VINYL SULFONE-MODIFIED PYRANOSES AND FURANOSES: SYNTHESIS AND MICHAEL ADDITION REACTIONS

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Ph. D. Thesis **Aditya K. Sanki** **October-2002**

VINYL SULFONE-MODIFIED PYRANOSES AND FURANOSES: SYNTHESIS AND MICHAEL ADDITION REACTIONS

Thesis
submitted to the
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for the degree of
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IN CHEMISTRY

by

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October-2002

Dedicated to my parents

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled **"Vinyl Sulfone-modified Pyranoses and Furanoses: Synthesis and Michael Addition Reactions"** submitted by **Mr. Aditya K. Sanki** was carried out under my supervision at the National Chemical Laboratory, Pune. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

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Dr. T. Pathak
(Research Guide)

DECLARATION

I hereby declare that the thesis entitled **"Vinyl Sulfone-modified Pyranoses and Furanoses: Synthesis and Michael Addition Reactions"** submitted for Ph.D. degree, to the University of Pune has not been submitted by me for any degree to any other University.

Date:
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----Aditya K. Sanki

CONTENTS

CHAPTER 1

A Review on Vinyl Sulfone-modified Carbohydrates and Nucleosides 1-27

CHAPTER 2

Synthesis of Vinyl Sulfone-modified Carbohydrates 28-114

CHAPTER 3

Diastereoselective Addition of Planar Heterocycles to Vinyl Sulfone-modified Carbohydrates 115-170

CHAPTER 4

Diastereoselective Addition of Carbon Nucleophiles to Vinyl Sulfone-modified Carbohydrates 171-213

Abbreviations

Ac	:Acetyl
Ac_2O	:Acetic anhydride
AcOH	:Acetic acid
$A^{(Bz)}{}_2$	:Dibenzoyl adenine
A^{Bz}	:Benzoyl adenine
Anhydr.	:Anhydrous
Ar	:*p*-Tolyl
Bn	:Benzyl
Bu	:n-Butyl
Bz	:Benzoyl
^{13}C	:Carbon-13 isotope
Cald	:Calculated
DCM (or, CH_2Cl_2)	:Dichloromethane
DBU	:1,8-Diazabicyclo[5,4,0]undec-7-ene
DMF	:Dimethylformamide
Et	:Ethyl
EtOAc	:Ethyl acetate
g	:Gram
H	:Hour
^{1}H	:Proton-1 isotope
Hz	:Hertz
IR	:Infra red
Me	:Methyl
MeOH	:Methanol
mL	:Milliliter
mmol	:Millimole
Ms	:Mesyl
MMPP	:Magnesium monoperoxy perphthalate
MMTr	:Monomethoxytrityl
MHz	:Mega Hertz
Mp	:Melting point
pet ether	:Petroleum ether

ppm	:Parts per million
PNB	:*p*-Nitrobenzoyl
Ph	:Phenyl
Py	:Pyridine
TBDMS	:*t*-Butyldimethylsilyl
p-TSA	:*p*-Toluenesulfonic Acid
THF	:Tetrahydrofuran
T	:Thymine
tlc	:Thin Layer Chromatography
TMG	:1,1,3,3-Tetramethylguanidine
p-Tol	:*p*-Methyl tolyl
Tr	:Trityl
Ts	:Tosyl
U	:Uracil

CHAPTER 1

A Review on Vinyl Sulfone-modified Carbohydrates and Nucleosides

Amongst various functionalized sulfones, α,β-unsaturated- or vinyl sulfones have now become generally accepted as useful intermediates in organic synthesis. The vinyl sulfones serve efficiently as both Michael acceptors and a 2π partner in cycloaddition reactions. Carbohydrates, on the other hand, are used extensively as chiral building blocks for the synthesis of various complex molecules. The preliminary requirement of such a synthesis is the functionalization of the sugar molecules at the monosaccharide level.

Carbohydrates are normally modified *via* their sulfonates, epoxides, olefins, ketones or olefinic derivatives. Due to the high reactivities of vinyl sulfones towards a wide variety of nucleophiles, vinyl sulfone-modified carbohydrates could be used to generate an array of modified monosaccharides. Vinyl sulfone-modified carbohydrates have the potential for utilization in organic synthesis because (a) almost all carbohydrates, either in pyranose or furanose forms, could be converted to their vinyl sulfone derivatives very easily -the first step being the simple nucleophilic displacements of sulfonates or regioselective opening of epoxides by alkyl or aryl mercaptans at various positions, (b) sulfone chemistry has been exploited extensively over decades and its compatibility with a wide variety of simple and complex molecules is well established and (c) after using the vinyl sulfone moiety as a tool for functionalization, whenever necessary, the sulfone group could be removed oxidatively to generate a carbonyl group, reductively to afford a methylene group or eliminated to generate a double bond.

Although vinyl sulfones have been used effectively in synthetic transformations, vinyl sulfone-modified carbohydrates are yet to be used extensively in synthetic organic chemistry. The methodologies discussed above are also applicable to the modification of the carbohydrate moieties of nucleosides. However, in the case of nucleosides, vinyl sulfone group may have the potential to be used for biological reactions. This chapter highlights this less studied area of the synthesis and Michael addition reactions of various nucleophiles to vinyl sulfone-modified carbohydrates.

CHAPTER 2

Syntheses of Vinyl Sulfone-modified Carbohydrates

Synthesis of methyl 2,3-dideoxy-4,6-*O*-(phenylmethylene)-3-*C*-phenyl sulfonyl-α-D-*erythro*-hex-2-enopyranoside **6** and the corresponding β-anomer **7** have been reported in the literature. However, the synthetic routes are lengthy and each anomer requires separate starting material for its synthesis.

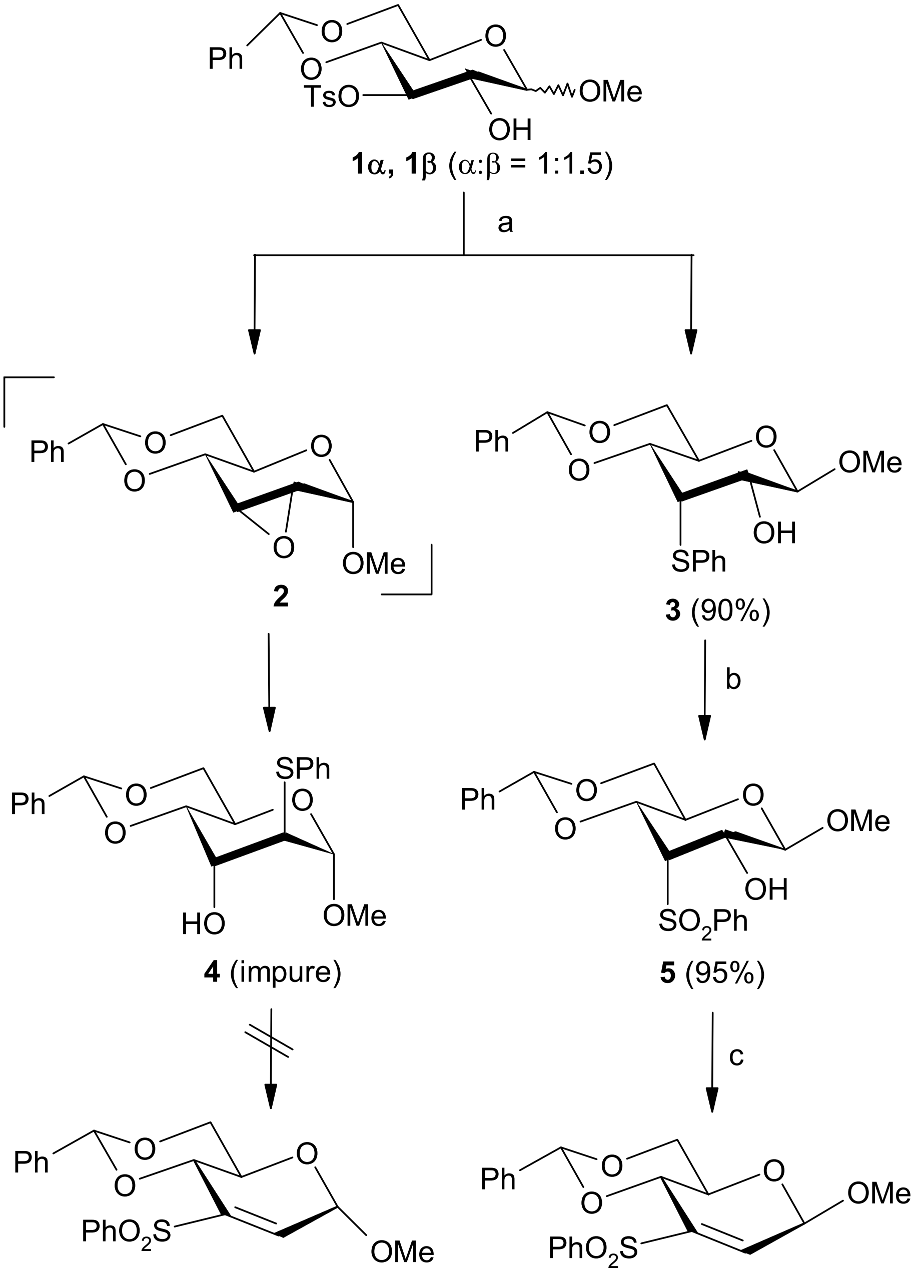
In order to study the diastereoselective addition of nucleophiles systematically, we required relatively large amount of anomerically pure **6** and **7**. We, therefore, decided to study the feasibility of an alternative sequence of reactions using a common intermediate for accessing both α- and β-vinyl sulfone derivatives. Synthesis was initiated by reacting the known tosylates **1α** and **1β** separately with thiophenol. The β-anomer **1β** produced the expected product **3**. Compound **3** was oxidized with MMPP (magnesium monoperoxyphthalate). The sulfone **5** on mesylation afforded directly the required vinyl sulfone-derivative **7** in high overall yield. Interestingly, the α-anomer **1α**, under the same reaction conditions followed a different pathway to generate **4** *via* epoxide **2**. The required vinyl sulfone **6** was, therefore, not accessible through this route (**Scheme 2.1**).

In order to broaden the scope of the studies related to the vinyl sulfone-modified carbohydrates and also to gather specific information on the reaction patterns of endocyclic mono-vinyl sulfones derived from pentofuranoses, we needed to develop a practical methodology for the synthesis of anomerically pure methyl 5-*O*-benzyl-2,3-dideoxy-3-*C*-tolylsulfonyl-α-D-*erythro*-pent-2-enofuranoside **14** and methyl 5-*O*-benzyl-2,3-dideoxy-3-*C*-tolylsulfonyl-β-D-*erythro*-pent-2-enofuranoside **15**.

A retrosynthetic analysis necessitated the nucleophilic displacement of the *p*-tolylsulfonyl group of the easily accessible starting material 5-*O*-benzyl- 1,2-*O*-isopropylidene-3-*O*-tosyl-α-D-*xylo*furanose **8**. Compound **8** was reacted with *p*-thiocresol at 120 °C to produce the *ribo*-analog **9** in 59% yield. Compound **9** on methanolysis produced an anomeric mixture of **10** and **11** in 78% yield. The anomers were separated at this stage and oxidized separately to the corresponding sulfone derivatives **12** and **13**, respectively. The sulfones **12** and **13** on treatment with mesyl chloride in pyridine afforded smoothly the desired vinyl sulfone-modified carbohydrates **14** and **15** in good to excellent yields. Although at this stage the less efficient conversion of **8** to **9** was acceptable, the major drawback of this methodology was the unacceptable ratio of **10** and **11** (1:10) in the mixture. The low ratio of α-anomer **10**, present in the mixture contributed to the poor overall yield of the vinyl sulfone derivative **14** (**Scheme 2.2**).

However, it was possible to synthesize a *xylo*-derivative **20** from 5-*O*-benzyl-1,2-*O*-isopropylidene-3-*O*-mesyl-α-D-*ribo*furanose **19** in 79% yield. Compound **20** on methanolysis produced the mixture of anomers **21** and **22** in a ratio 1.5:1 (**Scheme 2.3**). It was possible to access **14** and **15** *via* sulfones **23** and **24**. Although the ratio of formation of **21** and **22** was acceptable for the synthesis of both he anomers **14** and

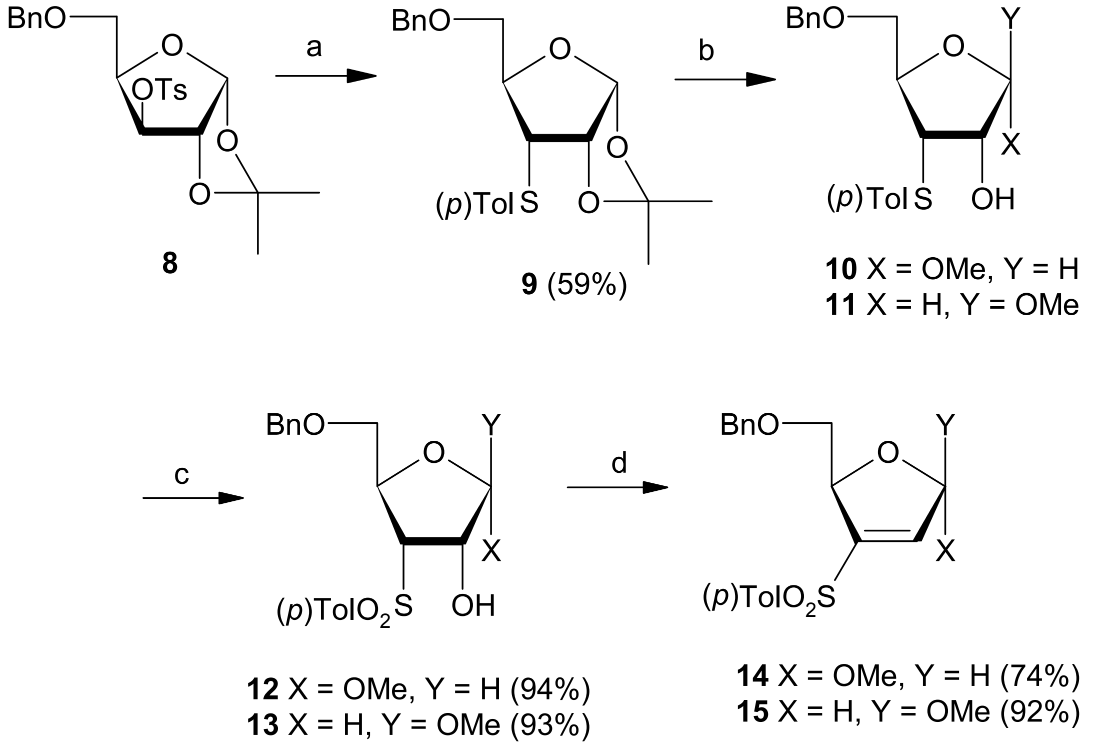
Scheme 2.1



Reagents and conditions: a. for **1**α: PhSH, NaOMe, DMF, 135-140 °C, 2.5-3 h; for **1**β: PhSH, NaOMe, DMF, 135-140 °C, 2 h; b. MMPP, MeOH, rt., 3 h; c. MsCl, Py., 0 °C-rt., 4 h.

15, the overall yield for each anomer again dropped due to the addition of two synthetic steps for converting **16** to the *ribo*-derivative **18** *via* a two-step oxidation-reduction process (**Scheme 2.3**).

Scheme 2.2



8

9 (59%)

10 X = OMe, Y = H
11 X = H, Y = OMe

12 X = OMe, Y = H (94%)
13 X = H, Y = OMe (93%)

14 X = OMe, Y = H (74%)
15 X = H, Y = OMe (92%)

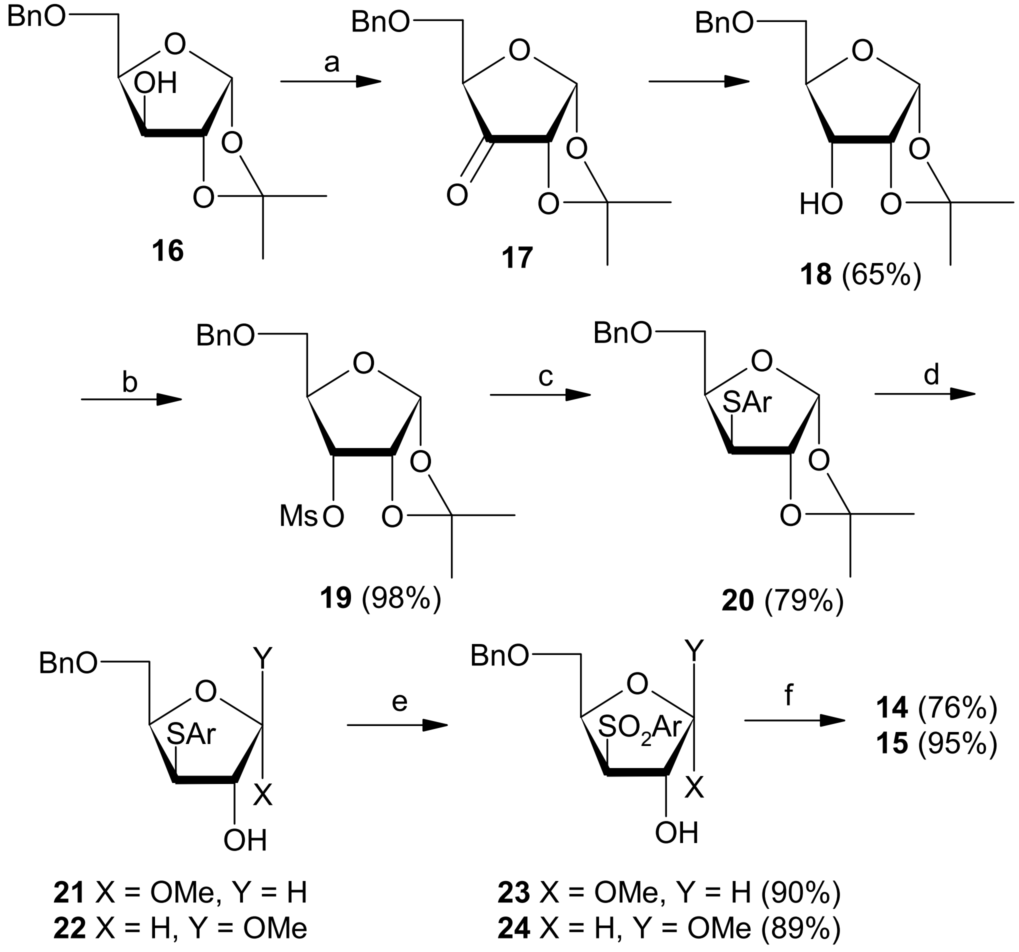
Reagents and conditions: a. *p*-Thiocresol, NaOMe, DMF, 115-120 °C, 3.5-4.0 h; b. MeOH, conc. H_2SO_4, 65-70 °C, 3 h, 78% (**10:11** = 1:10); c. MMPP, MeOH, rt., 3 h; d. MsCl, Py., 0 °C-rt., 18-24 h.

It was, however possible to circumvent all these shortcomings by first converting the *xylo*-derivative **8** to an anomeric mixture of **25** and **26** in a ratio 1:1.3 in high yield. Reactions of **25** and **26** with *p*-thiocresol proceeded smoothly to afford a mixture of 3-deoxy-3-*C*-*p*-tolylsulfide-D-*ribo*furanosides **10** and **11** in 94% yield. Compounds **10** and **11** were converted to **14** and **15** in the usual manner (**Scheme 2.4**).

Yet another route to **14** and **15** and related derivatives with trityl protecting group has also been studied. In this case anomerically pure epoxides **27/28** or **34/35** have been used as the starting materials. For the α-anomer, sulfides **29** and **30** with *arabino*-configurations were synthesized in good yields through regioselective opening of the *lyxo*-epoxides **27** and **28**, respectively by *p*-thiocresol. Compounds **29** and **30** were converted to the desired α-vinyl sulfones **14** and **33**, respectively in high yields by the sequential application of oxidation by MMPP, mesylation and base induced elimination reactions (**Scheme 2.5**).

The corresponding β-vinyl sulfones **15** and **38** were similarly synthesized in high yields *via xylo*-intermediates **22/24** and **36/37**, starting from the *ribo*-epoxides **34** and **35**, respectively (**Scheme 2.6**).

Scheme 2.3



16

17

18 (65%)

19 (98%)

20 (79%)

14 (76%)
15 (95%)

21 X = OMe, Y = H
22 X = H, Y = OMe

23 X = OMe, Y = H (90%)
24 X = H, Y = OMe (89%)

Ar = Tol(*p*)

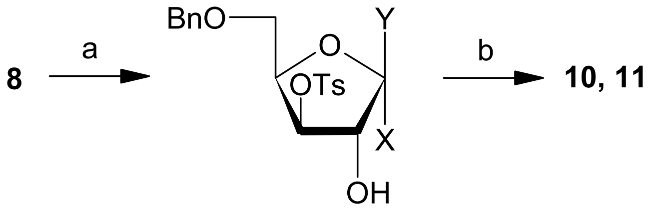
Reagents and conditions: a. (i) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -60 ^{o}C, 1.5 h; (ii) LAH, THF, 0 ^{o}C-rt., 3.5-4 h; b. MsCl, Py., 0 ^{o}C, 24 h; c. NaSTol(*p*), DMF, 145 ^{o}C, 3 h; d. MeOH, conc. H_2SO_4, 65-70 ^{o}C, 3 h, 89% (**21**:**22** = 1.5:1); e. MMPP, MeOH, rt., 3 h; f. MsCl, Py., 0 ^{o}C-rt., 24 h.

CHAPTER 3

Diastereoselective Addition of Planar Heterocycles to Vinyl Sulfone-modified Carbohydrates

Attempts are currently underway to synthesize novel nucleosides where the nucleobase is attached to the non-anomeric carbon atoms of the sugar moiety. One of the ways of synthesizing these molecules is to introduce the nucleobases directly at the non-anomeric carbon atom of carbohydrates; alternatively, heterocycles such as imidazoles can also be introduced and later converted to base-modified nucleosides *via* known synthetic manipulations.

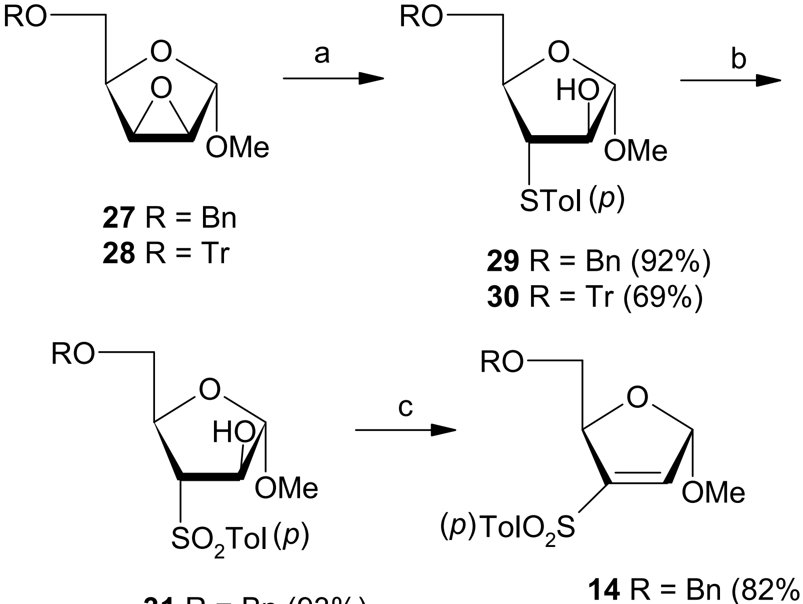
Scheme 2.4



25 X = OMe, Y = H
26 X = H, Y = OMe

Reagents and conditions: a. MeOH, conc. H_2SO_4, 65-70 °C, 3 h, 89% (**25**:**26** = 1:1.3); b. *p*-Thiocresol, NaOMe, DMF, 115-120 °C, 3.5-4.0 h, 94%.

Scheme 2.5



27 R = Bn
28 R = Tr

29 R = Bn (92%)
30 R = Tr (69%)

31 R = Bn (93%)
32 R = Tr (81%)

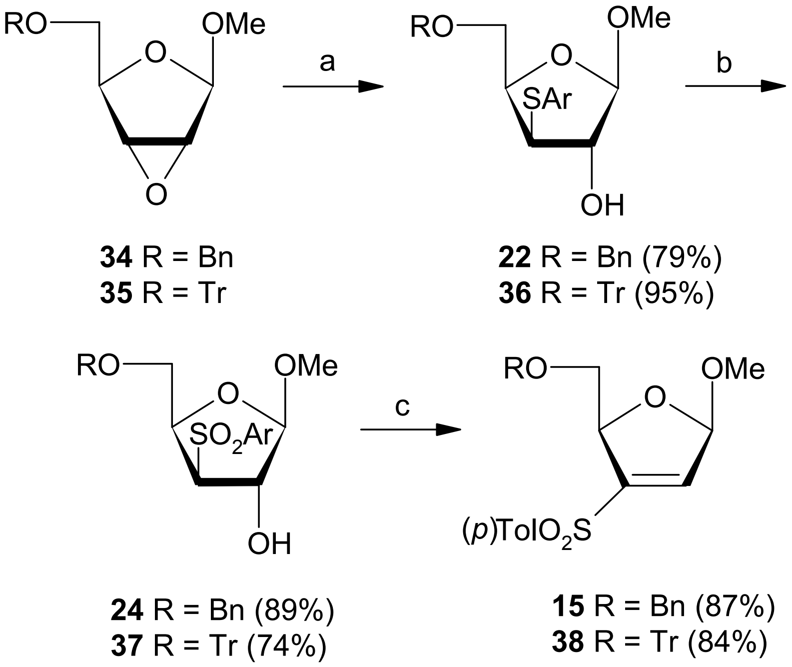
14 R = Bn (82%)
33 R = Tr (84%)

Reagents and conditions: a. *p*-Thiocresol, NaOMe, DMF, 80-90 °C, 2.5-3 h; b. MMPP, MeOH, rt., 2-3 h; c. MsCl, Py., 0 °C, 12-24 h.

Although amines added in diastereoselective fashion to **6** and **7**, the directive effect of the anomeric configuration on the stereochemical outcome of the reactions was not obvious. The addition of primary amines to **6** and **7** exclusively produced C-2 equatorial (*gluco*-) products. Secondary amines, on reaction with **7** produced only *gluco*-derivative whereas with **6** produced a mixture in which *gluco*- was still the predominant isomer (B. Ravindran, K. Sakthivel, C. G. Suresh and T. Pathak, *J. Org. Chem.*, **2000**, *65*, 2637). It was, therefore, necessary to carry out a study on the addition of planar heterocycles to vinyl sulfone-modified carbohydrates.

Diastereoselective additions to vinyl sulfone-modified hexopyranosyl derivatives: α-Vinyl sulfone **6** on treatment with imidazole, 1,2,4-triazole and thymine afforded single isomers **39-41**, respectively in high yields. Adenine, on the other hand, produced a mixture of isomers (only one isomer shown) **42** (**Scheme 3.1**).

Scheme 2.6



34 R = Bn
35 R = Tr

22 R = Bn (79%)
36 R = Tr (95%)

24 R = Bn (89%)
37 R = Tr (74%)

15 R = Bn (87%)
38 R = Tr (84%)

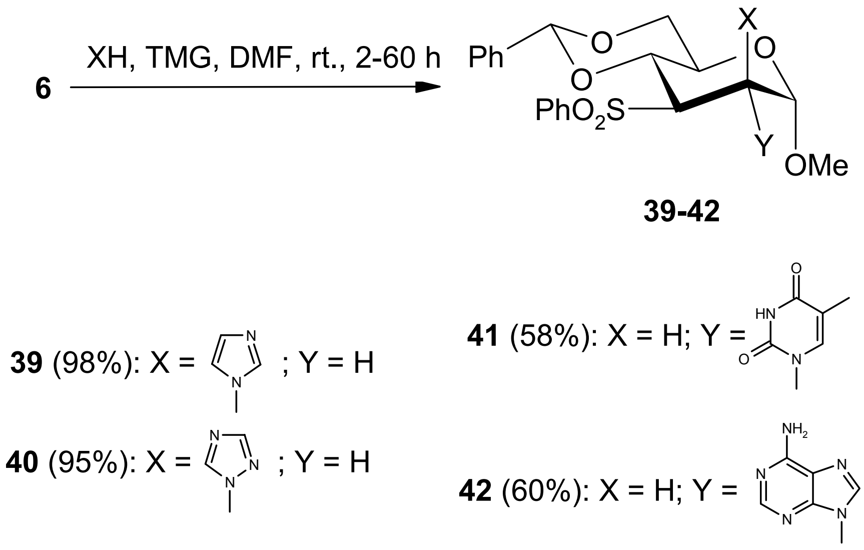
Ar = Tol(*p*)

Reagents and conditions: a. *p*-Thiocresol, NaOMe, DMF, 80-90 °C, 2.5-3.0 h; b. MMPP, MeOH, rt., 2.5-3.0 h; c. MsCl. Py., 0 °C, 12 h.

Moderate to good yields of **43**-**46** were obtained when β-vinyl sulfone **7** was reacted separately with the same set of nucleophiles (**Scheme 3.2**).

Diastereoselective additions to vinyl sulfone-modified pentofuranosyl derivatives: Reactions of α-vinyl sulfone **14** with imidazole, 1,2,4-triazole, thymine and adenine generated single isomers **47-50**, respectively in excellent yields (**Scheme 3.3**). The corresponding β-vinyl sulfone **15**, on reaction with imidazole, thymine and adenine produced single isomers **51**, **53** and **54**, respectively in high to moderate yields whereas 1,2,4-triazole generated **52**, which was a mixture of two isomers in approximately equal amounts (**Scheme 3.4**).

Scheme 3.1



39-42

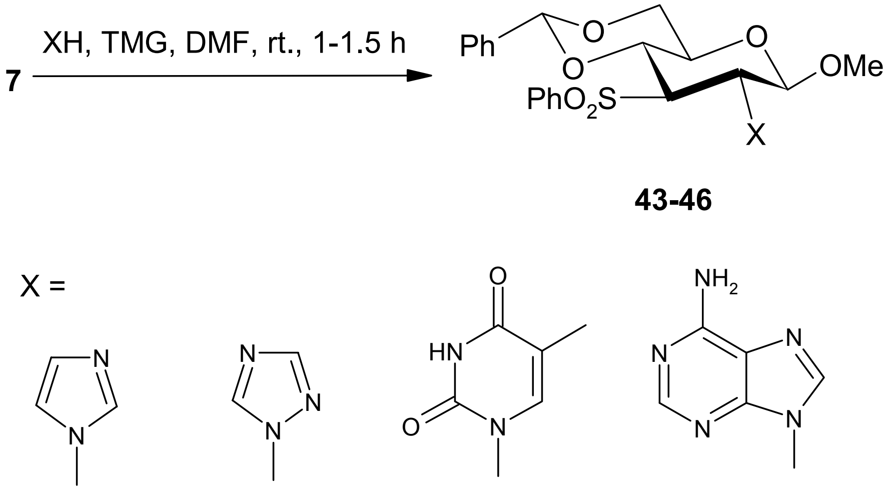
39 (98%): X = ; Y = H

40 (95%): X = ; Y = H

41 (58%): X = H; Y =

42 (60%): X = H; Y =

Scheme 3.2



43-46

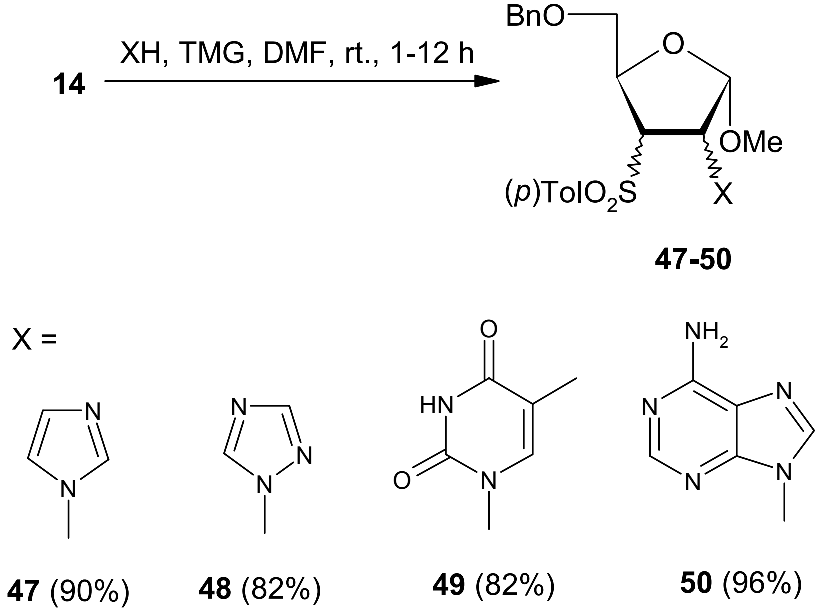
43 (70%) **44** (58%) **45** (90%) **46** (65%)

CHAPTER 4

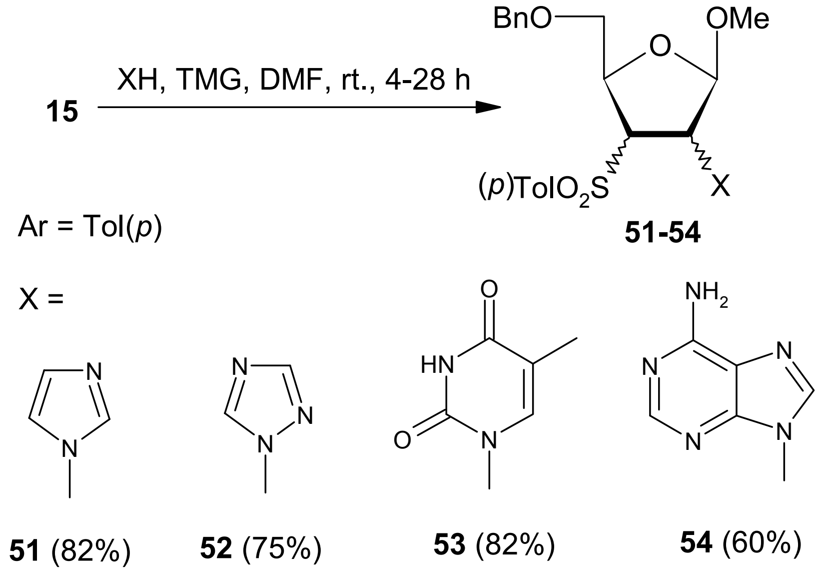
Diastereoselective Addition of Carbon Nucleophiles to Vinyl Sulfone-modified Carbohydrates

Branched-chain sugars, having carbon substituents at the non-terminal carbon atoms of the chains, are components of many natural products. Branched-chain sugars, on the other hand, constitute an important class of functionalized intermediates

Scheme 3.3



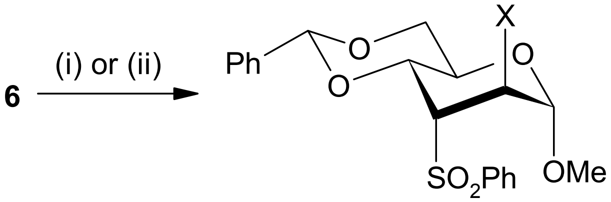
Scheme 3.4



,useful for further transformations. Michael-type addition reaction of carbon nucleophiles to vinyl sulfone-modified carbohydrates should be considered as an efficient route for the synthesis of branched-chain sugars. In this chapter we report that in the reactions between vinyl sulfone-modified carbohydrates and carbanions, the directing effect of the anomeric configurations has been fully realized.

Addition of carbon nucleophiles to vinyl sulfone-modified hexopyranosyl derivatives: Reactions of α-vinyl sulfone **6** with nitromethane and dimethyl malonate afforded single products **55** and **56**, respectively in good to excellent yields (**Scheme 4.1**). Interestingly, both the products were having three axially disposed functional groups on three consecutive carbon atoms (α-D-*altro*-configuration) of a six-membered system.

Scheme 4.1

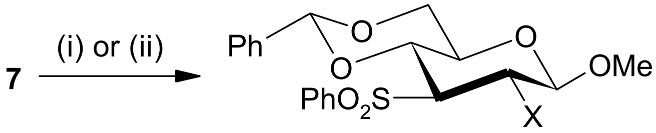


X = **55** CH_2NO_2 (60%)
56 $CH(CO_2Me)_2$ (82%)

(i) CH_3NO_2, NaOMe, MeOH, rt., 36 h
(ii) $CH_2(CO_2Me)_2$, NaH, THF, rt., 1.5 h

Under the same set of conditions, β-vinyl sulfone **7** reacted with nitromethane to produce the only isomer **57** in moderate yield whereas dimethyl malonate yielded a

Scheme 4.2



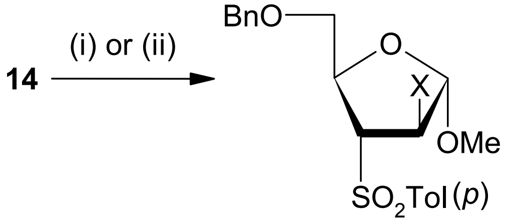
X = **57** CH_2NO_2 (56%)
58 $CH(CO_2Me)_2$ (86%)

(i) CH_3NO_2, NaOMe, MeOH, rt., 2 h
(ii) $CH_2(CO_2Me)_2$, NaH, THF, rt., 2 h

single isomer **58** in high yield (**Scheme 4.2**).

Addition of carbon nucleophiles to vinyl sulfone-modified pentofuranosyl derivatives: Compound **14** on reaction with nitromethane and dimethyl malonate yielded single isomers **59** and **60**, respectively in high yields (**Scheme 4.3**).

Scheme 4.3

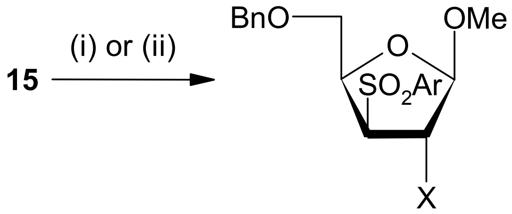


X = **59** CH_2NO_2 (73%)
60 $CH(CO_2Me)_2$ (74%)

(i) CH_3NO_2, NaOMe, MeOH, rt., 3 h
(ii) $CH_2(CO_2Me)_2$, NaH, THF, rt., 2.5 h

However, β-vinyl sulfone **15**, on reaction with nitromethane generated a mixture from which only **61** was identifiable. The carbanion generated from dimethyl malonate, on the other hand, yielded a single isomer **62** (**Scheme 4.4**).

Scheme 4.4



Ar = Tol (*p*) X = **61** CH_2NO_2 (55%)
62 $CH(CO_2Me)_2$ (87%)

(i) CH_3NO_2, ^tBuOK, THF, rt., 2 h
(ii) $CH_2(CO_2Me)_2$, NaH, THF, rt., 2.5 h

CHAPTER 1

A Review on Vinyl Sulfone-modified Carbohydrates and Nucleosides

1.1 Introduction

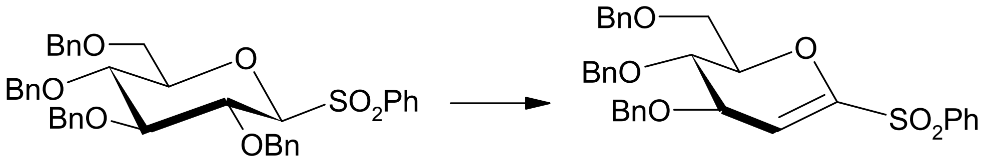
Amongst various functionalized sulfones, α,β-unsaturated- or vinyl sulfones have now become generally accepted as useful intermediates in organic synthesis. The vinyl sulfones serve efficiently as both Michael acceptors and a 2π–partner in cycloaddition reactions.[1a] Carbohydrates, on the other hand, are used extensively as chiral building blocks for the synthesis of various complex molecules.[2] The preliminary requirement of such a synthesis is the functionalization of the sugar molecules at the monosaccharide level.

Carbohydrates are normally modified *via* their sulfonates, epoxides, olefins, ketones or olefinic derivatives.[3] Due to the high reactivities of vinyl sulfones towards an array of nucleophiles,[1a] vinyl sulfone-modified carbohydrates could be used to generate a wide variety of modified monosaccharides. Vinyl sulfone-modified carbohydrates have the potential for utilization in organic synthesis because (a) almost all carbohydrates, either in pyranose or furanose forms, could be converted to their vinyl sulfone derivatives very easily -the first step being the simple nucleophilic displacements of sulfonates or regioselective (*trans*-diaxial) opening of epoxides by alkyl or aryl mercaptans at various positions,[3] (b) sulfone chemistry has been exploited extensively over decades and its compatibility with a wide variety of simple and complex molecules is well established,[1] and (c) after using the vinyl sulfone moiety as a tool for functionalization, whenever necessary, the sulfone group could be removed oxidatively to generate a carbonyl group,[1,4] reductively to afford a methylene group[1,5] or eliminated to generate a double bond.[1,6] Although vinyl sulfones have been used effectively in synthetic transformations, vinyl sulfone-modified carbohydrates are yet to be used extensively in synthetic organic chemistry. The methodologies discussed above are also applicable to the modification of the carbohydrate moieties of nucleosides. However, in the case of nucleosides, vinyl sulfone group may have the potential to be used for biological reactions. These aspects have been discussed separately immediate before describing the chemistry of the relevant nucleosides.

1.2 Vinyl sulfone-modified pyranoses

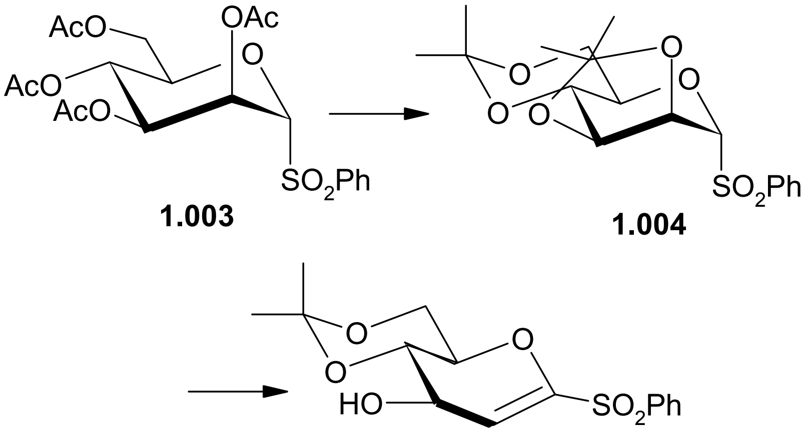
i. Sulfone group attached to C-1

Vinyl sulfone-modified carbohydrate was first reported in 1977 by Ferrier and co-workers when **1.002** was isolated as the product of a reaction in which an attempt was made to displace the phenylsulfonyl group from 2,3,4,6-tetra-*O*-benzyl-β-D- *gluco*-pyranosyl sulfone **1.001**.[7]



1.001 **1.002**

In order to access 1-sulfonyl glycals, D-mannosyl sulfone **1.003** was prepared from the corresponding thioglycoside by oxidation. The sulfone tetra-*O*-acetate **1.003** was deacetylated and the tetrol was converted to bisisopropylidene derivative **1.004**. The bisacetal **1.004** was subjected to base-promoted elimination to form the vinyl sulfone derivative **1.005**.[8]

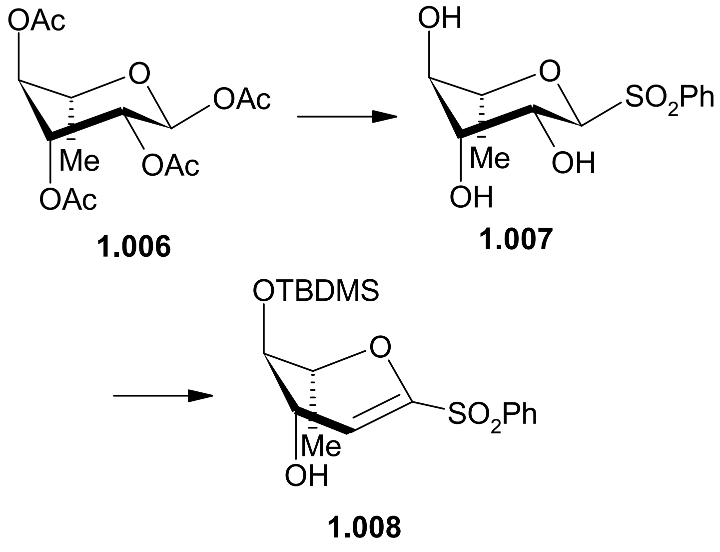


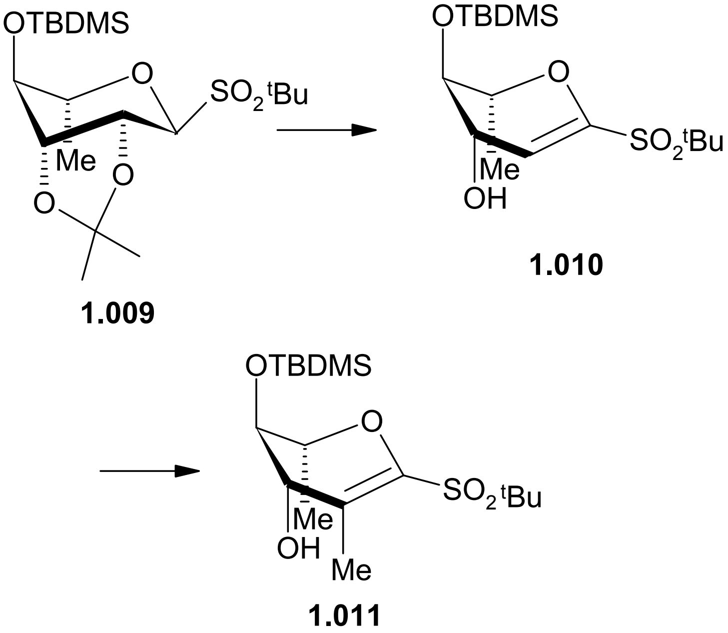
1.003 **1.004**

1.005

L-Rhamnopyranose tetra-*O*-acetate **1.006** was similarly converted to the corresponding vinyl sulfone **1.008** *via* phenyl thioglycoside **1.007**. Although vinyl sulfones like **1.005** and **1.008** are potential substrates for Michael additions, they did not undergo such reactions with methyl lithium or any other nucleophile.[8]

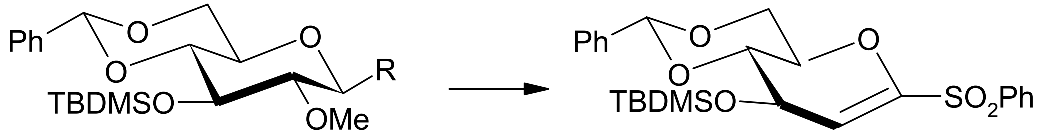
A more active vinyl sulfone **1.010** was synthesized and reacted with methyl lithium. No Michael addition occurred but lithiation at C-2 occurred instead. Subsequent reaction of the lithiated species with iodomethane produced 2-methyl vinyl sulfone **1.011**. The presence of the ring oxygen α to the sulfone group deactivates the double bond through delocalization of lone pair of electrons and makes these vinyl sulfone-modified carbohydrates too unreactive to undergo Michael addition.[8]





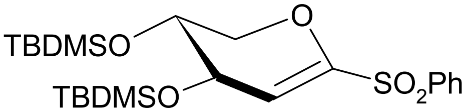
1-Tributylstannyl-D-glycals in general are valuable precursors for C-glycosylation reactions. The stannyl-D-glucals can be synthesized from 1-Phenylsulfonyl glucal **1.014**. Compound **1.014** can be obtained from the sulfone **1.013**, which was prepared from the selectively methylated derivative **1.012**.[9]

More recently, 1-phenylsulfonyl glycals **1.015-1.017** as well as **1.014** have been synthesized through modified routes. These glycals undergo an easy Ni(0)-catalyzed coupling with tributylstannylmagnesium bromide to give the corresponding 1-tributylstannyl glycals.[10]

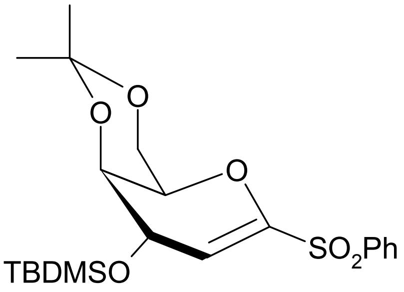


1.012 R = SPh
1.013 R =SO_2Ph

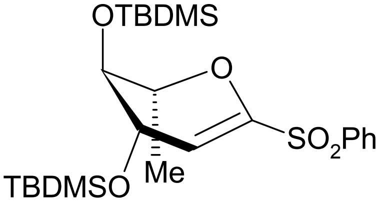
1.014



1.015



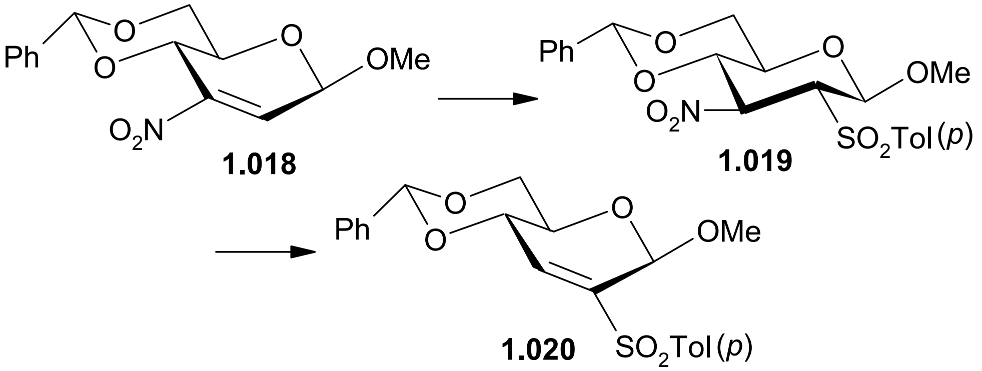
1.016



1.017

ii. Sulfone group attached to C-2

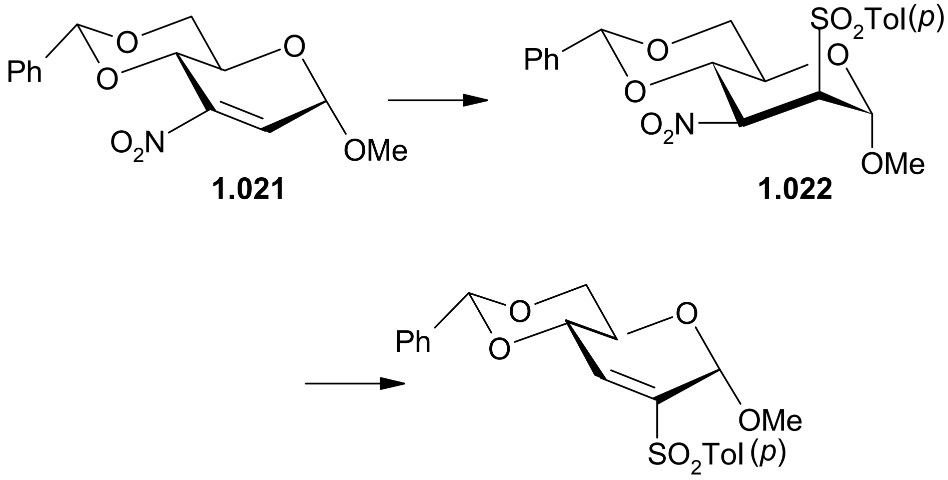
Sugar derivative having an α-sulfonylalkene moiety on a pyranose ring, hex-2-enopyranoside **1.020** was synthesized by reacting **1.018** with sodium *p*-toluenesulfinate in the presence of acetic acid followed by treatment of the *gluco*-derivative **1.019** with triethylamine.[11a] The α-anomer **1.023** was synthesized in very poor yield from the 3-nitro-hex-2-enopyranoside **1.021** *via manno*pyranoside derivative **1.022**.



1.018

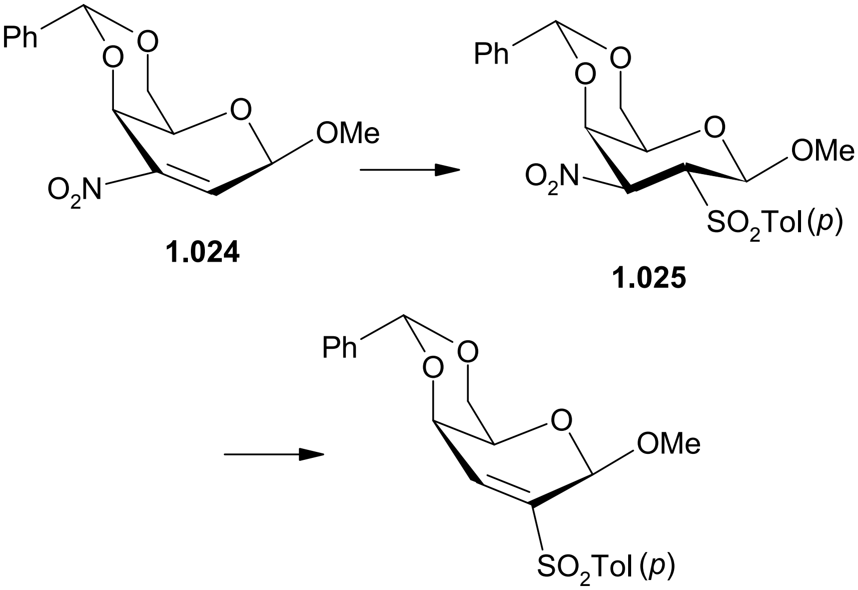
1.019

1.020



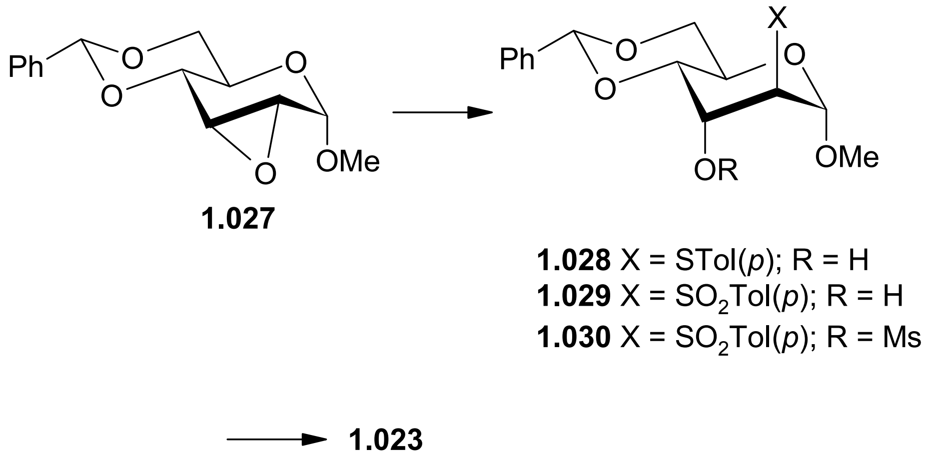
1.021 **1.022** **1.023**

The *galacto*-isomer **1.024** produced the corresponding sulfonyl alkene **1.026** in a similar fashion *via* **1.025**.[11a]



1.024 **1.025** **1.026**

Due to the difficulties in obtaining compound **1.023** through this route an alternative method for its preparation was developed. Thus, 2,3-anhydro-α-D-*allo*pyranoside **1.027** was treated with sodium *p*-toluenethiolate and the product **1.028** was oxidized to **1.029**. Compound **1.029** on mesylation in the presence of triethylamine afforded the vinyl sulfone **1.023** *via* mesylated derivative **1.030**.[11a]

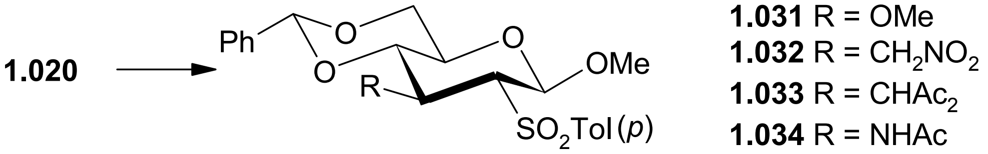


1.027

1.028 X = STol(*p*); R = H
1.029 X = SO_2Tol(*p*); R = H
1.030 X = SO_2Tol(*p*); R = Ms

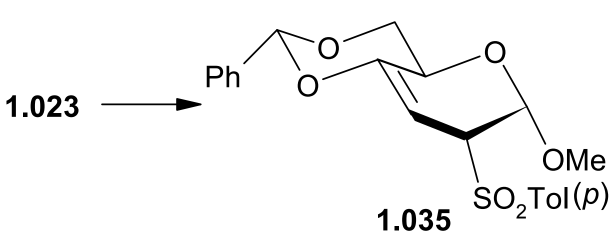
→ **1.023**

Vinyl sulfone **1.020**, on treatment with methanol, nitromethane, 2,4-pentanedione and ammonia produced the corresponding β-D-*gluco*-adducts **1.031**-**1.034**, respectively in high yields with high stereoselectivities.[11a]



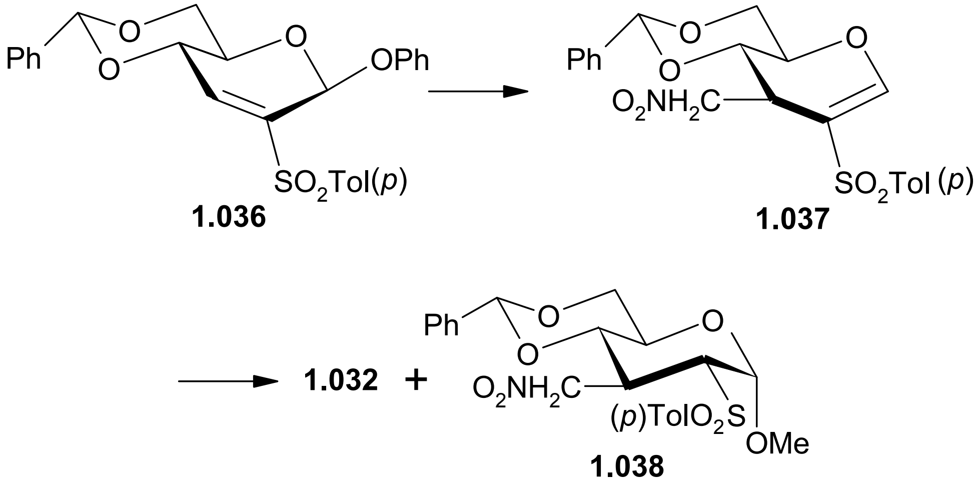
1.031 R = OMe
1.032 R = CH_2NO_2
1.033 R = $CHAc_2$
1.034 R = NHAc

Interestingly, vinyl sulfone **1.023** on treatment with sodium methoxide in methanol underwent elimination instead of addition to afford **1.035**.[11b]

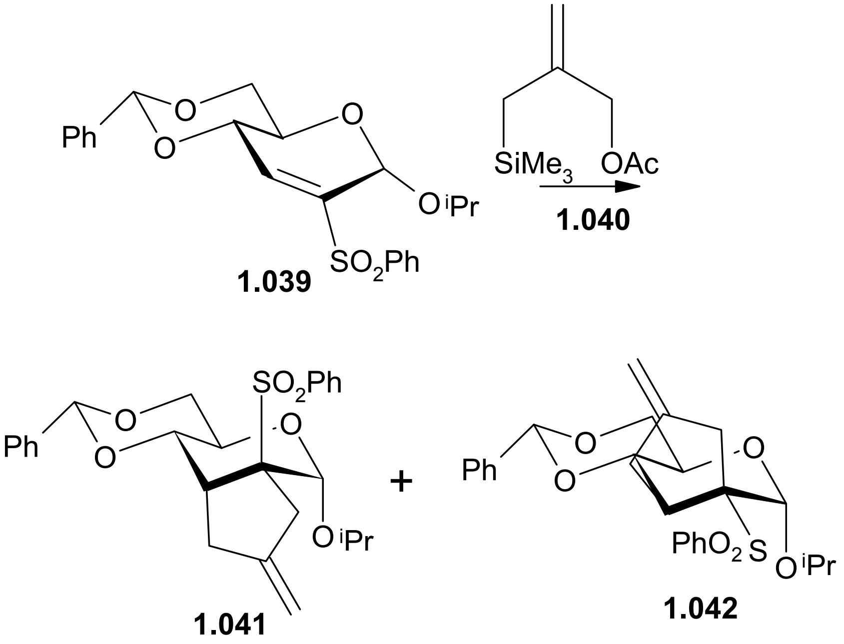


1.035

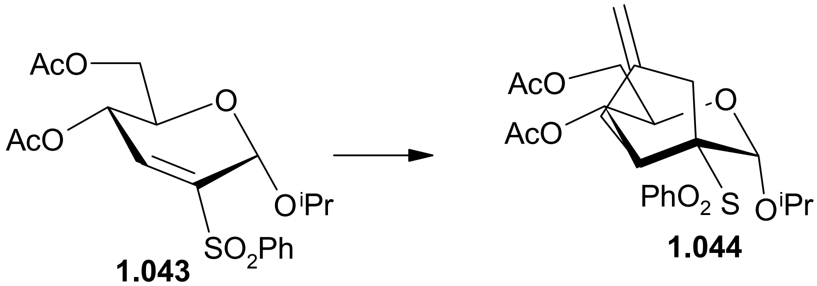
Treatment of the phenyl analog **1.036** with nitromethane led mainly to an S_N2' process to give 1-enitol derivative **1.037** having the *arabino*- configuration.[11b] It should be noted here that vinyl sulfone **1.037** can act as a Michael acceptor as opposed to the 1-sulfonyl glycals **1.005**, **1.008** or **1.010**. Thus, **1.037** on treatment with methanolic sodium methoxide afforded a mixture of α- and β-*gluco*pyranosides **1.032** and **1.038** in a ratio 2:3.[11b]



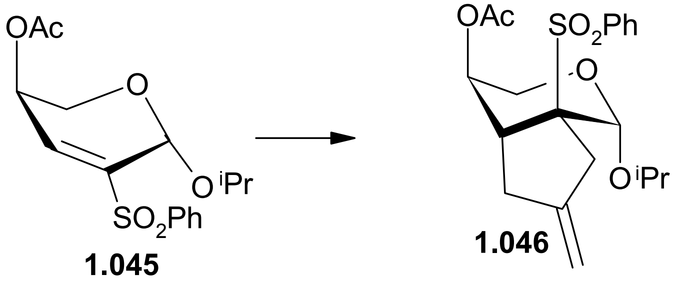
Substrates like **1.039** underwent (3+2) cylcoaddition with trimethylmethylene zwitterion precursor **1.040** in the presence of an *in situ*-generated Pd (0) catalyst to afford an inseparable mixture of two isomers **1.041** and **1.042**.[12]



Related vinyl sulfones **1.043** and **1.045**, on the other hand, produced the corresponding 5,6-bicycles **1.044** and **1.046**, respectively possessing *exo*-cyclic unsaturation. These reactions are thought to follow a two-step sequence involving an initial Michael-type addition to the electron deficient double bond followed by an attack of the resultant stabilized anion on the palladium complex.[12]



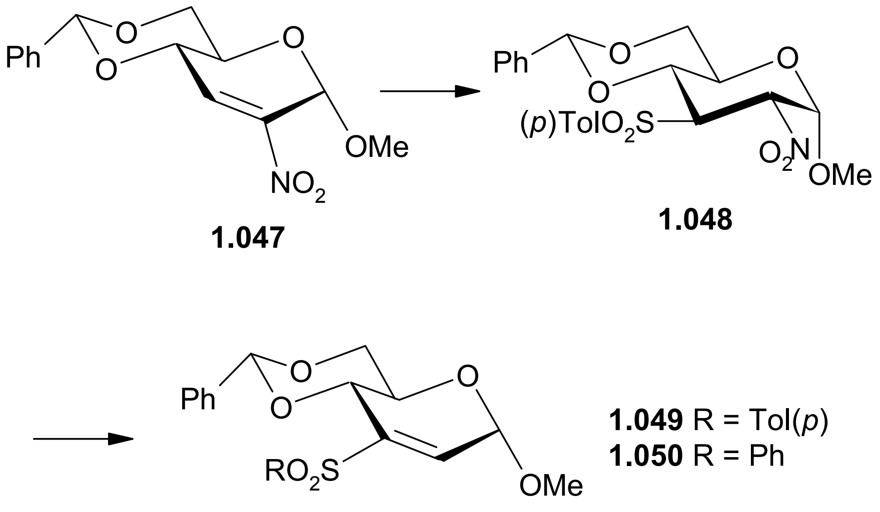
1.043 **1.044**



1.045 **1.046**

iii. Sulfone group attached to C-3

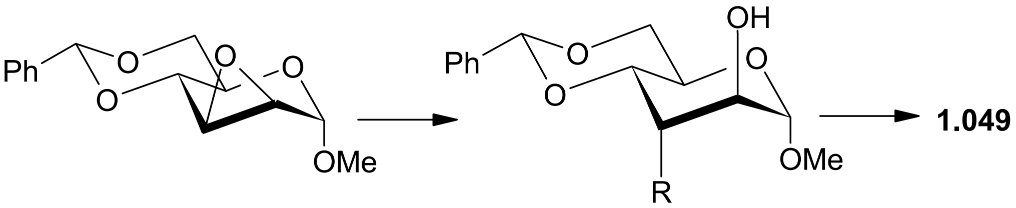
Although compound **1.020** was obtained in good overall yield by the addition of sodium *p*-toluenesulfinate to **1.018**, the α-anomeric regioisomer of the former, namely 3-(*p*)-tolylsulfonyl-hex-2-enopyranoside **1.049** was obtained in poor yield when synthesized from 2-nitrohex-2-enopyranoside **1.047**.[11a]



1.047 **1.048**

1.049 R = Tol(*p*)
1.050 R = Ph

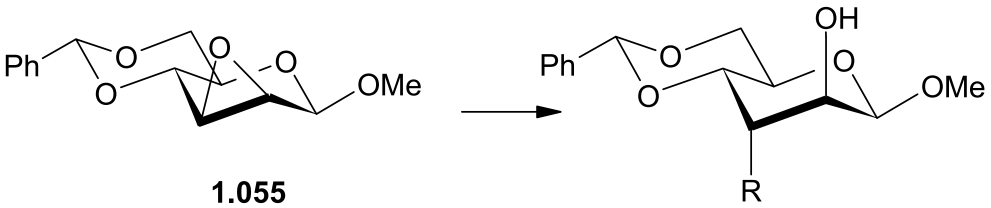
Therefore, an alternative route for the synthesis of **1.049** was devised from 2,3-anhydro-α-D-*manno*pyranoside **1.051**.[11a]



1.051

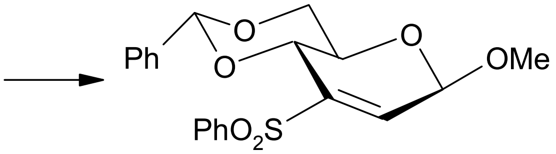
1.052 R = $SO_2Tol(p)$
1.053 R = SPh
1.054 R = SO_2Ph

The corresponding thiophenyl derivative **1.050** was synthesized as follows. Epoxide **1.051** was reacted with thiophenol in the presence of 1,1,3,3-tetramethylguanidine (TMG) to afford **1.053**. The corresponding sulfone derivative **1.054** was generated in quantitative yield by oxidizing **1.053** with magnesium monoperoxyphthalate (MMPP). Compound **1.054** was mesylated and the crude mesylated product was subjected to an elimination reaction with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_2Cl_2 to produce **1.050** in 88% overall yield (4 steps from **1.051**). Similarly, thiophenol in the presence of TMG opened epoxide **1.055** at the 3-position to generate **1.056**. Oxidation of **1.056** to **1.057**, followed by mesylation and DBU treatment generated the desired compound **1.058** in 75% overall yield (4 steps from **1.055**).[13]



1.055

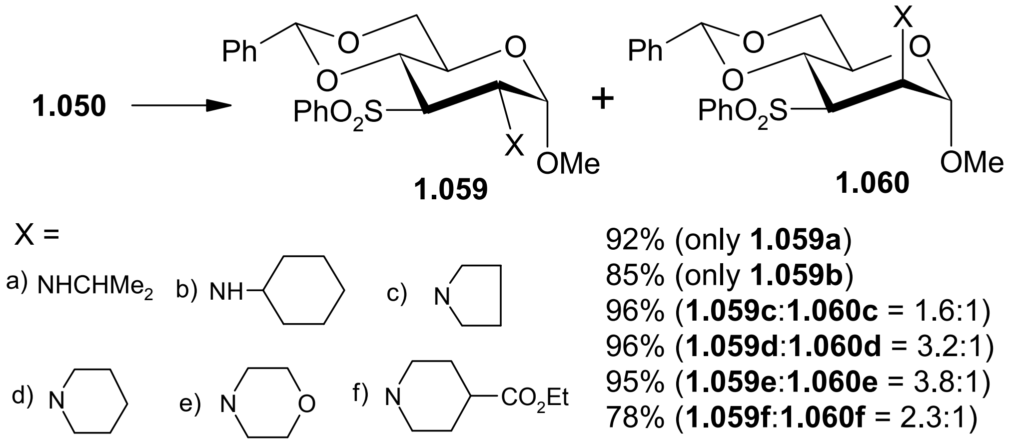
1.056 R = SPh
1.057 R = SO_2Ph



1.058

It is well documented that the stereochemical outcome of the nucleophilic attack at the planar carbonyl group at C-2 position of *threo*-hexopyranosid-2-ulose is controlled by the anomeric configuration.[14] It was logical to presume that this effect would also be pronounced in the case of Michael addition to *endo*-cyclic monovinyl sulfones derived from carbohydrates and decided to initiate a systematic study.

Anomerically pure α-vinyl sulfone derivative **1.050** was, therefore reacted with various primary and secondary amines. Primary amines, such as isobutylamine and cyclohexylamine were found to add diastereoselectively to produce single isomers **1.059a** and **1.059b**, respectively. The secondary amines, pyrrolidine, piperidine, morpholine and ethyl isonepicotate, on the other hand, generated a mixture of isomers (isomeric at C-2) having **1.059c**, **1.059d**, **1.059e** and **1.059f** as the major isomers, respectively. The major *gluco*-isomers, **1.059c-f** were separated by crystallization. One of the minor *manno*-isomers **1.060c** was isolated to unambiguously establish its structure.

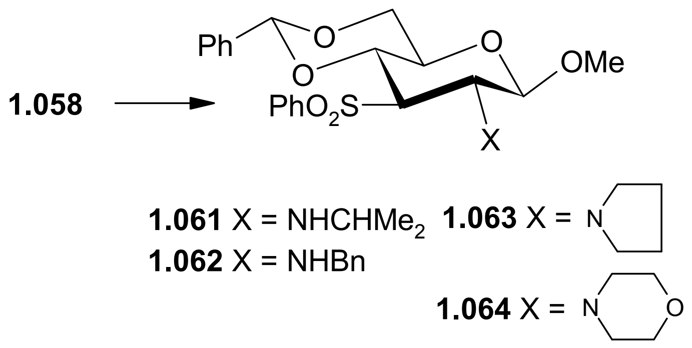


92% (only **1.059a**)
85% (only **1.059b**)
96% (**1.059c**:**1.060c** = 1.6:1)
96% (**1.059d**:**1.060d** = 3.2:1)
95% (**1.059e**:**1.060e** = 3.8:1)
78% (**1.059f**:**1.060f** = 2.3:1)

Similarly, the β-anomeric derivative **1.058** was treated with isobutylamine, benzylamine, pyrrolidine and morpholine. The primary as well as secondary amines were found to add diastereoselectively to produce single isomers **1.061**-**1.064,** respectively.[13,15]

It has been reported that the addition of *p*-toluenethiol to 1-(*p*)-tolylsulfonylcyclohexene produced *cis*-2-(*p*)-tolylmercapto-1-(*p*)-tolylsulfonylcyclohexane because an arylsulfonyl group, which had a much larger steric requirement than an arylmercapto group should tend to occupy an equatorial position.[16]

The stereochemistry of nucleophilic addition reactions to more complicated systems like 3-nitro-hex-2-enopyranosides[17] **1.021** and **1.018**, however, has been discussed in terms of electrostatic interactions,[17d] stereoelectronic control,[17d] steric hindrance,[17d]



1.058 →

1.061 X = $NHCHMe_2$

1.062 X = NHBn

1.063 X =

1.064 X =

$A^{(1,3)}$ strain[17e] and also hydrogen bonding.[17e] A generalization that the axial attack predominates over equatorial attack for **1.021** and the converse is true for **1.018** has been arrived at on the basis of reactions of **1.021** and **1.018** with several nucleophiles[17d] although one of the earliest work in this area with amines as nucleophiles contradicted[17b] this generalization; sterically demanding purine bases, however, added to **1.021** and **1.018** from the β-[17c] and α-[17a] sides, respectively.

In the light of above observations, it can be stated that the stereochemical course of addition of amines to **1.050** and **1.058** does not fully obey any of the precedence. In a partially rigid bicyclic system of **1.050** and **1.058**, the sterically bulky phenylsulfonyl group is expected to occupy the equatorial position. In the case of **1.050**, primary amines always attacked the C-2 center from equatorial direction to produce thermodynamically more stable diequatorial products. Interestingly, however, sterically bulky secondary amines, on reaction with **1.050** produced mixture of products, epimeric at C-2.[13] To explain the formation of mixture of products **1.059c-f** and **1.060c-f**, one has to bear in mind the established rules that (a) secondary amines carrying nonbonded electron pairs would face electrostatic repulsion by C1-O1 and C1-O5 bonds and (b) thermodynamically more stable diequatorial products should predominate.[17d] Nevertheless, to explain the formation of *manno*-isomers (such as **1.060c**), it is necessary to assume the existence of a stereoelectronic factor, responsible for repelling the incoming secondary amines from equatorial direction, although the exact nature of the hindrance cannot be rationalized at this point.[13]

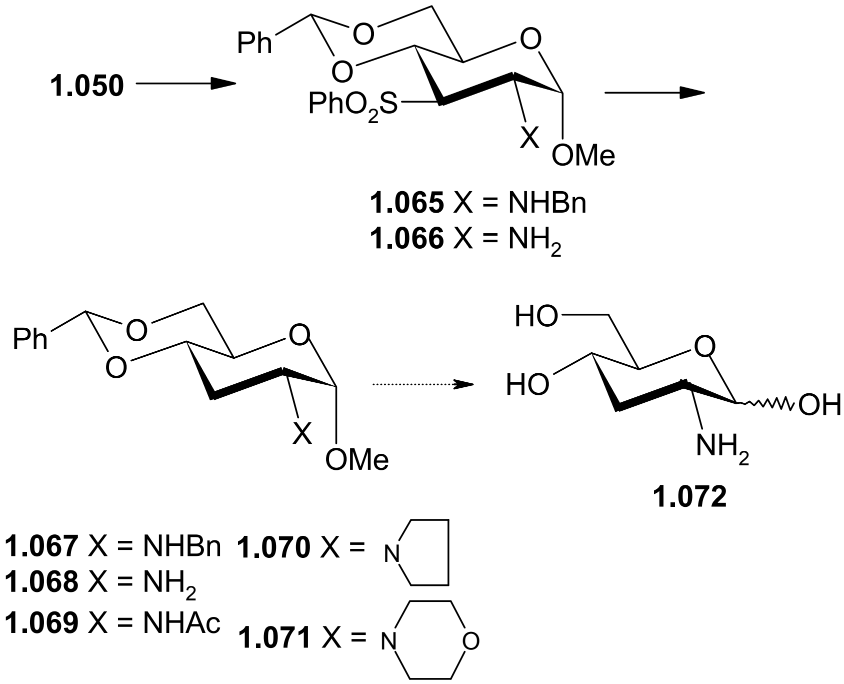
Compound **1.058**, on the other hand, on reaction with both primary and bulky secondary amines produced thermodynamically more stable diequatorial products. In this case, it is difficult to establish conclusively whether the electrostatic repulsion between attacking amines, C1-O1 and C1-O5 bonds directed the nucleophiles to attack the C-2 position of **1.058** from the equatorial direction resulting in the formation of single isomers **1.059**.[13] This observation, nevertheless, falls more in line with the generalized rule that in the case of a β-anomeric substrate, a nucleophile should approach C-2 site preferably from equatorial direction.[17d]

The diastereoselective addition of primary amines to **1.050** and **1.058** has been applied to the synthesis of a naturally occurring aminosugar D-lividosamine. D-Lividosamine (2-amino-2,3-dideoxy-D-glucose) **1.072**, isolated from *Streptomyces lividus*, is present in aminoglycoside antibiotics such as lividomycin-A, lividomycin–B and 3′-deoxykanamycin C.[18,19] There is also a need for the development of methodologies for introducing N-alkyl and N,N-dialkyl amino functions at the C-2 equatorial position of carbohydrates because studies on aminoglycoside antibiotics have shown that the steric and/or the varying basicity of amino groups as well as the deoxygenated centers in aminosugars play important role in determining the properties of aminoglycosides.[20,21]

The essence of the synthetic strategy leading to the preparation of D-lividosamine **1.072** and its alkylated analogues lies in the introduction of amino and N-alkyl amino groups. These must be introduced at the C-2 carbon of the pyranoses in equatorial configurations followed by (or prior to) deoxygenation at C-3 site.[19] There are only few reports on the synthesis of equatorially located N-alkyl and N,N-dialkyl-D-glucosamine derivatives *via* N-alkylation or N,N-dialkylation of glucosamine.[22,23] The other most commonly used methods for the synthesis of aminosugars, involved opening of epoxides **1.051** or **1.055** by amines that always produced the C-3 deoxy C-3 aminosugars and not the C-2 deoxy C-2 aminosugars.[24] Reactions of primary and secondary amines with methyl 2,3-anhydro-4,6-*O*-(phenylmethylene)-α-D-*allo*pyranoside, on the other hand, produced exclusively the C-2 deoxy C-2 amino products with C-N bond in the axial configuration.[25] None of the above methods could have been used as a general route for the synthesis of D-lividosamine and its analogs either because of the undesired configuration or position of the C-N bond and/or the additional functionalization of the C-3 hydroxyl group required for the deoxygenation of the C-3 center.

On the basis of earlier studies[13] it was anticipated that benzylamine would react with **1.050** and **1.058** to generate exclusively the *gluco*-isomer, from which the benzyl group could be removed reductively to generate the free amino function. In addition, the phenylsulfonyl group was suitably located in all these products to generate methylene groups at C-3 *via* reductive desulfonation leading to the synthesis of a reported intermediate **1.069** of D-lividosamine **1.072**. Several partially and fully protected analogs of D-lividosamine could be synthesized using a similar approach.

Thus, **1.050** on reaction with benzylamine in anhydr. MeOH produced **1.065** exclusively in 90% yield. Compound **1.065** was desulfonated on treatment with magnesium in MeOH[5] in 90% yield to generate the 2-N-benzylamino-2,3-dideoxy product **1.067**. Compound **1.067** was debenzylated to **1.068** on treatment with palladium hydroxide on charcoal. Crude **1.068** was isolated as the acetyl derivative **1.069**.[15]



1.065 X = NHBn
1.066 X = NH$_2$

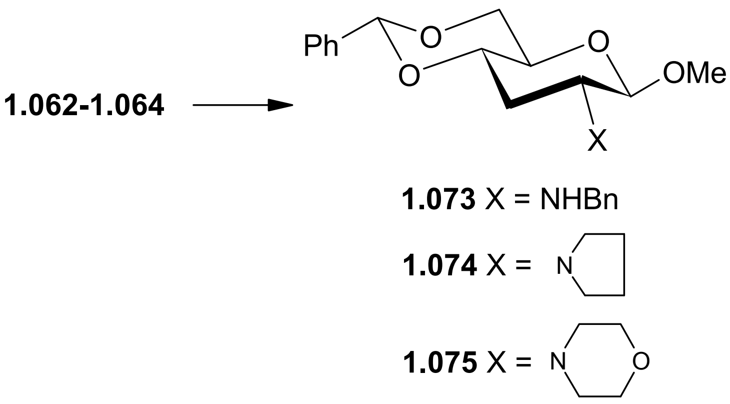
1.067 X = NHBn
1.068 X = NH$_2$
1.069 X = NHAc

1.070 X =

1.071 X =

1.072

However, to reduce the number of steps involved in the synthesis of **1.069**, compound **1.050** was reacted directly with conc. aq. ammonia in dioxane. The reaction produced a mixture of products although the desired deoxyaminosugar **1.066** was present in major amount (^{1}H NMR). The mixture was desulfonated as above and the free amino compound **1.068** was acylated. Pure **1.069** was crystallized out from benzene-pet ether mixture in 65% overall yield.[15] Similarly, the pyrrolidino- and morpholino-derivatives **1.059c** and **1.059e** were desulfonated to **1.070** and **1.071** in 91% and 85% yields, respectively. In the β-series, compounds **1.062**-**1.064** were desulfonated to **1.073**, **1.074** and **1.075** in 76%, 42% and 47% yields, respectively.[15]



1.062-1.064

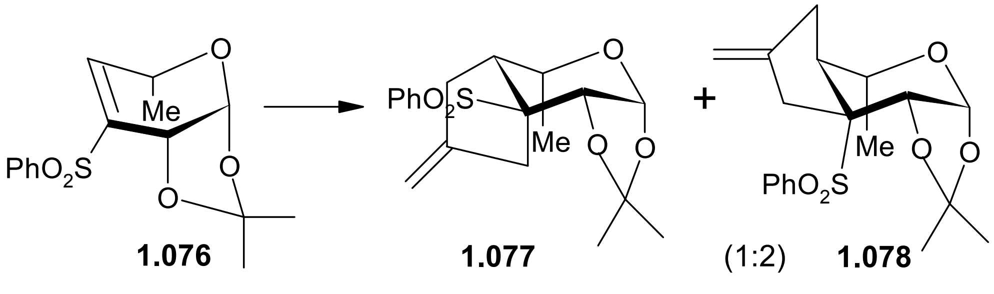
1.073 X = NHBn

1.074 X =

1.075 X =

$J_{1,2}$ Values of **1.065** (3.6 Hz) and **1.062** (6.6 Hz) are in line with the coupling constants expected for *gluco*-configuration.[15] However, the crystal structures of these two compounds represent a very interesting picture. The *endo*-cyclic bond lengths of the pyranose ring in the α-anomer **1.065** are shorter than the corresponding bonds in the β-anomer **1.062**. The pyranose ring is in the chair form in **1.065** and in the boat form in **1.062**. The phenylsulfonyl and the benzylamino groups are in equatorial positions in **1.065**, while the benzylamino group is axial in **1.062** because of the flipping of the ring.[26]

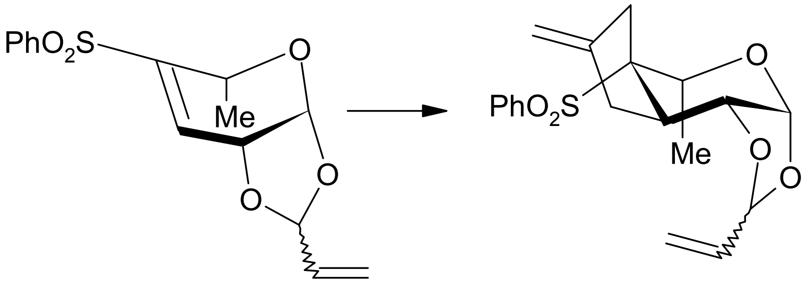
In continuation with the studies on the cycloaddition reactions of vinyl sulfone-modified carbohydrates, the 3,4-unsaturated sulfonyl derivative **1.076** was prepared from L-rhamnose and was treated with acetate **1.040** as previously described. The minor product **1.077** was obtained due to β-attack on the more hindered face of the sulfone and the major product **1.078** was a result of an α-attack on the less hindered face.[12]



1.076 **1.077** (1:2) **1.078**

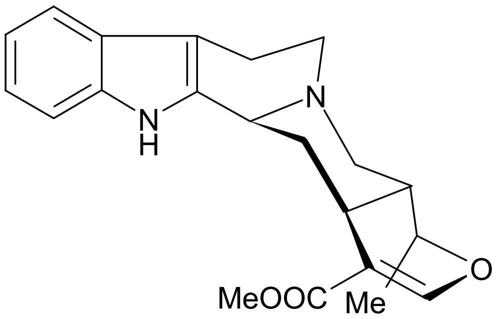
iv. Sulfone group attached to C-4

In order to obtain a single product instead of a mixture of **1.077** and **1.078**, it was possible to design a preferential α-attack by synthesizing a regioisomer of **1.076**. Thus, compound **1.079**, possessing a phenylsufonyl group at C-4 instead of C-3, underwent an α-attack *via* a chair-like transition state to afford only one product **1.080**.[12]

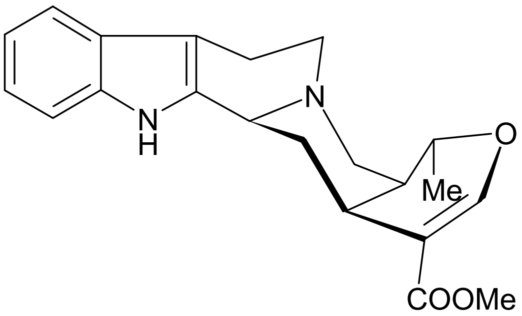


1.079 **1.080**

This methodology has been put to use in the synthesis of predecessors of the alkaloid ajmalicine **1.081** and tetrahydroalstonine **1.082**.[12]



1.081



1.082

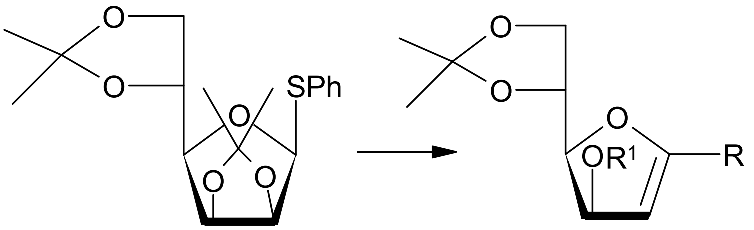
1.3 Vinyl sufone-modified furanoses

i. Sulfone group attached to C-1

A furanosyl 1-phenylsulfonyl glycal **1.084** has been synthesized from the sulfone **1.083** in two steps. The former has been converted to the corresponding 1-tributylstannyl glycal **1.085** using a methodology discussed above.[10]

ii. Sulfone group attached to C-3

Recently 2′,3′-dideoxynucleosides have received increased attention due to their activity against human immunodeficiency virus (HIV).[27,28] In principle, one of the most powerful strategies to functionalize the sugar moiety of a nucleoside should be the addition of a reagent across the double bond of a suitably protected pent-2′/3′-enofuranosyl nucleoside. The methodology of addition across the double bond was not

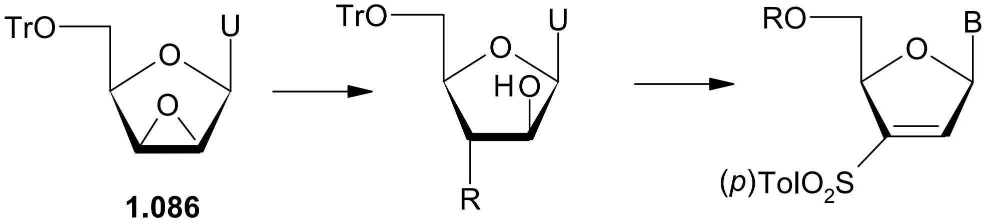


1.083

1.084 R = SO_2Ph, R^1 = TBDMS
1.085 R = $SnBu_3$, R^1 = TBDMS

successful with nucleosides partly due to the inert nature of the *endo*-cyclic double bond.[29] It was, therefore, necessary to enhance the reactivity of such a double bond. Vinyl sulfone, known for its efficiency as a Michael acceptor,[1a] was therefore selected as a tool for the functionalization of the sugar moiety of nucleosides.

2′,3′-*O*-Anhydro-*lyxo*uridine **1.086** was reacted with *p*-toluenethiolate to generate a mixture of regioisomers from which the 3′-functionalized derivative **1.087** was isolated. Compound **1.087** was oxidized to **1.088**, which on reaction with MsCl in pyridine produced **1.089**. N^6,N^6-Dibenzoyl-5′-*O*-(4-methoxytrityl)-3′-enesulfone derivative of adenosine **1.090** was also synthesized in a similar fashion.



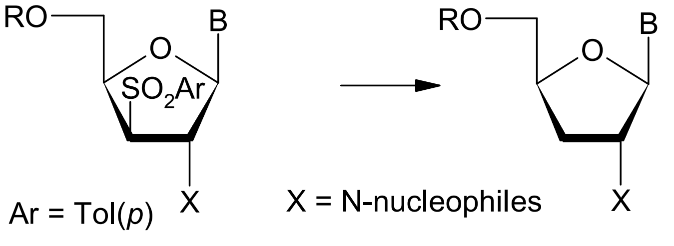
1.086

1.087 R = STol(*p*)
1.088 R = SO_2Tol(*p*)

1.089 B = U; R = Tr
1.090 B = $A^{(Bz)}{}_2$;
R = MMTr

Uridine derivative **1.089**, on Michael addition of various nucleophiles produced **1.091** (XH = ammonia, methylamine, benzylamine, glycine methyl ester, dimethylamine, pyrrolidine, piperdine, morpholine, methylmalonate and nitromethane). Desulfonation of **1.091** generated 2′,3′-dideoxy analogs **1.093**. Adenine derivative **1.090** also underwent similar addition reactions to generate **1.092** but the desulfonation step caused extensive glycosidic bond cleavage resulting in very poor yield of **1.094**.

Most of these addition reactions have produced *trans*- (*xylo*-) products; a few of the above reactions have produced a mixture of *cis*- and *trans*-products although the later was overwhelmingly the major product. It is highly probable that the β-configuration of the nucleobases in **1.089** and **1.090** played a decisive role in determining the configuration at C-2′-position of the products (either *xylo*- or *ribo*-) of Michael addition reactions.[29]



1.091 B = U; R = Tr
1.092 B =A or A^{Bz};
R = MMTr

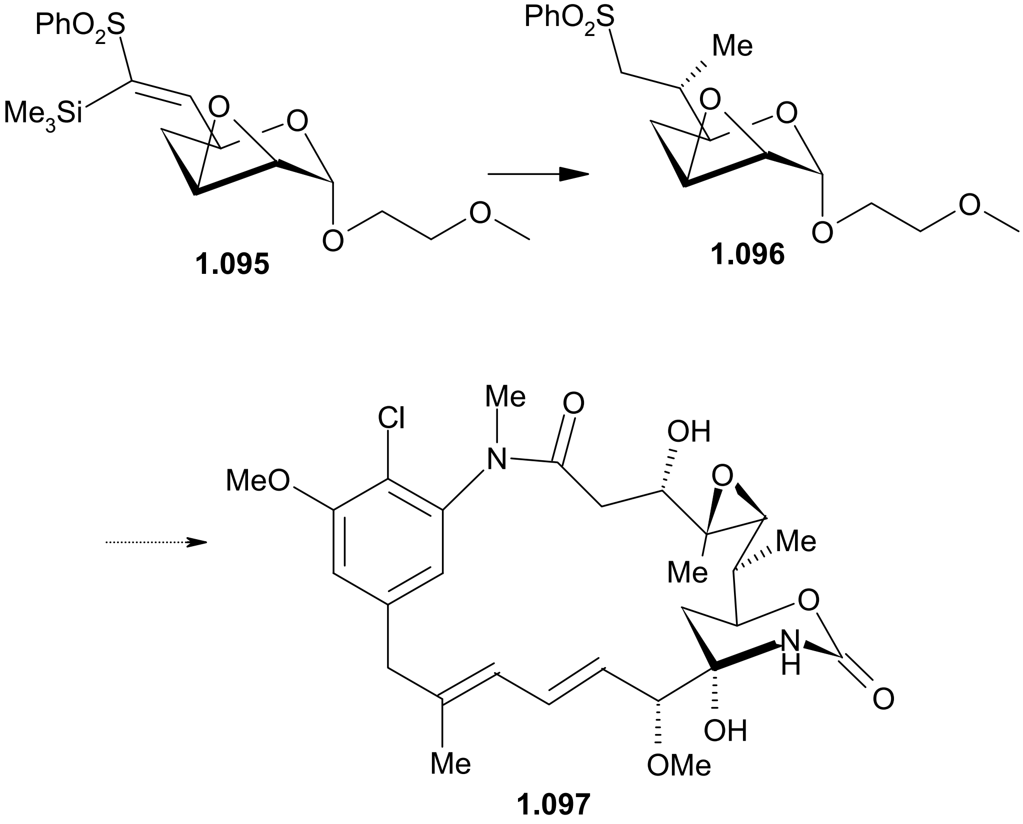
1.093 B = U; R = Tr
1.094 B =A or A^{Bz};
R = MMTr

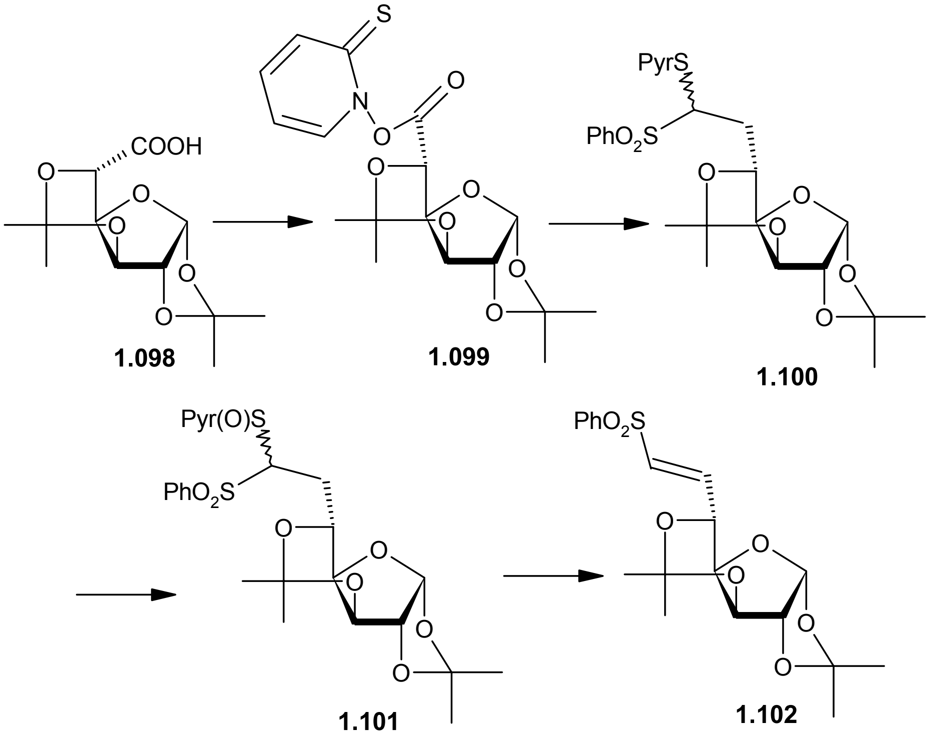
1.4 Sulfone group attached to an *exo*-cyclic carbon

Pyranose derivatives having a 2-phenylsulfonyl-2-trimethylsilyl vinyl group have been used for the synthesis of (±)-maytansinol **1.097** where the synthesis has been initiated by heteroconjugate addition of MeLi to **1.095** to obtain **1.096**. The addition of MeLi accomplished the complete acyclic stereoselection in the pyranosyl hetero-olefin **1.095**.[30]

A methodology using radical chemistry has been reported on the synthesis of vinyl sulfone-modified carbohydrates. Radicals, generated from isopropylidene uronic esters of 2-thiopyridone, add readily to electron-poor alkenes in a stereospecific fashion, leading to the functionalized chain-elongated furanosides through C-4; the acetal group has a directive effect in controlling chirality. Thus, the bisisopropylidene derivative of glucouronic acid **1.098** on conversion to its 2-thiopyridone derivative **1.099** and irradiation with tungstane lamp in the presence of phenyl vinyl sulfone as a radical trap afforded a mixture of isomers **1.100**. Oxidation to sulfoxide **1.101** followed by the elimination afforded pure alkene **1.102**.[31] It has been suggested by the authors that this type of functionalized hexoses (and pentoses) may be used as synthons for important natural products.[31]

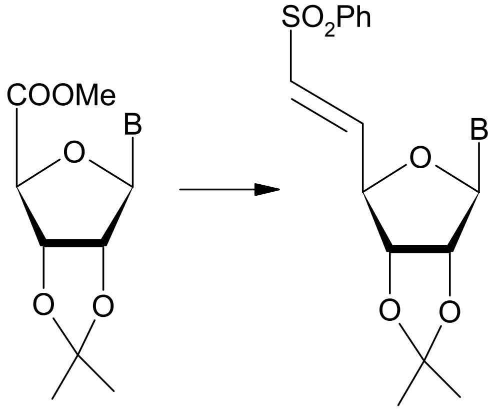
This chemistry has been extended to nucleosides for the functionalization of the 5′-ends of the carbohydrate moieties of nucleosides by vinyl sulfone group. The carboxylic acid derivative of isopropylidene uridine **1.103** was subjected to radical


PhO2S
Me3Si
1.095
PhO2S
Me
1.096
Cl
Me
MeO
OH
Me
Me
OH
Me
OMe
1.097


COOH
1.098
S
1.099
PyrS
PhO2S
1.100
Pyr(O)S
PhO2S
1.101
PhO2S
1.102

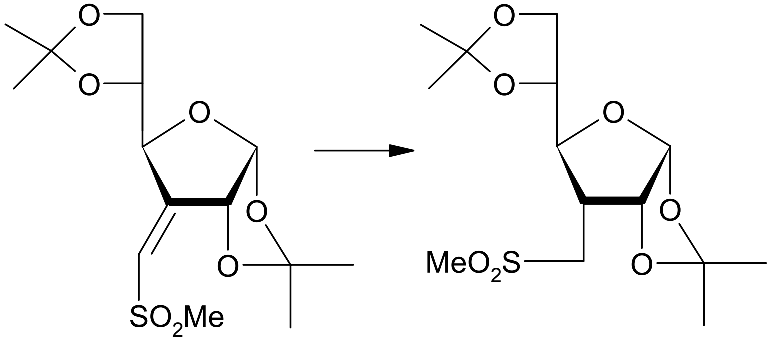
reaction in the presence of phenyl vinyl sulfone. The adduct, on oxidation and elimination afforded the vinyl sulfone **1.105** as a single compound. Similarly, the adenine derivative **1.106** has also been synthesized from **1.104**.[31]

1,2:5,6-Diacetone ulose, on reaction with a sulfone stabilized Horner-Emmons reagent [$(MeO)_2P(O)CH(Li)SO_2Me$] generated an *exo*-cyclic α,β-unsaturated sulfone **1.107** which was reduced to **1.108** with [$(Ph_3P)CuH]_6$.[32]



1.103 B = uracilyl
1.104 B = N^6-benzoyl adeninyl

1.105 B = uracilyl
1.106 B = N^6-benzoyl adeninyl



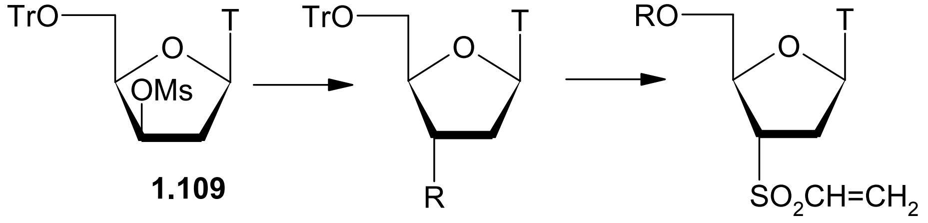
1.107

1.108

In an attempt to access anti-HIV drug more potent than 3′-azido-3′-deoxythymidine (AZT), it has been proposed to introduce reactive triatomic functional groups at the 3′-position of thymidine.[33] It was expected that a strongly electrophilic group would react with biological nucleophiles such as a non-functionalized thiol or an amino group present in an enzyme. Earlier attempts in this area were not successful because the functionalities attached to the 3′-end, namely thiocyanate or isothiocyanate were most probably not reactive enough to form covalent bonds with the enzyme tested.[33] Interestingly, vinyl sulfones were reported to inhibit the action of glyceraldehyde-3-phosphate dehydrogenase[34] and the vinyl sulfone containing dipeptides were shown[35] to be efficient cystein protease inhibitors through covalent bond formation with the enzymes. It was, therefore, decided to incorporate strongly electrophilic vinyl sulfone group into the carbohydrate moieties of nucleosides.

1-(2′-Deoxy-3′-*O*-mesyl-5′-*O*-trityl-β-D-*threo*-pentofuranosyl)thymine **1.109** was treated with marcaptoethanol in the presence of DBU to produce **1.110** in 64% yield. Compound **1.110** was easily oxidized by MMPP to **1.111** in 75% yield. Sulfone **1.111** was converted to the mesylated derivative in pyridine at +4 °C and the same pyridine solution was heated at 60 °C for 0.5 h to produce the desired vinyl sulfone **1.112** in 71% overall yield. Compound **1.112** could be detritylated, if necessary, to the free hydroxy derivative **1.113** under acidic conditions.[36]

Either the protected vinyl sulfone **1.112** or the deprotected derivative **1.113** was reacted with various nucleophiles in Michael fashion. Nucleophiles, such as, hydrazoic acid, morpholine, sodium salt of dimethylmalonate, 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane and thiophenol reacted smoothly with compound **1.112** to furnish compounds **1.114a**, **1.117c**, **1.120e**, **1.122f** and **1.123g**, respectively in excellent to moderate yields. Similarly, compound **1.113** reacted with benzylamine and imidazole in protic solvents at ambient temperature to produce compounds **1.116b** and **1.119d** (after benzoylation in the case of **1.112d**), respectively in high yields. The diaza crown ether product **1.122f** was characterized as N-acetyl derivative. Compounds **1.114a**, **1.120e** and **1.123g** were deprotected using 80% acetic acid at elevated temperature or using ion-exchange resins (IR 120H$^+$) and the products were converted to benzoyl derivatives **1.115a**, **1.121e** and **1.124g**, respectively in high yields;

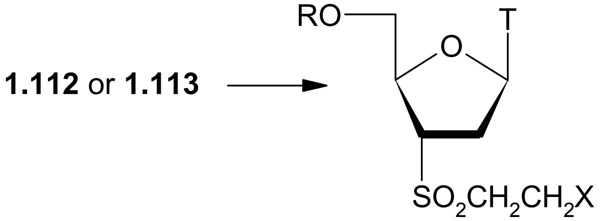


1.109

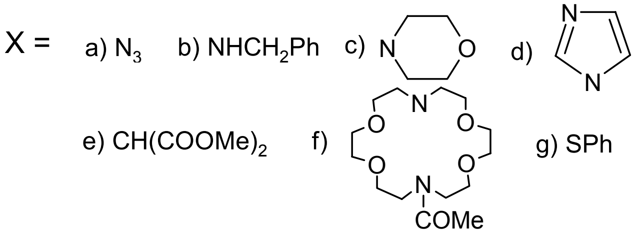
1.110 R = SCH_2CH_2OH
1.111 R = $SO_2CH_2CH_2OH$

1.112 R = Tr
1.113 R = H

compound **1.117c** was deprotected and isolated as the 5'-free hydroxy compound **1.118c**.[36]



1.114a R = Tr; X = a
1.115a R = Bz; X = a
1.116b R = H; X = b
1.117c R = Tr; X = c
1.118c R = H; X = c
1.119d R = Bz; X = d
1.120e R = Tr; X = e
1.121e R = Bz; X = e
1.122f R = Tr; X = f
1.123g R = Tr; X = g
1.124g R = Bz; X = g

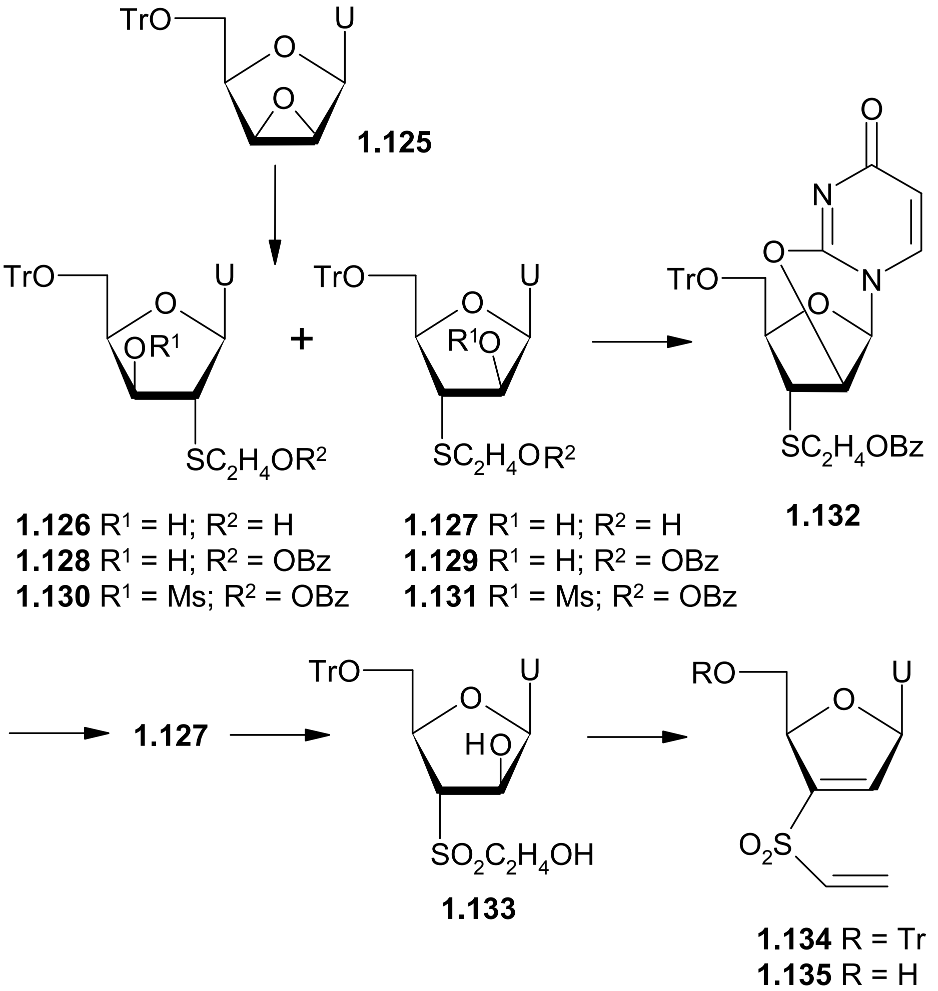


1.5 Bisvinyl sulfone-modified nucleoside

Like monovinylsulfones, bisvinylsulfone has also been reported to inhibit the action of glyceraldehyde-3-phosphate dehydrogenase.[34] Therefore, as an essential extension of the work reported above,[36] it was decided to incorporate a bisvinyl sulfone group[37,38] into the carbohydrate moiety of the uridine. It was also envisaged that nucleosides carrying bisvinyl sulfone group as part of the carbohydrate moieties, would generate bicyclic nucleosides[37] when reacted with appropriate nucleophiles. The synthesis of this new class of bicyclic nucleosides containing S,S-dioxide moiety will be interesting as other heterocycles containing this functional group, as a part of the ring, have been synthesized in the past. For example, 1-*O*-acetyl-2,3,4,6-tetra-*O*-methyl-5-thio-α-D-*gluco*pyranose S,S-dioxide[39] an analog of 1-*O*-acetyl-*gluco*pyranose, a thiadiazine S,S-dioxide diacyclonucleoside[40] and the sulfone of 4′-thiothymidine[41] were also synthesized to study the biological and biophysical properties.

The synthesis of the target bisvinyl sulfone-modified nucleoside starts with the epoxide **1.125**, which was reacted with mercaptoethanol in the presence of TMG to generate a mixture of 2′-deoxy-2′-*S*-(2-hydroxyethylthio)-5′-*O*-trityl-*xylo*uridine **1.126** and 3′-deoxy-

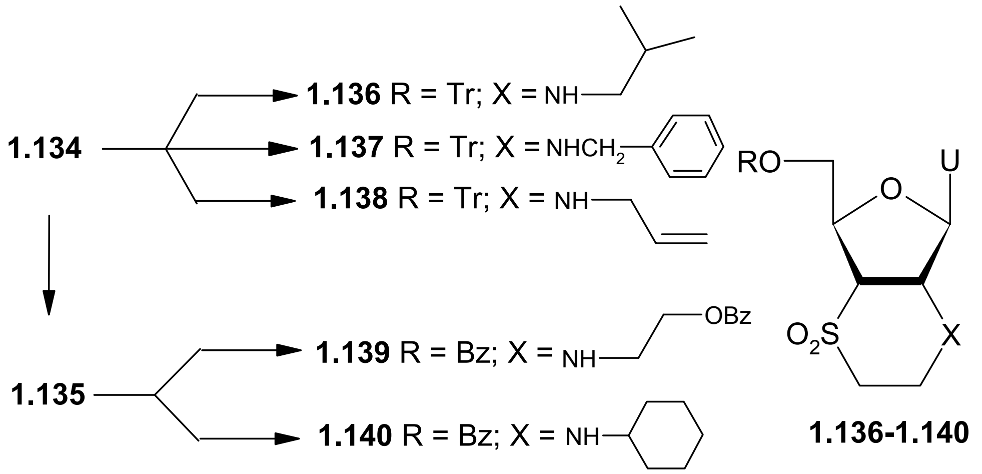
3′-*S*-(2-hydroxyethylthio)-5′-*O*-trityl-*ara*uridine **1.127**. As all efforts to separate the isomers failed, the primary hydroxyl groups of the hydroxyethylthio moieties of **1.126** and **1.127** were benzoylated selectively at 0 °C. After work-up, 2′ (3′)-hydroxyl groups of the crude benzoylated products **1.128** and **1.129** were mesylated at 0 °C. The resulting mesylated products **1.130** and **1.131** were heated at 100 °C in pyridine; intramolecular 2′,3′-epithiiranium ion formation followed by the attack of C-2 oxygen at the C-2′ center resulted in the formation of 2,2′-*O*-anhydro derivative **1.132** in 50% overall yield in four steps. Compound **1.132** was debenzoylated and the 2,2′-*O*-anhydro bridge was hydrolyzed by aq. sodium hydroxide treatment to produce **1.127** in 96% yield. Oxidation of **1.127** with MMPP produced 3′-deoxy-3′-*S*-(2-hydroxyethylsulfonyl)-5′-*O*-trityl-*ara*uridine **1.133** in 86% yield. Both of the hydroxyl groups of **1.133** were mesylated and the crude product obtained after work-up was heated at 40 °C in pyridine; elimination of the mesylates produced the desired bisvinyl



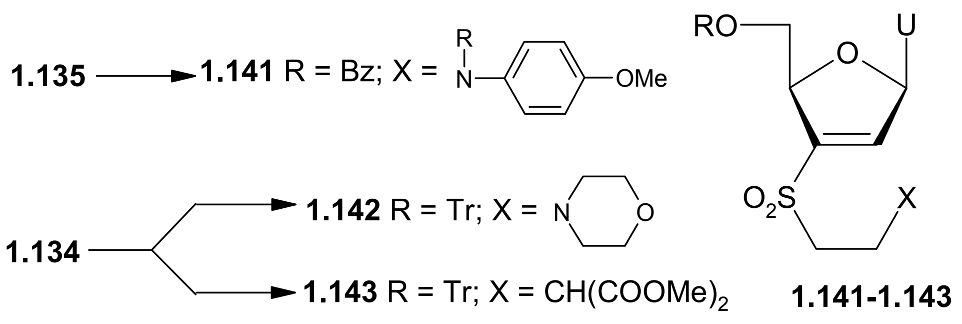
sulfonyl uridine **1.134** in 86% yield. Detritylation of **1.134** with 80% aq. acetic acid produced **1.135**.[42]

Compound **1.134** was reacted with primary amines, such as isobutylamine, benzylamine and allylamine in methanol to produce bicyclic derivatives **1.136**-**1.138,** respectively in high yields and in a stereoselective fashion. Crude bisvinyl sulfone **1.135**, obtained from **1.134** was reacted with ethanolamine and cyclohexylamine and the products were isolated as the benzoyl derivatives **1.139** and **1.140**, respectively.

One equivalent of *p*-anisidine reacted with **1.135** to produce a single compound. Attempted cyclization of this compound was unsuccessful even at elevated temperature. The product was isolated as its dibenzoyl derivative **1.141**. Morpholine and dimethylmalonate reacted with **1.134** to produce **1.142** and **1.143** in 92% and 86% yields, respectively. All these reactions demonstrated that the *exo*-cyclic vinyl sulfone group of **1.134** or **1.135** was more reactive than the *endo*-cyclic one.[42]



1.136-1.140



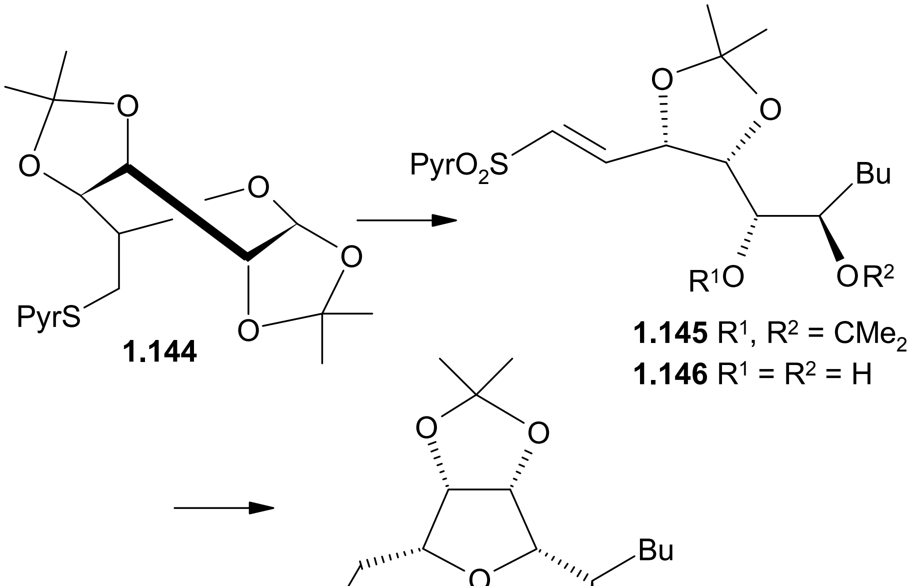
1.141-1.143

1.6 Vinyl sulfone group attached to open chain sugar derivatives

Sugar derived vinyl sulfone like **1.145** has been synthesized from aza-heterocycle/thiosugar hybrid **1.144** using a Grob-type heterocyclic process followed by the oxidation of the product.[43] Compound **1.146** underwent Michael-initiated ring closure process to build up a chiral polysubstituted oxolan system such as **1.147** with high stereoselectivity.[43] Compound **1.145** was reacted with morpholine to produce adduct **1.148** in 80% yield with *de* exceeding 94%.[44]

1.7 Conclusion

It has been established that vinyl sulfone-modified carbohydrates are very useful intermediates for the synthesis of several new deoxyaminosugars. It is evident from the work done in this laboratory[13,15,26] as well as work reported by others[11,12,43,44] that it is indeed possible to control the stereochemical outcome of Michael addition of nucleophiles to different centers of a given carbohydrate by utilizing the configurations of the neighboring functional groups at the vicinity of the reaction center.



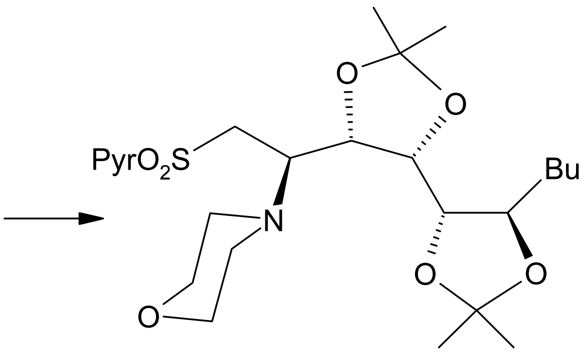
1.144

1.145 $R^1, R^2 = CMe_2$
1.146 $R^1 = R^2 = H$

1.147

In the area of nucleosides, a reactive triatomic analog of AZT, carrying the vinyl sulfone at the 3′-position has been prepared. This compound has been shown to react very efficiently with a variety of nucleophiles to generate new classes of modified nucleosides where the functional groups are attached to the C-3′ of a nucleoside through a flexible ethyl sulfone spacer.[36] A protocol has also been developed for the synthesis of a nucleoside carrying bisvinyl sulfone group. This is one of the rare examples of bisvinyl sulfone group attatched to a chiral appendage. This type of doubly functionalized nucleoside has the potential to generate a wide variety of modified nucleosides including a novel class of bicyclic thiazine S,S-dioxide derivatives.[41]

1.145 ⟶



1.148

Although several scattered examples of vinyl sulfone-modified carbohydrates have been compiled in this chapter, this powerful methodology of combining vinyl sulfone and carbohydrate for accessing biologically interesting modified monosaccharides and nucleosides or functionalized carbohydrates which may act as useful synthons in general remains underexplored and underutilized.

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CHAPTER 2

Syntheses of Vinyl Sulfone-modified Carbohydrates

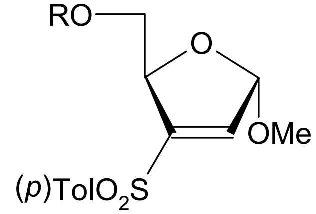
2.1 Introduction

We have pointed out in **Chapter 1** that the most common methods for the modification of monosaccharides involve the reactions of various reagents with sugar derived epoxides, tosylates and ketones, although several other minor methods are also reported.[1-3] However, several examples of Michael addition of nucleophiles to hex-2-enoses[4-6] and 3-nitro-hex-2-enopyranosides[7-12] have been reported. It has also been established in **Chapter 1** that carbohydrate modified monovinylsulfone[13] substituted nucleosides **1.112/1.113** and bisvinylsulfone substituted nucleosides **1.134/1.135**,[14] are useful synthons for the generation of new classes of nucleosides. We envisaged that due to the high reactivities of vinyl sulfones towards wide variety of nucleophiles, vinyl sulfone-modified carbohydrates could be utilized as a novel methodology for the generation of known as well as new modified monosaccharides. Accordingly, the known anomers, methyl 2,3-dideoxy-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfonyl-α-D-*erythro*-hex-2-enopyranoside **1.050** and methyl 2,3-dideoxy-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfonyl-β-D-*erythro*-hex-2-enopyranoside **1.058**[**15**] have been synthesized in our laboratory and subjected to reactions with various amines to produce dideoxyamino sugars of the type . The study has later been utilized for the synthesis of D-lividosamine derivative **1.069** (a component of aminoglycoside antibiotics) and its analogs **1.070-1.071**.[16]

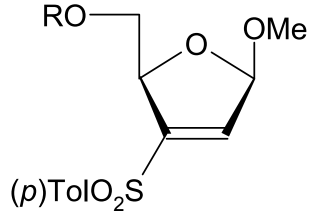
In order to broaden the scope of this study and also to gather information on the reaction patterns of *endo*-cyclic monovinylsulfones derived from pentofuranoses, we needed to develop a practical methodology for the synthesis of anomerically pure methyl 2,3-dideoxy-3-*C*-(*p*)-tolylsulfonyl-α-D-*erythro*-pent-2-enofuranosides (**2.001** or **2.002**) and methyl 2,3-dideoxy-3-*C*-(*p*)-tolylsulfonyl-β-D-*erythro*-pent-2-enofuranosides (**2.003** or **2.004**). Anomerically pure vinyl sulfone-modified pent-2-enofuranoses were needed because we wanted to use the anomeric configuration as a tool to direct the diastereoselectivity of addition of nucleophiles to the 2-position of these enofuranoses. However, this particular requirement imposed greater restrictions on the choice of methodologies for the synthesis of **2.001-2.004**.

2.2 Present Work

Synthesis of 2.001-2.004 from epoxides derived from carbohydrates: The known *lyxo*-epoxides **2.005**[**17**] and **2.006**,[18] synthesized from D-xylose, were treated separately with sodium salt of *p*-thiocresol in DMF at 80-90 °C to furnish sulfide derivatives **2.007** and **2.008**, respectively in good to excellent yields. Compounds **2.007** and **2.008**, when oxidized separately with MMPP in MeOH generated the corresponding sulfone derivatives **2.009** and **2.010**, respectively in high yields. Compounds **2.009** and **2.010**, on treatment with mesyl chloride in pyridine separately, afforded smoothly the desired vinyl sulfone-modified carbohydrates **2.001** and **2.002**, respectively in 82% and 84% yields.

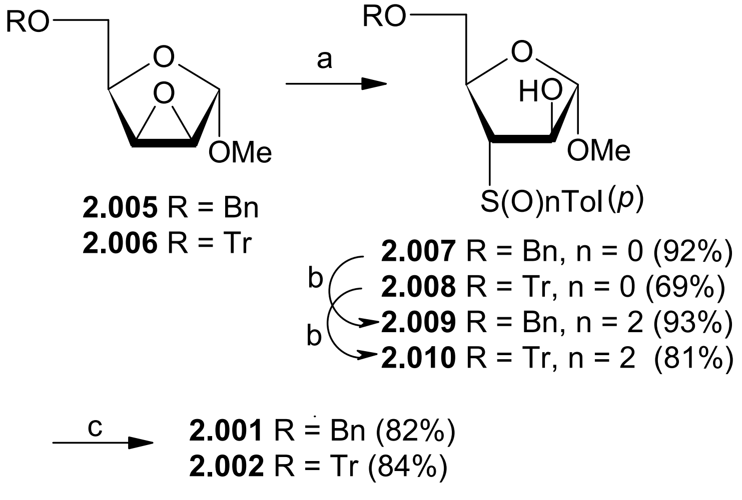


2.001 R = Bn
2.002 R = Tr



2.003 R = Bn
2.004 R = Tr

Similarly, the known *ribo*-epoxides **2.011**[19,20] and **2.012**[21] were treated separately with sodium salt of *p*-thiocresol in DMF at 80-90 °C to afford sulfide derivatives **2.013** and **2.014**, respectively with *xylo*-configuration in high yields. Compounds **2.013** and **2.014** were converted to the corresponding vinyl sulfones **2.003** and **2.004** *via* sulfone derivatives **2.015** and **2.016** in the usual manner as described above.



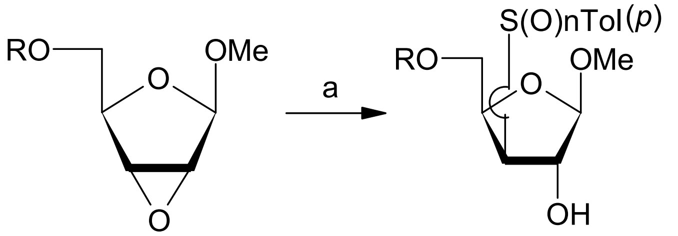
2.005 R = Bn
2.006 R = Tr

2.007 R = Bn, n = 0 (92%)
2.008 R = Tr, n = 0 (69%)
2.009 R = Bn, n = 2 (93%)
2.010 R = Tr, n = 2 (81%)

2.001 R = Bn (82%)
2.002 R = Tr (84%)

Reagents and conditions: a. *p*-Thiocresol, NaOMe, DMF, 80-90 °C, 2.5-3 h; b. MMPP, MeOH, rt., 2-3 h; c. MsCl, Py., 0 °C, 12-24 h.

Synthesis of 2.001 and 2.003 from 3-*O*-tosylated D-*xylo*furanose: In addition to the opening of the epoxide rings of **2.005/2.006** and **2.011/2.012** by thiolate nucleophiles, it is also possible to incorporate thiotolyl functionality at the 3-position of a pentofuranose derivative by simple nucleophilic displacement of a 3-*O*-tosyl group. Thus, a retrosynthetic analysis of the pathway leading to the synthesis of **2.001-2.004** necessitated the nucleophilic displacement of *p*-tolylsulfonyl group of the easily accessible starting material 5-*O*-benzyl-1,2-*O*-isopropylidene-3-*O*-tosyl-α-D-*xylo*furanose **2.017**.[22] Compound **2.017** was reacted with *p*-thiocresol in the presence of NaOMe in DMF at 120 $^{\circ}$C to produce sulfide derivative **2.018** with *ribo*-configuration in 59% yield. Compound **2.018** was deprotected and glycosylated in one step in the presence of conc. H_2SO_4 in MeOH to generate a mixture of two anomers **2.019** and **2.020** (1:10) in 78% yield. The anomers **2.019** and **2.020** were separated at this stage by chromatography and oxidized separately with MMPP in MeOH to the corresponding sulfones **2.021** and **2.022**, respectively in excellent yields. The sulfones **2.021** and **2.022** on treatment with mesyl chloride in pyridine afforded smoothly the desired vinyl sulfone-modified carbohydrates **2.001** and **2.003**, respectively in high yields.



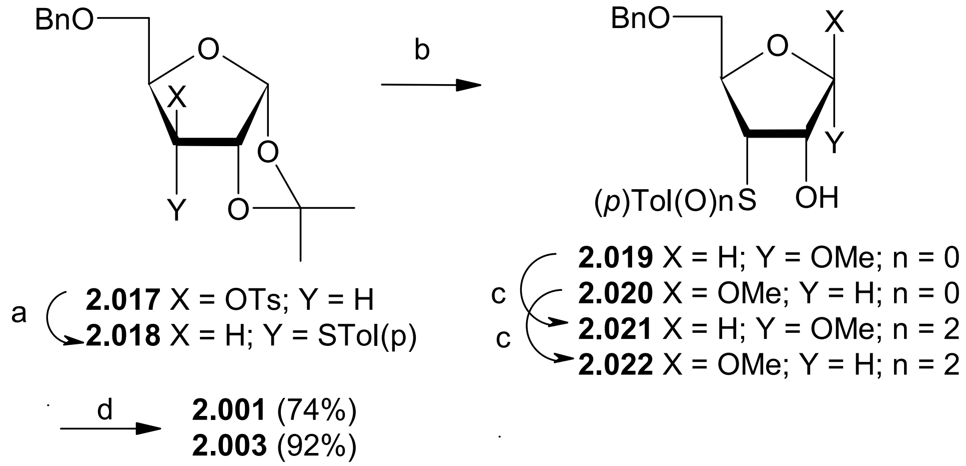
2.011 R = Bn
2.012 R = Tr

b
2.013 R = Bn, n = 0 (79%)
2.014 R = Tr, n = 0 (95%)
b
2.015 R = Bn, n = 2 (89%)
2.016 R = Tr, n = 2 (74%)

$\xrightarrow{c}$ **2.003** R = Bn (87%)
2.004 R = Tr (84%)

Reagents and conditions: a. *p*-Thiocresol, NaOMe, DMF, 80-90 $^{\circ}$C, 2.5-3.0 h; b. MMPP, MeOH, rt., 2.5-3.0 h; c. MsCl. Py., 0 $^{\circ}$C, 12 h.

Synthesis of 2.001 and 2.003 from 3-*O*-mesylated D-*ribo*furanose: 5-*O*-Benzyl-1,2-*O*-isopropylidene-3-*O*-mesyl-α-D-*ribo*furanose **2.026**, which had been synthesized from a known compound **2.023**[23] (*via* oxidation-reduction followed by mesylation), was subjected to nucleophilic displacement by *p*-thiocresol in the presence of NaOMe in DMF to generate a sulfide derivative **2.027** with *xylo*-configuration in 79% yield.



2.017 X = OTs; Y = H
2.018 X = H; Y = STol(p)

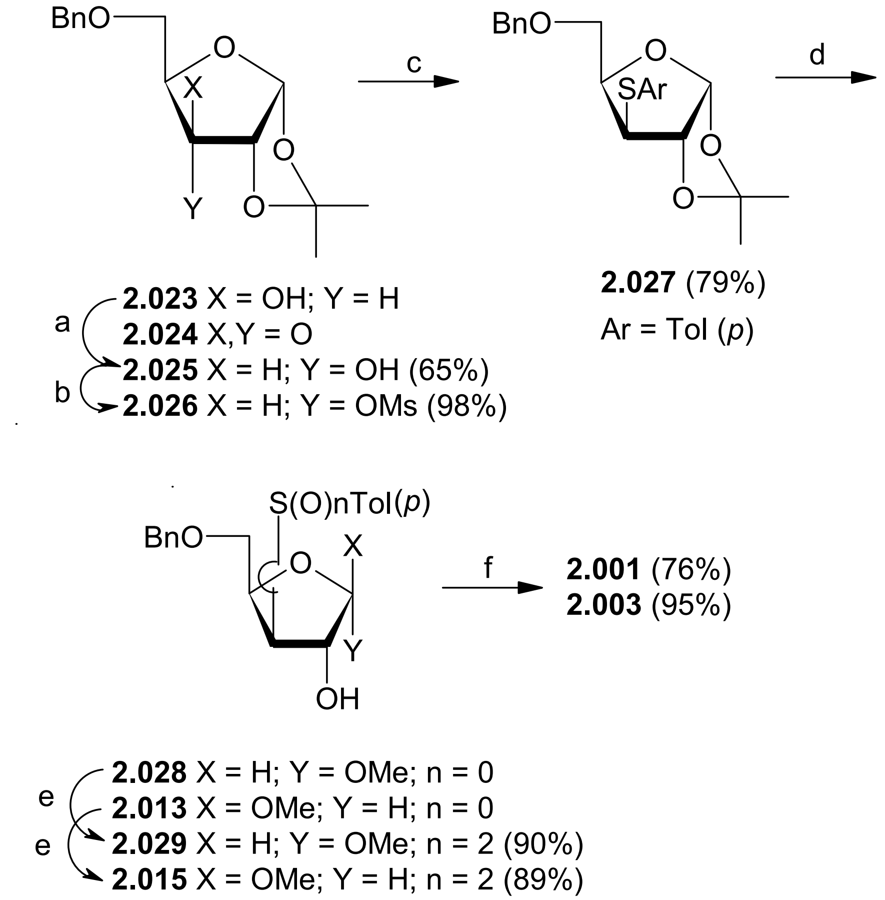
2.019 X = H; Y = OMe; n = 0
2.020 X = OMe; Y = H; n = 0
2.021 X = H; Y = OMe; n = 2
2.022 X = OMe; Y = H; n = 2

2.001 (74%)
2.003 (92%)

Reagents and conditions: a. *p*-Thiocresol, NaOMe, DMF, 115-120 ^{o}C, 3.5-4.0 h, 59%; b. MeOH, conc. H_2SO_4, 65-70 ^{o}C, 3 h, 78%, (**2.019**:**2.020** = 1:10); c. MMPP, MeOH, rt., 3 h (**2.021** = 94% & **2.022** = 93%); d. MsCl, Py., 0 ^{o}C-rt., 18-24 h.

Compound **2.027** was deprotected and glycosylated in the presence of conc. H_2SO_4 in MeOH in one step to afford a mixture of both α- and β-anomers **2.028** and **2.013** (1.5:1) in excellent yields. Compounds **2.028** and **2.013** were separated at this stage by flash chromatography. On treatment with MMPP in MeOH, compounds **2.028** and **2.013** produced the corresponding sulfones **2.029** and **2.015**, respectively in excellent yields. Compound **2.015** on treatment with mesyl chloride in pyridine smoothly generated the desired vinyl sulfone **2.003** in 95% yield whereas **2.029** generated the desired vinyl sulfone **2.001** in good yield.

Synthesis of 2.001 and 2.003 from 3-*O*-tosylated methyl D-*xylo*furanosides: The moderate yield of formation of the *ribo*-product **2.018** contributed adversely to the overall yield of **2.001** and **2.003**. This can be partly explained on the basis of the repulsion caused by the 1,2-*O*-isopropylidene group to the incoming thiolate nucleophile.[24] It was therefore, necessary to alter the strategy slightly by changing the sequence of reactions. Compound **2.017** was therefore, treated with conc. H_2SO_4 in MeOH to produce an anomeric mixture of **2.030** and **2.031** in a ratio of 1:1.3 (α:β) in 89% yield. Compounds **2.030** and **2.031** were treated with *p*-thiocresol in the presence of NaOMe in DMF at 115-120 ^{o}C to afford a mixture of 3-deoxy-3-*C*-(*p*)-tolylsulfide-D-*ribo*furanosides **2.019** and **2.020**, respectively in 94% yield. Compounds **2.019** and **2.020** were separated and converted to the desired vinyl sulfone-modified carbohydrates **2.001** and **2.003**, respectively in the usual manner described above.



2.023 X = OH; Y = H
2.024 X,Y = O
2.025 X = H; Y = OH (65%)
2.026 X = H; Y = OMs (98%)

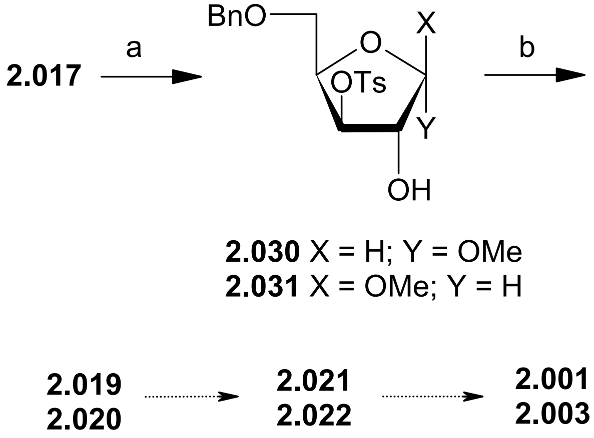
2.027 (79%)
Ar = Tol (*p*)

2.001 (76%)
2.003 (95%)

2.028 X = H; Y = OMe; n = 0
2.013 X = OMe; Y = H; n = 0
2.029 X = H; Y = OMe; n = 2 (90%)
2.015 X = OMe; Y = H; n = 2 (89%)

Reagents and conditions: a. (i) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -60 °C, 1.5 h; (ii) LAH, THF, 0 °C-rt., 3.5-4 h; b. MsCl, Py., 0 °C, 24 h; c. NaSTol(*p*), DMF, 145 °C, 3 h; d. MeOH, conc. H_2SO_4, 65-70 °C, 3 h, 89% (**2.028**:**2.013** = 1.5:1); e. MMPP, MeOH, rt., 3 h; f. MsCl, Py., 0 °C-rt., 24 h.

A New synthesis of hex-2-enopyranosides 1.050 and 1.058: In an attempt to devise an alternative methodology for the synthesis of **1.050** and **1.058** from a single starting material, the known tosylate **2.032**[25] was considered as a suitable starting material because it could be easily converted to a mixture of **2.033** and **2.034** (*via* deprotection, glycosylation followed by benzylidenation) in a ratio 1:1.5.[26] The anomers were separated on column. The β-anomer **2.034** was reacted with thiophenol in the presence of NaOMe in DMF to afford sulfide derivative **2.035**. Compound **2.035**, on oxidation with MMPP in MeOH produced the sulfone **2.036**. Compound **2.036** under mesylation condition generated smoothly the desired vinyl sulfone **1.058** in overall 79% yield (in 3 steps from **2.034**). The α-anomer **2.033**, when treated with the sodium salt of thiocresol, produced an undesired sulfide derivative, which did not produce the vinyl sulfone derivative **1.050**. Since it was reported[27] that **2.033** very easily formed the epoxide **1.027,** it is logical to conclude that under the reaction conditions *altro*-derivative **2.037** was formed[28] along with some other unidentified products. No further study was carried out on this reaction sequence because it did not produce the desired vinyl sulfone **1.050**.



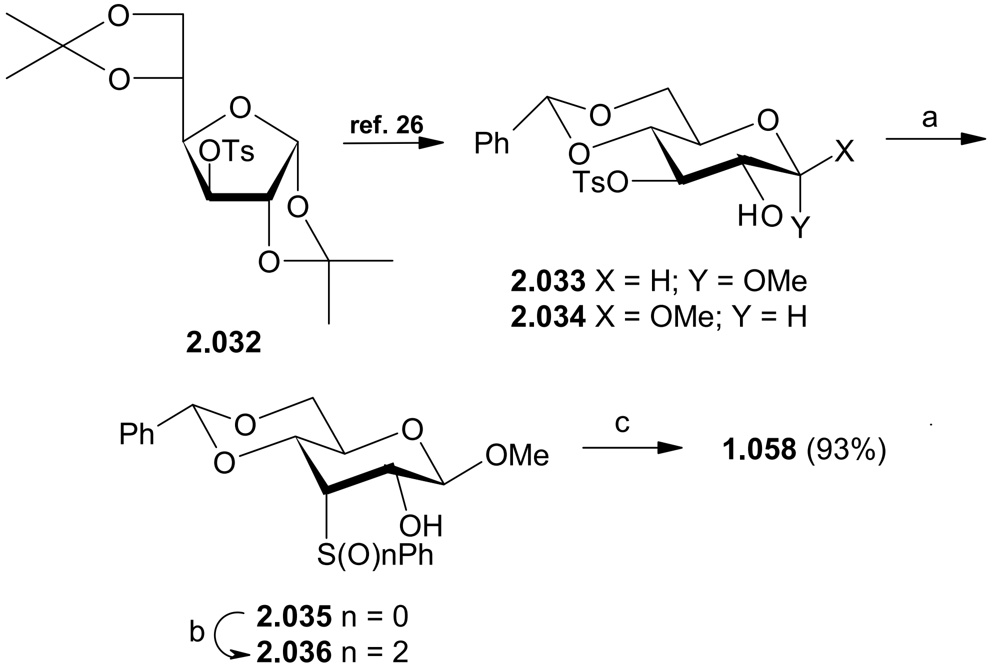
2.017

2.030 X = H; Y = OMe
2.031 X = OMe; Y = H

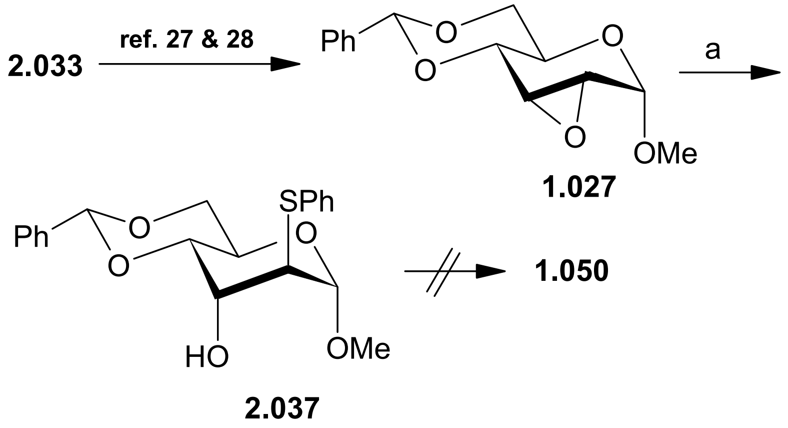
2.019
2.020
2.021
2.022
2.001
2.003

Reagents and conditions: a. MeOH, conc. H_2SO_4, 65-70 °C, 3 h, 89% (**2.030**:**2.031** = 1:1.3); b. *p*-Thiocresol, NaOMe, DMF, 115-120 °C, 3.5-4.0 h, 94%.

To overcome these problems and to have an easy access to both **1.050** and **1.058** through a single intermediate we studied another sequence of reactions where the known mesylated *allo*-derivative **2.038**[29] was treated with thiophenol in the presence of NaOMe in DMF to afford sulfide derivative **2.040** with *gluco*-configuration. Compound **2.040** was deprotected and glycosylated in a single operation by using acetyl chloride and MeOH to afford a mixture of 3-deoxy-3-phenylsulfide-hexopyranosides which were collected as the benzylidene derivatives **2.042** and **2.043** in a ratio 2.2:1 in good yields. The anomers **2.042** and **2.043** were separated on silica gel column and were converted separately to the corresponding sulfones **2.044** and **2.045** in excellent yields using MMPP in MeOH. In an alternative approach, compound **2.040** was oxidized with MMPP in MeOH to the corresponding sulfone **2.041** in excellent yield. Compound **2.041** was deprotected and glycosylated in the presence of acetyl chloride and MeOH in one step to generate a mixture of anomeric sulfones, which were collected as the benzylidene *gluco*-derivatives **2.044** and **2.045**, respectively in good yields in a ratio 1:1.8. The anomers were separated by column chromatography. Compounds **2.044** and **2.045** were mesylated and the mesylated derivatives on treatment with DBU produced the desired vinyl sulfone-modified hex-2-enopyranosides **1.050** and **1.058**, respectively in excellent yields.



Reagents and conditions: (a) PhSH, NaOMe, DMF, 135-140 °C, 2.5-3 h, 90%; (b) MMPP, MeOH, rt., 3 h, 95%; (c) MsCl, Py., 0 °C-rt., 4 h.

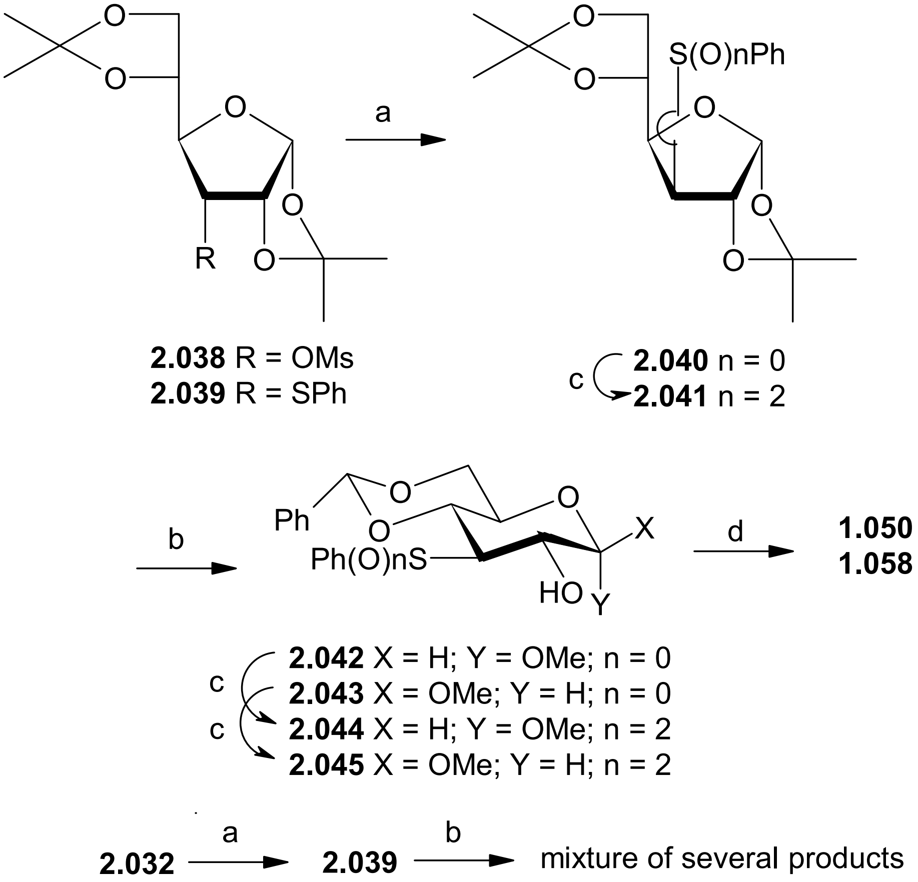


Reagents and conditions: (a) PhSH, NaOMe, DMF, 135-140 °C, 2 h, 39%.

In an alternative approach, **2.032** was converted to **2.039** by nucleophilic displacement. However, an attempt to synthesize **1.050** and **1.058** *via* compound **2.039** failed because the glycosylation step generated a mixture of several products.

2.3 Structural Assignment

The regio- and stereospecificities of attack of sodiumthiocresolate to C-3 positions of **2.005/2.006** and **2.011/2.012** were determined by the configurations of the epoxide rings and the anomeric configurations. It was, therefore a foregone conclusion that the α-*lyxo*-epoxides **2.005/2.006** would produce *arabino*-derivatives **2.007/2.008** and the β-*ribo*-epoxides would generate *xylo*-derivatives **2.013/2.014**. Similarly, backside attack of sodium thiocresolate at the C-3 positions of **2.017**, **2.026** and **2.030/2.031** would afford products **2.018**, **2.027** and **2.019/2.020**, respectively. In a similar fashion, **2.038** produced the *gluco*-derivative **2.040**.



Reagents and conditions: (a) PhSH, NaOMe, DMF, 120-125 °C, 2-4 h, **2.040** = 80% & **2.039** = 90%; (b) i. CH_3COCl, anhydr. MeOH, reflux, 24 h; ii.1,1-dimethoxytoluene, *p*-TSA, DMF,100 °C, 1 h, **2.042** + **2.043** = 71% (2.2:1) and **2.044** + **2.045** = 75% (1:1.8) (in two steps); (c) MMPP. MeOH, rt., 2-3 h, **2.041** = 94%, **2.044** = 92%, **2.045** = 90%; (d) i. MsCl, Py., 0 °C, 12 h; ii. DBU, CH_2Cl_2, rt., 15 minutes, **1.050** = 96%, **1.058** = 96% (in two steps).

However additional support for the structures, especially the relationships between H-1 and H-2 protons came from the analysis of the ^{1}H NMR spectrum. It is well documented in the literature[30-36] that for methyl α-D-pentofuranosides with D-*ribo*- and D-*xylo*-configurations, a coupling constant ($J_{1,2}$) value of 4.0-4.7 Hz is the characteristic of a *cis*-arrangement for H-1 and H-2 (**Table 2.1**) and for methyl β-D-pentofuranoside series with D-*ribo*- and D-*xylo*-configurations, a coupling constant ($J_{1,2}$) value of 0.0-2.0 Hz implied *trans*-arrangement of H-1 and H-2 (**Table 2.1**). Therefore, by comparing $J_{1,2}$ values of our compounds (**Table 2.3**) with those of the reported compounds, **2.019** (3.9 Hz) and **2.021** (4.9 Hz) were regarded as possessing α-*ribo*-configurations and **2.028** (4.4 Hz)/**2.029** (4.4 Hz) as having α-*xylo*-configurations. Similarly, by comparing the $J_{1,2}$ values of the corresponding β-series, compounds **2.020** (0 Hz), **2.022** (0 Hz) were concluded as having β-*ribo*-configurations and **2.013** (2.3 Hz), **2.015** (2.3 Hz), **2.014** (2.4 Hz) and **2.016** (3.0 Hz) as β-*xylo*-configurations. Furthermore, for methyl α-D-pentofuranosides with *arabino*- and *lyxo*-configurations, a coupling constant ($J_{1,2}$) value of 0.0-3.0 Hz indicated the *trans*-orientation of H-1 and H-2. For β-series, a value of 3.0-5.0 Hz is characteristic of a *cis*-arrangement for H-1 and H-2 (**Table 2.2**). Thus, configurations of compounds **2.007** (0.0 Hz), **2.009** (0.0 Hz), **2.008** (0.0 Hz) and **2.010** (2.0 Hz) were assigned as having α-*arabino*-configurations (**Table 2.3**).

It is also evident from **Table 2.1** that the chemical shifts of the methyl groups of methyl α-D-*ribo*furanosides as well as α-D-*xylo*furanosides with free OH groups at C-2 position (δ 3.44-3.47) were always more downfield than the corresponding values of methyl β-D-*ribo*furanosides and β-D-*xylo*furanosides (δ 3.25-3.36). In the case of our compounds, in a pair of anomers like **2.019** (δ 3.49)/**2.020** (δ 3.34), **2.021** (δ3.49)/ **2.022** (δ 3.26), **2.028** (δ 3.50)/**2.013** (δ 3.36) and **2.029** (δ 3.45)/**2.015** (δ 3.41) α-methoxy protons always appeared at a more downfield region. Interestingly, in the same pair of anomers C-1 carbons of α-anomers **2.019**, **2.021**, **2.028** and **2.029** (δ 101.2-103.2) appeared at a more upfield region than those of β-anomers **2.020**, **2.022**, **2.013** and **2.015** (δ 108.4-110.2). This observation is in agreement with the report[34] that the chemical shift values of C-1 ranging from δ 100.2-100.9 are characteristic of α-*xylo*-configurations and those of β-*xylo*-derivatives have their values ranging from δ 107.8-109.8.

In the case of the pyranosyl compounds, **2.033** and **2.034** were selected as starting materials to produce C-3 substituted *allo*-derivatives. Although **2.035** was the product of the substitution reactions as expected, the undesired *altro*-derivative **2.037** was obtained through a reported[27,28] sequence of reactions. In the case of **2.042** and **2.043**, C-S bonds at C-3 and the *gluco*-configurations of the compounds were predecided by selecting a starting material **2.040** from the known mesylate **2.038**.

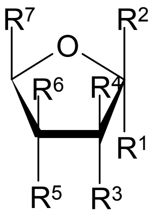


Figure 1

Table 2.1

$[\alpha]_D^T$, δ_{H-1}, $J_{1,2}$ and δ_{OMe} values of selected *ribo-* and *xylo*furanosides

$[\alpha]_D^T$	R^1	R^2	R^3	R^4	R^5	R^6	R^7	δ_{H-1}	$J_{1,2}$	δ_{OMe}	Ref.
Methyl α-D-*ribo*furanosides (in $CDCl_3$)											
+96.5	OMe	H	OH	H	OH	H	CH_2OBn	4.93	4.1	3.47	30
+77.6	OMe	H	OBn	H	OBn	H	CH_2OBn	4.86	4.0	3.44	30
+44.7	OMe	H	OTs	H	OTs	H	CH_2OBn	4.76	4.0	3.26	31
+54.0	OMe	H	OTs	H	OH	H	CH_2OBn	4.85	4.0	3.33	31
+77.4	OMe	H	OH	H	OTs	H	CH_2OBn	4.87	4.0	3.45	31
Methyl α-D-*xylo*furanosides (in $CDCl_3$)											
+118.0	OMe	H	OH	H	H	OH	CH_2OBn	4.94	4.6	3.44	30
+69.8	OMe	H	OH	H	H	OBn	CH_2OBn	4.95	4.6	3.44	30
+63.8	OMe	H	OBn	H	H	OBn	CH_2OBn	4.72	4.0	3.38	30
+194.0	OMe	H	OH	H	H	NH_2	CH_2OH	4.65	4.0	-----	32
+179.5	OMe	H	OH	H	H	NH_2	Me	4.65	4.0	-----	32
+124.5	OMe	H	OMe	H	H	OH	CH_2OBn	4.96	4.5	3.46	34
+89.3	OMe	H	OBn	H	H	OH	CH_2OBn	4.81	4.7	3.36	34
-----	OMe	H	OH	H	H	OTs	CH_2Bn	4.96	4.8	3.45	22
------	OMe	H	Br	H	H	OBz	CH_2Br	5.09	4.5	3.51	33
Methyl β-D-*ribo*furanosides (in $CDCl_3$)											
-49.6	H	OMe	OH	H	OH	H	CH_2OBn	4.80	0.0	3.30	30
+25.8	H	OMe	OBn	H	OBn	H	CH_2OBn	4.89	0.0	3.28	30
+31.9	H	OMe	OTs	H	OTs	H	CH_2OBn	4.95	0.0	3.22	31
+5.1	H	OMe	OH	H	OTs	H	CH_2OBn	4.82	0.0	3.25	31
-11.2	H	OMe	OTs	H	OH	H	CH_2OBn	4.83	1.0	3.24	31
Methyl β-D-*xylo*furanosides (in $CDCl_3$)											
-60.5	H	OMe	OH	H	H	OH	CH_2OBn	4.81	0.0	3.33	30
-43.2	H	OMe	OH	H	H	OBn	CH_2OBn	4.76	2.0	3.36	30
-22.7	H	OMe	OBn	H	H	OBn	CH_2OBn	4.89	1.3	3.38	30
-32.8	H	OMe	OMe	H	H	OH	CH_2OBn	4.92	1.0	3.40	34
-33.8	H	OMe	SCH_2Ph	H	H	Cl	CH_2OTs	4.77	1.9	3.25	35
-181.0	H	OMe	SCH_2Ph	H	H	NHAc	CH_2NHAc	4.75	1.9	3.32	35
-45.1	H	OMe	SCH_2Ph	H	H	OH	CH_2OH	4.65	1.4	3.27	35
-58.5	H	OMe	SCH_2Ph	H	H	OPNB	CH_2OPNB	4.90	1.0	3.39	35
-123.8	H	OMe	SCH_2Ph	H	H	OAc	CH_2OAc	4.65	1.5	3.26	35
-----	H	OMe	OH	H	H	OTs	CH_2Bn	4.81	0.0	3.36	22

Table 2.2

$[\alpha]_D^T$, δ_{H-1}, $J_{1,2}$ and δ_{OMe} values of selected *arabino-* and *lyxo*furanosides

$[\alpha]_D^T$	R^1	R^2	R^3	R^4	R^5	R^6	R^7	δ_{H-1}	$J_{1,2}$	δ_{OMe}	Ref.
Methyl α-D-*arabino*furanosides (in $CDCl_3$)											
+100.8	OMe	H	H	NH_2	OH	H	CH_2OH	4.50	2.0	------	32
+114.3	OMe	H	H	NH_2	OH	H	Me	4.40	3.0	------	32
+46.0	OMe	H	H	OBn	OBn	H	CH_2OBn	4.93	0.0	3.37	30
Methyl α-D-*lyxo*furanosides (in $CDCl_3$)											
+110.0	OMe	H	H	OH	H	OH	CH_2OBn	4.79	0.0	3.32	30
+17.0	OMe	H	H	OBn	H	OBn	CH_2OBn	5.00	2.4	3.35	30
Methyl β-D-*arabino*furanosides (in $CDCl_3$)											
-82.0	H	OMe	H	Br	OH	H	CH_2OBz	4.90	4.4	3.40	33
-----	H	OMe	H	Cl	OBn	H	CH_2OBn	4.88	3.7	3.33	36
------	H	OMe	H	Br	OBn	H	CH_2OBn	4.87	3.0	3.37	36
-----	H	OMe	H	I	OBn	H	CH_2OBn	4.75	3.7	3.35	36
------	H	OMe	H	N_3	OBn	H	CH_2OBn	4.58	3.3	3.35	36
-23.5	H	OMe	H	OH	SCH_2Ph	H	CH_2OH	4.69	4.4	3.42	35
+11.2	H	OMe	H	OPNB	SCH_2Ph	H	CH_2OPNB	5.04	5.0	3.27	35
-22.0	H	OMe	H	OAc	SCH_2Ph	H	CH_2OAc	4.92	4.3	3.27	35
-43.6	H	OMe	H	OBn	OBn	H	CH_2OBn	4.72	4.0	3.30	30
Methyl β-D-*lyxo*furanosides (in $CDCl_3$)											
-78.0	H	OMe	H	OH	H	OH	CH_2OBn	4.79	4.4	3.37	30
-49.1	H	OMe	H	OBn	H	OBn	CH_2OBn	4.81	4.8	3.41	30

It is reported[7-12,15,37-40] that for methyl 4,6-*O*-(phenylmethylene)-α-D-hexopyranosides with D-*gluco*-and D-*allo*-configurations, a coupling constant ($J_{1,2}$) value of 3.3-3.8 Hz is the characteristic of equatorial H-1/axial H-2 arrangements. For β-series, in general a relatively large value of $J_{1,2}$ (6.6-8.5 Hz) is characteristic of axial H-1/axial H-2 arrangement. For methyl α-D-*altro*- and D-*manno*-series of the above, a coupling constant ($J_{1,2}$) value of 0.6-1.7 Hz is characteristic of equatorial H-1/equatorial H-2 arrangements. The coupling constant values of **2.042** (3.5 Hz) and **2.044** (3.4 Hz) are consistent with $J_{1,2}$ values of reported compounds (3.3-3.8 Hz), and same of **2.043** (7.3 Hz) and **2.045** (6.9 Hz) are belonging to the range of 6.6-8.5 Hz of reported compounds.[35,36] Hence compounds **2.042** and **2.044** are concluded as having α-*gluco*-configurations and **2.043** and **2.045** are regarded as possessing β-*gluco*-configurations. Similarly, by comparison, it was inferred that compound **2.037** (0.0 Hz) is having α-*altro*-configuration and compounds **2.035** (8.3 Hz) and **2.036** (8.3 Hz) are having β-*allo*-configurations (**Table 2.4**).

It is evident from **Tables 2.1** and **2.2** that in general α-anomeric methyl glycofurano-

Table 2.3

Selected ^{1}H NMR chemical shift (δ) of synthesized pentofuranosides

α-intermediates	δ_{H-1}	$J_{1,2}$	δ_{OMe}	**C-1**		**β-intermediates**	δ_{H-1}	$J_{1,2}$	δ_{OMe}	**C-1**
2.001	5.88	4.4	3.39	107.5		**2.003**	5.72	0.0	3.42	107.3
2.002	5.90	4.4	3.30	107.5		**2.004**	5.78	0.0	3.48	107.7
2.007	4.92	0.0	3.38	109.4		**2.013**	4.81	1.9	3.36	109.3
2.008	4.99	0.0	3.39	109.4		**2.014**	4.88	2.4	3.43	109.6
2.009	4.86	0.0	3.25	108.9		**2.015**	4.87	2.3	3.41	110.2
2.010	5.03	2.0	3.37	109.0		**2.016**	4.94	3.0	3.46	110.9
2.019	4.97	3.9	3.49	103.2		**2.020**	4.98	0.0	3.34	108.4
2.021	4.95	4.9	3.49	101.9		**2.022**	4.84	0.0	3.26	108.4
2.028	4.98	4.4	3.50	101.2		**------**	----	----	----	----
2.029	4.98	4.4	3.45	101.3		**------**	----	----	----	----

Table 2.4

^{1}H NMR chemical shifts (δ) of the synthesized hexopyranosides

Compounds	δ_{H-1} **(ppm)**	$J_{1,2}$ **(Hz)**	δ_{OMe} **(ppm)**
2.035	4.40	8.3	3.60
2.036	5.11	8.3	3.57
2.037	4.81	0.0	3.35
2.042	4.77	3.5	3.41
2.043	4.36	7.3	3.55
2.044	4.87	3.4	3.48
2.045	4.45	6.9	3.60

sides show high and positive optical rotation values while β-anomeric methyl glycosides render either very small positive or negative values. In our case, methyl α-D-*ribo*furanosides, **2.018** (+100.1), **2.019** (+145.1), **2.021** (+100.9) and **2.026** (+88.2) have shown positive rotations and the corresponding β-intermediates **2.020** (-40.5) and **2.022** (-50.0) showed negative rotations. Methyl α-D-*xylo*furanosides **2.028** (+163.7) and **2.029** (+236.8) are having higher optical rotations than the corresponding β-intermediates **2.013** (+16.1) and **2.015** (+17.2), respectively. Similarly, benzylated or tritylated α-anomeric compounds **2.007** (+128.8)/**2.008** (+74.2) and **2.009** (+95.2)/**2.010** (+81.7) with *arabino*-configuration were showing higher rotation values than the β-anomeric *xylo*furanosides **2.013** (+16.1)/**2.014** (+56.9) and **2.015** (+17.2)/**2.016** (+40.9) as expected (**Tables 2.1** and **2.2**). Among 1,2-*O*-isopropylidene derivatives, intermediates with *xylo*-configuration **2.017** (-26.1) and **2.027** (-31.0) showed negative rotations whereas compounds **2.018** (+100.1) and **2.026** (+88.2) with *ribo*-configuration showed positive rotations. In the case of benzyl protected vinyl sulfone-modified carbohydrates, the α-anomer **2.001** (+5.9) is having higher rotation than the corresponding β-isomer **2.003** (-16.2) whereas the tritylated α-anomer **2.002**

(+17.1) is having slightly higher rotation than the β-anomer **2.004** (+11.4).

In the mass spectra, except for compounds **2.001** (M^+-48), **2.003** (M^+-124), **2.020** (M^+-MeOH) and **2.021** (M^+-O_2), **2.004**, **2.007-2.009**, **2.013-2.016**, **2.026-2.029**, **2.035**, **2.037**, **2.039-2.040, 2.042-2.044** showed peaks corresponding to M^+ ions. Most of the compounds rendered satisfactory elemental analysis.

2.4 Results and Discussion

A retrosynthetic analysis of the route to **2.001** and **2.003** necessitated the introduction of tolylthio group at the C-3 position of a pentose sugar. One of the easiest ways of forming a C-S bond would be the regioselective opening of epoxides derived from carbohydrates. Therefore, anomerically pure epoxides **2.005/2.006** or **2.011/2.012** have been used as starting materials. For α-vinyl sulfone, sulfides **2.007** and **2.008** with *arabino*-configuration were synthesized in 92% and 69% yields, through regioselective opening of the *lyxo*-epoxides **2.005** and **2.006**, respectively by *p*-thiocresol. Compounds **2.007** and **2.008** were converted to the desired α-vinyl sulfones **2.001** and **2.002**, respectively in high yields by sequential application of oxidation by MMPP, mesylation and base induced elimination reactions. The overall yield for **2.001** is 16% and the same for **2.002** is 13% in 9 steps each from D-xylose. Similarly, the β-vinyl sulfones **2.003** and **2.004** were synthesized *via xylo*-intermediates **2.013/2.014** and **2.015/2.016**, starting from the *ribo*-epoxides **2.011** and **2.012**, respectively. The overall yield for **2.003** is 6% and the same for **2.004** is 5% in 11 steps each from D-xylose. This route also allows the synthesis of vinyl sulfone-modified pentofuranoses having C-5 hydroxyl function masked with acid labile trityl protecting group.

It is also possible to introduce the *p*-tolylthio group at the C-3 position of the easily accessible starting material 5-*O*-benzyl-1,2-*O*-isopropylidene-3-*O*-tosyl-α-D-*xylo*furanose **2.017**. Thus, the *ribo*-analog **2.018** was generated in 59% yield by reacting **2.017** with *p*-thiocresol at high temperature. The moderate yield of the *ribo*-product **2.018** can be partly explained on the basis of the repulsion caused by the 1,2-*O*-isopropylidene group to the incoming nucleophile.[24] Compound **2.018** on methanolysis generated an anomeric mixture of **2.019** and **2.020** in 78% yield. Vinyl sulfone-modified carbohydrates **2.001** and **2.003** were obtained in the usual way. Although at this stage the less efficient conversion of **2.017** to **2.018** was acceptable, the major drawback of this methodology was the unacceptable ratio of **2.019** and **2.020** (1:10) in the mixture. The lower ratio of α-anomer **2.019** in the mixture of **2.019** and

2.020 contributed to the poor overall yield of the vinyl sulfone derivative **2.001** (1.3% in 9 steps from D-xylose); the same for β-vinyl sulfone is 17% (in 9 steps from D-xylose).

An examination of the percentage compositions of methyl furanosides of D-ribose, D-arabinose, D-xylose and D-lyxose revealed that the ratios of α- and β-furanosides present in equilibrium were 1:3.4, 3.1:1, 1:1.5 and only α-isomer, respectively.[41] Thus, the pattern of glycosylation of various pentose sugars dictated us to select a D-*xylo*-derivative based strategy for the synthesis of an anomeric mixture close to the ideal ratio of 1:1. Accordingly, it was possible to synthesize a *xylo*-derivative **2.027** from 5-*O*-benzyl-1,2-*O*-isopropylidene-3-*O*-mesyl-α-D-*ribo*furanose **2.026** in 79% yield. Compound **2.027** on methanolysis produced a mixture of anomers **2.028** and **2.013** in a ratio 1.5:1. Although this ratio was acceptable for the synthesis of both the anomers **2.001** and **2.003**, the overall yield again dropped due to the addition of two synthetic steps for converting *xylo*-derivative **2.023** to *ribo*-derivative **2.025** *via* a two-step oxidation-reduction process. Hence, the overall yield for α-vinyl sulfone **2.001** is 13% and the same for β-vinyl sulfone **2.003** is 11% (in 11 steps each from D-xylose).

It was, however, possible to circumvent all these shortcomings by first converting the *xylo*-tosylate derivative **2.017** to an anomeric mixture of **2.030** and **2.031** in a ratio 1:1.3 in high yields (89%). In the absence of any steric hindrance, the nucleophilic displacement of the tosyl group of the mixture of **2.030** and **2.031** by *p*-thiocresol proceeded smoothly to afford a mixture of 3-deoxy-3-*C*-(*p*)-tolylsulfide-D-*ribo*furanosides **2.019** and **2.020** in 94% yield. The anomers **2.019** and **2.020** were separated at this stage and were converted separately to **2.001** and **2.003** in the usual manner described above. In this case the overall yield of formation of **2.001** was 16% and the same for **2.003** was 26% (in 9 steps each from D-xylose).

After devising a route for the synthesis of hitherto unknown **2.001** and **2.003** using this novel approach, we turned our attention to the synthesis of known **1.050** and **1.058**. The existing routes for the synthesis of hex-2-enopyranose derivatives **1.050** and **1.058** are lengthy and each anomer requires separate starting material for its synthesis.[15] Starting from D-glucose, **1.050** was synthesized in 7 steps in 28% overall yield whereas synthesis of β-vinyl sulfone **1.058** was synthesized from methyl β-D-*gluco*pyranoside in 7 steps in 29% overall yield.

For the continuation of research in this area we require relatively large amount of anomerically pure **1.050** and **1.058** through a shorter route. In order to achieve this target we applied the glycosylation driven strategy for the selection of starting sugar for the synthesis of **1.050** and **1.058**. It has been reported that the equilibrium mixture of methyl-D-allosides in MeOH, contained more than 30% of furanosides[42,43] whereas D-glucose produced[41] methyl-D-pyranosides almost exclusively. Although the reported ratio of α- and β-anomers were not close to the ideal value of 1:1, in this case it was more important to get the methyl pyranosides without any contamination of the corresponding furanosides. This observation prompted us to study the feasibility of using the known tosylate **2.032** as the starting material,[25] which could be converted to an anomeric mixture of **2.033** and **2.034**[26] in a ratio 1:1.5. The β-anomer **2.034** was converted to **1.058** *via* the *allo*-derivatives **2.035** and **2.036**. The α-anomer **2.033** on treatment with thiophenol produced the undesired thiosugar **2.037** due to the *in situ* formation of 2,3-anhydro-*allo*-epoxide **1.027**.[27,28]

However, it was possible to incorporate thiophenyl group at the 3-position of the hexose prior to pyranoside formation to get two possible starting materials **2.039** and **2.040** by displacing the leaving groups of **2.032** and **2.038**, respectively by sodium thiophenolate. Here also, for reasons discussed above, the *gluco*-derivative **2.040** was the starting material of choice over the *allo*-derivative **2.039** because methanolysis of the later generated more than six products as expected.[42,43] Oxidation of **2.040** produced the sulfone derivative **2.041**. Methanolysis of **2.041** generated an anomeric mixture, which was isolated as the benzylidene derivatives **2.044** and **2.045** in a ratio 1:1.8. The anomers **2.044** and **2.045** were separated, oxidized and converted to the desired vinyl sulfone-modified hex-2-enopyranosides **1.050** and **1.058**, respectively in overall yields of 8% and 14% (from D-glucose in 10 steps for each of them). It was also possible to access **2.044** and **2.045** by first converting **2.040** to a mixture of anomers, which were isolated as their benzylidene derivatives **2.042** and **2.043** in a ratio of 2.2:1 by the above sequence of reactions. The overall yields through the later path for α-vinyl sulfone is 14% and the same for β-vinyl sulfone is 6%.

2.5 Conclusion

Both α- and β-anomers of vinyl sulfone-modified pent-2-enofuranosides **2.001-2.004** have been synthesized for the first time using epoxides derived from carbohydrates as starting materials as well as by taking advantage of the formation of α- and β-methyl glycosides in almost equal ratio only from derivatives of D-xylose. In the synthesis of α- and β-anomers of vinyl sulfone-modified hex-2-enopyranosides, a D-glucose derivative was selected over a D-allose compound as the starting material because the former almost exclusively produced the required methyl pyranosides. Compounds **1.050** and **1.058** have been synthesized earlier[15] from D-glucose in 14 steps (7 steps for each anomer). The present method makes use of common intermediates up to compounds **2.044** and **2.045**, thereby drastically reducing the overall purification steps. Although overall yields for both the methods are comparable, methyl β-D-*gluco*pyranoside, which has been used in the earlier synthesis,[15] is far too expensive as a starting material to be used in a large-scale multi-step synthesis.

2.6 Experimental

General methods. Melting points were determined in open-end capillary tubes and are uncorrected. Carbohydrates and other fine chemicals were obtained from commercial suppliers and are used without purification. Solvents were dried and distilled following the standard procedures.**[44]** TLC was carried out on precoated plates (Merck silica gel 60, f_{254}) and the spots were visualized with UV light or by charring the plate dipped in 5% H_2SO_4-MeOH solution. Column chromatography was performed on silica gel (60-120 or 230-400 mesh). ^{1}H NMR were recorded at 200 MHz using AC 200 MHz, at 300 MHz using MSL 300 MHz or at 500 MHz using DRX 500 MHz in $CDCl_3$ using the residual $CHCl_3$ as standard. ^{13}C NMR were recorded at 50.3 and 75 MHz in $CDCl_3$ using the triplet centered at δ77.27 as the standard. Optical rotations were recorded at 589 nm.

General procedure for the synthesis of 2.007, 2.008, 2.013 and 2.014: To a well stirred solution of **2.005**, **2.006**, **2.011** or **2.012** in DMF (4 mL/mmol) were added *p*-thiocresol (5 eq) and NaOMe (4 eq) and the mixture was heated at 80-90 °C for 2.5-3.5 h with stirring. After completion of the reaction (tlc), the reaction mixture was poured into saturated solution of NaCl (60 mL/mmol) and the product was extracted with EtOAc. The combined organic layers were dried over anhydr. Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to get a gummy residue. The residue was purified over silica gel column to obtain the title compound.

General procedure for the MMPP oxidation: To a well-stirred solution of the arylsulfide furanoses or pyranoses in distilled MeOH (20 mL/mmol) was added MMPP (5 eq) and the mixture was stirred for 2-3 h. After completion of the reaction (tlc), the solid mass was filtered off through celite bed. The filtrate was evaporated to dryness under reduced pressure and the solid residue thus obtained was dissolved in saturated

$NaHCO_3$. The aqueous solution was washed with EtOAc (4 x 30 mL). The combined organic layers were dried over anhydr. Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to get a residue. The residue was purified over silica gel column to obtain the sulfones **2.009**, **2.010**, **2.015**, **2.016**, **2.021**, **2.022**, **2.029**, **2.036**, **2.041**, **2.044** and **2.045**.

General procedure for the formation of 1.050, 1.058 and 2.001-2004: To a well stirred solution of the arylsulfonyl furanoses or pyranoses in pyridine (5 mL/mmol) was added mesyl chloride (4-6 eq) in pyridine (1 mL/mmol of MsCl) dropwise at 0 °C under nitrogen. After completion of the addition, the reaction mixture was kept at +4 °C. After 24 h (tlc), the reaction mixture was poured into ice-cold water (10 mL/mmol of sugar) and aqueous layer was extracted with $CHCl_3$ (3x20 mL). The combined organic layers were dried over anhydr. Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The crude material was purified over silica gel column to get any of the title compounds.

Methyl 5-*O*-benzyl-2,3-dideoxy-3-*C*-(*p*)-tolylsulfonyl-α-D-*erythro*-pent-2-enofuranoside 2.001: Compound **2.009** (0.48 g, 1.232 mmol) was converted to **2.001** following the general procedure described above. Eluent: EtOAc:pet ether (1:9).

Yield: 0.38 g, 82%.

Mp: Gummy.

$[\alpha]_D^{25}$: + 5.9° (c 0.927, $CHCl_3$).

IR ($CHCl_3$): 3444, 2358, 1953, 1892, 1776, 1724, 1596 cm^{-1}.

^{1}H NMR: δ 7.78 (2 H, d, *J* 8.3 Hz, aromatic), 7.30 (7 H, m, aromatic), 6.59 (1 H, s), 5.88 (1 H, d, *J* 4.4 Hz), 5.13 (1 H, m), 4.44 (2 H, s, $PhCH_2$), 3.85 (1 H, dd, *J* 10.7, 2.4 Hz), 3.60 (1 H, dd, *J* 10.7, 4.4 Hz), 3.39 (3 H, s, OMe), 2.42 (3 H, s, aromatic Me).

^{13}C NMR: δ 147.2, 137.0, 145.3, 138.1, 136.4, 130.1, 128.3, 127.5, 107.5 (C-1), 83.6, 73.3 (CH_2), 70.3 (CH_2), 54.6 (OMe), 21.6 (aromatic Me).

MS: m/z (EI) 326 (0.4 M^+-48), 251 (3), 236 (23), 219 (6), 139 (9), 105 (17), 91 (100), 77 (33), 65 (48).

Analysis: Cald. for $C_{20}H_{22}O_5S$: C, 64.15; H, 5.91; S, 8.56. Found: C, 64.48; H, 5.90; S, 8.67.

Methyl 2,3-dideoxy-3-*C*-(*p*)-tolylsulfonyl-5-*O*-trityl-α-D-*erythro*-pent-2-enofuranoside 2.002: Compound **2.010** (3.14 g, 5.77 mmol) was converted to **2.002** following the general procedure described above. Eluent: EtOAc:pet ether (1:4).

Yield: 2.56 g, 84%.

Mp: Hygroscopic fluffy material.

$[\alpha]_D^{26}$: +17.1° (c 1.07, $CHCl_3$).

IR ($CHCl_3$): 4214, 3479, 2401, 1596, 1490 cm^{-1}.

^{1}H NMR: δ 7.52 (2 H, d, *J* 8.3 Hz, aromatic); 7.2 (17 H, m, aromatic), 6.56 (1 H, s, H-2), 5.90 (1 H, d, *J* 4.4 Hz, H-1), 5.02 (1 H, m), 3.43 (1 H, dd, *J* 10.7, 2.4 Hz), 3.30 (3 H, s, OMe), 3.08 (1 H, dd, *J* 10.8, 4.9 Hz), 2.32 (3 H, s, aromatic Me).

^{13}C NMR: δ 147.5, 145.2, 143.9, 137.3, 136.3, 130.0, 128.8, 128.1, 127.8, 127.1, 107.5 (C-1), 86.9, 83.8, 64.7 (CH_2), 54.2 (OMe), 21.7 (aromatic Me).

MS: m/z (EI) 449 (<2), 243 (100), 165 (66), 91 (30).

Analysis: Cald. for $C_{32}H_{30}O_5S.1H_2O$: C, 70.57; H, 5.54; S, 5.88. Found: C, 70.60; H, 5.76; S, 6.75.

Methyl 5-*O*-benzyl-2,3-dideoxy-3-*C*-(*p*)-tolylsulfonyl-β-D-*erythro*-pent-2-enofuranoside 2.003: Compound **2.015** (0.25 g, 0.637 mmol) was converted to **2.003** following the general procedure described above. Eluent: EtOAc:pet ether (1:3).

Yield: 0.21 g, 87%.

Mp: Gummy material.

IR ($CHCl_3$): 1722, 1596, 1494 cm^{-1}.

$[\alpha]_D^{26}$: –16.2° (c 1.004, $CHCl_3$).

^{1}H NMR: δ 7.75 (2 H, d, *J* 8.3 Hz, aromatic), 7.30 (7 H, m, aromatic), 6.60 (1 H, s), 5.72 (1 H, s), 4.95 (1 H, d, *J* 6.3 Hz), 4.47 (2 H, s, $PhCH_2$), 3.83 (1 H, dd, *J* 10.7, 2.4 Hz), 3.50 (1 H, m), 3.42 (3 H, s, OMe), 2.43 (3 H, s, aromatic Me).

^{13}C NMR: δ 147.6, 136.6, 145.3, 138.2, 136.3, 130.0, 128.3, 127.5, 107.3 (C-1), 83.4, 73.2 (CH_2), 72.0 (CH_2), 55.3 (OMe), 21.6 (aromatic Me).

MS: m/z (EI) 250 (6 M^+-124), 236 (91 M^+-138), 218 (13 M^+-156), 139 (16), 105 (17), 91 (100), 77 (30), 65 (46).

Analysis: Cald. for $C_{20}H_{22}O_5S$: C, 64.15; H, 5.91; S, 8.56. Found: C, 64.41; H, 6.36; S, 8.81.

Methyl 2,3-dideoxy-3-*C*-(*p*)-tolylsulfonyl-5-*O*-trityl--β-D-*erythro*-pent-2-enofuranoside 2.004: Compound **2.016** (0.46 g, 0.838 mmol) was converted to **2.004** following the general procedure described earlier. Eluent: EtOAc:pet ether (1:4).

Yield: 0.37 g, 84%.

Mp: 131-132 °C.

$[\alpha]_D^{26}$: +11.4° (c 1.012, $CHCl_3$).

IR (Nujol): 3097, 3051, 3028, 1593, 1490, 1463, 1448, 1377 cm^{-1}.

^{1}H NMR: δ 7.53 (2 H, d, *J* 8.3 Hz, aromatic), 7.42 (6 H, dd, *J* 8.3, 2.4 Hz, aromatic), 7.34-7.25 (9 H, m, aromatic), 7.17 (2 H, d, *J* 7.8 Hz, aromatic), 6.64 (1 H, t, *J* 1.5, 1.4 Hz, H-2), 5.78 (1 H, s, H-1), 5.00 (1 H, d, *J* 6.8 Hz), 3.48 (3 H, s, OMe), 3.37 (1 H, dd, *J* 10.3, 2.0 Hz), 3.09 (1 H, dd, *J* 10.3, 6.8 Hz), 2.41 (3 H, s, aromatic Me).

^{13}C NMR: δ 147.4, 145.1, 143.9, 136.9, 136.2, 130.1, 128.9, 128.0, 127.1, 107.7 (C-1), 86.7, 83.7, 66.0 (CH$_2$), 55.9, 21.7 (aromatic Me).

MS: m/z (EI) 526 (0.1 M$^+$), 494 (0.1), 450 (0.8), 449 (0.9), 267 (0.9), 243 (100), 165 (36), 91 (16), 77 (9).

Analysis: Cald. for $C_{32}H_{30}O_5S$: C, 72.98; H, 5.73: S, 6.08. Found: C, 73.12; H, 5.72; S, 5.54.

Methyl 5-*O*-benzyl-3-deoxy-3-*C*-(*p*)-tolylsulfide-α-D-*arabino*furanoside 2.007: Compound **2.005** (0.57 g, 2.43 mmol) was converted to **2.007** following the general procedure described above. Eluent: EtOAc:pet ether (1:4).

Yield: 0.81 g, 92%.

Mp: Oily.

[α]$_D$^{26}: +128.8° (c 1.00, CHCl$_3$).

IR (Neat on KBr plate): 3438, 3062, 3030, 2866, 2833,1596, 1494, 1454, 1400 cm^{-1}.

^{1}H NMR: δ 7.30 (7 H, m, aromatic), 7.06 (2 H, d, *J* 8.3 Hz, aromatic), 4.92 (1 H, s, H-1), 4.61 (1 H, d, *J* 12.2 Hz), 4.48 (1 H, d, *J* 11.8 Hz), 4.42 (1 H, m), 4.13 (1 H, d, *J* 10.0 Hz), 3.77 (1 H, dd, *J* 10.7, 2.0 Hz), 3.56 (1 H, d, *J* 9.8 Hz), 3.44 (2 H, m), 3.38 (3 H, s, OMe), 2.29 (3 H, s, aromatic Me).

^{13}C NMR: δ 137.2, 136.6, 131.1, 129.5, 128.1, 127.5, 109.4 (C-1), 82.9, 81.0, 73.0 (CH$_2$), 69.4 (CH$_2$), 54.6 (OMe), 52.9, 20.6 (aromatic Me).

MS: m/z (EI) 360 (9 M$^+$), 328 (2), 221 (1), 189 (1), 179 (3), 165 (5), 124 (39), 91 (100).

Analysis: Cald. for $C_{20}H_{24}O_4S$: C, 66.64; H, 6.70; S, 8.89. Found: C, 66.34; H, 7.34: S, 8.89.

Methyl 3-deoxy-3-*C*-(*p*)-tolylsulfide-5-*O*-trityl-α-D-*arabino*furanoside 2.008: Compound **2.006** (5.1 g, 13.13 mmol) was converted to **2.008** following the general procedure described above. Eluent: EtOAc:pet ether (3:7).

Yield: 4.61 g, 69%.

Mp: Gummy.

[α]$_D$^{25}: +74.2° (c 1.09, CHCl$_3$).

IR (CHCl$_3$): 3442, 2831, 1666, 1492 cm^{-1}.

^{1}H NMR: δ 7.28 (17 H, m, aromatic), 6.98 (2 H, d, *J* 8.3 Hz, aromatic), 4.99 (1 H, s, H-1), 4.15 (2 H, a broad hump), 3.56 (1 H, dd, *J* 10.3, 2.5 Hz), 3.39 (3 H, s, OMe), 3.35 (1 H, m), 3.05 (1 H, dd, *J* 11.3, 4.0 Hz), 2.80 (1 H, d, *J* 2.5 Hz, OH), 2.27 (3 H, s, aromatic Me).

^{13}C NMR: δ 143.5, 136.8, 131.4, 131.2, 129.7, 128.6, 127.8, 127.0, 109.4, 87.1, 83.1, 81.3, 63.8 (CH_2), 54.9 (OMe), 53.5, 20.9 (aromatic Me).

MS: m/z (EI) 512 (4 M^+), 270 (2), 259 (2), 251 (3), 244 (8), 243 (100).

Analysis: Cald. for $C_{32}H_{32}O_4S.1H_2O$: C, 72.43; H, 6.07; S, 6.04. Found: C, 72.25; H, 6.45; S, 5.73.

Methyl 5-*O*-benzyl-3-deoxy-3-*C*-(*p*)-tolylsulfonyl-α-D-*arabino*furanoside 2.009: Compound **2.007** (0.59 g, 1.652 mmol) was converted to **2.009** following the general procedure described above. Eluent: EtOAc:pet ether (1:4).

Yield: 0.6 g, 93%.

Mp: Gummy.

$[\alpha]_D^{26}$: +95.2° (c 1.00, $CHCl_3$).

IR (Neat on KBr plate): 3481, 3062, 3030, 2925, 1596, 1494, 1454, 1402, 1363 cm^{-1}.

^{1}H NMR: δ 7.73 (2 H, d, *J* 8.3 Hz, aromatic), 7.29 (7 H, m, aromatic), 4.86 (1 H, s, H-1), 4.48 (5 H, m), 3.69 (2 H, m), 3.33 (1 H, dd, *J* 11.3(10.8), 3.9(3.4) Hz), 3.25 (3 H, s, OMe), 2.39 (3 H, s, aromatic Me).

^{13}C NMR: δ 144.9, 137.3, 134.9, 129.6, 128.3, 128.1, 127.5, 108.9, 77.2, 77.0, 73.1 (CH_2), 71.0, 69.4 (CH_2), 54.5 (OMe), 21.2 (aromatic Me).

MS: m/z (EI) 392 (<1.0 M^+), 343 (0.3), 301 (0.4), 271 (0.6), 262 (1.2), 243 (0.9), 205 (4), 155 (7), 107 (32), 92 (14), 91 (100).

Analysis: Cald. for $C_{20}H_{24}O_6S.0.25H_2O$: C, 60.50; H, 6.21; S, 8.07. Found: C, 60.43; H, 6.46; S, 8.21.

Methyl 3-deoxy-3-*C*-(*p*)-tolylsulfonyl-5-*O*-trityl-α-D-*arabino*furanoside 2.010: Compound **2.008** (3.82 g, 7.460 mmol) was converted to **2.010** following the general procedure described above. Eluent: EtOAc:pet ether (3:7).

Yield: 3.31 g, 81%.

Mp: 70-71 °C.

$[\alpha]_D^{25}$: +81.7° (c 1.01, $CHCl_3$).

IR ($CHCl_3$): 3479, 1637, 1596, 1492 cm^{-1}.

^{1}H NMR: δ 7.62 (2 H, d, *J* 8.3 Hz, aromatic), 7.29 (17 H, m, aromatic), 5.03 (1 H, d, *J* 2.0 Hz, H-1), 4.64 (1 H, m), 4.49 (1 H, m), 3.80 (1 H, m), 3.45 (1 H, dd, *J* 10.8, 2.0 Hz), 3.37 (3 H, s, OMe), 2.73 (2 H, m), 2.42 (3 H, s, aromatic Me).

^{13}C NMR: δ 145.1, 143.7, 135.3, 130.0, 128.7, 128.5, 127.9, 127.2, 109.0, 86.9, 77.3, 71.4, 63.9 (CH_2), 55.3, 21.7 (aromatic Me).

MS: m/z (EI) 287 (1), 259 (1), 244 (6), 243 (100), 228 (3), 165 (19).

Analysis: Cald. for $C_{32}H_{32}O_6S.1H_2O$: C, 68.31; H, 5.72; S, 5.69. Found: C, 68.01; H, 5.62; S, 6.78.

Methyl 5-*O*-benzyl-3-deoxy-3-*C*-(*p*)-tolylsulfide-β-D-*xylo*furanoside 2.013: Compound **2.011** (0.44 g, 1.851 mmol) was converted to **2.013** following the general procedure described above. Eluent: EtOAc:pet ether (1:9).

Yield: 0.53 g, 79%.

Mp: Gummy.

$[\alpha]_D^{30}$: +16.1° (c 1.04, $CHCl_3$).

IR (neat): 3425, 3062, 3031, 2923, 2862 cm^{-1}.

^{1}H NMR: δ 7.28 (7 H, m, aromatic), 7.03 (2 H, d, *J* 8.3 Hz, aromatic), 4.81 (1 H, d, *J* 1.9 Hz, H-1), 4.60 (1 H, m), 4.54 (2 H, s, $PhCH_2$), 4.25 (1 H, dd, *J* 4.9, 1.9 Hz), 3.76-3.63 (3 H, 2 x m), 3.36 (3 H, s, OMe), 3.25 (1 H, broad hump, OH), 2.27 (3 H, s, aromatic Me).

^{13}C NMR: δ 138.0, 136.0, 132.2, 130.3, 129.7, 128.1, 127.7, 127.4, 109.4 (C-1), 81.1, 79.9, 73.1 (CH_2), 71.2 (CH_2), 55.3 (OMe), 54.7, 20.8 (aromatic Me).

MS: m/z (EI) 360 (11 M^+), 328 (11), 149 (20), 135 (15), 124 (41), 91 (100).

Analysis: Cald. for $C_{20}H_{24}O_4S$: C, 66.64; H, 6.70; S, 8.89. Found: C, 66.32; H, 7.24; S, 8.81.

Methyl 3-deoxy-3-*C*-(*p*)-tolylsulfide-5-*O*-trityl-β-D-*xylo*furanoside 2.014: Compound **2.012** (1.3 g, 3.37 mmol) was converted to **2.014** following the general procedure described above. Eluent: EtOAc:pet ether (1:9).

Yield: 1.641 g, 95%.

Mp: 114-115 °C.

$[\alpha]_D^{26}$: +56.9° (c 1.008, $CHCl_3$)

IR ($CHCl_3$): 4212, 3608, 3431, 2399, 1492, 1448 cm^{-1}.

^{1}H NMR: δ 7.51 (6 H, d, *J* 6.8 Hz, aromatic), 7.25 (10 H, m, aromatic), 7.02 (3 H, dd, *J* 26.3, 7.8 Hz, aromatic), 4.88 (1 H, d, *J* 2.4 Hz, H-1), 4.57-4.49 (1 H, m), 4.35 (1 H, bs), 3.58 (1 H, t, *J* 6.9, 5.8 Hz), 3.43 (3 H, s, OMe), 3.41-3.32 (2 H, m), 2.65 (1 H, *J* 4.4 Hz, OH), 2.25 (3 H, s, aromatic Me).

^{13}C NMR: δ 144.2, 137.1, 132.1, 131.4, 129.9, 129.0, 127.8, 127.4, 109.6 (C-1), 87.1, 88.9, 81.2, 65.3 (CH_2), 55.9, 55.6, 21.1 (aromatic Me).

MS: m/z (EI) 512 (2 M$^+$), 269 (30), 243 (100).

Analysis: Cald. for $C_{32}H_{32}O_4S$: C, 74.97; H, 6.28; S, 6.25. Found: C, 75.00; H, 6.21; S, 6.22.

Methyl 5-*O*-benzyl-3-deoxy-3-*C*-(*p*)-tolylsulfonyl-β-D-*xylo*furanoside 2.015: Compound **2.013** (0.4 g, 1.11 mmol) was converted to **2.015** following the general procedure described above. Eluent: EtOAc:pet ether (3:7).

Yield: 0.39 g, 89%.

Mp: Gummy.

$[\alpha]_D^{27}$: +17.2° (c 1.10, $CHCl_3$).

IR ($CHCl_3$): 3479, 3087, 3062, 3029, 2927, 2869 cm^{-1}.

^{1}H NMR: δ 7.75 (2 H, d, *J* 8.0 Hz, aromatic), 7.31 (7 H, m, aromatic), 4.87 (1 H, d, *J* 2.3 Hz, H-1), 4.74 (1 H, dd, *J* 8.0, 2.0 Hz), 4.58 (2 H, s, $PhCH_2$), 4.48 (1 H, m), 3.91 (3 H, m), 3.41 (3 H, s, OMe), 3.00 (1 H, bs, OH), 2.42 (3 H, s, aromatic Me).

^{13}C NMR: δ 144.9, 137.8, 136.2, 129.7, 128.0, 127.5, 127.3, 110.2 (C-1), 78.1, 76.2, 73.1 (CH_2), 71.3, 69.8 (CH_2), 55.6 (OMe), 21.2 (aromatic Me).

MS: m/z (EI) 392 (<1 M$^+$), 360 (6), 205 (9), 187 (9), 155 (20), 139 (22), 107 (33), 99 (32), 99 (100).

Analysis: Cald. for $C_{20}H_{24}O_6S$: C, 61.20; H, 6.16; S, 8.17. Found: C, 61.37; H, 5.89; S, 9.14.

Methyl 3-deoxy-3-*C*-(*p*)-tolylsulfonyl-5-*O*-trityl-β-D-*xylo*furanoside 2.016: Compound **2.014** (1.38 g, 2.69 mmol) was converted to **2.016** following the general procedure described above. Eluent: EtOAc:pet ether (1:3).

Yield: 1.08 g, 74%.

Mp: 74-75 °C.

$[\alpha]_D^{26}$: +40.9° (c 1.00, $CHCl_3$).

IR (Nujol): 3469, 1596, 1490, 1463, 1448, 1377 cm^{-1}.

^{1}H NMR: δ 7.51-7.20 (19 H, a broad multiplet, aromatic), 4.94 (1 H, d, *J* 3.0 Hz, H-1), 4.75 (1 H, dd, *J* 2.5 (3.0), 7.8(8.3) Hz), 4.34 (1 H, m), 3.83 (1 H, t, *J* 58.3, 7.8 Hz), 3.42-3.64 (2 H, m), 3.46 (3 H, s, OMe), 2.82 (1 H, bs, OH), 2.43 (3 H, s, aromatic Me).

^{13}C NMR: δ 145.8, 144.5, 136.7, 130.7, 129.5, 128.6, 128.4, 127.6, 110.9, 87.5, 79.2, 77.2, 72.2, 64.5 (CH_2), 56.8, 21.8 (aromatic Me).

MS: m/z (EI) 544 (1 M$^+$), 470 (2), 405 (2), 360 (3), 243 (100).

Analysis: Cald. for $C_{32}H_{32}O_6S.2H_2O$: C, 66.18; H, 6.24; S, 5.52. Found: C, 66.28; H, 6.30; S, 5.93

5-*O*-benzyl-1,2-*O*-isopropylidene-3-*O*-tosyl-α-D-*xylo*furanose 2.017: *p*-Tolylsulfonyl chloride (6.12 g, 32.14 mmol) was added to a stirred solution of 5-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*furanose[22] (3.0 g, 10.71 mmol) in pyridine (50 mL) at 0 °C under nitrogen and the mixture was stirred at an ambient temperature. After 36 h, the reaction mixture was poured into an ice-water mixture (150 mL) and the aqueous phase was extracted with $CHCl_3$ (5 x 30 mL). The combined organic layers were dried over anhydr. Na_2SO_4, filtered and filtrate was concentrated to dryness under reduced pressure. Purification of the crude material by column chromatography using EtOAc:pet ether (1:4) generated the title compound **2.017** as a yellowish gum.

Yield: 4.53 g, 97%.

Mp: Gummy.

$[\alpha]_D^{26}$: –26.1° (c 1.06, $CHCl_3$).

IR (Nujol): 3046, 2871, 2360, 2339, 1703, 1596, 1454 cm^{-1}.

^{1}H NMR: δ 7.76 (2 H, d, *J* 8.3 Hz, aromatic), 7.2 (7 H, m, aromatic), 5.92 (1 H, d, *J* 3.4 Hz), 4.83 (1 H, d, *J* 2.9 Hz), 4.69 (1 H, d, *J* 3.9 Hz), 4.38 (3 H, m), 3.54 (2 H, dq), 2.38 (3 H, s, aromatic Me), 1.28 (3 H, s, Me), 1.46 (3 H, s, Me).

^{13}C NMR: δ 145.4, 137.8, 133.0, 130.0, 128.4, 127.9, 127.7, 127.6, 112.4, 104.8 (C-1), 83.2, 82.3, 77.9, 73.4 (CH_2), 66.9 (CH_2), 26.3 (3 H, s, Me), 26.6 (3 H, s, Me), 21.6 (aromatic Me).

MS: m/z (EI) 434 (5 M^+), 313 (4), 175 (8), 155 (43), 149 (9), 113 (24), 107 (13), 91 (100).

Analysis: Cald. for $C_{22}H_{26}O_7S$: C, 60.81; H, 6.02; S, 7.37. Found: C, 60.29; H 7.77; S, 7.94.

5-*O*-benzyl-3-deoxy-1,2-*O*-isopropylidene-3-*C*-(*p*)-tolylsulfide-α-D-*ribo*furanose 2.018: To a well stirred solution of NaOMe (1.98 g, 36.79 mmol) in DMF (40 mL) was added *p*-thiocresol (5.7 g, 45.99 mmol) and the mixture was stirred for 0.5 h. A solution of **2.017** (3.99 g, 9.19 mmol) in DMF (20 mL) was added and the reaction mixture was then heated at 120 °C. After 4 h, the mixture was cooled to room temperature and poured into brine (150 mL) solution. The aqueous phase was extracted with EtOAc (5 x 30 mL). The combined organic phases were dried over anhydr. Na_2SO_4, filtered and the filtrate was concentrated to dryness under reduced pressure. Purification of the crude product on silica gel using EtOAc:pet ether (1:19) yielded **2.018**.

Yield: 2.08 g, 59%.

Mp: Grayish gummy.

$[\alpha]_D^{26}$: +100.1° (c 1.02, $CHCl_3$).

IR ($CHCl_3$): 1492, 1454, 1384 cm^{-1}.

^{1}H NMR: δ 7.28 (9 H, m, aromatic); 5.84 (1 H, d, *J* 3.4 Hz, H-1), 4.80 (1 H, t, *J* 3.9 Hz), 4.37 (2 H, d, *J* 2.9 Hz, $PhCH_2$), 4.16 (1 H, m), 3.80 (1 H, dd, *J* 11.2, 1.5 Hz), 3.53 (2 H, m), 2.32 (3 H, s, aromatic Me), 1.56 (3 H, s, Me), 1.37 (3 H, s, Me).

^{13}C NMR: δ 137.9, 137.0, 131.9, 129.6, 128.0, 127.3, 111.8, 104.1, 81.3, 73.1 ($PhCH_2$), 67.6 (CH_2), 50.7, 26.5 (Me), 26.3 (Me), 20.8 (aromatic Me).

MS: m/z (EI) 386 (18 M^+), 328 (20), 207 (33), 163 (20), 123 (75), 91 (100).

Analysis: Cald. for $C_{22}H_{26}O_4S$: C, 68.36; H, 6.77; S, 8.29. Found: C, 68.25; H, 6.87; S, 8.62.

Methyl 5-*O*-benzyl-3-deoxy-3-*C*-(*p*)-tolylsulfide-α-D-*ribo*furanoside 2.019 & methyl 5-*O*-benzyl-3-deoxy-3-*C*-(*p*)-tolylsulfide-β-D-*ribo*furanoside 2.020: A solution of **2.018** (2.08 g, 5.39 mmol) and conc. H_2SO_4 (1 mL) in dry MeOH (30 mL) was heated under reflux in an inert atmoshphere. After 3.5 h, the reaction mixture was cooled to room temperature and neutralized by $BaCO_3$. The mixture was evaporated to dryness under reduced pressure and the residue was triturated with EtOAc (3 x 40 mL). The mixture was filtered through celite and the combined filtrates were concentrated to dryness under reduced pressure. Purification of the gummy residue over silica gel using EtOAc:pet ether (4:21) furnished a mixture of **2.019** and **2.020**. Compound **2.019** and **2.020** were isolated as colorless thick gum.

Total yield: 1.52 g, 78%.

Compound 2.019:

Isolated yield: 0.05 g, 2.6%.

Mp: Gummy.

$[\alpha]_D^{26}$: +145.1° (c 1.024, $CHCl_3$).

IR ($CHCl_3$): 3523, 1492 cm^{-1}.

^{1}H NMR: δ 7.31 (7 H, m, aromatic), 7.08 (2 H, d, *J* 8.3 Hz, aromatic), 4.97 (1 H, d, *J* 3.9 Hz), 4.53 (2 H, m, $PhCH_2$), 4.39 (1 H, m), 4.25 (1 H, m), 3.61 (3 H, m), 3.49 (3 H, s, OMe), 3.2 (1 H, d, *J* 9.8 Hz, OH), 2.33 (3 H, s, aromatic Me).

^{13}C NMR: δ 138.3, 137.3, 132.7, 131.7, 130.0, 128.6, 127.8, 103.2 (C-1), 82.9, 73.8 (CH_2), 71.9, 70.4 (CH_2), 55.5 (OMe), 52.8, 21.2 (aromatic Me).

MS: m/z (EI) 360 (3 M^+), 328 (2), 163 (4), 124 (38), 91 (100).

Analysis: Cald. for $C_{20}H_{24}O_4S$: C, 66.64; H, 6.70; S, 8.89. Found: C, 66.90; H, 6.72; S, 9.05.

Compound 2.020:

Isolated yield: 1.07 g, 55%.

Mp: Gummy.

$[\alpha]_D^{26}$: – 40.5° (c 1.01, $CHCl_3$).

IR ($CHCl_3$): 3444, 1951, 1888, 1598 cm^{-1}.

^{1}H NMR: δ 7.35 (7 H, m, aromatic), 7.11 (2 H, d, *J* 7.9 Hz, aromatic), 4.98 (1 H, s, H-1), 4.64 (2 H, s, $PhCH_2$), 4.17 (1 H, m), 3.98 (1 H, dd, *J* 3.9, 1.4 Hz), 3.71 (4 H, m), 3.34 (3 H, s, OMe), 2.90 (1 H, d, *J* 1.5 Hz, OH), 2.33 (3 H, s, aromatic Me).

^{13}C NMR: δ 138.5, 138.0, 132.1, 130.2, 129.9, 128.5, 127.6, 108.4 (C-1), 81.7, 74.9, 73.4 (CH_2), 71.8 (CH_2), 54.7 (OMe), 53.5, 21.1 (aromatic Me).

MS: m/z (EI) 360 (13 M^+), 328 (4), 124 (23), 123 (18), 91 (100).

Analysis: Cald. for $C_{20}H_{24}O_4S$: C, 66.64; H, 6.70; S, 8.89. Found: C, 66.80; H, 7.00; S, 8.82.

Methyl 5-*O*-benzyl-3-deoxy-3-*C*-(*p*)-tolylsulfonyl-α-D-*ribo*furanoside 2.021: Compound **2.019** (0.05 g, 0.127 mmol) was converted to **2.021** following the general procedure described above. Eluent: EtOAc:pet ether (3:7).

Yield: 0.04 g, 94%.

Mp: Gummy.

$[\alpha]_D^{26}$: +100.9° (c 1.006, $CHCl_3$).

IR ($CHCl_3$): 4214, 3531, 2401, 2343, 1730, 1596 cm^{-1}.

^{1}H NMR: δ 7.77 (2 H, d, *J* 8.3 Hz, aromatic), 7.31 (7 H, m, aromatic), 4.95 (1 H, d, *J* 4.9 Hz, H-1), 4.72 (1 H, dq, *J* 2.9, 2.0 Hz), 4.59 (1 H, d, *J* 12.2 Hz, PhCH), 4.46 (1 H, d, *J* 12.2 Hz, PhCH), 4.33-4.45 (1 H, m), 3.93 (1 H, m), 3.65 (1 H, dd, *J* 10.7, 1.9 Hz), 3.45-3.52 (5 H, m), 2.43 (3 H, s, aromatic Me).

^{13}C NMR: δ 144.8, 137.8, 136.9, 129.6, 128.7, 128.4, 127.7, 101.9 (C-1), 76.1, 73.5 (CH_2), 72.1, 69.5 (CH_2), 62.9, 55.3 (OMe), 21.6 (aromatic Me).

MS: m/z (EI) 360 (0.6 M^+-O_2), 205 (6.7), 175 (1.3), 155 (4.0), 139 (4.3), 117 (2.0), 91 (100).

Analysis: Cald. for $C_{20}H_{24}O_6S$: C, 61.20; H, 6.16; S, 8.17. Found: C, 61.21; H, 6.23; S, 8.09.

Methyl 5-*O*-benzyl-3-deoxy-3-*C*-(*p*)-tolylsulfonyl-β-D-*ribo*furanoside 2.022:

Compound **2.020** (0.95 g, 2.64 mmol) was converted to **2.022** following the general procedure described above. Eluent: EtOAc:pet ether (1:3).

Yield: 0.96 g, 93%.

Mp: 79-80 ^{o}C.

$[\alpha]_D^{26}$: –50.0^{o} (c 1.00, CHCl$_3$).

IR (CHCl$_3$): 4214, 3479, 2401, 1596 cm^{-1}.

^{1}H NMR: δ 7.80 (2 H, d, *J* 8.1 Hz, aromatic), 7.32 (7 H, m, aromatic), 4.93 (1 H, m), 4.84 (1 H, s, H-1), 4.54 (2 H, d, *J* 5.5 Hz, PhCH$_2$), 4.15 (1 H, t, *J* 4.3 Hz), 3.87 (2 H, m), 3.72 (1 H, dd, *J* 10.7, 2.2 Hz), 3.52 (1 H, dd, *J* 10.7, 5.5 Hz), 3.26 (3 H, s, OMe), 2.45 (3 H, s, aromatic Me).

^{13}C NMR: δ 145.5, 138.1, 136.4, 130.0, 128.2, 127.5, 108.4 (C-1), 77.1, 75.5, 73.3 (CH$_2$), 72.0 (CH$_2$), 65.1, 54.4 (OMe), 21.6 (aromatic Me).

MS: m/z (EI) 360 (0.5 M$^+$-MeOH), 271 (0.3), 243 (0.4), 205 (10), 155 (6), 107 (10), 91 (100).

Analysis: Cald. for $C_{22}H_{24}O_6S$: C, 61.20; H, 6.16; S, 8.17. Found: C, 61.06; H, 6.38; S, 8.47.

Methyl 5-*O*-benzyl-2,3-dideoxy-3-*C*-(*p*)-tolylsulfonyl-α-D-*erythro*-pent-2-enofuranoside 2.001: Compound **2.021** (0.38 g, 0.977 mmol) was converted to **2.001** following the general procedure described above. The reaction mixture was kept at + 4 ^{o}C for 12 h and then it was stirred for 8 h at ambient temperature.

Yield: 0.27 g, 74%.

Methyl 5-*O*-benzyl-2,3-dideoxy-3-*C*-(*p*)-tolylsulfonyl-β-D-*erythro*-pent-2-enofuranoside 2.003: Compound **2.022** (0.369 g, 0.941 mmol) was converted to **2.003** following the general procedure described above.

Yield: 0.32 g, 92%.

5-*O*-benzyl-1,2-*O*-isopropylidene-3-*O*-mesyl-α-D-*ribo*furanose 2.026: To a stirred solution of **2.025** (0.32 g, 1.14 mmol) was added a solution of mesyl choride (0.3 mL, 3.42 mmol) in dry pyridine (10 mL) dropwise at 0 ^{o}C under nitrogen atmosphere. After completion of addition, the reaction mixture was kept at +4 ^{o}C for 24 h. The reaction mixture was worked up as per the procedure mentioned for **2.017** to obtain an oil which was purified over silica gel using EtOAc:pet ether (1:4) to afford **2.026**.

Yield: 0.4 g, 98%.

Mp: Brown oil.

$[\alpha]_D^{26}$: +88.2^{o} (c 1.07, CHCl$_3$).

IR (CHCl$_3$): 3446, 2343, 1417, 1373, 1365 cm^{-1}.

^{1}H NMR: δ 7.43-7.26 (5 H, m), 5.85 (1 H, d, *J* 3.9 Hz, H-1), 4.87 (1 H, m), 4.77 (1 H, t, *J* 3.9 (4.4) Hz), 4.65 (1 H, d, *J* 12.2 Hz), 4.56 (1 H, d, *J* 11.7 Hz), 4.26 (1 H, dt, *J* 3.4 (3.8), 3.0 Hz), 3.76 (1 H, dd, *J* 11.7, 2.4 Hz), 3.65 (1 H, dd, *J* 11.7, 3.4 Hz), 3.05 (3 H, s, OMe), 1.58 (3 H, s, Me), 1.38 (3 H, s, Me).

^{13}C NMR: δ 137.7, 128.5, 127.8, 113.5, 104.1, 77.3, 76.6, 75.8, 73.7 (CH_2), 67.0 (CH_2), 38.3, 26.6.

MS: m/z (EI) 358 (14 M^+), 343 (6), 237 (7), 179 (23), 175 (13), 151 (14), 107 (22), 91 (100), 85 (18).

Analysis: Cald. for $C_{16}H_{22}O_7S$: C, 53.62; H, 6.18; S, 8.94. Found: C, 53.62; H, 6.17; S, 8.72.

5-*O*-benzyl-3-deoxy-1,2-*O*-isopropylidene-3-*C*-(*p*)-tolylsulfide-α-D-*xylo*furanose 2.027: Compound **2.026** (2.84 g, 7.93 mmol) was converted to **2.027** following a procedure for the synthesis of **2.018**. The reaction mixture was heated at 135-140 °C for 2.5-3 h. Eluent: EtOAc:pet ether (1:21).

Yield: 2.43 g, 79%.

Mp: Gummy.

$[\alpha]_D^{30}$: –31.0° (c 1.00, $CHCl_3$).

IR ($CHCl_3$): 2985, 2931, 1496 cm^{-1}.

^{1}H NMR: δ 7.36 (7 H, m, aromatic), 7.14 (2 H, d, *J* 7.8 Hz, aromatic), 5.94 (1 H, d, *J* 3.4 Hz, H-1), 4.70-4.53 (4 H, m), 3.83 (2 H, d, *J* 5.9 Hz, $PhCH_2$), 3.76 (1 H, d, *J* 3.9 Hz), 2.53 (3 H, s, aromatic Me), 1.53 (3 H, s, Me), 1.29 (3 H, s, Me).

^{13}C NMR: δ 137.9, 136.8, 130.8 129.8, 128.1, 127.6, 111.5, 104.7, 85.2, 77.9, 73.3 (CH_2), 69.2 (CH_2), 54.2, 26.5, 26.2, 20.8 (aromatic Me).

MS: m/z (EI) 386 (19 M^+), 233 (10), 207 (24), 205 (10), 178 (20), 139 (14), 124 (14), 123 (40), 107 (14), 99 (16), 91 (100).

Analysis: Cald. for $C_{22}H_{26}O_4S$: C, 68.36; H, 6.77; S, 8.29. Found: C, 68.03; H, 7.23; S, 8.29.

Methyl 5-*O*-benzyl-3-deoxy-3-*C*-(*p*)-tolylsulfide-α-D-*xylo*furanoside 2.028 and methyl 5-*O*-benzyl-3-deoxy-3-*C*-(*p*)-tolylsulfide-β-D-*xylo*furanoside 2.013: A solution of **2.027** (2.43 g, 6.29 mmol) and conc. H_2SO_4 (1 mL) in dry MeOH (70 mL) was heated under reflux. After 2.5 h, the reaction mixture was worked up as described for **2.019** and **2.020**. The anomers were separated on silica gel using EtOAc:pet ether (1:3) to give **2.028** and **2.013**.

Compound 2.028:

Yield: 1.2 g, 53%.

Mp: Yellowish gum.

$[\alpha]_D^{30}$: +163.7° (c 1.13, $CHCl_3$).

IR (neat): 3487, 3062, 3024, 2916, 1862 cm^{-1}.

^{1}H NMR: δ 7.37 (7 H, m, aromatic), 7.10 (2 H, d, *J* 8.3 Hz, aromatic), 4.98 (1 H, d, *J* 4.4 Hz, H-1), 4.60 (1 H, m), 4.60 (2 H, d, *J* 11.2 Hz, $PhCH_2$), 4.29 (1 H, dd, *J* 8.0, 4.6 Hz), 3.78 (2 H, d, *J* 3.9 Hz), 3.65 (1 H, t, *J* 7.8 Hz), 3.50 (3 H, s, OMe), 2.76 (1 H, bs, OH), 2.34 (3 H, s, aromatic Me).

^{13}C NMR: δ 137.7, 136.0, 132.3, 130.2, 129.4, 128.0, 127.3, 127.1, 101.2 (C-1), 77.4, 76.3, 72.9 (CH_2), 70.2 (CH_2), 55.0 (OMe), 54.0, 20.5 (aromatic Me).

MS: m/z (EI) 360 (13 M^+), 159 (11), 149 (11), 124 (100), 91 (61).

Analysis: Cald. for $C_{20}H_{24}O_4S$: C, 66.64; H, 6.70; S, 8.89. Found: C, 66.57; H, 7.07; S, 9.52.

Compound 2.013:

Yield: 0.81 g, 36%.

Methyl 5-*O*-benzyl-3-deoxy-3-*C*-(*p*)-tolylsulfonyl-α-D-*xylo*furanoside 2.029: Compound **2.028** (0.62 g, 1.72 mmol) was converted to **2.029** following the general procedure described above. Eluent: EtOAc:pet ether (3:7).

Yield: 0.61 g, 90%.

Mp: 127-128 °C.

$[\alpha]_D^{27}$: +236.8° (c 1.00, $CHCl_3$).

IR ($CHCl_3$): 3487, 2954, 2923, 2854 cm^{-1}.

^{1}H NMR: δ 7.79 (2 H, d, *J* 7.8 Hz, aromatic), 7.36 (7 H, m, aromatic), 4.98 (1 H, d, *J* 4.4 Hz, H-1), 4.62 (4 H, m), 4.09 (2 H, m), 3.74 (1 H, t, *J* 7.8 Hz), 3.45 (3 H, s, OMe), 3.00 (1 H, bs, OH), 2.42 (3 H, s, aromatic Me).

^{13}C NMR: δ 145.1, 138.2, 136.6, 129.9, 129.0, 128.0, 127.9, 101.3 (C-1), 76.6, 73.9, 73.6 (CH_2), 69.7 (CH_2), 69.4, 55.6 (OMe), 21.7 (aromatic Me).

MS: m/z (EI) 392 (<1 M^+), 360 (5 M^+-O_2), 115 (10), 139 (11), 107 (10), 99 (16), 99 (100).

Analysis: Cald. for $C_{20}H_{24}O_6S$: C, 61.20; H, 6.16. Found: C, 61.07; H, 6.05.

Methyl 5-*O*-benzyl-2,3-dideoxy-3-*C*-(*p*)-tolylsulfonyl-α-D-*erythro*-pent-2-enofuranoside 2.001: Compound **2.029** (0.5 g, 1.27 mmol) was converted to **2.001** following the general procedure.

Yield: 0.36 g, 76%.

Methyl 5-*O*-benzyl-3-*O*-tosyl-α-D-*xylo*furanoside 2.030 and methyl 5-*O*-benzyl-3-*O*-tosyl-β-D-*xylo*furanoside 2.031: A well-stirred solution of **2.017** (0.64 g, 1.48 mmol) and conc. H_2SO_4 (0.5 mL) in dry MeOH (60 mL) was heated under reflux in an inert atmosphere. After 4 h the mixture was cooled to room temperature, neutralized with pyridine and evaporated to dryness under reduced pressure to get a solid mass. The solid material was dissolved in saturated $NaHCO_3$ and extracted with EtOAc (4 x 30 mL). The combined organic layers were dried over anhydr. $Na_2SO_{4,}$ filtered and the filtrate was concentrated under reduced pressure to get a gummy residue. The anomers **2.030** and **2.031** (0.54 g, 89%) were separated over silica gel column using EtOAc:pet ether (1:4).

Compound 2.030:

Yield: 0.23 g, 38%.

^{1}H NMR ($CDCl_3$): δ 7.78 (2 H, d, *J* 7.8 Hz, aromatic H), 7.31 (7 H, bs, aromatic), 4.96 (1 H, d, *J* 4.8 Hz, H-1), 4.82 (1 H, t, *J* 4.4 Hz), 4.57-4.26 (4 H, m, $PhCH_2$ + 2 H), 3.59 (2 H, d, *J* 4.9 Hz), 3.45 (3 H, s, OMe), 2.82 (1 H, d, *J* 6.4 Hz, OH), 2.41 (3 H, s, aromatic Me).

Compound 2.031:

Yield: 0.28 g, 47%.

^{1}H NMR ($CDCl_3$): δ 7.76 (2 H, d, *J* 8.3 Hz, aromatic), 7.29 (7 H, m, aromatic), 4.81 (1 H, s, H-1), 4.76 (1 H, dd, *J* 5.9, 2.0 Hz), 4.47 (3 H, m, $PhCH_2$ + 1 H), 4.29 (1 H, broad hump), 3.58 (2 H, m), 3.36 (3 H, s, OMe), 3.0 (1 H, broad hump, OH), 2.41 (3 H, s, aromatic Me).

Compound 2.019 from 2.030: Compound **2.030** (1.71 g, 4.196 mmol) was converted to **2.019** following a procedure described for the synthesis of **2.018**. The reaction mixture was heated at 115-120 °C for 3.5 h.

Yield: 1.33 g, 88%.

Compound 2.020 from 2.031: Compound **2.031** (1.15 g, 3.705 mmol) was converted to **2.020** following a procedure described for the synthesis of **2.018**. The reaction mixture was heated at 115-120 °C for 3. h.

Yield: 1.11 g, 83%.

Compounds 2.019 and 2.020 from the mixture of 2.030 and 2.031: A mixture of compounds **2.030** and **2.031** (3.99 g, 9.19 mmol) was converted to the mixture of

2.019 and **2.020** following the procedure described for the synthesis of **2.018**.

Yield: 2.09 g, 94%.

Methyl 3-deoxy-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfide-β-D-*allo*pyranoside 2.035: To a well stirred solution of NaOMe (0.506 g, 9.38 mmol) in DMF (10 mL) was added dropwise thiophenol (1.2 mL, 11.726 mmol) under nitrogen at ambient temperature. After 15 minutes, **2.034** (0.98 g, 2.345 mmol) in DMF (20 mL) was added into the mixture and the mixture was heated at 135-140 °C. After 2 h, the mixture was cooled to room temperature, poured into brine (150 mL) and the aqueous phase was extracted with EtOAc (4 x 40 mL). The combined extracts were dried over anhydr. Na_2SO_4, filtered and the filtrate was evaporated to dryness under reduced pressure to get the crude material. Purification of the crude material over silica gel using EtOAc:pet ether (1:4) produced the title compound as a white solid.

Yield: 0.79 g, 90%.

Mp: 133-134 °C.

$[\alpha]_D^{26}$: –40.5° (c 1.00, $CHCl_3$).

IR ($CHCl_3$): 3475, 3018, 2401, 2358 cm^{-1}.

^{1}H NMR: δ 7.59 (2 H, m, aromatic), 7.39 (5 H, m, aromatic), 7.24 (3 H, t, *J* 3.4 Hz, aromatic), 5.60 (1 H, s, PHCH), 4.40 (2 H, m), 4.02 (5 H, m), 3.60 (3 H, s, OMe), 3.12 (1 H, d, *J* 8.8 Hz, OH).

^{13}C NMR: δ 137.4, 135.7, 132.8, 129.1, 128.2, 127.6, 126.4, 103.3, 101.5, 78.6, 70.4, 69.1 (CH_2), 65.4, 57.9, 57.3 (OMe).

MS: m/z (EI) 374 (6 M^+), 233 (2), 187 (3), 159 (9), 129 (20), 107 (100), 91 (75).

Analysis: Cald. for $C_{20}H_{22}O_5S$: C, 64.15; H, 5.91; S, 8.56. Found: C, 63.98; H, 5.81; S, 7.57.

Methyl 3-deoxy-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfonyl-β-D-*allo*pyranoside 2.036: Compound **2.035** (0.58 g, 1.54 mmol) was converted to **2.036** following the general procedure described above. Eluent: EtOAc:pet ether (3:7).

Yield: 0.59 g, 95%.

Mp: 129-130 °C.

$[\alpha]_D^{26.5}$: –46.3° (c 1.00, $CHCl_3$).

IR ($CHCl_3$): 3450, 3427, 3016, 1448 cm^{-1}.

^{1}H NMR: δ 7.76 (2 H, d, *J* 7.8 Hz, aromatic), 7.23 (8 H, a series of m, aromatic), 5.22 (1 H, s, PhCH), 5.11 (1 H, d, *J* 8.3 Hz, H-1), 4.87 (1 H, broad hump), 4.74 (1 H, m), 4.35(1 H, q), 4.18 (1 H, t, *J* 4.9 Hz), 3.85 (1 H, broad hump), 3.68 (1 H, q), 3.57 (3 H, s, OMe), 3.54 (1 H, m).

^{13}C NMR: δ 140.9, 136.1, 133.4, 128.7, 128.5, 128.3, 127.7, 125.9, 101.1 (C-1), 77.1, 76.3, 72.4, 69.3 (CH_2), 63.8, 63.2, 56.9 (OMe).

MS: m/z (EI) 233 (7), 187 (6), 159 (10), 127 (30), 107 (100), 91 (38), 77 (57).

Analysis: Cald. for $C_{20}H_{22}O_7S$ C, 59.10; H, 5.45; S, 7.88. Found: C, 58.97; H, 5.66; S, 7.86.

Methyl 2,3-dideoxy-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfonyl-β-D-*erythro*-hex-2-enopyranoside 1.058: Compound **2.036** (0.59 g, 1.472 mmol) was converted to **1.058** following the general procedure described above. The reaction mixture was stirred for 4 h allowing it to warm up from 0 °C to room temperature. Eluent: EtOAc:pet ether (2:3).

Yield: 0.53 g, 93%.

Methyl 2-deoxy-4,6-*O*-(phenylmethylene)-2-*C*-phenylsulfide-α-D-*altro*pyranoside 2.037: Compound **2.033** (0.17 g, 0.407 mmol) was converted to **2.037** following a procedure reported for **2.035**. Eluent: EtOAc:pet ether (1:4).

Yield: 0. 06 g, 39%.

IR ($CHCl_3$): 3500, 2360, 2331, 1671, 1583 cm^{-1}.

^{1}H NMR: 7.32 (10 H, m, aromatic), 5.61 (1 H, s, PhCH), 4.81 (1 H, s, H-1), 4.22 (3 H, m), 4.04 (1 H, dd, *J* 9.8, 3.0 Hz), 3.81 (1 H, t, *J* 8.3 Hz), 3.58 (1 H, d, *J* 2.4 Hz), 3.35 (3 H, s, OMe), 3.09 (1 H, d, *J* 5.8 Hz, OH).

^{13}C NMR: 137.3, 133.9, 131.0, 129.4, 129.1, 128.2, 127.6, 126.3, 102.2, 101.3, 76.4, 69.1 (CH_2), 68.8, 58.6, 55.7 (OMe), 51.6.

MS: m/z (EI) 374 (36 M$^+$), 343 (4), 165 (88), 152 (88), 123 (42), 105 (82), 91 (100), 77 (90).

Analysis: Cald. for $C_{20}H_{22}O_5S$: C, 64.15; H, 5.91; S, 8.56. Found: C, 63.90; H, 6.23; S, 8.27.

3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-phenylsulfide-α-D-*allo*furanose 2.039: Compound **2.032** (10.72 g, 25.88 mmol) was converted to **2.039** following the procedure reported for **2.035**. The reaction mixture was heated at 125 °C for 4 h. Eluent: EtOAc:pet ether (1:9).

Yield: 8.23 g, 90%.

Mp: 84-85 °C.

IR (Nujol): 1647, 1461 cm^{-1}.

^{1}H NMR: δ 7.50 (2 H, d, *J* 5.9 Hz, aromatic), 7.28 (3 H, m, aromatic), 5.81 (1 H, d, *J* 3.4 Hz, H-1), 4.77 (1 H, t, *J* 4.4,3.9 Hz), 4.17-4.45 (2 H, m), 4.04 (1 H, t, *J* 6.8, 9.3 Hz), 3.92 (1 H, t, *J* 7.9, 6.8 Hz), 3.29 (1 H, dd, *J* 9.8, 4.4 Hz), 1.58 (3 H, s, Me), 1.37 (3 H, s, Me), 1.30 (6 H, s, 2 x Me).

^{13}C NMR: δ 143.8, 132.0, 129.0, 127.4, 112.3, 109.6, 104.1, 81.7, 80.6, 75.7, 65.1 (CH_2), 52.5, 26.7, 26.5, 26.1.

MS: m/z (E1) 352 (27 M$^+$), 337 (13), 193 (100), 109 (76 M$^+$-PhS).

Analysis: Cald. for $C_{18}H_{24}O_5S$: C, 61.34; H, 6.86. Found: C, 61.26; H, 7.17.

3-Deoxy-1,2:5,6-di-*O*-isopropylidene-3-*C*-phenylsulfide-α-D-*gluco*furanose 2.040: Compound **2.038** (2.35 g, 6.96 mmol) was converted to **2.040** following a procedure reported for **2.035**. The reaction mixture was heated at 125 °C for 2 h. Eluent: EtOAc:pet ether (4%-10%).

Yield: 1.98 g, 80%.

Mp: 75-76 °C.

$[\alpha]_D^{26}$: –31.3° (c 1.06, $CHCl_3$).

IR ($CHCl_3$): 2889, 2434, 2401, 1944, 1868, 1583, 1481, 1454, 1375 cm^{-1}.

^{1}H NMR: δ 7.43 (2 H, dd, *J* 8.3, 1.5 Hz, aromatic), 7.40-7.19 (3 H, m, aromatic), 5.89 (1 H, d, *J* 3.4 Hz, H-1), 4.62 (1 H, d, *J* 3.5 Hz, H-2), 4.45-4.30 (2 H, m), 4.16 (1 H, dd, *J* 8.2, 5.5 Hz), 4.03 (1 H, dd, *J* 8.8, 4.4 Hz), 3.90 (1 H, d, *J* 3.4 Hz), 1.52 (3 H, s, Me), 1.45 (3 H, s, Me), 1.36 (3 H, s, Me), 1.27 (3 H, s, Me).

^{13}C NMR: δ 134.0, 130.3 129.2, 126.8, 111.9, 109.5, 105.0, 85.4, 80.0, 73.8, 67.7 (CH_2), 53.6, 26.9 (Me), 26.7 (Me), 26.3 (Me), 25.3 (Me).

MS: m/z (EI) 352 (30 M$^+$), 337 (29), 193 (58), 164 (25), 101 (100).

Analysis: Cald. for $C_{18}H_{24}O_5S$: C, 61.34; H, 6.86; S, 9.09. Found: C, 61.66; H, 7.66; S, 9.53.

3-Deoxy 1,2:5,6-di-*O*-isopropylidene-3-*C*-phenylsulfonyl-α-D-*gluco*furanose 2.041: Compound **2.040** (0.2 g, 0.565 mmol) was converted to **2.041** following the general procedure described above. Eluent: EtOAc:pet ether (1:3).

Yield: 0.2 g, 94%.

Mp: 158-159 °C.

$[\alpha]_D^{27}$: –0.5° (c 1.02, $CHCl_3$).

IR ($CHCl_3$): 2358, 2341, 1595, 1585, 1448 cm^{-1}.

^{1}H NMR: δ 7.96 (2 H, d, *J* 6.9 Hz, aromatic), 7.74-7.56 (3 H, m, aromatic), 5.96 (1 H, d, *J* 3.9 Hz, H-1), 4.96 (1 H, d, *J* 3.5 Hz, H-2), 4.83-4.73 (1 H, m), 4.31 (1 H, dd, *J* 8.8, 4.8

Hz), 4.18 (1 H, dd, *J* 8.8, 5.9 Hz), 4.02 (1 H, dd, *J* 8.8, 4.9 Hz), 3.87 (1 H, d, *J* 4.8 Hz), 1.49 (3 H, s, Me), 1.35 (3 H, s, Me), 1.29 (3 H, s, Me), 1.21 (3 H, s, Me).

^{13}C NMR: δ 139.6, 134.2, 129.5, 128.5, 112.4, 109.7, 105.0, 81.3, 80.2, 72.6, 69.9, 68.0 (CH_2), 26.7, 26.8, 26.4, 25.2.

MS: m/z (EI) 369 (12), 311 (7), 141 (17), 125 (13), 101 (100), 77 (28).

Analysis: Cald. for $C_{18}H_{24}O_7S$: C, 56.23; H, 6.28; S, 8.34. Found: C, 56.19; H, 6.90; S, 8.62.

Methyl 3-deoxy-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfide-α-D-*gluco*pyranoside 2.042 and Methyl 3-deoxy-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfide-β-D-*gluco*pyranoside 2.043: Acetyl chloride (0.2 mL, 2.451 mmol) was added drop-wise to a well stirred solution of **2.040** (0.173 g, 0.491 mmol) in anhydr. MeOH at an ambient temperature and the mixture was heated under reflux. After 24 h, the reaction mixture was neutralized with $BaCO_3$. The mixture was concentrated to dryness under reduced pressure to get a solid mass. The solid was triturated with EtOAc (30 mL) and the liquid was decanted. The process was repeated four times. The combined organic layers was passed through a celite bed. The filtrate was then concentrated to dryness under reduced pressure to get a mixture of methyl 3-deoxy-3-*C*-phenylsulfide-α- and -β-D-glucopyranosides. To a well stirred solution of the anomers (0.14 g, 0.491 mmol) in DMF (10 mL) was added a catalytic amount *p*-TSA and 1,1-dimethyl toluene (0.15 mL, 0.982 mmol) and the mixture was heated at 100 °C with stirring under reduced pressure. After 1 h, the reaction mixture was neutralized with pyridine. Excess DMF and other volatile matters were removed under reduced pressure. The residue thus obtained was dissolved in saturated $NaHCO_3$ solution and the aqueous phase was extracted with EtOAc (4 x 20 mL). Combined organic layers after usual work up generated solid material which on purification over silica gel using EtOAc:pet ether (1:3) produced a mixture of **2.042** and **2.043 (0.131 g, 71%)** . Compounds **2.042** and **2.043** were finally separated over silica gel using a mixture of acetone:chloroform:pet ether (7:7:86).

Compound 2.042:

Yield: 0.08 g, 44%.

Mp: 129-130 °C.

$[\alpha]_D^{27}$: +19.2° (c 1.00, $CHCl_3$).

IR ($CHCl_3$): 3444, 2725, 2360, 2324, 1456, 1373 cm^{-1}.

^{1}H NMR: δ 7.57-7.21 (10 H, series of m, aromatic), 5.41 (1 H, s, PhCH), 4.77 (1 H, d, *J* 3.5 Hz, H-1), 4.20 (1 H, dd, *J* 10.2, 4.9 Hz), 3.88-3.81 (1 H, m), 3.57 (1 H, t, *J* 10.3 Hz), 3.50-3.41 (1 H, m), 3.41 (3 H, s, OMe), 3.28 (1 H, t, *J* 10.3 Hz), 3.19 (1 H, t, *J* 10.3 Hz), 2.72 (1 H, d, *J* 6.3 Hz, OH).

^{13}C NMR: δ 137.3, 135.2, 131.3, 128.9, 128.6, 126.2, 101.6, 99.5, 78.5, 69.7, 69.0 (CH_2), 64.4, 55.4 (OMe), 52.4.

MS: m/z (EI) 374 (72 M^+), 237 (13), 165 (15), 129 (29), 107 (100), 91 (41), 77 (25).

Analysis: Cald. for $C_{20}H_{22}O_5S$: C, 64.15; H, 5.91. Found: C, 64.17; H, 6.37.

Compound 2.043:

Yield: 0.03 g, 16%.

Mp: 84-85 °C.

$[\alpha]_D^{27}$: –116.3° (c 0.92, $CHCl_3$).

IR ($CHCl_3$): 3502, 2360, 2331, 1471, 1452, 1386, 1365, 1217 cm^{-1}.

^{1}H NMR: δ 7.60-7.25 (10 H, m, aromatic), 5.45 (1 H, s, PhCH), 4.36 (1 H, d, *J* 7.3 Hz, H-1), 4.31 (1 H, dd, *J* 10.3, 4.4 Hz), 3.65 (1 H, t, *J* 10.2 Hz), 3.55 (3 H, s, OMe), 3.52-3.40 (1 H, m), 3.34-3.01 (4 H, m).

^{13}C NMR: δ 137.3, 135.6, 130.6, 129.2, 128.8, 128.4, 126.2, 105.4, 101.6, 77.9, 71.2, 69.5, 68.8 (CH_2), 57.4, 54.5.

MS: m/z (EI) 374 (65 M^+), 187 (13), 159 (11), 129 (21), 107 (100), 91 (84), 77 (52).

Analysis: Cald. for $C_{20}H_{22}O_5S$: C, 64.15; H, 5.91; S, 8.56. Found: C, 64.33; H, 5.81; S, 8.95.

Methyl 3-deoxy-4,6-*O*-(phenylmethylene)-3-*C*-phenylsufonyl-α-D-*gluco*pyranoside 2.044: Compound **2.042** (0.13 g, 0.35 mmol) was converted to **2.044** following the general procedure described above.

Yield: 0.13 g, 92%.

Mp: 104-105 °C.

$[\alpha]_D^{27}$: +37.8° (c 0.98, $CHCl_3$).

IR ($CHCl_3$): 3504, 2401, 2360, 23443, 1448, 1365 cm^{-1}.

^{1}H NMR: δ 7.81 (2 H, d, *J* 8.3 Hz, aromatic), 7.50 (1 H, t, *J* 8.0 Hz, aromatic), 7.30 (5 H, m, aromatic), 7.10 (2 H, d, *J* 7.3 Hz, aromatic), 5.44 (1 H, s, PhCH), 4.87 (1 H, d, *J* 3.4 Hz, H-1), 4.50-4.41 (2 H, m), 4.23 (1 H, dd, *J* 9.3, 3.9 Hz), 3.94-3.69 (4 H, m), 3.48 (3 H, s, OMe).

^{13}C NMR: δ 140.6, 136.5, 133.9, 129.3, 128.9, 128.8, 128.2, 126.4, 102.0, 98.9, 76.2, 69.4 (CH_2), 67.3, 65.9, 62.6, 55.6.

MS: m/z (EI) 406 (<1 M^+), 405 (1), 375 (<1), 233 (20), 187 (12), 159 (14), 127 930), 107 (100), 91 (34), 77 (60).

Analysis: Cald. for $C_{20}H_{22}O_7S$: C, 59.10; H, 5.45; S, 7.88. Found: C, 59.30; H, 5.48; S, 9.57.

Methyl 3-deoxy-4,6-*O*-(phenylmethylene)-3-*C*-phenylsufonyl-β-D-*gluco*pyranoside 2.045: Compound **2.043** (0.07 g, 0.181 mmol) was converted to **2.045** following the general procedure described above.

Yield: 0.07 g, 90%.

Mp: 145-146 °C.

$[\alpha]_D^{27}$: –78.6° (c 1.00, $CHCl_3$).

IR ($CHCl_3$): 3502, 2401, 2360, 2331, 1448, 1365 cm^{-1}.

^{1}H NMR: δ 7.83 (2 H, d, *J* 6.9 Hz, aromatic), 7.54 (1 H, t, *J* 7.3 Hz, aromatic), 7.31 (5 H, m, aromatic), 7.10 (2 H, dd, *J* 7.8, 1.9 Hz, aromatic), 5.40 (1 H, s, PhCH), 4.45 (1 H, d, *J* 6.9 Hz, H-1), 4.30 (1 H, dd, *J* 10.8, 4.8 Hz), 4.18 (1 H, dd, *J* 9.8, 7.3 Hz), 3.89-3.43 (5 H, m), 3.60 (3 H, s, OMe).

^{13}C NMR: δ 140.0, 136.5, 134.0, 129.4, 129.1, 128.9, 128.2, 126.3, 104.7, 101.7, 75.8, 69.2, 69.0 (CH_2), 68.5, 67.7, 57.6.

MS: m/z (EI) 265 (3), 233 (8), 187 (8), 159 (10), 127 (30), 107 (100), 91 (31), 77 (77).

Analysis: Cald. for $C_{20}H_{22}O_7S$: C, 59.10; H, 5.45; S, 7.88. Found: C, 58.88; H, 5.66; S, 8.40.

Methyl 3-deoxy-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfonyl-α-D-*gluco*pyranoside 2.044 and Methyl 3-deoxy-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfonyl-β-D-*gluco*pyranoside 2.045: Compound **2.041** (0.21 g, 0.557 mmol) was converted to an anomeric mixture of **2.044** and **2.045** (0.17 g, 75%) following the procedure described for **2.042** and **2.043**. The anomers were separated on silica gel. Eluent: acetone:chloroform:pet ether (1:1:8)

Compound 2.044: **Yield:** 0.02 g, 11%.

Compound 2.045: **Yield:** 0.05 g, 28%.

Methyl 2,3-dideoxy-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfonyl-α-D-*erythro*-hex-2-enopyranoside 1.050: To a well stirred solution of **2.044** (0.09 g, 0.214 mmol) in pyridine (2 mL) at 0 °C was added drop-wise mesyl chloride (0.1 mL, 1.071 mmol) in pyridine (3 mL) and the mixture was left at +4 °C. After 15 h the reaction mixture was worked up as described in the general procedure. A solution of the crude material in CH_2Cl_2 (10 mL) was treated with DBU (2 eq) for 15 min. Excess solvent was removed under reduced pressure. Purification of the crude residue over silica gel using

EtOAc:pet ether (2:3) furnished **1.050** as a solid.

Yield: 0.08 g, 96%.

Methyl 2,3-dideoxy-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfonyl-β-D-*erythro*-hex-2-enopyranoside 1.058: Compound **2.045** (0.05 g, 0.120 mmol) was converted to **1.058** following the procedure described for **1.050**.

Yield: 0.045 g, 96%.

2.7 References

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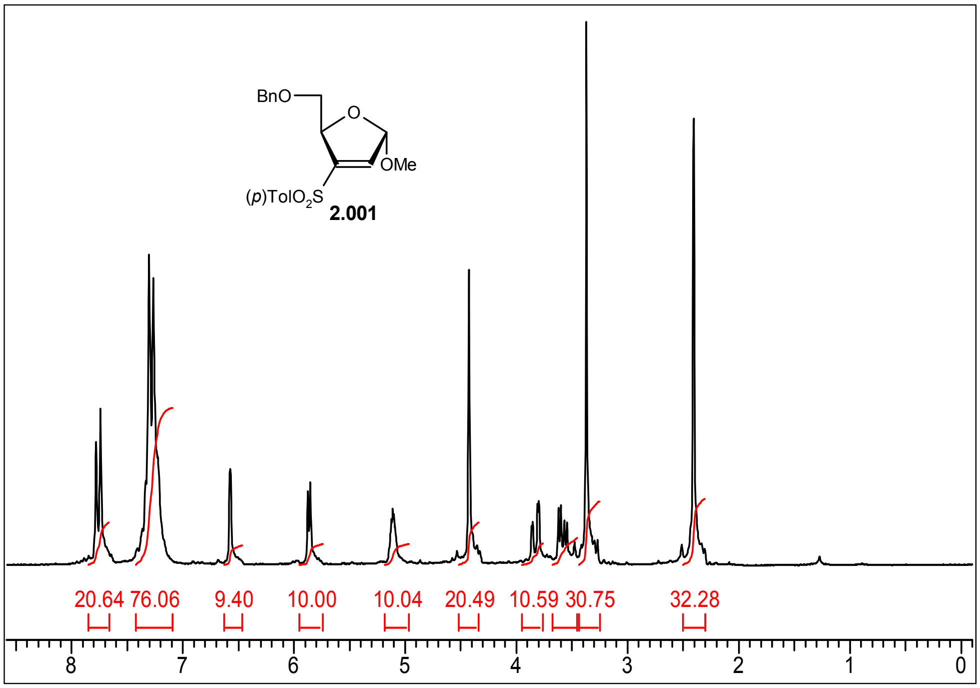
2.8 Spectra

^{1}H NMR of **2.001**



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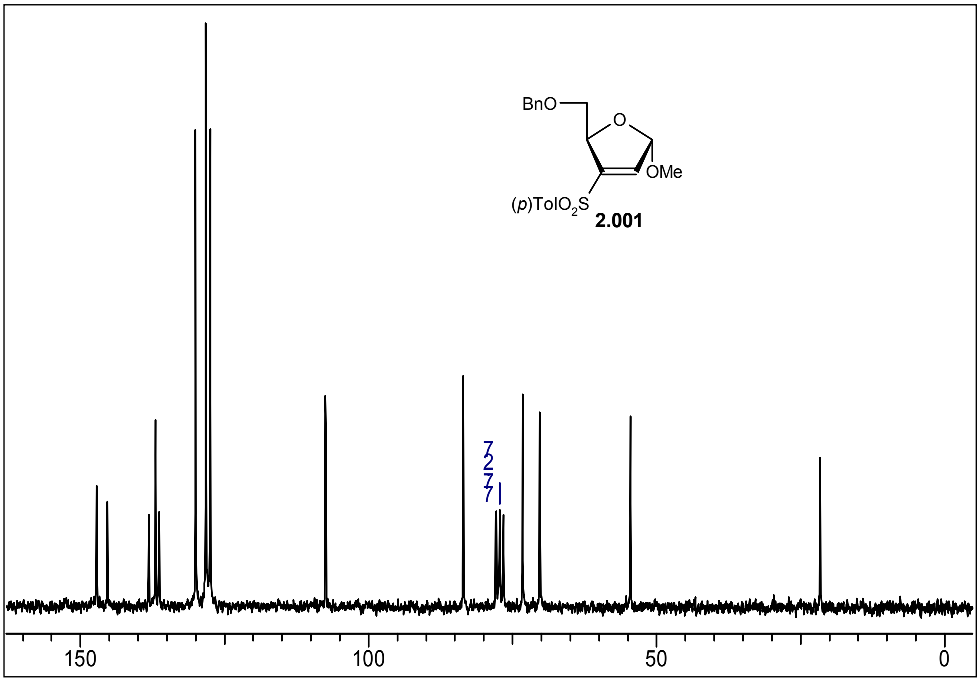

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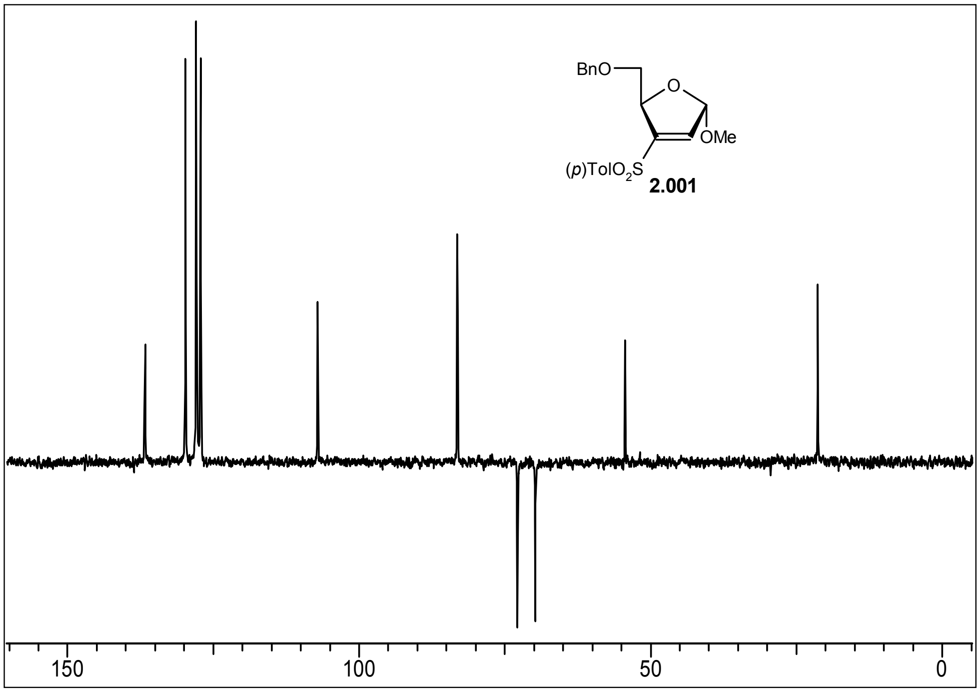

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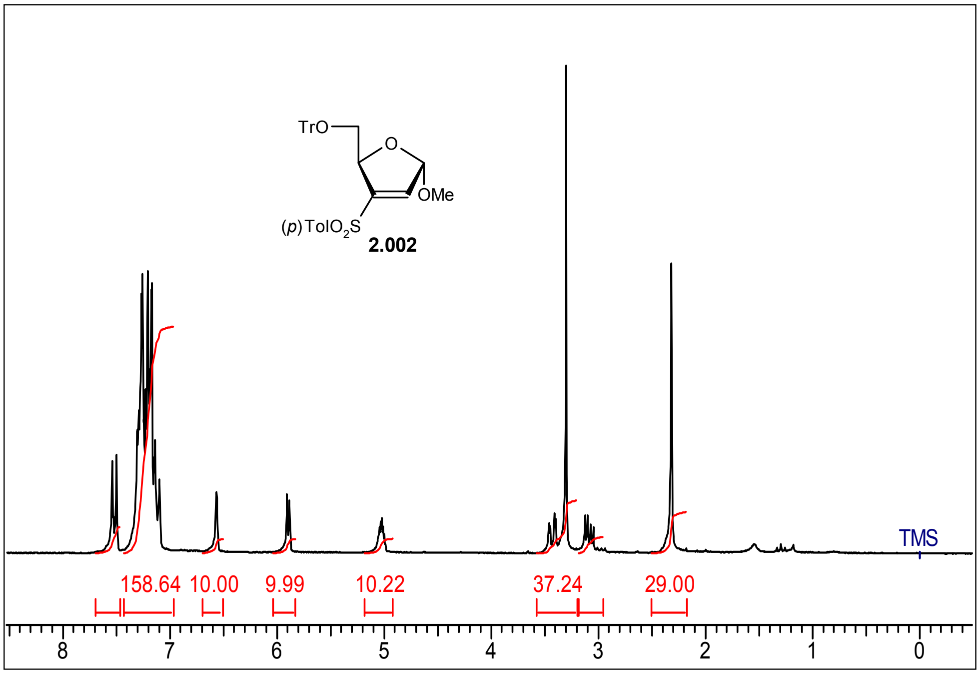

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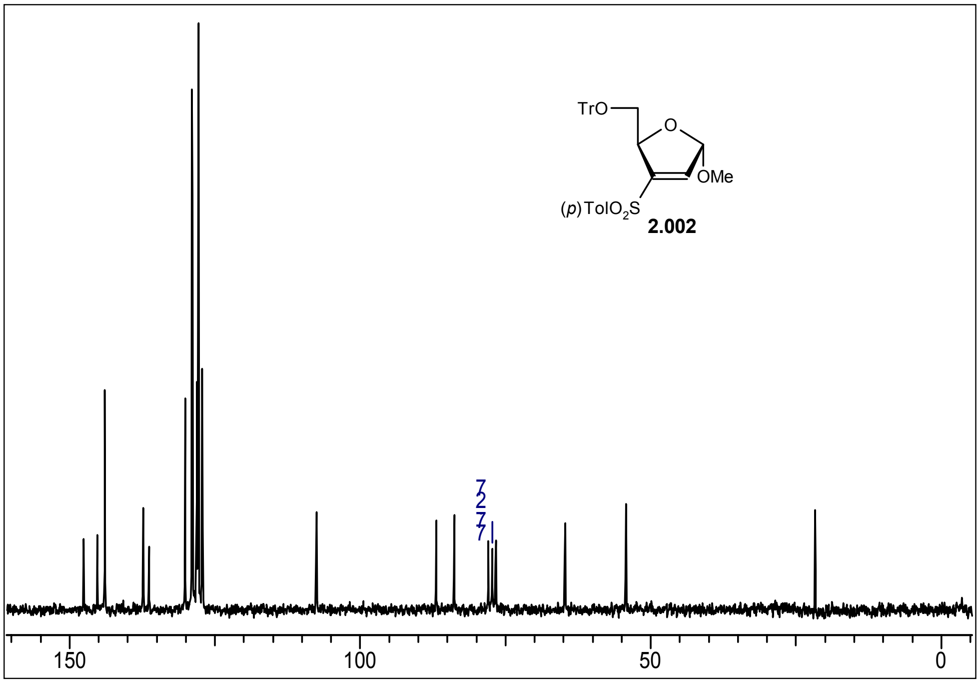

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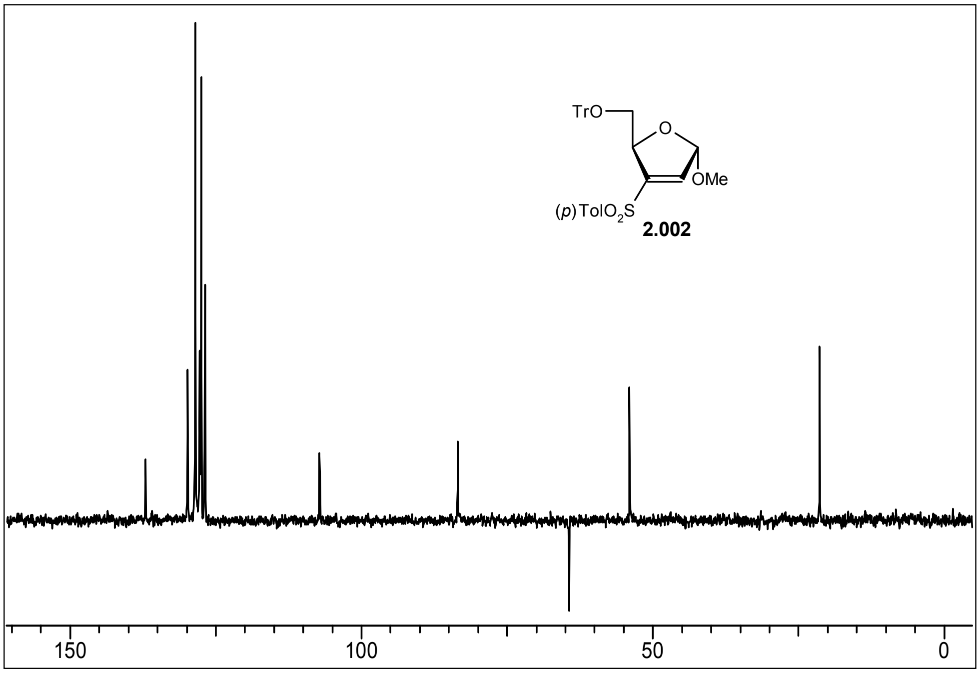

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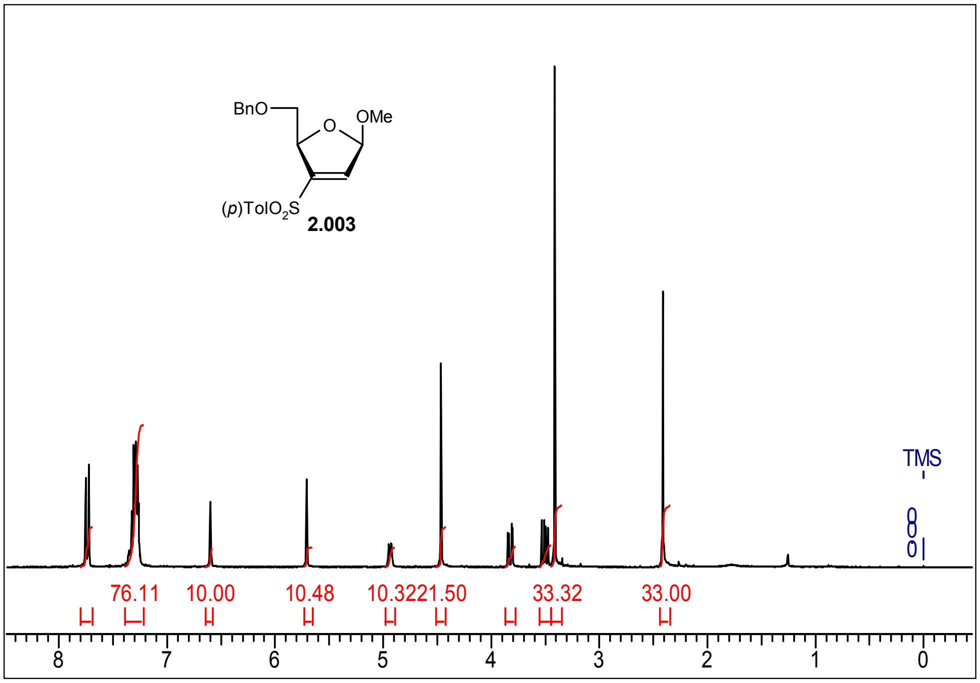

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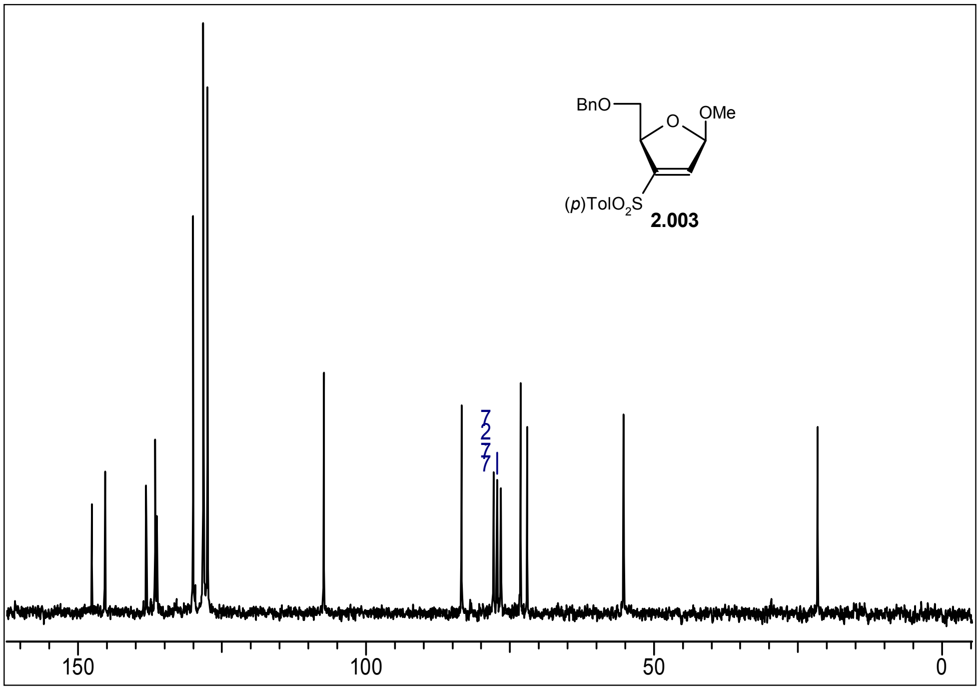

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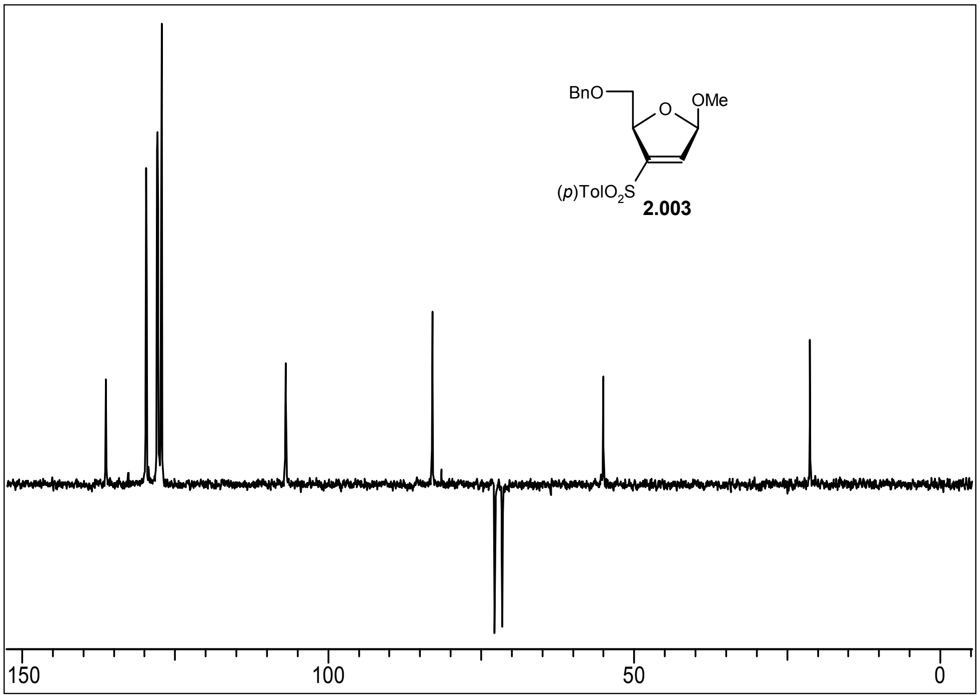

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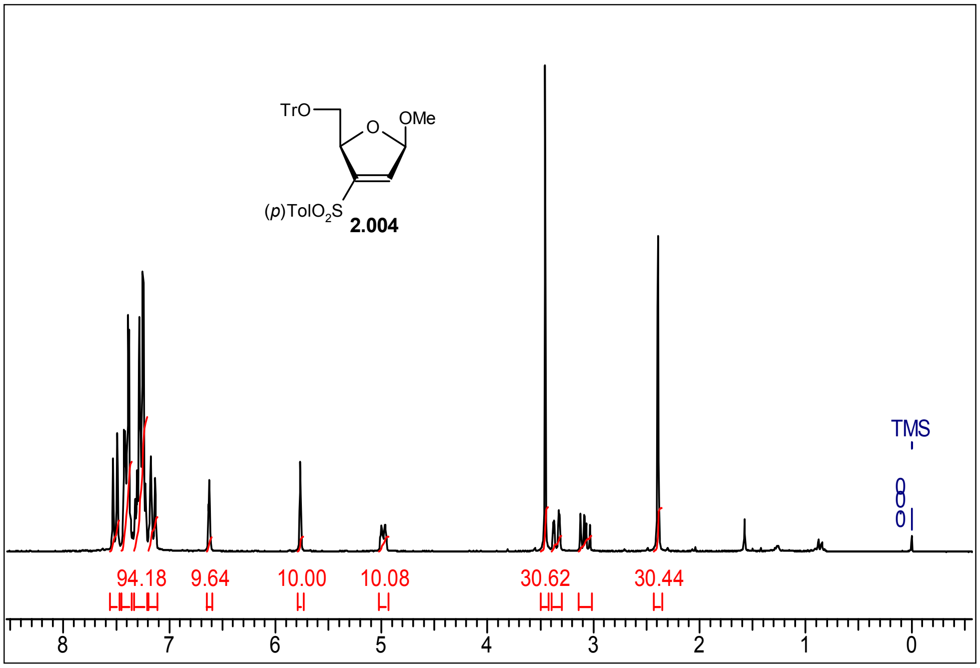

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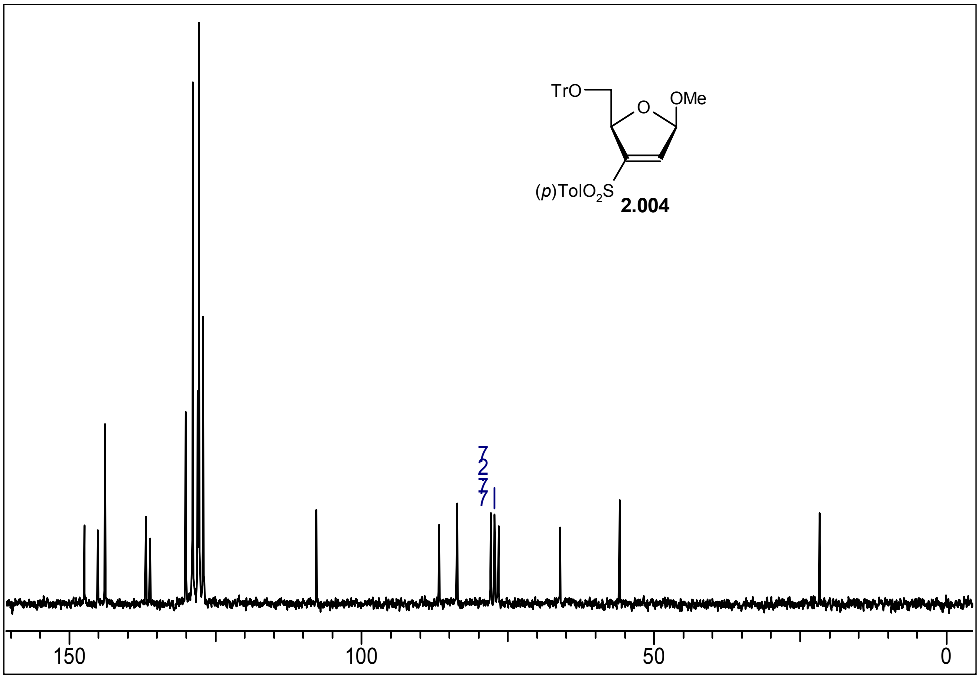

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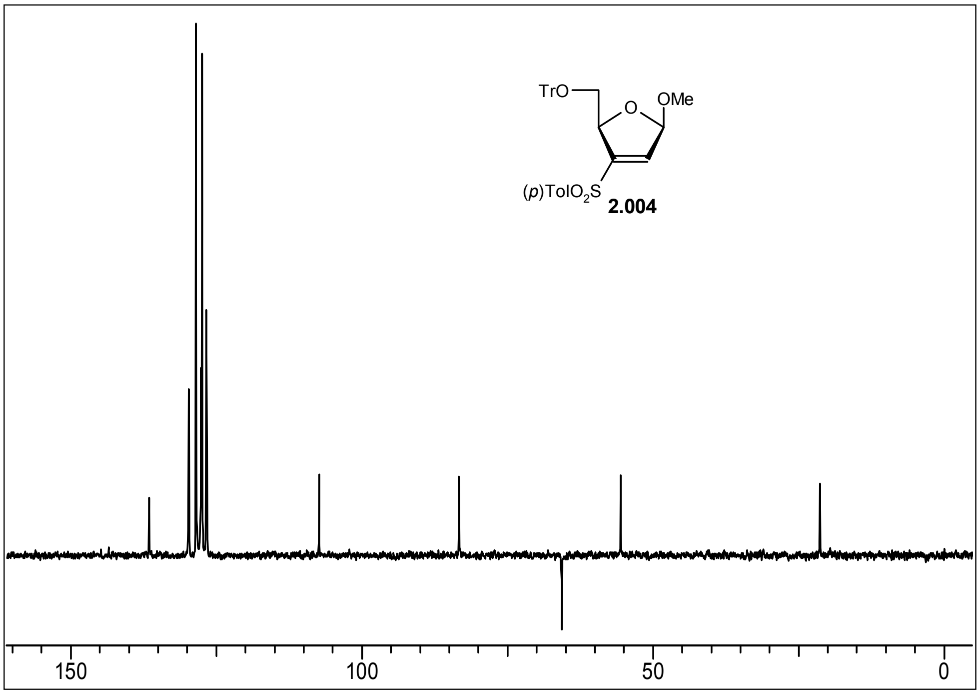

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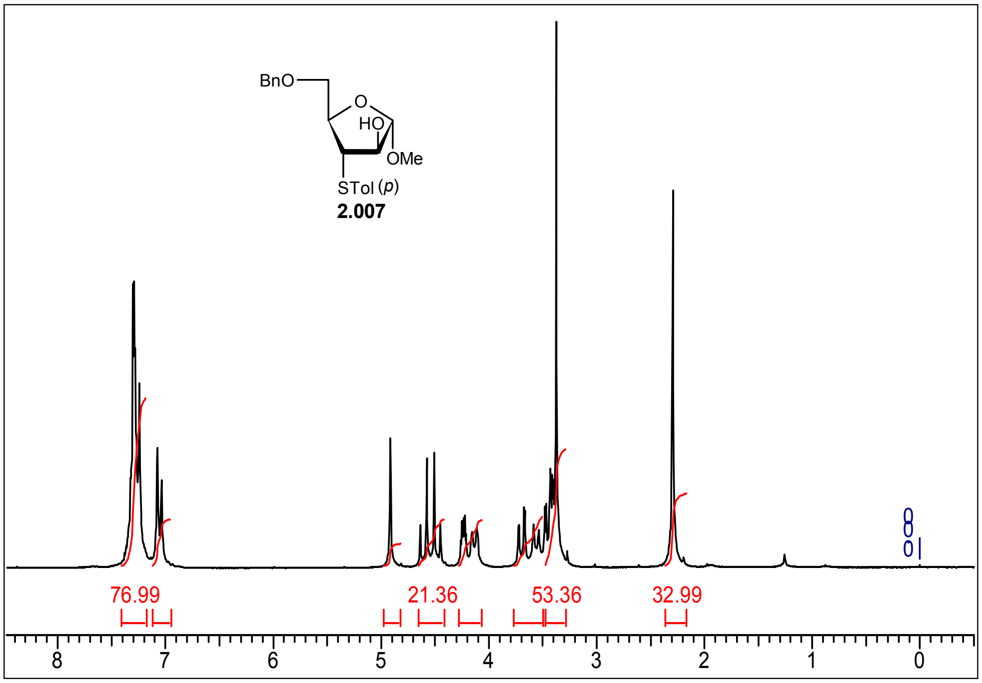

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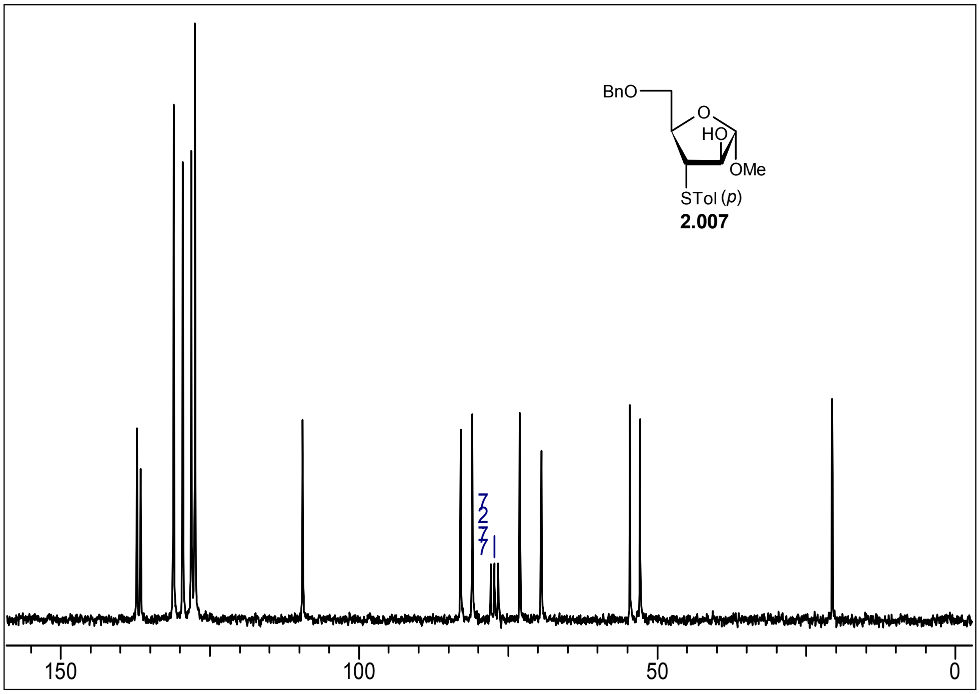

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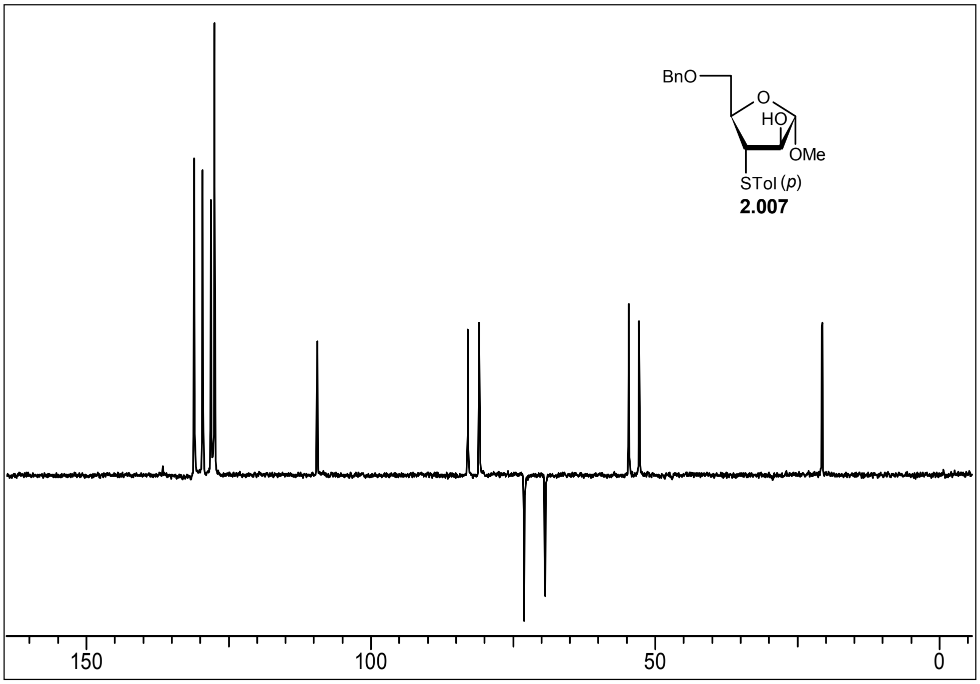

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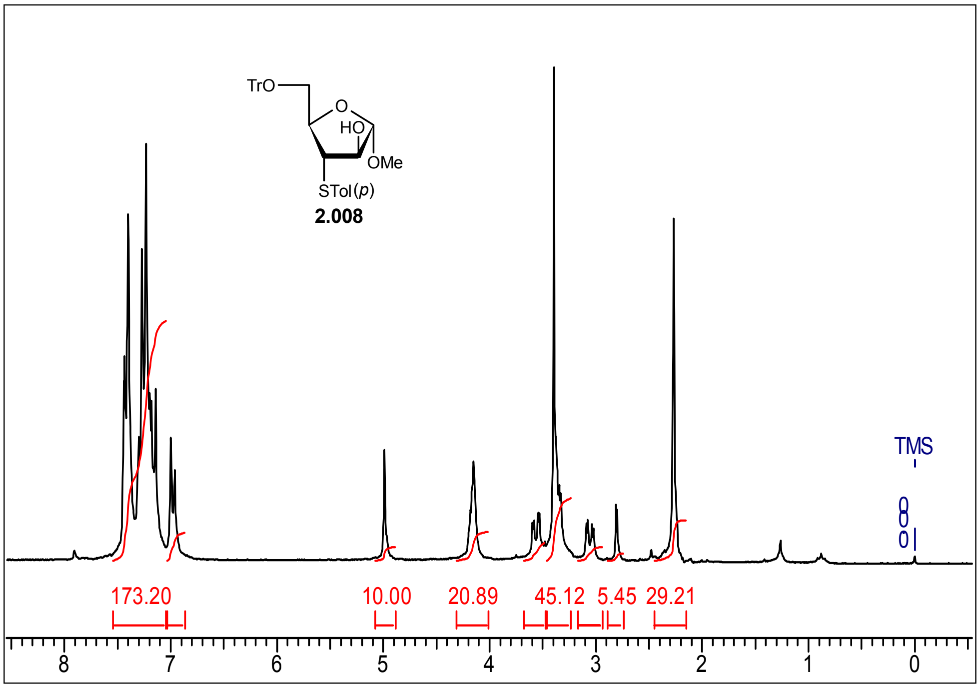

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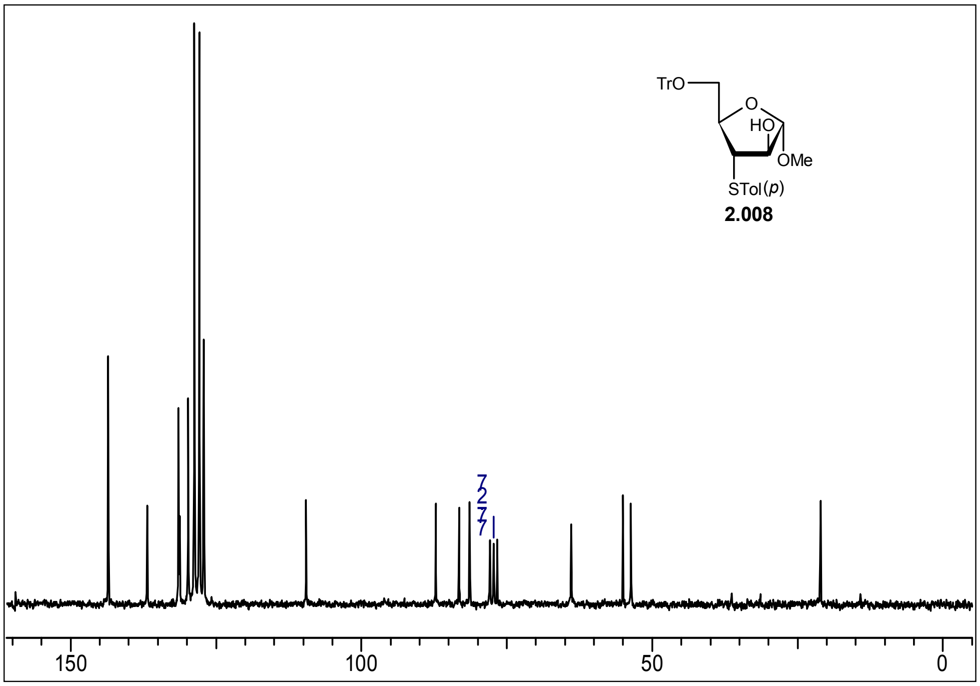

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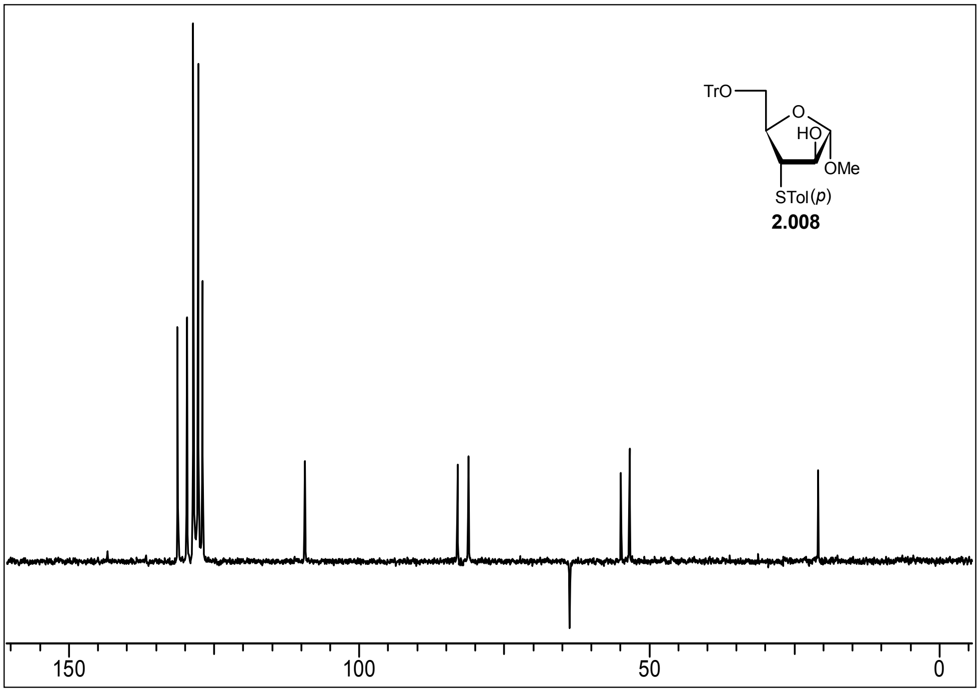

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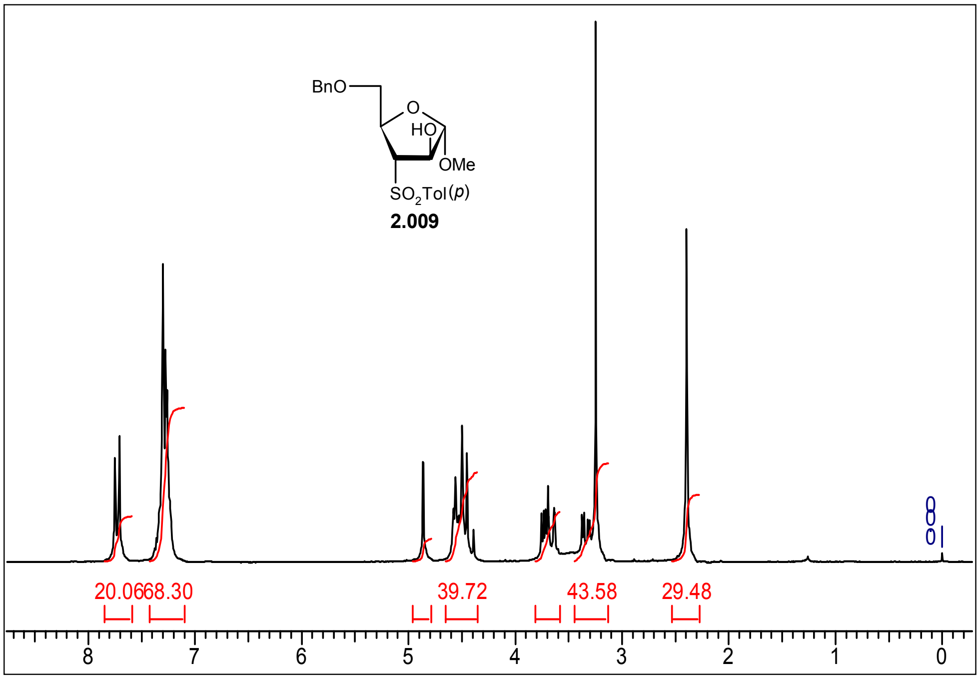

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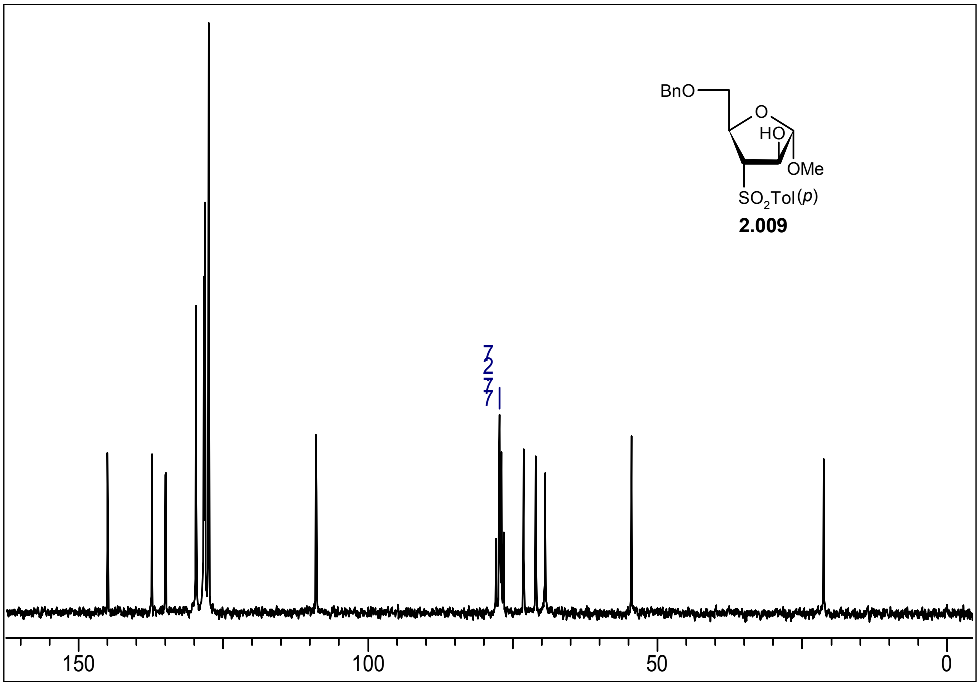

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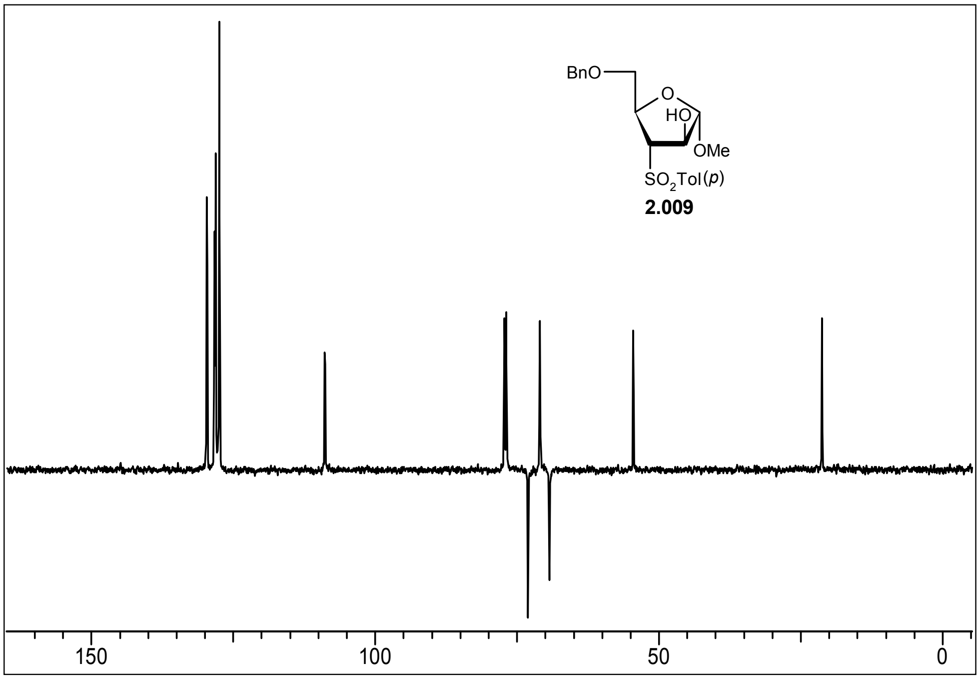

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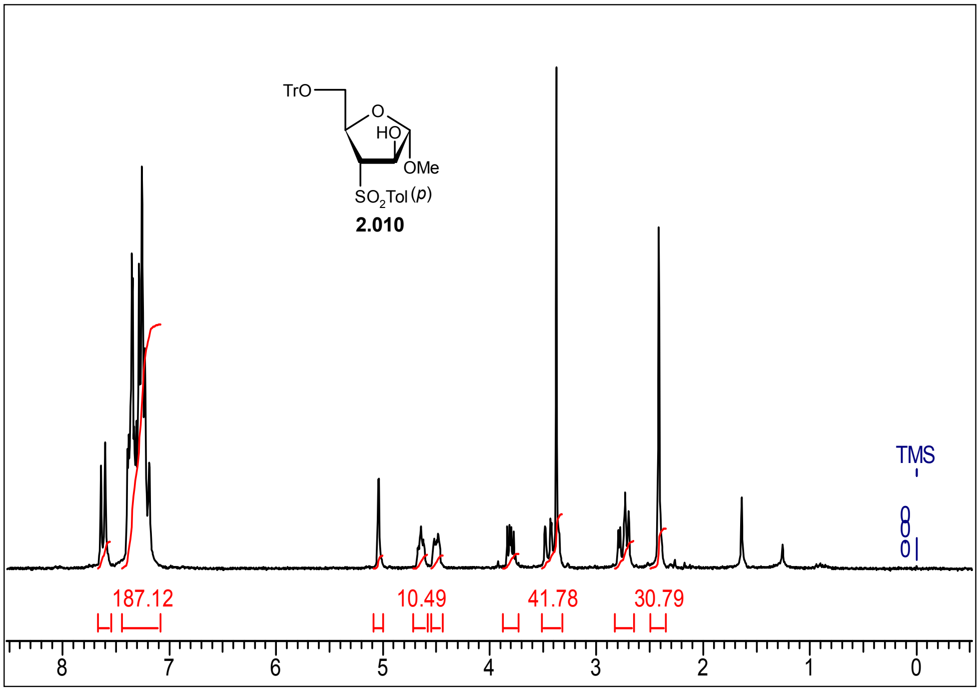

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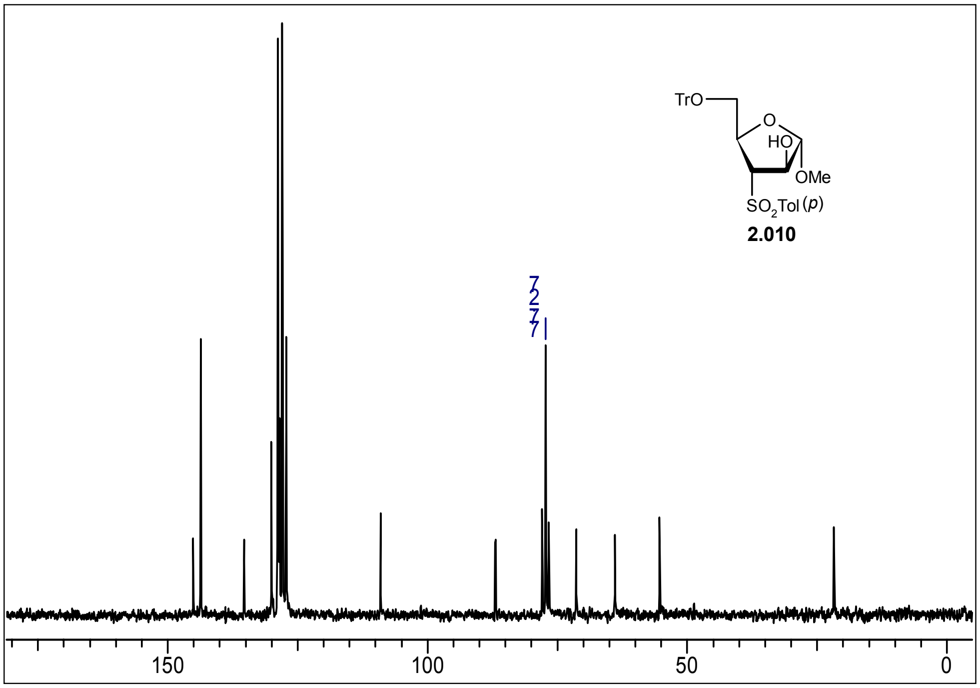

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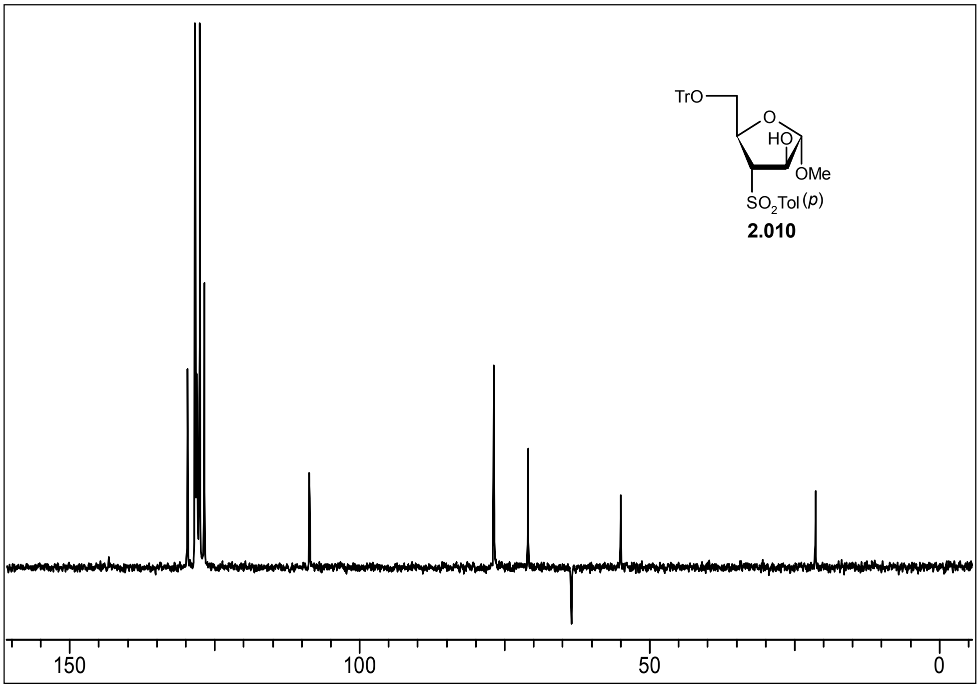

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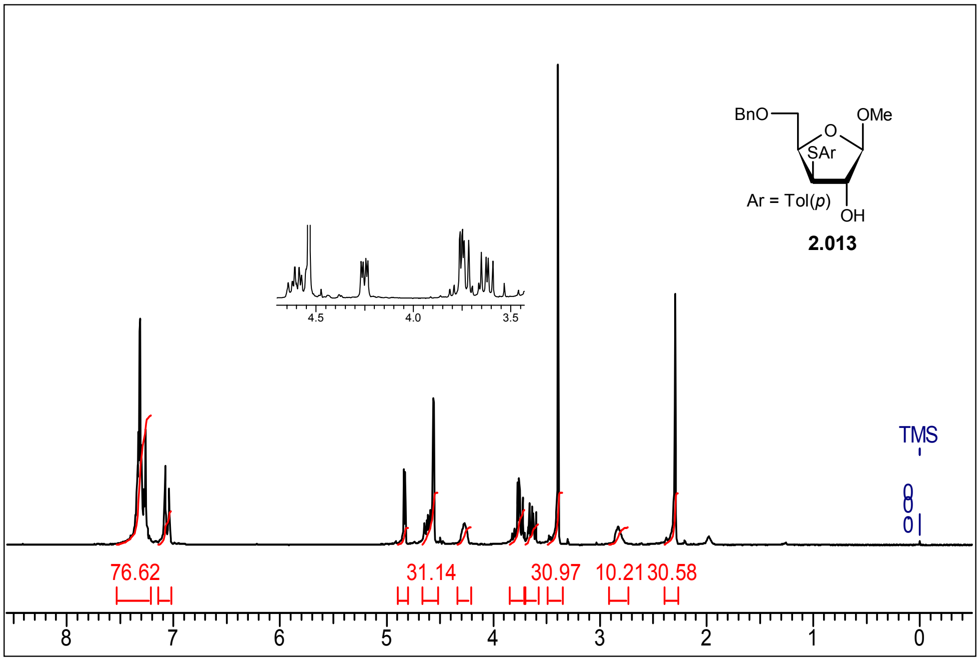

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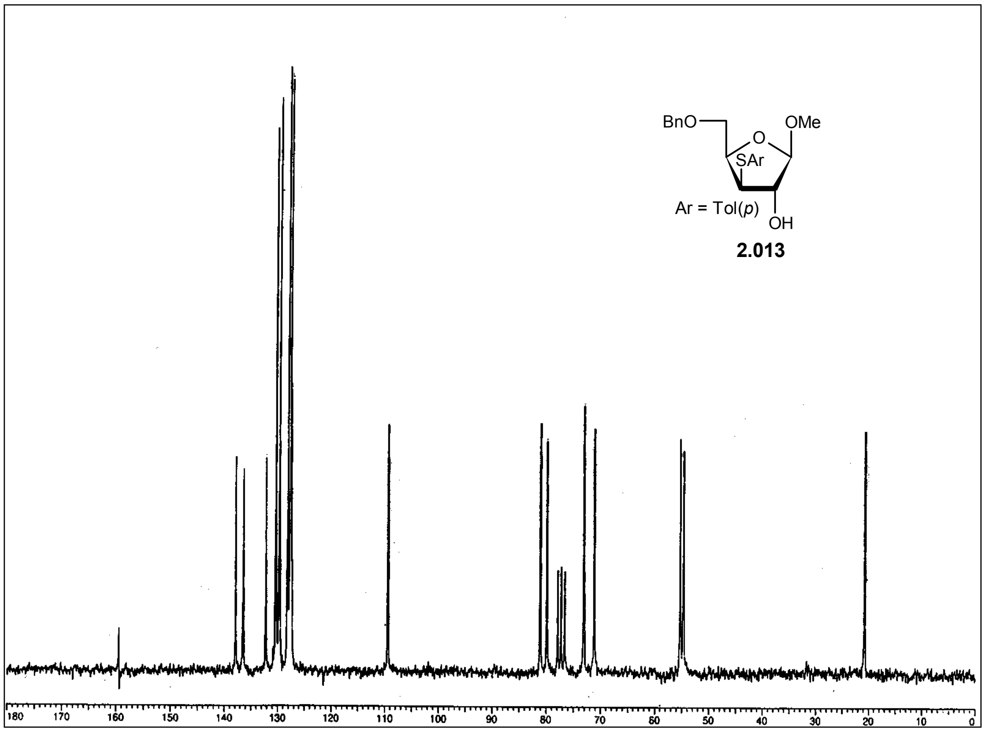

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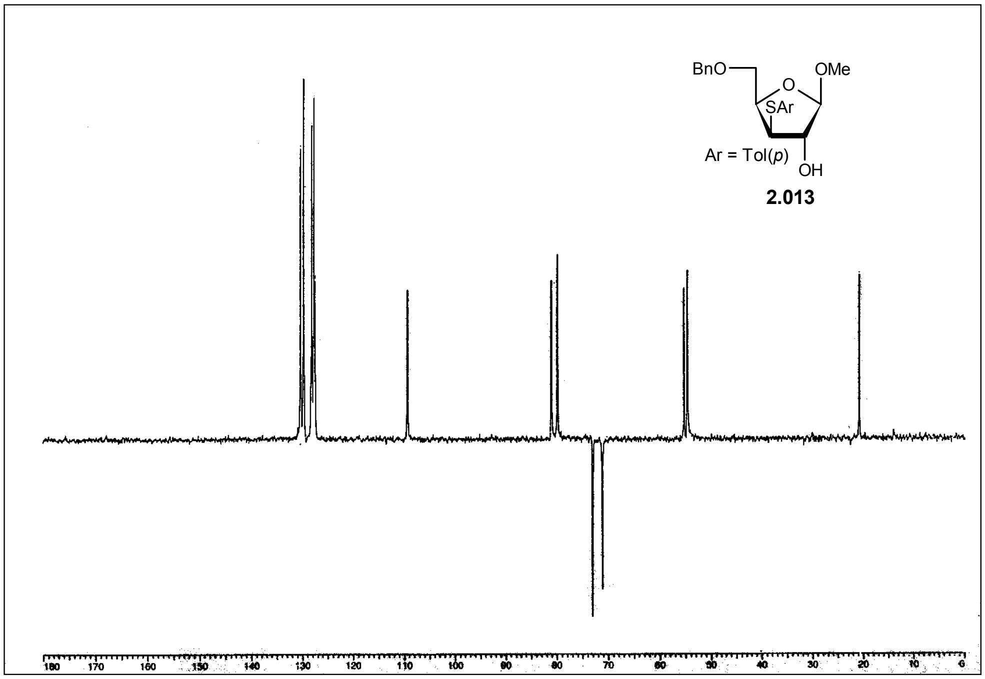

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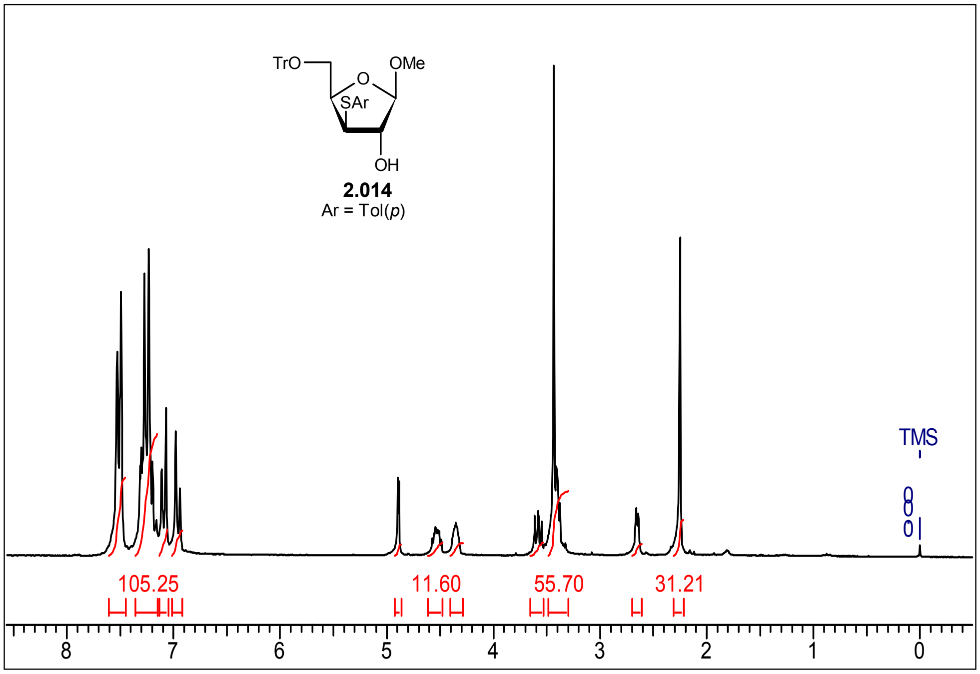

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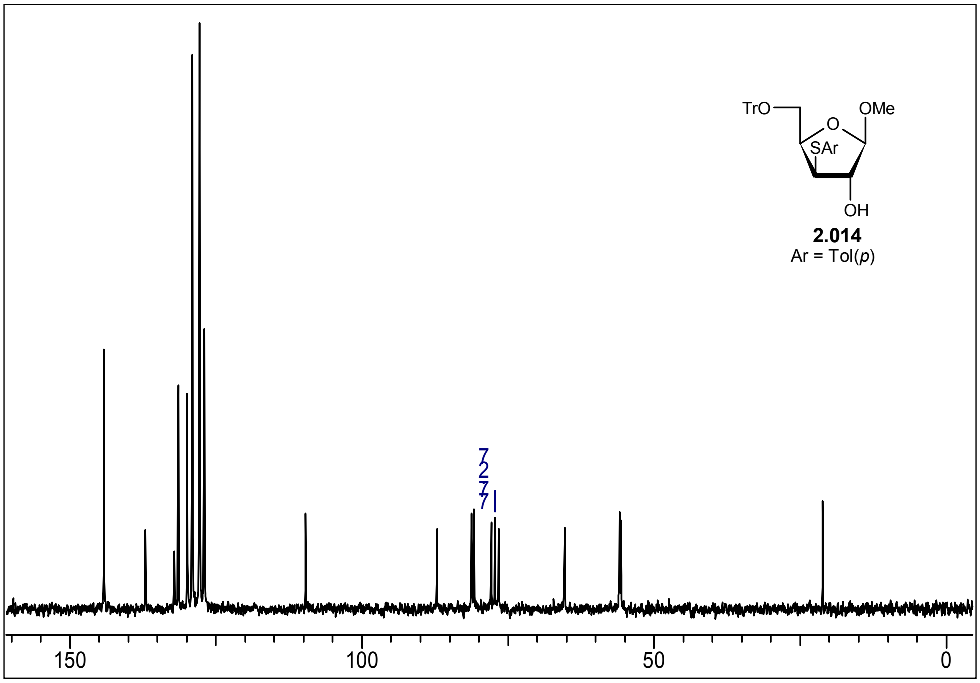

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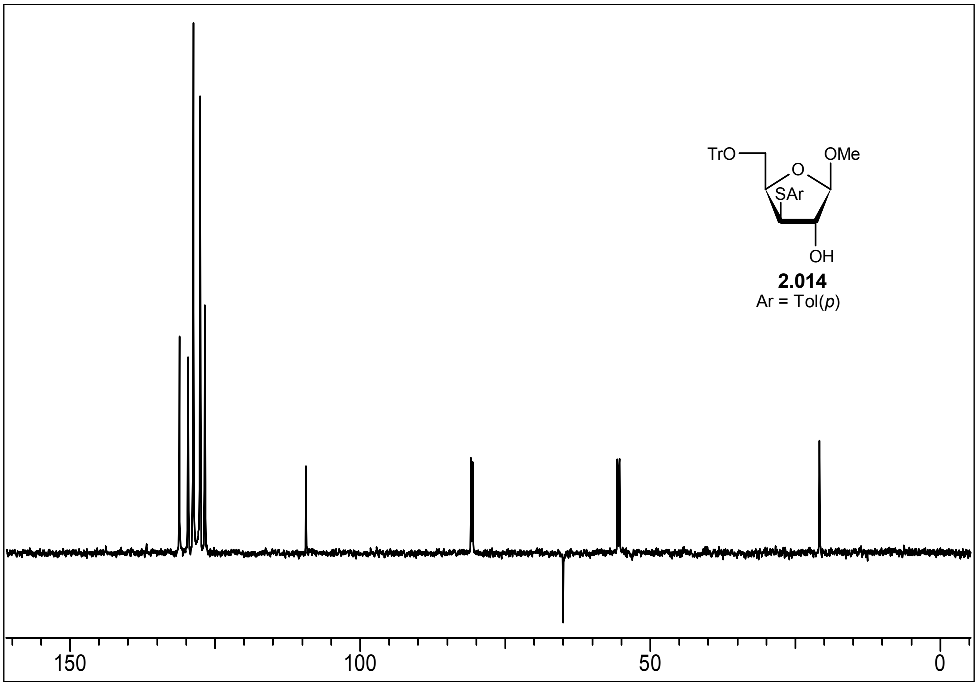

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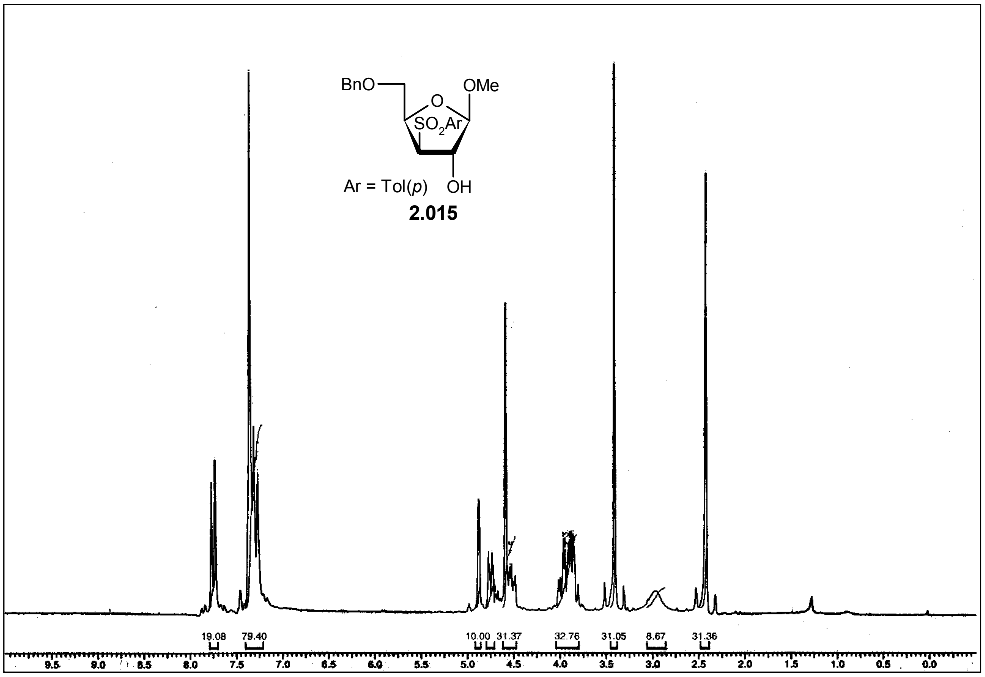

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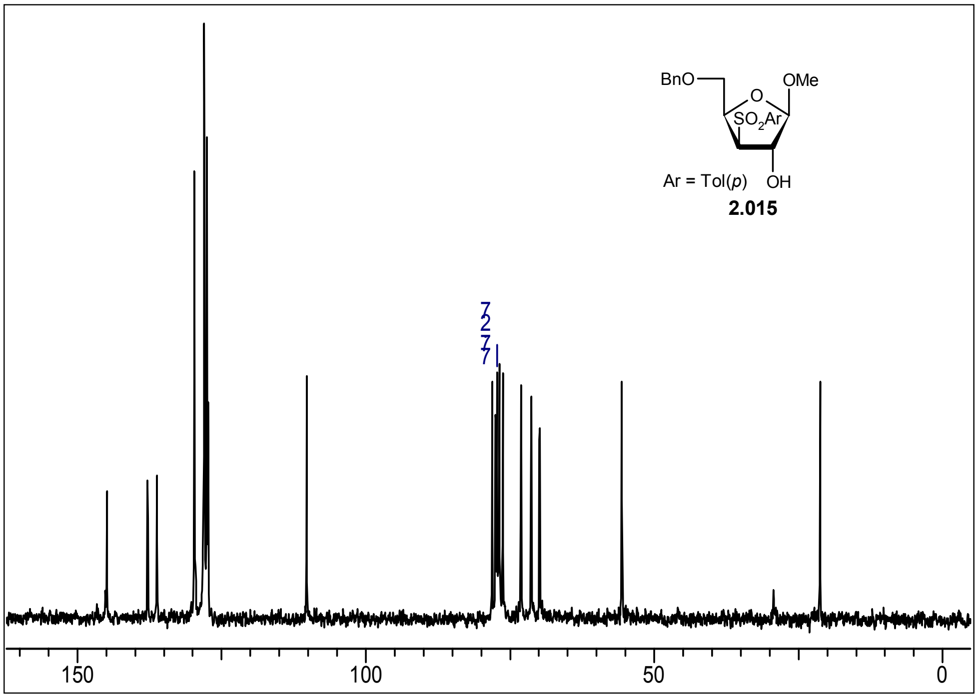
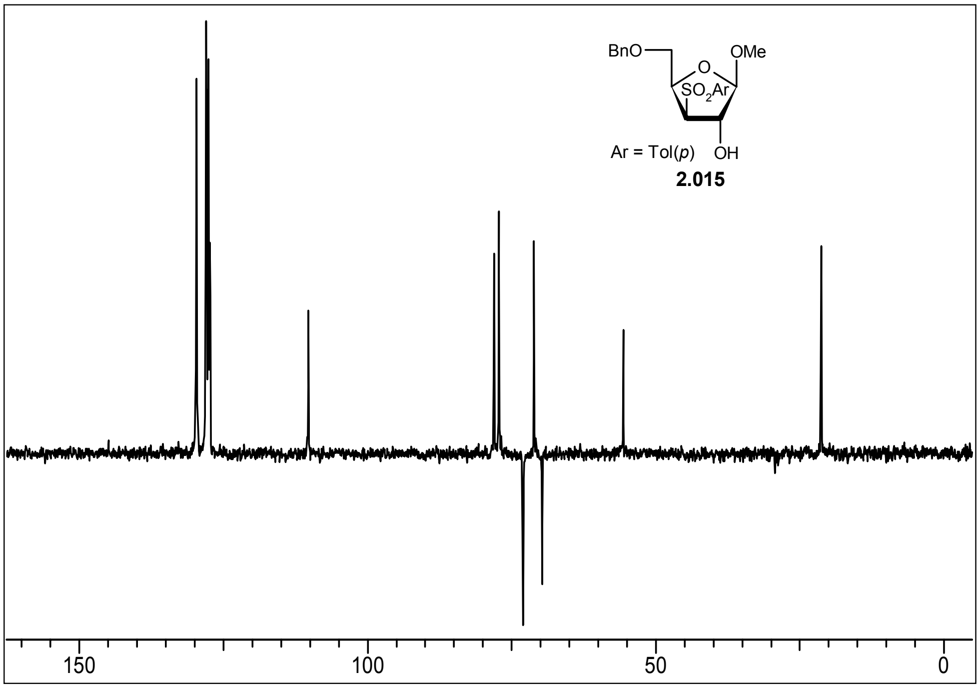


Dept of **2.015**



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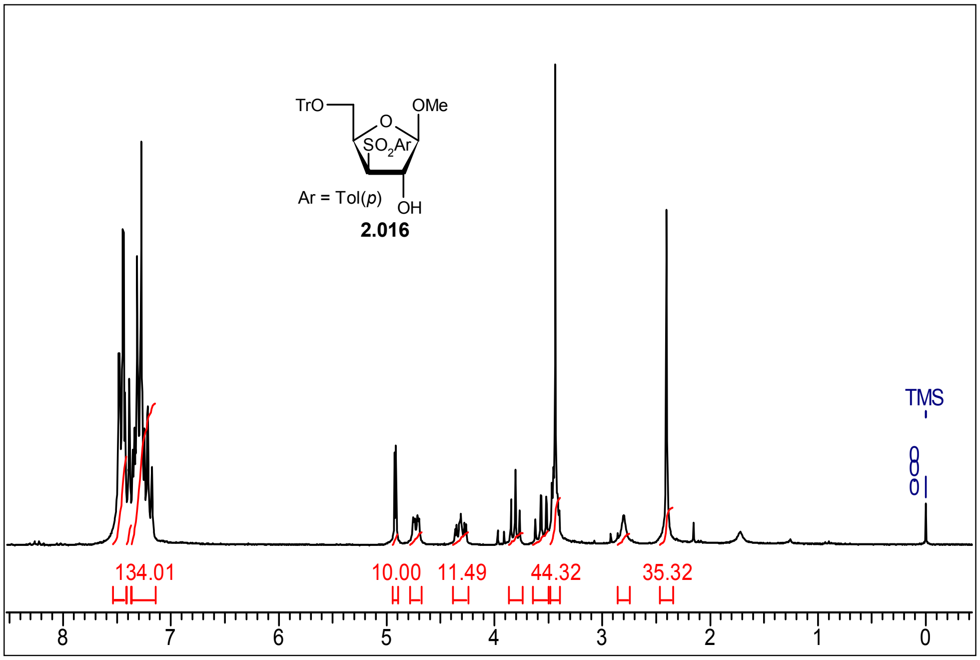

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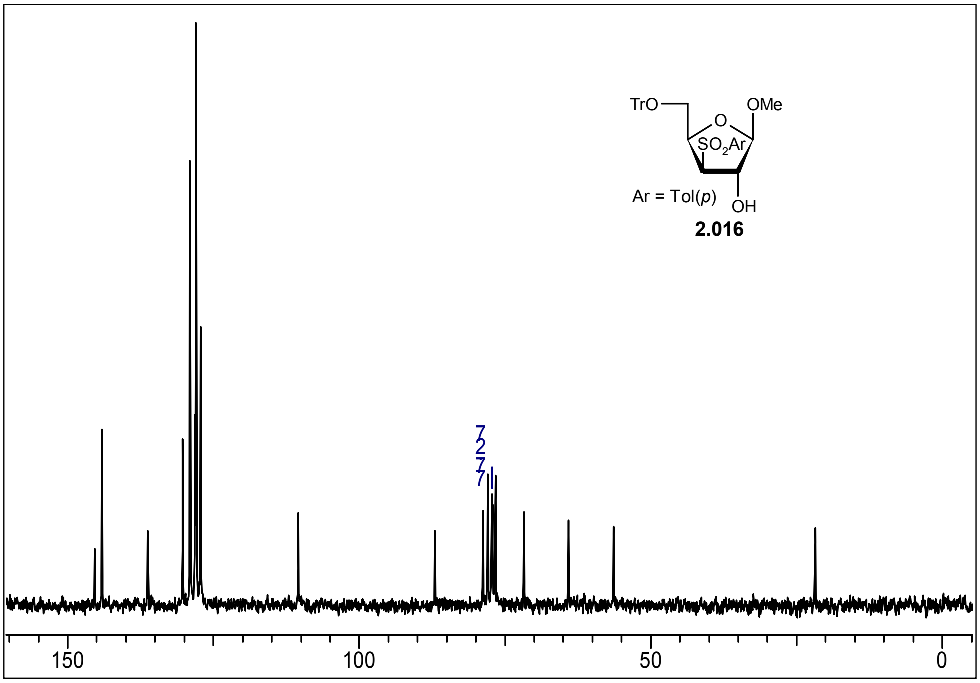

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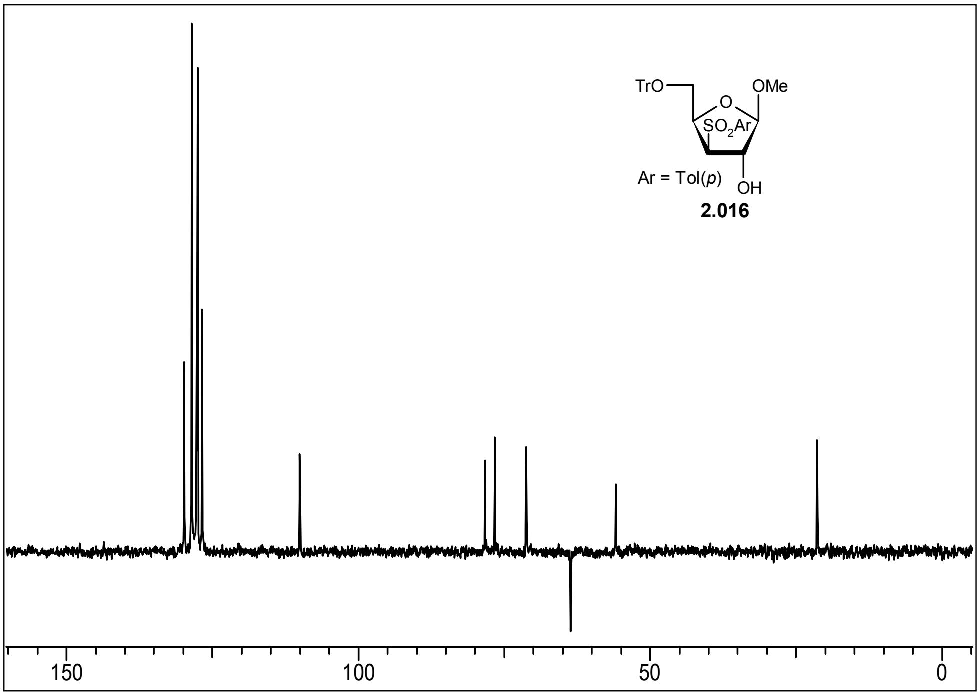

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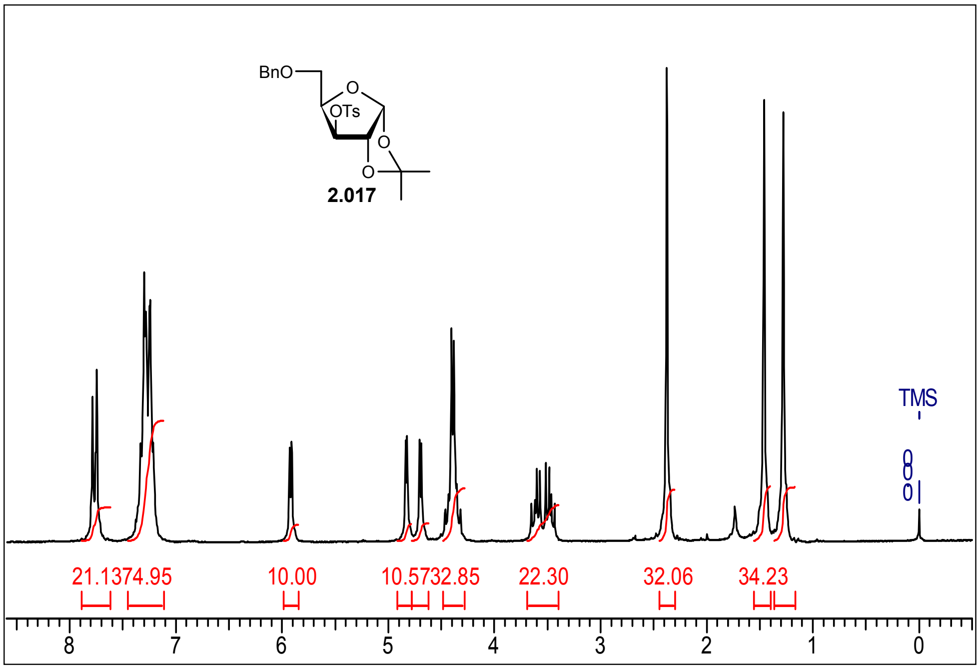

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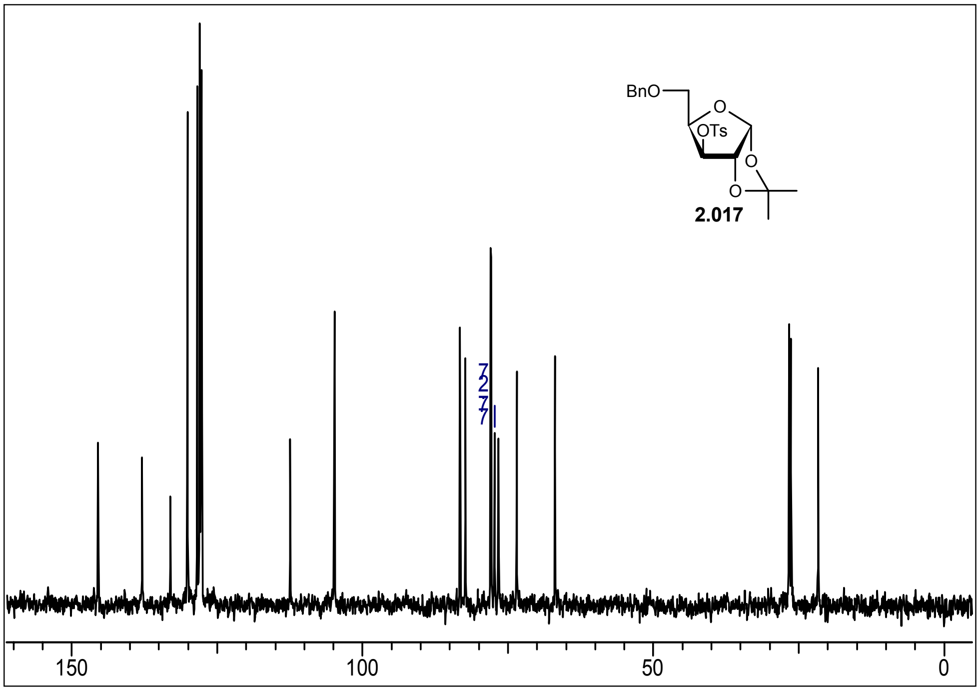

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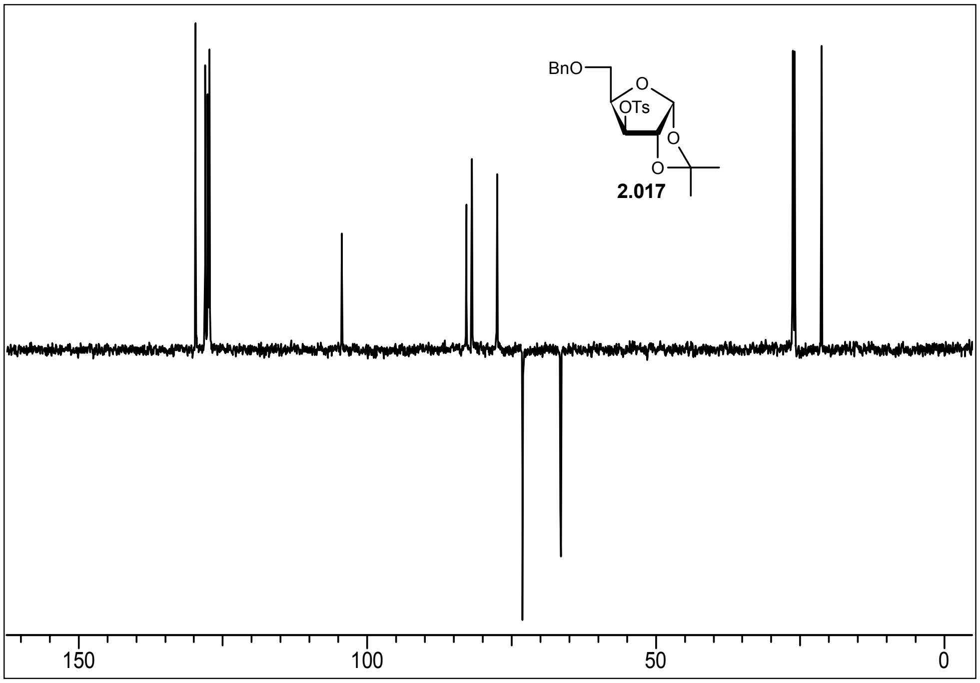

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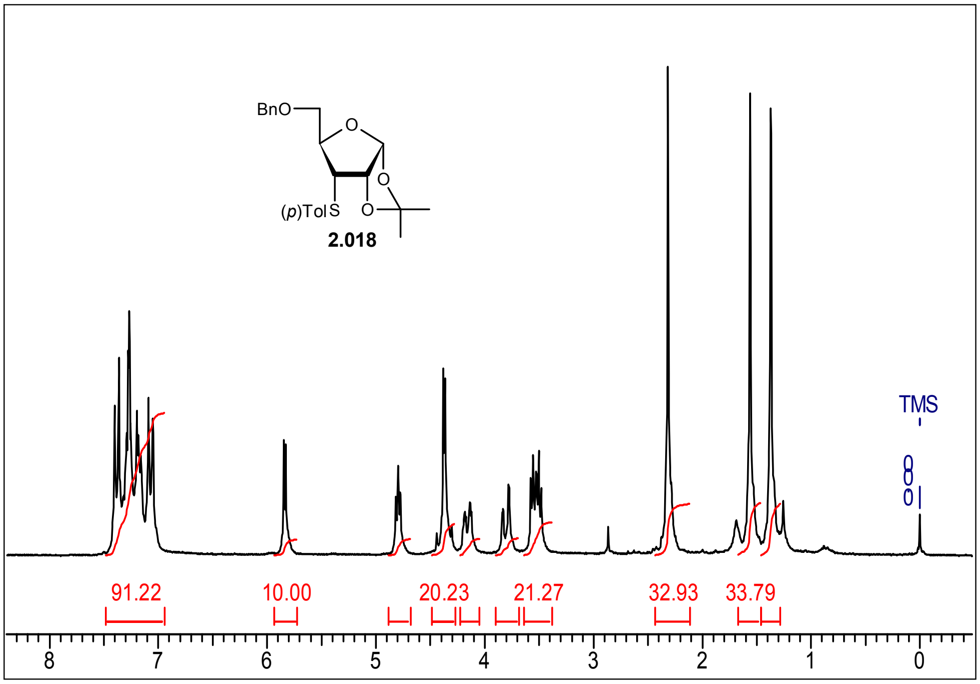

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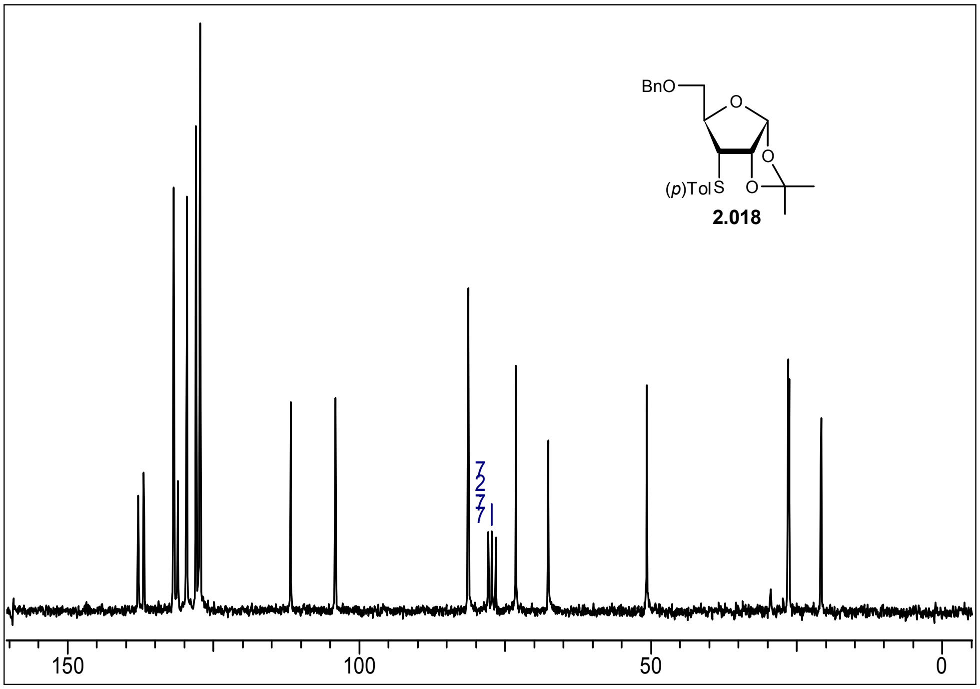

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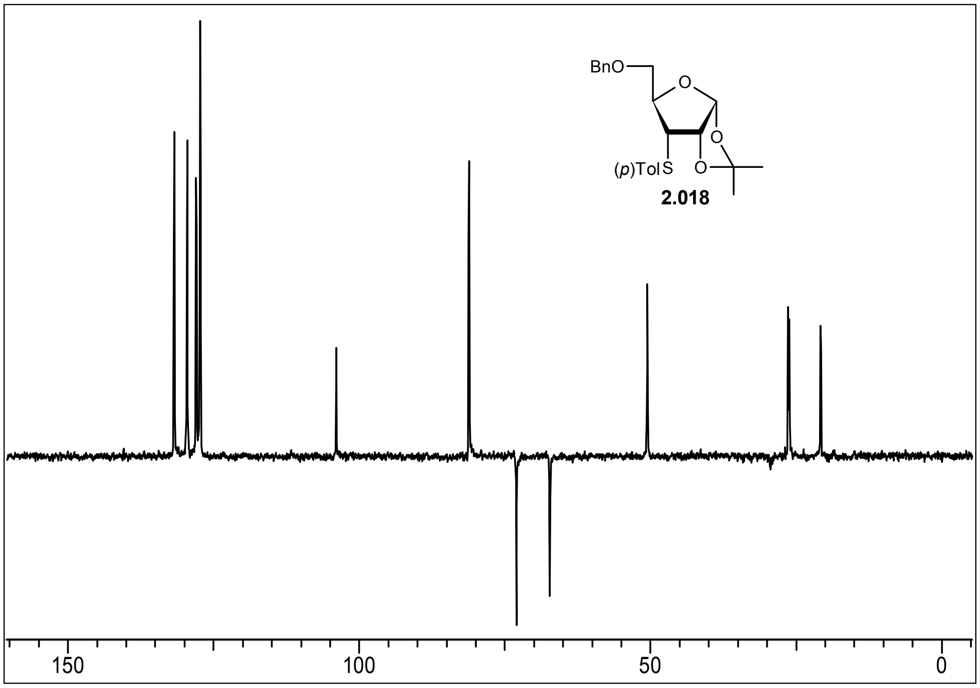

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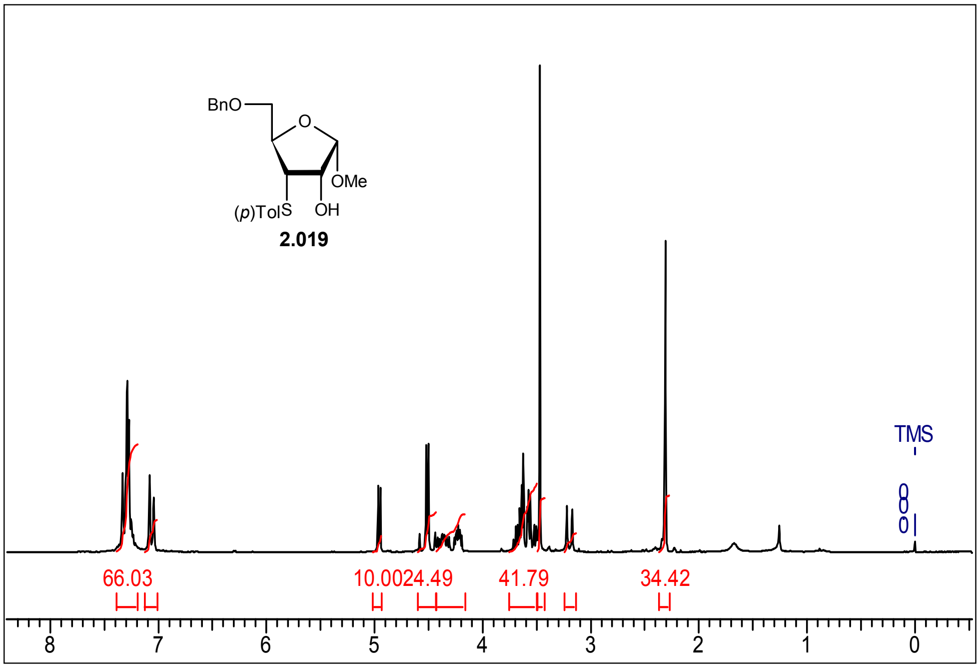

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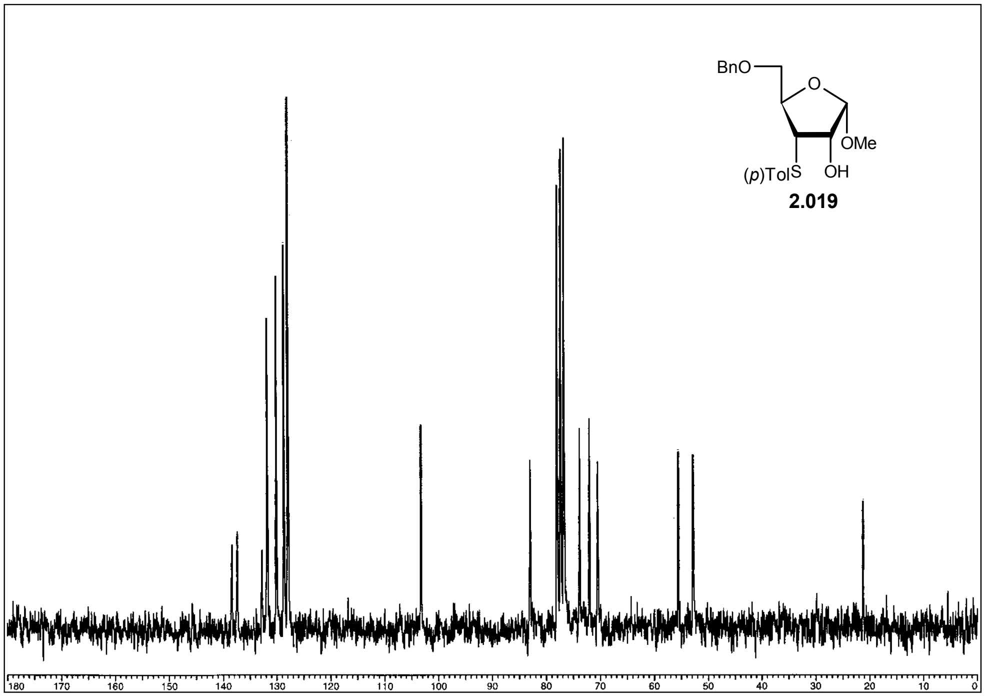

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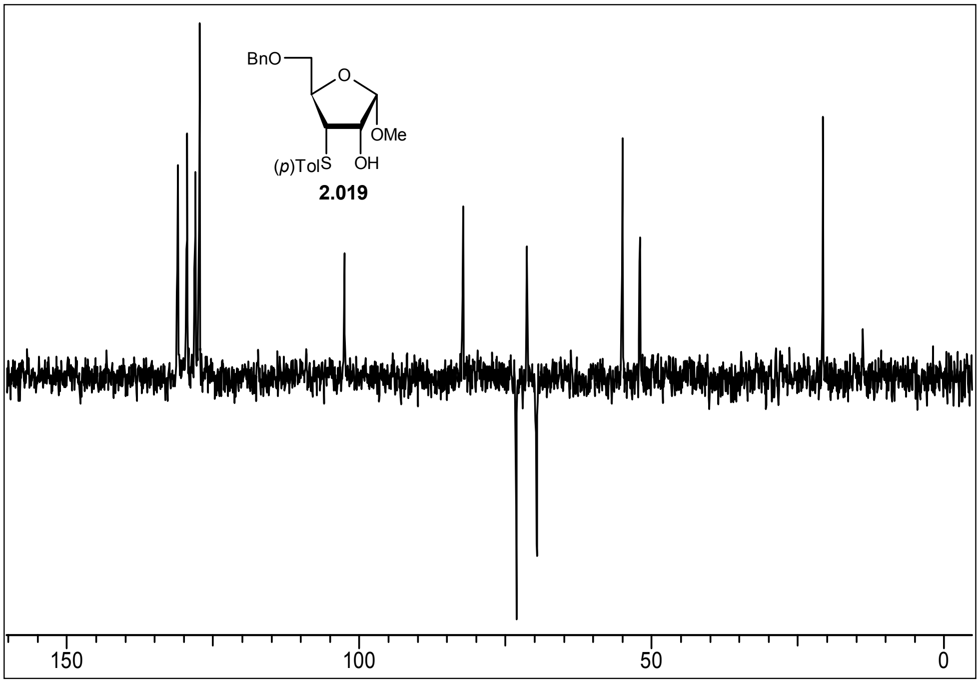

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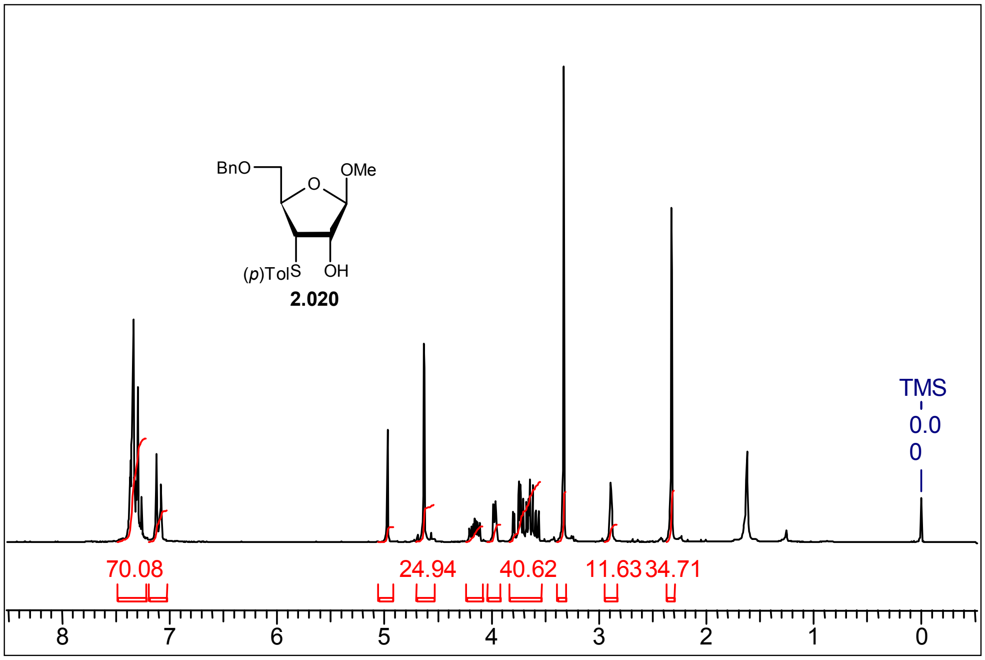

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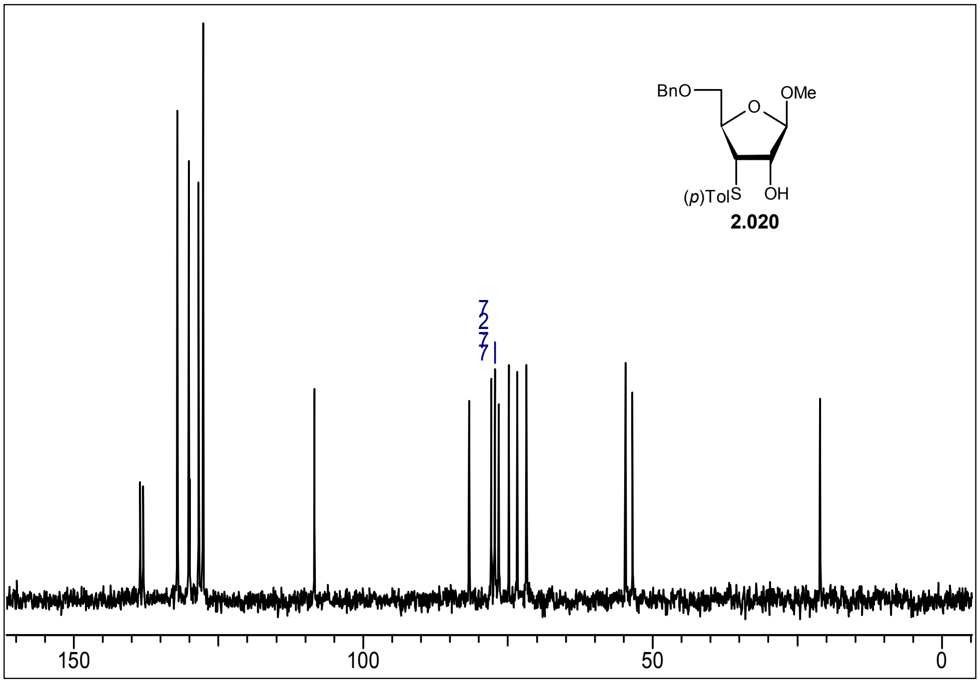

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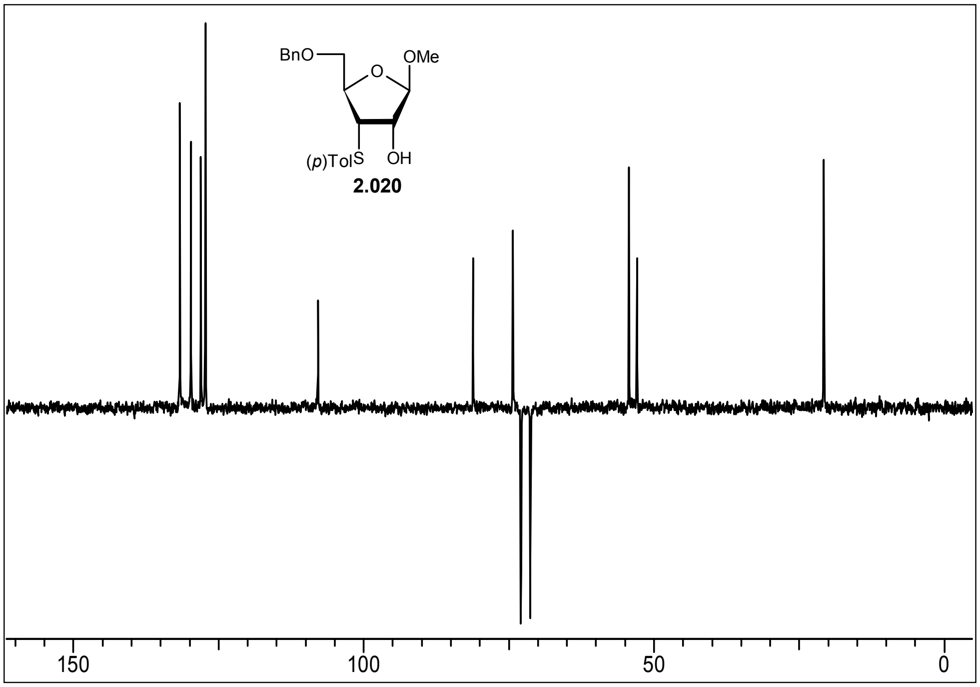

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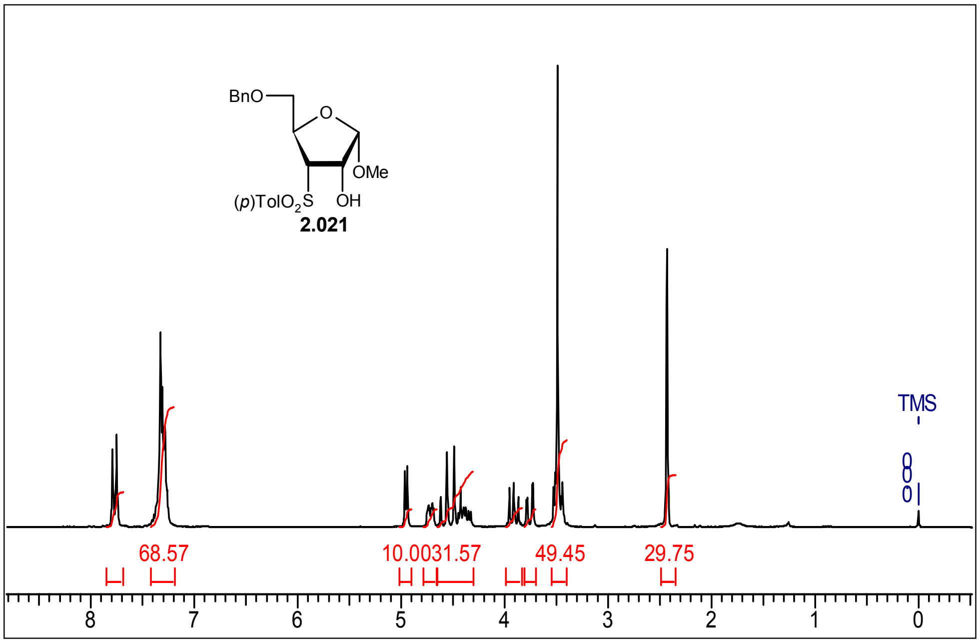

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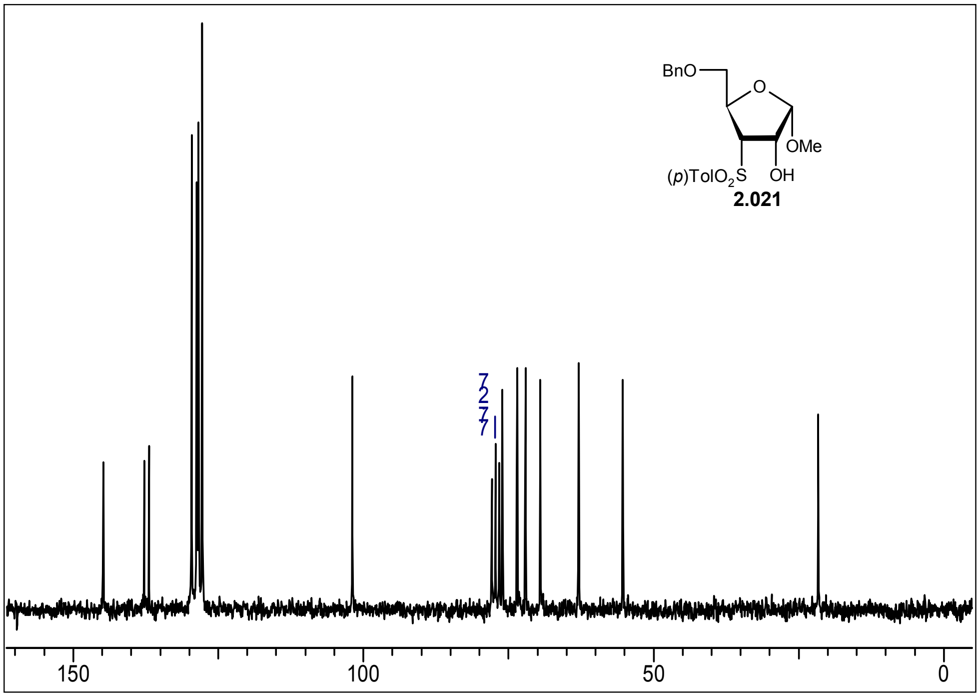

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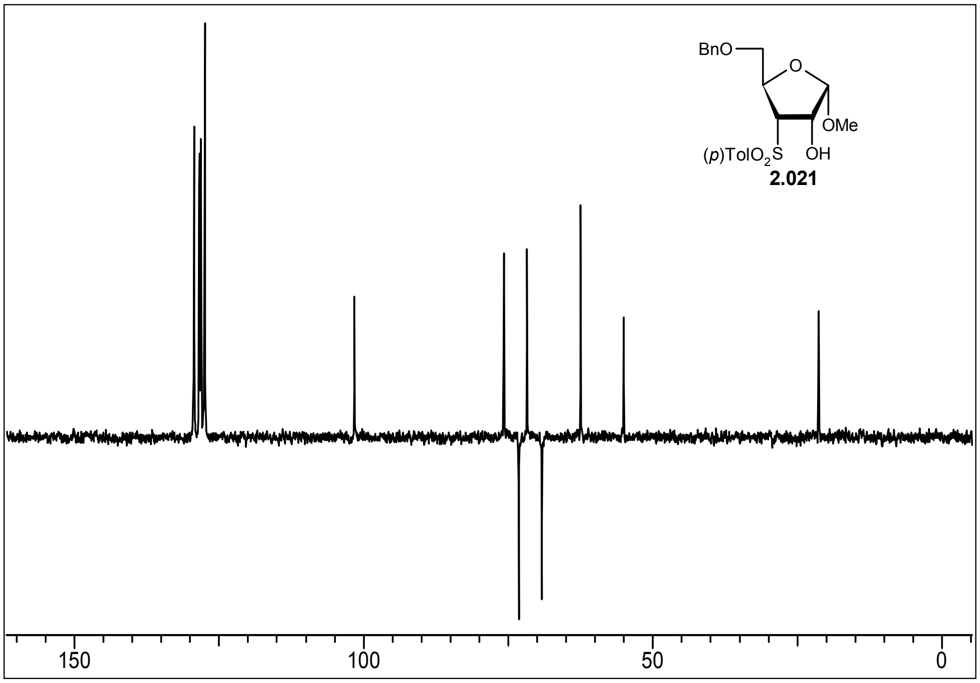

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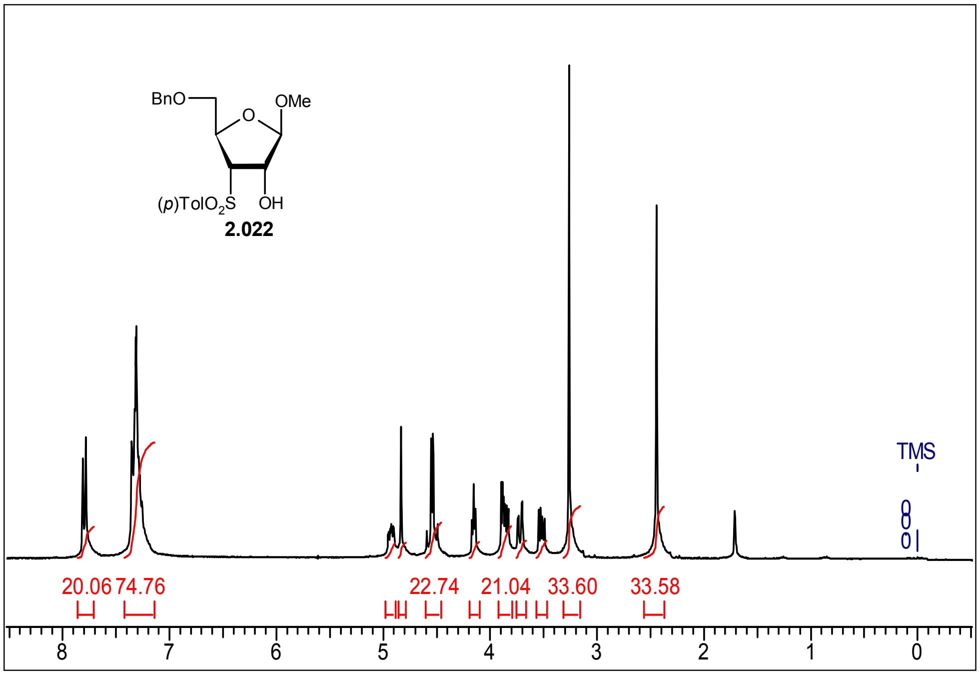

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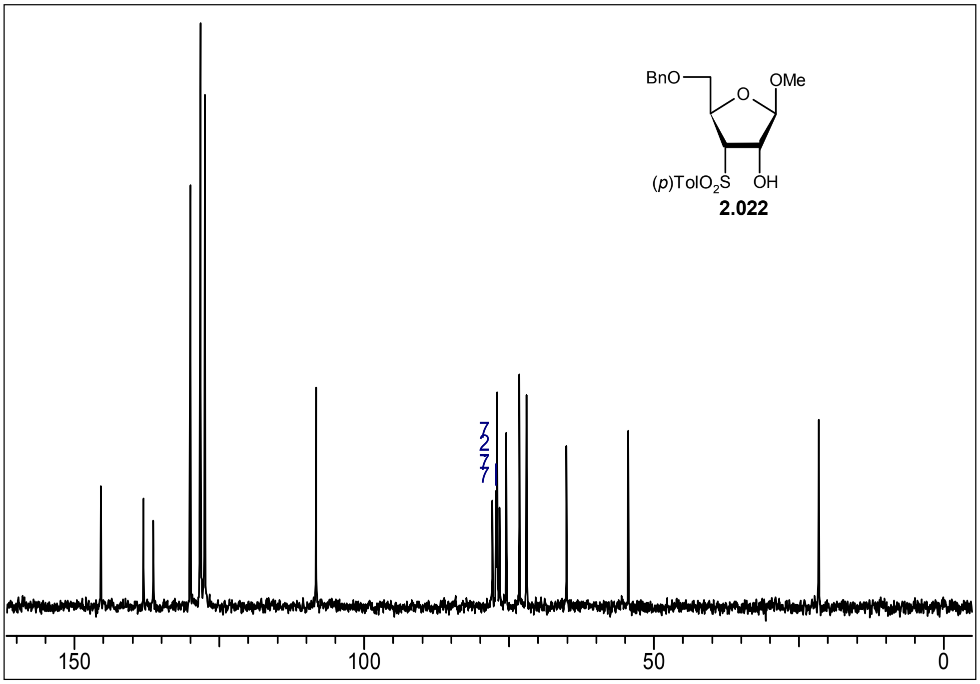

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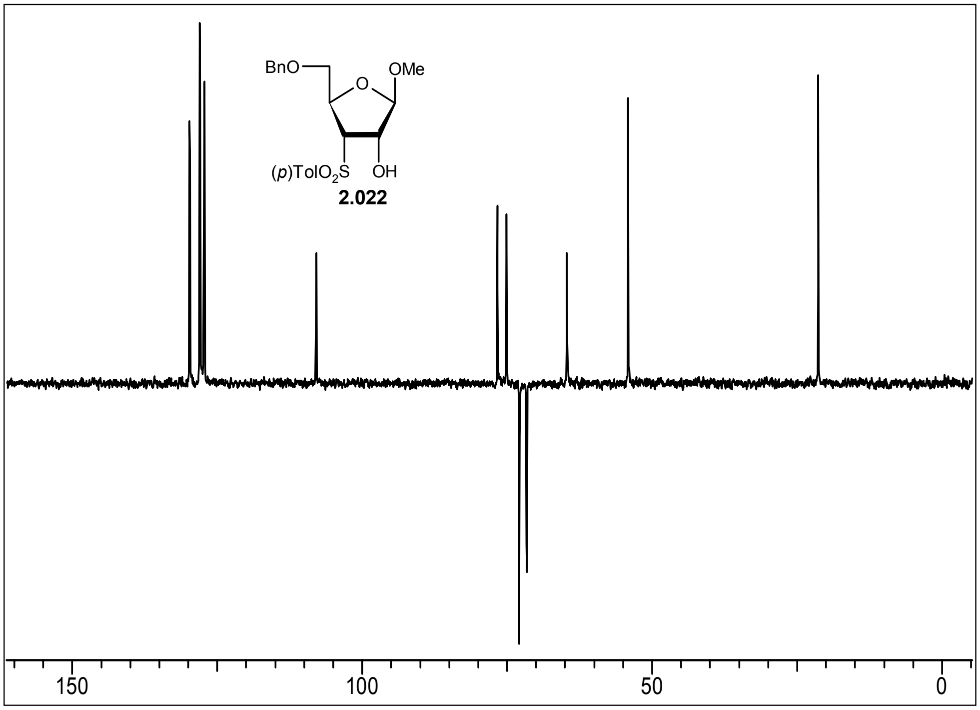

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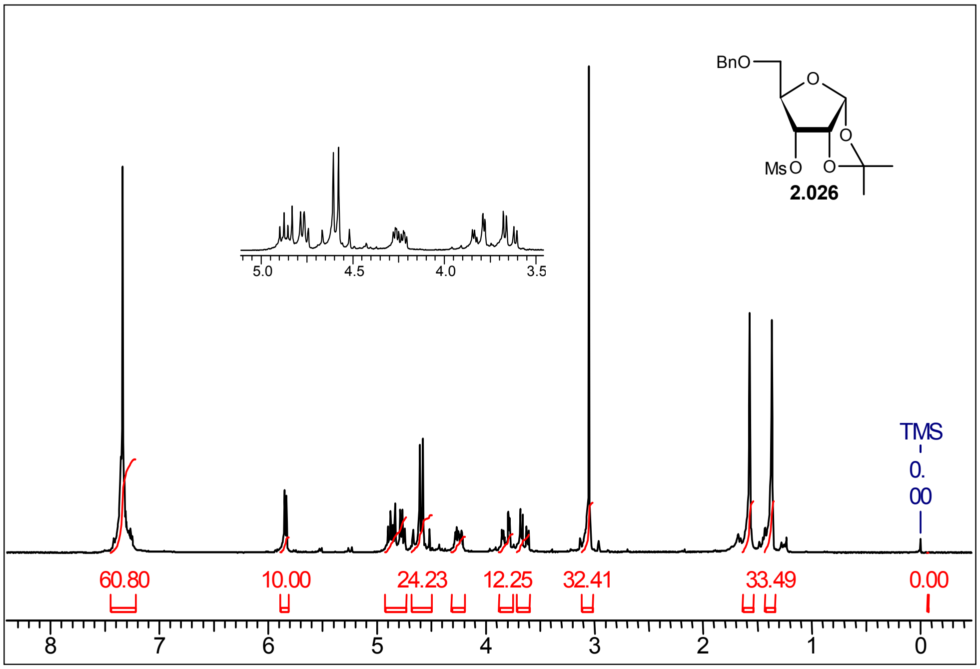

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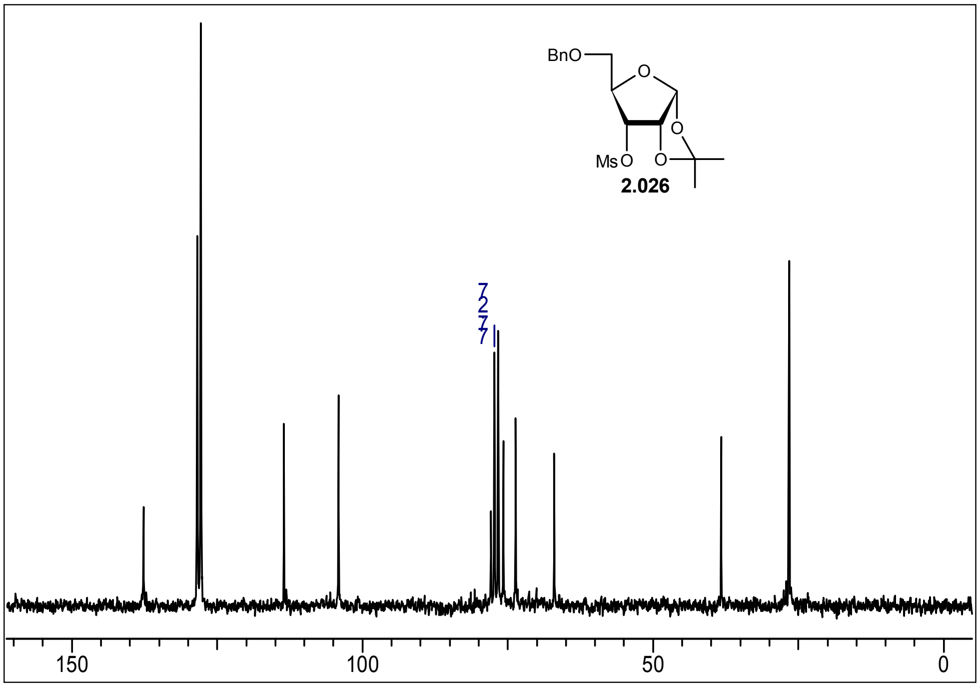

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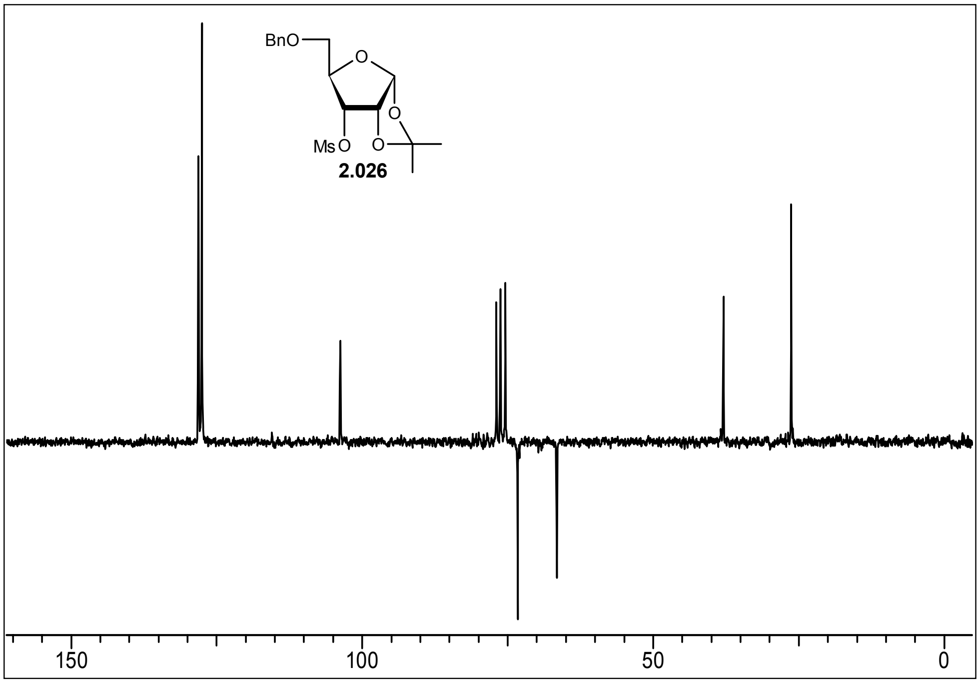

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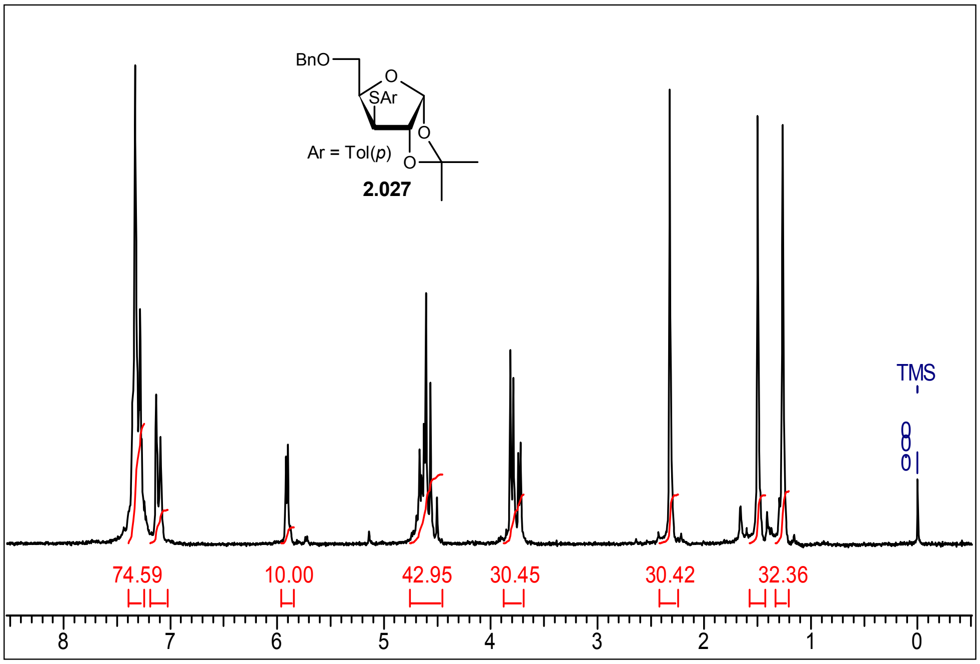

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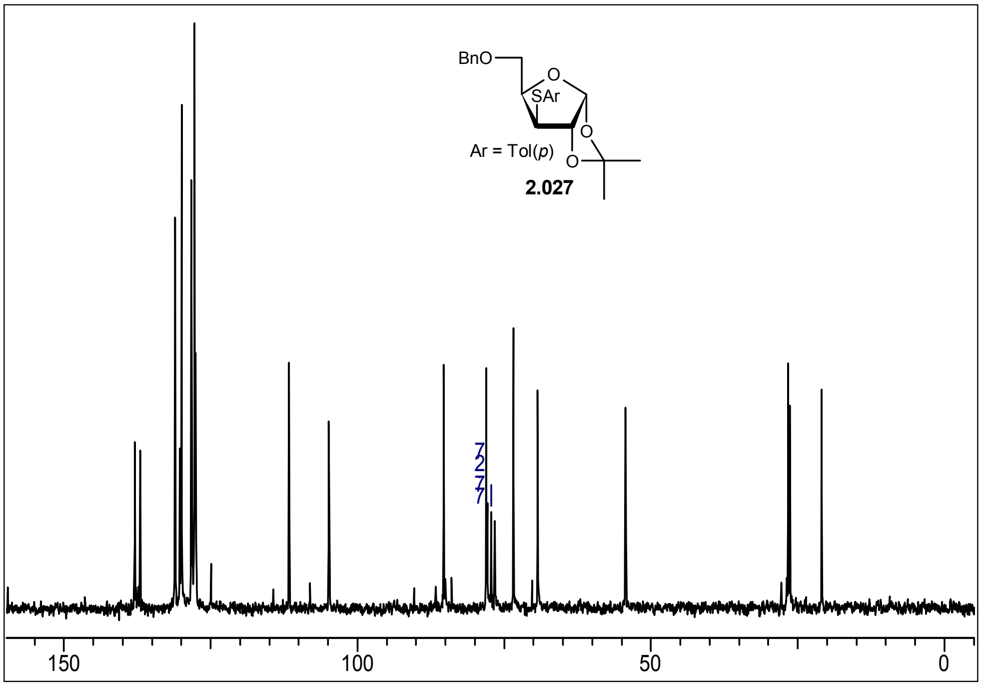

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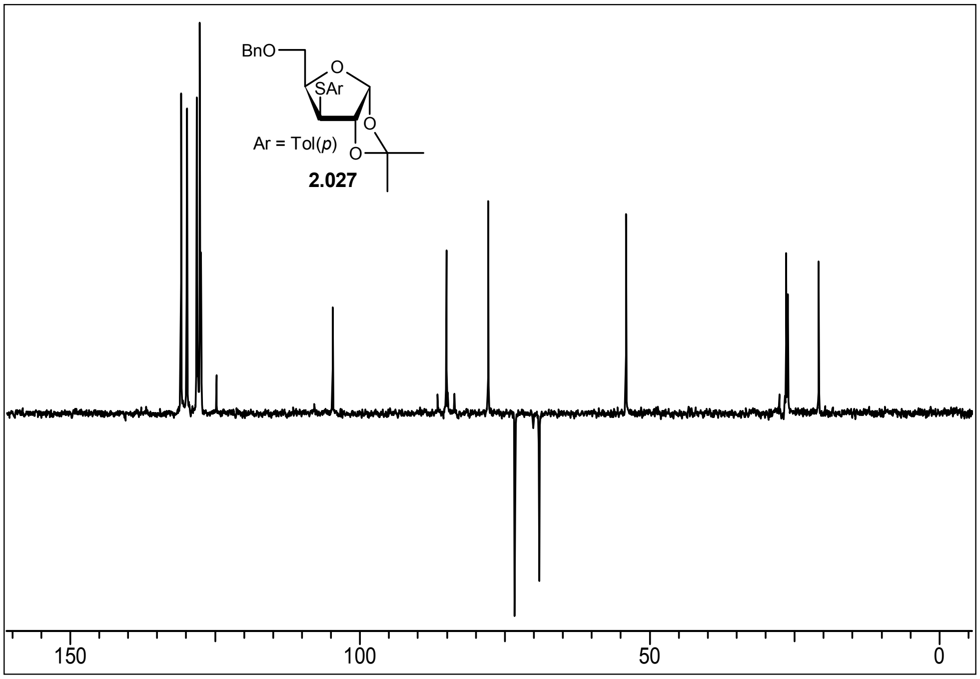

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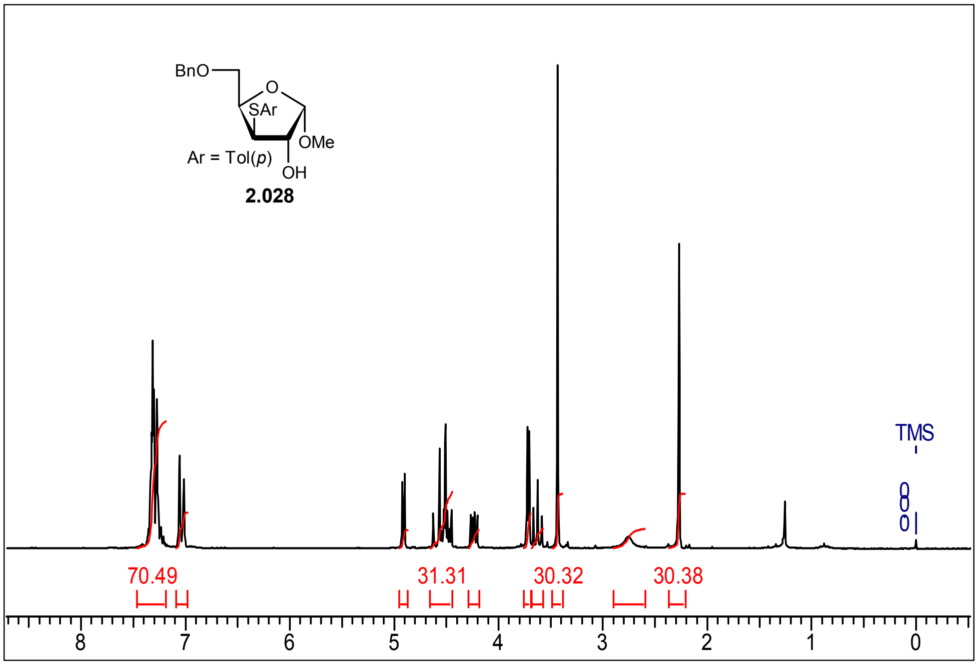

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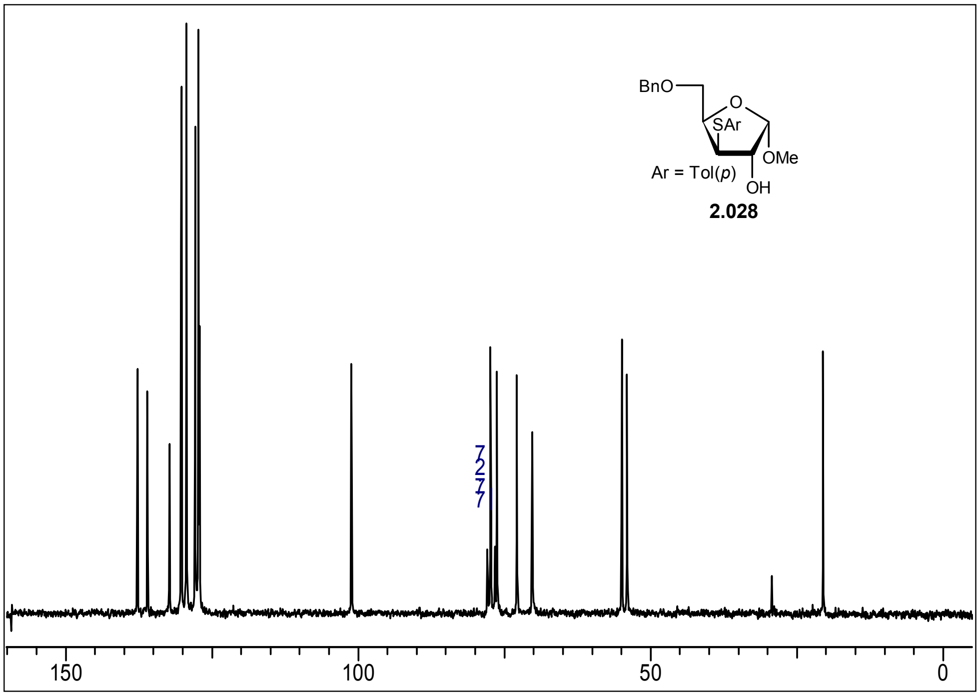

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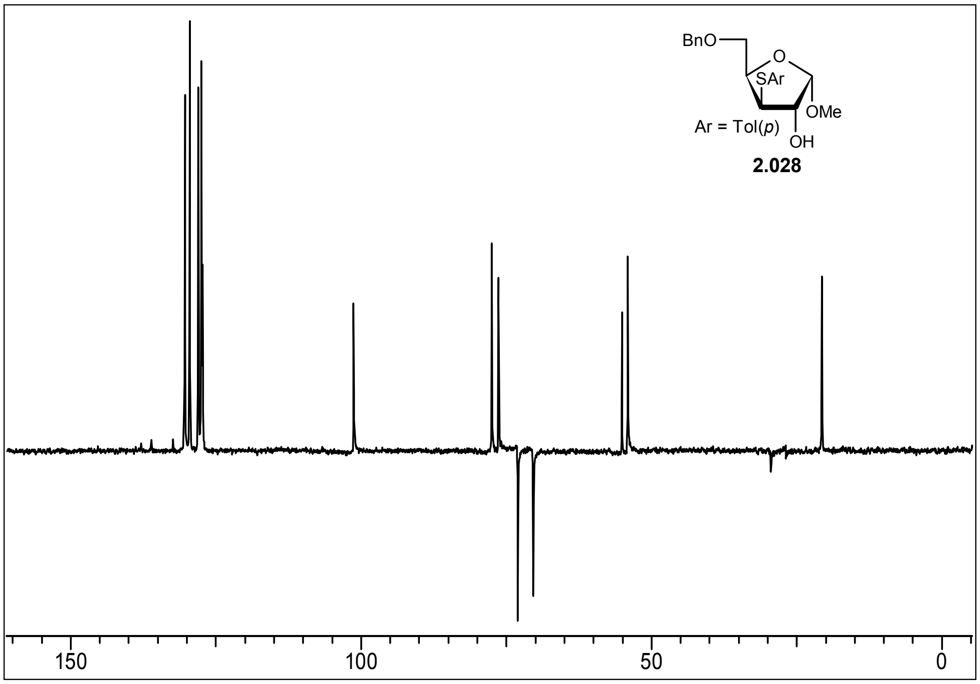

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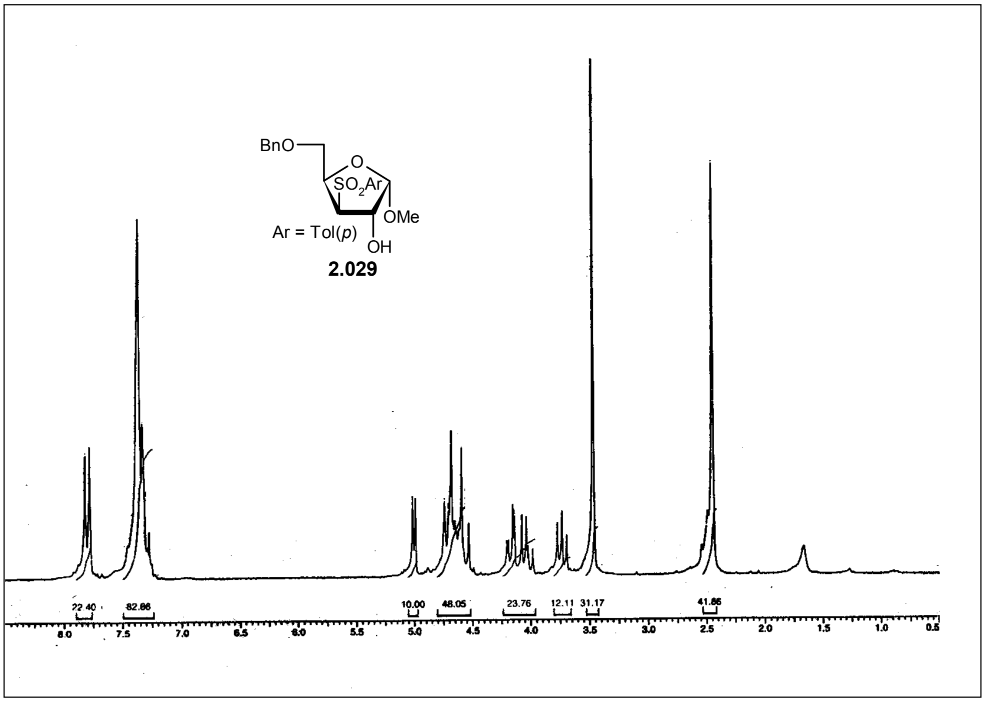

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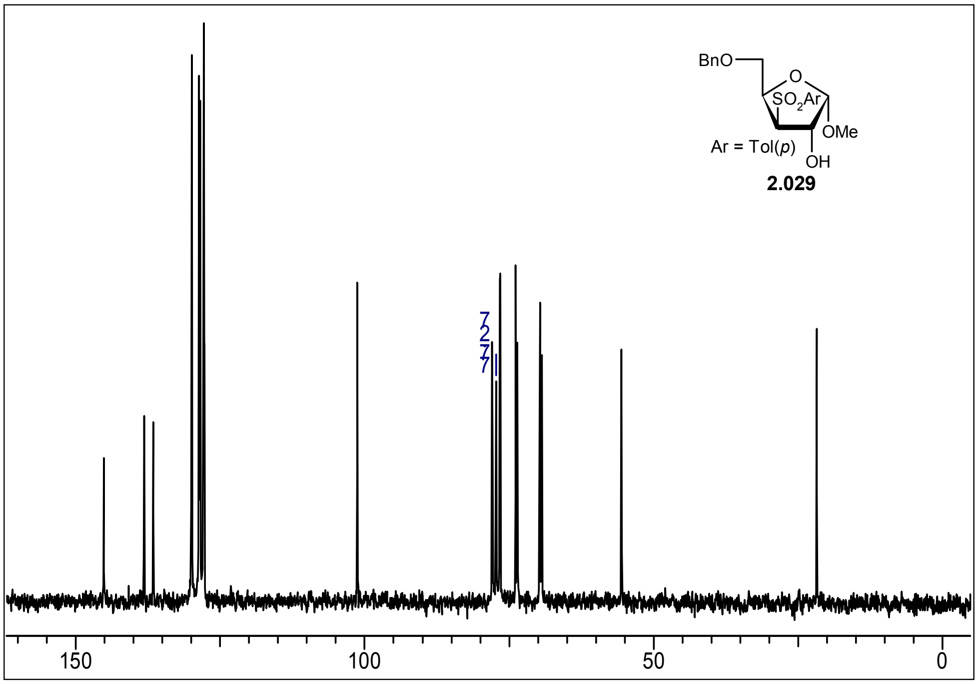

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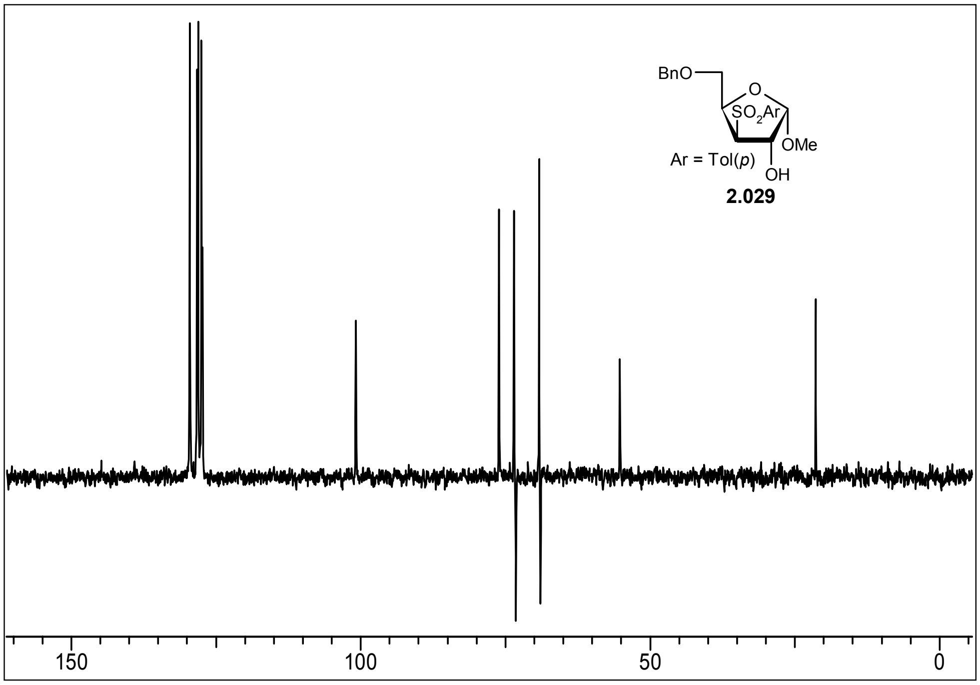

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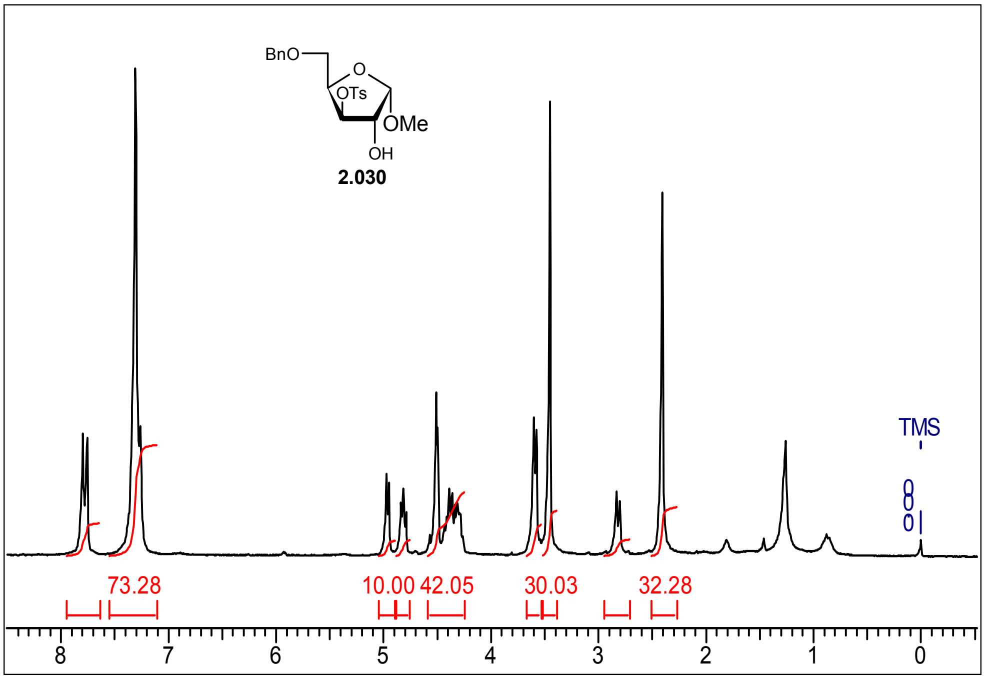

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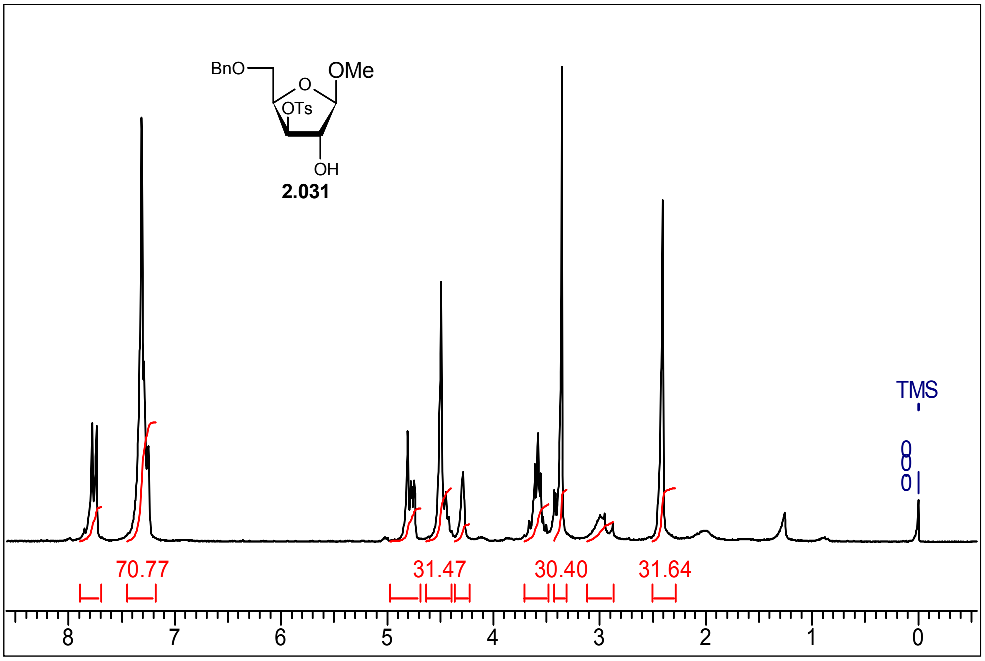

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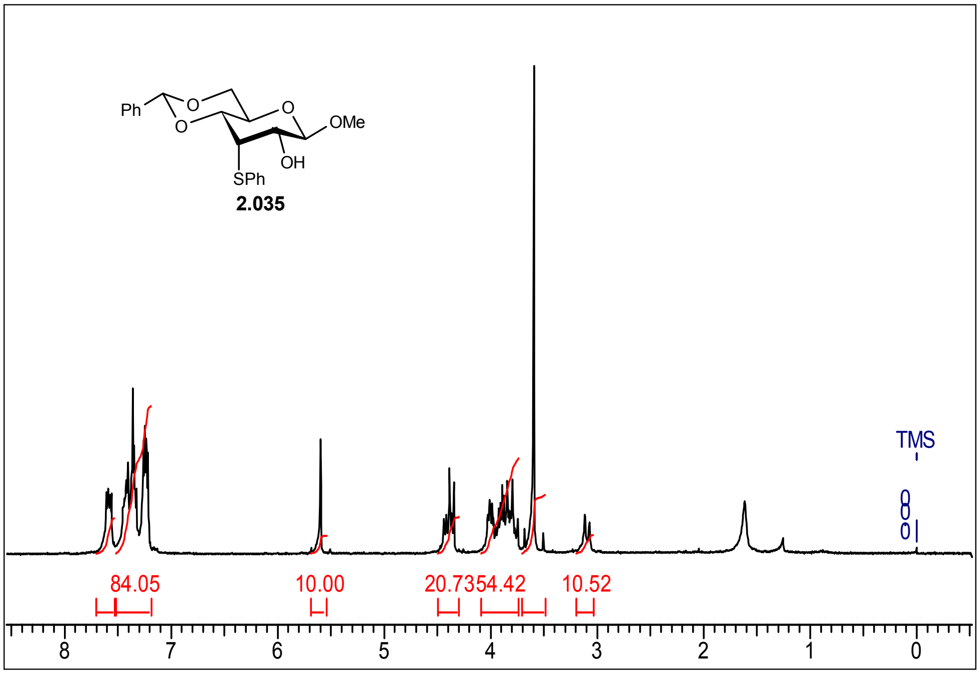

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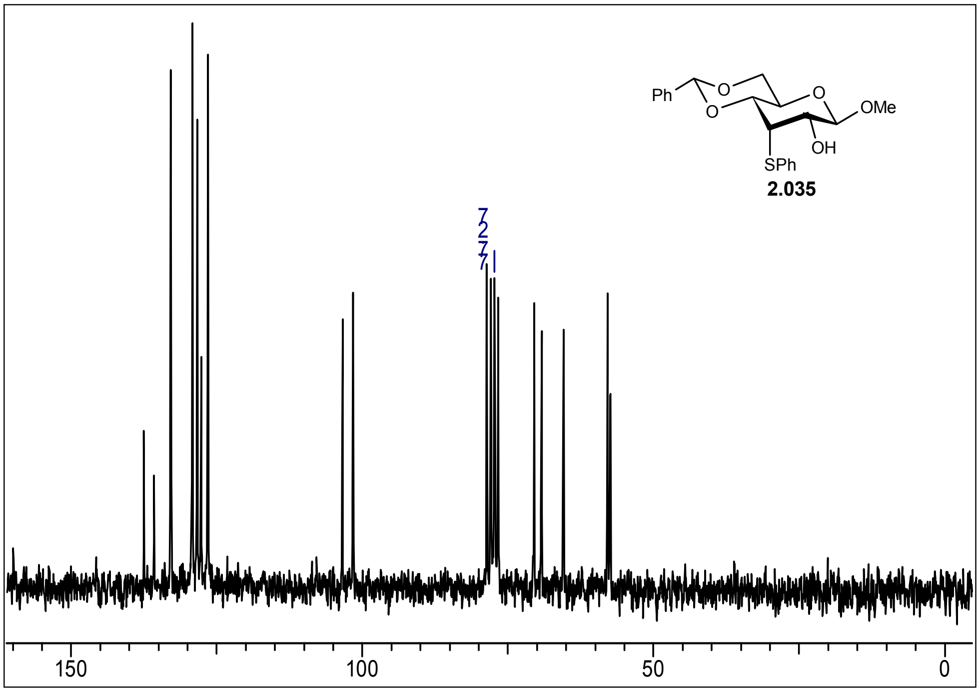

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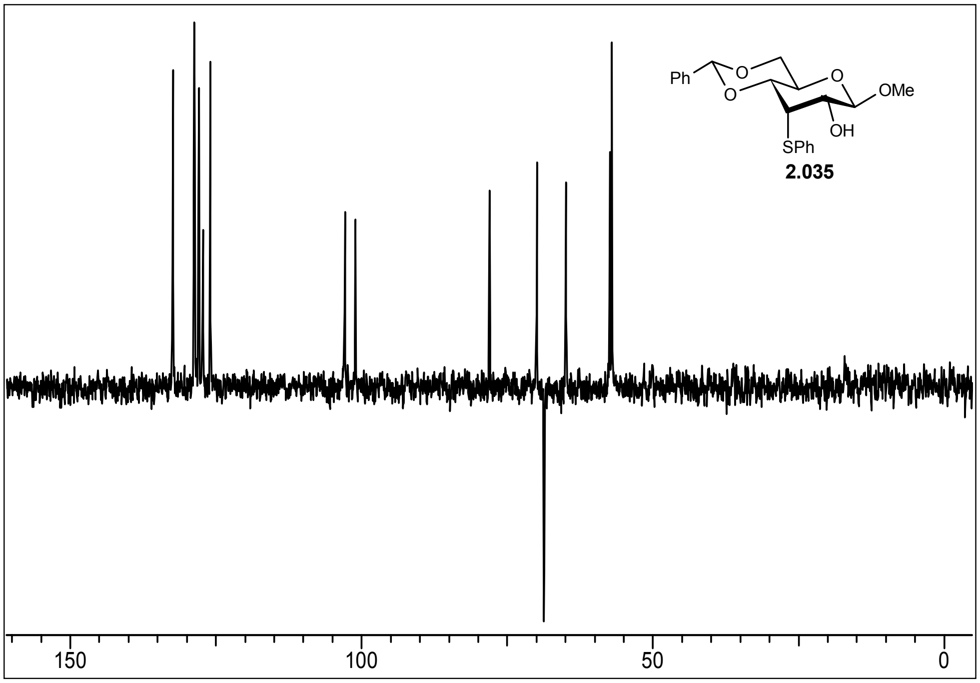

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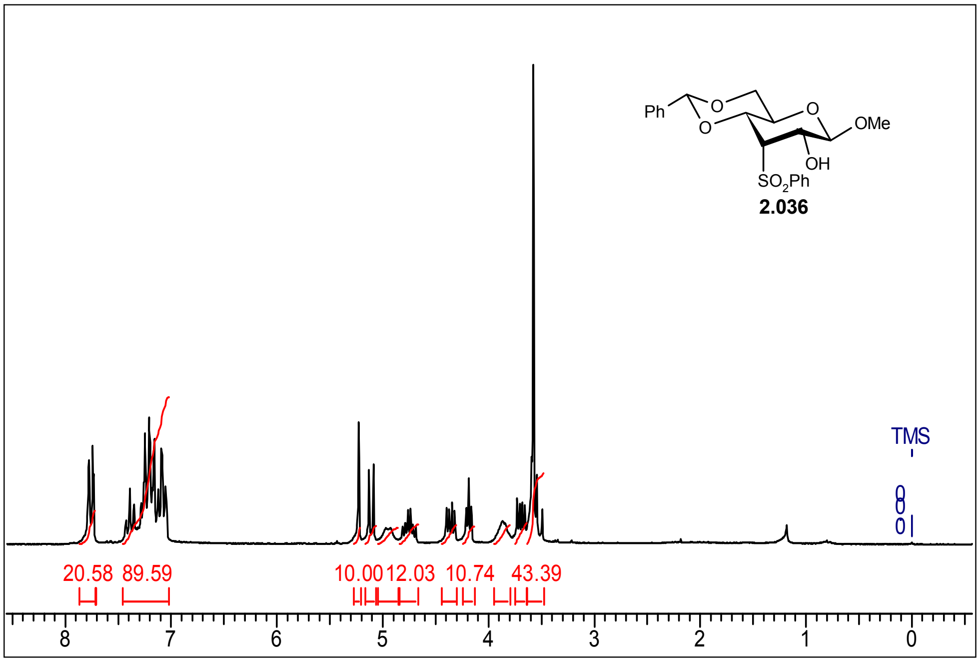

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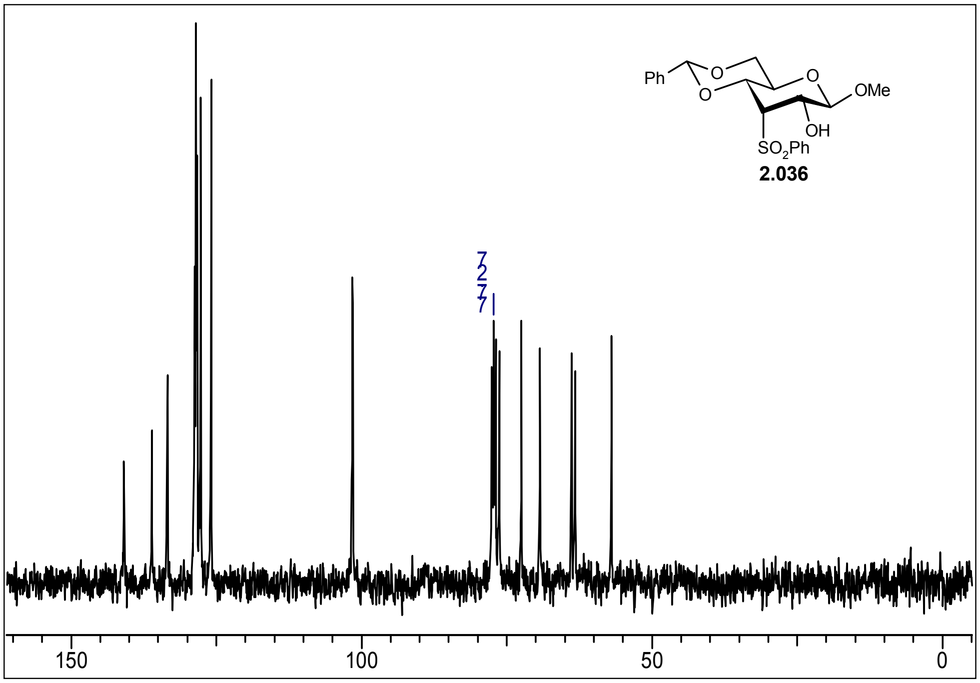

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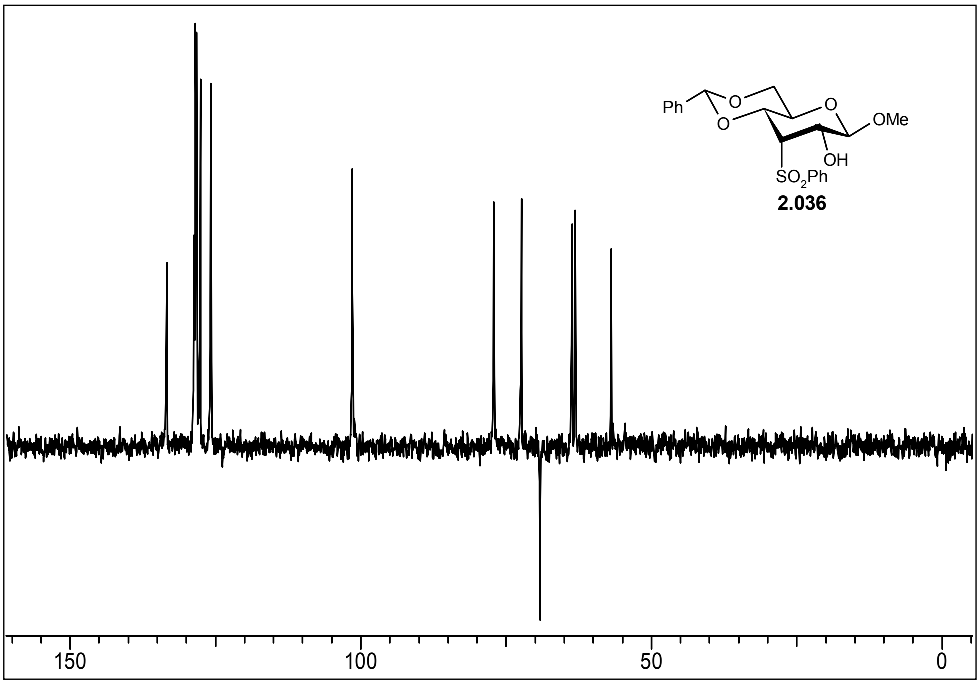

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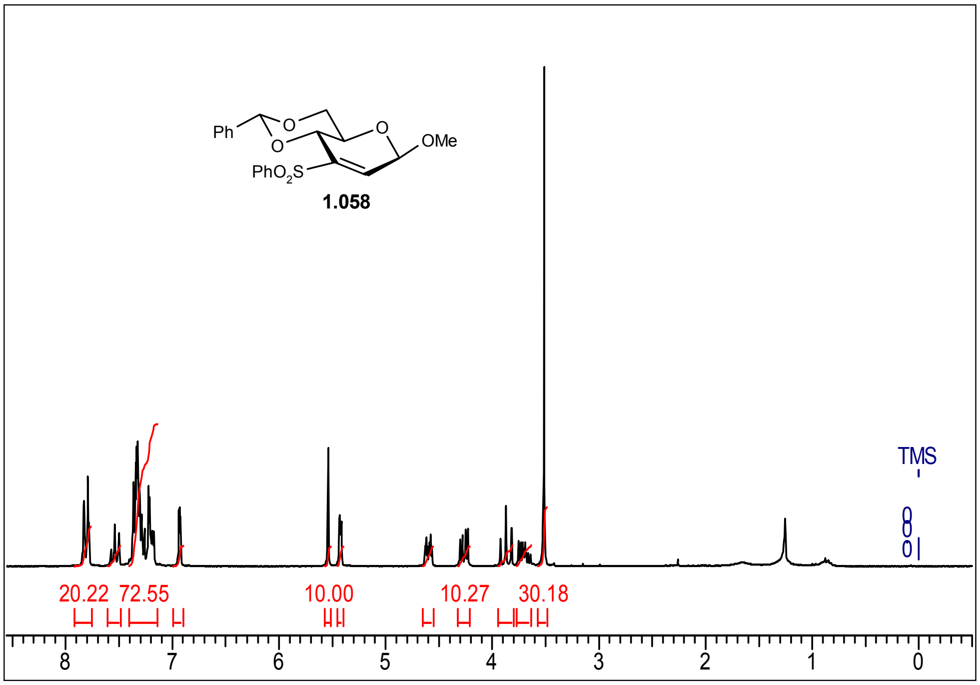

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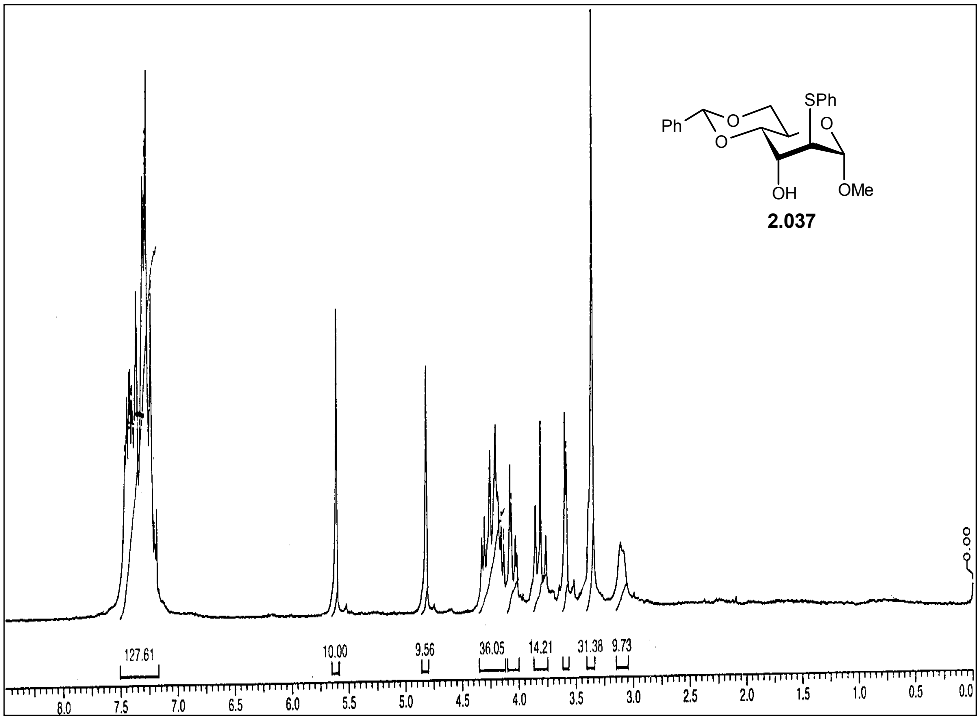

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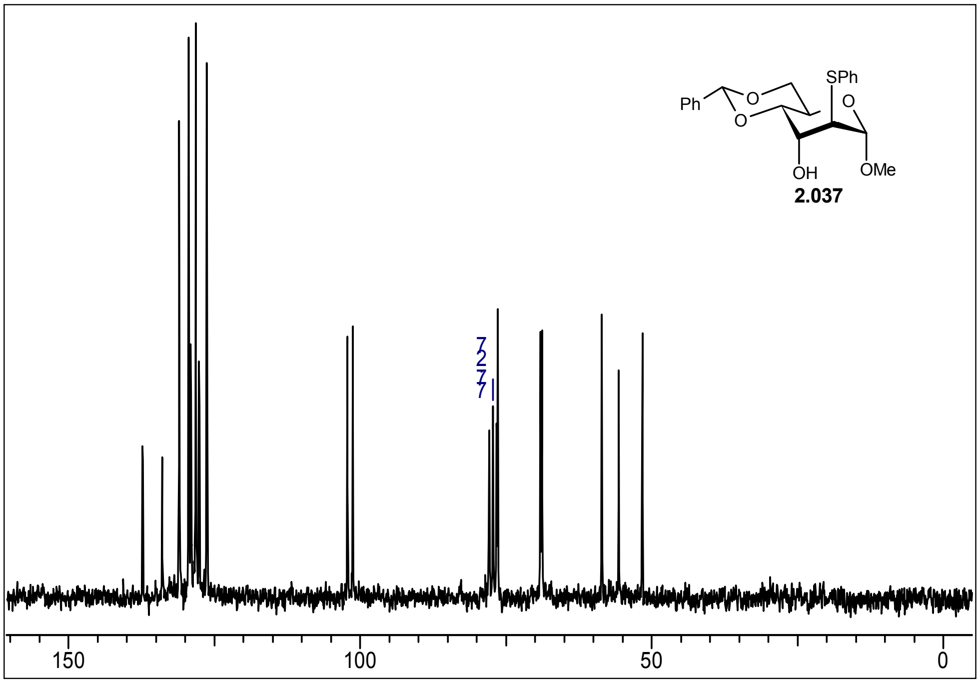

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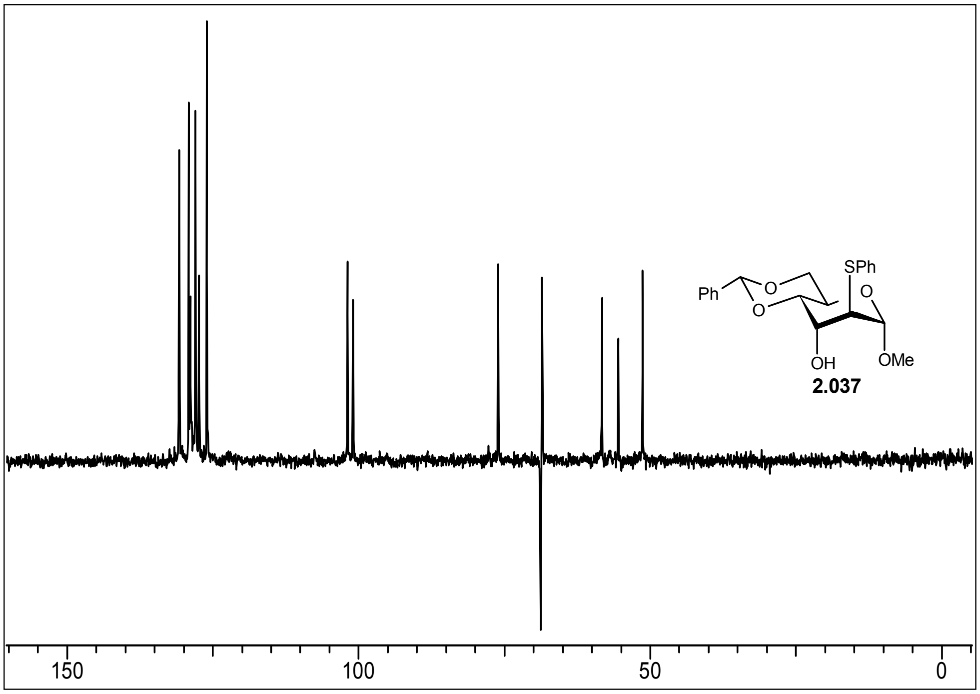

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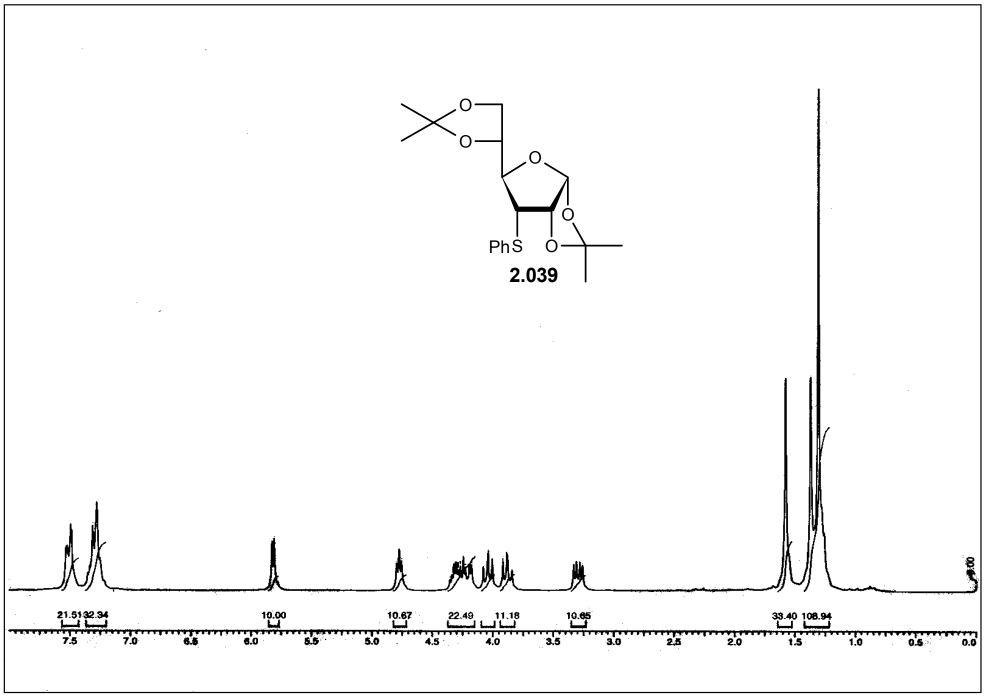

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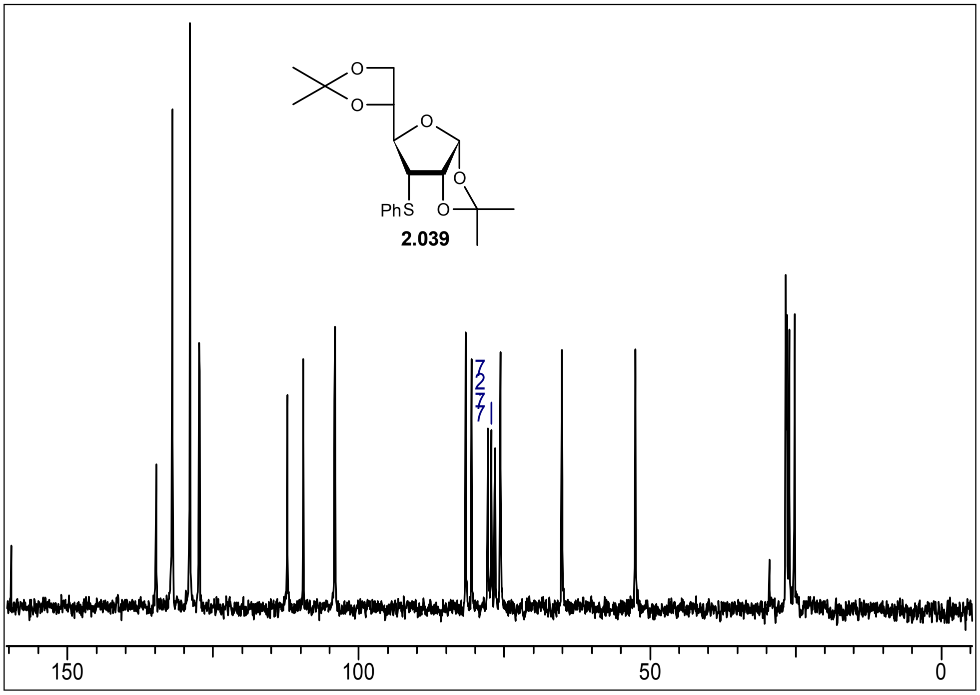
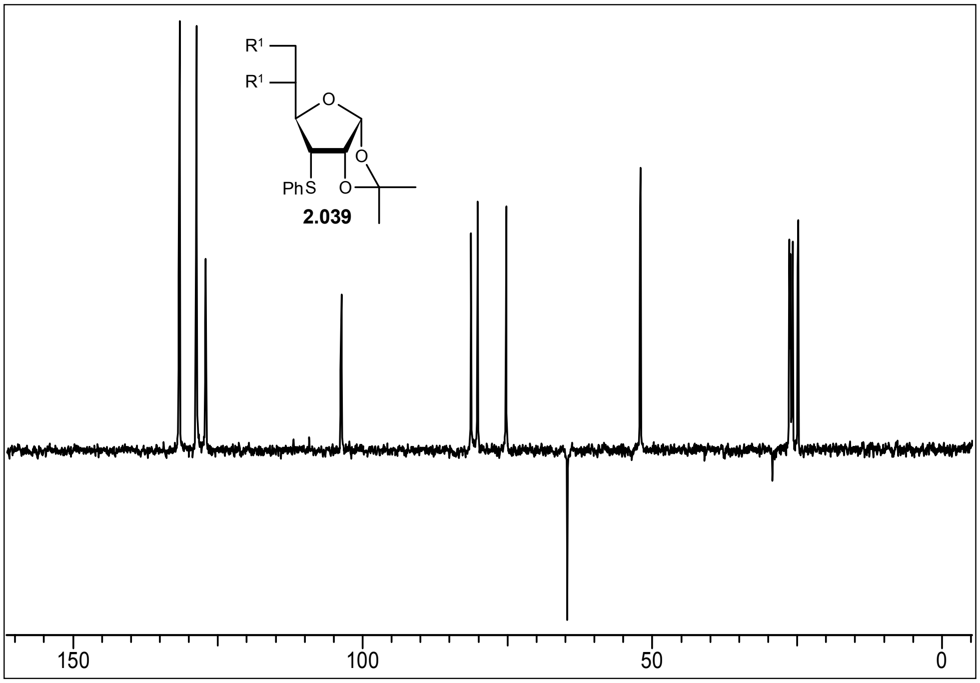


Dept of **2.039** (R^1, R^1 = *O*-isopropylidene)



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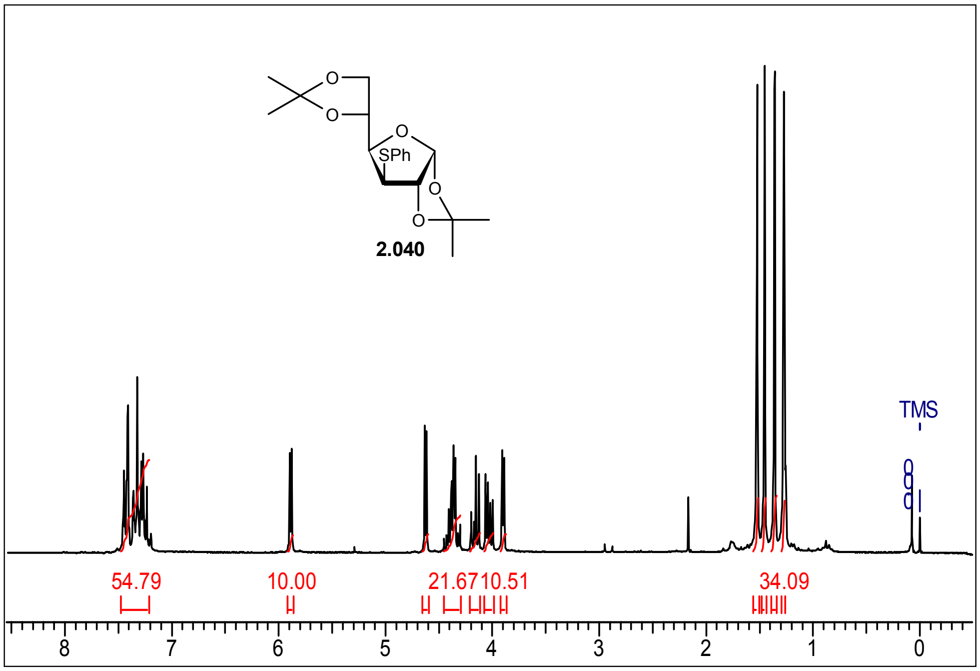

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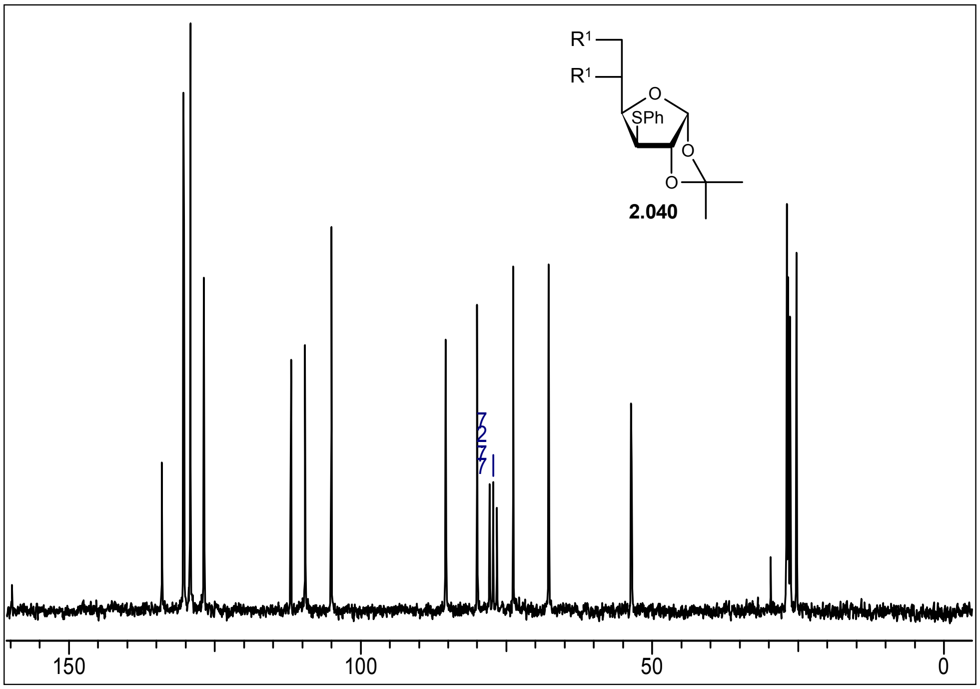
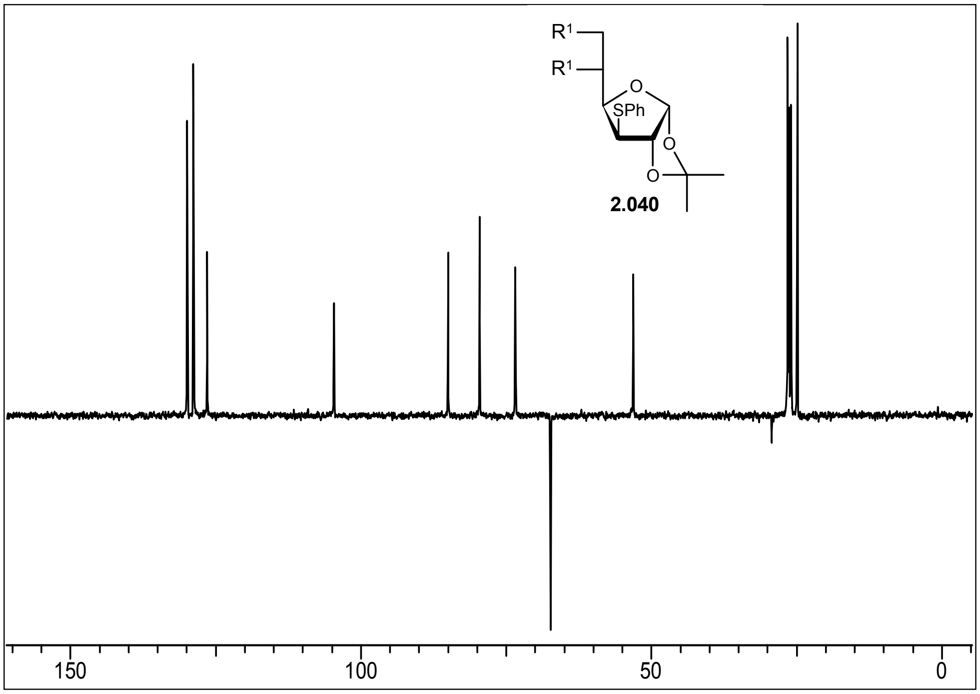


Dept of **2.040** (R^1, R^1 = *O*-isopropylidene)



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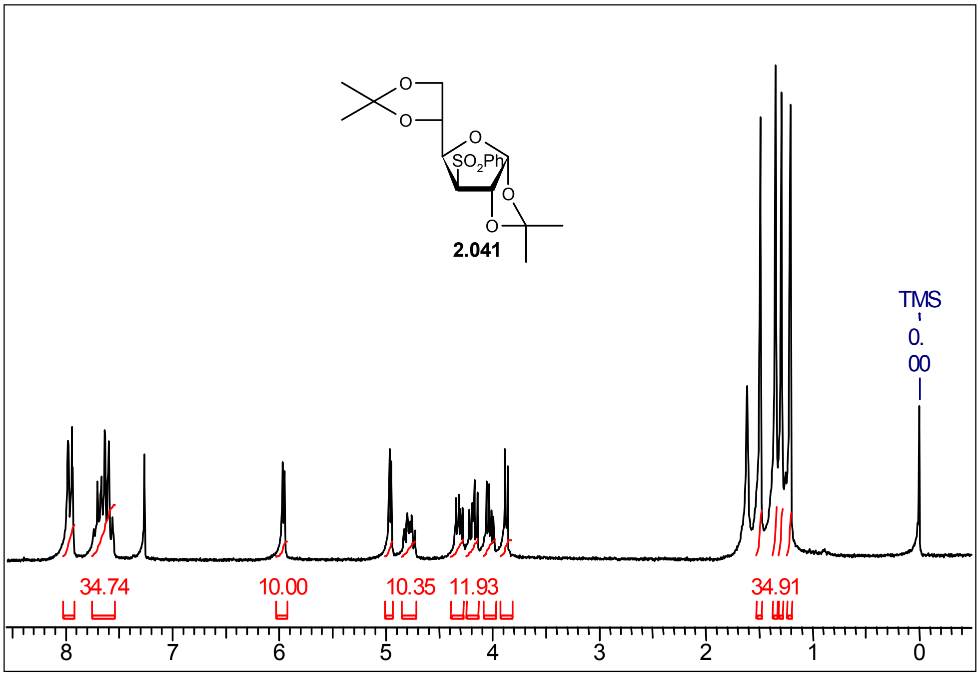
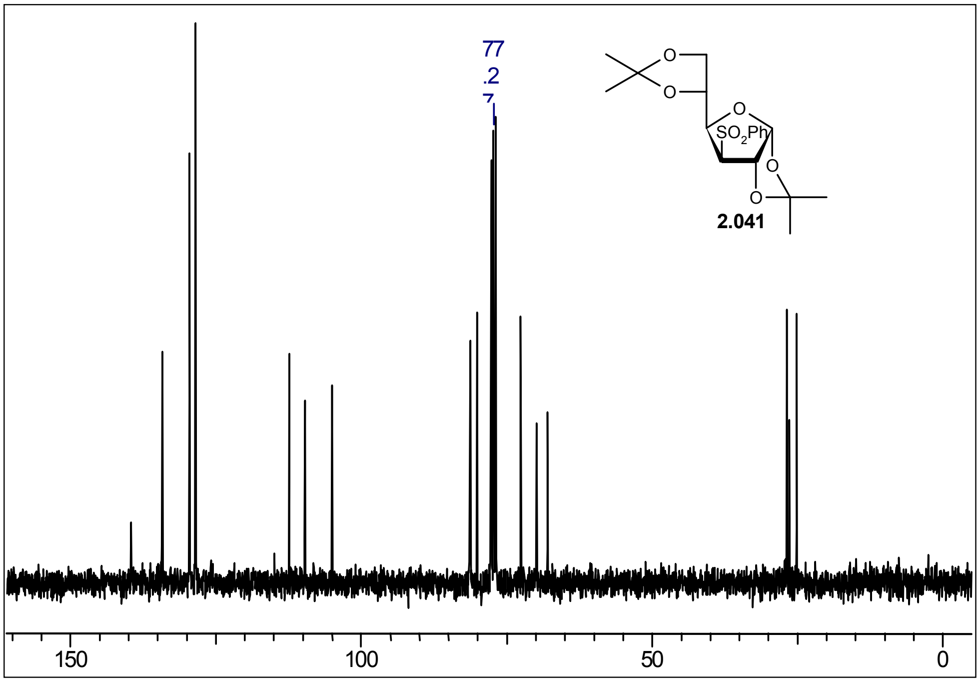
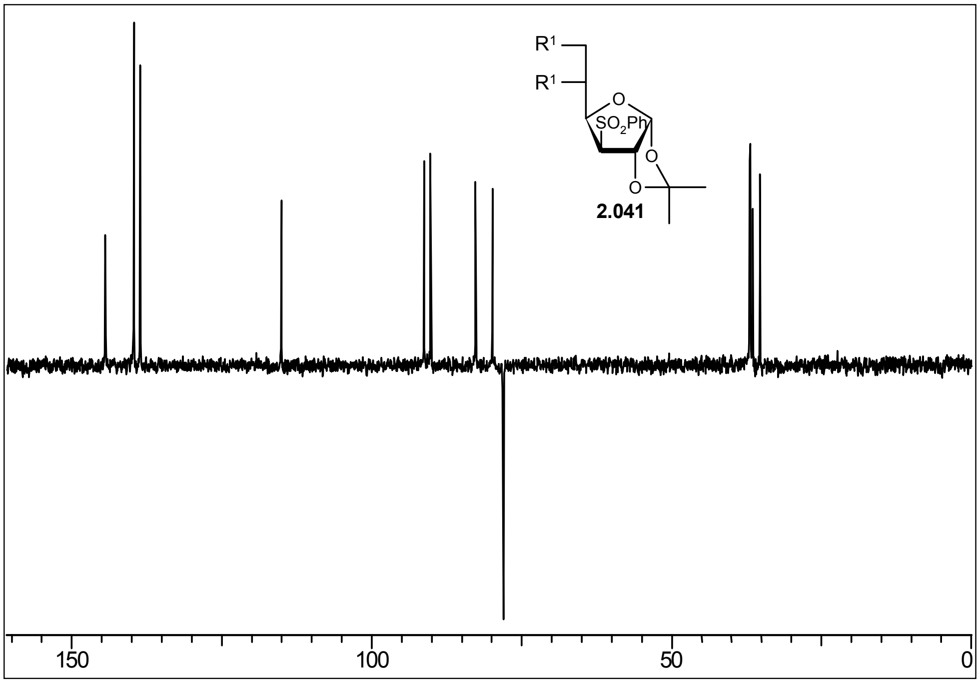


^{13}C NMR of **2.041**



Dept of **2.041** (R^1, R^1 = *O*-isopropylidene)



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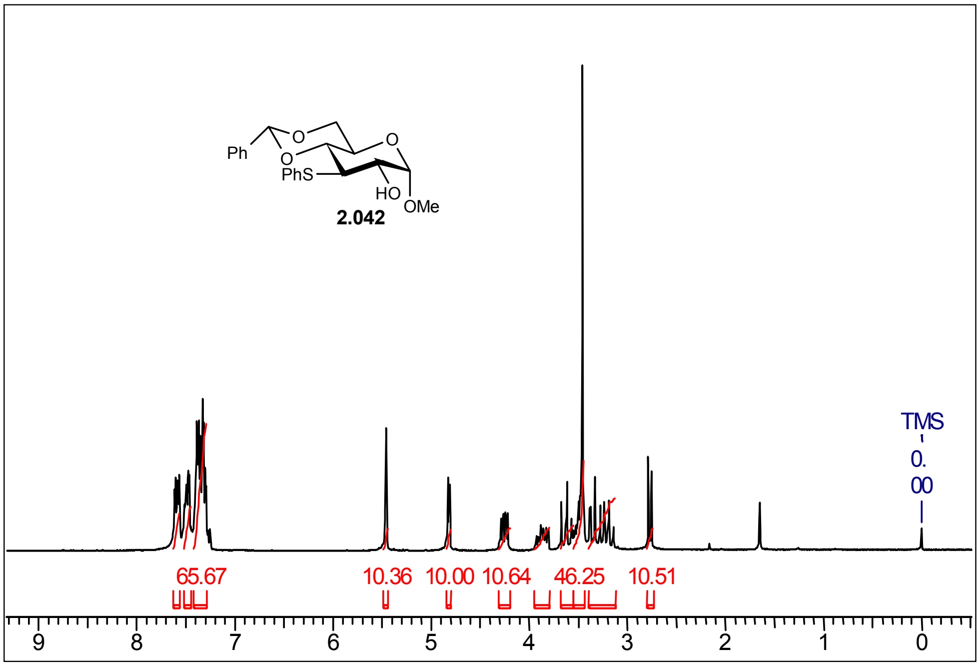

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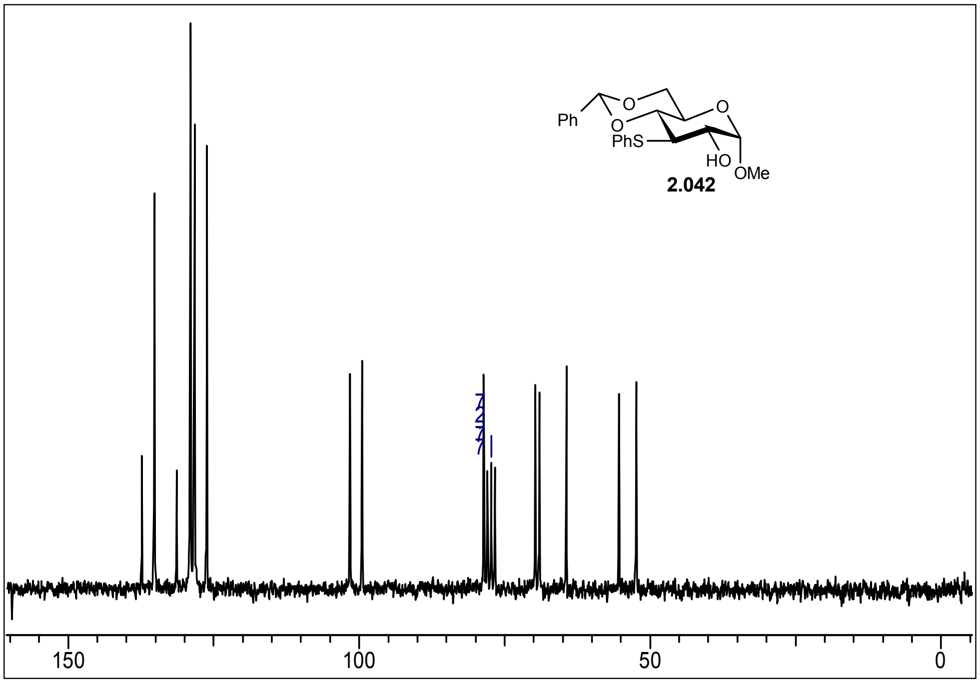

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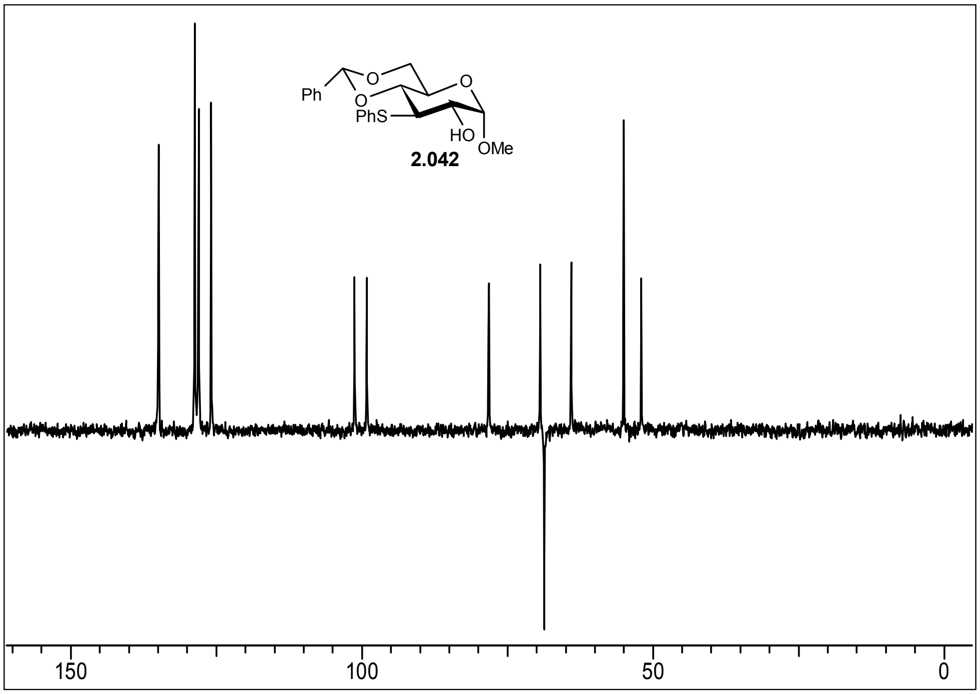

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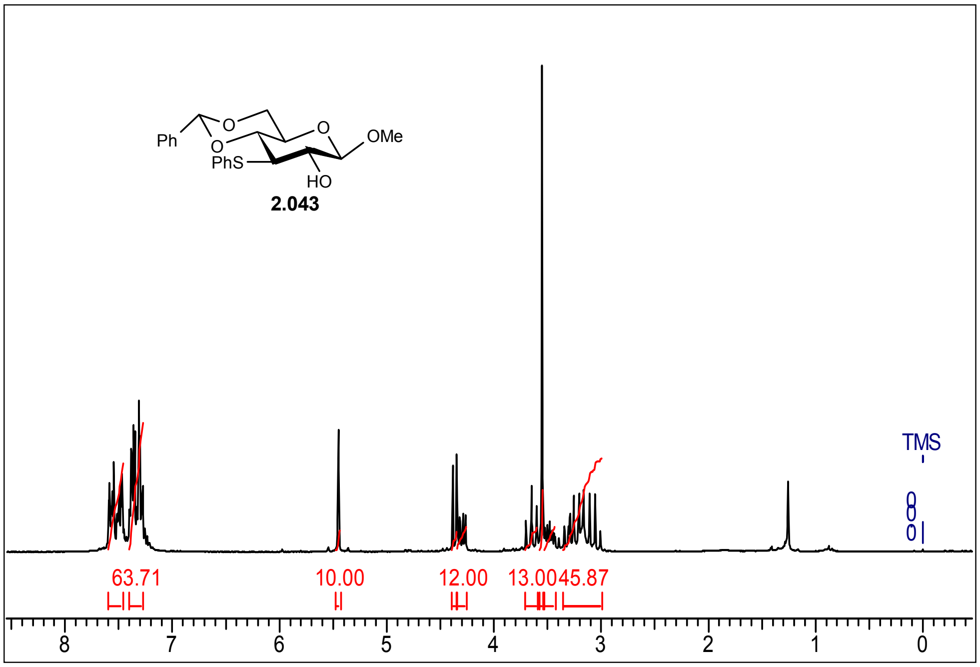

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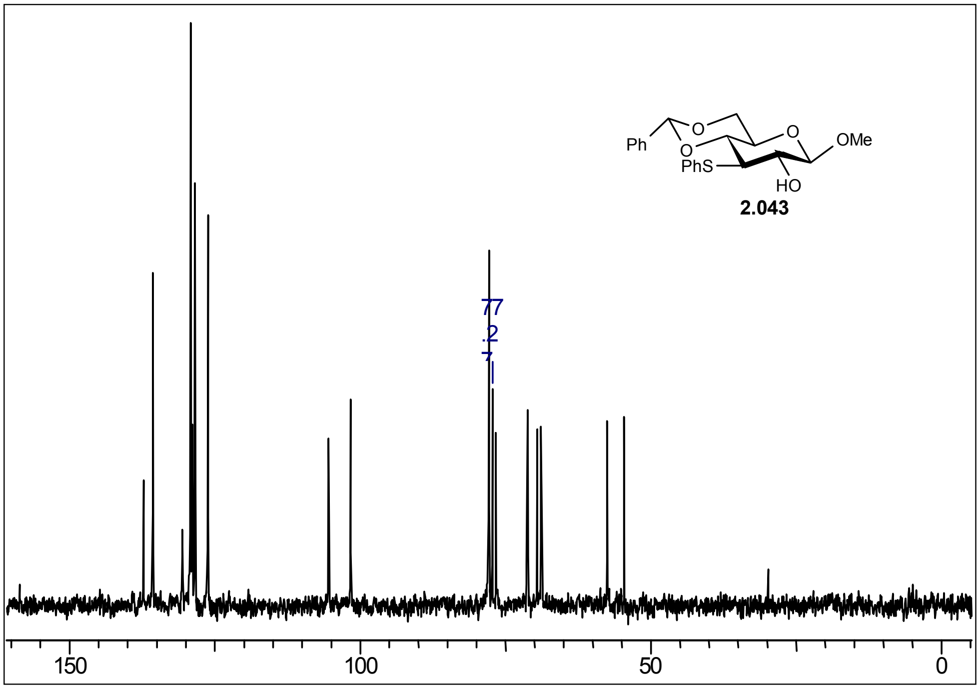

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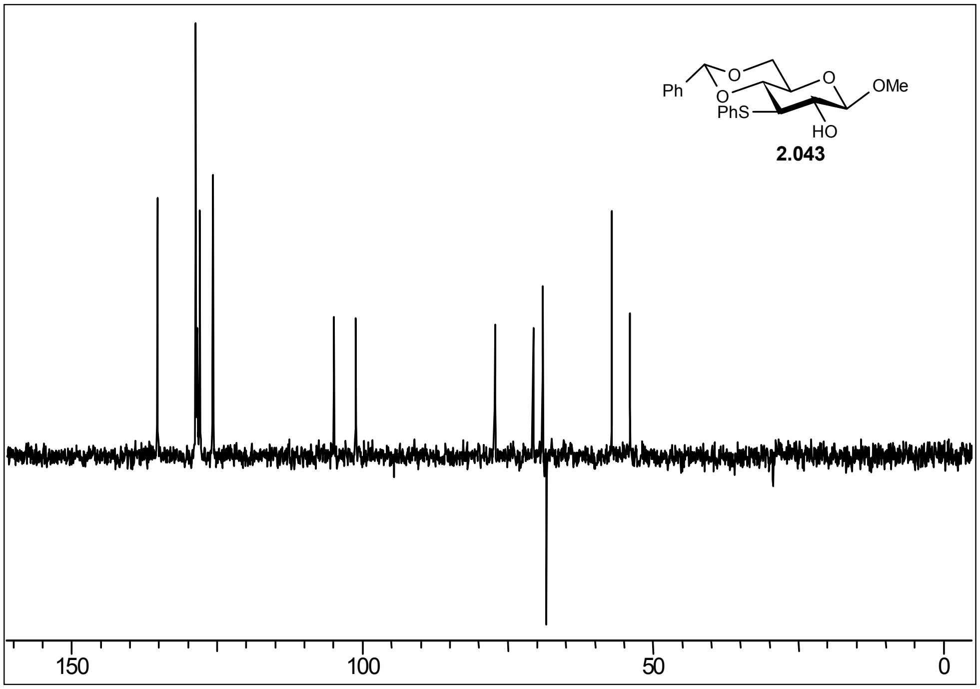

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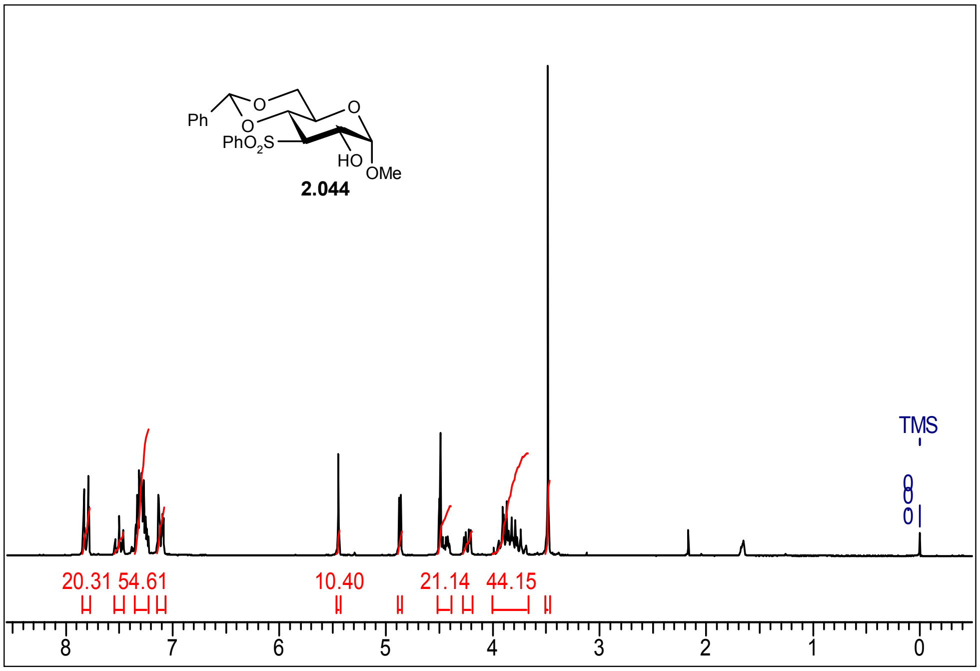

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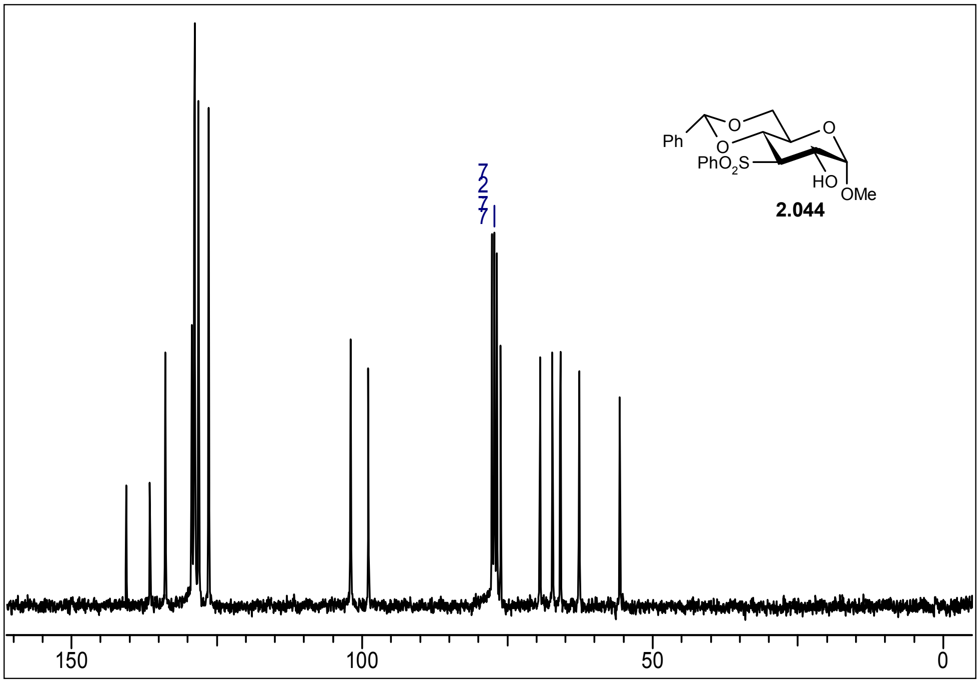

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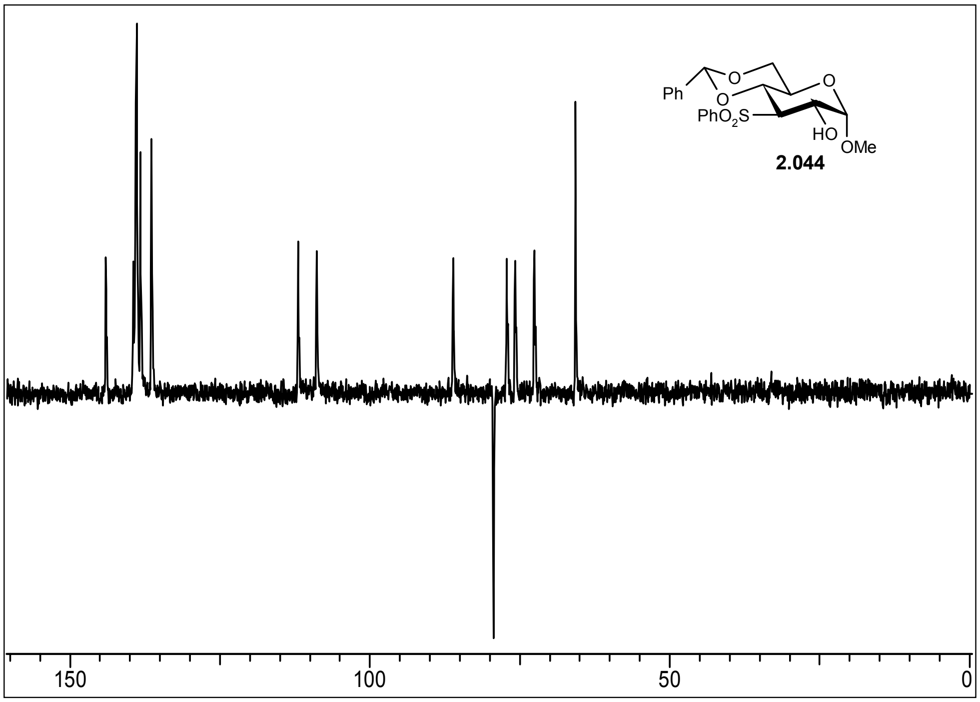

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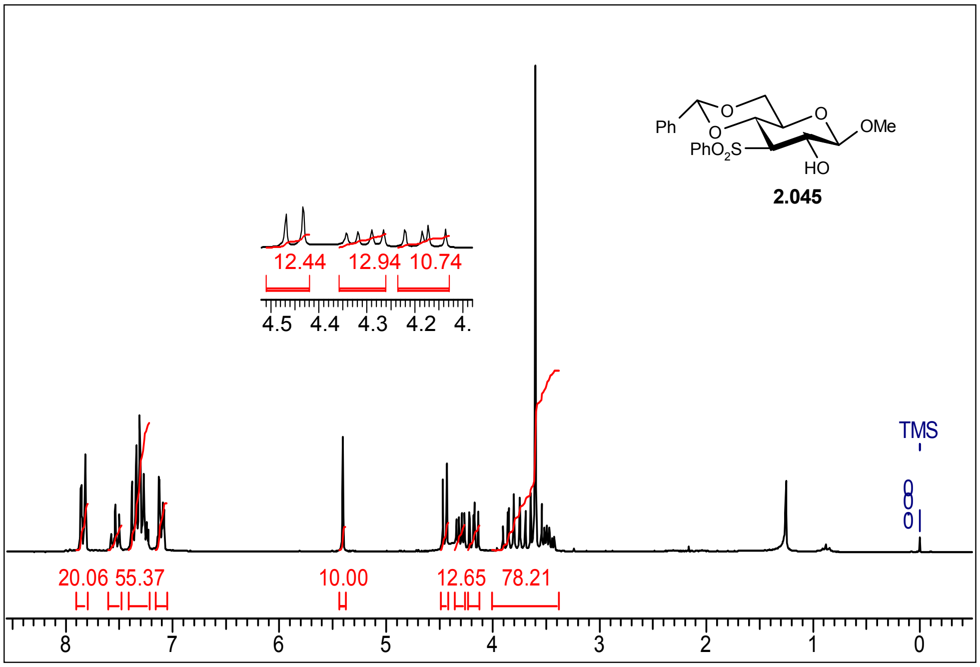

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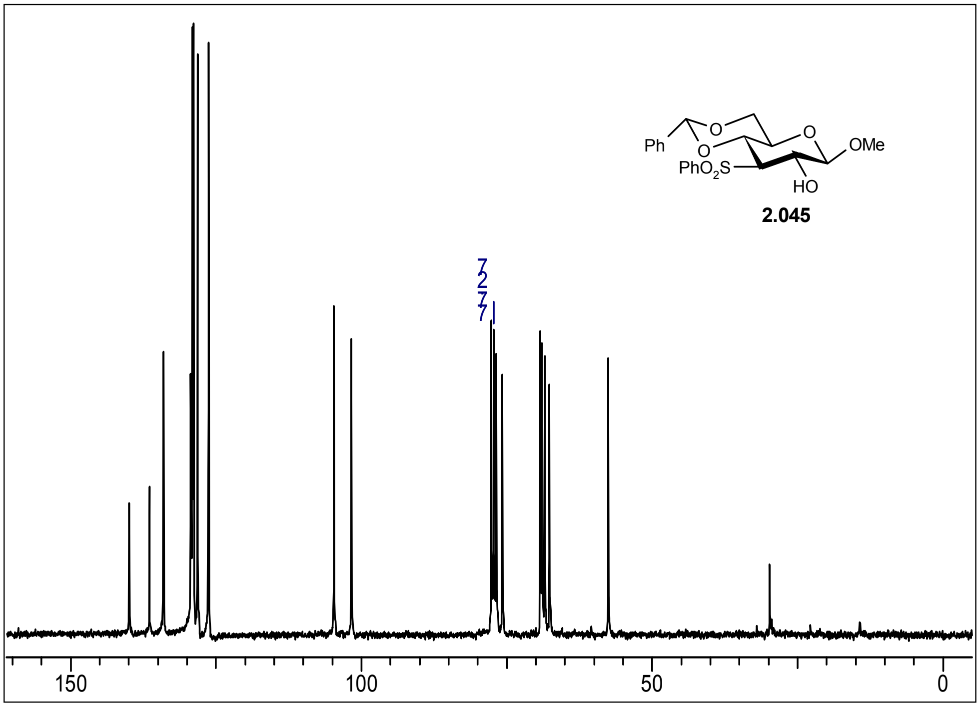
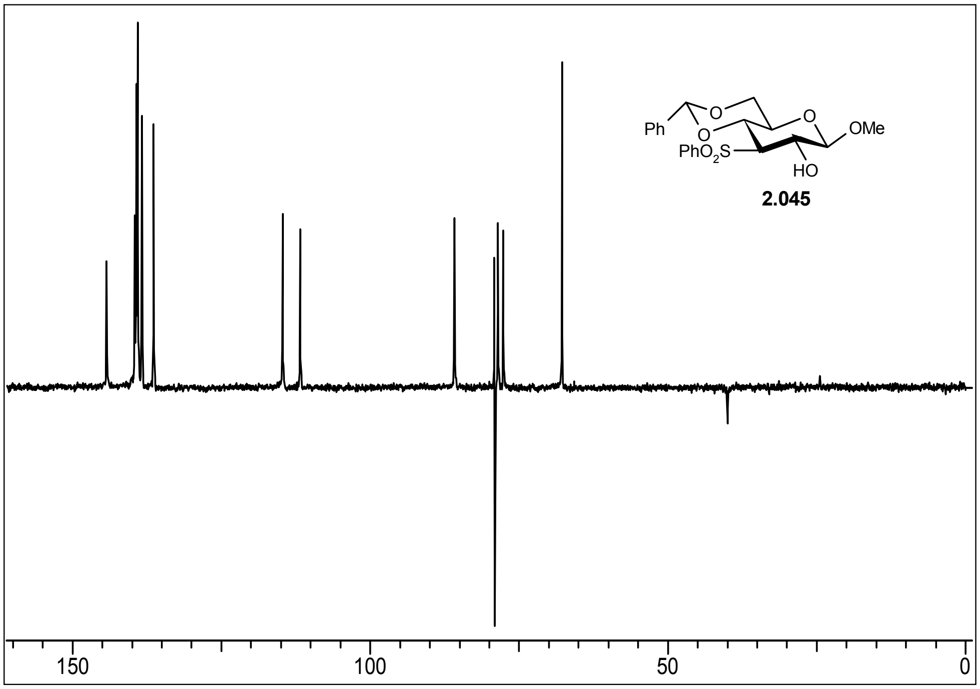


Dept of **2.045**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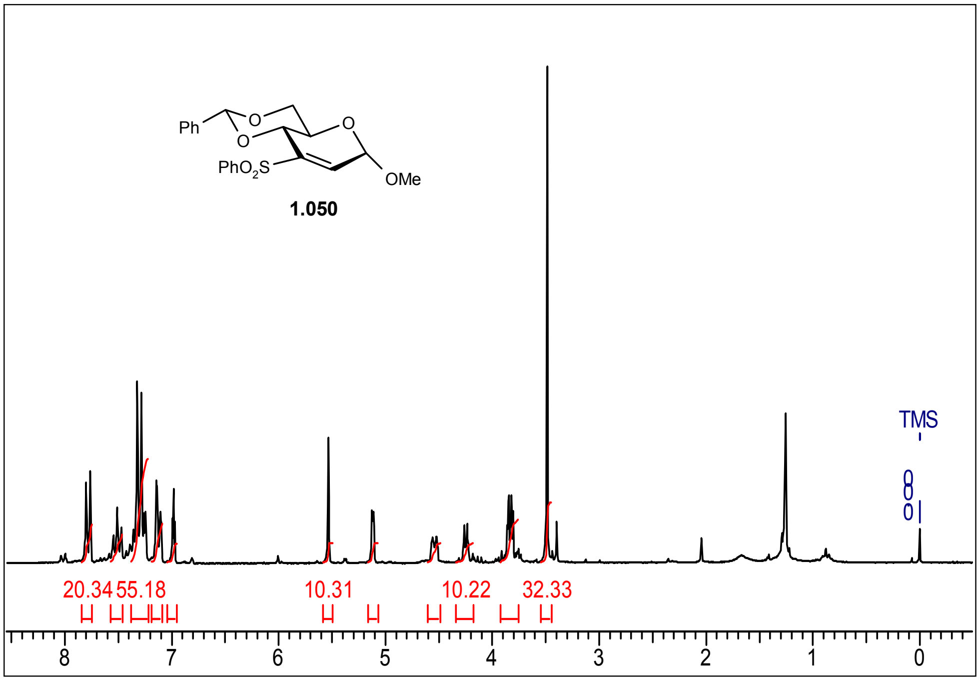
^{1}H NMR of **1.050**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CHAPTER 3

Diastereoselective Addition of Planar Heterocycles to Vinyl Sulfone-modified Carbohydrates

3.1 Introduction

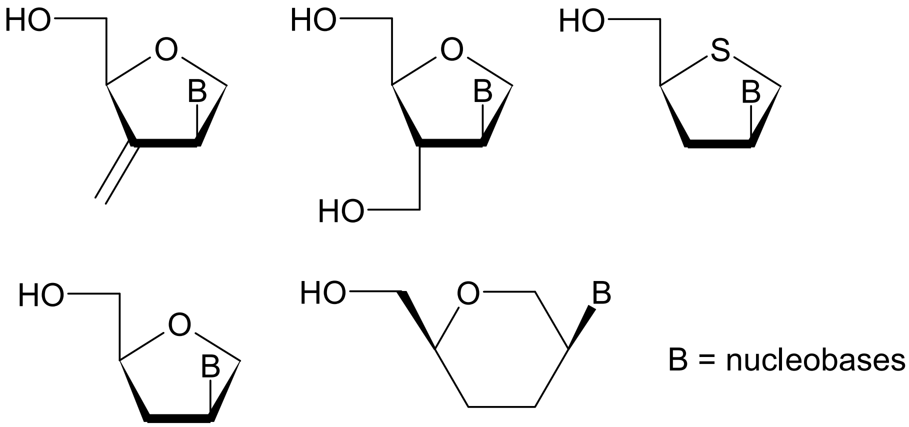
Isonucleosides are a novel class of nucleosides in which nucleobases are linked to the non-anomeric carbons of carbohydrates.[1] They are promising therapeutic agents of apparently very low toxicity and some of them show strong and selective anti-cancer and anti-viral activities. The bond connecting the nucleobase and carbohydrate has higher degree of stability towards acids and enzymatic deamination when compared to that of nucleosides.[2]

It is well documented that HIV can develop resistance to various 2′,3′- dideoxynucleosides analogs. Even though the dideoxynucleoside (ddN), such as 2′,3′-dideoxyinosine (ddI), 2′,3′-didexoycytidine (ddC), 3′-azido-3′-deoxythymidine (AZT) etc appear to be the most successful produgs, there remains a great need to synthesize new nucleosides. These compounds should exhibit a more favorable toxicity profile, are less susceptible to cross-resistance, and be active against resistant strains of HIV. The most common modifications of ddNs have been the strategic substitution on the carbohydrate moiety, elimination of the *endo*-cyclic oxygen of the carbohydrate moiety, or the introduction of an additional *endo*-cyclic oxygen to the carbohydrate moiety.[3]

Over the last few years many isonucleoside derivatives, such as *exo*-methylene-, branched-, 4′-thio-, pyranosyl and others have been reported to be promising therapeutic agents (**Figure 3.1**).[2,4] In almost all the cases, different nucleobases have been attached to C-2 of 1,4-anhydropentitols to generate isonucleosides. There are few reports[5-12] on the condensation of heterocycles such as imidazole, 1,2,3-triazole, 1,2,4-triazole, benzimidazole derivatives etc[12] with carbohydrate moieties for accessing new classes of nucleoside analogs. Few of them are naturally occurring and they exhibit sufficient degree of anti-viral and anti-tumor activities.[5-13]

The most common methods known in the literature for the synthesis of isonucleosides[2] are: (a) regioselective ring opening of epoxides by nucleobases, (b) nucleophilic substitution of sulfonates derived from 1,4-anhydropentitols by nucleobases, (c) substitution of an alcohol with a base under Mitsunobu conditions, (d) coupling of nucleoside bases directly with cyclic sulfates derived from carbohydrates[14], (e) preparation of nucleosides from aminoaldetols,[2] and (f) addition of nucleobases to activated olefins such as 2,3-dideoxy-hex-2-enopyranosid-4-uloses and 2,3-dideoxy-3-nitro-hex-2-enopyranosides.[15-19]

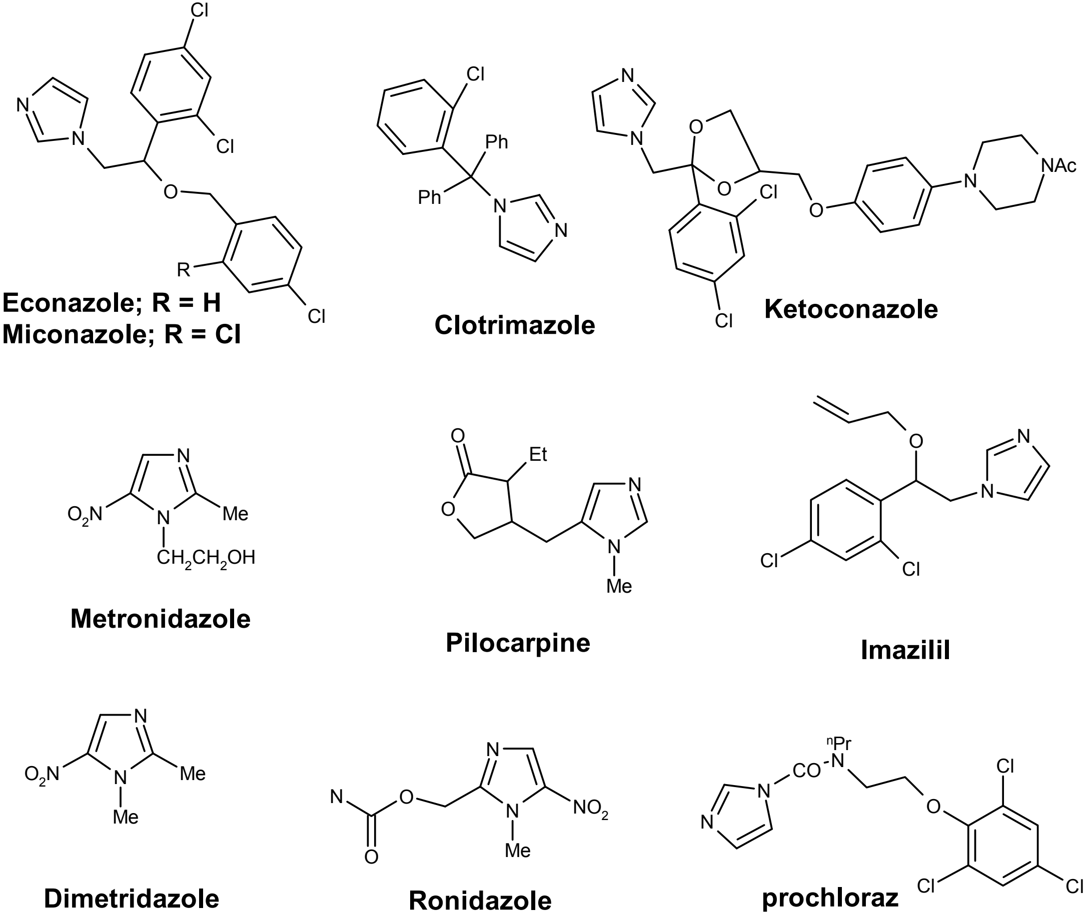
Figure 3.1



Heterocycles such as imidazole, triazole and their derivatives are considered as the basic building blocks for the construction of fungicides, bactericides, pharmaceuticals, veterinary products etc.[20-25] A survey of the literature suggested that a majority of this family of molecules possess either the imidazole or the triazole moiety as the key component for the manifestation of their biological activities. Moreover, in most of the cases, they are attached to an acyclic carbon chain. These nitrogen heterocycles block the biosynthesis of ergosterol, which is essential for the development of fungal cell membranes.[24]

Imidazole derivatives attached to acyclic systems, such as clotrimazole, miconazole, econazole, ketoconazole, imazilil, prochloraz, metronidazole, dimetridazole, ronidazole, pilocarpine etc[20-23] have been found to show broad spectrum of activities (**Figure 3.2**). The nitroimidazole derivatives, metronidazole, dimetridazole and ronidazole have found use in veterinary science and are particularly useful in treating parasitic diseases. There is a considerable interest in the studies of the nitroimidzoles which act as sensitizers of hypoxic tumor cells to radiation, and are used in the treatment of human cancer. 4-Nitroimidazoles are also gaining pharmacological significance as immunosuppressant, potential radiosentizers, in radiotherapy and as aldehyde dehydrogenase inhibitors. Miconazole, econazole, ketoconazole, clotrimazole and pilocarpine have been used as pharmaceuticals for treating fungal infection. Particularly pilocarpine has been used to produce miosis (pupillary constriction in the eye) and diaphoresis (sweating). Some of them have also found useful applications in Agronomy as toxic compounds.[20-24]

Figure 3.2



Econazole; R = H
Miconazole; R = Cl

Clotrimazole

Ketoconazole

Metronidazole

Pilocarpine

Imazilil

Dimetridazole

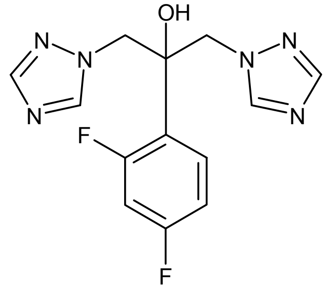
Ronidazole

prochloraz

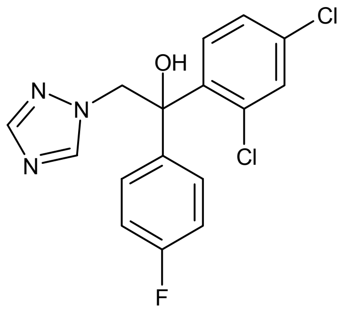
Triazole derivatives, such as fluconazole, tarconazole, ICI-153,066, triadimefon, propiconazole, 4-butyltriazole, triazophos, etc also have shown interesting biological properties. They are used as radiosensitizer of hypoxic cancer cells, potential anti-fungal agents and inhibitors of the biosynthesis of ergosterol. Compounds SC-505,60 and L-159,913 have found application in raising the blood pressure (**Figure 3.3**). Triazophos, a *O*-phosphorylated triazolinone is a well known insecticide and related derivatives are also known as fungicides.[20-24] Complex triazolyl glycol ethers are claimed to be plant growth regulator and fungicides. Many alkyl and aryl derivatives of mercaptotriazoles are active against fungi and other bacteria. Similarly, the action of mercaptotriazole derivative against *Mycobacterium tb* or of carbamates against fungi and animal parasites is also reported (**Figure 3.4**).[25]

Imidazoles and triazole derivatives have also been attached to the C-1 of carbohydrates to constitute new classes of nucleosides. Five membered-ring heterocyclic nucleosides structurally derived from 5-amino-1-β-D-*ribo*furanosyl- imidazole-4-carboxamide (AICAR, Acadenosine®) by the modification at the 5-position,

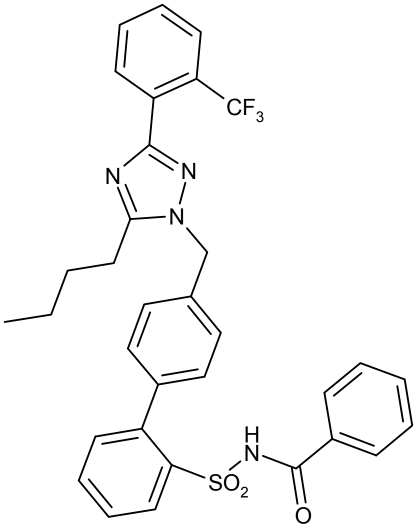
Figure 3.3



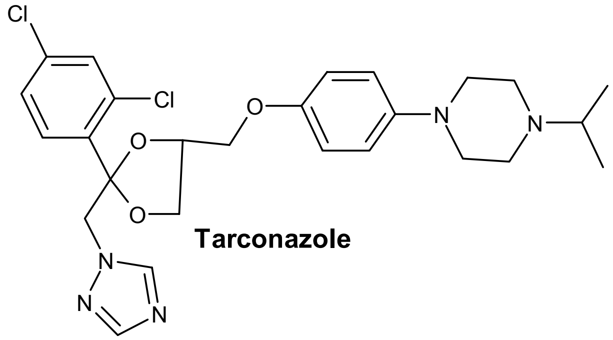
Fluconazole



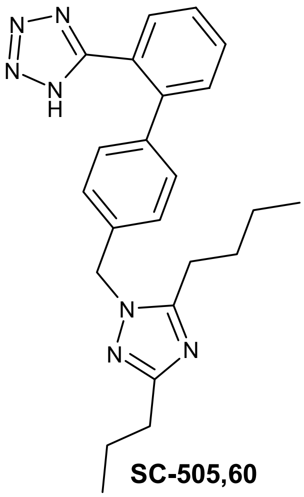
I C I 153,066



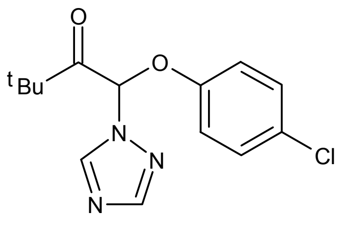
L-159, 913



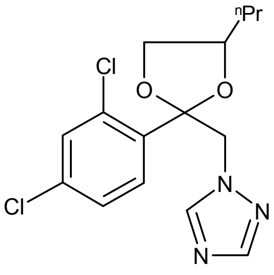
Tarconazole



SC-505,60

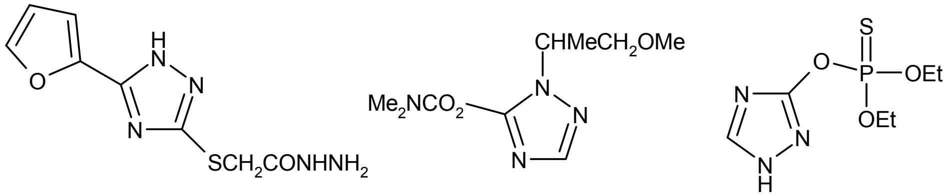


Triadimefon



Propiconazole

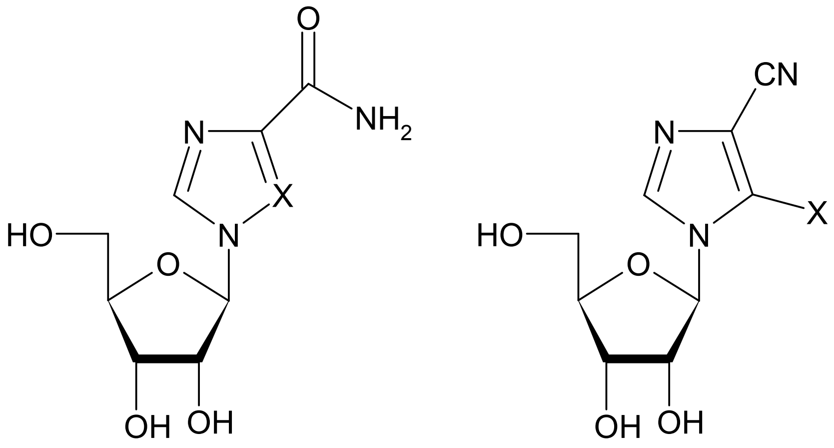
Figure 3.4



Mercaptotriazole derivative **Carbamate** **Triazophos**

such as bredinin and EICAR (5-Ethyn-1-β-D-*ribo*furanosylimidazole-4-carboxamide) are known to exhibit a broad spectrum of activity against a range of viruses including hepatitis C, influenza and respiratory syncytial virus.[26] The most promising compounds in this class of nucleosides are bredinin and 5-substituted derivatives such as EICAR. AICAR itself is a beneficial chemotherapetic for the treatment of stroke owing to its ability to act as an adenosine-regulating agent.[27] 5-Halo derivatives (X = I, Cl, Br) have also been reported for significant anti-viral activity (**Figure 3.5**).[28]

Figure 3.5



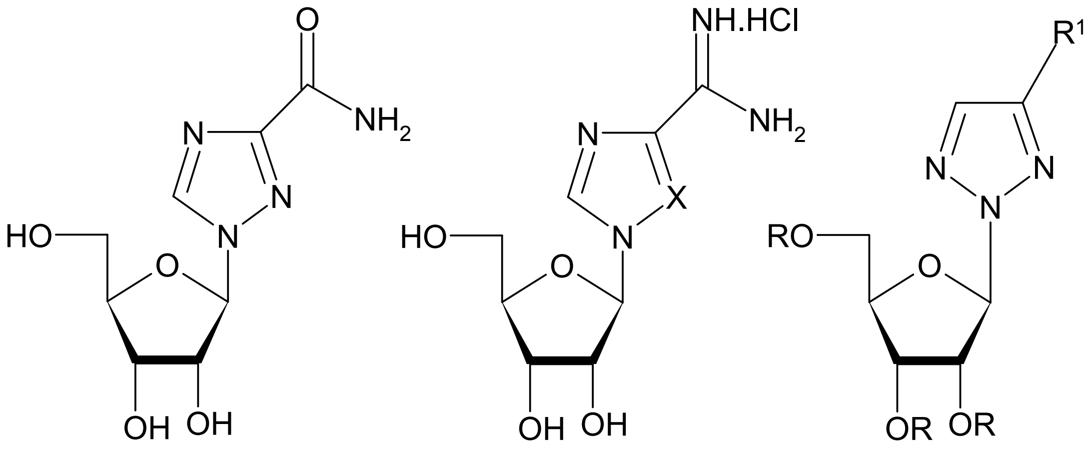
Bredinin X = C-OH
AICAR X = C-NH_2
EICAR X = C-C≡CH

5-Halo derivatives
(X = I, Br, Cl)

Bactericidal and fungicidal properties of triazole nucleosides have been reported.[26] Ribavirin (Virazole®, 1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide) is used in the treatment of RSV (Respiratory Syncytial Virus) infections, Lassa fever, Hepatitis (A, B and C), measles and mumps.[30-31] Some of the ribavirin derivatives, TCNR (1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamidine) and 5-amino-TCNR have been the most promising and act as competitive reversible inhibitors of human lymphoblast purine nuceloside phosphorylase.[32] Few of the triazole (1,2,3-) nucleosides (bactericidal I and bactericidal II) also have shown anti-fungal and anti-bacterial activities (**Figure 3.6**).[29]

The most common methods for the syntheses of these biologically important molecules involve the nucleophilic attack of a heterocycle to an epoxide or on the carbon carrying leaving groups. Although vinyl sulfone-modified carbohydrates have been used in a number of synthetic methodologies both in carbohydrates and nucleosides (**Chapter 1**), there is no report on the use of this particular type of carbohydrates as precursors for the attachment of planar heterocycles to the carbohydrate moieties. The major advantage of this methodology is that the addition of nucleobases to vinyl sulfone-modified carbohydrates provides a direct access to isonucleosides. On the other hand, the addition of imidazoles and triazoles in a similar fashion will open up a new avenue for accessing several biologically relevant new chemical entities. In this chapter we report the studies in this area.

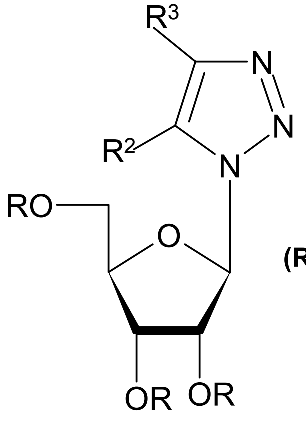
Figure 3.6



Ribavirin

TCNR X = N
5-Amino TCNR X = N-NH$_2$

Bactericidal I
(R = H; R^1 = CSNH$_2$)



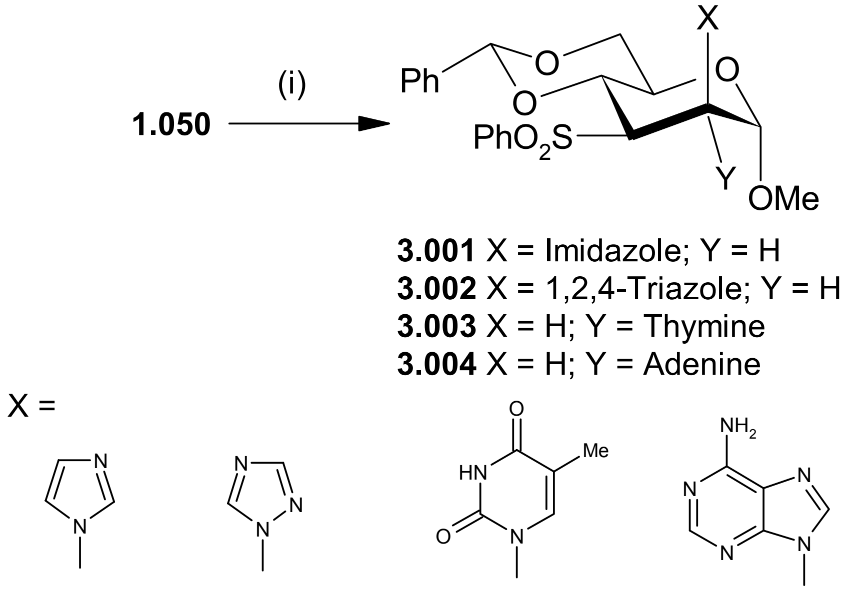
Bactericidal II
(R = H, Ac, Bz; R^1, R^2, R^3 = H, CN, NO$_2$, CO$_2$Me, NH$_2$, CSNH$_2$)

3.2 Present Work

Reactions of α-vinyl sulfone 1.050 with planar heterocycles (N-nucleophiles): α-vinyl sulfone **1.050**[33] on reaction with imidazole, 1,2,4-triazole and thymine in the presence of tetramethyl guanidine (TMG) in DMF at ambient temperature, generated single isomers **3.001**, **3.002**, and **3.003**, respectively in high yields. Adenine, on the other hand, under similar conditions afforded an inseparable mixture of compounds in a ratio of 2.2:1. However, by comparing the spectra of the small amount of compound that crystallized out from the mixture of adenine adducts with that of **3.003**, the major isomer present in the reaction mixture has been assigned the structure **3.004**.

Reactions of β-vinyl sulfone 1.058 with planar heterocycles (N-nucleophiles): Similarly, β-vinyl sulfone **1.058**[33] was treated with same set of nucleophiles mentioned above in the presence of TMG in DMF at ambient temperature to afford single isomers **3.005**, **3.006**, **3.007** and **3.008**, respectively in moderate to good yields.

Reactions of α-vinyl sulfone 2.001 with planar heterocycles (N-nucleophiles): Reactions of **2.001** with imidazole, 1,2,4-triazole, thymine and adenine in the presence of TMG in DMF at ambient temperature, yielded single isomers **3.009**, **3.010**, **3.011**, and **3.012**, respectively in high yields.



3.001 X = Imidazole; Y = H
3.002 X = 1,2,4-Triazole; Y = H
3.003 X = H; Y = Thymine
3.004 X = H; Y = Adenine

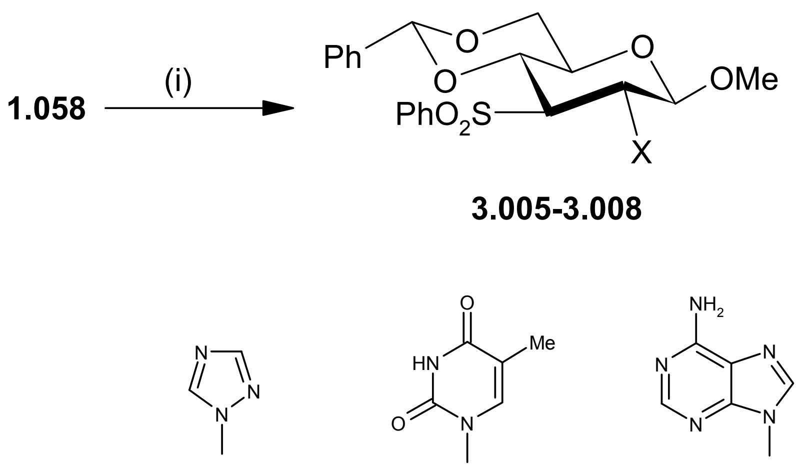
3.001 (2 h, 98%) **3.002** (5 h, 95%) **3.003** (4 h, 58%) **3.004** [60 h, 60%(2.2:1)]

Reagents and conditions: (i) XH, TMG, DMF, rt., 2-60 h.

Reactions of β-vinyl sulfone 2.003 with planar heterocycles (N-nucleophiles): Similarly, reactions of **2.003** with imidazole, thymine and adenine in the presence of TMG in DMF at ambient temperature, afforded single isomers **3.013**, **3.014** and **3.015**, respectively in high to moderate yields whereas under the same set of reaction conditions, 1,2,4-triazole on reaction with **2.003**, generated a mixture of two diastereomers **3.016** and **3.017** of approximately equal amounts (1:1).

3.3 Structural Assignment

We have already pointed out (**Section 2.3**, **Chapter 2**) that for methyl 4,6-O-(phenylmethylene)-α-D-hexopyranosides with D-*allo*- and D-*gluco*-configurations, a

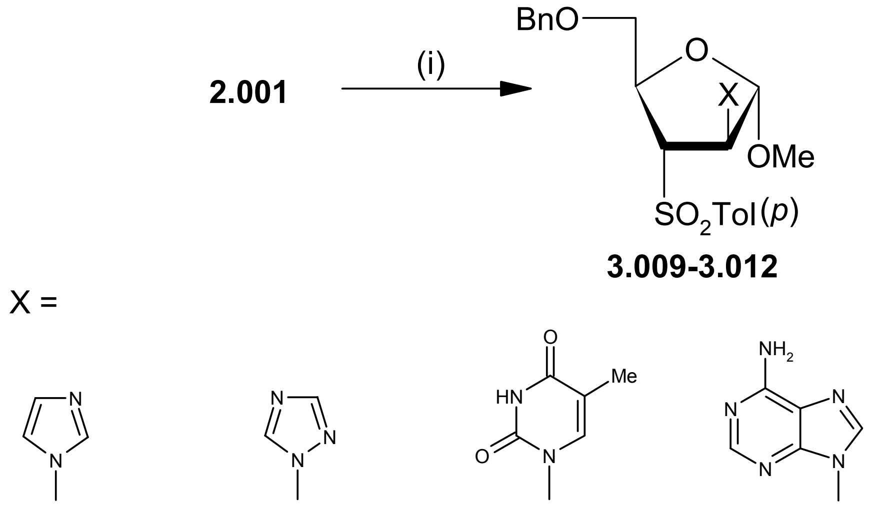

1.058 (i) **3.005-3.008**

X =

3.005 (1.5 h, 70%) **3.006** (1 h, 58%) **3.007** (1.5 h, 90%) **3.008** (1 h, 65%)

Reagents and conditions: (i) XH, TMG, DMF, rt., 1-1.5 h.

coupling constant ($J_{1,2}$) value of 3.3-3.8 Hz implies a characteristic arrangement of equatorial H-1/axial H-2. For D-*altro*- and D-*manno*-configurations a coupling constant ($J_{1,2}$) value of 0.6-1.7 Hz is the characteristic of equatorial H-1/equatorial H-2 arrangement. Hence, by comparing $J_{1,2}$ values (0.0-1.0 Hz) of compounds **3.001** and **3.002** (**Table 3.1**) with those of the known compounds **3.018** and **3.019** (**Table 3.2**), **3.001** and **3.002** were tentatively considered as possessing *manno*-configurations.

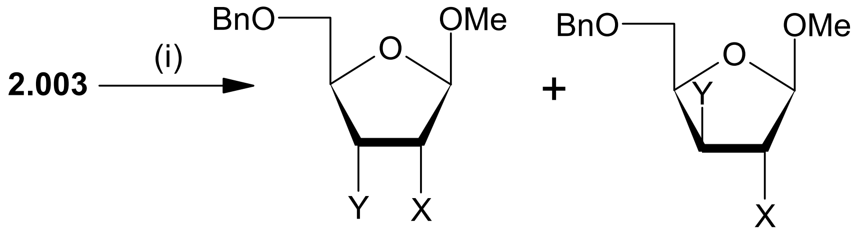

2.001 (i) **3.009-3.012**

X =

3.009 (12 h, 90%) **3.010** (1 h, 82%) **3.011** (1 h, 82%) **3.012** (1 h, 96%)

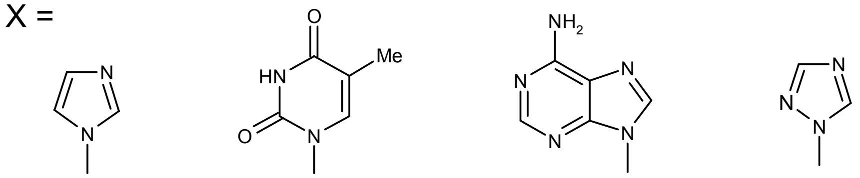
Reagents and conditions: (i) XH, TMG, DMF, rt., 1-12 h.

Similarly, $J_{1,2}$ values of 3.4 Hz each for compounds **3.003** and **3.004** (major isomer) were in well agreement with those of the reported compounds having *allo*- or *gluco*-configuration. So, it was concluded tentatively that **3.003** and **3.004** possess either *gluco*- or *allo*-configuration. In the case of compounds **3.005**, **3.006**, **3.007** and **3.008**, H-1 signals appeared as doublets with relatively large coupling constant ($J_{1,2}$) values of 7.30-7.90 Hz (**Table 3.1**). Having compared $J_{1,2}$ values of the known compounds **3.020** and **3.021** (**Table 3.2**) with our compounds, it was concluded that H-1 and H-2 were diaxially oriented and all isomers in β-series were assigned *gluco*-configuration.



3.013 Y = $SO_2Tol(p)$; X = Imidazolyl
3.015 Y = $SO_2Tol(p)$; X = Adeninyl
3.017 Y = $SO_2Tol(p)$; X = Triazolyl

3.014 Y = $SO_2Tol(p)$; X = Thyminyl
3.016 Y = $SO_2Tol(p)$; X = Triazolyl



3.013 (4 h, 82%) **3.014** (8 h, 82%) **3.015** (12 h, 60%) **3.016, 3.017** (1:1, 28 h, 75%)

Reagents and conditions: (i) XH, TMG, DMF, rt., 4-28 h.

^{13}C NMR spectra of *trans*-fused hexopyranoside derivatives have been studied thoroughly.[34] As per the report,[34] on changing a substituent from equatorial to axial position at C-2, a large shielding would be expected at C-4. This fact holds true in the case of **3.001**, **3.002** and **3.003**. C-4 peaks of **3.001** and **3.002** (δ74.3 and δ73.9, respectively) are more shielded than that of **3.003** (δ76.3). Similarly, for β-series (**3.005-3.008**) C-4 peaks appeared between δ75.4 to 76.6, indicating equatorial orientations of the substituents at C-2. Moreover, it is obvious from **Table 3.1** that OMe carbon is being more deshielded in β-series over those in α-series. Hence OMe peaks in compounds **3.005-**

3.008 appeared at higher δ-value (δ 56.7-57.8) compared to those of **3.001-3.003** (δ 55.1-55.7).

The structures of **3.002** ($J_{1,2}$ = 0.0 Hz) (**Figure 3.8**), **3.003** ($J_{1,2}$ = 3.4 Hz) (**Figure 3.9**) **3.006** ($J_{1,2}$ = 7.5 Hz) (**Figure 3.10**), and **3.007** ($J_{1,2}$ = 7.3 Hz) (**Figure 3.11**) are unambiguously confirmed by X-ray crystallography. By comparing the $J_{1,2}$ values of **3.001** ($J_{1,2}$ = 1.0 Hz) with that of **3.002** it was concluded that both are having *manno*-configurations. Similarly **3.003** and **3.004** (($J_{1,2}$ = 3.4 Hz) are having *gluco*-configurations. On the other hand, by comparing the $J_{1,2}$ values of **3.005** ($J_{1,2}$ = 7.3 Hz), **3.006** ($J_{1,2}$ = 7.6 Hz) and **3.008** ($J_{1,2}$ = 7.9 Hz) with that of **3.007** ($J_{1,2}$ = 7.3 Hz) it was concluded that all of them are having *gluco*-configurations.

Table 3.1

δ_{H-1}, δ_{OMe}, $J_{1,2}$ and $[\alpha]_D^T$ of synthesized compounds

Compounds	δ_{H-1} (ppm)	δ_{OMe} (ppm)	$J_{1,2}$ (Hz)	$[\alpha]_D^T$
3.001	4.87	55.2	1.0	−18.4
3.002	4.83	55.1	0.0	−35.9
3.003	4.72	55.7	3.4	−34.0
3.004	4.79	------	3.4 (Major)	-----
3.005	4.54	56.7	7.3	−24.7
3.006	4.74	57.8	7.5	−70.2
3.007	5.20	57.8	7.3	−38.0
3.008	5.14	56.9	7.9	−38.0

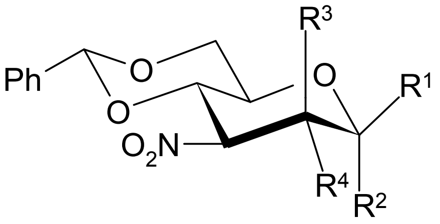


Figure 3.7

Table 3.2

Coupling constant data, $J_{1,2}$ of some selective compounds

Comp.	R^1	R^2	R^3	R^4	$J_{1,2}$ (Hz)	Ref.
3.018	H	OMe	Theophyllinyl	H	1.2	19

3.019	H	OMe	2,6-dichloropurinyl	H	1.2	19
3.020	OMe	H	H	Theophyllinyl	7.5	20
3.021	OMe	H	H	2,6-dichloropurinyl	8.0	20

Futhermore, It is also evident from the literature[33] that methyl 2,3-dideoxy-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfonyl-α-D-*gluco*pyranoside derivatives showed positive optical rotation while methyl 2,3-dideoxy-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfonyl-β-D-*gluco*pyranosides derivatives exhibited negative optical rotation values. Compounds **3.001**–**3.003** and **3.005**–**3.008** have shown negative rotations (**Table 3.1**). However, sign of rotation of only β-adducts **3.005-3.008** is in good agreement with that reported in the literature.

Table 3.3

δ_{H-1}, $J_{1,2}$ and $[\alpha]_D^T$ of synthesized compounds

Compounds	δ_{H-1}(ppm)	$J_{1,2}$ (Hz)	$[\alpha]_D^T$
3.009	4.98	0.0	+42.2
3.010	5.11	2.0	+53.3
3.011	4.90	1.0	+21.0
3.012	5.12	2.4	+45.0
3.013	4.96	0.0	−1.3
3.014	4.91	4.4	−44.0
3.015	5.14	0.0	+27.0
3.016	5.05	3.9	−5.0
3.017	5.08	0.0	+13.7

The products from the reactions of **2.001** with planar heterocycles (*N*-nucleophiles) were expected to have *arabino*-configuration for two reasons: a) α-methoxy group at C-1 would direct all four bulky nucleophiles to attack the C-2 position from the β-side of the furanose ring and b) the intermediate carbanion after the addition of a nucleophile would be protonated from the β-side of the furanose ring to push a bulky –SO_2Tol(*p*) group to the α-side of the ring.

It is clearly evident from the available data that the $J_{1,2}$ values of authentic methyl α-D-*arabino*furanosides (**Table 2.2**) including **2.007-2.010** (**Table 2.3**) range between 0.0-**3**.0 Hz. The $J_{1,2}$ values for authentic methyl α-D-*ribo*furanosides including **2.019** and **2.021** range between 4.0-4.9 Hz and the same for methyl α-D-*xylo*furanosides including **2.028-**

2.030, on the other hand are always ranging between 4.0-4.7 Hz (**Tables 2.1** and **2.3**). Excluding the possibility of any *lyxo*-derivative formation for steric reasons, the $J_{1,2}$ values of **3.009-3.012**, which ranged between 0.0-2.4 Hz, surely indicated the presence of *arabino*-configuration in these molecules. However, one of these compounds, **3.010**, which could be crystallized, was subjected to X-ray diffraction studies. The structure of **3.010** was unambiguously established as having the *arabino*-configuration (**Figure 3.12**) which was in line with the structural assignment on the basis of $J_{1,2}$ coupling constant.

Using the similar arguments mentioned above, we expected to obtain *xylo*-derivatives from the reactions between **2.003** and the planar heterocycles. It has also been reported earlier that Michael addition of various nucleophiles to vinyl sulfone-modified nucleosides **1.089** and **1.090** produced mainly the *xylo*-derivatives **1.091** and **1.092**, respectively although in limited number of cases *ribo*-derivatives were also

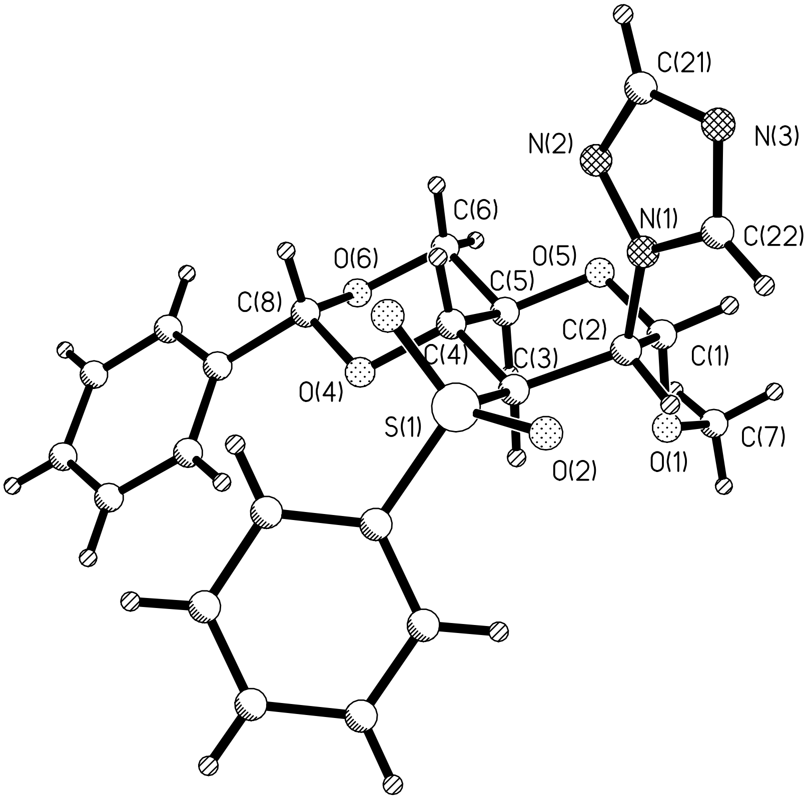


Figure 3.8 ORTEP Diagram of Compound 3.002

Selected bond lengths (Å) for compound 3.002	**Selected bond angles (deg) for compound 3.002**
C1 O1 1.393(5)	C1 O1 C7 112.0(3)
C1 C2 1.531(5)	N1 C2 C1 109.4(3)
O1 C7 1.430(6)	N1 C2 C3 115.0(3)
C2 N1 1.463(5)	C1 C2 C3 109.6(3)
C2 C3 1.532(5)	C4 C3 C2 110.8(3)
C3 C4 1.512(4)	C4 C3 S1 113.5(2)
C4 O4 1.424(4)	C2 C3 S1 111.2(2)
C4 C5 1.533(5)	O4 C4 C3 110.0(2)
O4 C8 1.422(4)	O4 C4 C5 106.2(3)
C8 O6 1.418(5)	C3 C4 C5 110.3(3)
O6 C6 1.420(5)	O3 S1 O2 119.0(2)
C6 C5 1.516(5)	O3 S1 C3 108.62(17)
S1 O3 1.421(3)	O2 S1 C3 106.52(17)
S1 O2 1.434(3)	C1 O5 C5 111.0(2)
S1 C3 1.814(3)	O1 C1 O5 112.4(3)
O5 C1 1.405(4)	O1 C1 C2 106.3(3)
O5 C5 1.416(4)	O5 C1 C2 112.3(3)

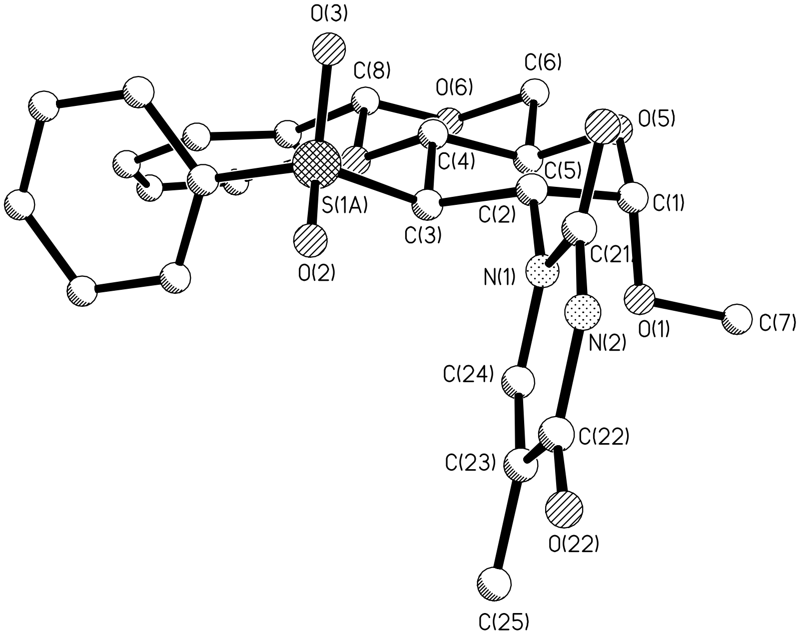


Figure 3.9 ORTEP Diagram of Compound 3.003[*]

Selected bond lengths (Å) for compound 3.003	**Selected bond angles (deg) for compound 3.003**
C1 O1 1.376(7)	C1 O5 C5 109.7(5)
C1 C2 1.525(8)	O1 C1 O5 113.6(6)
O1 C7 1.414(7)	O1 C1 C2 108.1(6)
C2 N1 1.473(7)	O5 C1 C2 111.4(6)
C2 C3 1.544(8)	C1 O1 C7 113.7(6)

C3 C4 1.521(8)	N1 C2 C1 110.5(6)
C4 O4 1.417(7)	N1 C2 C3 113.4(6)
C4 C5 1.496(9)	C1 C2 C3 114.2(6)
O4 C8 1.454(7)	C4 C3 C2 109.1(6)
C8 O6 1.371(7)	C4 C3 S1A 113.7(5)
C6 C5 1.512(8)	C2 C3 S1A 107.1(4)
O6 C6 1.413(8)	O4 C4 C5 108.8(6)
S1A O2 1.433(5)	O4 C4 C3 109.5(6)
S1A O3 1.436(4)	C5 C4 C3 111.6(6)
S1A C3 1.806(6)	O2 S1A O3 118.7(3)
O5 C1 1.421(7)	O2 S1A C3 107.7(3)
O5 C5 1.452(7)	O3 S1A C3 106.7(3)

*Crystal structure has two molecules in the asymmetric unit. The parameters given correspond to one of them.

obtained (**Chapter 1**). It is evident from the available data that the $J_{1,2}$ values of authentic methyl β-D-*xylo*furanosides (**Table 2.1**) including **2.013**, **2.015** and **2.031** range between 0.0-2.3 Hz and those of methyl β-D-*ribo*furanosides (**Table 2.1**) including **2.020** and **2.022** (**Table 2.3**) are close to 0.0 Hz. The $J_{1,2}$ values of 5-*O*-benzyl protected methyl β-D-*arabino*-derivatives (**Table 2.2**), however range between 3.0-4.0 Hz. Excluding the possibility of any *arabino*-derivative formation on the basis of steric consideration and literature evidence (**Chapter 1**), we have assigned *ribo*-

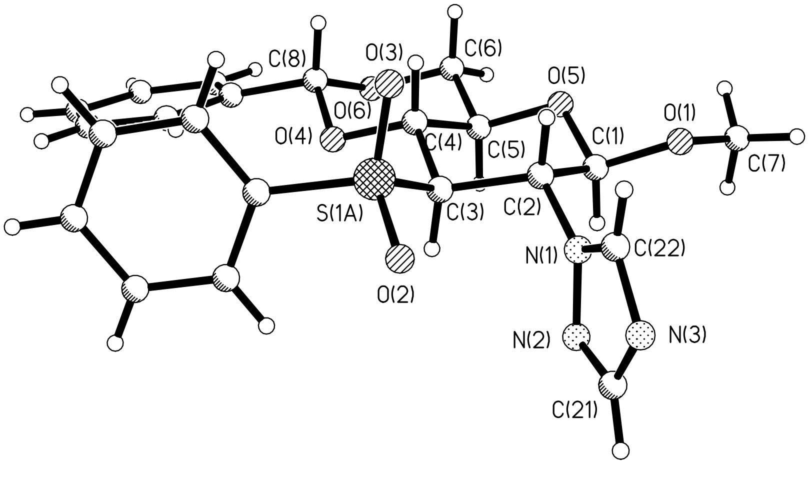


Figure 3.10 ORTEP Diagram of Compound 3.006*

Selected bond lengths (Å) for compound 3.006	Selected bond angles (deg) for compound 3.006
C1 O1 1.386(4)	C1 O1 C7 114.3(4)
C1 C2 1.528(5)	N1 C2 C1 109.0(3)
O1 C7 1.427(6)	N1 C2 C3 111.9(3)
C2 N1 1.465(4)	C1 C2 C3 112.7(3)
C2 C3 1.553(4)	O1 C1 O5 108.2(3)
C3 C4 1.532(4)	O1 C1 C2 107.1(3)
C4 O4 1.418(4)	O5 C1 C2 110.2(3)

C4 C5 1.528(5)	C4 C3 C2 108.6(2)
O4 C8 1.433(3)	C4 C3 S1A 113.3(2)
S1A O3 1.433(3)	C2 C3 S1A 106.4(2)
S1A O2 1.433(3)	C5 C4 C3 108.9(2)
S1A C3 1.817(3)	O3 S1A O2 119.6(2)
O5 C5 1.413(4)	O3 S1A C3 105.99(16)
O5 C1 1.421(4)	O2 S1A C3 106.62(16)

*Crystal structure has two molecules in the asymmetric unit. The parameters given correspond to one of them.

configuration to **3.013**, **3.015** and **3.017** ($J_{1,2}$ = 0.0 Hz for all three; **Table 3.3**). Although the $J_{1,2}$ values of **3.014** and **3.016** ($J_{1,2}$ = 4.4 Hz and 3.9 Hz, respectively; **Table 3.3**) were higher than those of related compounds mentioned above, X-ray diffraction experiments unambiguously established **3.016** as a *xylo*-derivative (**Figure 3.13**). We, therefore, assigned *xylo*-configuration to **3.014** as well. It should be mentioned here that the $J_{1,2}$ values of *C*-branched *xylo*-furanosyl derivatives **4.052** and **4.053** (synthesized from **2.003**), whose structures have been assigned unambiguously are 3.5 Hz and 3.9 Hz, respectively (see **Chapter 4** for detail). The structure of one of the *ribo*-isomers, **3.017** was also established conclusively on the basis of X-ray diffraction of its single crystal (**Figure 3.14**).

Moreover, compounds **3.009** (+42.2), **3.010** (+53.3), **3.011** (+21.0), **3.012** (+45.0), **3.015** (+27.0) and **3.017** (+13.7) have shown positive rotation values whereas

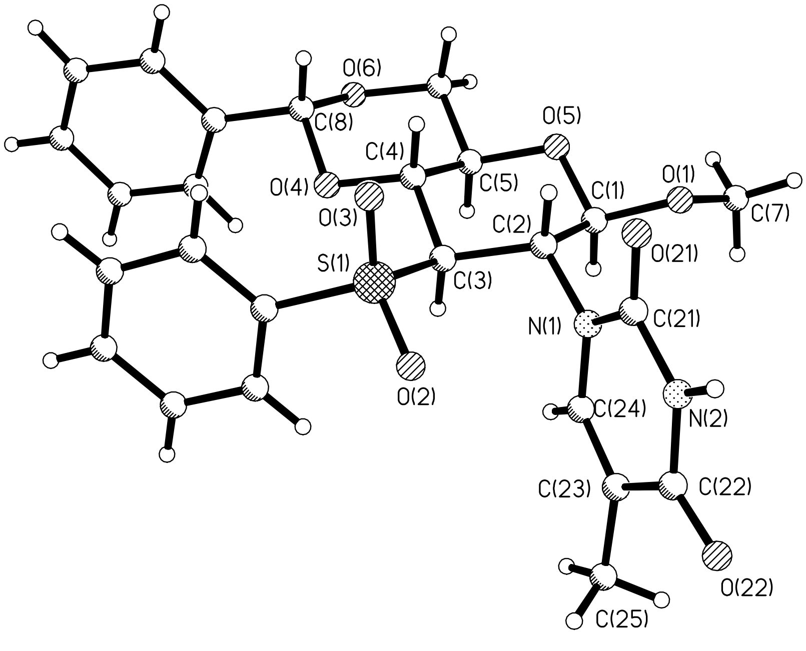


Figure 3.11 ORTEP Diagram of Compound 3.007

Selected bond lengths (Å) for compound 3.007	Selected bond angles (deg) for compound 3.007
C1 O1 1.371(4)	C1 O5 C5 111.4(2)
C1 C2 1.552(4)	O1 C1 O5 108.4(3)
O1 C7 1.430(5)	O1 C1 C2 106.7(2)
C2 N1 1.462(4)	O5 C1 C2 109.9(2)
C2 C3 1.543(4)	C1 O1 C7 113.5(3)
C3 C4 1.517(4)	N1 C2 C3 114.1(2)
C4 O4 1.415(4)	N1 C2 C1 109.7(2)
C4 C5 1.514(5)	C3 C2 C1 111.2(2)
O4 C8 1.428(4)	C4 C3 C2 107.1(2)
C8 O6 1.420(4)	C4 C3 S1 112.2(2)
C6 C5 1.521(4)	C2 C3 S1 110.64(19)
O6 C6 1.433(4)	O3 S1 O2 117.76(16)
S1 O3 1.425(2)	O3 S1 C3 107.40(15)
S1 O2 1.430(3)	O2 S1 C3 108.34(14)
S1 C3 1.810(3)	O4 C4 C3 111.6(2)
O5 C1 1.420(4)	C5 C4 C3 110.1(3)
O5 C5 1.425(4)	O5 C5 C4 110.4(2)

compounds **3.013** (–1.3), **3.014** (–44.0) and **3.016** (–5.0) have shown negative rotation. Thus, it can be inferred that in α-series, compounds **3.009**-**3.012** were belonging to a family having same configuration i.e., α-*arabino*-configurations. In β-series, compounds **3.013** (small –ve value), **3.015** and **3.017** were concluded as possessing β-*ribo*-configurations and **3.014** and **3.016** were concluded as having β-*xylo*-configurations. The signs of rotation for compounds having α-*arabino*-, β-*ribo*- and β-*xylo*-configurations are consistent with those of the reported compounds having similar

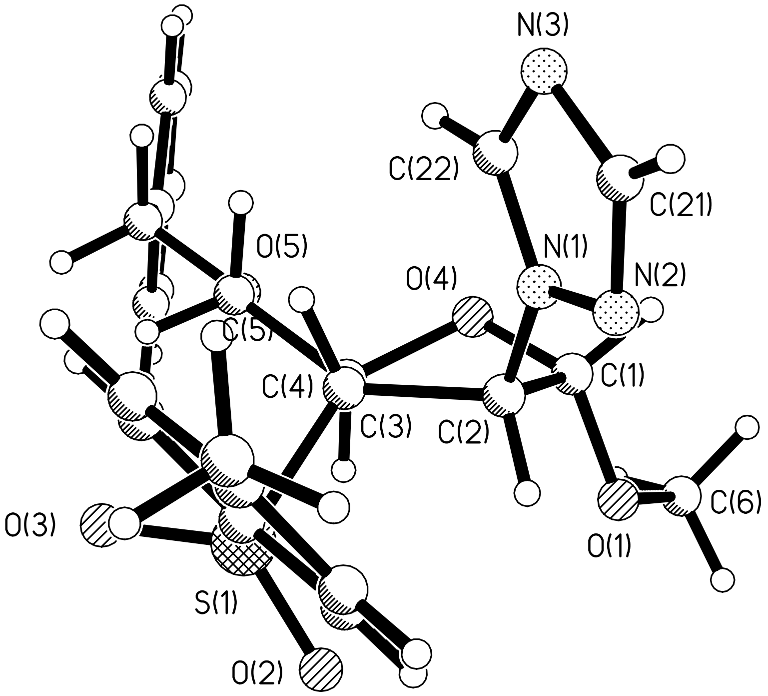


Figure 3.12 ORTEP Diagram of Compound 3.010

Selected bond lengths (Å) for compound 3.010	Selected bond angles (deg) for compound 3.010
C1 O1 1.397(12)	C2 C1 O1 105.5(7)
C1 O4 1.373(11)	O4 C1 O1 114.0(8)
C1 C2 1.554(11)	C2 C1 O4 105.6(7)
C2 C3 1.520(11)	C1 C2 N1 114.7(7)
C2 N1 1.420(11)	C1 C2 C3 103.1(7)
O1 C6 1.443(11)	C3 C2 N1 112.7(7)
C3 C4 1.545(10)	C3 C4 O4 102.7(6)
C4 O4 1.414(9)	C1 O4 C4 108.0(6)
C4 C5 1.510(12)	C2 C3 C4 104.0(6)
S1 O2 1.431(7)	C3 S1 O2 109.0(4)
S1 O3 1.428(6)	C3 S1 O3 107.0(4)
S1 C3 1.811(7)	O3 S1 O2 118.3(4)

configurations (**Chapter 2**, **Table 2.1** & **2.2**).

In the mass spectra, compounds **3.001-3.003**, **3.005-3.014** and **3.016-3.017** showed peaks corresponding to M^+ and some characteristic fragments. Most of the new compounds rendered satisfactory elemental analysis.

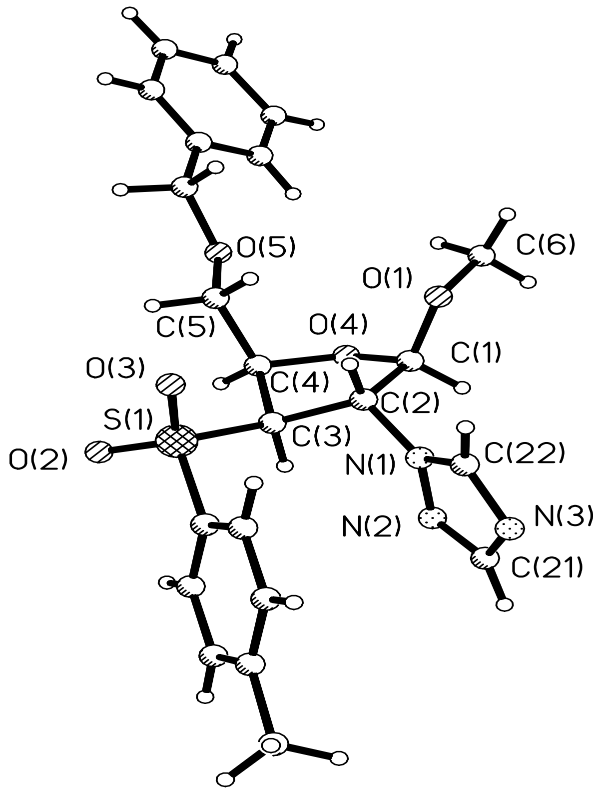


Figure 3.13 ORTEP Diagram of Compound 3.016

Selected bond lengths (Å) for compound 3.016	Selected bond angles (deg) for compound 3.016
C1 O1 1.357(12)	C1 O4 C4 110.1(6)
C1 C2 1.522(10)	C1 O1 C6 116.0(13)
O1 C6 1.419(14)	O1 C1 O4 111.9(7)
C2 N1 1.457(8)	O1 C1 C2 108.4(9)
C2 C3 1.528(9)	O4 C1 C2 106.4(7)
C3 C4 1.522(8)	N1 C2 C1 113.9(6)
C4 C5 1.527(11)	N1 C2 C3 114.7(5)
S1 O2 1.428(5)	C1 C2 C3 103.4(6)
S1 O3 1.432(5)	C4 C3 C2 101.6(5)
S1 C3 1.783(7)	O2 S1 O3 118.7(3)
O4 C1 1.399(10)	O2 S1 C3 106.3(3)
O4 C4 1.426(9)	O3 S1 C3 108.9(3)
C5 O5 1.406(8)	C4 C3 S1 116.4(5)
O5 C7 1.407(10)	C2 C3 S1 116.1(5)
C7 C8 1.524(12)	O4 C4 C3 101.6(5)

3.4 Results and Discussion

The diastereoselectivity of addition of nucleophiles to 2,3-dideoxy-3-*C*-nitro-hex-2-enopyranosides **1.021**/**1.018** have been discussed in terms of electrostatic interaction,[35] stereoelectronic control,[35] and steric hindrance,[35] A$^{(1,3)}$ strain[36] and also hydrogen bonding.[36] A generalization that the axial attack predominates over equatorial attack for α-vinyl compounds **1.021** and **1.050**, and the converse is true for β-vinyl compounds **1.018** and **1.058** has been arrived at on the basis of reactions of **1.018**, **1.021**, **1.050** and **1.058** with several nucleophiles.[33,35] However, when **1.021** and **1.018** were reacted with amines, thermodynamically more stable C-2 equatorial products were formed irrespective of the anomeric configuration of the Michael acceptor and steric bulk of the incoming nucleophiles.[18] On the other hand, addition of sterically demanding purine bases to **1.021** and **1.018** occurred from β-[17] and α-[19] side, respectively.

In theory, in a partially rigid bicyclic system like **1.050** or **1.058**, sterically demanding bulky phenylsulfonyl group should occupy the equatorial position after the nucleophilic addition. In fact, it has been reported that the addition of *p*-toluenethiol to 1-(*p*)-tolylsulfonyl-cyclohexene generated the thermodynamically less stable *cis*-2-(*p*)-tolylmercapto-1-(*p*)-tolylsulfonyl-cyclohexane and not the thermodynamically more stable *trans*-product.[37]

In the light of the above observations, it can be stated that the stereochemical course of addition of planar heterocycles (*N*-nucleophiles) does not fully abide by the above generalization in the case of α-adducts. Addition of imidazole and 1,2,4-triazole to **1.050** generated products **3.001** and **3.002**, respectively with *manno*-configuration, which are consistent with the reported observation.[18] Addition of thymine to **1.050** produced **3.003** with *gluco*-configuration. Adenine generated a mixture in which the major component **3.004** is having the *gluco*-configuration. The configurations at C-2 positions of **3.003** and **3.004**, are surprisingly different from those reported for purine adducts derived from vinyl nitro-modified carbohydrate **1.021** where the heterocycles attacked the C-2 position from the β-side.[17]

To explain the formation of *gluco*-isomers and mixture of products from α-vinyl sulfone, one has to bear in mind the established rules that (a) nitrogen nucleophiles carrying non-bonded electron pairs would face electrostatic repulsion from C_1-O_1 and C_1-O_5 bonds and (b) thermodynamically more stable diequatorial products should predominate.[35]

Nevertheless, to explain the formation of *manno*-isomers **3.001** and **3.002**, it is necessary to assume that in these cases the stereoelectronic repulsion caused by C_1-O_1 from the α-side of the ring to the incoming heterocycles was more important than the electrostatic repulsion from C_1-O_5 bond. Although this repulsion

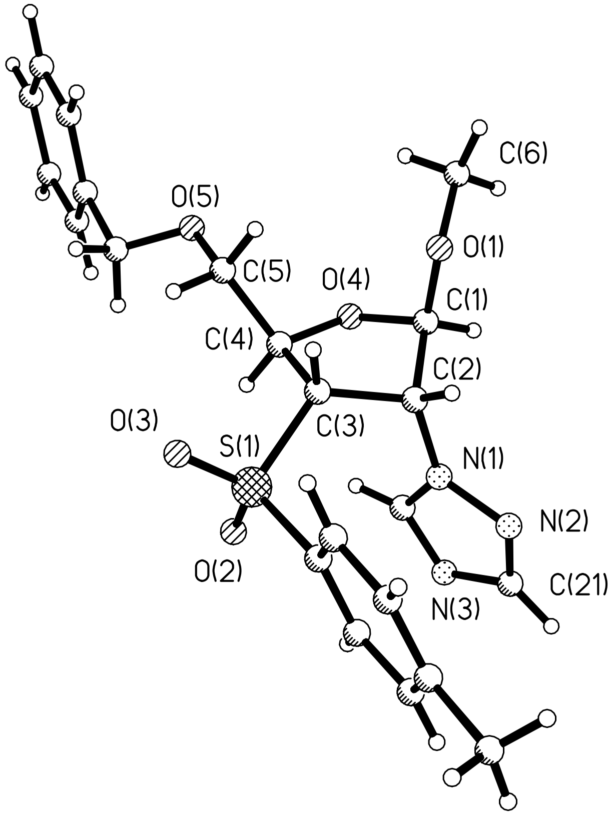


Figure 3.14 ORTEP Diagram of Compound 3.017

Selected bond lengths (Å) for compound 3.017	Selected bond angles (deg) for compound 3.017
C1 O1 1.400(5)	C1 O4 C4 109.5(3)
C1 C2 1.520(5)	O1 C1 O4 111.9(3)
O1 C6 1.419(5)	O1 C1 C2 107.5(3)
C2 N1 1.450(5)	O4 C1 C2 105.4(3)
C2 C3 1.529(6)	C1 O1 C6 113.4(3)
C3 C4 1.538(5)	N1 C2 C1 110.1(3)
C4 C5 1.504(6)	N1 C2 C3 116.4(3)
C5 O5 1.410(6)	C1 C2 C3 100.9(3)
O5 C7 1.333(7)	C2 C3 C4 104.4(3)
S1 O3 1.427(4)	C2 C3 S1 121.2(3)
S1 O2 1.442(3)	C4 C3 S1 110.6(3)
S1 C3 1.803(4)	O4 C4 C3 106.0(3)

O4 C1 1.408(5) O4 C4 1.429(5) C7 C8 1.514(8)	O3 S1 O2 118.1(2) O3 S1 C3 104.7(2) O2 S1 C3 109.38(19)

served our goal of attaching a nucleophile at C-2 in a direction (here axial) opposite to that of the anomeric α-methoxy group, the exact nature of the hindrance cannot be ascertained at this stage. On the other hand, reactions of β-vinyl sulfone **1.058** with imidazole, 1,2,4-triazole, thymine and adenine generated thermodynamically more stable diequatorial products. It is difficult to establish whether electrostatic repulsions between *N*-nucleophiles and C_1-O_5 bond directed the nucleophiles to attack the C-2 position of **1.058** from the equatorial direction resulting in the formation of single isomers **3.005-3.008**. This observation, nevertheless, is more in line with the generalized rule that in the case of an β-anomeric substrate, a nucleophile should approach C-2 site preferably from equatorial direction.[35]

Studies on the stereochemistry of nucleophilic addition to systems like 2,3-dideoxy-3-*C*-nitro-pent-2-enofuranosides[38] has not been attempted but there are reports on the regioselective opening of epoxides directed by the configurations at the anomeric center.[39] It has also been reported[40] that the addition of *p*-toluenethiol to 1-(*p*)-tolylsulfonyl cyclopentene system generated thermodynamically more stable *trans*-2-(*p*)-tolylmercapto-1-(*p*)-tolylsulfonyl cyclopentane. Moreover in the case of nucleosides it is known that Michael addition of various nucleophiles to vinyl sulfone-modified nucleosides **1.089** and **1.090** produced mainly the *xylo*-derivatives **1.091** and **1.092**, respectively although in limited number of cases *ribo*-derivatives were also obtained (**Chapter 1**).

Thus, in the light of above observations it can be concluded that addition of imidazole, 1,2,4-triazole, thymine and adenine to α-vinyl sulfone **2.001** should generate products with *arabino*-configurations which indeed is the case. In fact this observation is more in line with the general rule as discussed above that groups that are *trans*-related hinder substitution at the adjacent carbon atom from the same side. On the other hand, addition of the same set of nucleophiles to β-vinyl sulfone **2.003** produced two different sets of products, namely *ribo*-derivatives **3.013**, **3.015** and **3.017** and *xylo*-derivatives **3.014** and **3.016**. The approach of all nucleophiles to C-2 is most probably directed by the stereoelectronic effect of the anomeric methoxy group. For **3.009-3.012**, **3.014** and **3.016**, the *trans*-relationship of groups at C-2 and C-3 are also expected and follow literature precedences discussed above. However, an in depth analysis of the ring puckering caused by the stereoelectronic properties of thymine or triazole and their probable interactions with *p*-TolSO$_2$ group is required to explain the formation of *ribo*-derivatives **3.013, 3.015** and **3.017**, which is beyond the scope of the present study.

3.5 Conclusion

We have developed a general methodology for the synthesis of several biologically relevant molecules where planar heterocycles including thymine and adenine are attached to the C-2 positions of both hexose and pentose systems. This methodology has rendered a direct access to new isonucleosides. We anticipate that other nucleobases also can be condensed readily with vinyl sulfone-modified carbohydrates. This method has also provided easy access to imidazole and triazole nucleosides. In all the cases studied the diastereoselectivity of addition is directed by the configuration at the anomeric position.

3.6 Experimental

General methods: See **Chapter 2**.

General procedure for the synthesis of 3.001, 3.002, 3.005, 3.006, 3.009, 3.010, 3.013, 3.016 and 3.017: To a well-stirred solution of imidazole or 1,2,4-triazole (3-5 eq) and TMG (2-3 eq) in DMF (10 mL/mmol) was added appropriate vinyl sulfone-modified carbohydrate (1 eq) and the mixture was stirred at ambient temperature. After completion of the reaction (tlc), water (1 mL) was added and the excess solvent was evaporated under reduced pressure to obtain a solid mass. The solid residue was dissolved into saturated NaHCO$_3$ and the aq. layer was extracted with EtOAc (3 x 40 mL). The combined organic layers were dried over anhydr. Na$_2$SO$_4$, filtered and filtrate was concentrated to dryness under reduced pressure. The crude mass was purified over flash chromatography to get the title compound.

General procedure for the synthesis of 3.003, 3.004, 3.007, 3.008, 3.011, 3.012, 3.014 and 3.015: To a well-stirred solution of the appropriate nucleobase (7-9 eq) and TMG (5-7 eq) in DMF (10 mL/mmol) was added appropriate vinyl sulfone-modified carbohydrate (1 eq) and the mixture was stirred at ambient temperature. After completion of the reaction (tlc), the reaction mixture was diluted with EtOAc (80 mL/mmol) and undissolved solid was filtered off. The filtrate was washed with saturated NaHCO$_3$ solution and aq. phase was extracted with EtOAc (3 x 30 mL). The combined extracts were dried over anhydr.

Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The crude material was purified over flash chromatography to get the title compound.

Methyl 2,3-dideoxy-2-*C*-imidazolyl-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfonyl-α-D-*manno*pyranoside 3.001: Compound **1.050** (0.25 g, 0.644 mmol) was converted to a fluffy material **3.001** in 2 h following the general procedure described above. Eluent: EtOAc:pet ether (7:3).

Yield: 0.29 g, 98%.

Mp: 185 °C (decom.).

$[\alpha]_D^{27}$: –18.4° (c 1.00, $CHCl_3$).

IR (Nujol): 1461, 1379 cm^{-1}.

^{1}H NMR: δ 7.94 (1 H, s, imidazole H), 7.61 (2 H, d, *J* 7.4 Hz, aromatic), 7.50-7.09 (10 H, m), 5.50 (1 H, s, PhCH), 5.25 (1 H, d, *J* 3.4 Hz), 4.87 (1 H, d, *J* 1.0 Hz, H-1), 4.32 (2 H, m), 4.07-3.92 (3 H, m), 3.45 (3 H, s, OMe).

^{13}C NMR: δ 140.4, 139.1, 136.1, 133.5, 129.3, 128.7, 128.6, 128.1, 126.3, 120.3, 102.3, 100.4, 74.3 (CH_2), 68.9 (CH_2), 64.6, 61.9, 55.2.

MS: m/z (EI) 456 (<1 M^+), 247 (45), 157 (23), 149 (41), 121 (100), 105 (27), 91 (24), 77 (18).

Analysis: Cald. for $C_{23}H_{24}N_2O_6S$: C, 60.51; H, 5.29; N, 6.13; S, 7.02. Found: C, 60.22; H, 5.59; N, 6.09; S, 7.29.

Methyl 2,3-dideoxy-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfonyl-2-*C*-1,2,4-triazolyl-α-D-*manno*pyranoside 3.002: Compound **1.050** (0.2 g, 0.515 mmol) was converted to needle shaped crystal **3.002** in 5 h following the general procedure described above. Eluent: EtOAc:pet ether (3:7).

Yield: 0.22 g, 95%.

Mp: 157-158 °C [Recrystallized from EtOAc:pet ether (1:3)].

$[\alpha]_D^{26}$: –35.9° (c 1.01, $CHCl_3$).

IR ($CHCl_3$): 2360, 2339, 2225, 1780, 1583, 1510, 1448 cm^{-1}.

^{1}H NMR: δ 8.42 (1 H, s), 8.04 (1 H, s), 7.63 (2 H, d, *J* 7.3 Hz, aromatic), 7.48 (1 H, t, *J* 7.8 Hz, aromatic), 7.35-7.12 (7 H, m, aromatic), 5.60 (1 H, s, PhCH), 5.42 (1 H, d, *J* 4.4 Hz), 4.98 (1 H, dd, *J* 11.3, 8.8 Hz), 4.83 (1 H, s, H-1), 4.30 (1 H, dd, *J* 9.7, 3.9 Hz), 4.11-3.87 (3 H, m), 3.45 (3 H, s, OMe).

^{13}C NMR: δ 152.6, 147.0, 140.2, 136.5, 133.7, 129.3, 128.8, 128.2, 126.3, 102.2, 99.9, 73.9, 69.0 (CH_2), 65.0, 62.1, 56.9, 55.1.

MS: m/z (EI) 457 (6 M^+), 456 (6), 455 (7), 436 (35), 386 (7), 334 (7), 317 (34), 316 (68), 308 (47).

Analysis: Cald. for $C_{22}H_{23}O_6N_3S$. $2H_2O$: C, 53.54; H, 4.69; N, 8.51; S, 6.49. Found: C, 53.59; H, 4.66; N, 8.04; S, 6.88.

Methyl 2,3-dideoxy-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfonyl-2-*C*-thyminyl-α-D-*gluco*pyranoside 3.003: Compound **1.050** (0.2 g, 0.515 mmol) was converted to a plate shaped crystalline compound **3.003** in 4 h following the general procedure described above. Eluent: $CHCl_3$:MeOH (19:1).

Yield: 0.15 g, 58%.

Mp: 169-170 °C [Recrystallized from $CHCl_3$:pet ether (1:3)].

$[\alpha]_D^{26}$: $-34°$ (c 1.12, $CHCl_3$).

IR ($CHCl_3$): 4214, 2401, 1689 cm^{-1}.

^{1}H NMR: δ 8.87 (1 H, bs, NH), 7.80 (2 H, d, *J* 7.3 Hz, aromatic), 7.53-7.23 (9 H, m, aromatic + thymine H), 5.50 (1 H, dd, *J* 11.7, 3.9 Hz), 5.34 (1 H, s, PhCH), 4.72 (1 H, d, *J* 3.4 Hz, H-1), 4.25 (1 H, dd, *J* 10.3, 3.9 Hz), 4.07-3.68 (4 H, m), 3.40 (3 H, s, OMe), 1.93 (3 H, s, thymine Me).

^{13}C NMR: δ 163.7, 151.7, 139.3, 138.1, 136.5, 134.2, 129.4, 129.2, 128.9, 128.3, 126.3, 110.6, 101.9, 98.1, 76.6 (C-4), 69.1 (CH_2), 62.7, 61.6, 55.7, 51.2, 12.8 (thymine Me).

MS: m/z (EI) 514 (<1 M^+), 313 (20), 267 (41), 221 (32), 207 (100), 164 (41).

Analysis: Cald. for $C_{25}H_{26}N_2O_8S.1.5H_2O$: C, 55.55; H, 5.21; N, 5.18; S, 5.93. Found: C, 55.48; H, 5.25; N, 5.05; S, 5.61.

Methyl 2-*C*-adeninyl-2,3-dideoxy-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfonyl-α-D-*gluco*pyranosides 3.004: Compound **1.050** (0.2 g, 0.515 mmol) was converted to a mixture of isomers (0.16 g, 60%) in 60 h. Eluent: MeOH:$CHCl_3$ (1:19). A small amount of the major isomer contaminated with a small amount of minor isomer was isolated by crystallization [EtOAc:pet ether (1:3)].

Yield: 0.16 g, 60%.

^{1}H NMR: δ 8.42 (1 H, s, purine H), 8.01 (1 H, s, purine H), 7.64 (2 H, d, *J* 7.3 Hz, aromatic H), 7.39-7.17 (8 H, m, aromatic H), 5.83 (2 H, bs, NH_2), 5.47 (1 H, dd, *J* 12.3, 4.0 Hz), 5.41

(1 H, s), 4.79 (1 H, d, *J* 3.4 Hz, H-1), 4.50 (1 H, t, *J* 9.2 Hz), 4.30 (1 H, dd, *J* 10.3, 3.9 Hz), 4.10-3.98 (2 H, m), 3.80 (1 H, t, *J* 7.9 Hz), 3.36 (3 H, s, OMe).

Methyl 2,3-dideoxy-2-*C*-imidazolyl-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfonyl-β-D-*gluco*pyranoside 3.005: Compound **1.058** (0.37 g, 0.945 mmol) was converted to a fluffy material **3.005** in 1.5 h following the general procedure described above. Eluent: EtOAc:pet ether (3:1).
Yield: 0.3 g, 70%.
Mp: 82-83 ^{o}C.
[α]$_D^{26}$: –24.7^{o} (c 1.01, CHCl$_3$).
IR (Nujol): 4214, 2974, 2939, 2873, 2848, 1498, 1448 cm^{-1}.
^{1}H NMR (300 MHz): δ 7.60 (3 H, m), 7.45-7.25 (8 H, m, aromatic), 7.03 (1 H, s), 6.93 (1 H, s), 5.51 (1 H, s, PhCH), 4.64 (1 H, dd, *J* 10.6, 7.5 Hz), 4.54 (1 H, d, *J* 7.3 Hz, H-1), 4.38 (1 H, dd, *J* 10.7, 4.8 Hz), 4.22 (1 H, t, *J* 10.3 Hz), 4.02 (1 H, t, *J* 10.2 Hz), 3.86
(1 H, t, *J* 10.3 Hz), 3.66 (1 H, m), 3.35 (3 H, s, OMe).
^{13}C NMR: δ 140.1, 137.7, 136.4, 133.6, 129.4, 129.1, 128.9, 128.6. 128.0, 126.1, 117.3, 103.1, 101.5, 75.4 (C-4), 68.6 (CH$_2$), 67.5, 66.3, 57.5, 56.7.
MS: m/z (EI) 456 (<1 M$^+$), 247 (7), 239 (16), 209 (19), 149 (100), 105 (23), 91 (9), 77 (13).
Analysis: Cald. for $C_{23}H_{24}N_2O_6S$: C, 60.51; H, 5.29; N, 6.13; S, 7.02. Found: C, 60.43; H, 5.58; N, 6.02; S, 7.50.

Methyl 2,3-dideoxy-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfonyl-2-*C*-1,2,4-triazolyl-β-D-*gluco*pyranoside 3.006: Compound **1.058** (0.097 g, 0.25 mmol) was converted to a needle shaped crystalline compound **3.006** in 1 h following the general procedure described above. Eluent: EtOAc:pet ether (3:7).
Yield: 0.07 g, 58%.
Mp: 128-129 ^{o}C [Recrystallized from EtOAc:pet ether (1:3)].
[α]$_D^{26}$: –70.2^{o} (c 1.12, CHCl$_3$).
IR (CHCl$_3$): 3134, 2941, 2879, 2401, 2360, 2337, 1506, 1448 cm^{-1}.
^{1}H NMR (500 MHz, C$_6$D$_6$): δ 7.95 (1 H, s), 7.92 (1 H, s), 7.59 (2 H, d, *J* 7.6 Hz, aromatic), 7.22-7.09 (5 H, m, aromatic), 6.78 (1 H, m, aromatic), 6.69 (2 H, t, *J* 7.64 Hz, aromatic), 5.16 (1 H, s, PhC$\underline{\text{H}}$), 4.72 (1 H, q), 4.62 (1 H, t, *J* 10.76 Hz), 4.48 (1 H, d, *J* 7.54 Hz), 4.12 (1 H, dd, *J* 10.23, 9.55 Hz), 3.95 (1 H, dd, *J* 10.38, 4.87 Hz), 3.41 (1 H, t, *J* 10.2 Hz), 3.17 (1 H, dt, *J* 14.45, 4.83 Hz), 2.90 (3 H, s, OMe).

^{13}C NMR: δ 152.0, 145.8, 140.3, 136.3, 133.7, 129.2, 128.8, 128.2, 128.1, 126.2, 102.7, 101.7, 75.7 (C-4), 68.7 (CH_2), 67.6, 64.5, 58.0, 57.8.

MS: m/z (EI) 457 (<1 M^+), 316 (6), 210 (28), 150 (49), 91 (22), 81 (100), 77 (44).

Analysis: Cald. for $C_{22}H_{23}O_6N_3S.1H_2O$: C, 55.57; H, 4.87; N, 8.83; S, 6.74. Found: C, 55.45; H, 5.06; N, 8.78; S, 7.32.

Methyl 2,3-dideoxy-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfonyl-2-*C*-thyminyl-β-D-*gluco*pyranoside 3.007: Compound **1.058** (0.2 g, 0.515 mmol) was converted to a needle shaped crystalline compound **3.007** in 1.5 h following the general procedure described above. Eluent: $CHCl_3$:MeOH (49:1).

Yield: 0.24 g, 90%.

Mp: 234-235 °C [Recrystallized from EtOAc:pet ether (1:3)].

[α]$_D^{26}$: –38° (c 1.10, $CHCl_3$).

IR ($CHCl_3$): 4214, 3394, 2931, 2401, 1693 cm^{-1}.

^{1}H NMR (300 MHz): δ 9.50 (1 H, bs, NH), 7.72 (2 H, d, *J* 7.7 Hz, aromatic), 7.34-7.21 (6 H, m, aromatic), 7.01 (3 H, d, *J* 7.3 Hz), 5.31 (1 H, s, PhCH), 5.21 (1 H, d, *J* 7.3 Hz, H-1), 5.13 (1 H, d, *J* 10.2 Hz), 4.31 (1 H, dd, *J* 10.2, 4.8 Hz), 3.96 (2 H, t, *J* 9.5 Hz), 3.77 (1 H, t, *J* 10.2 Hz), 3.68 (1 H, q), 3.51 (3 H, s, OMe), 1.96 (3 H, s, thymine Me).

^{13}C NMR: δ 164.6, 151.1, 143.9, 140.4, 136.3, 133.8, 129.3, 129.0, 128.3, 128.1, 126.3, 110.8, 101.7, 100.2, 76.2 (C-4), 68.8 (CH_2), 67.3, 63.2, 61.7, 57.8, 12.4 (thymine Me).

MS: m/z (EI) 514 (<1 M^+), 374 (1), 313 (4), 247 (8), 207 (43), 81 (100), 91 (22), 77 (29).

Analysis: Cald. for $C_{25}H_{26}N_2O_8S.0.5H_2O$: C, 57.45; H, 5.20; N, 5.36; S, 6.13. Found: C, 57.36; H, 5.34; N, 5.10; S, 6.27.

Methyl 2-*C*-adeninyl-2,3-dideoxy-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfonyl-β-D-*gluco*pyranoside 3.008: Compound **1.058** (0.12 g, 0.317 mmol) was converted to an amorphous solid **3.008** in 1 h following the general procedure described above. Eluent: $CHCl_3$:MeOH (19:1).

Yield: 0.11 g, 65%.

Mp: 235-236 °C.

[α]$_D^{27}$: –38° (c 0.970, $CHCl_3$).

IR (Nujol): 3666, 3616, 3564, 3350, 3284, 2754, 2678, 1676, 1608 cm^{-1}.

^{1}H NMR: δ 8.22 (1 H, s, adenine H), 7.83 (1 H, s, adenine H), 7.46 (2 H, d, *J* 6.9 Hz, aromatic), 7.32 (4 H, m, aromatic), 7.21 (4 H, m, aromatic), 6.02 (2 H, bs, NH_2), 5.53 (1 H, s, PhCH), 5.46 (1 H, t, *J* 11.2 Hz), 5.14 (1 H, d, *J* 7.9 Hz, H-1), 4.74 (1 H, dd, *J* 11.2, 8.3 Hz), 4.41 (1 H, dd, *J* 15.6, 9.8 Hz), 3.91 (1 H, dd, *J* 10.2, 8.8 Hz), 3.88 (2 H, m), 3.34 (3 H, s, OMe).

^{13}C NMR: δ 155.8, 152.6, 149.7, 143.0, 140.4, 136.5, 133.6, 129.4, 128.8, 128.3, 127.9, 126.4, 120.3, 101.8, 101.1, 76.2 (C-4), 69.0 (CH_2), 67.9, 62.2, 57.9, 56.9.

MS: m/z (EI) 523 (4 M^+), 382 (120), 322 (27), 276 (11), 247 (31), 216 (76), 136 (86), 105 (58), 91 (46), 81 (100), 77 (64).

Analysis: Cald. for $C_{25}H_{25}N_5O_6S.1.5\ H_2O$: C, 54.54; H, 5.12; N, 12.77; S, 5.82. Found: C, 54.61; H, 5.16; N, 12.67; S, 5.98.

Methyl 5-*O*-benzyl-2,3-dideoxy-2-*C*-imidazolyl-3-*C*-(*p*)-tolylsulfonyl-α-D-*arabino*furanoside 3.009: Compound **2.001** (0.23 g, 0.622 mmol) was converted to a needle shaped crystalline compound **3.009** in 12 h following the general procedure described above. Eluent: acetone:$CHCl_3$:pet ether (1:1:3).

Yield: 0.24 g, 90%.

Mp: 158 -159 °C.

$[\alpha]_D^{26}$: +42.2° (c 1.07, $CHCl_3$).

IR ($CHCl_3$): 3757, 3724, 3622, 3111, 1498 cm^{-1}.

^{1}H NMR: δ 7.66 (2 H, d, *J* 7.8 Hz, aromatic), 7.30 (7 H, m, aromatic), 7.08 (1 H, s), 6.91 (2 H, s), 4.98 (1 H, s, H-1), 4.94 (1 H, d, *J* 4.4 Hz, H-1), 4.72 (1 H, dt, *J* 8.3, 2.0 Hz), 4.55 (2 H, dd, *J* 25.9, 12.2 Hz, $PhCH_2$), 4.03 (1 H, q), 3.88 (1 H, dd, *J* 11.2, 1.5 Hz), 3.45 (1 H, dd, *J* 11.2, 2.9 Hz), 3.34 (3 H, s, OMe), 2.43 (3 H, s, aromatic Me).

^{13}C NMR: δ 145.7, 137.4, 136.3, 135.0, 130.2, 128.4, 128.3, 127.7, 116.9, 107.9 (C-1), 77.6, 73.7 (CH_2), 69.5, 68.9 (CH_2), 64.7, 54.9 (OMe), 21.5 (aromatic Me).

MS: m/z (EI) 442 (1.3 M^+), 411 (6), 227 (52), 159 (36), 121 (6), 91 (100).

Analysis: Cald. for $C_{23}H_{26}N_2O_5S$: C, 62.42; H, 5.91; N, 6.33; S, 7.24. Found: C, 62.37; H, 5.91; N, 6.07; S, 7.30.

Methyl 5-*O*-benzyl-2,3-dideoxy-3-*C*-(*p*)-tolylsulfonyl-2-*C*-1,2,4-triazolyl-α-D-*arabino*furanoside 3.010: Compound **2.001** (0.27 g, 0.732 mmol) was converted to a needle shaped crystalline compound **3.010** in 1 h following the general procedure described above. Eluent: EtOAc:pet ether (3:7).

Yield: 0.26 g, 82%.

Mp: 106-107 °C [Recrystallized from EtOAc:pet ether (1:3)].

$[\alpha]_D^{26}$: +53.3° (c 1.01, $CHCl_3$).

IR ($CHCl_3$): 2401, 1720, 1596, 1506, 1454, 1361, 1315, 1305 cm^{-1}.

^{1}H NMR: δ 7.85 (2 H, d, *J* 10.7 Hz), 7.62 (2 H, d, *J* 8.3 Hz, aromatic), 7.33 (5 H, s, aromatic), 7.24 (2 H, d, *J* 8.3 Hz, aromatic), 5.19 (1 H, dd, *J* 6.4, 2.0 Hz), 5.12 (1 H, d, *J* 2.0 Hz, H-1), 4.65 (1 H, d, *J* 11.7 Hz), 4.51 (1 H, d, *J* 12.2 Hz), 4.77 (1 H, m), 4.41 (1 H, dd, *J* 13.2, 6.8 Hz), 3.84 (1 H, dd, *J* 11.2, 2.0 Hz), 3.58 (1 H, dd, *J* 11.2, 2.0 Hz), 3.36 (3 H, s, OMe), 2.40 (3 H, s, aromatic Me).

^{13}C NMR: δ 152.2, 145.5, 143.4, 137.5, 134.5, 129.8, 128.1, 128.0, 127.4, 106.6, 77.3, 73.3 (CH_2), 69.0 (CH_2), 67.0, 66.4, 55.3, 21.3 (aromatic Me).

MS: m/z (EI) 443 (2 M^+), 413 (2), 337 (3), 253 (3), 228 (8), 160 (6), 122 (26), 91 (100).

Analysis: Cald. for $C_{22}H_{25}N_3O_5S$: C, 59.58; H, 5.67; N, 9.47; S, 7.22. Found: C, 59.77; H, 5.96; N, 9.33; S, 7.71.

Methyl 5-*O*-benzyl-2,3-dideoxy-2-*C*-thyminyl-3-*C*-(*p*)-tolylsulfonyl-α-D-*arabino*furanoside 3.011: Compound **2.001** (0.35 g, 0.935 mmol) was converted to a fluffy mass **3.011** in 1 h following the general procedure described above. Eluent: MeOH:acetone:$CHCl_3$ (1:1:18).

Yield: 0.38 g, 82%.

Mp: 65-67 °C.

$[\alpha]_D^{25}$: +21° (c 1.09, $CHCl_3$).

IR ($CHCl_3$): 4214, 3392, 3218, 2929, 2871, 2401, 1689, 1596, 1458, 1377 cm^{-1}.

^{1}H NMR: δ 9.13 (1 H, s, NH), 7.80 (2 H, d, *J* 8.3 Hz, aromatic), 7.32 (7 H, m, aromatic), 7.13 (1 H, s), 5.39 (1 H, d, *J* 6.8 Hz), 4.90 (1 H, s, H-1), 4.59 (3 H, m), 4.16 (1 H, q), 3.97 (1 H, dd, *J* 10.8, 2.0 Hz), 3.74 (1 H, dd, *J* 11.2, 2.9 Hz), 3.26 (3 H, s, OMe), 2.43 (3 H, s, Me), 1.51 (3 H, s, Me).

^{13}C NMR: δ 163.6, 150.3, 145.8, 137.7, 137.4, 134.7, 130.2, 129.1, 128.7, 128.0, 112.3, 106.9, 77.6, 74.0 (CH_2), 69.6 (CH_2), 67.0, 63.4, 55.1 (OMe), 21.7 (aromatic Me), 12.0 (Me).

MS: m/z (EI) 500 (M^+), 468, 379, 285, 217, 79, 65 with <1%, 91 (100).

Analysis: Cald. for $C_{25}H_{28}N_2O_7S$: C, 59.97; H, 5.63; N, 5.59; S, 6.40. Found: C, 59.54; H, 5.29; N, 5.20; S, 7.06.

Methyl 2-*C*-adeninyl-5-*O*-benzyl-2,3-dideoxy-3-*C*-(*p*)-tolylsulfonyl-α-D-*arabino*furanoside 3.012: Compound **2.001** (0.31 g, 0.82 mmol) was converted to an amorphous solid **3.012** in 1 h following the general procedure described above. Eluent: MeOH:acetone:$CHCl_3$ (1:2:97).

Yield: 0.4 g, 96%.

Mp: 61-63 °C.

$[\alpha]_D^{25}$: +45° (c 1.09, $CHCl_3$).

IR ($CHCl_3$): 4214, 3481, 3409, 3355, 3176, 2927, 2869, 2401, 1639, 1596, 1473 cm^{-1}.

^{1}H NMR: δ 8.23 (1 H, s), 7.82 (1 H, s), 7.60 (2 H, d, *J* 8.3 Hz, aromatic), 7.37 (5 H, m, aromatic), 7.11 (2 H, d, *J* 7.9 Hz, aromatic), 5.98 (2 H, bs, NH_2), 5.37 (1 H, dd, *J* 6.4, 2.5 Hz), 5.12 (1 H, d, *J* 2.4 Hz, H-1), 4.85-4.72 (2 H, m), 4.64 (2 H, dd, *J* 28.3, 11.4 Hz, $PhCH_2$), 3.98 (1 H, dd, *J* 11.3, 1.5 Hz), 3.75 (1 H, dd, *J* 11.3, 2.4 Hz), 3.34 (3 H, s, OMe), 2.31 (3 H, s, aromatic Me).

^{13}C NMR: δ 155.8, 152.9, 149.3,145.4, 139.3, 137.8, 134.6, 129.7, 128.5, 128.3, 127.9, 127.7, 119.5, 106.8, 77.3, 73.8 (CH_2), 69.6 (CH_2), 66.1, 62.4, 55.7, 21.5 (aromatic Me).

MS: m/z (EI) 509 (<1 M^+), 478 (1), 418 (1.8), 403 (1.3), 354 (1.6), 294 (18), 219 (14), 188 (21), 136 (14), 91 (100).

Analysis: Cald. for $C_{25}H_{27}N_5O_5S$: C, 58.92; H, 5.33; N, 13.74; S, 6.29. Found: C, 59.06; H, 5.39; N, 13.77; S, 7.10.

Methyl 5-*O*-benzyl-2,3-dideoxy-2-*C*-imidazolyl-3-*C*-(*p*)-tolylsulfonyl-β-D-*ribo*furanoside 3.013: Compound **2.003** (0.39 g, 1.04 mmol) was converted to a cotton like crystalline **3.013** in 4 h following the general procedure described above. Eluent: acetone:$CHCl_3$:pet ether (1:1:3).

Yield: 0.38 g, 82%.

Mp: 128 -129 °C [Recrystallized from $CHCl_3$:pet ether (1:3)].

$[\alpha]_D^{26}$: –1.3° (c 1.12, $CHCl_3$).

IR ($CHCl_3$): 4214, 2966, 2933, 2866, 2401, 2360, 2341, 1596 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 7.33 (9 H, m, aromatic),

7.00 (2 H, d, *J* 11.2 Hz), 4.96 (1 H, s, H-1), 4.88 (1 H, d, *J* 5.9 Hz), 4.79 (1 H, m), 4.46 (2 H, dd, *J* 14.6, 12.2 Hz, $PhCH_2$), 4.26 (1 H, q), 3.59 (1 H, dd, *J* 10.7, 2.0 Hz), 3.34 (1 H, m), 3.30 (3 H, s, OMe), 2.42 (3 H, s, aromatic Me), 2.08 (1 H, broad hump).

^{13}C NMR ($CDCl_3$): δ 145.5, 137.6, 135.2, 130.0, 128.4, 128.1, 127.8, 127.6, 106.9 (C-1), 78.3, 73.3 (CH_2), 71.6 (CH_2), 65.0, 62.7, 54.6 (OMe), 21.7 (aromatic Me).

MS: m/z (EI) 442 (3 M^+), 227(18), 159 (10), 121 (6), 91 (100).

Analysis: Cald. for $C_{23}H_{26}N_2O_5S$: C, 62.42; H, 5.91; N, 6.33; S, 7.24. Found: C, 62.49; H, 6.12; N, 6.34; S, 7.56.

Methyl 5-*O*-benzyl-2,3-dideoxy-2-*C*-thyminyl-3-*C*-(*p*)-tolylsulfonyl-β-D-*xylo*furanoside 3.014: Compound **2.003** (0.24 g, 0.641 mmol) was converted to an amorphous solid **3.014** in 8 h following the general procedure described above.

Eluent: $CHCl_3$:MeOH (99:1).

Yield: 0.26 g, 82%.

Mp: 80-81 °C.

$[\alpha]_D^{25}$: –44° (c 1.12, $CHCl_3$).

IR ($CHCl_3$): 4214, 3678, 3629, 3392, 2931, 2401, 2360, 2343, 1691, 1596, 1465 cm^{-1}.

^{1}H NMR (300 MHz): δ 8.81 (1 H, bs, NH), 7.69 (2 H, d, *J* 8.1 Hz, aromatic), 7.38 (7 H, m, aromatic), 6.83 (1 H, s), 5.56 (1 H, dd, *J* 10.6, 4.7 Hz), 4.91 (1 H, d, *J* 4.4 Hz, H-1), 4.77 (1 H, m), 4.66 (2 H, dd, *J* 18.7, 12.1 Hz, $PhCH_2$), 4.04 (1 H, q), 3.87 (1 H, dd, *J* 10.3, 2.2 Hz), 3.74 (1 H, dd, *J* 10.3, 4.4 Hz), 3.31 (3 H, s, OMe), 2.41 (3 H, s, aromatic Me), 1.63 (3 H, s, pyrimidine Me).

^{13}C NMR (75 MHz): δ 163.4, 151.2, 146.2, 138.0, 137.2, 134.3, 130.2, 128.7, 128.6, 127.9, 127.7, 110.2, 101.4, 76.3, 73.6 (CH_2), 71.9 (CH_2), 63.2, 57.2, 55.3 (OMe), 21.7 (aromatic Me), 12.3 (thymidine Me).

MS: m/z (EI) 500 (6 M^+), 468 (6), 379 (2), 333 (3), 285 (6), 217 (12), 91 (100).

Analysis: Cald. for $C_{25}H_{28}N_2O_7S.1H_2O$: C, 57.89; H, 5.82; N, 5.40; S, 6.18. Found: C, 57.74; H, 5.52; N, 5.38; S, 6.86.

Methyl 2-*C*-adeninyl-5-*O*-benzyl-2,3-dideoxy-3-*C*-(*p*)-tolylsulfonyl-β-D-*ribo*furanoside 3.015: Compound **2.003** (0.38 g, 1.01 mmol) was converted to an amorphous solid **3.015** in 28 h following the general procedure described above. Eluent: MeOH:acetone:$CHCl_3$ (1:2:97).

Yield: 0.31 g, 60%.

Mp: 196 -198 °C.

$[\alpha]_D^{25}$: +27° (c 1.01, $CHCl_3$).

IR (Nujol): 3390, 3338, 3274, 3159, 1658, 1598, 1579 cm^{-1}.

^{1}H NMR: δ 8.20 (1 H, s), 7.99 (1 H, s), 7.37 (7 H, m, aromatic), 7.08 (2 H, d, *J* 8.3 Hz, aromatic), 5.95 (2 H, bs, NH_2), 5.40 (1 H, d, *J* 5.4 Hz), 5.18 (1 H, m), 5.14 (1 H, s, H-1), 4.58 (2 H, dd, *J* 17.6, 12.3 Hz, $PhCH_2$), 4.35 (1 H, t, *J* 7.3 Hz), 3.69 (1 H, dd, *J* 10.8, 2.9 Hz), 3.56 (1 H, dd, *J* 10.7, 6.3 Hz), 3.35 (3 H, s, OMe), 2.36 (3 H, s, aromatic Me).

^{13}C NMR: δ 155.7, 153.1, 150.6, 145.7, 140.0, 137.9, 135.2, 130.0, 128.7, 128.0, 119.5, 107.4 (C-1), 78.2, 73.7 (CH_2), 72.7 (CH_2), 64.5, 58.7, 55.4 (OMe), 21.8 (aromatic Me).

MS: m/z (EI) 354 (4), 219 (6), 188 (4), 154 (3), 136 (22), 91 (100).

Analysis: Cald. for $C_{25}H_{27}N_5O_5S$: C, 58.92; H, 5.33; N, 13.74; S, 6.29. Found: C, 59.44; H, 5.19; N, 13.13; S, 6.58.

Methyl 5-*O*-benzyl-2,3-dideoxy-3-*C*-(*p*)-tolylsulfonyl-2-*C*-1,2,4-triazolyl-β-D-*xylo*furanoside 3.016 and methyl 5-*O*-benzyl-2,3-dideoxy-3-*C*-(*p*)-tolylsulfonyl-2-*C*-1,2,4-triazolyl-β-D-*ribo*furanoside 3.017: Compound **2.003** (0.27 g, 0.732 mmol) was converted to the mixture of **3.016** and **3.017** (0.22 g, 75%) in 28 h following the general procedure described earlier. Eluent: EtOAc:pet ether (3:7).

Compound 3.016:

Yield: 0.08 g

Mp: 179-180 °C.

[α]$_D^{26}$: –5.0° (c 1.06, $CHCl_3$).

IR ($CHCl_3$): 4214, 3786, 3681, 3620, 2399, 2360, 2341, 1753, 1596, 1504, 1452 cm^{-1}.

^{1}H NMR: δ 7.76 (1 H, s), 7.65 (1 H, s), 7.49 (2 H, d, *J* 8.3 Hz, aromatic), 7.36 (5 H, m, aromatic), 7.16 (2 H, d, *J* 8.3 Hz, aromatic), 5.17 (1 H, dd, *J* 9.0, 3.6 Hz), 5.05 (1 H, d, *J* 3.9 Hz, H-1), 4.92 (1 H, dt, *J* 8.05, 3.4 Hz), 4.68 (3 H, s, $PhCH_2$ +1 H), 4.11 (2 H, m), 3.40 (3 H, s, OMe), 2.37 (3 H, s, aromatic Me).

^{13}C NMR (50 MHz, $CDCl_3$): δ 152.8, 145.7, 144.2, 138.1, 135.7, 130.1, 128.5, 128.0, 127.7, 108.1 (C-1), 78.9, 73.7 (CH_2), 69.8 (CH_2), 67.4, 66.3, 56.7, 21.7 (aromatic Me).

MS: m/z (EI) 443 (6 M$^+$), 412 (9), 255 (11), 228 (6), 91 (100).

Analysis: Cald. for $C_{22}H_{25}N_3O_5S$: C, 59.58; H, 5.67; N, 9.47; S, 7.22. Found: C, 59.92; H, 5.29; N, 9.36; S, 7.45.

Compound 3.017:

Yield: 0.02 g (Separated by recrystallization)

Mp: 82-83 °C [Recrystallized from EtOAc:pet ether (1:4)].

[α]$_D^{26}$: +13.7° (c 1.00, $CHCl_3$).

IR ($CHCl_3$): 4214, 3681, 3629, 2432, 2399, 2360, 1598, 1527, 1502, 1425 cm^{-1}.

^{1}H NMR: δ 8.25 (1 H, s), 7.92 (1 H, s), 7.54 (2 H, d, *J* 8.3 Hz, aromatic), 7.36-7.25 (7 H, m, aromatic), 5.14 (1 H, d, *J* 5.9 Hz), 5.08 (1 H, s, H-1), 4.75 (1 H, m), 4.42 (3 H, dd, *J* 22.4, 12.2 Hz, $PhCH_2$ +1 H), 3.72 (1 H, dd, *J* 11.3, 1.5 Hz), 3.38-3.26 (1 H, m), 3.34 (3 H, s, OMe), 2.44 (3 H, s, aromatic Me).

^{13}C NMR (125 MHz, $CDCl_3$): δ152.2, 145.8, 138.1, 135.9, 130.2, 128.6, 128.0, 127.7, 106.2, 78.9, 73.6 (CH_2), 70.8 (CH_2), 65.4, 64.1, 54.9 (OMe), 21.9 (aromatic Me).

MS: m/z (EI) 443 (10 M^+), 337 (7), 253 (12), 228 (25), 122 (10), 91 (100).

Analysis: Cald. for $C_{22}H_{25}N_3O_5S$: C, 59.58; H, 5.67; N, 9.47; S, 7.22. Found: C, 59.48; H, 5.64; N, 9.66; S, 7.69.

3.7 References

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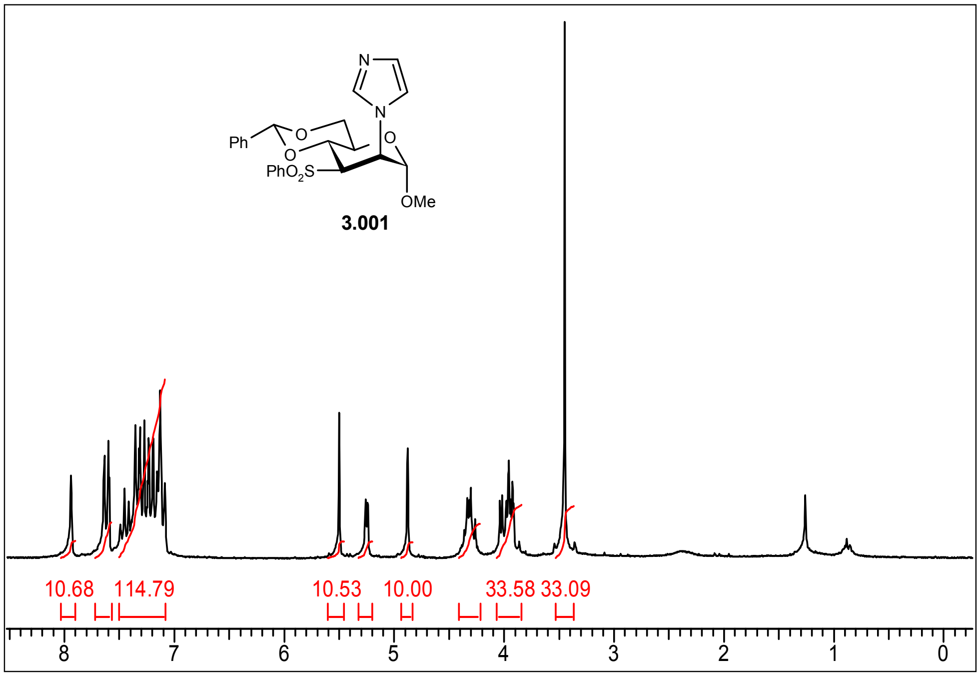
3.8 Spectra

^{1}H NMR of **3.001**



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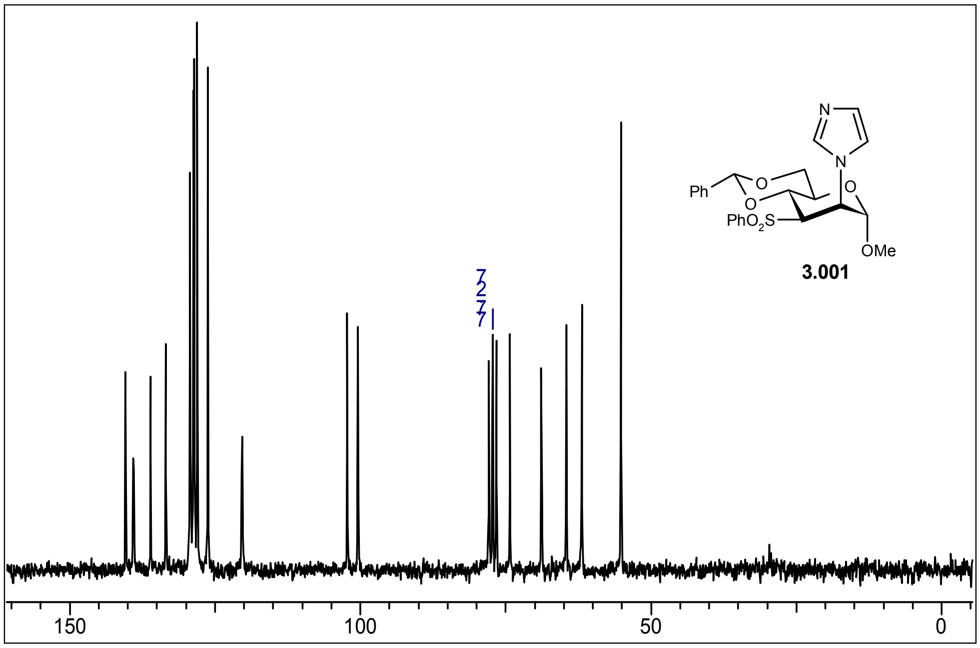
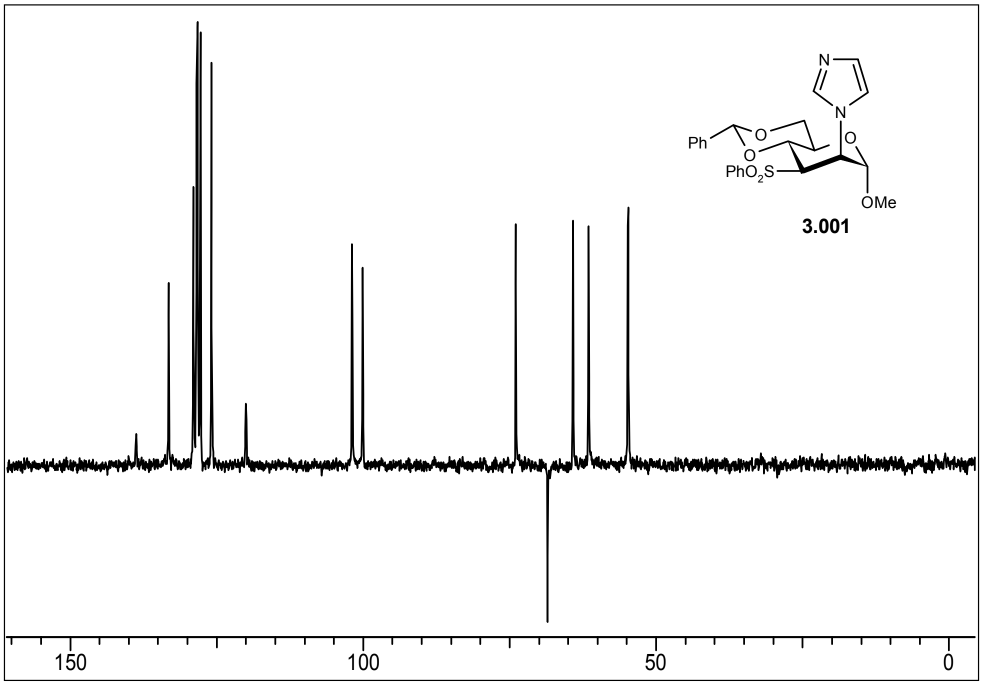


Dept of **3.001**



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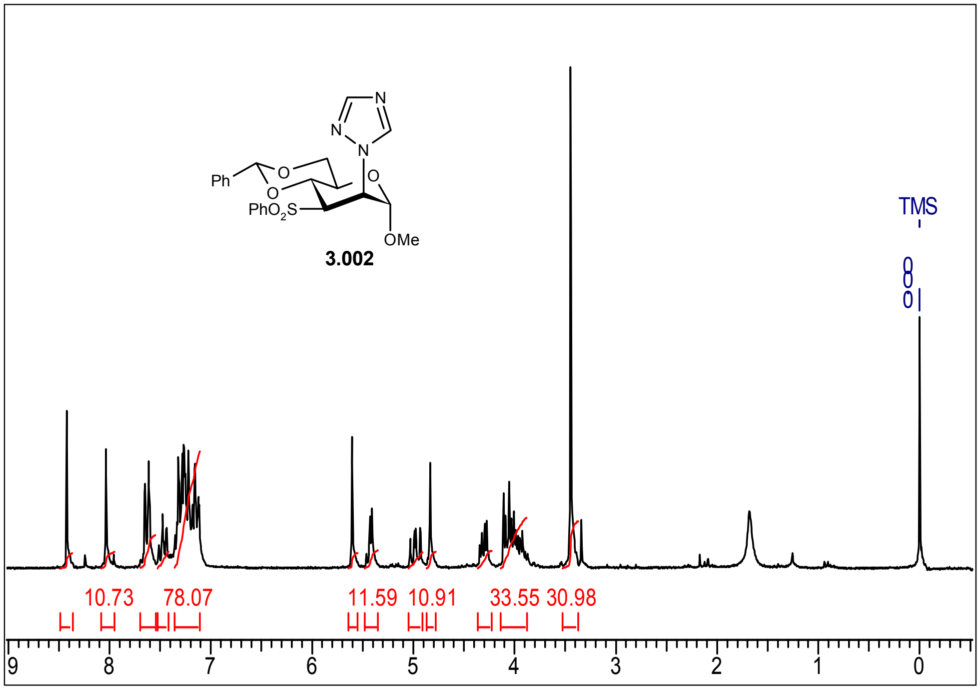

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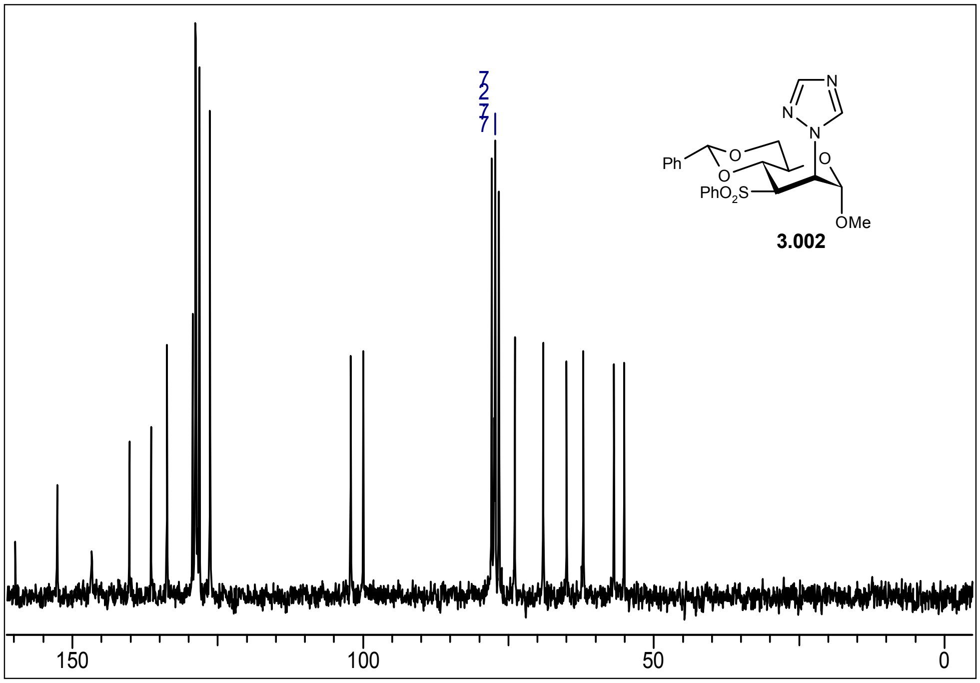

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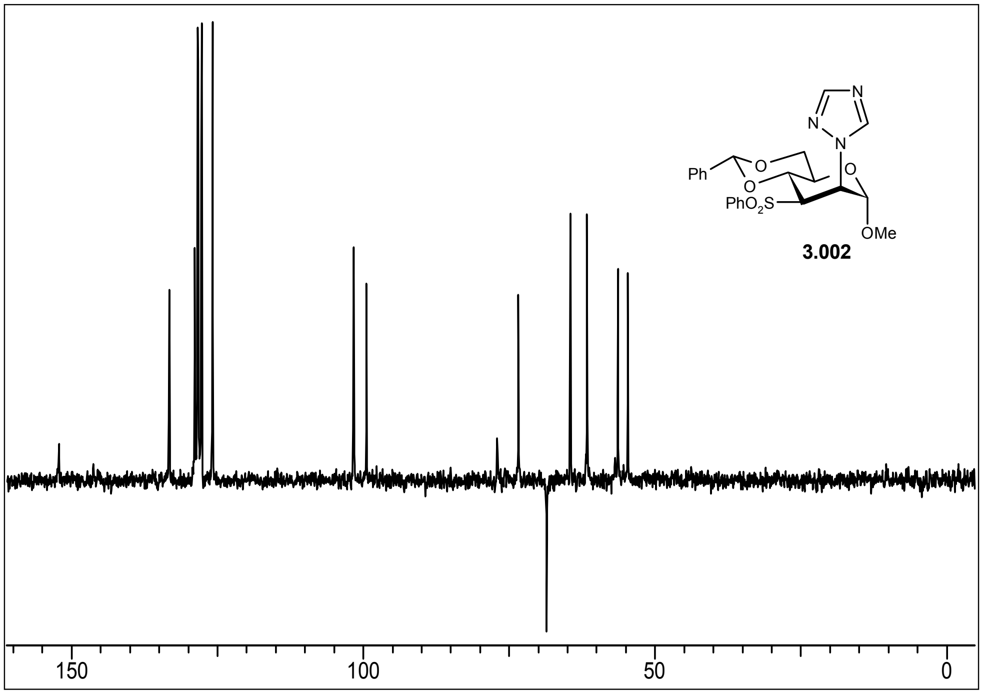

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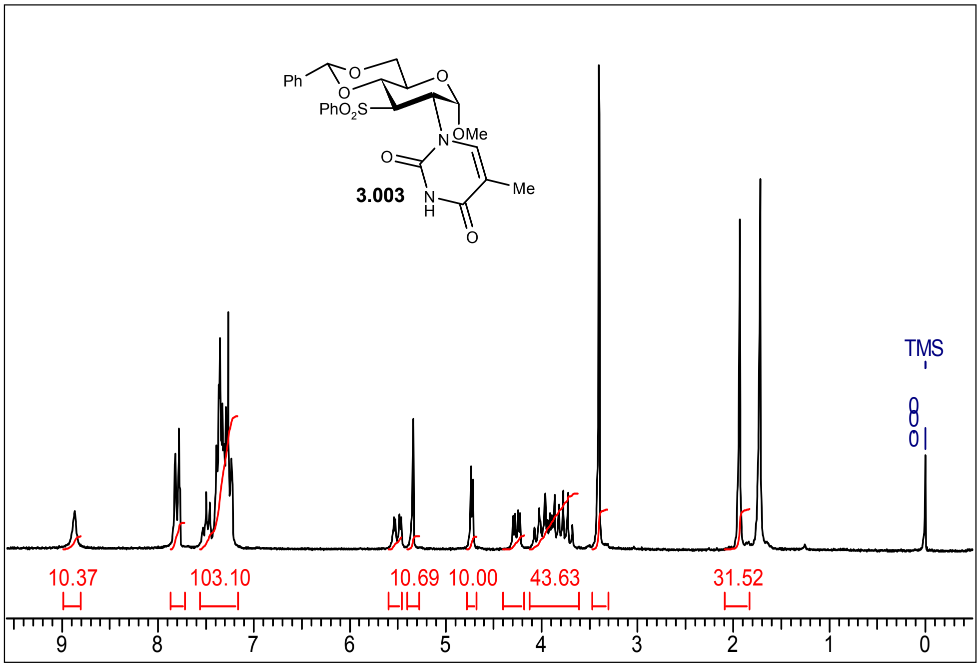

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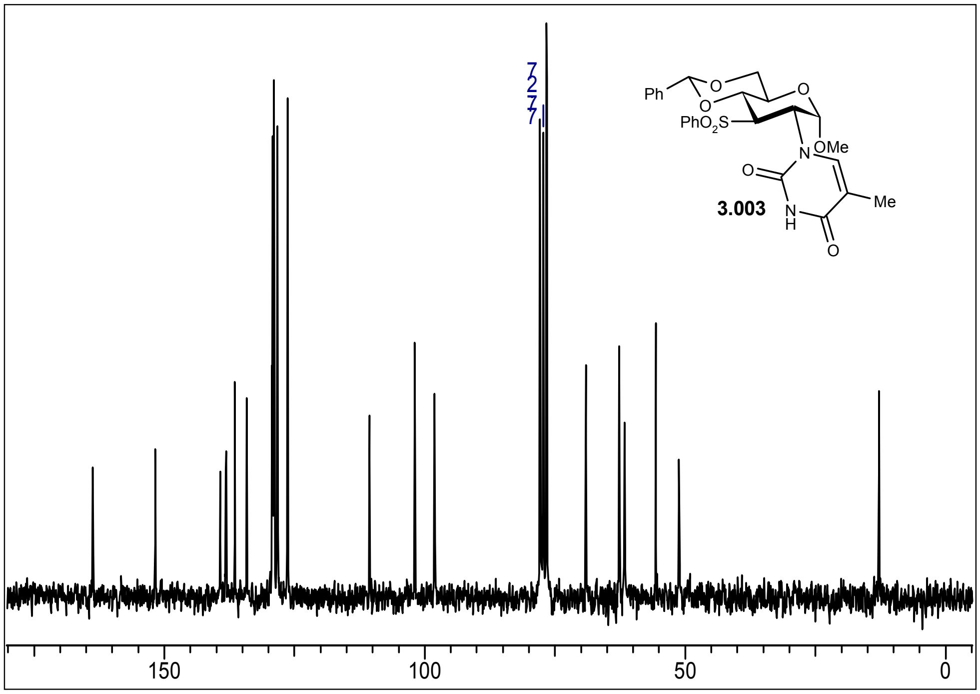

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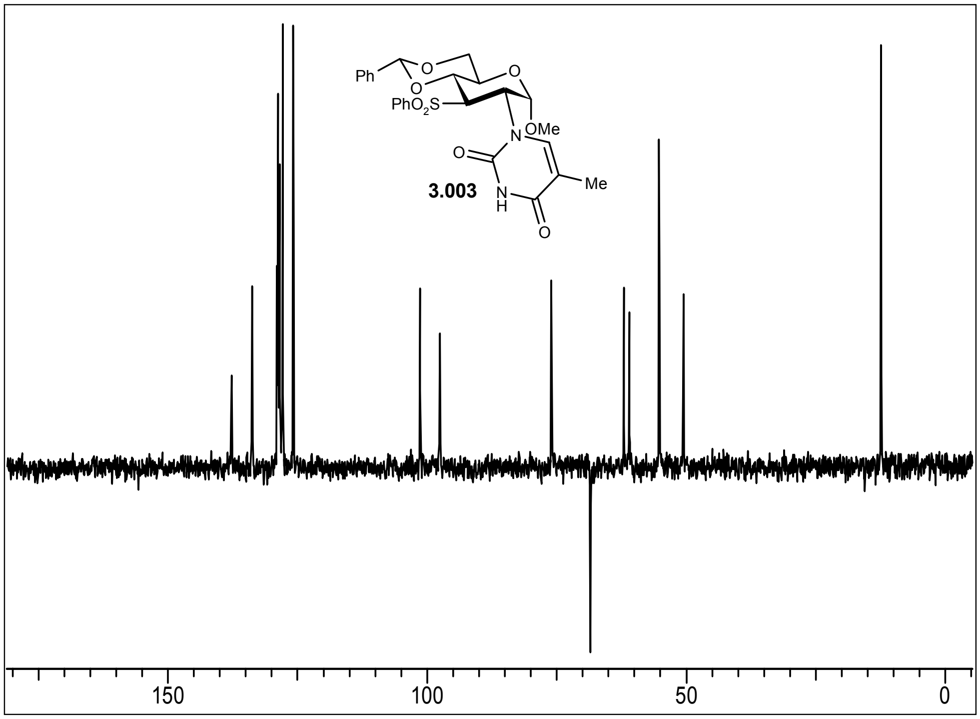

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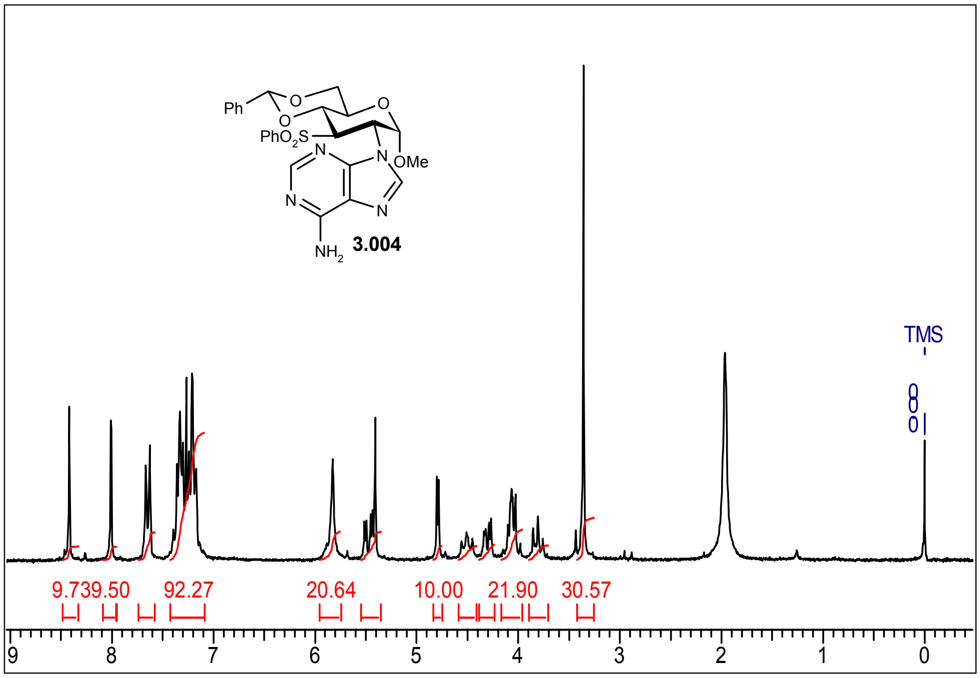

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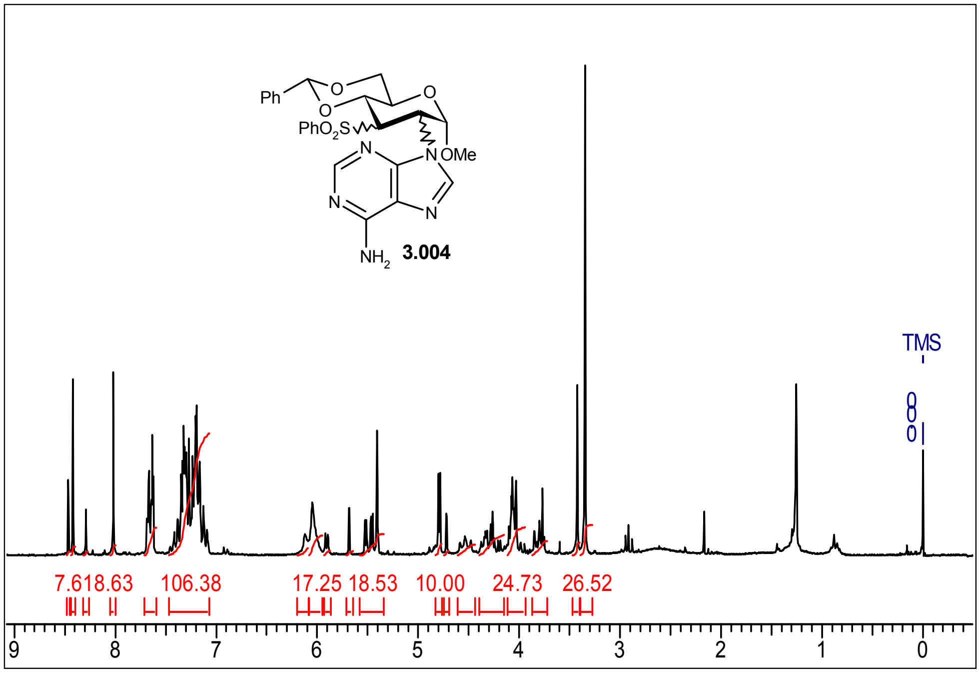

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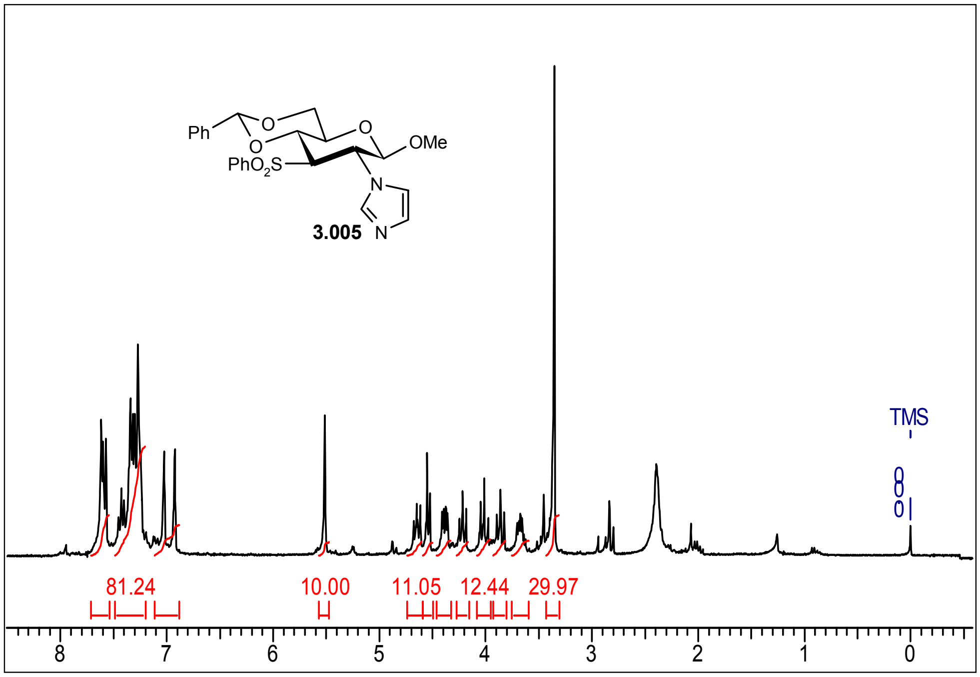

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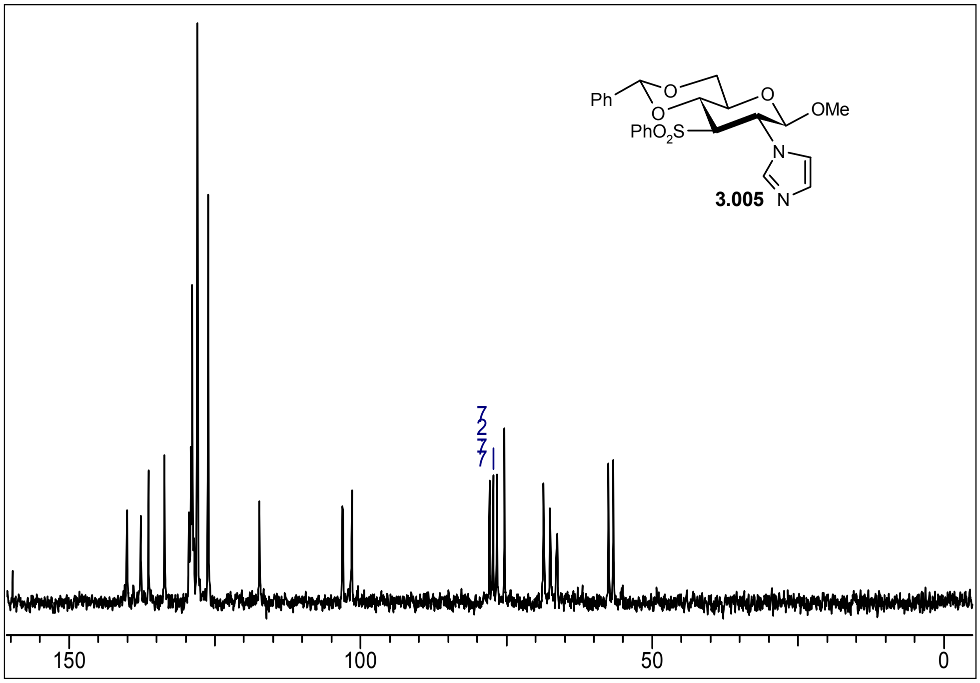

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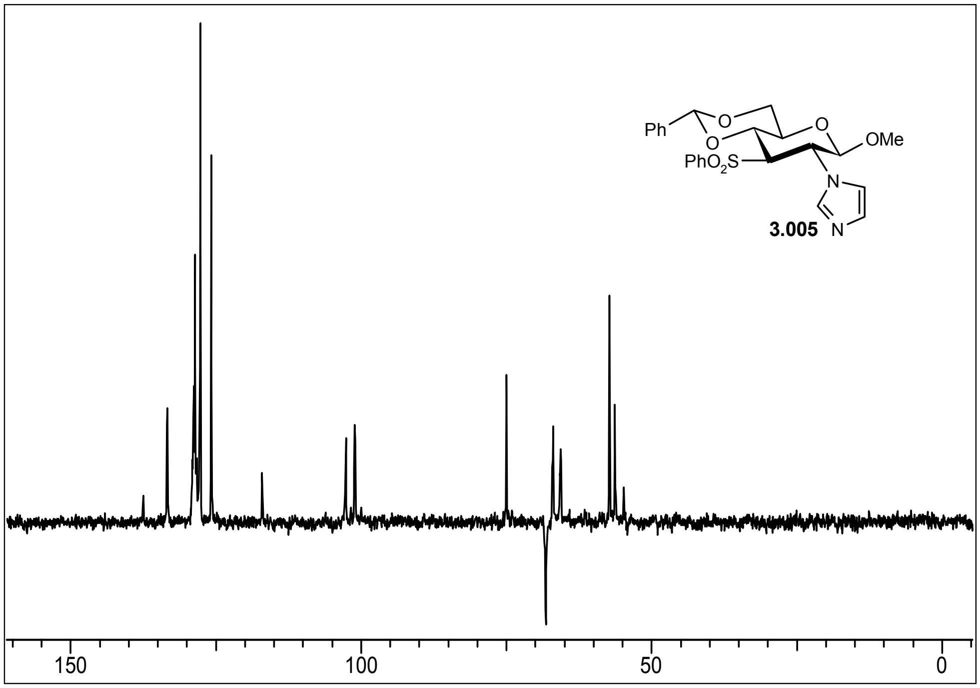

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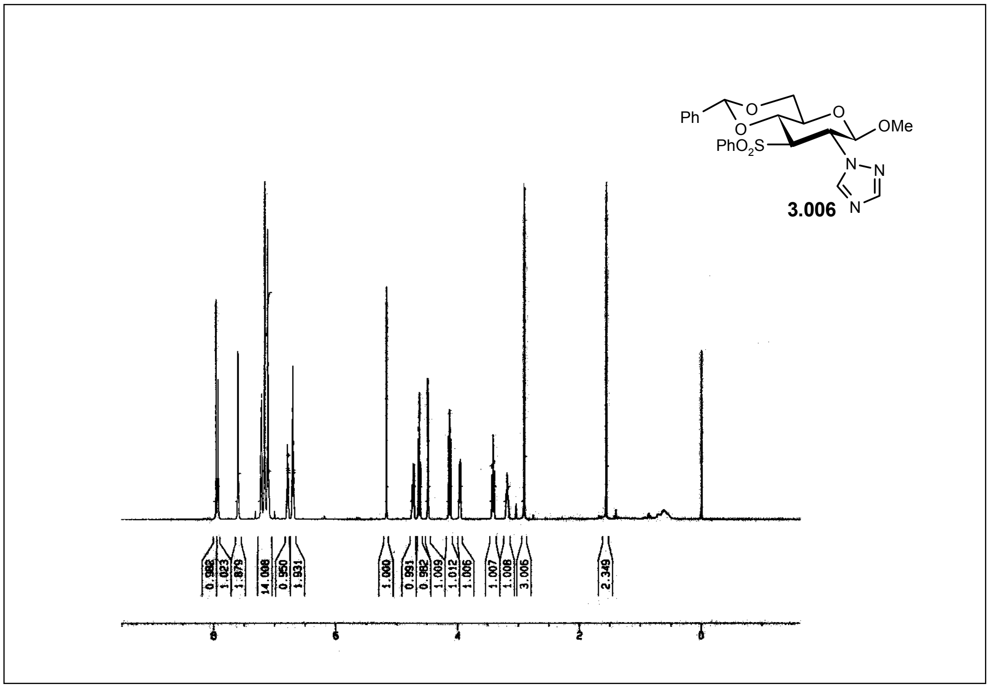

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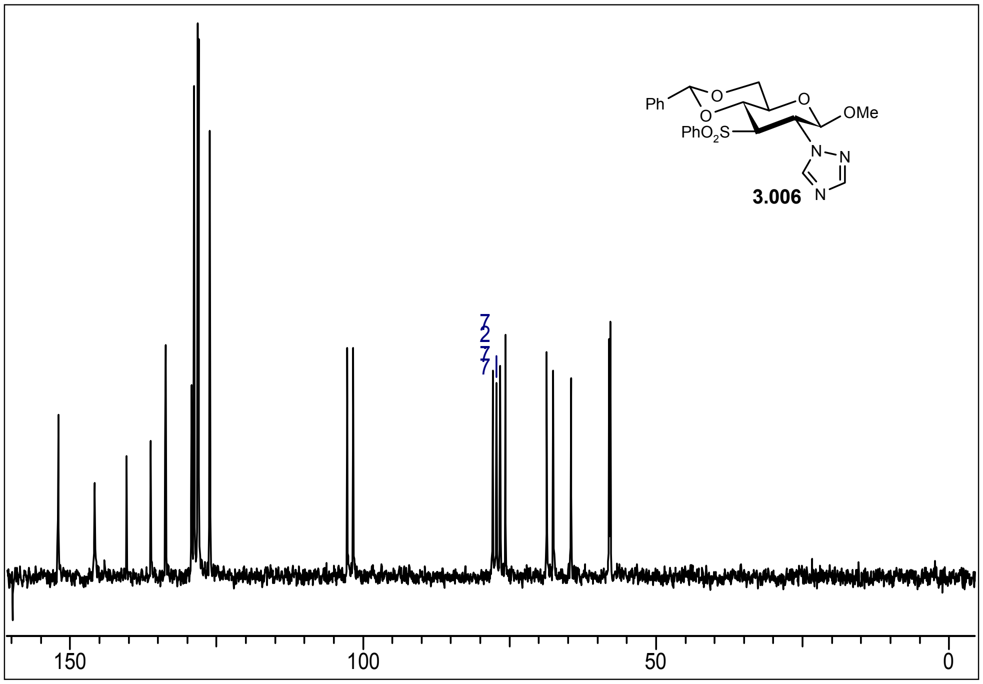

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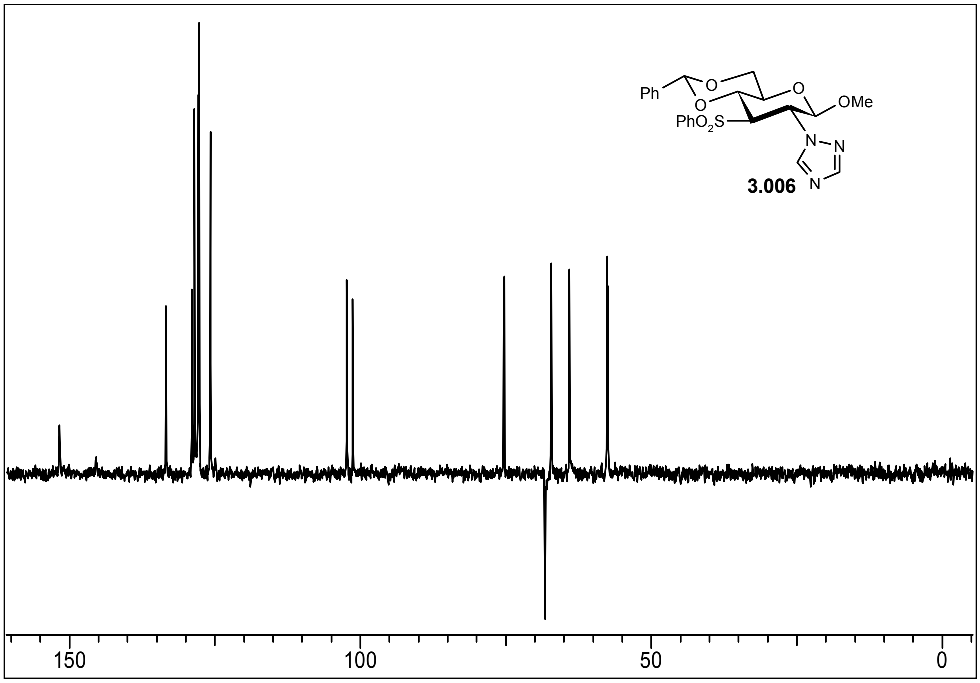

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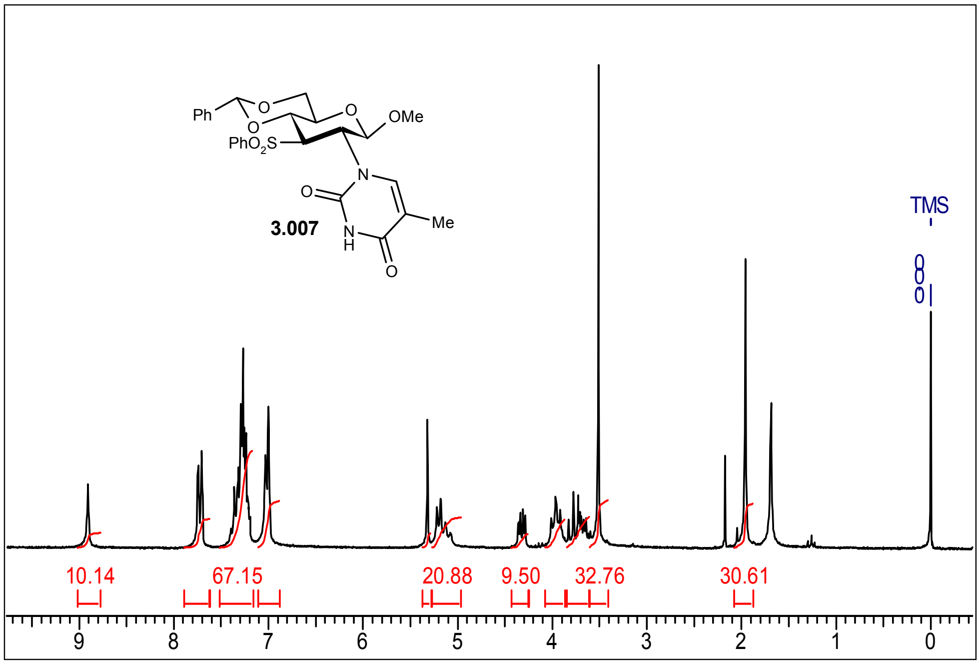

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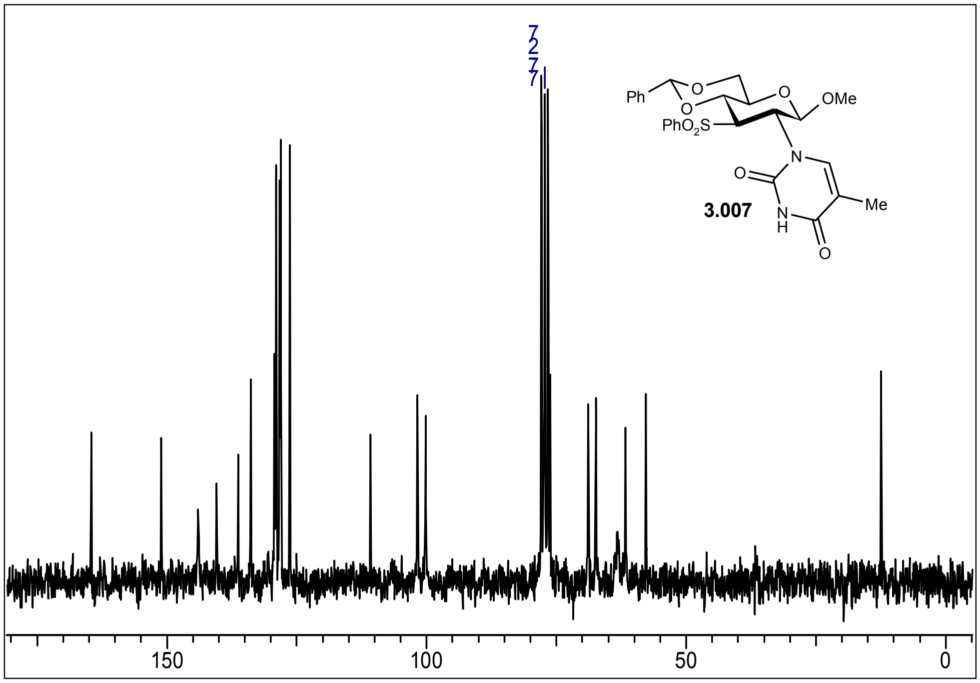

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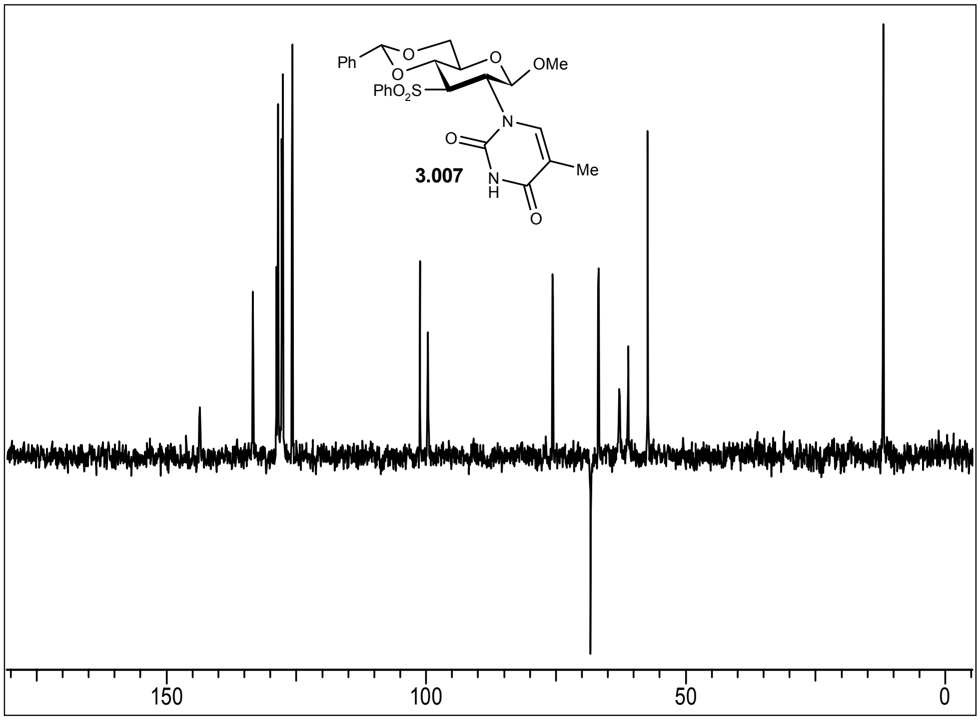

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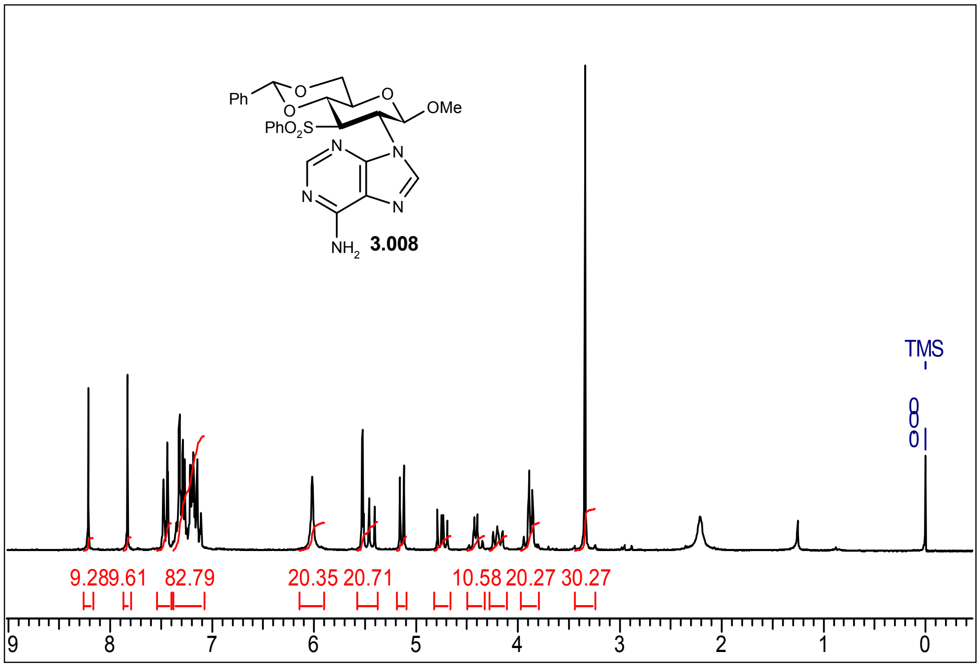
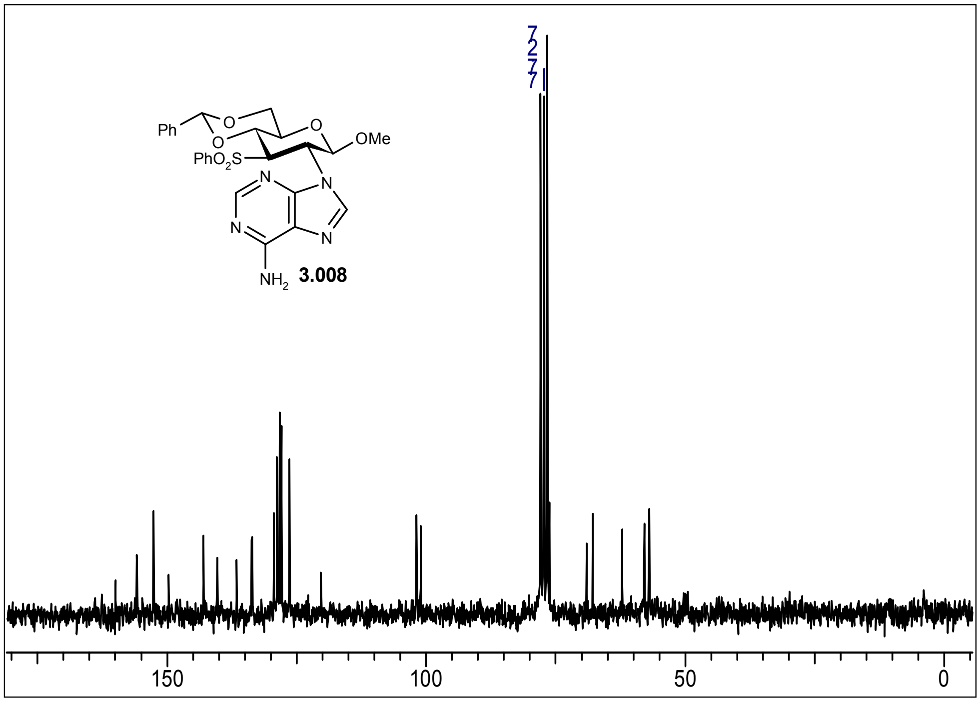


^{13}C NMR of **3.008**



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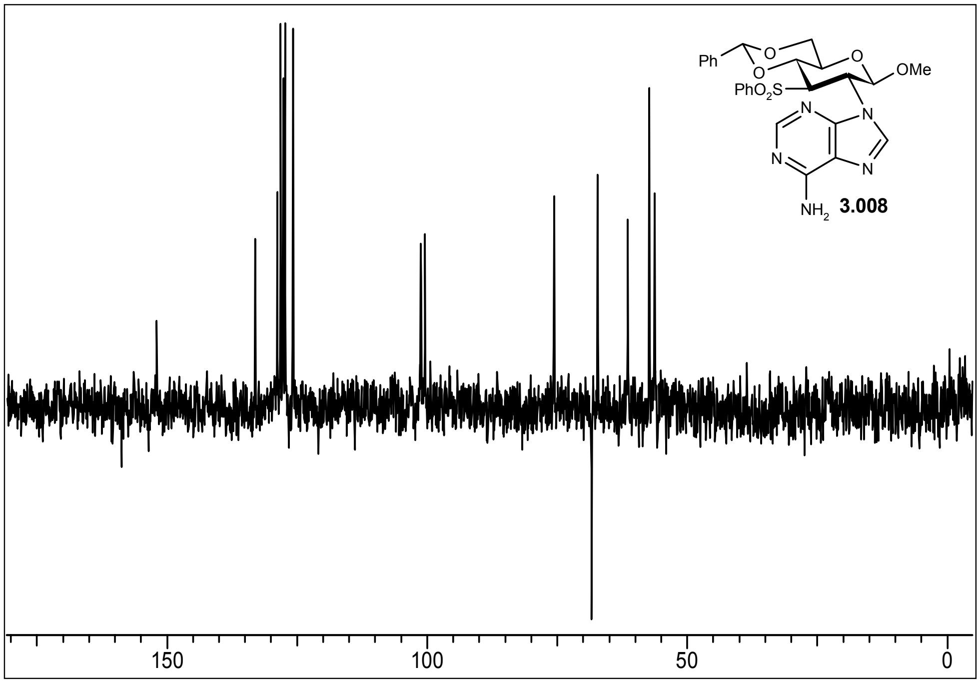

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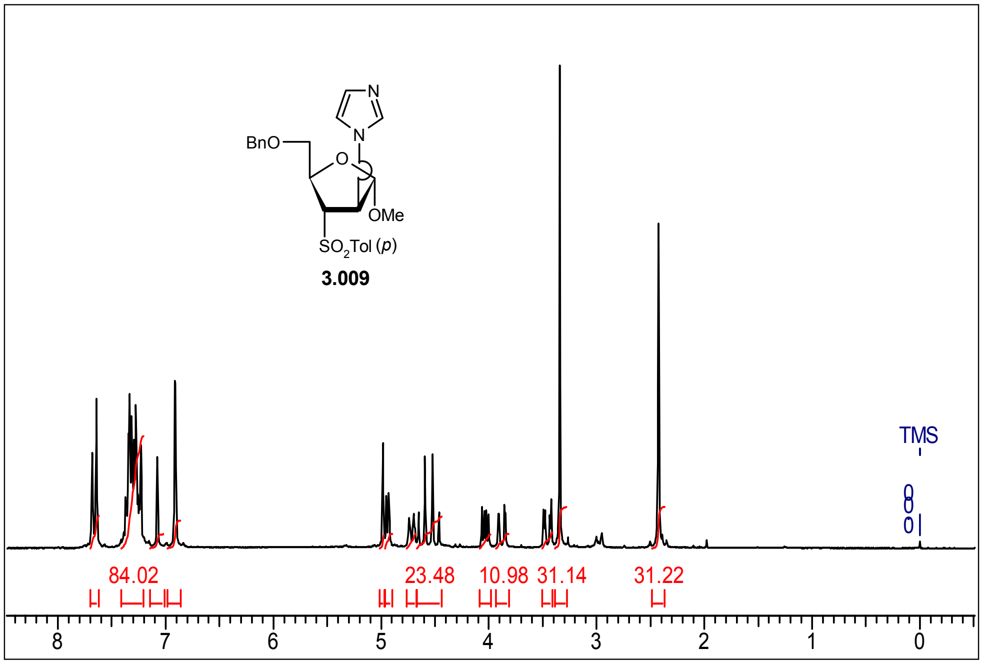

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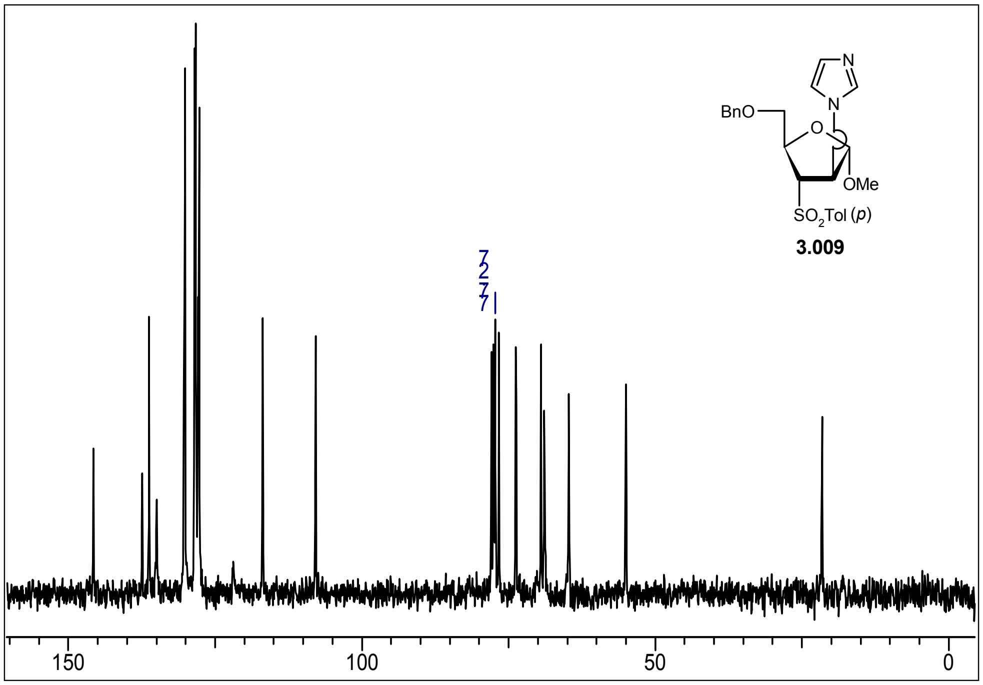

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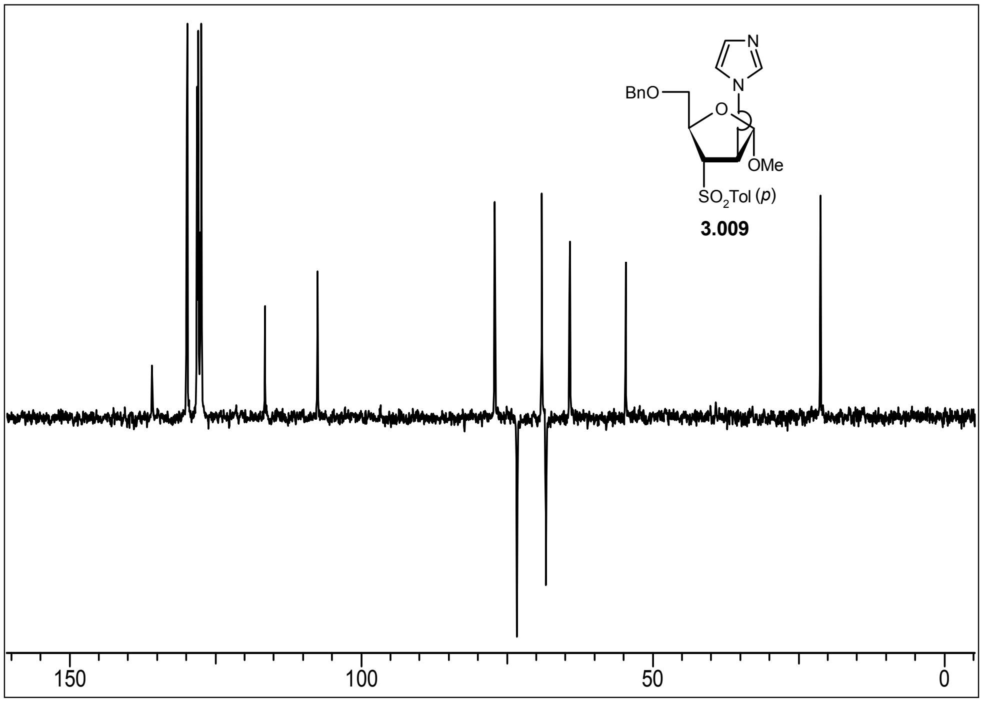

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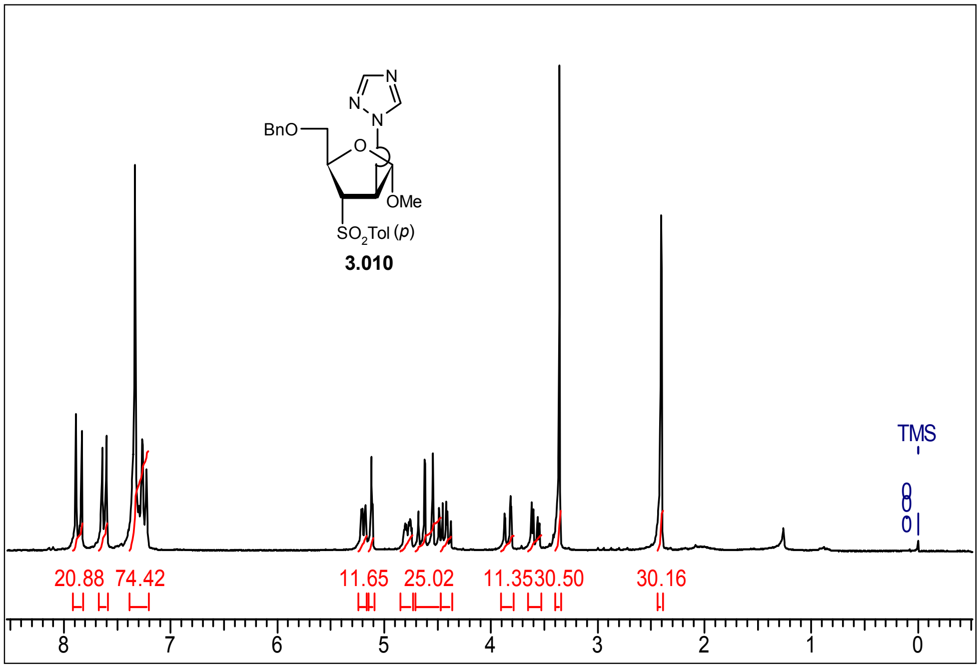

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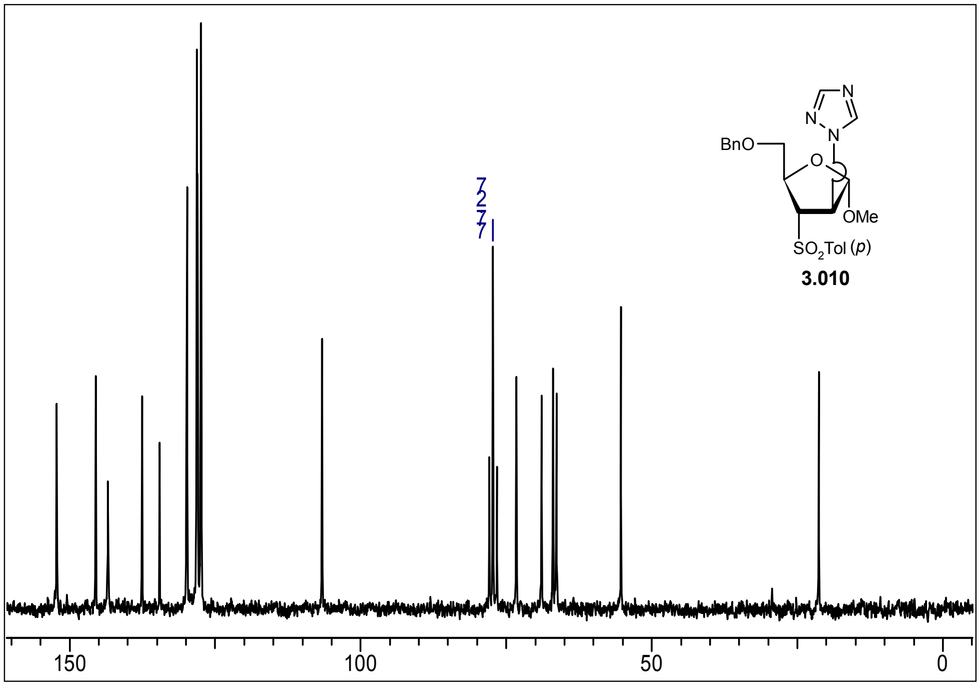

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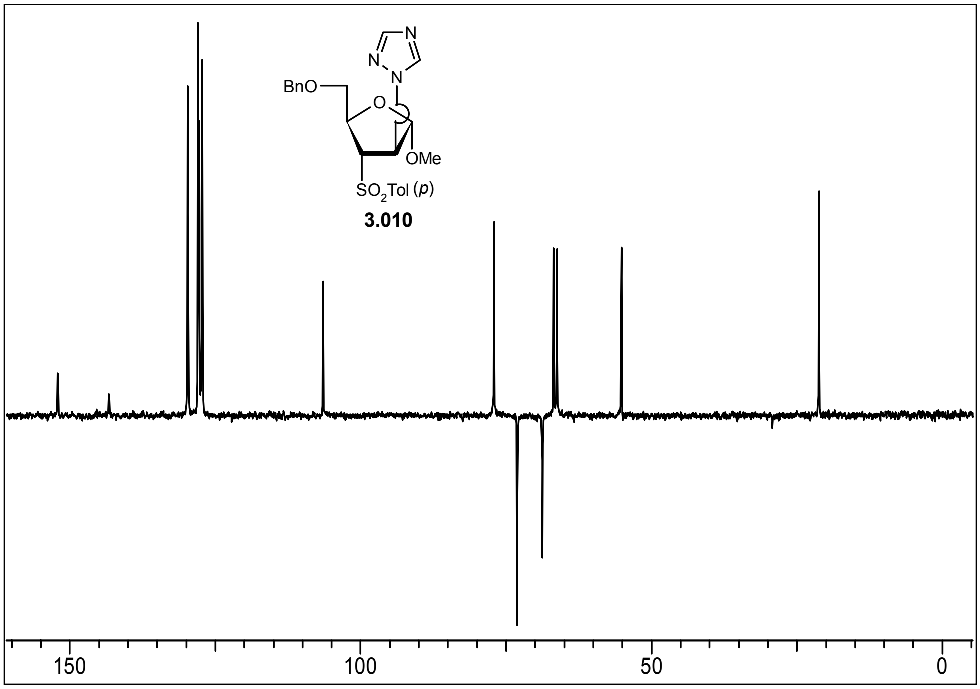

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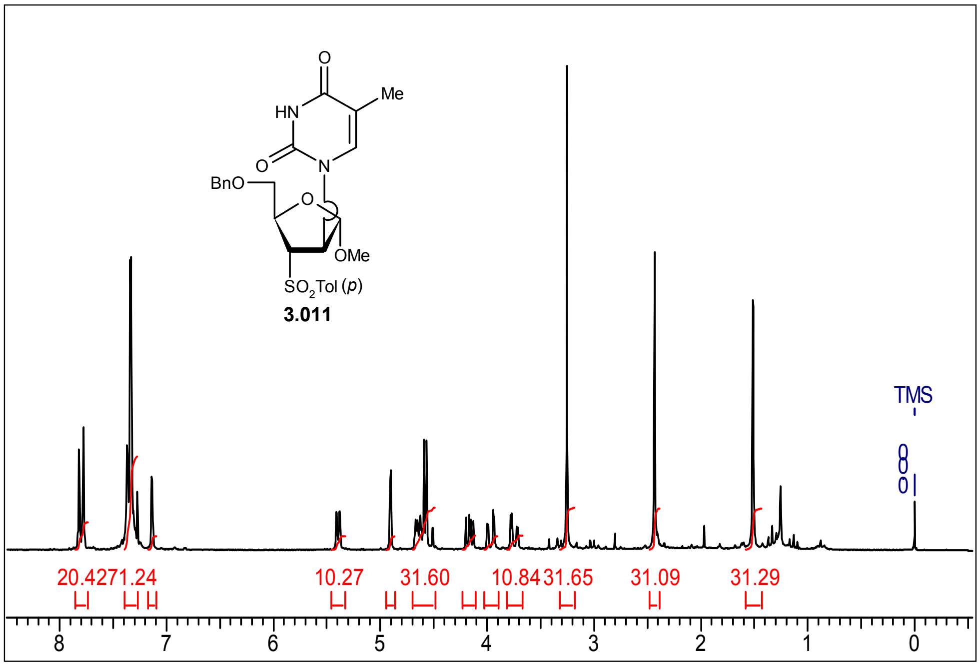
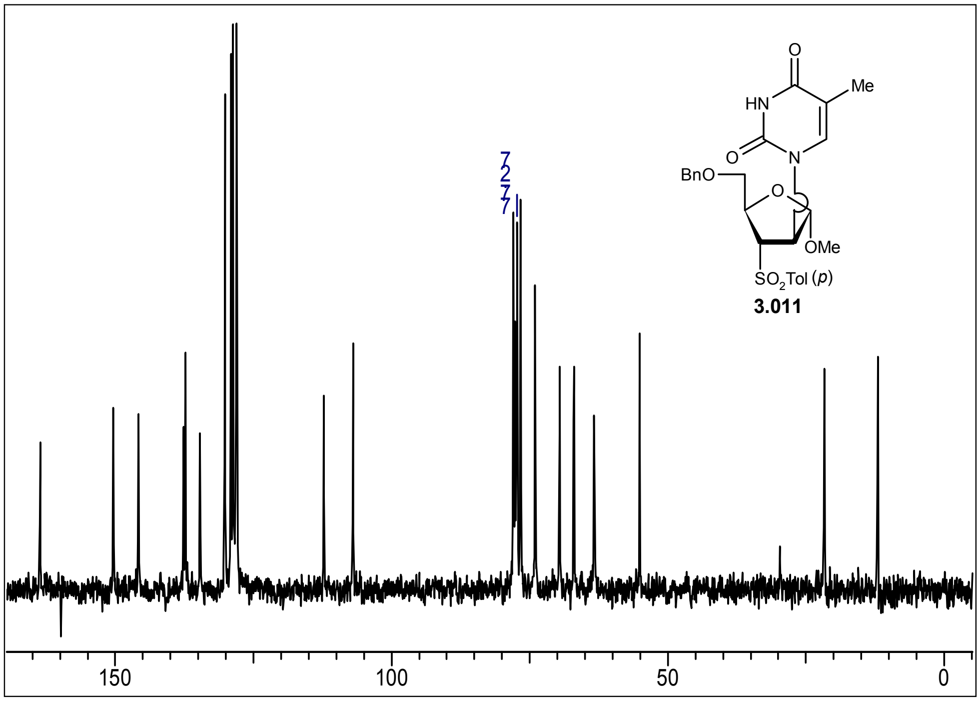
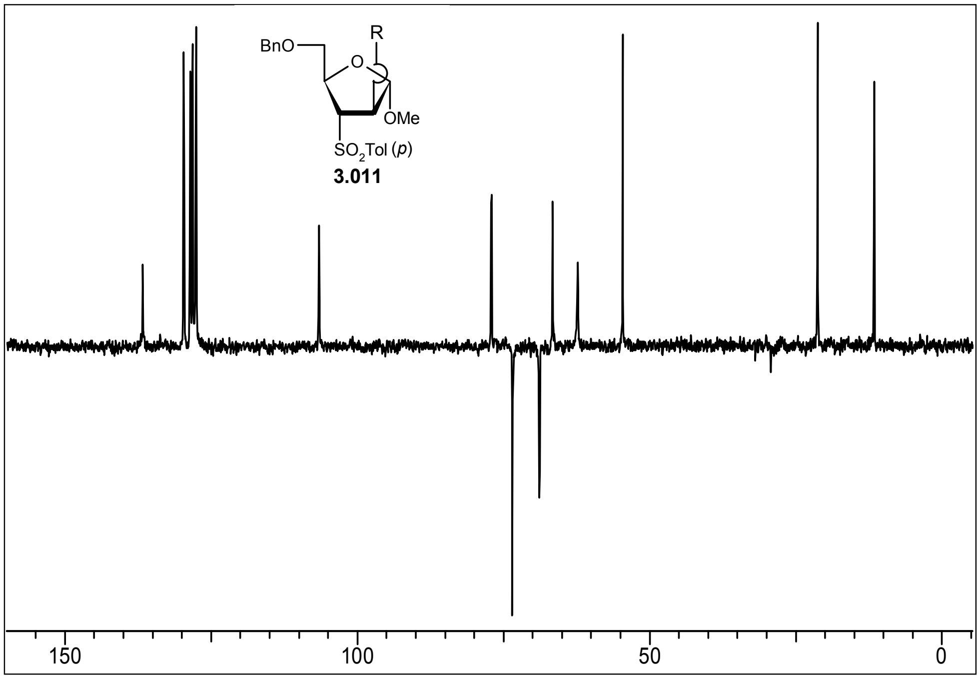


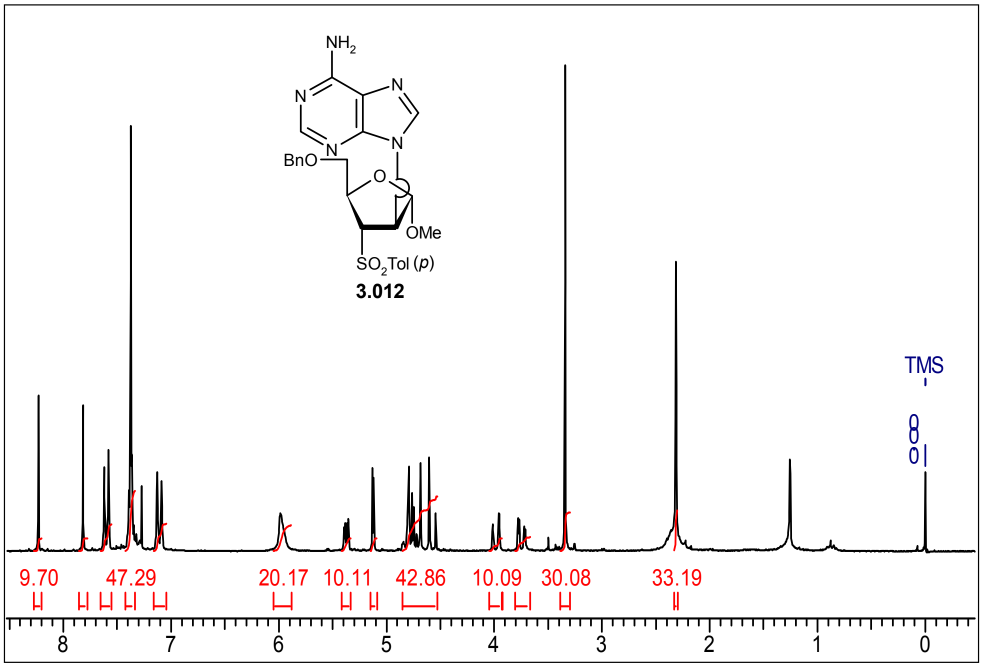
^{13}C NMR of **3.011**



Dept of **3.011** (R = Thyminyl)



^1H NMR of **3.012**



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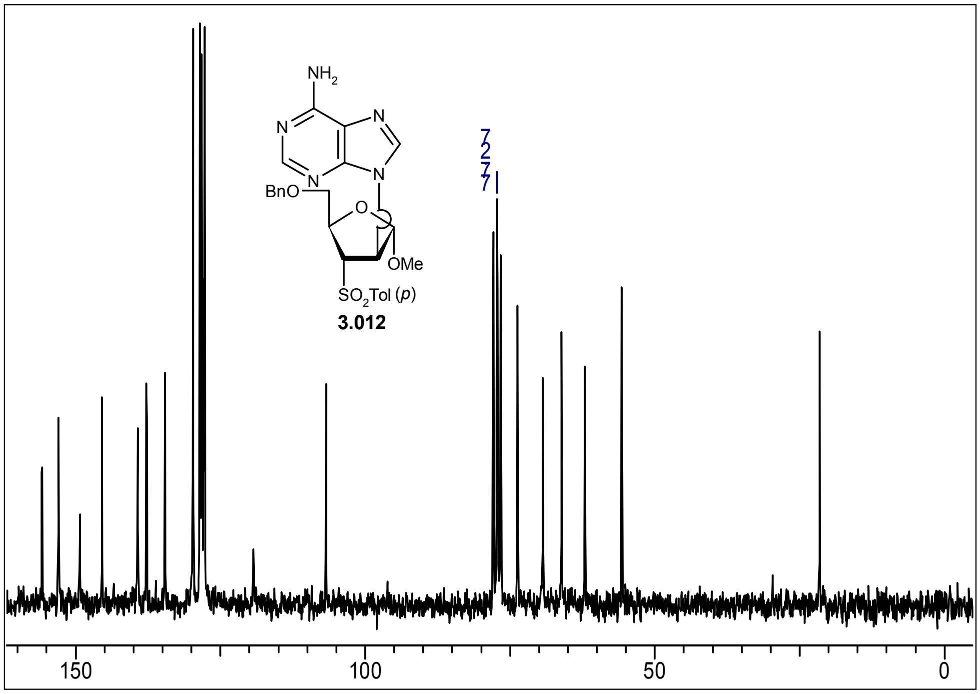

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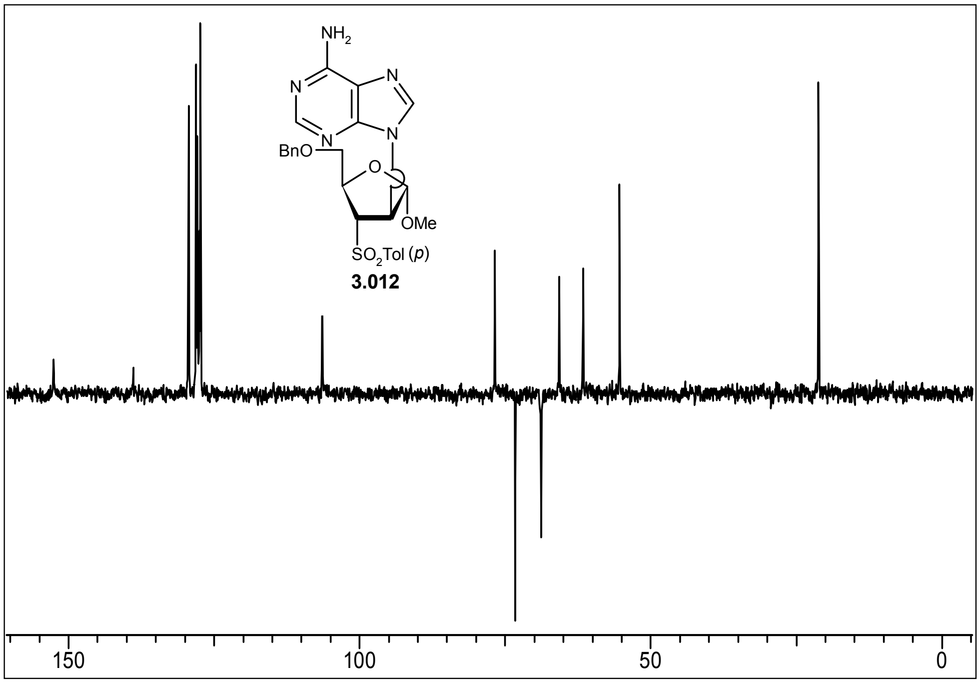

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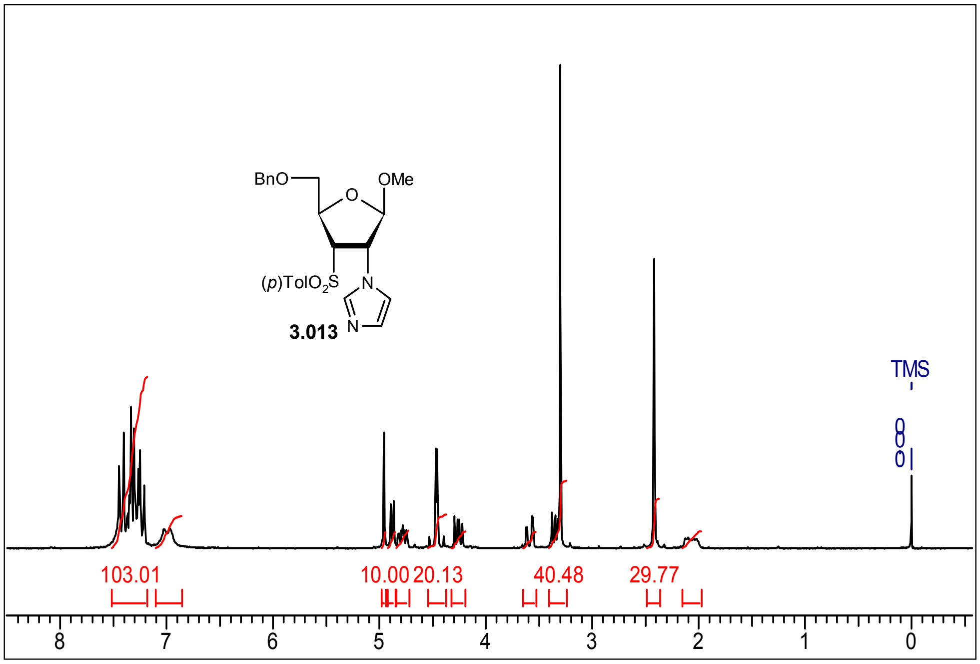

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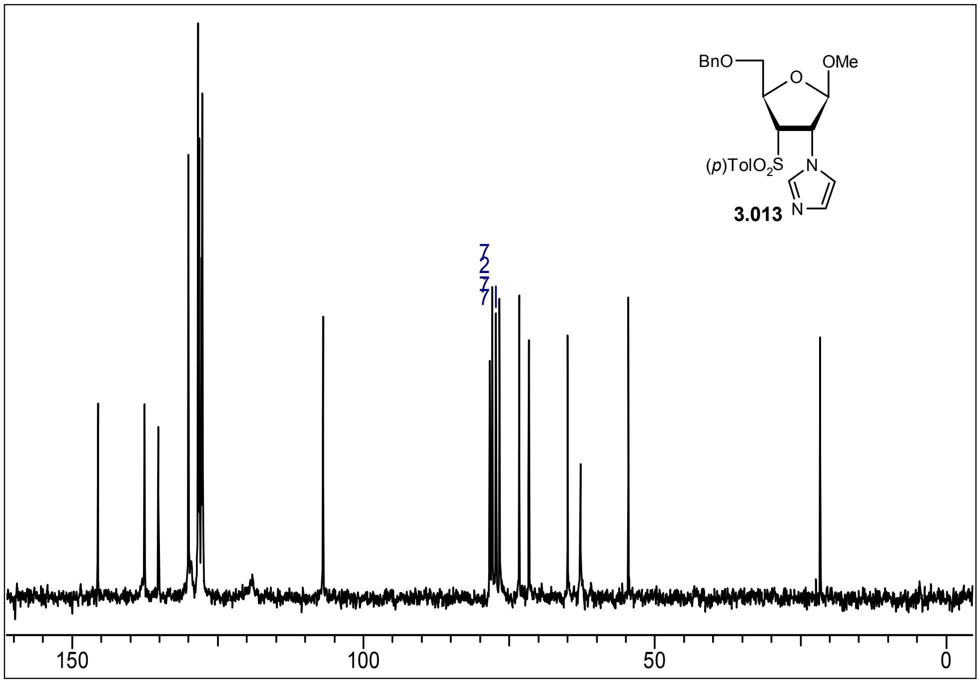

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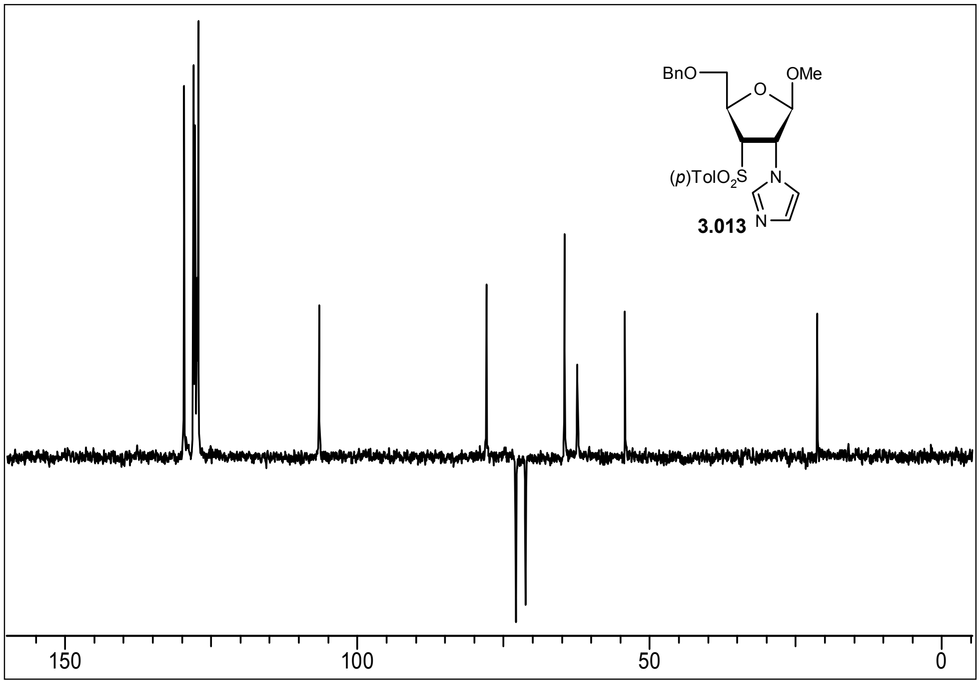

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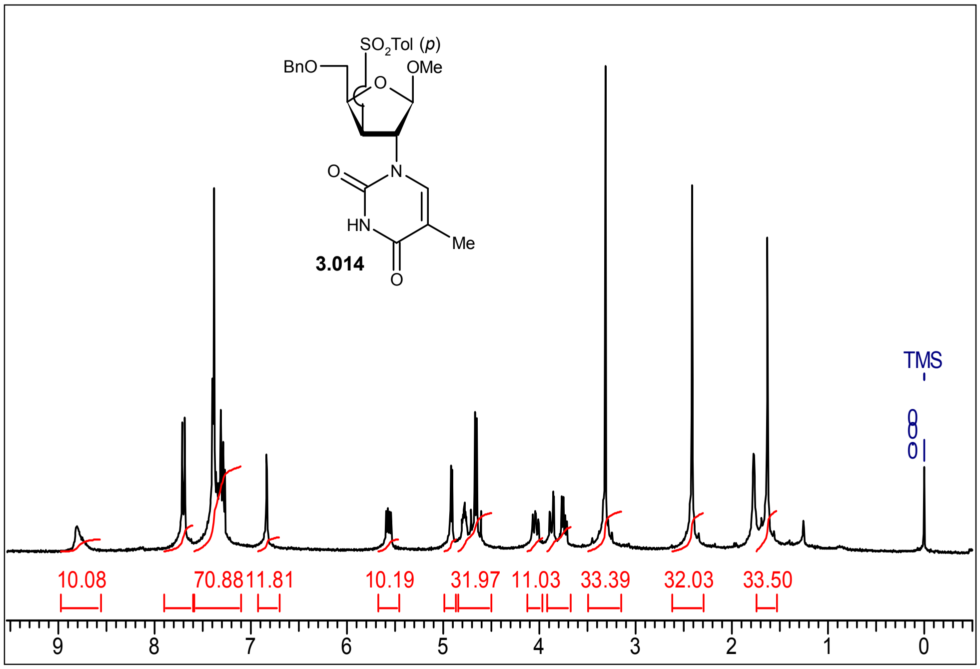

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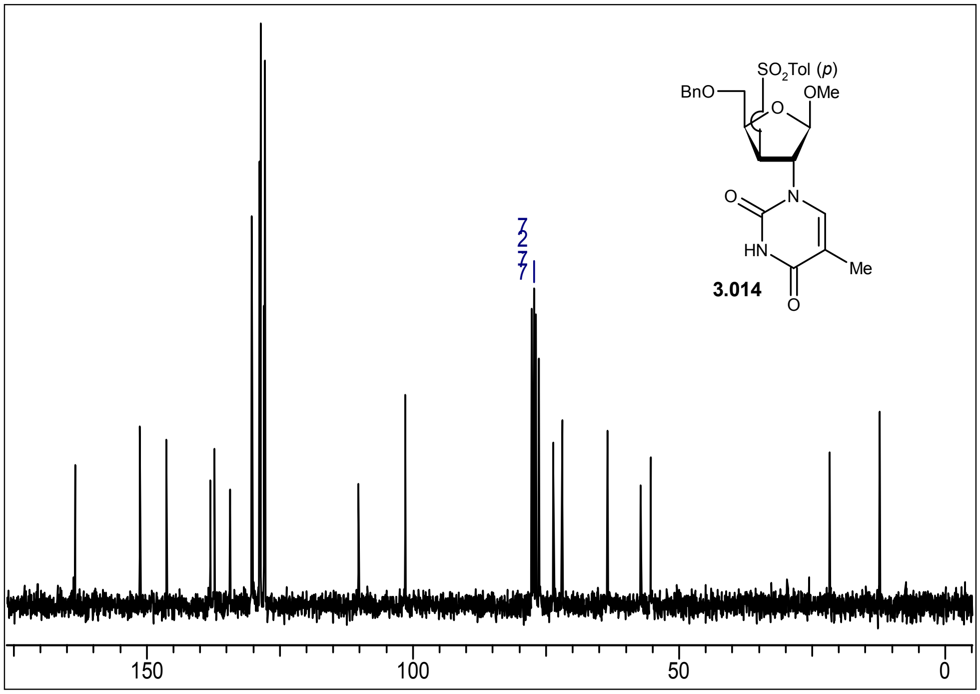

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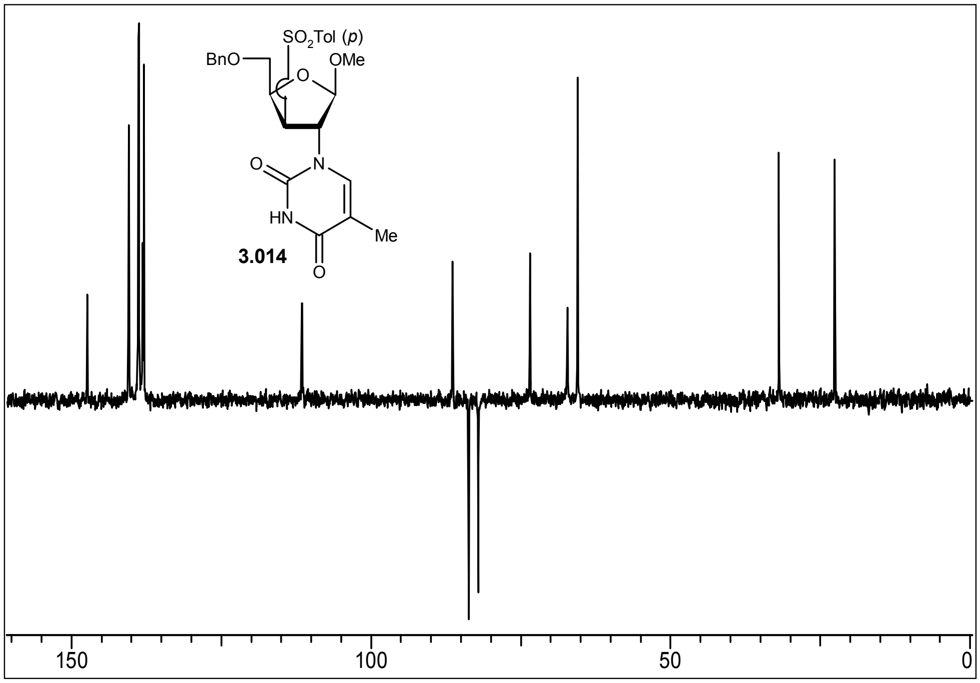

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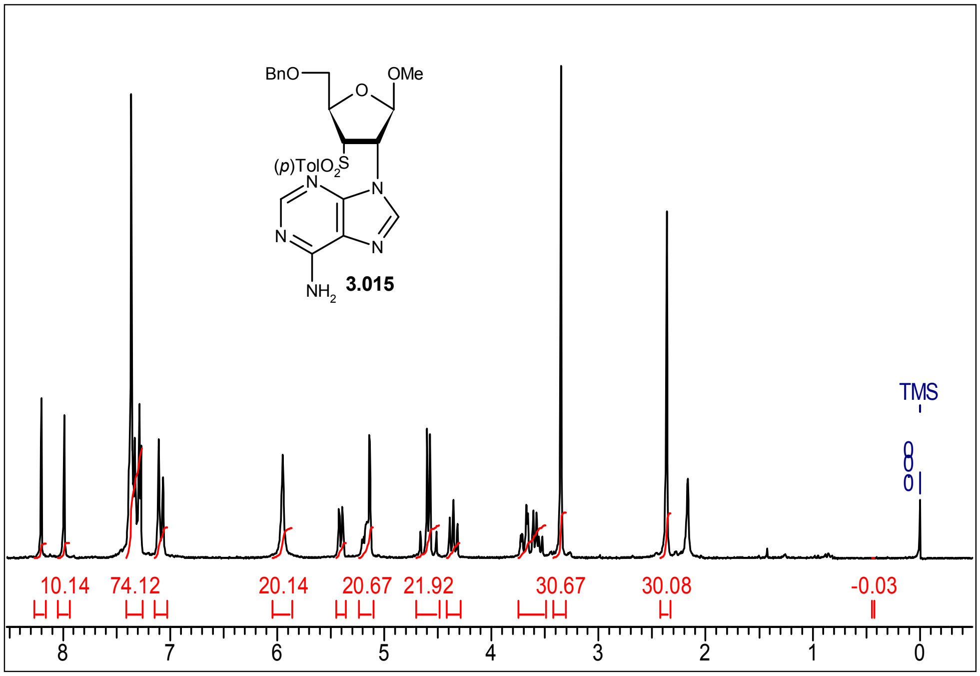

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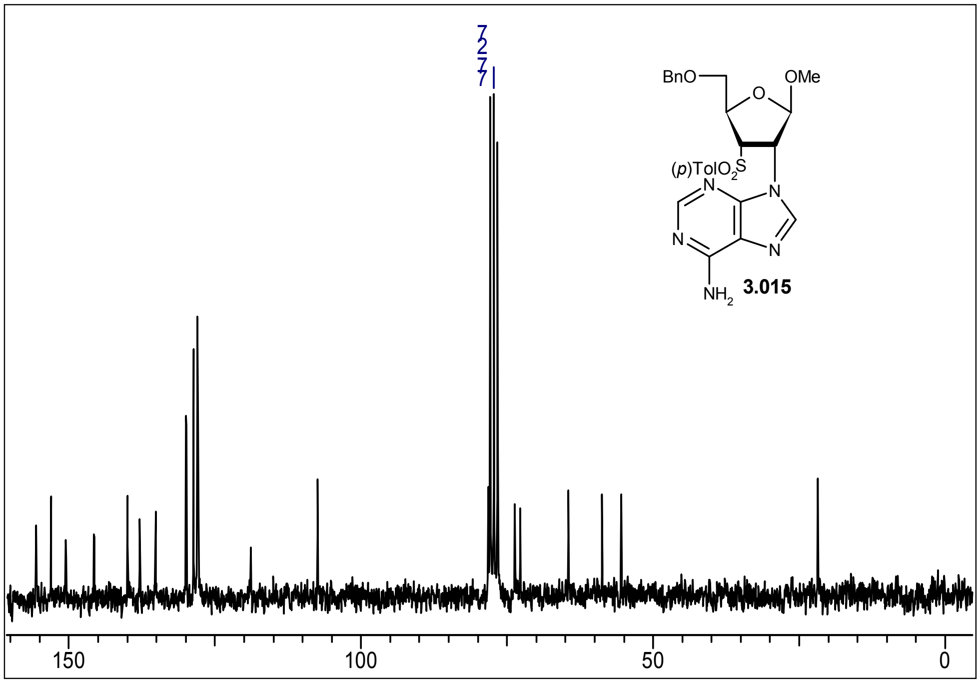

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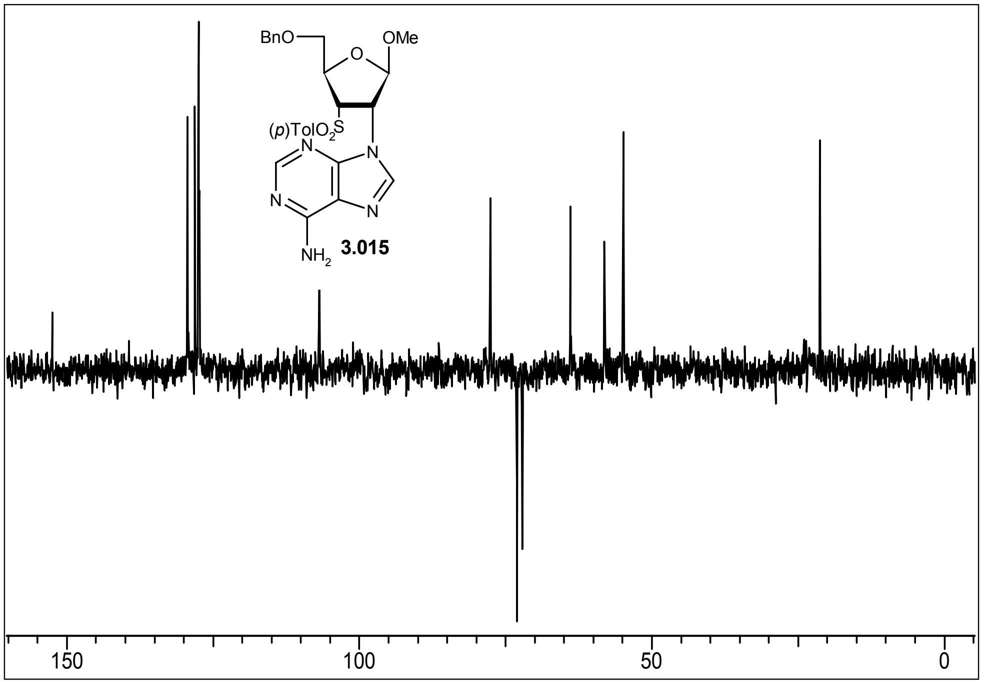

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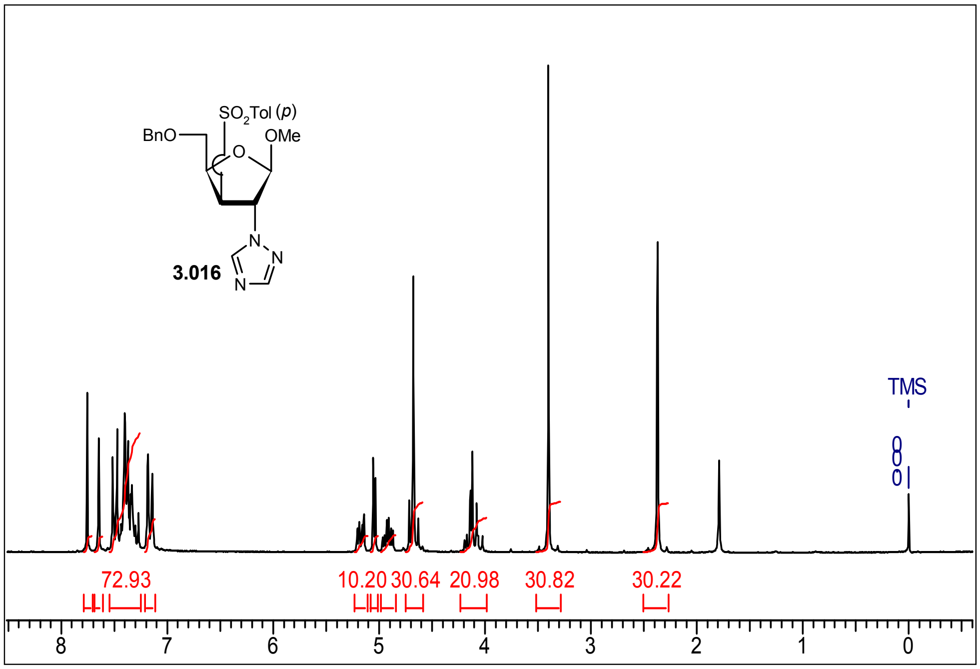

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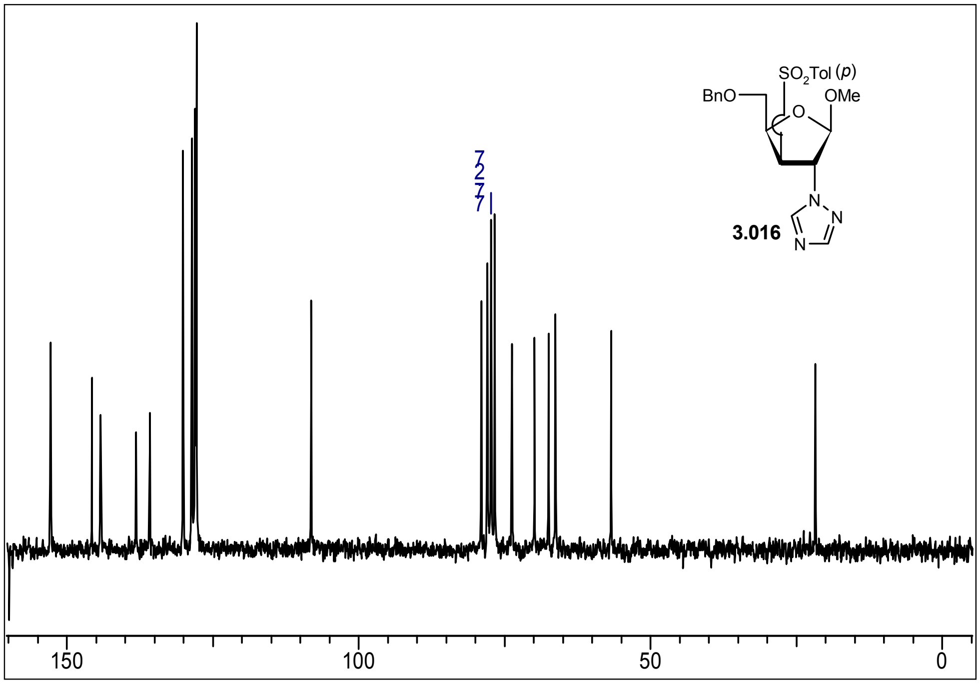

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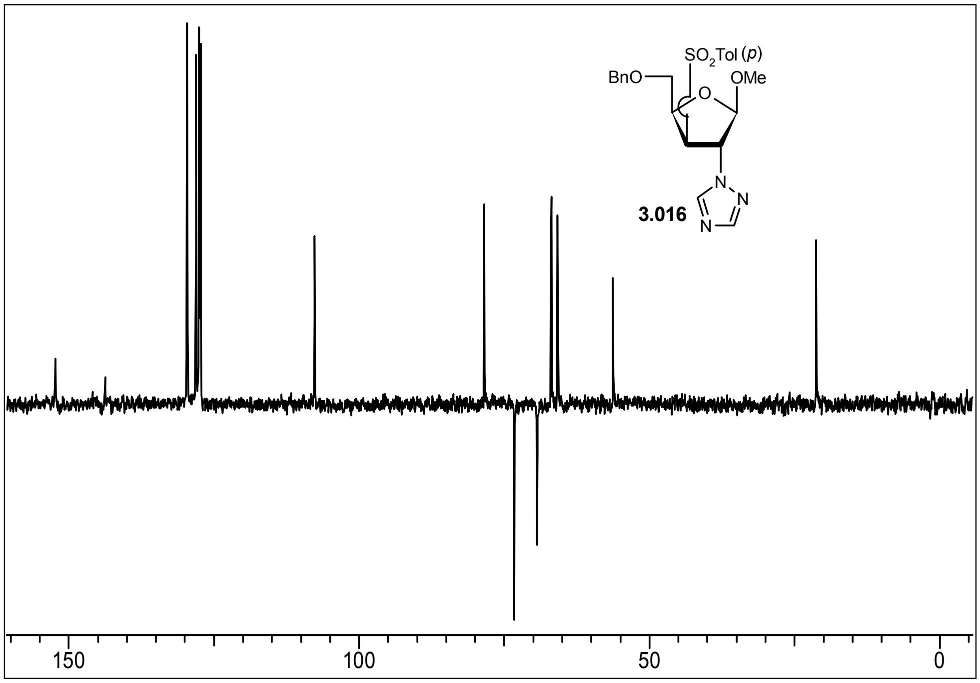

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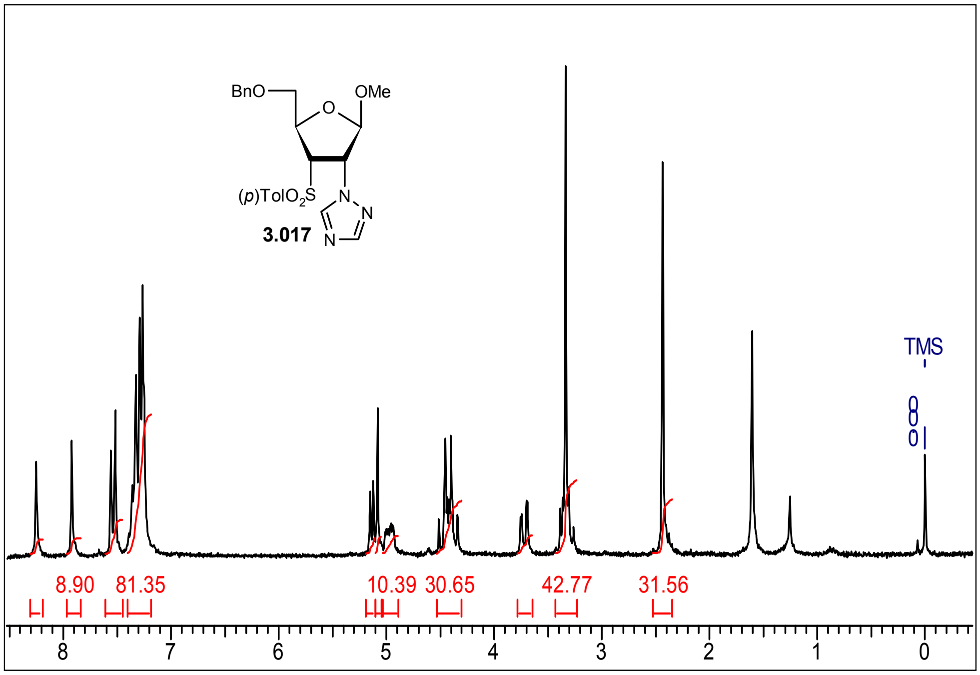

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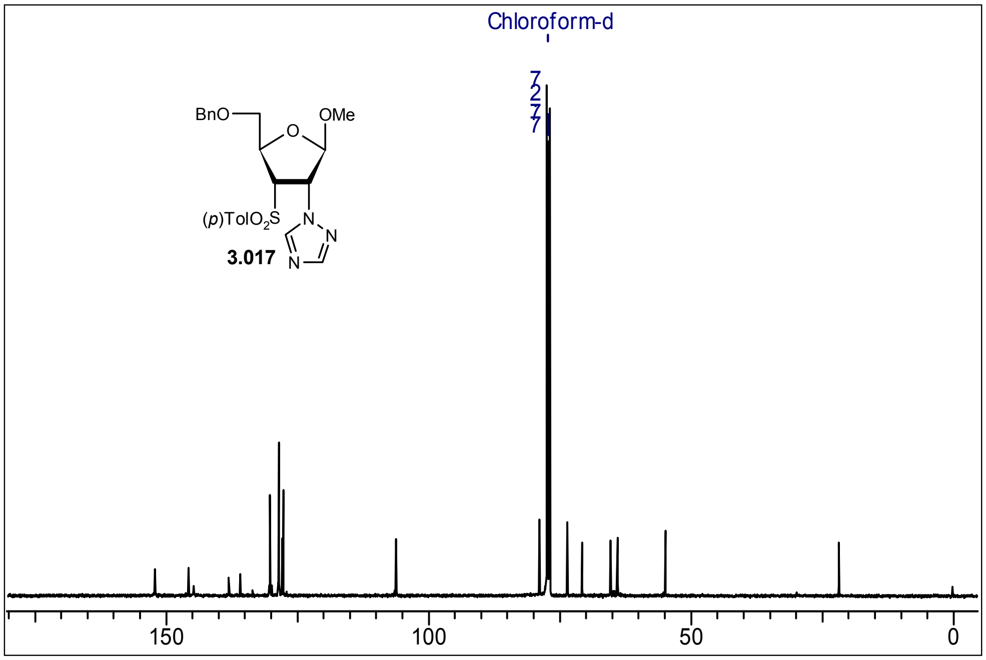
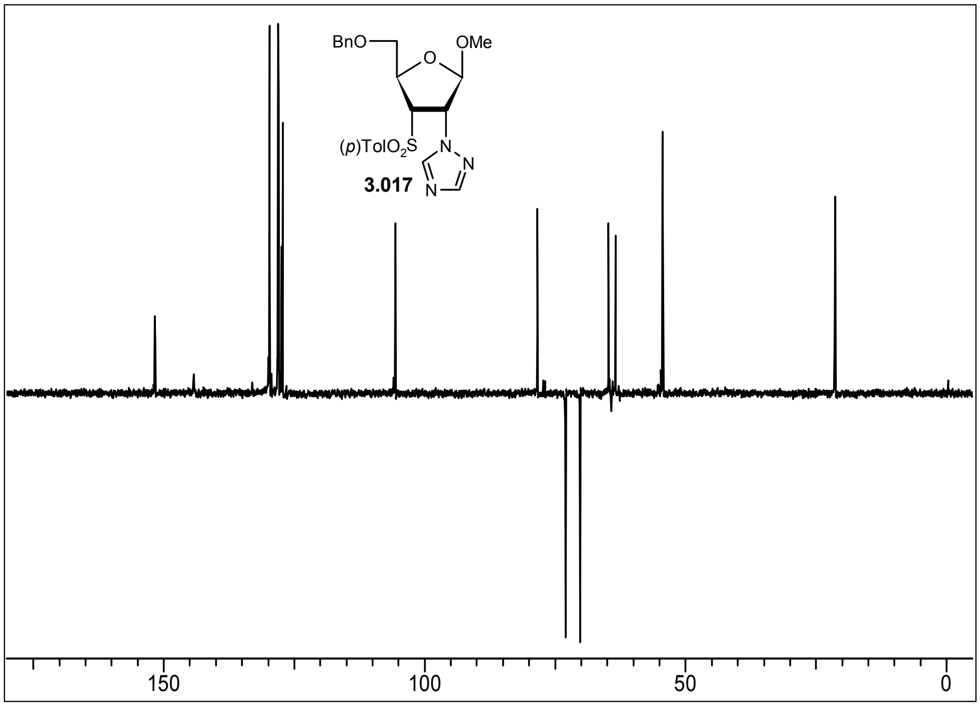


Dept of **3.017**



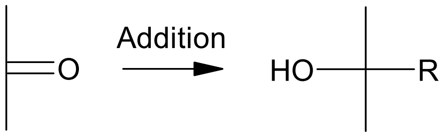
CHAPTER 4

Diastereoselective Addition of Carbon Nucleophiles to Vinyl Sulfone-modified Carbohydrates

4.1 Introduction

Branched-chain sugars, having carbon substituents at the non-terminal carbon atoms of the chain constitute an important class of modified carbohydrates.[1,2] They are regarded as glycosidic components of many natural products, especially of antibiotics.[1,2] They are also an important class of functionalized intermediates, useful for many synthetic transformations.[2-4] The most common methods for the syntheses of branched-chain sugars involve the addition of C-nucleophiles to glycosiduloses, sugar derived oxiranes, electron deficient olefinic sugars or the reduction of *C*-alkylidene glycosides.[1,2]

The addition of nucleophiles to suitable glycosiduloses has been extensively used for the synthesis of **Type-A** branched-chain sugars having polar substituents at the branching carbon atom (**Figure 4.1**).[1]



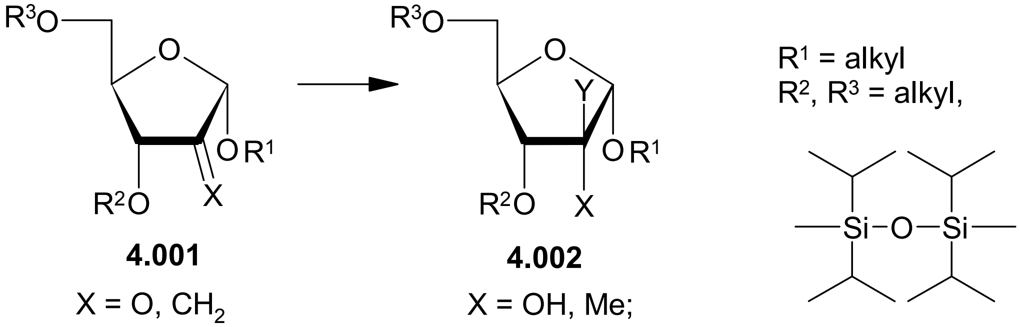
R = alkyl or aryl groups

Glycosiduloses **Type-A** branched-chain sugars

Figure 4.1

Nucleophilic addition to keto-sugars became disadvantageous because of the formation of two diastereomers although in certain fused ring systems, a stereospecific addition was often achieved.[1,5-6] However, studies on the stereochemistry of nucleophilic addition and reduction of 2-keto-sugars and its derivatives such as 2-C-alkylidenes have been investigated thoroughly.[7-15] In majority of the cases reactions of 2-keto-sugars and 2-C-alkylidenes proceeded in a stereoselective manner.[7-14] Thus, the addition of C-nucleophiles, derived mostly from Grignard reagents or other organometallic reagents, to the α-anomeric pentofuranosyl 2-keto-sugars and 2-C-alkylidenes **4.001** generated compounds **4.002** with the nucleophiles approaching the C-2 position from the β-face of the sugar ring.[7,8,10,13] However, there is a report dealing with the same side attack as well.[13] Similarly, β-anomeric substrates generated products, which resulted from the attacks of nucleophiles from the α-face of the sugar ring.[13]

Studies on the diastereoselectivity of nucleophilic addition to hexopyranosyl 2-keto-sugars and its related derivatives have also been investigated.[16-36] There are mainly two types of reactions reported with these compounds namely, nucleophilic addition of carbanions to 2-keto sugars or its derivatives[19,25,27,29,31] and their reductions with hydrides.[16,20-24,26,28,30,32-36] In most of the cases it is postulated that steric course of the carbonyl reduction of 2-keto-sugars is mainly dependent on the anomeric configuration.[16,20-24,26,28,30,32-36] Thus, addition of the C-nucleophiles to α-2-keto-sugars **4.003** afforded products **4.004** which resulted due to the attack from β-side.

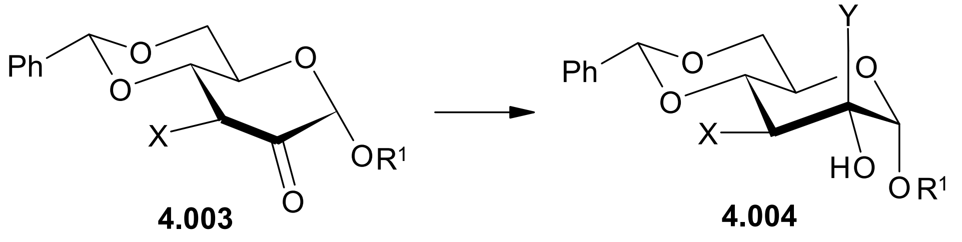


4.001
X = O, CH$_2$

4.002
X = OH, Me;
YH = C-nucleophiles

It should, however be pointed out that the presence of a sulfonyloxy or an acyloxy function at C-3 *vicinal* to C-2 invariably results in low stereoselectivities, indicating thereby the influence of the 3-OH protecting group on the *manno*/*gluco* ratios.[20,28,36] In the case of hydride based reductions the high and exclusive stereoanomeric control leads to α-D-glucosides from α-D-glycosiduloses while β-ulosides, correspondingly, were converted to β-glycosides of *manno*-configuration.[36] Addition to C-alkylidene glycopyranosides, on the other hand, has been used for the introduction of an axially oriented branch.[37]

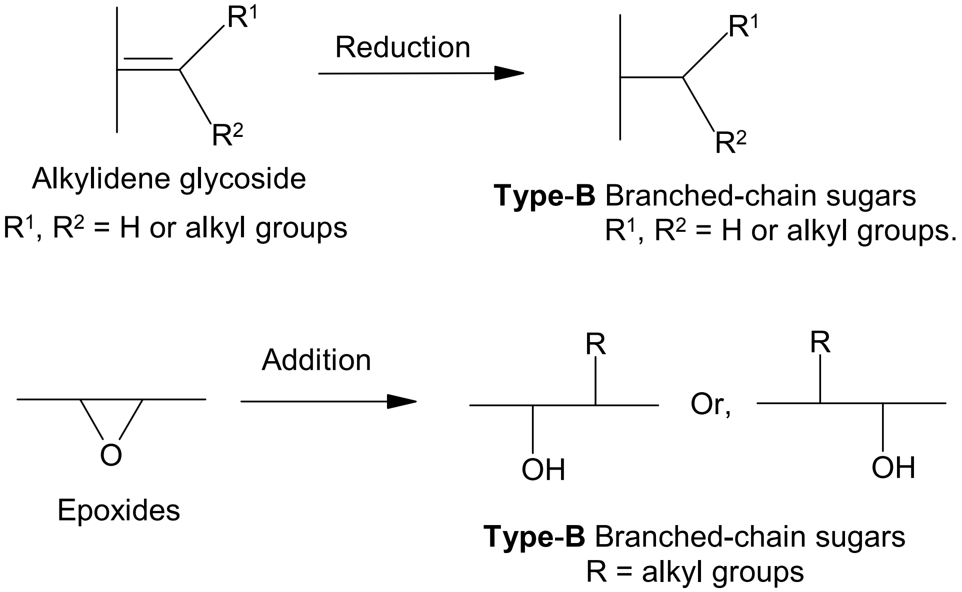
Reduction of alkylidene glycosides generates **Type**-**B** branched-chain sugars. The reaction of sugar derived oxiranes with carbon nucleophiles also provided a general



4.003
R1 = Me, allyl, Bn
X = OMe, OBn, H, OBz

4.004
R1 = Me, allyl, Bn
X = OMe, OBn, H, OBz
Y = C-nucleophiles

method for the synthesis of **Type-B** branched-chain sugars having no substituent at the branching carbon atom (**Figure 4.2**).



Alkylidene glycoside
R^1, R^2 = H or alkyl groups

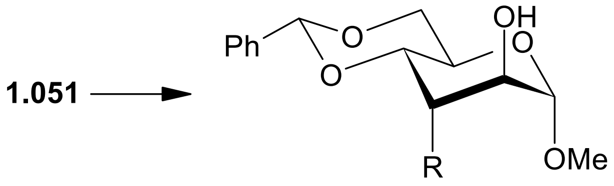
Type-B Branched-chain sugars
R^1, R^2 = H or alkyl groups.

Epoxides

Type-B Branched-chain sugars
R = alkyl groups

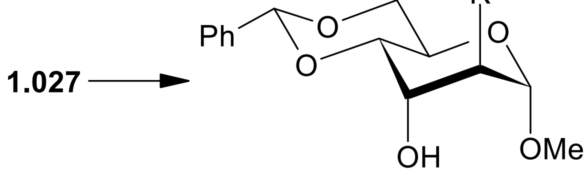
Figure 4.2

For example, diaxial ring opening of methyl 2,3-anhydro-4,6-*O*-(phenylmethylene)-α-D-*manno*pyranoside **1.051** with ethylmagnesium chloride or HCN, led to the formation of predominantly 3-substituted alcohols **4.005** & **4.006**, respectively.



4.005 R = Et
4.006 R = CN

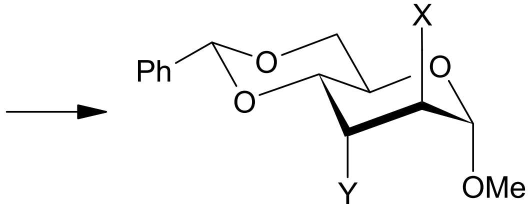
α-D-*Allo*pyranoside **1.027**, on the other hand, reacted with ethylmagnesium chloride or sodium salt of diethyl malonate to generate 2-substituted derivatives **4.007** and **4.008**, respectively.[38,39]



4.007 R = Et
4.008 R = CH_2COOEt

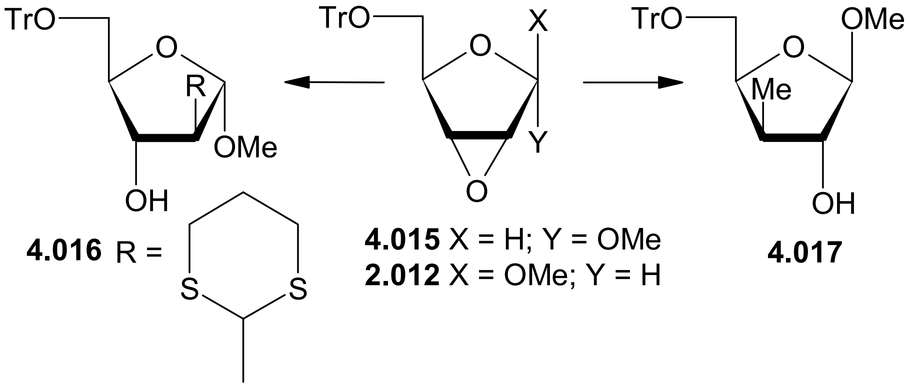
In the presence of Cp_2TiCl, the sugar-derived epoxide **1.027** underwent ring-scission with acrylonitrile, methyl vinyl ketone and methyl methacrylate to generate a mixture of 2-substituted **4.009**-**4.011** (major) and 3-substituted **4.012**-**4.014** (minor) branched-chain sugars.[40]

1.027



4.009 X = C_2H_4CN; Y = OH
4.010 X = C_2H_4COMe; Y = OH
4.011 X = $CH_2CHMeCOOMe$; Y = OH
4.012 X = OH; Y = C_2H_4CN
4.013 X = OH; Y = C_2H_4COMe
4.014 X = OH; Y = $CH_2CHMeCOOMe$

On the other hand, regioselective opening of methyl 2,3-anhydro-5-*O*-trityl-α-D-*ribo*furanoside **4.015** with 2-lithio-1,3-dithiane[41] and that of the β-anomer **2.012** with methylmagnesium chloride[42] afforded 2-*C*- and 3-*C*-alkyl derivatives **4.016** and **4.017**, respectively depending upon the anomeric configuration of the starting epoxide.

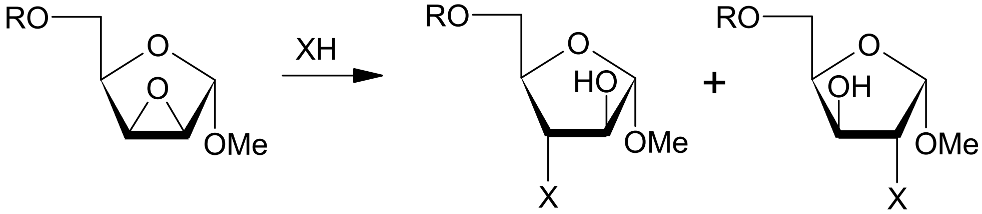


4.016 R =

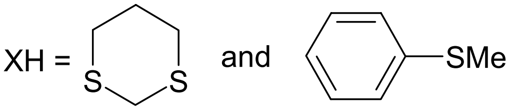
4.015 X = H; Y = OMe
2.012 X = OMe; Y = H

4.017

Similarly, compound **4.018** and its 5-OH protected derivatives **2.005**, **2.006**, **4.019** underwent nucleophilic scission of the epoxide ring in the presence of 2-lithio-1,3-dithiane to generate a mixture of 3-substituted **4.020**, **4.022**, **4.024**, **4.026** (major) and 2-substituted **4.021**, **4.023**, **4.025**, **4.027** (minor) products, respectively. Similar results were obtained when the same set of substrates were reacted with lithium salt of thioanisole.[43]



4.018 R = H — **4.020** — **4.021**
2.005 R = Bn — **4.022** — **4.023**
2.006 R = Tr — **4.024** — **4.025**
4.019 R = $^{t}BuPh_2Si$ — **4.026** — **4.027**



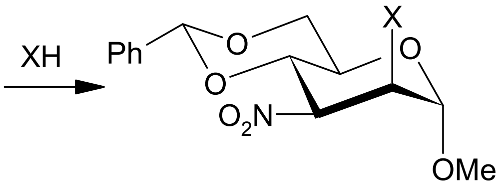
The steric course of the carbanion addition to nitro-alkenic sugars is also determined by the substituent that is *vicinal* to the center of nucleophilic attack. In most of the cases, the nucleophile attacks electron deficient carbon of the double bond with high preference from the opposite side to that of the *vicinal* substituent. This generalization was borne out by the addition of various nucleophiles to methyl 2,3-dideoxy-4,6-*O*-(phenylmethylene)-3-*C*-nitro-α-D-*erythro*-hex-2-enopyranoside **1.021** or its β- isomer, which generated[44-48] the thermodynamically less stable products with α-D-*manno*-configurations **4.028**-**4.034** or the respective β-D-*gluco*-compounds, [47,49,50] in high yields. Similarly, β-D-*threo*-analog **1.024** afforded addition products having the β-D-*galacto*-configuration **4.035**-**4.040** and not the alternative β-D-*talo*-compounds.[47,49]

Irradiation of methyl 2,3-dideoxy-4,6-*O*-(phenylmethylene)-3-*C*-nitro-β-D-*erythro*-hex-2-enopyranoside **1.018** in 1,3-dioxolane or in tetrahydrofuran afforded the D-*gluco*-isomers **4.041**-**4.043** and D-*manno*-isomers **4.044**-**4.045** having l,3-dioxolan-2-yl and tetrahydrofuran-2-yl group at C-2, respectively.[51]

Similarly, studies on the irradiation of 3-nitro-2-enopyranoside derivatives having α-D-*erythro*-, β-D-*threo*-, α-D-*threo*-configurations in 1,3-dioxolane affording various adducts in moderate yields have also been reported.[52] Results of irradiation of 3-C-nitro-D-*erythro*-hex-2-enopyranoside derivatives in methanol, ethanol and isopropanol are also reported.[53]

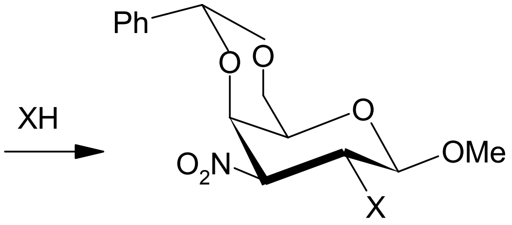
Hex-2-enopyranosid-4-ulose,[54-56] and hex-3-enopyranosid-2-ulose [56,57] have also been used as precursors for the syntheses of branched-chain sugars.[1] However, the usefulness of these compounds as precursors are limited because of the following drawbacks: (i) the products of the addition reactions are always either 2,3- or 3,4-dideoxy derivatives; (ii) 1,2- and 1,4-addition compete depending on the nature of nucleophiles; (iii) nucleophilic addition produces a mixture at C-2 (*ribo* and *lyxo*), and (iv) stereochemical outcome of the reduction of the carbonyl group (C-4) is dependent on the orientation of the C-2 substituent.[58-60]

1.021



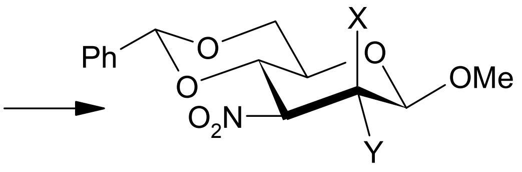
4.028 X = Me
4.029 X = CH=CH_2
4.030 X = CN
4.031 X = $CH(COOEt)_2$
4.032 X = CH_2COOMe
4.033 X = CH_2NO_2
4.034 X = $CH(COOMe)_2$

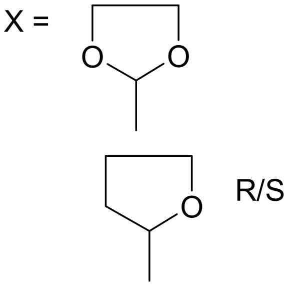
1.024



4.035 X = Me
4.036 X = CH=CH_2
4.037 X = CN
4.038 X = $CH(COOEt)_2$
4.039 X = CH_2COOMe
4.040 X = CH_2NO_2

1.018





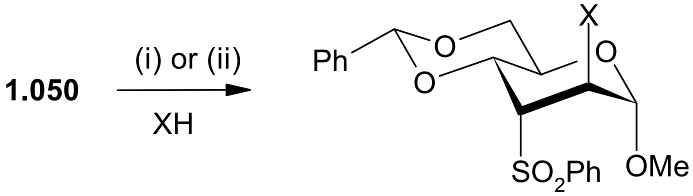
4.041 X = H; Y = 1,3-Dioxolanyl
4.042 X = H; Y = Oxolanyl(R)
4.043 X = H; Y = Oxolanyl(R)
4.044 X = 1,3-Dioxolanyl; Y = H
4.045 X = Oxolanyl; Y = H

Interestingly, there are only two reports[61] (**Chapter 1**) where vinyl sulfone-modified carbohydrates have been used as intermediates for the synthesis of branched chain sugars. However, no systematic study has been carried out yet on the use of vinyl sulfone-modified carbohydrates for the syntheses of branched-chain sugars. In this chapter we report on the diastereoselective addition of carbon nucleophiles to vinyl sulfone-modified pyranosides as well as furanosides as a route to branched-chain sugars.

4.2 Present work

Diastereoselective addition of nitromethane and dimethyl malonate to 1.050: α-Vinyl sulfone **1.050**[**62**] on reaction with nitromethane in the presence of NaOMe in MeOH at ambient temperature, generated **4.046** in moderate yield whereas dimethyl malonate in the presence of NaH in THF afforded **4.047** in high yield.

Diastereoselective addition of nitromethane and dimethyl malonate to 1.058: Under the same set of conditions mentioned for the reaction of **1.050**, β-vinyl sulfone **1.058**[**62**] was reacted with nitromethane and dimethyl malonate to afford **4.048** and **4.049** in moderate to high yields, respectively.

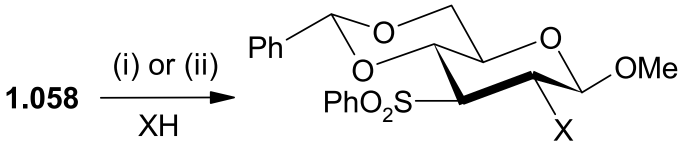


4.046 X = CH_2NO_2
4.047 X = $CH(COOMe)_2$

Reagents and conditions: (i) CH_3NO_2, NaOMe, MeOH, rt., 36 h, 60%; (ii) $CH_2(COOMe)_2$, NaH, THF, rt., 1.5 h, 82%.

Diastereoselective addition of nitromethane and dimethyl malonate to 2.001: α-Vinyl sulfone **2.001** on reaction with nitromethane in the presence of NaOMe in MeOH produced **4.050** in good yield whereas dimethyl malonate reacted with **2.001** in the presence of NaH in THF to generate **4.051** in high yield.

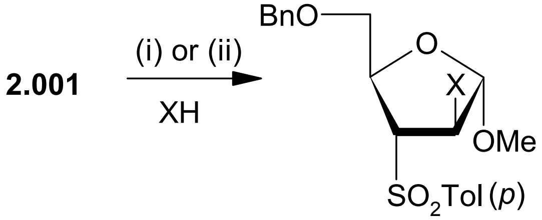
Diastereoselective addition of nitromethane and dimethyl malonate to 2.003: β-Vinyl sulfone **2.003** on reaction with nitromethane in the presence of ^tBuOK in THF afforded two products, out of which only **4.052** was identifiable in moderate yield. On the other hand, dimethyl malonate reacted with **2.003** in the presence of NaH in THF to yield a single isomer **4.053** in excellent yield.



4.048 X = CH_2NO_2
4.049 X = $CH(COOMe)_2$

Reagents and conditions: (i) CH_3NO_2, NaOMe, MeOH, rt., 2 h, 56%; (ii) $CH_2(COOMe)_2$, NaH, THF, rt., 2 h, 98%.

Synthesis of densely functionalized branched-chain sugars 4.055 and 4.057: Compound **4.047** was deprotected in the presence of HCl (0.01 N) in MeOH under reflux to afford the diol **4.054** quantitatively. The diol **4.054** was mesylated using mesyl chloride in pyridine to obtain monomesylate **4.055** in good yield. Similarly, **4.049** was deprotected with conc. HCl in EtOH at ambient temperature to get the diol **4.056** in excellent yield. The diol **4.056**, on mesylation afforded the monomesylate **4.057** in high yield under the same condition as described for **4.054**.



4.050 X = CH_2NO_2
4.051 X = $CH(COOMe)_2$

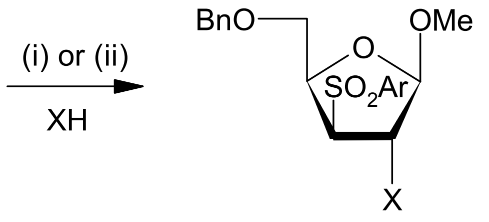
Reagents and conditions: (i) CH_3NO_2, NaOMe, MeOH, rt., 3 h, 73%; (ii) $CH_2(COOMe)_2$, NaH, THF, rt., 2.5 h, 74%.

4.3 Structural Assignment

It is reported[63,64] that in the case of methyl 4,6-*O*-(phenylmethylene)-α-D-hexopyranosides with D-*allo*- and D-*gluco*-configurations, a coupling constant ($J_{1,2}$) of 3.3-3.8 Hz implies characteristic of equatorial H-1 - axial H-2 relationship. For D-*altro*-

and D-*manno*-series, a coupling constant ($J_{1,2}$) of 0.6-1.7 Hz is the characteristic of equatorial H-1 - equatorial H-2 arrangement.

2.003



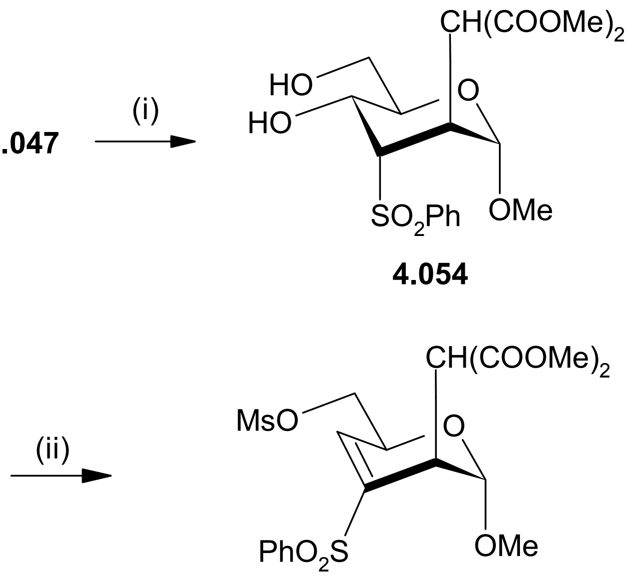
Ar = Tol (*p*)

4.052 X = CH_2NO_2
4.053 X = $CH(COOMe)_2$

Reagents and conditions: (i) CH_3NO_2, ${}^{t}BuOK$, THF, rt., 2 h, 55%; (ii) $CH_2(COOMe)_2$, NaH, THF, rt., 2.5 h, 87%.

Thus, by comparing $J_{1,2}$ value of **4.046** (0.0 Hz) and **4.047** (0.0 Hz) (**Table 4.3**) with those of the methyl 4,6-*O*-(phenylmethylene)-α-D-hexopyranosides as well as of the structurally similar branched-chain sugars (**Table 4.1**), it was inferred that compounds **4.046** and **4.047** were possessing either α-D-*altro*- or α-D-*manno*- configurations.

4.047

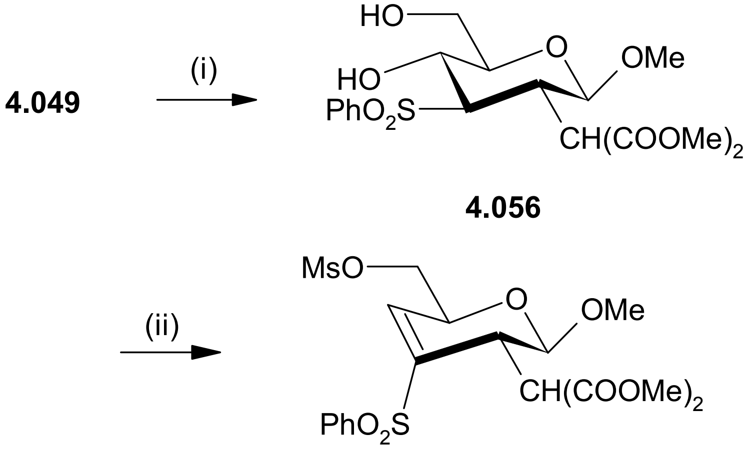


4.054

4.055

Reagents and conditions: (i) HCl(0.01 N), MeOH, relfux, 8 h, quantitative; (ii) MsCl, Py., 0 to +4 °C, 24 h, 63%.

Similarly, $J_{1,2}$ values of compounds **4.048** (8.3 Hz) and **4.049** (7.8 Hz) (**Table 4.3**) are very close to those of methyl 4,6-*O*-(phenylmethylene)-β-D-*gluco*pyranosides (8.1- 8.5 Hz) (**Table 4.2**) indicating diaxial orientation of H-2 and H-1 in either of **4.048** and **4.049**. So, compounds **4.048** and **4.049** were tentatively considered as possessing either β-D-*gluco*- or *allo*-configuration.



4.056

4.057

Reagents and conditions: (i) conc. HCl, EtOH, rt., 2.5 h, 84%;
(ii) MsCl, Py., 0 to +4 °C, 24 h, 92%.

Similar conclusions of diequatorial orientation of H-1 and H-2 for compounds **4.046** and **4.047** and diaxial orientation of the same set of protons for **4.048** and **4.049** were achieved by considering the study of their respective ^{13}C NMR spectra. It is known that the C-4 peak should be shielded more for a compound with the axial substituent at C-2. In other words, axial substituent at C-2 has a marked shielding effect over C-4.[64] This was clearly borne out by the signal arising out of C-4 for compound **4.046** (δ 74.9) and **4.047** (δ 75.2) over that of **4.048** (δ 76.9) and **4.049** (δ 76.2) (**Table 4.3**).

Furthermore, it is also evident from **Tables 4.1** and **4.2** that in general, methyl 4,6-*O*-(phenylmethylene)-α-D-*gluco*pyranosides and methyl 4,6-*O*-(phenylmethylene)-α-D-*altro*pyranoside showed positive rotation values and methyl 4,6-*O*-(phenylmethylene)-β-D-*gluco*pyranoside rendered negative rotation values. In our case, compounds **4.046** (+26.4) and **4.047** (+18.3) showed positive rotation and **4.048** (–64.4) and **4.049** (–98.2) showed negative rotation values (**Table 4.3**). However, it was necessary to determine unambiguously the configuration at C-3 of **4.046-4.049**. Hence, absolute configurations of all four compounds were established unambiguously with the help of their single crystal X-ray diffraction techniques (**Figure 4.4**-**4.7**).

As discussed in **Chapter 3**, the products from the reactions of **2.001** with carbon nucleophiles were expected to have *arabino*-configuration. It is also clear that the $J_{1,2}$ values of authentic methyl α-D-*arabino*furanosides (**Table 2.2**) including **2.007**-**2.010** (**Table 2.3**) range between 0.0-3.0 Hz. The $J_{1,2}$ values for authentic methyl α-D-*ribo*furanosides including **2.019** and **2.021** range between 4.0-4.9 Hz and the same for methyl α-D-*xylo*furanosides including **2.028**-**2.030**, on the other hand, are always

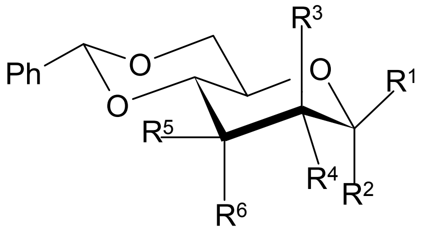


Figure 4.3

Table 4.1

$J_{1,2}$ and $[\alpha]_D^T$ of selected α-D-*gluco*-, *manno*-, *allo*- and *altro*-compounds

R^1	R^2	R^3	R^4	R^5	R^6	$J_{1,2}$	$[\alpha]_D^T$	Ref.
	Methyl 4,6-*O*-(phenylmethylene)-α-D-*gluco*pyranoside							
H	OMe	H	CH(CN)Ph (S)	NO_2	H	3.0	+21.2	65
H	OMe	H	CH(CN)Ph (R)	NO_2	H	3.8	+42.4	65
H	OMe	H	$CH(CN)_2$	NO_2	H	3.8		66
H	OMe	H	1,3-Dioxolan-2-yl	NO_2	H	3.6	+31.0	67
H	OMe	H	$CH(COOMe)_2$	NO_2	H	3.0	+126.0	68
H	OMe	H	$CH(COMe)_2$	NO_2	H	3.1	+30.2	68
H	OMe	H	CH_2COMe	NO_2	H	3.0	+84.3	68
	Methyl 4,6-*O*-(phenylmethylene)-α-D-*manno*pyranoside							
H	OMe	CN	H	NO_2	H	1.3	−14.7	44
H	OMe	CH_2COOMe	H	NO_2	H	1.0	+22.8	66
H	OMe	$CH(COOEt)_2$	H	NO_2	H	1.3	−33.4	66
H	OMe	CH(CN)Ph(S)	H	NO_2	H	0.0	−22.7	65
H	OMe	CH(CN)Ph(R)	H	NO_2	H	1.0	+13.3	65
H	OMe	Me	H	NO_2	H	<1	+55.0	47
H	OMe	$CH(COMe)_2$	H	NO_2	H	1.3	−129.0	66
H	OMe	$CH(COPh)_2$	H	NO_2	H	1.0	−26.2	66
H	OMe	$CH(COMe)CO_2Et$	H	NO_2	H	1.0	−103.0	66
H	OMe	$CH(CN)_2$	H	NO_2	H	1.0	+21.7	66
H	OMe	$CH(COOMe)_2$	H	NO_2	H	1.0	−30.2	68
H	OMe	1,3-Dioxolan-2-yl	H	NO_2	H	≤1.0	+25.0	67
	Methyl 4,6-*O*-(phenylmethylene)-α-D-*allo*pyranoside							

H	OMe	H	1,3-Dioxolan-2-yl	H	NO_2	3.6	+36.0	67
	Methyl 4,6-*O*-(phenylmethylene)-α-D-*altro*pyranoside							
H	OMe	CH_2COMe	H	H	NO_2	≤1.0	+15.4	68
H	OMe	CH(COMe)2	H	H	NO_2	10.5	-----	46*

* compound exists in boat form

ranging between 4.0-4.7 Hz (**Tables 2.1** and **2.3**). Excluding the possibility of any *lyxo*-derivative formation for steric reasons, the $J_{1,2}$ values of **4.050** and **4.051**, (0.0 Hz; **Table 4.4**) surely indicated the presence of *arabino*-configuration in these molecules. (In fact, single crystal X-ray diffraction technique unambiguously established the structure of **4.050** as *arabino*-configuration; **Figure 4.8**).

Table 4.2

$J_{1,2}$ and $[\alpha]_D^T$ of selected β-D-*gluco*- and *manno*-compounds

R^1	R^2	R^3	R^4	R^5	R^6	$J_{1,2}$	$[\alpha]_D^T$	Ref.
	Methyl 4,6-*O*-(phenylmethylene)-β-D-*gluco*pyranoside							
Ome	H	H	CN	NO_2	H	8.2	−42.2	50
Ome	H	H	Me	NO_2	H	8.5	−87.7	47
Ome	H	H	$CH=CH_2$	NO_2	H	8.3	−90.0	47
Ome	H	H	$CH(COMe)_2$	NO_2	H	8.1	−153.0	69
Ome	H	H	CH_2COPh	NO_2	H	8.4	−29.0	69
Ome	H	H	$CH(COPh)_2$	NO_2	H	8.1	−194.0	69
Ome	H	H	1,3-Dioxolan-2-yl	NO_2	H	8.8	−86.0	51
Ome	H	H	Oxolanyl (R)	NO_2	H	8.3	−60.4	51
Ome	H	H	Oxolanyl (S)	NO_2	H	8.3	−98.2	51
Ome	H	H	$CH(COOMe)_2$	NO_2	H	8.3	−69.0	48
	Methyl 4,6-*O*-(phenylmethylene)-β-D-*manno*pyranoside							
Ome	H	1,3-Dioxolan-2-yl	H	NO_2	H	2.2	−26.4	51
Ome	H	Oxolanyl (R)	H	NO_2	H	1.2	−61.6	51

Table 4.3

δ_{H-1}, δ_{C-4}, $J_{1,2}$ & $[\alpha]_D^T$ of synthesized hexopyranosides

Compounds	δ_{H-1} (ppm)	δ_{C-4}	$J_{1,2}$ (Hz)	$[\alpha]_D^T$ (deg.)
4.046	4.65	74.9	0.0	+26.4
4.047	4.58	75.2	0.0	+18.3
4.048	4.69	76.9	8.3	−64.4
4.049	5.17	76.2	7.8	−98.2

Using the similar arguments mentioned above, we expected to obtain *xylo*-derivatives from the reactions between **2.003** and carbon nucleophiles. It has also been reported earlier that Michael addition of various nucleophiles to vinyl sulfone-modified nucleosides **1.089** and **1.090** produced mainly the *xylo*-derivatives **1.091** and **1.092**, respectively although in limited number of cases *ribo*-derivatives were also obtained (**Chapter 1**). It is evident from the available data that the $J_{1,2}$ values of authentic methyl β-D-*xylo*furanosides (**Table 2.1**) including **2.013**, **2.015** and **2.031** range between 0.0-2.3 Hz and those of methyl β-D-*ribo*furanosides (**Table 2.1**) including **2.020** and **2.022** (**Table 2.3**) are close to 0.0 Hz. Although the $J_{1,2}$ values of **4.052** and **4.053** ($J_{1,2}$ = 3.5 Hz and 3.9 Hz, respectively; **Table 4.4**) were higher than those of related compounds mentioned above, X-ray diffraction experiments unambiguously determined **4.052** and **5.053** as *xylo*-derivatives (Single crystal X-ray diffraction technique unambiguously established the structure of **4.052** as *xylo*-configuration; **Figure 4.9**).

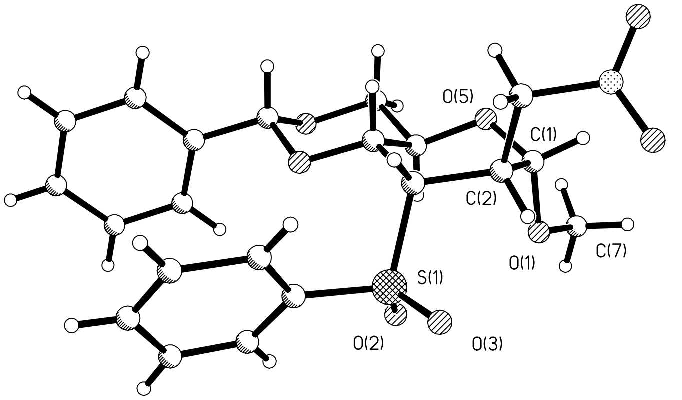


Figure 4.4 ORTEP Diagram of Compound 4.046

Selected bond lengths (Å) for compound 4.046	**Selected bond angles (deg) for compound 4.046**
O5 C1 1.431(10) C1 O1 1.413(11) C1 C2 1.512(12) O1 C7 1.435(12) C2 C3 1.527(11) C2 C21 1.553(11) C3 C4 1.538(10) C4 O4 1.394(8) C4 C5 1.545(11) S1 O2 1.440(7) S1 O3 1.450(8) S1 C3 1.834(9) O4 C8 1.427(10) C8 O6 1.419(10) O6 C6 1.425(9) C6 C5 1.528(12)	C1 O1 C7 110.9(8) C1 C2 C3 117.2(8) C1 C2 C21 110.7(7) C3 C2 C21 105.7(6) C2 C3 C4 111.5(7) C2 C3 S1 110.8(6) C4 C3 S1 113.3(6) O4 C4 C3 112.4(7) C3 C4 C5 113.2(7) O2 S1 O3 119.3(5) O2 S1 C3 110.4(4) O3 S1 C3 103.5(4) C5 O5 C1 114.4(7) O1 C1 O5 108.2(8) O1 C1 C2 108.2(8) O5 C1 C2 112.3(7)

It is also evident from the literature that in general, methyl α-D-*arabino*- and *lyxo*-furanosides showed relatively larger positive rotation values and methyl β-D-

Table 4.4

δ_{H-1}, $J_{1,2}$ & $[\alpha]_D^T$ of synthesized pentofuranosides

Compounds	δ_{H-1} (ppm)	$J_{1,2}$ (Hz)	$[\alpha]_D^T$ (deg.)
4.050	4.91	0.0	+58.8
4.051	4.96	0.0	+51.4
4.052	5.02	3.5	+14.3
4.053	5.11	3.9	+9.4

ribo- and *xylo*-furanosides rendered smaller positive to negative rotation (**Chapter 2, Table 2.1** and **2.2**). In our case, all compounds **4.050** (+58.8), **4.051** (+51.4), **4.052** (+14.3) and **4.053** (+9.4) showed positive rotation values. However, it should be noted that the magnitude of values is tending towards a smaller positive value from a large positive value. Hence by comparison it can also be inferred that compounds **4.050** and **4.051** were having α-D-*arabino*-configuration and compounds **4.052** and **4.053** were possessing β-D-*xylo*-configuration.

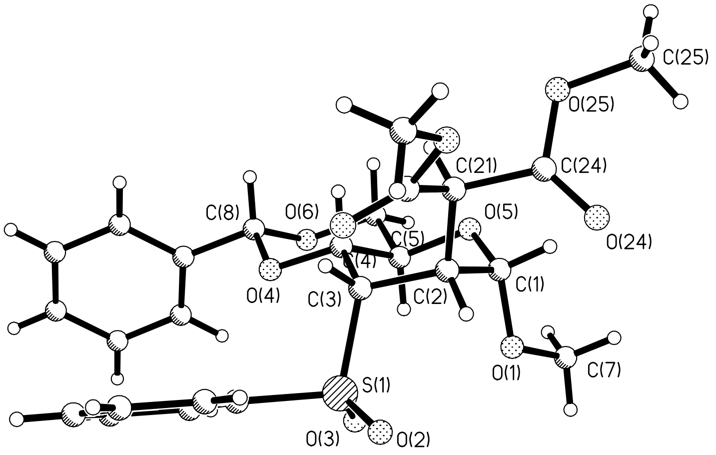


Figure 4.5 ORTEP Diagram of Compound 4.047

Selected bond lengths (Å) for compound 4.047	**Selected bond angles (deg) for compound 4.047**
C1 O1 1.403(4)	C1 O1 C7 114.4(3)
C1 C2 1.530(5)	C1 C2 C3 111.5(2)
O1 C7 1.429(4)	C1 C2 C21 111.2(3)
C2 C3 1.547(4)	C3 C2 C21 111.2(3)
C2 C21 1.549(4)	C4 C3 C2 110.7(2)
C3 C4 1.513(4)	C4 C3 S1 114.3(2)
C4 O4 1.423(3)	C2 C3 S1 112.3(2)
C4 C5 1.514(5)	C3 C4 C5 113.2(3)
S1 O3 1.432(2)	O3 S1 O2 118.76(16)
S1 O2 1.436(2)	O3 S1 C3 111.68(14)
S1 C3 1.821(3)	O2 S1 C3 106.43(13)
O5 C1 1.413(4)	C1 O5 C5 111.6(2)
O5 C5 1.428(4)	O1 C1 C2 105.1(3)

Compounds **4.046-4.053** have rendered satisfactory elemental analysis.

4.4 Results and Discussion

The stereochemistry of nucleophilic additions to system like 3-nitro-hex-2-enopyranosides **1.021** and **1.018** with various carbon nucleophiles have been studied.[43-44,47-48,50,63-69]

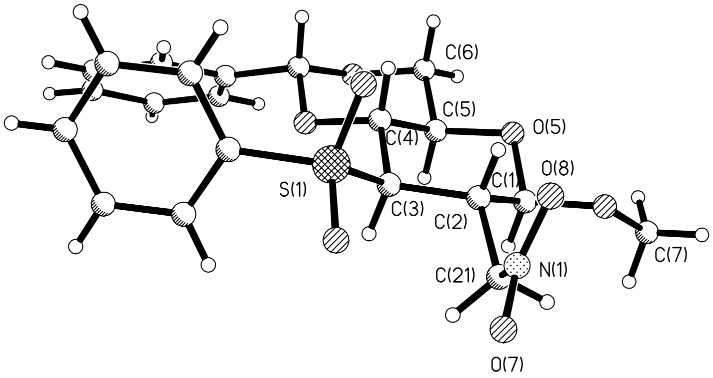


Figure 4.6 ORTEP Diagram of Compound 4.048

Selected bond lengths (Å) for compound 4.048	Selected bond angles (deg) for compound 4.048
C1 O1 1.377(9)	C1 O1 C7 113.3(7)
C1 C2 1.531(10)	C1 C2 C21 107.7(7)
O1 C7 1.440(9)	C1 C2 C3 109.3(7)
C2 C21 1.540(11)	C21 C2 C3 115.4(7)
C2 C3 1.542(10)	C4 C3 C2 111.8(6)
C3 C4 1.525(10)	C4 C3 S1 112.9(5)
C4 O4 1.422(9)	C2 C3 S1 107.3(5)
C4 C5 1.494(11)	O4 C4 C5 108.6(7)
S1 O2 1.429(6)	O2 S1 O3 119.2(4)
S1 O3 1.450(5)	O2 S1 C3 107.0(4)
S1 C3 1.818(7)	O3 S1 C3 105.9(4)
O5 C5 1.421(9)	C5 O5 C1 109.2(6)
O5 C1 1.423(10)	O1 C1 C2 108.6(7)

Addition of carbon nucleophiles to **1.021** generated the thermodynamically less stable C-2 axial products whereas under the same condition, **1.018** produced thermodynamically more stable C-2 equatorial products with *gluco*-configurations.[47-48,50-51,69] In almost all the cases, the nitro-group at C-3 has occupied equatorial position. However, at least in one case, the nitro-group at C-3 occupied the axial position to give rise to products with *altro*-configurations.[68] It is reported[46] that the *altro*-adducts exist in a slightly twisted-boat form.

In principle four possible products (*manno*-, *gluco*-, *allo*- and *altro*-) can be generated from the Michael addition of a nucleophile to a system like **1.050**. Addition of carbon nucleophiles to **1.050** afforded single isomer in each case. In theory, in a partially rigid bicyclic system like **1.050**, sterically demanding bulky phenylsulfonyl group should occupy the equatorial position after the nucleophilic addition.[70]

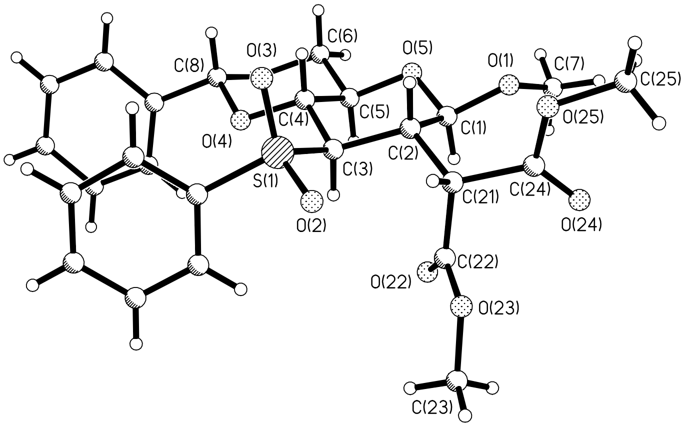


Figure 4.7 ORTEP Diagram of Compound 4.049

Selected bond lengths (Å) for compound 4.049	Selected bond angles (deg) for compound 4.049
C1 O1 1.387(2)	C1 O1 C7 113.58(18)
C1 C2 1.545(2)	C1 C2 C21 110.94(14)
O1 C7 1.433(3)	C1 C2 C3 109.60(12)
C2 C21 1.554(2)	C21 C2 C3 114.02(12)
C2 C3 1.567(2)	C4 C3 C2 108.92(12)
C3 C4 1.518(2)	C2 C3 S1 110.96(10)
C4 O4 1.422(2)	O4 C4 C3 110.22(13)
C4 C5 1.518(3)	C3 C4 C5 109.82(15)
O4 C8 1.422(2)	O3 S1 C3 107.78(9)
S1 O3 1.4317(17)	O2 S1 C3 107.69(8)
S1 O2 1.4347(17)	C1 O5 C5 111.07(15)
S1 C3 1.8132(15)	O1 C1 O5 106.17(15)
O5 C1 1.413(2)	O1 C1 C2 106.87(14)
O5 C5 1.417(2)	O5 C1 C2 112.76(16)

In our case, carbon nucleophile has approached the C-2 center of **1.050** from the axial direction to afford thermodynamically less stable diaxial products. The exact reasons for the stability of the *altro*-adducts containing three consecutive axial substituents at C-1, C-2 and C-3 in chair form is not clear.

Compound **1.058**, on the other hand, on reaction with nitromethane and dimethyl malonate generated thermodynamically more stable diequatorial products as expected. It is difficult to pinpoint the reasons behind the diastereoselectivity of addition of nucleophiles to **1.058**. Notwithstanding, this observation is consistent with the generalized rule[71-72] that in the case of an β-anomeric substrate, a nucleophile should approach the C-2 site preferentially from the equatorial direction.

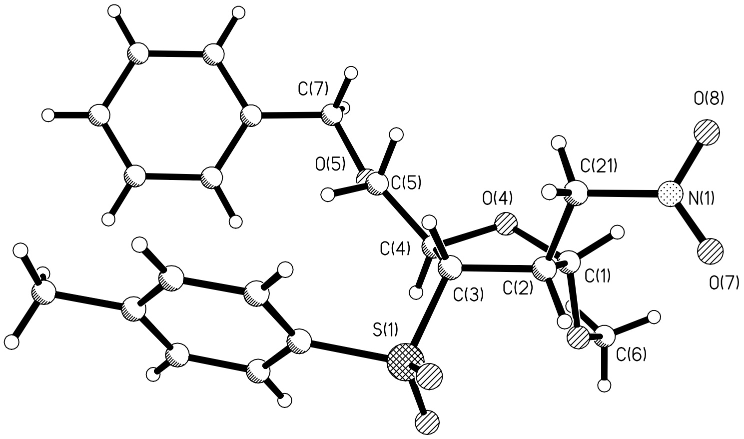


Figure 4.8 ORTEP Diagram of Compound 4.050

Selected bond lengths (Å) for compound 4.050	Selected bond angles (deg) for compound 4.050
C1 O1 1.405(5)	C1 O1 C6 113.6(4)
C1 C2 1.521(6)	C1 C2 C3 104.5(4)
O1 C6 1.412(5)	C1 C2 C21 111.8(4)
C2 C3 1.536(5)	C3 C2 C21 109.1(4)
C2 C21 1.544(6)	C2 C3 C4 105.4(3)
C3 C4 1.544(5)	C2 C3 S1 111.6(3)
C4 C5 1.492(5)	C4 C3 S1 116.0(3)
C5 O5 1.411(4)	O4 C4 C3 105.0(3)
O5 C7 1.430(5)	O2 S1 O3 119.1(2)
C7 C8 1.495(6)	O2 S1 C3 106.6(2)
S1 O2 1.438(3)	O3 S1 C3 108.1(2)
S1 O3 1.447(3)	C1 O4 C4 109.2(3)
S1 C3 1.777(4)	O1 C1 O4 111.6(4)
O4 C1 1.430(5)	O1 C1 C2 108.0(5)
O4 C4 1.438(4)	O4 C1 C2 104.9(4)

Studies on the stereochemistry of nucleophilic addition to systems like 2,3-dideoxy-3-*C*-nitro-pent-2-enofuranosides[73] have not been attempted. However, it has been reported[74] that the addition of *p*-toluenethiol to 1-(p)-tolylsulfonyl cyclopentene system generated thermodynamically more stable *trans*-2-(*p*)-tolylmercapto-1-(*p*)-tolylsulfonyl cyclopentane. Moreover, in the case of nucleosides it is known that Michael addition of various nucleophiles to vinyl sulfone-modified nucleosides **1.089** and **1.090** produced mainly the *xylo*-derivatives **1.091** and **1.092**, respectively although in limited number of cases *ribo*-derivatives were also obtained (**Chapter 1**). Therefore, it is not surprising that the addition of nitromethane and dimethyl malonate to **2.001** afforded single products **4.050** and **4.051** with the expected *arabino*-configurations. Similarly, compound **2.003**, on reaction with nitromethane and dimethyl malonate generated expected *xylo*-derivatives **4.052** and **4.053**.

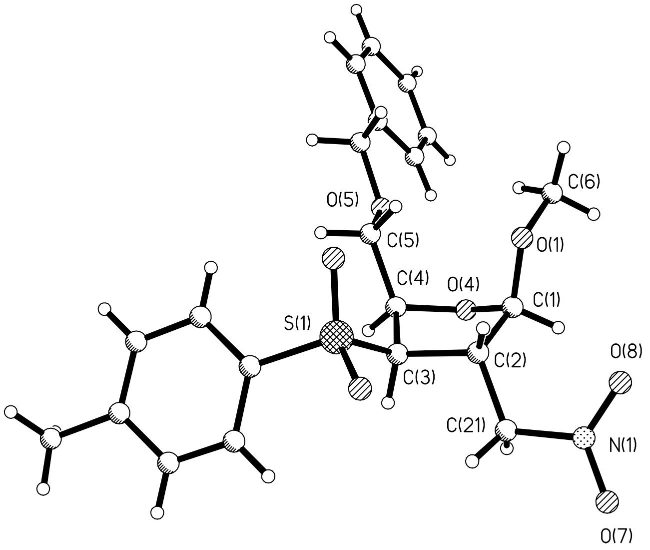


Figure 4.9 ORTEP Diagram of Compound 4.052

Selected bond lengths (Å) for compound 4.052	Selected bond angles (deg) for compound 4.052
C1 O1 1.395(3)	C1 O1 C6 113.0(2)
C1 C2 1.528(3)	C21 C2 C1 114.3(2)
O1 C6 1.433(3)	C21 C2 C3 108.6(2)
C2 C21 1.505(4)	C1 C2 C3 103.15(17)
C2 C3 1.556(3)	C4 C3 C2 105.20(17)
C3 C4 1.553(3)	C4 C3 S1 121.41(17)
C4 C5 1.500(4)	C2 C3 S1 109.29(16)
C5 O5 1.414(3)	O4 C4 C3 102.27(17)
O5 C7 1.392(4)	O2 S1 O3 118.28(12)
S1 O2 1.4300(17)	O2 S1 C3 105.02(11)
S1 O3 1.4309(19)	O3 S1 C3 110.37(11)
S1 C3 1.786(2)	C1 O4 C4 108.55(17)
O4 C1 1.413(3)	O1 C1 C2 107.4(2)
O4 C4 1.435(3)	O4 C1 C2 105.82(19)

4.5 Conclusion

We have successfully developed a general methodology for the synthesis of C-2 substituted branched-chain sugars using four vinyl sulfone-modified carbohydrates as starting materials. The anomeric configurations of both the pentofuranosyl and hexopyranosyl systems played a crucial role in influencing the diastereoselectivity of Michael addition reactions of the carbon nucleophiles.

4.6 Experimentals

General methods: See **Chapter 2**.

General procedure for the preparation of 4.046, 4.048 and 4.050: To a well stirred solution of NaOMe (8 eq) in MeOH (10 mL) was added nitromethane (10 eq) and the mixture was stirred for 0.5 h at ambient temperature under inert atmosphere. The appropriate vinyl sulfone-modified carbohydrate (1 eq) was added and the whole mixture was stirred at ambient temperature. After completion of the reaction (tlc), excess MeOH was removed under reduced pressure to get a solid mass. The solid residue was taken in CH_2Cl_2 (3 x 30 mL/mmol) and the mixture was stirred for 0.5 h. Any undissolved material was filtered. The combined filtrates were concentrated under reduced pressure to obtain the crude material, which was purified over silica gel to get the title compound.

General procedure for the preparation of 4.047, 4.049, 4.051 and 4.053: To a well stirred suspension of NaH (7 eq) in THF (5 mL) was added dimethyl malonate (10 eq) dropwise and the mixture was stirred for 0.5 h at ambient temperature. The appropriate vinyl sulfone-modified carbohydrate in THF (5 mL) was added dropwise and the mixture stirred at the same temperature. After completion of the reaction (tlc), excess THF was removed under reduced pressure to obtain an oily residue. The residue was dissolved in CH_2Cl_2 (40 mL/mmol) and the organic layer was washed thoroughly with aq. saturated $NaHCO_3$ (3 x 40 mL). The combined organic phases were dried over anhydr. Na_2SO_4, filtered and the filtrate was concentrated to dryness under reduced pressure to get the crude material. Purification of the crude material over silica gel afforded the title compound.

General procedure for the synthesis of 4.055 and 4.057: To a well stirred solution of a particular compound in pyridine (5 mL/mmol) was added mesyl chloride (5 eq/mmol) dropwise at 0 ^{o}C under N_2. The reaction mixture was kept at +4 ^{o}C for 18-24 h. After completion of the reaction (tlc), the reaction mixture was poured into ice-cold water (80-100 mL). The aqueous phase was extracted with EtOAc (4 x 30 mL). The combined organic layers were dried over anhydr. Na_2SO_4, filtered and the filtrate was concentrated to dryness under reduced pressure. The crude mesylates were purified over silica gel to afford the title compounds.

Methyl 2,3-dideoxy-3-*C*-nitromethyl-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfonyl-α-D-*altro*pyranoside 4.046: Compound **1.050** (0.3 g, 0.773 mmol) was converted to a needle shaped solid **4.046** in 36 h following the general procedure described above. Eluent: EtOAc:pet ether (1:5).

Yield: 0.21 g, 60%.

Mp: 188-189 ^{o}C [Recrystallized from EtOAc:pet ether (1:3)].

$[\alpha]_D^{25}$: +26.4^o (c 0.88, $CHCl_3$).

IR ($CHCl_3$): 3020, 1560 cm^{-1}.

^{1}H NMR (500 MHz): δ 7.77 (2 H, d, *J* 5.0 Hz, aromatic), 7.39 (6 H, m, aromatic), 7.17 (2 H, t, *J* 10 Hz, aromatic), 5.40 (1 H, s, PhCH), 4.85 (1 H, m), 4.76 (1 H, dd, *J* 13.6, 6.8 Hz, 1 H), 4.66 (1 H, s, H-1), 4.56 (1 H, dd, *J* 13.7, 8.1 Hz), 4.36 (1 H, q, *J* 10.5, 5.2 Hz), 3.94 (2 H, m), 3.65 (2 H, dd, *J* 19.1,10.4 Hz), 3.50 (3 H, s, OMe).

^{13}C NMR: δ 140.9, 138.1, 135.7, 132.3, 128.4, 127.6, 127.3, 125.7, 101.8, 96.5, 75.0 (CH_2), 74.0, 68.5 (CH_2), 60.2, 57.8, 54.3, 37.3.

MS: m/z (EI) 449 (2 M$^+$), 371 (4), 343 (7), 311 (24), 276 (15).

Analysis: Cald. for $C_{21}H_{23}O_8NS$: C, 56.11; H, 5.15; N, 3.11. Found: C, 56.31; H, 4.96; N, 3.27.

Methyl 2,3-dideoxy-2-*C*-bis(methoxycarbonyl)methyl-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfonyl-α-D-*altro*pyranoside 4.047: Compound **1.050** (0.2 g, 0.515 mmol) was converted to a needle shaped white solid **4.047** in 1.5 h following the general procedure described above. Eluent: EtOAc:pet ether (1:3).

Yield: 0.22 g, 82%.

Mp: 239–240 ^{o}C [Recrystallized from $CHCl_3$:pet ether (2:1)].

$[\alpha]_D^{27}$: +18.3^o (c 1.00, $CHCl_3$).

IR (Nujol): 1747, 1730, 1456, 1317, 1267 cm^{-1}.

^{1}H NMR: δ 7.77 (2 H, d, *J* 8.3 Hz, aromatic), 7.45-7.27 (6 H, m, aromatic), 7.16 (2 H, t, *J* 7.8 Hz, aromatic), 5.38 (1 H, s, PhCH), 4.79 (1 H, m), 4.58 (1 H, s, H-1), 4.32 (1 H, q), 3.98 (1 H, dd, *J* 10.3, 5.8 Hz), 3.80 (3 H, s, COOMe), 3.78 (3 H, s, COOMe), 3.88-3.72 (3 H, m), 3.60 (1 H, t, *J* 10.3 Hz), 3.46 (3 H, s, OMe).

^{13}C NMR: δ 168.1 (COOMe), 167.9 (COOMe), 42.9, 137.1, 132.9, 129.4, 128.4, 128.2, 126.8, 102.8, 98.2, 75.2, 69.8 (CH_2), 61.6, 58.7, 55.0 (OMe), 53.2, 39.0.

MS: m/z (EI) 520 (<1 M$^+$), 379 (6), 319 (32), 213 (21), 181 (37), 149 (43), 125 (48), 105 (80), 91 (80), 77 (100).

Analysis: Cald. for $C_{25}H_{28}O_{10}S$: C, 57.68; H, 5.41. Found: C, 57.64; H, 5.27.

Methyl 2,3-dideoxy-2-*C*-nitromethyl-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfonyl-β-D-*gluco*pyranoside 4.048: Compound **1.058** (0.37 g, 0.945 mmol) was converted to a brown colored needle shaped solid **4.048** in 2 h following the general procedure described above. Eluent: EtOAC:pet ether (1:5).

Yield: 0.31 g, 56%.

Mp: 149-150 °C [Recrystallized from EtOAc:pet ether (1:3)].

$[\alpha]_D^{25}$: –64.4° (c 0.97, $CHCl_3$).

IR (Nujol): 1558, 1448 cm^{-1}.

^{1}H NMR: δ 7.77 (2 H, d, *J* 8.3 Hz, aromatic), 7.28 (6 H, m, aromatic), 6.95 (2 H, d, *J* 7.8 Hz, aromatic), 5.59 (1 H, dd, *J* 14.3, 4.4 Hz), 5.31 (1 H, s, PhCH), 4.99 (1 H, dd, *J* 14.4, 2.7 Hz), 4.69 (1 H, d, *J* 8.3 Hz, H-1), 4.28 (1 H, dd, *J* 10.3, 4.4 Hz), 4.17-3.93 (2 H, m), 3.76 (1 H, t, *J* 10.3, 10.2 Hz), 3.55 (3 H, s, OMe), 3.49 (1 H, m), 2.72 (1 H, bs).

^{13}C NMR: δ 140.6, 136.3, 133.8, 129.4, 129.0, 128.6, 128.2, 126.5, 102.0, 76.9, 72.8 (CH_2), 69.0 (CH_2), 67.4, 62.5, 57.7, 39.6.

MS: m/z (EI) 448 (1), 402 (5), 342 (10), 248 (19), 149 (45).

Analysis: Cald. for $C_{21}H_{23}O_8NS$: C, 56.11; H, 5.15; N, 3.11. Found: C, 56.29; H, 5.20; N, 3.21.

Methyl 2,3-dideoxy-2-*C*-bis(methoxycarbonyl)methyl-4,6-*O*-(phenylmethylene)-3-*C*-phenylsulfonyl-β-D-*gluco*pyranoside 4.049: Compound **1.058** (0.35 g, 0.902 mmol) was converted to a needle shaped solid **4.049** in 2 h following the general procedure described above. Eluent: EtOAc:pet ether (1:3).

Yield: 0.46 g, 98%.

Mp: 98-99 °C [Recrystallized from EtOAc:pet ether (1:3)].

$[\alpha]_D^{27}$: –98.2° (c 0.9, $CHCl_3$).

IR ($CHCl_3$): 1739 cm^{-1}.

^{1}H NMR: δ 7.72 (2 H, dd, *J* 8.3, 2.0 Hz, aromatic), 7.35-7.18 (6 H, m, aromatic), 6.96 (2 H, dd, *J* 7.8, 1.5 Hz, aromatic), 5.21 (1 H, s, PhCH), 5.17 (1 H, d, *J* 7.8 Hz, H-1), 4.84 (1 H, d, *J* 4.4 Hz), 4.25 (1 H, dd, *J* 10.3, 4.4 Hz), 3.90 (2 H, m), 3.85 (3 H, s, COOMe), 3.75 (3 H, s, COOMe), 3.69 (1 H, m), 3.54 (1 H, m), 3.41 (3 H, s, OMe), 3.11 (1 H, m).

^{13}C NMR: δ 169.2 (COOMe), 168.9 (COOMe), 140.4, 136.3, 133.5, 129.1, 128.7, 128.3, 127.9, 126.2, 101.9, 101.6, 76.2, 69.0 (CH_2), 66.8, 64.2, 57.3, 52.6, 52.4, 50.1, 40.8.

MS: m/z (EI) 520 (1 M^+), 519 (4 M^+-1), 457 (29), 379 (100).

Analysis: Cald. for $C_{25}H_{28}O_{10}S$: C, 57.68; H, 5.41; S, 6.16. Found: C, 57.63; H, 5.04; S, 6.89.

Methyl 5-*O*-benzyl-2,3-dideoxy-2-*C*-nitromethyl-3-*C*-(*p*)-tolylsulfonyl-α-D-*arabino*furanoside 4.050: Compound **2.001** (0.17 g, 0.467 mmol) was converted to brown colored needle shaped solid **4.050** in 3 h following the general procedure described above. Eluent : EtOAc:pet ether (3:7).

Yield: 0.15 g, 73%.

Mp: 88-89 °C [Recrystallized from EtOAc: pet ether (1:3)].

$[\alpha]_D^{26}$: +58.8° (c 1.01, $CHCl_3$).

IR (Nujol): 3087, 3060, 3029, 1728, 1595, 1494 cm^{-1}.

^{1}H NMR: δ 7.74 (2 H, d, *J* 8.3 Hz, aromatic), 7.31 (7 H, m, aromatic), 4.91 (1 H, s, H-1), 4.52 (3 H, m), 4.35 (2 H, dd, *J* 12.7, 3.9 Hz), 3.71 (1 H, dd, *J* 10.7, 1.5 Hz), 3.61 (1 H, m), 3.35 (2 H, m), 3.26 (3 H, s, OMe), 2.46 (3 H, s, aromatic Me).

^{13}C NMR: δ 145.8, 137.7, 134.5, 130.3, 129.1, 128.7, 128.1, 127.9, 106.1, 77.5, 75.2 (CH_2), 73.8 (CH_2), 68.9 (CH_2), 64.8, 55.3 (OMe), 46.7, 21.9 (aromatic Me).

MS: m/z (EI) 405 (2), 373 (14), 357 (4), 299 (6), 267 (19), 155 (18), 139 (23), 111 (21), 99 (100).

Analysis: Cald. for $C_{21}H_{25}O_7NS$: C, 57.91; H, 5.78; N, 3.21; S, 7.36. Found: C, 57.89; H, 5.67; N, 3.01; S, 7.57.

Methyl 5-*O*-benzyl-2,3-dideoxy-2-*C*-bis(methoxycarbonyl)methyl-3-*C*-(*p*)-tolylsulfonyl-α-D-*arabino*furanoside 4.051: Compound **2.001** (0.22 g, 0.588 mmol) was converted to a white needle shaped solid **4.051** in 2.5 h following the general procedure described above. Eluent: EtOAc:pet ether (3:7).

Yield: 0.22 g, 74%.

Mp: 91-92 °C [Recrystallized from EtOAc:pet ether (1:3)].

$[\alpha]_D^{27}$: +51.4° (c 0.900, $CHCl_3$).

IR ($CHCl_3$): 4214, 3392, 2401, 1735, 1596 cm^{-1}.

^{1}H NMR: δ 7.71 (2 H, d, *J* 8.3 Hz, aromatic), 7.33 (7 H, bm, aromatic), 4.96 (1 H, s, H-1), 4.45 (3 H, m, $PhCH_2$), 3.89 (1 H, m), 3.74 (3 H, s, Me), 3.65 (3 H, s, Me), 3.52 (2 H, m), 3.28 (2 H, m), 3.23 (3 H, s, OMe), 2.44 (3 H, s, aromatic Me).

^{13}C NMR: δ 167.8 (C=O), 145.2, 137.9, 134.8, 129.9, 129.1, 128.0, 127.7, 106.1 (C-1), 77.8, 73.5 (CH_2), 69.3 (CH_2), 65.2, 54.9 (OMe), 52.7, 52.4, 47.4, 21.6 (aromatic Me).

MS: m/z (EI) 354 (9), 319 (42), 290 (15), 229 (42), 213 (35), 185 (39), 169 (68), 92 (100).

Analysis: Cald. for $C_{25}H_{30}O_9S$: C, 59.27; H, 5.96; S, 6.33. Found: C, 59.16; H, 6.64; S, 6.43.

Methyl 5-*O*-benzyl-2,3-dideoxy-2-*C*-nitromethyl-3-*C*-(*p*)-tolylsulfonyl-β-D-*xylo*furanoside 4.052: To a well stirred solution of ^{t}BuOK (0.16 g, 1.465 mmol) in THF

(4 mL) was added nitromethane (0.2 mL, 3.66 mmol) dropwise at 0 °C and the mixture was stirred at ambient temperature for 15 minutes. A solution of **2.003** (0.14 g, 0.366 mmol) in THF (4 mL) was added dropwise to the mixture. After 2 h, the reaction was worked up following the general procedure described above to get a brown residue. Purification of the residue over silica gel (230-400 mesh) with EtOAc:pet ether (4:21) afforded the title compound.

Yield: 0.09 g, 55%.

Mp: 125-126 °C.

$[\alpha]_D^{26}$: +14.3° (c 1.017, $CHCl_3$).

IR (Nujol): 1595, 1552, 1496, 1466, 1452, 1427 cm^{-1}.

^{1}H NMR: δ 7.74 (2 H, d, *J* 8.3 Hz, aromatic), 7.33 (7 H, d, *J* 7.3 Hz, aromatic), 5.02 (1 H, d, *J* 3.5 Hz, H-1), 4.58 (2 H, dd, *J* 14.2, 11.7 Hz, $PhCH_2$), 4.48-4.27 (3 H, m), 4.05-3.80 (3 H, m), 3.42 (3 H, s, OMe), 3.37-3.27 (1 H, m), 2.46 (3 H, s, aromatic Me).

^{13}C NMR: δ 146.0, 138.1, 135.9, 130.5, 128.6, 128.4, 128.2, 127.9, 107.5 (C-1), 78.5, 74.8 (CH_2), 73.7 (CH_2), 69.8 (CH_2), 65.8, 56.5, 45.9, 21.9 (aromatic Me).

MS: m/z (EI) 404 (7), 403 (8), 375 (10), 374 (14), 373 (51), 372 (26), 267 (29), 91 (100).

Analysis: Cald. for $C_{21}H_{25}O_7NS$: C, 57.91; H, 5.78; N, 3.21; S, 7.36. Found: C, 58.03; H, 5.91; N, 3.14; S, 7.56.

Methyl 5-*O*-benzyl-2,3-dideoxy-2-*C*-bis(methoxycarbonyl)methyl-3-*C*-(*p*)-tolylsulfonyl-β-D-*xylo*furanoside 4.053: Compound **2.003** (0.25 g, 0.668 mmol) was converted to a cotton like solid **4.053** in 2.5 h following the general procedure described above. Eluent: EtOAc:pet ether (3:7).

Yield: 0.29 g, 87%.

Mp: 99-100 °C [Recrystallized from EtOAc:pet ether (1:3)].

$[\alpha]_D^{27}$: +9.4° (c 1.00, $CHCl_3$).

IR ($CHCl_3$): 4214, 3685, 3616, 2401, 1747, 1737 cm^{-1}.

^{1}H NMR: δ 7.70 (2 H, d, *J* 8.3 Hz, aromatic), 7.32 (7 H, bs, aromatic), 5.16 (1 H, d, *J* 3.9 Hz, H-1), 4.57 (2 H, d, *J* 6.8 Hz), 4.43 (1 H, q), 4.17 (1 H, t, *J* 8.3 Hz), 3.92 (2 H, m), 3.73 (3 H, s, COOMe), 3.71 (3 H, s, COOMe), 3.49 (1 H, d, *J* 4.4 Hz), 3.40 (3 H, s, OMe), 3.20 (1 H, m), 2.44 (3 H, s, aromatic Me).

^{13}C NMR: δ 167.6 (C=O), 167.5 (C=O), 145.1, 137.9, 136.0, 129.9, 128.1, 127.6, 127.4, 106.5, 77.9, 73.1 (CH_2), 69.5 (CH_2), 65.7, 56.0 (OMe), 52.5, 50.0, 46.2, 21.4 (aromatic Me).

MS: m/z (EI) 506 (<1 M^+), 318 (19), 289 (10), 229 (190), 211 (13), 198 (16), 185 (7), 169 (41), 139 (30), 91 (100).

Analysis: Cald. for $C_{25}H_{30}O_9S$: C, 59.27; H, 5.96. Found: C, 59.04; H, 5.94.

Methyl 2,3-dideoxy-2-*C*-bis(methoxycarbonyl)methyl-3-*C*-phenylsulfonyl-α-D-*altro*pyranoside 4.054: To a well-stirred solution of **4.047** (1.5 g, 2.885 mmol) in MeOH (5 mL/mmol) was added 0.01 N HCl (20 mL/mmol). The reaction mixture was heated under reflux. After 8 h, $BaCO_3$ was added to neutralize the excess acid. The reaction mixture was then filtered through a celite bed and the filtrate was concentrated to dryness under reduced pressure to afford the crude material quantitatively. The product was taken directly to the next step.

Methyl 2,3,4-trideoxy-6-*O*-mesyl-2-*C*-bis(methoxycarbonyl)methyl-3-*C*-phenylsulfonyl-*erythro*-α-D-hex-3-enopyranoside 4.055: Compound **4.054** (1.25 g, 2.884 mmol) was converted to **4.055** following the general procedure described above. Eluent: EtOAc:pet ether (3:7).

Yield: 0.9 g, 63%.

$[\alpha]_D^{27}$: +31.6° (c 1.00, $CHCl_3$).

IR ($CHCl_3$): 3649, 1747, 1732, 1301, 1330, 1307, 1217 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 7.84 (2 H, d, *J* 7.3 Hz, aromatic), 7.59 (3 H, m, aromatic), 7.07 (1 H, s, H-4), 5.08 (1 H, s, H-1), 4.52 (1 H, bs), 4.31 (2 H, m), 4.08 (1 H, d, *J* 3.7 Hz), 3.76 (3 H, s, COOMe), 3.68 (3 H, s, COOMe), 3.29 (3 H, s, OMe), 3.09 (3 H, s, OMs), 3.00 (s, 1 H).

^{13}C NMR ($CDCl_3$): δ 168.3 (C=O), 166.9 (C=O), 137.9, 137.4, 136.3, 133.8, 129.2, 127.8, 97.6, 68.7 (CH_2), 66.7, 55.6 (OMe), 52.6, 50.1, 37.3.

MS: m/z (EI) 432 (18), 401(15), 364 (15), 351 (98), 319 (11), 291 (72), 255 (29), 195 (64), 167 (40), 153 (45), 137 (42), 125 (74), 79 (100).

Analysis: Cald. for $C_{19}H_{24}O_{11}S_2$: C, 46.33; H, 4.90; S, 13.02. Found: C, 45.92; H, 5.24; S, 13.26.

Methyl 2,3-dideoxy-2-*C*-bis(methoxycarbonyl)methyl-3-*C*-phenylsulfonyl-β-D-*gluco*pyranoside 4.056: To a well stirred solution of **4.049** (1.1 g, 2.115 mmol) in EtOH (5 mL/mmol) was added conc. HCl (1.0 mL/mmol). The reaction mixture was stirred at ambient temperature. After 2.5 h, $BaCO_3$ was added to neutralize the excess acid. The reaction mixture was filtered through a celite bed and the filtrate was concentrated to dryness under reduced pressure to get the crude material. Purification of the crude material over silica gel produced the title compound. Eluent: EtOAc:pet ether (2:3).

Yield: 0.77 g, 84%.

Methyl 2,3,4-trideoxy-6-*O*-mesyl-2-*C*-bis(methoxycarboxy)methyl-3-*C*-phenylsulfonyl-*erythro*-β-D-hex-3-enopyranoside 4.057: Compound **4.056** (0.57 g, 1.319) was converted to **4.057** as a yellowish gum following the general procedure described above. Eluent: EtOAc:pet ether (3:7).

Yield: 0.6 g, 92%

$[\alpha]_D^{27}$: –73.6° (c 1.00, $CHCl_3$).

IR ($CHCl_3$): 3616, 3444, 2358, 2341, 1732, 1346, 1215 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 7.86 (2 H, d, *J* 6.8 Hz, aromatic), 7.52-7.64 (3 H, m, aromatic), 7.21 (1 H, d, *J* 2.2 Hz, H-4), 5.08 (1 H, d, *J* 1.4 Hz, H-1), 4.61 (1 H, t, *J* 6.6 Hz), 4.28 (2 H, m), 3.94 (1 H, d, *J* 3.2 Hz), 3.76 (3 H, s, COOMe), 3.67 (3 H, s, COOMe), 3.24 (3 H, s, OMe), 3.07 (3 H, s, OMs), 3.04 (1 H, s).

^{13}C NMR ($CDCl_3$): δ 168.4 (C=O), 167.5 (C=O), 137.8, 136.8, 136.0, 133.9, 129.3, 128.1, 97.8, 69.2, 69.0 (CH_2), 56.0 (OMe), 52.8, 50.5, 37.5, 37.3.

MS: m/z (EI) 351 (18), 291 (6), 195 (19), 153 (31), 125 (55), 96 (57), 78 (100).

Analysis: Cald. for $C_{19}H_{24}O_{11}S_2$: C, 46.33; H, 4.90. Found: C, 46.33; H, 5.07.

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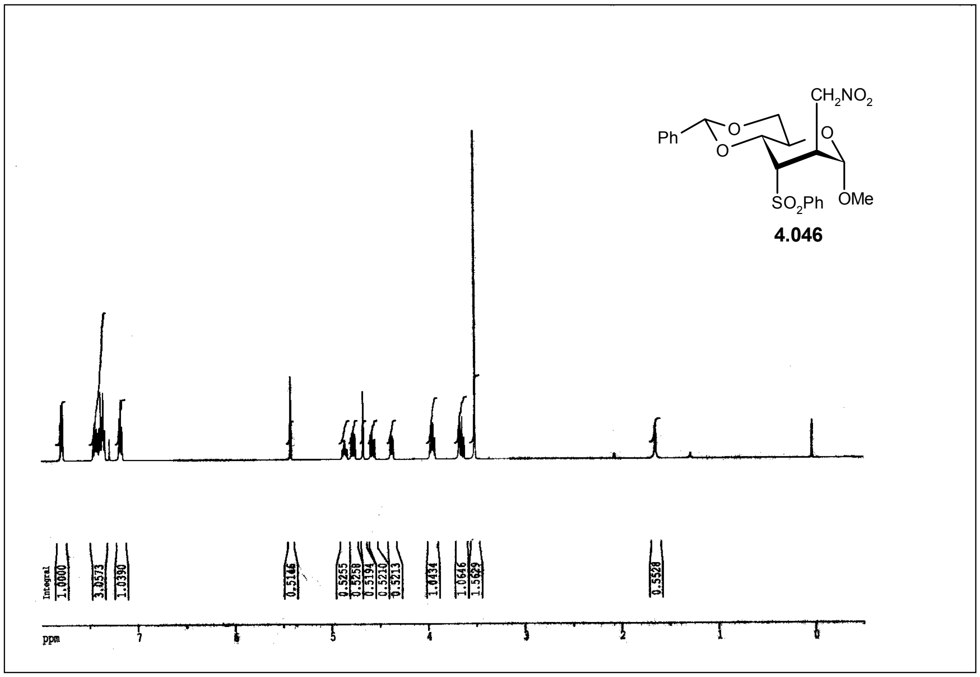
4.8 Spectra

^{1}H NMR of **4.046**



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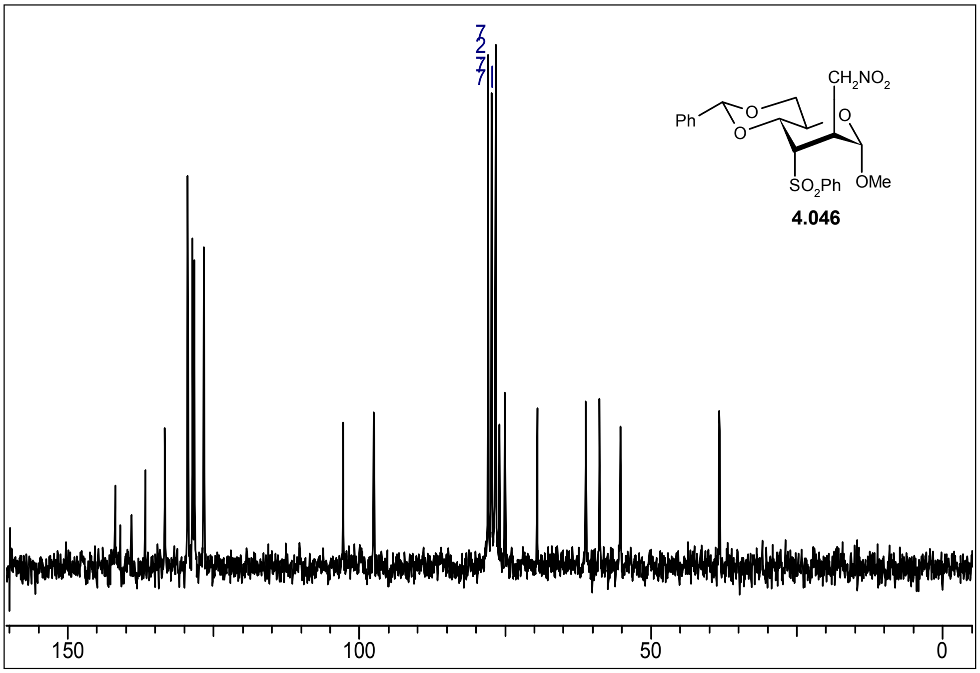
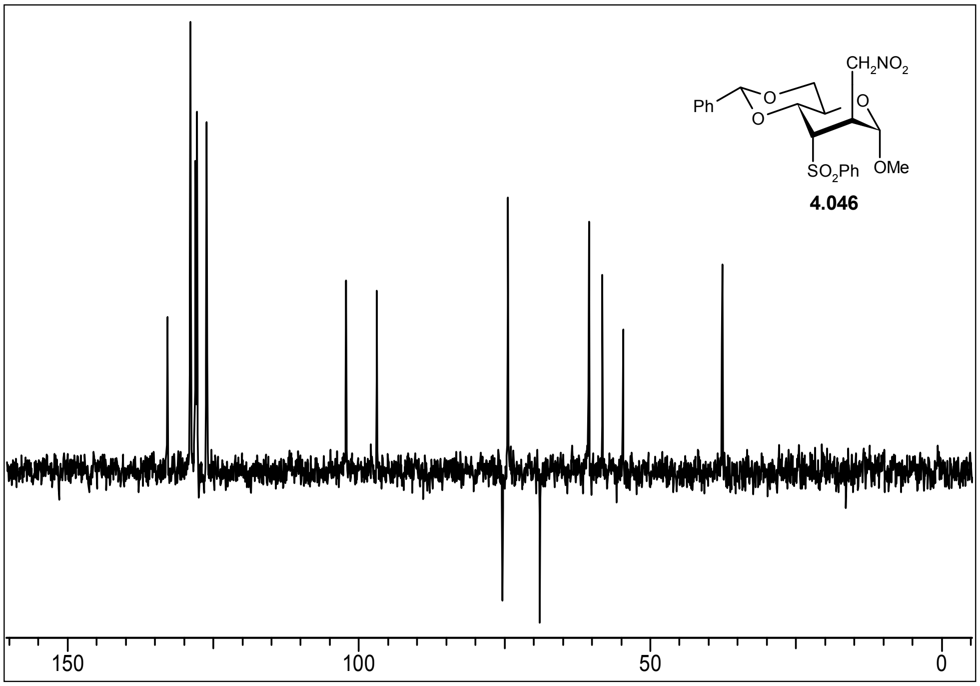


Dept of **4.046**



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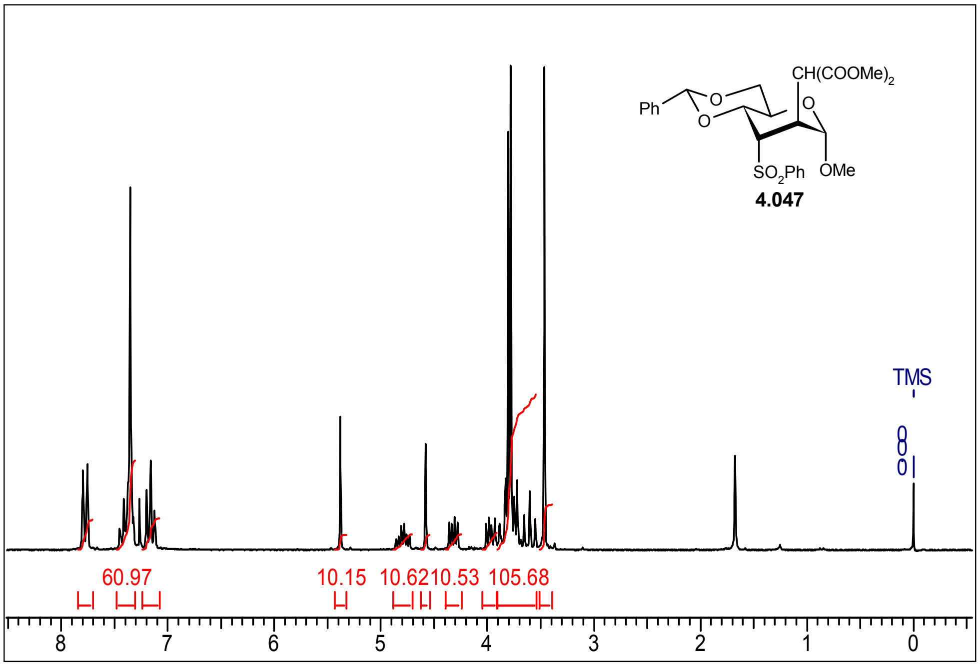

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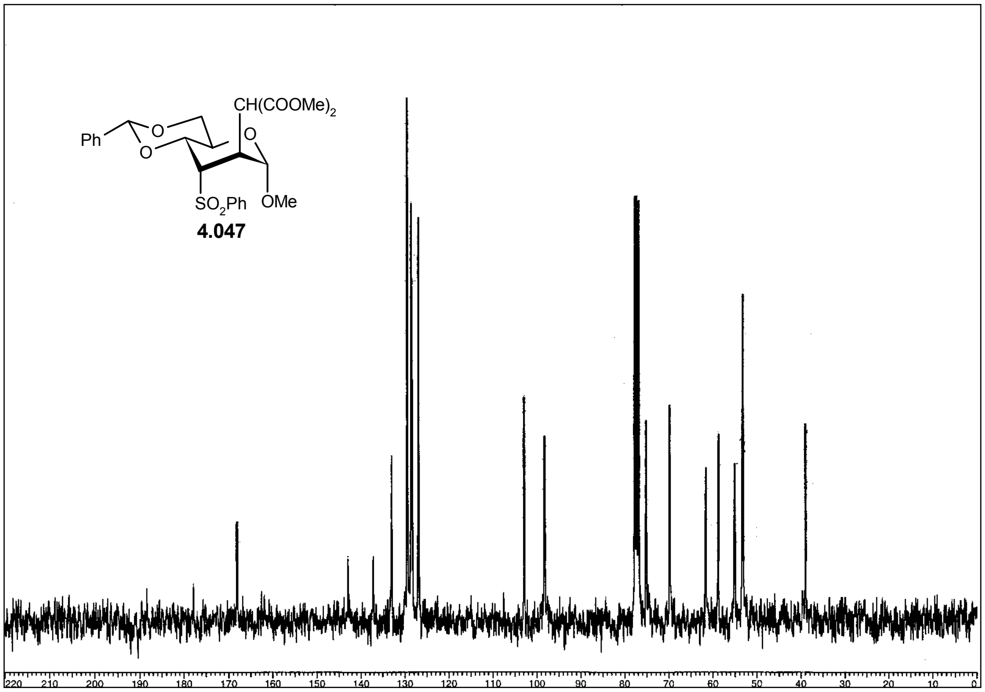

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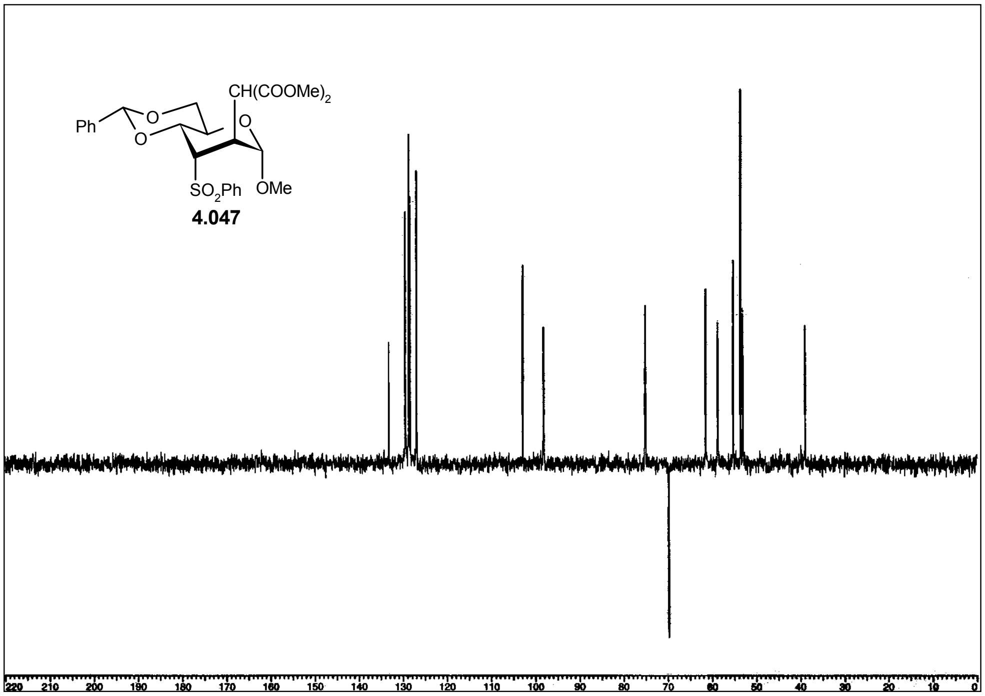

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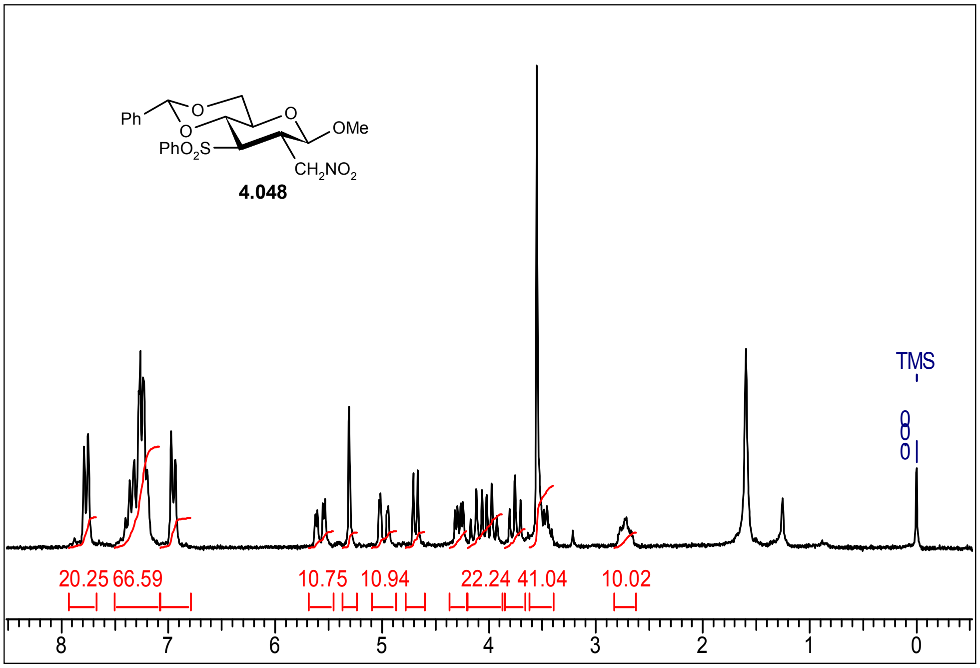

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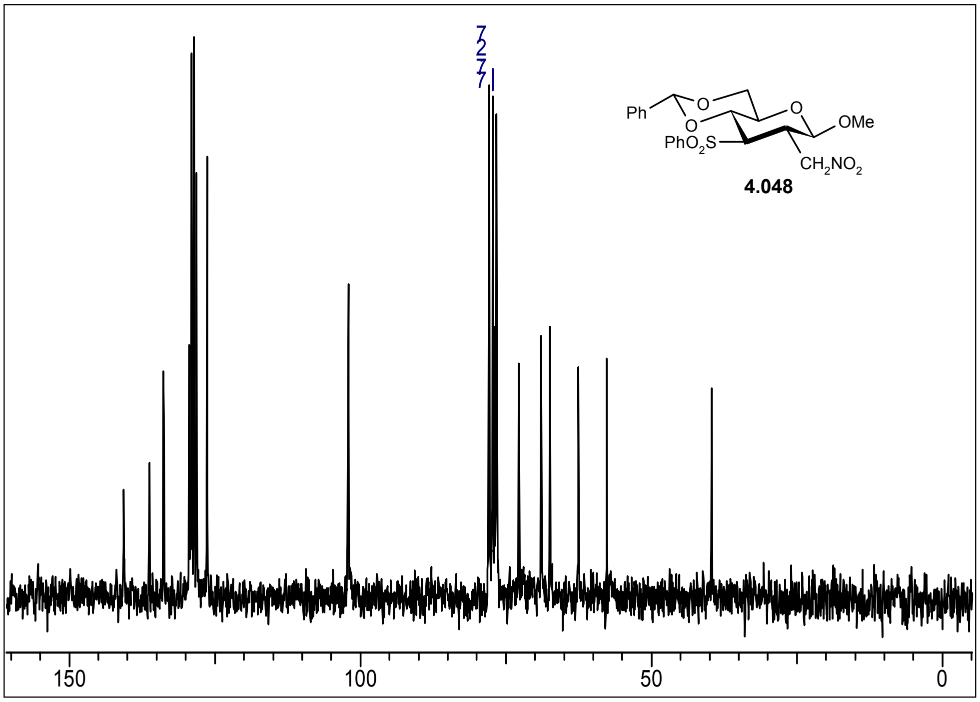

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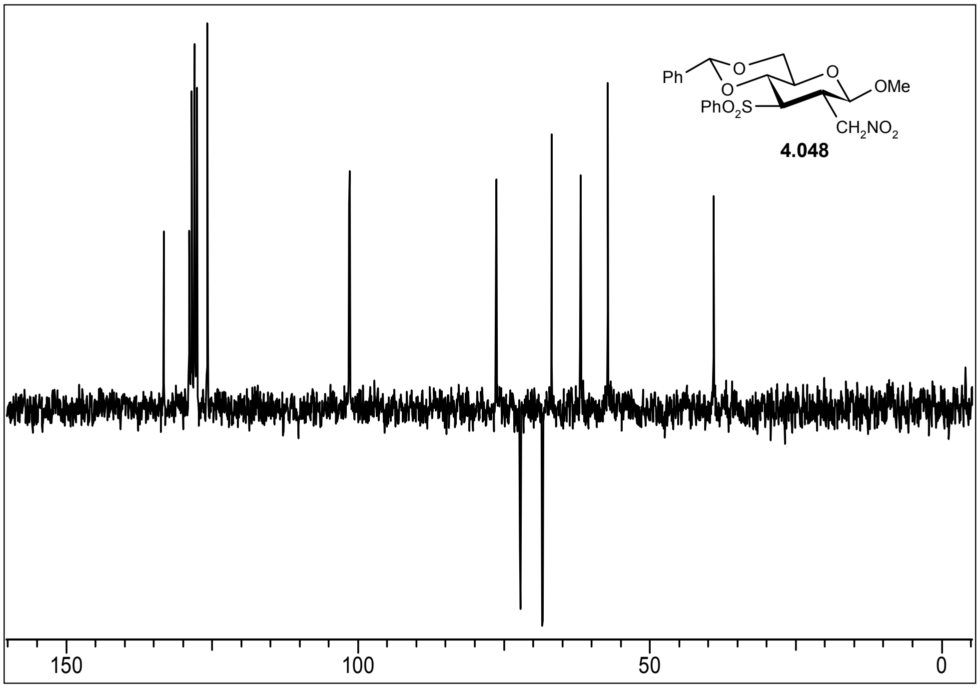
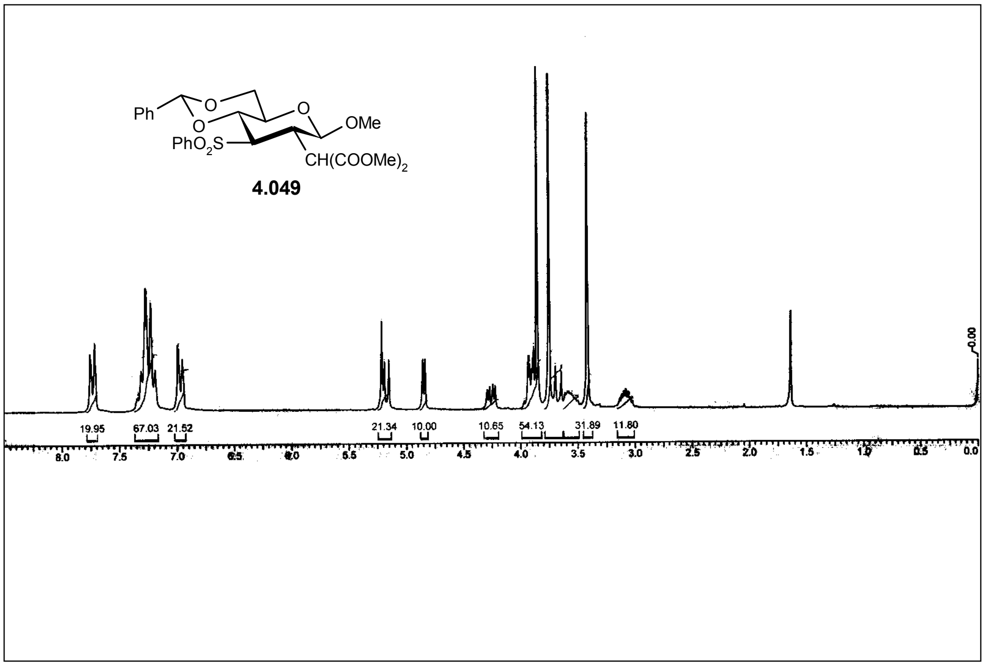
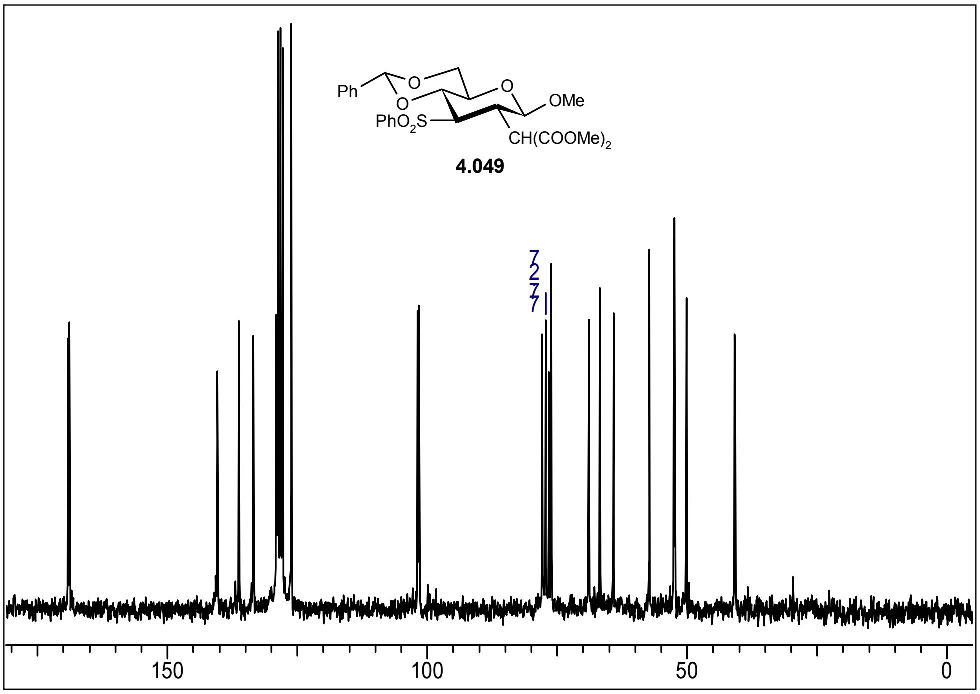


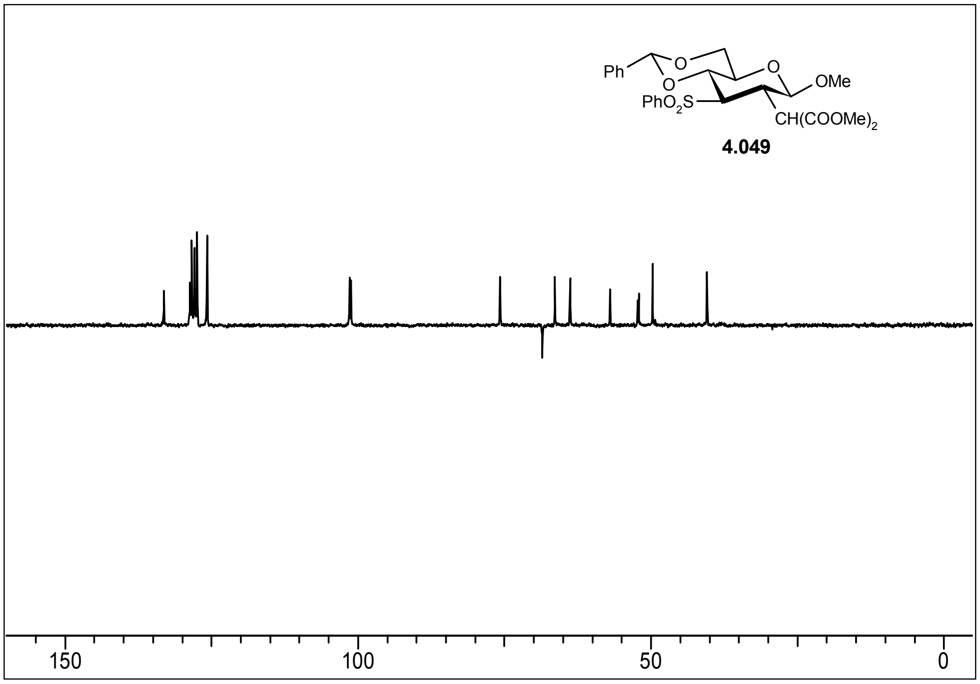
^{1}H NMR of **4.049**



^{13}C NMR of **4.049**



Dept of **4.049**



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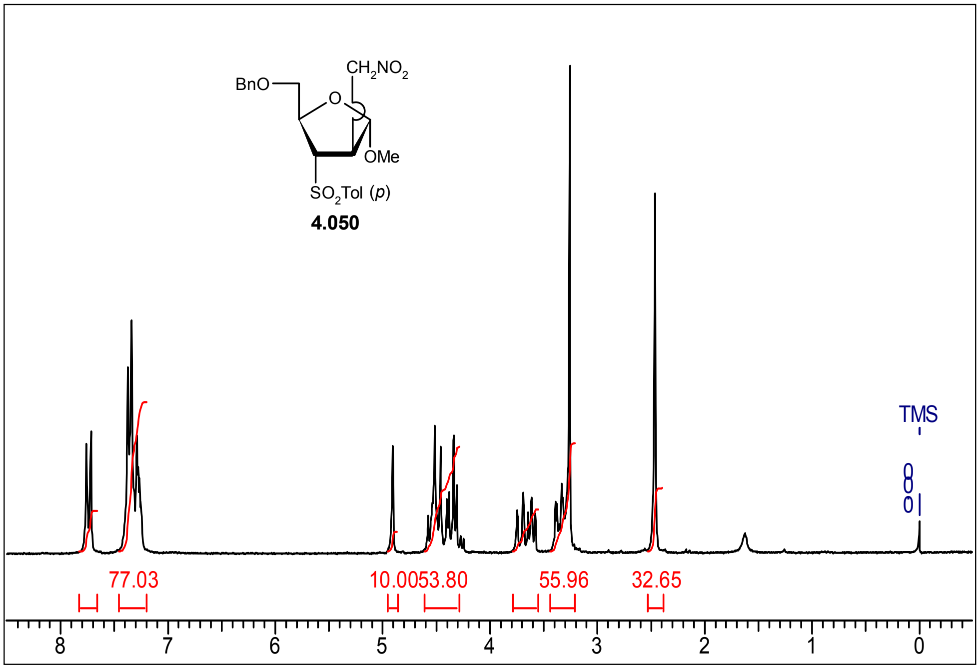

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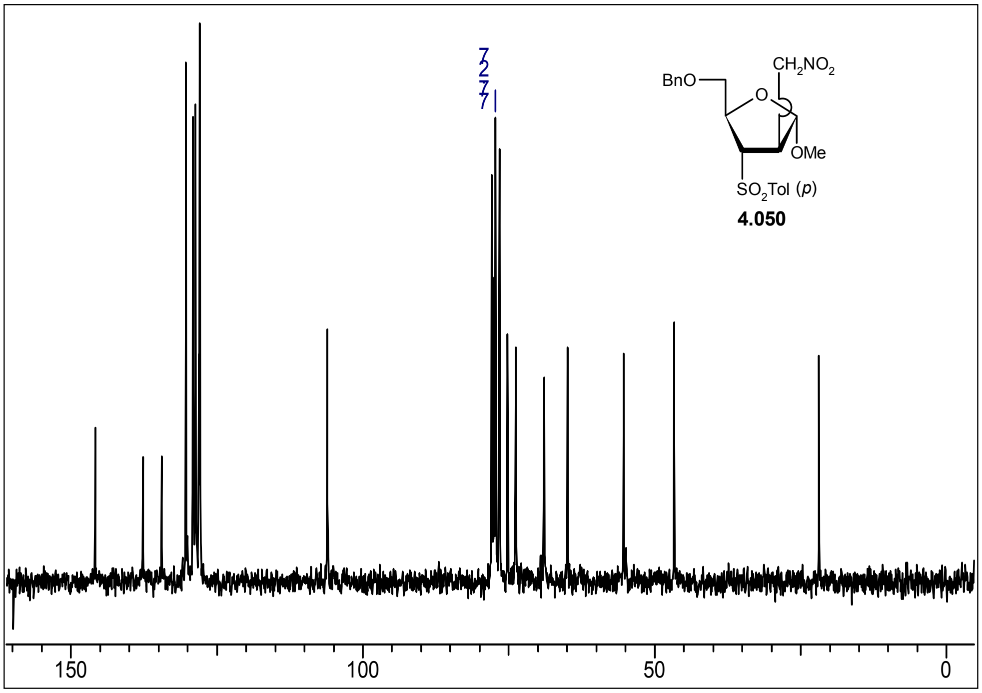

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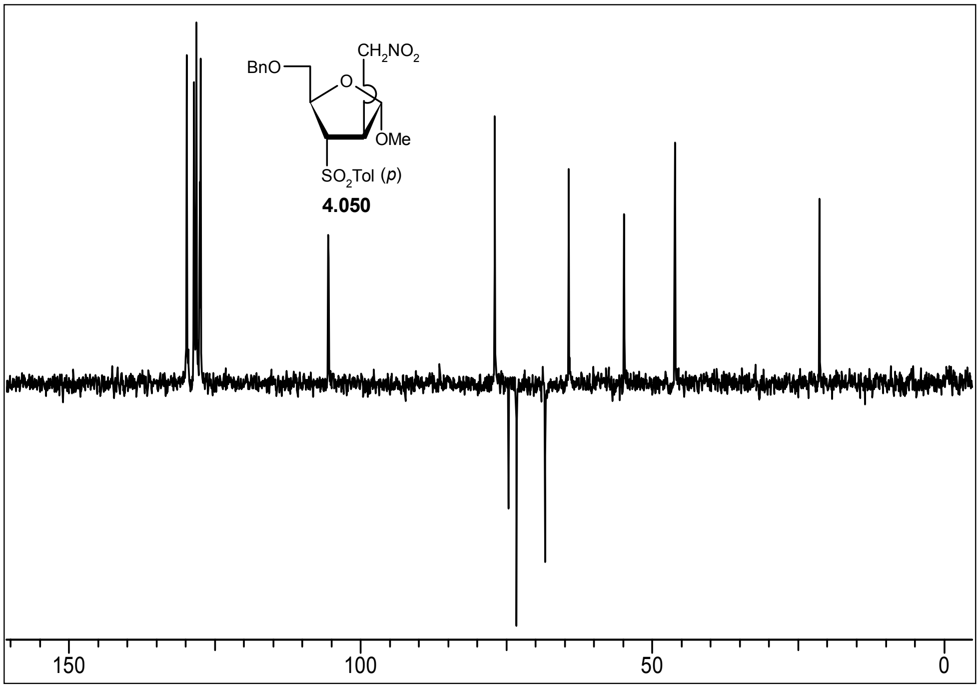
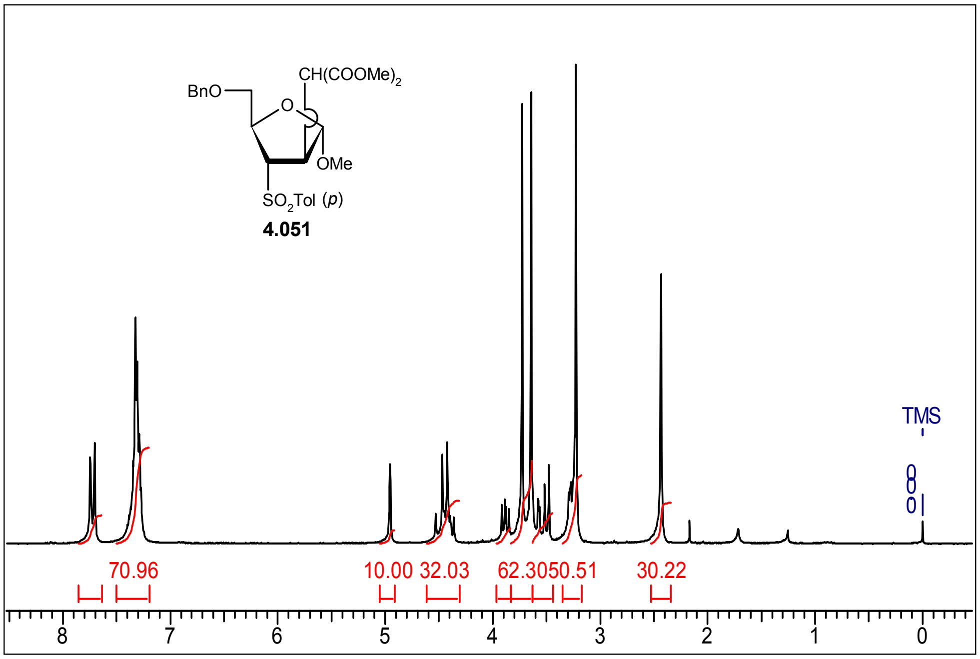


^{1}H NMR of **4.051**



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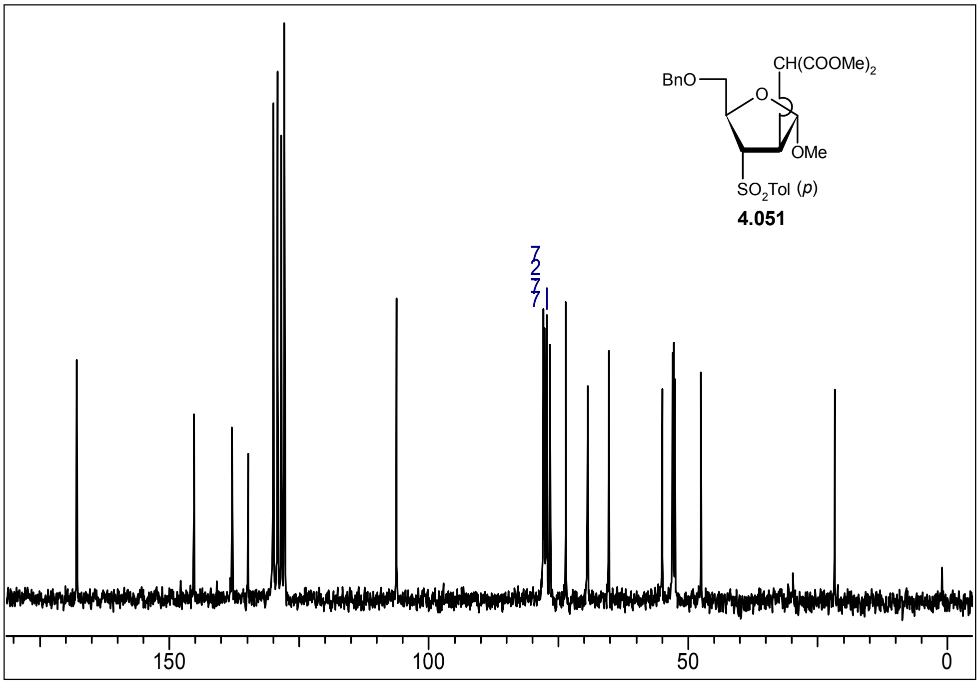

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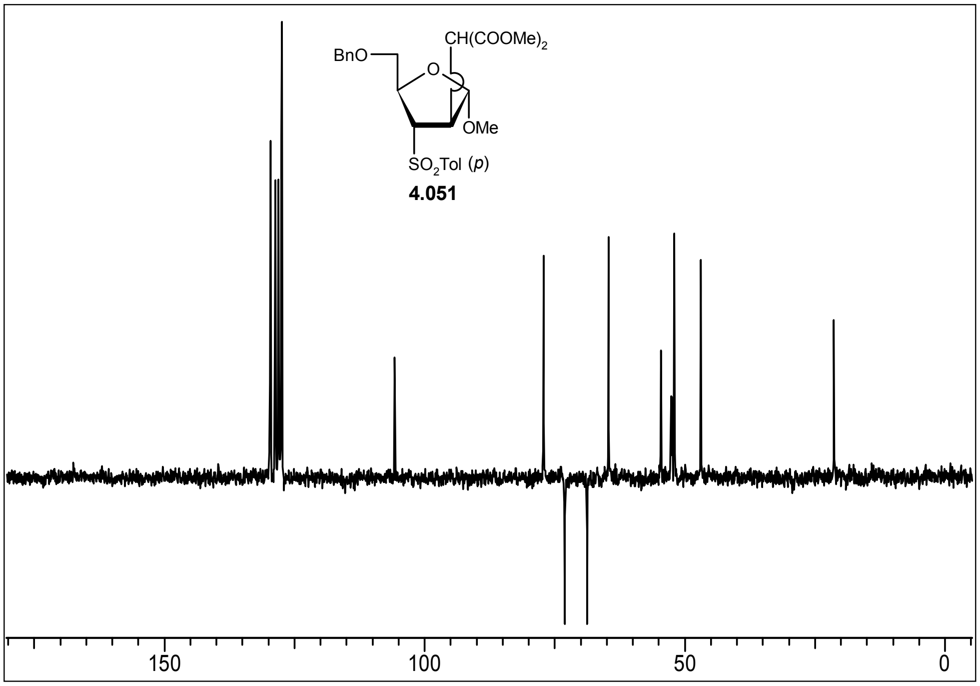

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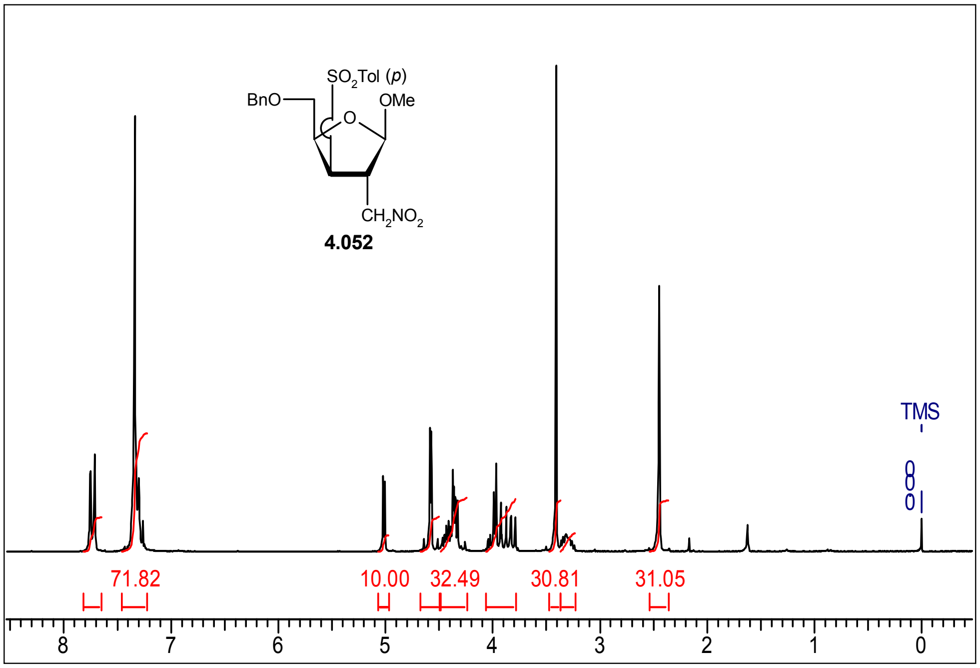

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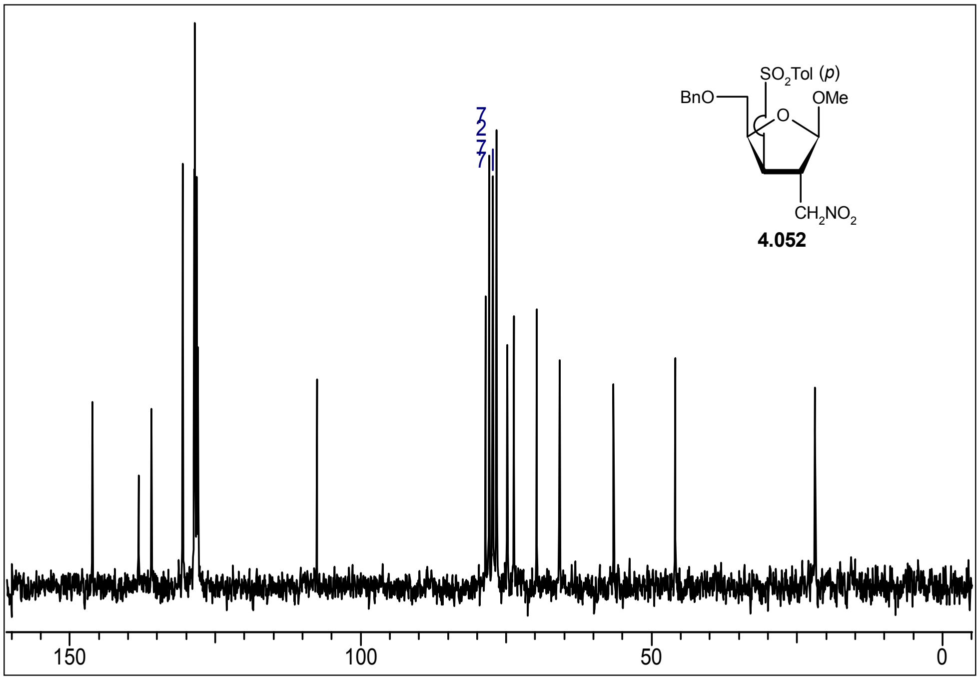

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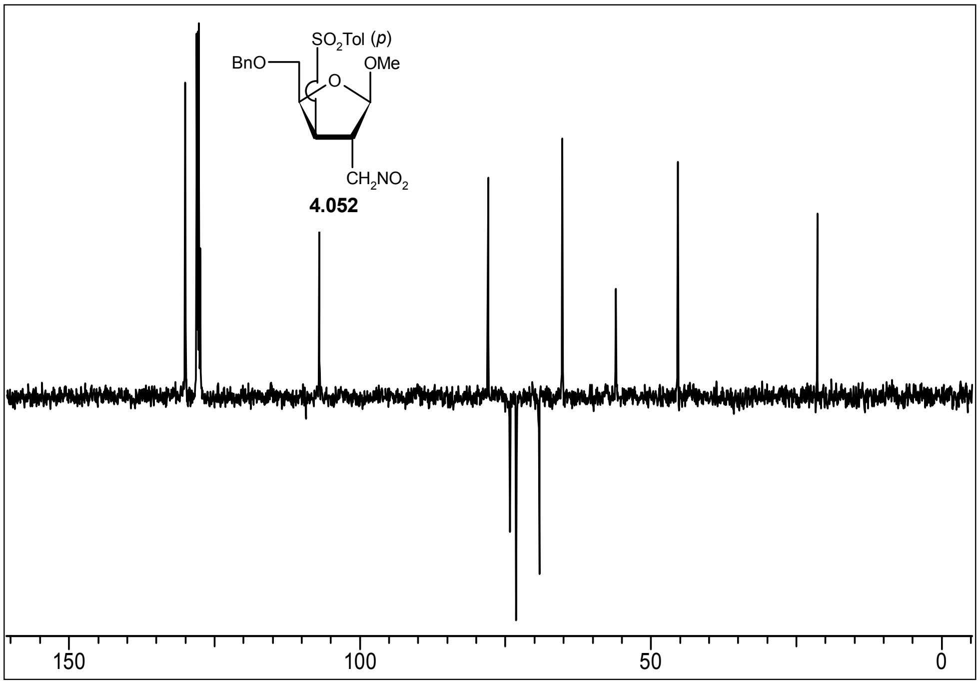

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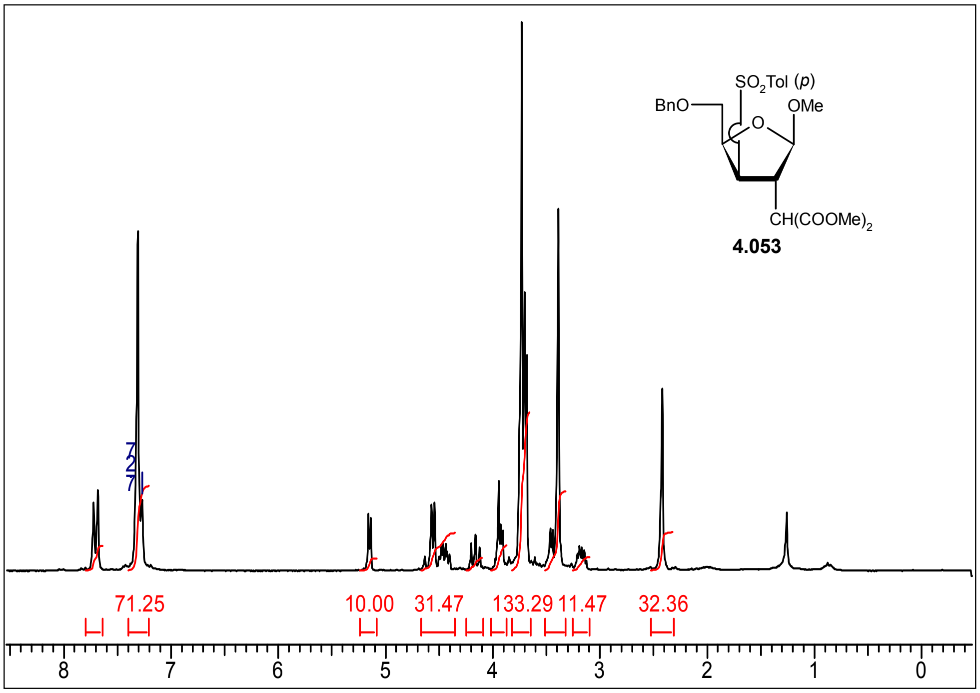

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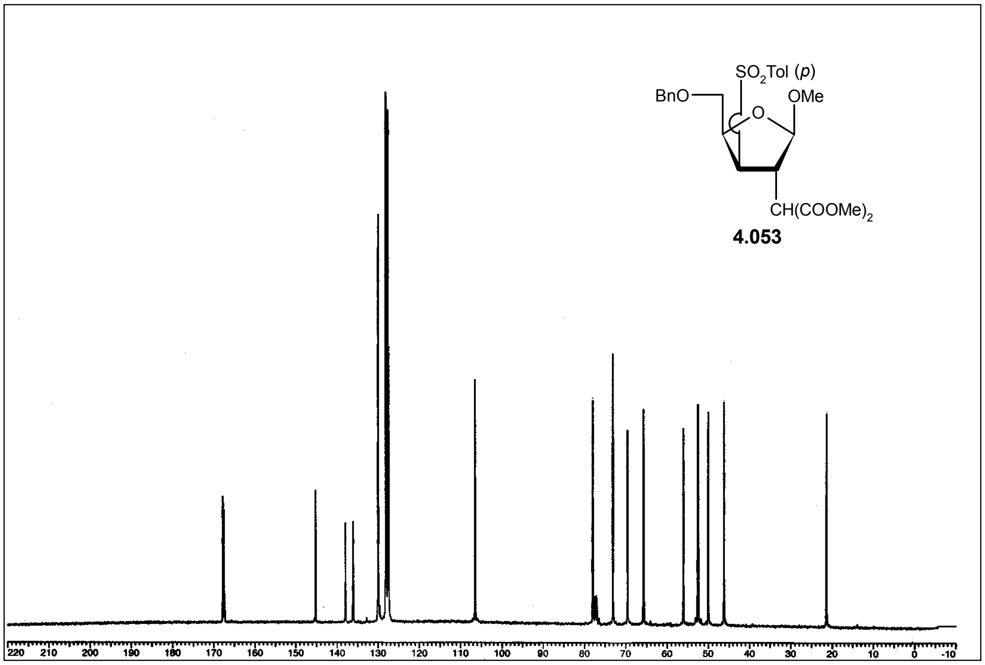

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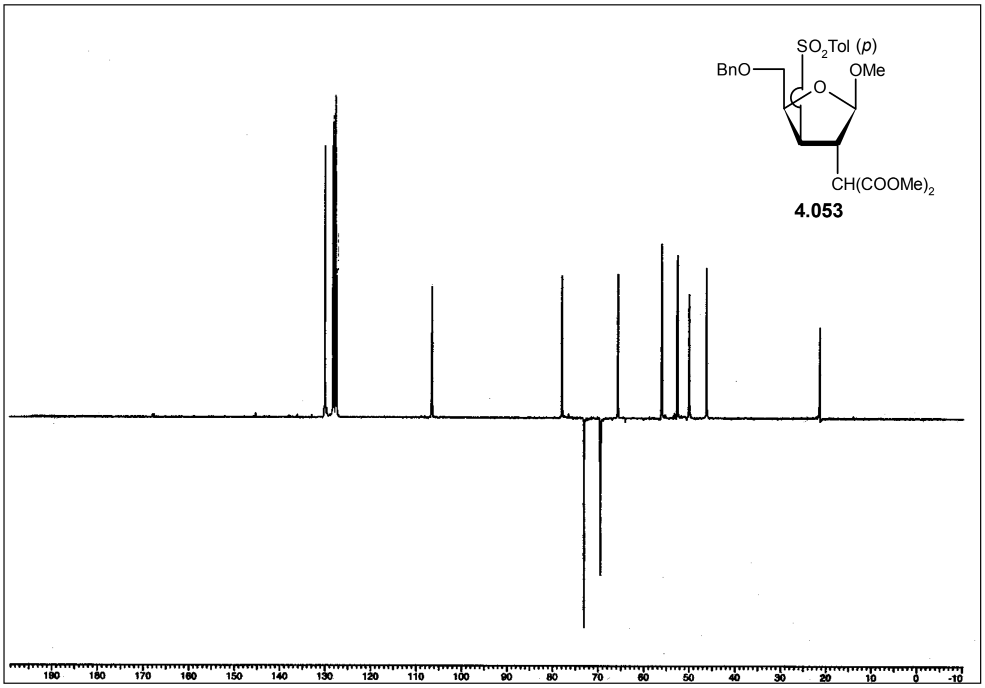

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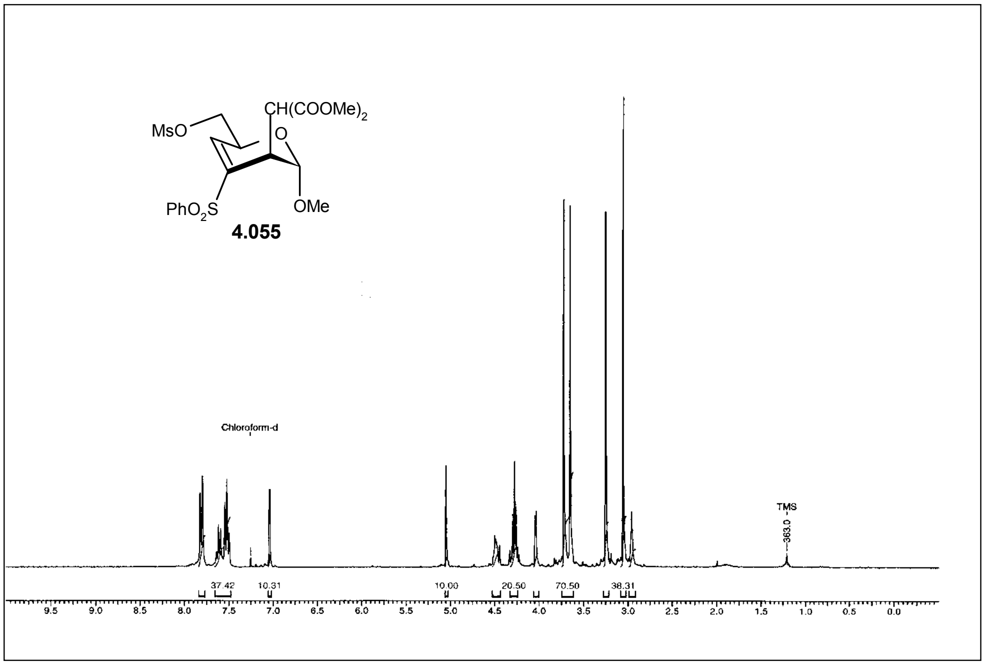
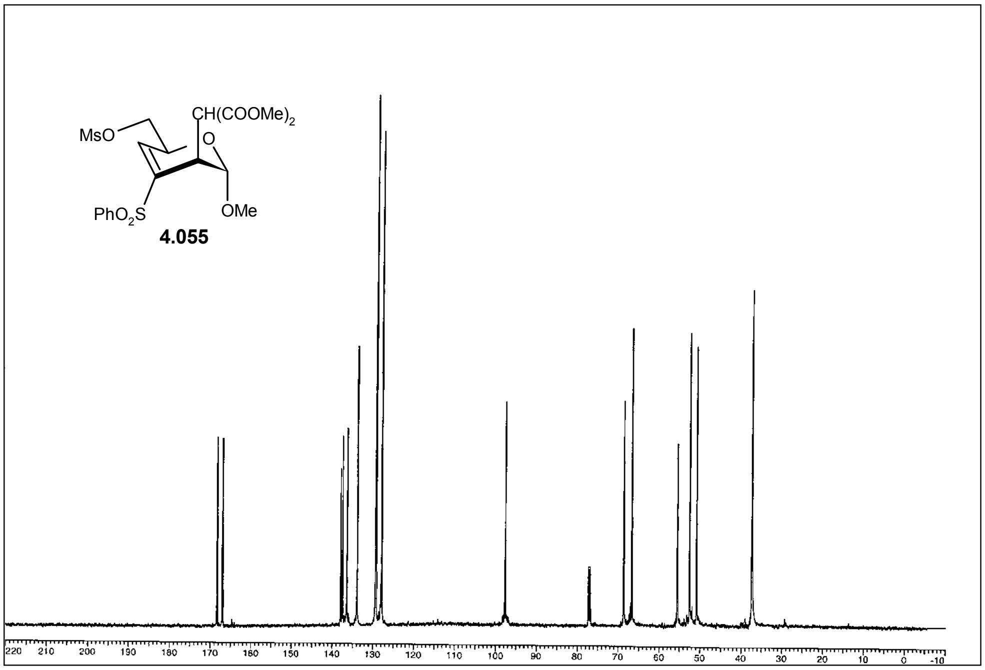


^{13}C NMR of **4.055**



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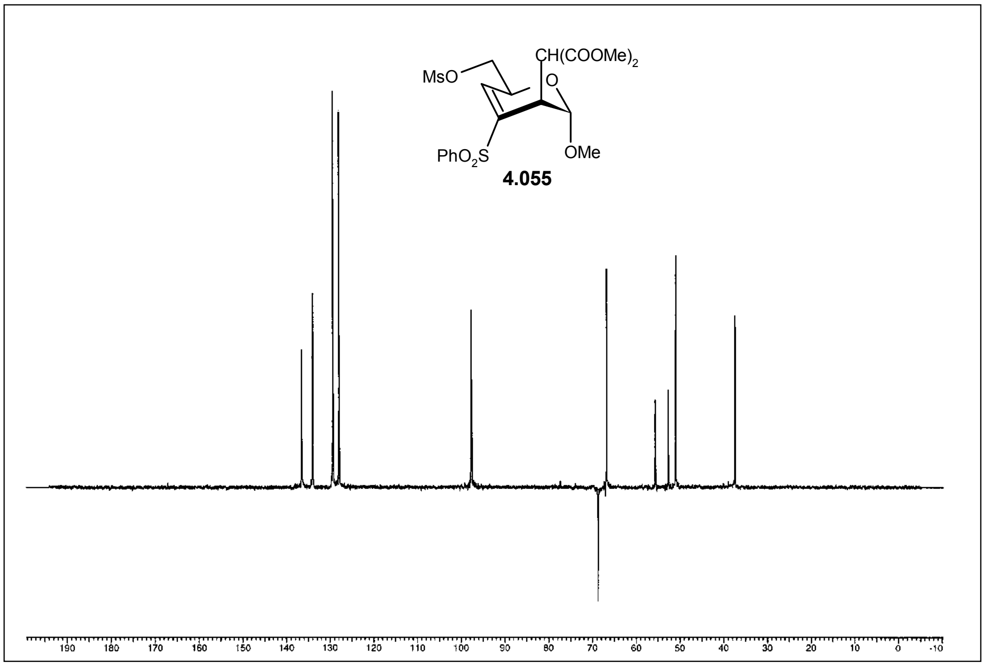
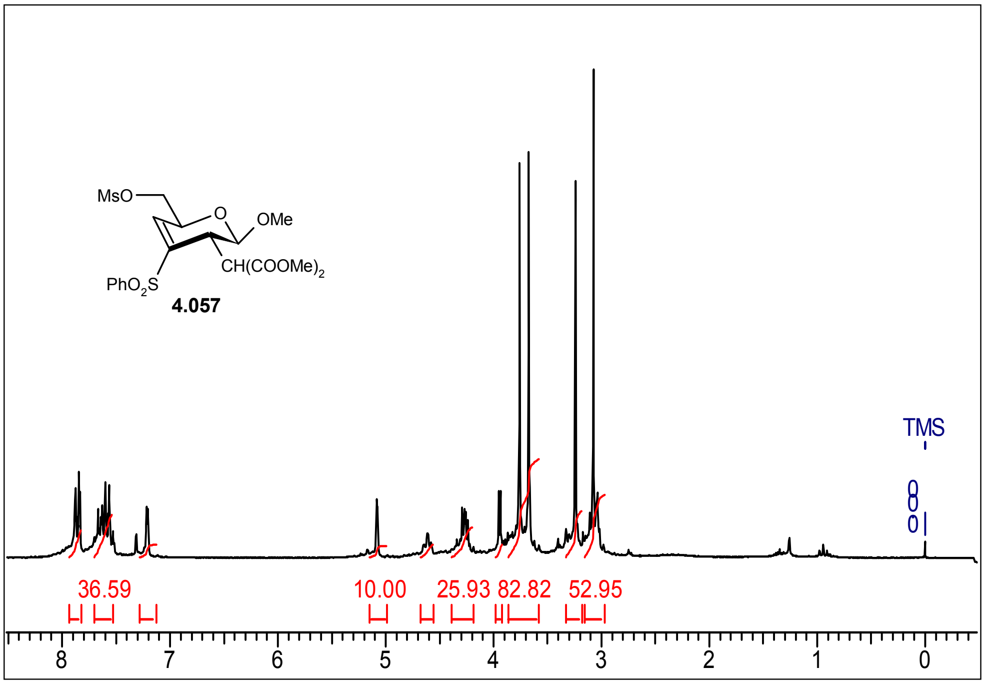
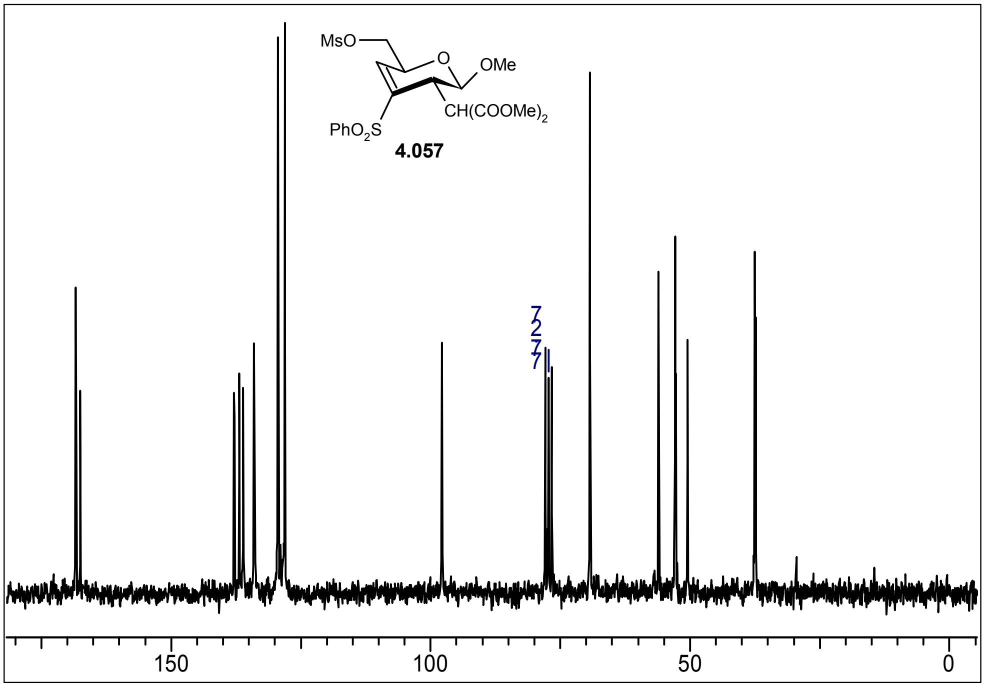


^{1}H NMR of **4.057**



^{13}C NMR of **4.057**



Dept of **4.057**