Utility of Sterically Strained Brønsted Salts as Organocatalysts for *C-C, C-O, O-Si* Bond Formations and Metal-Free *Si-H* Activation

A Thesis

Submitted in Partial Fulfilment of the

Requirements for the Degree of

Doctor of Philosophy

by

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Dedicated To My Mom and Brother

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STATEMENT

I hereby declare that the research work described in the thesis entitled "***Utility of Sterically Strained Brønsted Salts as Organocatalysts for C-C, C-O, O-Si Bond Formations and Metal-Free Si-H Activation***" is the outcome of investigations carried out by me under the supervision of **Dr. Pavan K. Kancharla** at Department of Chemistry, Indian Institute of Technology Guwahati, India, for the award of degree of Doctor of Philosophy.

In keeping with the general practice of reporting scientific observations, due acknowledgments have been made wherever the work described in this thesis is based on the findings of other investigators. Any omission that might have occurred by oversight or mistake is unintentional and gravely regretted.

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CERTIFICATE

This is to certify that the research work presented in the thesis entitled "***Utility of Sterically Strained Brønsted Salts as Organocatalysts for C-C, C-O, O-Si Bond Formations and Metal-Free Si-H Activation***" by **Ms. Rupa Bai Addanki** (Roll no: 176122021) for the award of the degree of Doctor of Philosophy is an authentic record of the results obtained from the research work carried out under my supervision at Department of Chemistry, Indian Institute of Technology Guwahati, India. The research work reported in his thesis is original and the same has not been submitted elsewhere for a degree.

August 2023

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List of Publications and Presentations

Publications

1. Exploiting the Strained Ion-Pair Interactions of Sterically Hindered Pyridinium Salts Toward S_N2 Glycosylation of Glycosyl Trichloroacetimidates. **Addanki, R. B.**; Moktan, S.; Halder, S. H.; Sharma, M.; Sarmah, B.K.; Bhattacharyya, K.; Kancharla, P. K. *J. Org. Chem.* **2024**, 89, *6*, 3713–3725.

2. TfO–···H–O–H Interaction-Assisted Generation of a Silicon Cation from Allylsilanes: Access to Phenylallyl Ferrier Glycosides from Glycals. **Addanki, R. B.**; Halder, S. H.; Kancharla, P. K. *Org. Lett*. **2022**, 24, *7*, 1465–1470.

3. Regio- and Stereoselective C-Glycosylation of Indoles Using o[1-(p-MeO-Phenyl)vinyl]benzoates (PMPVB) as Glycosyl Donors under Brønsted Acid Catalysis. Halder, S.; **Addanki, R. B.**; Kancharla, P. K. *J. Org. Chem*. 2023, 88, *3*, 1844–1854.

4. Glycosyl Ortho-[1-(p-MeOPhenyl)Vinyl]Benzoates (PMPVB) as Easily Accessible, Stable, and Reactive Glycosyl Donors for O-, S- and C-glycosylations Under Brønsted Acid Catalysis. Halder, S.; **Addanki, R. B**.; Moktan, S.; Kancharla, P. K. *J. Org. Chem.* **2022**, 87, *11*, 7033–7055.

5. Catalytic stereoselective synthesis of 2-deoxy α-glycosides using glycosyl ortho-[1-(p-MeOPhenyl)Vinyl]Benzoate (PMPVB) donors. Halder, S.; **Addanki, R. B.**; Kancharla, P. K. *Org. Biomol. Chem.* **2022**, *20*, 1874.

6. Sterically Strained Brønsted Pair Catalysis by Bulky Pyridinium Salts: Direct Stereoselective Synthesis of 2-Deoxy and 2,6-Dideoxy-β-thioglycosides from Glycals. Mukherji, A.; **Addanki, R. B**.; Halder, S.; Kancharla, P. K. *J. Org. Chem.* **2021**, 86, *23*, 17226–17243.

7. Three Step Synthesis of L-Altrose from D-glucal derived Perlin Aldehyde. Halder, S.; **Addanki, R. B**.; Kancharla, P. K. JICS, 2020, 97, *2*, 243-250.

Conferences attended & Awards

1. Received ***Young Scientist Award*** for Best Oral & Poster presentation at **CARBO-XXXVI, 2022-** an International conference held at IIT-Bombay**.**

2. Received Prize for ***Best Oral presentation*** at **Research Industrial Conclave- RIC-2022-** a national conference held at IIT-Guwahati**.**

3. Participated in Poster presentation for Chemical Research Society of India 28th National Symposium in Chemistry **(CRSI NSC-28)-2022** held at IIT-Guwahati**.**

4. Participated in Poster presentation for **NERC (national conference) 2022** held at IIT-Guwahati**.**

Members of the Doctoral Committee

Dr. Pavan Kumar Kancharla (Thesis supervisor)

Dr. Parameswar K. Iyer (Chairman)

Dr. Chandan Kumar Jana (Member)

Dr. Krishna Pada Bhabak (Member)

Abbreviations

AcOH	Acetic acid
ACN	Acetonitrile
Ac	Acetyl
Å	Angstrom
α	Alpha
β	Beta
BF_3	Boron trifluoride
BF_4	Tetrafluoroborate
Bn	Benzyl
Bz	Benzoyl
$BArF_4$	Tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
cat.	Catalytic/Catalyst
°C	Degree Celsius
CH_3	Methyl
$CDCl_3$	Deuterated chloroform
DNA	Deoxyribonucleic acid
DCM	Dichloromethane
DCE	1,2-Dichloroethane
DMF	N,N'-Dimethylformamide
DTBP	2,6-Di-*tert*-butylpyridine
DTBMP	2,6-Di-*tert*-butyl-4-methylpyridine
DIPEA	N,N'-Diisopropylethylamine
DMSO	Dimethyl sulfoxide
δ	Delta
Et	Ethyl
EOAc	Ethylacetate
Eq.	Equation
Equiv	Equivalent
Et_3SiH	Triethylsilane
Fmoc	Fluorenylmethyloxycarbonyl
g	Gram
Hz	Hertz
h	Hour
HCl	Hydrochloric acid
HBr	Hydrobromic acid
HPLC	High performance liquid chromatography
HRMS	High-resolution mass spectroscopy
IPA	Isopropyl alcohol
K_2CO_3	Potassium carbonate
LiBr	Lithium bromide
Mm	Millimetre
MeI	Methyl iodide

MHz	Mega hertz
min	Minute
Me	Methyl
ml	Millilitre
mg	Milligram
µl	Microlitre
$NaHCO_3$	Sodium bicarbonate
NIS	N-Iodosuccinimide
NaI	Sodium iodide
NaH	Sodium hydride
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
Nu	Nucleophile
PG	Protecing Group
Ph	Phenyl
PPh_3	Triphenylphosphine
ppm	Parts per million
RNA	Ribonucleic acid
RT	Room temperature
Tf	Triflate
Ts	Tosylate
TBAI	Tetra-n-butylammonium iodide
THF	Tetrahydrofuran
TTBP	2,4,6-Tri-butylpyrimidine
TTBPy	2,4,6-Tri-*tert*-butylpyridine
TES	Triethylsilyl
TMS	Trimethylsilane
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TIPS	Triisopropylsilyl
TIPDS	Tetraisopropyl disiloxane
TfOH	Triflic acid
TMSOTf	Trimethyltrifluoromethanesulfonate
TLC	Thin layer chromatography
UV	Ultraviolet
XRD	X-ray powder diffraction

Abstract

The contents of the thesis entitled "***Utility of Sterically Strained Brønsted Salts as Organocatalysts for C-C, C-O, O-Si Bond Formations and Metal-Free Si-H Activation***" have been divided into five chapters based on the experimental works, and results during my research period. The first chapter of the thesis is entitled the literature review of "Sterically strained Brønsted salts" which includes the study of strained bulky bases and their utility in various organic reactions. The second chapter shows the synthesis of Phenylallyl Ferrier-*C*-glycosides utilizing the sterically strained interactions of triflate anion with water molecule in activating allylsilanes by generating silyl cation. Chapter III showcased the synthetically interesting S_N2-type glycosylation of perbenzylated glycosyl trichloroacetimidates using tetrafluoroborate salt of sterically strained tri-*tert*-butylpyridine. In Chapter IV, we have shown the metal-free activation of the Si-H bond using bulky ion pair, TTBP-BArF salt. We have utilized this reactivity in various types of organic transformations. Chapter V includes a protocol for beta-selective mannosylation by utilizing protecting group influence on the mannosyl donor.

Chapter I…. The literature review of Sterically Strained Brønsted Salts

In 1966, H.C. Brown and Bernard Kanner reported an extensive study on bulky pyridine bases, about the occurrence of a steric hindrance toward the proton. The study was performed on several pyridine bases including pyridine, 2-picoline, 2,6-lutidine, and 2,6-tert-butylpyridine (DTBP). The study and similar reports highlighted the unusual behavior of DTBP and TTBPy (2,4,6-tri- tertbutylpyridine) toward proton with steric strain.

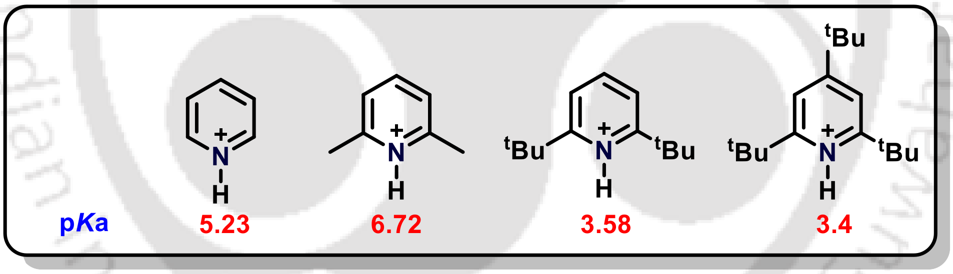


Figure 1. pKa values of bulky pyridine bases

The lower pKa (**Figure 1**) of these sterically strained bases is linked to their insusceptibility in the solvation of their ionic charge due to steric interference of the ortho-*tert*-butyl groups. This enables these bulky bases to have an interaction of N-H and water molecule or chloride atom in a hydrogen bonding distance only (**Figure 2**).

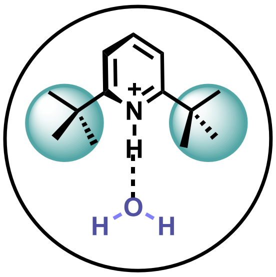
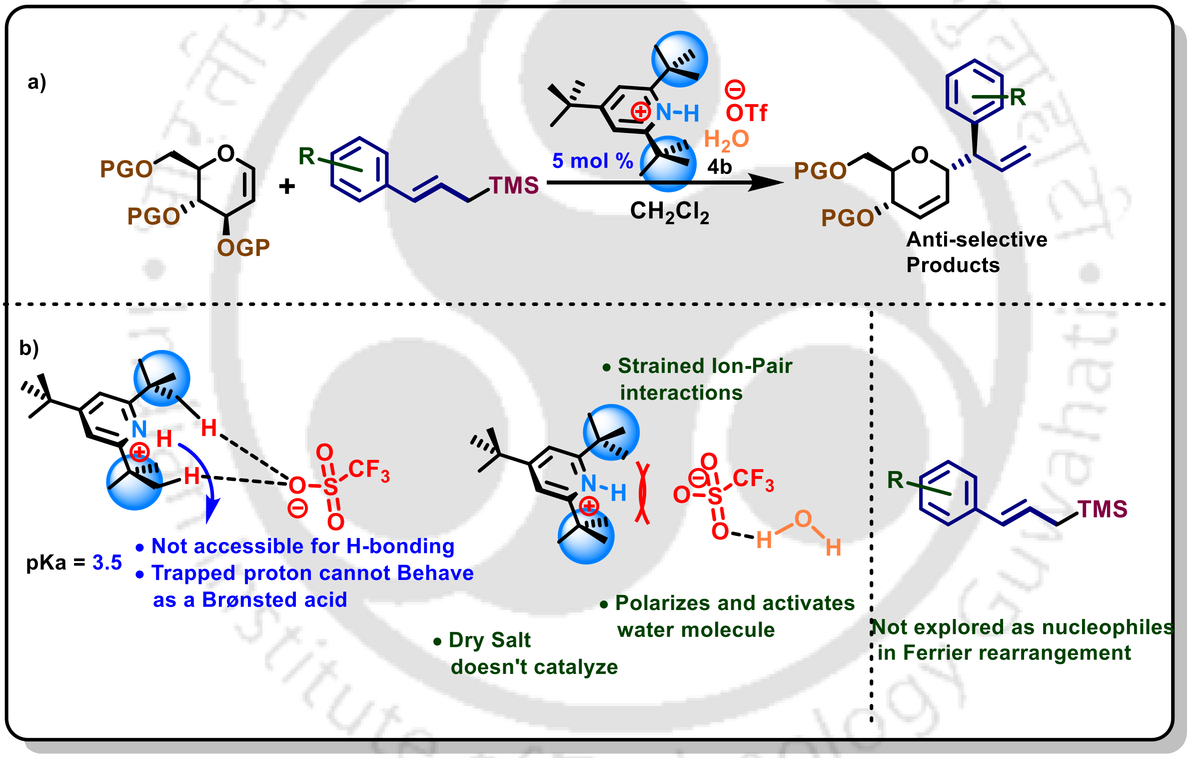


Figure 2. Sterically strained interaction of N-H of DTBP and H_2O

This unusual behaviour of the bulky bases have made them to be utilized as acid scavengers. Using the frustration generated between the ion pairs of these bulky Brønsted salts, our group has been exploring[3] their reactivity in glycosylations as organocatalysts.

Chapter II.. TfO-….H-O-H Interactions Assisted Generation of Silicon Cation from Allylsilanes*:* Access to Phenylallyl Ferrier Glycosides from Glycals

In this chapter, it was demonstrated that, the protonated salt bulky pyridinium triflate, TTBPyH.OTf, could catalyse the Ferrier Glycosylation of various glycals through a mild and efficient pathway. The sterically frustrated salt was noted to be able to activate the traces moisture trapped with the catalyst (a half hydrate) which turns out to be critical for activating allylsilane systems and further activating the glycals, resulting in a new interesting class of phenylallyl Ferrier glycosides diastereoselectively (**Scheme 1**).



Scheme 1. Current protocol and its advantages

C-glycosides are well known for their higher stability towards enzymatic and chemical hydrolysis processes when compared to *O*/*N*-glycosides. This has been one such key point that brought them greater attention as potential therapeutic agents and biological probes. The Ferrier rearrangement of any D-glycal to 2,3-unsaturated *C*-glycoside will go via an allyloxocarbenium ion where the nucleophile attacks at C-1 under normal conditions. In most of the literature reports, it was shown that su ch glycosylations via Ferrier rearrangements have shown higher stereoselectivity for α-isomer unless there is a forceful condition as the α-isomer is kinetically more stable and hence it is favoured. In general, the anomeric effect of the ring oxygen and the conformation of the pyranose ring favour α-attack of the incoming group, to produce the pseudoaxial glycoside. In literature, Strongly Lewis acidic Metal Salts or Excess BF_3Et_2O or Super acidic conditions were the generally used promoters for this kind of Ferrier glycosylations. Whereas the catalyst we investigated in this protocol is a highly bench-stable salt and very easy to handle catalyst. The activity of the catalyst comes from the bulkiness of the protonated pyridinium ion and the nakedness of the anion, while both the effects belied to cause frustration within the ion pair hence its reactivity as a good organocatalyst (**Figure 3**).

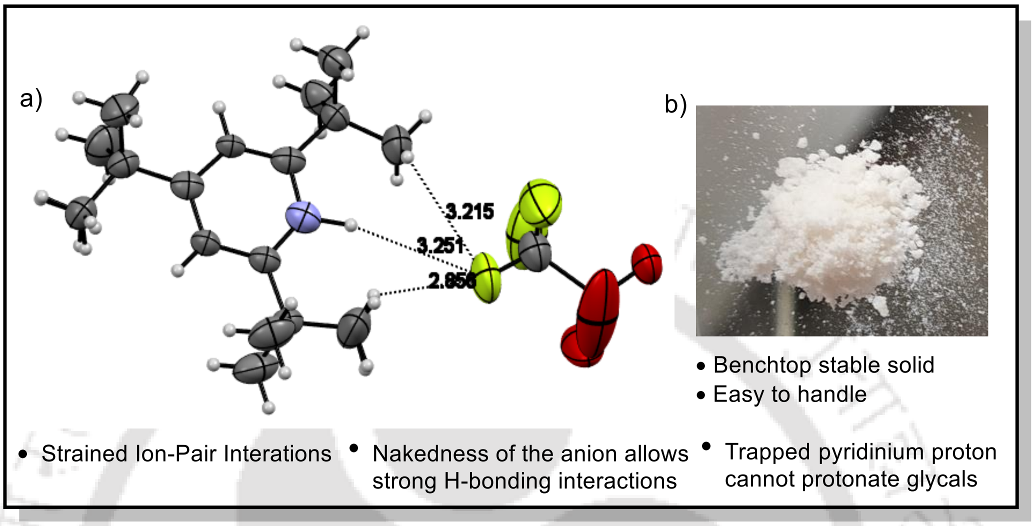


Figure 3. a) ORTEP diagram of TTBPyHOTf b) Picture of the salt

In conclusion, we demonstrated the potential of sterically hindered 2,4,6-tri-*tert*-butylpyridinium triflate salt as a stable, mild, and easy-to-handle organocatalyst for the diastereoselective synthesis of arylvinyl C-glycosides (**Scheme 1**). The ability to activate allylsilanes and silylenolethers via TfO^-...H-O-H interactions resulting in the generation of silicon cation opens up enormous possibilities. The concept can be applied to various organic transformations. Salt **4b** can be an excellent bench-stable alternative to the usually sensitive TMSOTf, specifically where silicon-based nucleophiles are used. The slow release of the highly Lewis acidic silicon cation could have great potential in organic synthesis. Exploration of these TfO^-...H-O-H interactions in catalyzing other organic transformations is under progress in our laboratory.

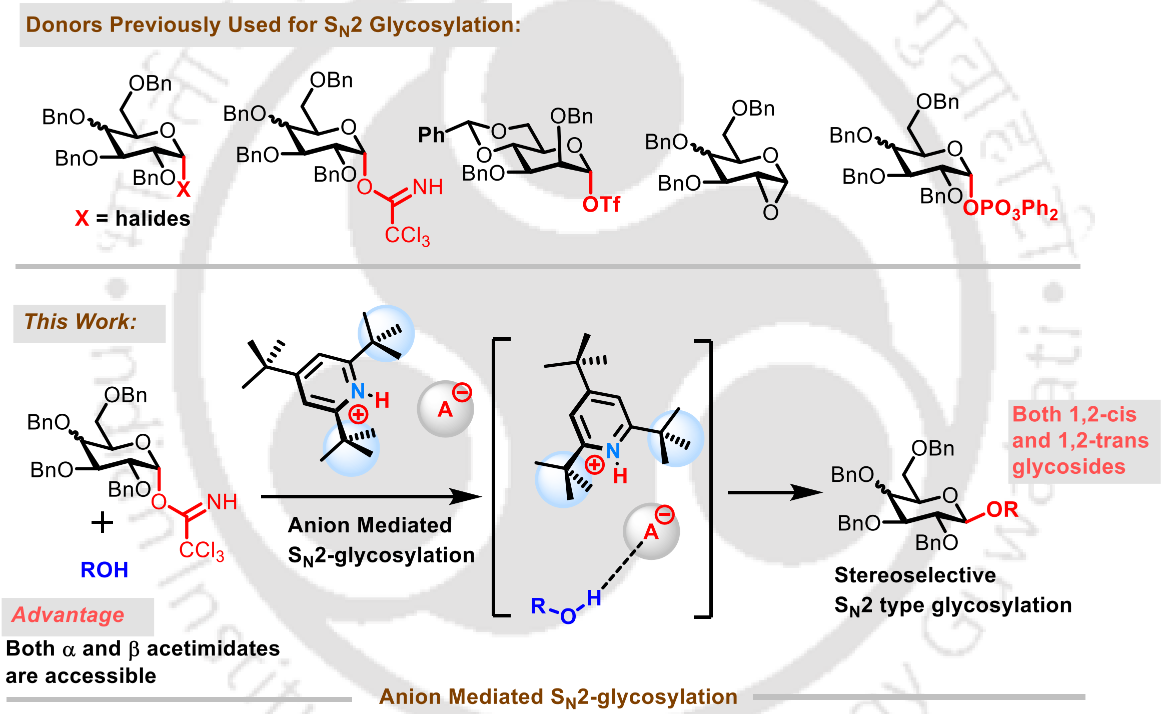
(*Org. Lett.* **2022**, *24*, 7, 1465–1470)

Chapter III… Exploiting the Strained Ion-Pair Interactions of Sterically Hindered Pyridinium Salts Toward S_N2 Glycosylation of Glycosyl Trichloroacetimidates

Here in this chapter, we demonstrate that strained and sterically hindered protonated 2,4,6-tri-tert-butylpyridinium (TTBPy) tetrafluoroborate, a crystalline, bench-stable salt serves as a mild and efficient organocatalyst for the S_N2 type displacement of glycosyl trichloroacetimidate towards the synthesis of highly selective β-gluco and both α and β-galactosides (**Scheme 2**).

To talk about the scope of this kind of S_N2 type glycoylations can be understood with the witnessing role of carbohydrates in controlling various biochemical processes,[5] development of strategies for the stereoselective construction of the glycosidic bonds to provide chemical access to these substrates continues to attract the attention of organic chemists.[6] The mechanism of the glycosylation reactions and in turn the stereochemical outcome is controlled by a variety of factors and usually ranges between the S$_N$1 and S$_N$2 continuum while mechanisms closer to the S$_N$2 end of the continuum would lead to high stereocontrol.[7] Seminal work by Crich and coworkers involving S$_N$2 reaction on the glycosyl triflate intermediates formed under stoichiometric pre-activation conditions, achieved high stereocontrol in *β*-mannosylation reactions.[8]

Schmidt and coworkers also pioneered the catalytic glycosylations of the glycosyl trichloroacetimidates,[9] the most widely used glycosyl donor. Specifically, the acceptor-catalyst interactions assisted protocols provide S$_N$2 kind of activation of glycosyl trichloroacetimidates.[10] Other pioneering works towards S$_N$2 glycosylation include the contributions from Taylor,[11] Toshima[12,] and Jacobsen[13] groups and more recently by Pederson and coworkers using pyrilium salts.[11] most of them utilised the donors shown in Scheme 2 for S$_N$2 type of glycosylations (**Scheme 2**).



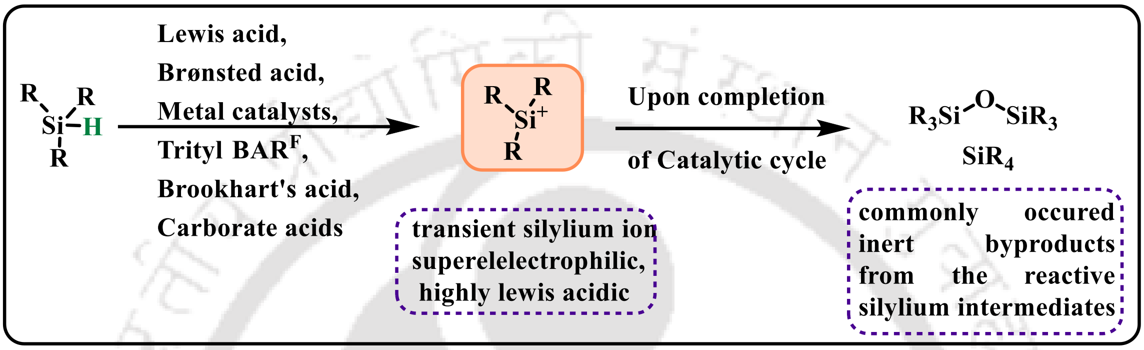
Scheme 2. Glycosyl Donors explored for S$_N$2 ype glycosylations and Current protocol

The strained ion-pair interactions between the sterically hindered pyridinium cation and the tetrafluoroborate anion infuse unusual reactivity to the ions resulting in the unique anion-assisted activation of alcohol. This mild activation of alcohol facilitates the S$_N$2-type displacement of glycosyl acetimidates giving rise to highly diastereoselective synthesis of *β*-gluco and galactosylation reactions. These unique interactions were established based on extensive IR and ^{1}H, ^{19}F, and ^{11}B NMR studies.

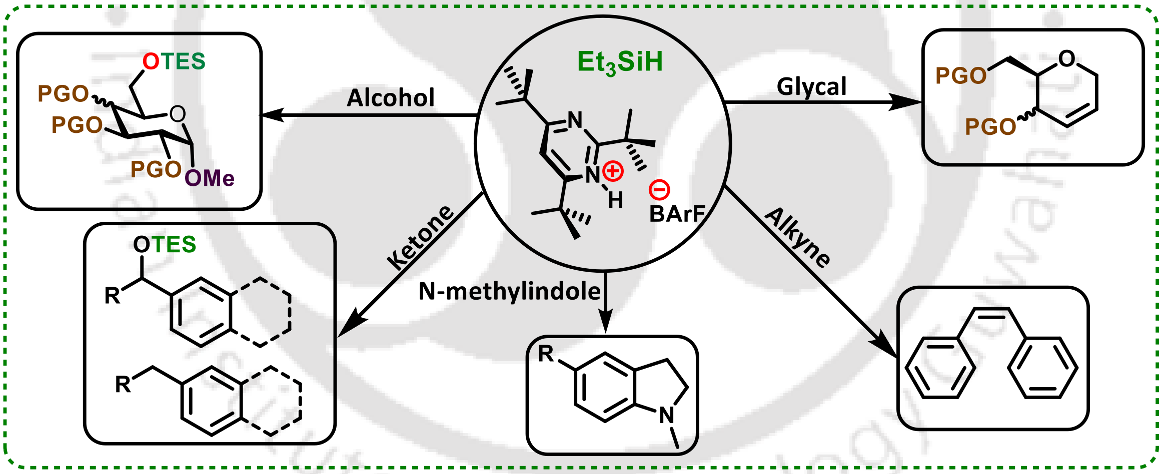
(*J. Org. Chem.* **2024**, 89, *6*, 3713–3725)

Chapter IV… Metal free Si-H bond activation utilizing Bulky 2,4,6-tri-*tert*-butylpyrimidinium (TTBP) salt of BArF

The superelectrophilic silylium cations though took many years to establish their existence in the condensed phase[1-3] have seen enormous progress in recent decades . Different types of reagent systems and additives including the transition metal catalysts via oxidative addition to the metals have been uitilized to generate silylium ions (**Figure 4.1**). Weakly coordinating anion chemistry has paved the way to stabilize, isolate and utilize these superelectrophilic species for various organic transformations.[4]



Scheme 3. Literature methods



Scheme 4. This work

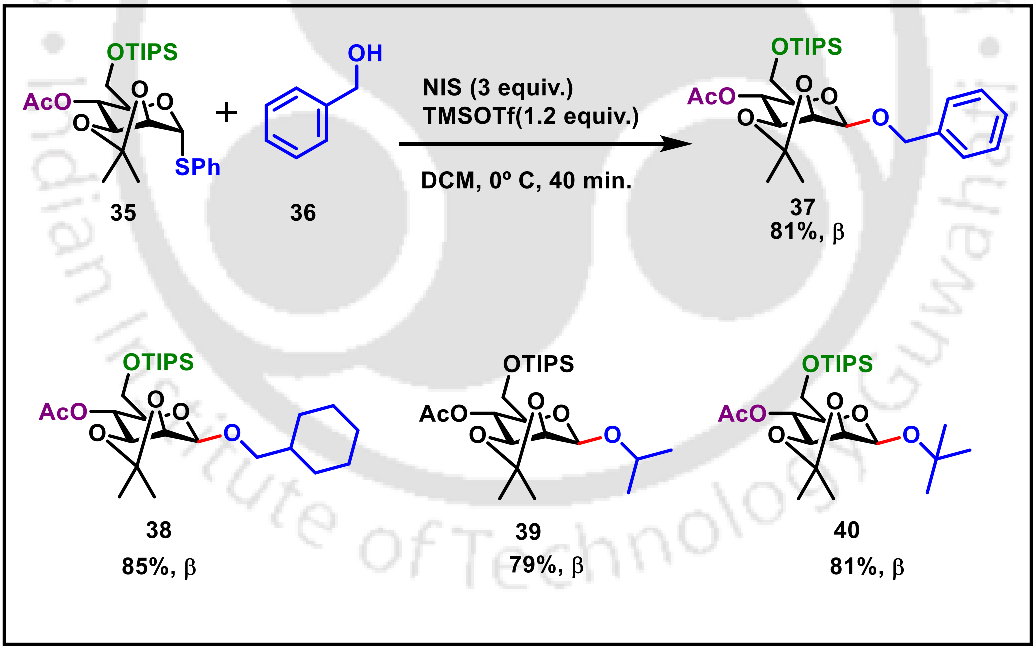
Utilising the frustration present within the ionic pair of TTBP (2,4,6-tri-*tert*-butylpyrimidine) and BArF due to their bulkiness and the relatively high Brønsted acidic nature of the bulky pyrimidine when compared to TTBPy, we successfully activated the Si-H bond and utilised it for various organic transformations. Various organic transformations were done effectively starting from synthesis of 1-deoxy Ferrier glycals, silyl protection of alcohols, reduction of different indoles to indoline derivatives and reduction of ketones. Reduction of diphenylacetylene to cis-stilbene selectively is an interesting observation (**Scheme 4**).

Manuscript under progress

Chapter V…Studies on the Stereoselective Glycosylation of Differentially Protected Mannose Thioglycoside Donors

In this chapter, we developed a novel donor for obtaining stereoselective mannosylations. From literature, it was seen that numerous efforts have been made towards the development of diastereoselective synthesis of the glycosydic linkage.[15] However, the synthesis of β-mannosidic linkage is one of the challenging classes of glycosylation reaction and the development of the benzylidine protected donor by Crich and co-workers has been the most successful and a breakthrough. They rely on the stability of the α-anomeric triflates in the presence of the 4,6-O-benzylidene protecting group which then undergoes and S_N2-inversion reaction leading to the formation of β-glycosides [16] In addition, in 2006, Kim group has obtained the stereospecific glycosylation with the benzylidine derived glycosyl pentenoate as the donor and with PhSeOTf as a promoter for achieving β-mannosides.[17]

We hypothesize that the locking of C2-C3 oxygens instead of C4-C6 oxygens in combination with an electron withdrawing acetate protecting group at O4 might also help us achieve the β-mannoside synthesis**.** Following which the reactivity of the synthesized donor (**35**) towards the diastereoselective glycosidic linkage has been studied**.** We have further carried out comparative glycosylations by varying the protecting groups of our donor and analysed the then varied stereochemical output**.**



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Manuscript under progress

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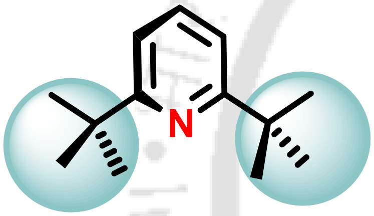
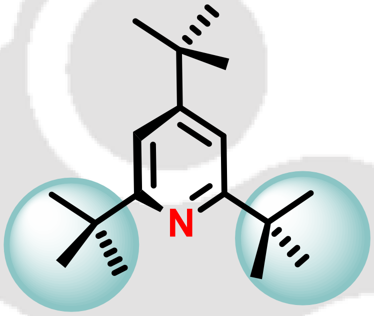
5.12 nOe Experiments: Stereochemistry assignment

Chapter I

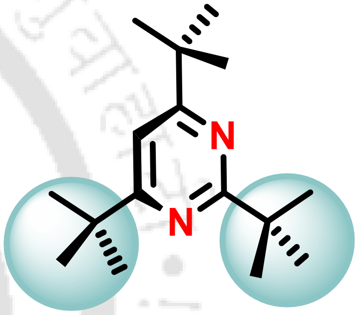
Utility of Sterically Strained Brønsted Salts



DTBP



TTBPy



TTBP

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Utility of Sterically Strained Brønsted Salts

1.1 Sterically bulky bases

Pyridine is a basic heterocyclic organic compound that is nothing but a benzene ring with one methine group replaced by a nitrogen atom. The presence of one nitrogen atom in the ring imparts electron-deficient nature to the N-heterocycles due to the inherent electron-withdrawing inductive (**I**) and mesomeric (**M**) effects of the nitrogen atom. Pyridine itself and many of its derivatives are present in natural products, agrochemicals, medicinal compounds, vitamins, etc. Many organic transformations include pyridine and many of its analogs which play efficient roles as reagents. Alkyl-substituted pyridines with increasing steric hindrance behave as non-nucleophilic bases and play crucial roles, for example as proton scavengers in reactions that involve strong acidic conditions in the reaction medium.

1.1.1 Emphasis on bulky pyridine bases: Their utility as Brønsted Salts

The basicity and nucleophilicity are variables based on the steric hindrance of the pyridine ring substituents. Hence, its alkyl substituted derivatives were well studied for their unusual trends in the basic strength and varied characteristics with increasing bulkiness. Among them, DTBP (2,6-di-*tert*-butylpyridine) introduced by H.C. Brown and Bernard Kanner in 1953, is among the first ones that grabbed the attention with interesting observations and studies.[1-2] The unprecedented observations made by this group involved an extensive study on the occurrence of steric hindrance toward the proton. The study was performed on several pyridine bases including pyridine, 2-picoline, 2,6-lutidine, and 2,6-*tert*-butylpyridine (DTBP). The series, pyridine, 2-picoline, and 2,6-lutidine, and pyridine, 2-isopropyl pyridine, and 2,6-diisopropyl pyridine have shown a linear trend on the p*K*a values without any deviation whereas with the series involving pyridine, 2-*tert*-butyl pyridine, and 2,6-di-*tert*-butylpyridine has a clear deviation from the linear

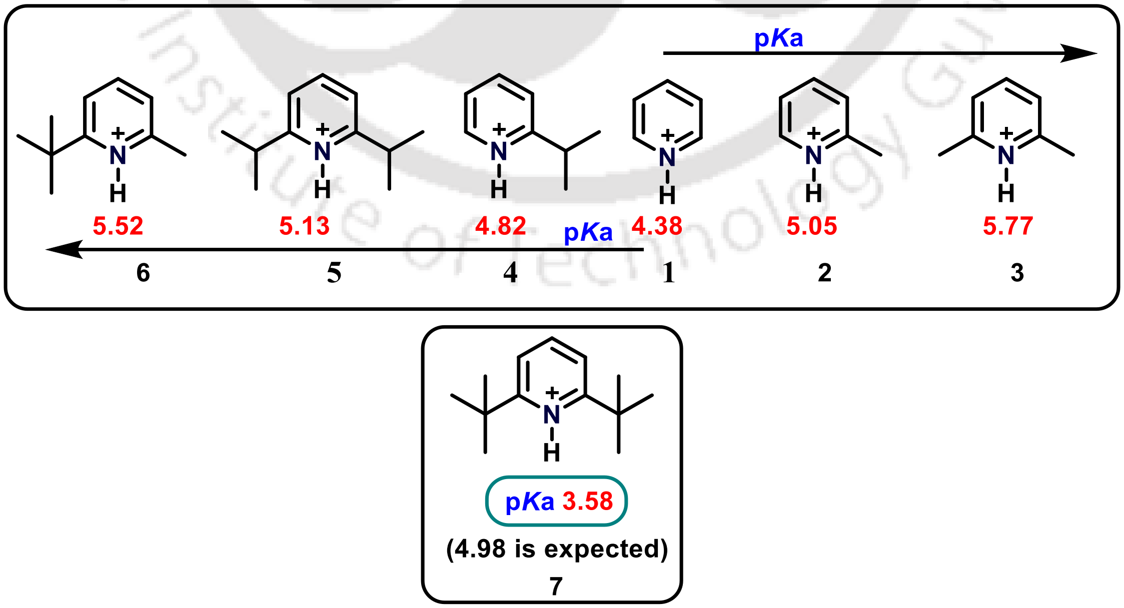


Figure 1.1 pKa values of pyridine bases in 50% ethanol-water

behavior, with a p*K*a value of 3.58 for DTBP which is 1.4 units lesser than the value calculated from simple additivity while the drifted value is attributed to the increased steric bulk at the ortho positions of the N-in the pyridine ring. The same reason was cited for the poor basicity of DTBP than Pyridine. Their study and similar reports highlighted the unusual behavior of DTBP and TTBPy (2,4,6-tri-*tert*-butylpyridine) toward proton with steric strain. The lower p*K*a (**Figure 1.1**) of these sterically strained bases[2] is linked to their insusceptibility toward solvation of their ionic charge due to the steric interference of the ortho-*tert*-butyl groups. The cationic [N-H]+ fails to have a strong hydrogen bond even with a single water molecule (**Figure 1.2**).[2]

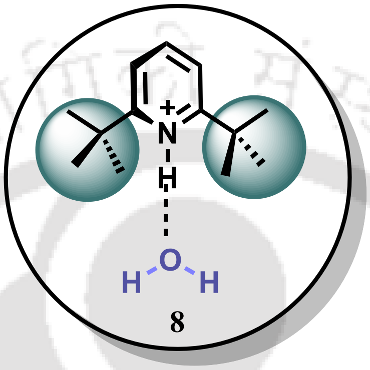
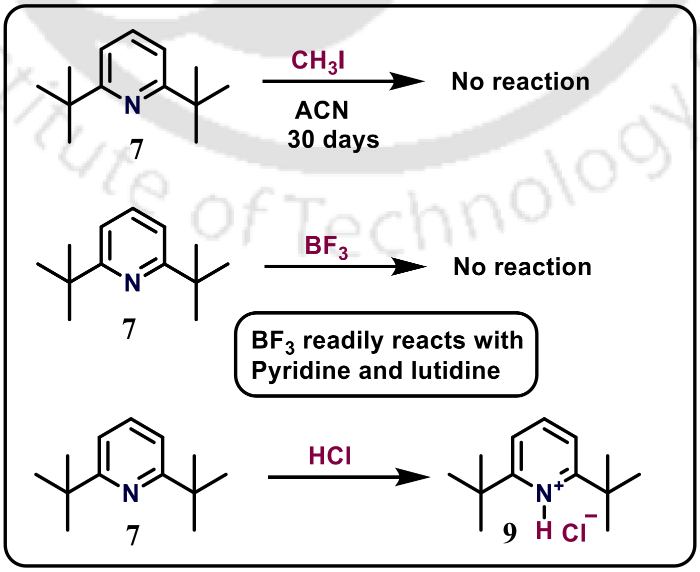


Figure 1.2 Sterically strained interaction of N-H of DTBP and H_2O

Contrary to the pyridine and simpler analogues, it was also observed that DTBP does not react with iodomethane even with prolonged reaction times. However, DTBP can be used to separate a mixture of BF_3 and HCl, a combination of Lewis and protic acids as it reacts only with HCl but not with BF_3 whereas simple pyridine and 2,4,6-trimethylpyridine (collidine) react with BF_3 as well.[3] Thus it can be used as a base that neutralizes acid in the reaction mixture (**Scheme 1**). Such ability of the hindered pyridines to be able to distinguish between Lewis and Bronsted acids led to the understanding that this class of pyridines can be used as proton scavengers.



Scheme 1. Utilizing DTBP to differentiate between protic acid and Lewis acid

Some studies were performed on the bulky pyridine bases namely, methyl 2,6-di-*tert*-butyl-pyridine (MDTBP or DTBMP), and was found even the smallest of hydrogen donor like HF is unable to hold strong hydrogen bonding interactions with the protonated MDTBP while collidine (2,4,6-trimethyl pyridine) forms a strong HF salt.[4] Also, direct studies were not performed, 2,4,6-tri-*tert*-butylpyridine (TTBPy) is also expected to have similar properties and expectedly is a much weaker base (p*K*a = 3.4). The solvation insusceptibility of the cationic pyridinium entity brings-in instability and thus affects the binding of the nitrogen lone pair with the proton. This effect is enhanced in DMSO, the pK_{DMSO} of DTBP is a much lower 0.81, indicating a much weaker hydrogen bonding of $DTBPH^+$ with the larger DMSO molecule (relative to H_2O).[5-6,11] Hence it is perceivable that the hydrogen bonding nature of solvent can be decisive in the behavior of Brønsted acid TTBPyH cation in solution.[6] However, the non-nucleophilic basic nature of TTBPy and its state of poor coordinating nature in its cationic form ($TTBPyH^+$) makes it a good choice as an acid quencher in a variety of reactions including glycosylations. A similar drop in p*K*a with increasing steric bulk on the pyridine ring was observed for 2,4,6-tri-*tert*-butylpyridine (TTBPy) as well (**Figure 1.3**).

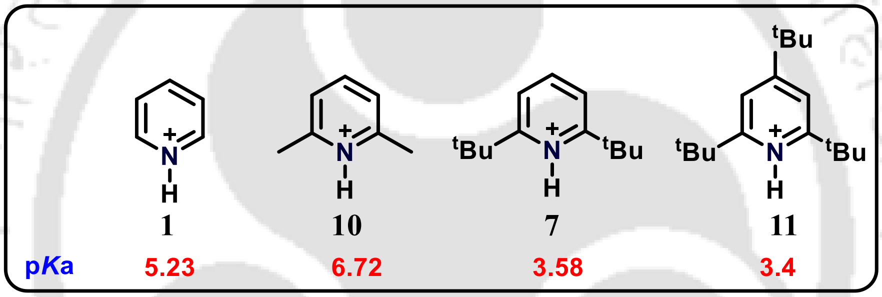


Figure 1.3 pKa values of bulky pyridine bases

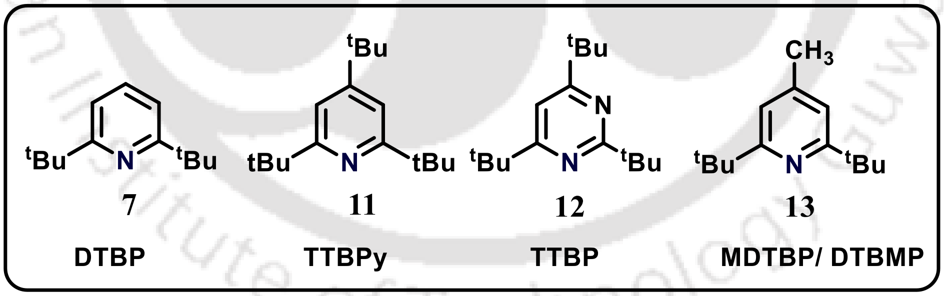
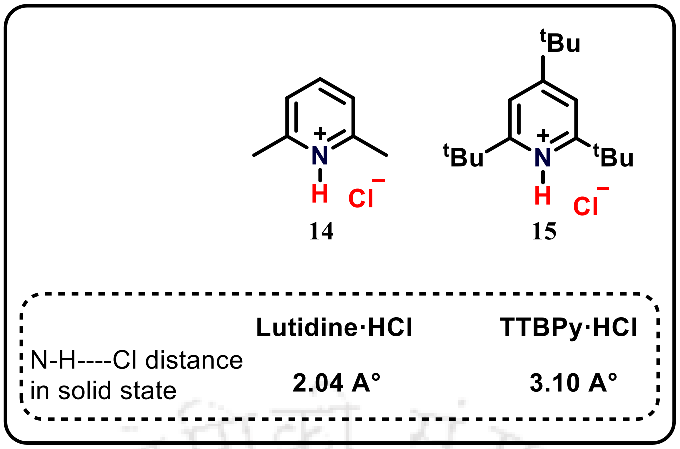


Figure 1.4 Bulky pyridine bases used as proton scavengers

Relative to pyridine and 2,6-lutidine, the hindered bases like TTBP, TTBPy, DTBP, and DTBMP are expected to possess high basic strength with the inductive effect of the electron-donating alkyl groups, while the steric hindrance took the critical role in altering their behaviors and leading to interesting applications.[5-7] This unusual behavior of the bulky bases helped chemists to use them as efficient acid scavengers owing to their non-nucleophilic basicity. Among the discussed sterically bulky pyridine bases, DTBP (2,6-di-*tert*-butylpyridine), TTBPy (2,4,6-tri-*tert*-butylpyridine), TTBP (2,4,6-tri-*tert*-butylpyrimidine), DTBMP (2,6-di-*tert*-butyl-4-methylpyridine), etc., were well explored for their unique reactivity (**Figure 1.4**). Interestingly, the bulky pyridine TTBPy has also found its utility in Frustrated Lewis Pair (FLP) reactivity.[17]



	Lutidine·HCl	TTBPy·HCl
N-H----Cl distance in solid state	2.04 A°	3.10 A°

Figure 1.5 N-H distance from anion for TTBPy-HCl

Interestingly, Kancharla’s group found that due to the inability of the N-H$^+$ of the hindered TTBPYH$^+$ to interact well with the anions, the ion-pairs also develop some intrinsic strain. And akin to FLP reactivity, these strained/frustrated ion-pairs can react or activate a third molecule. The group has been exploring this unusual reactivity in developing stereoselective glycosylation reactions in recent years. It was observed for the hydrochloride salt of TTBPy that the cavity of protonated [TTBPy-H]$^+$ is around ~3.27 Å, which can accommodate either a water molecule or a chloride anion within hydrogen bonding distance, however, no such interaction was found to exist between the cationic N−H and the anion and the N···Cl distance as observed in the XRD structure is ~3.10 Å in solid state (**Figure 1.5**)[6] that is much longer than the distance in less sterically hindered pyridinium hydrochloride.

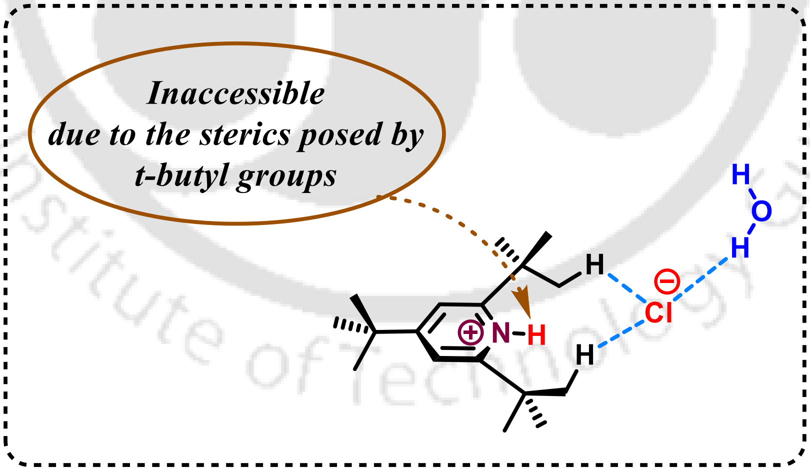


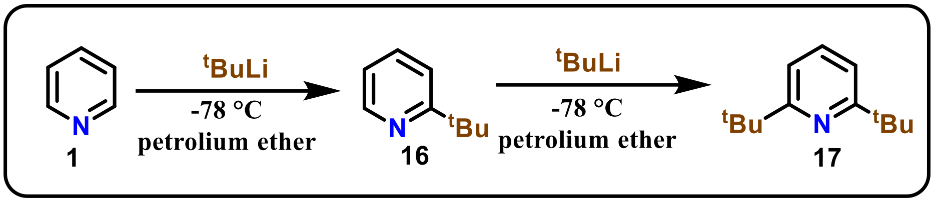
Figure 1.6 TTBPyHCl interaction with H_2O in solid state (Depiction of C−H···anion interactions from XRD data)

The Brønsted salt, TTBPy.HCl was successfully crystallized as a hydrate, where the solid-state XRD studies revealed the unperturbed cation [N-H]+ and the anion in H-bonding with the water molecule with an unusual Cl$^-$….H-O-H interactions were observed (**Figure 1.6**).[5-6]

1.2 Synthesis of sterically hindered pyridine bases

1.2.1 Synthesis of DTBP

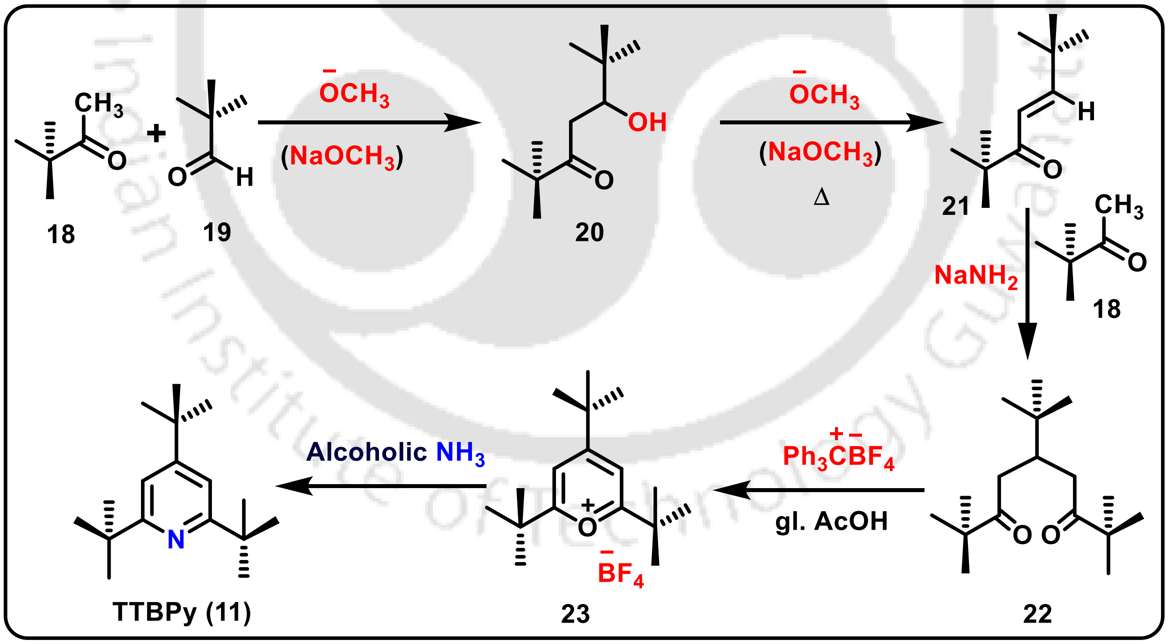
The synthesis of 2,6-di-*tert*-butyl pyridine (DTBP) was reported firstly by H.C. Brown's group in 1953, by alkylation using tert-butyl lithium in two steps (**Scheme 2**).[1]



Scheme 2. Synthesis of DTBP

1.2.2 Synthesis of TTBPy

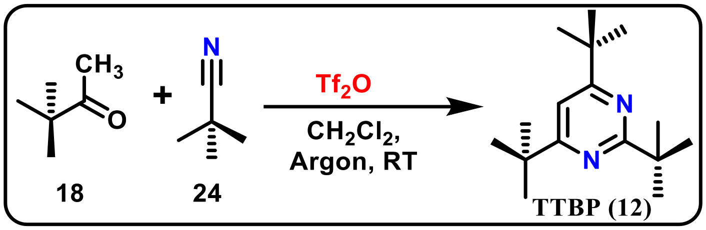
Another important non-nucleophilic bulky pyridine base, 2,4,6-tri-*tert*-butylpyridine (TTBPy), was first introduced in 1968 by Mach and Dimroth. It was synthesized starting from pinacolone and pivalaldehyde *via* 2,4,6-tri-*tert*-butylpyrylium salt under basic conditions. Initially, the methoxy ketone would be converted into the unsaturated ketone by heating under a basic medium which is further converted into pyrlium tetrafluoroborate salt upon treatment with trityl tetrafluoroborate in glacial acetic acid. By treating the pyrilium BF_4 with alcoholic ammonia, the final product 2,4,6-tri-*tert*-butylpyridine was formed quantitatively (**Scheme 3**).[8]



Scheme 3. Synthesis of TTBPy

1.2.3 Synthesis of TTBP

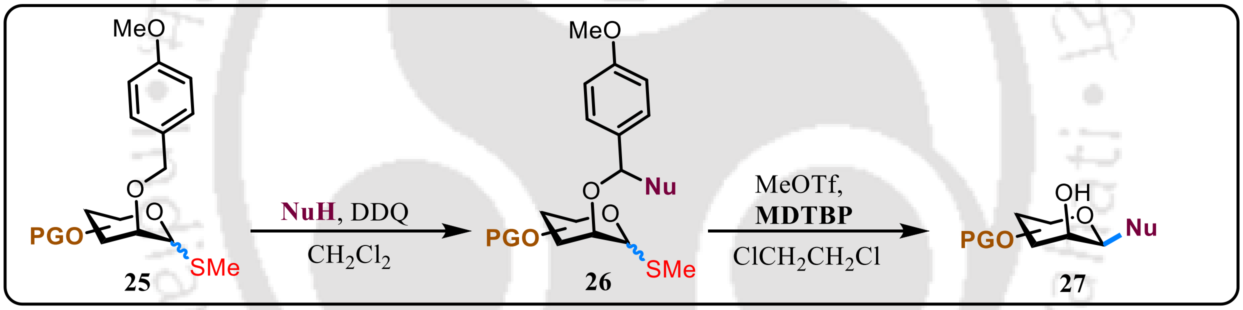
The more electron deficient variant of TTBPy, that is, 2,4,6-tri-*tert*-butylpyrimidine (TTBP) was prepared in gram scale in excellent yields by David Crich through an operationally simple method. Pinaclone and Pivalonitrile were reacted with triflic anhydride under anhydrous conditions at room temperature (**Scheme 4**).[11]



Scheme 4. Synthesis of TTBP

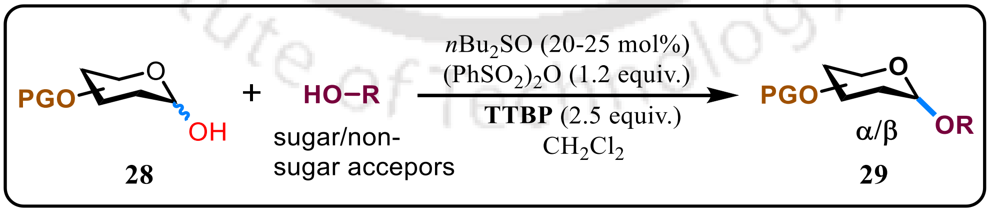
1.3 Utilization of sterically hindered pyridine bases in various organic transformations

In an approach to synthesizing *β*-mannosides efficiently, Ito and his coworkers presented an efficient protocol that proceeds stepwise through an *intramolecular aglycan delivery approach.* In this work, the aglycan unit was first installed onto the PMB (p-methoxy benzyl) ether which further transfers the nucleophile onto the glycosyl donor unit forming expected *β*-mannosides (**Scheme 5**).[9]



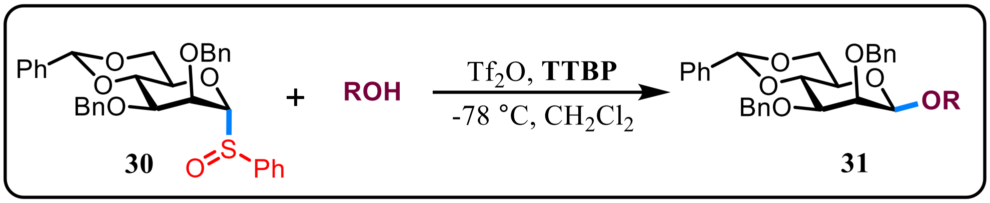
Scheme 5. Synthesize β-mannosides *via* intramolecular aglycan delivery approach

David Gin's group used the bulky pyridine base, TTBPy in a dehydrative glycosylation for the first time in a sulfoxide covalent catalysis for achieving glycosides (**Scheme 6**).[10]



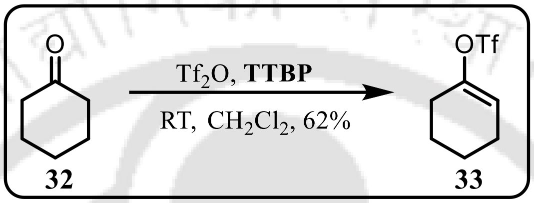
Scheme 6. Dehydrative glycosylation *via* sulfoxide covalent catalysis

Simultaneously, Crich and co-workers showed that the relatively in-expensive tri-tert-butylpyrimidine is equally efficient as the corresponding pyridine derivatives in *β*-mannosylations (**Scheme 7**).[11]



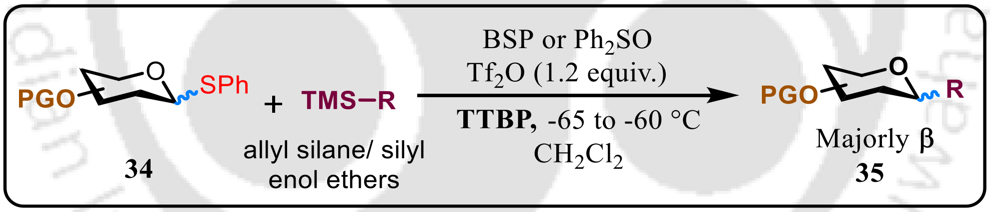
Scheme 7. Mannosylation using Tf_2O/TTBP reagent system

Further, this bulky base has also been utilized by Crich's group for vinyl triflate synthesis as well. Earlier, the same transformation was achieved in the presence of MDTBP, TTBPy by Stang[12] and coworkers (**Scheme 8**).[11]



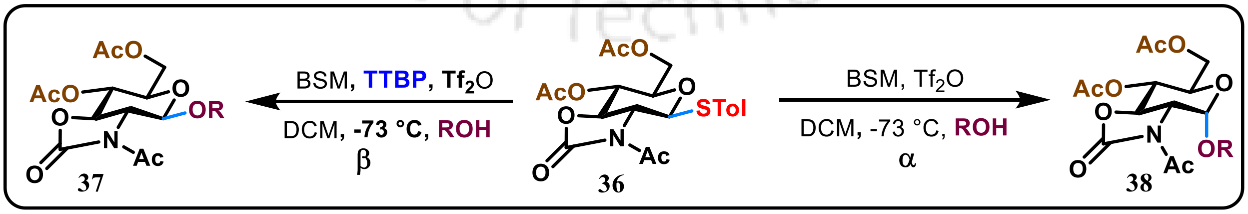
Scheme 8. Synthesis of vinyl triflate

In another protocol, 4,6-*O*-benzylidene-protected thioglycosides reacted with allylsilane and silyl enol ether activated by 1-benzenesulfinyl piperidine and triflic anhydride in the presence of 2,4,6-tri-*tert*-butyl pyrimidine (TTBP) gave the corresponding *C*-glycosides with *β*-anomers as major products (**Scheme 9**).[13]



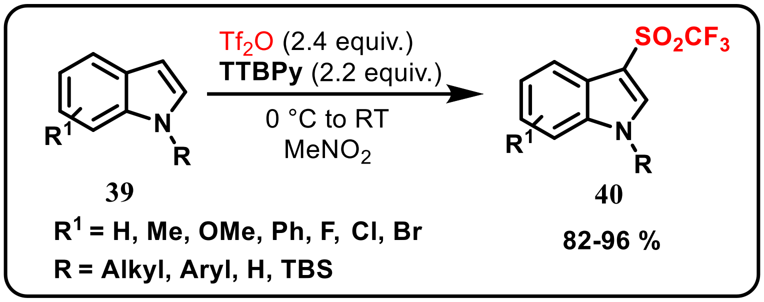
Scheme 9. Synthesis of *C*-glycosides from thiopyranosides using silylated nucleophiles

An interesting observation was noted from the work of Xin-Shan Ye's group in the year).[14]2008, where there was a complete switch of anomeric selectivity in the glycosylation of



Scheme 10. Stereoselectivity-controllable glycosylations of oxazolidinone-protected glucosamine

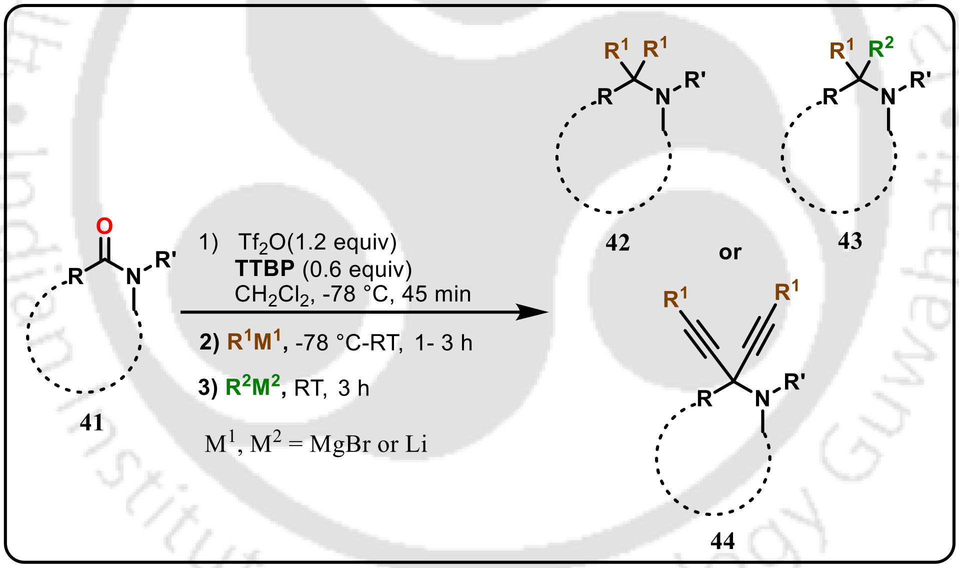
oxazoline protected glucosamine thioglycoside donors in the presence and absence of TTBPy, under pre-activation conditions. The presence of TTBPy provided the *β*-products selectively, while the absence of TTBPy provided the *α*-ones (**Scheme 10**



Scheme 11. Synthesis of Indole triflones

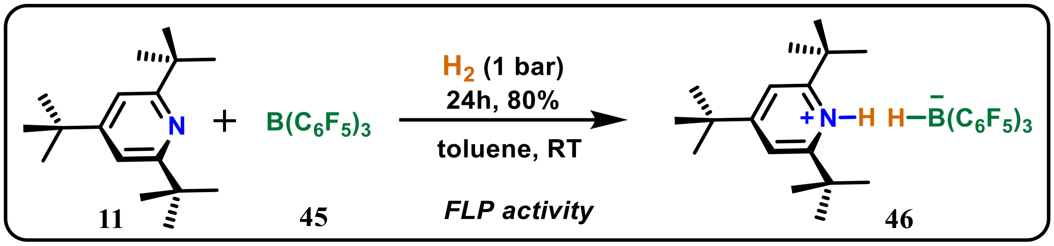
In a report, Norio Shibata and his co-workers successfully synthesized indole and bisindolyl triflones starting from a variety of indoles using Tf_2O and TTBPy reagent system in excellent yields (**Scheme 11**).[15]

Tf_2O/TTBP system was pronounced as the most advantageous reagent system combination by Huang's group recently in comparison with several other bulky pyridine bases for transformation of different types of amides through reductive alkylation/bisalkylation/dialkynylation in good yields (**Scheme 12)**.[16]



Scheme 12. Reduction of amides using Tf_2O/TTBP reagent system

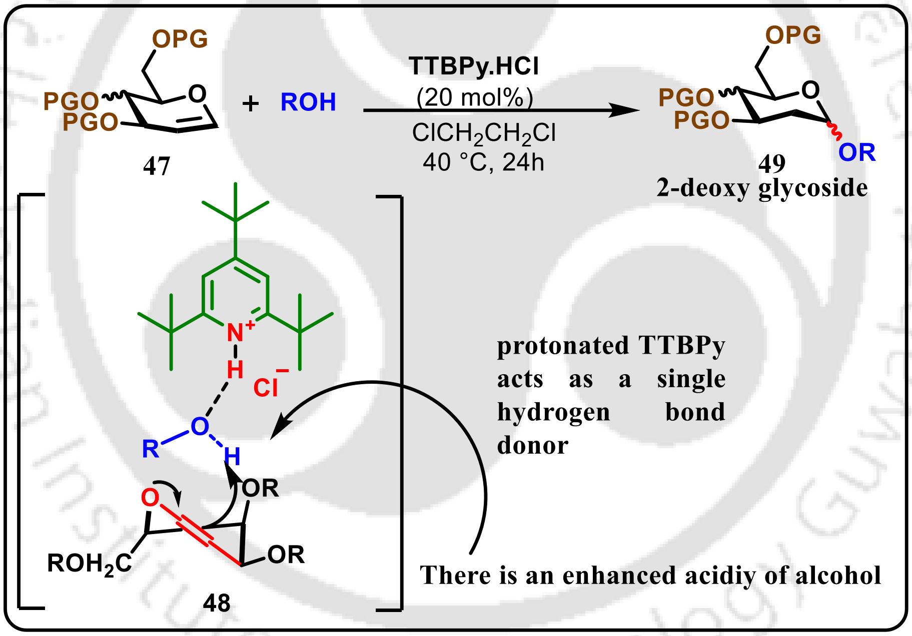
In an intriguing observation, Berke and his coworkers achieved the H_2 heterolysis in the presence of sterically hindered nitrogen bases and ($B(C_6F_5)_3$) as Lewis acid via the Frustrated Lewis Pair activity. molecule (**Scheme 13)**.[17] Their attempt to quantify the steric influence on FLP reactivity has shown that the steric strain of the pyridine base has an influence on the frustration created on it within the reaction vicinity, based on the boron-nitrogen (B-N) non-bonding distance. While some of the reactions of the H_2-heterolysis are reversible, the reaction with TTBPy forms stable ion-pairs.



Scheme 13. Heterolytic cleavage of H_2 by FLP using TTBPy and $B(C_6F_5)_3$

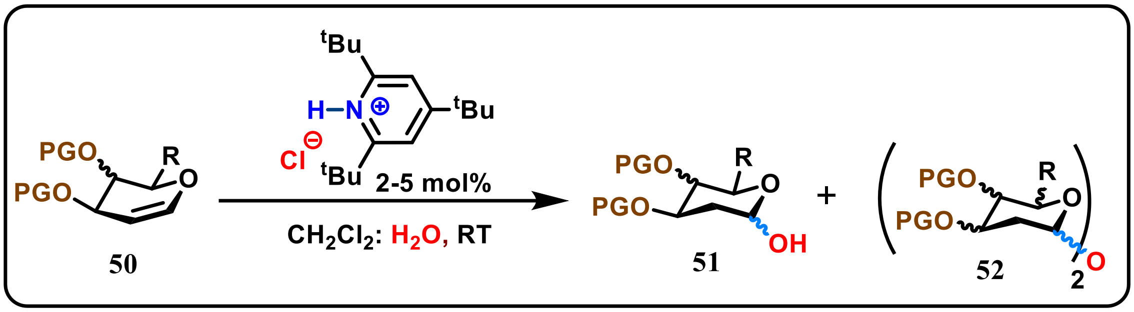
1.4 Utility of Sterically Strained Pyridinium Salts as Organocatalyst in Various Glycosylation Reactions

In 2019, for the first time, Brønsted salt of TTBPy has been utilized as an organocatalyst by our group, for stereoselective glycosylation. The hydrochloride salt of TTBPy was used as a catalyst, where the protonated TTBPy cation, behaves as a single hydrogen bond donor in activating the alcohol which in turn interacts with the glycal leading to 2-deoxy glycoside (**Scheme 14**).[5]



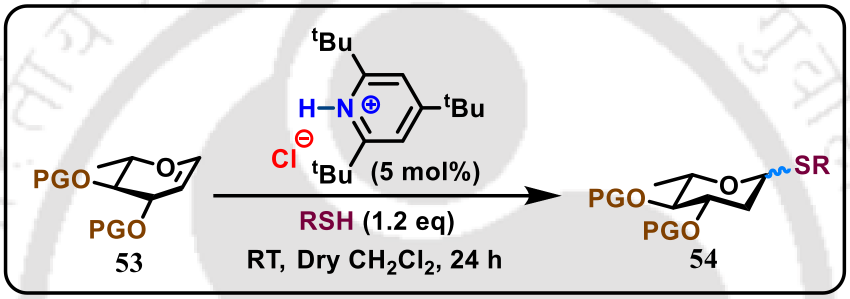
Scheme 14. Stereoselective glycosylation using TTBPy.HCl

In 2021, Kancharla's group reported another study based on TTBPy.HCl as a catalyst in the presence of water and was able to perform the hydration of glycals efficiently even with acid-sensitive protecting groups. From the mechanistic studies performed based on NMR experiments and XRD data, the interaction between the catalyst and water was analyzed. It was proposed from the observations that the catalyst's C−H···Anion Interactions Assisted the addition of water to glycals leading to the hemiacetals and dimers depending on the amount of water and catalyst (**Scheme 15**).[6]



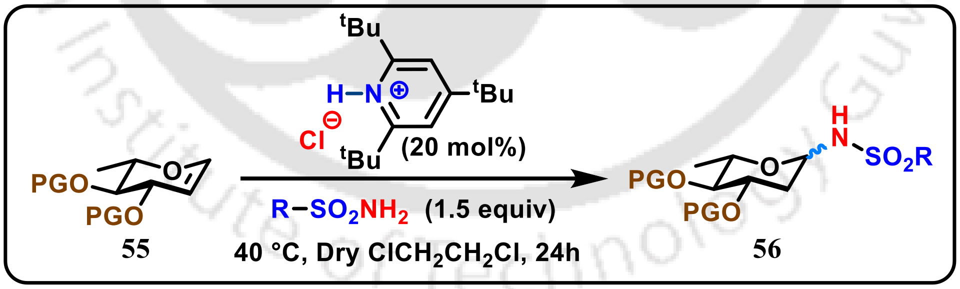
Scheme 15. Synthesis of hemiacetals via TTBPy.HCl catalysis

Later in the same year, the same group demonstrated that the bulky pyridinium chloride salt catalyzed the reaction of glycals with thiol acceptors leading to the stereoselective synthesis of 2-deoxy and 2,6-dideoxy thioglycosides (**Scheme 16**).[18]



Scheme 16. Stereoselective synthesis of thioglycosides

In 2022, it was found that sterically hindered 2,4,6-tri-*tert*-butyl pyridinium chloride catalysis could be utilized in synthesizing 2-deoxy,2,6-dideoxy sulfonamide glycosides *via* Cl^- …H-N interactions assisted addition of Sulfonamides to enol ethers (**Scheme 17**).[19]



Scheme 17. Stereoselective synthesis of glycosyl sulfonamides

1.5 Summary and Conclusion

In conclusion, many of these sterically hindered pyridine bases occupy an important place in organic chemistry as proton trapping agents, helping to quench the strong Brønsted acids released in the reaction medium. These bulky pyridine bases were also used as partners in FLP chemistry. In addition, Kancharla's group has found that the thus-formed Brønsted pairs can also be used as organocatalysts for various stereoselective glycosylation reactions triggered by unique strain within the ion-pair. By utilizing the frustration generated between the ion pairs of these bulky Brønsted salts, and understanding their distinctive chemistry, several other novel applications can be found under different environments within the reaction medium.

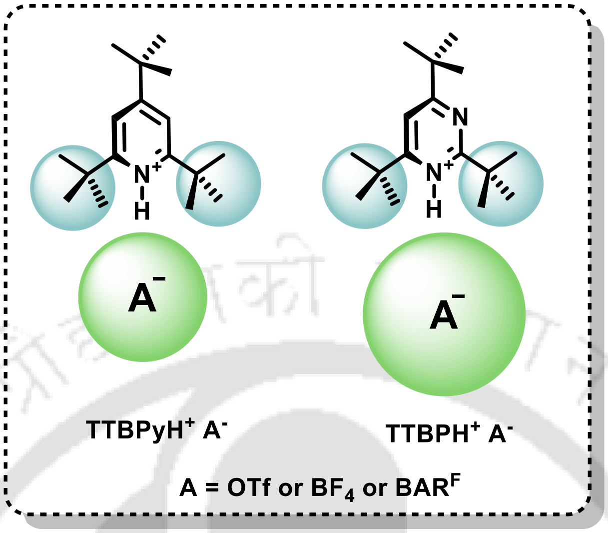


Figure 1.7 Sterically frustrated ion pairs of TTBPy and TTBP

In the upcoming chapters of this dissertation, the exploration of the bulky 2,4,6-tri-*tert*-butylpyridinium salts and 2,4,6-tri-*tert*-butylpyrimidinium salt as effective organocatalysts for stereoselective C-C, C-O bond formation and activation of Si-H bond in carbohydrate chemistry and non-carbohydrate chemistry is showcased also involving a lot of mechanistic studies. Steric strain present within these Brønsted ion pairs leads to frustration more specifically in non-polar solvents like dichloromethane, and methyl-*tert*-butyl due to their solvation insusceptibility in those solvents **(Figure 1.7)**. This unique chemistry assisted in exploiting the intriguing reaction protocols for diverse organic transformations in and outside carbohydrate chemistry, efficiently.

1.6 References

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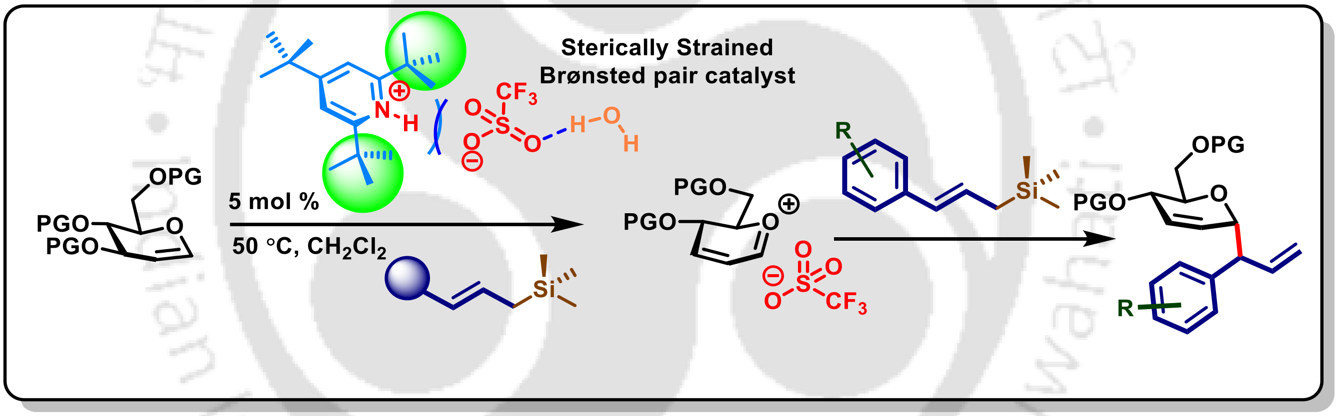
Chapter II

TfO$^-$….H-O-H Interactions Assisted Generation of Silicon Cation from Allylsilanes: Access to Phenylallyl Ferrier Glycosides from Glycals



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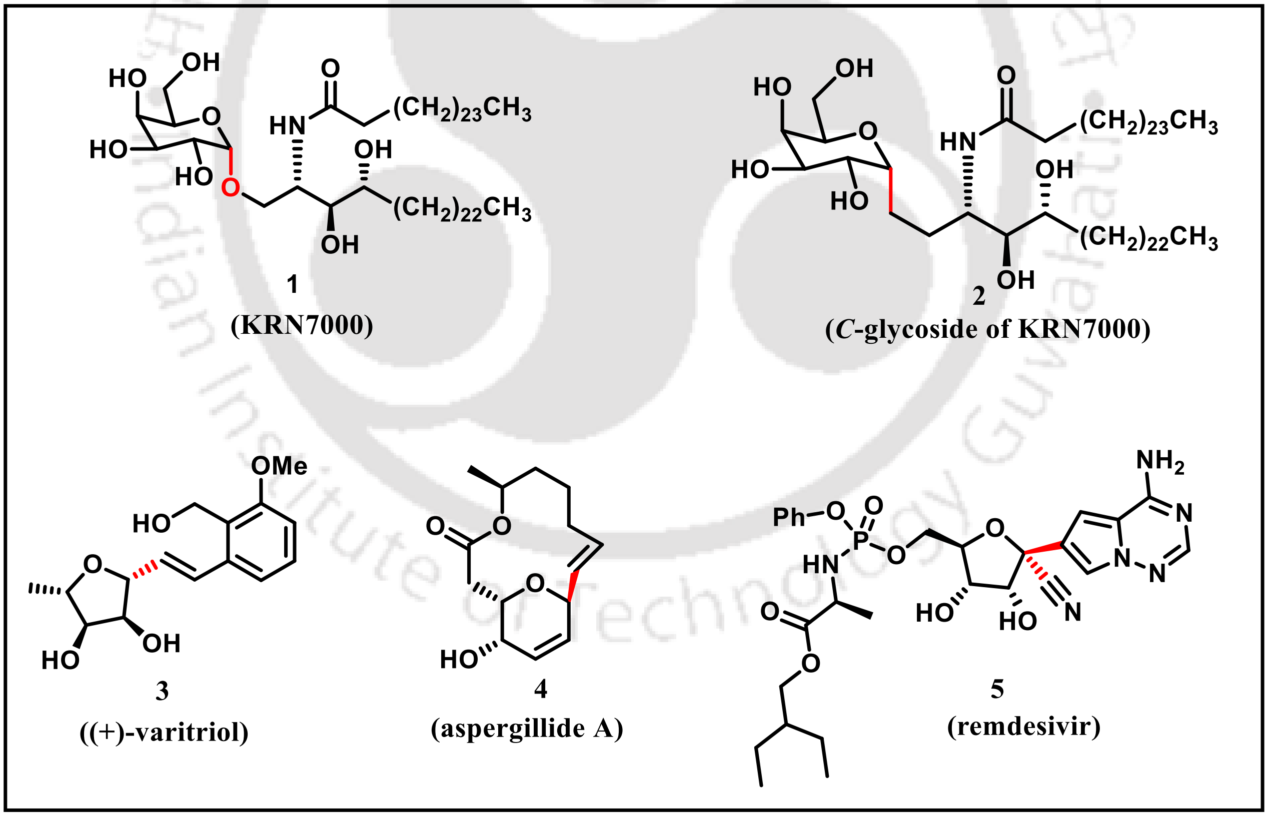
TfO^-….H-O-H Interactions Assisted Generation of Silicon Cation from Allylsilanes: Access to Phenylallyl Ferrier Glycosides from Glycals

2.1 Introduction

C-glycosides are well known for their higher stability towards enzymatic and chemical hydrolysis processes when compared to *O*/*N*-glycosides. This has been one such key point that brought them greater attention as potential therapeutic agents and biological probes. For example, the *C*-glycoside of *KRN7000* has been a wonderful mimic of its actual *O*-glycoside and was reported to show a thousand times higher activity as an anti-cancer drug and a hundredfold higher activity as an anti-malarial drug during its *in vitro* studies (**Figure 2.1**). The stronger C-C bond holds the key by making the molecules highly stable for chemical hydrolysis as well as in enzymatic vicinities.[1] Bioactive metabolites like (+)-*Varitriol*, isolated from the marine fungus *Emericella variecolor*, a highly potent antitumor natural product that consists of a C-C anomeric bond.[2] Aspergillides A−C isolated from the marine fungus *Aspergillus ostianus* were also important natural products that show antitumor properties effectively.[3] Nucleoside analogs like remidesivir have prominent RNA antiviral compounds with two C-C bonds at the anomeric site.[4]



1
(KRN7000)

2
(*C*-glycoside of KRN7000)

3
((+)-varitriol)

4
(aspergillide A)

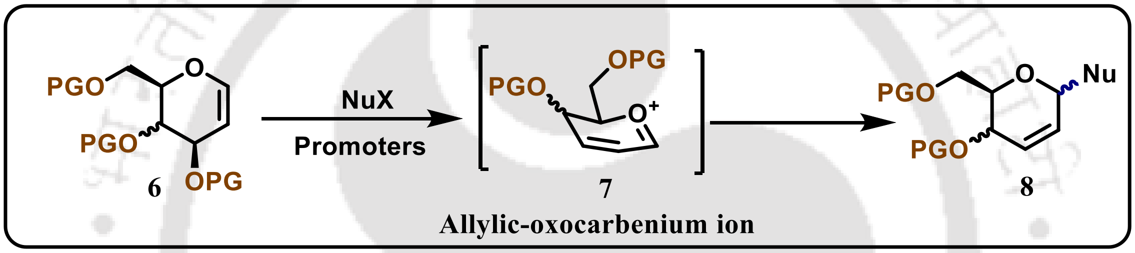
5
(remdesivir)

Figure 2.1. Some examples of *C*-glycosides with medicinal importance

2.1.1 Ferrier rearrangement

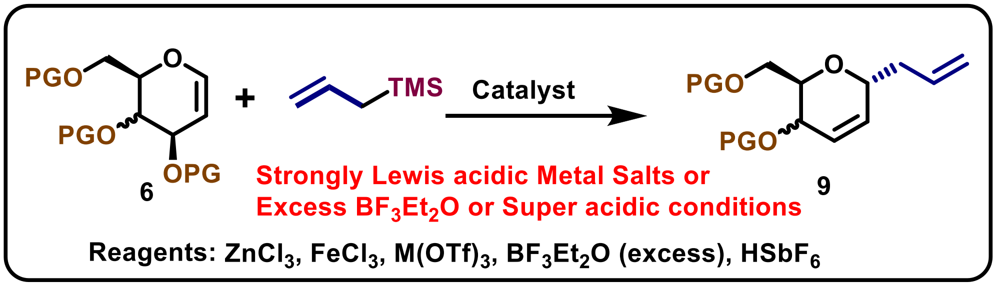
The nucleophilic substitution of a glycal through an allylic rearrangement is called the

Ferrier reaction (Ferrier rearrangement, FR) leading to the formation of a 2,3-unsaturated glycoside. This reaction was first reported[5] by Ferrier in 1962 and has been well-explored since then. There are a number of reports that have showcased the successful formation of FR-*C*-glycosides over the past three decades.[6] The Ferrier rearrangement of any D-glycal to 2,3-unsaturated *C*-glycoside will go via an allyloxocarbenium ion where the nucleophile attacks at *C*-1 under normal conditions (**Scheme 1**). Most of the literature reports showed that such glycosylations via Ferrier rearrangements have shown higher stereoselectivity for α-isomer unless there is a forceful condition to alter it. In the case of general glycosylations, D-galactal derivatives are expected to show higher α-selectivity, which knots the stereoelectronic factors to the quasi-axial disposition of C-4 groups in the D-galactal derivatives. But a higher stereoselectivity towards α-isomer was observed in most of the FR C-glycosylations, *N*-glycosylations, and *S*-glycosylations of D-glucal derivatives as well. In general glycosylations, the anomeric effect of the ring oxygen and the conformation of the pyranose ring favor α-attack of the incoming group, to produce the pseudoaxial glycoside.[5]



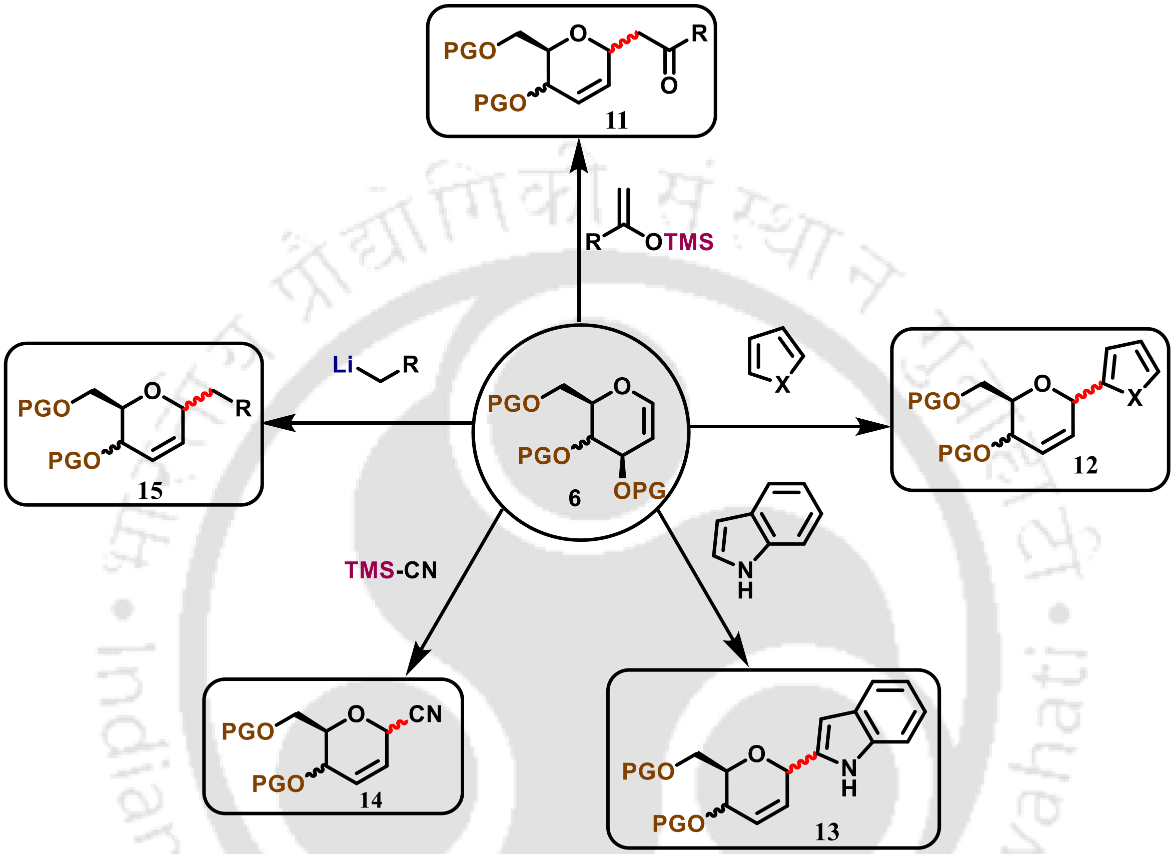
Scheme 1. A general mechanism of Ferrier glycoside formation through allyloxocarbenium ion

Ferrier rearrangement of glycals has been one of the classic reactions in synthetic carbohydrate chemistry and holds great potential for the synthesis of *C*-linked psuedoglycals and thereby *C*-glycosides.[6] Ferrier rearrangement is usually mediated by strongly Lewis acidic salts (**Scheme 2**) derived from transition metal/Lanthanides[6-8] or superacidic conditions[10] [In(OTf)$_3$, Bi(OTf)$_3$, ZrCl$_4$, HClO$_4$/SiO$_2$, Er(OTf)$_3$, Yb(OTf)$_3$ (in ionic liquids), InBr$_3$, InCl$_3$ (under microwave irradiation), La(NO$_3$)$_3$·6H$_2$O and AuCl$_3$] or in the presence of an excess amount of BF$_3$Et$_2$O (**Scheme 2**). Most importantly, *C*-Ferrier is not as well explored as *O*-Ferrier reactions. Also, Ferrier reaction on glycals is generally limited to the usage of allylTMS and simple silyl enol ethers as nucleophiles prominently[9] and the diastereoselectivity of the allyloxocarbenium ions using substituted allylTMS reagents has not been studied.



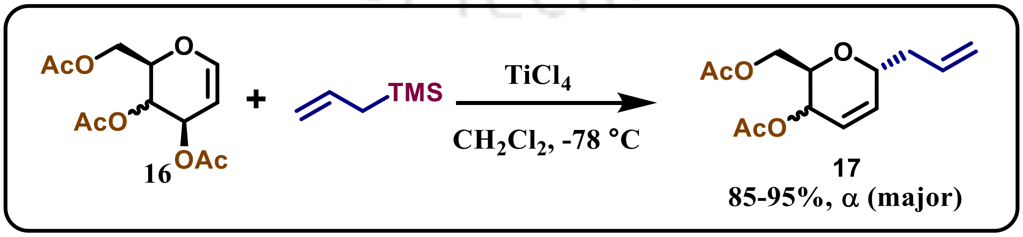
Scheme 2. Reagents utilized for activating allylTMS

Different nucleophiles were explored as nucleophiles for synthesizing Ferrier C-glycosides giving various products (**Scheme 3**). A variety of Indoles, Heterocyclic compounds, Alkyllithium compounds, silyl enolethers, Trimethylsilyl cyanide, etc., were some of the nucleophiles that were exploited giving various applications.[7]



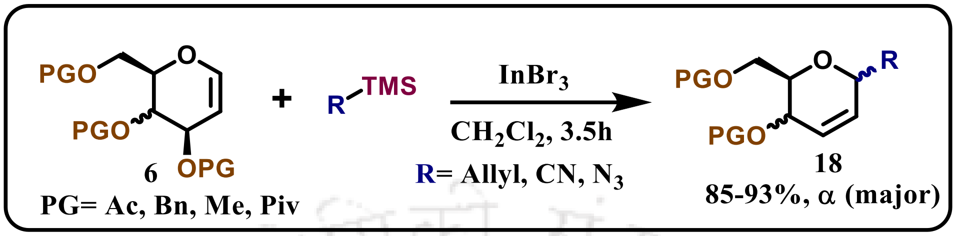
Scheme 3. Exploited nucleophiles for Ferrier *C*-glycosylation

Danishefsky *et al*. reported[9] the reactions of acetylated glycals with allyltrimethylsilane in the presence of equimolar quantities of Lewis acid, $TiCl_4$ giving Ferrier *C*-allyl glycosides with a varied selectivity towards α anomer based on stereochemistry of the pyranoses explored (**Scheme 4)**.



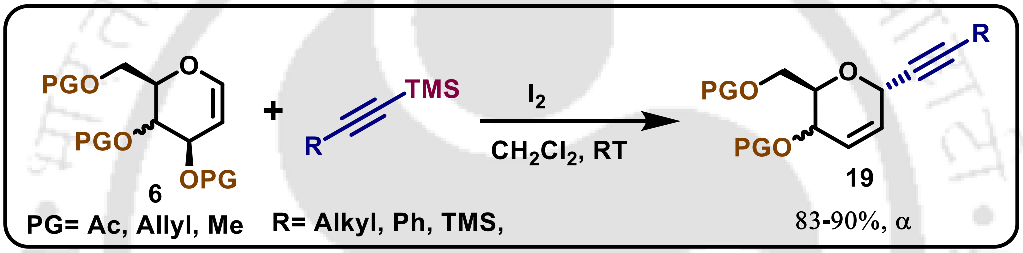
Scheme 4. Ferrier-*C*-glycosylation of glycals using $TiCl_4$

Yadav's group[10a] utilized $InBr_3$ as Lewis acid for reacting glucal/galactal (containing different protecting groups) and various silyl nucleophiles to synthesize Ferrier-*C*-glycosides in good yields with a superior selectivity towards α anomer (**Scheme 5)**. The same group has utilized Indium chloride for reacting heteroaromatics (N-boc Indole, Furans, thiophene) with glycals leading to the formation of Ferrier-C-glycoside derivatives with β-stereoselectivity in most of the cases.



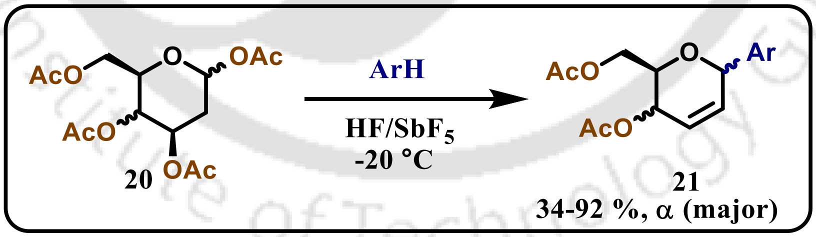
Scheme 5. Ferrier-*C*-glycosylation of glycals using $InBr_3$

In 2003, Yadav's group reported[10b] a protocol for Ferrier-type alkynylation of glycals with substituted alkynylsilanes by utilizing molecular iodine (**Scheme 6**).



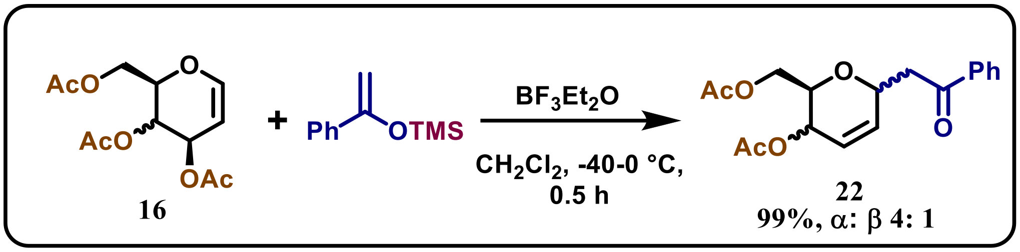
Scheme 6. Ferrier-*C*-glycosylation of glycals using molecular iodine

Thibaudeau and co-workers reported[10c] a protocol for the synthesis of Nitrogen-containing *C*-aryl 2,3-unsaturated glycosides under superacid conditions where they were able to characterize the intermediate, *allyloxycarbenium ion* through NMR study and DFT calculations. (**Scheme 7**).



Scheme 7. Ferrier-*C*-arylation of glycals under superacidic conditions

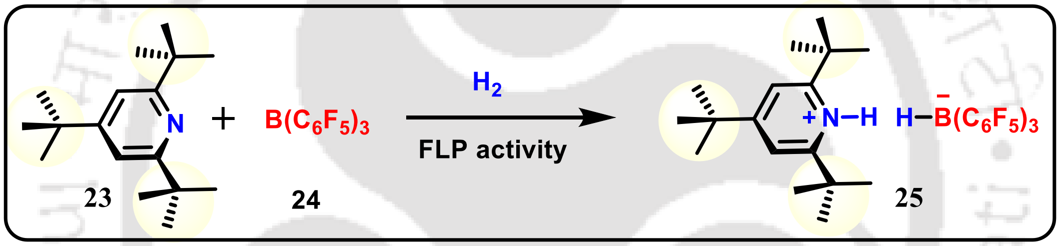
Condensation of silyl enol with acetylated glycals under Lewis acidic conditions leads to the expected Ferrier-*C*-pyranosides in quantitative yields favoring α-anomers. This observation was reportedly[11] first made by Fraser-Reid in 1981(**Scheme 8**).



Scheme 8. Ferrier-*C*-glycosylation of glycals with silyl enol ether

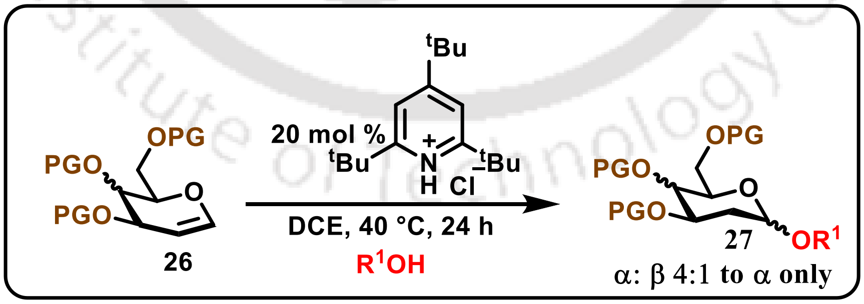
2.2 Literature preview on Bulky pyridine bases- their Frustrated Lewis Pair (FLP) behavior

Bulky pyridines like TTBP, TTBPy, and DTBP were well utilized as acid scavengers in various reactions where triflate salts, and strong acids like triflic acid were part of the reaction. The frustrated Lewis pairs (FLPs) concept was introduced[12a] by D. W. Stephan et al. with their remarkable discovery that H_2 can reversibly be activated by $[(2,4,6\text{-}C_6H_2Me_3)_2PC_6F_4B(C_6F_5)_2]$ which led to the development of the first metal-free catalyst for hydrogenations of bulky imines as one of the fruitful applications of this concept (**Scheme 9**).



Scheme 9. Reversible activation of H_2 through FLP reactivity of TTBPy

In 2011, 2,4,6-Tri-*tert*-butylpyridine (TTBPy) has been employed to split the hydrogen molecule heterolytically using its Lewis basicity in the context of FLP.[12b] But in general, the sterically hindered 2,4,6-tri-*tert*-butylpyridine that can differentiate between Lewis and Brønsted acids, is routinely used in organic chemistry as a proton trapping agent in various organic transformations, particularly in the synthesis of acyl triflates.[13] It is also used in glycosylation reactions to prevent the anomerization or decomposition of the products.[13b,c] It is generally used in excess or stoichiometric quantities to quench the superacids like triflic acid in acid-sensitive reactions.



Scheme 10. TTBPy·HCl Catalysed Glycosylation

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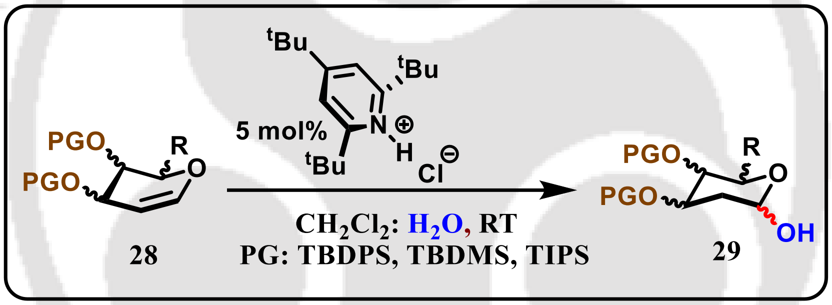
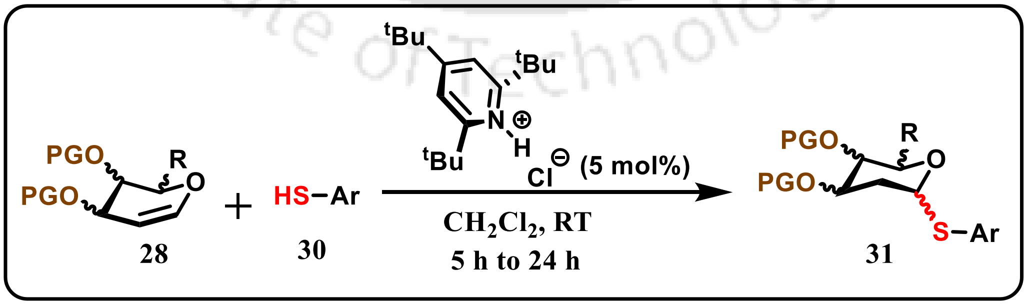
On the other hand, it is known for its relatively weak basicity in the aqueous solvent which is attributed to the solvation insusceptibility of the sterically hindered cationic site where the anions are comfortably solvated.[14a] However, in non-polar solvents, we hypothesized that the scenario is just reversed where the non-polar solvent could solvate the cation with the presence of the bulky hydrophobic tert-butyl groups, and the anions where the charge is exposed cannot be solvated. Besides, the steric hindrance around the solvated or unsolvated cation does not provide enough electronic stabilization to the anion. This imbues unusual reactivity to the anions associated with the tri-*tert*-butylpyridinium cation. In 2019, our group reported[14b] a stereoselective *O*-glycosylation of various glycals using the sterically hindered bulky 2,4,6-tri-*tert*-butyl-pyridinium hydrochloride salt as an efficient organocatalyst (**Scheme 10**). The study demonstrated the mechanism of action involving interesting single hydrogen bond mediated protonation of glycals instead of the generally conceived Brønsted acid pathway. It was even observed that the counter anions also play a crucial role in the outcome of the reaction.Recently, our group has demonstrated the unusual reactivity of the chloride anion associated with a sterically bulky protonated 2,4,6-tri-*tert*-butylpyridinium cation (N-H....Cl distance is unusually longer, 3.1 Å) to activate the water molecule *via* Cl^-...H-O-H interactions,[15] thereby utilizing the mild conditions in hydrating the acid-sensitive silyl-protected glycals (**Scheme 11**).



Scheme 11. TTBPy·HCl Catalysed Hydration of glycals

2-deoxy-thioglycosides were synthesized[16] utilizing hydrochloride salt of 2,4,6-tri-*tert*-butylpyridine as a catalyst for the addition of thiol to glycal via frustrated radical pair which was unprecedented in Brønsted pair catalysis (**Scheme 12**).



Scheme 12. Addition of thiols to glycals using TTBPy·HCl Catalysis

We were intrigued by the idea and were curious to understand whether such unique and mild A^- ...H-O-H interactions can be utilized for the synthesis of 2-*C*-glycosides or Ferrier *C*-glycosides

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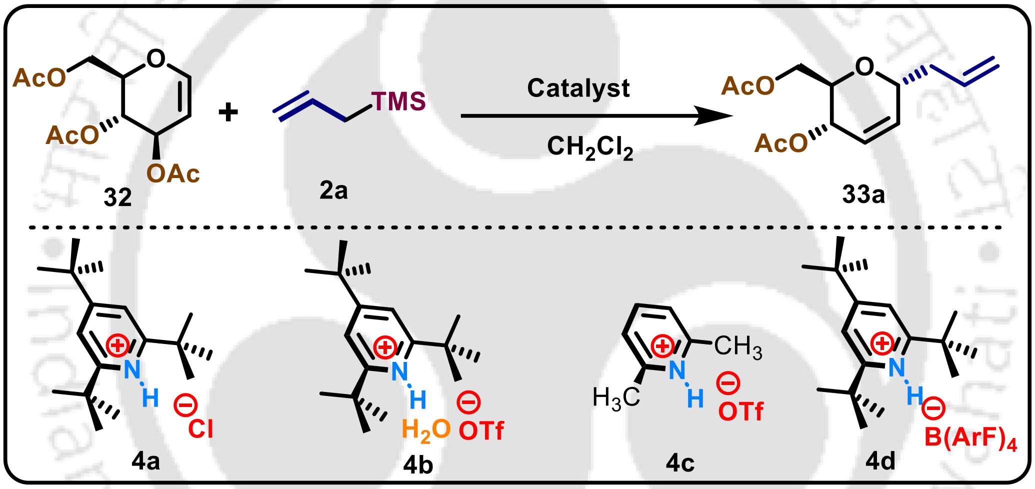
using allyltrimethylsilane derivatives as nucleophiles via 2-deoxyoxocarbenium ion or the allyloxycarbenium ion respectively. The difference in the nucleophilicity of the oxygen nucleophiles versus π-carbon nucleophiles, even with the additional assistance of the *β*-silicon effect, is significant.[17]

2.3 Results and Discussion

2.3.1 Initial Studies on Activation of Allyltrimethylsilane

We started our initial experiments by reacting the triacetylglucal with allylTMS in the presence of 20 mol% of chloride salt **4a** using dichloromethane as the solvent. Stirring the reaction mixture at 40 °C evenafter 24 h did not lead to any conversion of the starting materials. Increasing the temperature to 50 °C in a sealed tube did not have any effect on the reaction outcome.

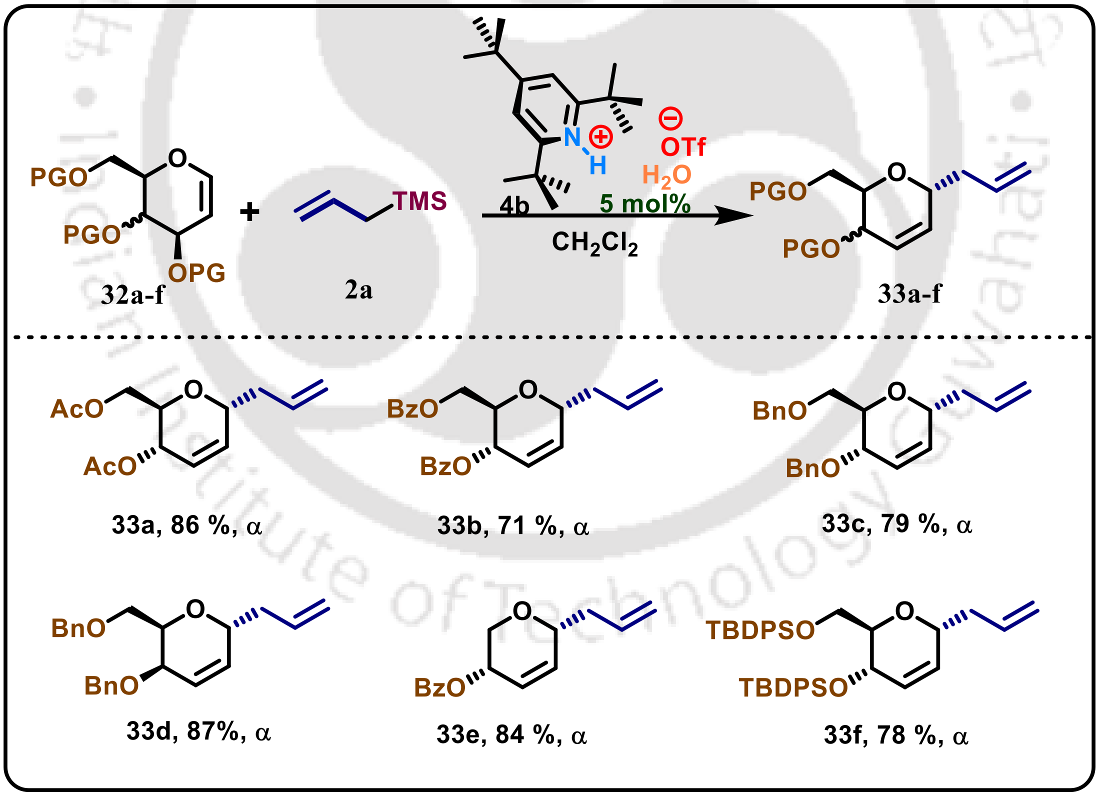
Table 1.1 Optimization studies



Ent	at.	Mol%	Temp.	Time	% Yield (α:β)
1	4a	20	40 °C	24 h	-
2	4a	20	50 °C	24 h	-
3	4b	20	RT	24 h	-
4^a	4b	20	40 °C	2 h	34 (α only)
5^a	4b	20	50 °C	20 min	85 (α only)
6^a	**4b**	**5**	**50 °C**	**20 min**	**86 (α only)**
7^a	4c	20	40 °C	24 h	-
8^a	4c	20	50 °C	24 h	-
9^{a,b}	4d	20	50 °C	24 h	-

Reaction conditions: Reactions were carried in 0.38 M CH_2Cl_2. a) Reaction was carried in a screwed cap vial. b) BArF: tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

However, when the reaction was performed with 20 mol% of triflate salt **4b** at 40 °C, 34 % of the product *C*- glycoside **3a** was obtained in 2 h. When the reaction was performed at 50 °C, the reaction went to completion in just 20 mins and provided the product with 85% yield as only *α*-isomer. The yield and selectivity remained intact even when the catalytic loading was reduced to 5 mol% giving rise to the product in 86% yield as an *α*-isomer. When tried with an even more weakly coordinating anion like BArF anion, the reaction did not lead to any product, revealing that the reaction is surprisingly specific to a triflate salt. To understand if other pyridinium triflate salts could catalyze the transformation, the reaction was performed with less-bulky lutidine triflate at 50 °C; however, it did not lead to any conversion even after heating for 24 h, which reiterated the specific reactivity of triflate associated with the sterically bulky 2,4,6-tri-*tert*-butylpyridine. Akin to the TTBPyHCl, N-H...$^{-}$OTf is 3.25 Å in comparison with N-H...$^{-}$Cl distance of 3.1 Å in TTBPyHCl salt, which is unusually longer relative to the simple N-H...$^{-}$OTf distance in simple pyridinium triflate salt.[10] In addition, surprisingly, the fluorine of the triflate is in H-bonding with C-Hs of [TTBPyH]$^+$ rather than the negatively charged oxygen of the triflate anion, unlike in the simple pyridinium triflate. The N-H$^+$....$^{-}$OTf distance in a simple PyHOTf is 2.19 Å. The unusually long distance between the ion-pair results in poor electronic stabilization and imbues unusual reactivity to the anions in the solution phase.

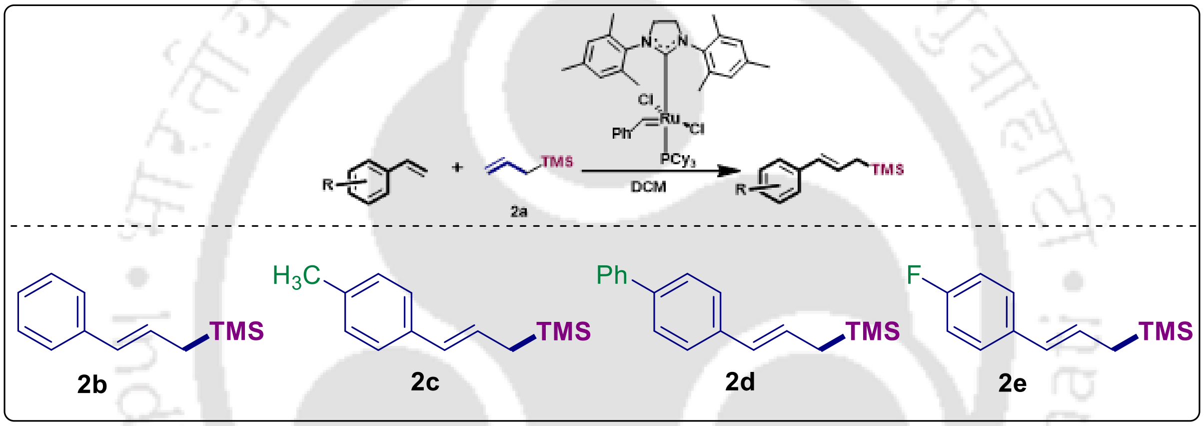


Scheme 13^a: Reaction of AllylTMS with various glycals

Reaction conditions: Reactions were carried in 0.38 M CH_2Cl_2. ^{a}Reaction was carried in a screwed cap vial. ^{b}BArF: tetrakis[3,5-bis(trifluoromethyl)phenyl]borate. ^{c}stereochemistry was determined from NMR analysis

With the optimized conditions in hand, the reaction was tested with other variously protected glucal, galactal, and xylal. The reactions with acetyl, benzoyl, and benzyl protecting groups all provided the *α*-*C*-allyl glycosides (**33a-33e**) in good yields (**Scheme 13**). Interestingly, though the conditions were mild, the reaction even with tri-TBDPS-glucal, led to the respective product (**33f**) in 74% yield. After this, we have decided to test the efficacy of the organocatalytic protocol with substituted allylsilanes as nucleophiles that might provide interesting products that will be relevant for the synthesis of various natural products. In addition, it is requisite to understand whether such substituted allylsilanes would provide linear or branched products via Ferrier rearrangement.

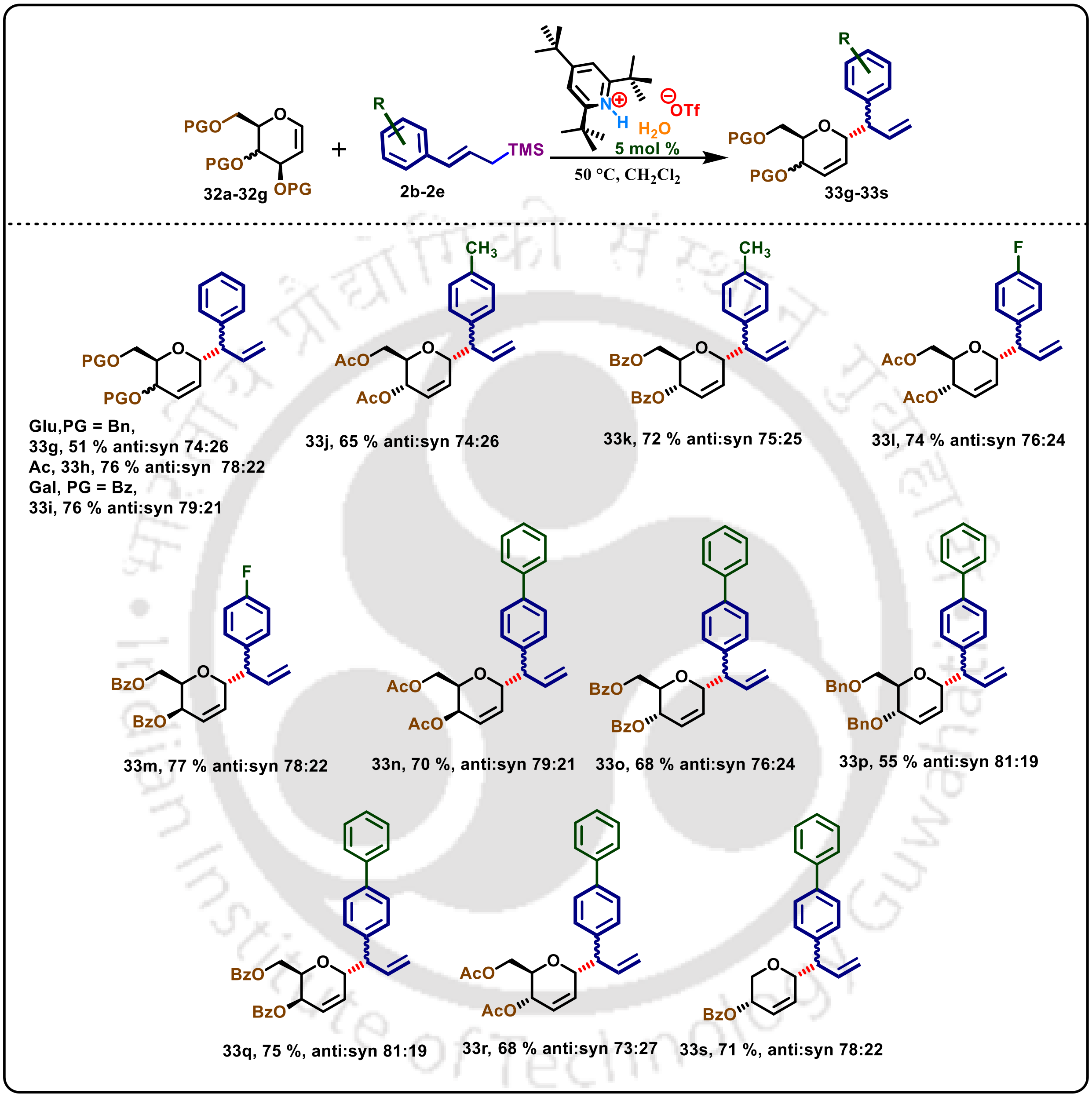
The substituted cinnamylsilanes (**2b-2e**) were synthesized from allyltrimethylsilane via cross-metathesis with substituted styrenes catalyzed by the second-generation Grubb's catalyst following a literature procedure (**Scheme 14**).[18]



Scheme 14: CinnamylTMS Derivatives synthesized via cross-metathesis

All the substituted cinnamylsilanes were obtained in good yields. Having these interesting nucleophiles in hand, we tested the current protocol with various glucal and galactal derivatives (**Scheme 15**).As expected, all the products (**33g-33s)** were obtained in moderate to good yields and most importantly, the products were obtained in a regio and stereoselective fashion. All the products gave the branched vinyl substituted products, and no linear phenylallyl glycosides have been observed. Besides, only two products with stereochemistry differing at allyl benzylic position are obtained out of the possible four diastereomers. Like the simple allylsilanes, the substituted allylsilanes too were selectively added to the α-face of the allyloxocarbenium ion, resulting in a diastereoselective mixture of *α*-C-glycosides with all the substituted cinnamylsilanes. Unlike the general *O*-glycosylation reactions, it is well accepted that the nucleophilic additions in Ferrier rearrangements usually proceed via S_N1 mechanisms where the nucleophile reacts on the allyloxocarbenium ions. Since both the gluco and galacto versions that differ at C-4 carbon provided complete *α*-selective products, it can be assumed that the pseudoequatorial orientation of the C-5 hydroxymethyl substituent could be determining the conformation of allyloxycarbenium ion resulting in the pseudoaxial orientation of the *p*-orbital of the oxocarbenium ion (**Figure 2.2**), and thereby dictating the facial selectivity in the stereochemical outcome of the Ferrier glycosides.

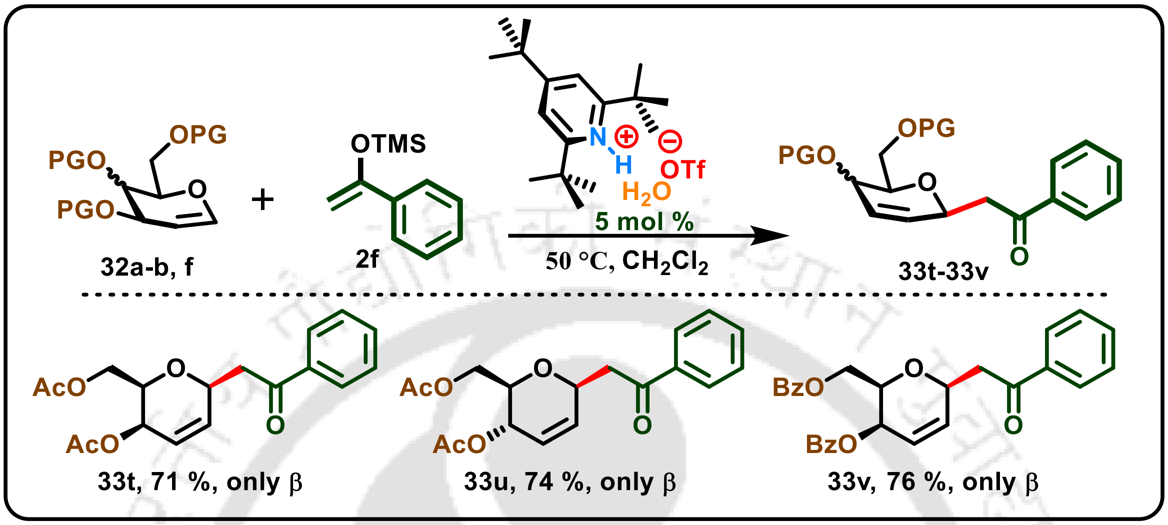
However, the observed selectivities align with the observations made earlier by other groups, including Bleriot and coworkers, where the structure of the intermediate allyloxocarbenium ion has been characterized under superacidic conditions.[10c]



Sche me 15: Reaction of cinnamylTMS derivatives with various glycals
Reaction conditions: 32a-f (1 equiv.) and silane (2b-e) (1.5 equiv.) dry CH_2Cl_2 (0.38 M) and 5 mol% of 4b, 30 min at 50 °C. Stereochemistry of the products was determined from NMR analysis.

2.3.2 Activation of Silylenolethers

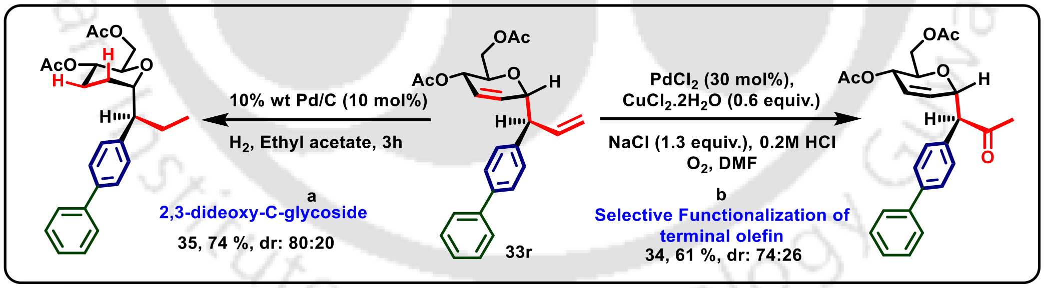
Later we extended the protocol to the relatively more nucleophilic silylenol ether as a nucleophile (**Scheme 16**). Intriguingly enough, the reaction of the silyl enolether **2f**[19] with acetyl protected glucal and acetyl and benzyl protected galactals provided the Ferrier products (**3t-3v**) in exclusively β-selectivity. While such a stereochemical outcome is difficult to rationalize, given the unique high reactivity of triflate associated with $[TTBPyH]^{+}$, it won't be a far-fetched idea to consider the allylglycosyl α-triflate as potential intermediates onto which relatively more nucleophilic silylenolethers might react in an S_N2 fashion leading to the β-selectivity.[12]



Scheme 16:^{a}. Reaction of Silylenolethers.

Reaction conditions: 32a-b,1f (1 equiv.) and phenylsilylenolether (2f) (1.5 equiv.) dry CH_2Cl_2 (0.38 M) and 5 mol% of 4b, 30 min at 50 °C. ^{a}stereochemistry of the products was determined from NMR analysis.

2.3.3 Application of substrates synthesized: Further functionalization



Scheme 17. Further functionalization of the branched vinyl substituted Ferrier-*C*-glycoside Reaction conditions: a) 0.1mmol of 33r, ethyl acetate (0.7ml), Pd/C (10% wt) (1.2 mg), H2, 3h. b) PdCl2 (5.3 mg), CuCl2.2H2O (10 mg), NaCl (8 mg.), 0.2 M HCl (1.3 mL), 35 °C, O2, 30 min. Then 3r (0.1 mmol) in DMF, 60 °C, 6 h. (stereochemistry of the products was determined from NMR analysis).

Also, to explore the synthetic potential of the unprecedented phenylallyl pseudoglycals (**33n-s**), one of the representative compounds (**33r**) has been subjected to hydrogenation reaction to obtain an interesting 2,3-di-deoxy biphenylethylglycoside **34**. In addition, taking advantage of the terminal double bond, the same compound has also been subjected to Wacker's oxidation conditions to provide the keto derivative **35** with 2,3-double bond intact, which can be further converted to interesting C2-C3 functionalized C-glycosides (**Scheme 17**).

2.4 Mechanistic Studies

To delve into the actual mechanism of the current mild catalysis, we have performed a few control experiments and NMR studies. One of the potential pathways is that the catalyst activates the donor initially and generates an allyloxycarbenium ion onto which the allylsilanes undergo a nucleophilic addition. However, when the reaction was performed in the absence of the silicon reagent, no activation of the glycal was observed, ruling out the donor-mediated activation (**Figure** 2.**2**. Eq1). On the other hand, when acceptor allylsilane was subjected to the reaction conditions with 1 equiv of the catalyst **4b** in the absence of the donor, a quick desilylation was observed, resulting in the formation of propene (**Figure** 2.2. Eq2). This suggests that the catalyst reacts with allylsilanes, resulting in the formation of a silicon cation, which could react with glycal to generate the allyloxycarbenium ion, which further undergoes a nucleophilic addition with another molecule of allylsilane.

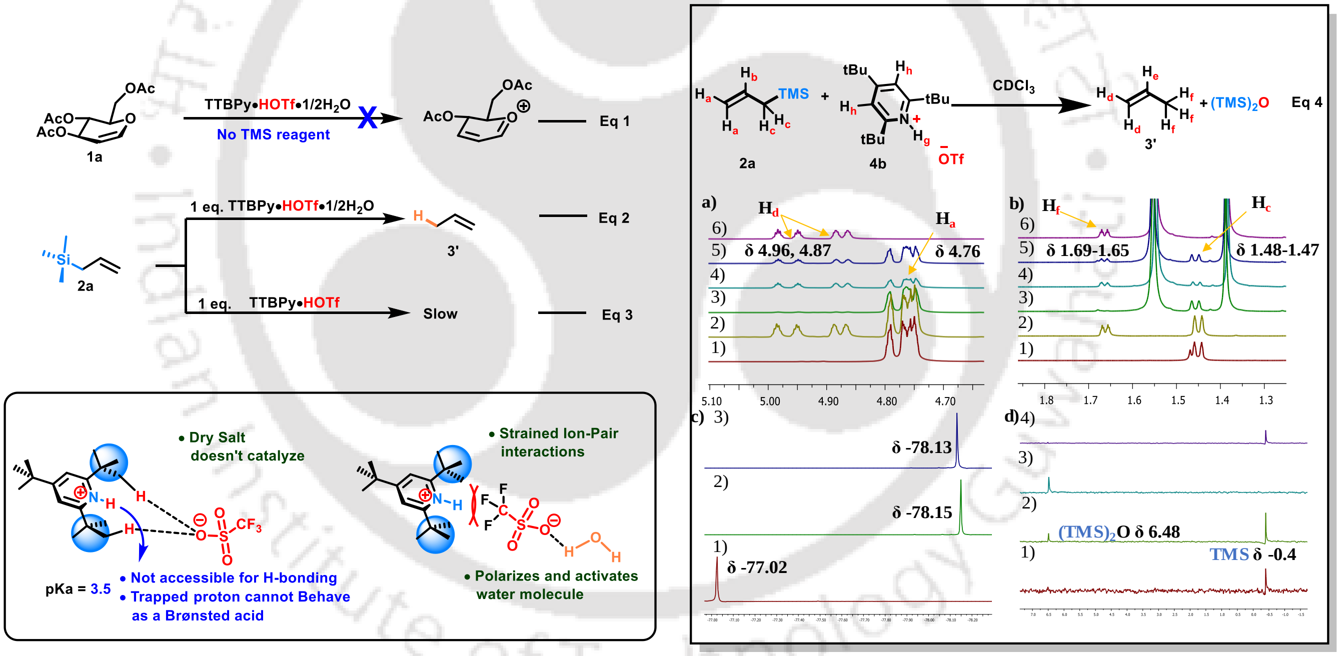


Figure 2.2 Investigation of the mechanism. (Eq 1-Reactivity of catalyst towards glucal (1a). Eq 2-Reactivity of catalyst towards allylTMS (2a). Eq 3-Reaction of dry catalyst towards allylTMS (2a). a) & b) the expanded spectra of the control experiment comparing the reactivity of dry and hydrated 4b. c) ^{19}F-NMR spectra of TfOH and **4b** and **4b** in reaction mixture Eq 4. d) ^{29}Si-NMR spectra of Eq 4 compared with similar reaction mixtures with 20 mol% of TfOH and **4c** as catalysts.)

Initially, it was assumed that triflate bound to the sterically hindered TTBPy could behave as a strong nucleophile[13] forming a pentacoordinated silicon that could react as a strong nucleophile giving the observed products. However, after careful analysis of the ^{1}H NMR data, it was found that the triflate salt **4b** exists as half hydrate where two naked triflate anions presumably polarize one H_2O molecule. Cognizant of such A^{-}..H-O-H interactions assisted alkene activation,[8] we performed the experiment with an ultra-dry **4b** under otherwise identical reaction conditions, where the allylsilane activation is found to be extremely slow (**Figure 2.2**. eq 3). Also, a ^{19}F NMR of **4b,** when recorded of the reaction mixture, did not resemble the ^{19}F chemical shift of triflic acid, suggesting the unique ability of such salts in activating the allyl silanes. Also, attempts to observe the silicon cation under the reaction conditions via ^{29}Si NMR only led to the observation of $(TMS)_2O$, which, however, suggests the release of silicon cation. Based on all the above observations, we propose that the frustrated triflate bound to $[TTBPyH]^{+}$ activates the allylsilanes via strong TfO^{-}....H-O-H interactions assisted by the *β*-silicon effect, thereby releasing the silicon cation, which further catalyzes the observed diastereoselective Ferrier reaction (**Figure 2.3**). However, when 5 mol% of the TMSOTf was directly used in the catalysis, led to a significant decrease in the yields of the product. This signifies the unique advantages of the benign, electronically neutral, bench-stable salt TTBPyHOTf, as an alternative to the relatively difficult-to-handle TMSOTf or TfOH in reactions with allylsilanes or silyl enol ethers as reagents. The inability of other TTBPy salts like the chloride and BArF salts to catalyze the reaction, emphasizes the anionic specificity of the transformation and the significance of the triflate anion under such unique catalysis.

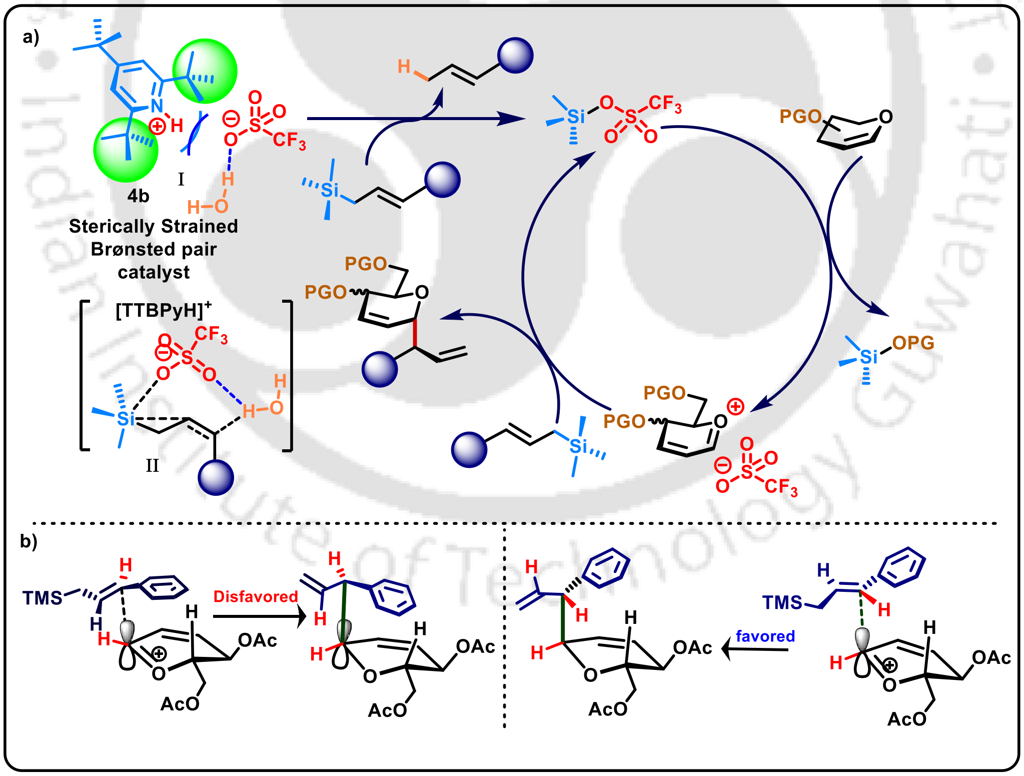


Figure 2.3 a) Proposed Mechanism. b) Probable approach of Silane in favoured/disfavoured conformations

In conclusion, we demonstrated the potential of sterically hindered 2,4,6-tri-*tert*-butylpyridinium triflate salt as a stable, mild, and easy to handle organocatalyst for the diastereoselective synthesis of arylvinyl C-glycosides. The ability to activate allylsilanes and silylenolethers via TfO^-...H-O-H interactions resulting in the generation of silicon cation opens up enormous possibilities. The concept can be applied to various organic transformations. The salt **4b** can be an excellent bench stable alternative to the usually sensitive TMSOTf, specifically where silicon-based nucleophiles are used. The slow release of the highly Lewis acidic silicon cation could have great potential in organic synthesis.

2.5 Experimental Section

2.5.1 General Information

All solvents purchased were of commercial grade and reagents purchased from Sigma-Aldrich, Merck, Carbosynth, Spectrochem, Alfa Aesar, Avra and used without further reaction purification.

2.5.2 Analysis

Reactions were monitored by TLC on Kieselgel 60 F254 (Merck). Detection was done by examination under UV light (254 nm) and by charring with 10% sulfuric acid in water. Purification was performed by both Ultra High-Performance Liquid Chromatography (UHPLC) using column [Particle size: (µ) 12, Dim: (mm) 250 x 10] in reverse phase and in normal phase using silica gel [Merck, 60-120 mesh]. Extracts were concentrated in vacuo using both Büchi rotary evaporator (bath temperatures up to 40 °C) at a pressure of either 15 mmHg (diaphragm pump) and 0.7 mmHg (oil pump), at rt. ^1H- and ^{13}C NMR were recorded on a Bruker 600 MHz, 500 MHz, and 400 MHz spectrometer using $CDCl_3$ as solvent. Chemical shift values are reported in ppm with the solvent as the internal standard ($CDCl_3$: δ 7.26 for ^1H, δ 77.16 for ^{13}C). Data are reported as follows: chemical shifts (δ), multiplicity (s = singlet, d = doublet, dd = doublet of doublet, ddd = doublet of doublet of doublets, dt = doublet of triplet, t = triplet, td = triplet of doublet, q = quartet, m = multiplet), etc., coupling constants J (Hz), and integration. High-resolution mass measurements were performed using Agilent technologies mass spectrometer (QTOF-ESI mode). The diastereomeric ratios were calculated from crude NMR. Specific rotation was recorded in Autopol II S2, the units of the specific rotation is (deg·mL)/(g·dm), and concentration *c* is given in g/100 ml. Suitable crystals for single crystal X-ray diffraction (SCXRD) analysis were obtained by dissolving "**4b**" in CH_2Cl_2 and CH_3OH (10:1) followed by slow evaporation of the solvent mixture at room temperature. The X-ray diffraction data were collected at 296 K with Mo Kα radiation (λ= 0.71073 Å) using a Micro focused based Bruker D8 QUEST diffractometer equipped with a graphite monochromator. Apex IV software was used for data collection and also for indexing the reflections and determining the unit cell parameters; the collected data were integrated using Saint Software. The structures were solved by Intrinsic phasing and refined by full-matrix least-squares calculations using SHELXTL 2018 software. All the non-H atoms were refined in the anisotropic approximation.

Following Glycals (**Figure 2.4**) were used in this study:

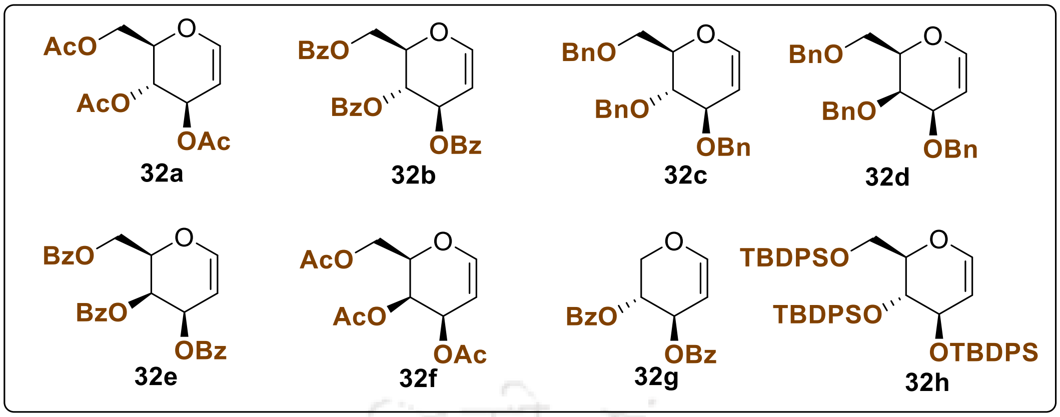
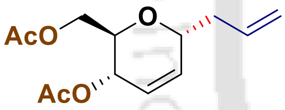


Figure 2.4 Glycals utilised in this study

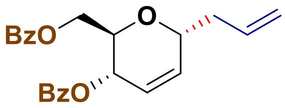
2.5.3. General Procedure

A solution of glycal **32a-h** (1 equiv.) and allyl trimethylsilane **2a-e** (1.5 equiv.) in dry CH_2Cl_2 (0.38 M) was taken in a screwed cap vial followed by the addition of catalyst **4b** (5 mol %). The reaction mixture was stirred at 50 °C for 30 min. After completion of the reaction, the crude reaction mixture was worked up with water, washed with brine, dried by Na_2SO_4, and concentrated in rotavapor. The resulting crude reaction mixture was purified through column chromatography to afford the Ferrier C-glycosylated product (**33a-33v**).



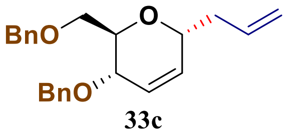
33a

((*2R,3S,6R*)-3-acetoxy-6-allyl-3,6-dihydro-2H-pyran-2-yl)methyl acetate (33a): Ferrier glycosylation of **32a** (49 mg, 0.18 mmol) with **2a** (30.9 mg, 0.27 mmol) according to **General procedure** afforded **33a** (39.4 mg, 86 %, α only) as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.5 (Hexane/EtOAc = 4:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.97 – 5.91 (m, 1H), 5.90 – 5.78 (m, 2H), 5.17 – 5.09(m, 3H), 4.28 (td, J = 5.7, 3.0 Hz, 1H), 4.24 (dd, J = 11.8, 6.6 Hz, 1H), 4.15 (dd, J = 11.9, 3.4 Hz, 1H), 3.96 (td, J = 6.4, 3.5 Hz, 1H), 2.51 – 2.43 (m, 1H), 2.36 – 2.30 (m, 1H), 2.08 (s, 6H). HRMS (ESI) m/z: calcd for $C_{13}H_{12}NO_5$ $[M+NH_4]^+$ 272.1498, found 272.1503. $[\alpha]^{35}_{D}$ = +0.04 (*c* 0.01, $CHCl_3$).



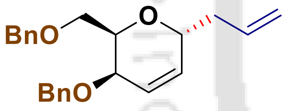
33b

(*2R,3S,6R*)-6-allyl-2-((benzoyloxy)methyl)-3,6-dihydro-2H-pyran-3-yl benzoate (33b): Ferrier glycosylation of **32b** (55.1 mg, 0.12 mmol) with **2a** (20.6 mg, 0.18 mmol) according to **General procedure A** afforded **33b** (32.2 mg, 71 %, α only) as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.5 (Hexane/EtOAc = 5:1, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 10.3, 4.1 Hz, 4H), 7.62 – 7.51 (m, 2H), 7.42 (dt, *J* = 10.5, 7.8 Hz, 4H), 6.04 – 5.99 (m, 1H), 5.97 (dd, *J* = 7.3, 5.3 Hz, 1H), 5.88 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H), 5.51 – 5.46 (m, 1H), 5.15 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.08 (d, *J* = 10.1 Hz, 1H), 4.54 (dd, *J* = 11.8, 4.0 Hz, 1H), 4.49 (dd, *J* = 11.8, 6.6 Hz, 1H), 4.39 (ddd, *J* = 7.7, 5.7, 1.9 Hz, 1H), 4.31 (td, *J* = 6.4, 4.1 Hz, 1H), 2.54 (dt, *J* = 14.6, 7.4 Hz, 1H), 2.43 – 2.35 (m, 1H).



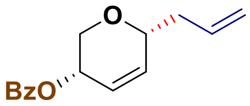
33c

(*2R,3S,6R*)-6-allyl-3-(benzyloxy)-2-((benzyloxy)methyl)-3,6-dihydro-2H-pyran (33c): Ferrier glycosylation of **32c** (51.2 mg, 0.12 mmol) with **2a** (20.6 mg, 0.18 mmol) according to **General procedure A** afforded **33c** (33.2 mg, 79 %, α only) as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.6 (Hexane/EtOAc = 6:1, v/v).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 6H), 7.28 – 7.23 (m, 4H), 5.91 (ddd, J = 12.2, 7.1, 5.1 Hz, 1H), 5.89 – 5.75 (m, 2H), 5.09 (dd, J = 16.3, 14.2 Hz, 2H), 4.60 (dd, J = 11.9, 5.3 Hz, 2H), 4.52 (d, J = 12.2 Hz, 1H), 4.48 (d, J = 11.6 Hz, 1H), 4.28 – 4.20 (m, 1H), 4.01 – 3.97 (m, 1H), 3.85 – 3.81 (m, 1H), 3.71 – 3.63 (m, 2H), 2.48 (dt, J = 14.3, 7.2 Hz, 1H), 2.30 (dt, J = 13.9, 6.8 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.3, 138.2, 134.6, 131.2, 128.4, 128.3, 128.2, 128.0, 127.8, 127.7, 127.6, 125.6, 117.3, 73.3, 72.1, 71.3, 71.0, 70.0, 69.2, 38.1. HRMS (ESI) m/z: calcd for $C_{23}H_{30}NO_3$ $[M+NH_4]^+$ 368.2226, found 368.2221. $[\alpha]_D^{35}$= +1.68 (*c* 0.01, $CHCl_3$).



33d

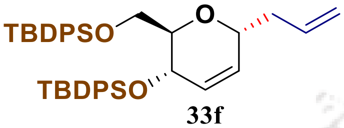
(*2R,3R,6R*)-6-allyl-3-(benzyloxy)-2-((benzyloxy)methyl)-3,6-dihydro-2H-pyran (33d): Ferrier glycosylation of **32d** (51 mg, 0.12 mmol) with **2a** (20.6 mg, 0.18 mmol) according to **General procedure A** afforded **33d** (36.6 mg, 87 %, α only) as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.5 (Hexane/EtOAc = 6:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.32 (m, 4H), 7.32 – 7.29 (m, 2H), 7.29 – 7.25 (m, 4H), 5.93 (dt, J = 10.4, 2.0 Hz, 1H), 5.90 – 5.82 (m, 1H), 5.85 – 5.82 (m, 1H), 5.11 (dd, J = 17.1, 1.4 Hz, 1H), 5.08 (d, J = 10.2 Hz, 1H), 4.61 (t, J = 12.0 Hz, 1H), 4.52 (d, J = 12.2 Hz, 1H), 4.47 (d, J = 11.5 Hz, 1H), 4.27 – 4.22 (m, 1H), 4.02 – 3.98 (m, 1H), 3.84 – 3.80 (m, 1H), 3.69 (dd, J = 10.4, 4.8 Hz, 1H), 3.65 (dd, J = 10.4, 3.2 Hz, 1H), 2.48 (dt, J = 14.3, 7.3 Hz, 1H), 2.31 (dt, J = 13.8, 6.8 Hz, 1H). HRMS (ESI) m/z: calcd for $C_{23}H_{30}NO_3$ $[M+NH_4]^+$ 368.2226, found 368.2227. $[\alpha]_D^{35}$= -0.3 (*c* 0.01, $CHCl_3$).



33e

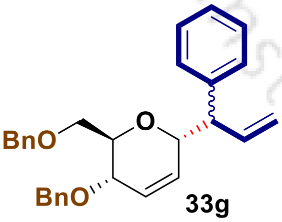
(*3S,6R*)-6-allyl-3,6-dihydro-2H-pyran-3-yl benzoate (33e): Ferrier glycosylation of **32g** (45.4 mg, 0.14 mmol) with **2a** (23.9 mg, 0.21 mmol) according to **General procedure A** afforded **33e**

(28.7 mg, 84 %, α only) as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.6 (Hexane/EtOAc = 5:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, J = 7.7 Hz, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.44 (t, J = 7.7 Hz, 2H), 6.00 – 5.94 (m, 2H), 5.86 (ddt, J = 17.1, 10.1, 7.0 Hz, 1H), 5.52 (t, J = 5.7 Hz, 1H), 5.14 (t, J = 14.3 Hz, 2H), 4.29 – 4.21 (m, 2H), 3.68 (dd, J = 11.2, 7.2 Hz, 1H), 2.39 (dt, J = 14.0, 7.0 Hz, 1H), 2.36 – 2.30 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.1, 133.9, 133.5, 133.1, 130.0, 129.7, 128.4, 124.7, 117.7, 73.3, 65.5, 65.4, 38.9. HRMS (ESI) m/z: calcd for $C_{15}H_{16}NaO_3$ $[M+Na]^+$ 267.0997, found 267.0997. $[\alpha]^{35}_{D}$= -0.24 (*c* 0.01, $CHCl_3$).



33f

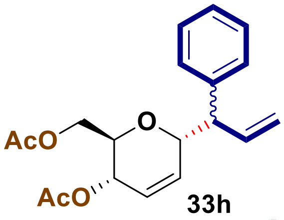
(((*2R,3S,6R*)-6-allyl-2-(((tert-butyldiphenylsilyl)oxy)methyl)-3,6-dihydro-*2H*-pyran-3-yl)oxy)(tert-butyl)diphenylsilane (33f): Ferrier glycosylation of **32h** (51.7 mg, 0.06 mmol) with **2a** (10.3 mg, 0.09 mmol) according to **General procedure A** afforded **33f** (30.3 mg, 78 %, α only) as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.7 (Hexane/EtOAc = 9:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 (d, J = 7.0 Hz, 2H), 7.63 (d, J = 7.1 Hz, 2H), 7.60 (t, J = 6.5 Hz, 4H), 7.39 (dt, J = 12.9, 7.2 Hz, 4H), 7.36 – 7.24 (m, 9H), 5.91 (dq, J = 9.8, 7.0 Hz, 1H), 5.59 (d, J = 10.5 Hz, 1H), 5.54 (d, J = 10.4 Hz, 1H), 5.12 (d, J = 17.1 Hz, 1H), 5.05 (d, J = 10.2 Hz, 1H), 4.10 (d, J = 6.1 Hz, 1H), 3.87 – 3.80 (m, 2H), 3.61 (dd, J = 10.2, 6.2 Hz, 1H), 2.47 (dt, J = 14.2, 7.1 Hz, 1H), 2.28 – 2.22 (m, 1H), 1.01 (s, 9H), 0.98 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 135.9, 135.8, 135.72, 135.7, 135.1, 134.2, 133.72, 133.7, 133.5, 130.2, 129.7, 129.6, 129.5, 128.4, 127.7, 127.54, 127.48, 116.8, 75.3, 71.7, 65.2, 63.9, 37.9, 29.7, 26.9, 26.8, 19.3, 19.2. HRMS (ESI) m/z: calcd for $C_{41}H_{50}NaO_3Si_2$ $[M+Na]^+$ 669.3196, found 669.3212. $[\alpha]^{35}_{D}$= +0.44 (*c* 0.01, $CHCl_3$).



33g

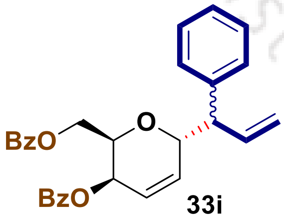
(*2R,3S,6S*)-3-(benzyloxy)-2-((benzyloxy)methyl)-6-(1-phenylallyl)-3,6-dihydro-*2H*-pyran (33g): Ferrier glycosylation of **32c** (50.1 mg, 0.12 mmol) with **2b** (34.3 mg, 0.18 mmol) according to **General procedure A** afforded **33g** (26.1 mg, 51 %, d.r.: 74:26, α only) as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.7 (Hexane/EtOAc = 6:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 9H), 7.28 – 7.24 (m, 8H), 7.23 – 7.18 (m, 4H), 6.24 (ddd, J = 17.8, 10.2, 7.9 Hz, 1H), 6.09 – 6.01 (m, 1H), 5.99 (d, J = 5.1 Hz, 1H), 5.87 (ddd, J = 7.3, 4.6, 2.7 Hz, 1H), 5.54 – 5.49 (m, 1H), 5.17 – 5.08 (m, 3H), 5.06 – 5.01 (m, 1H), 4.64 (dd, J = 12.3, 6.3 Hz, 1H), 4.62 – 4.60 (m, 1H), 4.57 (d, J = 11.5 Hz, 2H), 4.52 (d, J = 12.2 Hz, 1H), 4.49 – 4.47 (m, 1H), 4.47 – 4.40 (m, 4H), 4.34 (d, J = 12.3 Hz, 1H), 4.06 – 4.02 (m, 1H), 3.99

– 3.96 (m, 1H), 3.87 – 3.81 (m, 2H), 3.71 (dd, J = 10.5, 4.6 Hz, 1H), 3.69 – 3.65 (m, 2H), 3.61 (t, J = 8.7 Hz, 1H), 3.58 (dd, J = 10.6, 5.0 Hz, 1H), 3.48 (dd, J = 10.6, 2.9 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 141.3, 140.8, 139.0, 138.28, 138.26, 138.2, 138.1, 137.9, 129.91, 129.85, 128.7, 128.4, 128.34, 128.29, 128.2, 128.1, 128.0, 127.9, 127.8, 127.74, 127.7, 127.6, 127.5, 127.4, 126.8, 126.5, 126.4, 126.2, 125.6, 117.3, 117.1, 116.2, 75.6, 74.7, 73.3, 73.1, 72.1, 71.8, 71.2, 71.1, 71.0, 69.92, 69.87, 69.2, 54.2, 53.8. HRMS (ESI) m/z: calcd for $C_{29}H_{34}NO_3$ $[M+NH_4]^+$ 444.2539, found 444.2538. $[\alpha]^{35}_{D}$= +0.54 (*c* 0.01, $CHCl_3$).



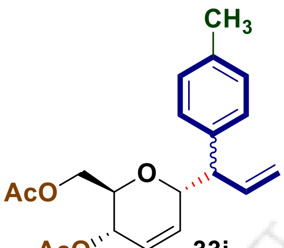
33h

((*2R,3S,6S*)-3-acetoxy-6-(1-phenylallyl)-3,6-dihydro-*2H*-pyran-2-yl)methyl acetate (33h): Ferrier glycosylation of **32a** (43.6 mg, 0.16 mmol) with **2b** (45.7 mg, 0.24 mmol) according to **General procedure A** afforded **33h** (40.2 mg, 76 %, d.r.: 78:22, α only) as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.6 (Hexane/EtOAc = 5:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 3H), 7.27 – 7.23 (m, 3H), 7.22 (d, J = 7.3 Hz, 2H), 6.24 – 6.16 (m, 1H), 6.10 (d, J = 10.4 Hz, 1H), 6.07 – 6.00 (m, 1H), 5.86 – 5.83 (m, 1H), 5.73 (dt, J = 10.5, 2.1 Hz, 1H), 5.62 (dd, J = 10.5, 1.7 Hz, 1H), 5.21 – 5.15 (m, 3H), 5.14 – 5.07 (m, 3H), 4.52 (dd, J = 8.7, 2.1 Hz, 1H), 4.46 (dd, J = 9.4, 2.0 Hz, 1H), 4.23 (dd, J = 11.9, 6.7 Hz, 1H), 4.20 – 4.12 (m, 2H), 4.01 – 3.95 (m, 3H), 3.66 (t, J = 8.7 Hz, 1H), 3.60 (t, J = 8.7 Hz, 1H), 2.09 (s, 6H), 2.08 (s, 1H), 1.95 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.9, 170.8, 170.4, 140.7, 140.3, 138.5, 137.6, 131.8, 131.5, 128.8, 128.5, 128.2, 128.0, 127.0, 126.7, 124.4, 124.2, 117.4, 116.5, 74.9, 73.8, 70.1, 69.6, 65.0, 64.9, 63.0, 62.7, 54.1, 53.8, 21.1, 20.9, 20.7. HRMS (ESI) m/z: calcd for $C_{19}H_{26}NO_5$ $[M+NH_4]^+$ 348.1811, found 348.1815. $[\alpha]^{35}_{D}$= +0.94 (*c* 0.01, $CHCl_3$).



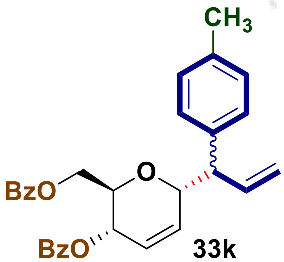
33i

((*2R,3R,6S*)-3-(benzoyloxy)-6-(1-phenylallyl)-3,6-dihydro-*2H*-pyran-2-yl)methyl benzoate (33i): Ferrier glycosylation of **32e** (55.2 mg, 0.12 mmol) with **2b** (34.3 mg, 0.18 mmol) according to **General procedure A** afforded **33i** (41.5 mg, 76 %, d.r.: 79:21, α only) as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.6 (Hexane/EtOAc = 5:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 – 8.02 (m, 4H), 7.85 (d, J = 7.2 Hz, 1H), 7.59 – 7.54 (m, 2H), 7.46 – 7.39 (m, 5H), 7.31 (t, J = 7.4 Hz, 2H), 7.27 – 7.20 (m, 4H), 7.18 (t, J = 7.4 Hz, 1H), 7.13 (t, J = 7.2 Hz, 1H), 6.29 (dd, J = 10.4, 2.7 Hz, 1H), 6.25 – 6.17 (m, 1H), 6.10 (ddd, J = 10.3, 5.2, 2.0 Hz, 1H), 6.04 (dt, J = 17.0, 9.8 Hz, 1H), 5.81 (dd, J = 10.4, 2.8 Hz, 1H), 5.40 (dd, J = 4.8, 2.6 Hz, 2H), 5.20 – 5.12 (m, 2H), 5.07 – 5.00 (m, 2H), 4.70 (d, J = 9.2 Hz, 1H), 4.64 – 4.59 (m, 2H), 4.54 (dd, J = 11.6, 4.3 Hz, 1H), 4.47 – 4.41 (m, 4H), 3.69 (t, J = 9.1 Hz, 1H), 3.65 (t, J = 8.6 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.4, 166.3, 166.0, 140.7, 140.2, 138.3, 137.6, 133.84, 133.8, 133.3, 133.1, 130.0, 129.8, 129.8, 129.7, 129.66, 128.8, 128.6, 128.5, 128.4, 128.33, 128.29, 128.2, 127.8, 127.0, 126.6, 122.7, 122.5, 117.4, 116.8, 75.7, 74.7, 69.0, 68.8, 64.5, 64.4, 63.8, 63.5, 53.6, 53.1. HRMS (ESI) m/z: calcd for $C_{29}H_{30}NO_5$ $[M+NH_4]^+$ 472.2124, found 472.2124. $[\alpha]_D^{35}$= -0.24 (*c* 0.01, $CHCl_3$).



33j

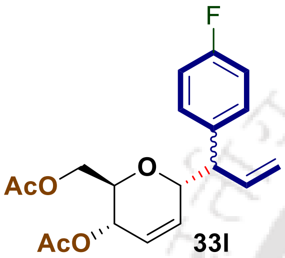
((*2R,3S,6S*)-3-acetoxy-6-(1-(p-tolyl)allyl)-3,6-dihydro-*2H*-pyran-2-yl)methyl acetate (33j): Ferrier glycosylation of **32a** (49.1 mg, 0.18 mmol) with **2c** (55.2 mg, 0.27 mmol) according to **General procedure A** afforded **33j** (40.3 mg, 65 %, d.r.: 74:26, α only) as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.7 (Hexane/EtOAc = 4:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.15– 7.11 (m, 4H), 7.10 (d, J = 8.0 Hz, 2H), 6.18 (ddd, J = 17.9, 10.2, 8.1 Hz, 1H), 6.10 (d, J = 10.1 Hz, 1H), 6.06 – 5.98 (m, 1H), 5.83 (dd, J = 9.4, 7.0 Hz, 1H), 5.72 (d, J = 10.5 Hz, 1H), 5.63 (d, J = 10.5 Hz, 1H), 5.18 – 5.11 (m, 5H), 5.07 (d, J = 17.0 Hz, 2H), 4.48 (dd, J = 8.6, 1.9 Hz, 1H), 4.44 (dd, J = 9.5, 1.8 Hz, 1H), 4.23 (dd, J = 11.9, 6.6 Hz, 2H), 4.20 – 4.13 (m, 3H), 4.02 – 3.95 (m, 2H), 3.62 (t, J = 8.7 Hz, 1H), 3.56 (t, J = 8.7 Hz, 1H), 2.33 (s, 3H), 2.32 (s, 3H), 2.09 (s, 6H), 2.08 (s, 3H), 1.96 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.9, 170.8, 170.5, 138.7, 137.8, 137.7, 137.2, 136.6, 136.1, 131.8, 131.7, 129.5, 129.2, 128.0, 127.8, 124.3, 124.2, 117.2, 116.2, 75.0, 73.9, 70.0, 69.5, 65.0, 64.95, 63.0, 62.7, 53.8, 53.3, 21.1, 21.05, 20.9, 20.7. HRMS (ESI) m/z: calcd for $C_{20}H_{24}NaO_5$ $[M+Na]^+$ 367.1521, found 367.1528. $[\alpha]_D^{35}$= +3.099 (*c* 0.02, $CHCl_3$).



33k

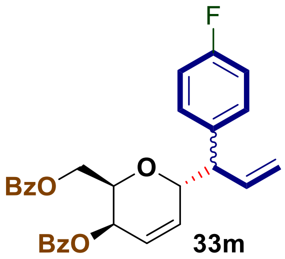
((*2R,3S,6S*)-3-(benzoyloxy)-6-(1-(p-tolyl)allyl)-3,6-dihydro-*2H*-pyran-2-yl)methyl benzoate (33k): Ferrier glycosylation of **32b** (55 mg, 0.12 mmol) with **2c** (36.8 mg, 0.18 mmol) according to **General procedure A** afforded **33k** (40.5 mg, 72 %, d.r.: 75:25, α only) as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.6 (Hexane/EtOAc = 6:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07–8.04 (m, 5H), 7.93 (d, J = 7.3 Hz, 1H), 7.61 – 7.53 (m, 3H), 7.48 – 7.38 (m, 6H), 7.16 – 7.09 (m, 5H), 6.99 (d, J = 7.8 Hz, 1H), 6.25 – 6.18 (m, 1H), 6.17

(d, J = 13.0 Hz, 1H), 6.05 (dd, J = 17.0, 9.9 Hz, 1H), 6.00 (d, J = 10.5 Hz, 1H), 5.90 (d, J = 10.5 Hz, 1H), 5.74 (d, J = 10.5 Hz, 1H), 5.50 – 5.45 (m, 1H), 5.40 – 5.38 (m, 1H), 5.19– 5.12 (m, 2H), 5.08 – 5.03 (m, 2H), 4.63 – 4.59 (m, 1H), 4.58 – 4.52 (m, 2H), 4.47 (dd, J = 11.8, 7.2 Hz, 1H), 4.44 – 4.40 (m, 2H), 4.37 (dd, J = 10.7, 5.8 Hz, 1H), 4.33 (td, J = 7.0, 3.4 Hz, 1H), 3.68 (t, J = 8.5 Hz, 1H), 3.63 (t, J = 8.4 Hz, 1H), 2.32 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 166.4, 166.3, 166.03, 166.00, 138.6, 138.0, 137.7, 137.6, 137.4, 136.5, 136.0, 133.3, 133.2, 133.1, 133.0, 132.3, 132.1, 129.81, 129.77, 129.7, 129.4, 129.2, 128.41, 128.38, 128.3, 128.2, 128.1, 127.8, 124.3, 124.0, 117.1, 116.4, 74.9, 73.7, 70.6, 69.9, 65.9, 65.7, 63.9, 63.6, 53.7, 53.3, 21.1. HRMS (ESI) m/z: calcd for $C_{30}H_{32}NO_5$ $[M+NH_4]^+$ 486.2280, found 486.2285. $[\alpha]^{35}_{D}$= +0.92 (*c* 0.01, CHCl$_3$).



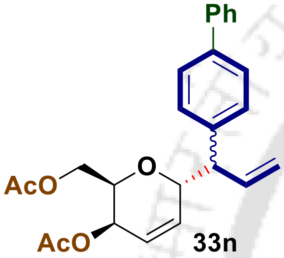
33l

((*2R,3S,6S*)-3-acetoxy-6-(1-(4-fluorophenyl)allyl)-3,6-dihydro-*2H*-pyran-2-yl)methyl acetate (33l): Ferrier glycosylation of **32a** (44.1 mg, 0.16 mmol) with **2e** (50.2 mg, 0.24 mmol) according to **General procedure A** afforded **33l** (41.4 mg, 74 %, d.r.: 76:24, α only) as a colorless syrup. The crude product was purified through column chromatography, R$_f$ = 0.6 (Hexane/EtOAc = 4:1, v/v). ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.23–7.17 (m, 3H), 7.05– 6.99 (m, 3H), 6.20 – 6.13 (m, 1H), 6.09 (d, J = 10.5 Hz, 1H), 6.28 – 5.96 (m, 1H), 5.85 (d, J = 10.5 Hz, 1H), 5.76 (d, J = 10.5 Hz, 1H), 5.64 (d, J = 10.4 Hz, 1H), 5.20 – 5.16 (m, 2H), 5.15 – 5.10 (m, 3H), 5-.10 – 5.04 (m, 2H), 4.47 (dd, J = 8.5, 1.8 Hz, 1H), 4.42 (dd, J = 8.9, 1.7 Hz, 1H), 4.25 – 4.21 (m, 1H), 4.20 – 4.12 (m, 2H), 4.01 – 3.94 (m, 2H), 3.63 (t, J = 8.7 Hz, 1H), 3.59 (t, J = 8.4 Hz, 1H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 170.9, 170.8, 170.5, 162.6, 162.4, 160.9, 160.7, 138.1, 137.5, 136.34, 136.32, 136.0, 135.9, 134.0, 132.8, 131.7, 131.3, 129.8, 129.7, 129.6, 129.5, 124.6, 124.2, 117.7, 117.5, 116.7, 115.6, 115.5, 115.3, 115.1, 74.7, 73.6, 70.2, 69.7, 64.79, 64.76, 62.8, 62.6, 53.3, 52.9, 21.1, 20.9, 20.7. HRMS (ESI) m/z: calcd for $C_{19}H_{25}FNO_5$ $[M+NH_4]^+$ 366.1717, found 366.1714. $[\alpha]^{35}_{D}$= +0.54 (*c* 0.01, CHCl$_3$).



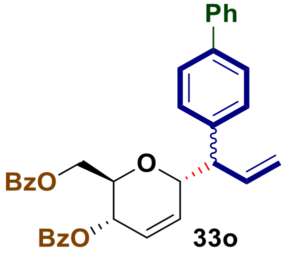
33m

((*2R,3R,6S*)-3-(benzoyloxy)-6-(1-(4-fluorophenyl)allyl)-3,6-dihydro-*2H*-pyran-2-yl)methyl benzoate (33m): Ferrier glycosylation of **32e** (55.3 mg, 0.12 mmol) with **2e** (37.7 mg, 0.18 mmol) according to **General procedure A** afforded **33m** (43.8 mg, 77 %, d.r.: 78:22, α only) as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.7 (Hexane/EtOAc = 6:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 – 8.03 (m, 5H), 7.83 (d, J = 7.4 Hz, 1H), 7.59–7.54 (m, 3H), 7.49 – 7.39 (m, 5H), 7.22 – 7.14 (m, 2H), 6.99 (t, J = 8.6 Hz, 2H), 6.81 (t, J = 8.6 Hz, 1H), 6.29 (dd, J = 10.4, 2.7 Hz, 1H), 6.22– 6.15 (m, 2H), 6.12 (ddd, J = 10.2, 5.0, 1.9 Hz, 1H), 6.01 – 5.93 (m, 1H), 5.81 (dd, J = 10.4, 2.6 Hz, 1H), 5.43 – 5.39 (m, 2H), 5.17 – 5.11 (m, 2H), 5.03 (t, J = 14.6 Hz, 2H), 4.67 – 4.60 (m, 2H), 4.57 (d, J = 8.9 Hz, 1H), 4.54 (dd, J = 11.7, 4.1 Hz, 1H), 4.47 – 4.41 (m, 4H), 3.71 – 3.60 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.4, 166.3, 165.98, 165.96, 162.6, 162.2, 160.9, 160.6, 137.9, 137.5, 136.34, 136.32, 135.92, 135.9, 133.7, 133.5, 133.3, 133.2, 129.8, 129.7, 129.62, 129.57, 129.2, 129.1, 128.5, 128.4, 128.3, 122.83, 122.75, 117.5, 117.0, 115.7, 115.6, 115.5, 115.3, 75.6, 74.4, 68.9, 64.34, 64.30, 63.7, 63.5, 52.6, 52.2. HRMS (ESI) m/z: calcd for $C_{29}H_{29}FNO_5$ $[M+NH_4]^+$ 490.2030, found 490.2034. $[\alpha]_D^{35}$= +0.18 (*c* 0.01, $CHCl_3$).



33n

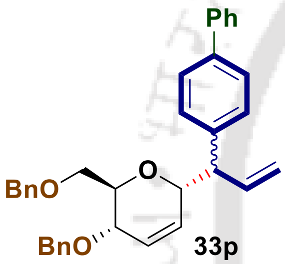
(*2R,3R,6S*)-6-(1-([1,1'-biphenyl]-4-yl)allyl)-2-(acetoxymethyl)-3,6-dihydro-*2H*-pyran-3-yl acetate (33n): Ferrier glycosylation of **32f** (49.3 mg, 0.18 mmol) with **2d** (72.1 mg, 0.27 mmol) according to **General procedure A** afforded **33n** (52.9 mg, 70 %, d.r.: 79:21, α only) as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.7 (Hexane/EtOAc = 6:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 – 7.55 (m, 5H), 7.43 (t, J = 6.8 Hz, 3H), 7.33 (dd, J = 12.8, 6.9 Hz, 2H), 7.29 – 7.24 (m, 2H), 6.27 – 6.18 (m, 2H), 6.08 – 6.00 (m, 2H), 5.99 – 5.93 (m, 1H), 5.81 (d, J = 10.4 Hz, 1H), 5.22 – 5.16 (m, 3H), 5.12 (d, J = 17.1 Hz, 1H), 5.09 (m, 2H), 4.63 (d, J = 9.1 Hz, 1H), 4.56 (d, J = 9.3 Hz, 1H), 4.26 – 4.21 (m, 2H), 4.21 – 4.15 (m, 2H), 4.10 – 4.04 (m, 2H), 3.69 (t, J = 9.1 Hz, 1H), 3.64 (t, J = 8.7 Hz, 1H), 2.08 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 1.86 (s, 3H). 13C NMR (126 MHz, CDCl3) δ 170.8, 170.7, 170.5, 140.9, 140.7, 140.0, 139.8, 139.6, 139.2, 138.4, 137.5, 133.6, 133.6, 128.8, 128.77, 128.6, 128.4, 127.5, 127.32, 127.25, 127.2, 127.01, 126.99, 122.8, 122.6, 117.5, 116.6, 75.6, 74.6, 68.6, 68.4, 63.7, 63.66, 63.1, 62.7, 53.2, 52.7, 22.7, 20.89, 20.86, 20.6. HRMS (ESI) m/z: calcd for $C_{25}H_{27}O_5$ $[M+H]^+$ 407.1858, found 407.1856. $[\alpha]_D^{35}$= +0.28 (*c* 0.01, $CHCl_3$).



33o

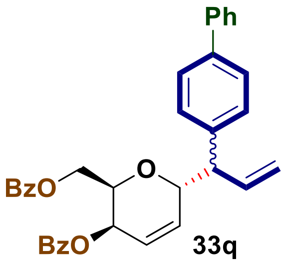
(*2R,3S,6S*)-6-(1-([1,1'-biphenyl]-4-yl)allyl)-2-((benzoyloxy)methyl)-3,6-dihydro-*2H*-pyran-3-

yl benzoate (33o): Ferrier glycosylation of **32b** (55.3 mg, 0.12 mmol) with **2d** (47.9 mg, 0.18 mmol) according to **General procedure A** afforded **33o** (43.3 mg, 68 %, d.r.: 76:24, α only) as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.5 (Hexane/EtOAc = 6:1, v/v). ^{1}H NMR (500 MHz, CDCl3) δ 8.05– 8.01 (m, 4H), 7.92 (d, J = 7.5 Hz, 1H), 7.58– 7.50 (m, 6H), 7.48 (d, J = 7.7 Hz, 1H), 7.45 – 7.37 (m, 8H), 7.36 – 7.28 (m, 5H), 6.30 – 6.22 (m, 2H), 6.14 – 6.06 (m, 1H), 6.03 (d, J = 10.5 Hz, 1H), 5.95 (d, J = 10.5 Hz, 1H), 5.82 (d, J = 10.5 Hz, 1H), 5.49 – 5.44 (m, 1H), 5.37 – 5.41 (m, 1H), 5.22 (d, J = 17.1 Hz, 1H), 5.18 (d, J = 10.2 Hz, 1H), 5.14 – 5.06 (m, 2H), 4.67 (d, J = 6.2 Hz, 1H), 4.61 (dd, J = 8.5, 1.8 Hz, 1H), 4.56 (dd, J = 11.8, 3.7 Hz, 1H), 4.50 (dd, J = 11.8, 7.1 Hz, 1H), 4.47 – 4.43 (m, 2H), 4.40 (dd, J = 10.7, 5.8 Hz, 1H), 4.34 (td, J = 6.7, 3.8 Hz, 1H), 3.77 – 3.68 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.42, 166.4, 166.1, 166.0, 140.8, 140.7, 139.9, 139.7, 139.5, 139.4, 138.2, 137.8, 133.29, 133.26, 133.1, 133.0, 132.3, 132.1, 129.84, 129.79, 129.76, 129.7, 128.77, 128.75, 128.7, 128.5, 128.44, 128.41, 128.33, 128.3, 127.4, 127.3, 127.2, 127.1, 127.01, 126.99, 124.4, 124.1, 117.7, 116.8, 74.8, 73.5, 70.8, 70.2, 65.8, 65.7, 63.8, 63.5, 53.8, 53.4. HRMS (ESI) m/z: calcd for $C_{35}H_{34}NO_5$ $[M+NH_4]^+$ 548.2437, found 548.2420. $[\alpha]_D^{35}$= +0.18 (*c* 0.01, $CHCl_3$).



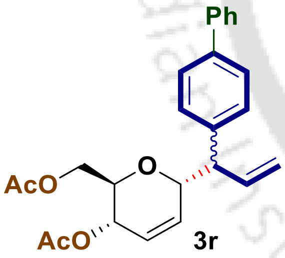
33p

(*2R,3S,6S*)-6-(1-([1,1'-biphenyl]-4-yl)allyl)-3-(benzyloxy)-2-(benzyloxy) methyl)-3,6-dihydro-*2H*-pyran (33p): Ferrier glycosylation of **32c** (50.1 mg, 0.12 mmol) with **2d** (48.1 mg, 0.18 mmol) according to **General procedure A** afforded **33p** (33.2 % mg, 55 %, d.r.: 81:19, α only) as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.7 (Hexane/EtOAc = 6:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 – 7.51 (m, 4H), 7.49 (d, J = 8.0 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.38 – 7.20 (m, 15H), 6.32 – 6.22 (m, 1H), 6.13 – 6.05 (m, 1H), 6.04 (d, J = 10.6 Hz, 1H), 6.00 (d, J = 10.7 Hz, 1H), 5.90 (d, J = 10.5 Hz, 2H), 5.60 (d, J = 10.5 Hz, 2H), 5.21 – 5.16 (m, 1H), 5.14 (d, J = 10.2 Hz, 2H), 5.07 (d, J = 17.1 Hz, 2H), 4.65 (d, J = 12.2 Hz, 3H), 4.58 (d, J = 11.5 Hz, 3H), 4.53 (d, J = 12.1 Hz, 2H), 4.48 (d, J = 9.6 Hz, 1H), 4.49 – 4.42 (m, 5H), 4.36 (d, J = 12.2 Hz, 1H), 4.09 – 4.01 (m, 2H), 4.04 (d, J = 6.6 Hz, 2H), 3.98 (d, J = 6.3 Hz, 1H), 3.92 –3.89 (m, 1H), 3.88 – 3.85 (m, 1H), 3.72 (dd, J = 10.3, 4.5 Hz, 2H), 3.71 – 3.68 (m, 1H), 3.68 – 3.64 (m, 1H), 3.60 (dd, J = 10.5, 5.0 Hz, 1H), 3.57 – 3.50 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 140.8, 139.9, 139.7, 138.9, 138.3, 138.1, 137.9, 129.99, 129.96, 128.8, 128.73, 128.65, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.75, 127.7, 127.6, 127.4, 127.2, 127.1, 127.03, 127.0, 126.4, 126.3, 117.2, 116.4, 75.5, 74.7, 73.3, 73.2, 71.9, 71.4, 71.1, 71.0, 69.9, 69.2, 69.0, 53.8, 53.5. HRMS (ESI) m/z: $C_{35}H_{38}NO_3$ $[M+NH_4]^+$ 520.2852, found 520.2843. $[\alpha]_D^{35}$= +0.28 (*c* 0.01, $CHCl_3$).



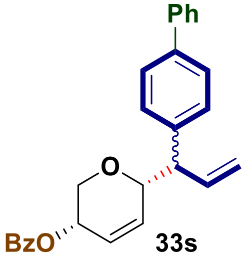
33q

(*2R,3R,6S*)-6-(1-([1,1'-biphenyl]-4-yl)allyl)-2-((benzoyloxy)methyl)-3,6-dihydro-*2H*-pyran-3-yl benzoate (33q): Ferrier glycosylation of **32e** (50.2 mg, 0.12 mmol) with **2d** (48.4 mg, 0.18 mmol) according to **General procedure A** afforded **33q** (43.7 mg, 75 %, d.r.: 81:19, α only) as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.5 (Hexane/EtOAc = 6:1, v/v). ^{1}H NMR (600 MHz, CDCl3) δ 8.08– 8.04 (m, 4H), 7.86 (d, J = 7.5 Hz, 1H), 7.55 (dd, J = 21.2, 7.7 Hz, 6H), 7.48 – 7.41 (m, 8H), 7.39 – 7.33 (m, 1H), 7.30 (d, J = 8.0 Hz, 2H), 6.31 (d, J = 10.3 Hz, 1H), 6.29 – 6.19 (m, 2H), 6.13 (dd, J = 8.5, 5.2 Hz, 1H), 6.11 – 6.04 (m, 1H), 5.89 (dd, J = 10.3, 2.6 Hz, 1H), 5.46 – 5.40 (m, 2H), 5.22 – 5.17 (m, 2H), 5.10 – 5.03 (m, 2H), 4.73 (d, J = 9.1 Hz, 1H), 4.66 (d, J = 8.8 Hz, 1H), 4.65 – 4.61 (m, 1H), 4.55 (dd, J = 11.6, 4.2 Hz, 1H), 4.52 – 4.45 (m, 3H), 3.76 – 3.66 (m, 2H).^{13}C NMR (151 MHz, $CDCl_3$) δ 166.4, 166.0, 140.7, 140.6, 139.9, 139.8, 139.33, 139.28, 138.2, 137.5, 133.82, 133.76, 133.3, 133.1, 133.0, 129.81, 129.76, 129.75, 129.7, 129.6, 128.8, 128.6, 128.4, 128.33, 128.27, 128.1, 127.5, 127.3, 127.1, 127.0, 122.8, 122.6, 117.6, 116.9, 75.7, 74.8, 69.0, 68.9, 64.5, 64.4, 63.8, 63.6, 53.2, 52.8. HRMS (ESI) m/z: calcd for $C_{35}H_{30}NaO_5$ $[M+Na]^+$ 553.1991, found 553.1975. $[\alpha]_D^{35}$= +0.14 (*c* 0.01, $CHCl_3$).



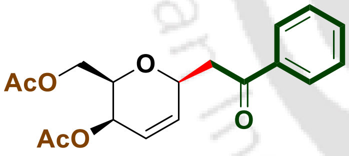
3r

(*2R,3S,6S*)-6-(1-([1,1'-biphenyl]-4-yl)allyl)-2-(acetoxymethyl)-3,6-dihydro-*2H*-pyran-3-yl acetate (33r): Ferrier glycosylation of **32a** (49.4 mg, 0.18 mmol) with **2d** (71.9 mg, 0.27 mmol) according to **General procedure A** afforded **33r** (49.8 mg, 68 %, d.r.: 73:27, α only) as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.5 (Hexane/EtOAc = 4:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 – 7.53 (m, 6H), 7.46 – 7.41 (m, 3H), 7.37 – 7.31 (m, 2H), 7.29 (d, J = 8.1 Hz, 2H), 6.27 – 6.19 (m, 1H), 6.13 (d, J = 10.6 Hz, 1H), 6.09 – 6.02 (m, 1H), 5.88 – 5.85 (m, 1H), 5.79 – 5.74 (m, 1H), 5.72 – 5.68 (m, 1H), 5.22 – 5.17 (m, 3H), 5.16 – 5.11 (m, 2H), 5.08 (s, 1H), 4.55 (dd, J = 8.7, 2.1 Hz, 1H), 4.50 (dd, J = 9.2, 1.9 Hz, 1H), 4.25 (dd, J = 11.9, 6.7 Hz, 1H), 4.21 – 4.15 (m, 2H), 4.04 – 3.98 (m, 3H), 3.70 (t, J = 8.7 Hz, 1H), 3.64 (t, J = 8.6 Hz, 1H), 2.10– 2.08 (m, 6H), 2.07 (s, 3H), 1.93 (s, 3H).^{13}C NMR (151 MHz, $CDCl_3$) δ 170.9, 170.8, 170.4, 140.9, 140.7, 139.92, 139.86, 139.6, 139.4, 138.4, 137.6, 131.8, 131.6, 128.78, 128.75, 128.7, 128.5, 127.5, 127.3, 127.2, 127.17, 126.99, 126.98, 124.5, 124.3, 117.5, 116.6, 74.9, 73.8, 70.2, 69.7, 64.97, 64.95, 63.0, 62.7, 53.9, 53.4, 21.1, 20.9, 20.7. HRMS (ESI) m/z: calcd for $C_{25}H_{27}O_5$ $[M+H]^+$ 407.1858, found 407.1856. $[\alpha]_D^{35}$= +1.0 (*c* 0.01, $CHCl_3$).



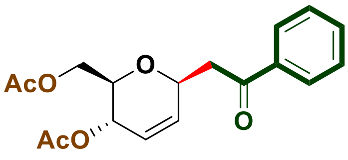
33s

(*3S,6S*)-6-(1-([1,1'-biphenyl]-4-yl)allyl)-3,6-dihydro-*2H*-pyran-3-yl benzoate (33s): Ferrier glycosylation of **32g** (51.9 mg, 0.16 mmol) with **2d** (64.1 mg, 0.24 mmol) according to **General procedure A** afforded **33s** (45.1 mg, 71 %, d.r.: 78:22, α only) as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.6 (Hexane/EtOAc = 5:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05– 8.01 (m, 3H), 7.62 – 7.53 (m, 6H), 7.43 (td, *J* = 7.5, 3.6 Hz, 5H), 7.36 – 7.31 (m, 4H), 6.26 – 6.19 (m, 1H), 6.15-6.08 (m, 2H), 6.00 (d, *J* = 10.5 Hz, 1H), 5.96 (d, *J* = 10.5 Hz, 1H), 5.81 (d, *J* = 10.5 Hz, 1H), 5.54-5.47 (m, 2H), 5.23 – 5.17 (m, 3H), 5.14 (d, *J* = 17.1 Hz, 1H), 4.55 – 4.51 (m, 1H), 4.51 – 4.47 (m, 1H), 4.31 (dd, *J* = 11.4, 5.0 Hz, 1H), 4.27 (dd, *J* = 11.3, 5.1 Hz, 1H), 3.71 (dd, *J* = 11.4, 7.0 Hz, 1H), 3.65 (dd, *J* = 11.2, 7.1 Hz, 1H), 3.61 (t, *J* = 8.1 Hz, 1H), 3.53 (t, *J* = 7.9 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.1, 166.1, 140.9, 140.8, 139.8, 139.7, 139.6, 138.0, 137.6, 133.1, 132.5, 132.0, 130.0, 129.7, 128.9, 128.8, 128.8, 128.7, 128.7, 128.4, 127.4, 127.2, 127.1, 127.07, 127.05, 125.7, 125.3, 117.5, 117.0, 76.6, 76.4, 65.6, 65.5, 65.3, 54.1, 53.9. HRMS (ESI) m/z: calcd for $C_{27}H_{24}NaO_3$ $[M+Na]^+$ 419.1623, found 419.1629. $[\alpha]_D^{35}$= +0.36 (*c* 0.01, $CHCl_3$).



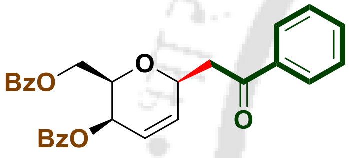
33t

((*2R,3R,6S*)-3-acetoxy-6-(2-oxo-2-phenylethyl)-3,6-dihydro-*2H*-pyran-2-yl)methyl acetate (33t): Ferrier glycosylation of **32f** (43.7 mg, 0.16 mmol) with **2f** (46.2 mg, 0.24 mmol) according to **General procedure A** afforded **33t** (37.9 mg, 71 %, β only) as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.5 (Hexane/EtOAc = 6:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (d, J = 7.3 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.7 Hz, 2H), 6.18 (dd, J = 10.3, 2.9 Hz, 1H), 6.03 (ddd, J = 10.2, 5.1, 2.0 Hz, 1H), 5.12 (d, J = 4.7 Hz, 1H), 5.03 (t, J = 6.7 Hz, 1H), 4.21 – 4.14 (m, 3H), 3.45 (dd, J = 16.1, 7.3 Hz, 1H), 3.11 (dd, J = 16.1, 6.5 Hz, 1H), 2.09 (s, 1H), 1.98 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 197.1, 170.8, 170.6, 136.8, 134.5, 133.5, 128.8, 128.2, 122.5, 69.5, 68.6, 63.6, 62.7, 41.0, 20.9, 20.7. HRMS (ESI) m/z: calcd for $C_{18}H_{20}NaO_6$ $[M+Na]^+$ 355.1158, found 355.1147. $[\alpha]_D^{35}$= -1.3 (*c* 0.01, $CHCl_3$).



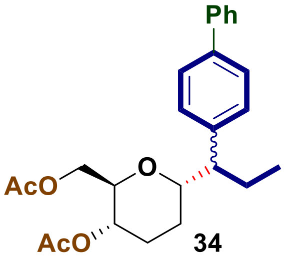
33u

((*2R,3S,6S*)-3-acetoxy-6-(2-oxo-2-phenylethyl)-3,6-dihydro-*2H*-pyran-2-yl)methyl acetate (33u): Ferrier glycosylation of **32a** (44.1 mg, 0.16 mmol) with **2f** (46.2 mg, 0.24 mmol) according to **General procedure A** afforded **33u** (37.1 mg, 74 %, β only) as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.4 (Hexane/EtOAc = 5:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 7.6 Hz, 2H), 7.58 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.2 Hz, 2H), 5.99 (d, J = 10.3 Hz, 1H), 5.77 (d, J = 10.2 Hz, 1H), 5.29 (d, J = 8.9 Hz, 1H), 4.89 – 4.83 (m, 1H), 4.21 – 4.12 (m, 2H), 3.81 – 3.77 (d, J = 3.4 Hz, 1H), 3.40 (dd, J = 16.7, 5.7 Hz, 1H), 3.08 (dd, J = 16.7, 7.1 Hz, 1H), 2.08 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.3, 170.9, 170.4, 137.0, 133.4, 132.4, 128.7, 128.2, 125.5, 74.5, 71.7, 65.4, 63.6, 43.9, 21.0, 20.8. HRMS (ESI) m/z: calcd for $C_{18}H_{20}NaO_6$ $[M+Na]^+$ 355.1158, found 355.1146. $[\alpha]_D^{35}$= +1.04 (*c* 0.01, $CHCl_3$).



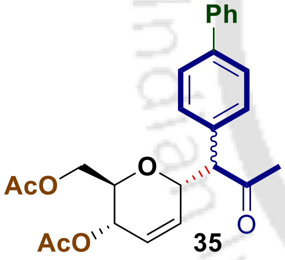
33v

((*2R,3R,6S*)-3-(benzoyloxy)-6-(2-oxo-2-phenylethyl)-3,6-dihydro-*2H*-pyran-2-yl)methyl benzoate (33v): Ferrier glycosylation of **32e** (55.1 mg, 0.12 mmol) with **2f** (35.1 mg, 0.18 mmol) according to **General procedure A** afforded **33v** (41.7 mg, 76 %, β only) as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.4 (Hexane/EtOAc = 6:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 – 8.05 (m, 2H), 7.96 – 7.90 (m, 4H), 7.59 – 7.54 (m, 2H), 7.51 (t, J = 7.4 Hz, 1H), 7.44 (q, J = 8.0 Hz, 4H), 7.35 (t, J = 7.8 Hz, 2H), 6.24 (dd, J = 10.3, 2.7 Hz, 1H), 6.20 (ddd, J = 10.3, 4.9, 1.8 Hz, 1H), 5.46 (dd, J = 4.6, 2.7 Hz, 1H), 5.19– 5.13 (m, 1H), 4.56 (dd, J = 11.4, 7.6 Hz, 1H), 4.50 (dd, J = 11.5, 5.1 Hz, 1H), 4.43 (ddd, J = 7.6, 5.1, 2.7 Hz, 1H), 3.53 (dd, J = 16.2, 7.7 Hz, 1H), 3.13 (dd, J = 16.2, 6.0 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 196.9, 166.3, 166.0, 136.7, 134.7, 133.4, 133.3, 133.0, 129.8, 129.67, 129.65, 128.7, 128.5, 128.3, 128.2, 122.6, 69.4, 68.9, 64.3, 63.4, 41.0. HRMS (ESI) m/z: calcd for $C_{28}H_{28}NO_6$ $[M+NH_4]^+$ 474.1917, found 474.1926. $[\alpha]_D^{35}$= -0.6 (*c* 0.01, $CHCl_3$).



34

(*2R,3S,6S*)-6-(1-([1,1'-biphenyl]-4-yl)propyl)-2-(acetoxymethyl)tetrahydro-*2H*-pyran-3-yl acetate (34): Hydrogenation of **33r** was done via Palladium catalysis following literature procedure[20]. The compound **33r** (41.1 mg, 0.10 mmol) was dissolved in 0.7 mL of ethyl acetate and were added 10mol% of Pd/C (10% wt) (1.2 mg) followed by purging of argon. Then Hydrogen balloon was attached to the reaction flask and the reaction mixture was stirred for 3h. The reaction was monitored on TLC. The crude product was purified by column chromatography to yield **34** (30.9 mg, 75 %, d.r.: 81:19, α only) as a colorless syrup. R_f = 0.6 (Hexane/EtOAc = 5:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, J = 7.3 Hz, 3H), 7.53 (d, J = 8.1 Hz, 2H), 7.43 (t, J = 7.7 Hz, 3H), 7.33 (dd, J = 14.0, 6.8 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 7.19 (d, J = 8.1 Hz, 2H), 4.75 (dd, J = 10.4, 6.1 Hz, 1H), 4.69 (dd, J = 9.8, 5.0 Hz, 1H), 4.42 (dd, J = 11.7, 7.1 Hz,1H), 4.20 (dd, J = 11.2, 7.3 Hz, 1H), 4.13 (dd, J = 11.7, 3.9 Hz, 1H), 3.99 (dd, J = 10.3, 6.3 Hz, 1H), 3.96 (d, J = 3.9 Hz, 1H), 3.94 (d, J = 4.2 Hz, 1H), 3.93 (s, 1H), 3.91 – 3.88 (m, 1H), 3.84 (dt, J = 10.2, 5.2 Hz, 1H), 2.78 (td, J = 10.8, 3.1 Hz, 2H), 2.15 – 2.10 (m, 5H), 2.09 (s, 3H), 2.05 (s, 3H), 2.03 – 1.97 (m, 1H), 2.03 – 1.98 (m, 1H), 1.93 (dd, J = 9.1, 4.4 Hz, 1H), 1.93 (dd, J = 9.1, 4.4 Hz, 1H), 1.86 (s, 3H), 1.85 – 1.80 (m, 1H), 1.76 (dt, J = 13.1, 6.9 Hz, 2H), 1.59 – 1.50 (m, 3H), 1.48 – 1.39 (m, 2H), 0.76 (dt, J = 14.8, 7.4 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.9, 170.8, 170.4, 170.3, 141.1, 141.0, 140.9, 140.8, 139.5, 138.9, 129.1, 128.8, 128.7, 127.23, 127.16, 127.0, 126.94, 126.88, 126.7, 75.5, 74.3, 71.9, 71.8, 67.7, 67.7, 62.4, 62.0, 49.8, 49.6, 25.3, 24.7, 24.5, 24.4, 23.9, 21.23, 21.2, 20.9, 20.7, 12.0, 11.9. HRMS (ESI) m/z: calcd for $C_{25}H_{34}NO_5$ $[M+NH_4]^+$ 428.2437, found 428.2435. $[\alpha]_D^{35}$= +0.48 (*c* 0.01, $CHCl_3$).



35

5(*2R,3S,6S*)-6-(1-([1,1'-biphenyl]-4-yl)-2-oxopropyl)-2-(acetoxymethyl)-3,6-dihydro-*2H*-pyran-3-yl acetate (35): To a two neck- round bottom flask were added $PdCl_2$ (30 mol%, 5.3 mg), $CuCl_2.2H_2O$ (0.6 equiv., 10 mg) and Sodium chloride (1.3 equiv, 8 mg.). Then the mixture was diluted with 0.2 M HCl (1.3 mL) and stirred vigorously at 35 °C by attaching O_2 balloon for 30 min. The alkene **33r** (42.1 mg, 0.10 mmol) was added to the same reaction flask by dissolving in DMF (0.5 mL) followed by stirring the reaction mixture at 60 °C for 6 h. Upon completion, the reaction mixture was extracted with CH_2Cl_2 (2 X 40 mL) and concentrated under vacuum[21]. The crude compound was purified by column chromatograohy affording **35** (23.1 mg, 54 %, d.r.: 81:19, α only) as a colorless syrup. R_f = 0.4 (Hexane/EtOAc = 5:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 – 7.55 (t, J = 8.6 Hz, 6H), 7.44 (t, J = 7.5 Hz, 3H), 7.38-7.33 (m, 4H), 6.12 (d, J = 10.4 Hz, 1H), 5.84 (d, J = 10.5 Hz, 1H), 5.77 (d, J = 10.5 Hz, 1H), 5.62 (d, J = 10.5 Hz, 1H), 5.12 (d, J = 5.9 Hz, 1H), 5.09 – 5.05 (m, 1H), 4.99 (dd, J = 10.1, 1.5 Hz, 1H), 4.91 (d, J = 8.7 Hz, 1H), 4.26 (dd, J = 11.8, 7.5 Hz, 1H), 4.16 (dd, J = 11.8, 3.5 Hz, 1H), 4.12 – 4.09 (m, 1H), 4.08 – 4.05 (m, 1H), 4.03 (d, J = 10.2 Hz, 2H), 4.00 – 3.96 (m, 1H), 2.23 (s, 3H), 2.15 (s, 3H), 2.13 (s, 3H), 2.09

(s, 6H), 1.89 (s, 3H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 206.2, 205.5, 170.9, 170.7, 170.4, 170.3, 141.1, 140.7, 140.4, 140.3, 134.3, 132.9, 131.8, 131.0, 129.9, 129.2, 129.1, 128.9, 128.8, 127.8, 127.7, 127.6, 127.5, 127.02, 127.0, 124.9, 124.7, 72.4, 70.7, 69.8, 65.1, 64.9, 62.7, 61.7, 61.6, 30.2, 30.1, 21.08, 21.07, 20.8, 20.7. HRMS (ESI) m/z: calcd for $C_{25}H_{30}NO_6$ $[M+NH_4]^+$ 440.2073, found 440.2073. $[\alpha]_D^{35}$= -0.6 (*c* 0.01, CHCl$_3$).

2.6. References

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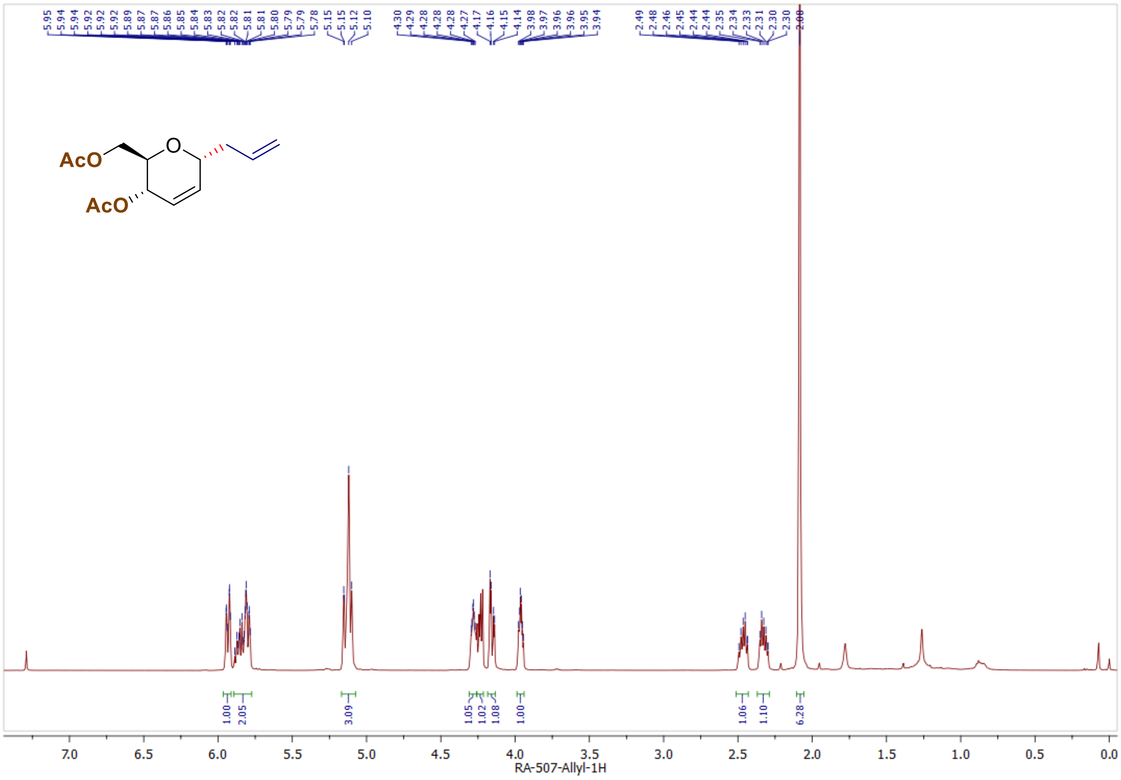
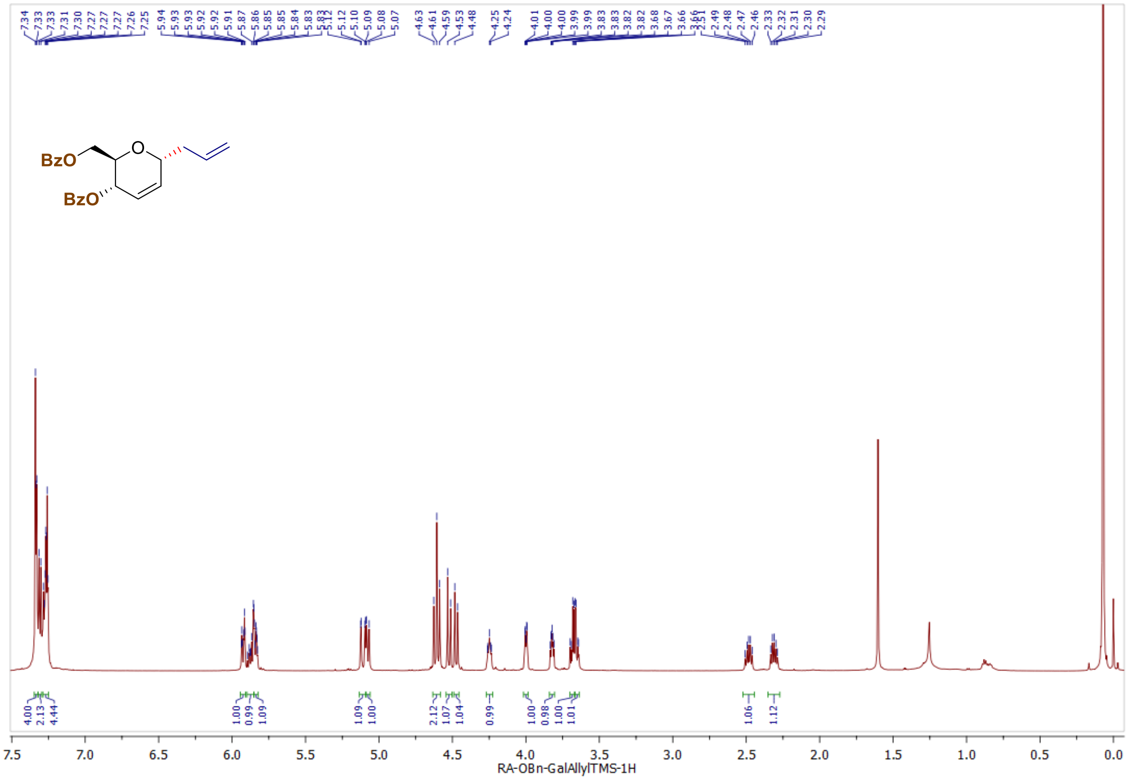
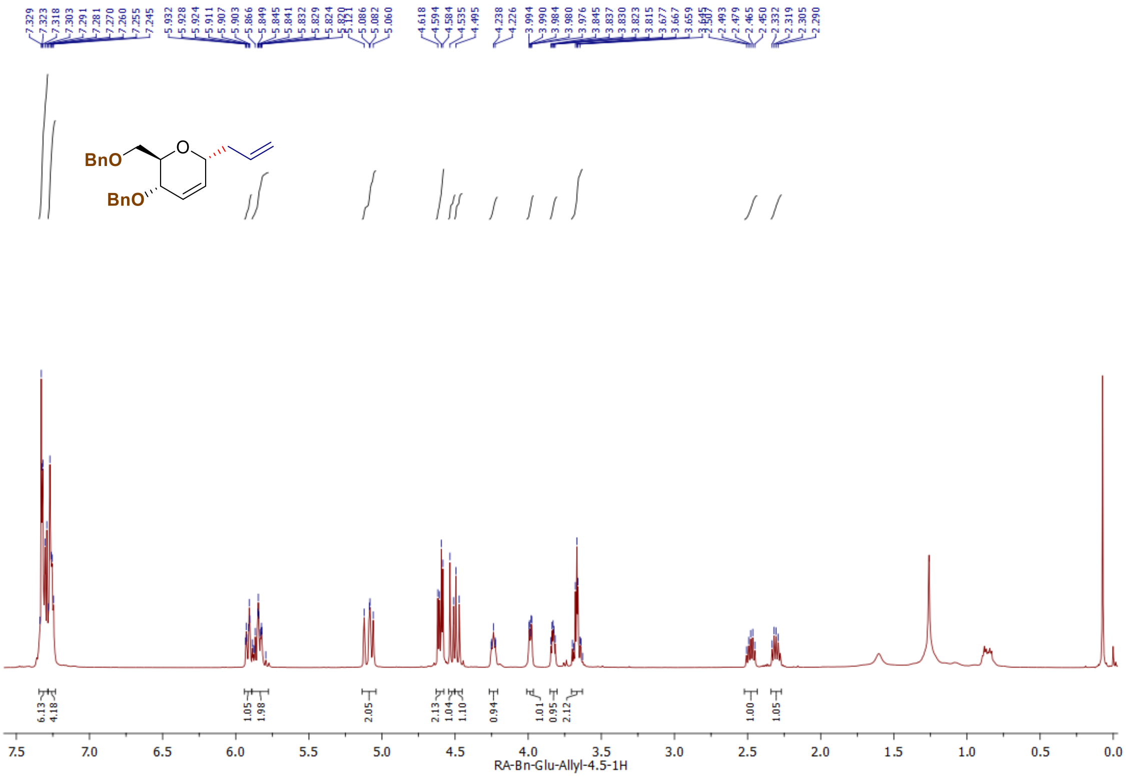
2.7 Spectra of Substrates



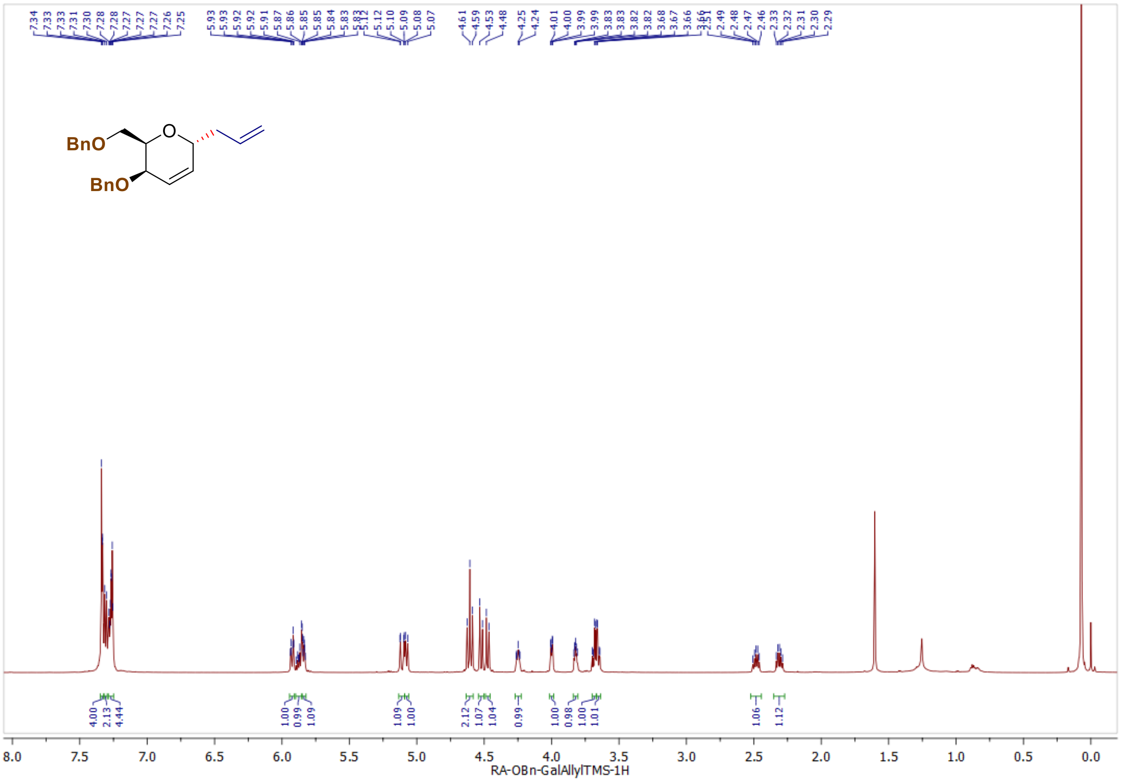
^{1}H NMR spectrum of **33a** (500 MHz, $CDCl_3$)



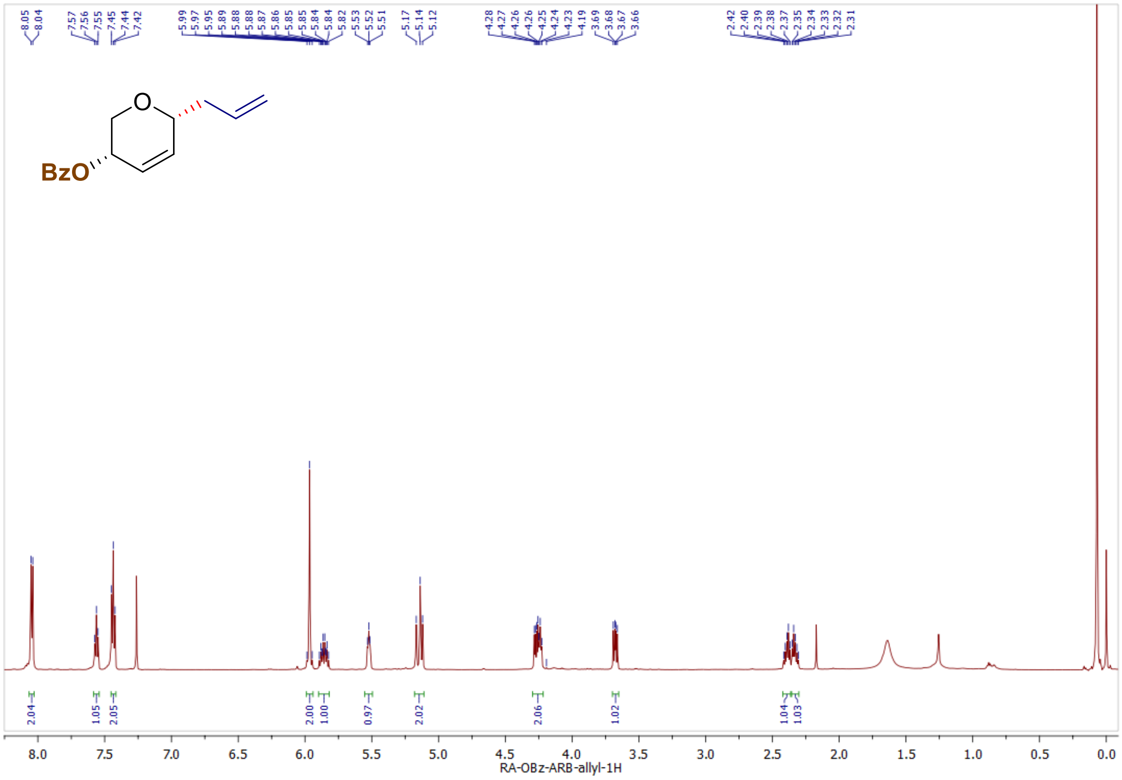
^{1}H NMR spectrum of **33b** (400 MHz, $CDCl_3$)



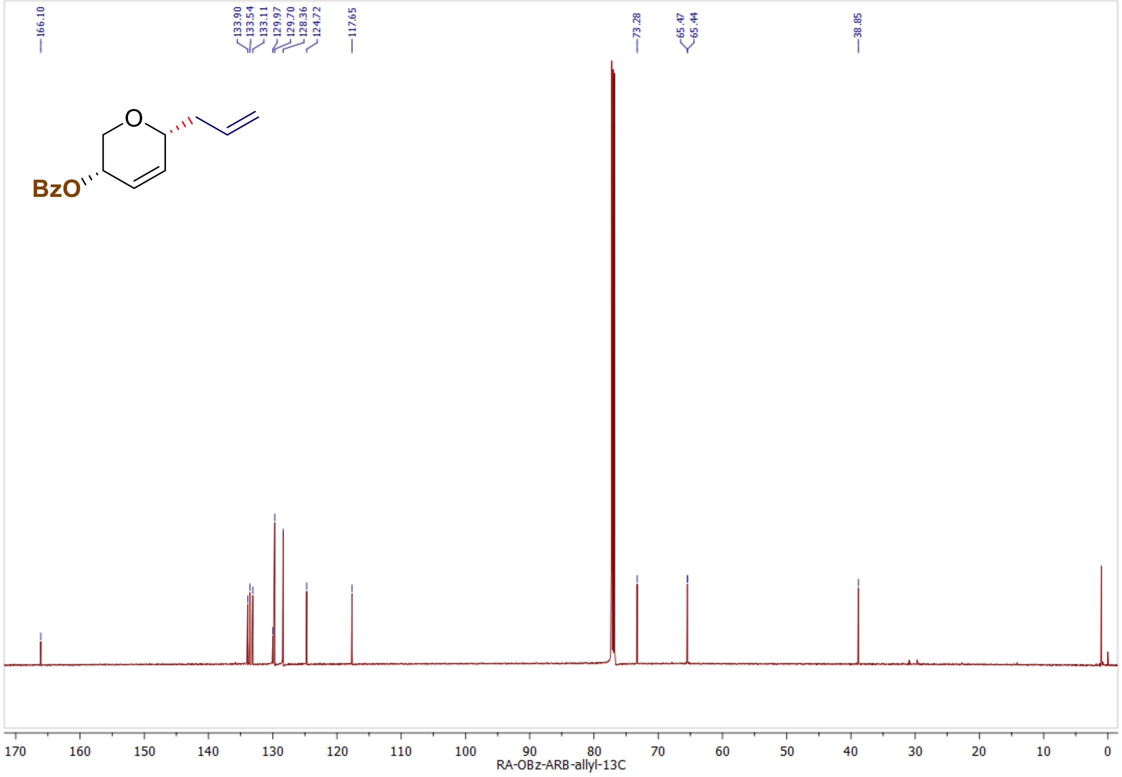
^{1}H NMR spectrum of **33c** (500 MHz, $CDCl_3$)



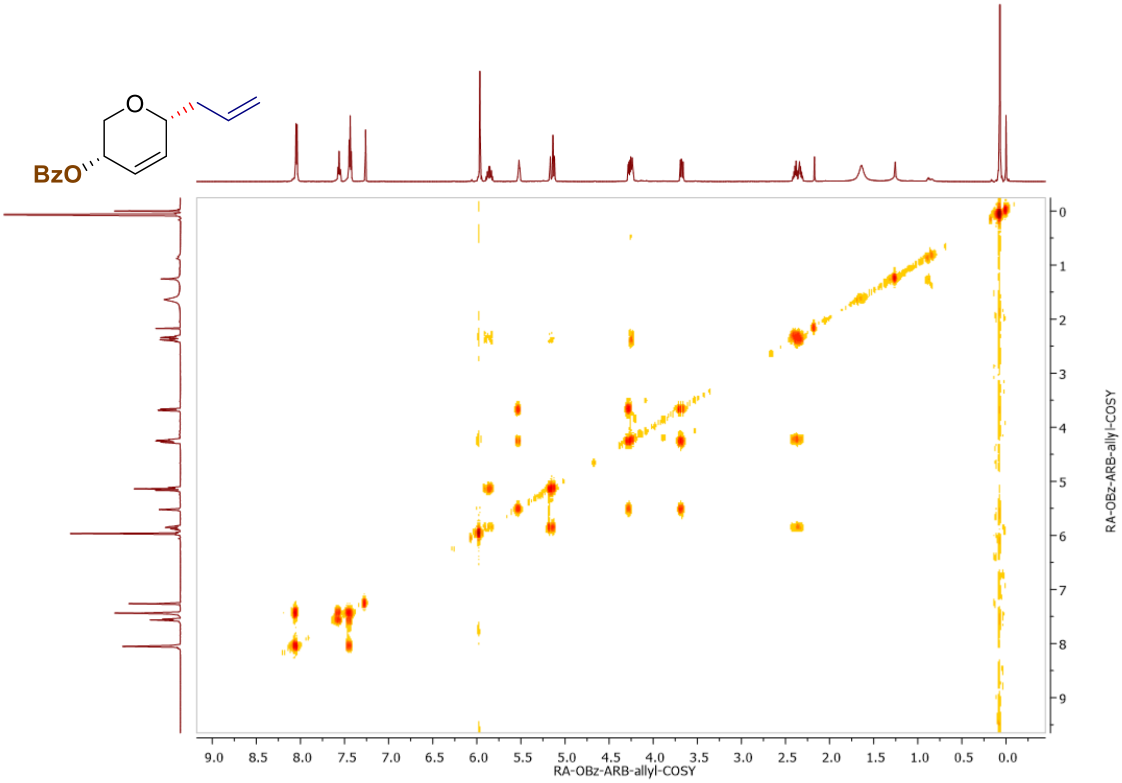
^{1}H NMR spectrum of **33d** (600 MHz, $CDCl_3$)



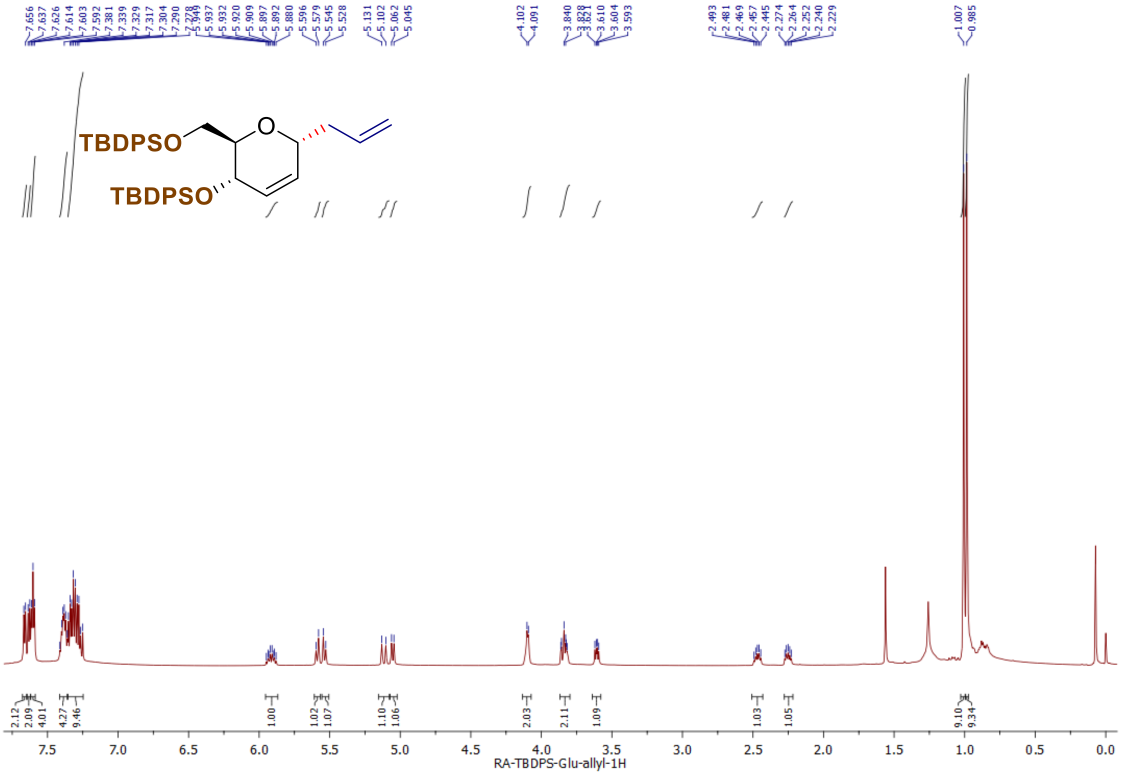
^{1}H NMR spectrum of **33e** (600 MHz, $CDCl_3$)



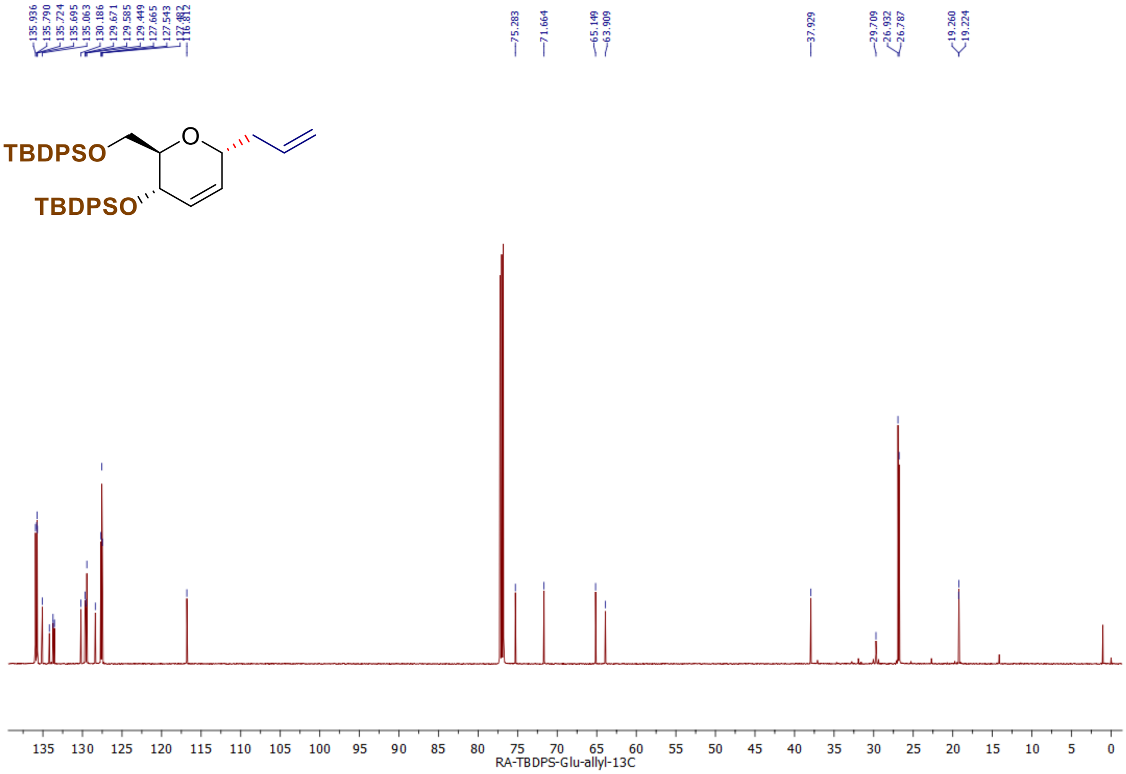
^{13}C NMR spectrum of **33e** (151 MHz, $CDCl_3$)



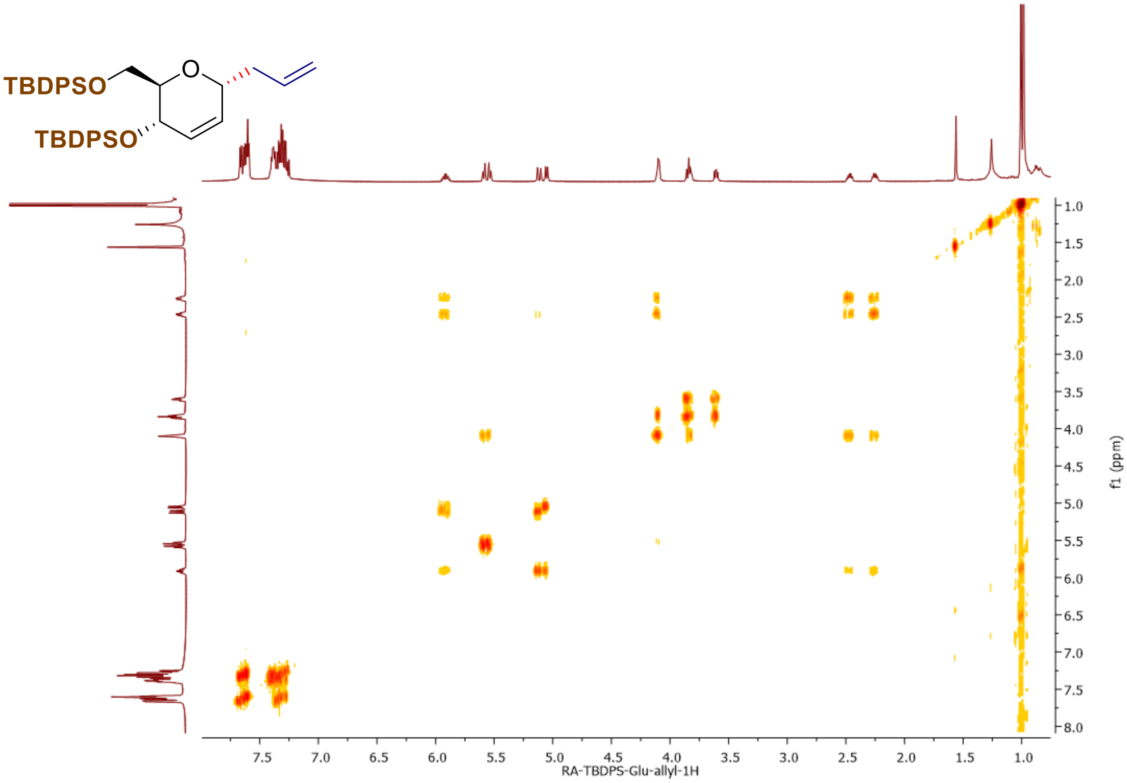
COSY NMR sperum of **33e** (600 MHz CDCl$_3$)



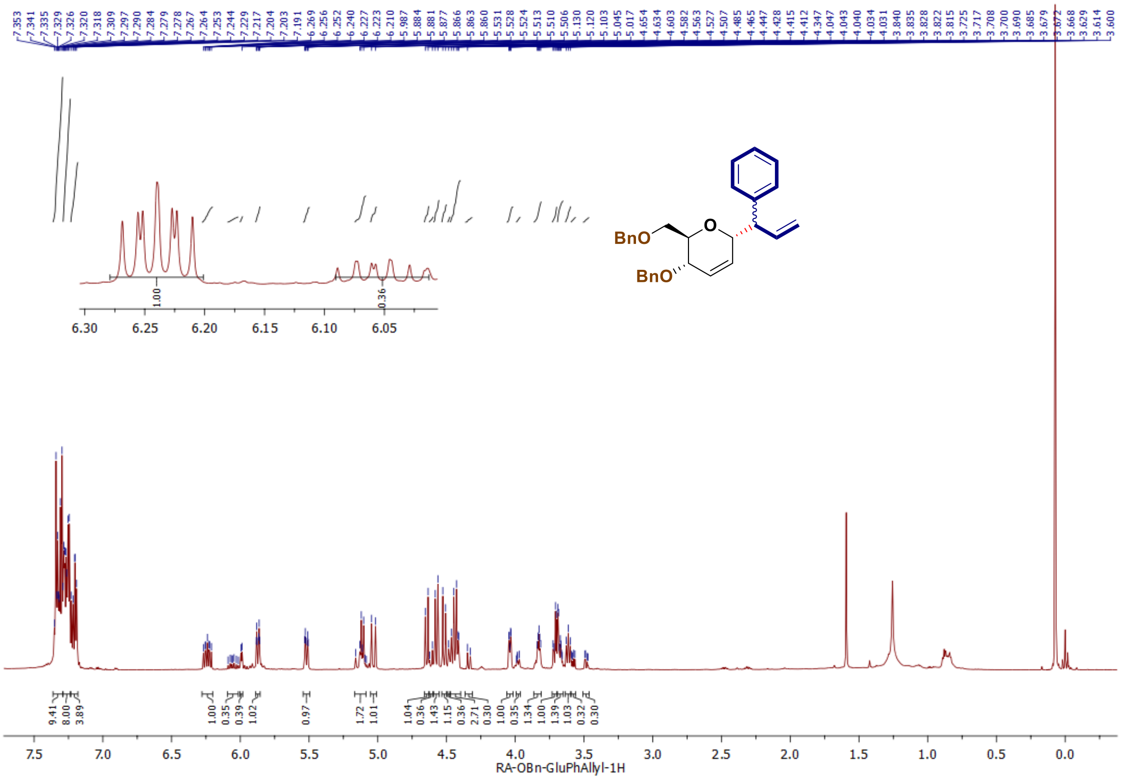
^{1}H NMR spectrum of **33f** (600 MHz, CDCl$_3$)



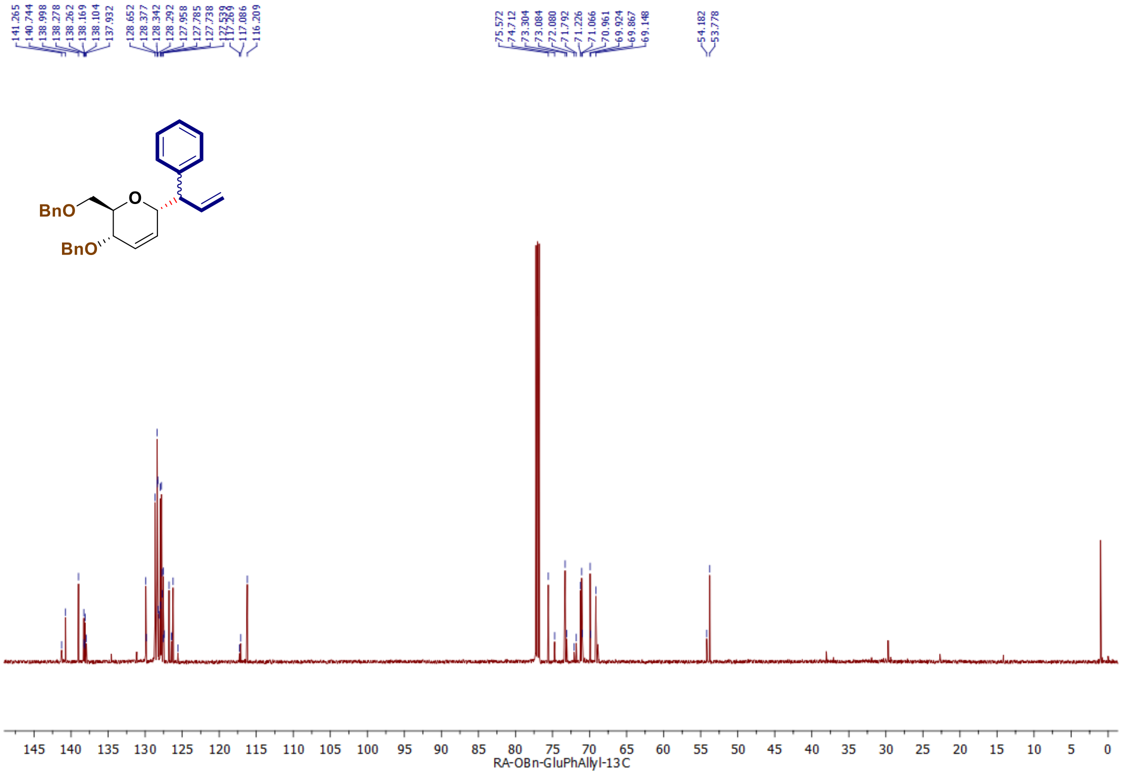
^{13}C NMR spectrum of **33f** (151 MHz, $CDCl_3$)



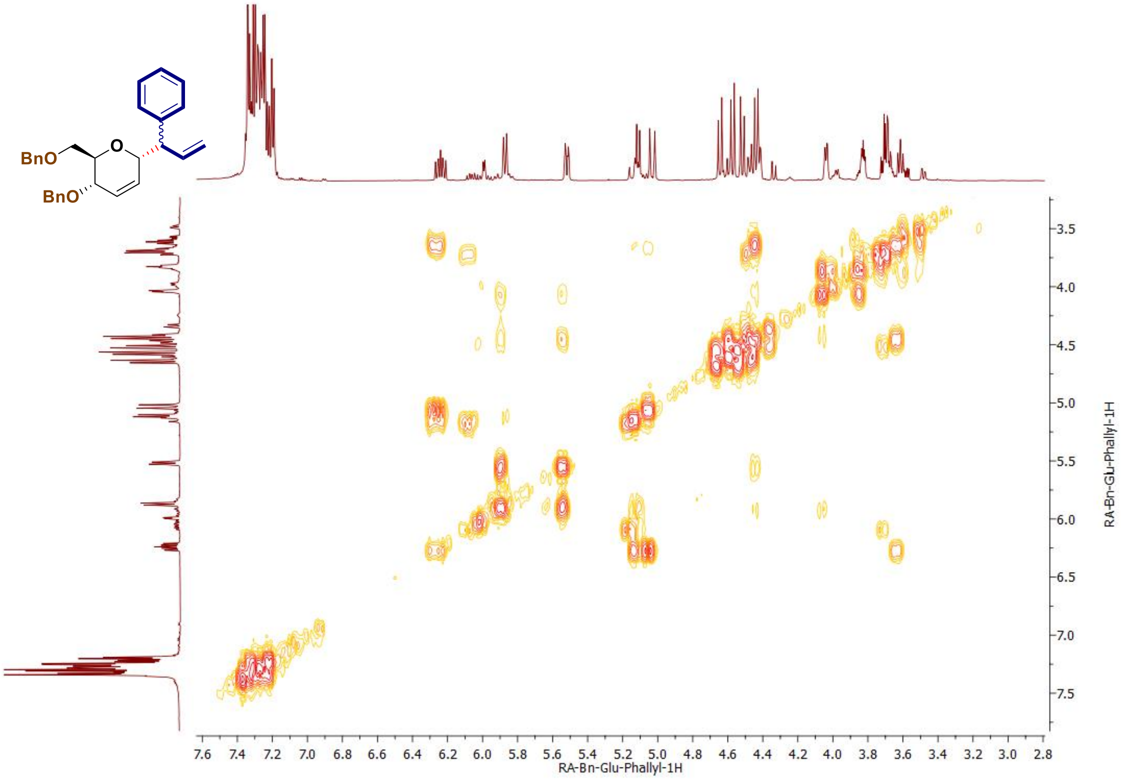
COSY NMR sperum of **33f** (600 MHz $CDCl_3$)



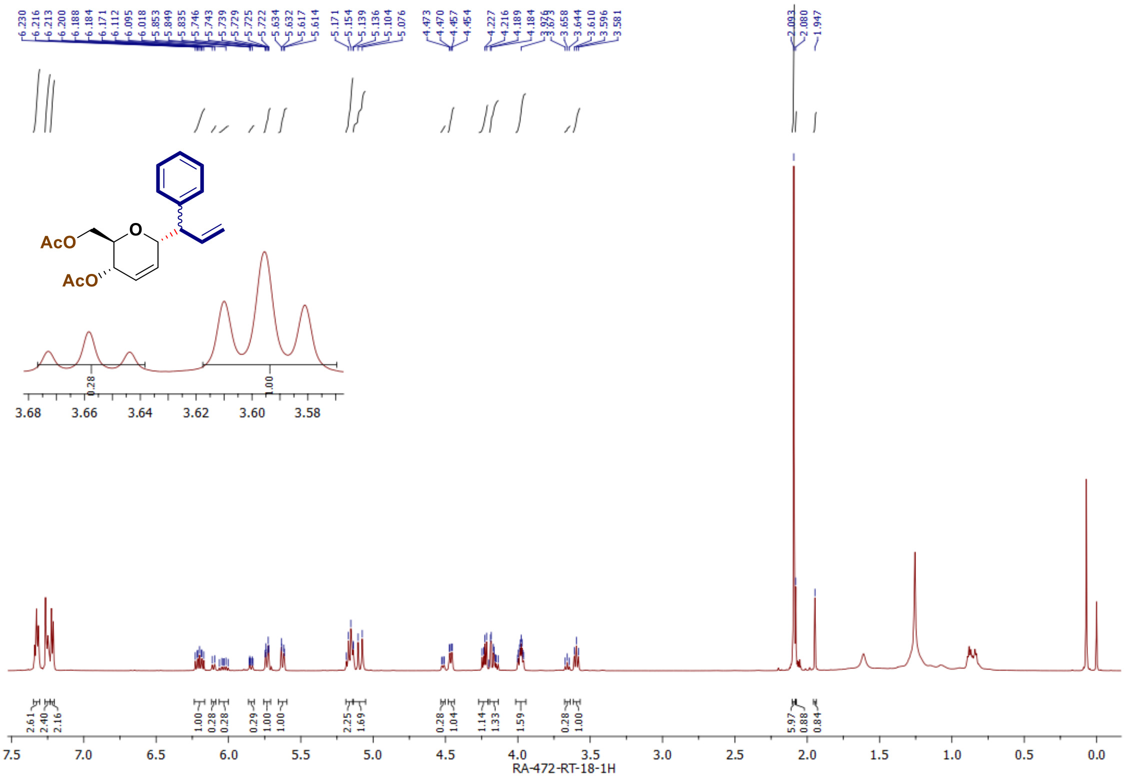
^{1}H NMR spectrum of **33g** (600 MHz, CDCl$_3$)



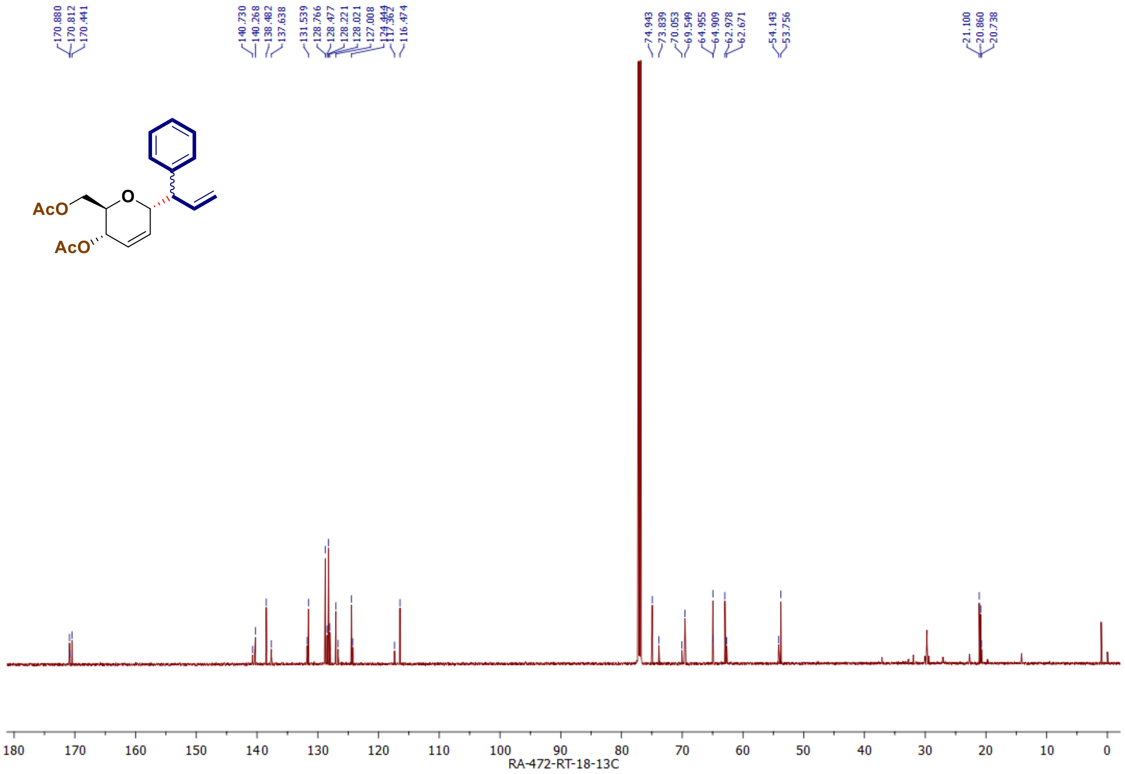
^{13}C NMR spectrum of **33g** (151 MHz, CDCl$_3$)



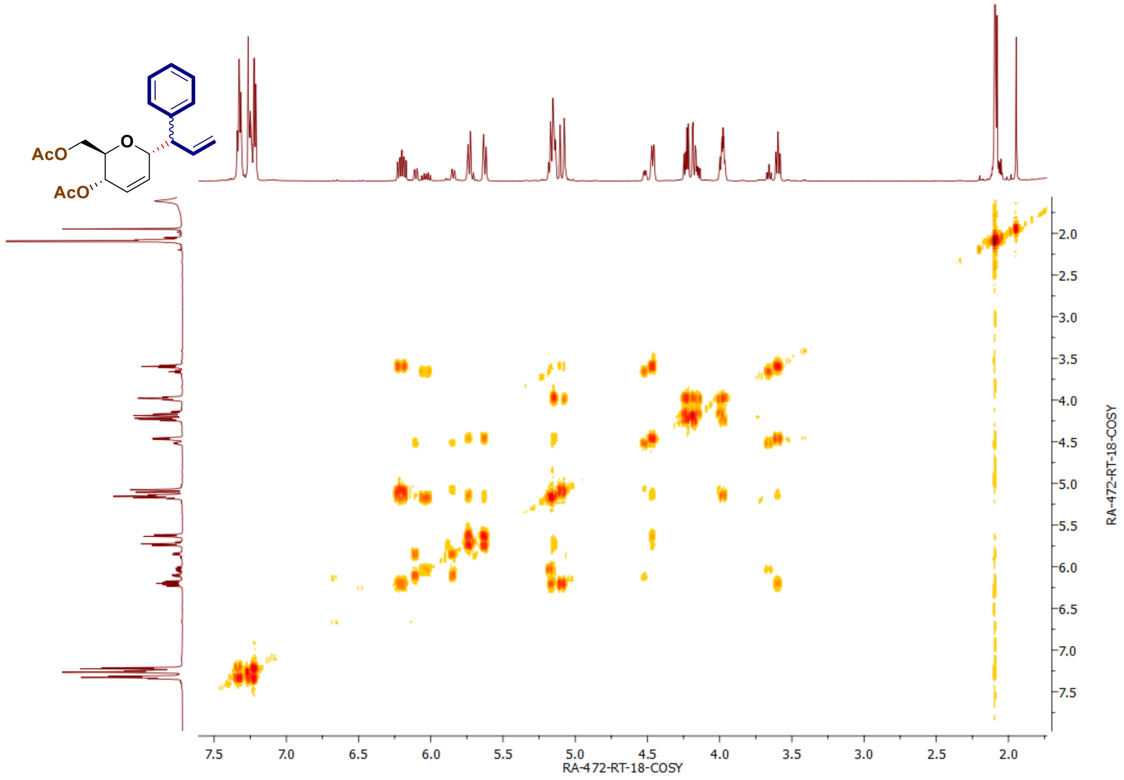
COSY NMR spectrum of **33g** (600 MHz, $CDCl_3$)



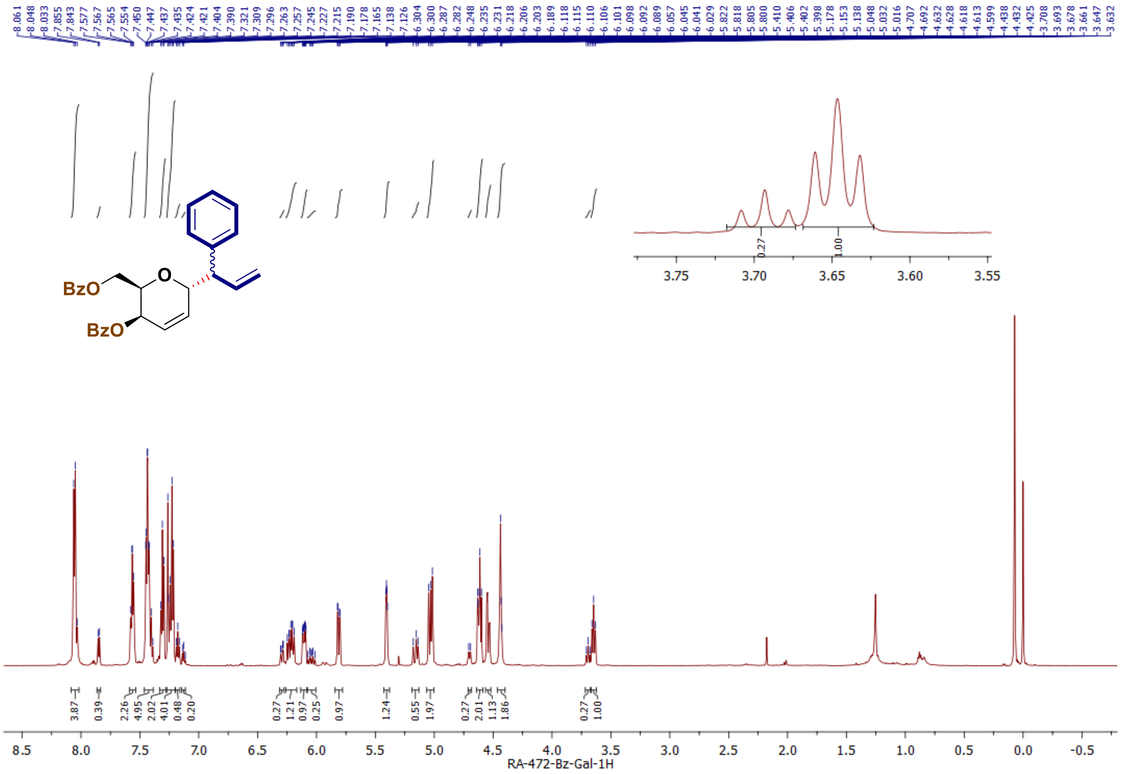
^1H NMR spectrum of **33h** (600 MHz, $CDCl_3$)



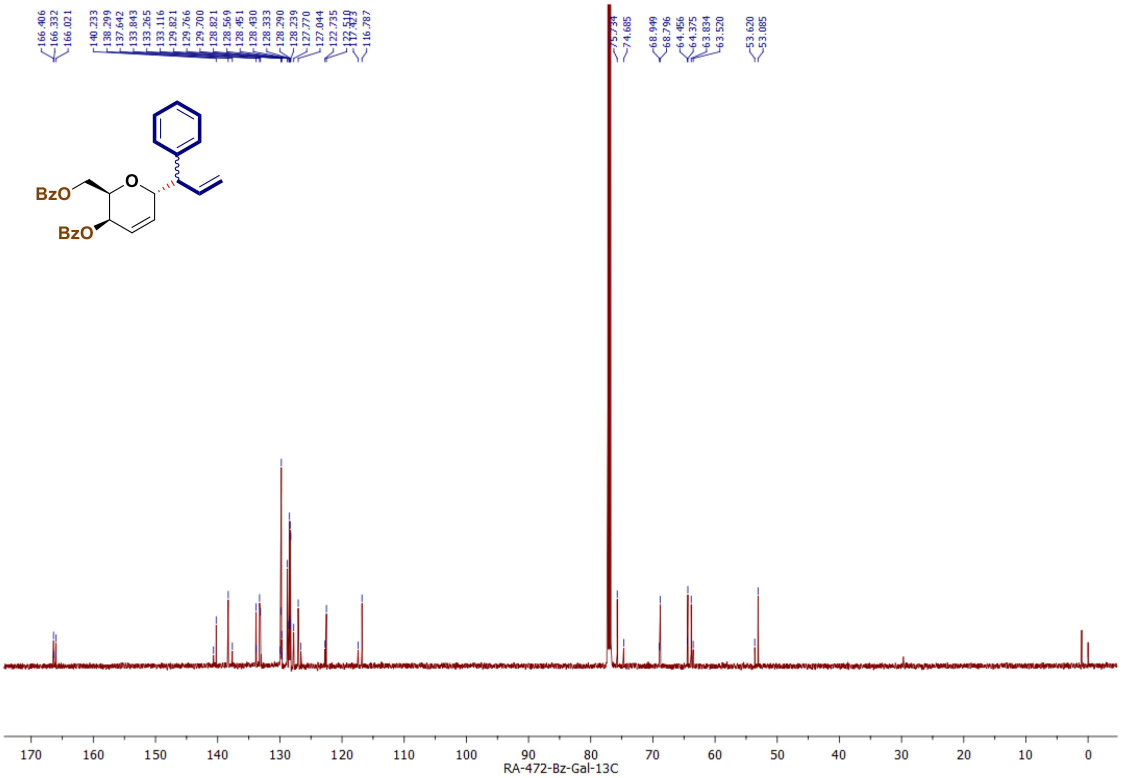
^{13}C NMR spectrum of **33h** (151 MHz, CDCl$_3$)



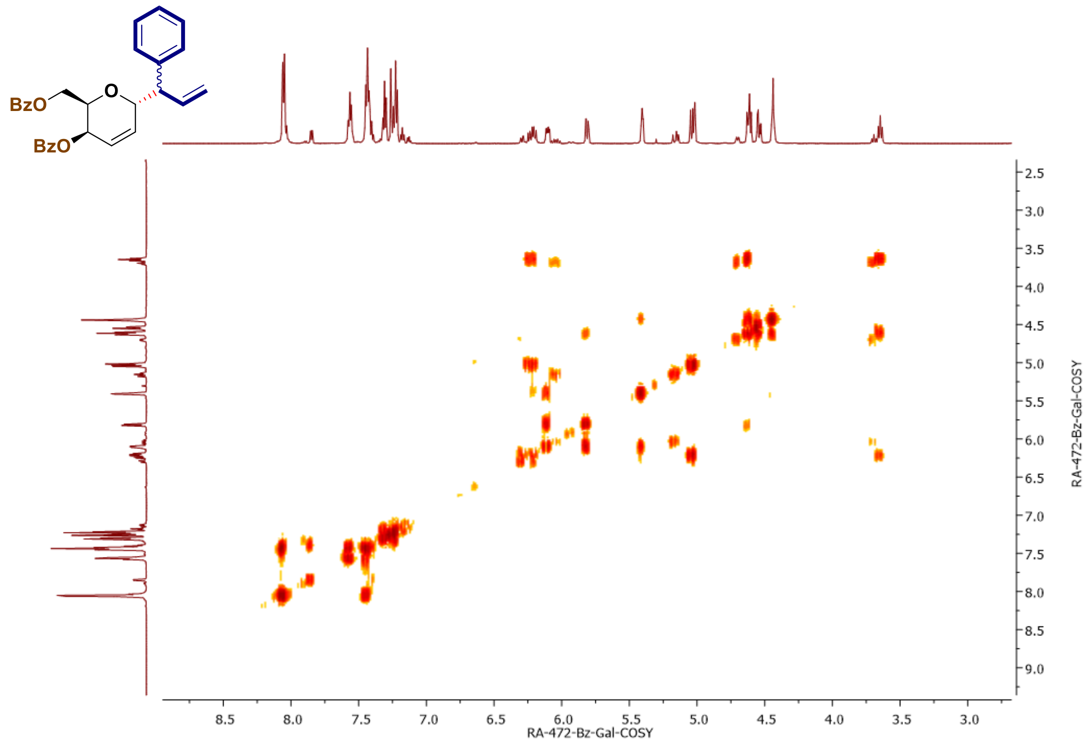
COSY NMR spectrum of **33h** (600 MHz, CDCl$_3$)



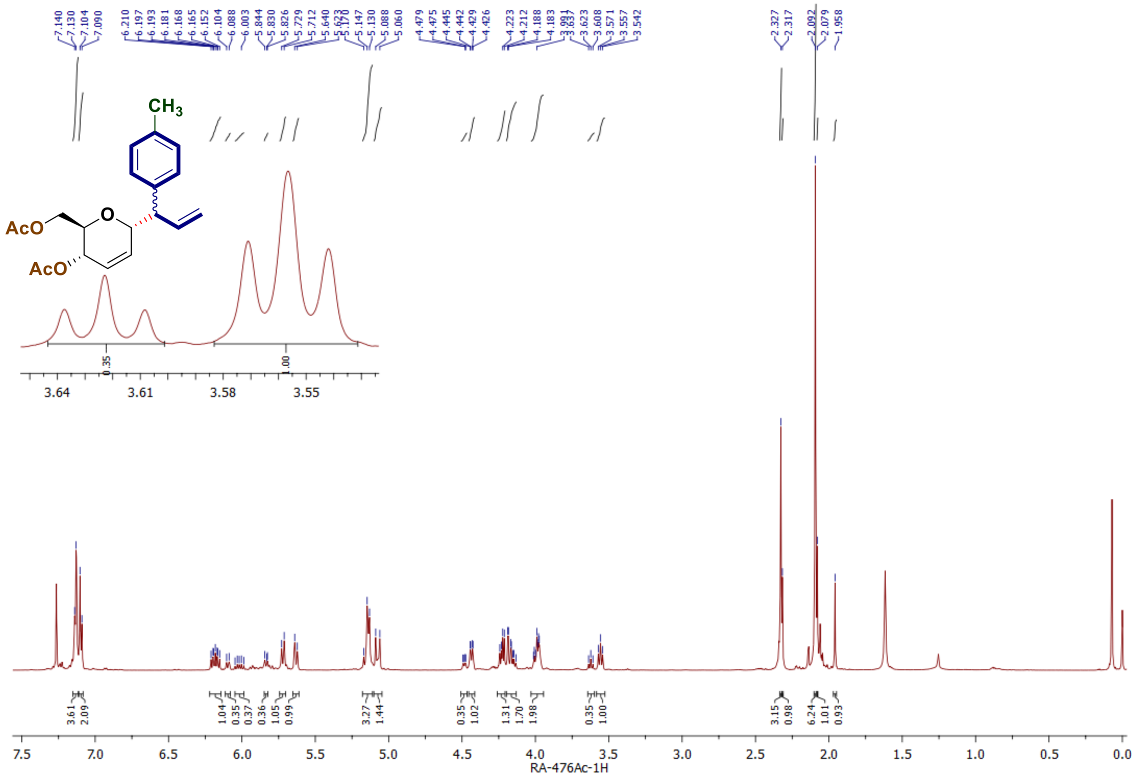
^{1}H NMR spectrum of **33i** (600 MHz, $CDCl_3$)



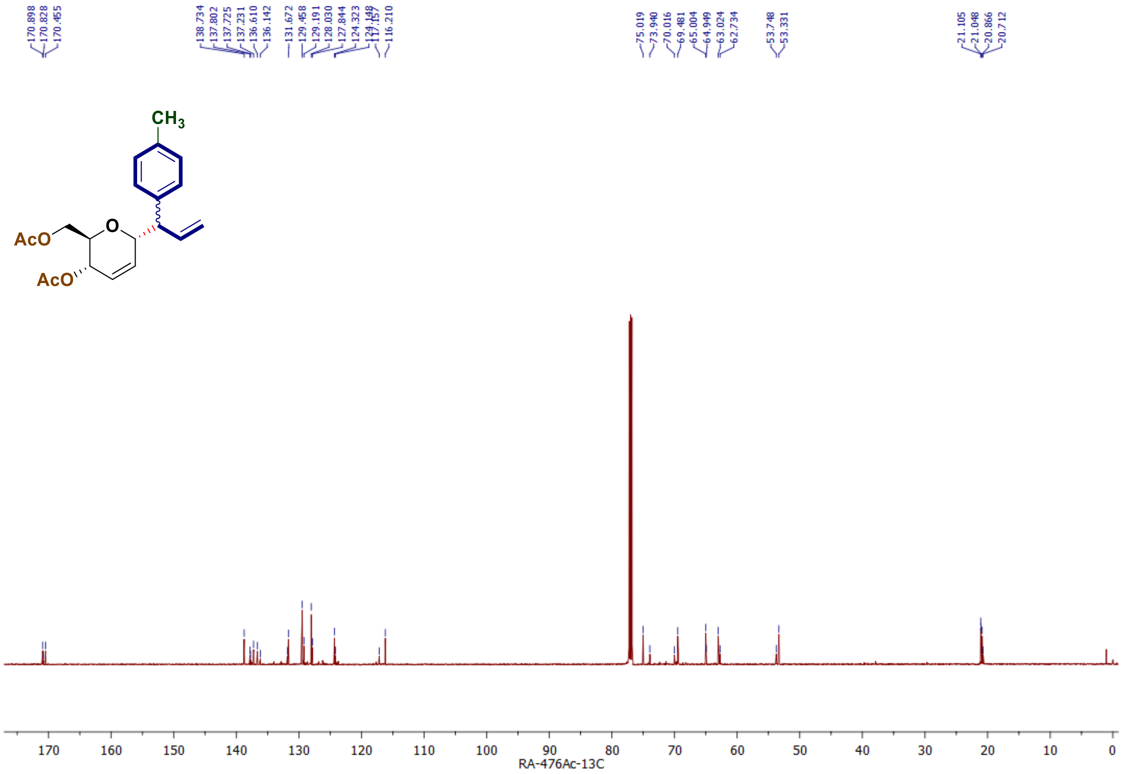
^{13}C NMR spectrum of **33i** (151 MHz, $CDCl_3$)



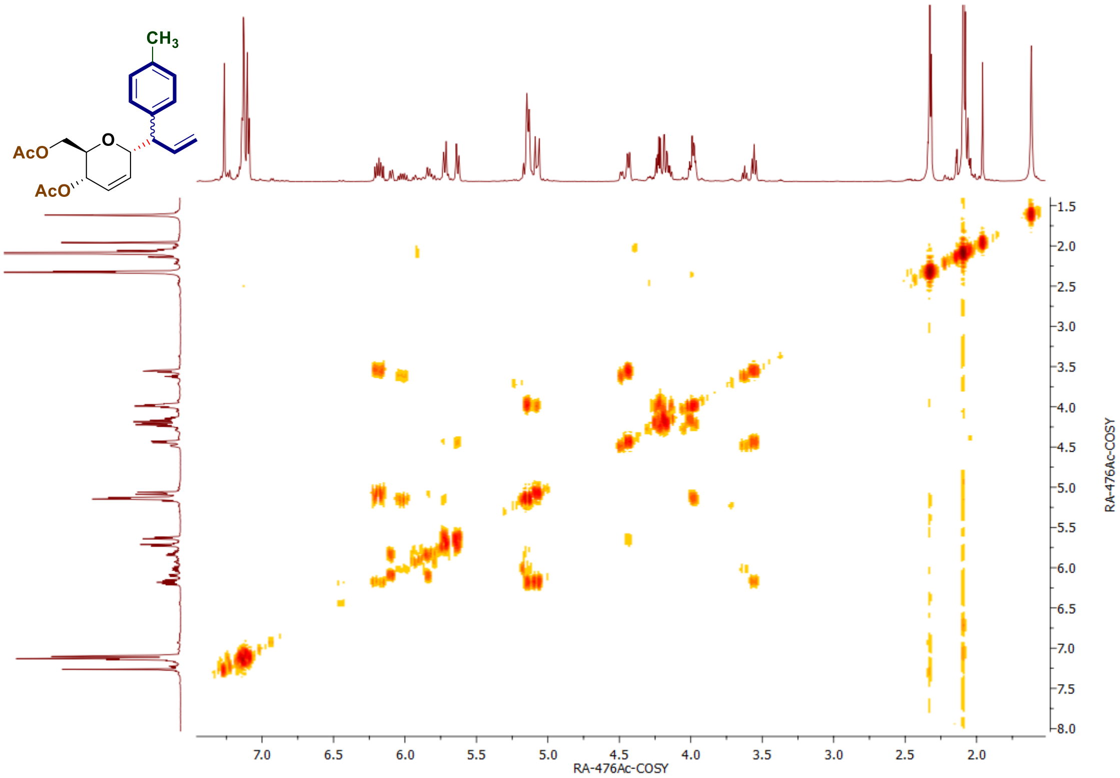
COSY NMR spectrum of **33i** (600 MHz, $CDCl_3$)



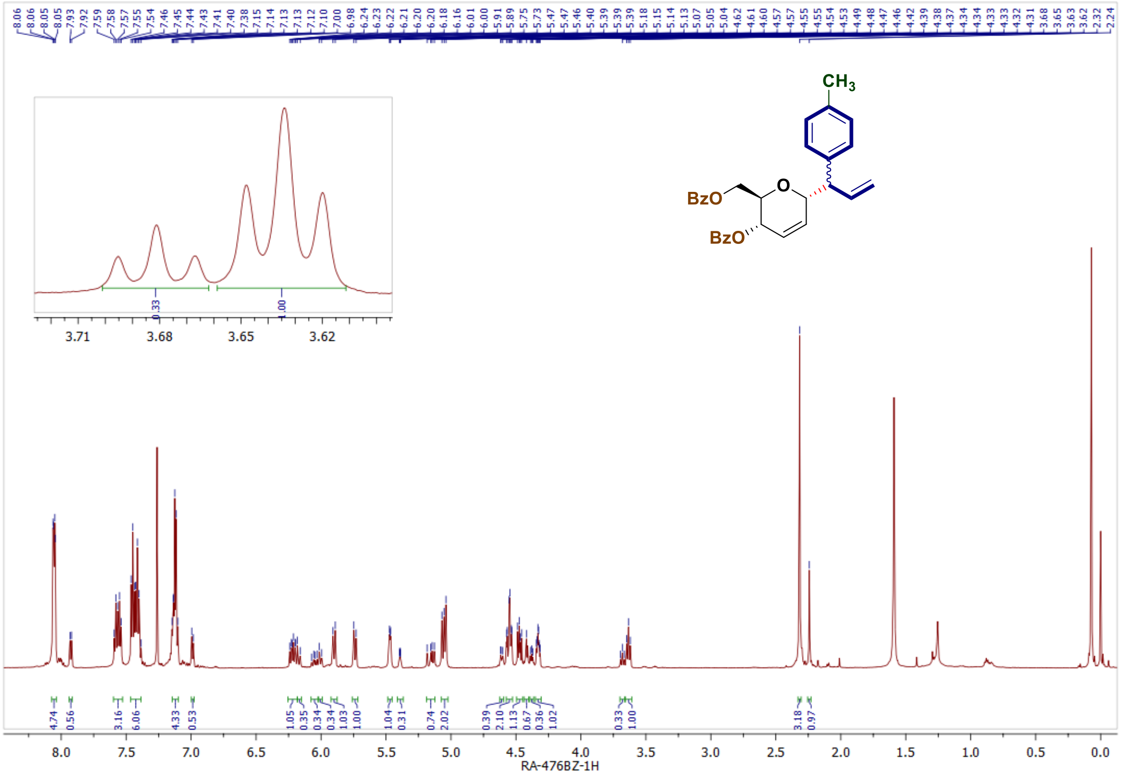
^{1}H NMR spectrum of **33j** (600 MHz, $CDCl_3$)



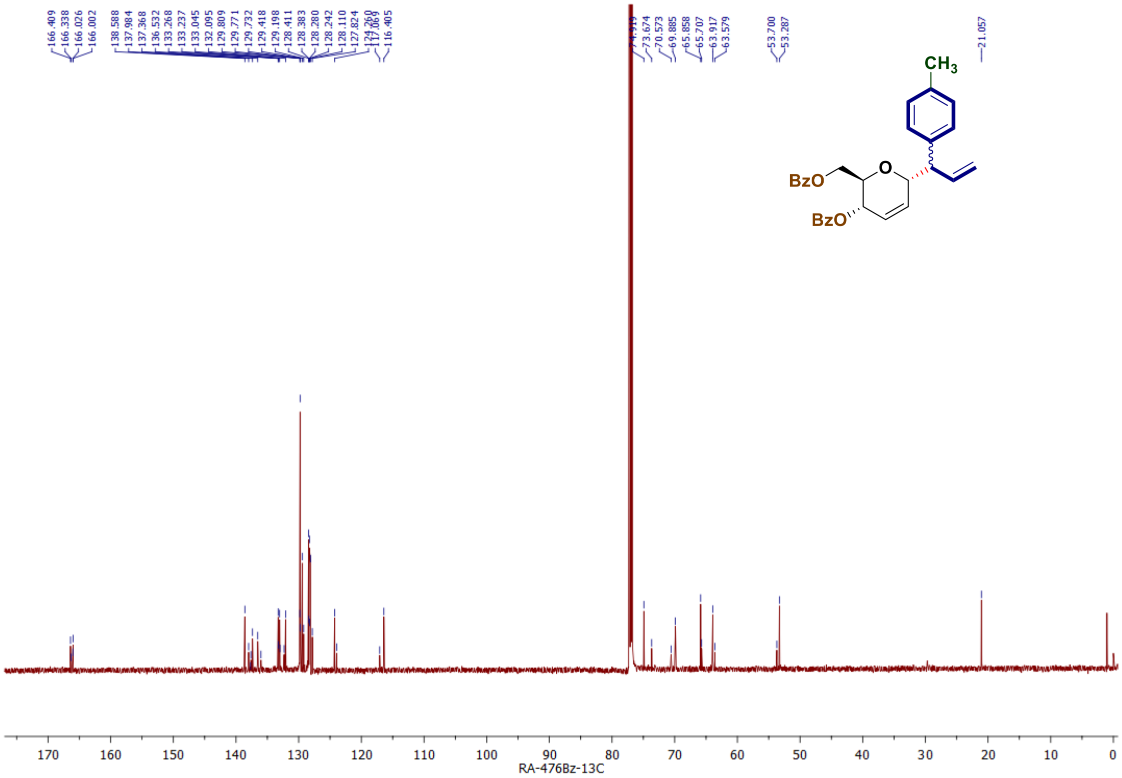
^{13}C NMR spectrum of **33j** (151 MHz, CDCl$_3$)



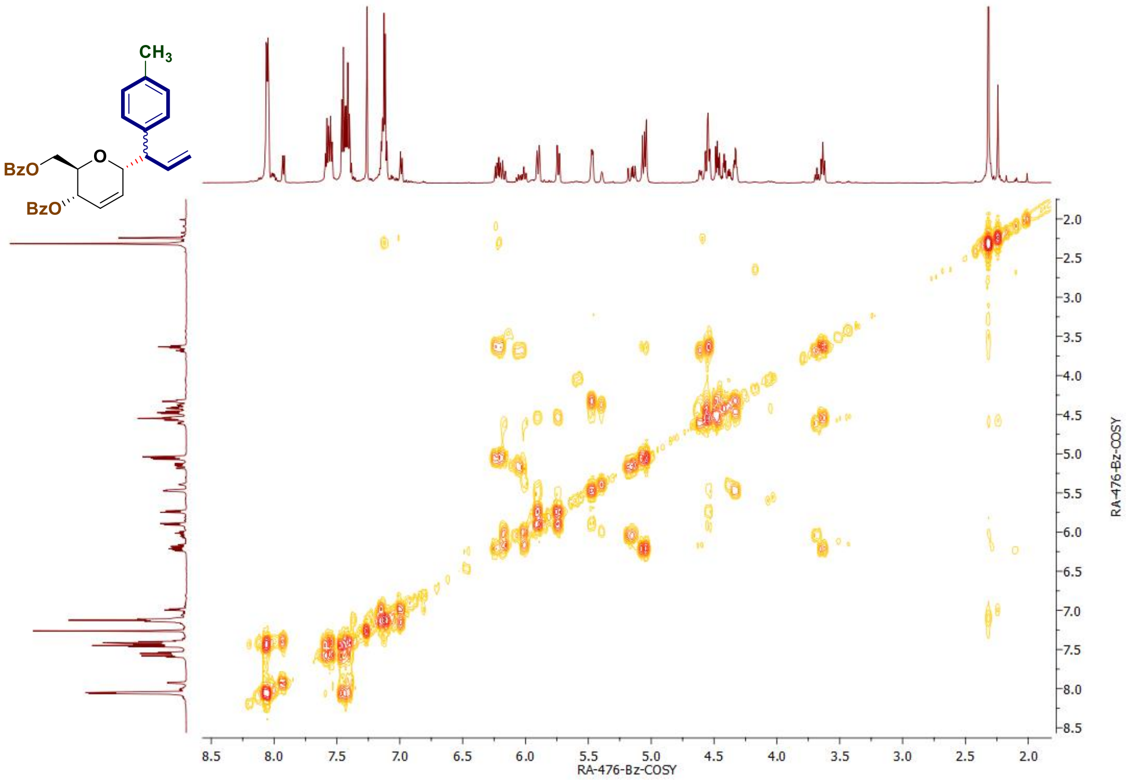
COSY NMR spectrum of **33j** (600 MHz, CDCl$_3$)



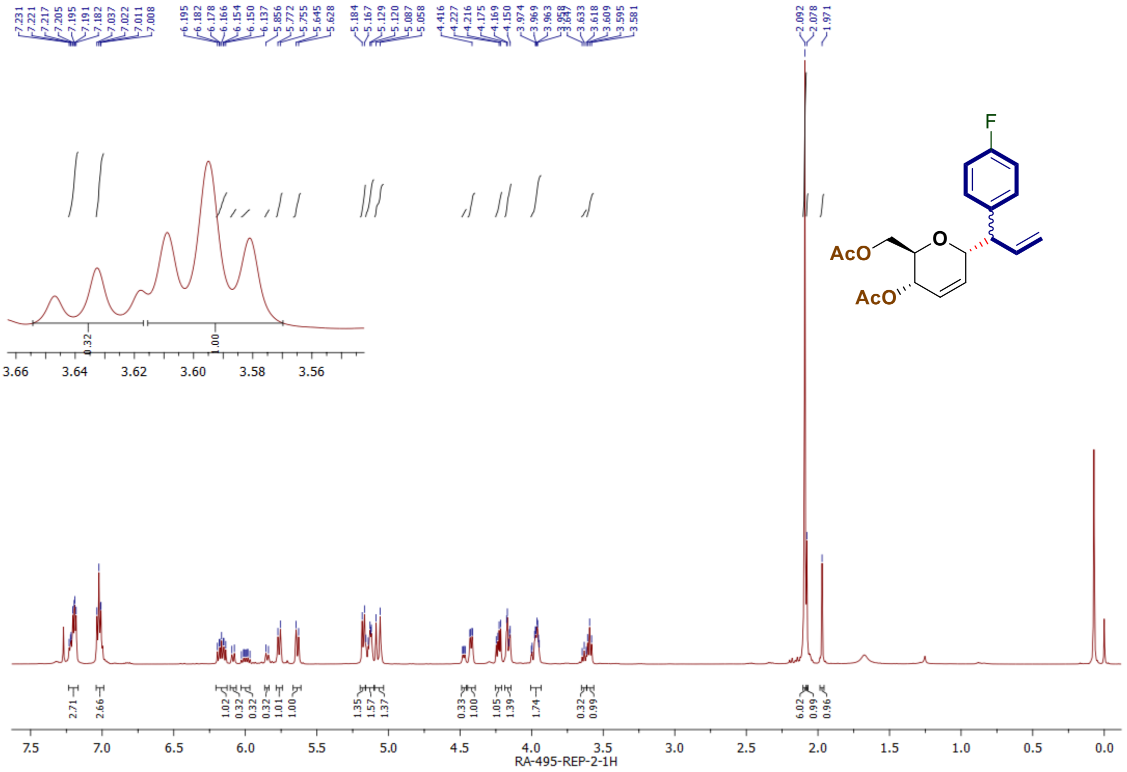
^{1}H NMR spectrum of **33k** (600 MHz, $CDCl_3$)



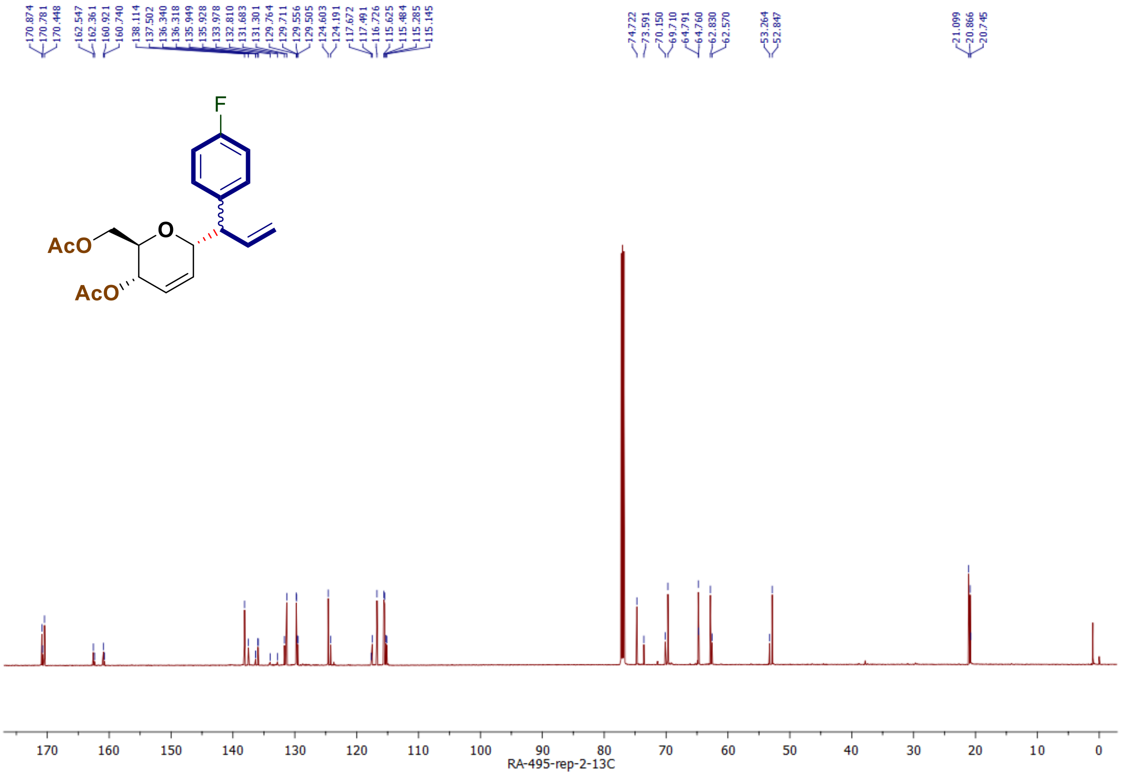
^{13}C NMR spectrum of **33k** (151 MHz, $CDCl_3$)



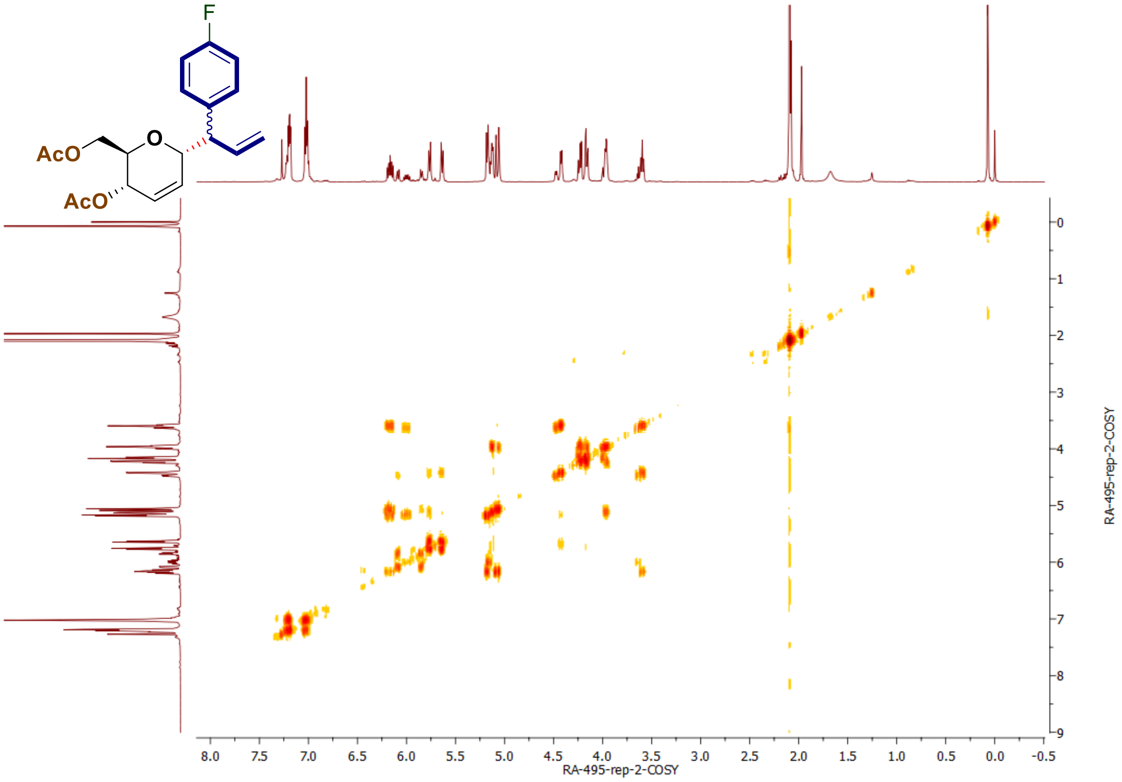
COSY NMR spectrum of **33k** (600 MHz, $CDCl_3$)



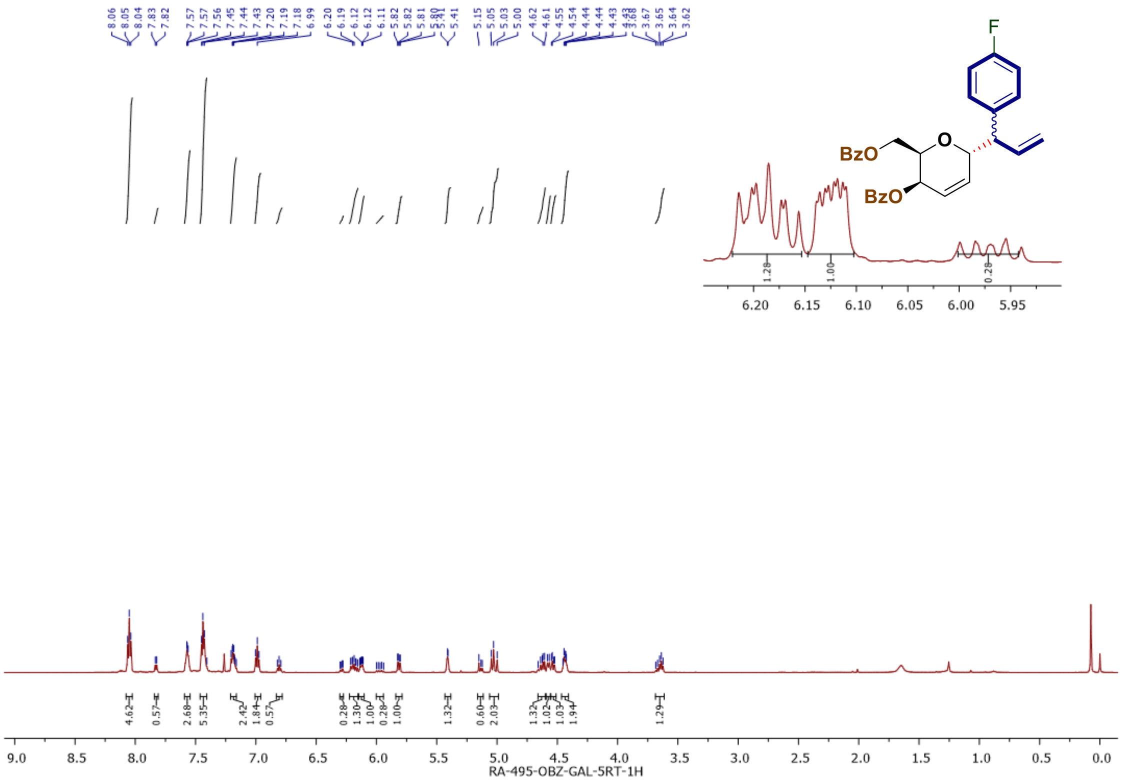
^{1}H NMR spectrum of **33l** (600 MHz, $CDCl_3$)



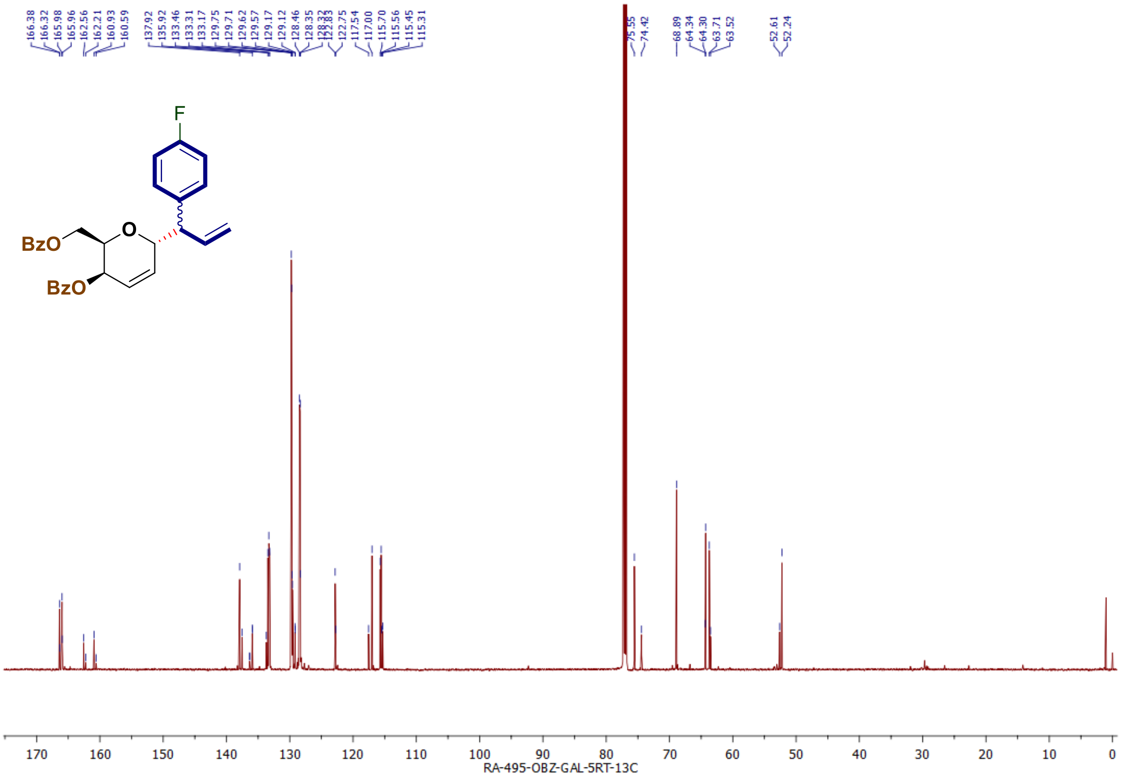
^{13}C NMR spectrum of **33l** (151 MHz, CDCl$_3$)



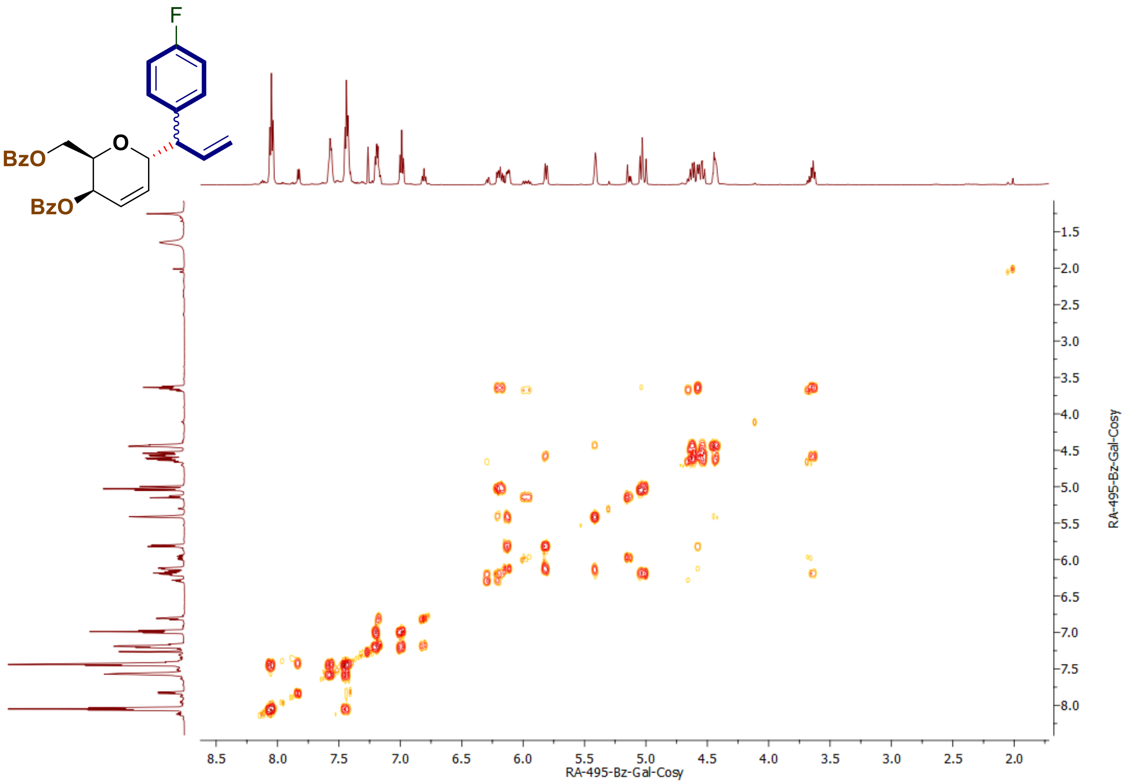
COSY NMR spectrum of **33l** (600 MHz, CDCl$_3$)



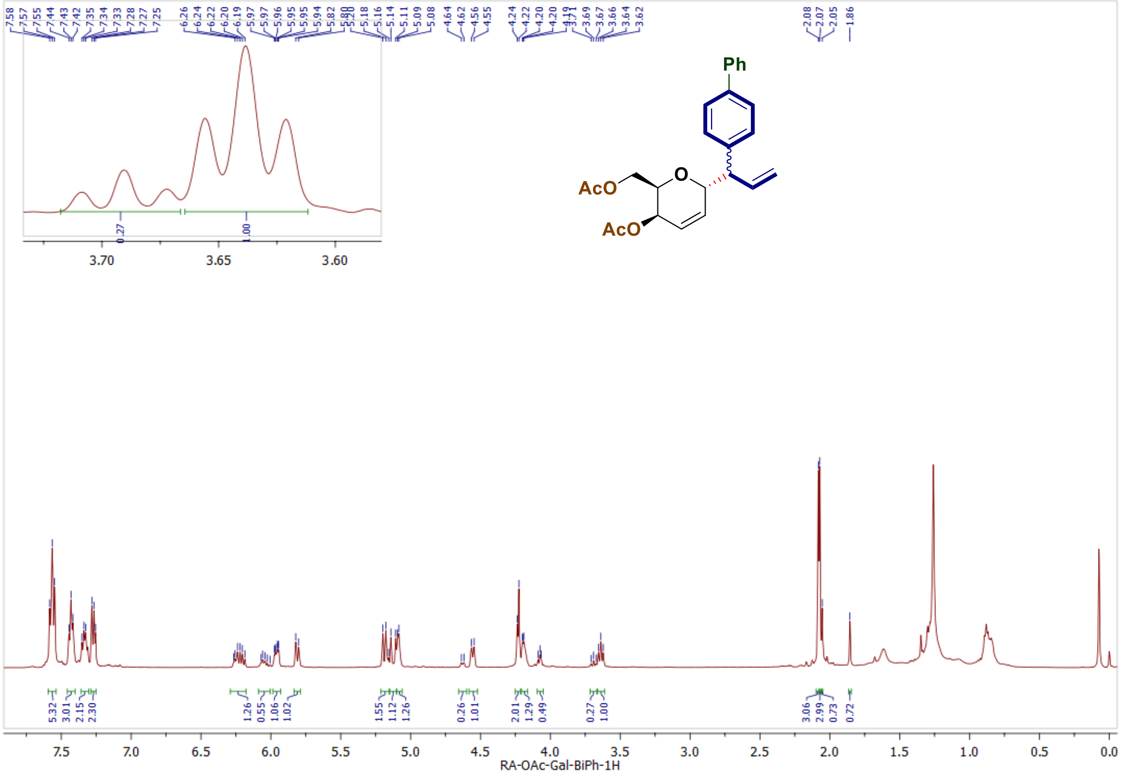
^{1}H NMR spectrum of **33m,** (600 MHz, CDCl$_3$)



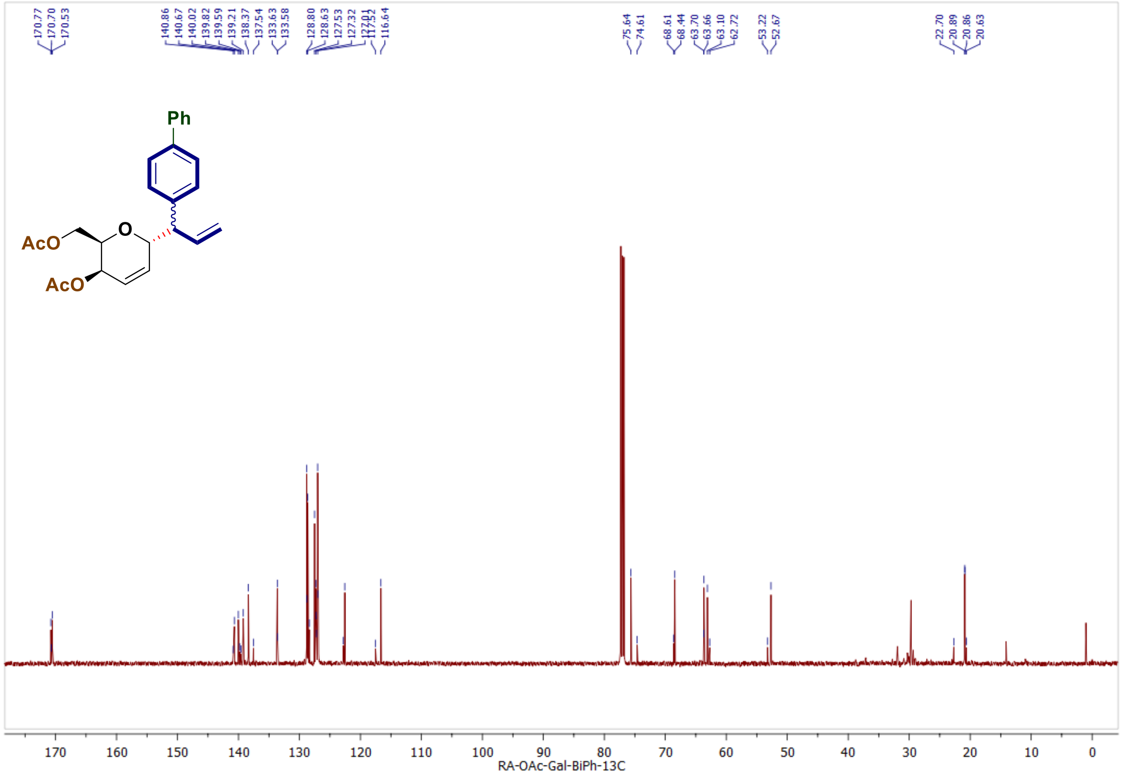
^{13}C NMR spectrum of **33m,** (151 MHz, CDCl$_3$)



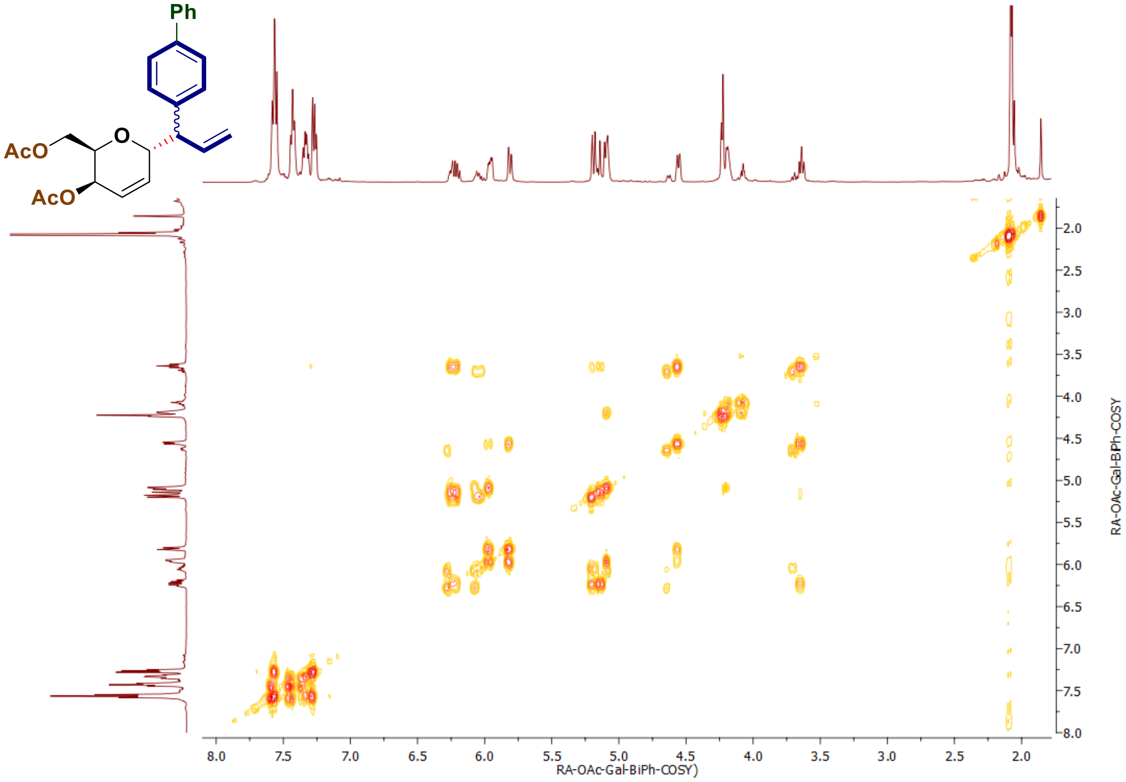
COSY NMR spectrum of **33m,** (600 MHz, CDCl$_3$)



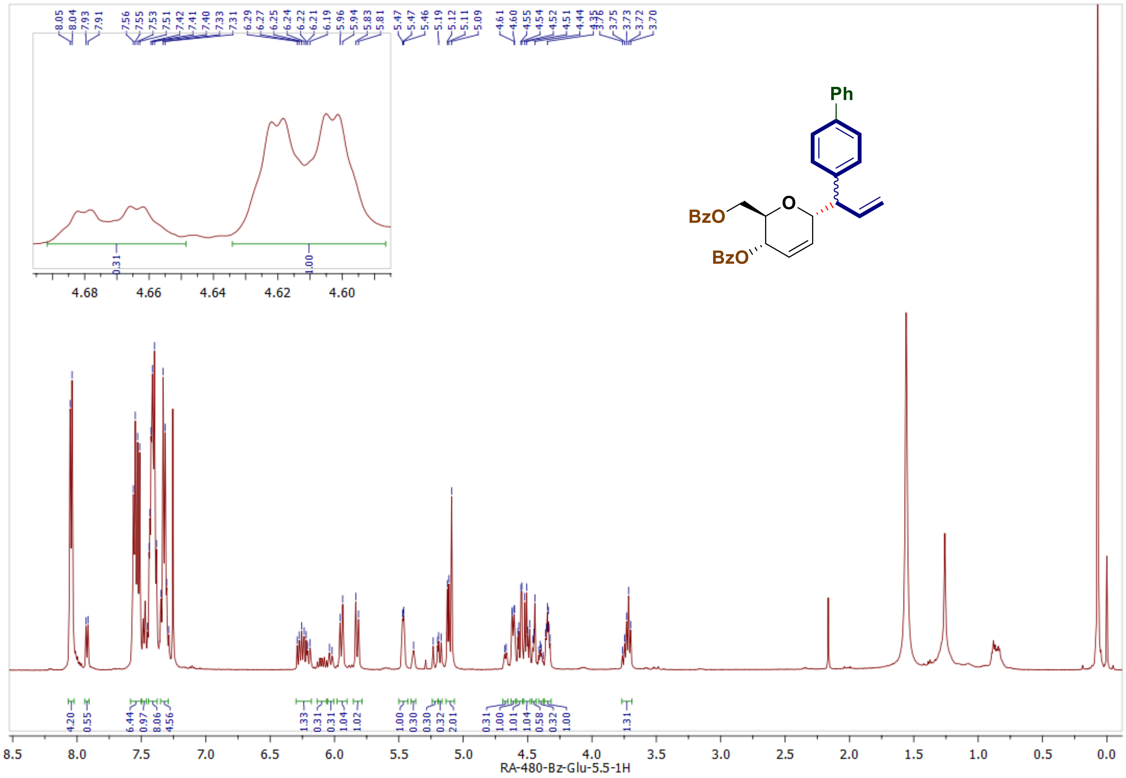
^{1}H NMR spectrum of **33n**, (600 MHz, CDCl$_3$)



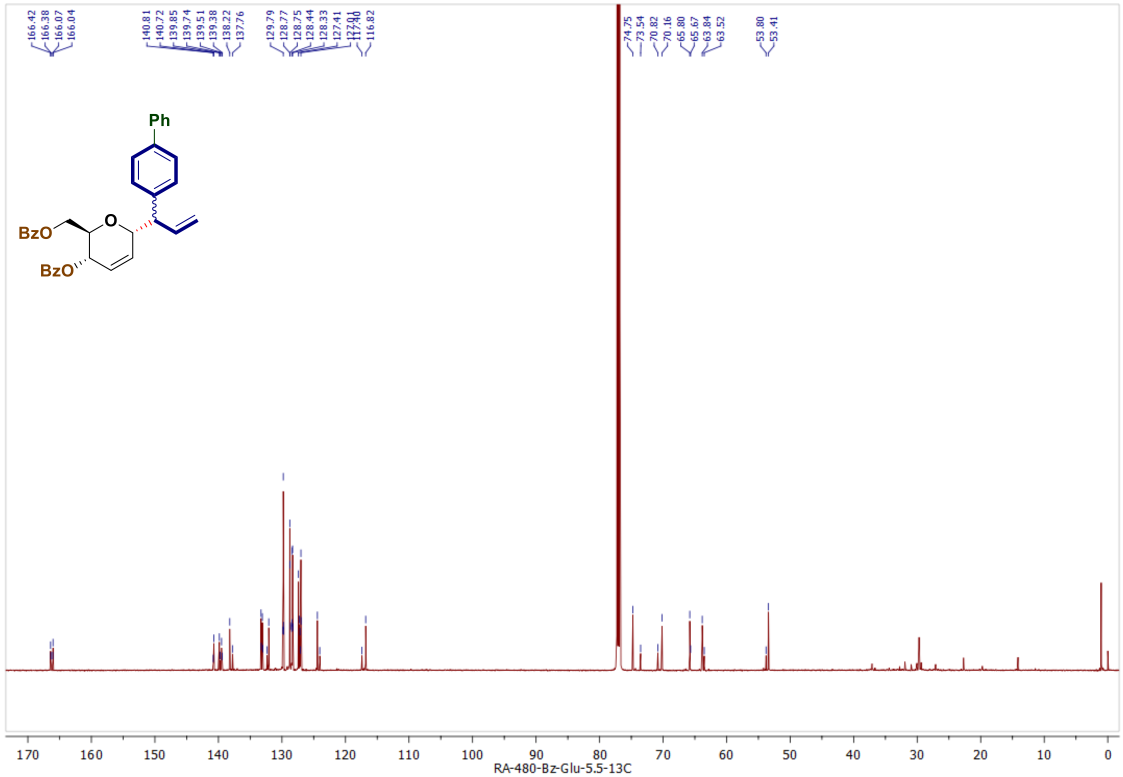
^{13}C NMR spectrum of **33n**, (151 MHz, CDCl$_3$)



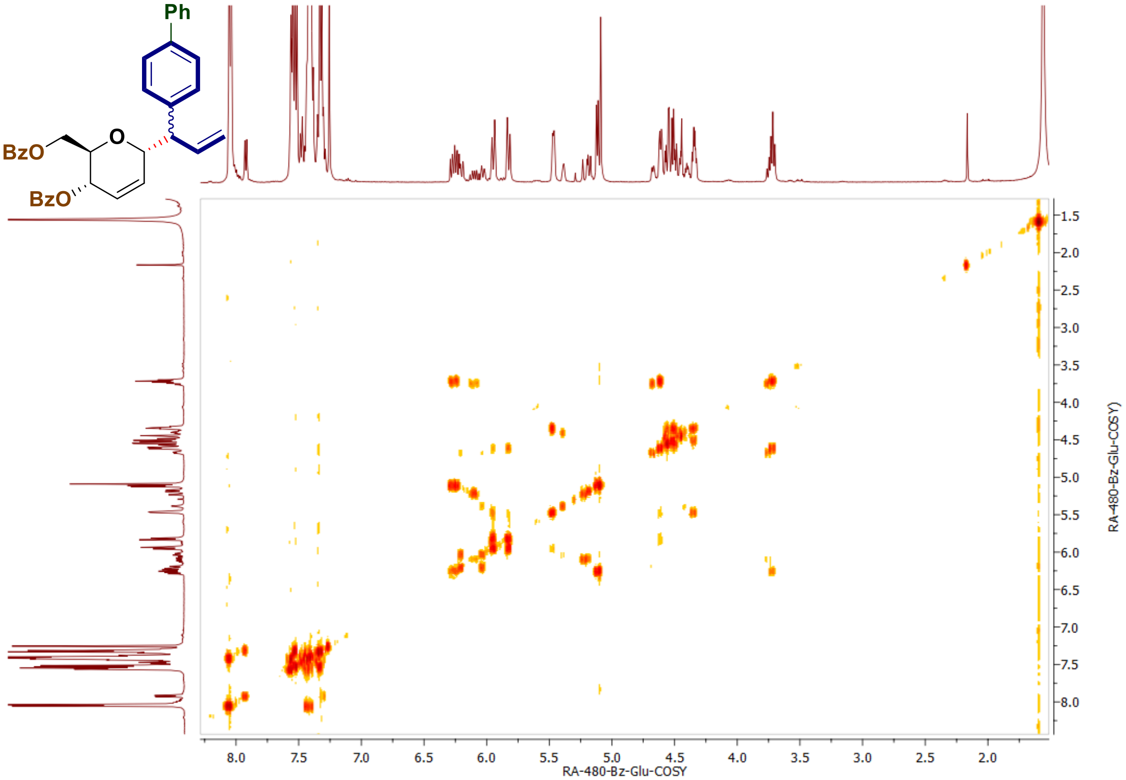
COSY NMR spectrum of **33n,** (600 MHz, CDCl$_3$)



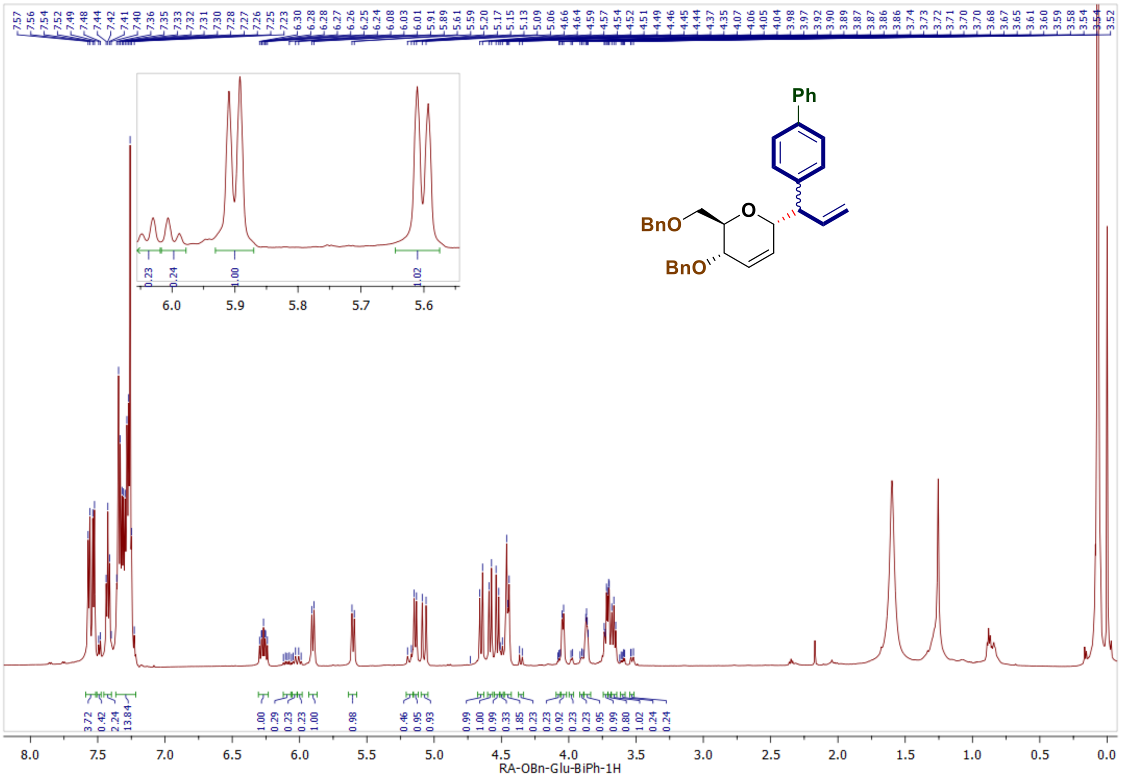
^{1}H NMR spectrum of **33o** (600 MHz, CDCl$_3$)



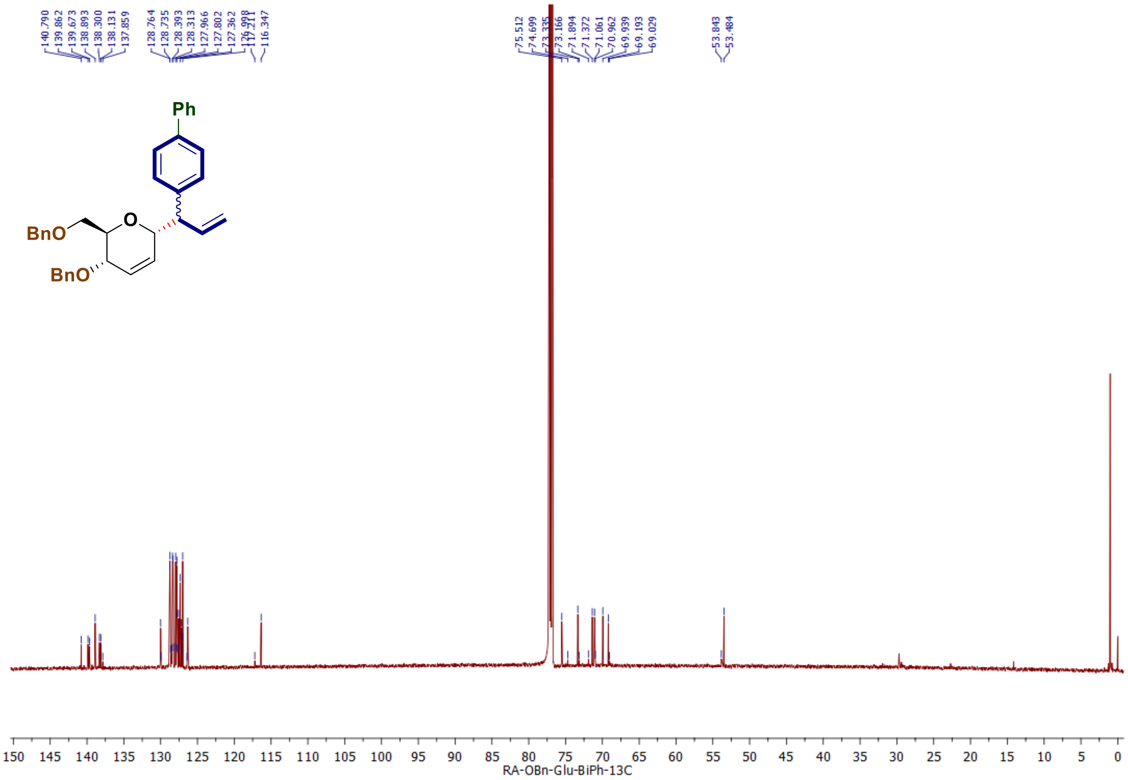
^{13}C NMR spectrum of **33o** (151 MHz, CDCl$_3$)



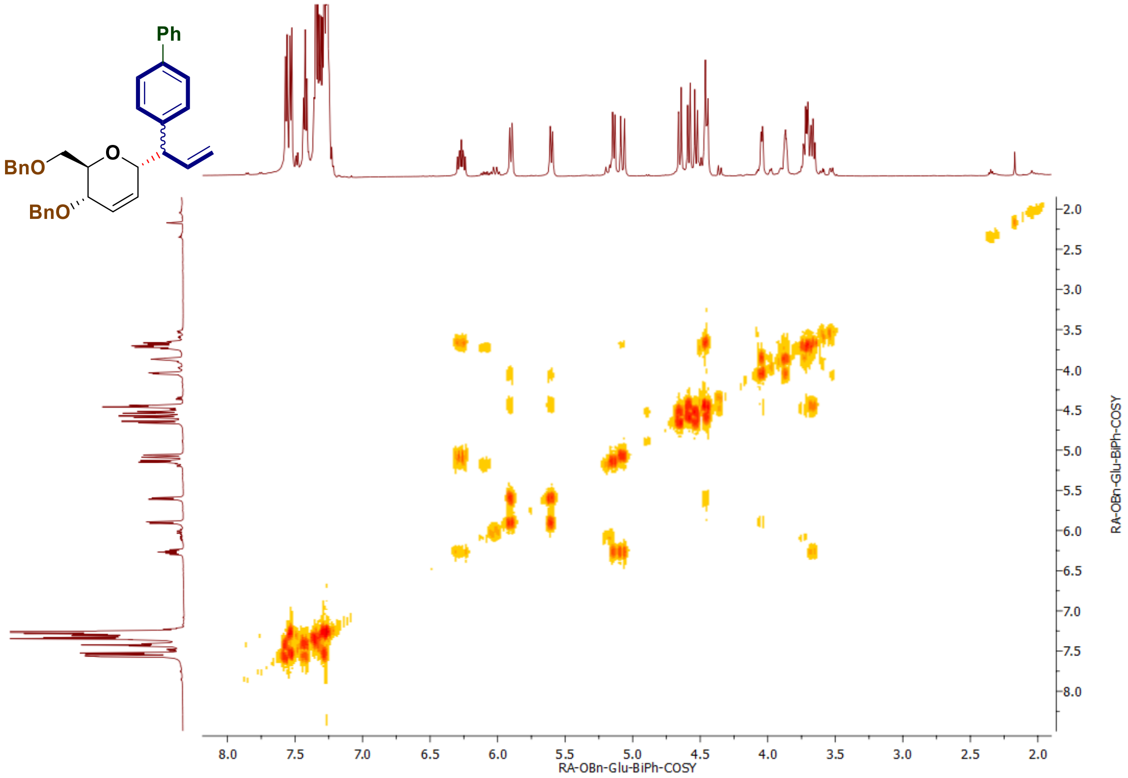
COSY NMR spectrum of **33o** (600 MHz, $CDCl_3$)



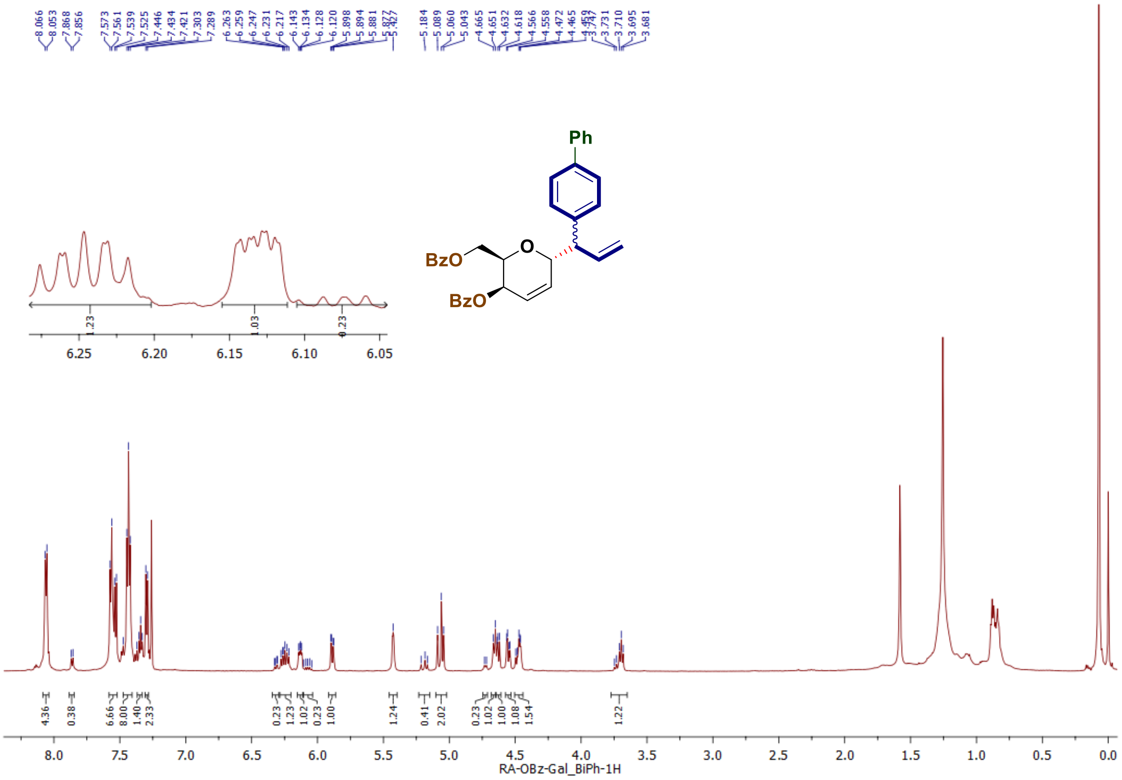
^{1}H NMR spectrum of **33p** (600 MHz, $CDCl_3$)



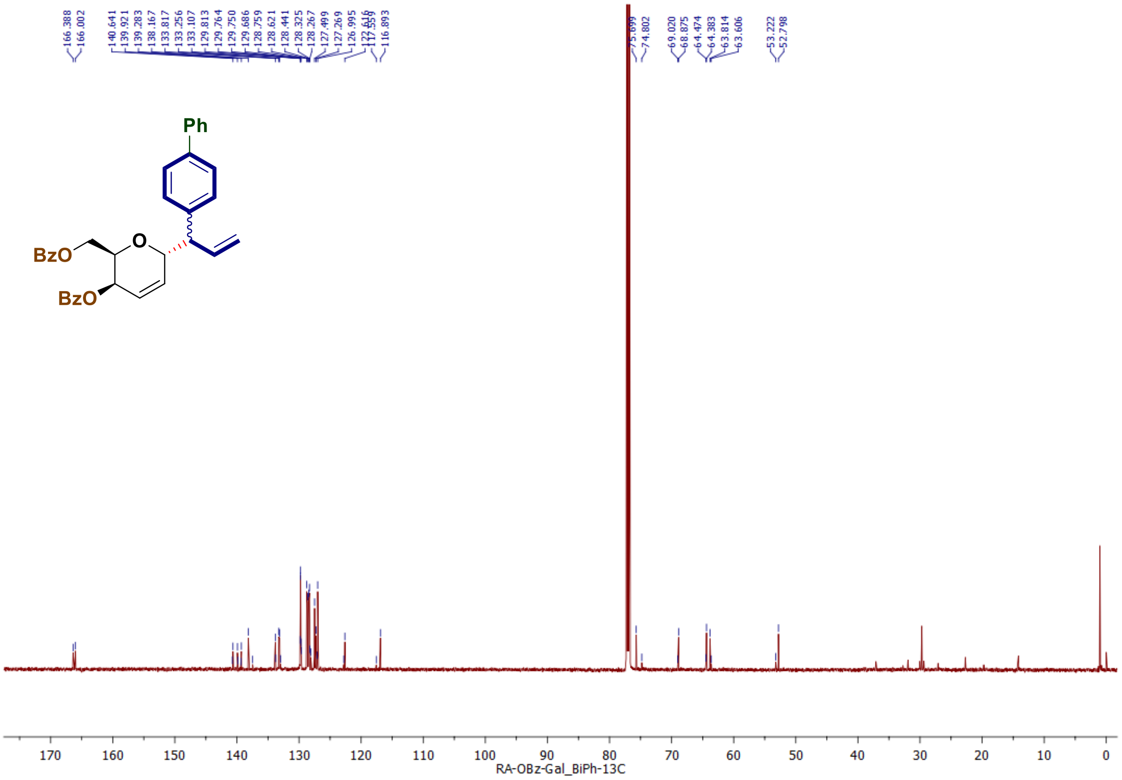
^{13}C NMR spectrum of **33p** (151 MHz, $CDCl_3$)



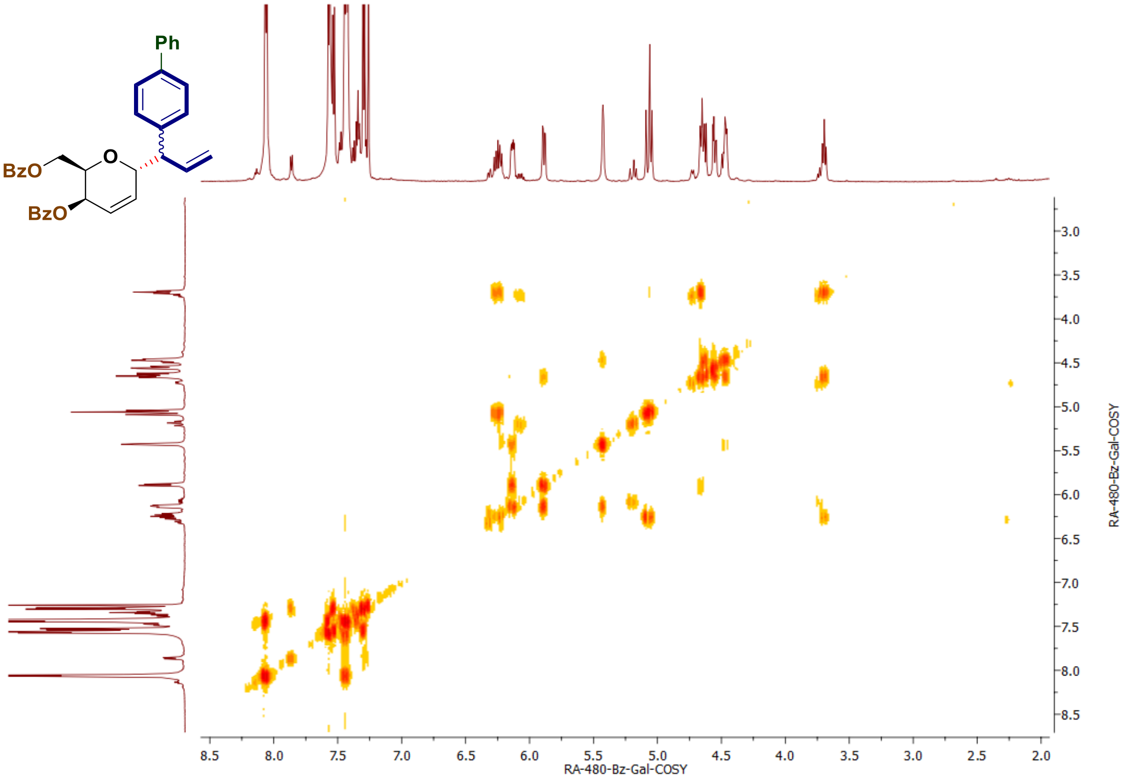
COSY NMR spectrum of **33p** (600 MHz, $CDCl_3$)



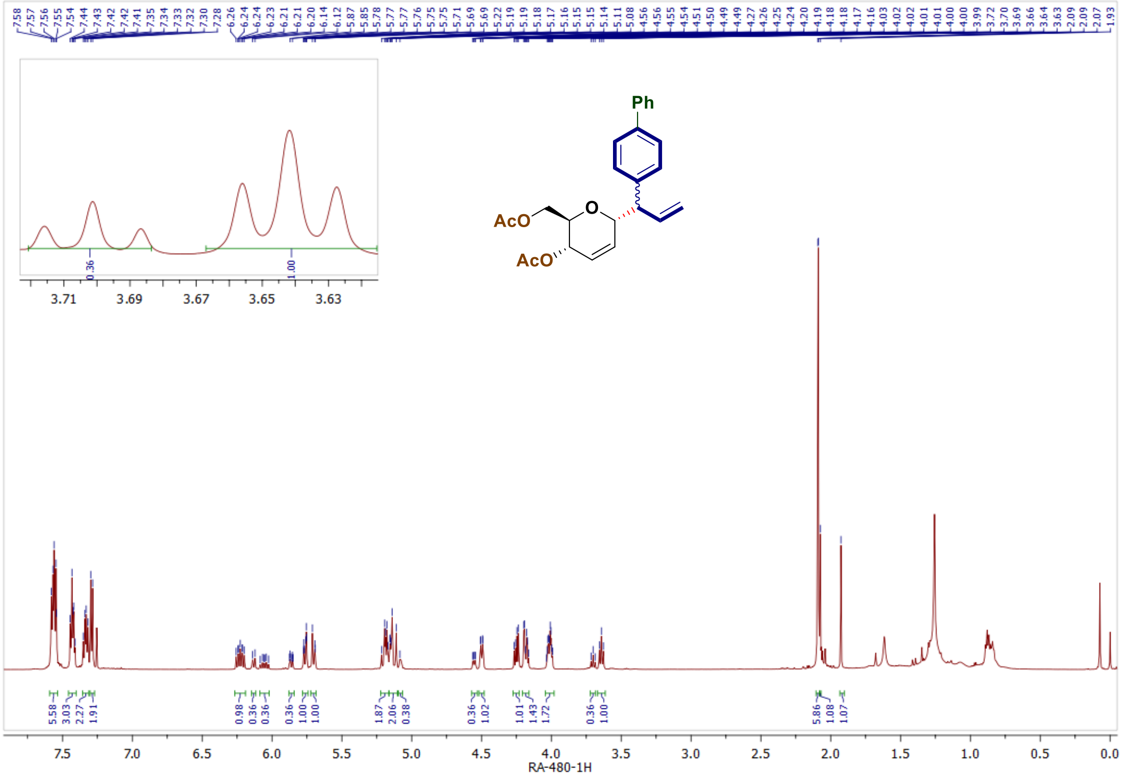
^{1}H NMR spectrum of **33q** (600 MHz, $CDCl_3$)



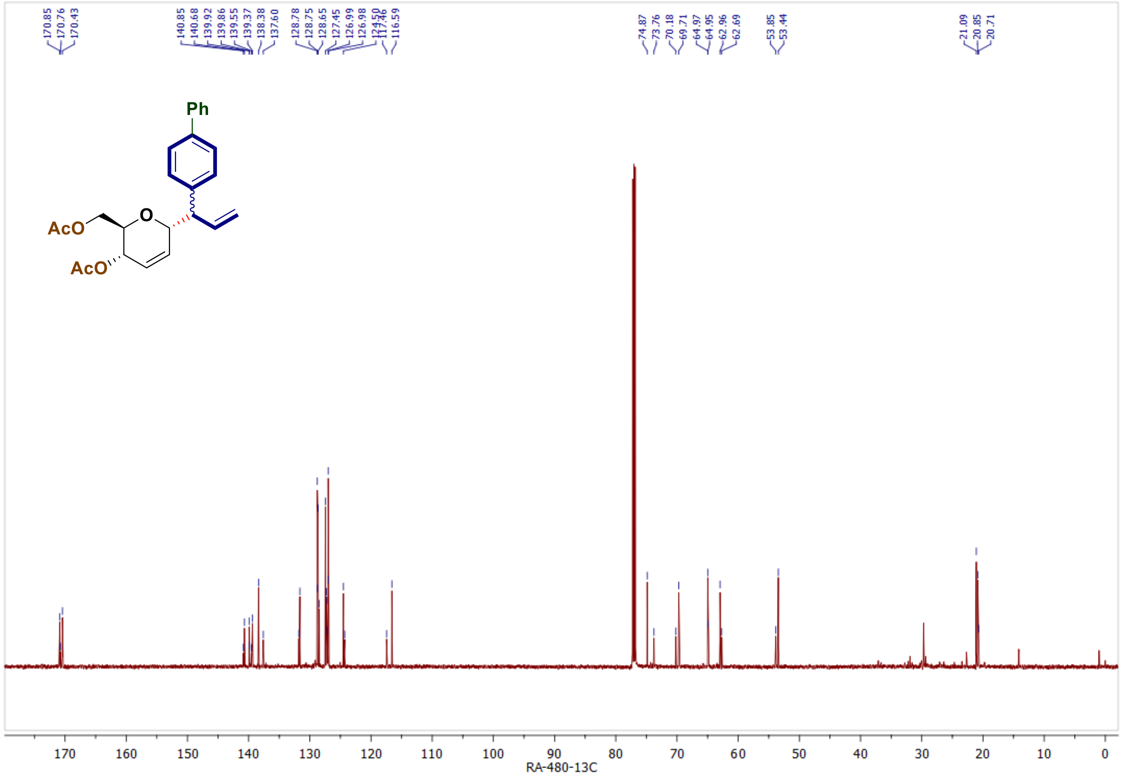
^{13}C NMR spectrum of **33q** (151 MHz, $CDCl_3$)



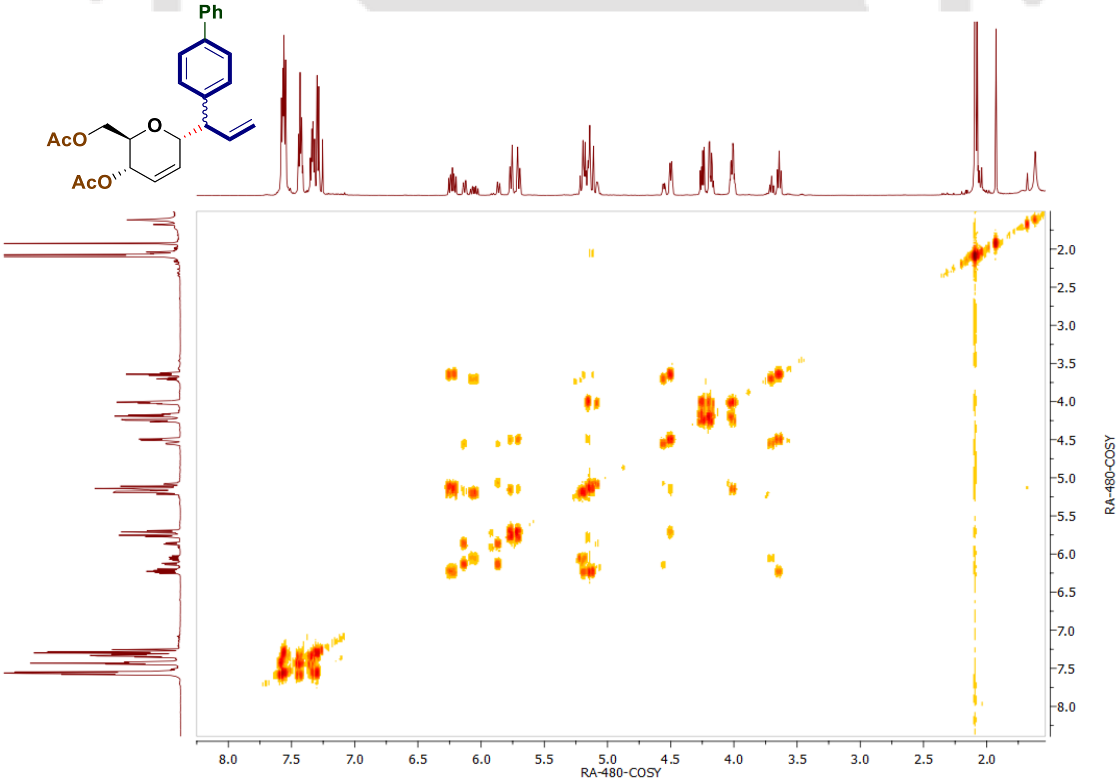
COSY NMR spectrum of **33q** (600 MHz, $CDCl_3$)



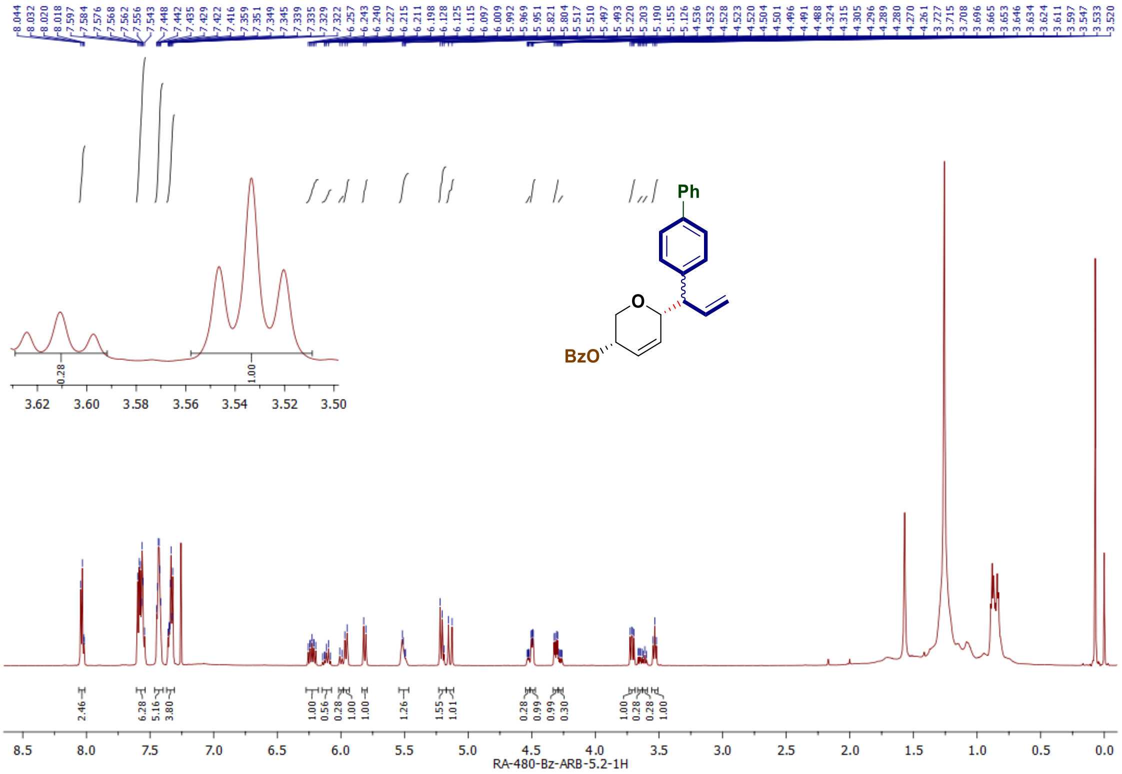
^{1}H NMR spectrum of **33r** (600 MHz, $CDCl_3$)



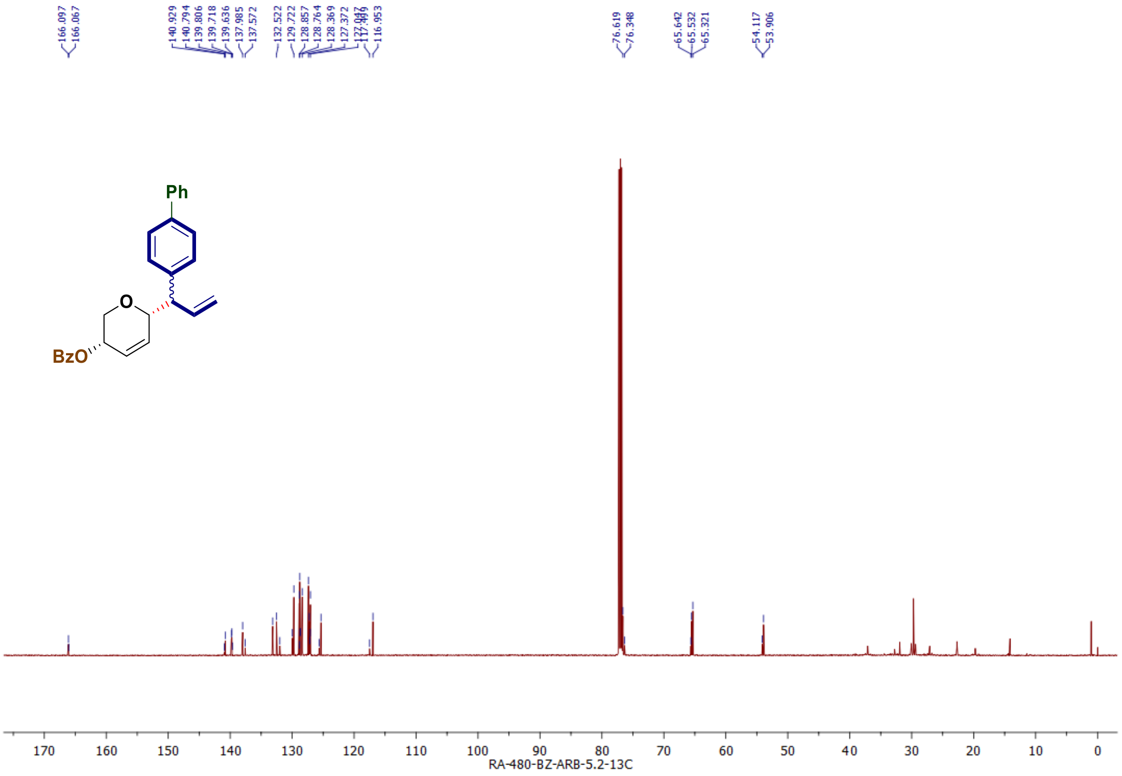
^{13}C NMR spectrum of **33r** (151 MHz, $CDCl_3$)



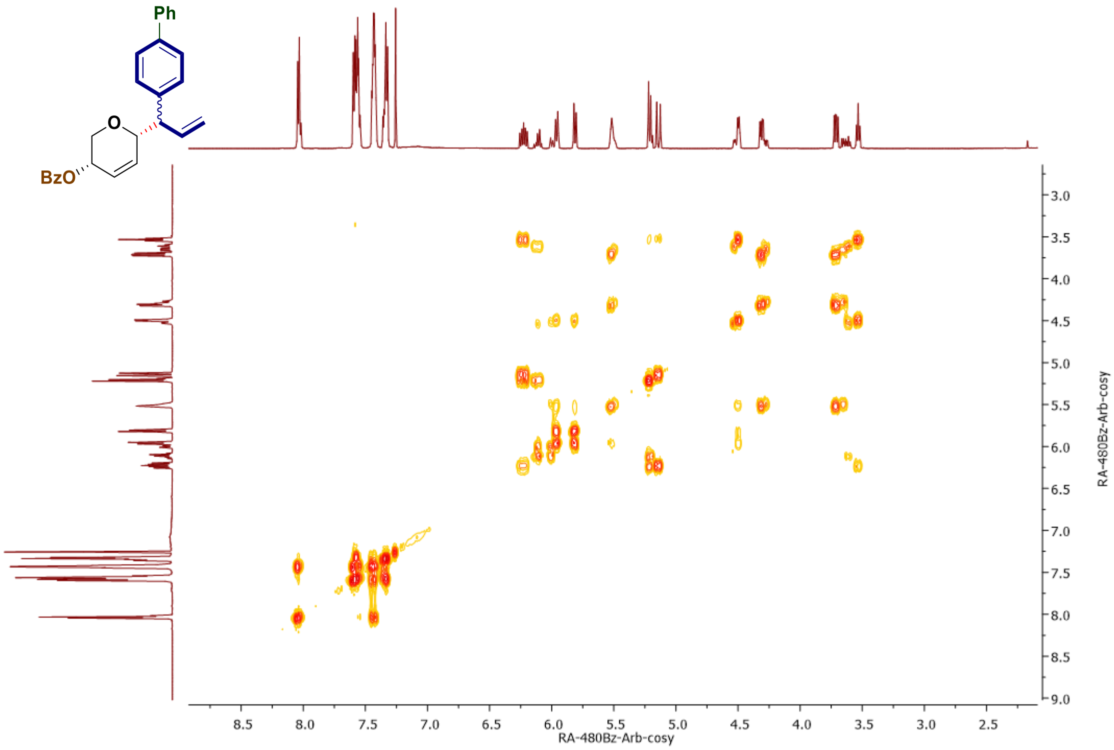
COSY NMR spectrum of **33r** (600 MHz, $CDCl_3$)



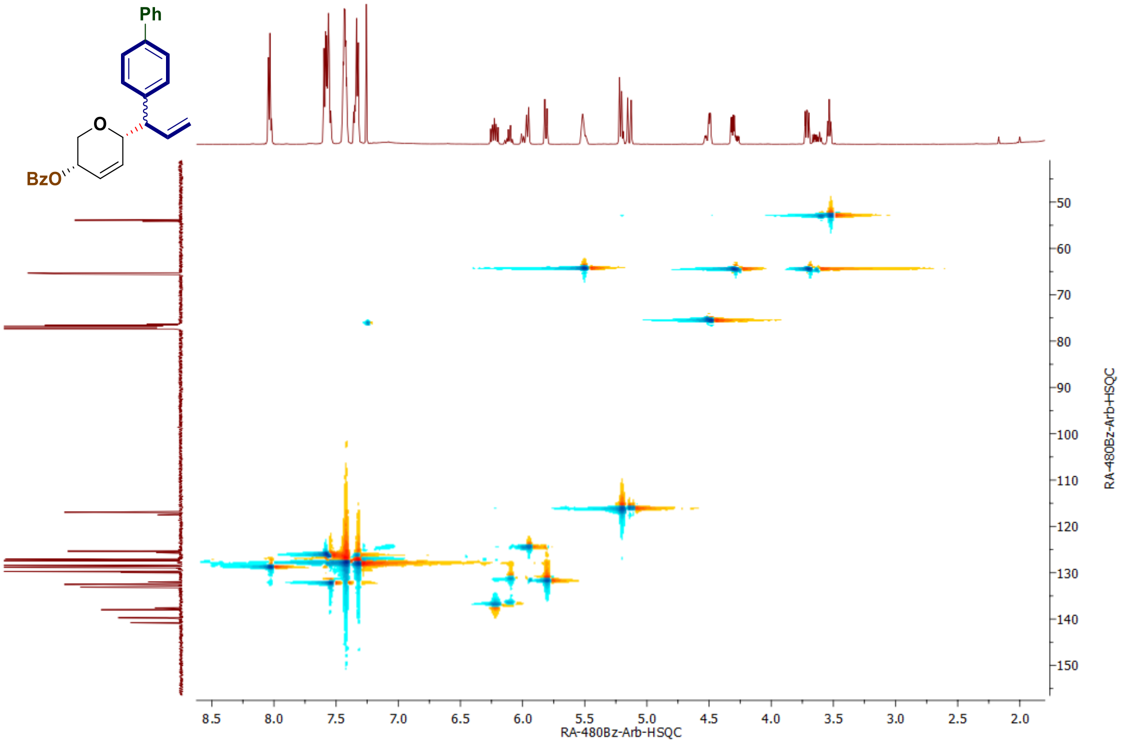
^{1}H NMR spectrum of **33s** (600 MHz, CDCl$_3$)



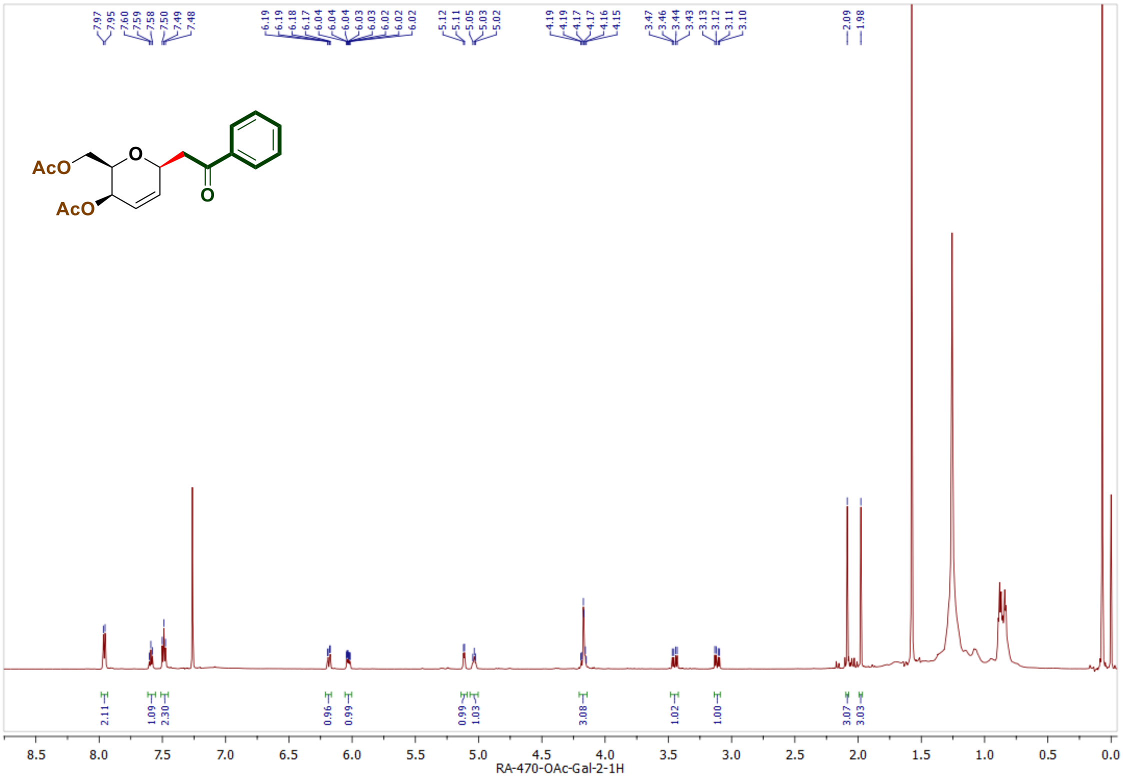
^{13}C NMR spectrum of **33s** (151 MHz, CDCl$_3$)



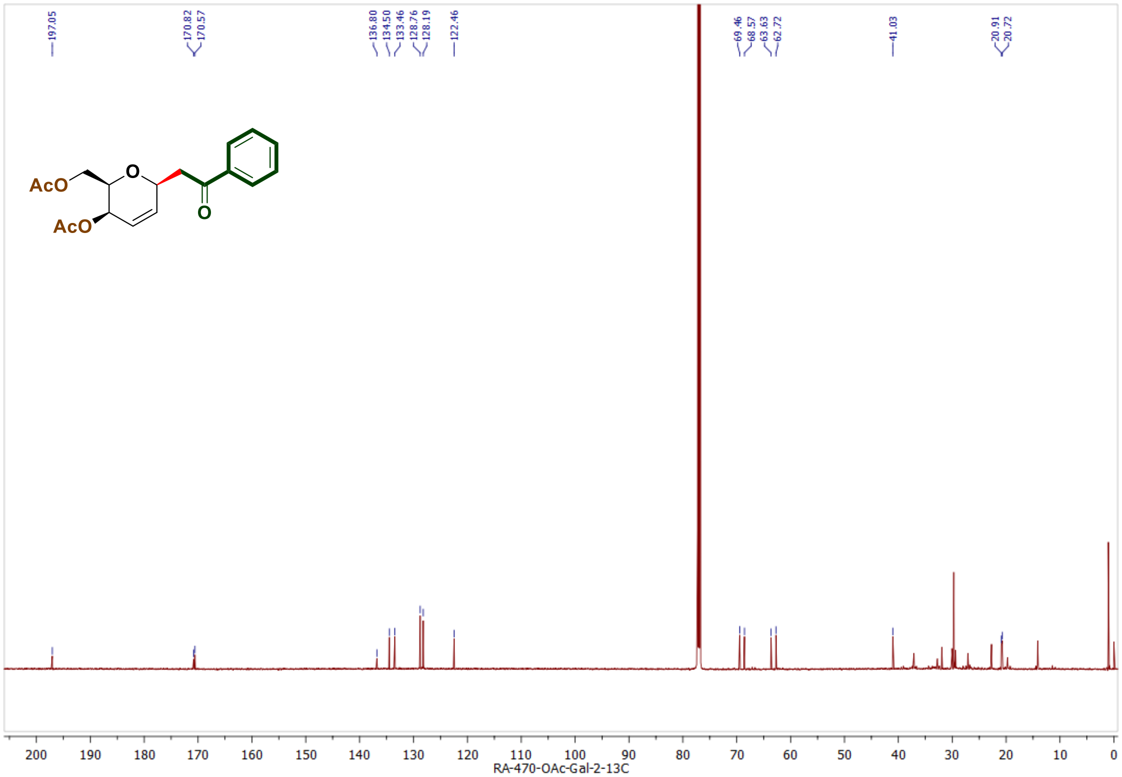
COSY NMR spectrum of **33s** (600 MHz, $CDCl_3$)



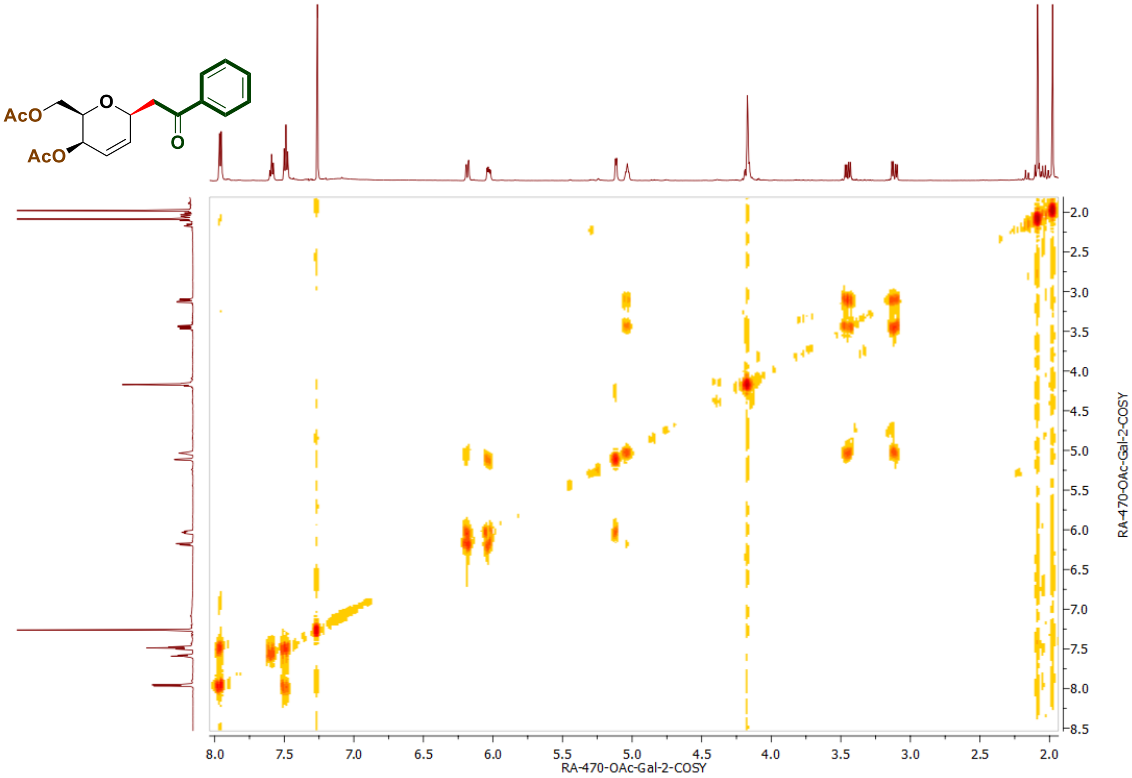
HSQC NMR spectrum of **33s** ($CDCl_3$)



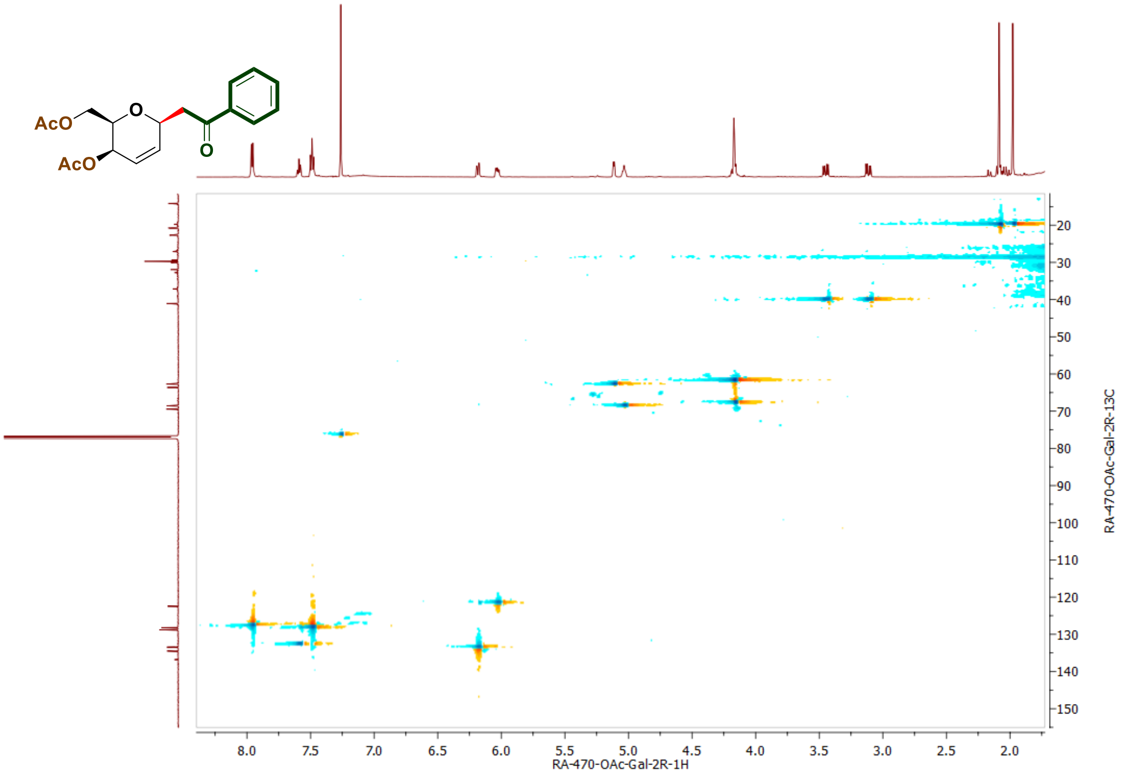
^{1}H NMR spectrum of **33t** (600 MHz, $CDCl_3$)



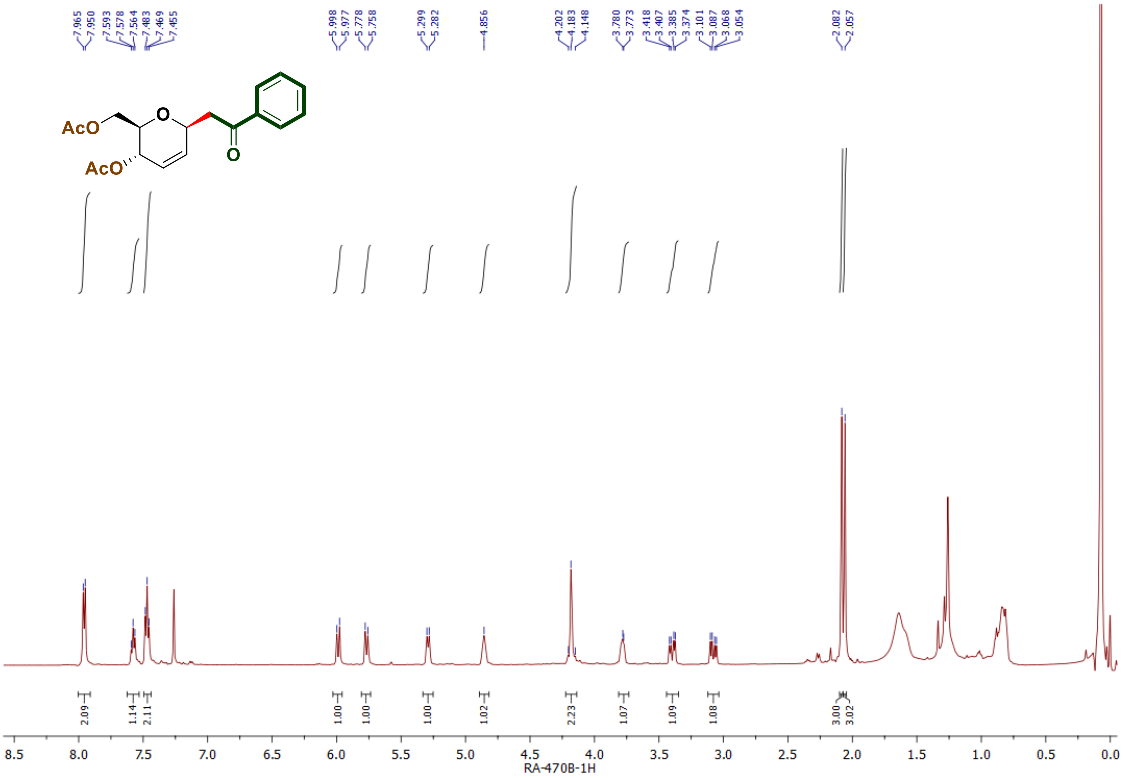
^{13}C NMR spectrum of **33t** (151 MHz, $CDCl_3$)



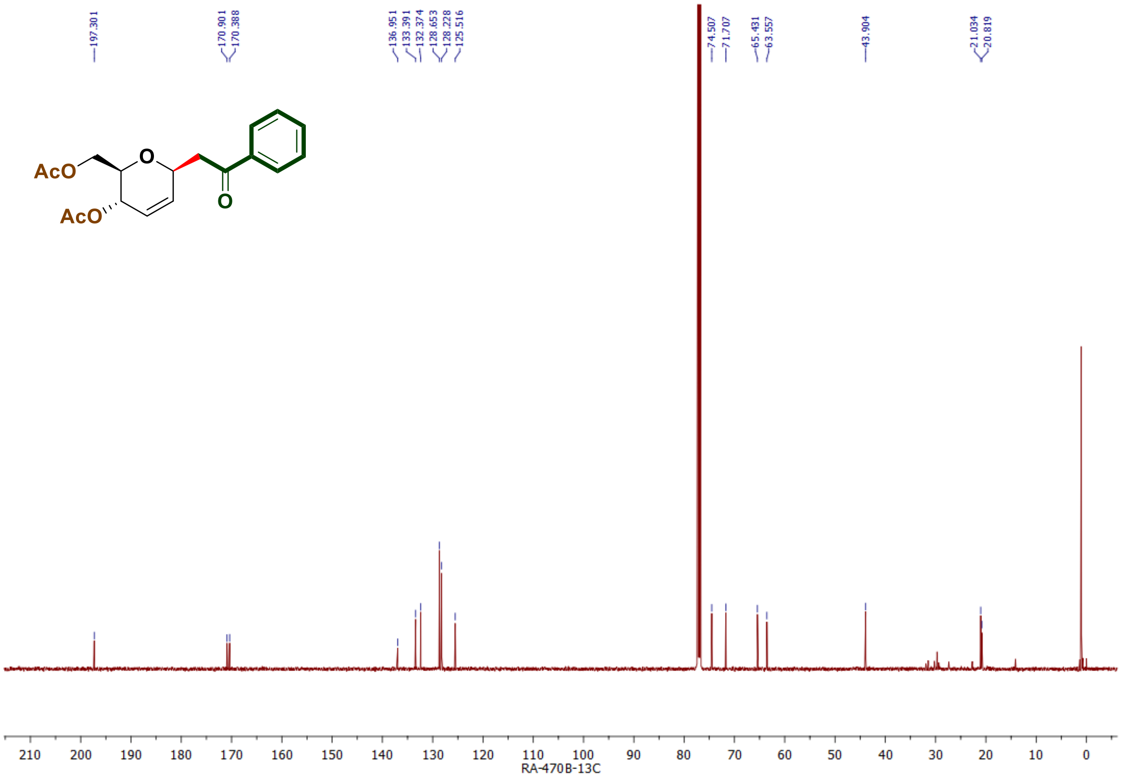
COSY NMR spectrum of **33t** (600 MHz, $CDCl_3$)



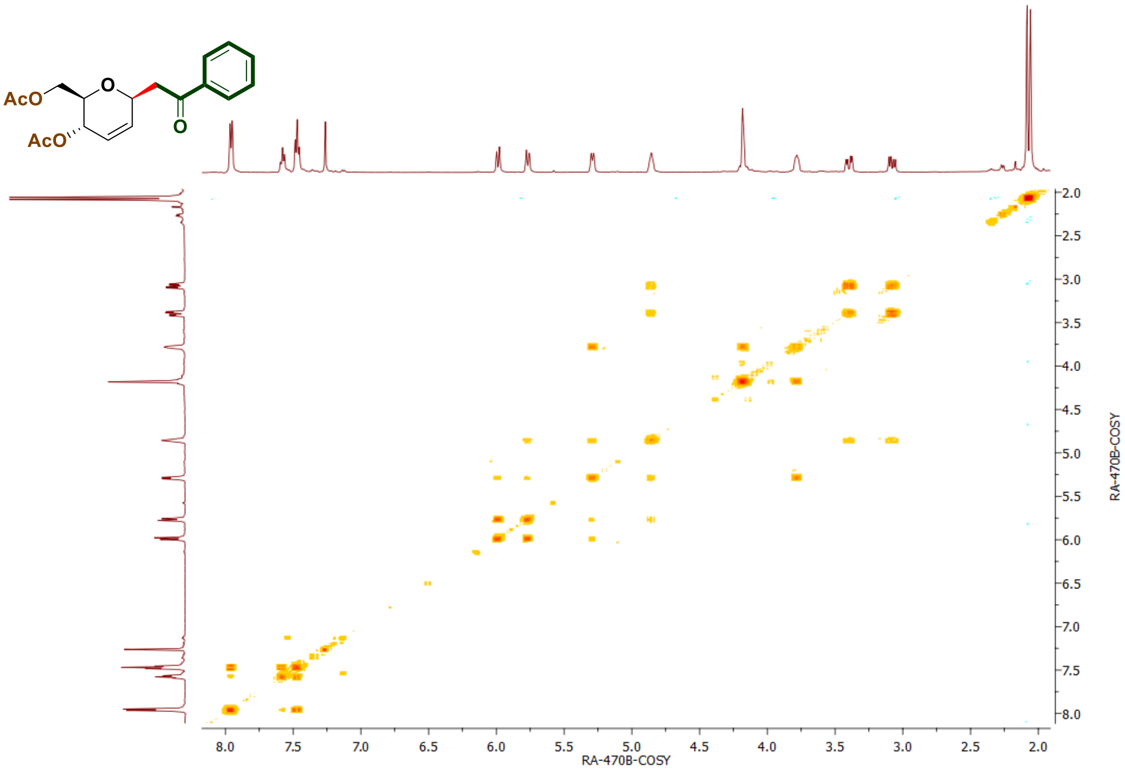
HSQC NMR spectrum of **33t** (600 MHz, $CDCl_3$)



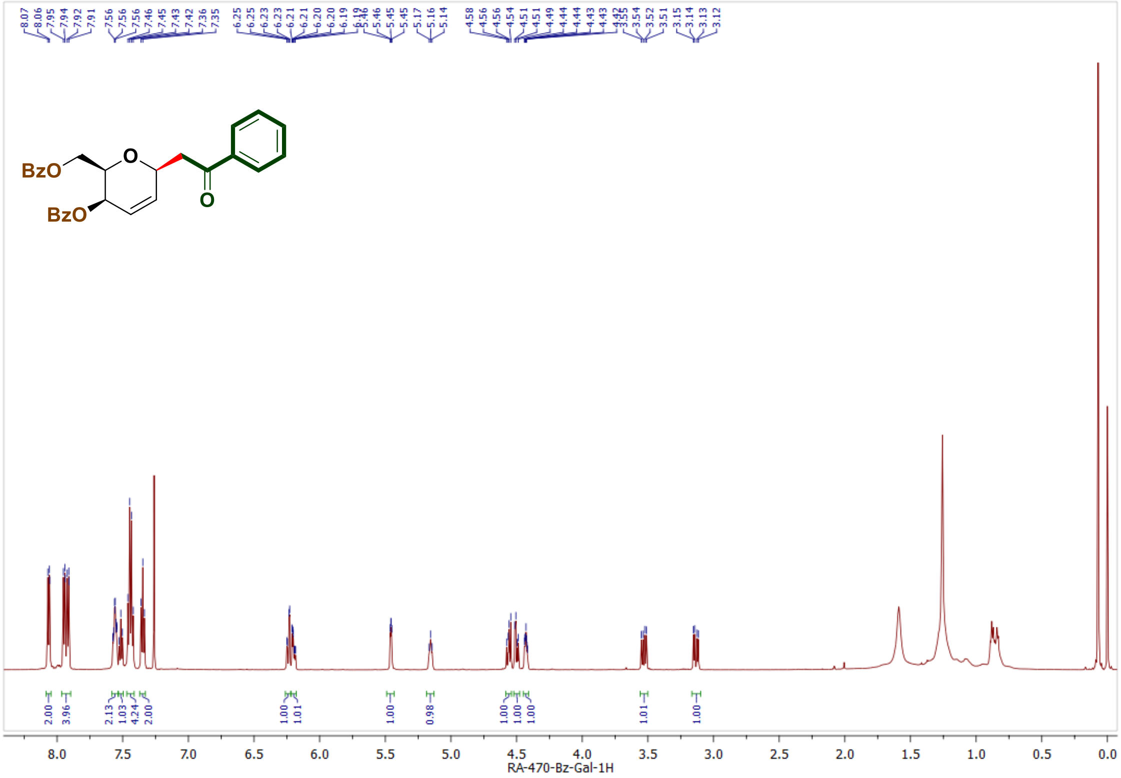
^{1}H NMR spectrum of **33u** (500 MHz, CDCl$_3$)



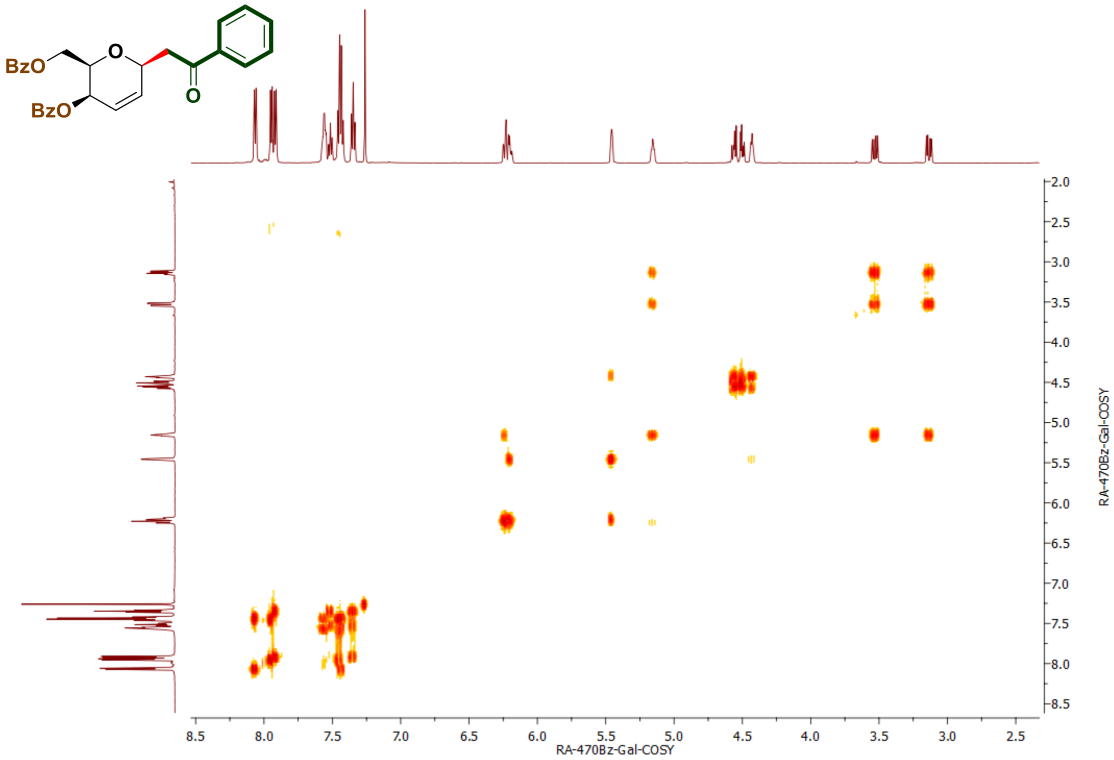
^{13}C NMR spectrum of **33u** (126 MHz, CDCl$_3$)



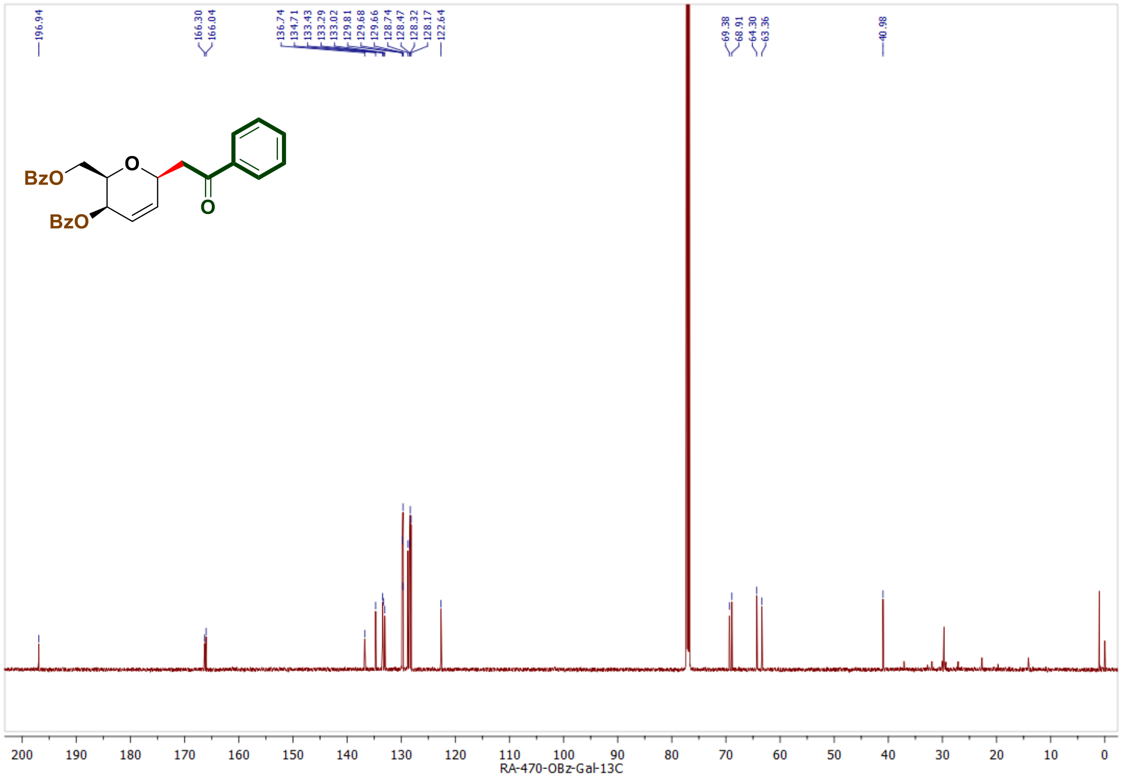
COSY NMR spectrum of **33u** (500 MHz, $CDCl_3$)



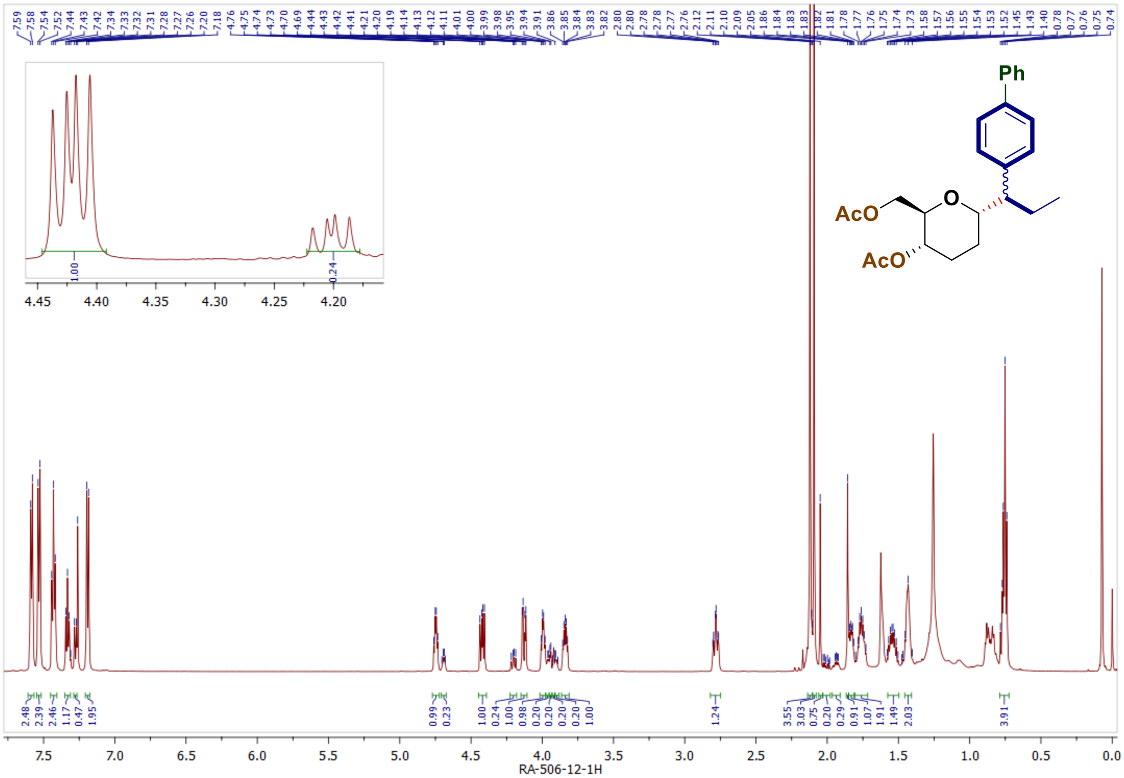
^{1}H NMR spectrum of **33v** (600 MHz, $CDCl_3$)



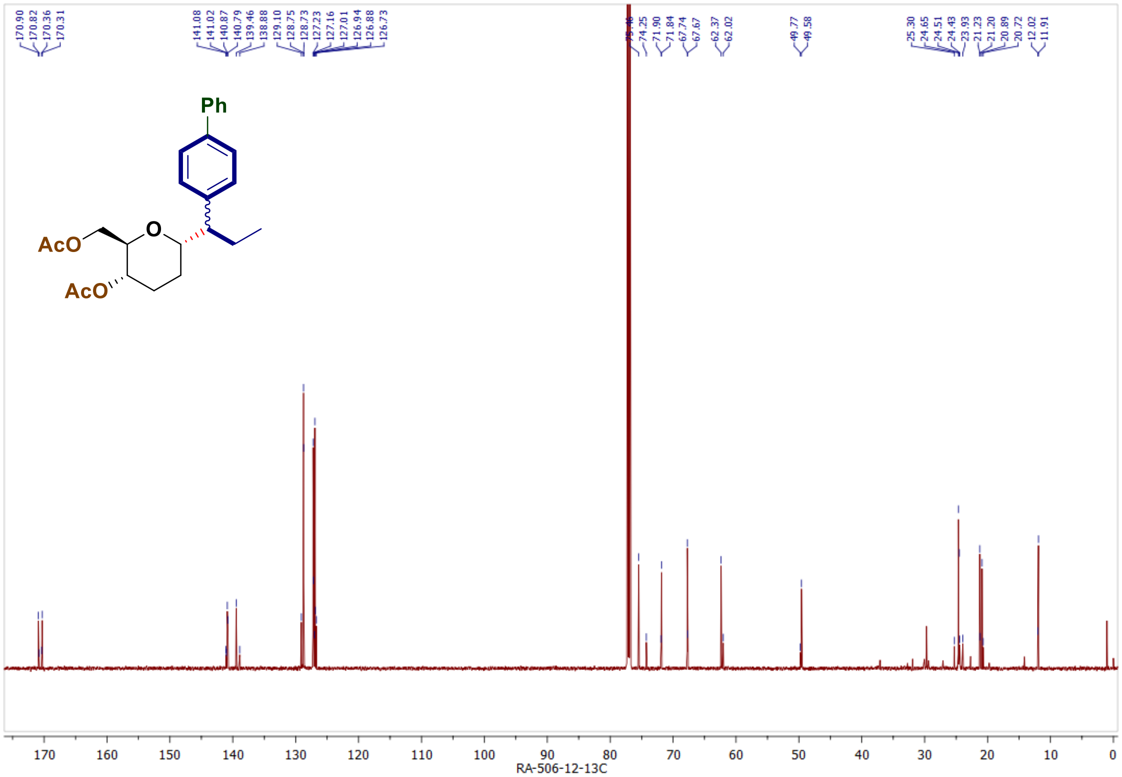
COSY NMR spectrum of **33v** (600 MHz, $CDCl_3$)



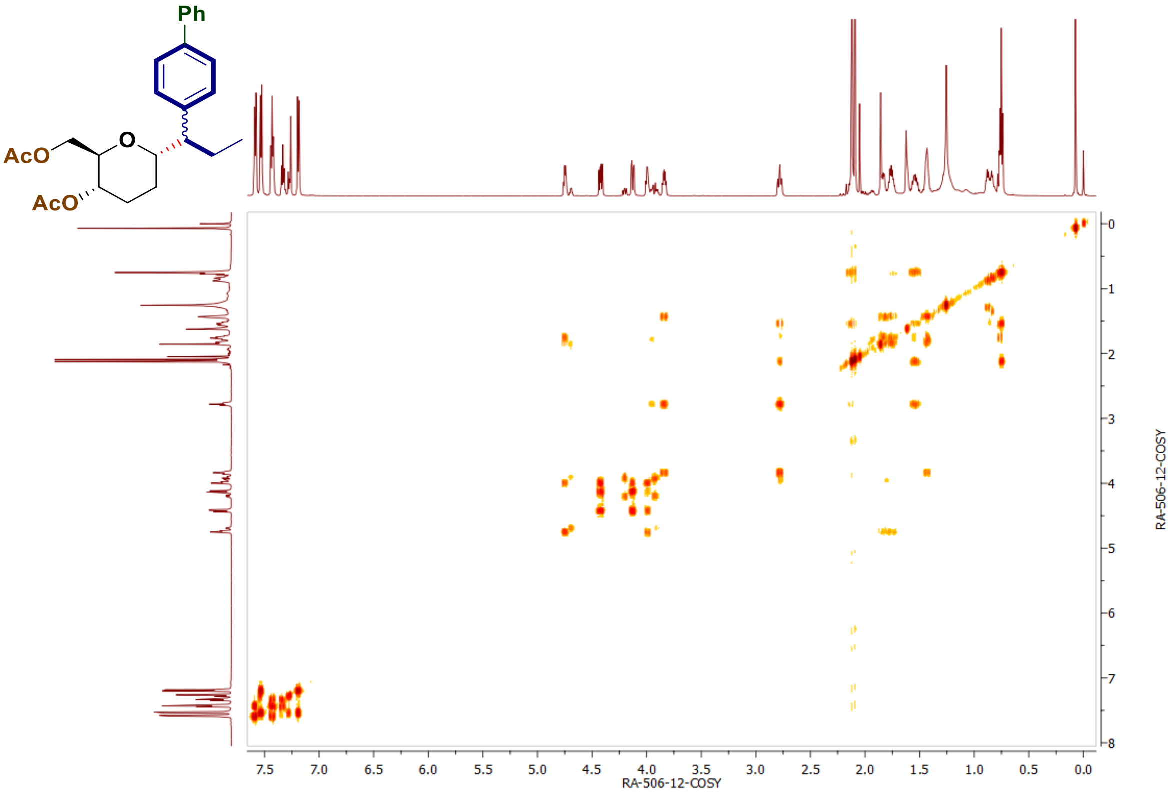
^{13}C NMR spectrum of **33v** (151 MHz, $CDCl_3$)



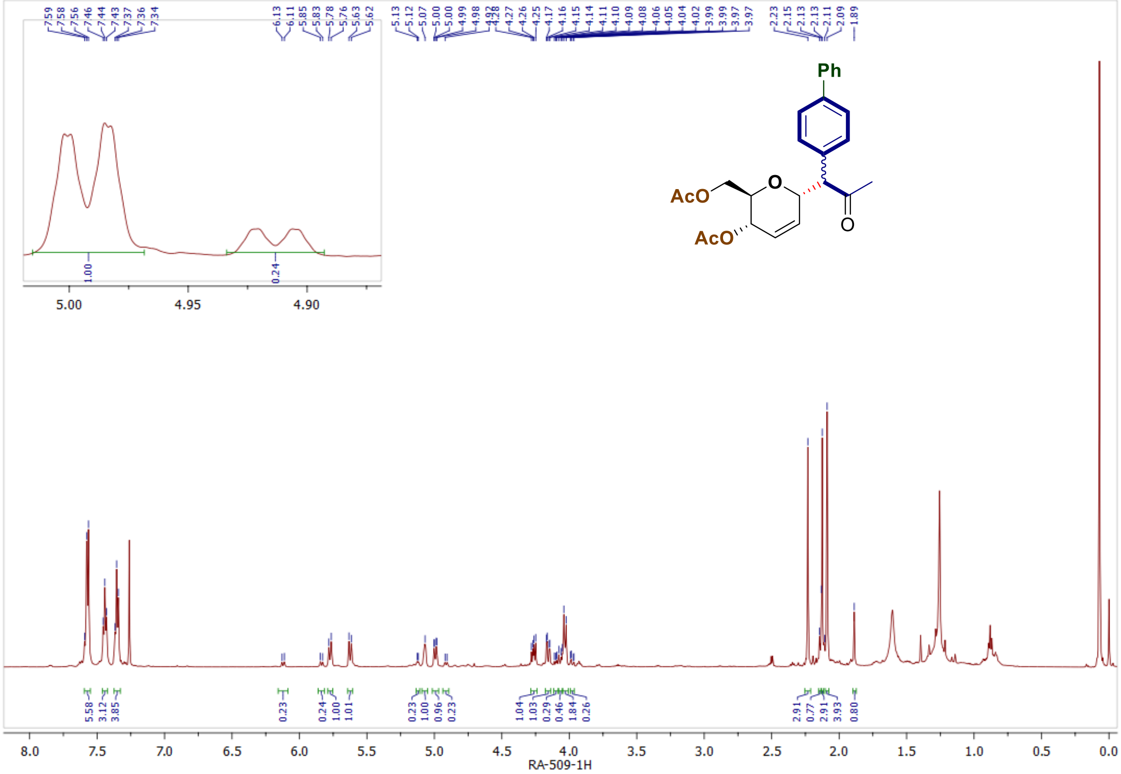
^{1}H NMR spectrum of **34** (600 MHz, $CDCl_3$)



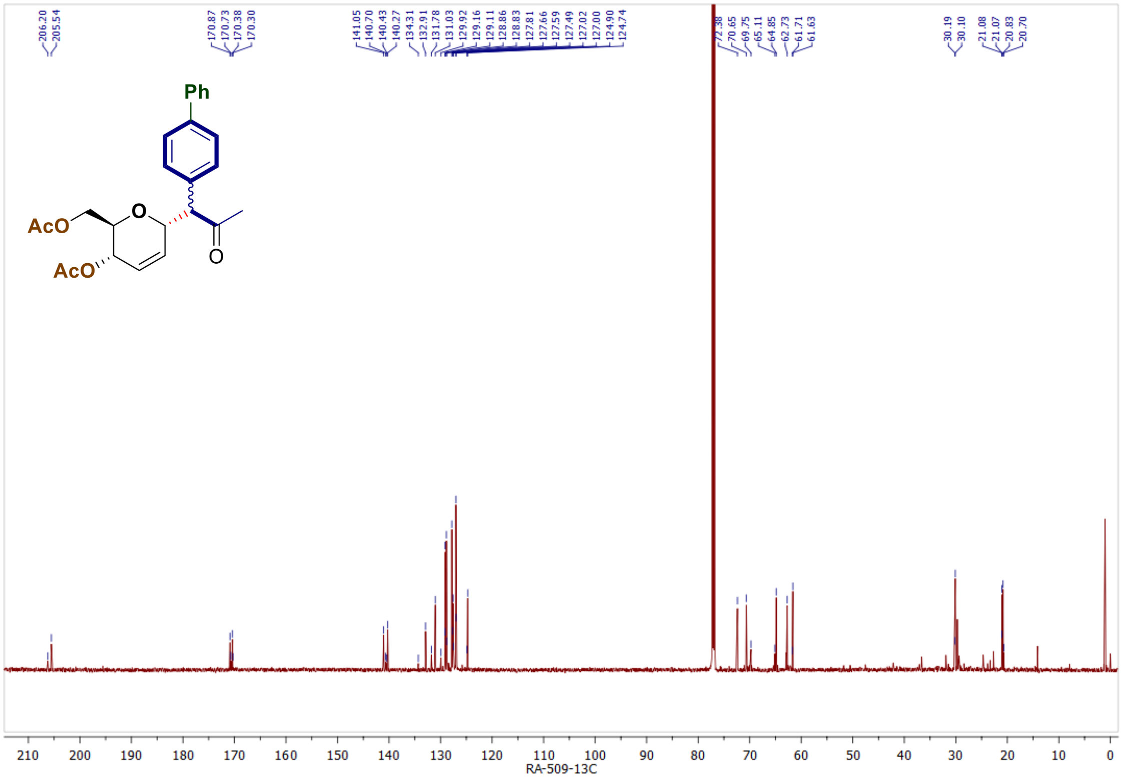
^{13}C NMR spectrum of **34** (151 MHz, $CDCl_3$)



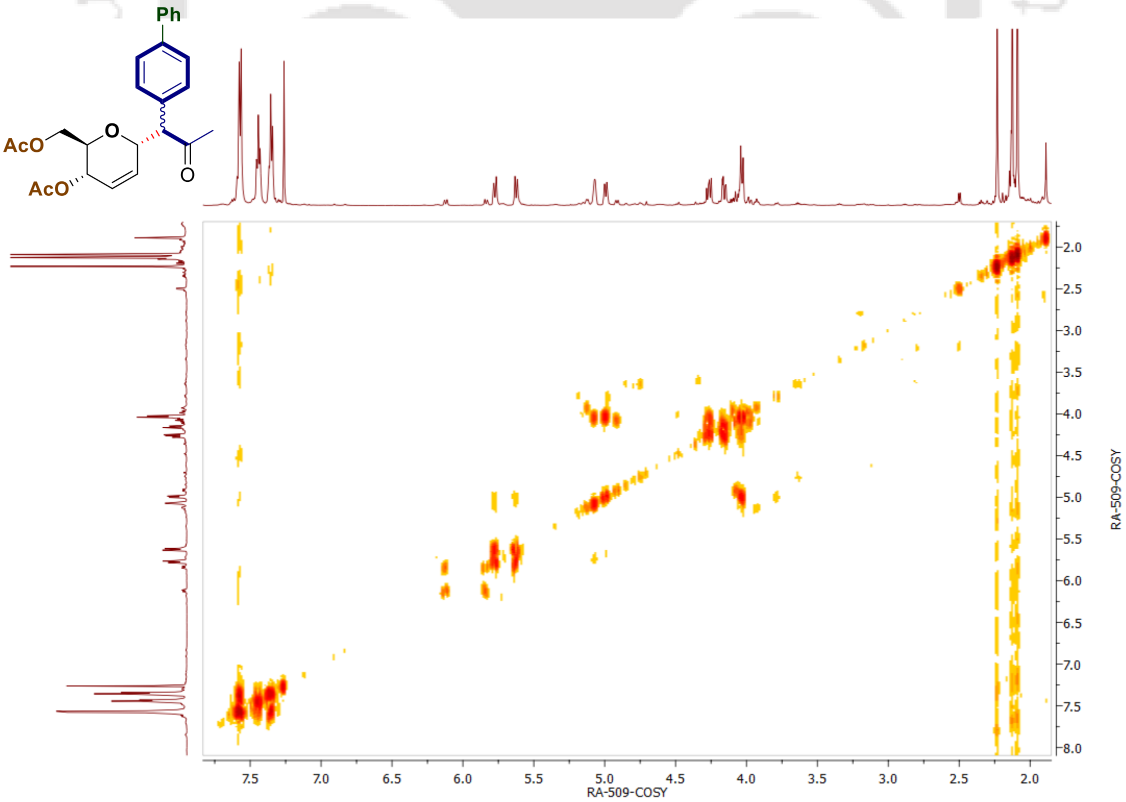
COSY NMR spectrum of **34** (600 MHz, $CDCl_3$)



^1H NMR spectrum of **35** (600 MHz, $CDCl_3$)



^{13}C NMR spectrum of **35** (151 MHz, CDCl$_3$)



COSY NMR spectrum of **35**, (600 MHz, CDCl$_3$)

2.8 Assignment of Stereochemistry

The stereochemistry of the representative compound has been studied using nOe technique as shown. Further, analyzing and matching of the chemical shifts and cosy analysis of the rest of the compounds with the representative compounds has been undertaken. The stereochemistry has been carefully assigned for all the compounds. In addition, some of the known compounds (simple allylated glycal) stereochemistry has also been matched with the literature reports as well. Some of the analysis is provided below.

2.8.1 nOe experiments of 33n (major isomer)

nOe Peak irradiated	**nOe peak enhanced**	**% of enhancement**
$\mathbf{H_{1}}$ at 4.56 ppm	$\mathbf{H_{2}}$ at 5.81 ppm	**2.25%**
	$\mathbf{H_{1a}}$ at 3.64 ppm	**1.02%**
$\mathbf{H_{1a}}$ at 3.64 ppm	$\mathbf{H_{5}}$ at 4.18 ppm	**3.79%**
	$\mathbf{H_{1b}}$ at 5.12 ppm	**1.45%**
	$\mathbf{H_{1}}$ at 4.55 ppm	**1.10%**
$\mathbf{H_{5}}$ at 4.18 ppm	$\mathbf{H_{4}}$ at 5.09 ppm	**5.66%**
	$\mathbf{H_{1a}}$ at 3.64 ppm	**4.98%**

Table 2. nOe data of major isomer of **33n**

Irradiation of $\mathbf{H_{5}}$ has led to enhancement of peaks belonging to $\mathbf{H_{4}}$ and $\mathbf{H_{1a}}$ by 5.66 % and 4.98 % respectively (**Figure 2.7**) establishing the α-linkage of the newly formed C-C bond in the major isomer.

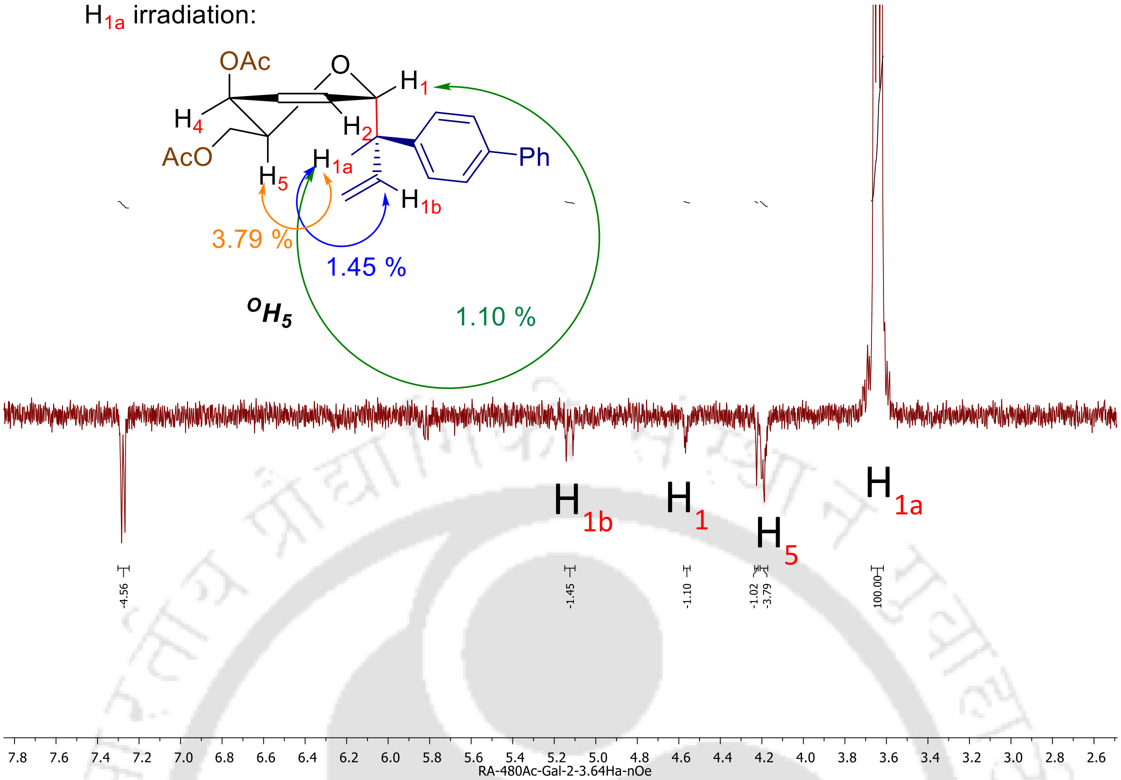


Figure 2.5

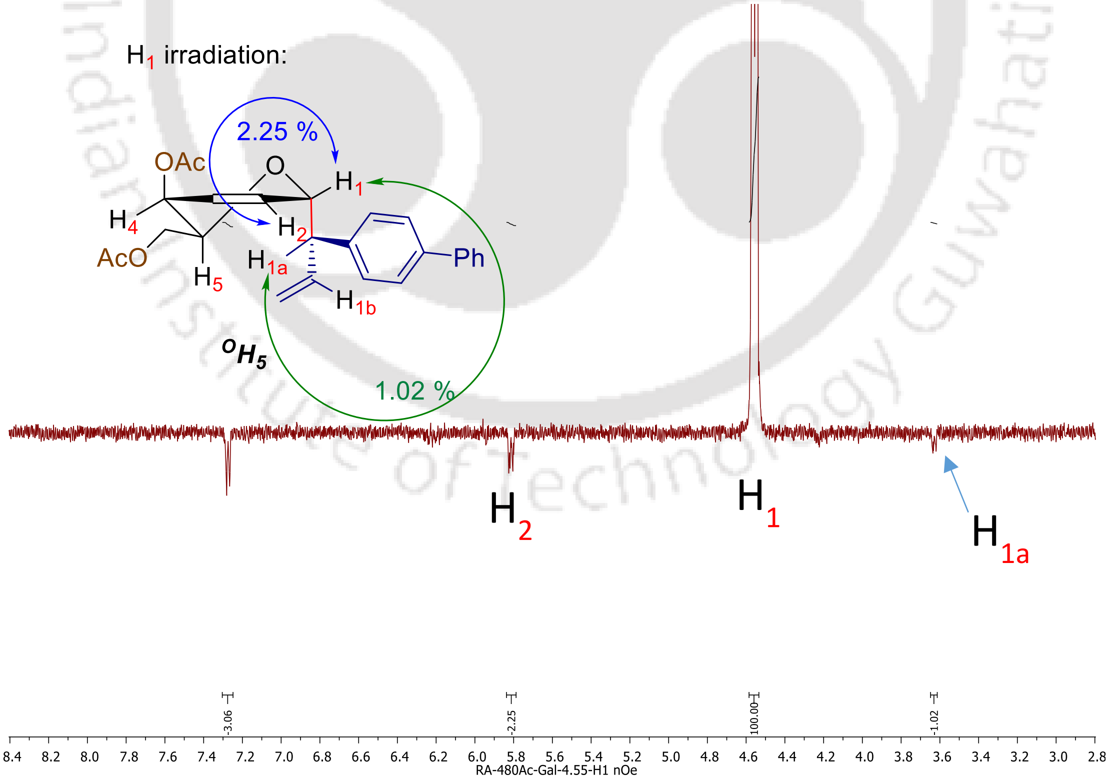


Figure 2.6

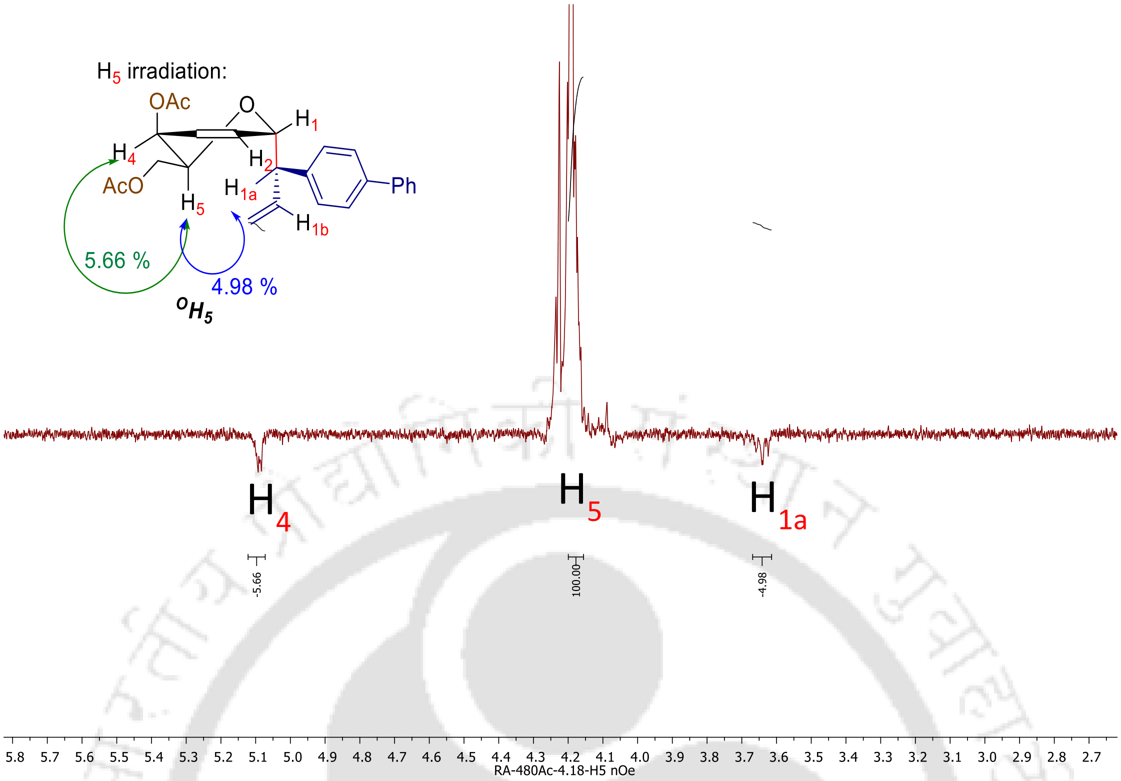


Figure 2.7

nOe of minor isomer of 33n:

nOe Peak irradiated	nOe peak enhanced	% of enhancement
H_1 at 4.63 ppm	**H_{1b}** at 6.04 ppm	**1.35%**
	H_{1a} at 3.69 ppm	**0.99%**
	H_2 at 5.81 ppm	**2.45%**
H_{1a} at 3.69 ppm	**H_1** at 4.63 ppm	**0.90 %**
	H_5 at 4.17 ppm	**3.91%**
	H_{1c} at 5.19 ppm	**1.52%**

Table 2. nOe data of minor isomer of **33n**

To further understand the stereochemistry of the diastereomers, we have performed nOe experiments on minor isomer also. When **H_1** was irradiated, there was enhancement of peak at 5.81 ppm by 2.45 % which corresponds to **H_2** and by 0.99 % enhancement of peak was observed at 3.64 ppm which is the benzylic proton **H_{1a}**. These observations are similar to the enhancements observed with that of the major isomer. In addition, enhancement of peak at 6.04 ppm by 1.35% corresponding to the olefinic proton (**H_{1b}, Figure 2.8**) has been observed.

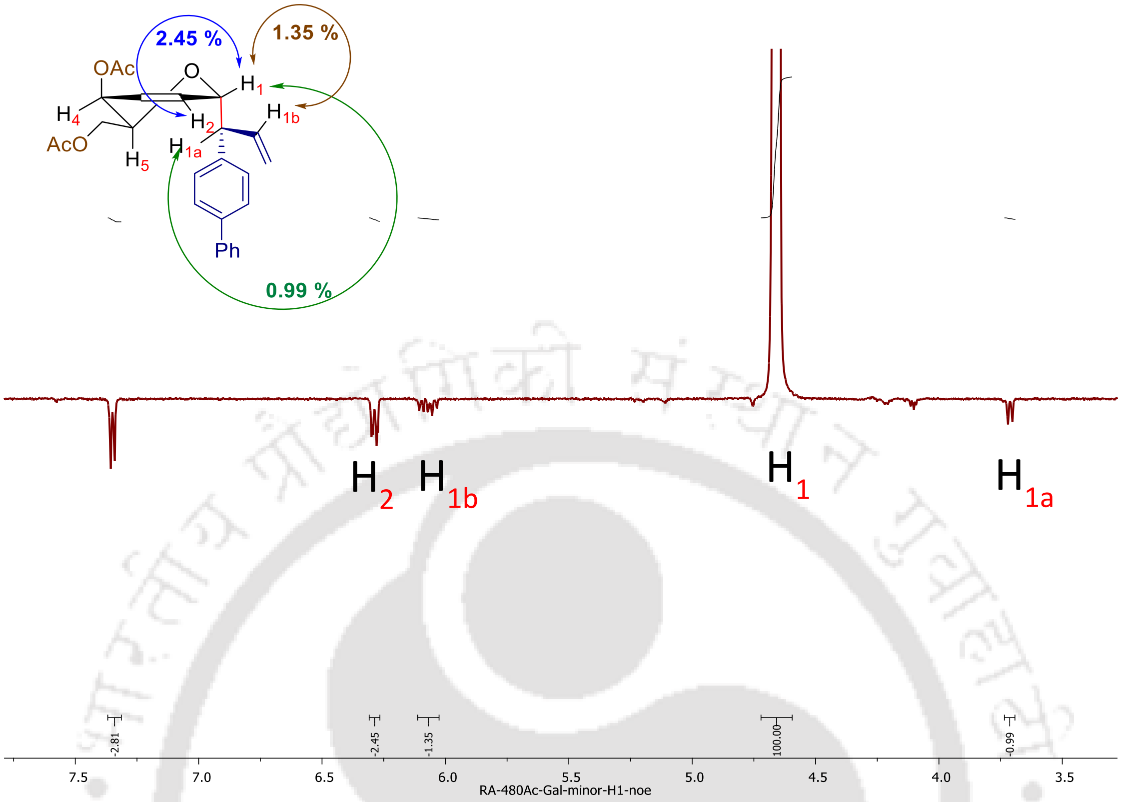


Figure 2.8

When benzylic proton **H_{1a}** was irradiated, there was enhancement of peak at 4.63 ppm by 0.90 % which corresponds to **H_1** and by 3.91 % enhancement of peak was observed at 4.17 ppm which is the **H_5**. These observations are similar to the enhancements observed with that of the major isomer. In addition, enhancement of peak at 5.19 ppm by 1.52% corresponding to the olefinic proton (**H_{1c}, Figure 2.9**) has been observed.

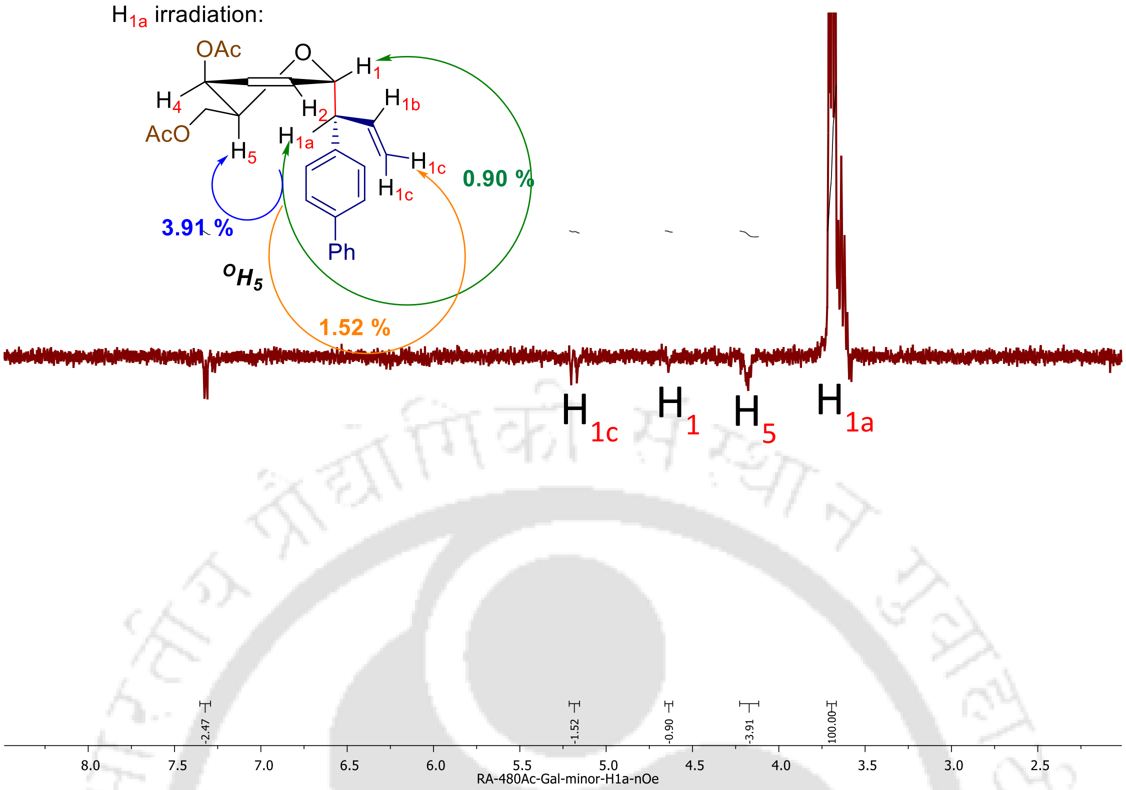


Figure 2.9

Major isomer	Minor isomer	Merged peaks
5.81 (d, J = 10.4 Hz, 1H(, (**H$_2$**)		6.27 – 6.18 (m, 2H(**H$_{1b(major)}$, H$_{2(minor)}$**
4.56 (d, J = 9.3 Hz, 1H) **H$_1$**	4.63 (d, J = 9.1 Hz, 1H(**H$_1$**	
3.64 (t, J = 8.7 Hz, 1H) **H$_{1a}$**	3.69 (t, J = 9.1 Hz, 1H) **H$_{1a}$**	
5.12 (d, J = 17.1 Hz, 1H(, **(H$_{1c\ or\ 1c'}$)**		5.22 – 5.16 (m, 3H(**(H$_{1c,c'}$)**
5.99 – 5.93 (m, 1H(**(H$_3$)**		6.08 – 6.00 (m, 2H(**H$_{1b(\ minor\ )}$, H$_{3(minor)}$**
4.26 – 4.21 (m, 2H), **H$_{6,6'}$**	4.10 – 4.04 (m, 2H) **H$_{6,6'}$**	5.09 (m, 2H), **H$_4$**
2.08 (s, 3H), 2.07 (s, 3H) **CH3 (AcO-)**	2.05 (s, 3H), 1.86 (s, 3H). **CH3 (AcO-)**	4.21 – 4.15 (m, 2H) **H$_5$**

Table 2.3 Coupling Constants of **33n**

The coupling constant for **H**$_{1a}$ of both major and minor diastereomers is similar, i.e., 8.7 Hz and 9.1 Hz respectively, suggesting that the dihedral angle between **H**$_{1}$ and **H**$_{1a}$ is about the same. Also, irradiation of **H**$_{1a}$ in both major and minor isomer resulted in the enhancement of **H**$_{5}$ proton indicating the α-linkage of the newly formed anomeric C-C bond in both the isomers. In addition, when **H**$_{1}$ was irradiated, mild enhancement of the vinylic proton (**H**$_{1b}$) has been observed in the minor isomer whereas such enhancement was not observed in the major isomer. Based on all the above data from nOe experiments and the coupling constants, though, inconclusive, we speculate that the major isomer is anti and the minor isomer is syn.

2.8.2 nOe experiments of 33u

The nOe experiment has given a supporting data for the attributed stereochemistry. When **H**$_{5}$ was irradiated (3.78 ppm), there was enhancement of peak at 4.85 ppm by 2.75 % which corresponds to **H**$_{1}$ and by 0.53 % enhancement of peak was observed at 5.29 ppm which correspomds to **H**$_{4}$. There was also enhancement observed at 4.15-4.19 ppm by 2.57% which corresponds to **H**$_{6,6'}$ (**Figure 2.10**).

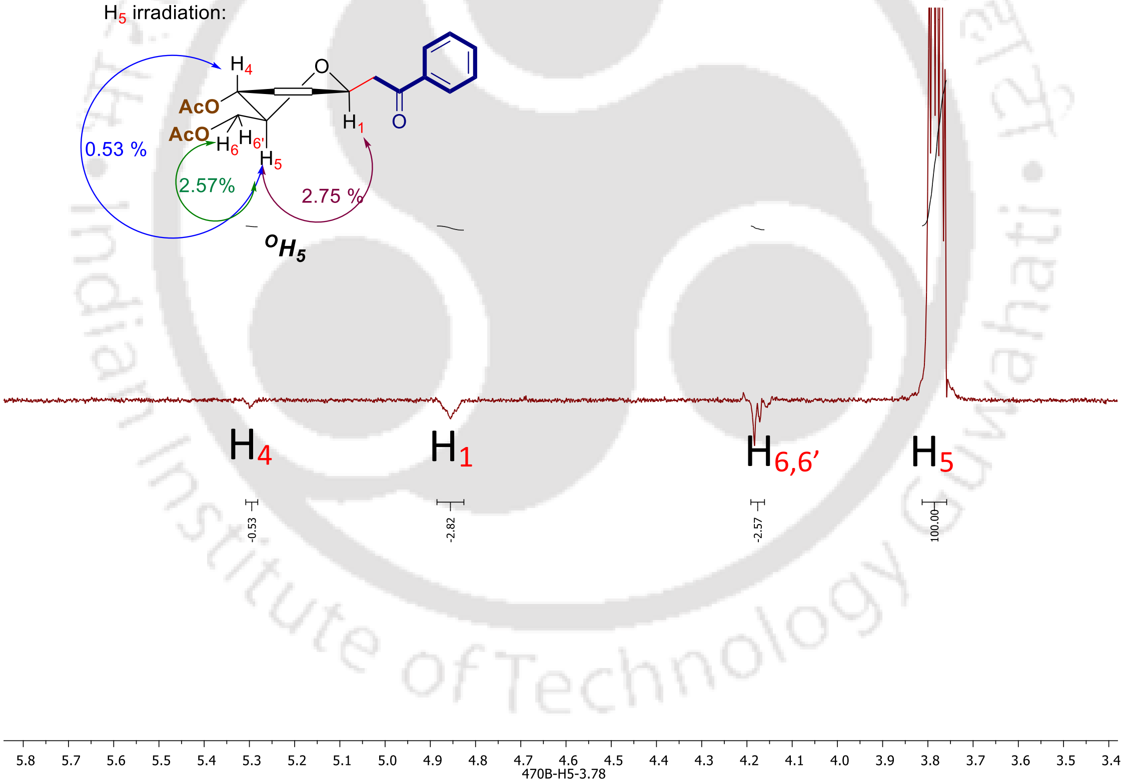


Figure 2.10

When **H**$_{1}$ was irradiated, there was enhancement by 2.7 % of peak at 3.78 ppm (**H**$_{5}$) and by 3.79 % which corresponds to **H**$_{5}$ and by 1.35 and 1.03 % enhancement of peaks was observed at 3.39 and 3.07 ppm which corresponds to **H**$_{1a,1a'}$ peak. There was also observed an enhancement of peak corresponding to **H**$_{3}$ at 5.99 ppm by 1.29 % (**Figure 2.11**). All these observations made and based on the literature report for the corresponding *α*-isomer of the same compound, it was confirmed

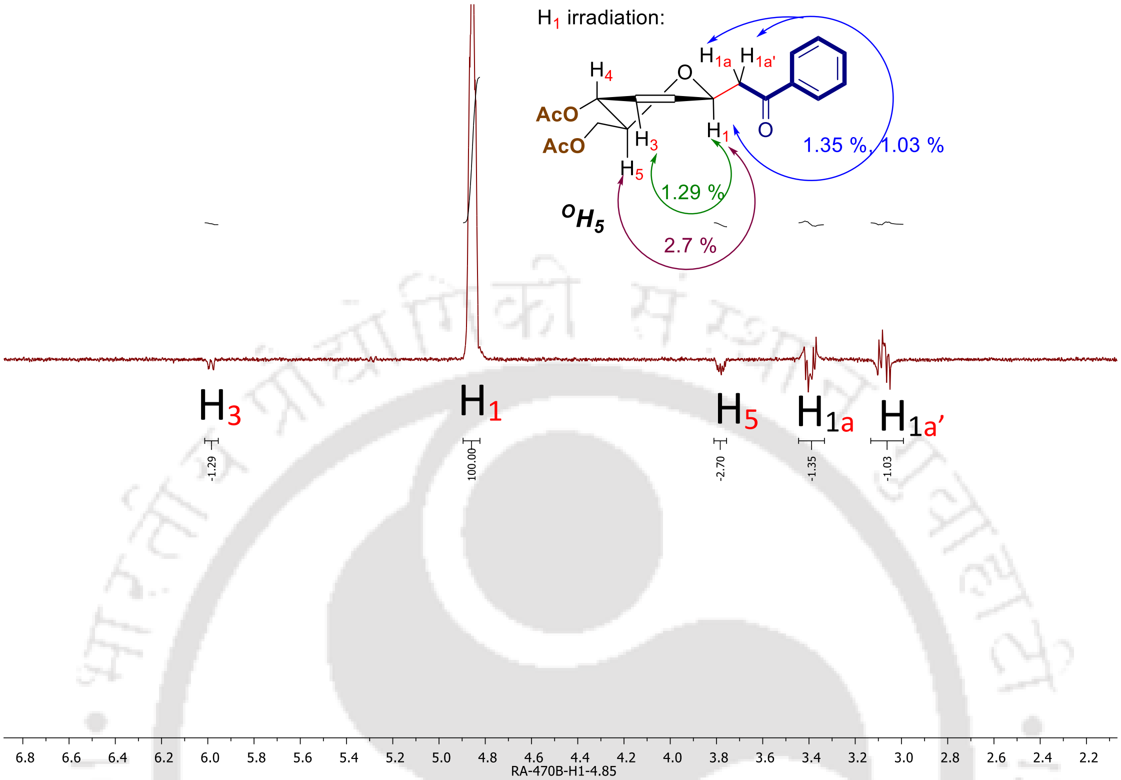
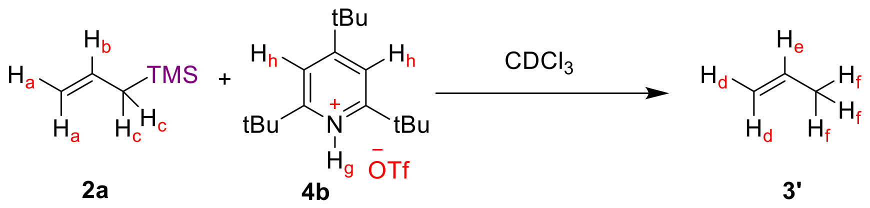

H1 irradiation:
H1a
H1a'
H4
O
AcO
AcO
H3
H1
O
H5
OH5
1.35 %, 1.03 %
1.29 %
2.7 %
H3
H1
H5
H1a
H1a'
-1.29
100.00
-2.70
-1.35
-1.03
6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2
RA-470B-H1-4.85

Figure 2.11

2.9. Mechanistic study: Spectral data



Scheme 18

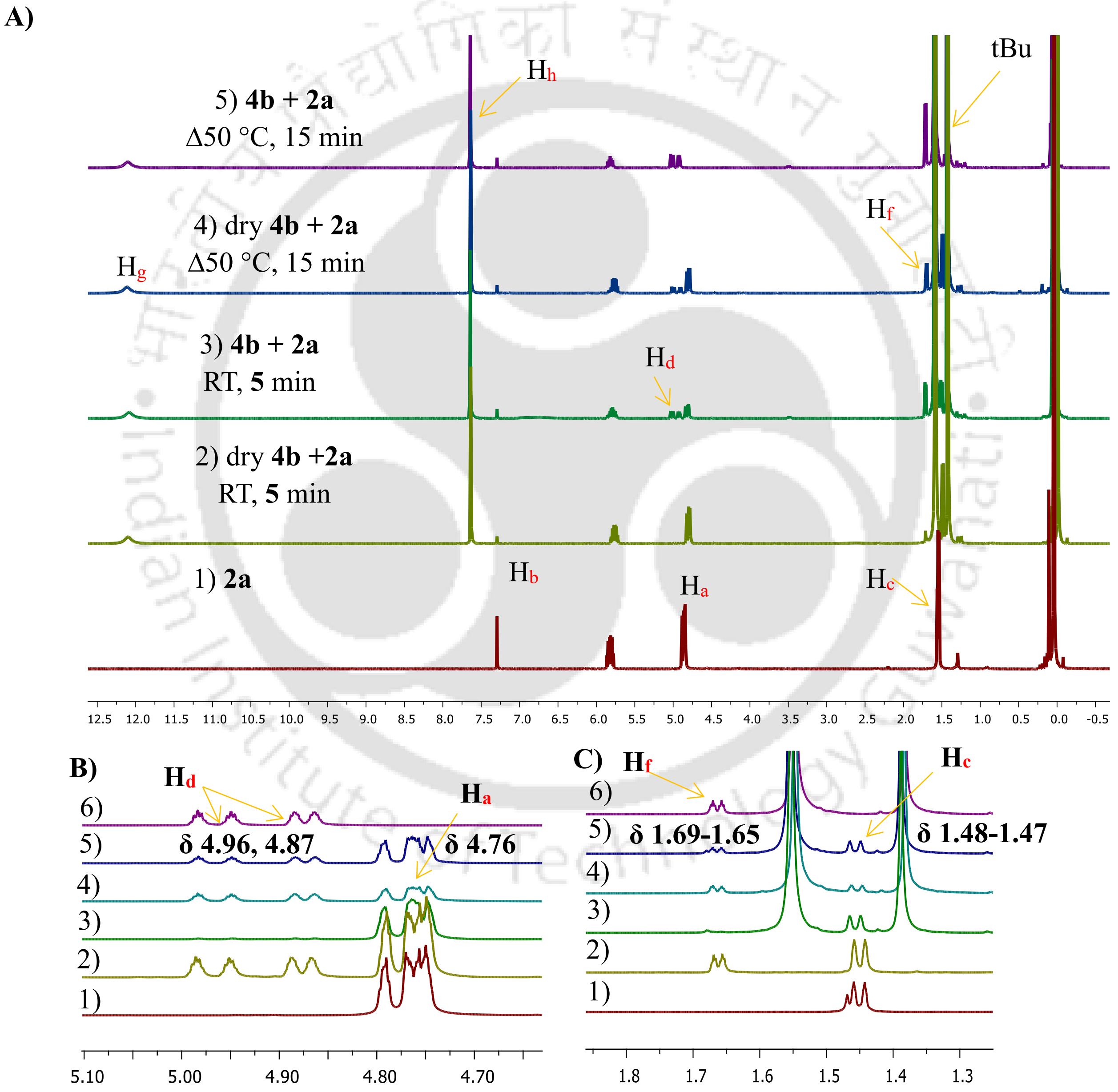
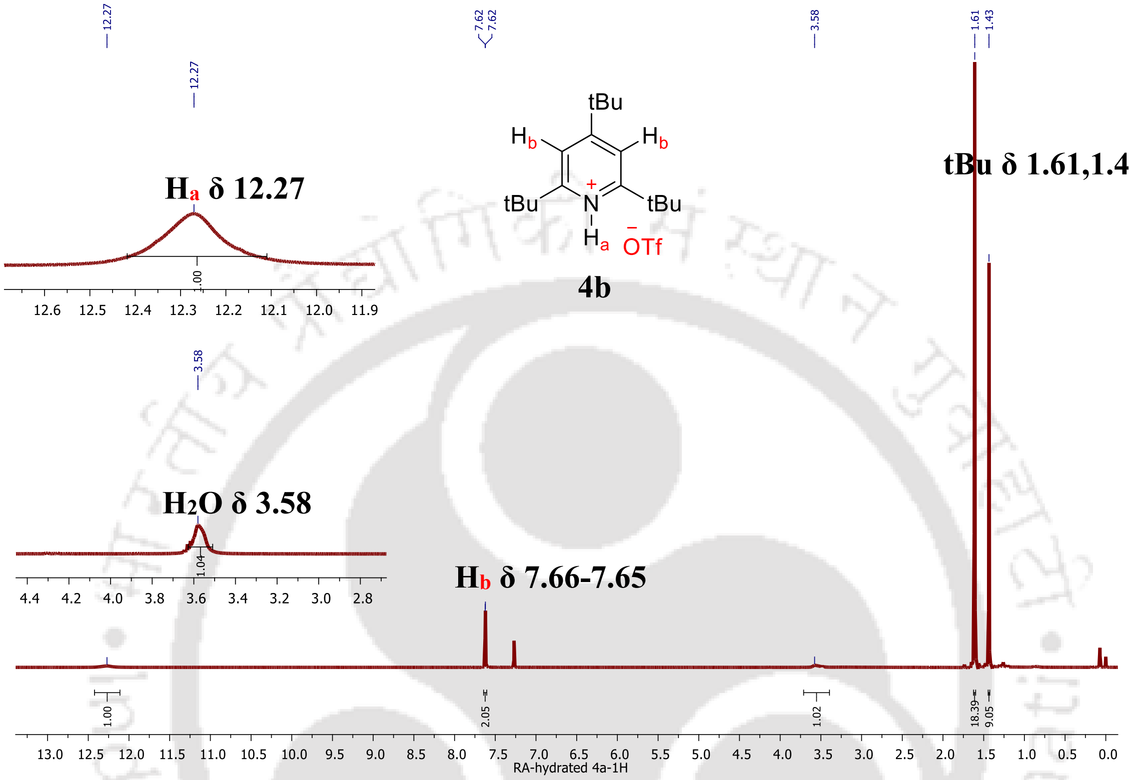
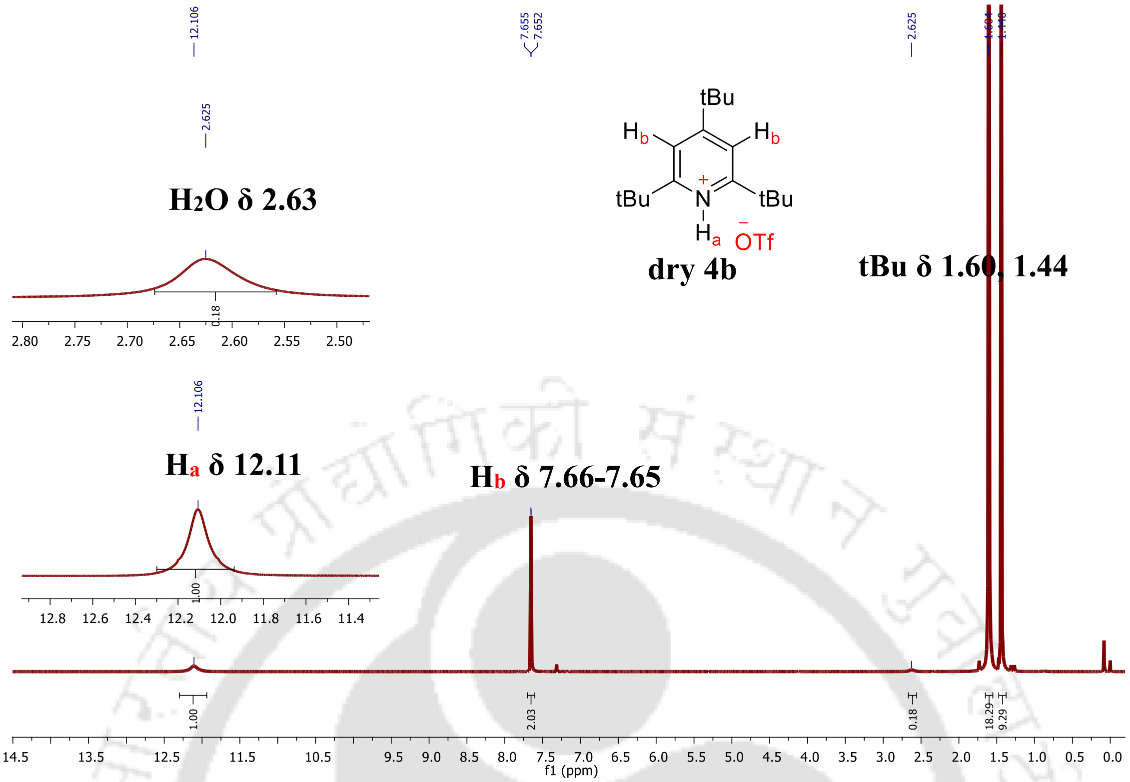


Figure 2.12: A) Investigation of the mechanism. 1) ^{1}H NMR of trimethylallylsilane (**2a**). 2) ^{1}H NMR of **2a** and dry **4b** (1:1 equiv.) in 500 μL of $CDCl_3$ (0.05 M) at room temperature after 5 min. 3) ^{1}H NMR of **2a** and **4b** (1:1 equiv.) in 500 μL of $CDCl_3$ (0.05 M) at room temperature after 5 min. 4) ^{1}H NMR of **2a** and

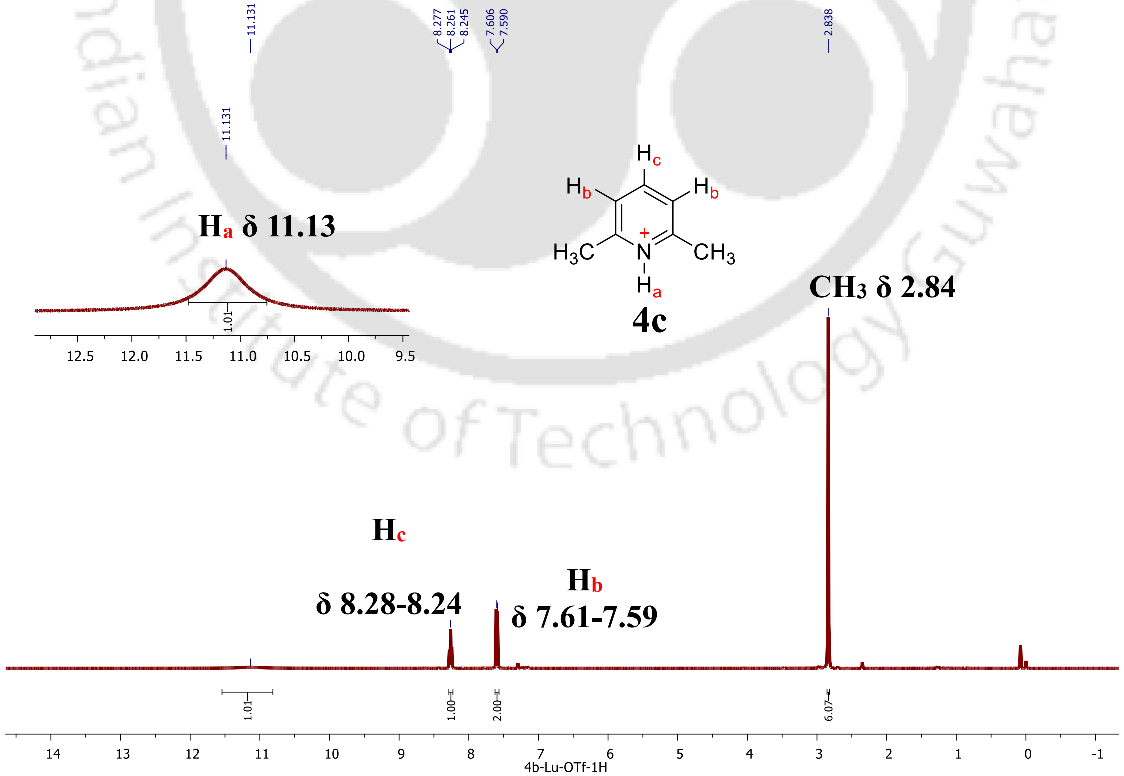
dry **4b** (1:1 equiv.) after heating at 50 °C for 15 min. 5) ^{1}H NMR of **2a** and **4b** (1:1 equiv.) after heating at 50 °C for 15 min. B) Expanded spectra showing H_d and H_a confirming the formation of Propene (**3'**) from **2a**. C) Expanded spectra showing H_f and H_c confirming the formation of Propene (**3'**) from **2a**.*In the case of dry **4b**, reaction doesn't proceed any further, the conversion happened was due to the traces of moisture present with the catalyst (check the NMR spectrum of dry **4b)**.



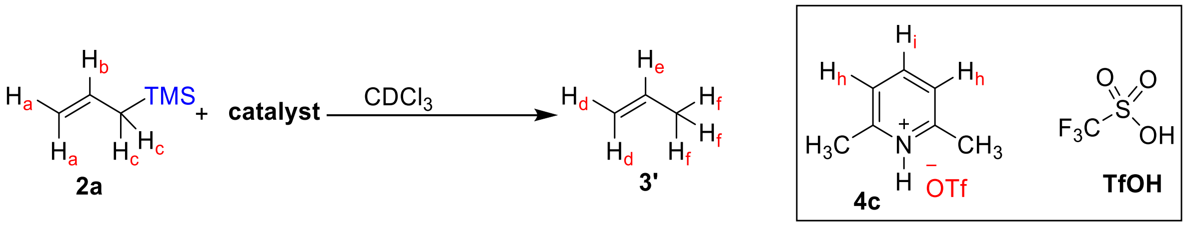
^{1}H-NMR spectrum of **4b**



^{1}H-NMR spectrum of dry **4b** (with trace quantity of trapped H_2O)



^{1}H-NMR spectrum of **4c**



Scheme 19

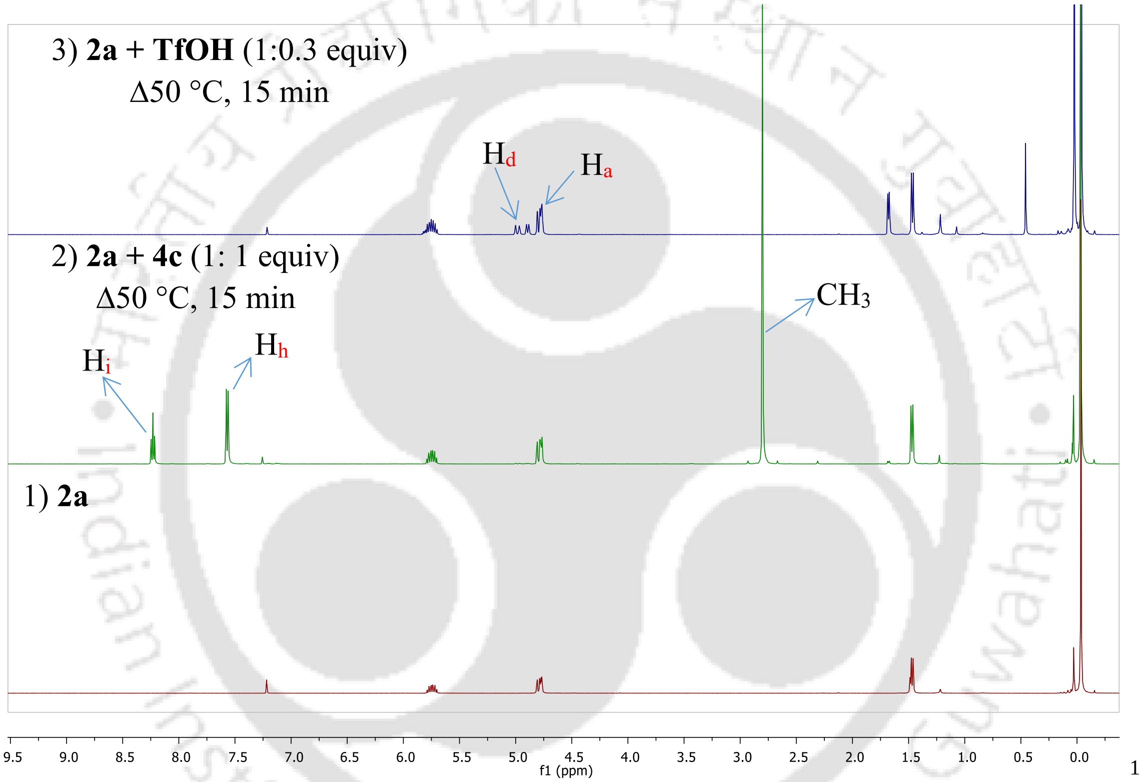
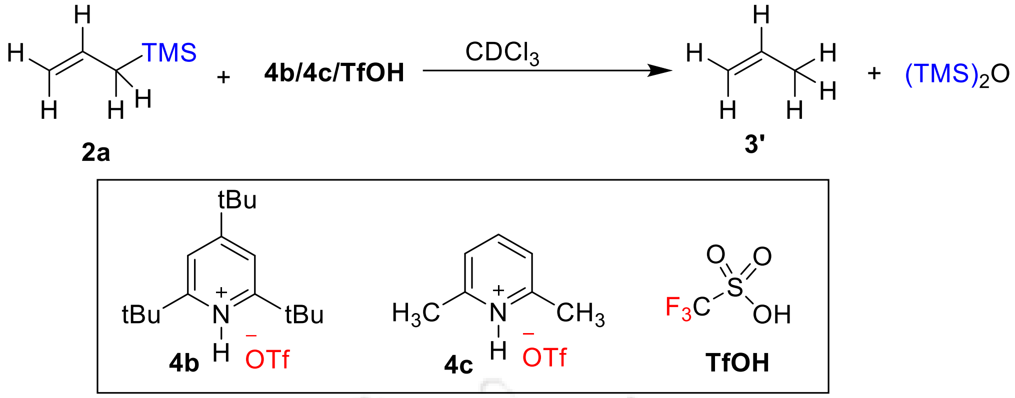


Figure 2.13: ^{1}H NMR spectra of **2a** and reaction mixtures (**Scheme 19**) 1) ^{1}H NMR of trimethylallylsilane (**2a**). 2) ^{1}H NMR of **2a** and **4c** (1:1 ratio) in 500 μL of $CDCl_3$ (0.05 M) after heating at 50 °C for 15 min. 3) ^{1}H NMR of **2a** and **TfOH** (1:0.3 ratio) in 500 μL of $CDCl_3$ (0.05 M) after heating at 50 °C for 15 min. (There was no progress observed after heating these reaction mixtures overnight.)



Scheme 20

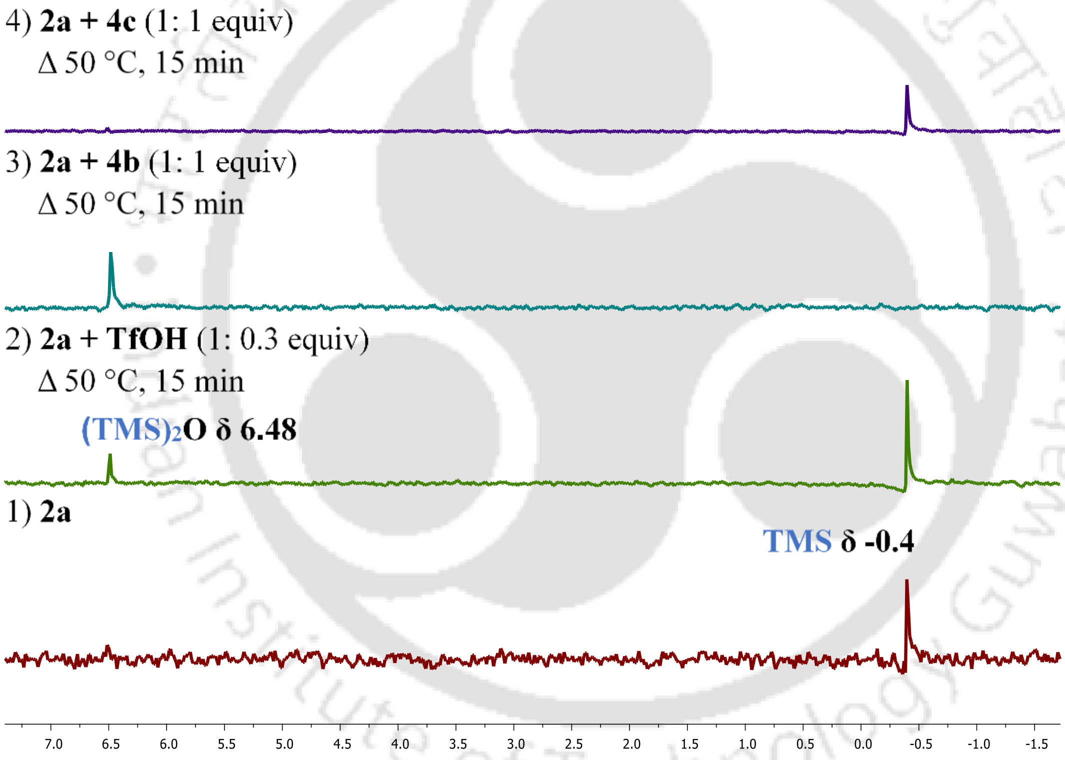
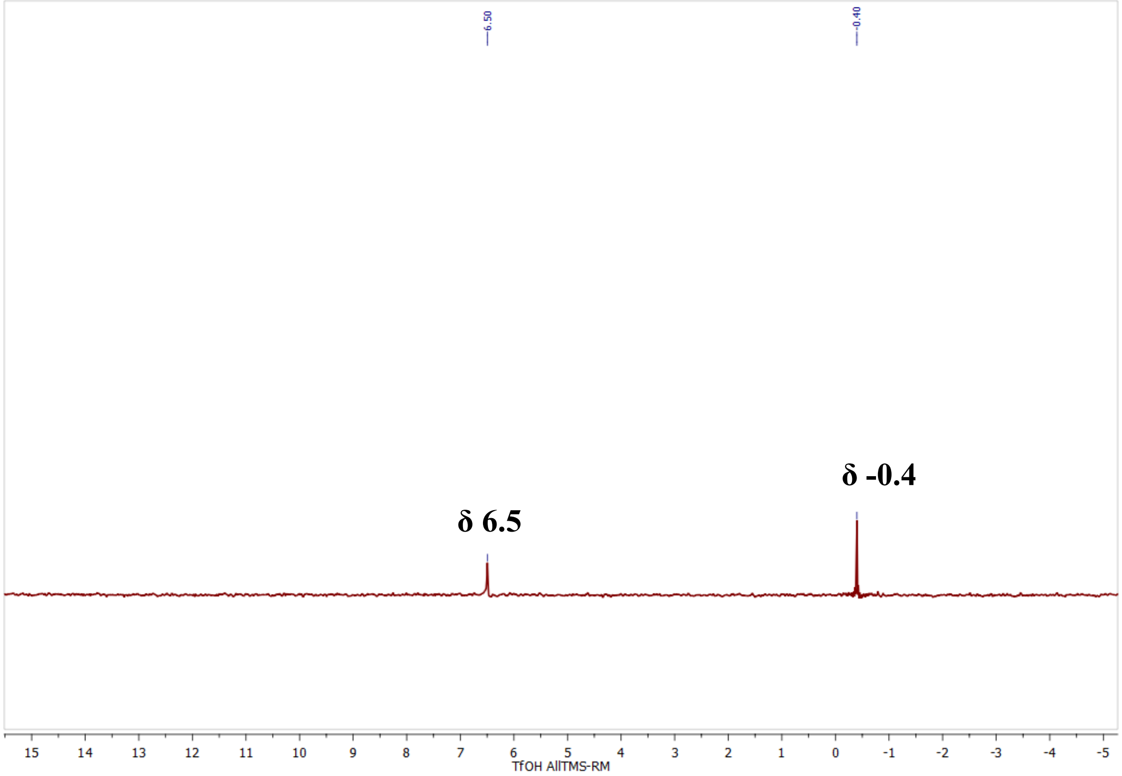
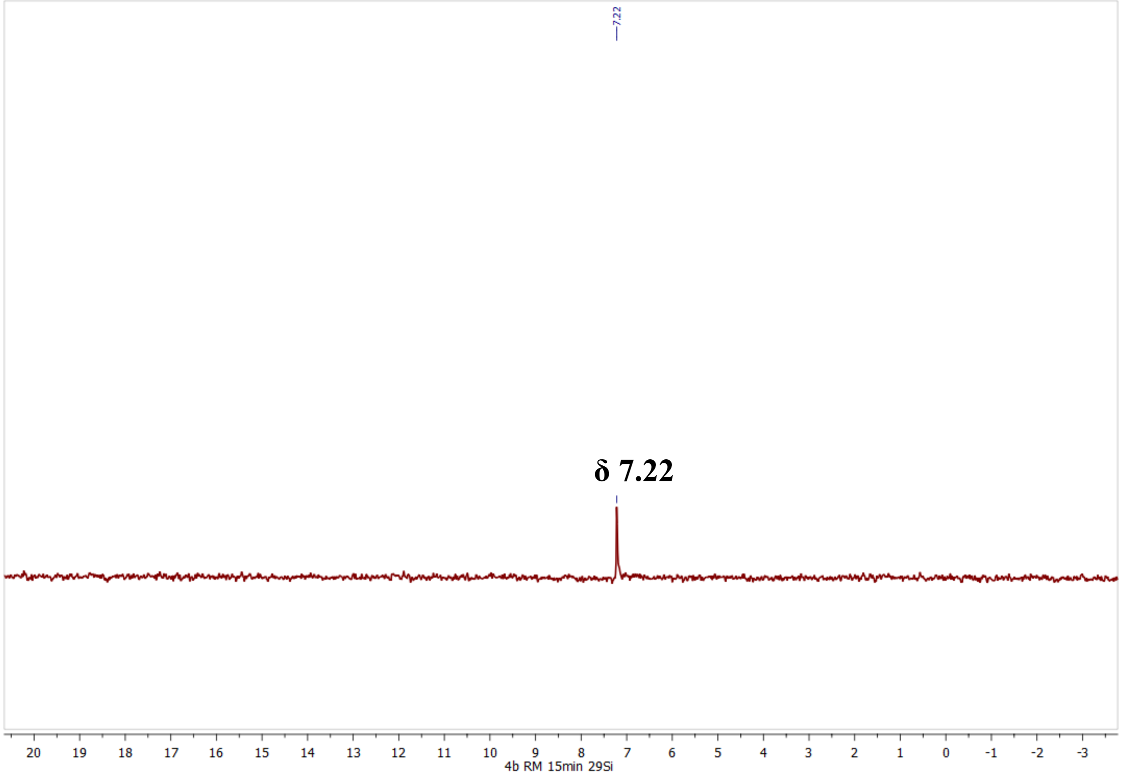


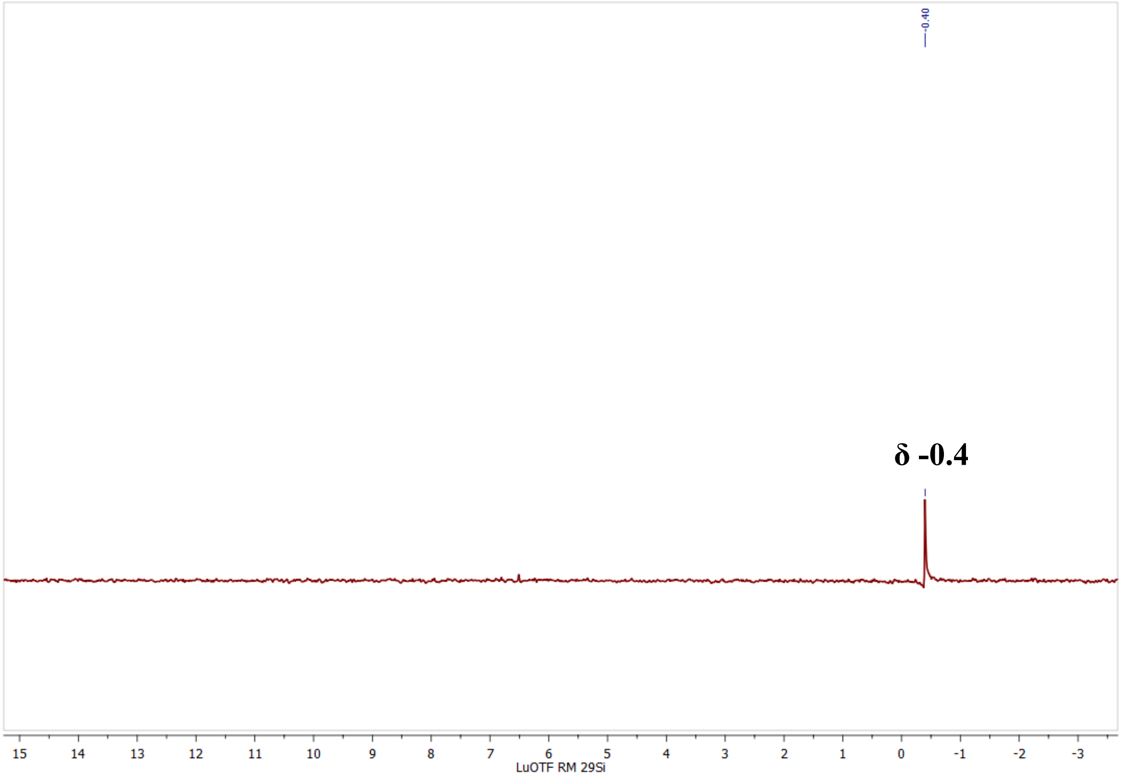
Figure 2.14: ^{29}Si NMR spectra of **2a** and reaction mixtures (**Scheme 20**) 1) ^{29}Si NMR of trimethylallylsilane (**2a**). 2) ^{29}Si NMR of **2a** and **TfOH** (1:0.3 ratio) in 500 µL of $CDCl_3$ (0.05 M) after heating at 50 °C for 15 min. 3) ^{29}Si NMR of **2a** and **4b** (1:1 ratio) in 500 µL of $CDCl_3$ (0.05 M) after heating at 50 °C for 15 min. 4) ^{29}Si NMR of **2a** and **4c** (1:1 ratio) in 500 µL of $CDCl_3$ (0.05 M) after heating at 50 °C for 15 min.



^{29}Si NMR of **2a** and **TfOH** (1:0.3 ratio) CDCl$_3$ (0.5M) (**Scheme 20**)



^{29}Si NMR of **2a** and **4b** (1:1 ratio) CDCl$_3$ (0.5M) (**Scheme 20**)



^{29}Si NMR of **2a** and **4c** (1:1 ratio) CDCl$_3$ (0.5M) (**Scheme 20**)

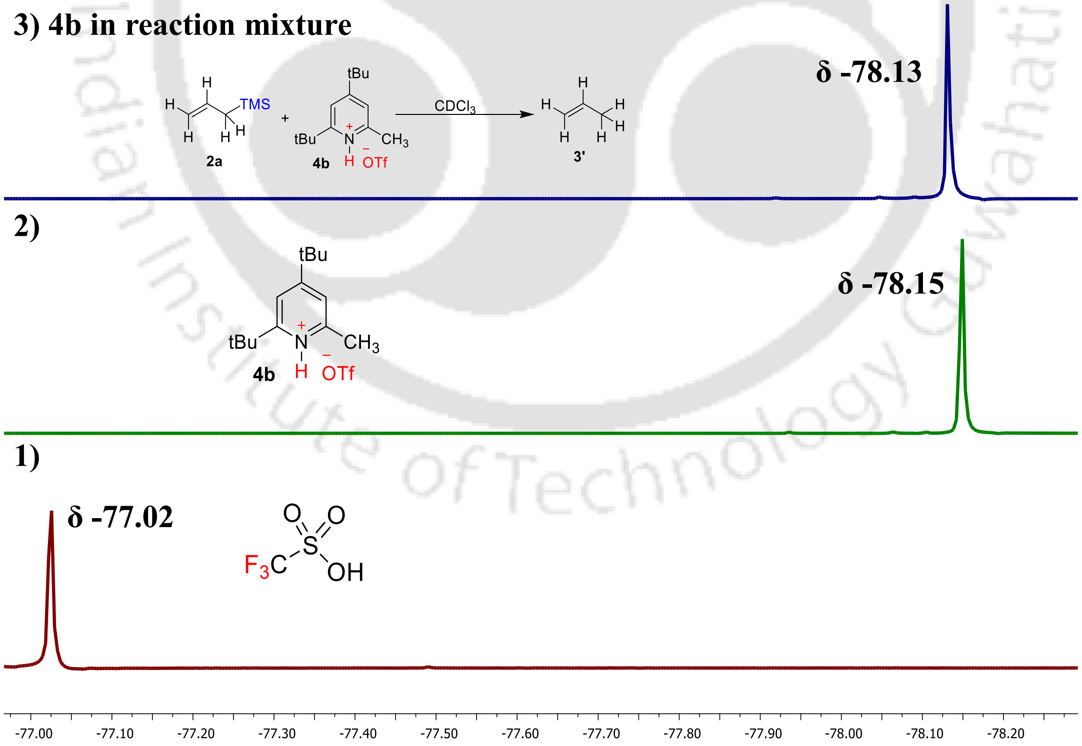
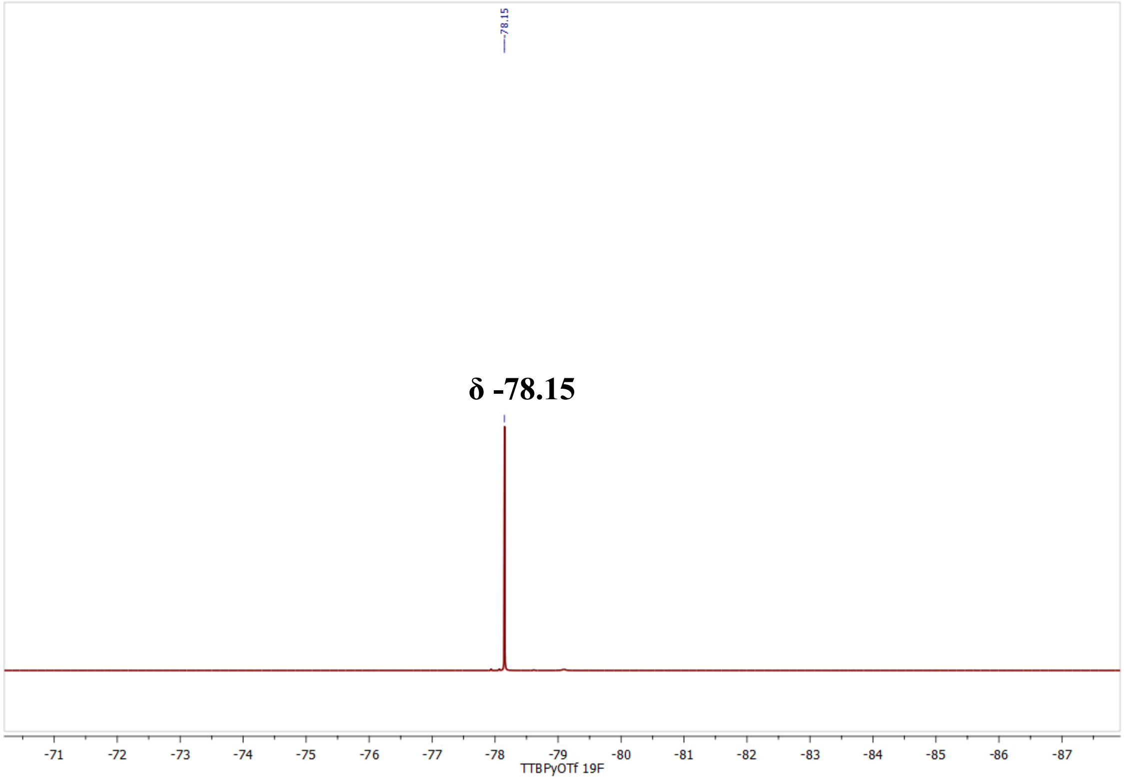
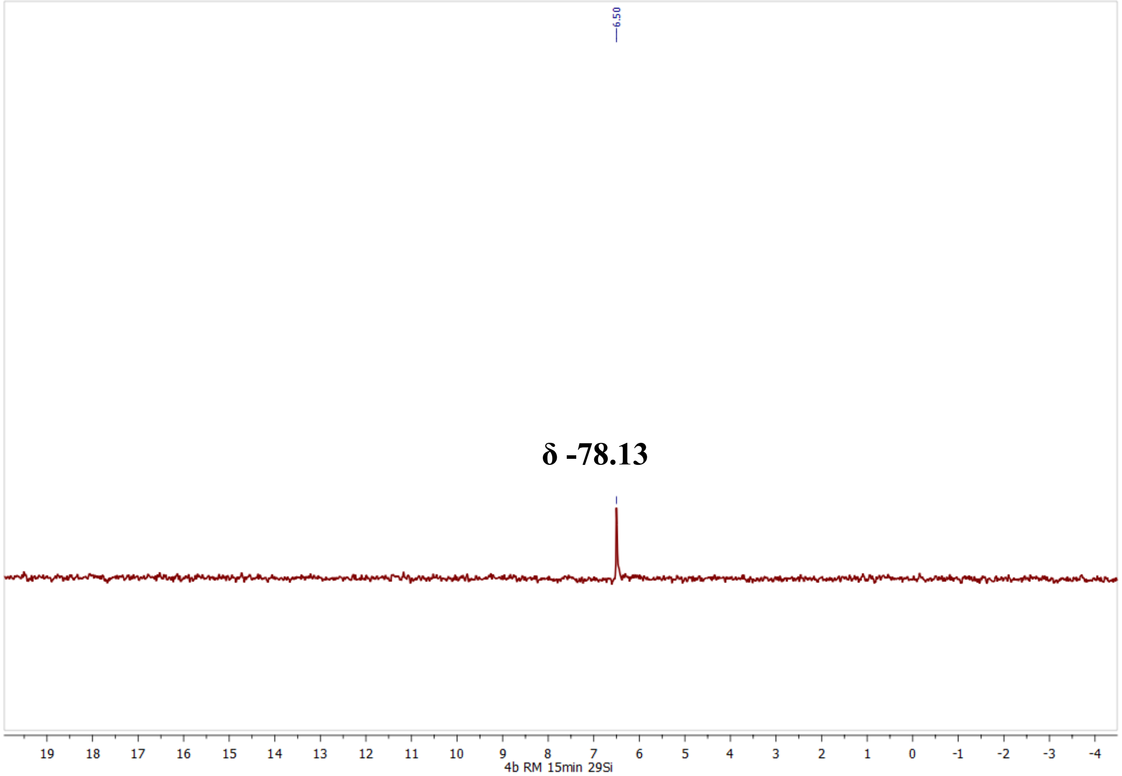


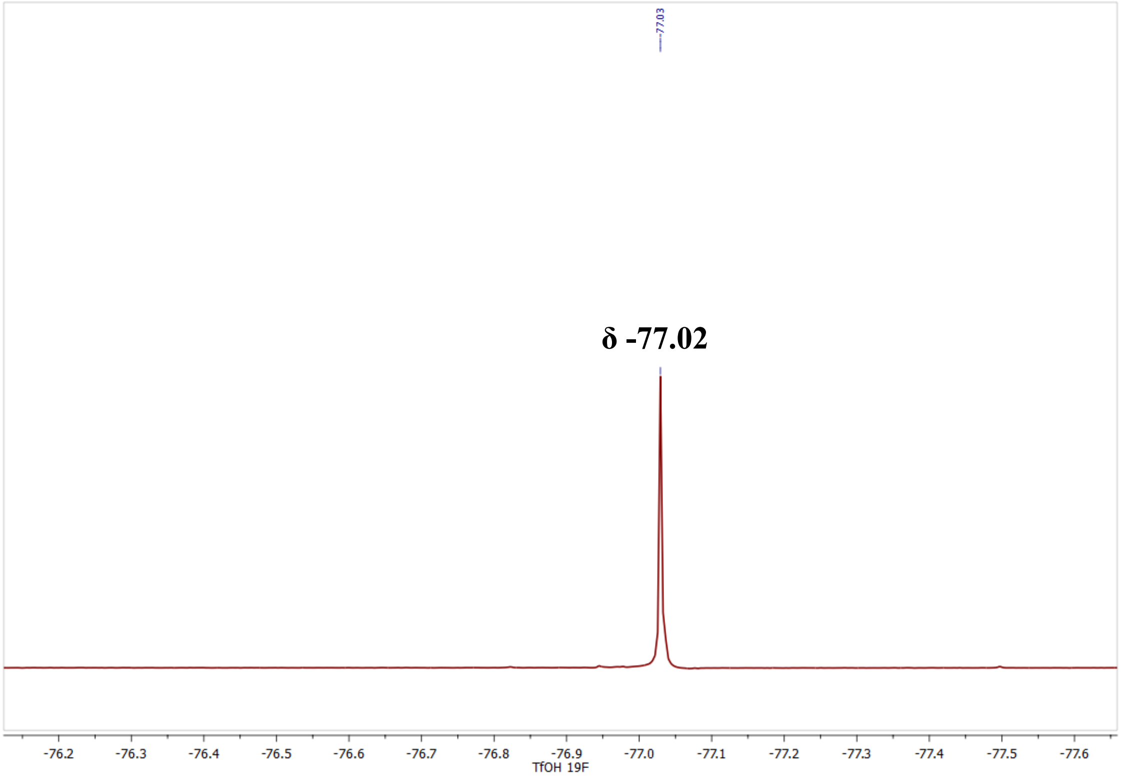
Figure 2.15: ^{19}F-NMR spectra of the TfOH and 4b and 4b in reaction mixture 1) ^{19}F-NMR of TfOH 2) ^{19}F-NMR of 4b. 3) ^{19}F-NMR of 4b in reaction mixture (0.05 M in CDCl$_3$).



^{19}F-NMR of **4b**



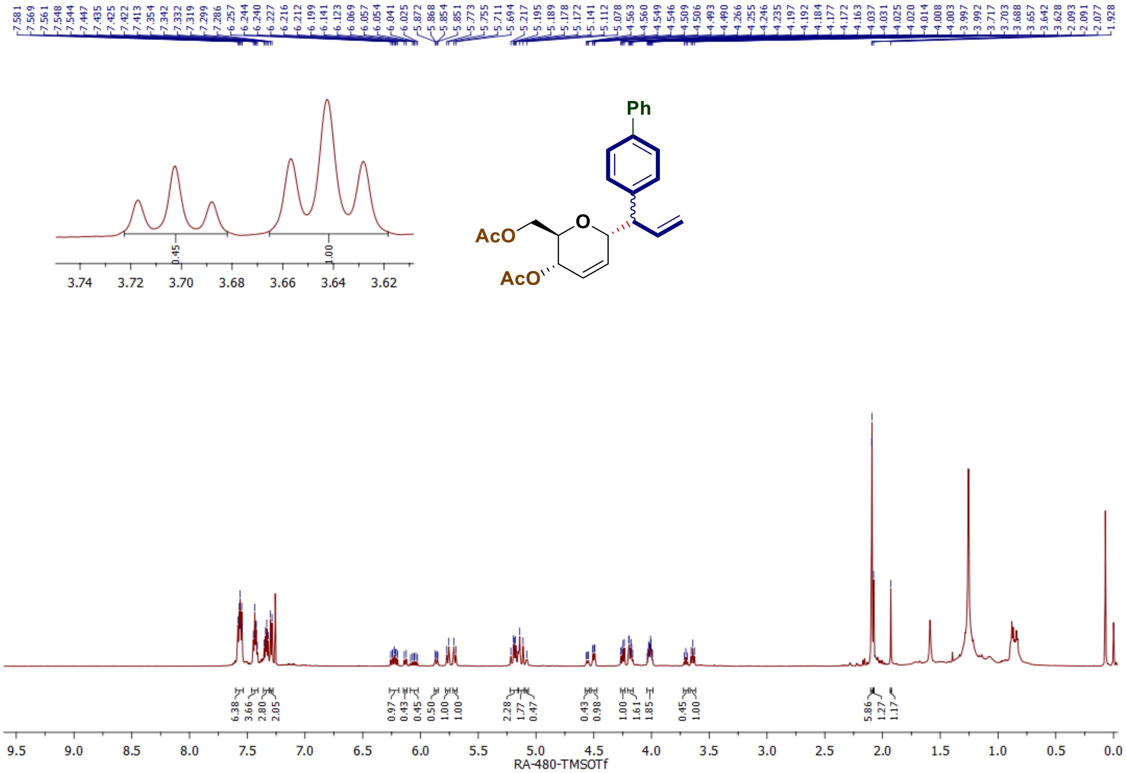
^{19}F-NMR of **4b** in reaction mixture (0.05 M in $CDCl_3$)



^{19}F-NMR of **TfOH**

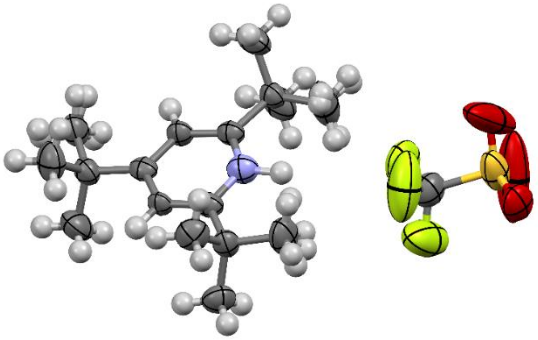
TMSOTf as catalyst:

Inorder to understand the reactivity and selectivity provided by TMSOTf in comparison with our catalyst **4b**, one of the substrates (**33r**) has been synthesised using 5mol% of TMSOTf. This has lead to a decreased yield. Both tri-OAc-glucal (**32a**) (49.1 mg, 0.18 mmol) and **2d** (72.2 mg, 0.27 mmol) were taken in a vial with CH_2Cl_2 as solvent and were added 5 mol% TMSOTf at 0 °C. The reaction mixture was stirred for completion yielding **33r** (27 mg, 37 %, 69:31). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 – 7.53 (m, 7H), 7.46 – 7.40 (m, 4H), 7.37 – 7.31 (m, 3H), 7.29 (d, J = 8.1 Hz, 2H), 7.31 – 7.28 (2H), 6.27 – 6.19 (m, 1H), 6.13 (d, J = 10.5 Hz, 1H), 6.09 – 6.02 (m, 1H), 5.89 – 5.83 (m, 1H), 5.76 (d, J = 10.5 Hz, 1H), 5.70 (d, J = 10.5 Hz, 1H), 5.23 – 5.15 (m, 1H), 5.16 –5.11 (m, 1H), 5.09– 5.07 (m, 1H), 4.55 (dd, J = 8.7, 2.0 Hz, 1H), 4.50 (dd, J = 9.2, 1.8 Hz, 1H), 4.25 (dd, J = 11.9, 6.7 Hz, 1H), 4.21 – 4.15 (m, 1H), 4.01 (ddt, J = 13.3, 7.0, 3.3 Hz, 1H), 3.70 (t, J = 8.7 Hz, 1H), 3.64 (t, J = 8.6 Hz, 1H), 2.09 (d, J = 1.2 Hz, 1H), 2.10– 2.08 (m, 3H), 1.93 (s, 3H).



^{1}H NMR spectrum of **33r** (from TMSOTf catalysis), (600 MHz, $CDCl_3$)

2.10 Crystal data of 4b



Bond precision: C-C = 0.0091 A Wavelength=0.71073

Crystal system:	Orthorhombic		
Cell:	a=20.0174(12)	b=9.2308(6)	c=11.5941(7)
	alpha=90	beta=90	gamma=90
Temperature:	273 K		
	Calculated		Reported
Volume	2142.3(2)		2142.3(2)
Space group	P n m a		P n m a
Hall group	-P 2ac 2n		-P 2ac 2n
Moiety formula	C17 H30 N, C F3 O3 S		?
Sum formula	C18 H30 F3 N O3 S		C18 H30 F3 N O3 S
Mr	397.49		397.49
Dx,g cm-3	1.232		1.232
Z	4		4
Mu (mm-1)	0.192		0.192
F000	848.0		848.0
F000’	848.99		
h,k,lmax	22,10,12		21,10,12
Nref	1608		1510
Tmin,Tmax			
Tmin’			

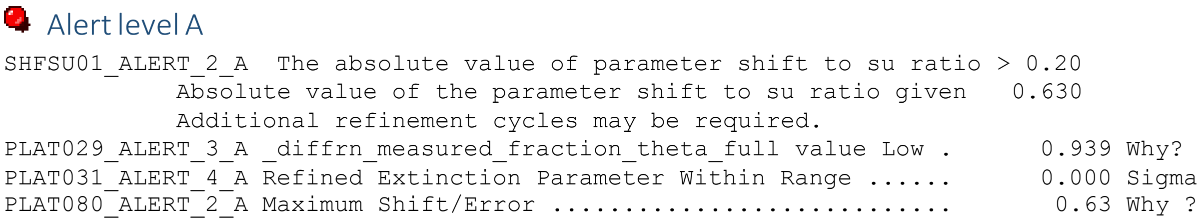
Correction method= Not given

Data completeness= 0.939 Theta(max)= 23.032

R(reflections)= 0.0998(1258)

wR2(reflections)= 0.2275 (1510)

S = 1.158 Npar= 152



Alert level A

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SHFSU01_ALERT_2_A  The absolute value of parameter shift to su ratio > 0.20
            Absolute value of the parameter shift to su ratio given   0.630
            Additional refinement cycles may be required.
PLAT029_ALERT_3_A _diffrn_measured_fraction_theta_full value Low .      0.939 Why?
PLAT031_ALERT_4_A Refined Extinction Parameter Within Range ......      0.000 Sigma
PLAT080_ALERT_2_A Maximum Shift/Error ...........................        0.63 Why ?
```

Author's response:

The crystal quality was poor. The crystal was grown by multiple times in different possible ways but it didn't serve for data collection, but the reported data is the best than other collected data. These alerts are shown owing to the disorder arises due to the equal distribution hydrogen atoms of tert-butyl groups in two places in space (space group= Pnma).

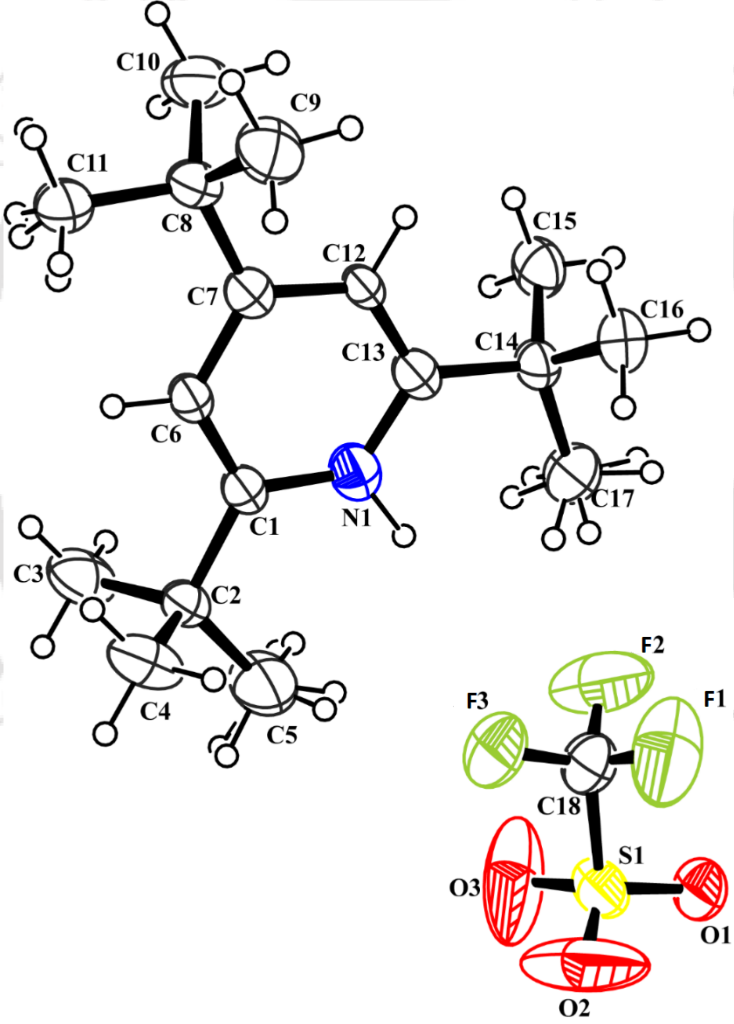
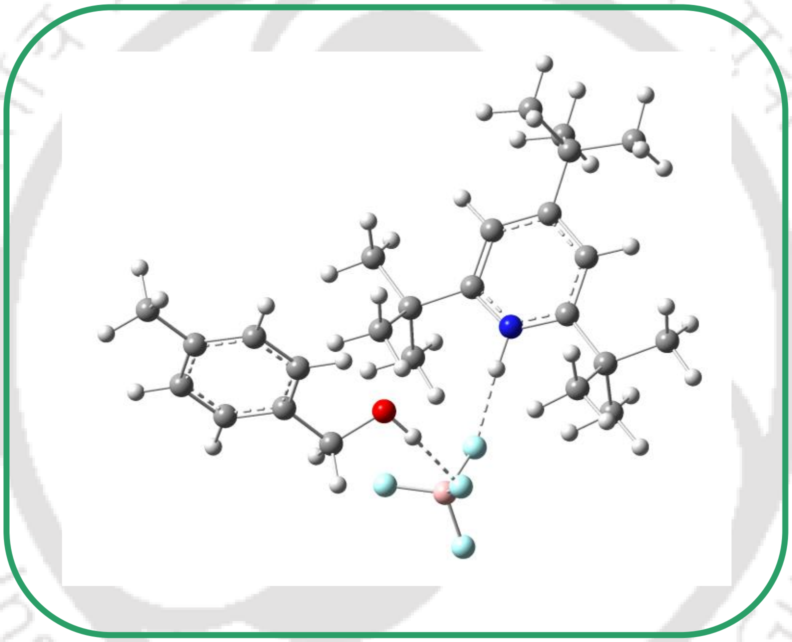


Figure 2.16: ORTEP view of **4b**. The thermal ellipsoid contour probability level is 35%.

Chapter III

Exploiting the Strained Ion-Pair Interactions of Sterically Hindered Pyridinium Salts Toward S_N2 Glycosylation of Glycosyl Trichloroacetimidates



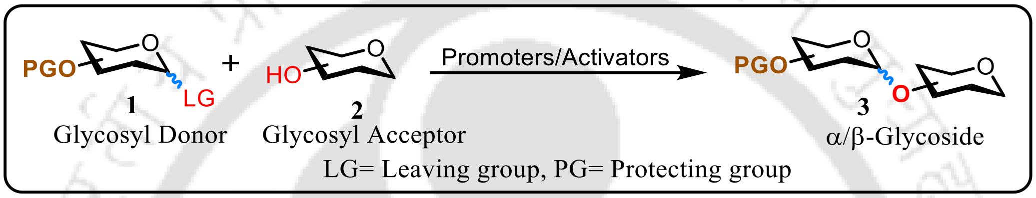
This Chapter was published in *J. Org. Chem.* **2024**, 89, *6*, 3713–3725.

Exploiting the Strained Ion-Pair Interactions of Sterically Hindered Pyridinium Salts Toward S_N2 Glycosylation of Glycosyl Trichloroacetimidates

3.1 Introduction

3.1.1 Glycosylation

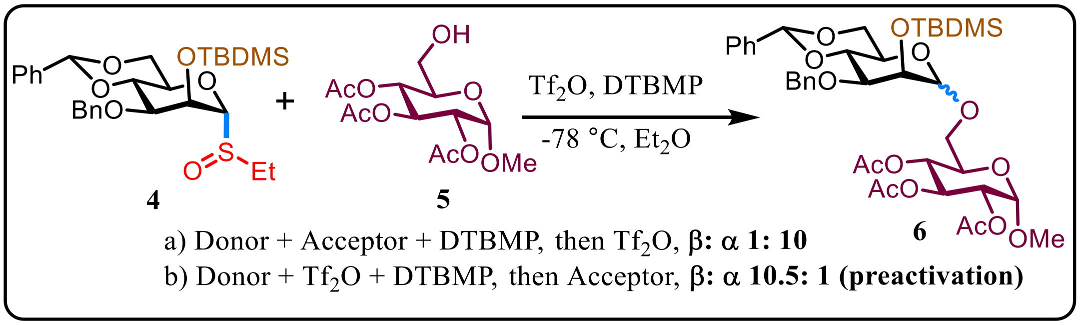
Glycosylation is an important modification where a glycosyl donor (glycan) unit is attached to an acceptor through an anomeric bond to form glycoconjugate. As one of the most abundant biopolymers, oligosaccharides are part of several biochemical processes and are important in therapeutic applications.[1] Chemical glycosylation occupies a great role in the discovery of Carbohydrate chemistry since it is the prevailing reaction by which complex carbohydrates like glycolipids, and glycoproteins are linked (**Scheme 1**).[1c]



Scheme 1. General Glycosylation reaction

3.1.2 Literature review

The critical part of glycosylation is in achieving the targeted stereochemistry of the glycosidic linkage. Premixing of glycosyl donor and acceptor followed by the addition of activators/promoters is the typical protocol for glycosylation. In this conventional pathway, several factors like stereo, electronic effects, and protecting groups are crucial in deciding the stereochemical outcome and usually give unfavorable results. To overcome this problem, a concept called "preactivation" was introduced which helped in achieving stereoselectivity efficiently. This was first observed by Crich and coworkers in 1996 and they successfully achieved the most challenging β-mannosides efficiently (**Scheme 2**).[2] The donor preactivation-based glycosylation is conducted through the complete activation of the donor in the presence of promoters to form reactive intermediates well before the addition of the acceptor. Individually, several groups worked on this preactivation concept and successfully achieved breakthrough results. [3]



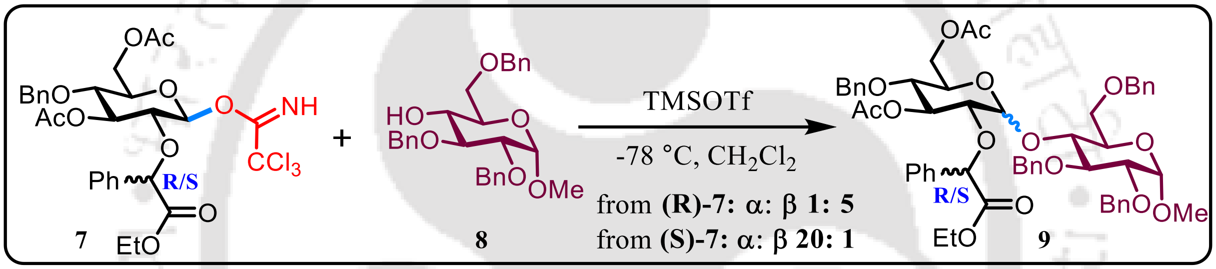
a) Donor + Acceptor + DTBMP, then Tf_2O, **β: α 1: 10**

b) Donor + Tf_2O + DTBMP, then Acceptor, **β: α 10.5: 1 (preactivation)**

Scheme 2. Synthesis of β-mannosides through preactivation

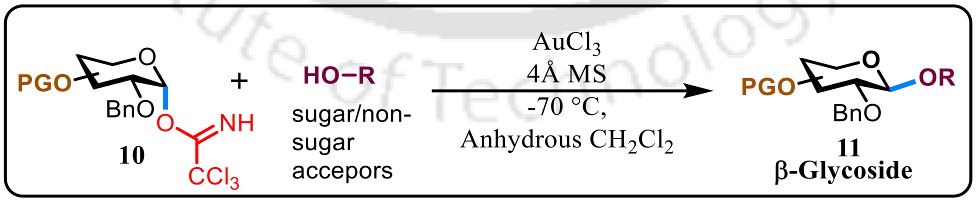
Targets like 1,2-*cis* linkages for obtaining *β*-mannosides and *α*-glucosides were a few of the most challenging tasks. Varying protecting groups selectively, utilizing chiral auxiliaries, and using participating solvents and additives that can impact the stereoselectivity, are all important factors for controlling the stereoselectivity of the glycosylation reactions. By locking the conformation of the donor at 4,6-position/2,3-position, there was a significant improvement observed in the stereoselectivity of the glycosylations. "Neighboring group participation" is in use traditionally to achieve 1,2-*trans* glycosidic linkage efficiently. On a similar note, chiral auxiliaries were introduced and employed through preactivation for 1,2-*cis* glycosidic linkage successfully. Utilizing the preactivation concept and the role of solvent showed an obvious impact on the stereoselectivity of the reaction outcome.

Geert-Jan Boons's group has reported a novel strategy for 1,2-*cis* glycosylation using a chiral auxiliary at the C-2 position which proceeds through the conventional neighboring group participation of the nucleophilic phenylsulfanyl moiety of the C-2 functionality with oxocarbenium ion (**Scheme 3**).[4]



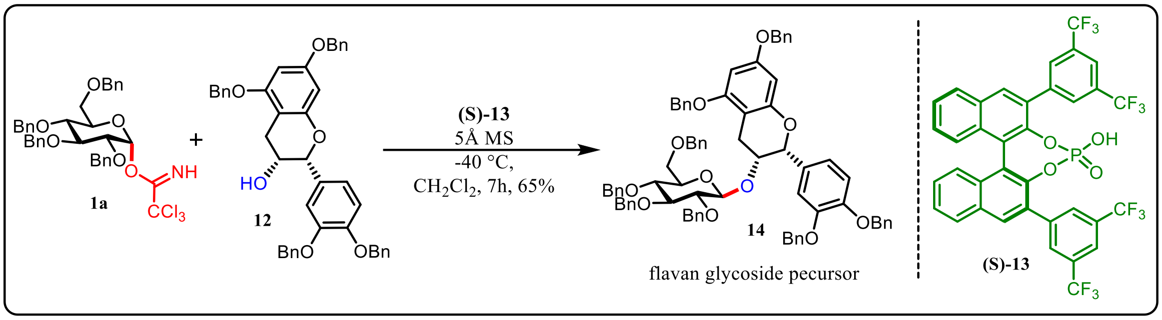
Scheme 3. Glycosylation utilizing chiral auxiliary

Schmidt and coworkers pioneered the catalytic glycosylations of the glycosyl trichloroacetimidates. In one of their works, they reported a protocol for stereoselective glycosylation using gold(III) chloride acid−base catalysis and reported β-glycosides majorly (**Scheme 4**).[6a] Specifically, the acceptor-catalyst interactions assisted protocols provide S$_N$2 kind of activation of glycosyl trichloroacetimidates.[6]



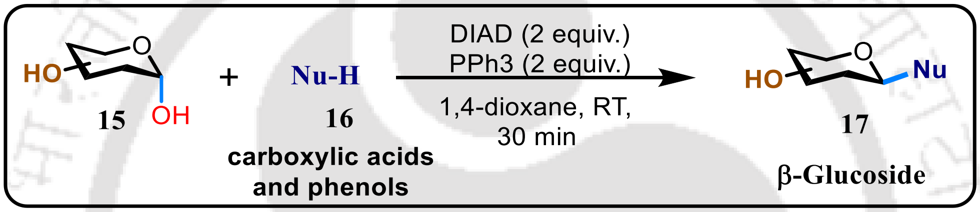
Scheme 4. Glycosylation using gold catalysis

Another pioneering work towards S$_N$2 glycosylation includes the contributions from Toshima[7a] (**Scheme 5**), where Brønsted acid chiral catalyst was utilized for stereoselective glycosylation via S$_N$2-type reactivity. They synthesized flavan glycoside precursor stereoselectively by treating glucosyl trichloroacetimidate under chiral Brønsted catalysis.

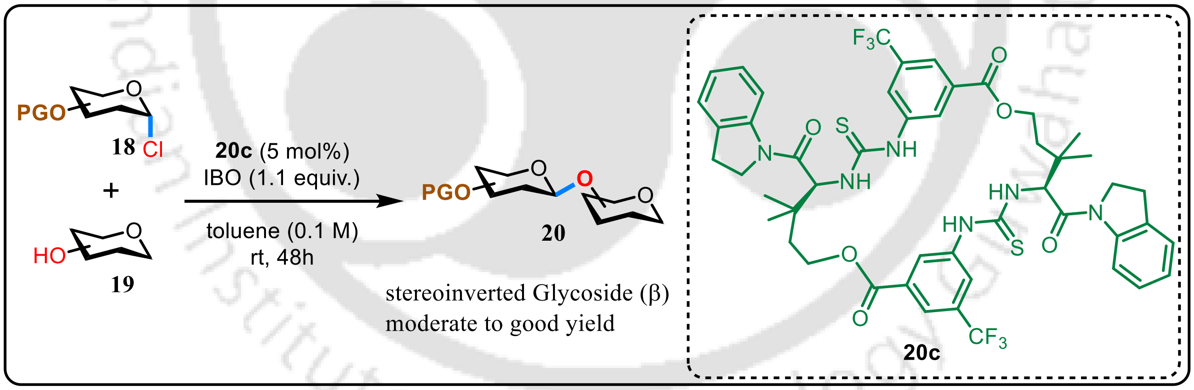


Scheme 5. Glycosylation using chiral Brønsted acid catalysis

In 2019, Takeo Kawabata and coworkers reported a simple protocol for S$_N$2-type stereoselective glycosylation starting from free pyranoses, and a variety of carboxylic acids, phenols, and imides under Mitsunobu conditions in dioxane which gave β-glycosides while they observed S$_N$1 type reactivity in DMF solvent (**Scheme 6**).[7b]

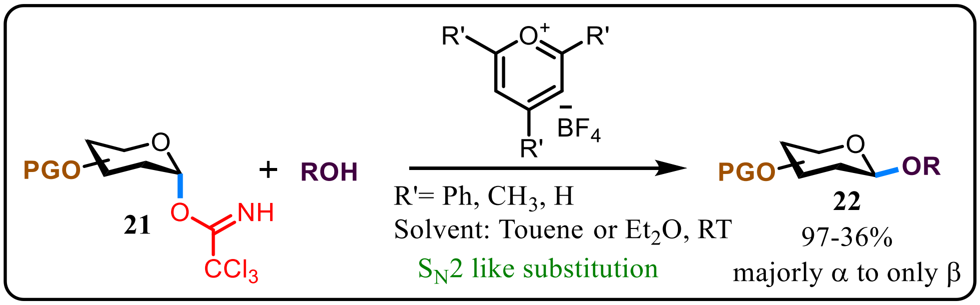


Scheme 6. Glycosylation of pyranoses under Mitsunobu conditions

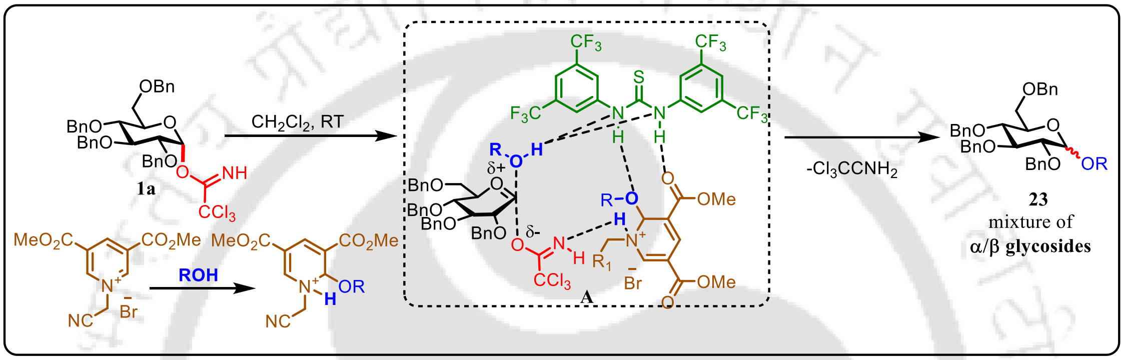


Scheme 7. S$_N$2-Glycosylation through macrocyclic bisthiourea catalysis

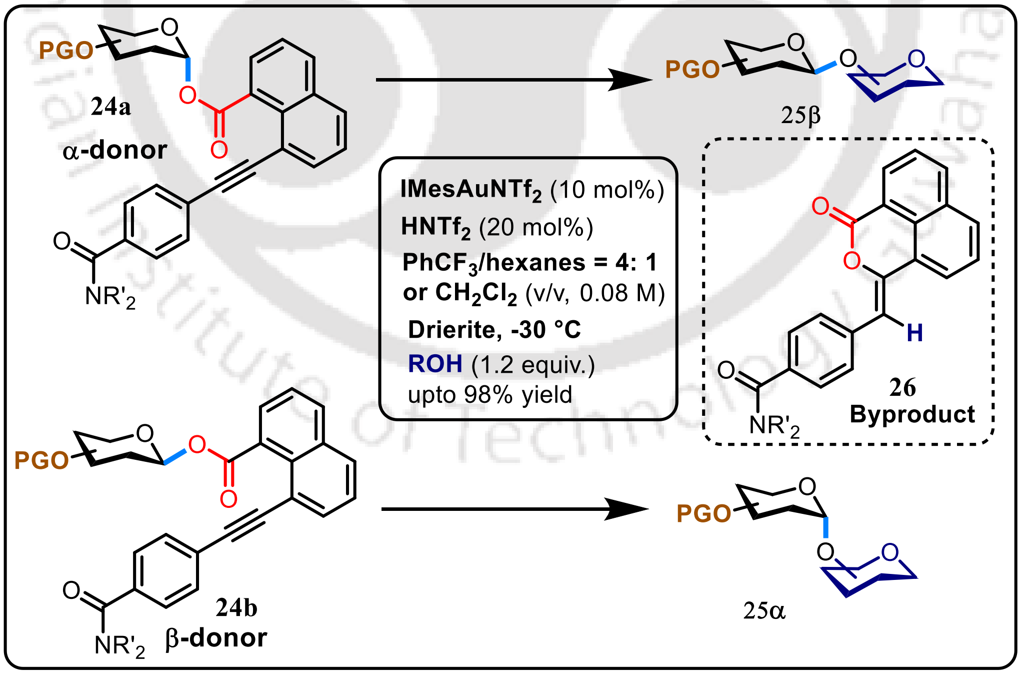
Jacobsen's group came up with a macrocyclic bis-thiourea derivative as a catalyst that can result in stereospecific S$_N$2 glycosylation through the activation of both donor (glycosyl chloride) and nucleophile (acceptor) simultaneously (**Scheme 7**).[7c] The glycosylation strategy by Pedersen's group involves the tandem activation of the electrophilic donor through proton transfer and nucleophile activation which leads to S$_N$2-like substitution on the protonated electrophilic trichloroacetimidate donor (**Scheme 8**).[8a] Attempts were made to utilize electron-deficient pyridinium salts for the activation of acetimidates, however, resulted in a complete loss of anomeric selectivity (**Scheme 9**).[8b]



Scheme 8: Glycosylation through tandem activation of donor and acceptor via pyrilium salts catalysis



Scheme 9. Glycosylation using pyridinium salt/thiourea cooperative catalysis



Scheme 10. S_N2 glycosylation directed by leaving group

Liming Zhang and co-workers recently reported a new method for S_N2 glycosylation with

J. Org. Chem. **2024**, 89, *6*, 3713–3725 a broadscope that involves a directive leaving group, an amide-functionalized 1-naphthoate. In this gold catalysed glycosylation, the amide group from the leaving moiety directs the attack of glycosyl acceptor through hydrogen bonding and also safeguards the stereoselectivity by trapping the oxocarbenium ion and hence expanding the scope for stereoinversion at the anomeric position (**Scheme 10**).[8c]

3.2 This work

Exploring the unique chemistry of bulky pyridine-based-ion pair catalysis, our group reported organocatalysis by TTBPy in its hydrochloride salt form for 2-deoxy-*O*-glycosylation and 2-deoxy S-glycosylation alongside hydration of glycals efficiently.[9] This unique chemistry of the bulky Brønsted salt was utilized for the synthesis of Ferrier-C-glycosides utilizing the frustrated behavior of TTBPy cation and triflate anion via the mild activation of a water molecule.[10] Despite the myriad glycosylation methods present in the literature, the development of practically simple alternative strategies with high stereocontrol is still desired. Since the time of Brown and Kanner's observation[11] of the inability of the sterically hindered 2,6-di-*tert*-butylpyridine to differentiate between Brønsted and Lewis acids, this molecule along with its 4-substituted analogs has occupied an interesting place in organic chemistry as non-nucleophilic bases.[12] These bulky bases have found utility as proton-trapping agents in glycosylation reactions to prevent anomerization.[13] It is presumed that the two ortho-*tert*-butyl groups shield the trapped proton. On the contrary, seminal studies by Bernasconi and Carre decipher that the rate of protonation of 2,6-di-*tert*-butylpyridine by hydronium ion is about 50-70 times slower than expected and is attributed to the sterics around the basic nitrogen site.[14] Brown and Kanner also suggested the improbability of the protonated $[N\text{-}H]^+$ to be stabilized by the anion via hydrogen bonding, unlike the other pyridine compounds.[15] The crystal structure of $TTBPyHBF_4$ shows that the ∠N-H-F bond angle is an unusual 93° against the usual linear 180° bond angle (**Fig. 3.1**). The anion is rather stabilized by

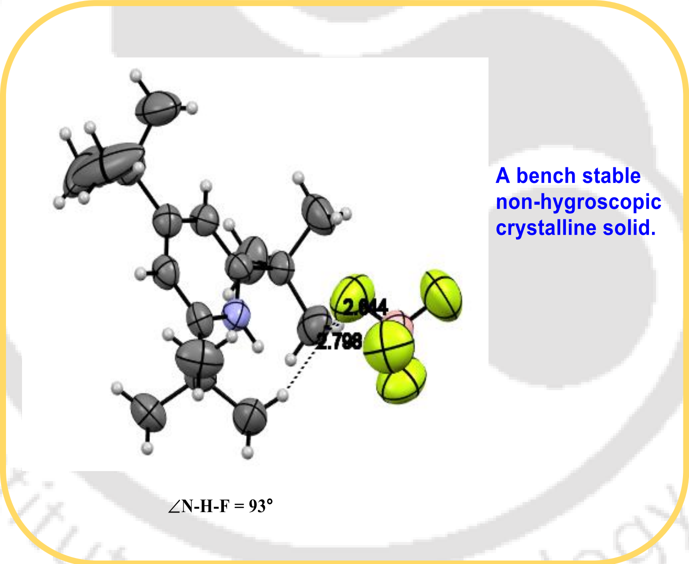


Fig. 3.1 ORTEP diagram of $TTBPyHBF_4$

unusual C-H...F interactions than the [N-H]+...F$^-$ interactions. We hypothesize that these poor electrostatic interactions between the ion-pair arising from the steric bulk around the cationic site results in poor/frustrated ion-pair interactions and would imbue unusual reactivity to the individual ions, particularly in relatively non-polar solvents like dichloromethane. In this protocol, we present the ability of these sterically strained Brønsted salts to catalyze an S_N2-type glycosylation of glycosyl trichloroacetimidates leading to the synthesis of both 1,2-*cis* and 1,2-*trans* gluco and galactosylation reactions.

3.3 Results and Discussion

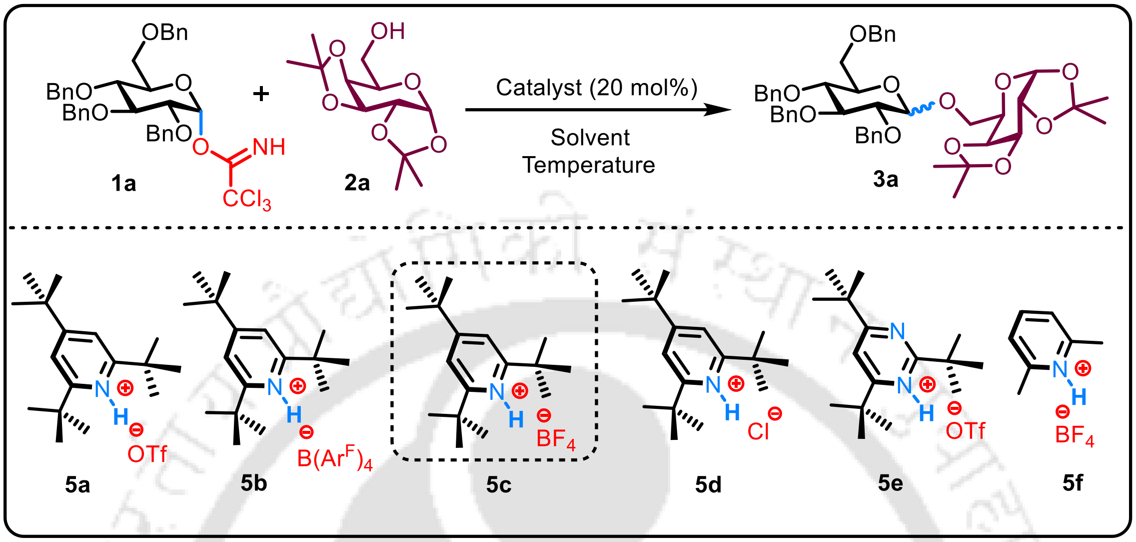
3.3.1 Optimization Studies

Our initial experiments started with a reaction of the *α*-glucosyl trichloroacetimidate donor (**1a**) with galactosyl acetonide 6-OH acceptor (**2a**) at 0 °C in CH_2Cl_2, using triflate salt of sterically hindered 2,4,6-tri-*tert*-butylpyridine (**5a**). To our pleasant surprise, the reaction led to the expected glycoside (**3a**) within just 10 min not only in a good yield of 77 % but also with an anomeric ratio of 38:62 in favor of *β* selectivity (Table 3.1, entry 1), indicating the involvement of S_N2 kind of reactivity. Then, we changed the anion to a more weakly coordinating BAr^F as the anion (**5b**), to understand the role of anion on the S_N2 reactivity. Interestingly, the reaction with catalyst **5b** resulted in 80% of the product **3a** with an increase in *β* selectivity (19:81 *α*:*β,* Table 3.1, entry 2) albeit in 35 min. Similarly, the reaction when tried with the tetrafluoroborate salt **5c** as the catalyst, resulted in 79% of **3a** in 30 min, at 0 °C in CH_2Cl_2, with almost similar anomeric selectivity 22:78 (*α*:*β*) (Table 3.1, entry 3). Intriguingly, the hydrochloride salt of TTBPy (**5d**) has proven to be less efficient and provided the product **3a** in 72% yield with a reversed stereoselectivity (62:38, *α*:*β*), (Table 3.1, entry 4) in 3 h. The reaction with the triflate salt of another similar proton trapping agent 2,4,6-tri-*tert*-butylpyrimidine (**5e**), has led to a similar result as observed with the corresponding triflate salt of bulky pyridine **5a** (Table 3.1, entry 5).

In order to see if the temperature has any effect on the selectivity, a reaction was performed with BAr^F **5b**, as the catalyst at -30 °C. However, the reaction led to a slight drop in the selectivity (82%, 24: 76, *α*:*β*, Table 3.1, entry 6). On the other hand, when the reaction was performed in MTBE as the solvent instead of CH_2Cl_2 at -30 °C, a significant increase in the *β*-selectivity was observed (80%, 10:90, *α*:*β*, Table 3.1, entry 7). The best result was obtained with the tetrafluoroborate salt **5c**, in MTBE as solvent at -30 °C (82%, 3:97 *α*:*β*, Table 3.1, entry 9). Curiously, this result is in stark contrast to Seeberger's observations that the solvents with lone pairs (MTBE) would lead to an increase in *α*-product.[17] Also, the current observed S_N2 reaction is almost solvent independent as it provides *β*-isomer as a major product in both DCM and MTBE. Interestingly, when the tetrafluoroborate salt of a sterically less hindered lutidine (**5f**) was utilized for glycosylation at -30 °C in CH_2Cl_2, the product was obtained in a very poor yield of 36%, albeit, still with high *β*-selectivity (16:84 *α*:*β*) (Table 3.1, entry 8). In addition, 39 % of the rearranged glycosyl amide byproduct was isolated. This experiment signifies the necessity of the steric bulk around the pyridinium site in controlling the reactivity and selectivity. We note in passing that the reaction also gave good β-selectivities with strong Lewis acids like TMSOTf (**5g**) and $BF_3.Et_2O$

(**5h**) (Table 3.1, entry 11 and 12 respectively), though the sterically hindered pyridinium catalysis is still superior (Table 3.1, entry 10).

Table 3.1 Optimization of reaction conditions



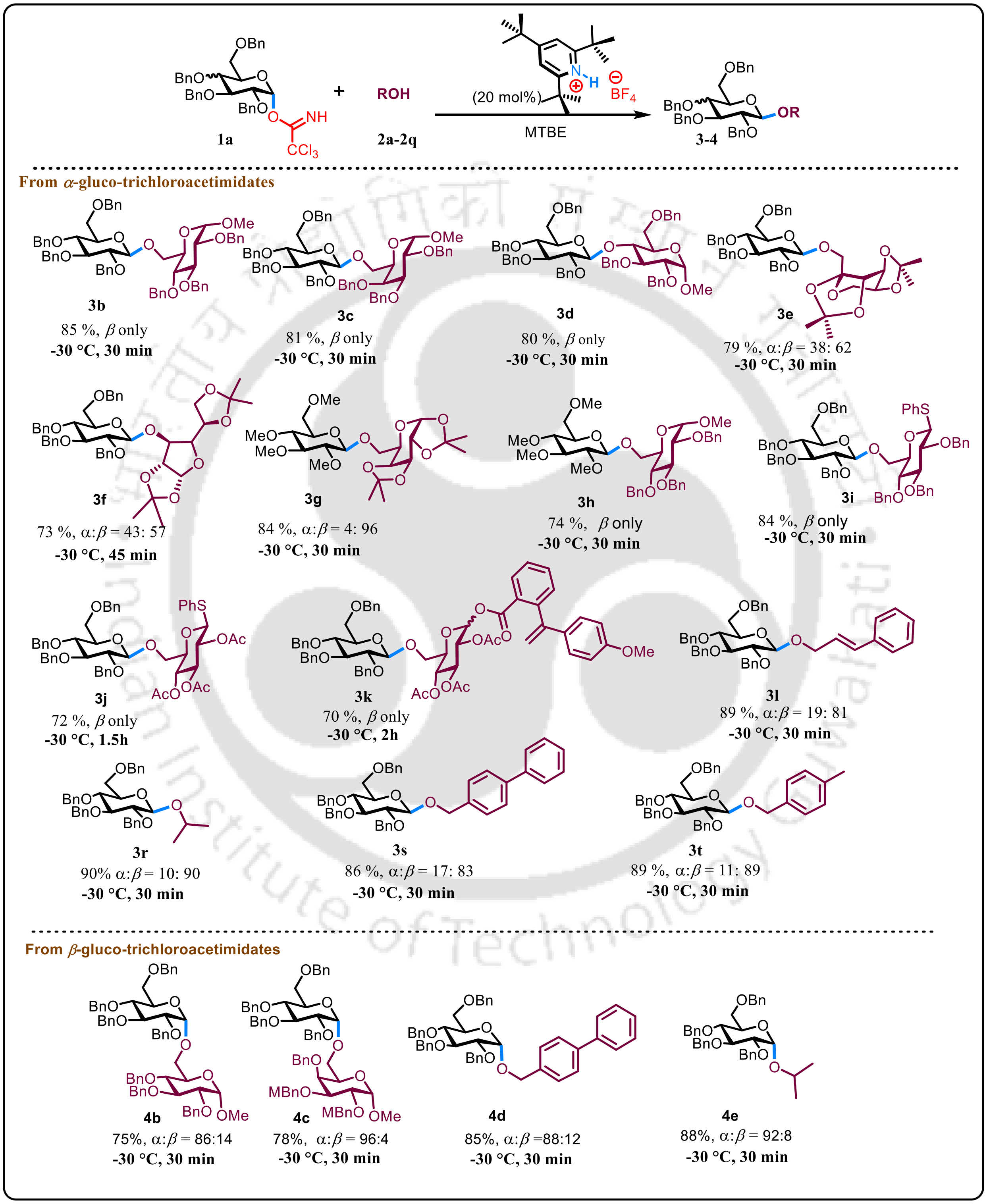
Ent	cat.	Solvent	Temp. in °C	Time (min)	Yield (%)	(α:β)[c]
1	**5a**	CH_2Cl_2	0	10	77	38:62
2	**5b**	CH_2Cl_2	0	35	80	19:81
3	**5c**	CH_2Cl_2	0	30	79	22:78
4	**5d**	CH_2Cl_2	0	180	72	62:38
5	**5e**	CH_2Cl_2	0	10	81	39:61
6	**5b**	CH_2Cl_2	-30	30	82	24:76
7	**5b**	MTBE	-30	30	80	10:90
8[b]	**5f**	CH_2Cl_2	-30	30	36	16:84
9	**5c**	CH_2Cl_2	-30	30	79	8: 92
10	**5c**	**MTBE**	**-30**	**30**	**82**	**3:97**
11	**5g**	MTBE	-30	30	77	27:73
12	**5h**	MTBE	-30	30	75	9:91

Reaction conditions: [a]Reactions were performed by taking 1 equiv. of donor and 1.5 equiv. of acceptor in solvent (0.14-0.15M) [b]39% of anomeric amide has been isolated alongside the product. [c]stereochemistry was determined from NMR analysis. **5g**: TMSOTf, **5h:** BF_3Et_2O.

It is interesting to note the extraordinary reactivity under such mild conditions. Also, the concentration of the reaction mixture was 0.14-0.16M with respect to the donor, which is found to be critical, and an excess dilution leads to the formation of the glycosylamide byproduct.

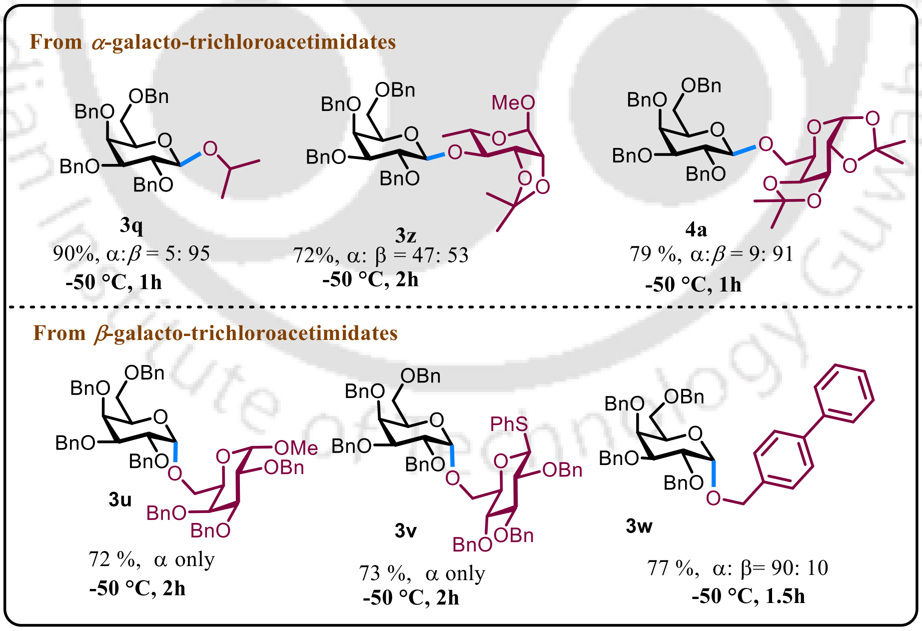
3.3.2 Substrate Scope[a]

With the optimized conditions in hand, we investigated the scope of this S_N2 transformation with various acceptors (**Scheme 11**). The coupling reactions between the α-glucose donor (**1a**)



Scheme 11. Reaction conditions a: 1 equiv. of trichloroacetimidate donor and 1.5 equiv. of acceptor in MTBE (0.14-0.15M) with 20 mol% of catalyst **5c**.

with various acceptors led to the expected disaccharides in excellent β-selectivities and good yields (**3a-3s**). The glucose-derived 4-OH secondary alcohol also provided the corresponding product **3d** as only β-isomer. Benzylated glucosyl 6-OH acceptor (**2b**) led to the formation of expected glycoside **3b** as an exclusive β-anomer with 85% yield. However, when sterically hindered acetonide protected fructose derived primary alcohol and acetonide protected glucose derived secondary alcohol were used as acceptors, the coupling products **3e** (33:67, α:β) and **3f** (43:57, α:β) respectively were obtained with a loss of preference towards β-selectivity. The tetramethoxy-protected α-glucotrichloroacetimidates also underwent the coupling in a stereoslective fashion giving rise to the corresponding products **3g** and **3h** in excellent β-selectivities. Some non-carbohydrate acceptors were also tried under the reaction conditions which also proved efficient in providing the corresponding glycosides (**3l**, **3r,** **3s,** and **3t**) in good yields and excellent stereoselectivities. In addition, we have also reacted the benzylated and acetylated thioglycoside 6-OH acceptors which led to the disaccharides **3i** and **3j** in 72% and 84% respectively, in very high *β*-selectivities Also, the PMPVB donor[15] based 6-OH acceptor provided the desired product **3k**. While the *β*-glucosyl trichloroacetimidate donor)**1e**) was treated with acceptors **2b** and **2r** which resulted in the respective disaccharides with good yields and stereoselectivity, **4b**)75 %, α: β = 86: 14(and **4c**)78 %, α: β = 96: 4(respectively. Also, we reacted the *β*-glucosyl donor (**1e**) with 4-phenylbenzyl alcohol (**2k**) and isopropanol (**2o**) that provided the expected monosaccharides **4d** (85%, α: β = 88: 12(and **4e** (88%, α: β = 92: 8) retaining the stereoselectivity)**Scheme 11**(. These results suggest that the current mild conditions can work as orthogonal conditions to other donors and can be used for oligosaccharide synthesis.



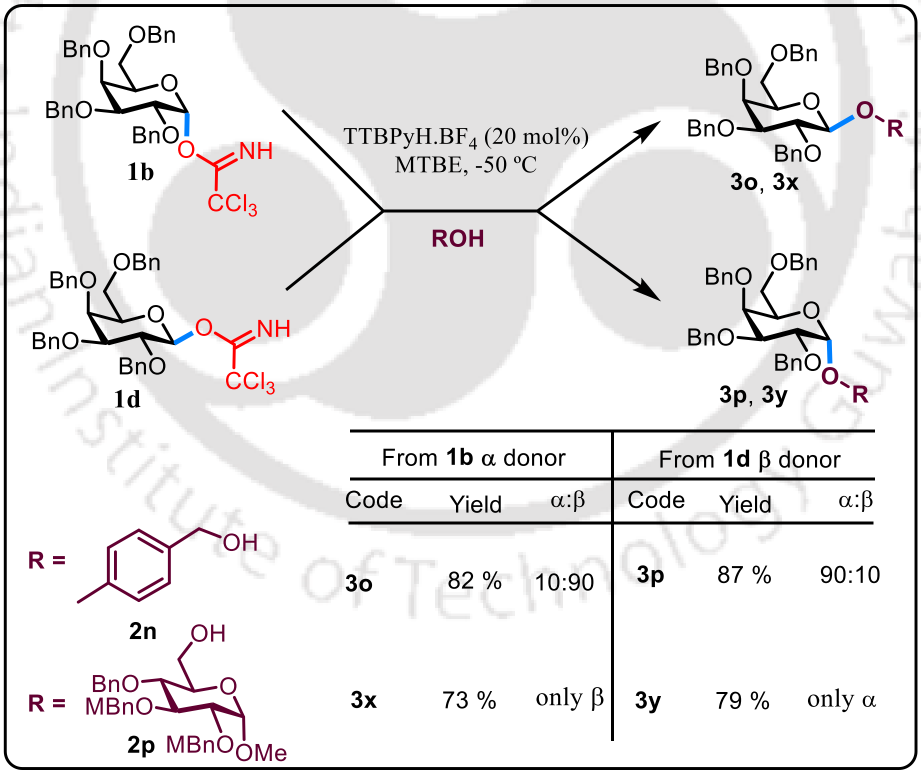
Scheme 12[a]**.** S_N2 type Glycosylation of Galactosyl Trichloroacetimidates

Reaction conditions[a]: 1 equiv. of trichloroacetimidate donor and 1.5 equiv. of acceptor in MTBE (0.14-0.15M) with 20 mol% of catalyst **5c**. stereochemistry of the products was determined from NMR analysis.

Next, we investigated the ability of this bulky pyridinium salt catalysis)**Scheme 12**(on the galactosyl trichloroacetimidate donors (**1b, 1d**). The tetra-OBn-protected galactosyl *α*-trichloroacetimidate also provided the *β*-isomers as the major products providing evidence that the S_N2 reactivity under the present catalytic conditions is unaffected by the change in the stereochemistry of O-4. With the alcohols tested, the *β*-selectivity is retained, albeit the selectivity is moderate with diacetonide galactose 6-OH acceptor (**4a**, 33:67, *α*:*β*) at -30 °C in MTBE, the S_N2 type reaction selectivity is achieved when the reaction was conducted at -50 °C (**4a**, 9:91, *α*:*β*). So all the galactosylation reactions were chosen to be performed at -50 °C. The rhamnosyl-based secondary acceptor (**2q**) resulted in the disaccharide (**3z**) albeit with lower stereoselectivity (72%, 47:53, *α*:*β*). Furthermore, when the *β*-galactosyl trichloroacetimidate donor)**1d**(was treated with acceptors **2c** and **2h** at -50 °C, resulted in the disaccharides **3u**)72%(and **3v**)73%(respectively with complete *α* selectivity while the 4-phenyl benzyl alcohol gave monosaccharide **3w**)77%, α: β = 90: 10( )**Scheme 12**(. Hence, this mild catalysis can be utilized for the synthesis of both 1,2-cis and 1,2-trans galactosides and glucosides as well.

3.4. Corroborative studies for S_N2 type reactivity

3.4.1 Reactions of α/ β-glycosyl trichloroacetimidates leading to inverted glycosidic linkages



R	From **1b** α donor Code	Yield	α:β	From **1d** β donor Code	Yield	α:β
2n	**3o**	82 %	10:90	**3p**	87 %	90:10
2p	**3x**	73 %	only β	**3y**	79 %	only α

Scheme 13: Reaction of α-galactosyl (**1b**) and β-galactosyl (**1d**) donors. **Reaction conditions:** 1 equiv. of *α*-galactosyl)**1b**(/*β*-galactosyl)**1d**(trichloroacetimidate donor and 1.5 equiv. of acceptor p-methylbenzylalcohol)**2n**) and glucosyl acceptor (**2p**(in MTBE (0.14-0.15M) with 20 mol% of catalyst **5c** at -50 °C.

In addition, when 4-methylbenzylalcohol)**2n**(, was reacted with both *α*-galactosyl)**1b**(and *β*-galactosyl)**1d**(trichloroacetimidate donors under the identical reaction conditions, provided the corresponding glycosylated products)**3o** & **3p** respectively(with complete reverse selectivity (**Fig. 3.2**). When the same experiment was performed with sugar (glucosyl) acceptor (**2p**) and galactosyl donors (**1b, 1d**). The α-donor (**1b**) resulted in β-glycoside (**3x**), while the β-donor (**1d**) resulted in he expected glycoside as α-anomer (**3y**) only in good yields (**Scheme 13**).

An experiment with an anomeric mixture of glucosyl-TCA donors was performed and interestingly, the product glycosides were obtained with an exactly opposite anomeric stereoselectivity (**Scheme 14**). All these results clearly demonstrate that the current protocol proceeds via an S_N2 mechanism leading to the inversion of the stereochemistry at the anomeric position.

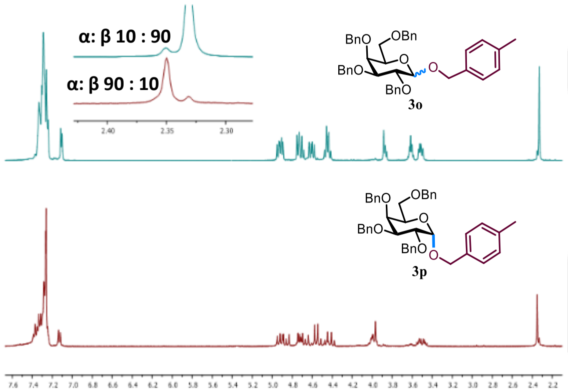
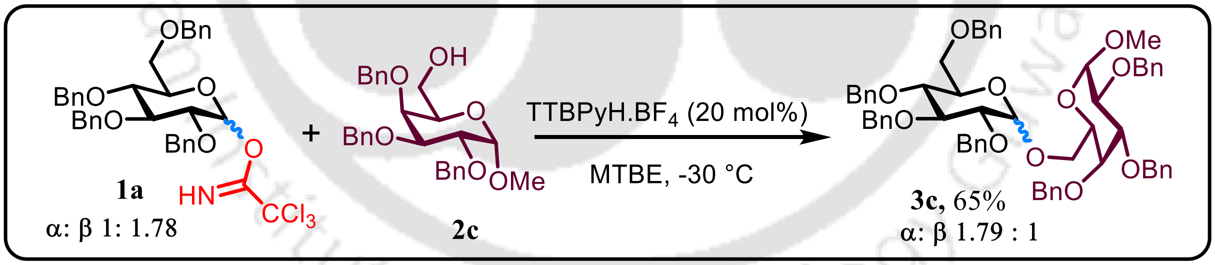


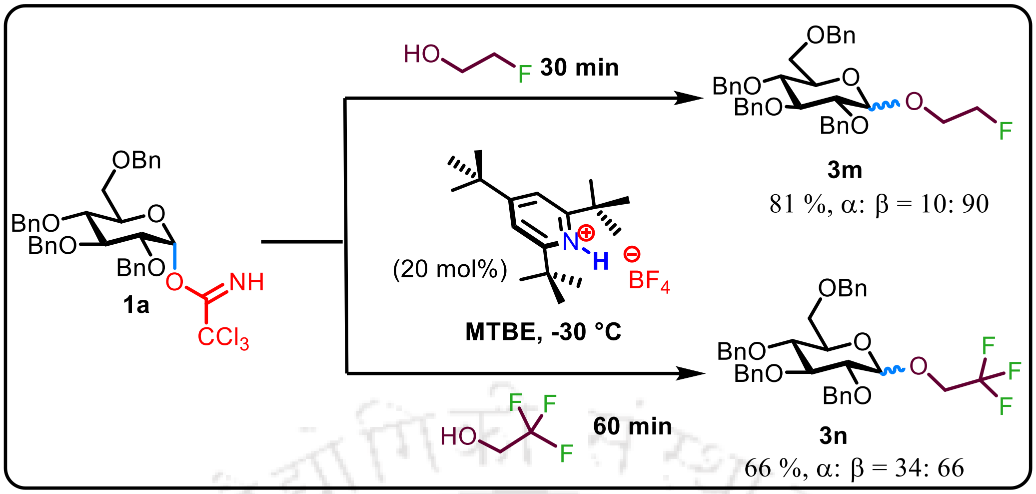
Fig. 3.2 NMR spectra of **3o** and **3p** showing the inversion in stereochemistry of products.



Scheme 14: Reaction of α/ β-glucosyl trichloroacetimidate (**1a**) mixture with 6-OH acceptor (**2c**)

3.4.2 Influence of Alcohol Nucleophilicity on S_N2 Glycosylation

Taking a cue from a recent study by Codee et al.[16] on utilizing fluorinated alcohols to dissect the mechanism between S_N1 and S_N2, we have treated the glucosyl donor **1a** with 2-flouroethanol)**2l**(and 2,2,2-trifluoroethanol)**2m**) as acceptors with a clear difference in their nucleophilicity. The reaction with monofluoroethanol provided the product **3m** in 81 % with α:β = 10:90 selectivity,

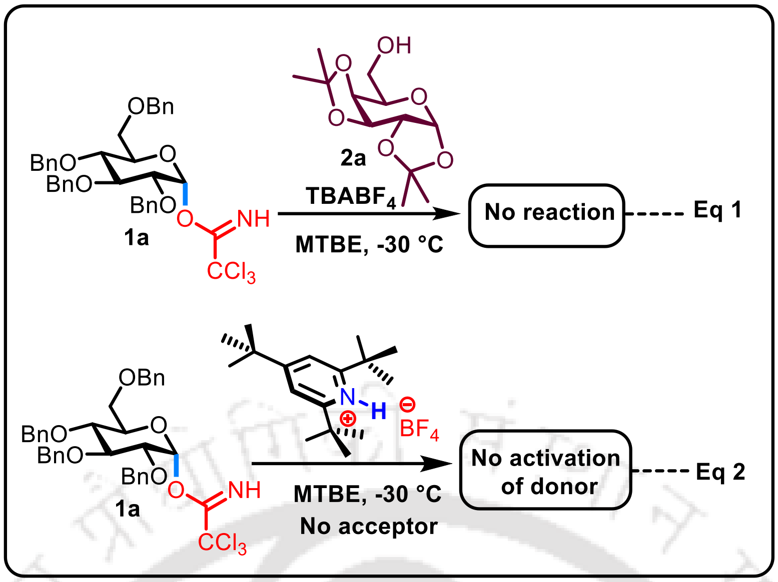


Scheme 15. Influence of acceptor' nucleophilicity **(**Reaction conditions: Reactions were performed by taking 1 equiv. of Donor (**1a**) and 1.5 equiv. of acceptor in solvent (0.14-0.15M). Stereochemistry of the products was determined from NMR analysis.)

while there was a drop in yield and selectivity when the poorly nucleophilic trifluoroethanol was used as a nucleophile. The product **3n** was obtained in 66 % yield and 34:66 α:β)Scheme 4). The erosion of *β*-selectivity with decreasing nucleophilicity can be attributed to the involvement of some S_N1 reactivity. This, however, also provides evidence for S_N2 kind of reactivity for all the other nucleophilic alcohols (**Scheme 15**).

3.5 Role of individual ions in the reaction

When donor **1a** was treated with catalyst **5c** in the absence of an acceptor under otherwise identical conditions, the donor remained unaffected (**Scheme 16**, Eq 2), establishing that the reaction proceeds via a donor-catalyst-acceptor interactions-driven mechanism. In order to understand the role of individual ions, donor **(1a)** and acceptor (**2a)** were treated with 20 mol% of $TBABF_4$ (tetrabutylammonium tetrafluoroborate) as catalyst under standard conditions. However, no reaction was observed reiterating the role of bulky pyridinium cation (**Scheme 16**, Eq 1).



Scheme 16. Reaction of glucosyl donor **1a** with acceptor **2a** with TBABF$_4$ (Eq 1); Reaction of glucosyl donor **1a** with TTBPyHBF$_4$ in the absence of acceptor

3.6 Understanding the Plausible Mechanism

To the best of our knowledge, this is the first of its kind study to quantify the strain within the ion-pair. In addition, we have also performed the Hirshfeld analysis at the DFT B3LYP level on the XRD data of TTBPyHBF$_4$ to observe the strong contact points between the cationic nitrogen and the anion (**Fig. 3.3**). However, as expected, the Hirshfeld analysis shows the absence of any such strong interaction between the cation and the anion. The contribution of N-F interactions to the crystal lattice is an almost negligible 0.6 %.

Hirshfeld Analysis:

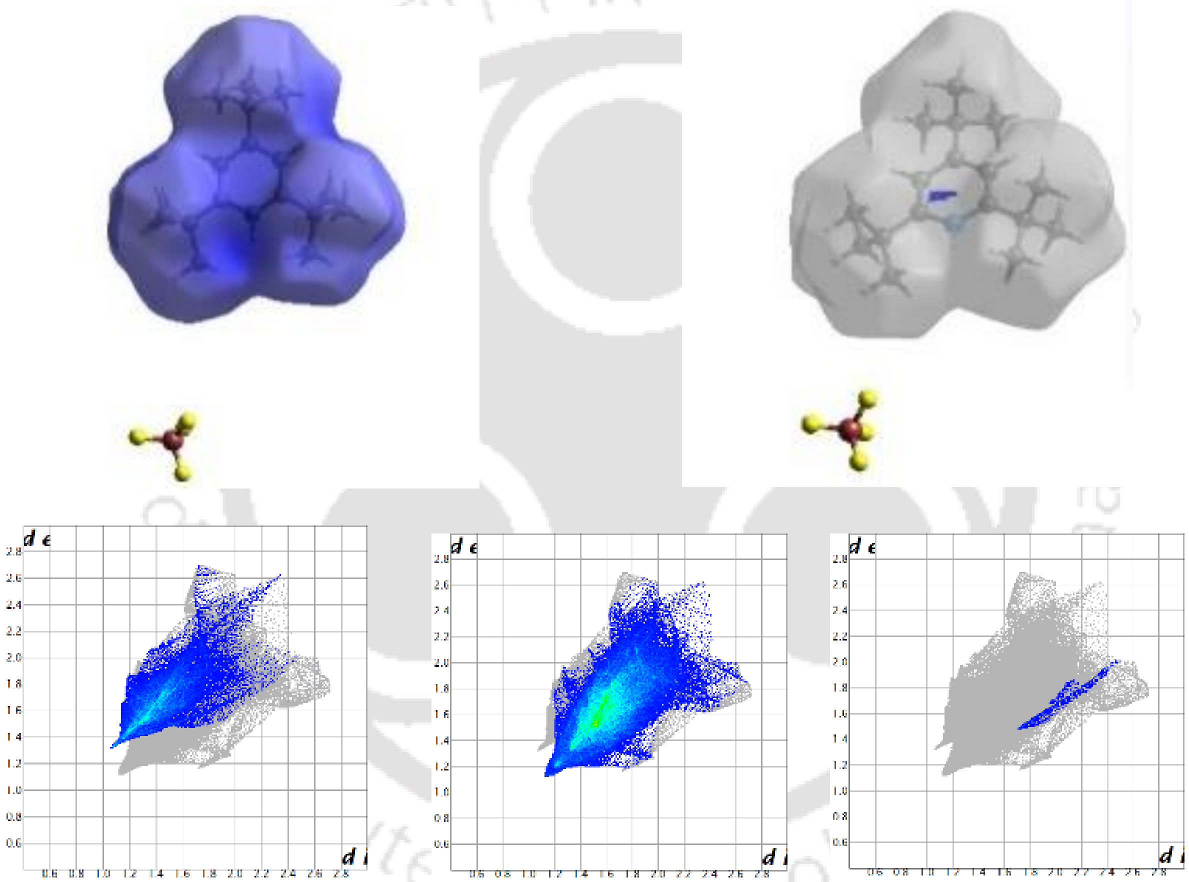


Fig. 3.3 Hirshfeld Surface Analysis of TTBPyHBF$_4$. a) Total Interactions b) Showing only N-F interactions c) Percentage contributions of H-F (22%), H-H (73%) & N-F (0.6%) interactions in the crystal packing.

In order to quantify the strain within the ion-pair of the bulky pyridinium salts due to the presence of *tert*-butyl groups at ortho to nitrogen, we have performed the geometry optimization studies of 2,6-di-*tert*-butylpyridinium chloride and the corresponding hypothetical 3,5-di-*tert*-butylpyridinium chloride (in which no such strain in the ion-pair is expected) using Kohn-Sham hybrid-DFT B3LYP[2] functional and the 6-31g(d) Pople basis set. Interestingly, the ortho-ion-pair is found to be ~4 kcal/mol (in both DCM and water solvent) higher in energy relative to the meta one indicating the amount of strain within the ion-pair (**Fig. 3.4 (1)**). Interestingly, when an IR spectrum was recorded of $TTBPyHBF_4$, in the presence and absence of *p*-methybenzylalcohol, there was no shift in the stretching frequency of [N-H] indicating the absence of any H-bonding between the cationic $[N\text{-}H]^+$ and the alcohol (**Fig. 3.4 (2)**). In addition, the ^{19}F-NMR spectrum of

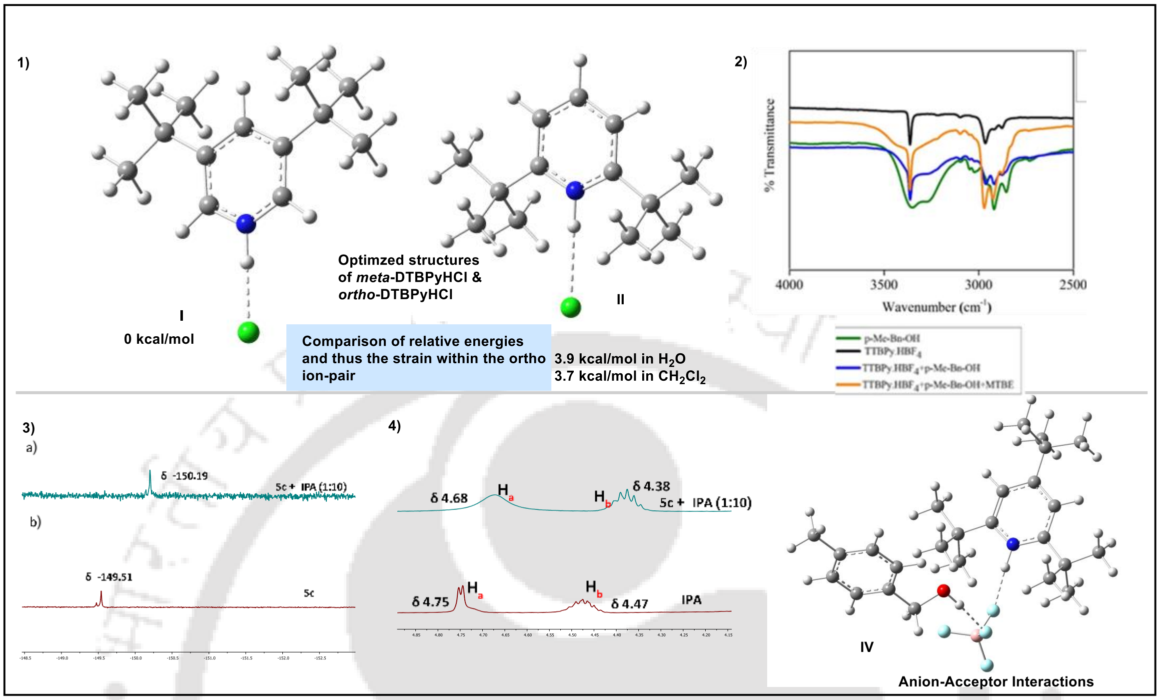


Fig. 3.4 1) Comparison of relative energies of ortho/meta-DTBP 2) Overlapped IR spectra of the catalyst/*p*-MeBnOH showcasing no change in N-H stretching frequency (Please refer to Experimental section for details) 3) a) ^{19}F-spectra of $TTBPyHBF_4$ + IPA b) $TTBPyHBF_4$ 4) Merged ^1H-NMR-spectra of $TTBPyHBF_4$ + IPA and IPA

the catalyst-acceptor (IPA) complex showed a noticeable shift (0.68 ppm) in the chemical shift of the ^{19}F signal corresponding to the BF_4^- anion (**Fig. 3.4 (3)**). Also, a corresponding shift of the alcohol proton and the non-exchangeable C-H proton is observed (**Fig. 3.4 (4)**), more details are mentioned in section **3.9**). Interestingly, the chemical shift of the alcohol proton has shifted upfield which also signifies that the hydroxyl group is interacting with the electron-rich part of the catalyst that is the anion, and not with the electron-deficient pyridinium cation. These studies (IR and NMR) suggest a strong interaction between the catalyst and the acceptor alcohols, albeit not the usually assumed H-bonding between the cationic $[N\text{-}H]^+$ and the alcohol but indicates the presence of unusual A-…H-O-R interactions leading to the observed outcome. The presence of three bulky *tert*-butyl groups on the pyridinium cation eliminates the possibility of any H-bonding interactions with the pyridinium cation, even with the counter anion. The resulting strain caused within the ion-pair would result in anions associated with this bulky pyridine, polarizing the alcohol, thus promoting the observed catalysis. Based on these experiments, we propose that the strained ion-pair activates the alcohol via a unique A-…H-O-R interactions and not via the $[N\text{-}H]^+$…H-bonding or via the π…H-bonding, resulting in S_N2 kind of mechanism leading to the stereochemical inversion at the anomeric position.

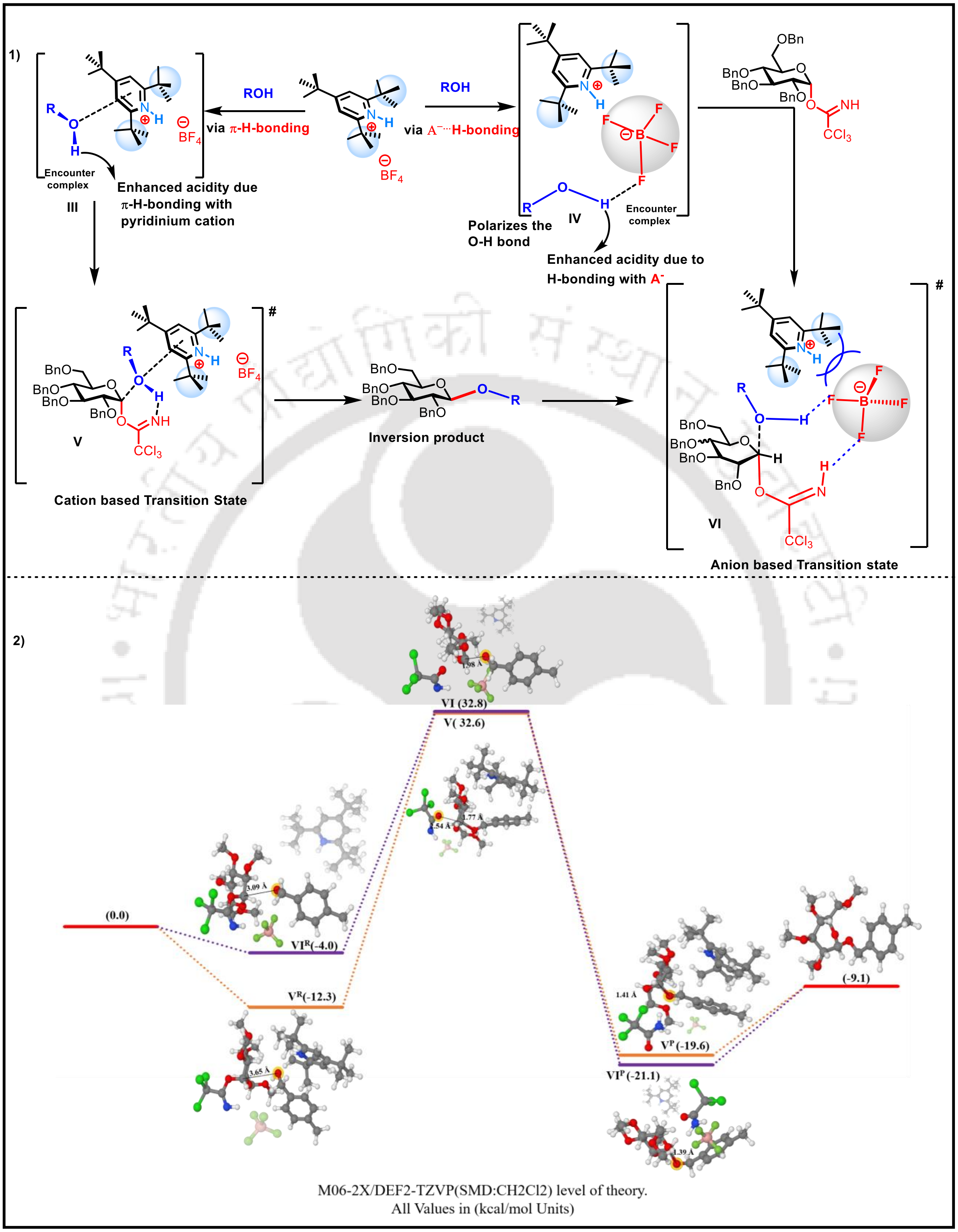


Fig. 3.5 1) Proposed Mechanism 2) Computed free energy (ΔG, in kcal/mol) profiles of the glycosylation reactions. Relative free energies (in kcal/mol) are calculated based on M06-2X/Def2-TZVP (SMD: Dichloromethane) single point energies and gas- phase free energy corrections obtained at the M06-2X/Def2-SVP level of theory.

To gain further insights into the mechanism (Fig. 3.5), we have carried out Density Functional Theory (DFT) calculations, and the resulting free energy profiles are illustrated in Figure 3.5 (2). The initial adduct exhibits two distinct conformations: (i) a cation-stabilized reactant (V^R) and (ii) an anion-stabilized reactant (VI^R). In V^R, acetamides interact with alcohol through inter-molecular interactions, with a closer distance to the neighboring anomeric carbon of approximately 3.09 Å. Interestingly, in this conformation, no anionic interaction with BF_4^- is observed; instead, pyridinium salt is stabilized through van der Waals interactions with alcohol with the closest center-to-center distance of 2.89 Å. Conversely, in VI^R, the alcohol forms a hydrogen bonding interaction with BF_4^- at a distance of approximately 1.79 Å, and the anomeric carbon engages in intermolecular interaction with alcohol at a distance of about 3.09 Å. Utilizing an SN2-like transition state, V^R transforms into V^P through transition state V with a $\Delta G^‡$ of 44.9 kcal/mol. In this transition state, the distance between the nucleophilic alcohol group and the anomeric carbon decreases to 1.95 Å, while the distance with the leaving trichloroacetimidates increases from 1.42 Å (V^R) to 2.32 Å (V). As the reaction proceeds towards the anion-stabilized reactant structure, the transition state appears at approximately 36.8 kcal/mol, approximately 8 kcal/mol lower than the cation-stabilized pathway. In this anion-stabilized pathway, the alcohol group approaches the anomeric carbon from 3.65 Å to 1.77 Å, while the distance of trichloroacetimidate becomes longer from 1.40 Å to 2.54 Å. Finally, both steps lead to the production of the final product with a release of -9.1 kcal/mol. The anion-stabilized pathway is shown to be more favorable than the cation-stabilized pathway, as evidenced by the lower energy transition state and overall reaction profile, providing the significance of hydrogen bonding interaction between alcohol and BF_4^- in the glycosylation reactions of trichloroacetimidates. The theoretical calculations performed also support the anionic pathway as observed by spectroscopic techniques.

3.7 Conclusion

In conclusion, we demonstrated the potential of sterically hindered 2,4,6-tri-*tert*-butylpyridinium tetrafluoroborate salt as a stable, mild, and easy-to-handle organocatalyst for the S_N2 glycosylation of trichloroacetimidates. The ability of the salts of the sterically hindered tri-*tert*-butylpyridine (which is generally used as a proton trapping agent in glycosylation reactions) to catalyze an S_N2 glycosylation leading to highly diastereoselective glycosides bears great significance not only to carbohydrate chemists but also to the generally organic chemists. The transformation is also catalyzed via the unique acceptor-based activation involving the role of both ions in the ion-pair. Exploring the utility of such sterically bulky pyridine salts for the synthesis of other glycosidic linkages is under process in our laboratory.

3.8 Experimental Section

3.8.1 General Information

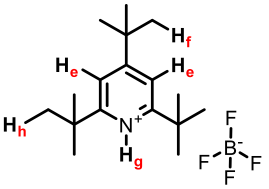
All solvents purchased were of commercial grade and reagents were purchased from Sigma-Aldrich, Merck, Carbosynth, Spectrochem, Alfa Aesar, Avra and used without further purification for reactions.

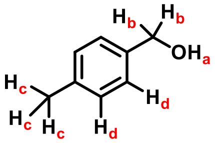
3.8.2 Analysis

Reactions were monitored by TLC on Kieselgel 60 F254)Merck(. Detection was done by examination under UV light)254 nm(and by charring with 10% sulfuric acid in water. Purification was performed by column chromatography in normal phase using silica gel]Merck, 60-120 mesh[. Extracts were concentrated in vacuo using both Büchi rotary evaporator)bath temperatures up to 40 °C(at a pressure of either 15 mmHg)diaphragm pump(and 0.7 mmHg)oil pump(, at rt. ^{1}H- and ^{13}C NMR were recorded on a Bruker 600 MHz,500 MHz, and 400 MHz spectrometer using $CDCl_3$ as solvent. Chemical shift values are reported in ppm with the solvent as the internal standard)$CDCl_3$: δ 7.26 for ^{1}H, δ 77.16 for ^{13}C(. Data are reported as follows: chemical shifts)δ(, multiplicity)s = singlet, d = doublet, dd = doublet of doublet, ddd = doublet of doublet of doublets, dt = doublet of triplet, t = triplet, td = triplet of doublet, q = quartet, m = multiplet(, etc., coupling constants J)Hz(, and integration. High-resolution mass measurements were performed using Agilent technologies mass spectrometer)QTOF-ESI mode(. The diastereomeric ratios were calculated from NMR data. Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments. IR was recorded in a PerkinElmer FT-IR spectrometer for solid sample or sample solution without using KBr pellet. The X-ray diffraction data were collected at 296 K with Mo Kα radiation (λ = 0.71073 Å) using a Micro focused Bruker D8 QUEST diffractometer equipped with a graphite monochromator. Apex IV software was used for data collection and also for indexing the reflections and determining the unit cell parameters; the collected data were integrated using Saint Software. The structures were solved by Intrinsic phasing and refined by full-matrix least-squares calculations using SHELXTL 2018 software. All the non-H atoms were refined in the anisotropic approximation.

3.9 Mechanistic studies

3.9.1 NMR experimental studies





5c: tri-*tert*-butylpyridinium tetrafluoroborate **2n: *p*-methylbenzylalcohol**

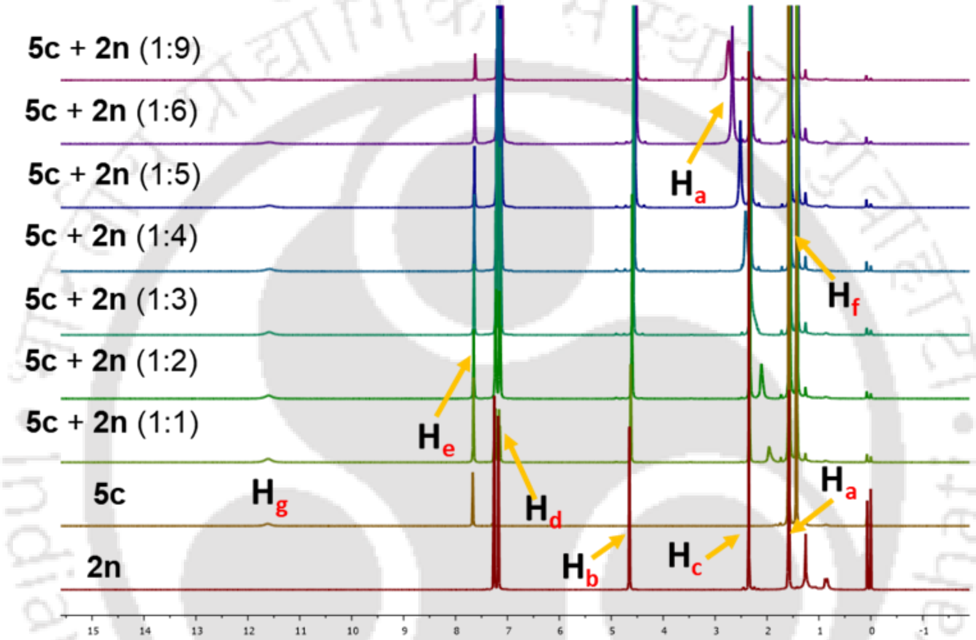


Fig. 3.5 ^{1}H-NMR spectra of catalyst **5c** with varied concentration of p-methylbenzylalcohol)**2n(** in CDCl$_3$)0.6mL(

To understand the interactions between the alcohol and catalyst **5c,** an NMR study was done by dissolving the catalyst)1.2 mg(in 0.6 ml of CDCl$_3$ with varied concentrations of alcohol)**2n**(from 1 to 9 equivalents. From **Fig.3.5** and **Fig.3.6**, the shift in the alcohol peaks with its increasing concentration within the solution is suggestive of close interaction with the catalyst evidently. There was a visible shift in the alocoholic proton)**H$_a$**(from 1.58 ppm to 2.75 ppm, and the benzylic proton)**H$_b$**(from 4.65 ppm to 4.52 ppm.

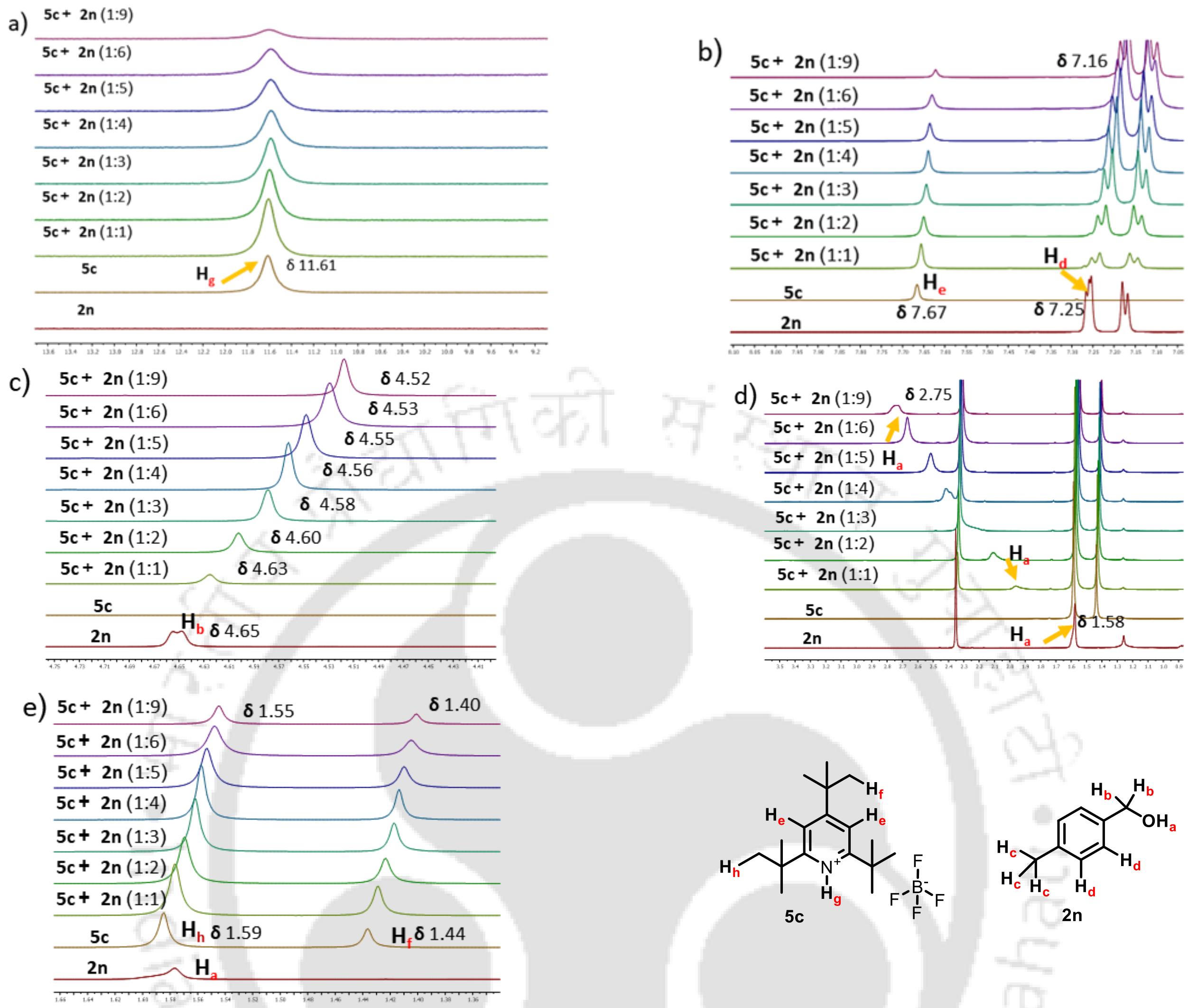


Fig. 3.6: Investigation of the mechanism. ^{1}H-NMR spectra of catalyst **5c** with varied concentration of p-methylbenzylalcohol)**2n(** in CDCl$_3$)0.6mL(. a(expanded spectra of **Fig.3.5** showing **H$_g$**, b(expanded spectra of **Fig.1** showing **H$_e$** & **H$_d$**, c(expanded spectra of **Fig.1** showing benzylic proton **H$_b$**, d(expanded spectra of **Fig.1** showing alcoholic proton **H$_a$** & e(expanded spectra of **Fig.1** showing tert-butyl protons of catalyst)**5c(** **H$_h$ & H$_f$**.

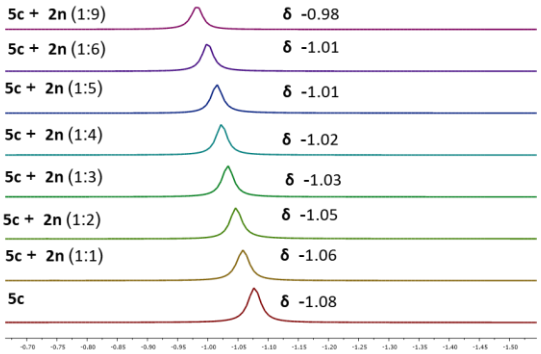


Fig. 3.7: ^{11}B-NMR of catalyst **5c** with varied concentration of p-methylbenzylalcohol)**2n(** in $CDCl_3$)0.6mL(.

Even though it was slight, there was a steady shift in both ^{11}B-NMR and ^{19}F-NMR, from -1.08 ppm to -0.98 ppm)**Fig.3.7**(and -149.57 ppm to -149.44 ppm)**Fig.3.8**(. This observation was also suggestive of close interaction alcohol with the anionic part of the catalyst, i.e., tetrafluoroborate.

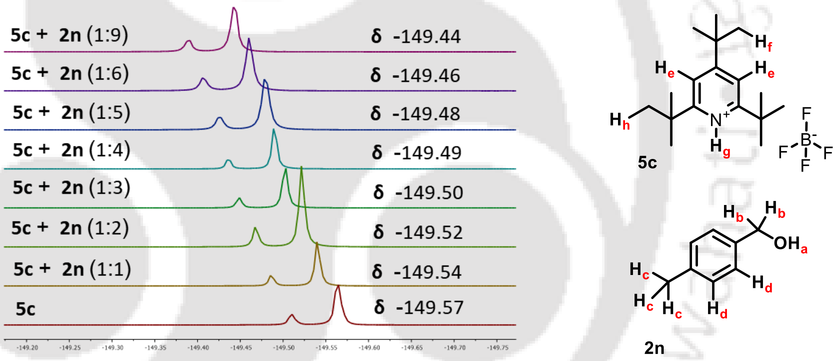


Fig.3.8: ^{19}F-NMR of catalyst **5c** with varied concentrations of p-methylbenzylalcohol)**2n(** in $CDCl_3$)0.6mL(.

We have performed another experiment with isopropyl alocohol)IPA(and catalyst **5c** in MTBE solvent.

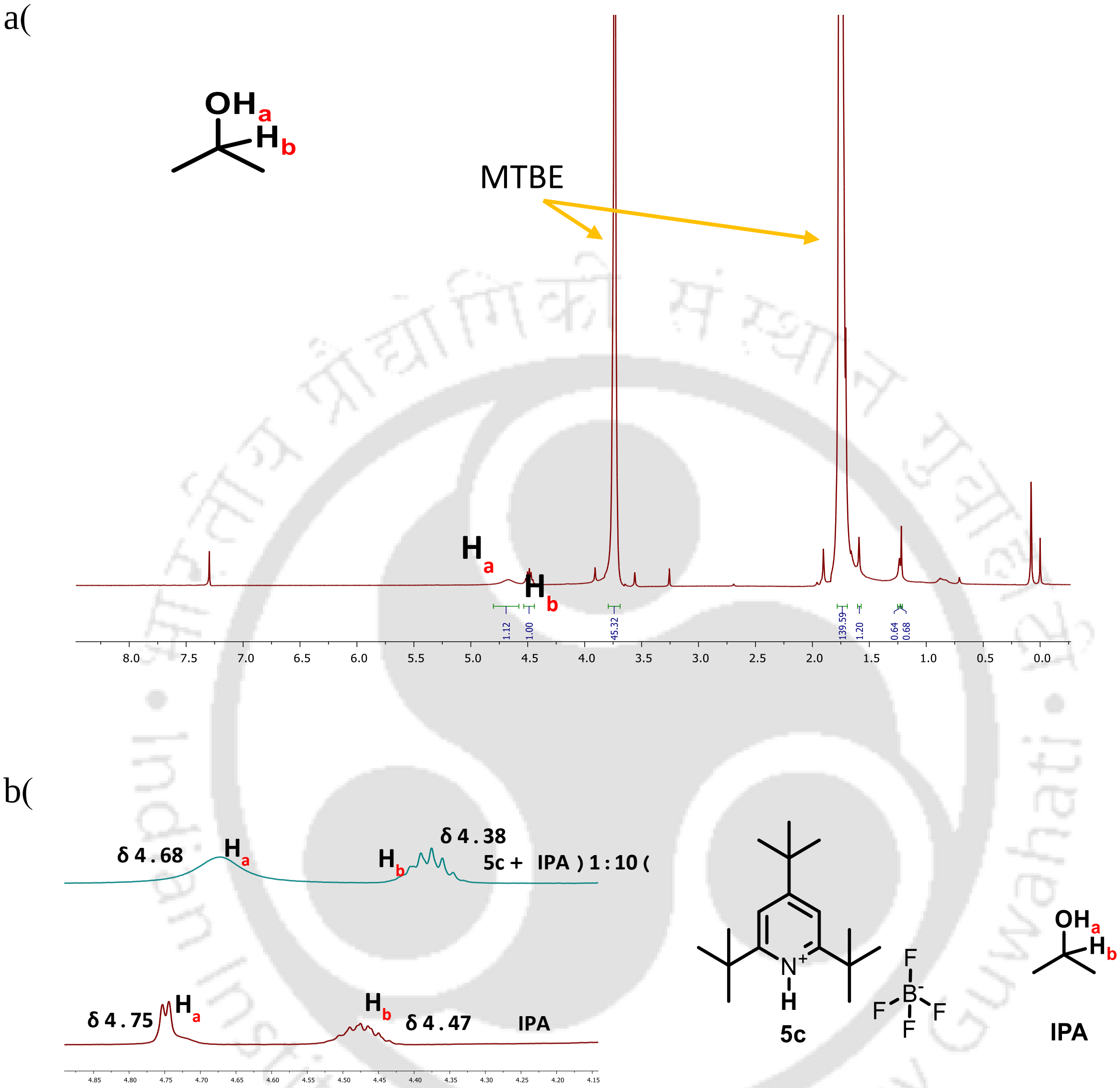


Fig. 3.9: a(^{1}H-NMR spectra of **5c**)0.038M in MTBE(and **IPA**)10 equiv wrt **5c**(in MTBE)75µl(in capillary, in $CDCl_3$)0.6mL(. b(Expanded spectra showing a shift in alcoholic proton **H**$_a$ with respect to **IPA**.

We have taken the catalyst **5c**)0.9 mg(in a melting point measuring capillary and then added 10 equiv. of alcohol to the same capillary and added MTBE solvent)75µl(, with a similar concentration as per the standard reaction protocol. The capillary was then carefully placed into an NMR tube with $CDCl_3$ and NMR was recorded at -30 °C and repeated the same experiment with IPA alone maintaining the same concentration. There was a shift in the peaks of IPA and the alcoholic proton H$_a$ from a doublet at 4.75 ppm to a broadened singlet at 4.68 ppm. The alcohol's multiplet at 4.47 ppm also shifted to 4.38 ppm)**Fig. 3.9**(.

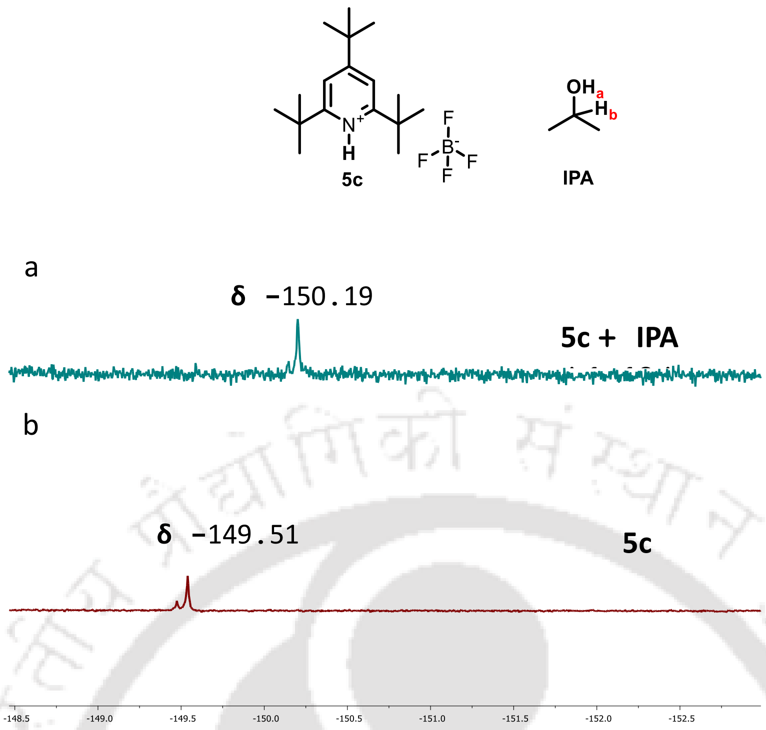


Fig. 3.10: ^{19}F-NMR spectra of a(**5c**)0.038M(and **IPA**)1:10(in MTBE)75µl(in a capillary, in CDCl$_3$)0.6mL(. b(**5c**)0.038M(in MTBE)75µl(in capillary, in CDCl$_3$)0.6mL(.

There was a shift in ^{19}F-NMR also when compared to catalyst **5c** as shown in **Fig. 3.10**, from -149.51 to -150.19 ppm which was again suggestive of anion interaction with alcohol.

3.9.2 IR Studies

IR studies were done with alcohol)**2n**(and catalyst 5**c**, to see if any shift occurred in the N-H stretch due to the interaction with alcohol. From the following IR plots)**Fig. 3.11** and **Fig. 3.12**(, it was observed that the catalyst TTBPyHBF$_4$ (**5c**) in the absence and presence of alcohol as well as in the presence of alcohol along with solvent)MTBE(showing the unperturbed N−H stretch.

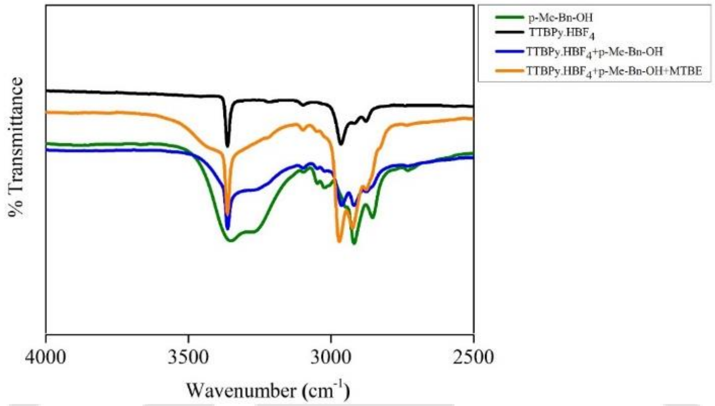


Fig. 3.11: IR plot of TTBPyHBF$_4$, p-Me-benzyl alcohol, and along with solvent showing N-H and alcohol stretch

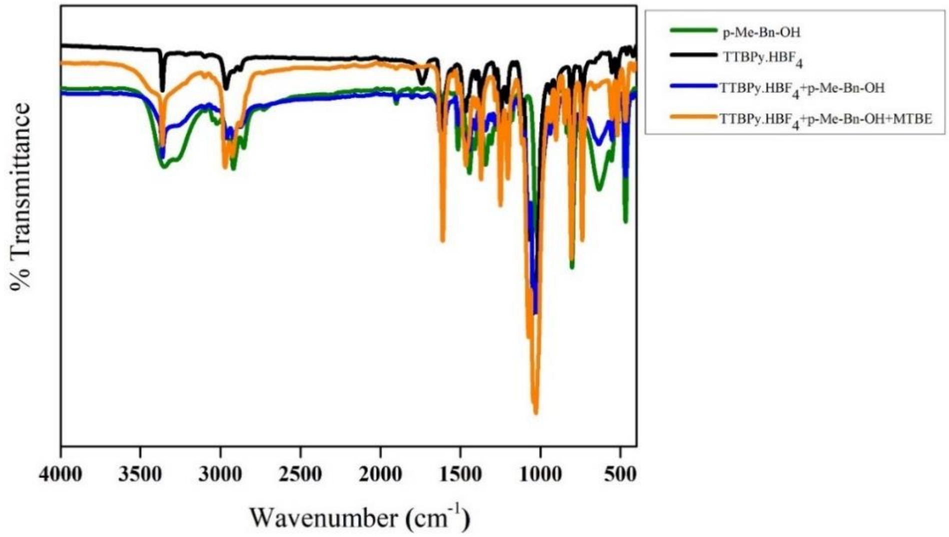
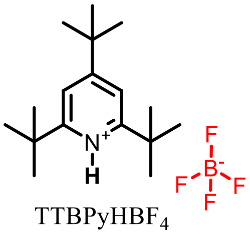
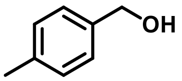


Fig.3.12: IR plot of TTBPyHBF$_4$, p-Me-benzyl alcohol and along with solvent)complete spectra(



TTBPyHBF$_4$

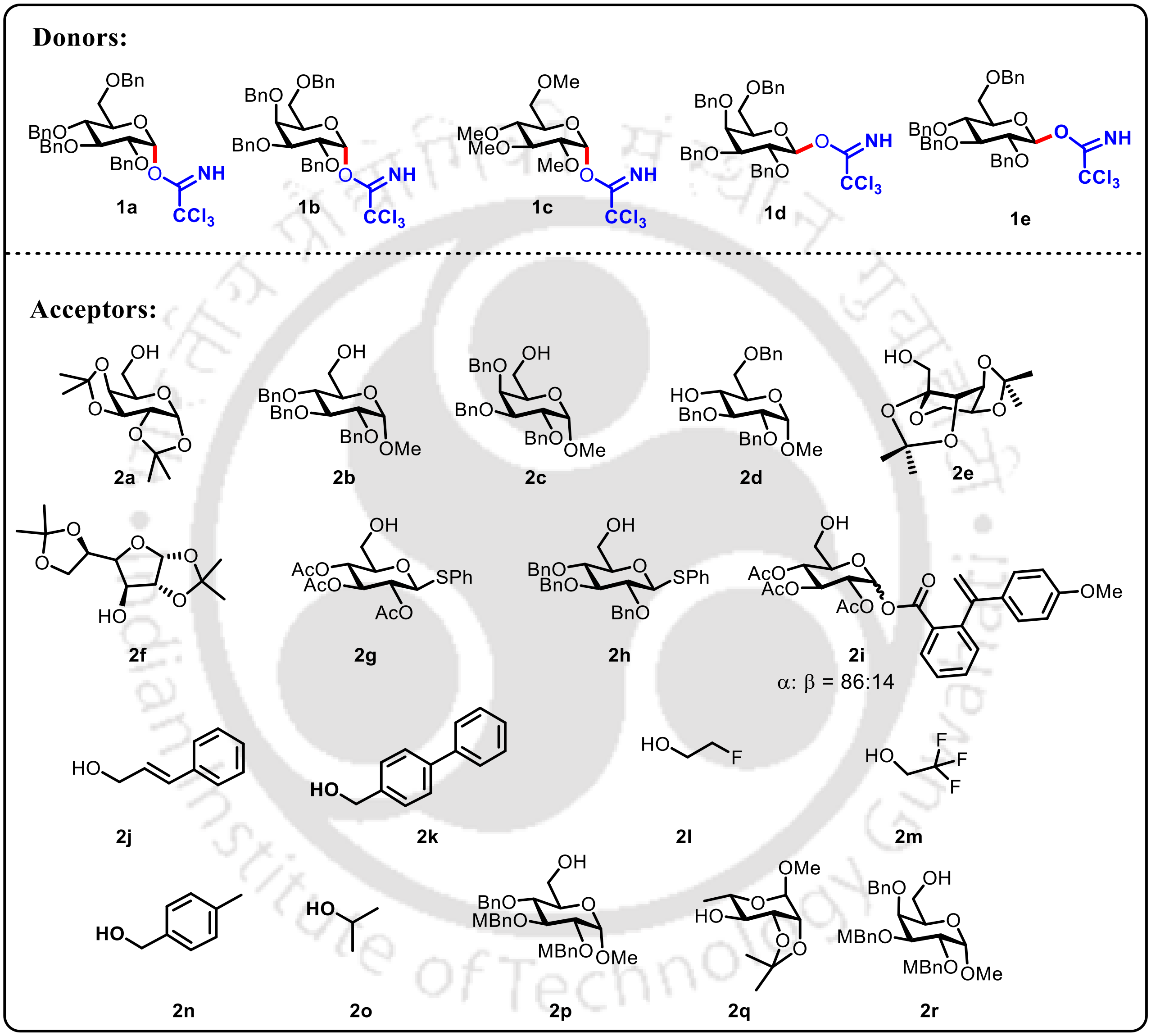


p-Me-Benzyl alcohol

3.10 Synthesis

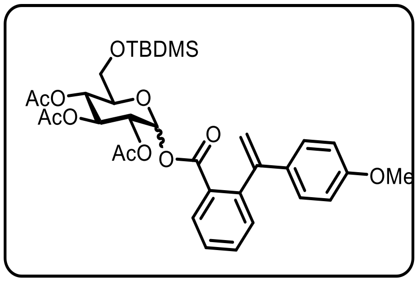
Donors and Acceptors utilized in this study:

The Glycosyl trichloroacetimidate donors)**1a-1d**(and acceptors)**2a-2h, 2p-2q**(were synthesized by following literature procedures (**Scheme 17**).[15,17-18]



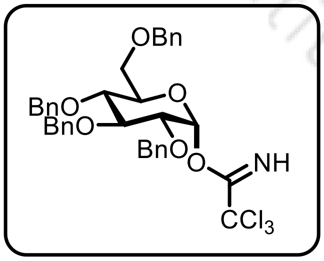
Scheme 17. Donors and acceptors utilized in the study

Preparation of 1-O-{2-]1-)4-Methoxyphenyl(vinyl[benzoyl}-2,3,4-tri-O-acetyl-D – glucopyranose)2i(:

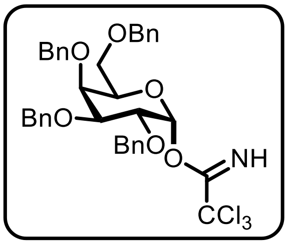


2i’: The 6-OTBDMS-protected PMPVB donor)**2i’**(was synthesized utilizing the reported procedure. [15] ^{1}H NMR)500 MHz, CDCl$_3$(δ 7.88)d, *J* = 7.8 Hz, 1H(,, 7.71 – 7.68)m, 1H(, 7.66)d, *J* = 7.8 Hz, 1H(, 7.52)t, *J* = 7.5 Hz, 1H(, 7.49 – 7.45)m, 1H(, 7.43)t, *J* = 7.6 Hz, 1H(, 7.38 – 7.33)m, 1H(, 7.28 – 7.23)m, 3H(, 7.16 – 7.12)m, 1H(, 6.84 – 6.77)m, 3H(, 6.39)d, *J* = 3.5 Hz, 1H(, 6.19)d, *J* = 3.5 Hz, 1H(, 5.76)s, 1H(, 5.53)s, 1H(, 5.48)t, *J* = 9.8 Hz, 1H(, 5.26 – 5.17)m, 1H(, 5.14)d, *J* = 9.9 Hz, 1H(, 5.12 – 5.09)m, 1H(, 5.05)s, 1H(, 5.03)d, *J* = 10.0 Hz, 1H(, 5.01 – 4.96)dd, *J* = 10.6, 3.5 Hz, 1H(, 4.25 – 4.16)m, 1H(, 3.87 – 3.83)m, 1H(, 3.78)s, 1H(, 3.76)s, 3H(, 3.67)d, *J* = 9.9 Hz, 1H(, 3.63)dd, *J* = 11.8, 3.8 Hz, 1H(, 3.46 – 3.36)m, 4H(, 2.00)s, 1H(, 1.98)s, 3H(, 1.95)s, 3H(, 1.95)s, 1H(, 1.91 – 1.87)m, 4H(, 0.84)s, 2H(, 0.84)s, 9H(, -0.02)s, 4H(, -0.03)s, 3H(.^{13}C NMR)151 MHz, CDCl$_3$(δ 170.5, 170.3, 169.8, 169.3, 169.2, 168.6, 167.8, 166.2, 166.1, 159.3, 159.3, 148.3, 147.5, 143.4, 143.2, 133.2, 132.6, 132.5, 132.0, 131.9, 131.2, 131.0, 130.9, 130.4, 130.3, 129.7, 129.6, 128.8, 128.2, 128.1, 127.6, 113.7, 113.6, 112.8, 90.1, 88.9, 72.4, 72.2, 70.6, 70.5, 69.6, 69.5, 68.4, 68.2, 67.8, 61.7, 61.2, 55.3, 55.2, 25.8, 20.8, 20.7, 20.6, 20.5, 20.4, 18.3, -5.4, -5.5, -5.6. NMR matched with the literature data. HRMS)ESI) m/z:]M+NH$_4$[$^+$ calcd for C$_{34}$H$_{48}$NO$_{11}$Si 674.2991; Found 674.3010. The compound **2i’** was then treated with TBAF-THF following the literature procedure for desilylation giving compound **2i** which was purified using column chromatography)73 % yield(.

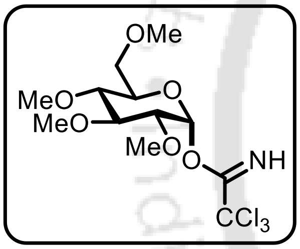
Preparation of the donors 1a-1e:



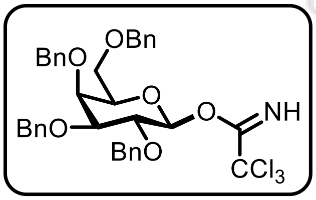
2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl trichloroacetimidate (1a): To a solution of 2,3,4,6-tetra-*O*-benzyl-glucopyranose[15] (1.71 g, 3.17 mmol) in dry CH$_2$Cl$_2$at 0 °C, trichloroacetonitrile (3.17 mL, 31.65 mmol, 10 equiv.) was added slowly under inert atmosphere followed by the addition of DBU (142 µL, 0.95 mmol, 0.3 equiv.). The reaction was stirred at room temperature for completion. A few drops (3-5) of Triethylamine were added to the reaction mixture immediately upon completion of the reaction based on TLC monitoring. Then the reaction mixture was concentrated and purified through column chromatography (using n-hexane/EtOAc = 6/1 containing 1% Et_3N) to give **1a** (yield 1.78 g, 82%) as a colorless syrup. $R_f = 0.6$ (Hexane/EtOAc = 5:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.36 – 7.23 (m, 19H), 7.15 (d, J = 7.0 Hz, 2H), 6.52 (d, J = 3.1 Hz, 1H), 4.95 (d, J = 11.0 Hz, 1H), 4.88 – 4.80 (m, 2H), 4.74 (d, J = 11.7 Hz, 1H), 4.67 (d, J = 11.7 Hz, 1H), 4.59 (d, J = 12.1 Hz, 1H), 4.53 (d, J = 10.7 Hz, 1H), 4.46 (d, J = 12.0 Hz, 1H), 4.05 (t, J = 9.3 Hz, 1H), 3.99 (d, J = 10.0 Hz, 1H), 3.81 – 3.73 (m, 3H), 3.66 (d, J = 10.9 Hz, 1H).[17a,2a]



2,3,4,6-Tetra-O-benzyl-α-D-galactopyranosyl trichloroacetimidate (1b): Synthesised from 2,3,4,6-tetra-*O*-benzyl-galactopyranose[15] following similar procedure give for **1a**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.35 – 7.22 (m, 20H), 6.52 (d, J = 2.6 Hz, 1H), 4.97 (d, J = 11.3 Hz, 1H), 4.81 (d, J = 11.9 Hz, 1H), 4.77 – 4.71 (m, 3H), 4.59 (d, J = 11.2 Hz, 1H), 4.49 – 4.44 (m, 1H), 4.39 (d, J = 11.7 Hz, 1H), 4.24 (dt, J = 11.6, 8.7 Hz, 1H), 4.18 – 4.15 (m, 1H), 4.05 (s, 1H), 4.02 (d, J = 10.0 Hz, 1H), 3.63 – 3.59 (m, 1H), 3.56 (dd, J = 8.4, 5.0 Hz, 1H). [17a,2a]

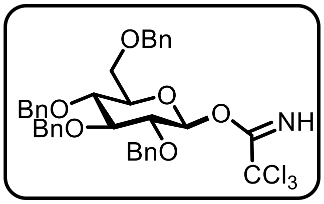


2,3,4,6-Tetra-O-methyl-α-D-glucopyranosyl trichloroacetimidate (1c): Synthesised from 2,3,4,6-tetra-*O*-methyl-glucopyranose[18] following similar procedure give for **1a**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.61 (s, 1H), 6.49 (d, J = 3.3 Hz, 1H), 3.82 (d, J = 10.0 Hz, 1H), 3.67 – 3.65 (m, 4H), 3.64 – 3.62 (m, 1H), 3.61 (d, J = 3.1 Hz, 1H), 3.60 – 3.59 (m, 2H), 3.58 – 3.54 (m, 6H), 3.51 – 3.47 (m, 4H), 3.43 – 3.38 (m, 6H), 3.37 – 3.33 (m, 1H), 3.12 (q, J = 7.3 Hz, 1H).[17]
1H).[17]



2,3,4,6-Tetra-O-benzyl-β-D-galactopyranosyl trichloroacetimidate (1d): To a solution of 2,3,4,6-tetra-*O*-benzyl-galactopyranose[15] (641 mg, 1.19 mmol) in dry CH_2Cl_2 (10 mL) was added trichloroacetonitrile (1.0 mL, 9.97 mmol) and K_2CO_3 (713 mg, 5.16 mmol) at room temperature. The solution was stirred at room temperature for 21 h, and then the reaction mixture was concentrated. The residue was purified by silica gel column chromatography (Elution: n-hexane/EtOAc = 4/1 containing 1% Et3N) to give **1d** (yield: 561 mg, 65%) as a colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.35 – 7.26 (m, 20H), 5.75 (d, J = 7.4 Hz, 1H), 4.97 –

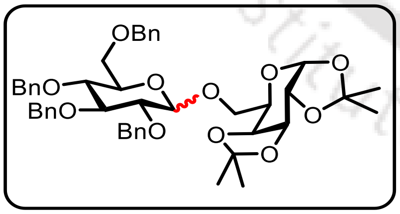
4.89 (m, 2H), 4.82 (d, J = 10.5 Hz, 1H), 4.74 – 4.71 (m, 2H), 4.63 (d, J = 11.4 Hz, 1H), 4.48 (d, J = 11.7 Hz, 1H), 4.42 (d, J = 11.8 Hz, 1H), 4.12 – 4.08 (m, 1H), 3.97 (s, 1H), 3.76 (d, J = 4.7 Hz, 1H), 3.68 – 3.59 (m, 3H).[2a]



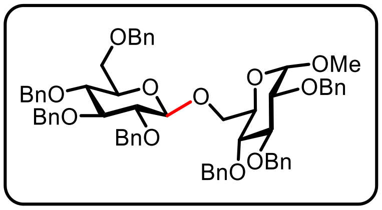
2,3,4,6-Tetra-O-benzyl-β-D-glucopyranosyl trichloroacetimidate (1e): To a solution of 2,3,4,6-tetra-*O*-benzyl-galactopyranose[15] (641 mg, 1.19 mmol) in dry CH_2Cl_2 (10 mL) was added trichloroacetonitrile (1.0 mL, 9.97 mmol) and K_2CO_3 (713 mg, 5.16 mmol) at room temperature. The solution was stirred at room temperature for 21 h, and then the reaction mixture was concentrated. The residue was purified by silica gel column chromatography (Elution: n-hexane/EtOAc = 4/1 containing 1% Et_3N) to give **1d** (yield: 518 mg, 60%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.30 (dd, J = 14.2, 6.3 Hz, 18H), 7.20 – 7.14 (m, 2H), 5.80 (d, J = 6.3 Hz, 1H), 4.92 (dd, J = 13.8, 11.1 Hz, 2H), 4.79 (dd, J = 24.4, 10.5 Hz, 3H), 4.65 – 4.51 (m, 3H), 3.75 (d, J = 2.6 Hz, 4H), 3.65 (s, 2H). [2a]

3.10.1 General Procedure

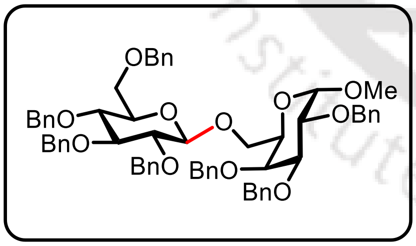
A solution of glycosyl trichloroacetimidate donor)0.16M( )**1a-e,** 1 equiv.(and acceptor)**2a-o,** 1.5 equiv.(in anhydrous MTBE)Methyl tert-butyl ether(was taken in a round-bottom flask and was chilled the vessel to -30 °C followed by the addition of 20 mol% of tri-tert-butylpyridinium tetrafluoroborate)**5c**(under argon atmosphere. The reaction was monitored on TLC. After completion of the reaction, the reaction was quenched with triethylamine. The crude reaction mixture was concentrated and worked up with CH_2Cl_2/water, washed with brine, dried by Na_2SO_4, and concentrated in rotavapor. The resulting crude reaction mixture was purified through column chromatography to afford the glycosylated product)**3a-3z, 4a-4e**(in good yields)91-66%(.



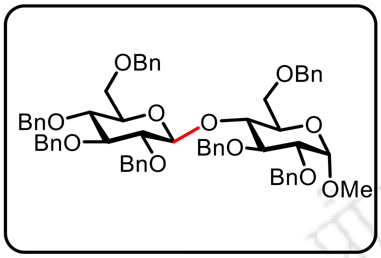
1,2;3,4-Di-O-isopropylidene-6-O-)2,3,4,6-tetra-O-benzyl- D -gluco-pyranosyl(- ***D*** -***galactopyranose***)***3a***(: Glycosylation of **1a**)50.1 mg, 0.07 mmol(with **2a**)28.6 mg, 0.11 mmol(according to **General Procedure** afforded **3a** as a colorless syrup)46.9 mg, 82 %, α: β = 3: 97(. The crude product was purified through column chromatography, R_f = 0.5)Hexane/EtOAc = 5:1, v/v(. ^{1}H NMR)500 MHz, $CDCl_3$(δ 7.41 – 7.39)m, 2H(, 7.34 – 7.21)m, 19H(, 7.16 – 7.09)m, 2H(, 5.56)d, J = 5.0 Hz, 1H(, 5.04)d, J = 11.2 Hz, 1H(, 4.95)d, J = 11.0 Hz, 1H(, 4.80)d, J = 10.8 Hz, 1H(, 4.77)d, J = 11.0 Hz, 1H(, 4.71)d, J = 11.2 Hz, 1H(, 4.62 – 4.55)m, 2H(, 4.55 – 4.48)m, 2H(, 4.45)d, J = 7.8 Hz, 1H(, 4.31)dd, J = 5.0, 2.4 Hz, 1H(, 4.24)dd, J = 7.9, 1.7 Hz, 1H(, 4.15)dd, *J* = 10.7, 3.7 Hz, 1H(, 4.09 – 4.07)m, 1H(, 3.75 – 3.70)m, 2H(, 3.68)dd, *J* = 10.8, 4.4 Hz, 1H(, 3.65 – 3.58)m, 2H(, 3.48 – 3.40)m, 2H(, 1.50)s, 3H(, 1.45)s, 3H(, 1.32 – 1.29)m, 6H(. The NMR data was matching with the literature report.[15]



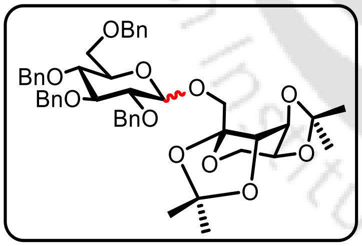
Methyl 2,3,4-tri-O-benzyl-6-O-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-α-D-glucopyranoside (**3b(:** Glycosylation of **1a**)50.0 mg, 0.07 mmol(with **2b**)50.1 mg, 0.11 mmol(according to **General Procedure** afforded **3b** as a colorless syrup)58.7 mg, 85 %, β only(. The crude product was purified through column chromatography, R_f = 0.6)Hexane/EtOAc = 5:1, v/v(. ^{1}H NMR)600 MHz, $CDCl_3$(δ 7.36 – 7.28)m, 15H(, 7.29 – 7.23)m, 13H(, 7.21 – 7.14)m, 7H(, 4.98)d, *J* = 6.5 Hz, 1H(, 4.96)d, *J* = 6.3 Hz, 1H(, 4.91)dd, *J* = 12.9, 7.3 Hz, 1H(, 4.81 – 4.76)m, 4H(, 4.75)d, *J* = 11.1 Hz, 1H(, 4.72)d, *J* = 11.1 Hz, 1H(, 4.65)d, *J* = 12.1 Hz, 1H(, 4.61)d, *J* = 3.3 Hz, 1H(, 4.59)d, *J* = 12.3 Hz, 1H(, 4.55 – 4.49)m, 3H(, 4.35)d, *J* = 7.8 Hz, 1H(, 4.18)d, *J* = 9.8 Hz, 1H(, 3.99)t, *J* = 9.3 Hz, 1H(, 3.83)dd, *J* = 9.8, 3.1 Hz, 1H(, 3.72)d, *J* = 10.0 Hz, 1H(, 3.67)dd, *J* = 9.7, 4.9 Hz, 2H(, 3.63)t, *J* = 9.0 Hz, 1H(, 3.57)t, *J* = 9.3 Hz, 1H(, 3.53 – 3.46)m, 3H(, 3.46 – 3.40)m, 1H(, 3.32)s, 3H(. ^{13}C NMR)151 MHz, $CDCl_3$(δ 138.8, 138.5, 138.4, 138.3, 138.2, 138.11, 138.07, 128.43, 128.37, 128.34, 128.32, 128.31, 128.1, 128.0, 127.92, 127.89, 127.85, 127.8, 127.7, 127.64, 127.59, 127.6, 127.52, 127.49, 103.8, 98.0, 84.8, 82.1, 82.0, 79.6, 78.0, 77.9, 75.70, 75.66, 75.02, 74.98, 74.87, 74.86, 73.4, 73.3, 69.8, 69.0, 68.5, 55.2. The NMR data was matching with the literature report.[19]



Methyl 2,3,4-tri-O-benzyl-6-O-)2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl(-α-D-galactopyranoside (3c): Glycosylation of **1a**)50.4 mg, 0.07 mmol(with **2c**)51.3 mg, 0.11 mmol(according to **General Procedure** afforded **3c** as a colorless syrup)55.2 mg, 81 %, β only(. The crude product was purified through column chromatography, R_f = 0.6)Hexane/EtOAc = 5:1, v/v(. ^{1}H NMR)600 MHz, $CDCl_3$(δ 7.38 – 7.33)m, 6H(, 7.32 – 7.29)m, 12H(, 7.29 – 7.24)m, 16H(, 7.16 – 7.12)m, 2H(, 4.94)d, *J* = 11.3 Hz, 1H(, 4.89)d, *J* = 10.7 Hz, 1H(, 4.84 – 4.79)m, 3H(, 4.77)d, *J* = 10.9 Hz, 1H(, 4.70 – 4.66)m, 3H(, 4.65 – 4.62)m, 2H(, 4.57)d, *J* = 12.1 Hz, 1H(, 4.52)d, *J* = 10.8 Hz, 1H(, 4.52)d, *J* = 10.8 Hz, 1H(, 4.38)d, *J* = 7.8 Hz, 1H(, 4.04)dd, *J* = 10.0, 3.5 Hz, 1H(, 3.93 – 3.89)m, 2H(, 3.88 – 3.82)m, 2H(, 3.74 – 3.67)m, 3H(, 3.66 – 3.59)m, 2H(, 3.43 – 3.38)m, 2H(, 3.29)s, 3H(. ^{13}C NMR)151 MHz, CDCl$_3$(δ 138.8, 138.6, 138.5, 138.47, 138.14, 138.07, 128.38, 128.36, 128.34, 128.25, 128.10, 128.06, 127.93, 127.86, 127.8, 127.74, 127.7, 127.64, 127.59, 127.53, 127.51, 103.7, 98.8, 84.6, 82.4, 79.0, 77.7, 76.4, 75.7, 75.5, 75.0, 74.8, 74.71, 74.66, 73.6, 73.5, 73.4, 69.7, 69.2, 68.8, 55.4. The NMR data was matching with the literature report.[19]

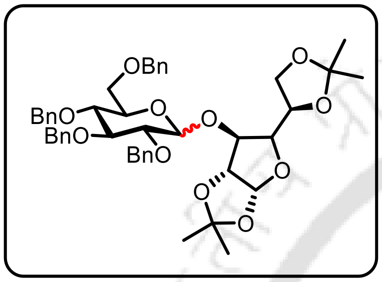


***Methyl-6,2,3-tri-O-benzyl-4-O-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-α-D-glucopyranoside*)3d(:** Glycosylation of **1a**)50.1 mg, 0.07 mmol(with **2d**)51.1 mg, 0.11 mmol(according to **General Procedure** afforded **3d** as a colorless syrup)55.9 mg, 80 %, β only(. The crude product was purified through column chromatography, R$_f$ = 0.5)Hexane/EtOAc = 5:1, v/v(. ^{1}H NMR)500 MHz, CDCl$_3$(δ 7.37 – 7.22)m, 33H(, 7.14 – 7.08)m, 2H(, 4.99)d, J = 11.4 Hz, 1H(, 4.90)d, J = 9.8 Hz, 1H(, 4.81 – 4.77)m, 2H(, 4.73)dt, J = 11.5, 4.1 Hz, 3H(, 4.56)d, J = 6.8 Hz, 1H(, 4.54)d, J = 5.4 Hz, 1H(, 4.52)d, J = 11.5 Hz, 1 H(, 4.45)d, J = 12.6 Hz, 1H(, 4.37)d, J = 12.1 Hz, 1 H(, 4.36 - 4.39)m, 2 H(, 3.96)dd, J = 9.4, 9.4 Hz, 1H(, 3.77)t, J = 9.2 Hz, 1H(, 3.71 – 3.68)m, 1H(, 3.57 - 3.61)m, 1 H(, 3.59)dd, J = 10.1, 2.9 Hz, 2H(, 3.56)d, J = 3.0 Hz, 1H(, 3.52)ddd, J = 19.5, 10.1, 7.0 Hz, 2H(, 3.40 – 3.36)m, 1H(, 3.36)s, 3H(, 3.31 – 3.26)m, 1H(. The NMR data was matching with the literature report.[19]

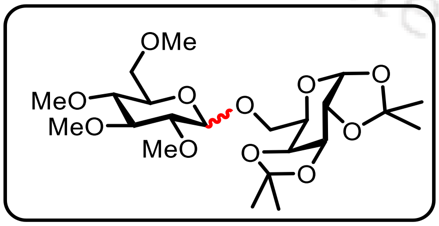


***2,3;4,5-Di-O-isopropylidene-1-O-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyl)-β-D-fructopyranose*)3e(:** Glycosylation of **1a**)51.0 mg, 0.07 mmol(with **2e**)29.5 mg, 0.11 mmol(according to **General Procedure** afforded **3e** as a colorless syrup)43.3 mg, 79 %, α: β = 38:62(. The crude product was purified through column chromatography, R$_f$ = 0.5)Hexane/EtOAc = 5:1, v/v(. ^{1}H NMR)600 MHz, CDCl$_3$(δ 7.38 – 7.34)m, 4H(, 7.34 – 7.24)m, 25H(, 7.20 – 7.17)m, 2H(, 7.14 – 7.11)m, 1H(, 5.00)d, J = 10.7 Hz, 1H(, 4.91)d, J = 10.9 Hz, 1H(, 4.88)d, J = 11.0 Hz, 1H(, 4.85)d, J = 3.4 Hz, 1H(, 4.82)d, J = 10.9 Hz, 1H(, 4.79)d, J = 11.0 Hz, 1H(, 4.76)d, J = 7.5 Hz, 1H(, 4.74)d, J = 8.3 Hz, 1H(, 4.68)d, J = 10.7 Hz, 1H(, 4.67 – 4.61)m, 2H(, 4.60 – 4.56)m, 1H(, 4.56 – 4.53)m, 3H(, 4.52 – 4.49)m, 2H(, 4.47)d, J = 10.9 Hz, 1H(, 4.44)d, J = 12.1 Hz, 1H(, 4.24 – 4.21)m, 2H(, 3.98 – 3.90)m, 4H(, 3.89)d, J = 10.6 Hz, 1H(, 3.85 – 3.82)m, 1H(, 3.78

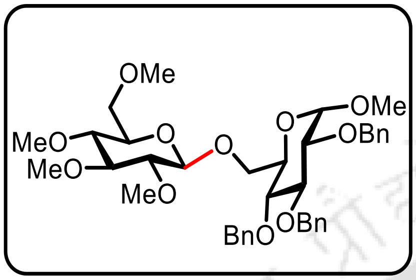
– 3.74)m, 2H(, 3.73 – 3.72)m, 1H(, 3.71)dd, *J* = 10.5, 2.1 Hz, 1H(, 3.68)d, *J* = 9.3 Hz, 1H(, 3.67 – 3.64)m, 2H(, 3.62)dd, *J* = 10.7, 1.7 Hz, 1H(, 3.57)dd, *J* = 9.6, 3.5 Hz, 1H(, 3.51 – 3.47)m, 1H(, 3.45 – 3.42)m, 1H(, 3.40)d, *J* = 10.6 Hz, 1H(, 1.53)s, 3H(, 1.52)s, 3H(, 1.48)s, 3H(, 1.44)s, 3H(, 1.42)s, 3H(, 1.36)s, 3H(, 1.31)s, 3H(. ^{13}C NMR)151 MHz, CDCl$_3$(δ 138.7, 138.6, 138.5, 138.43, 138.40, 138.2, 137.9, 128.39, 128.37, 128.36, 128.32, 128.27, 128.1, 128.0, 127.9, 127.82, 127.75, 127.74, 127.67, 127.65, 127.61, 127.59, 127.5, 108.9, 108.8, 108.7, 103.2, 102.24, 102.18, 98.2, 84.8, 82.5, 81.9, 80.3, 77.8, 77.5, 75.7, 75.5, 75.1, 75.0, 74.9, 73.7, 73.5, 73.1, 71.1, 71.0, 70.4, 70.24, 70.16, 70.1, 69.5, 69.4, 68.9, 68.2, 61.13, 61.09, 26.7, 26.6, 26.02, 25.97, 25.7, 25.5, 24.12, 24.09. The NMR data was matching with the literature report.[18]



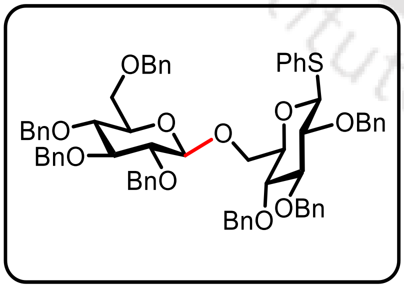
1,2;4,6-Di-O-isopropylidene-3-O-(2,3,4,6-tetra-O-benzyl-D-glucopyranosyl)-β-D-glucofuranose **)3f(**: Glycosylation of **1a**)49.1 mg, 0.07 mmol(with **2f**)28.1 mg, 0.11 mmol(according to **General Procedure** afforded **3f** as a colorless syrup)73 %, α: β = 43:57(. The crude product was purified through column chromatography, R$_f$ = 0.6)Hexane/EtOAc = 4:1, v/v(. ^{1}H NMR)500 MHz, CDCl$_3$(δ 7.38 – 7.24)m, 31H(, 7.20 – 7.15)m, 2H(, 7.16 – 7.13)m, 3H(, 5.99)d, *J* = 3.7 Hz, 1H(, 5.76)d, *J* = 3.7 Hz, 1H(, 5.00)d, *J* = 10.8 Hz, 1H(, 4.92)d, *J* = 6.3 Hz, 1H(, 4.90)d, *J* = 6.4 Hz, 1H(, 4.84 – 4.77)m, 1H(, 4.76)d, *J* = 10.8 Hz, 1H(, 4.73)s, 1H(, 4.66)d, *J* = 10.8 Hz, 1H(, 4.61)d, *J* = 12.2 Hz, 1H(, 4.59 – 4.55)m, 1H(, 4.52)dd, *J* = 16.1, 5.2 Hz, 1H(, 4.45)dd, *J* = 16.8, 6.9 Hz, 1H(, 4.36)d, *J* = 6.8 Hz, 1H(, 4.26)dd, *J* = 7.4, 3.7 Hz, 1H(, 4.20)t, *J* = 8.4 Hz, 1H(, 4.07)d, *J* = 6.3 Hz, 1H(, 3.87)t, *J* = 6.7 Hz, 1H(, 3.71)q, *J* = 9.2 Hz, 1H(, 3.62)dt, *J* = 16.6, 10.0 Hz, 1H(, 3.49 – 3.41)m, 1H(, 3.39)d, *J* = 8.0 Hz, 1H(, 1.49)s, 3H(, 1.46)s, 3H(, 1.42)s, 6H(, 1.34)s, 3H(, 1.32)s, 6H(, 1.31)s, 3H(. The NMR data was matching with the literature report.[19]



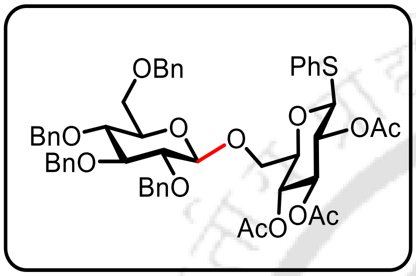
1,2;3,4-Di-O-isopropylidene-6-O-(2,3,4,6-tetra-O-methyl- D -glucopyranosyl)- D -galactopyranose (3g): Glycosylation of **1c**)27.0 mg, 0.07 mmol(with **2a**)28.1 mg, 0.11 mmol(according to **General Procedure** afforded **3g** as a colorless syrup)28.1 mg, 84 %, α: β = 4:96(. The crude product was purified through column chromatography, R$_f$ = 0.5)Hexane/EtOAc = 4:1, v/v(. ^{1}H NMR)600 MHz, CDCl$_3$(δ 5.52)dd, *J* = 14.8, 5.0 Hz, 1H(, 4.59)dd, *J* = 7.9, 1.8 Hz, 1H(, 4.32 – 4.28)m, 2H(, 4.23)d, J = 7.9 Hz, 1H(, 4.07)dd, J = 10.9, 3.5 Hz, 1H(, 4.01)dd, J = 5.6, 1.6 Hz, 1H(, 3.66)dt, J = 15.0, 7.5 Hz, 1H(, 3.63 – 3.60)m, 4H(, 3.59)s, 3H(, 3.55)dd, J = 10.8, 4.4 Hz, 1H(, 3.52)s, 3H(, 3.39)s, 3H(, 3.25– 3.23)m, 1H(, 3.18 – 3.13)m, 2H(, 3.00)dd, J = 10.0, 6.2 Hz, 1H(, 1.50)s, 3H(, 1.44)s, 3H(, 1.32)s, 6H(. ^{13}C NMR)151 MHz, $CDCl_3$(δ 109.4, 108.6, 104.1, 96.3, 86.1, 83.7, 79.2, 74.5, 71.4, 71.2, 70.7, 70.5, 69.4, 67.6, 60.8, 60.40, 60.36, 59.3, 26.0, 25.2, 24.4. HRMS)ESI(m/z: [M+NH_4[$^+$ calcd for $C_{22}H_{42}NO_{11}$ 496.2752; Found 496.2734.



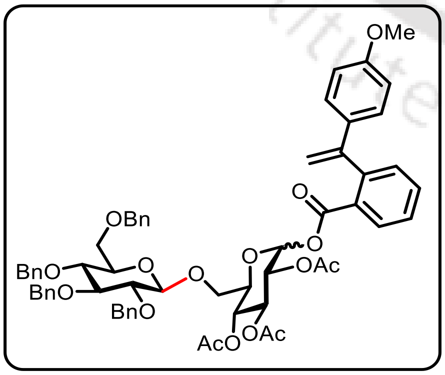
***Methyl 2,3,4-tri-O-benzyl-6-O-(2,3,4,6-tetra-O-methyl-β-D-glucopyranosyl)-α-D-glucopyranoside*)3h(:** Glycosylation of **1c**)27.2 mg, 0.07 mmol(with **2b**)49.9 mg, 0.11 mmol(according to **General Procedure** afforded **3h** as a colorless syrup)35.4 mg, 74 %, β only(. The crude product was purified through column chromatography, R_f = 0.6)Hexane/EtOAc = 4:1, v/v(. ^{1}H NMR)400 MHz, $CDCl_3$(δ 7.37 – 7.27)m, 15H(, 4.97)d, J = 10.8 Hz, 1H(, 4.89)d, J = 10.8 Hz, 1H(, 4.84 – 4.76)m, 1H(, 4.66)d, J = 4.1 Hz, 1H(, 4.63)d, J = 2.7 Hz, 1H(, 4.60)d, J = 3.5 Hz, 1H(, 4.21)d, J = 7.7 Hz, 1H(, 4.13)d, J = 9.3 Hz, 1H(, 3.99)t, J = 9.3 Hz, 1H(, 3.79)dd, J = 10.0, 3.0 Hz, 1H(, 3.66)dd, J = 10.8, 4.6 Hz, 1H(, 3.61)s, 3H(, 3.60 – 3.56)m, 4H(, 3.54)d, J = 5.0 Hz, 1H(, 3.53 – 3.50)m, 4H(, 3.37)s, 3H(, 3.36)s, 3H(, 3.27 – 3.20)m, 1H(, 3.14)t, J = 8.8 Hz, 1H(, 3.10 – 2.99)m, 2H(. ^{13}C NMR)151 MHz, $CDCl_3$(δ 138.7, 138.4, 138.2, 128.5, 128.42, 128.40, 128.13, 128.09, 127.9, 127.8, 127.7, 127.6, 103.5, 98.0, 86.6, 83.5, 82.1, 79.8, 79.6, 78.0, 75.9, 74.9, 74.8, 73.4, 71.6, 69.8, 68.3, 60.8, 60.7, 60.4, 59.4, 55.1. HRMS)ESI) m/z: [M+NH_4[$^+$ calcd for $C_{38}H_{54}NO_{11}$ 700.3691; Found 700.3669. The NMR data was matching with the literature report.[19]



Phenyl 2,3,4-tri-O-benzyl-6-O-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (3i): Glycosylation of **1a**)50.4 mg, 0.07 mmol(with **2h**)60.0 mg, 0.11 mmol(according to **General Procedure** afforded **3i** as a colorless syrup)62.6 mg, 84 %, β only(. The crude product was purified through column chromatography, R_f = 0.6)Hexane/EtOAc = 5:1, v/v(. ^{1}H NMR)500 MHz, $CDCl_3$(δ 7.50 – 7.43)m, 2H(, 7.32 – 7.28)m, 2H(, 7.27 – 7.12)m, 31H(, 7.11 – 7.10)m, 5H(, 4.87)dd, *J* = 11.0, 5.5 Hz, 1H(, 4.83)d, *J* = 11.0 Hz, 1H(, 4.78 – 4.71)m, 2H(, 4.71 – 4.68)m, 1H(, 4.67 – 4.61)m, 3H(, 4.58)m, 3H(, 4.52)dd, *J* = 10.8, 6.1 Hz, 2H(, 4.47 – 4.39)m, 2H(, 4.41 – 4.31)m, 2H(, 3.90)dt, *J* = 10.7, 5.9 Hz, 1H(, 3.87 – 3.73)m, 3H(, 3.64 – 3.55)m, 3H(, 3.52)dd, *J* = 13.8, 4.9 Hz, 2H(, 3.49 – 3.42)m, 2H(, 3.35 – 3.30)m, 1H(. ^{13}C NMR)126 MHz, CDCl$_3$(δ 138.9, 138.8, 138.7, 138.6, 138.53, 138.51, 138.5, 138.4, 138.3, 138.2, 138.1, 134.4, 131.8, 131.4, 129.0, 128.9, 128.6, 128.5, 128.45, 128.4, 128.2, 128.1, 128.02, 127.98, 127.9, 127.84, 127.8, 127.75, 127.7, 127.2, 127.1, 103.8, 87.9, 87.8, 84.8, 84.3, 82.5, 82.2, 80.0, 79.4, 77.9, 77.89, 75.79, 75.75, 75.1, 74.9, 74.50, 73.90, 69.0, 68.7. The NMR data was matching with the literature report.[15]

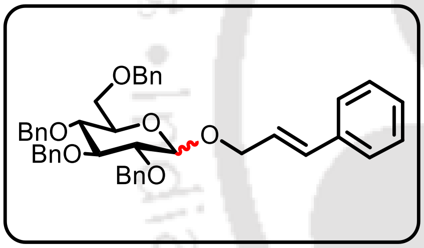


Phenyl 2,3,4-tri-O-acetyl-6-O-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside **)3j(:** Glycosylation of **1a**)47.9 mg, 0.07 mmol(with **2g**)44.5 mg, 0.11 mmol(according to **General Procedure** afforded **3j** as a colorless syrup)30.1 mg, 72 %, β only(. The crude product was purified through column chromatography, R$_f$ = 0.5)Hexane/EtOAc = 5:1, v/v(. ^{1}H NMR)600 MHz, CDCl$_3$(δ 7.37 – 7.25)m, 23H(, 7.24 – 7.22)m, 2H(, 5.45)s, 1H(, 4.66 – 4.62)m, 1H(, 4.55)t, *J* = 10.2 Hz, 2H(, 4.51)dd, *J* = 11.6, 5.3 Hz, 2H(, 4.45)t, *J* = 12.0 Hz, 2H(, 4.14 – 4.10)m, 1H(, 4.0 – 3.97)m, 1H(, 3.91 – 3.85)m, 1H(, 3.82)dd, *J* = 10.6, 4.0 Hz, 1H(, 3.71 – 3.68)m, 1H(, 3.31 – 3.23)q, *J* = 7.0 Hz, 7H(, 1.33)s, 3H(, 1.32)s, 3H(, 1.31)s, 3H(. ^{13}C NMR)151 MHz, CDCl$_3$(δ 171.2, 171.0, 170.3, 138.1, 137.6, 137.4, 128.6, 128.52, 128.48, 128.4, 128.02, 128.00, 127.97, 127.8, 127.7, 103.2, 86.5, 84.9, 78.4, 76.1, 73.31, 73.25, 71.9, 69.4, 58.9, 22.7. The NMR data was matching with the literature report.[19]

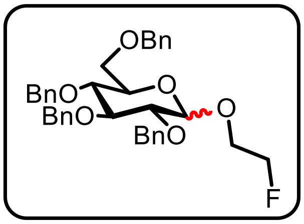


1-O-)2-)1-phenylvinyl(benzoyl(-2,3,4,6-tetra-O-benzyl-)2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)-D-glucopyranose (3k)**:** Glycosylation of **1a**)51.0 mg, 0.07 mmol(with **2i**)α**:** β = 86**:** 14**(**)60.1 mg, 0.11 mmol(according to **General Procedure** afforded **3k** as a colorless syrup

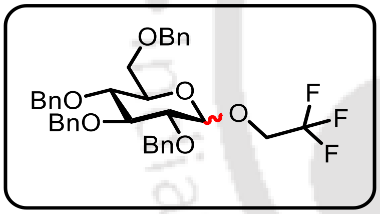
)52.1 mg, 70 %, β only(. The crude product was purified through column chromatography, R_f = 0.5)Hexane/EtOAc = 4:1, v/v(. ^{1}H NMR)600 MHz, $CDCl_3$(δ 7.87)d, *J* = 6.9 Hz, 1H(, 7.82)dd, *J* = 7.8, 0.9 Hz, 1H(, 7.67)dd, *J* = 7.8, 0.9 Hz, 1H(, 7.53 – 7.48)m, 1H(, 7.42 – 7.36)m, 1H(, 7.32 – 7.29)m, 8H(, 7.29 – 7.26)m, 10H(, 7.26 – 7.24)m, 5H(, 7.23 – 7.21)m, 2H(, 7.16 – 7.12)m, 3H(, 7.07)d, *J* = 8.9 Hz, 3H(, 6.82 – 6.78)m, 2H(, 6.73)d, *J* = 8.9 Hz, 1H(, 6.47)d, *J* = 3.7 Hz, 1H(, 6.21)t, *J* = 6.2 Hz, 1H(, 5.79)s, 1H(, 5.77)s, 1H(, 5.52)d, *J* = 8.1 Hz, 1H(, 5.30)s, 1H(, 5.25)t, *J* = 9.6 Hz, 1H(, 5.05 – 5.01)m, 1H(, 5.00)s, 1H(, 4.97 – 4.93)m, 1H(, 4.90 – 4.87)m, 3H(, 4.80)d, *J* = 10.9 Hz, 1H(, 4.75 – 4.73)m, 1H(, 4.61 – 4.57)m, 3H(, 4.54 – 4.48)m, 3H(, 4.37)d, *J* = 7.8 Hz, 1H(, 4.35 – 4.33)m, 1H(, 4.32)d, *J* = 7.7 Hz, 1H(, 3.98 – 3.91)m, 1H(, 3.81)dd, *J* = 10.9, 1.9 Hz, H(, 3.77 – 3.74)m, 2H(, 3.73)s, 3H(, 3.71)s, 1H(, 3.69 – 3.64)m, 3H(, 3.62 – 3.55)m, 3H(, 3.44 – 3.37)m, 4H(, 1.99)s, 1H(, 1.98)s, 3H(, 1.96)s, 1H(, 1.94)s, 3H(, 1.89)s, 1H(, 1.88)s, 3H(.^{13}C NMR)151 MHz, $CDCl_3$(δ 170.3, 170.1, 169.8, 169.5, 168.4, 166.0, 159.3, 148.3, 147.3, 143.5, 143.3, 138.6, 138.4, 138.1, 138.1, 133.2, 132.4, 132.0, 131.0, 130.5, 130.1, 129.7, 128.4, 128.3, 128.3, 128.2, 128.2, 128.1, 128.0, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6, 127.6, 127.5, 113.8, 113.6, 113.5, 112.7, 103.8, 103.7, 91.9, 89.8, 88.7, 84.5, 81.9, 77.7, 75.7, 75.65, 75.0, 74.9, 74.8, 74.6, 73.5, 71.0, 70.9, 70.2, 70.2, 69.5, 69.4, 68.9, 68.4, 68.3, 67.9, 55.2, 55.2, 22.7, 20.7, 20.6, 20.5, 20.4, 20.3. HRMS)ESI) m/z: $[M+NH_4[^+$ calcd for $C_{62}H_{68}NO_{16}$ 1082.4533; Found 1082.4505.



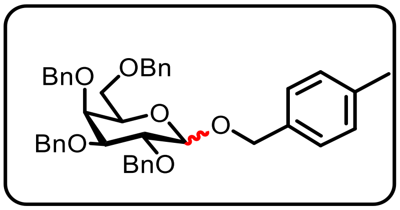
Cinnamyl-2,3,4,6-tetra-O-benzyl-D-glucopyranoside (3l)**:** Glycosylation of **1a**)50.6 mg, 0.07 mmol(with **2j**)15.1 mg, 0.11 mmol(according to **General Procedure** afforded **3l** as a colorless syrup)40.9 mg, 89 %, α: β = 19: 81(. The crude product was purified through column chromatography, R_f = 0.5)Hexane/EtOAc = 5:1, v/v(. ^{1}H NMR)600 MHz, $CDCl_3$(δ 7.40 – 7.24)m, 25H(, 7.24 – 7.20)m, 2H(, 7.17 – 7.11)m, 2H(, 6.63)dd, *J* = 21.1, 16.1 Hz, 2H(, 6.31)dt, *J* = 15.9, 5.9 Hz, 2H(, 5.00)t, *J* = 10.7 Hz, 1H(, 4.93)d, *J* = 10.9 Hz, 1H(, 4.87)d, *J* = 3.4 Hz, 1H(, 4.84 – 4.82)m, 1H(, 4.82 – 4.77)m, 2H(, 4.76)d, *J* = 11.0 Hz, 1H(, 4.65 – 4.60)m, 2H(, 4.60 – 4.56)m, 2H(, 4.55)d, *J* = 4.5 Hz, 1H(, 4.53 – 4.49)m, 2H(, 4.47)dd, *J* = 11.5, 4.6 Hz, 1H(, 4.35 – 4.28)m, 1H(, 4.18)dd, *J* = 12.7, 7.3 Hz, 1H(, 4.03)t, *J* = 9.3 Hz, 1H(, 3.84)d, *J* = 9.6 Hz, 1H(, 3.75)d, *J* = 10.4 Hz, 1H(, 3.74 – 3.71)m, 1H(, 3.71 – 3.67)m, 2H(, 3.66 – 3.63)m, 2H(, 3.63 – 3.56)m, 2H(, 3.51)t, *J* = 8.4, 3.0 Hz, 1H(, 3.47)dd, *J* = 9.5, 4.0 Hz, 1H(, 3.45 – 3.42)m, 1H(. ^{13}C NMR)151 MHz, $CDCl_3$(δ 138.9, 138.6, 138.5, 138.24, 138.18, 138.15, 138.1, 137.9, 136.6, 136.5, 133.7, 132.7, 128.6, 128.5, 128.4, 128.14, 128.07, 128.0, 127.9, 127.84, 127.82, 127.77, 127.75, 127.72, 127.70, 127.64, 127.61, 127.6, 126.6, 126.5, 125.4, 124.9, 102.7, 95.7, 84.7, 82.3, 82.2, 79.8, 77.9, 77.8, 75.8, 75.7, 75.1, 75.0, 74.9, 73.5, 73.4, 70.3, 70.0, 69.0, 68.5, 67.8. The NMR data was matching with the literature report.[21]



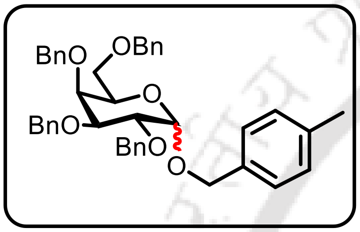
(2’-fluoro)-ethyl-2,3,4,6-tetra-O-benzyl-D-glucopyranoside (3m)**:** Glycosylation of **1a**)50.4 mg, 0.07 mmol(with **2l**)7.3 mg, 0.11 mmol(according to **General Procedure** afforded **3m** as a colorless syrup)34.9 mg, 81 %, α: β = 10: 90(. The crude product was purified through column chromatography, R$_f$ = 0.6)Hexane/EtOAc = 5:1, v/v(. ^{1}H NMR)500 MHz, CDCl$_3$(δ 7.45 – 7.22)m, 20H(, 7.15)dd, *J* = 7.3, 2.4 Hz, 2H(, 5.00 – 4.91)m, 2H(, 4.84 – 4.76)m, 2H(, 4.71)d, *J* = 10.8 Hz, 1H(, 4.69 – 4.63)m, 1H(, 4.63 – 4.57)m, 1H(, 4.56 – 4.50)m, 2H(, 4.48)d, *J* = 6.1 Hz, 1H(, 4.45)d, *J* = 7.8 Hz, 1H(, 4.11)dddd, *J* = 33.1, 12.1, 4.7, 2.5 Hz, 1H(, 4.03 – 3.98)m, 1H(, 3.86)dddd, *J* = 25.1, 12.3, 7.3, 2.8 Hz, 1H(, 3.73)dd, *J* = 10.8, 2.0 Hz, 1H(, 3.70 – 3.62)m, 2H(, 3.59)t, *J* = 9.3 Hz, 1H(, 3.51 – 3.43)m, 2H(, 3.39 – 3.35)m, 1H(. ^{13}C NMR)126 MHz, CDCl$_3$(δ 138.6, 138.4, 138.0, 128.39, 128.38, 128.0, 127.9, 127.8, 127.8, 127.72, 127.69, 127.6, 103.8, 84.5, 83.3, 82.1, 82.0, 77.7, 75.7, 75.0, 74.9, 74.8, 73.5, 69.0, 68.9, 68.8. ^{19}F NMR)471 MHz, CDCl$_3$(δ -218.22, -219.00. HRMS)ESI) m/z: [M+NH$_4$[$^+$calcd for C$_{36}$H$_{43}$FNO$_6$ 604.3069; Found 604.3060.



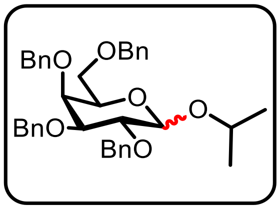
(2’2’2’-trifluoro)-ethyl-2,3,4,6-tetra-O-benzyl-D-glucopyranoside (3n)**:** Glycosylation of **1a**)50.2 mg, 0.07 mmol(with **2m**)11.0 mg, 0.11 mmol(according to **General Procedure** afforded **3n** as a colorless syrup)28.7 mg, 66 %, α: β = 34: 66(. The crude product was purified through column chromatography, R$_f$ = 0.5)Hexane/EtOAc = 5:1, v/v(. ^{1}H NMR)500 MHz, CDCl$_3$(δ 7.36 – 7.27)m, 25H(, 7.16 – 7.12)m, 3H(, 5.00)d, *J* = 5.2 Hz, 1H(, 4.98)d, *J* = 5.2 Hz, 1H(, 4.94)d, *J* = 5.4 Hz, 1H(, 4.91)d, *J* = 5.0 Hz, 1H(, 4.84 – 4.77)m, 4H(, 4.71 – 4.66)m, 1H(, 4.64 – 4.57)m, 3H(, 4.55 – 4.48)m, 3H(, 4.22)dq, *J* = 12.5, 8.7 Hz, 1H(, 4.00 – 3.92)m, 2H(, 3.88)q, *J* = 8.7 Hz, 1H(, 3.73 – 3.69)m, 2H(, 3.67 – 3.65)m, 1H(, 3.64 – 3.60)m, 2H(, 3.50)t, *J* = 8.0 Hz, 1H(, 3.47 – 3.43)m, 1H(. ^{19}F NMR)471 MHz, CDCl$_3$(δ -73.53, -74.11. The NMR data was matching with the literature report.[20]



(4'-methyl)-benzyl-2,3,4,6-tetra-O-benzyl-D-galactopyranoside (3o)**:** Glycosylation of **1b**)50 mg, 0.07 mmol(with **2n**)13.6 mg, 0.11 mmol(according to **General Procedure** at **-**50 °C, afforded **3o** as a colorless syrup)40.9 mg, 87 %, α: β = 10: 90(. The crude product was purified through column chromatography, $R_f = 0.5$)Hexane/EtOAc = 6:1, v/v(.^{1}H NMR)600 MHz, $CDCl_3$(δ 7.37 – 7.22)m, 25H(, 7.11)d, J = 7.4 Hz, 2H(, 4.94)d, J = 11.8 Hz, 1H(, 4.93 – 4.88)m, 2H(, 4.74)d, J = 12.4 Hz, 2H(, 4.69)d, J = 11.8 Hz, 1H(, 4.62)d, J = 11.7 Hz, 1H(, 4.59)d, J = 11.9 Hz, 1H(, 4.48 – 4.40)m, 3H(, 3.90 – 3.83)m, 2H(, 3.68 – 3.58)m, 2H(, 3.55 – 3.48)m, 2H(, 2.35)s, 1H(, 2.33)s, 3H(. ^{13}C NMR)151 MHz, $CDCl_3$(δ 138.7, 138.64, 138.55, 138.0, 137.3, 134.6, 129.0, 128.5, 128.4, 128.23, 128.18, 128.1, 127.9, 127.8, 127.6, 127.5, 102.7, 82.3, 79.6, 75.2, 74.5, 73.6, 73.54, 73.47, 73.1, 70.8, 68.9, 21.2. HRMS)ESI) m/z: $[M+NH_4[^+$ calcd for $C_{42}H_{48}NO_6$ 662.3476; Found 662.3453.

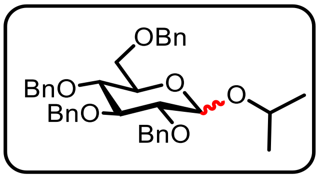


(4'-methyl)-benzyl-2,3,4,6-tetra-O-benzyl-D-galactopyranoside (3p)**:** Glycosylation of **1d**)50.1 mg, 0.07 mmol(with **2n**)13.5 mg, 0.11 mmol(according to **General Procedure** at **-**50 °C, afforded **3p** as a colorless syrup)38.7 mg, 82 %, α: β = 90: 10(. The crude product was purified through column chromatography, $R_f = 0.5$)Hexane/EtOAc = 6:1, v/v(. ^{1}H NMR)400 MHz, $CDCl_3$(δ 7.39 – 7.27)m, 23H(, 7.24)d, *J* = 3.4 Hz, 2H(, 7.13)d, *J* = 7.7 Hz, 2H(, 4.96 – 4.91)m, 2H(, 4.89)d, *J* = 3.3 Hz, 1H(, 4.85)d, *J* = 11.7 Hz, 1H(, 4.76 – 4.68)m, 3H(, 4.65)d, *J* = 12.4 Hz, 1H(, 4.61 – 4.51)m, 4H(, 4.49 – 4.43)m, 2H(, 4.39)d, *J* = 11.8 Hz, 1H(, 4.00)dd, *J* = 5.7, 2.9 Hz, 2H(, 3.98 – 3.95)m, 2H(, 3.53)dd, *J* = 9.4, 6.8 Hz, 1H(, 3.47)dd, *J* = 9.3, 6.0 Hz, 1H(, 2.35)s, 3H(, 2.33)s, 1H(. ^{13}C NMR)151 MHz, $CDCl_3$(δ 138.9, 138.7, 138.6, 138.1, 137.9, 137.4, 134.3, 129.3, 129.0, 128.6, 128.4, 128.3, 128.22, 128.20, 127.9, 127.6, 127.7, 127.53, 127.50, 127.47, 127.4, 127.1, 95.8, 79.2, 76.5, 75.1, 74.7, 73.5, 73.2, 73.1, 69.4, 69.0, 68.9, 65.3, 50.9, 21.2. HRMS)ESI) m/z: $[M+NH_4[^+$ calcd for $C_{42}H_{48}NO_6$ 662.3476; Found 662.3460.

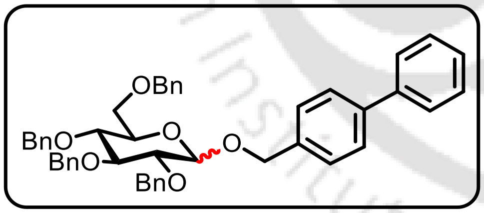


isopropyl-2,3,4,6-tetra-O-benzyl-D-galactopyranoside (3q)**:** Glycosylation of **1b**)49.7 mg, 0.07 mmol(with **2o**)6.6 mg, 0.11 mmol(according to **General Procedure** at **-**50 °C, afforded **3q** as a colorless syrup)38.1 mg, 90 %, α: β = 5: 95(. The crude product was purified through column chromatography, $R_f = 0.6$)Hexane/EtOAc = 5:1, v/v(. ^{1}H NMR)600 MHz, $CDCl_3$(δ 7.38 – 7.24)m, 20H(, 4.94)d, J = 4.4 Hz, 1H(, 4.92)d, J = 5.4 Hz, 1H(, 4.75)dd, J = 11.0, 7.3 Hz, 2H(, 4.70

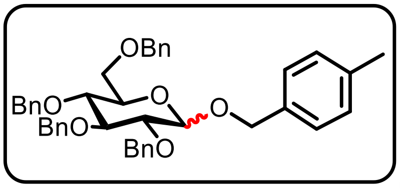
)d, J = 11.8 Hz, 1H(, 4.62)d, J = 11.7 Hz, 1H(, 4.46 – 4.39)m, 3H(, 3.98)dt, J = 12.2, 6.2 Hz, 1H(, 3.88 – 3.85)m, 1H(, 3.78)t, J = 8.7 Hz, 1H(, 3.57)d, J = 6.2 Hz, 2H(, 3.53 – 3.48)m, 2H(, 1.27)d, J = 6.6 Hz, 3H(, 1.21)d, J = 6.1 Hz, 3H(. ^{13}C NMR)151 MHz, CDCl$_3$(δ 138.9, 138.7, 138.6, 138.0, 128.42, 128.35, 128.3, 128.23, 128.15, 127.9, 127.8, 127.54, 127.52, 102.5, 95.5, 82.4, 79.6, 75.2, 74.5, 73.6, 73.5, 73.4, 73.1, 72.1, 69.1, 23.7, 22.2. The NMR data was matching with the literature report.[17]



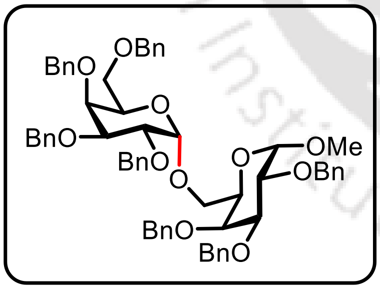
isopropyl-2,3,4,6-tetra-O-benzyl-D-glucopyranoside (3r)**:** Glycosylation of **1a**)49.9 mg, 0.07 mmol(with **2o**)6.5 mg, 0.11 mmol(according to **General Procedure** afforded **3r** as a colorless syrup)38.1 mg, 90 %, α: β = 5: 95(. The crude product was purified through column chromatography, R$_f$ = 0.5)Hexane/EtOAc = 5:1, v/v(. ^{1}H NMR)600 MHz, CDCl$_3$(δ 7.38 – 7.24)m, 20H(, 7.17)d, J = 6.9 Hz, 2H(, 7.13)d, J = 6.8 Hz, 1H(, 4.97)d, J = 10.9 Hz, 1H(, 4.92)d, J = 10.9 Hz, 1H(, 4.81)d, J = 10.7 Hz, 1H(, 4.78)d, J = 10.9 Hz, 1H(, 4.70)d, J = 10.9 Hz, 1H(, 4.60)d, J = 12.3 Hz, 1H(, 4.58 – 4.52)m, 2H(, 4.46)d, J = 7.9 Hz, 1H(, 4.07 – 3.96)m, 1H(, 3.73)d, J = 10.6 Hz, 1H(, 3.68 – 3.60)m, 2H(, 3.54)t, J = 9.3 Hz, 1H(, 3.47 – 3.41)m, 2H(, 1.31)d, J = 6.1 Hz, 3H(, 1.26 – 1.21)m, 3H(, 1.18)d, J = 6.0 Hz, 1H(. ^{13}C NMR)151 MHz, CDCl$_3$(δ 139.0, 138.7, 138.6, 138.31, 138.26, 138.2, 138.0, 128.38, 128.36, 128.3, 128.2, 128.0, 127.9, 127.74, 127.71, 127.65, 127.6, 127.5, 102.2, 94.8, 84.9, 82.3, 82.1, 79.9, 78.0, 75.7, 75.14, 74.99, 74.8, 73.4, 72.4, 70.0, 69.2, 69.0, 68.6, 23.7, 23.2, 22.2, 21.2. The NMR data was matching with the literature report.[17]



(4'-phenyl)-benzyl-2,3,4,6-tetra-O-benzyl-D-glucopyranoside (3s)**:** Glycosylation of **1a**)50.5 mg, 0.07 mmol(with **2k**)20.5 mg, 0.11 mmol(according to **General Procedure** afforded **3s** as a colorless syrup)44.8 mg, 86 %, α: β = 17: 83(. The crude product was purified through column chromatography, R$_f$ = 0.6)Hexane/EtOAc = 5:1, v/v(. ^{1}H NMR)600 MHz, CDCl$_3$(δ 7.61 – 7.57)m, 2H(, 7.56 – 7.53)m, 2H(, 7.48 – 7.42)m, 5H(, 7.38 – 7.24)m, 23H(, 7.17)d, *J* = 7.0 Hz, 2H(, 7.14)d, *J* = 6.9 Hz, 1H(, 5.03 – 4.99)m, 1H(, 4.98)d, *J* = 10.9 Hz, 1H(, 4.93)d, *J* = 10.9 Hz, 1H(, 4.87)d, *J* = 3.3 Hz, 1H(, 4.85 – 4.81)m, 2H(, 4.79)d, *J* = 10.9 Hz, 1H(, 4.76 – 4.69)m, 3H(, 4.64)d, *J* = 12.2 Hz, 1H(, 4.61)d, *J* = 6.8 Hz, 1H(, 4.60 – 4.56)m, 2H(, 4.55)d, *J* = 8.9 Hz, 2H(, 4.48)d, *J* = 11.3 Hz, 1H(, 4.05)t, *J* = 9.2 Hz, 1H(, 3.83)d, *J* = 9.8 Hz, 1H(, 3.78)d, *J* = 10.7 Hz, 1H(, 3.74 – 3.67)m, 2H(, 3.67 – 3.60)m, 2H(, 3.60 – 3.57)m, 1H(, 3.55)t, *J* = 8.3 Hz, 1H(, 3.49)dd, *J* = 8.6, 4.0 Hz, 1H(. ^{13}C NMR)151 MHz, CDCl$_3$(δ 140.9, 140.8, 140.7, 138.9, 138.6, 138.4, 138.3, 138.2, 138.1, 138.0, 136.5, 136.2, 129.0, 128.8, 128.5, 128.4, 128.4, 128.2, 128.0, 127.9, 127.9, 127.9, 127.8, 127.8, 127.7, 127.6, 127.6, 127.3, 127.3, 127.2, 127.1, 102.6, 95.8, 84.8, 82.4, 82.2, 79.9, 77.9, 77.8, 75.7, 75.1, 75.0, 74.9, 73.5, 73.5, 73.1, 70.9, 70.4, 69.0, 68.9, 68.4. HRMS)ESI) m/z: [M+NH$_4$[$^+$ calcd for C$_{47}$H$_{50}$NO$_6$ 724.3633; Found 724.3611.

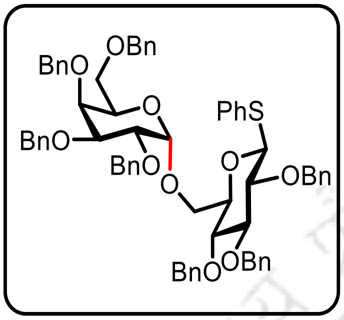


(4'-methyl)-benzyl-2,3,4,6-tetra-O-benzyl-D-glucopyranoside (3t)**:** Glycosylation of **1a**)50.1 mg, 0.07 mmol(with **2n**)13.2 mg, 0.11 mmol(according to **General Procedure** afforded **3t** as a colorless syrup)41.9 mg, 89 %, α: β = 11: 89(. The crude product was purified through column chromatography, R$_f$ = 0.6)Hexane/EtOAc = 5:1, v/v(. ^{1}H NMR)600 MHz, CDCl$_3$(δ 7.37 – 7.31)m, 5H(, 7.30 – 7.24)m, 16H(, 7.18 – 7.11)m, 5H(, 4.99)d, *J* = 10.9 Hz, 1H(, 4.97 – 4.88)m, 3H(, 4.83 – 4.79)m, 1H(, 4.77)d, *J* = 10.9 Hz, 1H(, 4.70)d, *J* = 10.9 Hz, 1H(, 4.67 – 4.59)m, 3H(, 4.57)d, *J* = 12.2 Hz, 1H(, 4.54)d, *J* = 10.9 Hz, 1H(, 4.51 – 4.46)m, 1H(, 4.03)t, *J* = 9.3 Hz, 1H(, 3.81)d, *J* = 9.7 Hz, 1H(, 3.76)d, *J* = 10.6 Hz, 1H(, 3.70)dd, *J* = 10.7, 4.5 Hz, 1H(, 3.66 – 3.57)m, 2H(, 3.55)dd, *J* = 9.7, 3.4 Hz, 1H(, 3.51)t, *J* = 8.1 Hz, 1H(, 3.49 – 3.44)m, 1H(, 2.35 – 2.31)m, 3H(. ^{13}C NMR)151 MHz, CDCl$_3$(δ 138.9, 138.6, 138.5, 138.3, 138.2, 138.1, 138.0, 137.9, 137.5, 137.5, 137.4, 134.4, 134.1, 129.2, 129.1, 129.0, 128.6, 128.4, 128.3, 128.2, 128.2, 128.0, 127.9, 127.8, 127.7, 127.7, 127.6, 127.6, 127.6, 127.5, 127.1, 102.4, 95.3, 84.8, 82.3, 82.2, 79.9, 77.9, 77.8, 75.7, 75.1, 75.0, 74.9, 74.8, 73.5, 72.9, 71.0, 70.3, 69.0, 68.9, 65.3, 21.2, 21.1. HRMS)ESI) m/z: [M+NH$_4$[$^+$ calcd for C$_{42}$H$_{48}$NO$_6$ 662.3476; Found 662.3455.

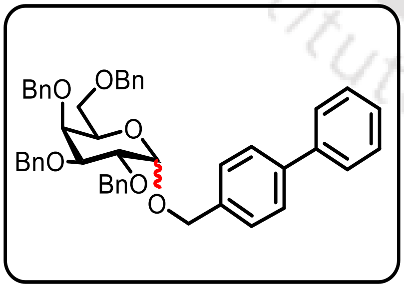


Methyl 2,3,4-tri-O-benzyl-6-O-)2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl(-α-D-galactopyranoside **)3u(**: Glycosylation of **1d**)49.8 mg, 0.07 mmol(with **2c**)50.1 mg, 0.11 mmol(according to **General Procedure** at -50 °C, afforded **3u** as a colorless syrup)51.6 mg, 72 %, α only(. The crude product was purified through column chromatography, R$_f$ = 0.5)Hexane/EtOAc = 5:1, v/v(. ^{1}H NMR)500 MHz, CDCl$_3$(δ 7.38 – 7.31)m, 10H(, 7.32 – 7.21)m, 30H(, 4.95 – 4.87)m, , 2H(, 4.84 – 4.81)m, 1H(, 4.80 – 4.72)m, 5H(, 4.69)d, *J* = 11.6 Hz, 1H(, 4.64)d, *J* = 1.7 Hz, 1H(, 4.63 – 4.60)m, 1H(, 4.56)d, *J* = 7.3 Hz, 1H(, 4.53)d, *J* = 7.3 Hz, 1H(, 4.45)d, *J* = 11.7 Hz, 1H(, 4.37)d, *J* = 11.7 Hz, 1H(, 4.02)dd, *J* = 10.0, 3.6 Hz, 1H(, 3.99 – 3.95)m, 2H(, 3.93)d, *J* =

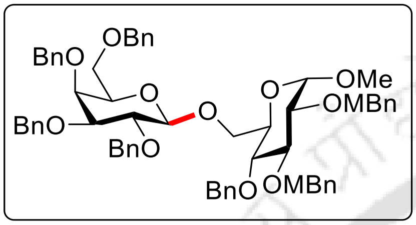
2.7 Hz, 1H(, 3.91 – 3.89)m, 1H(, 3.89 – 3.86)m, 2H(, 3.70)dd, *J* = 9.9, 6.3 Hz, 1H(, 3.58 – 3.53)m, 1H(, 3.49)dd, *J* = 9.2, 5.5 Hz, 1H(, 3.44 – 3.38)m, 1H(, 3.26)s, 3H(. ^{13}C NMR)101 MHz, CDCl$_3$(δ 138.8, 138.7, 138.64, 138.61, 138.5, 137.9, 128.39, 128.37, 128.35, 128.32, 128.29, 128.2, 128.12, 128.08, 127.9, 127.8, 127.72, 127.67, 127.6, 127.5, 127.4, 98.7, 98.1, 79.0, 78.8, 77.2, 76.4, 76.2, 75.4, 74.81, 74.77, 74.62, 73.55, 73.5, 73.4, 73.2, 72.6, 69.3, 69.1, 68.6, 67.3, 55.2. The NMR data was matching with the literature report.[19]



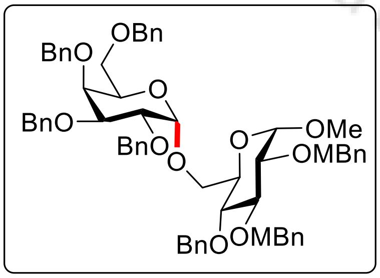
Phenyl 2,3,4-tri-O-acetyl-6-O-(2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl)-1-thio-β-D-glucopyranoside (3v): Glycosylation of **1d**)49.5 mg, 0.07 mmol(with **2h**)58.1 mg, 0.11 mmol(according to **General Procedure** at -50 °C, afforded **3v** as a colorless syrup)56.1 mg, 73 %, α only(. The crude product was purified through column chromatography, R$_f$ = 0.5)Hexane/EtOAc = 6:1, v/v(.^{1}H NMR)600 MHz, CDCl$_3$(δ 7.54)dd, *J* = 6.4, 3.2 Hz, 2H(, 7.37)d, *J* = 7.5 Hz, 4H(, 7.35 – 7.26)m, 22H(, 7.26 – 7.19)m, 9H(, 7.17 – 7.11)m, 3H(, 4.95 – 4.88)m, 2H(, 4.82 – 4.64)m, 9H(, 4.63 – 4.59)m, 2H(, 4.59 – 4.54)m, 2H(, 4.42)d, *J* = 11.6 Hz, 1H(, 4.36)d, *J* = 11.8 Hz, 1H(, 4.01)dd, *J* = 10.0, 3.6 Hz, 1H(, 3.95 – 3.90)m, 3H(, 3.89 – 3.81)m, 3H(, 3.65)t, *J* = 6.3 Hz, 1H(, 3.58)dd, *J* = 9.3, 2.7 Hz, 1H(, 3.53 – 3.48)m, 3H(. ^{13}C NMR)151 MHz, CDCl$_3$(δ 138.8, 138.7, 138.7, 138.6, 138.4, 138.3, 138.0, 134.1, 131.6, 128.8, 128.4, 128.4, 128.3, 128.2, 128.2, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 127.5, 127.5, 127.4, 127.3, 127.0, 98.2, 87.4, 84.1, 79.1, 76.4, 75.6, 74.8, 74.3, 74.0, 73.6, 73.4, 72.8, 69.2, 68.7, 67.2. The NMR data was matching with the literature report.[20]



***(4'-phenyl)-benzyl-2,3,4,6-tetra-O-benzyl-D-galactopyranoside (3w)*:** Glycosylation of **1d**)50.1 mg, 0.07 mmol(with **2k**)20.4 mg, 0.11 mmol(according to **General Procedure** at -50 °C, afforded **3w** as a colorless syrup)39.8 mg, 77 %, α: β = 90: 10(. The crude product was purified through column chromatography, R$_f$ = 0.6)Hexane/EtOAc = 5:1, v/v(. ^{1}H NMR)600 MHz, CDCl$_3$(δ 7.61 – 7.57)m, 3H(, 7.55)d, *J* = 7.9 Hz, 2H(, 7.47 – 7.42)m, 5H(, 7.39)d, *J* = 7.4 Hz, 2H(, 7.37 – 7.27)m, 17H(, 7.25 – 7.24)m, 2H(, 4.99)d, *J* = 12.2 Hz, 1H(, 4.95)d, *J* = 11.7 Hz, 1H(, 4.93)d, *J* = 2.9 Hz, 1H(, 4.86)d, *J* = 11.6 Hz, 1H(, 4.78 – 4.69)m, 4H(, 4.64 – 4.54)m, 3H(, 4.50)d, *J* = 7.6 Hz, 1H(, 4.47 – 4.42)m, *J* = 11.7 Hz, 1H(, 4.39)d, *J* = 11.7 Hz, 1H(, 4.05)dd, *J* = 9.9, 3.0 Hz, 1H(, 4.03 – 3.96)m, 3H(, 3.57 – 3.51)m, 1H(, 3.50 – 3.45)m, 1H(. ^{13}C NMR)151 MHz, CDCl$_3$(δ 140.9, 140.7, 138.9, 138.7, 138.63, 138.61, 138.1, 136.5, 128.9, 128.8, 128.4, 128.36, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.11, 127.08, 102.8, 96.2, 79.2, 76.5, 75.1, 74.8, 73.5, 73.27, 73.25, 69.6, 69.0, 68.8, 65.2. HRMS)ESI) m/z: [M+NH$_4$[$^+$ calcd for C$_{47}$H$_{50}$NO$_6$ 724.3633; Found 724.3616.

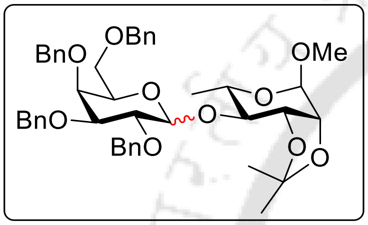


Methyl 4-O-Benzyl-2,3-di-p-methyl-O-benzyl-6-O-(2,3,4,6-tetra-O-benzyl-β-D-galactopyranosyl)-α- D-glucopyranoside (3): Glycosylation of **1b**)50.1 mg, 0.073 mmol(with **2p**)54 mg, 0.11 mmol(according to **General Procedure** at **-**50 °C, afforded **3x** as a colorless syrup (54.2 mg, 73 %, α only). The crude product was purified through column chromatography, R$_f$ = 0.5)Hexane/EtOAc = 5:1, v/v(. ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.33 – 7.30 (m, 7H), 7.29 – 7.27 (m, 6H), 7.26 – 7.19 (m, 14H), 7.17 –7.15 (m, 2H), 7.13 – 7.10 (m, 4H), 4.94 – 4.88 (m, 3H), 4.78 – 4.69 (m, 6H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.53 (d, *J* = 3.5 Hz, 1H), 4.49 (d, *J* = 11.2 Hz, 1H), 4.41 (q, *J* = 11.8 Hz, 2H), 4.30 (d, *J* = 7.7 Hz, 1H), 4.13 – 4.11 (m, 1H), 3.94 (t, *J* = 9.3 Hz, 1H), 3.88 (d, *J* = 2.4 Hz, 1H), 3.86 – 3.78 (m, 2H), 3.61 – 3.58 (m, 2H), 3.55 (dd, *J* = 9.1, 5.4 Hz, 1H), 3.49 – 3.46 (m, 3H), 3.42 (t, *J* = 9.5 Hz, 1H), 3.29 (s, 3H), 2.34 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 138.8, 138.7, 138.5, 138.46, 137.9, 137.6, 137.2, 135.9, 135.2, 129.1, 129.0, 128.4, 128.34, 128.27, 128.26, 128.22, 128.15, 128.1, 128.0, 127.9, 127.8, 127.7, 127.54, 127.49, 127.47, 127.4, 104.2, 98.0, 82.3, 81.9, 79.7, 79.3, 78.2, 75.5, 75.2, 74.8, 74.6, 73.6, 73.5, 73.4, 73.2, 72.9, 69.9, 68.7, 68.6, 55.1, 21.19, 21.18. HRMS)ESI) m/z:]M+Na[$^+$ calcd for C$_{64}$H$_{70}$NaO$_{11}$ 1038.4810; Found 1038.4823.

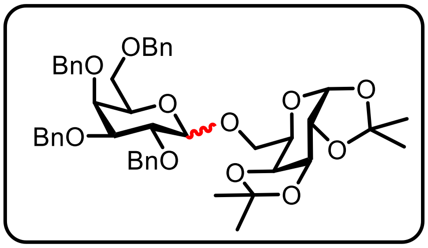


Methyl 4-O-Benzyl-2,3-di-p-methyl-O-benzyl-6-O-(2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl)-α- D-glucopyranoside (3y): Glycosylation of **1d**)50.2 mg, 0.073 mmol(with **2p**)54.1 mg, 0.11 mmol(according to **General Procedure** at **-**50 °C, afforded **3y** as a colorless syrup (58.7 mg, 73 %, β only). The crude product was purified through column chromatography,

R_f = 0.5)Hexane/EtOAc = 5:1, v/v(. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 – 7.33 (m,, 4H), 7.31 – 7.22 (m, 25H), 7.20 – 7.17 (m, 2H), 7.13 (d, *J* = 7.8 Hz, 2H), 7.08 (d, *J* = 7.8 Hz, 2H), 4.97 (d, *J* = 3.5 Hz, 1H), 4.93 – 4.90 (m, 2H), 4.85 (d, *J* = 11.0 Hz, 1H), 4.78 (d, *J* = 11.9 Hz, 1H), 4.74 (d, *J* = 10.6 Hz, 1H),, 4.72 (d, *J* = 5.1 Hz, 1H), 4.70 (d, *J* = 5.1 Hz, 1H), 4.67 (dd, *J* = 11.8, 2.4 Hz, 2H), 4.58 – 4.50 (m, 3H), 4.49 (d, *J* = 3.5 Hz, 1H), 4.42 (d, *J* = 11.8 Hz, 1H), 4.35 (d, *J* = 11.8 Hz, 1H), 4.01 (dd, *J* = 9.4, 3.5 Hz, 1H), 3.97 – 3.92 (m, 2H), 3.91 – 3.87 (m, 2H), 3.79 – 3.73 (m, 2H), 3.70 (d, *J* = 10.8 Hz, 1H), 3.55 (t, *J* = 9.3 Hz, 1H), 3.52 – 3.46 (m, 2H), 3.39 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.28 (s, 1H), 2.35 (s, 1H), 2.30 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.9, 138.8, 138.75, 138.5, 138.1, 137.5, 137.2, 135.9, 135.2, 129.1, 129.0, 128.4, 128.3, 128.25, 128.21, 128.16, 128.1, 127.8, 127.7, 127.7, 127.6, 127.5, 127.42, 127.37, 98.0, 97.9, 79.9, 78.3, 78.0, 76.5, 75.6, 75.2, 75.0, 74.8, 73.3, 73.2, 72.9, 72.6, 70.3, 69.4, 68.9, 66.5, 55.0, 21.2, 21.16. The NMR data was matching with the literature report.[15]



Methyl 6-Deoxy-4-O-(2,3,4,6-tetra-O-benzyl- D -galactopyranosyl)-2,3-O-isopropylidene-α- L –pneumopyranoside (3z): Glycosylation of **1b**)51.1 mg, 0.075 mmol(with **2q** (24.4 mg, 0.11 mmol(according to **General Procedure** at -50 °C, afforded **3z** as a colorless syrup (38.8 mg, 70 %, α: β = 47: 53(. The crude product was purified through column chromatography, R_f = 0.5)Hexane/EtOAc = 6:1, v/v(. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 5H), 7.35 – 7.27 (m, 42H), 4.95 (d, *J* = 5.3 Hz, 1H), 4.94 (d, *J* = 2.4 Hz, 2H), 4.91 (d, *J* = 11.1 Hz, 1H), 4.85 (d, *J* = 6.7 Hz, 1H), 4.83 (d, *J* = 2.4 Hz, 1H), 4.82 (d, *J* = 2.6 Hz, 1H), 4.78 – 4.72 (m, 4H), 4.73 – 4.69 (m, 3H), 4.62 – 4.57 (m, 2H), 4.48 (d, *J* = 11.9 Hz, 1H), 4.42 (d, *J* = 3.6 Hz, 2H), 4.41 – 4.37 (m, 2H), 4.25 – 4.19 (m, 2H), 4.13 – 4.11 (m, 1H), 4.07 (t, *J* = 5.6 Hz, 3H), 3.96 (dd, *J* = 10.2, 2.6 Hz, 1H), 3.88 (d, *J* = 2.2 Hz, 1H), 3.72 (dt, *J* = 13.4, 6.6 Hz, 2H), 3.67 – 3.64 (m, 1H), 3.64 – 3.58 (m, 4H), 3.56 – 3.54 (m, 1H), 3.52 – 3.48 (m, 2H), 3.38 (s, 3H), 3.33 (s, 3H), 3.31 – 3.29 (m, 1H), 3.28 (d, *J* = 6.3 Hz, 1H), 1.44 (s, 3H), 1.37 (s, 3H), 1.31 (s, 3H), 1.30 (d, *J* = 6.5 Hz, 6H), 1.24 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.98, 138.96, 138.8, 138.7, 138.66, 138.3, 138.1, 137.9, 128.4, 128.32, 128.3, 128.26, 128.17, 128.15, 128.1, 127.9, 127.8, 127.75, 127.7, 127.6, 127.52, 127.50, 127.47, 127.42, 127.39, 127.36, 109.2, 109.0, 102.1, 98.8, 98.0, 97.8, 82.3, 80.2, 79.7, 79.4, 78.6, 78.1, 76.1, 75.92, 75.85, 75.0, 74.9, 74.6, 74.5, 74.4, 73.9, 73.48, 73.45, 73.3, 73.2, 72.5, 68.8, 68.7, 67.7, 64.9, 64.4, 54.8, 54.6, 28.0, 27.8, 26.4, 26.3, 17.9, 17.4. The NMR data was matching with the literature report.[15]



1,2;3,4-Di-O-isopropylidene-6-O-(2,3,4,6-tetra-O-benzyl-D-galacto-pyranosyl)-D-galactopyranose (4a)**:** Glycosylation of **1b** (50.3 mg, 0.07 mmol) with **2m** (28.9 mg, 0.11 mmol) according to **General Procedure** at **-**30 °C, afforded **4a** as a colorless syrup (41.6 mg, 79 %, α: β = 9: 91). The crude product was purified through column chromatography, R$_f$ = 0.6 (Hexane/EtOAc = 5:1, v/v). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.44 (d, J = 6.1 Hz, 2H), 7.38 – 7.26 (m, 20H), 5.56 (d, J = 5.0 Hz, 1H), 5.04 (d, J = 11.0 Hz, 1H), 4.92 (d, J = 11.6 Hz, 1H), 4.80 – 4.73 (m, 2H), 4.70 (d, J = 11.5 Hz, 2H), 4.62 – 4.54 (m, 3H), 4.43 – 4.39 (m, 3H), 4.30 (dd, J = 5.0, 2.3 Hz, 1H), 4.21 (dd, J = 7.9, 1.7 Hz, 1H), 4.12 (dd, J = 10.5, 3.6 Hz, 1H), 4.07 (d, J = 7.3 Hz, 1H), 3.88 (d, J = 2.4 Hz, 1H), 3.82 (dd, J = 9.7, 7.7 Hz, 1H), 3.68 (dd, J = 10.5, 7.4 Hz, 1H), 3.60 – 3.54 (m, 2H), 3.54 – 3.47 (m, 2H), 3.31 (q, J = 7.2 Hz, 1H), 1.49 (s, 3H), 1.43 (s, 3H), 1.31 (s, 6H). The NMR data was matching with the literature report.[19]

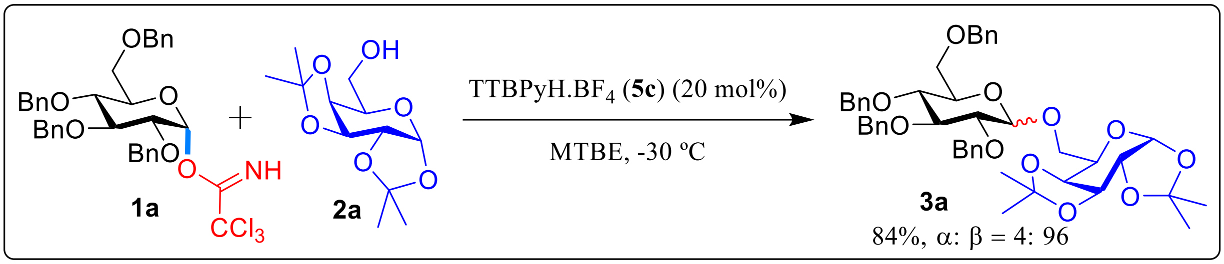
Methyl 2,3,4-tri-O-benzyl-6-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-α-D-glucopyranoside (**4b):** Glycosylation of **1e** (50.0 mg, 0.07 mmol) with **2b** (50.1 mg, 0.11 mmol) according to **General Procedure** afforded **4b** as a colorless syrup (51.8 mg, 75 %, α: β = 86:14). The crude product was purified through column chromatography, R$_f$ = 0.6 (Hexane/EtOAc = 5:1, v/v). ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.35 – 7.32 (m, 8H), 7.31 (d, J = 1.7 Hz, 3H), 7.30 – 7.29 (m, 7H), 7.28 (t, J = 3.3 Hz, 7H), 7.27 (s, 6H), 7.25 – 7.22 (m, 4H), 7.21 – 7.14 (m, 2H), 7.11 (dd, J = 7.2, 1.9 Hz, 2H), 4.96 (dt, J = 5.9, 3.6 Hz, 3H), 4.92 (d, J = 11.0 Hz, 2H), 4.83 – 4.80 (m, 2H), 4.80 – 4.75 (m, 2H), 4.73 – 4.69 (m, 1H), 4.67 (s, 2H), 4.63 (d, J = 11.2 Hz, 1H), 4.60 – 4.57 (m, 2H), 4.57 (d, J = 5.3 Hz, 1H), 4.54 (s, 1H), 4.44 (d, J = 10.9 Hz, 1H), 4.40 (d, J = 12.1 Hz, 1H), 4.01 – 3.93 (m, 2H), 3.82 (dd, J = 11.5, 4.5 Hz, 1H), 3.80 – 3.76 (m, 2H), 3.75 (d, J = 2.7 Hz, 1H), 3.70 (d, J = 12.9 Hz, 1H), 3.66 (s, 1H), 3.64 (d, J = 3.2 Hz, 1H), 3.62 (d, J = 2.9 Hz, 1H), 3.61 (d, J = 3.4 Hz, 1H), 3.55 (d, J = 3.5 Hz, 1H), 3.53 (d, J = 3.3 Hz, 1H), 3.51 (s, 1H), 3.46 (dd, J = 9.6, 3.5 Hz, 1H), 3.35 (s, 3H), 3.33 (s, 1H). ^{13}C{^{1}H} NMR (151 MHz, CDCl$_3$) δ 138.8, 138.4, 138.4, 138.4, 138.1, 137.9, 128.5, 128.4, 128.4, 128.4, 128.3, 128.2, 128.1, 128.0, 128.0, 128.0, 127.9, 127.9, 127.9, 127.9, 127.7, 127.7, 127.7, 127.7, 127.6, 127.6, 127.6, 127.6, 103.7, 98.0, 97.9, 97.2, 82.1, 81.7, 80.1, 79.9, 77.7, 77.6, 77.3, 77.1, 76.8, 75.7, 75.5, 74.9, 73.4, 73.4, 72.5, 70.3, 70.2, 68.4, 66.0, 55.2. The NMR data was matching with the literature report.[2a]

Methyl 4-O-Benzyl-2,3-di-p-methyl-O-benzyl-6-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-α- D-galactopyranoside (4c): Glycosylation of **1e** (50.2 mg, 0.073 mmol) with **2r** (54.1 mg, 0.11 mmol) according to **General Procedure**, afforded **4c** as a colorless syrup (58.0 mg, 78 %, α: β = 96:4). The crude product was purified through column chromatography, R$_f$ = 0.5 (Hexane/EtOAc = 5:1, v/v).H NMR (400 MHz, CDCl$_3$) δ 7.34 – 7.26 (m, 18H), 7.23 (dd, J = 6.6, 3.2 Hz, 8H), 7.18 – 7.08 (m, 7H), δ 4.96 – 4.89 (m, 2H), 4.80 (dt, *J* = 11.3, 3.8 Hz, 4H), 4.75 (d, *J* = 5.1 Hz,1H), 4.72 (d, *J* = 3.8 Hz, 2H), 4.68 (s, 1H), 4.66 – 4.60 (m, 4H), 4.59 – 4.53 (m, 2H), 4.44 (t, *J* = 12.1 Hz, 2H), 3.96 (d, *J* = 3.3 Hz, 1H), 3.95 – 3.90 (m, 2H), 3.88 (d, *J* = 6.2 Hz, 2H), 3.80 (d, *J* = 9.8 Hz, 1H), 3.73 – 3.67 (m, 2H), 3.61 (s, 2H), 3.53 (dd, *J* = 9.6, 3.4 Hz, 1H), 3.40 (dt, *J* = 11.6, 5.7 Hz, 1H), 3.32 (s, 3H), 2.34 (d, *J* = 10.1 Hz, 6H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 138.7, 138.6, 138.3, 138.2, 137.9, 137.4, 137.2, 135.8, 135.4, 129.1, 129.0, 128.4, 128.4, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.7, 127.7, 127.6, 127.6, 98.8, 97.2, 82.0, 79.7, 78.9, 77.6, 76.1, 75.6, 75.5, 75.0, 74.6, 73.5, 73.3, 73.2, 70.3, 69.1, 68.2, 67.1, 55.4, 21.2. The NMR data was matching with the literature report.[15]

(4'-phenyl)-benzyl-2,3,4,6-tetra-O-benzyl-D-glucopyranoside (4d)**:** Glycosylation of **1e** (50.5 mg, 0.07 mmol) with **2k** (20.5 mg, 0.11 mmol) according to **General Procedure** afforded **4d** as a colorless syrup (44.0 mg, 85 %, α: β = 12: 88). The crude product was purified through column chromatography, R_f = 0.6 (Hexane/EtOAc = 5:1, v/v). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.57 (dd, *J* = 12.7, 7.7 Hz, 4H), 7.50 – 7.41 (m, 4H), 7.38 – 7.25 (m, 21H), 7.17 (d, *J* = 2.6 Hz, 1H), 7.16 – 7.11 (m, 2H), 5.01 (d, *J* = 10.9 Hz, 1H), 4.97 – 4.90 (m, 1H), 4.87 (d, *J* = 3.6 Hz, 1H), 4.84 (s, 1H), 4.81 (d, *J* = 6.7 Hz, 1H), 4.76 (d, *J* = 8.0 Hz, 1H), 4.75 – 4.70 (m, 1H), 4.69 (s, 1H), 4.62 (d, *J* = 5.4 Hz, 1H), 4.60 – 4.55 (m, 2H), 4.53 (d, *J* = 2.3 Hz, 1H), 4.48 (d, *J* = 11.5 Hz, 2H), 4.05 (t, *J* = 9.3 Hz, 1H), 3.83 (dd, *J* = 10.6, 1.6 Hz, 1H), 3.76 (d, *J* = 1.7 Hz, 1H), 3.72 (d, *J* = 3.5 Hz, 1H), 3.71 – 3.67 (m, 1H), 3.65 (d, *J* = 6.1 Hz, 1H), 3.61 – 3.56 (m, 2H). (151 MHz, CDCl$_3$) δ 140.8, 140.8, 138.8, 138.2, 138.2, 137.9, 136.2, 129.0, 128.8, 128.8, 128.4, 128.4, 128.2, 128.0, 128.0, 127.9, 127.9, 127.9, 127.7, 127.7, 127.6, 127.6, 127.3, 127.2, 127.1, 102.6, 95.7, 84.7, 82.2, 79.9, 77.7, 77.2, 77.0, 76.8, 75.8, 75.1, 73.5, 73.1, 70.4, 68.9, 68.3. HRMS)ESI) m/z: [M+Na[$^+$ calcd for C$_{47}$H$_{50}$NO$_6$ 724.3633; Found 724.3633.

isopropyl-2,3,4,6-tetra-O-benzyl-D-glucopyranoside (4e)**:** Glycosylation of **1e** (49.9 mg, 0.07 mmol) with **2o** (6.5 mg, 0.11 mmol) according to **General Procedure** afforded **4e** as a colorless syrup (37.3 mg, 88 %, α: β = 92: 8). The crude product was purified through column chromatography, R_f = 0.5 (Hexane/EtOAc = 5:1, v/v). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40 – 7.24 (m, 19H), 7.19 – 7.15 (m, 1H), 7.15 – 7.10 (m, 2H), 5.00 (d, *J* = 10.9 Hz, 1H), 4.82 (ddd, *J* = 25.7, 15.4, 5.6 Hz, 4H), 4.63 (dd, *J* = 15.3, 12.1 Hz, 2H), 4.51 – 4.41 (m, 2H), 3.99 (t, *J* = 9.3 Hz, 1H), 3.90 (dd, *J* = 12.4, 6.2 Hz, 1H), 3.85 (d, *J* = 11.0 Hz, 1H), 3.73 (dd, *J* = 10.5, 3.5 Hz, 1H), 3.68 – 3.59 (m, 2H), 3.55 (dd, *J* = 9.6, 3.7 Hz, 1H), 1.31 (d, *J* = 6.2 Hz, 1H), 1.22 (d, *J* = 6.3 Hz, 3H), 1.18 (d, *J* = 6.1 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ 139.0, 138.8, 138.5, 138.0, 128.4, 128.4, 128.4, 128.2, 128.2, 128.00, 127.9, 127.9, 127.8, 127.7, 127.6, 127.6, 127.5, 102.2, 94.8, 84.8, 82.3, 82.1, 79.9, 78.0, 77.9, 77.3, 77.0, 76.8, 75.7, 75.1, 75.0, 74.8, 73.5, 73.1, 72.4, 70.0, 69.2, 69.0, 68.5, 23.7, 23.2, 22.2, 21.2. The NMR data was matching with the literature report.[2a]

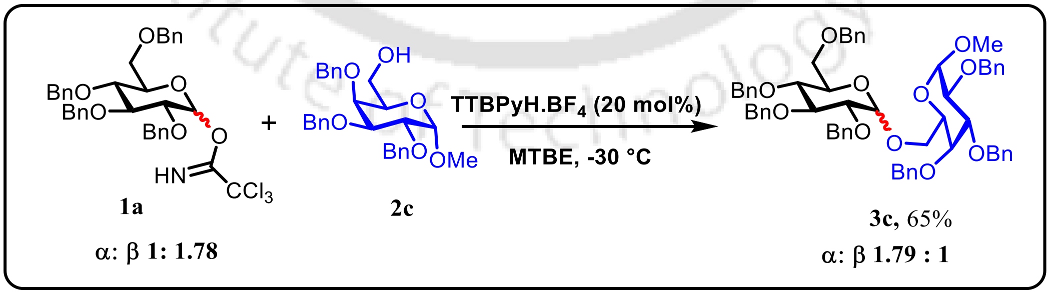
3.10.2 Gram scale synthesis of 3a



Scheme 18

Glycoside **3a** was synthesized on a gram scale to realize the efficiency of the protocol. It was observed that the stereochemical output of the protocol remained uncompromised in large-scale synthesis as well. The reaction mixture has to be cooled to -30 °C before the addition of the catalyst. A solution of α-glucosyltrichloroacetimidate donor (0.16M) (**1a,** 1.1 g, 1.6 mmol) and acceptor (**2a,** 1.5 equiv., 2.4 mmol, 630 mg) in anhydrous MTBE (Methyl tert-butyl ether) was taken in a round-bottom flask and the vessel was chilled to -30 °C followed by the addition of 20 mol% of **5c** (TTBPyH.BF_4) under argon atmosphere. The reaction was monitored on TLC. After completion of the reaction, the reaction mixture was quenched with triethylamine. The crude reaction mixture was concentrated and worked up with CH_2Cl_2/water, washed with brine, dried by Na_2SO_4, and concentrated under vacuum. The resulting crude reaction mixture was purified through column chromatography to afford the glycosylated product (**3a**) in good yield and great stereoselecivity (1.056g, 84%, α: β = 4: 96). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.36 – 7.21 (m, 19H), 7.15 – 7.11 (m, 2H), 5.57 (d, *J* = 5.0 Hz, 1H), 5.05 (d, *J* = 11.1 Hz, 1H), 4.95 (d, *J* = 10.9 Hz, 1H), 4.80 (d, *J* = 10.9 Hz, 1H), 4.77 (d, *J* = 11.0 Hz, 1H), 4.72 (d, *J* = 11.1 Hz, 1H), 4.61 (d, *J* = 12.1 Hz, 1H), 4.58 – 4.53 (m, 1H), 4.50 (d, *J* = 10.5 Hz, 1H), 4.46 (d, *J* = 7.8 Hz, 1H), 4.31 (dd, *J* = 4.9, 2.4 Hz, 1H), 4.24 (dd, *J* = 8.0, 1.7 Hz, 1H), 4.16 (dd, *J* = 10.6, 3.6 Hz, 1H), 4.11 – 4.06 (m, 1H), 3.75 – 3.67 (m, 3H), 3.67 – 3.57 (m, 2H), 3.49 – 3.38 (m,, 2H), 1.50 (s, 3H), 1.45 (s, 3H), 1.33 – 1.30 (m, 6H).[15]

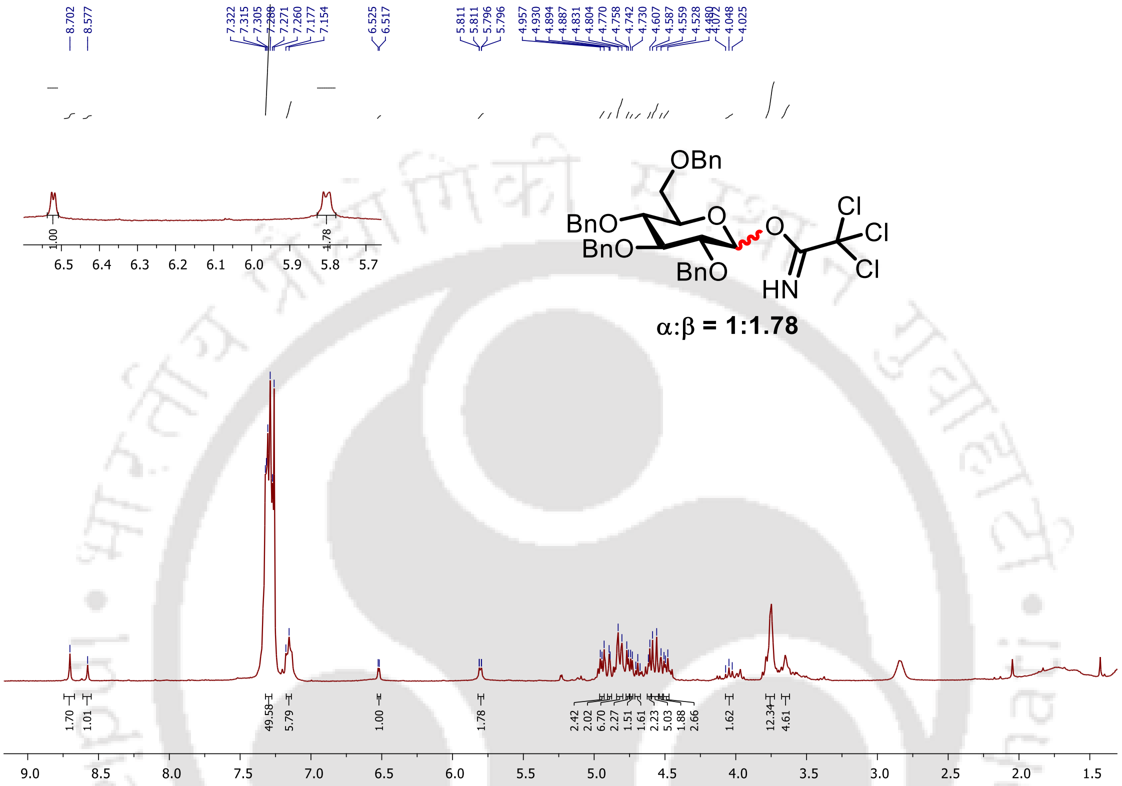
3.10.3 Reaction of α/β mixture of gluco-TCA donors



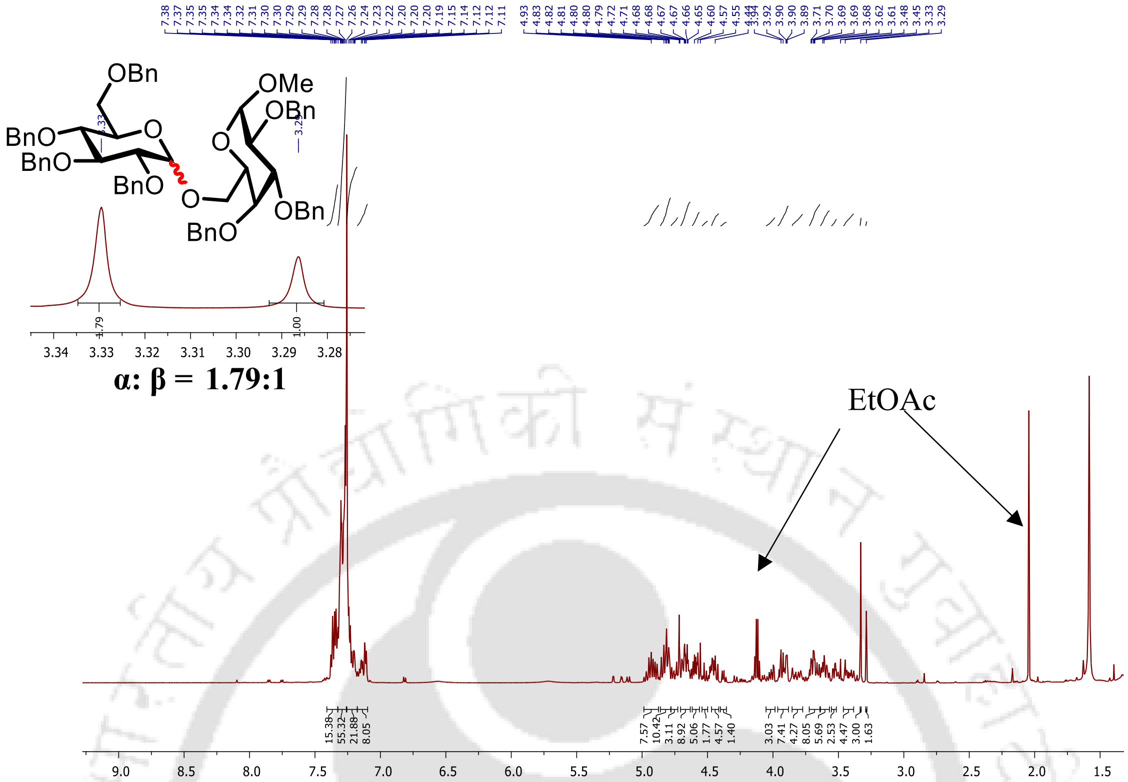
Scheme 19

Procedure: A solution of glucosyltrichloroacetimidate donor (0.16M) (**1a**, 1 equiv., 41 mg) and acceptor (**2c**, 1.5 equiv. 41.8 mg) in dry MTBE (Methyl tert-butyl ether) was taken in a round-bottom flask and was chilled to -30 °C followed by the addition of 20 mol% of tri-*tert*-

butylpyridinium tetrafluoroborate (**5c**) under argon atmosphere. The reaction was monitored on TLC. After completion of the reaction, the crude reaction mixture was concentrated and worked up with CH_2Cl_2/water, washed with brine, dried by Na_2SO_4, concentrated in rotavapor. The resulting crude reaction mixture was purified through column chromatography to afford the glycosylated product (**3c**)[19] in 65% (38.4 mg) yield.



^{1}H NMR spectrum of **1a**)400 MHz, $CDCl_3$(



^{1}H NMR spectrum of **3c**,)600 MHz, CDCl$_3$(

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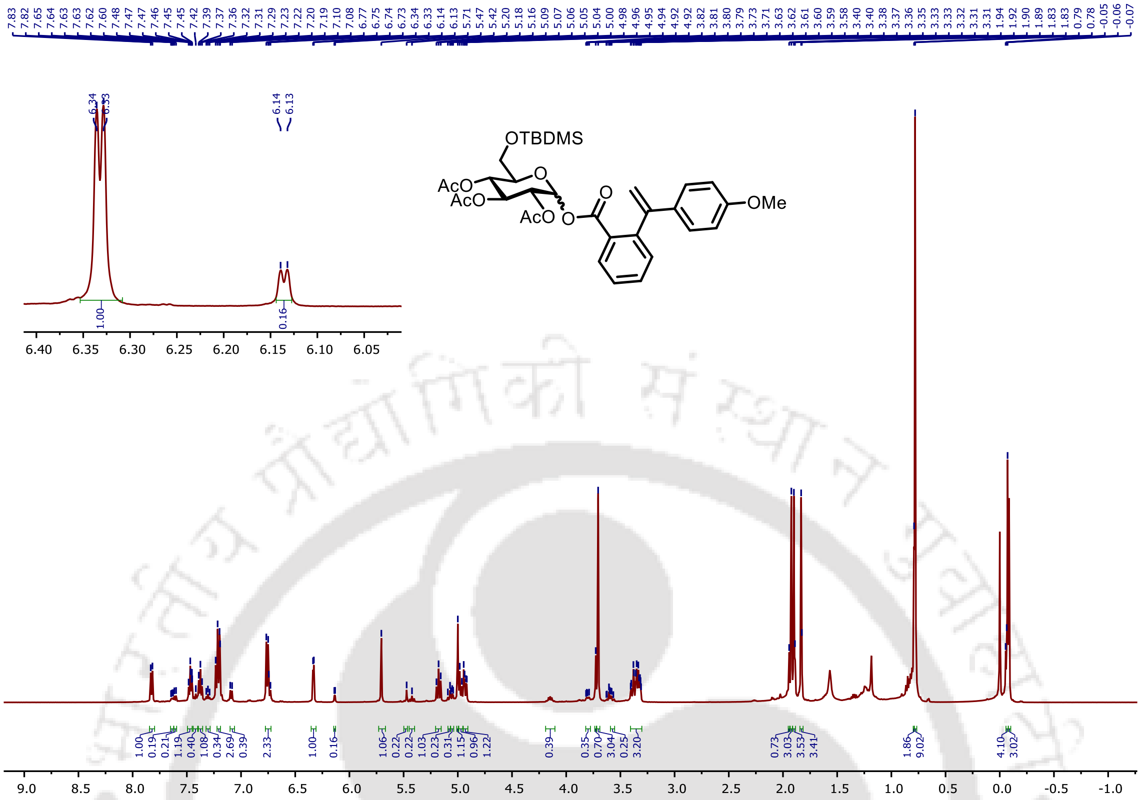
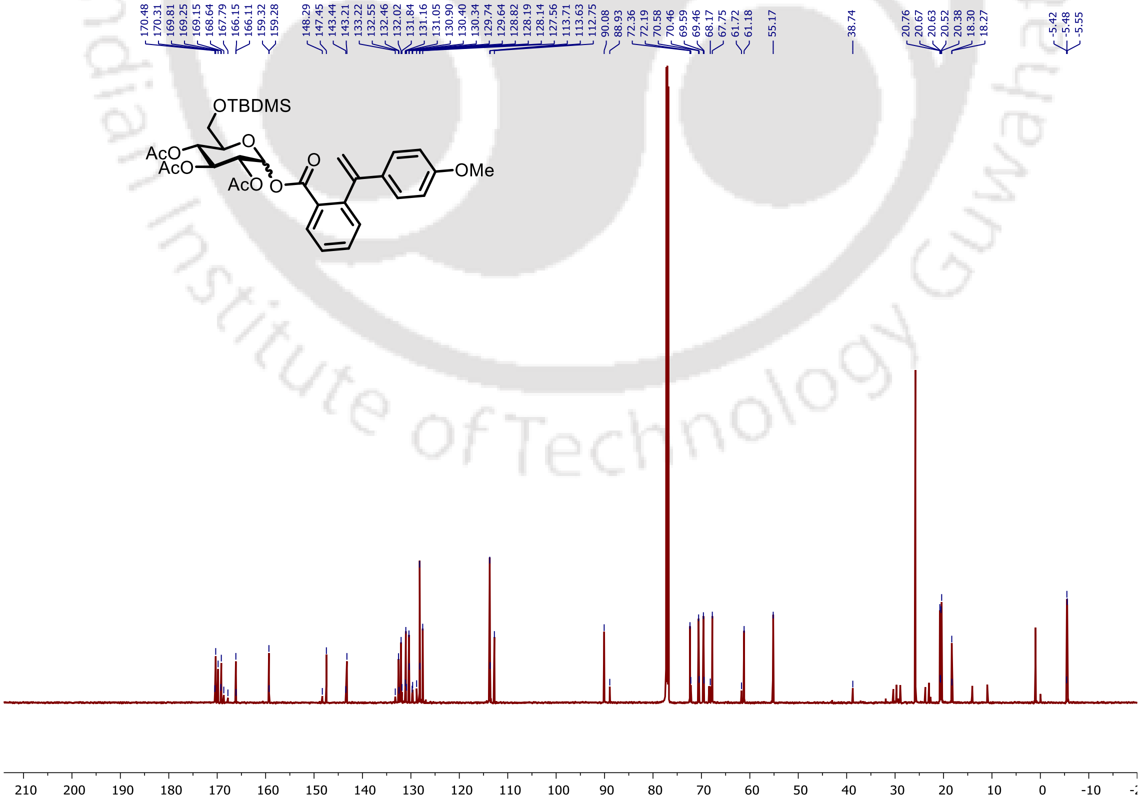
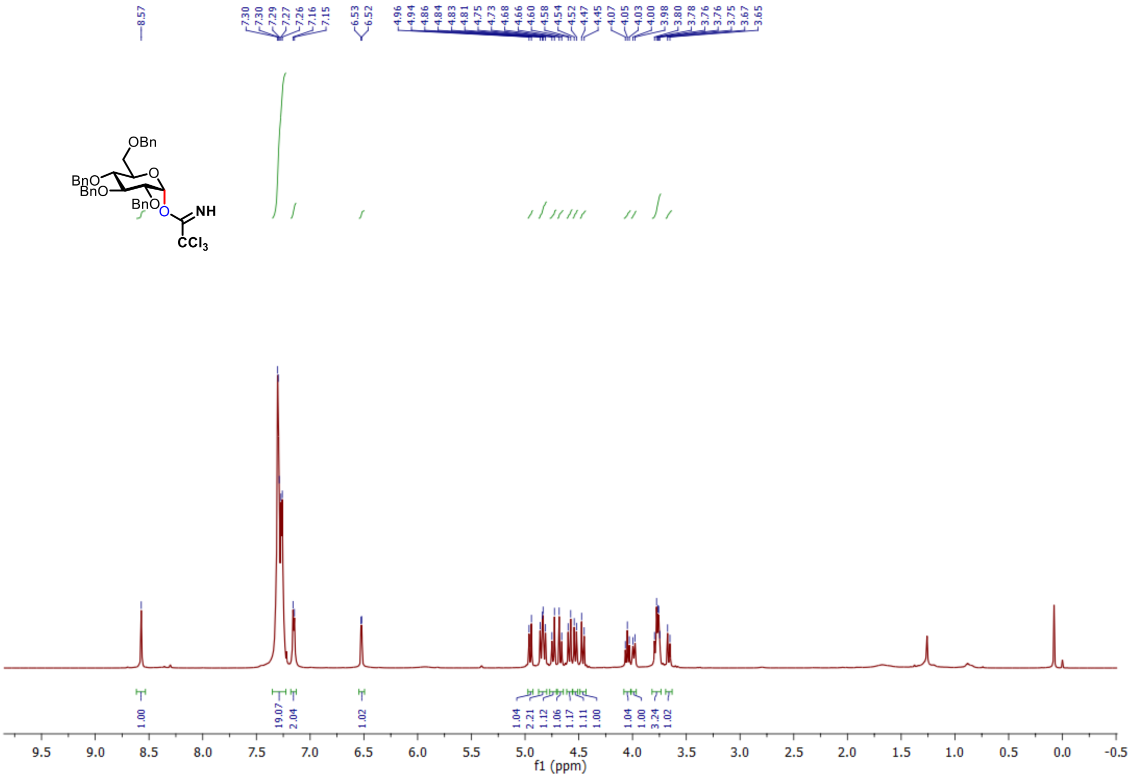
3.12 Specroscopic data



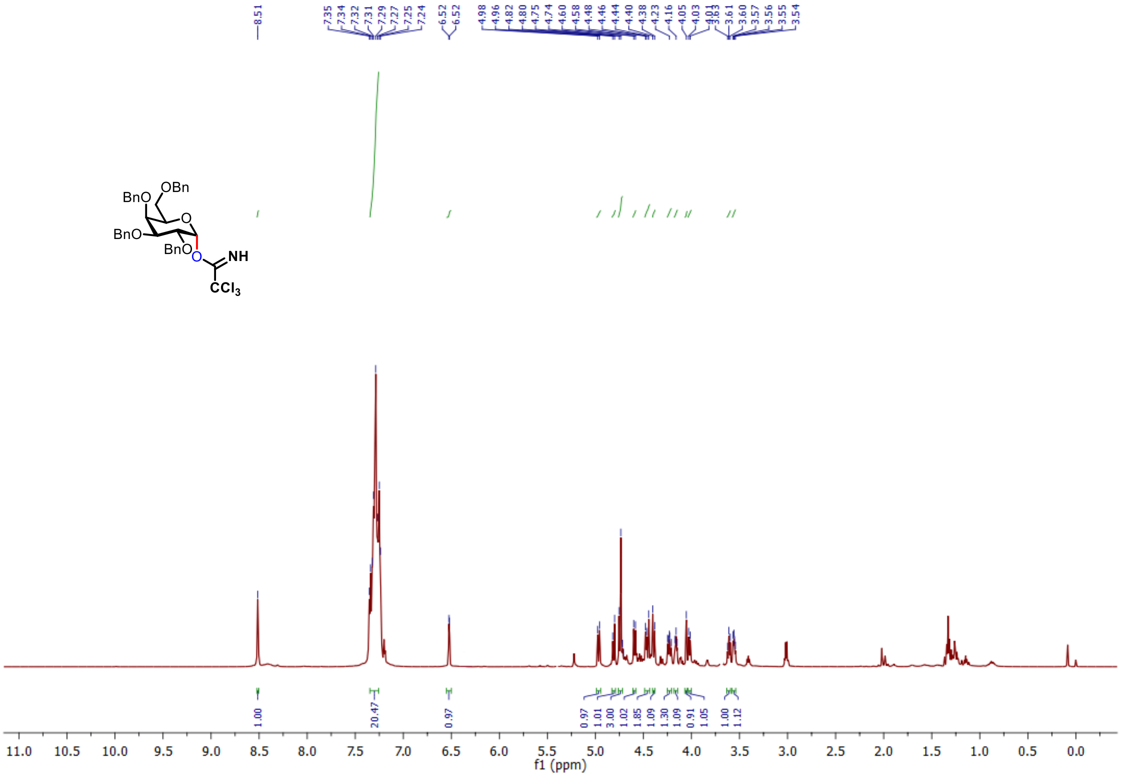
^{1}H NMR spectrum of **2i’,**)500 MHz, CDCl$_3$(



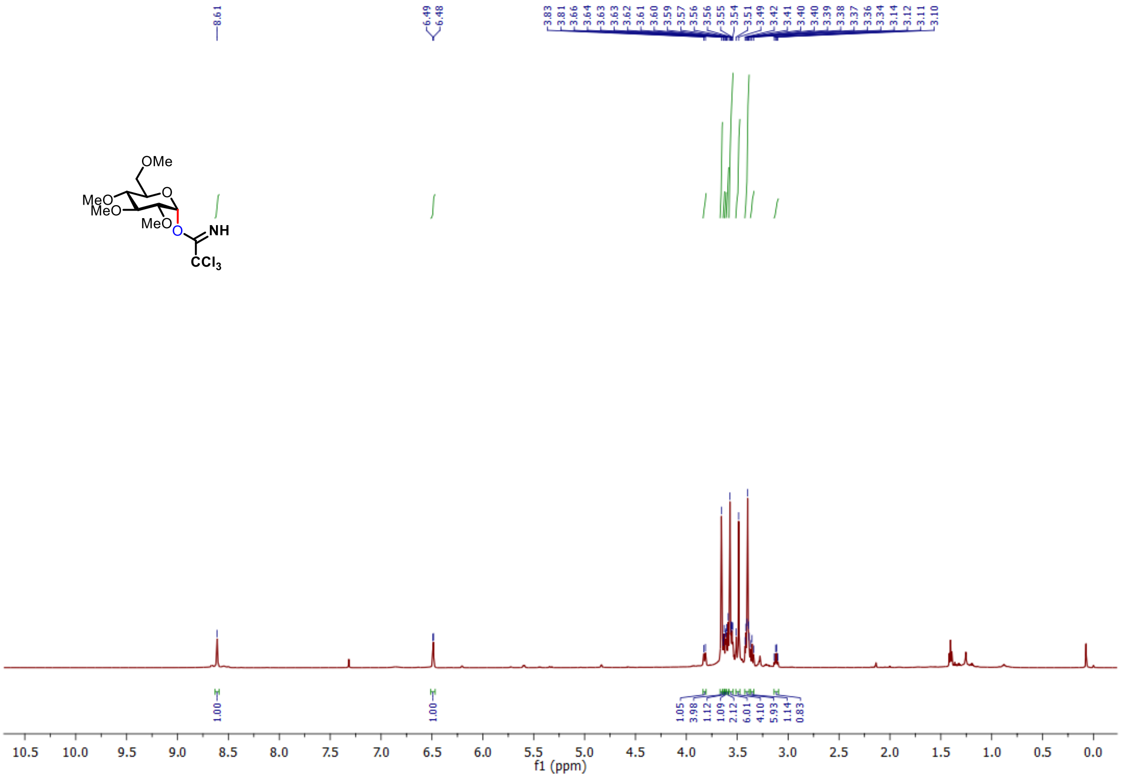
^{13}C NMR spectrum of **2i’,**)151 MHz, CDCl$_3$(



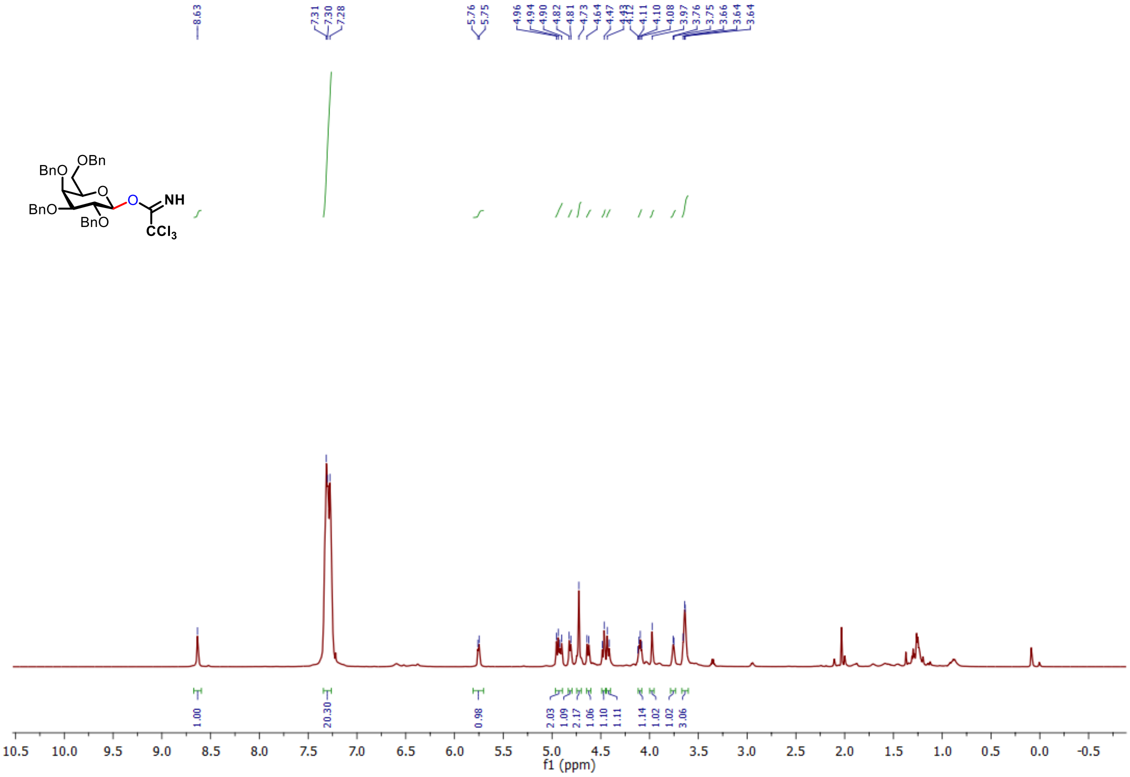
^{1}H NMR spectrum of **1a,**)500 MHz, CDCl$_3$(



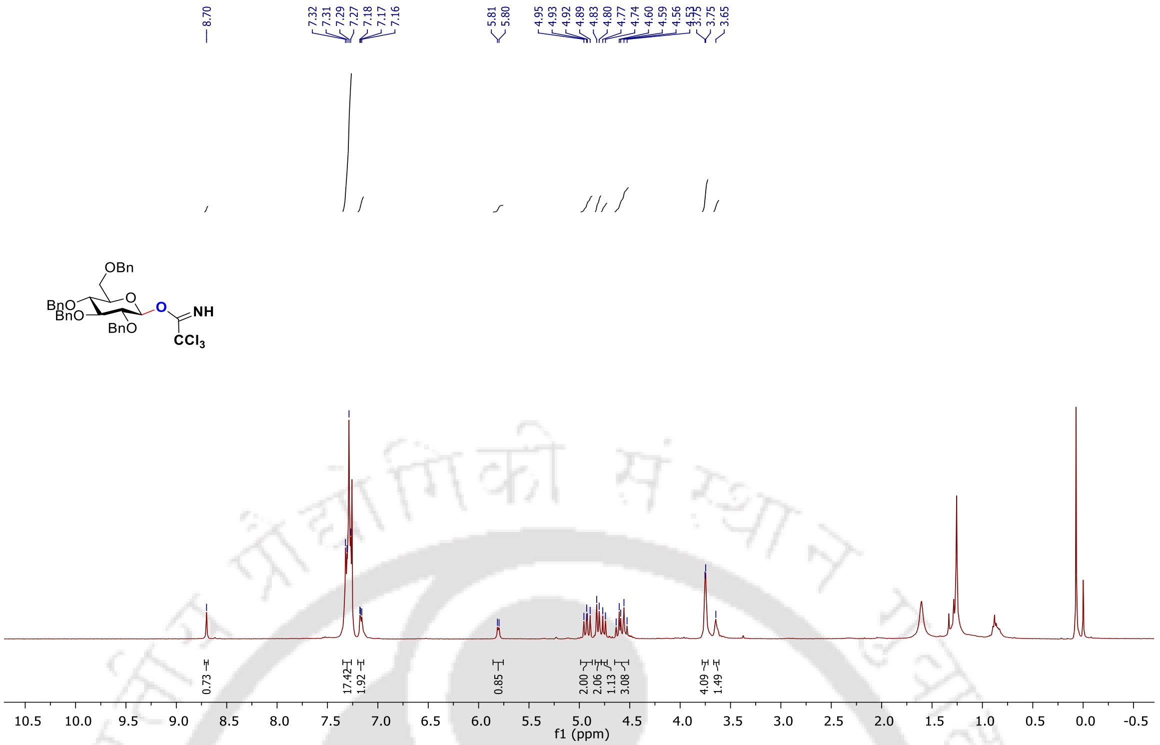
^{1}H NMR spectrum of **1b,** (600 MHz, CDCl$_3$(



^{1}H NMR spectrum of **1c,** (600 MHz, CDCl3(



^{1}H NMR spectrum of **1d,** (600 MHz, CDCl3(



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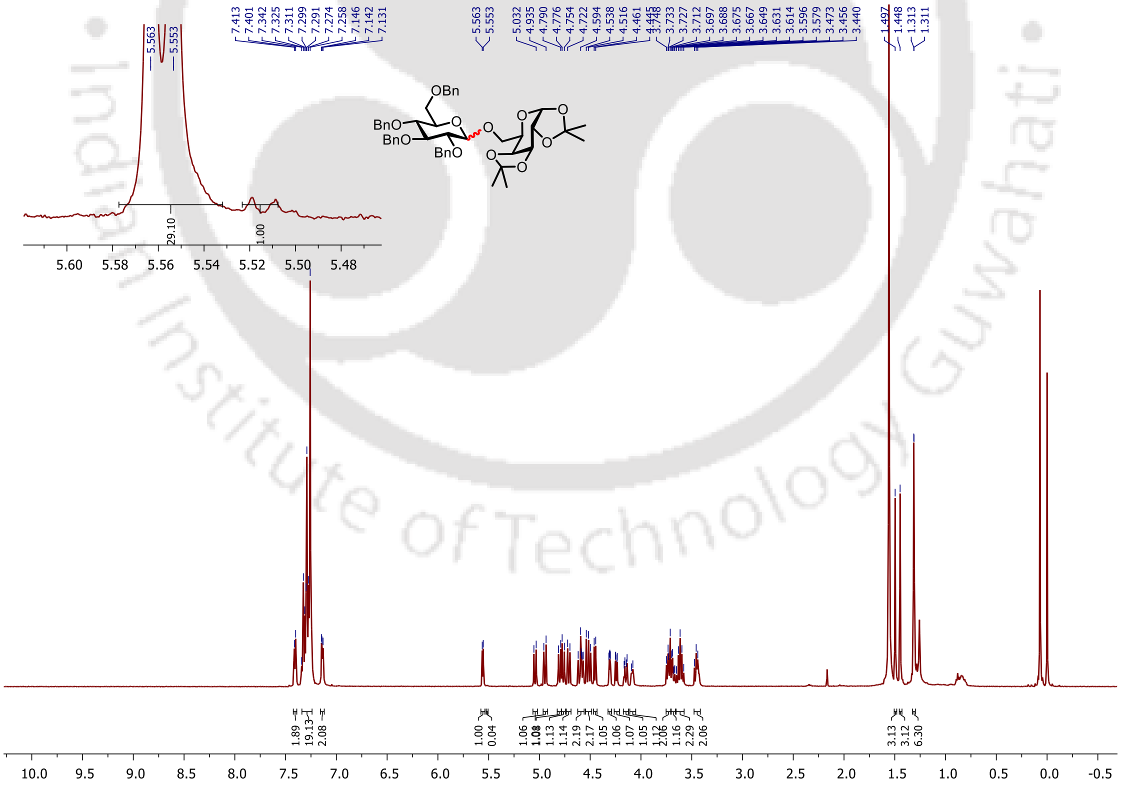
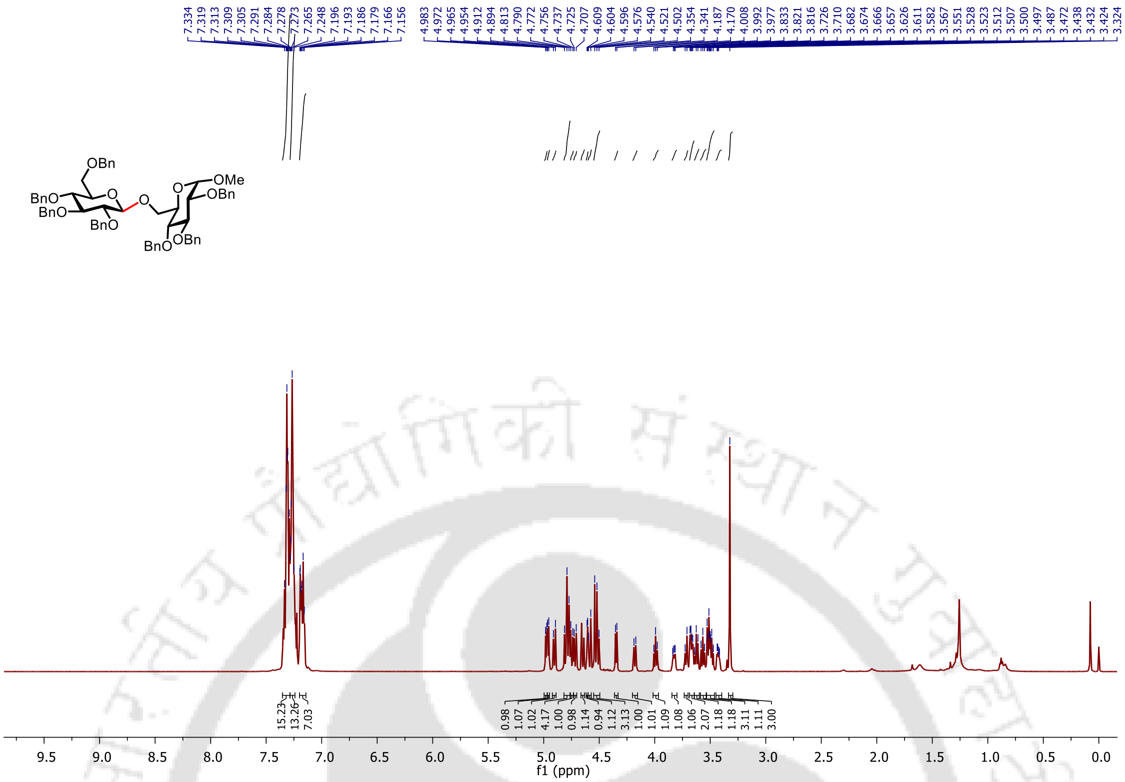
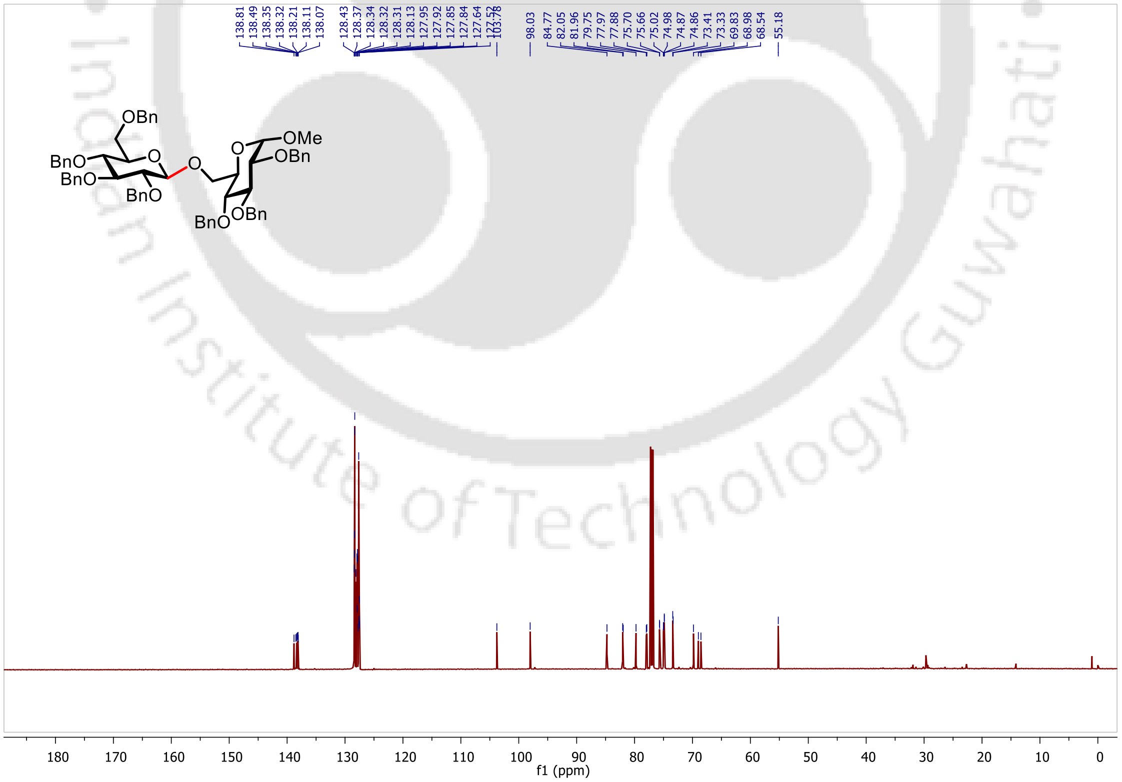


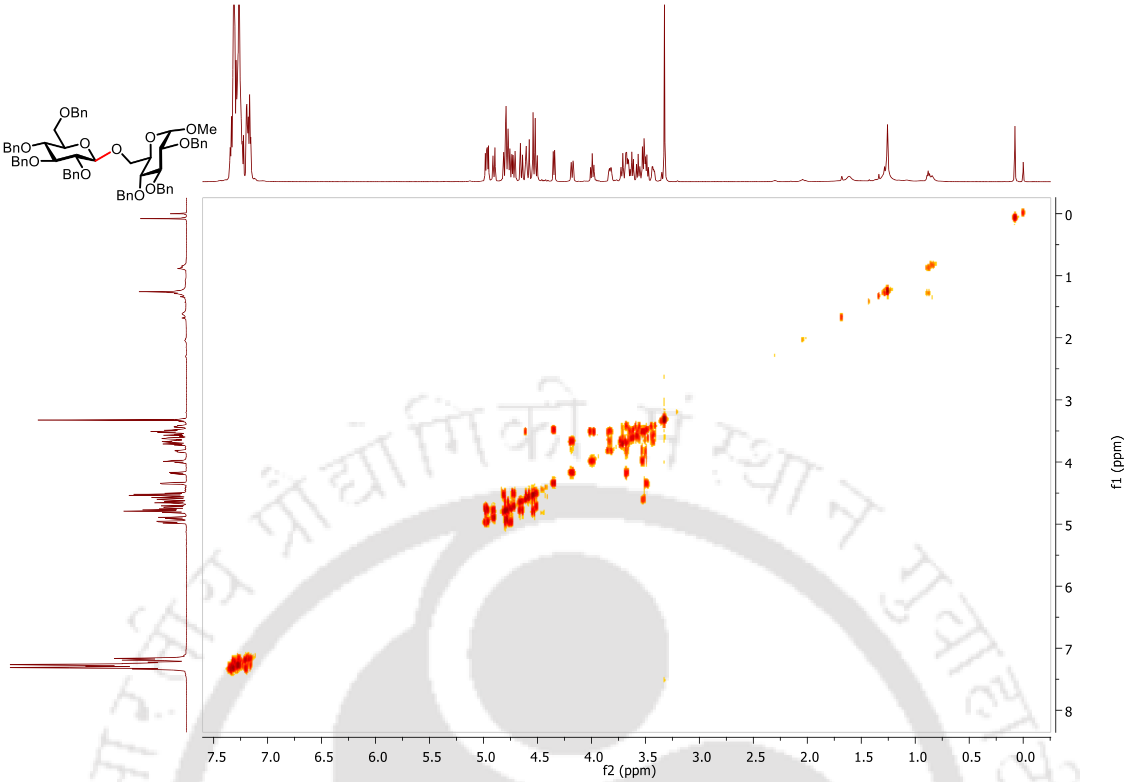
^{1}H NMR spectrum of **3a,**)500 MHz, CDCl$_3$(



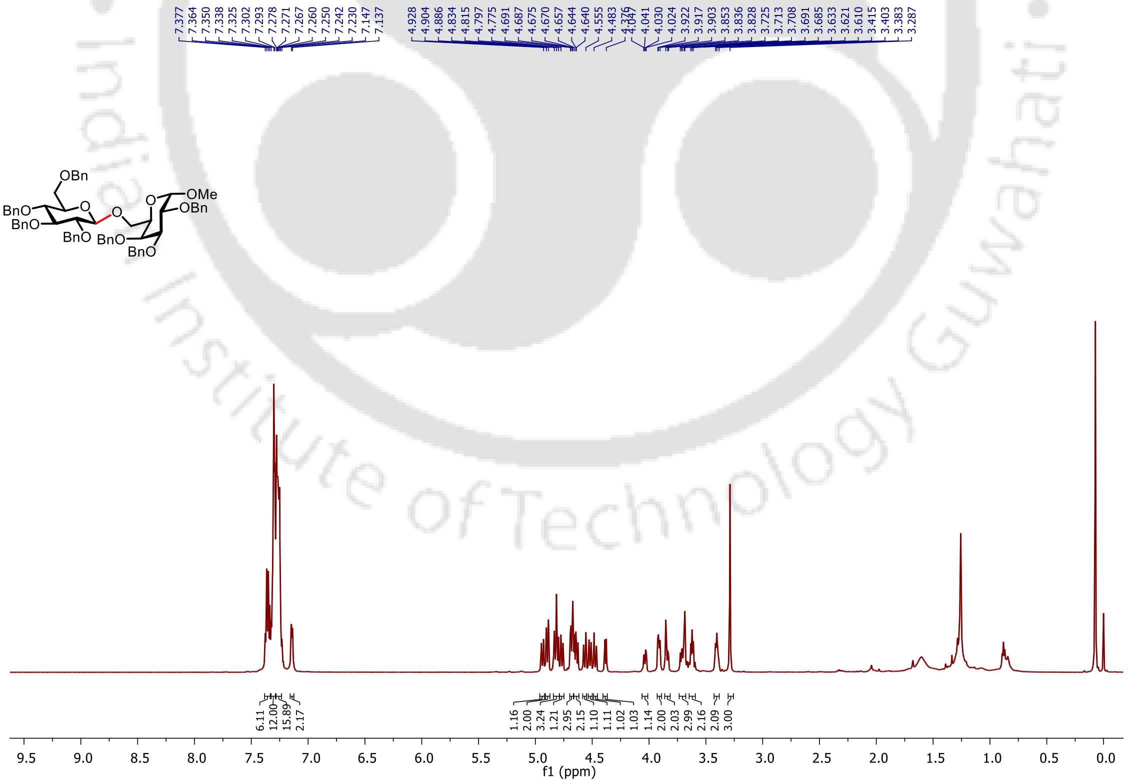
^{1}H NMR spectrum of **3b,**)600 MHz, CDCl$_3$(



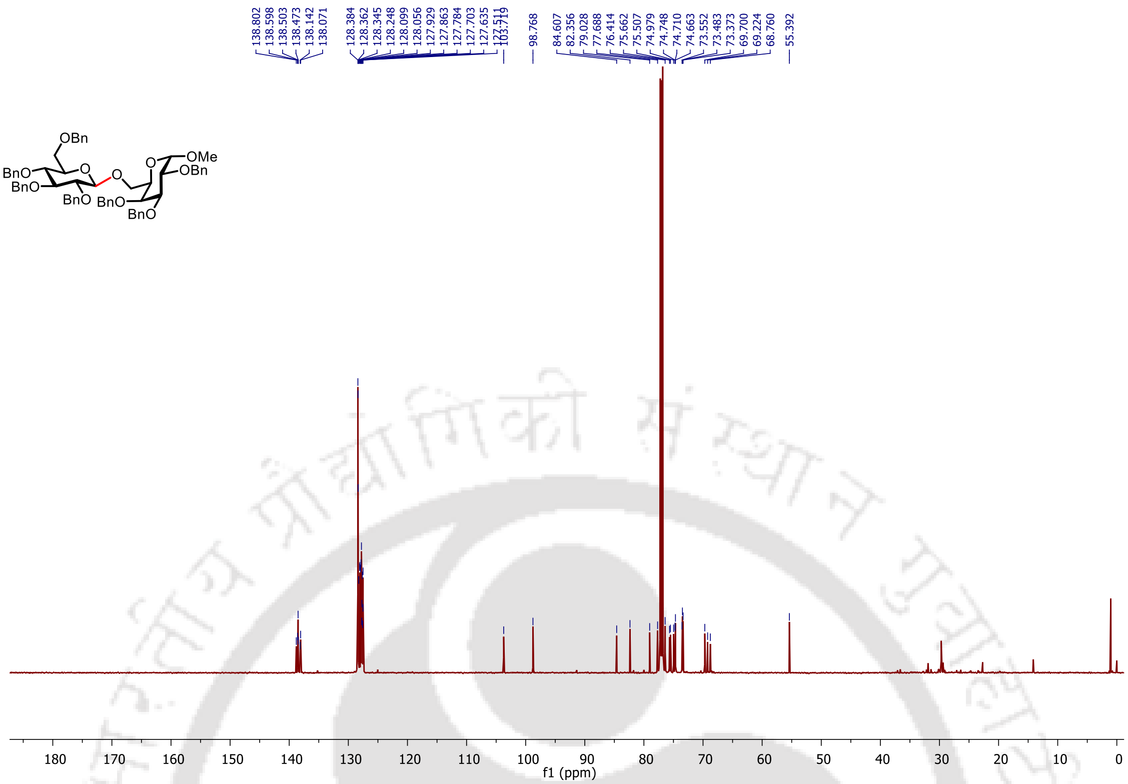
^{13}C NMR spectrum of **3b,**)151 MHz, CDCl$_3$(



COSY spectrum of **3b,**)600 MHz, $CDCl_3$(



^{1}H NMR spectrum of **3c,**)600 MHz, $CDCl_3$(



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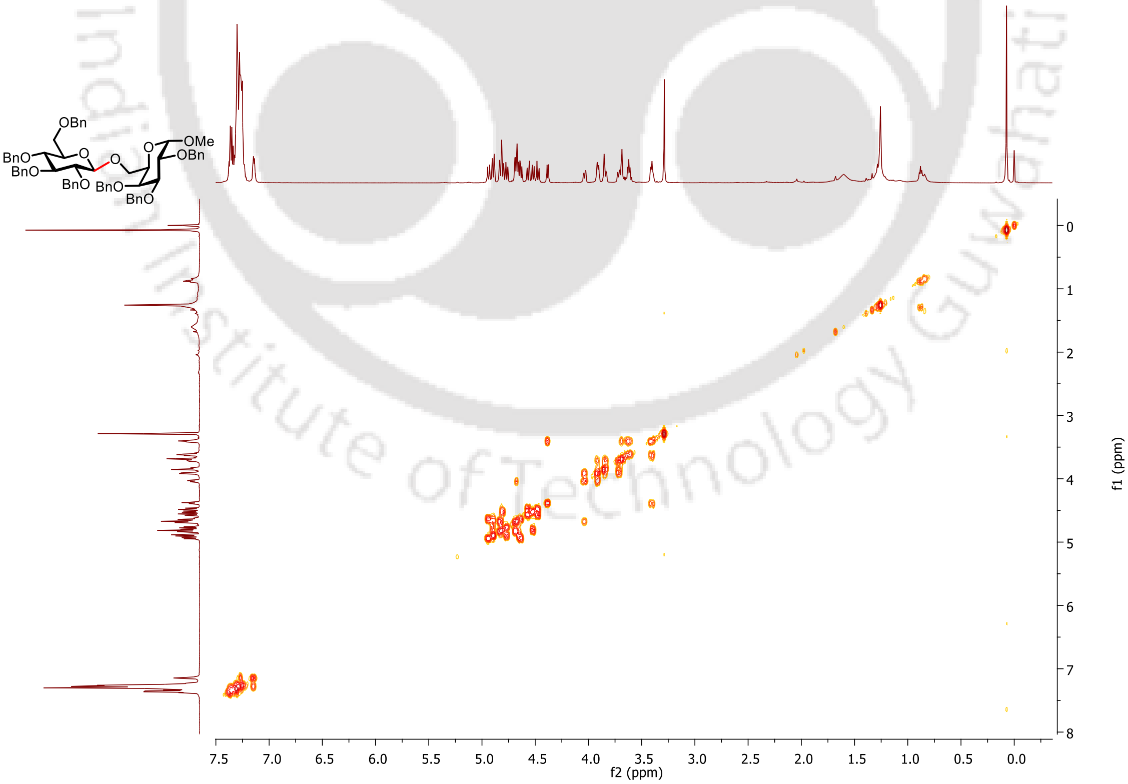
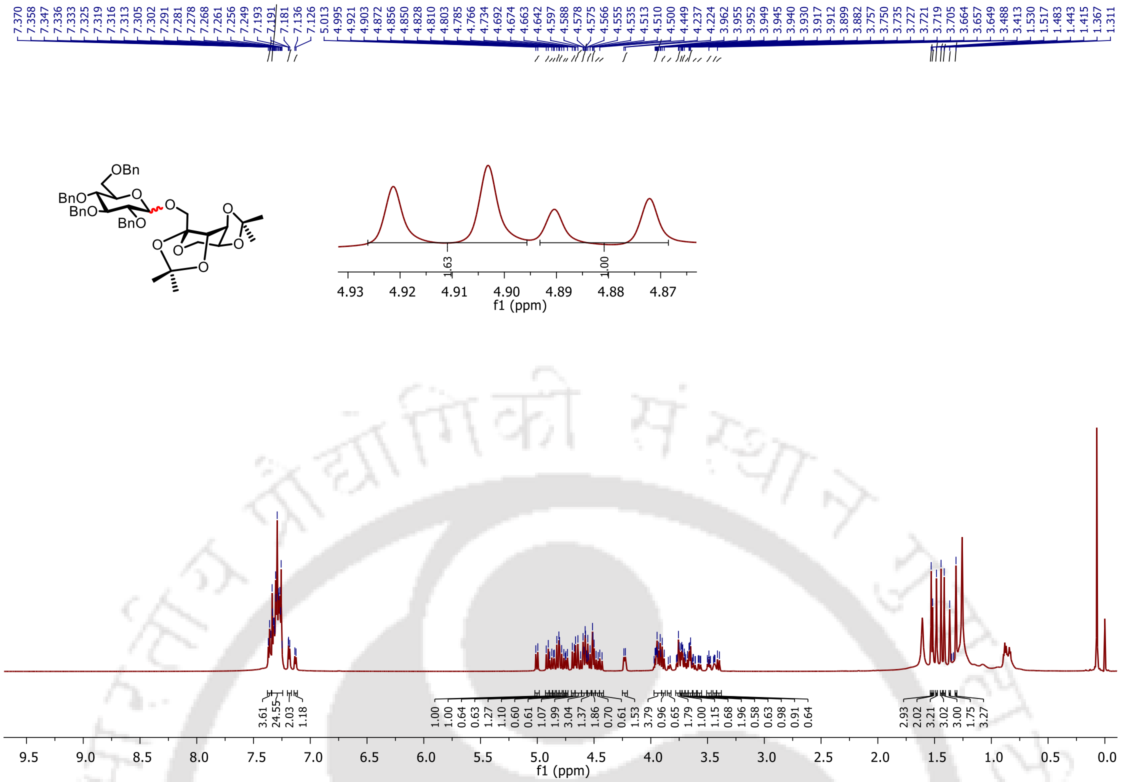


COSY spectrum of **3c,**)600 MHz, CDCl$_3$(



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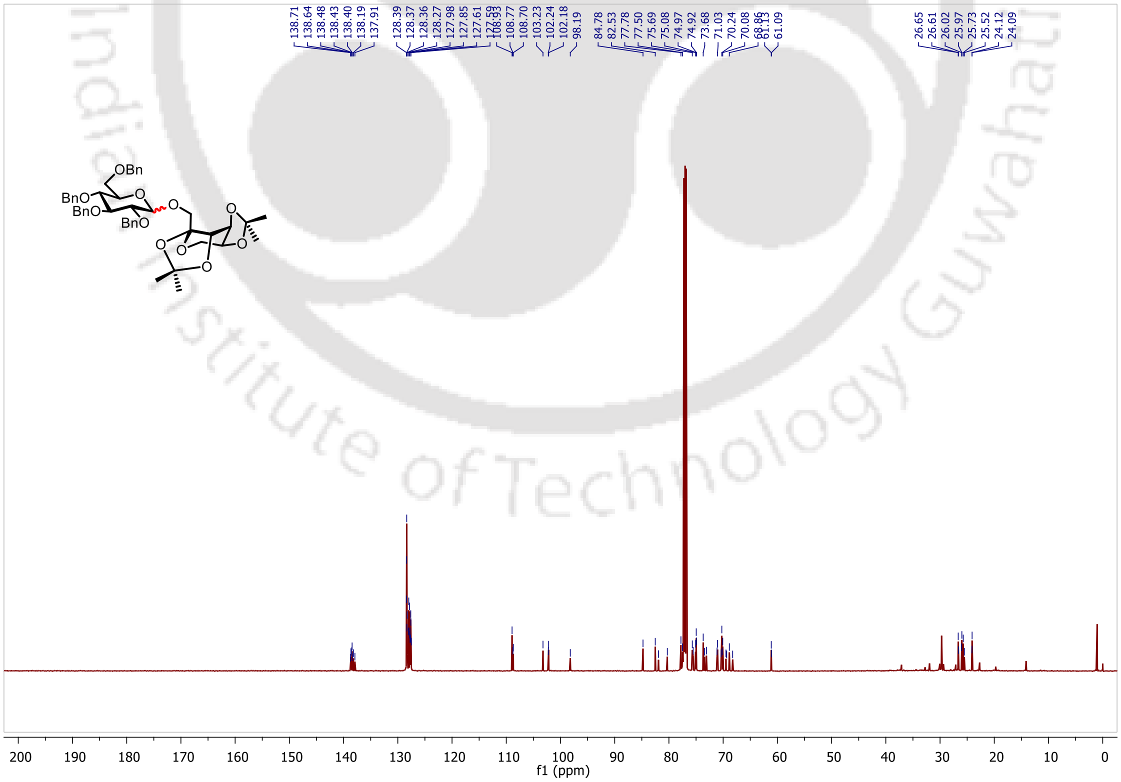

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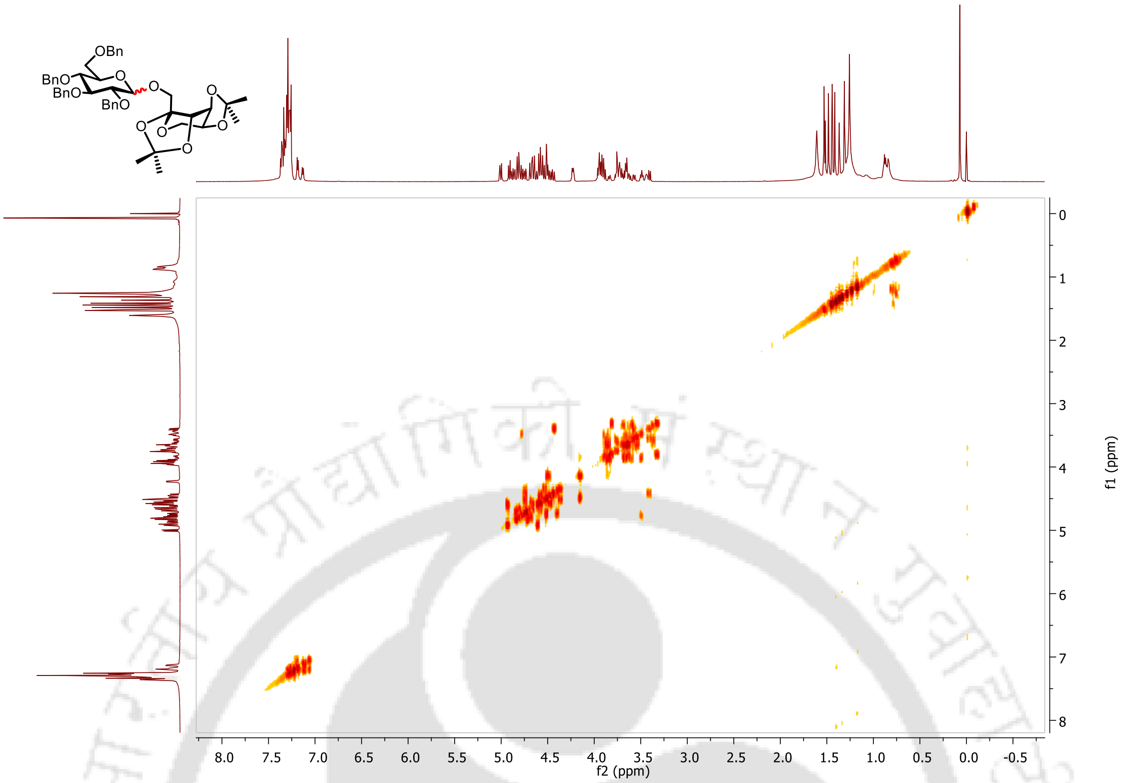

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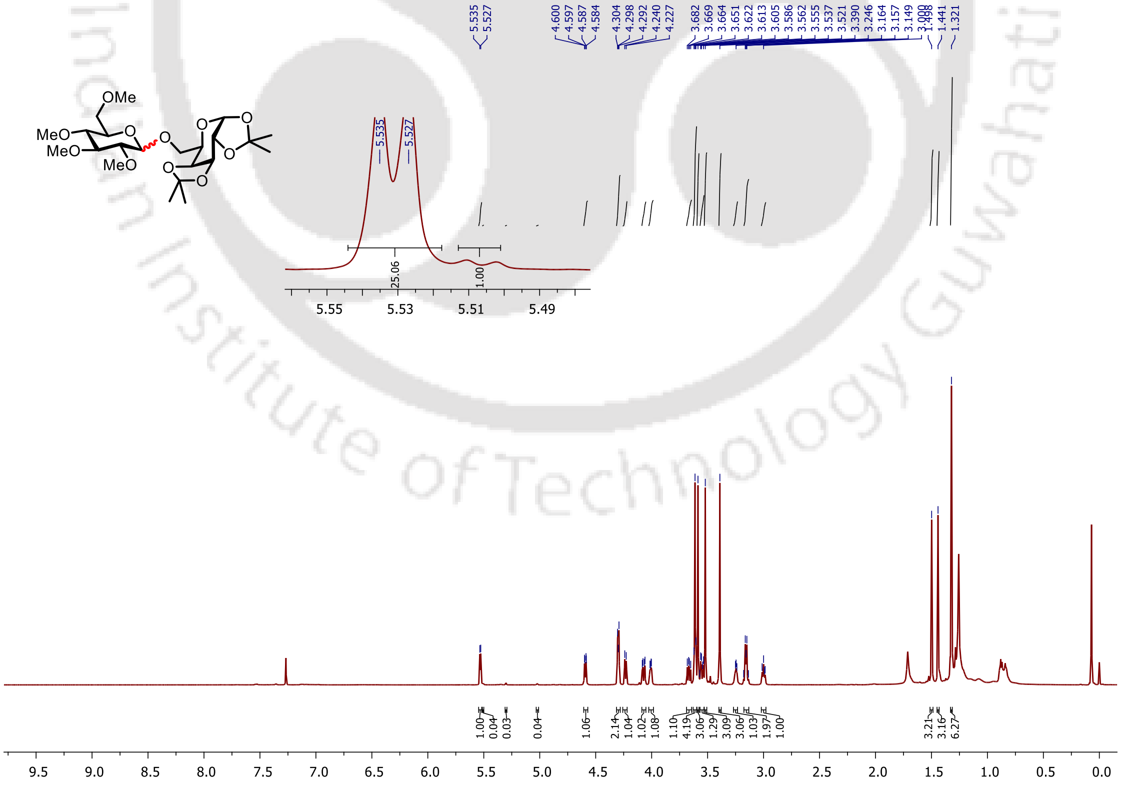

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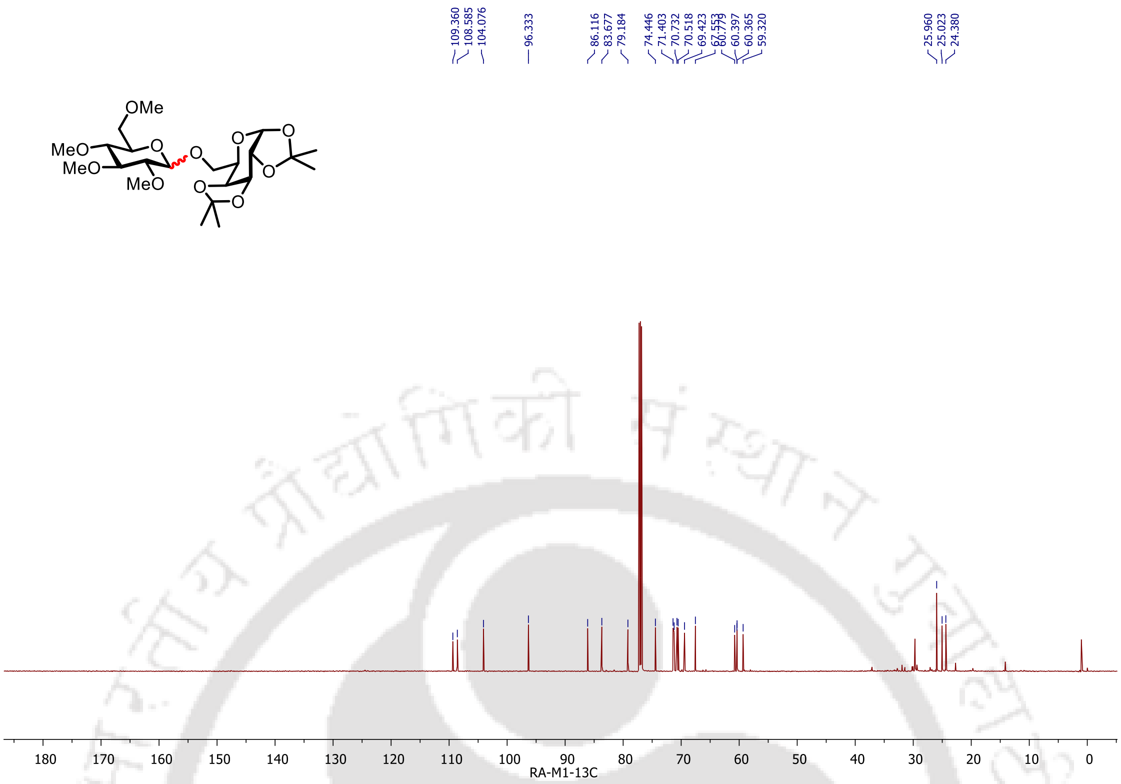

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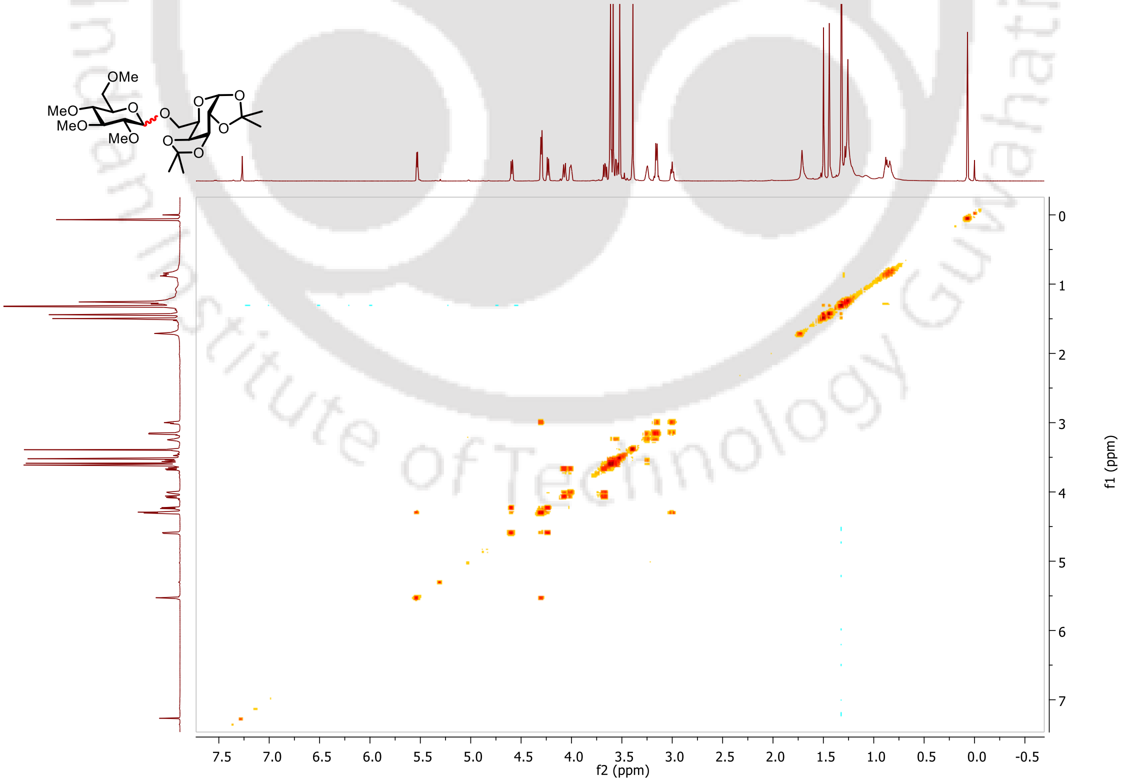

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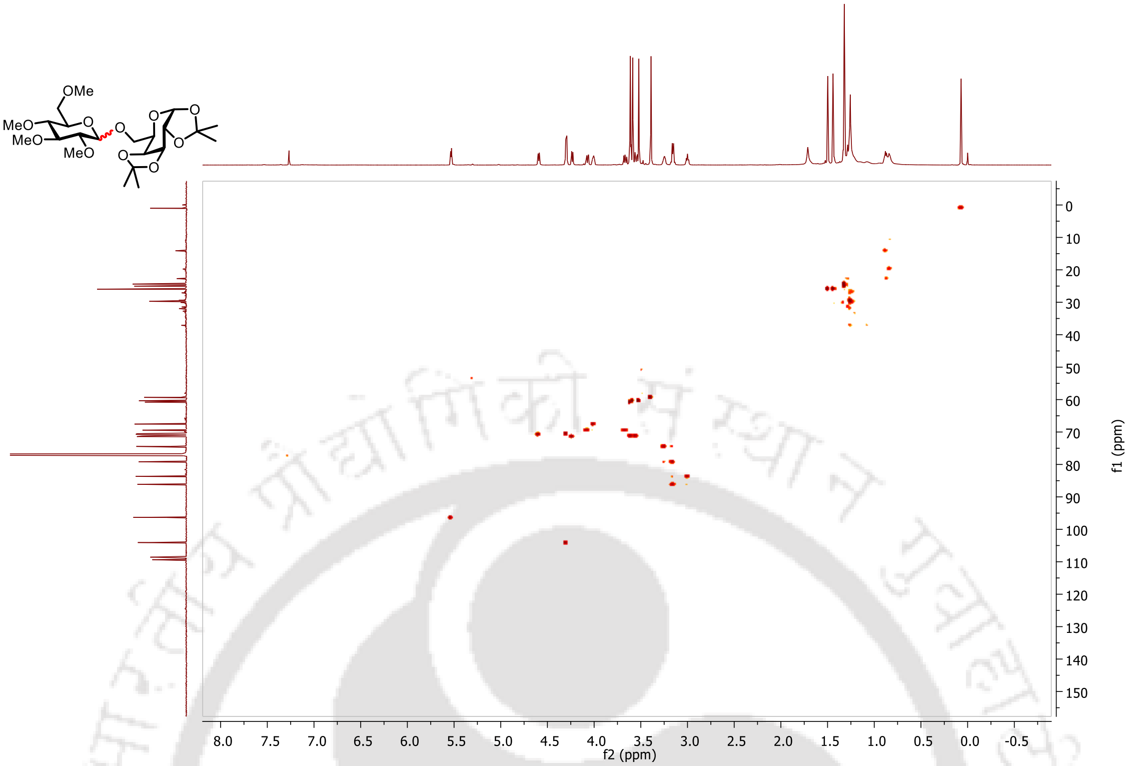

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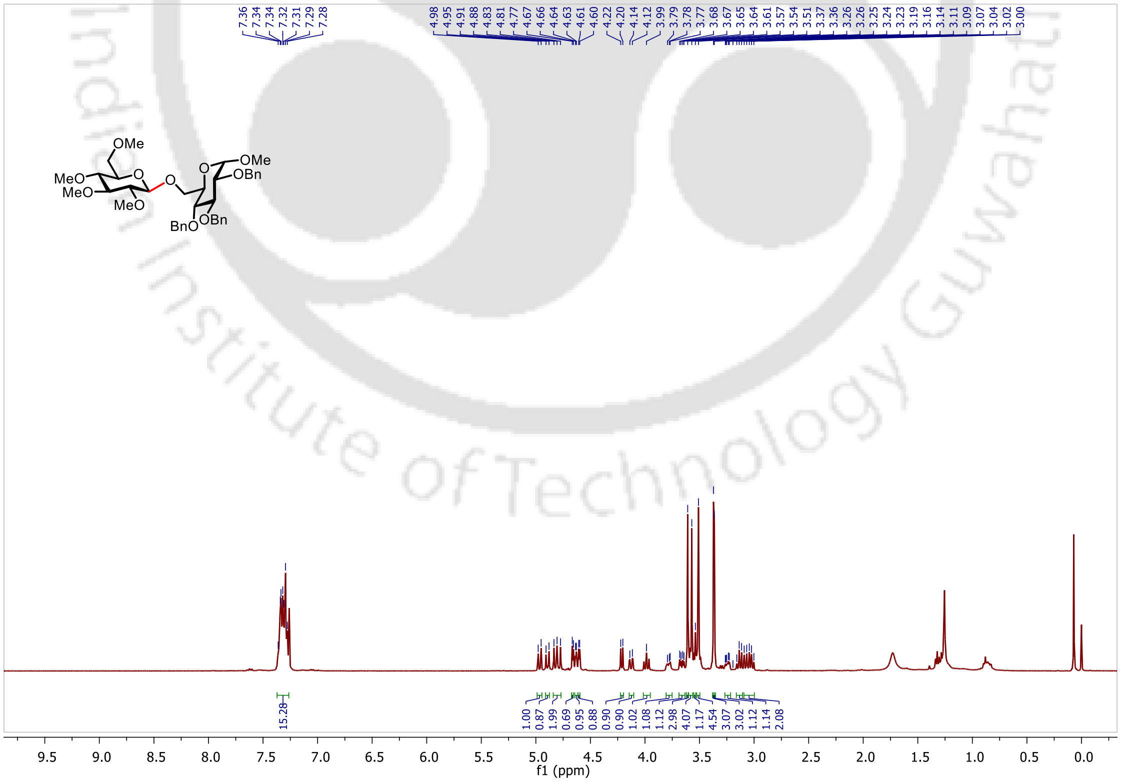
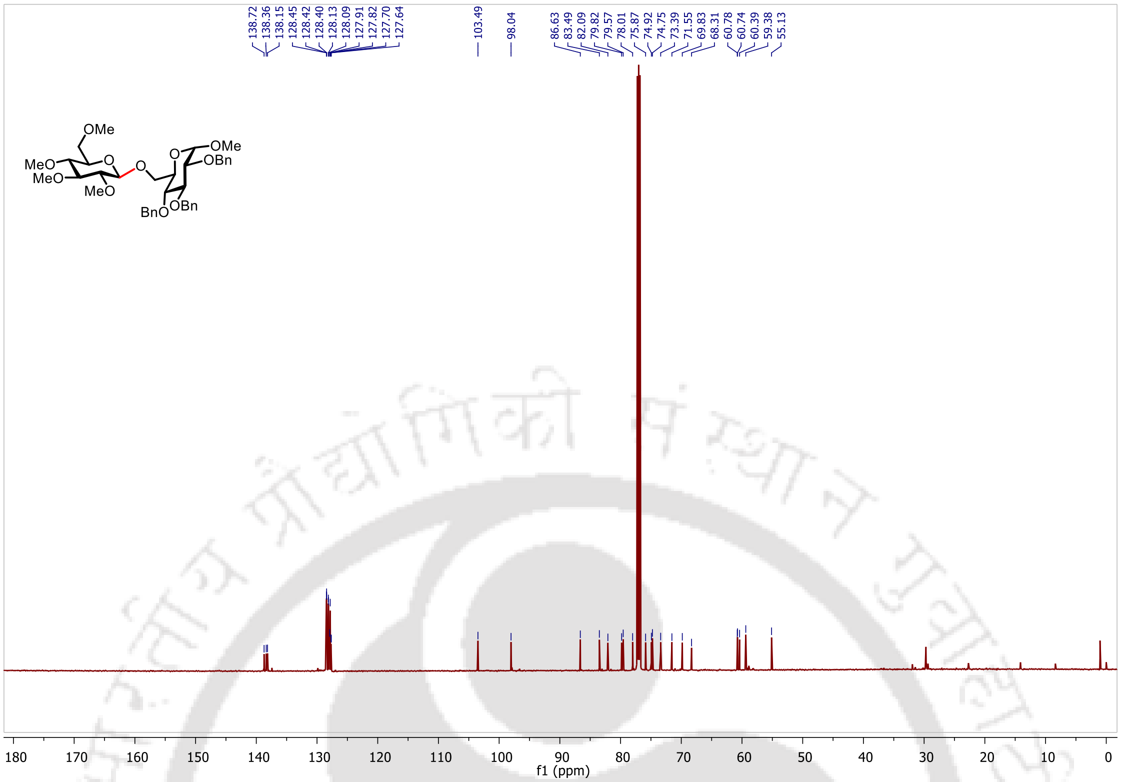
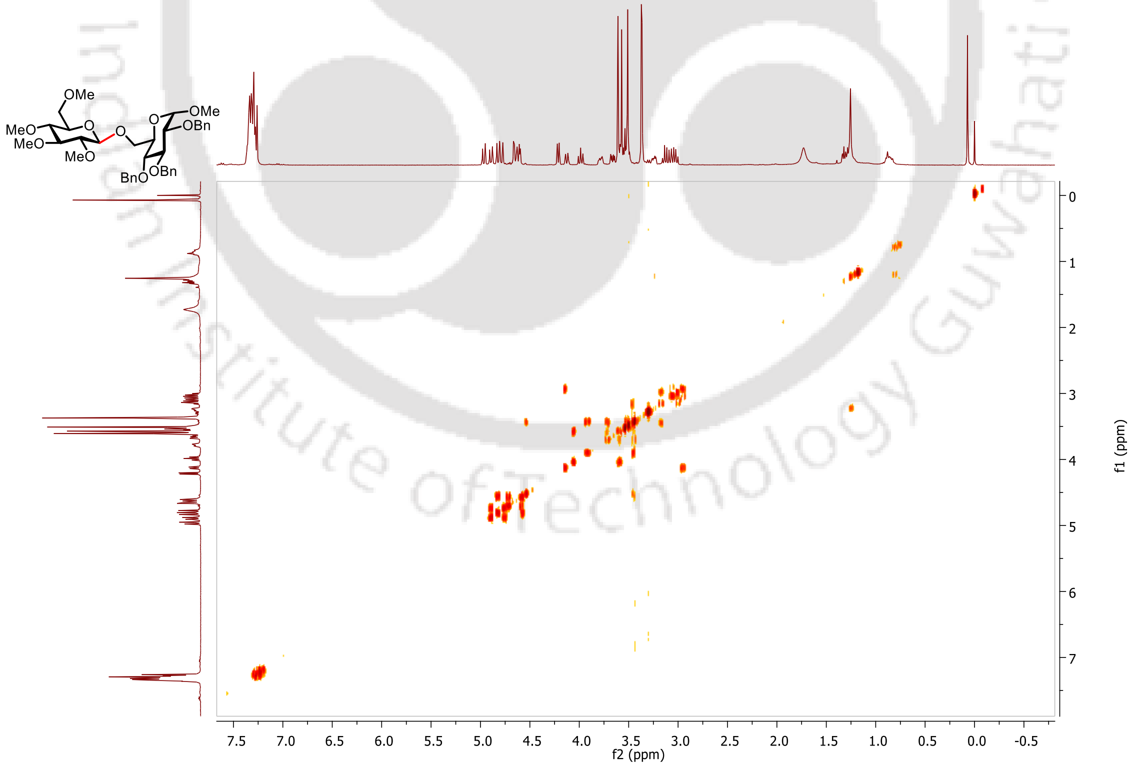


^{1}H NMR spectrum of **3h,**)600 MHz, CDCl$_3$(



^{13}C NMR spectrum of **3h,**)600 MHz, CDCl$_3$(



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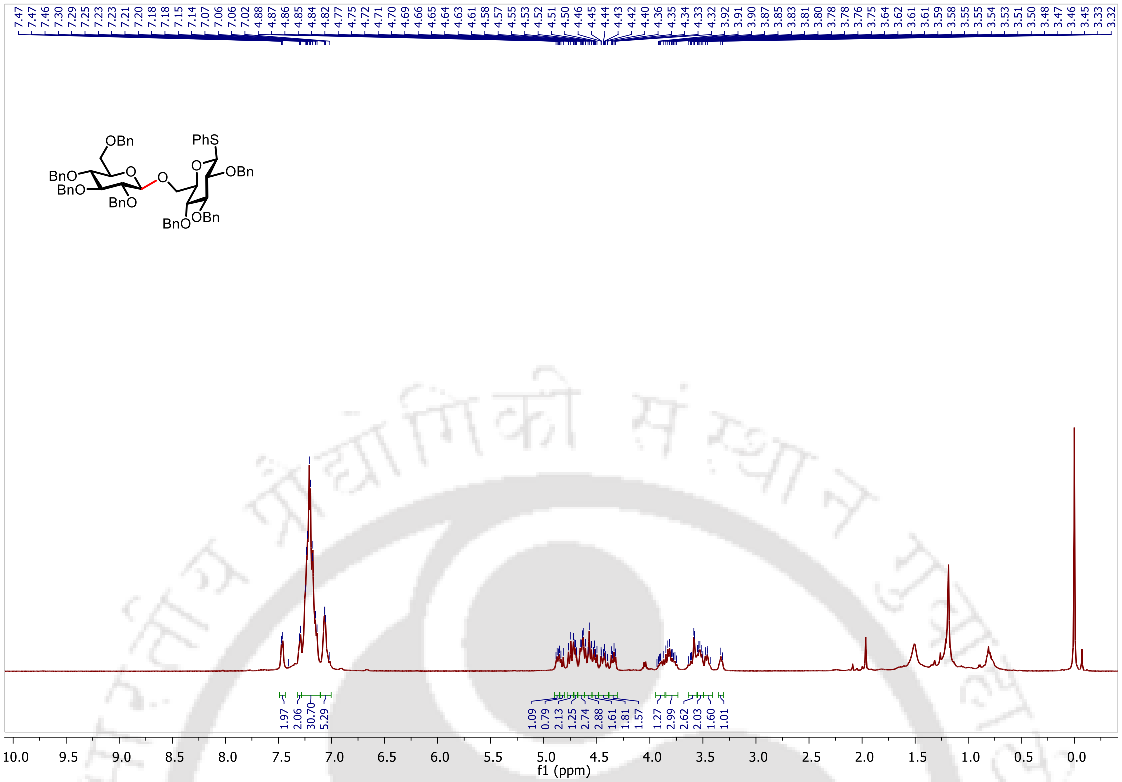

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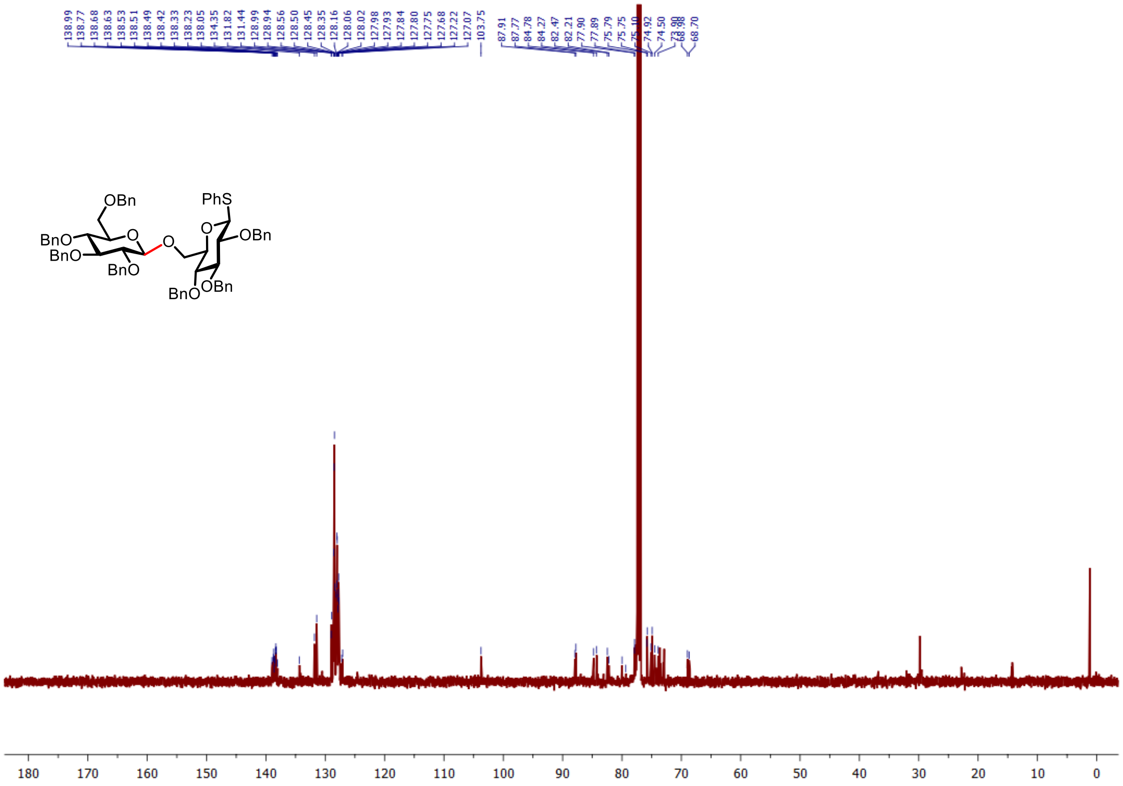

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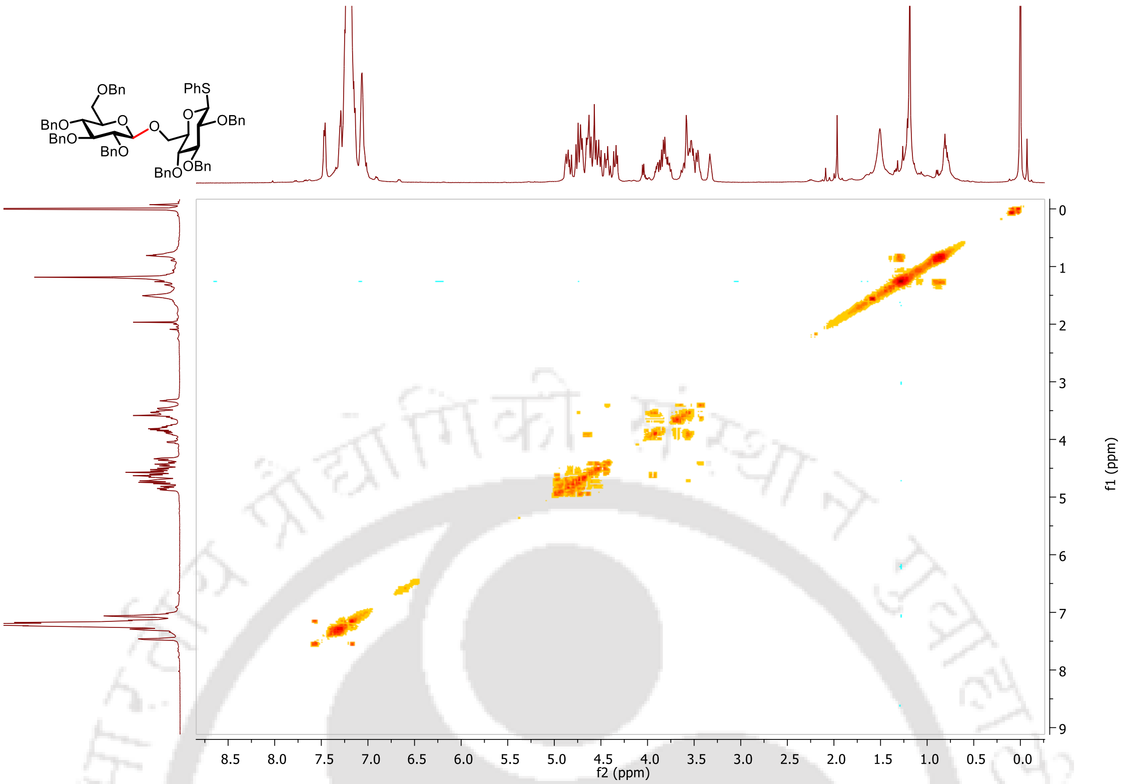

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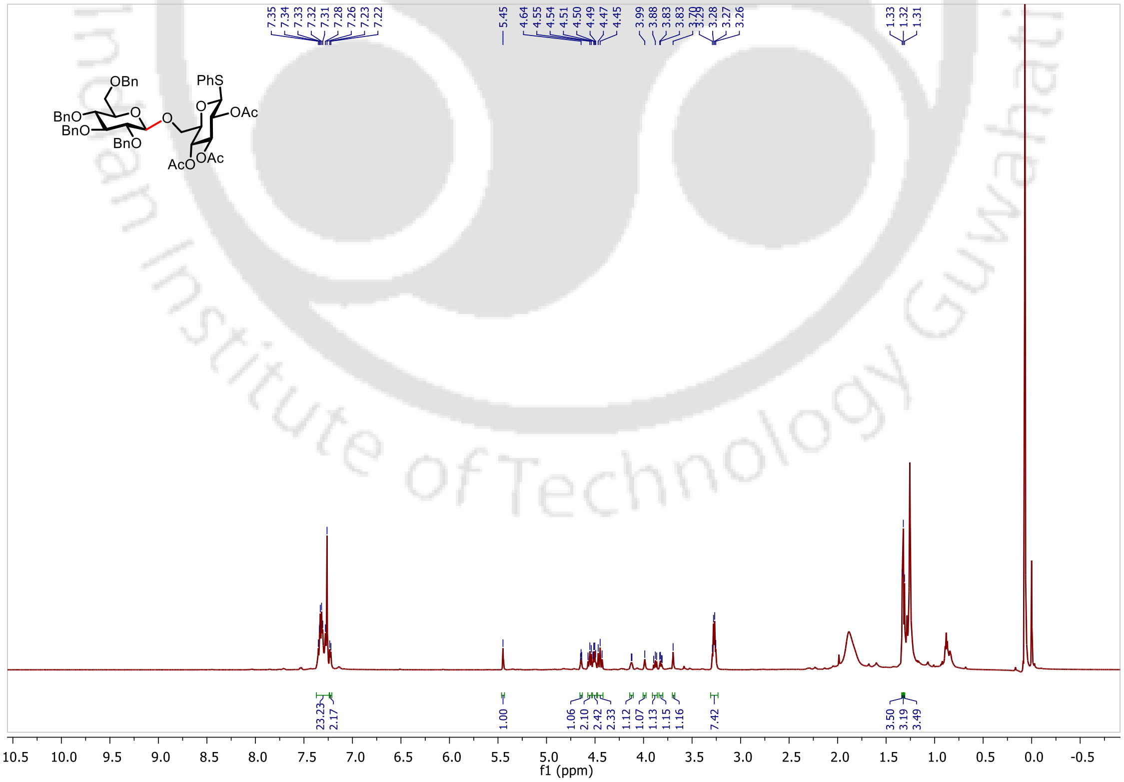

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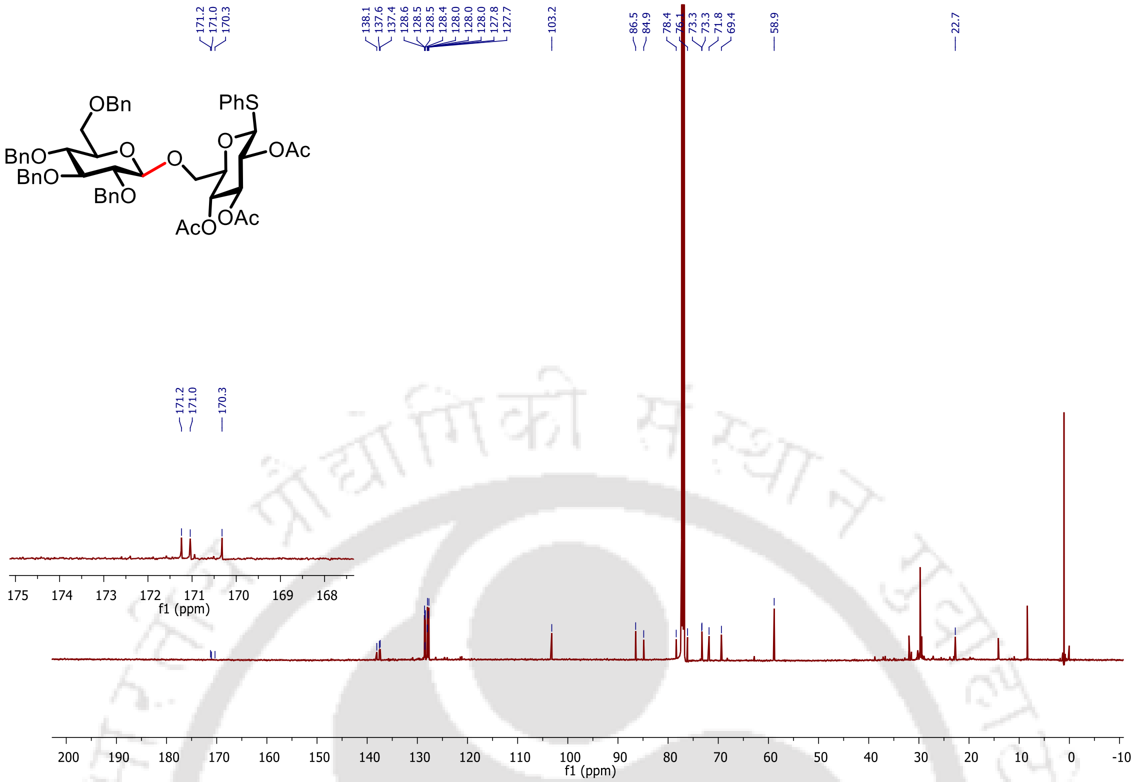

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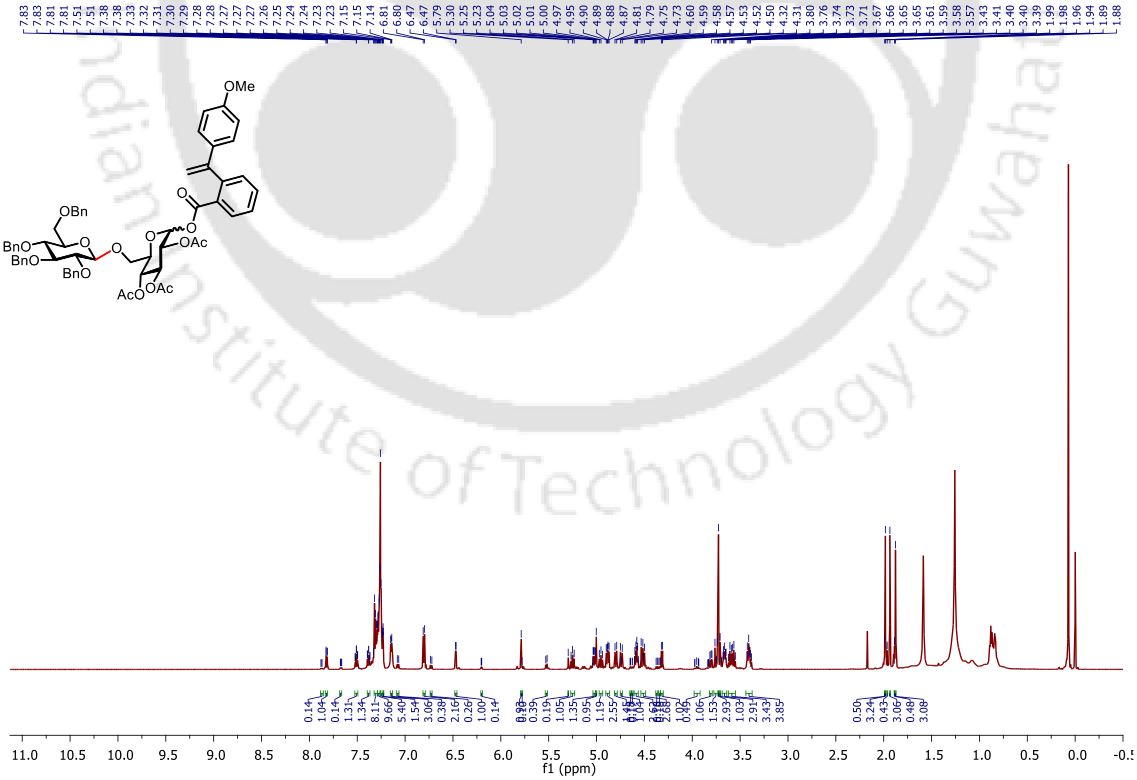

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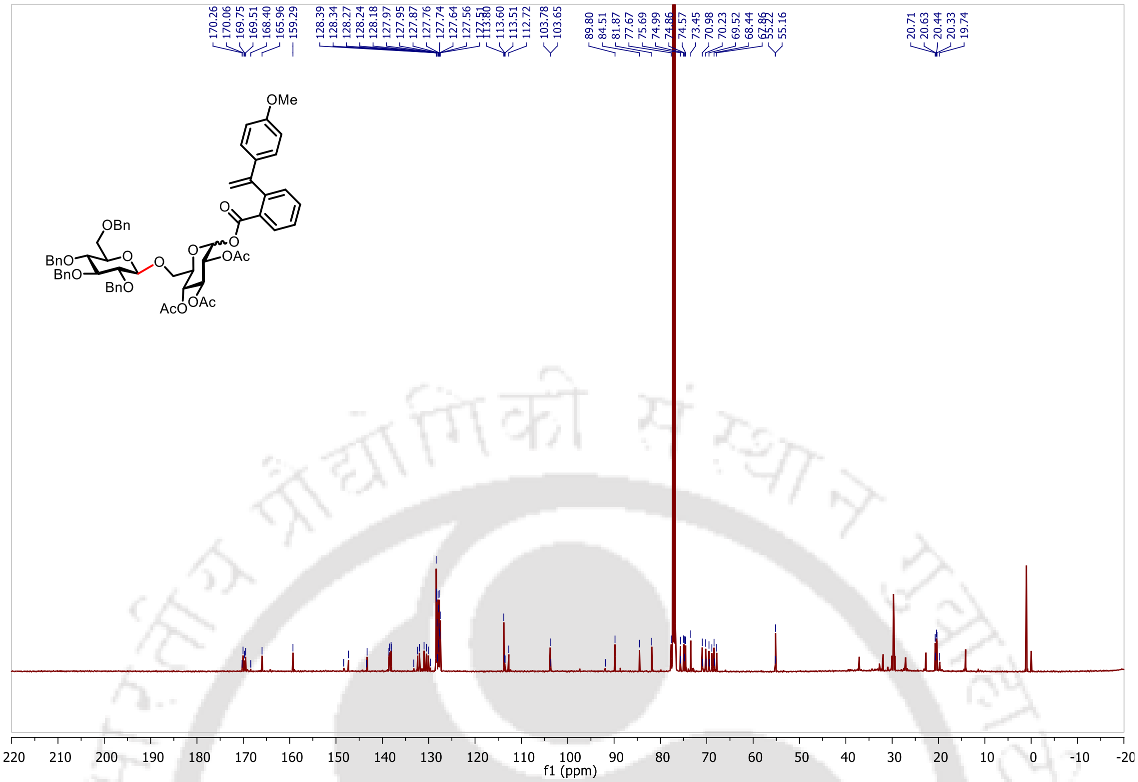

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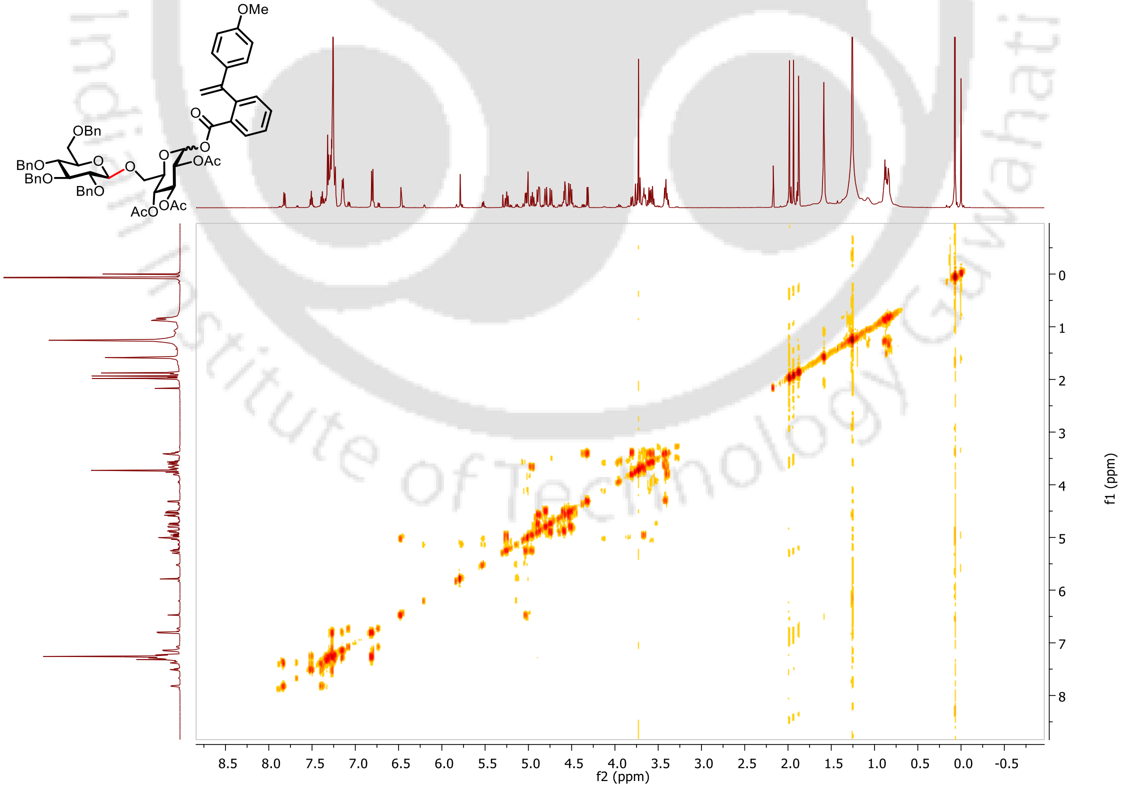

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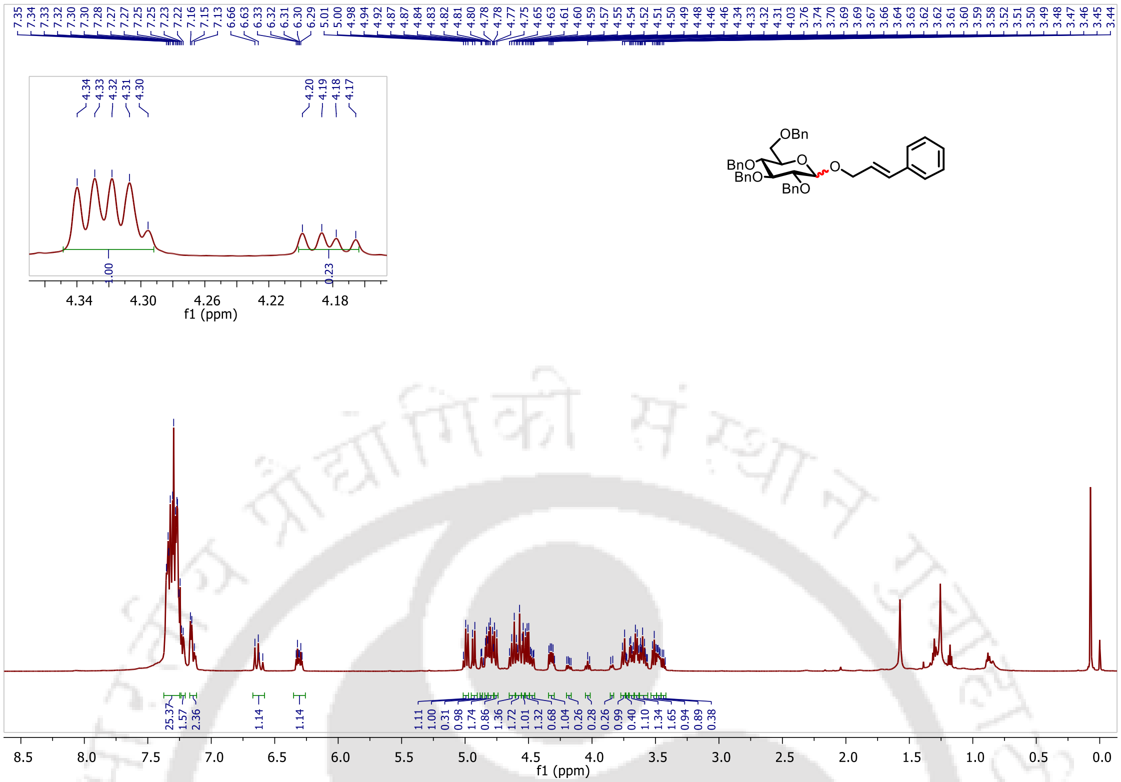

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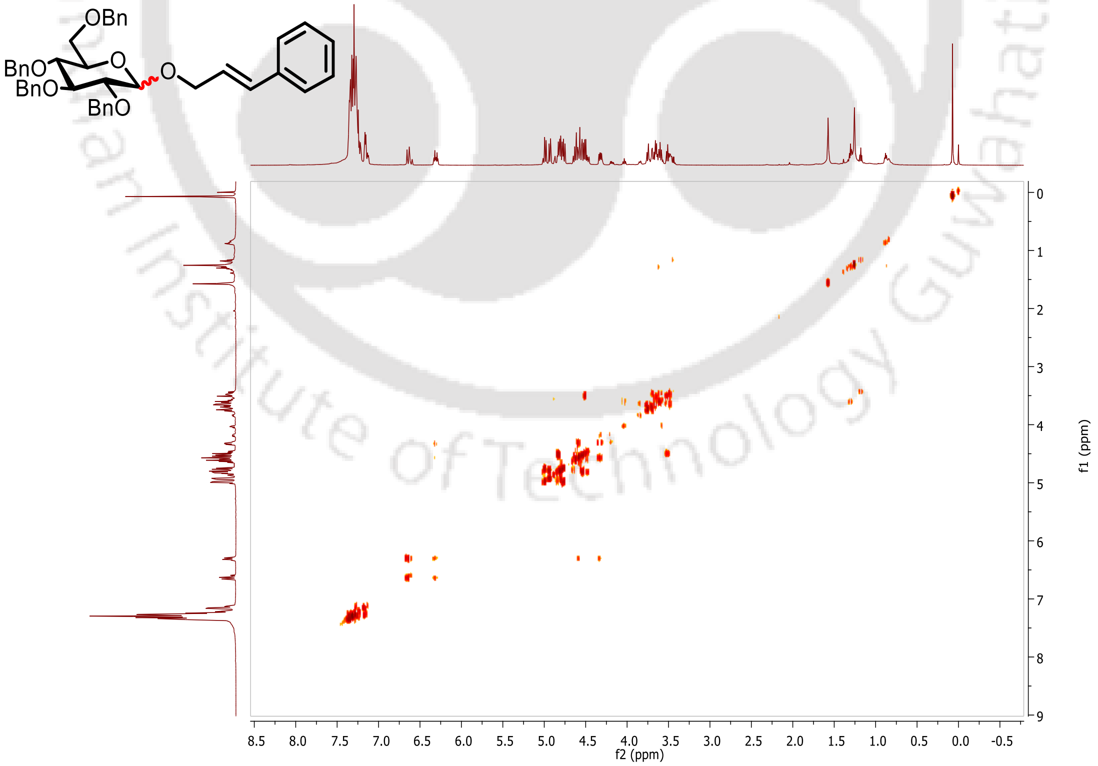

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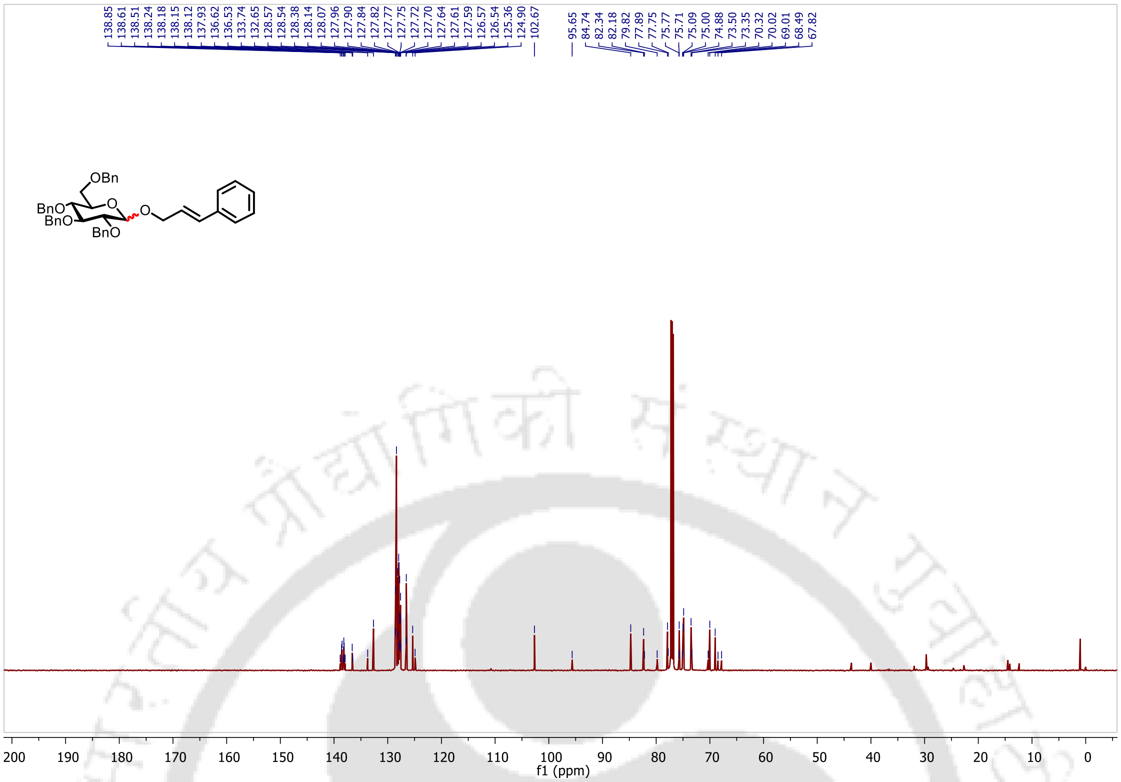

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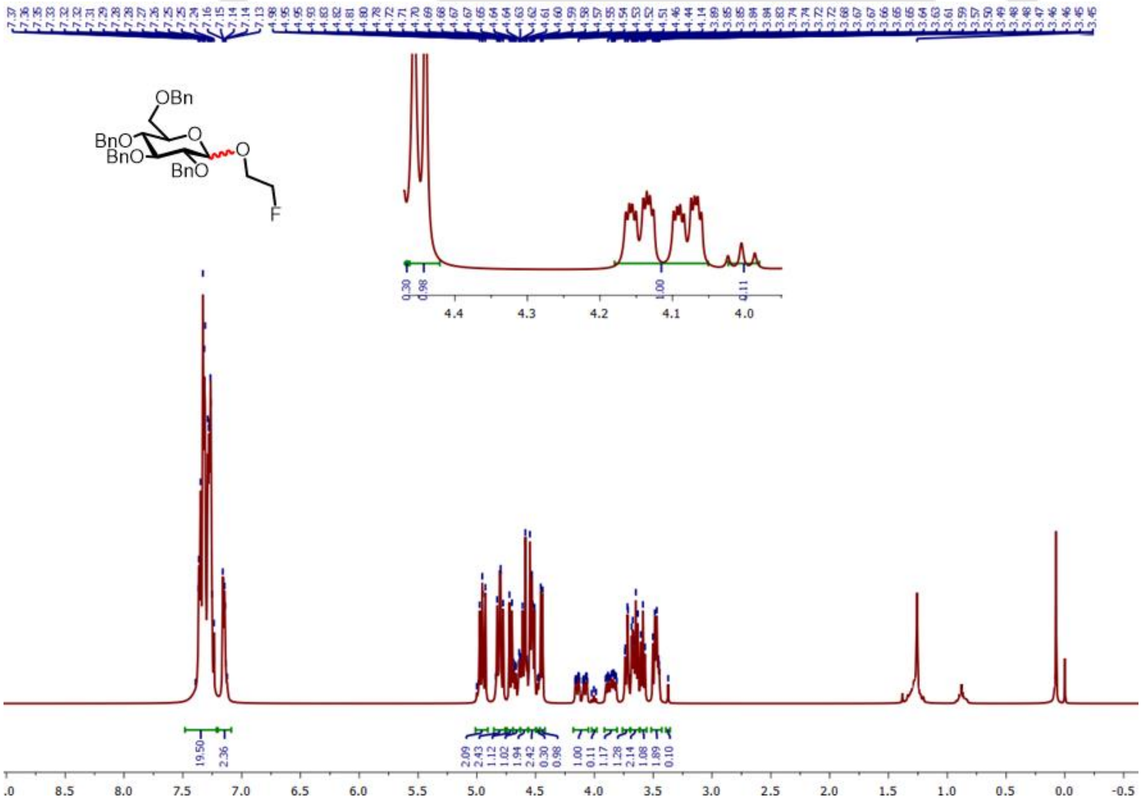
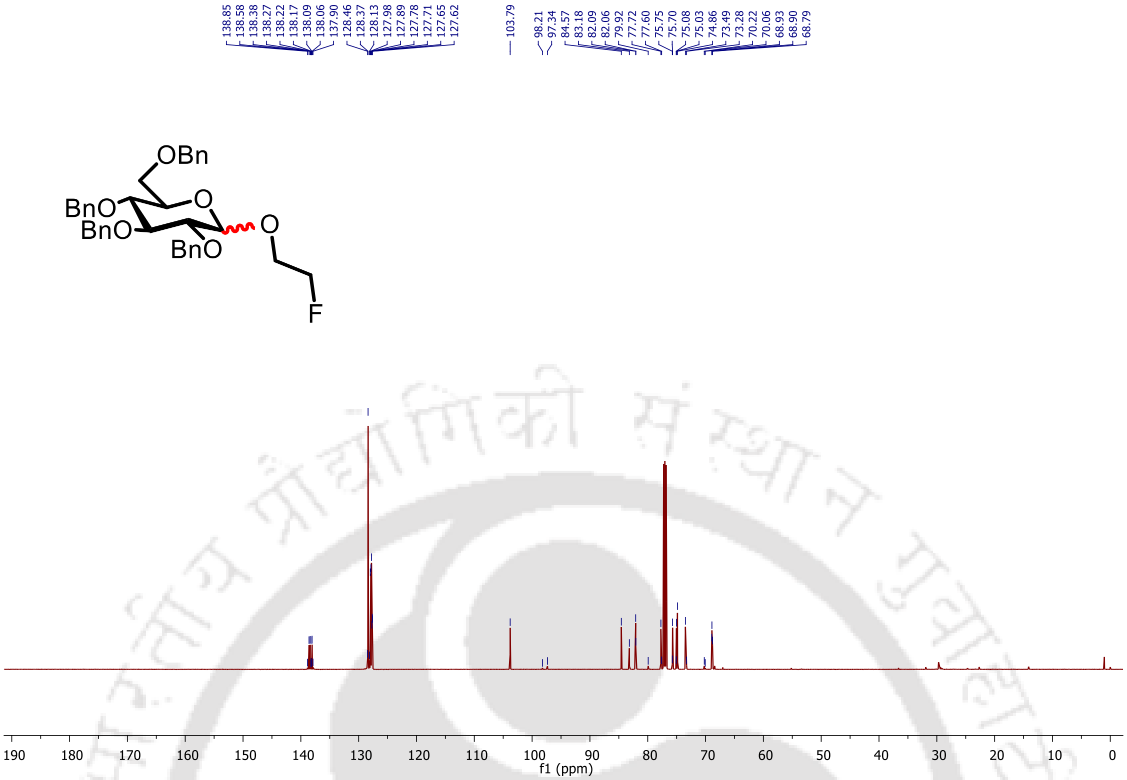
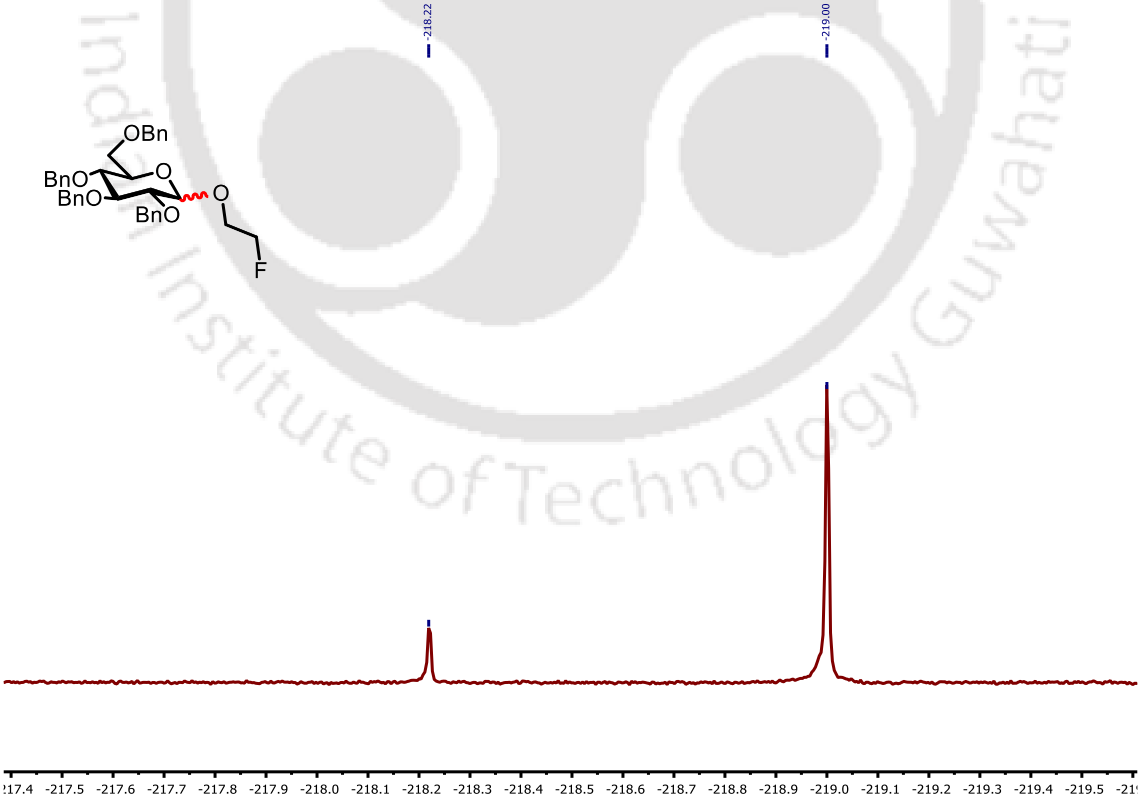


^{1}H NMR spectrum of **3m,**)500 MHz, $CDCl_3$(



^{13}C NMR spectrum of **3m,**)126 MHz, $CDCl_3$(



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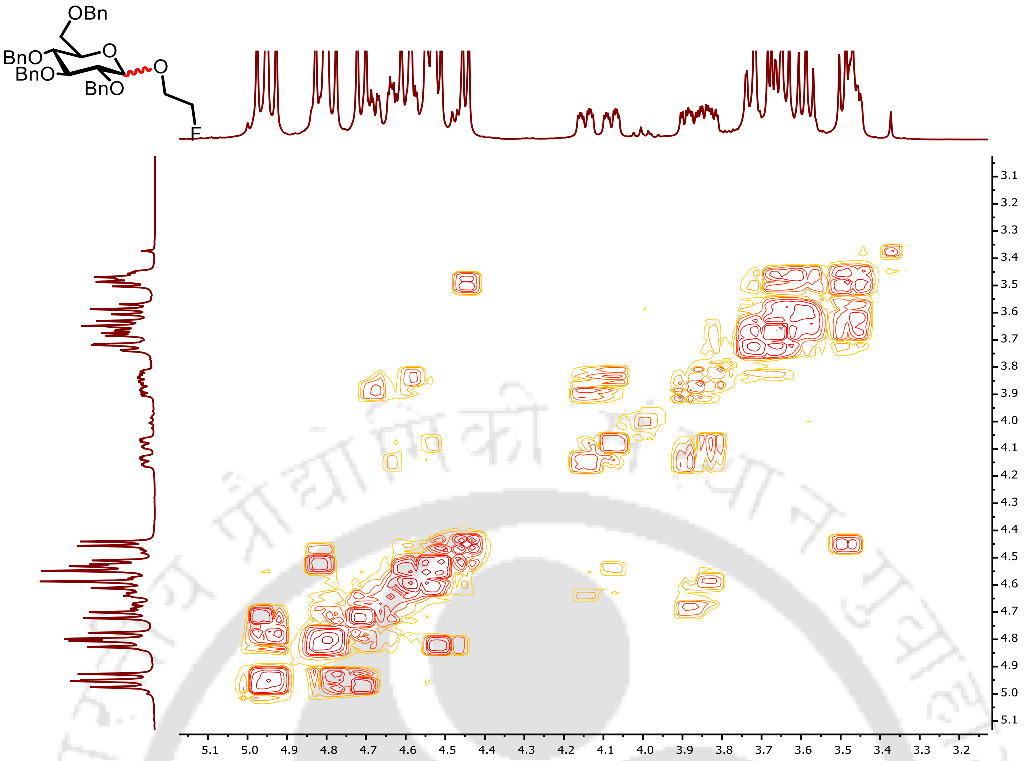

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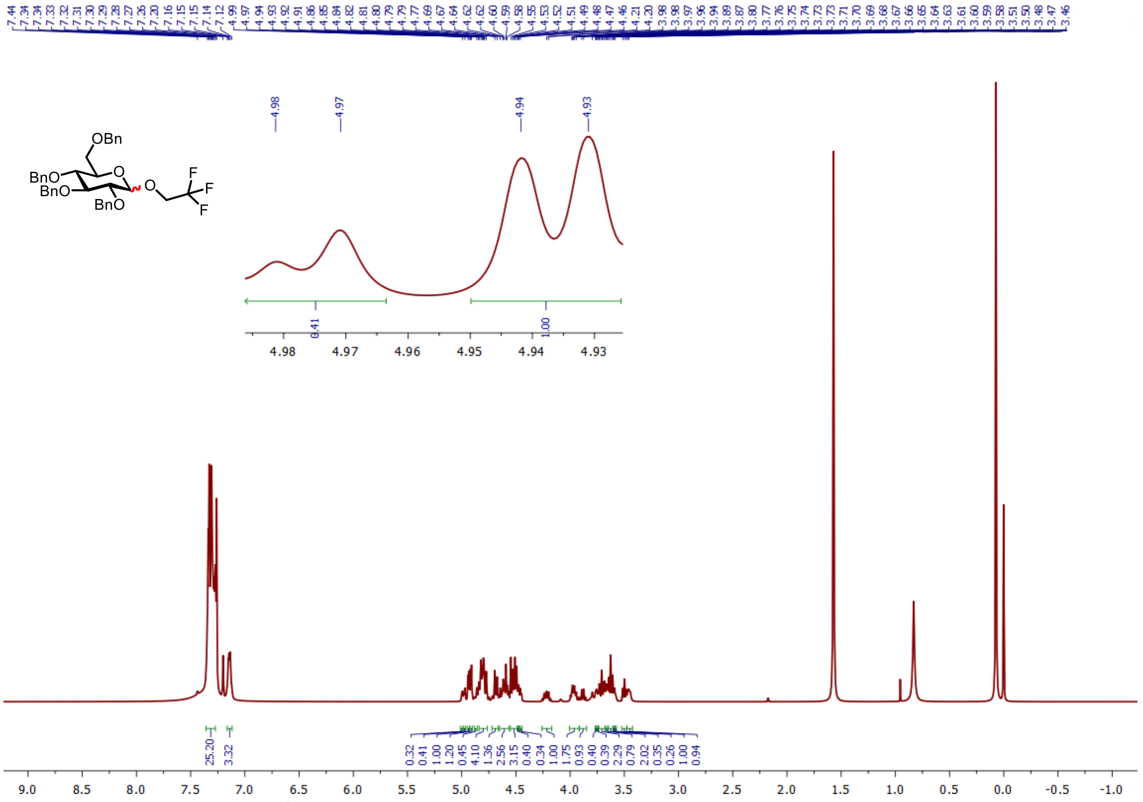

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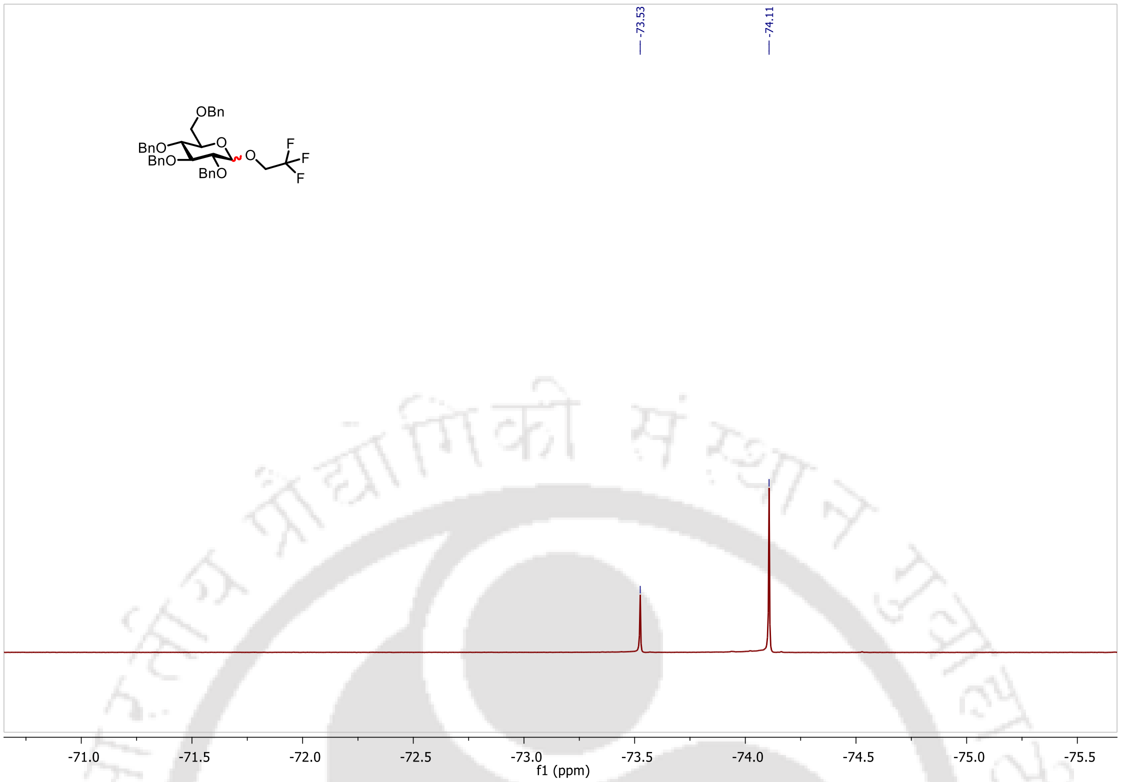

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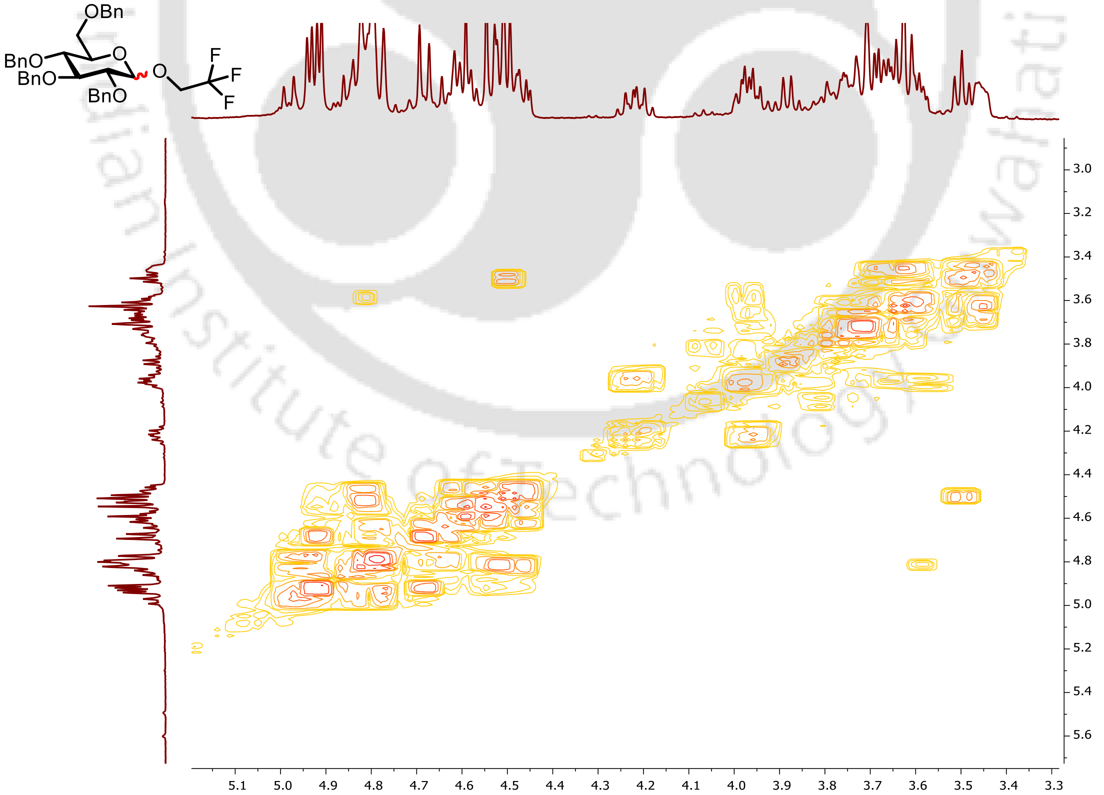

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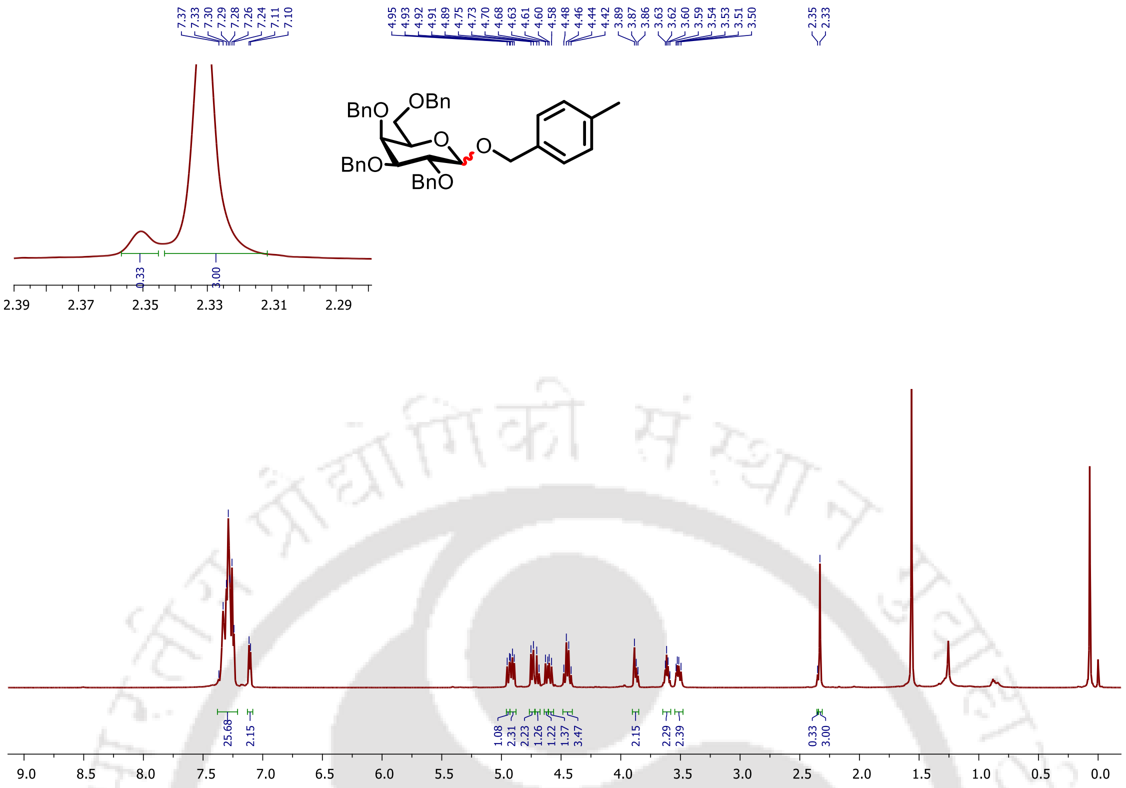

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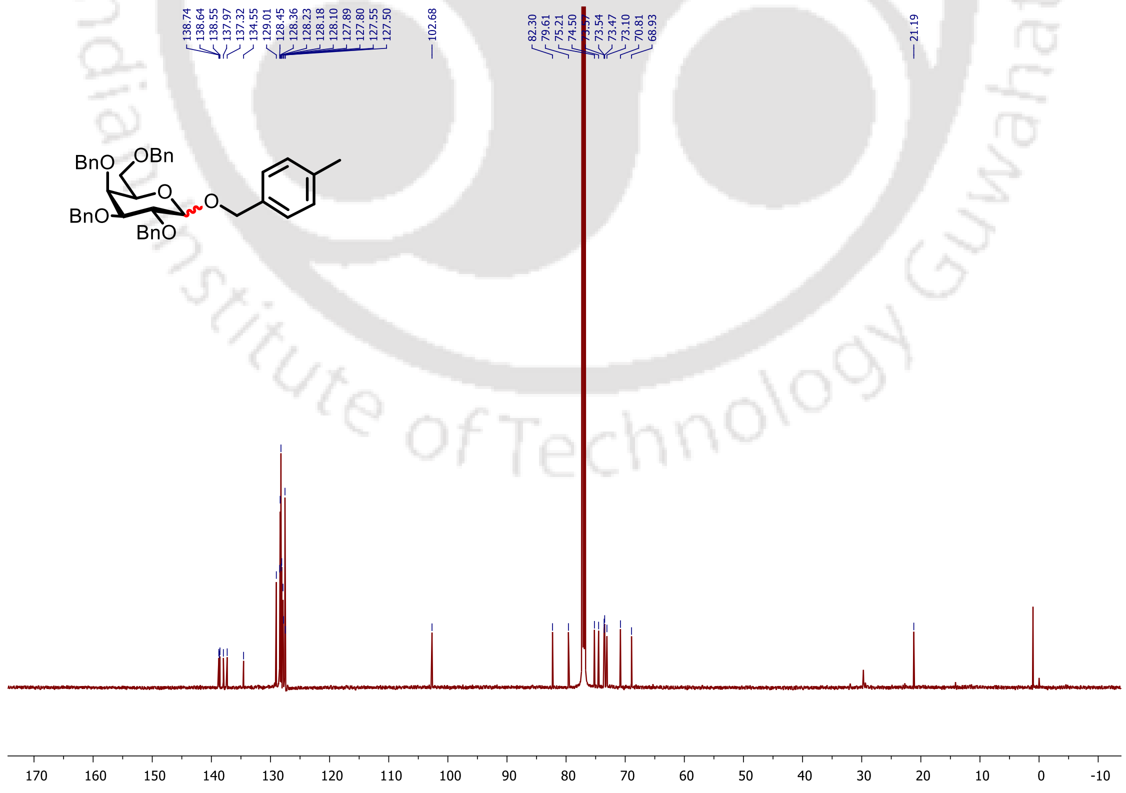

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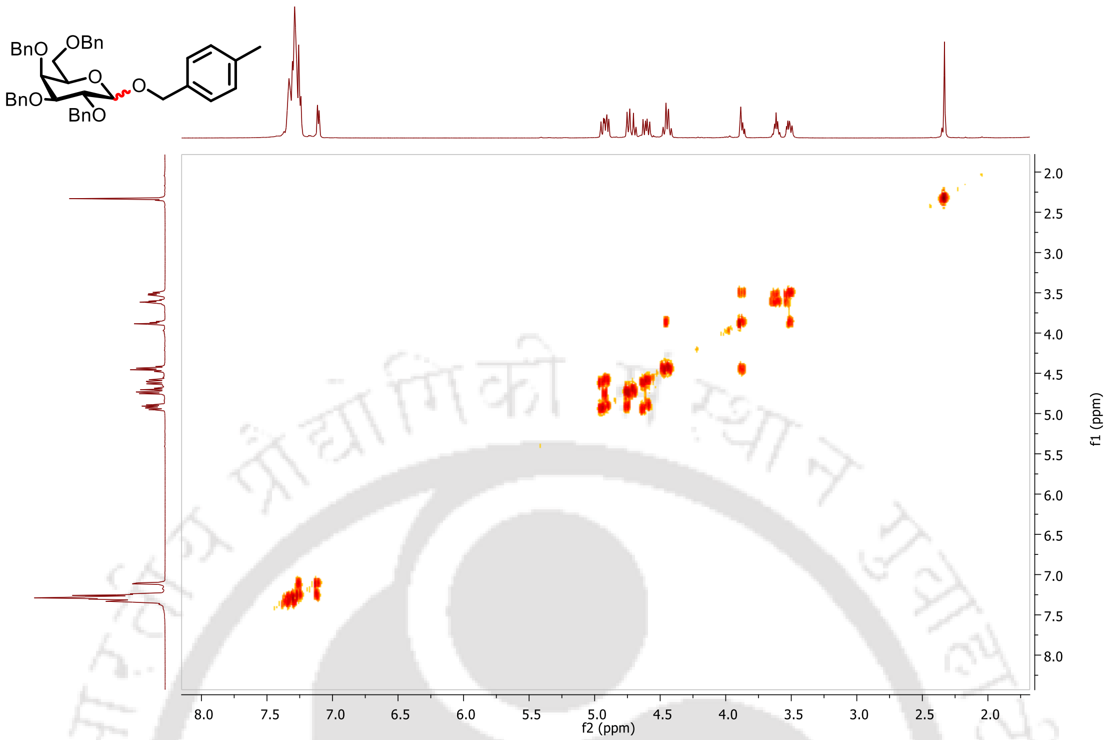

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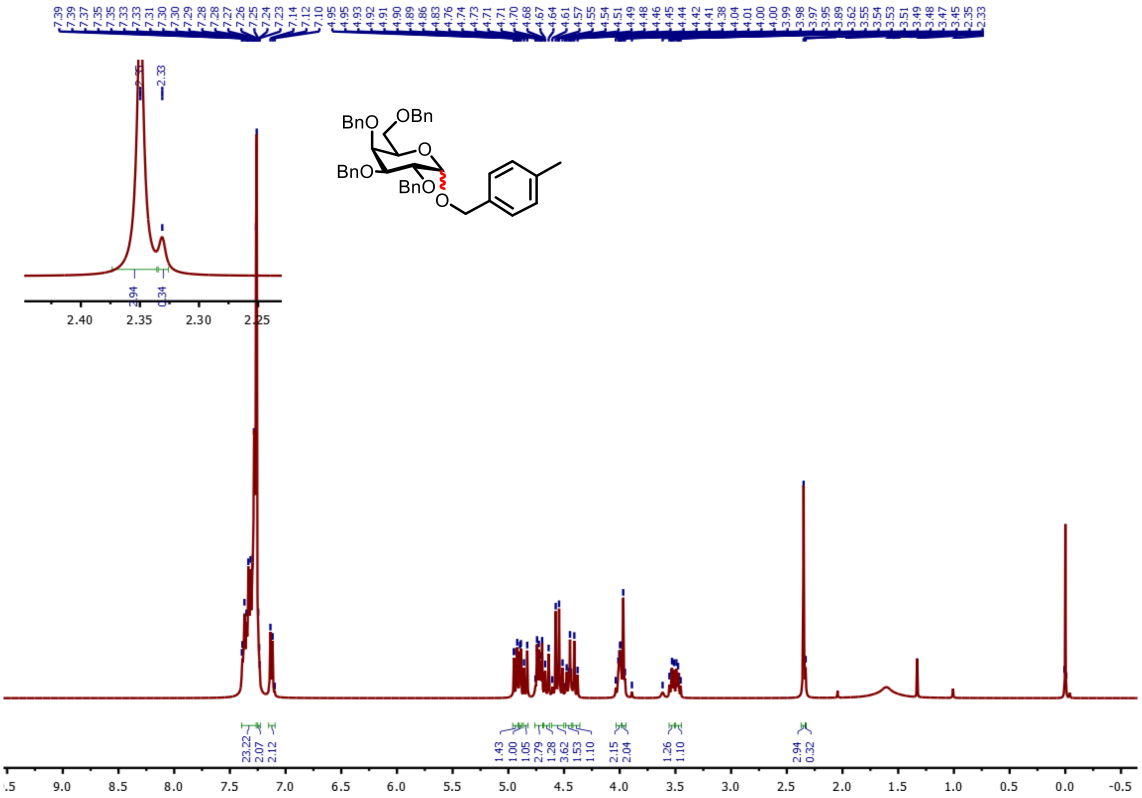

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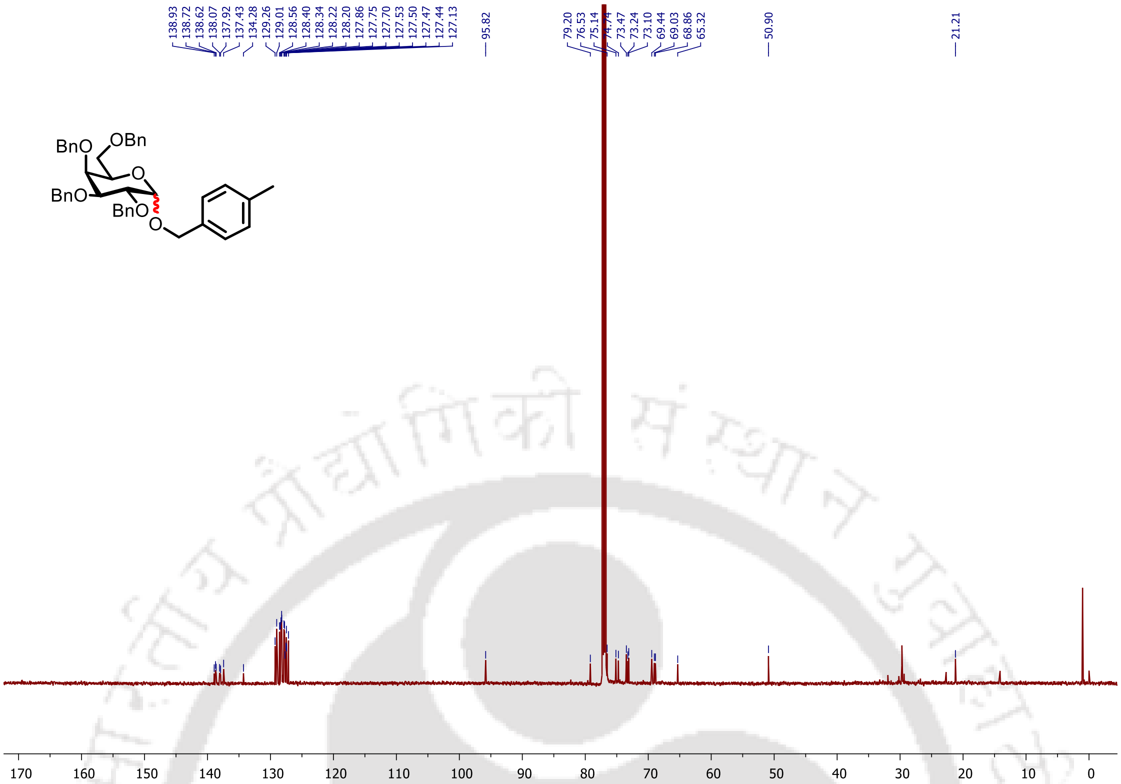

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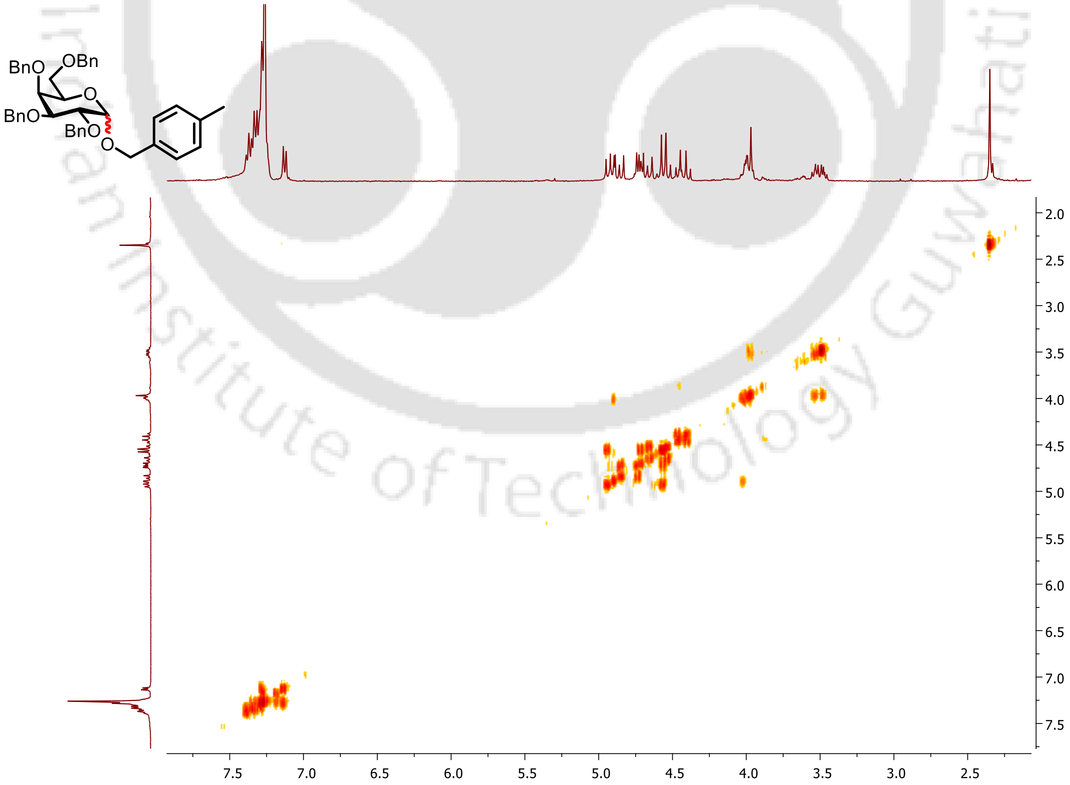

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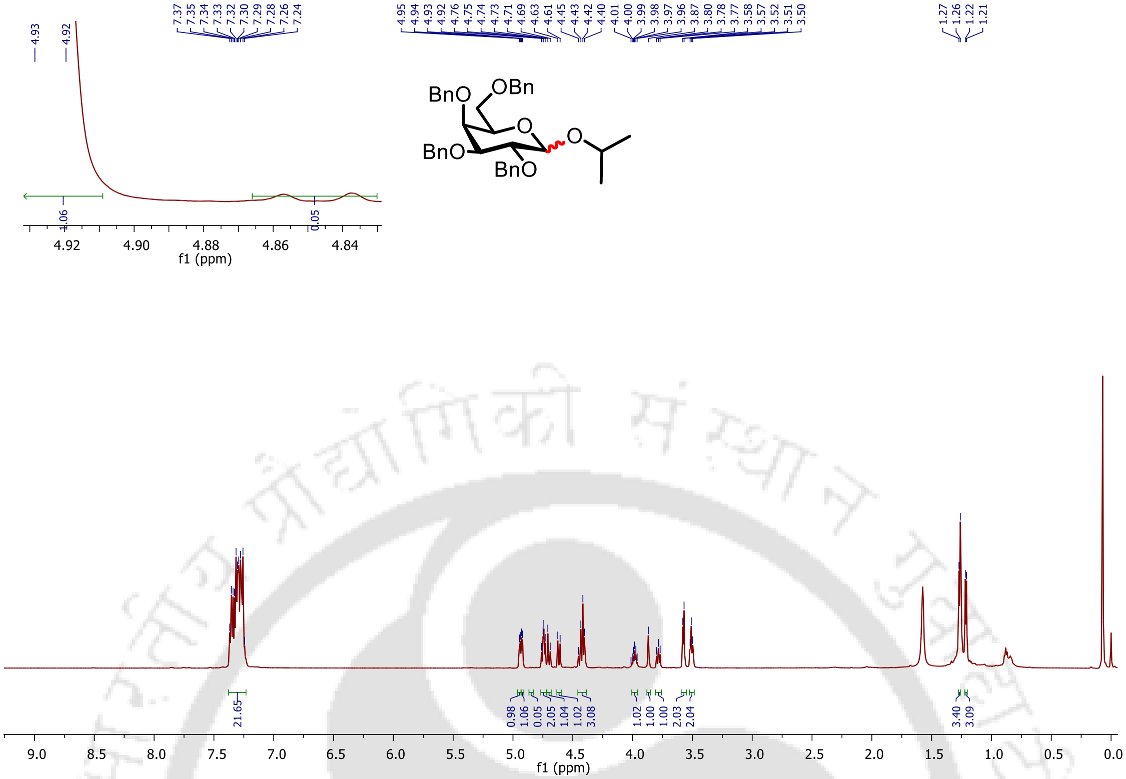

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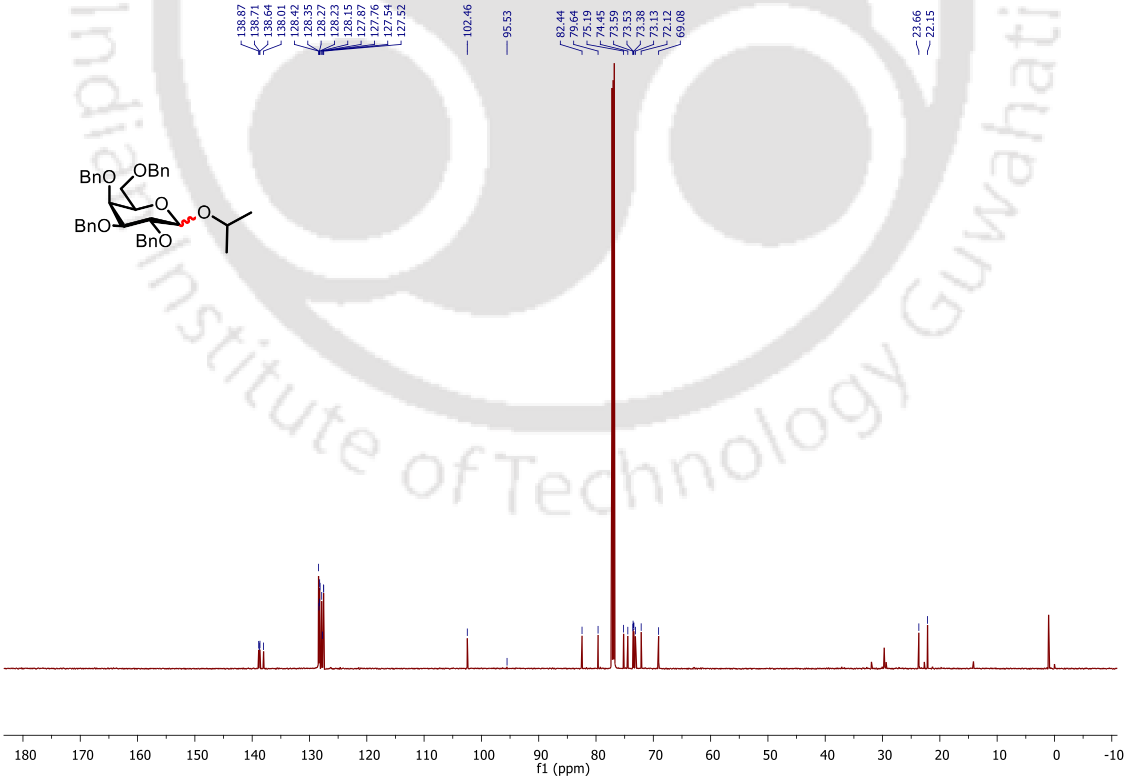

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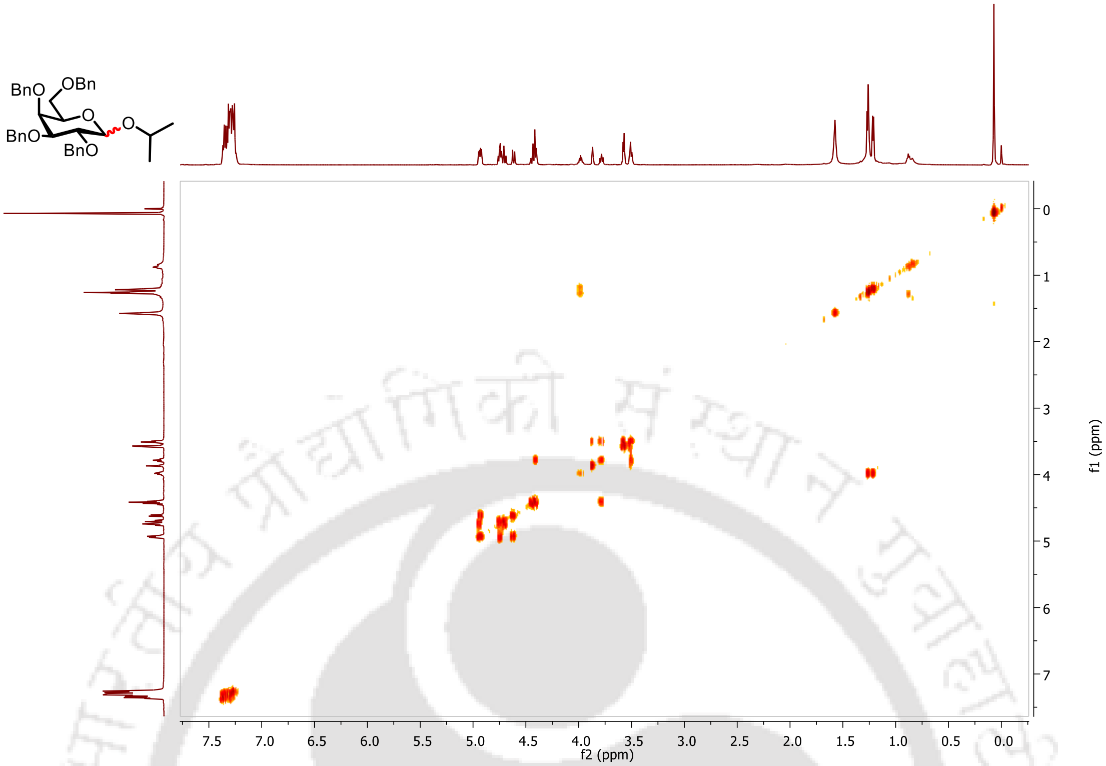
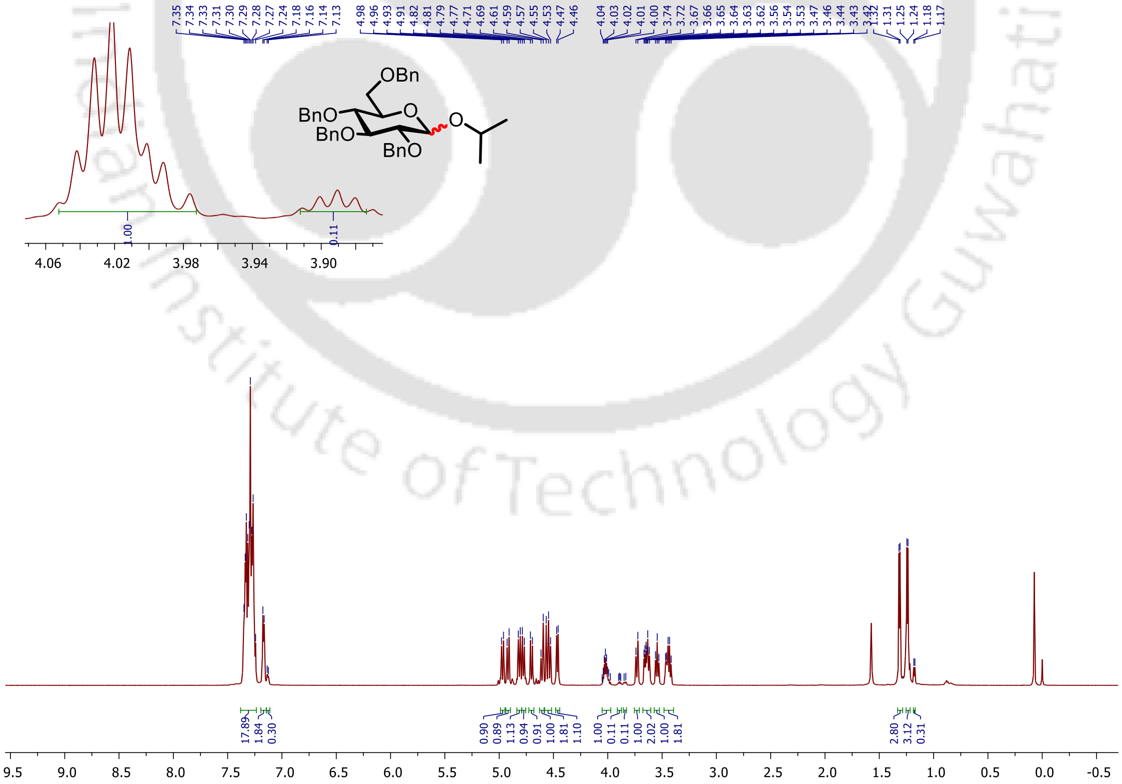


COSY NMR spectrum of **3q,**)600 MHz, CDCl3(



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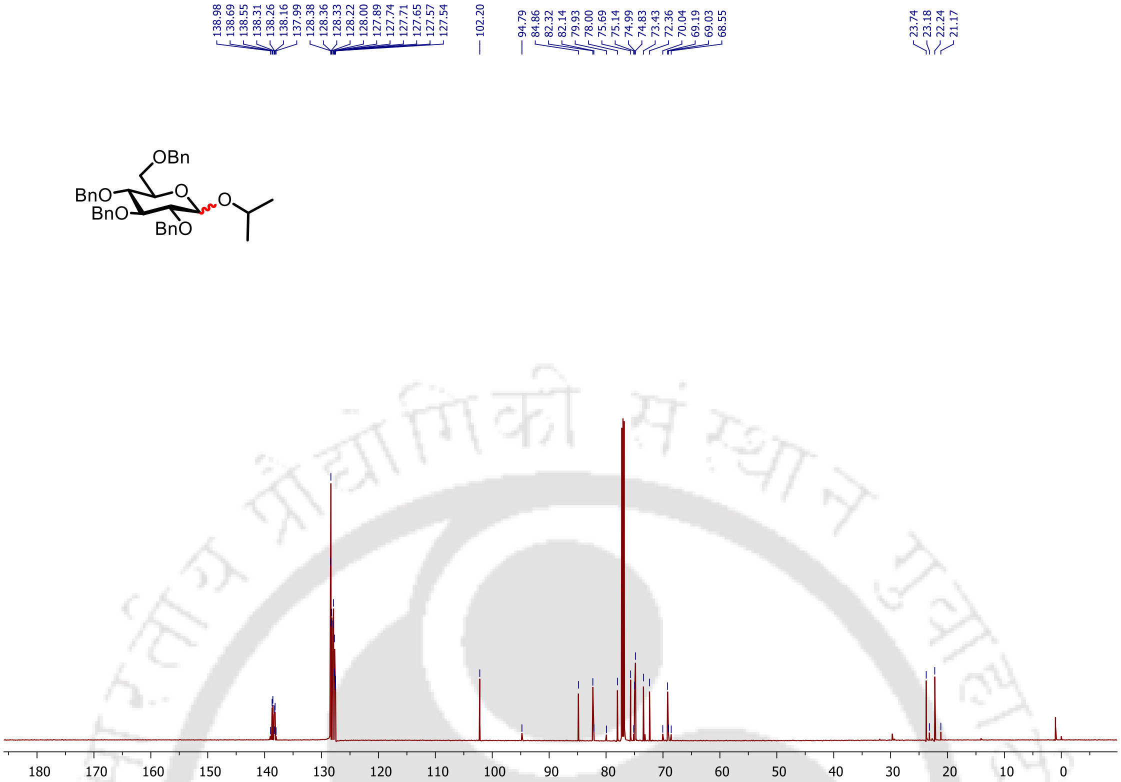

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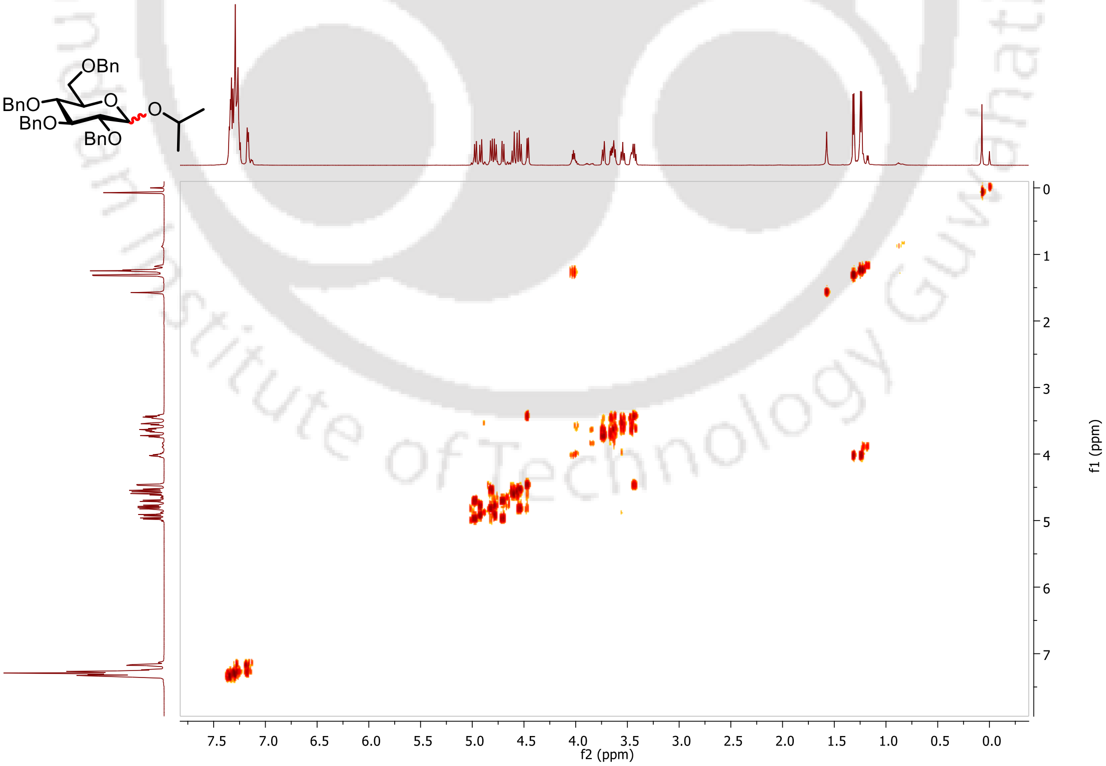

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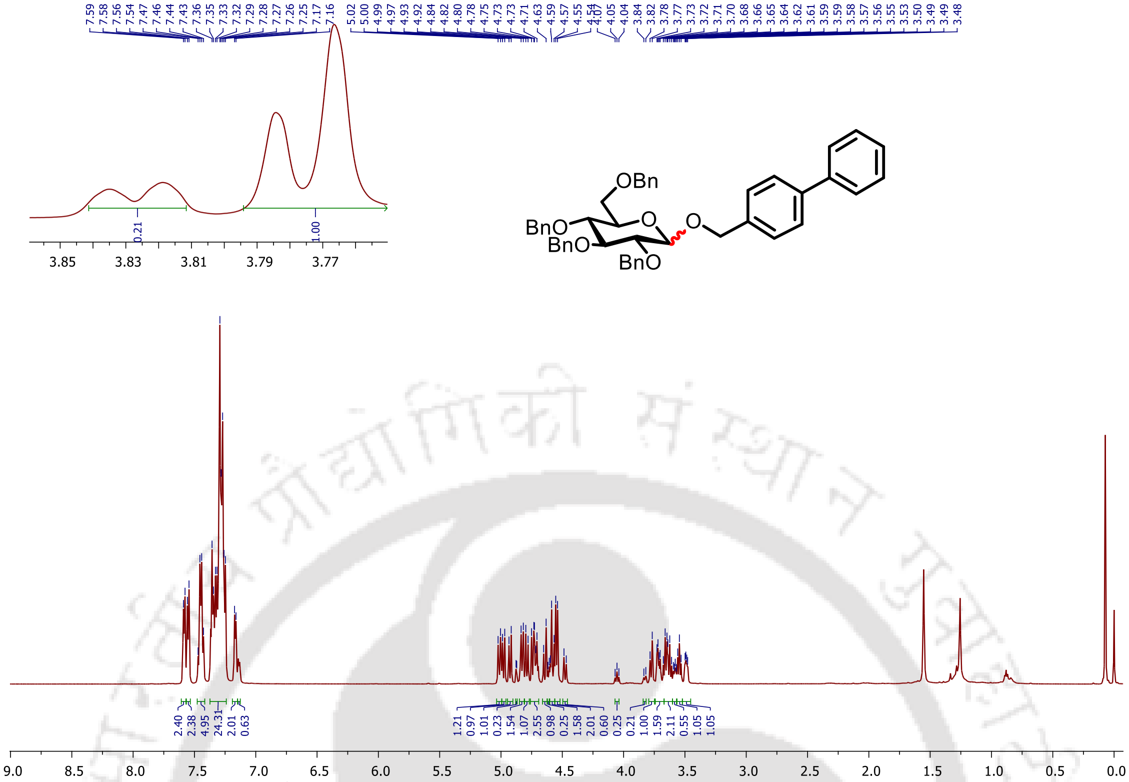

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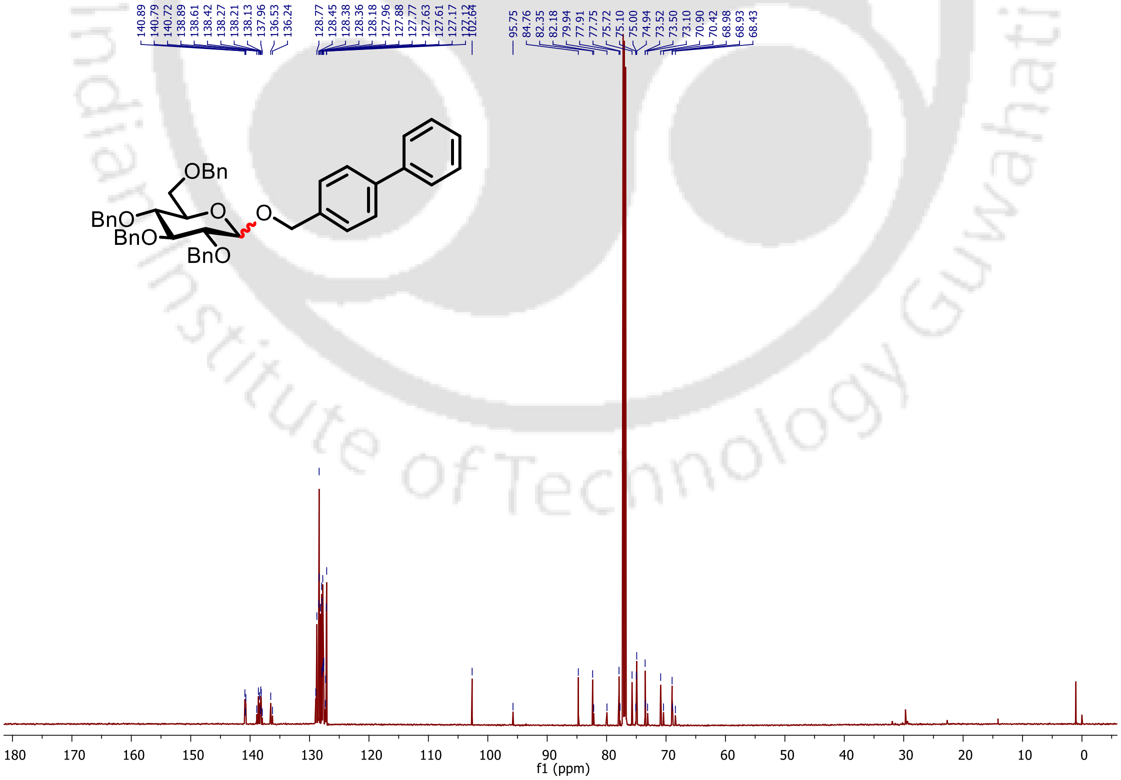

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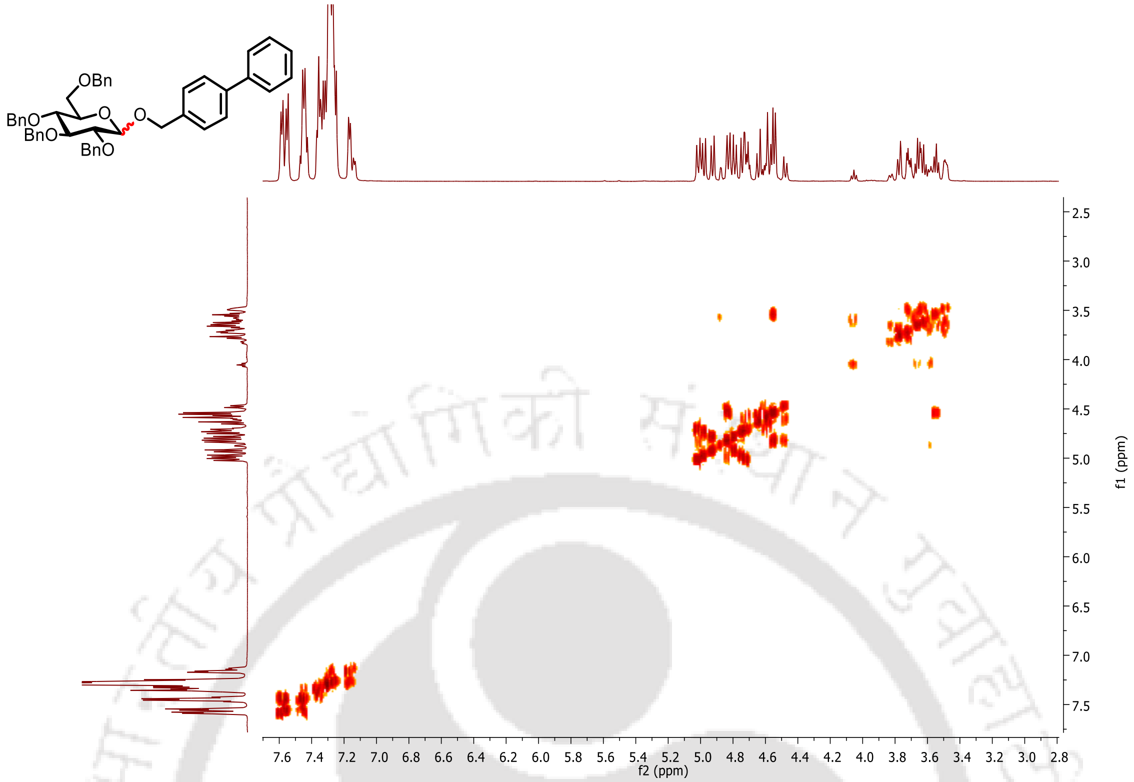

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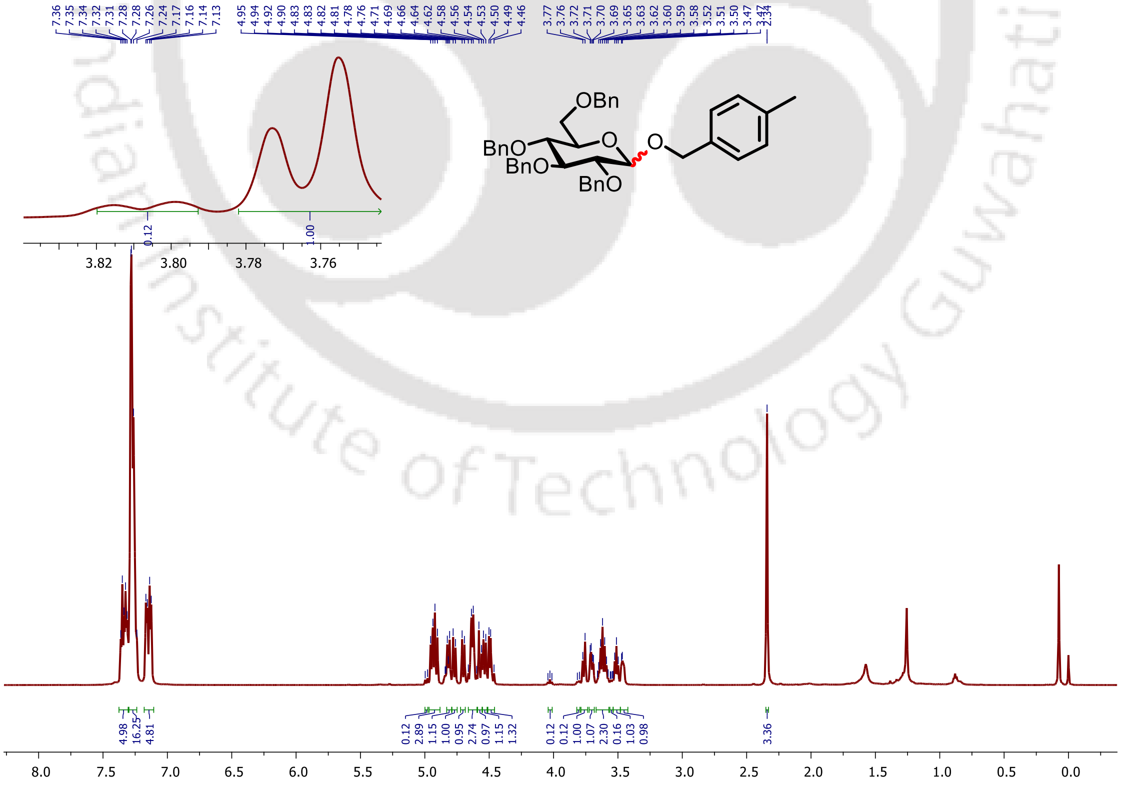
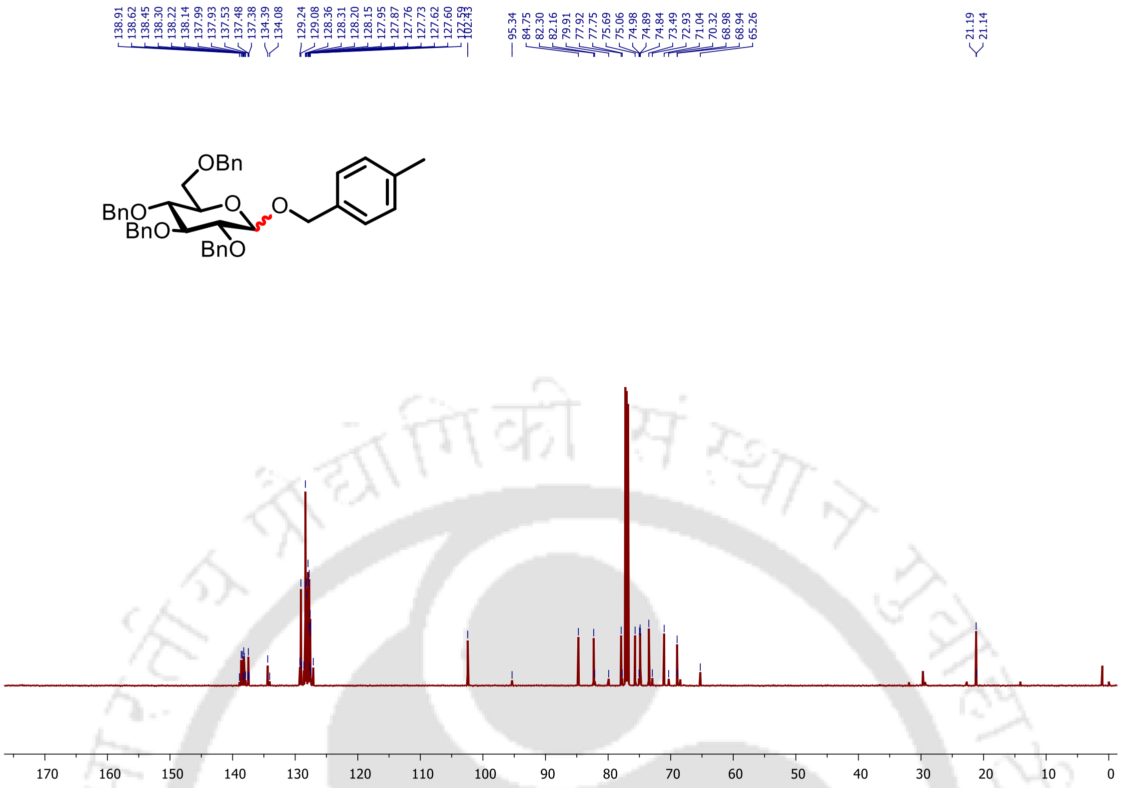
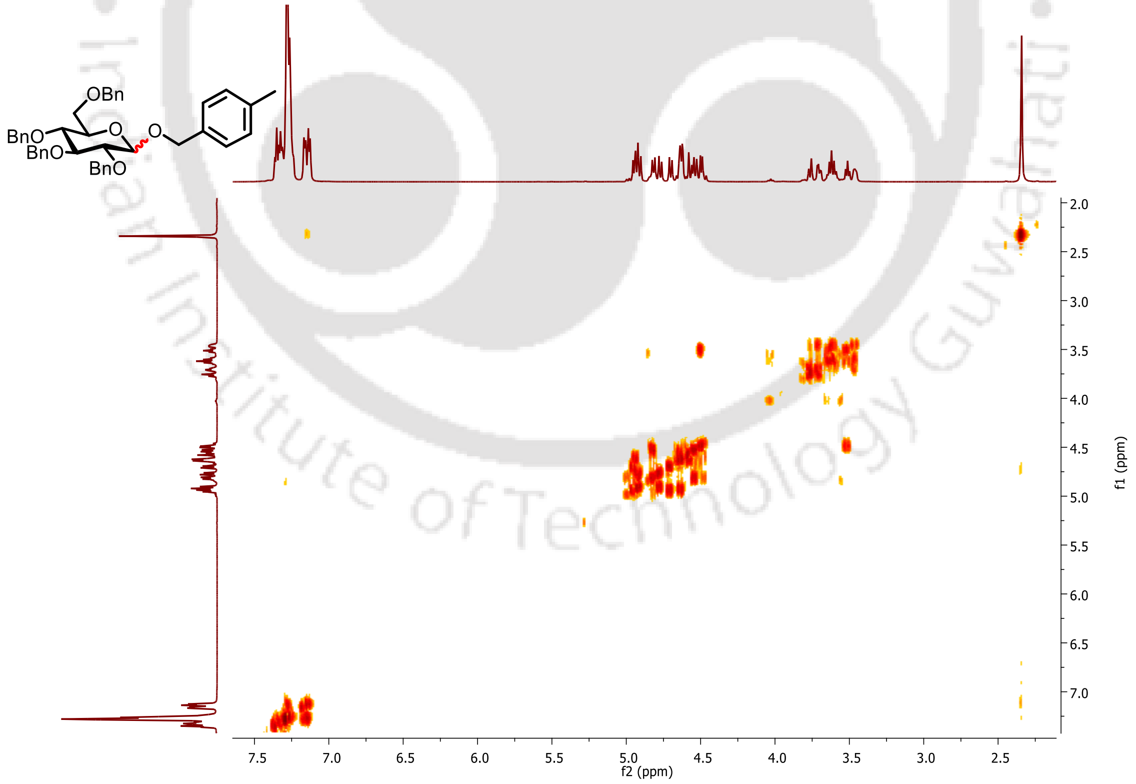


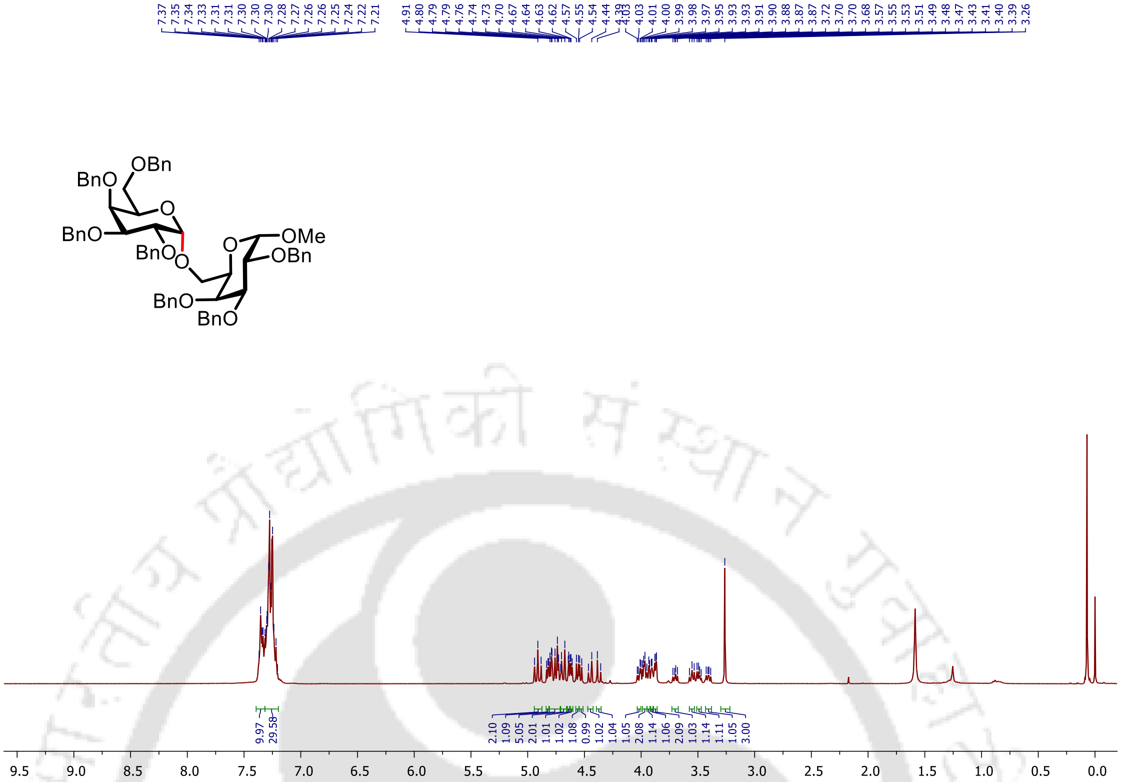
^{1}H NMR spectrum of **3t,**)600 MHz, $CDCl_3$(



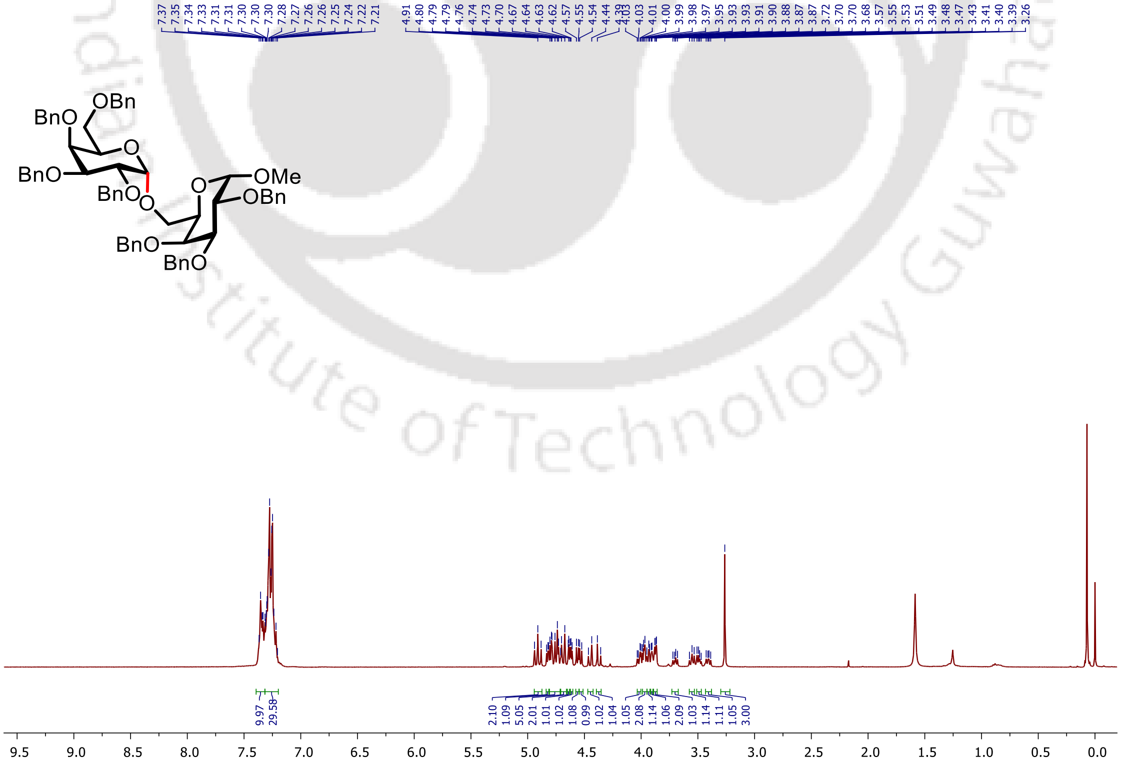
^{13}C NMR spectrum of **3t,**)151 MHz, CDCl$_3$(



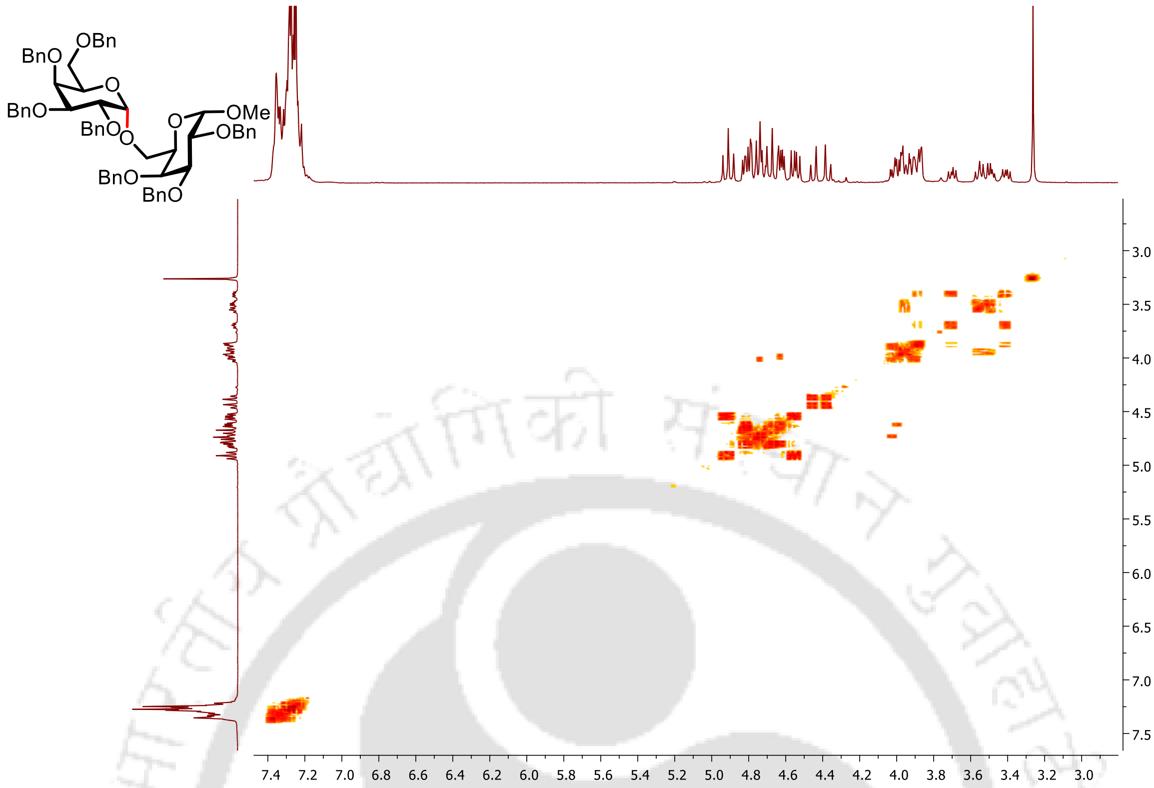
COSY NMR spectrum of **3t,**)600 MHz, CDCl$_3$(



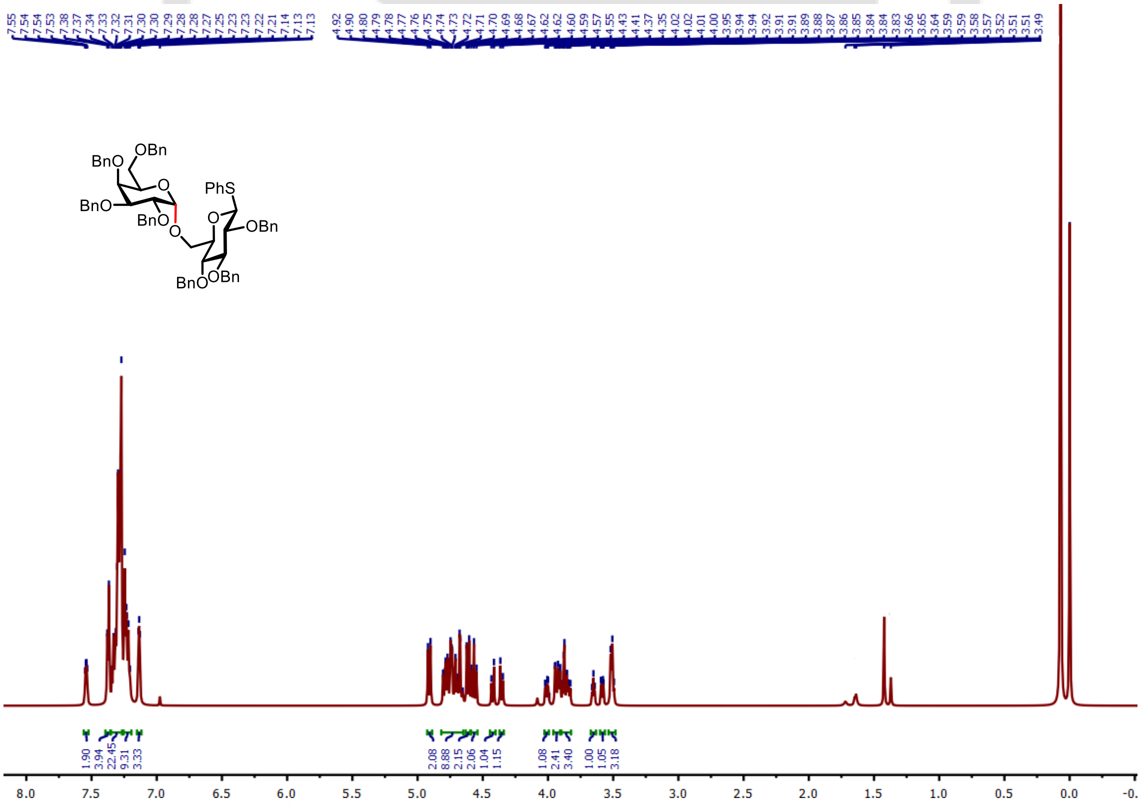
^{1}H NMR spectrum of **3u,**)500 MHz, CDCl$_3$(



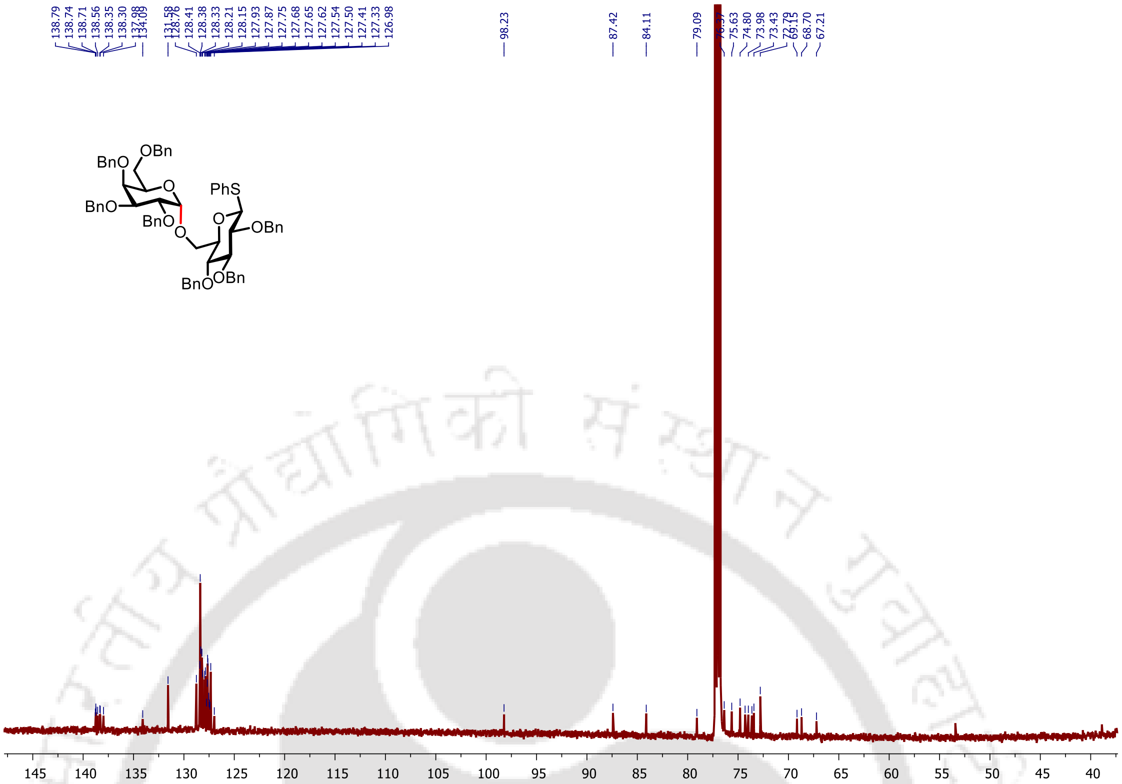
^{13}C NMR spectrum of **3u,**)101 MHz, CDCl$_3$(



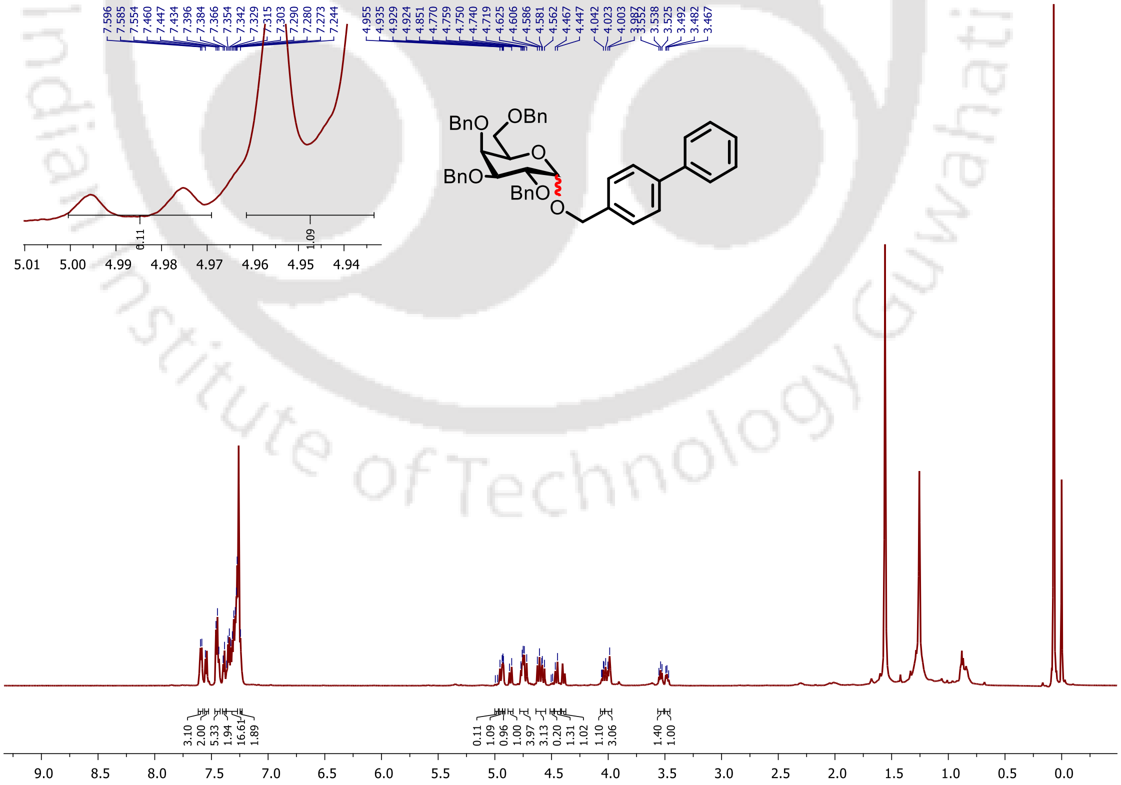
COSY NMR spectrum of **3u,**)500 MHz, CDCl$_3$(



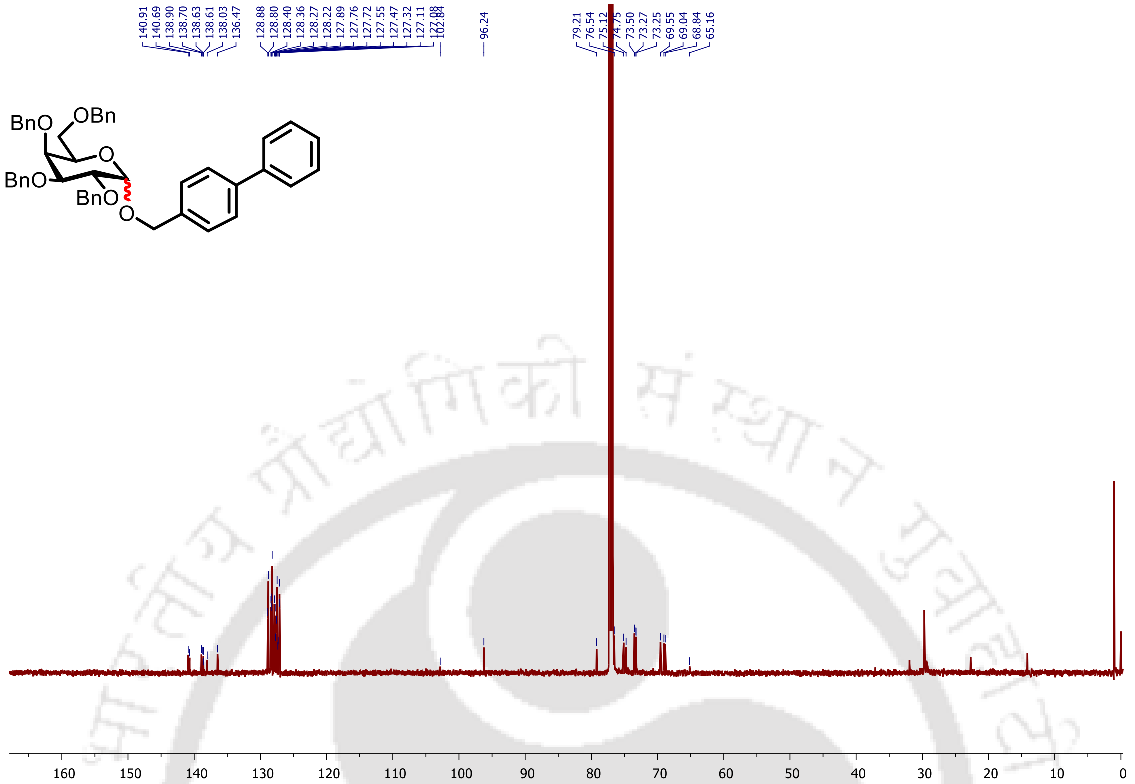
^{1}H NMR spectrum of **3v,**)600 MHz, CDCl$_3$(



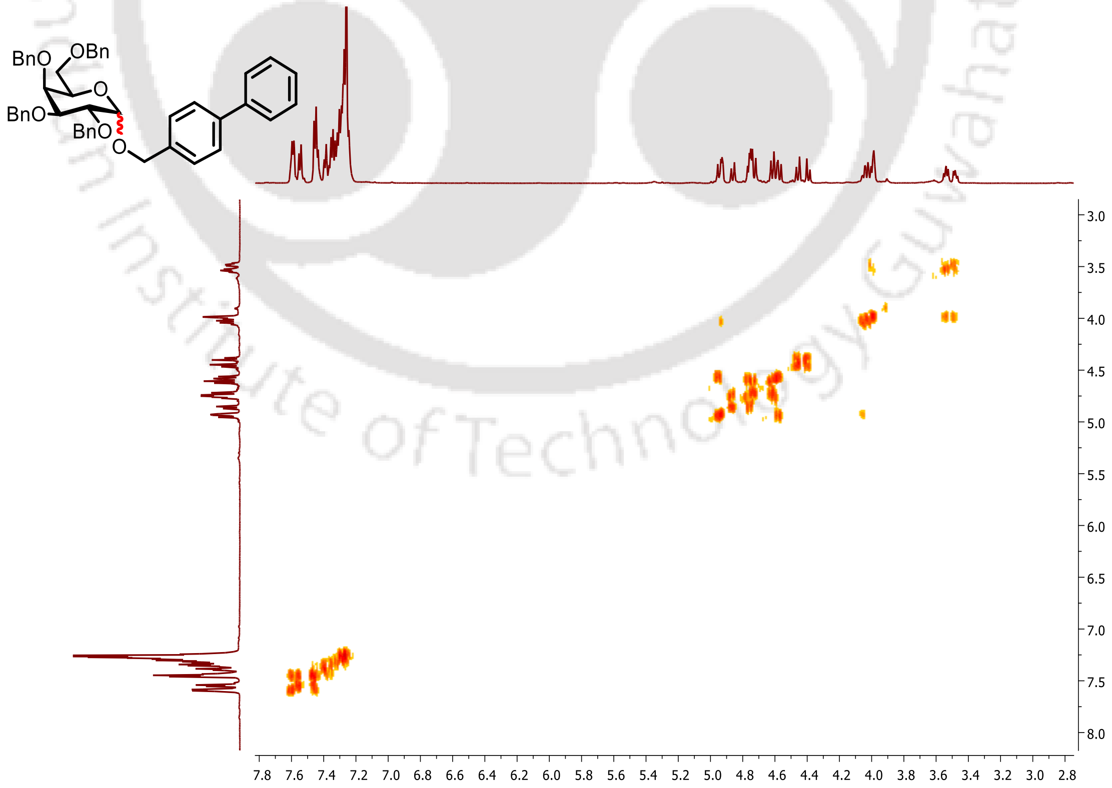
^{3}C NMR spectrum of **3v,**)151 MHz, CDCl$_3$(



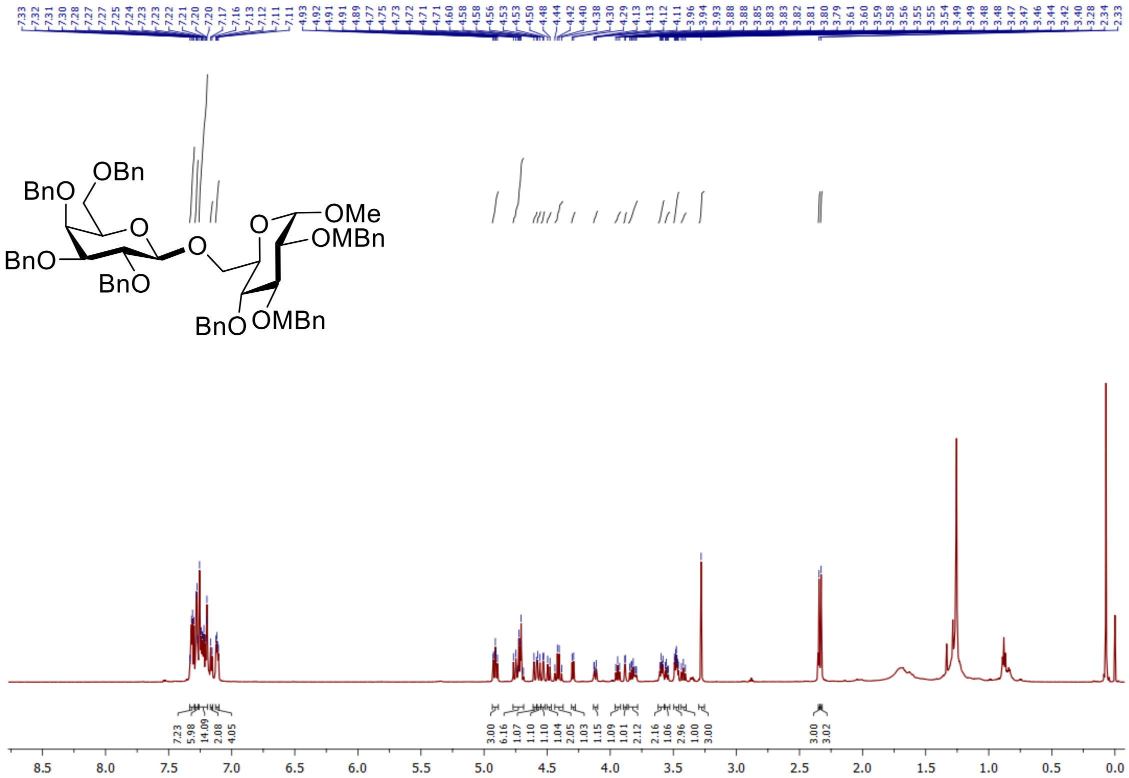
^{1}H NMR spectrum of **3w,**)600 MHz, CDCl$_3$(



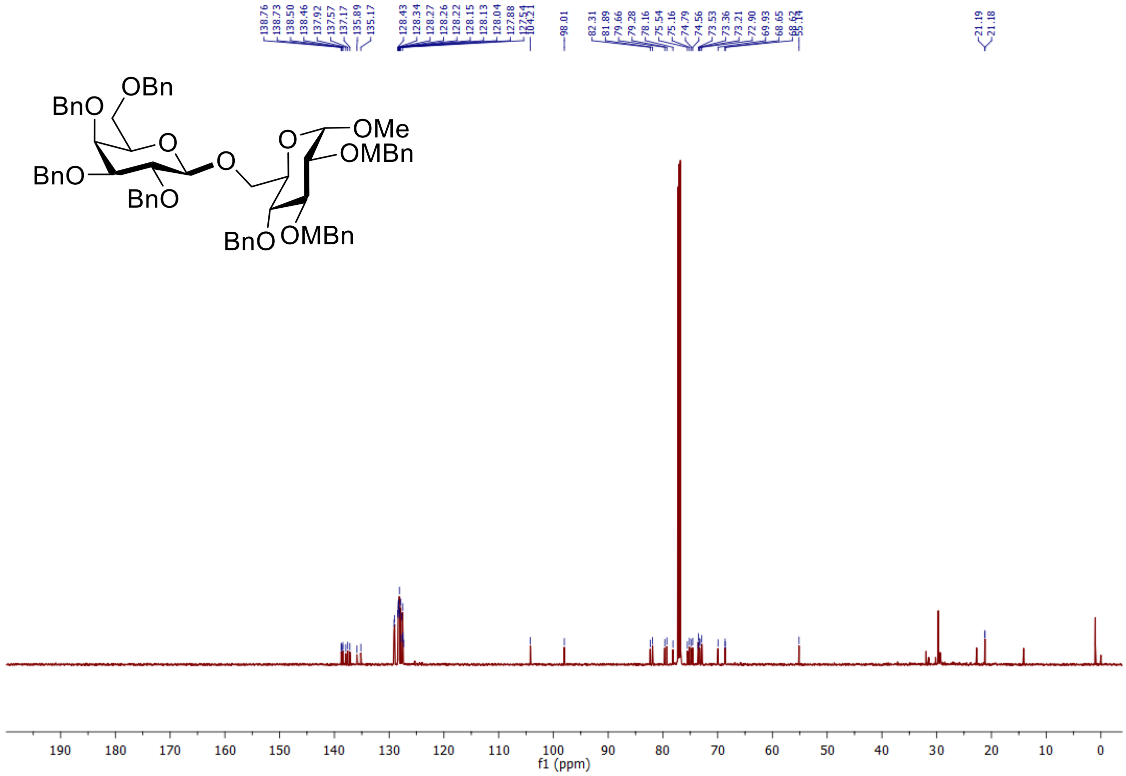
^{13}C NMR spectrum of **3w,**)151 MHz, CDCl$_3$(



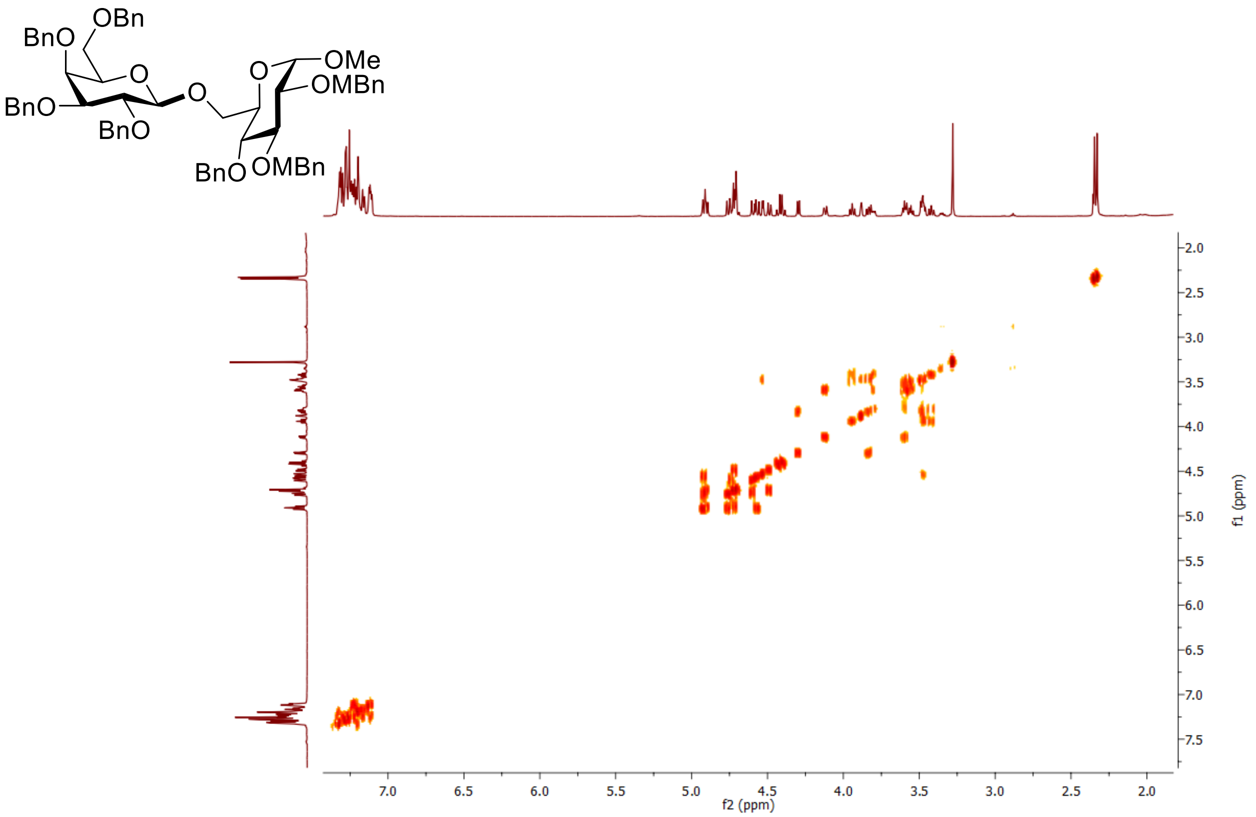
COSY NMR spectrum of **3w,**)600 MHz, CDCl$_3$(



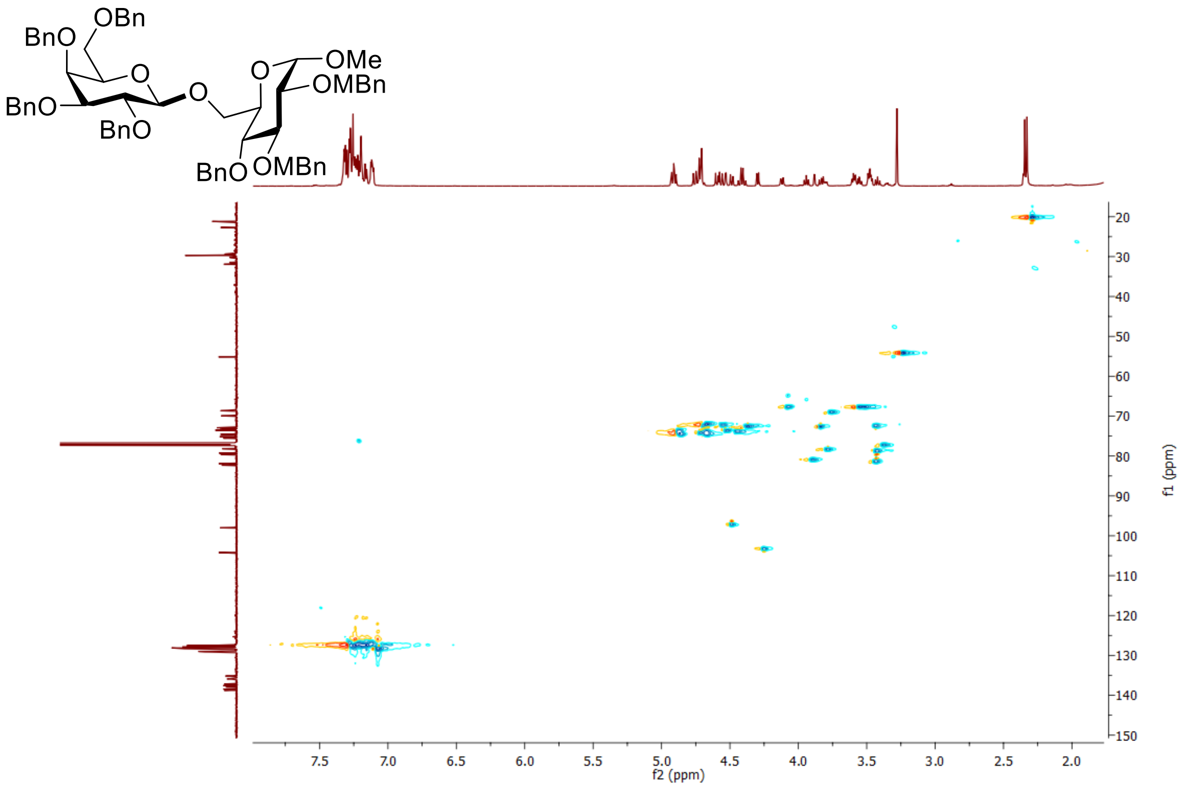
^{1}H NMR spectrum of **3x,**)600 MHz, CDCl$_3$(



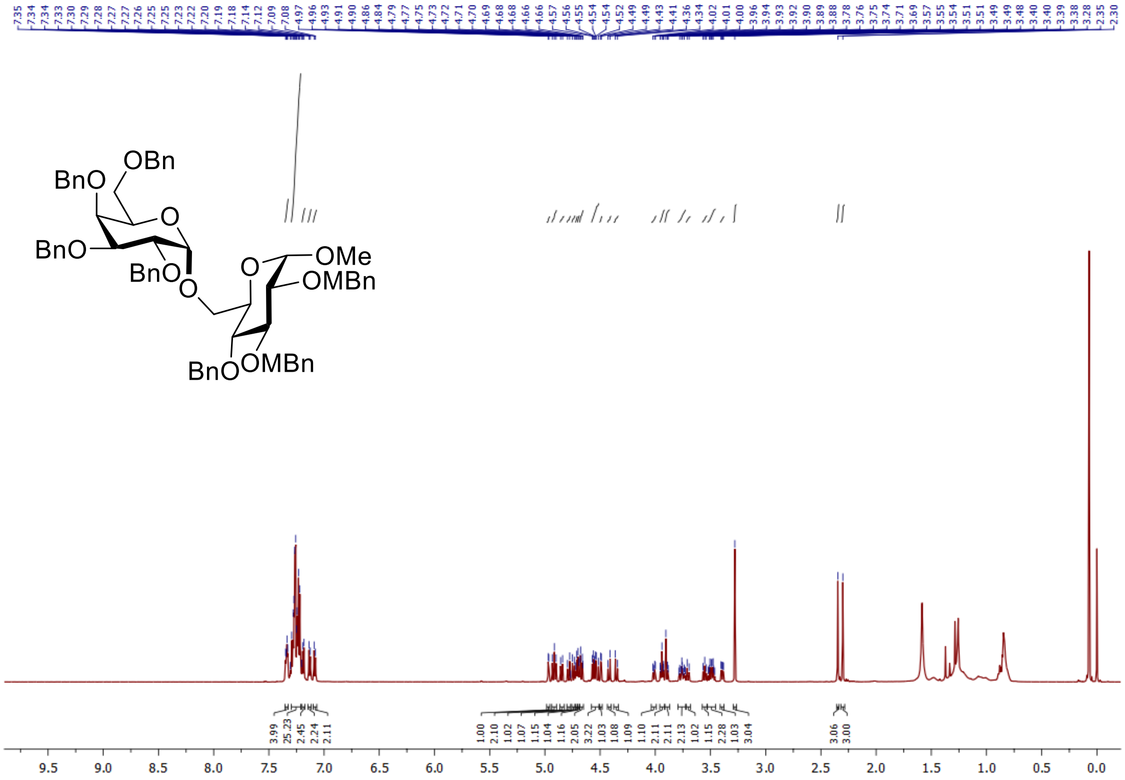
^{13}C NMR spectrum of **3x,**)151 MHz, CDCl$_3$(



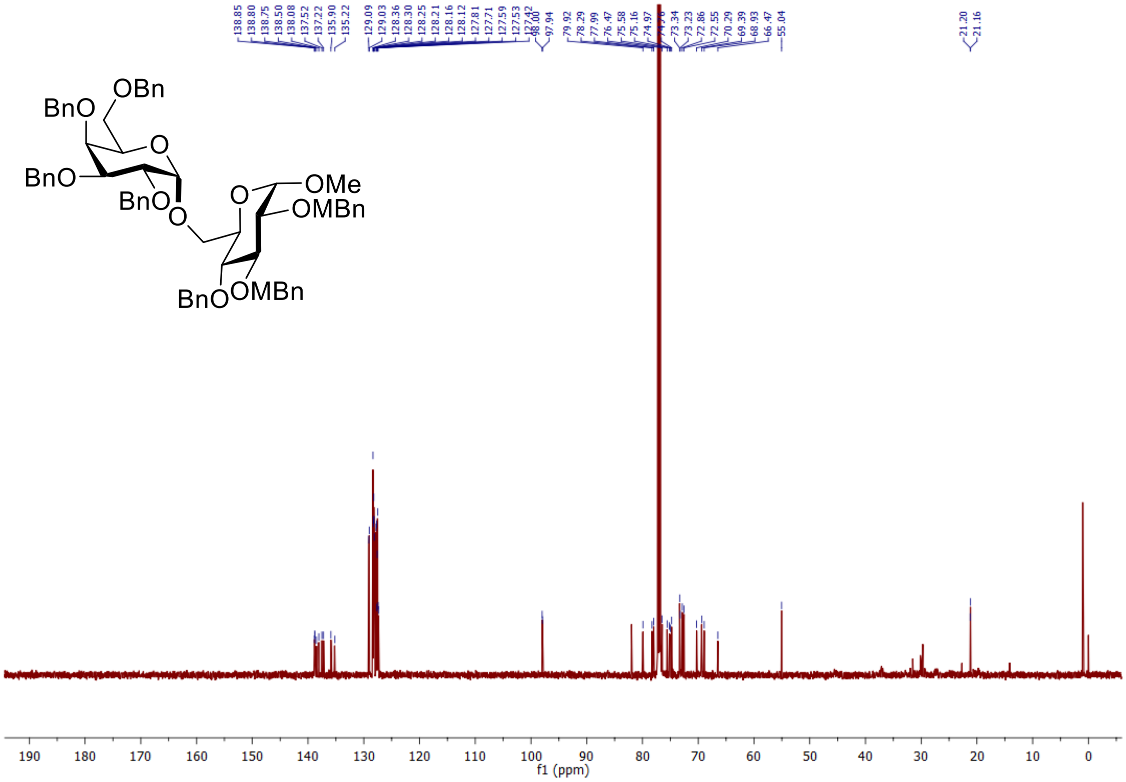
COSY NMR spectrum of **3x,**)600 MHz, CDCl$_3$(



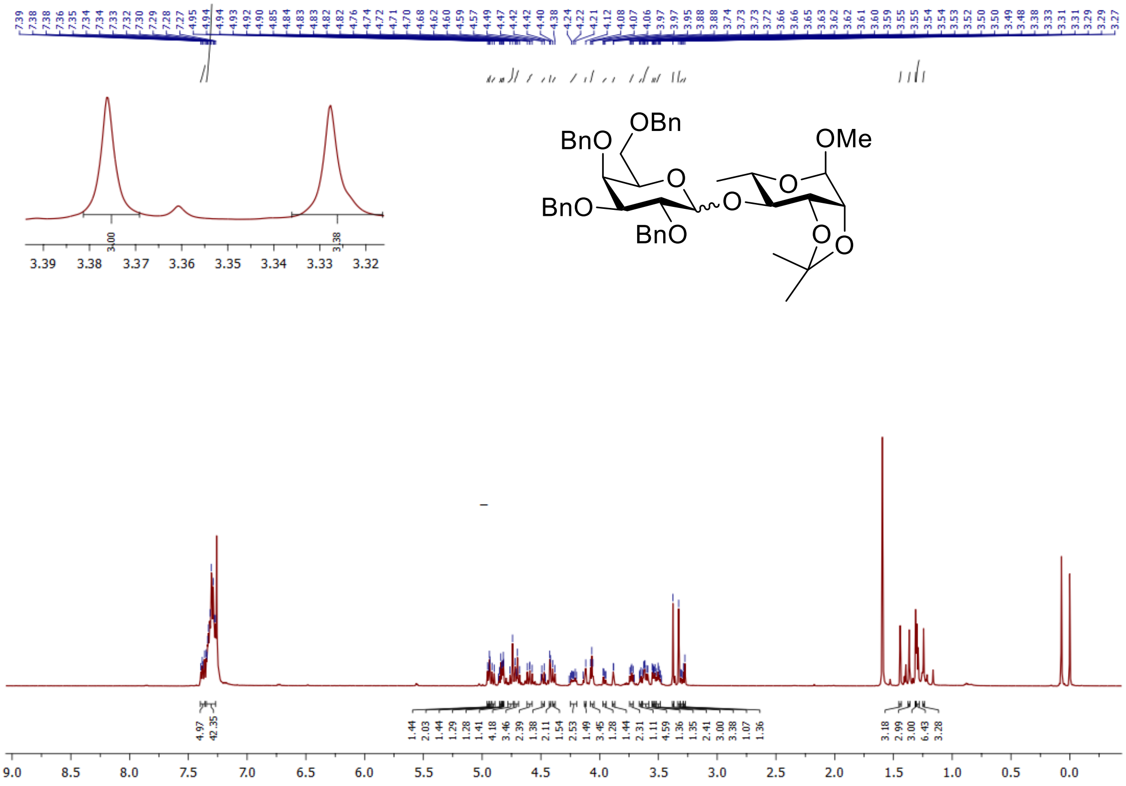
HSQC NMR spectrum of **3x,**)600 MHz, CDCl$_3$(



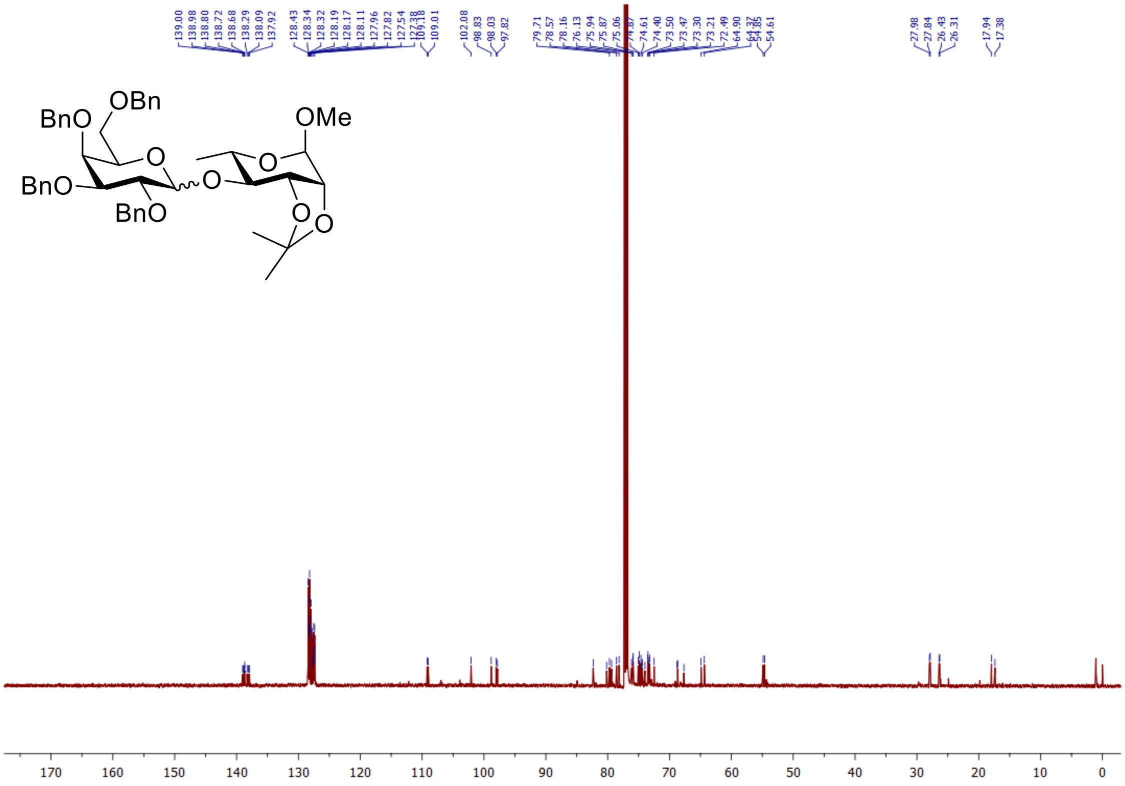
^{1}H NMR spectrum of **3y,**)600 MHz, CDCl$_3$(



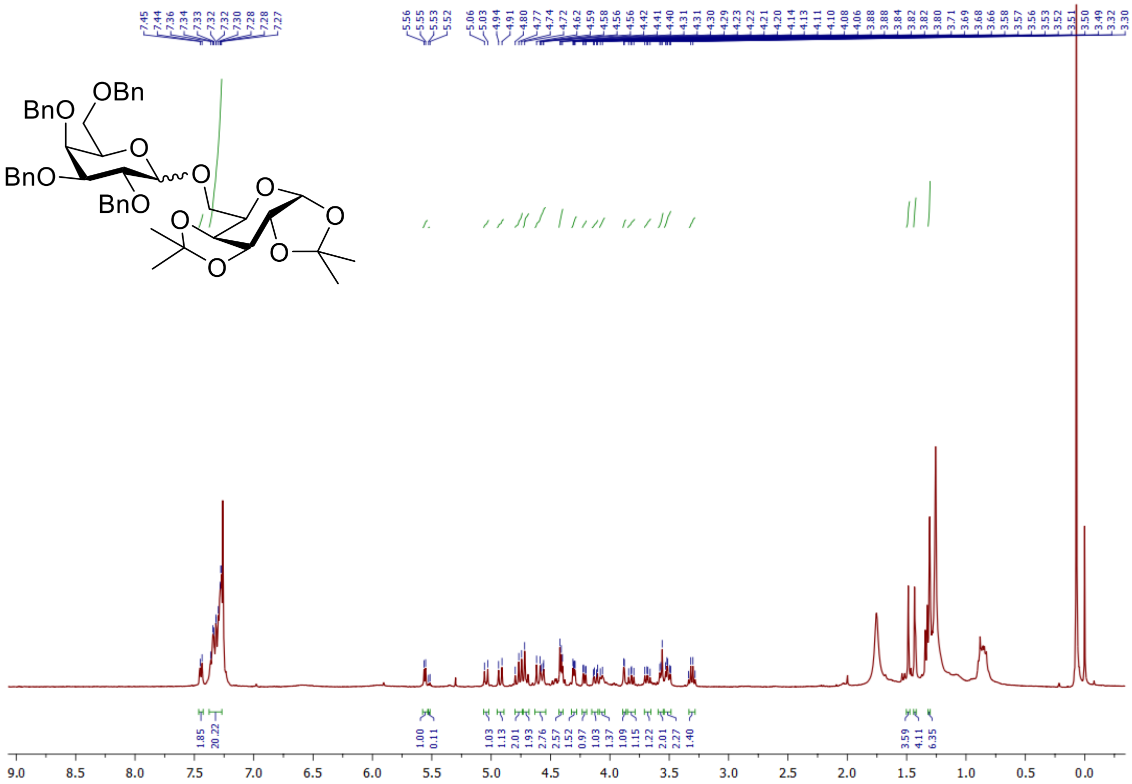
^{13}C NMR spectrum of **3x,**)151 MHz, CDCl$_3$(



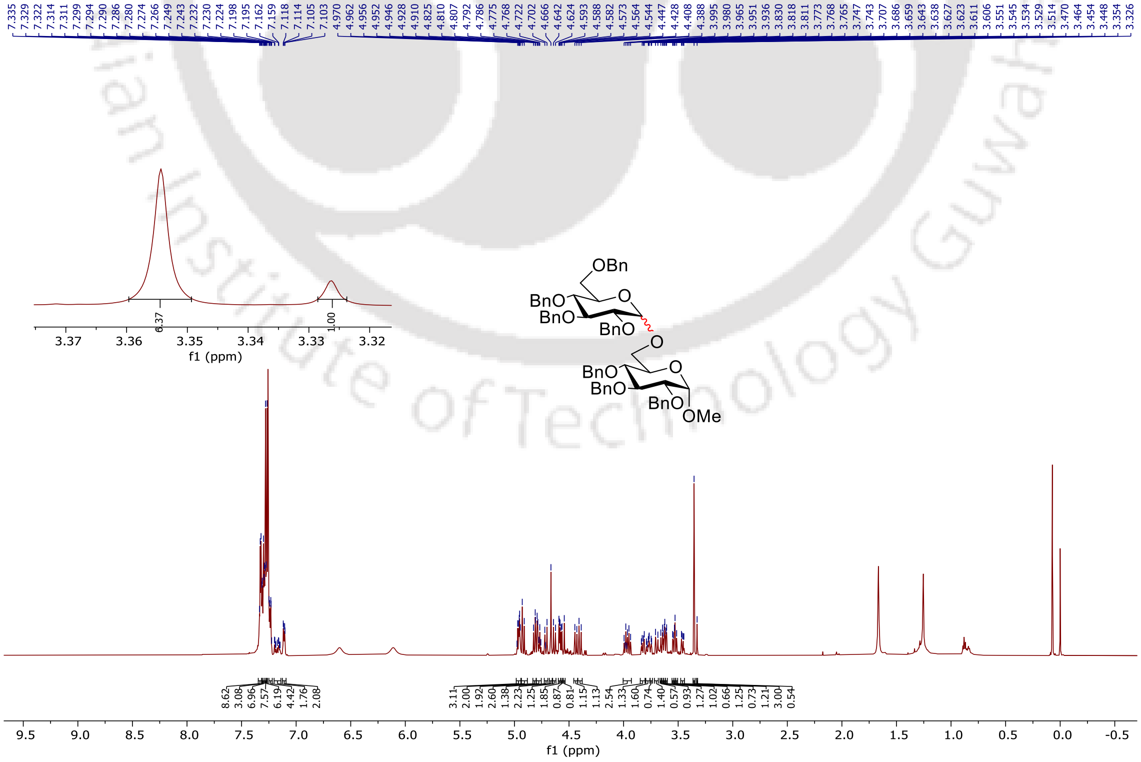
^{1}H NMR spectrum of **3z,**)600 MHz, CDCl$_3$(



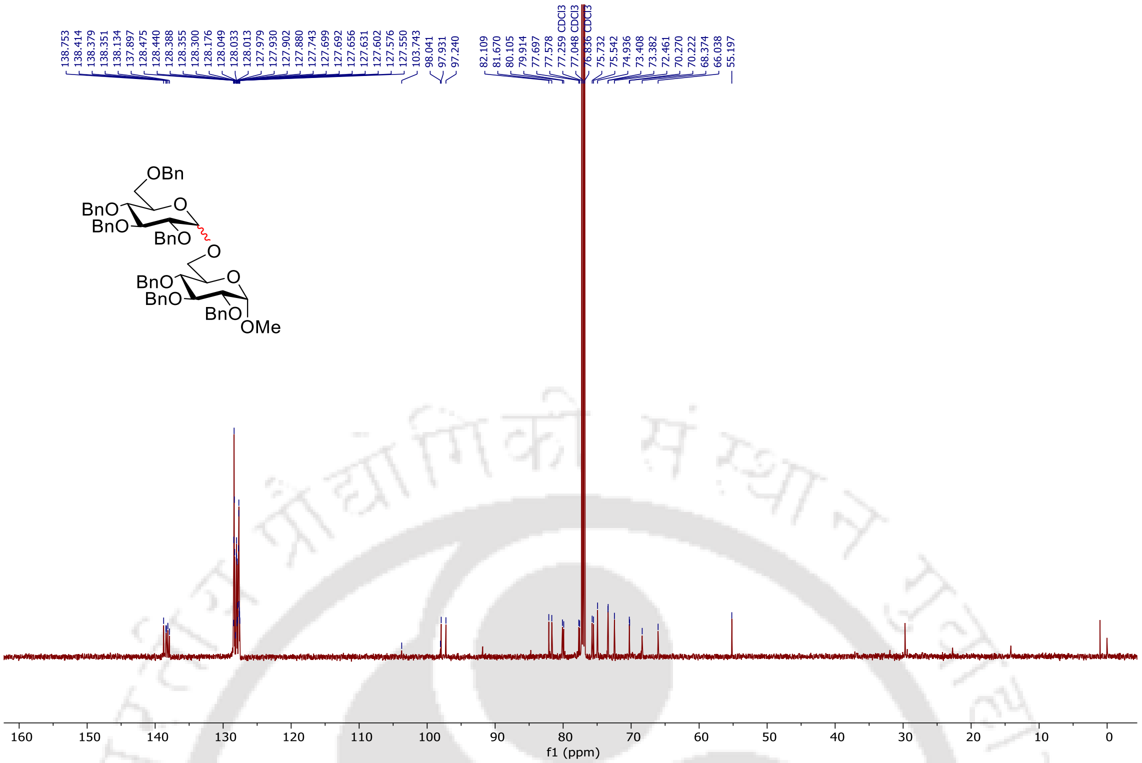
^{13}C NMR spectrum of **3z,**)151 MHz, CDCl$_3$(



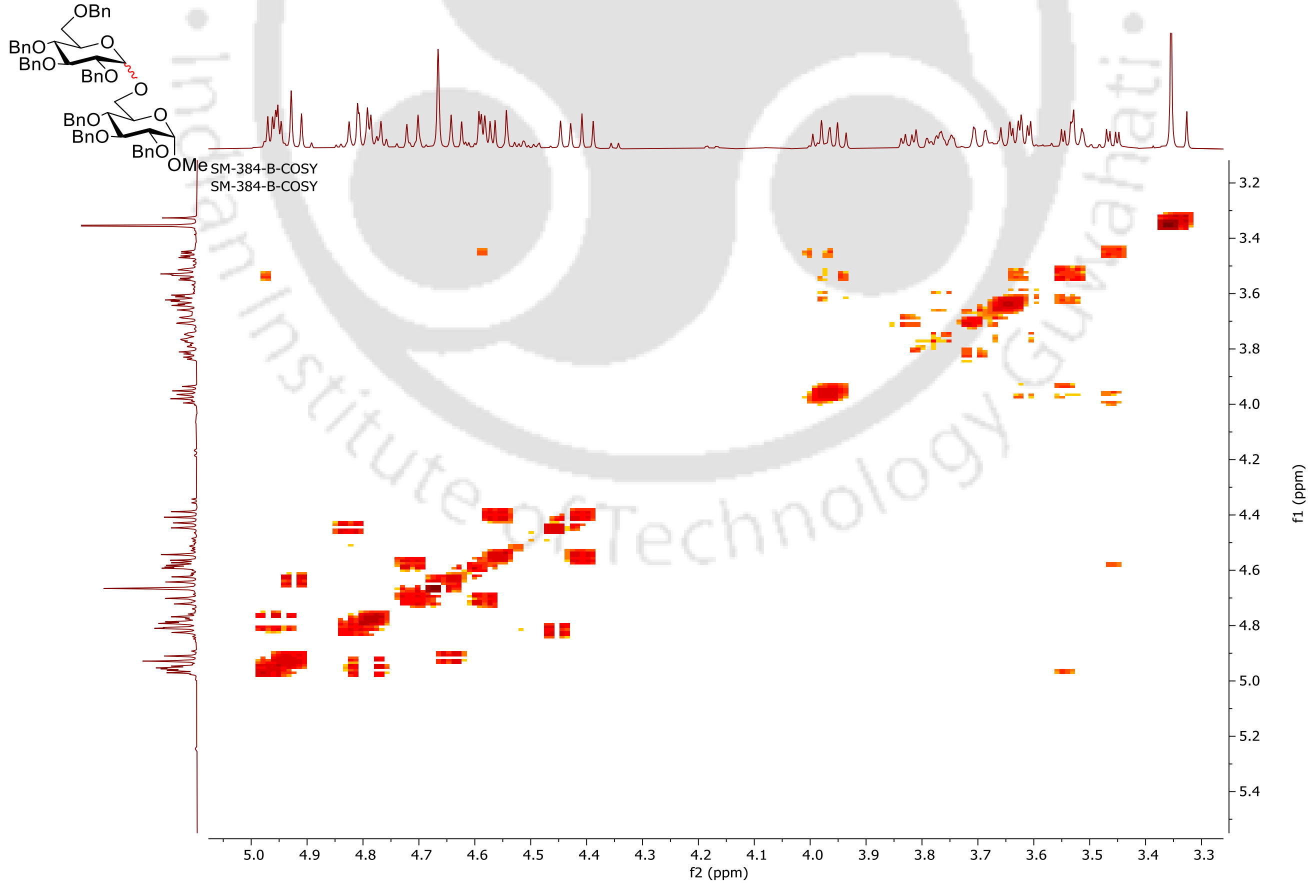
^{1}H NMR spectrum of **4a,**)400 MHz, CDCl$_3$(



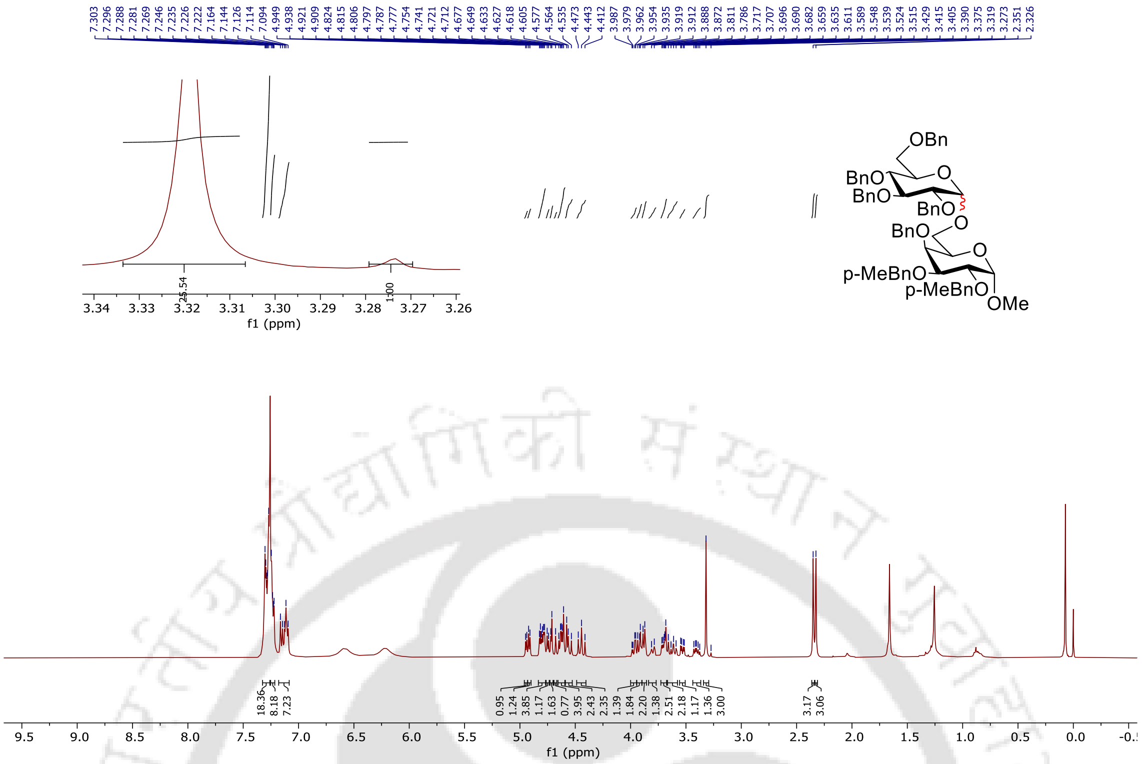
^{1}H NMR spectrum of **4b,**)600 MHz, CDCl$_3$(



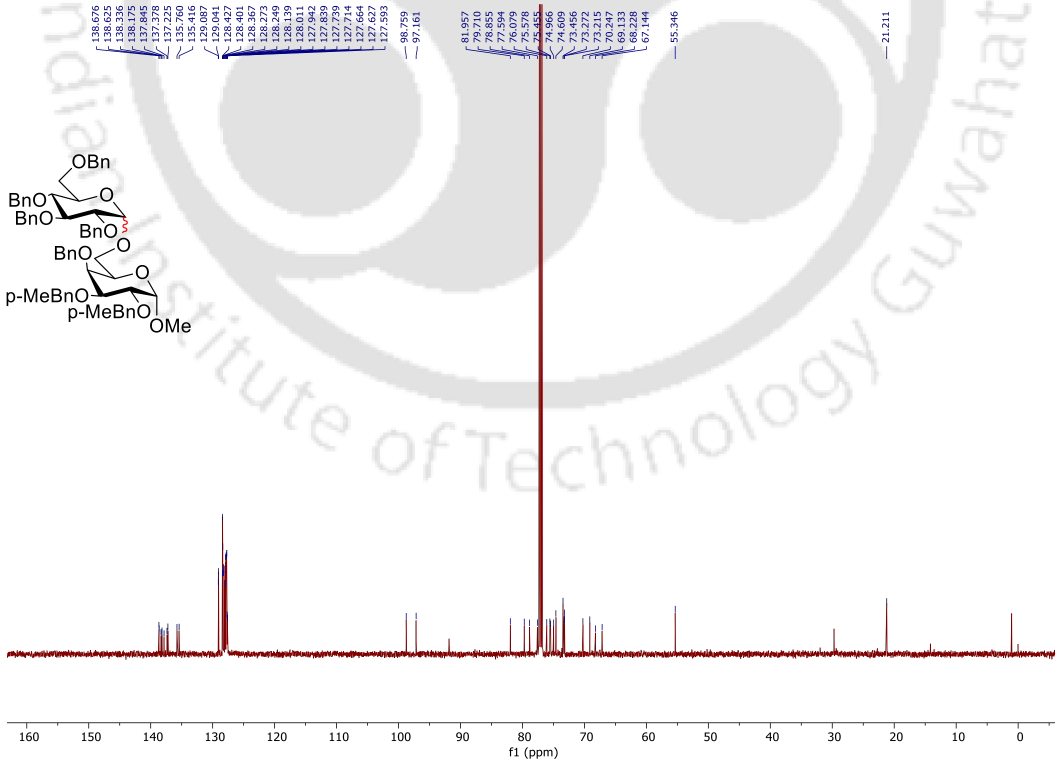
^{13}C{1H} NMR spectrum of **4b,**)151 MHz, CDCl$_3$(



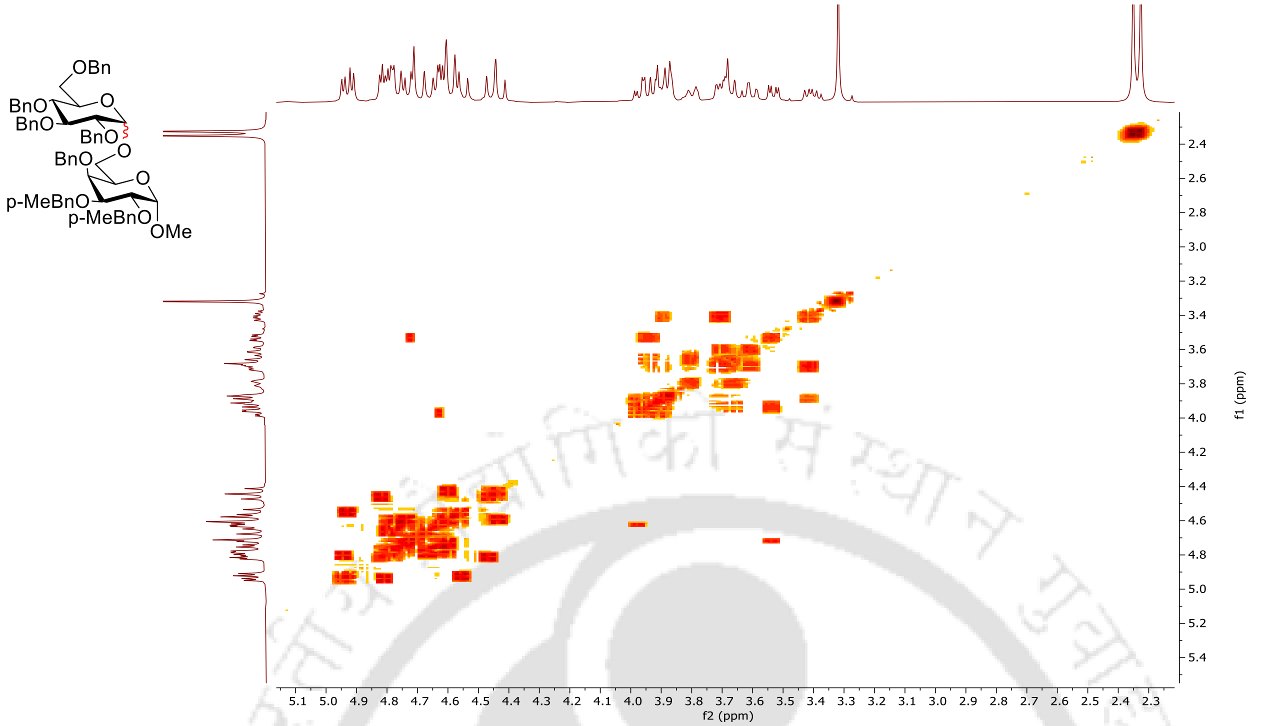
COSY NMR spectrum of **4b,**)400 MHz, CDCl$_3$(



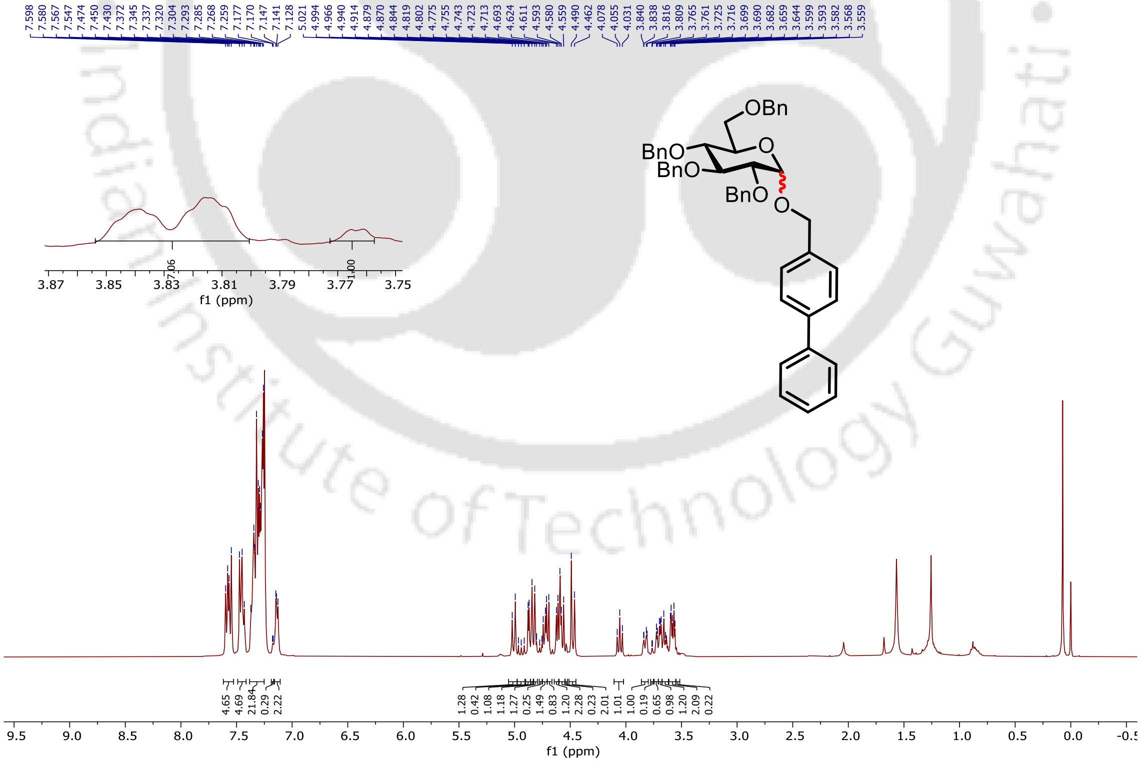
^{1}H NMR spectrum of **4c,**)400 MHz, CDCl$_3$(



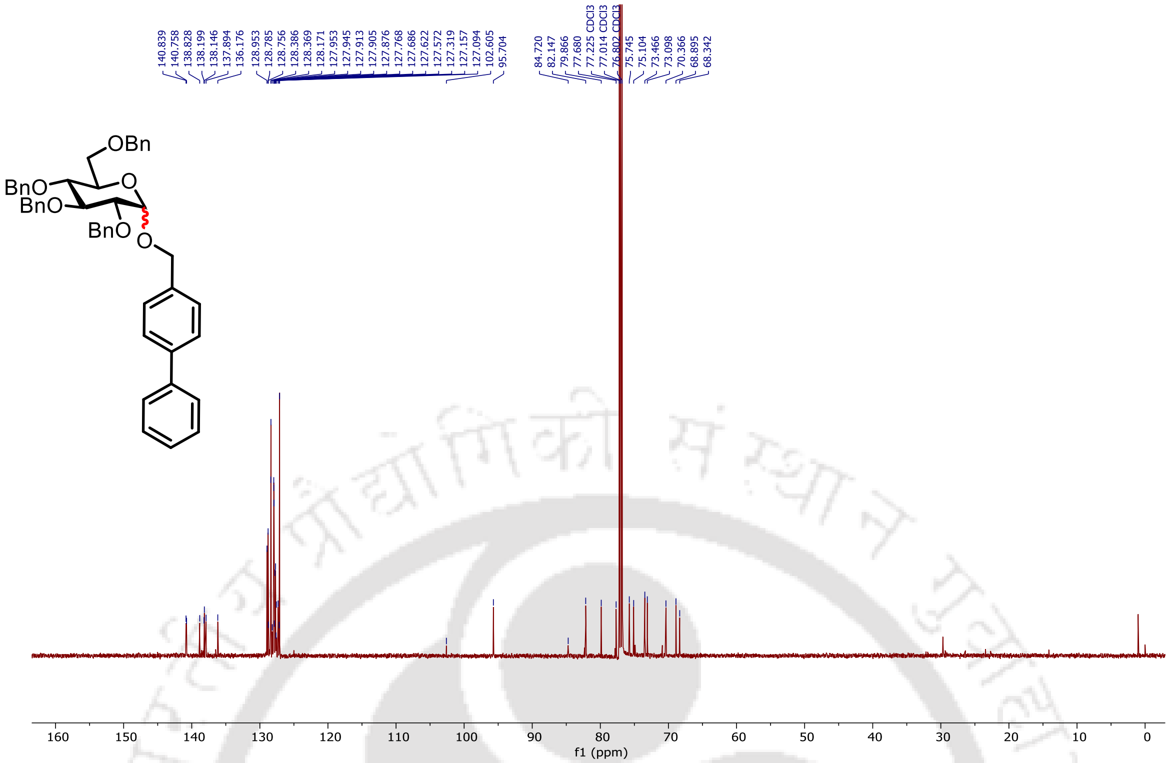
^{13}C{1H} NMR spectrum of **4c,**)151 MHz, CDCl$_3$(



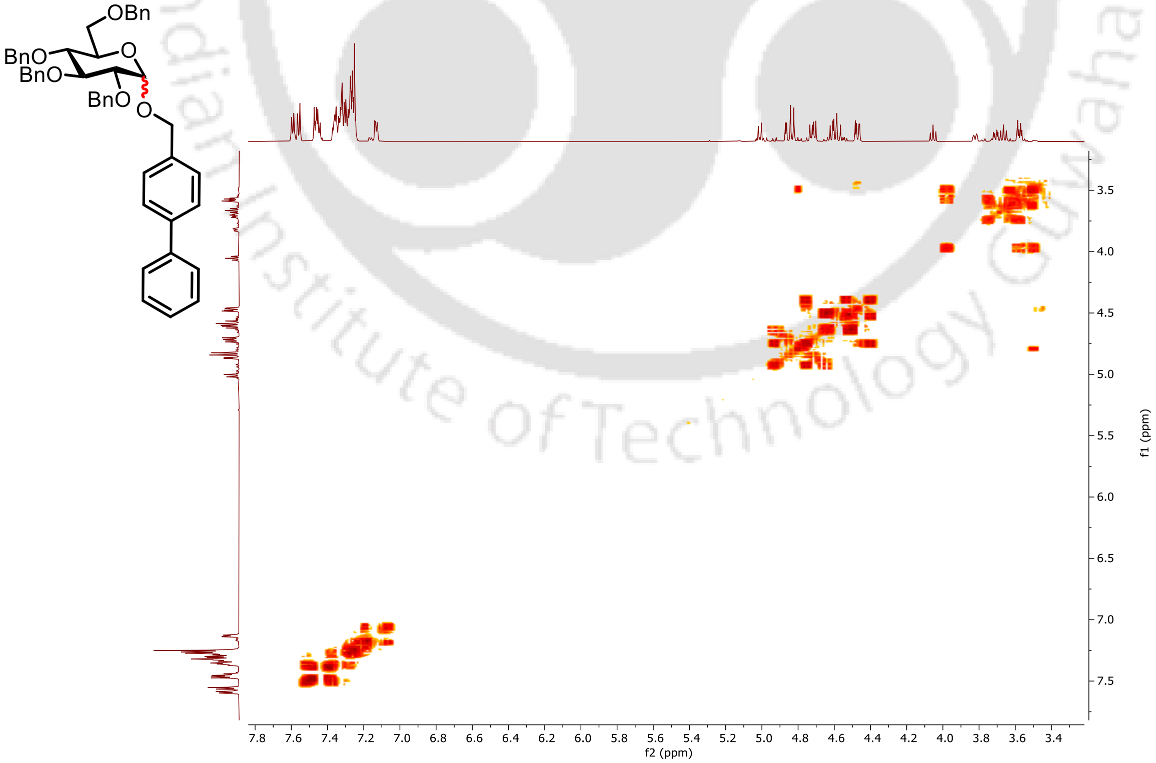
COSY NMR spectrum of **4c,**)400 MHz, CDCl$_3$(



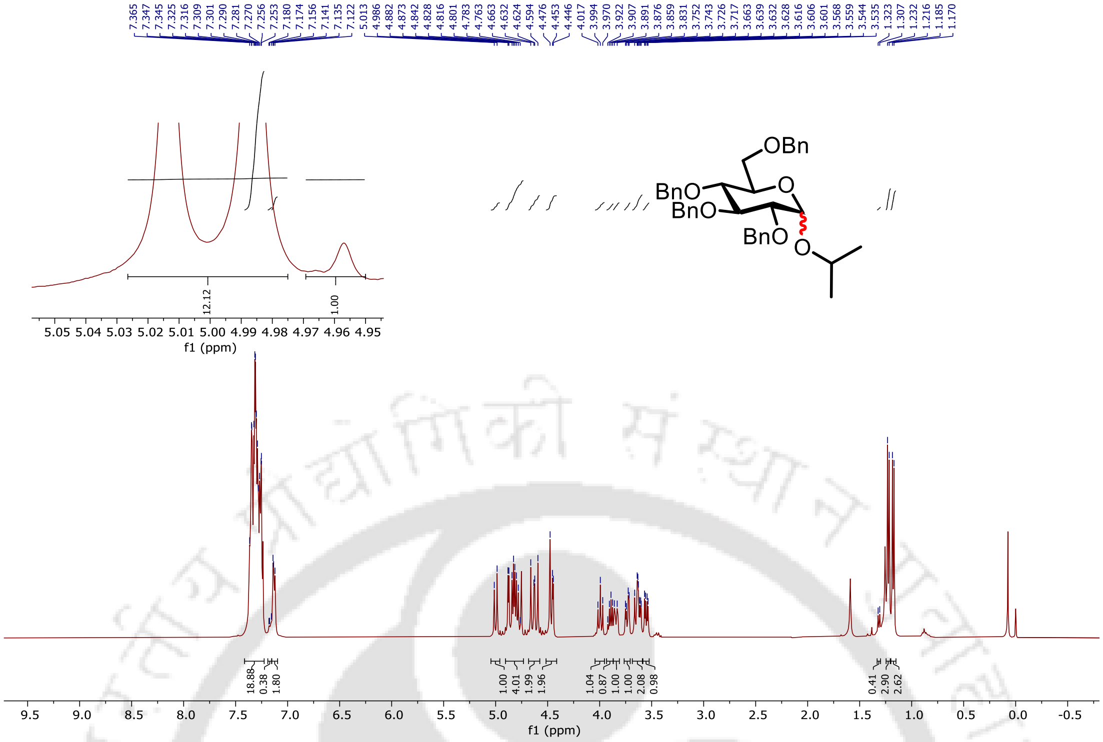
^{1}H NMR spectrum of **4d,**)400 MHz, CDCl$_3$(



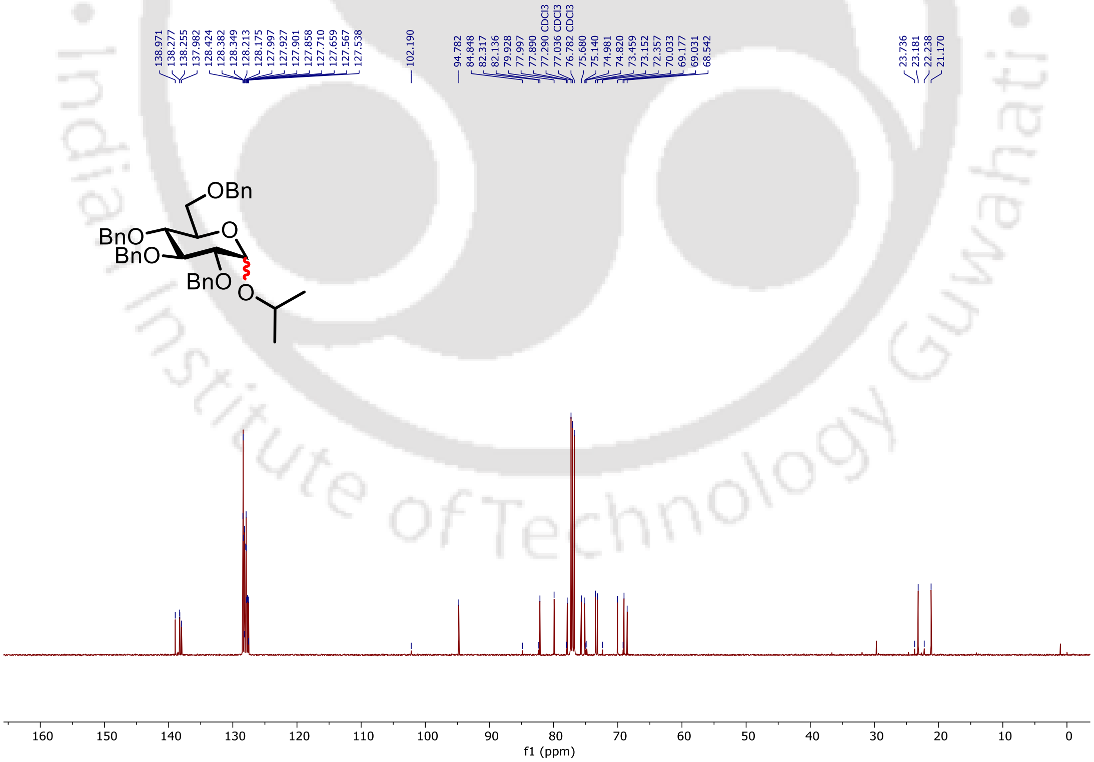
^{13}C{1H} NMR spectrum of **4d,**)151 MHz, CDCl$_3$(



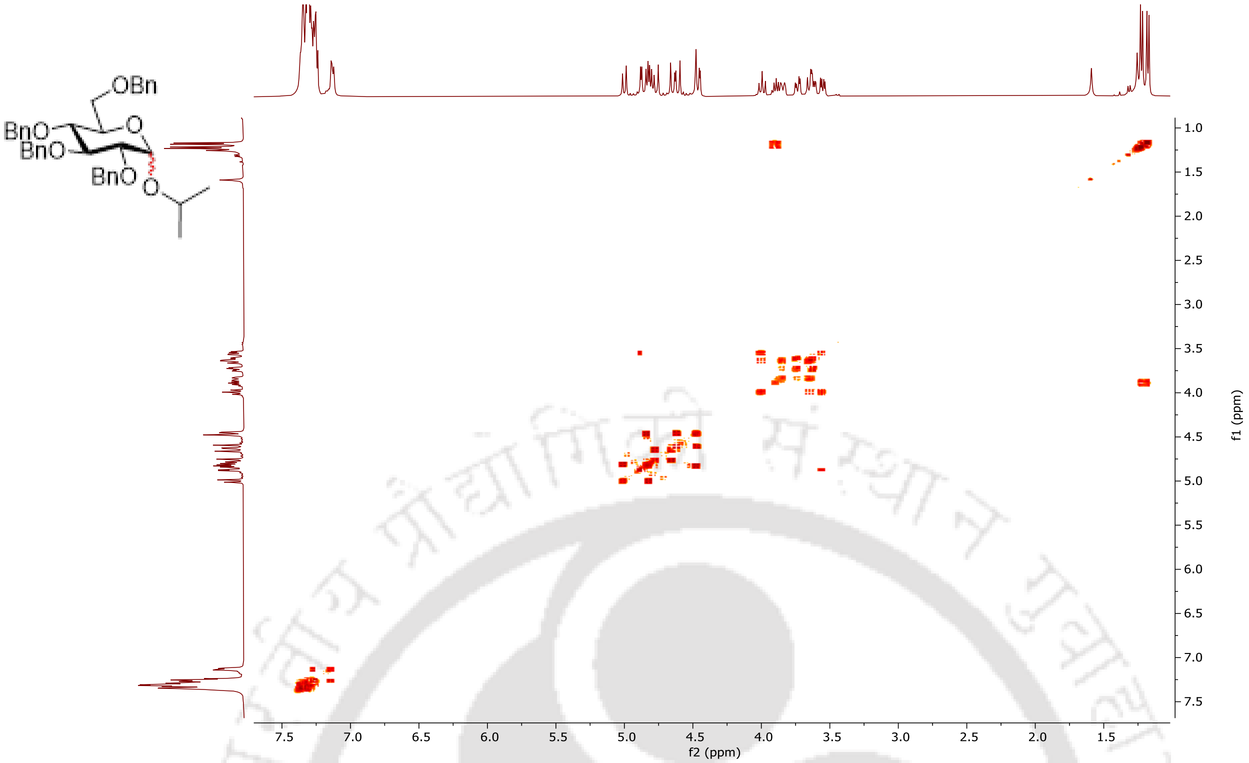
COSY NMR spectrum of **4d,**)400 MHz, CDCl$_3$(



^{1}H NMR spectrum of **4e,**)400 MHz, $CDCl_3$(



^{13}C{1H} NMR spectrum of **4d,**)126 MHz, $CDCl_3$(



COSY NMR spectrum of **4e,**)400 MHz, CDCl$_3$(

3.13 Crystallographic data of 5c

The crystal was grown by dissolving the catalyst **5c** in DCM by the slow evaporation method.

Bond precision:	C-C = 0.0062 A		Wavelength=0.71073
Cell:	a=20.036)5(	b=20.036)5(	c=9.675)3(
	alpha=90	beta=90	gamma=90
Temperature:	293 K		

	Calculated	Reported
Volume	3884)2(	3884)2(
Space group	P 42/n	P 42/n
Hall group	-P 4bc	-P 4bc
Moiety formula	C17 H30 N, B F4	?
Sum formula	C17 H30 B F4 N	C17 H30 B F4 N
Mr	335.23	335.23
Dx,g cm-3	1.147	1.147
Z	8	8
Mu)mm-1(	0.092	0.092
F000	1440.0	1440.0
F000'	1440.86	
h,k,lmax	23,23,11	23,23,11
Nref	3223	3225
Tmin,Tmax		
Tmin'		

Correction method= Not given	
Data completeness= 1.001	Theta)max(= 24.495
R)reflections(= 0.0922) 1678(	wR2)reflections(= 0.2742) 3225(
S = 1.478	Npar= 217

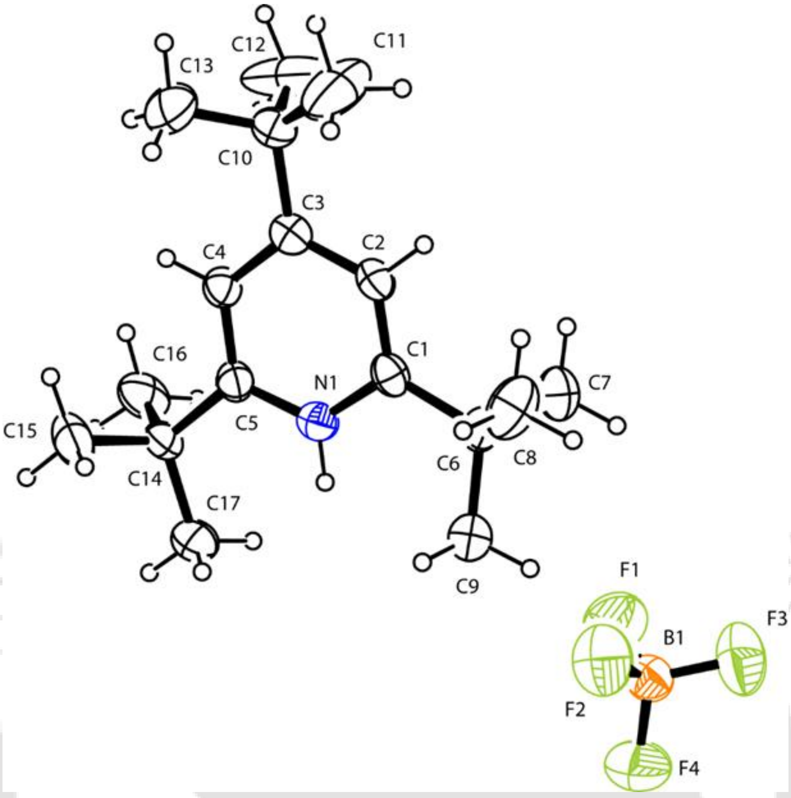


Fig. 3.13 Ortep view of **5c**. The thermal ellipsoid contour probability level is 35%

3.14 Computational studies

All calculations were performed using the Gaussian-16 program package[1]. Full geometry optimizations were carried out using Kohn-Sham hybrid-DFT B3LYP[2] level of theory and the 6-31g)d(Pople basis set[3]. The optimised stationary points were then characterized by frequency calculations at the same method and basis set to confirm that they reside at minima)no imaginary frequency(on the potential energy surface. To take into account the use of solvent in the experimental setup, the Polarizable Continuum Model)PCM(was used for the calculations. Free energies were calculated by using frequency calculations at room temperature.

Table S1: Free Energies)G(and Total Energies)E(of all the optimized structures given in Hartree along with the number of imaginary frequencies[a]

Compound	Free energy (G)	Total energy (E)	No of imaginary frequency
I-H_2O	-1023.362835	-1023.645016	0
II-H_2O	-1023.356549	-1023.6427107	0
I-DCM	-1023.358494	-1023.6406109	0
II-DCM	-1023.352609	-1023.6387438	0
IV-H_2O	-1530.698671	-1531.2443787	0
IV-DCM	-1530.698635	-1531.2426962	0

Table S2: The Cartesian coordinates)xyz(for all optimized structures are presented

I-H2O

C	-1.18415200	-0.97813600	-0.00005700
C	-1.23421400	0.41253000	-0.00000400
C	0.00150300	1.07793700	0.00004400
C	1.23544400	0.40924800	0.00001400
C	1.18169200	-0.98129300	-0.00005700
H	-0.00354000	-2.67718400	-0.00012100
H	-2.05563600	-1.61790000	-0.00009600
H	0.00292600	2.16279600	0.00009600
H	2.05146000	-1.62338800	-0.00006900
C	-2.55731800	1.19127500	0.00000500
C	2.56063200	1.18445100	0.00000800
C	-2.61937000	2.08014200	-1.26505600
H	-3.55705300	2.64672100	-1.27162000
H	-1.79549400	2.80053300	-1.30222400
H	-2.58137400	1.47233000	-2.17583000
C	-2.61927300	2.08021000	1.26502900
H	-3.55695800	2.64678600	1.27164700
H	-2.58119200	1.47244800	2.17583300
H	-1.79539300	2.80060400	1.30207700
C	-3.77780500	0.25116100	0.00007300
H	-3.80324800	-0.38826900	-0.88971800
H	-3.80319100	-0.38820200	0.88991100
H	-4.69391400	0.85035600	0.00007800
C	3.77860500	0.24108400	-0.00030200

H	4.69630300	0.83784200	-0.00021400
H	3.80236100	-0.39859500	0.88935300
H	3.80225700	-0.39815600	-0.89027400
C	2.62485200	2.07341000	-1.26488500
H	1.80291600	2.79603000	-1.30171400
H	3.56405900	2.63746200	-1.27151900
H	2.58503200	1.46590900	-2.17578800
C	2.62518700	2.07298400	1.26517800
H	2.58558300	1.46517500	2.17588400
H	3.56441000	2.63700800	1.27176200
H	1.80328900	2.79562200	1.30246800
N	-0.00207600	-1.61654900	-0.00007600
Cl	-0.00669300	-4.66882900	0.00003900

II-H2O

C	-1.21124700	-0.89209900	0.00006300
C	-1.20516000	-2.28337400	-0.00062000
C	0.00024700	-2.97668500	-0.00116700
C	1.20555400	-2.28324100	-0.00077000
C	1.21145900	-0.89196000	-0.00002900
H	-0.00003300	0.78090900	0.00024000
H	0.00029200	-4.06203700	-0.00192300
N	0.00008100	-0.25872200	0.00019100
H	2.14019300	-2.82444100	-0.00102300
H	-2.13969700	-2.82474000	-0.00067500
C	2.49250900	-0.05441200	0.00041900

C	-2.49238400	-0.05471000	0.00044600
C	3.74135700	-0.95878200	0.00111400
H	3.79232300	-1.59472800	-0.88925100
H	4.63062100	-0.32112600	0.00155900
H	3.79129400	-1.59473100	0.89153200
C	2.53055200	0.82350100	1.27626700
H	3.46618200	1.39342000	1.28717900
H	1.70478300	1.53902000	1.30796700
H	2.50254000	0.20057700	2.17742000
C	2.53150300	0.82298300	-1.27578300
H	3.46715700	1.39288700	-1.28635500
H	2.50402700	0.19969600	-2.17669900
H	1.70575400	1.53850300	-1.30831000
C	-3.74110300	-0.95932000	0.00109500
H	-4.63046600	-0.32181800	0.00162800
H	-3.79193500	-1.59521000	-0.88931200
H	-3.79094700	-1.59534100	0.89146900
C	-2.53064600	0.82325200	1.27624200
H	-1.70503200	1.53896600	1.30784900
H	-3.46638600	1.39298000	1.28716600
H	-2.50241700	0.20050400	2.17752300
C	-2.53169200	0.82265000	-1.27578500
H	-2.50340600	0.19934100	-2.17667600
H	-3.46788100	1.39164300	-1.28661100
H	-1.70665000	1.53900300	-1.30828500

Cl	-0.00038700	3.15358600	-0.00098300

I-DCM

C	-1.18216500	-0.98429800	0.00001700
C	-1.23473500	0.40664700	-0.00000200
C	0.00009000	1.07362900	-0.00003300
C	1.23480900	0.40644400	-0.00002000
C	1.18203800	-0.98448600	0.00000600
H	-0.00018800	-2.68913700	0.00001700
H	-2.05222800	-1.62634800	-0.00000500
H	0.00019900	2.15858100	-0.00008100
H	2.05201700	-1.62665700	0.00004500
C	-2.55896000	1.18367100	-0.00000100
C	2.55916100	1.18324500	-0.00000300
C	-2.62263300	2.07257900	-1.26493700
H	-3.56109800	2.63789800	-1.27194600
H	-1.79982900	2.79430300	-1.30219000
H	-2.58360700	1.46509000	-2.17588400
C	-2.62260100	2.07258300	1.26493900
H	-3.56105100	2.63793100	1.27193100
H	-2.58361400	1.46510300	2.17589200
H	-1.79978700	2.79429500	1.30219700
C	-3.77808300	0.24175600	0.00000400
H	-3.80246000	-0.39784900	-0.88964800
H	-3.80244600	-0.39784300	0.88966300
H	-4.69538900	0.83916800	0.00000600

C	3.77812400	0.24111000	-0.00010800
H	4.69554000	0.83835300	-0.00002400
H	3.80236500	-0.39860300	0.88947400
H	3.80238100	-0.39838400	-0.88984600
C	2.62295300	2.07223300	-1.26487300
H	1.80031100	2.79414500	-1.30205100
H	3.56154500	2.63733800	-1.27187200
H	2.58376100	1.46482000	-2.17586500
C	2.62300200	2.07204700	1.26500300
H	2.58385000	1.46449600	2.17590400
H	3.56158700	2.63716500	1.27205900
H	1.80034900	2.79394000	1.30231500
N	-0.00011400	-1.62113700	0.00001500
Cl	-0.00043600	-4.64016500	-0.00000900

II-DCM

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C	-1.20503800	-2.26962900	-0.00007300
C	-0.00045300	-2.96354300	-0.00021800
C	1.20430000	-2.26993600	-0.00018800
C	1.21072900	-0.87807800	0.00003200
H	0.00008100	0.80143000	0.00004500
H	-0.00060200	-4.04905400	-0.00039600
N	-0.00010300	-0.24321200	0.00009700
H	2.13892200	-2.81109200	-0.00041200
H	-2.13981900	-2.81053300	-0.00024400

C	2.49638400	-0.04638700	0.00004500
C	-2.49647800	-0.04585900	0.00006500
C	3.74091100	-0.95729600	0.00012800
H	3.78944300	-1.59341800	-0.89042300
H	4.63291800	-0.32354400	0.00016800
H	3.78931600	-1.59338900	0.89070200
C	2.54114900	0.83051200	1.27646100
H	3.48122000	1.39309400	1.28715800
H	1.72118200	1.55235300	1.30761900
H	2.50921900	0.20713800	2.17739400
C	2.54141600	0.83066100	-1.27618500
H	3.48153600	1.39316900	-1.28665800
H	2.50955200	0.20746600	-2.17724200
H	1.72155500	1.55262000	-1.30735800
C	-3.74113400	-0.95656300	0.00049000
H	-4.63304200	-0.32266600	0.00000600
H	-3.78953900	-1.59315800	-0.88971900
H	-3.78983200	-1.59217000	0.89140300
C	-2.54095700	0.83141400	1.27622400
H	-1.72100400	1.55329400	1.30695700
H	-3.48105800	1.39393000	1.28701100
H	-2.50870400	0.20837200	2.17739000
C	-2.54121100	0.83071800	-1.27659000
H	-2.51128200	0.20695100	-2.17730100
H	-3.48024100	1.39501000	-1.28650400

H	-1.71994300	1.55098500	-1.30899300
Cl	0.00057000	3.09567000	-0.00019000
IV-H2O			
C	2.70338100	1.25142000	0.22832500
C	3.93661000	1.21119300	-0.40199100
C	4.56062100	-0.00325900	-0.72821100
C	3.88779800	-1.18313600	-0.39142100
C	2.64995600	-1.16000800	0.23994400
H	1.19572000	0.07929200	0.98947300
N	2.10980600	0.05754600	0.52111800
H	4.32713300	-2.14057600	-0.62080900
H	4.42111400	2.14550600	-0.64314200
C	1.86311000	-2.41354400	0.63235700
C	1.97643500	2.54155200	0.61848600
C	1.63842400	-2.42273400	2.16578100
H	1.03801000	-1.57505100	2.50139100
H	1.10398100	-3.33838700	2.44072200
H	2.59441700	-2.41411200	2.70072300
C	2.63356300	-3.69195200	0.24919700
H	2.03941300	-4.56049700	0.54919200
H	2.80161600	-3.76413500	-0.83061400
H	3.59958700	-3.75955900	0.76092600
C	0.50693900	-2.42035000	-0.11641600
H	-0.02940600	-3.34295400	0.13034800
H	-0.13844500	-1.58589200	0.16306300

H	0.66053200	-2.39686700	-1.20078900
C	2.78627500	3.78033700	0.18905300
H	2.23423500	4.67792100	0.48383900
H	3.76653400	3.82134700	0.67586200
H	2.93040200	3.82220300	-0.89592400
C	0.59688700	2.59464800	-0.08506700
H	-0.08252300	1.80963100	0.25247200
H	0.12183300	3.55530700	0.14199300
H	0.70933800	2.52290700	-1.17256400
C	1.79935600	2.58368100	2.15773700
H	2.76952300	2.54245700	2.66485200
H	1.31134300	3.52455200	2.43412900
H	1.17449100	1.76606000	2.52274400
B	-1.78555400	0.07706700	2.03304000
F	-0.34591800	0.14785600	2.03393000
F	-2.25156400	0.91994300	0.99185600
F	-2.16263800	-1.23857100	1.77498800
F	-2.26010600	0.51871000	3.25586800
C	5.92635500	0.00065800	-1.42526600
C	6.44838500	-1.42163100	-1.70073100
H	5.77805900	-1.98380000	-2.36029900
H	7.42161400	-1.35723300	-2.19775900
H	6.58768900	-1.99345200	-0.77653600
C	6.94786100	0.73427300	-0.52093700
H	6.65956000	1.77282400	-0.33034000

H	7.05562800	0.22710200	0.44410900
H	7.92711700	0.74446000	-1.01188900
C	5.79657400	0.74894000	-2.77529200
H	5.07665300	0.25121100	-3.43417100
H	5.47657600	1.78723700	-2.64254300
H	6.76884700	0.76124700	-3.27992600
C	-6.00011100	-1.30251800	-0.42992200
C	-7.25950200	-0.69818900	-0.41400500
C	-7.49160400	0.50936200	-1.08475700
C	-6.41583600	1.09206300	-1.77222100
C	-5.15984500	0.48688700	-1.79478800
C	-4.93352900	-0.72244600	-1.12499000
H	-5.84724400	-2.23533600	0.10982000
H	-8.07165500	-1.16808800	0.13664600
H	-6.56483200	2.03406800	-2.29666500
H	-4.33654100	0.95611100	-2.32540600
C	-3.57842100	-1.40915300	-1.17740000
H	-3.55613200	-2.11327100	-2.01971600
H	-3.43114400	-1.99596500	-0.26086600
O	-2.48878100	-0.52088400	-1.38845700
H	-2.40824500	0.02026300	-0.57866600
C	-8.85266200	1.16724300	-1.07332000
H	-9.29710700	1.18399500	-2.07676500
H	-9.54612800	0.63823800	-0.41205800
H	-8.79228800	2.20870200	-0.73485900

IV-DCM

C	2.94918500	0.61358000	-0.70172000
C	3.85830900	-0.41654700	-0.91174300
C	3.83477700	-1.58352400	-0.13972400
C	2.85392900	-1.67658800	0.86031400
C	1.94006500	-0.65914300	1.08158600
H	1.35463800	1.20577700	0.44683300
N	2.02755700	0.44653800	0.28594700
H	2.80000300	-2.55975300	1.47931800
H	4.59341200	-0.29908100	-1.69160700
C	0.84611500	-0.69856900	2.15210100
C	2.92791500	1.91657800	-1.50596900
C	0.90460300	-2.01476900	2.95129500
H	1.85713100	-2.13462300	3.47845700
H	0.11011700	-2.00232400	3.70363100
H	0.74252800	-2.89095100	2.31442200
C	-0.54103400	-0.60518900	1.46953000
H	-1.32003400	-0.68059300	2.23584700
H	-0.69474200	0.33816000	0.94289500
H	-0.68287800	-1.42741900	0.75978400
C	1.04664400	0.47965300	3.13873400
H	0.28323900	0.42103400	3.92199500
H	2.03007000	0.42487000	3.61836900
H	0.94536500	1.45053400	2.64975500
C	4.02077000	1.91176100	-2.59237500

H	3.96927400	2.85568700	-3.14341200
H	5.02639400	1.83344700	-2.16576500
H	3.88024700	1.09952100	-3.31355700
C	1.55207800	2.07480000	-2.20124500
H	0.72945900	2.19298100	-1.49333600
H	1.57465900	2.97344700	-2.82729900
H	1.34092200	1.21742600	-2.84985200
C	3.19176900	3.11036400	-0.55295800
H	4.16000500	3.00477700	-0.05154300
H	3.21207900	4.03540900	-1.13918500
H	2.41108400	3.21355700	0.20337600
B	-0.98041800	3.32396400	0.70933400
F	0.30075600	2.68061500	0.86075500
F	-1.36847300	3.18055600	-0.64825600
F	-1.89903100	2.67756800	1.53110500
F	-0.85340300	4.66402400	1.03094000
C	4.82575900	-2.73459500	-0.34893700
C	4.03370200	-4.02017600	-0.69442700
H	3.45770300	-3.89222200	-1.61751400
H	4.73312400	-4.85039400	-0.84141300
H	3.34053800	-4.30518000	0.10329300
C	5.62357400	-2.95157800	0.96104700
H	6.19269100	-2.05459800	1.22887800
H	4.97310000	-3.20682600	1.80352500
H	6.33151800	-3.77624700	0.82389400

C	5.82227300	-2.45159700	-1.48833600
H	5.31681000	-2.31485600	-2.45077200
H	6.43400800	-1.56510500	-1.28736100
H	6.50157700	-3.30385600	-1.59136700
C	-4.88505300	-0.98509600	-1.59808200
C	-5.75061000	-2.07395800	-1.70986100
C	-6.69000100	-2.36298600	-0.70982100
C	-6.73179600	-1.51963700	0.40885500
C	-5.86127200	-0.43501500	0.52685400
C	-4.92791100	-0.14807100	-0.47632400
H	-4.16383700	-0.78117700	-2.38351400
H	-5.69750100	-2.70993300	-2.59132300
H	-7.44929400	-1.71829300	1.20226900
H	-5.91091800	0.19746900	1.41106400
C	-4.02860300	1.06203100	-0.36359900
H	-3.86549100	1.30980000	0.69417500
H	-4.53795800	1.93329800	-0.81262700
O	-2.79275200	0.82106600	-1.02592200
H	-2.27171100	1.64302100	-0.94474900
C	-7.60576800	-3.56050900	-0.82083800
H	-7.85102000	-3.78161200	-1.86521700
H	-7.13760100	-4.46131500	-0.40143500
H	-8.54266500	-3.40015700	-0.27689200

3.15 Transition State Calculations:

In this work, Gaussian G16 software was employed to conduct density functional theory (DFT) computations.[1] Conformation searching was initially carried out using the CREST software.[2] The geometry calculations, based on the lowest conformer structure were performed using M06-2X functional with The Def2-SVP basis set.[3,4] Following geometry optimizations, frequency calculations were conducted to confirm the absence of a saddle point for the intermediate structure and the presence of one imaginary frequency for the transition state. To consider the influence of dichloromethane solvents, an implicit solvation model using the SMD solvation model, was applied for the single point energy calculations.[5]

Reaction Coordinates

- ➢ V^R (cation-reactant)

C	-2.62516700	0.75144800	1.14244200
C	-2.11208000	-0.59512900	1.65827200
C	-2.62808500	-1.74377000	0.79532200
C	-2.31465700	-1.47345400	-0.67806200
C	-2.82665300	-0.08481200	-1.05429000
H	-1.01119000	-0.60928400	1.58587000
H	-3.72261500	0.77111200	1.26379100
H	-1.21191800	-1.45106600	-0.79771900
H	-2.54839900	0.16516600	-2.09086500
H	-3.72592700	-1.81560600	0.90048600
O	-2.27664900	0.90195600	-0.23219500
C	-2.06535400	1.93684200	1.88605900
H	-2.47228000	2.86401900	1.44485900
H	-2.38340800	1.87901100	2.94204200
O	-0.65713700	1.93462600	1.79280800
C	-0.06177000	3.05144100	2.40881500
H	-0.44355100	3.99203500	1.97611800
H	-0.26277100	3.05484000	3.49405700
H	1.01958900	2.99510200	2.23584700

O	-2.51915300	-0.76859000	2.99002800
O	-2.00367600	-2.94009500	1.19481500
O	-2.90051900	-2.37335000	-1.56043000
O	-4.22507500	-0.12606600	-0.92635800
C	-1.46740800	-0.82452300	3.91790700
H	-1.90880400	-0.93382300	4.91594200
H	-0.80750100	-1.68822600	3.72068100
H	-0.85816800	0.09837500	3.89388000
C	-2.79724700	-3.76831000	2.01647000
H	-3.13582200	-3.23199700	2.91587200
H	-3.68048300	-4.13975500	1.46832900
H	-2.17933300	-4.62506100	2.31308700
C	-2.29403200	-3.63496400	-1.67535100
H	-1.19397000	-3.54088200	-1.72324300
H	-2.54641600	-4.29937600	-0.83581200
H	-2.65380700	-4.08243200	-2.61001600
C	-4.94785000	0.97020700	-1.24677300
C	-6.42345400	0.68169300	-0.94380100
Cl	-6.53807500	0.30420500	0.80710100
Cl	-6.93298800	-0.73497100	-1.88501200
Cl	-7.44007600	2.06076900	-1.31767200
N	-4.56372800	2.07873300	-1.68659000
H	-3.54897700	2.13417300	-1.78416600
C	3.37198900	4.17816000	-1.12078000
C	2.01712600	4.23498100	-0.75860800
C	1.20629700	3.10678200	-0.83188400
C	1.72969300	1.88031900	-1.26030200
C	3.07499200	1.81791500	-1.62357400
C	3.88503000	2.95250300	-1.55673700
H	1.59389600	5.18584400	-0.42584800
H	0.14968300	3.16814100	-0.55411100
H	3.49238400	0.86725400	-1.96963600
H	4.93485200	2.88993800	-1.85526100
C	4.22984800	5.41400000	-1.06995500
H	3.98424400	6.08947100	-1.90318700
H	4.06745200	5.97297400	-0.13810100
H	5.29639000	5.16622000	-1.14456900
C	0.86501800	0.64711200	-1.24613300
H	1.36840300	-0.16134300	-1.79826500
H	-0.09928600	0.84873500	-1.74415400
O	0.63968700	0.17913100	0.06889900
C	3.95686600	-0.17987600	1.13723700

C	5.15359500	-0.07472800	0.43696500
C	5.43298200	-0.91779700	-0.64243200
C	4.48573000	-1.90674300	-0.95668800
C	3.30221400	-2.02159400	-0.24658400
N	3.08336600	-1.12476000	0.74199900
H	5.86512100	0.68686900	0.74806800
H	4.67795400	-2.61686200	-1.76078100
C	6.71173400	-0.80501600	-1.46622700
C	7.62629400	0.30879700	-0.95083700
H	7.95237600	0.12375600	0.08316900
H	8.52680000	0.35888600	-1.57766100
H	7.13564500	1.29243300	-0.99585200
C	7.46863300	-2.14316900	-1.39970600
H	6.88128500	-2.97222700	-1.81890500
H	8.39776600	-2.06705300	-1.98203900
H	7.73399500	-2.39629300	-0.36305900
C	6.32191600	-0.49687200	-2.92325000
H	5.68957300	-1.28519700	-3.35620700
H	5.78139100	0.45883700	-2.99634500
H	7.23006100	-0.42127500	-3.53812800
C	3.63611700	0.68184500	2.35176700
C	3.65616800	2.16030300	1.93342300
H	3.44491700	2.78846400	2.81154400
H	4.63764100	2.45891000	1.53786600
H	2.90441300	2.36286600	1.15699300
C	4.72712600	0.42134200	3.40750000
H	4.51517700	1.02442700	4.30171700
H	4.75110800	-0.63709500	3.70479800
H	5.72491600	0.70213300	3.04308500
C	2.27008700	0.33305200	2.95404900
H	1.44973200	0.51904300	2.24578000
H	2.22768500	-0.71368200	3.29679100
H	2.09779100	0.96498700	3.83612800
C	2.30220600	-3.15432800	-0.46167600
C	1.79217100	-3.13627700	-1.91077400
H	1.16029200	-2.25713000	-2.10132200
H	2.61493300	-3.14058800	-2.63988900
H	1.18457400	-4.03445300	-2.09047100
C	1.11402700	-3.05417300	0.50022500
H	0.39712600	-3.85957300	0.29474000
H	1.42651000	-3.16354200	1.55174100
H	0.56612500	-2.10778800	0.38286800

C	3.05222500	-4.47492400	-0.19917700
H	3.47359500	-4.49782600	0.81620300
H	2.34887900	-5.31378400	-0.29727000
H	3.86897600	-4.63303900	-0.91753300
H	2.15012600	-1.11203500	1.16160900
H	0.10534300	0.84580700	0.54583000

➢ V^{TS}(cation TS)

C	-2.86336200	2.15314400	0.11758300
C	-2.11605800	1.22399700	1.08243700
C	-2.01011700	-0.19289500	0.51027000
C	-1.15687000	-0.05522400	-0.74718200
C	-1.83892700	0.93751000	-1.70013100
H	-1.07912700	1.59534100	1.22635500
H	-3.94341800	2.02801100	0.29428800
H	-0.20697800	0.40021100	-0.41227600
H	-2.07849500	0.57025300	-2.69935000
H	-3.00539700	-0.57908900	0.24359700
O	-2.67243400	1.83099200	-1.26901700
C	-2.46045700	3.60230100	0.26433000
H	-3.12495200	4.24027200	-0.34113100
H	-2.54902700	3.89588200	1.32439500
O	-1.11827900	3.74321600	-0.17808300
C	-0.62698300	5.06492600	-0.06218600
H	-1.22306900	5.75983000	-0.67468500
H	-0.65596400	5.39756700	0.98768300
H	0.41219400	5.06657300	-0.41497300
O	-2.80364600	1.30074500	2.29571900
O	-1.36016600	-1.06215000	1.40664700
O	-0.77744500	-1.22864000	-1.39184400
O	-3.98029100	-0.41856900	-1.90745500
C	-2.00914800	1.34192000	3.45132900
H	-2.68286400	1.49816200	4.30209200
H	-1.45156300	0.40274100	3.60251500
H	-1.28804500	2.17977500	3.41045500
C	-2.26311800	-1.84385400	2.17747500
H	-2.90111900	-1.20687900	2.80792000
H	-2.92387600	-2.43584600	1.52336500
H	-1.66074300	-2.51243900	2.80607500
C	-1.76622800	-2.25069800	-1.56032600

H	-2.07127600	-2.65026400	-0.57988900
H	-2.66274900	-1.87674000	-2.06935500
H	-1.27607600	-3.04577400	-2.13424300
C	-5.01331300	0.08209000	-1.38188000
C	-5.75061700	-0.84047600	-0.32409800
Cl	-5.42290400	-0.17805100	1.32232800
Cl	-5.10480100	-2.51239800	-0.36016300
Cl	-7.49137900	-0.89746100	-0.58944300
N	-5.55700900	1.24339300	-1.47885700
H	-5.02450500	1.76900300	-2.17671000
C	4.14219900	3.05075200	-0.33648800
C	2.86861200	2.98224700	0.23813500
C	1.77846200	2.47452300	-0.46867900
C	1.92700100	2.03754000	-1.78792000
C	3.19439800	2.11191900	-2.37375600
C	4.28284800	2.60355100	-1.65645400
H	2.71738800	3.35827200	1.25379700
H	0.79693400	2.46358700	0.01073700
H	3.33004000	1.80298100	-3.41317400
H	5.25802500	2.67284700	-2.14454500
C	5.31099200	3.59952400	0.43838100
H	5.05214600	4.54993000	0.92526100
H	5.62577200	2.90338900	1.23338400
H	6.17714600	3.77403900	-0.21266500
C	0.77381000	1.49437400	-2.59420700
H	0.70948300	0.39635100	-2.50801200
H	0.90495900	1.74149800	-3.65677000
O	-0.49853100	1.99571200	-2.18260200
C	3.18988200	-0.73899100	1.53147800
C	4.38315600	-0.46127300	0.88501800
C	4.79416100	-1.21448000	-0.22864700
C	3.95109800	-2.24168900	-0.66562800
C	2.74527300	-2.50553500	-0.03108700
N	2.41333400	-1.72416400	1.01742000
H	5.01266300	0.33424000	1.27275000
H	4.23994100	-2.87422000	-1.50412000
C	6.13903000	-0.99925300	-0.91548900
C	6.88873100	0.20397400	-0.33907400
H	7.14095800	0.05965200	0.72190300
H	7.83245900	0.34015200	-0.88449300
H	6.30246800	1.12856700	-0.44104300
C	6.98908000	-2.26629600	-0.70190300

H	6.51953300	-3.15515700	-1.14671200
H	7.97069900	-2.13129000	-1.17802600
H	7.15090900	-2.45937800	0.36844000
C	5.91188000	-0.77647100	-2.42044200
H	5.43435800	-1.64255200	-2.89977200
H	5.28217000	0.10727700	-2.59534800
H	6.88011800	-0.61716100	-2.91581800
C	2.72125900	-0.10483100	2.83334900
C	3.72071200	0.95132200	3.30866600
H	3.35047200	1.40515100	4.23771600
H	4.70661000	0.51341500	3.52147900
H	3.84124300	1.75211000	2.56511600
C	2.62876100	-1.22084500	3.89318300
H	2.34782600	-0.78053000	4.85984600
H	1.86341100	-1.97141200	3.64211700
H	3.59278000	-1.73477800	4.01682700
C	1.34103900	0.54237600	2.64655600
H	1.39255400	1.36296700	1.91797000
H	0.56667400	-0.16608100	2.31110200
H	1.01045100	0.95678600	3.60954900
C	1.84428500	-3.66882900	-0.41706500
C	1.49333300	-3.54848300	-1.90872600
H	0.95273600	-2.61259100	-2.10446600
H	2.39197700	-3.58690200	-2.54059000
H	0.85257700	-4.39382100	-2.19761900
C	0.56551100	-3.68519600	0.42612300
H	-0.08309100	-4.50107000	0.08026800
H	0.78408200	-3.88495500	1.48890000
H	-0.00429900	-2.74796000	0.33356600
C	2.63361100	-4.96848800	-0.16854900
H	2.92829600	-5.06283100	0.88677600
H	1.99870800	-5.82826000	-0.42500000
H	3.53946400	-5.02119700	-0.78882900
H	1.50674100	-1.89752500	1.45891800
H	-0.52737900	2.77417800	-1.56506800

- ➢ V^{P}(cation product)

C	2.77313100	2.20112600	0.90456700
C	1.35137400	2.60715000	1.30142500
C	0.56716500	2.99109900	0.05229300

C	0.40114700	1.73252600	-0.78787000
C	1.73911200	0.94912200	-0.89831200
H	0.84991700	1.74829900	1.78214400
H	3.34748500	3.13584900	0.81458700
H	-0.31175100	1.08656000	-0.24797800
H	1.95963100	0.78485200	-1.96722600
H	1.14535900	3.75527200	-0.49894100
O	2.83407300	1.60900400	-0.38859100
C	3.44980800	1.37662200	1.98718500
H	4.39911400	0.97444700	1.59021300
H	3.68248400	2.06085500	2.82555800
O	2.62059700	0.33556700	2.43627500
C	3.17368700	-0.35387200	3.52717600
H	4.16728600	-0.76562400	3.27947000
H	3.27991600	0.30586800	4.40671400
H	2.49620700	-1.17975600	3.78298100
O	1.46377100	3.67583500	2.20380500
O	-0.71742600	3.49126500	0.35836900
O	-0.18087500	1.95148800	-2.04806100
O	5.82312600	-3.00714100	0.33167400
C	0.65619400	3.58758400	3.34954600
H	0.93804300	4.41335500	4.01395600
H	-0.41607600	3.67735200	3.10222900
H	0.82115500	2.63177400	3.87787300
C	-0.79627000	4.90010600	0.44649900
H	-0.06772600	5.29559100	1.16880500
H	-0.61533100	5.36539600	-0.53809400
H	-1.81266200	5.15348400	0.77421700
C	0.44564300	2.91904100	-2.86060300
H	0.18343200	3.94340700	-2.54561000
H	1.54416600	2.81710500	-2.85137100
H	0.08688900	2.76586700	-3.88595700
C	5.12318500	-2.08706500	0.01007600
C	5.50857600	-1.19198800	-1.21976600
Cl	4.08643200	-1.01795900	-2.30403600
Cl	6.82825400	-1.91982700	-2.10985300
Cl	5.98670300	0.41678600	-0.62418900
N	4.00479500	-1.68737600	0.64929800
H	3.70461600	-2.26464600	1.42542000
C	-1.43289600	-3.66503300	1.85480400
C	-0.59306800	-2.64280300	2.30963300
C	0.15538800	-1.86491000	1.42308900

C	0.06744800	-2.08975400	0.04774000
C	-0.74749300	-3.12597900	-0.41726400
C	-1.48037700	-3.90408800	0.47421300
H	-0.50971700	-2.45969700	3.38471400
H	0.82527700	-1.08018900	1.78557900
H	-0.79124100	-3.34096700	-1.48863500
H	-2.08603700	-4.73121100	0.09507700
C	-2.26151300	-4.47748800	2.81553700
H	-1.71015100	-4.68531900	3.74242200
H	-3.18290800	-3.94081800	3.09880300
H	-2.56183200	-5.43646500	2.37313100
C	0.84600500	-1.24954200	-0.93255100
H	0.14152600	-0.75193000	-1.62495300
H	1.50986200	-1.88517400	-1.54651800
O	1.61836500	-0.29144000	-0.24790500
C	-3.54926800	0.17660700	0.92834900
C	-4.04676500	-1.07847000	0.61892200
C	-4.46070800	-1.39183800	-0.68590000
C	-4.33626800	-0.39688000	-1.66166000
C	-3.82831300	0.85811600	-1.35660400
N	-3.42904700	1.07450800	-0.08393500
H	-4.13604800	-1.81189500	1.41452900
H	-4.67130200	-0.58099000	-2.68173200
C	-5.09117700	-2.73282300	-1.04699100
C	-5.18487800	-3.66420200	0.16442200
H	-5.83124000	-3.24462400	0.94967600
H	-5.62331100	-4.62207400	-0.14695200
H	-4.19502100	-3.87087500	0.59549800
C	-6.51247200	-2.47290400	-1.58040200
H	-6.50664700	-1.86239400	-2.49437500
H	-6.98999800	-3.43249700	-1.82422700
H	-7.13171300	-1.96421100	-0.82733800
C	-4.24197600	-3.40295600	-2.14082200
H	-4.18950200	-2.79063700	-3.05247100
H	-3.21810600	-3.58238400	-1.78520100
H	-4.69070900	-4.36903100	-2.41249000
C	-3.21754300	0.65691900	2.33407700
C	-3.47736000	-0.45061700	3.35749400
H	-3.22863200	-0.07520800	4.35918900
H	-4.53301100	-0.75849800	3.36929800
H	-2.84746900	-1.33021900	3.16049600
C	-4.12256900	1.86261100	2.65260100

H	-3.92719500	2.20001900	3.67993200
H	-3.92663100	2.71760600	1.98655400
H	-5.18669700	1.59675700	2.57493400
C	-1.74496400	1.08114300	2.40654500
H	-1.08326400	0.24441100	2.14137500
H	-1.52534000	1.93441200	1.74819500
H	-1.51115200	1.39217100	3.43517700
C	-3.81042800	1.99603800	-2.36983500
C	-3.00824700	1.55871500	-3.60645500
H	-1.97079900	1.32906500	-3.33041400
H	-3.45688700	0.68079300	-4.09251800
H	-3.00748600	2.37710300	-4.34090700
C	-3.19904200	3.27049300	-1.78170000
H	-3.20831600	4.05469100	-2.55084500
H	-3.79086200	3.65376500	-0.93324000
H	-2.15719100	3.11638100	-1.46693800
C	-5.27286400	2.27755400	-2.76671400
H	-5.87617500	2.56559100	-1.89339900
H	-5.29585200	3.10682100	-3.48782800
H	-5.74411000	1.40560300	-3.24140700
H	-3.00780800	1.98395200	0.12948100
H	3.35622600	-0.98284900	0.29811400

- ➢ VI^{R}(anion reactant)

C	-2.04801900	1.23840600	-1.13193200
C	-2.30402900	2.29476800	-0.05506000
C	-2.14419100	1.71081800	1.34304400
C	-0.78327700	1.03305200	1.44780200
C	-0.65509700	0.00473300	0.33257600
H	-1.54800500	3.09161000	-0.16637500
H	-2.86274900	0.49183700	-1.07917200
H	0.01182100	1.77346800	1.25859700
H	0.33008800	-0.47342300	0.34257200
H	-2.92353200	0.94624100	1.51428500
O	-0.79888600	0.60054400	-0.91031200
C	-2.03669200	1.82635400	-2.53710800
H	-1.58386300	1.06900800	-3.20314200
H	-3.07746500	2.00911000	-2.84163800
O	-1.36989800	3.05379400	-2.64731200
C	0.03666000	2.96275500	-2.53844500

H	0.36504400	2.81965300	-1.49653700
H	0.42890200	2.10826800	-3.10953000
H	0.45393500	3.90277600	-2.92433300
O	-3.60030200	2.82692400	-0.21706600
O	-2.23767100	2.73436600	2.31053000
O	-0.59214800	0.41376500	2.68720200
O	-1.67592100	-0.96471900	0.54848700
C	-3.62409000	4.19230900	-0.54503300
H	-4.67247200	4.47252200	-0.71674900
H	-3.22343900	4.80619400	0.28212600
H	-3.03497200	4.39306300	-1.45535400
C	-3.48706500	2.81665400	2.93804800
H	-4.29820600	2.97016800	2.20748600
H	-3.70426300	1.90191400	3.51921600
H	-3.45613600	3.67074700	3.62862200
C	0.18912800	1.16800300	3.57940800
H	1.17703400	1.38853500	3.13987400
H	-0.30816900	2.11567500	3.84307000
H	0.32126900	0.56449500	4.48796000
C	-1.76039500	-2.00100700	-0.30659200
C	-3.00684000	-2.81854200	0.07711600
Cl	-4.44242900	-1.75036800	-0.04341700
Cl	-2.84539300	-3.37354800	1.76435400
Cl	-3.22941800	-4.20893900	-0.98137900
N	-1.04406600	-2.33177800	-1.27540200
H	-0.24876400	-1.70518100	-1.45493900
C	7.10939100	-0.35387900	0.55641400
C	6.16405400	-0.58092900	-0.45307800
C	4.80166500	-0.61078200	-0.17492500
C	4.34100600	-0.40592800	1.13314300
C	5.27834100	-0.17577000	2.14030500
C	6.64545400	-0.15374000	1.85802800
H	6.49939300	-0.73938900	-1.48132000
H	4.09139100	-0.79486700	-0.98445200
H	4.93323700	-0.00910900	3.16411600
H	7.36346300	0.02551800	2.66274700
C	8.58186700	-0.32876900	0.23358300
H	8.91004400	-1.28698400	-0.19714500
H	8.81141400	0.45464200	-0.50447500
H	9.18440700	-0.13619500	1.13183800
C	2.85462500	-0.38342900	1.41304300
H	2.68227300	-0.48153100	2.49663900

H	2.38199600	-1.24560400	0.91277300
O	2.24946700	0.82150800	1.01223400
H	2.27967400	0.88222100	0.03870700
B	1.95010300	-0.20760100	-2.34248400
F	1.64989800	-1.10520000	-1.28238600
F	0.86913100	-0.12818900	-3.20550100
F	3.09184100	-0.64761300	-2.99723500
F	2.20641500	1.05141100	-1.74597200

➢ VI^{TS}(anion TS)

C	1.18189800	0.42660000	1.54535100
C	1.43729400	1.87288900	1.13976900
C	1.60103300	2.00479200	-0.37237300
C	0.28992200	1.53366400	-0.99428200
C	-0.13374500	0.18000100	-0.43591800
H	0.57174200	2.49067800	1.44318700
H	2.06853500	-0.17611000	1.30216500
H	-0.47074700	2.24253500	-0.62887100
H	-0.40702400	-0.62667700	-1.11107400
H	2.43432300	1.37067600	-0.70739500
O	0.09523100	-0.15768400	0.79185000
C	0.88672500	0.25034100	3.02331600
H	0.48539100	-0.77012500	3.16049800
H	1.84108700	0.34233900	3.55978700
O	0.02463700	1.21653000	3.56384400
C	-1.32240400	1.05552900	3.18487200
H	-1.51383700	1.43331400	2.16352100
H	-1.62126100	-0.00341900	3.20524000
H	-1.93729700	1.63277600	3.88850900
O	2.59585200	2.30962500	1.80583400
O	1.80247200	3.35345500	-0.72690500
O	0.18132500	1.54250900	-2.38445300
O	1.86493200	-0.74735200	-1.20049000
C	2.38098000	3.37047400	2.70181100
H	3.33775200	3.57786000	3.19918800
H	2.05203800	4.27994300	2.16738800
H	1.62390800	3.10346900	3.45799800
C	3.15583900	3.69324800	-0.88882000
H	3.73077900	3.52638700	0.03508100

H	3.62272700	3.09898500	-1.69559400
H	3.19723000	4.75624400	-1.16241400
C	1.36126100	1.41109400	-3.15464900
H	1.98045100	2.31950700	-3.06709000
H	1.94236100	0.52530100	-2.86472900
H	1.03073900	1.31844600	-4.19746900
C	2.47748700	-1.65869400	-0.56276100
C	4.03267400	-1.56521900	-0.76700500
Cl	4.59029200	-0.05798200	0.05935800
Cl	4.41142900	-1.40663800	-2.50964400
Cl	4.94375300	-2.93060800	-0.11107800
N	2.09003700	-2.56129600	0.25869900
H	1.07017800	-2.49889700	0.35539000
C	-6.98844600	0.15695300	-0.92810200
C	-6.19246100	-0.92751000	-0.53615800
C	-4.81588900	-0.92056300	-0.73198500
C	-4.19564800	0.18479100	-1.33012600
C	-4.98169400	1.26991200	-1.71863400
C	-6.36285900	1.25486400	-1.52367900
H	-6.65861900	-1.79529900	-0.06331000
H	-4.21480600	-1.77364200	-0.40817800
H	-4.50599200	2.13755300	-2.18213500
H	-6.96448600	2.11121000	-1.83812100
C	-8.47830700	0.13006800	-0.70200000
H	-8.95975300	1.03226500	-1.10264200
H	-8.93615200	-0.74559900	-1.18581500
H	-8.71146700	0.06791700	0.37166000
C	-2.70022300	0.20394400	-1.50635700
H	-2.39133100	0.92034800	-2.27964900
H	-2.34917100	-0.80150000	-1.78714800
O	-2.04020400	0.60499500	-0.30639300
H	-2.35501600	0.02284900	0.43723600
B	-2.24289200	-2.21713600	1.33791300
F	-1.71942000	-2.15559300	0.03245200
F	-1.24156800	-2.36505100	2.27537900
F	-3.20794600	-3.19936000	1.41636600
F	-2.88392300	-0.93837300	1.56220400

➢ VI^{P}(anion product)

C	-1.97199500	-0.87158600	0.57099300

C	-3.48874500	-0.66133200	0.56626800
C	-3.79913100	0.67933700	-0.08358200
C	-3.19702200	0.70260100	-1.48451700
C	-1.71916400	0.29583900	-1.48562500
H	-3.94673800	-1.46945400	-0.03055100
H	-1.51669800	-0.02092200	1.11731800
H	-3.73691400	-0.03646900	-2.09694000
H	-1.11809300	1.10089800	-1.02683900
H	-3.32527100	1.45777700	0.54688800
O	-1.49689600	-0.89773700	-0.76560500
C	-1.56715700	-2.15759400	1.27259300
H	-0.47614600	-2.29289300	1.19639000
H	-1.83628600	-2.04743000	2.33503900
O	-2.24644000	-3.27901800	0.76658100
C	-1.51480200	-3.99952900	-0.20374200
H	-1.31578600	-3.38497000	-1.09438200
H	-0.54583700	-4.32987600	0.20291900
H	-2.12244000	-4.87227100	-0.47974000
O	-3.98853400	-0.67035900	1.88386100
O	-5.17946000	0.92605500	-0.19630100
O	-3.33686600	1.93368000	-2.15245800
O	-0.00127500	1.94972600	0.59412300
C	-4.72486600	-1.82082400	2.21427600
H	-4.96625700	-1.76114400	3.28419500
H	-5.66875300	-1.86330500	1.63965600
H	-4.15014300	-2.74032900	2.01618100
C	-5.75601000	1.59700800	0.88968400
H	-5.69072500	1.01483600	1.82090600
H	-5.26799000	2.57566300	1.06118700
H	-6.81073100	1.77717000	0.64107400
C	-3.05180200	3.08427800	-1.40382000
H	-3.86188100	3.31544900	-0.68888400
H	-2.10163000	3.01215900	-0.84400500
H	-2.97397700	3.91770500	-2.11500400
C	0.96921400	1.25740400	0.84132800
C	2.11829200	1.93627600	1.66681900
Cl	3.62529100	1.00806300	1.71941700
Cl	1.49618500	2.13887300	3.32884800
Cl	2.43645800	3.54025100	0.96796900
N	1.13559000	-0.02443900	0.55486300
C	3.60746000	0.08884700	-1.69877200
C	2.75488200	-0.93863900	-2.12302800

C	1.48858800	-0.65205000	-2.61976000
C	1.03728200	0.66923900	-2.71226800
C	1.87559900	1.69601600	-2.27507200
C	3.14770300	1.40699400	-1.77542000
H	3.06816500	-1.97924500	-2.01274000
H	0.81532100	-1.46721200	-2.89167900
H	1.52172600	2.73058000	-2.29273200
H	3.78121600	2.21886700	-1.40870100
C	4.95482400	-0.25453100	-1.12254500
H	5.47306600	0.64040400	-0.75070900
H	4.82138200	-0.96676600	-0.29423900
H	5.59342900	-0.73800800	-1.87776600
C	-0.33553700	0.95197200	-3.27865500
H	-0.32991900	0.80860400	-4.37000500
H	-0.61961700	2.00227900	-3.08829200
O	-1.33096300	0.07676500	-2.79853600
H	0.45449000	-0.50195700	-0.04086700
B	2.29912800	-3.13566000	0.28101000
F	3.05772600	-2.04329100	0.79550600
F	1.89850900	-3.96031800	1.31974800
F	3.06853300	-3.81708400	-0.65392200
F	1.15413800	-2.59549800	-0.34310500
H	1.99102300	-0.55844500	0.72896400

Reactants

- ➢ 1a (2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl trichloroacetimidate)

C	-1.28462900	-1.14838100	-0.07040400
C	-2.19238800	0.01282900	0.33258900
C	-1.45889500	1.34252900	0.20934500
C	-0.89847700	1.48296000	-1.20329300
C	-0.05177300	0.25274200	-1.52290200
H	-3.04694300	0.02545000	-0.36536700
H	-0.44931100	-1.21171500	0.65073200
H	-1.74255900	1.48227000	-1.91921600
H	0.31386200	0.28841800	-2.56134500
H	-0.60535500	1.35584400	0.91123100

O	-0.77414900	-0.92431500	-1.38354400
C	-2.01242600	-2.47219100	-0.06292400
H	-1.35210400	-3.24088500	-0.50783800
H	-2.21135700	-2.75328100	0.98879500
O	-3.20715300	-2.36020200	-0.78159600
C	-3.90558200	-3.56752000	-0.87224500
H	-3.31224400	-4.34021800	-1.39405300
H	-4.17465600	-3.95677200	0.12746900
H	-4.82548900	-3.38462500	-1.44079400
O	-2.63113400	-0.18663600	1.65245100
O	-2.33700400	2.40774600	0.47561300
O	-0.10673000	2.62012600	-1.35862200
O	1.04975400	0.28704800	-0.63527800
C	-4.02918300	-0.18087200	1.80200700
H	-4.24894300	-0.36299100	2.86156700
H	-4.45711100	0.79225100	1.50622400
H	-4.49467900	-0.97435800	1.19201900
C	-2.19897700	2.96367400	1.76038900
H	-2.33790100	2.20189500	2.54414400
H	-1.20527900	3.42795800	1.88714900
H	-2.96812000	3.73912200	1.86745300
C	-0.78176400	3.74919200	-1.85618400
H	-1.17159200	3.56380700	-2.87372900
H	-1.61846000	4.03963700	-1.20424400
H	-0.05236700	4.56682700	-1.90526700
C	1.99204200	-0.66836000	-0.73263700
C	3.05204200	-0.41005000	0.34722300
Cl	2.22209000	-0.46981200	1.93368700
Cl	3.73794200	1.21172700	0.10164800
Cl	4.32882600	-1.61699600	0.30487800
N	2.06710100	-1.65011600	-1.50934500
H	1.25170600	-1.72090200	-2.12108700

- ➢ 2n (p-methylbenzylalcohol)

C	-1.84119100	-0.08928800	0.00510200
C	-0.97495100	-1.18105000	-0.11147100
C	0.40599400	-1.00316900	-0.17016000
C	0.96065800	0.27750600	-0.11105200
C	0.10097100	1.37254600	0.01002800
C	-1.27853800	1.19142000	0.06166900

H	-1.39060500	-2.19028100	-0.16214300
H	1.07247700	-1.86238600	-0.26420800
H	0.51676900	2.38198800	0.06534700
H	-1.93380100	2.06092500	0.15378700
C	-3.33227900	-0.28301100	0.09886700
H	-3.63863100	-1.23757900	-0.34911900
H	-3.66163600	-0.28776400	1.14954500
H	-3.87187100	0.52647900	-0.41149300
C	2.45906400	0.46559800	-0.20639600
H	2.74122900	1.40271700	0.30903600
H	2.74828000	0.58884200	-1.26199800
O	3.18812700	-0.63557600	0.26690900
H	2.91440700	-0.80164500	1.17645700

- ➢ 5c (2,4,6-tri-tert-butylpyridine + BF_4-)

C	0.66080100	-1.18303900	-0.00002700
C	-0.73095500	-1.21805300	0.00000400
C	-1.47923600	-0.03843000	-0.00001500
C	-0.77929300	1.18694400	-0.00005600
C	0.59981800	1.22015100	-0.00006400
N	1.24841100	0.02617700	-0.00004100
H	-1.22222700	-2.18856500	0.00003200
H	-1.32597900	2.12726200	-0.00009000
C	-3.00304700	-0.03236500	-0.00000700
C	-3.58104300	-1.44949900	0.00008100
H	-3.28054300	-2.01379200	0.89515700
H	-4.67773800	-1.39275300	0.00009900
H	-3.28061300	-2.01390500	-0.89495500
C	-3.48867300	0.70711000	1.26032500
H	-3.15011400	1.75254100	1.28335100
H	-4.58760200	0.71331400	1.27614900
H	-3.13638300	0.20742600	2.17425000
C	-3.48867500	0.70701500	-1.26040300
H	-3.15024000	1.75248600	-1.28340000
H	-3.13626000	0.20737000	-2.17430200
H	-4.58760300	0.71309200	-1.27631600
C	1.52947700	-2.43360900	-0.00000700
C	1.19980300	-3.25212600	-1.26103100
H	1.81607800	-4.16188700	-1.27362000

H	0.14579900	-3.56145700	-1.28133900
H	1.41186100	-2.68033700	-2.17581400
C	1.19980900	-3.25207000	1.26105900
H	1.81603800	-4.16186300	1.27365600
H	1.41192700	-2.68026000	2.17581500
H	0.14579000	-3.56134900	1.28141800
C	3.02226700	-2.08541000	-0.00001900
H	3.31903400	-1.52403800	-0.90070100
H	3.31905400	-1.52406400	0.90067400
H	3.60744900	-3.01386500	-0.00003500
C	1.47487100	2.46470600	-0.00000100
C	0.61329300	3.72867800	-0.00027100
H	-0.02273100	3.78605000	-0.89518500
H	-0.02299200	3.78626800	0.89444400
H	1.26761400	4.61044700	-0.00026700
C	2.35733700	2.45063300	-1.26181900
H	2.98031900	3.35529700	-1.27990600
H	3.04231100	1.58834600	-1.29007200
H	1.74548500	2.43595900	-2.17477900
C	2.35677700	2.45075800	1.26222100
H	3.04164300	1.58840100	1.29086800
H	2.97980800	3.35538500	1.28048200
H	1.74450800	2.43623200	2.17490400
H	2.26743300	0.05066600	-0.00005000

B	0.00000000	0.00000000	0.00000000
F	0.80974600	0.80974600	0.80974600
F	-0.80974600	-0.80974600	0.80974600
F	0.80974600	-0.80974600	-0.80974600
F	-0.80974600	0.80974600	-0.80974600

Products

- 3o ((4’-methyl)-benzyl-2,3,4,6-tetra-O-benzyl-D-galactopyranoside)

C	-1.86897500	1.07636300	-1.23263400
C	-1.87035300	0.90201900	0.28440100
C	-2.59401500	-0.39546900	0.62013500

C	-1.80451400	-1.57869200	0.05626900
C	-0.97205200	-1.15565800	-1.17921600
H	-0.83068000	0.84236600	0.64483600
H	-2.90199400	1.33446500	-1.52255900
H	-1.09962100	-1.87889200	0.84545400
H	-0.90650800	-2.02302600	-1.86153800
H	-3.58803600	-0.34905300	0.13644800
O	-1.56331000	-0.13560300	-1.91319700
C	-0.99307900	2.23259300	-1.68533800
H	-0.83200100	2.13604100	-2.77559400
H	-1.54444200	3.17430000	-1.49934700
O	0.22671900	2.25524700	-0.99958700
C	1.06469800	3.29211800	-1.41926500
H	1.31145800	3.20526300	-2.49290900
H	0.60096300	4.28167200	-1.24928100
H	1.99450000	3.23202200	-0.83891400
O	-2.52378300	2.01522900	0.83982000
O	-2.74376800	-0.55956900	2.00717900
O	-2.58219200	-2.72045700	-0.19592800
C	-1.88152400	2.54153100	1.97474400
H	-2.47960700	3.39120200	2.32816800
H	-1.80724400	1.78913500	2.77730000
H	-0.86674700	2.89443100	1.72159900
C	-4.00721200	-0.20681200	2.50528200
H	-4.25351100	0.84496800	2.28532900
H	-4.79722500	-0.85241300	2.08011100
H	-3.98560800	-0.35470000	3.59246900
C	-3.60693200	-2.58337900	-1.14631100
H	-4.50361700	-2.09519300	-0.72568900
H	-3.28442400	-2.00823300	-2.03132100
H	-3.89152100	-3.59431500	-1.46466500
C	5.04289000	-0.17194800	0.67898900
C	3.97973900	0.67268800	0.35400000
C	2.74653400	0.16687600	-0.06306400
C	2.55608700	-1.21057000	-0.15951400
C	3.61328200	-2.06773700	0.16431400
C	4.83797600	-1.55488000	0.57533100
H	4.11900400	1.75425200	0.42911700
H	1.91646500	0.82820500	-0.31858400
H	3.47575200	-3.15016500	0.09419100
H	5.65383800	-2.23813400	0.82378700
C	6.37047900	0.37187800	1.13941200

H	6.39994000	1.46671600	1.06389400
H	6.56599000	0.10020100	2.18778300
H	7.19596500	-0.03444800	0.53697100
C	1.23755500	-1.78158000	-0.61618600
H	0.87818900	-2.51772000	0.12936900
H	1.37326800	-2.33294400	-1.56770300
O	0.30932800	-0.74760300	-0.79288800

- ➢ Leaving Group (2,2,2-trichloroacetimidic acid)

O	1.41068400	1.76972100	0.00063400
C	1.22942300	0.58445600	0.00047900
C	-0.21832200	-0.01585500	0.00002600
Cl	-0.40891000	-1.03483300	-1.45483200
Cl	-1.40873700	1.26855600	0.00106500
Cl	-0.40917400	-1.03740500	1.45305300
N	2.19518800	-0.35861200	0.00056200
H	3.15865600	-0.05067900	0.00012000
H	1.97890700	-1.34581500	-0.00001400

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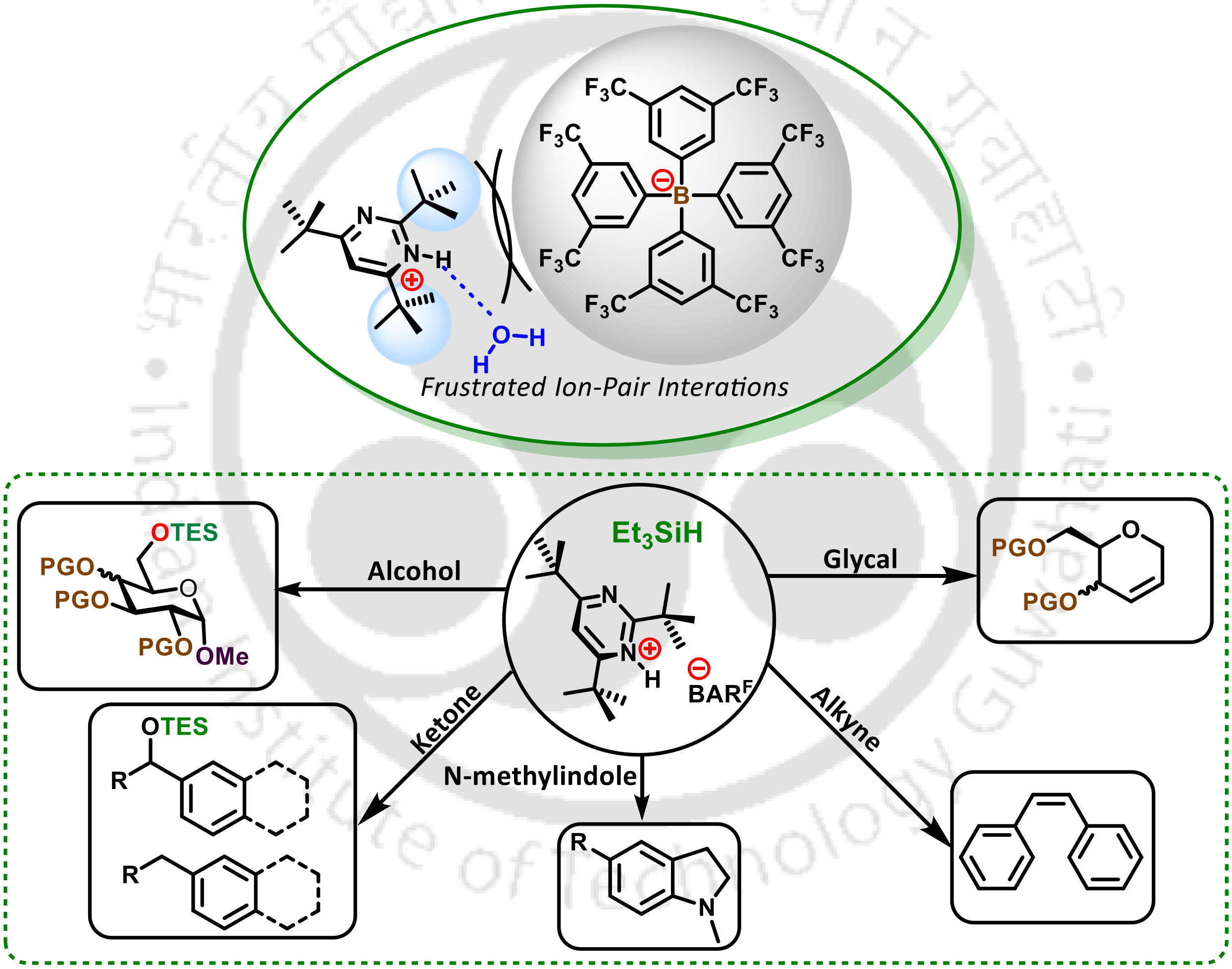
Chapter IV

Activation of Si-H bond under Metal-free conditions: Its applications



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Activation of Si-H bond under Metal-free conditions: Its applications

4.1 Introduction

The superelectrophilic silylium cations though took decades to establish their existence in the condensed phase[1-3] have seen enormous progress in recent decades (**Figure 4.1**). The advent of weakly coordinating anion chemistry has paved the way to stabilize, isolate, and utilize these superelectrophilic species for various organic transformations, which was not possible earlier. The activation of the Si-H bond has been one of the ways to generate highly reactive silicon cations and is achieved using different kinds of catalysts and additives including the transition metal catalysts via oxidative addition to the metals.[4] Several reports discussed the Si-H bond cleavage heterolytically, resulting in interesting silylium cations (**Figure 4.1**).[5-7] A Few p-block elements have been studied in view of forming the highly reactive silylium cations by the activation of the Si-H bond through their Lewis acidity by increasing the δ^+ character of Si-atom.[8, 13b] Once the silylium cation is formed or present in the reaction mixture, it is seen functionalizing several organic moieties in an effective means with its superelectrophilicity.[12] The presence of a Lewis base, like carbonyl group also been proven to affect the activation of Si-H bond heterolytically in light of FLP chemistry.[13]

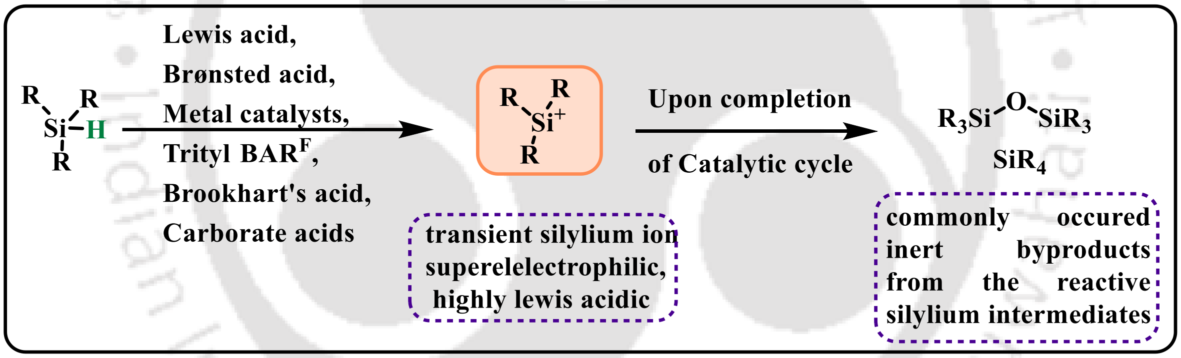
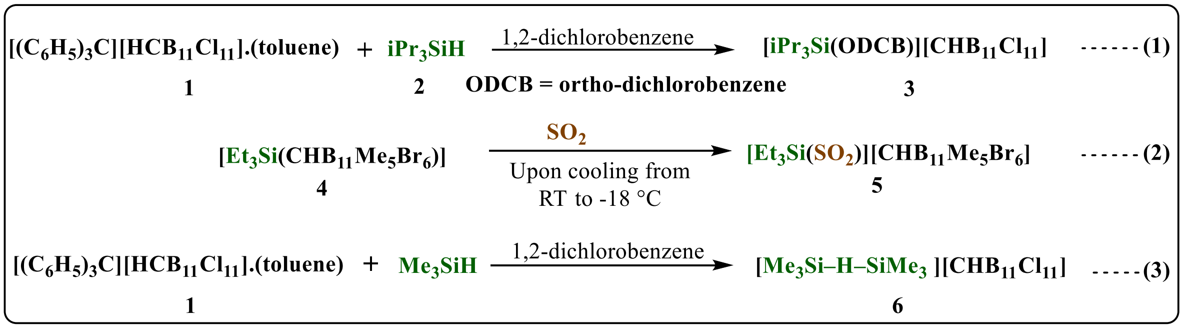


Figure 4.1 Insights on previous methods for the silyl cation generation

4.1.1 Literature reports

Sizeable research is done in studying the formation of silylium cations through the well-established Bartlett-Condon-Schneider (BCS) reaction. The Corey's reaction of hydride acceptor



Scheme 1. Silylium ion stabilization with carboranes and solvent molecules

from hydrosilanes, where the generated silylium ion is stabilized with weakly coordinating anions (WCA) like carborates[10] or solvent molecules (**Scheme 1**),[10a] BArF (**Scheme 2**)[10b] as donors. There are several studies done that help understand their behavior as efficient catalysts in several organic transformations because of their enormous Lewis acidity through the regeneration of active catalyst, the silylium ion in reaction medium by protonation.[5,7]

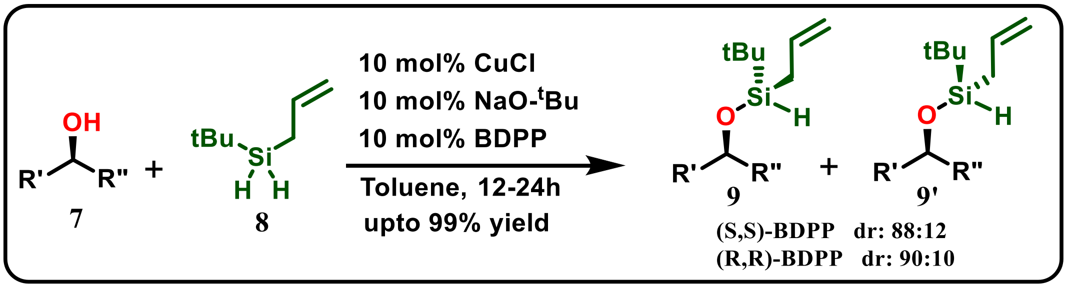
$$\underset{\mathbf{7}}{[(C_6H_5)_3C][B(C_6F_5)_4]} + Et_3SiH \xrightarrow[\text{yellow solid to white solid 2days}]{\text{toluene}} \underset{\mathbf{8}}{[Et_3Si(toluene)][B(C_6F_5)_4]} + \underset{\mathbf{9}}{(C_6H_5)_3CH}$$

triphenylmethane (**9**) was removed through hexnae wash

Scheme 2. Silylium ion stabilization with solvent and BArF anion

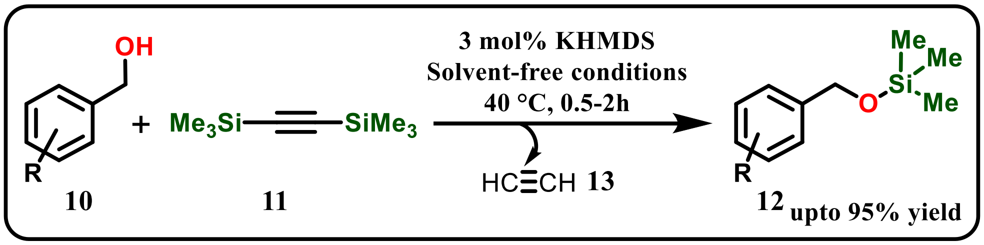
The preparation of these reactive intermediates involving molecular acids like halogenated carborates[14] (Reed's carborate acids) is termed costly and tedious despite the resulting highly Lewis acidic and strongly electrophilic silylium ions which are useful in catalysis. An intriguing point observed in some of the research findings about silylium cations is regarding their catalysis in the presence of protic impurities like water from undried solvents.[15-17] Apparently, the presence of traces of water is also enough to quench the silylium cation and hamper its anticipated catalytic applications in the reaction medium. This results in the protonated silanol intermediates ($R_3Si(OH_2)^+$) formed as Lewis adducts with the silylium ion (corroborated with XRD crystallographic characterizations)[16] which in turn, are nothing but strong Brønsted acids. These crucial findings warrant the *competing* proton catalysis in the reaction medium from silylium ion catalysis. However the researchers' observations state that the electrophilic proton can hold a role in regenerating[17] the silylium cation through the "self-repair of catalyst" and hence it is worth mentioning statement[12] that "*traces of water present in the reaction is not detrimental to silylium ion catalysis, but leading to disiloxanes as the inert byproducts*".

The silylium ion chemistry has shown diverse applications of synthetic interest as well as catalysis.[5a,7a,12,18] Through the activation of the Si-H bond of readily available, simple, and stable hydrosilanes, applications like hydrosilylation[4a,8,13a] of aldehydes, imines,[19] ketones,[20] nitriles,[21] alkenes,[22] alkynes[23,] and alcoholysis[24] are well explored. The silane activation is used in cleaving the alkyl ethers,[25] deoxygenation of alcohols,[26] hydrosilylation of Pyridines[27,] and also hydrodefluorination[28] owing to their fluorophilicity alongside high electrophilicity.



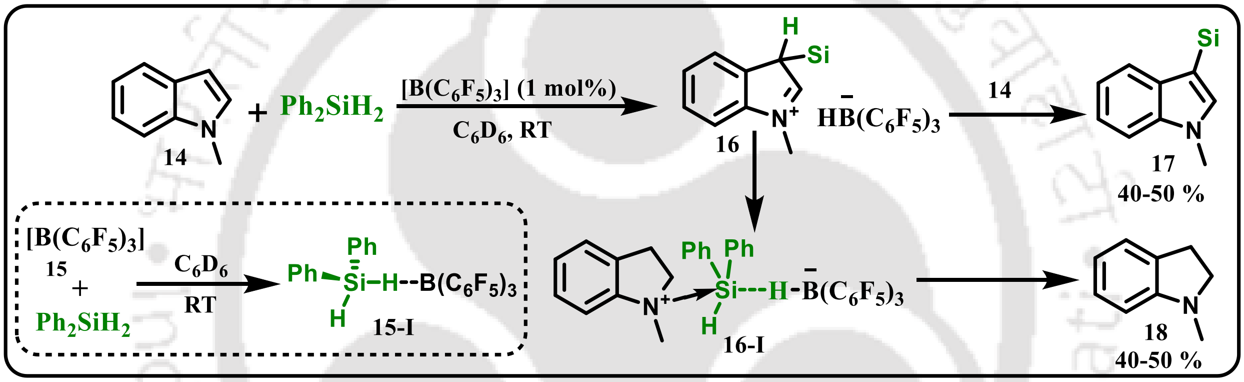
Scheme 3. Catalytic Asymmetric Silane Alcoholysis[24a]

Disproportionation of indoles using $B(C_6F_5)_3$ and R_2SiH_2 *via* silylation was reported with indoline as a byproduct in 40-50% (**Scheme 5**).[1]

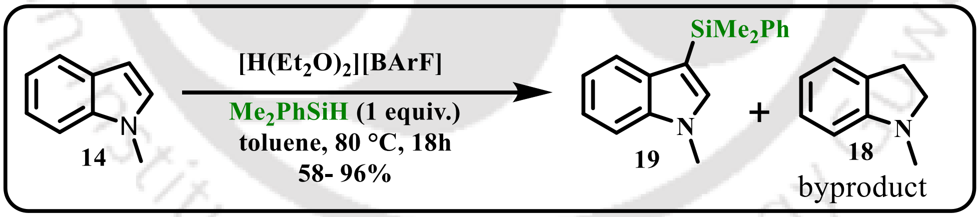


Scheme 4. Silylation of Alcohols with Alkynylsilanes[24b]

Oestreich group synthesized C-3 silyl indoles via proton catalysis using Brookhart's acid ($[H(Et_2O)_2]^+[BArF]^-$) and hydrosilanes where indolines were observed as byproducts due to the competing silylium ion catalysis (**Scheme 6**).[7b]



Scheme 5. Disproportionation reaction of indoles



Scheme 6. Proton-catalyzed C-H silylation of indoles

2,4,6-tri-*tert*-butylpyrimidine (TTBP) is well known for its utility as a proton scavenger[31-32] in reactions involving strong acids like triflic acids, where it is expected to take up the proton generated in-situ and quench the acid but not to behave as a Brønsted acid by itself. The utility of bulky pyridine bases (TTBP, TTBPy, etc.,) as acid scavengers is solely based on this advantage arising from the bulky alkyl groups present at the *ortho* positions to the protonated pyridinium/pyrimidinium ion. The sterically strained ion pairs as organocatalysts in several glycosylation reactions were explored by our group in the past and also currently.[31-32] Pyrimidines are usually electron-deficient and the counter-ions, the pyrimidinium cations are relatively more acidic. From the previous chapter, we found that the tri-*tert*-butylpyridinium salts behave as strained ion pairs and can activate alcohols and allylsilanes (**Figure 4.2**).

We were curious to understand the behavior of the more electron-deficient and highly sterically hindered tri-*tert*-butylpyrimidinium salts. We envisioned that due to the strain within the ion-pair added to the electron-deficient nature, would make the cation entity even more unstable and the resulting ion-pair should behave as a much stronger Bronsted acid and can activate silanes to generate silyl cations. Alongside a weakly coordinated anion, it is equivalent to a proton sandwiched between two weakly coordinating entities. Also, the steric bulk around the nitrogen would not allow the bulky pyrimidine to quench the Lewis acidity of the silicon cation. However, in this chapter, we show that these sterically hindered pyrimidinium salts activate water/alcohol[31a,32a] which in turn activates the Si-H bond.

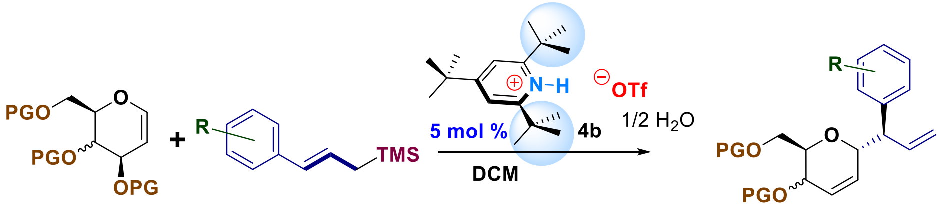
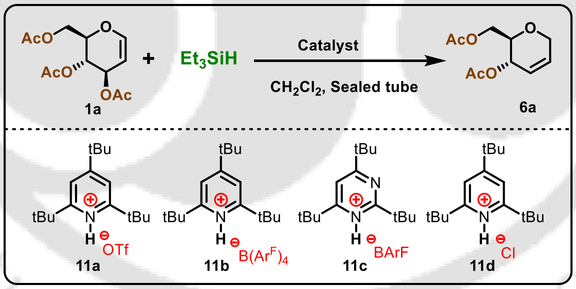


Figure 4.2 Activation of allylsilanes by tri-*tert*-butylpyridinium triflate

4.2 This Work: Results and Discussion

4.2.1 Activation of Si-H bond: 1-deoxy glycal formation: Optimization studies

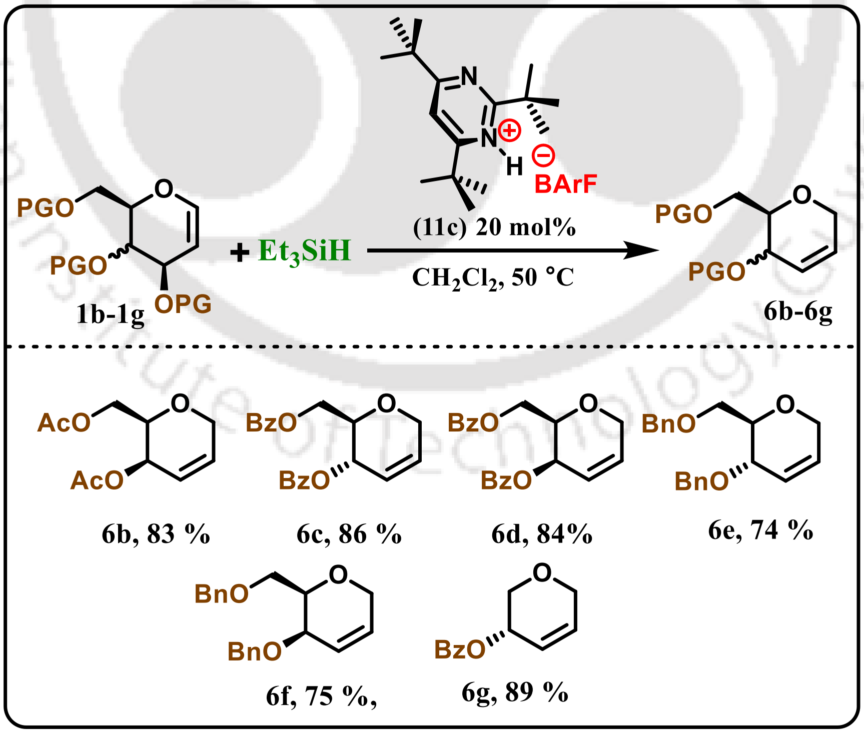
We started our initial experiments with TTBPyH.OTf (**11a**) to see if triethylsilane can be activated



entry	catalyst	catalyst mol%	Temp. (°C)	Time	Yield (%)
1	**11a**	20	RT	-	--[a]
2	**11a**	20	50	30 min	--[b]
3	**11b**	20	RT	--	--[a]
4	**11b**	20	50	30 min	34
5	**11c**	20	RT	--	--[a]
6	**11c**	20	50	30 min	86
7	**11d**	20	50	--	--[a]
8	**11c**	5	50	30 min	37
9	**11c**	**10**	**50**	**30 min**	**84**[c]

Table 4.1 Reaction Conditions: glycal **1a** (1 equiv.), Triethylsilane (3 equiv.) in CH_2Cl_2 (0.34-0.42M). a) starting material remained as such. b) starting material was decomposed. c) performed the reaction in Youngs' pressure tube/sealed tube by applying *vacuum* before heating the reaction mixture to 50 °C.

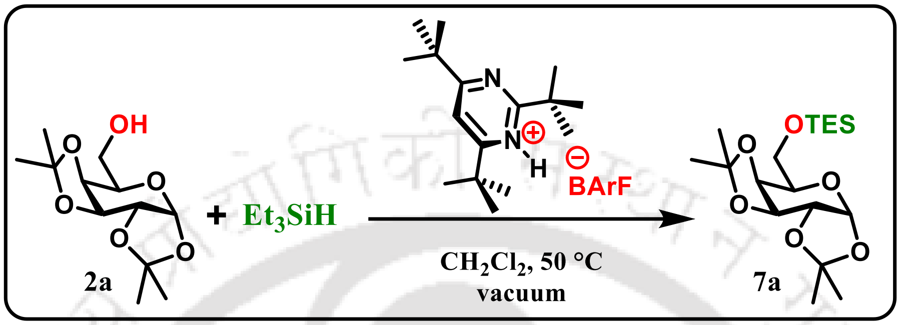
and donate its hydride to the glycal (**1a**) in the reaction medium with CH_2Cl_2 as the solvent.1-deoxyglycals are usually achieved by strong Lewis acid catalysts like $BF_3.OEt_2$ in the presence of triethylsilanes. To our surprise, the triflate salt did not give the expected product (Table 4.1, Entry 1) but the starting material got decomposed upon heating the reaction mixture to 50 °C (Table 4.1, Entry 2). When we changed the anion to sterically bulkier and non-coordinating BArF (**11b**), there was no reaction at RT (Table 4.1, Entry 3), but there was the formation of the expected product (**6a**) when the reaction was performed at 50 °C although in low yield of 34% in 60 min leaving the remaining starting material (**1a**) unaffected (Table 4.1, Entry 4). After observing this result, we changed the cation to tri-*tert*-butylpyrimidinium with BArF as the counter ion. The catalyst **11c** (20 mol%) was able to give the expected product in 86% yield at 50 °C while being unreactive at RT (Table 4.1, Entry 6). There was no reaction with hydrochloride salt (**11d**) even at 50 °C (Table 4.1, Entry 7). With better reaction conditions in hand with catalyst **11c**, we tried a reaction with decreased catalyst loading (5%) which resulted in lowered yield, 37% (Table 4.1, Entry 8). When we used 10 mol% of **11c**, with 3 equivalents of triethylsilane gave 84% of **6a** in 30 min (Table 4.1, Entry 9). Instead of triethylsilane, the same reaction was performed on **1a** with triphenylsilane (2 equiv.), which has also resulted in expected product **6a** in 80% yield in 40 min. Upon getting the optimized conditions, the reactions were performed on different glycals with varied functional groups and sugars which resulted in good to excellent yields. Glycals (**1b-1g**) with Benzoyl and Benzyl protecting groups were also treated with triethylsilane under standard conditions, which lead to expected 1-deoxy-ferrier glycals in 74-89% yields. All these reactions were performed in a screwed cap vial or schlenk flask or sealed tube.



Scheme 7. Reaction Conditions: glycal (**1b-1g,** 1 equiv.), Triethylsilane (3 equiv.) in CH_2Cl_2 (0.34-0.42M) and catalyst **11c** (10 mol%), screwed cap vial/Schlenck flask/Youngs' pressure tube/sealed tube, *vacuum*, 50 °C.

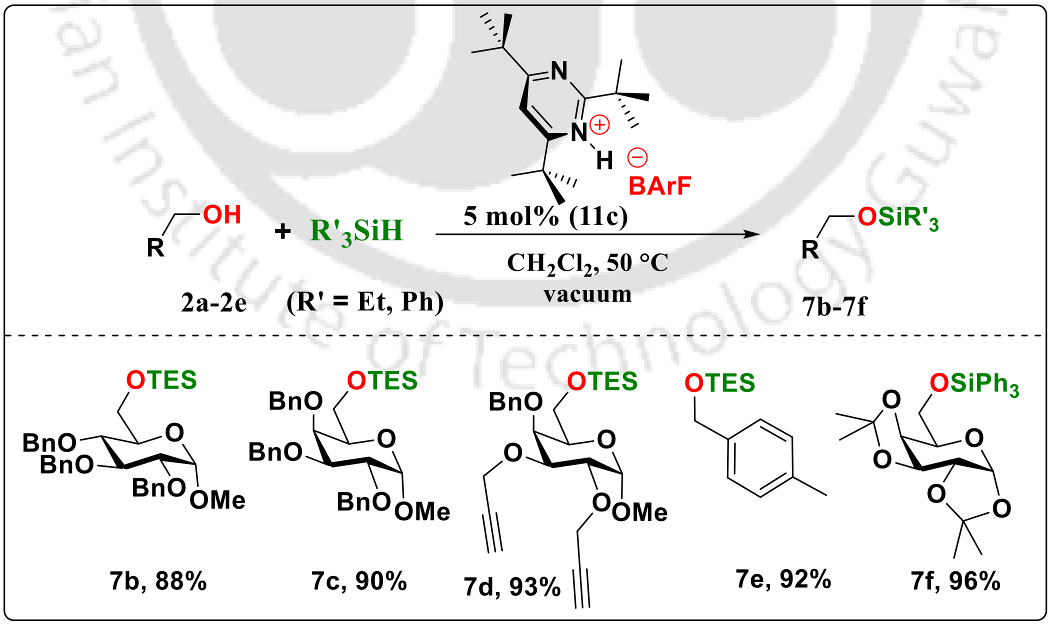
4.2.2 Silyl cation trapping: Silylation of alcohols

To test the ability of the sterically hindered pyrimidine salt **11c** to activate the Si-H bond and to generate the silyl cation, we tested the conditions towards the silylation of alcohols under this hindered pyrimidine catalysis. For that purpose, sugar alcohol **2a** was treated under standard conditions.



entry	catalyst	catalyst mol%	Temp. (°C)	Time	Yield (%)
1	**11c**	10	50	8h	61
2	**11c**	20	50	3.5h	77
3	**11c**	10	50	1.5h	83[a]
4	**11c**	5	50	1.5h	86[a]

Table 4.2 Reaction Conditions: alcohol (**2a**, 1 equiv.), Triethylsilane (2 equiv.) in CH_2Cl_2 (0.34-0.42M) and catalyst. a) Performed the reaction in Youngs' pressure tube/ ace pressure tube by applying *vacuum* before heating the reaction mixture to 50 °C.



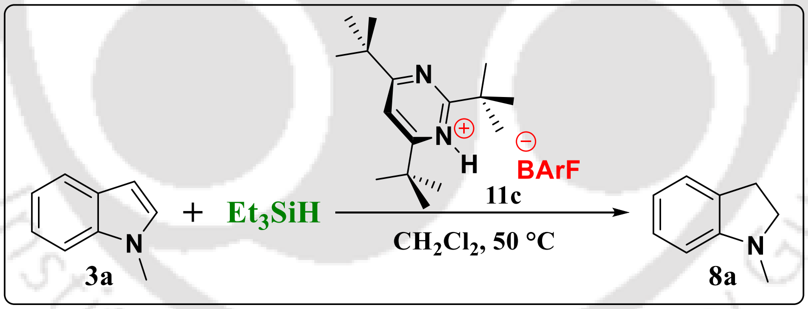
Scheme 8. Reaction Conditions: alcohol (**2a-2e**, 1 equiv.), Triethylsilane/Triphenylsilane (2 equiv.) in CH_2Cl_2 (0.34-0.42M) and catalyst (5 mol%), reactions were performed in Youngs' pressure tube/ ace pressure tube by applying *vacuum* before heating the reaction mixture to 50 °C.

The reaction was completed in 8h with 10 mol% of catalyst (**11c**) giving the expected product in 61% yield (Table 4.2, entry 1). When we increased the catalyst loading to 20 mol%, the reaction was completed in 3h giving **7a** in 77% yield (Table 4.2, entry 2). Then we performed the reaction under *vacuum* in Youngs' pressure tube/ace pressure tube at 50 °C which led to 83% of expected product **7a** in 1.5h (Table 4.2, entry 3). We tried to decrease the catalyst loading further to 5 mol%, which resulted in 86% of **7a** in 1.5h (Table 4.2, entry 4).

Taking this as the optimized condition, different sugar alcohols (**2a-2d**) were treated with triethylsilane/ triphenylsilane resulting in the expected products (**7b-7d, 7f)** in excellent yields (88-96%). To observe if non-sugar alcohols can be utilized, *p*-methyl benzyl alcohol (**2e**) was treated under standard conditions, giving the expected product **7e** in 92% yield (**Scheme 2**). In all these reactions, the alcohol (**2a-2e**) and catalyst (**11c**) were dissolved in dry CH_2Cl_2 (0.38M) followed by the addition of silane under argon atmosphere, and in the absence of atmosphere.

4.2.3 Reduction of indoles using Silane

Encouraged by the efficiency of the current protocol in the activation of Si-H bond in reaction medium under mild conditions, we were curious to see if the reactivity can be utilized for the silylation of indoles under metal-free conditions. When simple Indole was reacted with triethylsilane under standard conditions, with 5 mol% of the catalyst, there was no reaction. Upon reacting N-methyl indole with triethylsilane under standard conditions (with 5 mol% catalyst), there was no reaction (Table 4.3, entry 1).

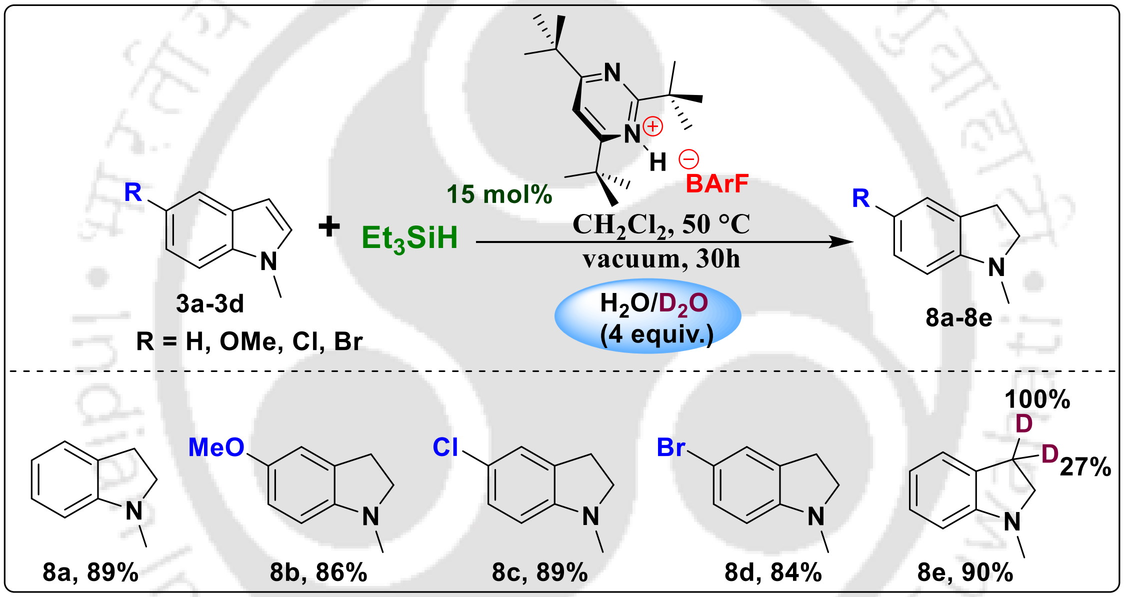


entry	equiv. of Et_3SiH	catalyst mol%	equiv. of H_2O	Time	Yield (%)
1	3	5	-	3d	-
2	3	10	-	3d	15
3	4	10	-	3d	26
4	5	15	-	3d	30
5	5	15	2	2d	65
6	**5**	**15**	**4**	**1.5d**	**86**

Table 4.3. Reaction Conditions: N-Me-indole (1 equiv.), Triethylsilane in CH_2Cl_2 (0.34-0.42M) and catalyst **11c**, Youngs' pressure tube/ ace pressure tube, *vacuum*, 50 °C.

When N-methyl indole (**3a**) was treated with 3 equiv. of triethylsilane and 10 mol% of catalyst, under otherwise standard conditions, there was formation of N-methyl indoline (**8a**) although in poor yield (15%) (Table 4.3, entry 2) and there was not much improvement in yield with 4-5 equiv of triethylsilane even after 3 days of reaction time giving **8a** in 26-30% yield (Table 4.3, entry 3&4 respectively). To understand the origins of the source of the proton, the reaction was repeated by adding 2 equiv. of water under otherwise standard conditions (Table 4.3, entry 5) which resulted in the formation of **8a** in 65% yield in 2 days. With 4 equiv. of water, the starting material was completely consumed giving 86% of N-methyl indoline (**8a**) in 1.5 days (Table 4.3, entry 6).

Elated by the metal-free hydrogenation of indoles to indolines under these conditions, we have treated a few substituted N-methyl indoles (**3b-3d**) to yield the reduced products, N-methyl indolines (**8b-8d**) in very good yields (84-89%).



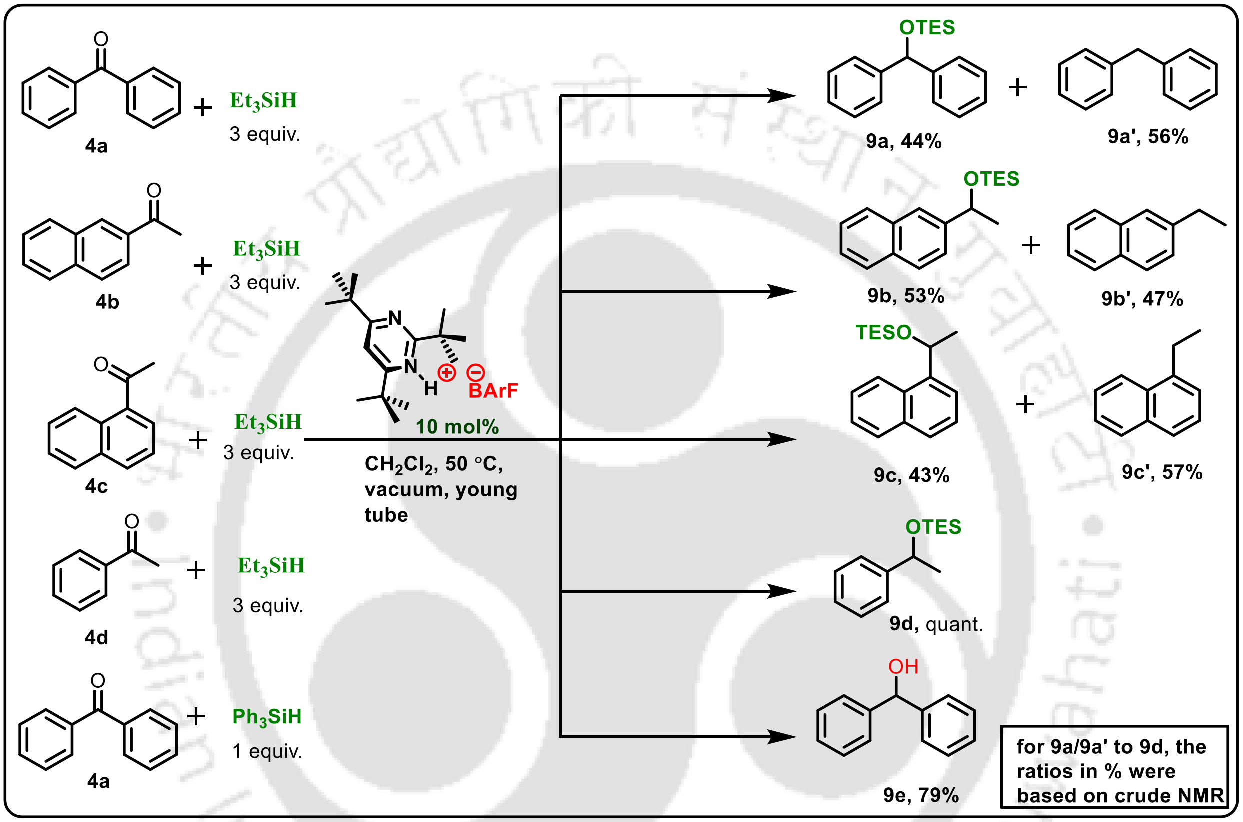
Scheme 9. Reaction Conditions: N-Me-indole (1 equiv.), Triethylsilane (5 equiv.) in CH_2Cl_2 (0.34-0.42M), H_2O/D_2O (4 equiv.), catalyst **11c** (15 mol%), Youngs' pressure tube/ace pressure tube, *vacuum*, 50 °C

As a piece of evidence for the role of water in the formation of reduced indole products, we have treated N- methyl indole (**3a**) with D_2O (4 equiv.) and triethylsilane under standard conditions, which led to the deuterated N-methylindoline (**8e**) in excellent yield (89%). However, it was interesting to note a 27% H/D scrambling of the existing indole C-3 proton along with the 100 % incorporation of a new deuterium. (**8e, Scheme 9**).

4.2.4 Reduction of ketones using Silane

Encouraged by the results of Si-H activation under metal-free conditions, we tried to reduce ketones using the current protocol, with 10 mol% of catalyst **11c**. When we treated benzophenone

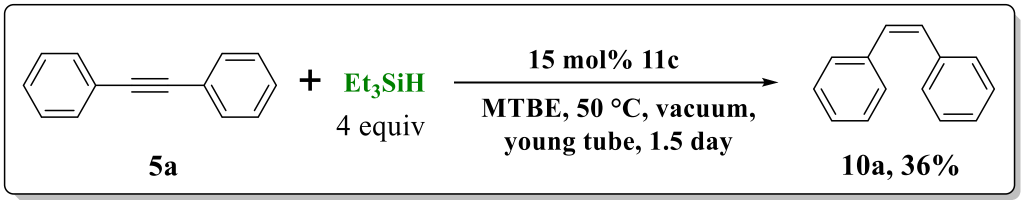
(**4a**) with 3 equiv. of TESiH, we have observed the formation of both partially reduced (**9a**) and completely reduced (**9a'**) products in a 44:56 ratio (based on crude ^{1}H NMR analysis). Similarly, 1-acetylnaphthalene (**4b**) and 2-acetylnaphthalene (**4c**) also resulted in a mixture of products. However, simple acetophenone (**4d**) resulted in the quantitative formation of only the partially reduced silylether product (**9d**) exclusively. When we treated benzophenone **4a** with one equivalent of bulky triphenylsilane under otherwise standard conditions, resulted in diphenylmethanol (**9e**) in 79% yield.



Scheme 10. Reaction Conditions: ketone (**4a-4d**, 1 equiv.), Triethylsilane/ Triphenylsilane in CH_2Cl_2 (0.34-0.42M) and 10 mol% 11c, Youngs' pressure tube/ace pressure tube, *vacuum*, 50 °C.

4.2.5 Reduction of Alkyne using Silane

Encouraged by the metal-free reductions under the bulky pyrimidinium catalysis, we tested the current protocol toward the highly challenging reduction of alkynes. When diphenylacetylene (**5a**) was treated with triethylsilane under 15 mol% of catalyst **11c** in CH_2Cl_2, no reaction was



Scheme 10. Reduction of Diphenylacetylene

observed. However, the same reaction when performed under MTBE as the solvent resulted in the formation of 36% of the partially reduced cis-stilbene (**10a**) (**Scheme 10**). Unfortunately, the yields of the reaction could not be increased despite changing various parameters.

4.3 Mechanistic Studies

4.3.1 Control experiments

Control experiments were performed which gave interesting insights into the reaction mechanism. The reaction presented in Eq1-Eq3, reveals the significance of the bulky pyrimidinium salt in the observed catalytic transformations (**Figure 4.2**).

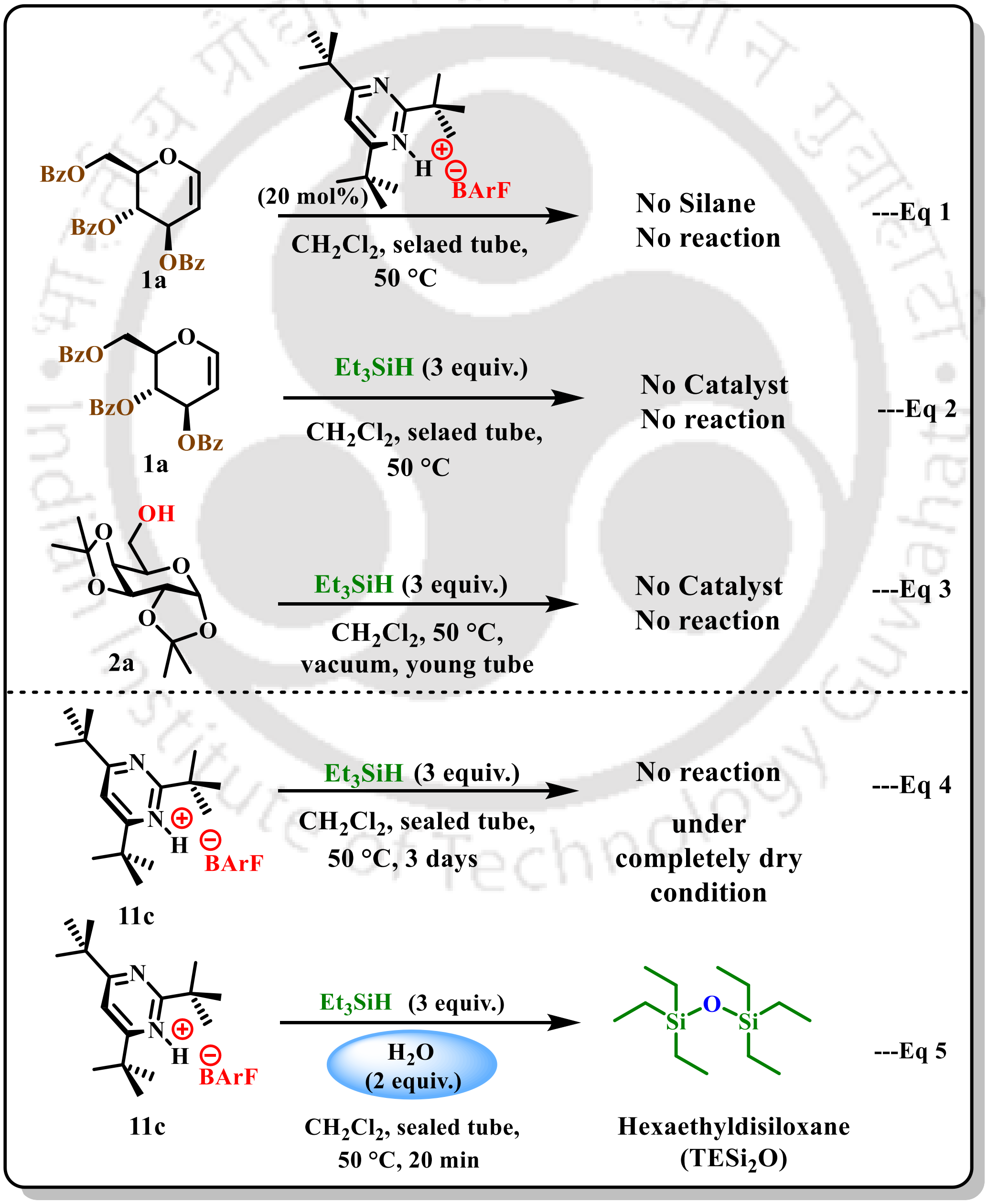


Figure 4.2. Control experiments

The glycal (**1a**) was reacted with the catalyst in the absence of silane under otherwise standard conditions, where the starting material remain unchanged for days (**Figure 4.2, Eq 1**). When glycal (**1a**) was reacted with silane in the absence of catalyst under otherwise standard conditions, the starting material remains unreacted for days (**Figure 4.2, Eq 2**). Similarly, the alcohol protection too does not work when performed in the absence of the catalyst **11c**. (**Figure 4.2, Eq 3**). Interestingly, it was observed that there was no reaction under completely dry conditions in the case of 1-deoxy glycal formation. To understand if the reaction between bulky pyrimidnium cation and triethylsilane would lead to the generation of silyl cation via a dehydrogenative pathway, we reacted 1 equiv. of the catalyst **11c** with distilled triethylsilane (1 equiv.) and refluxed it to 50 °C both in $CDCl_3$ (dry) or CH_2Cl_2 (dry) separately. However, no reaction was observed (**Figure 4.2, Eq 4**). On the other hand, the same reaction was performed in the presence of 2 equiv. of H_2O, the quantitative formation of hexaethyldisiloxane (TES-O-TES) was observed in 20 mins (**Figure 4.2, Eq 5**).

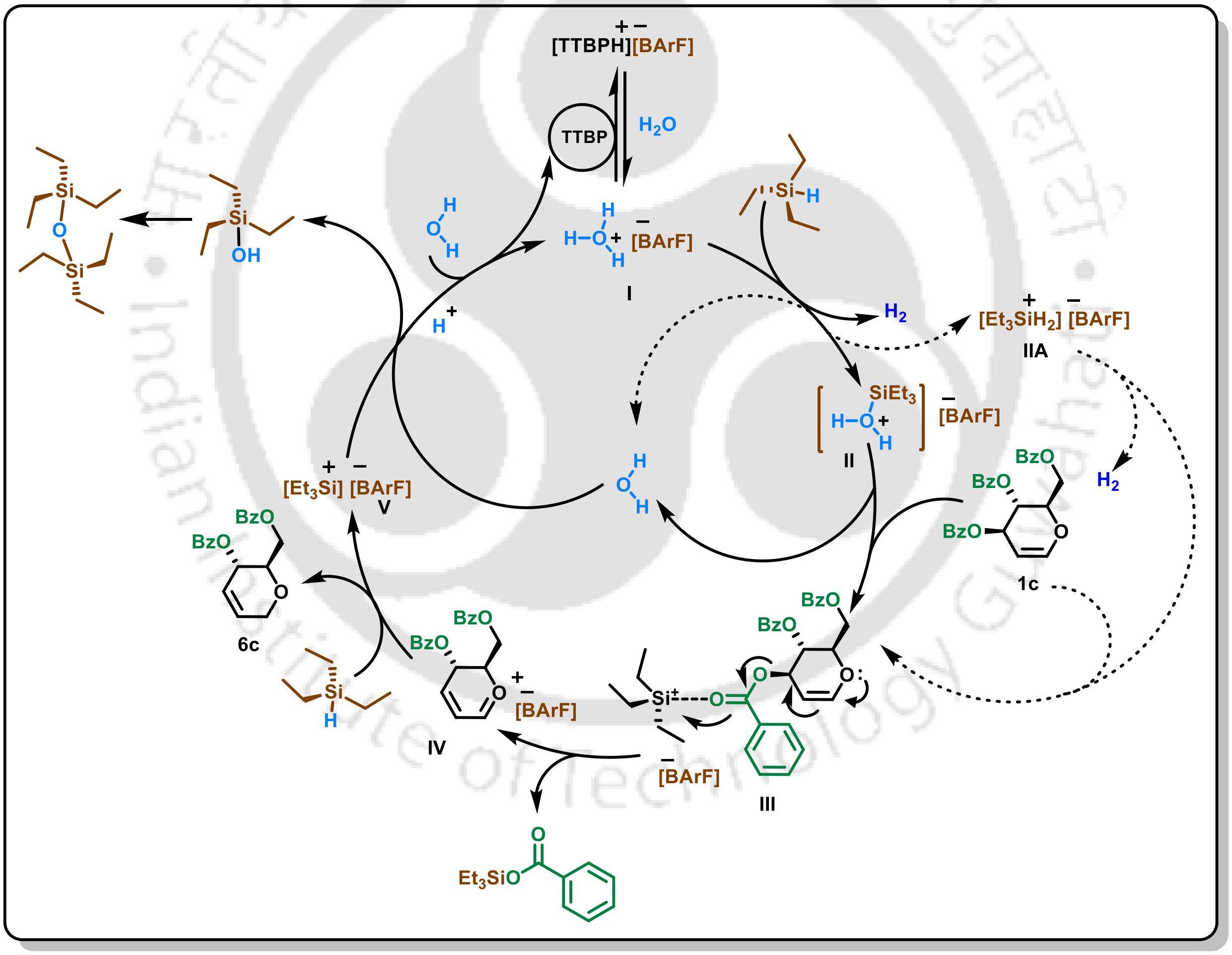


Figure 4.3. Proposed mechanism for the formation of 1-deoxy glycal

The reaction mixture was concentrated under *vacuum* to remove solvent and dissolved in $CDCl_3$ and recorded the ^1H NMR. In a reaction when a stoichiometric amount of water was not present in the reaction mixture, the formation of tetraethylsilane (Et_4Si) was observed along with hexaethyldisiloxane in crude NMR (Please refer to Experimental section).

4.3.2 Proposed Mechanisms

Based on the understanding gained from the control experiments and insights from the literature, mechanisms were proposed for the reactions. The sterically and hence electronically strained catalyst, $[TTBPH]^+[BArF]^-$ was believed to activate the water molecule present in the reaction mixture leading to the transient and highly acidic hydronium BArF (**I**), which can form a protonated silanol-based silylium intermediate (**II**) or dihydrosilylium based intermediate (**IIA**) which may further interact with the glycal eliminating H_2O or H_2 respectively leading to the formation of oxocarbenium ion (**IV**) through silylium ion interaction (**III**) with the leaving moiety at C-3 position of glycal (**1a**) followed by the elimination of Et_3SiOBz. The hence-formed reactive intermediate (**IV**) reacts with the triethylsilane leading to 1-deoxy Ferrier glycal (**6c**) as the product, generating silylium BArF (**V**) which leads to the inert byproduct hexaethyldisiloxane via triethylsilanol and hence regenerating the hydronium BArF (**I**) (**Figure 4.3**).

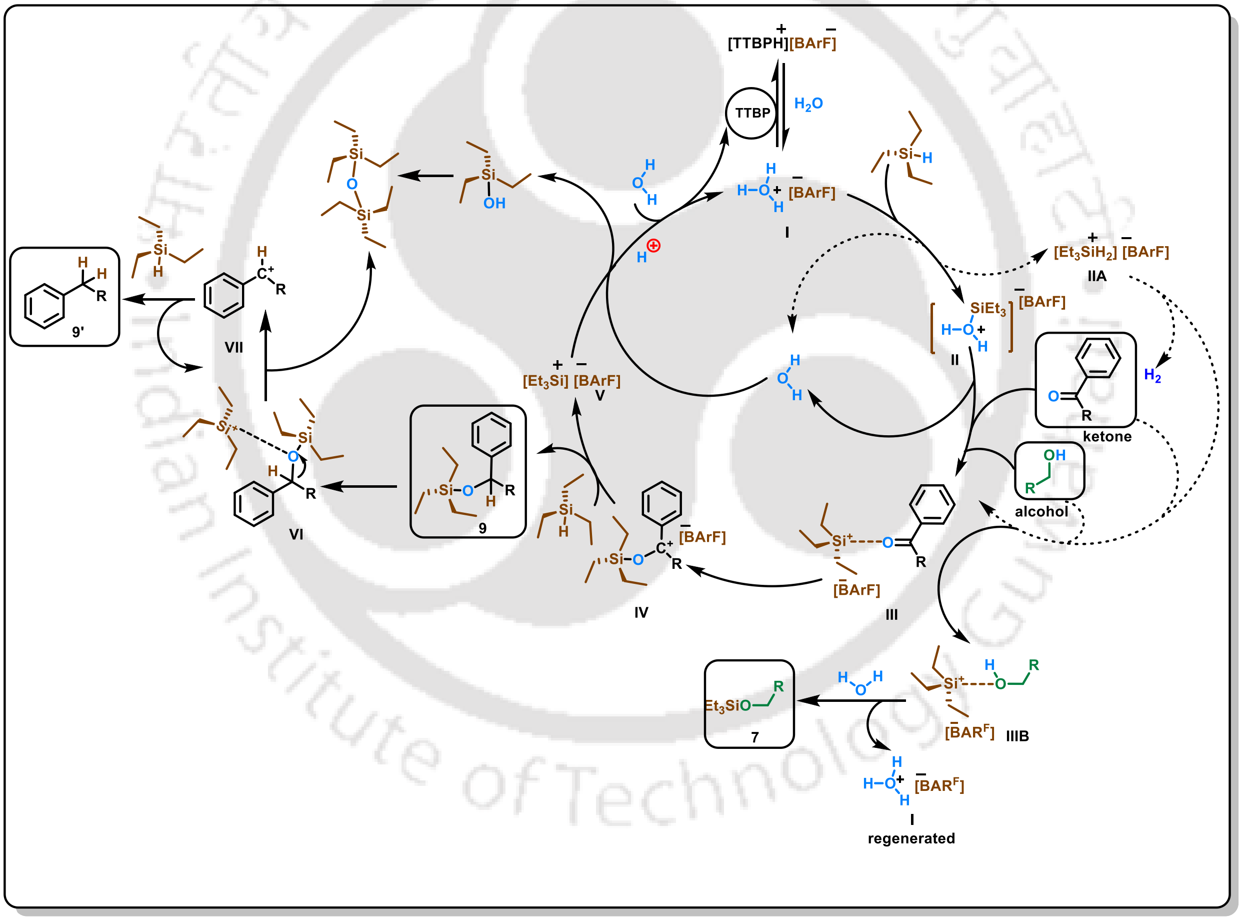


Figure 4.4. Proposed mechanism for the reduction of ketones and silylation of alcohol

Similar to the mechanism proposed for glycal (**Figure 4.4**), the reduction of indoles can be explained similarly. The hydronium BArF (**I**) formed in the reaction mixture may lead to the protonated silanol (**II**) or intermediate **III**, which reacts with nucleophilic N-methylindole (**3a**) forming intermediate **III** which upon reacting with water molecule will transform into iminium intermediate (**IV**).

This Wheland intermediate (**IV**), reacts with triethylsilane leading to the formation of indoline (**8a**). The iminium intermediate (**IV**) can be attacked by triethylsilane to give back the starting material indole and intermediate **IIA**. This intermediate again can lead to III by reacting with indole and the catalytic cycle can proceed to the reduced product, N-methylindoline (**8a**) as shown in **Figure 4.5**

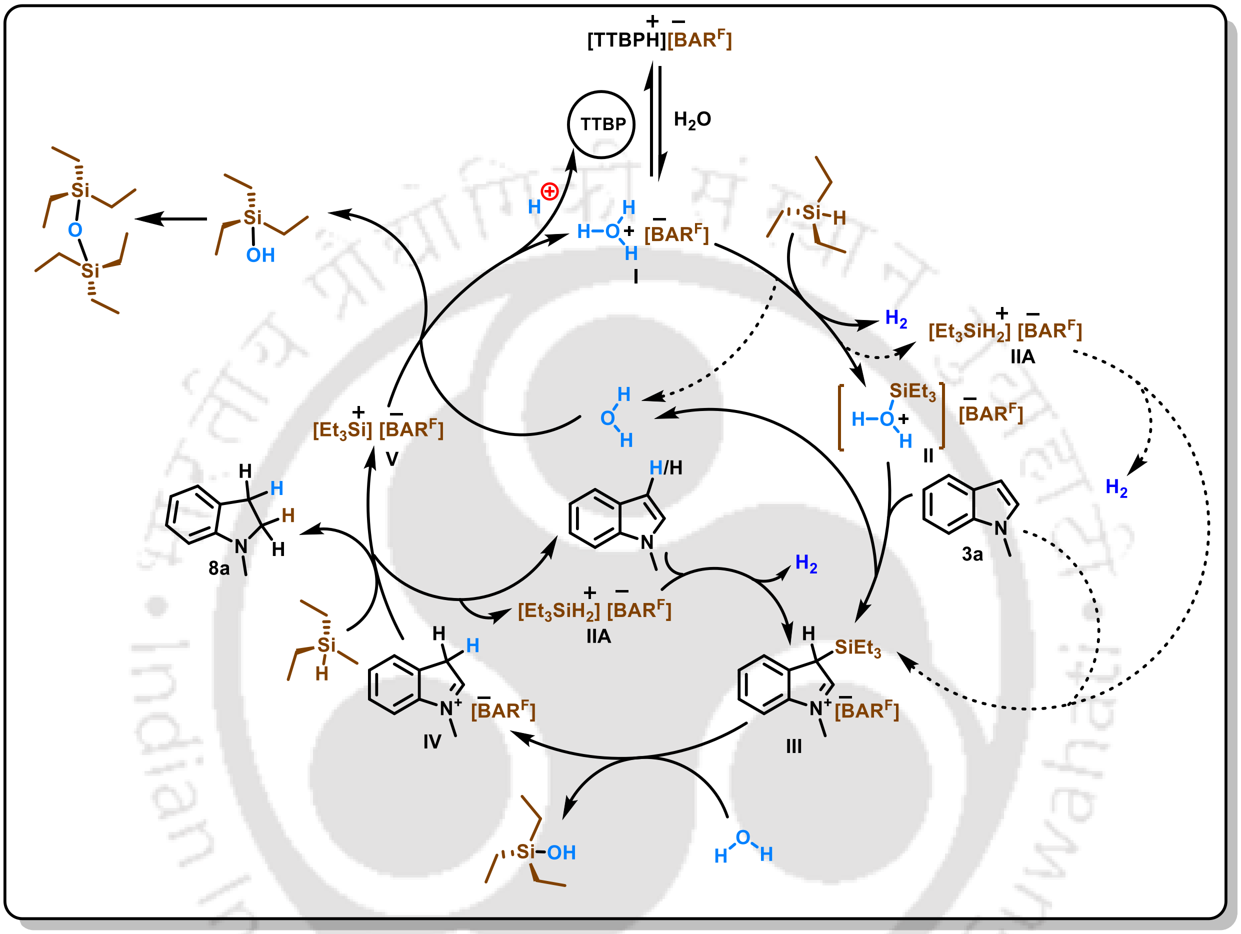


Figure 4.5. Proposed mechanism for reduction of N-methylindole

4.4 Experimental section

4.4.1. General Information

All solvents purchased were of commercial grade and reagents were purchased from Sigma-Aldrich, Merck, Carbosynth, Spectrochem, Alfa Aesar, Avra and used without further purification for reactions.

4.4.2. Analysis*:*

Reactions were monitored by TLC on Kieselgel 60 F254)Merck(. Detection was done by examination under UV light)254 nm(and by charring with 10% sulfuric acid in water. Purification was performed by column chromatography in normal phase using silica gel]Merck, 60-120 mesh[.

Extracts were concentrated in vacuo using both Büchi rotary evaporator)bath temperatures up to 40 °C(at a pressure of either 15 mmHg)diaphragm pump(and 0.7 mmHg)oil pump(, at rt. ^{1}H- and ^{13}C NMR were recorded on a Bruker 600 MHz,500 MHz, and 400 MHz spectrometer using $CDCl_3$ as solvent. Chemical shift values are reported in ppm with the solvent as the internal standard)$CDCl_3$: δ 7.26 for ^{1}H, δ 77.16 for ^{13}C(. Data are reported as follows: chemical shifts)δ(, multiplicity)s = singlet, d = doublet, dd = doublet of doublet, ddd = doublet of doublet of doublets, dt = doublet of triplet, t = triplet, td = triplet of doublet, q = quartet, m = multiplet(, etc., coupling constants J)Hz(, and integration. High-resolution mass measurements were performed using Agilent technologies mass spectrometer)QTOF-ESI mode(. The diastereomeric ratios were calculated from NMR data. Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments. The X-ray diffraction data were collected at 296 K with Mo Kα radiation (λ = 0.71073 Å) using a Micro focused based Bruker D8 QUEST diffractometer equipped with a graphite monochromator. Apex IV software was used for data collection and also for indexing the reflections and determining the unit cell parameters; the collected data were integrated using Saint Software. The structures were solved by Intrinsic phasing and refined by full-matrix least-squares calculations using SHELXTL 2018 software. All the non-H atoms were refined in the anisotropic approximation.

4.4.3. Starting materials used in this study)Glycals, Alcohols, Indoles, Ketones, Alkyne(

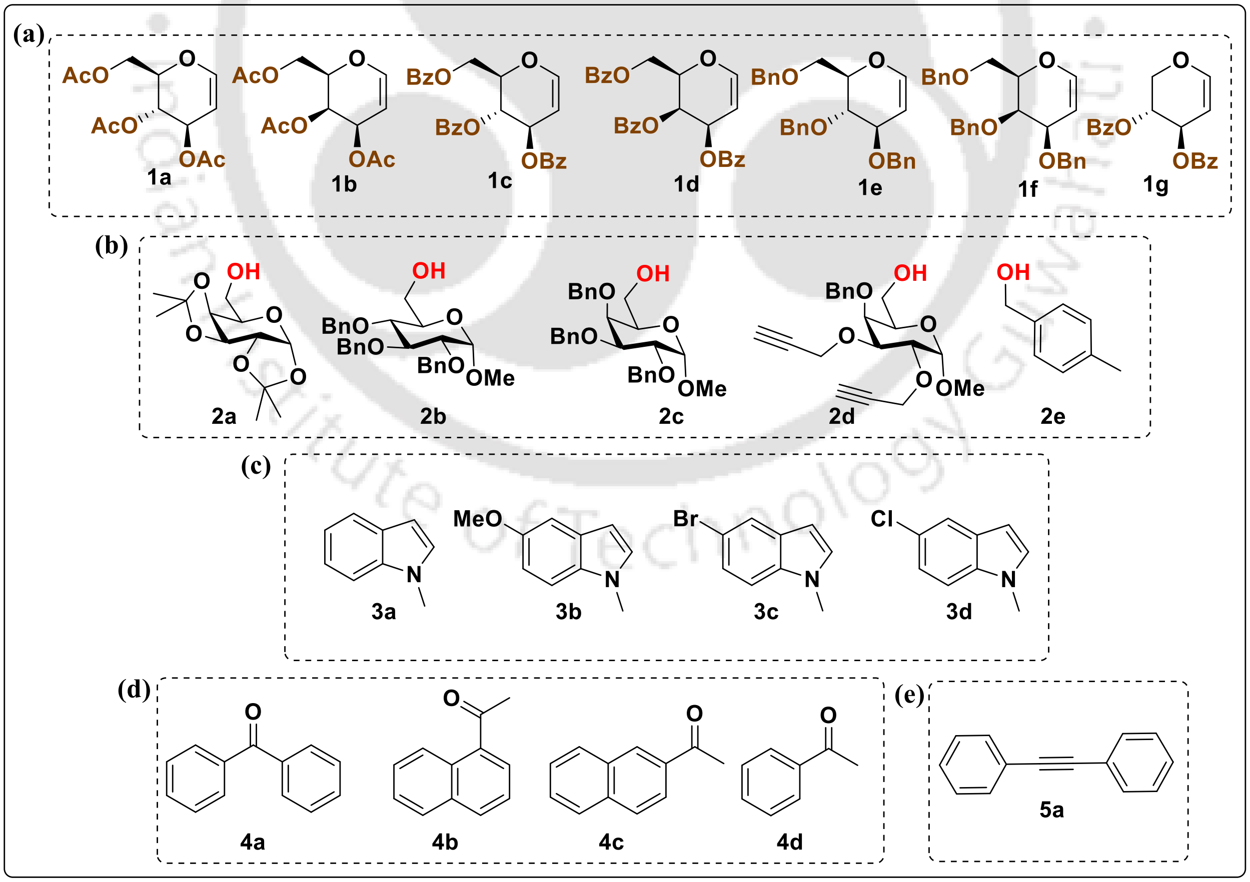


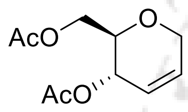
Figure 4.6 Compounds utilized as starting materials])**a**(to)**e**([in this study

The starting materials)**Figure 4.6**(, glycals[32a] **1a-1g**, alcohols[31a] **2a-2d** were synthesized according to literature procedures. N-methylindoles were prepared by N-methylation of respective indoles following literature reports, by reacting with sodium hydride and iodomethane.

4.5 General Procedure A: synthesis of 1-deoxy glycals

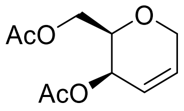
4.5.1 Synthesis of 1-deoxy Ferrier glycals from glycals

A solution of glycal **1a-g**)1 equiv.(and triethylsilane)2 equiv.(in dry CH_2Cl_2)0.32 - 0.38 M(was taken in a screwed cap vial or sealedtube followed by the addition of catalyst **11c**)10 mol %(. The reaction mixture was stirred at 50 °C for 30 min. The reaction was monitored on TLC. After completion of the reaction, the crude reaction mixture was worked up with water, washed with brine, dried by Na_2SO_4, concentrated in rotavapor. The resulting crude reaction mixture was purified through column chromatography to afford the 1-deoxy ferrier glycal as product)**6a-6g**(.



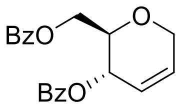
6a

6a: Ferrier glycosylation of **1a**)52 mg, 0.19 mmol(with triethylsilane)43.5 mg, 0.38 mmol(according to **General Procedure A** afforded **6a**)33.6 mg, 84 %(as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.4)Hexane/EtOAc = 4:1, v/v(. ^{1}H NMR)600 MHz, $CDCl_3$(δ 5.96)dd, *J* = 10.3, 1.7 Hz, 1H(, 5.77)dd, *J* = 10.3, 2.1 Hz, 1H(, 5.27)dd, *J* = 6.1, 2.0 Hz, 1H(, 4.23)dd, *J* = 12.4, 2.4 Hz, 3H(, 4.18)dd, *J* = 12.1, 6.0 Hz, 1H(, 3.74)ddd, *J* = 8.4, 6.1, 2.7 Hz, 1H(, 2.11)s, 3H(, 2.09)s, 3H(. ^{13}C NMR)151 MHz, $CDCl_3$(δ 171.0, 170.4, 129.6, 124.3, 73.9, 65.3, 65.2, 63.4, 21.1, 20.9. NMR data were matched with the literature.[33a]



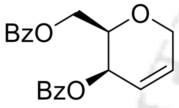
6b

6b: Ferrier glycosylation of **1b**)51.3 mg, 0.19 mmol(with triethylsilane)43.8 mg, 0.38 mmol(according to **General Procedure A** afforded **6b**)33.8 mg, 83 %(as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.5)Hexane/EtOAc = 4:1, v/v(. ^{1}H NMR)600 MHz, $CDCl_3$(δ 6.11)dd, *J* = 10.2, 2.3 Hz, 1H(, 6.04 – 5.99)m, 1H(, 5.13 – 5.09)m, 1H(, 4.34)ddd, *J* = 17.2, 3.3, 1.8 Hz, 1H(, 4.22)qd, *J* = 11.7, 6.2 Hz, 3H(, 3.89)ddd, *J* = 7.2, 5.0, 2.3 Hz, 1H(, 2.09)s, 3H(, 2.09)s, 3H(. ^{13}C NMR)151 MHz, $CDCl_3$(δ 170.8, 170.6, 132.4, 122.2, 73.8, 65.8, 64.3, 63.4, 20.93, 20.85. NMR data were matched with the literature.[33a]



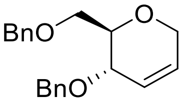
6c

6c: Ferrier glycosylation of **1c**)88.0 mg, 0.19 mmol(with triethylsilane)45 mg, 0.38 mmol(according to **General Procedure A** afforded **6c**)55.2 mg, 86 %(as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.4)Hexane/EtOAc = 3:1, v/v(. ^{1}H NMR)600 MHz, $CDCl_3$(δ 8.06 – 8.01)m, 4H(, 7.60 – 7.49)m, 2H(, 7.40)ddd, J = 27.6, 17.6, 9.9 Hz, 4H(, 6.04 – 5.99)m, 1H(, 5.96 – 5.90)m, 1H(, 5.67 – 5.62)m, 1H(, 4.60)dd, J = 12.0, 3.1 Hz, 1H(, 4.47)dd, J = 12.0, 6.1 Hz, 1H(, 4.35 – 4.25)m, 2H(, 4.10 – 4.04)m, 1H(. ^{13}C NMR)151 MHz, $CDCl_3$(δ 166.53, 166.04, 133.38, 133.14, 129.97, 129.88, 129.86, 128.54, 128.43, 124.51, 74.13, 66.42, 65.34, 64.22. NMR data were matched with the literature.[33b]



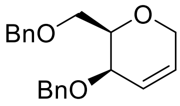
6d

6d: Ferrier glycosylation of **1d**)89.1 mg, 0.19 mmol(with triethylsilane)45 mg, 0.38 mmol(according to **General Procedure A** afforded **6d**)54.0 mg, 84 %(as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.5)Hexane/EtOAc = 3:1, v/v(. ^{1}H NMR)600 MHz, $CDCl_3$(δ 8.07)dd, J = 8.2, 1.2 Hz, 2H(, 8.02)dd, J = 8.2, 1.2 Hz, 2H(, 7.59 – 7.52)m, 2H(, 7.47 – 7.38)m, 4H(, 6.20 – 6.13)m, 2H(, 5.46 – 5.40)m, 1H(, 4.63)dd, J = 11.6, 7.4 Hz, 1H(, 4.50)dd, J = 11.6, 5.1 Hz, 1H(, 4.43 – 4.38)m, 1H(, 4.30 – 4.25)m, 1H(, 4.14)ddd, J = 7.4, 5.1, 2.3 Hz, 1H(. ^{13}C NMR)151 MHz, $CDCl_3$(δ 166.5, 166.2, 133.3, 133.2, 132.8, 130.0, 129.9, 129.9, 128.6, 128.5, 122.3, 74.1, 65.9, 65.1, 63.9. NMR data were matched with the literature.[33b]



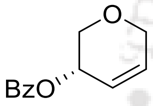
6e

6e: Ferrier glycosylation of **1e**)81.0 mg, 0.19 mmol(with triethylsilane)45 mg, 0.38 mmol(according to **General Procedure A** afforded **6e**)42.5 mg, 72 %(as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.6)Hexane/EtOAc = 7:1, v/v(. ^{1}H NMR)600 MHz, $CDCl_3$(δ 7.36 – 7.24)m, 10H(, 5.93)dd, J = 10.4, 1.9 Hz, 1H(, 5.88 – 5.84)m, 1H(, 4.61)dd, J = 11.9, 3.2 Hz, 2H(, 4.55)d, J = 12.3 Hz, 1H(, 4.45)d, J = 11.5 Hz, 1H(, 4.25 – 4.16)m, 2H(, 4.05)d, J = 8.3 Hz, 1H(, 3.72)dd, J = 10.4, 2.1 Hz, 1H(, 3.64)dd, J = 10.4, 5.3 Hz, 1H(, 3.60)ddd, J = 7.8, 5.3, 2.1 Hz, 1H(. ^{13}C NMR)151 MHz, $CDCl_3$(δ 138.30, 138.27, 128.54, 128.50, 128.33, 128.07, 127.90, 127.77, 125.72, 76.48, 73.62, 71.23, 70.62, 69.70, 65.72. NMR data were matched with the literature.[33a]



6f

6f: Ferrier glycosylation of **1f**)78.1 mg, 0.19 mmol(with triethylsilane)44 mg, 0.38 mmol(according to **General Procedure A** afforded **6f**)44.4 mg, 75 %(as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.5)Hexane/EtOAc = 7:1, v/v(. ^{1}H NMR)500 MHz, $CDCl_3$(δ 7.36 – 7.30)m, 5H(, 7.30 – 7.24)m, 6H(, 6.04)dd, *J* = 10.4, 2.1 Hz, 1H(, 6.01 – 5.97)m, 1H(, 4.65)dd, *J* = 12.0, 5.5 Hz, 2H(, 4.55)dd, *J* = 12.0, 3.3 Hz, 2H(, 4.32)d, *J* = 16.1 Hz, 1H(, 4.17)d, *J* = 16.9 Hz, 1H(, 3.84 – 3.70)m, 4H(. ^{13}C NMR)126 MHz, $CDCl_3$(δ 138.8, 138.3, 131.6, 128.5, 128.4, 128.0, 127.9, 127.74, 127.68, 123.7, 76.9, 73.7, 70.7, 70.1, 68.7, 66.0. NMR data were matched with the literature.[33c]



6g

6g: Ferrier glycosylation of **1g**)63.1 mg, 0.19 mmol(with triethylsilane)45 mg, 0.38 mmol(according to **General Procedure A** afforded **6c**)34.8 mg, 90 %(as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.5)Hexane/EtOAc = 6:1, v/v(. ^{1}H NMR)500 MHz, $CDCl_3$(δ 8.13 – 8.04)m, 3H(, 7.63)dd, *J* = 7.4, 6.1 Hz, 2H(, 7.56)t, *J* = 7.4 Hz, 1H(, 7.50 – 7.37)m, 5H(, 6.12)dd, *J* = 10.3, 2.1 Hz, 1H(, 6.04)ddd, *J* = 10.3, 2.1, 1.3 Hz, 1H(, 5.34 – 5.31)m, 1H(, 4.27)d, *J* = 17.0 Hz, 1H(, 4.14)dd, *J* = 17.0, 2.0 Hz, 1H(, 4.05)dd, *J* = 12.4, 2.4 Hz, 1H(, 3.94)dd, *J* = 12.4, 3.3 Hz, 1H(.

4.6 Synthesis of Methyl-2,3-di-*O*-propargyl-4-*O*-benzyl-α-D-galactopyranoside)2d(

A reaction mixture of **2d”**)1.2 g, 4.25 mmol(in DMF was treated with NaH)225 mg, 9.35 mmol(at 0 °C followed by the addition of Propargyl bromide)1.12 g, 9.35 mmol(at the same temperature. Upon reaction completion, excess sodium hydride was quenched with Methanol. The crude reaction mixture was concentrated under *vacuum* and diluted with water and extracted with CH_2Cl_2)3 X 15 mL(. The combined organic layers were washed with brine and dried over Na_2SO_4 and concentrated in vacuo. The crude mixture was purified by column chromatography)4: 1 Hexane: EtOAc(to give **2d’** as a white solid)1.24 g, 82 % yield(. ^{1}H NMR)600 MHz, $CDCl_3$(δ 7.55 – 7.52)m, 2H(, 7.38 – 7.32)m, 3H(, 5.55)s, 1H(, 5.07)d, *J* = 3.1 Hz, 1H(, 4.44 – 4.39)m, 2H(, 4.38 – 4.31)m, 3H(, 4.28)dd, *J* = 12.4, 1.3 Hz, 1H(, 4.15 – 4.10)m, 1H(, 4.11 – 4.08)m, 1H(, 3.71 –

3.69)s, 1H(, 3.47)s, 3H(, 2.48 – 2.38)m, 2H(. ^{13}C NMR)151 MHz, $CDCl_3$(δ 137.7, 129.0, 128.2, 126.4, 101.3, 99.3, 80.1, 80.0, 75.2, 74.9, 74.8, 74.7, 74.6, 69.4, 62.4, 59.1, 57.6, 55.5. Methyl-2,3-di-propargyl-4,6-*O*-benzylidene-α-D-galactopyranoside)0.51 mg, 1.42 mmol, **2d'**(was dissolved in CH_2Cl_2/ Et_2O)1:1, 10 ml(and stirred at room temperature under inert atmosphere. After 10 min, $LiAlH_4$)376.1 mg, 9.9 mmol(was added to the reaction mixture at 0 °C slowly, and the reaction mixture was heated to reflux for 10 min. Upon cooling it to 0 °C, a solution of $AlCl_3$)950.1 mg, 7.1 mmol(dissolved in Diethyl ether)2- 3 mL(was added and the mixture was heated to reflux for 1 h. Upon completion of the reaction, the reaction mixture was cooled down and excess $LiAlH_4$ was quenched by the addition of EtOAc. The reaction mixture was diluted with Et_2O and washed with water. The water layer was extracted with diethyl ether and the combined organic layers were concentrated under *vacuum*. The crude mixture was purified by using column chromatography)4: 1, Hexane: EtOAc(to form **2d**)336 mg, 66% yield(as a colorless syrup. ^{1}H NMR)600 MHz, $CDCl_3$(δ 7.43 – 7.38)m, 2H(, 7.37 – 7.34)m, 2H(, 7.31)t, *J* = 7.2 Hz, 1H(, 5.00 – 4.96)m, 2H(, 4.68)d, *J* = 11.7 Hz, 1H(, 4.41)ddd, *J* = 16.0, 6.8, 2.3 Hz, 2H(, 4.33)ddd, *J* = 12.8, 11.8, 2.2 Hz, 2H(, 4.10)dd, *J* = 9.9, 3.6 Hz, 1H(, 3.98 – 3.93)m, 2H(, 3.78 – 3.70)m, 2H(, 3.52 – 3.48)m, 1H(, 3.41)s, 3H(, 2.46)t, *J* = 2.2 Hz, 1H(, 2.45)t, *J* = 2.2 Hz, 1H(. ^{13}C NMR)151 MHz, $CDCl_3$(δ 138.1, 128.7, 128.5, 128.0, 98.7, 80.3, 80.0, 78.7, 76.1, 75.1, 74.7, 74.6, 74.5, 70.2, 62.3, 59.0, 58.9, 55.3.

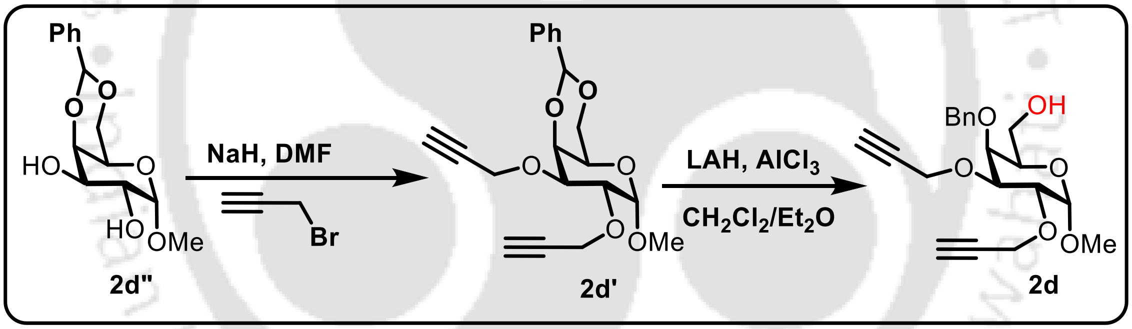
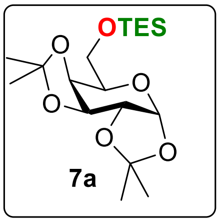


Figure 4.7 Preparation of Methyl-2,3-di-*O*-propargyl-4-*O*-benzyl-α-D-galactopyranoside)**2d**(

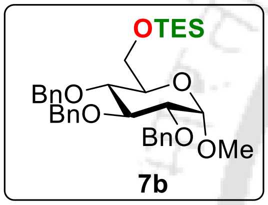
4.7 General Procedure B: Silylation of alcohols

Synthesis of Triethylsily/Triphenylsilyl protected alcohols: Solution of alcohol **2a-e**)1 equiv.(and silane)2 equiv.(in dry CH_2Cl_2)0.32 - 0.38 M(was taken in a young sealedtube or schlenk flask, followed by the addition of catalyst **11c**)5 mol %(. The reaction flask was given *vacuum* and sealed before it was kept for stirring at 50 °C for 30 min. The reaction was monitored on TLC. After completion of the reaction, the crude reaction mixture was worked up with water, washed with brine, dried by Na_2SO_4, concentrated in rotavapor. The resulting crude reaction mixture was purified through column chromatography to afford the triethylsilyl/triphenylsilyl protected alcohol as product)**7a-7f**(.



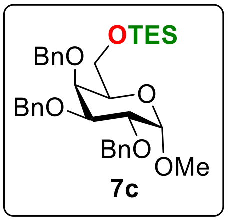
7a

7a: Reaction of **2a**)40.2 mg, 0.15 mmol(with triethylsilane)36 mg, 0.31 mmol(according to **General Procedure B** afforded **7a**)49.9 mg, 86 %(as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.7)Hexane/EtOAc = 6:1, v/v(. ^{1}H NMR)600 MHz, $CDCl_3$(δ 5.51)d, *J* = 5.0 Hz, 1H(, 4.59)dd, *J* = 8.0, 2.2 Hz, 1H(, 4.31)dd, *J* = 8.0, 1.6 Hz, 1H(, 4.29)dd, *J* = 5.0, 2.3 Hz, 1H(, 3.86 – 3.78)m, 2H(, 3.73)dd, *J* = 9.7, 5.8 Hz, 1H(, 1.53)s, 3H(, 1.44)s, 3H(, 1.33)s, 3H(, 1.32)s, 3H(, 1.00 – 0.92)m, 9H(, 0.65 – 0.56)m, 6H(. ^{13}C NMR)151 MHz, $CDCl_3$(δ 109.10, 108.50, 96.42, 70.98, 70.70, 70.67, 68.40, 61.65, 26.14, 26.07, 25.04, 24.42, 6.79, 4.47. NMR data were matched with the literature.[34]



7b

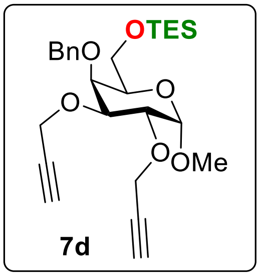
7b: Reaction of **2b**)70.2 mg, 0.15 mmol(with triethylsilane)35 mg, 0.30 mmol(according to **General Procedure B** afforded **7b**)77.0 mg, 88 %(as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.7)Hexane/EtOAc = 6:1, v/v(. ^{1}H NMR)600 MHz, $CDCl_3$(δ 7.37 – 7.25)m, 15H(, 4.97)d, *J* = 10.8 Hz, 1H(, 4.88)d, *J* = 11.0 Hz, 1H(, 4.81)d, *J* = 10.8 Hz, 1H(, 4.78)d, *J* = 12.1 Hz, 1H(, 4.67)d, *J* = 12.1 Hz, 1H(, 4.63)d, *J* = 11.0 Hz, 1H(, 4.61)d, *J* = 3.5 Hz, 1H(, 3.99)t, *J* = 9.3 Hz, 1H(, 3.81 – 3.74)m, 1H(, 3.61)ddd, *J* = 9.9, 4.1, 2.1 Hz, 1H(, 3.55 – 3.47)m, 2H(, 3.36)s, 3H(, 0.93)t, *J* = 8.0 Hz, 9H(, 0.58)qd, *J* = 7.9, 2.3 Hz, 6H(. ^{13}C NMR)151 MHz, $CDCl_3$(δ 139.0, 138.7, 138.4, 128.6, 128.5, 128.22, 128.20, 127.97, 127.96, 127.8, 127.7, 98.0, 82.3, 80.3, 77.9, 75.9, 75.1, 73.5, 71.7, 62.2, 55.1, 6.9, 4.6. NMR data were matched with the literature.[35]



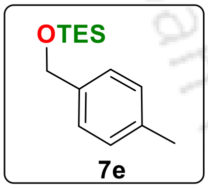
7c

7c: Reaction of **2c**)70.1 mg, 0.15 mmol(with triethylsilane)35 mg, 0.30 mmol(according to **General Procedure B** afforded **7c**)78.7 mg, 90 %(as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.6)Hexane/EtOAc = 7:1, v/v(. ^{1}H NMR)600 MHz, $CDCl_3$(δ 7.47 – 7.23)m, 15H(, 4.96)d, *J* = 11.4 Hz, 1H(, 4.86)d, *J* = 11.8 Hz, 1H(, 4.83

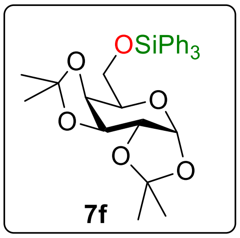
)d, J = 12.1 Hz, 1H(, 4.73)d, J = 11.8 Hz, 1H(, 4.71 – 4.67)m, 2H(, 4.61)d, J = 11.4 Hz, 1H(, 4.03)dd, J = 10.0, 3.6 Hz, 1H(, 3.94 – 3.91)m, 1H(, 3.71)t, J = 6.5 Hz, 1H(, 3.63)dd, J = 10.0, 6.0 Hz, 1H(, 3.60 – 3.53)m, 1H(, 3.36)s, 1H(, 0.93)t, J = 8.0 Hz, 1H(, 0.61 – 0.54)m, 1H(. ^{13}C NMR)151 MHz, $CDCl_3$(δ 139.1, 139.0, 138.7, 128.50, 128.46, 128.4, 128.3, 128.2, 127.8, 127.64, 127.61, 98.9, 79.4, 76.7, 75.2, 74.9, 73.7, 73.4, 71.3, 61.9, 55.3, 6.9, 4.5. NMR data were matched with the literature.[35]



7d: Reaction of **2d**)55.1 mg, 0.15 mmol(with triethylsilane)36 mg, 0.31 mmol(according to **General Procedure B** afforded **7d**)67.5 mg, 93 %(as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.6)Hexane/EtOAc = 6:1, v/v(. ^{1}H NMR)500 MHz, $CDCl_3$(δ 7.39)d, J = 7.3 Hz, 2H(, 7.33)t, J = 7.3 Hz, 2H(, 7.28)d, J = 7.2 Hz, 1H(, 4.96)d, J = 11.5 Hz, 1H(, 4.92)d, J = 3.3 Hz, 1H(, 4.65)d, J = 11.5 Hz, 1H(, 4.45 – 4.24)m, 5H(, 4.08)dd, J = 10.0, 3.4 Hz, 1H(, 4.04 – 4.00)m, 1H(, 3.97 – 3.90)m, 1H(, 3.76 – 3.72)m, 1H(, 3.69 – 3.64)m, 1H(, 3.58 – 3.63)m, 1H(, 3.40)s, 3H(, 2.44 – 2.39)m, 2H(, 0.94)t, J = 7.9 Hz, 5H(, 0.58)dd, J = 15.6, 7.8 Hz, 3H(. ^{13}C NMR)151 MHz, $CDCl_3$(δ 138.5, 128.5, 128.3, 128.1, 128.0, 127.3, 98.4, 80.2, 79.9, 78.6, 76.0, 74.9, 74.6, 74.3, 74.0, 70.8, 61.5, 58.7, 58.6, 58.3, 54.8, 6.5, 4.2.



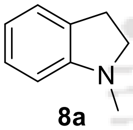
7e: Reaction of **2e**)18 mg, 0.15 mmol(with triethylsilane)34 mg, 0.29 mmol(according to **General Procedure B** afforded **7e**)32.1 mg, 92 %(as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.6)Hexane/EtOAc = 6:1, v/v(.^{1}H NMR)500 MHz, $CDCl_3$(δ 7.21)d, J = 7.7 Hz, 2H(, 7.12)d, J = 7.6 Hz, 2H(, 4.69)s, 1H(, 2.32)s, 2H(, 0.96)dd, J = 17.5, 9.0 Hz, 9H(, 0.64)q, J = 7.9 Hz, 6H(. ^{13}C NMR)151 MHz, $CDCl_3$(δ 138.4, 136.7, 129.0, 126.5, 64.78, 21.2, 6.93, 6.91, 6.6, 4.7. NMR data were matched with the literature.[36]



7f: Reaction of **2a**)40.5 mg, 0.15 mmol(with triphenylsilane)80.3 mg, 0.31 mmol(according to **General Procedure B** afforded **7f**)77.4 mg, 96 %(as a colorless syrup. The crude product was purified through column chromatography, R_f = 0.6)Hexane/EtOAc = 6:1, v/v(. ^{1}H NMR)500 MHz, $CDCl_3$(δ 7.64)d, *J* = 7.1 Hz, 5H(, 7.57)d, *J* = 6.9 Hz, 1H(, 7.43 – 7.38)m, 3H(, 7.35)t, *J* = 7.2 Hz, 6H(, 5.49)d, *J* = 4.9 Hz, 1H(, 4.59)d, *J* = 7.9 Hz, 1H(, 4.36)d, *J* = 7.9 Hz, 1H(, 4.34 – 4.26)m, 1H(, 4.03 – 3.89)m, 3H(, 1.45)s, 3H(, 1.37)s, 3H(, 1.33 – 1.29)m, 6H(. ^{13}C NMR)151 MHz, $CDCl_3$(δ 135.93, 135.61, 134.12, 133.45, 130.14, 129.94, 128.17, 127.93, 109.18, 108.59, 96.39, 70.95, 70.70, 68.22, 62.51, 26.18, 26.06, 25.08, 24.56.

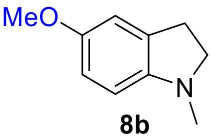
4.8 General Procedure C: Reduction of N-methyl indole derivatives

A solution of N-Methyl indole **3a-e**)1 equiv.(, silane)5 equiv.(, and water)H_2O/D_2O( )4 equiv.(in dry CH_2Cl_2)0.32 - 0.38 M(was taken in a young sealedtube or schlenk flask, followed by the addition of catalyst **11c**)15 mol %(. The reaction flask was given *vacuum* and sealed before it was kept for stirring at 50 °C for reaction completion. The reaction was monitored on TLC. After completion of the reaction, the crude reaction mixture was worked up with water, washed with brine, dried by Na_2SO_4, concentrated in rotavapor. The resulting crude reaction mixture was purified through column chromatography to afford the N-Methyl indoline as product)**8a-8f**(.



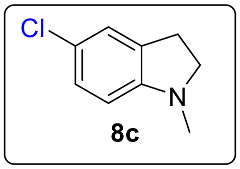
8a

8a: Reaction of **3a**)16.2 mg, 0.12 mmol(with triethylsilane)72 mg, 0.62 mmol(and H_2O)9 mg, 0.5 mmol(according to **General Procedure C** afforded **8a**[7])14.6 mg, 89 %(as a colorless liquid. The crude product was purified through column chromatography, R_f = 0.2)Hexane(.^{1}H NMR)600 MHz, $CDCl_3$(δ 7.11 – 7.05)m, 2H(, 6.67)t, *J* = 7.3 Hz, 1H(, 6.51 – 6.46)m, 1H(, 3.28)t, *J* = 8.2 Hz, 2H(, 2.94)t, *J* = 8.1 Hz, 2H(, 2.75)s, 3H(. ^{13}C NMR)151 MHz, $CDCl_3$(δ 153.5, 130.4, 127.5, 124.4, 117.9, 107.4, 56.3, 36.4, 28.9. NMR data were matched with the literature.[37a]



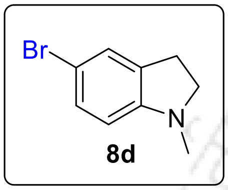
8b

8b: Reaction of **3b**)19.2 mg, 0.12 mmol(with triethylsilane)70 mg, 0.60 mmol(and H_2O)9 mg, 0.5 mmol(according to **General Procedure C** afforded **8b**)16.9 mg, 86 %(as a colorless liquid. The crude product was purified through column chromatography, R_f = 0.3)Hexane(. ^{1}H NMR)500 MHz, $CDCl_3$(δ 6.74)d, *J* = 0.9 Hz, 1H(, 6.65)dd, *J* = 8.4, 2.3 Hz, 1H(, 6.51 – 6.37)m, 1H(, 3.74)s, 3H(, 3.23)t, *J* = 8.0 Hz, 2H(, 2.91)t, *J* = 7.9 Hz, 2H(, 2.71)s, 3H(. NMR data were matched with the literature.[37a]



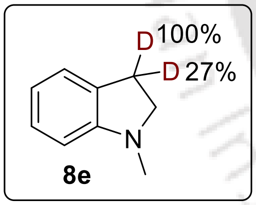
8c

8c: Reaction of **3c**)20.0 mg, 0.12 mmol(with triethylsilane)70.0 mg, 0.60 mmol(and H_2O)9 mg, 0.5 mmol(according to **General Procedure C** afforded **8c**)18.0 mg, 89 %(as a colorless liquid. The crude product was purified through column chromatography, $R_f = 0.4$)Hexane/EtOAc = 19:1, v/v(. ^{1}H NMR)500 MHz, $CDCl_3$(δ 7.08 – 6.95)m, 2H(, 6.36)dd, $J = 19.3$, 14.7 Hz, 1H(, 3.29)t, $J = 8.2$ Hz, 2H(, 2.91)t, $J = 8.2$ Hz, 2H(, 2.72)s, 3H(. ^{13}C NMR)126 MHz, $CDCl_3$(δ 152.2, 132.3, 127.1, 124.6, 122.4, 107.8, 56.3, 36.3, 28.6. NMR data were matched with the literature.[37a]



8d

8d: Reaction of **3d**)24.8 mg, 0.12 mmol(with triethylsilane)68.0 mg, 0.59 mmol(and H_2O)9 mg, 0.5 mmol(according to **General Procedure C** afforded **8d**)21.4 mg, 84 %(as a pale yellow syrup. The crude product was purified through column chromatography, $R_f = 0.3$)Hexane/EtOAc = 19:1, v/v(. ^{1}H NMR)600 MHz, $CDCl_3$(δ 7.17 – 7.14)m, 2H(, 6.32)d, $J = 8.8$ Hz, 1H(, 3.30)t, $J = 8.2$ Hz, 2H(, 2.92)t, $J = 8.2$ Hz, 2H(, 2.73)s, 3H(. ^{13}C NMR)151 MHz, $CDCl_3$(δ 152.6, 132.8, 130.0, 127.4, 109.5, 108.5, 56.2, 36.2, 28.6. NMR data were matched with the literature.[37a]



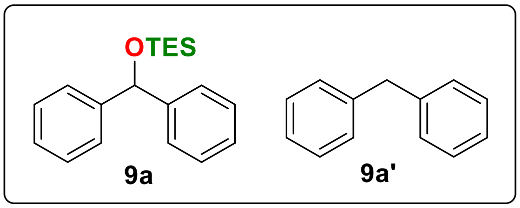
8e

8e: Reaction of **3a**)50.0 mg, 0.38 mmol(with triethylsilane)221.7 mg, 1.91 mmol(and D_2O)30 mg, 1.52 mmol(according to **General Procedure C** afforded **8e**[6])14.6 mg, 89 %(as a colorless liquid. The crude product was purified through column chromatography, $R_f = 0.2$)Hexane(. ^{1}H NMR)500 MHz, $CDCl_3$(δ 7.08)t, $J = 5.8$ Hz, 2H(, 6.67)t, $J = 7.3$ Hz, 1H(, 6.49)d, $J = 8.0$ Hz, 1H(, 3.33 – 3.22)m, 2H(, 3.02 – 2.84)m, 1H(, 2.75)s, 3H(. ^{13}C NMR)126 MHz, $CDCl_3$(δ 153.6, 130.4, 127.5, 124.42, 124.40, 117.9, 107.3, 56.2, 56.1, 36.4, 29.8, 28.9, 28.7, 28.6, 28.4. NMR data were matched with the literature.[37b]

4.9 General Procedure D: Reduction of ketone

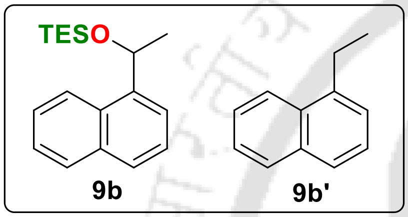
A solution of ketone **4a-e**)1 equiv.(and silane in dry CH_2Cl_2)0.32 - 0.38 M(was taken in a young sealedtube or schlenk flask, followed by the addition of catalyst **11c**)10 mol %(. The reaction flask was given *vacuum* and sealed before it was kept for stirring at 50 °C for reaction completion)3-

5h(. The reaction was monitored on TLC. After completion of the reaction, the crude reaction mixture was concentrated under *vacuum* using rotavapor. NMR spectra were recorded for the crude reaction mixture showing the reduced products of the ketone.



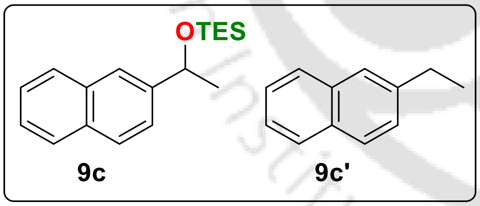
9a **9a'**

9a and 9a': Reaction of **4a**)27.5 mg, 0.15 mmol(with triethylsilane)52.7 mg, 0.45 mmol(according to **General Procedure D** afforded **9a** and **9a'**)44% and 56% respectively, based on crude NMR(. NMR data were matched with the literature.[38]



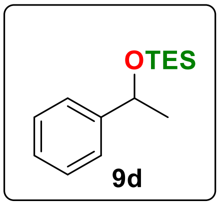
9b **9b'**

9b and 9b': Reaction of **4b**)25.5 mg, 0.15 mmol(with triethylsilane)52.3 mg, 0.45 mmol(according to **General Procedure D** afforded **9b** and **9b'**)53% and 47% respectively, based on crude NMR(. **9b:** ^{1}H NMR)500 MHz, $CDCl_3$(δ 8.08)d, *J* = 8.2 Hz, 1H(, 7.85)d, *J* = 7.8 Hz, 1H(, 7.71)dd, *J* = 13.1, 7.7 Hz, 2H(, 7.52 – 7.39)m, 3H(, 5.59)q, *J* = 6.1 Hz, 1H(, 1.58)d, *J* = 6.2 Hz, 3H(, 0.94 – 0.85)m, 9H(, 0.66 – 0.53)m, 6H(. NMR data were matched with the literature.[38]



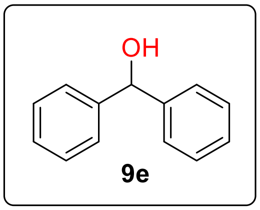
9c **9c'**

9c and 9c': Reaction of **4c**)25.7 mg, 0.15 mmol(with triethylsilane)52.7 mg, 0.45 mmol(according to **General Procedure D** afforded **9c** and **9c'**)43% and 57% respectively, based on crude NMR(. NMR data were matched with the literature.[38]



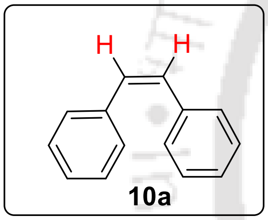
9d

9d: Reaction of **4d**)18.1 mg, 0.15 mmol(with triethylsilane)52.6 mg, 0.45 mmol(according to **General Procedure D** afforded **9d**)100 % conversion based on crude NMR(. ^{1}H NMR)500 MHz, $CDCl_3$(δ 7.38 – 7.25)m, 4H(, 7.21)d, *J* = 6.5 Hz, 1H(, 4.93 – 4.81)m, 1H(, 1.42)d, *J* = 6.0 Hz, 3H(, 0.91)t, *J* = 7.7 Hz, 9H(, 0.63 – 0.52)m, 6H(. NMR data were matched with the literature.[38]


9e

9e: Reaction of **4a**)27.7 mg, 0.15 mmol(with triethylsilane)39.6 mg, 0.15 mmol(according to **General Procedure D** afforded **9e**)84 %(. ^{1}H NMR)400 MHz, $CDCl_3$(δ 7.39 – 7.30)m, 8H(, 7.28 – 7.23)m, 2H(, 5.81)d, *J* = 3.0 Hz, 1H(, 2.29)d, *J* = 3.4 Hz, 1H(. NMR data were matched with the literature.[38]

4.10 General Procedure E: Reduction of Diphenylacetylene


10a

A solution of Diphenylacetylene **5a**)1 equiv., 51.3 mg, 0.29 mmol(and triethylsilane)4 equiv., 133.2 mg, 1.15 mmol(in MTBE)0.32 - 0.38 M(was taken in a young sealedtube or schlenk flask, followed by the addition of catalyst **11c**)15 mol %(. The reaction flask was given *vacuum* and sealed before it was kept for stirring at 50 °C. The reaction was monitored on TLC. After 1 1.5 days, the crude reaction mixture was concentrated and diluted with CH_2Cl_2)5 mL(. The reaction mixture was worked up with water, washed with brine, dried by Na_2SO_4, concentrated in rotavapor. The resulting crude reaction mixture was purified through column chromatography to afford the *cis*-stilbene)**10a**([39] as product in 36%,)18.7 mg(yield. ^{1}H NMR)600 MHz, $CDCl_3$(δ 7.29 – 7.14)m, 10H(, 6.60)s, 2H(. ^{13}C NMR)151 MHz, $CDCl_3$(δ 137.4, 130.4, 129.0, 128.4, 127.2.

4.11 Mechanistic Study through NMR Experiments:

The reaction under moisture-free conditions showed that TESiH remained as such)**Figue 4.8, Eq 1**(, and the reaction with water has shown complete conversion of TESiH into Hexaethyldisiloxane])$TESi_2O$(/)Et_3Si($_2O$([within 20 min)**Figue 4.8, Eq 2**(. A solution of catalyst **11c**)0.030 g, 0.027 mmol(, triethylsilane)0.0095 g, 0.081 mmol(, and water)H_2O( )2 equiv.(in dry CH_2Cl_2)0.32 - 0.38 M(was taken in a sealedtube. The reaction flask was given *vacuum* and sealed before it was kept for stirring at 50 °C for 20 min. The reaction mixture was concentrated under *vacuum* to remove solvent and dissolved in $CDCl_3$)0.5 ml(and recorded NMR.

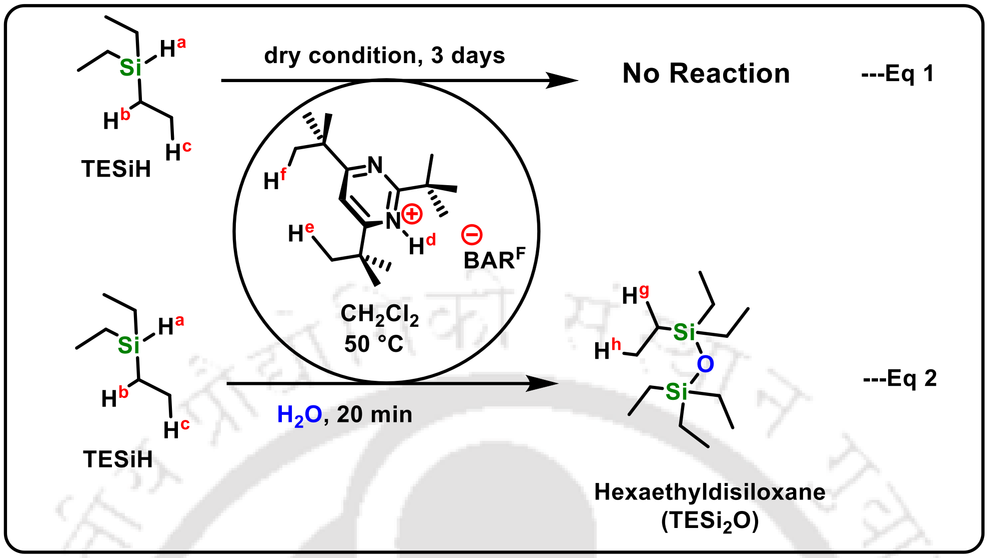


Figure 4.8 Control Reactions of TESiH with catalyst **11c** without and with H_2O

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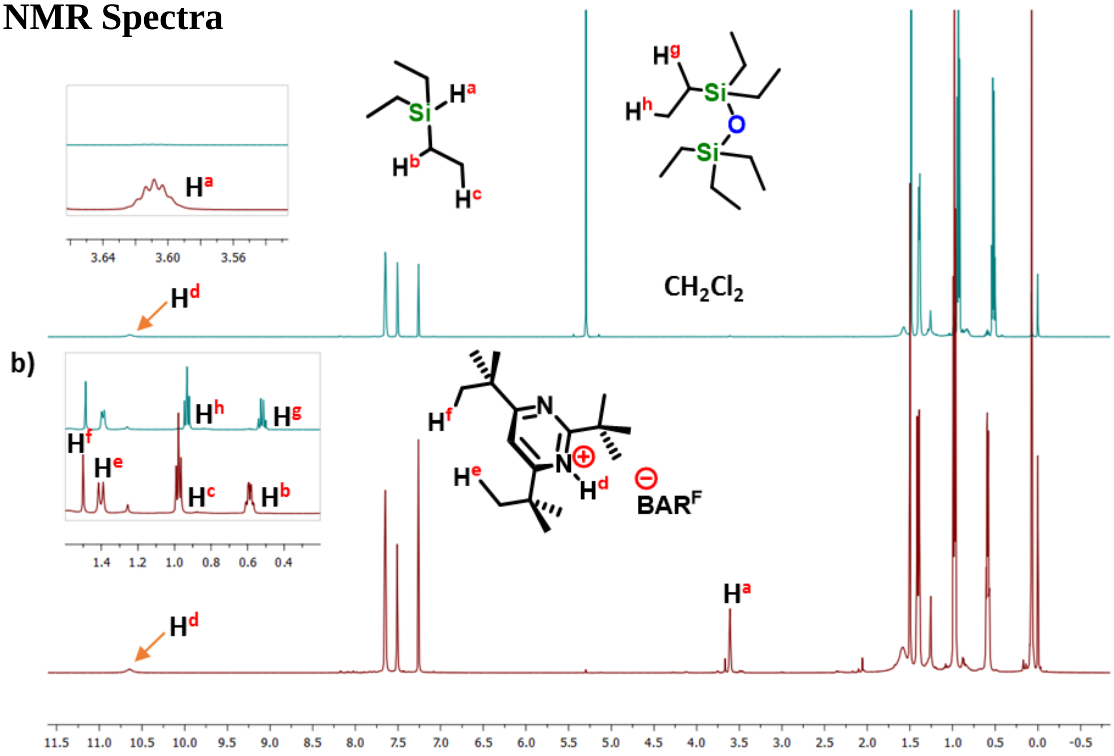
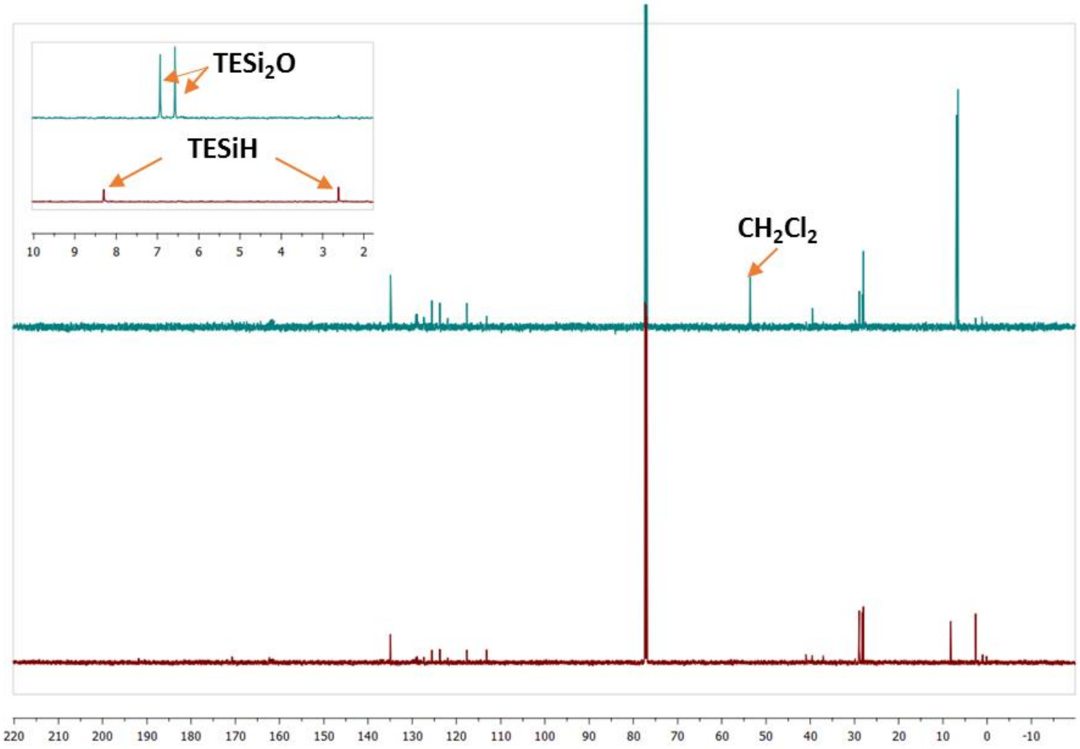
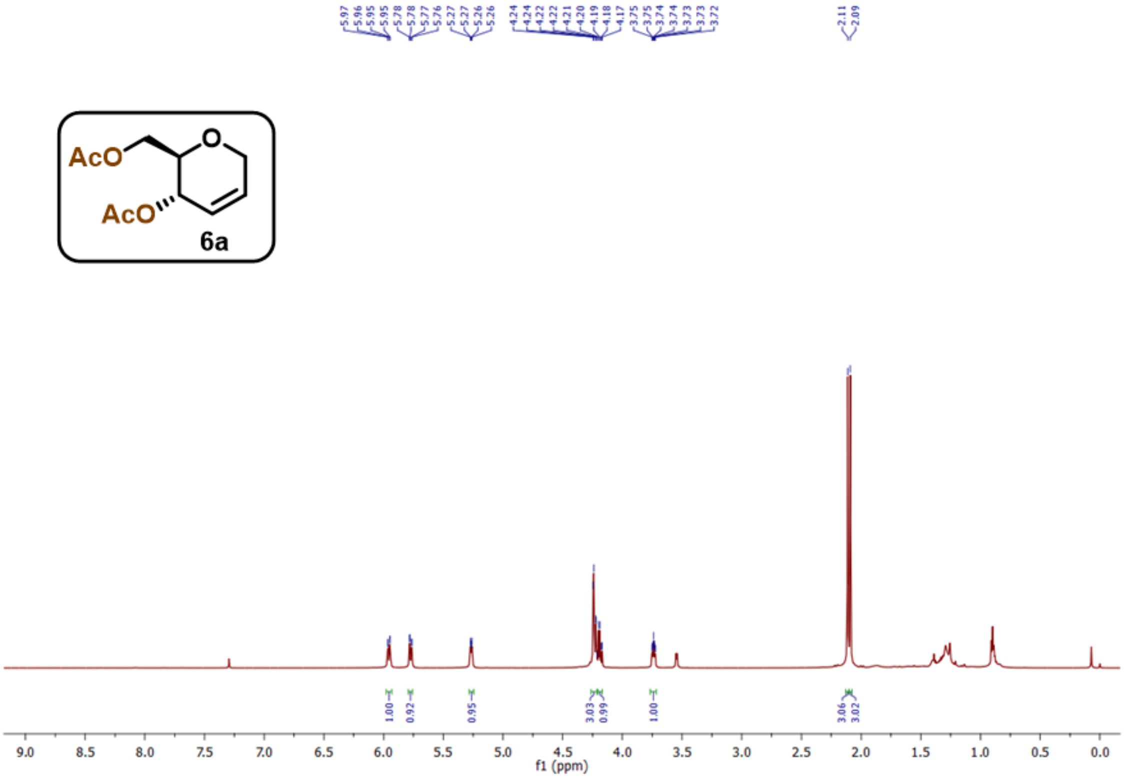
4.13 NMR Spectra



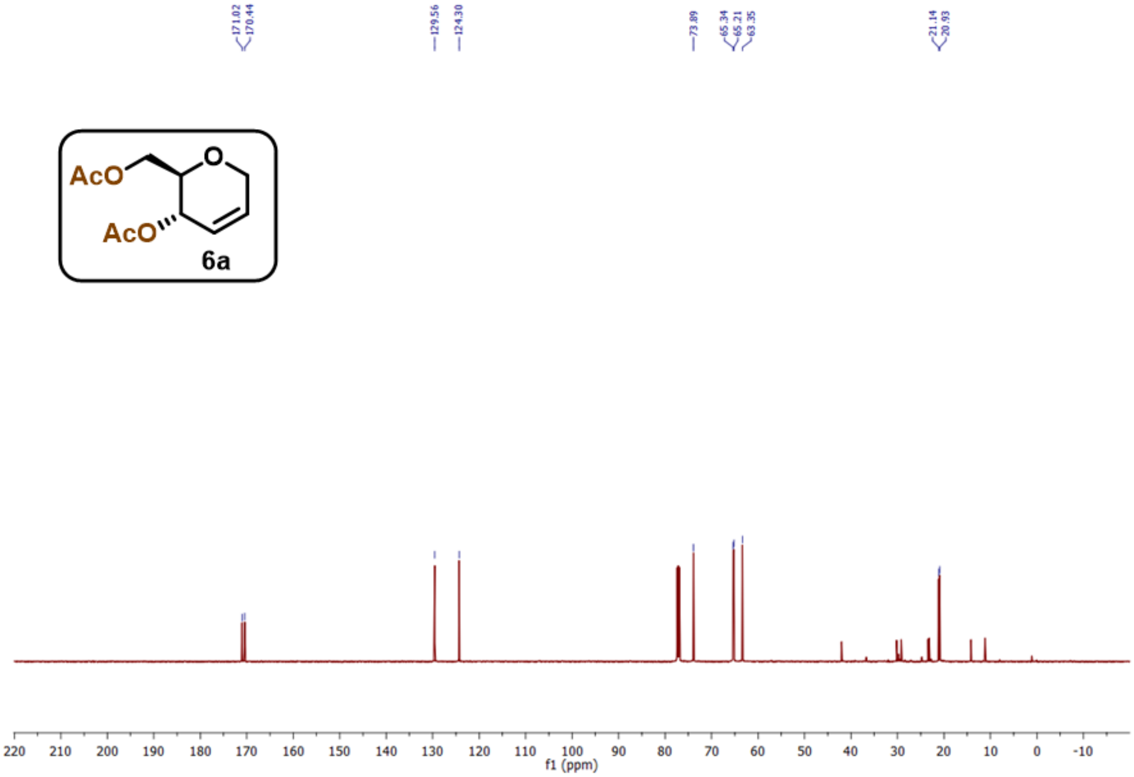
^{1}H NMR stacking spectrum of a(crude reaction mixture of **11c** and TESiH)Fig.3a(and b(its starting materials)600 MHz, $CDCl_3$(



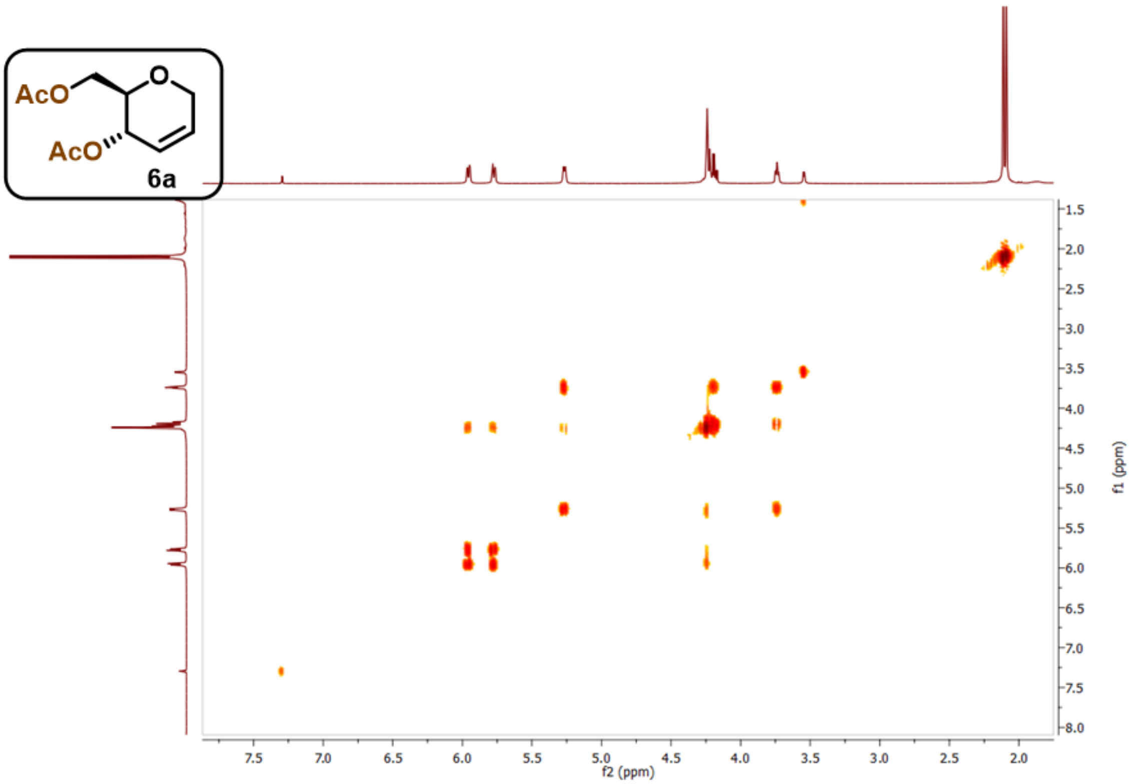
^{13}C NMR stacking spectrum of a(crude reaction mixture of **11c** and TESiH)Fig.3a(and b(its starting materials)151 MHz, $CDCl_3$(



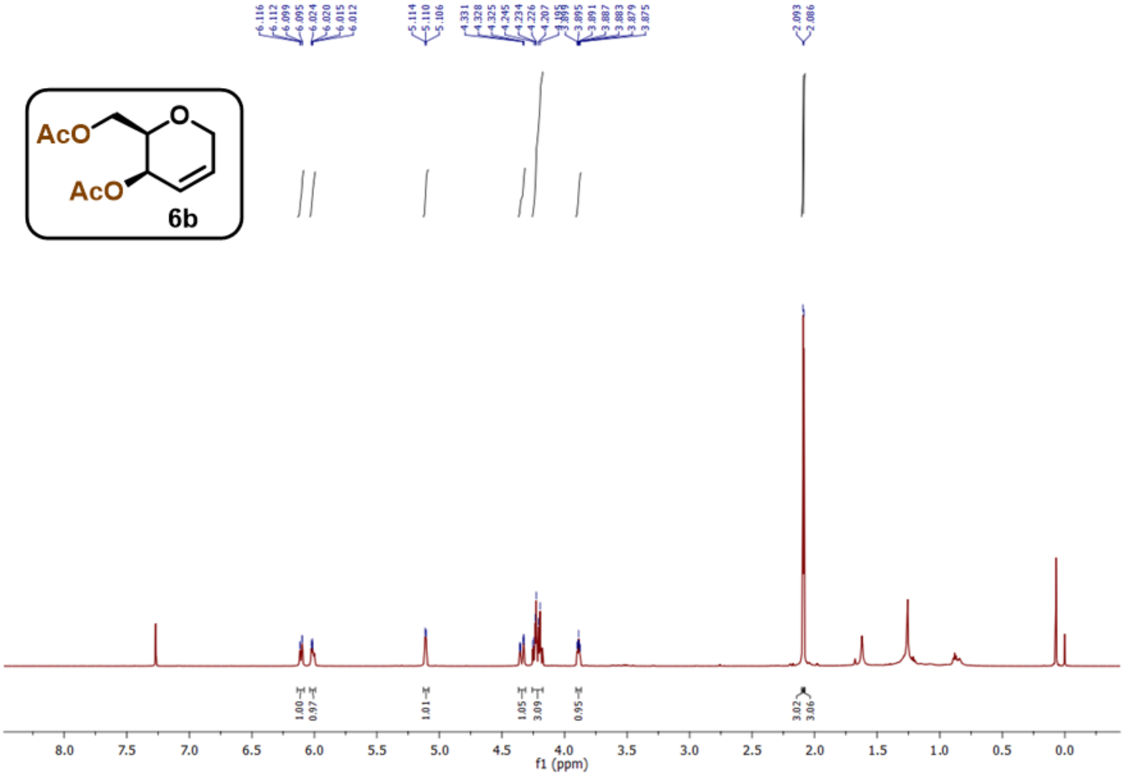
^{1}H NMR spectrum of **6a**,)600 MHz, $CDCl_3$(



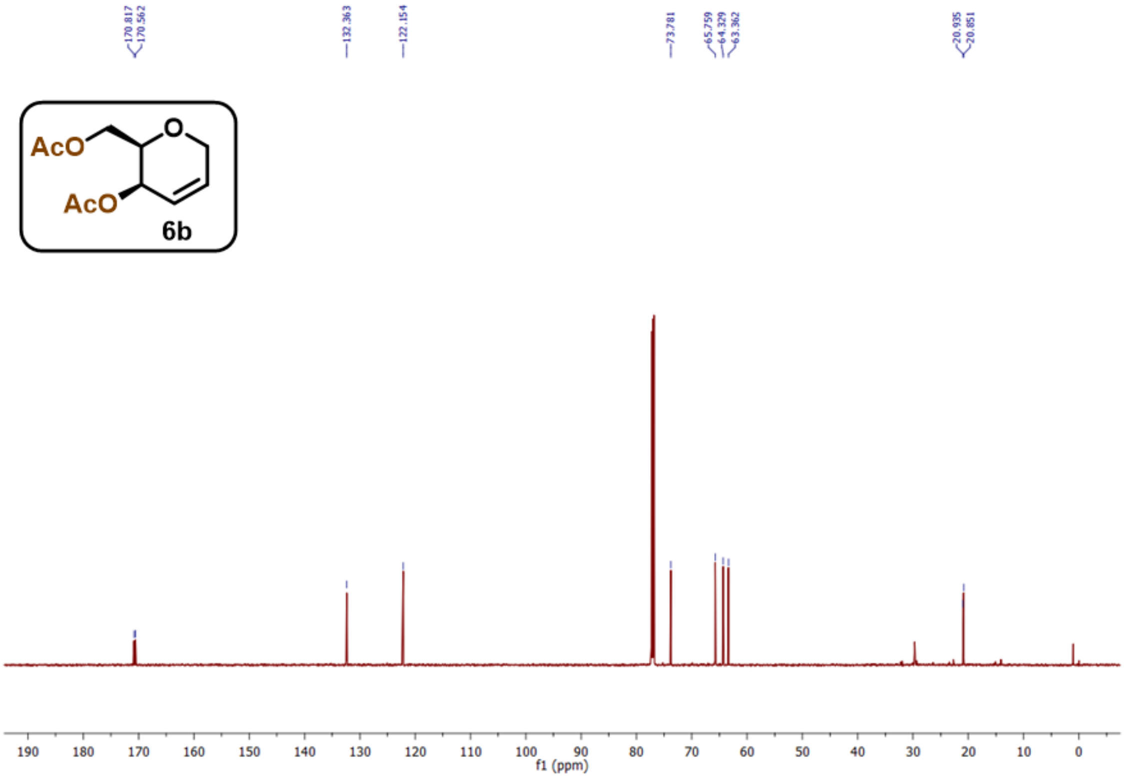
^{13}C NMR spectrum of **6a**,)151 MHz, $CDCl_3$(



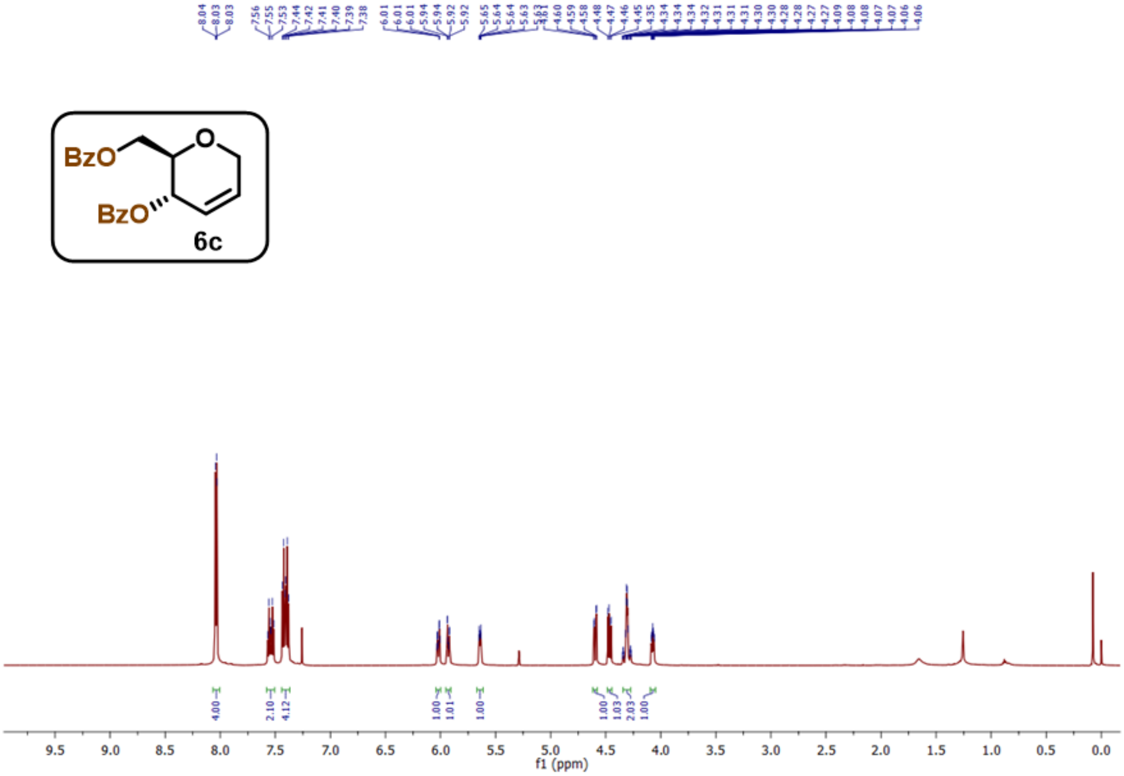
COSY NMR spectrum of **6a**,)600 MHz, $CDCl_3$(



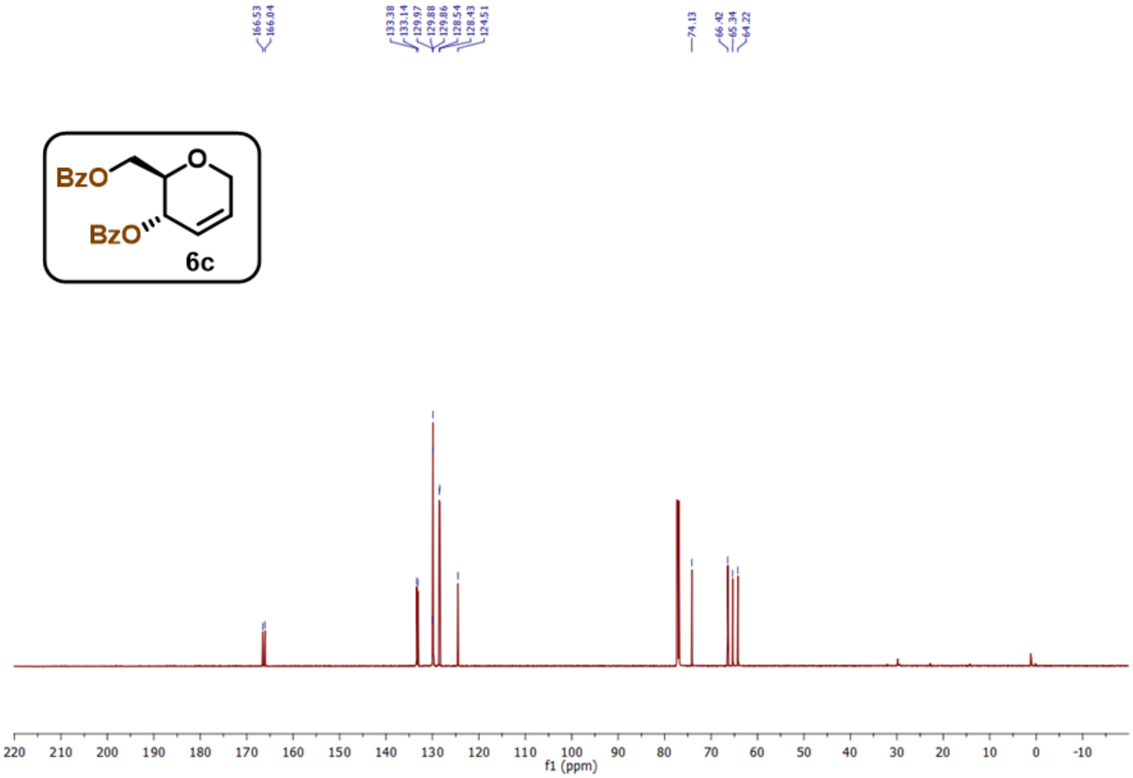
^{1}H NMR spectrum of **6b**,)600 MHz, $CDCl_3$(



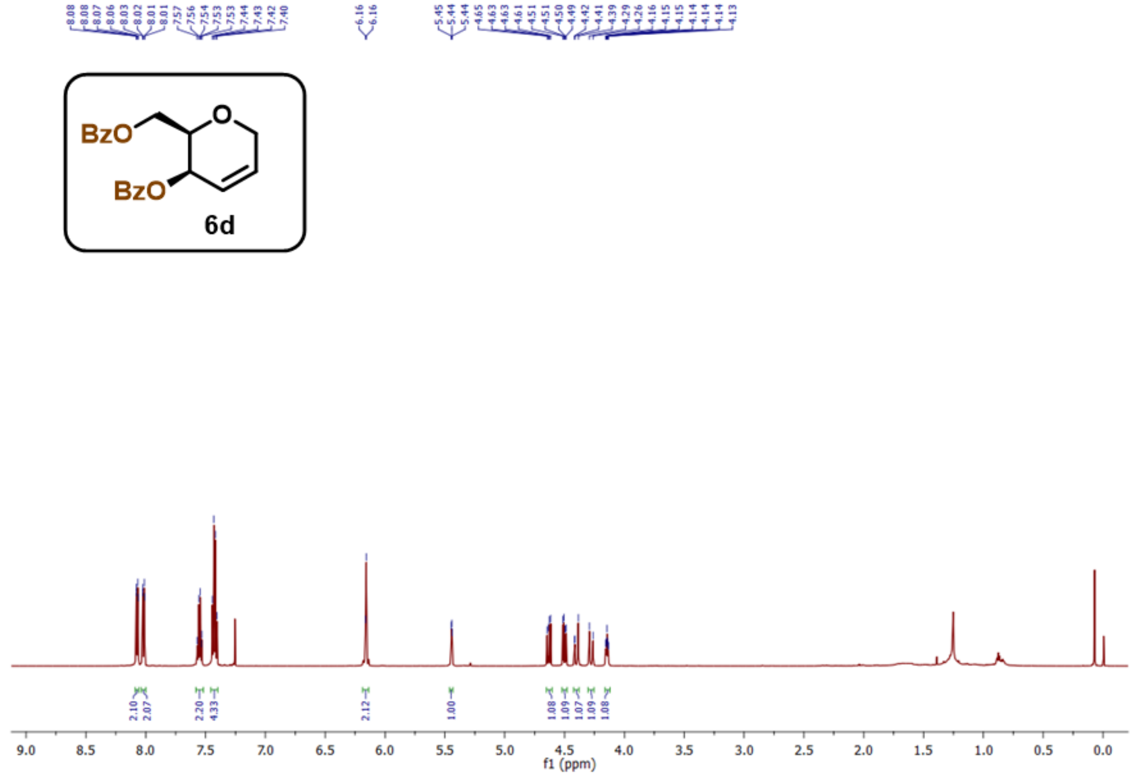
^{13}C NMR spectrum of **6b**,)151 MHz, $CDCl_3$(



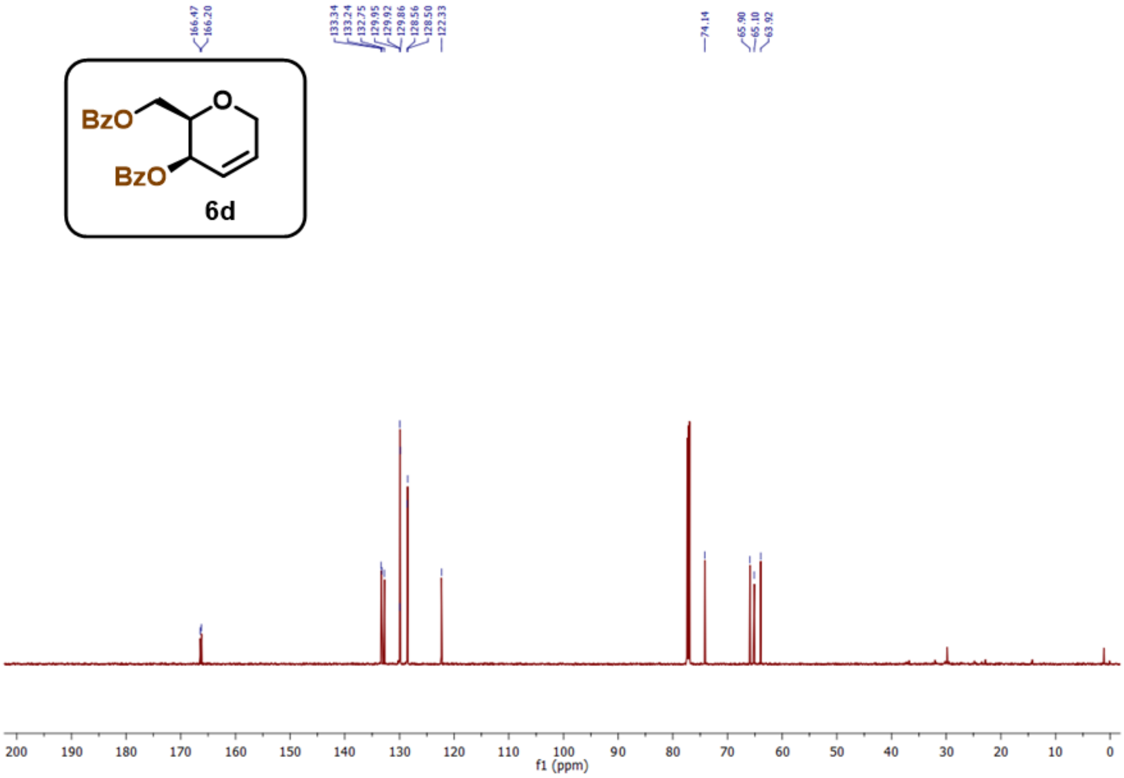
^{1}H NMR spectrum of **6c**,)600 MHz, $CDCl_3$(



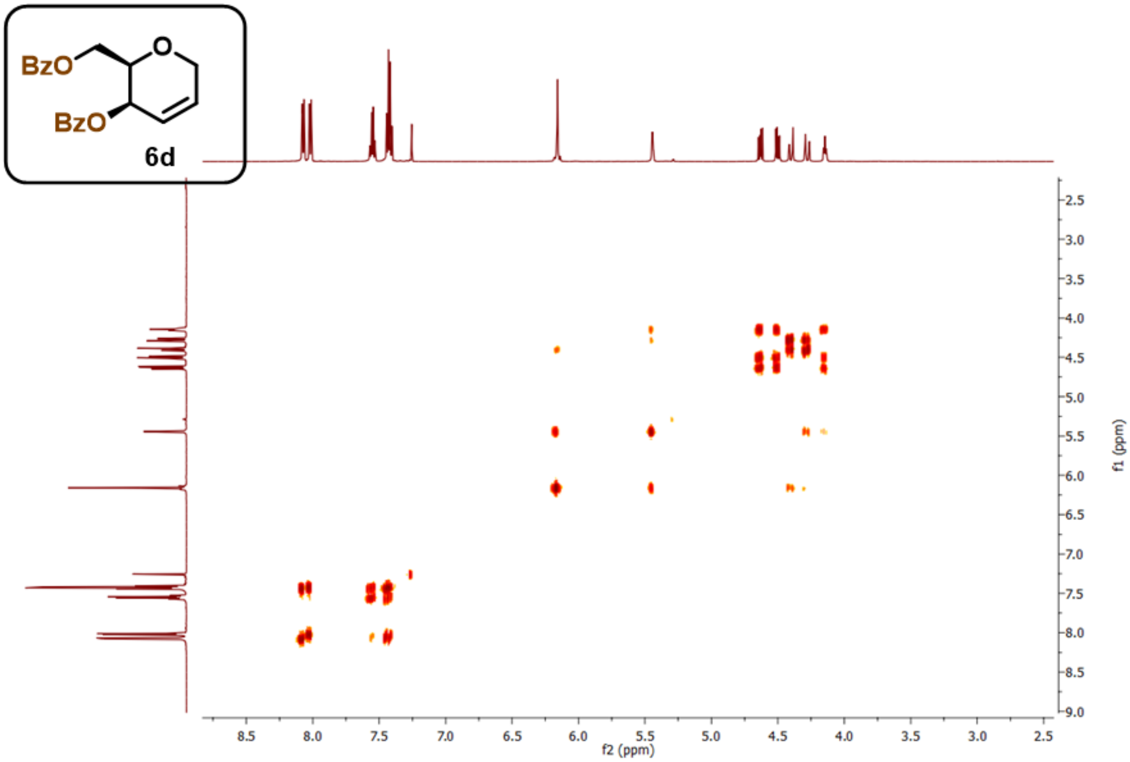
^{13}C NMR spectrum of **6c**,)151 MHz, $CDCl_3$(



^{1}H NMR spectrum of **6d**,)600 MHz, $CDCl_3$(



^{13}C NMR spectrum of **6d**,)151 MHz, CDCl$_3$(



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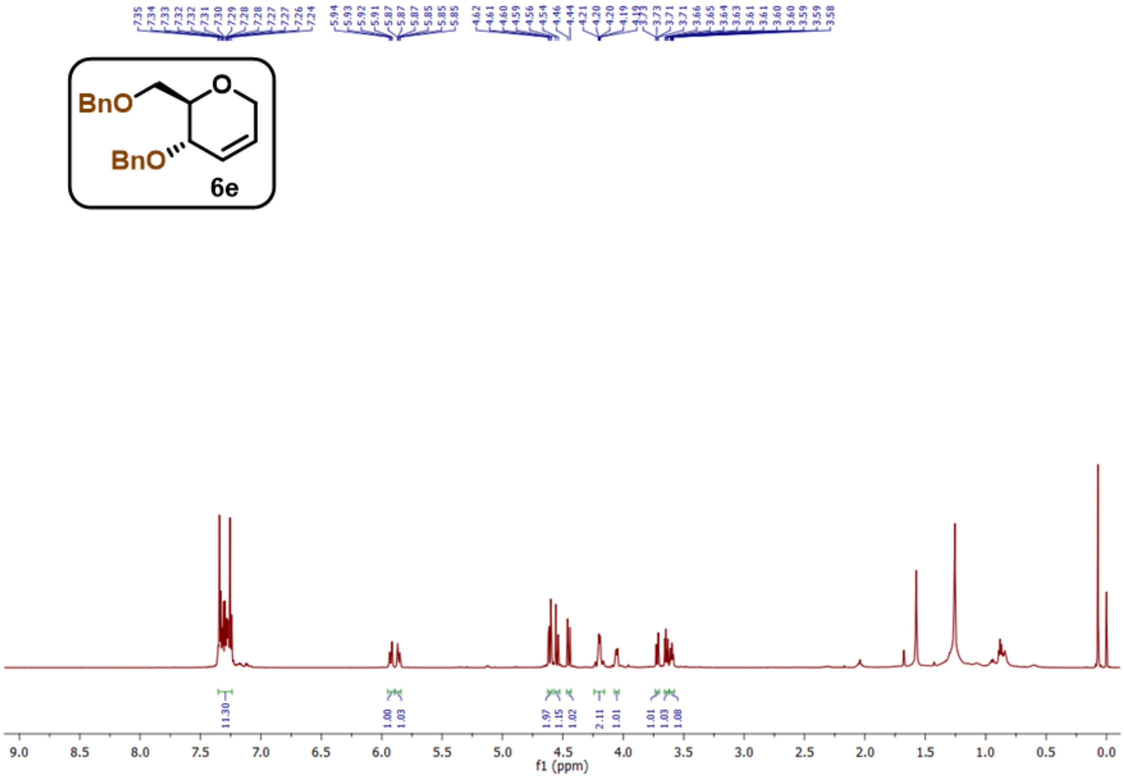

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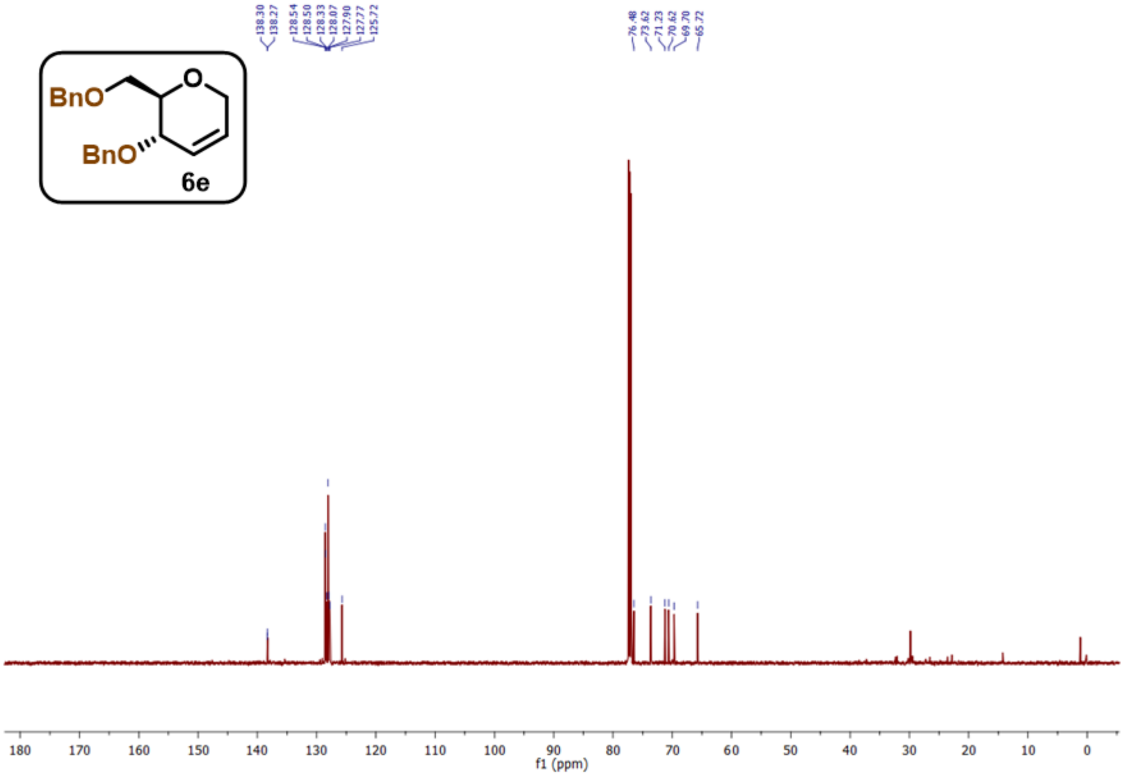

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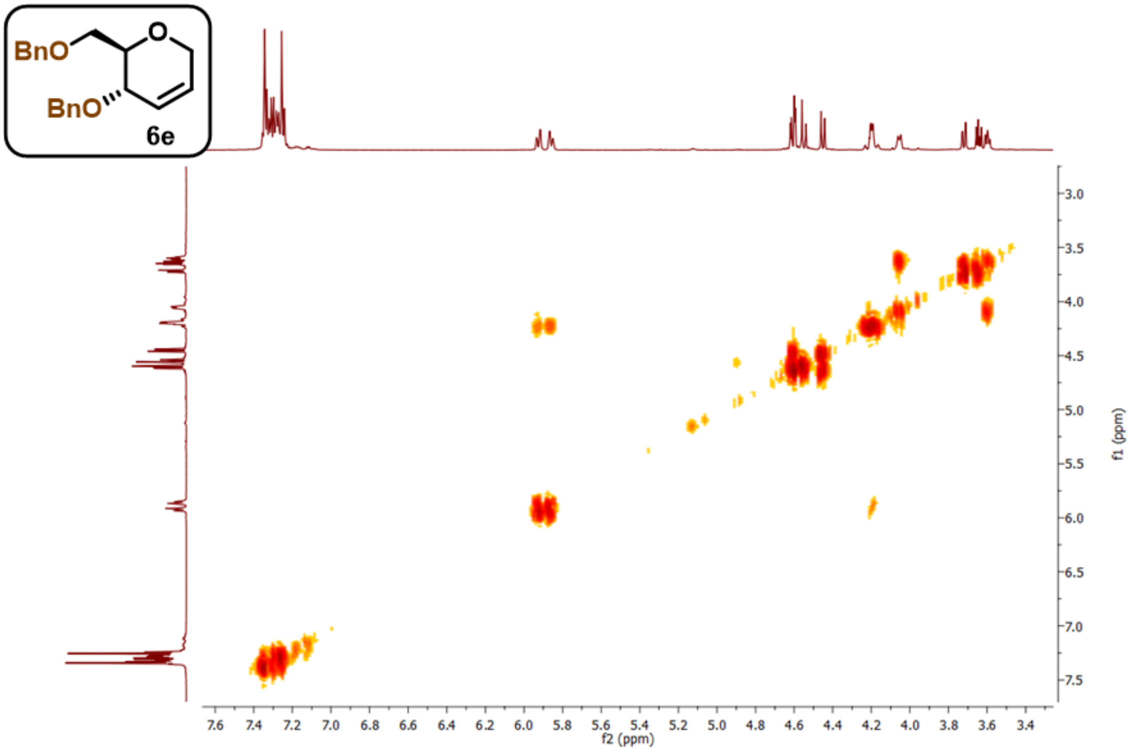
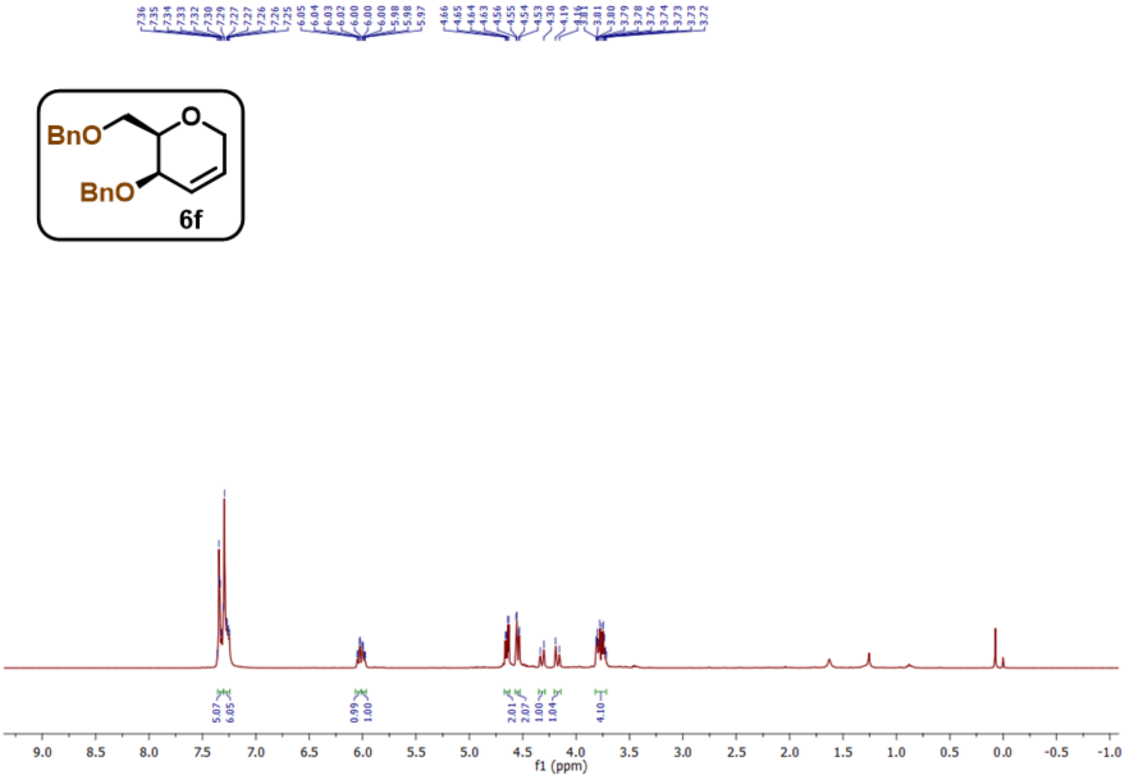


COSY NMR spectrum of **6e**,)600 MHz, CDCl$_3$(



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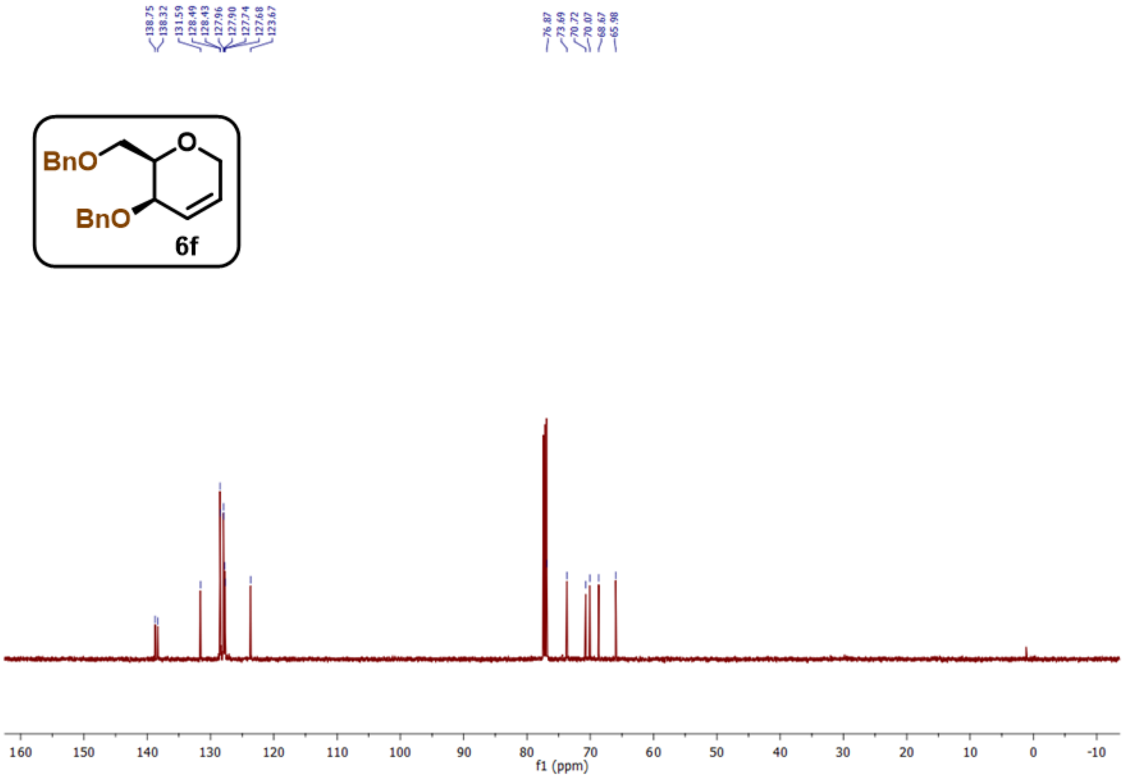

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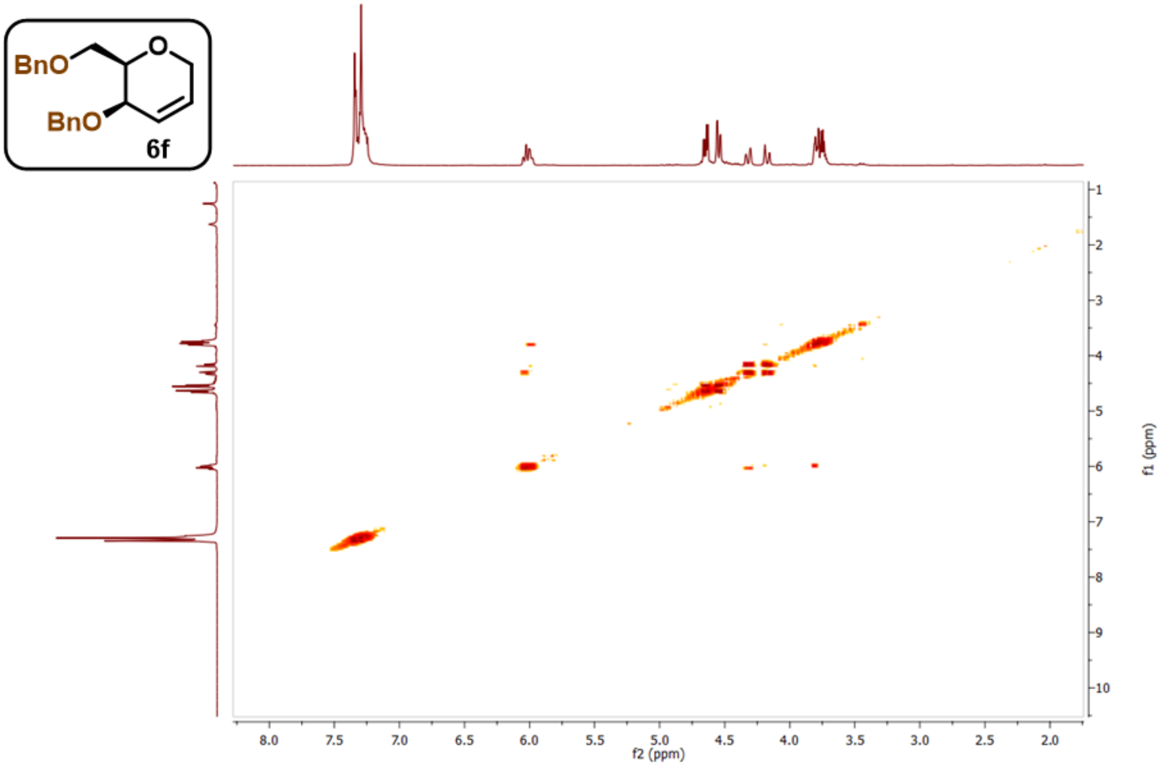

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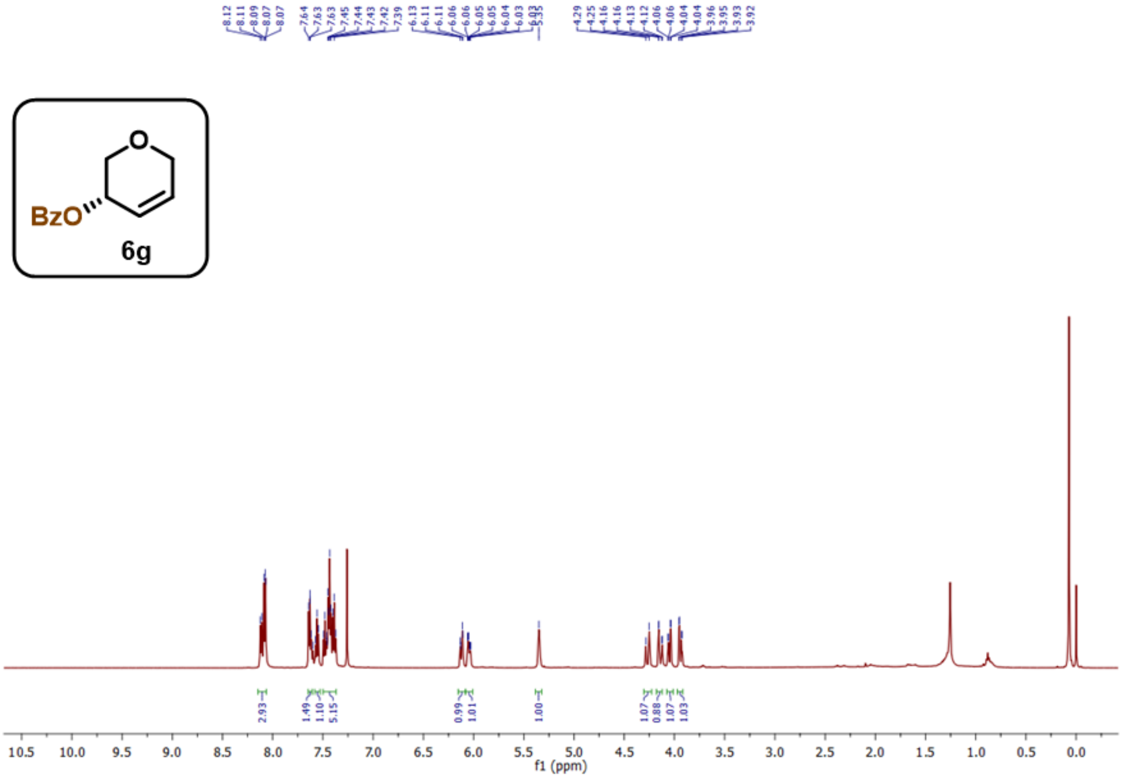

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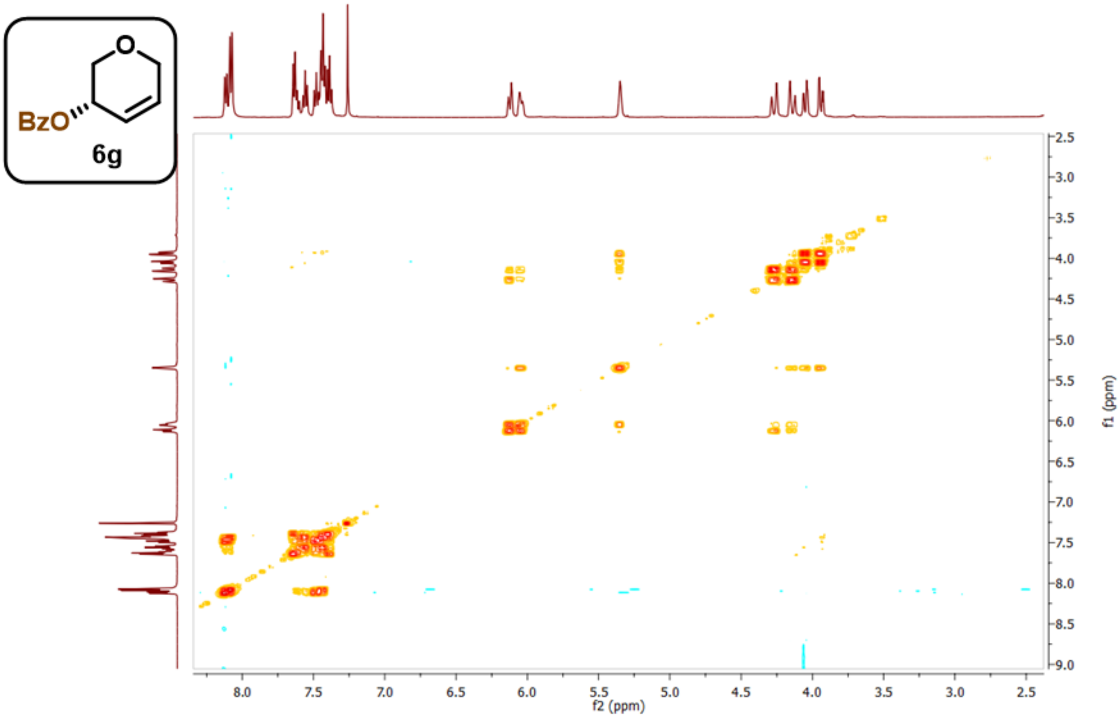

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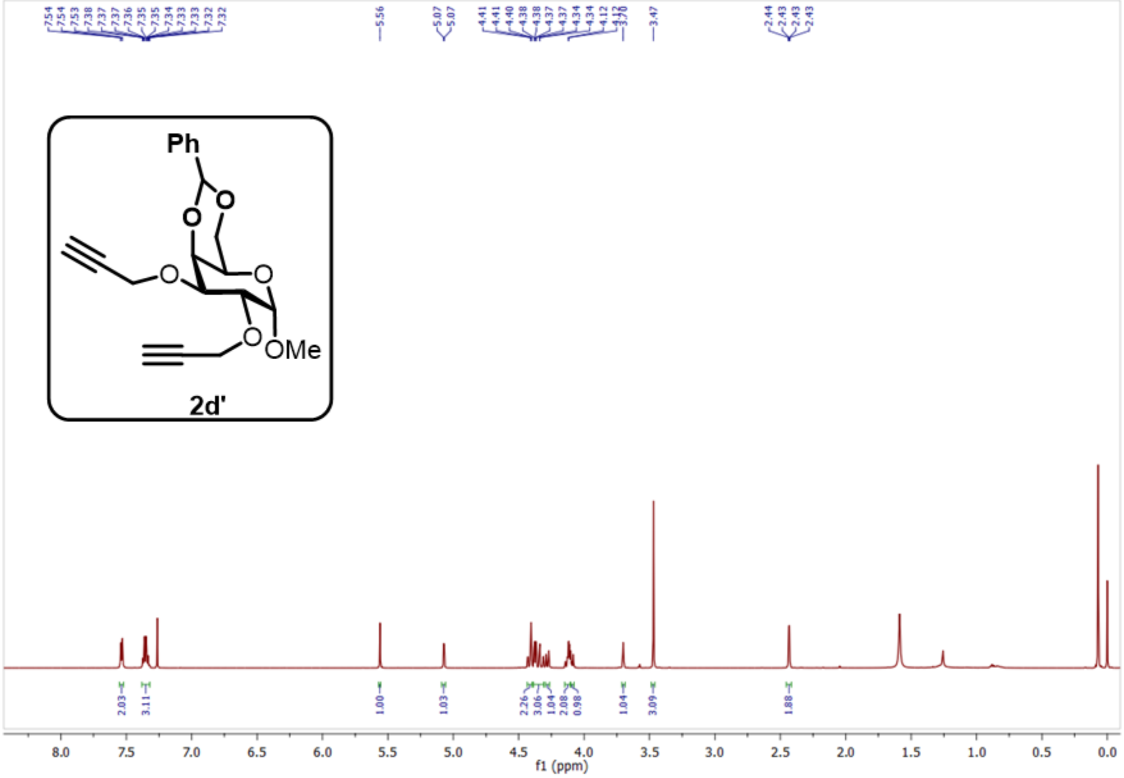

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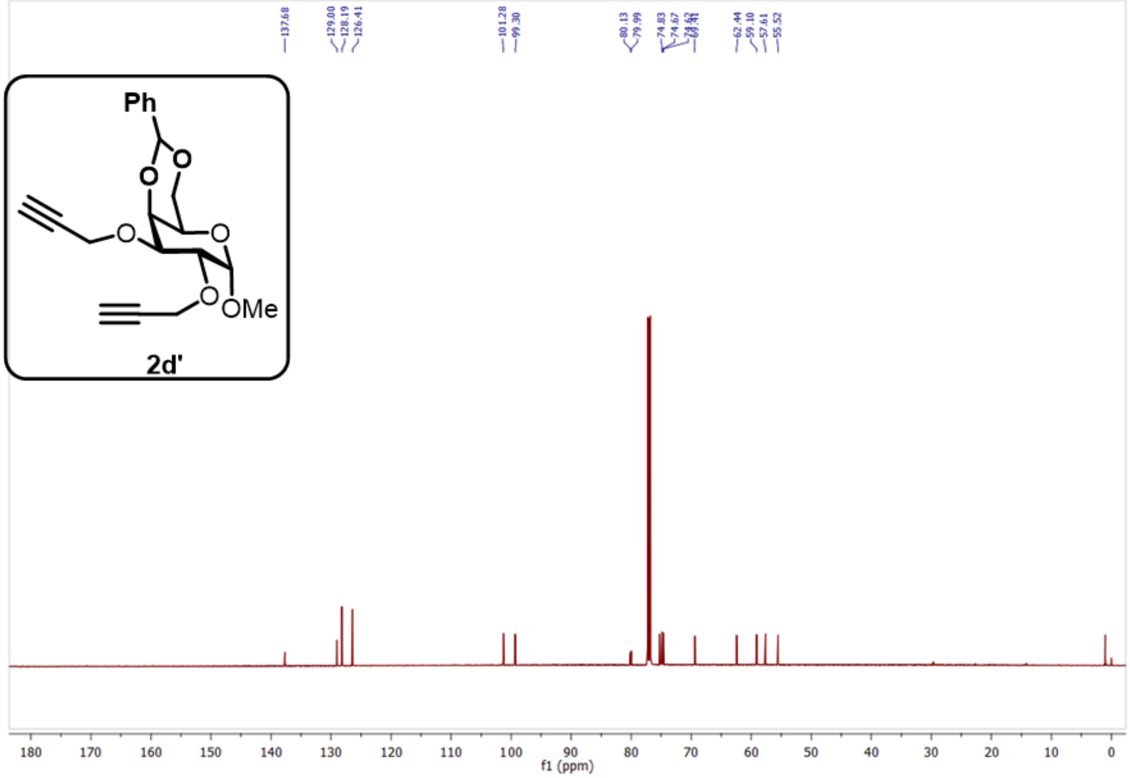

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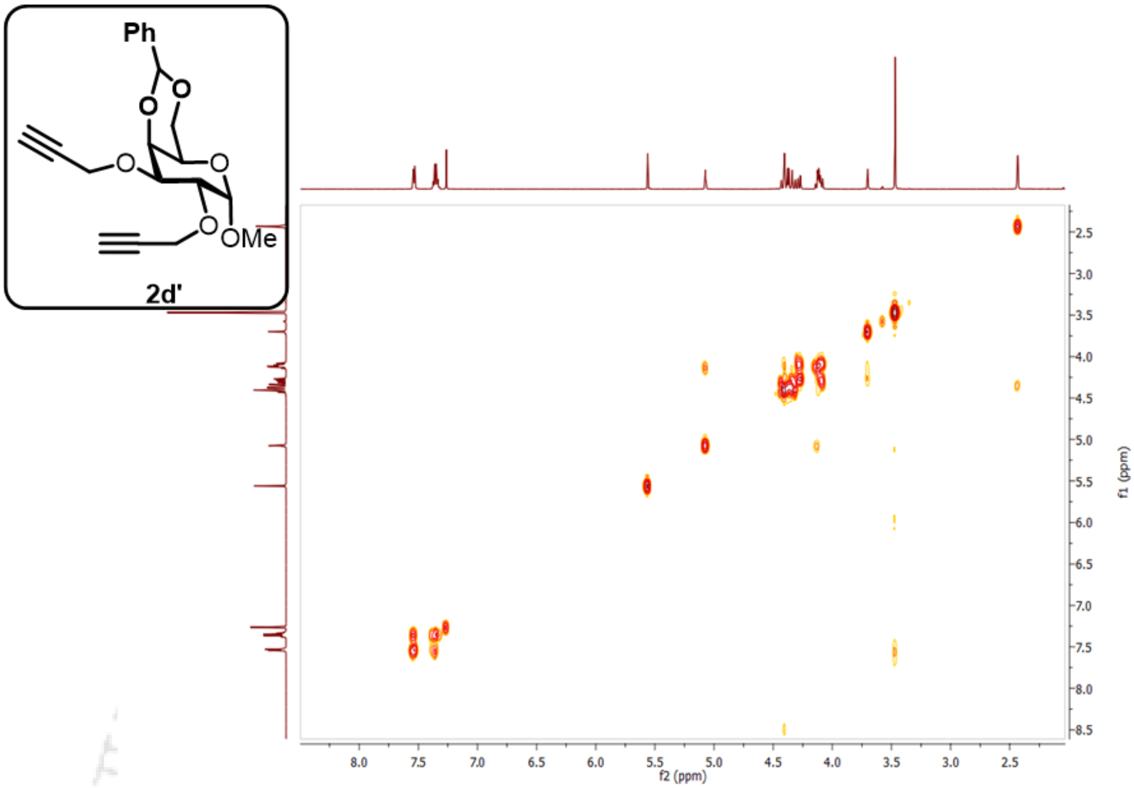

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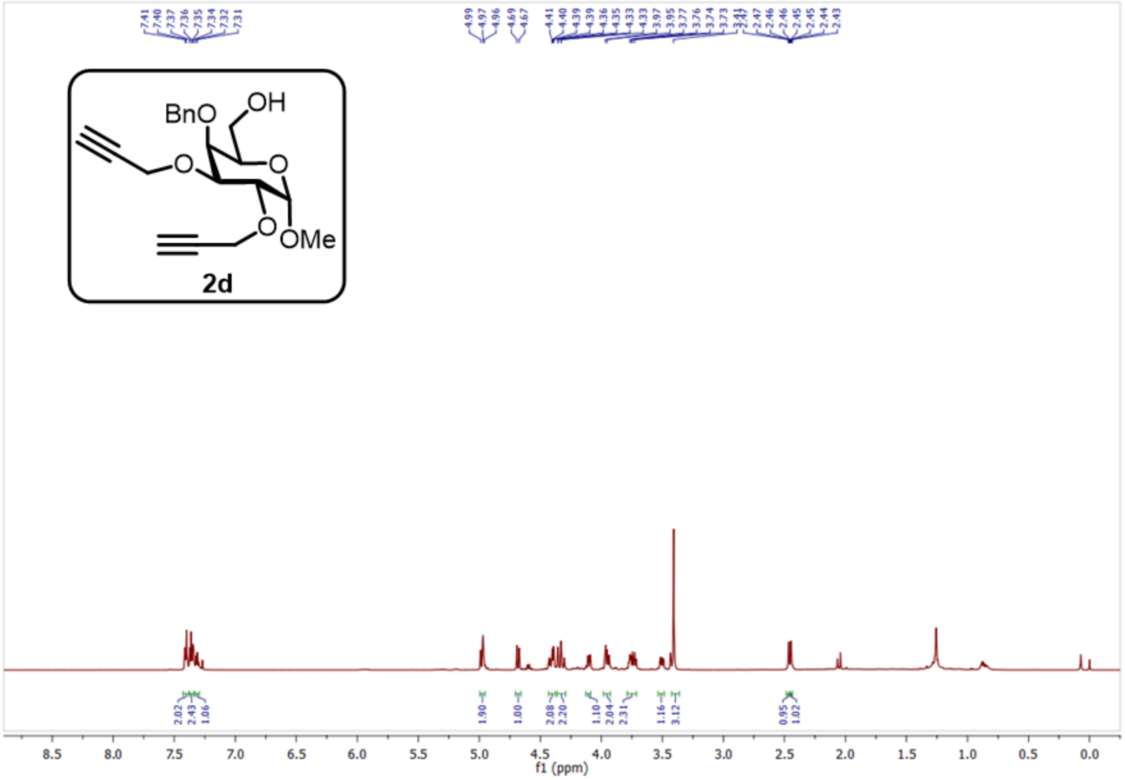

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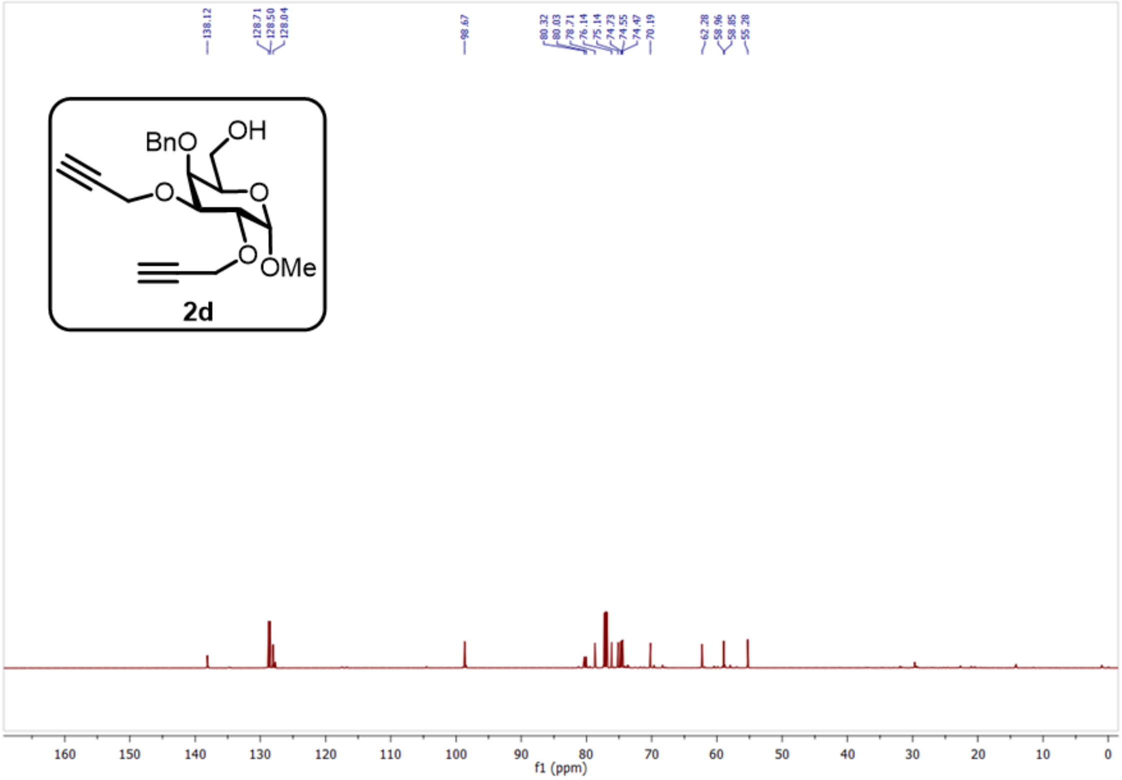

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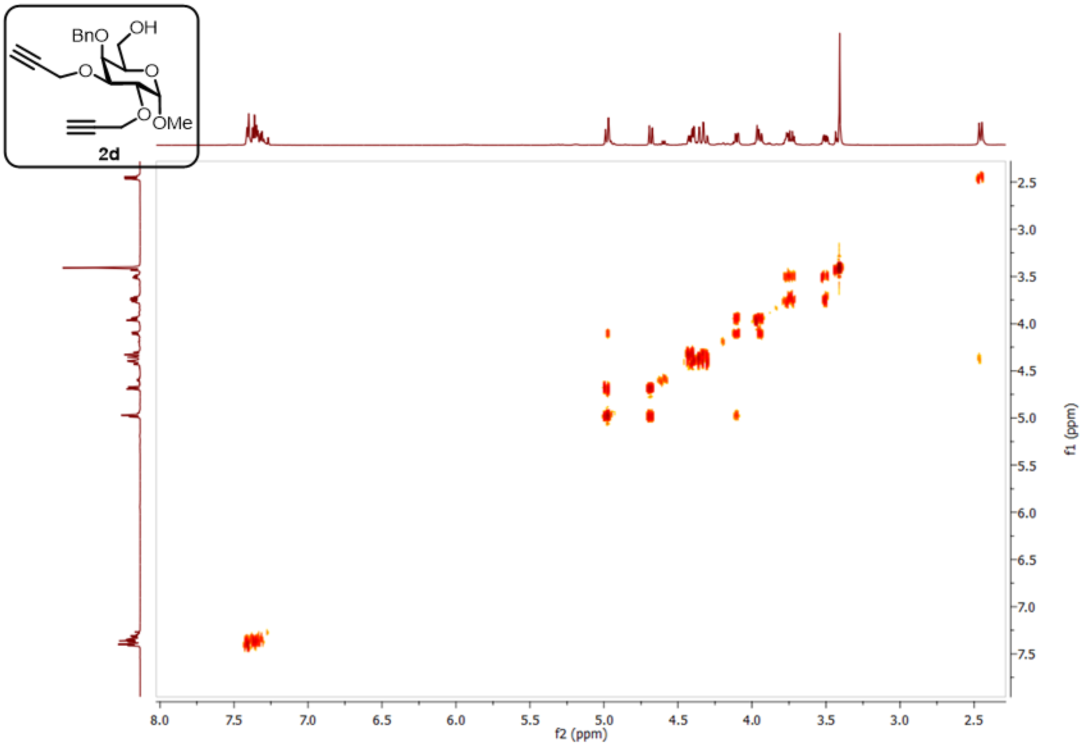

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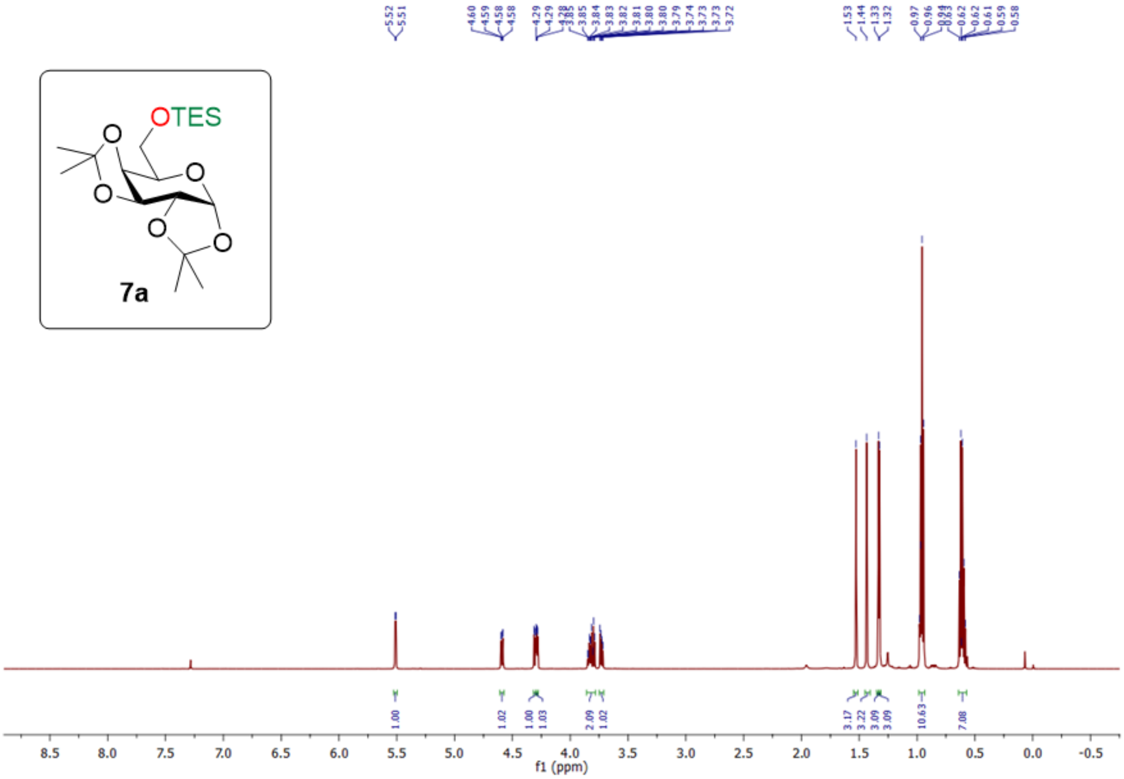

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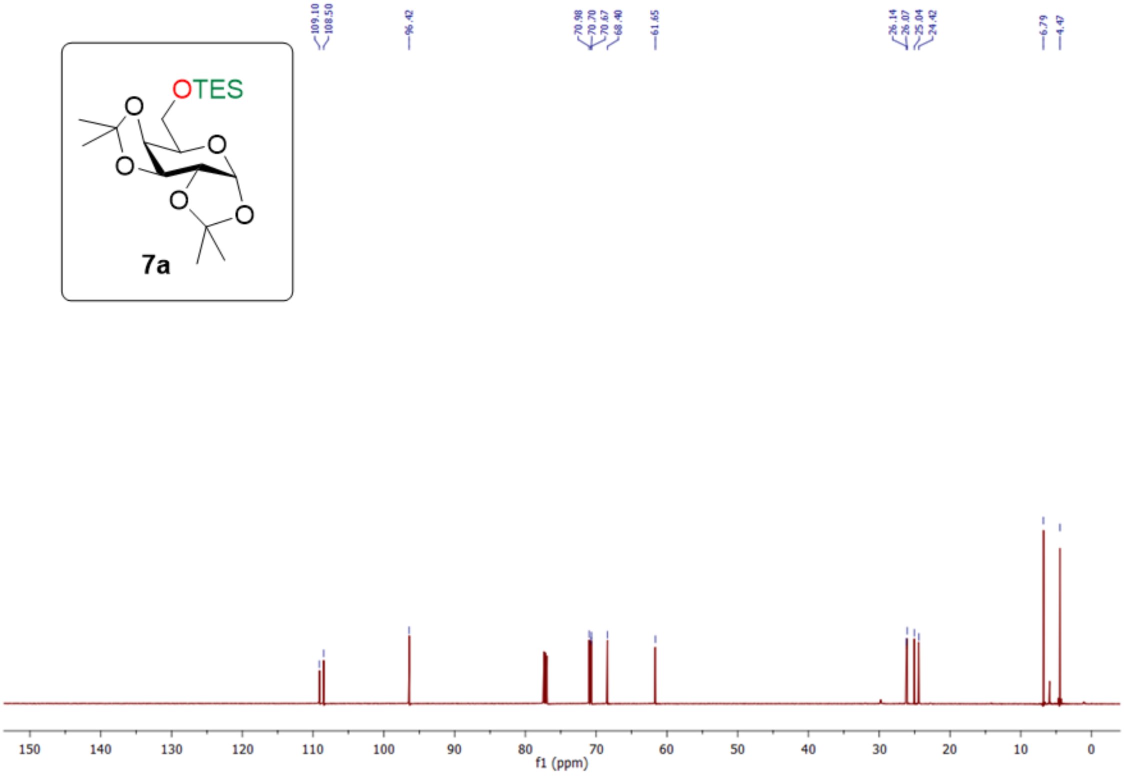

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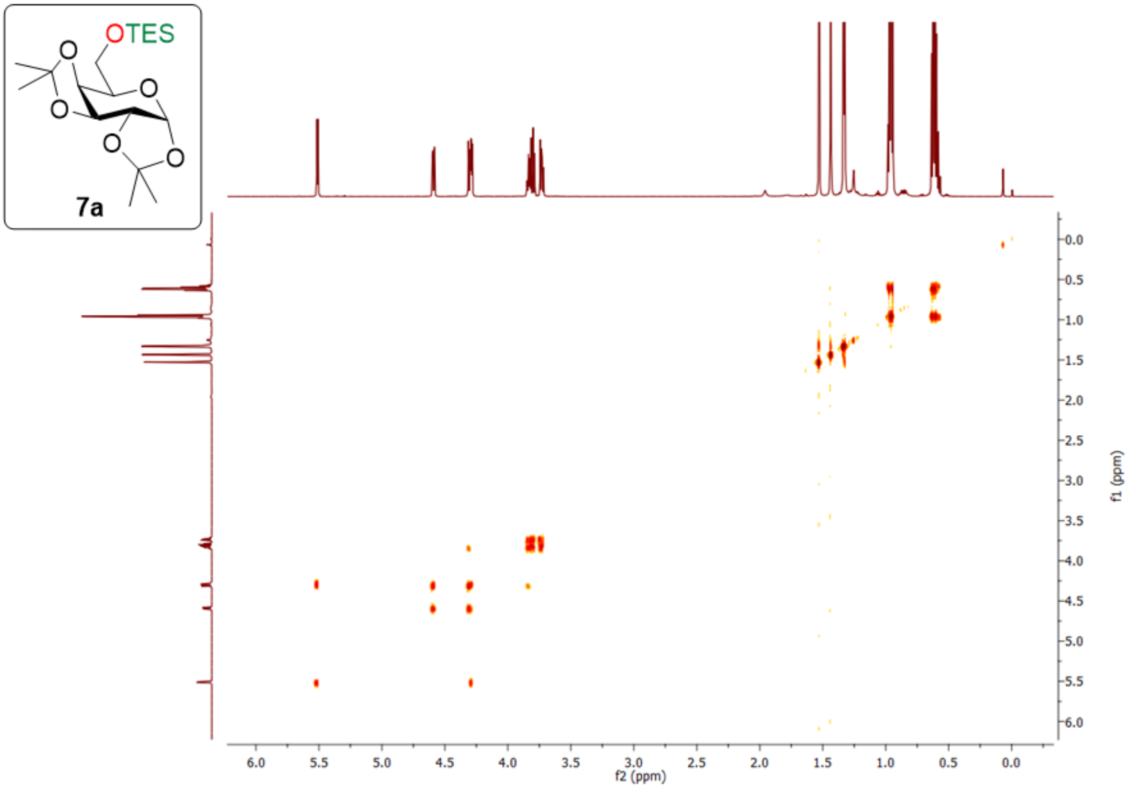

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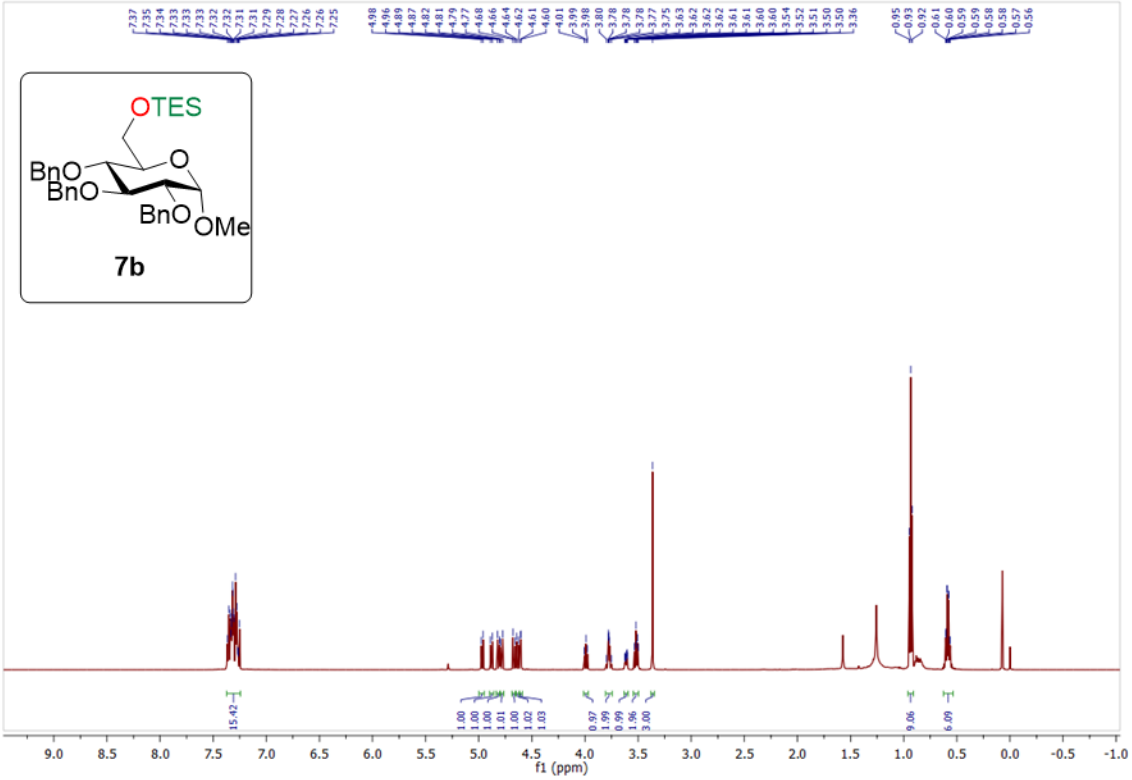

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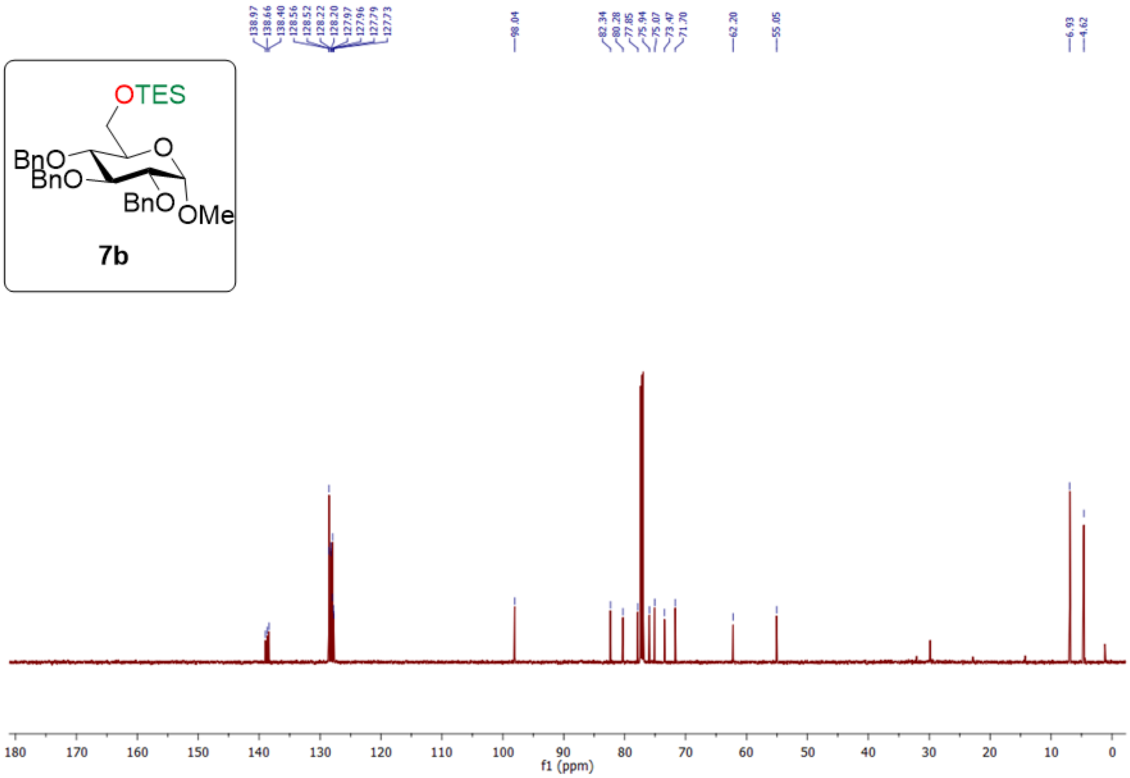

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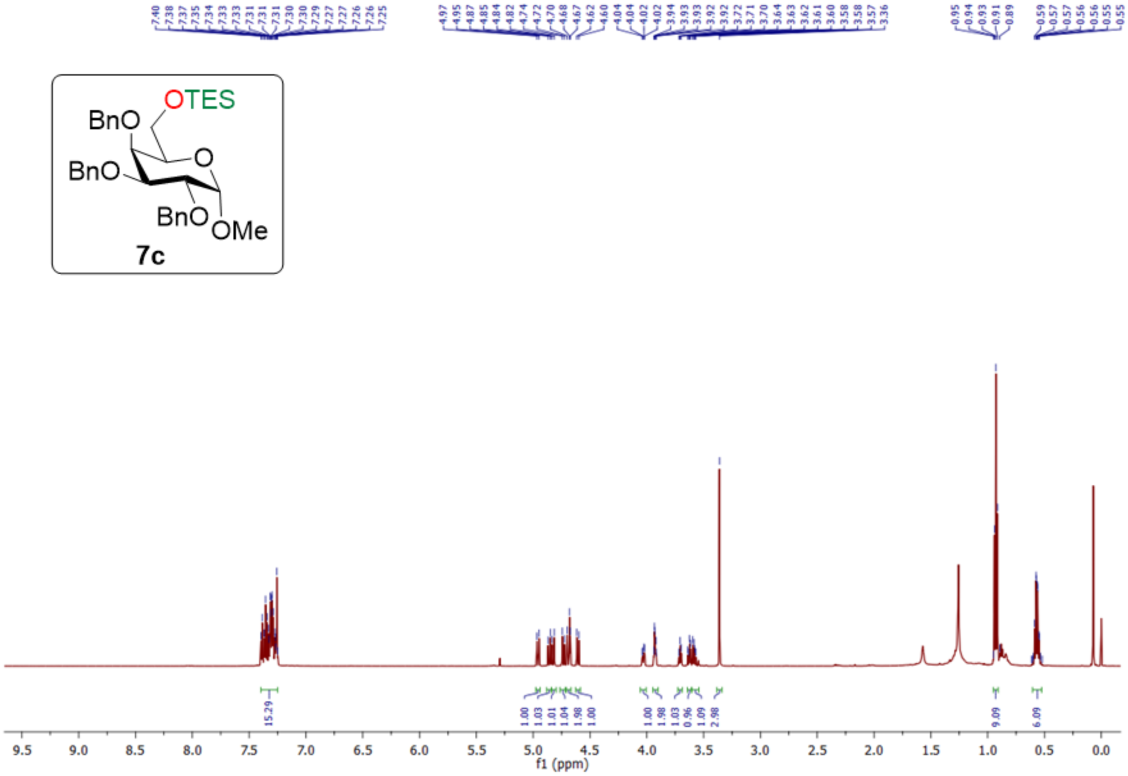

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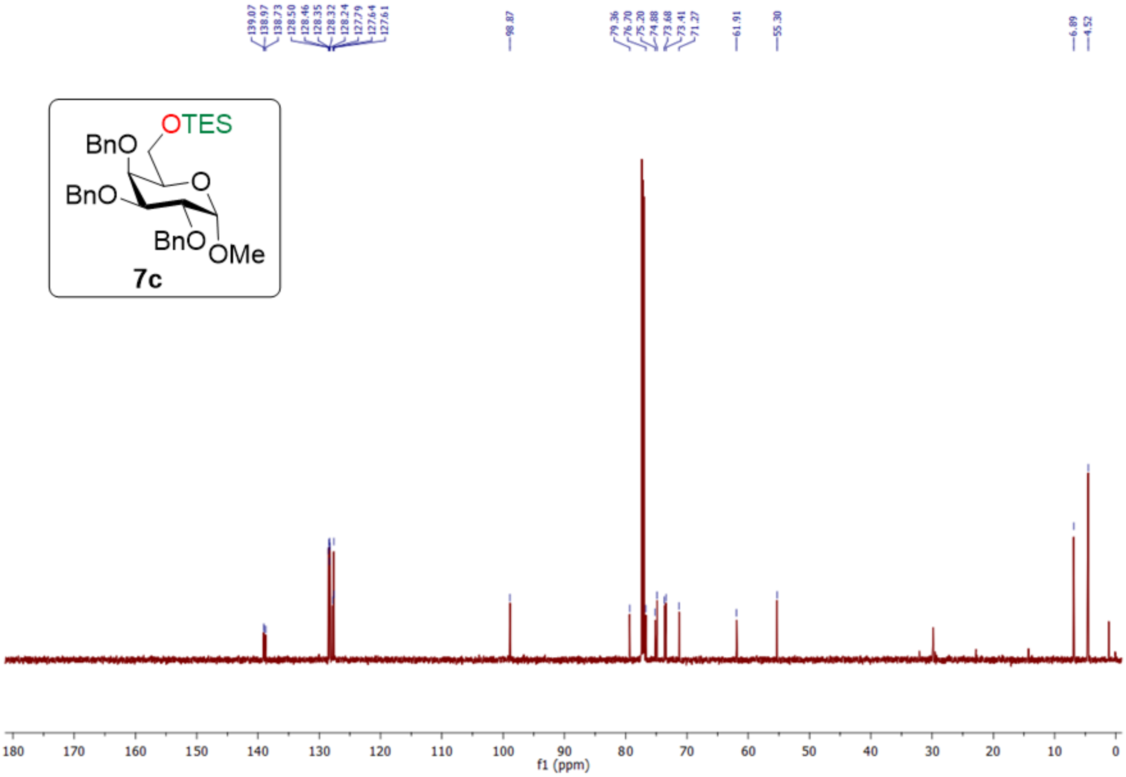

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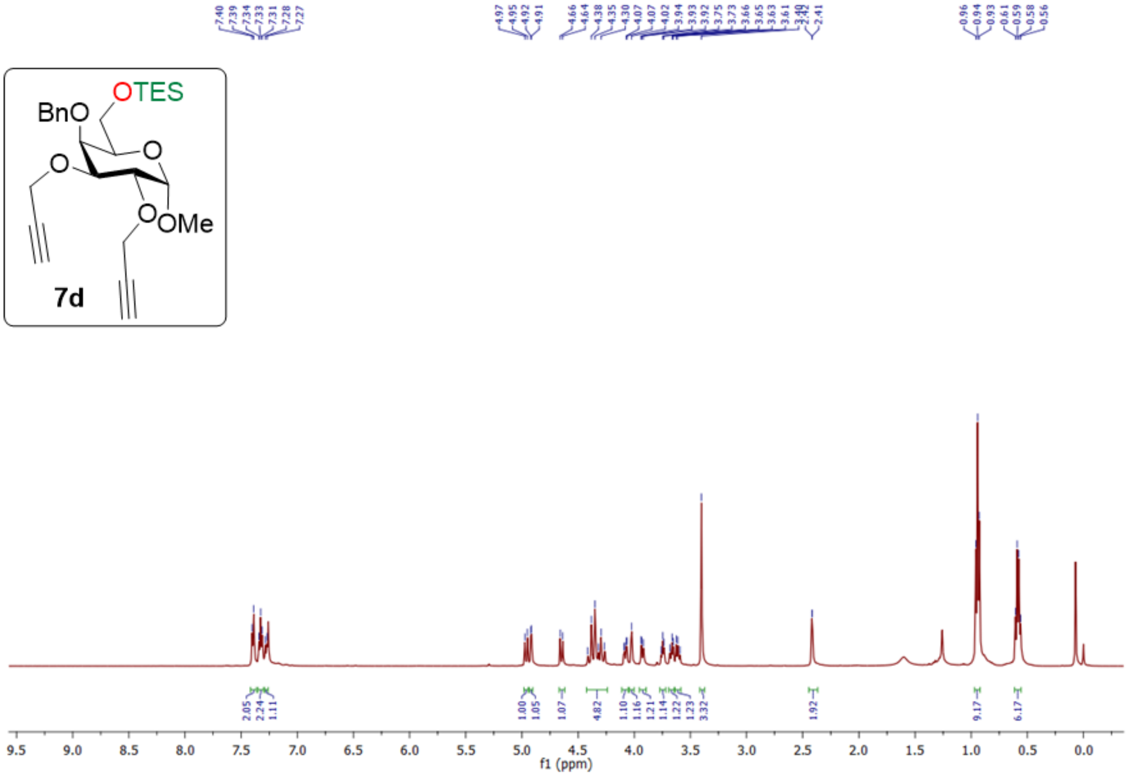

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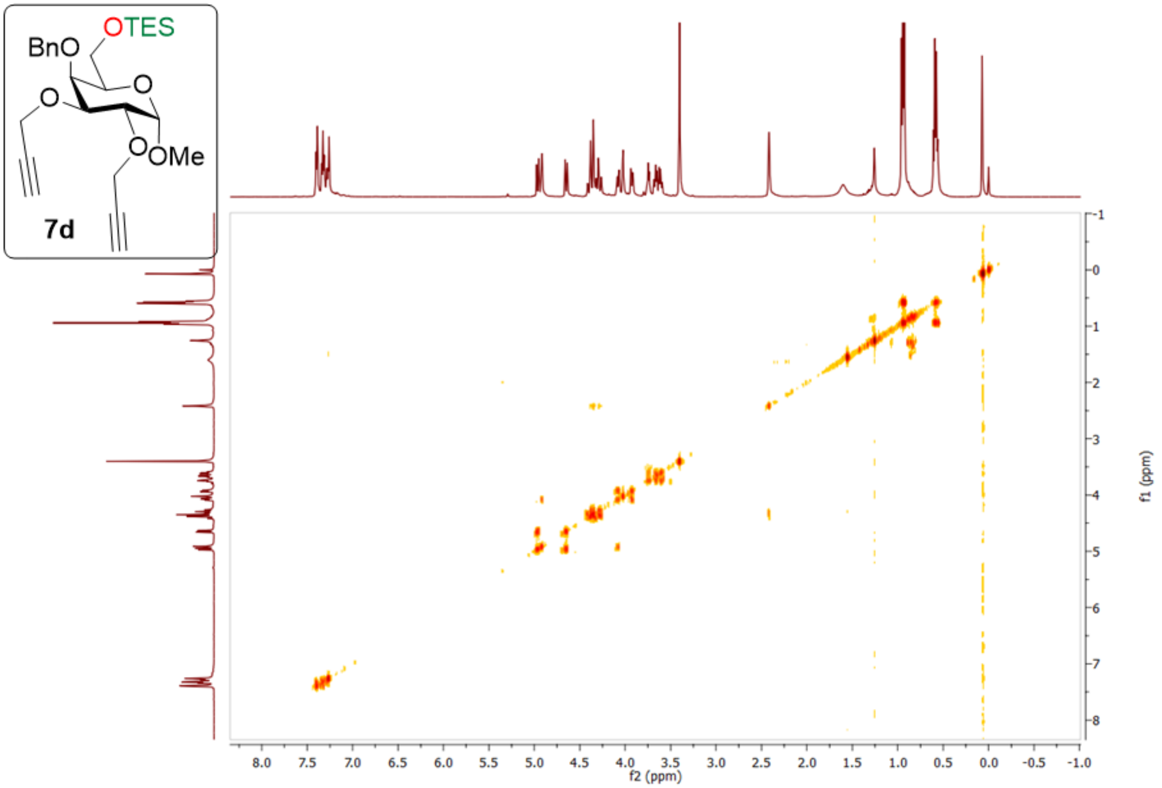

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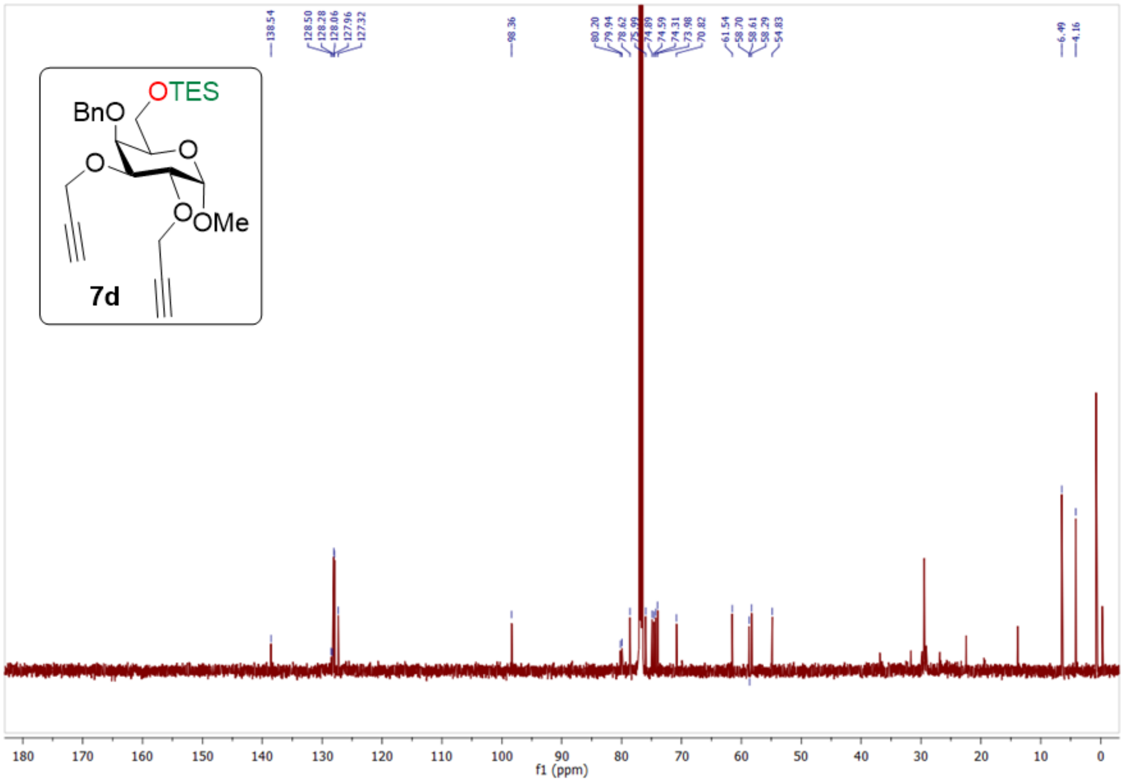

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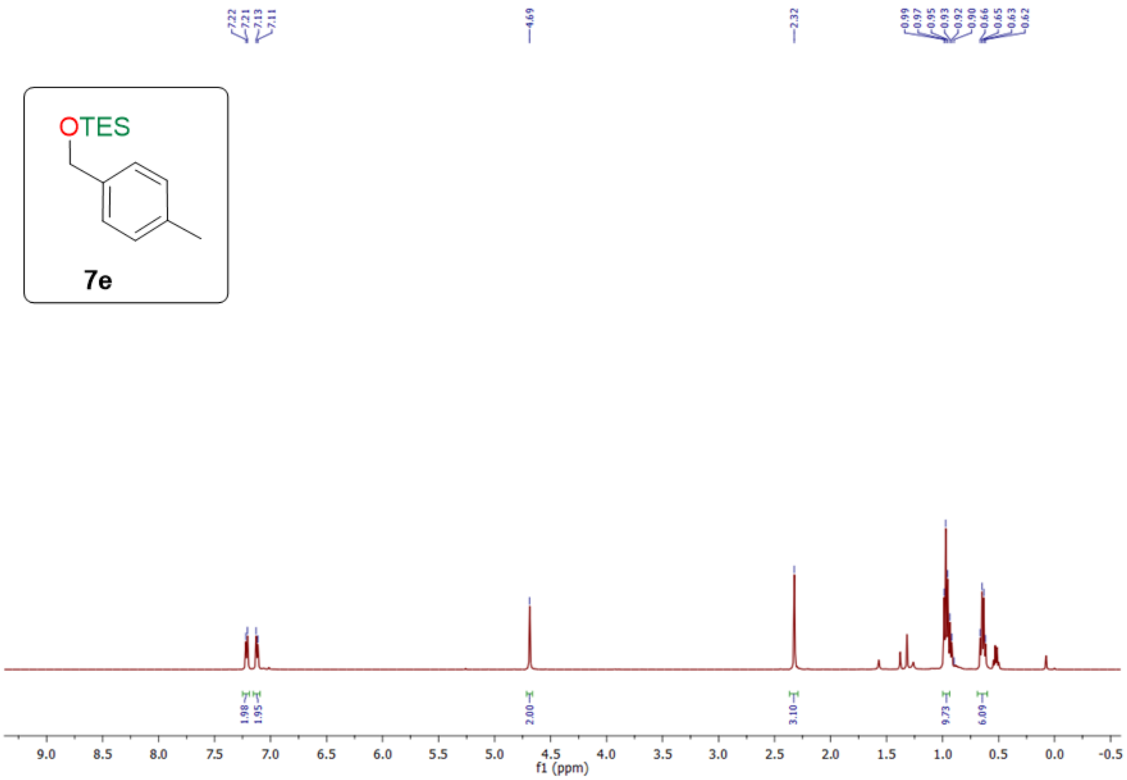

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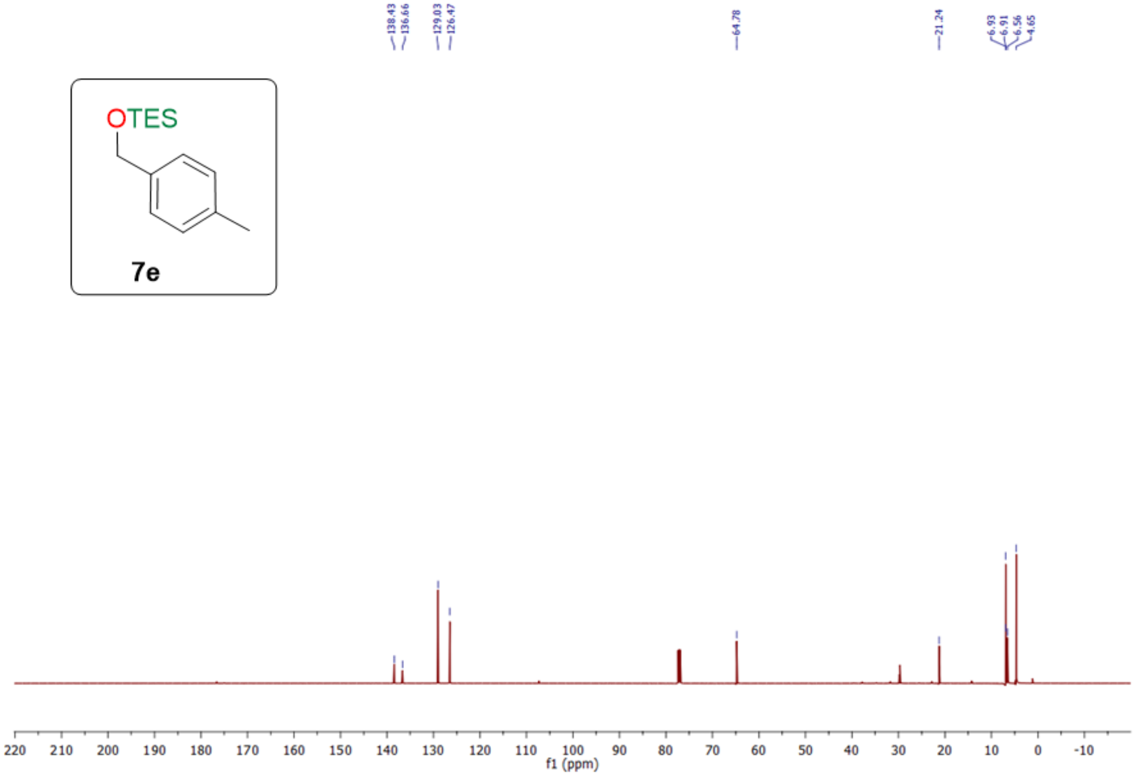

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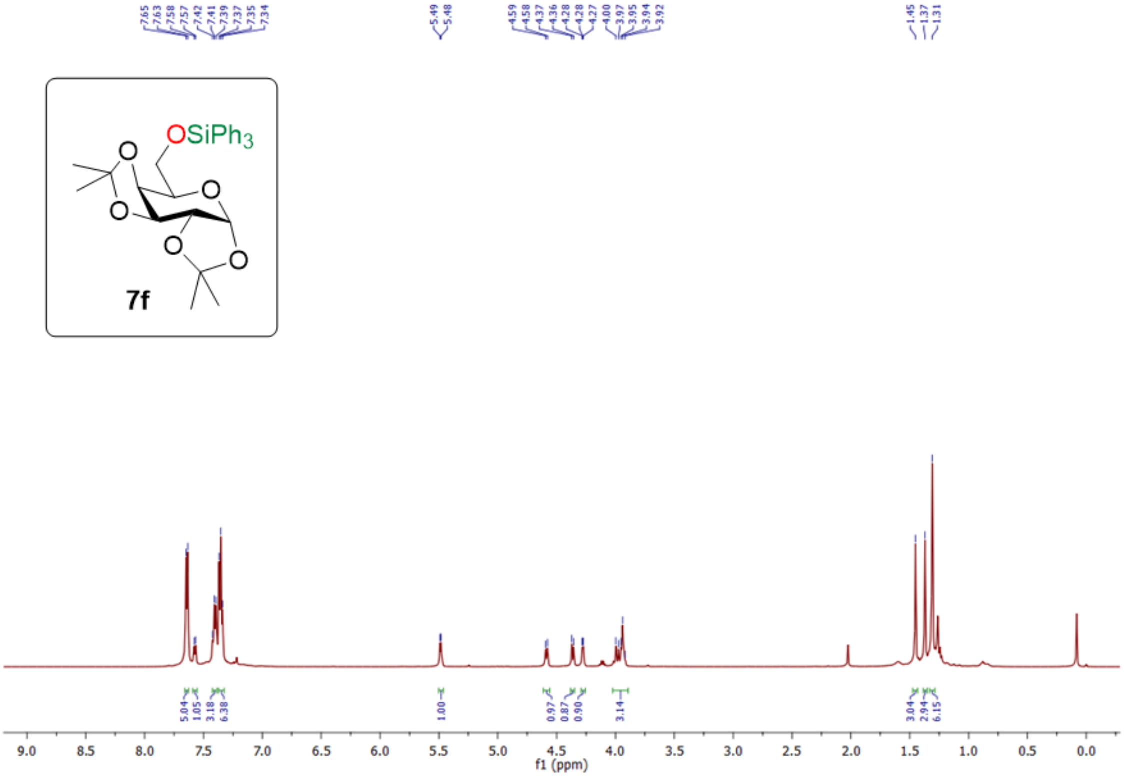

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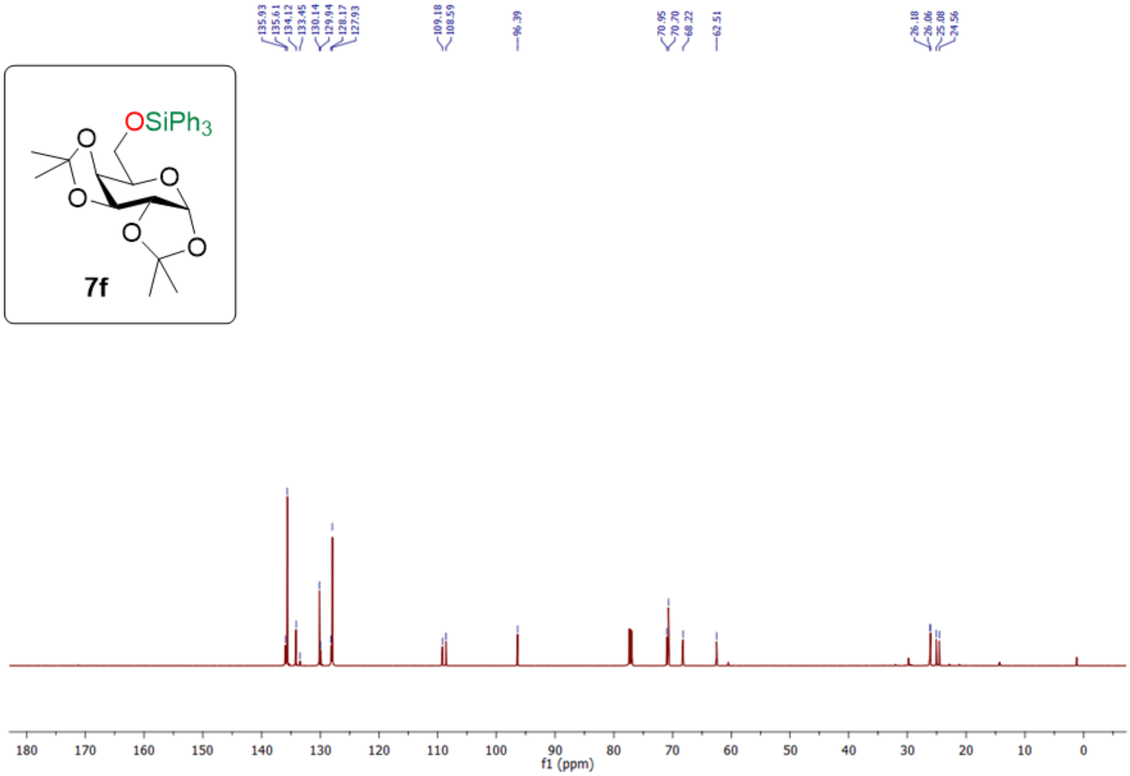

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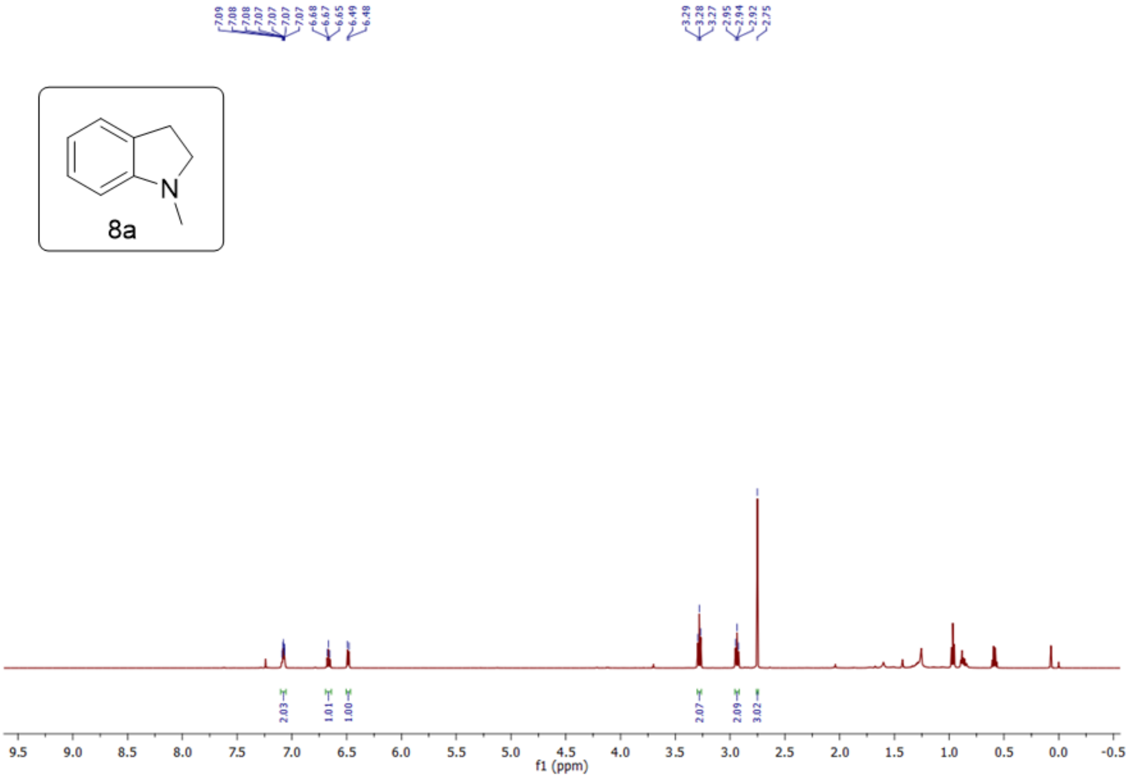

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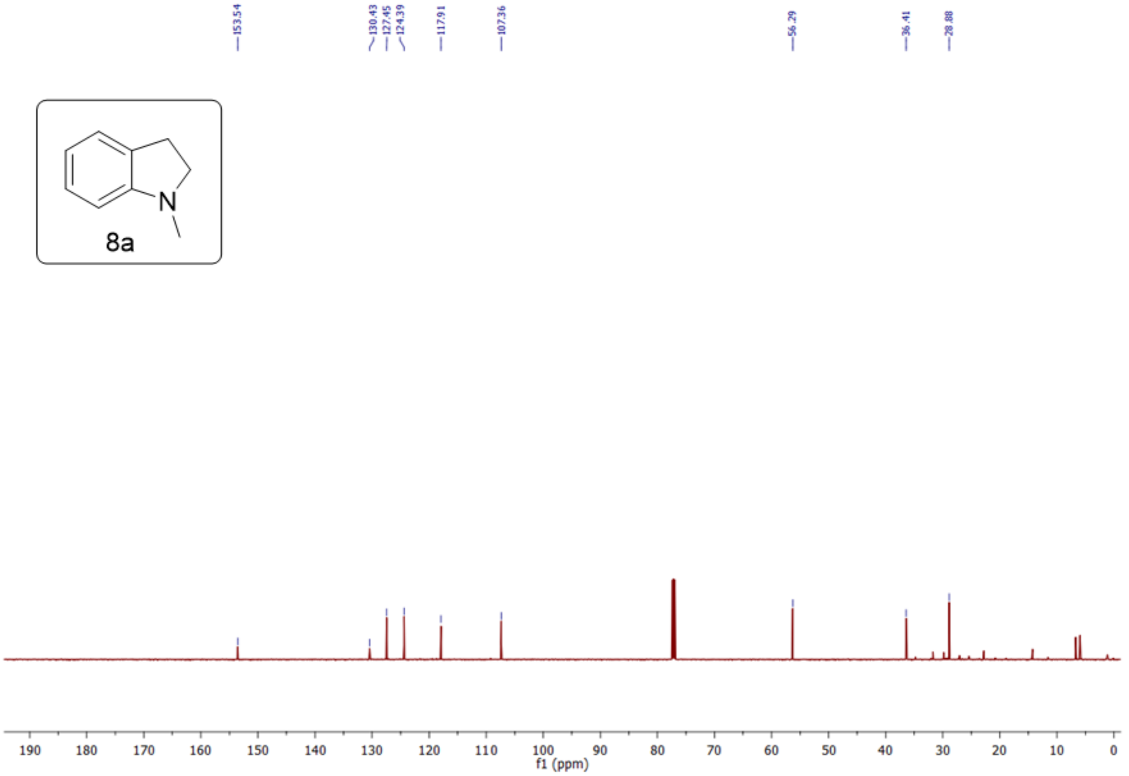

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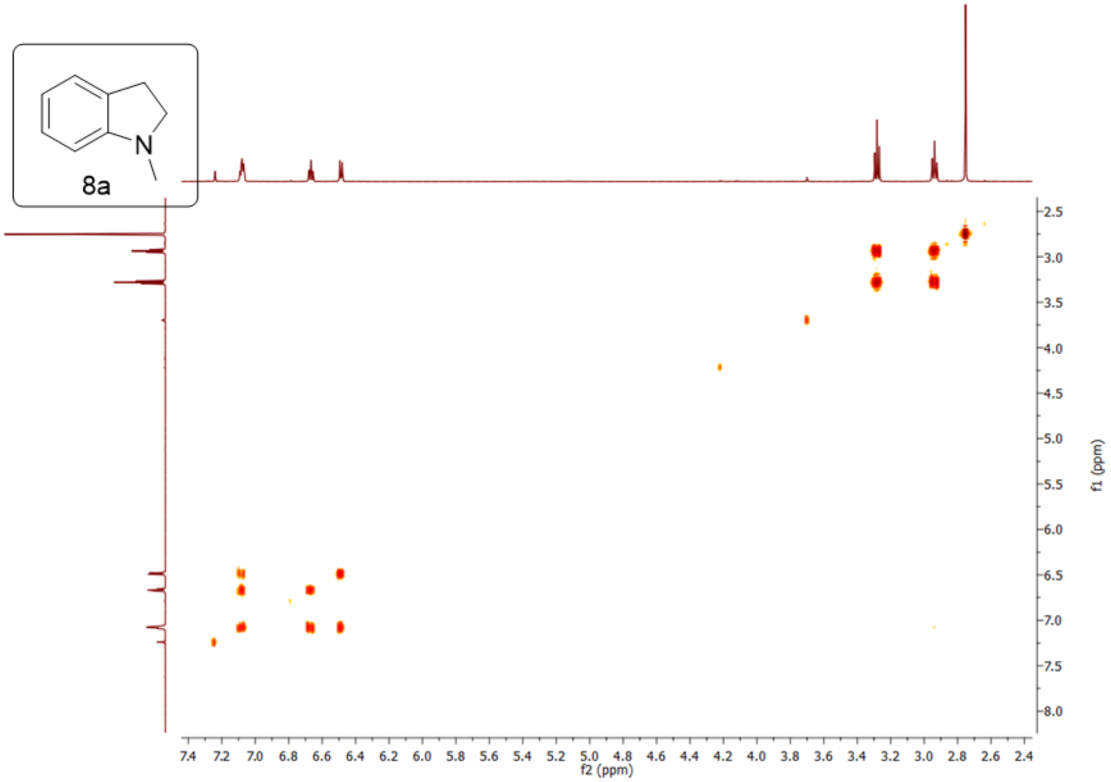

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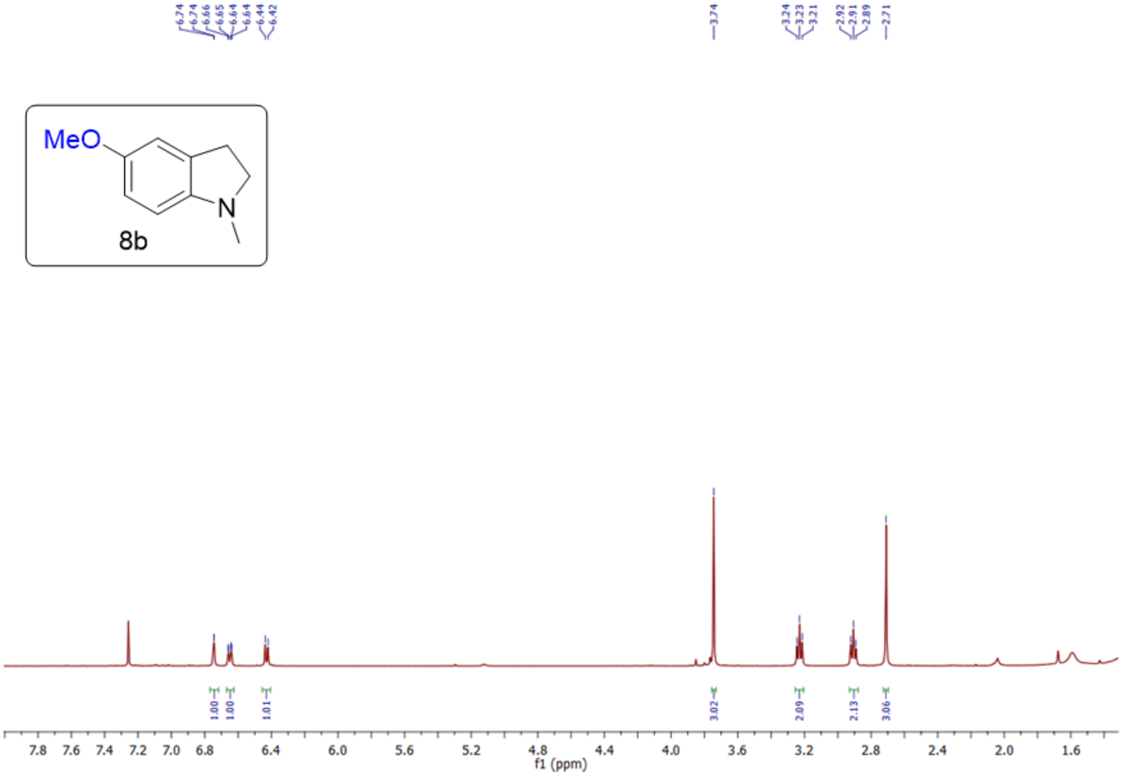

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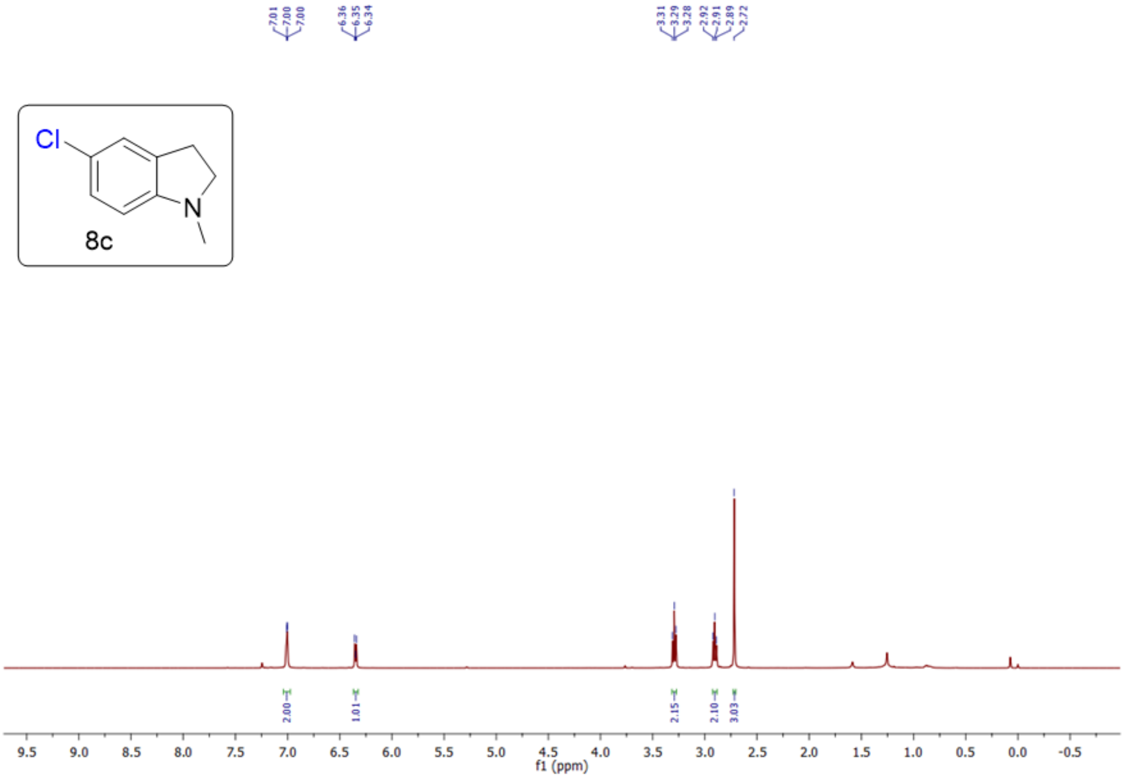

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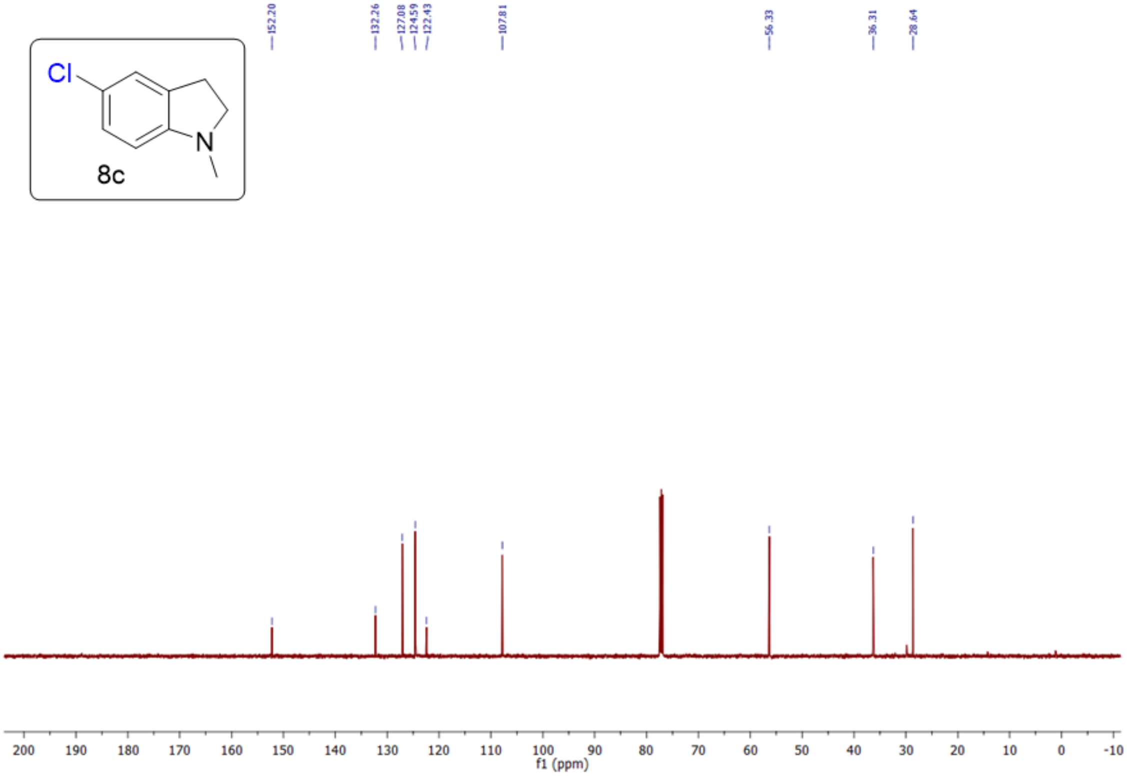

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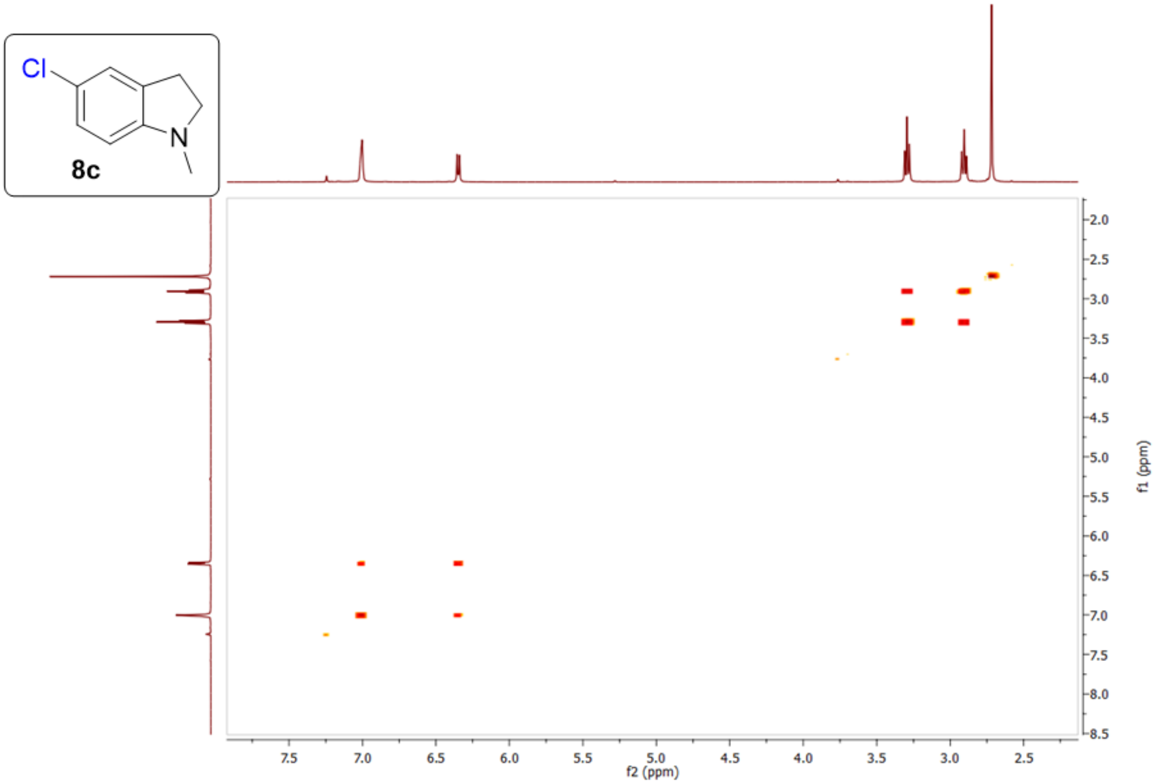

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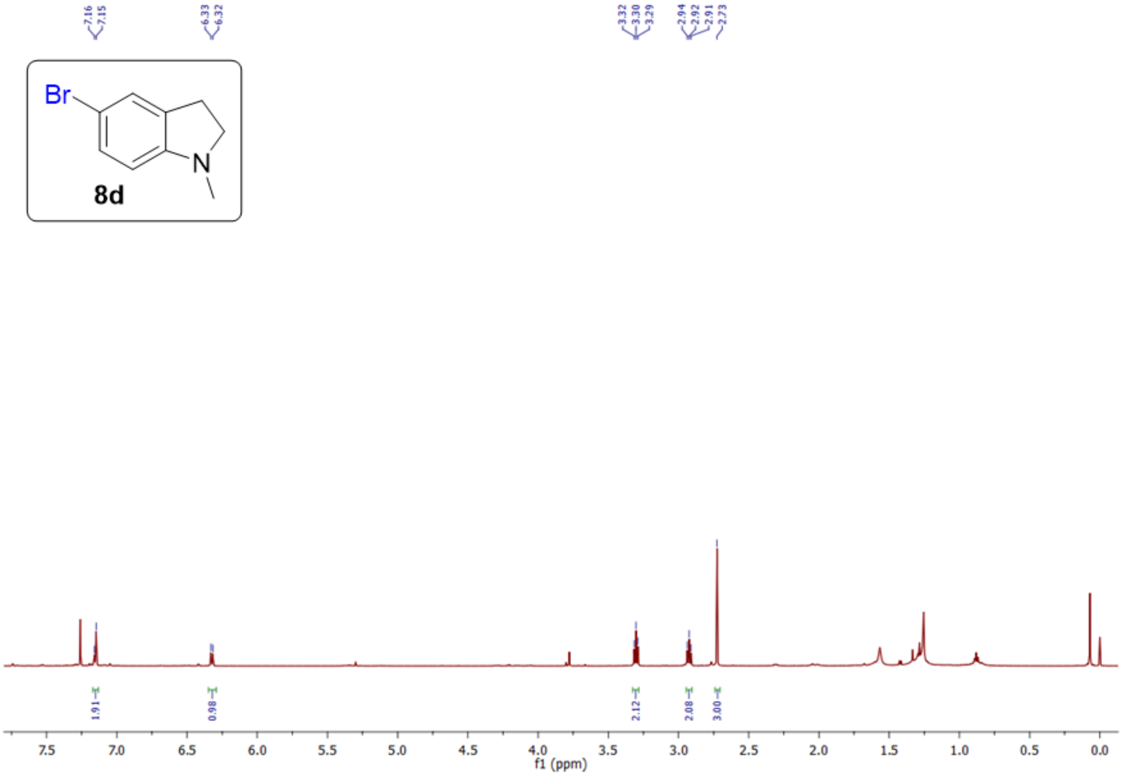

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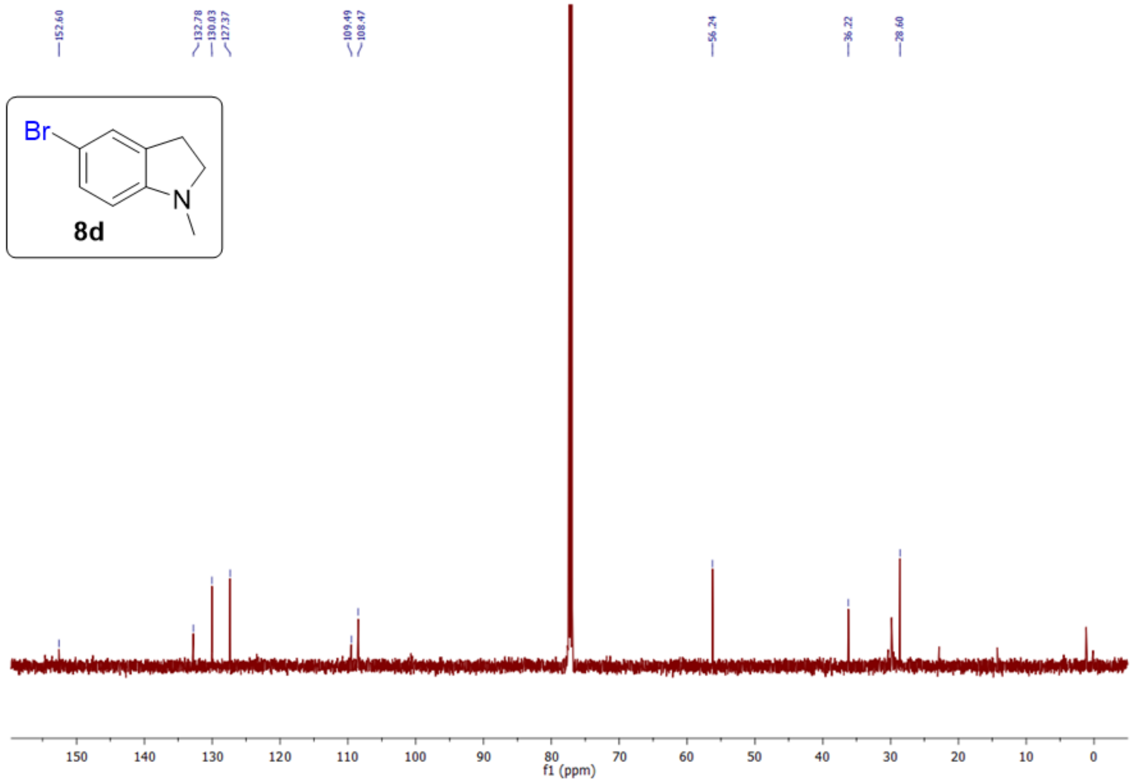

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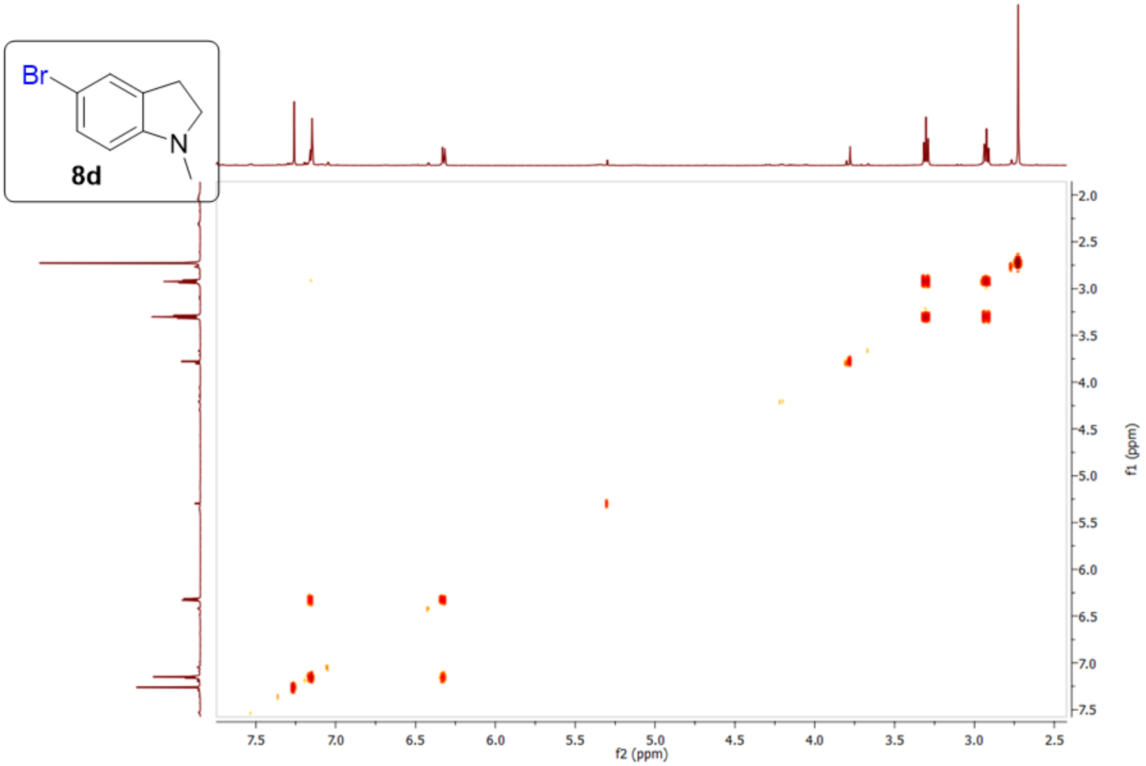

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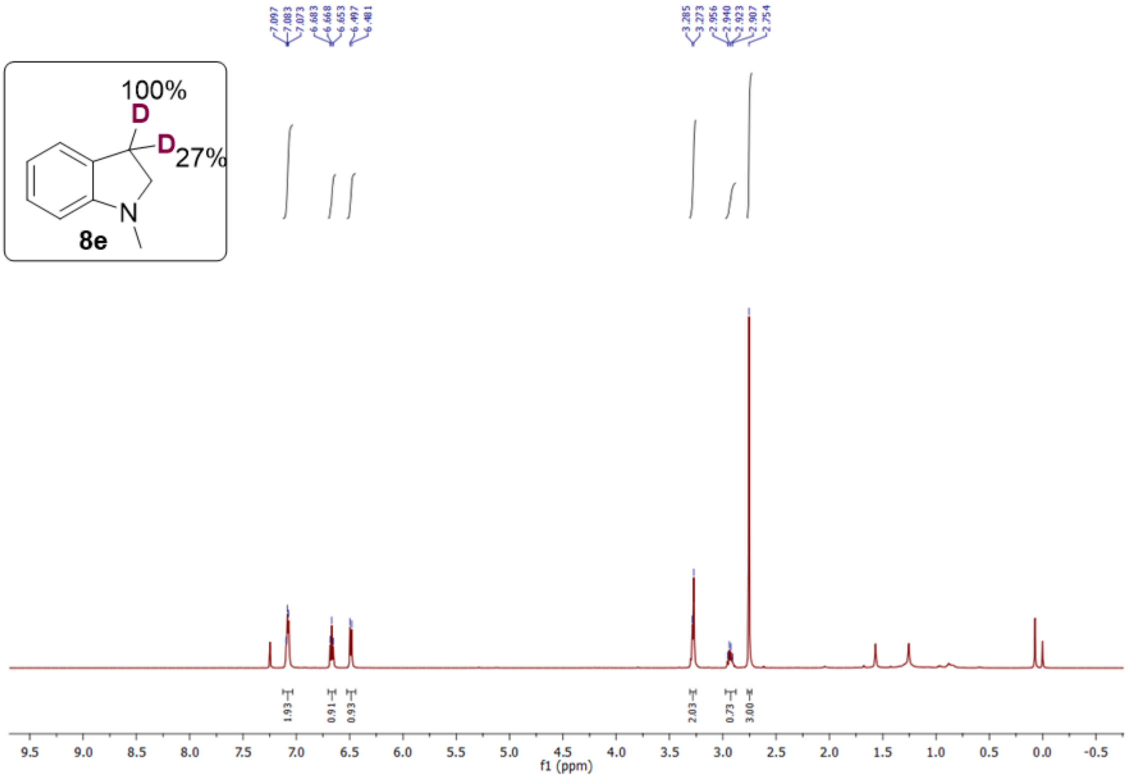

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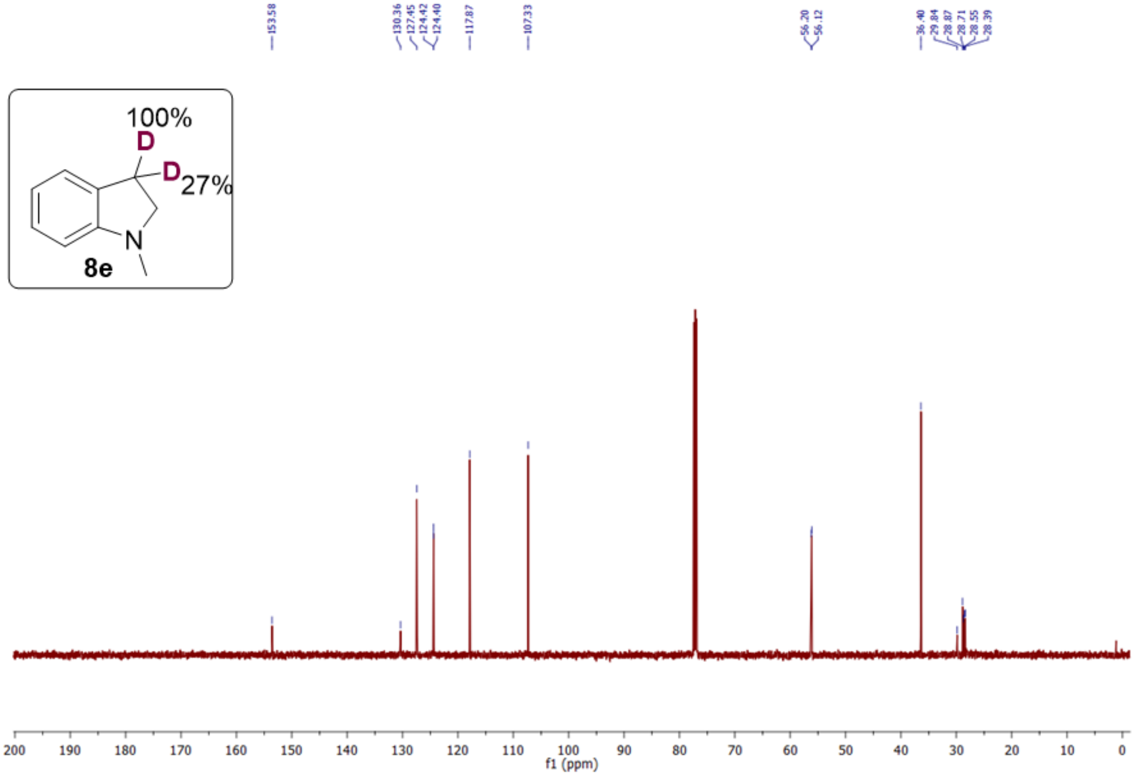

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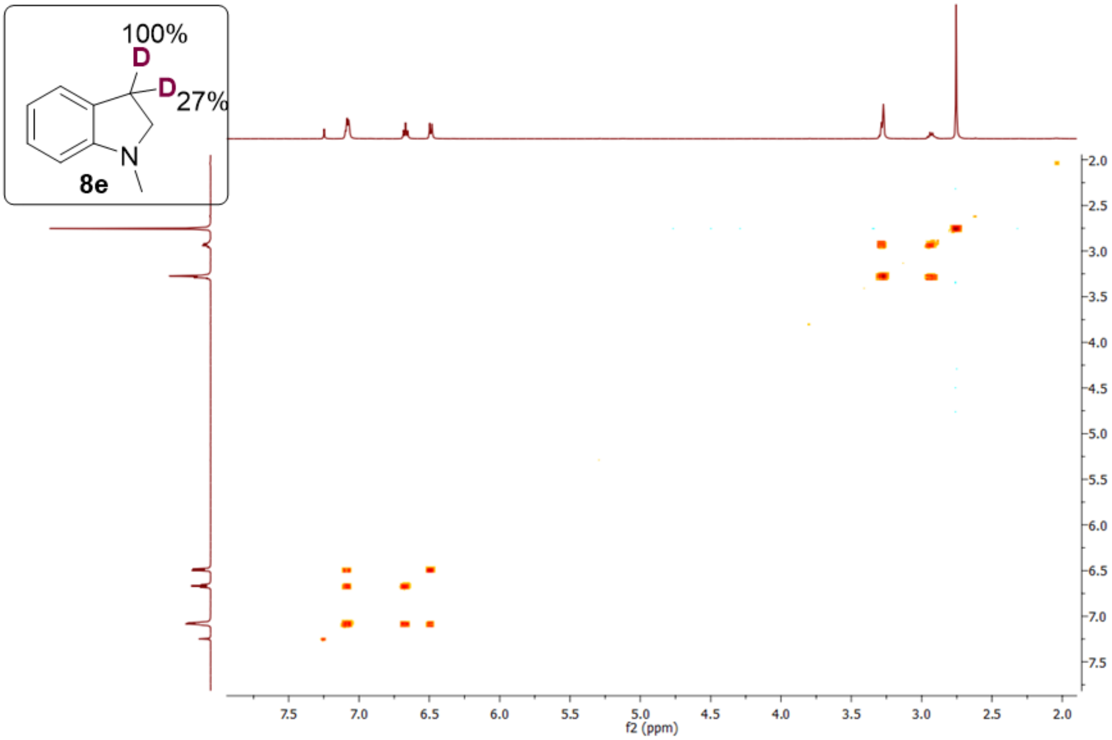

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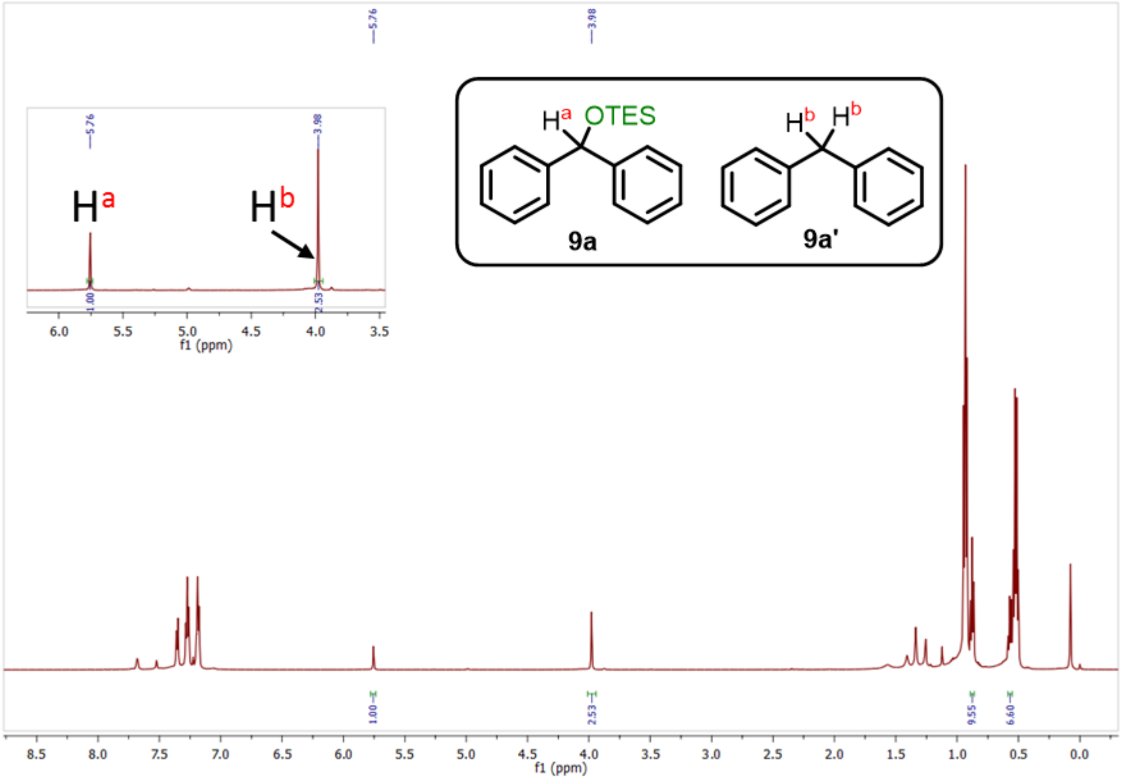

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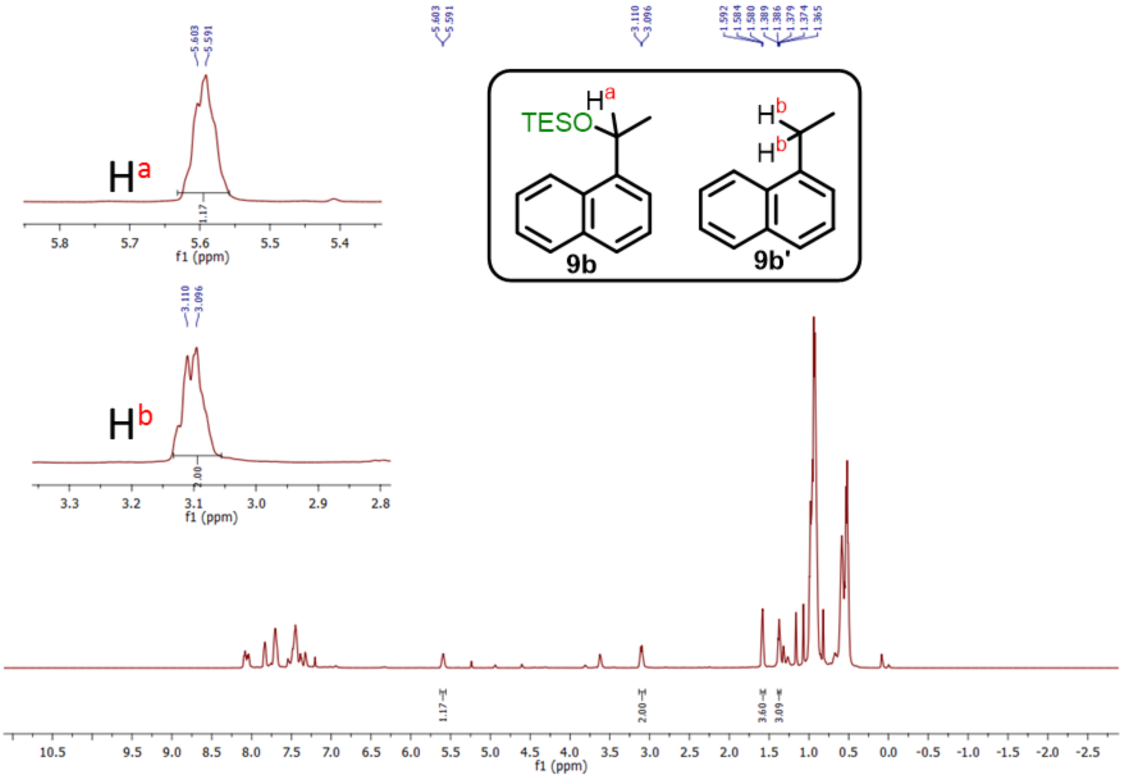

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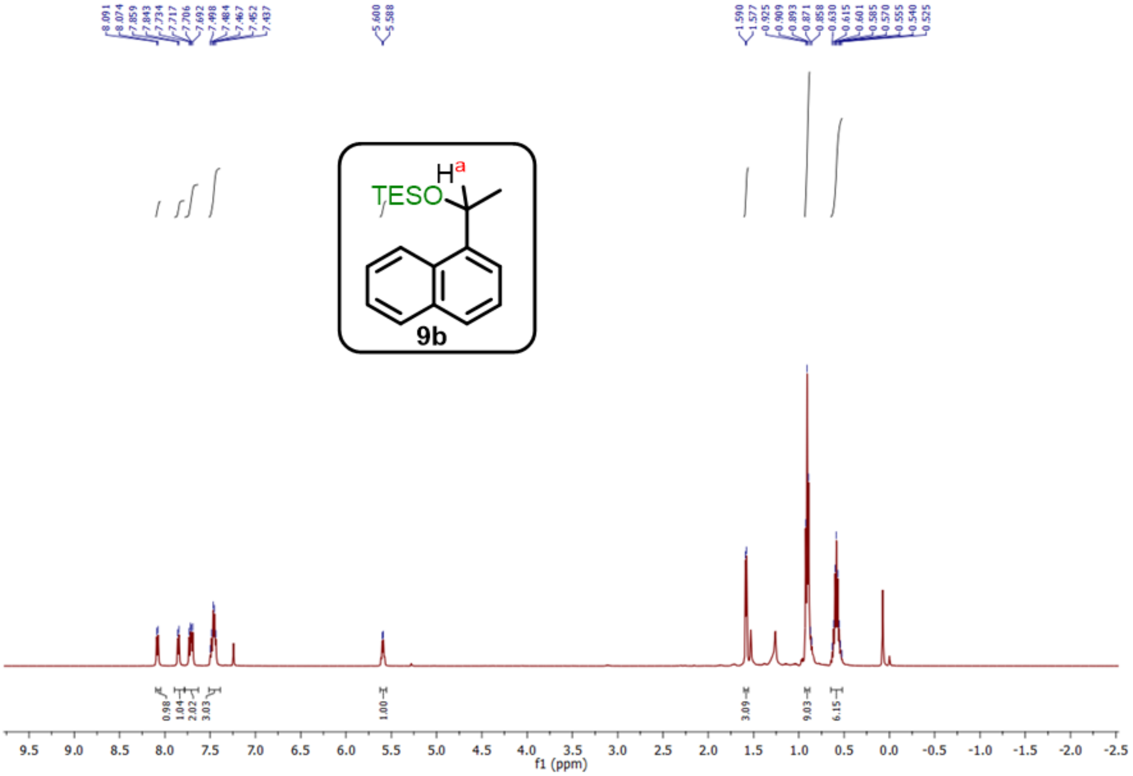

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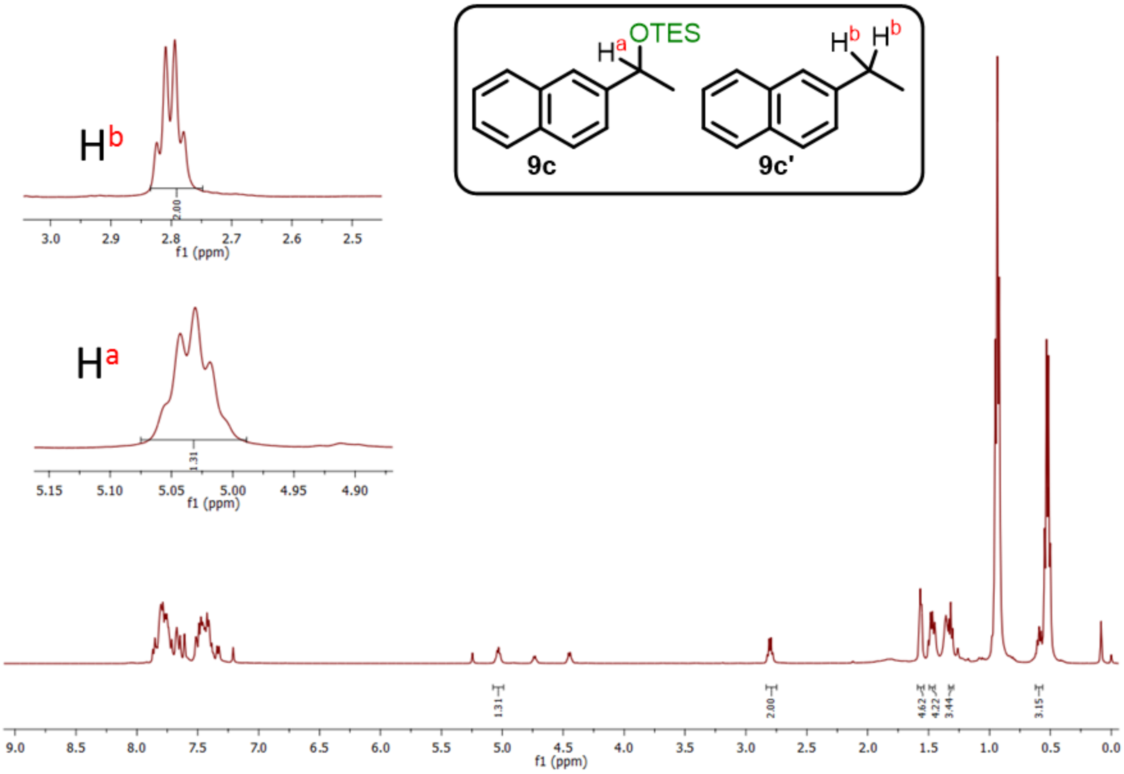

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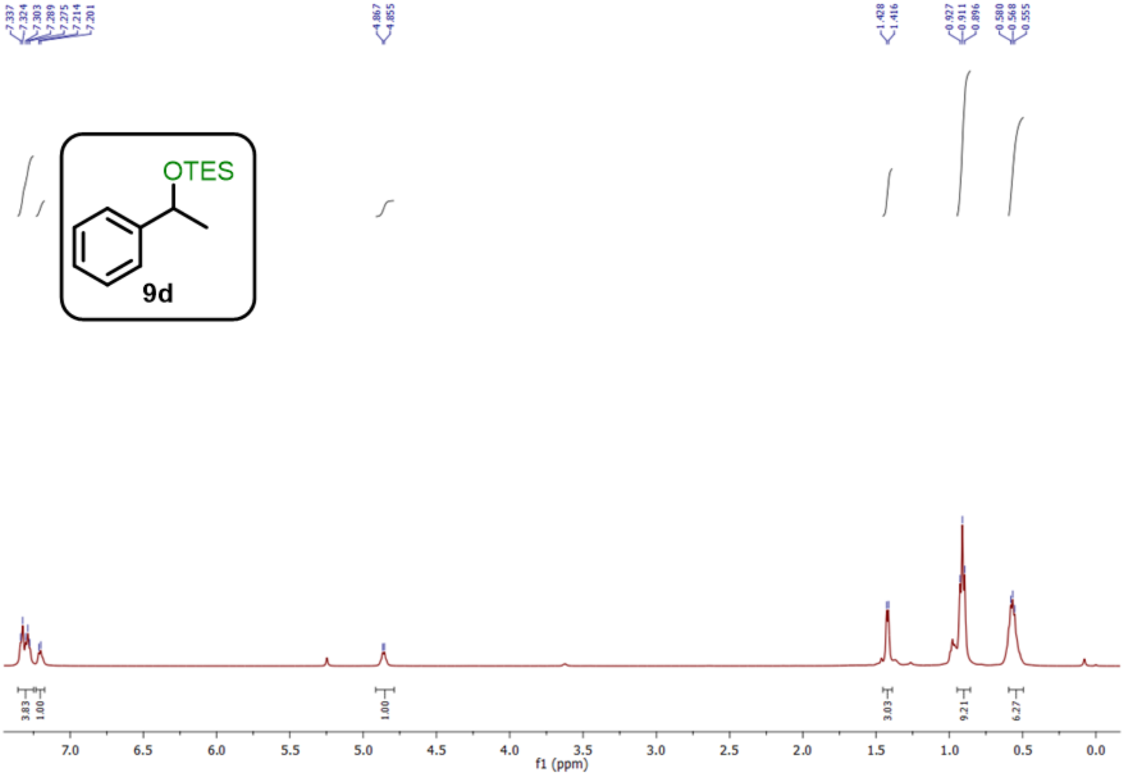

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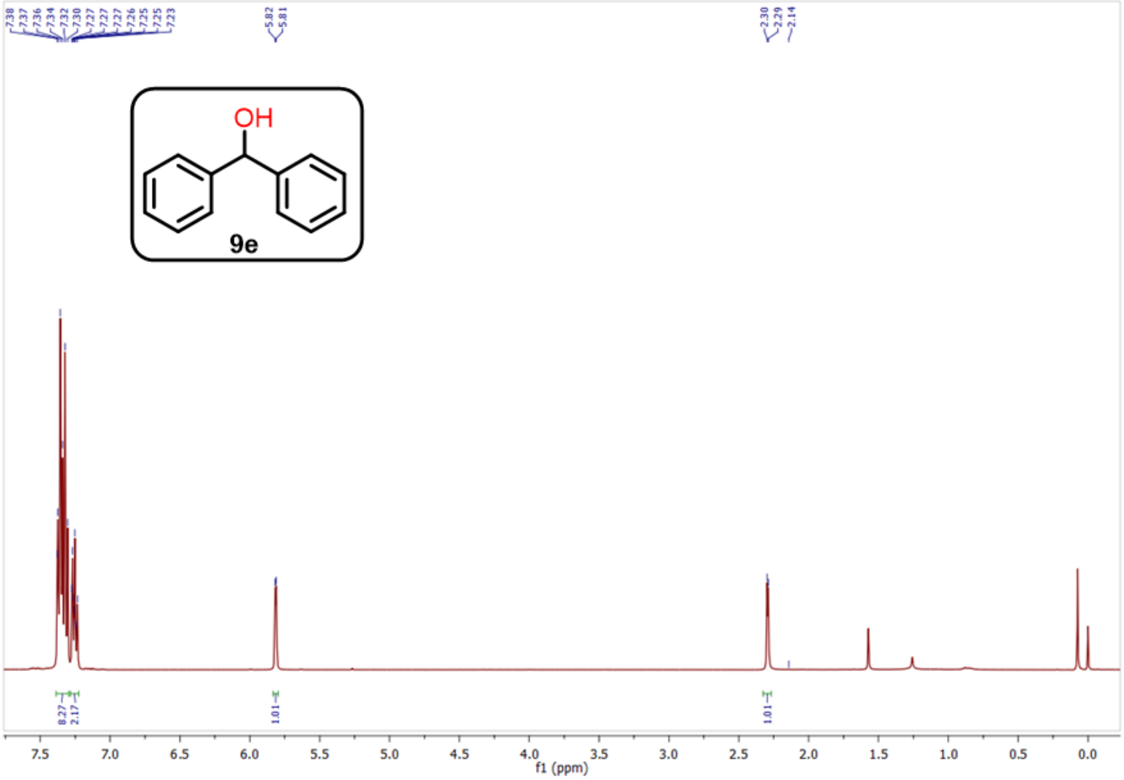

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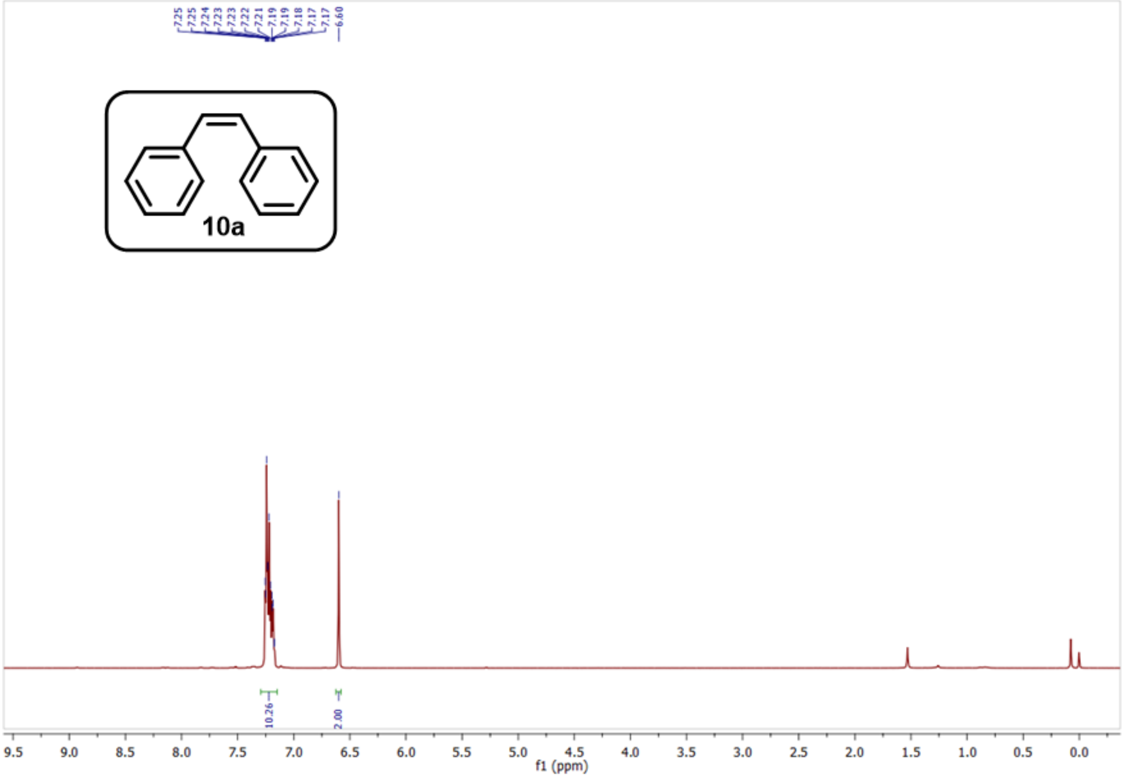

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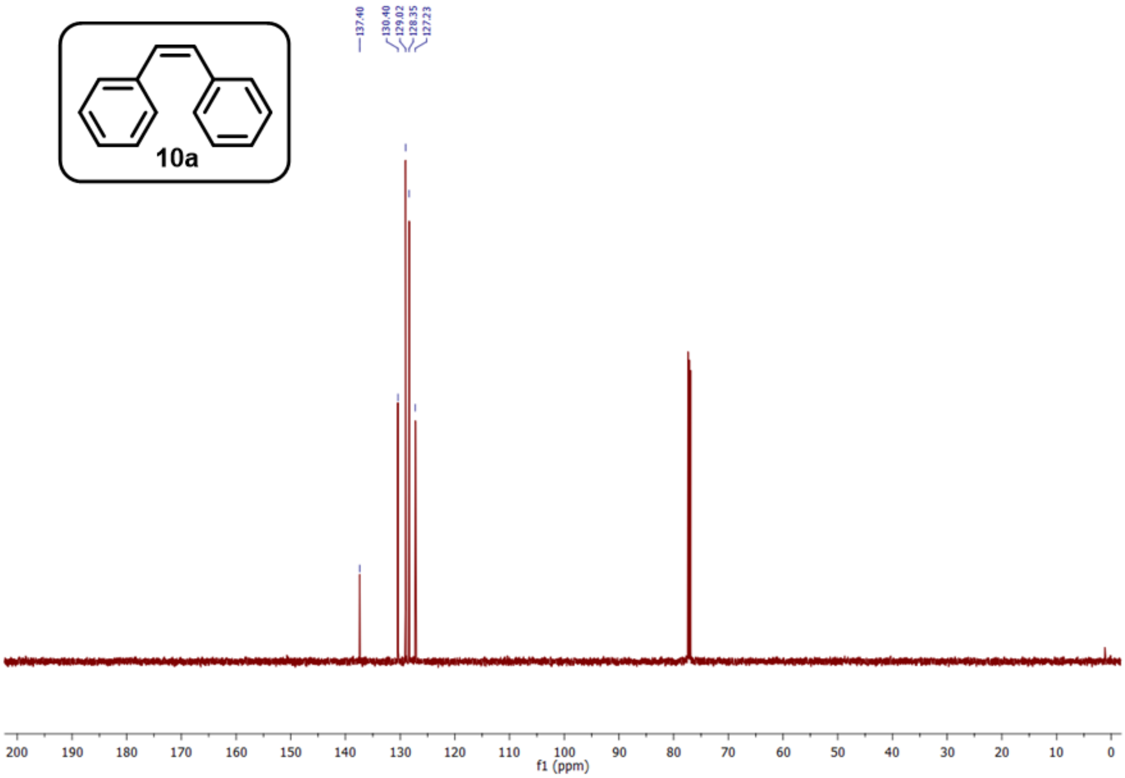

^{13}C NMR spectrum of **10a**,)151 MHz, CDCl$_3$(

4.14 Crystallographic data of 11c

Bond precision: C-C = 0.0158 A Wavelength=0.71073

Cell: a=13.923(2) b =14.515(3) c =25.817(4)

alpha = 90 beta = 96.013(7) gamma = 90

Temperature: 293 K

	Calculated	Reported
Volume	5188.7(15)	5188.7(15)
Space group	P 21/n	P 21/n
Hall group	-P 2yn	-P 2yn
Moiety formula	C32 H12 B F24, C16 H29 N2	?
Sum formula	C48 H41 B F24 N2	C48 H43 B F24 N2
Mr	1112.64	1114.65
Dx,g cm-3	1.424	1.427
Z	4	4
Mu (mm-1)	0.143	0.143
F000	2256.0	2264.0
F000’	2258.05	
h,k,lmax	14,15,27	14,15,27
Nref	6452	6434
Tmin, Tmax		
Tmin’		

Correction method= Not given

Data completeness = 0.997 Theta (max) = 22.103

R (reflections) = 0.1216(3234) wR2(reflections) = 0.3587(6434)

S = 1.033 Npar = 686

The following ALERTS were generated. Each ALERT has the format

test-name_ALERT_alert-type_alert-level.

Click on the hyperlinks for more details of the test.

Alert level A

THETM01_ALERT_3_A The value of sine(theta_max)/wavelength is less than 0.550 Calculated sin(theta_max)/wavelength = 0.5294

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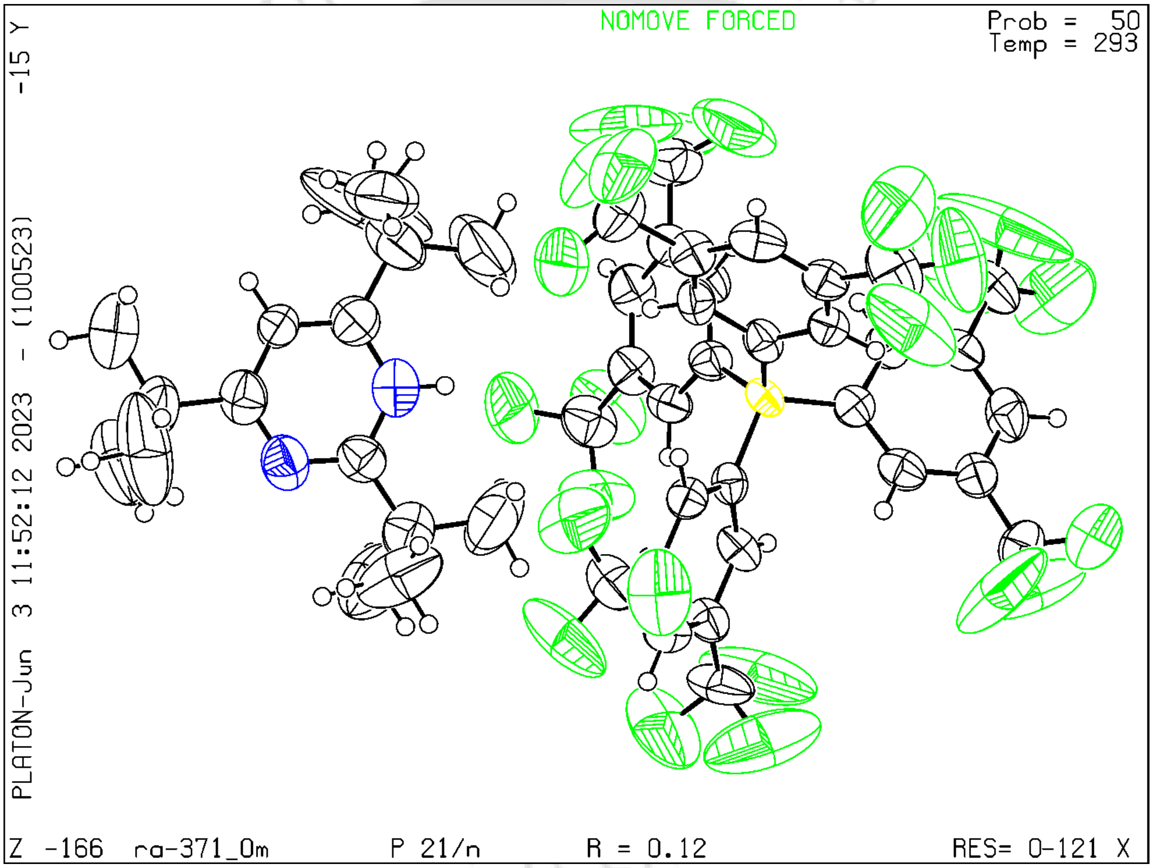
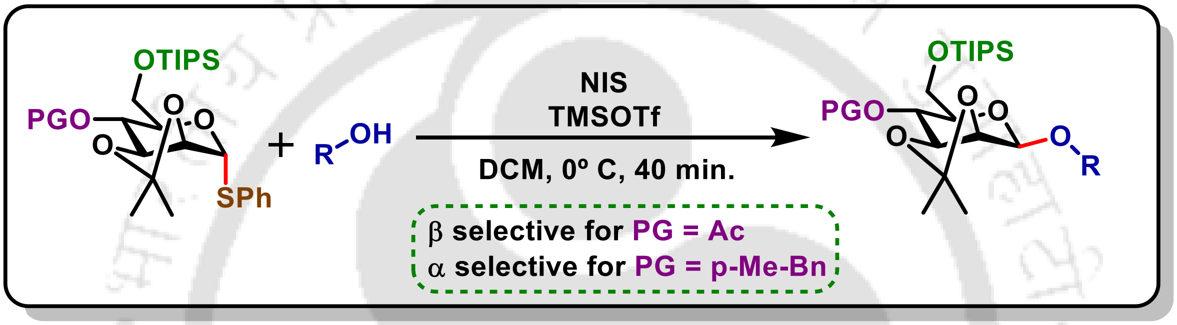


Ortep view of **11c**. The thermal ellipsoid contour probability level is 50%.

Chapter V

Studies on the Stereoselective Glycosylation of Novel Mannose Derived Thioglycosides



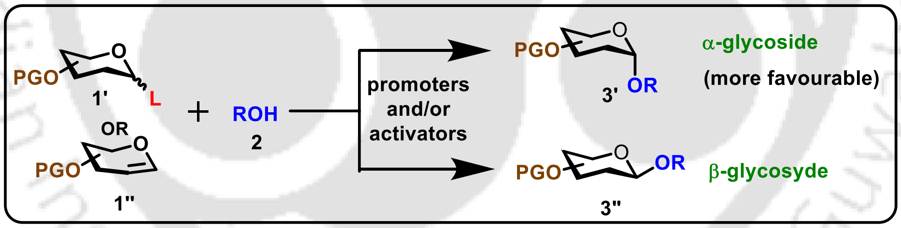
Manuscript under progress

Studies on the Stereoselective Glycosylation of Novel Mannose Derived Thioglycosides

5.1 Glycosylation: Introduction

In nature, carbohydrates are found as oligosaccharides like cellulose, chitin, etc., or as glycoconjugates like glycopeptides and glycolipids, in which each oligosaccharide unit is joined to another unit through glycosidic bonds, through glycosylation.[1-3] The process of glycosylation involves an electrophilic sugar moiety (also known as a glycosyl donor) reacting with another sugar or non-sugar nucleophile (also known as a glycosyl acceptor) (**Scheme 1**). While it is important to develop more feasible methods for chemical glycosylations, factors to synthesize glycoconjugate molecules like glycopeptides, glycolipids, and oligosaccharides of synthetic and biological importance. In general glycosylation, exists a possibility of either α-anomer or β-anomer or both.

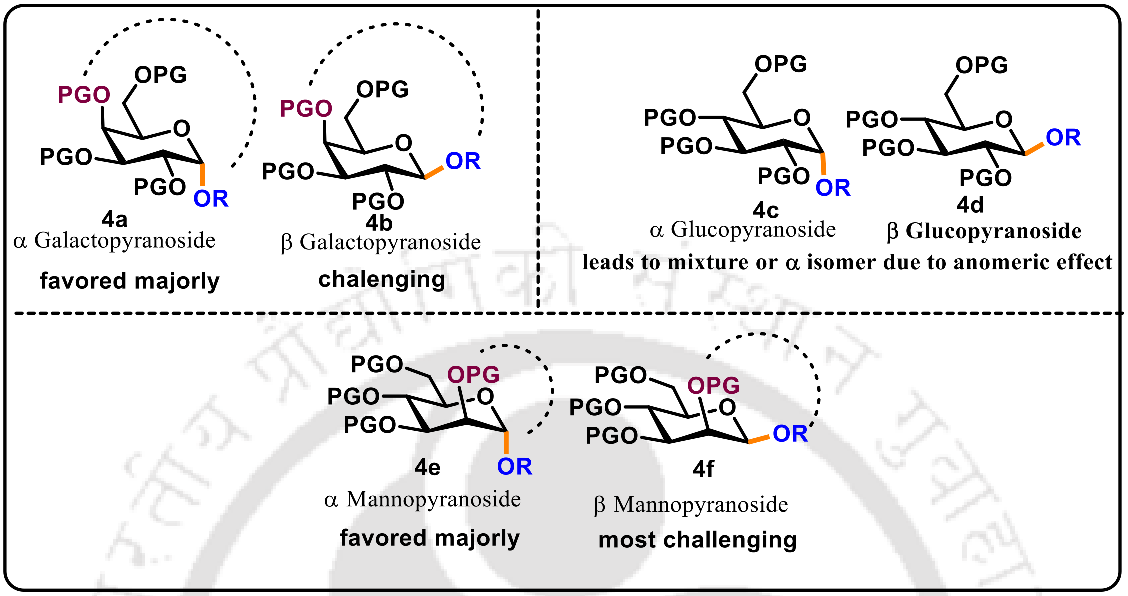
Obtaining a single isomer as a product takes great effort sometimes while several factors take a key role in controlling the selectivity of the reaction output. The first thing is the anomeric effect which favors the formation of α-glycoside in general.[4] Protecting groups of the concerned sugar moiety hydroxyl groups also play a crucial role in posing electronic effects on the reactants (armed-electron rich, disarmed-electron deficient, super-armed, super-disarmed) and also through *neighboring group participation* which also takes a key role on the stereoselectivity.[5] Stereochemical constraints posed by the donor or acceptors to be used are the key issues that are found really challenging in carbohydrate chemistry.[5-6]



Scheme 1. General Glycosylation

In the aspects of developing synthetic methodologies, glucosylations, and galactosylations were studied enormously and seem to get functionalized and influenced bit easily to result in the expected stereochemistry. Mannosylations were well documented in the literature and it is to be considered as the most challenging in the oligosaccharide synthesis that comes from its skeletal stereochemistry which makes it relatively tricky to arrive at β-mannosides. Despite being the most difficult, still, the 1,2-*cis*-β-glycoside linkages were discussed more due to their presence in several naturally occurring and biologically important glycoconjugates and oligosaccharides. Out of many attempts for achieving β-mannosylations, the far-reaching approach has been from Crich and coworkers.[8,15]

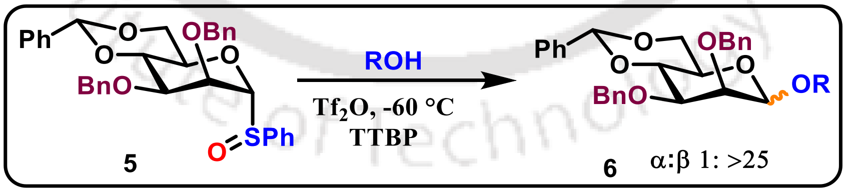
In a glycoside of mannose, when the H_1 and H_2 are *trans* to each other, the glycosidic bond will prefer to remain in axial orientation, which corresponds to an α-isomer. If the H_1/H_2 reside *cis* to each other, the glycosidic bond will be an equatorial orientation that corresponds to a β-isomer, the challenging one due to steric hindrances posed by C2 substituent. The case is different for both glucose and galactose (**Scheme 2**).



Scheme 2. Steric constraints and difference between gluco/galacto/mannopyranosides

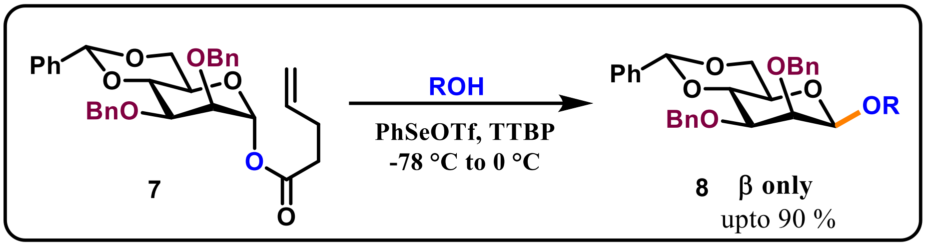
5.2 Literature reports

Numerous efforts have been made toward the development of the diastereoselective synthesis of the glycosidic linkage.[1,7,9] However, the synthesis of β-mannosidic linkage is one of the challenging classes of glycosylation reaction, and the development of the benzylidine-protected donor by Crich and coworkers has been the most successful and most used glycosyl donor for the synthesis of such compounds. They rely on the stability of the α-anomeric triflates in the presence of the 4,6-*O*-benzylidene protecting group which then undergoes an S_N2-inversion reaction leading to the formation of β-glycosides (**Scheme 3**).[2]

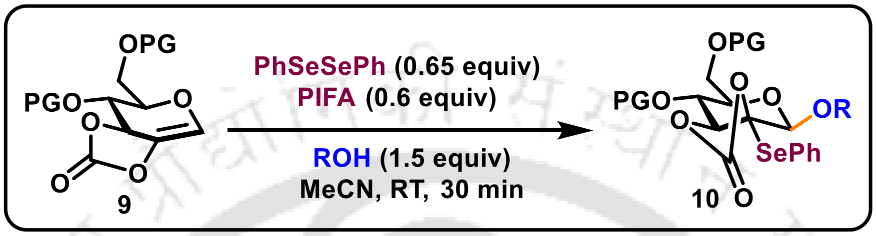


Scheme 3. β- Mannosylation through Benzylidine protected donor by Crich

In addition, in 2006, Kim's group obtained the stereospecific glycosylation with the benzylidine-derived glycosyl pentenoate as the donor and with PhSeOTf as a promoter for achieving β-mannosides (**Scheme 4**).[3] There was a recent report from Zhongjun Li's group, where they utilized 2,3-O-Carbonate-2-hydroxyglucal for synthesizing β-Mannosides through Phenylselenoglycosylation, in good yields (**Scheme 5**).[13]



Scheme 4. β- Mannosylation through Benzylidine derived pentenoate donor



Scheme 5. Synthesis of β- Mannosides through C2-C3 carbamate glycal

From the several findings made by Crich's group towards mannosylations, it is observed that the variations in protecting groups at *O*-2, *O*-4, and *O*-6 are instigating the high chances of achieving β-selectivity (**Figure 5.1**).[14-15] We realized that reducing the bulk at the *O*-2 protecting group would further lead to a high β/α ratio.

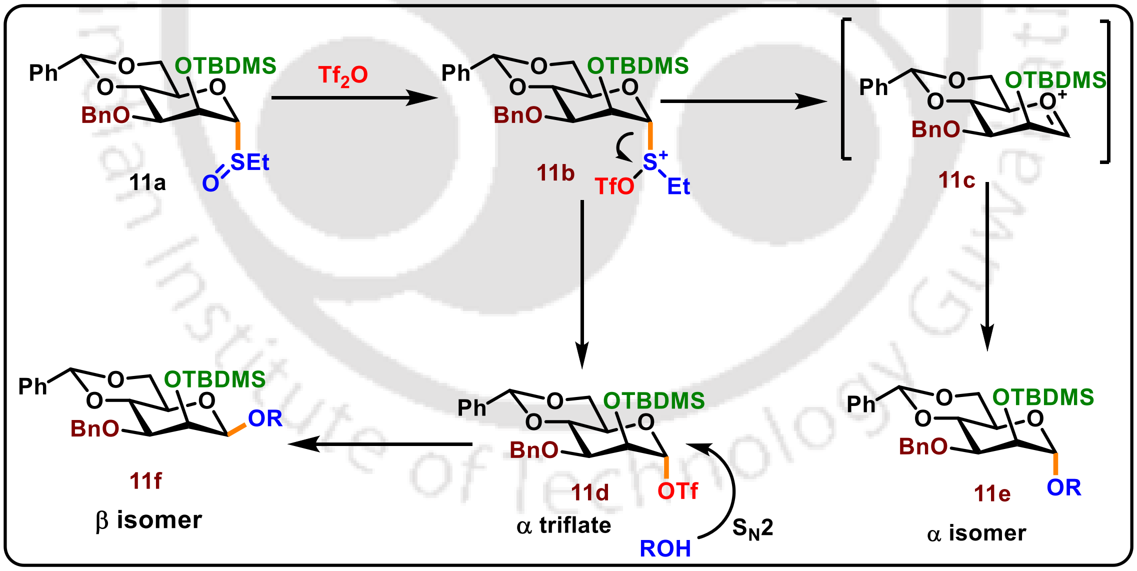
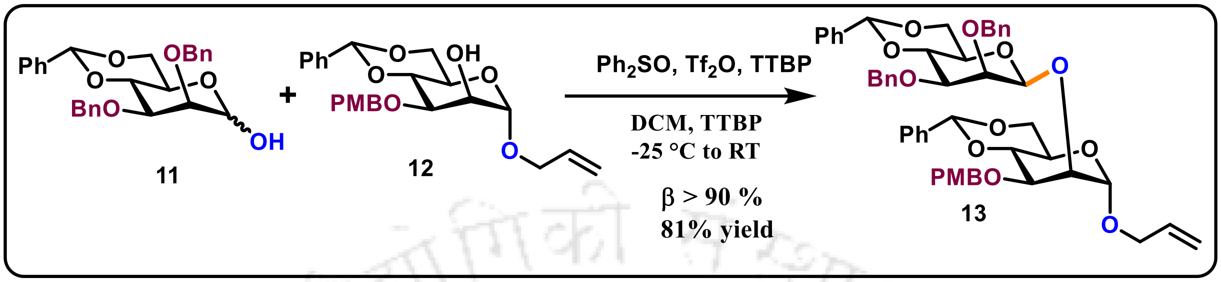


Figure 5.1. Crich's approach towards β-mannosylation

In another work by Beak et al, they discussed and studied the effect of electron-withdrawing groups at various positions on the sugar, *O6, O4, and O3* which supported the idea that electron-withdrawing group substitution on sugar moiety would directly enhance the stability of intermediate, anomeric triflate the reaction medium and hence leading to more of β-product. While the distant acyl functional group at *O6* and *O3* were encouraging the α-isomer formation through remote participation.[11] In 2005, Codee and Seeberger developed a dehydrative coupling strategy that showed efficient installation of β-manosidic linkages through a putative mechanism (**Scheme 6)**. Though their protocol showed high stereoselectivity for secondary nucleophiles, it did compromise in the case of primary alcohols.[12]



Scheme 6. Dehydrative coupling to synthesize β-mannosides

5.3 This Work: Scope and Discussion

The extensive study done by Crich and coworkers inspires carbohydrate chemists to understand the variations in reactivity by providing rigidity of the sugar's protecting groups. We hypothesize that the locking of C2-C3 oxygens instead of C4-C6 oxygens in combination with an electron withdrawing acetate protecting group at O4 might also help us achieve the β-mannoside synthesis and hence design a donor (**Figure 5.2**). Following this, the reactivity of the synthesized donor towards the diastereoselective glycosidic linkage has been studied**.** We have further carried out comparative glycosylations by varying the protecting groups of our donor and analyzed the varied stereochemical output**.**

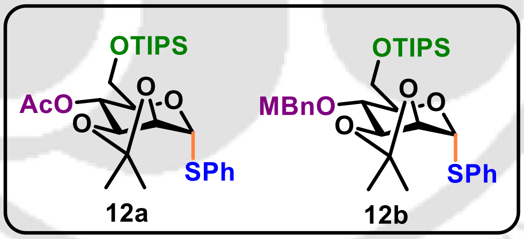
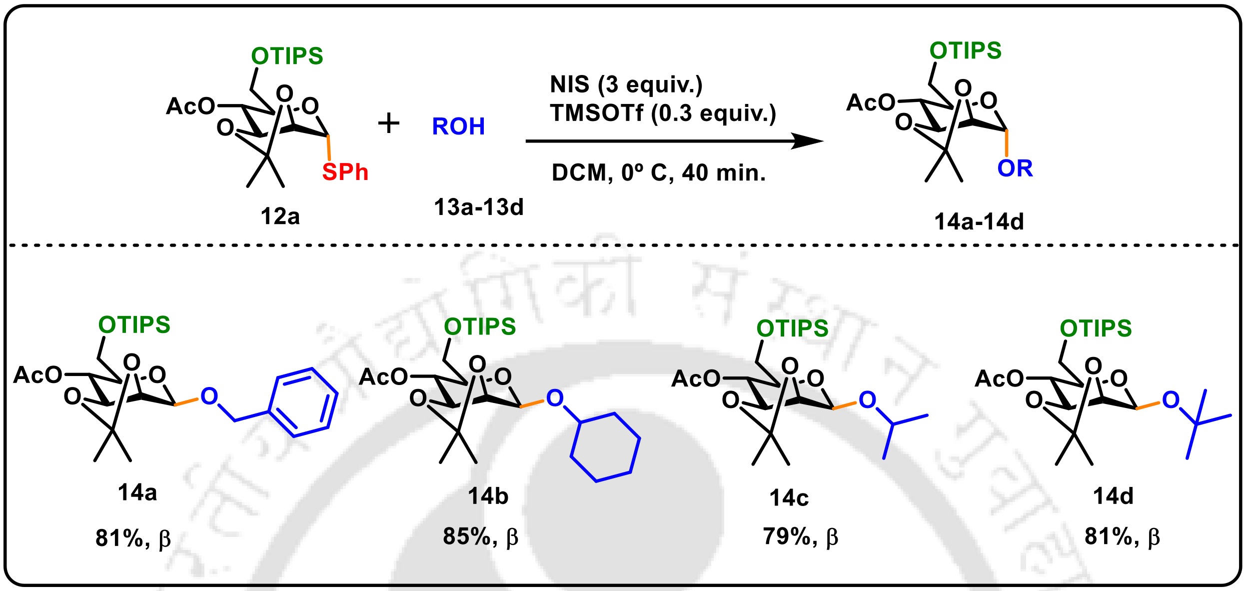


Figure 5.2 Mannosyl Donor with C2-C3 oxygens locked

5.3.1 Substrate scope

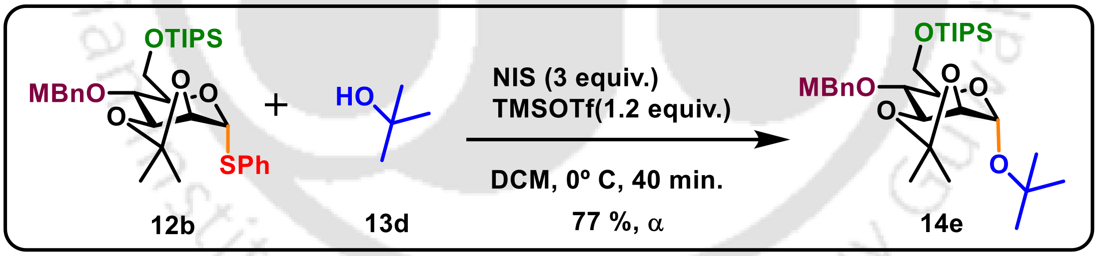
We have synthesized the donor (**12a,126b)** from α-thio-mannopyranoside by following simple and standard protocols. The procedure is discussed in the experimental section in detail. Initially, with the new donor in hand (**12a**), we tried a standard protocol using NIS and TMSOTf as reagent systems and performed the glycosylation using different types of non-sugar alcohols which included primary, secondary, tertiary, and aryl alcohol. To our surprise, all these reactions resulted in β-selective mannosyl monosaccharides in good yields (**Scheme 7**).

We believed that locking the O2-O3 with the acetonide protection controls the electron flow of the system as well as sterically decreasing the crowd at C-2 oxygen hence allowing the nucleophile to attack from the upper side whereas the electron-withdrawing caused by acetyl protection also has its role in stabilizing the intermediates of the reaction, probably α-triflates and hence leading to S_N2 type inversion reactivity.



Scheme 7. Synthesis of β-selective mannosyl monosaccharides

To see the effect of the electron-withdrawing group at the C-4 position, we replaced the electron-withdrawing acetyl-protecting group with the p-methyl benzyl (MBnO-) group. To our surprise, it led to α-monosaccharide (**Scheme 8**) exclusively.

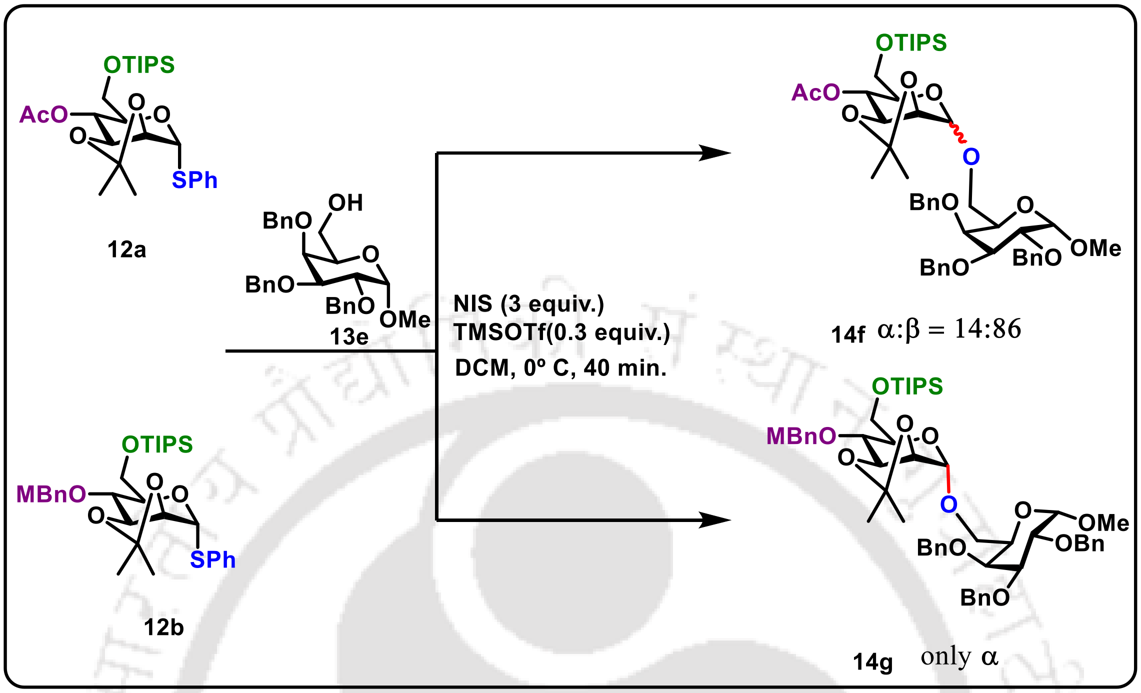


Scheme 8. Variation in reaction outcome with change in protecting group at C-4 oxygen

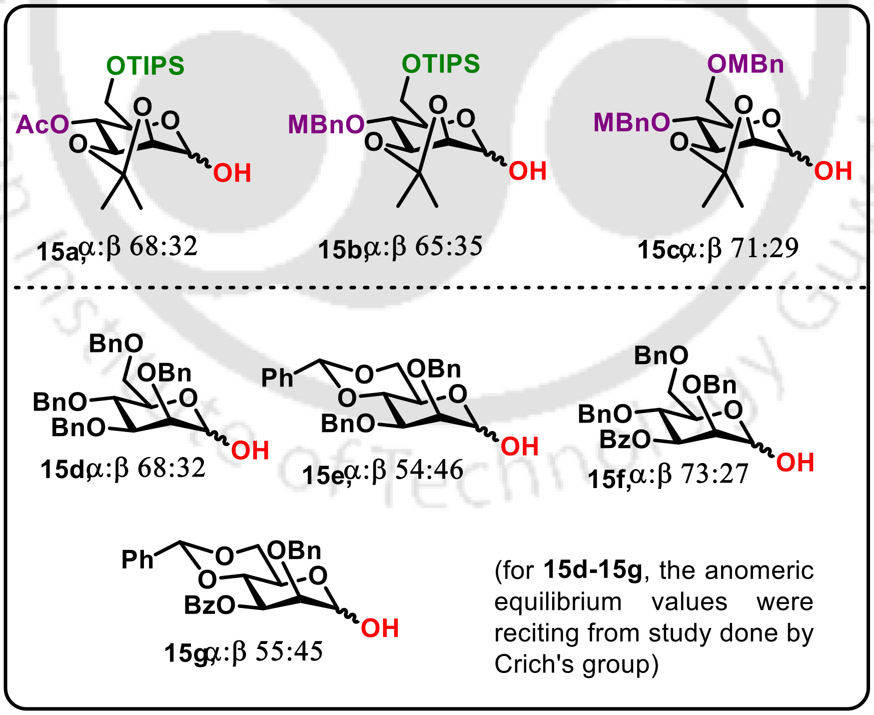
To understand the donor efficiency further, a glycosylation reaction was done using galactosyl acceptor (**13d**) which gave β-isomer as the major product with donor **12a,** whereas with benzylated donor **12b,** it resulted in α-disaccharide (**Scheme 9**).

5.3.2 Anomeric Equilibrium Study

The role of protecting the group was something that was very curious to us and hence we planned to perform an anomeric equilibrium experiment following Crich's and coworkers study.[16] They have reported a detailed study on the protecting group role on mannopyranoside anomeric equilibrium in $CDCl_3$. This anomeric equilibrium experiment gave us insights that the donors that were synthesized in this protocol are stabilizing the β-mannopyranose to a good extent in the solution. The details of this study were mentioned in the experimental section (**Table 5.1**).



Scheme 8. Synthesis of disaccharides



(for **15d-15g**, the anomeric equilibrium values were reciting from study done by Crich's group)

Table 5.1 Anomeric Equilibrium experiment performed in $CDCl_3$ solution

5.4 Conclusion

All these observations gave us insights into understanding the role of rigid protecting groups like acetonide on the donor reactivity nature, like benzylidine protected donor by Crich and coworkers. The rigid nature of the protecting group at C2, and C3-oxygens and the electronic nature of the protecting group at C-4 oxygen can be studied further and utilized in mannosylations for tuning the stereoselectivity outcome of the reaction.

5.5 Experimental Section

5.5.1 General Information

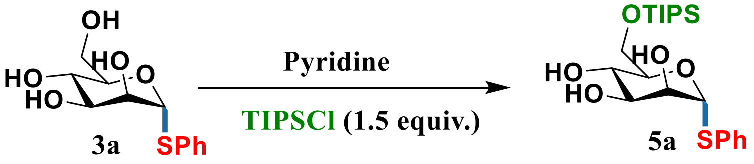
All solvents purchased were of commercial grade and reagents purchased from Sigma-Aldrich, Merck, Carbosynth, Spectrochem, Alfa Aesar, Avra and used without further reaction purification.

5.5.2 Analysis

Reactions were monitored by TLC on Kieselgel 60 F254 (Merck). Detection was done by examination under UV light (254 nm) and by charring with 10% sulfuric acid in water. Purification was performed by both Ultra High-Performance Liquid Chromatography (UHPLC) using column [Particle size: (µ) 12, Dim: (mm) 250 x 10] in reverse phase and in normal phase using silica gel [Merck, 60-120 mesh]. Extracts were concentrated in vacuo using both Büchi rotary evaporator (bath temperatures up to 40 °C) at a pressure of either 15 mmHg (diaphragm pump) and 0.7 mmHg (oil pump), at rt. ^{1}H- and ^{13}C NMR were recorded on a Bruker 600 MHz, 500 MHz, and 400 MHz spectrometer using $CDCl_3$ as solvent. Chemical shift values are reported in ppm with the solvent as the internal standard ($CDCl_3$: δ 7.26 for ^{1}H, δ 77.16 for ^{13}C). Data are reported as follows: chemical shifts (δ), multiplicity (s = singlet, d = doublet, dd = doublet of doublet, ddd = doublet of doublet of doublets, dt = doublet of triplet, t = triplet, td = triplet of doublet, q = quartet, m = multiplet), etc., coupling constants J (Hz), and integration. High-resolution mass measurements were performed using Agilent technologies mass spectrometer (QTOF-ESI mode). The diastereomeric ratios were calculated from crude NMR. Specific rotation was recorded in Autopol II S2, the units of the specific rotation is (deg·mL)/(g·dm), and concentration *c* is given in g/100 ml.

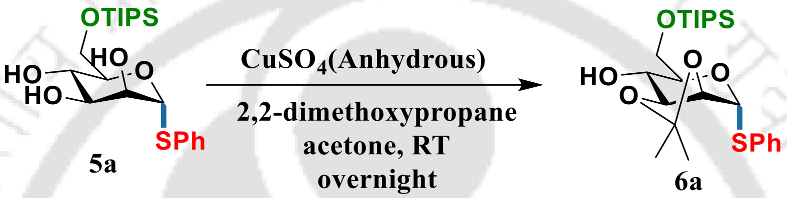
5.6 Synthesis

Phenyl -6-*O*-triisopropylsilyl-1-thio-α-D-mannopyranoside (5a)



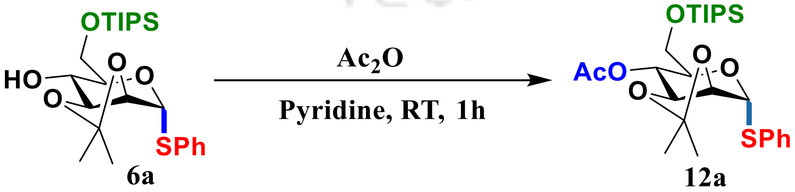
To an oven-dried RB, was added **3a** (2.75g, 10.11 mmol) and anhydrous pyridine followed by TIPSCl (1.5 equiv., 2.92 g, 15.16 mmol) under inert atmosphere at 0 °C. The reaction mixture was stirred overnight at room temperature. After completion, the reaction mixture was then diluted with CH_2Cl_2 (50 mL) and washed with 1M HCl solution, saturated aqueous $NaHCO_3$, and then with brine. The organic layer was dried over anhydrous Na_2SO_4. The filtrate was concentrated under reduced pressure and purified by column chromatography giving Phenyl-6-*O*-triisopropylsilyl-1-thio-α-D-mannopyranoside (**5a**) as colorless syrup, 3.42 g, 79%). $R_f = 0.4$ (Hexane/EtOAc = 1:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (d, *J* = 6.9 Hz, 2H), 7.18 – 7.09 (m, 3H), 5.43 (s, 1H), 4.85 (s, 1H), 4.36 (s, 2H), 4.13 (d, *J* = 15.8 Hz, 1H), 4.10 (dd, *J* = 9.2, 4.7 Hz, 1H), 3.94 (dd, *J* = 10.3, 4.9 Hz, 1H), 3.86 – 3.80 (m, 1H), 3.79 (d, *J* = 4.7 Hz, 2H), 1.03 – 0.92 (m, 21H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 133.24, 130.42, 127.84, 126.18, 86.99, 71.45, 71.21, 71.06, 69.33, 63.80, 16.95, 11.07 – 10.44.

Phenyl 2,3-*O*-isopropylidene-6-*O*-triisopropylsilyl-1-thio-α-D-mannopyranoside (6a)



In an oven-dried RB flask, **5a** (3.42 g, 7.99 mmol) was taken, and was added acetone, anhydrous $CuSO_4$ (10 g, 0.063 mol), and 2,2-dimethoxypropane (1.2 mL, 3 equiv.). The reaction mixture was stirred overnight at room temperature. TLC was checked which indicated completion of the reaction. Then reaction mixture was filtered and the filtrate was concentrated and purified by column chromatography by giving phenyl 2,3-*O*-isopropylidene-6-*O*-triisopropylsilyl-1-thio-α-D-mannopyranoside (**5**) as a colorless syrup (2.92 g, 78 %). $R_f = 0.4$ (Hexane/EtOAc = 4:1, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.41 (m, 2H), 7.32 – 7.23 (m, 3H), 5.76 (s, 1H), 4.33 (d, *J* = 5.7 Hz, 1H), 4.20 (t, *J* = 5.8 Hz, 1H), 407 – 4.00 (m, 1H), 3.93 – 3.86 (m, 2H), 3.83 (dd, *J* = 10.4, 6.0 Hz, 1H), 3.42 (d, *J* = 2.1 Hz, 1H), 1.53 (d, *J* = 10.5 Hz, 3H), 1.37 (s, 3H), 1.10 – 0.99 (m, 21H).^{13}C NMR (101 MHz, $CDCl_3$) δ 133.35, 131.81, 128.96, 127.53, 109.75, 83.79, 78.17, 75.96, 72.30, 69.72, 64.89, 28.03, 26.37, 17.88, 11.79.

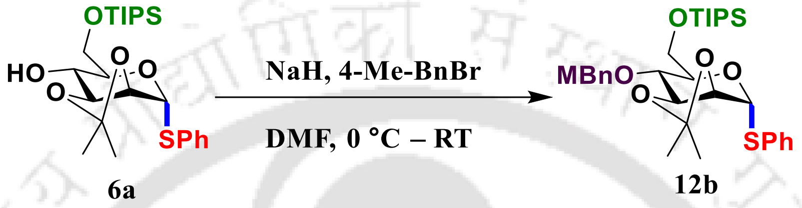
Phenyl 2,3-*O*-isopropylidene-4-*O*-acetyl-6-*O*-triisopropylsilyl-1-thio-α-D-mannopyranoside (12a)



In an oven-dried round bottom flask, compound **6a** (1.283 g, 2.60 mmol) was taken followed by the addition of Pyridine (3 mL) and acetic anhydride (0.7 mL) at 0 °C and then stirred at room temperature for 1h. After completion, the reaction mixture was concentrated and purified through column chromatography as colorless sticky liquid **12a** (1.3 g, 93%). $R_f = 0.6$ (Hexane/EtOAc =

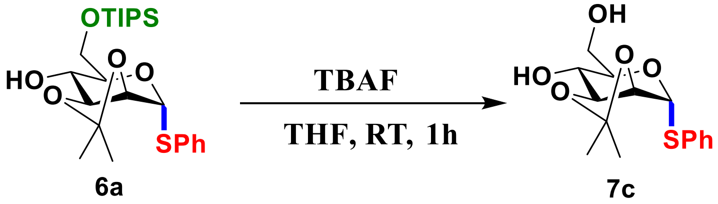
9:1, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.51 (m, 2H), 7.27 (q, *J* = 5.6 Hz, 3H), 5.79 (s, 1H), 5.16 (dd, *J* = 10.0, 7.7 Hz, 1H), 4.36 (d, *J* = 5.4 Hz, 1H), 4.25 (dd, *J* = 7.1, 5.8 Hz, 1H), 4.20 – 4.14 (m, 1H), 3.77 (dd, *J* = 11.2, 5.1 Hz, 1H), 3.71 (dd, *J* = 11.2, 2.5 Hz, 1H), 2.11 – 2.07 (m, 3H), 1.57 (s, 3H), 1.36 (s, 3H), 1.05 – 0.99 (m, 21H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.55, 132.63, 130.56, 127.91, 126.44, 109.07, 83.01, 75.42, 74.99, 69.89, 68.96, 61.76, 26.53, 25.53, 19.94, 16.85, 10.88. HRMS (ESI) m/z: calcd for $C_{26}H_{43}O_6SSi$ $[M+H]^+$ 511.2550, found 511.2761.

Phenyl 2,3-*O*-isopropylidene-4-*O*-(4'-methyl benzyl)-6-*O*-triisopropylsilyl-1-thio-α-D-mannopyranoside (12b)



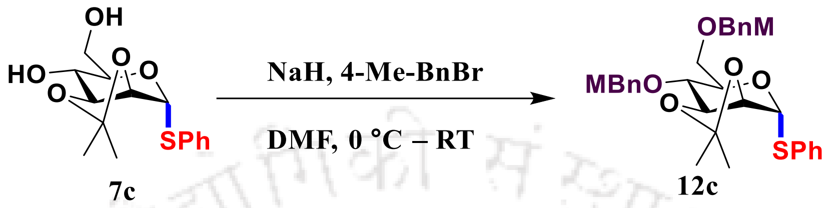
In an oven-dried round bottom flask, compound **6a** (1.1 g, 2.35 mmol) was taken. Dissolved in DMF (5 mL) and stirred at 0 °C followed by the addition of sodium hydride (1.1 equiv., 0.103 g, 2.59 mmol). The reaction was stirred for 15 minutes followed by the addition of 4-mehyl benzylbromide (1.1 equiv., 0.478 g, 2.58 mmol) at 0 °C and left for completion. The reaction mixture was then quenched with 0.1-0.2 ml of methanol and concentrated on rotavap to remove the methanol. Then the crude mixture was diluted with CH_2Cl_2 (20 mL) and washed with cold water and then with brine solution. The organic layer was dried over anhydrous Na_2SO_4. The filtrate was concentrated under reduced pressure and purified by column chromatography, obtained as colorless syrup **12b** (1.15 g, 91%). R_f = 0.8 (Hexane/EtOAc = 9:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.2 Hz, 2H), 7.28 – 7.22 (m, 5H), 7.13 (d, *J* = 7.7 Hz, 2H), 5.77 (s, 1H), 4.85 (d, *J* = 11.1 Hz, 1H), 4.61 (d, *J* = 11.1 Hz, 1H), 4.37 – 4.32 (m, 2H), 4.05 – 4.00 (m, 1H), 3.91 (dd, *J* = 11.1, 3.9 Hz, 1H), 3.81 (d, *J* = 10.0 Hz, 1H), 3.75 (dd, *J* = 9.9, 6.5 Hz, 1H), 2.33 (s, 3H), 1.51 (s, 3H), 1.38 (s, 3H), 1.08 – 1.00 (m, 21H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 137.3, 135.2, 133.9, 131.3, 128.9, 128.8, 128.1, 127.2, 109.4, 83.8, 78.7, 76.5, 75.4, 73.2, 71.2, 62.4, 27.9, 26.5, 21.2, 18.0, 17.9, 17.7, 11.9.

Phenyl 2,3-*O*-isopropylidene-1-thio-α-D-mannopyranoside (7c)



In an oven-dried RB flask, **6a** (510.0g, 1.01 mmol) was taken and dissolved in 5 mL of THF, followed by the addition of TBAF (tetrabutylammonium fluoride, 1.5 equiv, 427.4 mg, 1.6 mmol) at room temperature. The reaction was monitored on TLC. Upon completion, the crude reaction mixture was concentrated under vacuum and purified through column chromatography giving compound **7c** as colorless sticky syrup, 302.6 mg, 89 %. R_f = 0.3 (Hexane/EtOAc = 3:1, v/v). The compound was utilized in the next step as such.

Phenyl 2,3-*O*-isopropylidene-4,6-di-*O*-(4'-methyl benzyl)-1-thio-α-D-mannopyranoside (12c)



In a round bottom flask, **7c** (0.3 g, 0.96 mmol) was taken. Dissolved in DMF (3 mL) and stirred at 0 °C followed by the addition of sodium hydride (2.2 equiv., 0.051 g, 2.12 mmol). The reaction was stirred for 15 minutes followed by the addition of 4-mehyl benzylbromide (2.2 equiv., 0.392 g, 2.12 mmol) at 0 °C and left for completion. The reaction mixture was then quenched with 0.1-0.2 ml of methanol and concentrated on rotavap to remove the methanol. Then the crude mixture was diluted with CH_2Cl_2 (20 mL) and washed with cold water and then with brine solution. The organic layer was dried over anhydrous Na_2SO_4. The filtrate was concentrated under reduced pressure and purified by column chromatography, obtained as colorless syrup, **12c** (0.461 g, 92%). R_f = 0.7 (Hexane/EtOAc = 9:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 – 7.47 (m, 2H), 7.25 – 7.20 (m, 2H), 7.17 – 7.13 (m, 4H), 7.13 – 7.08 (m, 4H), 5.78 (s, 1H), 4.82 (d, *J* = 11.1 Hz, 1H), 4.51 (dd, *J* = 16.5, 11.6 Hz, 2H), 4.43 – 4.29 (m, 3H), 4.24 – 4.19 (m, 1H), 3.68 (dd, *J* = 10.5, 5.1 Hz, 2H), 3.63 (dd, *J* = 10.8, 1.8 Hz, 1H), 2.32 (s, 6H), 1.52 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 137.3, 137.1, 135.2, 135.1, 133.4, 131.9, 129.2, 128.94, 128.92, 128.1, 127.8, 127.5, 127.1, 109.6, 84.2, 78.6, 76.4, 75.8, 73.1, 72.9, 70.0, 68.8, 28.0, 26.4, 21.16, 21.15.

5.6.1 Acceptors and Donors used for glycosylations

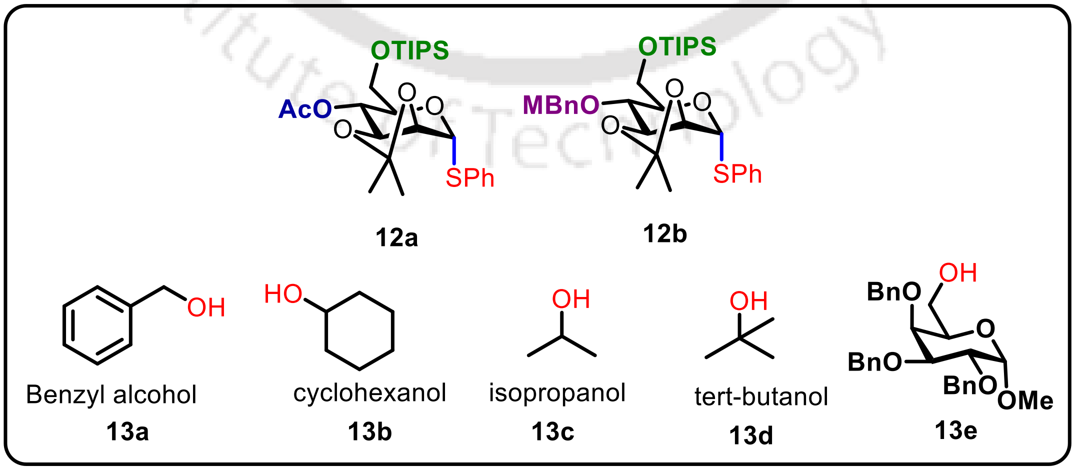
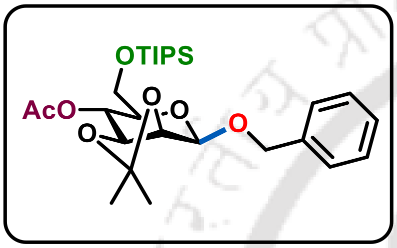


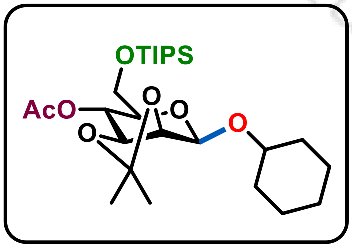
Table 5.2

5.7 General procedure A for glycosylation

In an oven-dried round bottom flask with activated molecular sieves (4Å), were taken. N-Iodosuccinimide (2 equiv.), Phenyl 2,3-O-isopropylidene-4-O-acetyl/(4'-methyl benzyl)-6-O-triisopropylsilyl-1-thio-α-D-mannopyranoside (**12a/12b**) (1 equiv.) and alcohol (2 equiv.) were added to this RB by dissolving in DCM (0.6 ml) flask under inert atmosphere. After stirring for about 20 min, TMSOTf (0.3 equiv.) was added at 0 °C and left for completion. Then reaction mixture was quenched by triethylamine. The reaction mixture was filtered, washed with brine, passed through Na_2SO_4, and concentrated under vacuum. The crude reaction mixture was purified by column chromatography leading to the glycoside as β-isomer predominantly with good yields (75-80%). The stereochemistry of the glycosides was confirmed by NMR.



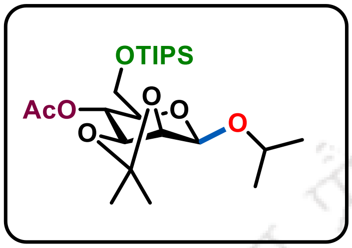
Benzyl-2,3-*O*-isopropylidene-4-*O*-acetyl-6-*O*-triisopropylsilyl-1-β-D-mannopyranoside (14a)
Glycosylation of **12a** (70.1 mg, 0.14 mmol) with BnOH (**13a**) (2 equiv., 29.7 mg, 0.27 mmol) according to **General procedure A** afforded **14a** (56.6 mg, 81 %, β only) as a colorless syrup. The crude product was purified through column chromatography. $R_f = 0.5$ (Hexane/EtOAc = 6:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.2 Hz, 2H), 7.34 (dt, *J* = 21.7, 7.1 Hz, 3H), 5.07 (dd, *J* = 9.1, 6.7 Hz, 1H), 4.94 (t, *J* = 12.9 Hz, 1H), 4.80 (d, *J* = 12.4 Hz, 1H), 4.67 (s, 1H), 4.22 – 4.11 (m, 2H), 3.84 (dd, *J* = 10.8, 6.5 Hz, 1H), 3.79 – 3.72 (m, 1H), 3.42 (ddd, *J* = 9.3, 6.6, 3.1 Hz, 1H), 2.04 (d, *J* = 16.2 Hz, 3H), 1.60 (s, 3H), 1.37 (s, 3H), 1.13 – 1.06 (m, 21H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 207.00, 169.64, 169.32, 136.50, 128.87, 128.47, 128.10, 111.15, 95.39, 77.38, 75.73, 74.50, 70.08, 70.01, 63.48, 29.71, 27.39, 26.16, 17.97, 17.95, 11.93. HRMS (ESI) m/z: calcd for $C_{27}H_{48}NO_7Si$ $[M+NH_4]^+$ 526.3195, found 526.3196.



Cyclohexyl-2,3-*O*-isopropylidene-4-*O*-acetyl-6-*O*-triisopropylsilyl-1-β-D-mannopyranoside (14b):

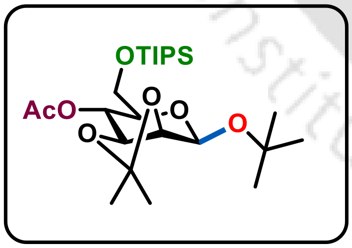
Glycosylation of **12a** (70.5 mg, 0.14 mmol) with CyOH (13**b**) (2 equiv., 27.7 mg, 0.28 mmol) according to **General procedure A** afforded **14b** (58.8 mg, 85 %, β only) as a colorless syrup.

The crude product was purified through column chromatography. $R_f = 0.5$ (Hexane/EtOAc = 6:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.05 (dd, *J* = 9.0, 6.1 Hz, 1H), 4.86 (s, 1H), 4.23 – 4.16 (m, 2H), 3.78 (dt, *J* = 20.6, 10.4 Hz, 1H), 3.75 – 3.65 (m, 2H), 3.51 – 3.43 (m, 1H), 2.08 (s, 3H), 1.94 (t, *J* = 16.0 Hz, 1H), 1.76 (dd, *J* = 8.6, 3.8 Hz, 2H), 1.60 – 1.54 (m, 9H), 1.49 – 1.42 (m, 1H), 1.36 (d, *J* = 7.5 Hz, 3H), 1.14 – 1.00 (m, 21H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.71, 111.12, 96.53, 78.04, 77.36, 75.86, 74.93, 70.05, 63.63, 33.54, 27.42, 26.16, 25.57, 21.03, 17.93, 14.13, 11.93. HRMS (ESI) m/z: calcd for $C_{26}H_{52}NO_7Si$ $[M+NH_4]^+$ 518.3513, found 518.3631.



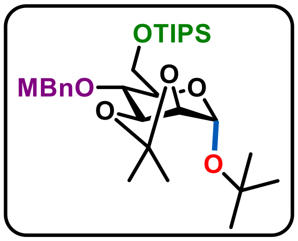
Isopropyl-2,3-*O*-isopropylidene-4-*O*-acetyl-6-*O*-triisopropylsilyl-1-β-D-mannopyranoside (14c)

Glycosylation of **12a** (70.2 mg, 0.14 mmol) with iPrOH (**13c**) (2 equiv., 16.7 mg, 0.28 mmol) according to **General procedure A** afforded **14c** (50.1 mg, 79 %, β only) as a colorless syrup. The crude product was purified through column chromatography. $R_f = 0.4$ (Hexane/EtOAc = 6:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.11 – 5.04 (m, 1H), 4.81 (s, 1H), 4.21 (t, *J* = 8.3 Hz, 2H), 4.06 (tq, *J* = 12.2, 6.1 Hz, 1H), 3.80 (dd, *J* = 10.7, 6.3 Hz, 1H), 3.74 (dd, *J* = 10.8, 3.0 Hz, 1H), 3.50 – 3.44 (m, 1H), 2.09 (d, *J* = 12.8 Hz, 3H), 1.58 (s, 3H), 1.37 (s, 3H), 1.30 (d, *J* = 6.3 Hz, 3H), 1.21 (d, *J* = 6.1 H, 3H), 1.11 – 1.03 (m, 21H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.66, 111.12, 96.90, 77.34, 75.84, 74.90, 72.15, 69.97, 63.58, 27.39, 26.15, 23.35, 22.70, 21.67, 21.03, 17.91, 14.13, 11.92. HRMS (ESI) m/z: calcd for $C_{23}H_{48}NO_7Si$ $[M+NH_4]^+$ 478.3200, found 478.3212.



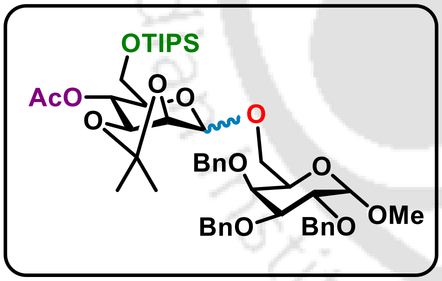
Tert-butyl-2,3-*O*-isopropylidene-4-*O*-acetyl-6-*O*-triisopropylsilyl-1-β-D-mannopyranoside (14d):

Glycosylation of **12a** (70.2 mg, 0.14 mmol) with tBuOH (**13d**) (2 equiv., 20.1 mg, 0.28 mmol) according to **General procedure A** afforded **14d** (52.9 mg, 81 %, β only) as a colorless syrup. The crude product was purified through column chromatography. $R_f = 0.5$ (Hexane/EtOAc = 5:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.04 (dt, *J* = 13.3, 6.6 Hz, 1H), 4.90 (s, 1H), 4.20 (t, *J* = 6.2 Hz, 1H), 4.12 (t, *J* = 8.2 Hz, 1H), 3.77 (dt, *J* = 18.2, 9.1 Hz, 1H), 3.71 (dd, *J* = 10.7, 3.2 Hz, 1H), 3.51 – 3.43 (m, 1H), 2.07 (s, 3H), 1.58 (s, 3H), 1.37 (s, 3H), 1.32 (s, 9H), 1.06 – 1.04 (m, 21H). ^{13}C NMR (151 MHz, CDCl3) δ 169.70, 111.02, 99.25, 93.30, 77.43, 76.34, 75.90, 75.71, 70.72, 70.15, 63.70, 48.53, 28.69, 28.54, 27.45, 26.11, 21.01, 17.91, 11.85. HRMS (ESI) m/z: calcd for $C_{24}H_{50}NO_7Si$ $[M+NH_4]^+$ 492.3357, found 492.3357.



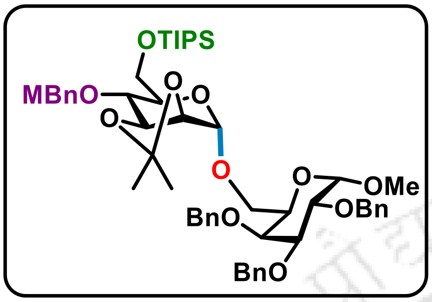
Tert-butyl-2,3-*O*-isopropylidene-4-*O*-(4'-methyl benzyl)- 6-*O*-triisopropylsilyl-1-α-D-mannopyranoside (14e)

Glycosylation of **12b** (70.5 mg, 0.12 mmol) with tBuOH (**13d**) (2 equiv., 18.2 mg, 0.24 mmol) according to **General procedure A** afforded **14e** (50.1 mg, 77 %, α only) as a colorless syrup. The crude product was purified through column chromatography. R_f = 0.5 (Hexane/EtOAc = 6:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 7.9 Hz, 2H), 7.12 (d, *J* = 7.8 Hz, 2H), 4.88 (d, *J* = 1.9 Hz, 1H), 4.76 (d, *J* = 11.4 Hz, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 4.29 (t, *J* = 6.0 Hz, 1H), 4.11 (dd, *J* = 6.1, 1.9 Hz, 1H), 3.91 (dd, *J* = 10.4, 3.2 Hz, 1H), 3.73 (dd, *J* = 10.4, 6.3 Hz, 1H), 3.58 (dd, *J* = 8.6, 5.9 Hz, 1H), 3.46 – 3.40 (m, 1H), 2.33 (s, 3H), 1.55 (s, 3H), 1.38 (s, 3H), 1.27 (d, *J* = 16.0 Hz, 9H), 1.13 – 1.00 (m, 21H).



Methyl 2,3,4-tri-*O*-benzyl-6-*O*-)2,3-*O*-isopropylidene-4-*O*-acetyl-6-*O*-triisopropylsilyl-mannopyranosyl)- α-D-galactopyranoside (14f)

Glycosylation of **12a** (70.1 mg, 0.14 mmol) with **13e** (2 equiv., 0.127 mg, 0.28 mmol) according to **General procedure A** afforded **14f** (92.1 mg, 78 %, α: β 14: 86) as a colorless syrup. The crude product was purified through column chromatography. R_f = 0.4 (Hexane/EtOAc = 4:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.3 Hz, 2H), 7.37 – 7.34 (m, 5H), 7.33 – 7.26 (m, 9H), 4.97 (dd, *J* = 7.5, 4.9 Hz, 1H), 4.95 (d, *J* = 6.2 Hz, 1H), 4.91 – 4.87 (m, 1H), 4.83 (dd, *J* = 11.9, 5.6 Hz, 1H), 4.79 – 4.73 (m, 2H), 4.71 – 4.67 (m, 1H), 4.67 (d, *J* = 3.7 Hz, 1H), 4.64 (d, *J* = 11.7 Hz, 1H), 4.26 (d, *J* = 7.7 Hz, 1H), 4.11 (dt, *J* = 9.8, 4.9 Hz, 1H), 4.06 (dd, *J* = 10.0, 3.6 Hz, 1H), 3.94 (dd, *J* = 10.0, 2.6 Hz, 1H), 3.89 (d, *J* = 2.0 Hz, 1H), 3.85 (t, *J* = 7.3 Hz, 1H), 3.77 (tt, *J* = 14.7, 7.5 Hz, 2H), 3.73 – 3.66 (m, 2H), 3.65 – 3.59 (m, 1H), 3.52 (s, 3H), 3.40 (dd, *J* = 8.5, 7.0 Hz, 1H), 3.35 (s, 3H), 2.05 (s, 3H), 1.55 (s, 3H), 1.35 (s, 3H), 1.09 – 0.99 (m, 24H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.68, 138.86, 138.54, 138.45, 128.64, 128.49, 128.43, 128.38, 128.33, 128.26, 128.12, 127.88, 127.75, 127.63, 127.57, 127.54, 109.86, 105.12, 98.94, 96.63, 79.40, 76.58, 76.18, 75.64, 74.39, 74.22, 73.64, 73.58, 69.94, 69.43, 68.62, 65.45, 63.01, 55.39, 27.60, 26.50, 20.97, 17.93, 11.94.



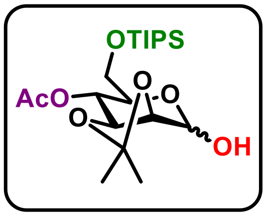
Methyl 2,3,4-tri-O-benzyl-6-O-)2,3-*O*-isopropylidene-4-*O*-(4'-methyl benzyl)- 6-*O*-triisopropylsilyl- α-mannopyranosyl)- α-D-galactopyranoside (14g)

Glycosylation of **12b** (79.1 mg, 0.14 mmol) with **13e** (2 equiv., 0.127 mg, 0.28 mmol) according to **General procedure A** afforded **14g** (103.9 mg, 81 %, α only) as a colorless syrup. The crude product was purified through column chromatography. R_f = 0.5 (Hexane/EtOAc = 4:1, v/v). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.4 Hz, 1H), 7.35 (t, *J* = 7.3 Hz, 4H), 7.32 – 7.27 (m, 8H), 7.26 – 7.23 (m, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 7.12 (d, *J* = 7.7 Hz, 2H), 4.93 (d, *J* = 11.6 Hz, 1H), 4.88 (d, *J* = 11.7 Hz, 1H), 4.81 (d, *J* = 10.7 Hz, 2H), 4.75 (d, *J* = 11.7 Hz, 1H), 4.73 (s, 1H), 4.68 (d, *J* = 12.1 Hz, 1H), 4.65 (d, *J* = 3.6 Hz, 1H), 4.63 (d, *J* = 11.7 Hz, 1H), 4.55 (d, *J* = 11.2 Hz, 1H), 4.22 (t, *J* = 6.2 Hz, 1H), 4.04 (dd, *J* = 10.0, 3.6 Hz, 1H), 3.92 (dd, *J* = 10.0, 2.6 Hz, 1H), 3.90 – 3.86 (m, 3H), 3.80 (dd, *J* = 10.9, 4.7 Hz, 1H), 3.78 – 3.74 (m, 1H), 3.70 (dd, *J* = 9.3, 5.6 Hz, 1H), 3.56 (dd, *J* = 10.1, 6.8 Hz, 1H), 3.50 (dd, *J* = 10.1, 3.5 Hz, 1H), 3.40 – 3.36 (m, 1H), 3.32 (s, 3H), 2.34 (d, *J* = 10.6 Hz, 3H), 1.50 (s, 3H), 1.35 (s, 3H), 1.07 – 1.02 (m, 21H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.8, 138.5, 138.4, 137.3, 135.4, 129.0, 128.6, 128.4, 128.4, 128.3, 128.1, 127.8, 127.7, 127.6, 127.5, 109.2, 98.8, 96.7, 79.4, 78.9, 76.5, 75.6, 75.2, 74.4, 74.1, 73.6, 73.5, 73.0, 69.8, 68.6, 65.2, 62.8, 55.4, 28.0, 26.5, 21.2, 18.02, 17.97, 12.0.

5.8 Synthesis of hemiacetals:

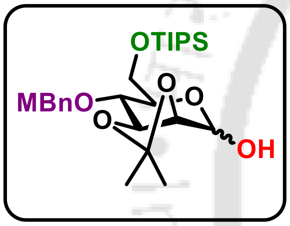
General procedure B

In an oven-dried round bottom flask, 1-thio-α-D-mannopyranoside (**6a/6b/6c**) was added and dissolved in a mixture of acetone: water (9:1, 5 mL/0.21 mmol) and placed at 0 °C followed by the addition of N-Bromosuccinimide (NBS, 2 equiv.). The reaction mixture was stirred at room temperature and the reaction was monitored on TLC. Upon completion, the reaction mixture was concentrated under vacuum to remove acetone and diluted with CH_2Cl_2 (20mL), extracted with brine passed through Na_2SO_4, and concentrated under vacuum. The crude reaction mixture was purified by column chromatography leading to hemiacetals in good yields.



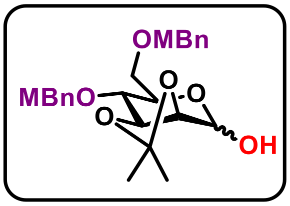
2,3-*O*-isopropylidene-4-*O*-acetyl-6-*O*-triisopropylsilyl-D-mannopyranose (8a)

Reaction of **6a** (105 mg, 0.21 mmol) with NBS (2 equiv., 74.3 mg, 0.42 mmol) according to **General procedure B** afforded **8a** (71.2 mg, 83 %, α: β 85: 15) as a colorless syrup. The crude product was purified through column chromatography. R_f = 0.3 (Hexane/EtOAc = 3:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.46 (d, *J* = 2.8 Hz, 1H), 5.25 (t, *J* = 5.1 Hz, 1H), 5.03 (dd, *J* = 10.0, 7.7 Hz, 1H), 4.97 (dt, *J* = 10.7, 5.3 Hz, 1H), 4.40 – 4.35 (m, 1H), 4.27 (dd, *J* = 7.3, 5.8 Hz, 1H), 4.22 (dd, *J* = 6.5, 2.0 Hz, 1H), 4.17 (d, *J* = 5.5 Hz, 1H), 3.98 – 3.89 (m, 1H), 3.88 – 3.78 (m, 1H), 3.79 – 3.66 (m, 2H), 3.21 (d, *J* = 3.1 Hz, 1H), 2.09 – 2.07 (m, 4H), 1.56 (s, 3H), 1.53 (s, 1H), 1.37 (s, 1H), 1.35 (s, 3H), 1.14 – 1.00 (m, 26H).



2,3-*O*-isopropylidene-4-*O*-(4’-methyl benzyl)-6-*O*-triisopropylsilyl-D-mannopyranose (8b)

Reaction of **6b** (120.3 mg, 0.21 mmol) with NBS (2 equiv., 75.2 mg, 0.42 mmol) according to **General procedure B** afforded **8b** (79.8 mg, 79 %, α: β 87: 13) as a colorless syrup. The crude product was purified through column chromatography. R_f = 0.3 (Hexane/EtOAc = 4:1, v/v). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23 – 7.19 (m, 2H), 7.14 (d, *J* = 7.7 Hz, 2H), 5.25 (d, *J* = 6.0 Hz, 1H), 5.00 (dd, *J* = 11.1, 2.0 Hz, 1H), 4.75 (d, *J* = 11.2 Hz, 1H), 4.62 – 4.58 (m, 1H), 4.47 (dd, *J* = 6.5, 5.0 Hz, 1H), 4.43 (t, *J* = 6.1 Hz, 1H), 4.22 (dd, *J* = 6.8, 2.0 Hz, 1H), 4.17 (d, *J* = 6.3 Hz, 1H), 3.96 – 3.88 (m, 2H), 3.88 – 3.82 (m, 1H), 3.76 (t, *J* = 6.5 Hz, 1H), 3.61 (d, *J* = 11.1 Hz, 1H), 3.55 (d, *J* = 6.2 Hz, 1H), 2.35 – 2.32 (m, 4H), 1.70 (s, 1H), 1.50 (s, 3H), 1.37 (s, 1H), 1.36 (s, 3H), 1.13 – 1.02 (m, 26H).

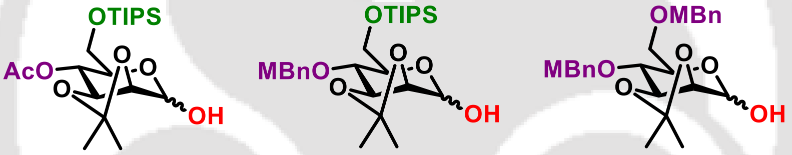


2,3-*O*-isopropylidene-4,6-di-*O*-(4’-methyl benzyl)-D-mannopyranose (8c)

Reaction of **6c** (109.3 mg, 0.21 mmol) with NBS (2 equiv., 75.2 mg, 0.42 mmol) according to **General procedure B** afforded **8c** (74.7 mg, 83 %, α: β 87: 13) as a colorless syrup. The crude product was purified through column chromatography. R_f = 0.5 (Hexane/EtOAc = 4:1, v/v).^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20 (d, *J* = 7.8 Hz, 1H), 7.15 (s, 1H), 7.14 – 7.11 (m, 2H), 7.10 (d, *J* = 7.9 Hz, 1H), 5.36 (s, 1H), 4.98 (d, *J* = 8.4 Hz, 1H), 4.77 (d, *J* = 11.3 Hz, 1H), 4.65 (d, *J* = 11.3 Hz, 1H), 4.57 – 4.43 (m, 2H), 4.34 (t, *J* = 6.3 Hz, 1H), 4.20 (dd, *J* = 6.5, 2.2 Hz, 1H), 4.15 (d, *J* = 5.9 Hz, 1H), 4.02 (ddd, *J* = 9.0, 6.6, 2.5 Hz, 1H), 3.74 (s, 1H), 3.70 (dd, *J* = 10.4, 2.6 Hz, 1H), 3.68 – 3.61 (m, 1H), 3.55 (dd, *J* = 10.3, 6.5 Hz, 1H), 3.48 (dd, *J* = 9.2, 6.7 Hz, 1H), 2.35 – 2.31 (m, 7H), 1.51 (s, 1H), 1.49 (s, 3H), 1.37 (s, 1H), 1.36 (s, 3H).

5.9 Anomeric Equilibrium study:[16] Details

The hemiacetals (**8a/8b/8c**) were dissolved individually in $CDCl_3$ (600 μL) and recorded for NMR at 600 MHz. The solutions of $CDCl_3$ were heated to 50 °C by keeping them in an oil bath. The spectra were monitored for each sample at 1h intervals for the first 4h and then at 3h intervals for the next 9h (second phase). As there was not much change noticed at the end of the second phase, the samples were then monitored after heating for the next 24 hours. The final ratio of anomers at equilibrium is reported in **Table 5.1**.



15a
α:β 68:32

15b
α:β 65:35

15c
α:β 71:29

5.10 References

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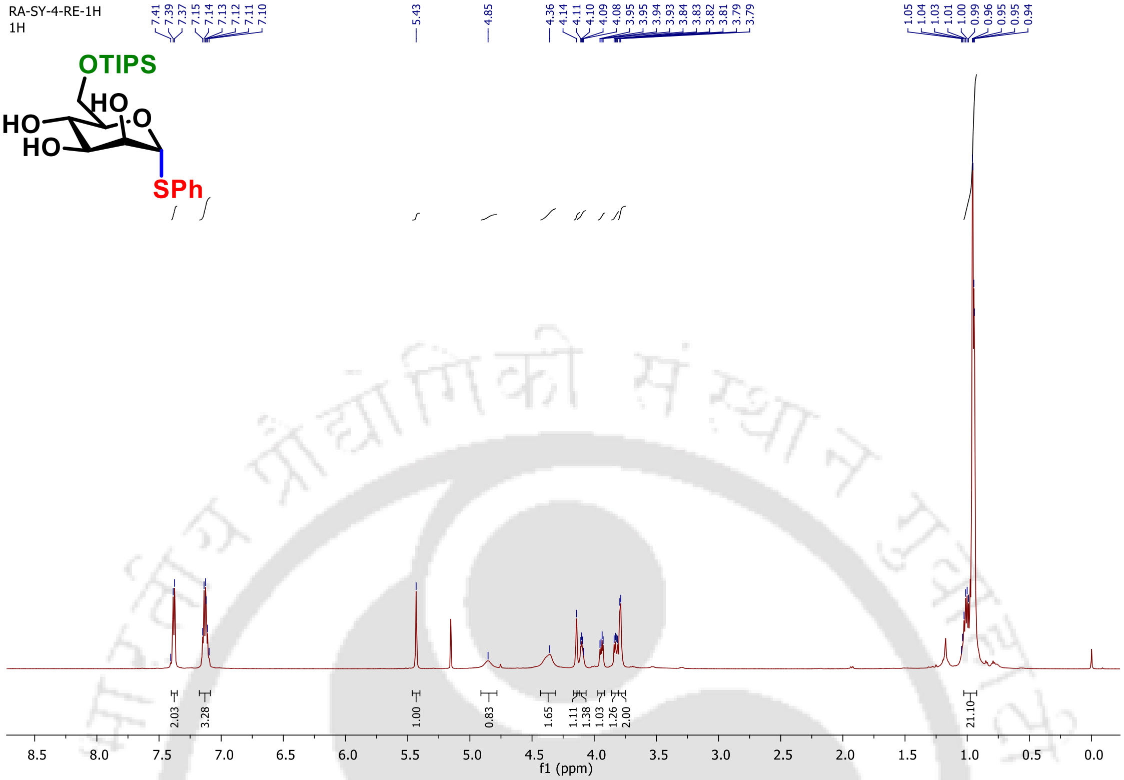
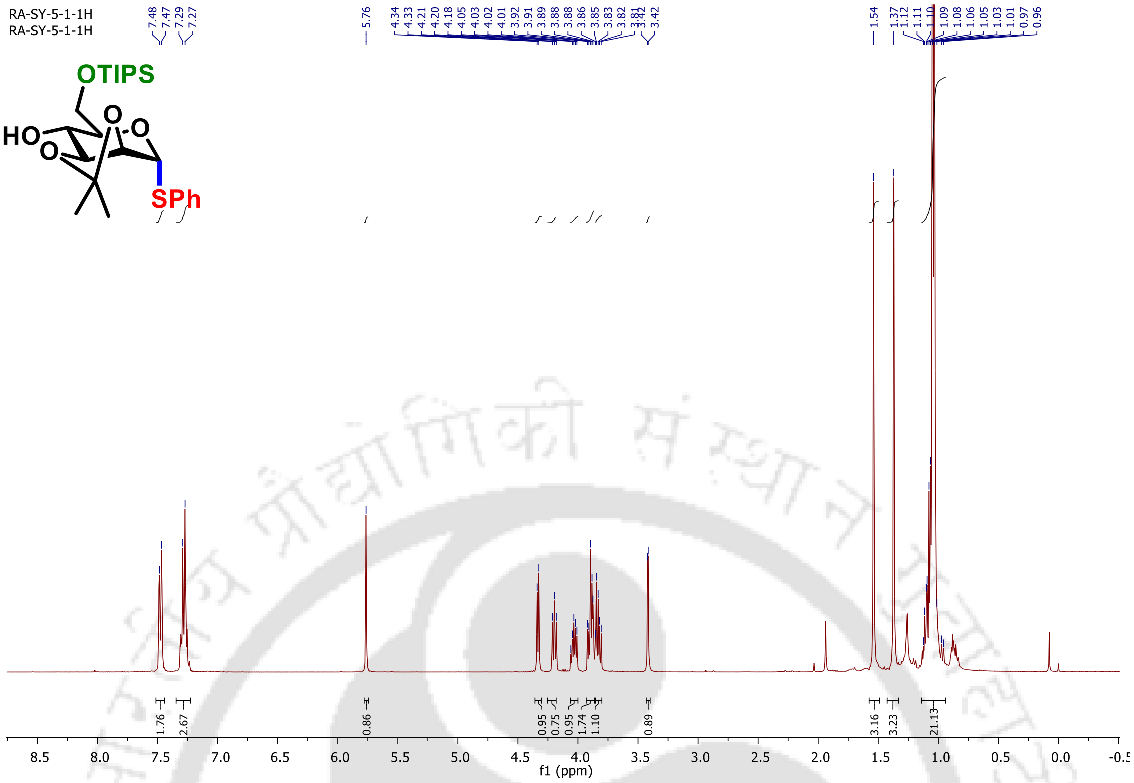
5.11 Spectral data

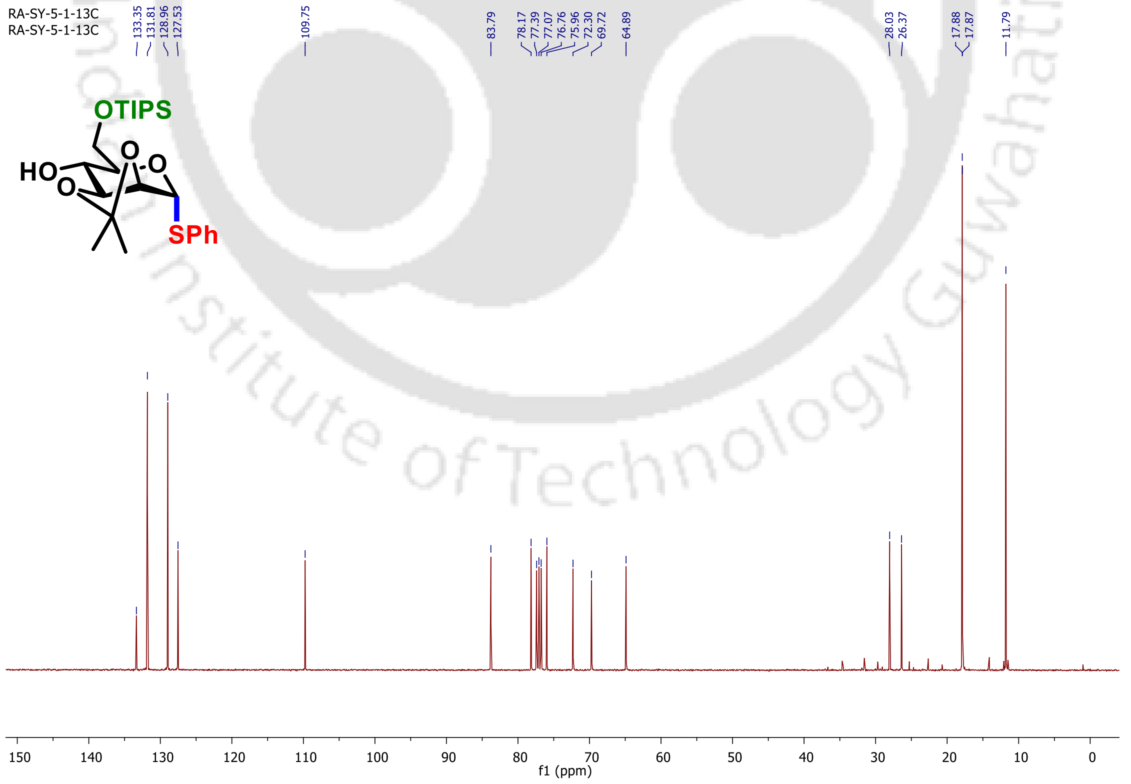


^{1}H NMR of compound **4** ($CDCl_3$, 600 MHz)

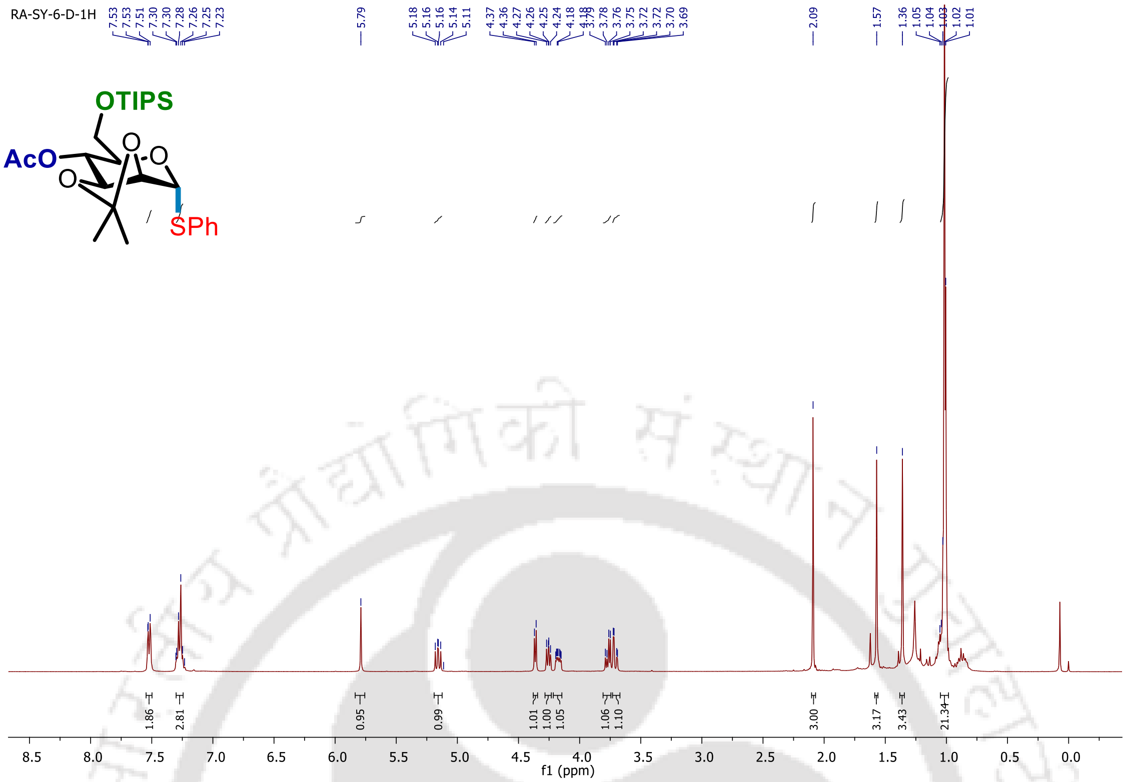
^{13}C NMR of compound **4** ($CDCl_3$, 150 MHz)



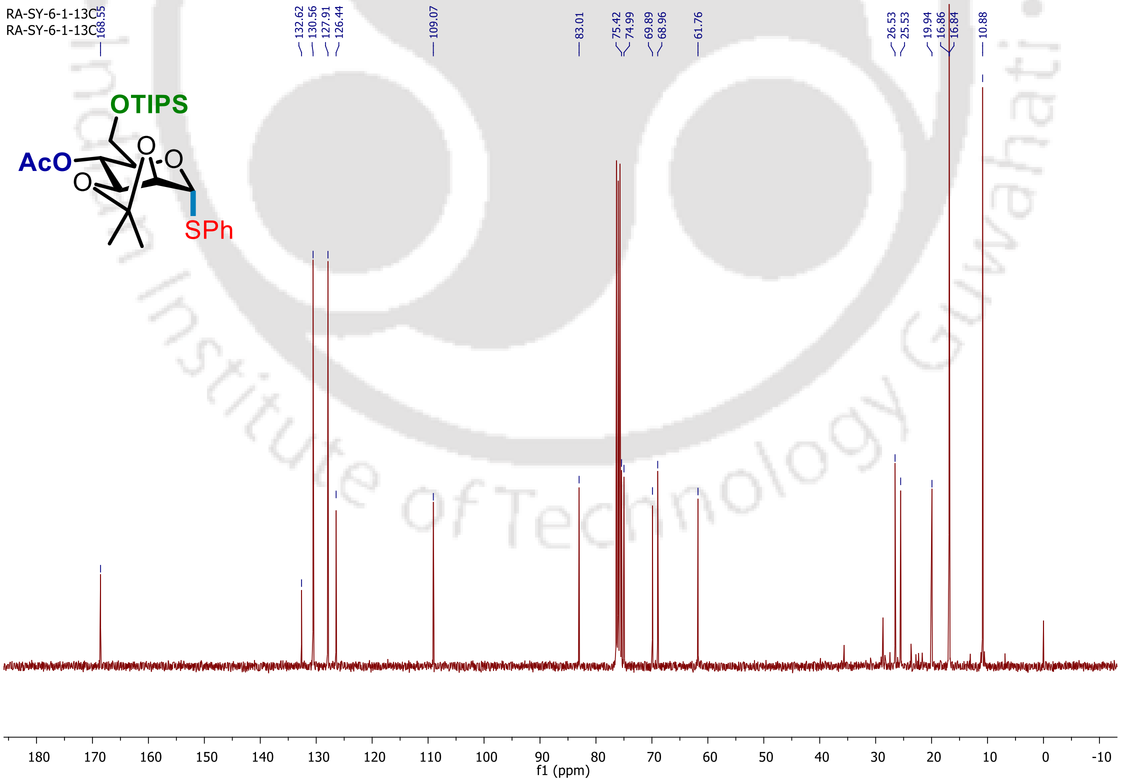
^{1}H NMR of compound **5** (CDCl$_3$, 400 MHz)



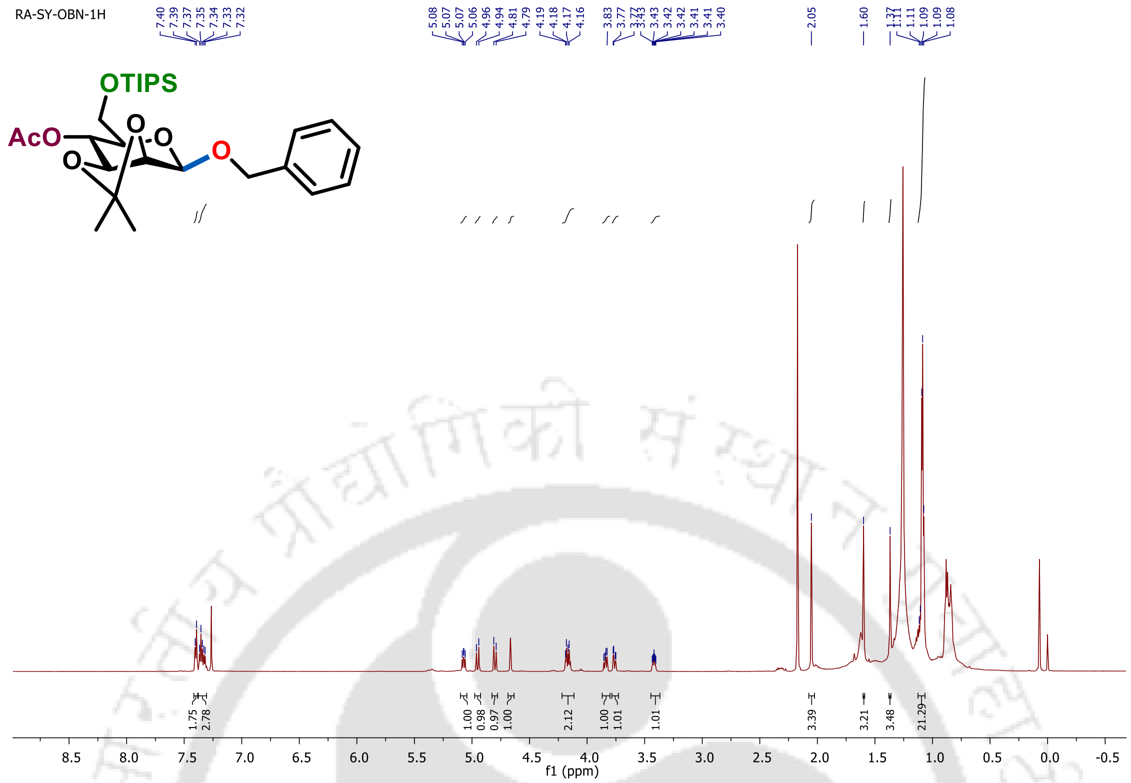
^{13}C NMR of compound **5** (CDCl$_3$, 100 MHz)



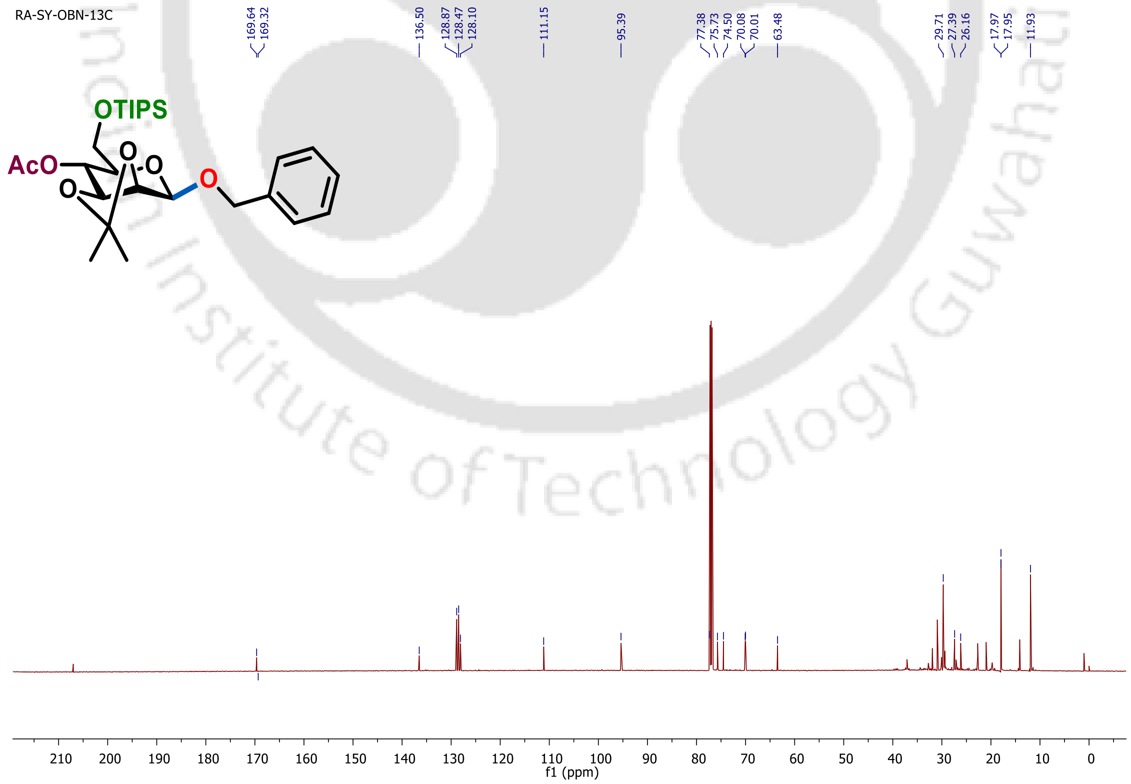
^{1}H NMR of compound **12a** (CDCl$_3$, 400 MHz)



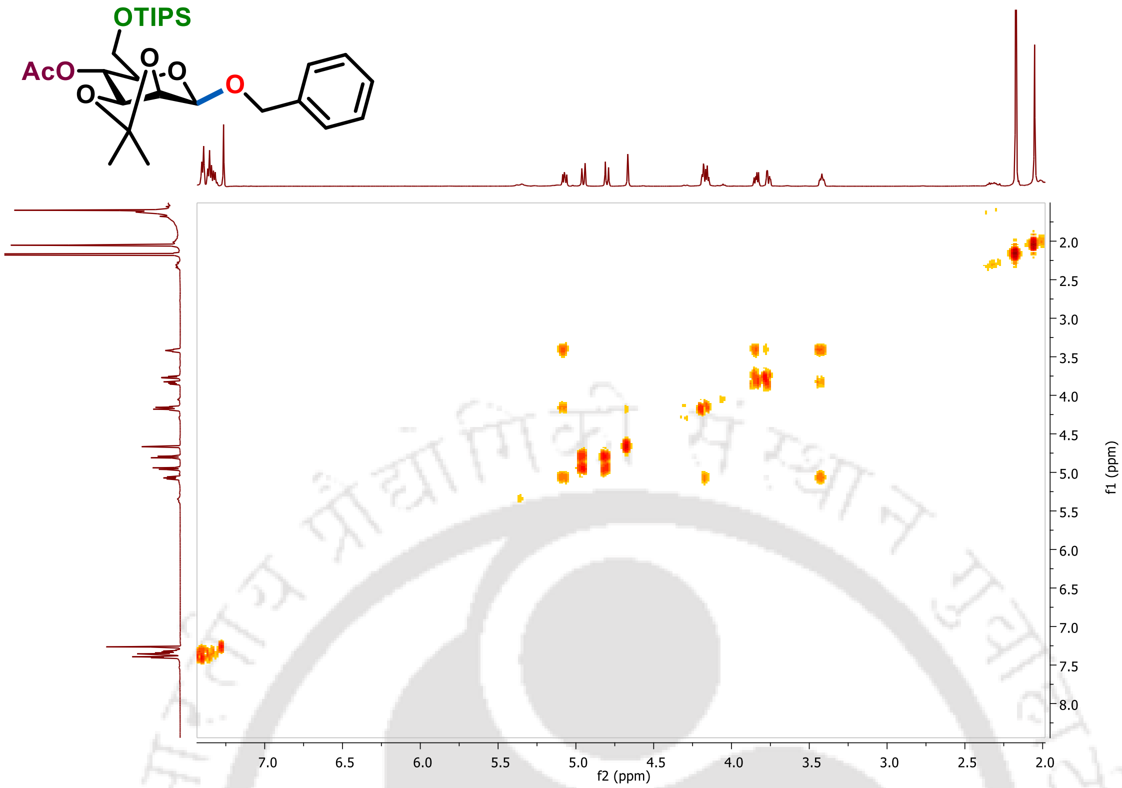
^{13}C NMR of compound **12a** (CDCl$_3$, 100 MHz)



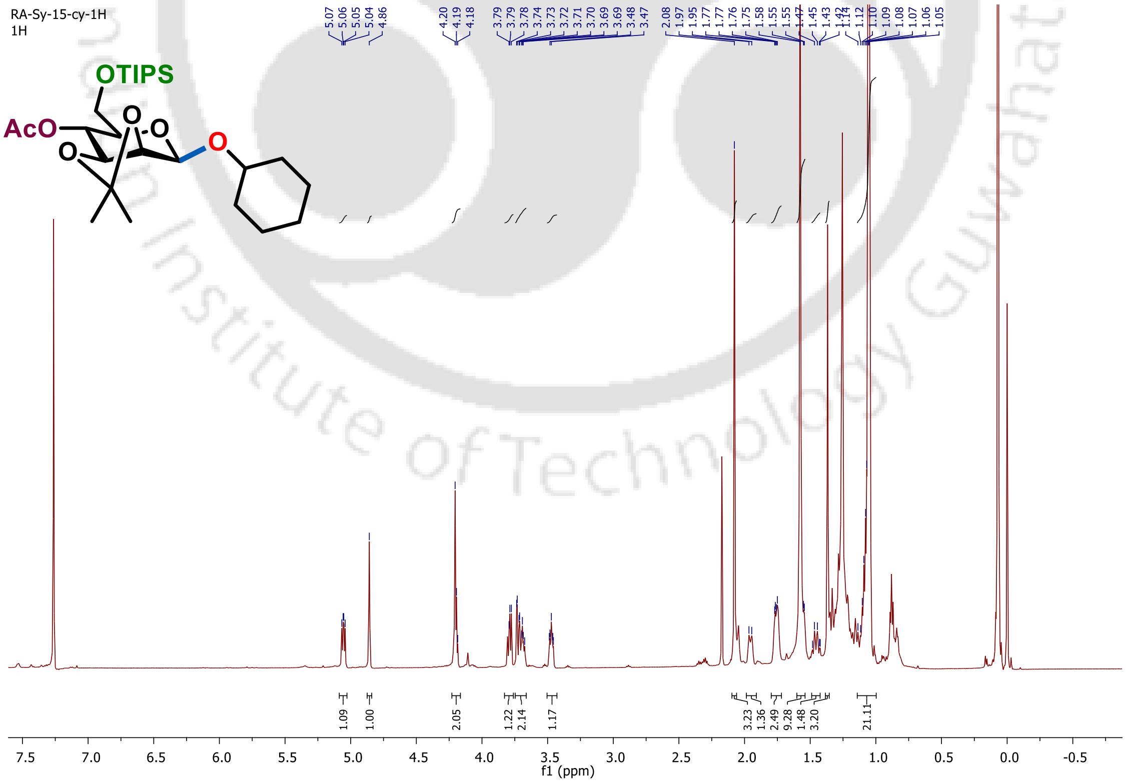
^{1}H NMR of compound **14a** (CDCl$_3$, 600 MHz)



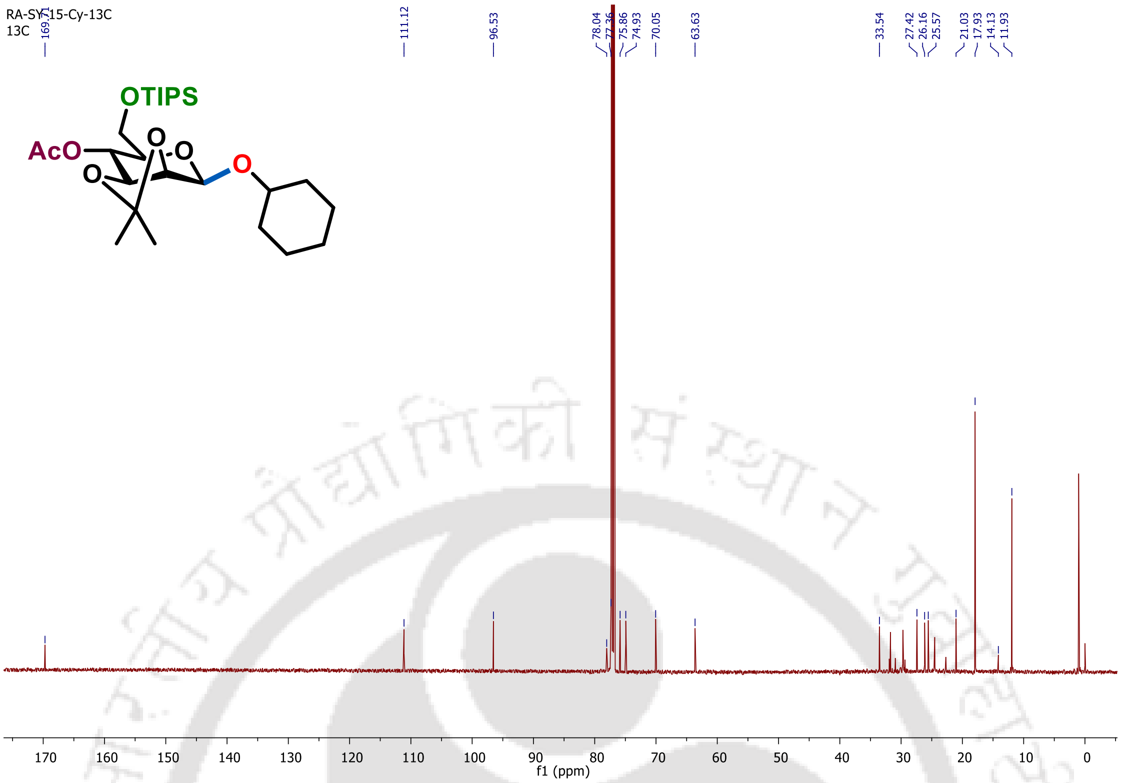
^{13}C NMR of compound **14a** (CDCl$_3$, 151 MHz)



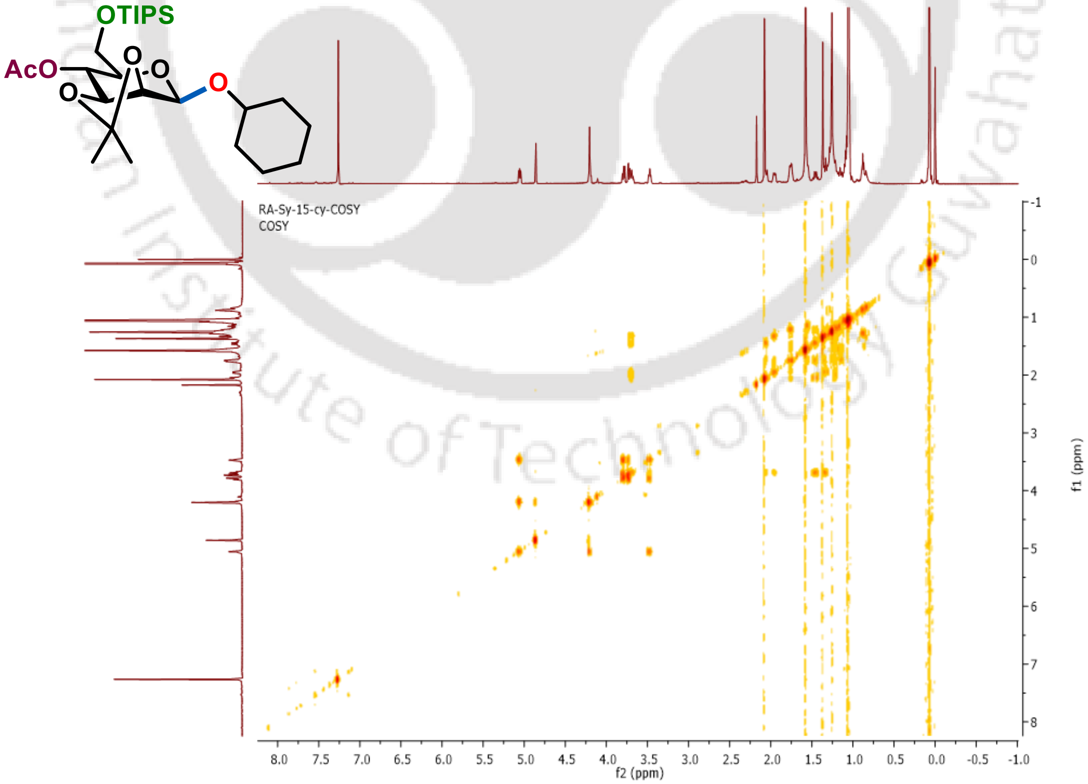
COSY NMR of compound **14a** ($CDCl_3$, 600 MHz)



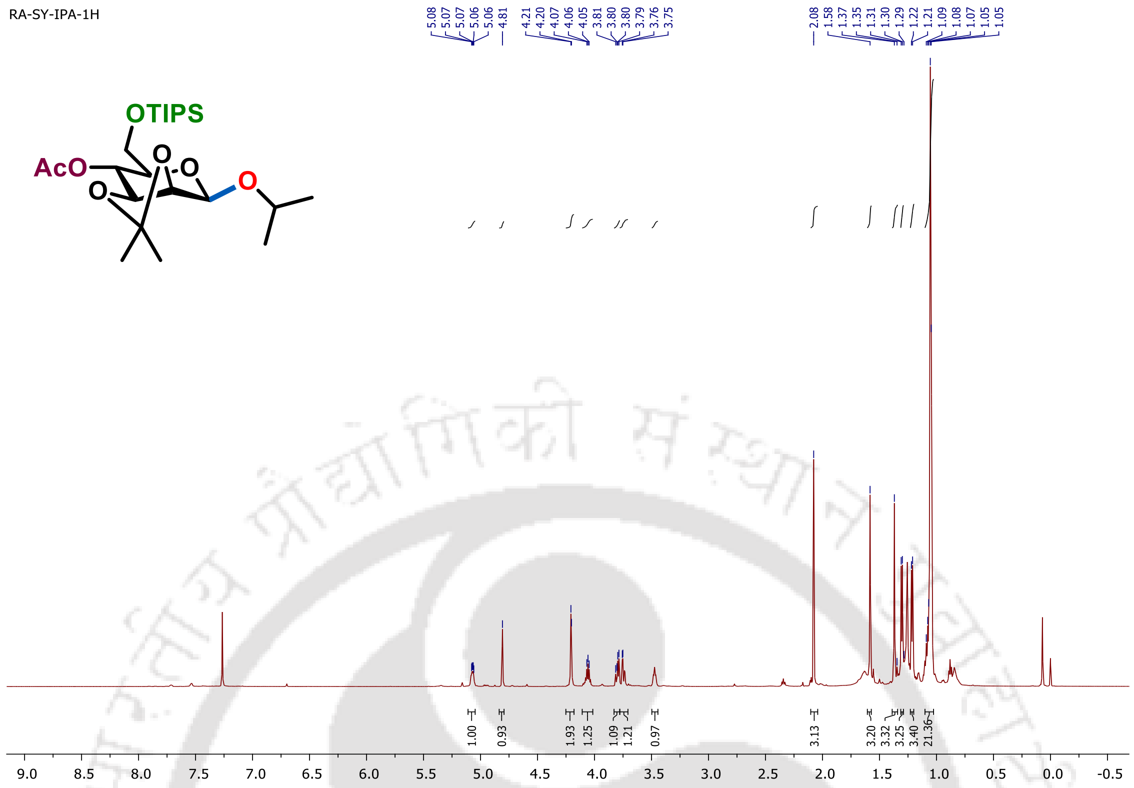
^{1}H NMR of compound **14b** ($CDCl_3$, 600 MHz)



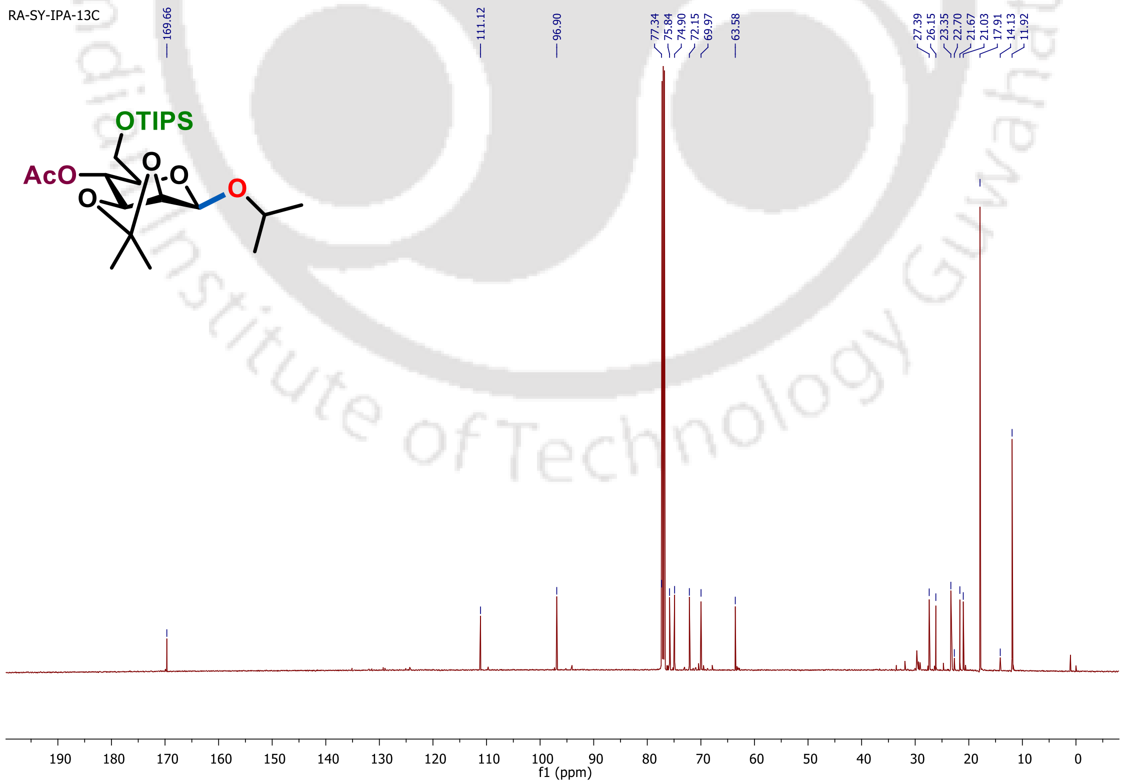
^{13}C NMR of compound **14b** (CDCl$_3$, 151 MHz)



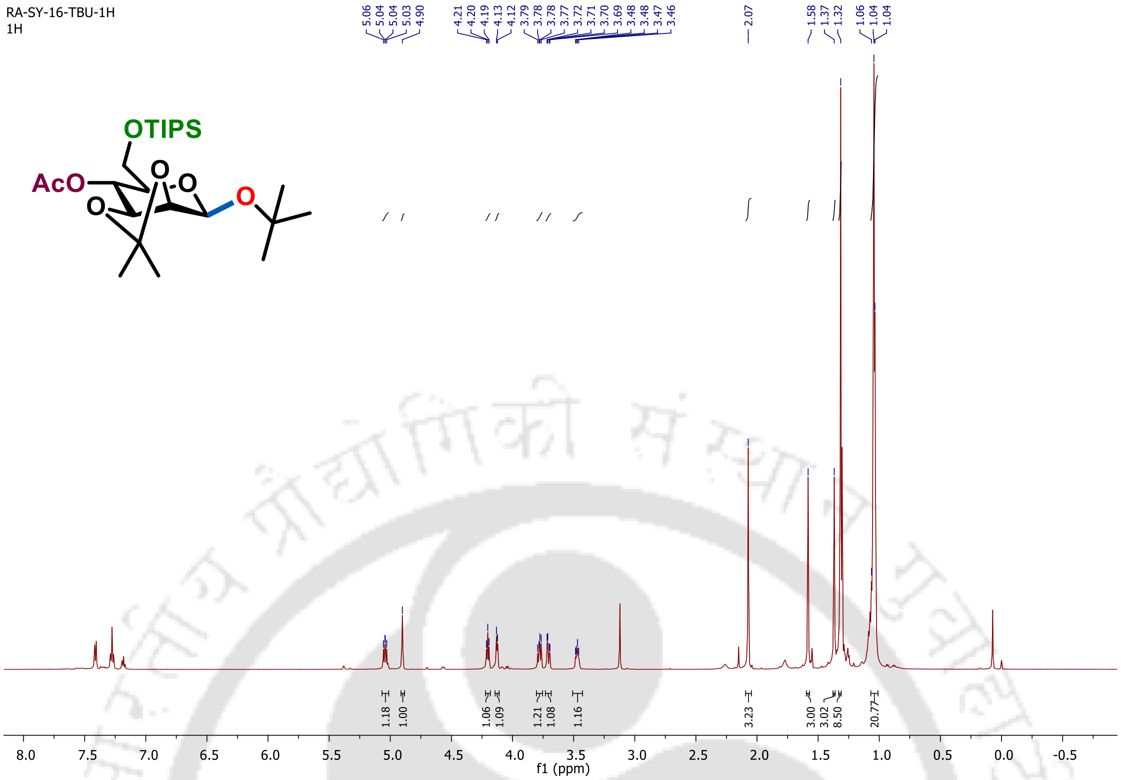
COSY NMR of compound **14b** (CDCl$_3$, 600 MHz)



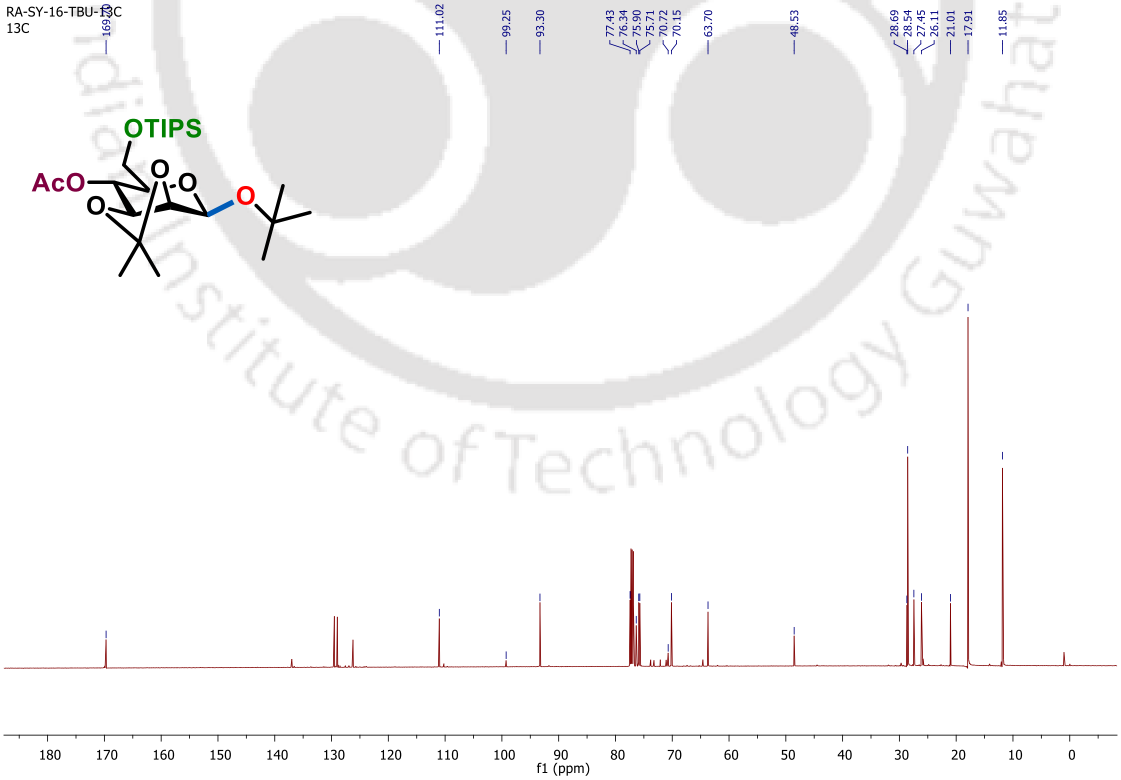
^{1}H NMR of compound **14c** ($CDCl_3$, 600 MHz)



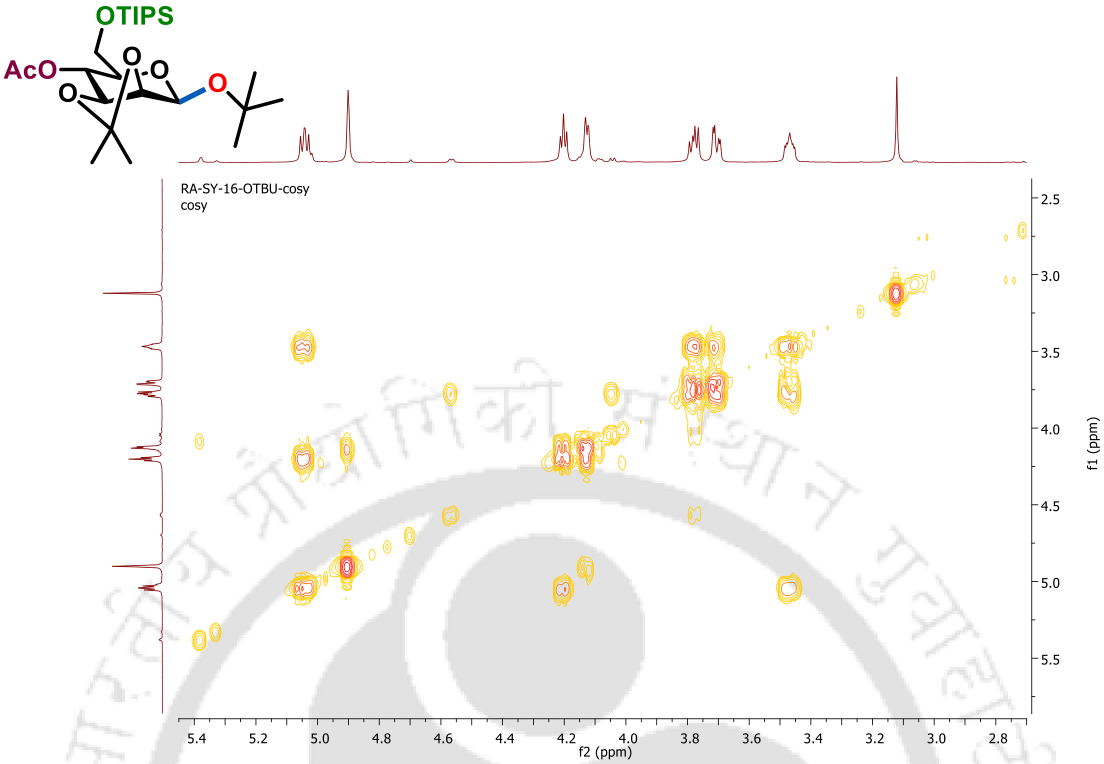
^{13}C NMR of compound **14c** ($CDCl_3$, 151 MHz)



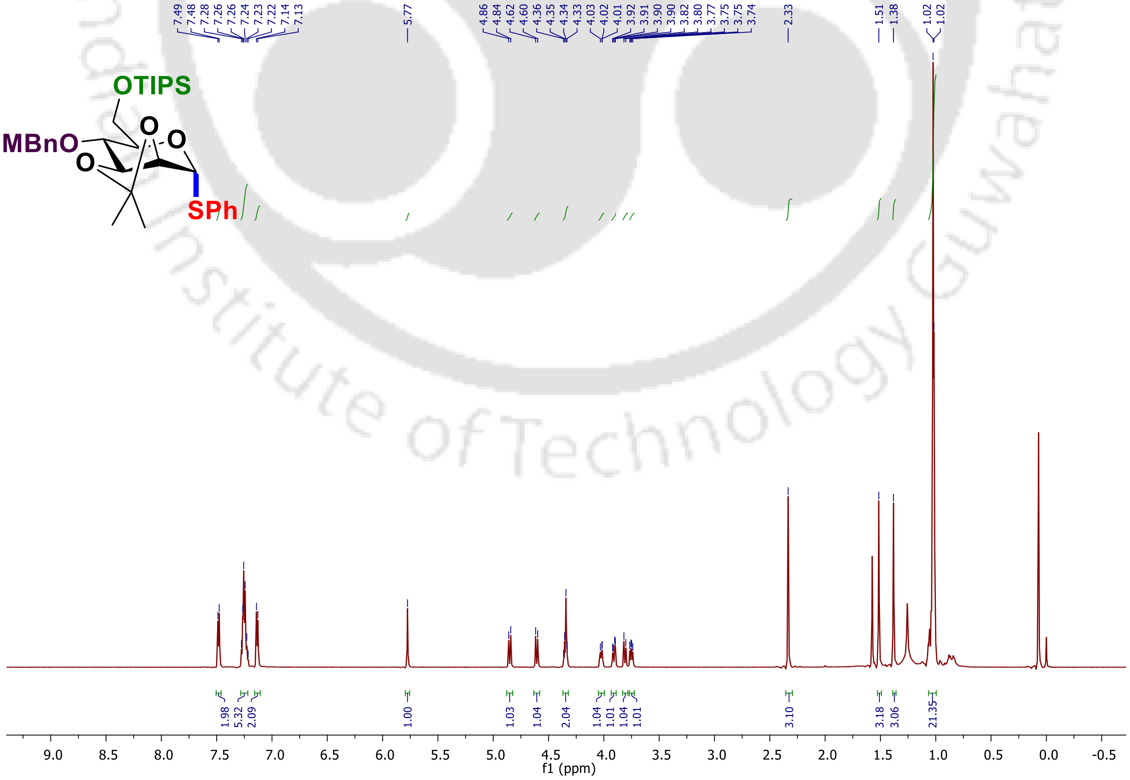
^{1}H NMR of compound **14d** (CDCl$_3$, 600 MHz)



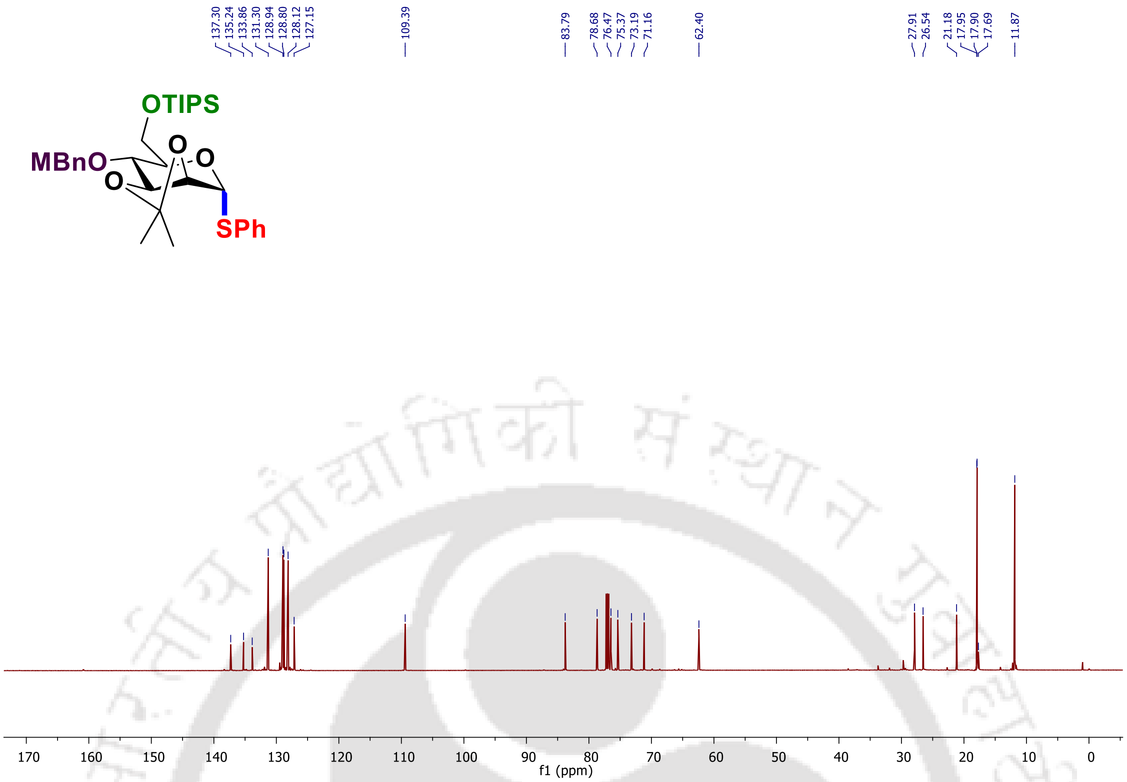
^{13}C NMR of compound **14d** (CDCl3, 151 MHz)



COSY of compound **14d** ($CDCl_3$, 600 MHz)



^{1}H NMR of compound **12b** ($CDCl_3$, 600 MHz)



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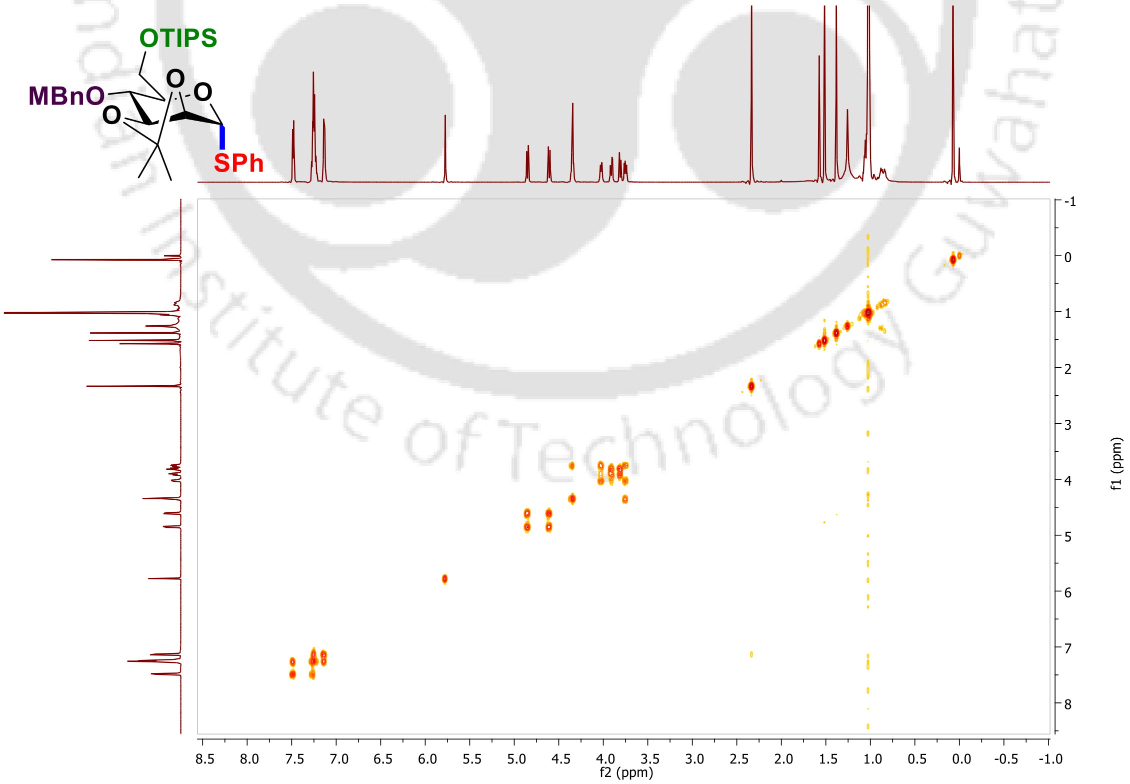
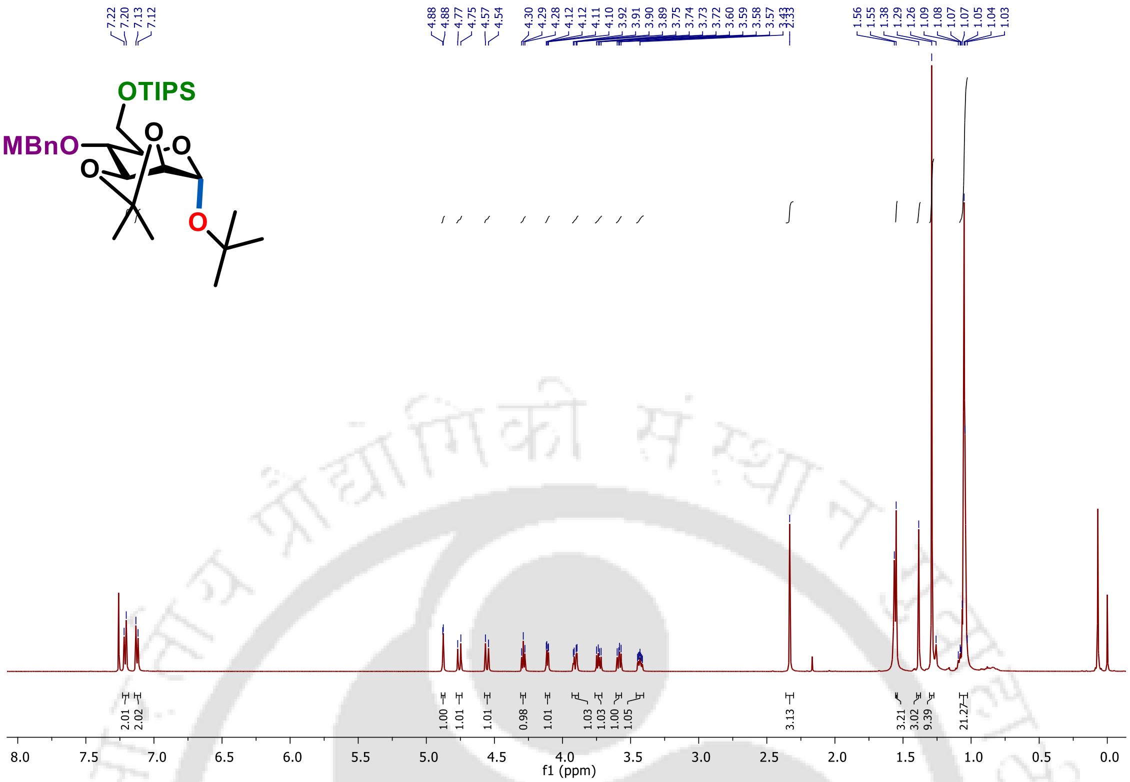
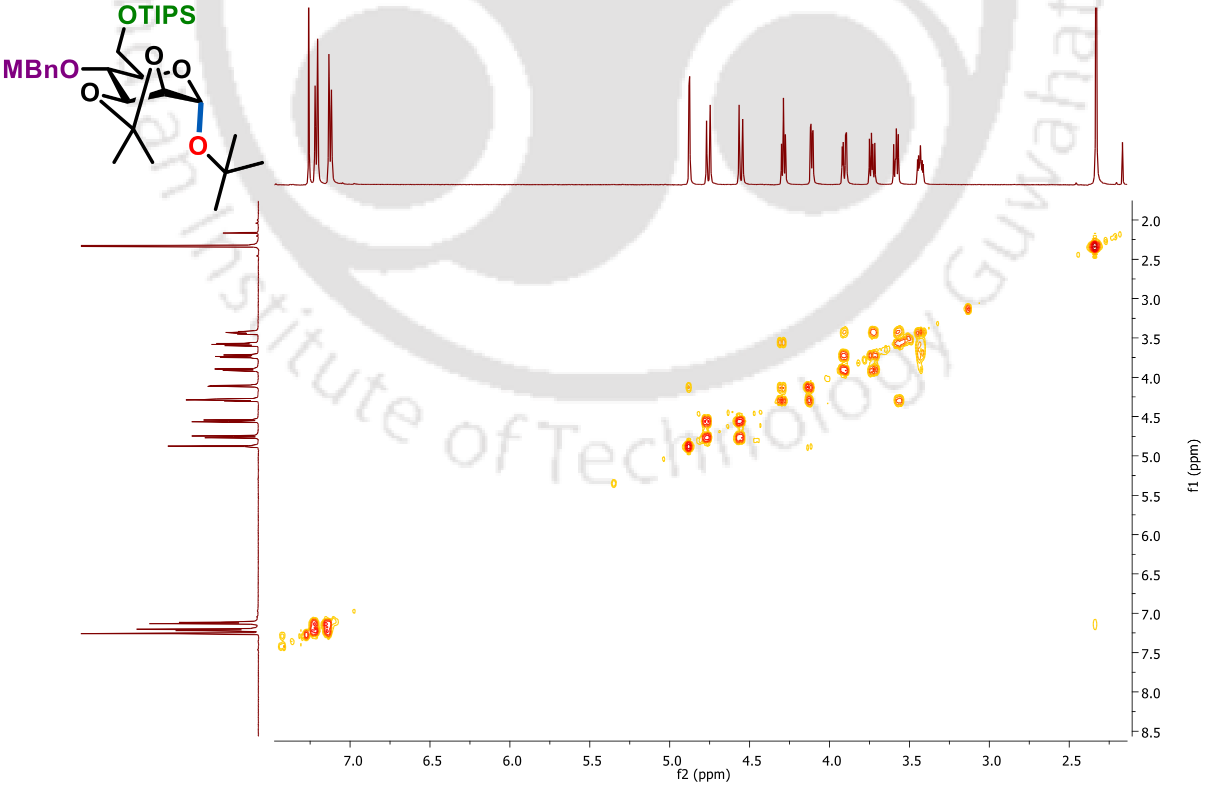


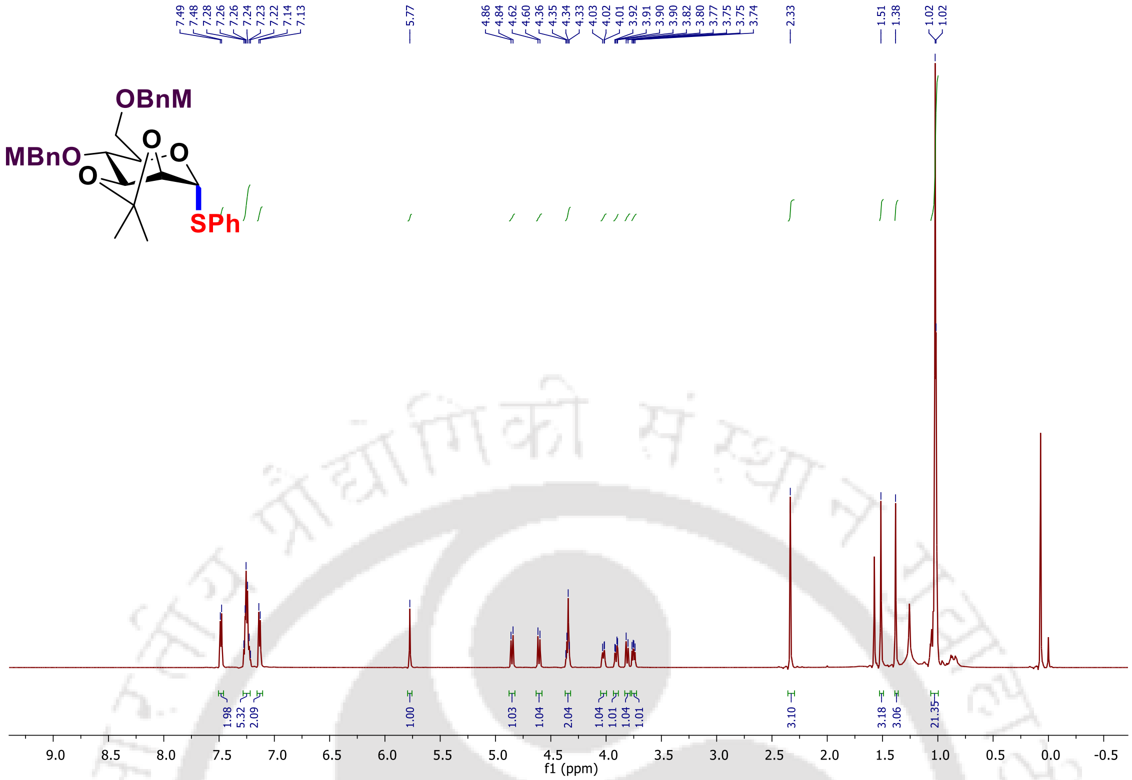
COSY of compound **12b** (CDCl$_3$, 600 MHz)



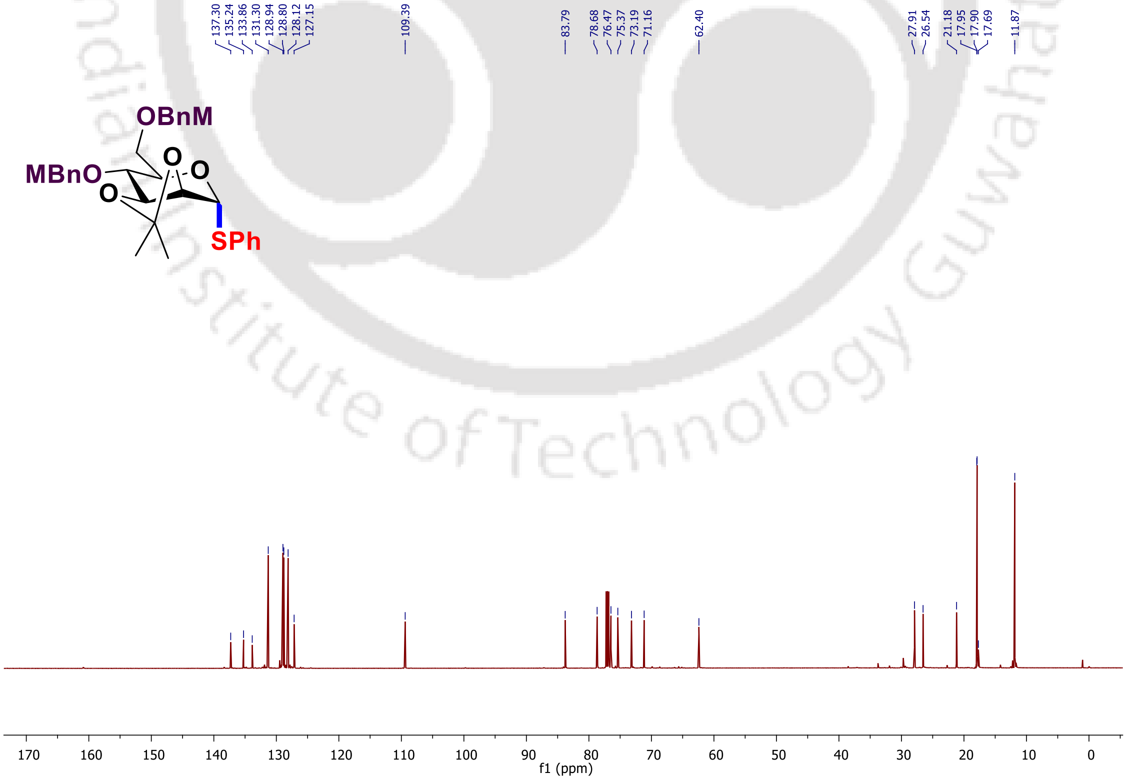
^{1}H NMR of compound **14e** ($CDCl_3$, 500 MHz)



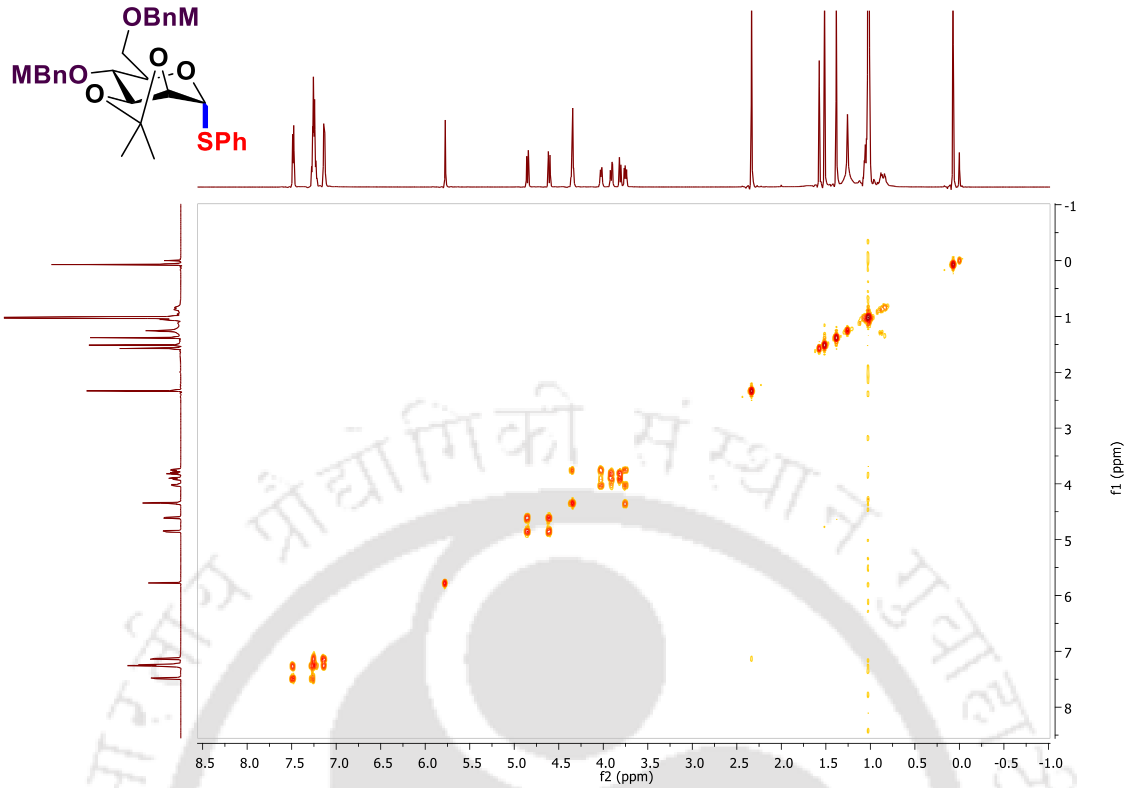
COSY NMR of compound **14e** ($CDCl_3$, 500 MHz)



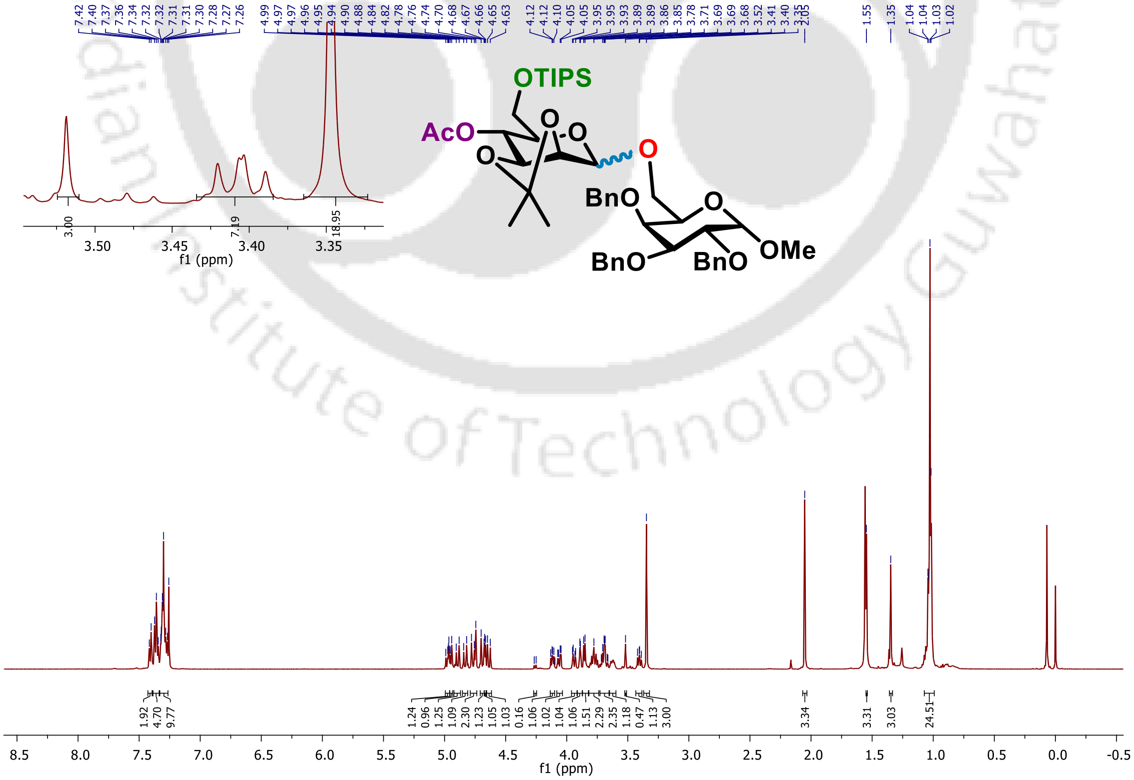
^{1}H NMR of compound **12c** (CDCl$_3$, 600 MHz)



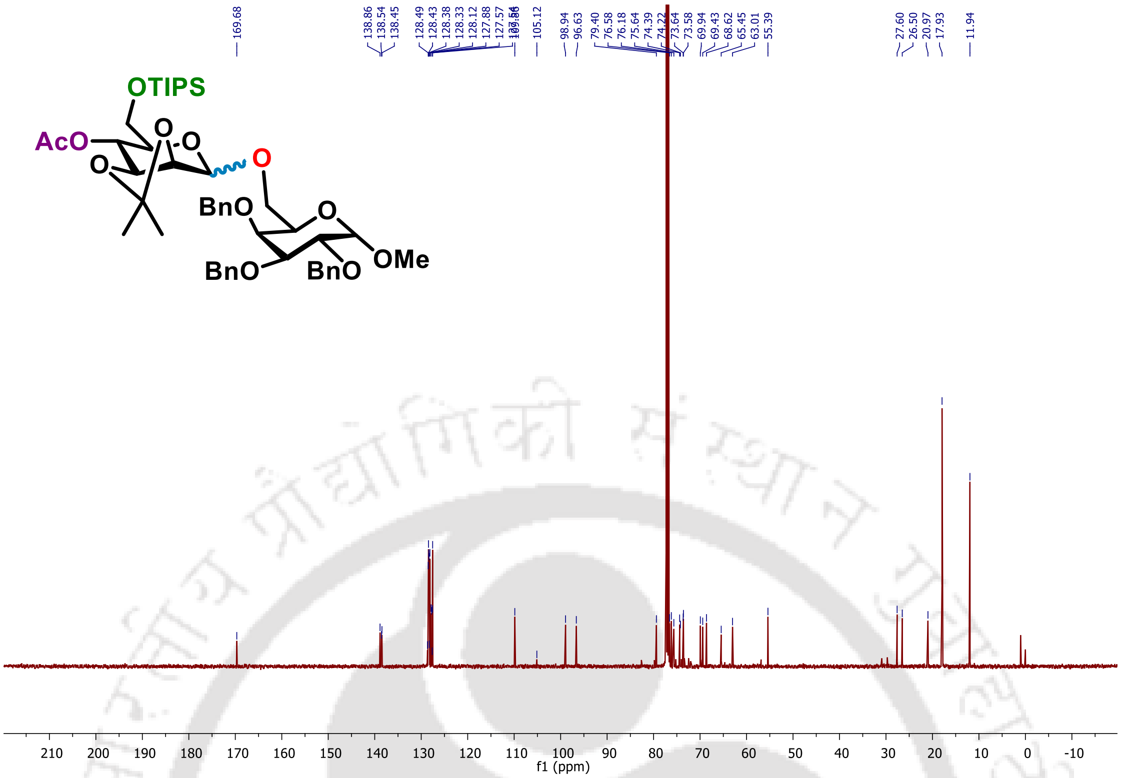
^{13}C NMR of compound **12c** (CDCl3, 151 MHz)



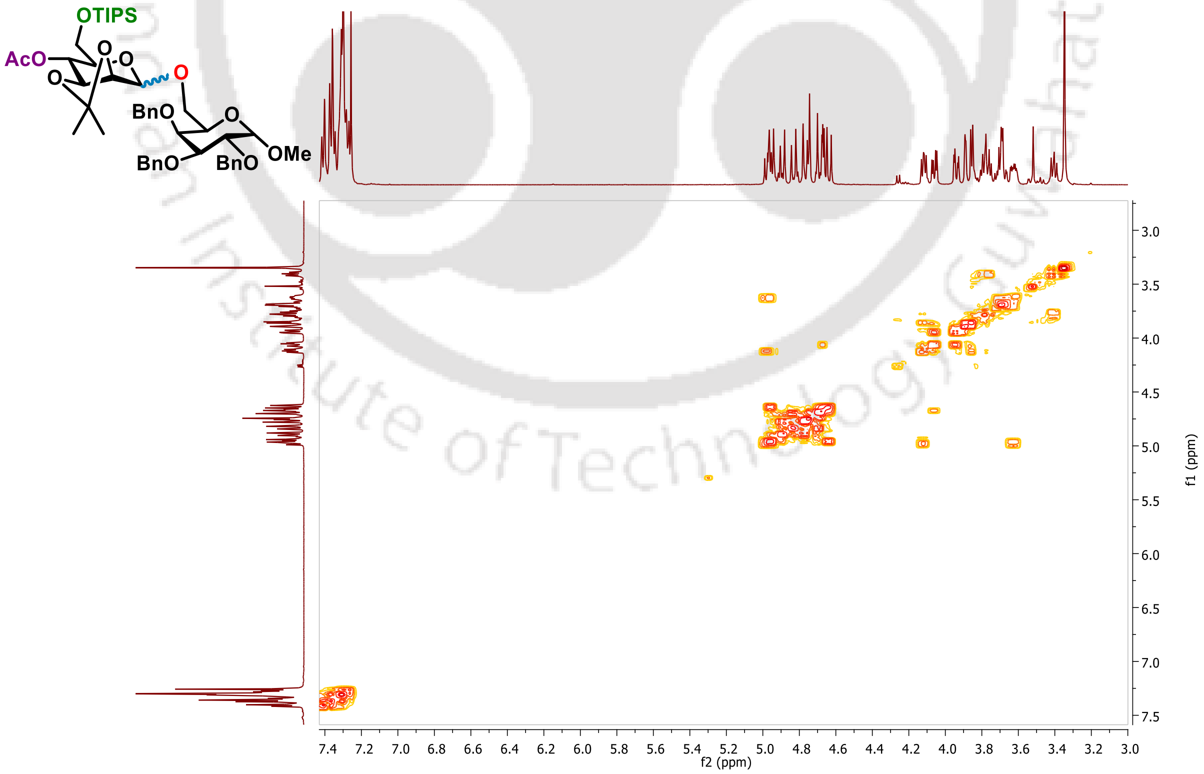
COSY NMR of compound **12c** ($CDCl_3$, 600 MHz)



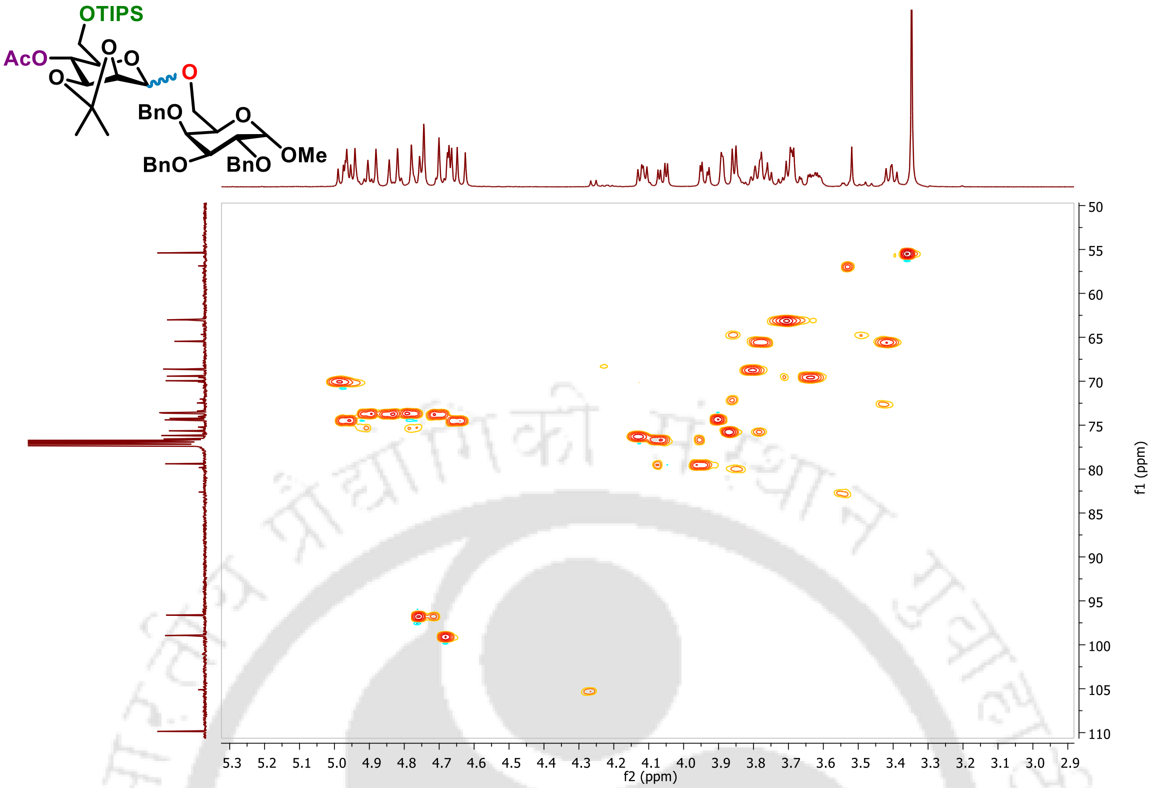
^{1}H NMR of compound **14f** ($CDCl_3$, 500 MHz)



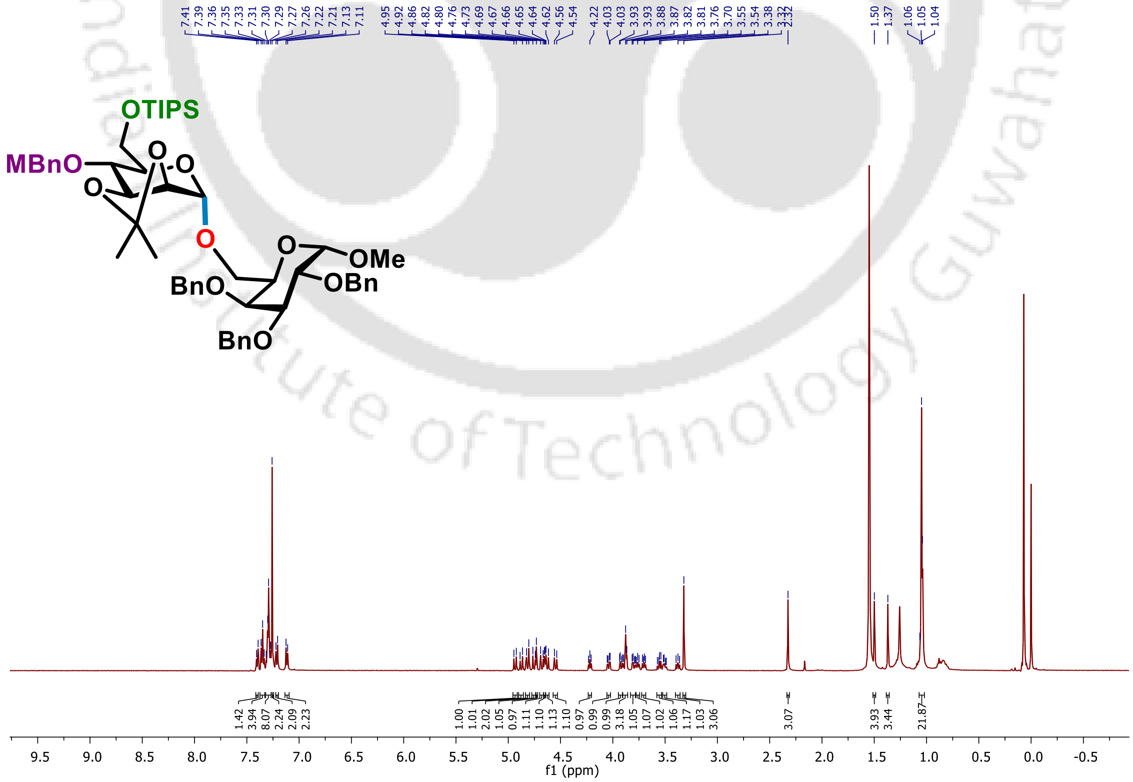
^{13}C NMR of compound **14f** (CDCl3, 126 MHz)



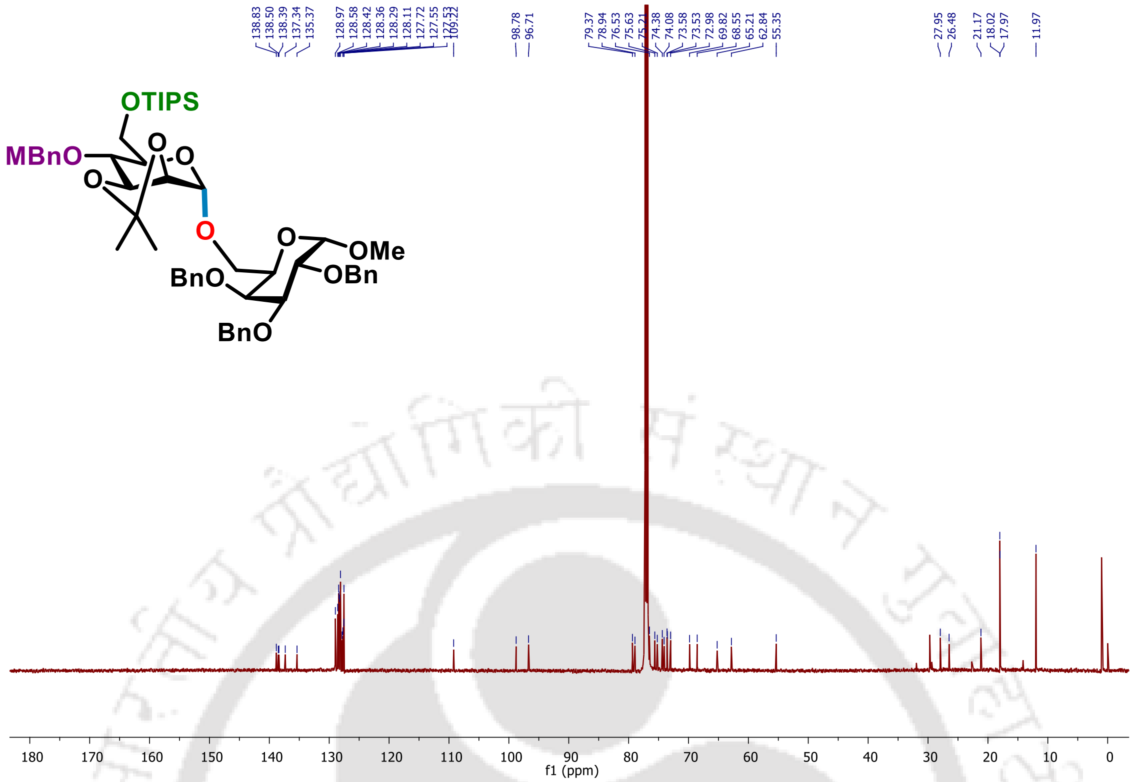
COSY NMR of compound **14f** (CDCl$_3$, 500 MHz)



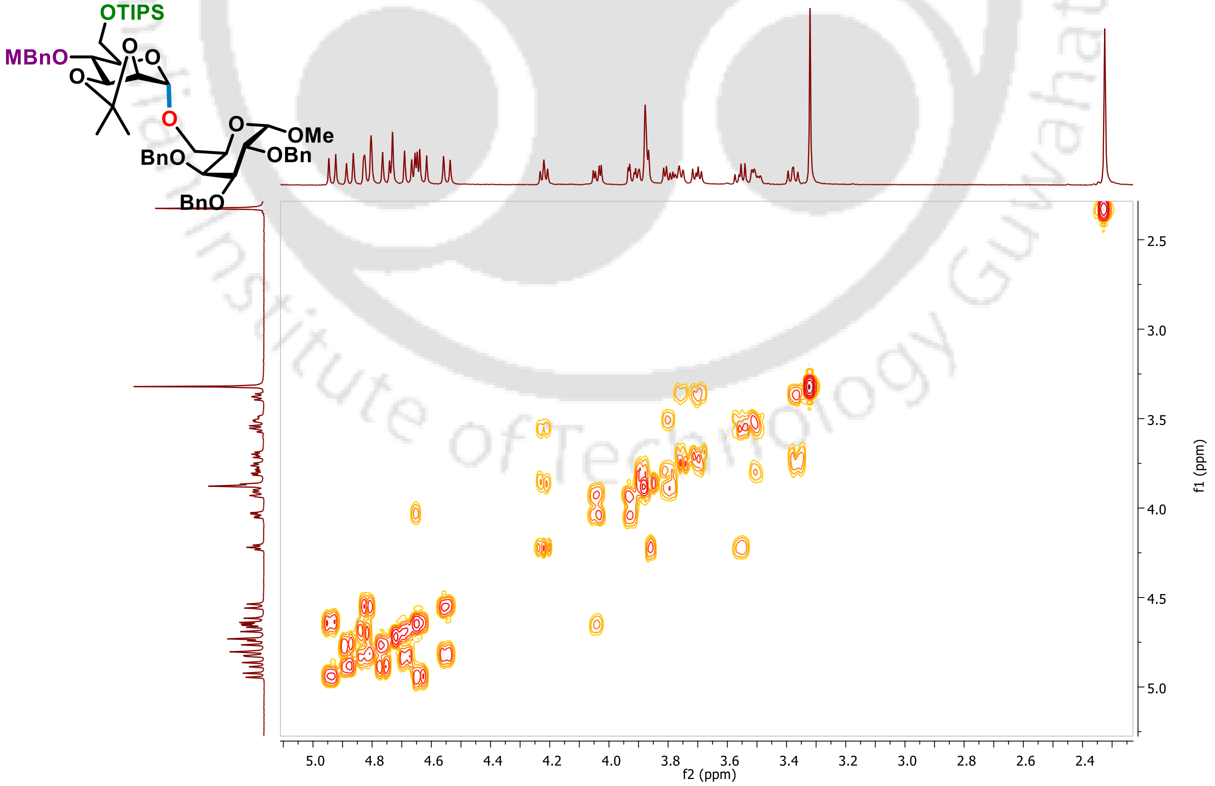
HSQC NMR of compound **14f** ($CDCl_3$, 500 MHz)



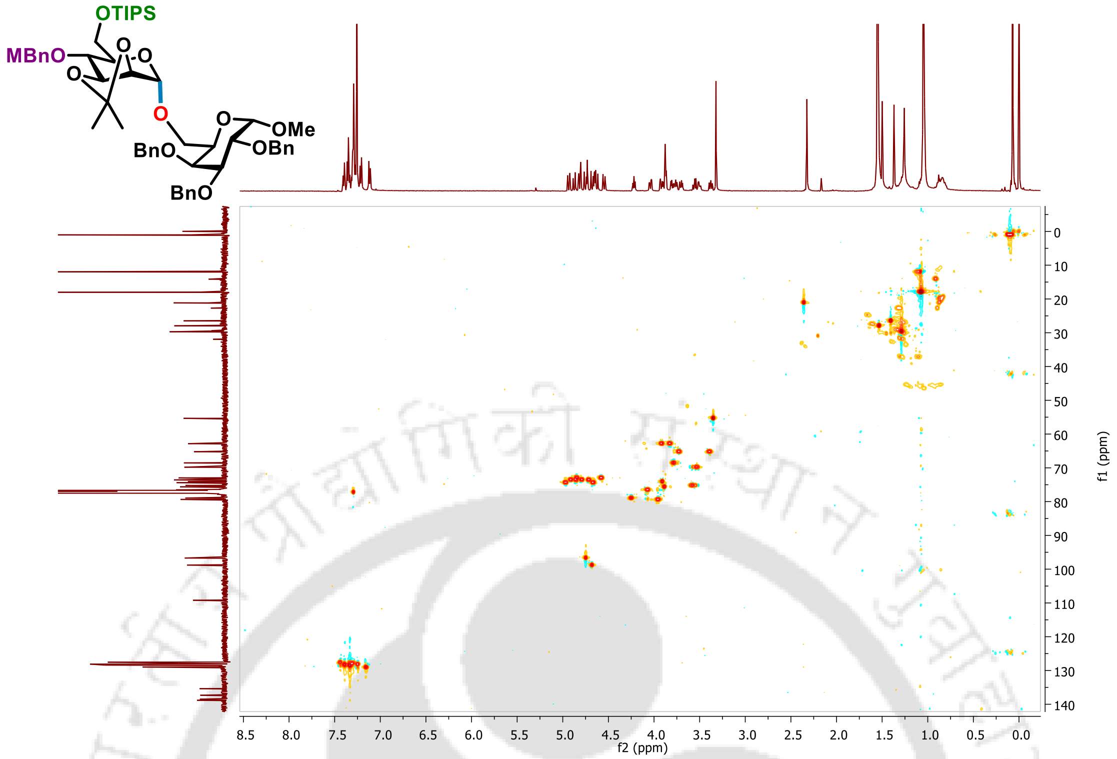
^{1}H NMR of compound **14g** ($CDCl_3$, 500 MHz)



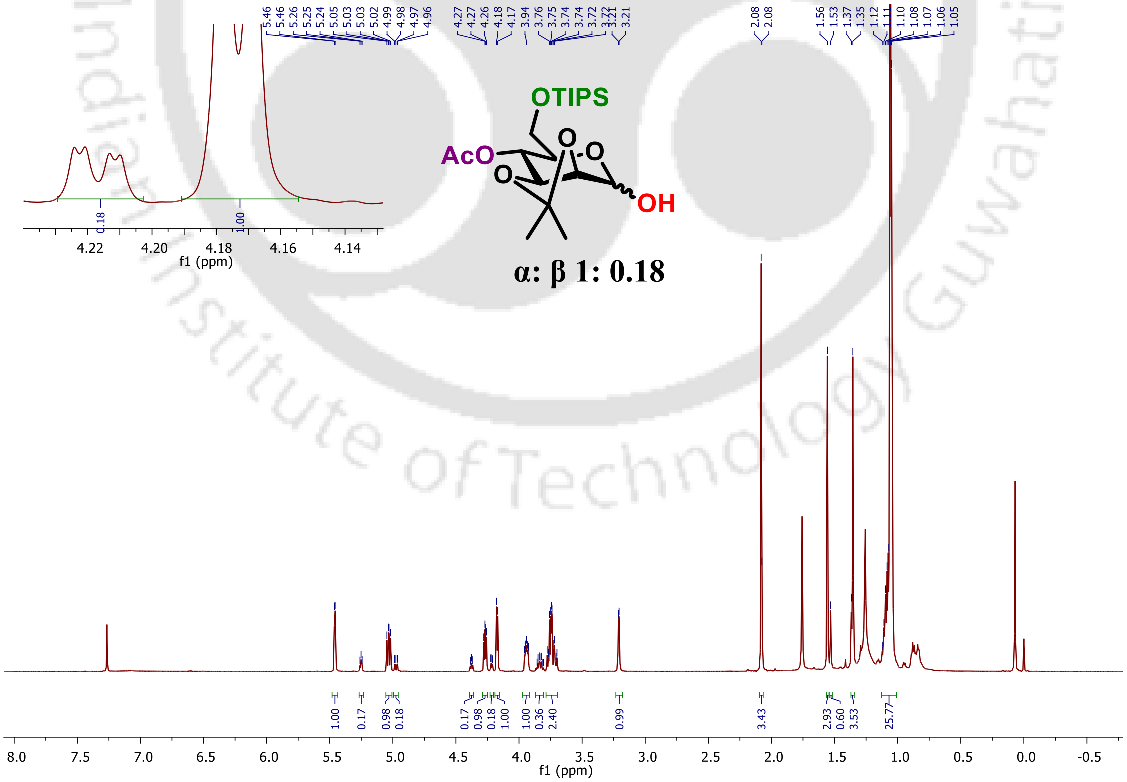
^{13}C NMR of compound **14g** (CDCl3, 151 MHz)



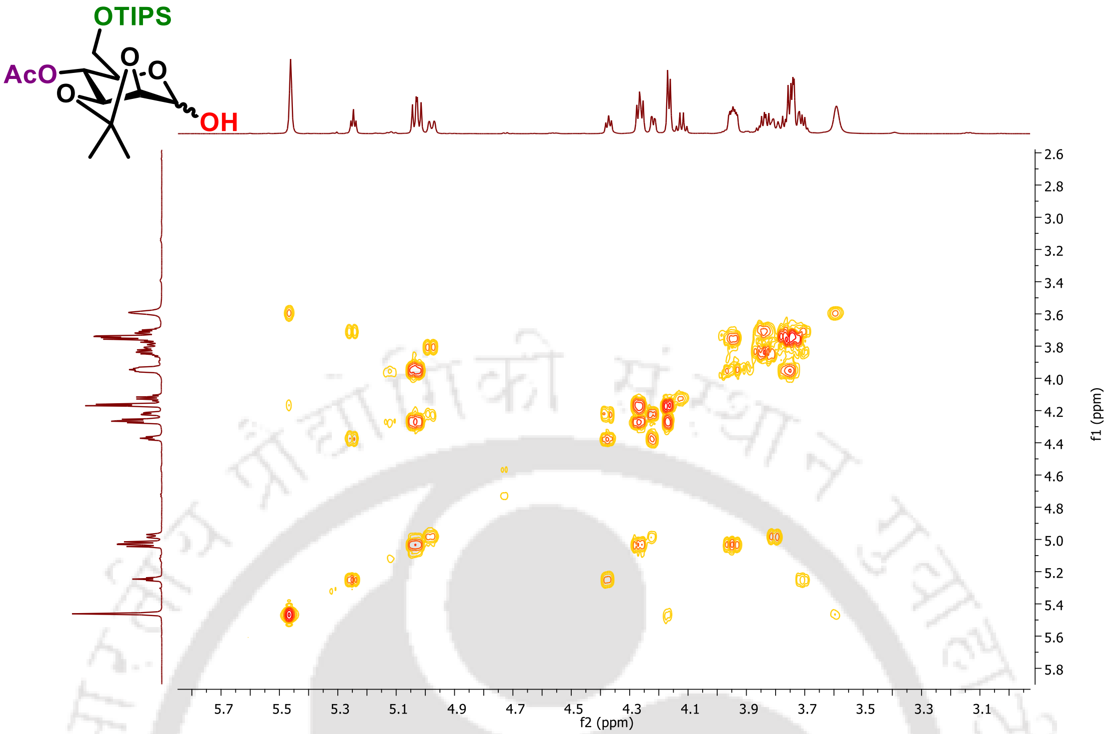
COSY NMR of compound **14g** ($CDCl_3$, 500 MHz)



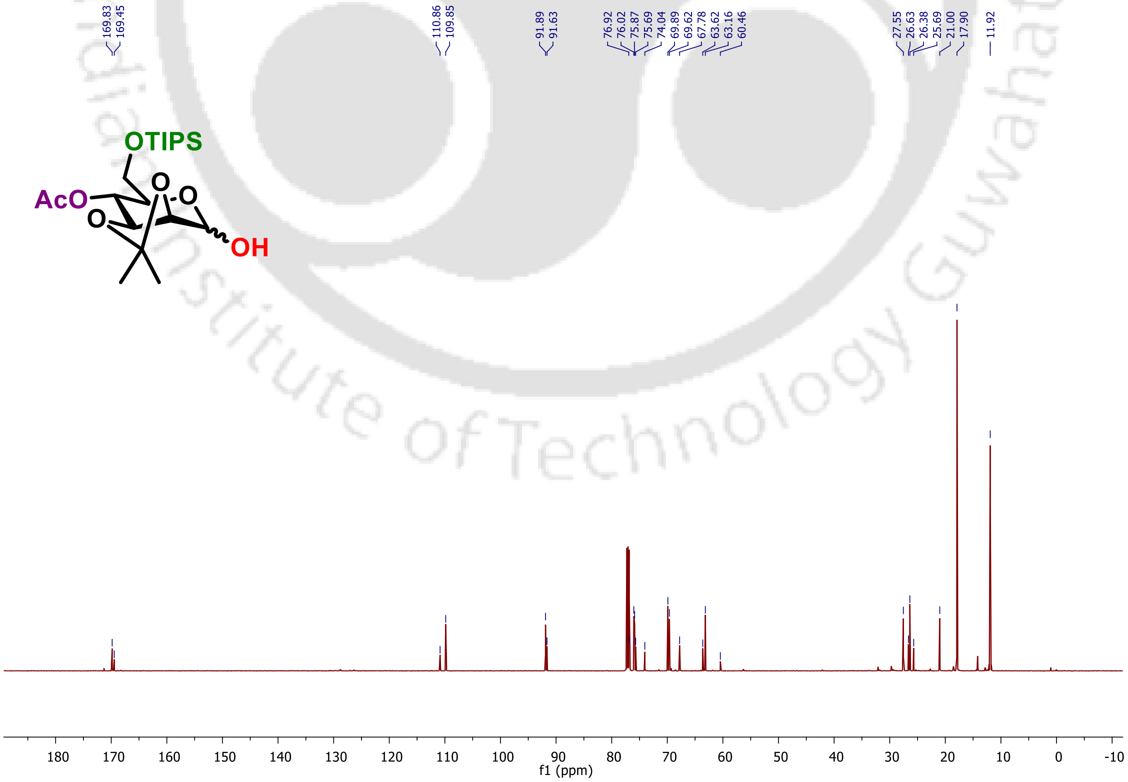
HSQC NMR of compound **14g** (CDCl$_3$, 500 MHz)



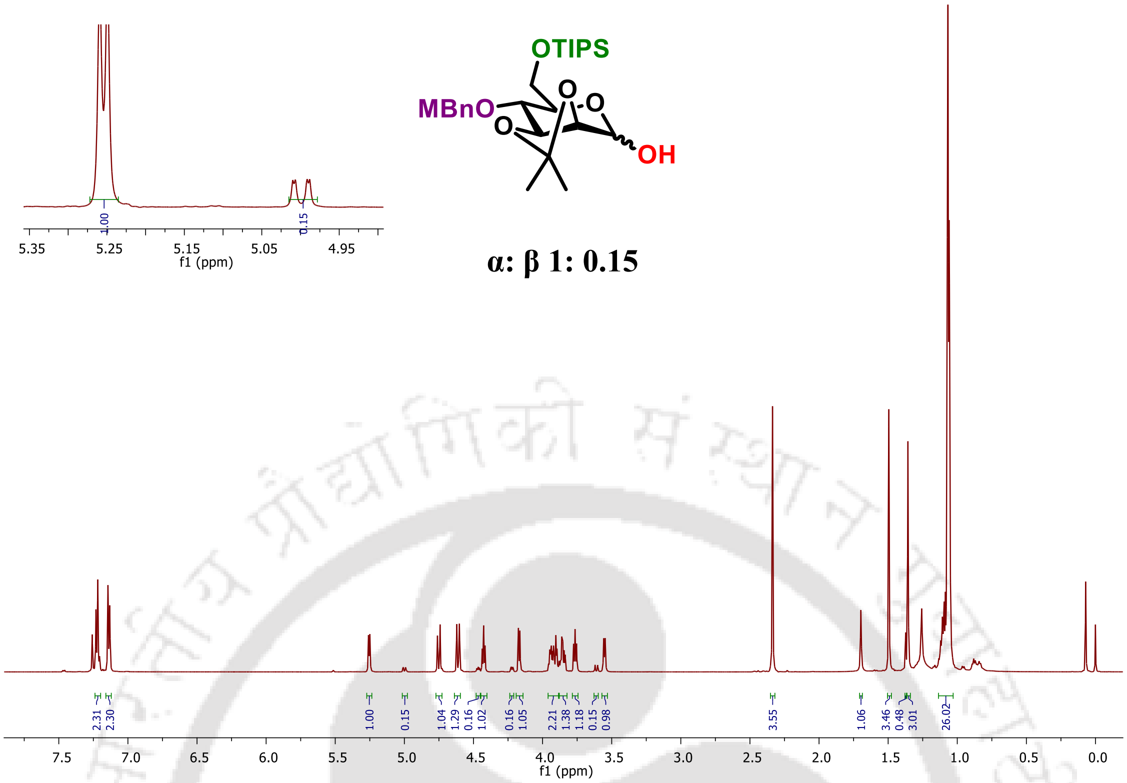
^{1}H NMR of compound **15a** (CDCl$_3$, 600 MHz)



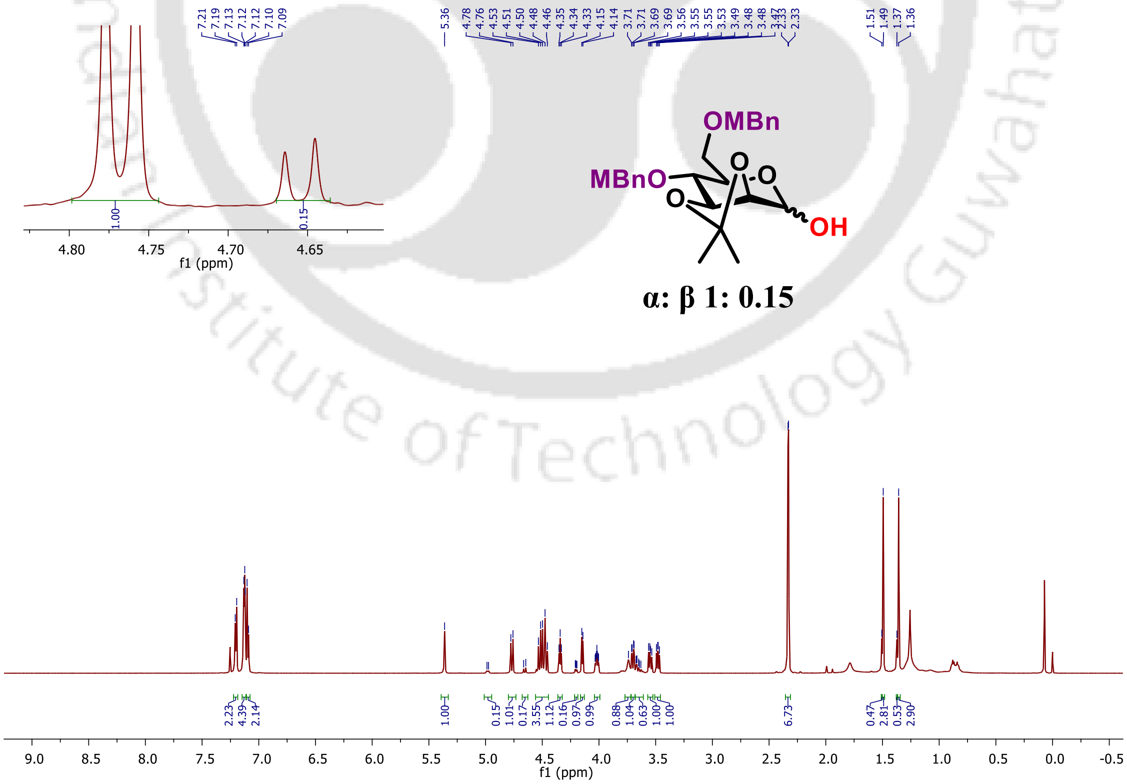
COSY NMR of compound **8a** (CDCl$_3$, 600 MHz)



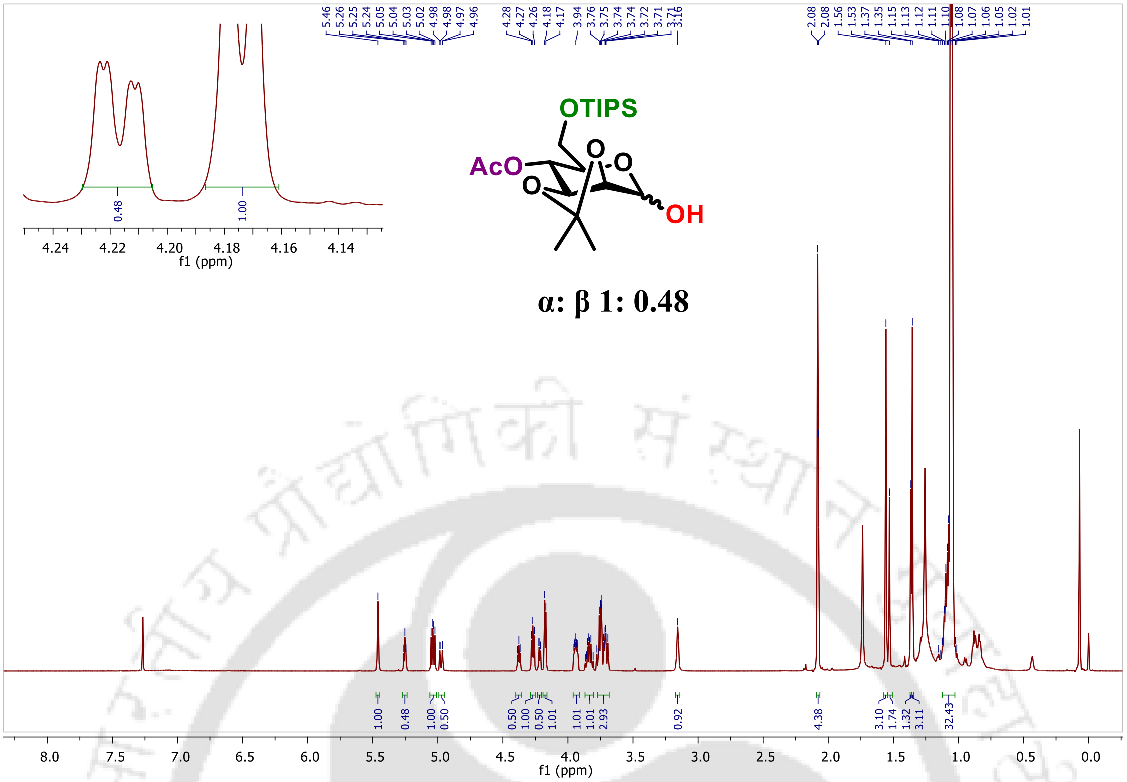
^{13}C NMR of compound **8a** (CDCl3, 151 MHz)



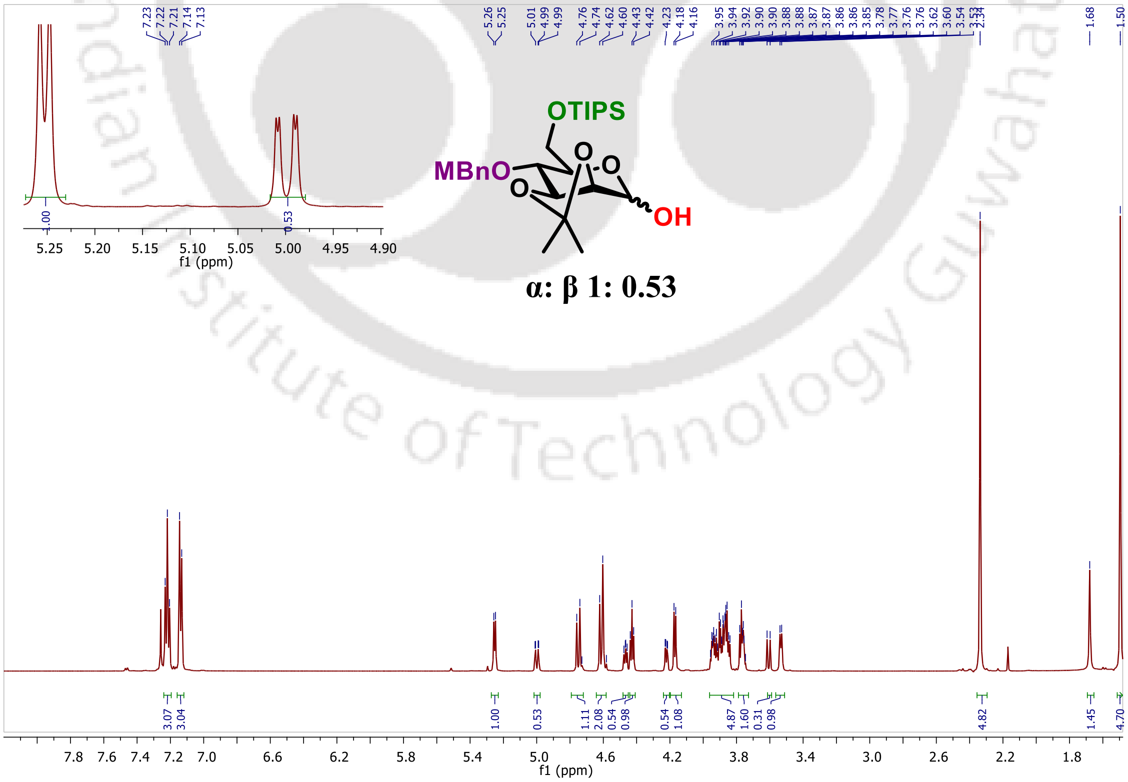
^{1}H NMR of compound **8b** (CDCl$_3$, 600 MHz)



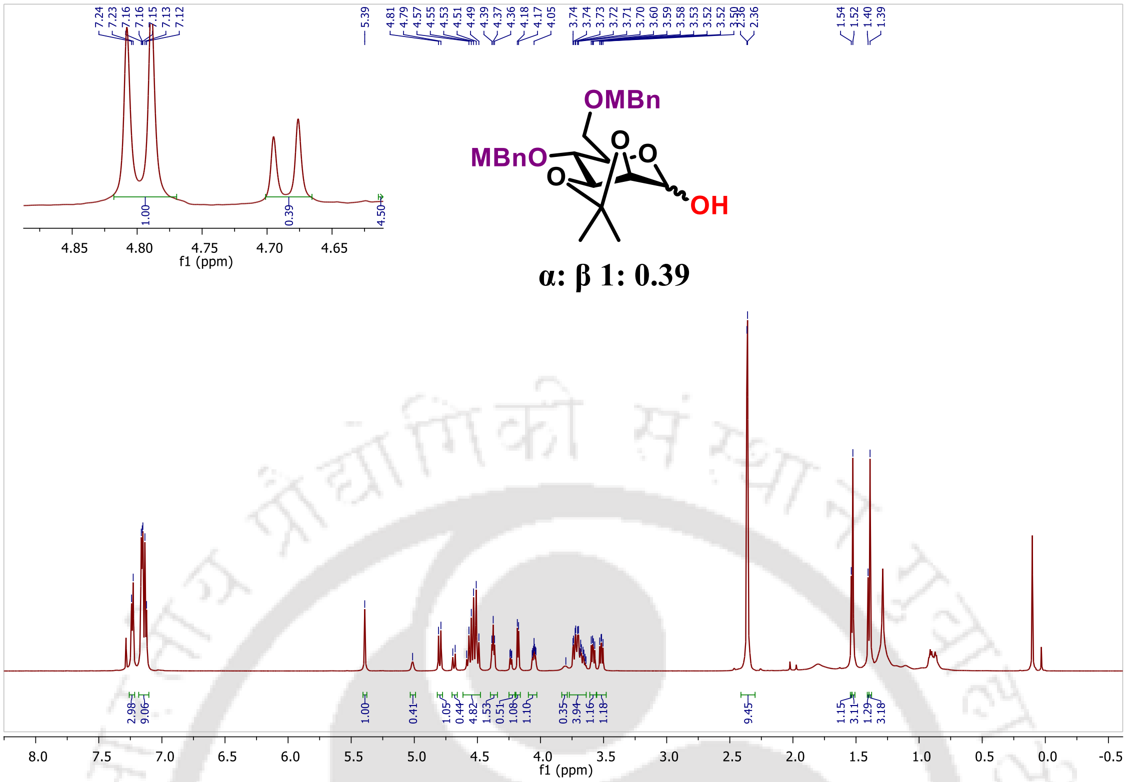
^{1}H NMR of compound **8c** (CDCl$_3$, 600 MHz)



^{1}H NMR of compound **15a** ($CDCl_3$, 600 MHz) (after anomeric equilibrium experiment)



^{1}H NMR of compound **15b** ($CDCl_3$, 600 MHz) (after anomeric equilibrium experiment)

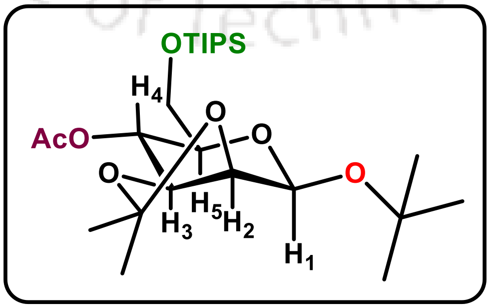


^{1}H NMR of compound **15c** (CDCl$_3$, 600 MHz) (after anomeric equilibrium experiment)

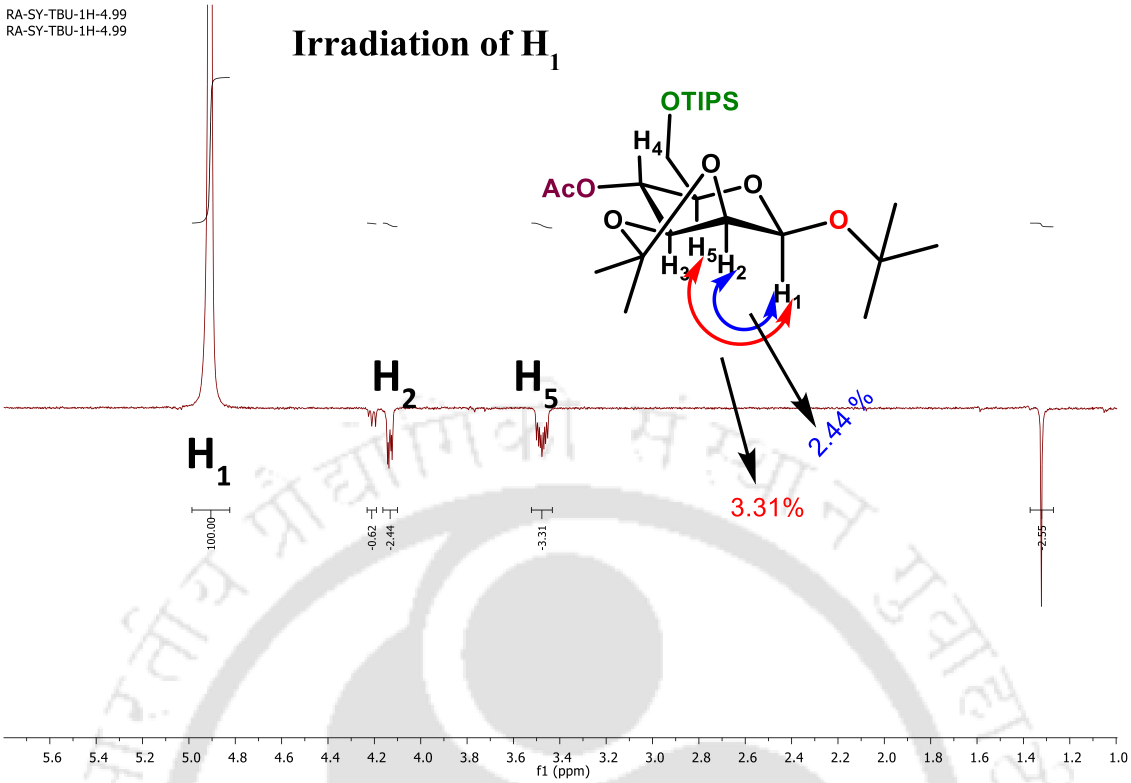
5.12 nOe Experiments: Stereochemistry assignment

Irradiation of H_1 of compound 14d:

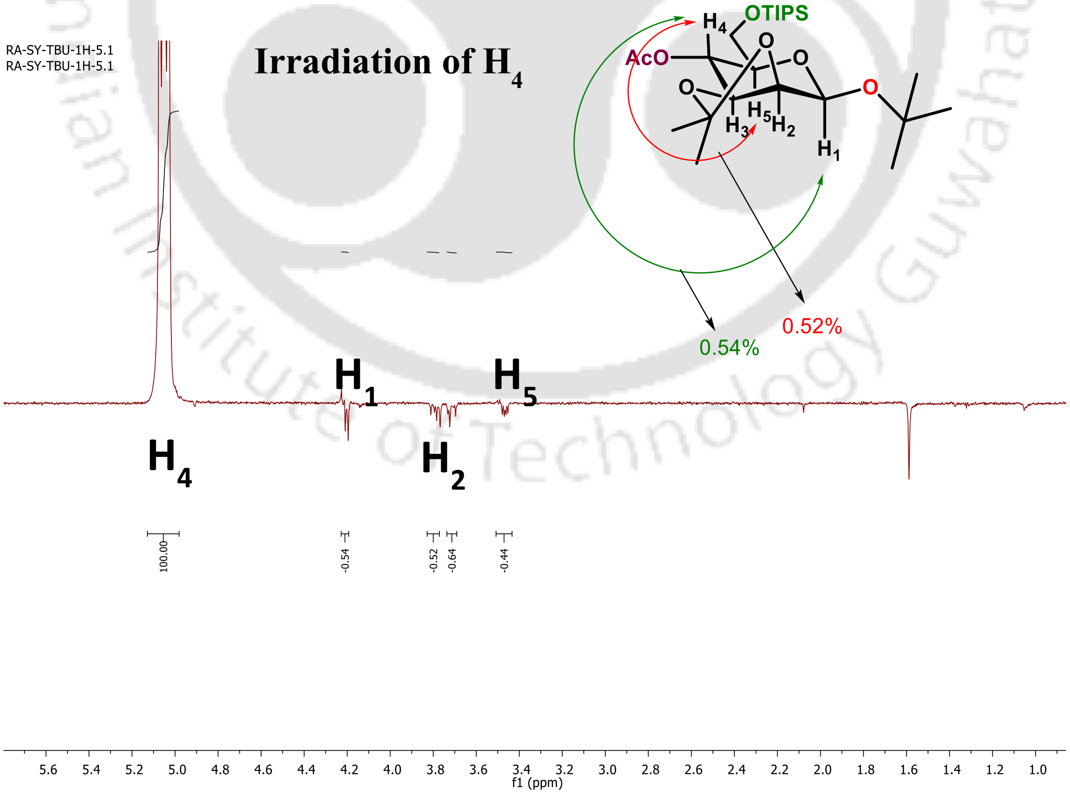
Based on COSY and HSQC and other NMR data, it was understood that the anomeric proton $\mathbf{H_1}$ of **14d** appears at **4.9 ppm**. After irradiation of $\mathbf{H_1}$, there was considerable enhancement of $\mathbf{H_2}$ (at 4.12 ppm) and $\mathbf{H_5}$ (at 3.46 ppm) protons by 2.44 % and 3.31% respectively. Thus, it is clear that anomeric proton H_1 is *cis* to both H_2 and H_5. Upon irradiation of $\mathbf{H_4}$ (5.04 ppm), there is less enhancement of $\mathbf{H_1}$ (at 4.9 ppm) and $\mathbf{H_2}$ (at 4.12 ppm) proton by 0.54 % and 0.52% respectively. Thus, it is clear that anomeric proton H_1 is *trans* to $\mathbf{H_4}$.



Based on the observations made from both the nOe experiments performed, it is understood that the product that is formed from our glycosylation method from the donor **12a** is a β-anomer.



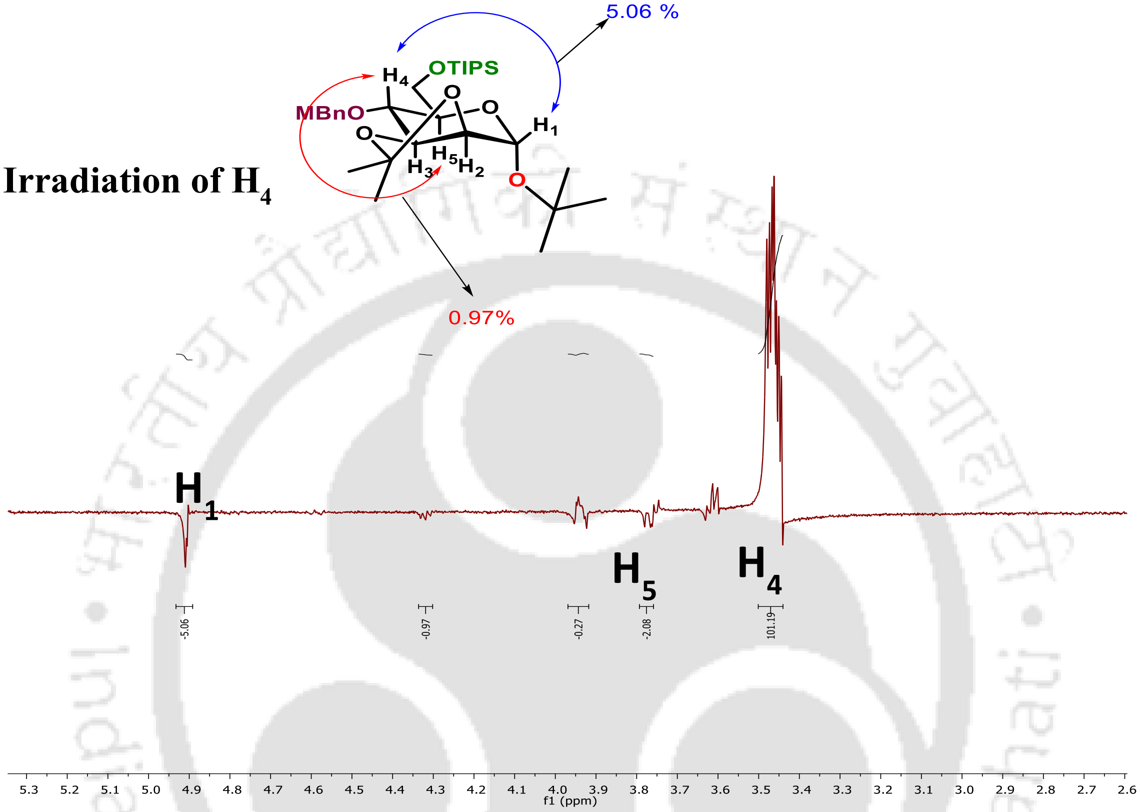
nOe of **14** (**H₁** irradiation), $CDCl_3$ 500 MHz



nOe of **14d** (**H₄** irradiation), $CDCl_3$ 500 MHz

nOe of Compound 14e

In the case of **15**, when **H$_4$** was irradiated only **H$_1$** peak got enhanced by 5.06% while no other protons had similar enhancement. This further supports that anomeric proton **H$_1$** is in cis relation with **H$_4$**, hence it is expected to be α-anomer.



nOe of **14e** (**H$_4$** irradiation), $CDCl_3$ 500 MHz