may this glorify God…

ABSTRACT

A series of rigid neoglycoclusters and dimers were synthesized from sugar alkynes using Sonogashira coupling. Rigid dimers consisting of two mannoside or galactoside derivatives tethered to a phenylacetylene core were constructed. By oxidative coupling of glycosidic terminal acetylenes, rigid dimers consisting of two mannoside residues tethered to a diphenyl-di-acetylene core were synthesized. Utilizing the ortho-, meta- and para- acetylene substituted phenyls, rigid dimers having monosaccharide units oriented at 60°, 120° and 180° with each other were generated.

Convergent synthesis of glycosidic clusters emanating from a benzene core was attained utilizing $Co_2(CO)_8$ catalyzed cyclotrimerization of acetylenes disubstituted with monosaccharide residues. Trimers and hexamers, including a hexameric "molecular asterisk" were constructed. Galactoside and mannoside clusters were synthesized.

Semi- rigid dimers were also synthesized by *O*-glycosidation of dihydroxybenzene and 2-butyn-1,4-diol.

Preliminary binding studies of the mannoside dimers, trimer and hexamers revealed that the hexamer and rigid dimers having two phenyl-acetylenes at the core have promising activity vs. the phytohemagglutinin *from Canavalia ensiformis* (ConA.). Optimum binding with ConA was demonstrated by the para-disubstituted di-phenyl-diacetylene and the molecular asterisk. These two

compounds showed comparable activities giving an indication of the minimum binding requirements of mannosaccharide conjugates with Concanavalin A.

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I am indebted to my supervisor for giving me this opportunity to work with him and for directing this research.

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LIST OF ABBREVIATIONS

Ac	acetate
Ala	alanine
Arg	arginine
Asn	asparagine
Asp	aspartic acid
Bs	broad singlet
Bu	n-butyl
Bu^n	n-butyl
cat.	catalytic
Con. A	Concanavalin A.
COSY	shift correlation spectroscopy
d	doublet
dba	trans,trans-dibenzylideneacetone
dd	doublet of doublet
ddd	doublet of doublet of doublet
DMF	dimethylformamide
DMSO	dimethylsulfoxide
ES	electrospray
Et_3N	triethylamine
FAB	fast atom bombardment
Gln	glutamine
h	hours

HMQC	heteronuclear multiple quantum coherence
Hz	Hertz
HRMS	high resolution mass spectra
IP_3	1,4,5-triphosphate receptor
IR	infrared
Leu	leucine
L_n	ligand
M	molar; metal
MeOH	methanol
Me	methyl
MHz	megaHertz
min.	minutes
mmol	milli molesl
mol	moles
MP	melting point
MS	mass spectra
m/z	mass to charge ratio
NaOMe	sodium methoxide
NMR	nuclear magnetic resonance
O.D.	optical density
ppm	parts per million
Rf	retention factor
r.t.	room temperature

rxn	reaction
s	singlet
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSOTf	trimethylsilyltriflate
Tyr	tyrosine
μmol	micromoles

Chapter 1. Introduction

1.1. Glycodendrimers

Carbohydrate chemistry has taken great strides in the last two decades. Modifications in the carbohydrate structure were made possible such that novel structures were synthesized. An interesting class of these novel structures is the glycodendrimers. Glycodendrimer is a term coined for a carbohydrate dendrimer.[1] Dendrimer itself comes from the Greek words "dendron" which means tree and "meros" which means part. They were called earlier as cascade molecules. These molecules emanate from a core, and like a tree they steadily ramify with each subsequent branching unit[2] (Fig. 1.1.1 and Fig. 1.1.2).

Recently, neoglycoconjugates with this dendrimer architecture were constructed (Fig. 1.1.3). Glycoside residues were anchored on a dendrimer core. The first synthesis of this novel class of neoglycoconjugates appeared in 1993.[3] Glycodendrimers with various core structures such as L-lysine[3,4], gallic acid[5], polyamidoamine (PAMAM)[6] (Fig. 1.1.3), and phosphotriester backbone[7] were synthesized. Synthesis was designed such that the valencies, shapes, and carbohydrate contents of these dendrimers could be varied at will.[1a]

The synthesis of these neoglycoconjugates was driven by a search for optimizing carbohydrate-protein interactions. It was established that multivalency enhances binding with proteins by as much as a factor of 2000.[6d,8] Other factors

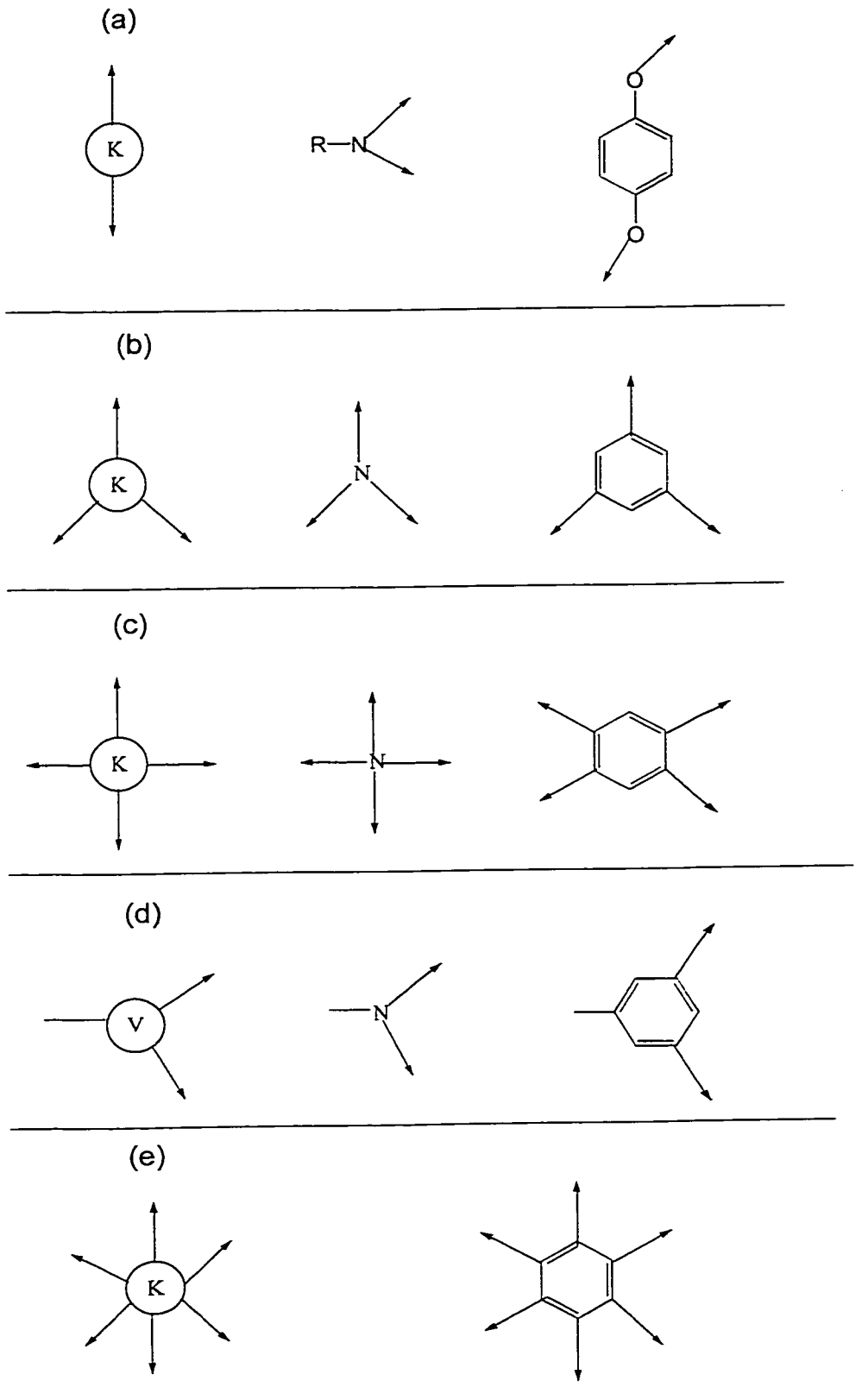
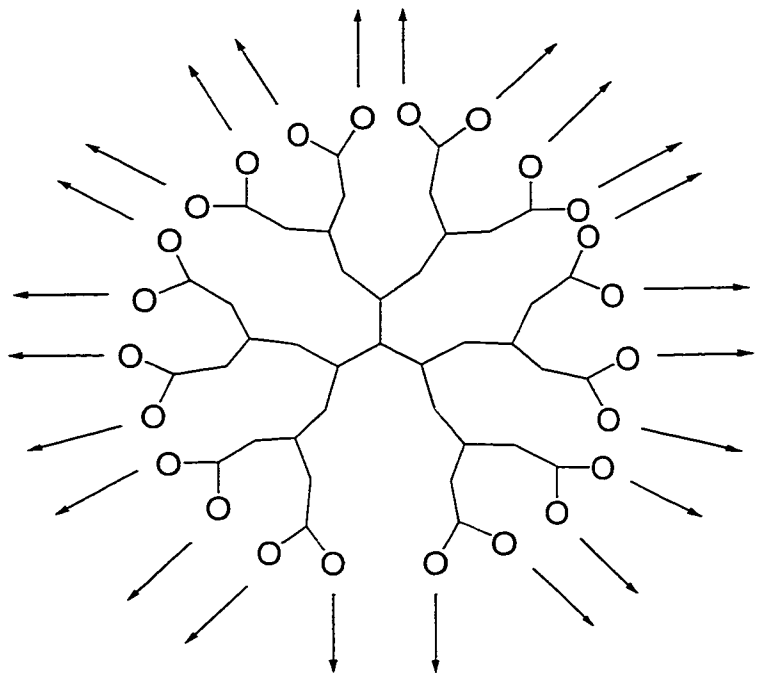


Figure 1.1.1. Design of dendrimers (a) with divalent (b) trivalent (c) tetravalent, (e) hexavalent core units and (d) V branch units.

(a)



(b)

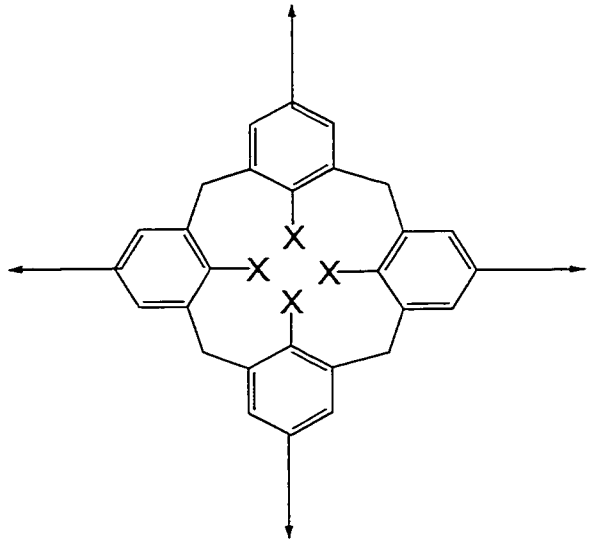


Figure 1.1.2. Dendrimer structures.

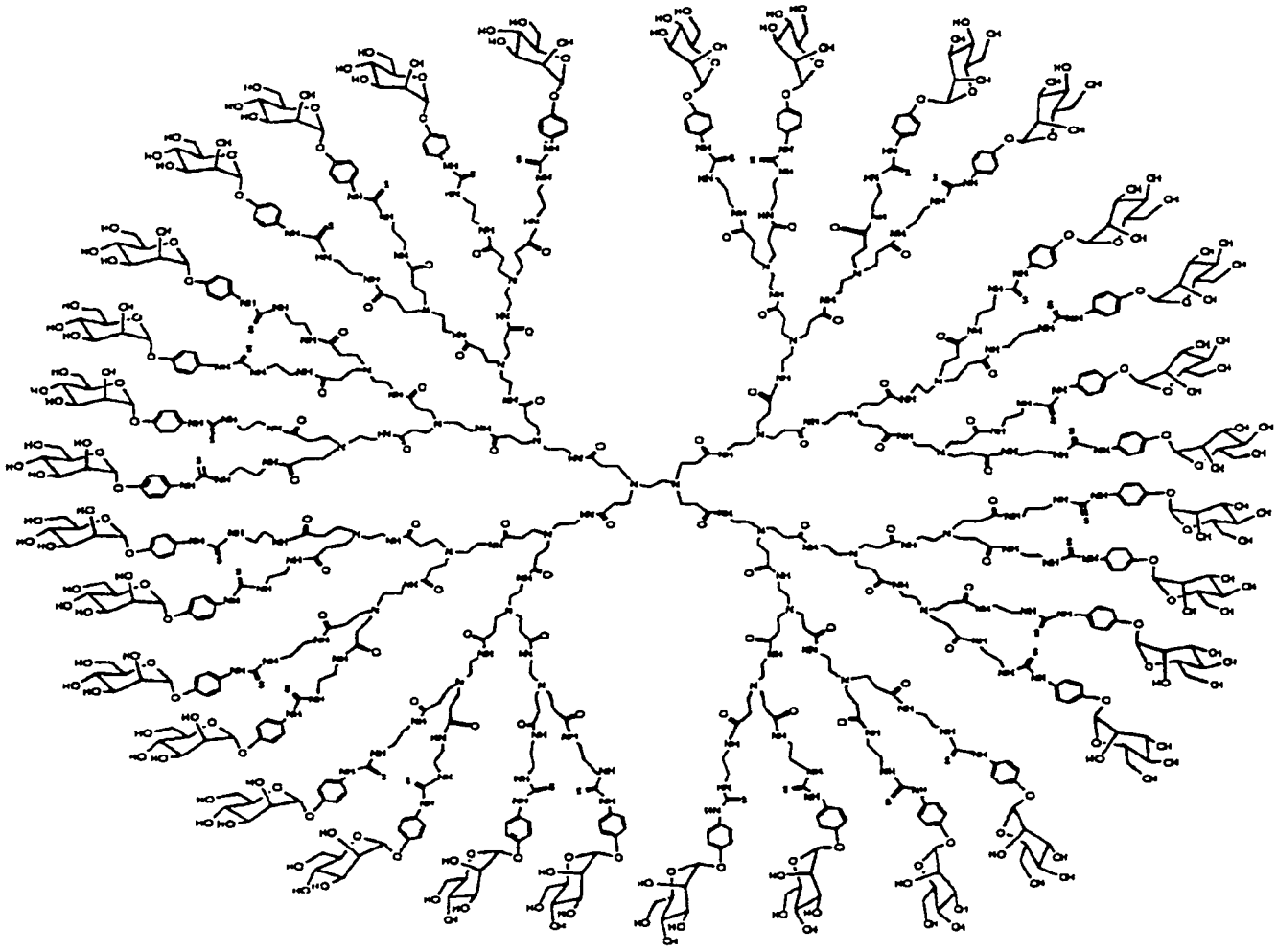


Figure 1.1.3. Mannopyranosylated PAMAM dendrimer.

that influence protein-carbohydrate binding are structure, shape, size, and geometry.[9] Multivalency studies can also be done on neoglycoproteins[1b,10] and glycopolymers.[1b,11] However, quantitative measurements by biophysical methods are hampered in these macromolecules due to their heterogeneity.

The study of the effect of multivalency on the binding between proteins and carbohydrates is part of a new focus in molecular biochemistry on the interaction between biological systems through multiple, simultaneous molecular contacts. Polyvalency is known to exist between cells and viruses, cells and bacterium, cells and other cells such as neutrophil and arterial endothelial cells, cells and polyvalent molecules such as bacteria, antibodies and macrophages, and between transcription factors and multiple sites on DNA.[12] A macrophage binds to a bacterium (or other pathogens) through antibodies. After recognizing a surface ligand (usually a protein) on the bacterium, binding occurs bivalently. The macrophage then recognizes (with Fc receptors) the mannose residues on the constant region "tail" of the antibody, and binds multivalently to the antibody-decorated pathogen.(Fig. 1.1.4).[12]

Carbohydrates are known to participate in these recognition events by carbohydrate-protein interactions.[23] Carbohydrate-protein interactions has been investigated by studying lectin-carbohydrate binding.[13, 14] Lectins are defined as "a carbohydrate-binding protein (or glycoprotein) of non-immune origin which agglutinates cells and/ or precipitates glycoconjugates".[15]

Of this class, plant lectins exhibit low specificity; i.e. they are selective and differ in the type of carbohydrate structures they recognize with low affinity.[16] Concanavalin A, a legume lectin isolated from Jack bean (*Canavalia ensiformis*)[13] is known to bind specifically to mannose and glucose residues (Fig. 1.1.5).

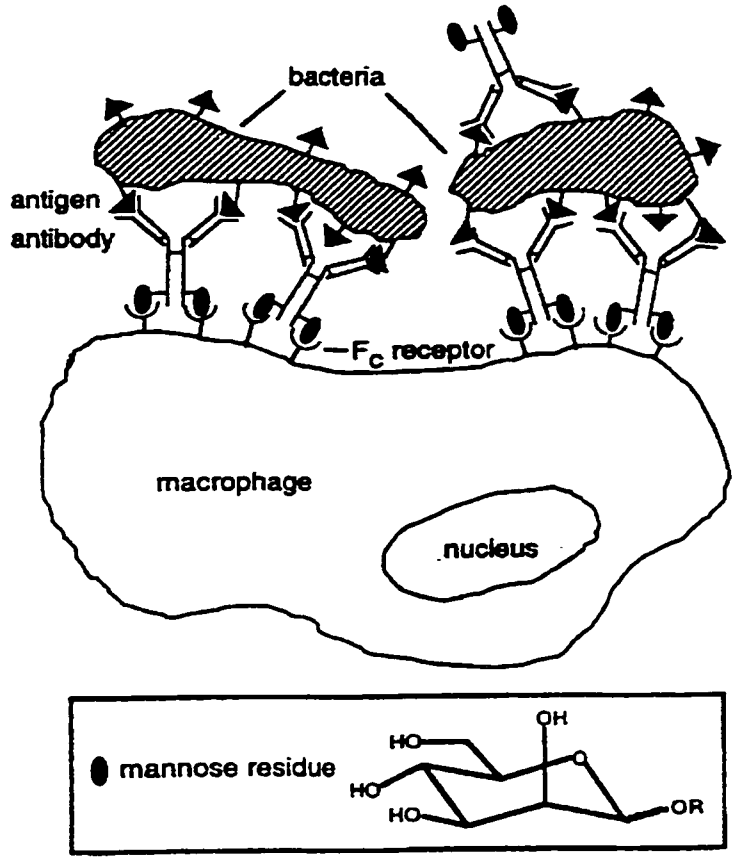
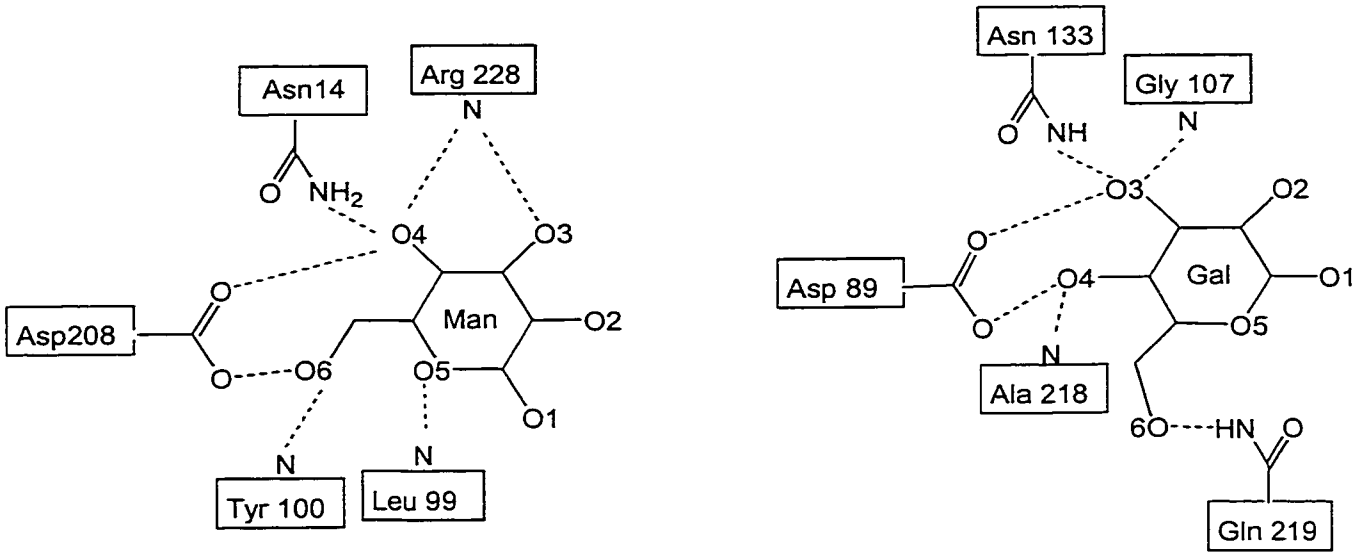


Figure 1.1.4. Polyvalent binding of macrophage to bacterium (or other pathogens) through antibodies.



Mannose/Glucose
(Canavalia ensiformis)

Galactose
(*Erythrina corallodendron*)

Figure 1.1.5. Monosaccharide recognition (left) Schematic diagram of the binding of mannose to Conanavalin A. (right) recognition of galactose by *Erythrina corallodendron*.[13]

1.2. Glycoclusters

To fine-tune the geometry and valency requirements, binding of clusters were studied. In a model study,[17] mannosylated dendrimers with L-lysine cores of valencies of 2,4,8 and 16 showed a 5.3 fold increase in binding with *Concanavalin A.* (*Con A.*) between the dimeric and tetrameric forms, whereas only a two-fold increase was observed between the octavalent and hexavalent forms. The smaller size of glycoclusters thus provide a better scaffold to study the binding activity. In view of a possible medicinal application, small clusters

would be better candidates as drugs than the higher molecular weight glycodendrimers due to their smaller size, hence, better bioavailability.

In a study of galactopyranoside clusters built on L-lysyl-L-lysine, the trimer (Fig. 1.2.1) was found to be more potent than mono- or di-valent clusters by a factor of 27.[18]

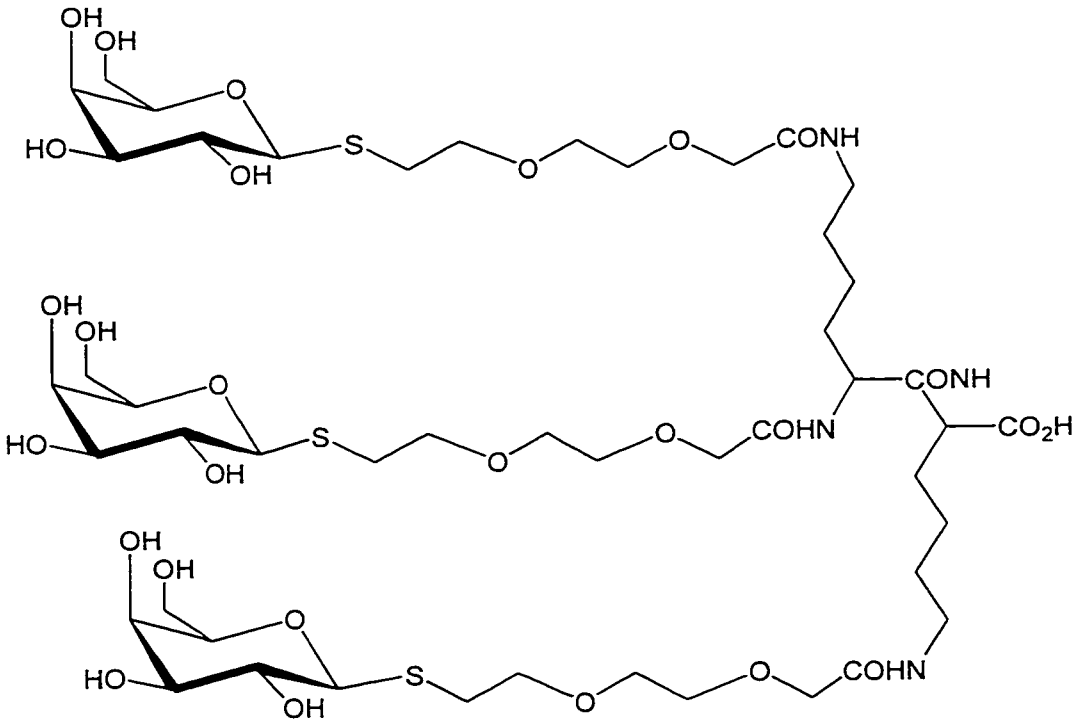


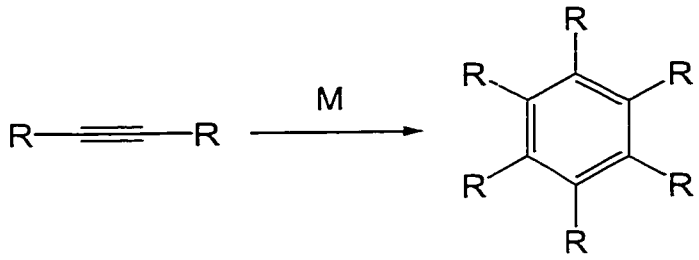
Figure 1.2.1. Trimer built on L-lysyl-L-lysine.[18]

A trivalent mannoside cluster built from raffinose dilysyl conjugates demonstrated strong binding properties on mannose macrophage receptors.[19] Tetravalent monosaccharide and trisaccharide mannosyl clusters were found to be 140 and 1155 times more potent inhibitors than monomeric methyl α-C-

mannopyranoside against pea lectin and *Con. A.*[20] Optimization of activity of the clusters were also studied by varying the intramannosyl distance.[21] It was also found that α-aromatic aglycons contribute significantly to the binding interactions.[22]

1.3 Cyclotrimerization

The following thesis describes the synthesis of novel glycoclusters containg a benzene core. Transition metal catalyzed cyclotrimerization of substituted acetylenes to benzene derivatives provide an elegant route to these neoglycoconjugates. Acetylene and substituted acetylenes undergo cycloaddition in one step in the presence of a metal catalyst (Scheme 1.3.1). This carbocyclization is a well-known reaction and can be achieved with many transition metals including Co, Ni, Pd, Cr, Rh, Fe, and Ta. This topic is extensively reviewed.[23]



Scheme 1.3.1. Cyclotrimerization of substituted acetylenes.

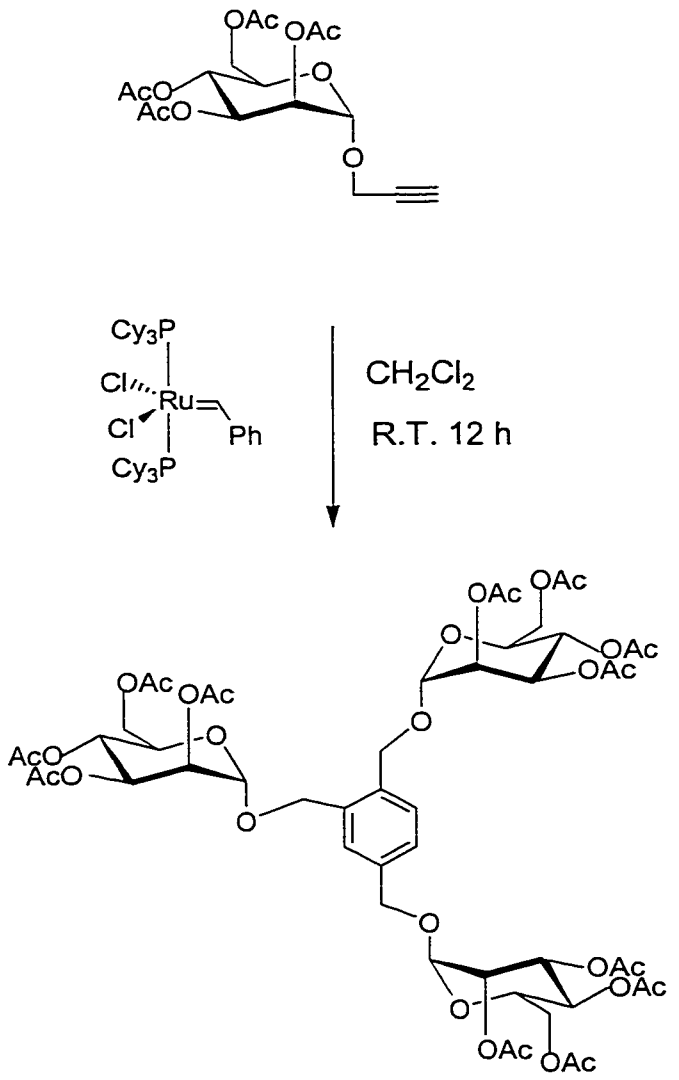
The reaction proceeds with high regio and chemoselectivity. Unsymmetrically substituted alkynes typically give benzenes with the larger substituents in position 1,2 and 4.[23c]

A trivalent cluster where three mannose residues tethered on a benzene core was reportedly synthesized from 2-propynyl α-D-mannopyranoside using Grubbs catalyst.[24] (Scheme 1.3.2). The reported yield for a reaction in CH_2Cl_2 under room temperature for 12 hours was 66-75%.

With cobalt octacarbonyl as catalyst, 2-propynyl-α-D mannosides were catalyzed to the corresponding trimer under reflux for 2 hours in dioxane[25]. Kaufman and Sidhu[26] first reported similar synthesis. They reported low yields (40%) and long reaction times (up to 21 days).

Hecht and Frechet[27] constructed novel benzene-core dendrimers by cyclotrimerization of benzylated acetylenes with $Co_2(CO)_8$ as catalyst (Fig. 1.3.1). Palladium catalyzed cyclotrimerization of benzylated acetylenes was also reported by Duchene and Vogtle[28] (Scheme 1.3.3).

In the following thesis, mannosyl residues were tethered on this scaffold, producing a novel neoglycocluster. The aromatic core would lend it interesting physical properties as well as a new scaffold to investigate binding studies with proteins.



Scheme 1.3.2. Trimerization of 2-propynyl α-D-mannopyranoside catalyzed by Grubb's catalyst.

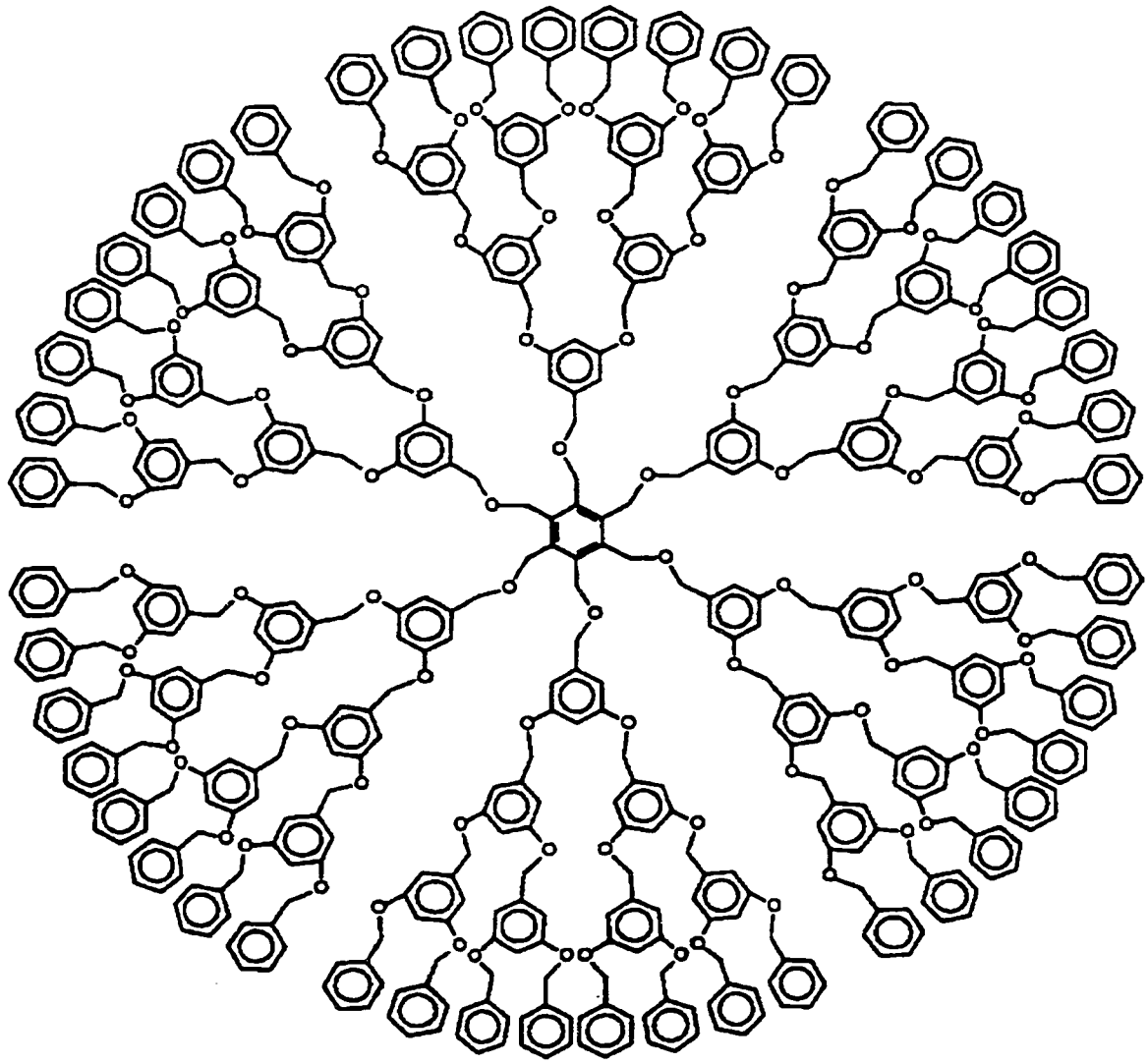
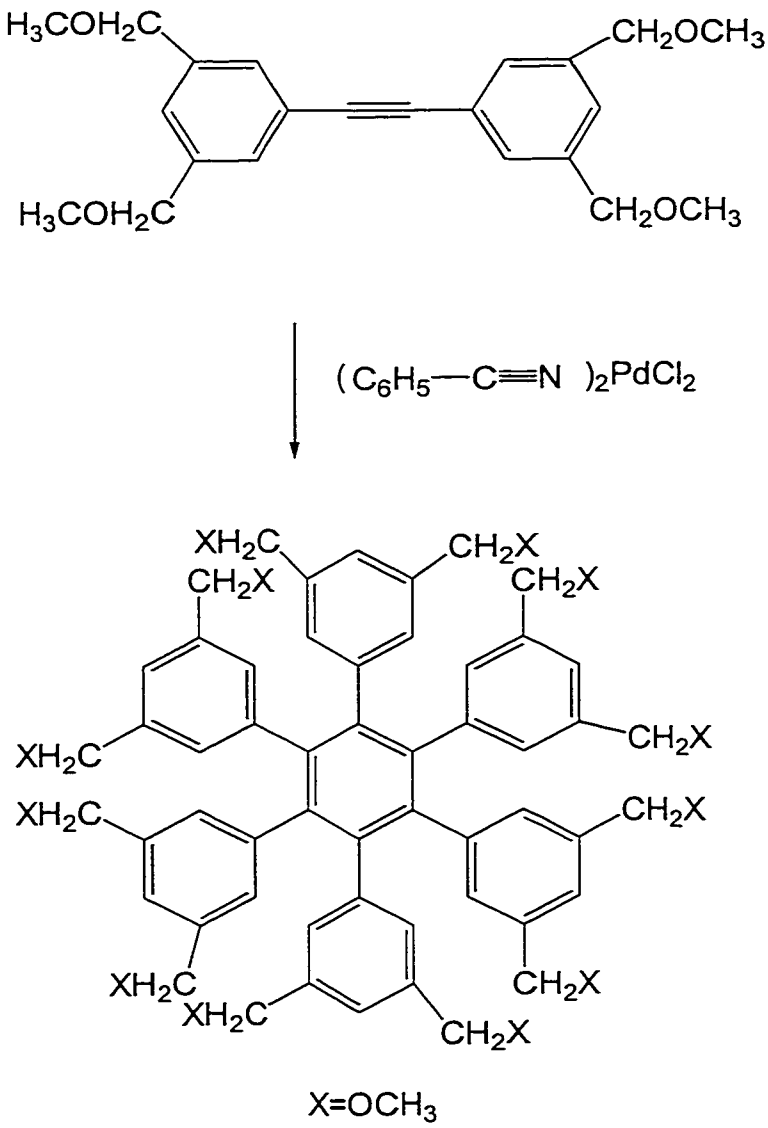


Figure 1.3.1. Frechet's dendrimer.

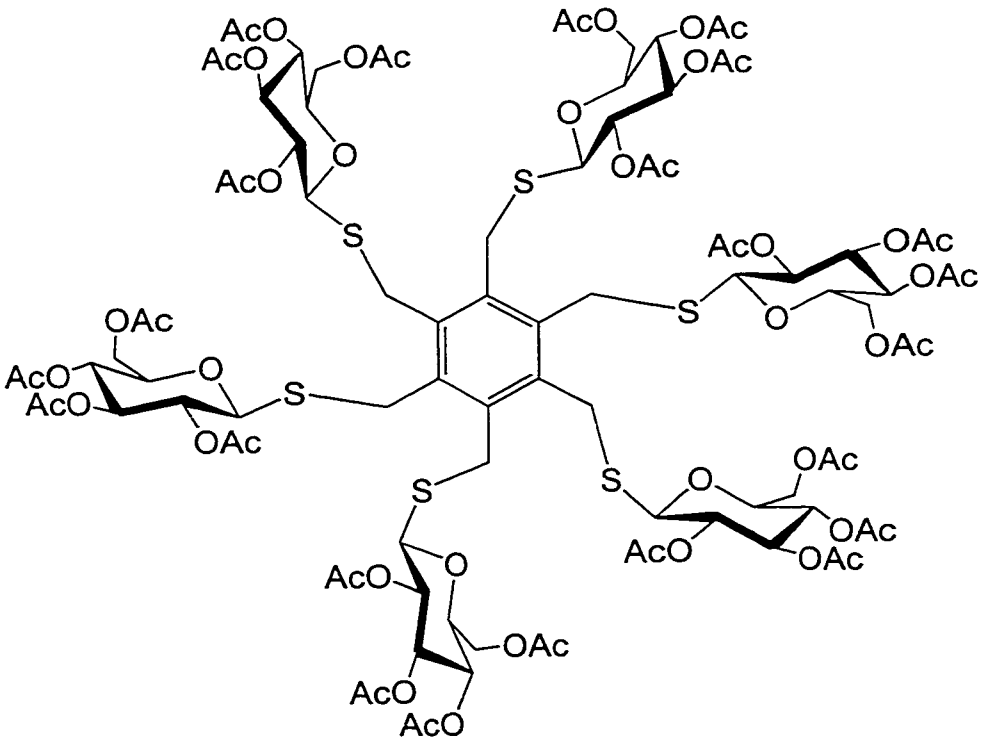


Type I cluster

Scheme 1.3.3. Synthesis of dodecafunctionalized host molecule (Type I cluster).

The only report of synthesis of this kind of glycocluster with monosaccharide pendants was that of Kaufman and Sidhu.[25] They constructed hexameric glucosyl clusters of the type I and II. By cobalt octacarbonyl

catalyzed cyclotrimerization of the corresponding glucosyl substituted symmetrical alkynes, the hexamers of type I and II were obtained in 40 and 95% yields. The thio hexamer (Fig. 1.3.2) was obtained in 29% yield from cyclotrimerization of 2,3,4,6-tetra-O-acetyl-β-D-1-thio-glucopyranose with $Co_2(CO)_8$ as catalyst.



Type II cluster

Figure 1.3.2. Kaufman and Sidhu's thio-glucosyl hexamer (type II cluster).

1.3. Dimers

Divalent α-D-mannopyranoside ligands grafted on p-isothiocyanatophenyl demonstrated high level of binding with *Con A*.[21] Dimannoside clusters demonstrated binding properties almost as high as dendritic mannosides[1a] (Fig. 1.4.1) . One hypothesis for the improved binding of clusters is the formation of cross-linked lattices with the lectins[29] (Fig. 1.4.2). It is the object of this thesis to synthesize and explore the activities of various rigid sugar dimers to determine the optimum valency and geometry requirements for mannosyl conjugates - *Con A* binding.

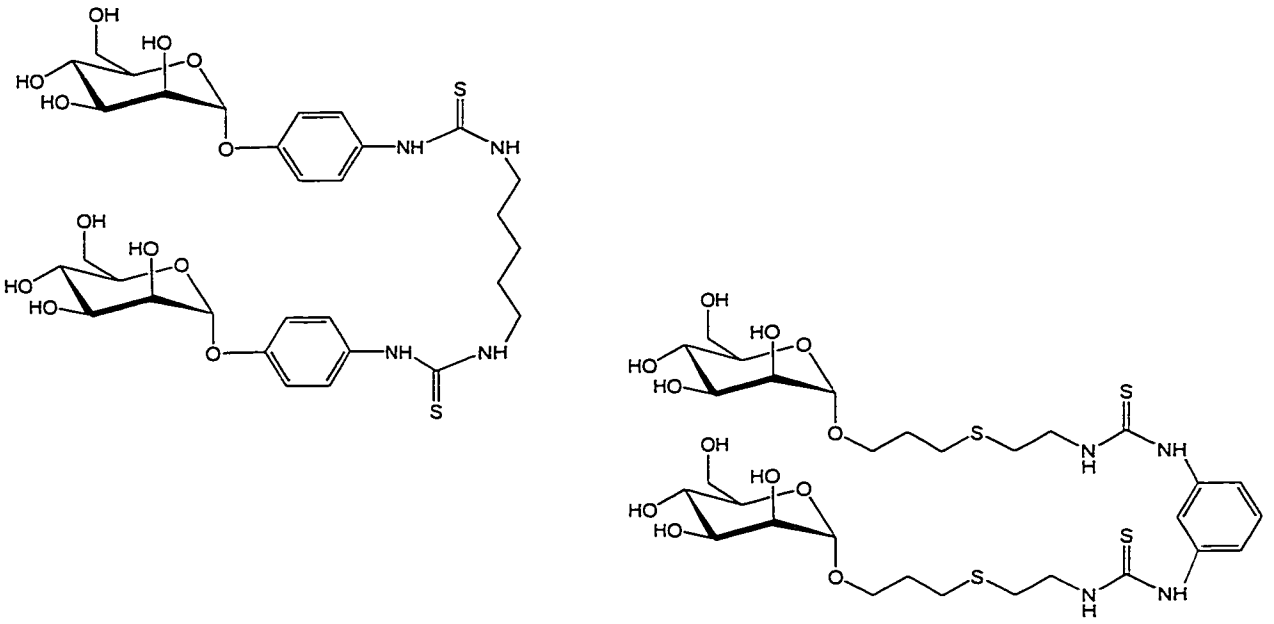


Figure 1.4.1 Divalent mannosylated clusters

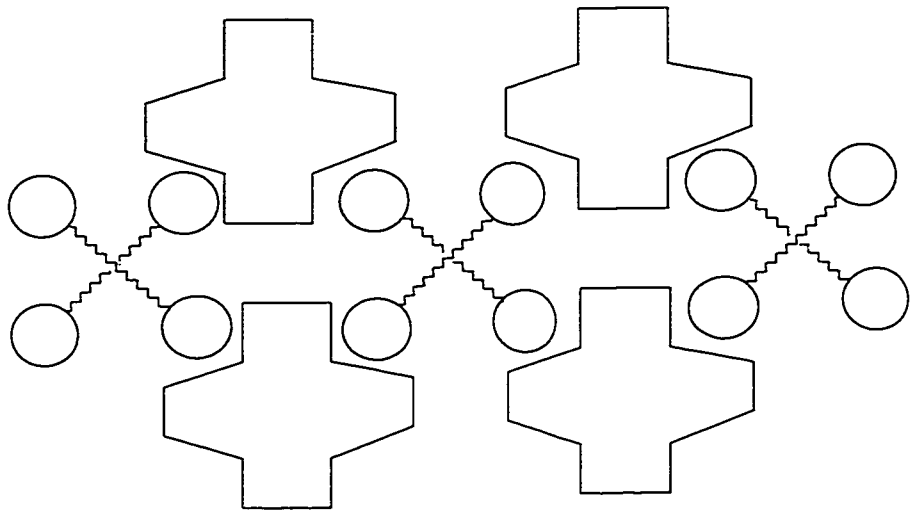


Figure1.4.2. Schematic representation of possible cross-linked lattices which can form upon binding tetravalent carbohydrate ligands to tetravalent Con. A.

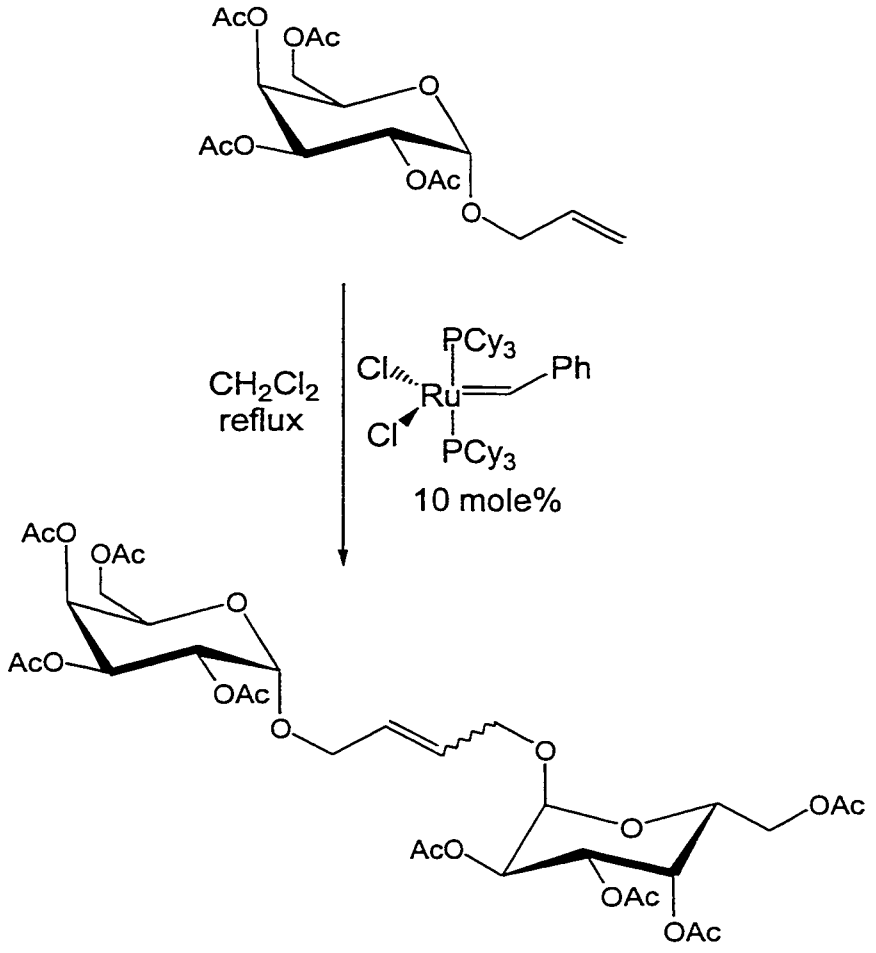
In the last 2 years, "rigid" sugar dimers were synthesized by metathesis of alkenes (Scheme 1.4.1).

Recently, our group constructed "rigid" sugar dimers by olefin metathesis. With Grubb's catalyst, several *O*-allyl, C-allyl and –pentenyl D-galactopyranoside and lactoside homodimers were prepared in high yields.[30] Divalent sialoside homodimer derivatives were also synthesized with this method.[31] Heterodimers consisting of different sugars on each tethering end were also successfully obtained with Ruthenium catalyzed cross-metathesis.[25] A review on the application of olefin metathesis to the synthesis of carbohydrate dimers details the facility of this method.[32] These sugar dimers were held by alkene bonds and were coined "sugar rods".

Sugar rods belong to a class of molecules coined "molecular rods". Molecular rods are rigid molecules usually oligomers that have held the fascination of synthetic chemists because its rigidity lends itself interesting physical properties; hence, novel applications. One main application of molecular rods is its use as spacers and wires that mediate directional flow of electrons, photons and possibly protons or other ions. A second application is its use as construction elements in supramolecular assemblies and giant molecules.[33]

Phenylacetylenes provide a rigid backbone to graft on the dimeric glycoconjugates. Glycoconjugates built on phenylacetylenes would thus have a high level of shape persistence, thus mimicking the macromolecular systems found in nature such as proteins and nucleic acids.[34] Analogues with wide structural diversity can be generated on this scaffold.

Phenylacetylene, as a rigid backbone, would define highly specific spatial orientations of the carbohydrate substituents. Ortho-, meta- and para-substituted phenylacetylenes provide definite valence angles of 60°, 120°, and 180° between the carbohydrate ligands (Fig. 1.4.3).[34]



Scheme 1.4.1. Grubb's catalyzed synthesis of rigid sugar dimers.

Interesting molecular structures have been constructed with oligophenylacetylenes. They are very stable molecules and one of the most easily handled molecular rods. Because of its structural and photophysical features, these structures have been synthesized and studied as candidates for

liquid crystals and nanotechnological applications such as antenna supramolecules.[33]

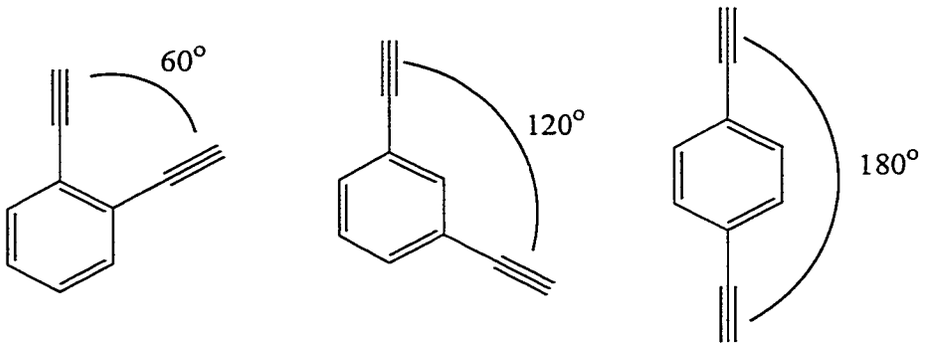


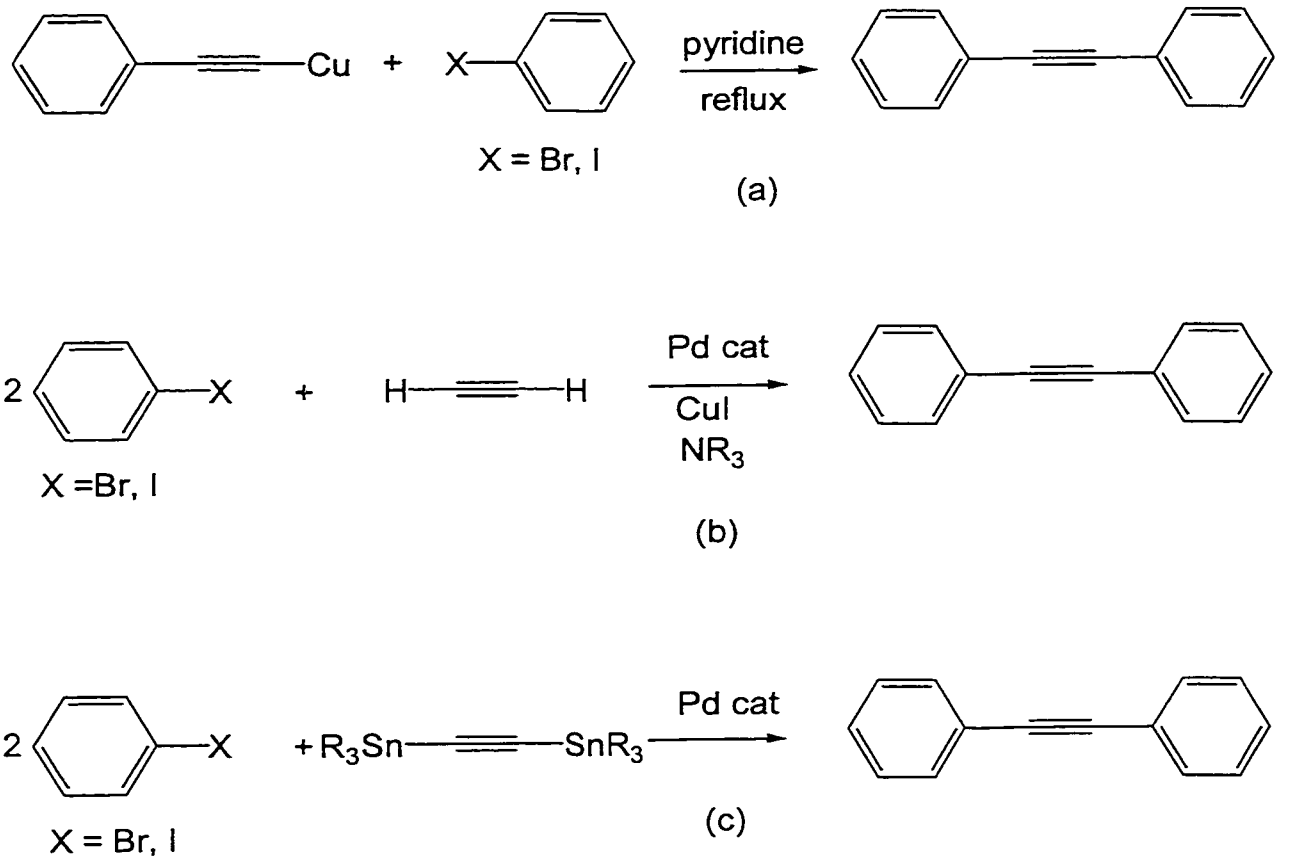
Figure 1.4.3. Phenylacetylene angles.[34]

A facile route to phenylacetylenes are the newer transition metal mediated coupling reactions (Scheme 1.4.2).[33] Stephans-Castro reaction utilizes vigorous conditions for the coupling of aryl bromides or iodides with copper(I)-arylacetylenides. Milder conditions are provided by palladium-catalyzed and copper(I) iodide co-catalyzed reactions by Cassar, Sonogashira-Hagihara and Heck.[36] Coupling can also be achieved in the absence of copper(I) iodide when stannylacetylene derivatives are employed in a Stille reaction.[36]

1.4.1. Sonogashira Coupling

One of the most straightforward methods for the preparation of disubstituted aryl acetylenes is the palladium-catalyzed coupling of terminal

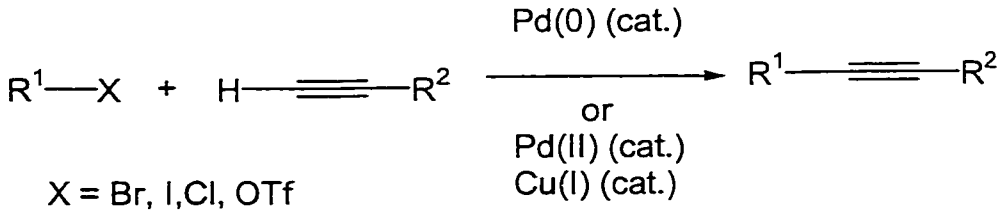
alkynes with aryl halides which was first introduced by Sonogashira et al in 1975[35]. The reaction proceeds smoothly under mild conditions in the presence of



Scheme 1.4.2. Routes to phenylacetylenes (a) Stephans-Castro coupling, (b) Sonogashira-Hagihara, (c) Stille reaction by Tamao.

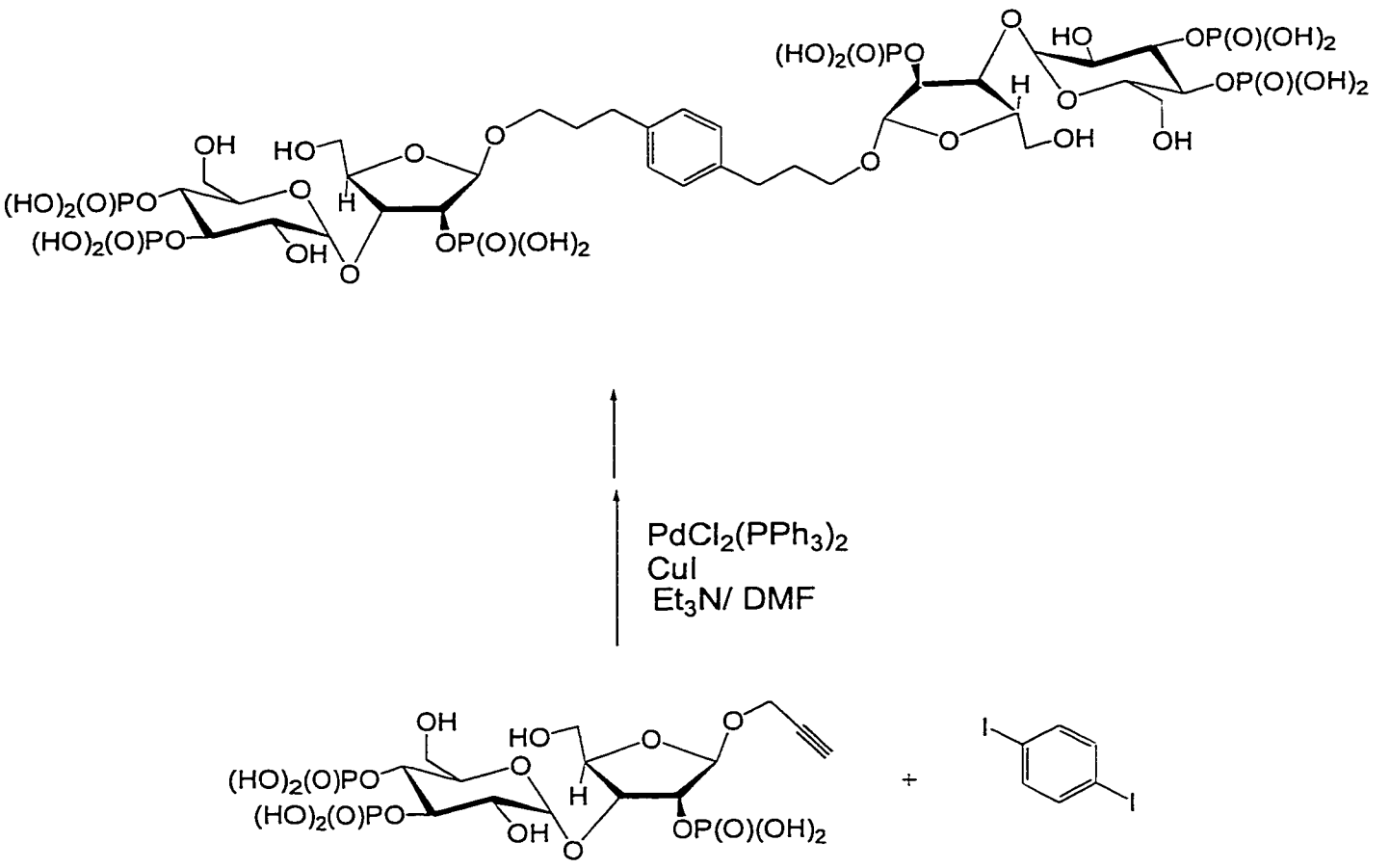
a Pd complex catalyst and cuprous iodide cocatalyst[36] (Scheme 1.4.3). The solvent is usually an amine and R^1 may represent an aryl, (cyclo-)olefinic group or an allenic system.[36] There are no limitations to the nature of R^2. This method is now widely used for the construction of aryl alkynes or enyne systems. As a

source of palladium, $PdCl_2(PPh_3)_2$ in diethylamine or triethylamine are commonly used. In many cases, $Pd(PPh_3)_4$, $Pd(OAc)_2$, $Pd(OAc)_2(PPh_3)_2$, $Pd_2(dba)_3$, or $PdCl_2(CH_3CN)_2$ have been used.[36]



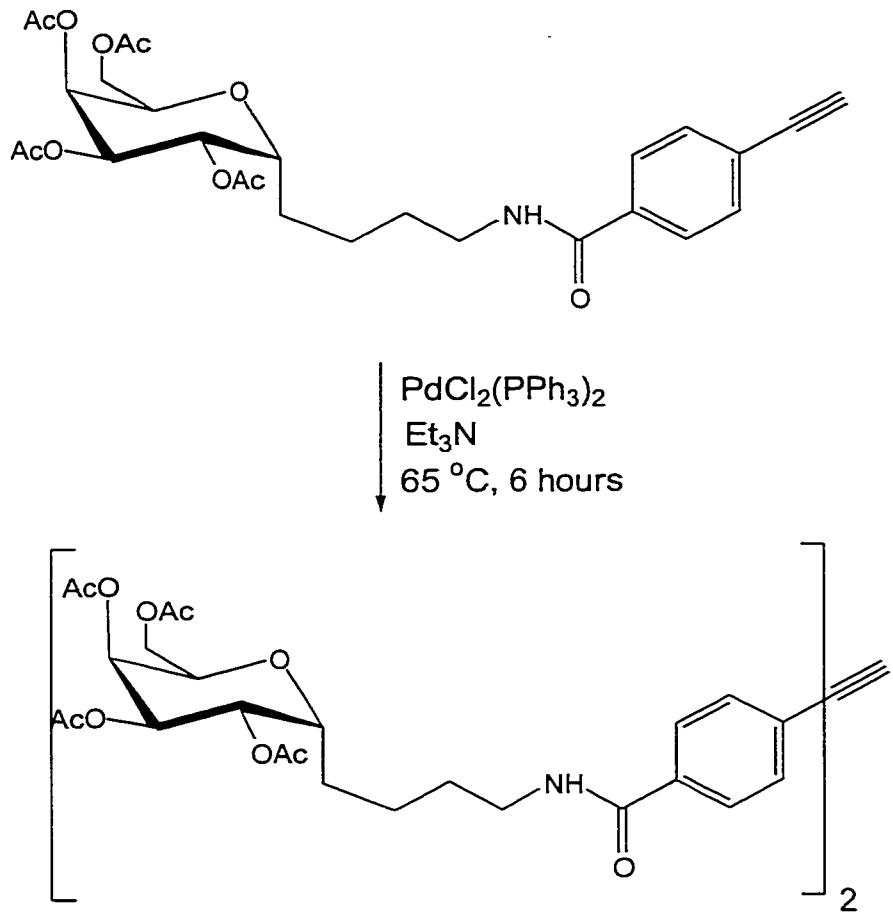
Scheme 1.4.3. Sonogashira coupling of terminal alkynes.

There are a few examples of carbohydrate substituted phenylacetylenes that are reported in the literature. One interesting example is in the construction of clustered disaccharides consisting of two and four IP_3 units anchored via a spacer to a central phenyl core.[37] The clusters were synthesized to study the precise mechanism of IP_3 mediated Ca^{2+} channel opening. The intermediate rigid dimer was efficiently synthesized by Sonogashira coupling (Scheme 1.4.4).



Scheme 1.4.4. Synthesis of adenophosphatin A clusters.

Burli[38] et al reported the Sonogashira coupling of two units of 1,4-dialkynylated glucoside to one unit of dibromopyridine with $PdCl_2(PPh_3)_2$ and CuI as catalysts. In our own group, $PdCl_2(PPh_3)_2$ was shown to be an effective catalyst in the coupling of acetylene-O-glycosides[25] and more recently C-glycosides[39] obtaining symmetrically substituted acetylenes (Scheme 1.4.5).

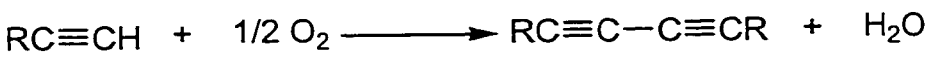


Scheme 1.4.5. Sonogashira coupling of acetylene C-glycosides.

To synthesize a symmetrically substituted acetylene, a thioglycoside was coupled under Sonogashira reaction with $Pd_2(dba)_3$ as catalyst.[40] To obtain O-glycosides substituted with a terminal acetylene group, 2-propynyl glycosides were coupled under Sonogashira conditions with $Pd(PP_3)_4$ as catalyst.[41]

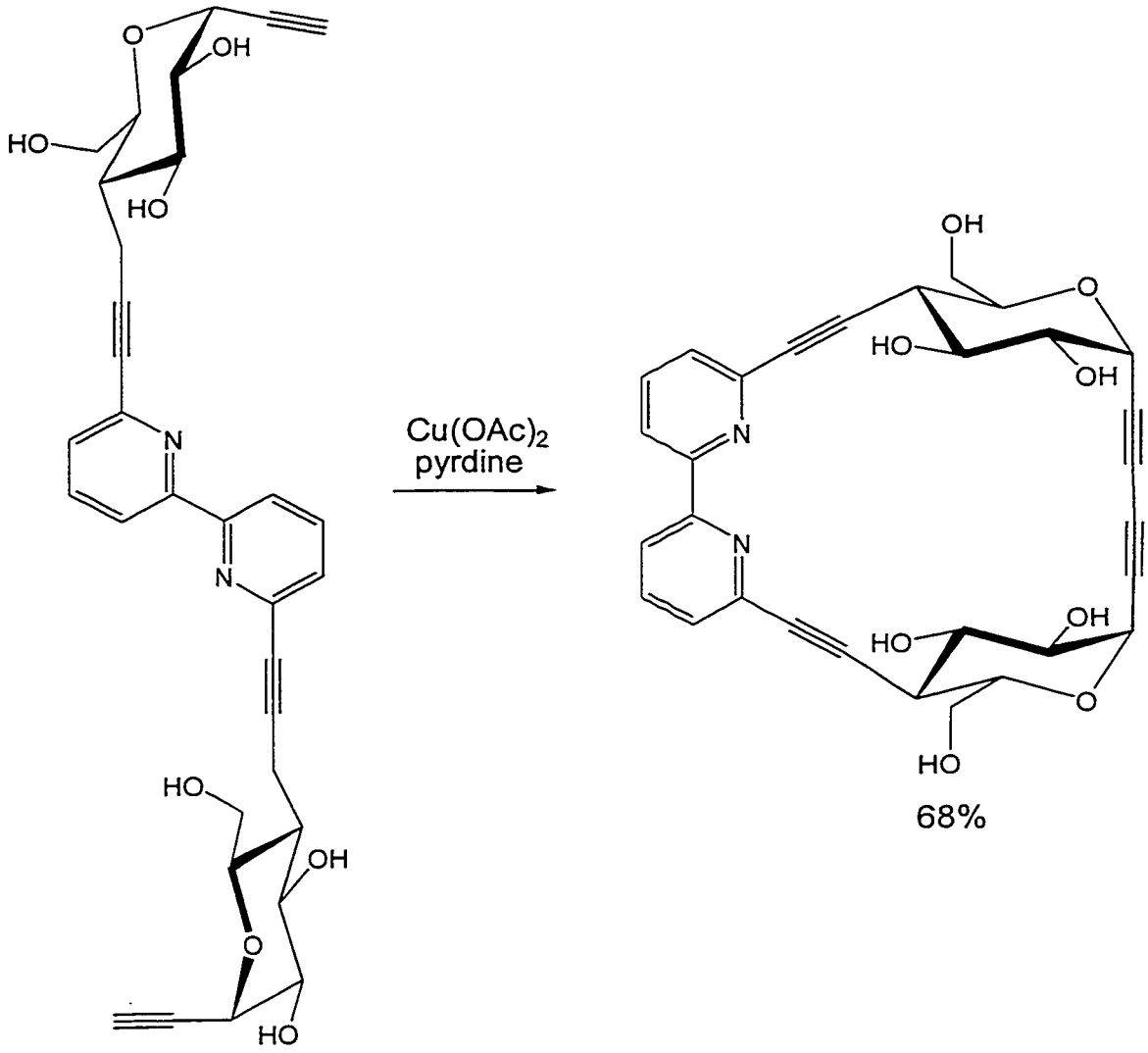
1.4.2. Hay's Coupling

To investigate the effect of the length of spacers, it was the object of this thesis to generate analogues of the Sonogashira coupling products that contain two acetylene functionalities in the core. An efficient route to these molecules is via modified Hay's coupling[42] (Scheme 1.4.6). In this reaction, two terminal acetylenes are oxidatively coupled with copper(I) halide as catalyst. This method was reported more than a century ago by Glaser.[40] The original procedure used preformed copper acetylide. Hay demonstrated that tertiary amine complexes of copper(I) salts catalyze the oxidation effectively[42]. Cupric acetate[43], $Pd(PPh_3)_4$ and CuI[44], $PdCl_2(PPh_3)_2$ and CuI and iodine[45], and cuprous or cobaltous chloride[46] are among the catalysts used in this reaction.



Scheme 1.4.6. Glaser oxidation of terminal acetylenes.

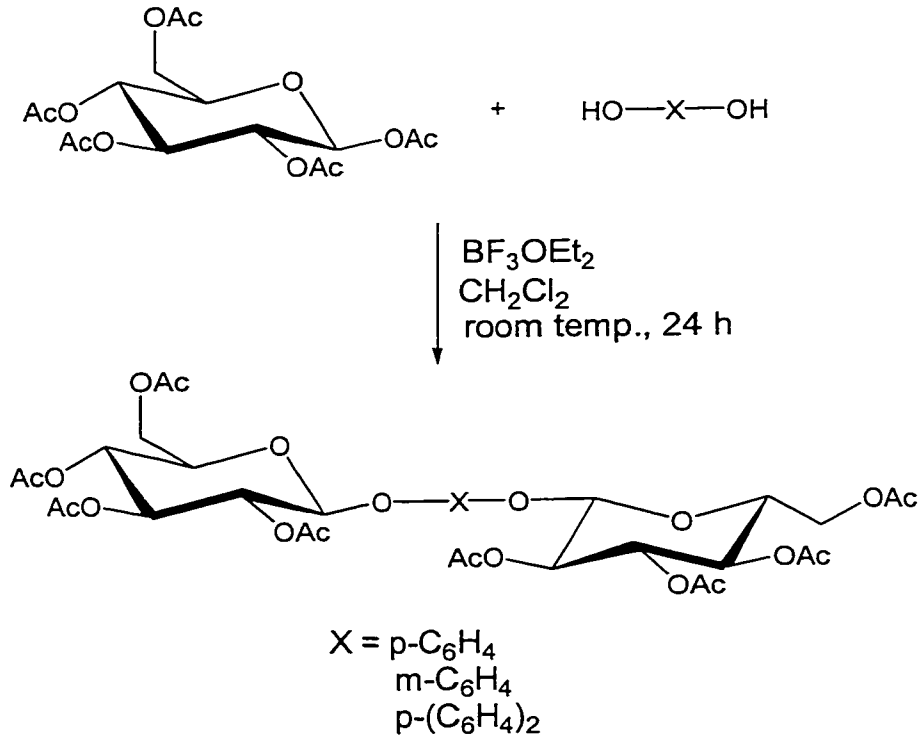
Novel structures are obtainable with the application of Glaser oxidation to neoglycoconjugate synthesis. One of the few examples of these is in the synthesis of cyclic host molecules by Burli et al[38, 47] (Scheme 1.4.7).



Scheme 1.4.7. Synthesis of macrocyclic bipyridine.[38]

1.4.3. Lewis Acid Catalyzed *O*-Glycosidation

Rigid dimers can also be accessed from Lewis acid catalyzed O-glycosidation of rigid structures such as disubstituted acetylenes and diphenols. BF_3OEt_2 catalyzed O-glycosidation of hydroquinone was reported by Smits et al.[48] Rigid dimers and trimers were synthesized by Patch et al[49] using $ZnCl_2$ catalyzed O-glycosylation of dihyroxyphenols and trihydroxyphenols (Scheme 1.4.8).



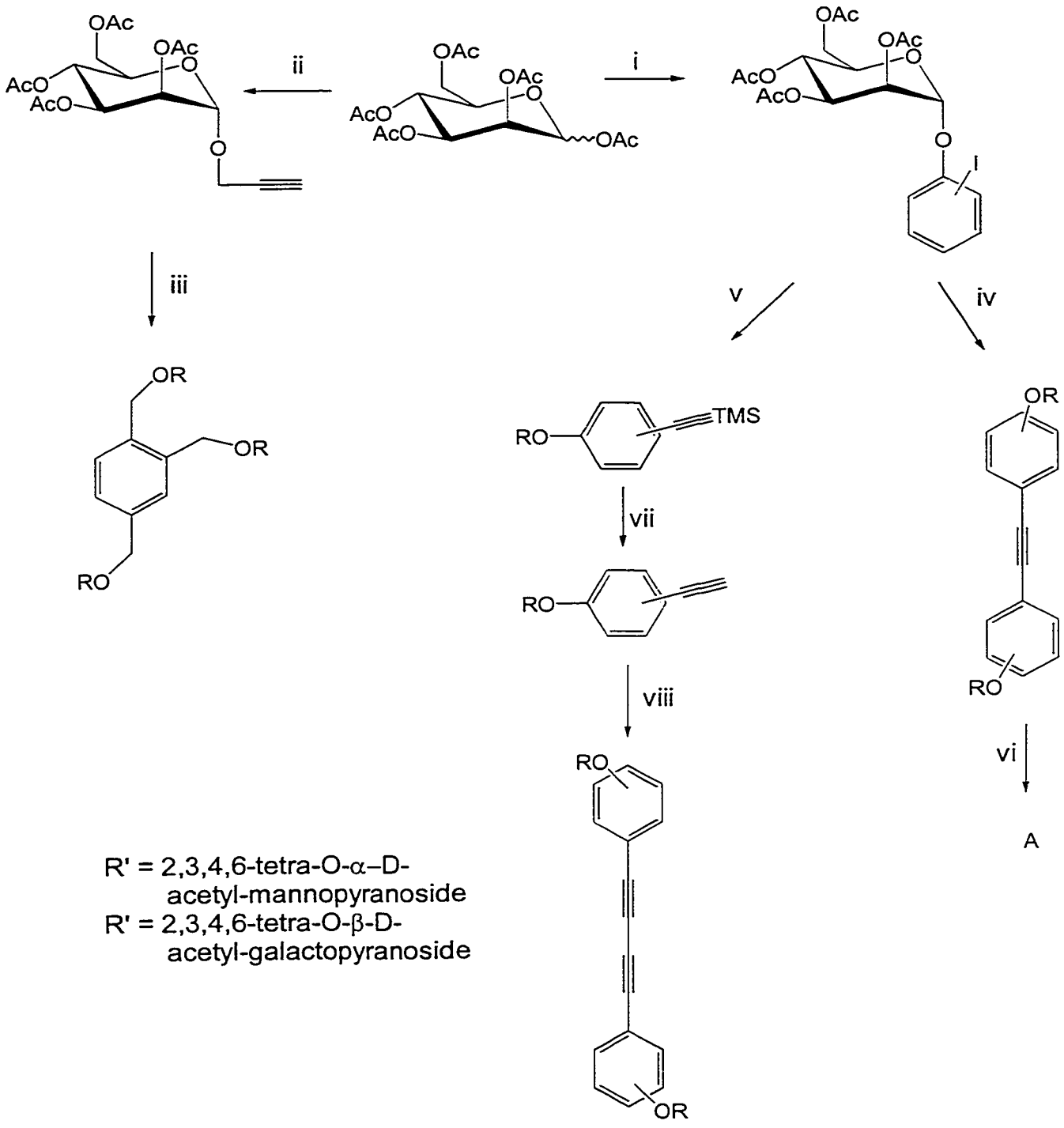
Scheme 1.4.8. Glucosylation of glucose pentaacetate with dihydroxy aromatic compounds.[48]

1.5. Synthetic Scheme

In the search for neoglycoconjugates with binding activities with lectins, it is the object of this thesis to generate rigid glycosidic clusters and dimer analogues and determine their binding activities. Comparison of binding activities of ortho-, meta- and para- substituted dimers would aid in determination of optimum geometry requirements for better binding with the lectin Concanavalin A. The dimers and clusters were synthesized following the general synthetic route outlined in Scheme 1.4.1.

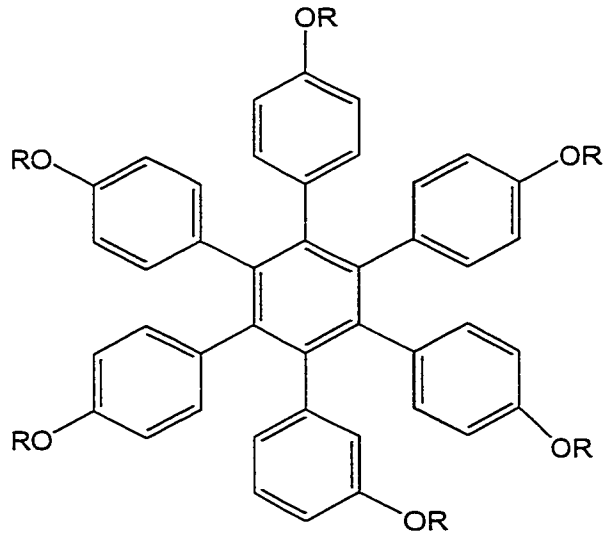
Rigid dimers were synthesized by Sonogashira coupling of substituted alkynes (iv), Hay's coupling of terminal acetylenes (viii), and *O*-glycosidation of a dihydroxydiphenyl compound. Clusters were synthesized by cyclotrimerization of terminal acetylene compounds (iii) and disubstituted acetylene compounds (vi) (Scheme 1.5.1).

The sugars used were monosaccharides of mannose and galactose.



Scheme 1.5.1. Synthesis of dimers and clusters. Reaction scheme followed. (i) iodophenol, BF_3OEt_2, CH_2Cl_2; (ii) propargyl alcohol, BF_3OEt_2, CH_2Cl_2; (iii), (vi) $Co_2(CO)_8$, dioxane, reflux; (v) acetylene TMS, $Pd(PPh_3)_4$, Et_3N-DMF, 60 °C; (vi) acetylene, $PdCl_2(PPh_3)_2$, CuI, Et_3N (vii) Bu_4NF,CH_3COOH, THF; (viii) $Cu(OAc)_2$, pyridine, reflux

A



R = 2,3,4,6-tetra-O-acetyl-
α–D--mannopyranoside
R' = 2,3,4,6-tetra-O-acetyl-
β-D-galactopyranoside

Figure 1.5.1. Structure of A from Scheme 1.5.1.

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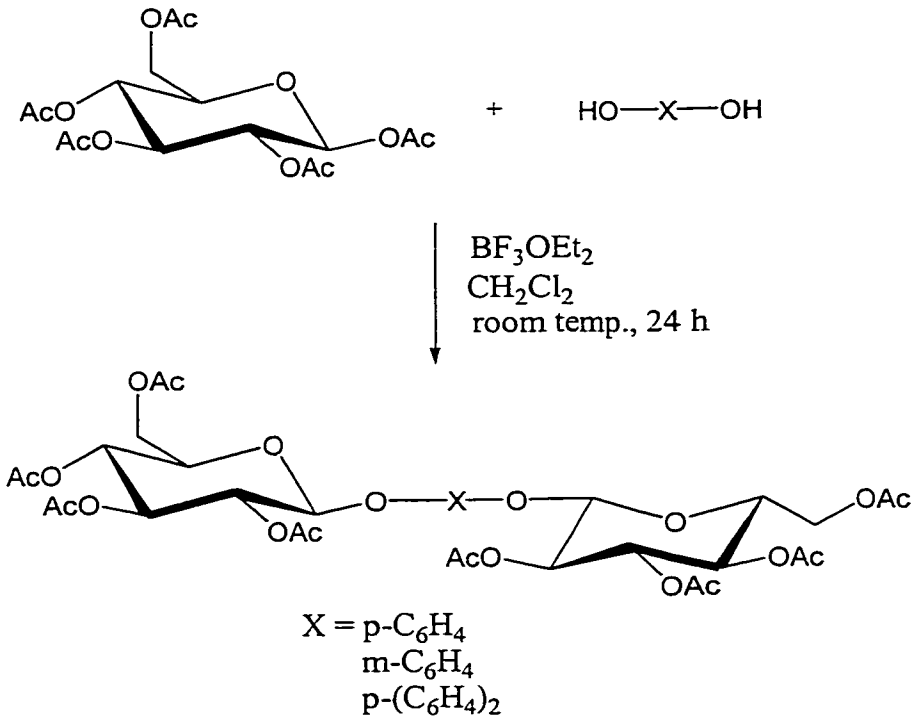
Chapter 2. Synthesis of Starting Materials

2.1 Introduction

The first step in the synthesis is the functionalization of monosaccharides with aryl or alkynyl groups. Some of the parameters to be considered in this step are: regioselectivity, stereoselectivity, especially of the anomeric substituents, stability of glycosyl donors and yield.

The technique of *O*-glycosidation has advanced to several variations since the classical Koenigs-Knorr synthesis.[1] A modification of this method was developed by Helferich and Shimitz-Hillebrecht[2] where glucose pentaacetate is coupled with phenol in the presence of $ZnCl_2$ or TsOH. Since then, several Lewis acids were found to promote this type of glycosidation including TMSOTf,[3] BF_3-OEt_2,[4] $FeCl_3$[5] and $SnCl_5$.[6]

More recently, various arylβ-D-glucopyranosides were successsfully synthesized under BF_3OEt_2 catalyzed conditions. Substituted phenols were O-glycosylated with glucose pentaacetate[4d] (Scheme 2.1). The rate of reaction is dependent on the substitutuent on the phenol ring. Di-β-glucosides were synthesized from the O-glycosidation of dihydroxyaromatic compounds. Good stereocontrol was achieved.



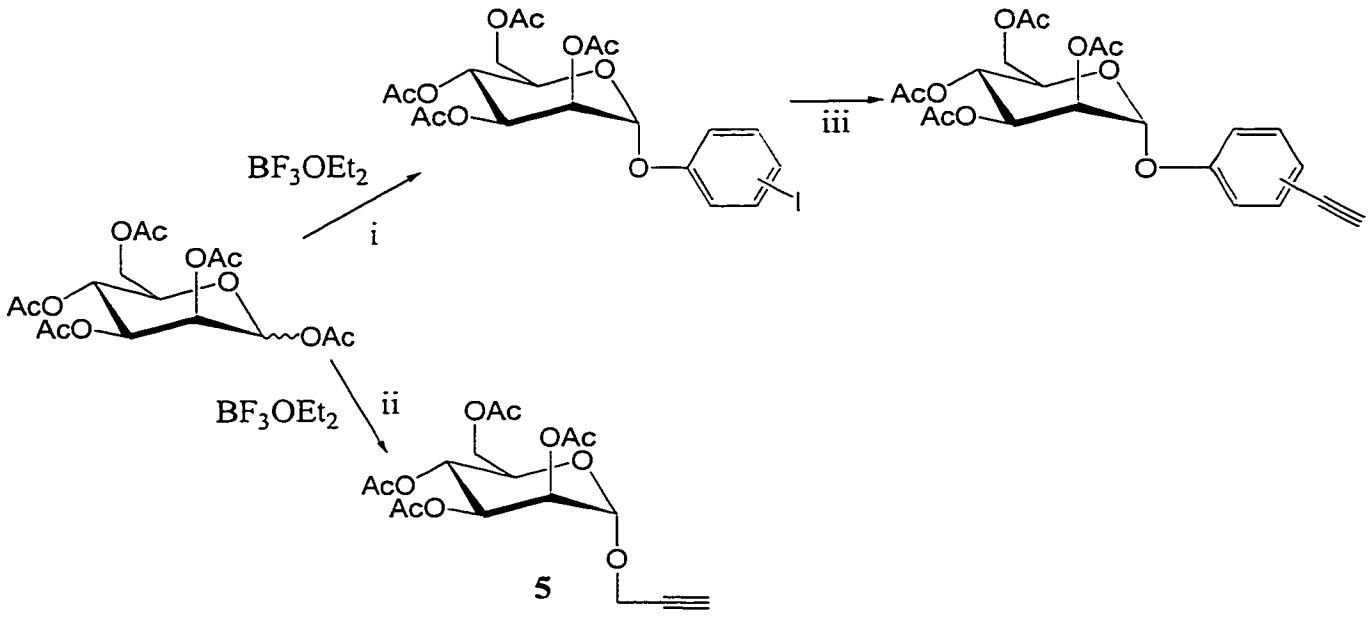
Scheme 2.1. Glucosylation of glucose pentaacetate with dihydroxy aromatic compounds.

Although, the method is commonly applied to anomeric acetates, alkoxyacetates, benzoates[7], trifluoroacetates[8] and 1-thio-glycosides[9] are occasionally used.

BF_3OEt_2 was also shown to be an effective promoter in the synthesis of *O*-glycosides from totally *O*-unprotected glycosyl donors.[4b] *O*-unprotected sugars were directly arylated on the anomeric position by fluorobenzenes substituted with electron withdrawing substituents using BF_3OEt_2 as catalyst.[10]

2.2. Results and Discussion

The first target was the synthesis of carbohydrate conjugates functionalized with an iodophenyl group or a 2-propynyl group. Both were achieved by Lewis acid catalyzed arylation or alkynylation of the anomeric carbon of the fully acetylated monosaccharide.



Scheme 2.2.1 BF_3OEt_2 catalyzed synthesis of starting materials: (i) iodophenol, BF_3OEt_2, CH_2Cl_2, ,(ii) propargyl alcohol, BF_3OEt_2, CH_2Cl_2, (iii) (a) acetylene TMS, $Pd(PPh_3)_4$, DMF-Et_3N, 60°C(b)Bu_4NF, CH_3COOH, THF

2.2.1. BF_3OEt_2 Catalyzed *O*-Glycosidation

With BF_3-OEt_2 (2.0 equivalents) as catalyst, mannose pentaacetate (1.0 equivalent) was arylated with iodophenol (1.8 equivalent) in CH_2Cl_2. 1-*O*-glycosidation was complete in 17 hours[5c]. Ortho- , meta- and para-iodophenyl mannosides were obtained from the corrresponding ortho-, meta- and para-iodophenol (Table 2.2.1). The ease of glycosidation decreases from para > meta > ortho substitution in the phenyl ring substrate. The coupling constant of the H-1 proton (d,1.9 Hz) and the H-2 proton (dd, J=1.9 Hz, J=3.5 Hz) (Fig. 2.2.1) indicates that the α anomer was obtained. In the case of galactose pentaacetate, the β anomer of para-iodophenyl galactoside was synthesized as shown by ^1H NMR (H-1: d, J=7.9 Hz).

Alkynylated glycosides were obtained following the method of Mereyala et al.[4c] Mannose pentaacetate (1.0 equivalent) was alkynylated at the anomeric carbon with propargyl alcohol (1.2 equivalent) and BF_3OEt_2 (1.5 equivalent) as catalyst (Table 2.2.2) . Again, the α anomer was obtained as shown by ^1H NMR. In the case of galactose pentaacetate, because of the anchimeric participation of the C-2 acetate, alkynylation occurred resulting in the β anomer.

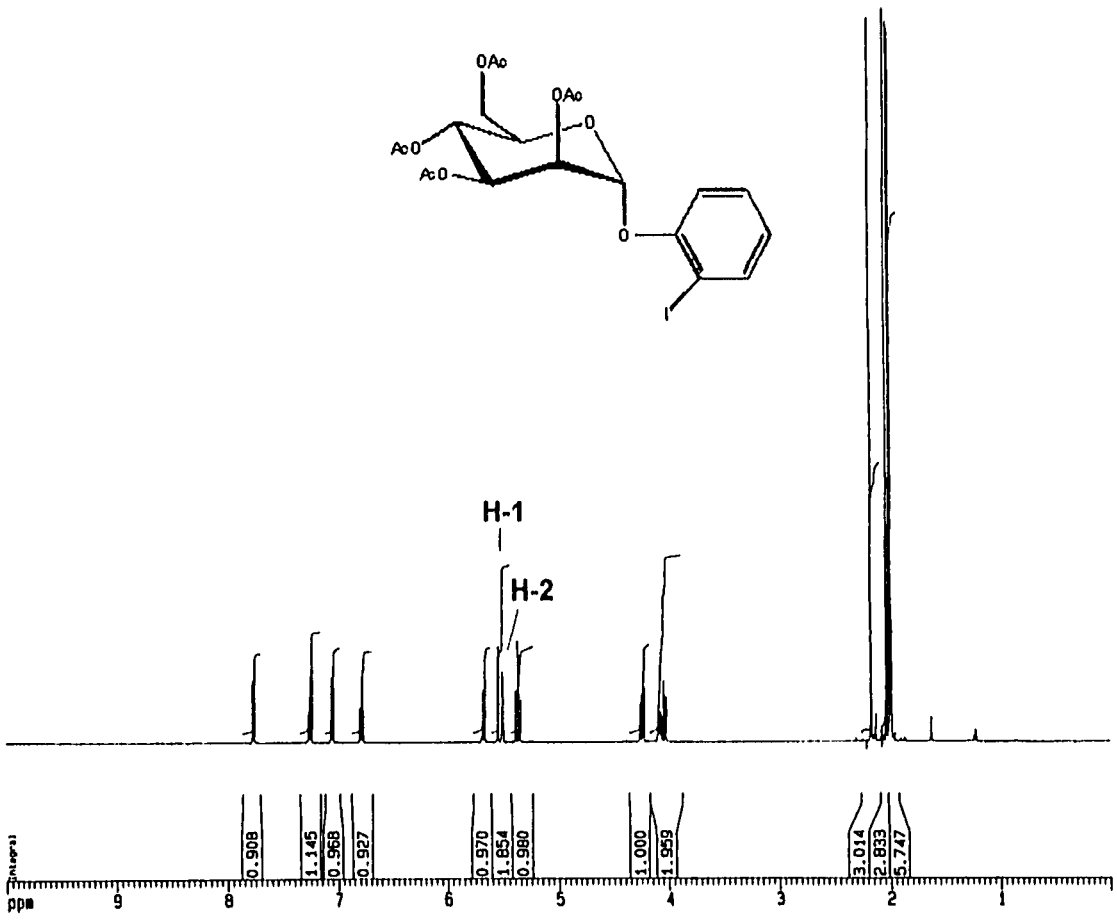
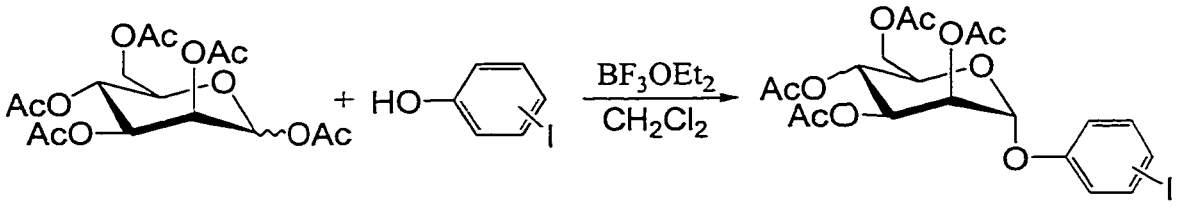


Figure 2.2.1. ^{1}H NMR (500 MHz, $CDCl_3$) of ortho-iodophenyl (2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside) (**3**).

Table 2.2.1. Synthesis of *O*-arylglycoside analogs.



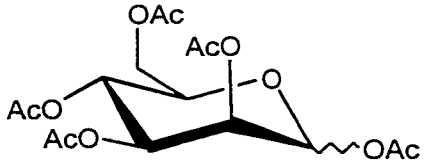
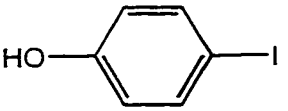
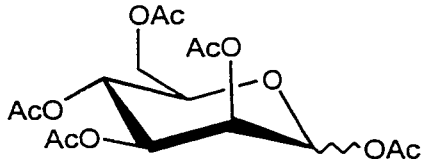
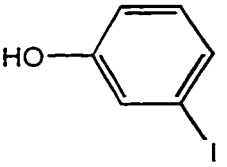
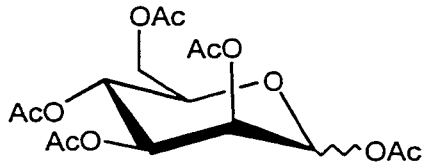
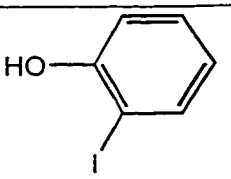
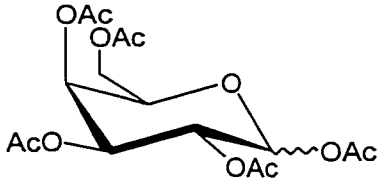
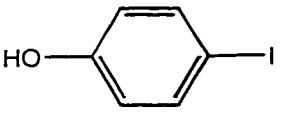
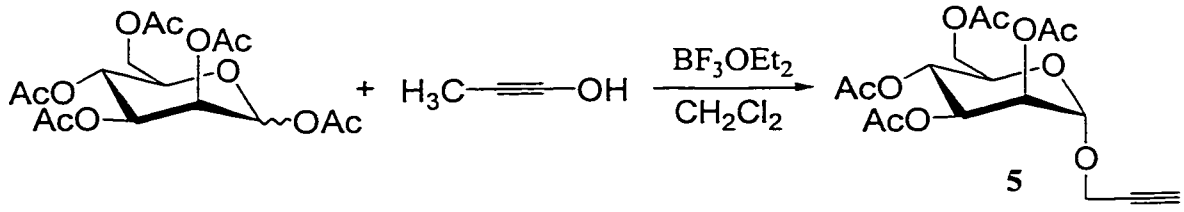
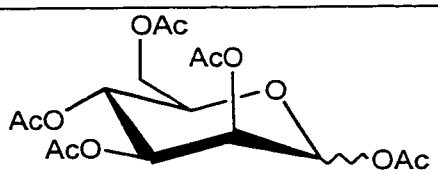
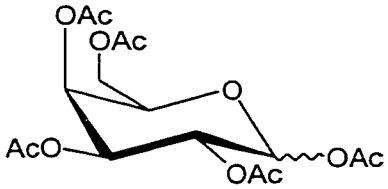
monosaccharide	iodophenol	product	yield (%)
		**1**	81
		**2**	63
		**3**	36
		**4**	98

Table 2.2.2. Synthesis of propynyl glycosides.



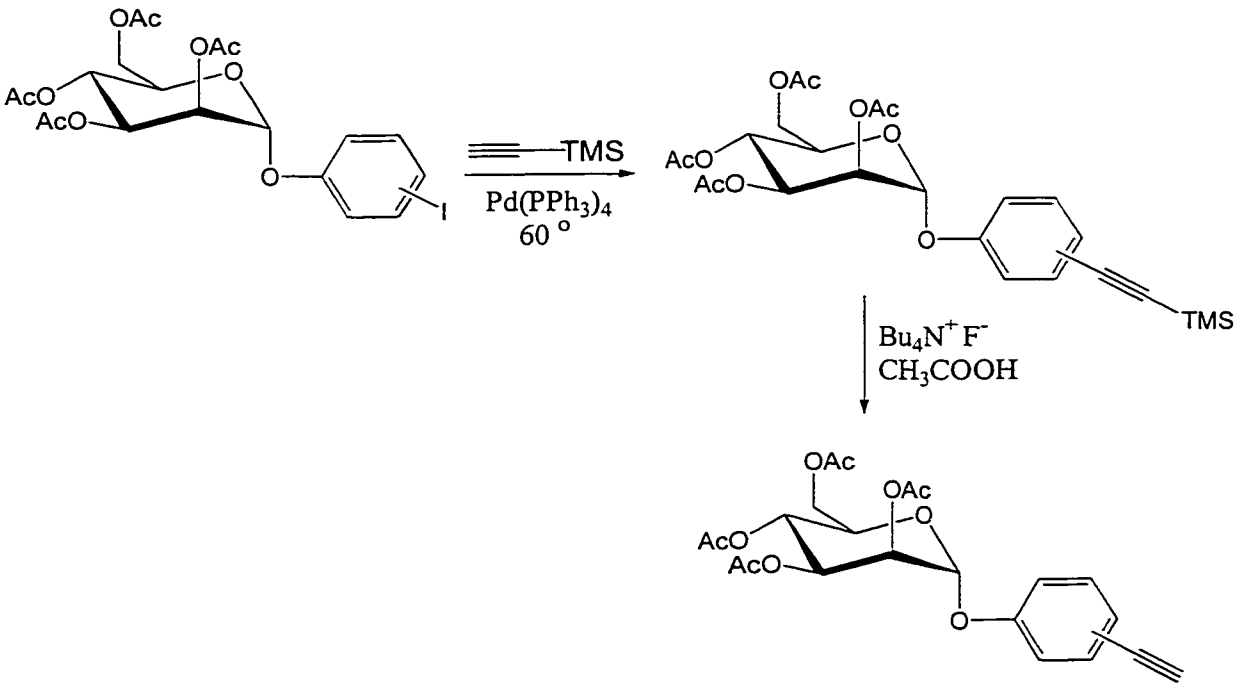
penta-*O*-acetylglycoside	propynyl glycoside	yield (%)
	**5**	78
	**6**	79

2.2.2. Terminal Acetylenes

The iodophenylmannosides were converted to ethynylphenyl mannosides by Sonogashira coupling with ethynyl-trimethyl-silane. The reaction was catalyzed by $Pd(PPh_3)_4$ (10 mole%) and carried out at 60 °C in Et_3N - DMF. In the same pot, the acetylene group was deprotected with tetrabutylammonium

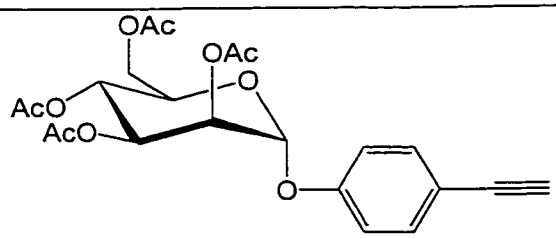
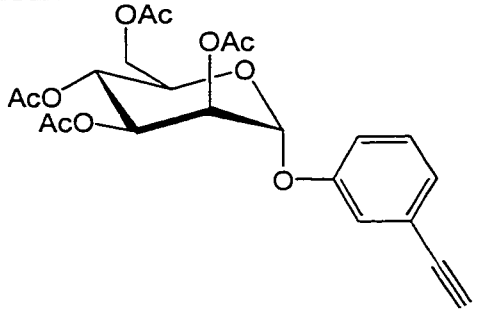
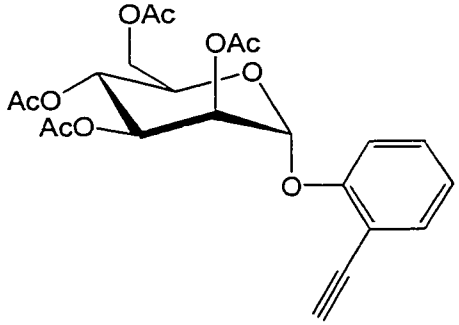
fluoride and acetic acid in THF (Scheme 2.2.1). The yields obtained were 55-58% (Table 2.2.3). The ease of substitution decreased from para > meta > ortho substitution in the phenyl ring.

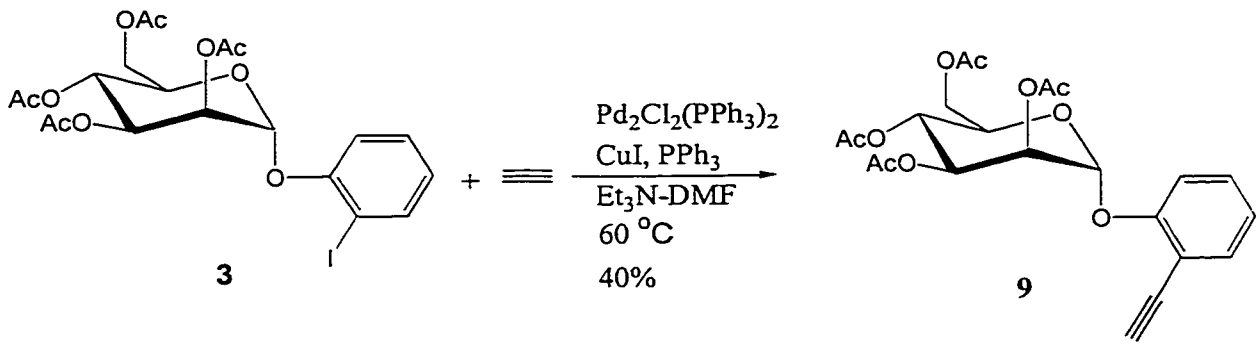
Ethynylation of 2-iodophenyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside with this method produced mostly decomposition products. It was then obtained from the Sonogashira coupling of 2-iodophenyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside with acetylene gas, (catalyzed by $PdCl_2(PPh_3)_2$ and CuI) where it was obtained as a side product (44% yield).



Scheme 2.2.1. Synthesis of ethynylphenyl mannopyranoside.

Table 2.2.3. Generation of ethynylphenyl mannopyranoside analogs (Scheme 2.2.1).

Starting material	Product	Code	yield(%)
4-iodophenyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside **1**		**7**	58
3-iodophenyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside **2**		**8**	55
2-iodophenyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside **3**		**9**	10



Scheme 2.2.2. Synthesis of 2-ethynylphenyl mannopyranoside (**9**).

2.3. Conclusions

BF_3OEt_2 catalyzed *O*-glycosidation of para-, meta- and ortho-iodophenols was successful and produced with high yields and anomeric selectivity. The same Lewis acid succesfully alkynylated mannose and galactose pentaacetate with high yields and anomeric selectivity. Sonogashira coupling succesfully obtained the terminal acetylene-phenylmannosides. In all cases, the ease of *O*-glycosidation proceeded in decreasing order from para > meta > ortho substituents on the phenyl ring.

2.4. Experimental Methods

General Methods

^{1}H NMR and ^{13}C NMR spectra were obtained from either a Varian Gemini-200 z or a Bruker AMX500 spectrometer at 500, 300; or 200 MHz for protons and 125.7; 75; or 50.3 MHz for carbons, respectively. Proton chemical shifts are given relative to internal chloroform (7.24 ppm) for $CDCl_3$ solutions. Carbon chemical shifts are given relative to $CDCl_3$ (77.0 ppm). Special analyses were performed by the first order approximations and were based on shift correlation spectroscopy (COSY), heteronuclear multiple quantum coherence (HMQC), and 1- and 2-dimensional distortionless enhancement by polarization transfer (DEPT) experiments. Multiplicities of the NMR signals were reported using the following abbreviations: singlet (s), broad singlet (bs), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), multiplet (m).

Mass spectra were recorded on a Kratos IIH (FAB-glycerol) instrument. Xenon was used as the neutral carrier atom in FAB-MS experiments.

Melting points were determined on a Gallenkamp apparatus and are uncorrected.

Optical rotation ($[\alpha]_D$) values were determined using a Perkin-Elmer (model 241) set at the sodium D line (589 nm) and were run at room temperature.

Infrared spectra were obtained on a Bomem-Michelson MB-100 FT/IR spectrophotometer neat on KBr plates.

Reactions were monitored by thin-layer chromatography using Kieselgel 60 F_{254} precoated 0.25 mm thick aluminum backed plates and the compounds were detected by short wave UV light or by an ammonium molybdate solution (2.5% w/v). TLC plates were heated to 150 °C when necessary.

Purifications were performed by gravity or flash column chromatography on ing silica gel (230-400 mesh, E. Merck No. 9385).

All reactions, unless stated otherwise, were carried out in oven dried flasks under a nitrogen atmosphere. Methylene chloride was dried over CaH_2 and distilled prior to use. Propargyl alcohol was distilled prior to use. All chemical reagents were obtained from commercial suppliers and used as is, unless stated otherwise.

Synthesis of iodophenylglycosides

4-Iodophenyl 2,3,4,6-tetra*-O-*acetyl*-α-*D-mannopyranoside **(1)**

Boron trifluoride diethyl etherate (1.3 mL, 10.3 mmol) was added via a syringe to a solution of penta-O-acetyl-α/β-mannopyranoside (2.0 g, 5.2 mmol) and 4-iodophenol (2.0 g, 9.3 mmol) in dry methylene chloride (40 mL), cooled to 0°C kept under N_2. The reaction mixture was allowed to come to room temperature and the course of the reaction was followed by TLC (ethyl acetate/ hexane 1/1) until complete disappearance of the starting material (18 hours). Workup was effected by washing 3x with saturated $NaHCO_3$ solution, 2x with 2M HCl and 2x with water. After drying over $MgSO_4$ and evaporation of solvents in

vacuo, the crude product was purified by column chromatography on silica using gradient elution with hexane/ ethyl acetate 3/1 then hexane/ethyl acetate 2/1. The purified product was obtained as a white solid (2.3 g, 81% yield); m.p. = 127-129 °C; $[\alpha]_D^{23}$ = +65 ° (c=1.0, $CHCl_3$); IR (neat) 1751, 1483, 1386, 1224 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 7.57 (C_6H_4, d, J=9.0 Hz, 2H), 6.85 (C_6H_4, d, J=9.0 Hz, 2H), 5.50 (H-3, dd, $J_{3,4}$=10.1Hz, $J_{2,3}$=3.5 Hz, 1H), 5.46 (H-1, d, J=1.9 Hz, 1H), 5.40 (H-2, dd, $J_{1,2}$=1.9 Hz, $J_{2,3}$=3.5 Hz), 5.33 (H-4, dd, J=10.0 Hz, J=10.0 Hz, 1H), 4.24 (H-6a, dd, $J_{6a,5}$=5.5 Hz, $J_{6a,6b}$=12.4 Hz, 1H), 4.02 (m, 2H, H-5,6b), 2.17, 2.03, 2.00 ($COCH_3$, 3 s, 12H); ^{13}C NMR ($CDCl_3$, 75 Mhz,): δ(ppm) 170.5, 170.0, 169.7 (C=O), 155.4, 138.5, 118.8, 85.8 (C_6H_4), 95.8 (C-1), 69.4, 69.3, 68.8, 65.8 (C-2, C-3, C-4, C-5), 62.1 (C-6), 20.9- 20.7 ($CO\underline{C}H_3$); FAB-MS $[M+K]^+$, *m/z* (rel. intensity %) calcd for $C_{20}H_{23}IO_{10}K$ 589.00; found 589.21 (9.5)

***4-Iodophenyl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside* (4)**

Reaction of penta-*O*-acetyl-α/β-galactopyranoside (2.9 g, 7.6 mmol) with para-iodophenol (3.0 g, 13.6 mmol) with boron trifluoride diethyl etherate as acid (1.75 mL., 13.8 mmol) yielded the peracetylated 4-iodophenyl galatopyranoside in 98% yield (2.8 g). The course of the reaction was followed by TLC (hexane/ethyl acetate 1/1) until complete disappearance of the starting material (19 hours). After standard workup procedures the product was purified by column chromatography on silica gel with gradient elution starting from hexane/ethyl acetate 3/1 then 1/1 to yield the purified product as white solid

(98% yield); m.p. = 55-56 °C; $[\alpha]_D^{23}$ = + 10° (c=1.0, $CHCl_3$); IR (neat): 1749, 1482, 1368, 1227 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ(ppm) 7.56 (C_6H_4, 2d, J=8.9 Hz, 2H), 6.75 (C_6H_4, 2d, J=8.9 Hz, 2H), 5.44 (H-2, dd, J= 10.5, J=7.9 Hz, 1H), 5.43 (H-4, dd, J=3.5, J=1.1 Hz, 1H), 5.08 (H-3, dd, $J_{2,3}$=10.5 Hz, $J_{3,4}$=3.5 Hz, 1H), 4.98 (H-1, d, J=7.9 Hz, 1H), 4.19 (H-6a, dd, $J_{6a,6b}$=11.13 Hz, $J_{5\text{-}6a}$=7.2 Hz, 1H), 4.03 (H-6b, dd, $J_{6a,6b}$=11.3 Hz, $J_{5,6b}$=6.0 Hz, 1H), 4.03 (H-5, dd, $J_{5,6a}$=7.2 Hz, $J_{5,6b}$=6.0 Hz, 1H), 2.15, 2.04, 2.04, 1.98 ($COCH_3$, 4 s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ(ppm) 170.4, 170.3, 170.1, 169.4 (C=O), 156.3, 138.5, 119.2, 86.1 (C_6H_4), 99.5 (C-1), 71.2, 70.8, 68.6, 66.8 (C-2, C-3, C-4, C-5), 61.4 (C-6), 20.8, 20.7, 20.6 ($CO\underline{C}H_3$); FAB-MS $[M+K]^+$, *m/z* (rel. intensity %) calcd for $C_{20}H_{23}IO_{10}K$: 589.00; found: 589.09 (18.5)

***3-Iodophenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside* (2)**

Reaction of penta-*O*-acetyl-α/β-mannopyranoside (2.0 g, 5.2 mmol) with 3-iodophenol (2.1 g, 9.4 mmol) with boron trifluoride diethyl etherate as acid (1.1 mL, 8.7 mmol) yielded the peracetylated 3-iodophenyl mannopyranoside in 63% yield (1.2 g) The course of the reaction was followed by TLC (hexane/ethyl acetate 1/1) until complete disappearance of the starting material (22 hours). After standard workup procedures the product was purified by column chromatography on silica gel with hexane/ethyl acetate 2/1 as the eluent. The purified product was obtained as a white solid (63% yield); m.p. = 108 – 109 °C; $[\alpha]_D^{23}$ = +41.0° (c=1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ(ppm) 7.47 (C_6H_4, dd, J=1.7 Hz, J=2.0 Hz, 1H), 7.37 (C_6H_4, ddd, J=1.3 Hz, J=2.9 Hz, J=7.5

Hz, 1H), 7.01 (C_6H_4, m, 2H), 5.49 (H-3, dd, $J_{3,2}$=3.5 Hz, $J_{3,4}$=10.0 Hz, 1H), 5.46 (H-1, d, J=1.8 Hz, 1H), 5.38 (H-2, dd, 1H, $J_{1,2}$=1.9 Hz, $J_{2,3}$=3.6 Hz, 1H), 5.31 (H-4, dd, J=10.1 Hz, 10.1 Hz, 1H), 4.24 (H-6a, dd, $J_{5,6a}$= 6.0 Hz, $J_{6a,6b}$=12.3 Hz, 1H), 4.05 (H-5, H-6b, m, 2H), 2.16, 2.03, 2.02, 2.00 ($COCH_3$, 4 s, 12H); ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ(ppm) 170.4, 169.8, 169.5, 169.6 (C=0), 155.9 (C_6H_4), 132.2 (C_6H_4), 130.9 (C_6H_4), 125.6 (C_6H_4), 116.1 (C_6H_4), 95.8 (C-1), 69.3 (C-5), 69.2 (C-2), 68.7 (C-3), 65.8 (C-4), 62.1 (C-6), 20.8, 20.7, 20.6 ($CO\underline{C}H_3$); FAB-MS $[M+1]^+$, *m/z* (rel. intensity %): calculated for $C_{20}H_{23}IO_{10}$: 551.04; found: 551.13 (0.9)

***2-Iodophenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside* (3)**

Reaction of penta-*O*-acetyl-α/β-mannopyranoside (1.0 g, 2.6 mmol) with 2-iodophenol (1.0 g, 4.4 mmol) with boron trifluoride diethyl etherate as acid (0.60 mL., 4.7 mmol) yielded the peracetylated 2-iodo-phenyl-mannopyranoside in 36% yield (0.5 g). The course of the reaction was followed by TLC (hexane/ethyl acetate 1/1) until complete disappearance of the starting material (17 hours). After standard workup procedures the product was purified by column chromatography on silica gel with hexane/ ethyl acetate 3/2 as eluent to yield the purified product as white solid (36% yield); m.p. = 143 – 144 °C; $[\alpha]_D^{23}$ = + 32.0° (c=1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ(ppm) 7.76 (C_6H_4, dd, J=1.6 Hz, J=7.8 Hz, 1H), 7.26 (C_6H_4, m, 1H), 7.05 (C_6H_4, dd, J=1.3 Hz, J=8.3Hz, 1H), 6.79 (C_6H_4, ddd, J=1.3Hz, J=7.6Hz, J=8.9Hz, 1H), 5.68 (H-3, dd, $J_{2,3}$=3.4 Hz, $J_{3,4}$=10.1 Hz, 1H), 5.55 (H-1, dd, J=1.8 Hz, 1H), 5.51 (H-2, dd, $J_{1,2}$=1.9 Hz,

$J_{2,3}$=3.4 Hz, 1H), 5.38 (H-4, dd, J=10.1, 10.1 Hz), 4.25 (H-6a, $J_{5,6a}$=5.2Hz, $J_{6a,6b}$= 2.2Hz, 1H), 4.09 (H-5, m, 1H), 4.04 (H-6b, m, 1H), 2.17, 2.04, 2.01, 2.00 ($COCH_3$, 4 s, 12H); ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ(ppm) 170.4, 169.9, 169.7, 169.7 (C=O), 154.4, 139.7, 129.4, 124.7, 115.0 (C_6H_4), 95.2 (C-1), 69.8 (C-5), 69.3 (C-2), 68.9 (C-3), 65.8 (C-4), 62.0 (C-6), 20.8, 20.7, 20.6, 20.6 ($CO\underline{C}H_3$); FAB-MS $[M+1]^+$, *m/z* (rel. intensity %) calcd for $C_{20}H_{23}O_{10}$ 551.04; found 551.13 (4.2), 550.11 (0.9)

Synthesis of propynyl sugars

***2-Propynyl 2,3,4,6-tetra-O-acetyl-α -D-mannopyranoside* (5)**

Boron trifluoride diethyl etherate (0.70 mL, 13.1 mmol) was added via a syringe to a mixture of α/β-D-mannopyranose pentaacetate (5.0 g, 12.9 mmol) and freshly distilled propargyl alcohol (0.83 ml, 15.6 mmol) in dry CH_2Cl_2 (60 ml), cooled to 0°C and kept under N_2. The reaction mixture was allowed to come to room temperature and the course of the reaction was followed by TLC on silica gel (ethyl acetate/ hexane 1/1) until complete disappearance of the starting material (2 hours). After completion of the reaction, $NaHCO_3$ (1.6 g) was added and the reaction mixture was stirred for a further 30 minutes. The reaction mixture was filtered and washed with CH_2Cl_2. The filtrate was washed with water (2 x), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel with hexane/ethyl acetate 1/1 as eluent. A colorless syrup that solidifies to a white powder on standing was obtained (3.9 g, 78%); m.p: = 94-95 °C; $[\alpha]_D^{23}$ = + 60.0° (c=1.0,

$CHCl_3$); Lit.[11] m.p = 100 °C, Lit.[11] $[\alpha]_D^{22}$ = 56°. IR (neat): 3262, 2994, 2964, 2118, 1750, 1079, 1051 cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz): δ(ppm) 5.31 (H-3, dd, $J_{2,3}$=3.4 Hz, $J_{3,4}$=10.0 Hz, 1H), 5.26 (H-4, dd, J=10.0, J=10.3 Hz, 1H), 5.24 (H-2, dd, $J_{1,2}$=1.8 Hz, $J_{2,3}$=3.3 Hz, 1H), 5.00 (H-1, d, J=1.7 Hz, 1H), 4.25 (H-6a, m, 1H), 4.08 (H-6b, dd, $J_{5,6b}$=12.3, $J_{6a,6b}$=12.2 Hz, 1H), 3.99 (H-5, m, 1H), 4.24 ($^{-H_2C-}\equiv$, d, J=2.4 Hz, 2H), 2.44 ($\equiv-H$, t, J=2.4 Hz, 1H), 2.13, 2.07, 2.00, 1.96 ($COCH_3$, 4 s, 12H); ^{13}C NMR ($CDCl_3$, 125.7): δ(ppm) 170.5, 169.8, 169.7, 169.6 (C=O), 96.2 (C-1), 77.9, 75.5 ($-\equiv-$), 69.3, 68.9, 68.9 (C-3, C-4, C-5), 66.0 (C-2), 62.3 (C-6), 54.9 ($^{-H_2C-}\equiv$), 20.8, 20.6, 20.6, 20.6 ($CO\underline{C}H_3$); FAB-MS $[M+K]^+$, *m/z* (rel. intensity %): calcd for $C_{17}H_{22}O_{10}K$: 425.08; found: 425.11 (18.4)

2-Propynyl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside [4c] **(6)**

Reaction of α/β-D-galactopyranose pentaacetate (2.0 g, 5.2 mmol) with propargyl alcohol (0.36 ml, 6.7 mmol) and BF_3-Et_2O (0.97 mL, 7.9 mmol) yielded the propynyl galactopyranoside in 79% yield (1.6 g) The reaction time was 2 hours. $NaHCO_3$ (0.6 g) was used to quench the reaction. The product was purified by column chromatography on silica gel with hexane/ethyl acetate 1/1 as eluent. A colorless syrup that solidifies to a white powder on standing was obtained (1.6 g, 79% yield); m.p. 70 °C; $[\alpha]_D^{23}$ = -33.2° (c=1.9, $CHCl_3$); Lit[4c] m.p.: 55-57 °C; Lit.[4c] $[\alpha]_D^{23}$ = –23° (c=1.0 $CHCl_3$); IR (KBr): 3247, 2096, 1744 cm^{-1}; ^1H NMR ($CDCl_3$, 500 Mhz,): δ(ppm) 5.37 (H-4, dd, J=3.4, J=3.4 Hz, 1H), 5.19 (H-2, dd, J=10.0, J=10.4 Hz, 1H), 5.03 (H-3, dd, $J_{3,4}$=3.4 Hz, $J_{2,3}$=10.4 Hz,

1H), 4.69 (H-1, d, J=8.0 Hz, 1H), 4.13 (H-6, m, 2H), 3.91 (H-5, m, 1H), 4.35 ($^{-H_2C-}\equiv$, d, J=2.4 Hz, 2H), 2.44 ($-\equiv-H$, t, J=2.4 Hz, 1H), 2.12, 2.04, 1.96 ($COCH_3$, 3s, 12H); ^{13}C NMR ($CDCl_3$, 125.7 Mhz): δ(ppm) 170.3, 170.2, 170.1, 169.5 (C=O), 98.6 (C-1), 78.2 ($-C\equiv C-$), 70.8, 70.8 (C-3, C-5), 68.5 (C-4), 67.0 (C-2), 61.2 (C-6), 55.9 ($^{-H_2C-}\equiv$), 20.7, 20.6, 20.6, 20.5 ($CO\underline{C}H_3$); FAB-MS $[M+1]^+$, *m/z* (rel. intensity %) calcd for 387.12; found 387.13 (1.5), 386.12 (2.3)

Synthesis of Terminal Acetylenes

***4-ethynylphenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside* (7)**

TMS Acetylene (0.50 ml, 3.5 mmoles) was added via a syringe, to a solution of 4-iodophenyl tetra-O-acetyl-mannopyranoside (**1**) (1.0 g, 1.9 mmol) and palladium tetrakis triphenyl phosphine ($Pd(PPh_3)_4$) (0.11 g, 0.09 mmol) in a mixture of Et_3N-DMF (60 mL-1mL), kept under nitrogen. The reaction mixture was heated to 60 °C for 24 hours at which time reaction was judged complete by TLC (hexane/EtOAc 1/1). The reaction mixture was washed with 2MHCl (3x), saturated $NaHCO_3$ (2x) and H_2O (2x) and dried over $NaSO_4$. The solvent was removed under reduced pressure and the concentrate was passed through a short column with hexane/EtOAc 1/1 as eluent. The solvent was removed under reduced pressure. The concentrate was dissolved in 20 ml THF. A solution of 10 drops tetrabutyl ammonium fluoride (1M in THF) and 1 drop acetic acid in 2 ml THF was added dropwise. After 2 hours, the solvent was removed in vacuo. The product was purified by column chromatography on silica gel with

hexane/ethyl acetate 2/1 as eluent to yield the pure compound as a yellow solid (0.50 g, 58% yield); m.p. = 93 - 95°C; $[\alpha]_D^{23}$ = + 33.8° (c=1.3, $CHCl_3$); IR (neat): 3277, 2960, 2108, 1751, 1228, 1036, 837, 758 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ(ppm) 7.41 (C_6H_4, d, J=8.9 Hz, 2H), 7.01 (C_6H_4, d, J=8Hz, 2H), 5.48 (H-3, dd, $J_{2,3}$=3.5 Hz, $J_{3,4}$=10.1 Hz, 1H), 5.50 (H-1, d, J=1.4 Hz, 1H), 5.40 (H-2, dd, $J_{1,2}$=2.0 Hz, $J_{2,3}$=3.6 Hz, 1H), 5.32 (H-4, dd, J=10.1, J=10.1 Hz, 1H), 4.23 (H-6a, dd, $J_{5\text{-}6a}$=5.7 Hz, $J_{6a\text{-}6b}$=12.4 Hz, 1H), 4.03 (H-5, H-6b, m, 2H), 3.00 (—≡—H , s, 1H), 2.16, 2.02, 2.00, 1.99 ($COCH_3$, 4 s, 12H); ^{13}C NMR ($CDCl_3$, 125.7 Mhz): δ(ppm) 170.4, 169.9, 169.8, 169.6 (C=O), 155.7 (C-ipso-C_6H_4), 133.6, 116.4 (C_6H_4), 95.6 (C-1), 82.9, 76.6 (—C≡C—), 69.3 (C-5), 69.2 (C-2), 68.7 (C-3), 65.8 (C-4), 62.0 (C-6), 20.8, 20.6, 20.6 ($CO\underline{C}H_3$); FAB-MS $[M+K]^+$, *m/z* (rel. intensity %): calcd for $C_{22}H_{24}O_{10}K$ 487.10; found 486.70 (23.2)

***3-ethynylphenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside* (8)**

TMS Acetylene (0.77 mL, 5.4 mmol) was added via a syringe, to a solution of 3-iodophenyl tetra-*O*-acetyl-mannopyranoside (**2**) (1.5 g, 2.7 mmol) and palladium tetrakis triphenyl phosphine ($Pd(PPh_3)_4$) (0.17 g, 0.1 mmol) in a mixture of Et_3N-DMF (30 ml-3ml), kept under nitrogen. The reaction mixture was heated to 60 °C for 2 ½ hours during which time reaction was judged complete by TLC (hexane/EtOAc 1/1). The reaction mixture was washed with 2M HCl (3x), saturated $NaHCO_3$ (2x) and H_2O (2x) and dried over $NaSO_4$. The solvent was removed under reduced pressure and the concentrate was passed through a short column with hexane/EtOAc 1/1 as eluent. The solvent was removed in

vacuo. The concentrate was dissolved in 20 ml THF. A solution of 5 drops tetrabutyl ammonium fluoride (1M in THF) and 5 drops of acetic acid 5 ml THF was added dropwise. After 2 hours, the solvent was removed in vacuo. The product was purified by column chromatography on silica gel with hexane/ethyl acetate 2/1 as eluent to yield the pure compound as a yellow gel (0.7 g, 55% yield); $[\alpha]_D^{23}$ = + 83.4° (c=2.6, $CHCl_3$); IR (neat): 3266, 2960, 1752, 1224, 1135, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ(ppm) 7.23 (C_6H_4, dd, J=2.5 Hz, 1H), 7.22 (C_6H_4, d, J=8.0 Hz, 1H), 7.16 (C_6H_4, ddd, J=1.2 Hz, J=2.4 Hz, J=10.0 Hz, 1H), 7.05 (C_6H_4, ddd, J=1.1 Hz, J=2.6 Hz, J=8.2 Hz, 1H), 5.51 (H-3, dd, $J_{2,3}$=3.5 Hz, $J_{3,4}$=10.0 Hz, 1H), 5.48 (H-1, d, J=1.8 Hz, 1H), 5.40 (H-2, dd, $J_{1,2}$=1.9 Hz, $J_{2,3}$=3.5 Hz, 1H), 5.31 (H-4, dd, J=10.0 Hz, J=10.0 Hz, 1H), 4.25 (H-6a, dd, $J_{5,6a}$=6.5 Hz, $J_{6a,6b}$=12.4 Hz, 1H), 4.06 (H-5, H-6b, m, 2H), 3.04 (—≡—H , s, 1H), 2.16, 2.02, 2.01, 2.01 ($COCH_3$, 4 s, 12H); ^{13}C NMR ($CDCl_3$, 125.7 Mhz): δ(ppm) 170.5, 169.9, 169.8, 169.7 (C=O), 155.3 (C-ipso-C_6H_4), 129.5, 126.9 (C_6H_4), 123.4 (C-ipso- C_6H_4), 119.9, 117.6 (C_6H_4), 95.8 (C-1), 82.9, 77.6 (—C≡C—), 69.2 (C-5), 69.2 (C-2), 68.7 (C-3), 65.9 (C-4), 62.1 (C-6), 21.0, 20.8, 20.6, 20.6 ($CO\underline{C}H_3$); HRMS (FAB) $[M+K]^+$: calcd for $C_{22}H_{24}O_{10}K$ 487.1007 found 487.1785 *m/z*

2-ethynylphenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside **(9)**

2-iodophenyl tetra-O-acetyl-mannopyranoside (**3**) (0.1 g, 0.19 mmol) in Et_3N (30 mL) was stirred under N_2 for 30 minutes. Dichloro-bis(triphenyl)phoshine

palladium(II) ($PdCl_2(PPh_3)_2$) (1.6 mg, 0.23μmol) was added to the mixture. After 5 minutes of stirring under N_2 for 5 minutes, Copper(I) iodide (CuI) (3.9 mg, 2.5 μmol) and triphenyl phosphine (PPh_3) (3.5 mg, 0.13 μmol) were added to the mixture and stirred for a further 5 minutes. Acetylene gas was bubbled through the reaction mixture which was then heated to 60 °C. The reaction was followed by TLC (hexane/EtOAc 2/1) and was judged to be complete after 7 hours. The solvent was removed under reduced pressure and the concentrate was then passed through a column of silica gel, with hexane/EtOAc 2/1 as eluent. The purified product was obtained as a white solid (0.037 g, 44% yield); m.p. = 127 °C; $[\alpha]_D^{23}$ = + 38.3° (c=1.2, $CHCl_3$);); IR (neat): 3271, 2907, 1742, 1240, 1137, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ(ppm) 7.45 (C_6H_4, dd, J=1.6 Hz, J=7.6 Hz, 1H), 7.27 (C_6H_4, ddd, J=1.7 Hz, J=7.7 Hz, J=8.5 Hz, 1H), 7.08 (C_6H_4, d, J=8.1 Hz, 1H), 7.01 (C_6H_4, ddd, J=0.9 Hz, J=7.6 Hz, J=8.5 Hz, 1H), 5.63 (H-3, dd, $J_{2,3}$=3.5 Hz, $J_{3,4}$=10.1 Hz, 1H), 5.57 (H-1, d, J=1.8 Hz, 1H), 5.3 (H-2, dd, $J_{1,2}$=1.9 Hz, $J_{2,3}$=3.5 Hz, 1H), 5.35 (H-4, dd, J=10.0 Hz, J=10.1 Hz, 1H), 4.24 (H-6a, dd, $J_{5\text{-}6a}$=5.4 Hz, $J_{6a\text{-}6b}$=12.1 Hz, 1H), 4.19 (H-5, m, 1H), 4.05 (H-6b, dd, $J_{5,6b}$=2.1 Hz, $J_{6a,6b}$=12.1 Hz, 1H), 3.32 (—≡—H , s, 1H), 2.17, 2.03, 2.00, 1.99 ($COCH_3$, 4 s, 12H); ^{13}C NMR ($CDCl_3$, 125.7 Mhz): δ(ppm) 170.4, 169.9, 169.7, 169.7 (C=O), 156.6 (C-ipso-C_6H_4), 133.9, 130.0, 123.1, 115.6 (C_6H_4), 113.6 (C-ipso- C_6H_4), 96.4 (C-1), 82.4, 78.8 (—c≡c—), 69.6 (C-5), 69.5 (C-2), 68.8 (C-3), 65.9 (C-4), 62.1 (C-6), 20.8, 20.7, 20.6, 20.6 ($CO\underline{C}H_3$); FAB-MS $[M+K]^+$, *m/z* (rel. intensity, %): calcd for $C_{22}H_{24}O_{10}K$ 487.10; found 487.14 (7.4)

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Chapter 3. Synthesis of Rigid Sugar Dimers

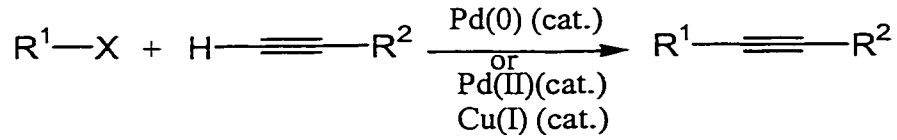
3.1. Introduction

Synthesis of rigid aryl-sugar dimers was initiated to explore structure-activity relationships and as intermediates for the cyclotrimerization. Two mannose or two galactose residues were joined by an acetylene moiety forming different variations of sugar rods. To construct the dimers, two general approaches were taken. One approach was Lewis-acid promoted *O*-glycosidation of pentaacetyl D-mannose. The second is transition metal catalyzed coupling. The first method used in this strategy is Sonogashira coupling. The second method is oxidative coupling of two terminal alkynes.

3.1.1. Sonogashira Coupling

One of the most straightforward methods for the preparation of disubstituted aryl acetylenes is the palladium-catalyzed coupling of terminal alkynes with aryl halides which was first introduced by Sonogashira et al in 1975.[1]

The reaction proceeds smoothly under mild conditions in the presence of a Pd-complex catalyst and copper (I) iodide cocatalyst (Scheme 3.1.1). The solvent is usually an amine which also serves to bind the hydrogen halide eliminated.[2a]



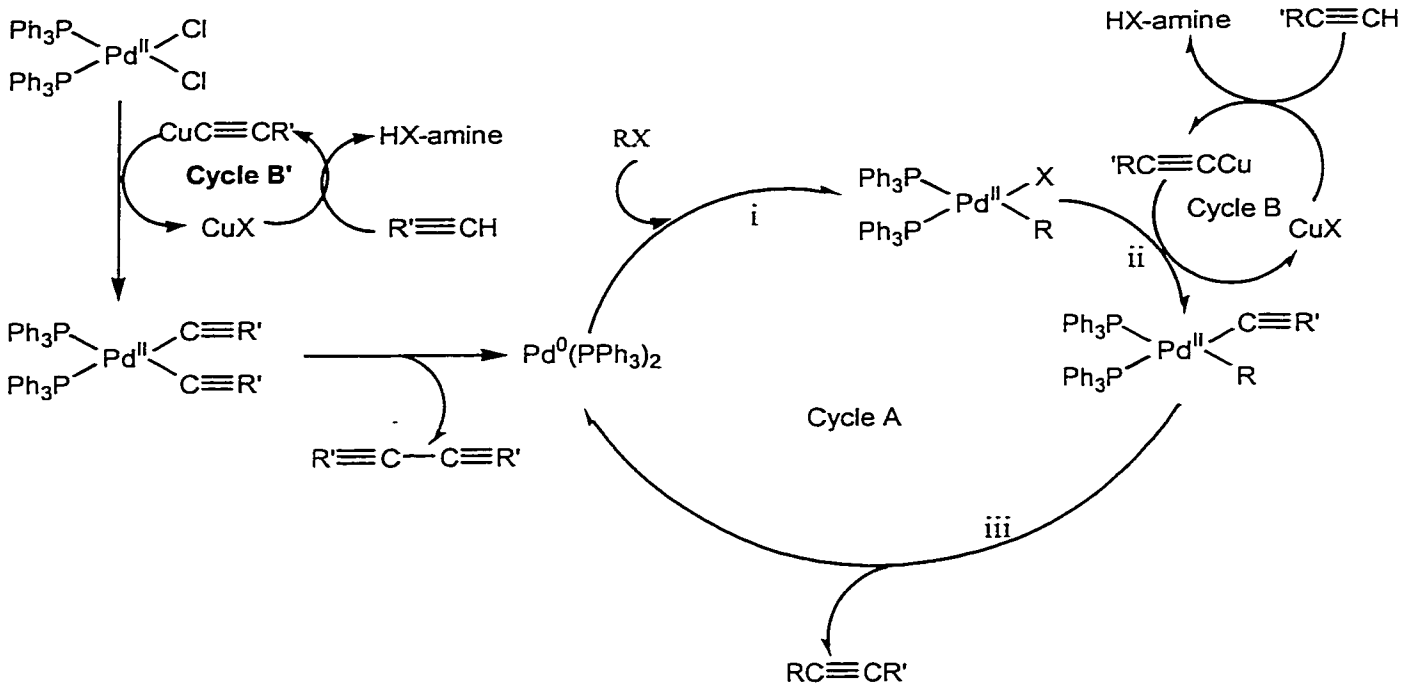
R^1 = aryl, alkenyl
X= BR, I, Cl, Otf

Scheme 3.1.1. Sonogashira coupling.

R may represent an aryl, hetaryl, (cyclo-)olefinic group or an allenic system. There are no limitations to to the nature of R^2. In the case of acetylene itself, the product is a disubstituted acetylene. This method is now widely used for the construction of conjugated aryl alkynes or enyne systems.[2]

As a source of palladium, $PdCl_2(PPh_3)_2$ in diethylamine or triethylamine is commonly used. In many cases, $Pd(OAc)_2$, or $Pd(OAc)_2(PPh_3)_2$,[3] or $Pd_2(dba)_3$ or $Pd_2Cl_2(CH_3CN)_2$ plus 2 equivalents of a tertiary phosphine L which are reduced in situ to the catalytically active Pd^0L_2, have been used.[2b]

Sonogashira proposed a reaction scheme constructed by a combination of two catalytic cycles A and B (Scheme 3.1.2). This protocol is based on the discovery of CuI-catalyzed transmetallation in amine.[4] When $PdCl_2(PPh_3)_2$ is used, a Pd-acetylide complex is formed which undergoes reductive elimination to form the $Pd^0(PPh_3)_2$. Oxidative addition of the sp^2 halide to Pd(0), which undergoes nucleophilic attack by the acetylide anion and subsequent reductive elimination affords the disubstituted acetylene and $Pd(PPh_3)_2$.[2b]



Scheme 3.1.2. Mechanism for Sonogashira reaction i) oxidative addition, ii) transmetallation, iii) reductive elimination.

If tetrakis (triphenylphosphine) palladium(0) is used, it was proposed[2] that the oxidative addition product is formed first, which then enters the cycle (Scheme 3.1.3).

$$R'X + Pd(PPh_3)_4 \longrightarrow R'PdX(PPh_3)_2 + 2PPh_3$$

Scheme 3.1.3. Activation of $Pd(PPh_3)_4$.

Sonogashira coupling is rarely used in the synthesis of carbohydrate conjugates. One interesting example is in the construction of clustered disaccharides consisting of two and four IP_3 units anchored via a spacer to a central phenyl core.[6]

Only two more application of the reaction to carbohydrate synthesis was found. Burli et al[7] coupled two units of 1,4-dialkynylated glucoside to one unit of dibromo-bipyridine under Sonogashira conditions $PdCl_3(PPh_3)_2$, CuI, and Et_3N. Roy[8] et al used $Pd(PPh_3)_4$ to synthesize sugar dimers with a benzene-acetylene core.

3.1.2. Oxidative coupling

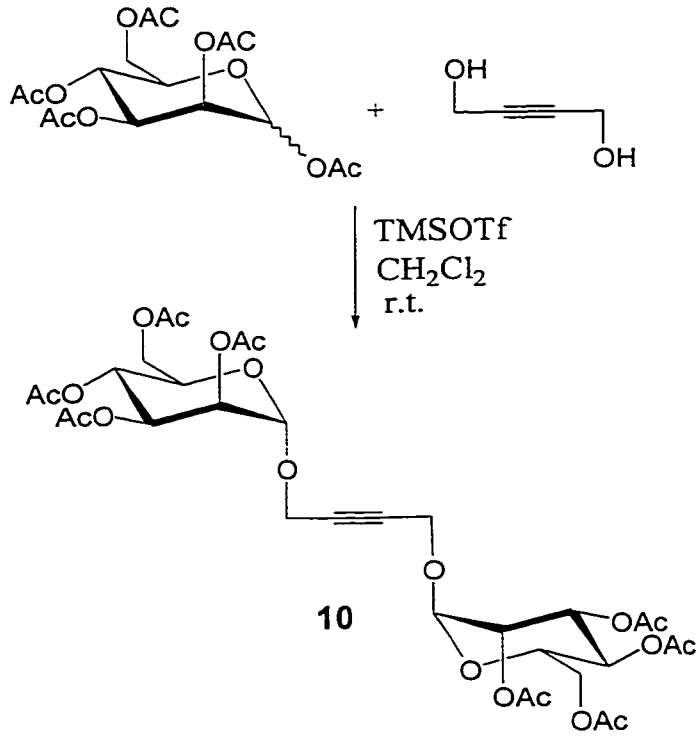
Analogues containing two acetylene units in the core were generated by oxidative coupling of two two terminal alkynes. Symmetrical dimers were constructed by homocoupling of mannose conjugates containg a terminal acetylene functionality. This was done following a modification of Hay's method.[9]

3.2. Results and Discussion

3.2.1. Lewis Acid Catalyzed *O*-Glycosidation

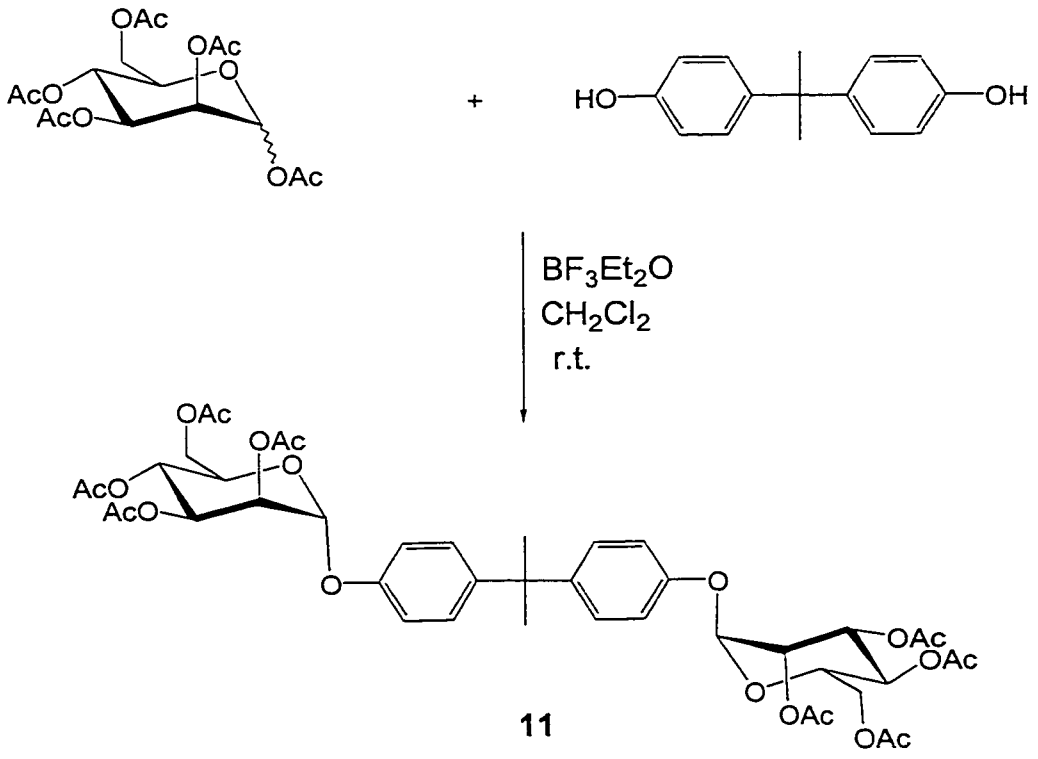
The first approach that was taken to construct the dimers was the Lewis-acid promoted *O*-glycosidation of pentaacetyl-D-mannose. Giovenzena et al[10]

reported the synthesis of 2-butyne-1,4-di-yl glucoside from 2-butyne-1,4-diol promoted by trimethylsilyltriflate. They reported a yield of 34% of the β-anomer. Following this method, a non-benzene containing dimer consisting of two mannose residues tethered on 2-butyne was synthesized (Scheme 3.2.1). Reaction of 2.0 equivalents of mannose pentaacetate with 1.0 equivalent of 2-butyne-1,4-diol and 1.0 equivalent of trimethylsilyltriflate yielded the α-anomer of **10** in 27% yield. The H-1 protons appeared as a doublet (J=1.6 Hz) and the H-2 protons appeared as a doublet of doublets (J= 1.8 Hz, J=3.2 Hz) confirming the α-anomeric configuration.



Scheme 3.2.1. Synthesis of 2-butyn-1,4-dimannoside.

$BF_3{\cdot}Et_2O$ promoted *O*-glycosidation of the bisphenol was used to synthesize a mannose dimer containing a diphenyl core (Scheme 3.2.2). Reaction of 2.0 equivalents of mannose pentaacetate with 1.0 equivalent of bisphenol and 3.4 equivalents of $BF_3{\cdot}Et_2O$ yielded dimer **11** in 49% yield. The H-1 protons appeared as a singlet and the H-2 protons appeared as a doublet of doublets (J=1.8 Hz, J=3.3 Hz) confirming the α-anomeric configuration (Fig. 3.2.1).



11

Scheme 3.2.2. *O*-glycosidation of bisphenol A.

3.2.2. Sonogashira Coupling

The second approach utilized was dimerization by Sonogashira coupling. Mannosyl dimers (**13**, **14**) tethered on a single benzene core were synthesized using palladium tetrakistriphenylphosphine as catalyst. The desired compounds were obtained by reaction between 2.1 equivalents of 2-propynyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (**5**) and 1 equivalent of the diiodobenzene in DMF-Et_3N 1-1 with 10 mole% of $Pd(PPh_3)_4$ as catalyst at 60 °C for four hours (Scheme 3.2.3). The method works well for ortho and meta diiodobenzenes as well as different analogues synthesized in Roy's group[8] (**12**, **15**, **16**). The yield decreases from para to ortho substitution in the benzene ring.

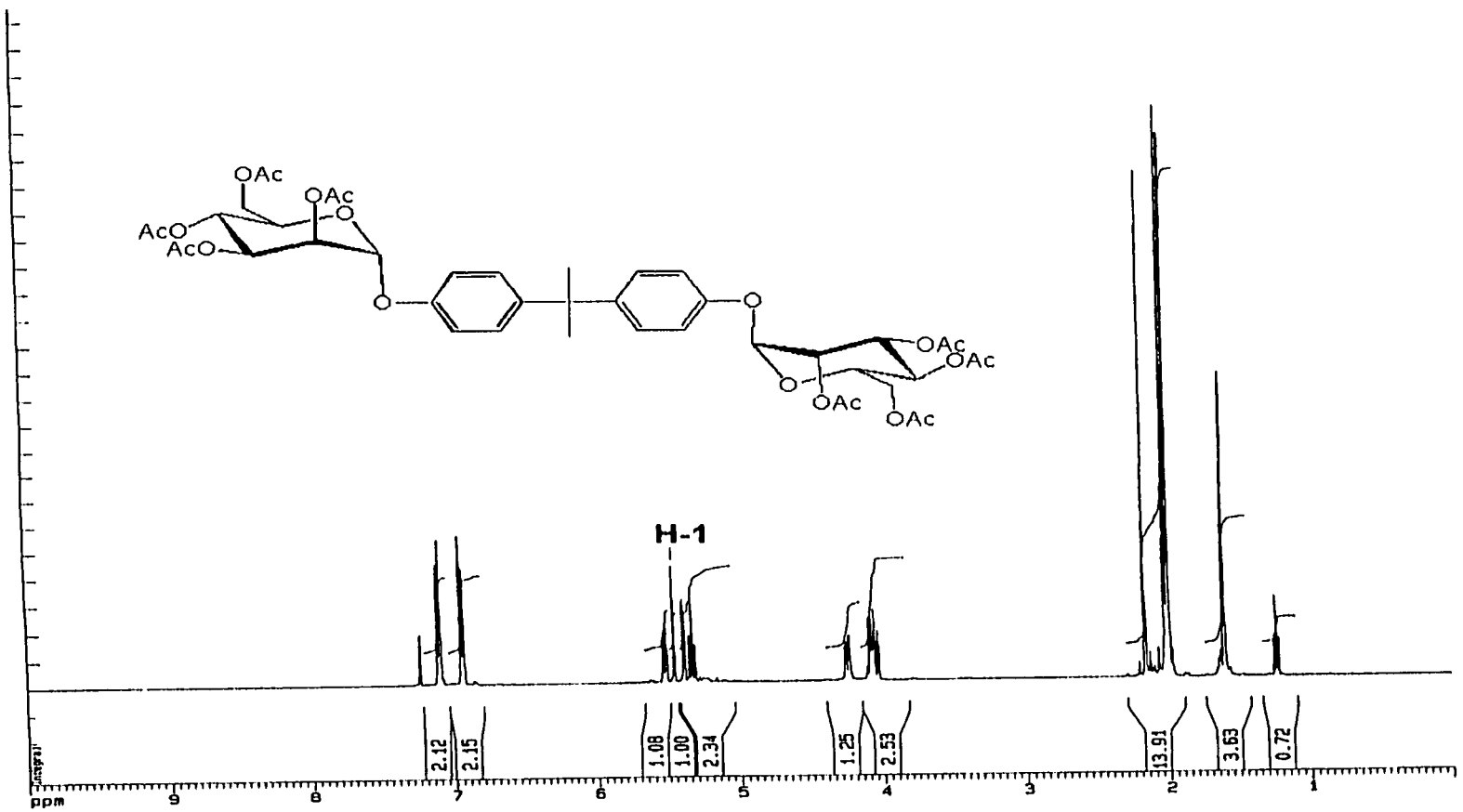
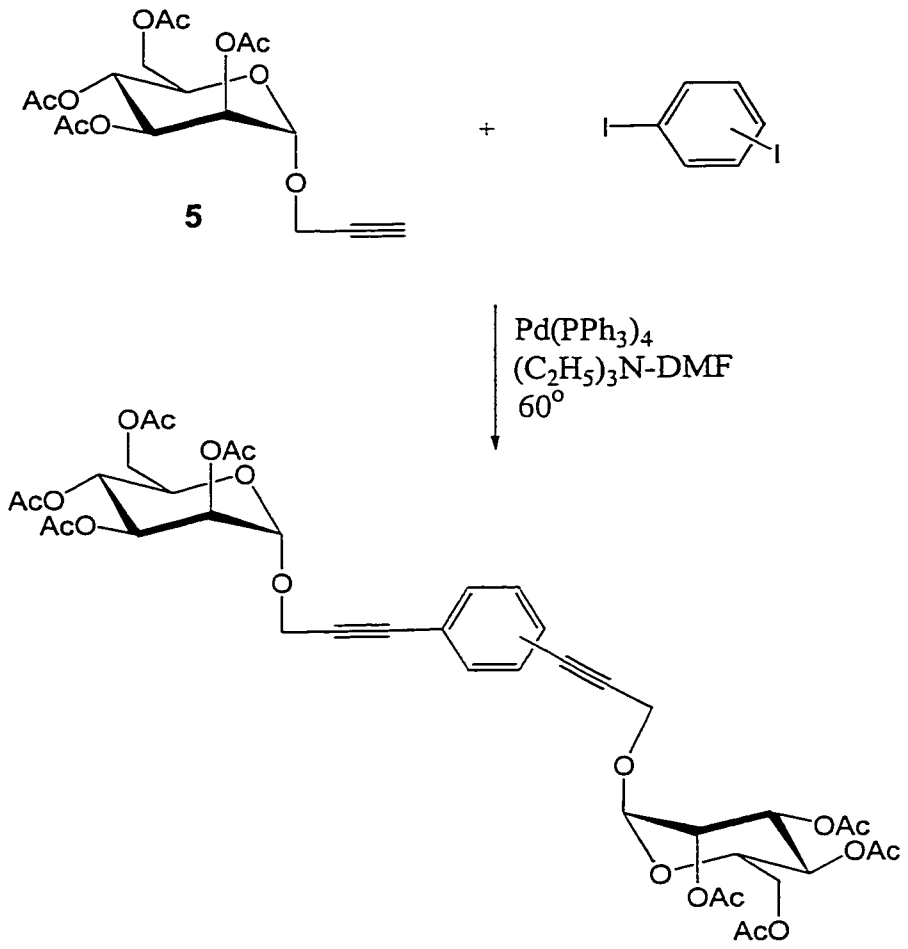


Figure 3.2.1. ^{1}H NMR (500 MHz, $CDCl_3$) of bis-para(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)diphenylisopropane(**11**).



Scheme. 3.2.4. Sonogashira coupling of diiodobenzene with 2-propynyl 2,3,4,6-tetra-O-acetylglycoside.

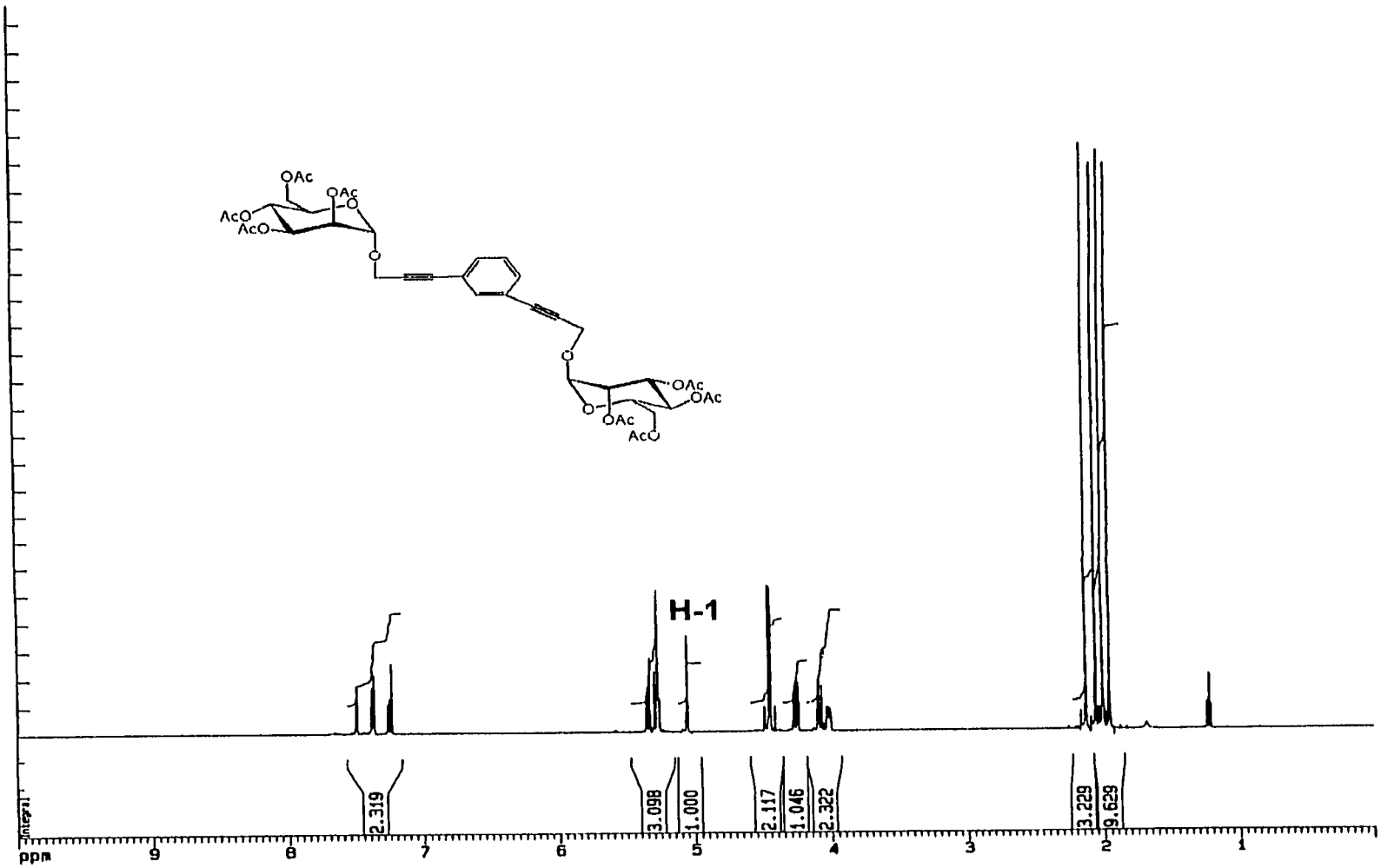
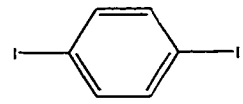
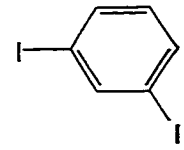
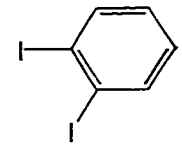
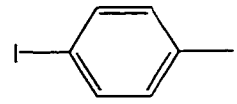
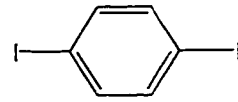
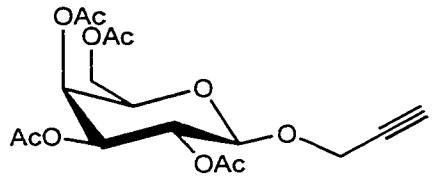


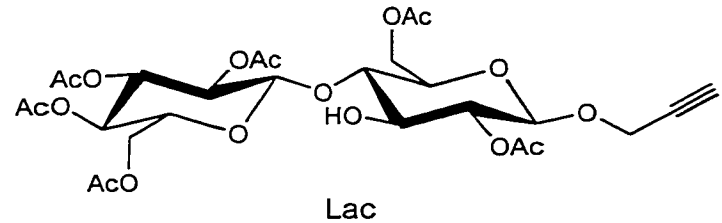
Figure 3.2.2. ^{1}H NMR (500 MHz, $CDCl_3$) of **13**.

Table 3.2.1. Generation of mono-benzene dimannoside analogs.

R_1	R_2	product	yield (%)
Man (**5**)		**12**	100[8]
Man (**5**)		**13**	88
Man (**5**)		**14**	82
Gal (**6**)		**15**	72[8]
Lac		**16**	71[8]



Gal (**6**)



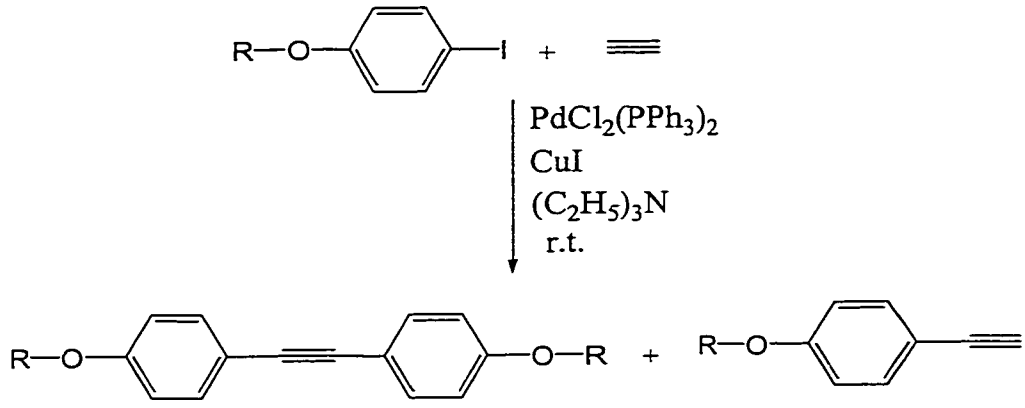
Lac

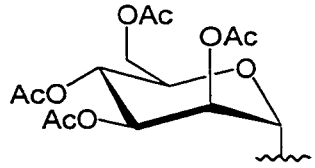
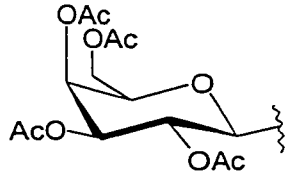
Sugar dimers containing a diphenyl core (**17**, **18**, **21**, **23**) were also synthesized by the Sonogashira coupling. Dimerization of iodophenyl glycosides

with acetylene gas were catalyzed by 1.0 mole% $PdCl_2(PPh_3)_2$ and 8 mole% CuI with triethylamine as the solvent (and base) at room temperature for 24 hours.

Galactosyl (**18**) and mannosyl dimers (**17**) (Fig. 3.2.3, Fig. 3.2.4) were synthesized with this method. It was found that the terminal acetylene derivative (**7**, **8**, **9**, **19**) was a byproduct in all cases (Table 3.2.2, Scheme 3.2.3, and Scheme 3.2.4, Fig. 3.2.5).

Table 3.2.2. Sonogashira coupling of iodophenyl glycoside with acetylene.



R	Dimer		Monomer	
	Yield (%)	compd	yield (%)	compd
	58	**17**	27	**7**
	80	**18**	14	**19**

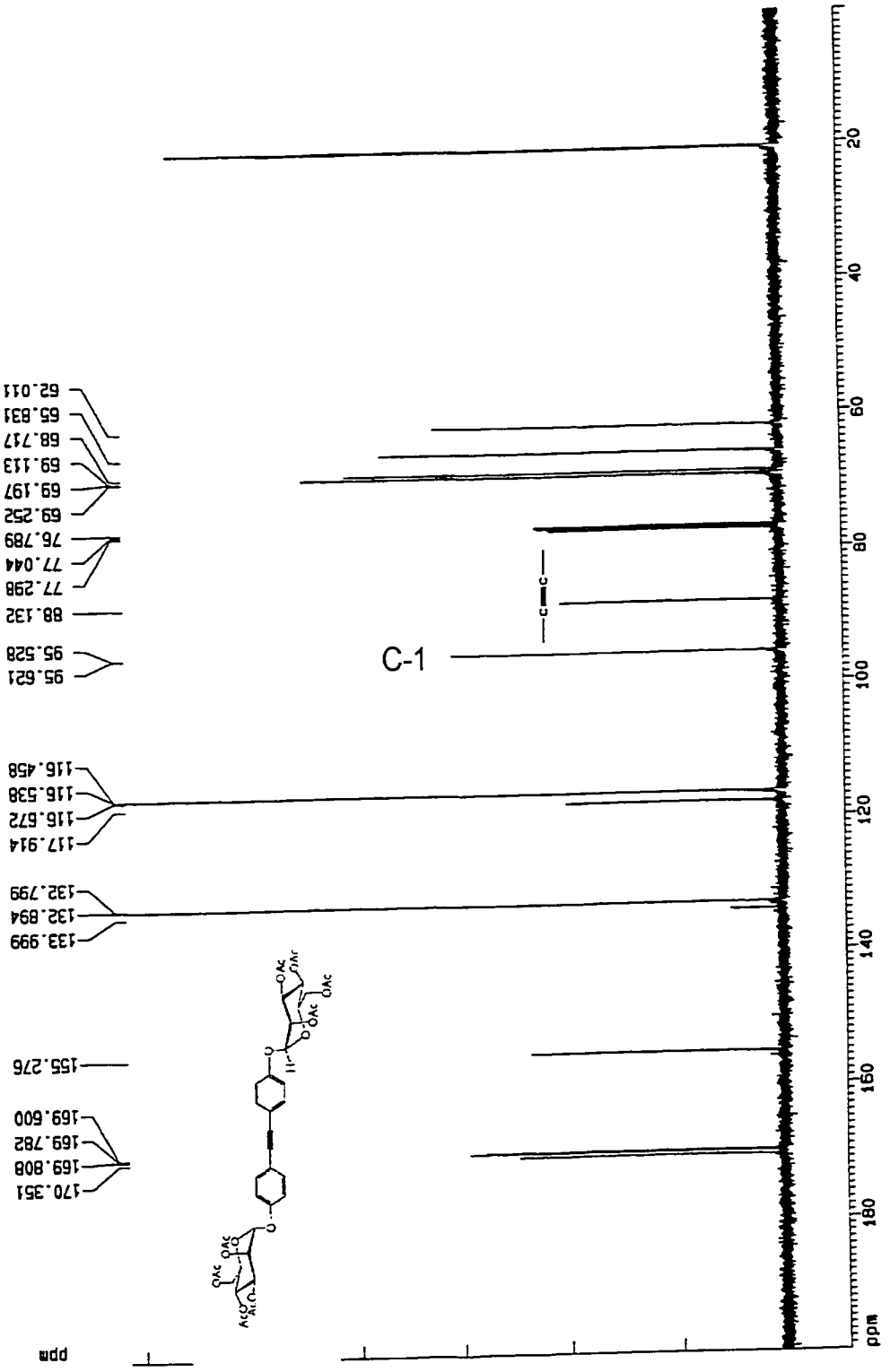


Figure 3.2.3. ^{13}C NMR (500 MHz, $CDCl_3$) of mannopyranoside dimer **17**.

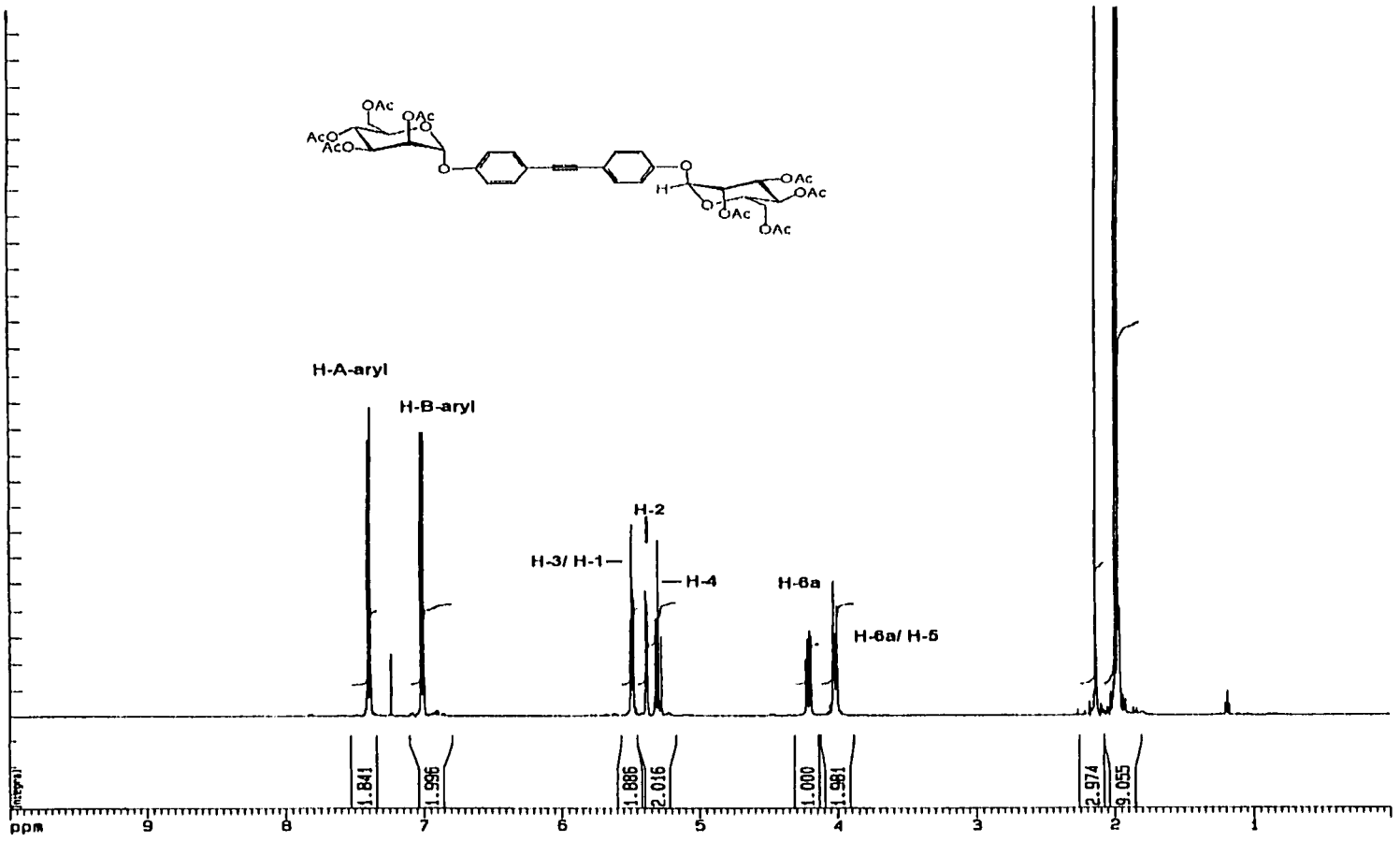


Figure 3.2.4. ^{1}H NMR (500 MHz, $CDCl_3$) of mannopyranoside dimer **17**.

Attempts at synthesis of ortho and meta mannosyl dimers resulted in a mixture of dimers containing one and two acetylene units (Scheme 3.2.3 and Scheme 3.2.4). The di-yne and the mono-yne derivatives are indistinguishable by TLC on silica gel. They exhibit the same Rf on a prep. HPLC on a column of C_{18}. Thus, with ortho-iodophenyl mannopyranoside or meta-iodophenyl mannopyranoside as the substrate, the pure dimer was not isolated. For both cases the presence of a molecular ion peak of 909 *m/z* corresponding to the mono-yne $C_{42}H_{46}O_{20}K$ and of 933 *m/z* corresponding to the di-yne $C_{44}H_{46}O_{20}K$was the first indication that the seemingly pure isolate was not pure. The second indication was the presence of two anomeric carbons in the ^{13}C spectra at 95-97 ppm. Also the prescence of both acetylene carbon peaks of both the mono-yne (at about 89 ppm and the di-yne at 78-81 ppm and 74-78 ppm).

In the dimerization of meta-iodophenyl mannopyranoside, the mono-yne (**20**) is formed in a 1:1.4 ratio with the corresponding di-yne (**21**) (Scheme 3.2.3). This was established by the ratios of the intensities of the ^1H NMR C_6H_4 peaks [mono-yne (**20**): 7.08 ppm (dd, J=1.2 Hz, J=2.6 Hz), 7.07 (dd, J=1.3 Hz, J=2.6 Hz)]; [di-yne (**21**): 7.05 ppm (dd, J=1.1 Hz, J=2.6 Hz), 7.03 (dd, J=1.0 Hz, J=2.5 Hz)]. The position of the C_6H_4 peak of the mono-yne (**20**) in relation to the C_6H_4 of the di-yne (**21**) was established by comparison of the ^1H NMR of the corresponding mono-yne (**20**) and di-yne (**21**).

In the dimerization of the ortho-iodophenyl mannopyranoside, the formation of the mono-yne (**23**) is favored over di-yne (**22**) in a 2:1 ratio (Scheme 3.2.4). This was established by the ratios of intensities of the ^1H

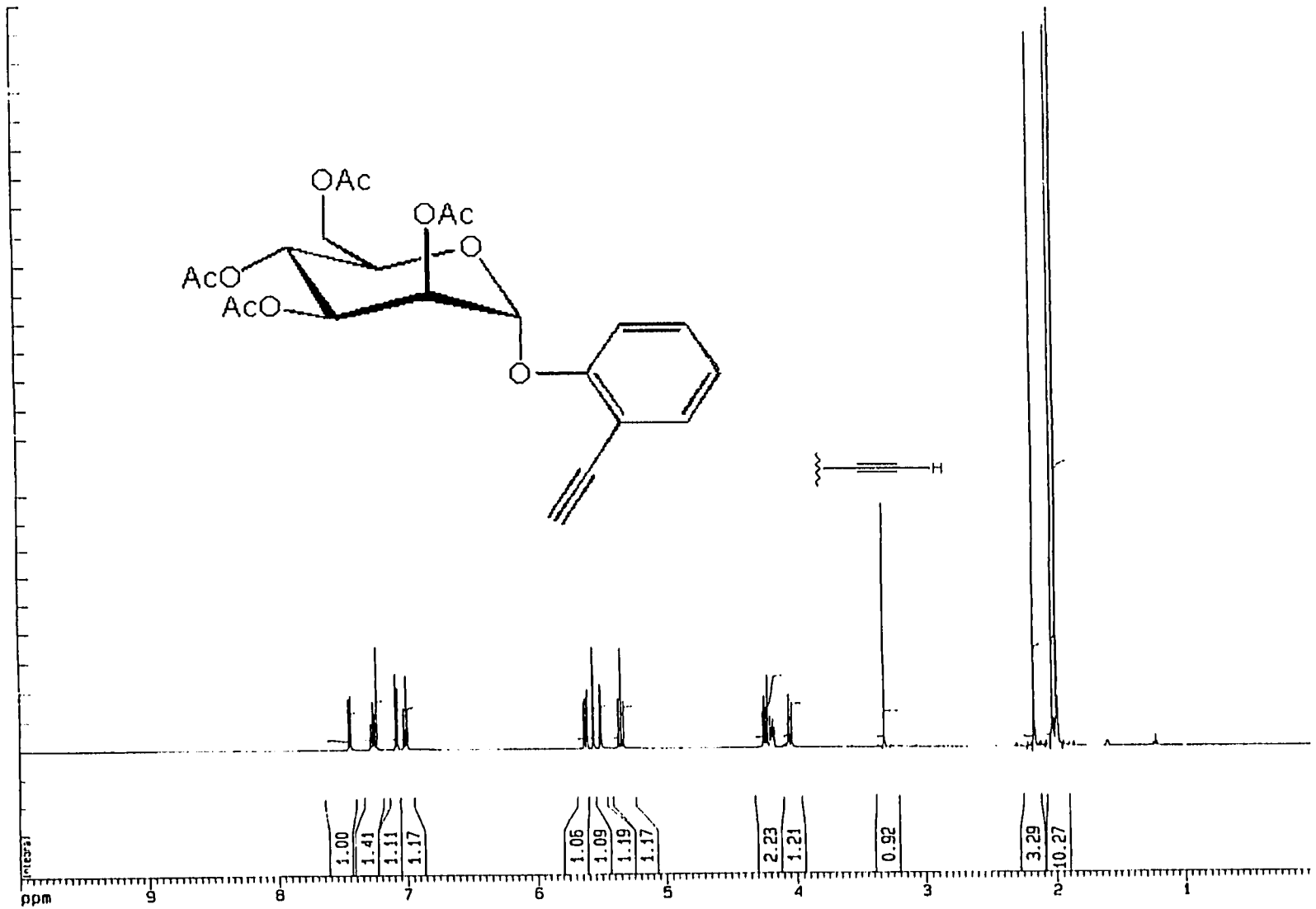


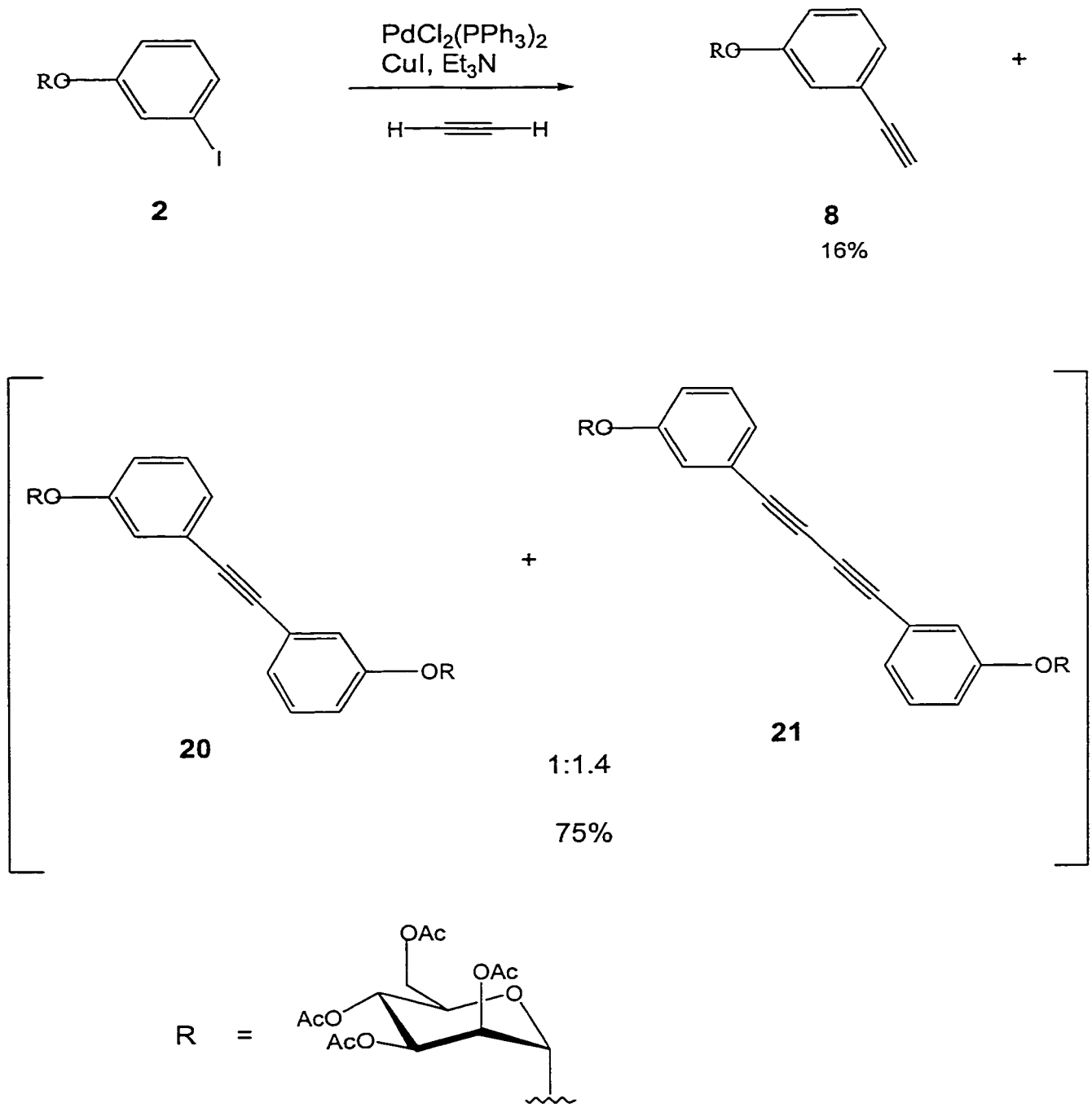
Figure 3.2.5. ^{1}H NMR (500 MHz, $CDCl_3$) of ortho acetylene monomer **9.**

NMR C_6H_4 peaks [mono-yne (**22**): 7.72 ppm (dd, J=1.6 Hz, J=7.7 Hz)] and (di-yne (**23**): 7.54 ppm (dd, J=1.7 Hz, J=7.7 Hz)]. Again, the ^1H NMR of the corresponding mono-yne (**22**) and di-yne (**23**) established the position of the C_6H_4 peak of the mono-yne in relation to the di-yne.

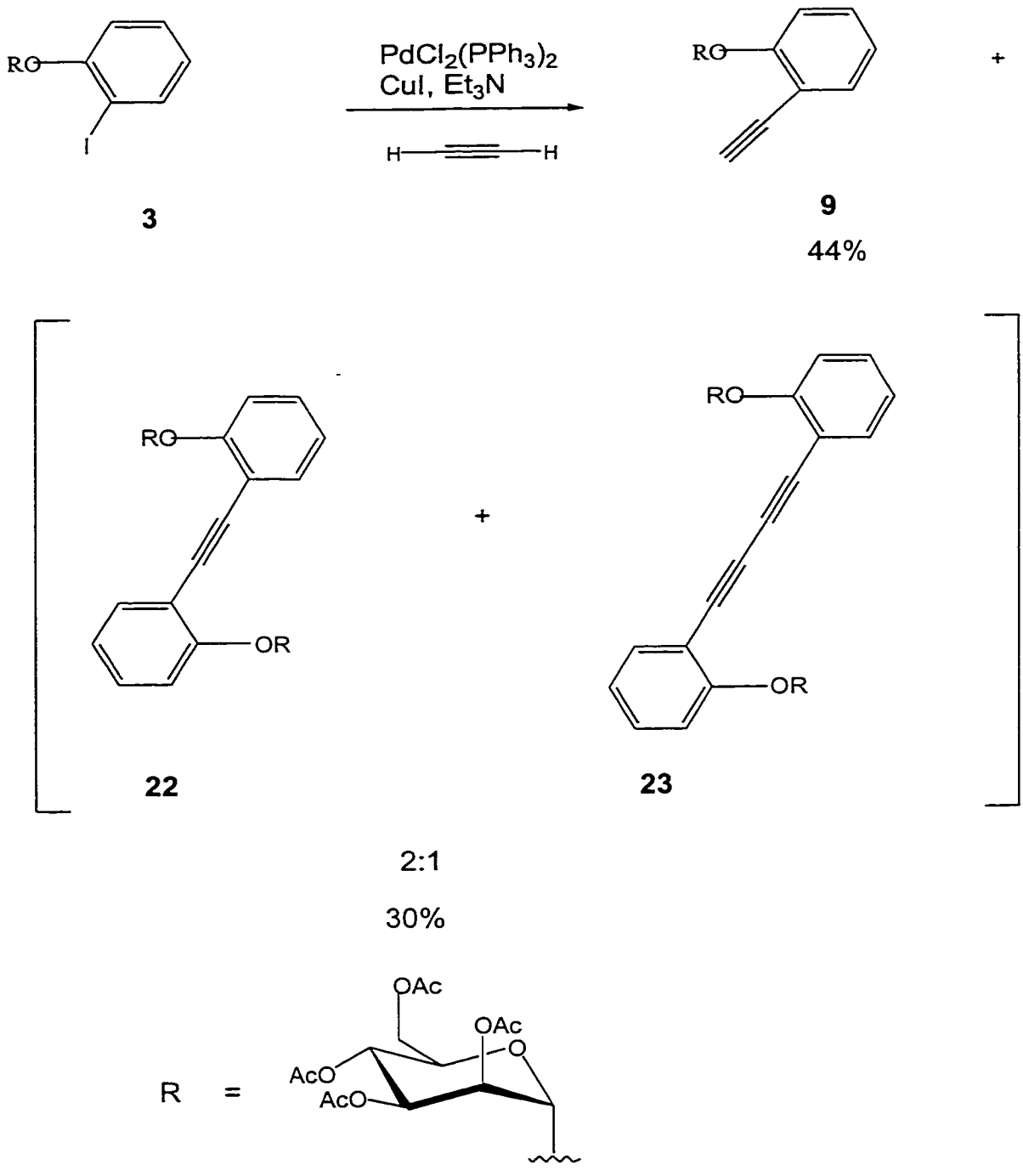
Manipulation of reaction parameters (Table 3.2.3) did not give favorable results. The reaction with $PdCl_2(PPh_3)_2$ does not proceed without CuI. Below 8% of CuI no dimer was formed. At 8% CuI, 12% $PdCl_2(PPh_3)_2$ the di-yne is formed along with the mono-yne. Change of catalyst to $Pd(PPh_3)_4$ in Et_3N 60 °C resulted in messy side products. No reaction was observed at room temperature. Change of solvent to Et_3N-DMF 1:1 (catalyst: $Pd(PPh_3)_4$) and heating at 60°C gave similar results.

Table 3.2.3. Results of variation of Sonogashira conditions.

Catalyst	mole %	Co-catalyst	Mole %	Solvent	Rxn temp.	Results
$PdCl_2(PPh_3)_2$	2	----	----	Et_3N	r.t.	no rxn
"	15	----	----	Et_3N	r.t.	no rxn
"	8	CuI	1	Et_3N	r.t.	no dimer
"	9	CuI	3	Et_3N	r.t.	no dimer
"	12	CuI	8	Et_3N	r.t.	mono-yne +di-yne
$Pd(PPh_3)_4$	10	----	----	Et_3N	r.t.	No rxn
"	10	----	----	Et_3N	60 °C	side products
"	10	----	----	Et_3N-DMF 1:1	60 °C	side products



Scheme 3.2.3. Sonogashira coupling products of meta-iodophenyl mannopyranoside with acetylene gas.

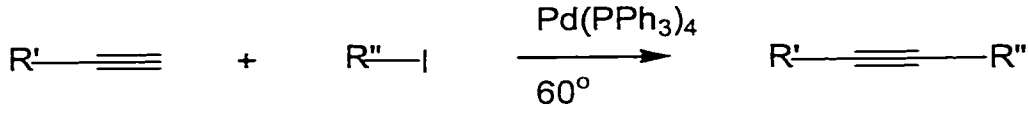


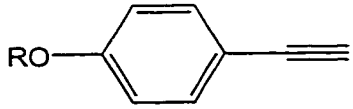
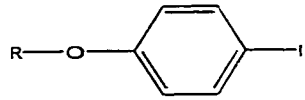
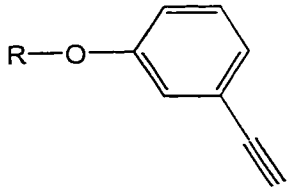
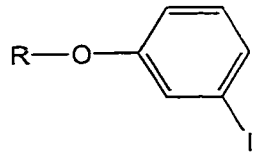
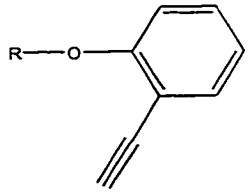
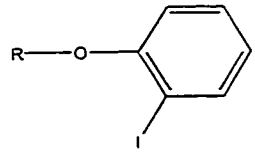
Scheme 3.2.4. Sonogashira coupling of ortho-iodophenyl mannopyranoside with acetylene gas.

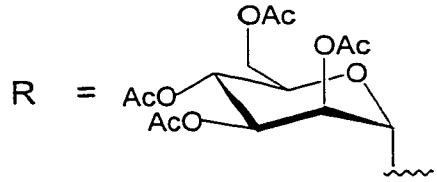
A different route was then taken to construct the ortho and mannosyl dimers (**20** and **22**). To stop the incorporation of two acetylene units in the core of the structure, the terminal acetylene was synthesized or isolated from the Sonogashira reaction and reacted with 2.0 equivalents of the ortho-iodophenyl mannoside or meta-iodophenyl mannoside using $Pd(PPh_3)_4$ as the catalyst (10.0 mole%) in a DMF-Et_3N 1-1 solvent (Table 3.2.4). The pure dimer held by one acetylene unit was isolated. This was established by the absence of a molecular ion peak 24 units higher than expected (933 *m/z)* and a single anomeric carbon signal in ^{13}C (Fig. 3.2.6). Therefore, only the mass corresrresponding to $C_{42}H_{46}C_{20}K$ in FAB MS 909 *m/z* was found for the ortho dimer and the meta dimer.

The para dimer (**17**) was also synthesized by this route. The conversion of acetylenephenyl mannoside (**7**, **8**, **9**) was found to be stoichiometric. Excellent yields were obtained (80-100%). Glaser oxidation was therefore circumvented by this route.

Table 3.2.4. Generation of mono-acetylenated dimers.



R'	R"	yield (%)	Dimer
 **7**	 **1**	80	**17**
 **8**	 **2**	100	**20**
 **9**	 **3**	100	**22**



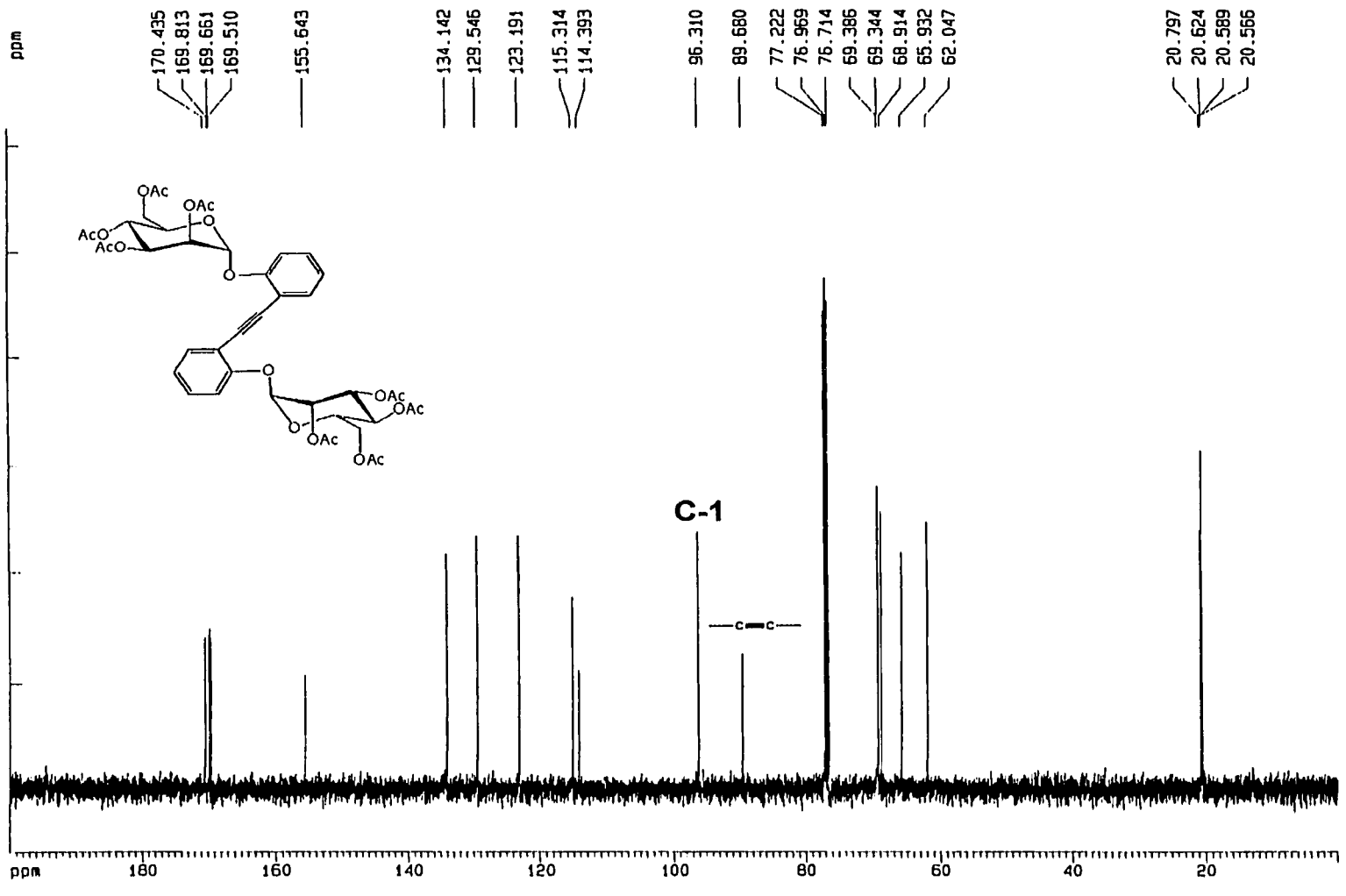


Figure 3.2.6. ^{13}C NMR (500 MHz, $CDCl_3$) of ortho mannopyranoside dimer **22**.

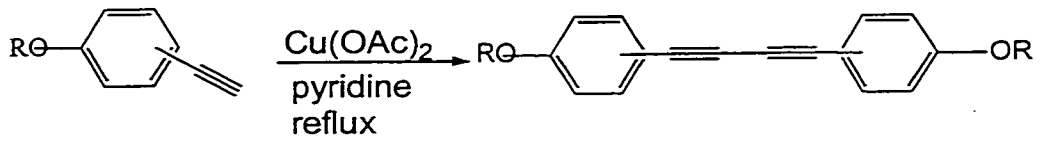
3.2.3. Homocoupling of Terminal Acetylenes

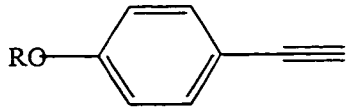
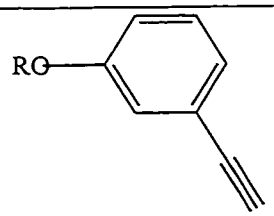
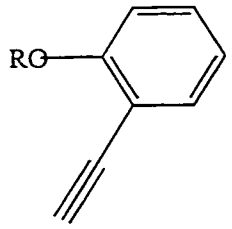
The next class of dimers synthesized was the diphenyldimers containing two acetylene units in the core (**21**, **23**, **24**) (Fig. 3.2.7). This was achieved by oxidative coupling of the terminal acetylene mannosyl derivatives (**7**, **8**, **9**) with $Cu(Oac)_2$ as catalyst (5 mol%) in pyridine (Table 3.2.5). Yields in the order of 47 % to 68% were obtained. The ease of coupling decreased from ortho > meta > para substitution in the phenyl ring.

It was thus demonstrated that *O*-glycosides substituted with terminal phenylacetylene undergo Hay's coupling with very good yields and reasonable reaction periods. Ortho, meta and para substituted glycosidic phenylacetylenes all undergo oxidative coupling with very good yields.

Thus, mannosyl dimers with a diphenyl-diethynyl spacer were generated.

Table 3.2.5. Generation of di-acetylenated dimers.



Starting material		Product	yield (%)
	**7**	**24**	47
	**8**	**21**	58
	**9**	**23**	63

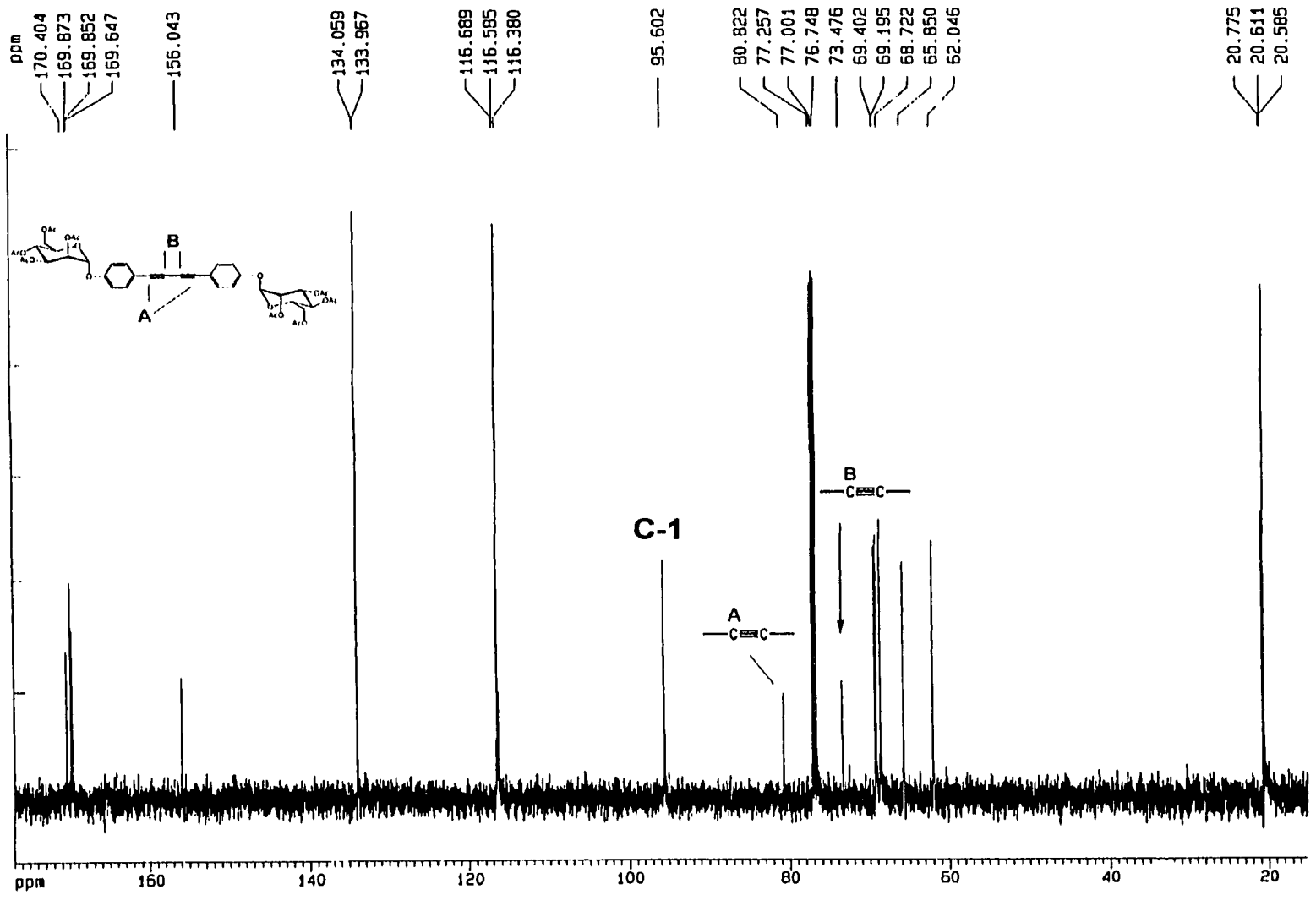


Figure 3.2.7. ^{13}C NMR of para mannopyranoside dimer **24**.

3.3. Conclusions

Rigid mannosyl and galactosyl dimers containing a phenyl-acetylene core were successfully constructed.

It was shown that peracetylated *O*-mannoside and *O*-galactoside as substituent on the halobenzene ring permit Sonogashira coupling with good yields at a reasonable reaction period.

Most Sonogashira coupling proceed first with the synthesis of the terminal acetylene prior to the coupling. It was shown that this step is eliminated and direct coupling of glycosidic iodobenzenes is possible with acetylene gas.

With para mannosyl and galactosyl iodobenzenes, Glaser coupling was not evident. However, this occurs with ortho and meta mannosyl iodobenzene. It was shown that Glaser coupling is circumvented by the synthesis of the ortho and meta terminal acetylenes prior to coupling.

This report shows that iodobenzenes substituted with glycosyl groups in the ortho, meta and para position undergo Sonogashira coupling with good yields. The yield decreases from para > meta > ortho substitution. Similarly, ortho-, meta- and para-diiodobenzenes under Sonogashira coupling with 2-propynyl glycosides give very good yields.

It was shown that Sonogashira conditions provide an efficient and mild method to obtain the rigid glycosyl dimers. It was also shown that the glycoside functionalized with terminal acetylenes undergo Hay's coupling with good yields.

Lewis-acid catalyzed coupling of mannosides to alcohols successfully generated the non-benzene or non-acetylene containing sugar dimers with a lower yield than the transition metal catalyzed coupling.

3.4. Experimental Methods

General Methods

^{1}H NMR and ^{13}C NMR spectra were obtained from either a Varian Gemini-200 MHz or a Bruker AMX500 spectrometer at 500, and 200 MHz for protons and 125.7 and 50.3 MHz for carbons, respectively. Proton chemical shifts are given relative to internal chloroform (7.24 ppm) for $CDCl_3$ solutions. Carbon chemical shifts are given relative to $CDCl_3$ (77.0 ppm). Special analyses were performed by the first order approximations and were based on shift correlation spectroscopy (COSY), heteronuclear multiple quantum coherence (HMQC), and 1- and 2-dimensional distortionless enhancement by polarization transfer (DEPT) experiments. Multiplicities of the NMR signals were reported using the following abbreviations: singlet (s), broad singlet (bs), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), multiplet (m).

Mass spectra were recorded on a Kratos IIH (FAB-KI-glycerol or FAB-glycerol) instrument. Xenon was used as the netural carrier atom in FAB-MS experiments.

Melting points were determined on a Gallenkamp apparatus and are uncorrected.

Optical rotation ($[\alpha]_D$) values were determined using a Perkin-Elmer (model 241) set at the sodium D line (589 nm) and were run at room temperature.

Infrared spectra were obtained on a Bomem-Michelson MB-100 FT/IR spectrophotometer neat on KBr plates.

Elemental analysis was performed on a CE Elemental Analyzer, model NC2500 (Carlo Erba) by the G.G. Hatch Isotope Laboratories of the department of earth sciences department of the University of Ottawa.

Reactions were monitored by thin-layer chromatography using Kieselgel 60 F_{254} precoated 0.25 mm thick aluminum backed plates and the compounds were detected by short wave UV light or by an ammonium molybdate solution (2.5% w/v). TLC plates were heated to 150 °C when necessary.

Purifications were performed by gravity or flash column chromatography on silica gel (230-400 mesh, E. Merck No. 9385).

All reactions, unless stated otherwise, were carried out in oven dried flasks under a nitrogen atmosphere. Methylene chloride was dried over CaH_2 and distilled prior to use. All chemical reagents were obtained from commercial suppliers and used as is, unless stated otherwise.

***1,4*-Bis-*(2,3,4,6-tetra*-O-*acetyl*-α-D-*mannopyranosyl)but-2-yne* (10)**

Trimethylsilyltrifluoroacetate ($CF_3SO_3Si(CH_3)_3$) (0.25 mL, 1.4 mmole) was added via a syringe to a solution of mannose pentaacetate (1.0 g, 2.7 mmol) and 2-butyne-1,4-diol (0.12 g, 1.4 mmol) in dry CH_2Cl_2 (50 mL), cooled to O°C and under a stream of N_2. The solution was allowed to come to room temperature and stirred for a further 6 hours after which time the reaction was judged complete by TLC (hexane/ ethyl acetate 1/1). The reaction mixture was washed with saturated $NaHCO_3$ (2x) and H_2O (2x). The organic layer was dried over $NaSO_4$, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel using gradient elution (hexane/ ethyl acetate 1/1 then hexane/ ethyl acetate 1/2). The compound was obtained as a white crystalline solid (0.2 g, 27% yield); m.p = 52 – 53 °C; $[\alpha]_D^{23}$ = + 68.9° (c=0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ(ppm) 5.30 (H-3, dd, $J_{2,3}$=3.9 Hz, $J_{3,4}$=10.0 Hz, 2H), 5.27 (H-4, dd, J=9.8 Hz, J=10.8 Hz, 2H), 5.23 (H-2, dd, $J_{1,2}$=1.8 Hz, $J_{2,3}$=3.2 Hz, 2H), 4.95 (H-1, d, J=1.6 Hz, 2H), 4.26 (H-6a, $^{-H_2C-\equiv}$, m, 6H), 4.07 (H-6b, m, 2H), 3.96 (H-5, m, 2H), 2.12, 2.12, 2.06, 1.95 ($COCH_3$, 4 s, 24H); ^{13}C NMR ($CDCl_3$, 125.7 Mhz,): δ(ppm) 170.5, 169.8, 169.7, 169.6 (C=O), 95.1 (C-1), 81.6 ($-C\equiv C-$), 69.3 (C-2), 68.9 (C-3, C-5), 68.9 (C-3, C-5), 66.0 (C-4), 62.3 (C-6), 54.9 ($^{-H_2C-\equiv}$), 20.7, 20.6, 20.6, 20.5 ($CO\underline{C}H_3$); HRMS (FAB) $[M+1]^+$ calcd for $C_{32}H_{42}O_{20}$: 747.23473; found: 747.2221 *m/z*

Synthesis of Monobenzene Mannoside Dimers

1,3-Bis-[1,1'(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)prop-2,2'-ynyl]benzene (13)

Nitrogen gas was bubbled through a solution of 2-propynyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (**5**) (1.3 g, 3.3 mmol) and 1,3-diiodobenzene (0.51 g, 1.5 mmol) in DMF-Et_3N (13 mL-13mL) for 25 minutes. Palladium tetrakis triphenylphosphine ($Pd(PPh_3)_4$) (0.17 g, 0.14 mmol) was added and the mixture was stirred under N_2 for 5 minutes. The reaction mixture was heated to 60 °C and stirred under a stream of N_2 for 4 hours after which time the reaction was judged complete by TLC (hexane/ethyl acetate 1/1). The reaction mixture was cooled and dissolved in diethylether – toluene (100 mL-50 mL), then washed with 2M HCl (2x), saturated $NaHCO_3$ soln. (1x), then with H_2O (1x). The crude extract was then purified by column chromatography in silica gel with hexane/ethyl acetate 2/3 as eluent. The product was obtained as a yellow crystalline solid (1.2 g, 88% yield); m.p. = 74 °C; $[\alpha]_D^{23}$ = 34 ° (c=1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz,): δ(ppm) 7.50 (C_6H_4, s, 1H), 7.38 (C_6H_4, dd, J=1.43 Hz; J=7.8 Hz, 2H), 7.36 (C_6H_4, d, J=7.9 Hz, 1H), 5.35 (H-3, dd, $J_{3,2}$=3.4 Hz, $J_{3,4}$=10.0 Hz, 2H), 5.28 (H-4, dd, J=10.0 Hz, J=10.0 Hz, 2H), 5.28 (H-2, dd, $J_{1,2}$=2.5 Hz, $J_{2,3}$=4.3 Hz, 2H), 5.06 (H-1, d, J=1.5 Hz, 2H), 4.46 ($^{-}H_2C-\equiv$, d, J=5.1 Hz, 4H), 4.27 (H-6a, dd, $J_{5,6a}$=5.2 Hz, $J_{6a,6b}$=12.3 Hz, 2H), 4.11-4.06 (H-6b, m, 2H), 4.04-4.01 (H-5, m, 2H), 2.13, 2.06, 2.01, 1.96 ($COCH_3$, 4 s, 24H); ^{13}C NMR ($CDCl_3$, 125.7 Mhz,): δ(ppm) 170.5, 169.8, 169.8, 169.6 (C=O), 134.9, 132.0, 128.5 (C_6H_4), 122.4 (C-ipso- C_6H_4), 96.2 (C-1), 86.1, 83.9 (—≡—), 69.4 (C-2, C-4),

69.0, 68.9 (C-3, C-5), 66.0 (C-2, C-4), 62.3 (C-6), 55.5 ($^{-}H_2C-\equiv$), 20.8, 20.6, 20.6, 20.6 ($CO\underline{C}H_3$); HRMS (FAB) $[M+K]^+$ calcd for $C_{40}H_{46}O_{20}K$ 885.2220; found: 885.2211 *m/z*

***1,2-Bis-[1,1'(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)prop-2,2'-ynyl]benzene* (14)**

Nitrogen gas was bubbled through a solution of 2-propynyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (**5**) (0.40g, 1.03 mmol) and 1,2-diiodobenzene (0.17 g, 0.51 mmol) in DMF-Et_3N (10 mL-10mL) for 25 minutes. Palladium tetrakis phosphine ($Pd(PPh_3)_4$) (0.054 mg, 0.047 mmol) was added and the mixture was stirred under N_2 for 5 minutes. The reaction mixture was heated to 60 °C and stirred under a stream of N_2 for 4 hours after which time the reaction was judged complete by TLC (hexane/ethyl acetate 1/1). The reaction mixture was cooled and dissolved in diethylether – toluene (100 mL-50 mL), then washed with 2M HCl (2x), saturated $NaHCO_3$ soln. (1x), then with H_2O (1x). The crude extract was then purified by column chromatography in silica gel with hexane/ethyl acetate 1/1 as eluent. The product was obtained as a yellow crystalline solid (0.3532 g, 82% yield); m.p. = 80 °C; $[\alpha]_D^{23}$ = 51.3 ° (c=1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz,): δ(ppm) 7.38 (C_6H_4, d, J=5.8 Hz, 1H), 7.37 (C_6H_4, d, J=5.8 Hz, 1H), 7.22 (C_6H_4, d, J=5.8 Hz, 1H), 7.21 (C_6H_4, d, J=5.8 Hz, 1H), 5.30 (H-3, dd, $J_{3,2}$=3.3 Hz, $J_{3,4}$=6.9 Hz, 2H), 5.28 (H-4, dd, J=9.6 Hz, J=10.5 Hz, 2H), 5.24 (H-2, dd, $J_{1,2}$=1.8 Hz, $J_{2,3}$=3.3 Hz, 2H), 5.08 (H-1, d, J=1.5 Hz, 2H), 4.49 ($^{-}H_2C-\equiv$, s, 4H), 4.23 (H-6a, dd, $J_{5,6a}$=4.9 Hz, $J_{6a,6b}$=12.3 Hz, 2H), 4.05-4.01 (H-5, H-6b, m,4H), 2.09, 2.00, 1.97, 1.91 ($COCH_3$, 4 s, 24H); ^{13}C NMR ($CDCl_3$,

125.7 Mhz,): δ(ppm) 170.4, 169.7, 169.6, 169.5 (C=O), 132.0, 128.3 (C_6H_4), 124.6 (C-ipso- C_6H_4), 96.2 (C-1), 87.3, 85.4 (–≡–), 69.3 (C-5), 68.9 (C-2), 68.9 (C-3), 65.9 (C-4), 62.1 (C-6), 55.6 ($^{-}H_2C$—≡), 20.8, 20.7, 20.5, 20.4 ($CO\underline{C}H_3$); HRMS (FAB) $[M+K]^+$ calcd for $C_{40}H_{46}O_{20}K$: 885.22; found: 885.38 *m/z*

Dibenzene Dimers

***4,4'-Bis-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)diphenylisopropane* (11)**

Boron trifluoride diethyl etherate (0.95 mL, 7.5 mmol) was added via a syringe to a solution of mannose pentaacetate (1.72 g, 4.4 mmol) and bisphenol A (0.49 g, 2.2 mmol) in dry CH_2Cl_2 (70 mL) cooled to O °C and under N_2. The solution was allowed to come to room temperature and was further stirred under a stream of N_2 for 24 hours, during which time reaction was judged complete by TLC (hexane/ ethyl acetate 1/1). The reaction mixture was washed with sat. $NaHCO_3$ (2x), 2M HCl(2x), and H_2O (2x). The organic layer was dried over $NaSO_4$, filtered and the solvent was removed under reduced pressure. The concentrate was purified by silica gel chromatography with hexane/ ethyl acetate 1/1 as eluent. The compound was obtained as white crystalline solid (0.8 g, 49% yield); m.p. = 79 °C; $[\alpha]_D^{23}$ = 62.7 ° (c=1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz,): δ(ppm) 7.10 (C_6H_4, d, J=8.8 Hz, 4H), 6.9 (C_6H_4, d, J=8.8 Hz, 4H), 5.52 (H-3, dd, $J_{3,2}$=3.4 Hz, $J_{3,4}$=10.0 Hz, 2H), 5.46 (H-1, s, 2H), 5.39 (H-2, dd, $J_{1,2}$=1.8 Hz, $J_{2,3}$=3.3 Hz, 2H), 5.33 (H-4, dd, J=10.0 Hz, J=10.0 Hz, 2H), 4.25 (H-6a, dd, $J_{5,6a}$=4.9 Hz, $J_{6a,6b}$=12.1 Hz, 2H), 4.11-4.03 (H-5, H-6b, m,4H), 2.12, 2.02, 2.00, 1.99 ($COCH_3$,

4 s, 24H), 1.60 (Ph-C(C<u>H</u>$_3$)$_2$, s, 6H); ^{13}C NMR ($CDCl_3$, 125.7 Mhz,): δ(ppm) 171.1, 170.45, 169.9, 169.9, 169.7 (C=O), 153.6, 145.2 (C-ipso- C_6H_4), 127.8, 127.7 (C_6H_4), 95.9 (C-1), 69.4 (C-5), 69.0 (C-2), 68.9 (C-3), 62.5 (C-4), 62.1 (C-6),), 41.9 (Ph-<u>C</u>(CH_3)$_2$), 30.9 (Ph-C(<u>C</u>H_3)$_2$), 21.0, 20.8, 20.6 (CO<u>C</u>H_3); HRMS (FAB) $[M+K]^+$ calcd for $C_{43}H_{52}O_{20}K$: 927.2689; found: 927.2997 *m/z*; Anal. Calcd for $C_{43}H_{52}O_{20}$: C 58.10, H 5.90; found: C 57.75, H 5.92

Synthesis of mono-alkyne dimers

***Bis-para-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)diphenylacetylene* (17)**

Nitrogen gas was bubbled through a mixture of 4-iodo-phenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (**1**) (1.0g, 1.81 mmol) in 30 mL of triethylamine. Dichloro-bis(triphenyl)phosphine palladium(II) ($PdCl_2(PPh_3)_2$) (0.014 g, 0.019 mmol) was added and the mixture was stirred under a stream of N_2 for 5 minutes. Copper (I) iodide (CuI) (0.025 g, 0.13 mmol) and triphenylphosphine (PPh_3) (0.012 g, 0.047 mmole) were added and stirring was continued under N_2 for a further 5 minutes. The reaction mixture was heated to 60 °C with acetylene gas bubbling through for 5 hours. The reaction was judged complete by TLC (hexane/ ethyl acetate 1/1). The solvent was removed under reduced pressure, redissolved in CH_2Cl_2 and washed with H_2O (2x). The organic extract was dried over $NaSO_4$, filtered and concentrated under reduced pressure. The concentrate was purified by silica gel chromatography with hexane/ ethyl acetate 1/1 as eluent. The compound was obtained as yellow crystalline solid (0.4598 g,

58% yield); m.p. = 89 °C; $[\alpha]_D^{23}$ = 117.5 ° (c=1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz,): δ(ppm) 7.40 (C_6H_4, dd, J=2.1 Hz, J=6.8 Hz, 4H), 7.01 (C_6H_4, dd, J=2.1 Hz, J=6.8 Hz, 4H), 5.48 (H-3, dd, $J_{2,3}$=3.5 Hz, $J_{3,4}$=9.9 Hz, 2H), 5.49 (H-1, d, J=1.8 Hz, 2H), 5.39 (H-2, dd, $J_{1,2}$=1.7 Hz, $J_{2,3}$=3.5 Hz, 2H), 5.30 (H-4, dd, J=10.0 Hz, J=10.0 Hz, 2H), 4.21 (H-6a, dd, $J_{5,6a}$=6.0 Hz, $J_{6a,6b}$=12.7 Hz, 2H), 4.03-4.00 (H-5, H-6b, m, 4H), 2.14, 2.00, 1.98, 1.97 ($COCH_3$, 4 s, 24H); ^{13}C NMR ($CDCl_3$, 125.7 Mhz,): δ(ppm) 170.4, 169.8, 169.8, 169.6 (C=O), 155.3 (Cipso-C_6H_4), 132.9, 116.5 (C_6H_4), 95.6 (C-1), 88.1 (—≡—), 69.2 (C-5), 69.2 (C-3), 68.7 (C-2), 65.8 (C-4), 62.0 (C-6), 20.7, 20.6 ($CO\underline{C}H_3$); HRMS FAB $[M]^+$ calcd for $C_{42}H_{46}O_{20}$: 870.26; found: 870.32*m/z*; Anal. Calcd for $C_{42}H_{46}O_{20}$: C 57.93, H 5.32; found: C 57.32, H 5.31

***Bis-para-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)diphenylacetylene* (18)**

Nitrogen gas was bubbled through a mixture of 4-iodo-phenyl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside (**4**) (0.98 g, 1.8 mmol) in 30 mL of triethylamine. Dichloro-bis(triphenyl)phosphine palladium(II) ($PdCl_2(PPh_3)_2$) (0.020 g, 0.029 mmol) was added and the mixture was stirred under a stream of N_2 for 5 minutes. Copper(I) iodide (CuI) (0.051 g, 0.27 mmol) was added and stirring was continued under N_2 for a further 5 minutes. The mixture was stirred at room temperature with acetylene gas bubbling through the solution for 24 hours. The reaction was judged complete by TLC (hexane/ ethyl acetate 1/1). The reaction mixture was dissolved in CH_2Cl_2 and washed with H_2O (2x). The organic extract was dried over $NaSO_4$, filtered and concentrated under reduced

pressure. The concentrate was purified by silica gel chromatography with hexane/ ethyl acetate 3/2 as eluent. The compound was obtained as yellow crystalline solid (0.6234 g, 80% yield); m.p. = 110-112 °C; $[\alpha]_D^{23}$ = + 14.0° (c=1.0, $CHCl_3$); IR (neat): 2936, 1751, 1228, 1067, 838 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ(ppm) 7.42 (C_6H_4, d, J=8.8 Hz, 4H), 6.9 (C_6H_4, d, J=8.8 Hz, 4H), 5.47 (H-2, dd, J=10.4, J=10.5 Hz, 2H), 5.4 (H-4, dd, J=2.7, J=3.4 Hz, 2H), 5.10 (H-3, dd, 2H, $J_{3,4}$=3.4 Hz, $J_{2,3}$=10.4 Hz, 2H), 5.05 (H-1, d, J=7.9 Hz, 2H), 4.21 (H-6a, dd, $J_{5,6a}$=7.1 Hz, $J_{6a,6b}$=11.4 Hz), 4.14 (H-6b, dd, $J_{5,6a}$=6.2 Hz, $J_{6a,6b}$=11.3 Hz, 2H), 4.06 (H-5, m, $J_{5,6a}$=7.1 Hz, $J_{6a,6b}$= 11.4 Hz, 2H), 2.16, 2.04, 2.04, 1.99 ($COCH_3$, 4 s, 24H); ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ(ppm) 170.3, 170.2, 170.1, 169.3, 156.6 (C=O), 134.0, 132.9, 118.2, 116.8 (C_6H_4), 99.3 (C-1), 88.2(−C≡C−), 71.1 (C-5), 70.8 (C-3), 68.6 (C-4), 66.8 (C-2), 61.3 (C-6), 20.7, 20.6, 20.5 ($CO\underline{C}H_3$); FAB-MS $[M+1]^+$ *m/z* (rel. intensity %) calcd for $C_{42}H_{47}O_{20}$: 871.27; found: 871.27 (0.2), 870.35 (0.4)

***4-ethynylphenyl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside* (19)**

Synthesis of **18** yielded 4-ethynylphenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (**19**) as side product (0.11 g, 14% yield, yellow crystalline solid); m.p. = 54 – 56 °C; $[\alpha]_D^{23}$ = + 4.0° (c=1.5, $CHCl_3$); IR (neat): 3279, 2936, 2108, 1748, 1235, 1065, 839 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz,): δ(ppm): 7.23 (C_6H_4, d, J=8.9 Hz, 2H), 6.91 (C_6H_4, d, J=8.9 Hz, 2H), 5.47 (H-2, dd, J=10.4, J=10.5 Hz, J=10.43 Hz, 1H), 5.44 (H-4, dd, J=3.4, J=3.5 Hz, 1H), 5.09 (H-3, dd, $J_{3,4}$=3.4 Hz, $J_{2,3}$=10.4 Hz, 1H), 5.03 (H-1, d, J=7.9 Hz, 1H), 4.20 (H-6a, dd,

$J_{5,6a}$=7.1 Hz, $J_{6a,6b}$= 11.4 Hz, 1H), 4.14 (H-6b, dd, $J_{5,6b}$=6.2 Hz, $J_{6a,6b}$=11.4 Hz, 1H), 4.05 (H-5, dd, $J_{5,6a}$=7.2 Hz, $J_{5,6b}$=7.1 Hz, 1H), 3.01 (—≡—H, s, 1H), 2.16, 2.04, 2.04 ($COCH_3$, 3 s, 12H); ^{13}C NMR ($CDCl_3$, 125.7 Mhz,): δ(ppm) 170.3, 170.1, 169.3 (C=O), 157.0 (Cipso- C_6H_4), 133.6 (C_6H_4), 117.0 (Cipso- C_6H_4), 117.0 (C_6H_4), 99.2 (C-1), 90.0, 76.6 (—c≡c—), 71.1 (C-5), 70.7 (C-3), 68.5 (C-2), 66.8 (C-4), 61.3 (C-6), 20.6, 20.6, 20.5 ($COCH_3$); FAB-MS $[M+1]^+$ *m/z* (rel. intensity %) calcd for $C_{22}H_{24}O_{10}$: 449.15; found 449.22 (1.2), 448.31 *m/z* (1.3)

***Bis-meta-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)diphenylacetylene* (20)**

Nitrogen gas was bubbled through a solution of 3-ethynylphenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (**8**) (0.33 g, 0.074 mmol) and 3-iodophenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (**2**) (0.82 g, 0.15 mmole) in Et_3N-DMF (20 mL-2mL) for 15 minutes. Palladium tetrakistriphenylphosphine ($Pd(PPh_3)_4$) (0.086 g, 0.0074 mmole) was added and the mixture was stirred under N_2 gas for 5 minutes. Reaction was continued at 60 °C under a stream of N_2 gas for 24 hours. Reaction was judged complete by TLC (hexane/ ethyl acetate 1/1). The reaction mixture was dissolved in $CHCl_3$ and washed with 2M HCl (3x), then with saturated $NaHCO_3$ (2x) then with H_2O (2x). The organic extract was dried over $NaSO_4$, filtered, and the solvent removed under reduced pressure. The concentrate was purified by column chromatography on silica gel (hexane/ethyl acetate 1/1). The compound was obtained as a yellowish crystalline powder (0.32 g, 100% yield); m.p. = 78 – 79 °C; $[\alpha]_D^{23}$ = + 126.0° (c=1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ(ppm) 7.26 (C_6H_4, m, 4H), 7.19 (C_6H_4, ddd, J=1.1 Hz,

J=2.3 Hz, J=7.7 Hz, 2H), 7.05 (C_6H_4, ddd, J=1.0 Hz, J=2.5 Hz, J=8.3 Hz, 2H), 5.53 (H-3, dd, $J_{2,3}$=3.5 Hz, $J_{3,4}$=10.3 Hz, 2H), 5.51 (H-1, d, J=2.00 Hz, 2H), 5.42 (H-2, dd, $J_{1,2}$=1.9 Hz, $J_{2,3}$=3.6 Hz, 2H), 5.33 (H-4, dd, J=10.2 Hz, J=10.1 Hz, 2H), 4.26 (H-6a, dd, $J_{5,6a}$=6.1 Hz, $J_{6a,6b}$=12.4 Hz, 2H), 4.09-4.07 (H-5, m, 2H), 4.06-4.04 (H-6b, m, 2H), 2.17, 2.03, 2.01, 2.01 ($COCH_3$, 4 s, 24H); ^{13}C NMR ($CDCl_3$, 125.7 Mhz,): δ(ppm) 170.5, 169.9, 169.8, 169.7 (C=O), 155.4, (Cipso-C_6H_4), 129.6, 126.4 (C_6H_4), 124.3 (Cipso- C_6H_4), 119.3, 117.2, (C_6H_4), 95.8 (C-1), 89.1 (−c≡c−), 69.3 (C-5), 69.2 (C-2), 68.8 (C-3), 66.0 (C-4), 62.1 (C-6), 20.8, 20.6, 20.6 ($COCH_3$); HRMS (FAB) $[M+K]^+$ calcd for $C_{42}H_{46}O_{20}K$: 909.2220; found: 909.2027 *m/z*

***Bis-ortho-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)diphenylacetylene* (22)**

Nitrogen gas was bubbled through a solution of 2-ethynylphenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (**9**) (0.33 g, 0.074 mmol) and 2-iodophenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (**3**) (0.10 g, 0.19 mmole) in Et_3N-DMF (20 mL-2mL) for 15 minutes. Palladium tetrakistriphenylphosphine ($Pd(PPh_3)_4$) (0.012 g, 0.010 mmole) was added and the mixture was stirred under N_2 gas for 5 minutes. Reaction was continued at 60 °C under a stream of N_2 gas for 22 hours. Reaction was judged complete by TLC (hexane/ ethyl acetate 1/1). The reaction mixture was dissolved in $CHCl_3$ and washed with 2M HCl (3x), then with saturated $NaHCO_3$ (2x) then with H_2O (2x). The organic extract was dried over $NaSO_4$, filtered, and the solvent removed under reduced pressure. The concentrate was purified by column chromatography on silica gel (hexane/ethyl

acetate 1/1). The compound was obtained as a yellowish crystalline powder (0.0424 g, 100% yield); m.p. = 148 °C; $[\alpha]_D^{23}$ = + 34.0° (c=1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ(ppm) 7.43 (C_6H_4, dd, J=1.5 Hz, J=7.6 Hz, 2H), 7.25 (C_6H_4, dd, J=1.6 Hz, J=8.5 Hz, 2H), 7.13 (C_6H_4, d, J=8.0 Hz, 2H), 7.07 (C_6H_4, ddd, J=0.9 Hz, J=7.6 Hz, J=8.3 Hz, 2H), 5.67 (H-3, dd, $J_{2,3}$=3.5 Hz, $J_{3,4}$=10.0 Hz, 2H), 5.64 (H-1, d, J=1.6 Hz, 2H), 5.59 (H-2, dd, $J_{1,2}$=1.8 Hz, $J_{2,3}$=3.4 Hz, 2H), 5.37 (H-4, dd, J=10.0 Hz, J=10.0 Hz, 2H), 4.29-4.23 (H-5/ H-6a, m, 4H), 4.04 (H-6b, d, $J_{5,6b}$=5.2 Hz, $J_{6a,6b}$=10.2 Hz, 2H), 2.17, 2.01, 1.96, 1.98, ($COCH_3$, 4 s, 24H); ^{13}C NMR ($CDCl_3$, 125.7 Mhz,): δ(ppm) 170.4, 169.7, 169.5 (C=O), 155.6 (Cipso- C_6H_4), 134.1, 129.6, 123.2, 115.3 (C_6H_4), 114.9 (Cipso- C_6H_4), 96.3 (C-1), 89.7 ($-C\equiv C-$), 69.9 (C-3), 69.4 (C-5), 69.3 (C-2), 65.9 (C-4), 62.0 (C-6), 20.8, 20.6, 20.6, 20.6 ($COCH_3$); HRMS (FAB) $[M+K]^+$ calcd for $C_{42}H_{46}O_{20}K$: 909.2220; found: 909.2176 *m/z*

Synthesis of di-alkynylated mannoside dimers

***Bis-para-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)diphenyl-but-1,3-diynyl* (24)**

4-ethynylphenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (**7**) (0.23 g, 0.52 mmol) and Copper(II) acetate [$Cu(Oac)_2H_2O$] (0.011 g, 0.054 mmol) were refluxed in pyridine (20 mL) under a stream of N_2 gas. Reaction was followed by TLC on silica gel (hexane/ ethyl acetate 1/1) and was judged complete after 48 hours. The reaction mixture was washed with 2M HCl (3x), then with saturated $NaHCO_3$ (2x) then with H_2O (2x). The organic extract was dried over $NaSO_4$,

filtered and the solvent was removed under reduced pressure. The concentrate was purified by column chromatography on silica gel with hexane ethyl acetate 1/1 as eluent. The compound was obtained as yellow crystalline powder (0.1084 g, 47% yield); m.p. = 89-88 °C; $[\alpha]_D^{23}$ = + 79.0° (c=1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz,): δ(ppm) 7.63 (C_6H_4, d, J=8.6 Hz, 4H), 7.06 (C_6H_4, d, J=8.7 Hz, 4H), 5.53 (H-3, dd, $J_{2,3}$=3.5 Hz, $J_{3,4}$=8.0 Hz, 2H), 5.43 (H-1, s, 2H), 5.44 (H-2, dd, $J_{1,2}$=1.8 Hz, $J_{2,3}$=3.5 Hz, 2H), 5.34 (H-4, dd, J=10.0 Hz, J=10.1 Hz, 2H), 4.26 (H-6a, dd, $J_{5,6a}$=5.2 Hz, $J_{6a,6b}$=12.4 Hz, 2H), 4.09-4.03 (H-5, H-6b, m, 4H), 2.20, 2.05, 2.04, 2.02 ($COCH_3$, 4 s, 24H); ^{13}C NMR ($CDCl_3$, 125.7 Mhz,): δ(ppm) 170.4, 169.9, 169.8, 169.6 (C=O), 156.0 (Cipso-C_6H_4), 134.1, 116.6 (C_6H_4), 95.6 (C-1), 80.8, 73.5 (—≡—), 69.4 (C-5), 69.2 (C-2),68.7 (C-3), 65.9 (C-4), 62.0 (C-6), 20.8, 20.6, 20.6 ($CO\underline{C}H_3$); HRMS (FAB) $[M+K]^+$ calcd for $C_{44}H_{46}O_{20}K$: 933.2220; found: 933.1648 *m/z*

***Bis-meta-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)diphenyl-but-1,3-diynyl* (21)**

3-ethynylphenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (**8**) 0.10 g 0.22 mmol) and copper (II) acetate [$Cu(Oac)_2H_2O$] (0.0044 g, 0.022 mmol) were refluxed in pyridine (10 mL) under a stream of N_2 gas. The reaction was followed by TLC on silica gel (hexane/ ethyl acetate 1/1) and was judged complete after 48 hours. The reaction mixture was washed with 2M HCl (3x), then with saturated $NaHCO_3$ (2x) then with H_2O (2x). The organic extract was dried over $NaSO_4$, filtered and the solvent was removed under reduced pressure. The concentrate was purified by column chromatography on silica gel using

gradient elution (hexane ethyl acetate 2/1 then hexane/ ethyl acetate 1/1). The compound was obtained as yellow crystalline powder (0.058 g, 58% yield); m.p. = 85 °C; $[\alpha]_D^{23}$ = + 73.8° (c=2.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ(ppm) 7.28 (C_6H_4, m, 2H), 7.25 (C_6H_4, d, J=8.0 Hz, 2H), 7.21 (C_6H_4, ddd, J=1.2 Hz, J=2.5 Hz, J=8.0 Hz, 2H), 7.08 (C_6H_4, ddd, J=1.2 Hz, J=2.5 Hz, J=8.1 Hz, 2H), 5.51 (H-3, dd, $J_{2,3}$=3.5 Hz, $J_{3,4}$=10.0 Hz, 2H), 5.48 (H-1, d, J=1.8 Hz, 2H), 5.41 (H-2, dd, $J_{1,2}$=1.8 Hz, $J_{2,3}$=3.5 Hz, 2H), 5.32 (H-4, dd, J=10.0 Hz, J=10.0 Hz, 2H), 4.25 (H-6a, dd, $J_{5,6a}$=6.465 Hz, $J_{6a,6b}$=12.642 Hz, 2H), 4.12-4.04 (H-5, H-6b, m, 4H), 2.18, 2.04, 2.03, 2.01 ($COCH_3$, 4 s, 24H); ^{13}C NMR ($CDCl_3$, 125.7 Mhz): δ(ppm) 170.6, 169.9, 169.9, 169.715 (C=O), 155.4 (Cipso-C_6H_4), 129.8, 127.4, (C_6H_4), 123.0 (Cipso- C_6H_4), 120.2, 118.3 (C_6H_4), 95.9 (C-1), 81.1, 74.1 (−c≡c−), 69.3 (C-2/ C-5), 68.8 (C-3), 66.0 (C-4), 62.2 (C-6), 20.8, 20.6, 20.6 ($CO\underline{C}H_3$); HRMS (FAB) $[M+K]^+$ calcd for $C_{44}H_{46}O_{20}K$: 933.2220; found: 933.2387 *m/z*

***Bis-ortho-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)diphenyl-but-1,3-diynyl* (23)**

2-ethynylphenyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (**9**) (0.12 g, 0.27 mmol) and copper(II) acetate ($Cu(Oac)_2H_2O$) (0.0029 g, 0.014 mmole) were refluxed in pyridine (10 mL) under a stream of N_2 gas. Reaction was followed by TLC on silica gel (hexane/ ethyl acetate 1/1) and was judged complete after 24 hours. The reaction mixture was washed with 2M HCl (3x), then with saturated $NaHCO_3$ (2x) then with H_2O (2x). The organic extract was dried over $NaSO_4$, filtered and the solvent was removed in vacuo. The concentrate was purified by column chromatography on silica gel using gradient elution (hexane ethyl acetate

1/1 then ethyl acetate: pure). The compound was obtained as yellow crystalline powder (0.078 g, 63% yield); m.p. = 74-76 °C; $[\alpha]_D^{23}$ = + 5.3° (c=1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ(ppm) 7.56 (C_6H_4, dd, J=1.8 Hz, J=7.7 Hz, 2H), 7.3 (C_6H_4, ddd, J=1.7 Hz, J=8.0 Hz, J=8.4 Hz, 2H), 7.10 (C_6H_4, d, J=8.1 Hz, 4H), 7.03 (C_6H_4, m, 2H), 5.64 (H-3, dd, $J_{2,3}$=3.5 Hz, $J_{3,4}$=10.0 Hz, 2H), 5.59 (H-1, d, J=1.8 Hz, 2H), 5.55 (H-2, dd, $J_{1,2}$=1.9 Hz, $J_{2,3}$=3.5 Hz, 2H), 5.36 (H-4, dd, J=9.9 Hz, J=9.9 Hz, 2H), 4.30-4.23 (H-5, H-6a, m, 4H), 4.11-4.05 (H-6b, m, 2H), 2.17, 2.01, 2.01, 1.99, ($COCH_3$, 4 s, 24H); ^{13}C NMR ($CDCl_3$, 125.7 Mhz,): δ(ppm) 170.04, 169.8, 167.8, 169.4 (C=O), 157.3 (Cipso-C_6H_4), 134.5, 130.3, 123.2, 116.0 (C_6H_4), 113.6 (Cipso- C_6H_4), 96.8 (C-1), 79.5, 77.7 (−c≡c−), 69.5 (C-5), 69.4 (C-2), 68.7 (C-3), 65.9 (C-4), 62.1 (C-6), 21.0, 20.5, 20.6, 20.6 ($CO\underline{C}H_3$); HRMS (FAB) $[M+K]^+$ calcd for $C_{44}H_{46}O_{20}K$: 933.2220; found: 933.2621 *m/z*

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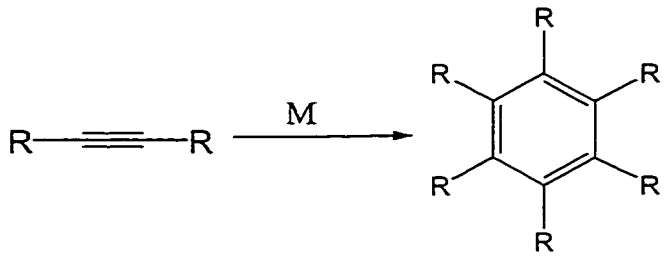
Chapter 4. Cyclotrimerization Products

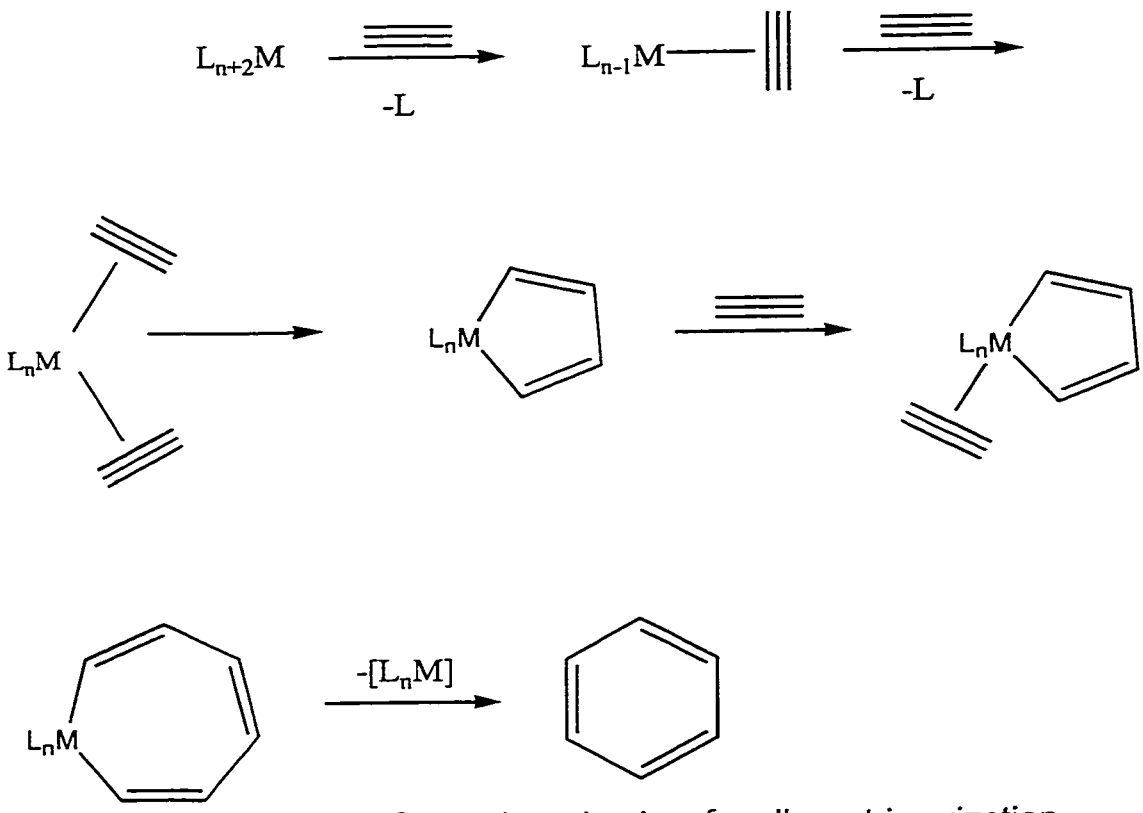
4.1. Introduction

Transition metal catalyzed cyclotrimerization of acetylene to benzene derivatives provide an elegant route to a novel class of dendrimers containing a benzene core. Acetylenes and substituted acetylenes undergo cycloaddition in one step in the presence of a metal catalyst (Scheme 4.1.1). This carbocyclization is a well-known reaction and can be achieved with many transition metals including Co[1], Ni[2], Pd[3], Cr[4], Rh[5], Fe[8a], Ta[6] and more recently, activated Zr-Ti.[7] This topic has been extensively reviewed.[1a,8]



Scheme 4.1.1. [2+2+2] cycloaddition of of alkynes.

A common mechanism for this type of reaction is illustrated in Scheme 4.1.2.[8a,8c] Two alkyne molecules coordinate respectively to a single metal center. Oxidative coupling occurs resulting in the formation of a metallacyclopentadiene and oxidation of the metal, thus opening a coordination site. A third alkyne molecule may insert to give a transient metallacycloheptatriene.[8a,8c] Finally, a benzene product is released.

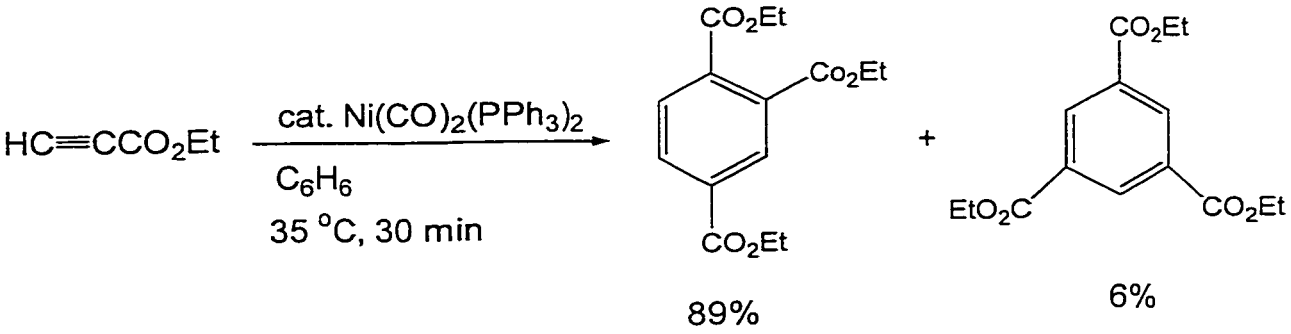


Scheme 4.1.2. General mechanism for alkyne trimerization.

The reaction proceeds with high chemo- , regio- and stereoselectivity. Cyclotrimerization of unsymmetrical substituted alkynes typically produces benzene with the larger substituents in positions 1,2 and 4.[8a] This can be explained by the preference in the oxidative coupling step to link the least hindered alkyne carbons.

Cr(VI) catalyst[8a] trimerizes propyne to give a 4:1 ratio of 1,2,4-trimethylbenzene to 1,3,5-trimethylbenzene. Phosphine nickel carbonyls are often highly selective although their reactivity is limited mostly to terminal alkynes, preferably with electron-withdrawing substituents.[2a](Scheme 4.1.3). $Co_2(CO)_8$ is generally a more reactive catalyst for intermolecular [2+2+2] alkyne

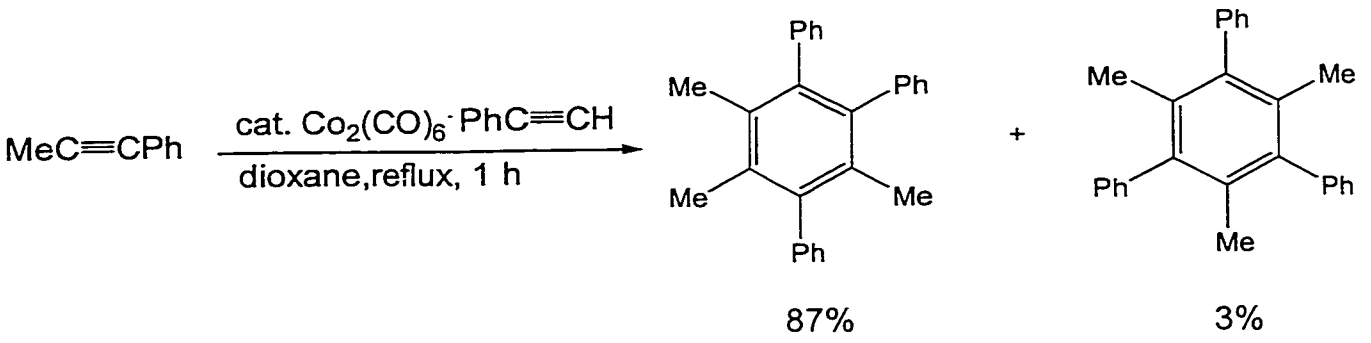
cyclization.[8c] They often give both high yields and selectivities, especially in dioxane as solvent (Scheme 4.1.4).



Scheme 4.1.3. Trimerization by phosphine nickel carbonyl.

The mechanism for $Co_2(CO)_8$ catalyzed trimerization is characterized by the formation of dinuclear complexes and a "flyover complex" intermediate prior to the trimerized product[8a] (Scheme 4.1.5).

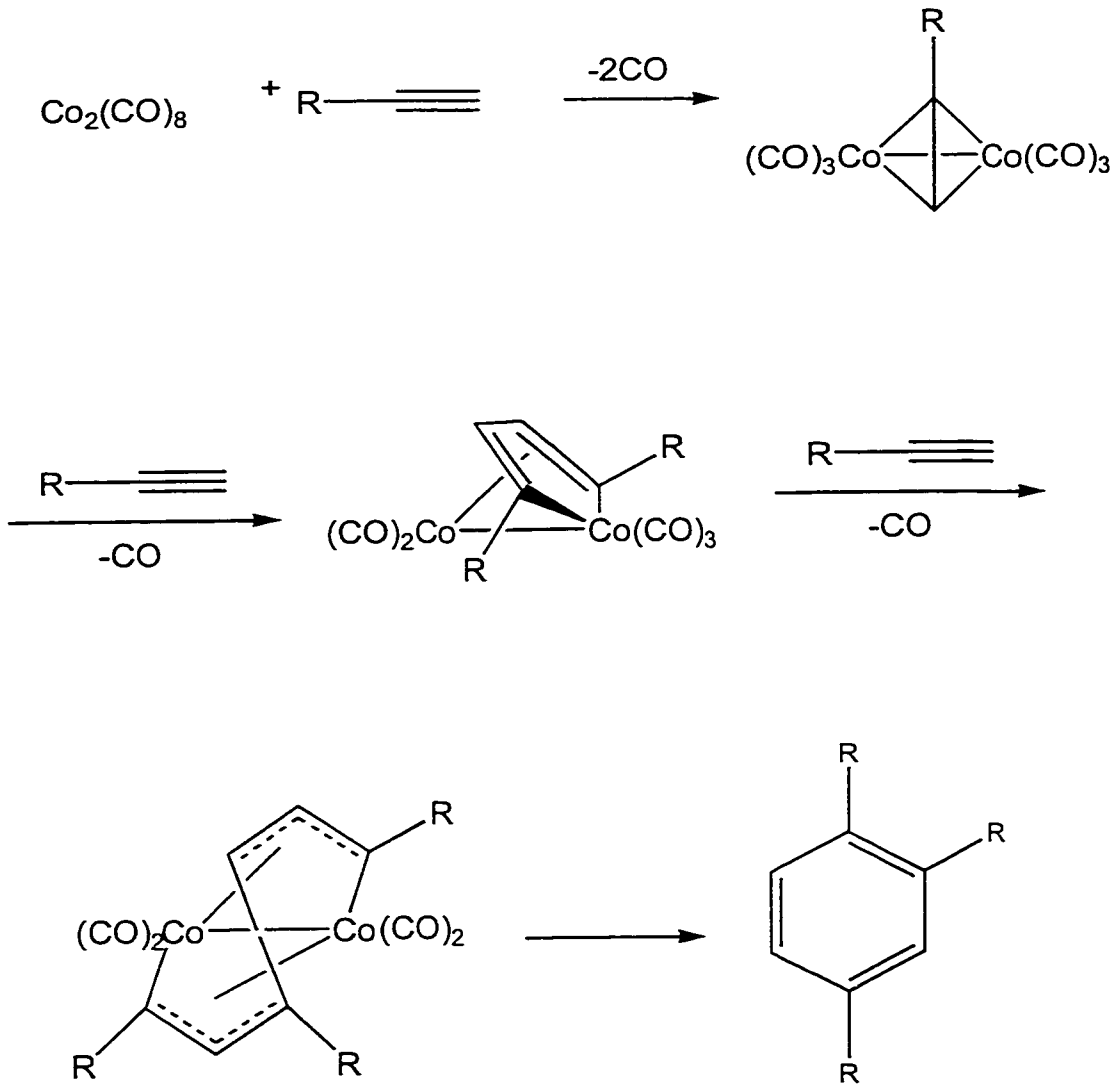
(η^5-indenyl)$Rh(C_2H_4)_2$ favors the trimerization of 3,3-dimethyl-1-butyne (t-butylacetylene) giving rise to 1,2,4-tri(t-butyl)benzene in 76% yield and only 8% of the 1,3,5-isomer.[9]



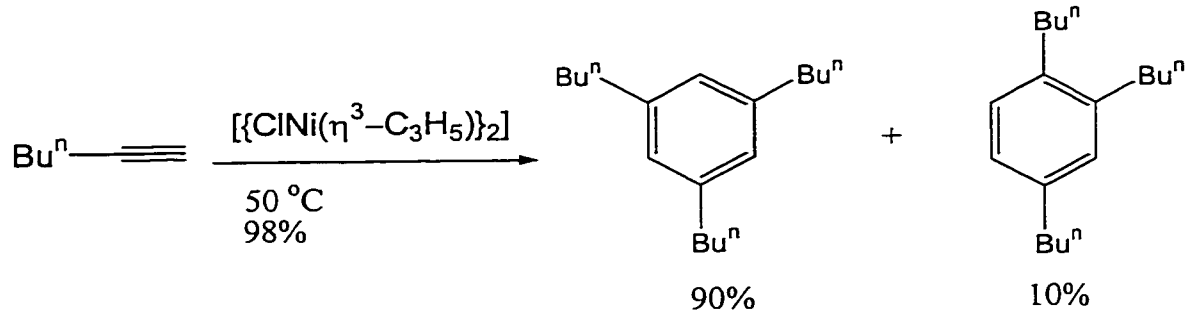
Scheme 4.1.4. Cobalt catalyzed cyclotrimerization.

Certain Ni based catalysts favors the 1,3,5-trisubstituted benzene as product. $(Bu_3P)NiBr_2$ converted (S)-3-methyl-1-butyn-3-ol exclusively into the corresponding 1,3,5-trisubstituted benzene in moderate yield[10]. $[(\eta^3\text{-allyl})NiCl]_2$ yields the 1,3,5-trisubstituted benzenes from terminal alkynes in good yields[8c] (Scheme 4.1.6).

$PdCl_2$ favors the formation of the 1,3,5-trisubstituted benzene. It was shown that this reaction follows a different mechanism that involves a ring-closure subsequent to a cylclopentadienyl methyl metal derivative.[11, 3a] Other high-valent metal catalysts such as $NbCl_5$[8a] appear to involve similar steps in the mechanism as $PdCl_2$ (sequential insertion and non-formation of the metallacyclopentadiene). Regioselectivity however varies from one system to the next.



Scheme 4.1.5. Mechanism for $Co_2(CO)_8$ catalyzed alkyne trimerization.



Scheme 4.1.6. 1,3,5-regioisomer preferred in Ni catalyzed alkyne trimerization.

Other transition metals that catalyze intermolecular [2+2+2] alkyne cyclization are : $AlCl_3$,[8a] Me_3SiCl/ Pd/C,[8c] Ziegler type catalysts such as $TiCl_4/Albu^i_3$,[8a] $TiCl_4/AlEt_2Cl$,[12] commercial heterogeneous catalysts such as K_2CrO_4 on silica /alumina support, and activated metal catalysts (prepared by the reduction of the corresponding metal halide with alkali metals in an ethereal solvent) such as Zr-Ti.[7] There are more reports for intramolecular[1a,1c-i] [2+2+2] alkyne cycloaddition than intermolecular cycloaddition.[1a,1b]

The only report on cyclotrimerization of neoglygoconjugates was in 1980 by Kaufman and Sidhu.[13]

4.2. Results and Discussion

4.2.1. Trimers

The next target was the construction of clusters consisting of a benzene core surrounded by pendant monosaccharide groups. $Co_2(CO)_8$ catalyzed cyclotrimerization of glycosylated acetylenes achieved the goals.

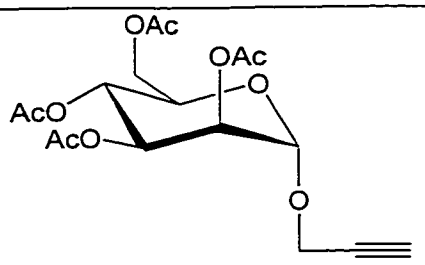
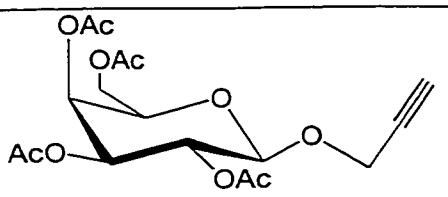
Sugar trimers having three pendant monosaccharide moieties tethered on a benzene core was constructed (**26**, **27**). The clusters were synthesized in one step from 2-propynyl glycosides using $Co_2(CO)_8$ (10 mole %) as catalyst. The reaction proceeded at reflux under nitrogen gas. Good yields (60%) were obtained in about 2 hours reaction time. The same synthesis was reported[13] involving long reaction times (5.5 days for the galactoside and 21 days for the mannoside trimer) and lower yields (30-41%).

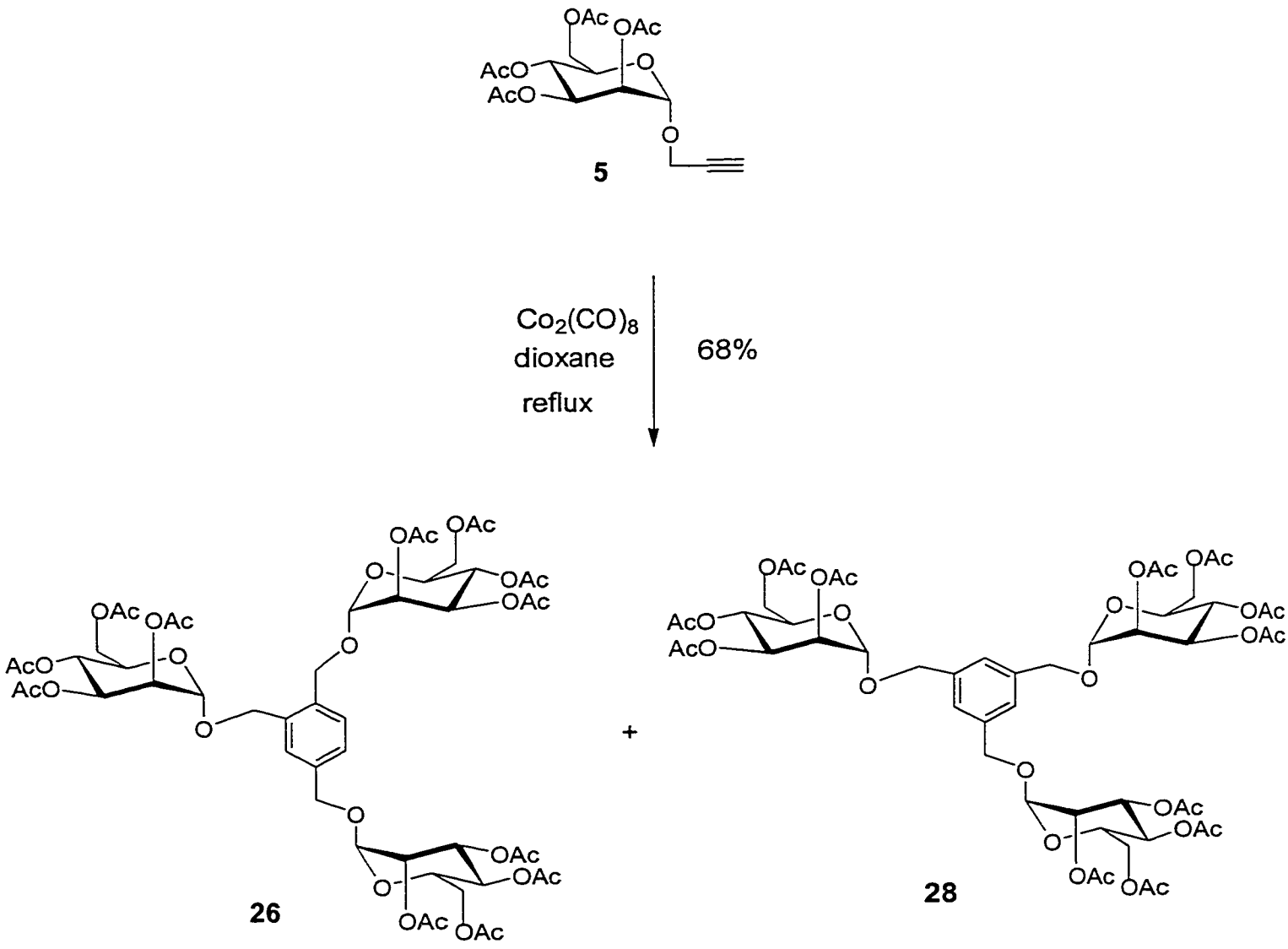
Consistent with the mechanism, the 1,2,4-regioisomer (**26**, **27**) was preferred over the 1,3,5-regioisomer (**28**, **29**) in a 9:1 ratio. The two regioisomers showed the same Rf on TLC. The ratio was established by comparing the intensity of the ^1H NMR C_6H_4 peaks. In the case of the mannosyl derivative, the 1,2,4 regiosiomer (**26**) showed aromatic peaks at δ 7.37 ppm (d, J=7.8 Hz), 7.31 (dd, J=1.2 Hz, J=7.5 Hz), 7.28 (s), while the 1,3,5-regioisomer (**28**) showed an aromatic peak signal at δ 7.23 (s) ppm. In the case of the galactosyl derivative, the 1,2,4 regioisomer (**27**) showed aromatic peaks at δ 7.30 ppm (d, J=7.8Hz), 7.24 (s), 7.2 (dd, J=1.5, J=7.8 Hz), while the 1,3,5-regioisomer (**29**) showed an aromatic peak signal at δ 7.15 (s) ppm.

The presence of 1,3,5 regioisomer was further established by ^{13}C signals at 137.1 ppm (C_6H_4- 1,3,5 isomer) for the mannosyl 1,3,5 trimer (**28**) and 137.4 ppm (C_6H_4- 1,3,5 isomer) for the galactosyl 1,3,5 trimer (**29**).

The reaction proceeded with retention of the anomeric configuration. Thus, the α-1-*O*-mannosyl trimer (**26**) and the β-1-*O*-galactosyl trimer (**27**) were obtained.

Table 4.2.1. Synthesis of sugar trimers.

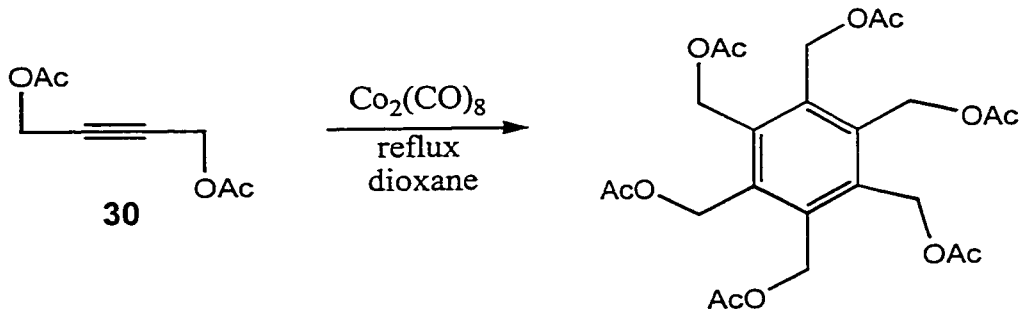
propynyl glycoside		yield (%)	Trimer
5		68	**26**
6		63	**27**



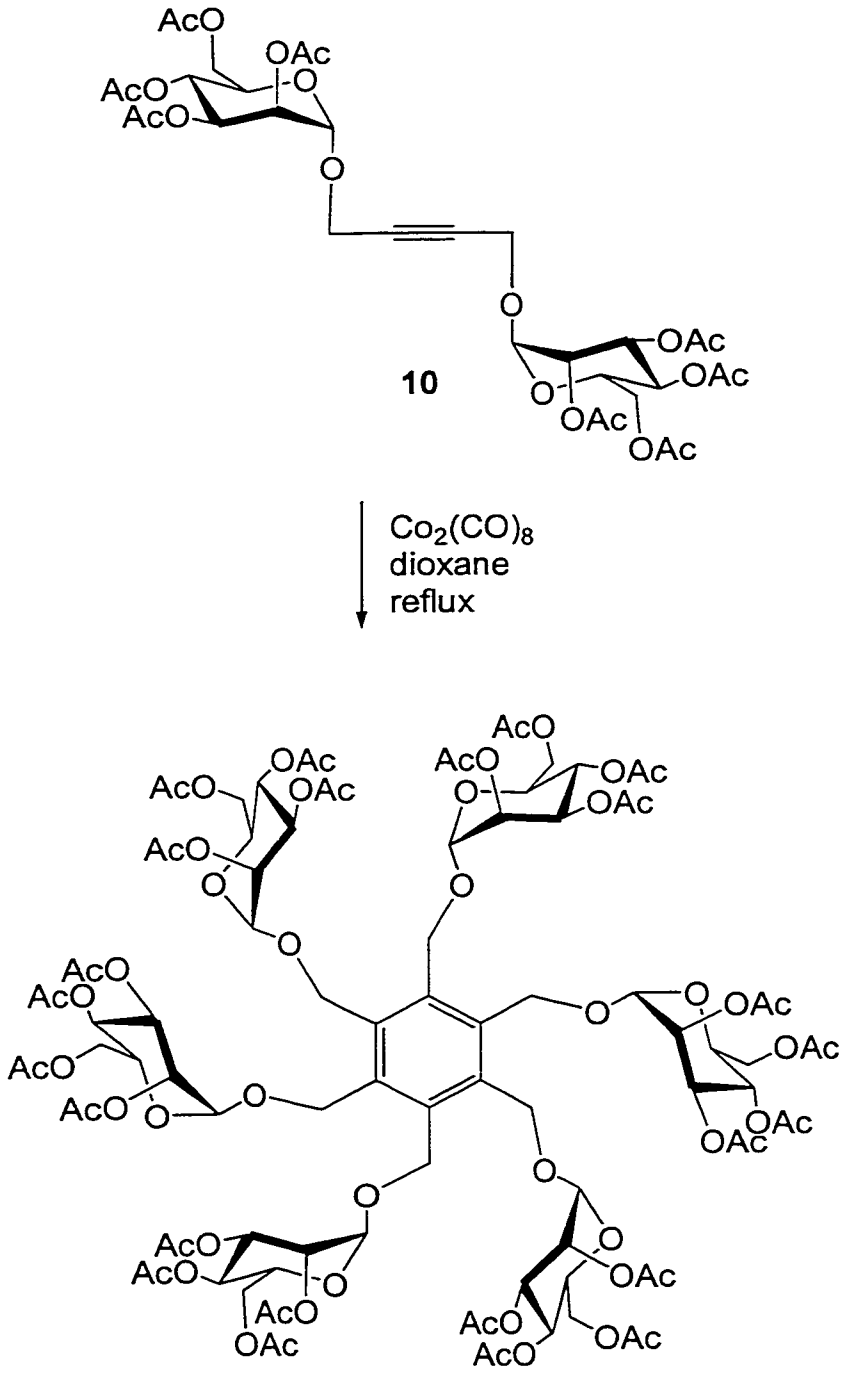
Scheme 4.2.1. Trimerization of 2-propynyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (**5**).

4.2.2. Hexamers

A novel class of multivalent glycoconjugates was synthesized consisting of a benzene core fully substituted with monosaccharides. By cyclotrimerization of symmetrically substituted acetylenes, different variants were generated. The reaction proceeded under the same conditions as the trimerization ($Co_2(CO)_8$ (15 mole%, refluxing dioxane).[13] The hexamers (**31**, **32**, **33**, **34**) were obtained in good yields (39-64 %) at short reaction times (2-24 hours). (Scheme 4.2.2, Scheme 4.2.3, Scheme 4.2.4, Scheme 4.2.5). The reaction proceeded with retention of anomeric configuration. Thus, the anomeric proton of mannose retained its α position in the hexamer and that of the galactose retained its β position (Fig.4.2.3).



Scheme 4.2.2. Cyclotrimerization of 2-butyn-1,4-diacetate.



32

Scheme 4.2.3. Cyclotrimerization of 1,4-bis-(2,3,4,6-tetra-O-α-D-mannopyranosyl)but-2-yne (**10**).

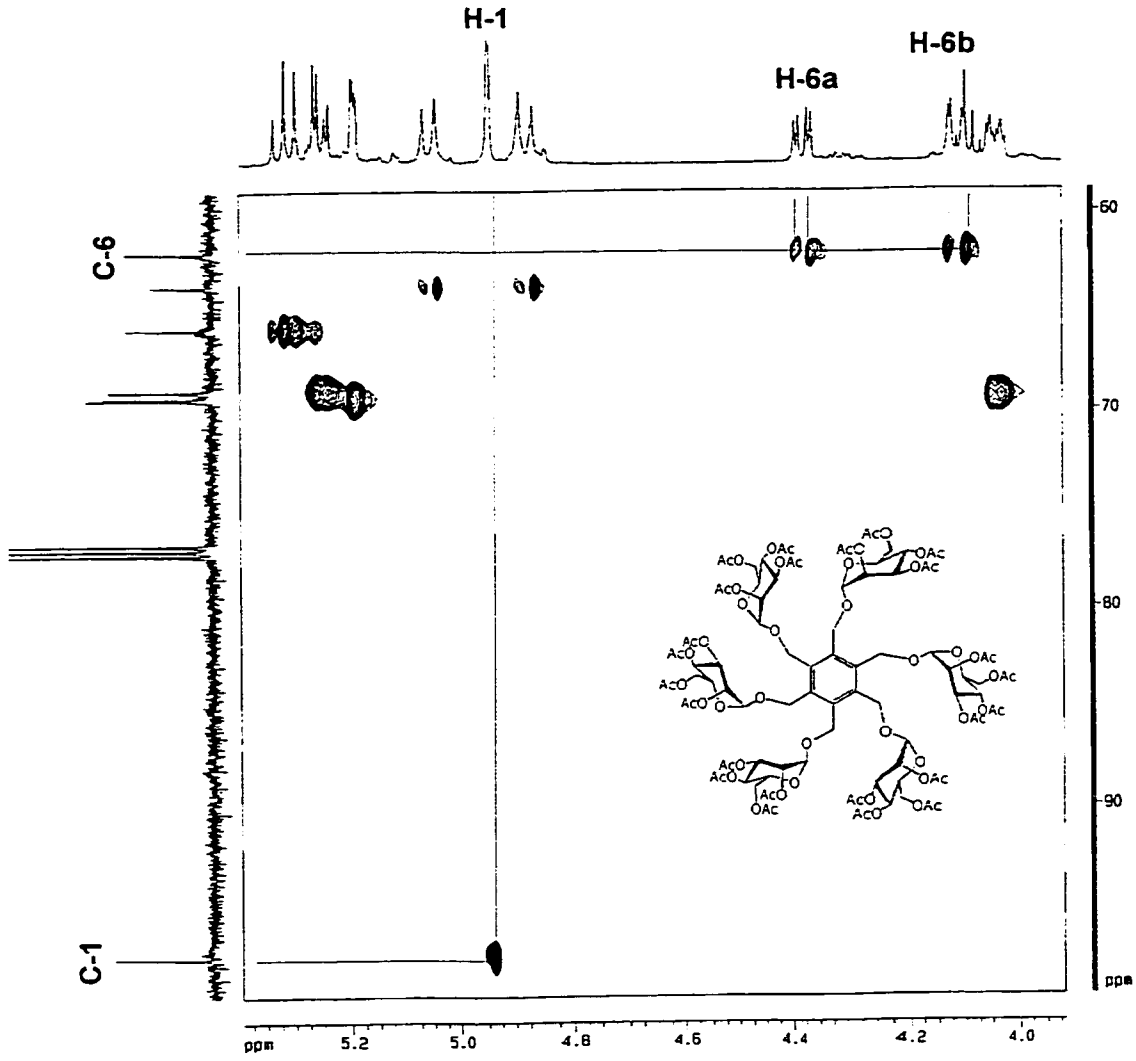


Figure 4.2.1. HMQC ($CDCl_3$) of mannopyranoside hexamer **32**.

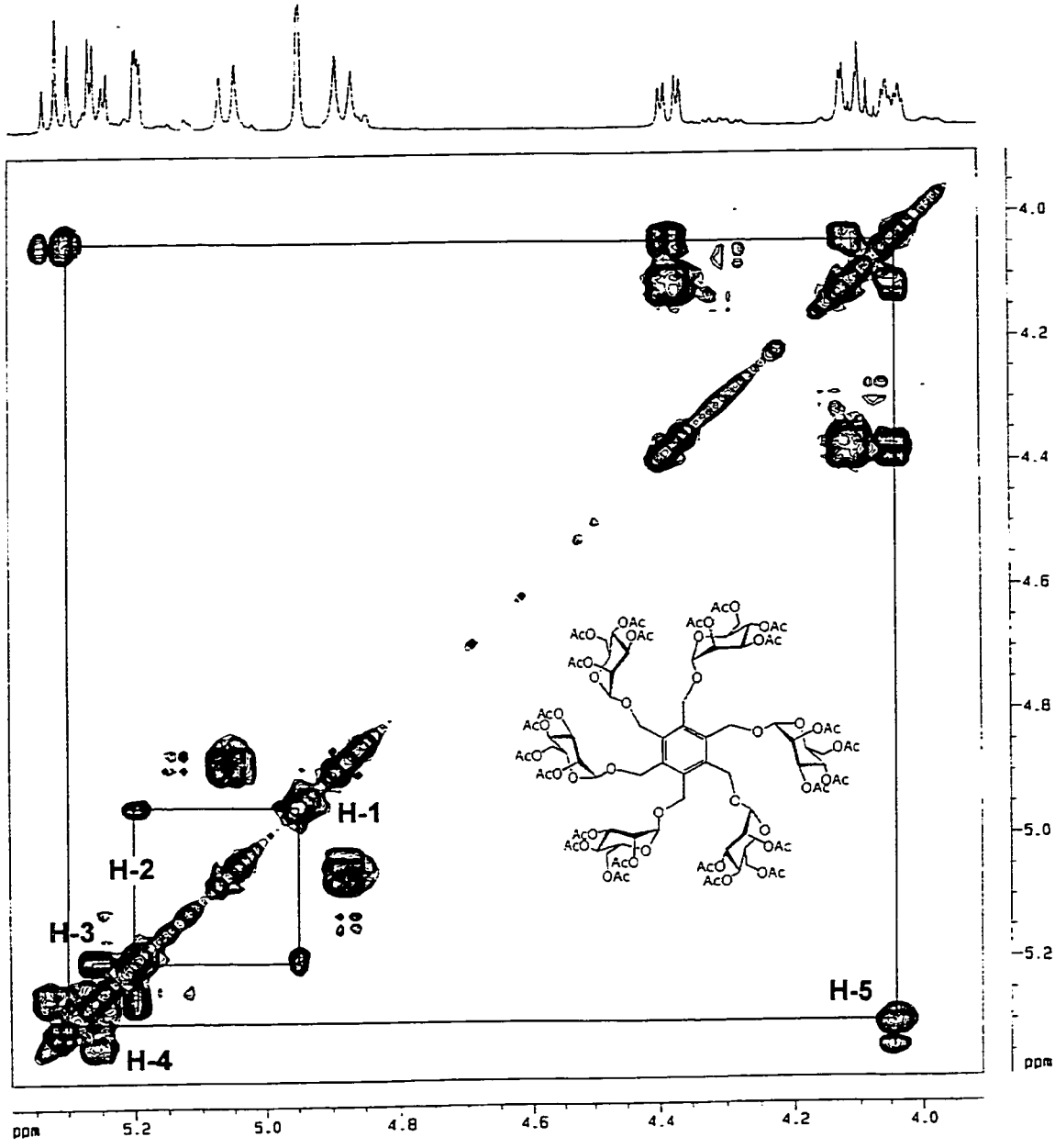
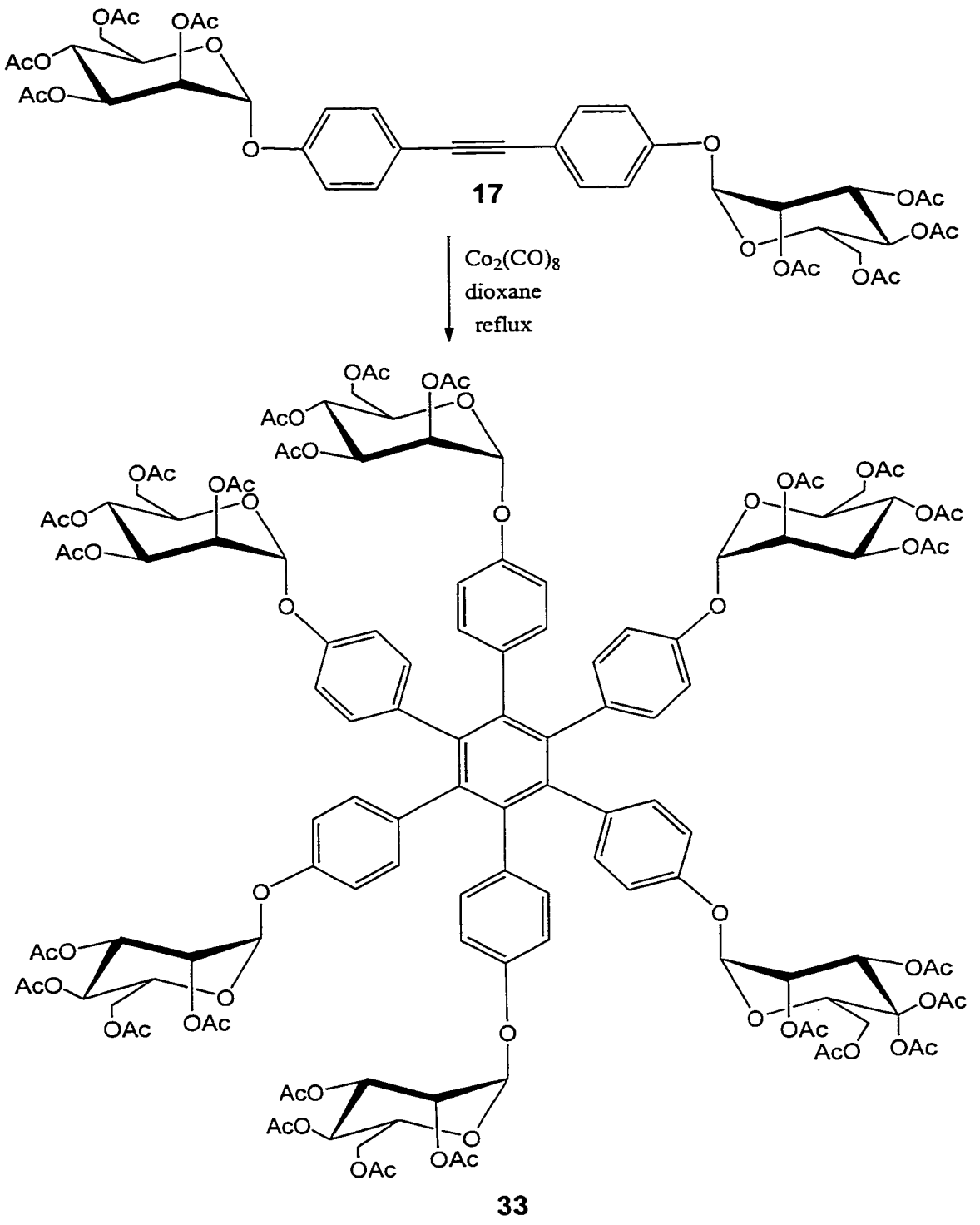
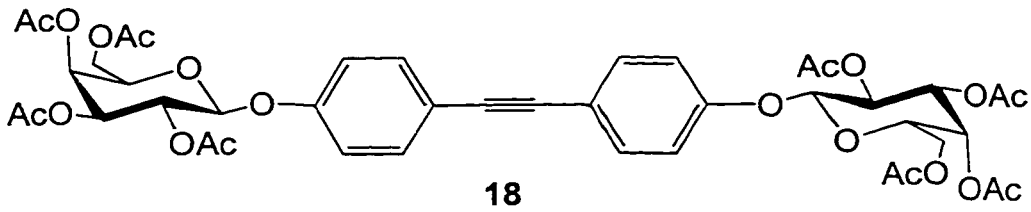


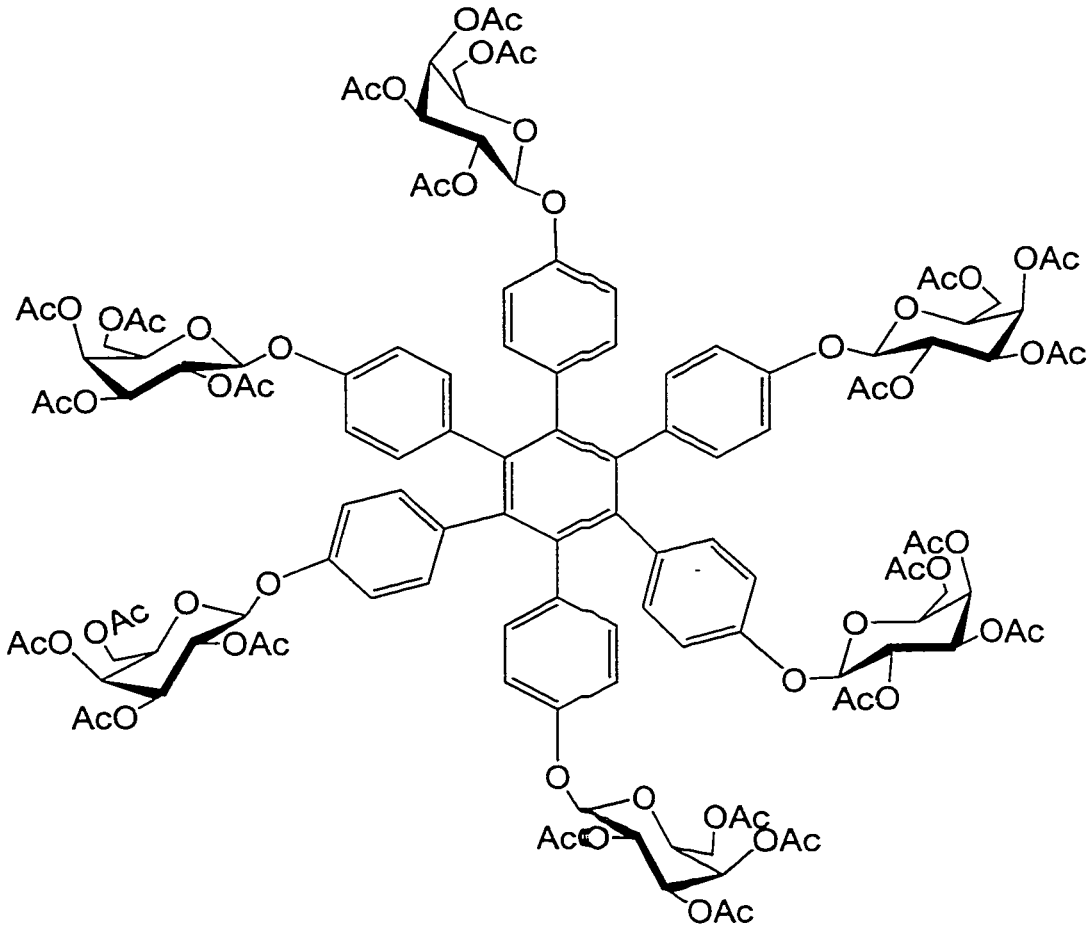
Figure 4.2.2. COSY ($CDCl_3$) of mannopyranoside hexamer **32**.



Scheme 4.2.4. Cyclotrimerization of bis-para-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)diphenylacetylene (**17**)



18



34

Scheme 4.2.5. Cyclotrimerization of bis-para-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)diphenylacetylene (**18**).

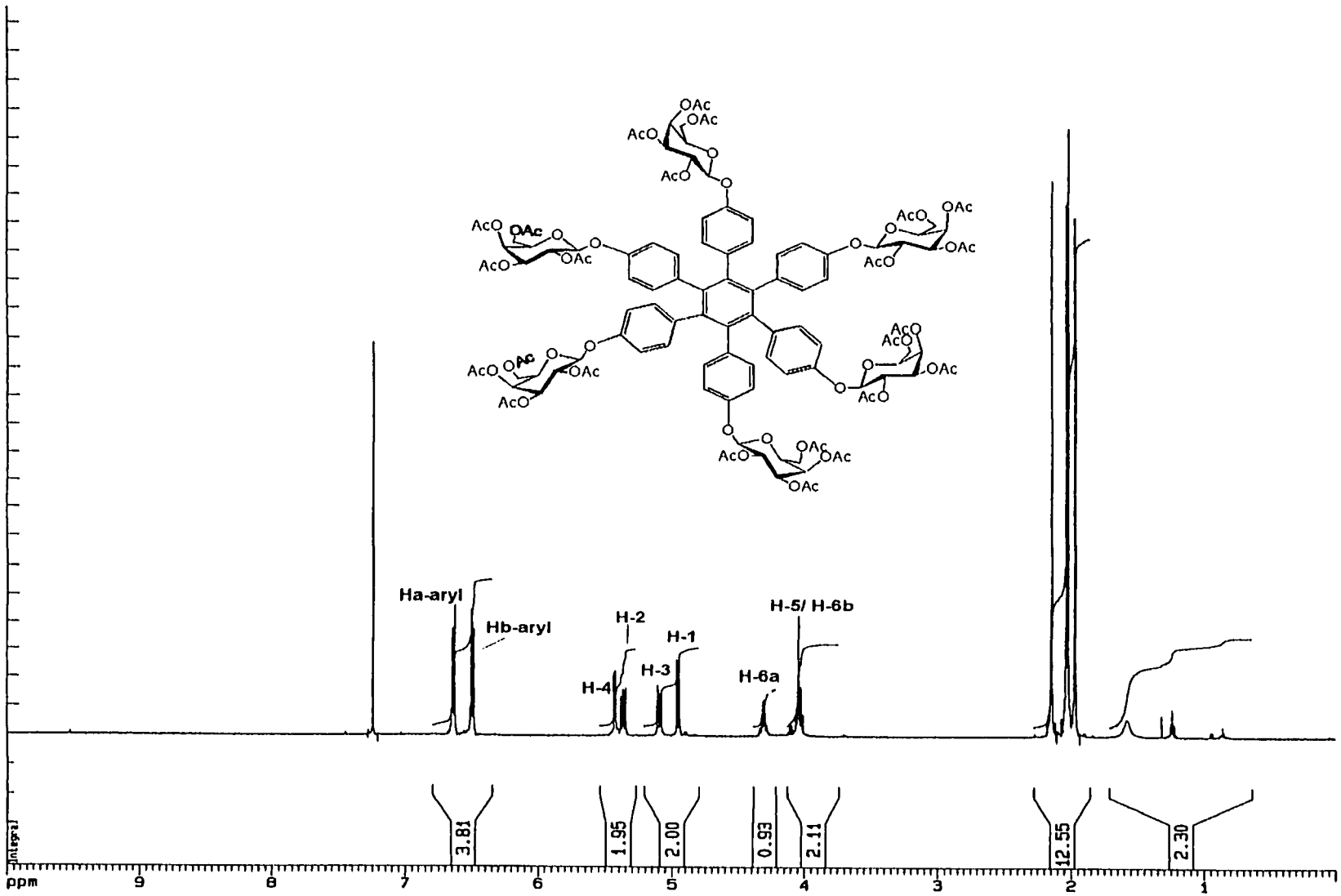


Figure 4.2.3. ^{1}H NMR (500 MHz, $CDCl_3$) of galactopyranoside hexamer **34.**

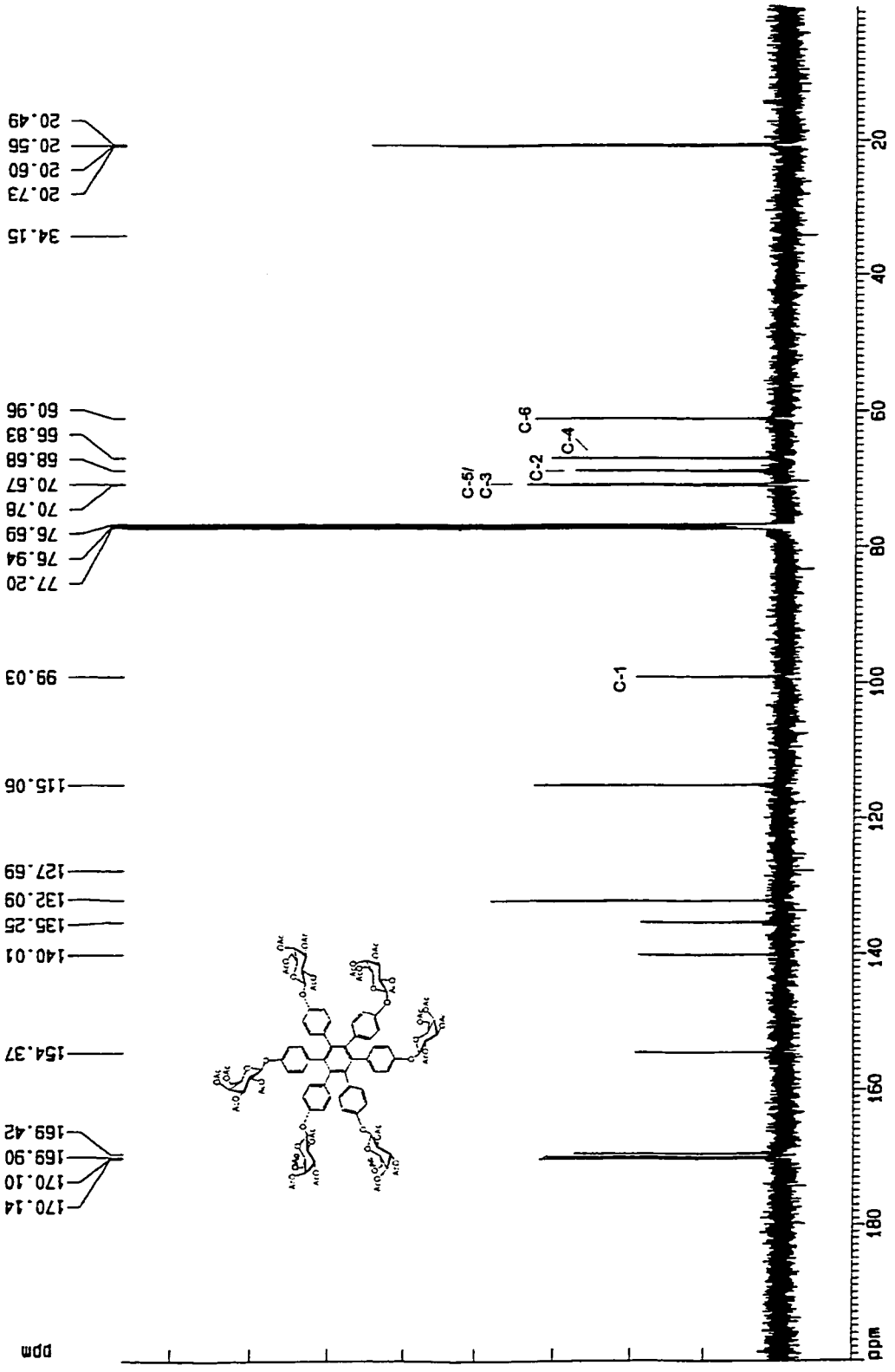


Figure 4.2.4. ^{13}C NMR (500 MHz, $CDCl_3$) of galactopyranoside hexamer **34**.

Table 4.2.2. Synthesis of hexamers.

dimer		hexamer	yield %	Reaction time (h)
2-butyn-1,4-diacetate	**30**	**31**	39	2
1,4-Bis-(2,3,4,6-tetra-O-acetyl)but-2-yne	**10**	**32**	61	20
Bis-para-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)diphenylacetylene	**17**	**33**	42	24
Bis-para-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)diphenylacetylene	**18**	**34**	64	17

4.3 Conclusion

Sugar clusters were successfully synthesized in one step by $Co_2(CO)_8$ catalyzed cyclotrimerization of the corresponding acetylene-containing glycosides. Good yields were obtained under shorter reaction periods than were previously reported.[13]

The glycosidic conjugates were shown to be stable to the cyclotrimerization conditions catalyzed by $Co_2(CO)_8$. As expected from the mechanism, the unsymmetrically substituted glycosidc acetylenes, preferentially formed the 1,2,4 regioisomer.

Most of the trimerizations reported usually involve internal acetylenes. Thus, it was shown that symmetrically substituted glycosidic acetylenes undergo trimerization with $Co_2(CO)_8$ as catalyst.

4.4. Experimental Methods

General Method

^{1}H NMR and ^{13}C NMR spectra were obtained from either a Varian Gemini-200 or a Bruker AMX500 spectrometer at 500, and 200 MHz for protons and 125.7 and 50.3 MHz for carbons, respectively. Proton chemical shifts are given relative to internal chloroform (7.24 ppm) for $CDCl_3$ solutions. Carbon chemical shifts are given relative to $CDCl_3$ (77.0 ppm). Special analyses were performed by the first order approximations and were based on shift correlation spectroscopy (COSY), heteronuclear multiple quantum coherence (HMQC), and 1- and 2-dimensional distortionless enhancement by polarization transfer (DEPT) experiments. Multiplicities of the NMR signals were reported using the following abbreviations: singlet (s), broad singlet (bs), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), multiplet (m).

Mass spectra were recorded on a Kratos IIH (FAB-KI-glycerol or FAB-glycerol) instrument. Xenon was used as the neutral carrier atom in FAB-MS experiments.

Elemental analysis was performed on a CE Elemental Analyzer, model NC2500 (Carlo Erba) by the G.G. Hatch Isotope Laboratories of the department of earth sciences of the university of Ottawa.

Melting points were determined on a Gallenkamp apparatus and are uncorrected.

Optical rotation ($[\alpha]_D$) values were determined using a Perkin-Elmer (model 241) set at the sodium D line (589 nm) and were run at room temperature.

Infrared spectra were obtained on a Bomem-Michelson MB-100 FT/IR spectrophotometer neat on KBr plates.

Reactions were monitored by thin-layer chromatography using Kieselgel 60 F_{254} precoated 0.25 mm thick aluminum backed plates and the compounds were detected by short wave UV light or by an ammonium molybdate solution (2.5% w/v). TLC plates were heated to 150 °C when necessary.

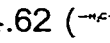
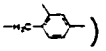
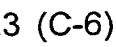
Purifications were performed by gravity or flash column chromatography on silica gel (230-400 mesh, E. Merck No. 9385).

All reactions, unless stated otherwise, were carried out in oven dried flasks under a nitrogen atmosphere. 1,4 dioxane was distilled prior to use. All chemical reagents were obtained from commercial suppliers and used as is, unless stated otherwise.

Cyclotrimerization of Acetylenic Sugars: Synthesis of Sugar Trimers

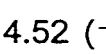
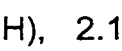
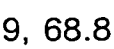
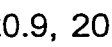
1,2,4-Tris-{[(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)oxy]methyl}= benzene (26)

A solution of 2-propynyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (**5**) (0.51 g, 1.3 mmol) in 5 mL freshly distilled 1,4-dioxane was refluxed under a stream of N_2 gas. After 5 minutes of reflux, dicobalt octacarbonyl ($Co_2(CO)_8$) (0.045 g, 0.13 mmol) was added. The reaction mixture was refluxed for a further 2 hours, after which time, the reaction was judged complete by TLC on silica gel (ethyl

acetate/ toluene 6.4/ 3.2). The solvent was evaporated under reduced pressure and the concentrate was purified by column chromatography on silica gel with hexane/ethyl acetate 1/ 2 as eluent. The cyclotrimerized product was obtained as white crystalline powder (0.0.32 g, 63 % yield).; m.p.=: 74 °C; $[\alpha]_D^{23}$ = +56.0° (c=1.5, $CHCl_3$); Lit.[4] $[\alpha]_D^{23}$ = +77.8° (c=1.0 $CHCl_3$); ^1H NMR ($CDCl_3$, 500 Mhz,): δ(ppm) 7.37 (H_a-C_6H_4, d, 1H, J=7.8 Hz, 1H), 7.3 (H_b- C_6H_4, dd, 1H, J=1.2 Hz, J=7.5 Hz, 1H), 7.28 (H_c- C_6H_4, s, 1H), 7.23 (C_6H_4- 1,3,5 isomer, s), 5.33 (H-3, m,3H), 5.28 (H-4, m, 3H), 5.20 (H-2, m, 3H), 4.83 (H-1, m, 3H), 4.27 (H-6a, m, 3H), 4.07 (H-6b, m, 3H), 4.00 (H-5, m, 3H), 4.62 ( , m, 6H), 2.10 2.09, 2.08, 2.00, 1.99, 1.94, 1.93 ($COCH_3$, overlapping singlets, 36 H); ^{13}C NMR ($CDCl_3$, 125.7 Mhz,): δ(ppm) 170.6, 170.5, 169.8, 169.7, 169.7, 169.6, 169.6, 169.5 (C=O), 137.1 (C_6H_4- 1,3,5 isomer), 136.7, 135.0, 134.8, 130.0, 129.3, 128.1 (C_6H_4-1,2,4 isomer), 127.4 (C_6H_4- 1,3,5 isomer), 96.9, 96.8, 96.7 (C-1), 69.5, 69.4, 69.4 (C-2), 69.2, 69.0, 69.0 (C-3), 68.9 () , 68.8, 68.7 (C-5), 67.4, 66.8 (), 66.1, 66.0, 66.0 (C-4), 62.4, 62.3 (C-6), 21.0, 20.8, 20.7, 20.6, 20.5 ($CO\underline{C}H_3$); FAB-MS $[M+K]^+$ *m/z* (rel. intensity, %) : calcd for $C_{51}H_{66}O_{30}K$: 1197.33; found: 1197.42 (0.4)

***1,2,4-Tris-{[(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)oxy]methyl}= benzene* (27)**

A solution of 2-propynyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (**6**) (0.12 g, 0.30 mmol) in 5 mL freshly distilled 1,4-dioxane was refluxed under a stream of N_2 gas. After 5 minutes of reflux, dicobalt octacarbonyl ($Co_2(CO)_8$) (0.014 g,

0.041 mmol) was added. The reaction mixture was refluxed for a further 2 hours, after which time, the reaction was judged complete by TLC on silica gel (ethyl acetate/ toluene 6.4/ 3.2). The solvent was evaporated under reduced pressure and the concentrate was purified by column chromatography on silica gel with hexane/ethyl acetate 1:2 as eluent. The cyclotrimerized product was obtained as white crystalline powder (0.070 g, 60 % yield); m.p. = 99 °C; $[\alpha]_D^{23}$ = -51.7° (c=2.3, $CHCl_3$); Lit[1] $[\alpha]_D^{23}$ = + 77.0°; ^1H NMR ($CDCl_3$, 500 Mhz): δ(ppm) 7.30 (H_a-C_6H_4, d, 1H, J=7.8 Hz, 1H), 7.24 (H_c-C_6H_4, s, 1H), 7.20 (H_b-C_6H_4, dd, J=1.5, J= 7.8 Hz, 1H), 7.15 (C_6H_4-1,3,5 isomer), 5.35 (H-4, dd, J=1.8, J=1.4 Hz, 3H), 5.20 (H-2, m, 3H), 4.98 (H-3, m, 3H), 4.50 (H-1, m, 3H), 4.52 ( , m, 3H), 4.58 ( , m, 3H), 4.12 (H-6, m, 6H), 3.89 (H-5, m, 3H), 2.12, 2.11, 2.11, 2.02, 2.01, 1.99, 1.96, 1.94, 1.93, 1.93, 1.93, 1.90 ($COCH_3$, overlapping singlets, 36 H); ^{13}C NMR ($CDCl_3$, 125.7 Mhz): δ(ppm) 170.3, 170.1, 170.0, 170.0, 169.2 (C=O), 137.4 (C_6H_4-1,3,5 isomer), 136.8, 135.0, (Cipso- C_6H_4), 128.8 (C_a- C_6H_4), 128.2 (C_c- C_6H_4), 127.4 (C_b- C_6H_4), 126.6 (C_6H_4-1,3,5 isomer), 100.1, 100.0, 99.9 (C-1), 70.8, 70.7 (C-3/ C-5), 70.3 (), 68.9, 68.9, 68.8 (C-2), , 68.6, 68.1 (), 67.0, 67.0 (C-4), 61.2, 61.1, 61.1 (C-6), 20.9, 20.6, 20.6, 20.6, 20.5 ($CO\underline{C}H_3$); FAB-MS $[M+K]^+$calcd for $C_{51}H_{66}O_{30}K$: 1197.33; found: 1198.40 *m/z*

***Acetic acid pentakis-acetoxymethyl-benzyl ester* (31)**

A solution of 2-butyn-1,4-diacetate (**30**) (1.0 g, 6.0 mmol) in 5 mL freshly distilled 1,4-dioxane was refluxed under a stream of N_2 gas. After 5 minutes of reflux, dicobalt octacarbonyl ($Co_2(CO)_8$) (0.31 g, 0.90 mmol) was added. The reaction mixture was refluxed for a further 2 hours, after which time, the reaction was judged complete by TLC on silica gel (hexane/ ethyl acetate 1/1). The solvent was evaporated under reduced pressure and the concentrate was purified by column chromatography on silica gel with hexane/ethyl acetate 1/1 as eluent. The cyclotrimerized product was obtained as white crystalline powder (0.40 g, 39 % yield); m.p. = 157 - 158°C; $[\alpha]_D^{23}$ = 0.0° (c=1.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ(ppm) 5.36 (Ph-CH_2, s, 12H), 2.03 ($COCH_3$, s, 18H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ(ppm) 170.3 (C=O), 137.6 (C_6H_4), 72.4 (Ph-$\underline{C}H_2$), 20.8 (CO$\underline{C}H_3$); FAB MS $[M+1]^+$ *m/z* (rel. intensity %) calculated for $C_{24}H_{30}O_{12}$: 510.17; found 510.44 (0.7)

***1,2,3,4,5,6-Hexakis-{[(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)oxy]= methyl}benzene* (32)**

A solution of 1,4-Bis-(2,3,4,6-tetra-O-α-D-mannopyranosyl)but-2-yne (**10**) (0.59 g, 0.79 mmole) in 5 mL freshly distilled 1,4-dioxane was refluxed under a stream of N_2 gas. After 5 minutes of reflux, dicobalt octacarbonyl ($Co_2(CO)_8$) (0.040 g, 0.12 mmol) was added. The reaction mixture was refluxed for a further 20 hours,

after which time, the reaction was judged complete by TLC on silica gel (ethyl acetate/ toluene 10/ 1). The solvent was evaporated under reduced pressure and the concentrate was purified by column chromatography on silica gel with $CHCl_3$/ ethyl acetate 1/10 as eluent. The cyclotrimerized product was obtained as white crystalline powder (0.36 g, 61 % yield); m.p. = 102 - 104°C; $[\alpha]_D^{23}$ = + 87.0 ° (c=1.0, $CHCl_3$); IR (neat) 2940, 1750, 1435, 1371, 1226, 1083, 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ(ppm) 5.30 (H-4, dd, J=9.9, J=9.9 Hz, 6H), 5.25 (H-3, dd, $J_{2,3}$=3.4 Hz, $J_{3,4}$=10.1 Hz, 6H), 5.19 (H-2, dd, $J_{1,2}$=1.7 Hz, $J_{2,3}$=3.4 Hz, 6H), 5.05 (Ph-C$\underline{H}_2$, d, J=12 Hz, 6H), 4.94 (H-1, d, J=1.4 Hz, 6H), 4.88 (Ph-C$\underline{H}_2$', d, J=12 Hz, 6H), 4.38 (H-6a, m, $J_{5,6a}$=3.9 Hz, $J_{6a,6b}$=12.5 Hz, 6H), 4.11 (H-6b, dd, $J_{5,6a}$=2.6 Hz, $J_{6a,6b}$=12.5 Hz, 6H), 4.05 (H-5, m, 6H), 2.11, 2.08, 1.99, 1.91 ($COCH_3$, 4 s, 72H); ^{13}C NMR ($CDCl_3$, 125.7 Mhz): δ(ppm) 170.6, 169.9, 169.7, 169.6 (C=O), 137.7 (C_6H_4), 97.554 (C-1), 69.4, 69.3 (C-2, C-5), 69.0 (C-3), 65.9 (C-4), 63.7 (Ph-$\underline{C}H_2$), 62.0 (C-6) 20.8, 20.6, 20.6, 20.6 (CO$\underline{C}H_3$); HRMS (FAB) $[M+K]^+$ calcd for $C_{96}H_{126}O_{60}K$: 2279.6513; found 2279.6592 *m/z*; Anal. Calcd for $C_{96}H_{126}O_{60}$: C 51.47, H 5.67; found: C 51.37, H 5.79

***Hexakis-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)hexaphenylbenzene* (33)**

A solution of bis-para-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)diphenyl= acetylene (**17**) (0.35 g, 0.40 mmol) in 5 ml freshly distilled 1,4-dioxane was refluxed under a stream of N_2 gas. After 5 minutes of reflux, dicobalt octacarbonyl ($Co_2(CO)_8$) (0.019 g, 0.056 mmol) was added. The reaction mixture was refluxed for a further 24 hours, after which time, the reaction was judged

complete by TLC on silica gel (ethyl acetate/ toluene 6.4/ 1.5). The solvent was evaporated under reduced pressure and the concentrate was purified by column chromatography on silica gel with hexane/ ethyl acetate 1/ 4 as eluent. The cyclotrimerized product was obtained as yellow crystalline powder (0.14 g, 42 % yield); m.p. = 85 °C; $[\alpha]_D^{23}$ = + 0.0 ° (c=1.1, $CHCl_3$); ; IR 2940, 1750, 1435, 1371, 1226 cm^{-1}; ^1H NMR ($CDCl_3$, 500 Mhz): δ(ppm) 6.62 (C_6H_4, d, J=8.749 Hz, 12H), 6.58 (C_6H_4, d, J=8.466 Hz, 12H), 5.40 (H-3), dd, $J_{2,3}$=3.7 Hz, $J_{3,4}$=10.0 Hz, 6H), 5.26 (H-2, H-4, dd, J=9.7 Hz, J=10.7 Hz, 12H), 5.24 (H-1, s, 6H), 4.20 (H-6a, dd, $J_{5,6a}$=5.2 Hz, $J_{6a,6b}$=12.5 Hz, 6H), 3.93 (H-5, H-6b, m, 12H), 2.10, 2.00, 1.99, 1.98, 1.94, 1.94 ($COCH_3$, overlapping singlets, 72H); ^{13}C NMR ($CDCl_3$, 125.7 Mhz): δ(ppm) 170.3, 169.8, 169.7, 169.7, (C=O), 153.3, 139.9, 135.3, 132.3, 115.2 (C_6H_4), 96.0 (C-1), 69.4, 69.2, 69.0, 68.8 (C-2, C-3, C-5), 65.8 (C-4), 20.9, 20.7, 20.6 ($CO\underline{C}H_3$); FAB-MS $[M+K]^+$ *m/z* (rel. intensity %) calcd for $C_{126}H_{138}O_{60}$: 2649.74; found: 2650.70 (0.1)

***Hexakis-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)hexaphenylbenzene* (34)**

A solution of bis-para-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)diphenyl= acetylene (**18**) (0.12 g, 0.13 mmol) in 5 mL freshly distilled 1,4-dioxane was refluxed under a stream of N_2 gas. After 5 minutes of reflux, dicobalt octacarbonyl ($Co_2(CO)_8$) (0.0060 g, 0.018 mmol) was added. The reaction mixture was refluxed for a further 17 hours, after which time, the reaction was judged complete by TLC on silica gel (ethyl acetate/ toluene 6.4/ 1.5). The solvent was evaporated under reduced pressure and the concentrate was

purified by column chromatography on silica gel with hexane/ ethyl acetate 1/ 5 as eluent. The cyclotrimerized product was obtained as brown crystalline powder (0.075 g, 64 % yield); m.p. = 328 °C; $[\alpha]_D^{23}$ = + 144.2 ° (c=1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 Mhz): δ(ppm) 6.64 (Ha-C_6H_4, d, J=8.8 Hz, 12H), 6.49 (Hb-C_6H_4, d, J=8.8 Hz, 12H), 5.43 (H-4, d, J=3.5 Hz), 5.37 (H-2, dd, J=10.4 Hz, J=10.0 Hz, 6H), 5.09 (H-3, dd, $J_{3,4}$=3.4 Hz, $J_{2,3}$=10.5 Hz, 6H), 4.95 (H-1, d, J=8.0 Hz, 6H), 4.31 (H-6a, dd, $J_{5,6a}$=4.6 Hz, $J_{6a,6b}$=8.3 Hz, 6H), 4.03 (H-5, H-6b, m, 12H), 1.97, 2.02, 2.03, 2.14 ($COCH_3$, 4s, 72H); ^{13}C NMR ($CDCl_3$, 125.7 Mhz): δ(ppm) 170.1, 169.9, 169.4 (C=O), 154.4, 140.0, 135.2 (Cipso-C_6H_4), 132.1 (C_b-C_6H_4), 115.1 (C_a-C_6H_4), 99.0 (C-1), 70.8 (C-5), 70.7 (C-3), 68.7 (C-2), 66.8 (C-4), 61.0 (C-6), 20.7, 20.6, 20.5 ($CO\underline{C}H_3$); FAB-MS $[M+K]^+$ *m/z* (rel. intensity %) calcd for $C_{126}H_{138}O_{60}$ 2649.74; found: 2650.09 (0.5)

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Chapter 5. Binding Studies with ConA.

5.1. Introduction

In the past 20 years, a great stride in the understanding of carbohydrate-protein interaction was made due to insights gained from lectin-carbohydrate binding.[1]

Goldstein et al defined a lectin as "a carbohydrate-binding protein (or glycoprotein) of non-immune origin which agglutinates cells and/ or precipitates glycoconjugates".[2]

Of this class, plant lectins exhibit low specificity; i.e. they are selective and differ in the type of carbohydrate structures they recognize with low affinity.[3]

Binding occurs in the so-called carbohydrate recognition domain (CRD) of lectins.[4] Factors that influence binding are: the presence of both calcium and a transition metal ion[6], hydrogen bonding, van der Waals interactions between aromatic residues (Tyr12 in Conacanavalin A.)[5] and hydrophobic interactions with side chain atoms of Tyr12, Leu 99 and Tyr 100.[5] The carbohydrate recognition domain (CRD) of lectins typically consists of hydrogen bonding from backbone and side chain amide group donors to oxygen lone pair acceptors and from carbohydrate hydroxy group donors to backbone and side chain carbonyls.[4]

Multivalent lectins are known to form crosslinked complexes with a multivalent ligand.[3] In many cases, this results in an insoluble complex or a

precipitate. Biophysical methods takes advantage of this phenomenon to measure carbohydrate-protein interactions.

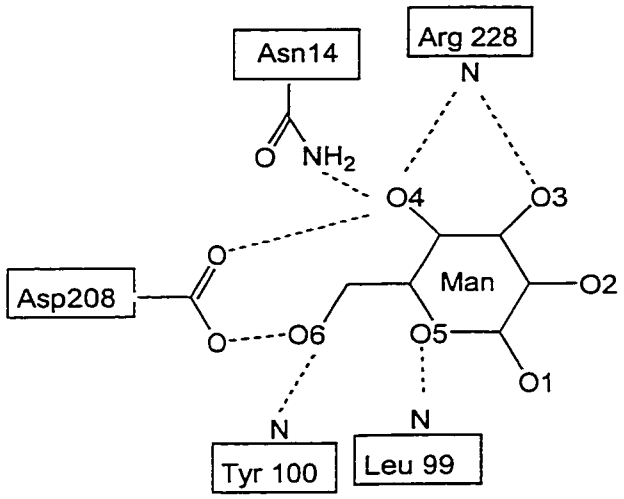
In one technique, the amount of protein or ligand in the protein is measured by chemical means using assays for glycan or protein. In another technique, the complex is salted out or precipitated by ammonium sulfate.[3]

Measurement of the turbidity has been successfully utilized to determine optimum geometry, multivalency and spacer requirements for optimum binding of neoglycoclusters[6] and glycodendrimers[7] with Concanavalin A.

Concanavalin A is a legume lectin isolated from Jack bean (*Canavalia ensiformis*).[5] "It is the first legume lectin to be isolated, sequenced, and characterized by x-ray crystallography.[5]

Concanavalin A recognizes mannose and glucose (Fig. 5.1.1).[5] The 3-D structure of the mannose-ConA complex is determined by x-ray crystallography and shows highly specific sites for the binding (Fig. 5.1.2).[3]

In this study, the effect of multivalency, geometric orientation of each carbohydrate substituent in a dimer (ortho, meta or para), and spacer in a dimer is evaluated. The binding is measured by the amount of precipitate formed when ConA interacts with the mannosyl conjugates.



Mannose/Glucose
(Canavalia ensiformis)

Figure 5.1.1. Monosaccharide recognition. Schematic diagram of the binding of mannose to Concanavalin A.[5]

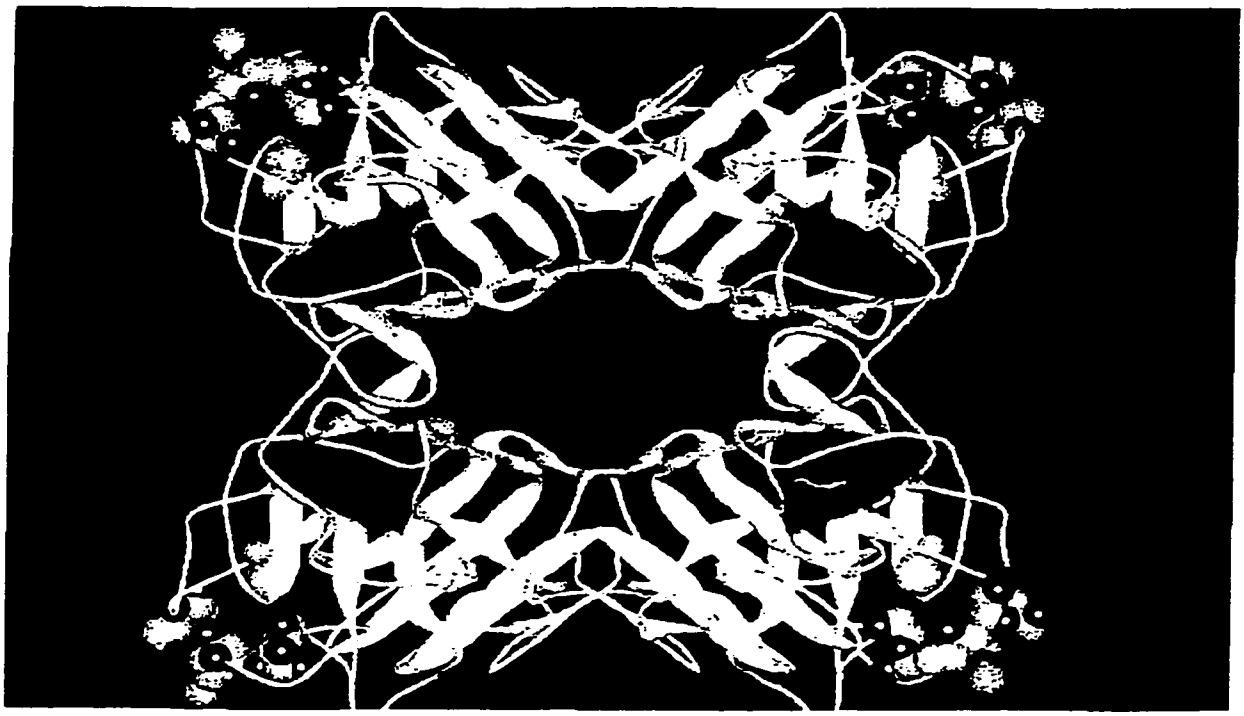


Figure 5.1.2. Structure of tetrameric ConA. The trimannoside ligand is indicated in space-filling mode and the coordinated Ca^{++} and Mn^{++} are shown as the large grey balls and small black balls, respectively.[3]

5.2. Turbidimetric Assay of Deacetylated Compounds

The mannosyl dimers (**11**, **13**, **14**, **17**, **20**, **21**, **22**, **23**, **24**), the mannosyl trimer (**26**), and the mannosyl hexamers (**31** and **32**) were deacetylated under Zemplén conditions (NaOMe, MeOH). The ability of the deacetylated clusters to form insoluble complexes were measured by turbidimetric formation with Concanavalin A. Time course formation of turbidity between Con A and the glycoclusters **35** - **46** were measured at 490 nm. Formation of precipitate was

observed immediately after addition of Con A to compounds **35, 38, 39, 40,** and **43.** Turbidity was measured up to 2 hours and found to be constant.

Initial testing of the hexamers **35, 36,** the trimer **37,** dimers **38** and **39** showed an interesting trend where the trend of activity is: hexamer **35** > dimer di-yne **39** > dimer mono-yne **38** > trimer **37.** The hexamer **36** did not show any activity (Chart 5.2.1, Chart 5.2.2).

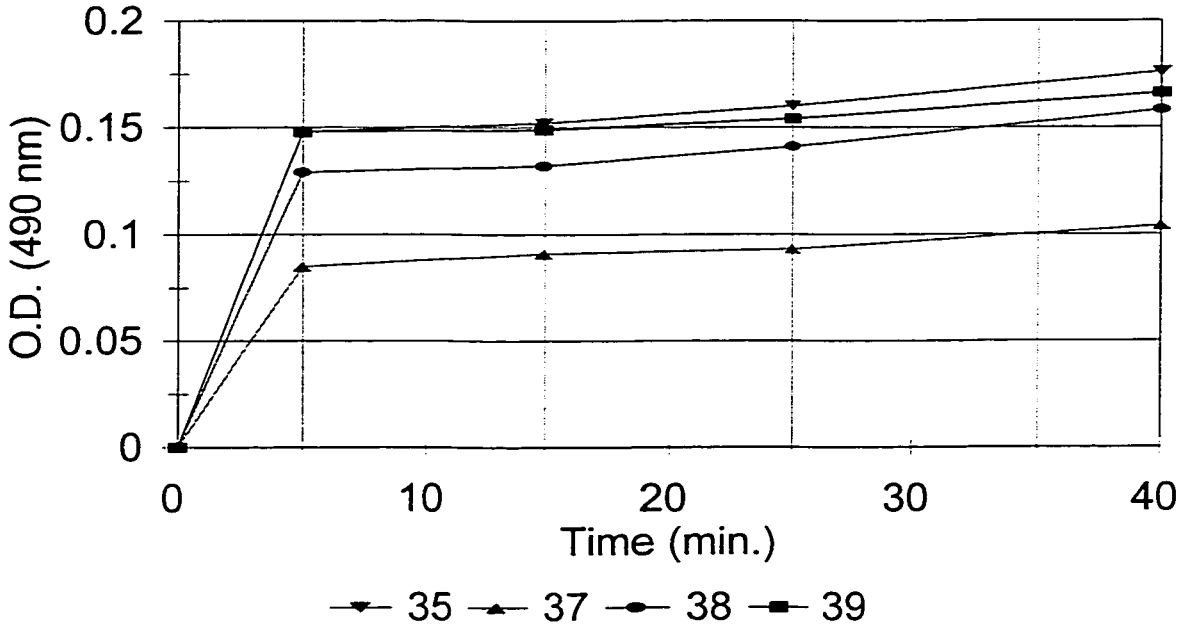


Chart 5.2.1. Time course turbidimetric analysis of glycocluster: **35,** trimer **37,** dimers **38, 39.**

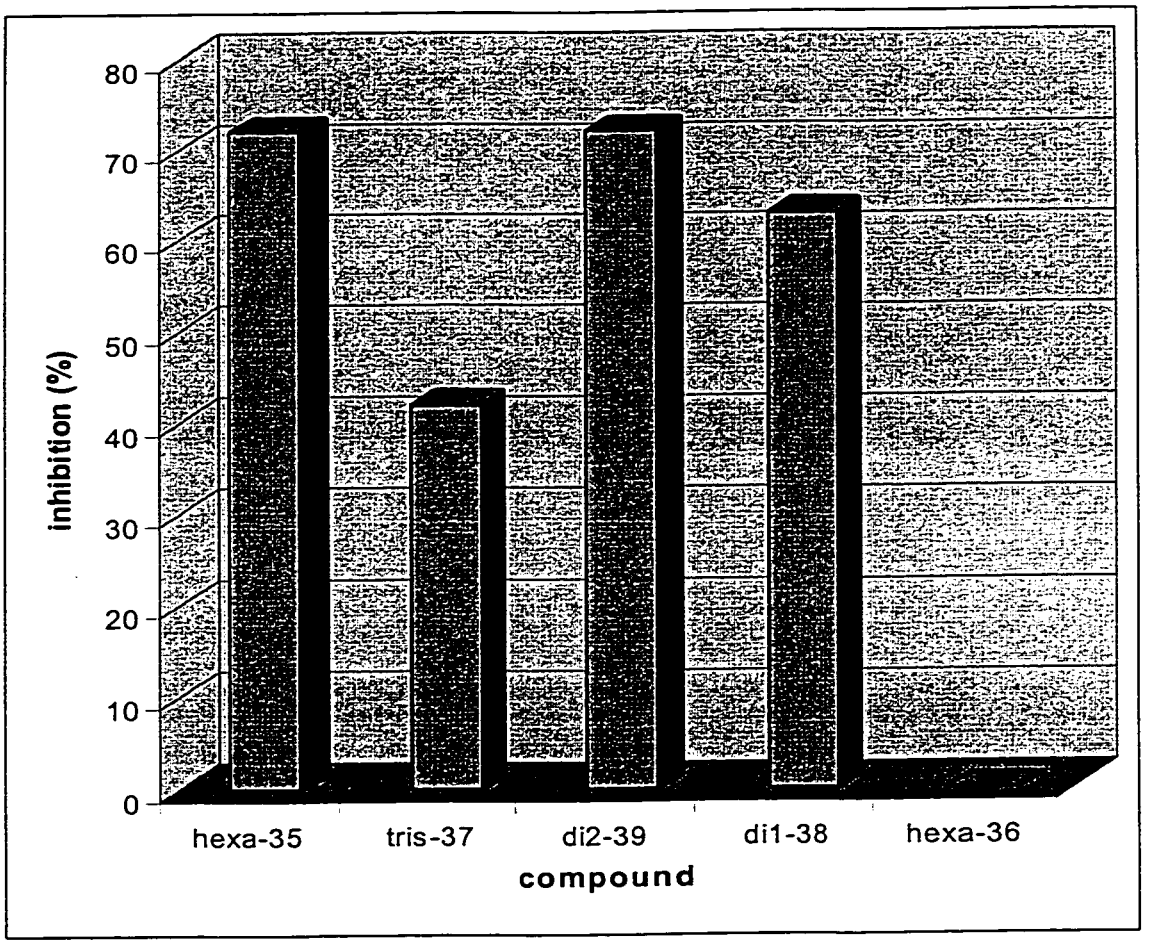
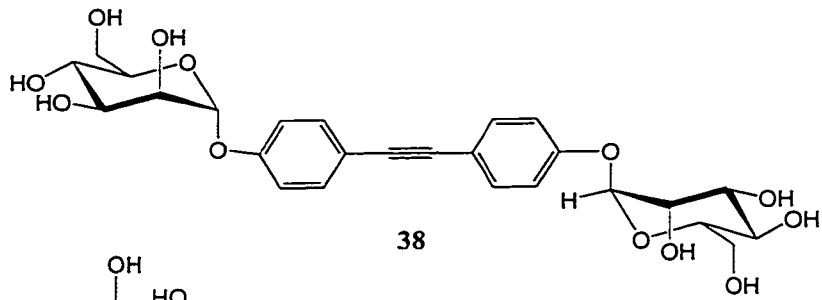
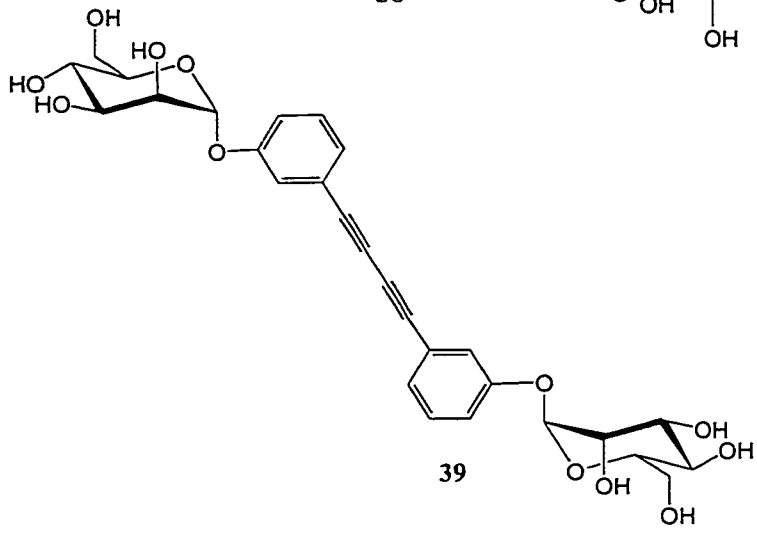


Chart 5.2.2. Comparison of % crosslinking of compounds with ConA after 5 minutes (100% inhibition based on crosslinking of compound **35** after 60 minutes). Compounds: hexamer **35**, hexamer **36**, trimer **37**, dimer **39**, dimer **39**.

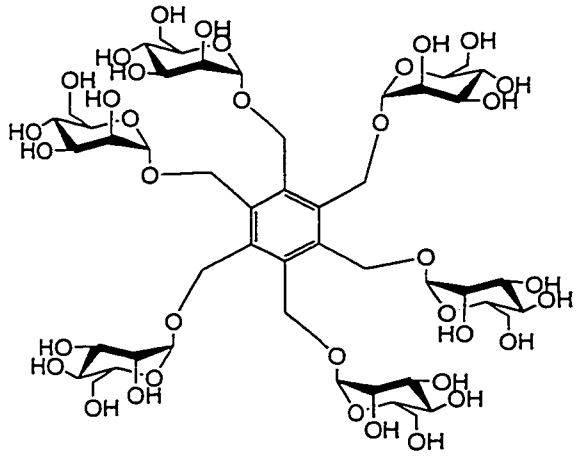
Comparison of all the compounds revealed the following trend in activity: hexamer **35** > di-ynes **39**, **40**, **43** > mono-ynes **38**, **41**, **42** > non-rigid dimers **44** – **46** (Chart 5.2.3, Chart 5.2.4). The dimers containing only one benzene ring **44**, **45** core or no acetylene groups showed low activity **46**. It should be noted that these dimers are semi-rigid. Also, para mono-yne **38** is more active than ortho di-yne **43** (see also Chart 5.2.5). The trend in activity between the di-ynes are: para **40** > meta **39** > ortho **43** (see Chart 5.2.4, Chart 5.2.5).



38

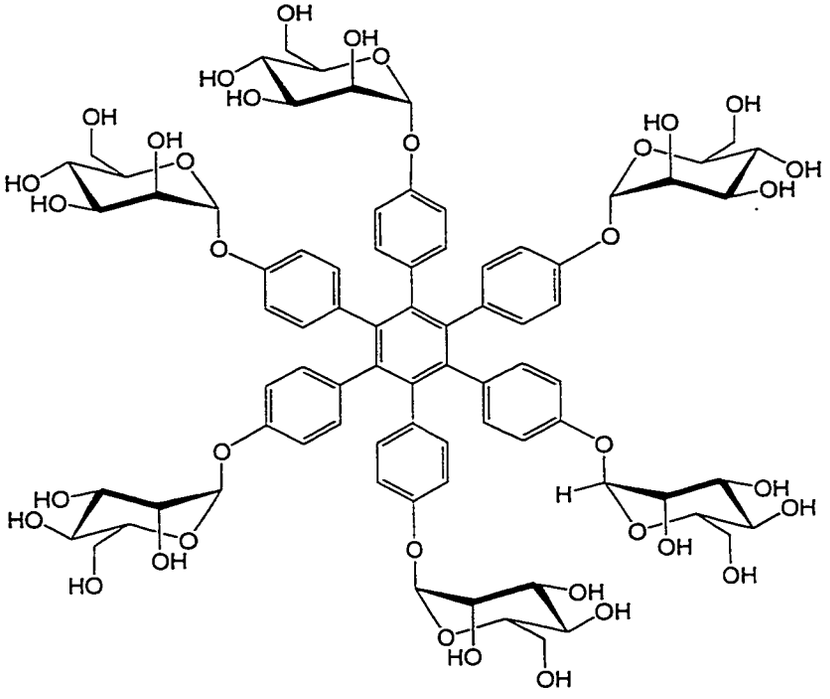


39



36

Figure 5.2.1a. Neoglycoconjugates in chart 5.2.1 - chart 5.2.5.



35

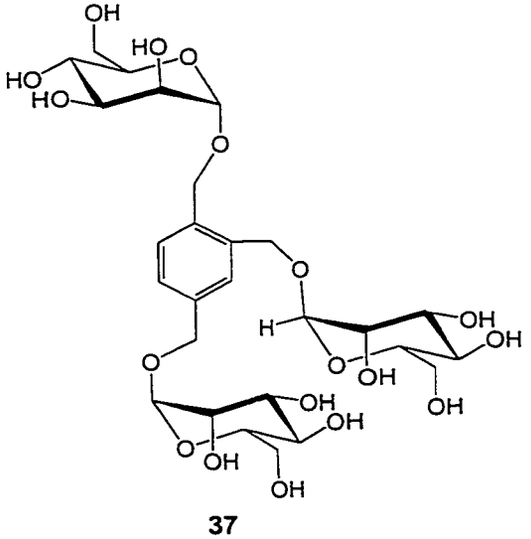


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Figure 5.2.1b. Neoglycoconjugates in chart 5.2.1 - chart 5.2.5.

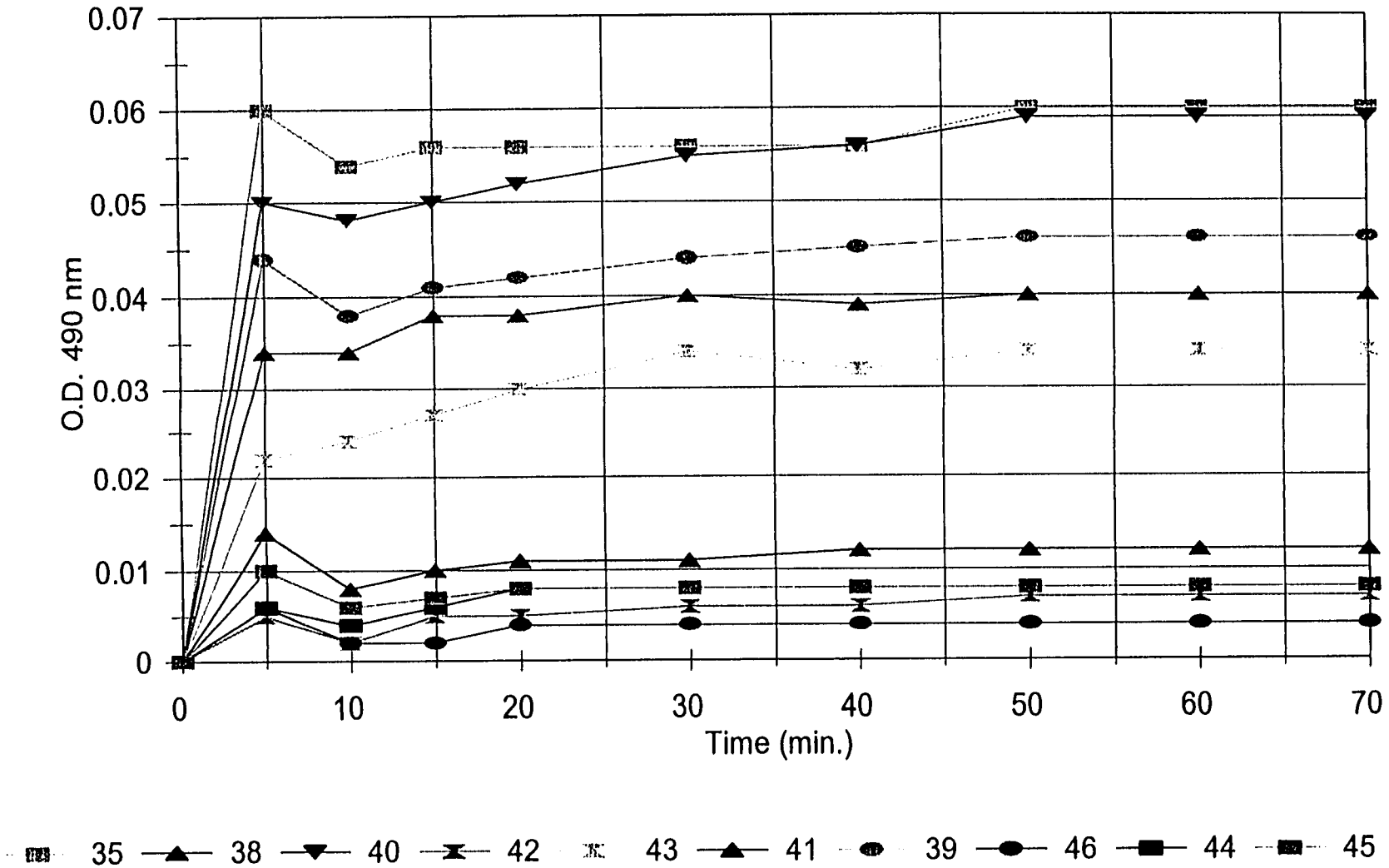


Chart 5.2.2. Time course turbidimetric testing of hexamer **35**, dimers **38** – **46**.

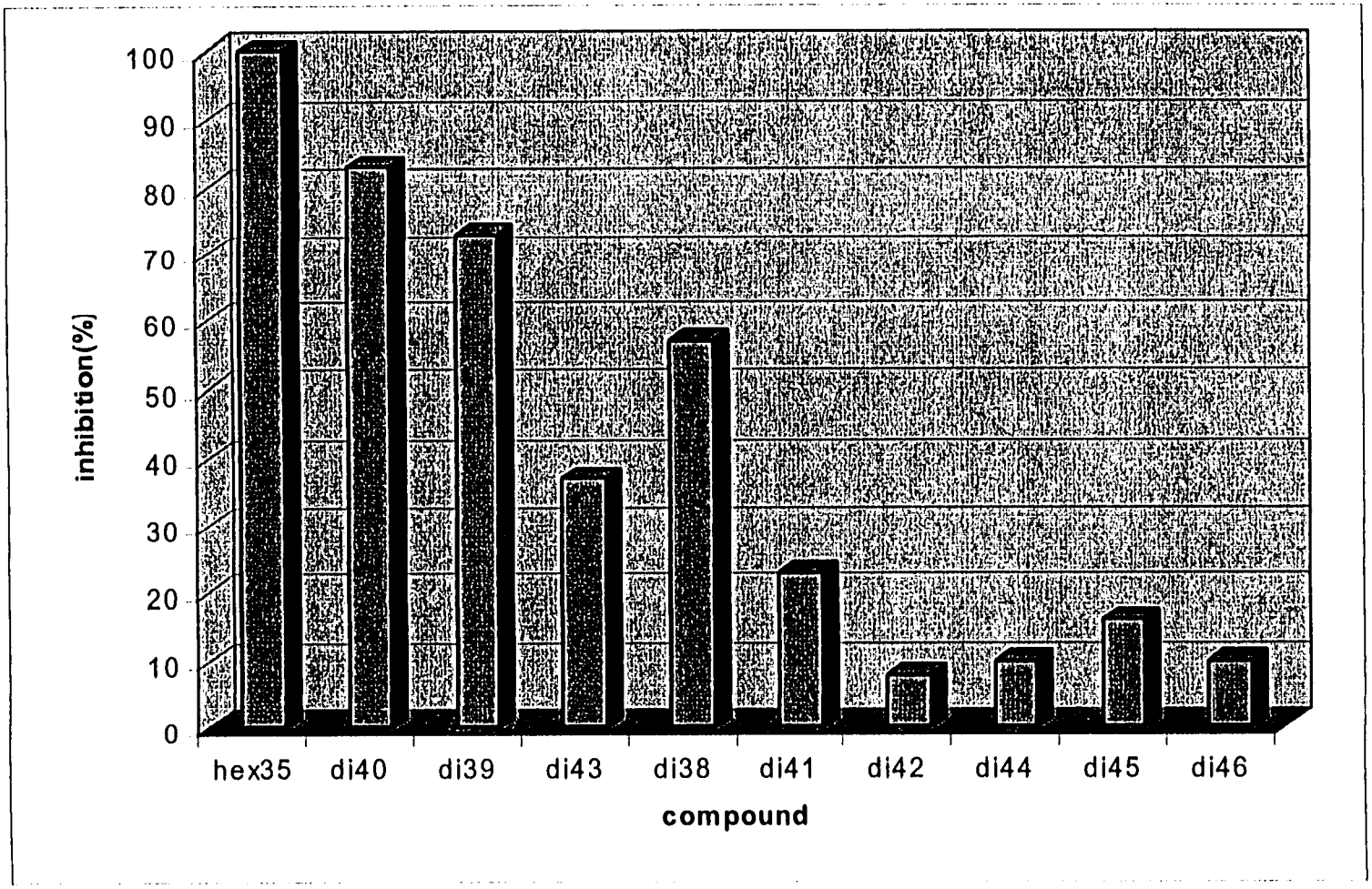
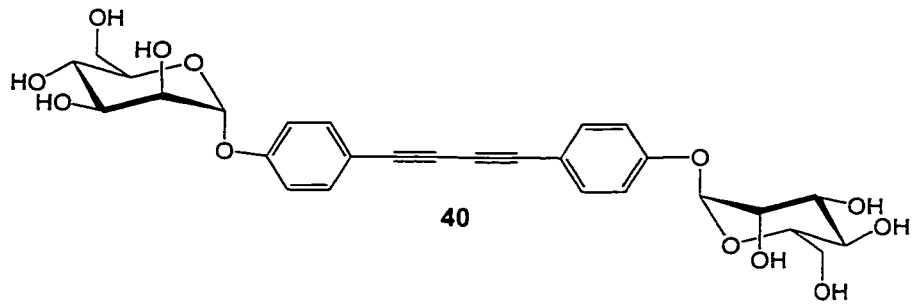
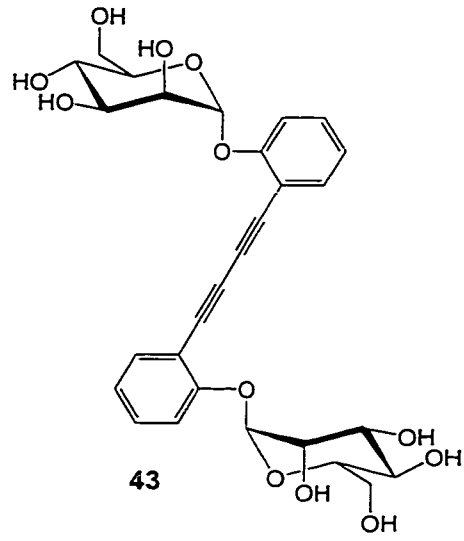


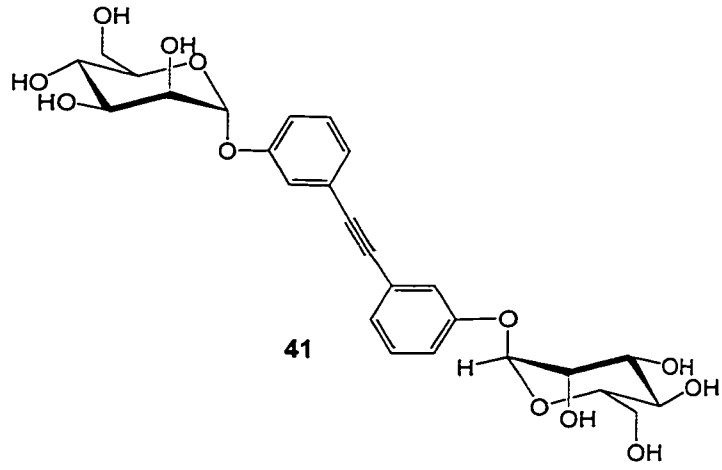
Chart 5.2.4. Comparison of % crosslinking of compound with ConA. after 5 minutes.(100% inhibition based on crosslinking of compound **35** after 70 minutes). Compounds: hexamer **35**, dimers: **38- 46**.



40



43



41

Figure 5.2.2a. Dimers in chart 5.2.3, chart 5.2.4, chart 5.2.5.

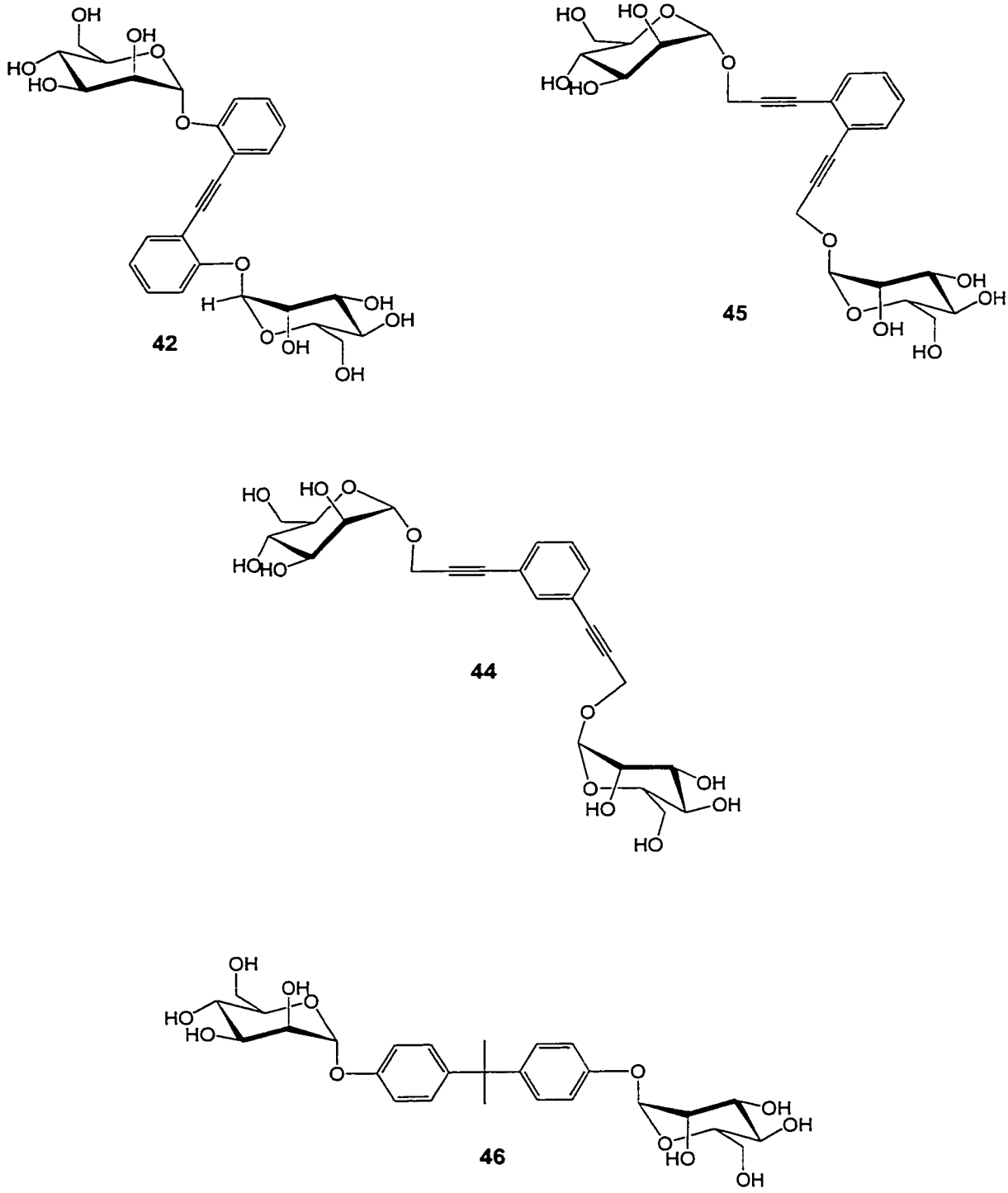


Figure 5.2.2b. Dimers in chart 5.2.3, chart 5.2.4 (dimers with low activity).

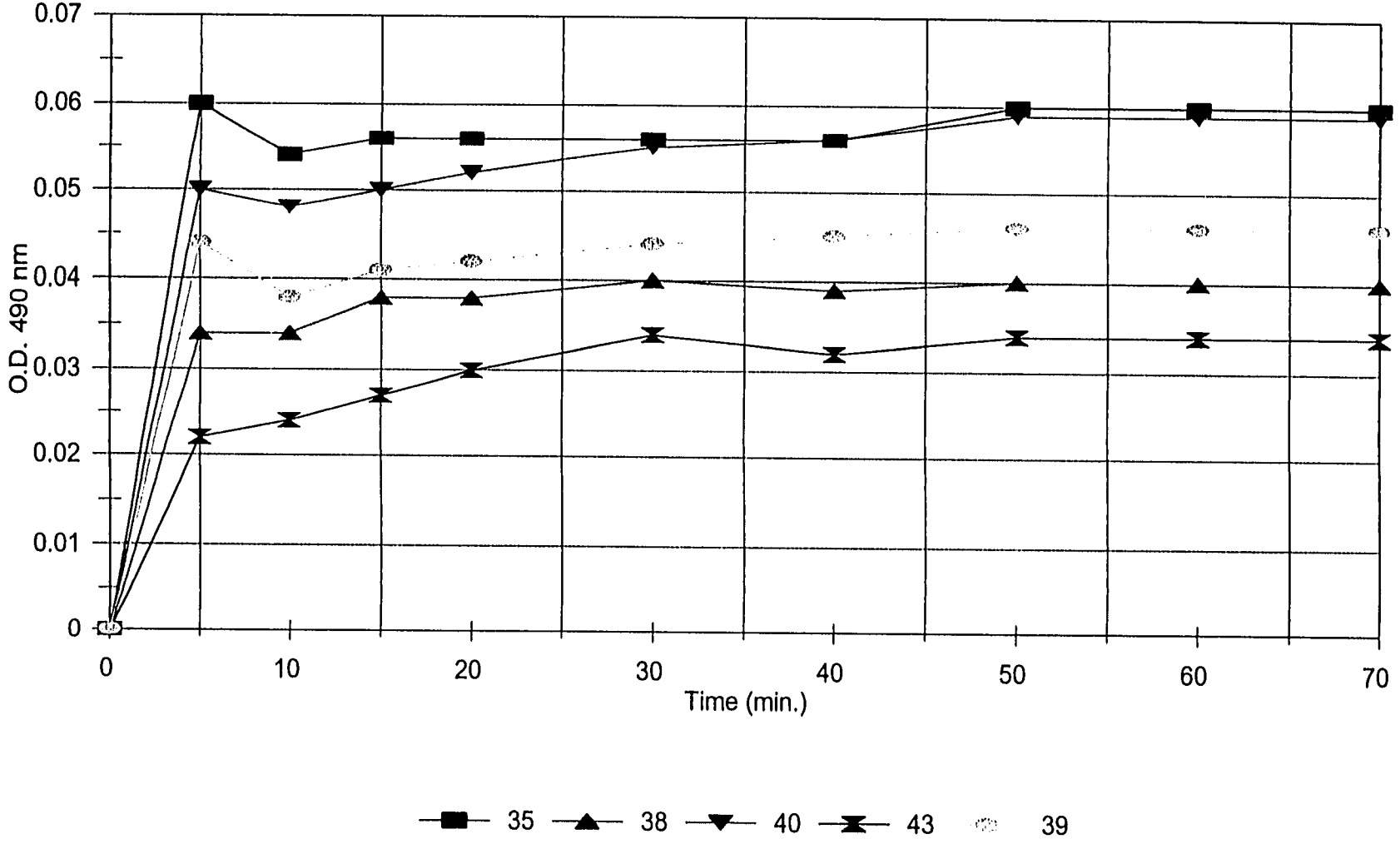


Chart 5.2.5. Time course turbidimetric testing of hexamer **35**, dimers **38**, **39**, **40**, **43**.

The mono-ynes (**41** and **42**), dimers with only one benzene core (**44** and **45**), and nonacetylene dimer **46** demonstrated very low activity (Chart 5.2.3, Chart 5.2.4).

An important observation was that the activity of the hexamer **35** and the para-di-yne **40** is comparable (Chart 5.2.5).

5.2. Conclusion

Time course turbidimetric testing indicated that the hexamer **35** and dimers containing a di-acetylene-di-phenyl core **39** and **40** has strong binding activity with ConA. It was demonstrated that the spacer requirement was optimized in dimers separated by two phenyl and two acetylene units in the core. The geometry requirement indicated for maximum activity of dimers was para orientation of each mannose to each other. It was also demonstrated that the more congested hexamer (consisting of only one benzene core **36**) has no binding activity towards Con A.

5.4. Experimental Methods

General Methods

^{1}H NMR and ^{13}C NMR spectra were obtained from either a Varian Gemini-200 z or a Bruker AMX500 spectrometer at 500, and 200 MHz for protons and 125.7 and 50.3 MHz for carbons, respectively. Proton chemical shifts are given relative to internal DMSO (2.49 ppm) for dmsod[6] solutions and to internal HOD (4.65 ppm) for D_20 solutions. Carbon chemical shifts are given relative to DMSO (39.5 ppm) and to internal HOD (2.21 ppm) for D_2O solutions. Special analyses were performed by the first order approximations and were based on shift correlation spectroscopy (COSY), heteronuclear multiple quantum coherence (HMQC), and 1- and 2-dimensional distortionless enhancement by polarization transfer (DEPT) experiments. Multiplicities of the NMR signals were reported using the following abbreviations: singlet (s), broad singlet (bs), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), multiplet (m).

Mass spectra were recorded on a Kratos IIH (FAB-KI-glycerol or FAB-glycerol) instrument. Xenon was used as the neutral carrier atom in FAB-MS experiments. Electrospray mass spectra was determined on Micromass Quattro LC 12-2.

Melting points were determined on a Gallenkamp apparatus and are uncorrected.

Optical rotation ($[\alpha]_D$) values were determined using a Perkin-Elmer (model 241) set at the sodium D line (589 nm) and were run at room temperature.

Infrared spectra were obtained in DMF, MeOH, or DMSO solution on KBr plates on a Bomem-Michelson MB-100 FT/IR spectrophotometer.

Optical densities (O.D.) for turbidimetric assays were measured on a Dynatech MR600 Microplate Reader.

Lyophilization were carried out on a VIRTIS-24 freeze dryer.

Reactions were monitored by thin-layer chromatography using Kieselgel 60 F_{254} precoated 0.25 mm thick aluminum backed plates and the compounds were detected by short wave UV light or by an ammonium molybdate solution (2.5% w/v). TLC plates were heated to 150 °C when necessary.

The lectin *Canavalia ensiformis* (Concanavalin A) was purchased from Sigma (C # 2631).

General procedure for the Zemplén reaction

To a solution of the appropriate protected sugar in MeOH was added, 10 drops of a solution of 1M NaOMe in MeOH. The reaction solution was left to stir at room temperature until TLC indicated completion of the reaction. Amberlite IR-120 (H^+) resin was then added until the pH is neutral. The solution was then filtered and the resin and remaining flask were washed with MeOH, then with H_2O. Methanol was removed under reduced pressure and the remaining liquid was lyophilized.

Turbidimetric analysis

Equivalent amounts of the compounds (corresponding to 9.1 μmol monosaccharide residue) were delivered separately into microtiter wells. 80 μl of Con A (10.0 mg in 1000 μl of PBS) was delivered via a microsyringe in each well. PBS solution was added to each well so that the total liquid in each well is 120 μl. Blank was run on a solution of 80 μl of Con A solution and 40 μl of PBS. The optical density (hν = 490 nm) was monitored for 2 h at room temperature. Each test was done in triplicate. The turbidity was measured on Dynatech MR 600 microplate reader at regular time intervals.

Deacetylation of hexamers

Hexakis-(α-D-mannopyranosyl)hexaphenylbenzene (35)

The compound was obtained by deacetylation of hexakis-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)hexaphenylbenzene) (**33**) (0.14 g, 0.056 mmol) using the general method. The solution turned cloudy after stirring overnight in sodium methoxide (10 drops, 1M in MeOH). Dimethylsulfoxide (30 ml) was added and the solution turned clear. The product was obtained as brown sticky solid was obtained (0.089 g, 100% yield); MP = 187 °C; $[\alpha]_D^{23}$ = + -0.9 ° (c=1.1, DMSO); IR (DMF): 3452 cm^{-1}; ^1H NMR ($DMSOD_6$ 500 MHz): δ(ppm) 6.67 (C_6H_4, d, J=7.8 Hz, 12H), 6.54 (C_6H_4, d, J=8.0 Hz, 12H), 5.09 (H-1, s, 6H), 3.70 (H-2, s, 6H), 3.56 (H-3, d, J=7.5 Hz, 6H), 3.54 (H-6b, d, J=10.3 Hz, 6H), 3.48 (H-4, H-6a, m, 12H), 3.19 (H-5, bs, 6H); ^{13}C-NMR ($DMSOD_6$, 125.7 MHz): δ(ppm) 153.8,

140.0, 134.4 (Cipso-aryl), 132.1 (C_6H_4), 115.5 (C_6H_4), 98.9 (C-1), 74.5 (C-5), 70.8 (C-3), 70.2 (C-2), 66.5 (C-4), 60.6 (C-6)

***Hexakis-{[(α-D-mannopyranosyl)oxo]hexamethyl}benzene* (36)**

The compound was obtained by deacetylation of hexakis-{[(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)oxy]methyl}benzene (**32**) (0.087 g, 0.039 mmol) using the general method (94% yield, 0.0454 g, white solid); MP = 166 – 167 °C; $[\alpha]_D^{23}$ = + 73.3 ° (c=0.9, MeOH); ^{1}H NMR (D_2O, 500 MHz): δ(ppm) 5.18 (Ph-CH_2, d, J=12.5, 6H), 5.02 ($PhCH_2$, d, J=12.1 Hz, 6H), 5.03 (H-1, s, 6H), 3.96 (H-2, bs, 6H), 3.80 (H-3/ H-6, m, 12H), 3.74 (H-4, dd, J=9.74 Hz, J=9.7 Hz, 6H), 3.57 (H-5, m, 6H); ^{13}C NMR (D_2O, 125.7 MHz): δ(ppm) 137.4 (Cipso-aryl), 99.6 (C-1), 73.0 (C-5), 70.0 (C-3), 69.7 (C-2), 66.0 (C-4), 63.1 (Ph-C$\underline{H_2}$), 60.1 (C-6)

Deacetylation of trimer

***1,2,4-Tris-{[(α-D-mannopyranosyl)*oxy]methyl}*benzene* (37)**

The compound was obtained by deacetylation of 1,2,4-tris-{[(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)oxy}methyl}benzene (**28**) (0.098 g, 0.082 mmol) using the general method (91% yield, 0.049 g, yellow solid); MP = 75 °C; $[\alpha]_D^{23}$ = + 118.9 ° (c=0.9, MeOH); ^{1}H NMR (D_2O, 500 MHz): δ(ppm) 7.56 (H_a- C_6H_4/ H_c-C_6H_4, bd, J=7.9 Hz, 2H), 7.50 (H_b- C_6H_4, d, J=7.8 Hz, 1H), 7.48 (C_6H_4-1,3,5-isomer), 5.03 (H-1, s, 3H), 4.92 (CH_2, d, J=12.0 Hz, 1H), 4.91 (CH_2, d, J=11.9 Hz, 1H), 4.85 (CH_2, s, 1H), 4.78 (CH_2, d, J=11.9 Hz, 1H), 4.77 (CH_2, d, J=12.0 Hz,

1H), 4.68 (CH_2, d, J=11.8 Hz, 1H), 4.02 (H-2, m, 3H), 3.89 (H-6a, m, 3H), 3.86 (H-3, dd, $J_{2,3}$=3.4 Hz, $J_{3,4}$=9.2 Hz, 3H), 3.82 (H-6b, m, 3H), 3.74 (H-4, dd, J=9.7 Hz, J=9.6 Hz, 3H), 3.62 (H-5, m, 3H); ^{13}C NMR (D_2O, 125.7 MHz): δ(ppm) 139.9, 137.3 (C-aryl-1,3,5 isomer), 135.3, 134.9 (Cipso-aryl), 129.9, 129.3, 128.2 (C-aryl), 99.2, 99.1, 99.9 (C-1), 72.6, 72.6 (C-5), 70.1 (C-3), 69.6 (C-2), 68.4, 66.4, 66.30 ($\underline{C}H_2$), 66.2 (C-4), 60.3 (C-6); FAB MS $[M+K]^+$ *m/z* (rel. intensity %) cald for $C_{27}H_{42}O_{18}K$: 693.20; found: 693.26 (0.4)

Deacetylation of mono-alkynylated dimers

***Bis-para-(α-D-mannopyranosyl)diphenylacetylene* (38)**

The compound was obtained by deacetylation of bis-para-[(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)diphenylacetylene (**17**) (0.11 g, .0.12 mmol) using the general method (97% yield, 0.067 g, yellow solid); m.p. = 240 – 242 °C; $[\alpha]_D^{23}$ = +114.0 ° (c=1.0, DMF); ^1H NMR ($DMSOD_6$, 500 MHz): δ(ppm) 7.44 (C_6H_4, d, J=8.7 Hz, 4H), 7.09 (C_6H_4, d, J=8.8 Hz, 4H), 5.41 (H-1, d, J=1.2 Hz, 2H), 5.04 (C2-OH, d, J=4.3 Hz, 2H), 4.82 (C4-OH, d, J=5.7 Hz, 2H), 4.74 (C3-OH, d, J=6.0 Hz, 2H), 4.44 (C6-OH, t, J=5.9 Hz, 2H), 3.82 (H-2, bs, 2H), 3.66 (H-3, m, 2H), 3.58 (H-6a, m, 2H), 3.36 (H-4, m, 2H), 3.47 (H-5, H-6b, m, 4H); ^{13}C-NMR ($DMSOD_6$, 125.7 MHz): δ(ppm) 156.4 (Cipso- C_6H_4), 132.7 (C_6H_4), 117.0 (C_6H_4), 115.9 (Cipso- C_6H_4), 98.7 (C-1), 88.1 (—≡—), 75.1 (C-4), 70.6 (C-3), 70.0 (C-2), 66.7 (C-5), 61.0 (C-6); FAB MS $[M+K]^+$ *m/z* (rel. intensity %) calcd for

$C_{26}H_{30}O_{12}K$: 573.14; found: 573.16 (2.3); $[M]^+$ cald for $C_{26}H_{30}O_{12}$: 534.17; found: 534.17 (0.6)

***Bis-meta–(α-D-mannopyranosyl)diphenylacetylene* (41)**

The compound was obtained by deacetylation of bis-meta-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)diphenylacetylene (**20**) (0.11 g, 0.12 mmol) using the general method (100% yield, 0.0660 g, yellow solid); m.p. = 80 °C; $[\alpha]_D^{23}$ = +74.0 ° (c=1.0, DMSO); IR (DMF): 3540 cm^{-1}; ^1H NMR ($DMSOD_6$, 500 MHz): δ(ppm) 7.33 (H_b-C_6H_4, dd, J=8.0 Hz, J=7.9 Hz, 2H), 7.25 (H_d-C_6H_4, dd, J=1.9 Hz, J=3.6 Hz, 2H), 7.19 (H_a-C_6H_4, d, J=7.6 Hz, 2H), 7.12 (H_c-C_6H_4, m, 2H), 5.42 (H-1, d, J=1.6 Hz, 2H), 5.01 (C2-OH, d, J=4.4 Hz, 2H), 4.81 (C4-OH, J=5.7 Hz, 2H), 4.73 (C3-OH, d, J=6.0 Hz, 2H), 4.46 (C6-OH, t, J=5.9 Hz, 2H), 3.82 (H-2, bs, 2H), 3.67 (H-3, m, 2H), 3.59 (H-6a, ddd, $J_{OH\text{-}6a}$=5.8 Hz, $J_{5,6a}$=7.8 Hz, $J_{6a\text{-}6b}$=11.8 Hz, 2H), 3.52-3.43 (H-5, H-6b, m, 4H), 3.39 (H-4, M, 2H); ^{13}C-NMR ($DMSOD_6$, 125.7 Hz): δ(ppm) 156.3 (Cipso- C_6H_4), 130.0 (C_b- C_6H_4),123.1 (C_a- C_6H_4), 119.3 (C_d- C_6H_4),117.9 (C_c- C_6H_4), 98.6 (C-1), 89.1 (—≡—), 75.1 (C-4), 70.6 (C-3), 70.0 (C-2), 66.7 (C-5), 61.0 (C-6); FAB MS $[M+1]^+$ *m/z* (rel. intensity %) calcd for $C_{26}H_{30}O_{12}$: 535.17; found: 535.12 (1.7)

***Bis-ortho -(α-D-mannopyranosyl)diphenylacetylene* (42)**

The compound was obtained by deacetylation of bis-ortho-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)diphenylacetylene (**22**) (0.041 g, 0.048 mmol) using the general method (100% yield, 0.025 g, yellow solid); m.p. = 104 °C; $[\alpha]_D^{23}$ =

+3.8 ° (c=1.0, DMF); IR (DMF): 3545.0 cm^{-1}; ^1H NMR ($DMSOD_6$, 200 MHz): δ(ppm) 7.51 (H_a-C_6H_4, dd, J =1.4 Hz, J=9.0 Hz, 2H), 7.34-7.25 ($H_{a'}$-C_6H_4, H_b-C_6H_4, m, 4H), 7.04 ($H_{b'}$-C_6H_4, ddd, J=1.3 Hz, J=8.2 Hz), 5.50 (H-1, s, 2H), 4.11 (C-OH, bs, 8H), 3.94 (H-2, d, J=1.65 Hz, 2H), 3.82 (H-3, m, 2H), 3.62, 3.43 (H-4, H-5, H-6, m, 6H); ^{13}C-NMR ($DMSOD_6$, 50.2 MHz): δ(ppm) 156.6, 132.9, 130.0, 122.3, 116.5, 113.7 (C_6H_4), 99.2 (C-1), 88.0 (—≡—), 75.2, 70.8, 70.2, 67.0, 66.6 (C-2, C-3, C-4, C-5), 61.0 (C-6); ES MS $[M + NH_4]^+$ calcd for $C_{26}H_{30}O_{12}$ *m/z*: 552 found: 552 (2.56)

Deacetylation of di-alkynylated dimers

***Bis-para-(α-D-mannopyranosyl)diphenylbut-1,3-diynyl* (40)**

The compound was obtained by deacetylation of bis-para-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)diphenyl-but-1,3-diynyl (**24**) (0.098 g, 0.12 mmol) using the general method (100% yield, 0.064 g, yellow solid); m.p. = 163 °C; $[\alpha]_D^{23}$ = +89.2 ° (c=1.2, DMF); IR (DMF): 3561.0 cm^{-1}; ^1H NMR ($DMSOD_6$, 500 MHz): δ(ppm) 7.52 (H_a-C_6H_4, d, J=8.6 Hz, 4H), 7.11 (H_b-C_6H_4, d, J=8.7 Hz, 4H), 5.44 (H-1, s, 2H), 5.07 (C2-OH, s, 2H), 4.85 (C4-OH, d, J=4.8 Hz, 2H), 4.76 (C3-OH, d, J=3.8 Hz, 2H), 4.46 (C6-OH, bs, 2H), 3.82 (H-2, bs, 2H), 3.66 (H-3, dd, $J_{2,3}$=4.5, $J_{3,4}$=8.3 Hz, 2H), 3.59-3.45 (H-4, H-6a, m, 4H), 3.41 (H-6b, m), 3.34 (H-5, m, 2H); ^{13}C-NMR ($DMSOD_6$, 125.7 MHz): δ(ppm) 157.4, 113.7 (Cipso-C_6H_4), 134.0 (C_a- C_6H_4), 117.1 (C_b- C_6H_4), 98.6 (C-1), 81.5, 72.9 (—≡—), 75.2

(C-5), 70.6 (C-3), 69.9 (C-2), 66.6 (C-4), 61.0 (C-6); FAB MS $[M - 4\ OH]^+$ *m/z* (rel. intensity %) calculated for $C_{28}H_{28}O_8$: 486.13; found: 486.21 (12.3)

***Bis-meta-(α-D-mannopyranosyl)diphenyl-but-1,3-diynyl* (39)**

The compound was obtained by deacetylation of bis-meta-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)diphenyl-but-1,3-diynyl (**21**) (0.023 g, 0.027 mmol) using the general method (100% yield, 0.015 g, yellow solid); m.p. = 80 °C; $[\alpha]_D^{23}$ = + 71.0 ° (c=1.0, DMF); IR (DMF): 3540 cm^{-1}; ^1H NMR ($DMSOD_6$, 500 MHz): δ(ppm) 7.35 (H_b-C_6H_4, dd, J=8.0 Hz, J=8.0 Hz, 2H), 7.29 (H_d-C_6H_4, bs, 2H), 7.23 (H_a-C_6H_4, d, J=7.7 Hz, 2H), 7.18 (H_c-C_6H_4, ddd, J=1.6 Hz, J=2.4 Hz, J=8.2 Hz, 2H), 5.39 (H-1, d, J=1.6 Hz, 2H), 5.09 (C2-OH, d, J=4.4 Hz, 2H), 4.87 (C4-OH, J=5.7 Hz, 2H), 4.71 (C3-OH, d, J=6.0 Hz, 2H), 4.53 (C6-OH, t, J=5.8 Hz, 2H), 3.81 (H-2, bs, 2H), 3.65 (H-3, m, 2H), 3.58 (H-6a, m, 2H), 3.41 (H-5, H-6b, m, 4H), 3.36 (H-4, m, 2H); ^{13}C-NMR ($DMSOD_6$, 125.7 MHz): δ(ppm) 156.3 (Cipso-C_6H_4), 130.2 (C_b-C_6H_4), 126.2 (C_a-C_6H_4), 121.4 (Cipso-C_6H_4), 120.0 (C_d-C_6H_4),119.2 (C_c-C_6H_4), 98.9 (C-1), 81.7 (—≡—), 75.1 (C-4), 73.3 (—≡—), 70.6 (C-3), 69.9 (C-2), 66.7 (C-5), 61.0 (C-6); HRMS FAB $[M+K]^+$ calcd for $C_{26}H_{30}O_{12}K$: 597.1374; found: 597.2025

***Bis-ortho-(α-D-mannopyranosyl)diphenyl-but-1,3-diynyl* (43)**

The compound was obtained by deacetylation of bis-ortho-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)diphenyl-but-1,3-diynyl (**23**) (0.070 g, 0.082 mmol) using the general method. (99% yield, 0.046 g, white solid); m.p. = 130-132 °C;

$[\alpha]_D^{23}$ = - 0.8 ° (c=1.3, DMF); IR (DMF): 3544.0 cm^{-1}; ^1H NMR ($DMSOD_6$, 500 MHz): δ(ppm) 7.55 (H_a-C_6H_4, dd, =1.5 Hz, J=7.7 Hz, 2H), 7.41 (H_b-C_6H_4, ddd , J=1.6 Hz, J=8.3 Hz, 2H), 7.30 ($H_{a'}$-C_6H_4, d, J=8.4 Hz, 2H),7.04 ($H_{b'}$- C_6H_4, dd, J=7.5 Hz, J=7.4 Hz, 2H), 5.48 (H-1, s, 2H), 5.07 (C2-OH, d, J=4.4 Hz, 2H), 4.94 (C3-OH, d, J=5.5 Hz, 2H), 4.9 (C4-OH, d, J=5.8 Hz, 2H), 4.43 (C6-OH, t, J=5.8 Hz, 2H), 3.91 (H-2, bs, 2H), 3.75 (H-3, m, 2H), 3.59 (H-6a, m,2H), 3.55-3.50 (H-4, m, 2H), 3.48-3.36 (H-5, H-6a, m, 4H); ^{13}C-NMR ($DMSOD_6$, 125.7 MHz): δ(ppm) 158.1 (Cipso-C_6H_4), 134.1 (C_a-C_6H_4), 131.3 (C_b-C_6H_4), 122.2 ($C_{b'}$-C_6H_4), 116.0 ($C_{a'}$- C_6H_4), 99.1 (C-1), 78.7, 77.2 (—≡—), 75.2 (C-5), 70.6 (C-3), 69.9 (C-2), 66.6 (C-4), 61.0 (C-6); ES MS $[M]^+$ calculated for $C_{26}H_{30}O_{12}$: 558; found: 558 *m/z*

Deacetylation of monobenzene dimers

***1,3-Bis-[1,1'(α-D-mannopyranosyl)-prop-2,2'-ynyl]benzene* (44)**

The compound was obtained by deacetylation of 1,3-bis-[1,1'(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)-prop-2,2'-ynyl]benzene (**13**) (0.35 g, 0.42 mmole) using the general method (100% yield, 0.20 g, yellow solid); m.p. = 65 °C; $[\alpha]_D^{23}$ = +137.7 ° (c=1.3, MeOH); ^1H NMR ($DMSOD_6$, 500 MHz): δ(ppm) 7.49 (C_6H_4, d, J=6.5 Hz, 2H), 7.47 (C_6H_4, bs, 1H), 7.41 (C_6H_4, dd, J=7.1 Hz, J=8.3 Hz, 1H), 4.85 (H-1, s, 2H), 4.83 (C2-OH, d, J=4.30 Hz, 2H), 4.74 (C4-OH, d, J=5.4 Hz, 2H), 4.59 (C3-OH, d, J=6.0 Hz, 2H), 4.50 (C6-OH, t, J=6.1 Hz, 2H), 4.46 ($^{-H_2C}$—≡, s, 2H), 4.46 ($^{-H_2C}$—≡, s, 2H), 3.66 (H-2, H-6a, m, 4H), 3.45 (H-3, H-6b, m, 4H),

3.34 (H-5, m, 2H), 3.31-3.22 (H-4, m, 2H); ^{13}C-NMR (DMSOD$_6$, 125.7 MHz): δ(ppm) 134.0, 131.8, 129.3, (C_6H_4), 122.4 (Cipso- C_6H_4), 98.4 (C-1), 85.6, 84.5 (—≡—), 74.5 (C-4), 70.9 (C-3), 70.1 (C-2), 66.9 (C-5), 61.2 (C-6), 53.6 ($^{-}H_2C$—≡); HRMS FAB $[M+K]^+$ calcd for $C_{24}H_{30}O_{12}$: 549.1374; found: 549.1404*m/z*

***1,2-Bis-[1,1'(α-D-mannopyranosyl)-prop-2,2'-ynyl]benzene* (45)**

The compound was obtained by deacetylation of 1,2-bis-[1,1'(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)-prop-2,2'-ynyl]benzene (**14**) (0.15 g, 0.018 mmol) using the general method (100% yield, 0.087 g, yellow solid); m.p. = 92 °C; $[\alpha]_D^{23}$ = +129.27 ° (c=1.2, MeOH); ^{1}H NMR (DMSOD$_6$, 200 MHz): δ(ppm) 7..51 (C_6H_4,d, J=6.4 Hz, 1H), 7.50 (C_6H_4, d, J=5.6 Hz, 1H), 7.40 (C_6H_4, d, J=5.6 Hz, 1H), 7.38 (C_6H_4, d, J=5.5 Hz, 1H), 4.93 (H-1, bs, 2H), 4.86 (C-OH, d, J=4.4 Hz, 2H), 4.78 (C-OH, d, J=4.4 Hz, 2H), 4.65 (C-OH, d, J=5.5 Hz, 2H), 4.55 (C-OH, t, J=4.2 Hz, 2H), 4.51, 4.49 ($^{-}H_2C$—≡, 2 s, 4H), 3.64- 3.46 (H-2, H-3, H-4, H-5, H-6, 10H); ^{1}H NMR (D_2O exchange in DMSOD$_6$, 50.7 MHz): δ(ppm) 7.51 (C_6H_4,d, J=5.2 Hz, 1H), 7.49 (C_6H_4,d, J=5.67 Hz, 1H), 7.39 (C_6H_4,d, J=5.7 Hz, 1H), 7.38 (C_6H_4,d, J=5.3 Hz, 1H), 4.92 (H-1, d, J=1.2 Hz, 2H), 4.50, 4.48 ($^{-}H_2C$—≡, 2 s, 4H), 3.70-3.35 (H-2, H-3, H-4, H-5, H-6, m, 10H); ^{13}C NMR (DMSOD$_6$, 50.3 MHz) δ(ppm): 132.0, 128.9, 124.3 (C_6H_4), 98.2 (C-1), 89.7, 84.2 (—≡—), 74.4, 70.9, 70.2, 70.1, 66.7 (C-2, C-3, C-4, C-5), 61.1, 61.0 (C-6, C-6'), 53.6 (CH_2); ES MS $[M - 8(OH)]^+$ calcd for $C_{22}H_{26}O_{12}$ – 8(OH): 346.1; found: 346.8 *m/z*

Deacetylation of non-acetylene dimer

***4,4'-Bis-(α-D-mannopyranosyl)diphenylisopropane* (46)**

The compound was obtained by deacetylation of 4,4'-bis-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)diphenylisopropane (**11**) (0.11 g, 0.12 mmol) using the general method (95% yield, 0.065 g, yellowish solid); m.p. = 114 °C; $[\alpha]_D^{23}$ = +107.5 ° (c=1.6, DMF); ^{1}H NMR ($DMSOD_6$, 200 MHz): δ(ppm) 7.11 (C_6H_4, d, J=8.8Hz, 4H), 7.0 (C_6H_4, d, J=8.8Hz, 4H), 5.3 (H-1, d, J=1.6Hz, 2H), 3.92 (C2-OH, C3-OH, C4-OH, br s, 6H), 3.78 (C6-OH, t, J=2.9Hz, 2H), 3.62-3.55 (H-2, H-3, H-4, m, 6H), 3.47-3.16 (H-5, H-6, m, 6H), 2.07 (CH_3, s, 6H); ^{13}C-NMR ($DMSOD_6$, 50.3 MHz): δ(ppm) 154.4, 143.9, 127.6, 116.2 (C_6H_4), 99.1 (C-1), 74.9, 70.7, 70.2, 67.0, 66.8 (C-2, C-3, C-4, C-5), 61.1 (C-6), 30.7 [$Ph_2\underline{C}(CH_2)$], 25.2 (CH_3); ES MS $[M+NH_4]^+$ *m/z* (rel. intensity, %) calcd for $C_{27}H_{36}O_{12}$: 570; found: 570 (3.50)

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Claims to Original Research

1. New neoglyconconjugates synthesized are: the: mannose and galactose hexamers, dialkynyl diphenyl mannosyl dimers, monoacetylene diphenyl mannosyl and galactosyl dimers, bisphenyl mannosyl dimer, mono-acetylene non-benzene mannosyl dimer, acetylene phenyl mannosyl monomers, and the ortho and meta iodophenylmannosides.

2. This is the first report of the synthesis of phenyl glycoconjugates containing a terminal acetylene moiety.

3. This is the first report of the application of Hay's coupling to the synthesis of dialkynyl diphenyl glycosyl dimers.

4. Application of Sonogashira coupling to the synthesis of neoglycoconjugates consisting of two glycoside residues tethered to a diphenylmonoacetylene core.

5. A new variation in Sonogashira coupling which results in the synthesis of the terminal acetylene phenyl glycosyl monomers by coupling of iodophenyl mannosides with acetylene gas.

6. Application of BF_3OEt_2 catalyzed *O*-glycosidation to ortho and meta iodophenyl substrates and comparison of ease of reaction between ortho, meta and para substrates.

7. Comparison of ease of Sonogashira coupling between ortho, meta and para iodophenylmannosides with acetylene TMS and acetylene gas.

8. Generation of ortho, meta and para analogues of mannoside dimers.

9. Comparison of binding activity (with lectins) between trimers, hexamers and dimer mannoside conjugates.

10. Comparison of binding activity (with lectins) between mannoside dimers where the mannoside residues are oriented in 60°, 120° and 180° to each other.