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Ferrocenium Salt Aided Substitution Reactions and Synthesis of Glycosylated Curcumin Derivatives

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By

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ABSTRACT

FERROCENIUM SALT AIDED SUBSTITUTION REACTIONS AND SYNTHESIS OF GLYCOSYLATED CURCUMIN DERIVATIVES

The employment of transition metal complexes in organic synthesis has advanced significantly. The discovery of transition metal catalyst is provided the synthetic community with powerful tools for accelerating reactions, making them more selective and efficient. Many chemical reactions do not happen without a catalyst system. High yields and selectivity can be attained by reactions that are catalyzed by transition metals. Significant developments regarding issues of sustainability and greenness were achieved through employment of catalysts. Catalysts can accelerate reactions and lower reaction temperature, thereby saving time and energy.

Iron-based catalysts have several advantages in chemical industries. Iron is cheap, environmentally friendly, non-toxic, and abundant in nature. Reactions with iron-based catalysts can potentially be performed at lower temperatures, with applications in the pharmaceutical industries and research sectors. Among other, ferrocene has been employed as a catalyst. The sandwich structure of ferrocenes allows substituents to be introduced on the cyclopentadienyl rings, which allows for catalyst tuning.

Our group previously found that ferrocenium cations with a 3+ oxidation state of iron catalyzed propargylic substitution reactions at low temperatures. Ferrocenium salts with a 3+ oxidation state is the oxidized version of ferrocene. Ferrocenium cations are mild- Lewis acids and can act as one-electron oxidants. Ferrocenium catalysts were successfully employed in Friedel-Crafts alkylation, nucleophilic substitution,

allylation, and oxidation reactions. Ferrocenium-based catalysts are well soluble in most organic solvents like CH_2Cl_2, CH_3OH and CH_3CN.

The first aim of the research aim was to investigate ferrocenium cations as catalysts to perform etherification reaction with propargylic alcohols. Propargylic alcohols are often utilized as starting materials in organic synthesis, they feature a hydroxyl unit and terminal alkyne connected to the same carbon. Direct substitution of a hydroxyl unit with an alcohol nucleophile will afford a propargylic ether product, which feature a tetrasubstituted carbon center. We synthesized three different propargylic alcohols for this study. We decided to place cyclopropyl and cyclo-butyl ring substituents on phenyl substituted propargylic alcohols and later we substituted the phenyl ring with thiophenyl unit. These modifications were made to obtain better understand the reaction mechanism and to study how changing groups can impact the reaction time. Commercially available ferrocenium hexafluorophosphate and freshly synthesized ferrocenium boronic acid hexafluoro antimonate were utilized as catalysts in this study to perform etherification reactions with propargylic alcohols and various nucleophiles (mainly primary and secondary alcohols). We found out that the ferrocenium salts were catalytically active and that the reaction proceeds through an ionic mechanism.

Carbohydrates are important biomolecules playing pivotal roles in many cellular processes. Even though these natural compounds are found in nature, it can be difficult to obtain them in adequate amounts or in the pure form. Innovative techniques were applied to synthesize these therapeutically active carbohydrates. These biologically active compounds are often used in vaccines and pharmaceuticals. Glycosylation is a key step to chemically synthesize oligo- and polysaccharides.

In the second aim of the research, ferrocenium salts were utilized to obtain a glycosidic bond between a glycosyl donor with a good leaving group and glycosyl acceptor with a free hydroxyl unit. Glycosyl donors with different leaving groups including glycosyl halides, *n*-pentenyl, thioethyl and trichloroacetimidate were investigated. We discovered that glycosyl halides, particularly glycosyl chlorides and fluorides performed well as glycosyl donors. Ferrocenium boronic acid hexafluoroantimonate and ferrocenium tetrafluoroborate were employed as promoters to perform glycosylation reactions.

Sepsis, an infectious disorder, can result in multiple organ dysfunction. It can lead to septic shock. Advanced therapeutic strategies are required to target sepsis. Some natural compounds like curcumin are known to treat inflammation. Curcumin, a natural compound found primarily in the spice turmeric, is a traditional medicine herb. Curcumin has been widely studied for its anti-inflammatory, antifungal, and antimalarial properties. However, its therapeutic value is limited due to its poor water solubility and bioavailability. To increase the solubility and bioavailability of curcumin, we modified the structure by introducing substituents on to the central methylene carbon and also attached sugar units on to the phenolic groups of the aromatic rings where we attempted to employ ferrocenium catalyzed glycosylation reactions described above.

In the final research aim, several glycosylated curcumin derivatives along with structural modifications at the core were synthesized to make them well water-soluble and chemically more stable. The glycosylated curcumin derivatives showed increased solubility and stability; their physiological activity is currently under investigation in other research groups in the chemistry department.

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LIST OF ABBREVATIONS

Å .....Ångström

Ac .....Acetyl

Ac_2O.....Acetic anhydride

AcCl …… Acetyl chloride

AcOH .....Acetic acid

$AcFcSbF_6$…….…… Acetyl ferrocenium hexa fluoroantimonate

$AgBF_4$…….……..……Silver tetraborofluorate

$AgClO_4$….....Silver perchlorate

$AgNTf_2$……. Silver bis(trifluoromethane sulfonimide)

Ag_2O .....Silver(I) oxide

AgOTf .....Silver(I) trifluoromethanesulfonate

$AgSbF_6$……..…..Silver hexafluoroantimonate

$BF_3{\cdot}Et_2O$ .....Boron trifluoride etherate

BHT……..……..……2,6-di-tert-butyl-4-methylphenol

$BH_3{\cdot}THF$.....Borane tetrahydrofuran complex

Bn .....Benzyl

BnBr .....Benzyl bromide

$BiCl_3$……..…….……..Bismuth (III) chloride

BuLi.....Butyl lithium

Bu_3SnH .....Tributyltin (IV) hydride

Bu_2SnO .....Dibutyltin (IV) oxide

Bz .....Benzoyl

BzCl.....Benzoyl chloride

CaH_2 .....Calcium hydride

$CDCl_3$ .....Deuterated chloroform

CD_3OD.....Deuterated methanol

$CHCl_3$ .....Chloroform

CH_2Cl_2…….....Dichloromethane

CH_3COCH_3 .....Acetone

$ClCH_2CH_2Cl$ 1,2-Dichloroethane

$ClPO(OPh)_2$……..…….Chloro-diphenyl phosphonate

$CO_2(CO)_8$….……Dicobalt octacarbonyl

$(COCl)_2$…….……Oxalyl chloride

$(CO(OCCl_3)_2)$…….……Tri-phosgene

$[CoCp_2]PF_6$……. Cobaltocenium hexafluorophosphate

d .....Doublet

dd .....Doublet of doublets

DIPEA…….....*N*, *N*-Diisopropylethylamine

DMAP 4-Dimethylaminopyridine

DMF .....*N, N*-Dimethylformamide

Et .....Ethyl

Et_2O .....Diethyl ether

EtOAc..... Ethyl acetate

EtOH..... Ethanol

$FeCl_3$ .....Iron (III) chloride

$FcBF_4$……. Ferrocenium tetra fluoroborate

$[FcB(OH)_2]SbF_6$……..Ferrocenium boronic acid hexa fluoroantimonate

$Fe(CF_3SO_3)_2$……..Iron (II) trifluoromethanesulfonate

$[FeCp(CO)_2]OTf$……Cyclopentadienyliron dicarbonyl dimer

$Fe(NO_3)_3$…….Iron (III) nitrate

$FePF_6$…….Ferrocenium hexafluorophosphate

$FeSO_4$…….…….Iron (II) sulfate

h..... Hour(s)

HBF_4……Tetra-fluoro boric acid

HCl .....Hydrogen chloride

$HClO_4$……. Perchloric acid

H_2O.....Water

$HNTf_2$…….…… Triflimide

HR MS .....High Resolution mass spectrometry

$HAuCl_4$…….…….…….Chloroauric acid

Hz .....Hertz

$InCl_3$……... Indium (III) chloride

k .....Kilo

K_2CO_3.....Potassium carbonate

M .....Molar

m ..... Multiplet

Me ..... Methyl

MeCN ..... Acetonitrile

MeOH..... Methanol

min ..... Minute(s)

MS..... Molecular sieves

MW .....Molecular weight

m/z ..... Mass to charge ratio

Na .....Sodium

NaH.....Sodium hydride

$NaHCO_3$ .....Sodium bicarbonate

NaOH.....Sodium hydroxide

NaOMe ..... Sodium methoxide

$Na_2S_2O_3$ .....Sodum thiosulfate

n-BuLi……*n*-butyllithium

NBS..... *N*-Bromosuccinimide

NMR ..... Nuclear magnetic resonance

Ph..... Phenyl

ppm ..... Parts per million

Py .....Pyridine

Rf..... Retention factor

rt ..... Room temperature

s ..... Singlet

SEt ..... Ethylthio

$SnCl_2$ ..... Tin (II) chloride

$SnCl_4$ ..... Tin (IV) chloride

$SOCl_2$ ..... Thionyl Chloride

t ..... Triplet

TBAB ..... Tetra butyl ammonium bromide

TEMPO……(2,2,6,6-tetramethylpiperidine-1-yl)oxyl

TfOH ..... Trifluoromethanesulfonic (triflic) acid

THF .....Tetrahydrofuran

$TiCl_4$.....Titanium (IV) Chloride

TLC ..... Thin layer chromatography

TMS……Trimethyl silyl

TMSOTf.....Trimethylsilyl trifluoromethanesulfonate

$Yb(OTf)_3$……..……Ytterbium triflate

Table of Contents

LIST OF SCHEMES

Chapter 1

Chapter 2

Chapter 3

Chapter 4

LIST OF TABLES

Chapter 2

Chapter 3

Chapter 4

LIST OF FIGURES

Chapter 2

Chapter 4

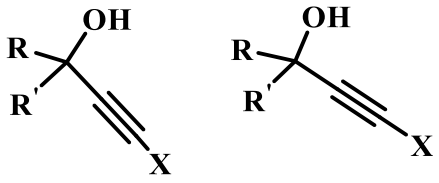
CHAPTER 1

1.1. Introduction

1.1.1 Overview of propargylic alcohols

Propargylic alcohols are readily accessible and act as a valuable starting material in organic synthesis.[1] Often, they are applied as intermediates in the synthesis of natural products.[3,5] Propargylic moieties engage in a great variety of reactions including substitution, addition, and cyclization reactions. They can either rearrange into a conjugated carbonyl group or transform into allenes.[2] Consequently, propargylic alcohols are employed as important building blocks in the complicated synthetic routes of natural products and in modern synthesis of organic compounds.[3]

Propargylic alcohols can be easily synthesized from ketones and terminal alkynes. They feature an alkyne and a hydroxyl group, which are connected to the same carbon.[4] There are two types of propargylic alcohols, one with a terminal and another with an internal alkyne unit (Scheme 1.1). This research mainly examines propargylic alcohols with a terminal alkyne unit.



X = H, TMS, R, Ar
R & R' = Ph, Me

Scheme 1.1 Internal and terminal alkyne propargylic alcohols

Characteristics of terminal alkynes are that they undergo cross-coupling reactions and that can be involved in cycloaddition reactions. The fairly acidic hydrogen atom of the alkyne expands the scope of propargylic subunits, and consequently they are utilized in the synthesis of natural products.[5]

Direct substitution of the hydroxyl group with nucleophiles will result in quaternary carbon centers which gives access to the sophisticated synthesis of fine chemicals and natural products. Bioactive alkyne units consisting of a propargylic functionality were reported in the literature for several compounds such as efavirenz, siphonodiol and dynemicin-A.[5]

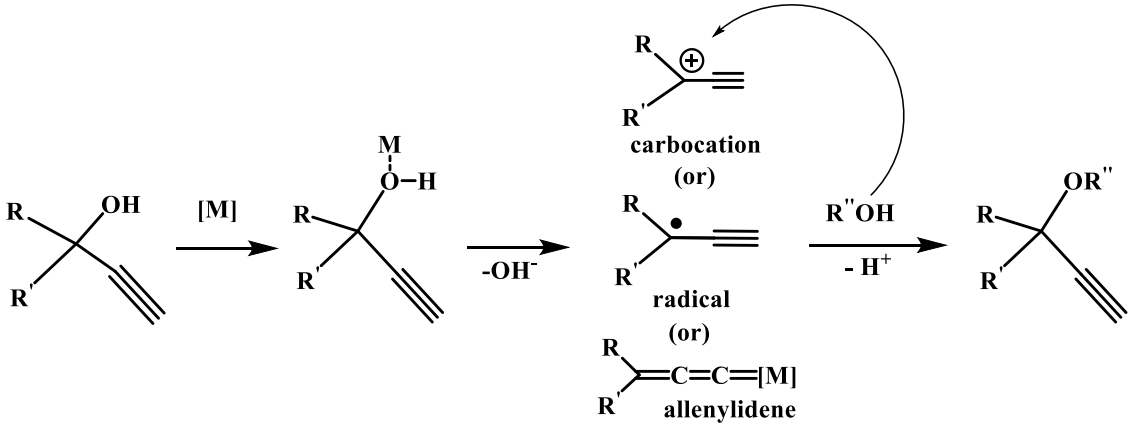
Allylic substitution reactions are well studied but transition metal catalyzed substitution reactions of propargylic alcohols are not well developed.[5b] The complex nature of propargylic alcohols promotes Rupe and Meyer-Schuster rearrangements which lead to potentially yield diminishing side products such as aldehydes, ketones, or allenes.[6,7] These reactions are often observed in acidic medium utilizing strong acids. Although many transition metal complex systems were developed as catalyst or promoter, they often require high temperatures.[90]

The most fundamental propargylic substitution reactions were developed by Lockwood and Nicholas in 1972 utilizing an organocobalt complex as a catalyst to obtain propargylic substitution products.[8, 9] Stoichiometric amounts of the cobalt complex $CO_2(CO)_8$ were employed to stabilize cation intermediates. This system constitutes in a multistep process, and due to the toxic nature of $CO_2(CO)_8$, it did not gain much popularity. Therefore, the reactivity of various Lewis acids (such as $TiCl_4$ or TMSOTf, BF_3Et_2O, and $SnCl_4$) and Brønsted acids were tested to perform propargylic substitution reactions. Due to the limited applicability, they are currently not widely used.[10]

Since then, several transition metals were tested as catalysts in the reaction including copper,[11] nickel,[12] titanium,[13] silver,[14] ruthenium,[15] rhodium,[16] iridium,[17] iron,[18] and bismuth[19] for the direct activation of propargylic alcohols. Some of these catalyst systems are toxic and required additives and high temperatures. In 2006, Zahn and his

co-workers developed a catalyst system with $FeCl_3$ and $InCl_3$ for the activation of terminal and internal propargylic alcohols.[18] This system did not require high temperature or additives.

According to the literature, these substitution replacement reactions proceed via the formation of a carbocation[20], allenylidene[21], or radical[22] as an intermediate in the presence of the metal catalyst. The coordination of a metal with the oxygen from the hydroxyl unit (OH) detaches the hydroxide unit (OH^-) from the propargylic alcohol and forms a carbocation as an intermediate. Then a nucleophilic attack takes place to give the substituted ether product. This would constitute a S_N1 type ionic mechanism.[23]

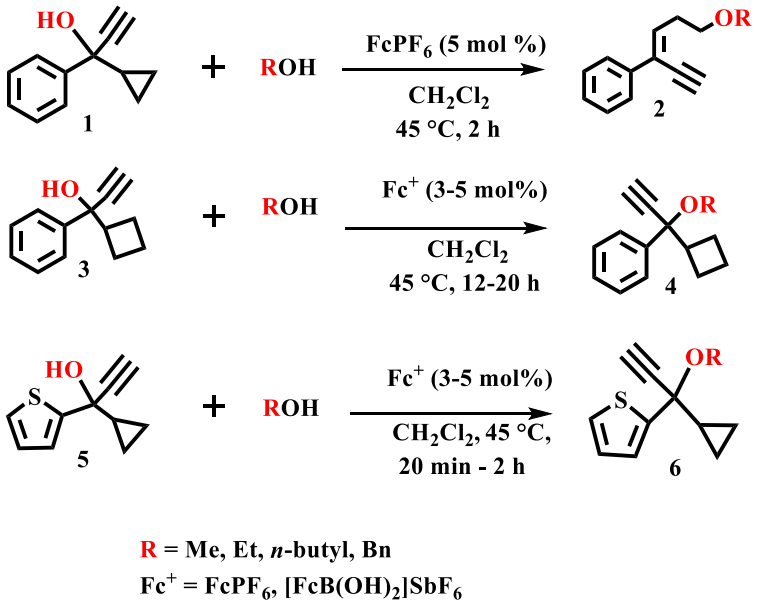


Scheme 1.2 Possible intermediates in the etherification reaction

Previously in our lab, we proved the efficacy of ferrocenium hexafluoro phosphate (which will be abbreviated as $FcPF_6$) as a catalyst for performing etherification reactions at 45 °C.[24] The propargylic unit substituents R, R′ (Scheme 1.2) consist of either an aliphatic methyl side chain or aromatic rings. Unfortunately, these reactions took much longer, about 8 hours to 3 days to go to completion.

This research aimed to investigate etherification reactions with different cyclic substituents on the propargylic alcohols to accelerate the reaction. Simultaneously, we

were developing more reactive ferrocenium based catalyst system to obtain higher yields without any side products or rearrangements. We made sure that one of the propargylic alcohol substituents was an aromatic ring while the other was a closed ring (cyclo-propyl and cyclo-butyl).[25, 26]

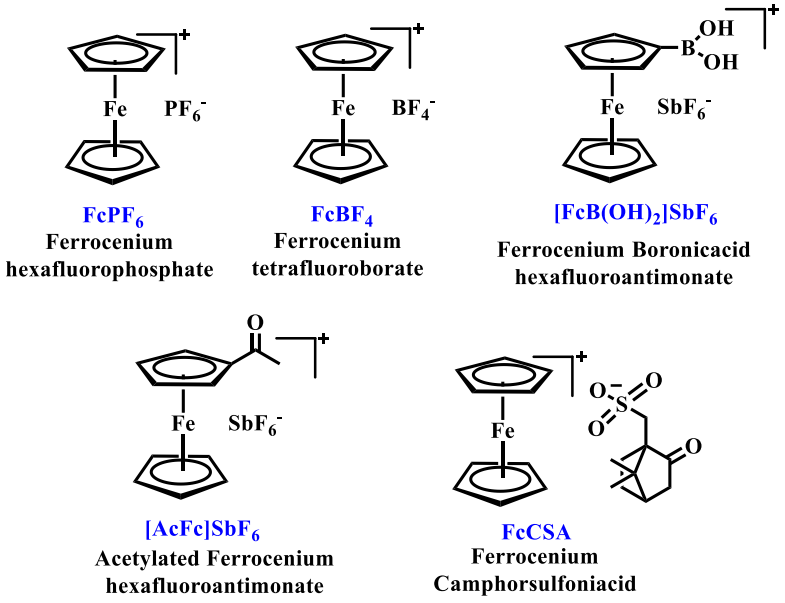


R = Me, Et, *n*-butyl, Bn
Fc^+ = $FcPF_6$, $[FcB(OH)_2]SbF_6$

Scheme 1.3 Etherification reaction of different propargylic alcohols with ferrocenium salts

When an etherification reaction was performed in between phenyl cyclopropyl propargylic alcohol **1** and *n*-butanol, it provided ene-yne product ether product **2** in 2 hours (Scheme 1.3). We synthesized a propargylic alcohol with cyclo-butyl unit, to investigate whether cyclic substituents can accelerate the substitution reaction. Etherification reaction between cyclo-butyl propargylic alcohol **3** and *n*-butanol resulted in the phenyl cyclo-butyl ether product **4** after 12 h (Scheme 1.3). Then we tested electron rich thienyl cyclopropyl propargylic alcohol **5** with *n*-butanol as nucleophile which provided the thienyl ether product **6** in 20 minutes reaction time (Scheme 1.3). We employed two different catalyst systems ($FcPF_6$ and

[$FcB(OH)_2SbF_6$) for this study (Scheme 1.4). Several reactions were performed to investigate the mechanism and the result of this study are explained in Chapter 2.



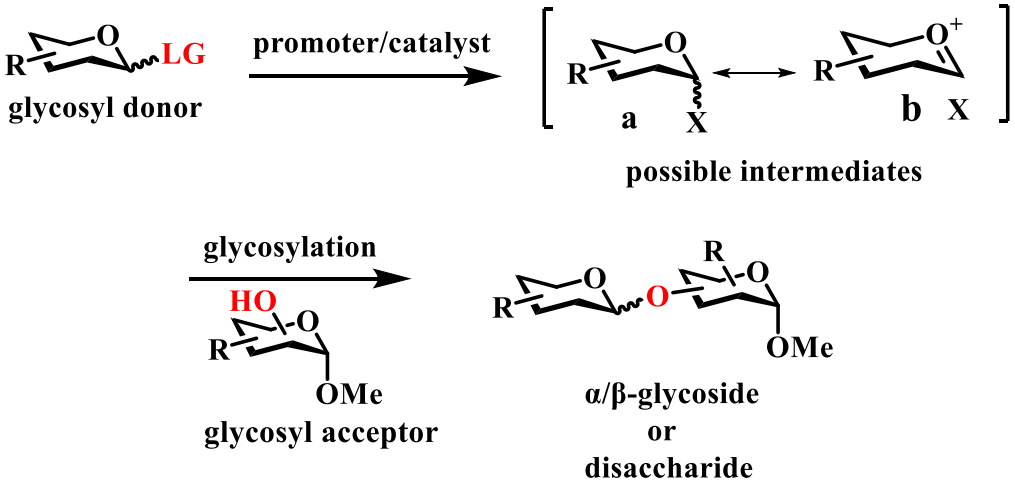
Scheme 1.4 Structures of Ferrocenium salts (Fc^+) that were tested in performing etherification reactions

1.2 Introduction of carbohydrates

In recent years, chemically synthesized carbohydrates have been employed in the development of medicines,[27] vaccines,[28] and antibiotics.[29] Even though they are available in nature, obtaining the pure form of oligosaccharides in sufficient amounts is a challenge. Innovative strategies were applied for the synthesis of oligosaccharides. These complex structures play essential roles in biological processes, including interactions with receptors/cells, molecular and immunological recognition.[30] Applications and functions of carbohydrates gained a lot of attention from medicinal, biological and glyco-chemists. The necessity of bio-active carbohydrates prompted in finding various ways to synthesize them.

1.2.1 Glycosylation Reaction

In a traditional glycosylation reaction, a glycosyl donor which bears a leaving group gets activated in the presence of a catalyst/promoter and forms an oxacarbenium ion as an intermediate (which is resonance-stabilized). Then the nucleophilic attack takes place, and here the nucleophiles bear a free hydroxyl group, resulting in the formation of a disaccharide.[31] The attack of the nucleophile can happen from either the top or from the bottom to provide α/β-Glycoside. Sometimes the nucleophiles attack promoters when they are connected with the leaving group. This complex nature of glycosylation reaction mechanism illustrates that they can involve in both S_N1 and S_N2 substitution reactions.[32]



Scheme 1.5 Glycosylation reaction mechanism

New approaches to obtain a glycosidic bond with good stereoselectivity remains challenging. Protecting groups were introduced to control the selectivity of a glycosidic bond.[33] Most of the current achievements relied on Lewis acid or Brønsted acid promoters applied in stoichiometric amounts.[34] The reaction conditions like temperature, promoter or a catalyst system, time and steric hindrance can affect the selectivity.[35] In this aspect, the leaving group on the glycosyl donor plays an important

role. As a result, numerous chemical glycosylation methodologies were developed by employing halides,[36] phosphates,[37] *n*-pentenyl glycans,[38] sulfoxides,[39] propargyl glycosides[40] and thiol-Glycosides[41] as donors.

1.2.2 Overview of Glycosyl halides

Glycosyl halides, mainly bromides and chlorides, remain prominent glycosyl donors from the 18th century. In 1879, Michael performed glycosylation reactions utilizing glycosyl chlorides as donors.[42] Mukaiyama and his co-workers introduced glycosyl fluorides as donors for the first time in 1981.[43] A Lewis acid, such as $SnCl_2$, was used to activate the fluoride donor, and silver salts were added as additives to improve the activation protocol.[44] Glycosyl fluorides have higher thermal and chemical stability when compared to glycosyl bromides, iodides, and chlorides.[45]

1.2.2a Synthesis and activation of glycosyl fluoride

Glycosyl halides are obtained by replacing a free hydroxyl group (at the anomeric carbon) by a halogen. The synthesis of glycosyl fluorides from hemiacetals can be accomplished in many ways by employing different fluorinating agents such as tetra-n-butylammonium fluoride,[46] sulfur (VI) hexafluoride,[47] diethylamino sulfur trifluoride (DAST)[48] and *N, N*-diethyl-α, α-difluoro(m-methylbenzyl) amine (DFMBA)[49].

Many different activating promoter systems including tin-,[50] silicon-,[51] boron-,[52] aluminum-,[50] gallium-,[53] magnesium-,[50] lithium,[54] calcium-,[55] titanium-,[56] zirconium-,[57] or copper-based[58] reagents and salts were employed in combination with the additives such as silver perchlorate, potassium carbonate and boron trifluoride etherate to activate the glycosyl fluoride donors. Protic acids and anhydrides such as triflic anhydrides,[59] trifluoromethanesulfonic acid (TfOH),[60] perchloric acid ($HClO_4$),[61]

triflimide[60] ($HNTf_2$) were introduced to activate the fluoride donors at lower temperatures.

In synthetic carbohydrate chemistry, halides act as intermediates for synthesizing natural glycosides such as anthocyanins,[62] saponins,[63] hydroxyanthraquinone[62]. Fluoride as a glycosyl donor was employed in the total synthesis of cyclodextrin,[64] tumor-associated Le^x family of sialyl dimeric[65] and glycosphingolipids[66].

1.2.2b Synthesis and activation of glycosyl chloride

In 1870 Colley synthesized glycosyl chloride by utilizing acetyl chloride (AcCl).[67] Subsequently, more efficient methods have been developed for the synthesis of glycosyl chlorides from hemiacetals by employing chlorinating reagents such as thionyl chloride[68] ($SOCl_2$), chloroenamine,[69] oxalyl chloride ($(COCl)_2$),[70] tri-phosgene ($OC(OCCl_3)_2$),[71] triphenyl phosphine with hexachloroacetone[72] and *n*-butyllithium (*n*-BuLi) with chloro-diphenyl phosphonate ($ClPO(OPh)_2$).[73]

The versatility nature of transition metals attracted carbohydrate chemists to employ them as catalysts for performing the glycosylation reaction with glycosyl chloride donor. Silver,[74] mercury,[75] cadmium,[76] and tin salts[77] were employed as promoters. Due to the toxicity nature of these promoter systems, they were not widely used. Later in the 20th century, silver oxides with a triflic acid combination were used in high loads, which drastically increased the reaction rate and resulted in high yields.[78] Organocatalysts using thioureas were employed as catalysts resulted in poor selectivity and long reaction time (24 h).[79] Recently non-toxic iron (III) chloride was introduced to perform glycosylation reactions which resulted in moderate to good yields.[80] Aside from being environmentally friendly, iron (III) compounds have many applications.[80] It can be used as a non-toxic metal catalyst in the pharmaceutical industry and medicinal

chemistry for manufacturing drugs.[81] Thus, a Lewis acid mediated catalyst system based on iron is preferred over previously described catalysts.

1.2.3 Glycosylation reactions with iron-based salts

Iron is less expensive than other metals, and abundant in nature.[82] A few iron salts such as iron (III) nitrate ($FeNO_3)_3$,[83] iron (II) trifluoromethanesulfonate[84] ($FeCF_3SO_3)_2$ and iron (II) sulfate[85] ($FeSO_4$) were utilized as catalysts for performing *O*-Glycosylation reactions. While many iron catalysts have been reported, most of them generate proton (which will be the driving force of reaction) and are less soluble in organic solvents.[86] This has led to develop milder approaches to perform glycosylation reactions. Ferrocenium based catalyst systems are easily obtained by oxidizing ferrocene with oxidizing agents such as $AgSbF_6$, $AgBF_4$, $AgNTf_2$, $FeCl_3$ and *p*-benzoquinone.[87] When oxidized, ferrocene with 2+ oxidation state converts to ferrocenium with a 3+ oxidation state. These salts are mild, Lewis acidic, and can act as a one-electron oxidants.[82,86] Due to these advantages, ferrocenium catalysts were successfully employed for performing Friedel-Crafts alkylation,[89] nucleophilic substitutions,[86] allylations,[90] and oxidation reactions[91]. The sandwich structure of ferrocene compound allows substituents to be introduced to tune the cyclopentadienyl rings.[92]

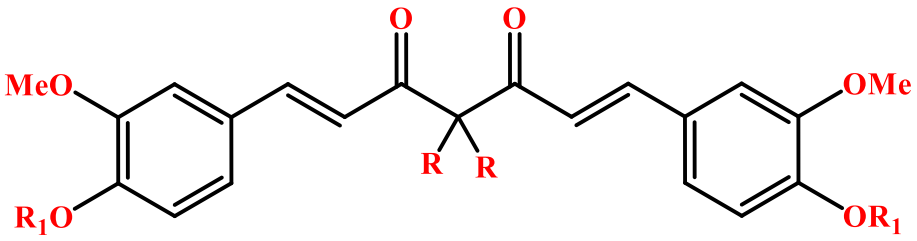
A major part of our research involves in developing more efficient ferrocenium based catalyst systems. Relying on our previous knowledge[86] and considering similarities between the etherification and glycosylation reactions, we chose to use ferrocenium based promoter system for carrying out glycosylation reactions.

Glycosyl donors with different leaving groups including halides (chloride, bromide and fluoride), thioethyl (SEt), *O*-pentynyl, and trifluoro acetimidate were screened. Glycosyl chloride and fluoride were found to be the good donors in combination with

glycosyl acceptors. For the first time, ferrocenium based catalysts ($FcPF_6$, $FcBF_4$, $AcFcSbF_6$, $[FcB(OH)_2]SbF_6$) were screened to promote the glycosylation reaction. When the glycosylation reactions were performed by employing $FcBF_4$, and $[FcB(OH)_2]SbF_6$, disaccharides were obtained in good yields. This approach is described in Chapter 3. We are trying to synthesize propargylic ethers and disaccharides with high yields and good stereoselectivity by employing ferrocenium based derivatives as catalysts or promoters.

1.3 Synthesis of Curcumin Derivatives

Sepsis an infectious disorder can lead to septic shock.[91] It is caused by excessive impairment of the host immune response.[92] Few natural compounds have anti-inflammatory and anti-malarial effects that can help in regulating inflammation.[93] Curcumin, a natural compound found in the spice turmeric is used as an herb and food coloring agent in southeast Asia.[94] Curcumin has a broad therapeutic window, but it is not widely used in pharma industry due to its poor water solubility and bioavailability.[95] When curcumin is taken orally or injected intravenously, 75% of it is excreted in the feces.[96] It indicates curcumin's rapid metabolism and poor absorption qualities.[97] Since the structure of curcumin is not chemically stable, we modified the structure by introducing methyl or benzyl groups on to the central methylene carbon. This alkylation helped to stop keto-enol tautomerism from happening.[98] To increase the chemical stability and water solubility of curcumin, we decided to synthesize curcumin glycosides. Usually, glycosides from the plants act as a secondary metabolite.[99] Glycosylation can reduce the toxicity of biosynthetic intermediates and xenobiotics, while increasing stability and solubility of the aglycones.[100]



R = CH_3, CH_2Ph
R_1 = glycosylation

Scheme 1.6 Structure of curcumin where modifications are done

From our previous knowledge on obtaining glycosidic bond between a glycosyl donor and a glycosyl acceptor by employing ferrocenium salts as promoters, we decided to a perform glycosylation reaction between alkylated curcumin and glycosyl bromides.[101] Structurally modified curcumin with two hydroxyl groups on the aromatic rings was utilized as a glycosyl acceptor and glycosyl bromides as donors (galactosyl and glucosyl bromide) were employed to obtain a glycosidic bond (Scheme 1.6). Unfortunately, these reactions did not proceed as expected. As a result, we decided to perform glycosylation reactions in the presence of a phase transfer catalyst.[102]

In the final Chapter 4 the experimental details of glycosylated curcumin derivatives, along with simple structural modifications were explained in detail. Newly synthesized curcumin derivatives showed increased solubility and stability. Their physiological activity is currently under investigation in other research groups in the chemistry department.

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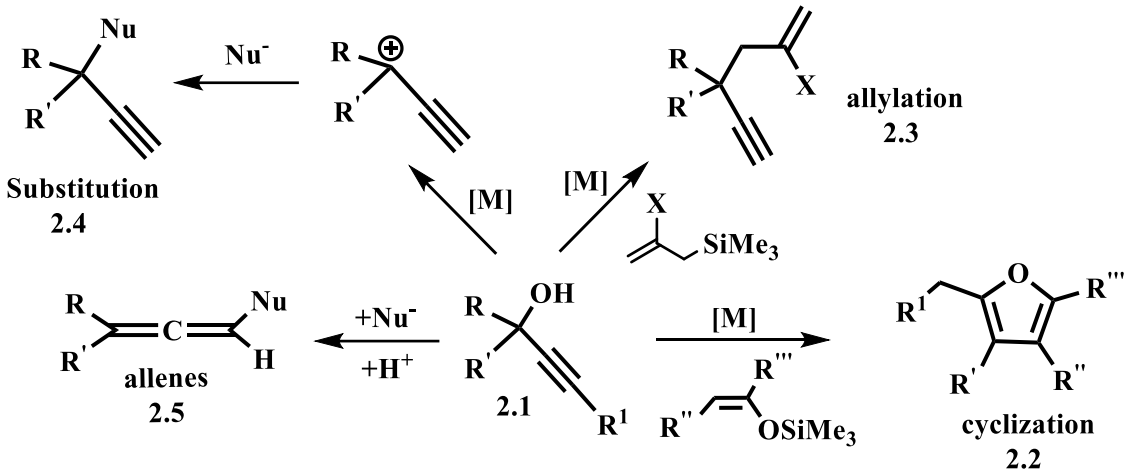
CHAPTER 2

Ferrocenium cations as catalysts for the etherification of cyclopropyl-substituted propargylic alcohols: ene-yne formation and mechanistic insights

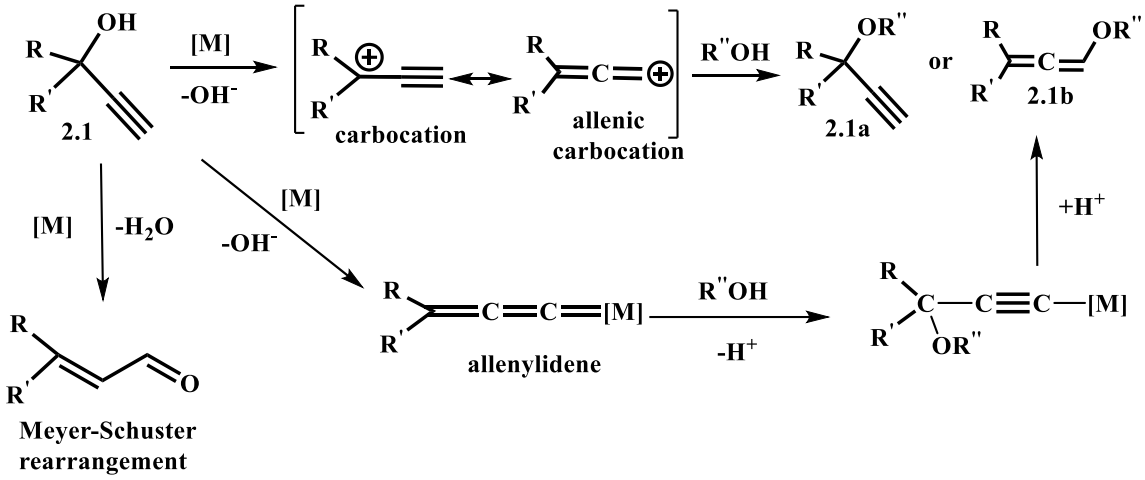
2.1 Introduction

Propargylic alcohols (**2.1** in Scheme 2.1) are compounds with a hydroxyl and alkyne group connected to the same carbon atom. They are easily accessible starting material for organic synthesis.[1] They can undergo several transformations through the hydroxyl group or the triple bond to form allenes **2.5**, allylation products **2.3**, addition or substitution products **2.4**, or cyclization products **2.2** as shown in Scheme **2.1**.[2, 3]



Scheme 2.1 Transformation of propargylic alcohols

Direct substitution or activation of the hydroxyl functionality by a nucleophile will afford a propargylic ether product **2.1** (Scheme 2.2), which feature a tetrasubstituted carbon center.[3] The increased structural complexity of the propargylic compounds attracts pharmaceutical companies to utilize them in the synthesis of fine chemicals.[4] The bi-functionality nature of propargylic alcohols leads to yield-diminishing rearrangements such as allene formation, ketone, or aldehyde formation (via Meyer-Schuster or Rupe rearrangement) as shown in the Scheme 2.2.[5, 6] A catalyst system must be employed to make the reaction work and to obtain the ether products.[7]

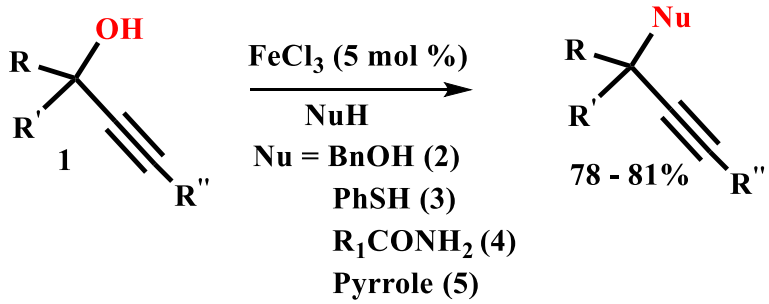


Scheme 2.2 Rearrangement of propargylic alcohols

Catalytic activation of propargylic alcohols by a nucleophile can result in achieving high yields.[10] A variety of Lewis acid, and Brønsted acid catalysts were used in propargylic etherification reactions, but they are less suitable for structurally complex molecules containing hydroxyl units. Simple catalyst systems lack selectivity and frequently result in rearrangements.[2] Transition metals can be a good alternative in this situation because of their ability to react with propargylic alcohols or activate them in a selective manner. Several transition metals have been reported to perform propargylic etherification reactions (which are substitution reaction)[7] such as bismuth,[8] copper,[9] gold,[10] palladium,[11] rhodium,[12] iridium,[13] and ruthenium[14]. Generally, high temperatures are required for catalytic activation. Highly reactive and tunable catalyst systems are scarce.[7] Only a few catalysts systems do not require high temperatures (such as $FeCl_3$, $InCl_3$ and $BiCl_3$)[7] or additives to perform etherification reactions.[15]

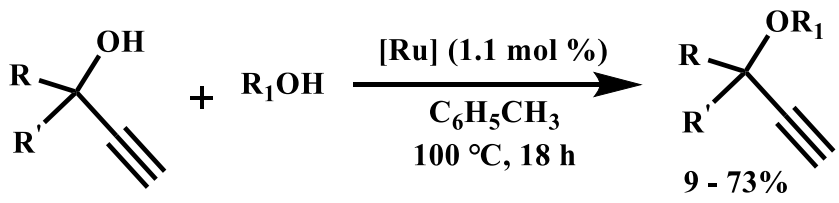
When transition metals such as gold, cobalt and ruthenium were used in the propargylic substitution reactions as catalysts, it had led to concerns that their traces might be found in final products, in which is especially problematic in pharmaceuticals and food additives.[10] In this aspect, iron catalysis has several advantages when compared with

other transition metals. Iron is environmentally friendly metal, non-toxic, inexpensive, and abundant.[2, 16] Zhan reported[7, 17] iron-catalysis utilizing $FeCl_3$ for internal propargylic alcohol **1** (Scheme 2.2a) with different carbon and heteroatom centered nucleophiles (**2-5**, Scheme 2.2a) for propargylic substitution reactions. Zanotti described[18] catalytic activity of $[Fe(Cp)(CO)_2]OTf$ (10 mol%) for propargylic alcohol **1** (Scheme 2.2a), which resulted in six different propargylic ethers ranging from 9 to 72% isolated yields. When compared to other metals, iron catalysis has poor selectivity and reactivity issues.[10]



Scheme 2.2a $FeCl_3$- catalyzed propargylic etherification reactions (from the literature)

As part of our research agenda on the activation of propargylic alcohols, we started screening for iron-based catalyst systems for the activation of propargylic alcohols. Catalytic activity of ferrocenium cations is not widely explored for etherification reactions.[19a] Previously in our lab, we disclosed the efficacy of commercially available ferrocenium hexafluoro phosphate (which will be subsequently abbreviated as $FcPF_6$) as a catalyst for performing etherification reactions at 40 °C with one or two aromatic substituents on the propargylic alcohols (Scheme 2.7).[19b] Interestingly, when compared to other catalyst systems like ruthenium allenylidene complex,[19c] $FcPF_6$ can perform the title reaction at lower temperatures (rt - 45 °C).



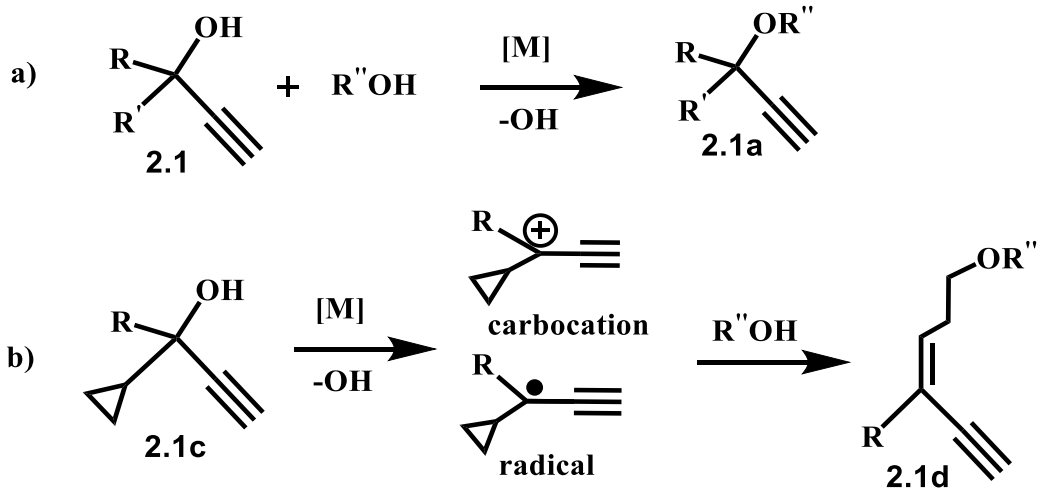
Scheme 2.2b [Ru]- catalyzed propargylic etherification reactions (from the literature)

Ferrocenium salts with, a 3+ oxidation state on Fe are the oxidized versions of ferrocene which exhibits a 2+ oxidation state. They can act as a one-electron oxidant and might enable radical reactions.[20]

2.2 Objectives

Propargylic substitution reactions may proceed via the formation of a radical intermediate in the presence of a metal as shown in the Scheme 2.3. To test the possibility of a radical mechanism, we decided to employ radical clock substrates while performing the substitution reactions. If the reaction proceeds via radicals, the radical clock rearranges to produce rearranged products, such as ene-ynes **2.1d** (Scheme 2.3b) which can be investigated spectroscopically.[21, 22]

We synthesized propargylic alcohols with different substituents to investigate a potential radical mechanism. First, we tested cyclopropyl substituted propargylic alcohol **2.1c** (Scheme 2.3b) in the presence of alcohols to investigate whether they result in ene-yne products **2.1d** (Scheme 2.3b).



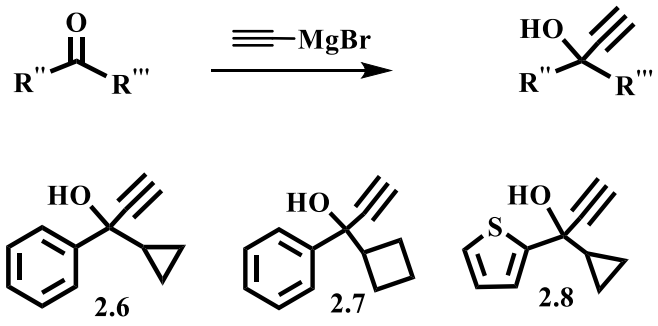
Scheme 2.3 a) General propargylic substitution reaction. b) Potential intermediates before ene-yne formation.

According to the literature, when different catalyst systems such as $HAuCl_4$,[23] $Yb(Otf)_3$,[24] TfOH,[25] and ruthenium salts were employed,[26] the title reaction proceeded via the formation of various intermediates (radical, carbocation and allenic-carbocation). The drawbacks of these catalyst systems are the usage of nucleophiles as solvents in large quantities,[23] the cost of the metal complexes is high, and they require high temperatures. Reported here, is an efficient ferrocenium catalyst system for etherification reactions of propargylic alcohols. In this wok, mechanistic investigations were performed to establish an ionic mechanism[27] which proceeded via the formation of a carbocation as an intermediate in the presence of $FcPF_6$ with one aromatic substituent and one closed ring substituent on the propargylic alcohols (**2.1c** in Scheme 2.3), which resulted in ene-yne ether products **2.1d**.

2.3 Results and Discussion

During the screening process, we tested a variety of propargylic alcohols to decrease the reaction time and to obtain insight into the mechanism. To examine whether cyclic

substituents, in general, can speed up the substitution reaction, we decided to place cyclopropyl and cyclo-butyl rings on the propargylic alcohols and substituted the phenyl ring with an electron-rich thiophenyl unit. As shown in Scheme 2.3, cyclopropyl rings would ring-open if a carbon-centered radical is formed during the reaction, allowing for the investigation of potential radical intermediates. According to the literature, phenyl cyclo-propyl propargylic alcohol **2.6** was synthesized easily from commercial phenyl cyclo-propyl ketone and the addition of ethynyl group was accomplished with ethynyl magnesium chloride (a Grignard reagent, Scheme 2.4).[28, 29] The same procedure was employed to synthesize phenyl cyclo-butyl **2.7** and thienyl cyclo-propyl **2.8** substituted propargylic alcohols as shown in the Scheme 2.4.

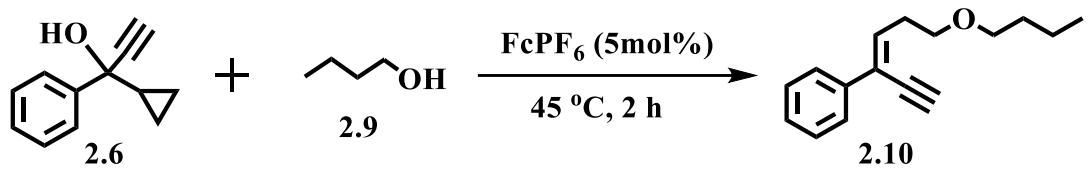


Scheme 2.4 Synthesis of propargylic alcohols

From our previous knowledge, we knew etherification reactions can be catalyzed in the presence of $FcPF_6$ at 40 °C in CH_2Cl_2 by utilizing primary and secondary alcohols as nucleophiles with phenyl cyclo-propyl propargylic alcohol.[19] For the test reaction (as shown in Scheme 2.5), we utilized 5 mol% of $FcPF_6$ and almost equimolar ratios of phenyl cyclo-propyl propargylic alcohol **2.6** and *n*-butanol **2.9** at 40 °C in CH_2Cl_2 resulted in cyclo-propyl ring opening to obtain ene-yne product **2.10** within 2 hours of reaction time. No additives were added, and no side products were observed. The title

reaction can also be performed in $ClCH_2CH_2Cl$ (entry 2, Table 2.1). Other solvents were also tested, such as THF, which resulted in 44% product conversion (entry 3, Table 2.1). In toluene, the reaction did not proceed at all because the catalyst $FcPF_6$ is not soluble in toluene (entry 4, Table 2.1). When *n*-butanol was employed as a solvent or as a nucleophile in excess, the conversion rate of product dropped to 25% (entry 5, Table 2.1). Interestingly the reaction did not proceed at all when cobaltocenium hexafluorophosphate [$CoCp_2PF_6$] was employed as a catalyst (entry 6, Table 2.1). Cobaltocene is an 18-valence electron complex that acts as a Lewis acid rather than a one-electron oxidant and turned out to be catalytically inactive. $FcPF_6$ on the other hand, is a 17-valence electron complex that can act as a Lewis acid and a one-electron oxidant.

To further explore the reaction mechanism of substitution reactions, we employed radical scavengers such as 2,6-di-tert-butyl-4-methylphenol (which will be abbreviated as BHT) and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (which will be abbreviated as TEMPO).[35] As seen, TEMPO slowed the conversion to 34% (entry 7, table 2.1) whereas BHT did not inhibit the reaction and a 94% conversion was obtained (entry 8, table 2.1). This is evidence that the title reaction does not follow a free radical mechanism, at least not primarily. Results are shown in Table 2.1.



Scheme 2.5 Screening for solvent and mechanism

Table 2.1 Preliminary results

Entry[a]	Solvent	Conversion (%)
1	**CH_2Cl_2**	**97**
2	**$ClCH_2CH_2Cl$**	**95**
3	**THF**	**44**
4	**toluene**	**None**
5	***n*-butanol**	**25**
6	**CH_2Cl_2/$[CoCp_2]PF_6$**	**None**
7	**CH_2Cl_2/TEMPO**	**34[c]**
8	**CH_2Cl_2/BHT**	**98[d]**

[a] Typical Conditions: propargylic alcohol (0.6 mmol) and alcohol (0.6 mmol) in the solvent (1 mL) catalyzed by $FcPF_6$ (5 mol%) for 2 hours at 40 – 45 °C. [b] Conversions were determined by gas chromatography. [c] In the presence of TEMPO (20 – 100 mol%) for 16 h. [d] In the presence of BHT (20 – 100 mol%) for 16 h.

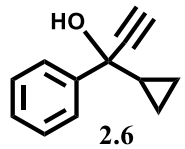
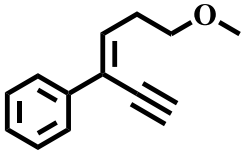
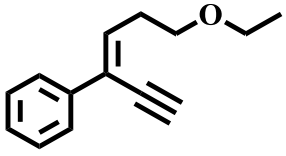
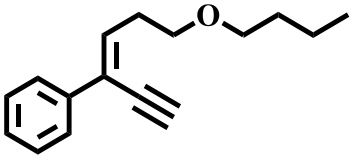
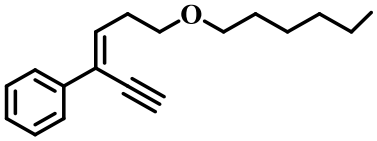
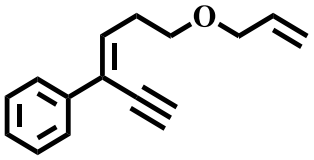
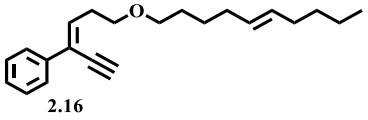
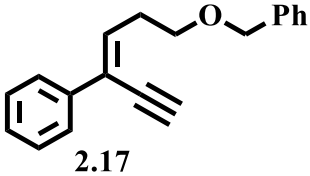
The ferrocenium ion presumably assists in the formation of a carbocation intermediate, which will eventually react with the hydroxyl group on the nucleophile to give the desired propargylic ether product.[30] Eventually, these initial substitution reactions with phenyl substituent and cyclo-propyl ring substituent lead to the ether products in Table 2.2.[33] When primary alcohols were employed as nucleophiles, we were able to obtain 35 to 73% isolated ene-yne products (**2.11 – 2.17**, entries 1-7, Table 2) within 2 hours

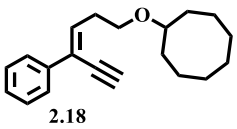
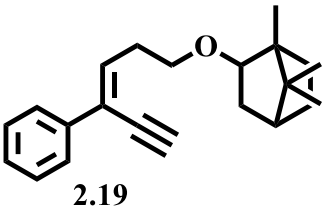
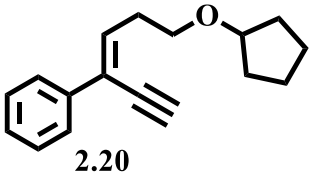
of the reaction time. Secondary alcohols gave 35 to 45% isolated yields (**2.18 – 2.20**, entries 8-10, Table 2) due to their lower nucleophilic nature. All the reactions were monitored by GC and the ene-yne products were isolated utilizing column chromatography techniques and were characterized by NMR spectroscopy.

In the ^{1}H NMR spectra, the olefinic methine proton peak always showed up around 6.3 ppm, which is clear evidence of the ene-yne products.[24, 25] The terminal alkyne protons appeared around 2.3 ppm for all the ether products. The alkyne carbon peak appeared around 80 and 83 ppm in the ^{13}C{^{1}H} NMR spectra. In the IR spectra, ≡CH stretches around 3300 cm^{-1} were noticed, which represents the alkyne unit, and no hydroxyl stretch was observed, which is clear evidence that all the propargylic starting materials were converted into the ether products. According to the literature, NOE correlation between phenyl proton and olefinic methine proton point towards an *E*-isomer.[25] We performed NOE NMR spectroscopy experiment on one compound (2.14) and found that it matches the literature.[25] So, we assigned the same configuration to the rest of the compounds in Table 2.2. ^{1}H NMR spectra displayed baseline purity and GC-MS data matched products.

Unfortunately, these ene-yne products decomposed after a few days (in solid state and in liquid form). The isolated products contained trace amounts of iron, which could have led to oxidative decomposition. Because of these reasons, we could not gather proper elemental analysis, they were about 1% low on carbon, as expected for oxidative decomposition.

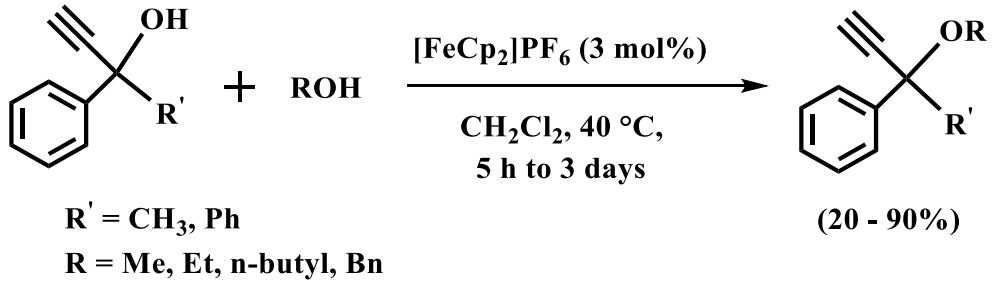
Table 2.2 Synthesis of ene-yne ether products

Entry [a]	Propargylic alcohol	Catalyst	Product	Yield (%) [b]
1	 **2.6**	$[FeCp_2]PF_6$, CH_2Cl_2, 40 °C, 2.5 h	 **2.11**	50
2	2.6	$[FeCp_2]PF_6$, CH_2Cl_2, 40 °C, 1.25 h	 **2.12**	73
3	2.6	$[FeCp_2]PF_6$, CH_2Cl_2, 40 °C, 2 h	 **2.13**	37
4	2.6	$[FeCp_2]PF_6$, CH_2Cl_2, 40 °C, 2 h	 **2.14**	60
5	2.6	$[FeCp_2]PF_6$, CH_2Cl_2, 40 °C, overnight	 **2.15**	35
6	2.6	$[FeCp_2]PF_6$, CH_2Cl_2, 40 °C, 2 h	 **2.16**	50
7	2.6	$[FeCp_2]PF_6$, CH_2Cl_2, 40 °C, 1.25 h	 **2.17**	47

8	2.6	$[FeCp_2]PF_6$, CH_2Cl_2, 40 °C, 1.6 h	 **2.18**	41
9	2.6	$[FeCp_2]PF_6$, CH_2Cl_2, 40 °C, 2 h	 **2.19**	35
10	2.6	HBF_4, CH_2Cl_2, 40 °C, 1 h	 **2.20**	45

[a] Typical conditions: propargylic alcohol (0.6 mmol) and alcohol (0.6 mmol) in CH_2Cl_2 (1 mL) catalyzed by $FcPF_6$ (5 mol%) for 2 hours at 40 – 45 °C (except for the entry 5). [b] The ether products were isolated by column chromatography.

Previously in our lab, when we proved the efficacy of $FcPF_6$ with phenyl methyl or diphenyl propargylic alcohols (R′=CH_3, Ph in Scheme 2.6) the reaction times were between 5 hours to 3 days to go to completion (Scheme 2.6).[19] When we synthesized phenyl propargylic alcohol with a cyclopropyl substituent, it shortened the reaction time, and we were able to obtain the ene-yne products within 2 hours.



Scheme 2.6 Previous work

To find out more the reaction mechanism, we started monitoring the reaction between phenyl cyclopropyl propargylic alcohol **2.6** and *n*-butanol **2.9** by GC and observed the

formation of the ring-closed substitution product within 20 minutes. Consumption started to give after 20 minutes the ring-closed product **2.10a.** Eventually, after 20 minutes the cyclopropyl ring started opening to give ene-yne product **2.10**. We isolated the ring-closed product by utilizing column chromatography techniques and were able to obtain it in 23% yield, which exhibited 95% NMR pure.[33] In the ^{1}H NMR, spectral peaks around 0 and 1 ppm, which represent cyclo-propyl ring are still present. As seen from the plot between conversion rate of starting material, intermediate and ene-yne product vs. the reaction time, we were able to notice the consumption of the propargyl alcohol starting material (which is shown as a solid line in Figure 2.1), formation of the ring-closed intermediate (which is shown as a dashed line in Figure 2.1) and the cyclo-propyl ring-opened ene-yne product (which is shown as a dotted line in Figure 2.1) over the course of 60 minutes.

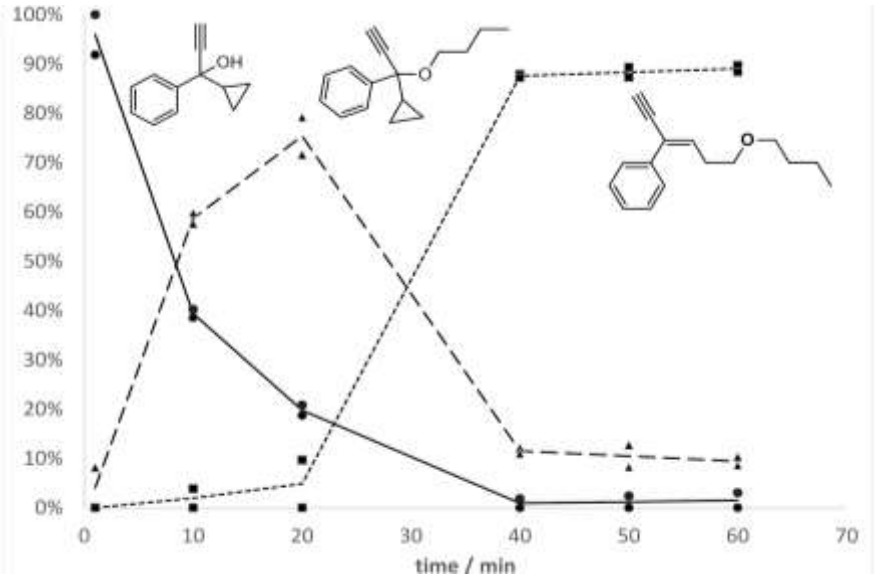
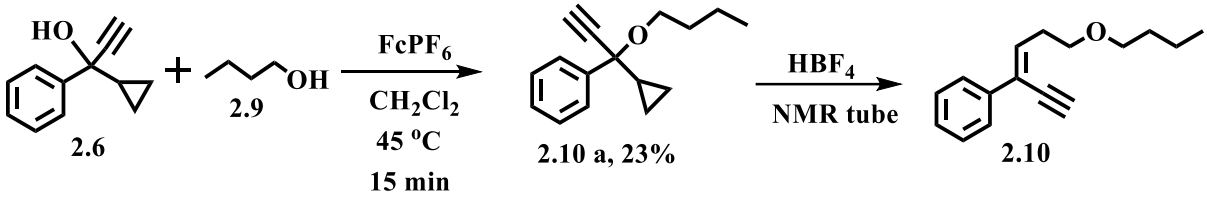


Figure 2.1 Formation of the intermediate and ene-yne over time (Experiment and the plotting was provided by Michael Barnes-Flaspoler)

This observation gave us a detailed view of the reaction mechanism, suggesting that the ring-closed product forms through an ionic mechanism, and the cyclo-propyl ring helps

in stabilizing the positive charge of the carbocation intermediate.[31] In the presence of a Lewis acid or a metal, the cyclo-propyl ring rearranges to give the ene-yne product. To prove this assumption, we performed a reaction in the NMR tube with the intermediate ring-closed product **2.10a** and added a small amount of tetrafluoro boric acid (HBF_4), which is a Brønsted acid. After 1 hour, we observed the ring-opened ene-yne product along with some side products (Scheme 2.7). This observation demonstrates the initial formation of a ring-closed product, and the ring-opening can be accomplished by an acid, indicating an ionic mechanism with a carbocation intermediate.



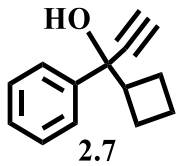
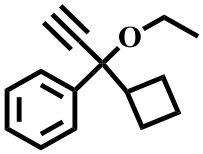
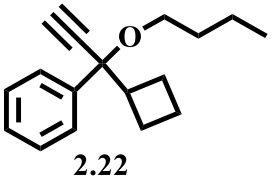
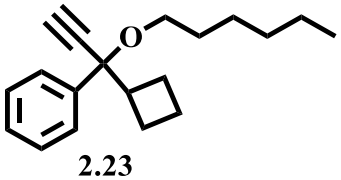
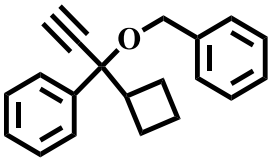
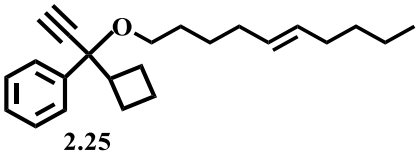
Scheme 2.7 Reaction Sequence

Therefore, the etherification reactions with phenyl cyclopropyl propargylic alcohol led to ene-yne products **2.21**-**2.25** in Table 2.3. The products decomposed after a few days, presumably due to the presence of trace amounts of iron. Therefore, we employed more stable ferrocenium boronicacid hexafluoro antimonate (which will be abbreviated as $[FcB(OH)_2]SbF_6$)[30] as a catalyst. Employment of this catalyst resulted in an inseparable mixture of ring-closed and ring-opened products, and we did not follow up on this approach any further.

Next, we started synthesizing propargylic alcohol with a cyclobutyl ring substituent **2.7** in Table 2.3, hoping it will accelerate the reaction and we did not expect the four-membered ring to open. However, the reaction with phenyl cyclobutyl propargylic alcohol **2.7** and alcohols (primary and secondary) took 16 hours, which is much longer than anticipated, and the ring stayed intact. We performed these reactions with both the

catalyst systems ($FcPF_6$ and $[FcB(OH)_2]SbF_6$ and were able to obtain 40 to 55% isolated yields **2.21 – 2.25** as shown below in the Table 2.3.[33]

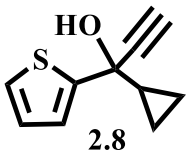
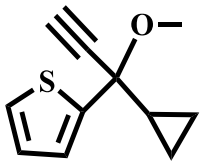
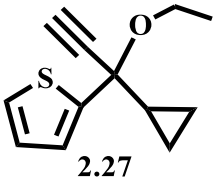
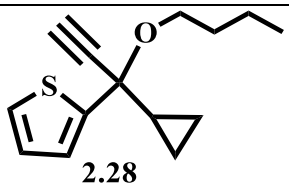
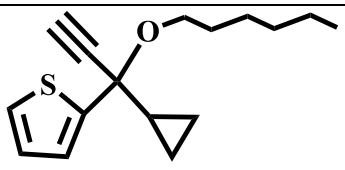
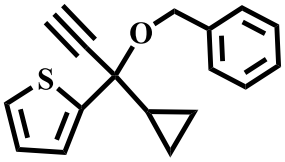
Table 2.3 Synthesis of phenyl cyclo-butyl propargylic ethers

Entry [a]	Propargylic alcohol	Catalyst	Product	Yield (%) [b]
1	 **2.7**	$[FcB(OH)_2]SbF_6$, CH_2Cl_2, 45 °C, 8 -16 h	 **2.21**	43
2	**2.7**	$[FeCp_2]PF_6$ CH_2Cl_2, 40 °C, 8 -16 h	 **2.22**	40
3	**2.7**	$[FcB(OH)_2]SbF_6$, CH_2Cl_2, 45 °C, 12 – 20 h	 **2.23**	43
4	**2.7**	$[FcB(OH)_2]SbF_6$, CH_2Cl_2, 45°C, 8 -16 h	 **2.24**	55
5	**2.7**	$[FcB(OH)_2]SbF_6$, CH_2Cl_2, 45 °C, 8 -16 h	 **2.25**	42

[a] Typical conditions: propargylic alcohol (0.6 mmol) and alcohol (0.6 mmol) in CH_2Cl_2 (1 mL) catalyzed by $[FcB(OH)_2]SbF_6$ (3 mol%) for 12 - 20 hours at 45 °C (except for the entry 2, $FcPF_6$ (5 mol%)). [b] The ether products were isolated by column chromatography.

To further investigate the impact of the aromatic ring system on the efficiency of the reaction, we replaced the phenyl ring with a thienyl ring. Surprisingly, the reaction between thienyl cyclo-propyl propargylic alcohol **2.8** (Table 2.4) and *n*-butanol **2.9** resulted in the ether product **2.28** within 20 minutes of the reaction time. The electron-rich thienyl ring on the propargylic alcohol accelerated the reaction. The accelerated reaction provides evidence that the reaction proceeds through a carbocation intermediate. The carbocation is stabilized by the electron-rich thienyl ring, facilitating its formation.

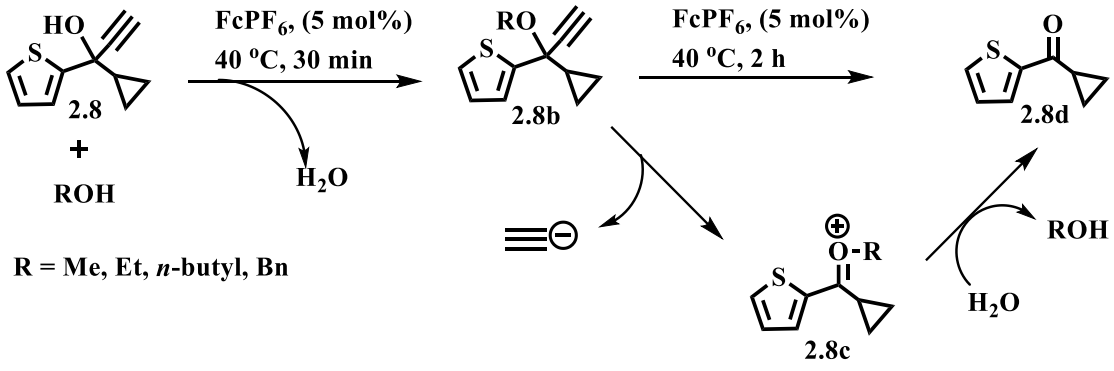
Table 2.4 Synthesis of thienyl cyclo-propyl ether products

Entry [a]	**Propargylic alcohol**	**Catalyst**	**Product**	**Yield (%)** [b]
1	 **2.8**	$[FeCp_2]PF_6$, CH_2Cl_2, 40 °C, 45 min	 **2.26**	56
2	**2.8**	$[FeCp_2]PF_6$, CH_2Cl_2, 40 °C, 1h	 **2.27**	42
3	**2.8**	$[FcB(OH)_2]SbF_6$, CH_2Cl_2, 8 -16 h, rt	 **2.28**	44
4	**2.8**	$[FeCp_2]PF_6$, CH_2Cl_2, 40 °C, 2 h	 **2.29**	39
5	**2.8**	$[FeCp_2]PF_6$, CH_2Cl_2, 8 -16 h, rt	 **2.30**	27

[a] Typical conditions: propargylic alcohol (0.6 mmol) and alcohol (0.6 mmol) in CH_2Cl_2 (1 mL) catalyzed by $FcPF_6$ (5 mol%) at 45 °C for 1-2 h (except for the entry 3, $[FcB(OH)_2]SbF_6$ (3 mol%) and entry 5, $FcPF_6$ (5 mol%) for 8 – 16 h). [b] The ether products were isolated by column chromatography.

A similar reaction was performed using hexanol as the nucleophile. The formation of the ether product was about 80% complete within 10 minutes and showed 100% conversion after 30 minutes, as shown by GC. Even though the product formation occurs in 20 minutes, we let the reaction continue for 2 hours and were able to obtain 27 to 56% yields of the substitution products **2.26**-**2.30** (entries 1-5, Table 2.4) with primary and secondary alcohols as nucleophiles. Column chromatography techniques were performed to isolate thienyl propargylic ether products from **2.26 – 2.30** as shown in the Table 2.4.[33]

An extended reaction time resulted in the loss of the terminal alkyne unit presumably through a carbocation intermediate which can then be hydrolyzed easily with the water molecule that is generated during the formation of the ether product. This resulted in the conversion of the thienyl ether product **2.8b** to the thienyl cyclopropyl ketone **2.8d** starting material, as established by GC. The proposed mechanism is shown below in Scheme 2.8.



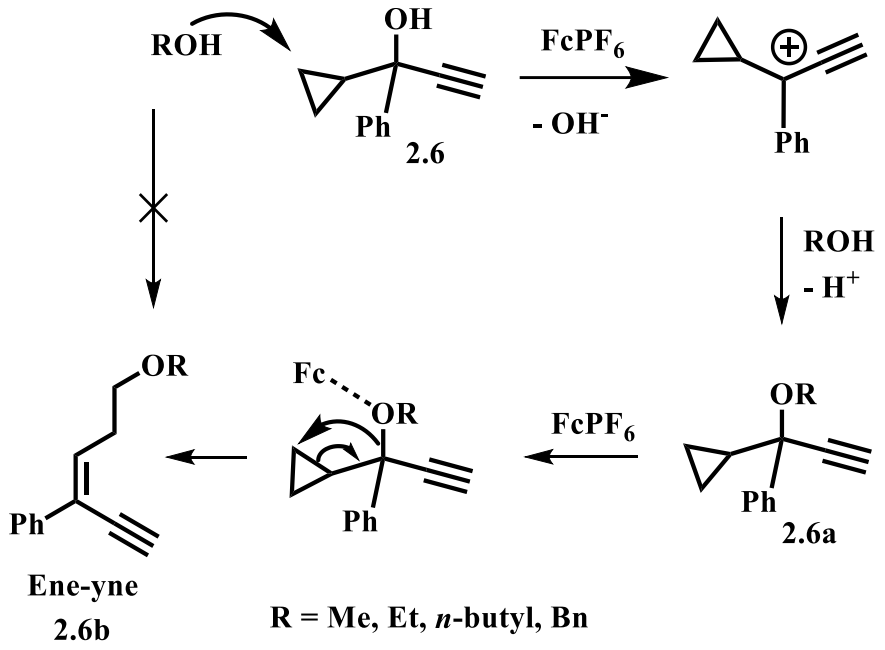
Scheme 2.8 Proposed reaction mechanism of the decomposition of the thienyl cyclo-propyl propargylic ether 2.8b

We performed similar reactions with $[FcB(OH)_2]SbF_6$ as a catalyst and found that it is less reactive (because it resulted in lower yields and required longer reaction time) compared to $FcPF_6$. An advantage of $[FcB(OH)_2]SbF_6$ is that we were able to retain the iron on the column. This led to a deceleration of the decomposition of the ether products and gave correct elemental analysis.

Overall, it was determined that among the three different propargylic alcohols, the thienyl cyclopropyl starting material **2.8** is the most reactive one. When we performed etherification reactions previously with phenyl methyl propargylic alcohol ($R'=CH_3$, Ph in Scheme 2.6), the reaction needed 8 hours to go to completion. It is evident that the cyclopropyl unit on the propargylic alcohol can accelerate the nucleophilic substitution reactions when compared with the cyclobutyl **2.7** or methyl substituents ($R'=CH_3$, Ph in Scheme 2.6).

The sulfur atom in the thienyl propargylic alcohol somehow inhibits the ring-opening process, and it reacts faster when compared with the phenyl propargylic alcohol **2.6** (Scheme 2.9). The ferrocenium cation presumably assists in the formation of carbocation as an intermediate, then the nucleophile attack takes place to form ring closed (**2.11** to **2.25**, Table 2 and 3) products for both the starting materials (**2.6** and **2.7**, Table 2 and 3). Eventually, the ring opens for the phenyl cyclo-propyl propargyl alcohol **2.6** (Scheme 2.9). The nucleophilic attack does not directly take place on the cyclopropyl ring. The proposed mechanistic pathway for phenyl cyclopropyl propargylic alcohol **2.6** is shown below in the Scheme 2.9. The ring-opening behavior

of phenyl propargyl alcohol after substitution leads to a S_N1 type ionic mechanism for the initial substitution.[31]



Scheme 2.9 Reaction mechanism of the phenyl cyclo-propyl propargylic alcohol

2.4 Conclusion

We showed the efficacy of ferrocenium cations as a catalyst for performing etherification reactions involving terminal tertiary propargylic alcohols with primary and secondary alcohols as nucleophiles in substitution reactions. The roles of substituents on the propargylic alcohols were studied and discovered that the thienyl cyclo-propyl propargylic alcohol **2.8** can accelerate the reaction. The cyclopropyl substituted propargylic alcohol **2.6** ring-opened to give ene-yne products within 2 hours whereas, with the thienyl cyclopropyl and phenyl cyclobutyl propargylic alcohols, the rings stayed intact. Overall, these findings point towards an ionic mechanism.

2.5 Experimental Section

2.5.1 General

All chemicals, ferrocenium hexafluorophosphate ($FcPF_6$) and cobaltocenium hexafluorophosphate ($[CoCp_2]PF_6$) were used as supplied by Sigma-Aldrich. CH_2Cl_2 was freshly distilled from CaH_2. 1-Cyclo-propyl-1-phenylprop-2-yn-1-ol **2.6**, Scheme 2.4, 1-cyclo-propyl-1-(thiophen-2-yl) prop-2-yn-1-ol **2.8**, Scheme 2.4, 1-cyclobutyl-1-phenylprop-2-yn-1-ol **2.7**, Scheme 2.4, and ferrocenium boronic acid hexafluoroantimonate ($[FcB(OH)_2]SbF_6$) were synthesized following the literature.[30] All NMR spectra for characterization were collected at room temperature on a Bruker Advance 300 MHz instrument; all chemical shifts (δ) are reported in ppm and are referenced to a residual solvent signal. All assignments are tentative. IR spectra were collected on a Thermo Nicolet 360 FT-IR spectrometer. HRMS measurements were performed on a MaXis plus quadrupole time-of-flight mass spectrometer (Bruker) with atmospheric pressure photoionization (APPI). EI masses were recorded on a HP 5988A GC–MS instrument. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA, USA.

2.5.2 (6-Methoxyhex-3-en-1-yn-3-yl) benzene (2.11)

In a screw cap pressure vial, 1-phenyl-1-cyclopropyl-2-yne-1-ol (**2.6**, 0.100 g, 0.581 mmol) was dissolved in CH_2Cl_2 (2 mL). Methanol (0.0185 g, 0.593 mmol) and $FcPF_6$ (0.010 g, 0.030 mmol) were added, and the sealed vial was heated at 45 °C for 2.5 hours. The reaction mixture was filtered through a short pad of silica gel using CH_2Cl_2 (2 – 4 mL). The product was obtained by column chromatography on alumina (2.5 × 30 cm, 9:1 v/v hexanes/EtOAc) as an orange-colored oil (**2.11**, 0.054 g, 0.290 mmol, 50 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 – 7.65 (m, 2H, aromatic), 7.42 – 7.31 (m,

3H, aromatic), 6.61 (t, J_{HH} =7 Hz, C=CH, 1H), 3.60 (t, J = 7 Hz, 2H, OCH_2), 3.44 (s, 3H, CH), 3.41 (s, ≡CH, 1H), 2.86 (q, J_{HH} = 7 Hz, 2H, OCH_2) ppm; $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$): δ = 137.5 (s, C=CH), 136.2 (s, aromatic), 128.4 (s, aromatic), 127.8 (s, aromatic), 126.0 (s, aromatic), 124.1 (s, C=CH), 83.5 (s, HC≡C), 80.7 (s, HC≡C), 71.5 (s, $=CCH_2$), 58.7 (s, CH_2O), 31.7 (s, CH_3); IR (ATR, neat): $\tilde{\nu}$ = 3283 (m), 2922 (m), 2870 (m), 2825 (m) cm^{-1}; *m/z* (%): 185 (30) $[M - H]^+$, 171 (10) $[M - CH_3]^+$, 156 (50) $[M+H–O\ CH_3]^+$, 141 (100) $[M - C_2H_5O]^+$, 128 (60) $[M+H–C_3H_7O]^+$, 115 (100) $[M+H–C_4H_8O]^+$, 45 (90) $[C_2H_5O]^+$.

2.5.3 6-Ethoxy-3-phenyl-3-en-1-yne (2.12)

In a screw cap pressure vial, 1-phenyl-1-cyclopropyl-2-yne 1-ol (**2.6,** 0.116 g, 0.623 mmol) was dissolved in CH_2Cl_2 (2 mL). Ethanol (0.031 g, 0.674 mmol) and $FcPF_6$ (0.010 g, 0.030 mmol) were added, and the sealed vial was heated at 45 °C for 75 minutes. The reaction mixture filtered through a short pad of silica gel and the filtrate was chromatographed (2 × 30 cm alumina, 1:1 v/v EtOAc/hexanes 1:9) to obtain the product 6-ethoxy-3-phenyl-3-en-1-yne (**2.12,** 0.091 g, 0.455 mmol, 73 %) as an orange oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, J_{HH} = 7.0 Hz, 2H, aromatic), 7.46 – 7.31 (m, 3H, aromatic), 6.61 (t, J_{HH} = 7.4 Hz, C=CH, 1H), 3.65 – 3.54 (m, 4H, CH_2OCH_2), 3.28 (s, ≡CH, 1H), 2.72 (q, J_{HH} = 7.0 Hz, 2H, CH_2CH_3), 1.15 (t, J_{HH} = 7.0 Hz, 3H, CH_3) ppm; $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$): δ = 137.5 (s, C=CH), 136.4 (s, aromatic), 128.4 (s, aromatic), 127.7 (s, aromatic), 126.0 (s, aromatic), 124.0 (s, C=CH), 83.4 (s, C≡CH), 80.7 (s, C≡CH), 69.3 (s, OCH_2), 66.2 (s, $C=CHCH_2$), 31.9 (s, $CHCH_2O$), 15.5 (s, CH_3) ppm.

2.5.4 (6-Butoxyhex-3-en-1-yn-3-yl) benzene (2.13)

In a screw cap pressure vial, 1-phenyl-1-cyclopropyl-2-yne-1-ol (**2.6**, 0.105 g, 0.610 mmol) was dissolved in CH_2Cl_2 (2 mL). *n*-Butanol (0.045 g, 0.608 mmol) and $FcPF_6$ (0.010 g, 0.030 mmol) were added, and the vial was sealed and heated at 45 °C for 2 hours. The reaction mixture was filtered through silica gel, using CH_2Cl_2 (2 – 4 mL). The product was obtained by column chromatography on alumina (2.5 × 30 cm, 9:1 v/v hexanes/EtOAc) as a yellow-colored oil (**2.13**, 0.052 g, 0.228 mmol, 37 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53 – 7.51 (m, 2H, aromatic), 7.28 – 7.16 (m, 3H, aromatic), 6.48 (t, 1H, J_{HH} = 7 Hz, =CH), 3.49 (t, J_{HH} = 7 Hz, 2H, OCH_2), 3.38 (t, 2H, J_{HH} = 7 Hz, OCH_2), 3.27 (s, 1H, ≡CH), 2.72 (q, J_{HH} = 7 Hz, 2H, CH_2), 1.54 – 1.34 (m, 2H, CH_2), 1.36 – 1.26 (m, 2H, CH_2), 0.85 (t, 3H, J_{HH} = 7 Hz, CH_3) ppm; $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$): δ = 137.6 (s, C=CH), 136.5 (s, aromatic), 128.4 (s, aromatic), 127.7 (s, aromatic), 126.0 (s, aromatic), 123.9 (s, C=CH), 83.4 (s, C≡CH), 80.8 (s, C≡CH), 70.8 (s, OCH_2), 69.5 (s, OCH_2), 31.90 (s, CH_2), 31.86 (s, CH_2), 19.4 (s, CH_2), 14.0 (s, CH_3) ppm; IR (ATR, neat): $\tilde{\nu}$ = 3288 (m), 3055 (w), 2973 (m), 2926 (w) cm^{-1}; ESI-MS *m/z* (%): 185 (20) $[M - C_3H_7]^+$, 155 (15) $[M - C_4H_9O]^+$, 141 (50) $[M - C_5H_{11}O]^+$, 128 (40) $[M - C_6H_{12}O]^+$, 115 (50) $[M - C_7H_{13}O]^+$, 57 (100) $[C_4H_9]^+$.

2.5.5 (6-(Hexyloxy) hex-3-en-1-yn-3-yl) benzene (2.14)

1-Cyclopropyl-1-phenylprop-2-yn-1-ol (**2.6**, 0.103 g, 0.598 mmol) was added to a screw cap pressure vial and dissolved in CH_2Cl_2 (2 mL). 1-Hexanol (0.075 g, 0.669 mmol) was added followed by $FcPF_6$ (0.012 g, 0.037 mmol). The sealed vial was then heated to 45 °C for 2 hours. The mixture was filtered through a short pad of silica using CH_2Cl_2 (2 – 4 mL). The product was obtained by chromatography on a neutral alumina oxide (Aluminar®) column (2.5 × 30 cm, 9:1 v/v hexanes/EtOAc) to give the product as a yellow-colored oil (**2.14**, 0.093 g, 0.361 mmol, 60 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54 – 7.51 (m, 2H, aromatic), 7.28 – 7.19 (m, 3H, aromatic), 6.48 (t, J_{HH} = 7 Hz,

1H, alkene), 4.07 (s, 0.16 H, ferrocene), 3.48 (t, J_{HH} = 7 Hz, 2H), 3.36 (t, J_{HH} = 7 Hz, 2H), 3.26 (s, 1H), 2.75 – 2.68 (q, J_{HH} = 7 Hz, 2H), 1.50 (q, J_{HH} = 7 Hz, 2H), 1.31 – 1.22 (m, 6H), 0.80 (t, J_{HH} = 7 Hz, 3H) ppm; $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$): δ = 137.6 (s, C=CH), 136.5 (s, aromatic), 128.4 (s, aromatic), 127.8 (s, aromatic), 126.0 (s, aromatic), 124.0 (s, C=CH), 83.5 (s, C≡CH), 80.8 (s, C≡CH), 71.1 (s, CH_2O), 69.5 (s, CH_2O), 68.0 (s, trace amount ferrocene), 31.9 (s, CH_2), 31.8 (s, CH_2), 29.8 (s, CH_2), 26.0 (s, CH_2), 22.7 (s, CH_2), 14.2 (s, CH_3) ppm; IR (ATR, neat): $\tilde{\nu}$ = 3288 (m), 3060 (w), 3024 (w), 2927 (s), 2854 (s), 2790 (m) cm^{-1}; ESI-MS *m/z* (%): 255 (5) $[M - 1]^+$, 155 (30) $[M - C_6H_{13}O]^+$, 141 (100) $[M - C_7H_{15}O]^+$, 128 (70) $[M - C_8H_{16}O]^+$, 115 (95) $[M - C_9H_{17}O]^+$; HRMS (APPI): *m/z* calcd. for $C_{18}H_{25}O$: 257.1905 $[M + H]^+$, found 257.1900.

2.5.6 6-Alloxy-3-phenyl-3-en-1-yne (2.15)

In a screw cap pressure vial, 1-phenyl-1-cyclopropyl-2-yne-1-ol (**2.6**, 0.094 g, 0.547 mmol) was dissolved in CH_2Cl_2 (2 mL). Allyl alcohol (0.031 g, 0.534 mmol) and $FcPF_6$ (0.010 g, 0.030 mmol) was added, and the vial was sealed and heated at 45 °C overnight. The reaction mixture was filtered through a short pad of silica gel with CH_2Cl_2 (2 – 4 mL). The product was obtained by column chromatography on alumina (2.5 × 30 cm, 9:1 v/v hexanes/EtOAc) as an orange-colored oil (**2.15**, 0.041 g, 0.193 mmol, 35 %). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.54 – 7.49 (m, 2H, aromatic), 7.28 – 7.19 (m, 3H, aromatic), 6.48 (t, J_{HH} = 7 Hz, C=CH, 1H), 5.90 – 5.80 (m, $CH=CH_2$, 2H), 4.16 (t, J_{HH} = 5.48 Hz, O CH_2, 2H), 3.93 (t, J_{HH} = 7 Hz, O CH_2, 2H), 3.52 (t, J_{HH} = 7.4 Hz, O CH_2 CH_2, 2H), 3.27 (s, C≡CH, 1H), 2.73 (q, J_{HH} = 7.3 Hz, CH CH_2, 2H) ppm; $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$): δ = 137.5 (s, C=), 136.4 (s, aromatic), 136.2 (s, C=), 128.4 (s, aromatic), 127.8 (s, aromatic), 126.0 (s, aromatic), 124.1 (s, C=), 117.1 (C= CH_2), 83.5 (s, C≡CH), 80.7 (s, C≡CH), 71.9 (s, O CH_2), 69.1 (s, O CH_2), 68.0 (s, trace amount ferrocene), 31.9 (s, =CH CH_2) ppm; IR (ATR, neat): $\tilde{\nu}$ = 3267 (m), 3023 (w), 2853 (m) cm^{-1}; ESI-MS

m/z (%): 184 (10) $[M - C_2H_4]^+$, 155 (20) $[M - C_3H_5O]^+$, 141 (50) $[M - C_4H_7O]^+$, 128 (40) $[M - C_5H_8O]^+$, 115 (50) $[M - C_6H_9O]^+$, 41 ($[C_3H_5]^+$, 100 %).

2.5.7 6-(trans-5-Decoxy)-3-phenyl-3-en-1-yne (2.16)

In a screw cap pressure vial, 1-phenyl-1-cyclopropyl-2-yne-1-ol (**2.6**, 0.110 g, 0.639 mmol) was dissolved in CH_2Cl_2 (2 mL) and trans-5-decanol (0.100 g, 0.641 mmol) and $FcPF_6$ (0.010 g, 0.030 mmol) were added. The sealed vial was heated at 45 °C for 2 hours. The reaction mixture was filtered through a short pad of silica gel by using CH_2Cl_2 (2 – 4 mL). The product was obtained by column chromatography on alumina (2.5 × 30 cm, 9:1 v/v hexanes/EtOAc) as an orange-colored oil (**2.16**, 0.099 g, 0.319 mmol, 50 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54 – 7.52 (m, 2H, aromatic), 7.29 – 7.18 (m, 3H, aromatic), 6.49 (t, J_{HH} = 7 Hz, 1H, C=CH), 5.32 (q, J_{HH} = 3 Hz, 2H, HC=CH), 3.50 (t, J_{HH} = 7 Hz, 2H, O CH_2), 3.36 (t, J_{HH} = 7 Hz, 2H, O CH_2), 3.27 (s, 1H, ≡CH), 2.72 (q, J_{HH} = 7 Hz, 2H, CH_2), 1.96 – 1.80 (m, 4H, 2 CH_2), 1.55 – 1.47 (m, 2H, CH_2), 1.39 – 1.31 (m, 2H, CH_2), 1.29 – 1.22 (m, 4H, 2 CH_2), 0.82 (t, J_{HH} = 7 Hz, 3H, CH_3) ppm; $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$): δ = 137.6 (s, C=), 136.5 (s, aromatic), 130.8 (s, C=), 130.0 (s, C=), 128.4 (s, aromatic), 127.7 (s, aromatic), 126.0 (s, aromatic), 123.9 (s, C=CH), 83.4 (s, C≡CH), 80.8 (s, C≡CH), 70.9 (s, O CH 2), 69.5 (s, O CH_2), 32.4 (s, CH_2), 32.4 (s, CH_2), 31.89 (s, CH_2), 31.85 (s, CH_2), 29.2 (s, CH_2), 26.2 (s, CH_2), 22.3 (s, CH_2), 14.1 (s, CH_3) ppm; ESI-MS *m/z* (%): 309 (5) $[M - 1]^+$, 155 (30) $[M - C_{10}H_{19}O]^+$, 141 (60) $[M - C_{11}H_{21}O]^+$, 128 (50) $[M - C_{12}H_{22}O]^+$, 115 (100) $[M - C_{13}H_{23}O]^+$; IR (ATR, neat): $\tilde{\nu}$ = 3289 (m), 3021 (w), 2923 (s), 2853 (s), 2790 (w) cm^{-1}.

2.5.8 6-Benzoxy-3-phenyl-3-en-1-yne (2.17)

In a screw cap pressure vial, 1-phenyl-1-cyclopropyl-2-yne-1-ol (**2.6**, 0.108 g, 0.627 mmol) was dissolved in CH_2Cl_2 (2 mL) and benzyl alcohol (0.068 g, 0.630 mmol) and

$FcPF_6$ (0.010 g, 0.030 mmol) were added. Then the vial was sealed and heated at 45 °C for 75 minutes. The reaction mixture was filtered through a short pad of silica gel using CH_2Cl_2 (2 – 4 mL). The product 6-benzoxy-3-phenyl-3-en-1-yne was obtained by column chromatography on alumina (2.5 × 30 cm, 9:1 v/v hexanes/EtOAc) as an orange-colored oil (**2.17**, 0.077 g, 0.294 mmol, 47 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63–7.59 (m, 2H, aromatic), 7.37–7.26 (m, 8H, aromatic), 6.57 (t, J_{HH} = 7 Hz, C=CH, 1H), 4.55 (s, 2H, O CH_2Ph), 4.16 (0.5 H, ferrocene), 3.36 (t, J_{HH} = 7 Hz, 2H, O CH_2), 3.35 (s, 1H, C≡CH), 2.85 (q, J_{HH} = 7 Hz, 2H, CH CH_2) ppm; ^{13}C{^{1}H} (75 MHz, $CDCl_3$): δ = 138.4 (s, C=), 137.6 (s, aromatic), 136.42 (s, aromatic), 136.38 (s, aromatic), 128.53 (s, aromatic), 128.49 (s, aromatic), 127.8 (s, aromatic), 127.7 (s, aromatic), 126.0 (s, aromatic), 124.2 (s, =C), 83.7 (s, C≡CH), 80.8 (s, C≡CH), 73.0 (s, O CH_2), 69.1 (s, O CH_2), 31.9 (s, CH CH_2) ppm; ESI-MS *m/z* (%): 261 (5) $[M - 1]^+$, 141 (20) $[M - C_8H_9O]^+$, 114 (20) $[M - C_{10}H_{12}O]^+$, 91 (100) $[C_7H_7]^+$; IR (ATR, neat): $\tilde{\nu}$ = 3282 (w), 3026 (m), 2853 (m) cm^{-1}.

2.5.9 ((4-Phenylhex-3-en-5-yn-1-yl) oxy) cyclooctane (2.18)

1-phenyl-1-cyclopropyl-2-yne-1-ol (**2.6**, 0.071 g, 0.413 mmol) was added to a screw cap vial and dissolved in CH_2Cl_2 (1 mL). Cyclooctanol (0.076 g, 0.593 mmol) was added followed by the addition of $FcPF_6$ (0.012 g, 0.037 mmol). The sealed vial was heated to 45 °C for 100 minutes. The solvent was removed, and the residue was chromatographed on a neutral alumina (Aluminar®) column (2.5 × 30 cm, 9:1 v/v hexanes/EtOAc) to give the product as an orange-colored oil (**2.18**, 0.060 g, 0.213 mmol, 52 %). For further purification, the product was chromatographed on a silica column (2.5 × 10 cm, 9:1 v/v hexanes/EtOAc) to give the product as a yellow-colored oil (0.048 g, 0.170 mmol, 41 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54 – 7.50 (m, 2H, aromatic), 7.28 – 7.16 (m, 3H, aromatic), 6.49 (t, J_{HH} = 7Hz, 1H, =CH), 4.08 (s, 0.16H,

ferrocene), 3.49 (t, J_{HH} = 7 Hz, 2H, CH_2), 3.39 – 3.33 (m, 1H, HCOH), 3.26 (s, 1H, C≡CH), 2.69 (q, J_{HH} = 7 Hz, 2H), 1.80 – 1.30 (m, 14H, 7 CH_2) ppm; $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$): δ = 137.6 (s, =C), 136.8 (s, aromatic), 128.4 (s, aromatic), 127.8 (s, aromatic), 126.0 (s, aromatic), 123.8 (s, =C), 83.4 (s, C≡CH), 80.8 (s, C≡CH), 79.9 (s, CH_2O), 68.0 (s, trace amount ferrocene), 66.9 (s, CHO), 32.3 (s, CH_2), 31.6 (s, CH_2), 27.4 (s, CH_2), 25.5 (s, CH_2), 23.2 (s, CH_2) ppm; IR (ATR, neat): $\tilde{\nu}$ = 3289 (m), 3026 (w), 2915 (s), 2849 (s) cm^{-1}; ESI-MS *m/z* (%): 281 (5) $[M - 1]^+$, 141(80) $[M - C_9H_{17}O]^+$, 128 (75) $[M - C_{10}H_{18}O]^+$, 114 (100) $[M - C_{11}H_{20}O]^+$; HRMS (APPI): *m/z* calcd. For $C_{20}H_{27}O$: 283.2061 $[M + H]^+$, found 283.2056.

2.5.10 1,7,7-Trimethyl-2-((4-phenylhex-3-en-5-yn-1-yl) oxy) bicyclo[2.2.1]heptane (2.19)

1-phenyl-1-cyclopropyl-2-yne-1-ol (**2.6**, 0.100 g, 0.581 mmol) was added to a screw cap vial and dissolved in CH_2Cl_2 (1 mL). l-Borneol (1,7,7-trimethyl bicyclo[2.2.1]heptan-2-ol, 0.089 g, 0.576 mmol) was added followed by the addition of $FcPF_6$ (0.010 g, 0.030 mmol). The vial was heated to 45 °C for 120 minutes. The solvent was removed, and the residue was chromatographed on a neutral alumina oxide (Aluminar®) column (2.5 × 30 cm, 9:1 v/v hexanes/EtOAc) to give the product as an orange-colored oil (**2.19**, 0.063 g, 0.204 mmol, 35 %). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.53 -7.50 (m, 2H, aromatic), 7.28 – 7.16 (m, 3H, aromatic), 6.50 (t, J_{HH} = 7 Hz, 1H, =CH), 4.07 (s, 0.4H, ferrocene), 3.55 – 3.42 (m, 3H), 3.27 (s, 1H, ≡CH), 2.68 (q, J_{HH} = 7 Hz, 2H), 2.05 – 1.89 (m, 2H), 1.62 – 1.53 (m, 2H), 1.19 – 1.11 (m, 2H), 0.94 (dd, J_{HH} = 13 Hz, J_{HH} = 3 Hz, 1H), 0.80 (s, 3H), 0.76 (s, 6H) ppm; $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$): δ = 137.7 (s, =C), 137.2 (s, aromatic), 128.4 (s, aromatic), 127.7 (s, aromatic), 125.9 (s, aromatic), 123.6 (s, =C), 84.7 (s, C≡CH), 83.3 (s, OCH), 80.9 (s, C≡CH), 68.9 (s, CH_2O), 68.0 (trace amount ferrocene), 49.3 (s, CH), 47.8 (s, CH), 45.0 (s, CH), 36.4 (s,

CH), 32.3 (s, CH), 28.4 (s, CH), 26.7 (s, CH), 19.9 (s, CH_3), 18.9 (s, CH_3), 14.1 (s, CH_3) ppm; IR (ATR, neat): $\tilde{\nu}$ = 3303 (m), 3056 (w), 3024 (w), 2945 (s), 2869 (s) cm^{-1}; HRMS (APPI): *m/z* calcd. For $C_{22}H_{29}O$: 309.2218 $[M + H]^+$, found 309.2210.

2.5.11 (6-(Cyclopentyloxy) hex-3-en-1-yn-3-yl) benzene (2.20)

1-Cyclopropyl-1-phenylprop-2-yn-1-ol (**2.6**, 0.103 g, 0.598 mmol) was added to a 5-mL screw cap vial and dissolved in CH_2Cl_2 (1 mL). Cyclopentanol (0.050 g, 0.581 mmol) was added followed by the addition of HBF4 (ca 5.0 µL of a diethyl ether complex). The vial was then heated at 40 °C for 1 hour and the solvent was removed. The residue was chromatographed on a neutral alumina oxide (Aluminar®) column (2.5 × 30 cm, 9:1 v/v hexanes/EtOAc) to give the product as an orange oil (**2.20**, 0.065 g, 0.270 mmol, 45 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 – 7.65 (m, 2H, aromatic), 7.43 – 7.31 (m, 3H, aromatic), 6.62 (t, 1H, J_{HH} = 7 Hz, C=CH), 4.02 – 3.97 (m, 1H, OCH), 3.60 (t, 2H, J_{HH} = 7 Hz, O CH_2), 3.42 (s, 1H, C≡CH), 2.84 (q, 2H, J_{HH} = 7 Hz, O CH_2 CH_2), 1.84 – 1.50 (m, 8H, 4 CH_2) ppm; $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$): δ = 137.6 (s, =C), 136.7 (s, aromatic), 128.4 (s, aromatic), 127.7 (s, aromatic), 125.9 (s, aromatic), 123.9 (s, =C), 83.4 (s, HC≡C), 81.4 (s, OCH), 80.8 (s, HC≡C), 67.5 (s, CH_2O), 32.4 (s, CH_2), 32.2 (s, CH_2), 23.6 (s, CH_2) ppm. ESI-MS *m/z* (%): 239 (10) $[M – H]^+$, 141 (100) $[C_6H_{11}O]^+$, 128 (70) $[M – C_7H_{12}O]^+$, 114 (75) $[M – C_8H_{14}O]^+$, 69 (50) $[C_5H_9]^+$.

2.5.12 (1-Cyclobutyl-1-ethoxyprop-2-yn-1-yl) benzene (2.21)

In a screw-cap pressure vial, 1-cyclobutyl-2-yn-ol (**2.7**, 0.100 g, 0.537 mmol) was dissolved in CH_2Cl_2 (1 mL) and ethanol (0.025 g, 0.543 mmol) and $[FcB(OH)_2]$ SbF_6 (0.008 g, 0.017 mmol) were added. Then the vial was heated at 45 °C overnight. The product was filtered through a short pad of silica gel using CH_2Cl_2 (2 – 4 mL). The product (1-cyclobutyl-1-ethoxyprop-2-yn-1-yl) benzene was obtained by column

chromatography on alumina (2.5 × 30 cm, 9:1 v/v hexanes/EtOAc) as a yellow-colored oil (**2.21**, 0.050 g, 0.233 mmol, 43 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 – 7.43 (m, 2H, aromatic), 7.27 – 7.16 (m, 3H, aromatic), 3.58 – 3.53 (dd, 1H, J_{HH} = 7 Hz, J_{HH} = 2.1 Hz, OCHH′), 3.12 – 3.07 (dd, 1H, J_{HH} = 7.2 Hz, J_{HH} = 1.8 Hz, OCHH′), 2.64 (s, 1H, C≡CH), 2.60 (q, J_{HH} = 8 Hz, CH), 2.19 (quint, J_{HH} = 10.5 Hz, 1H, CH), 1.89 – 1.86 (m, 2H, 2CH), 1.65 – 1.60 (m, 3H, 3CH), 1.11 (t, J_{HH} = 7.0 Hz, 3H, CH_3) ppm; ^{13}C{^{1}H} (75 MHz, $CDCl_3$): δ = 140.8 (s, aromatic), 128.0 (s, aromatic), 127.6 (s, aromatic), 126.3 (s, aromatic), 82.2 (s, C≡C), 81.8 (s, C≡C), 76.5 (s, CC≡CH), 47.1 (s, CH), 23.8 (s, CH_2), 23.5 (s, CH_2), 16.2 (s, CH_2), 15.4 (s, CH_3) ppm; IR (ATR, neat): $\tilde{\nu}$ = 3303 (m), 3056 (w), 3024 (w), 2945 (s), 2869 (s) cm^{-1}; ESI-MS *m/z* (%): 214 (5) $[M]^+$, 159 (20) $[M - C_4H_7]^+$, 115 (50) $[M + H–C_4H_7–O\ CH_2\ CH_3]^+$, 77 (40) $[Ph]^+$, 53 (100) $[C_4H_5]^+$; HRMS (APPI): *m/z* calcd. For $C_{15}H_{18}O$, 214.1357 $[M]^+$, found 214.1360; elemental analysis calcd. (%) for $C_{15}H_{18}O$: C 84.07, H 8.47; found C 83.88, H 8.28.

2.5.13 (1-Cyclobutyl-1-butoxyprop-2-yn-1-yl) benzene (2.22)

In a screw-cap pressure vial, 1-cyclobutyl-2-yn-ol (**2.7**, 0.100 g, 0.537 mmol) was dissolved in CH_2Cl_2 (1 mL) and *n*-butanol (0.040 g, 0.540 mmol) and $FcPF_6$ (0.010 g, 0.030 mmol) were added. Then the vial was heated at 45 °C for overnight. The product was filtered through a short pad of silica gel using CH_2Cl_2 (2 – 4 mL). The product (1-cyclobutyl-1-butoxyprop-2-yn-1-yl) benzene was obtained by column chromatography on alumina (2.5 × 30 cm, 9:1 v/v hexanes/EtOAc) as an orange-colored oil (**2.22**, 0.052 g, 0.214 mmol, 40 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 – 7.42 (m, 2H, aromatic), 7.27 – 7.16 (m, 3H, aromatic), 3.50 (dd, 1H, J_{HH} = 6 Hz, J_{HH} = 2 Hz, OCHH′), 3.05 (dd, 1H, J_{HH} = 6 Hz, J_{HH} = 2 Hz, OCHH′), 2.64 (s, 1H, C≡CH), 2.60 (quin, 1H, J_{HH} = 8 Hz, CH), 2.20 (dquin, J_{HH} = 10 Hz, J_{HH} = 1 Hz, 1H, CH), 1.91 (quin, 1H, J_{HH} = 9 Hz, CH), 1.85 – 1.79 (m, 1H, CH), 1.66 – 1.57 (m, 2H, CH_2), 1.53 – 1.45 (m, 3H, CH + CH_2),

1.30 (quin, J_{HH} = 7 Hz, 2H, CH_2), 0.817 (t, J_{HH} = 7 Hz, 3H, CH_3) ppm; $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$): δ = 140.8 (s, aromatic), 128.0 (s, aromatic), 127.5 (s, aromatic), 126.4 (s, aromatic), 82.3 (s, C≡), 81.5 (s, C≡), 76.5 (s, CC≡CH), 64.6 (s, O CH_2), 47.1 (s, OCH), 32.1 (s, CH_2), 23.7 (s, CH_2), 23.5 (s, CH_2), 19.5 (s, CH_2), 16.9 (s, CH_2), 14.4 (s, CH_3) ppm; ESI-MS *m/z* (%): 241 (5) $[M - H]^+$, 186 (50) $[M - C_4H_9]^+$, 115 (50) $[M + H–C_4H_9O–C_4H_7]^+$, 55 (50) $[C_4H_7]^+$; IR (ATR, neat): $\tilde{\nu}$ = 3302 (m), 3059 (w), 2956 (s), 2932 (s), 2866 (s) cm^{-1}.

2.5.14 (1-Cyclobutyl-1-hexoxyprop-2-yn-1-yl) benzene (2.23)

In a screw-cap pressure vial, 1-cyclobutyl-2-yn-ol (**2.7**, 0.100 g, 0.537 mmol) was dissolved in CH_2Cl_2 (1 mL) and 1-hexanol (0.055 g, 0.539 mmol) and $[FcB(OH)_2]$ SbF_6 (0.008 g, 0.017 mmol) were added. Then the vial was heated at 45 °C overnight. The product was filtered through a short pad of silica gel using CH_2Cl_2 (2 – 4 mL). The product (1-cyclobutyl-1-hexoxyprop-2-yn-1-yl) benzene was obtained by column chromatography on alumina (2.5 × 30 cm, 9:1 v/v hexanes/EtOAc) as a pale-yellow colored oil (**2.23**, 0.063 g, 0.233 mmol, 43 %). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.46 – 7.42 (m, 2H, aromatic), 7.27 – 7.16 (m, 3H, aromatic), 3.48 (dd, 1H, J_{HH} = 6 Hz, J_{HH} = 2 Hz, OCHH′), 3.04 (dd, 1H, J_{HH} = 6.3 Hz, J_{HH} = 2.4 Hz, OCHH′), 2.63 (s, 1H, C≡CH), 2.60 (quin, 1H, J_{HH} = 8 Hz, CH), 2.20 (dquin, J_{HH} = 10 Hz, J_{HH} = 2 Hz, 1H, CH), 1.91 (quin, 1H, J_{HH} = 9 Hz, CH), 1.84 – 1.76 (m, 1H, CH), 1.68 – 1.56 (m, 2H, CH_2), 1.53 – 1.45 (m, 3H, CH + CH_2), 1.27 – 1.16 (m, 6H, 3 CH_2), 0.80 (t, J_{HH} = 8 Hz, 3H, CH_3) ppm; $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$): δ = 140.9 (s, aromatic), 128.0 (s, aromatic), 127.5 (s, aromatic), 126.4 (s, aromatic), 82.4 (s, C≡), 81.5 (s, C≡), 76.5 (s, CC≡CH), 65.0 (s, O CH_2), 47.1 (s, OCH), 31.8 (s, CH_2), 30.0 (s, CH_2), 25.9 (s, CH_2), 23.7 (s, CH_2), 23.5 (s, CH_2), 22.7 (s, CH_2), 16.9 (s, CH_2), 14.1 (s, CH_3) ppm; IR (ATR, neat): $\tilde{\nu}$

= 3303 (m), 3059 (w), 2929 (s), 2859 (m) cm^{-1}; elemental analysis calcd. (%) for $C_{19}H_{26}O$: C 84.39, H 9.69; found C 84.15, H 9.47.

2.5.15 (1-(Benzyloxy)-1-cyclobutylprop-2-yn-1-yl) benzene (2.24)

1-Cyclobutyl-phenylprop-2-yn-ol (**2.7**, 0.100 g, 0.537 mmol) was added to a screw cap vial and dissolved in CH_2Cl_2 (1 mL). Benzyl alcohol (0.058 g, 0.536 mmol) was added followed by [FcB$(OH)_2$] SbF_6 (0.008 g, 0.0017 mmol). The vial was then sealed and heated at 45 °C for 20 hours. The solvent was removed, and the residue was chromatographed on a neutral alumina oxide (Aluminar®) column (2.5 × 30 cm, 9:1 v/v hexanes/EtOAc) to give the product as a yellow oil (**2.24**, 0.082 g, 0.297 mmol, 55 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 – 7.50 (m, 2H, aromatic), 7.29 – 7.17 (m, 8H, aromatic), 4.60 (d, J_{HH} = 11 Hz, 1H, OCHH′), 4.11 (d, J_{HH} = 11 Hz, 1H, OCHH′), 2.72 – 2.67 (m, 2H, ≡CH, CH), 2.27 – 2.24 (m, 1H, CH), 2.01 – 1.83 (m, 2H, 2CH), 1.69 – 1.56 (m, 3H, 3CH) ppm; ^{13}C{^{1}H} (75 MHz, $CDCl_3$): δ = 140.4 (s, aromatic), 139.0 (s, aromatic), 128.3 (s, aromatic), 128.2 (s, aromatic), 127.9 (s, aromatic), 127.6 (s, aromatic), 127.4 (s, aromatic), 126.5 (s, aromatic), 82.2 (s, C≡), 82.0 (s, ≡C), 77.3 (s, CC≡CH), 67.0 (s, O CH_2), 47.2 (s, CH), 23.9 (s, CH_2), 23.7 (s, CH_2), 17.0 (s, CH_2) ppm; IR (ATR, neat): $\tilde{\nu}$ = 3286 (m), 3059 (w), 3027 (w), 2975 (m), 2937 (m), 2960 (m) cm^{-1}; elemental analysis calcd. (%) for $C_{20}H_{20}O$: C 86.92, H 7.29; found C 87.16, H 7.26 %.

2.5.16 I-(1-Cyclobutyl-1-(hex-3-en-1-yloxy) prop-2-yn-1-yl) benzene (2.25)

In a vial, 1-phenyl-1-cyclobutyl-2-yne-1-ol (**2.7**, 0.100 g, 0.537 mmol) was dissolved in CH_2Cl_2 (1 mL) and trans-5-decanol (0.082 g, 0.525 mmol) and [FcB$(OH)_2$] SbF_6 (0.008 g, 0.017 mmol) were added. The sealed vial was heated at 45 °C overnight. The product was filtered through a short pad of silica gel using CH_2Cl_2 (2 – 4 mL). The

product 6-benzoxy-3-phenyl-3-en-1-yne was obtained by neutral Aluminar® column chromatography (2 × 30 cm, 9:1 v/v hexanes/EtOAc) as a yellow oil (**2.25**, 0.074 g, 0.228 mmol, 42 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 – 7.57 (m, 2H, aromatic), 7.44 – 7.31 (m, 3H, aromatic), 5.45 (br s, 2H, CH=CH), 3.63 (q, J_{HH} = 7 Hz, 1H, OCHH′), 3.19 (q, J_{HH} = 7 Hz, 1H, OCHH′), 2.79 (s, 1H, ≡CH), 2.76 (q, J_{HH} = 8 Hz, 1H), 2.34 (quin, J_{HH} = 7 Hz, 1H), 2.11 – 2.04 (m, 6H, 3 CH_2), 1.82 – 1.60 (m, 5H), 1.51 – 1.34 (m, 6H, 3 CH_2), 0.95 (t, J_{HH} = 6 Hz, 3H, CH_3) ppm; ^{13}C{^{1}H} (75 MHz, $CDCl_3$): δ = 140.8 (s, C=C), 130.7 (s, aromatic), 130.1 (s, aromatic), 128.0 (s, aromatic), 127.6 (s, aromatic), 126.4 (s, C=C), 82.3 (s, C≡), 81.6 (s, C≡), 76.6 (s, CC≡CH), 64.8 (s, OCH_2), 47.2 (s, CH), 32.5 (s, CH_2), 32.4 (s, CH_2), 31.9 (s, CH_2), 29.4 (s, CH_2), 26.2 (s, CH_2), 23.8 (s, CH_2), 23.5 (s, CH_2), 22.3 (s, CH_2), 16.9 (s, CH_2), 14.1 (s, CH_3) ppm; IR (ATR, neat): $\tilde{\nu}$ = 3302 (w), 2926 (s), 2858 (m) cm^{-1}; elemental analysis calcd. (%) for $C_{23}H_{32}O$: C 85.13, H 9.94; found C 85.12, H 9.88.

2.5.17 2-(1-Cyclopropyl-1-methoxyprop-2-yn-1-yl) thiophene (2.26)

In a screw-cap pressure vial, 1-thienyl-1-cyclopropyl-2-yne-1-ol (**2.8**, 0.107 g, 0.600 mmol) was dissolved in CH_2Cl_2 (2 mL) and methanol (0.020 g, 0.625 mmol) and $FcPF_6$ (0.010 g, 0.030 mmol) were added. Then the vial was heated at 45 °C. After 45 minutes, the product was filtered through a short pad of silica gel using CH_2Cl_2 (2–4 mL). The product was obtained by column chromatography on alumina (2.5 × 30 cm, 9:1 v/v hexanes/EtOAc) as an orange oil (**2.26**, 0.065 g, 0.338 mmol, 56 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21 (d, J_{HH} = 6 Hz, 1H), 7.13 (d, J_{HH} = 4 Hz, 1H), 6.90 (t, J_{HH} = 5 Hz, 1H), 3.24 (s, 3H, OCH_3), 2.55 (s, 1H, ≡CH), 1.41–1.36 (m, 1H, CH), 0.83–0.78 (m, 1H, CH), 0.59–0.43 (m, 3H, 3CH) ppm; ^{13}C{^{1}H} (75 MHz, $CDCl_3$): δ = 144.7 (s, aromatic), 124.1 (s, aromatic), 123.8 (s, aromatic), 123.5 (s, aromatic), 77.8 (s, ≡C), 76.0 (s, C≡), 73.6 (s, CC≡CH), 50.4 (s, O CH_3), 20.6 (s, CH), 1.4 (s, CH_2), 0.0 (s, CH_2)

ppm; IR (ATR, neat): $\tilde{\nu}$ = 3281 (w), 2933 (w), 2823 (m) cm^{-1}; elemental analysis calcd. (%) for $C_{11}H_{12}OS$: C 68.71, H 6.29; found C 68.55, H 6.08.

2.5.18 2-(1-Cyclopropyl-1-ethoxyprop-2-yn-1-yl) thiophene (2.27)

In a screw-capped pressure vial, 1-thienyl-1-cyclopropyl-2-yne-1-ol (**2.8**, 0.140 g, 0.785 mmol) was dissolved in CH_2Cl_2 (2 mL) and ethanol (0.036 g, 0.781 mmol) and $FcPF_6$ (0.010 g, 0.030 mmol) were added. Then the vial was sealed and heated at 45 °C. After 60 minutes, the product was filtered through a short pad of silica gel using CH_2Cl_2 (2–4 mL). The product was obtained by column chromatography using alumina (2.5 × 30 cm, 9:1 v/v hexanes/EtOAc) as an orange oil (**2.27**, 0.069 g, 0.334 mmol, 42 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 (d, J_{HH} = 5 Hz, 1H), 7.27 (d, J_{HH} = 4 Hz, 1H), 7.03 (t, J_{HH} = 4 Hz, 1H), 3.78 (q, J_{HH} = 8 Hz, 1H, OCHH′), 3.44 (q, J_{HH} = 7 Hz, 1H, OCHH′), 2.67 (s, ≡CH, 1H), 1.53–1.50 (m, 1H, CH), 1.27 (t, J_{HH} = 9 Hz, 3H, CH_3), 0.96 – 0.93 (m, 1H, CH), 0.71 – 0.59 (m, 3H, CH_2 + CH) ppm; $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$): δ = 147.8 (s, aromatic), 126.2 (s, aromatic), 125.5 (s, aromatic), 125.4 (s, aromatic), 80.5 (s, ≡C), 75.2 (s, ≡C), 60.5 (s, O CH_2), 23.1 (s, CH), 15.4 (s, CH_3), 3.6 (s, CH_2), 2.2 (s, CH_2) ppm; IR (ATR, neat): $\tilde{\nu}$ = 3286 (m), 3007 (w), 2972 (m) cm^{-1}; ESI-MS *m/z* (%): 205 (10) $[M - H]^+$, 178 (30) $[M + H– CH_3CH_2]^+$, 165 (50) $[M – C_3H_5]^+$, 161 (30) $[M – CH_3\ CH_2O]^+$, 53 (100) $[C_4H_5]^+$, 45 (80) $[CH_3\ CH_2O]^+$.

2.5.19 1-Cyclopropyl-1-(thiophen-2-yl) prop-2-yn-1-ol (2.28)

1-cylopropyl-1-(thiophen-2-yl) prop-2-yn-1-ol (**2.8**, 0.100 g, 0.561 mmol) was added to a screw cap vial and dissolved in CH_2Cl_2 (1 mL). *n*-Butanol (0.042 g, 0.568 mmol) was added followed by the addition of $[FcB(OH)_2]\ SbF_6$ (0.008 g, 0.017 mmol). Then the vial was kept at room temperature overnight. The reaction mixture was filtered through a short pad of silica gel using CH_2Cl_2 (2 – 4 mL). The mixture was

chromatographed on a neutral alumina oxide (Aluminar®) column (2.5 × 30 cm, 9:1 v/v hexanes/EtOAc) to give the product as a pale-yellow oil (**2.28**, 0.058 g, 0.247 mmol, 44 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19 (dd, J_{HH} = 5 Hz, J_{HH} = 1 Hz, 1H, aromatic), 7.12 (dd, J_{HH} = 4 Hz, J_{HH} = 1 Hz, 1H, aromatic), 6.88 (dd, J_{HH} = 5 Hz, J_{HH} = 4 Hz, 1H, aromatic), 4.09 (s, trace amount ferrocene), 3.57 (dt, J_{HH} = 6 Hz, J_{HH} = 2 Hz, 1H), 3.22 (dt, J_{HH} = 6 Hz, J_{HH} = 2 Hz, 1H), 2.52 (s, 1H, ≡CH), 1.52 – 1.18 (m, 5H, CH + 2 CH_2), 0.80 (t, J_{HH} = 7 Hz, 4H, CH_3 + CH), 0.60 – 0.36 (m, 3H, CH + CH_2) ppm; $^{13}C\{^{1}H\}$ (75 MHz, $CDCl_3$): δ = 147.8 (s, aromatic), 126.0 (s, aromatic), 125.4 (s, aromatic), 125.3 (s, aromatic), 80.8 (s, ≡CH), 76.9 (s, C≡), 75.0 (s, CC≡CH), 67.9 (s, ferrocene), 64.5 (s, CH_2O), 31.8 (s, CH), 23.1 (s, CH), 19.3 (s, CH), 13.9 (s, CH), 3.4 (s, CH), 2.1 (s, CH) ppm; HRMS (APPI): *m/z* calcd. For $C_{14}H_{18}OS$: 234.1078 $[M]^+$, found 234.1072. IR (ATR, neat): $\tilde{\nu}$ = 3287(m), 3081 (w), 3003 (w), 2955 (m), 2929 (m), 2868 (m) cm^{-1}; elemental analysis calcd. (%) for $C_{14}H_{18}OS$: C 71.75, H 7.74; found C 71.61, H 7.53.

2.5.20 2-(1-Cyclopropyl-1-(hexyloxy) prop-2-yn-1-yl) thiophene (2.29)

1-cylopropyl-1-(thiophen-2-yl) prop-2-yn-1-ol (**2.8**, 0.100 g, 0.561 mmol) was added to a screw-cap pressure vial and dissolved in CH_2Cl_2 (2 mL). 1-Hexanol (0.058 g, 0.568 mmol) was added followed by the addition of $FcPF_6$ (0.012 g, 0.037 mmol). The vial was then heated to 45 °C for 2 hours. The reaction mixture was filtered through a short pad of silica gel using CH_2Cl_2 (2–4 mL). The product was obtained by column chromatography on a neutral alumina oxide (Aluminar®) column (2.5 × 30 cm, 9:1 v/v hexanes/EtOAc) as an orange oil (**2.29**, 0.058 g, 0.221 mmol, 39 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20 (dd, J_{HH} = 5 Hz, J_{HH} = 1 Hz, 1H, aromatic), 7.12 (dd, J_{HH} = 4 Hz, J_{HH} = 1 Hz, 1H, aromatic), 6.88 (dd, J_{HH} = 4 Hz, J_{HH} = 4 Hz, 1H, aromatic), 3.56 (dt, J_{HH} = 7 Hz, J_{HH} = 10 Hz, 1H, OCHH′), 3.22 (dt, J_{HH} = 10 Hz, J_{HH} = 7 Hz, 1H,

OCHH′), 2.53 (s, ≡CH, 1H), 1.56 – 1.42 (m, 2H, CH_2), 1.42 – 1.38 (m, 1H, CH), 1.30 – 1.12 (m, 6H, 3 CH_2), 0.80 (t, J_{HH} = 7, 4H, CH_3 + CH), 0.60 – 0.37 (m, 3H, CH + CH_2) ppm; $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$): δ = 147.8 (s, aromatic), 126.0 (s, aromatic), 125.4 (s, aromatic), 125.3 (s, aromatic), 80.7 (s, ≡C), 76.9 (s, CC≡CH, 75.0 (s, C≡), 67.9 (trace ferrocene), 64.8 (s, O CH_2), 31.6 (s, CH_2), 29.7 (s, CH_2), 25.8 (s, CH_2), 23.1 (s, CH_2), 22.6 (s, CH_2), 14.1 (s, CH_3), 3.5 (s, CH_2), 2.1 (s, CH_2) ppm; IR (ATR, neat): $\tilde{\nu}$ = 3300 (m), 3085 (w), 3008 (w), 2927 (s), 2857 (s), 2108 (w), 2070 (w), 1944 (w) cm^{-1}; ESI-MS *m/z* (%): 261 (5) $[M - H]^+$, 220 (70) $[M - C_6H_{13}]^+$, 137 (30) $[M - C_4H_3S - C_3H_5]^+$, 43 (100) $[C_3H_7]^+$, 41 (95) $[C_3H_5]^+$; HRMS (APPI): *m/z* calcd. For $C_{16}H_{22}OS$: 262.1391 $[M]^+$, found 262.1378.

2.5.21 2-(1-(Benzyloxy)-1-cyclopropylprop-2-yn-1-yl) thiophene (2.30)

1-Cyclopropyl-1-(thiophen-2-yl)2-yn-1-ol (**2.8**, 0.100 g, 0.561 mmol) was added to a screw-cap pressure vial and dissolved in CH_2Cl_2 (1 mL). Benzyl alcohol (0.060 g, 0.556 mmol) was added followed by $FcPF_6$ (0.010 g, 0.030 mmol). The vial was then sealed and kept at room temperature overnight. The solvent was removed, and the residue was chromatographed on a neutral alumina oxide (Aluminar®) column (2.5 × 30 cm, 9:1 v/v hexanes/EtOAc) to give the product as yellow oil (**2.30**, 0.04 g, 0.15 mmol, 27 %). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.28 – 7.16 (m, 7H, aromatic), 6.90 (dd, J_{HH} = 4 Hz, J_{HH} = 5 Hz,1H), 4.63 (d, 1H, J_{HH} = 11 Hz, OCHH′), 4.30 (d, 1H, J_{HH} = 11 Hz, OCHH′), 4.08 (s, ferrocene), 2.61 (s, 1H, C≡CH), 1.51 – 1.42 (m, 1H, CH), 0.91 – 0.85 (m, 1H, CH), 0.60 – 0.44 (m, 3H, CH + CH_2) ppm; $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$): δ = 147.3 (s, aromatic), 138.5 (s, aromatic), 128.3 (s, aromatic), 127.8 (s, aromatic), 127.4 (s, aromatic), 126.2 (s, aromatic), 125.9 (s, aromatic), 125.7 (s, aromatic), 80.6 (s, ≡C), 75.7 (s, ≡C), 68.0 (s, CH_2O), 67.0 (s, trace ferrocene), 23.3 (s, CH), 3.7 (s, CH_2), 2.4 (s,

CH_2) ppm; IR (ATR, neat): $\tilde{\nu}$ = 3283 (m), 3007 (m), 2902 (m), 2863 (m) cm^{-1}; ESI-MS *m/z* (%): 161 (30) $[M - OCH_2Ph]^+$, 91 (100) $[CH_2Ph]^+$, 77 (30) $[Ph]^+$.

2.5.22 (1-Butoxy-1-cyclopropylprop-2-yn-1-yl) benzene (2.10 a)

Cyclopropyl-phenylprop-2-yn-ol (**2.6**, 0.124 g, 0.717 mmol) was added to a 5-mL screw cap vial and dissolved in CH_2Cl_2 (1 mL). *n*-Butanol (**2.9**, 0.064 g, 0.863 mmol) was added followed by the addition of $FcPF_6$ (0.010 g, 0.031 mmol). The vial was then sealed and heated at 40 °C for 15 minutes. The sample was filtered through a short pad of silica and the solvent was removed. The residue was chromatographed on a neutral alumina oxide (Aluminar®) column (2.5 × 30 cm, 90:10 v/v hexanes/EtOAc) to give the product as an orange oil in about 95 % spectroscopic purity (**2.10 a**, 0.037 g, 0.162 mmol, 23 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54 – 7.51 (m, 2H, aromatic), 7.31 – 7.16 (m, 3H, aromatic), 3.54 (dt, J_{HH} = 9 Hz, J_{HH} = 6 Hz, 1H, OCHH′), 3.13 (dt, J_{HH} = 9 Hz, J_{HH} = 6 Hz, 1H, OCHH′), 2.53 (s, 1H, C≡CH), 1.52 -1.45 (m, 2H, CH_2), 1.35–1.20 (m, 3H, CH_2 + CH), 0.81 (t, J_{HH} = 8 Hz, 3H, CH_3), 0.77 – 0.70 (m, 1H, CH), 0.49 – 0.30 (m, 3H, CH_3) ppm; $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$): δ = 142.5 (s, aromatic), 128.0 (s, aromatic), 127.6 (s, aromatic), 126.1 (s, aromatic), 81.0 (s, CC≡), 80.2 (s, C≡CH), 76.0 (s, C≡CH), 64.5 (s, OCH $_2$), 32.0 (s, CH_2), 22.8 (s, CH_2), 19.4 (s, CH), 13.9 (s, CH_3), 3.3 (s, CH_2), 1.8 (s, CH_2) ppm.

2.5.23 Ring opening of 2.10 by HBF4 to obtain ene-yne (2.10)

Dissolve **2.10 a** in $CDCl_3$ add a drop of HBF4 (as diethyl ether complex). ^{1}H and $^{13}C\{^1H\}$ NMR spectra were recorded. The spectra data of **2.10** matched with the **2.13** from Table 2. Diethyl ether peak was noticed in the NMR. ^{1}H NMR (δ, $CDCl_3$): 7.53 – 7.51 (m, 2H, aromatic), 7.28 – 7.16 (m, 3H, aromatic), 6.48 (t, 1H, J_{HH} = 7 Hz, =CH), 3.49 (t, J_{HH} = 7 Hz, 2H, O CH_2), 3.40 (q, J_{HH} = 7Hz, diethyl ether), 3.38 (t, 2H, J_{HH} =

7 Hz, OCH_2), 3.27 (s, 1H, ≡CH), 2.72 (q, J_{HH} = 7 Hz, 2H, CH_2), 1.54 – 1.34 (m, 2H, CH_2), 1.36 – 1.26 (m, 2H, CH_2), 1.13 (t, J_{HH} = 7 Hz, diethyl ether), 0.85 (t, 3H, J_{HH} = 7 Hz, CH_3) ppm; $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$): δ = 137.6 (s, aromatic), 136.5 (s, = CH_2), 128.4 (s, aromatic), 127.7 (s, aromatic), 126.0 (s, aromatic), 123.9 (s, PhC=), 83.4 (s, C≡CH), 80.7 (s, C≡CH), 70.7 (s, O CH2), 69.5 (s, O CH_2), 65.9 (s, diethyl ether), 31.9 (s, CH_2), 31.8 (s, CH_2), 19.4 (s, CH_2), 15.3 (s, diethyl ether), 14.0 (s, CH_3) ppm.

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CHAPTER 3

O-Glycosylation Reactions with Ferrocenium Salts

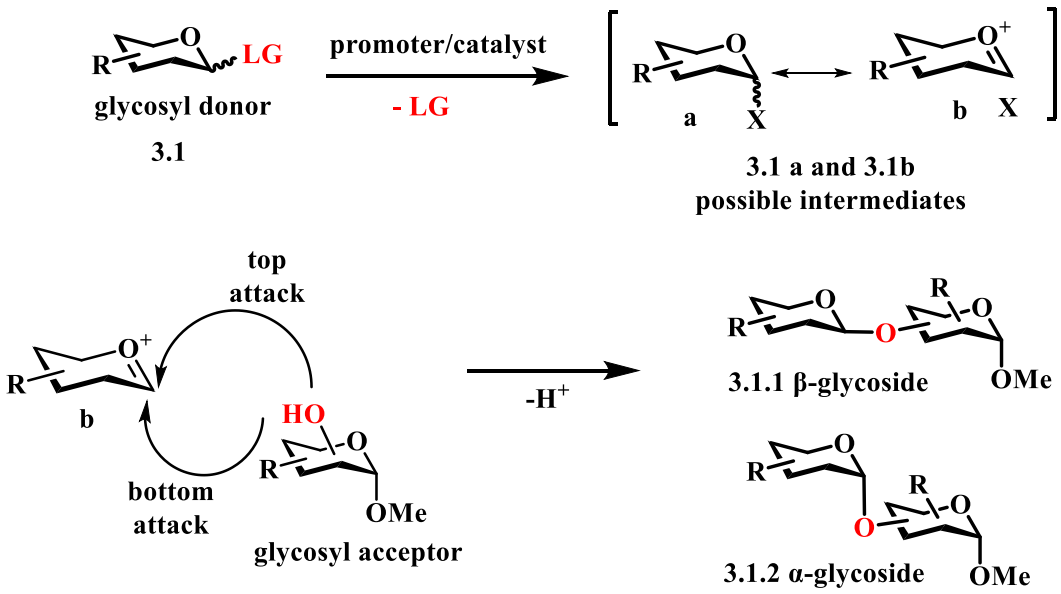
3.1 Introduction

Carbohydrates are the most diverse and abundant bio-macromolecules, and they play a key role in biological activities.[1] These bioactive natural compounds take part in

cellular processes[2] and can regulate tumor cells,[3] metastasis,[4] and immune responses.[5] The comprehensive study of synthetic carbohydrates has become an increasingly interesting study in modern-day science. These applications lead to include carbohydrates in the field of bio-medical research to develop vaccines.[6] Extraction of pure carbohydrate molecules from natural source is difficult, so the synthesis of glycol molecules has become the main approach in research and for pharmaceutical companies.[7]

The key step to synthesize therapeutically active carbohydrates is to form a glycosidic linkage between the glycosyl donor (which consists of a leaving group on the anomeric carbon) and glycosyl acceptor (with the free hydroxyl group). The glycosylation reactions do not work without an activator or catalyst. Depending on the sophisticated nature of the catalyst system or promoter, the additive and the reaction temperature, the new glycosidic bond can be attained in high yields with α or β-selectivity (Scheme 3.1).[8]

Several catalyst systems, including Lewis acids,[9a,9b] Brønsted acids,[9a,9b] and transition metals[9b,9c,9d] were employed in catalytic or stoichiometric amounts to perform glycosylation reactions. Lewis acids such as Au(I) or Ni-(II) based promoters were used to perform glycosylation, however higher temperatures (110 °C) were needed[10a] and the diastereoselectivity was totally depended on the nature of nickel cation[10b]. Some Brønsted acid catalysts require ionic liquids along with protic acids to perform glycosylation reactions.[10c,d,e] Metal based systems are less explored in the literature. To overcome these limitations, we began investigating iron-based catalysts.

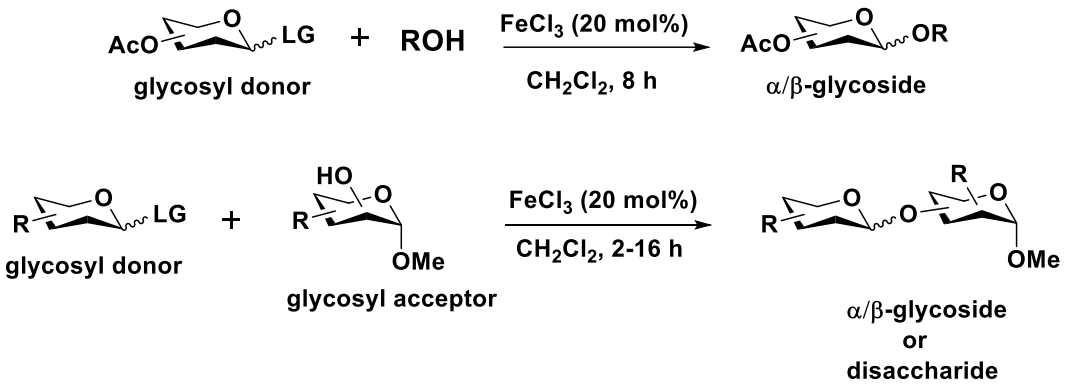


Scheme 3.1 α/β-Glycosidic bond formation mechanism

Iron is abundant in nature and less expensive than other metals. A few iron-based salts such as $FeCl_3$,[11c,d,e] $Fe(CF_3SO_3)$,[12] $FeSO_4$,[13] and $Fe(NO_3)_3$ were successfully utilized as catalysts to obtain glycosides.[14] These non-toxic, iron-based catalyst systems are environmentally friendly.[11a,b] Some of the salts like $Fe(CF_3SO_3)_2$ are not completely soluble in organic solvents, whereas others might generate protons in solution, which might help in carrying out the reaction.[15] According to the literature, $FeCl_3$ can easily activate glycosyl bromides,[16] hemiacetals,[17] acetates,[18] and aryl glycosides when employed as a catalyst or a co-catalyst.[19]

Glycosyl halides are one of the most prominent donors in carbohydrate chemistry.[22] Their preparation may date back to 19th century when G. H. Posner and Michael employed DAST (diethylamino sulfur trifluoride) and oxalyl or thionyl chloride agents for the synthesis of glucosyl fluoride and chloride.[23] Activation of glycosyl chlorides requires stoichiometric amounts of metal catalysts, such as Ag^I and Hg^{II}, which are toxic.[24] They often generate HCl and HBr as side products, so acid scavengers (2,6-di-tert-butylpyridine) were added to capture them.[25]

Recent studies by Jacobsen and Ye, demonstrated that glycosyl chlorides can be easily synthesized and activated without adding any metal complexes based on hazardous metals.[26] Urea or thiourea based catalyst systems resulted in α:β ratio ranging from 1:1 to 1:99, but they require high temperatures (80 °C), additives (K_2CO_3), and long reaction times (12-24 h).[26] In recent years, iron-(III) chloride (which will be abbreviated as $FeCl_3$) has been reported as a catalyst for performing *O*-Glycosylation reactions with glycosyl chlorides, as shown in Scheme 3.1.[11]



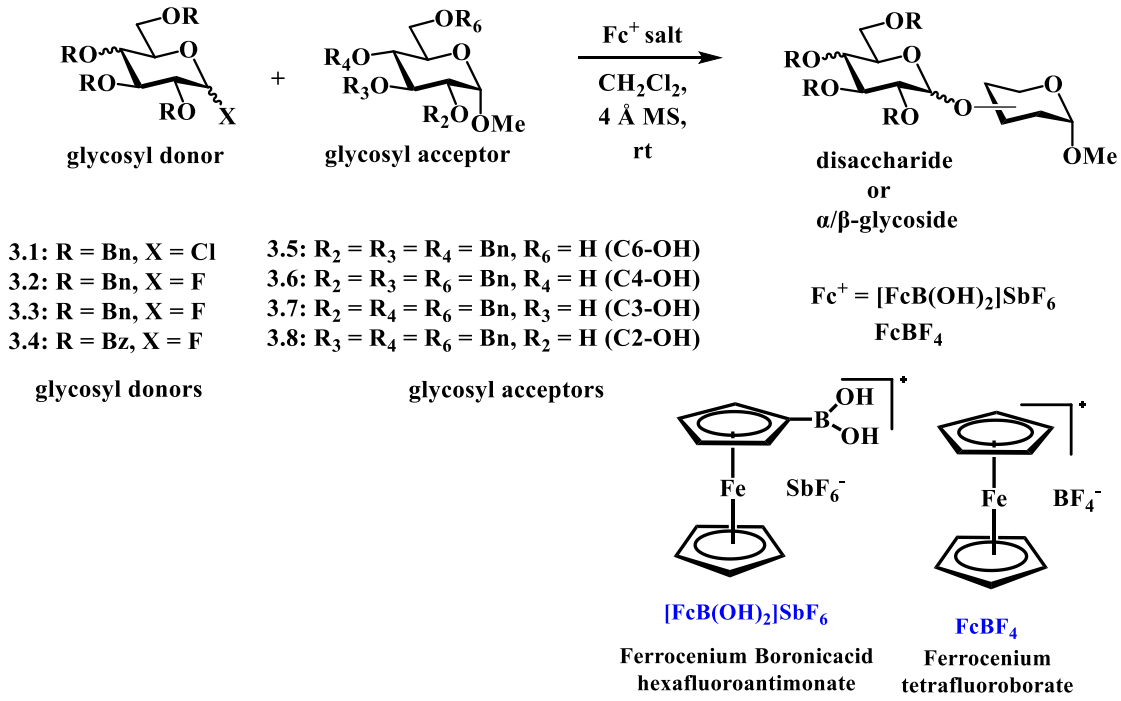
Scheme 3.1 $FeCl_3$ Catalyzed glycosylation reactions (from the literature)

3.2 Objective

Our primary goal was to investigate iron catalysts to perform glycosylation reactions and to identify a catalyst that is soluble in organic solvents without producing H^+ in solution, such as $FeCl_3$. Previously we demonstrated the efficacy of ferrocenium cations in etherification reactions with propargylic alcohols and nucleophiles (primary and secondary alcohols) to obtain ether products.[20] The reactivity of ferrocenium salts can be tuned by introducing substituents on the cyclopentadienyl rings.[21] With our prior knowledge and considering similarities between propargylic substitution reactions and glycosylation reactions, we decided to employ ferrocenium salts as promoters.

3.3 Results and Discussion

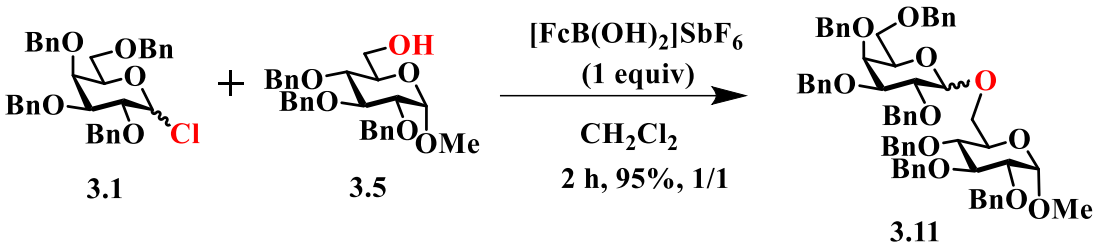
We aim to identify iron-based catalyst systems that can perform title reactions at low temperatures to obtain high yield and good stereoselectivity. We set out to investigate a new strategy using either $[FcB(OH)_2]SbF_6$ (ferrocenium boronic acid hexafluoro antimonate)[27a] or $FcBF_4$ (ferrocenium tetrafluoro borate) as a promoter for the activation of glycosyl halide donors. These ferrocenium-based salts are completely soluble in organic solvents such as CH_2Cl_2. We are introducing ferrocenium-based promoters for the glycosylation reactions for the first time in Scheme 3.2.



Scheme 3.2 Glycosyl donors, acceptors and ferrocenium salts (that were utilized for this study)

For screening reactions, we chose benzylated galactosyl chloride **3.1** as the donor and benzylated glucosyl with a free hydroxyl unit (OH) on the primary carbon C-6 (**3.5**) as the acceptor (Scheme 3.3). We employed an equimolar ratio of freshly synthesized ferrocenium boronic acid hexafluoroantimonate (which will be abbreviated as

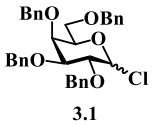
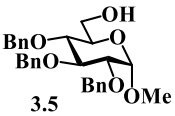
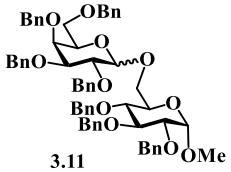
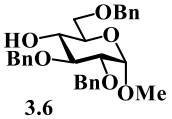
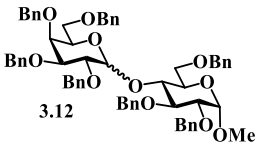
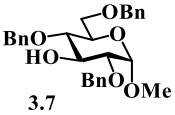
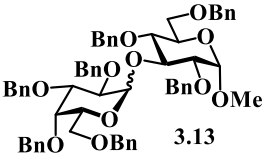
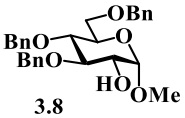
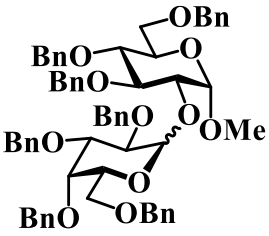
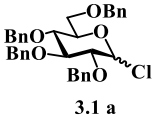
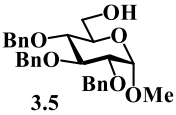
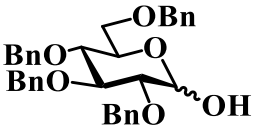
[FcB(OH)$_2$]SbF$_6$) as the promoter in CH_2Cl_2 to obtain **3.11** in 95% yield (Scheme 3.3). This reaction was performed under inert conditions with argon at room temperature, and 4 Å molecular sieves were added. During screening we also tested different ferrocenium salts such as $FcPF_6$, $FcBF_4$, KFcpSbF$_6$ (keto ferrocenophanium hexafluoro antimonate) and glycosyl donors such as glycosyl bromides, fluorides, acetates. Through the screening experiments, we optimized the reaction conditions and decided to utilize 60 mol% of the promoter ([FcB(OH)$_2$]SbF$_6$).



Scheme 3.3 Glycosylation with ferrocenium salt to obtain disaccharide

Glycosylation between freshly synthesized galactosyl chloride **3.1** (2 equiv.) with the most reactive C6-OH (**3.5**, 1 equiv.) gave the corresponding disaccharide **3.11** (Table 3.1, Entry 1) in 86% isolated yield. Decreasing trend of yields ranging from 45 to 64 % were noticed when secondary glycosyl acceptors (**3.6, 3.7** and **3.8**) were utilized. Results, including reaction time, yield and α:β ratios are shown below in Table 3.1. Steric differences between primary and secondary glycosyl acceptors resulted in lower yields for the secondary acceptors.

Table 3.1 Optimized reaction conditions and yields for galactosyl chloride donor (3.1)

Entry [a]	Donor	Acceptor	Product	Promoter	Time, Yield, [b] α/β
1	 3.1	 3.5	 3.11	$[FcB(OH)_2]SbF_6$ 60 mol %	4 h 86% 1/1.1
3	**3.1**	 3.6	 3.12	$[FcB(OH)_2]SbF_6$ 60 mol %	6 h 64% 1.2/1
4	**3.1**	 3.7	 3.13	$[FcB(OH)_2]SbF_6$ 60 mol %	6 h 63% 1.6/1
5	**3.1**	 3.8	 **3.14**	$[FcB(OH)_2]SbF_6$ 60 mol %	6 h 45% 1.2/1
6	 3.1 a	 3.5	 **3.1 b**	$[FcB(OH)_2]SbF_6$ 60 mol %	14 h

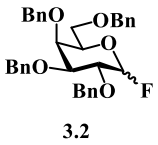
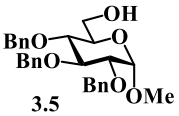
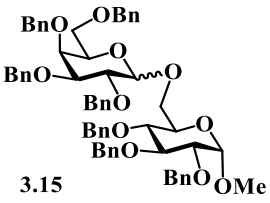
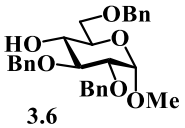
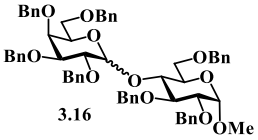
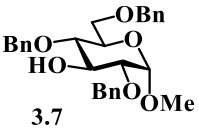
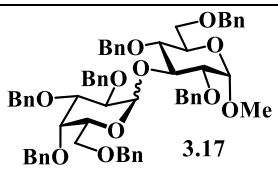
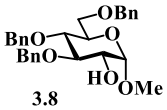
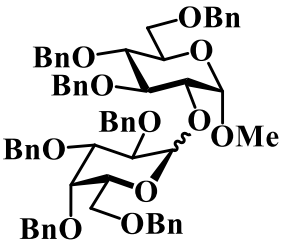
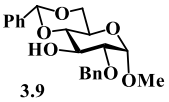
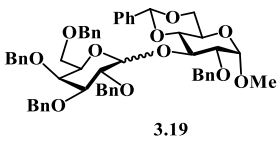
[a] Typical reaction conditions: The galactosyl chloride **3.1** (0.03 mmol, 2 equiv.), glycosyl acceptors (**3.6**, **3.7** and **3.8**, 0.015 mmol, 1 equiv.), 4 Å sieves and the ferrocenium salt in CH_2Cl_2 at room temperature. [b] Isolated yield after column chromatography.

Following the general success of galactosyl chloride acceptor **3.1**, we investigated glucosyl chloride **3.1a** (Table 3.1, Entry 6). Contrary to our hypothesis, glycosylation did not happen. Instead, all the glucosyl chloride donor was hydrolyzed **3.1b** (Table

3.1, Entry 6). Next, we synthesized benzylated (Bn) and benzoylated (Bz) galactosyl bromide donors **3.28a** and **3.28b**. These donors turned out to be unstable and did not give any appreciable amounts of disaccharides.

When the freshly synthesized galactosyl fluoride donor **3.2** was employed as a donor to perform glycosylation with the C6-OH acceptor **3.5**, it provided disaccharide **3.15** in 50% yield within 2 hours. We employed 70 mol% of $FcBF_4$ as the promoter. When the same reaction was performed with secondary acceptors **3.6**, **3.7** and **3.8**, we were able to obtain disaccharides **3.16**-**3.18** (Table 3.2, entries 2-4) in 31 to 42 % yield. We then increased the amount of the ferrocenium salt from 70-100 mol% to investigate the impact on the yield. With increased promoter load, the yield decreased to 42%, and we were only able to isolate the hydrolyzed donor. The reaction with benzylidene protected acceptor **3.9** provided disaccharide **3.19** (Table 3.2, entry 5) in 10% yield when 70 mol% of $FcBF_4$ was utilized. In this case, the yield increased from 10 to 42 % with the increased amount of promoter load (100 mol%).

Table 3.2 Optimized reaction conditions for galactosyl fluoride donor (3.2)

Entry	Donor	Acceptor	Product	Promoter	Time, Yield, α/β
1	 3.2	 3.5	 3.15	$FcBF_4$, 70 mol %	2 h, 50%, 1/1.3
2	**3.2**	 3.6	 3.16	$FcBF_4$, 70 mol %	6 h, 31%, 1/1
3	**3.2**	 3.7	 3.17	$FcBF_4$, 70 mol %	6 h, 34%, 2.3/1
4	**3.2**	 3.8	 3.18	$FcBF_4$, 70 mol %	6 h, 32%, 1.6/1
5	**3.2**	 3.9	 3.19	$FcBF_4$, 70 mol %	12 h, 10%, 1.8/1

[a] Typical reaction conditions: The galactosyl fluoride **3.2** (0.05 mmol), glycosyl acceptors (**3.6**, **3.7, 3.8** and **3.9**, 0.06 mmol), 4 Å sieves and the ferrocenium salt in CH_2Cl_2 at room temperature. [b] Isolated yield after column chromatography.

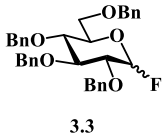
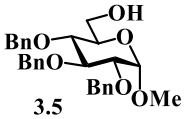
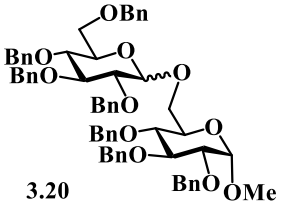
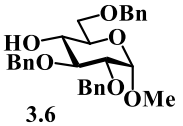
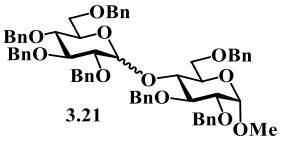
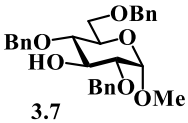
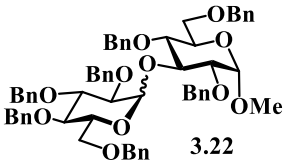
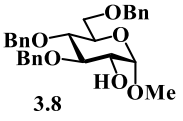
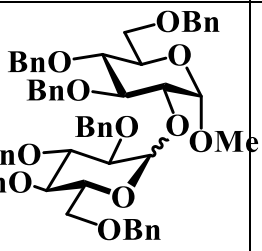
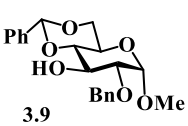
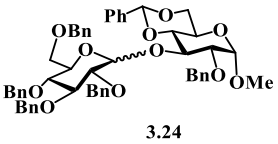
According to the literature, metal catalysts can generate small amounts of Brønsted acids in solution, which can diminish the yield.[27b] To test this hypothesis, we performed a reaction with galactosyl fluoride and C6-OH acceptor in the presence of acid scavenger di-tert-butyl pyridine (DTBP). In the presence of DTBP, the yield decreased

drastically. This experiment would show that the reaction may be Brønsted-acid catalyzed. However, we do not know whether the scavenger just shuts down the catalyst.

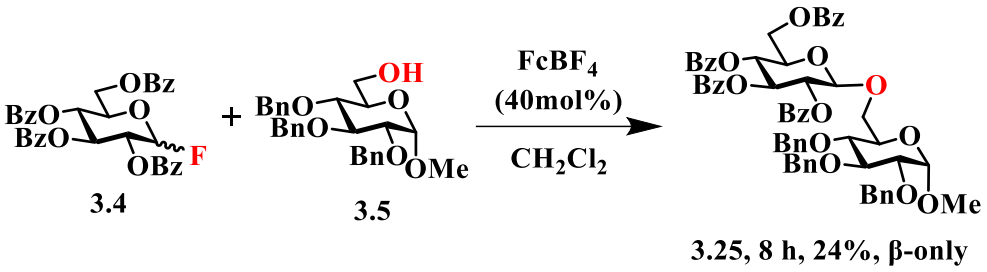
Glycosylation between glucosyl fluoride donor **3.3** and glycosyl acceptors **3.5**, **3.6**, **3.7** and **3.8** utilizing 70 mol% of $FcBF_4$ in CH_2Cl_2 resulted in obtaining disaccharides ranging from 45 to 52 % yield within 4 to 8 hours of reaction time. The results are shown in detail in Table 3.3. The reaction with benzylidene protected C3 acceptor **3.9** took 16 hours and afforded disaccharide **3.24** in a poor yield of 12% yield. When the benzoyl protected glucosyl fluoride donor **3.4** was reacted with the C6 acceptor **3.5** for 8 hours, we were able to obtain disaccharide **3.25** in 24% yield (Scheme 3.4). In this case, only the β-isomer formed.

Finally, we employed sterically hindered secondary alcohol **3.10** (cholesterol) to obtain glycosidic bond with glucosyl and galactosyl fluoride donors **3.3** and **3.2**. This reaction took approximately 8 to 14 hours at room temperature resulting in 55% and 87% yields (Scheme 3.5). All the products reported were isolated using column chromatography techniques and α/β-ratios were determined by NMR techniques. No side products were noticed when performing the reactions. No additives were added.

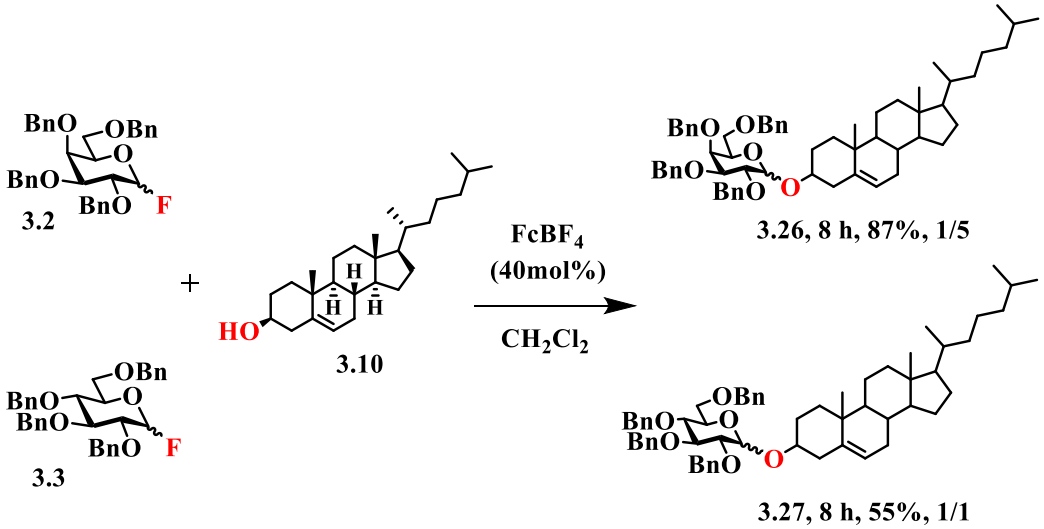
Table 3.3 Optimized reaction conditions for glucosyl fluoride donor (3.3)

Entry [a]	Donor	Acceptor	Product	Promoter	Time, Yield, [b] α/β
1	 3.3	 3.5	 3.20	$FcBF_4$, 70 mol %	4 h, 45%, 1.6/1
2	**3.3**	 3.6	 3.21	$FcBF_4$, 70 mol %	8 h, 52%, 1.5/1
3	**3.3**	 3.7	 3.22	$FcBF_4$, 70 mol %	8 h, 48%, 1/1
4	**3.3**	 3.8	 **3.23**	$FcBF_4$, 70 mol %	8 h, 46%, 1/1
5	**3.3**	 3.9	 3.24	$FcBF_4$, 70 mol %	16 h, 12%, 1/1

[a] Typical reaction conditions: The galactosyl fluoride **3.2** (0.05 mmol), glycosyl acceptors (**3.6**, **3.7, 3.8** and **3.9**, 0.06 mmol), 4 Å sieves and the ferrocenium salt in CH_2Cl_2 at room temperature. [b] Isolated yield after column chromatography.

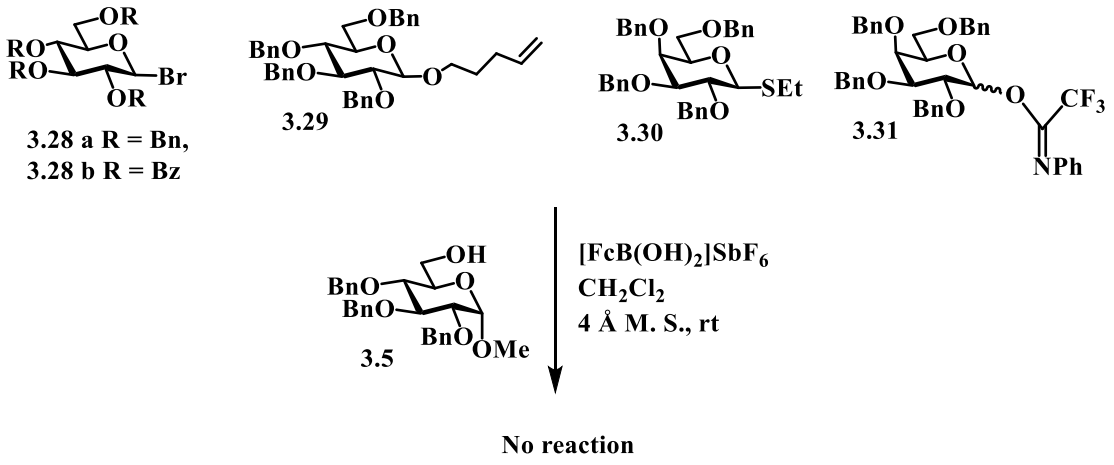


Scheme 3.4 $FcBF_4$ promoted glycosylation reaction with benzoyl protected glucosyl fluoride donor 3.4



Scheme 3.5 Glycosidic bond formation between cholesterol and glycosyl donors 3.2 and 3.3 with the ferrocenium catalyst $FcBF_4$

These findings show that an efficient promoter system is dependent on the nature of the leaving group. We began testing other leaving groups to learn more about the mode of activation. When glycosyl donors with different leaving groups, such as bromide (**3.28a** and **3.28b**), *n*-pentenyl **3.29**, thioethyl **3.30** and trichloroacetimidate **3.31** were investigated for performing glycosylation reaction with ferrocenium salt $[FcB(OH)_2]SbF_6$, reactions did not proceed at all (Scheme 3.6).



Scheme 3.6 Other glycosyl donors with different leaving groups were investigated for titled reaction with the ferrocenium salt $[FcB(OH)_2]SbF_6$

The general affinity of the iron atom towards the oxygen in carbohydrates is a challenge for iron-based promoters. Glycosyl donors and acceptors both contain several oxygen atoms either from the glycans or from the protecting groups. The iron-based promoter might have complexed with oxygen, thereby preventing it from acting as a promoter. This resulted in lower yields, even with high amounts of promoter loading (40 to 70 mol%). When benzoyl protected glycosyl donor was employed in glycosylation reaction, **3.25** was obtained in 24% yield with only β-selectivity (Scheme 3.4). The low yield is due to the extra number of carbonyl units, which offers additional opportunity for the iron atom to coordinate. Higher yields of 55 to 87% were obtained, when cholesterol with only one oxygen atom was employed as an acceptor.

3.4 Conclusion

In conclusion, we introduced for the first time ferrocenium-based, tunable promoters for performing glycosylation reactions. This new system helps in activating glycosyl halide donors to react with common glycosyl acceptors to obtain disaccharides in moderate to good yields of 10 to 95% isolated yields with α/β ratios ranging from 1/1

to β-only. We performed these reactions at room temperature with 40 – 100 mol % of ferrocenium salt promoters ($[FcB(OH)_2]SbF_6$, $FcBF_4$). To reduce the promoter load we will investigate towards the synthesis of more reactive ferrocenium catalysts by modifying the cyclopentadienyl rings.

3.5 Experimental Section

3.5.1 General

Chemicals 1,2,3,4,6-penta-*O*-acetyl-D-Glucopyranose, 1,2,3,4,6-penta-*O*-acetyl-D-Galactopyranose were purchased from Carbosynth. Diethylamino sulfur trifluoride (DAST) was purchased from TCI. Thionyl chloride, and *N*, *N*-dimethyl formamide were purchased from Sigma Aldrich. These chemicals were used without any further purification. Dry CH_2Cl_2 was obtained by following standard distillation procedure.[28] CH_2Cl_2 was freshly distilled from calcium hydride, to remove water. Molecular sieves (4 Å) were crushed and activated for 3 h at 375 ℃ and allowed to cool in vacuo prior to use. Reactions were monitored by TLC on Kieselgel F254. Compounds were detected under UV light and by charring with 10% sulfuric acid in methanol. Column chromatography was performed with silica gel 60 (70-230 mesh). The NMR spectra of the products matched those in the literature.

^1H NMR, and 2D NMR spectra were recorded in $CDCl_3$ using a Bruker instrument (300 MHz) and referenced to a residual solvent signal. Exact masses were obtained on Agilent 6230 ESI TOF LCMS mass spectrometer.

3.5.2 Synthesis of Glycosyl Halides

3.5.2a 2,3,4,6-Tetra-*O*-benzyl-α/β-D-Galactopyranosyl chloride (3.1) [11a]

To a solution of 2,3,4,5-tetra-*O*-benzyl-α/β-D-Galactopyranose (1.0 g, 1.8 mmol) in $ClCH_2CH_2Cl$ (10 - 15 mL) and *N*, *N*-dimethyl formamide (0.5 mL), thionyl chloride (0.6 g, 5.5 mmol) was added dropwise and allowed to stir under argon for 1 h at 0 °C. The reaction was monitored by TLC. After the reaction was complete, the reaction mixture was concentrated in vacuo and dissolved in a mixture of ethyl acetate and hexanes as eluent (10 mL, 1:1, v/v). Then the reaction mixture was passed through a short pad of silica gel and rinsed with the mixture of ethyl acetate and hexanes (1:1, v/v). Evaporation of the solvents afforded the title compound **3.1** as a colorless oil (1.0 g, 1.7 mmol, 98% yield). NMR spectral data of **3.1** matched the literature.

3.5.2b 2,3,4,6-Tetra-*O*-benzyl-α/β-D-Galactopyranosyl fluoride (3.2) [23]

To a solution of 2,3,4,5-tetra-*O*-benzyl-α/β-D-Galactopyranose (0.7 g, 1.3 mmol) in THF (12 mL) under argon at 0 °C, diethylamino sulfur trifluoride (DAST) (0.3 g, 1.6 mmol) was added. The cooling bath was removed, and the reaction mixture was allowed to stir at room temperature. The reaction was monitored by TLC and complete after 20 minutes. Methanol (0.3 mL) was added at 0 °C and allowed to stir for 5 min. The reaction mixture was concentrated in vacuo, washed with saturated $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2. The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified by silica gel column chromatography using ethyl acetate and hexanes as eluent (1:4, v/v) to afford the title compound **3.2** as a colorless oil (0.6 g, 1.1 mmol, 86%). NMR spectral data of **3.2** matched the literature.

3.5.2c 2,3,4,6-Tetra-*O*-benzyl-α/β-D-Glucopyranosyl fluoride (3.3)[23]

To a solution of 2,3,4,5-tetra-*O*-benzyl-α/β-D-Glucopyranose (0.9 g, 1.7 mmol) in THF (15 mL) under argon at 0 °C, DAST (0.3 g, 1.9 mmol) was added. The cooling bath

was removed, and the reaction mixture was allowed to stir at room temperature. The reaction was monitored by TLC. After 20 min, the reaction was complete. Methanol (0.5 mL) was added at 0 °C and the mixture allowed to stir for 5 min. The reaction mixture was concentrated in vacuo and washed with saturated $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2. The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude product was purified by silica gel column chromatography utilizing ethyl acetate and hexanes as eluent (1/4, v/v) which afforded the title compound **3.3** as a colorless oil (0.7 g, 1.3 mmol, 81% yield). NMR spectral data of **3.3** matched the literature.

3.5.2d 2,3,4,6-Tetra-*O*-benzoyl-α/β-D-Glucopyranosyl fluoride (3.4)[23]

To a solution of 2,3,4,5-tetra-*O*-benzoyl-α/β D-Glucopyranose (1.0 g, 1.6 mmol) in THF (15 mL) under argon at 0 °C, DAST (0.324 g, 2 mmol) was added. The cooling bath was removed, and the reaction mixture was allowed to stir at room temperature. The reaction was monitored by TLC. After 20 min, the reaction was complete. Methanol (0.5 mL) was added at 0 °C and stirred for 5 min. The reaction mixture was concentrated in vacuo, washed with saturated $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2. The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. Then the crude product was purified by silica gel column chromatography utilizing ethyl acetate and hexanes (1/4, v/v) as eluent which afforded the title compound **3.4** as a white foam in (0.204 g, 0.34 mmol, 23%). NMR spectral data of **3.4** matched the literature.

3.5.3 Synthesis of disaccharides

3.5.3a Method A

To a solution of the galactosyl chloride donor (**3.1**, 0.035 mmol) and the glycosyl acceptor[29] (**3.5, 3.6**, **3.7** and **3.8**, 0.015 mmol) in CH_2Cl_2, 4 Å molecular sieves were added and allowed to stir under argon for 20 min at room temperature. Then the ferrocenium salt ($[FcB(OH)_2]SbF_6$, 0.009 mmol, 60 mol%) was added as a promoter[30] and the reaction was allowed to stir for 4-6 h at rt.

3.5.3b Method B

To a solution of glycosyl fluoride donor (**3.2** and **3.3**, 0.05 mmol), and glycosyl acceptor (**3.5, 3.6**, **3.7**, **3.8** and **3.9**, 0.06 mmol)[29, 31, 32] in CH_2Cl_2, 4 Å molecular sieves were added and allowed to stir under argon for 20 min at room temperature. Then the ferrocenium salt ($FcBF_4$, 0.035 mmol, 70 mol%) was added as a promoter and allowed to stir for 2-16 h at rt.

3.5.3c Method C

To a solution of glycosyl fluoride donor (**3.4**, 0.05 mmol), and glycosyl acceptor[29] (**3.5,** 0.04 mmol) in CH_2Cl_2, 4 Å molecular sieves were added and allowed to stir under argon for 20 min at room temperature. Then the ferrocenium salt ($FcBF_4$, 0.016 mmol, 40 mol%) was added as a promoter and the reaction was allowed to stir for 8 h at rt.

3.5.3d Method D

To a solution of glycosyl fluoride donor (**3.2**, **3.3** & **3.4**, 0.02 mmol), and cholesterol (**3.10**, 0.02 mmol) in CH_2Cl_2, 4 Å molecular sieves were added and allowed to stir under argon for 20 min at room temperature. Then ferrocenium salt ($FcBF_4$, 0.008 mmol, 40 mol%) was added as a promoter and allowed to stir for 8-14 h at rt.

Reactions were monitored by TLC. After the reaction was over, the reaction mixture was filtered through a pad of celite and rinsed with CH_2Cl_2. Evaporation of solvent

afforded the crude product which was purified by silica gel column chromatography utilizing ethyl acetate and hexanes (slowly increase the ratio of ethyl acetate) as solvents to afford the corresponding disaccharides.

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-Galactopyranosyl)-α-Dglucopyranoside (3.11) [11a, 33, 34]

The title compound was obtained as colorless oil in 86% (13 mg, 0.012 mmol) yield (α/β = 1/1.1) by following method A.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.33 (d, *J* = 7.7 Hz, 1H, diastereomer β), 3.34 (s, 3H), 3.31 (s, 3H). NMR spectral data of **3.11** matched the literature. HR FAB MS $[M+Na]^+$ calcd for $C_{62}H_{66}O_{11}Na^+$ 1009.45; found 1009.46.

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-Galactopyranosyl)-α-Dglucopyranoside (3.12) [11a, 34]

The title compound was obtained as colorless oil in 64% (10 mg, 0.010 mmol) yield (α/β = 1.2/1) by following method A. NMR spectral data of **3.12** matched the literature.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74 (d, *J* = 3.61 Hz, 1H), 3.36 (d, *J* = 3.82 Hz, 6H). HR FAB MS $[M+Na]^+$ calcd for $C_{62}H_{66}O_{11}Na^+$ 1009.45; found 1009.44.

Methyl 2,4,6-tri-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-Galactopyranosyl)-α-Dglucopyranoside (3.13) [11a, 34]

The title compound was obtained as colorless oil in 63% (9 mg, 0.0094 mmol) yield (α/β = 1.6/1) by following method A.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (d, *J* = 3.1 Hz, 1H, diastereomer α), 3.39 (s, 3H), 3.29 (s, 3H). NMR spectral data of **3.13** matched the literature. HR FAB MS $[M+Na]^+$ calcd for $C_{62}H_{66}O_{11}Na^+$ 1009.45; found 1009.46.

Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-Galactopyranosyl)-α-Dglucopyranoside (3.14) [11a, 33]

The title compound was obtained as colorless oil in 45% (7 mg, 0.0067 mmol) yield (α/β = 1.2/1) by following method A.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.91 (d, *J* = 3.8 Hz, 1H, diastereomer α), 3.30 (dd, = 14.6, 7.5 Hz, 6H). NMR spectral data of **3.14** matched the literature. HR FAB MS $[M+Na]^+$ calcd for $C_{62}H_{66}O_{11}Na^+$1009.45; found 1009.46.

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-Galactopyranosyl)-α-Dglucopyranoside (3.15) [11a, 34]

The title compound was obtained as colorless oil in 50% (27 mg, 0.027 mmol) yield (α/β = 1/1.3) by following method B.

^{1}H NMR (300 MHz, CDCl3) δ 4.07 (d, *J* = 10.69 Hz, 1H, diastereomer α), 3.21 (S, 6H). NMR spectral data of **3.15** matched the literature. HR FAB MS $[M+Na]^+$ calcd for $C_{62}H_{66}O_{11}Na^+$ 1009.45; found 1009.44.

Methyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-Galactopyranosyl)-α-Dglucopyranoside (3.16) [11a, 34]

The title compound was obtained as colorless oil in 31% (17 mg, 0.017 mmol) yield (α/β = 1/1) by following method B.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (d, *J* = 3.5 Hz, 1H, diastereomer α), 3.44 (d, *J* = 10.8 Hz, 6H). NMR spectral data of **3.16** matched the literature. HR FAB MS $[M+Na]^+$ calcd for $C_{62}H_{66}O_{11}Na^+$ 1009.45; found 1009.44.

Methyl 2,4,6-tri-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-Galactopyranosyl)-α-Dglucopyranoside (3.17) [11a, 34]

The title compound was obtained as colorless oil in 34% (20 mg, 0.020 mmol) yield (α/β = 2.3/1) by following method B.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57 (d, *J* = 3.0 Hz, 1H, diastereomer α), 3.24 (d, *J* = 13.6 Hz, 6H). NMR spectral data of **3.17** matched the literature. HR FAB MS $[M+Na]^+$ calcd for $C_{62}H_{66}O_{11}Na^+$ 1009.45; found 1009.40.

Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-Galactopyranosyl)-α-Dglucopyranoside (3.18) [11a]

The title compound was obtained as an oil in 32% (18 mg, 0.018 mmol) yield (α/β = 1.6/1) by following method B.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 (d, *J* = 3.6 Hz, 1H, diastereomer α), 3.48 (d, *J* = 5.9 Hz, 6H). NMR spectral data of **3.18** matched the literature. HR FAB MS $[M+Na]^+$ calcd for $C_{62}H_{66}O_{11}Na^+$ 1009.45; found 1009.44.

Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-Dgalactopyranosyl)-α-D-Glucopyranoside (3.19) [35]

The title compound was obtained as colorless oil in 10% (4 mg, 0.0045 mmol) yield (α/β = 1.8/1) by following method B.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (d, *J* = 2.9 Hz, 1H), 3.37 (s, 3H). NMR spectral data of **3.19** matched the literature. HR FAB MS $[M+Na]^+$ calcd for $C_{55}H_{58}O_{11}Na^+$ 917.39; found 917.38.

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-Glucopyranosyl)-α-Dglucopyranoside (3.20) [11a, 34]

The title compound was obtained as colorless oil in 45% (24 mg, 0.024 mmol) yield (α/β = 1/1) by following method B.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.94 (d, *J* = 2.8 Hz, 1H), 3.34 (d, *J* = 7.5 Hz, 6H). NMR spectral data of **3.20** matched the literature. HR FAB MS $[M+Na]^+$ calcd for $C_{62}H_{66}O_{11}Na^+$ 1009.45; found 1009.44.

Methyl 2,4,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-Glucopyranosyl)-α-Dglucopyranoside (3.21) [11a, 34]

The title compound was obtained as colorless oil in 52% (25 mg, 0.025 mmol) yield (α/β = 1.5/1) by following method B.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.6 (d, *J* = 3.5 Hz, 1H), 3.42 (d, *J* = 3.9 Hz, 6H). NMR spectral data of **3.21** matched the literature. HR FAB MS $[M+Na]^+$ calcd for $C_{62}H_{66}O_{11}Na^+$ 1009.45; found 1009.44.

Methyl 2,4,6-tri-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-Glucopyranosyl)-α-Dglucopyranoside (3.22) [11a, 34]

The title compound was obtained as colorless oil in 48% (28 mg, 0.028 mmol) yield (α/β = 1/1) by following method B.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (d, *J* = 3.3 Hz, 1H), 3.39 (d, *J* = 5.7 Hz, 6H). NMR spectral data of **3.22** matched the literature. HR FAB MS $[M+Na]^+$ calcd for $C_{62}H_{66}O_{11}Na^+$ 1009.45; found 1009.44.

Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-Glucopyranosyl)-α-Dglucopyranoside (3.23) [11a]

The title compound was obtained as colorless oil in 46% (23 mg, 0.023 mmol) yield (α/β = 1/1) by following method B.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.72 (d, *J* = 2.8 Hz, 1H), 3.39 (s, 6H). NMR spectral data of **3.23** matched the literature. HR FAB MS $[M+Na]^+$ calcd for $C_{62}H_{66}O_{11}Na^+$ 1009.45; found 1009.44.

Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-Dglucopyranosyl)-α-D-Glucopyranoside (3.24) [26a]

The title compound was obtained as colorless oil in 12% (6 mg, 0.0067 mmol) yield (α/β = 1/1) by following method B.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61 (d, *J* = 3.4 Hz, 1H), 3.43 (s, 3H). NMR spectral data of **3.24** matched the literature. HR FAB MS $[M+Na]^+$ calcd for $C_{55}H_{58}O_{11}Na^+$ 917.39; found 918.

Methyl 6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-Glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-Dglucopyranoside (3.25)[11a]

The title compound was obtained as colorless oil in 24% (10 mg, 0.0095 mmol) yield (β-only) by following method C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (t, *J* = 9.5 Hz, 1H), 4.21 (d, *J* = 11.1 Hz, 1H). NMR spectral data of **3.25** matched the literature. HR FAB MS $[M+Na]^+$ calcd for $C_{62}H_{58}O_{15}Na^+$ 1065.37; found 1065.36.

Cholesteryl 2,3,4,6-tetra-*O*-benzyl-α/β-D-Galactopyranoside (3.26)[11c]

The title compound was obtained as colorless oil in 87% (17 mg, 0.019 mmol) yield (α/β = 1/5) by following method D.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.27 (d, *J* = 18.3 Hz, 1H), 4.93 (d, *J* = 12.3 Hz, 2H). NMR spectral data of α/β-Glycoside **3.26** matched the literature. HR FAB MS $[M+Na]^+$ calcd for $C_{61}H_{80}O_6Na^+$ 931.59; found 931.58.

Cholesteryl 2,3,4,6-tetra-*O*-benzyl-α/β-D-Glucopyranoside (3.27) [11c]

The title compound was obtained as colorless oil in 55% (12 mg, 0.013 mmol) yield (α/β = 1/1) by following method D.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.28 (d, *J* = 18.5 Hz, 1H), 3.42 (d, *J* = 8.7 Hz, 2H), 0.98 (d, *J* = 6.8 Hz, 7H). NMR spectral data of α/β-Glycoside **3.27** matched the literature. HR FAB MS $[M+Na]^+$ calcd for $C_{61}H_{80}O_6Na^+$ 931.59; found 931.58.

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CHAPTER 4

Synthesis Of Novel Glycosylated Curcumin Derivatives

4.1 Introduction

Sepsis is a life-threatening infectious disorder caused by excessive impairment of the host immune response.[1] It can result in multiple organ dysfunctions and can lead to septic shock.[2] In intensive care units, sepsis is the leading cause of death for burn, infection, and trauma patients.[3] Advanced therapeutic strategies are required to target sepsis.[4] Some natural compounds have anti-inflammatory effects that can help regulate sepsis.[5] Turmeric, a medicinal herb plant that belongs to the family of Zingiberaceae (ginger species), has an important bioactive polyphenol constituent.[6]

For many years, natural products have been a primary source of pharmaceutical drugs.[7] Curcumin, a natural compound found primarily in the spice turmeric, is a traditional medicine herb.[8] It is a yellow-colored polyphenol compound isolated from the herb rhizome of the *Curcuma longa L.*, an Asian tropical plant.[9] Turmeric can be grown in tropical and subtropical climates and is native to Southeast Asia, India, and Indonesia.[10] It has been used as an herb and as a food-coloring agent because it can be easily extracted from turmeric and is inexpensive.[11] Curcumin and its derivatives have been widely studied due to their anti-inflammatory,[12] anti-malarial,[13] anti-microbial,[14] anti-tumor,[15] antioxidant,[16] anticancer,[17] anti-leishmanial[18] and anti-aging properties.[19] Curcumin's unique feature is its lack of toxicity; large amounts (8 g per day)[20a] can be consumed, implying that it can serve as a valuable scaffold for the development of therapeutic compounds.[20b,c]

Several studies have been published claiming that this natural product can aid in the prevention of numerous diseases, including cancer.[21] Irrespective of its pharmacokinetic or pharmacodynamic properties, curcumin is not frequently used in clinical studies because of its poor performance against disease models and because of

its toxic effects under clinical conditions.[21b] Poor bioavailability, is due to the consequence of low water solubility and low chemical stability, particularly at alkaline pH.[22] Curcumin is insoluble in water and can undergo hydrolytic degradation at neutral pH.[23] Low water solubility of curcumin limits its practical and pharmacological applications.[24] When curcumin is taken orally or injected intravenously, 75% of it is excreted in the feces, indicating rapid metabolism and poor absorption.[25] To increase the bioavailability of curcumin, nanoparticles,[26] phospholipids,[27] and liposome complexes[28] were introduced with some success.

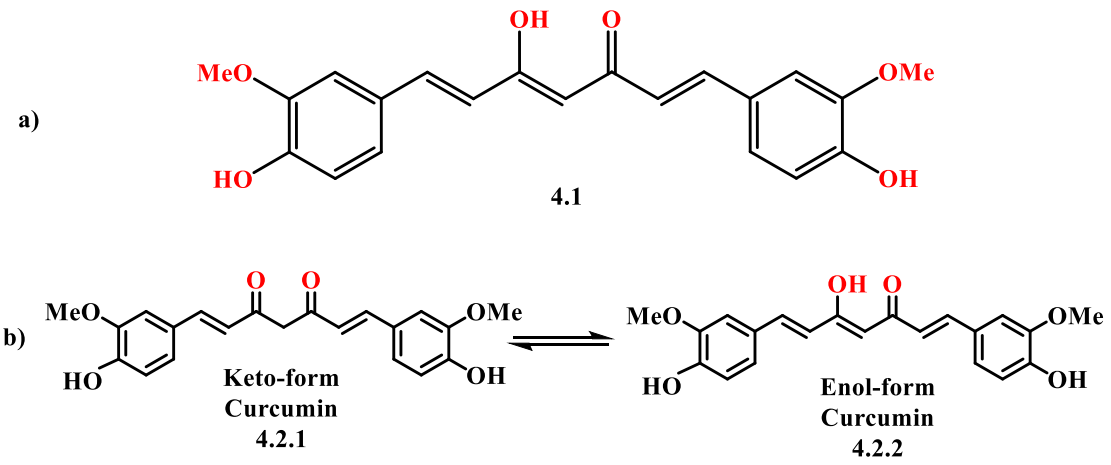


Figure 4.1 a) Structure of the curcumin in enol-form that is utilized for this study. b) Keto-Enol tautomerism of curcumin

Glycosides from the plants act as secondary metabolites.[29] These can conjugate glycans into endogenous metabolic intermediates as well as xenobiotics.[30] Glycosylation can reduce the toxicity of biosynthetic intermediates and xenobiotics, while increasing stability and solubility of the aglycones.[31, 32] Since the chemical structure of curcumin is vital to its biological activity, several synthetic modifications were investigated to overcome the obstacles of poor absorption and rapid metabolism.[24] A few of these studies focused on modifying the chemical structure of curcumin by introducing metal complexes to enhance its biological activity.[33] To improve stability, the di-ketone

moiety was replaced with cyclopentanone analogues.[34] Curcumin compounds were glycosylated to increase their water-solubility.[35]

4.2 Objective

We intended to apply the ferrocenium-promoted glycosylation method (from the previous chapter) in the synthesis of curcumin derivatives. Our practical synthetic approach to curcumin derivatives addresses both the stability and solubility concerns. This study reports the experimental details of synthesizing glycosylated curcumin derivatives, along with simple structural modifications to make them completely soluble in water and chemically stable in alkaline and buffered solutions.

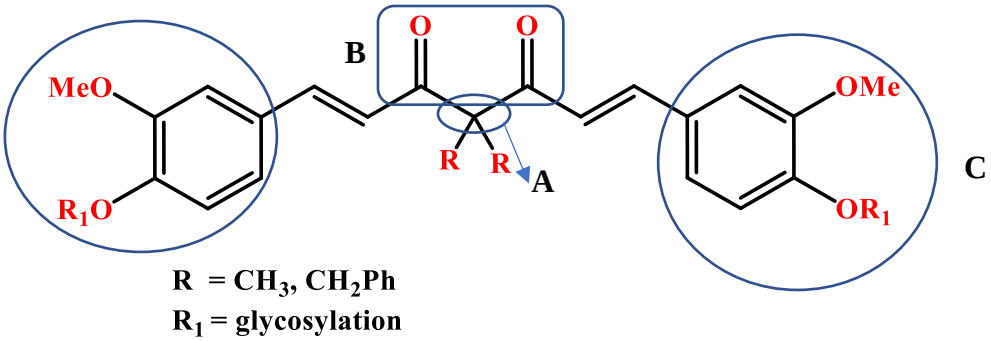


Figure 4.2 Modifications to the curcumin structure that could be made for this study A) Modified active methylene carbon B) 1,3-diketone C) Aromatic functionality with OCH_3 and OH groups (where acylation and glycosylation happens)

4.3 Results and Discussion

Curcumin was isolated in crystalline form for the first time in 1870 by Vogel Jr..[36] Chemically, curcumin is identified as 1, 7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione.[37] The unique structure of curcumin (Figure 4.1) has methoxy groups on phenol units connected with a seven-carbon chain consisting of 1,3-diketone

moiety. This diketone often is involved in keto-enol tautomerism as shown in Figure 4.1b.[38] In the solid-phase and in acidic solutions, the enol-form (4.2.2, Figure 4.1b) is the most energetically stable.[24] Deprotonation of the enol-form happens quickly under mild alkaline conditions and results in the formation of an enolate functionality. The structure of curcumin is linear and planar.[24]

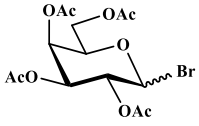
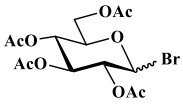
The synthesis of glycosyl curcuminoids was performed in a few steps, and the reaction sequence is summarized in Scheme 4.1. The chemical stability and solubility of synthesized glycosyl curcuminoids were evaluated by UV-vis spectroscopy. Commercially available curcumin (**4.1**, Scheme 4.1), which mainly exists in the enol-form, was utilized for this study. In the first step of synthesis, the two phenolic hydroxyl units were protected via acetylation, then alkylation on the central methylene carbon was performed to chemically stabilize the curcumin.[39]

Protection of two free OH groups was performed with acetic anhydride and pyridine by dissolving curcumin (**4.1**, Scheme 4.1) in dry CH_2Cl_2.[39] The reaction was refluxed for 2 hours to obtain acetylated curcumin (**4.2**, Scheme 4.1) in 98% yield. Iodomethane along with potassium carbonate was added to the solution of acetylated curcumin (**4.2**, Scheme 4.1) in dry acetone. Overnight reflux resulted in methylated curcumin (**4.3**, Scheme 4.1) in 92% yield.[39] Once the substituents were introduced, de-acetylation was performed with sodium hydroxide by dissolving methylated curcumin (**4.3**, Scheme 4.1) in methanol. The reaction was stirred for 2 hours at room temperature to obtain the de-acetylated methylated curcumin derivative which is a known compound (**4.4**, Scheme 4.1) in 82% yield.[39]

From our previous work, we know that $FcBF_4$ and $[FcB(OH)_2]SbF_6$ can be used as promoters to obtain glycosidic bonds between glycosyl donors (with a good leaving

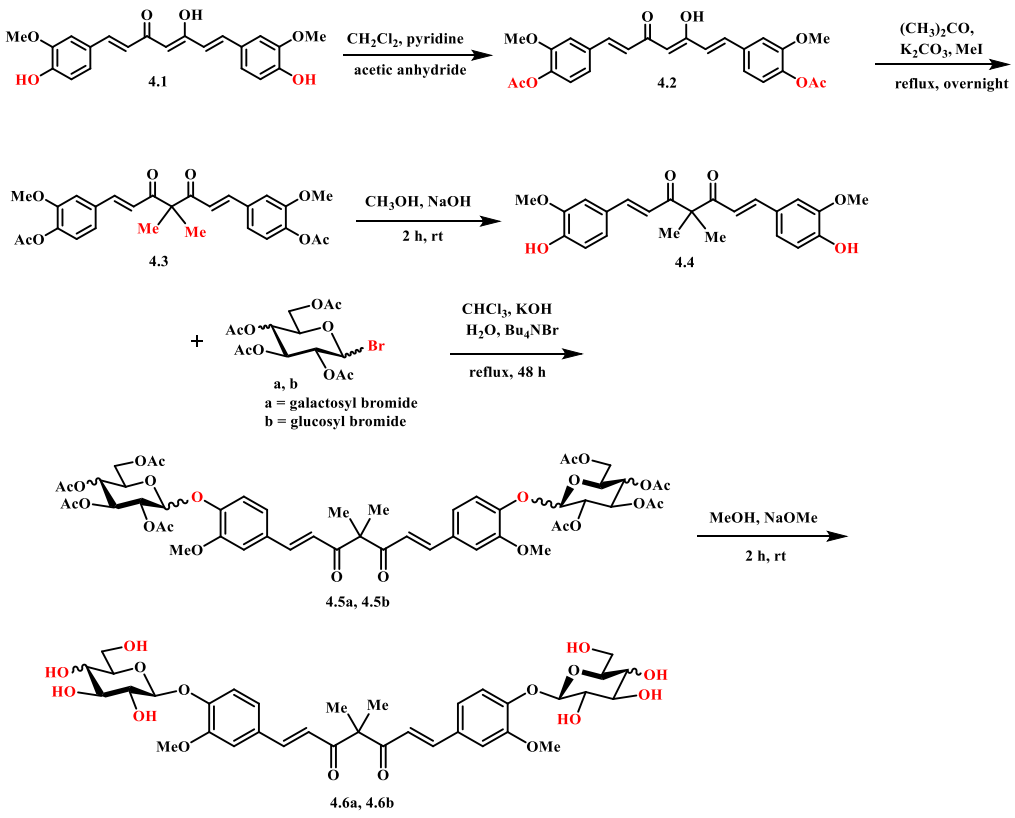
group) and the most commonly used glycosyl acceptors.[43] As a result, we attempted to form a glycosidic bond between the two phenolic hydroxyl groups of the compound (**4.4** and **4.8**, 1 equiv., Scheme 4.1) and galactosyl bromide (**a**, 2.2 equiv., Scheme 4.1) using 1-2 equivalents of ferrocenium salts ($FeCl_3$, $FcPF_6$, $FcBF_4$ and $[FcB(OH)_2]SbF_6$) in CH_2Cl_2 solvent. These reactions (entries 1-7, Table 4.1) were monitored by TLC. Unfortunately, these reactions did not proceed as expected. Over the course of time from 24 – 48 h, no product formation was observed on the TLC plate. Decomposition of ferrocenium catalyst was noticed by the color change from dark blue to orange. As a result, we decided to perform glycosylation reactions in the presence of phase transfer catalyst between the two hydroxyl units and acetylated galactosyl bromide.[40]

Table 4.1 Screening reactions to obtain glycosidic bond between curcumin derivatives and glycosyl bromides with ferrocenium salts

Entry [a]	Curcumin derivatives	Glycosyl bromides	Ferrocenium salts	Temperature	Solvent
1	**4.4**	 Galactosyl bromide **a**	$FcBF_4$	rt	CH_2Cl_2
2	**4.4**	**a**	$FcPF_6$	rt	CH_2Cl_2
3	**4.4**	**a**	$[FcB(OH)_2]SbF_6$	rt	CH_2Cl_2
4	**4.4**	**a**	$FeCl_3$	rt	CH_2Cl_2
5	**4.4**	 Glucosyl bromide **b**	$[FcB(OH)_2]SbF_6$	rt	CH_2Cl_2
6	**4.4**	**b**	$FcBF_4$	rt	CH_2Cl_2
7	**4.8**	**a**	$FeCl_3$	rt	CH_2Cl_2

[a] Typical conditions: Curcumin derivatives (0.126 mmol, 1 equiv.), glycosyl bromides (0.267 mmol, 2.2 equiv.), ferrocenium salts (1-2 equiv.) in CH_2Cl_2 (3-5 mL) at room temperature for 24-48 h.

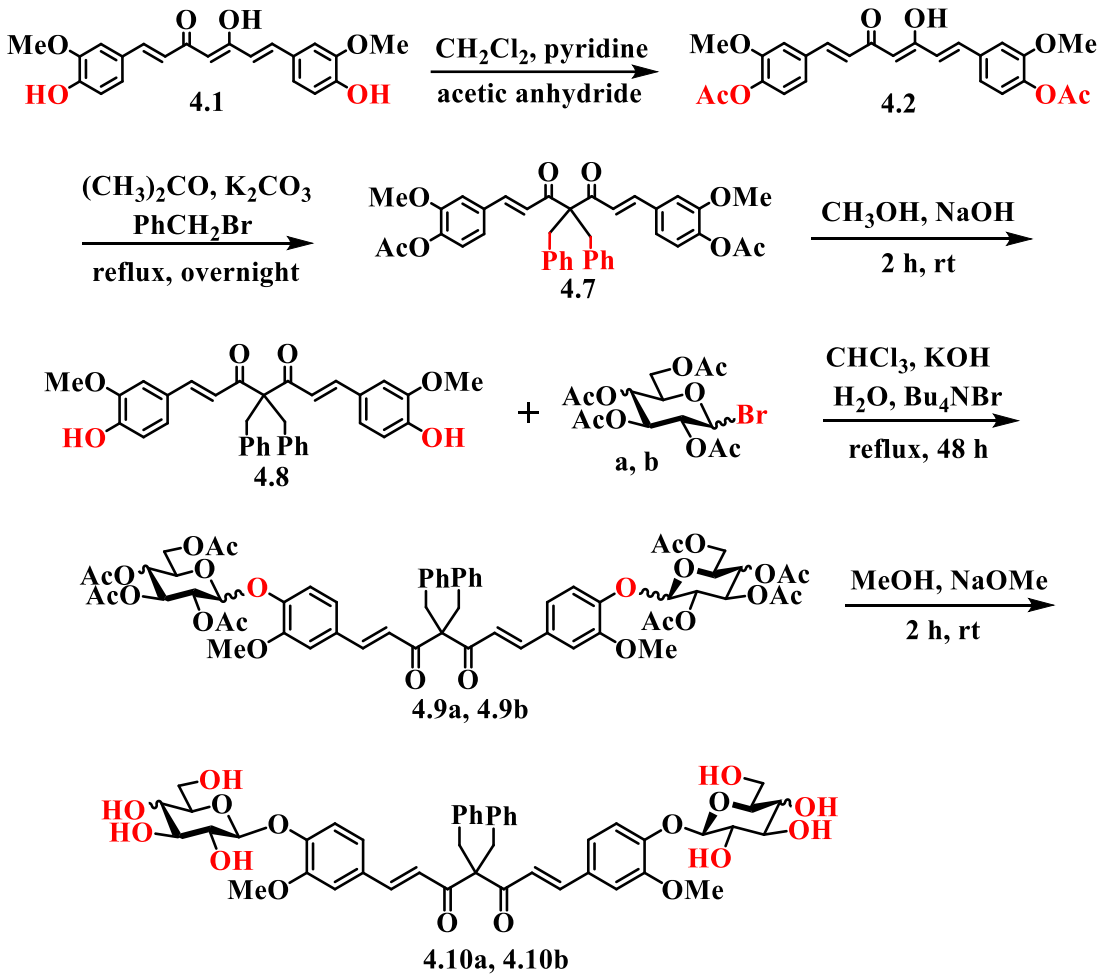
Potassium hydroxide in H_2O solution was added to the $CHCl_3$ dissolved de-acetylated methylated curcumin (**4.4**, 1 equiv., Scheme 4.1) and stirred for 20 minutes. The potassium ion forms a complex with the 1,3-diketone unit to stabilize the curcumin in solution.[40] The decolorization of the organic layer confirms the formation of a complex between potassium salt and curcumin, with simultaneous pigment transfer to the aqueous portion.[40] Over the course of 20 minutes, acetylated galactosyl bromide (**a**, 2.2 equiv., Scheme 4.1) in $CHCl_3$ was added and stirred. The reaction mixture was treated with Bu_4NBr (tetrabutylammonium bromide), (1 equiv.) in H_2O and refluxed for 48 hours. This resulted in 63% isolated yield of methylated acetylated galactosidase curcumin (**4.5a**, Scheme 4.1).



Scheme 4.1 Synthesis of glycosylated methylated curcumin derivatives 4.6a and 4.6b

In the final step, the synthesis of desired molecule, glycosylated methylated curcumin derivative (**4.6a**, Scheme 4.1) was achieved by de-acetylation in the presence of sodium methoxide (NaOMe).[41, 42] Compound **4.5a** from Scheme 4.1 was dissolved in methanol, and 3 mL of 0.1M NaOMe was added and stirred at room temperature for 2 hours to obtain the desired product (**4.6a,** Scheme 4.1) in 78% yield.

The synthesis of methylated acetylated diglucuronide curcumin derivative **4.5b** (Scheme 4.1) compound was achieved by treating methylated curcumin **4.3** (Scheme 4.1) in $CHCl_3$ with potassium hydroxide in H_2O in the presence of Bu_4NBr (1 equiv.) in H_2O followed by the addition of freshly synthesized bromo acetylated glucopyranoside (**b**, Scheme 4.1) in $CHCl_3$. The reaction mixture was then refluxed for 48 hours. The methylated acetylated diglucuronide curcumin derivative **4.5b** (Scheme 4.1) was purified from the crude reaction mixture by column chromatography to obtain the product in 60% yield. Deacetylation of compound **4.5b** (Scheme 4.1) in the presence of 0.1M NaOMe in MeOH, followed by acidification with H^+ resin, resulted in glucosyl methylated curcumin **4.6b** (Scheme 4.1) in 77% yield.



Scheme 4.2 Synthesis of glycosylated benzylated curcumin derivatives 4.10a and 4.10b

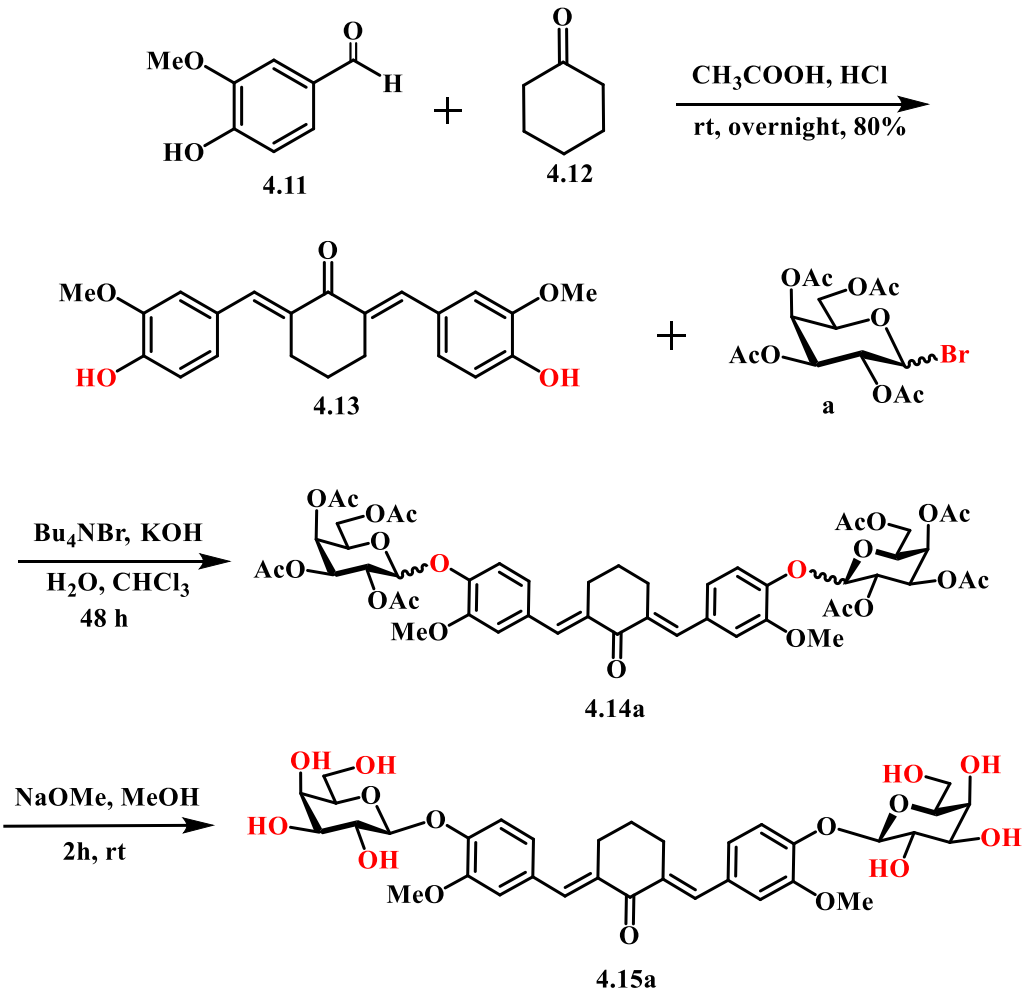
The reaction between acetylated curcumin (**4.2**, Scheme 4.2) and benzyl bromide in the presence of potassium carbonate resulted in acetylated benzylated curcumin (**4.7**, Scheme 4.2) in 72% yield.[39] Deacetylation of **4.7** (from the Scheme 4.2) compound with NaOH in MeOH for 2 hours obtained deacetylated benzylated curcumin (**4.8**, Scheme 4.2) in 95% yield.[39] Then the glycosylation between deacetylated benzylated curcumin (**4.8**, Scheme 4.2) and glycosyl bromides (galactosyl bromide (**a**) and glucosyl bromide (**b**), Scheme 4.2) in the presence of Bu_4NBr provided **4.9a** in 65% yield and **4.9b** (Scheme 4.2) in 71% yield. Deacetylation of these curcumin derivatives

were both performed with 0.1M NaOMe solution in MeOH to obtain **4.10a** (Scheme 4.2) in 71% and **4.10b** (Scheme 4.2) in 40% yield.

According to the literature, the chemical stability of curcumin may be enhanced by eliminating the active methylene group and carbonyl moiety.[44] To test this hypothesis, we synthesized glycosylated mono-carbonyl curcumin derivatives. The synthesis of mono-carbonyl curcumin (**4.13**, Scheme 4.3) with cyclohexanone (**4.12**, Scheme 4.3) and vanillin (**4.11**, Scheme 4.3) was performed as mentioned in the literature.[45] Potassium hydroxide and tetrabutylammonium bromide were dissolved in H_2O, and a glycosylation reaction between $CHCl_3$-dissolved mono-carbonyl curcumin (**4.13**) and glycosyl bromides (**a** and **b**) resulted in the glycosidic bond formation (Scheme 4.3). We were able to obtain **4.14a** (0.32 g, 0.312 mmol, Scheme 4.3) in 74% yield. The compound **4.14a** (Scheme 4.3) was deacetylated by NaOMe solution (0.1M in MeOH). The yellow solution was purified over a silica pad and provided **4.15a** (76%, 0.10g, 0.15mmol, Scheme 4.3)**.**

All the reactions were monitored by TLC using ethyl acetate and hexanes (4:6, v/v, 10 mL) as the mobile phases. Column chromatography techniques were applied to separate the compounds. The amount of unreacted glycosyl bromide or hydrolyzed glycosyl compounds were recovered from the column and ranged between 15 and 25%. The spectral and analytical data of the products, such as ^{1}H and ^{13}C NMR, IR, and mass spectroscopy, were completely consistent with the proposed structures. The presence of methyl and benzyl units on the center methylene carbon prevented tautomerism from occurring; instead, we only observed the keto-form of curcumin by ^{1}H NMR and IR. In the IR spectra the C=O stretch of 1,3-diketone peaks appeared at 1664 cm^{-1}. The C=O stretch of acetate groups from glycosyl bromides appeared at 1740 cm^{-1}. In the ^{1}H NMR spectrum, the anomeric proton peaks of the glycosyl bromides (**a** and **b**) appeared as a

doublet between δ 6.5 and 6.7 ppm. In the glycosylated products (**4.5a, 4.5b, 4.9a** and **4.9b**) the anomeric proton peak shifted to δ 4.5 to 5 ppm. The change in the chemical shift clearly shows a glycosidic bond between the anomeric carbon and phenolic oxygen had formed.[52]



Scheme 4.3 Synthesis of glycosylated mono-carbonyl curcumin derivatives 4.15a

The IR spectra of the compounds (**4.6a, 4.6b, 4.10a** and **4.10b**) exhibited the hydroxyl absorption as a broad stretch at 3330-3337 cm^{-1}, representing all the hydroxyl groups (after the deacetylation process) from the sugar units. After collecting all the analytical data, (^{1}H, ^{13}C NMR, IR, and Mass data), the curcumin glycosides were utilized for the experimental studies such as UV-Vis and fluorescence measurements.

4.3.1 Stability and Solubility Studies (by Palak Sondhi from Dr. Keith J. Stine's lab)

Stability and solubility studies were performed on glycosylated curcumin compounds (**4.6a** and **4.10a**) by UV-Visible spectroscopy.[23a, 47]

4.3.1a Stability study by time resolved UV-Visible spectroscopy

The percent degradation of the curcumin derivatives **4.6a** and **4.10a** were monitored for 2 hours by time resolved UV-Vis spectroscopy. Compounds **4.6a** and **4.10a** were dissolved in 1% DMSO (dimethyl sulfoxide) and phosphate buffered saline to give a 25 μM solution (PBS, pH 7.4). The calculated value of percent degradation resulted in 2.3 ± 0.52% for **4.6a** and 5.4 ± 1.8% for **4.10a**. The molar extinction coefficients for **4.6a** (Figure 4.3) was 30,934 M^{-1} cm^{-1} and for **4.10a** (Figure 4.4) 22,934 M^{-1} cm^{-1}. **4.6a** and **4.10a** are both stable over the course of 2-hour study, however, a decrease in the intensity was observed for **4.10a** (Figure 4.4) indicating some decomposition.

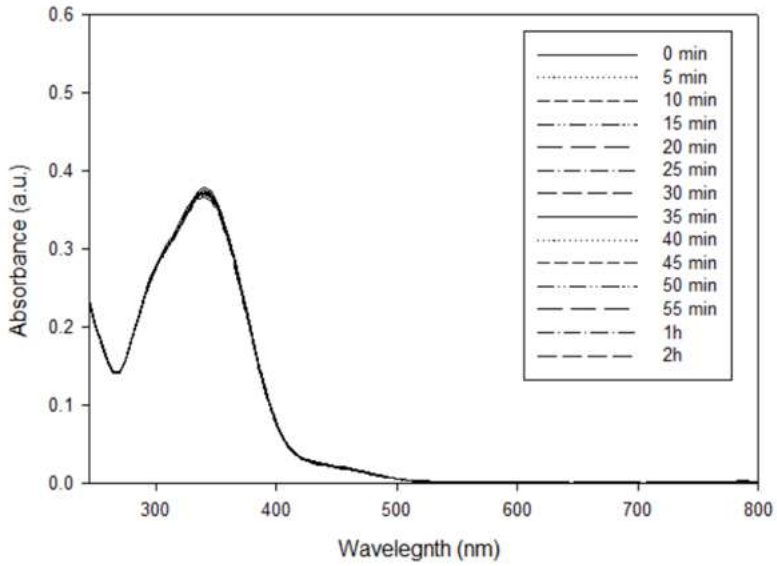


Figure 4.3 Stability study by UV-Vis on compound 4.6a, 25 μM in 1% DMSO and PBS (plotted by Palak Sondhi)

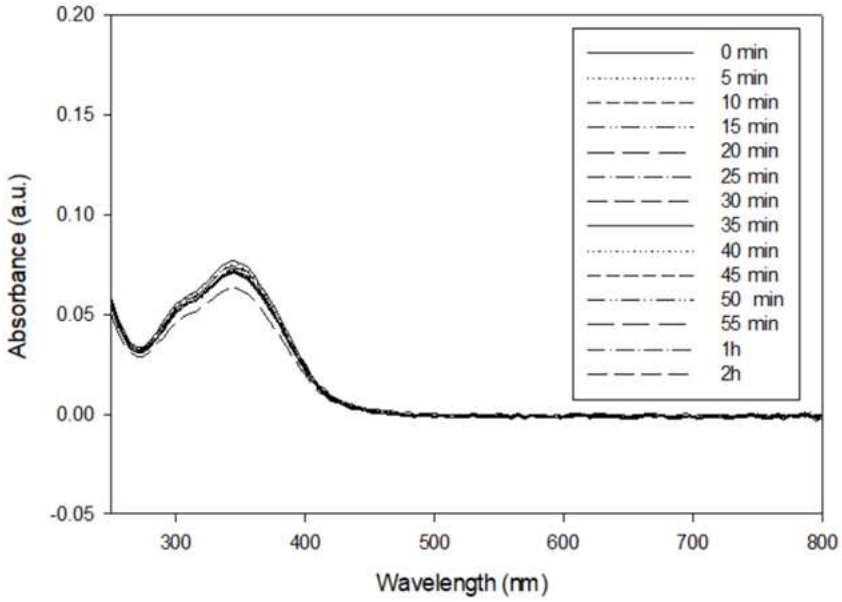


Figure 4.4 Stability study by UV-Vis on compound 4.10a, 25 µM in 1% DMSO (dimethyl sulfoxide) and PBS (plotted by Palak Sondhi)

4.3.1b Solubility of curcumin and it's derivatives by UV-Visible Spectroscopy

The Stine group prepared saturated solutions of curcumin and its derivatives (**4.6a, 4.6b, 4.10a, 4.10b** and **4.15a**) in the same solvent system using 1% DMSO + PBS. These were kept on a shaker overnight and centrifuged in the next morning. Then the supernatants were collected to perform UV-Vis studies.[47] Calibration studies were performed to calculate molar extinction coefficient values which were put in the Beer-Lambert law along with absorbance values (of the supernatant) to calculate the solubility (mg/L). Results are shown in Figure 4.5. The solubility order of curcumin derivatives is as follows: curcumin < **4.15a** < **4.10b** < **4.6b** < **4.10a** < **4.6a**. So, far the galactosidase methylated curcumin derivative **4.6a** has the highest solubility. The increase in solubility of these derivatives is due to the addition of more polar units (OH). Hydroxyl units from the two glycans units attached to the curcumin core increase the hydrophilicity and consequently the water solubility of the curcumin derivatives.

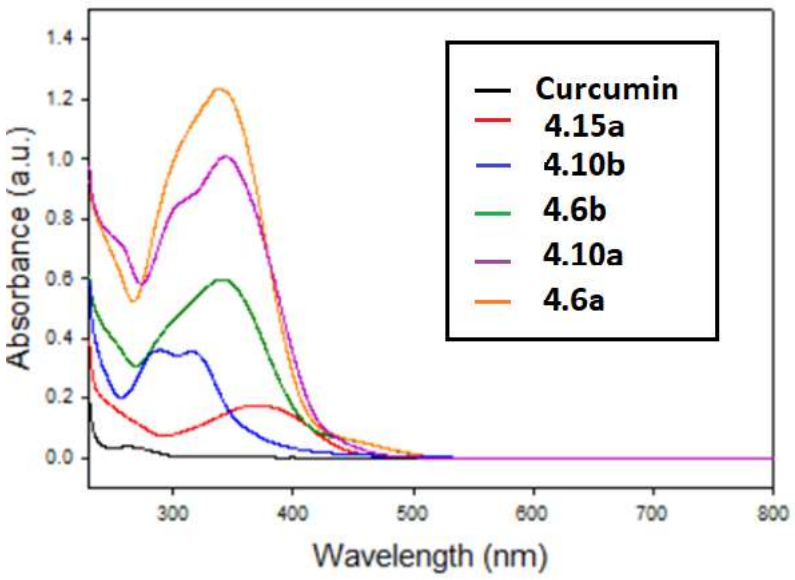


Figure 4.5 UV-Vis Spectra was used to calculate the solubility of curcumin and its derivatives 4.6a, 4.6b, 4.10a, 4.10b and 4.15a (plotted by Palak Sondhi)

Table 2 Solubility was calculated based on absorbance, and extinction coefficient values of curcumin and its derivatives

Entry[a]	Compound	Solubility mg/L	Absorbance	Extinction Coefficient (M^{-1} cm^{-1})
1	Curcumin	0.0002	0.005	27,200
2	**4.15a**	0.003	0.173	63,600
3	**4.10b**	0.010	0.34	32,800
4	**4.6b**	0.018	0.584	32,400
5	**4.10a**	0.044	1.01	22,934
6	**4.6a**	0.039	1.23	30,934

[a] Typical conditions: A saturated solution of curcumin and its derivatives were prepared in the buffer at pH 7.4 (1% DMSO+PBS) and centrifuged it in the next morning.

4.3.1c Fluorescence Measurements

Fluorescence measurements compiled in Table 3 were performed on curcumin derivatives (**4.6a, 4.6b, 4.10a, 4.10b** and **4.15a**) with and without adding the MD-2 protein to calculate the binding affinity. Solutions of curcumin derivatives with different concentrations ranging from 0.3 μM to 30 μM were prepared in 1% DMSO and PBS.[49] Fluorescence titrations were carried out at an excitation wavelength of 340 nm for compounds **4.6a** and **4.6b**, 345 nm for **4.10a** and **4.10b**, and 380 nm for **4.15a**. The fluorescence intensity was recorded before and after the addition of the MD-2 protein (with a 50 nM concentration). The variation of the intensity for all the concentrations were calculated and plotted against the concentration of curcumin derivatives to get specific binding affinities. Small dissociation constant (K_d) values represent a strong binding interaction between the curcumin derivatives and MD-2 protein. In that scenario the order of binding is as follows **4.10b** > **4.14a** > **4.6b** > **4.6a** > **4.10a**. The glucosyl benzyl curcumin derivative **4.10b** with 0.3519 K_d (Table 3) value has a good binding affinity towards the MD-2 protein, when compared to the other curcumin derivatives. These are preliminary data, and more measurements are underway in the laboratory of Prof. Keith J. Stine.

Table 3 MD-2 interaction studies with curcumin derivatives using fluorescence[48]

Entry	Compound	Dissociation Constant (K_D)
1	**4.6a**	9.9416
2	**4.10a**	30.7643
3	**4.6b**	5.9332
4	**4.10b**	0.3519
5	**4.14a**	1.6126

4.3.2 Cell-Culture Studies (performed by Cristina Sinobas Pereira and plotted by Dr. Michael R. Nichols)

THP-1 cell is a human leukemia monocytic cell line.[50] THP-1 cells were used for toxicity and LPS antagonist studies on **4.6a**. When THP cells were treated with compound **4.6a** at 100μM concentration, TNF-α production with LPS was inhibited. In this regard, cell viability assay studies in the presence of **4.6a** were evaluated, and it was determined that **4.6a** is not toxic at higher concentrations. These are only preliminary data; more measurements are now being performed.

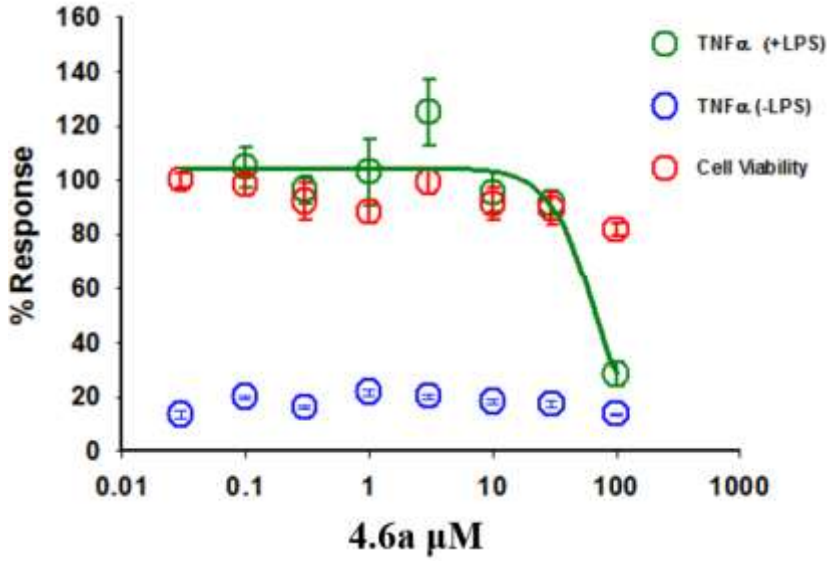


Figure 4.1 LPS antagonist and toxicity studies on de-acetylated galactosyl methylated (4.6a) curcumin compound 4.6a (Experiments were done by Cristina Sinobas Pereira and plotted by Dr. Michael R. Nichols)

4.4 Conclusion

Herein for the first time the experimental details of the synthesis of alkylated and water-soluble glycosylated curcumin derivatives are reported. The proposed synthetic pathways are straightforward, inexpensive and are a practical, modifiable synthesis of

these novel compounds in gram quantities. This general synthesis allows for the access to a variety of curcumin derivatives. Glycosylated compounds **4.6a, 4.6b, 4.10a** and **4.10b** are very well soluble in H_2O and DMSO and showed increase stability. We anticipate that these modifications of curcumin will enhance the bioavailability, and thus these derivatives could be useful in the investigation of a new generation of biologically active compounds. Preliminary MD-2 binding, and cell culture studies were promising. These chemical properties may assist in the broadening of their applications in the food and pharmaceutical sectors.

4.5 Experimental Procedures

^{1}H NMR, and ^{13}C NMR spectra were recorded in deuterated solvents using a Bruker instrument (300 MHz). Solvent signals were used as an internal reference and the chemical shifts are referred in terms of ppm. Exact masses were obtained on Agilent 6230 ESI TOF LCMS mass spectrometer. IR spectra were recorded on a Thermo Nicolet 360 FT-IR Spectrometer. Chemicals such as acetic anhydride, pyridine, iodomethane, benzyl bromide were purchased from Sigma Aldrich and Thermo Fischer. 1,2,3,4,6-penta-*O*-acetyl-D-Glucopyranose, 1,2,3,4,6-penta-*O*-acetyl-D-Galactopyranose were purchased from Carbosynth and curcumin was purchased from TCI. These chemicals were used without any further purification. Dry solvents were obtained by standard distillation procedures.[51] Column chromatography purifications were performed with Silica Gel 60 (70-230 mesh). Reactions were monitored by thin-layer chromatography (TLC) on pre-coated Silica Gel Kieselgel 60 F_{254} plates with UV detection. Compounds were detected under UV light and by charring with 10% sulfuric acid in methanol.

4.5.1 Synthesis of Glycosylated Curcumin Derivatives[39]

The compounds are synthesized according to a literature procedure from Dong et al.[39] In a N_2 evacuated Schlenck flask, curcumin (**4.1**, 1 g, 2.7 mmol) was dissolved in CH_2Cl_2 (10 mL), then acetic anhydride (0.8 g, 8.1 mmol) and pyridine (0.6 g, 8.1 mmol) were added and refluxed for 2 h. To quench the reaction, MeOH (20 mL) was added stirred for 20 minutes. Then the solvents were evaporated under vacuum to obtain yellow colored acetylated curcumin **4.2** (98%, 1.2 g, 2.6 mmol) as a powder, which was used without further purification. Methyl or benzyl groups were introduced by dissolving acetylated curcumin (**4.2**, 0.5 g, 1.1 mmol) in acetone (10 mL), then K_2CO_3 (0.4 g, 3.3 mmol) and iodomethane (0.5 g, 3.3 mmol) or benzyl bromide (5.6 g, 3.3 mmol) were added and refluxed overnight. K_2CO_3 was filtered off and the filtrate was collected and evaporated under vacuum. The products were obtained as yellow solids **4.3** (0.53 g, 1.10 mmol, 92%) and **4.7** (0.5 g, 0.78 mmol, 72%,).

These acetylated compounds (**4.3**, 0.8 g, 1.65 mmol) or (**4.7**, 1.2 g, 1.89 mmol) were dissolved in MeOH (10 mL) and NaOH (0.15 g, 3.7 mmol) was added and allowed it to stir for 2 h at room temperature. Methanol was evaporated under reduced pressure. NaOH was neutralized by adding a few drops of acetic acid. Then the workup was performed by dissolving the reaction mixture in CH_2Cl_2 (2 x 20 mL) and washed with H_2O (40 mL). $MgSO_4$ was added to the CH_2Cl_2 layer. The solvent was removed, and the product was dried in high vaacum to obtain the de-acetylated products yellow solids **4.4** (0.49 g, 1.23 mmol, 82%,) and **4.8** (0.9 g, 1.8 mmol, 95%,).[39]

4.5.2 Synthesis of Glycosyl Bromides[46a, 46b]

4.5.2a Galactosyl Bromide (a)

1,2,3,4,6-penta-*O*-acetyl-D-Galactopyranose (5 g, 12.8 mmol) is dissolved in dry CH_2Cl_2 (20 mL), 33% HBr in AcOH (5.25 mL, 87.9 mmol) was added at 0 ℃ and stirred for 1 h. Reaction was monitored on TLC with 30% EtOAc and hexanes as gradient. Then the reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with cold H_2O (40 mL), aq. $NaHCO_3$ (30 mL) and H_2O (50 mL). The organic layer was collected and dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain galactosyl bromide (**a**, 4.3 g, 10.45 mmol, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.7 (d, *J* = 3.7 Hz, 1H, H-1), 5.54 (s, 1H, H-3), 5.45 (dd, *J* = 2.82 Hz, 1H, H-2), 5.06 (dd, 1H, H-4), 4.51 (t, *J* = 6.4 Hz, 1H, H-5), 4.16 (m, 2H, H-6a, 6b), 2.18 (s, 3H), 2.14 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H).

4.5.2b Glucosyl Bromide (b)[46a]

1,2,3,4,6-penta-*O*-acetyl-D-Glucopyranose (5 g, 12.8 mmol) is dissolved in dry CH_2Cl_2 (20 mL), 33% HBr in AcOH (5.25 mL, 87.9 mmol) was added at 0 ℃ and stirred for 1 h. Reaction was monitored on TLC with 30% EtOAc and hexanes as gradient. Then the reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with cold H_2O (40 mL), aq. $NaHCO_3$ (30 mL) and H_2O (50 mL). The organic layer was collected and dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain glucosyl bromide (**b**, 3.9 g, 9.5 mmol, 74%,). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 (d, *J* = 3.8 Hz, 1H, H-1), 5.49 (t, *J* = 9.7 Hz, 1H, H-2), 5.10 (t, *J* = 9.8 Hz, 1H, H-3), 4.77 (dd, *J* = 9.98 Hz, 1H, H-4), 4.26 (t, *J* = 6.28 Hz, 2H, H-6a, 6b), 4.06 (d, *J* = 11 Hz, 1H, H-5), 2.04 (s, 6H), 1.99 (s, 3H), 1.97 (s, 3H).

4.5.3 Synthesis of Glycosylated Methylated Curcumin Derivatives[40]

Galactosyl pyranose Methylated Curcumin (4.5a)

To a solution of methylated de-acetylated curcumin (**4.4**, 0.15 g, 0.37 mmol) in $CHCl_3$ (5 mL), KOH (0.76 g, 1.36 mmol in 5 mL H_2O) was added and stirred for 20 min. Freshly synthesized galactosyl pyranose bromide (**a**, 0.47 g, 1.14 mmol) in $CHCl_3$ was added and stirred for 20 min. NBu_4Br (0.12 g, 0.37 mmol in 5 mL H_2O) was added and the mixture was refluxed for 48 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with H_2O (2 x 20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography utilizing ethyl acetate and hexanes (slowly increase the ratio of ethyl acetate) as solvents to afford the title compound **4.5a** (0.25 g, 0.24 mmol, 63%) as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 16 Hz, 2H, CH), 7.01 (s, 4H, aromatic CH), 6.94 (s, 2H, aromatic CH), 6.59 (d, *J* = 16 Hz, 2H, CH), 5.44 (t, 2H, H-2), 5.36 (s, 2H, H-3), 5.03 (dd, *J* = 12 Hz, 2H, H-4), 4.86 (d, *J* = 8 Hz, 2H, H-1), 4.09 (m, 4H, H-6a, 6b), 3.92 (t, *J* = 7 Hz, 2 H, H-5), 3.77 (s, 6 H, 2 OCH_3), 2.10 (s, 6 H, 2 CH_3), 1.99 (s, 12 H, 4 CH_3), 1.94 (s, 6 H, 2 CH_3), 1.41 (s, 6 H, 2 CH_3). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$) δ 196.9 (s, 2 C=O), 169.3 (s, 4 C=O), 169.2 (s, 4 C=O), 169.2 (s, 4 C=O), 168.4 (s, 4 C=O), 149.6 (s, OCH_3), 147.5 (s, OCH_3), 142.7 (s, CH), 129.5 (s, CH), 121.5 (s, aromatic), 119.6 (s, aromatic), 118.1 (s, aromatic), 112.9 (s, aromatic), 111.1 (s, aromatic), 110.8 (s, aromatic), 99.8 (s, anomeric, C-1), 70.1 (s, C-5), 69.6 (s, C-3), 67.4 (s, C-2), 65.8 (s, C-4), 59.9 (s, C-6), 20.8 – 19.3 (m, 2 CH_3). IR (ATR, neat): $\tilde{\nu}$ = 2961 (m), 1741 (s), 1669 (m), 1254 (s), 1211 (s), 1049 (s) cm^{-1}. HR FAB MS $[M+Na]^+$ calcd for $[C_{51}H_{60}O_{24}Na]^+$ 1079.3362; found 1079.3367.

Methylated De-Acetylated Galactosyl Curcumin (4.6a)

To the methylated galactosyl curcumin (**4.5a**, 0.28 g, 0.24 mmol) in MeOH, a few drops of 0.1 M NaOMe solution were added and stirred for 2 h at room temperature. Dowex® H^+ resin was added to neutralize and stirred for 20 min. The resin was filtered off and the filtrate was concentrated under reduced pressure. A pad of silica was used to filter the crude mixture to afford **4.6a** as a yellow solid (0.16 g, 0.22 mmol, 78%, β-only). ^{1}H NMR (300 MHz, CD_3OD) δ 7.69 (d, *J* = 16 Hz, 2H, CH), 7.2 (m, 6H, aromatic CH), 6.92 (d, *J* = 16 Hz, 2H, CH), 3.91 (s, 2 H, H-6a), 3.85 (s, 2 H, H-6b), 3.74 (m, 4 H, H-2, H-3), 3.58 (d, *J* = 6 Hz, 2 H, H-5), 3.36 (s, 2 H, H-4), 3.32 (s, 6 H, 2 OCH_3), 1.48 (s, 6 H, 2 CH_3). $^{13}C\{^1H\}$ NMR (75 MHz, CD_3OD) δ 201.6 (s, C=O), 201.5 (s, C=O), 152.4 (s, OCH_3), 151.7 (s, OCH_3), 147.4 (s, C=O), 146.6 (s, C=O), 131.4 (s, aromatic), 128.8 (s, aromatic), 126.2 (s, aromatic), 122.5 (s, aromatic), 121.0 (s, aromatic), 118.5 (s, aromatic), 113.9 (s, aromatic), 103.9 (s, anomeric, C-1, β), 78.3 (s, C-5), 75.9 (s, C-3), 73.3 (s, C-2), 71.3 (s, C-4), 63.6 (s, C-6), 23.07 (s, 2 CH_3), 20.2 (s, CH_3). IR (ATR, neat): $\tilde{\nu}$ = 3337 (b), 2928 (m),1578 (s), 1507 (s), 1254 (s), 1211 (s), 1049 (s), 983 (s) cm^{-1}. HR FAB MS $[M+Na]^+$ calcd for $[C_{35}H_{44}O_{16}Na]^+$ 743.2552; found 743.2522.

Methylated Glucosyl pyranose Curcumin (4.5b)

To a solution of methylated de-acetylated curcumin **4.4** (0.2 g, 0.50 mmol) in $CHCl_3$ (5 mL), KOH (0.10 g, 1.81 mmol in 5 mL H_2O) was added and stirred for 20 min. Freshly synthesized glucosyl pyranose bromide (**b**, 0.62 g, 1.51 mmol) in $CHCl_3$ (5-10 mL) was added and stirred for 20 min. NBu_4Br (0.16 g, 0.50 mmol in 5 mL H_2O) was added and refluxed for 48 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with H_2O (2 x 20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography utilizing ethyl acetate and hexanes (slowly increase the ratio of ethyl acetate) as solvents to afford the title compound **4.5b** (0.32 g, 0.30 mmol, 60%) as a yellow solid. ^{1}H NMR (300 MHz,

$CDCl_3$) δ 7.58 (d, *J* = 16 Hz, 2H, CH), 7.0 (s, 4H, Aromatic CH), 6.94 (s, 2H, Aromatic CH), 6.62 (d, *J* = 16 Hz, 2H, CH), 5.22 (d, *J* = 6 Hz, 2H, H-2), 5.12 (d, *J* = 10 Hz, 2H, H-3), 4.93 (d, *J* = 6 Hz, 2H, H-1), 4.22 (dd, *J* = 5, 12 Hz, 2H, H-4), 4.07 (m, 4H, H-6a, 6b), 3.84 (t, 2 H, H-5), 3.76 (s, 6 H, 2 OCH_3), 2.0 – 1.97 (m, 24 H, 8 CH_3), 1.41 (s, 6 H, 2 CH_3). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 197.9 (s, 2 C=O), 170.6 – 169.5 (m, 8 C=O), 150.5 (s, OCH_3), 148.6 (s, OCH_3), 144.8 (s, CH), 130.9 (s, CH), 122.4 (s, aromatic), 120.6 (s, aromatic), 119.2 (s, aromatic), 111.7 (s, aromatic), 100.4 (s, anomeric, C-1), 72.3 (s, C-3), 71.3 (s, C-5), 68.1 (s, C-2), 61.6 (s, C-4), 60.8 (s, OCH_3), 20.9 – 20.6 (m, CH_3). IR (ATR, neat): $\tilde{\nu}$ = 2970 (m), 1739 (s), 1507 (s), 1208 (s), 1049 (s), 981 (s) cm^{-1}.

Methylated De-Acetylated Glucosyl Curcumin (4.6b)

To the methylated glucosyl curcumin **4.5b** (0.45 g, 0.42 mmol) in MeOH, a few drops of 0.1 M NaOMe solution were added and stirred for 2 h at room temperature. Dowex® H^+ resin was added to neutralize, and the reaction mixture was stirred for 20 min. The resin was filtered off and the filtrate was concentrated under reduced pressure. A pad of silica was used to filter the crude product to afford **4.6b**, yellow solid (0.23 g, 0.32 mmol, 77%, β-only). ^1H NMR (300 MHz, CD_3OD) δ 7.67 (d, *J* = 15 Hz, 2H, CH), 7.14 (m, 6H, aromatic CH), 6.79 (d, *J* = 8 Hz, 2H, CH), 4.65 (s, 2H, H-1), 4.09 (m, 2 H, H-6a), 3.89 (m, 2 H, H-6b), 3.84 (m, 2 H, H-2), 3.67 (m, 2 H, H-3), 3.53 – 3.46 (m, 4 H, H-4, H-5), 3.33 (s, 6 H, 2 OCH_3), 1.47 (s, 6 H, 2 CH_3). $^{13}C\{^1H\}$ NMR (75 MHz, CD_3OD) δ 201.6 (s, 2 C=O), 152.4 (s, OCH_3), 151.6 (s, OCH_3), 147.4 (s, C=O), 146.4 (s, C=O), 131.6 (s, aromatic), 128.8 (s, aromatic), 126.2 (s, aromatic), 125.1 (s, aromatic), 122.6 (s, aromatic), 120.9 (s, aromatic), 118.4 (s, aromatic), 117.4 (s, aromatic), 114.1 (s, =CH), 113.4 (s, =CH), 103.2 (s, anomeric, C-1, β), 79.4 (s, C-5), 79.02 (s, C-3), 77.5 (s, C-2), 75.9 (s, C-4), 72.9 (s, C-6), 57.7 (s, OCH_3), 31.3 (s, 2

CH_3), 23.03 (s, CH_3). IR (ATR, neat): $\tilde{\nu}$ = 3335 (b), 2926 (m), 1577 (s), 1508 (s), 1256 (s), 1050 (s), 981 (s) cm^{-1}. HR FAB MS $[M+Na]^+$ calcd for $[C_{35}H_{44}O_{16}Na]^+$ 743.2525; found 743.2522.

4.5.4 Synthesis of Glycosylated Benzylated Curcumin Derivatives

Galactosyl Pyranose Benzylated Curcumin (4.9a)

To a solution of de-acetylated benzylated curcumin (**4.8**, 0.5 g, 0.91 mmol) in $CHCl_3$ (10 mL), KOH (0.18 g, 3.28 mmol in 5 mL H_2O) was added and stirred for 20 min. Freshly synthesized galactosyl pyranose bromide (**a**, 0.94 g, 2.27 mmol) was added by dissolving in $CHCl_3$ (10 mL), stir for 20 min. NBu_4Br (0.29 g, 0.91 mmol in 7 mL H_2O) was added and the reaction mixture was refluxed for 48 h. The reaction mixture was diluted with CH_2Cl_2 (40 mL), washed with H_2O (2 x 30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography utilizing ethyl acetate and hexanes (slowly increase the ratio of ethyl acetate) as solvents to afford the title compound (**4.9a**, 1.1 g, 0.91 mmol, 65%) as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 15 Hz, 2H, CH), 7.12 (d, *J* = 7 Hz, 8H, aromatic CH), 7.02 (m, *J* = 7 Hz, 6H, aromatic CH), 6.8 (s, 2H, aromatic CH), 6.45 (d, *J* = 15 Hz, 2H, CH), 5.46 – 5.42 (t, 2H, H-2), 5.35 (s, 2H, H-3), 5.02 (dd, *J* = 3, 10 Hz, 2H, H-4), 4.86 (d, *J* = 8 Hz, 2H, H-1), 4.08 (m, 4H, H-6a, 6b), 3.92 – 3.97 (t, 2 H, H-5), 3.73 (s, 6 H, 2 OCH_3), 3.3 (s, 4H, 2 CH_2), 2.09 (s, 6 H, 2 CH_3), 1.96 (m, 18 H, 6 CH_3). $^{13}C\{^1H\}$ NMR (75 MHz, CD_3OD) δ 196.7 (s, 2, C=O), 170.2 (s, 2, C=O), 170.2 (s, 2, C=O), 169.7 (s, 2, C=O), 169.4 (s, 2, C=O), 150.6 (s, OCH_3), 149.5 (s, OCH_3), 136.4 (s, aromatic), 130.4 (s, aromatic), 129.7 (s, aromatic), 122.6 (s, aromatic), 121.9 (m, aromatic), 118.9 (s, aromatic), 111.8 (m, aromatic), 100.7 (s, anomeric, C-1), 70.9 (s, C-5), 70.1 (s, C-3), 68.4 (s, C-2), 68.0 (s, C-4), 66.8 (s, C-6), 20.7 – 20.4 (m, 2

CH_2). IR (ATR, neat): ṽ = 2995 (m), 1742 (s), 1593 (m), 1506 (m), 1208 (s), 1030 (s) cm^{-1}. HR FAB MS $[M+Na]^+$ calcd for $[C_{63}H_{68}O_{24}Na]^+$ 1231.3961; found 1231.3993.

De-Acetylated Galactosyl Benzylated Curcumin (4.10a)

To the galactosyl benzylated curcumin (**4.9a**, 0.5 g, 0.41 mmol) in MeOH (7 mL), a few drops of 0.1 M NaOMe solution was added and stirred for 2 h at room temperature. Dowex® H^+ resin was added to neutralize and stir for 20 min. The resin was filtered off and the filtrate was concentrated under reduced pressure. A pad of silica was used to filter the crude product to afford **4.10a**, yellow solid (0.25 g, 0.28 mmol, 71%, β-only). ^1H NMR (300 MHz, CD_3OD) δ 7.61 (d, *J* = 15 Hz, 2H, CH), 7.13 (s, 11 H, Aromatic CH), 7.05 – 6.98 (m, 5H, CH), 6.69 (d, *J* = 16 Hz, 2 H, CH), 3.89 (s, 2 H, H-6a), 3.84 (s, 2 H, H-6b), 3.79- 3.73 (m, 4 H, H-2, H-3), 3.67 (d, 2 H, H-5), 3.59 (dd, 2 H, H-4), 3.36 (s, 4 H, CH_2), 3.33 (s, 6 H, 2 OCH_3). $^{13}C\{^1H\}$ NMR (75 MHz, CD_3OD) δ 201.2 (s, 2 CO), 153.3 (m, 2 OCH_3), 146.9 (s, CH), 140.6 (s, aromatic), 134.3 (s, aromatic), 132.8 (s, aromatic), 131.7 (s, aromatic), 130.4 (s, aromatic), 126.7 (s, aromatic), 119.7 (s, aromatic), 115.4 (s, aromatic), 105.2 (s, anomeric, C-1, β), 79.5 (s, C-5), 77.1 (s, C-3), 74.6 (s, C-2), 72.7 (s, C-4), 64.9 (s, C-6), 42.1 – 41.8 (m, 2 CH_2). IR (ATR, neat): ṽ = 3336 (b), 2920 (b), 1588 (m), 1506 (s), 1255 (s), 1047 (s), 983 (s) cm^{-1}. HR FAB MS $[M+Na]^+$ calcd for $[C_{47}H_{52}O_{16}Na]^+$ 895.3149; found 895.3148.

Glucosyl pyranose Benzylated Curcumin (4.9b)

To a solution of de-acetylated benzylated curcumin (**4.8**, 0.25 g, 0.45 mmol) in $CHCl_3$ (5 mL), KOH (0.09 g, 1.64 mmol in 5 mL H_2O) was added and stirred for 20 min. Freshly synthesized glucosyl pyranose bromide (**b**, 0.5 g, 1.14 mmol) dissolved in $CHCl_3$ (7 mL), was added and stirred for 20 min. NBu_4Br (0.15 g, 0.45 mmol in 5 mL H_2O) was added and the reaction mixture was refluxed for 48 h. The reaction mixture

was diluted with CH_2Cl_2 (20 mL), washed with H_2O (2 x 20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography utilizing ethyl acetate and hexanes (slowly increase the ratio of ethyl acetate) as solvents to afford the title compound **4.9b** (0.26 g, 0.22 mmol, 47%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, *J* = 15 Hz, 2H, CH), 7.13 (d, *J* = 7 Hz, 8H, aromatic CH), 7.02 (d, *J* = 7 Hz, 6H, aromatic CH), 6.76 (s, 2H, aromatic CH), 6.46 (d, 2H, CH), 5.21 (d, *J* = 8 Hz, 2H, H-2), 5.11 – 5.08 (m, 2H, H-3), 4.99 - 4.97 (m, 2H, H-4), 4.96 (d, *J* = 7 Hz, 2H, H-1), 4.08 -4.03 (m, 4H, H-6a, 6b), 3.78 (s, 2 H, H-5), 3.72 (s, 6 H, 2 OCH_3), 3.30 (s, 4H, 2 CH_2), 2.01-1.97 (s, 24 H, 8 CH_3). $^{13}C\{^1H\}$ NMR (75 MHz, CD_3OD) δ 199.5 (s, C=O), 199.3 (s, C=O), 173.2 (s, C=O), 173.1 (s, C=O), 172.9 (s, C=O), 172.3 (s, C=O), 172.1 (s, C=O), 171.9 (s, C=O), 153.2 (s, OCH_3), 151.5 (s, OCH_3), 149.5 (s, =CH), 146.8 (s, =CH), 145.5 (s, =CH), 139.1 (s, aromatic), 133.2 (s, aromatic), 130.8 (s, aromatic), 129.3 (s, aromatic), 126.8 (s, aromatic), 125.4 – 125.1 (m, aromatic), 123.2 (s, aromatic), 121.8 (s, aromatic), 117.5 (s, aromatic), 114.1 (s, aromatic), 112.6 (s, aromatic), 105.2 (s, anomeric, β C-1), 102.7 (s, anomeric, α C-1), 76.7 (s, C-5), 74.8 (s, C-3), 74.3 (s, C-2), 73.6 (s, C-4), 70.8 (s, OCH_3), 64.6 (s, C-6), 58.8 – 58.6 (m, CH_3), 23.4 – 23.2 (m, 2 CH_2). IR (ATR, neat): $\tilde{\nu}$ = 2960 (m), 1739 (s), 1507 (s), 1215 (s), 1048 (s), 981 cm^{-1}. HR FAB MS $[M+Na]^+$ calcd for $[C_{63}H_{68}O_{24}Na]^+$ 1231.3942; found 1231.3993.

De-Acetylated Glucosyl Benzylated Curcumin (4.10b)

To the glucosyl benzylated curcumin (**4.9b**, 0.5 g, 0.41 mmol) in MeOH (7 mL), a few drops of 0.1 M NaOMe solution was added and stirred for 2 h at room temperature. Dowex® H^+ resin was added to neutralize and stir for 20 min. The resin was filtered off and the filtrate was concentrated under reduced pressure. A pad of silica was used to filter the crude product to afford **4.10b** as a yellow solid (0.25 g, 0.28 mmol, 71%, β-

only). ^{1}H NMR (300 MHz, CD_3OD) δ 7.61 (d, *J = 15 Hz*, 2H, CH), 7.17 - 7.09 (m, 11H, aromatic CH), 7.05 – 7.02 (m, 5 H, aromatic CH), 6.65 (d, *J = 15 Hz*, 2 H, CH), 3.89 (s, 2 H, H-6a), 3.79 (s, 2 H, H-6b), 3.73 (s, 4 H, CH_2), 3.69 (s, 2 H, H-2), 3.61 (d, 2 H, H-3), 3.57 (d, 2H, H-4), 3.40 (d, 2H, H-5), 3.36 (s, 6 H, 2 OCH_3). $^{13}C\{^{1}H\}$ NMR (75 MHz, CD_3OD) δ 206.4 (s, 2 CO), 152.1 (m, 2 OCH_3), 146.7 (m, CH), 142.2 (s, aromatic), 139.4 (s, aromatic), 132.9 (s, aromatic), 130.6 (s, aromatic), 128.4 (s, aromatic), 125.8 (s, aromatic), 117.9 (s, aromatic), 113.1 (s, aromatic), 103.5 (s, anomeric, C-1, β), 79.6 (s, C-5), 76.4 (s, C-3), 72.4 (s, C-2), 63.9 (s, C-4), 57.9 (s, C-6), 40.6 (s, 2 CH_2), 30.01 (s, CH_2), 30.3 (s, CH_2). IR (ATR, neat): $\tilde{\nu}$ = 3360 (b), 2920 (b), 1580 (m), 1507 (s), 1256 (s), 1045 (s) cm^{-1}.

4.5.5 Synthesis of Galactosidase Mono-Carbonyl Curcumin Derivative

Synthesis of Mono-Carbonyl Curcumin (4.13) [45]

To a solution of vanillin (1 g, 6.57 mmol) and cyclohexanone (0.7 mL, 6.57 mmol) ethanol (2 mL) was added. Then concentrated HCl (0.2 mL) was added slowly and stirred overnight at 30 ℃. Glacial acetic acid (AcOH) and H_2O (1:1) were added to the reaction mixture and filtered under vacuum using a Buchner funnel. The solid residue was washed with ethanol (3 mL) and water (5-7 mL). The yellow colored solid (1.4 g, 3.87 mmol, 59%) was dried under reduced pressure. NMR spectral data of 4.13 matched the literature. ^{1}H NMR (300 MHz, DMSO-D_6) δ 7.67 (s, 2 H, 2 CH), 7.02 - 7.00 (d, 2 H, aromatic CH), 6.99 – 6.87 (m, 4 H, aromatic CH), 5.79 (s, 2 H, aromatic OH), 3.90 (s, 6 H, 2 OCH_3), 2.88 – 2.84 (s, 4 H, 2 CH_2), 1.77 – 1.73 (m, 2 H, CH_2).

Galactosyl Mono-Carbonyl Curcumin (4.14a)

Mono carbonyl curcumin (**4.13**, 0.4 g, 1.09 mmol) was dissolved in $CHCl_3$ (5 mL), KOH (0.12 g, 2.18 mmol in 5 mL H_2O) solution was added and stirred for 10 min. A

solution of galactosyl bromide (**a**, 1 g, 2.4 mmol in 7 mL $CHCl_3$) was added and stirred for 10 min. Then a solution of NBu_4Br (0.35 g, 1.09 mmol) in H_2O (5 mL) was added and refluxed for 48 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with H_2O (2 x 20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate and hexanes (slowly increase the ratio of ethyl acetate) as solvents to afford the title compound **4.14a** (1.12 g, 0.31 mmol, 74%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 2 H, 2 CH), 7.22- 7.06 (d, *J* = 8 Hz, 2 H, aromatic CH), 7.01 – 6.85 (m, 4 H, aromatic CH), 5.48 (t, 2H, H-2), 5.37 (s, 2H, H-3), 5.07 (dd, *J* = 3, 10 Hz, 2H, H-4), 4.90 (d, *J* = 8.05 Hz, 2H, H-1), 4.17 - 4.11 (m, 2H, H-6a), 4.09 - 4.05 (m, 2H, H-6b), 4.02 - 3.95 (t, *J* = 7 Hz, 2 H, H-5), 3.77 (s, 6 H, 2 OCH_3), 2.85 (s, 4 H, 2 CH_2), 2.11 (s, 6 H, 2 CH_3), 2.07 (s, 6 H, 2 CH_3), 2.02 - 1.95 (d, 12 H, 4 CH_3), 1.80 - 1.73 (s, 2 H, CH_2). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 190.0 (s, CO), 170.4 (s, CO), 170.3 (s, CO), 170.2 (s, CO), 169.7 (s, CO), 169.5 (s, CO), 150.1 (s, $COCH_3$), 146.4 (s, $COCH_3$), 135.8 (s, CCH), 135.7 (s, CCH), 135.5 (s, aromatic), 133.9 (s, aromatic), 132.4 (s, aromatic), 128.3 (s, aromatic), 119.1 (s, aromatic), 115.1 (s, aromatic), 100.9 (s, anomeric), 71.00 (s, C-5), 70.6 (s, C-3), 68.5 (s, C-2), 66.3 (s, C-4), 61.2 (s, CH_2), 21.1 – 20.3 (m, CH_3). IR (ATR, neat): $\tilde{\nu}$ = 2935 (m), 1743 (s), 1506 (s), 1209 (s), 1050 (s) cm^{-1}. HR FAB MS $[M+Na]^+$ calcd for $[C_{50}H_{59}O_{23}Na]^+$ 1027.3424; found 1050.3442.

De-Acetylated Galactosyl Mono-Carbonyl Curcumin (4.15a)

To the galactosyl mono-carbonyl curcumin **4.14a** (0.2 g, 0.19 mmol) in MeOH (7 mL), a few drops of 0.1 M NaOMe solution were added and stirred for 2 h at room temperature. Dowex® H^+ resin was added to neutralize and stir for 20 min. The resin was filtered off and the filtrate was concentrated under reduced pressure. A pad of silica was used to filter the crude product to afford **4.15a** as a yellow solid (0.10 g, 0.14 mmol,

76%, β-only). ^{1}H NMR (300 MHz, DMSO-D_6) δ 6.84 (s, 2 H, 2 CH), 6.43 – 6.28 (dt, *J* = 9, 14.5 Hz, 5 H, aromatic CH), 6.13 (d, *J* = 8 Hz, 1 H, aromatic CH), 4.22 (d, *J* = 6 Hz, 2H, H-1), 3.07 (s, 6 H, 2 OCH_3), 3.00 (s, 2 H, H-6a), 2.92 – 2.86 (m, 2 H, H-6b), 2.81 (d, 2 H, H-2), 2.78 – 2.76 (m, 2 H, H-3), 2.76 – 2.73 (m, 2 H, H-5), 2.14 (d, 2 H, H-4), 0.97 (s, 2 H, CH_2). $^{13}C\{^{1}H\}$ NMR (75 MHz, CD_3OD) δ 193.9 (s, CO), 153.8 (s, 2 CO), 153.1 (s, 2 CO), 152.6 (s, 2 CO), 152.3 (s, 2 CO), 140.7 (s, $COCH_3$), 138.6 (s, $COCH_3$), 134.4 (s, CCH), 132.1 (s, CCH), 129.5 (s, aromatic), 128.6 (s, aromatic), 120.7 (d, aromatic), 119.8 (m, aromatic), 105.5 (s, anomeric, C-1, β), 80.7 (s, CHO), 78.6 (s, C-5), 75.3 (s, C-3), 73.3 (s, C-2), 65.5 (s, C-4), 60.7 (s, C-6), 33.1 (s, CH_2), 22.7 (s, CH_2). IR (ATR, neat): $\tilde{\nu}$ = 3335 (b), 2921 (m), 1581 (m), 1507 (s), 1242 (s), 1127 (s), 1030 (s), 986 cm^{-1}. HR FAB MS $[M+Na]^+$ calcd for $[C_{34}H_{43}O_{15}Na]^+$ 691.2524; found 691.2596.

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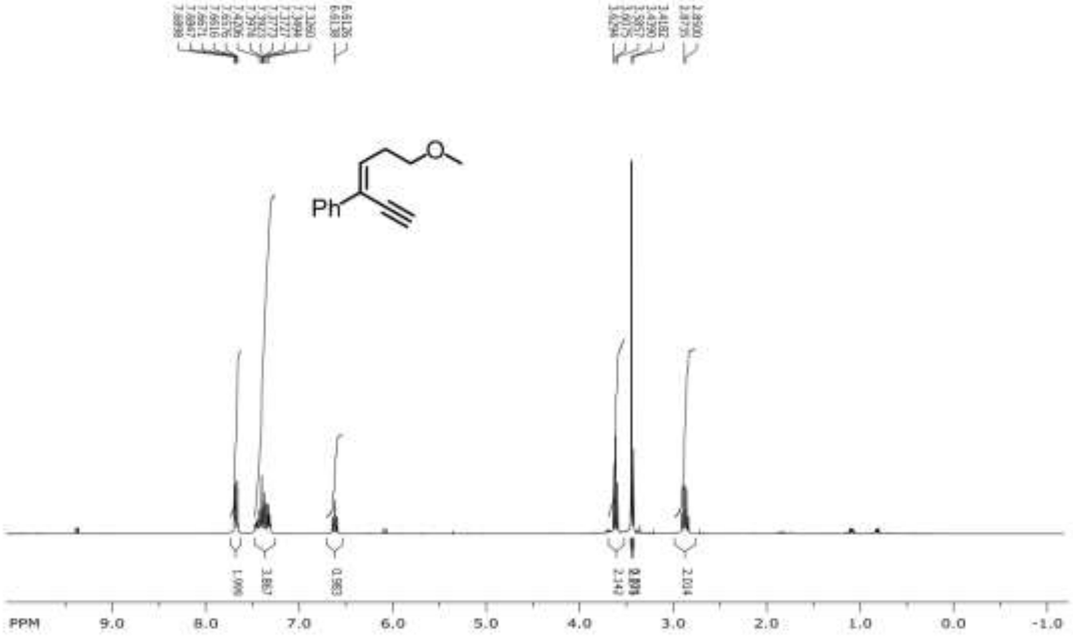
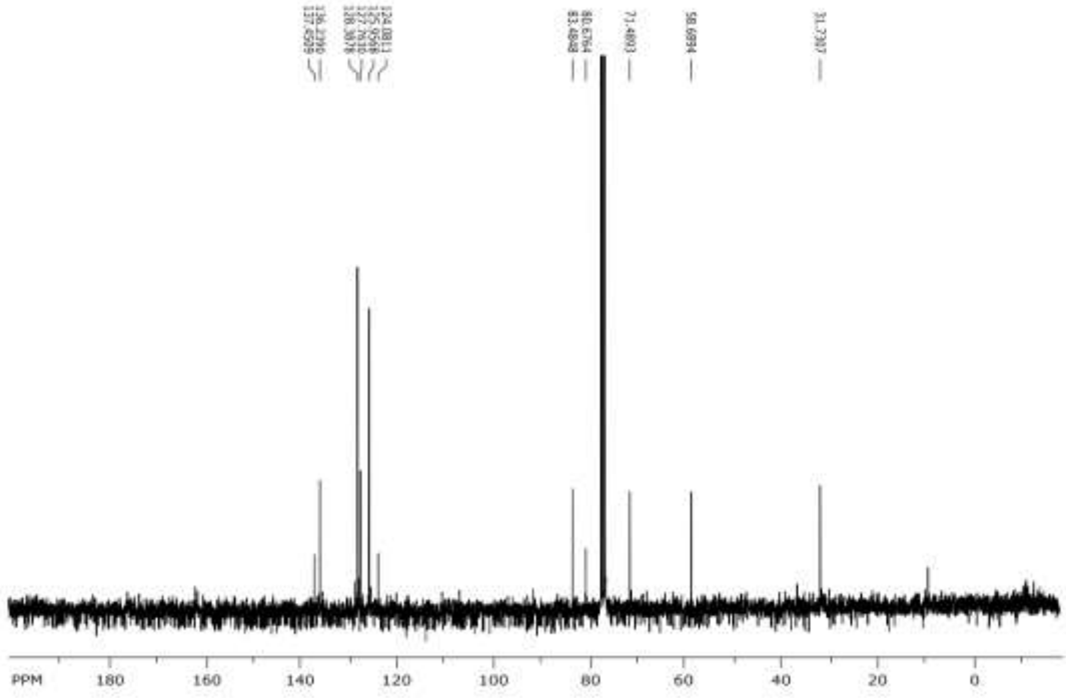
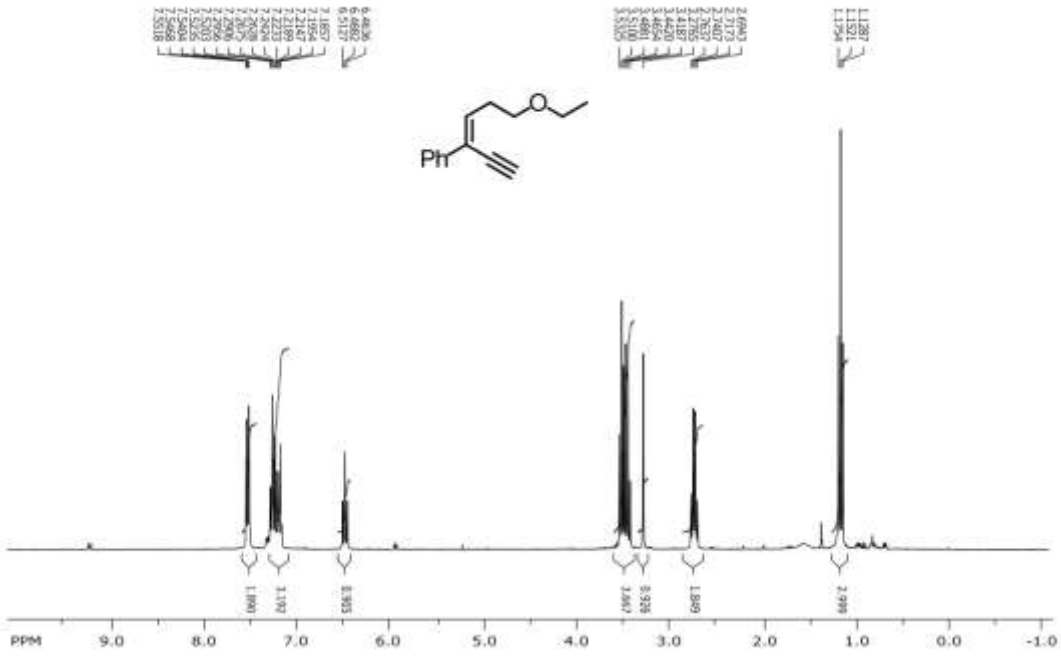
APPENDIX



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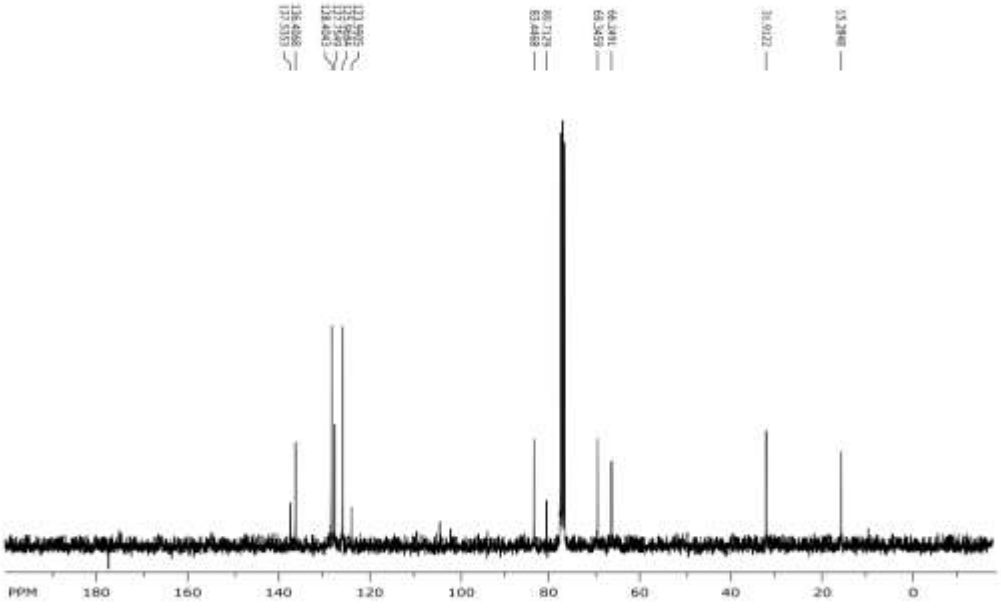
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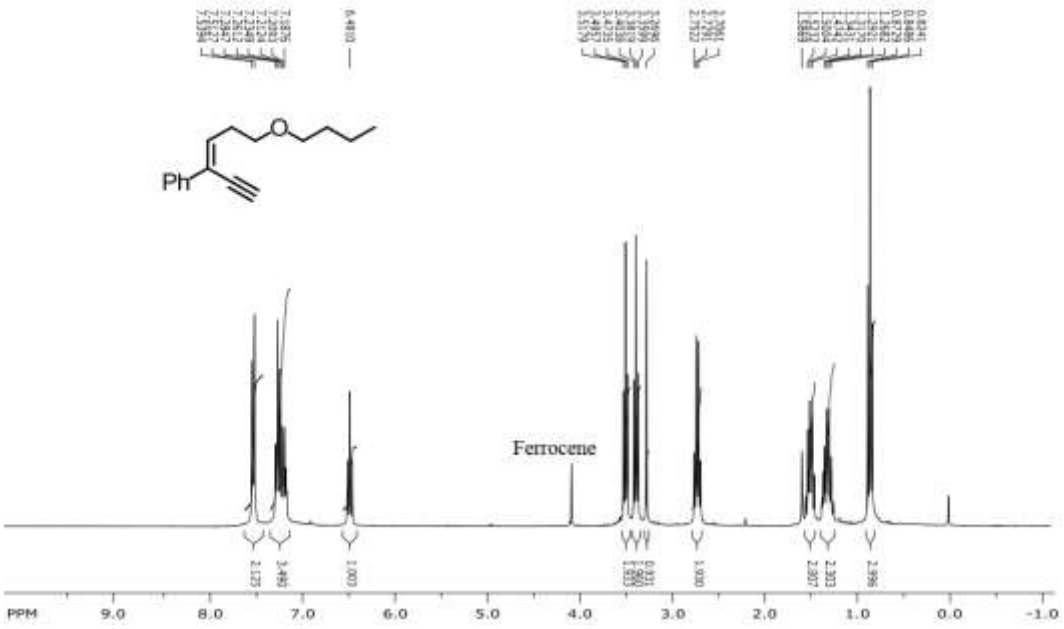
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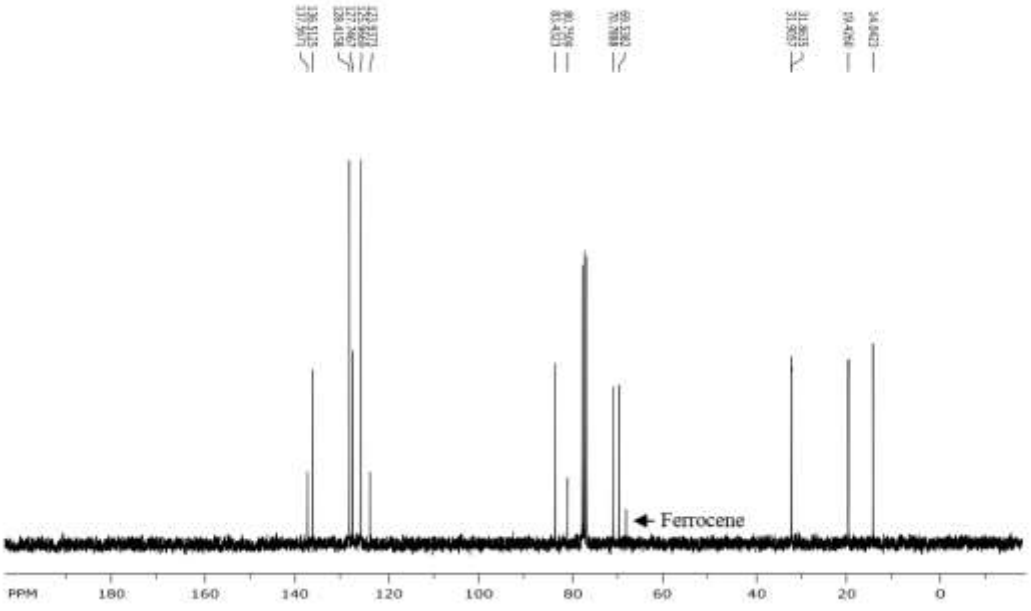
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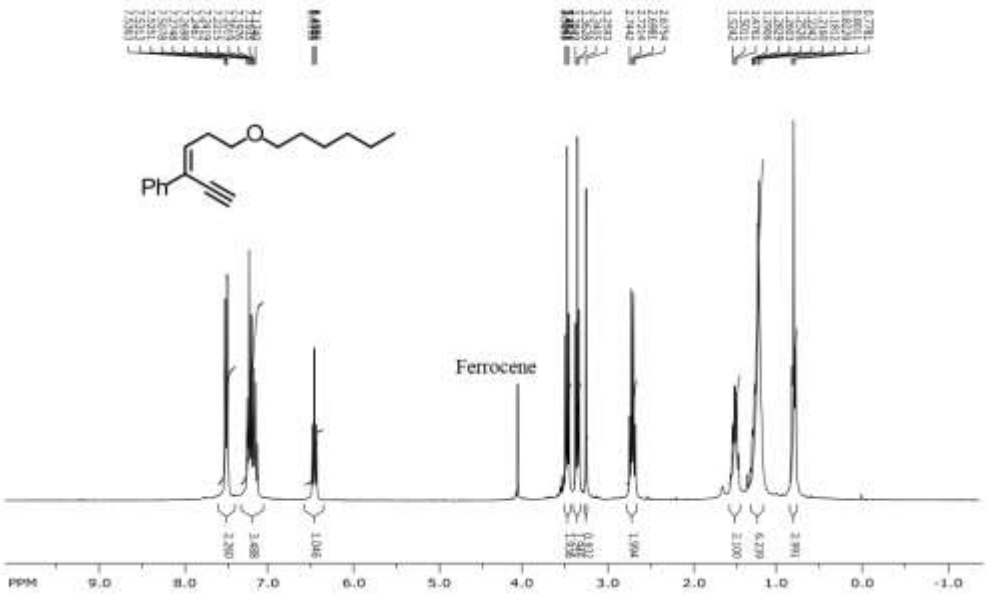
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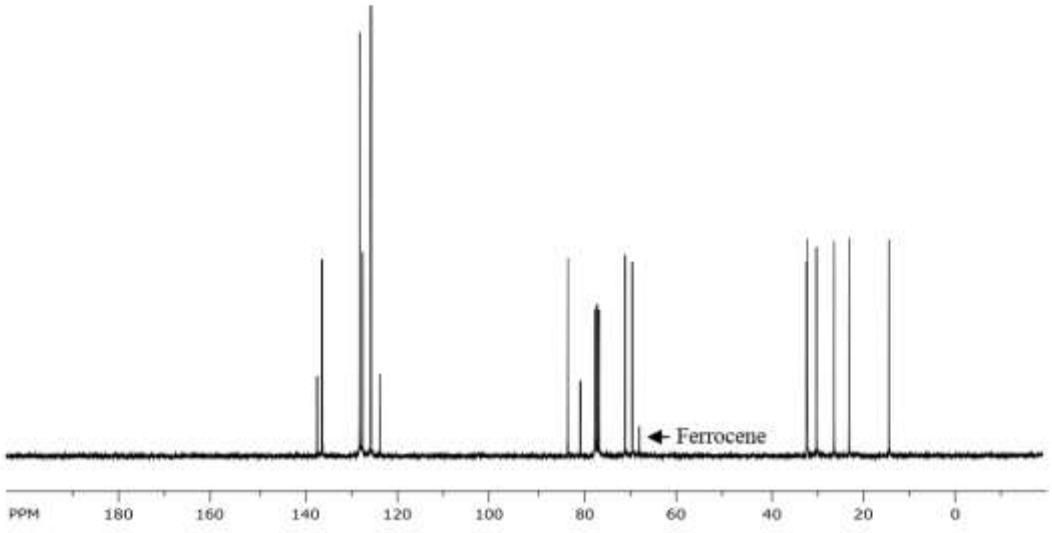
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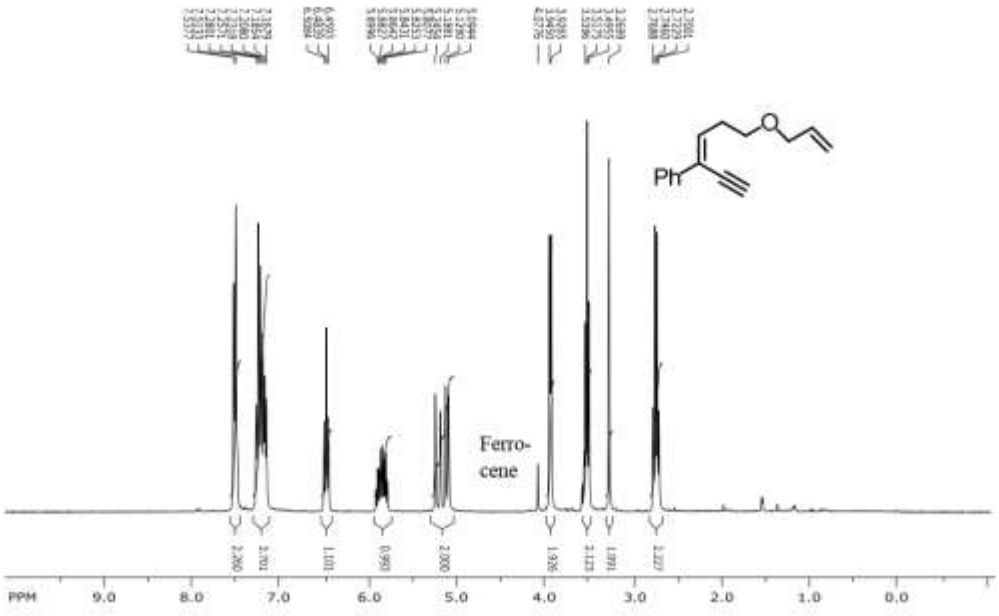
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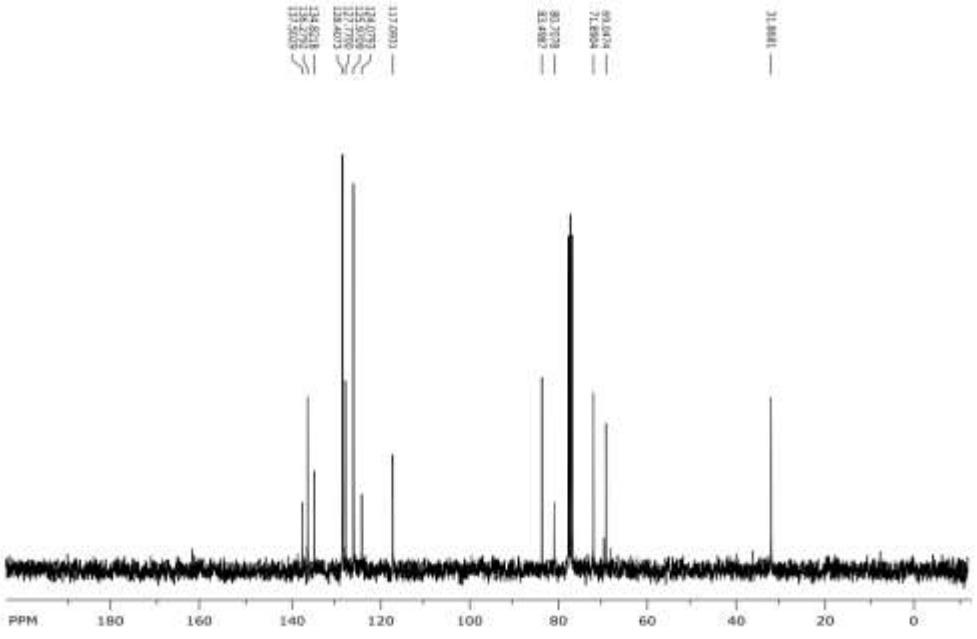
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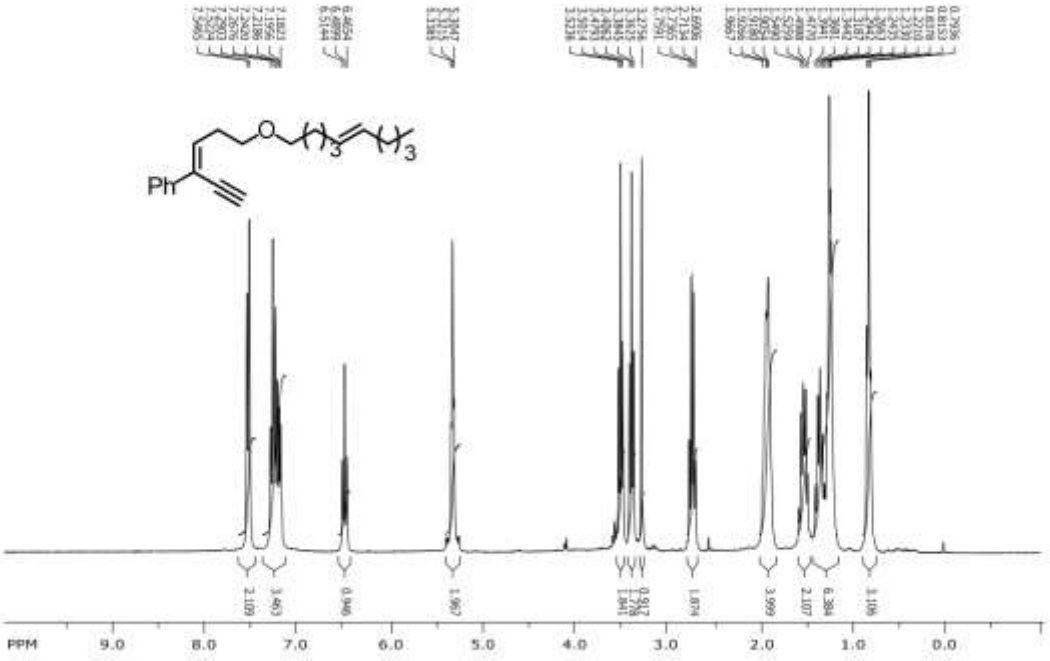
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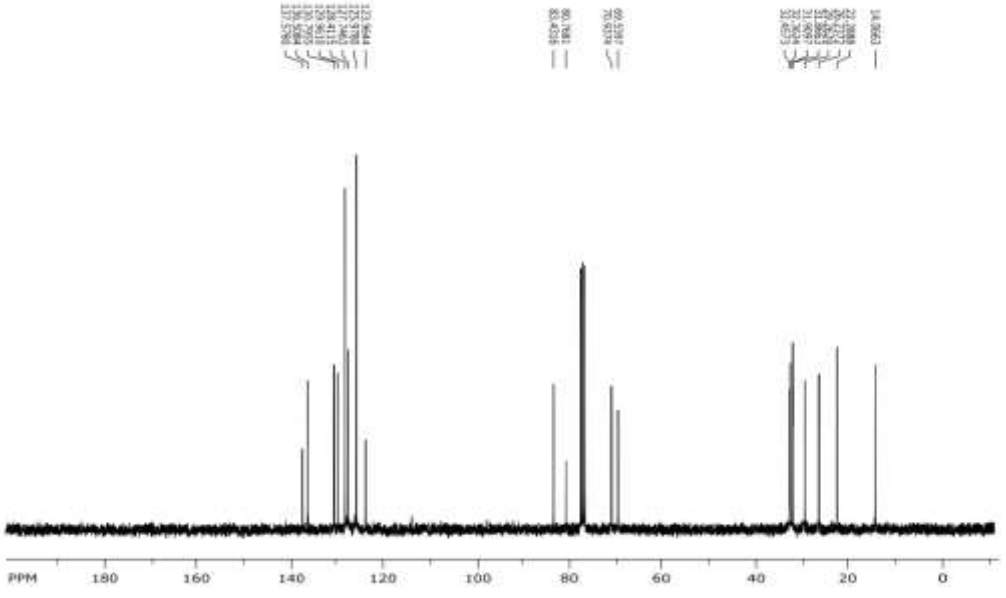
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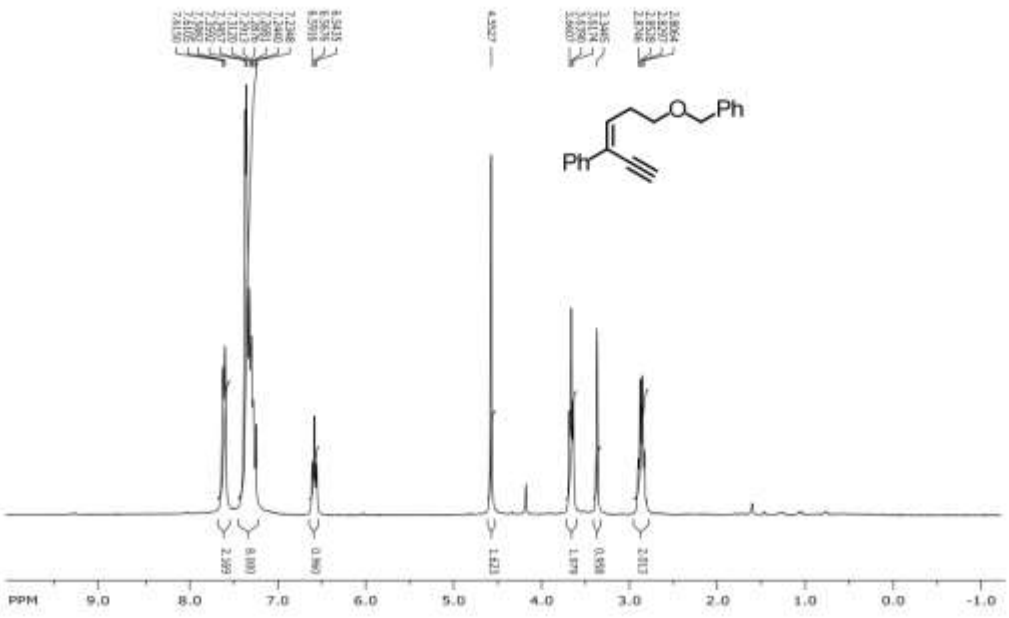
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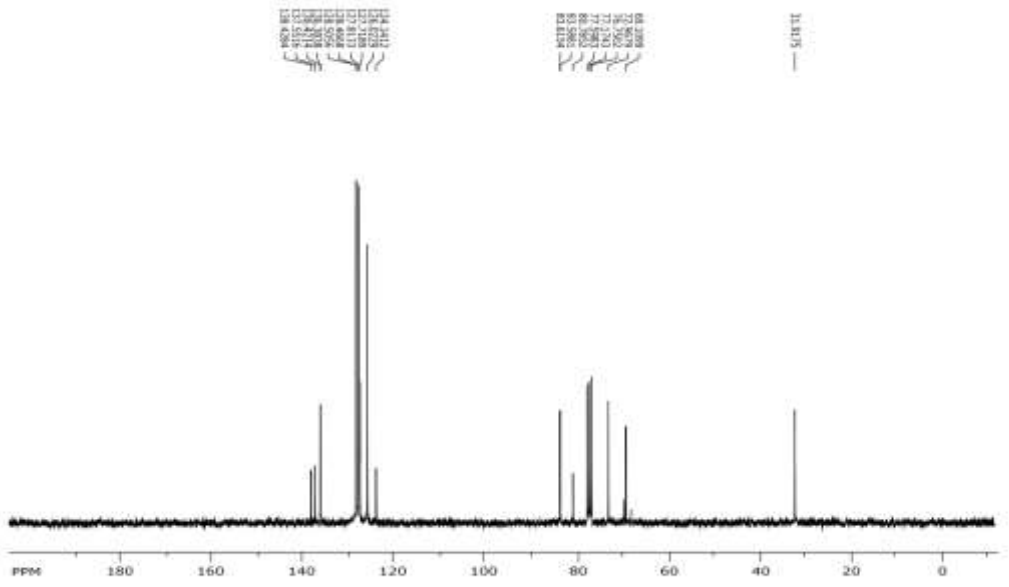
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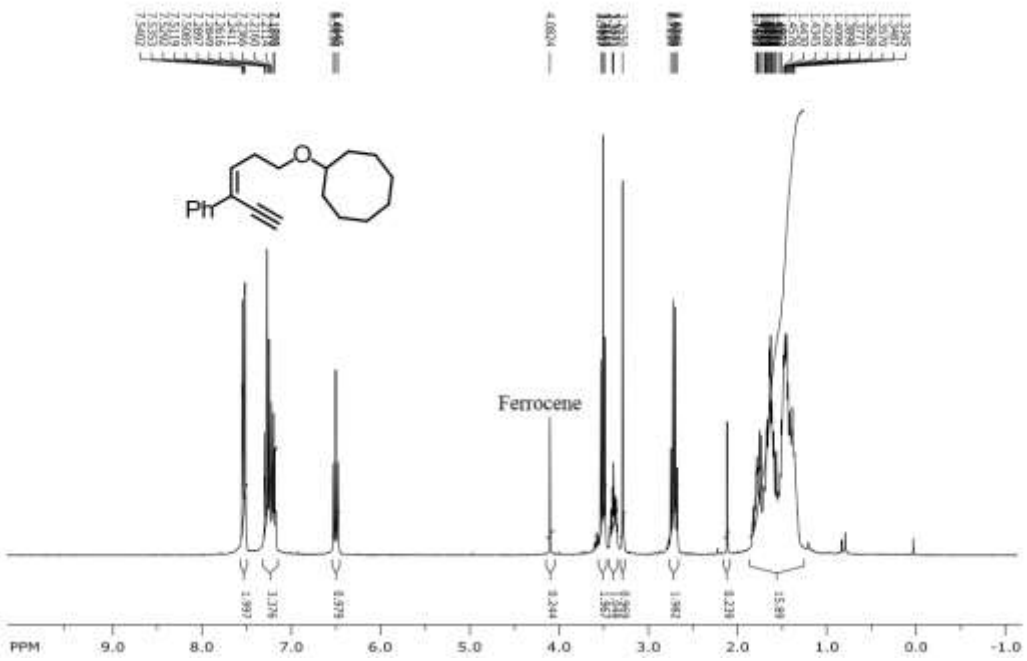
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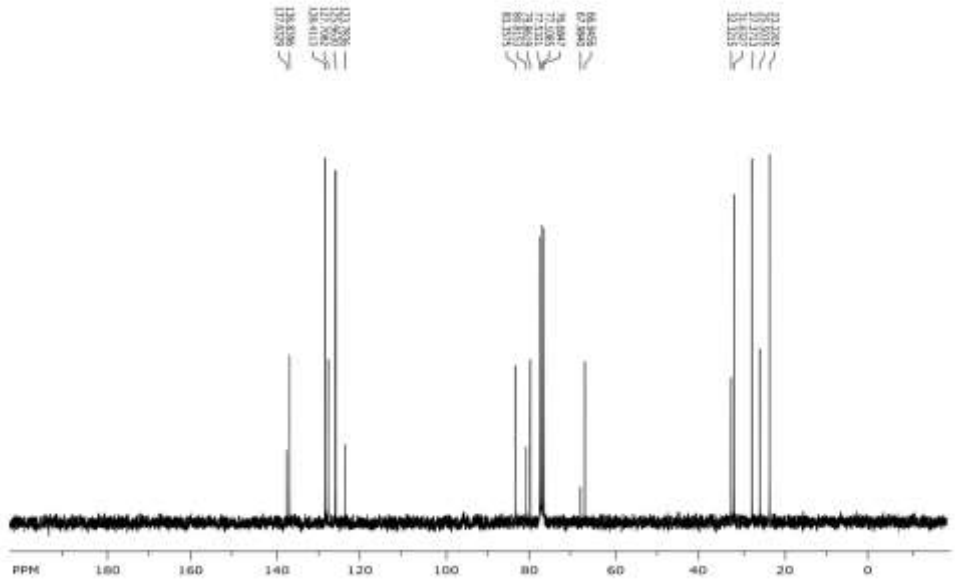
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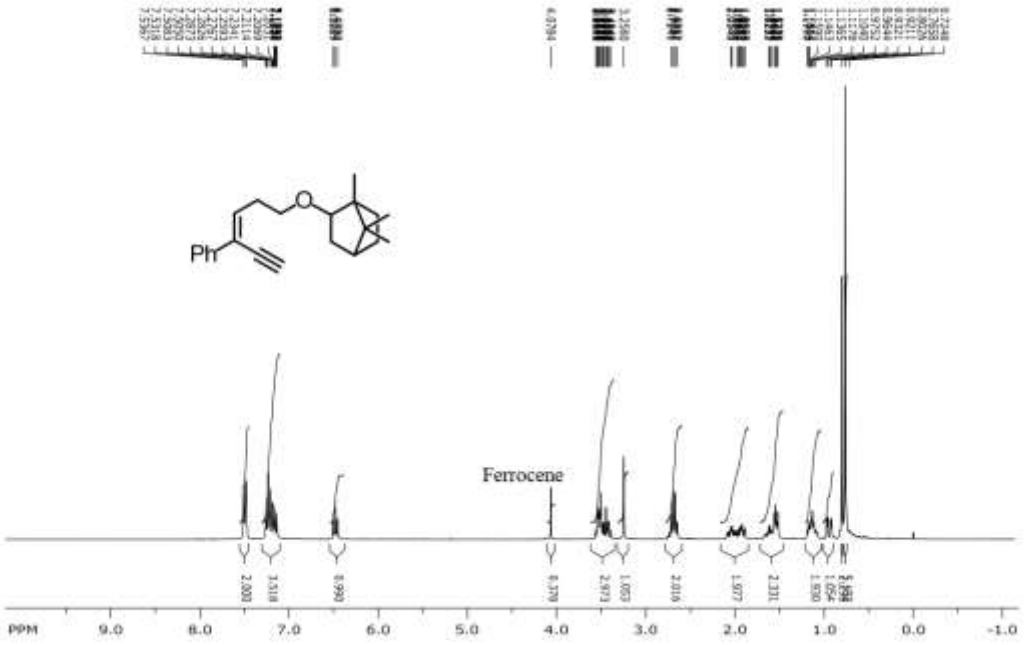
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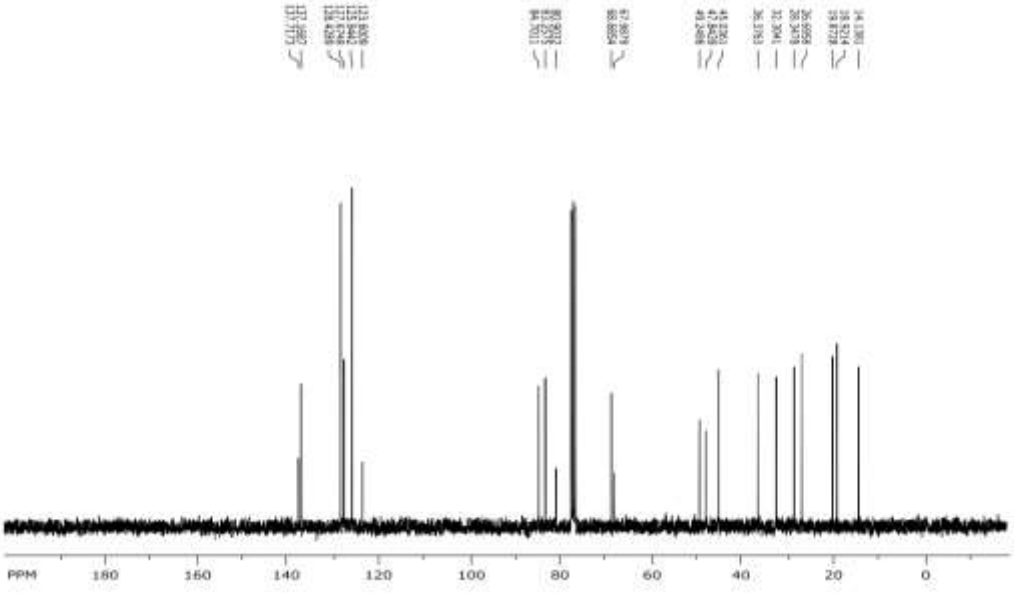
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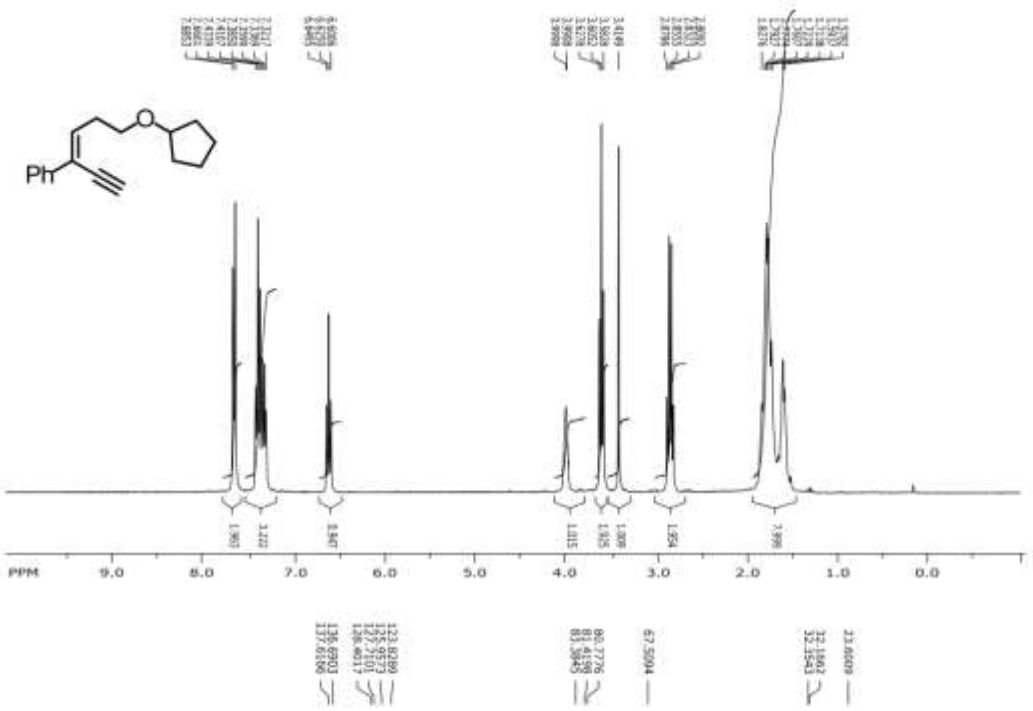
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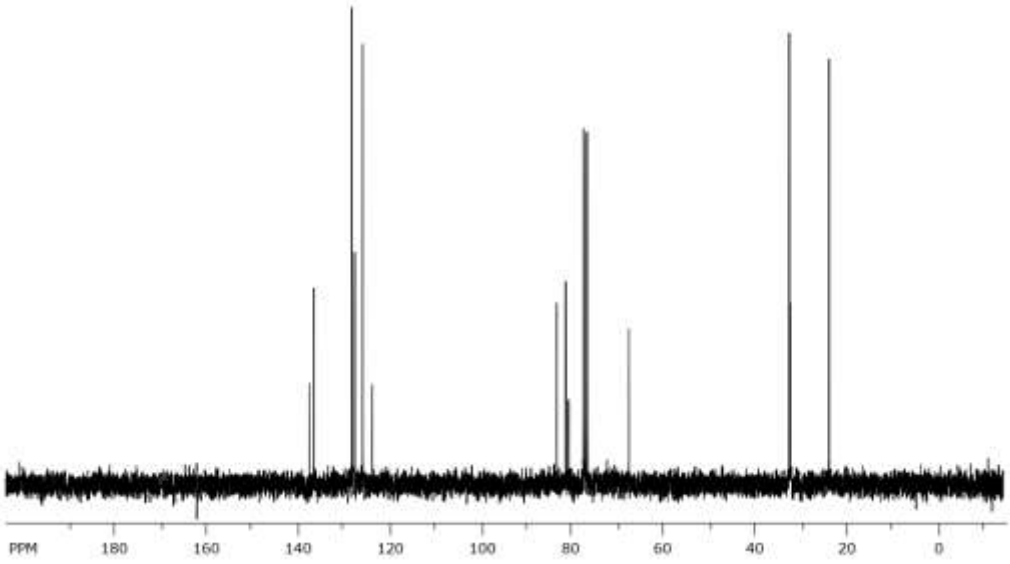
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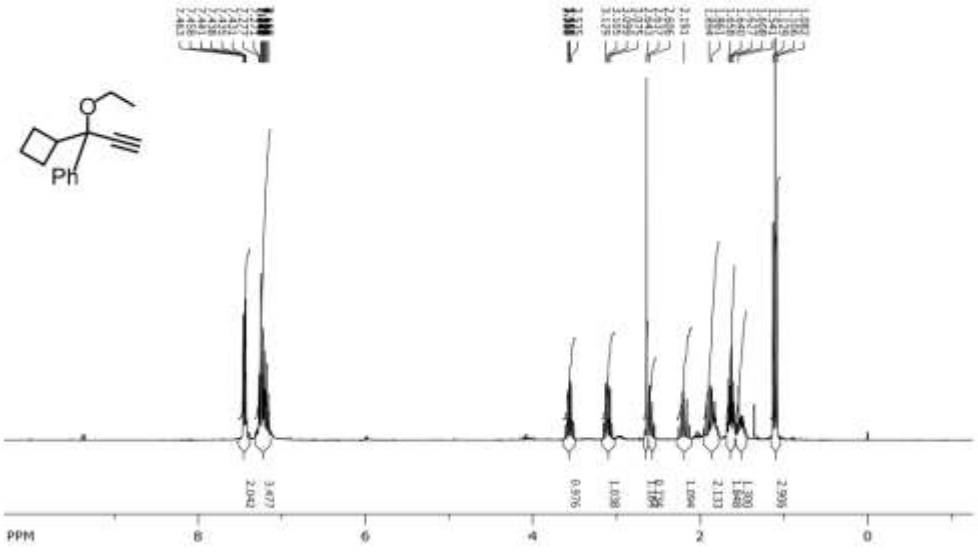
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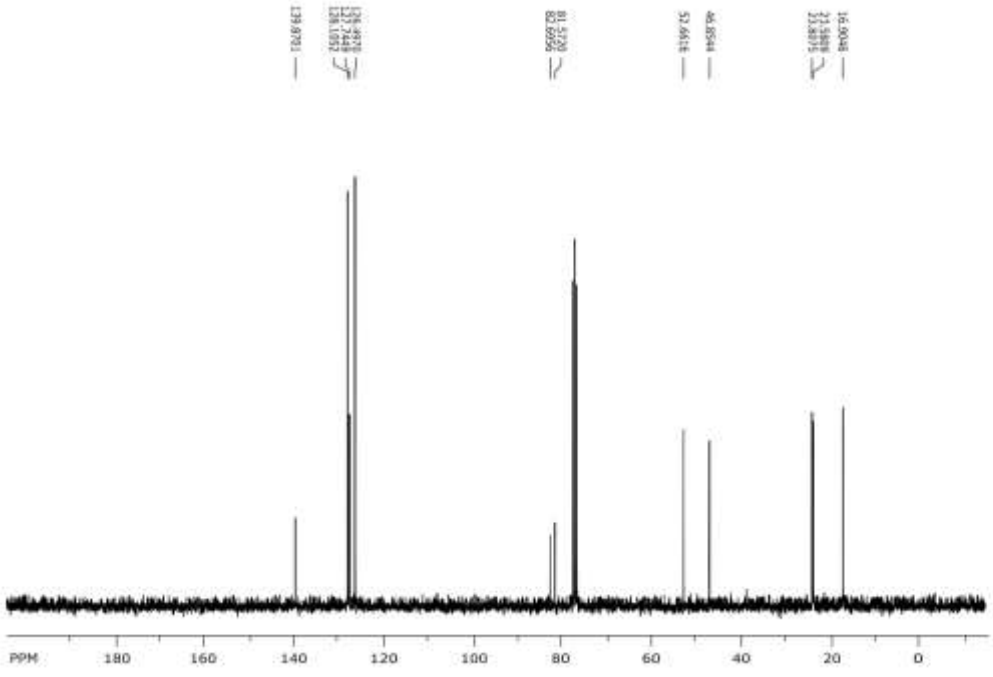
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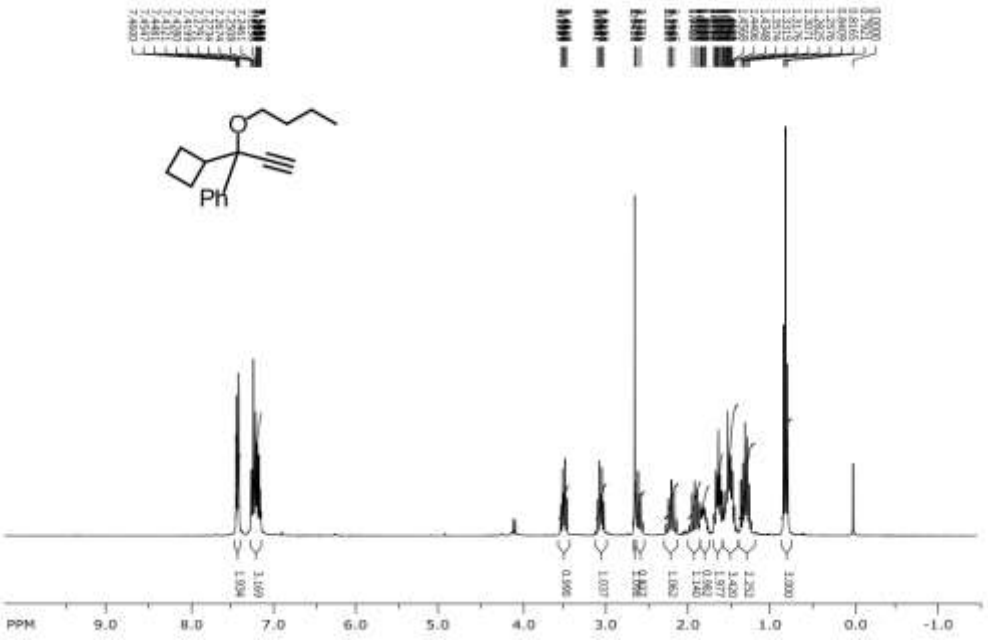
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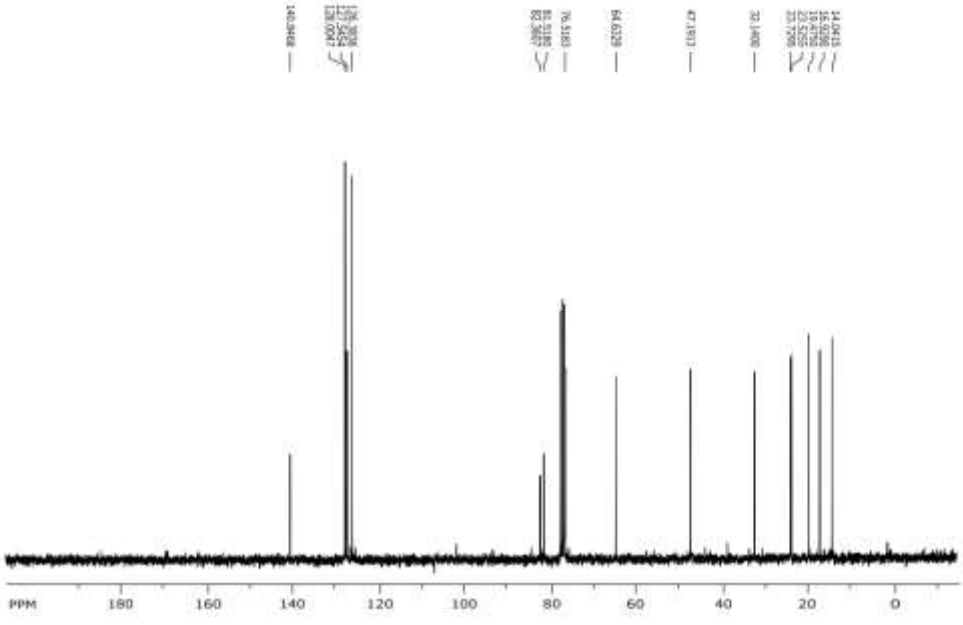
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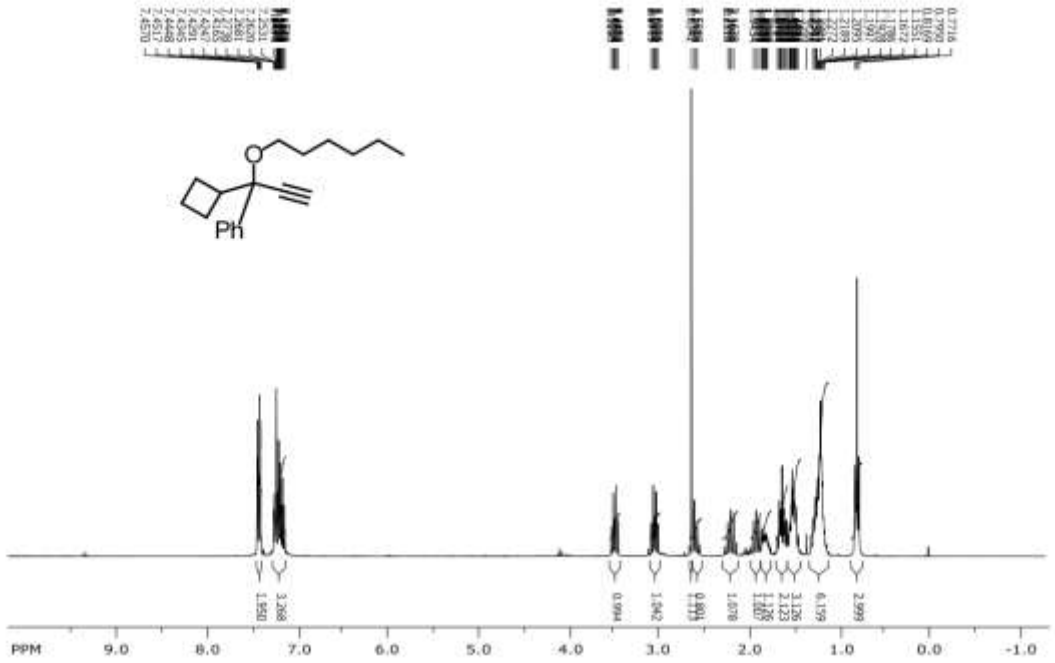
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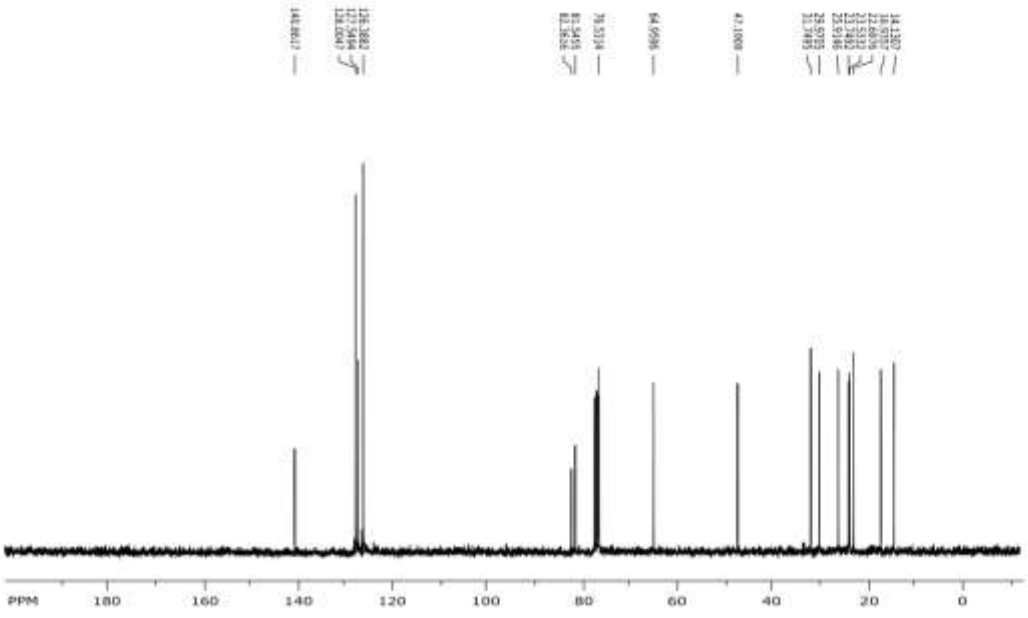
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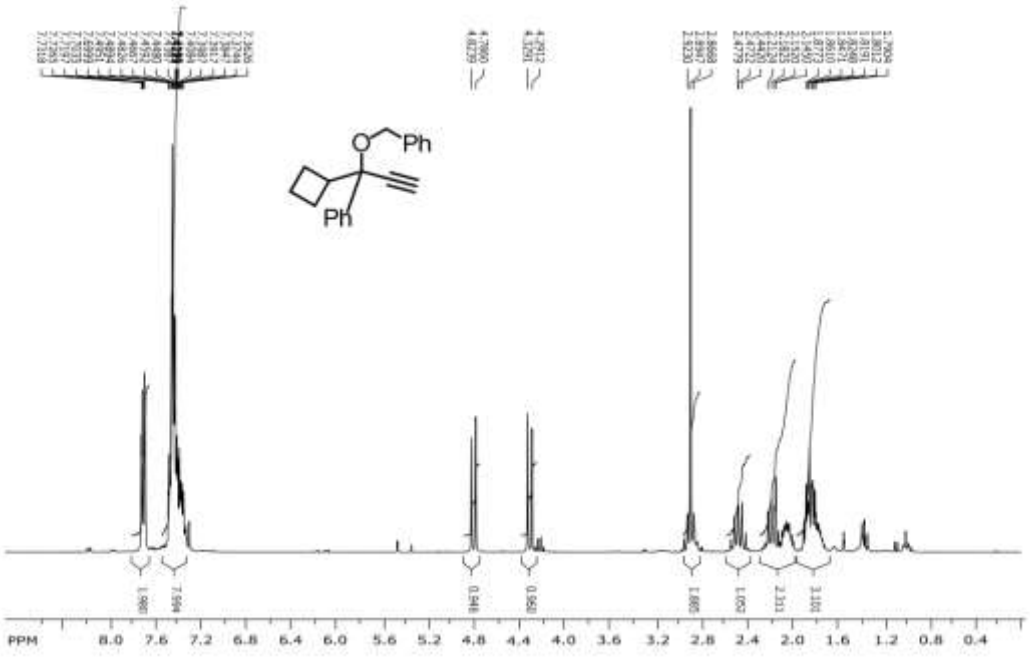
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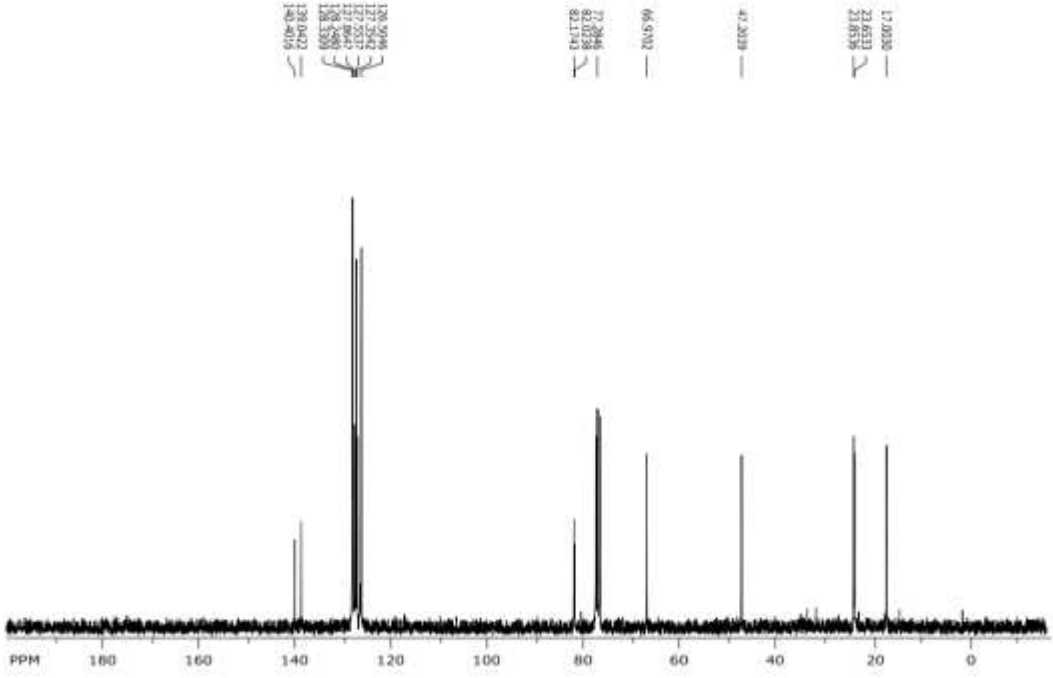
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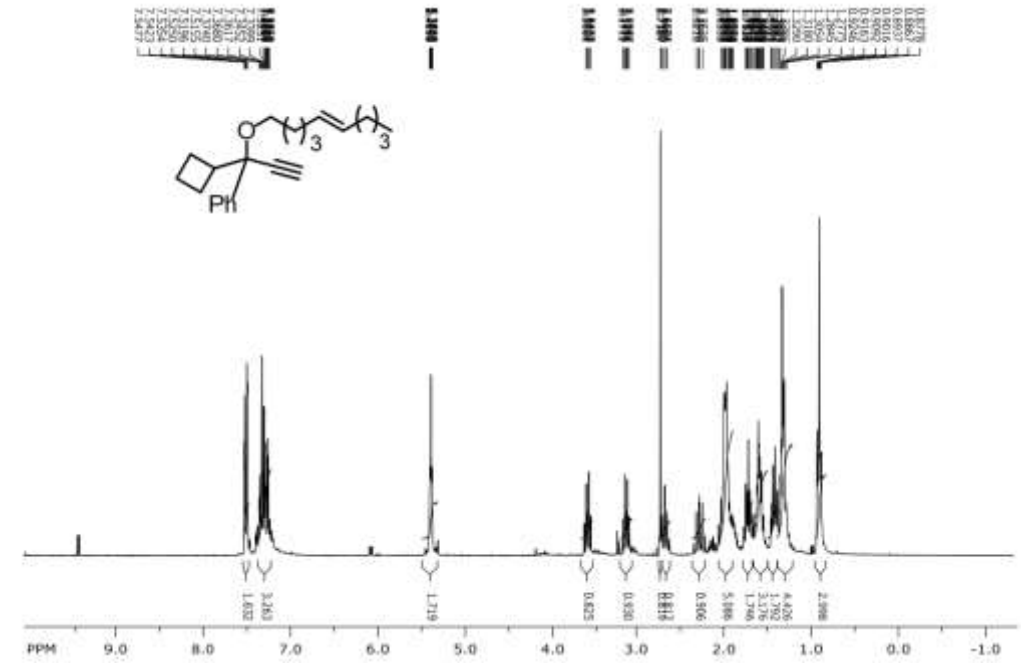
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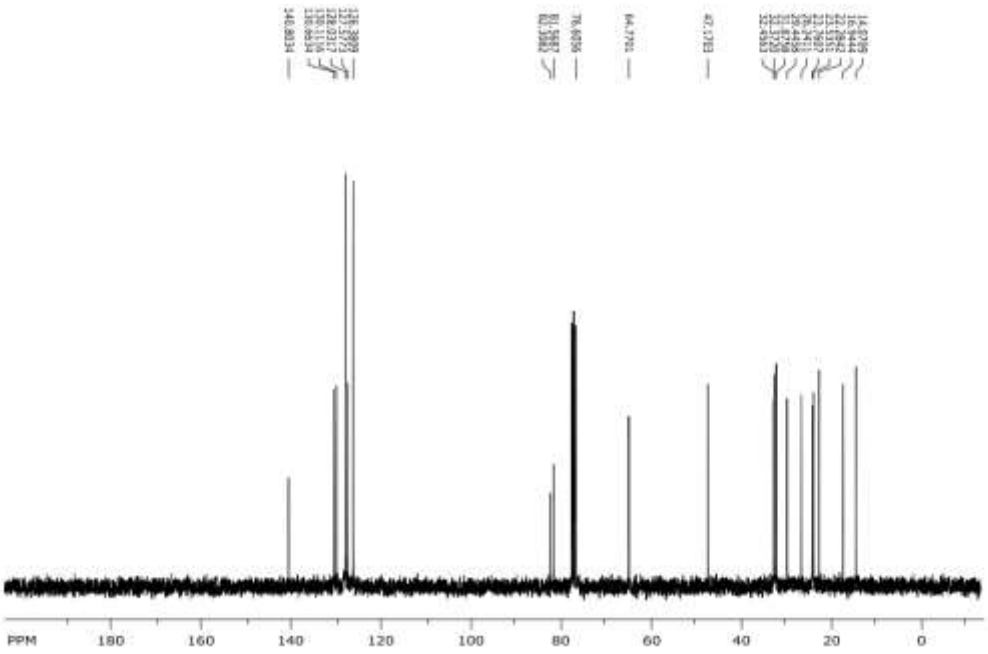
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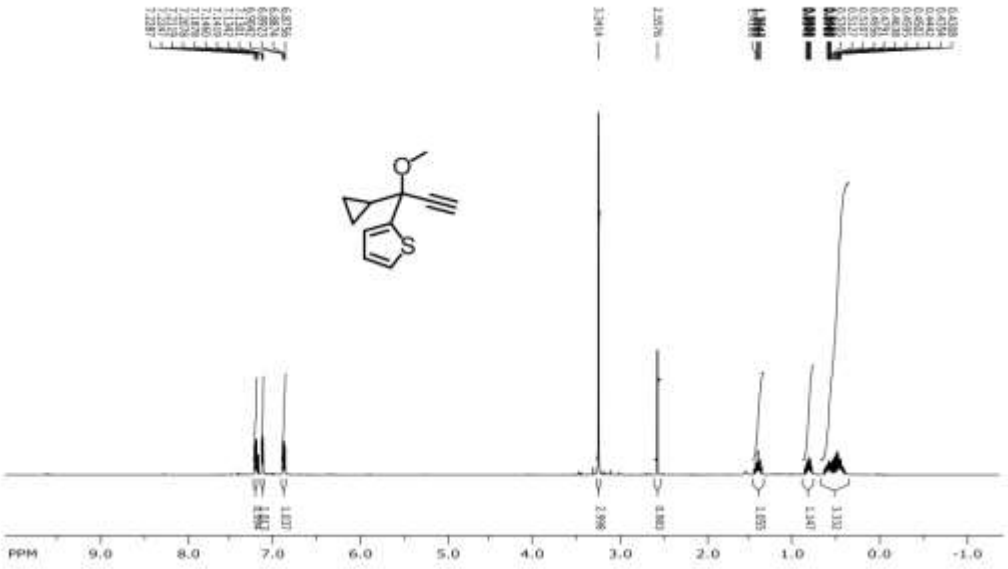
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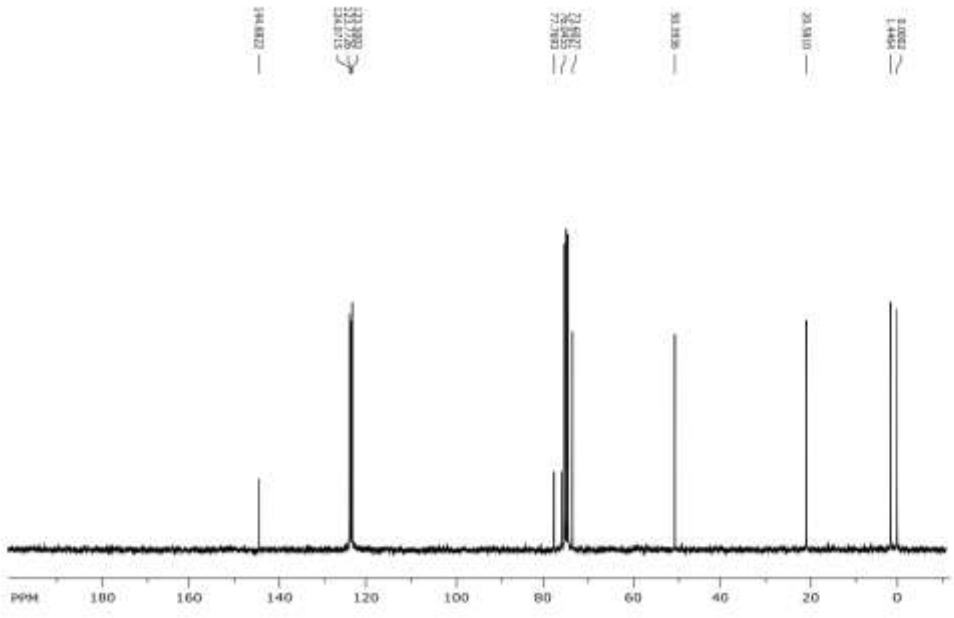
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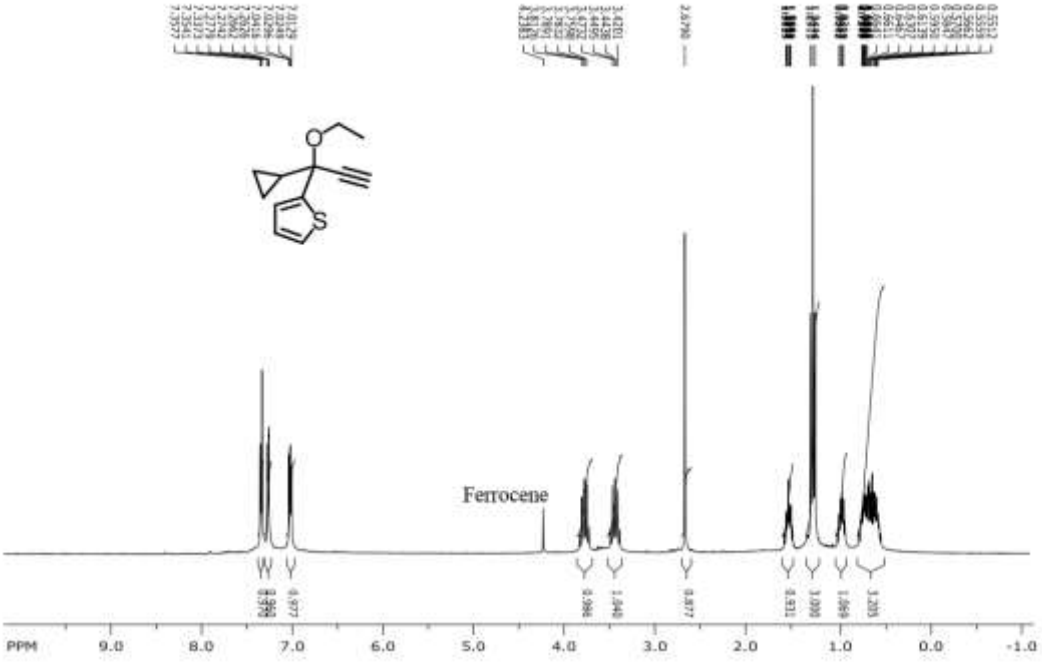
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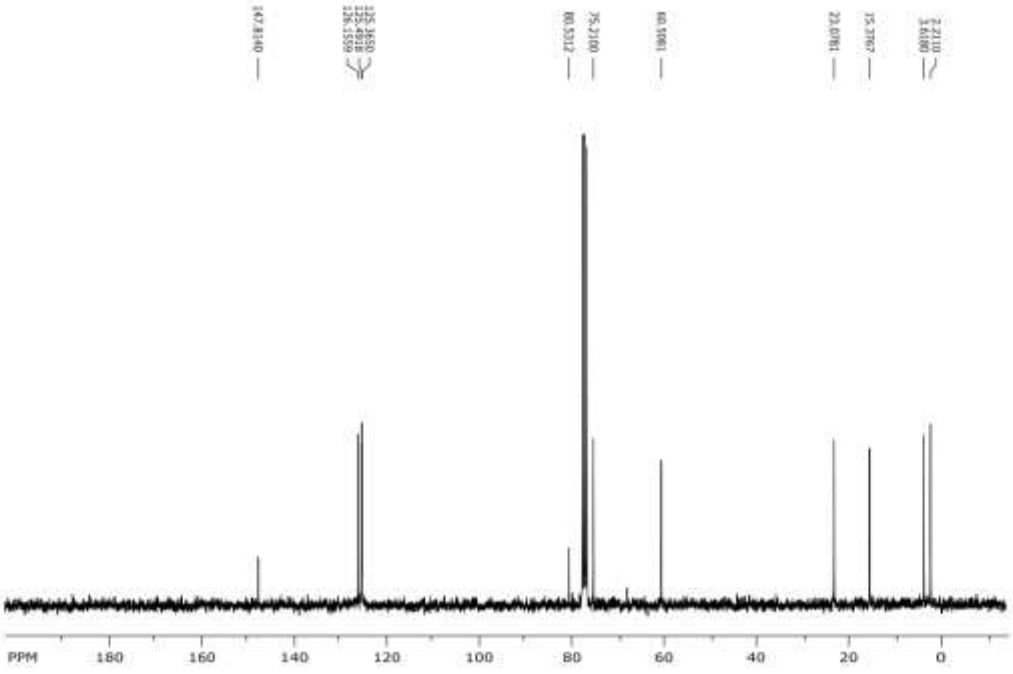
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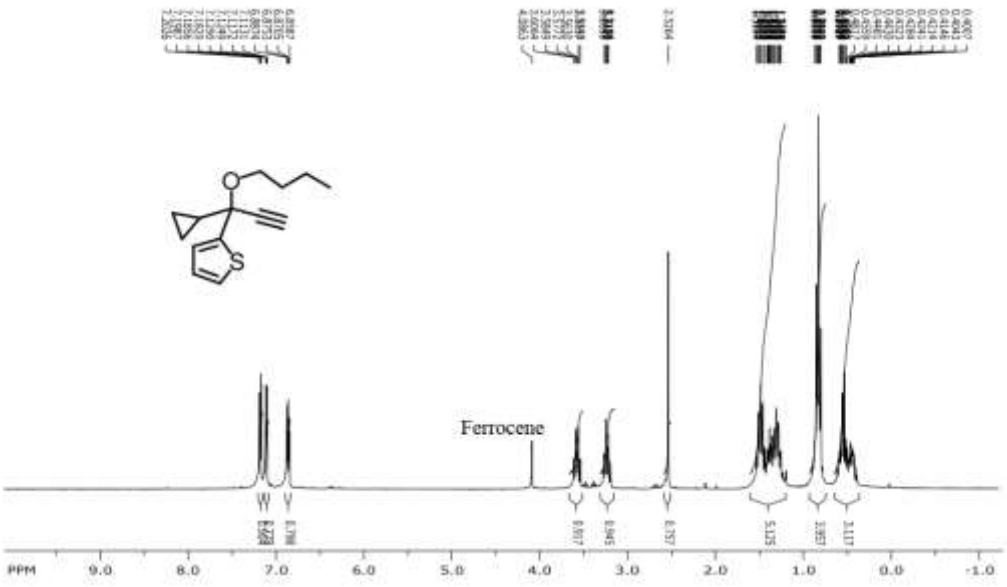
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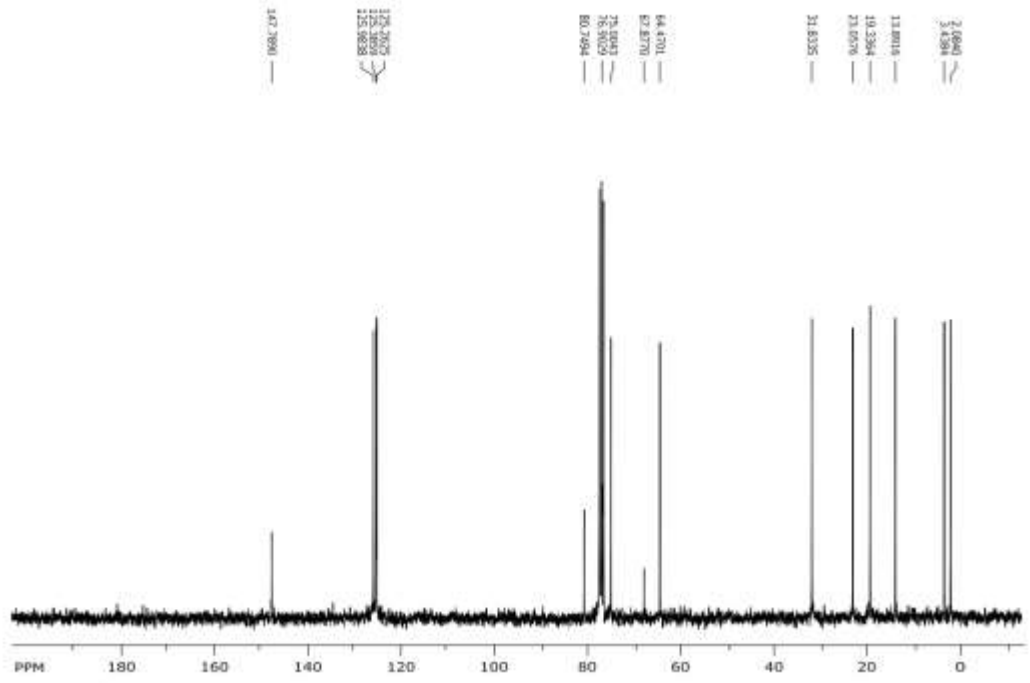
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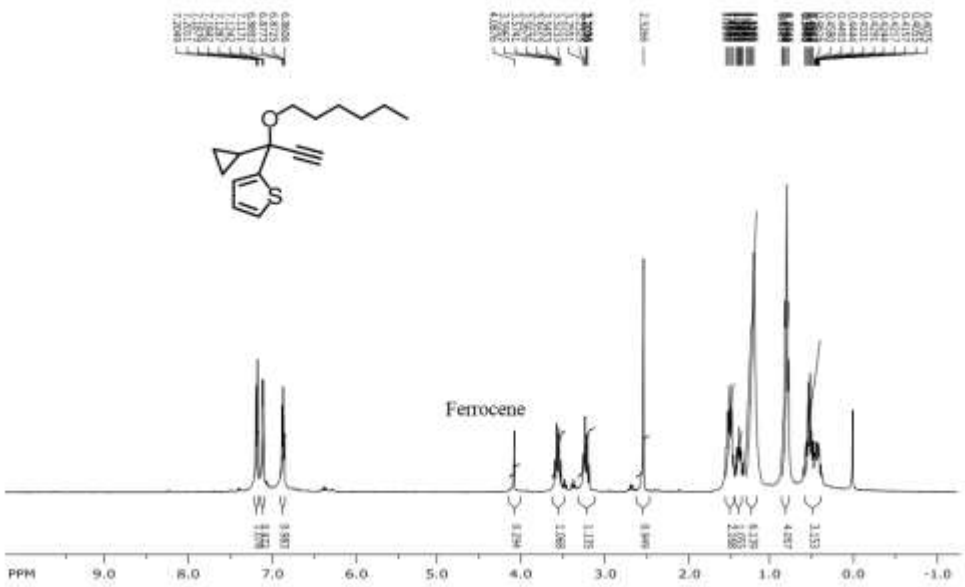
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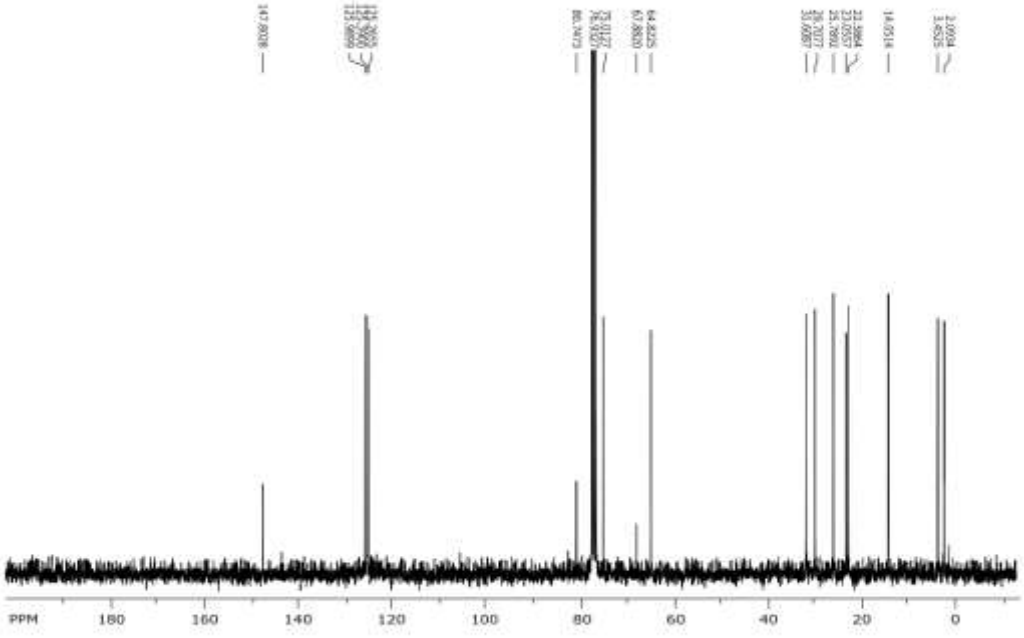
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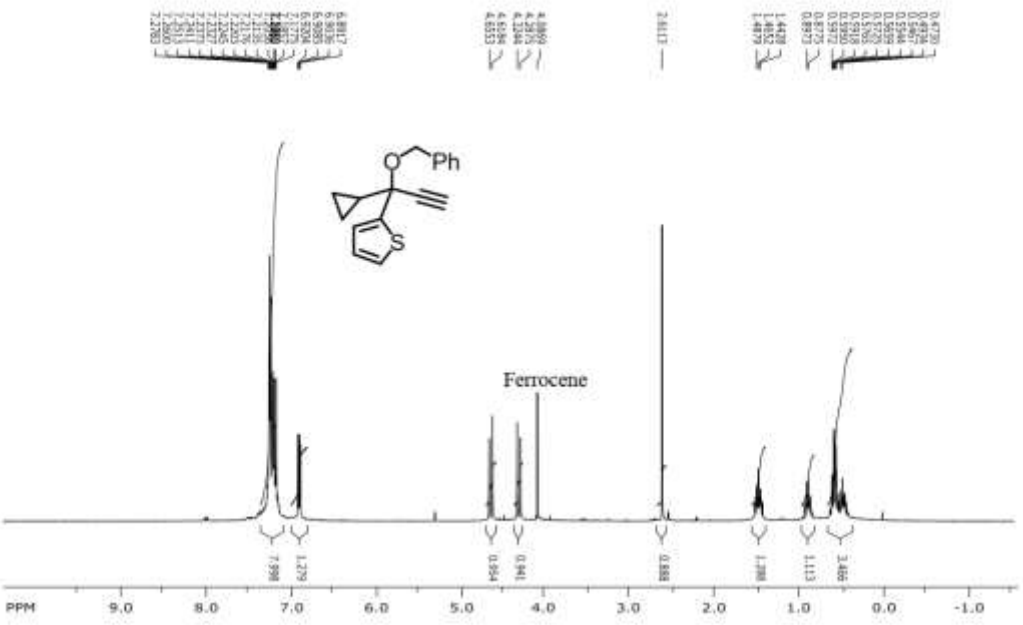
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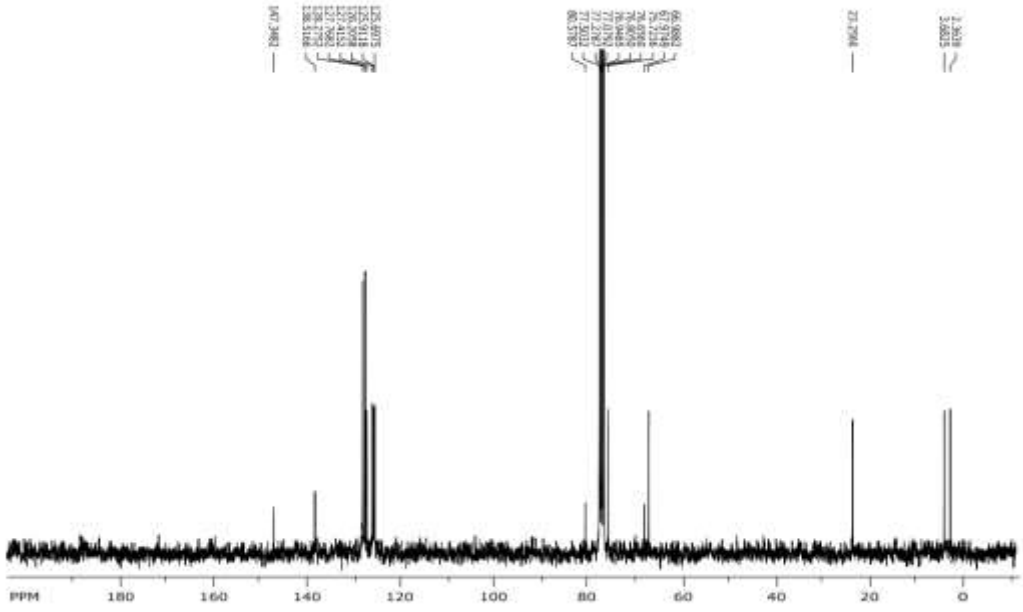
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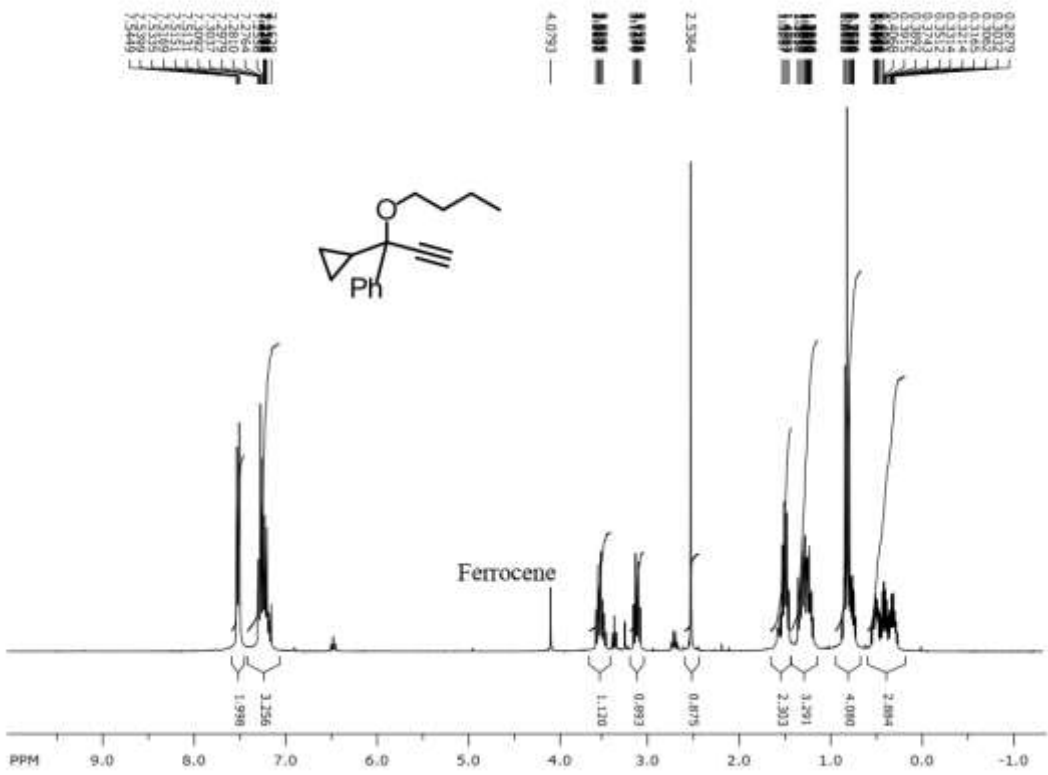
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Ferrocene
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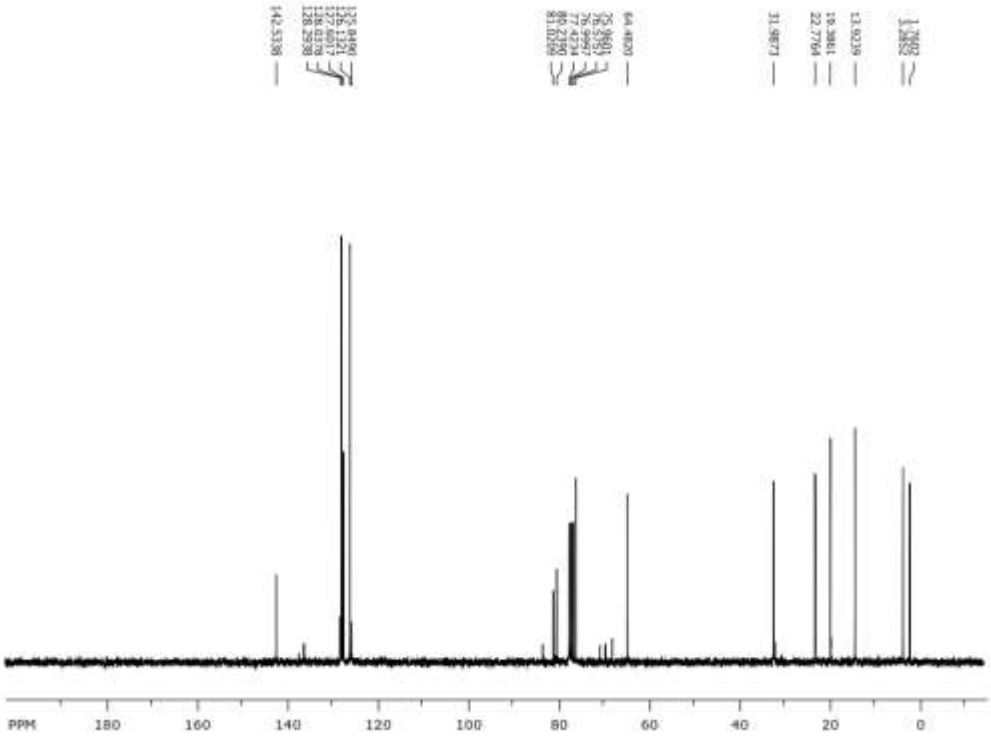
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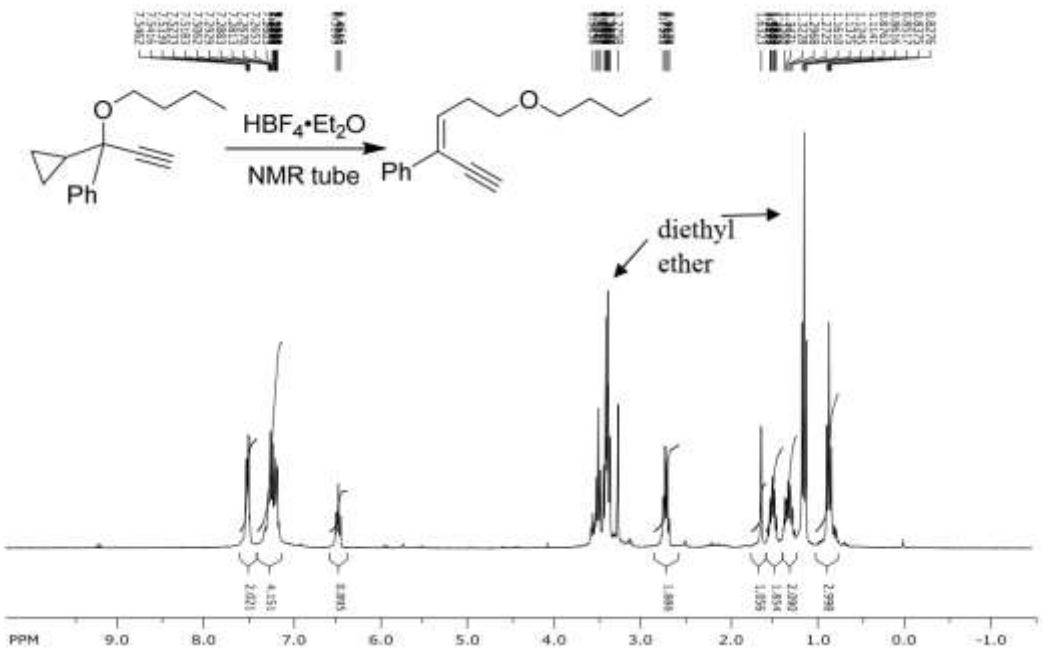
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NMR tube
Ph
O
Ph
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ether
PPM
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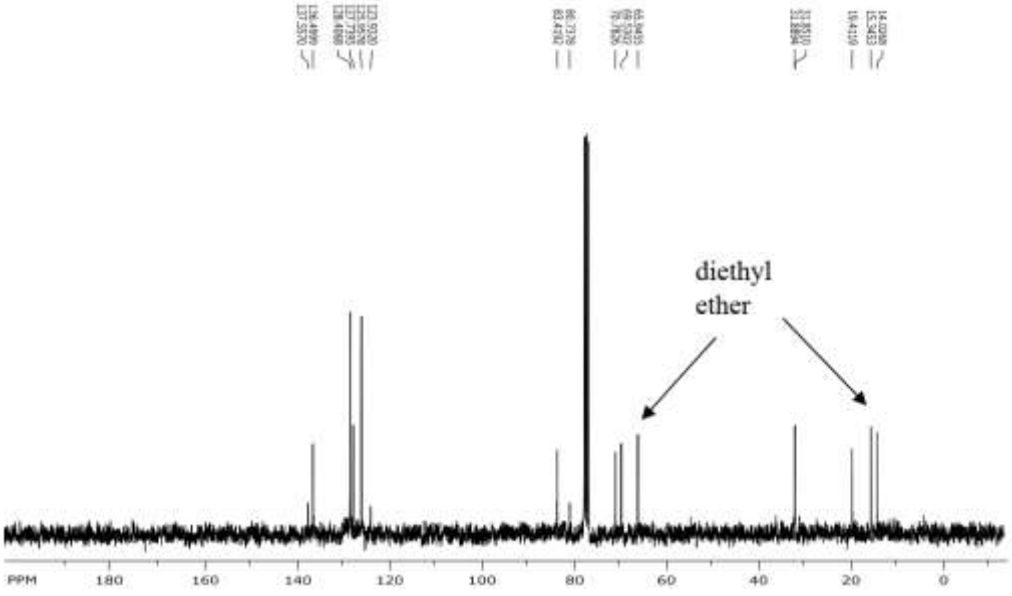
-1.0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ether
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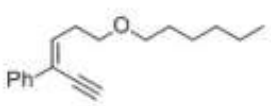
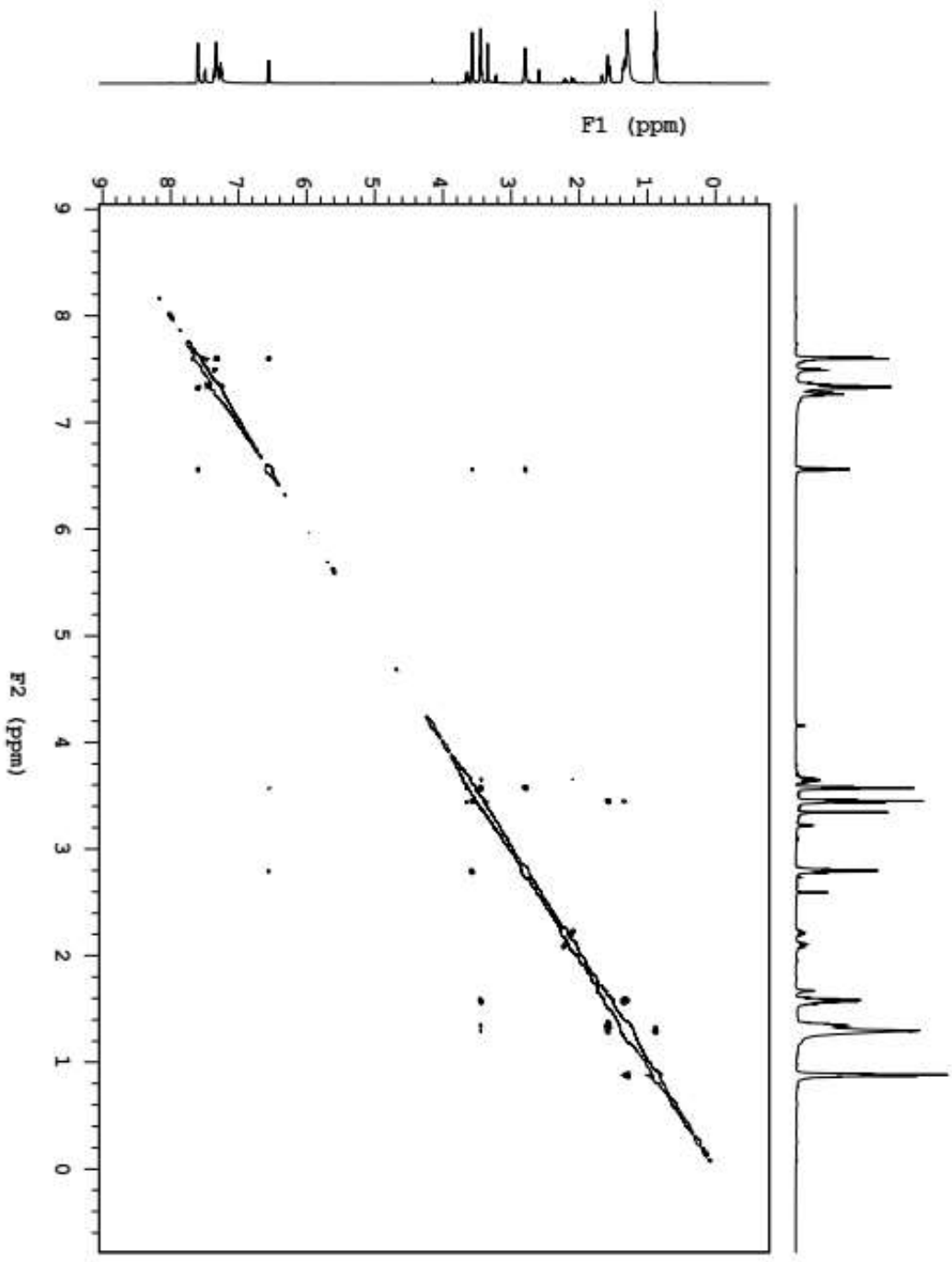
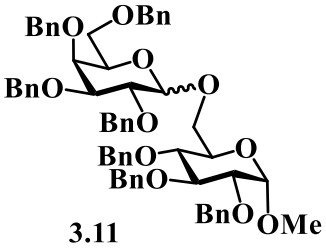
0

NOE Experiment of ene-yne

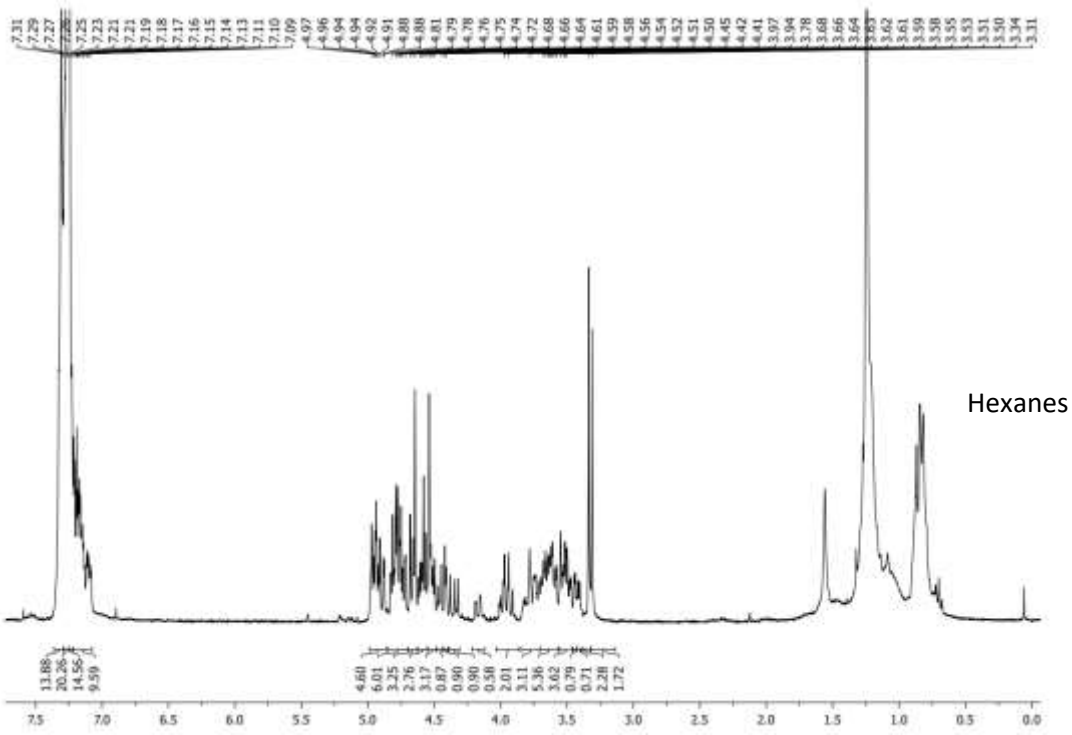


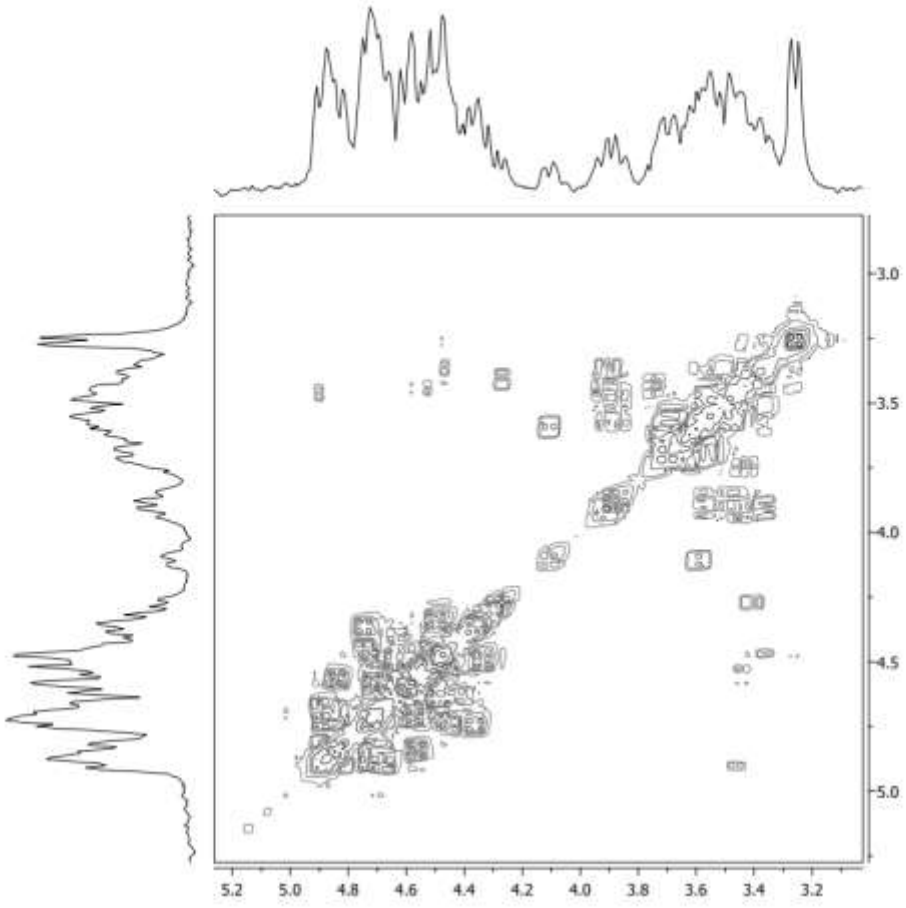




3.11

Table 3.1, entry 1

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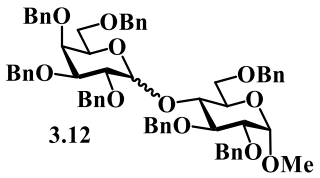
3.4
3.2



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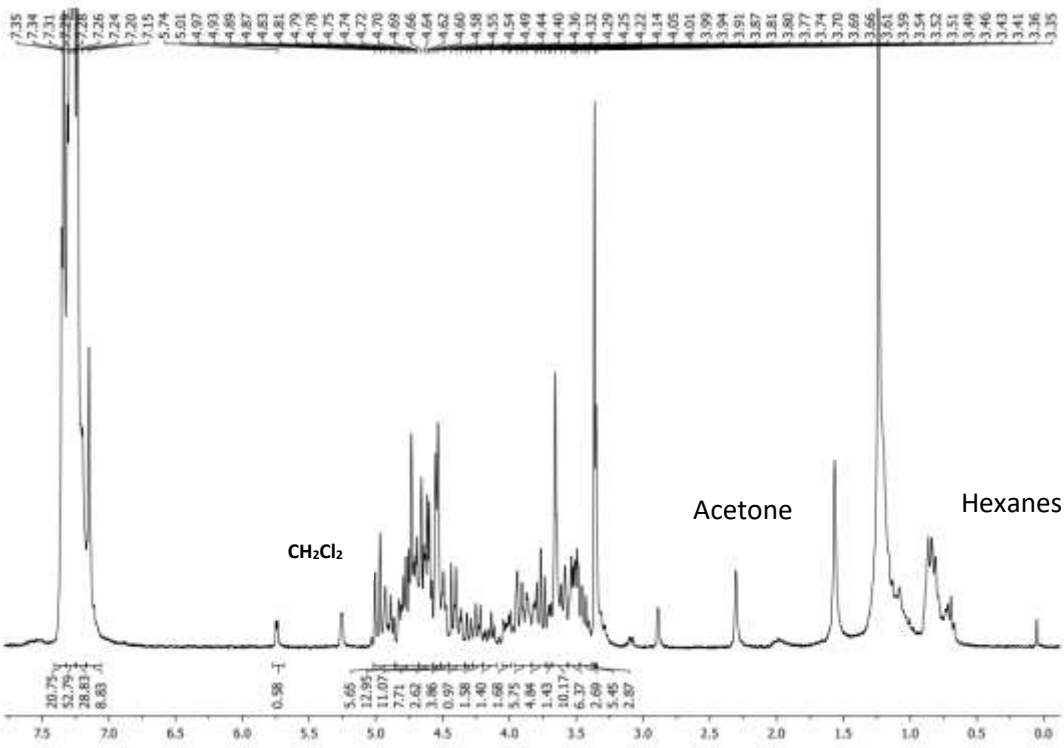

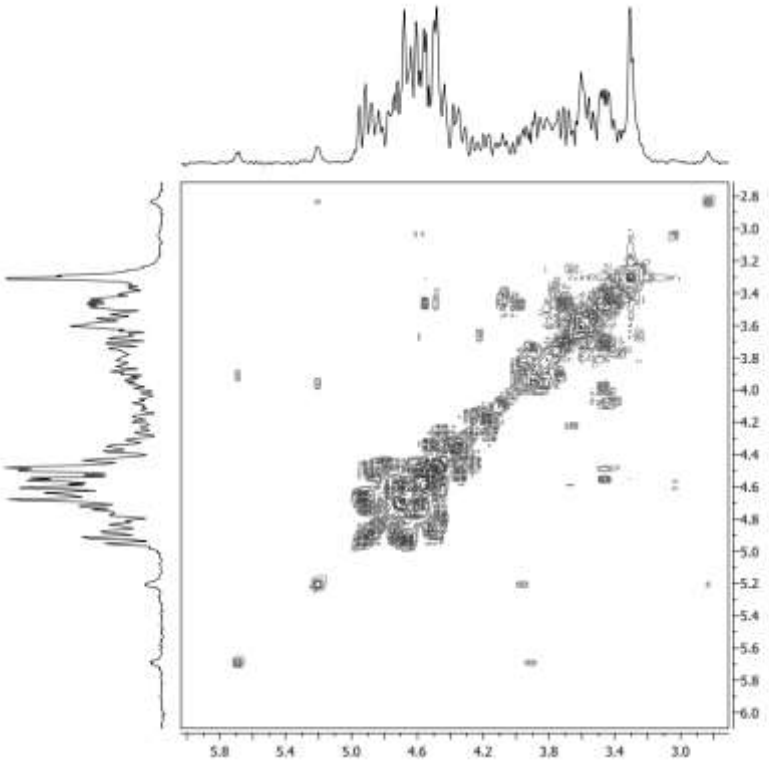
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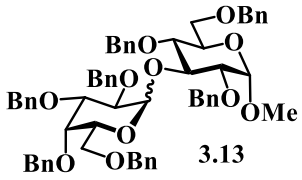

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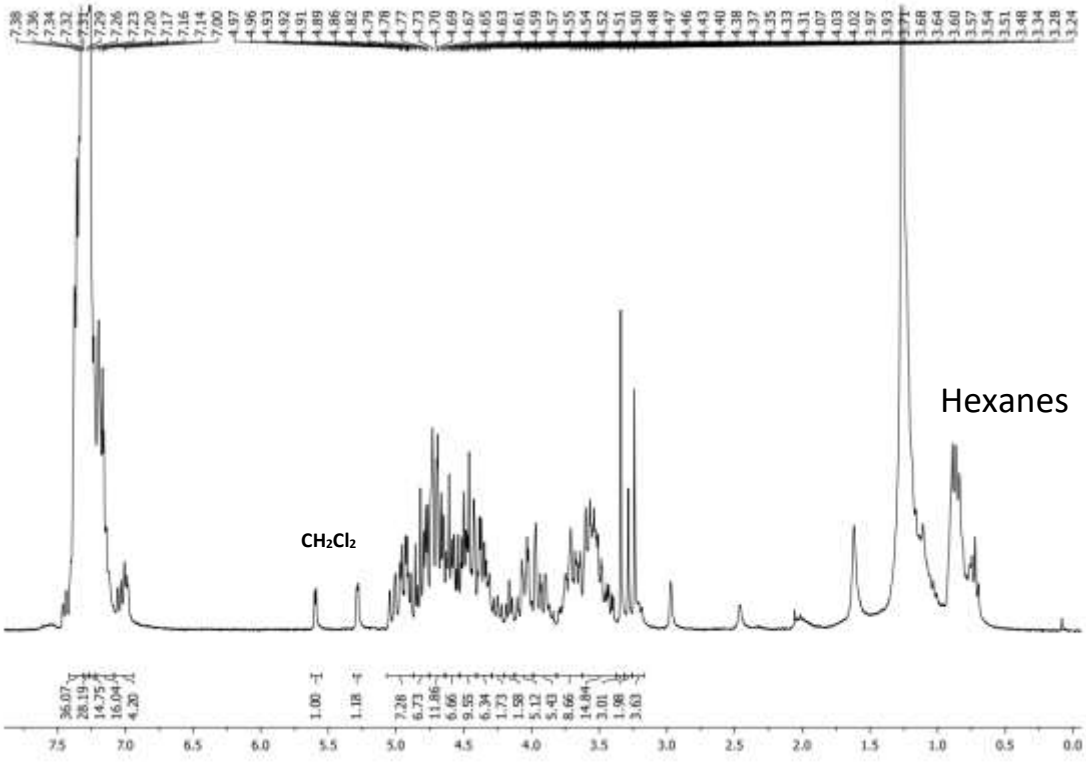

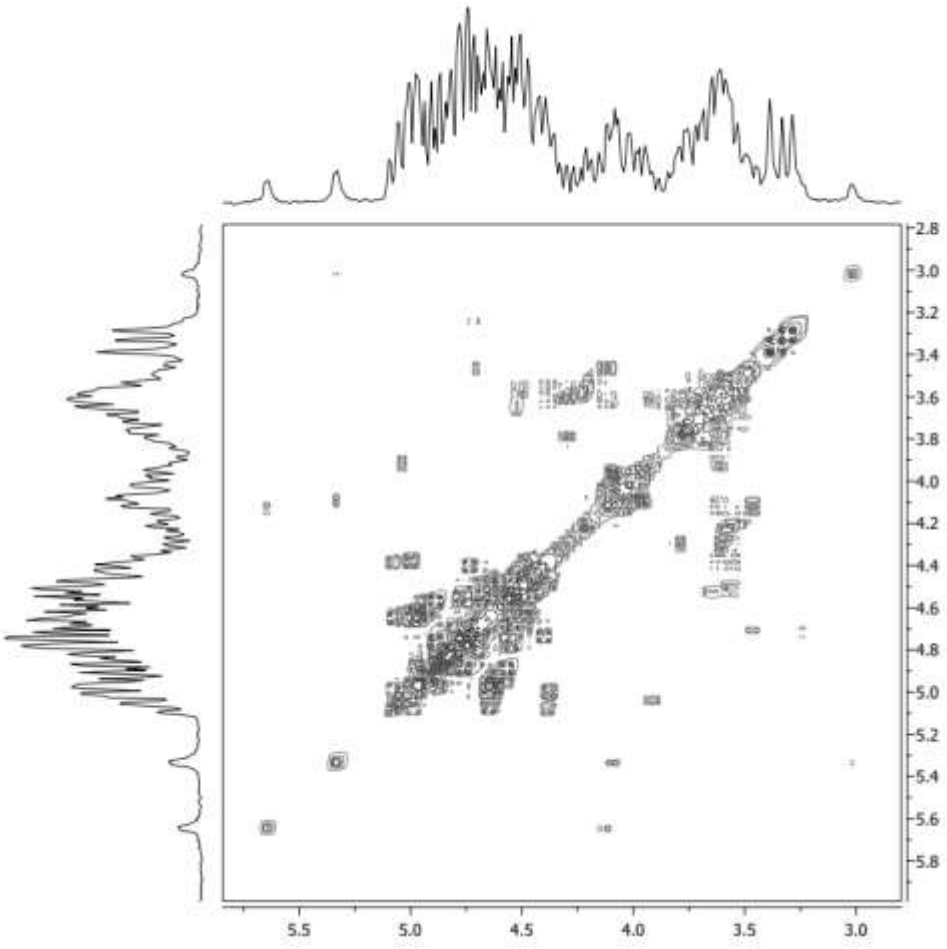
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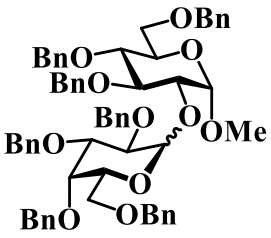

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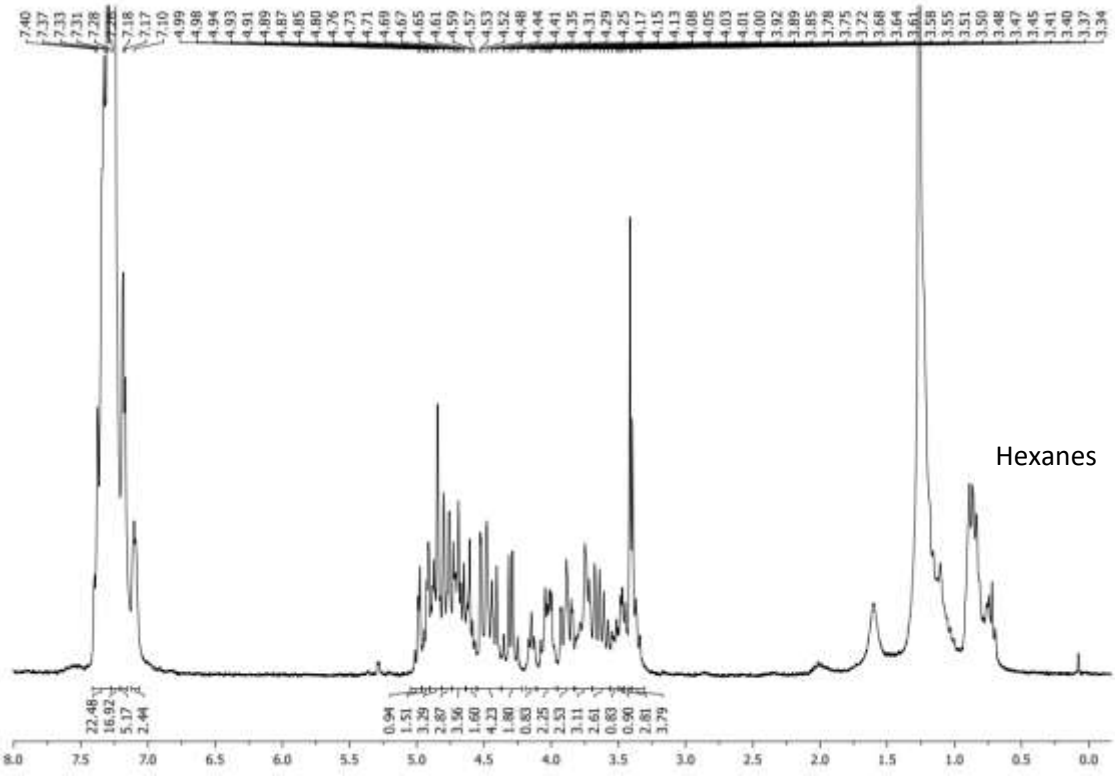
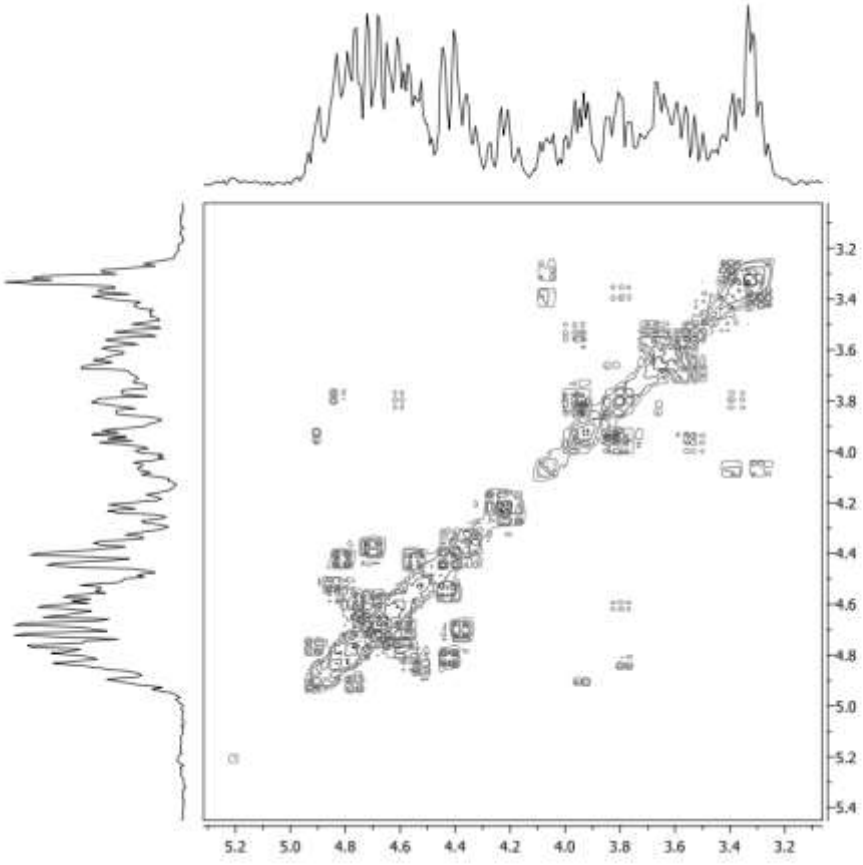
Table 3.1, entry 4

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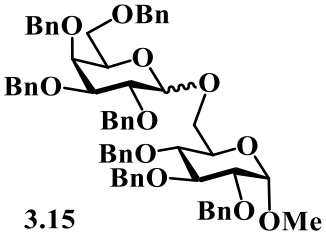
3.2



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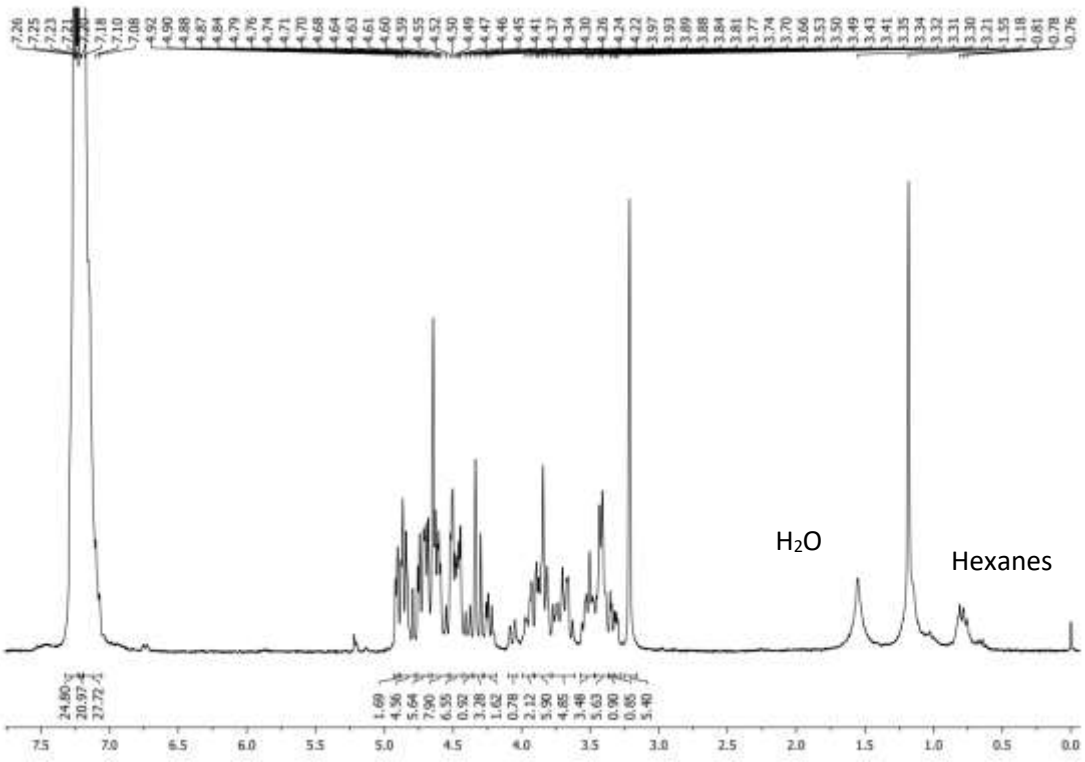

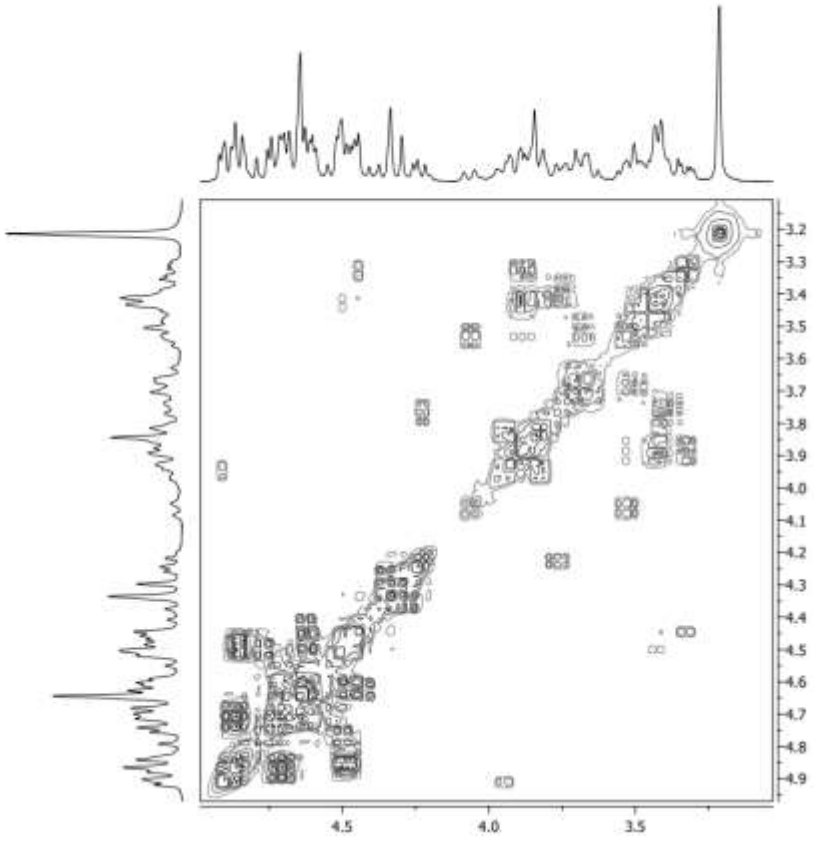
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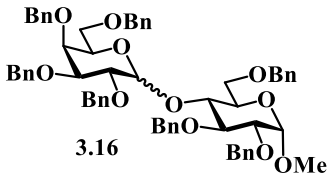

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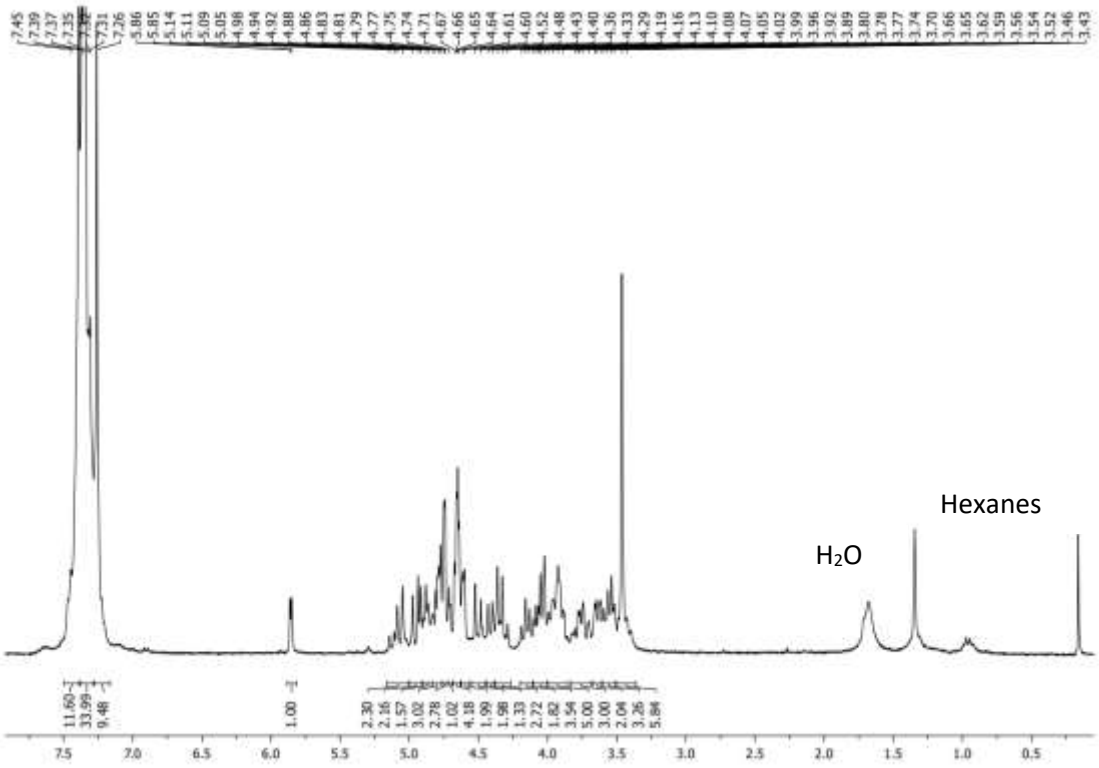

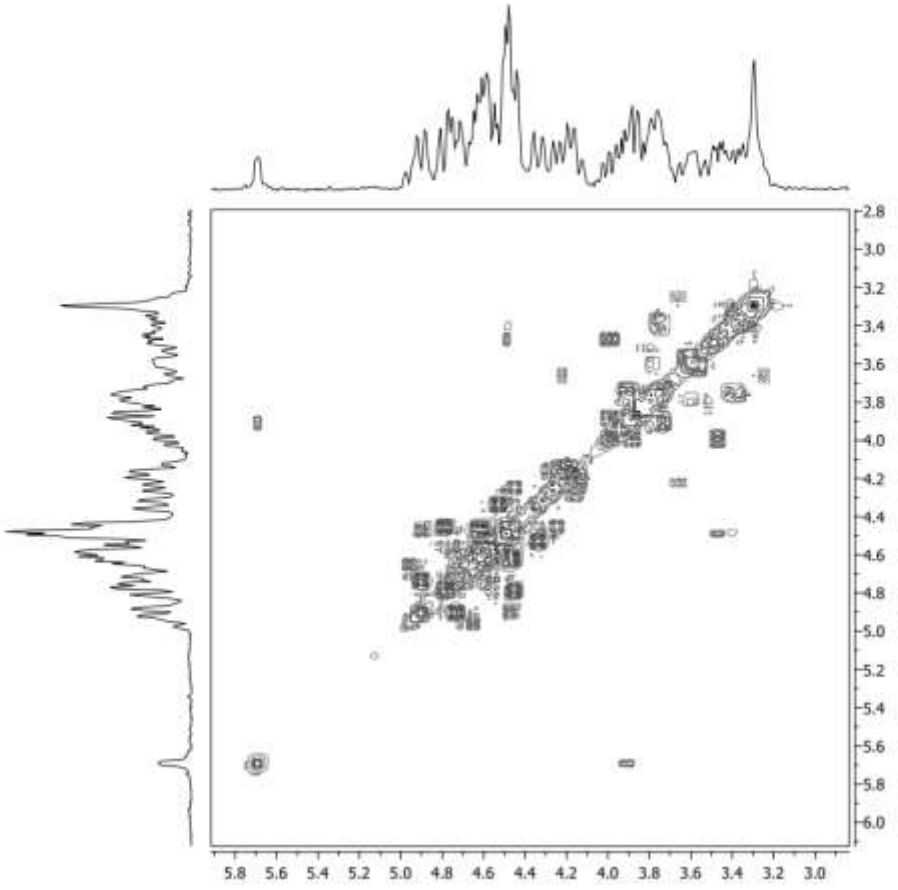
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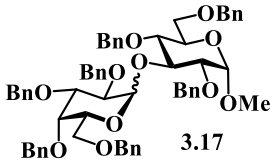

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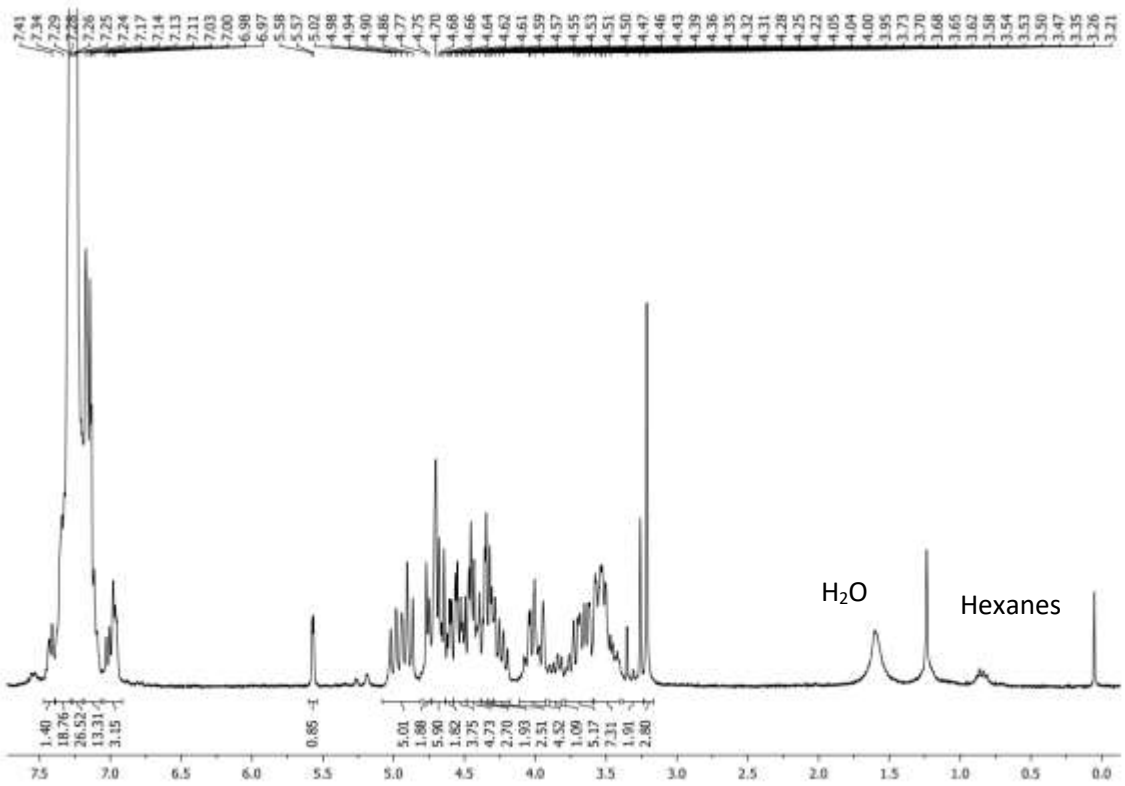

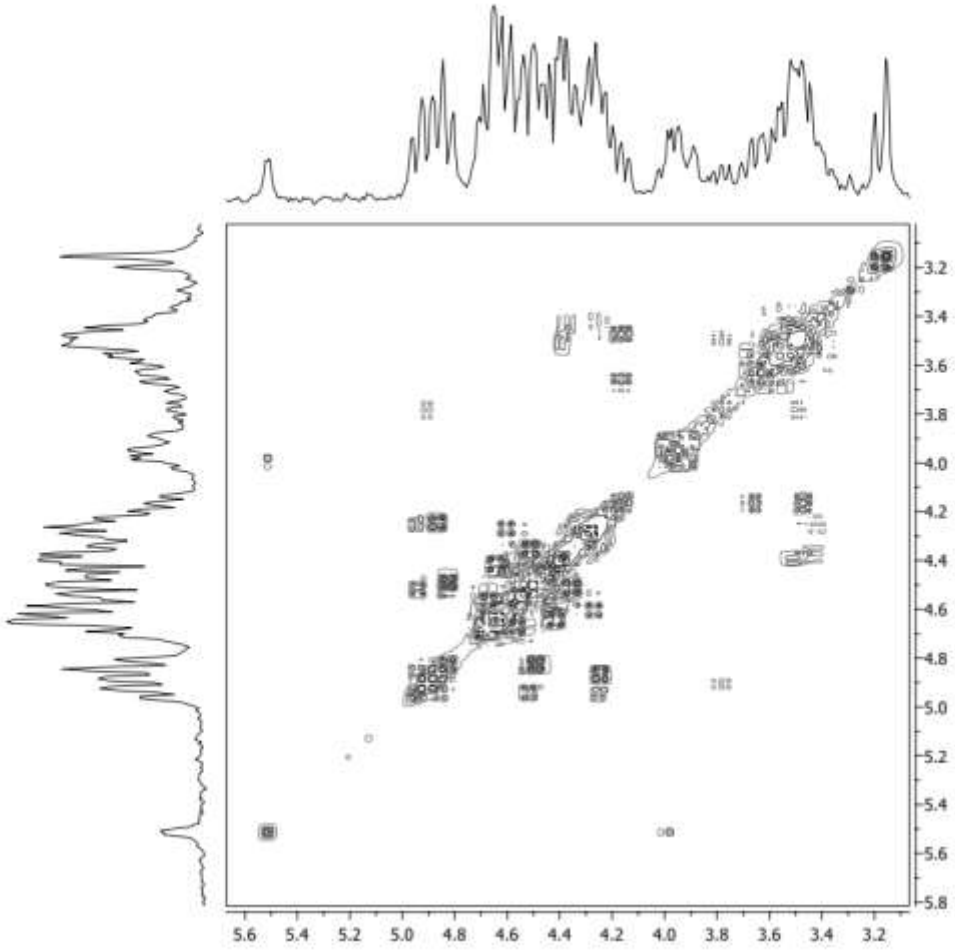
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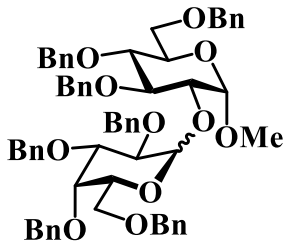

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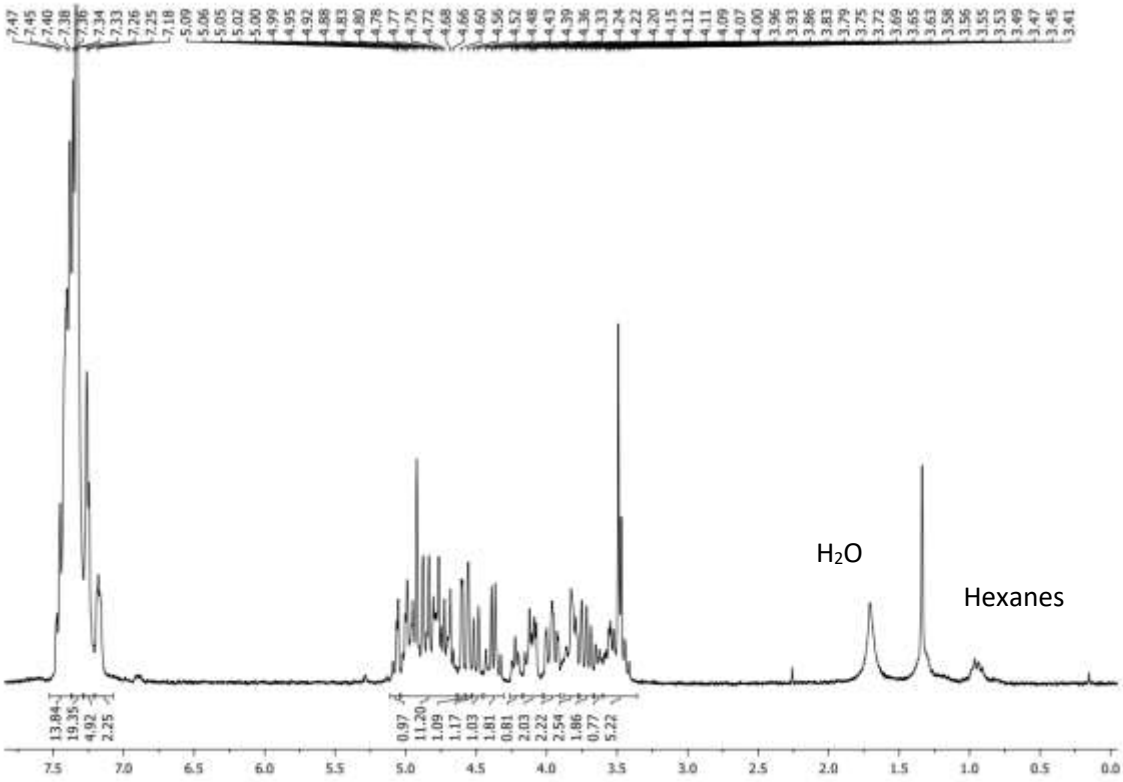

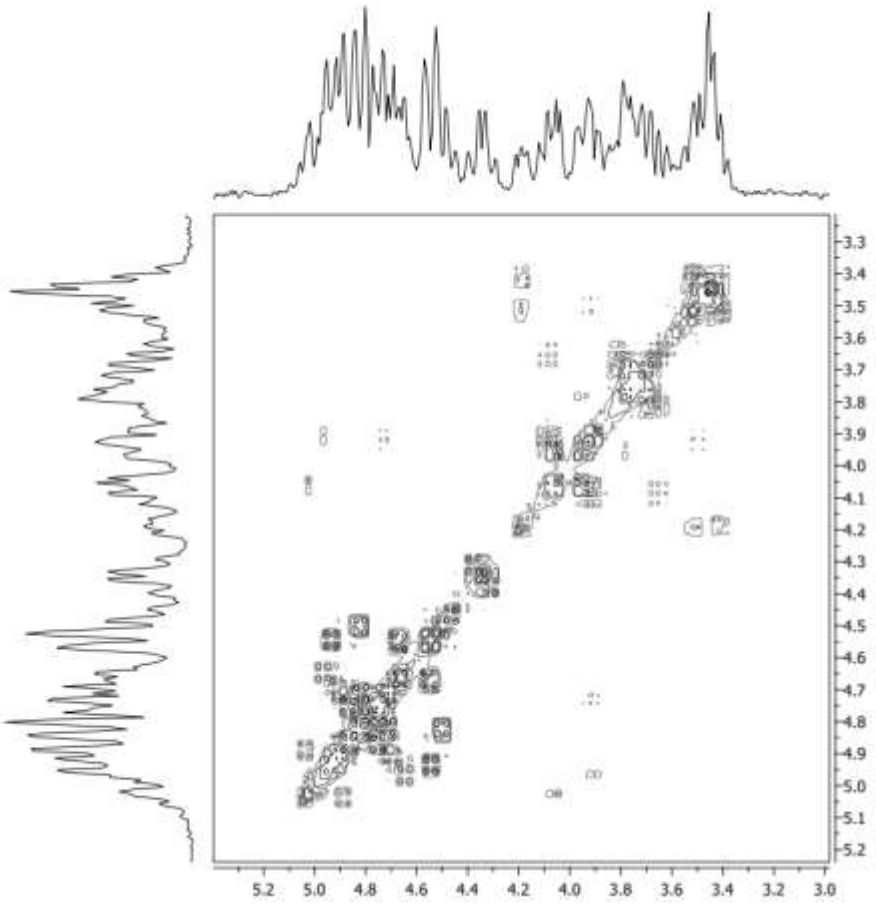
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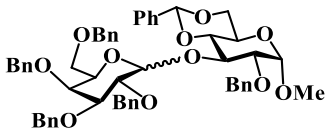

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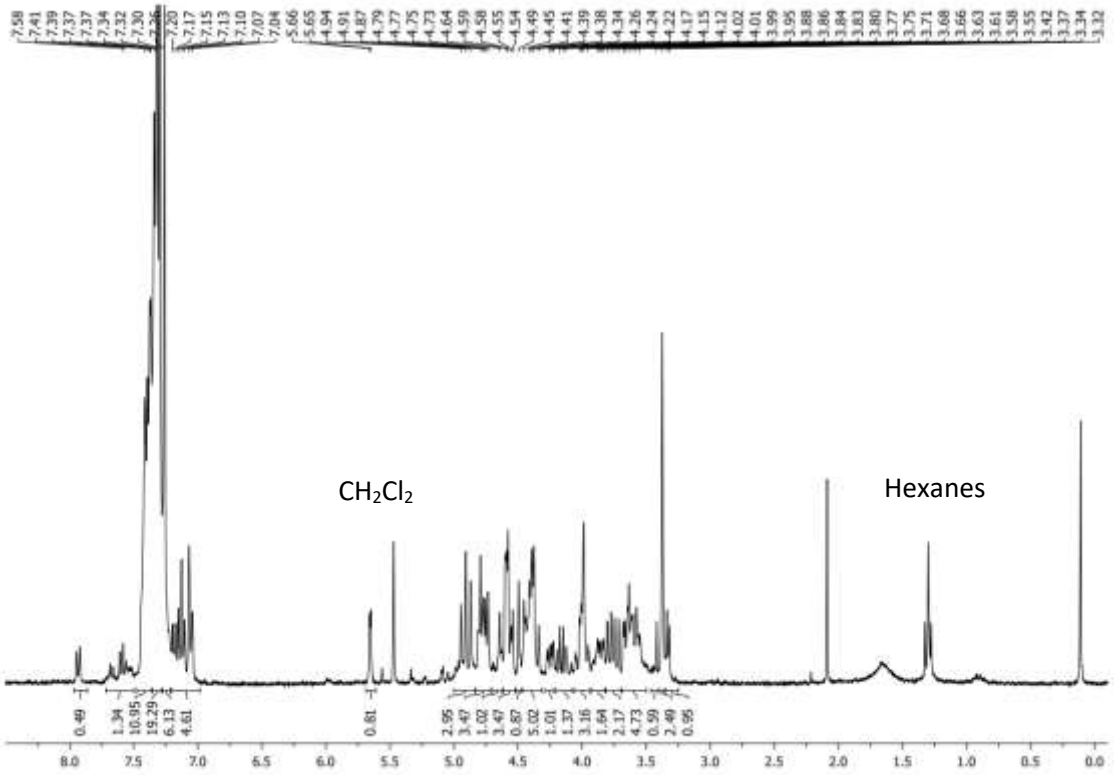

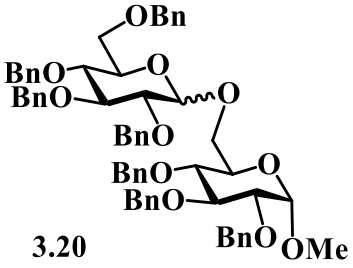

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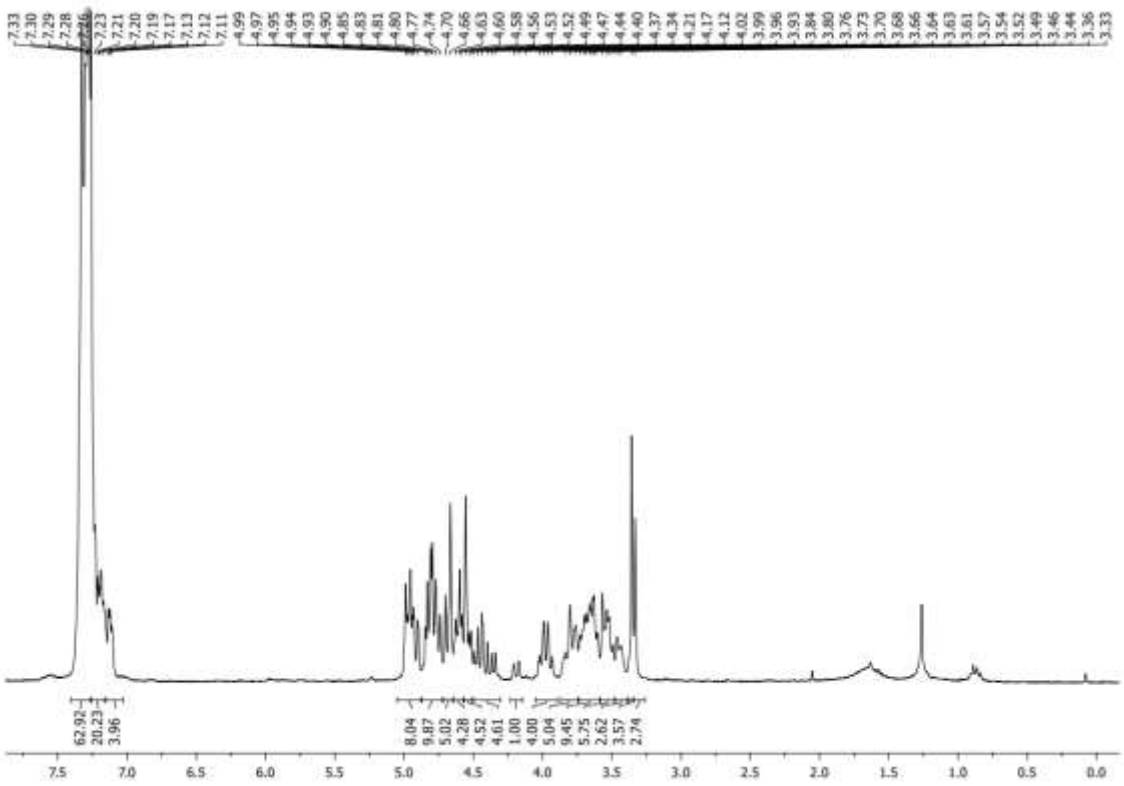

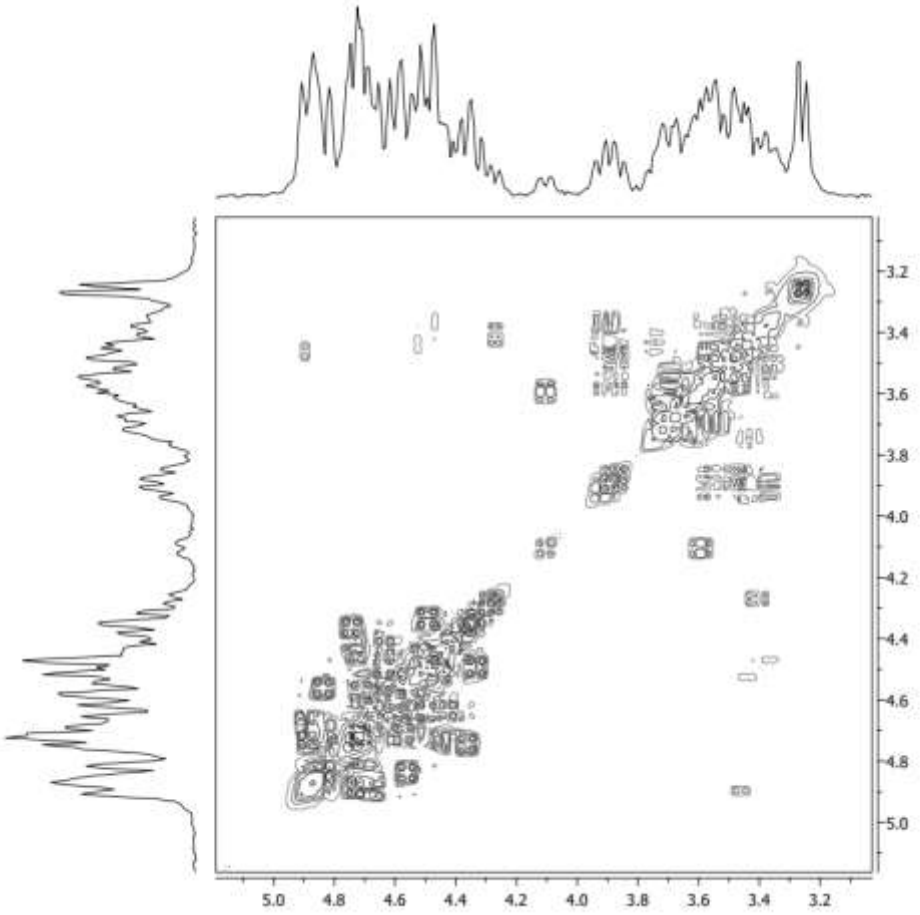
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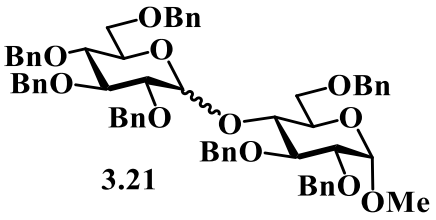

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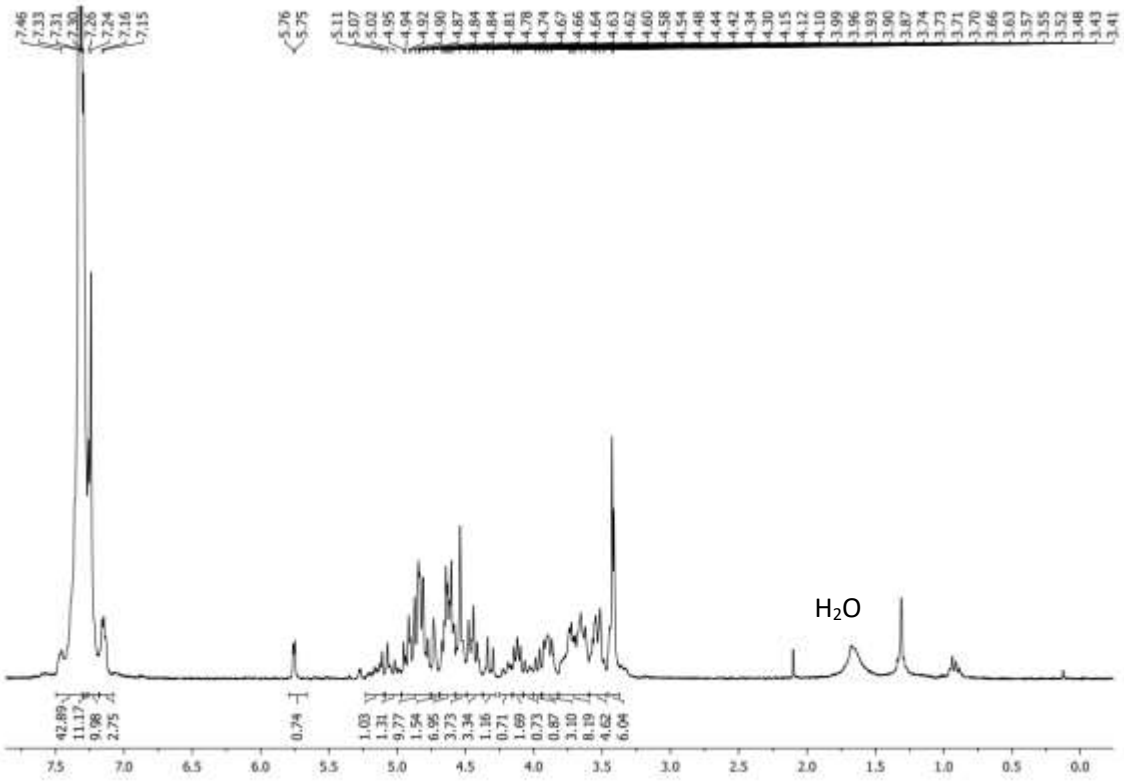

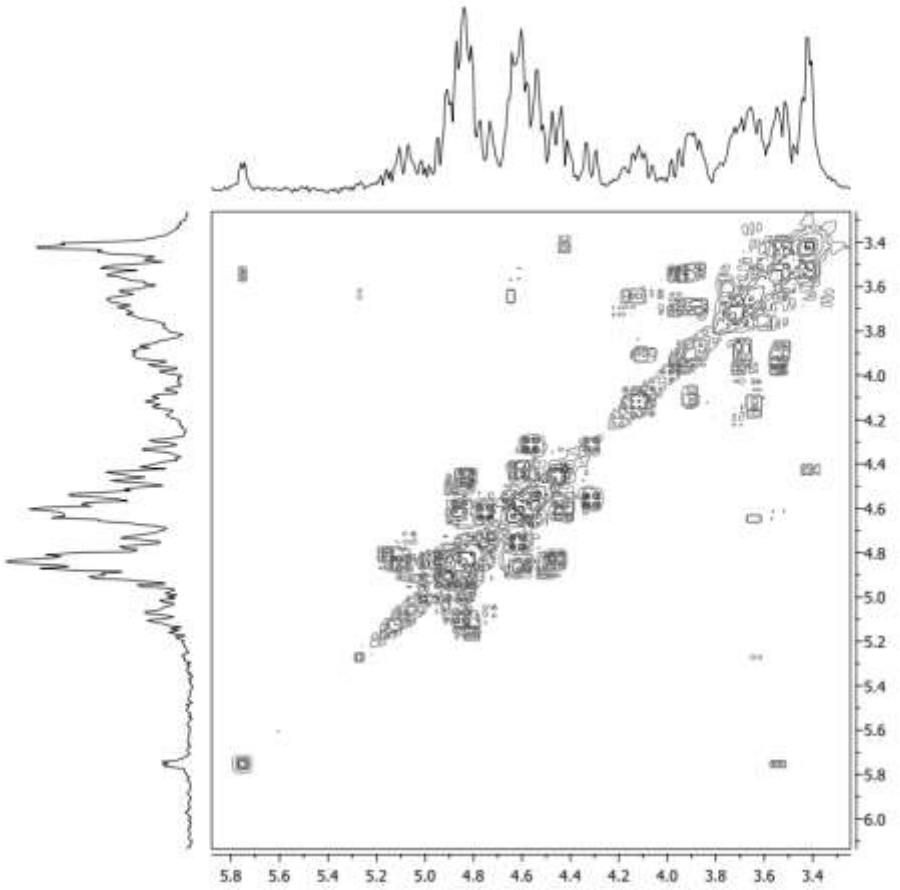
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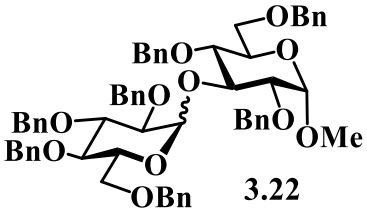

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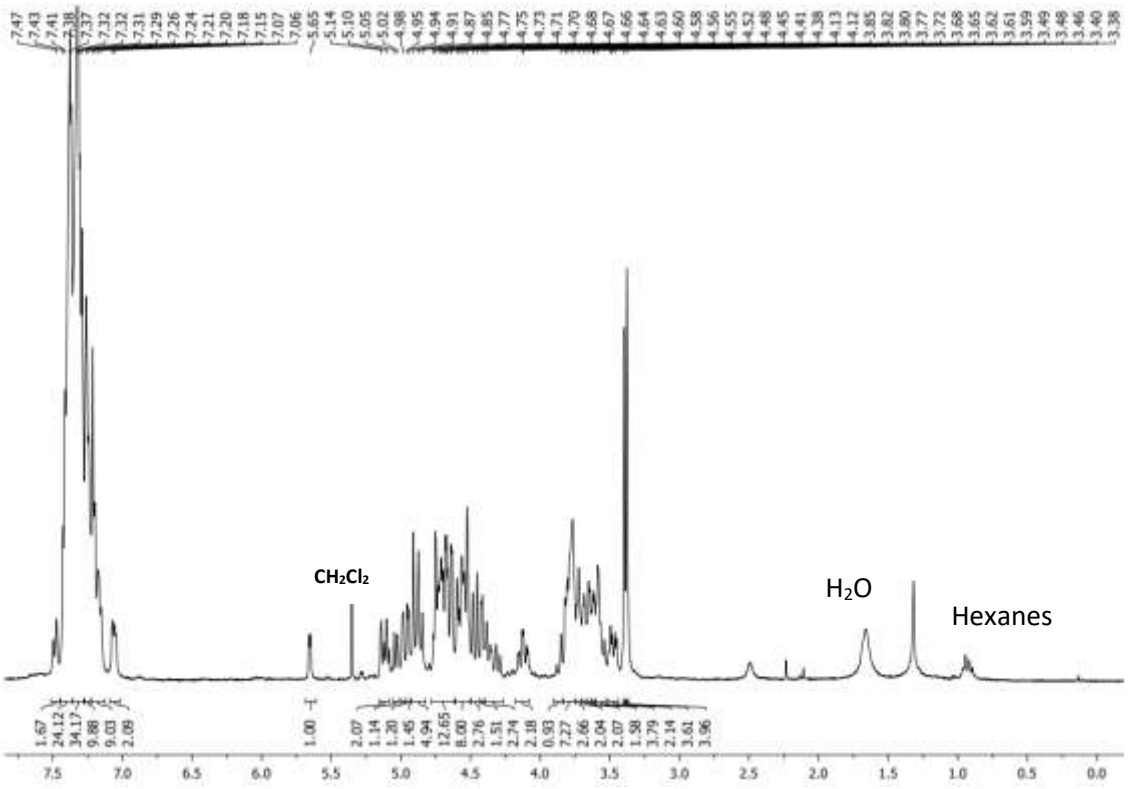

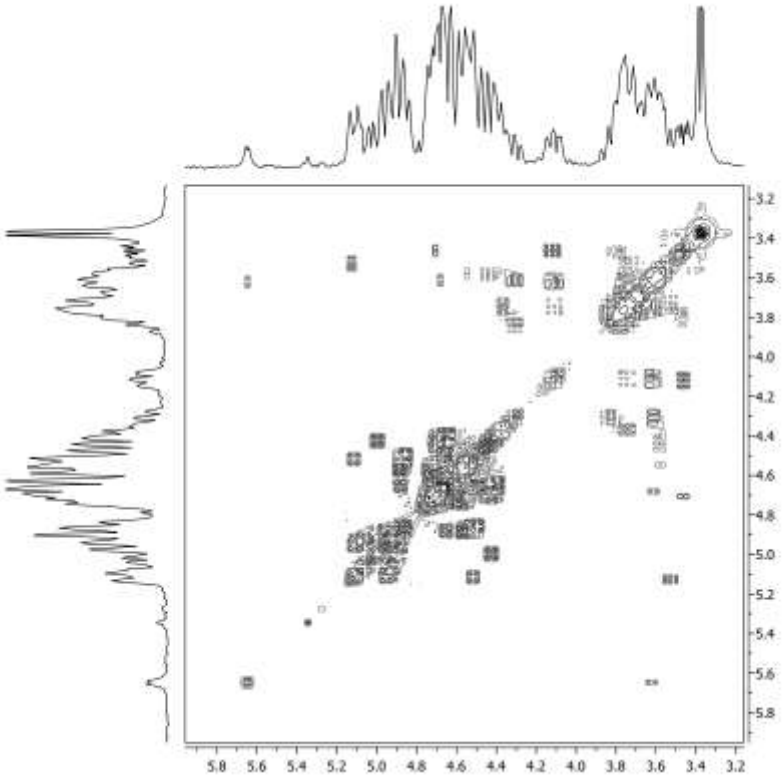
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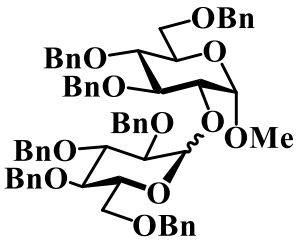
3.2



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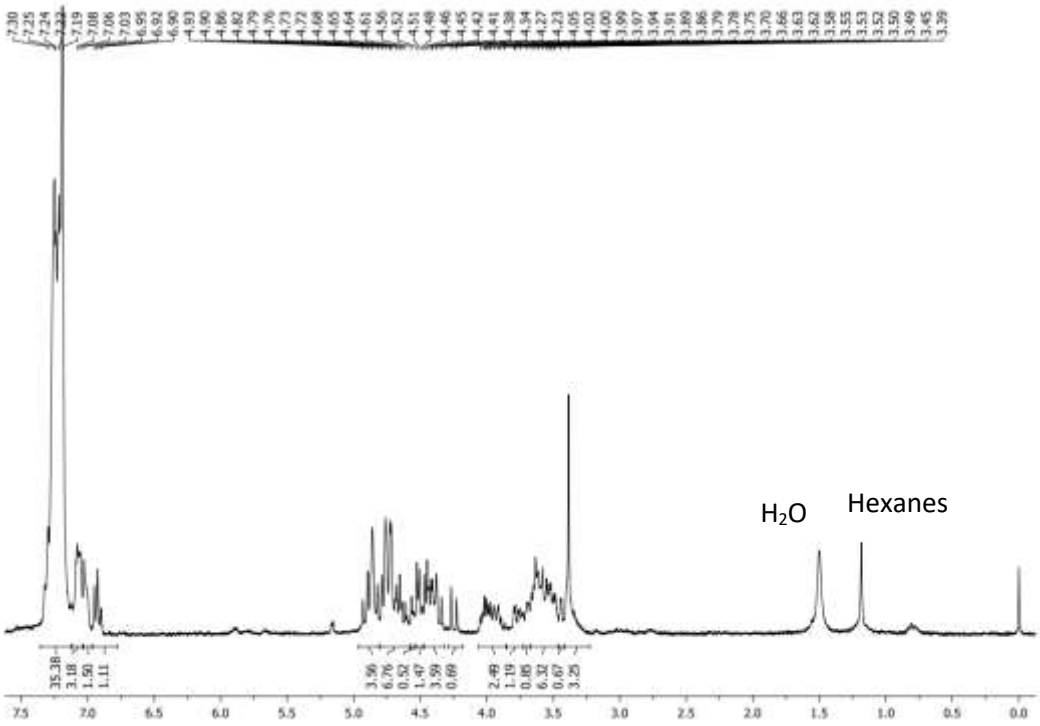

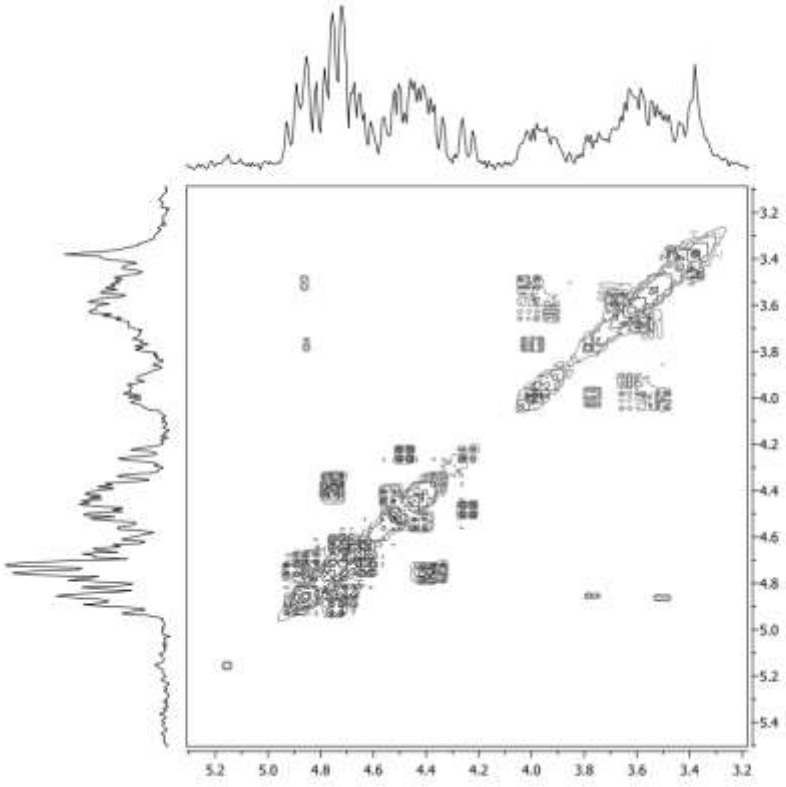
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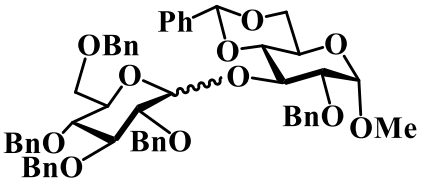

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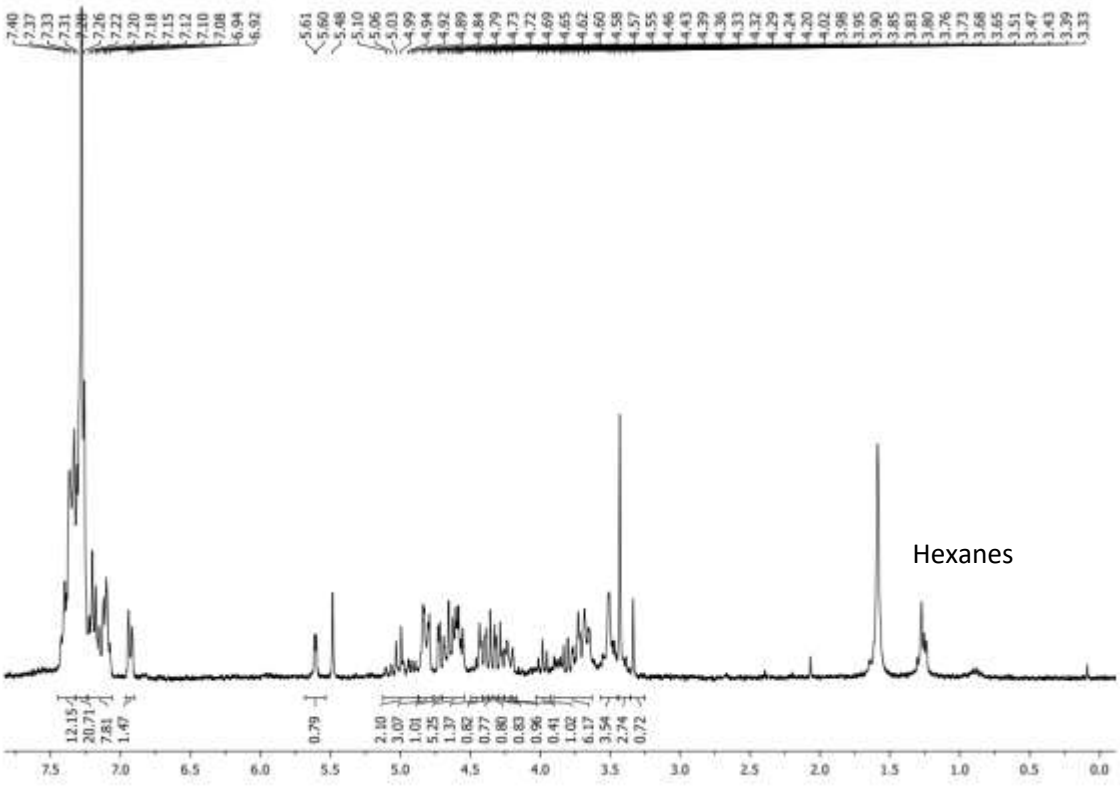

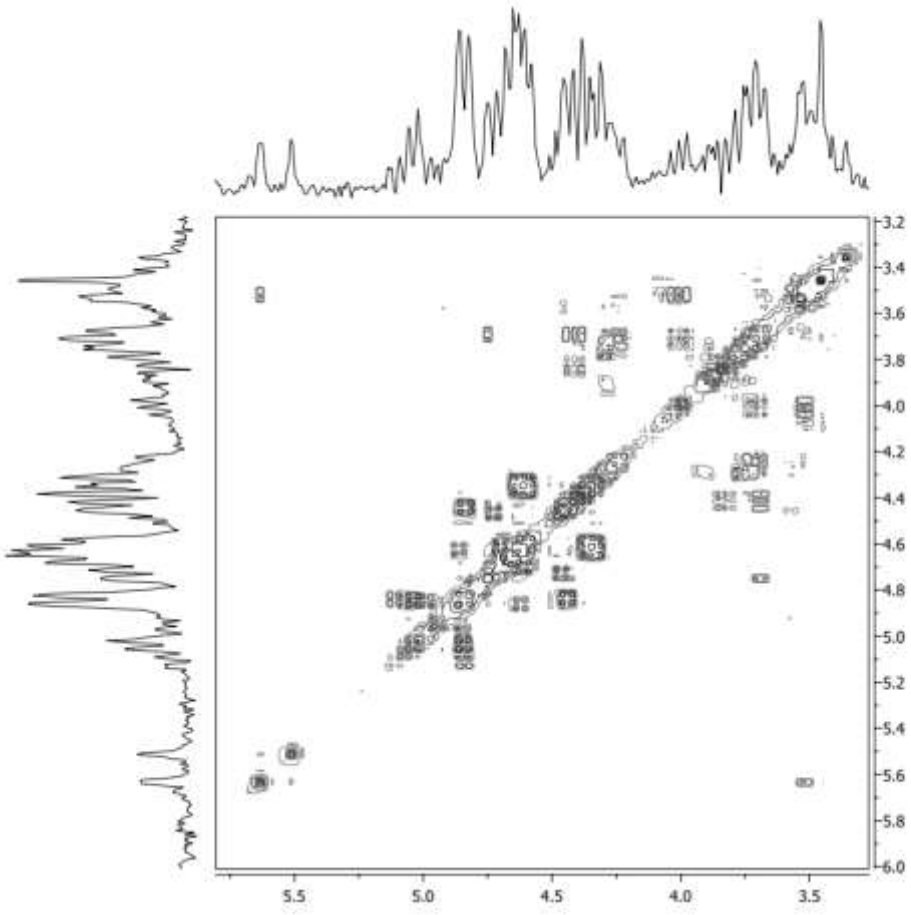
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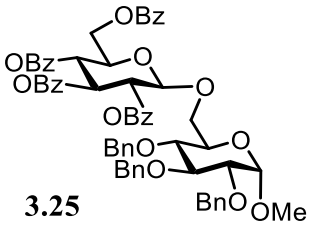
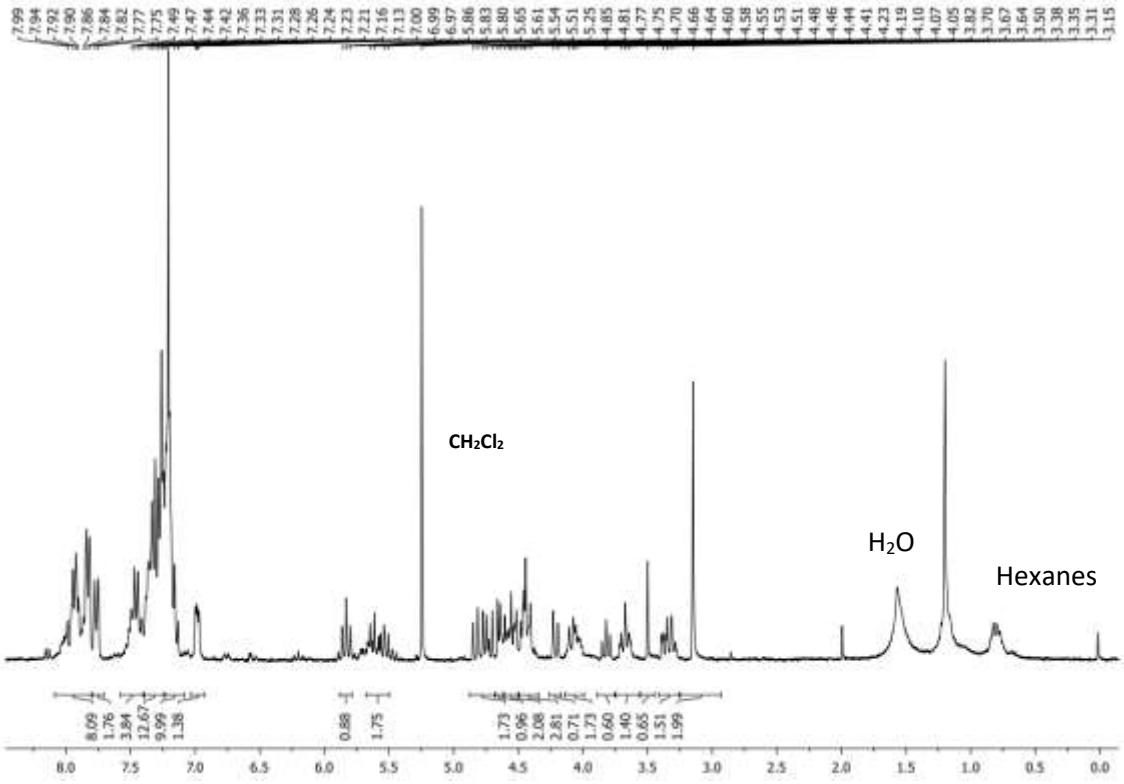
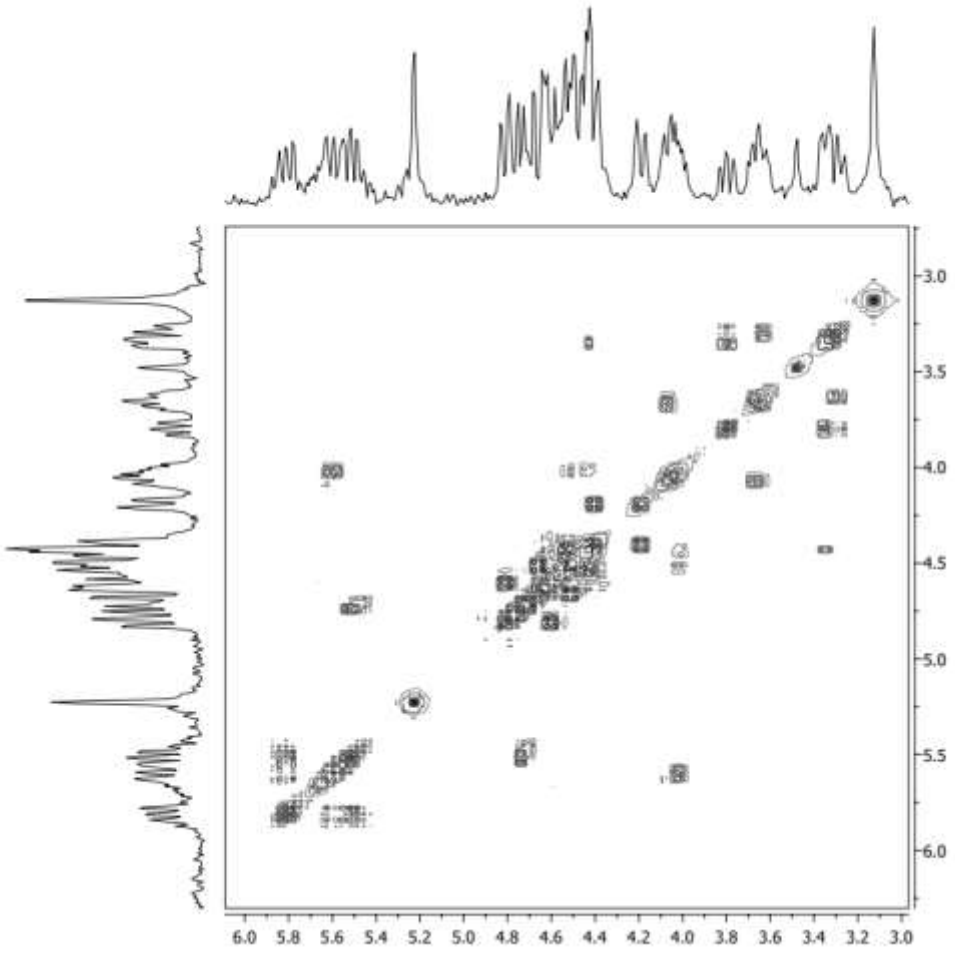


3.25

Scheme 3.4

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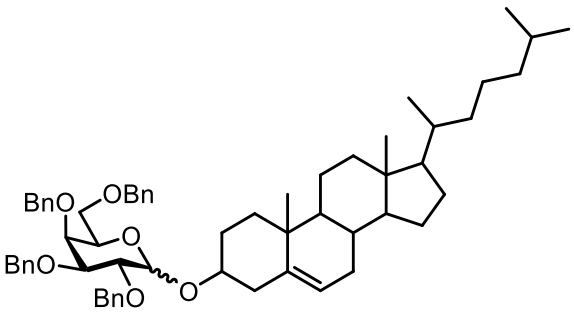
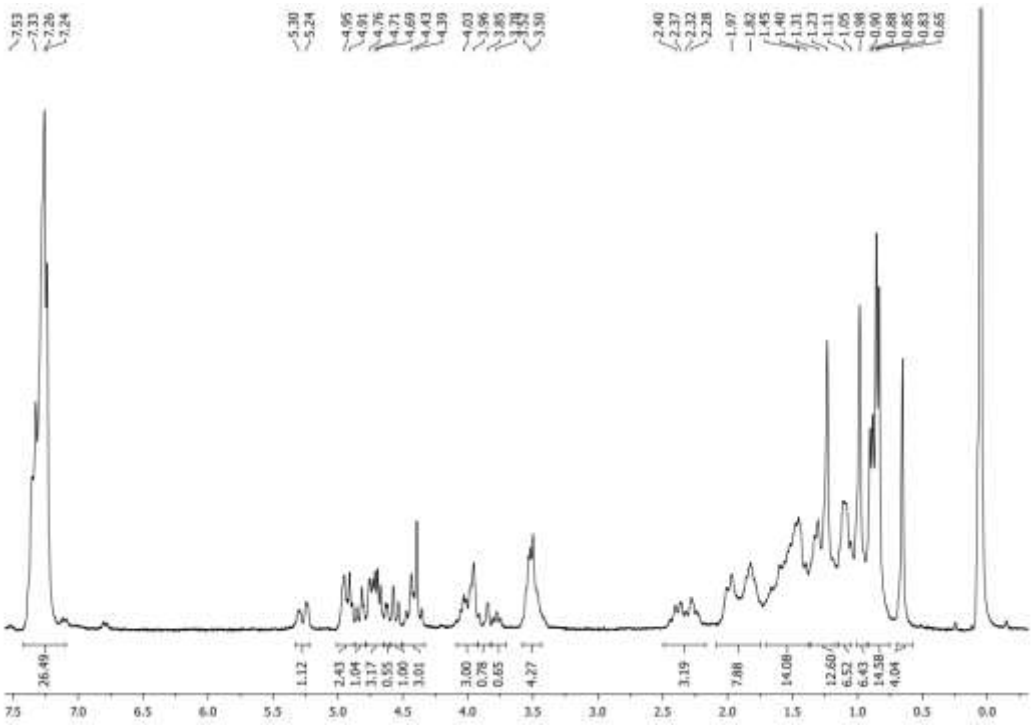
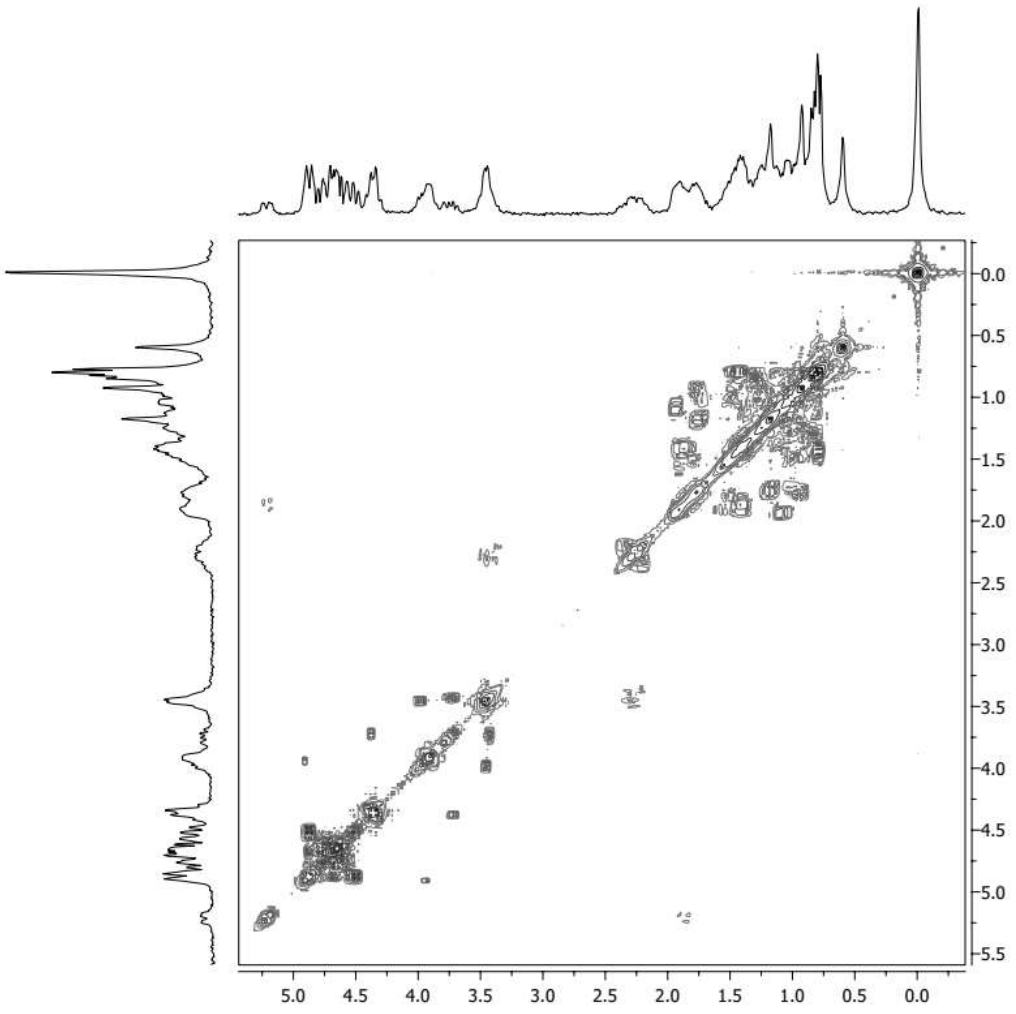


3.26

Scheme 3.5

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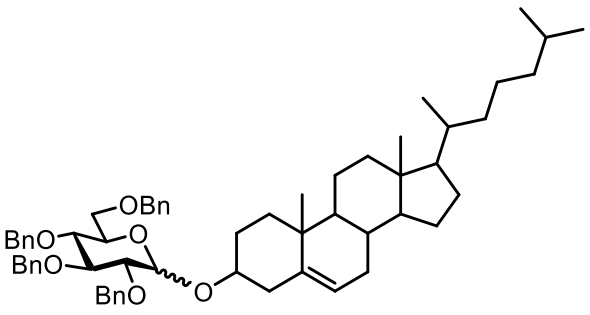
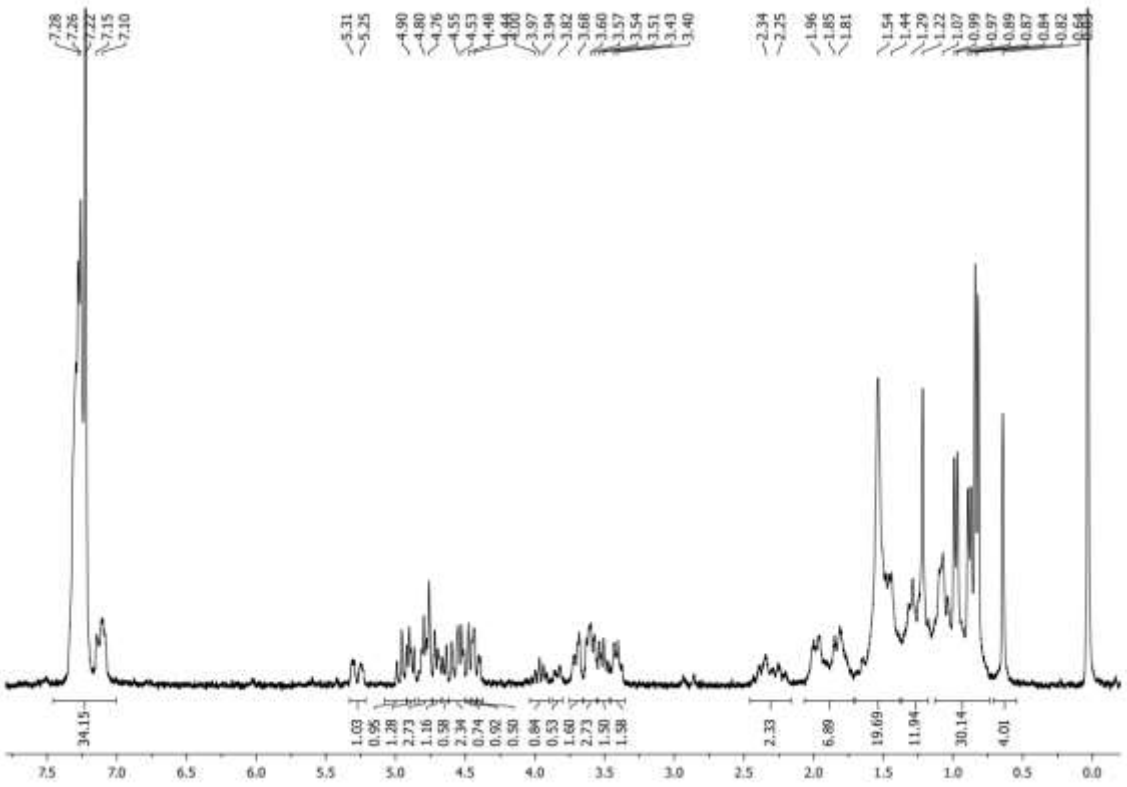
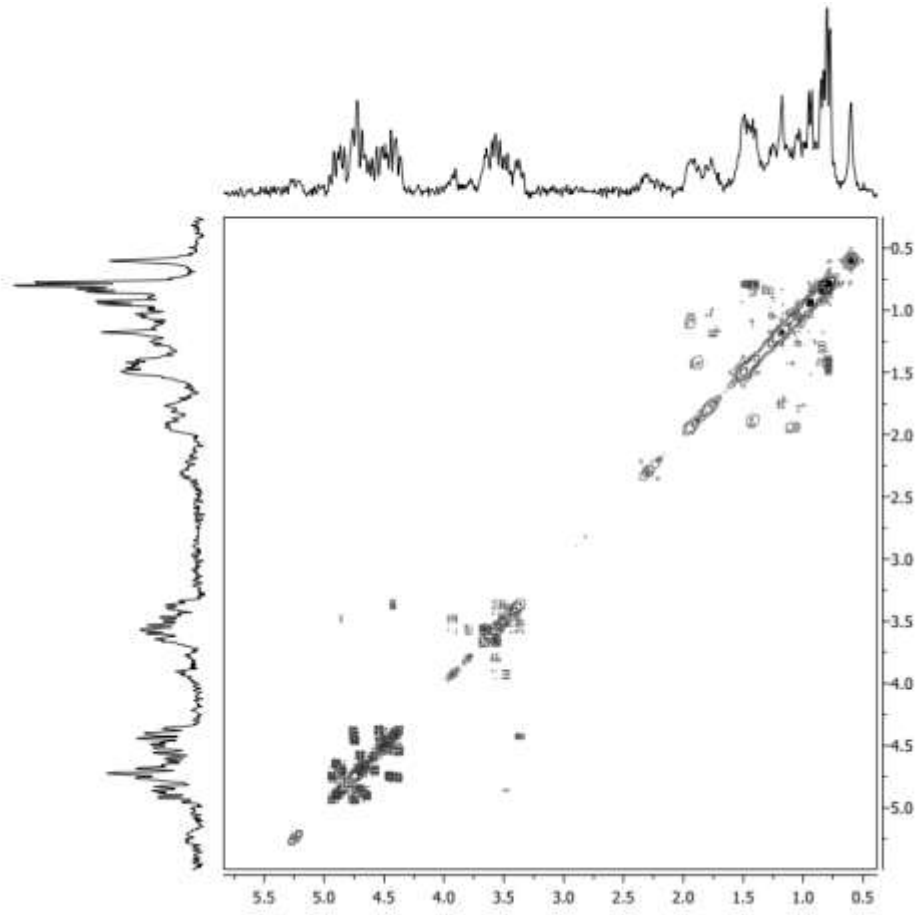


3.27

Scheme 3.5

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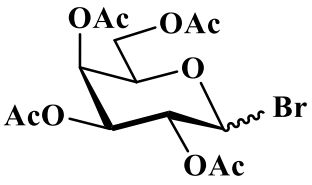

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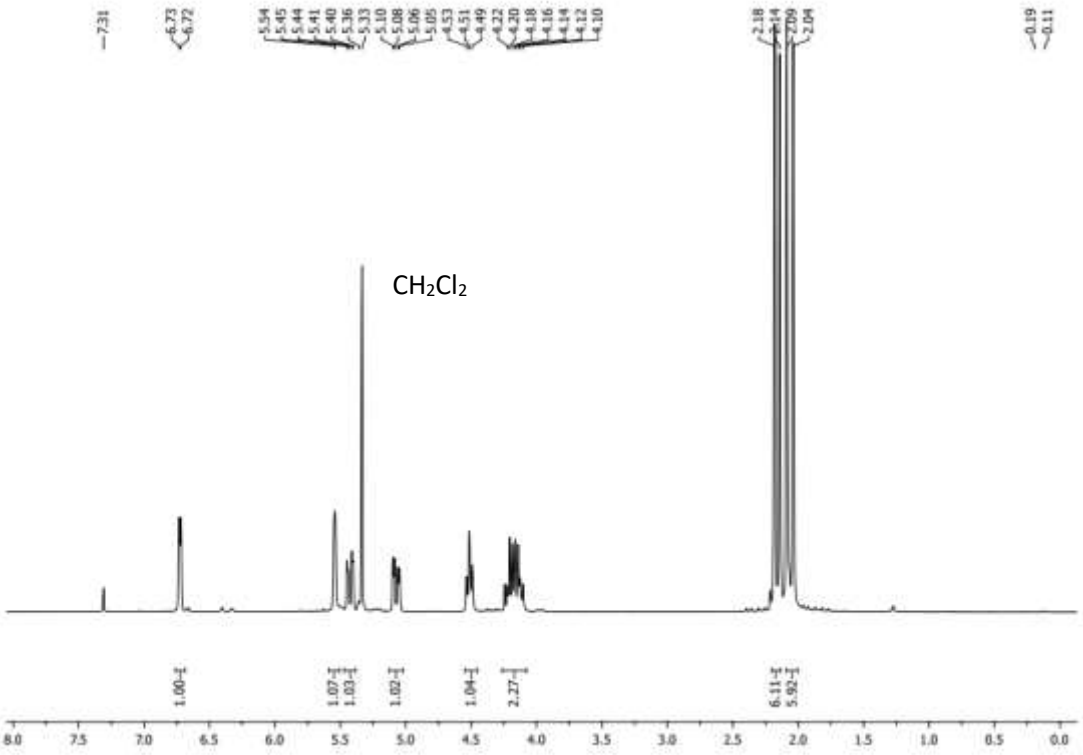

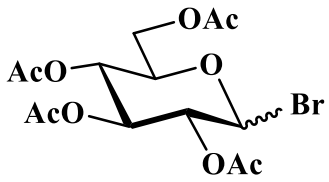

Glucosyl bromide
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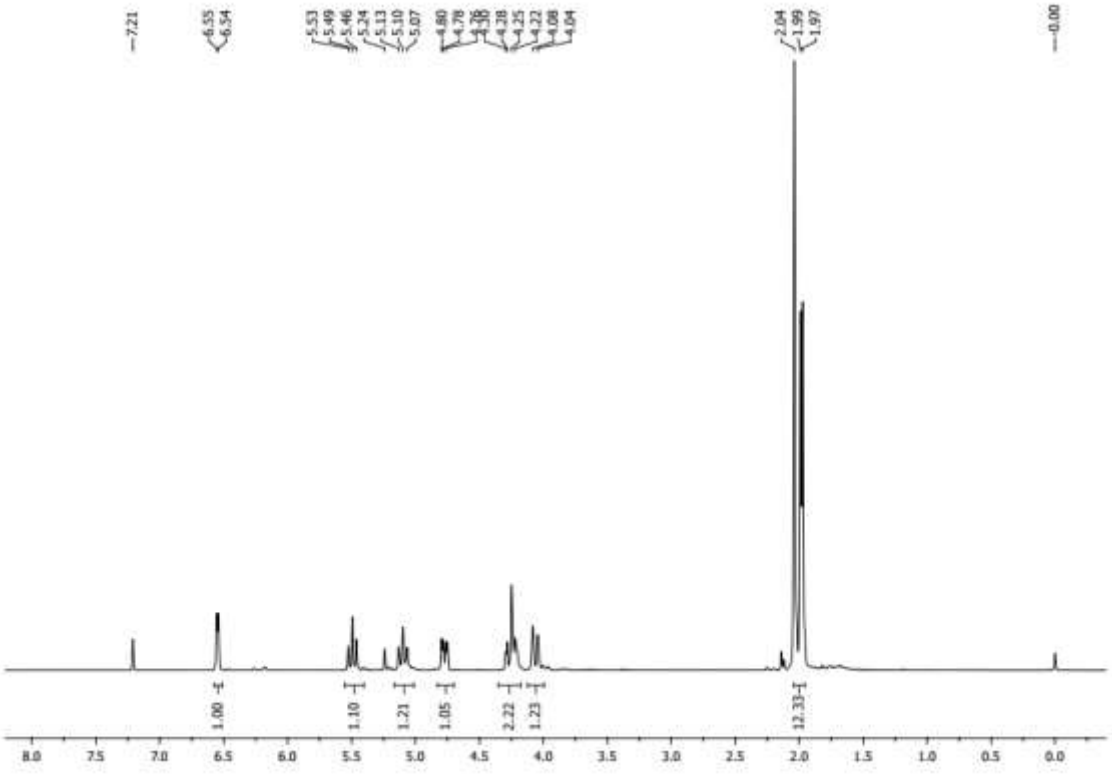
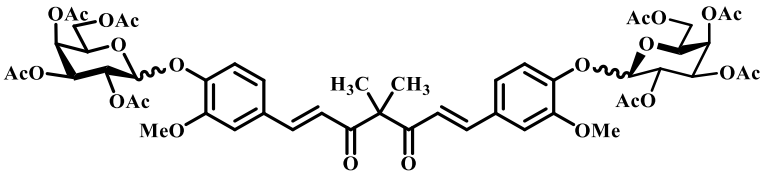
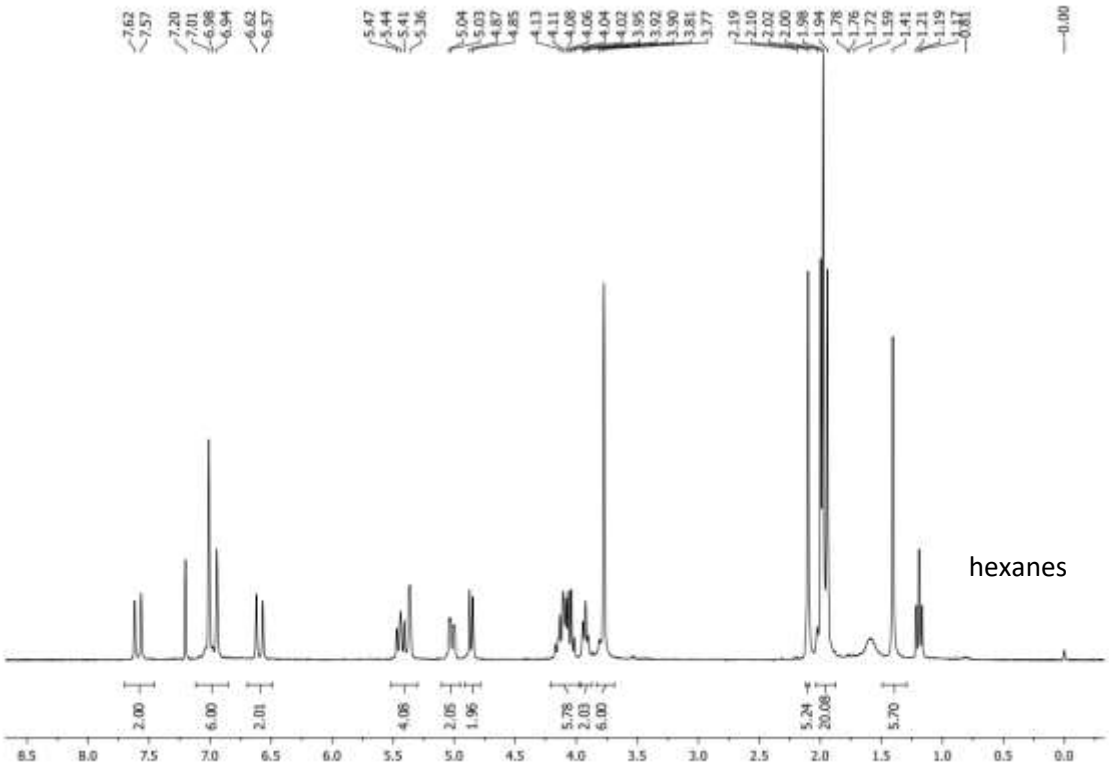
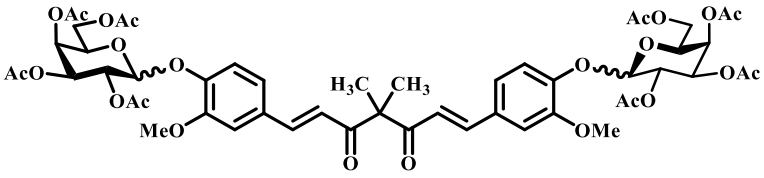


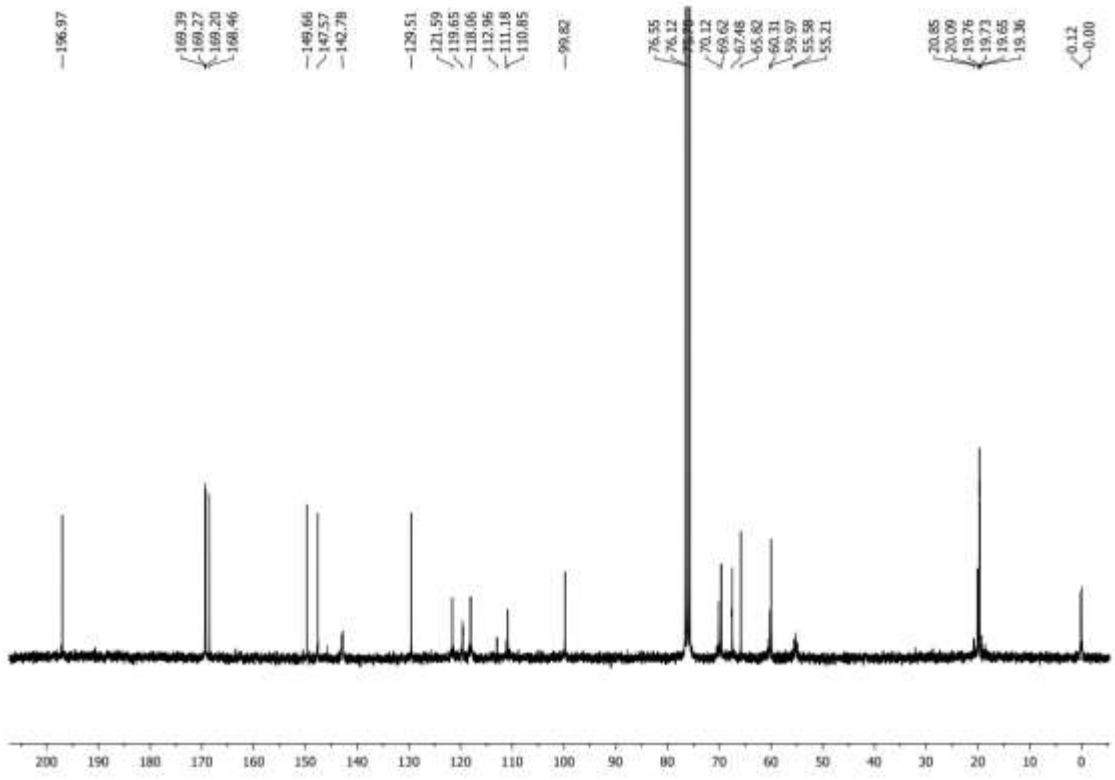


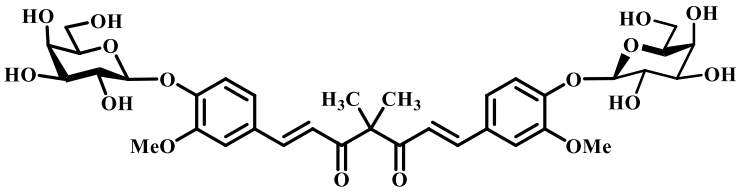
4.5a, Scheme 4.1



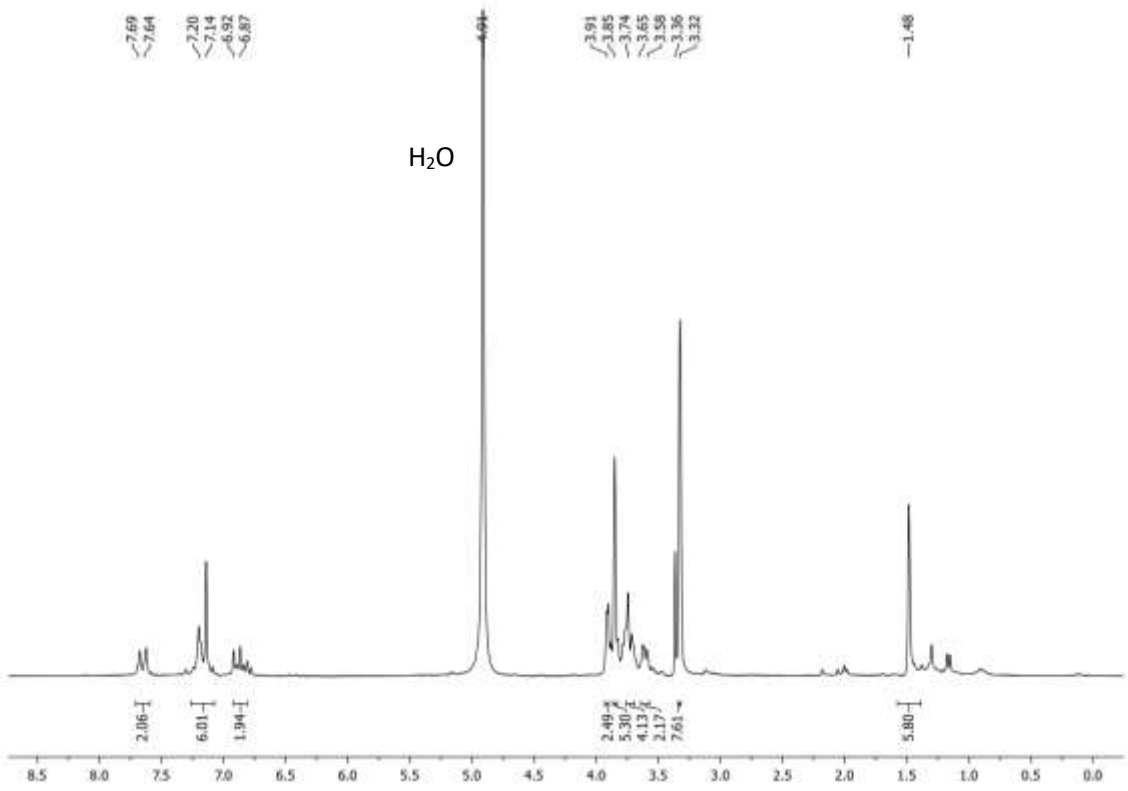


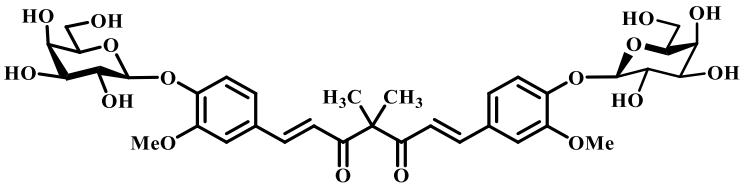
4.5a, Scheme 4.1



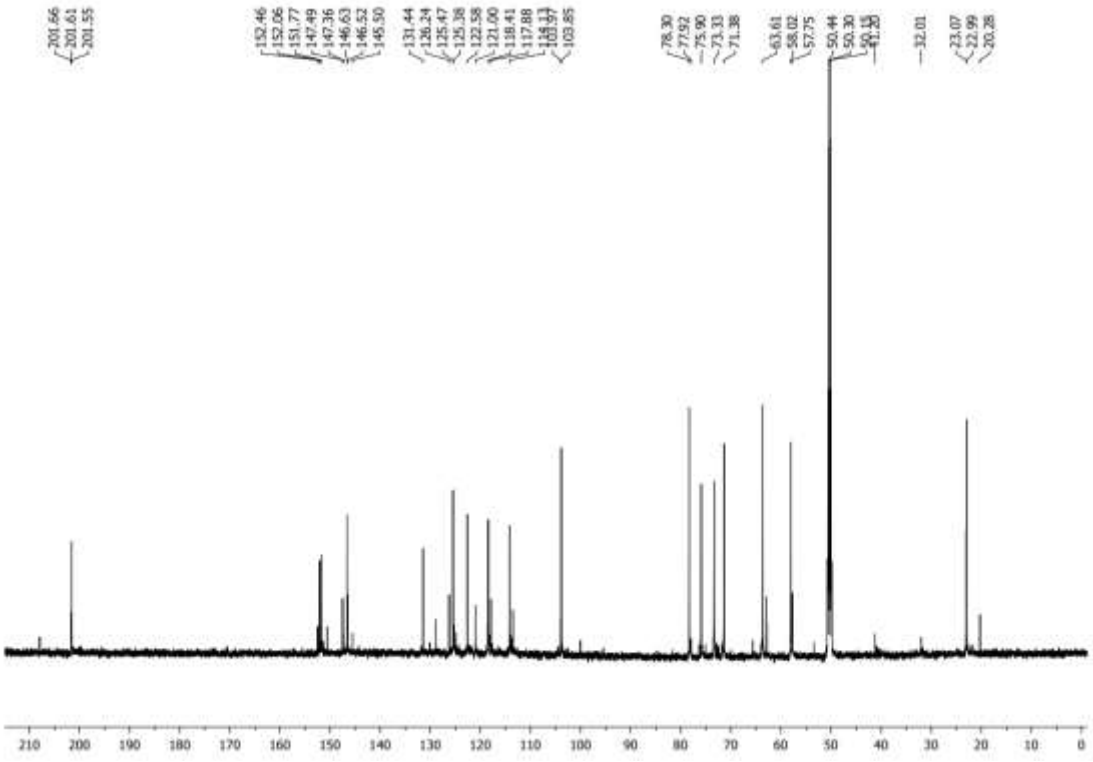


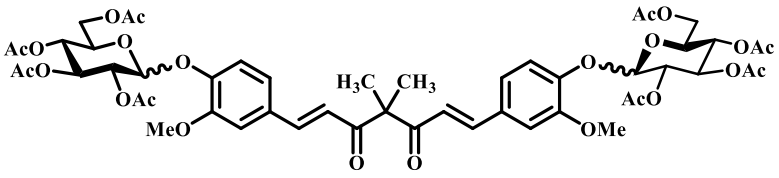
4.6a, Scheme 4.1



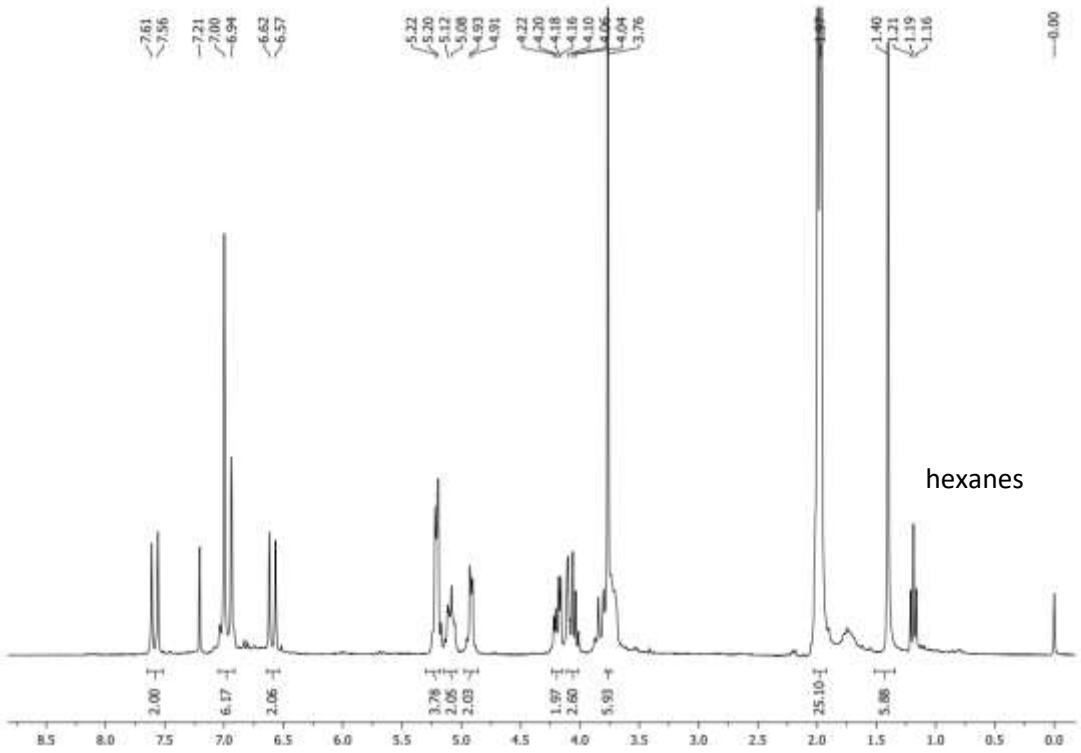


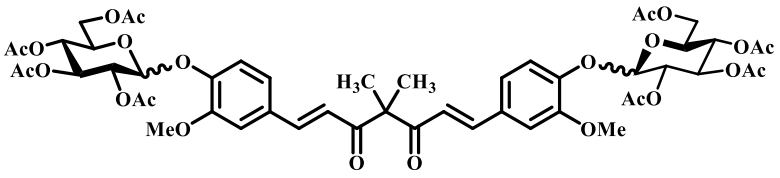
4.6a, Scheme 4.1



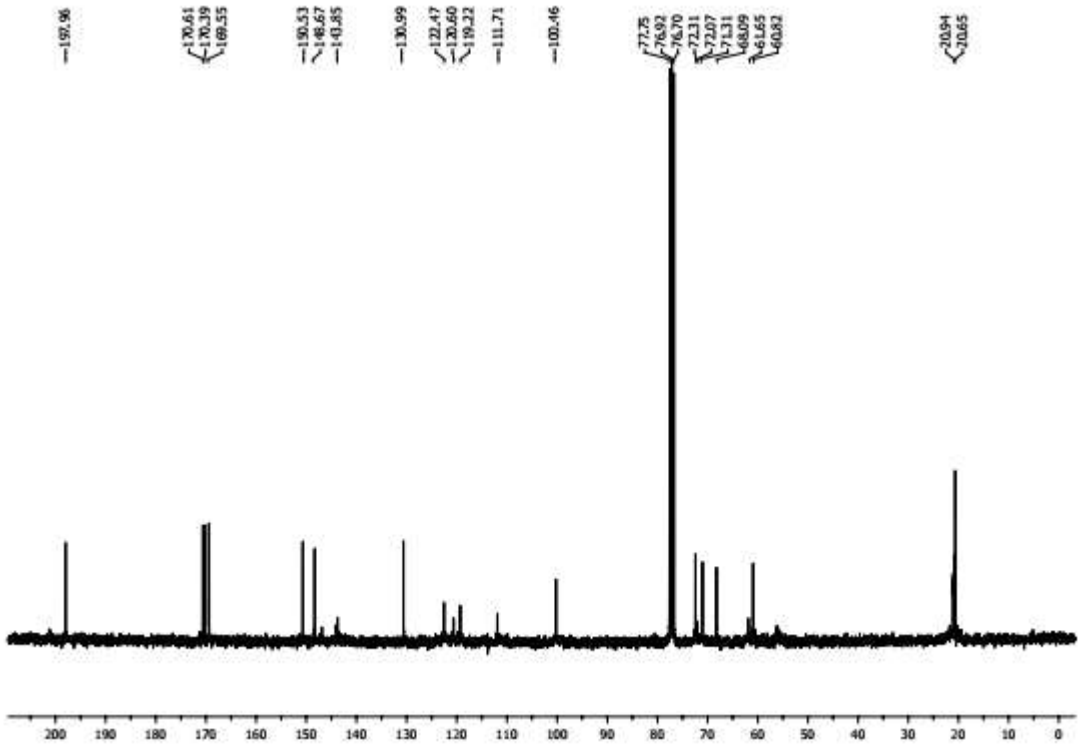


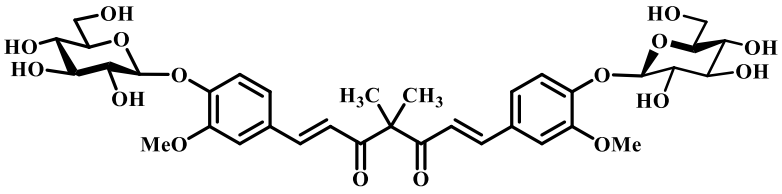
4.5b, Scheme 4.1



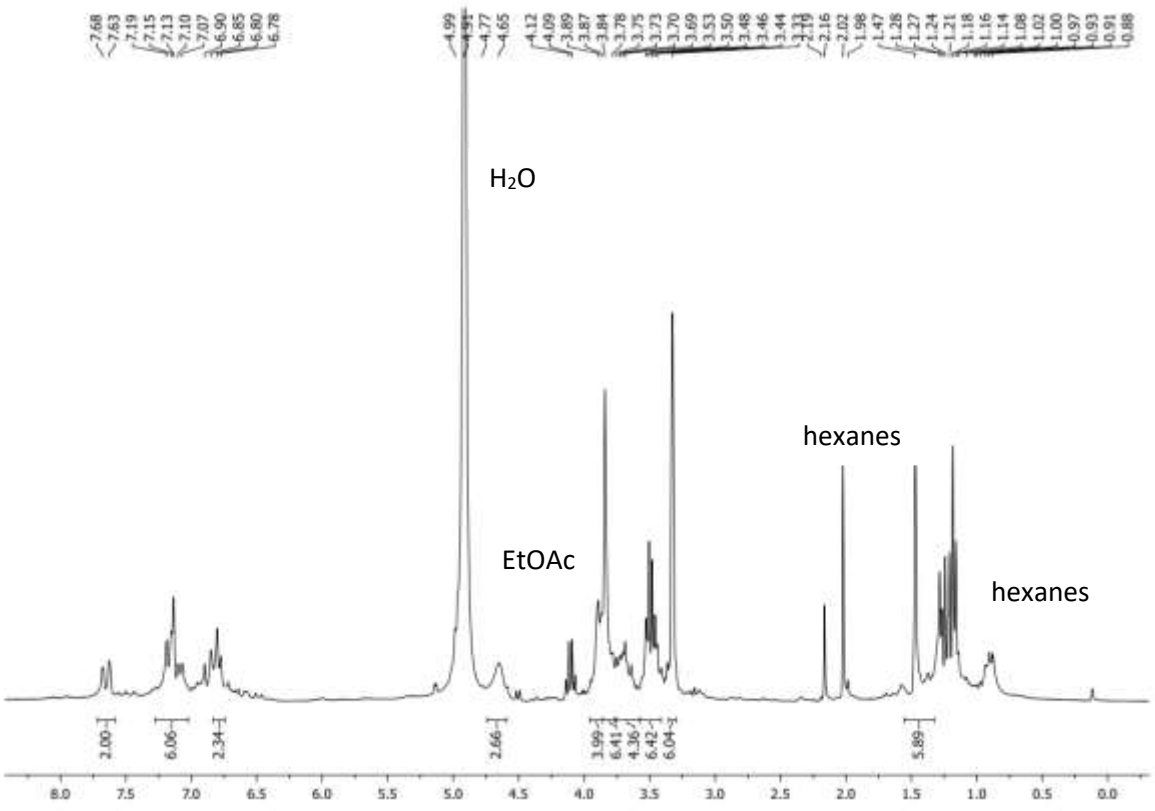


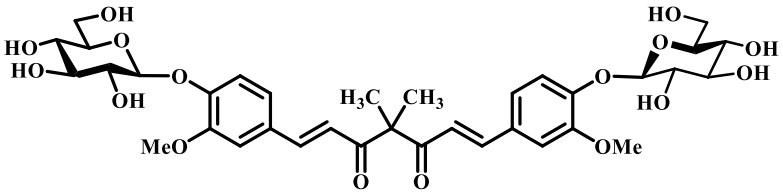
4.5b, Scheme 4.1



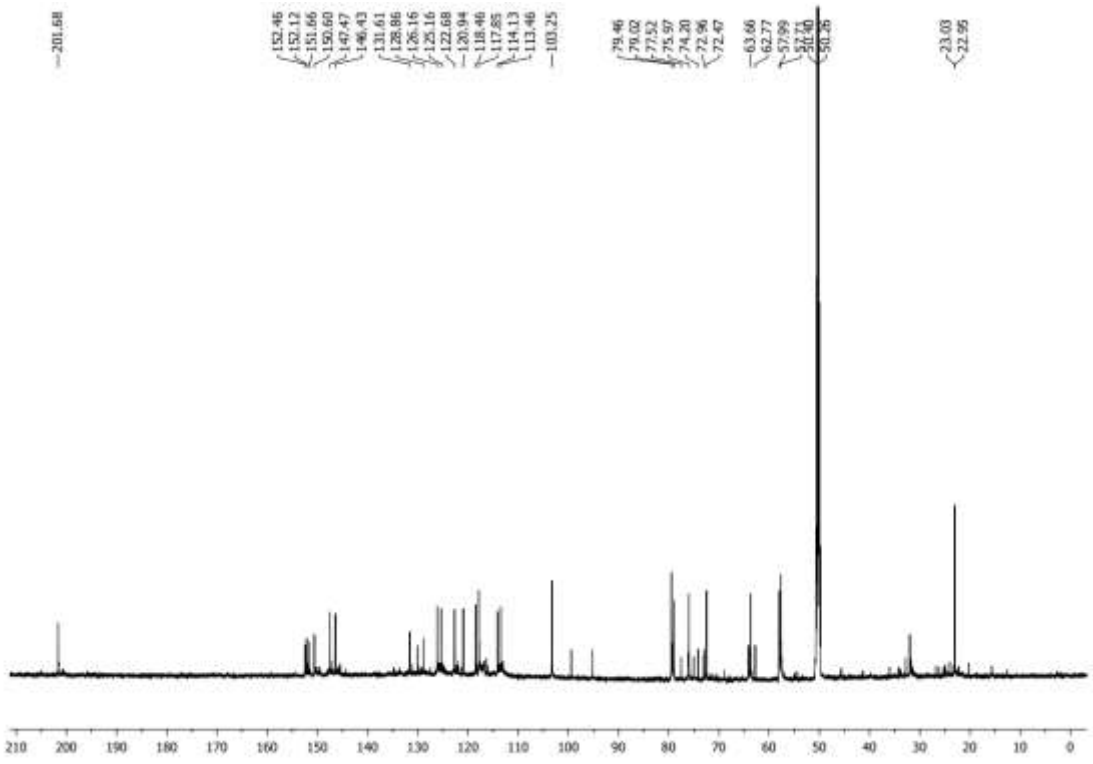


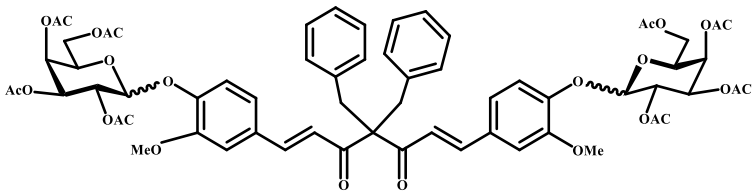
4.6b, Scheme 4.1



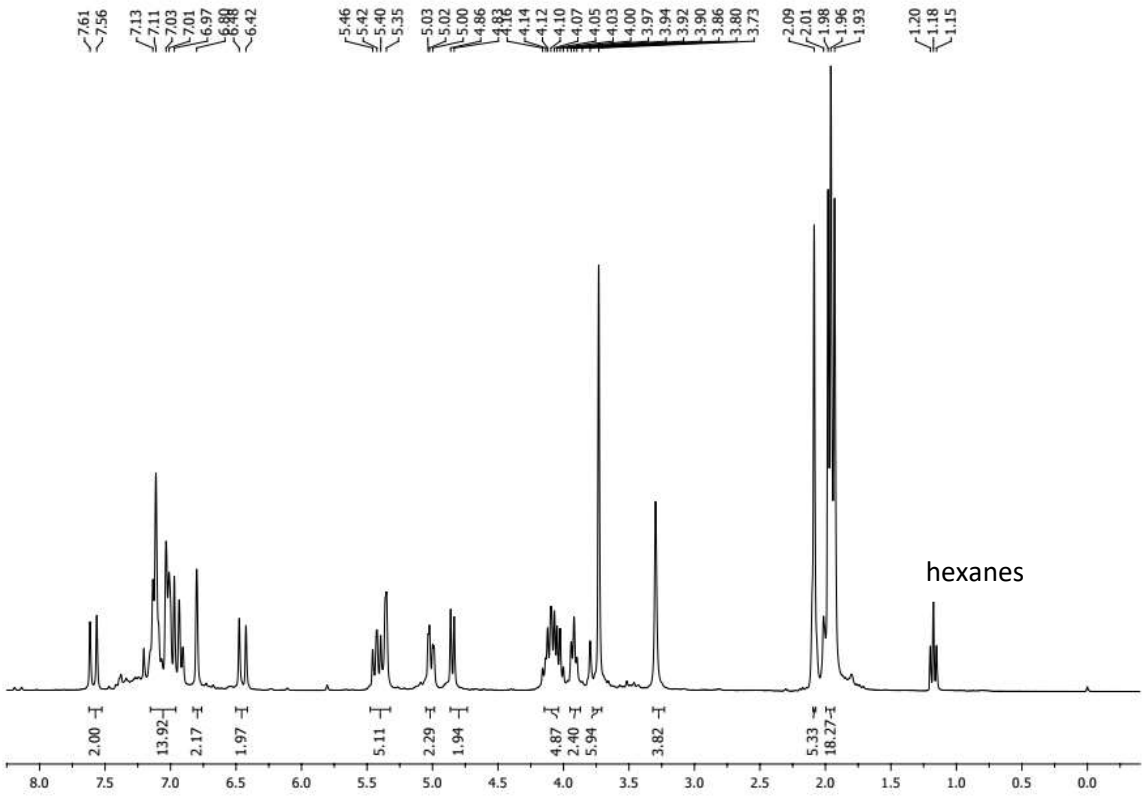


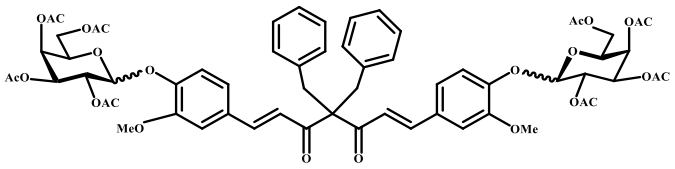
4.6b, Scheme 4.1



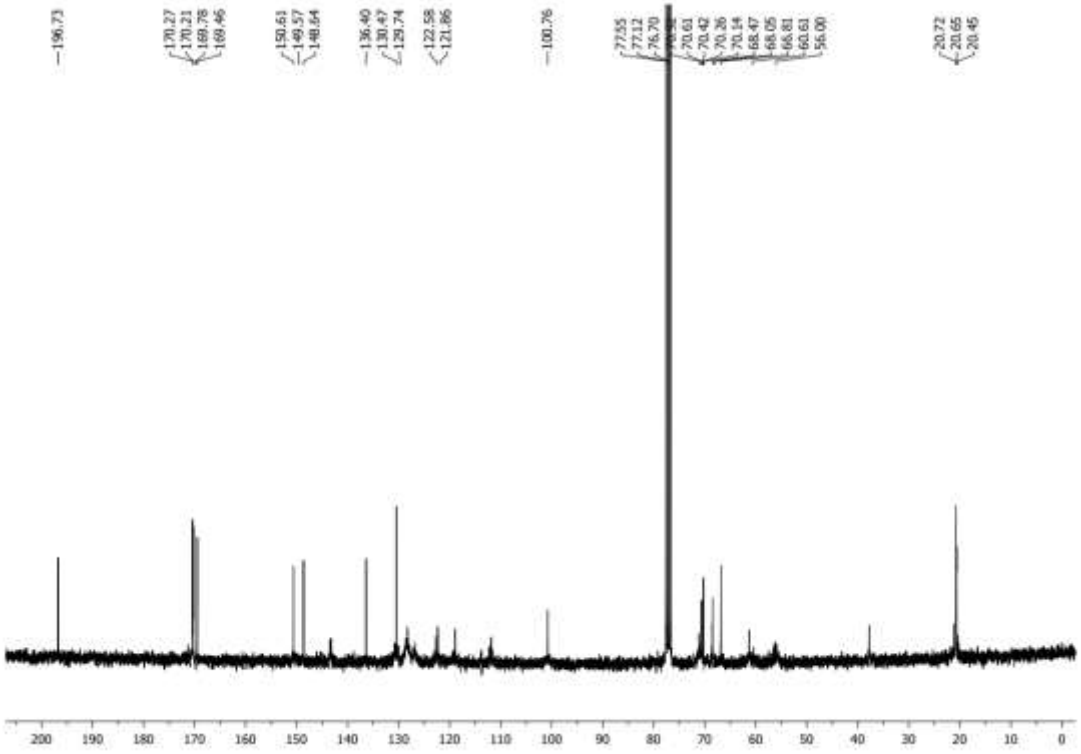


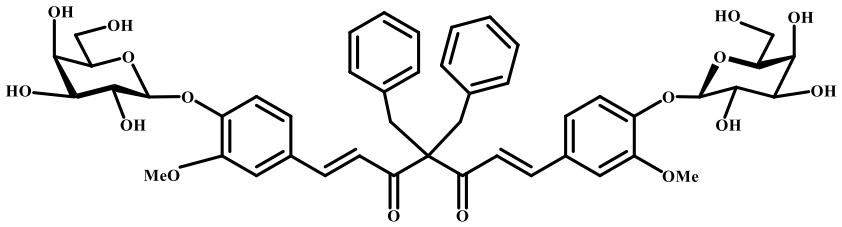
4.9a, Scheme 4.2



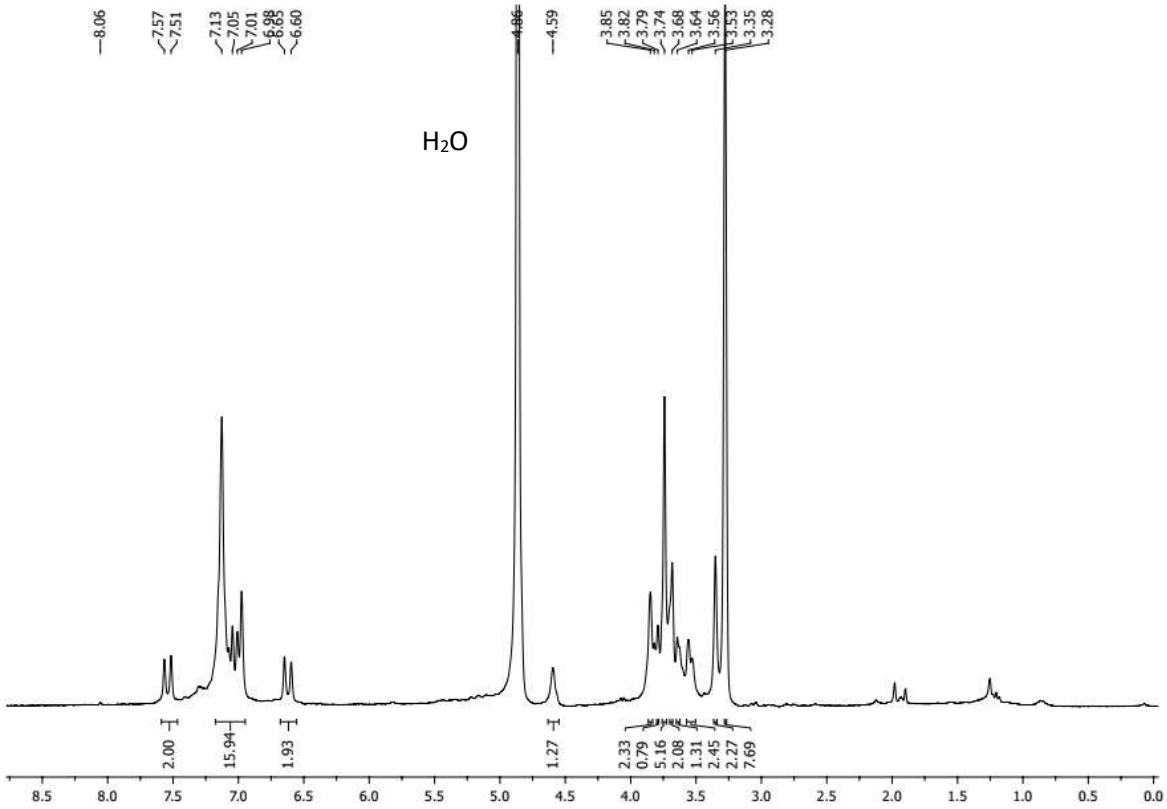


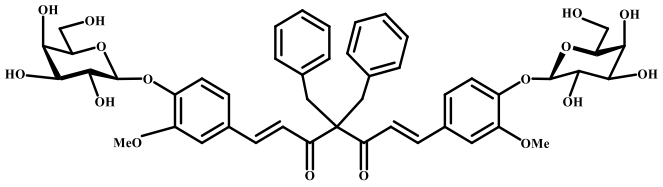
4.9a, Scheme 4.2



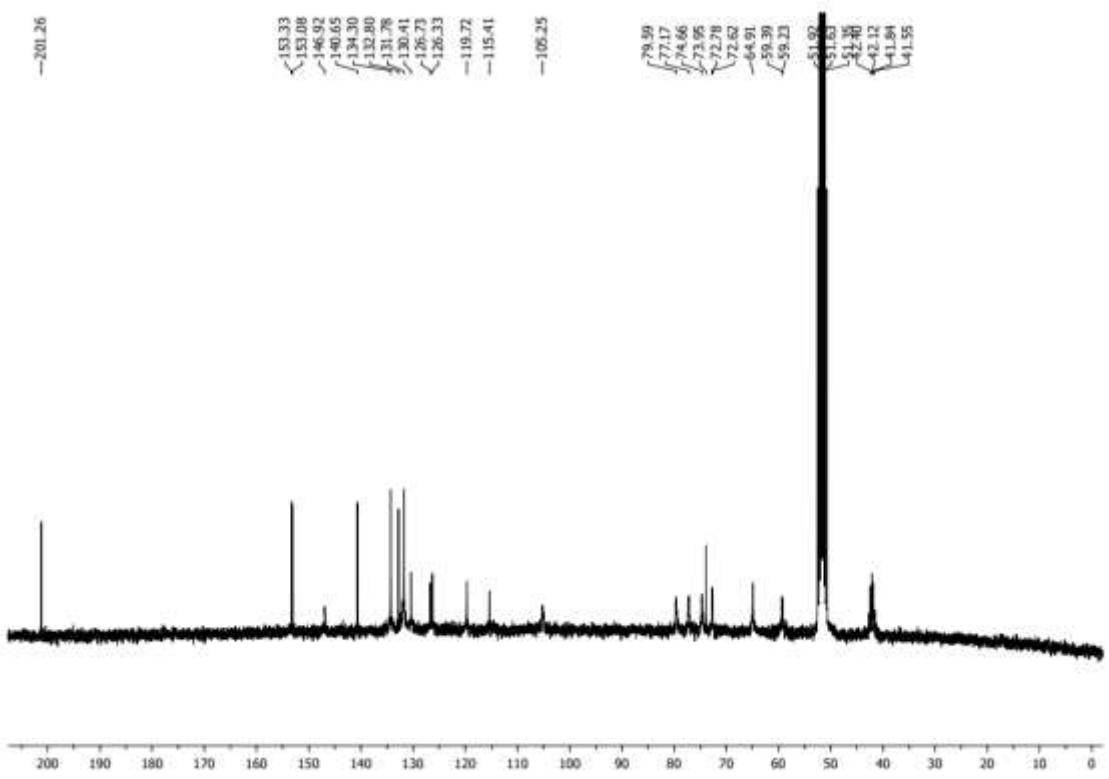


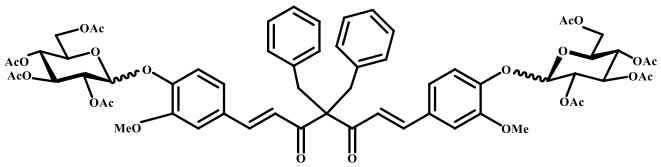
4.10a, Scheme 4.2



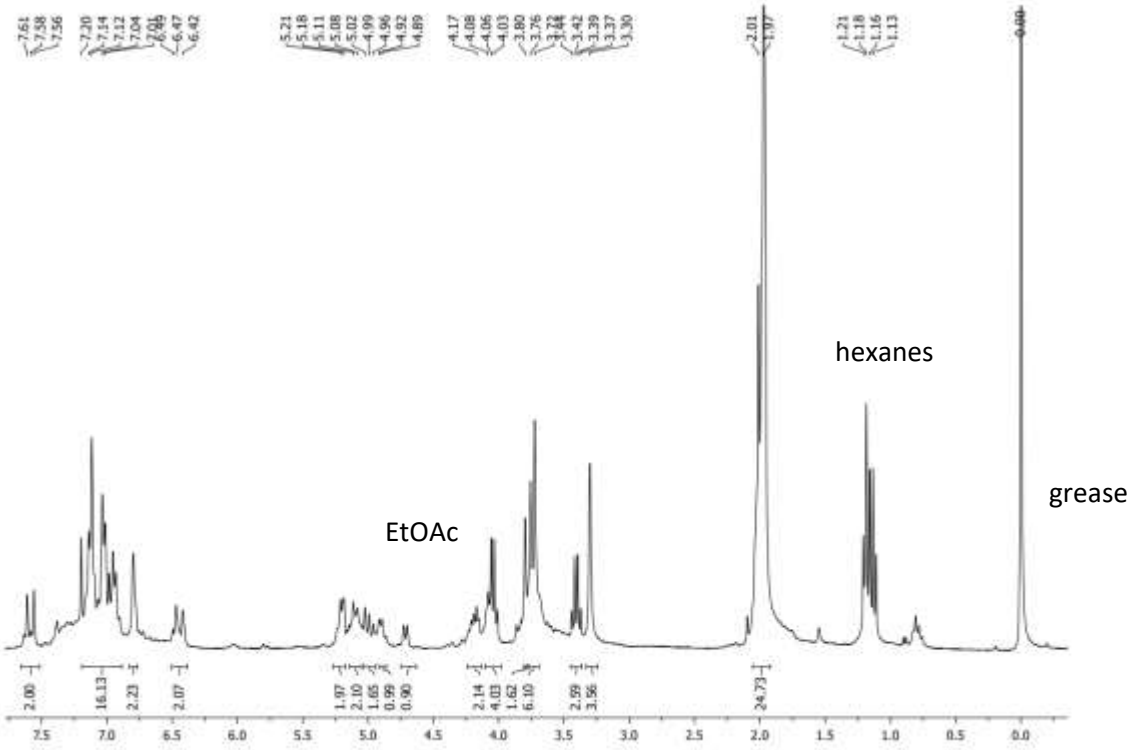


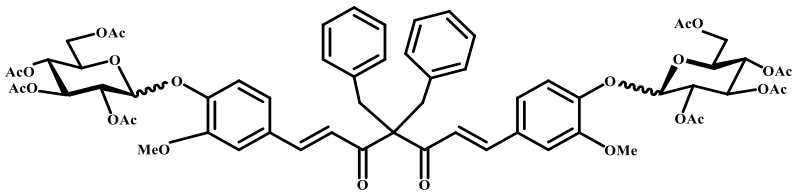
4.10a, Scheme 4.2



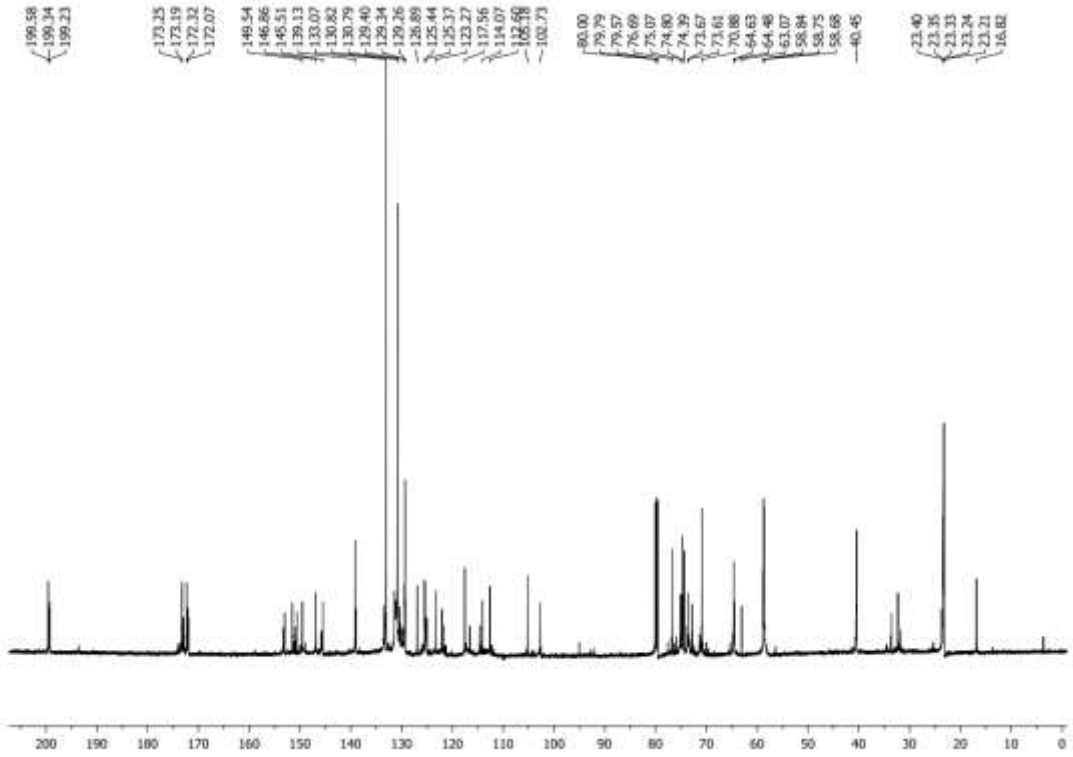


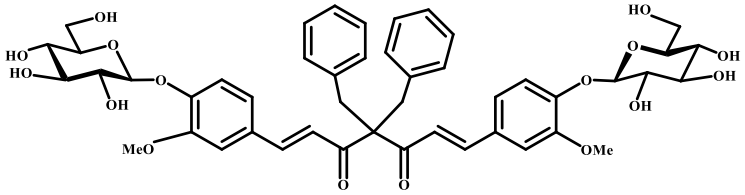
4.9b, Scheme 4.2



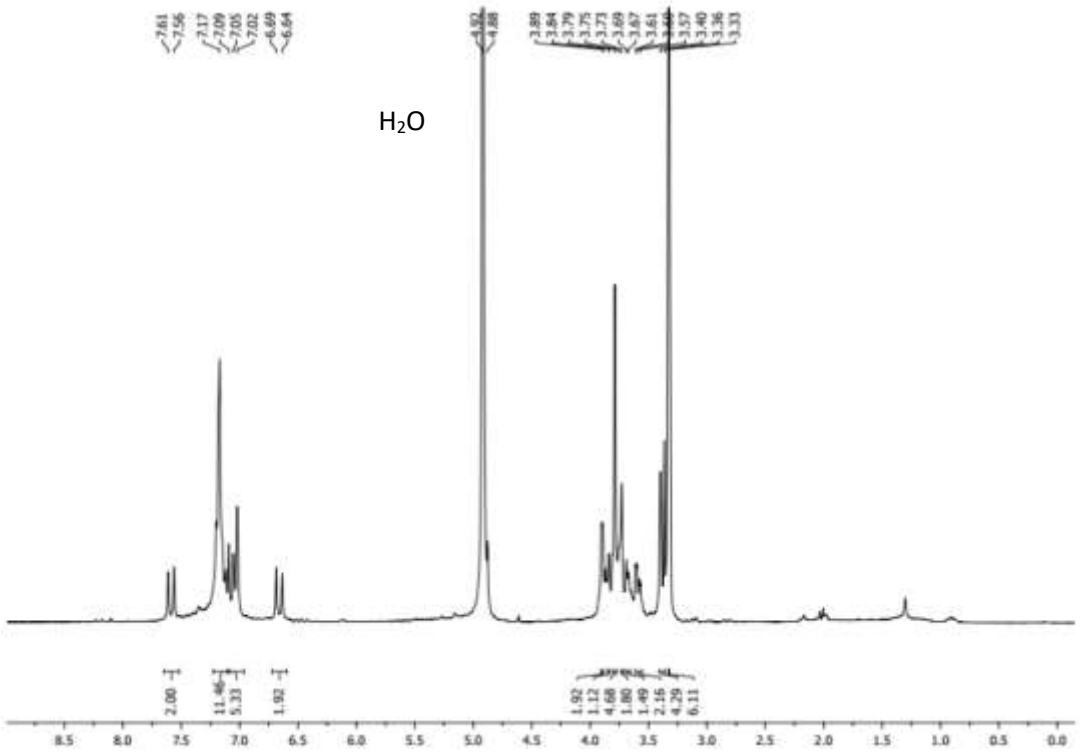


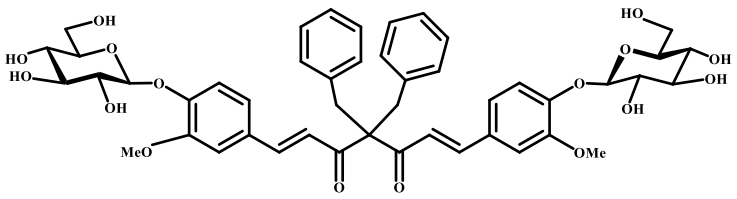
4.9b, Scheme 4.2



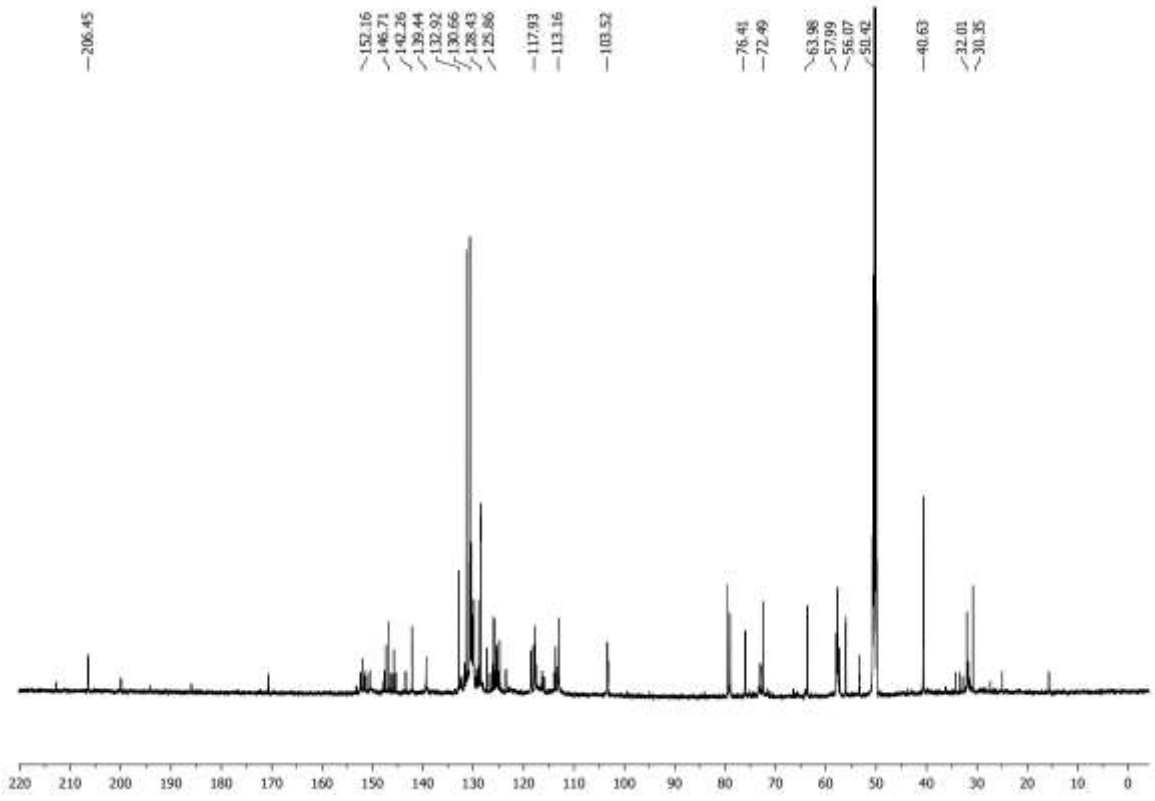


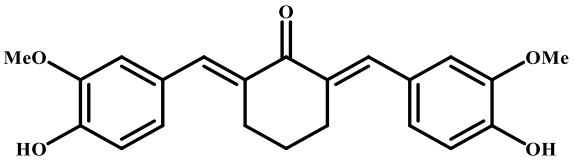
4.10b, Scheme 4.2



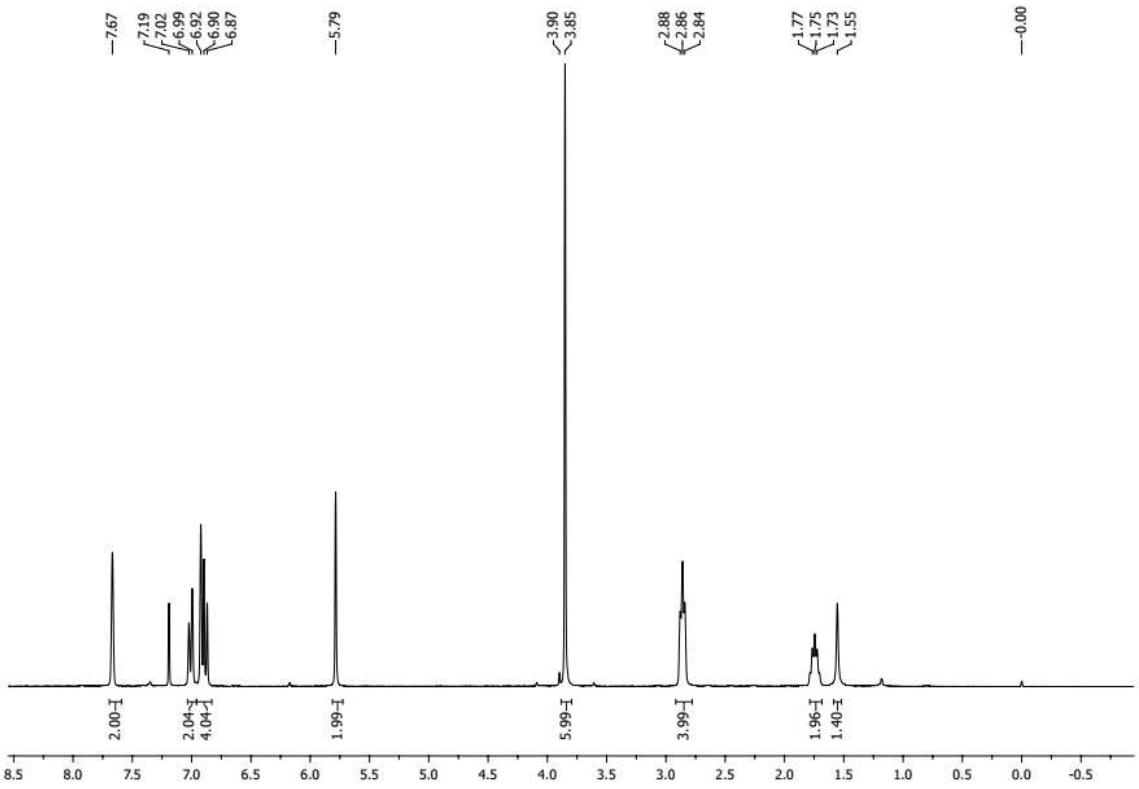


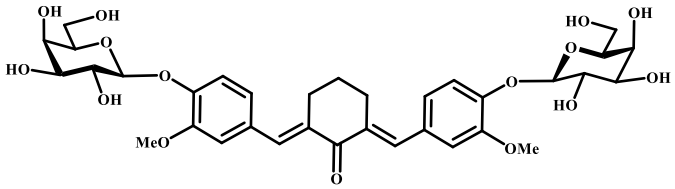
4.10b, Scheme 4.2



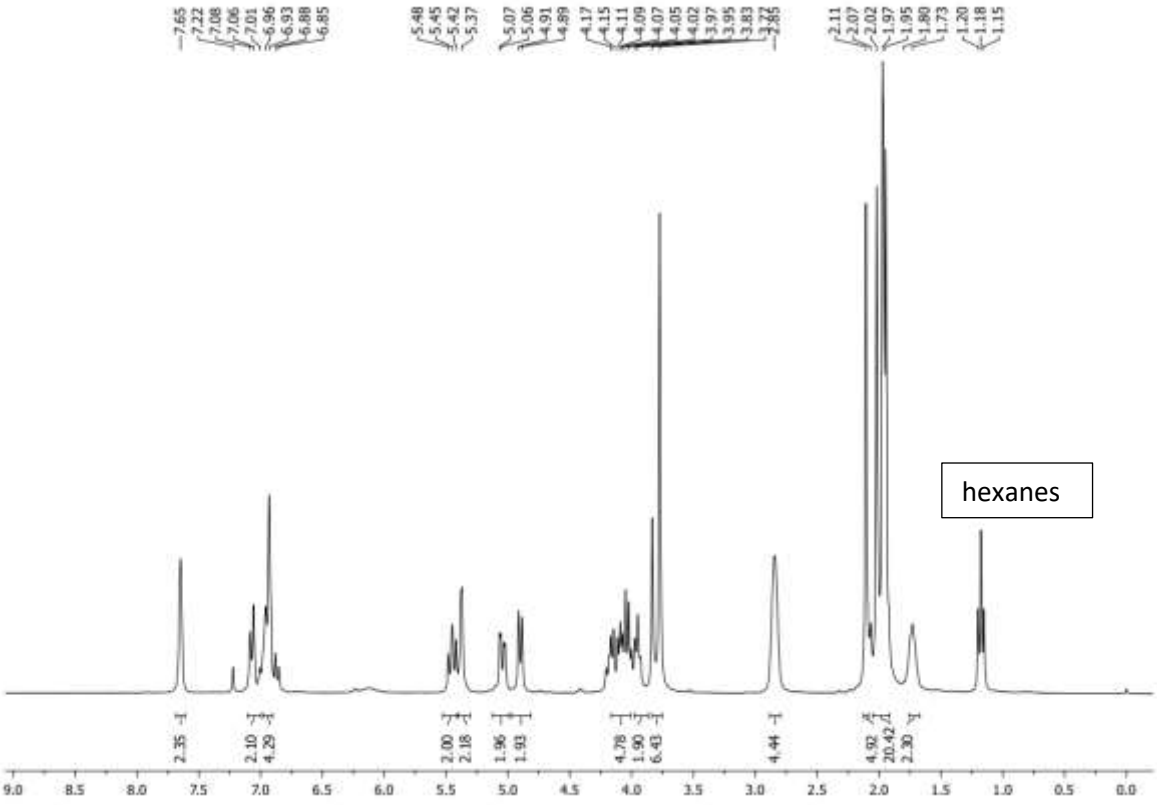


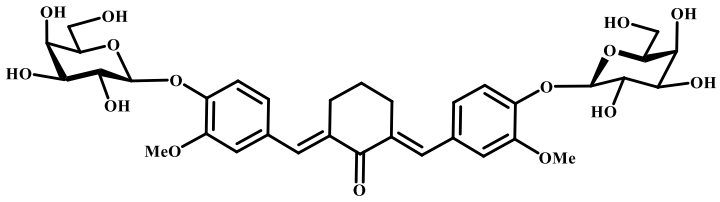
4.13, Scheme 4.3



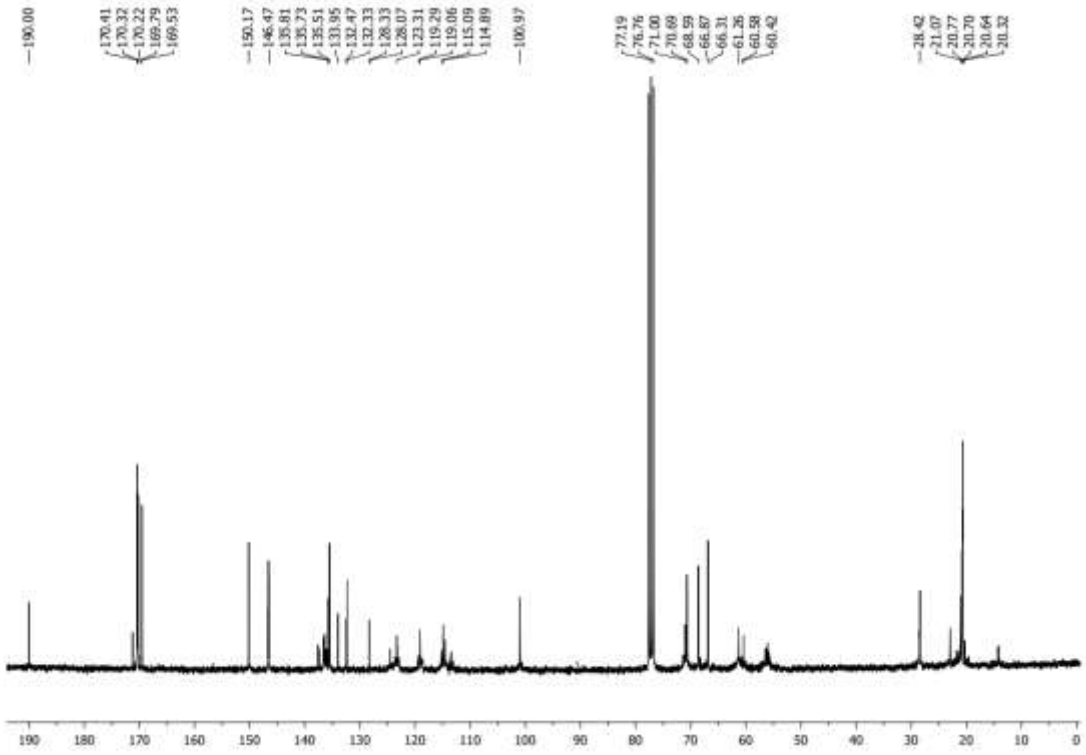


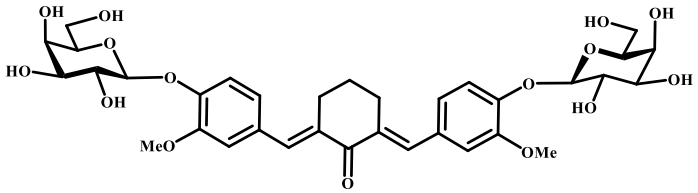
4.14a, Scheme 4.3



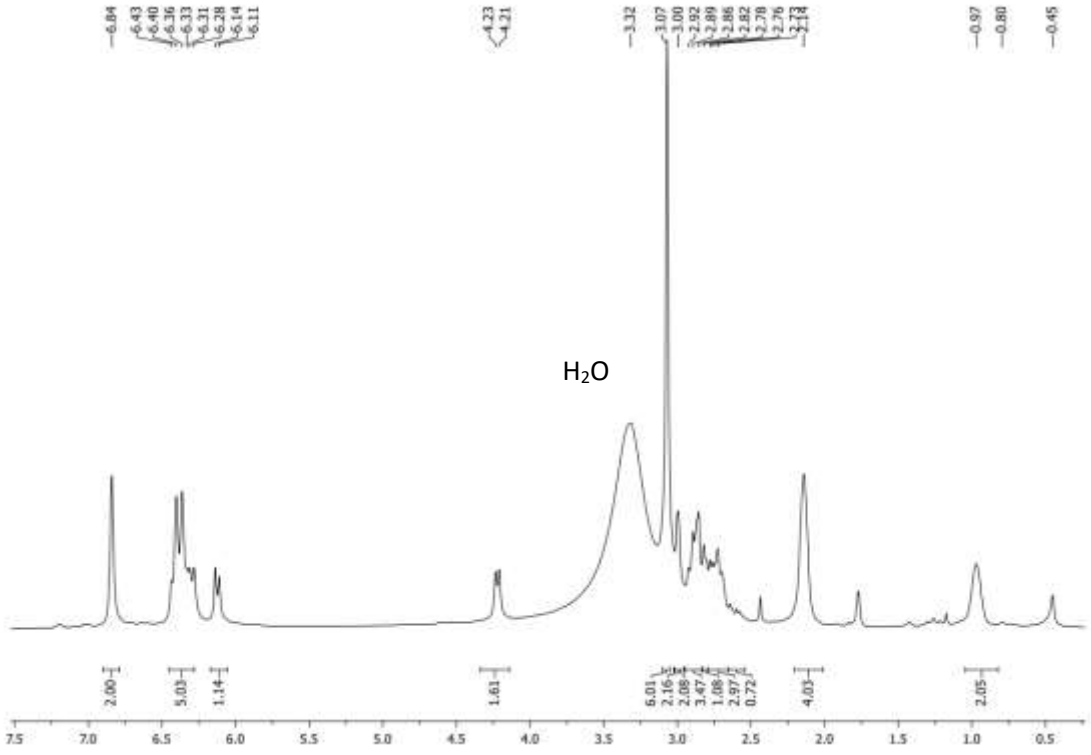


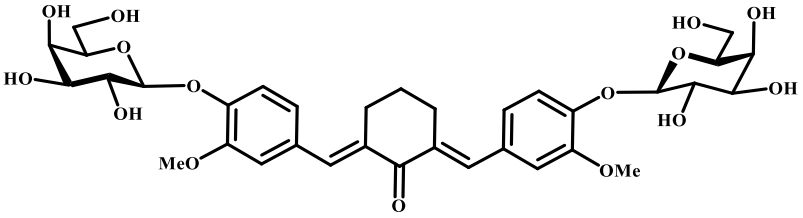
4.14a, Scheme 4.3





4.15a, Scheme 4.3





4.15a, Scheme 4.3