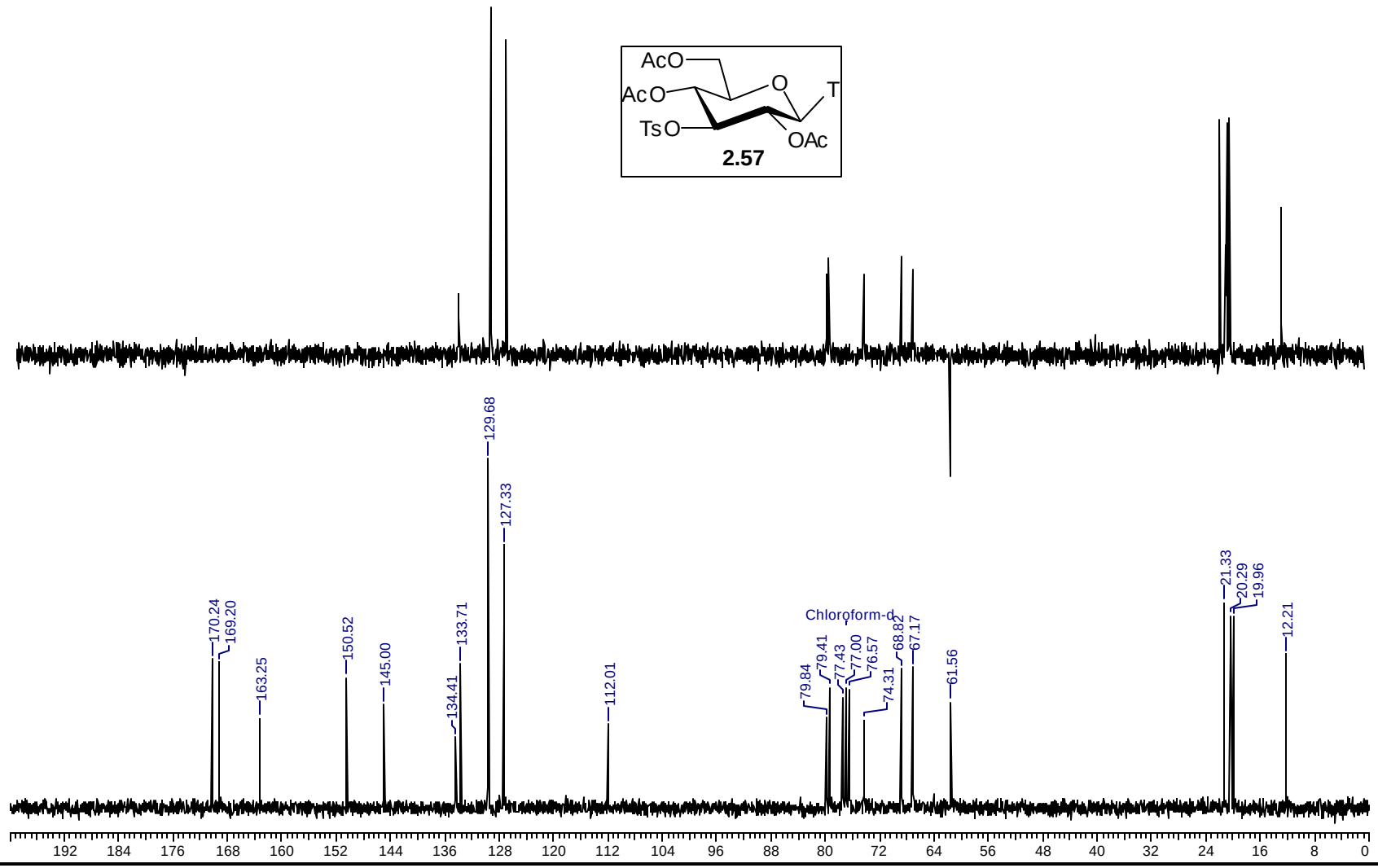
^{1}H NMR for **2.57**

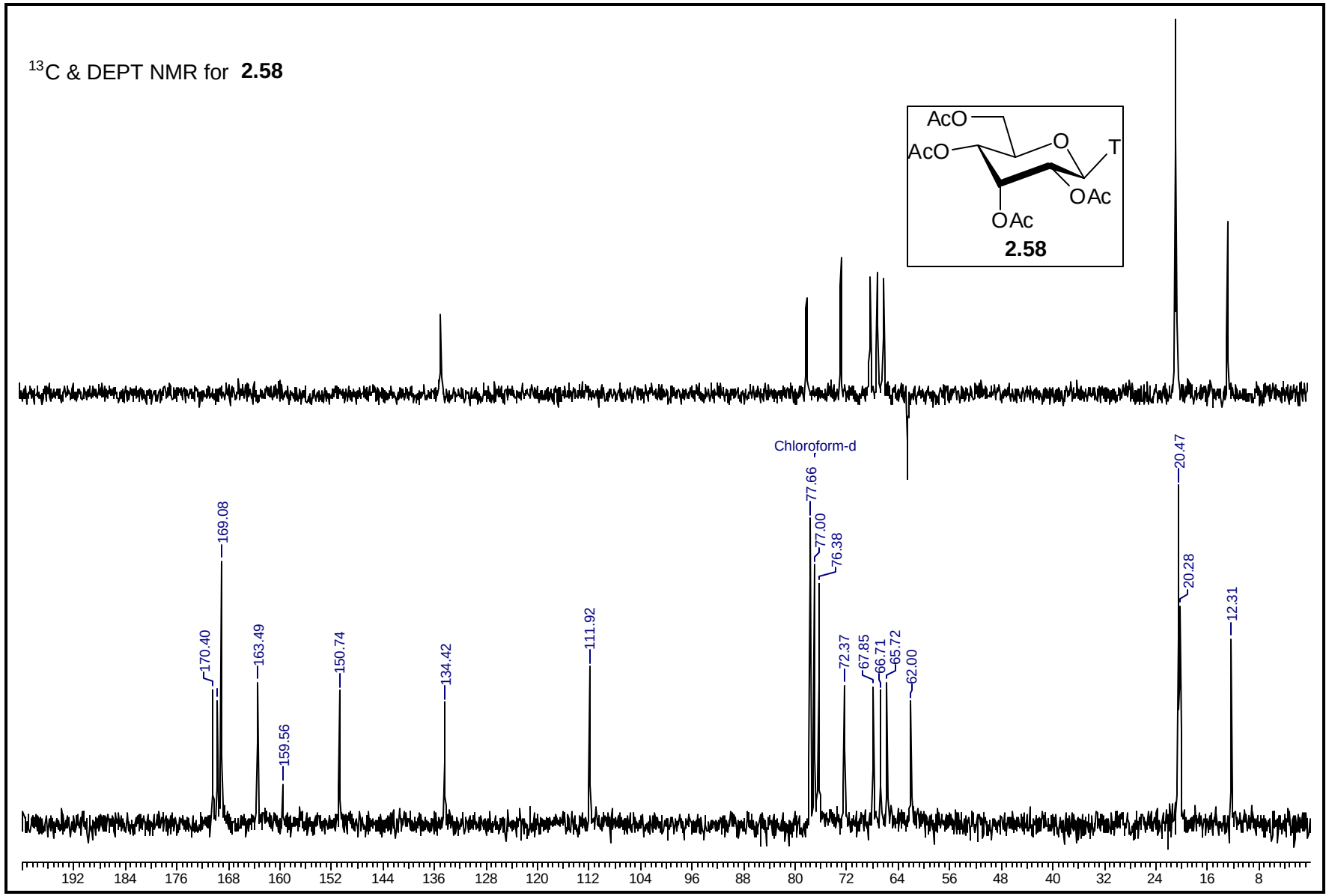


^{13}C & DEPT NMR for **2.57**

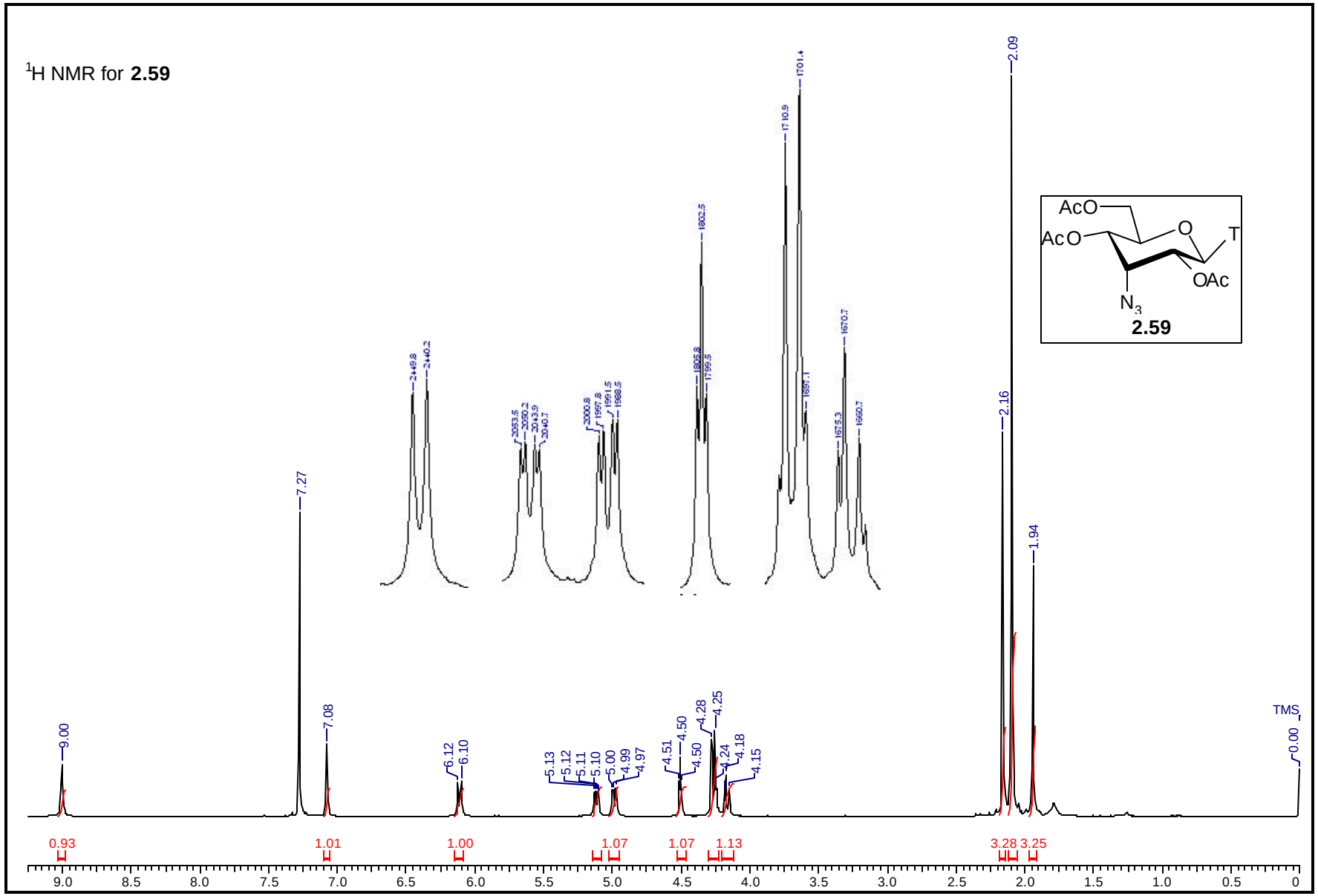


^{1}H NMR for **2.58**

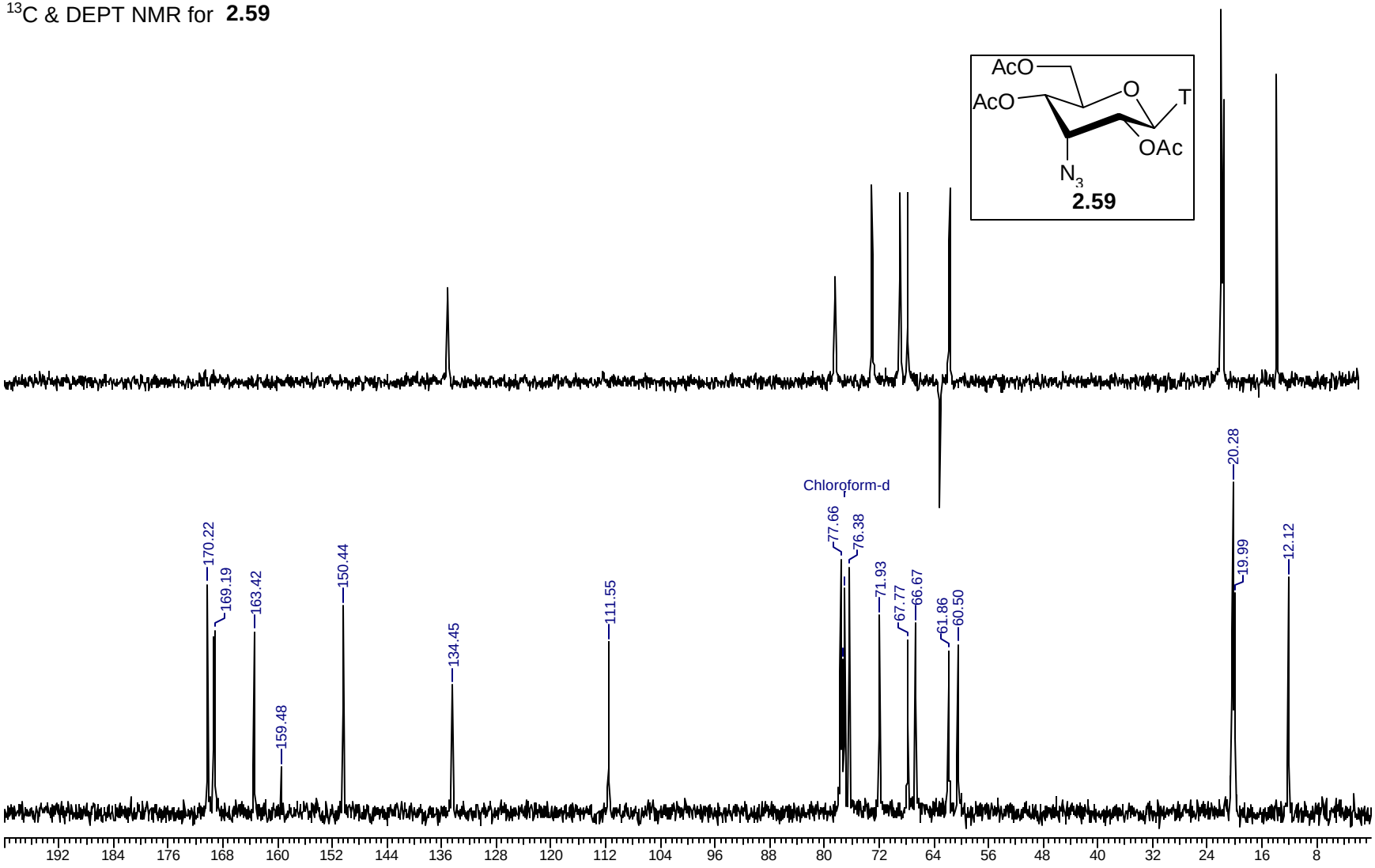
2.58

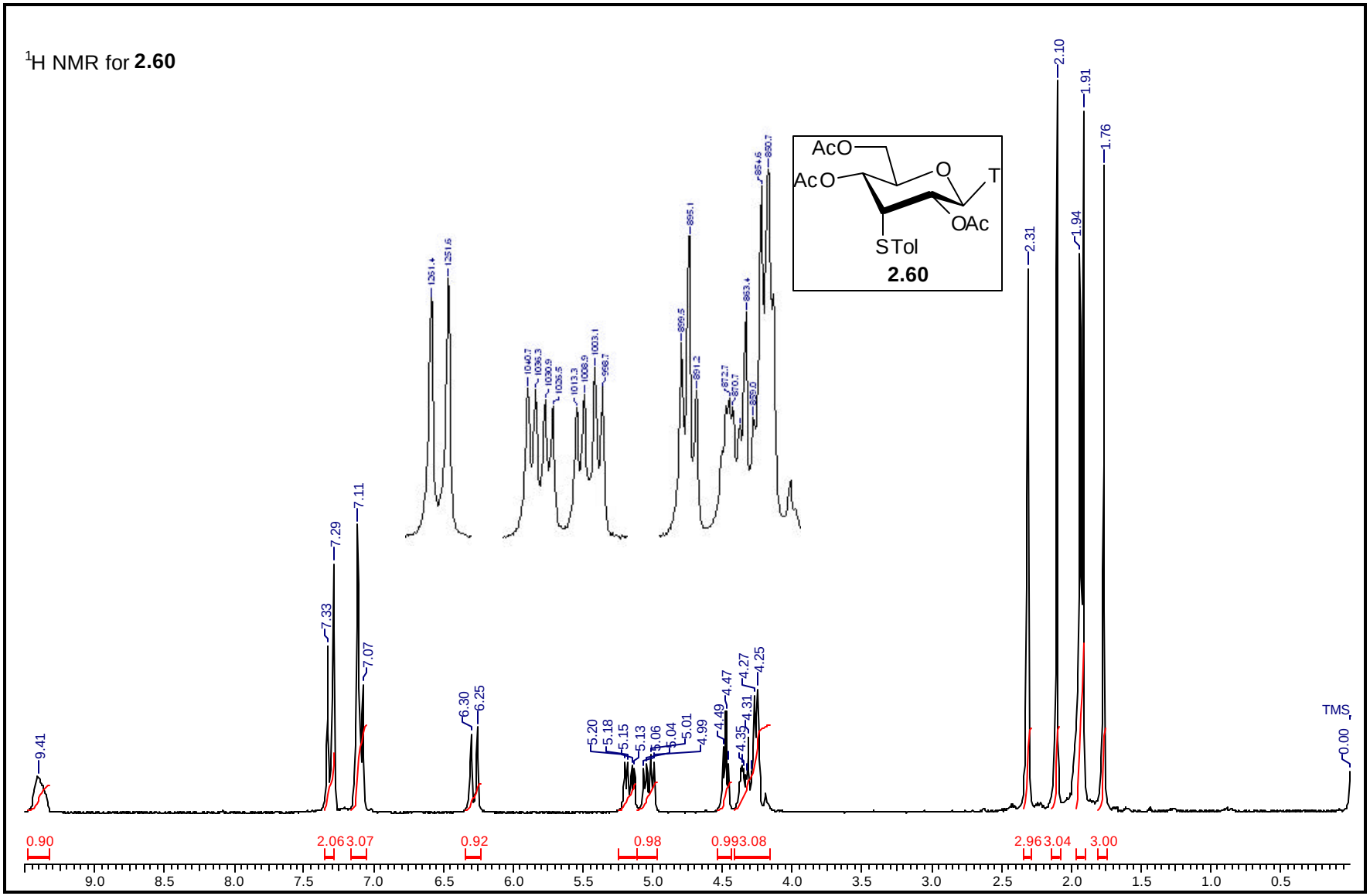

^{13}C & DEPT NMR for **2.58**
AcO
AcO
O
T
OAc
OAc
2.58
Chloroform-d
170.40
169.08
163.49
159.56
150.74
134.42
111.92
77.66
77.00
76.38
72.37
67.85
66.71
65.72
62.00
20.47
20.28
12.31
192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8

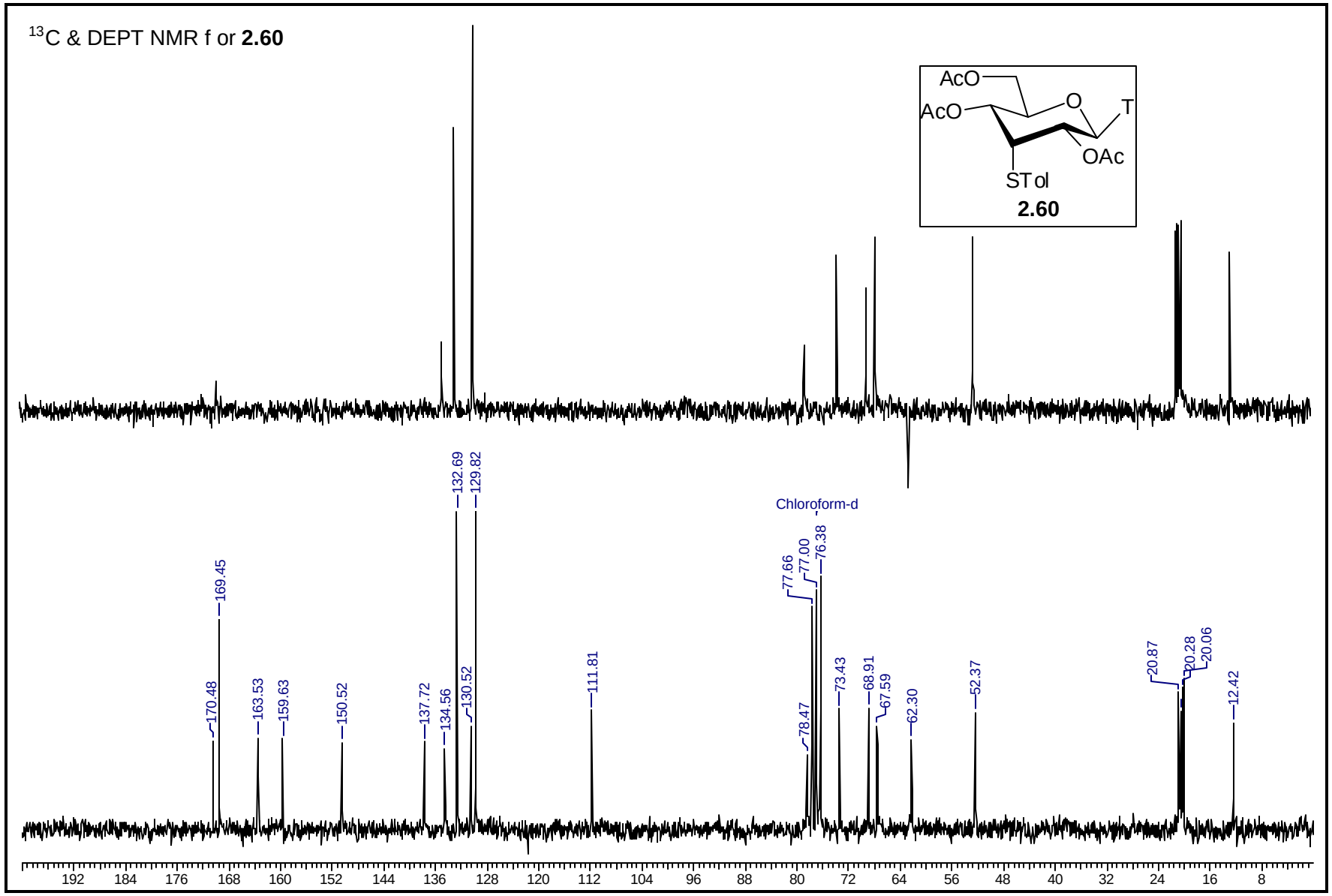
^{1}H NMR for **2.59**



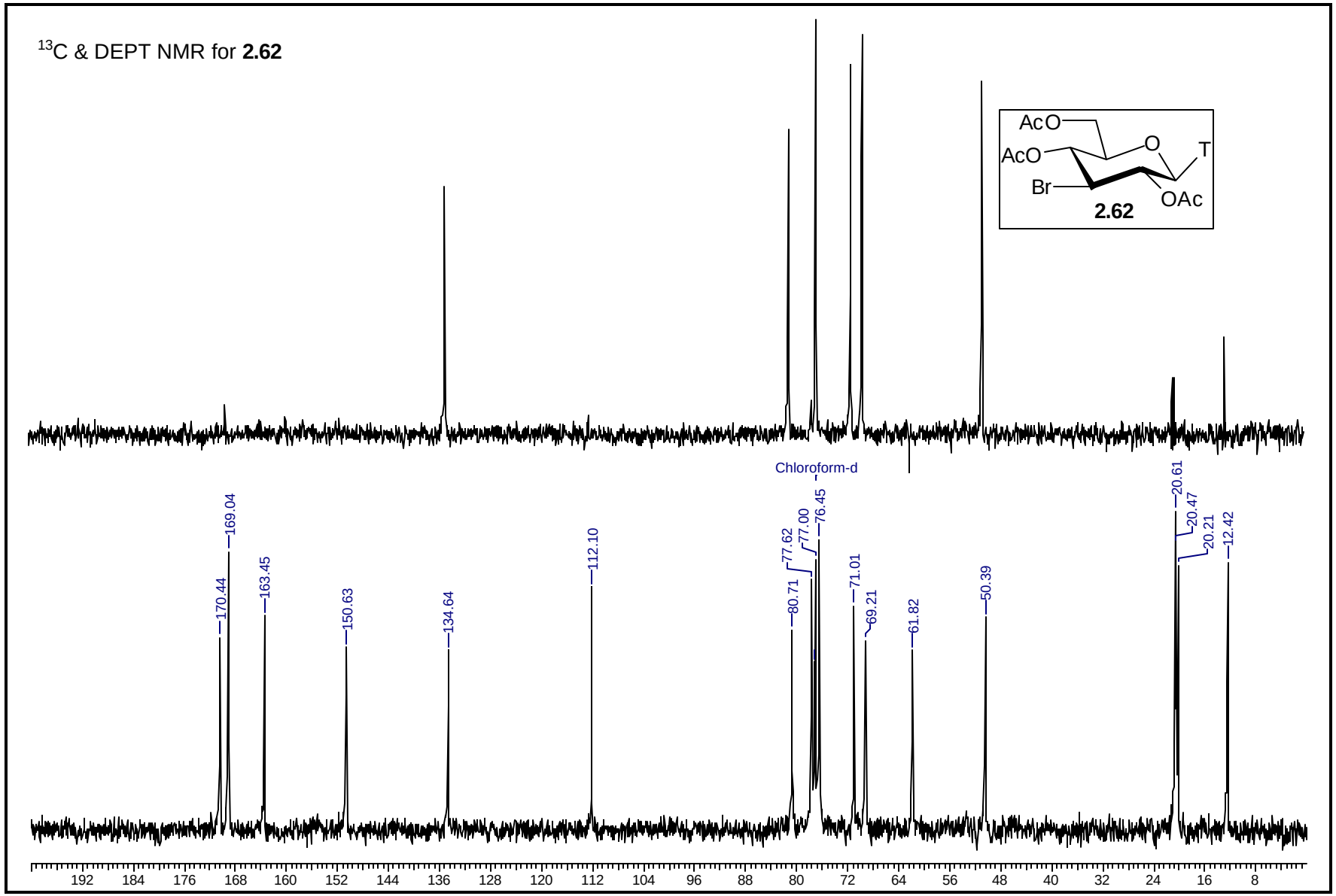
^{13}C & DEPT NMR for **2.59**



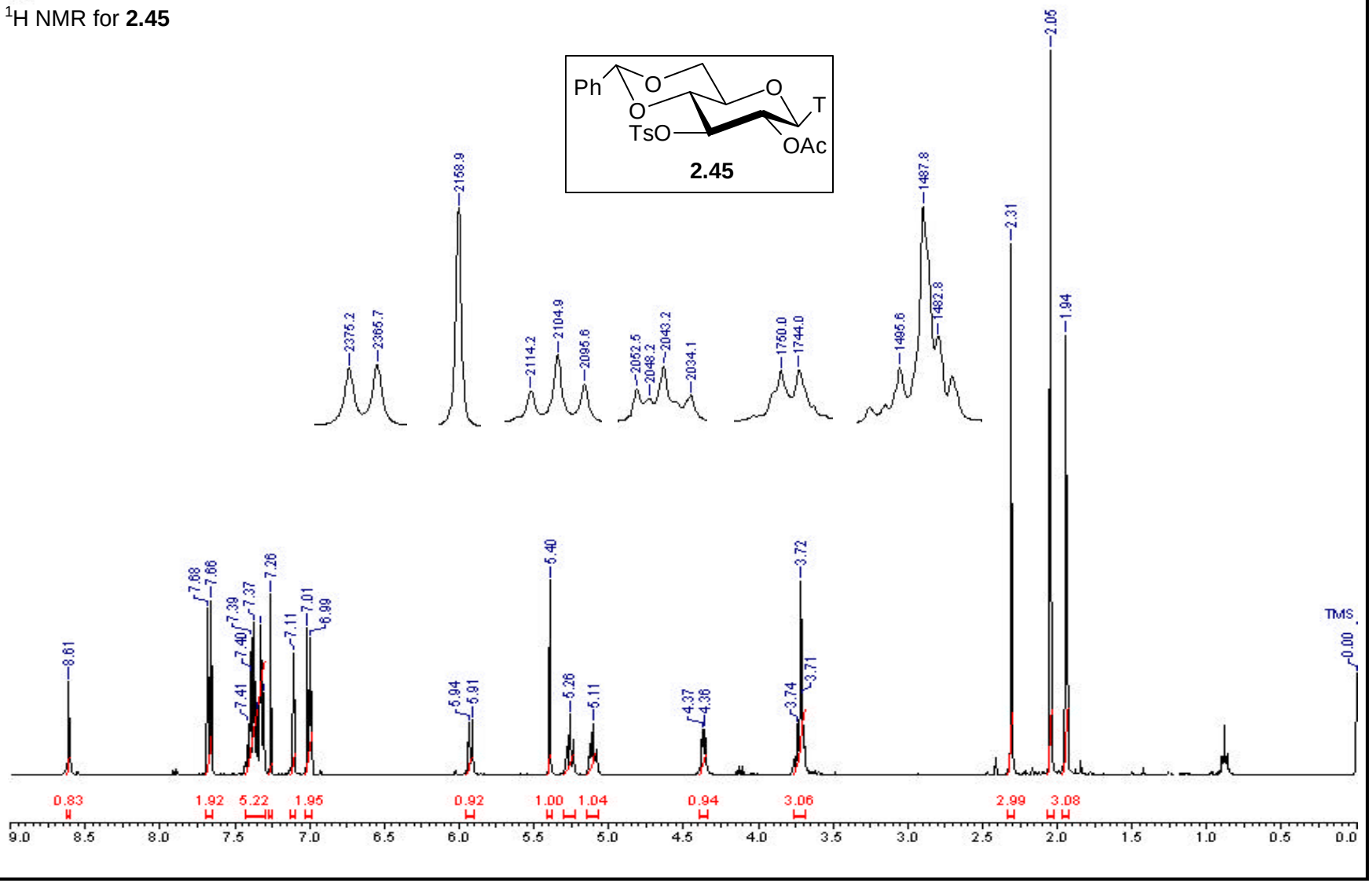

1H NMR for 2.60
AcO
AcO
O
T
OAc
STol
2.60
9.41
7.33
7.29
7.11
7.07
6.30
6.25
5.20
5.18
5.15
5.13
5.06
5.04
5.01
4.99
4.49
4.47
4.35
4.31
4.27
4.25
2.31
2.10
1.94
1.91
1.76
TMS
0.00
0.90
2.06
3.07
0.92
0.98
0.99
3.08
2.96
3.04
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

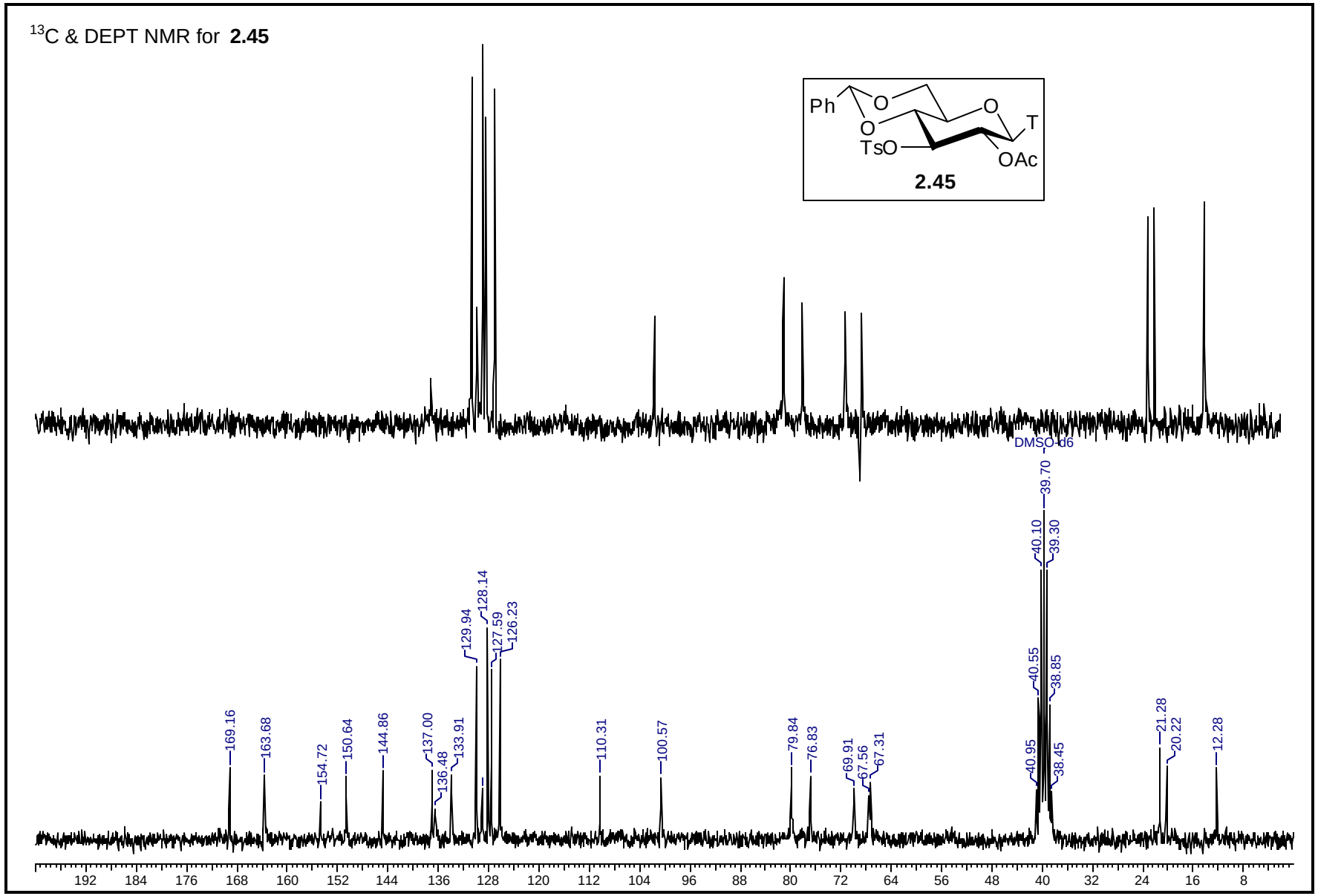

^{13}C & DEPT NMR f or **2.60**
AcO
AcO
O
T
OAc
STol
2.60
Chloroform-d
132.69
129.82
169.45
77.66
77.00
76.38
170.48
163.53
159.63
150.52
137.72
134.56
130.52
111.81
78.47
73.43
68.91
67.59
62.30
52.37
20.87
20.28
20.06
12.42
192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8

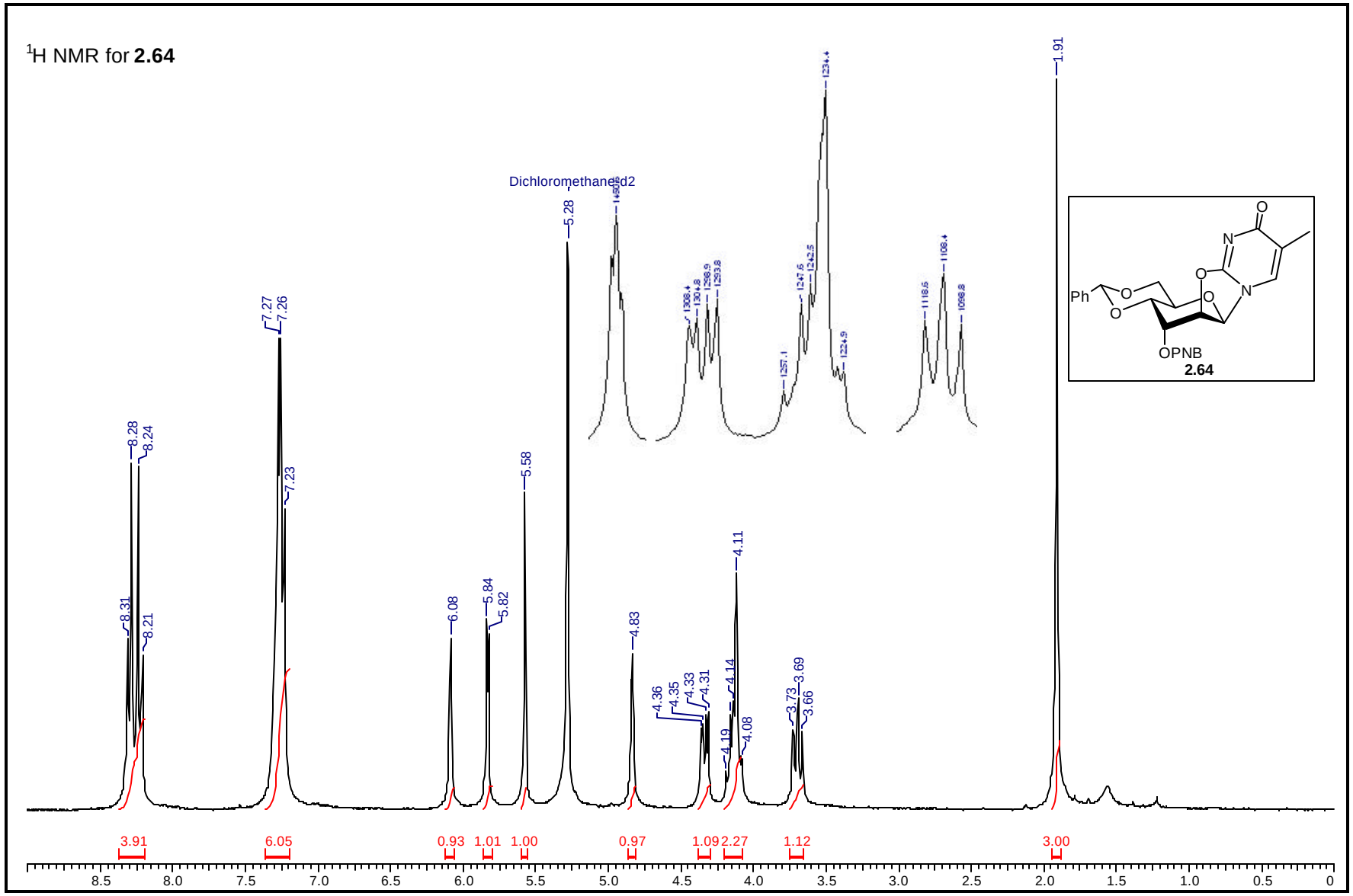
^{1}H NMR for **2.62**

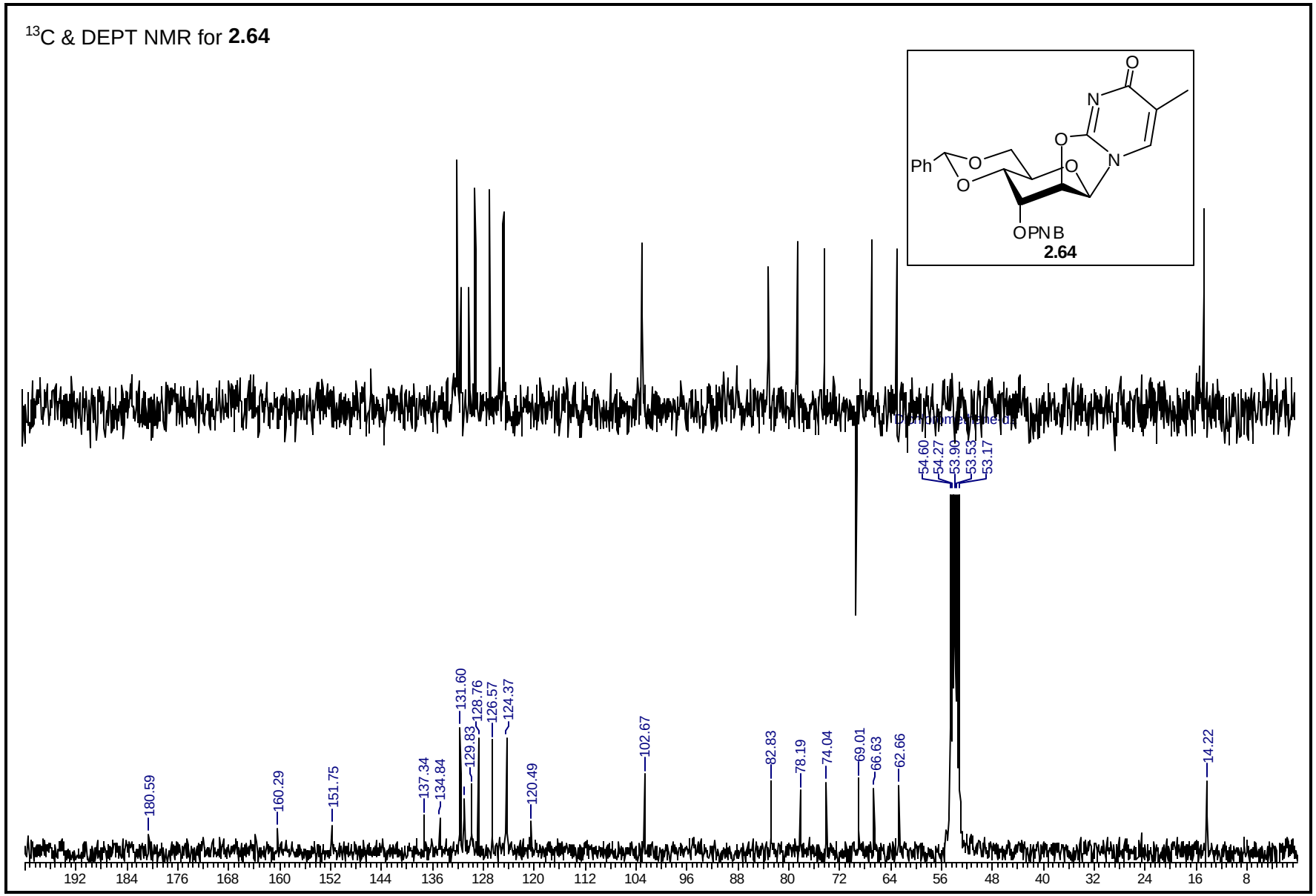

^{13}C & DEPT NMR for **2.62**
AcO
AcO
O
T
Br
OAc
2.62
Chloroform-d
170.44
169.04
163.45
150.63
134.64
112.10
80.71
77.62
77.00
76.45
71.01
69.21
61.82
50.39
20.61
20.47
20.21
12.42
192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8

^{1}H NMR for **2.45**

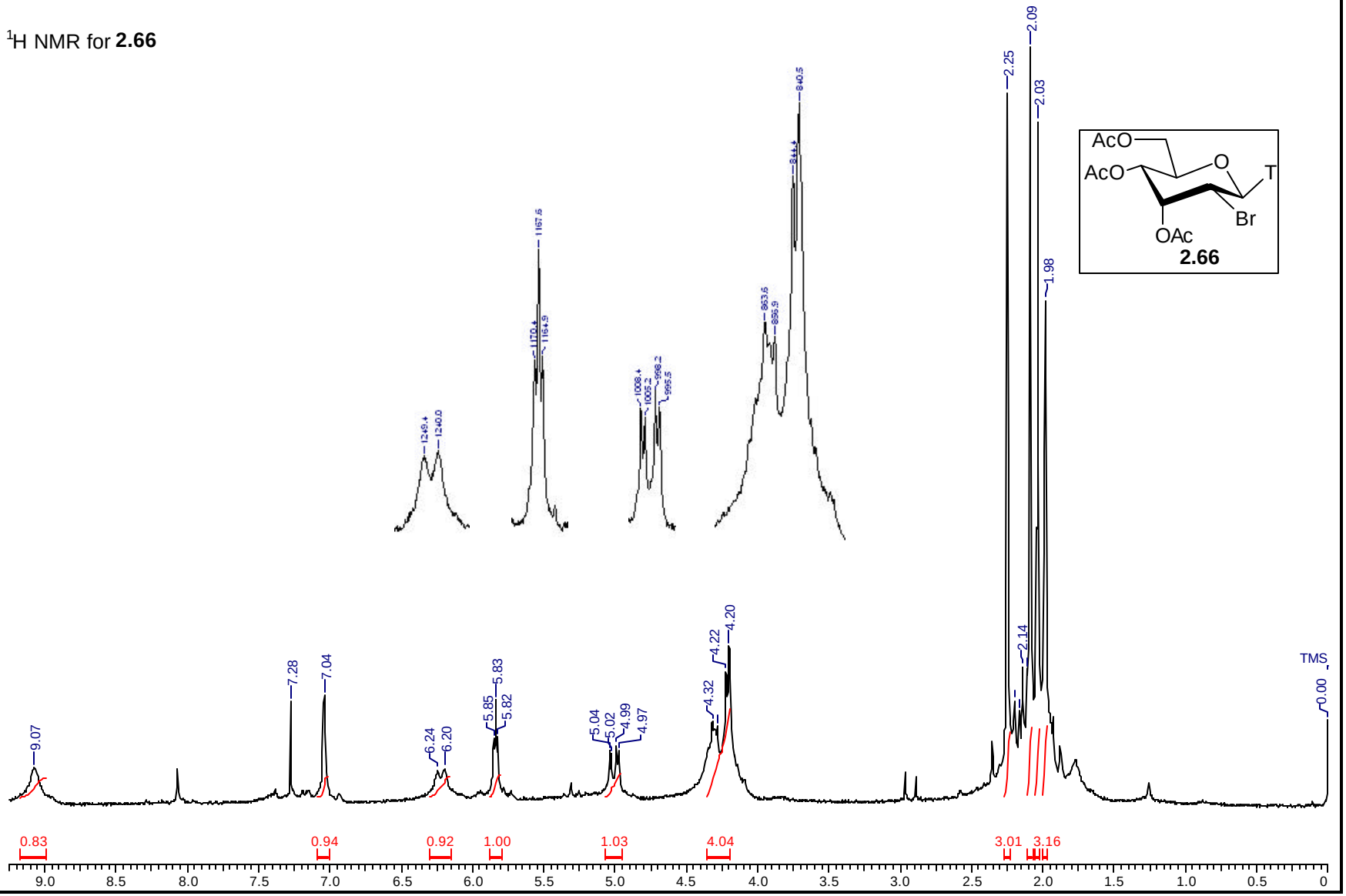


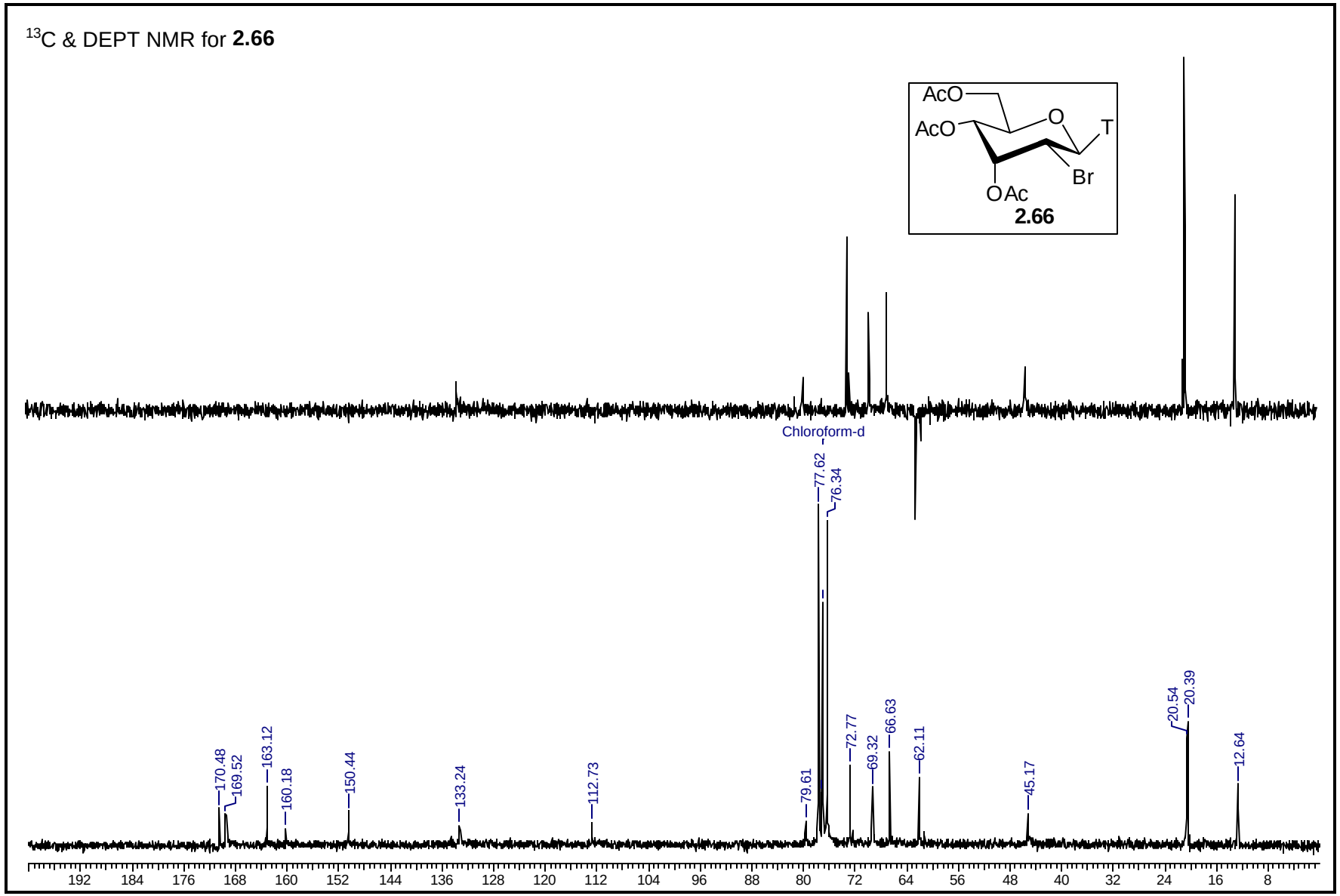

13C & DEPT NMR for 2.45
Ph
O
O
O
T
TsO
OAc
2.45
DMSO-d6
169.16
163.68
154.72
150.64
144.86
137.00
136.48
133.91
129.94
128.14
127.59
126.23
110.31
100.57
79.84
76.83
69.91
67.56
67.31
40.95
40.55
40.10
39.70
39.30
38.85
38.45
21.28
20.22
12.28
192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8

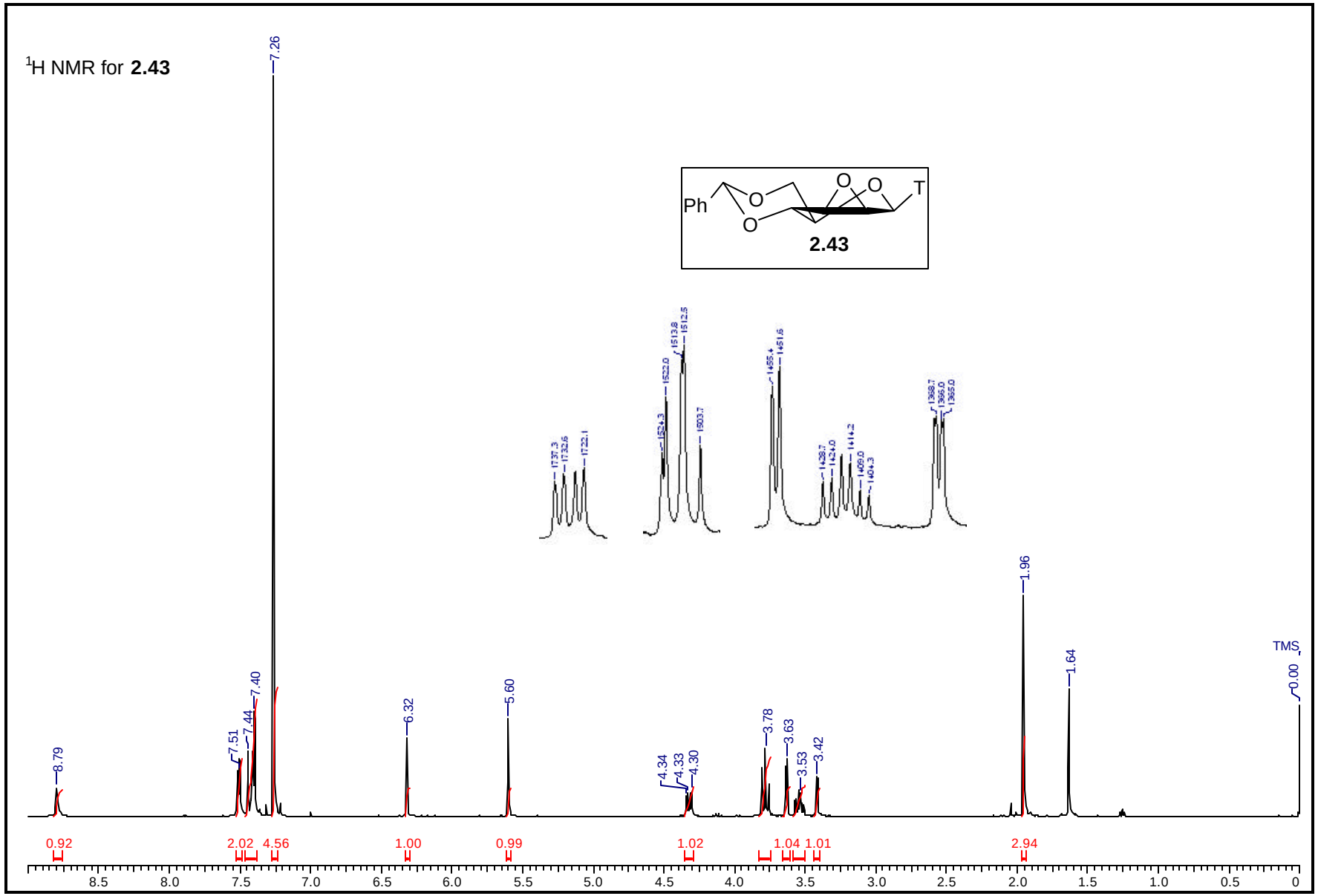

1H NMR for 2.64
Dichloromethane-d2
5.28
1.91
7.27
7.26
8.28
8.24
7.23
5.58
8.31
8.21
6.08
5.84
5.82
4.83
4.11
4.36
4.35
4.33
4.31
4.14
4.19
4.08
3.73
3.69
3.66
Ph
O
N
OPNB
2.64
3.91
6.05
0.93
1.01
1.00
0.97
1.09
2.27
1.12
3.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0


13C & DEPT NMR for 2.64
O
N
O
N
Ph
O
O
O
OPNB
2.64
Dichloromethane-d2
54.60
54.27
53.90
53.53
53.17
180.59
160.29
151.75
137.34
134.84
131.60
129.83
128.76
126.57
124.37
120.49
102.67
82.83
78.19
74.04
69.01
66.63
62.66
14.22
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8

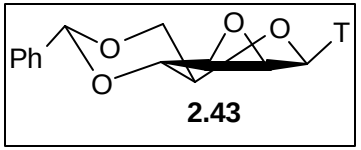
^{1}H NMR for **2.66**



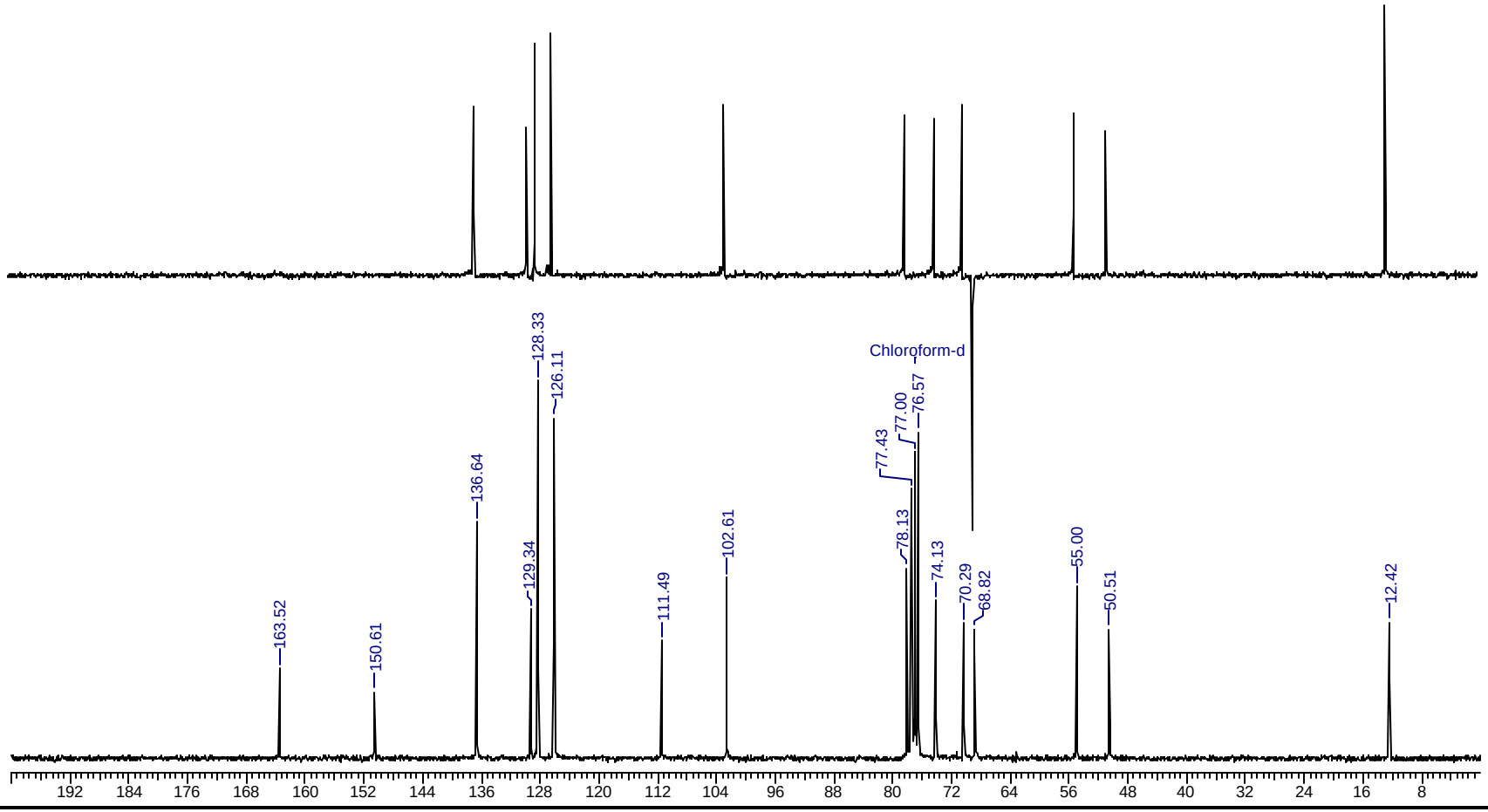

^{13}C & DEPT NMR for **2.66**
AcO
AcO
O
T
Br
OAc
2.66
Chloroform-d
170.48
169.52
163.12
160.18
150.44
133.24
112.73
79.61
77.62
76.34
72.77
69.32
66.63
62.11
45.17
20.54
20.39
12.64
192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8


^{1}H NMR for **2.43**
Ph
O
O
O
O
T
2.43
7.26
8.79
7.51
7.44
7.40
6.32
5.60
4.34
4.33
4.30
3.78
3.63
3.53
3.42
1.96
1.64
TMS
0.00
0.92
2.02
4.56
1.00
0.99
1.02
1.04
1.01
2.94

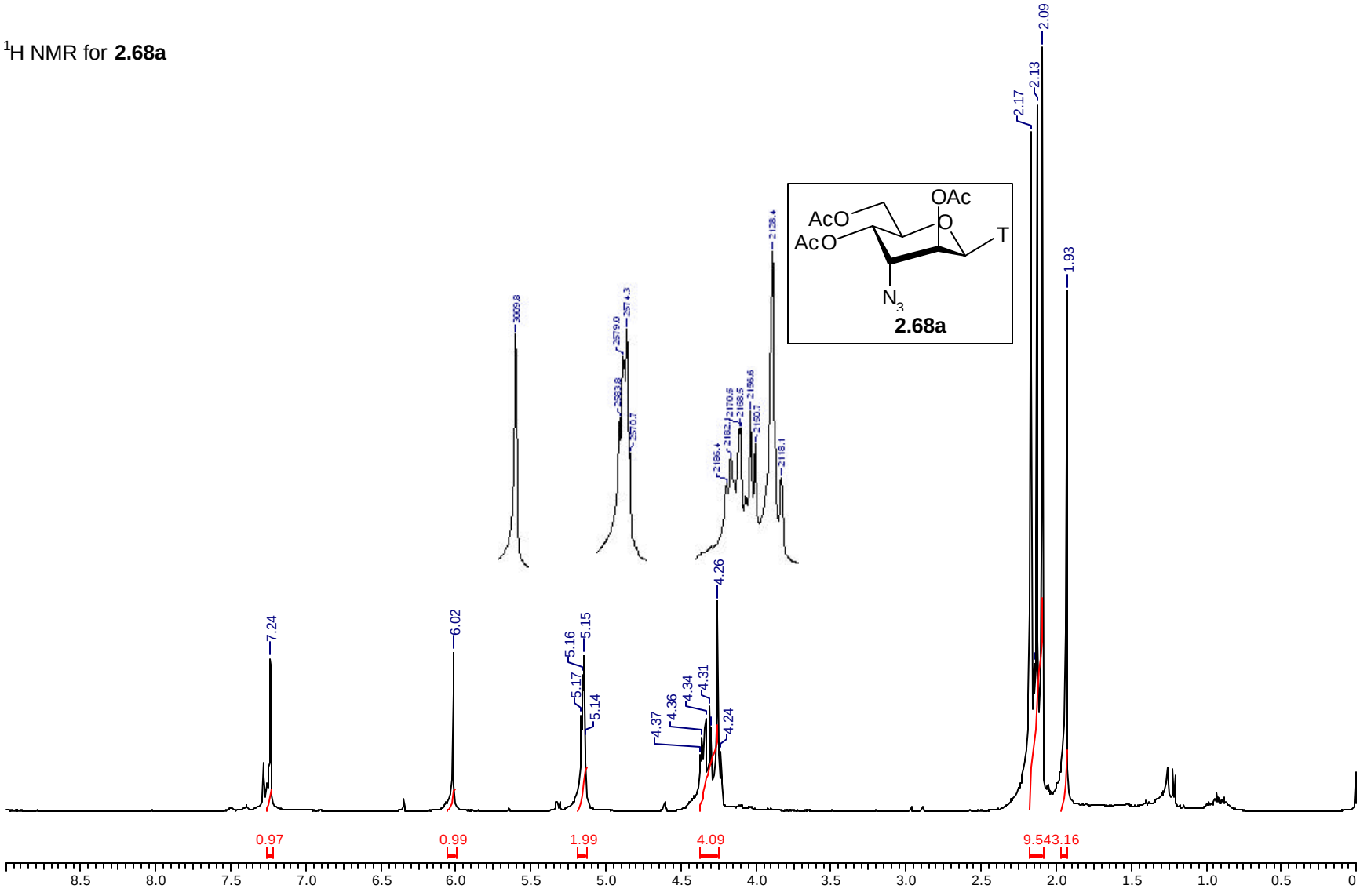
^{13}C & DEPT NMR for **2.43**



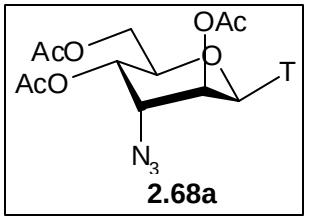
2.43



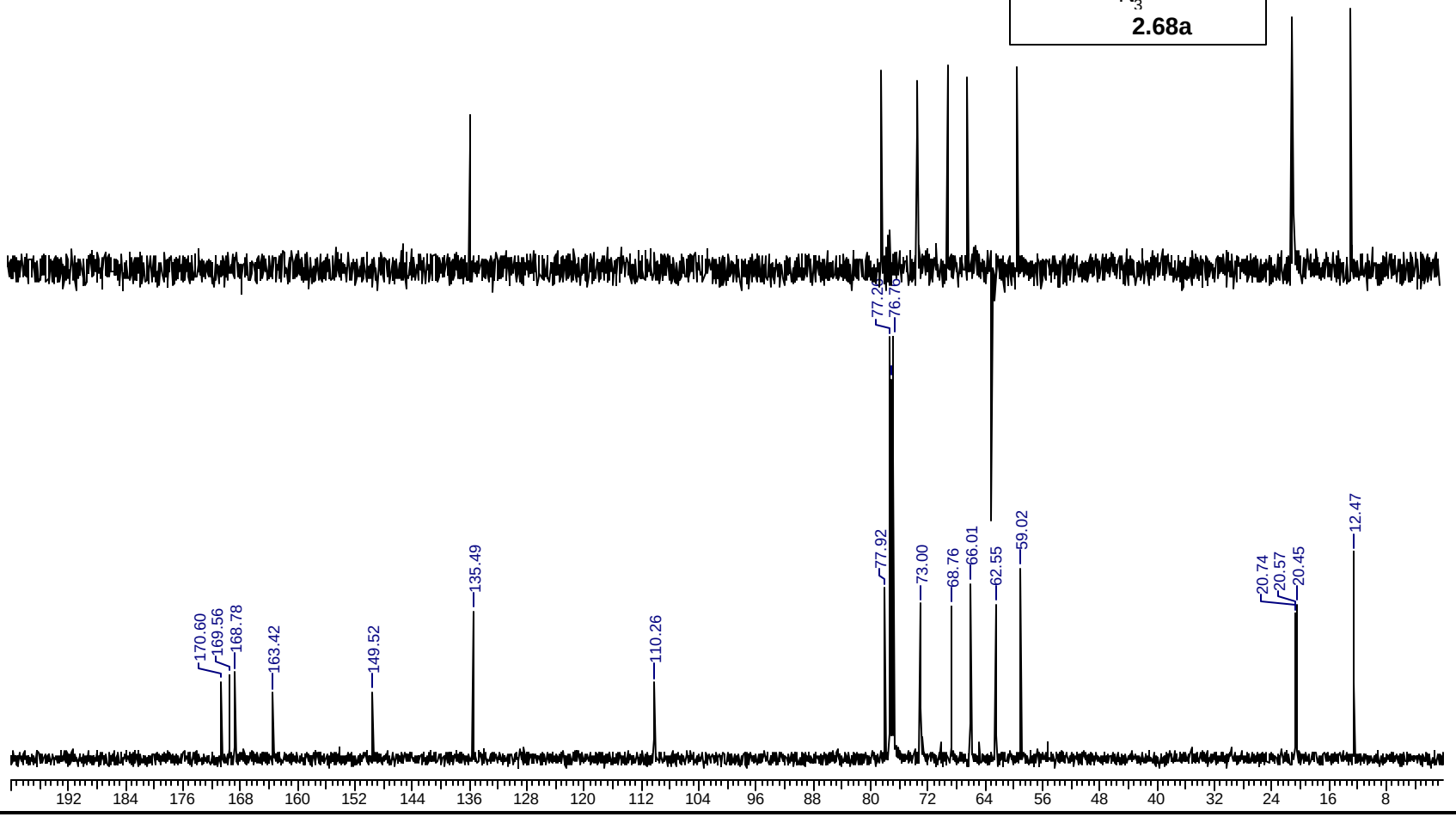
^{1}H NMR for **2.68a**

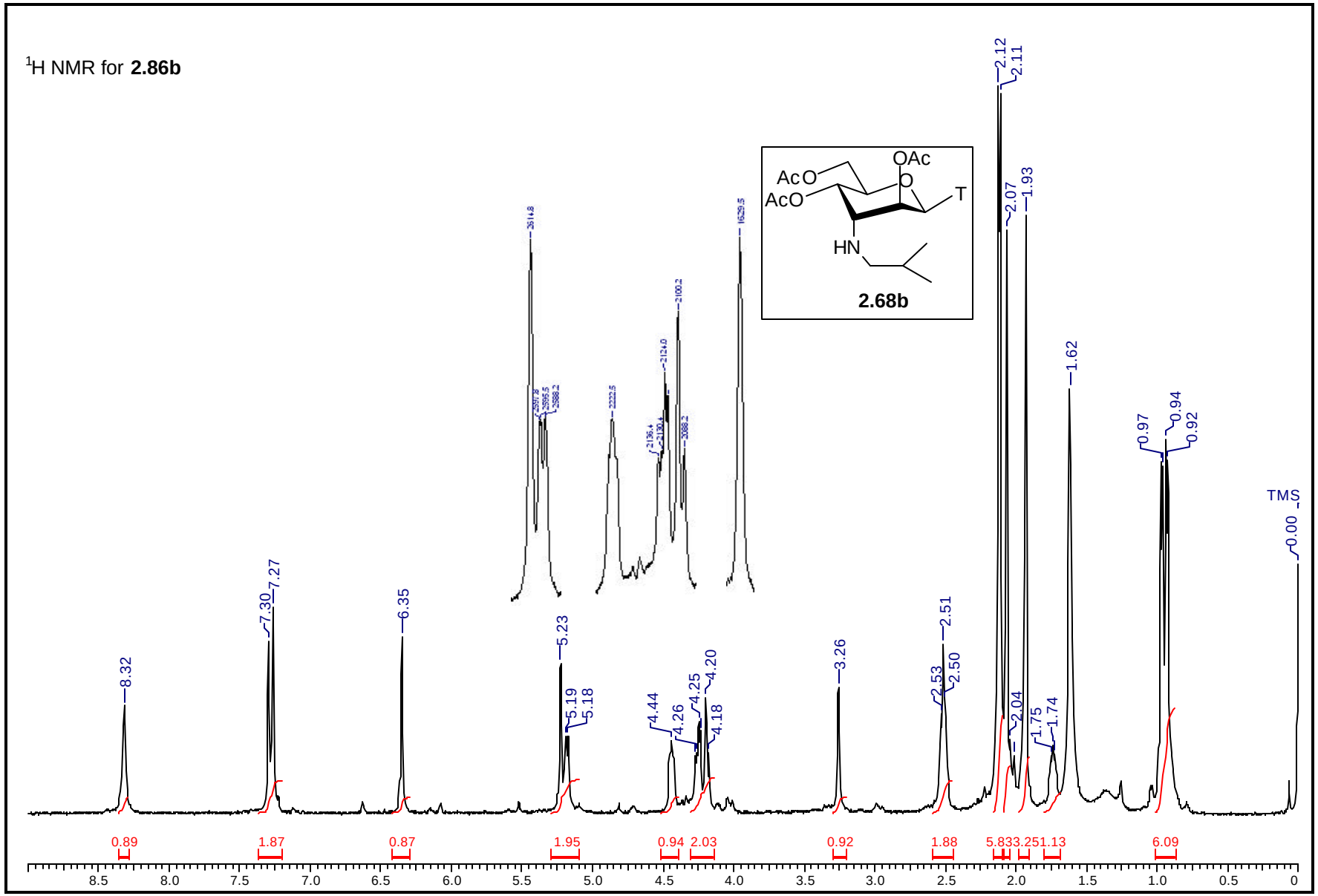


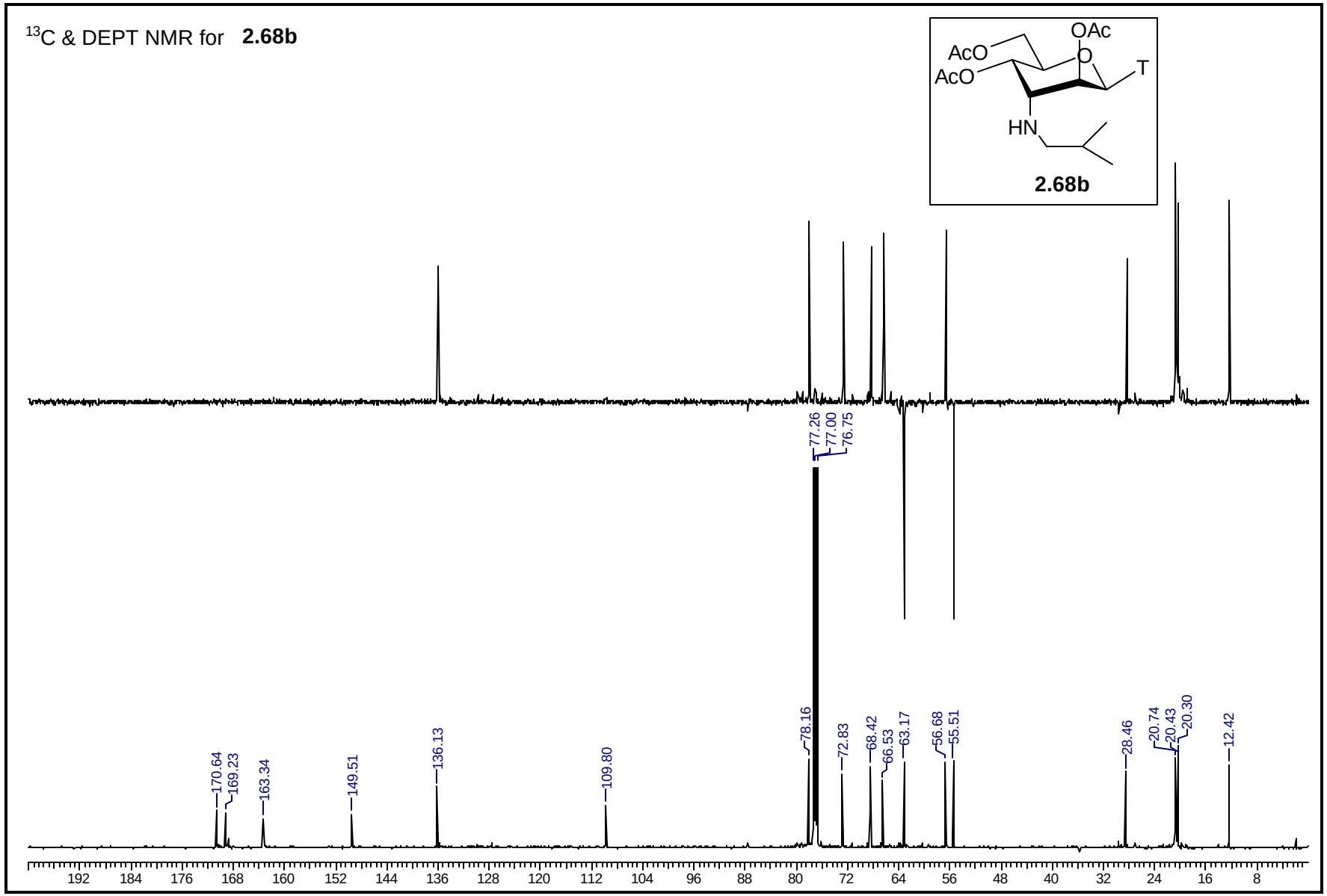
^{13}C & DEPT NMR for **2.68a**



2.68a



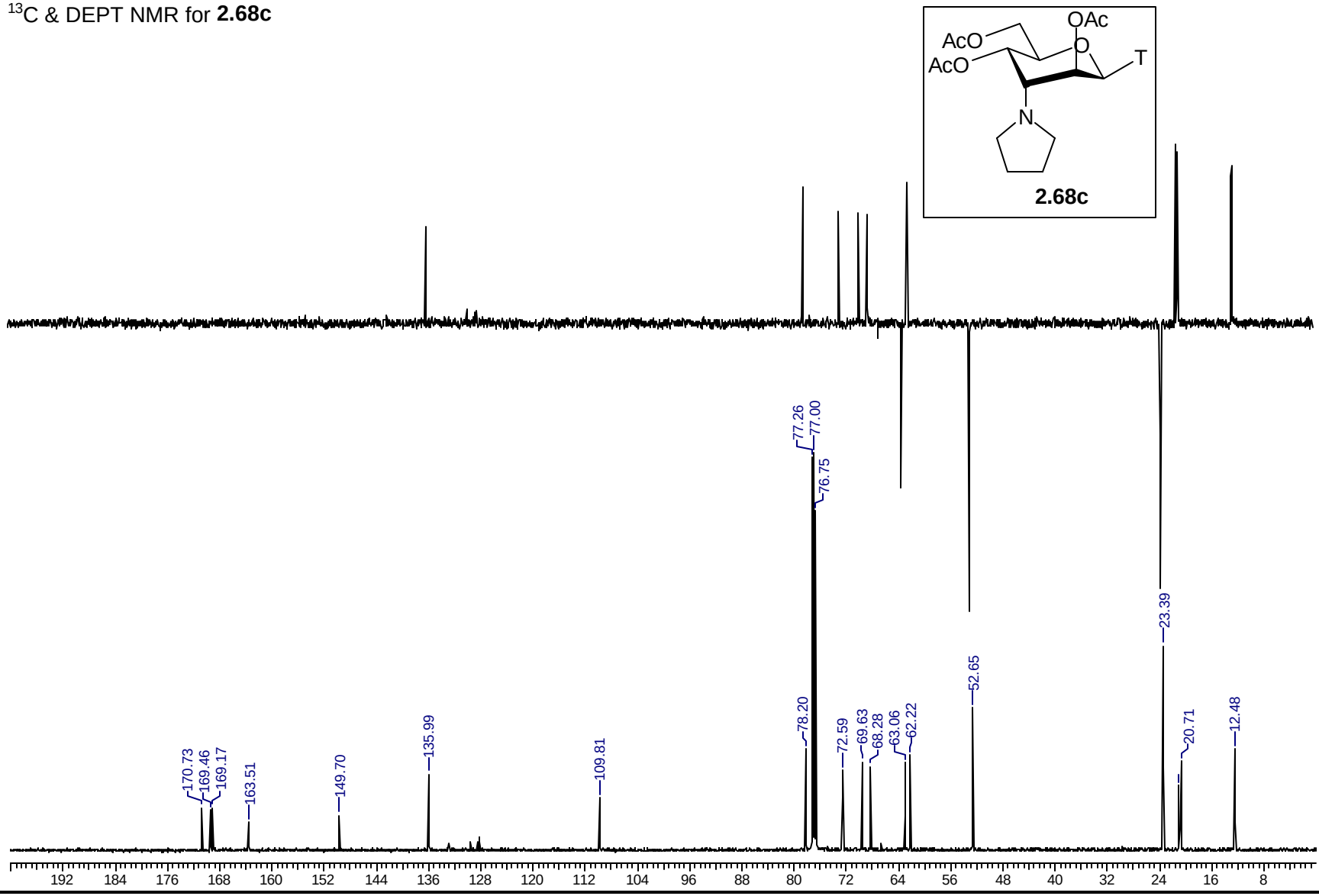

1H NMR for 2.86b
AcO
AcO
OAc
O
T
HN
2.68b
8.32
7.30
7.27
6.35
5.23
5.19
5.18
4.44
4.26
4.25
4.20
4.18
3.26
2.53
2.51
2.50
2.12
2.11
2.07
1.93
2.04
1.75
1.74
1.62
0.97
0.94
0.92
TMS
0.00
0.89
1.87
0.87
1.95
0.94
2.03
0.92
1.88
5.83
3.25
1.13
6.09


13C & DEPT NMR for 2.68b
OAc
AcO
AcO
O
T
HN
2.68b
77.26
77.00
76.75
170.64
169.23
163.34
149.51
136.13
109.80
78.16
72.83
68.42
66.53
63.17
56.68
55.51
28.46
20.74
20.43
20.30
12.42
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8

^{1}H NMR for **2.68c**

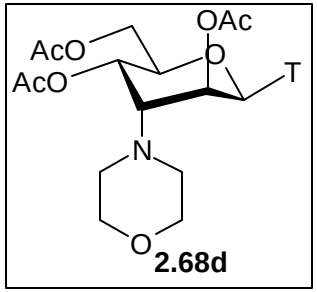
2.68c

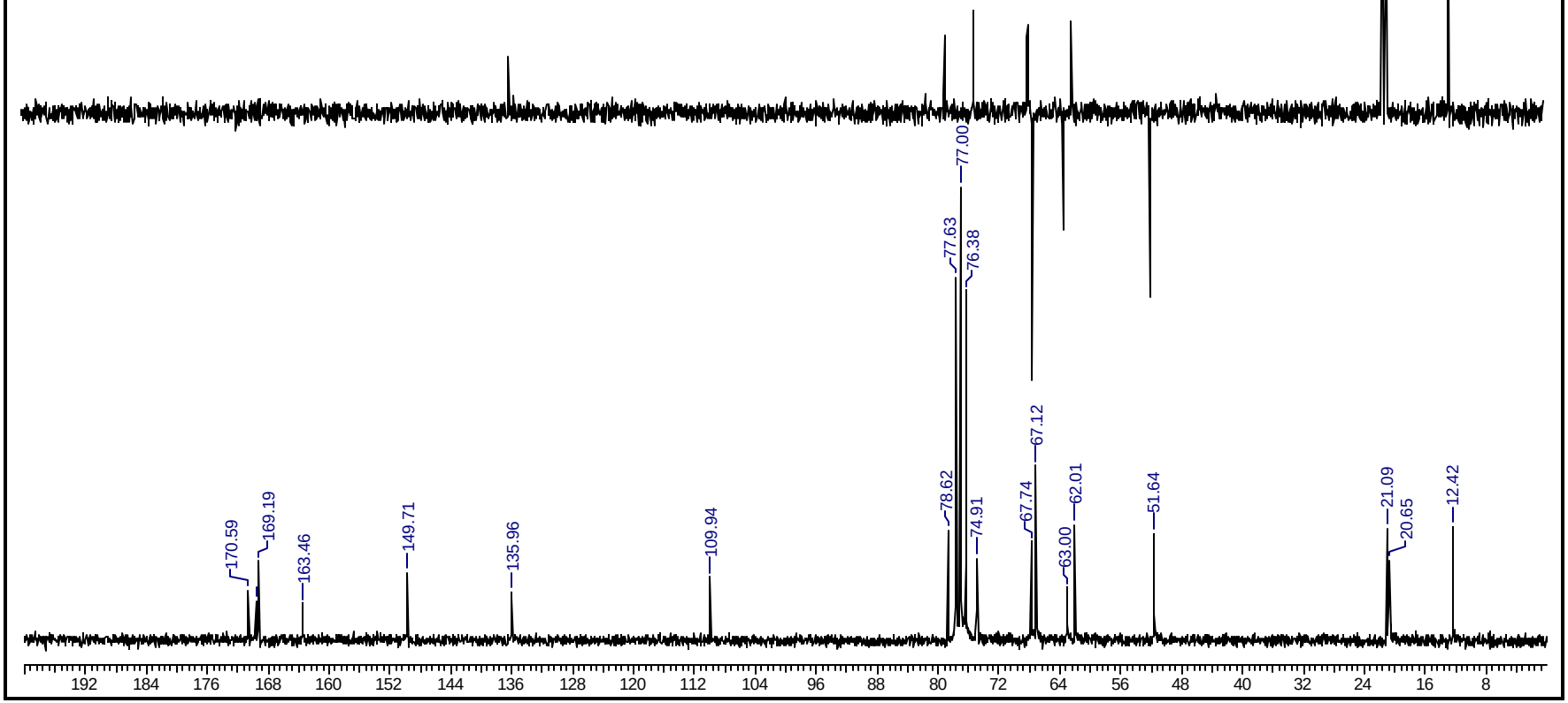
^{13}C & DEPT NMR for **2.68c**



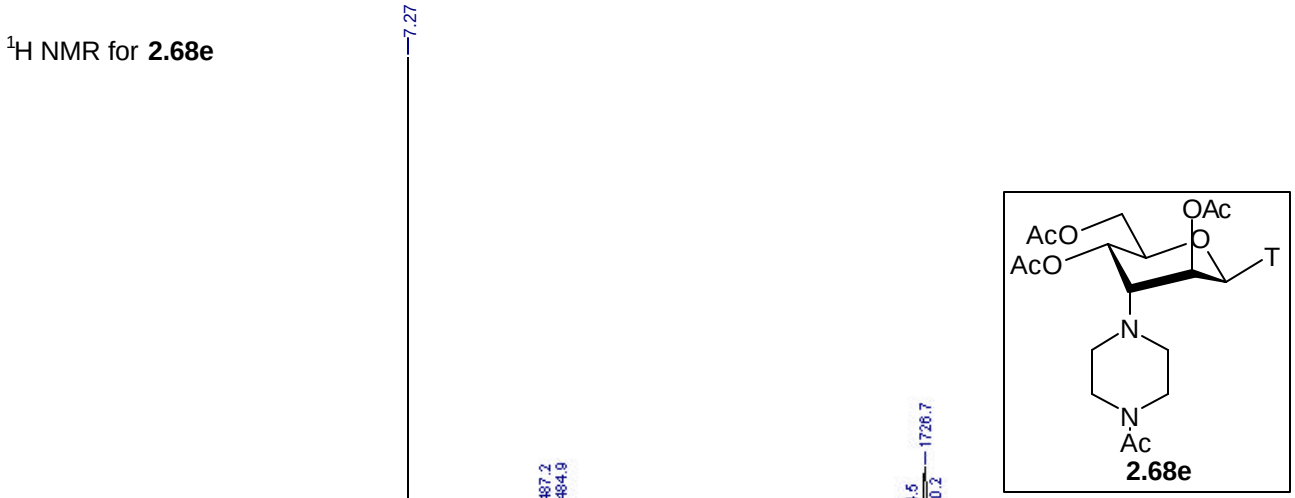
^{1}H NMR for **2.68d**

^{13}C & DEPT NMR for **2.68d**

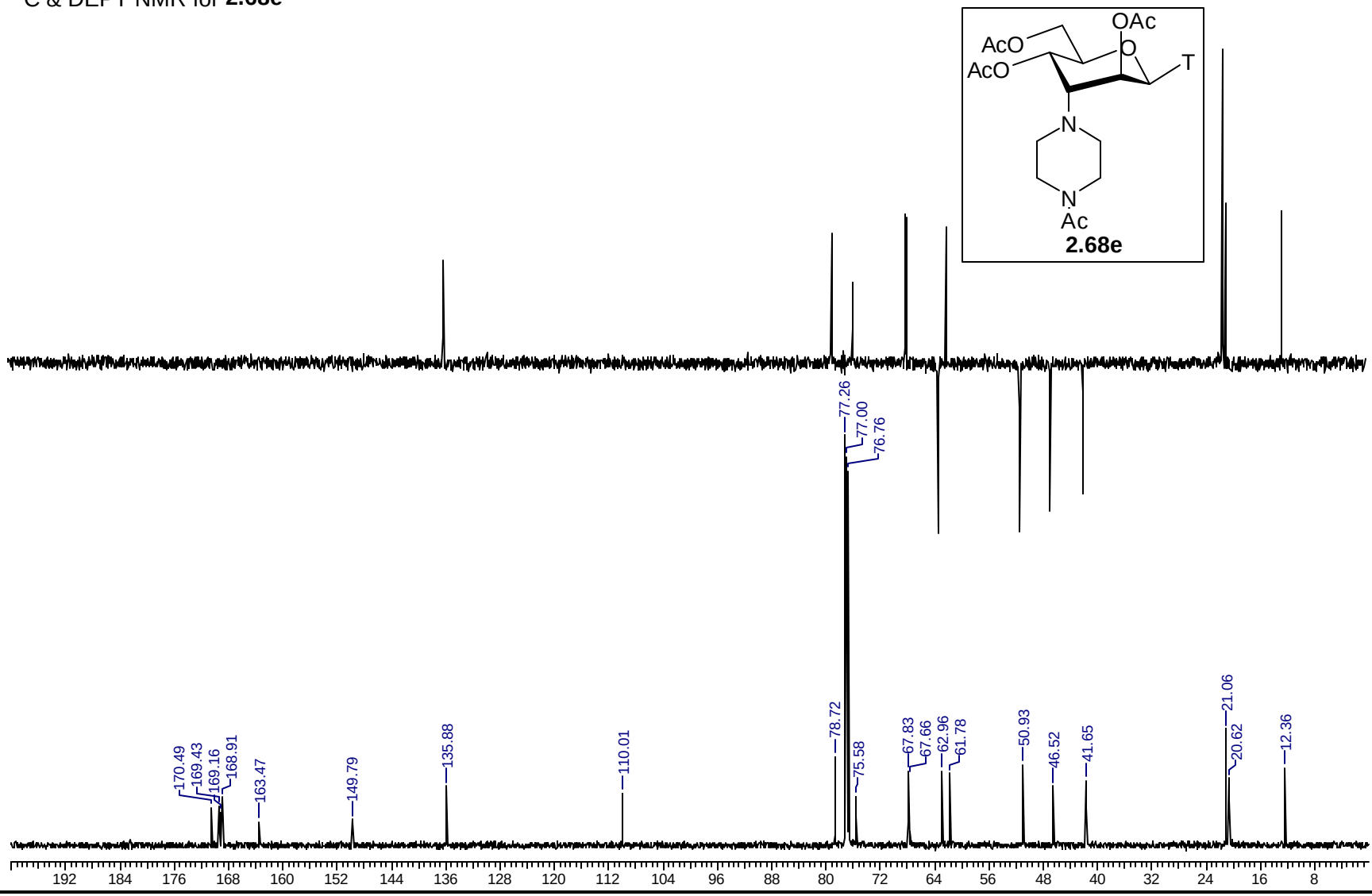




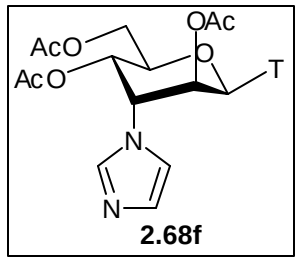
^{1}H NMR for **2.68e**



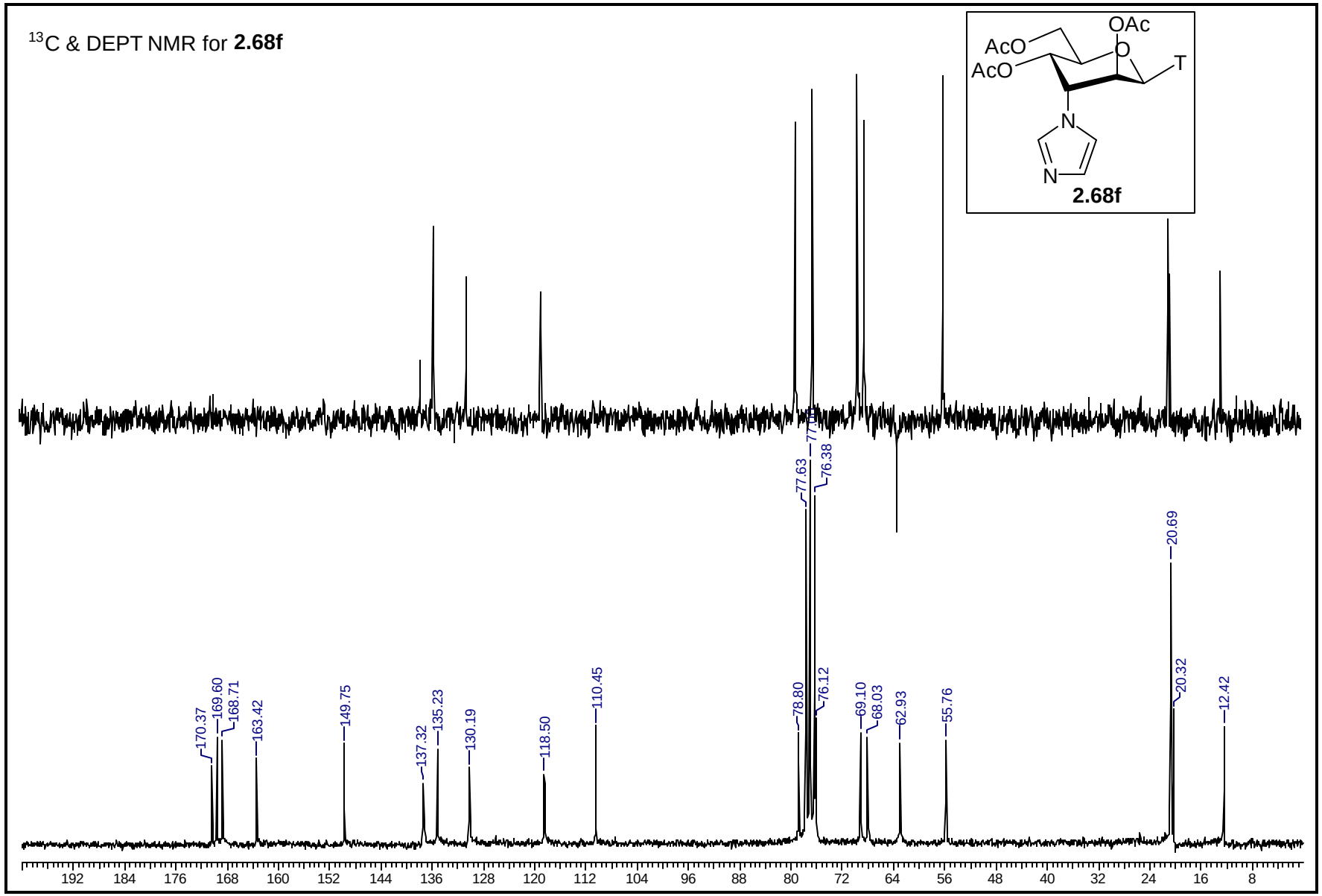
^{13}C & DEPT NMR for **2.68e**

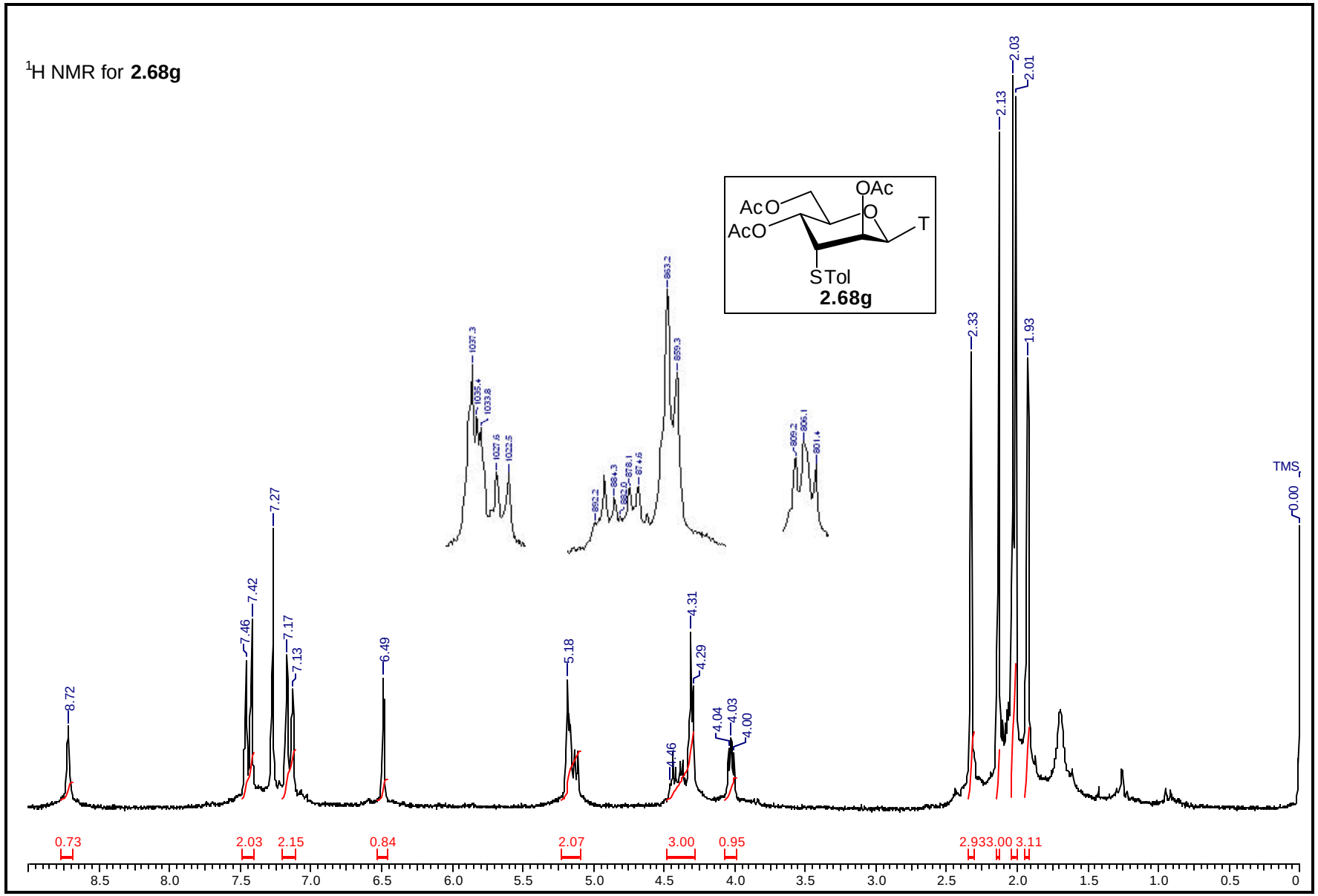


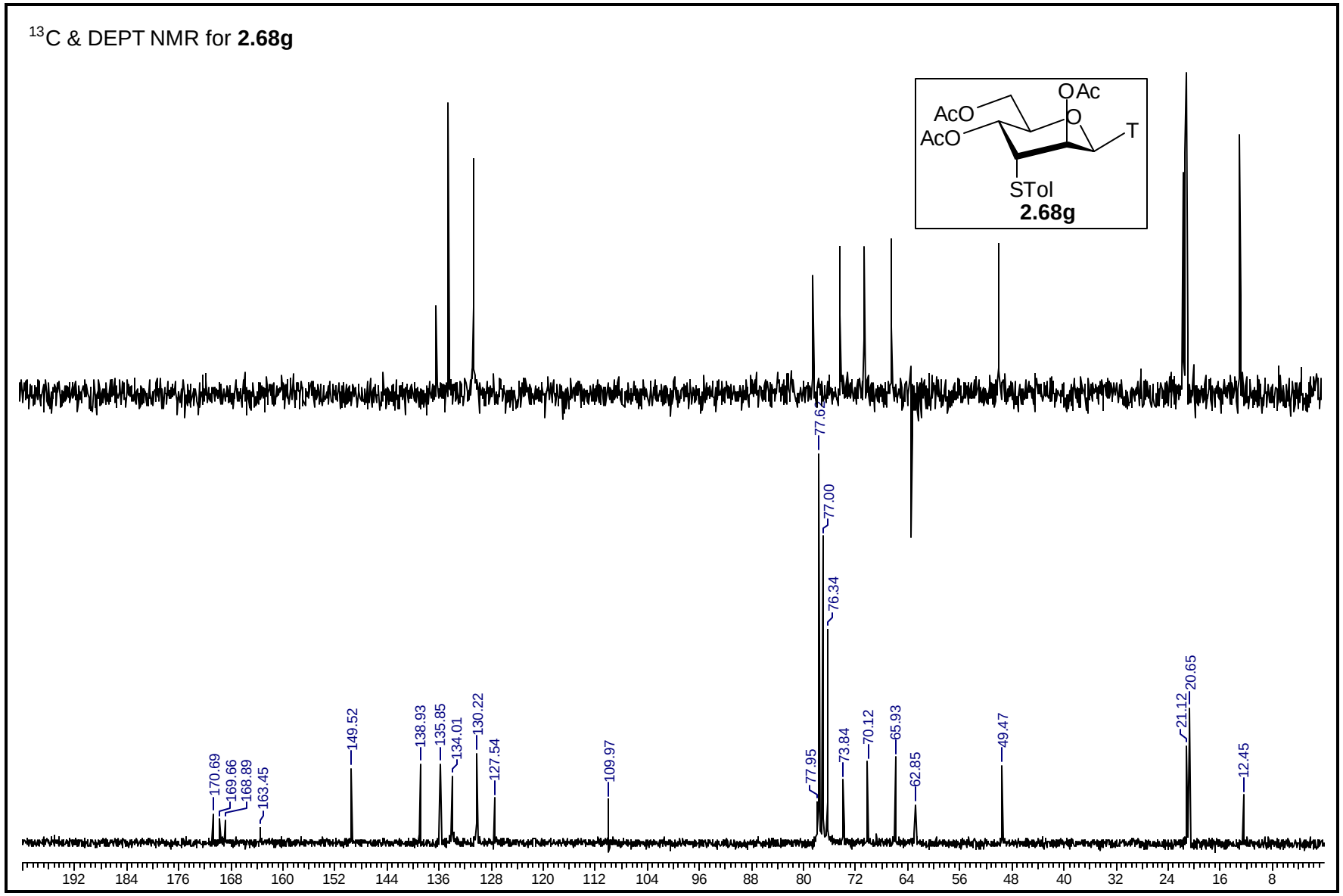
^{1}H NMR for **2.68f**

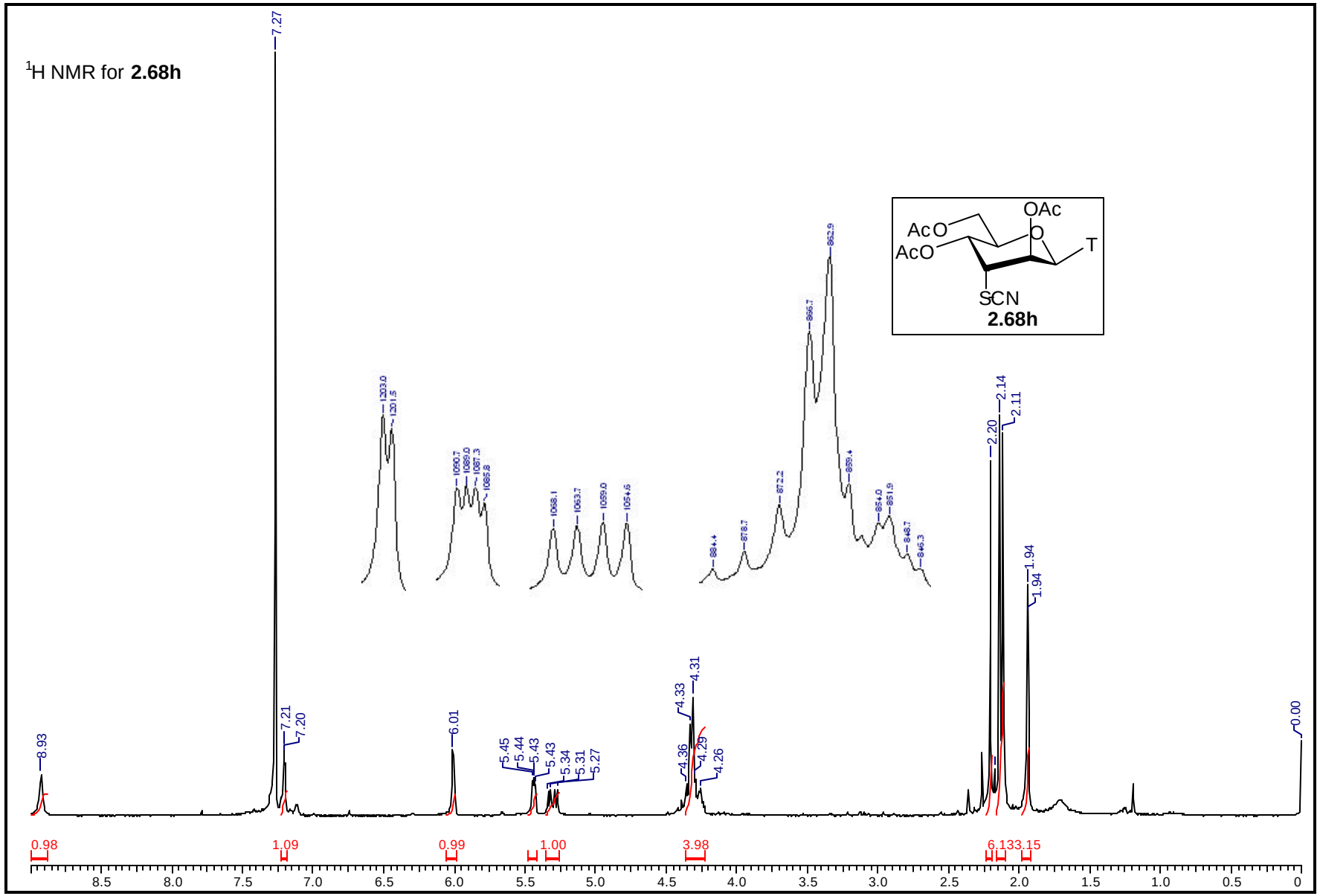


2.68f

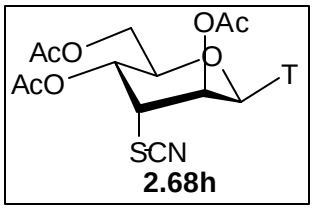

13C & DEPT NMR for 2.68f
OAc
AcO
AcO
O
T
N
N
2.68f
170.37
169.60
168.71
163.42
149.75
137.32
135.23
130.19
118.50
110.45
77.63
77.12
76.38
78.80
76.12
69.10
68.03
62.93
55.76
20.69
20.32
12.42
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8

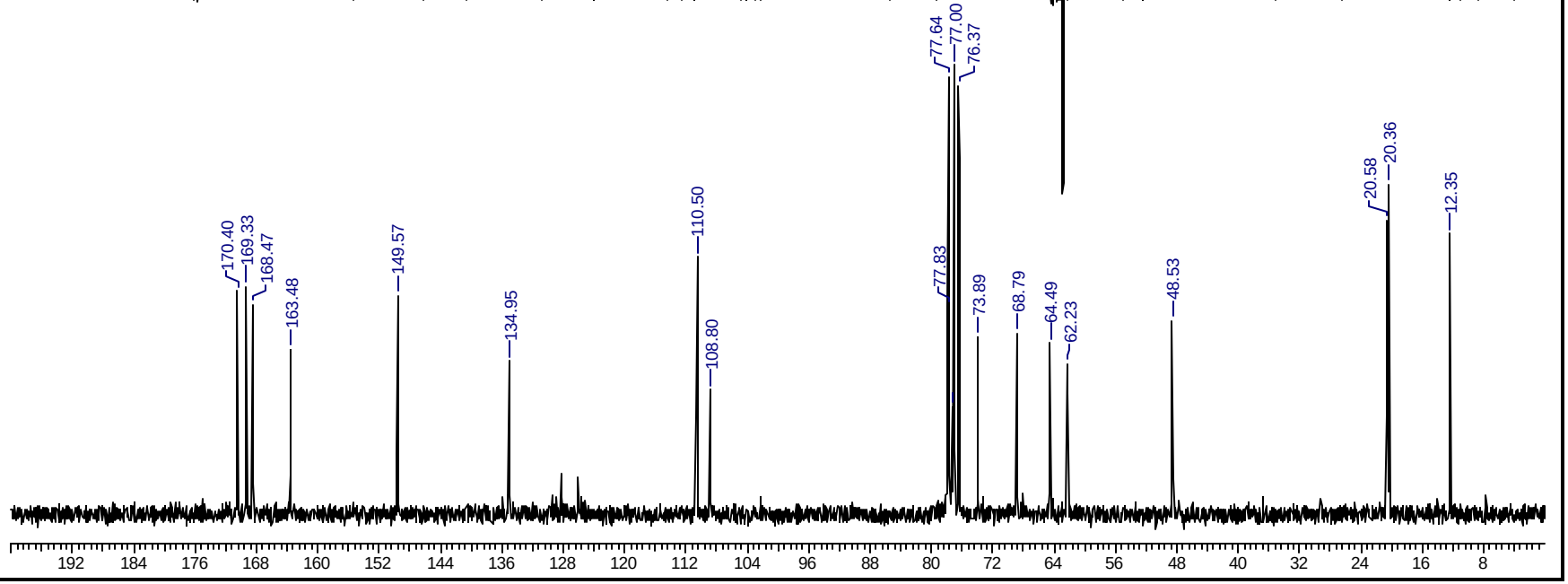

1H NMR for 2.68g
AcO
AcO
OAc
O
T
STol
2.68g
8.72
7.46
7.42
7.27
7.17
7.13
6.49
5.18
4.46
4.31
4.29
4.04
4.03
4.00
2.33
2.13
2.03
2.01
1.93
TMS
0.00
0.73
2.03
2.15
0.84
2.07
3.00
0.95
2.93
3.00
3.11


13C & DEPT NMR for 2.68g
OAc
AcO
AcO
O
T
STol
2.68g
77.62
77.00
76.34
170.69
169.66
168.89
163.45
149.52
138.93
135.85
134.01
130.22
127.54
109.97
77.95
73.84
70.12
65.93
62.85
49.47
21.12
20.65
12.45
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8

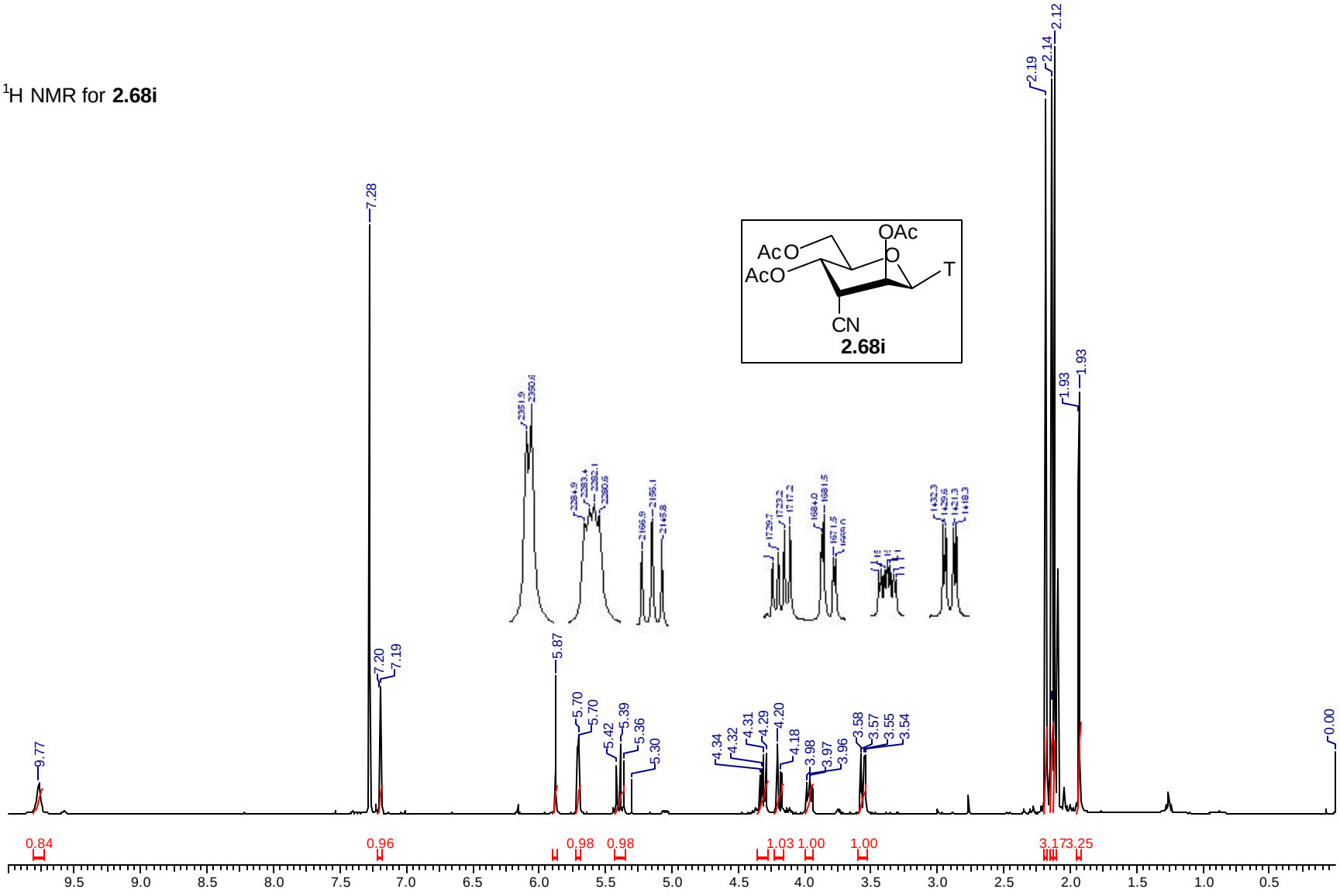

1H NMR for 2.68h
AcO
AcO
OAc
O
T
SCN
2.68h
8.93
7.27
7.21
7.20
6.01
5.45
5.44
5.43
5.43
5.34
5.31
5.27
4.33
4.31
4.36
4.29
4.26
2.20
2.14
2.11
1.94
1.94
0.00
0.98
1.09
0.99
1.00
3.98
6.13
3.15
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

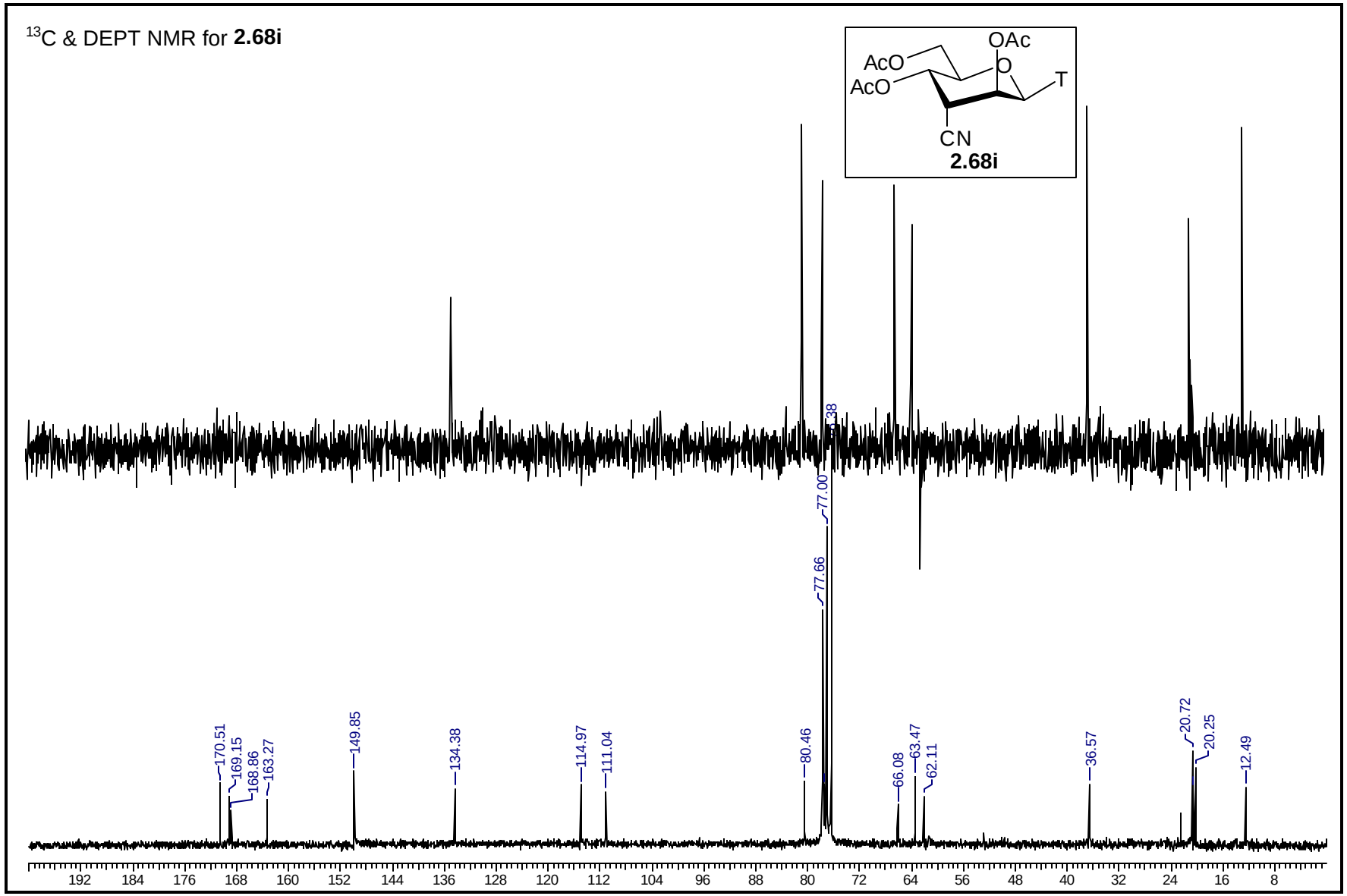
^{13}C & DEPT NMR for **2.68h**

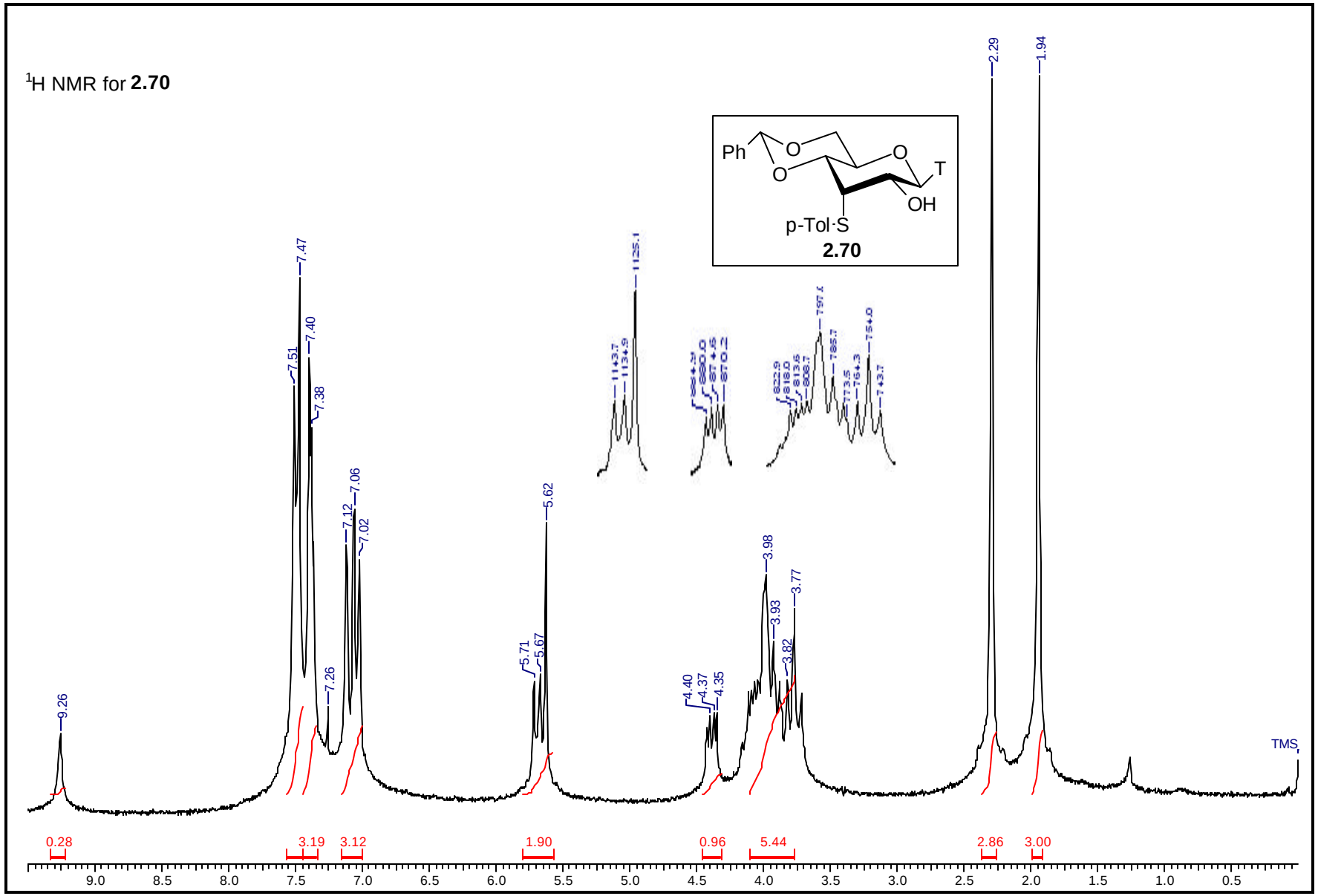


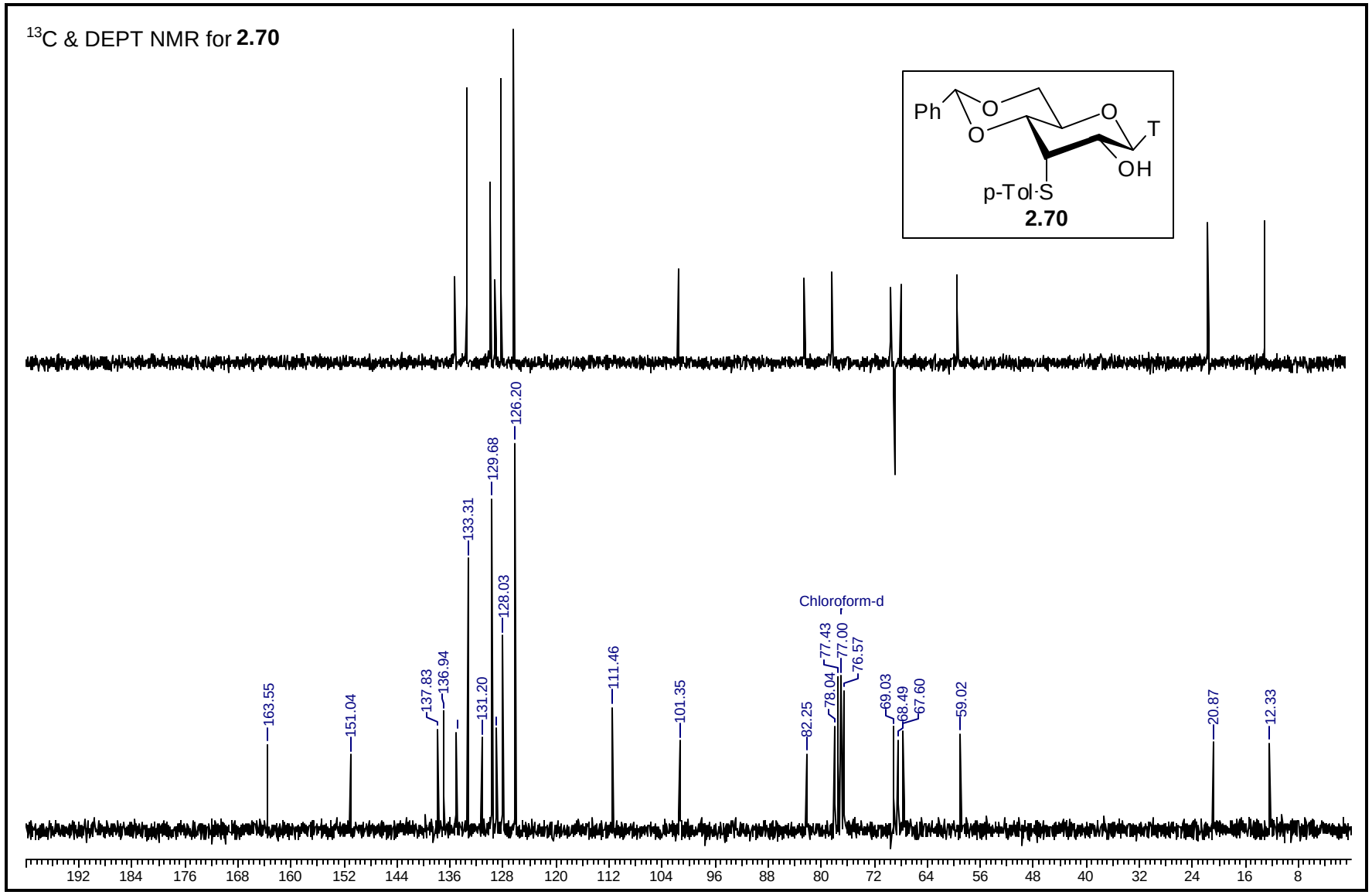


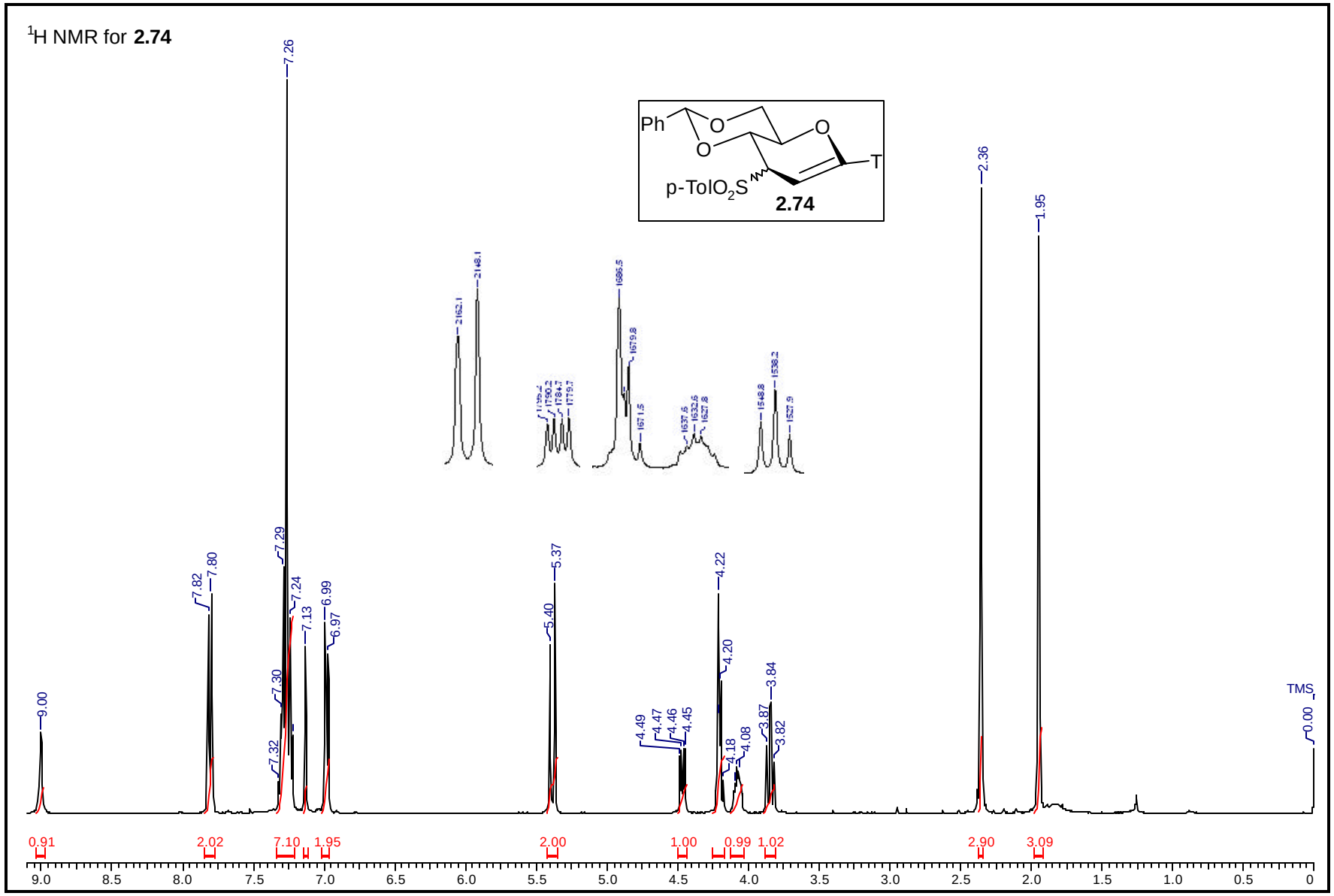
^{1}H NMR for **2.68i**



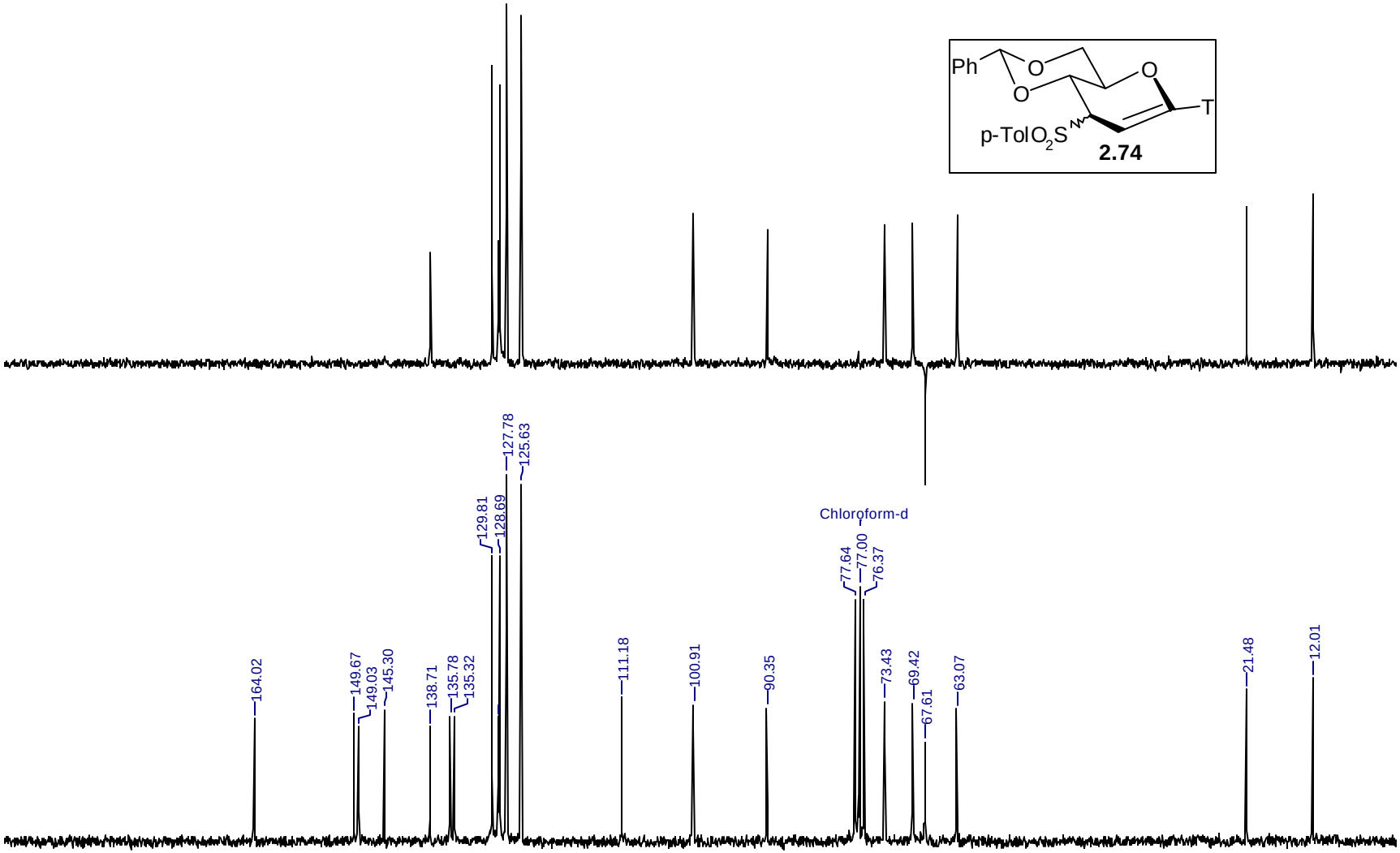

13C & DEPT NMR for 2.68i
OAc
AcO
AcO
O
T
CN
2.68i
170.51
169.15
168.86
163.27
149.85
134.38
114.97
111.04
80.46
77.66
77.00
76.38
66.08
63.47
62.11
36.57
20.72
20.25
12.49
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8

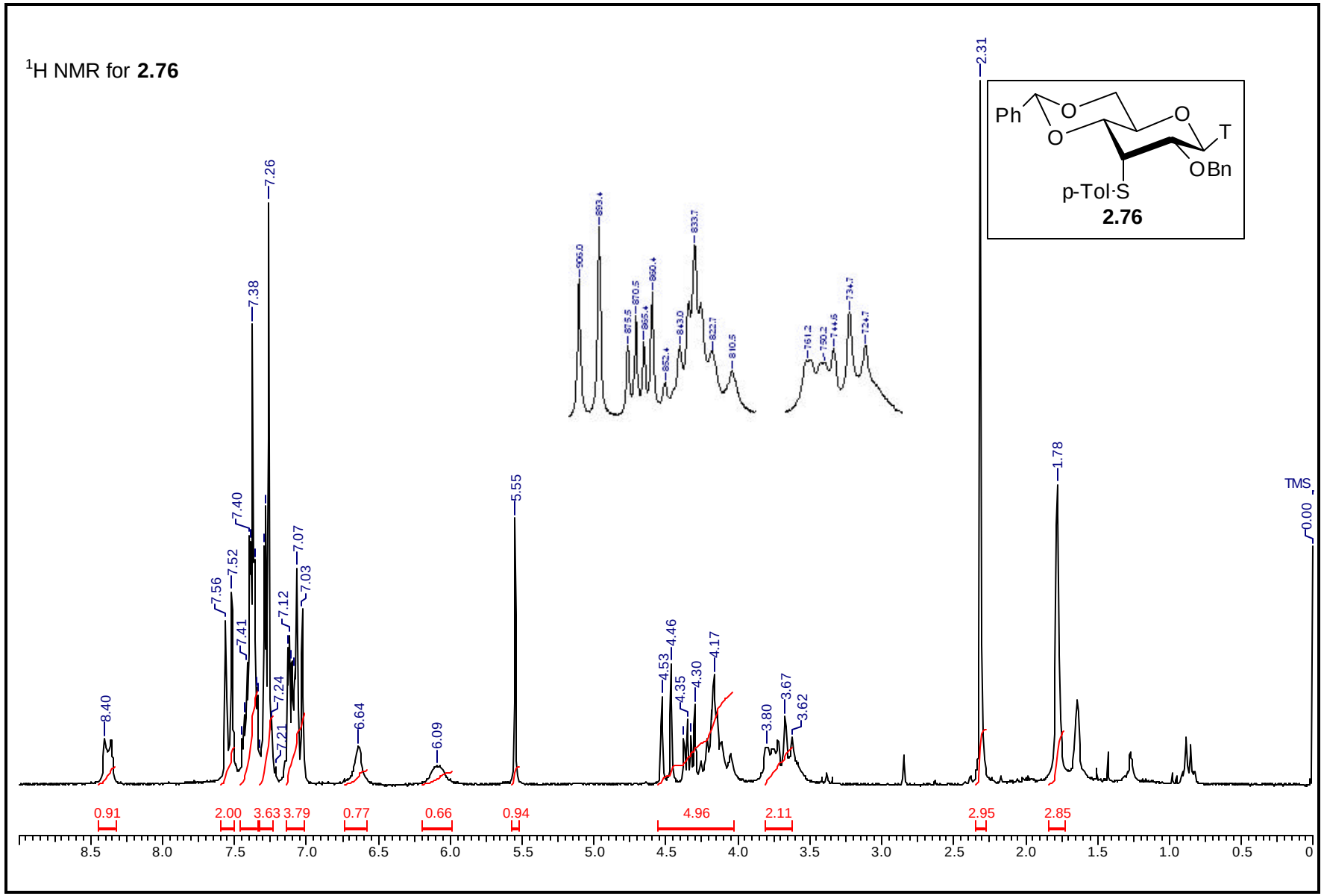

1H NMR for 2.70
Ph
O
O
O
T
OH
p-Tol·S
2.70
9.26
7.51
7.47
7.40
7.38
7.26
7.12
7.06
7.02
5.71
5.67
5.62
4.40
4.37
4.35
3.98
3.93
3.82
3.77
2.29
1.94
TMS
0.28
3.19
3.12
1.90
0.96
5.44
2.86
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

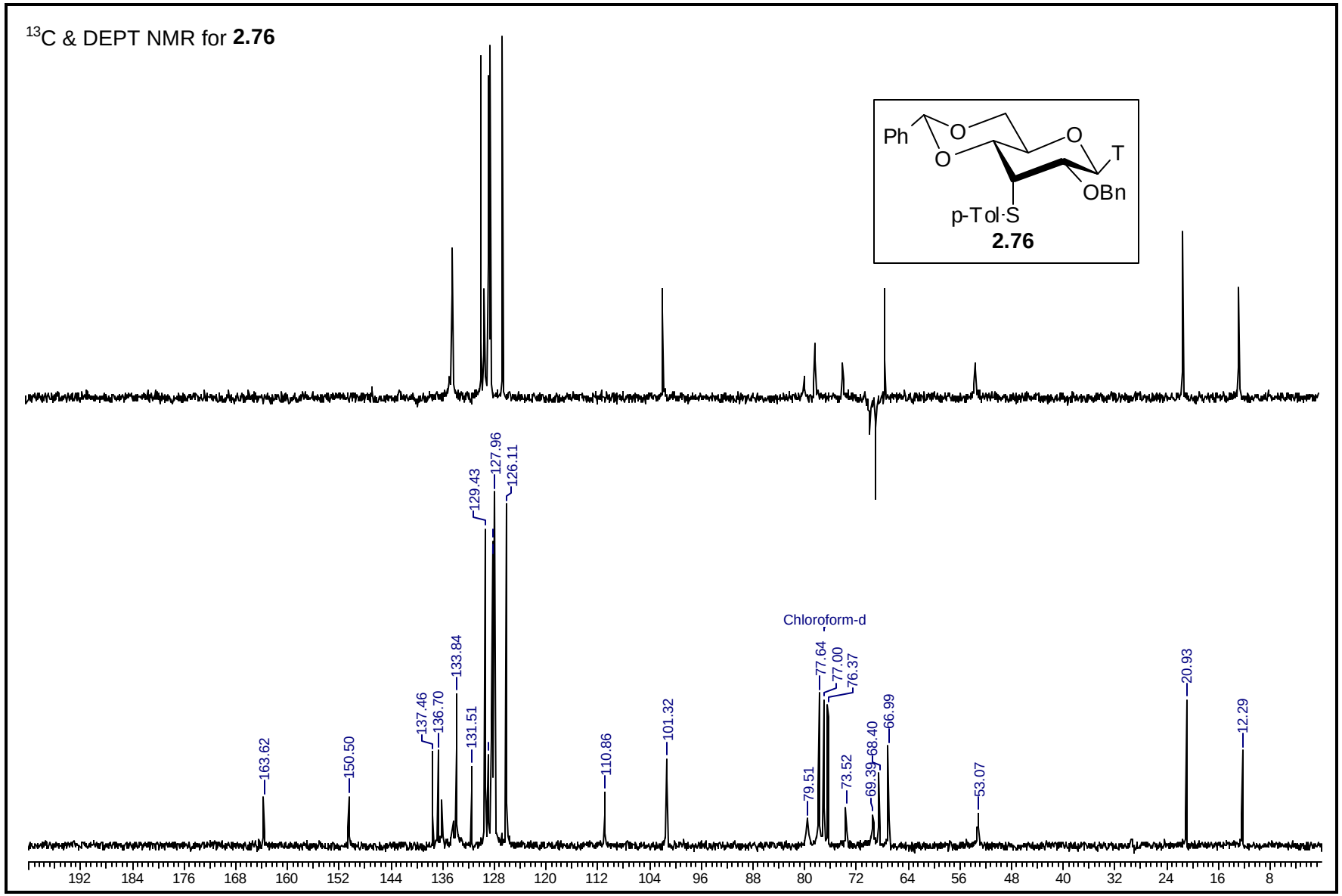

13C & DEPT NMR for 2.70
Ph
O
O
O
T
OH
p-Tol·S
2.70
126.20
129.68
133.31
128.03
Chloroform-d
77.43
77.00
76.57
163.55
151.04
137.83
136.94
131.20
111.46
101.35
82.25
78.04
69.03
68.49
67.60
59.02
20.87
12.33
192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8

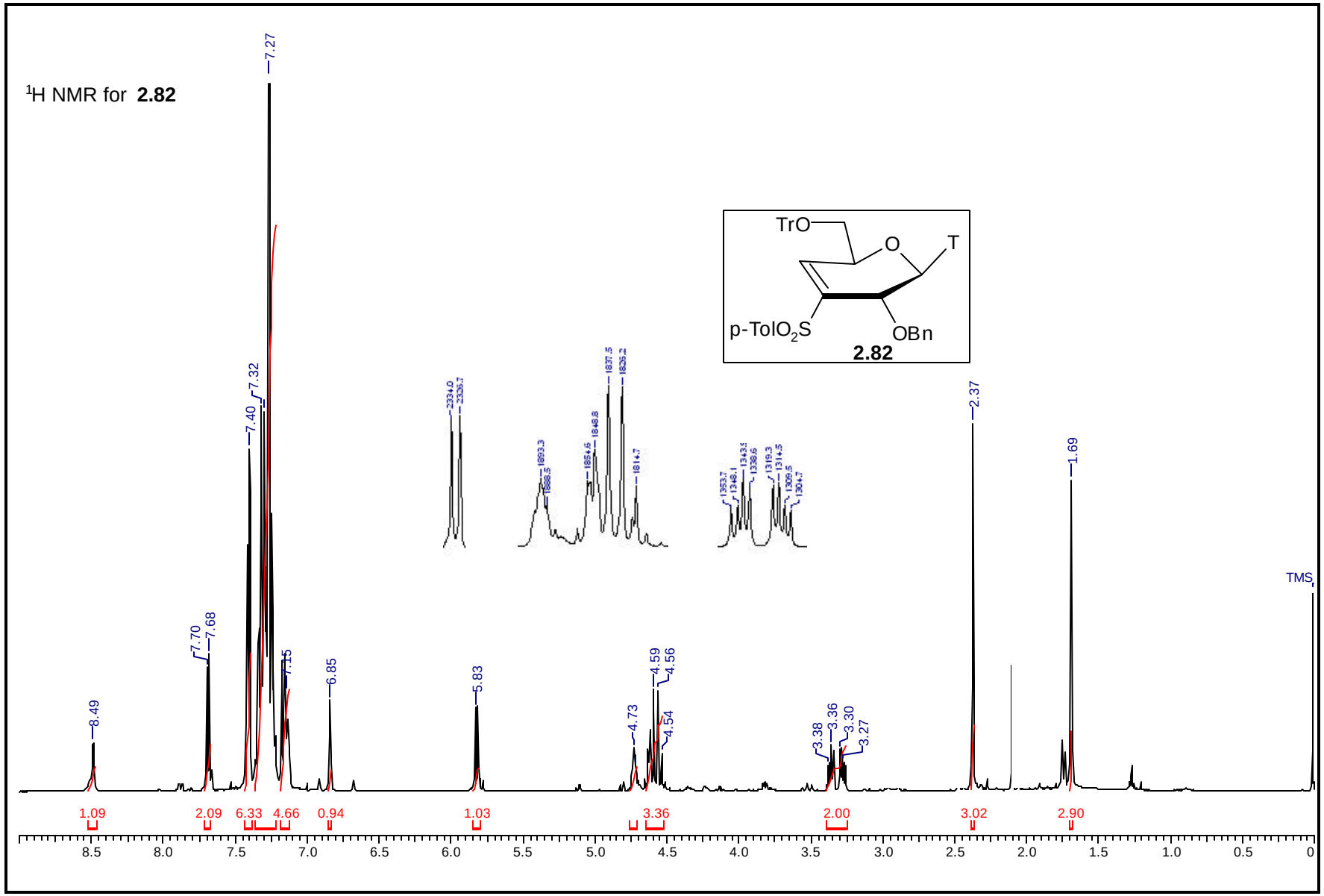

1H NMR for 2.74
Ph
O
O
O
T
p-TolO2S
2.74
9.00
7.82
7.80
7.32
7.30
7.29
7.26
7.24
7.13
6.99
6.97
5.40
5.37
4.49
4.47
4.46
4.45
4.22
4.20
4.18
4.08
3.87
3.84
3.82
2.36
1.95
TMS
0.00
0.91
2.02
7.10
1.95
2.00
1.00
0.99
1.02
2.90
3.09
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

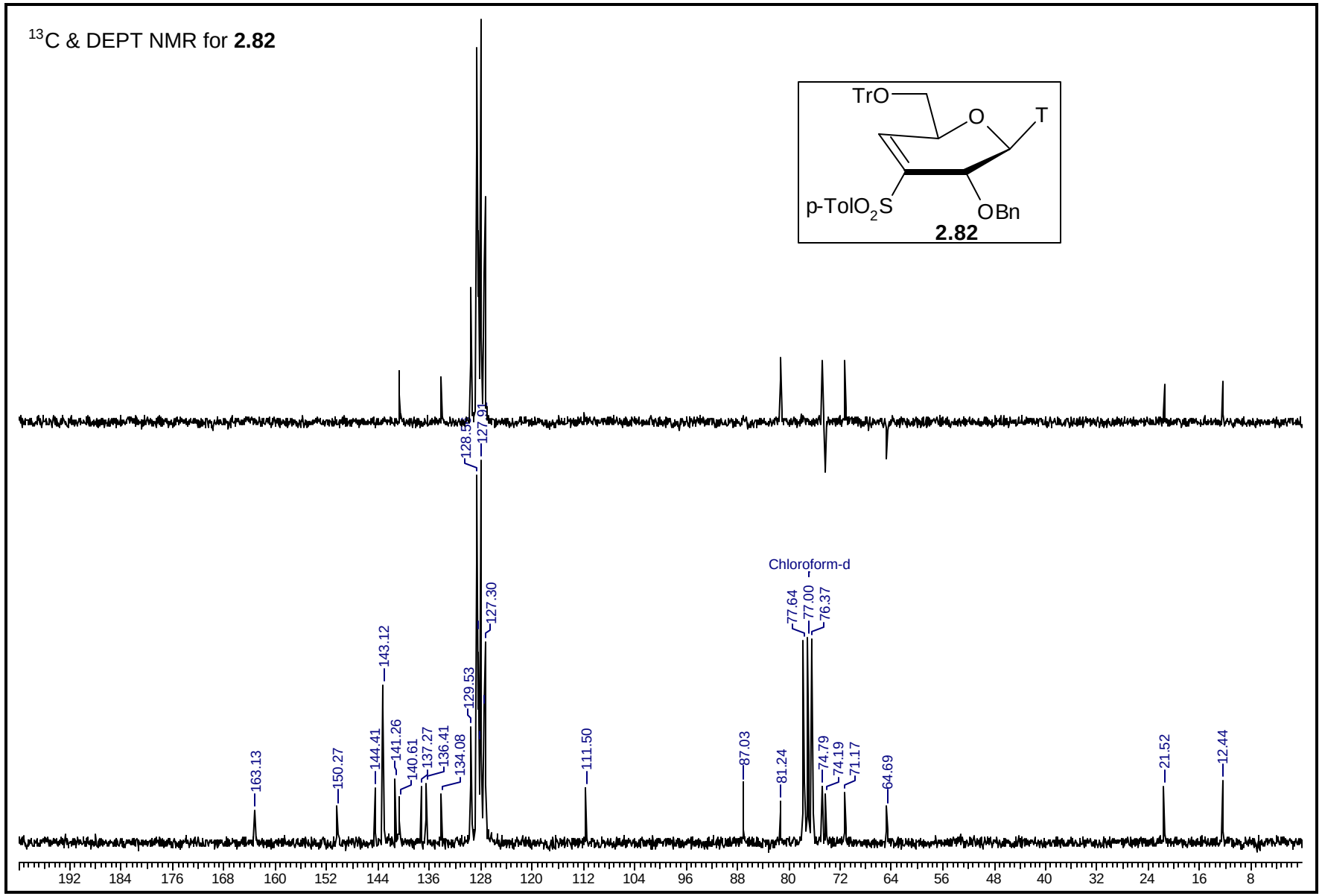
^{13}C & DEPT NMR for **2.74**

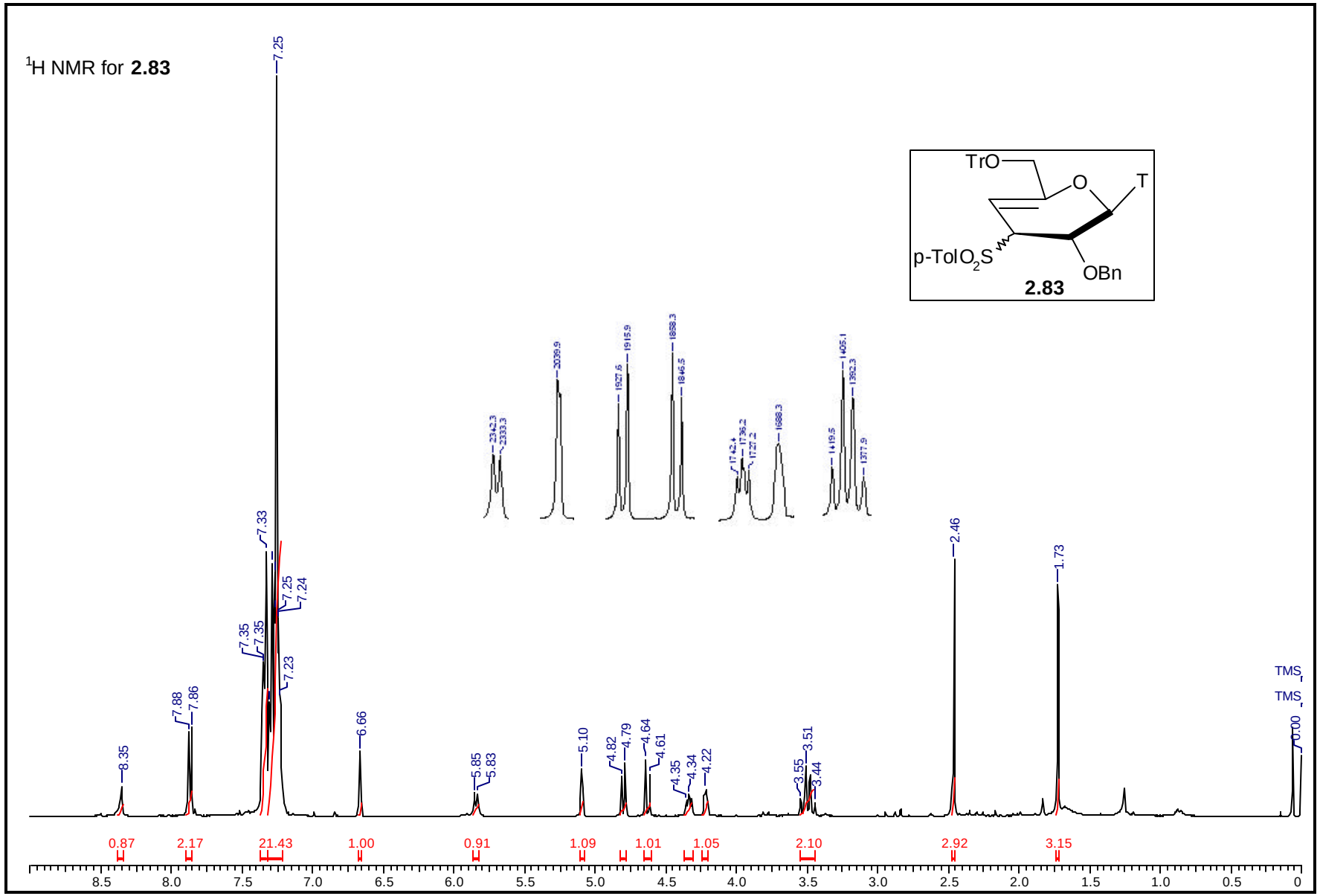


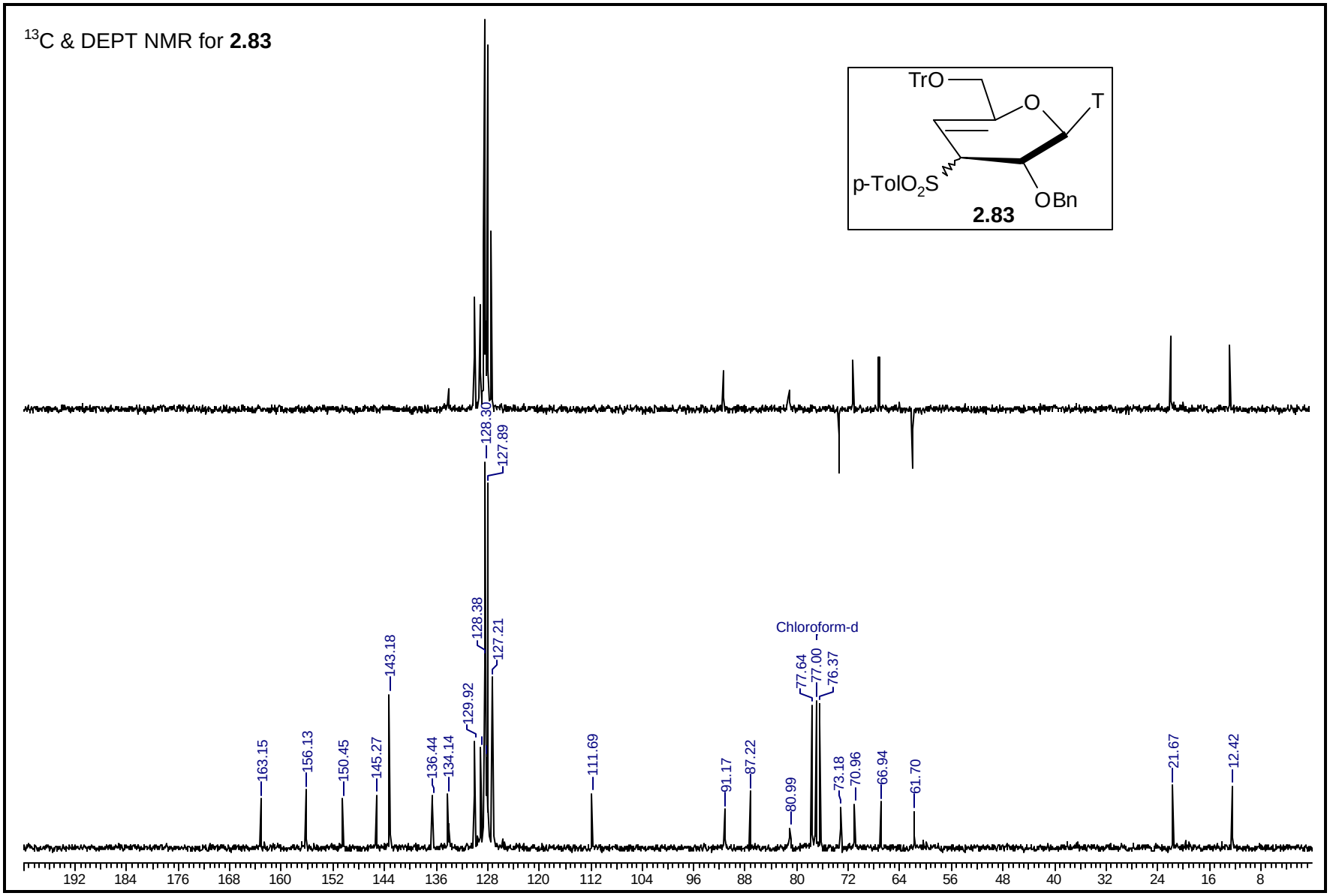

1H NMR for 2.76
Ph
O
O
O
T
OBn
p-Tol·S
2.76
2.31
1.78
TMS
0.00
8.40
7.56
7.52
7.41
7.40
7.38
7.26
7.24
7.21
7.12
7.07
7.03
6.64
6.09
5.55
4.53
4.46
4.35
4.30
4.17
3.80
3.67
3.62
0.91
2.00
3.63
3.79
0.77
0.66
0.94
4.96
2.11
2.95
2.85
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0


13C & DEPT NMR for 2.76
Ph
O
O
O
T
OBn
p-Tol·S
2.76
163.62
150.50
137.46
136.70
133.84
131.51
129.43
127.96
126.11
110.86
101.32
Chloroform-d
79.51
77.64
77.00
76.37
73.52
69.39
68.40
66.99
53.07
20.93
12.29
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8


^{1}H NMR for **2.82**
TrO
O
T
p-TolO$_2$S
OBn
2.82
7.27
7.40
7.32
8.49
7.70
7.68
7.15
6.85
5.83
4.73
4.59
4.56
4.54
3.38
3.36
3.30
3.27
2.37
1.69
TMS
1.09
2.09
6.33
4.66
0.94
1.03
3.36
2.00
3.02
2.90
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0


^{13}C & DEPT NMR for **2.82**
TrO
O
T
p-TolO$_2$S
OBn
2.82
128.55
127.91
Chloroform-d
77.64
77.00
76.37
127.30
143.12
129.53
163.13
150.27
144.41
141.26
140.61
137.27
136.41
134.08
111.50
87.03
81.24
74.79
74.19
71.17
64.69
21.52
12.44
192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8


^{1}H NMR for **2.83**
TrO
O
T
p-TolO$_2$S
OBn
2.83
8.35
7.88
7.86
7.35
7.35
7.33
7.25
7.25
7.24
7.23
6.66
5.85
5.83
5.10
4.82
4.79
4.64
4.61
4.35
4.34
4.22
3.55
3.51
3.44
2.46
1.73
TMS
TMS
0.00
0.87
2.17
21.43
1.00
0.91
1.09
1.01
1.05
2.10
2.92
3.15
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0


13C & DEPT NMR for 2.83
TrO
O
T
p-TolO2S
OBn
2.83
128.30
127.89
128.38
127.21
Chloroform-d
77.64
77.00
76.37
163.15
156.13
150.45
145.27
143.18
136.44
134.14
129.92
111.69
91.17
87.22
80.99
73.18
70.96
66.94
61.70
21.67
12.42
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8