SYNTHESE VON CYCLISCHEN

DISACCHARIDEN

DURCH

INTRAMOLEKULARE GLYCOSYLIERUNG

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Patrick Claude

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Dekan :	Prof. Dr.rer.nat. S. Laufer
1. Berichterstatter:	Prof. Dr. rer. nat. T. Ziegler
2. Berichterstatter:	Prof. Dr. rer. nat. M. Maier

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The beauty of scientific research is the endless learning

process and adventure, that leaving us so many

universes to discover which requires

on our part , regardless our level

Wisdom and modesty

Dedication

I dedicate my thesis to my wonderful parents who endlessly manifested toward me their deepest affection and support throughout all the all the delicate periods of my life.

I am so lucky to have you as parents, and I deeply love you

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Abbreviations

Ac	Acetyl
Ac_2O	Acetic anhydride
AgOTf	Silver trifluoromethanesulphonate
Bn	Benzyl
BnBr	Benzyl bromide
Bz	Benzoyl
BzCl	Benzoyl chloride
$BF_3.Et_2O$	Boron trifluoride etherate
Bu_2 SnO	Dibutyl tin oxide
$(Bu)_4NHSO_4$	Tetrabutylammoniumhydrogensulphate
^{t}Bu	tert-Butyl
CH_2Cl_2	Dichloromethane
CH_2I_2	Methyl iodide
$Ce(NH_4)_4NO_3$	Cerium(IV) ammonium nitrate
CsF	Cesium fluoride
COSY	Correlated Spectroscopy
DAST	Dimethylaminosulfurtrifluoride
DCC	*N*,*N*-Dicyclohexylcarbodiimide
DCE	Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-*p*-benzochinone
DEPT	Distortionless Enhancement by Polarization Transfer
DMAP	4-(Dimethylamino) pyridine
DMST	Dimethyl (methylthio)sulphonium triflate

DMF	*N*,*N*-Dimethylformamide
DTBP	2,6-di-tert-butyl-pyridine
DTBMP	2,6-di-tert-butyl-methylpyridine
Et_2O	Diethylether
EtOH	Ethanol
EtOAc	Ethyl acetate
Et_3N	Triethyl amine
Fmoc	9-Fluorenylmethoxycarbonyl
Fuc	Fucose
Gal.	Galactose
Glc	Glucose
GlcNAc	*N*-Acetylglucosamine
h	Hour
HBr	Hydrobromic acid
HCl	Hydrochloric acid
HCO_2H	Formic acid
H_2SO_4	Sulfuric acid
HPLC	High pressure liquid chromatography
HMBC	Heteronuclear multi-bond correlation
HV	High vacuum
HOBt	1-Hydroxy- benzotriazol
Man	Mannose
MeOH	Methanol
MeOTf	Methy Triflate
MeCN	Acetonitrile

min	Minute
Ms	Mesylate
MBnBr	Methoxybenzyl bromide
Me_2SiCl_2	Dimethylsilyl chloride
$MeNO_2$	Nitromethane
MPM	*para*-Methoxy-benzylchloride
NBS	*N*-bromosuccinimide
NIS	*N*- Iodosuccinimide
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
NaH	Sodium hydride
$NaBH_4$	Sodium borohydride
$NaBH_3$ CN	Sodium cyanoborohydride
Ph	Phenyl
PMB	*p*-Methoxybenzyl
PMBCl	*p*-Methoxybenzylchloride
PhSK	Potassium benzothionolate
PheSeK	Potassium phenylselenate
$Pd(Ph_3)_4$	Tetra-kis phenyl palladium
$Pd(Ph_3)_4RhCl$	Tetra-kis tetraphenyl palladium rhodium chloride (*Willkinson's catalyst*)
$Pd(OH)_2$	Palladium (II) hydroxide
PhTh	Phthaloyl
Rha	Rhamnose
$SnCl_2$	Tin(II) chloride
Tf	Trifluoromethanesulphonyl

TfOH	Trifluoromethane sulphonic acid
TFA	Trifluoroacetic acid
TMS	Trimethylsilyl
TMSOTf	Trifluoromethanesulphonic acid trimethylsilylster
TOCSY	Total correlation spectroscopy
Trt	Trityl
Ts	Tosyl
p-TsOH	*p*-Toluosulphonic acid
Z	Benzyloxycarbonyl

Introduction

The ability to synthesize organic molecules of pharmaceutical, material or other interest is at the cornerstone of organic chemistry. Whether trained on natural products, conducting conducting a polymer, a semisynthetic enzyme, the science of organic chemisty empowers us to understand the world around us. Throughout the years, the significant advances in the pharmaceutical, and medical sectors have given features to to many classes of natural sciences as a prominent and mature discipline, in which one of them, the field of carbohydrate chemistry or glycochemistry. Indeed, the world of carbohydrate chemistry appears to have emerged into it's own. The diversity of structures makes it possible by nature's carbohydrate building set is greater than that of oligonucleotides, or oligopeptides, and has given carbohy-hydrates a pivotal role in different areas of chemistry and biology. These range from interacting systems in embryonic development, control of cell adhesion and cell activation to the provision of energy sources and structural platforms.

Glycoconjugates.

Carbohydrates[1,2] possess a large number of functionalities at least one carbonyl and several hydroxyl functions per monosaccharide. Sugars are frequently bounded to other biomolecules to form other kinds of compounds. The combinations of these are called glycoconjugates.
More complex carbohydrates can be linked to proteins, peptide, lipids, to produce different classes of glycoconjugates, glycoproteins, glycopeptides, glycolipids. Glycoproteins are biopolymers consisting of a polypeptide backbone one or more covalently linked to a carbohydrate They are found in soluble form in the blood, in the cytosol or in subcellular organelles. Further more, they are basic constituents of all cell membranes. In eucaryotes cells, they are integrated into the lipid bilayers, so that the oligosaccharide moieties are exposed to the extracellular side of the membrane. They form a carbohydrate coat called glycolyx. The glycolyx polysccharides constitute a major component in eucaryotic cell surface to form a layer of 140 nm in depth.

Structure of Glycoproteins.

Protein contain more oligosaccharide chains. The three major chemical linkages of in which carbohydrates backbone are covalently bound to proteins are the following:

N-glycosidic: (fig. 1)

These glycoconjugates are called N-glycoproteins or N-glycans. [1,2,3,4,5,6,7]
In these types of glycoproteins, the oligosaccharide moiety is always bound to the side chain via an N-glycoside linkage to N-glucose amine which forms the non-reducing end of all N-glycans.

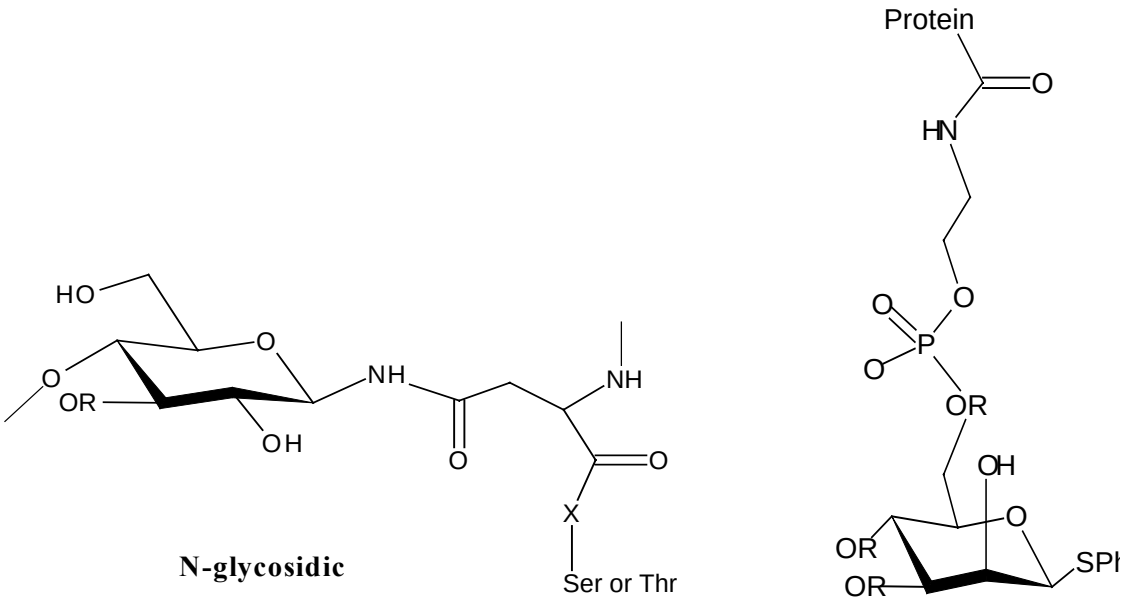
O-glycosidic: (fig.1).

The resulting conjugates are named O-glycoproteins or O -glycans.[1,2,3,4,5,6]
In the case of O-glycoproteins, the reducing end of the oligosaccharide chain are linked to a hydroxyl group of acid residues such as, serine, threonone, and hydroxylysine. The nature of the saccharide moiety bound to the peptide chain varies with the complexity of the sugar.

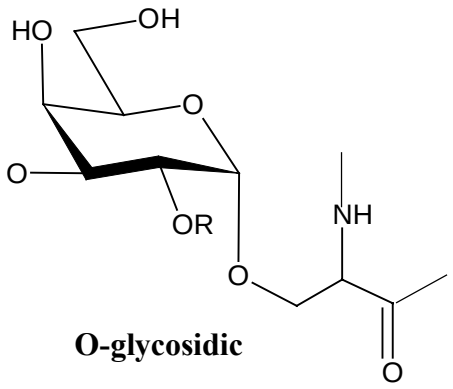
Ethaloamine Phosphate: (fig. 1).

This type of linkage between proteins and carbohydrates moieties occur in glycophosphadyl Inisitols called GPI anchors, which anchor proteins to cell membranes.

Fig. 1.



N-glycosidic



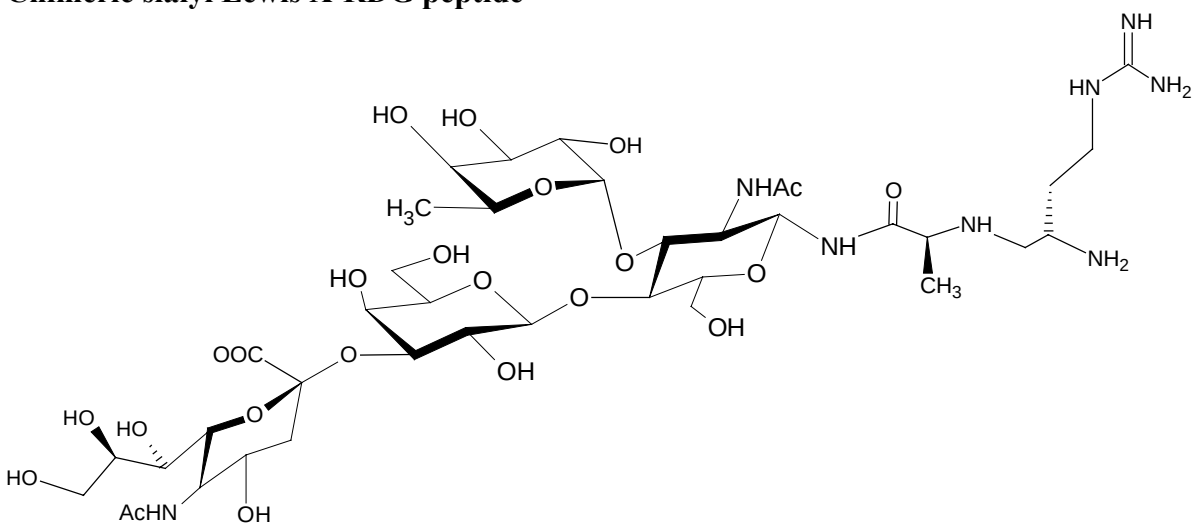
O-glycosidic

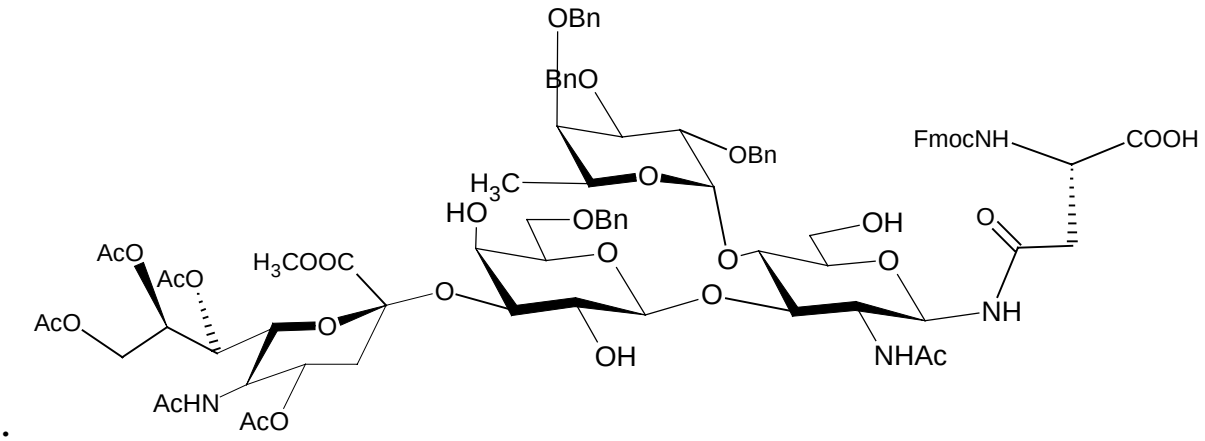
Glycopeptides

Glycopeptides are defined as fragments of glycoproteins consisting of saccharide units which are covalently linked to peptide backbone . They are implied in glycoconjugates such as Sialyl Lewis X, and A. these glycopeptides are of particular pharmacological importance because they are described as stage-specific embryonic and tumor associated antigens. They have been identified as ligands of selectins. Selectins are carbohydrates recognizing receptors in the surface of endothelial cells involved in cell adhesion phenomenon. Both of these regioisomeric tetrasaccharides are tumor associated antigens specifically expressed in carcinoma cells and involved I-metastasis. Sialyl $X^{(7,8,9,10,16)}$ is mainly found on transformed epithelial liver's cells, lung, and stomach. Sialyl A is expressed in carcinomas in the intestine, pancreas, and small cells lung carcinomas. Chemical structures examples are depicted in fig. **2**.

Fig. 2.

Chimeric sialyl Lewis X-RDG peptide





Sialyl Lewis A-asparagine.

Glycolipids

Glycolipids [1,2,5,6] are a combination of sugar covalently bound to a lipid. The sugar contents moieties are constituents of a class of glycolipids called glycoshingolipids. They form a variable from a monosaccharide, to a polysaccharide unit, galactose and glucose.

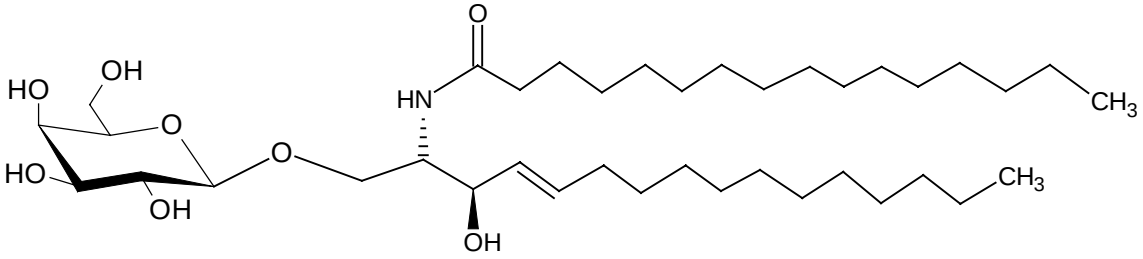
They are amphiphilic components of plama membrane of all vertebrate cells and occur in intracellular membranes of the secretory and endocytic pathways e.g. in golgi (trans Golgi network).

As all lipids, glycoshingolipids contain a hydrophylic and lipophilic part. The lipophilic part consist of either a 1,2 di-O-diacetylglycol, or n-acylshingosin. The hydrophilic entity in glycoshingolipids is N-acylshingosin and is called ceramide. It anchors complex GSL's in the outer leaflet of plasma membrane so that, their hydrophillic oligosaccharide residue faces the extracellular space.

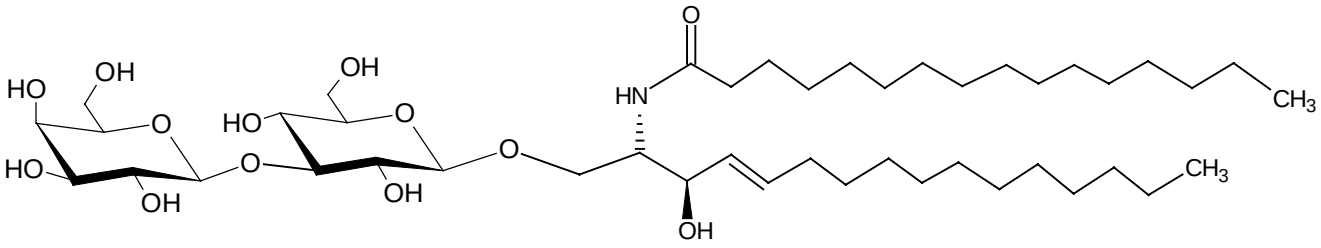
The nature of both the hydrophilic chains in the ceramide moiety and in paticular their carbohydrate content varies considerably. Among the structures known are two examples.

The simple shingolipids are called cerebrosides and contain only one monosaccharide per saccharide per ceramide, such as glucosyl cerebrosides and galactosyl cerebrosides. (Fig. **3**).

Fig. 4.



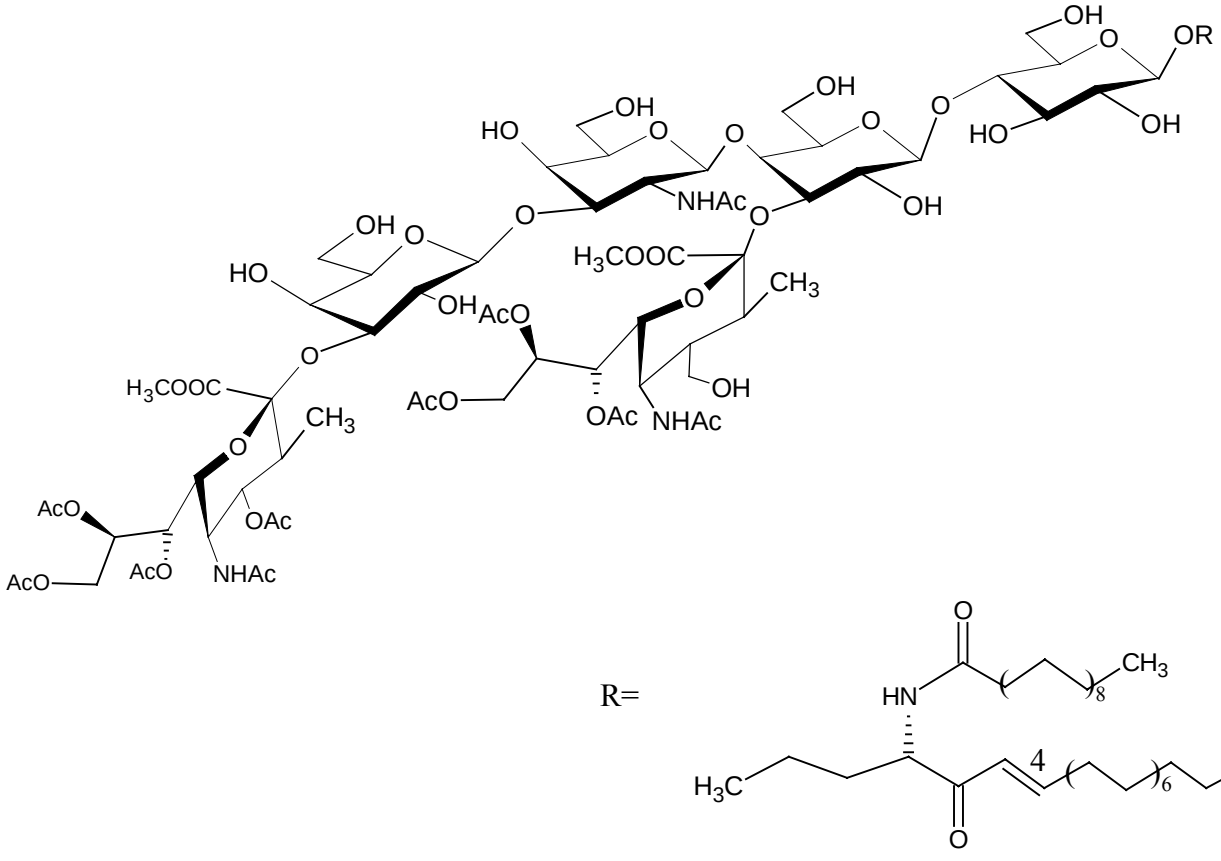
Galctosyl Cerebroside



Lactosyl Cerebroside

The latter are widely spread and distributed in the membranes of neural cells. The most complex sphingolipids are called gangliosides. Gangliosides are enriched in the brain, prevailing neuronal and particular synapting membranes as well as in growth cones. The oligosaccharide chains of glycoshingolipids are binding sites for lectins, specific carbohydrates, recognizing problems such as, bacterial toxins, binding proteins of viruses antibodies which by means of binding cell surfaces might influence activity. An example of many known structures is showed in fig. **4**.

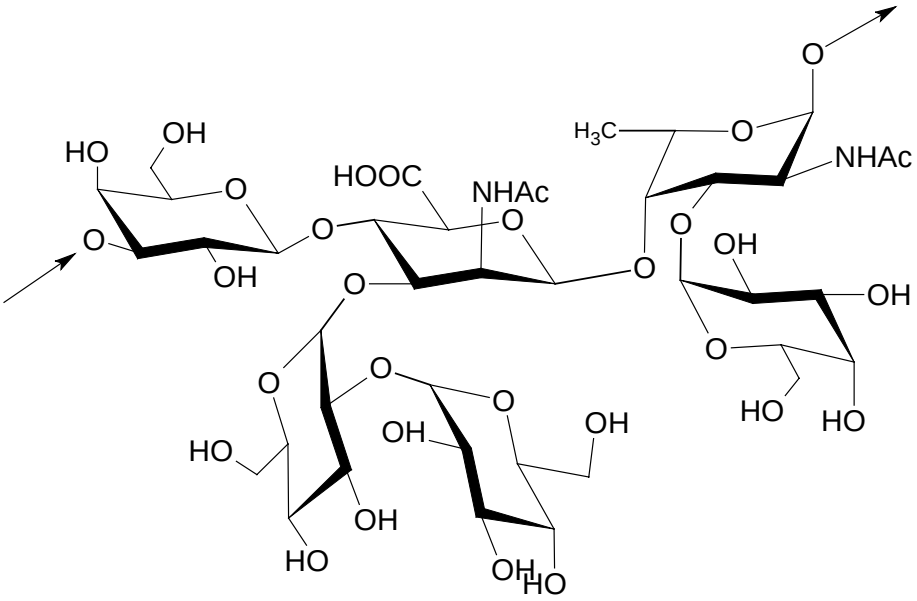
Fig. 4.

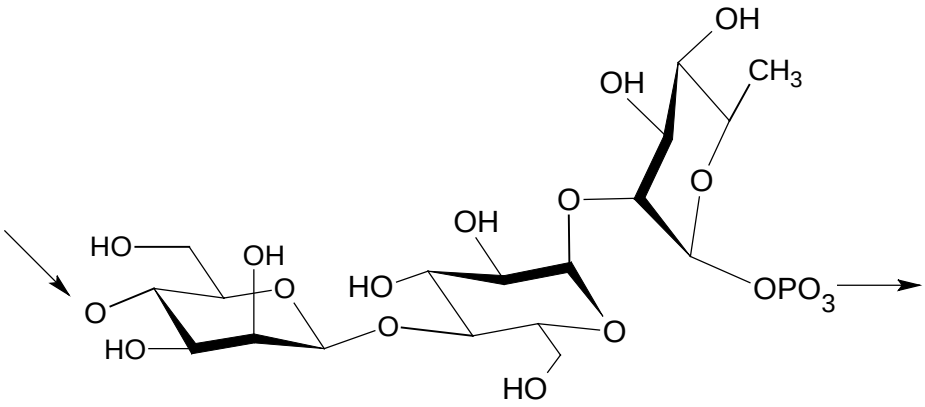


Capsular polysaccharides [10,15] are a class of carbohydrates found in different types of bacteria and organism.The structural determination of capsular polysaccharides was analysed by Heidelberger in 1923, who demonstrated that, in fact, a particular type of specific polysaccharide antigen was able to precipitate quantitatively, antibodies produced by animals by injection of the homologous whole organism. He and his associates demonstrated in a subsequent pioneering work that pneunococcal polysaccharides provide a type- specific protection against pneunoccocal infections. This phenominal success lead to the promising future of a polysaccharide vaccine's development. One of the organism that produces this class of carbohydrate is the Streptococcus Pneumoniae[13,14,15,16]. Streptococcus pneumoniae are Gram-positive organism which like the group B Streptococcus pneumoniae, have a common group antigen (C-substances), and different type-specific, capsular polysaccharides. There are at least 84 known type-specificities, and these have been designated types 1-84 in the American system. Bacteria of this genius are the main cause of otitis media in junevils and pneumonia in immunocompromised individuals. This latter infection is unfortunately one of the major cause of death in the industrialised countries. Nowdays, many investigations are being conducted toward a desirable vaccine against S. pneumoniae.

Among the many structures of capsular polysaccharides from S. pneumoniae are type 12 F and 19F (Fig. **5**.)

Fig. 5.





Structural Analysis

The rapid development of more materials and analytical techniques [1,2] have led to significant progresses to the understanding of structural complications of biological functions of carbohydrates, so important for the medical and pharmaceutical field and the development of new drugs Techniques such as, column chromatography, analytical and preparative HPLC largely facilitates seperations of isomers and their purifications which constituted in the past a hurdle that hampered early carbohydrate chemistry.

The structural analysis of carbohydrates has been revolutionized by a new efficient methods of NMR spectroscopy, one dimensional and especially the development of two dimentional NMR such as, H-COSY, C-C COSY, HMBC, NOESY, TOCSY, ROESY, etc. These NMR spectrosopic techniques have emerged to such point that, subtle events can now be probed e.g. the role of sructure and dynamics, is the binding of oligosaccharides to complementary receptors.

New frontiers for the analysis of micogram quantities of complexed carbohydrates has been opened. The mass spectroscopic analysis carbohydrates containing molecules, underwent a revolution with matrix assited laser desorption/time of flight and, electrospray ionization technique such as, FAB, and High performance Electropherisis now used to probe cellular glycosylation events with the ultimate goal of cell analysis.

Structural informations derived from X-ray crystallography and molecular modelling have also gained a large importance in explaining for example regio-stereoselective intramolecular reactions in complex carbohydrates.

The advances explained above, can be matched in parallel of impressive development of molecular biology, and the application of molecular biological techniques in structural biology. The use of these different techniques in molecular biology, allow to better elucidate the biosynthesis studies of carbohydrates and their derivatives. Knowledge of biosynthetic pathways, can be extremely advantageous for treatment of diseases, the engeneering of desired properties in carbohydrates, process enzymes, or carbohydrates polymers and design of carbohydrate based therapeutics, immunodiagnostics, and vaccines.

GENERAL AND THEORETICAL PART

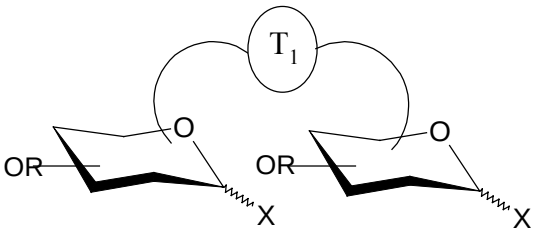
INTRAMOLECULAR GLYCOSYLATION METHODS

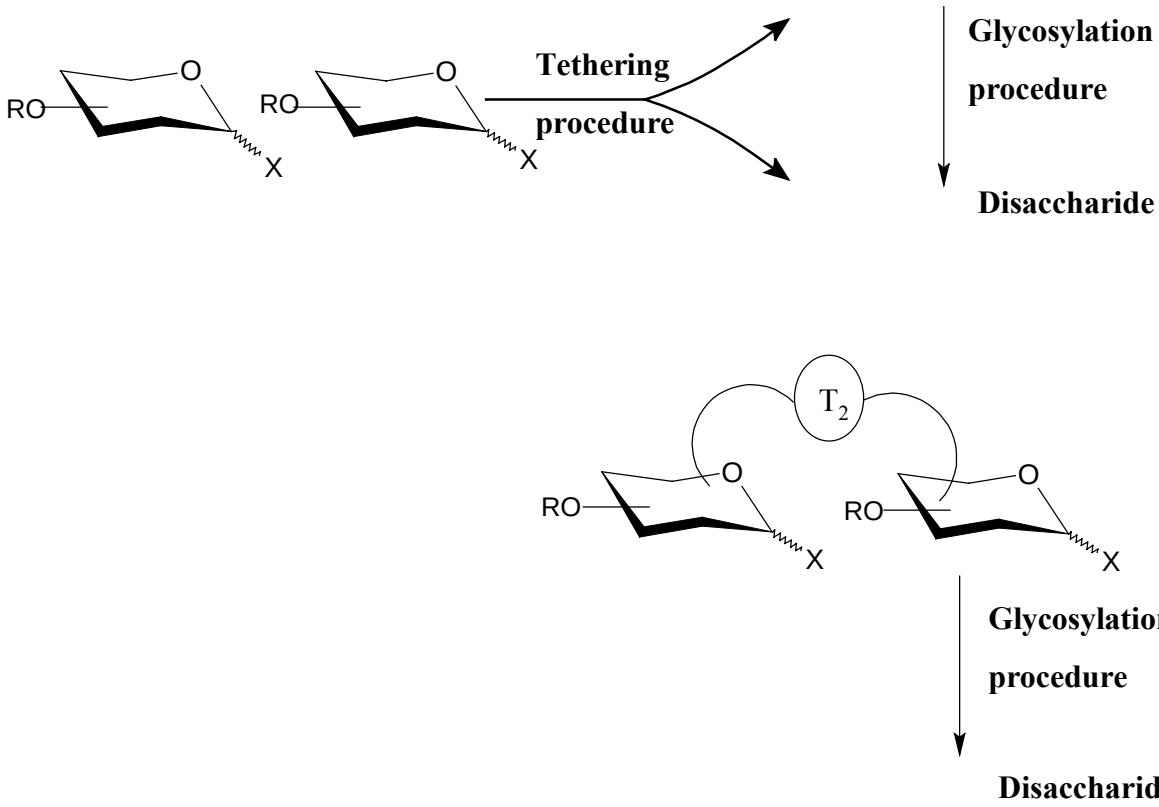
During decades in glycochemistry, chemist have been faced with the challenge of a cumbersome task,to conceive an efficient method for the stereocontrolled synthesis of oligosaccharides. The glycosylation reaction between a glycosyl donor and acceptor bearing free hydroxyl group leads to unpleasant anomeric outcomes due to the formation of several undesirable anomeric mixtures.

The problems usually encountered are the lack of regioselectivity and stereoselectivity.
To circumvent this problem, organic chemist introduced an ingeneous and appealing method of intramolecular glycosylation.
This term is define as a type of reaction in which aglycosyl donor is linked to a glycosyl acceptor by means of a tether producing a O-glycoside bond.
The tether can be temporary and is removed during glycosylation, or a stable tether that is cleaved after glycosylation reaction. (Scheme **1**)

Scheme 1.

T_1= temporary tether, T_2= stable tether





Intramolecular glycosylation reactions are divided into three classes of spacer-mediated - linkages of the acceptor to donor. (Scheme **2**).

Leaving Group Bases Intramolecular Glycosylation:
The glycosyl acceptor is attached to the leaving group od the glycosyl donor. Upon release of the leaving group, the acceptor atom is transfered to the anomeric carbon.

Linkage of the Acceptong Atom via a Bifunctional Group:
The acceptor is linked to the glycosyl acceptor via a bifunctional group, generally 2'- O.
Once the leaving group is released, linkage to the accepting atom leads to cleavage of bifunctional group in the same step or later during the work up (" functional based intramolecular glycosylation"), "temporary silicon connection", " silicon tethered intramolecular gly cosylation").

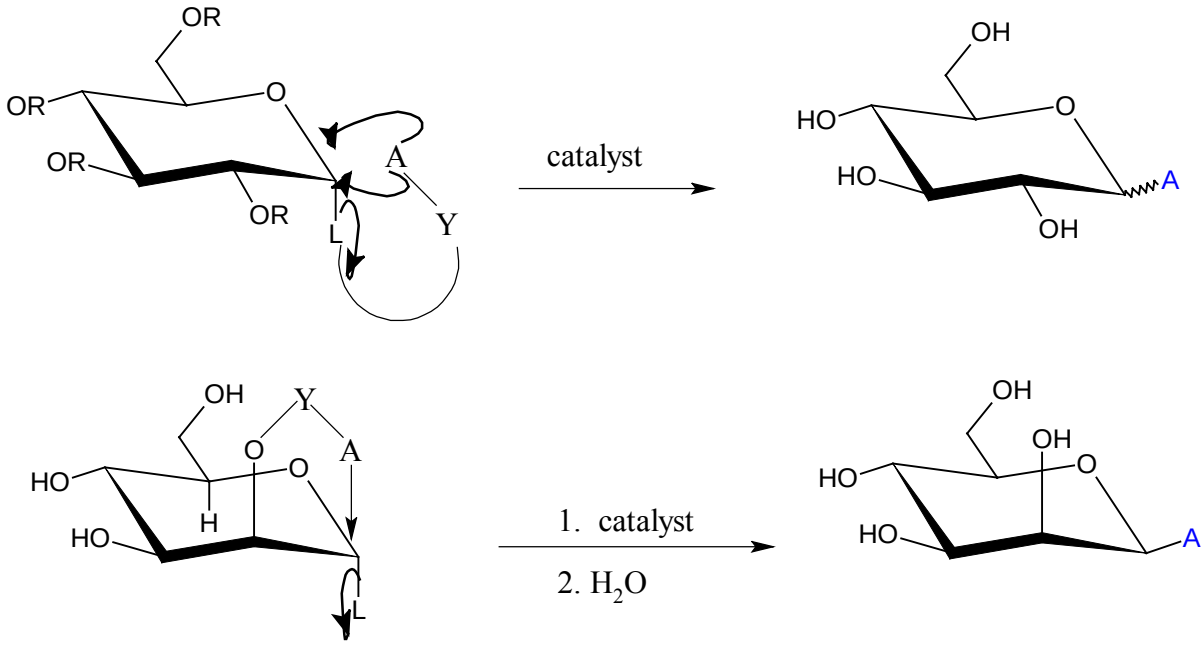
Spacer-mediated Linkage via Nonreacting Centers :
Here the glycosyl acceptor is linked through a tether at any finctional substituent to at any position of the glycosyl donor and contain generally one or more unprotected hydroxyl groups to be glycosylated.

CHAPTER I

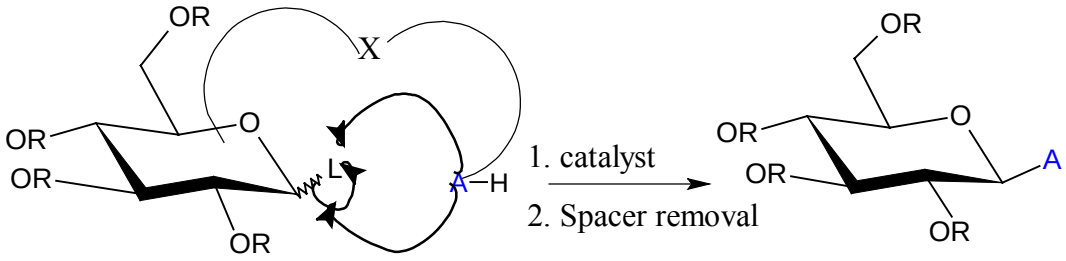
LEAVING GROUP BASES

INTRAMOLECULAR GLYCOSYLATION

Scheme 2.



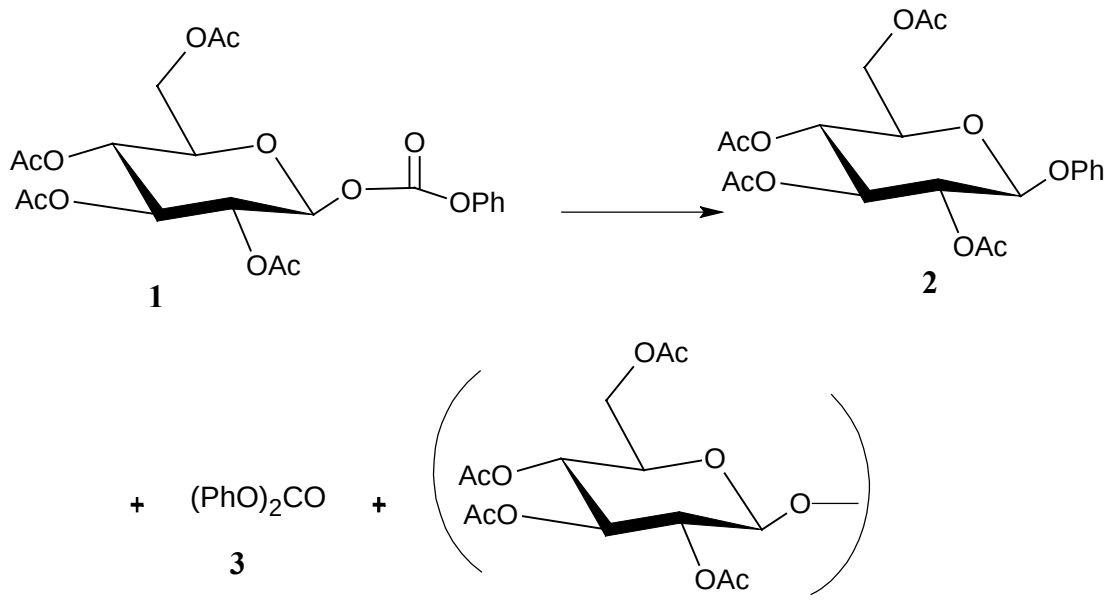
Scheme 3.



Leaving group Bases Intramolecular Glycosylation

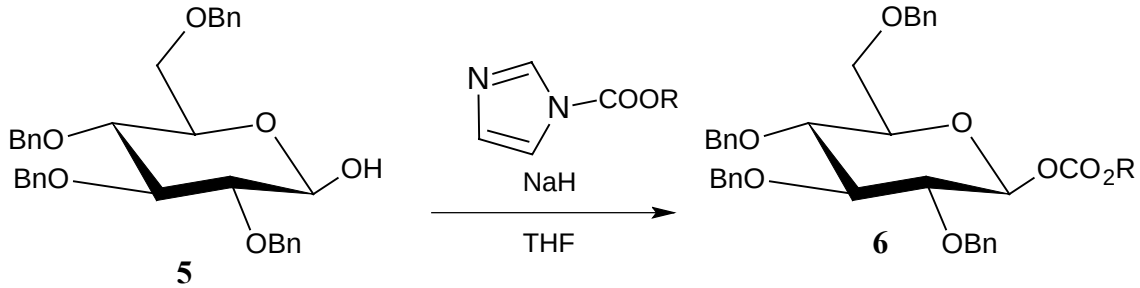
The first example of this type of intramolecular glycosylation was reported by Yoshiharu Ishido and coworkers in 1973, [18,19] for the synthesis of phenyl-ß-D glucopyranoside.They were inspired by the theory that the replacement of alkoxy moiety of the alkyl aryl carbonates with a hemiacetal moiety such as glycosyloxy substituents might bring about a considerable enhancement of their their reactivity. Indeed the pyrolysis of the phenyloxycarbonyl ß-Dglucose tetraacetate at 170°C afforded 74% overall yield , that is 46% phenyl 2,3,4,6, tetra-O-acetyl- ß-D glucopyranoside **(2)**. diphenyl carbonate **(3)** in 11%, and bis(2,3,4,6-tetra-O-acetyl-ß-D-glucopyranose 1,1 carbonate **(4)** in 17% yield . (Scheme **4**.)

Scheme 4.



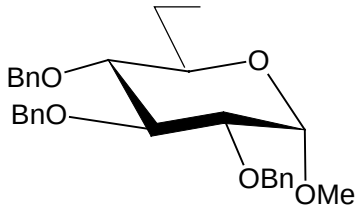
A decade later a novel decarboxylated intramolecular glycosylation was reported by Ikegami et al.[20] by using carbonate as a connector between donor and acceptor glycosyl. In a first synthetic investigation, 2,3,4,6-tetra-O-benzyl-ß-D-glucopyranose **5** was the donor candidate of choice.The instability of clorofornates, and risk of mixed carbonate formations prompted them to other alternatives. Scanning carbonates by the choice of 4-nitrophenyl carbonates (activating group **X**=4-nitrophenoxy) and imidazolide(**X**=imidazoyl) to be the proper candidates because of their moderate reactivity to connect to two different alcohols sequentially.
Reaction of the tetrabenzylated ß-D - glucose donor with 4-nitrophenylcarbonate, in the presence of NaH in THF afforded mixed carbonates as anomeric mixtures.With carbodiimidazole the desired product was obtained and use instead of 4-nitrophenyl carbonate (Scheme **5**.)

Scheme 5.



They than examined intramolecular decarboxylation reaction by surveying promoters with TMSOTf, TBDMSOTf. The use of different solvents was also crucial for the obtention of higher selectivity. In propionitrile, no reaction occured while with other solvents such as, toluene and mesitylene, 62 to 85% yield were afforded, (see table1)

Table 1.

entry	R	catalyst and solvent	yield	α/ß
1		TMSOTf, mesitylene	78%	16:84
		TBDMSOTf, mesitylene	72 %	16:84

Application of this glycosylation reactions to galactopyranose 1-carbonates **8** was somewhat confusing, with yiels obtained between 62 to 72%, and an anomeric out come predominantly alpha glycosidic bond. The lower yield of ß-anomer afforded from these glycosylations is rationalised by the the enhancement of alpha selectivity. No explaination of this curious selectivity had been elucidated, the location of the 4-O-benbyl group on the galactopyranose which interact with the Lewis acid (trialkyl triflate), and might play a role in the stereochemical outcome ot the reaction. These reactions are summarized in the following (Scheme **6** and table **2**).

Scheme 6.

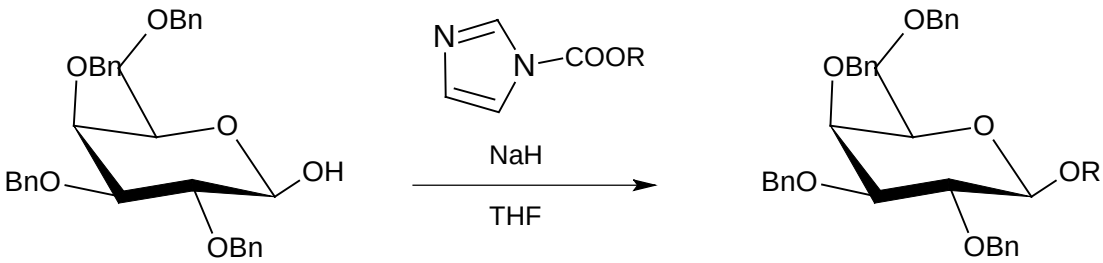
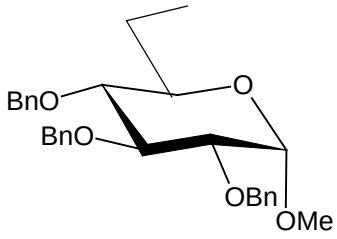
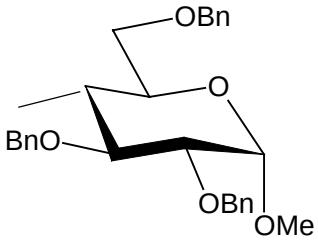
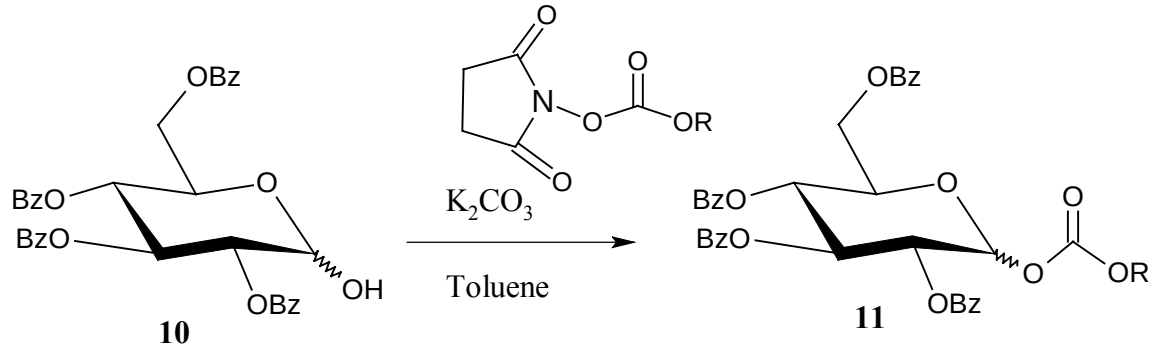


Table 2.

entry	R	catalyst and solvent	yield	α/β
1		TMSOTf toluene	83%	46:54
		TBDMSOTf, toluene	62%	62:38
2		TMSOTf toluene	83%	42:58
		TBDMSOTf, toluene	62%	34:68

In a futher investigation, Shiro Ikegami and coworkers prepared mixed ß-carbonates of benzoylated protected donors by using an N-succinimidyl group for activation of the acceptor alcohol **OR**,[21] and smooth decarboylation with TMSOTf afforded preferentially ß-glycosides in exellent yield. Herein, were glucose and galactose benzoylated pyranose choosen as donor, candidates, and as acceptor, glucose and galactose benzylated pyranoses. (Scheme **7**, and table **3**).

Scheme 7.



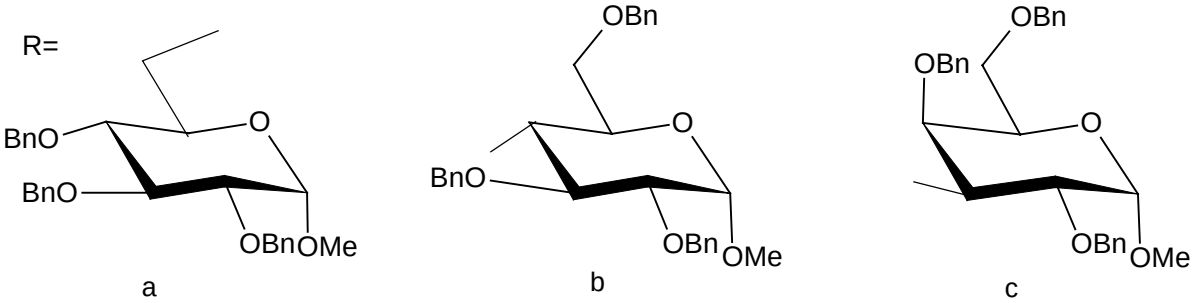
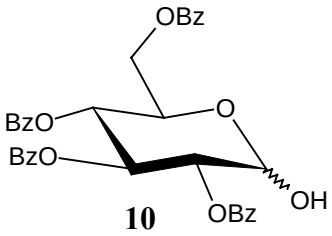


Table 3.

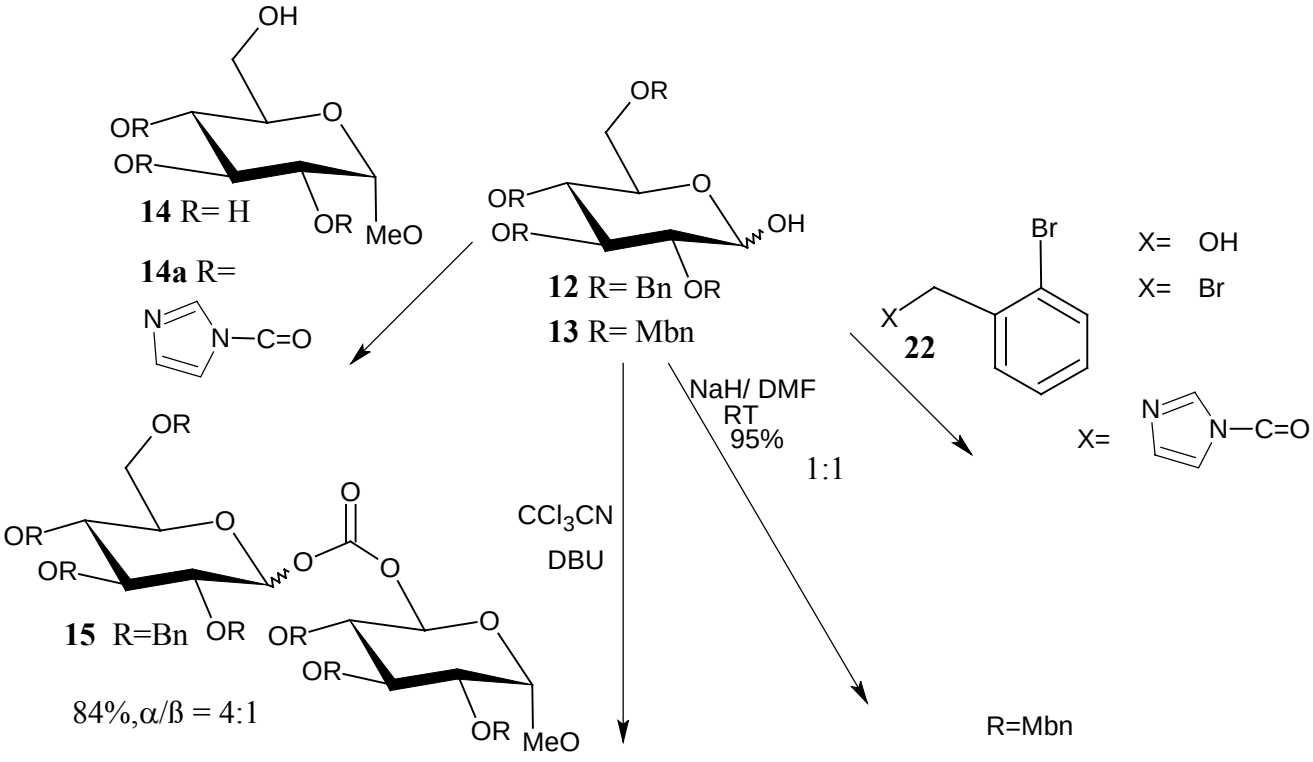
donor sugar	Base (eq.)	R= acceptor	solvent	yield (%)	
 **10**	K_2CO_3 1.1	a	toluene	88	1:99
	K_2CO_3 1.1	b	toluene	79	1:99

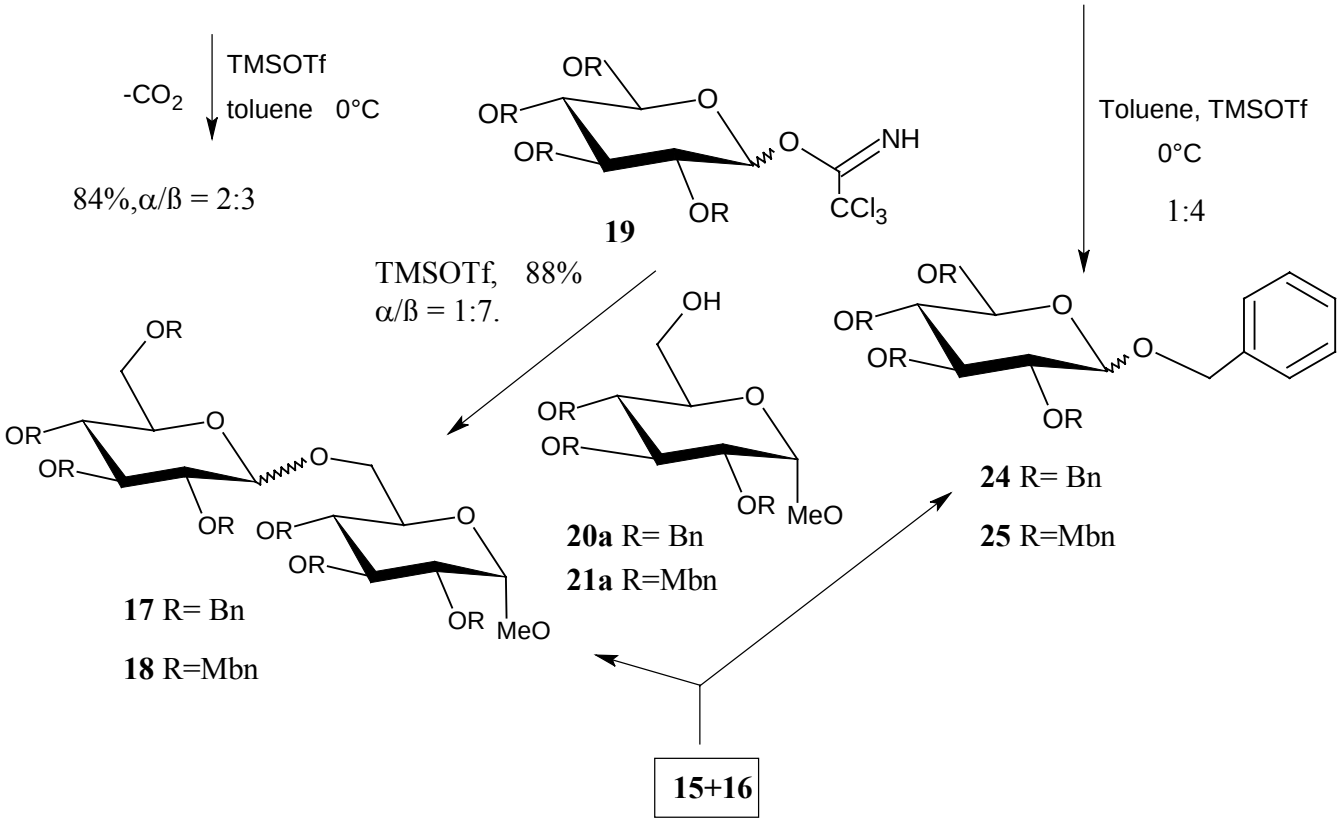
Glycosylation reaction with TMSOTf, in toluene resulted to the exclusive obtention of ß-glycosydic bond disaccharide with anomeric ratio of 1:99.

The same investigations carried out with benzoylated protected galactose derivatives in the same conditions gave the same predominantly ß-anomeric dissacharide with also exellent yields.

The decarboxylation glycosylation was reinvestigated by Smith et al.[22] in order to distinguish between intra versus intermolecular reaction. They differentiated intramolecular versus inter molecular reaction courses by ligating two glycosyl donors and acceptors, each of similar reactivity via the leaving group. (See below scheme **8**).

Scheme 8.





The combination of **12**,**13**, and reacting with imidazolecarboxylate **14** and **14a** leads to mixed Carbonat **15,16** with α/ß mixtures respectively. The following treatment of both compounds with TMSOTf resulted to decarboxylative lost of CO_2 and the desired dissacharides **17** and **18** in high yield. When the synthesis of **17**,**18**,**24**,**25** were established, the starting materials **12**,**13**, underwent con vertion to the corresponding imidates **19**, and glycosylation with **13** activated by TMSOTf afforded the same desired dissaccharide **17**, **25** in high yields. Products **23**, and **25**, were obtained by α anomeric O-alkylation of **12**,**13**, and **14a** as alkylating agent, which led to α/ß mixtures 1:1. For the decisive competition reactions experiments, equimolar amounts of **15** and **16** were used under varying condtions. This is summarized in the below table **4**. As observed in none of the experiments, a preference for formation of **17** and **18** was produced by intramolecular glycosylation reaction; the cross products **21** and **22** were practically found in equal amounts. Less products **21** and **22** were obtained for the use borontrifluoride as an activator; the attribution of this reason that the O-(3-methylbenzyl)- protected glycosyl donor moiety show less stability in comparison with O-benzyl protection. Products **17** and **18** are than less stable under the condition condition reactions, decarboxylation glycosylation follows an intermolecular reaction course. It is assumed that TMSOTf , for instance, disintegrates the mixed carbonates under loss of CO_2 into glycosyl triflates(contact ion pairs) and silylated acceptors which with long persistence

lead to complete scrambling in product formation. They therefore demonstrated, that decarboxylative glycosylation follows an intermolecular reaction course.(Table **4**)

Table 4.

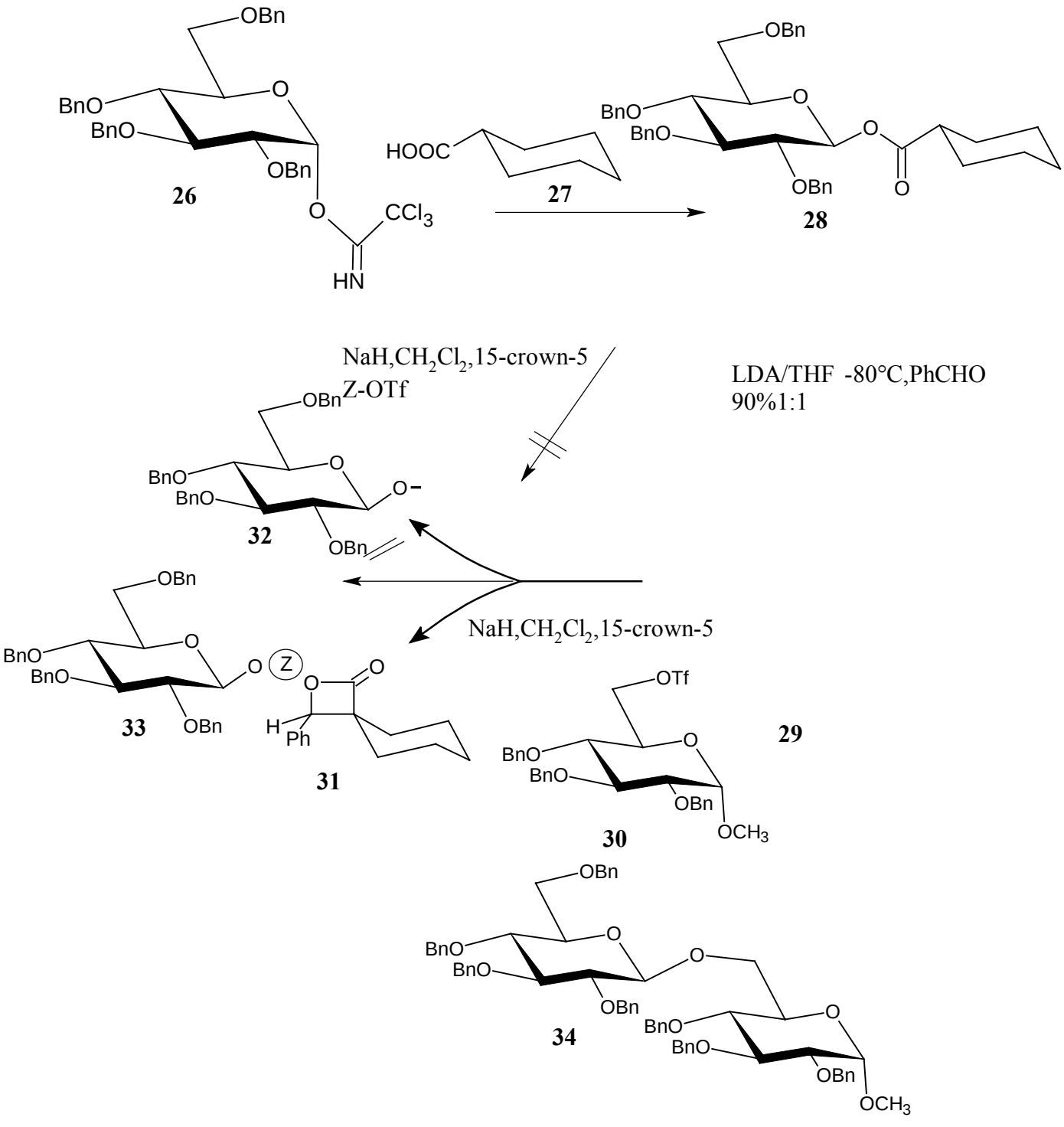
Competition experiments: Decarboxylative glycosylation with equimolar amounts of 5 and 6.

Entry	Reaction conditions			yields (%)			
	Solvent	Promoter(1:1 eq.)	Temp[° C]	**17**	**24**	**25**	**18**
1	Toluene	TMSOTf	0°C	37 (α:ß=1:1.5)	37	44 (α:ß = 1:2.5)	41
2	Mesitylene	TMSOTf	0°C	35 (α:ß= 1:3.7)	35	45 (α::ß =1:3.6)	45
3	Toluene	TBDMSOTf	0°C	40 (α:ß= 1:2)	40	41 (α::ß =1:3.5)	41
4	Mesitylene	TBDMSOTf	0°C	40 (α:ß= 1:3.6)	40	43 (α::ß =1:3.6)	43
5	Toluene	BF_3OEt_2	r.t.	37 (α:ß=1.4:1)	37	44 (α:ß = 1:1)	41

By these competion experiments, Smith *et al.* demonstrated that decarboxylation glycosylation follows an intermolecular course.

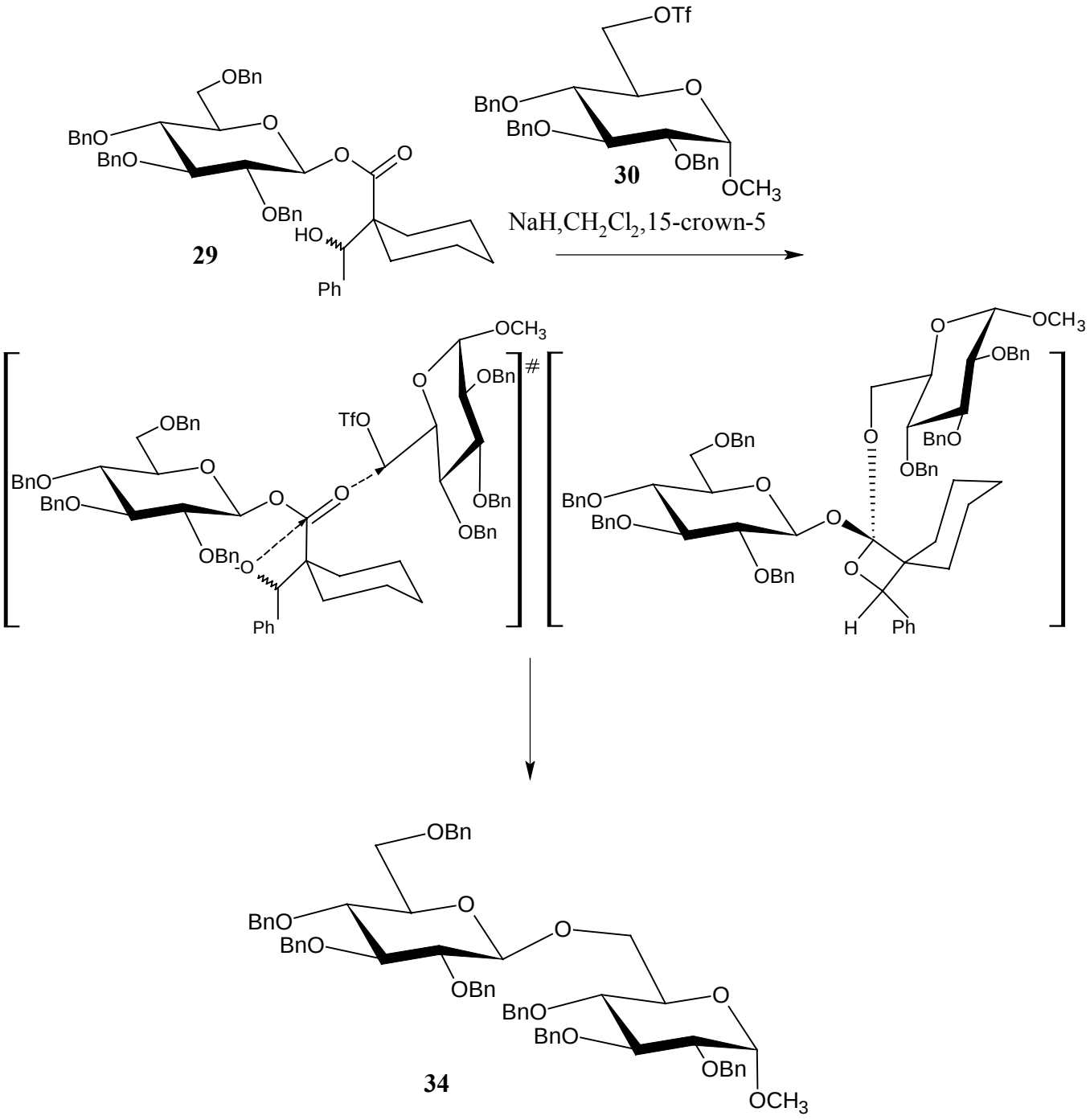
The successful investigations in showing that decarboxylative glycosylation was partially or completely intermolecular, prompted Smith and coworkers [(23)] to further elaborations toward new systems of intramolecular glycosylations, and this with the in "situ tethering" of cleaving group based intramolecular glycosylation. Here orthoester intermediates were generated and presumed to transform diastereoselectively into glycosides and ß-lacones. The acceptor was presented as a result of the reaction between α- D-glucosyltrichloroacetimidate **26** with cyclohexane carboxylic **27** acid to the desired ß-connected glucoside **28**. Aldol condensation with benzaldehyde and lithiumdiisopropylamide (LDA) furnished 1:1-diasteromeric mixture of ß-hydroxycarboxlate **29**. (Scheme **10**.)

Scheme 10.



Reaction of **29** with **30** in the presence of NaH and 15-crown-5 as a base system afforded the disaccharide **33** with a very good selectivity with a α/ ß ratio of 1:6, at 0°C this ratio was increased to 1:10. The formation of the desired ß-D-disaccharide is rationalized by the mecanism depicted in the below scheme **11**.

Scheme 11.

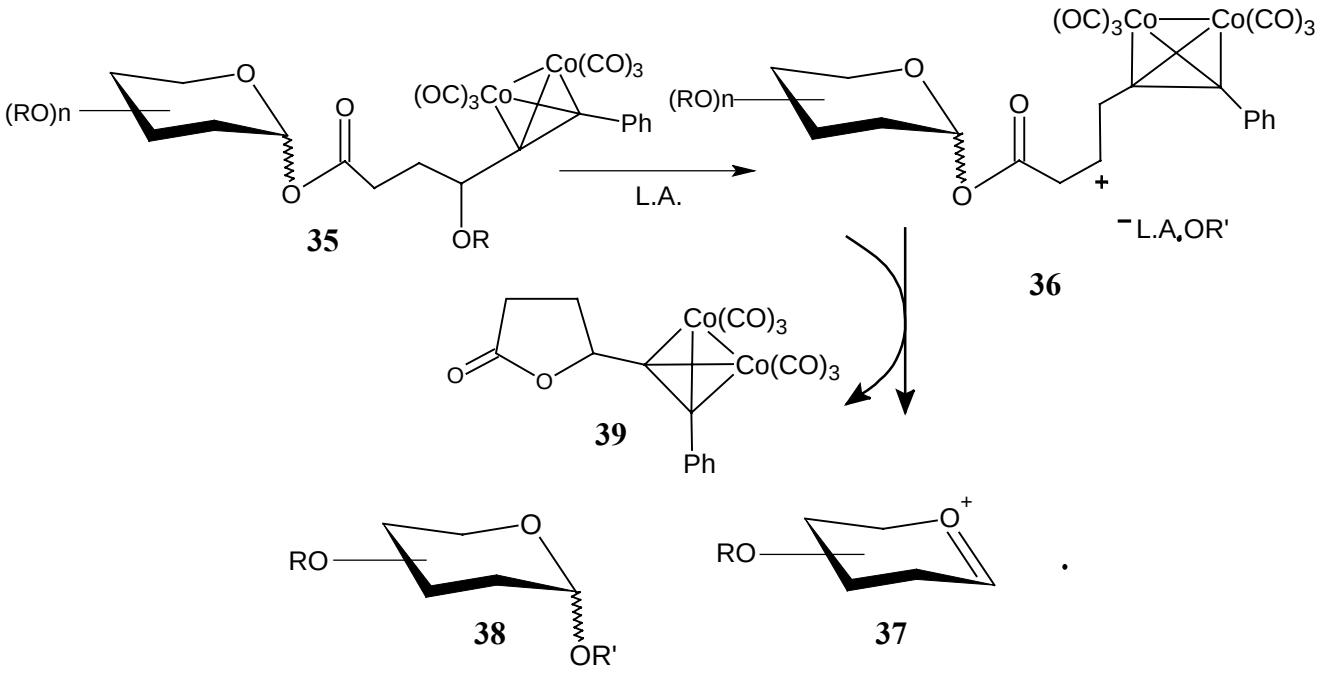


The reaction of **29** with α-D-glucopyranoside-6-O- triflate **30** in the presence of NaH-15- crown-5 as a base yielded first a strong alkylating agent on the hydroxy group of compound **29**. A nucleophilic attack of the oxide oxygen of the carbonyl group with concomitant alkylation of the more accessible carbonyl oxygen lead to the formation of an orthoester intermediate **A,** which

intermediate comprise a highly substituted four membered ring. Intramoelcular transformation of intermediate **B** by an intramolecular 1,3 glycosyl shift will alleviate steric strain, thus furnishing disaccharide **34** and ß-lactone **31**. (See scheme **11**).

In another case Mijoji Hanaoka and coworkers reported a reaction based on an alkyne $Co_2(CO)_6$ complex[24]. Here,a glycosyl -6-phenyl-5hexynoate glucose derivative was converted into a corresponding cobalt complex. Activation with a Lewis acid,(TMSOTf), afforded the production of the propyl cation specie which is stabilised by the cobalt complex moiety. The alkoxy acceptor moiety is released and intramolecularly captures the oxonium donor **37**and generate **38**.(Scheme **12**.)

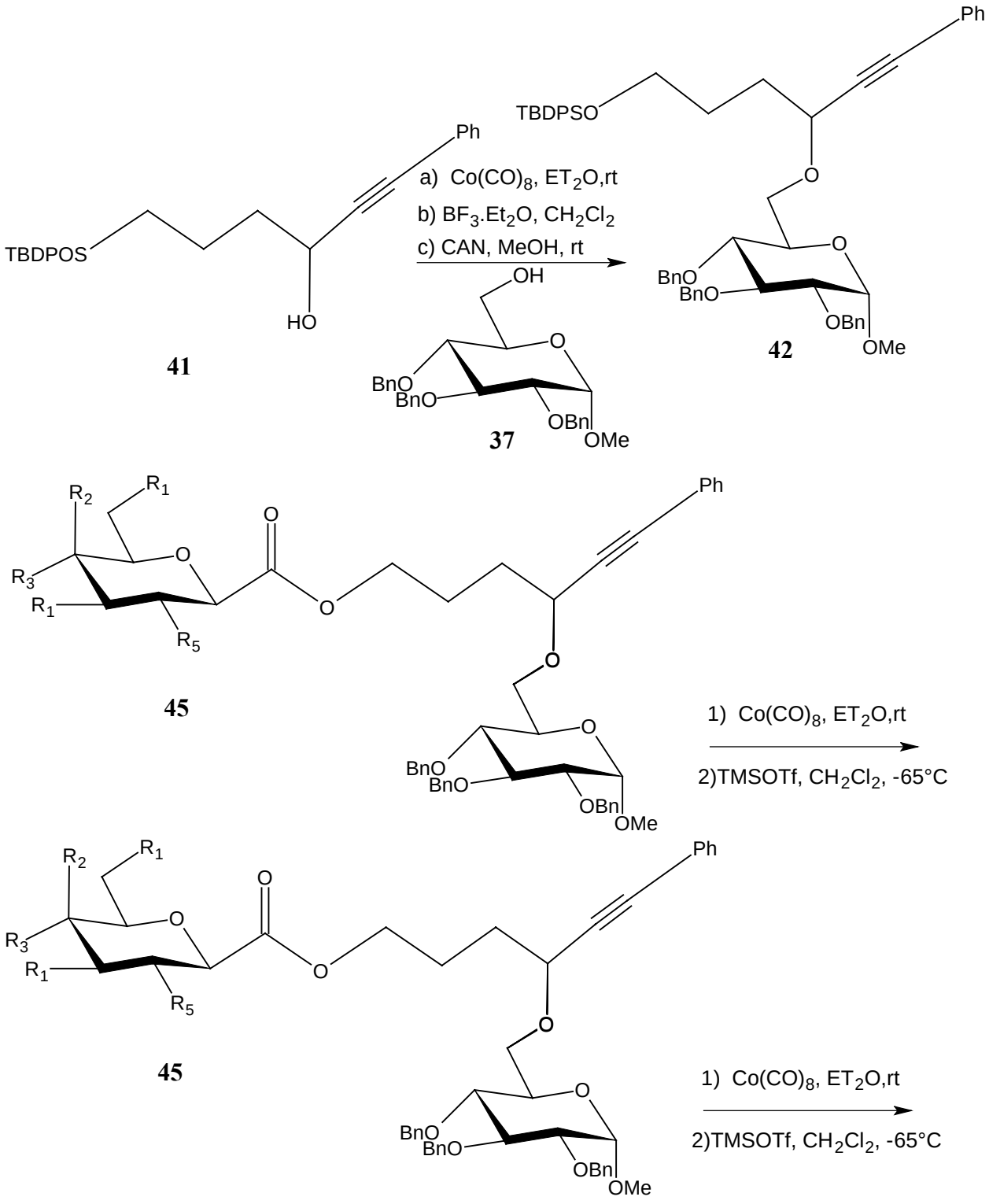
Scheme 12

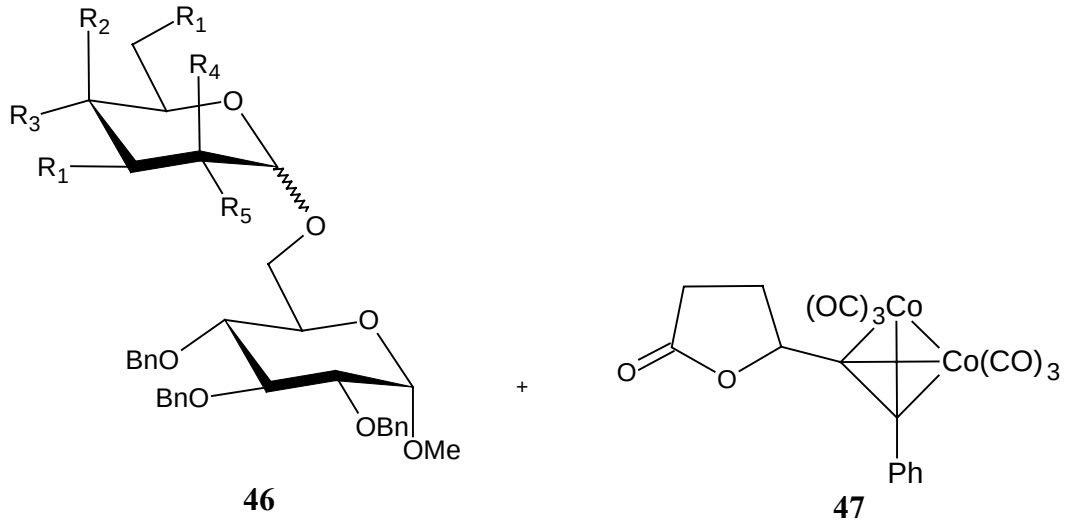


In applying this method to the synthesis of various disaccharides, the starting substrates chosen were glucosyl, and mannosyl hexynoate donor, and tetrabenzylated glucose acceptor. Reaction complexation of compound **40** by $Co(CO)_8$, followed by treatment with the tetrabenzylated glucosyl acceptor **41** with $BF_3.OEt_2$ in CH_2Cl_2 at 0°C, and decomplexation with CAN afforded **42** at 74% oveall yield. Removal of the protecting group at the primary alcohol with TBAF gave alcohol alcohol **43** in 92%yield. The oxydation of compund **9** with DCC in DMF furnished the corresponding acid derivative, which than was submitted to esterification

with glycosyl donors **44** to produce **45** between 48 to 79% yield. The tethered disaccharide was than exposed to glycosylation reaction by complexation with the cobalt complex, activation with TMSOTf in dichloromethane or acetonitrile at very low temperature to obtain the disaccharide **46**. (Scheme **13**, fig.**6**)

Scheme 13.





46 **47**

Fig. 6.

a: $R^1 = R^3 = R^5 = OBn$, $R^2 = R^4 = H$, **b**:$R^1 = R^2 = R^5 = OBn$, $R^3 = R^4 = H$
c: $R^1 = R^3 = R^4 = OBn$, $R^2 = R^5 = H$, **d**: $R^1 = R^3 = R^5 = OBz$, $R^2 = R^4 = H$
e: $R^1 = R^3 = R^4 = OBz$, $R^4 = R^5 = H$

Table 5.

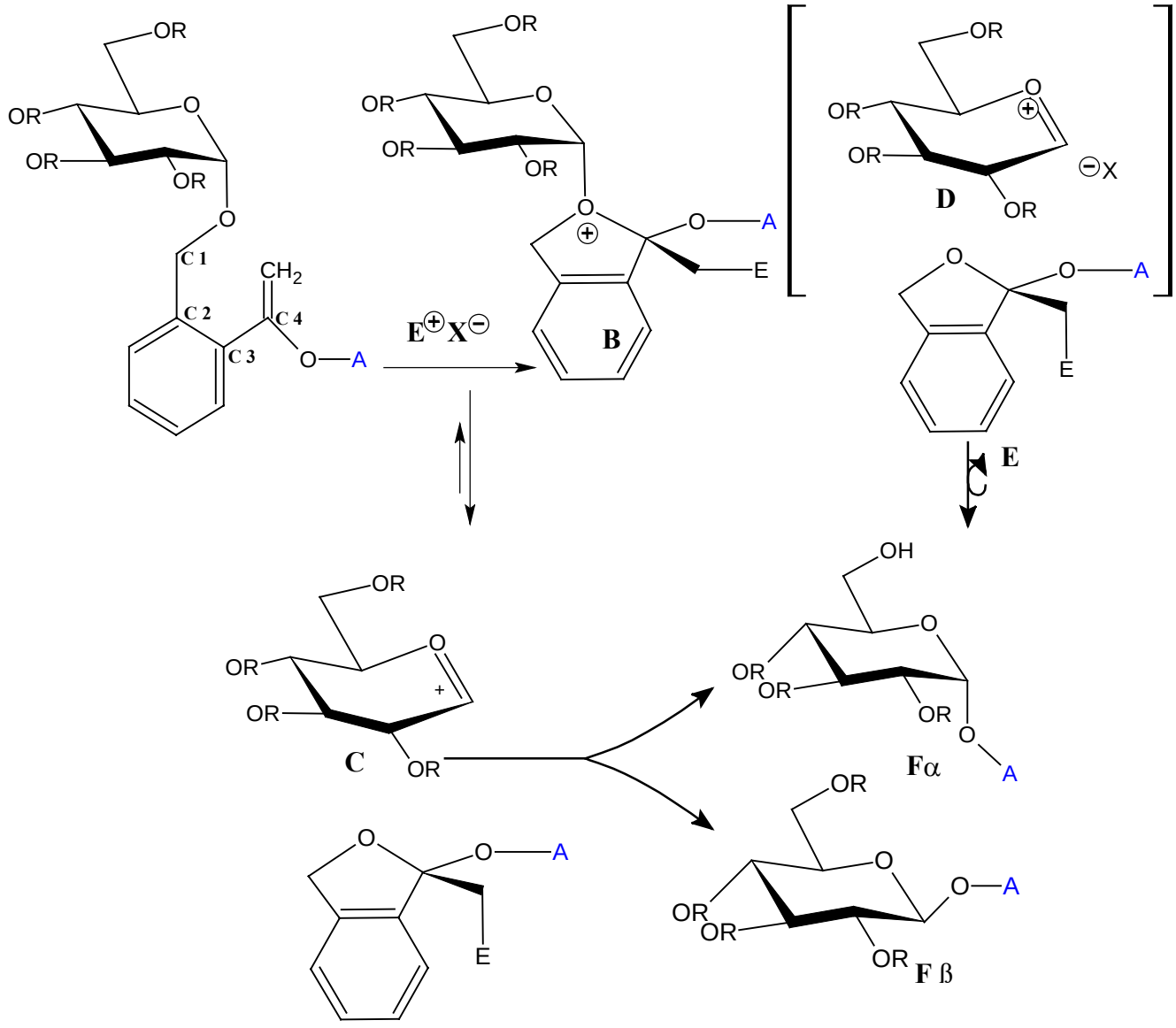
Glycosylation reaction of 11 *via* Internal Delivery Pathway

entry	substrate	α:β	solvent	temp(°C)	time	product(%)	(α:β)	**4** (%)
1	**35a**	(42:58)	EtCN	-65	10	**46a** (74)	(9: 91)	82
2	**35b**	(65:35)	EtCN	-65	1.5	**46b** (76)	(20:80)	87
3	**35c**	(26:74)	CH_2CL_2	-65	10	**46c** (65)	(94:4)	70
4	**35d**	(45:55)	EtCN	-65	1h	**46b** (37)	(1:99)	86
4	**35e**	(29:71)	EtCN	-65	10 min	**46b** (37)	(1:99)	86

By taking advantage of the inherent useful property of alkyne- $Co_2(CO)_6$ complex, precisely the easy generation and stabilization of popynyl cation by cobalt complex moiety, they had developped a new glycosylation method in which depending of the nature of the protecting groups, almost exclusively β or α anomeric outcome was obtainable. The most interesting results were with benzoate with its neighboring group participation starting with substrates **35d** and **35 e** in dichloromethane glycosylation reaction gave quantitative anomeric outcome β for the former and α for the latter.(See above table **5**).

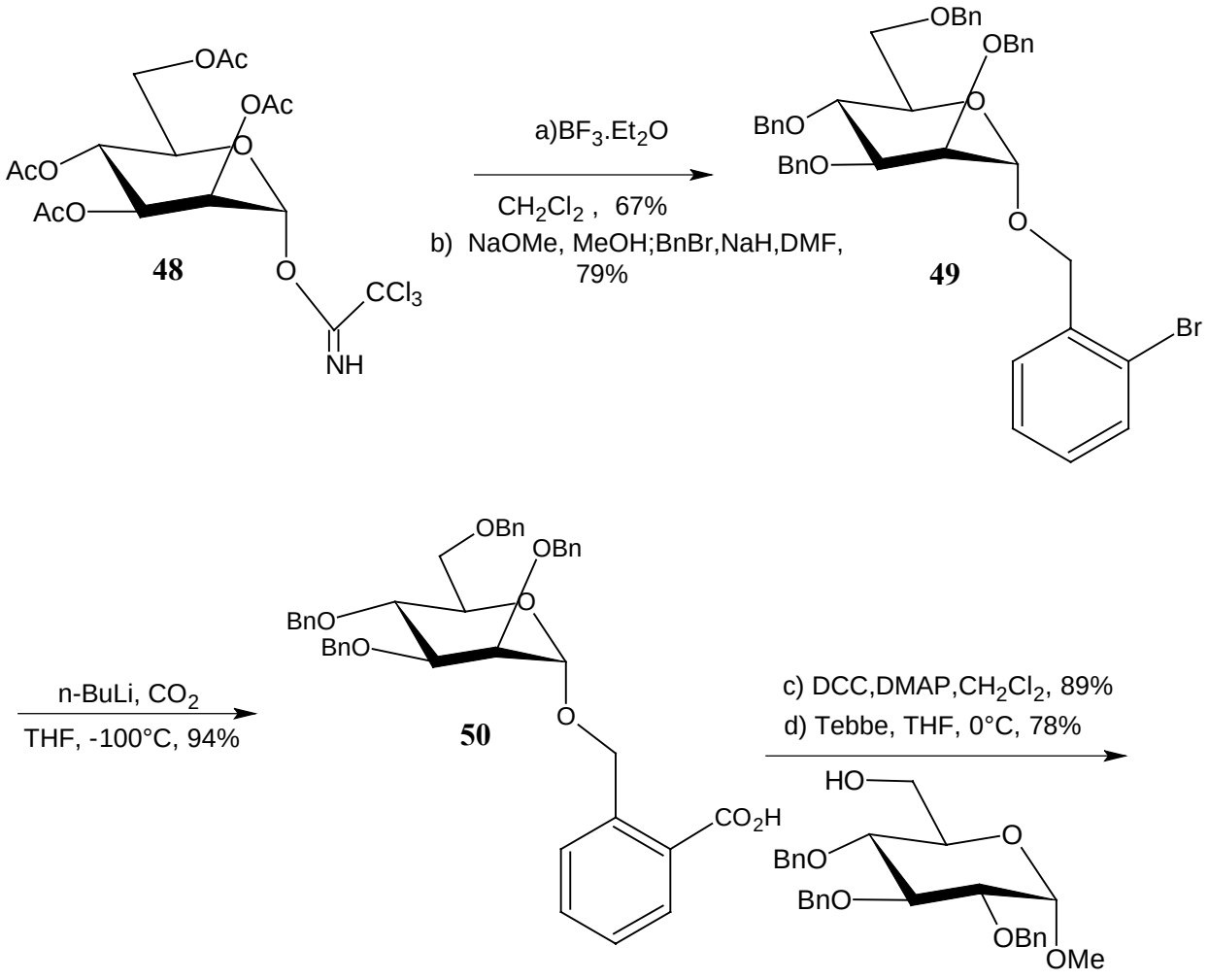
A pentenyl-type activation has been introduced by Smith et al.in order to study an intramole cular glycosylation. [25] A donor anomeric center and acceptor moiety are linked via a spacer consisting of a 4-alkoxypentadienloxy leaving group. The first step is the modification of the cis 2,4 pentadienyloxyl and attachement of the the acceptor moiety **O-A** at **C-4**, via an enolether linkage, which facilitate activation of **C-4-C-5** double bond by reaction with an electrolyte E⊕ X⊖ but also generates a close proximity of the anomeric carbon with the acceptor moity in intermediate **B**. Reaction between the pentadienyl spacer linked to the donor and an electrophile ensures bond reorganisation in a cage, either bond cleavage between anomeric cation an oxonium oxygen (**C** and **D**), resulting of a charged C^{+}donor moiety, **C** and nucleophilic oxygen of the acceptor linked to the spacer. The two outcome of this interaction are **F**α or **F**ß-glycosydic bond Fα, Fß. (Scheme **14**.)

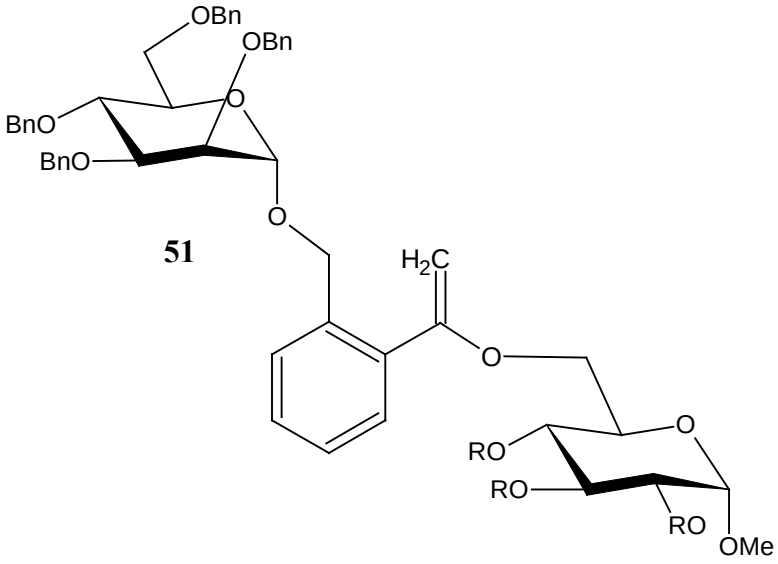
Scheme 14.



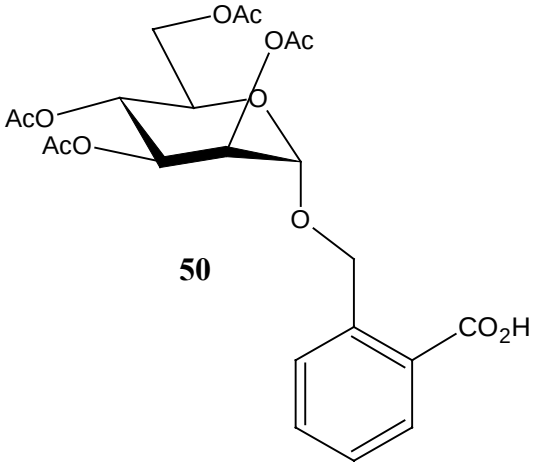
To test this concept detailed in the above scheme synthesis of disaccharides involving gluco-pyranoside and mannopyranoside were investigated.The first step involves the mannosylation of bromobenzyl alcohol with the tetraacetated α–D-manno acetimidate, **48** activated by BF_3.OEt, followed by deacetilation with NaOMe/MeOH and O-benzylation with BnBr in the presence of NaH in THF afforded α-D-mannopyranoside **49.** Carboxy- lation reaction by CO_2, in the presence of n-butyllithium in THF at -100°C furnished the benzoic acid derivateve **50**. Ester formation of **50** with and 4-O unprotected α-D- methylgluco pyranoside acceptor **20** in the presence of DCC/ DMAP and, methylation with Tebbe reagent gave the tethered disaccharide **51.** The same reaction route with a 6-O unprotected glucose **52** acceptor furnished the tethered dissacharide **53** Both disaccharides underwent glycosylation with phenylselenyl trifluoromethane sulfonate (PheSeOTf) in toluene at 0°C to afford both disaccharides **54** and **55** in 78 and 80% overall yield with excusively α as anomeric outcome, (Scheme **15**)

Scheme 15.

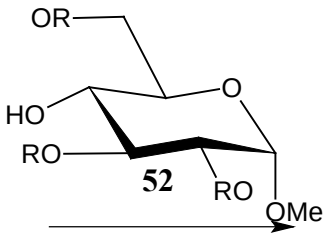




51



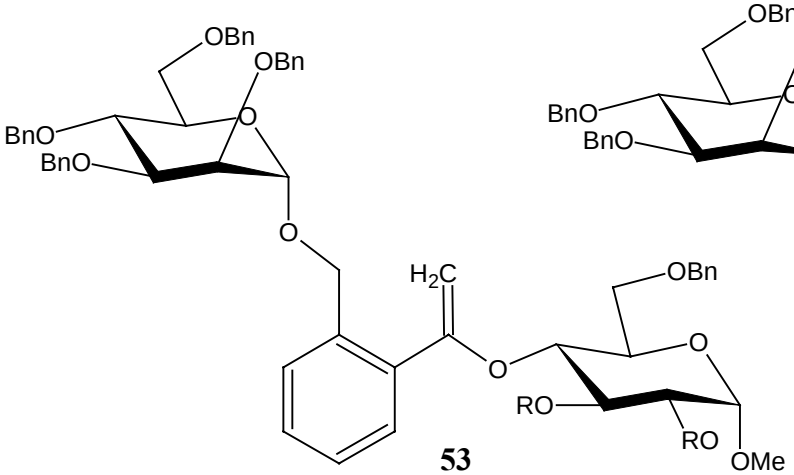
50



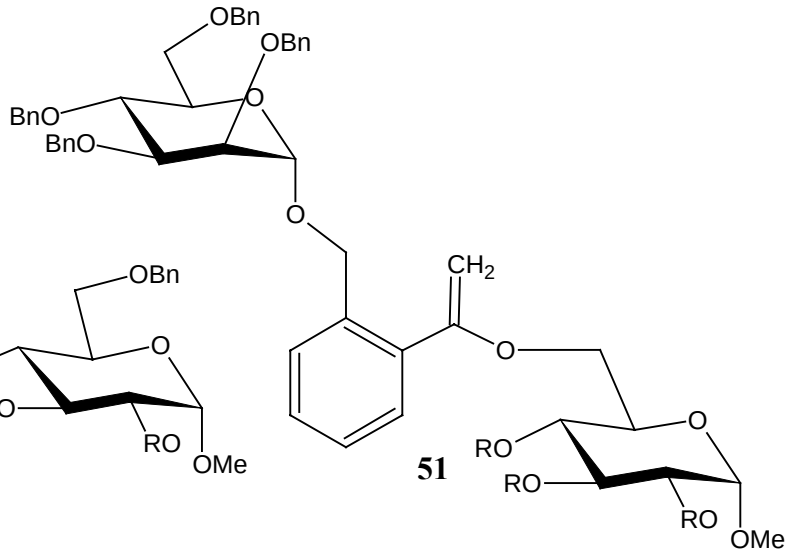
52

e) DCC,DMAP,CH_2Cl_2, 77%

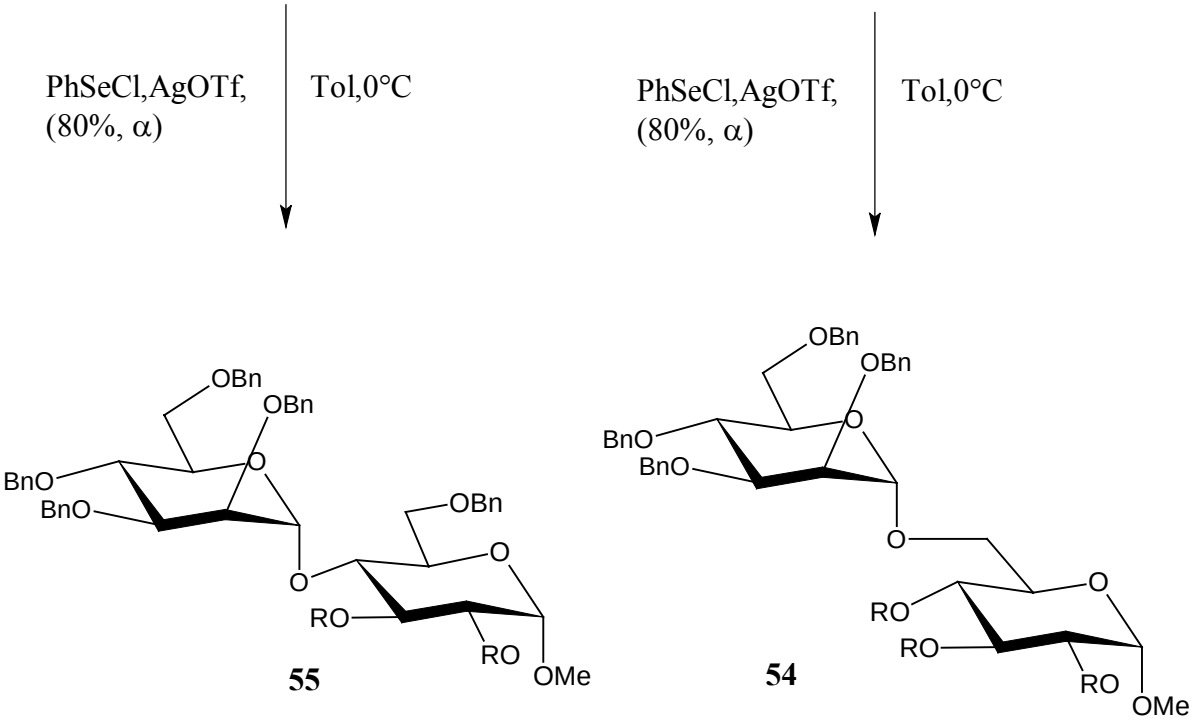
f) Tebbe, THF, 0°C, 80%



53

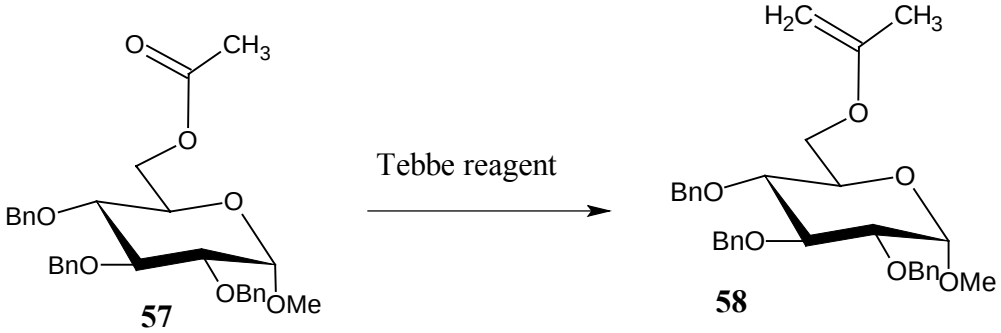


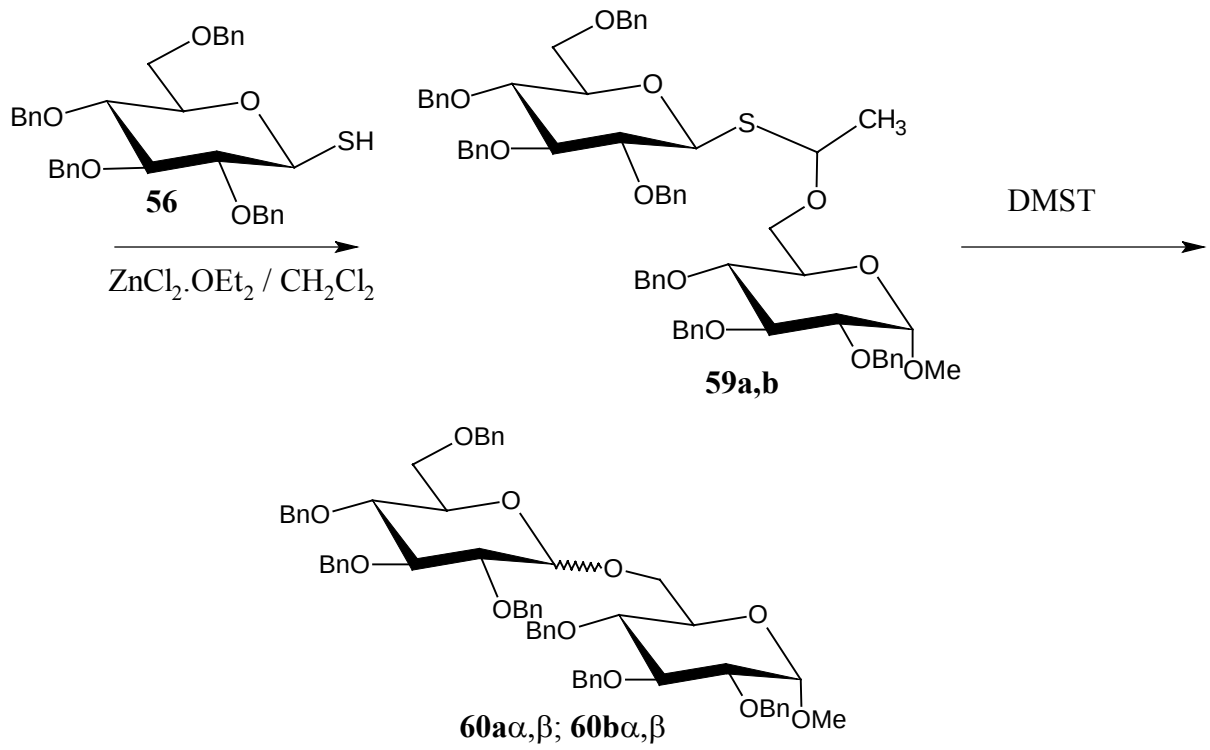
51



The same experiments were conducted with glucose donors and acceptors, independant of the configuration of the starting material, similar ratios α/ß were obtained and at low temperature, predominantly ß-linked disaccharides were formed. Crossover experiments were effected verifying intermolecular reaction . They have further investigated on the leaving group intra-versu intermolecular glycoside bond formation. [26] One example proposed was the thioglycoside approach in which the acceptor was ligated to the leaving group in order to enforce glycoside bond formation via an intramolecular (1,3)-(1,4)-(1,5)-, or (1,9) shift. One first investigation implies the construction of a C_1 bridge.The synthetical route involved first, the conversion of 6-O-acetyl-2,3,4-tri-O-benzylglucoside **57** to the enol ether **58** with Tebbe reagent. Reaction between tetra-O-benzyl-1-thio glucose (**56**) with the enolether (**58**) with $ZnCl_2.OEt_2$ complex as Lewis acid catalyst furnished (**59a,b**) in 56% yield with an α:β diastereomer mixture 1:1. Reaction of **59b** with DMST furnished the glucopyranosides disaccharide **60a, 60b** in 27% yield with 1:1 anomeric mixture. (Scheme **16**.)

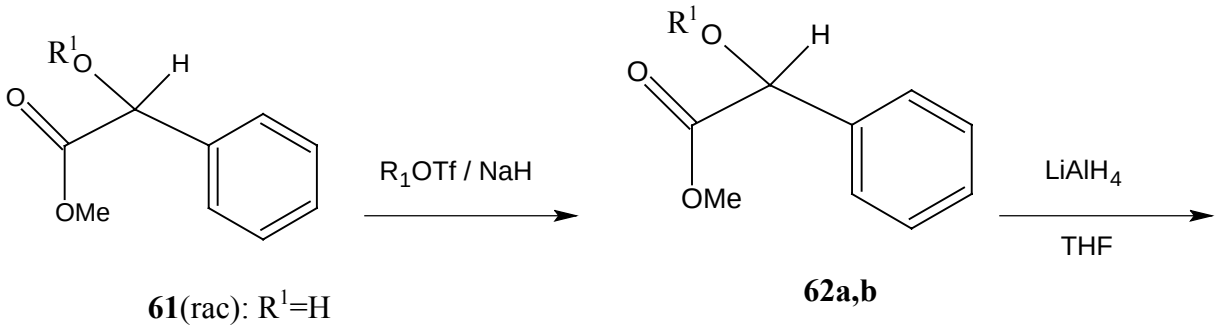
Scheme 16.





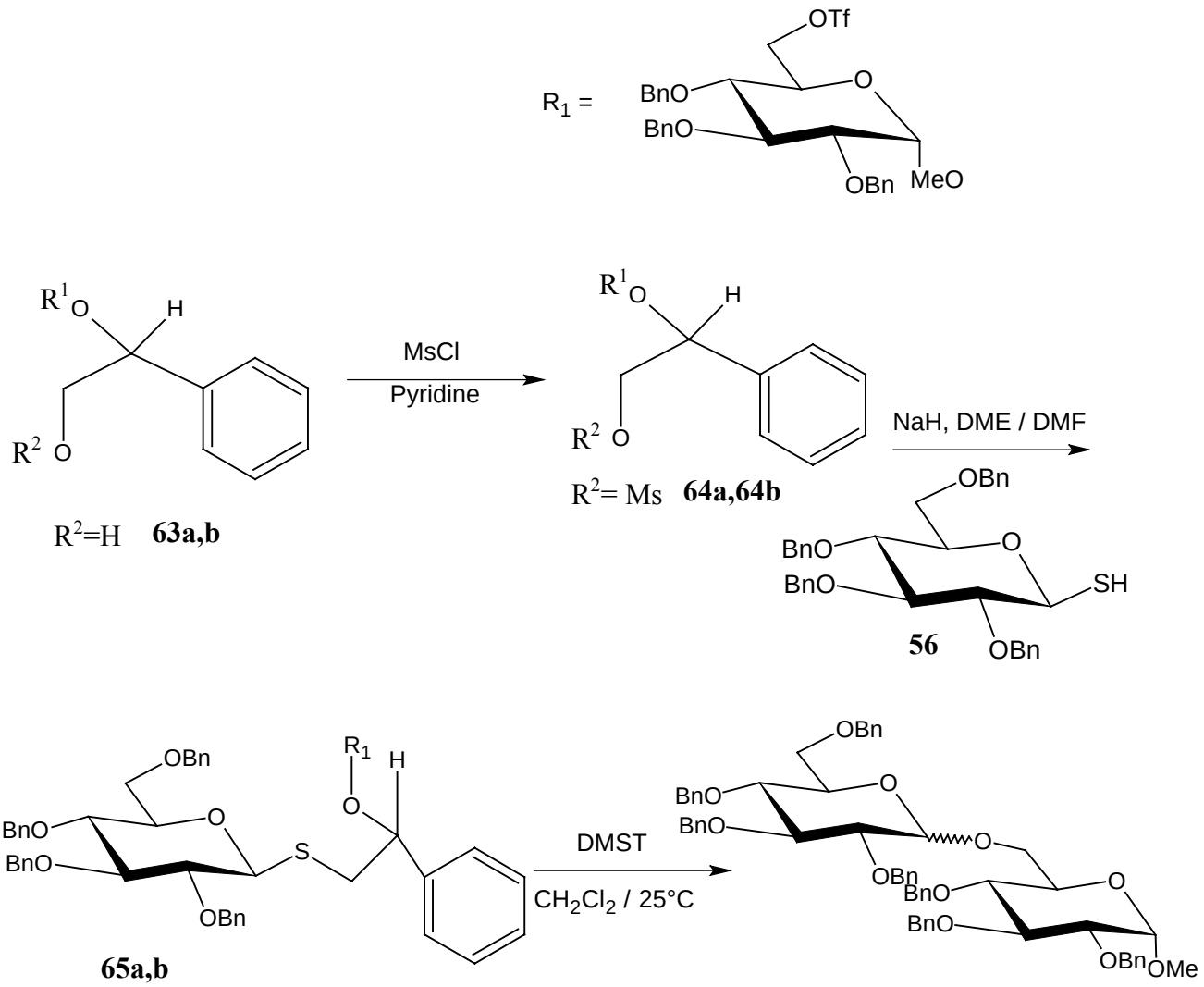
Attention has been focused on C_2 bridge systems in which the anomeric oxgen could be oriented to close comformational proximity to the anomeric center, via five connected atoms. Racemic methyl mandelate **61** was chosen as tether, and O-alkylation with ethyl trifluoromethane sulfonate and also 6-O-trifluoromethanesulfonate of 2,3,4, tri-O-benzyl-α-D-glucopyranoside afforded **62a,62b.** Reduction with lithium aluminum hydride in THF furnished the diol derivatives **63a,b**, which upon treatment with methanesulfonyl chloride yielded quantitatively **64a,64b**. Treatment of these with 2,3,4,6-tetra-O- benzyl-1-thio-ß-D- glucopyranose (**56**) in DME/DMF solvent mixture in the presence of NaH, afforded ß-thioglycoside (**65a,65b**) as diastereomer mixtures. Seperation of isomers by chromatography and treatment of **65a** with dimethyl(methylthio) sulfonium triflate (DMST) afforded (**66a,66b**) up to 80% yield with preferably ß anomer (Scheme **17)**.

Scheme 17.



61(rac): R^1=H

62a,b



The other isomer **10a** was submitted to the same treatment by DMST in acetonnitrile gave slightly more ß-anomer as expected in dichloromethane α- anomer was the ex pected slightly slighty predominant observed anomer. The conformational flexibility of bridged systems of (**10a,10b**) encouraged the investigation with a more rigid cyclic tether, trans-2- hydroxyindane **11** and its homologue **14**. Both were converted using 1-thioglucoside **1** into cis substituted derivatives **12h,l** and **13**, respectively. Treatment with ethyliodide as acceptor chosen in the presence of sodium hydride as base,5-crown-5, in DMF, gave **13a,16a**. Glycosylation reaction with DMST as activator resulted in 80%yield with the same anomeric outcomes as (**5a,b**), thus poor anomer selectivity. These results raised doubts as to an intramolecular reaction course in the glycosylations (Scheme **18**.)

Scheme 18.

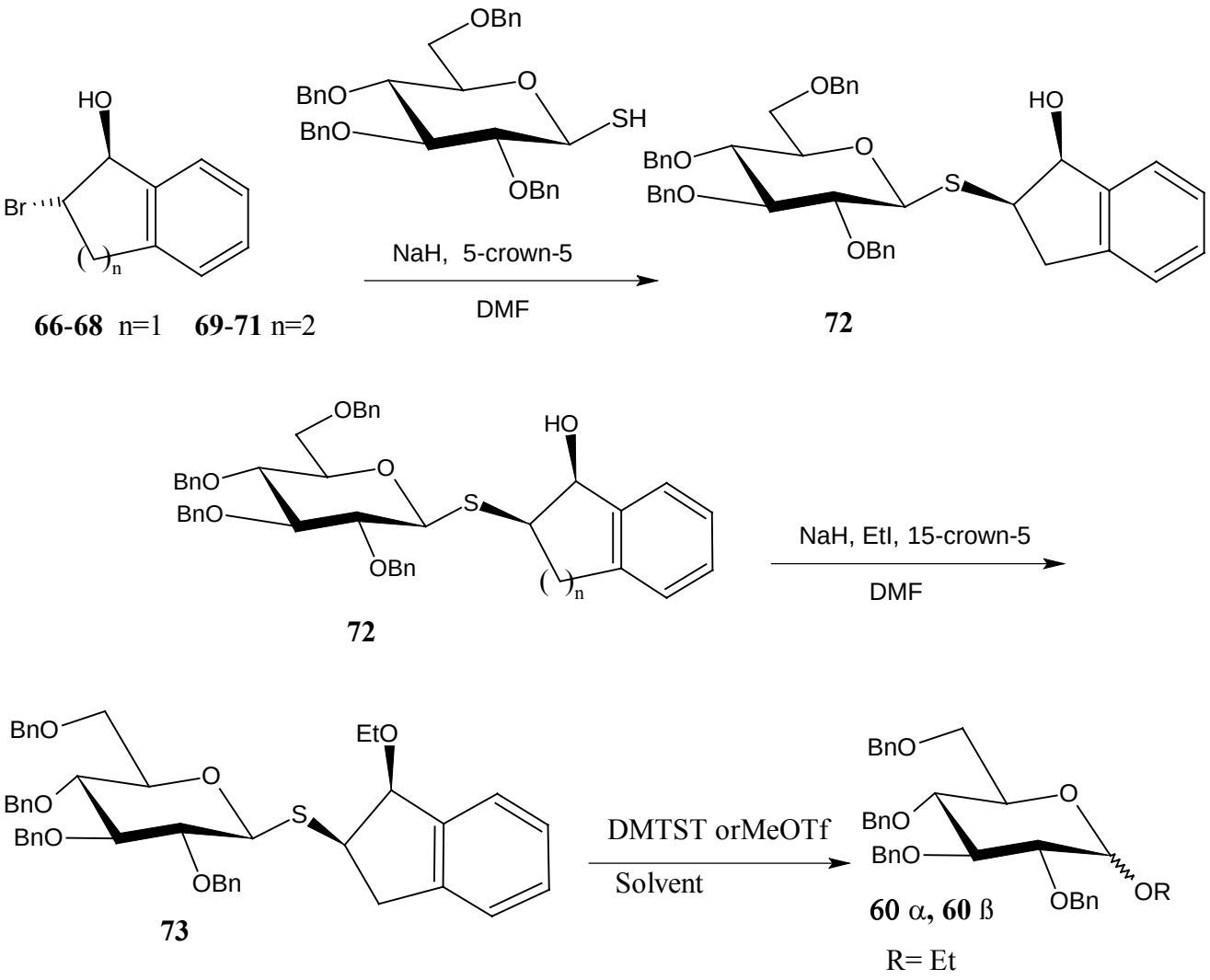
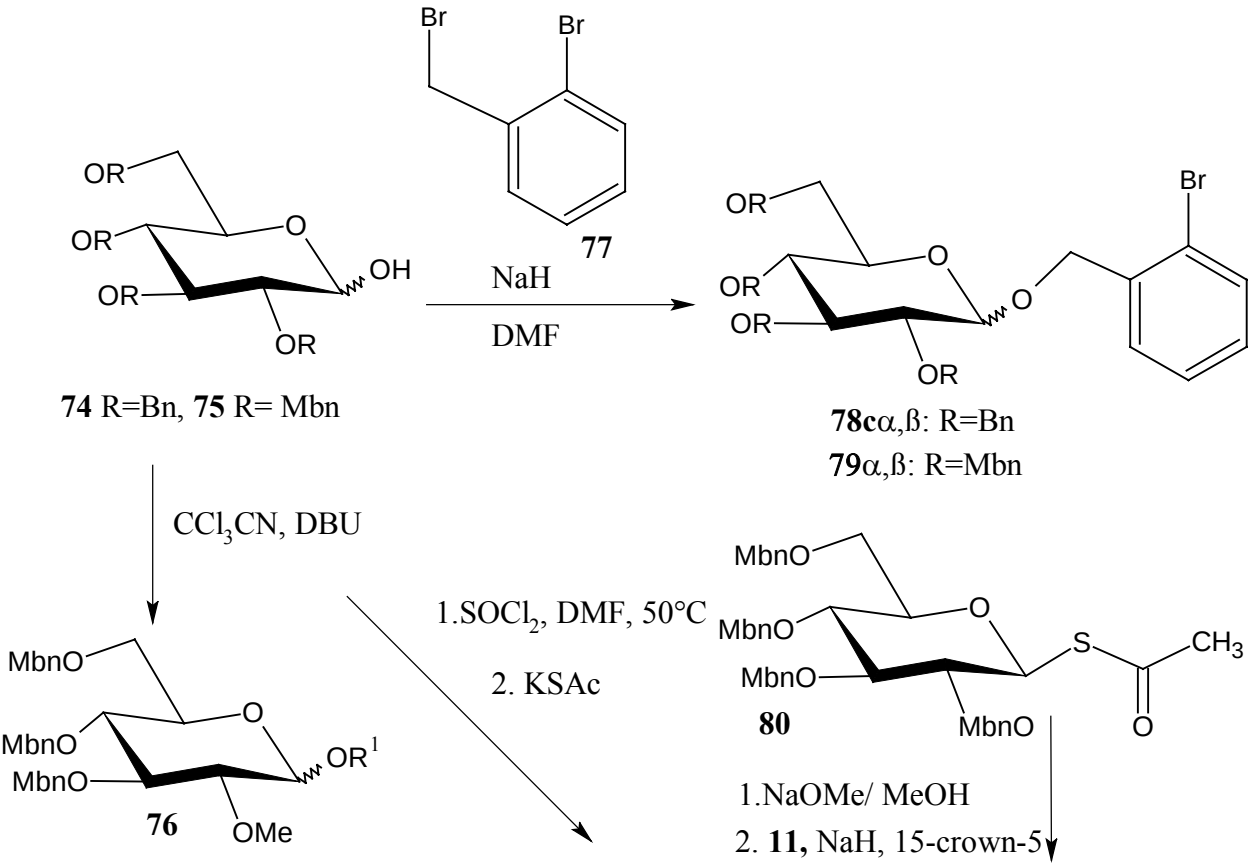


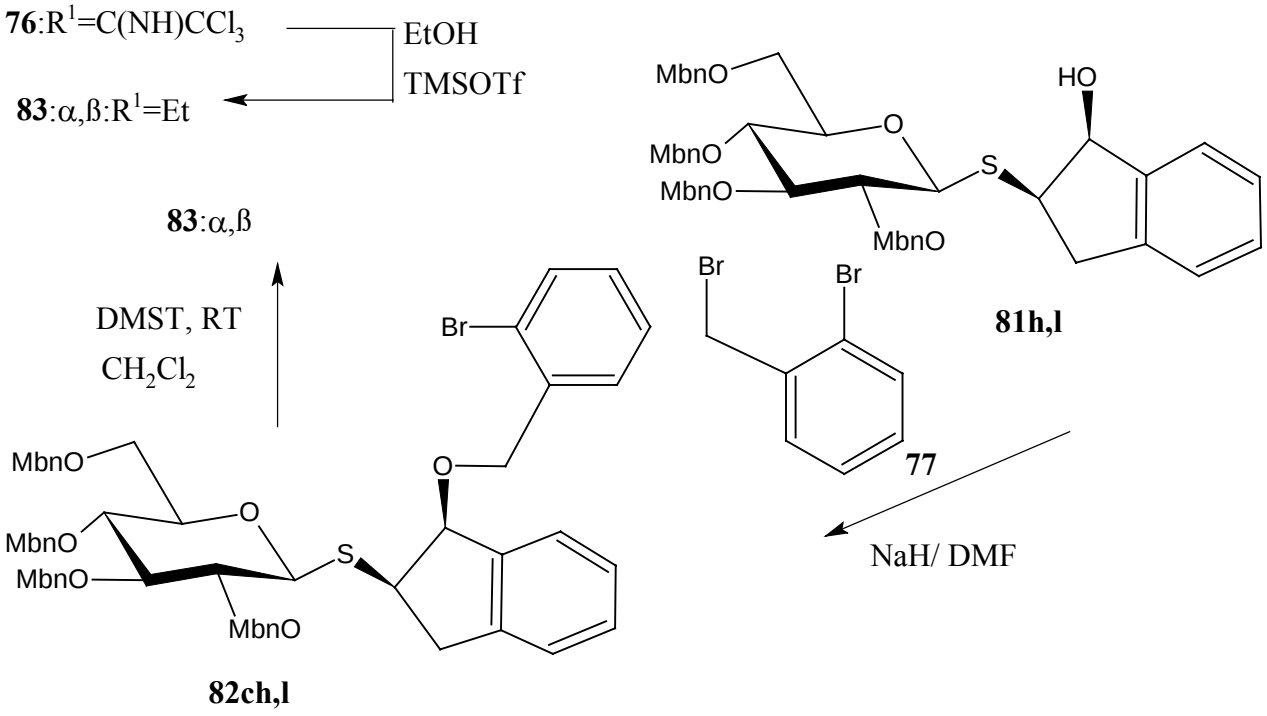
Table 6.

Solvent	Temperature	Promoter	Yield (%)	α/ ß
CH_2Cl_2	25°C	DMTST (1.1 eq.)	80	1:1
CH_2Cl_2	-20°C	DMTST (2.0 eq.)	24	1:3
CH_2Cl_2	25°C	MeOTf (1.2 eq.)	78	1:1
Toluene	25°C	MeOTf (2.0 eq.)	70	1:1
MeCN	25°C	DMTST (1.5 eq.)	47	1:3
CH_2Cl_2	25°C	MeOTf (1.2 eq.)	60	1:1

Judging from the above table **73** of results, more ß-anomer was obtained with acetonitrile used as solvent. The other above cases low anomeric selectivity occured. These outcomes show and rationalize every reason of an intermolecular reaction and no intramolecular glycosylation.
In a further investigation, they ligated through the leaving group two different glycosyl donors and acceptor moieties, each of approximate similar reactivity. Tetra-O-benzyl glucose **74** and tetra-O-(3-methybenzyl) glucose **75** fulfil the donors requirement. The primary alcohols such as ethanol and bromobenzyl alcohol satisfied the acceptor's requirement. Transformation of **75** to trichloroacetimidate **76** followed by glycosylation with ethanol yielded **83 α,ß**.
The required Mbn-protected acetylthio derivative **80** was obtained from the starting material **75** by reaction with thionyl chloride in DMF at 50°C than potassium acetate. Removal of the S-acetyl group by Zemplén reagent (MeO^- in methanol followed by reaction with hydroxyindane, NaH, in DMF, furnished the hydroxyindanyl thioglycosides **81h,l** required as starting material for competition experiments. Activation of the latter with DMTST,in dichloromethane, at 25°C, gave 64% overall yield of **83** with a 1:1 **α/ß** ratio. Competition reaction with **69a** and **82ch,l** in the presence of DMTST provided not only **60a** and **79c**, but also crossover products **60c** and **79c**, thus clearly indicating that the glycosylation mainly or exclusively followed an intermolecular course. (See scheme **19**, **20**).

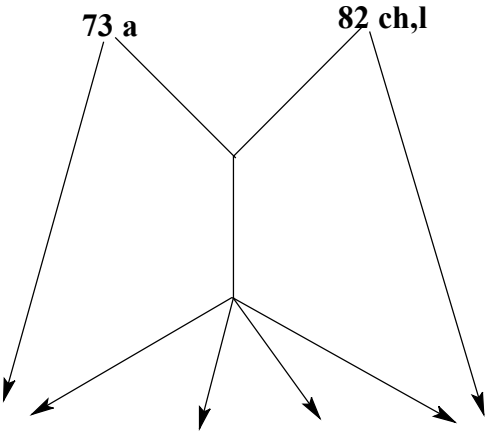
Scheme 19.





Competition Experiments

Scheme 20.



	60aα,ß	**60c**α,ß	**83a**α,ß	**83c**α,ß
I.	30%, 1:1	60%, 1:1	30%, 1:1	32%, 1:1
II.	35%, 1:1	51%, 1:1	14%, 1:1	34%, 1:1

Competition experiments with **73a** and **82ch,l** ; reagents and conditions:**DMTST** (5eq.), $\mathbf{CH_2I_2}$, room temp : with **81ch**; **II**: with **81cl**

Through competition experiments Smith *et al.* prooved from these results that the leaving group based glycosylations follow an intermolecular course rather than intramolecular, although intramolecular (1,3), (1,4), (1,5)-shifts of the donor to acceptor seem to be readily available. Activation of the glycosyl donor moiety in these systems obviously led to solvent- and/ or counterion-stabilized intermediates, which experiences a life long enough to search intermolecularly for sites of reactivity. Despite the high yield obtention of product formation, the desired stereocontrol of an intramolecular course was not reached.

CHAPTER II

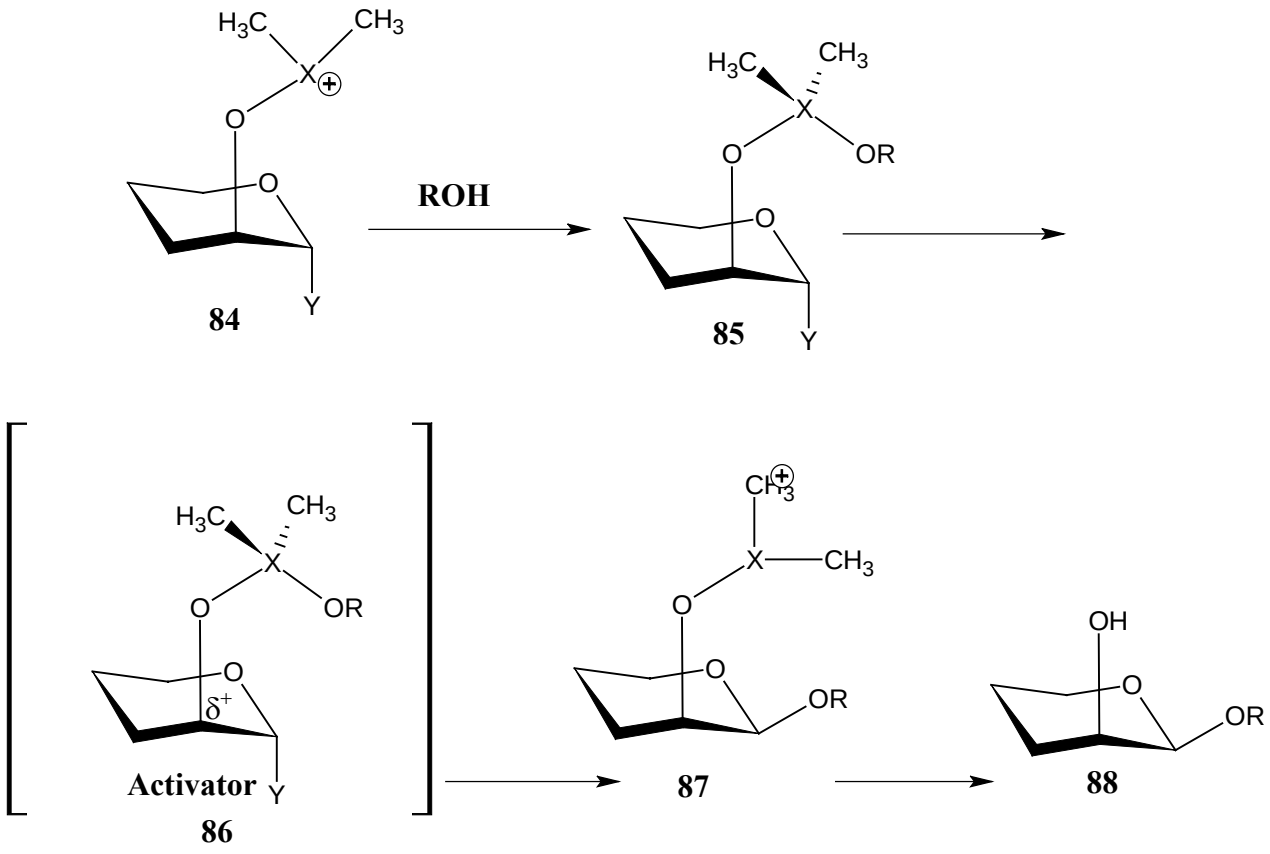
LINKAGE OF THE ACCEPTING ATOM VIA BIFUNCTIONAL GROUP

Linkage of the Accepting Atom via a Bifunctional Group
Intramolecular Aglycon Delivery

In the early 1990's, Hindsgaul et al.[28,29,30] reported the first stereocontrolled synthesis of ß-mannosides, by applying the method of "Intramolecular Aglycon Delivery".

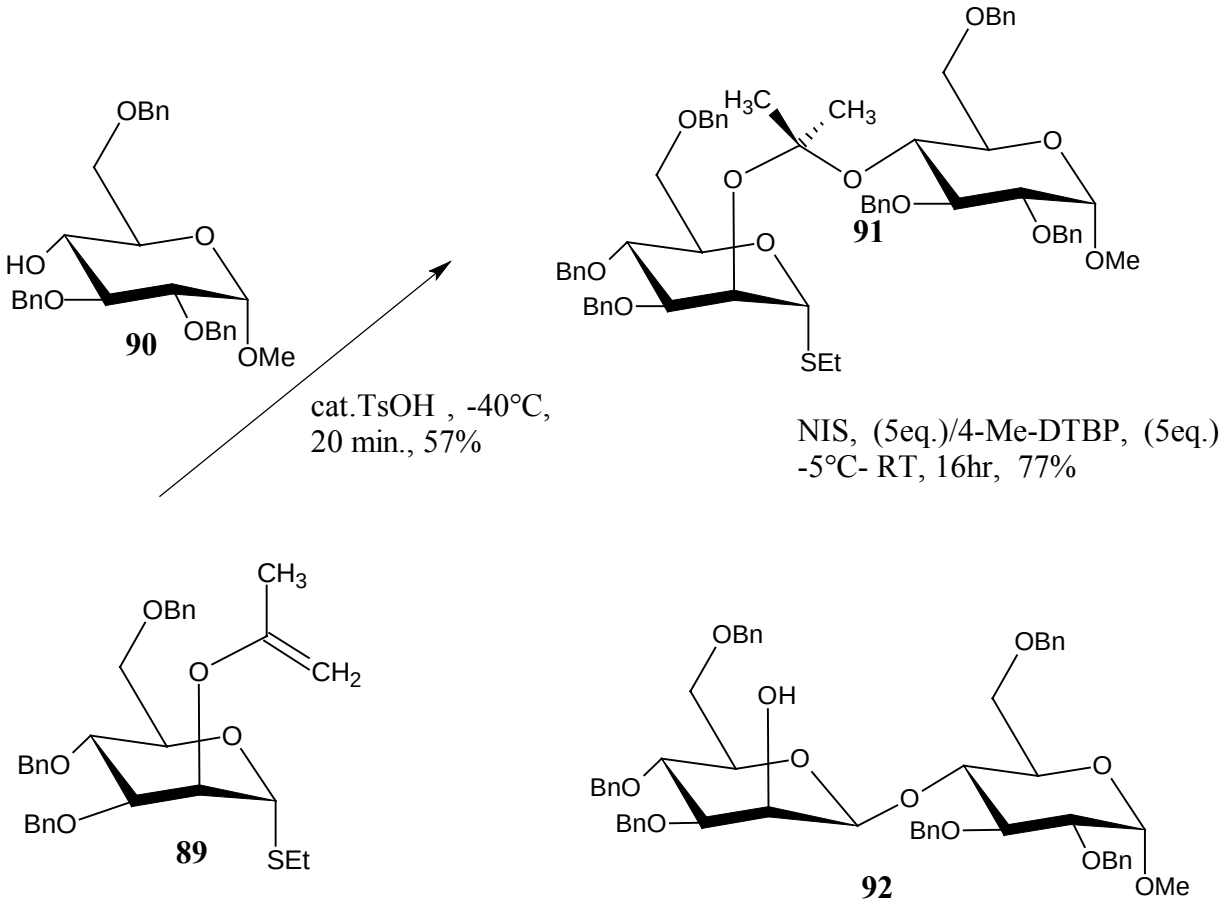
The general strategy of this involves covalent attachement of an aglycon alcohol **ROH** on an O-2 of a glycosyl donor **84** via a bifunctional CR_2 os SiR_2 linker to give a linked disaccharide **85**. In the second step, the leaving group is activated and attack at the anomeric center leading to intramolecular delivery of the aglycon in a concerted reaction to give intermediate **87,** and then quenched with water to give **88** (Scheme **21**).

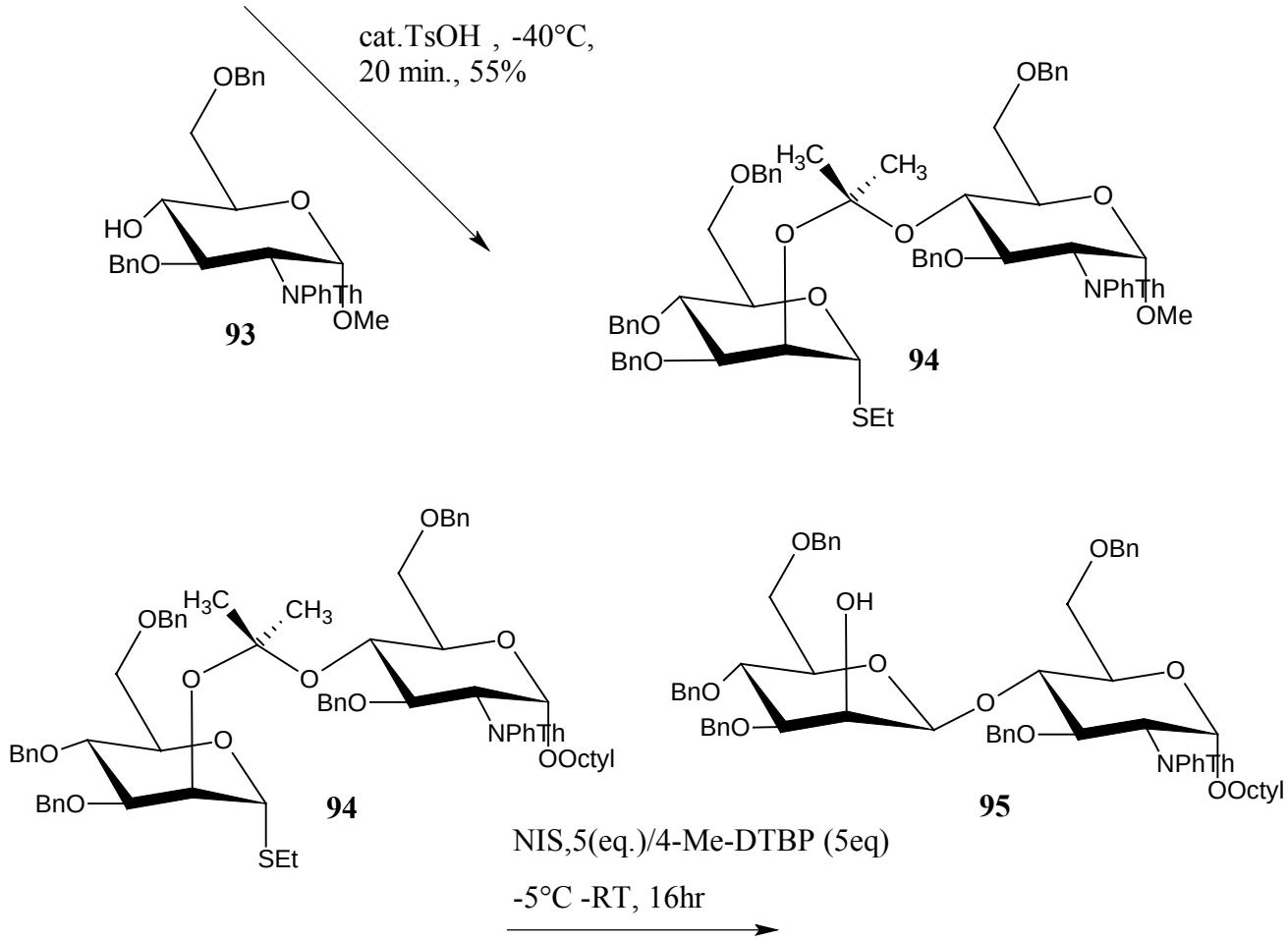
Scheme 21.



This novel method was used in the synthesis of ß-mannosides[29] which presented quiet a hurdle in previous years for carbohydrate chemist to obtain. Hindsgaul and coworkers approached the isopropyldene ketal-tether as chosen for a bifunctional group. Starting with mannosyl donor vinyl tether **89** and reaction with 2,3,6,tri-O-Benzyl-α-D-methoxy gluco-pyranside **90** in th presence of TsOH as catalyst to produce the tethered ketal disaccharide **91**, and the same reaction with another acceptor, a dibenzylated phtaloglucosamine**93**, produced 57% of the isoprenyl ketal dissacharide **95** for the former, and 55% yield of for the latter **94**. Glycosylation reaction of both bridged ketal disaccharides **91**, **94** with (NIS, 5 equiv.) and 4-methyl-di-t-butyl pyridine (4-Me-DTBP,5 equiv.) in dichloromethane at -5°C warming to room temperature overnight afforded the ß disaccharides **92** and **95** in 77% and 55% yields. (Scheme **22**).

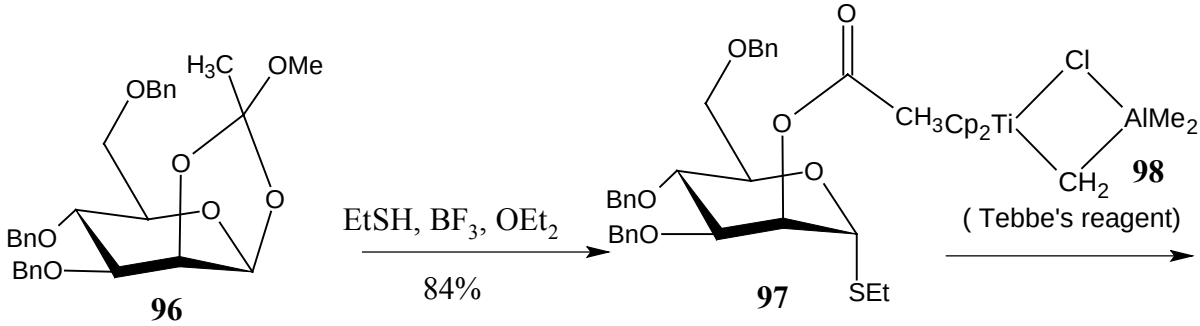
Scheme 22.

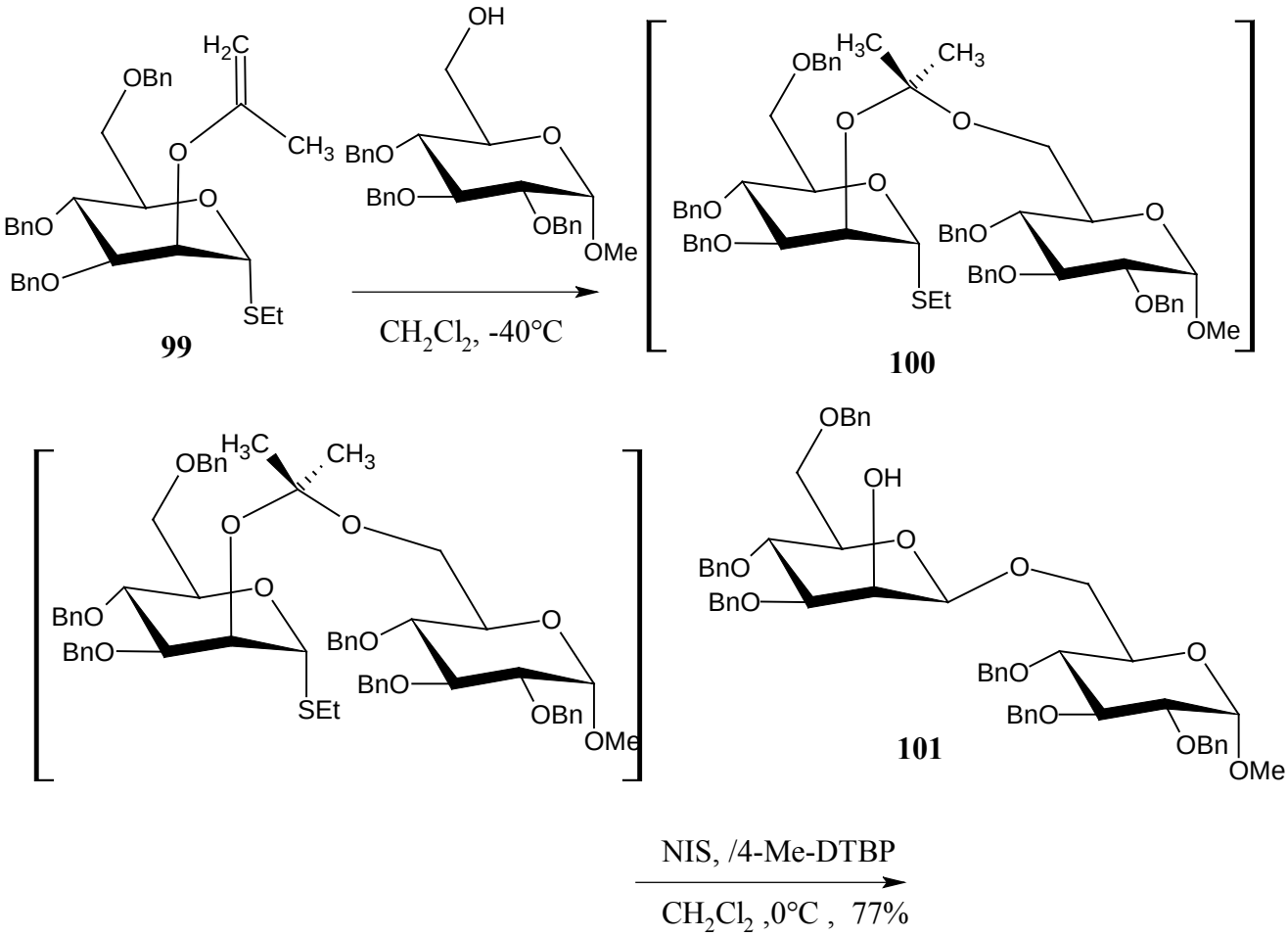




They also applied this method with another methyl-1-O-2,3,4-tri-O-benzyl-α-D-glucose acceptor which beared a free 6-O-hydroxyl group[30] (Scheme).Starting with a 1,2, orthoester of a tribenzylated mannosyl derivative **96** and thiation reaction by ethanethiol in the presence of boron trifluoride etherate gave acetate **97** which was methenylated with Tebbe's reagent **98** in toluene gave the propenyl ether **99.** Reaction of **99** with the tribenzylated α-D-glucosyl acceptor **20** yielded the ketal tethered disaccharide **100** which was subjected to glycosylation with NIS/4-Me-DTBP in CH_2Cl_2 at 0°C to furnish the ß-D- manoside **101** with 77% yield (Scheme **23**).

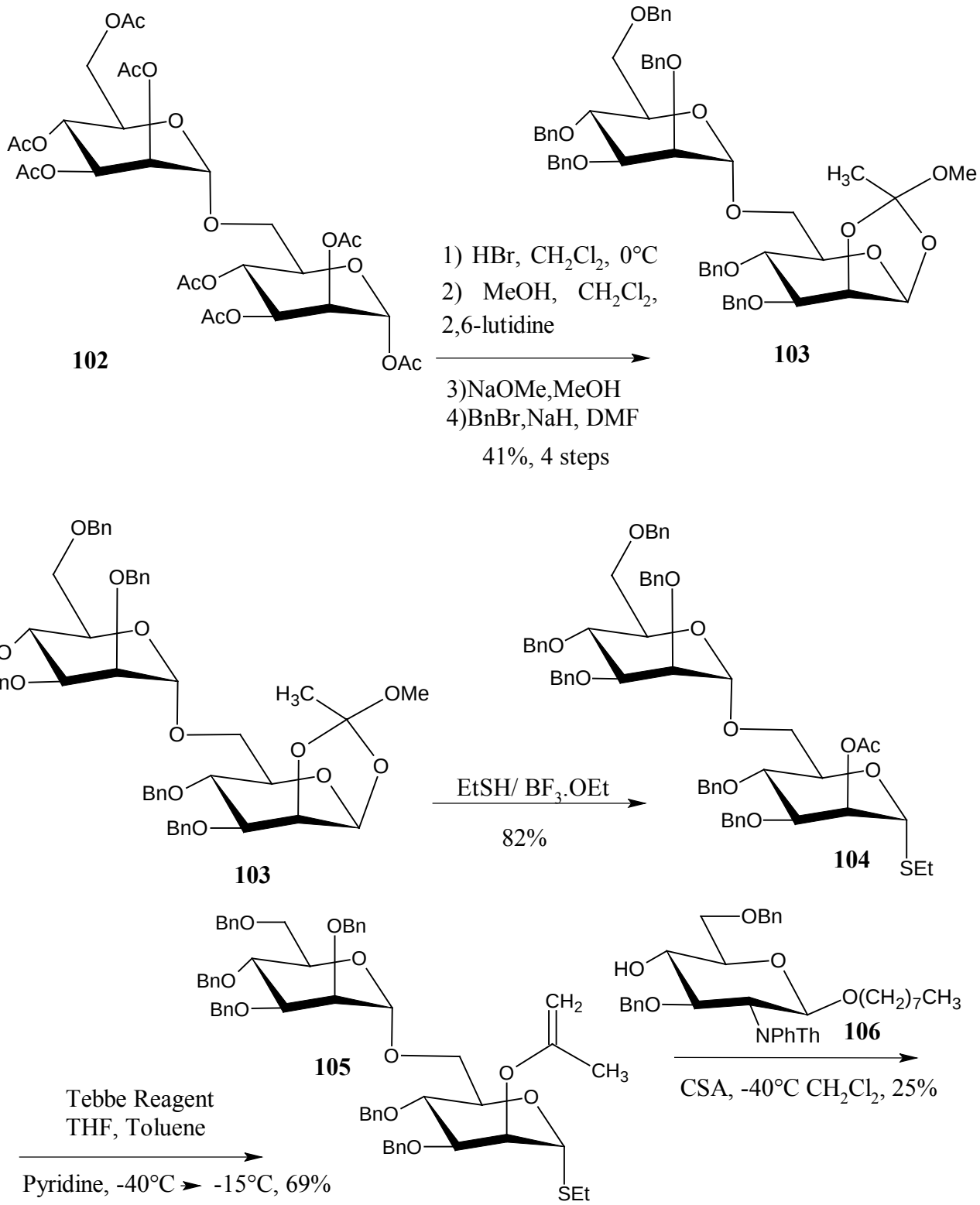
Scheme 23.

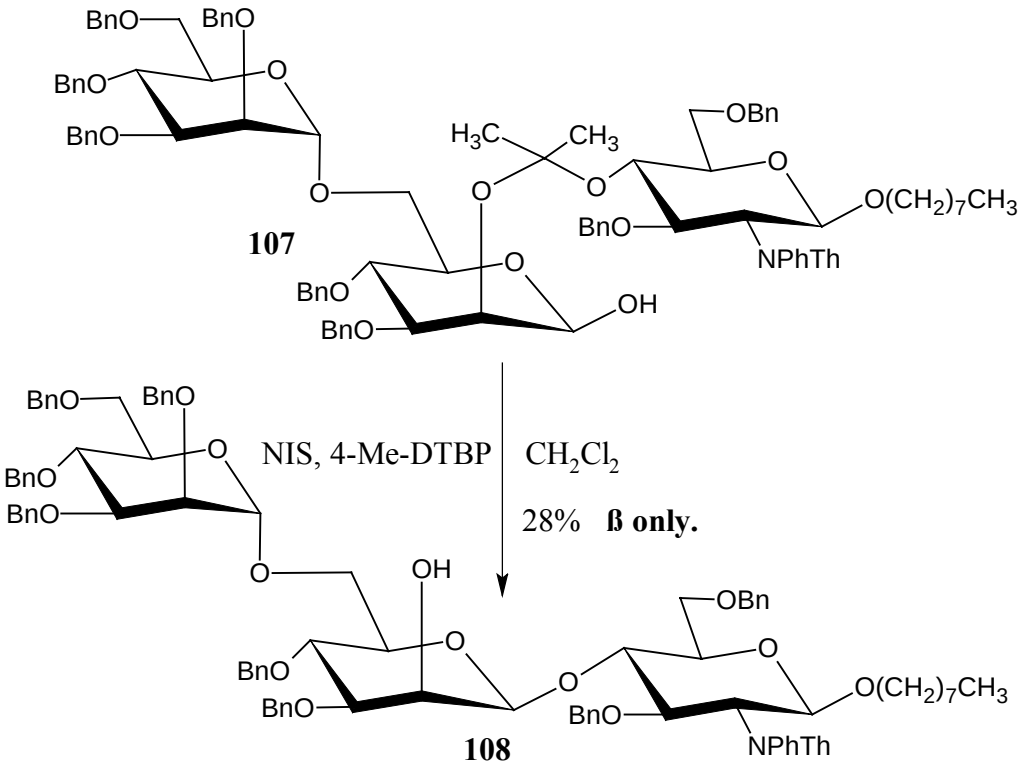




Application of this concept to more complex system such as the core pentasaccharide unit of N-glycoprotein showed the limitations of this methodology.From observations, the isopropylidene acetals are sensitive to the size of the vinyl ether. The acetal acid sensivity increases with increased complex of the structure, and must be stored with a stabilizing base in order to avoid decomposition at room temperature when left overnight. However,the synthesis of more trisaccharides involving mannosyls was attempted. The ß-anomeric outcome as major isomer obtained, indicated good stereoselectivity but glycosylation reaction afforded modest yield of product. (Scheme **24**)

Scheme 24.

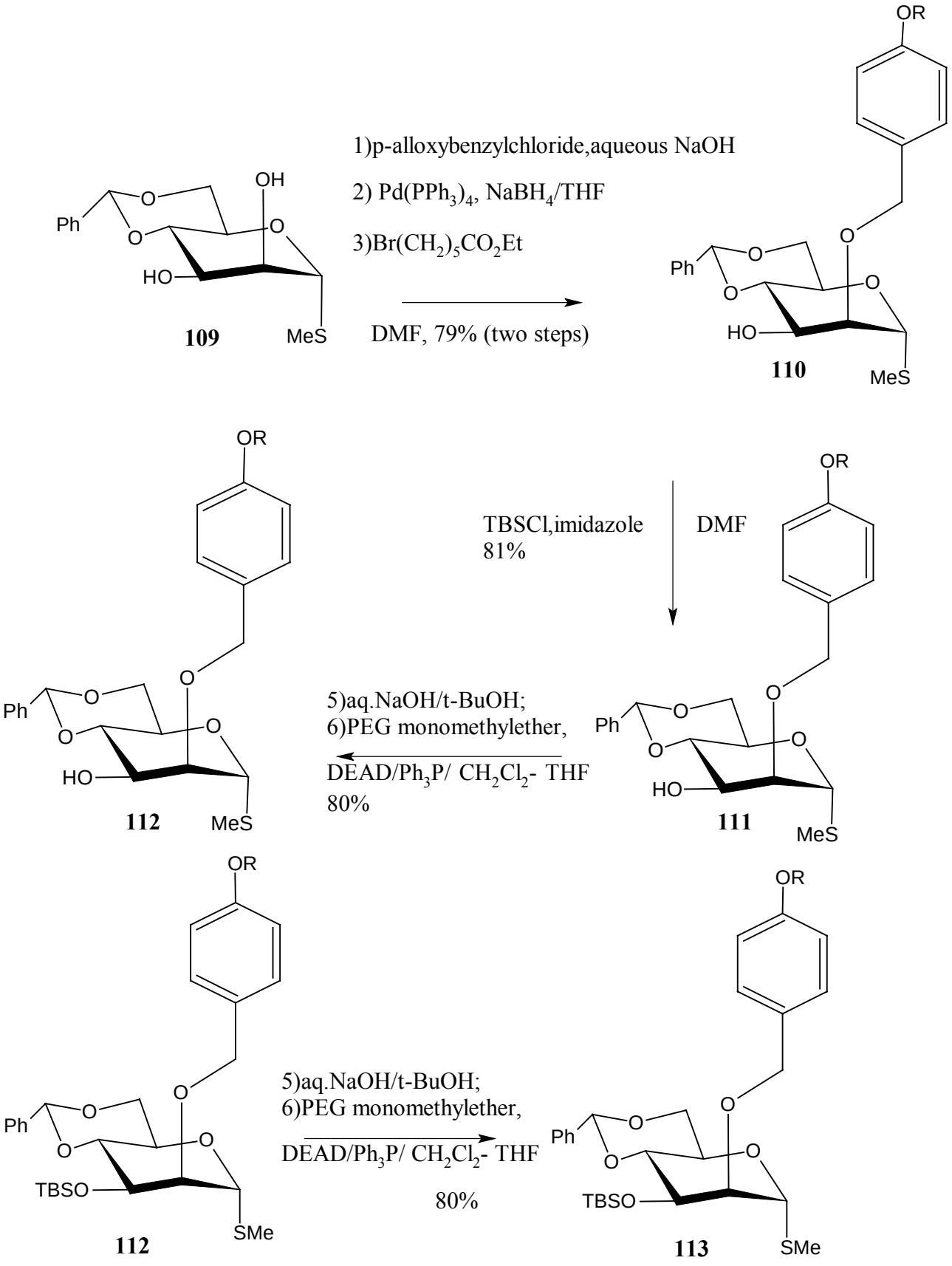

OAc
AcO
AcO
AcO
O
OAc
AcO
AcO
OAc
102
1) HBr, CH2Cl2, 0°C
2) MeOH, CH2Cl2,
2,6-lutidine
3)NaOMe,MeOH
4)BnBr,NaH, DMF
41%, 4 steps
OBn
BnO
BnO
BnO
H3C
OMe
103
EtSH/ BF3.OEt
82%
104
SEt
105
CH2
CH3
Tebbe Reagent
THF, Toluene
Pyridine, -40°C ➤ -15°C, 69%
HO
O(CH2)7CH3
NPhTh
106
CSA, -40°C CH2Cl2, 25%

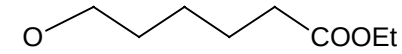


Methoxybenbylidene Acetal- Tethered Acceptor

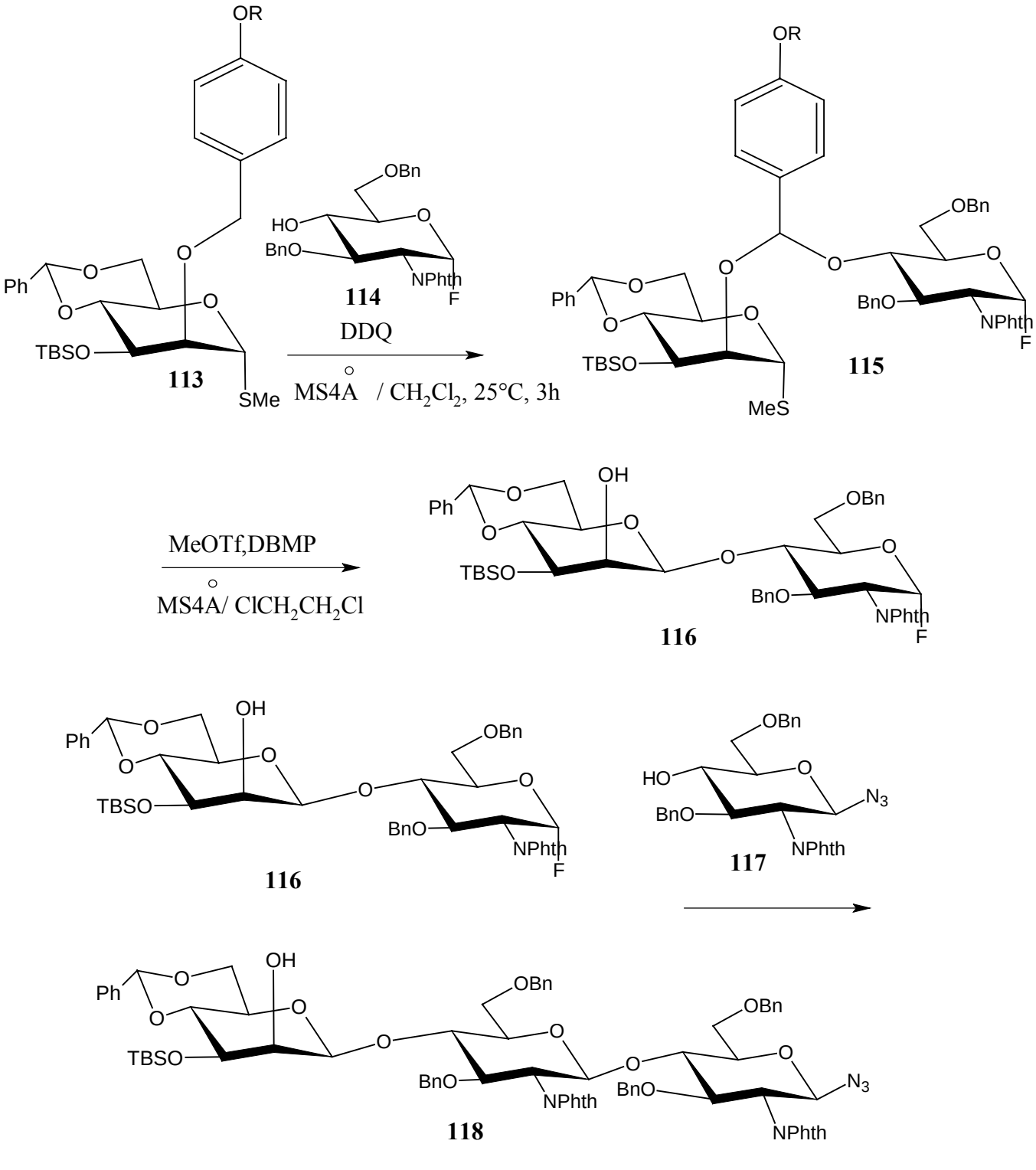
Ogawa et al. reported the "Para-methoxybenzyl assisted Intramolecular Aglycon Delivery" for the stereocontrolled synthesis of ß-mannosides[31,32,33].The incorporation of the p-methoxy benzylidene was to avoid the unfavorable ketal formation. It was designed as a bifunctional group for attachement of a glycosyl donor to glycosyl acceptor. Another advantage was that acetal formation was achieved via oxydation of a methoxybenzylidene group and addition of the acceptor to the methoxybenzylcarbenium ion intermediate. Furthemore, the purification of the acetal is not required; it can be immediatly used for glycosylation step by activation of glycosyl fluoride with silver perchlorate or tin tetrachloride. This method was applied to a ß-manno-sylation incorporated in a di-and trisaccaride on polymer support.The polymer support system serves as a "gatekeeper" where the product is released in a monopolymeric phase,while most of the by product remains retained on the polymer. (See reactions in scheme **25**, **26**, **27**)

Scheme 25.


1)p-alloxybenzylchloride,aqueous NaOH
2) Pd(PPh3)4, NaBH4/THF
3)Br(CH2)5CO2Et
DMF, 79% (two steps)
109
110
TBSCl,imidazole
81%
DMF
5)aq.NaOH/t-BuOH;
6)PEG monomethylether,
DEAD/Ph3P/ CH2Cl2- THF
80%
111
112
5)aq.NaOH/t-BuOH;
6)PEG monomethylether,
DEAD/Ph3P/ CH2Cl2- THF
80%
112
113

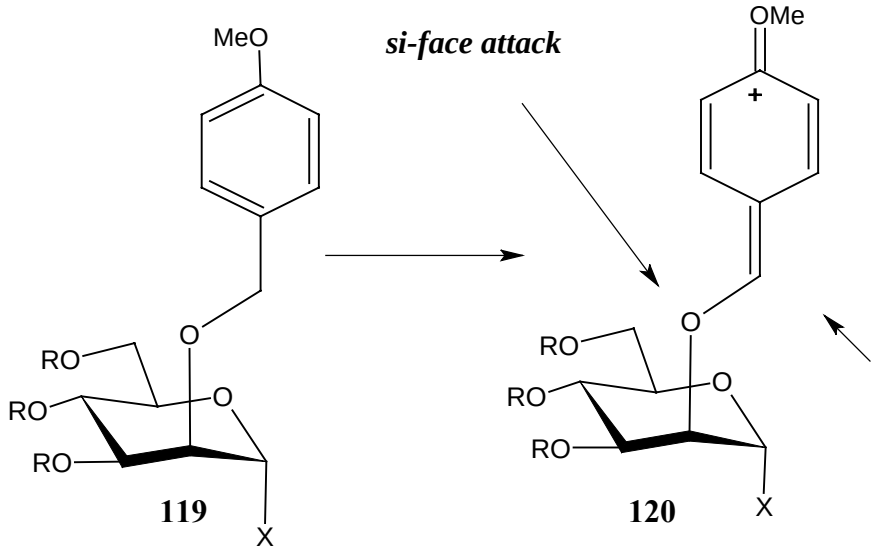
R=  OR= $O(CH_2)_5CO_2(CH_2CH_2O)_n$-OMe

Scheme 26.

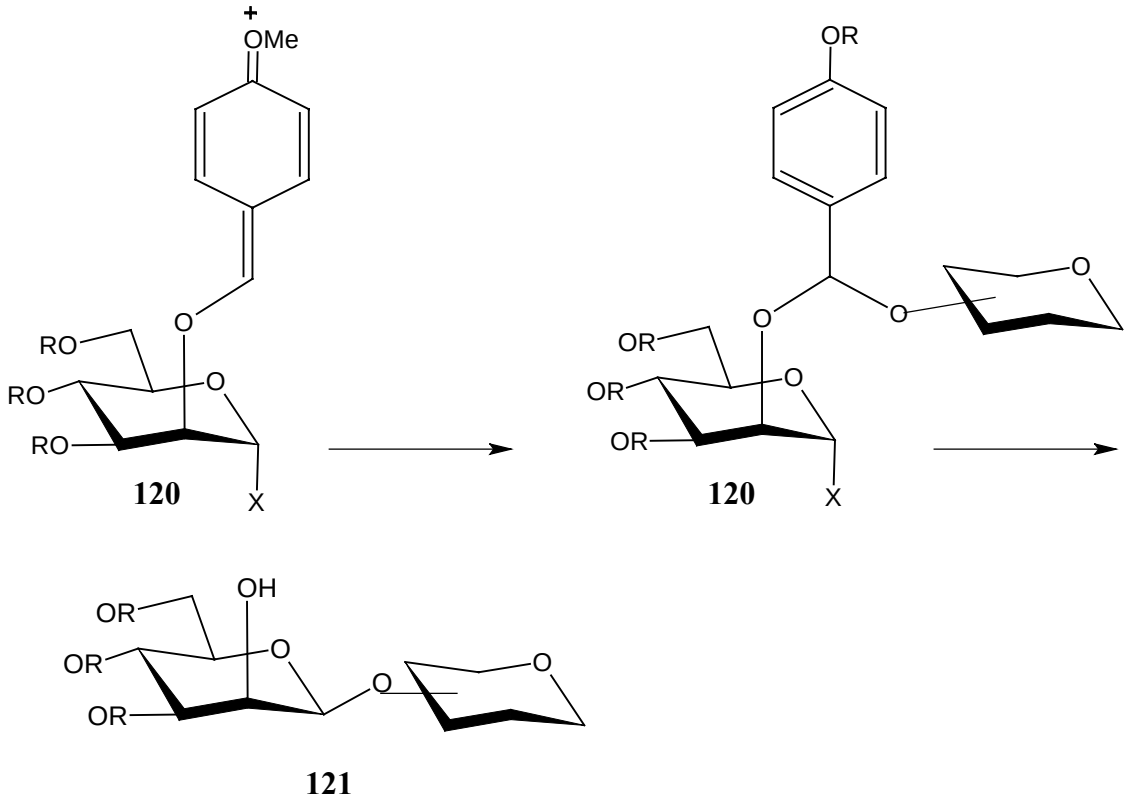


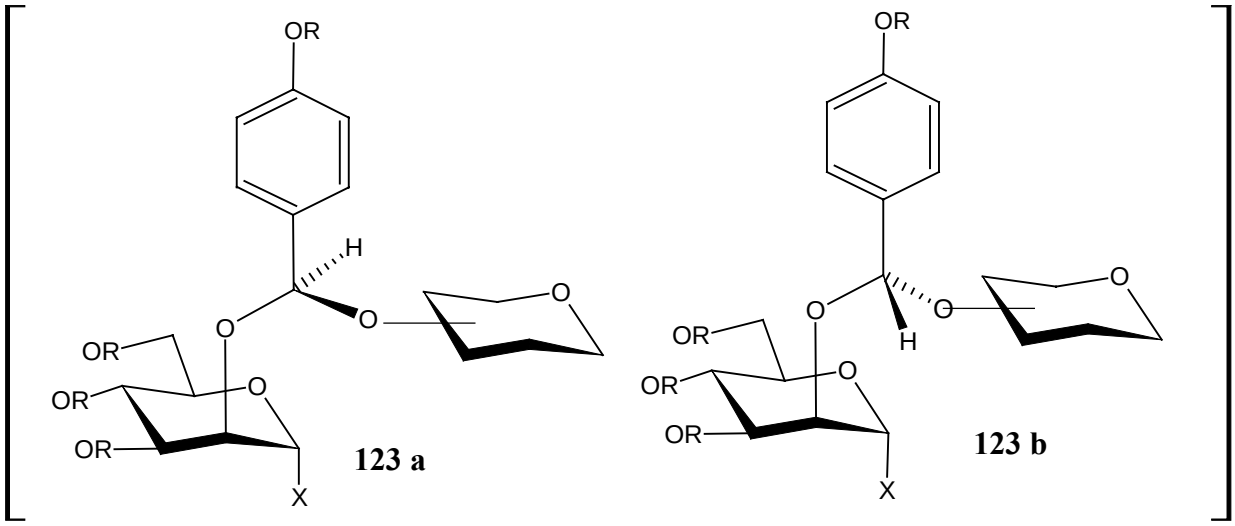
Mindfull of their success with the p-methoxybenzyl-assisted ß-mannosylation intramolecular aglycon delivery, they were prompted to persue with a detailed study of the stereochemistry of mixed acetals. the acetalic carbon is stereogenic, which renders possible the formation of two diasteomers. (Scheme **28**, **29**).

Scheme 28.



Scheme 29.

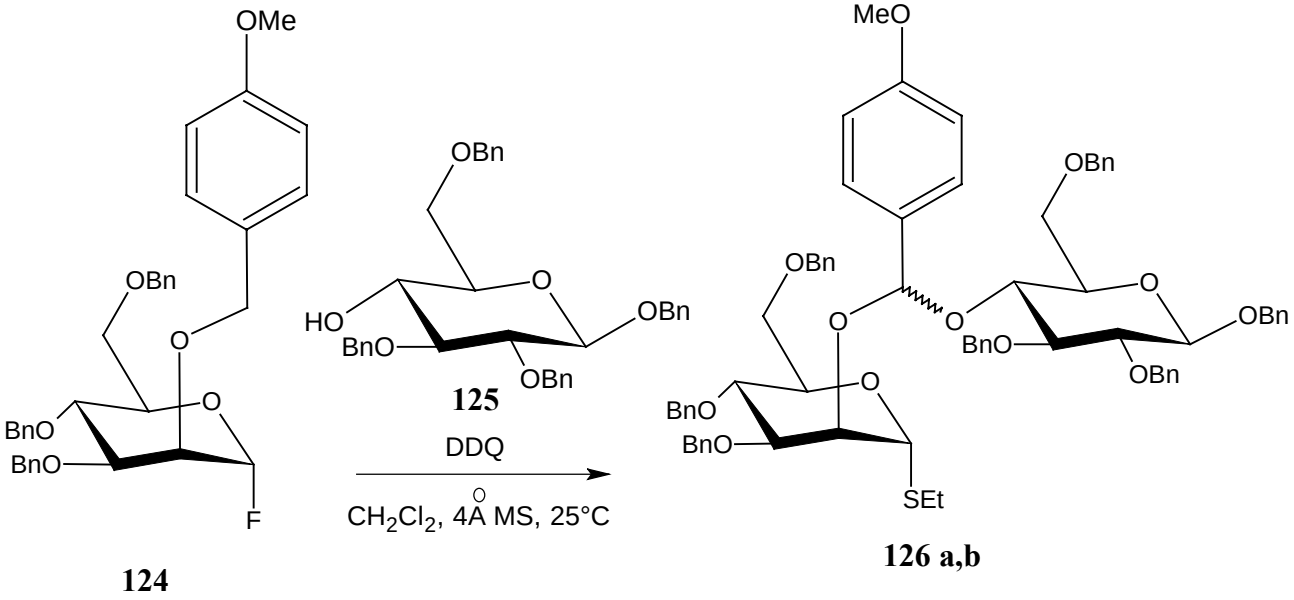


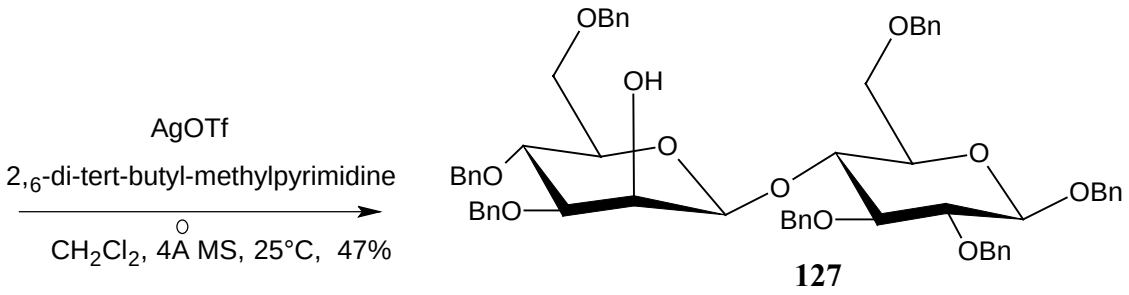


S-isomer (by *re* attack) R-isomer (by si attack)

Questions were considered as to the stereoselectivity of their transformation, and what diastereo isomer is preferably formed. If the process is not stereoselective, do both isomers give IAD products with equal efficiency? For a conclusive and objective observtion preparation of a mannosyl based mixed acetal was prepared. Reaction of of the tribenzylated mannosyl fluorinated C-2 PMB-protected donor was reacted with C-4 unprotected glucose donor with DDQ in dichloromethane to obtain the acetal isomer. Their NMR analysis revealed the obtention of diastereomers in greater as 95% diastereomeric purity. (Scheme **30**)

Scheme 30.





127

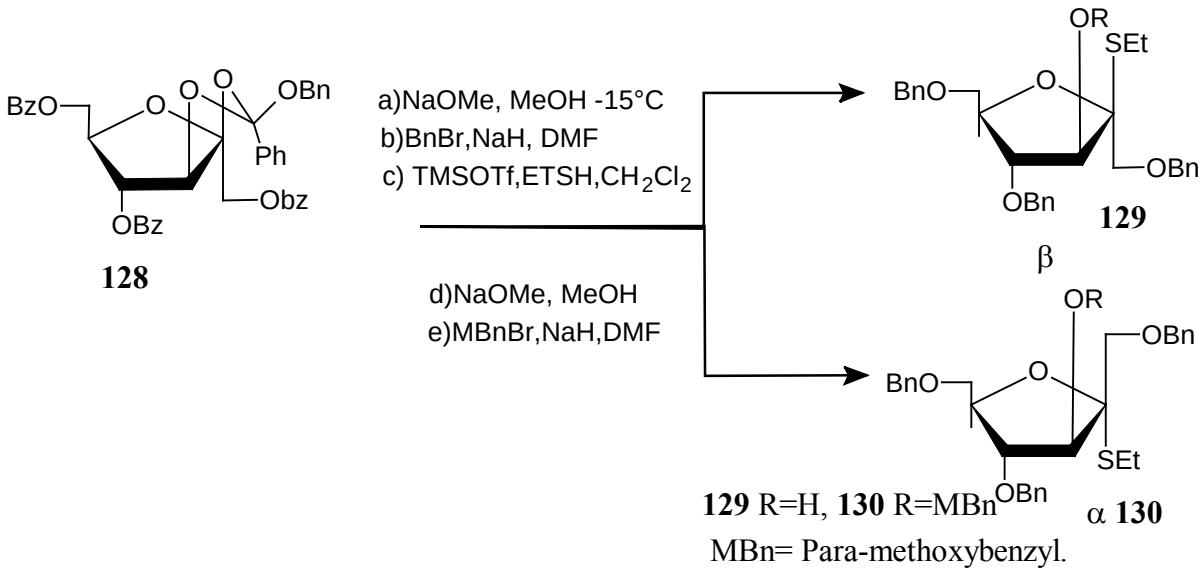
Glycosylation reaction with silver triflate in dichloromethane ar room temperature afforded the ß-linked dissacharide exclusively with 47% yield. This result demonstrate that intramolecular aglycon delivery is insensitive to the stereochemisty of the acetal.

The methodological success of " Intramolecular Aglycon Delivery" by Ito and Ogawa [31,32] in synthesizing the difficult ß-D-*manno*-configuration an higher saccharides that contain ß-D- *mannosides* attracted their attention and motivated of Oscarson and Krog-Jensen toward, the synthesis of ß-D fructofuranosides[36,37], extremely difficult to obtain by conventional glycosylation methods, since this is a motif present in capsular polysaccharides from *Haemophilus influenzae.* Here,the donor of choice was the α-D-fructofuranosyl orthoester **128** and debenzoylation with sodium methoxide in methanol,and benzylation gave **129** in an overall yield of 64%. Rearrangement with trimethysilyltrifluoromethanesulfonate in the presence of a large excess of ethyl mercaptan produce an insperable α/ß mixture of 1,4,6-tri-O-benzyl-2-thio- D-fructofuranoside. Debenzoylation of this mixture with sodium methoxide afforded 3-OH compounds, easily seperable by standard silica gel chromatography to **129** α and **129**ß with 74 and 22% yield. Para-methoybenzylation reaction produced the intermediates **130** α (91%), **130** ß (68%) yield, thus ready for acetal tethering with acceptors.

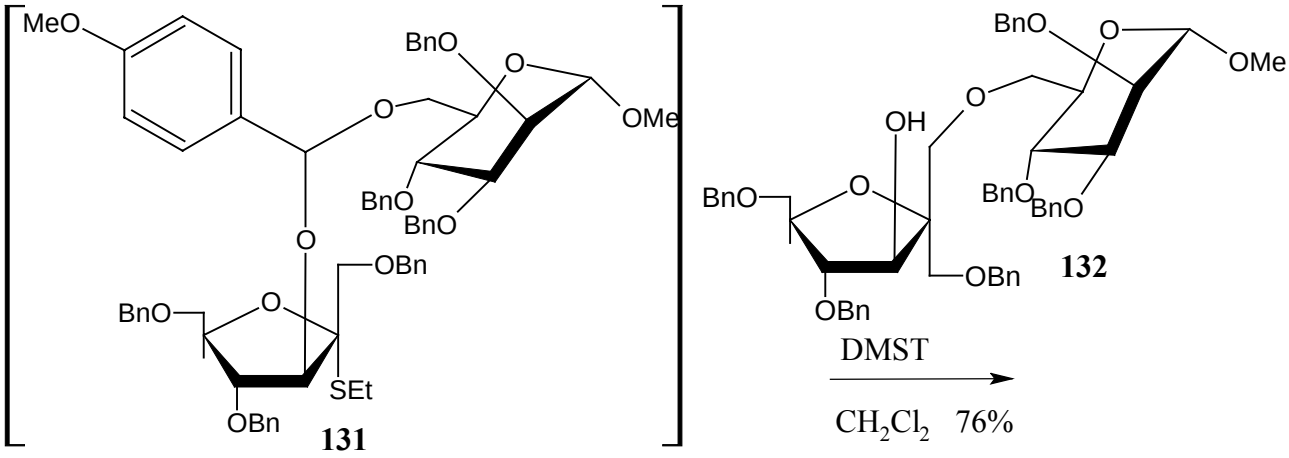
Reaction of **130α** with DDQ and the tribenzylated mannosyl acceptor **20** yielded the desired desired mixed acetal **131**. Activation of **131** with DMST in dichloromethane furnished excusively the β linked fructofuranoside **132** in 76 % yield. A glycosylation reaction with another bulkier 4,6-O- benzyledene protected mannosyl acceptor **132** and DMST or IDCT in the same solvent afforded exclusively the same anomeric outcome β- fructofuranoside **134** in the same yield as the latter.

Through "Intramolecular Aglycon Delivery" stereospecific formation of β-linked fructofura - nosides can be perfomed in high yields by internal delivery of the acceptor from a 3-O-(p-me thoxy-benzyledene) acetal of a thioglycoside donor after activation with a thiophilic promoter, DMST, IDCP, and IDCT. (See all reaction descriptions in scheme **31**,**32**,**33**).

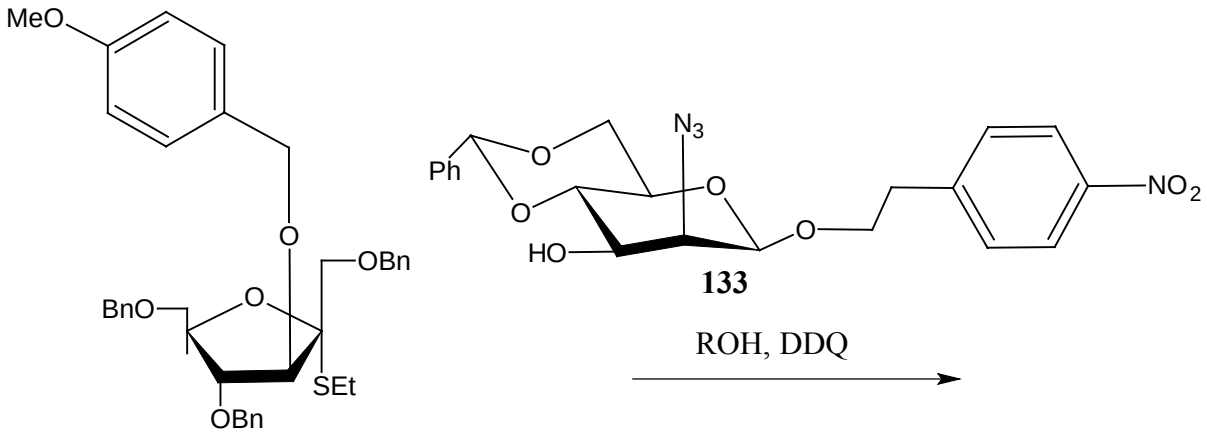
Scheme 31.

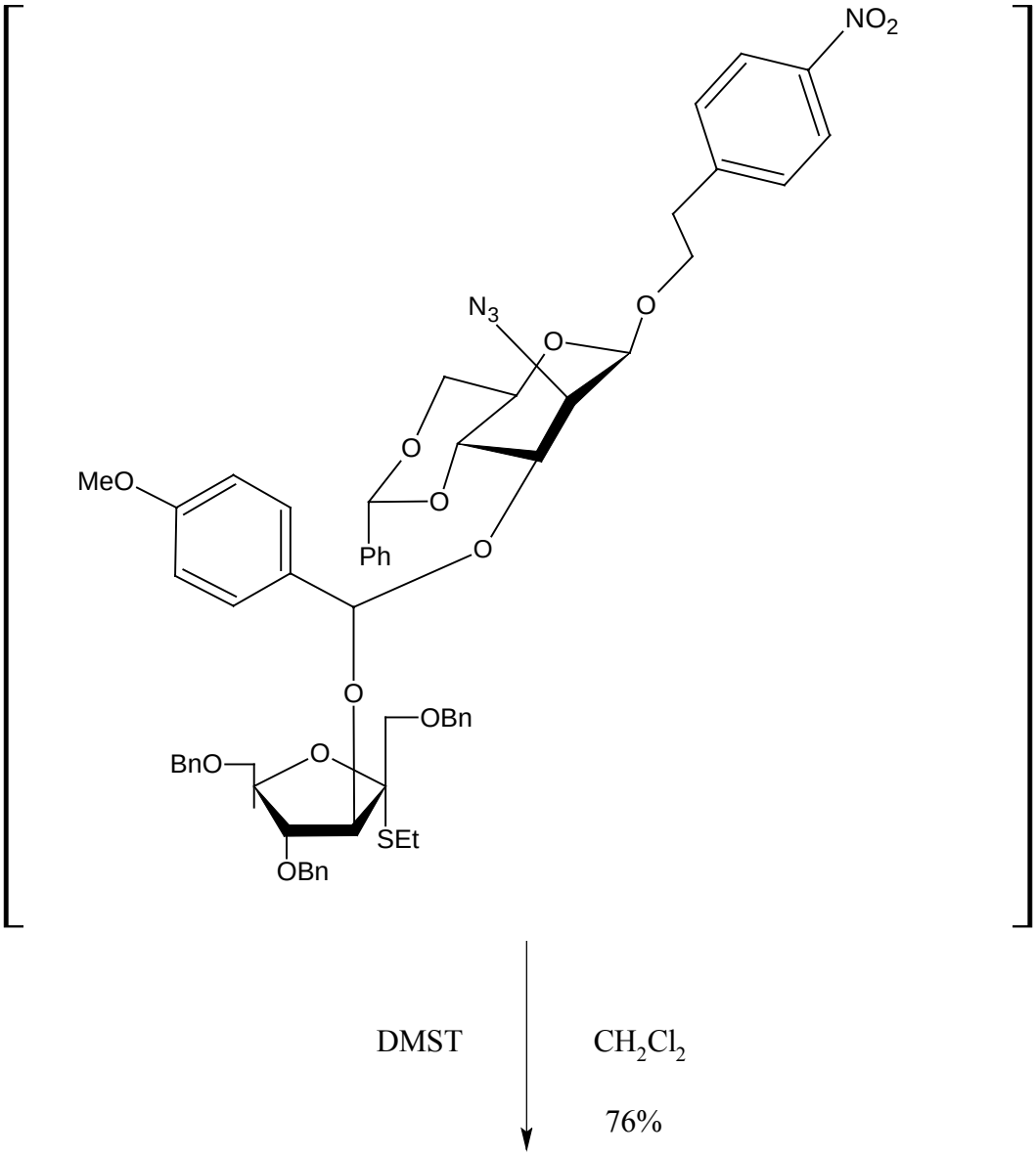


Scheme 32.



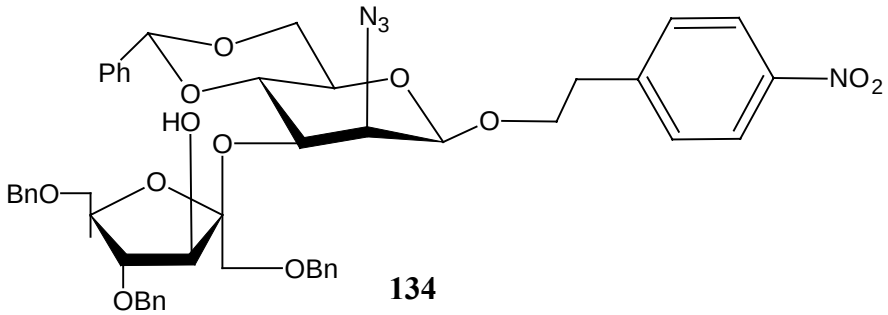
Scheme 33.





DMST CH_2Cl_2

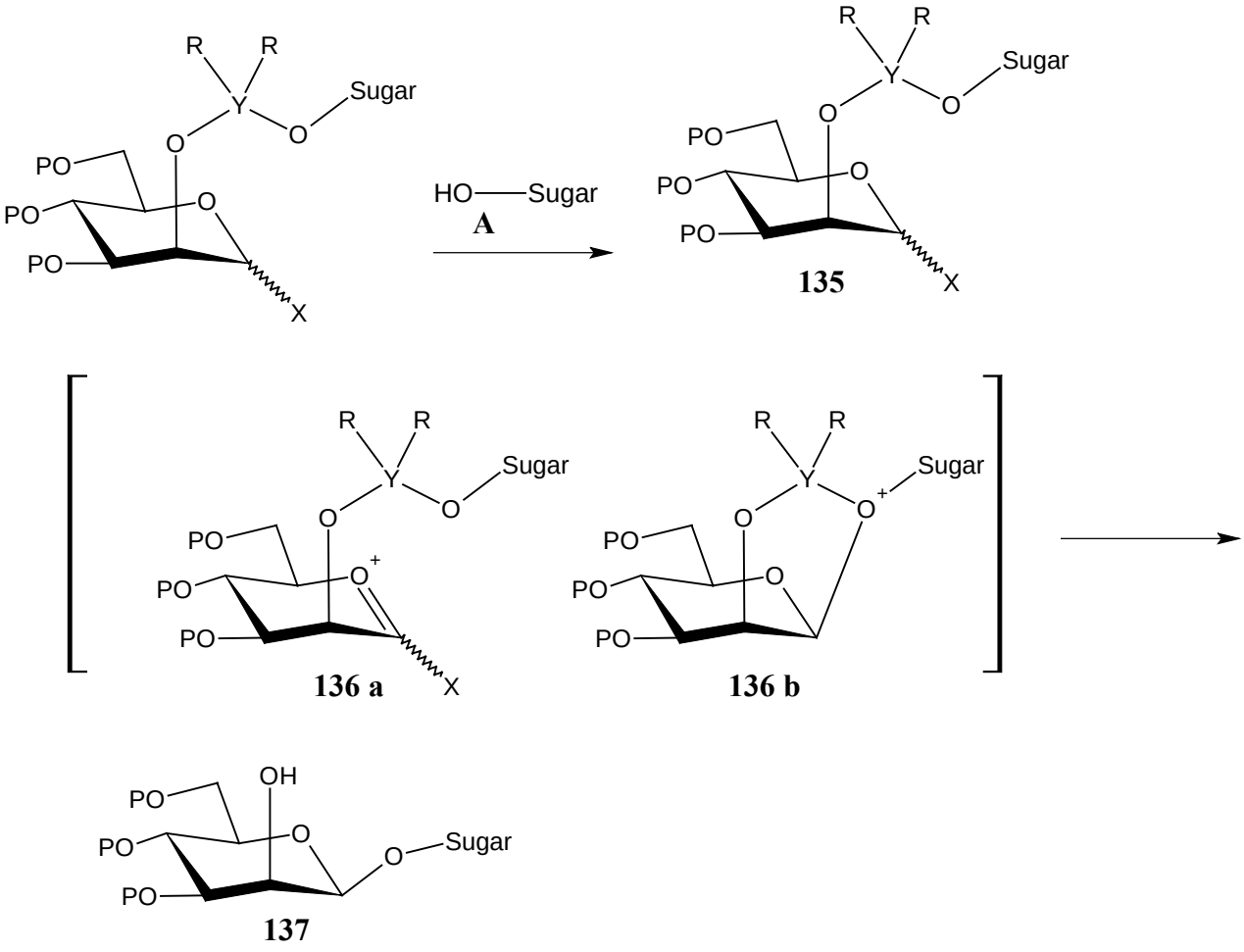
76%



134

An almost identical concept was reported by Gilbert Stork and coworkers with the silicon connection approach. [38,39] They illustrated their approach,in which a carbohydrate **A** is attached via a temporary connector **Y**, dimethyl silane to a properly chosen acceptor **B**, than a glycosylation reaction by a chosen activation method to produce the desired ß-mannosyl glycoside, as shown in the following scheme **34**.

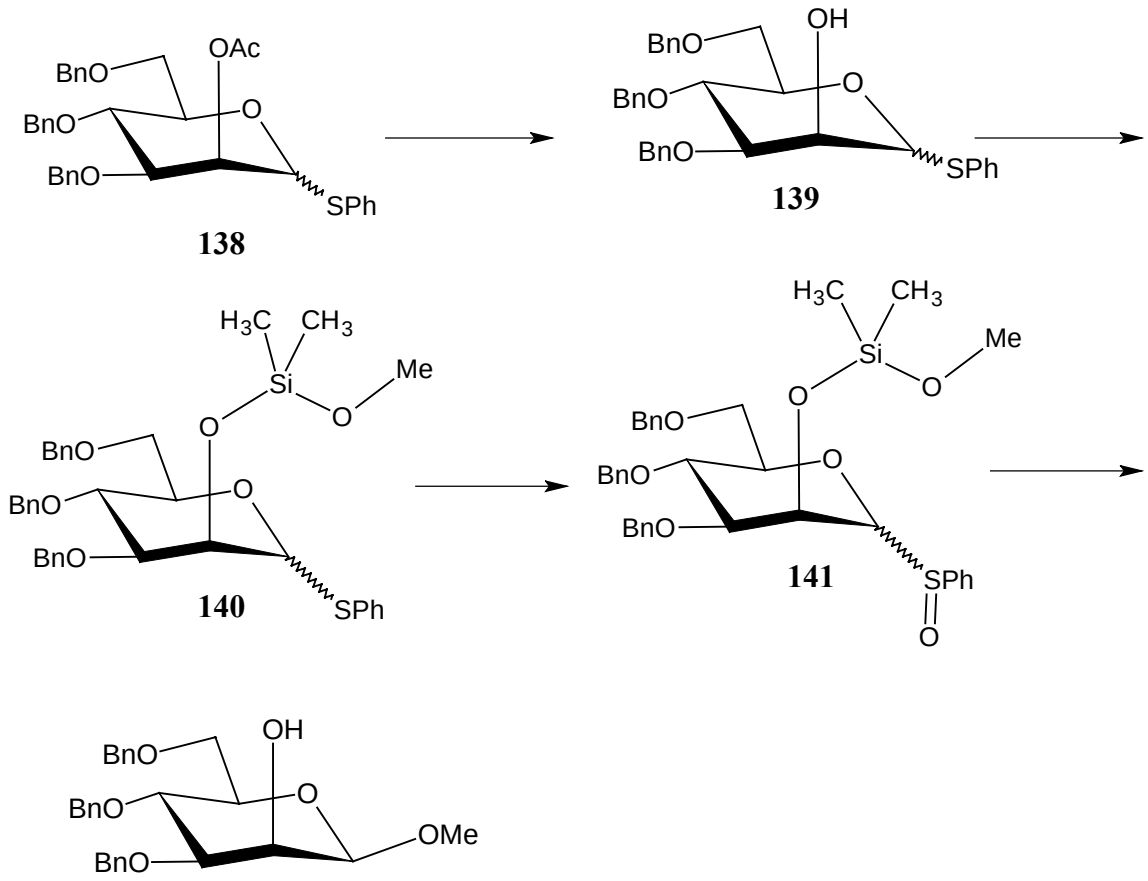
Scheme 34.



Before any attempted disaccharide sythesis with a mannosyl glycoside,the feasability of this method was examined for a simple ß-methyl and ß-isopropyl-mannosides.They were chosen as examples because of the difficulty of their obtention by conventional methods. Beginning with a phenyl-1-thio-3,4,6,tri-O-benzyl 2-O-acetyl- -D-mannopy- ranoside **138** as donor and it's deacetylation freed the free hydroxyl **139** which is converted to the methoxysilane **140** by reaction with chloromethoxydimethylsilane.The phenylthio group was converted to a good departing group **141**, that is oxydation with a perbenzoic acid. Activation with triflic acid, 2,6 di-tert-butylpyridine in dichloromethane produced successfully the ß-mannoside **142** .

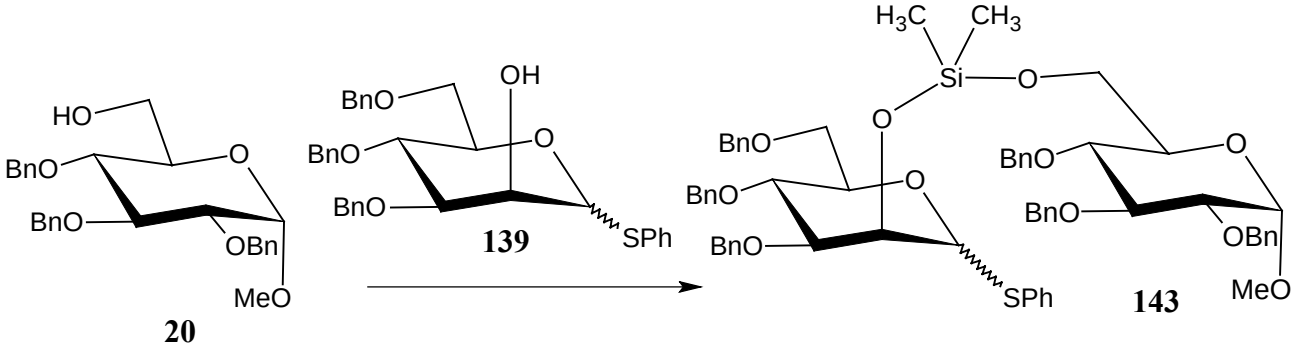
With this desired anomeric outcome, was application with an glucose acceptor α-D-methyl-tri-O-benzyl-D-glucopyranoside possible.(Scheme **35**)

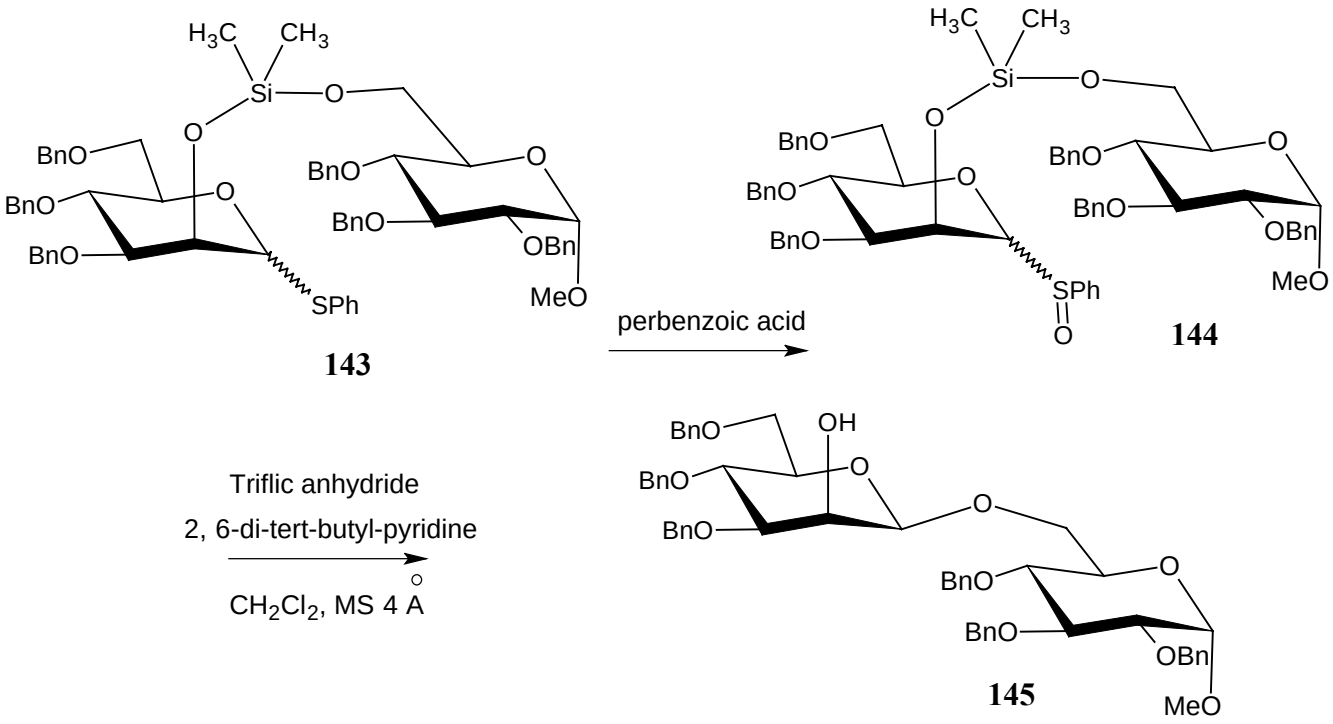
Scheme 35.



Conversion of the acceptor **20** to its chlorodimethylsilylether followed by reaction with the free alcohol of the donor **139** gave the tethered disaccharide **143**.Oxidation of the phenylthio group with a perbenzoic acid gave the sulfone **144**, and glycosylation reaction with triflic acid and 2,6-di-tert-butylpyridine afforded 61% yield of the ß-disaccharide. Reactions are detailed below in scheme **36**.

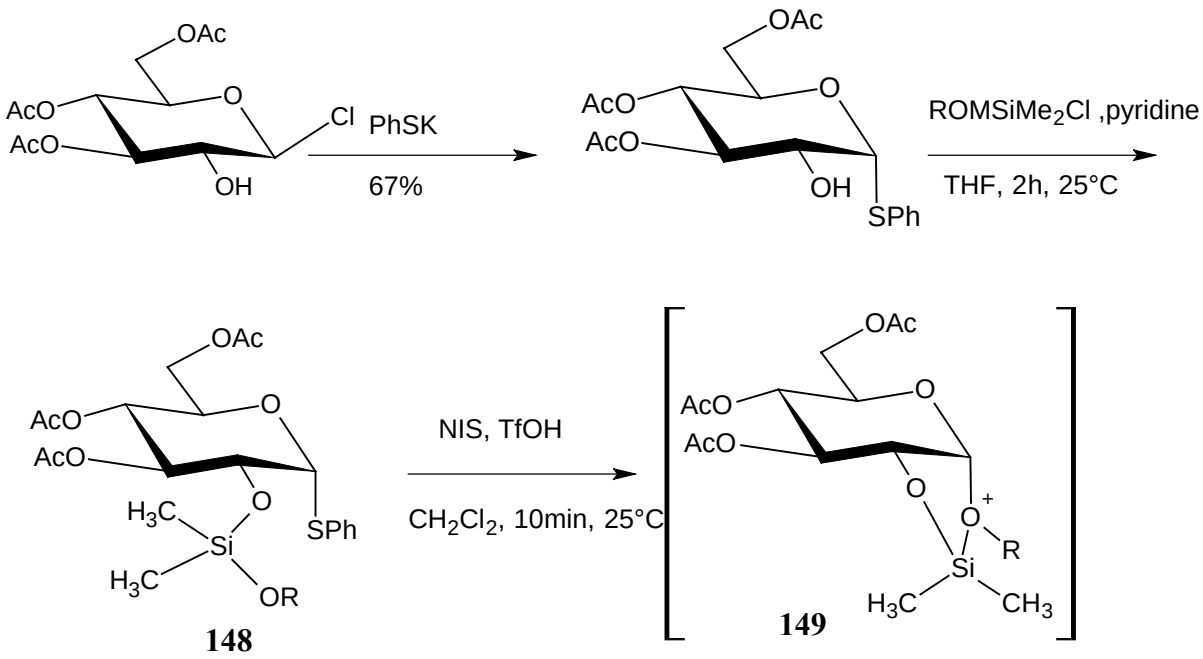
Scheme 36.

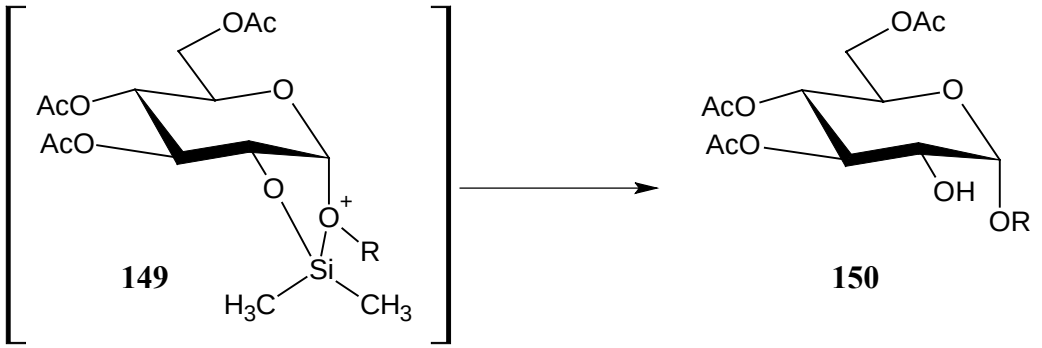




The silicon tethered approach was also a method of choice used by Bols *et al*. in the synthesis of α-glycosides. The application of this approach [40,41.] is aimed toward the glycosylation of a weakly nucleophilic sugar hydroxy group, and to thioglycosides. From a chlorotriacetylated α-D-glucopyranoside was formed the thioglycoside **2** in 63% yield, by reaction with potassium benzothiolate. (Scheme **37**)

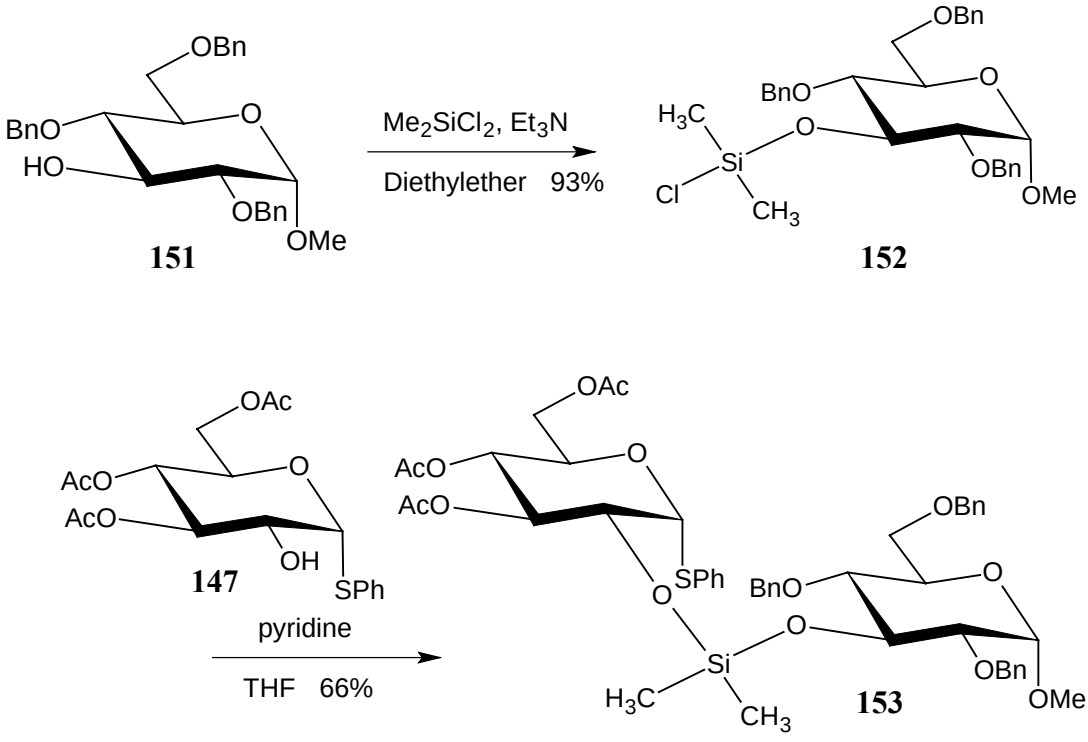
Scheme 37.

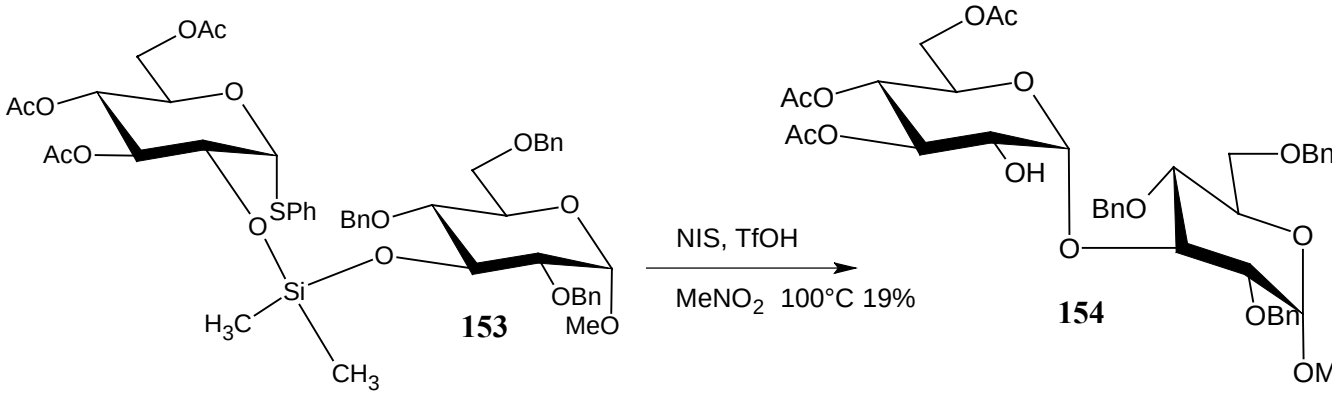




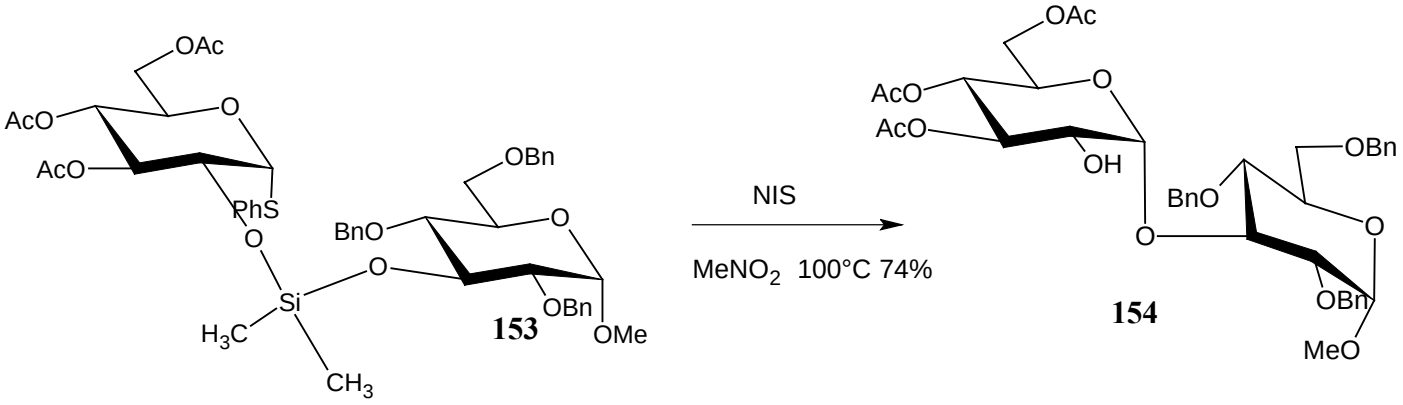
When R=octyl, and cyclohexyl 59% for the former and 62% yield for the latter was obtained with only α products detectable. Intramolecular glycosylation was performed using the thioglycoside activation method with NIS/ triflic acid as promoter for the synthesis of α-glucosides and galctosides. First, silylation of methyl 2,4,6-tri-O-benzyl- α-D- glucopyranose **151** with Me_2SiCl_2 in the presence of triethyl amine yielded essentially **152** in 93% yield. A further silylation reaction of phenylthio-3,4,6-tri-O-acetyl-α-D-glucopyranose with **147** gave the silylated tethered disaccharide **153** in 66% yield. Glycosylation reaction with NIS, with a catalytical amount of triflic acid in nitromethane at 100°C led to a dissapointing 19% yield of **154**. However with further experiments showing the possibility of omitting TfOH significantly increases the yield to 74% of **154**, with no ß-glucoside observable (Scheme **38, 39**).

Scheme 38.

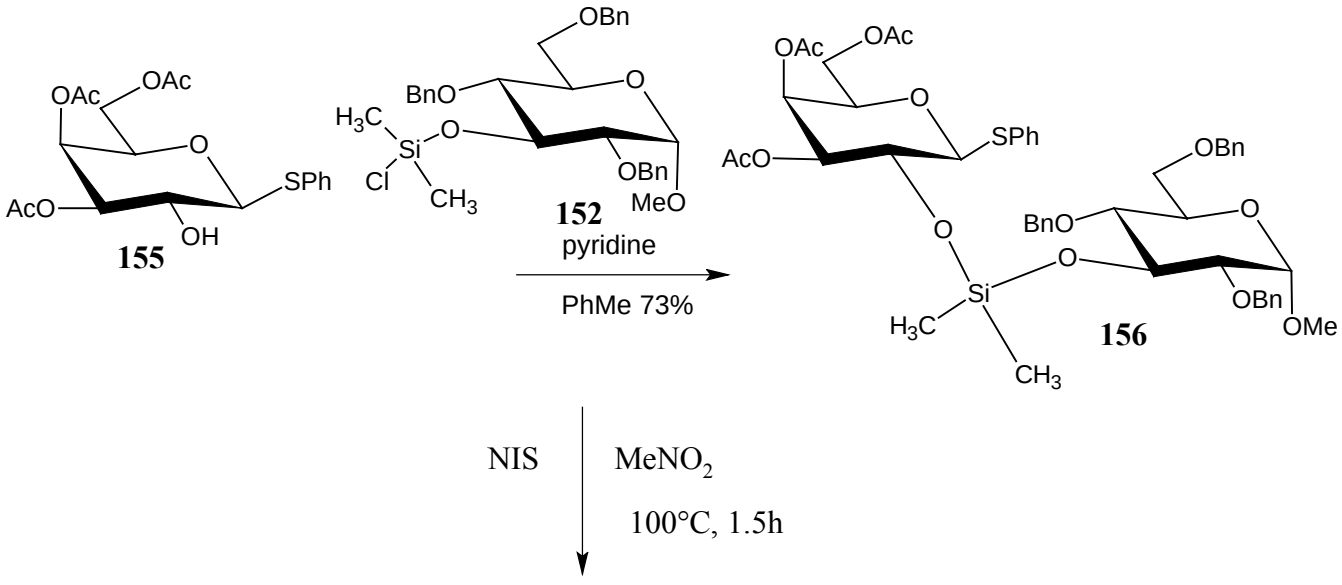


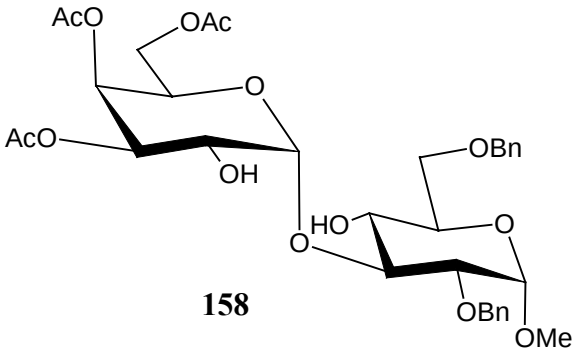


Glycosylation omitting TfOH

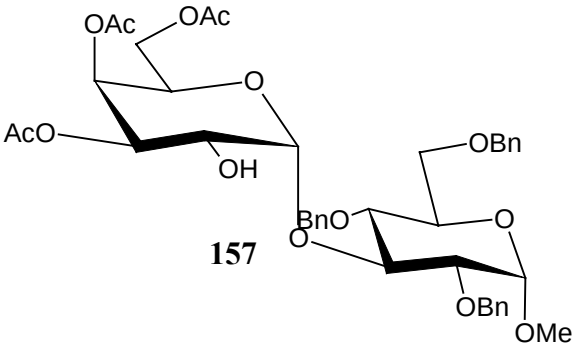


Glycosylation involving galactose donor
Scheme 39.





158

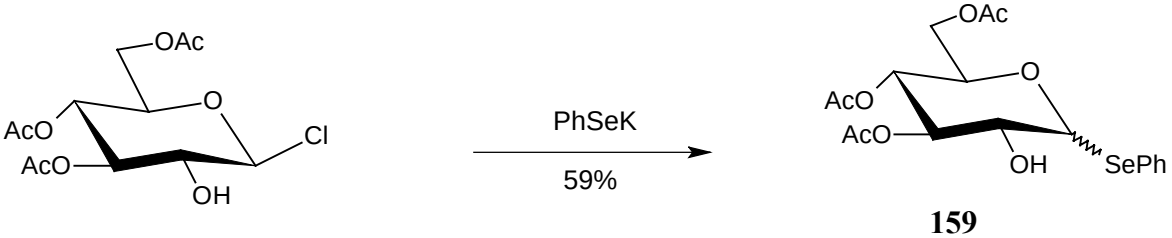


157

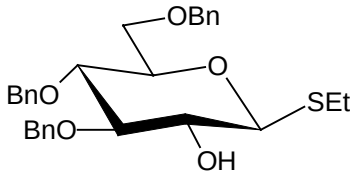
Here in the case of the galactoside **156**, glycosylation with NIS in nitromethane at 100°C produced two α-products **157, 158**. The expected α-galactoside in 32% yield and, another α-galac- toside with 49% yield. Surprisingly, this second product was debenzylated at the 4-position of the glucose acceptor. Thus a combined yield of 3-O-galactoside of the reaction was 81%.

The performance of the silicon tether method was reported in the synthesis of Kojitriose[(42)], a constituent of intracellular teichoic acids with RNA binding properties, obtained from Strepoccoci. The glycoside donor of choice employed was ethyl-thio-tri-O-benzyl-ß-D-gluco-pyranoside **160** Reaction with chlorodimethysilane in pyridine,and donor 1,3,4,6, tetra-O-benzyl α-D-glucopyranoside **161** as acceptor afforded the sylilated tethered disaccharide **162** in 35% overall yield for both steps. Glycosylation reaction with NIS in nitromethane gave stereo-specifically α-glycoside **163** in 45% yield. The formation of the trisaccharide was subjected to the same reaction pattern as the former, with 3,4,6-tri-O- acetyl-1-seleno-α-D- glucopyranoside **159**, prepared from glucosyl **146** by reacting with potassium phenylselenate in 59% yield and α/ß 1:3 ratio.The sylilated tethered trisaccharide **164** was obtained in exellent yield 82%. Internal glycosidation of **164** with NIS in nitromethane afforded two products, trisaccharide **165** and aglycone **167**. After chromatographic seperation , the trisaccharide **165** was isolated in 45% yield. Deacetylation with NaOMe in methanol, and debenzylation by hydrogenation gave kijotriose **166** in quantitative yield (Scheme **40**).

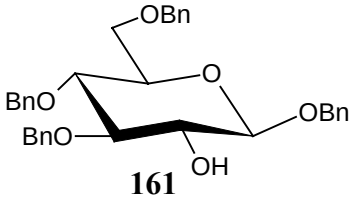
Scheme 40.



159

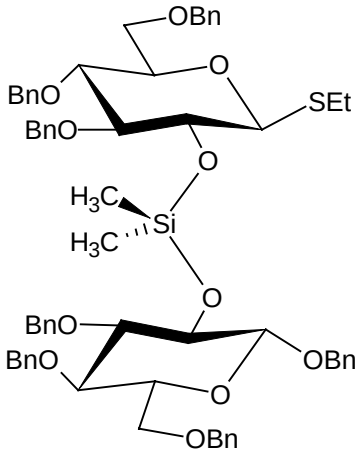


160

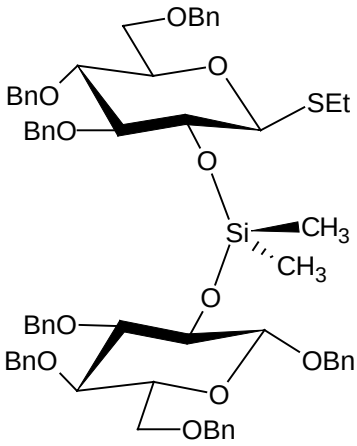


161

Me_2SiCl_2
pyridine



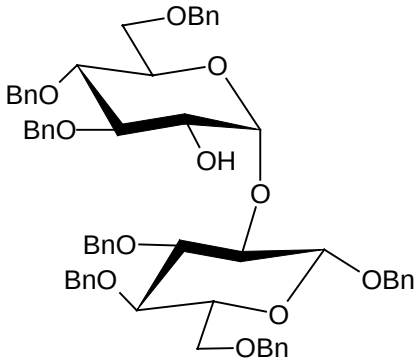
162



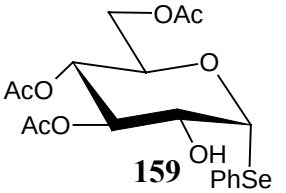
162

NIS

Nitromethane 45%



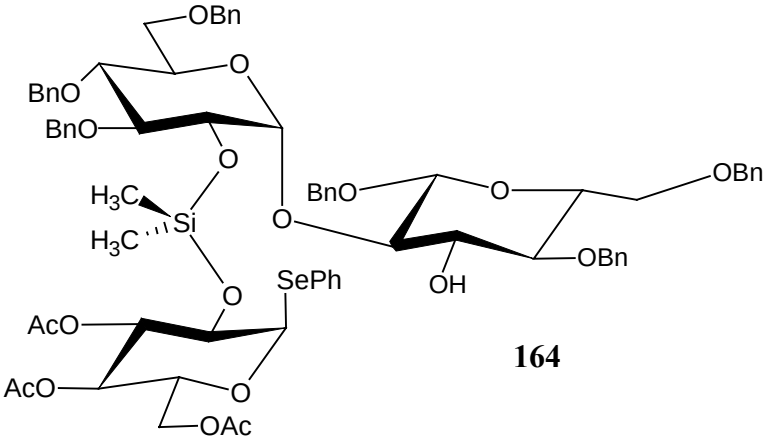
163



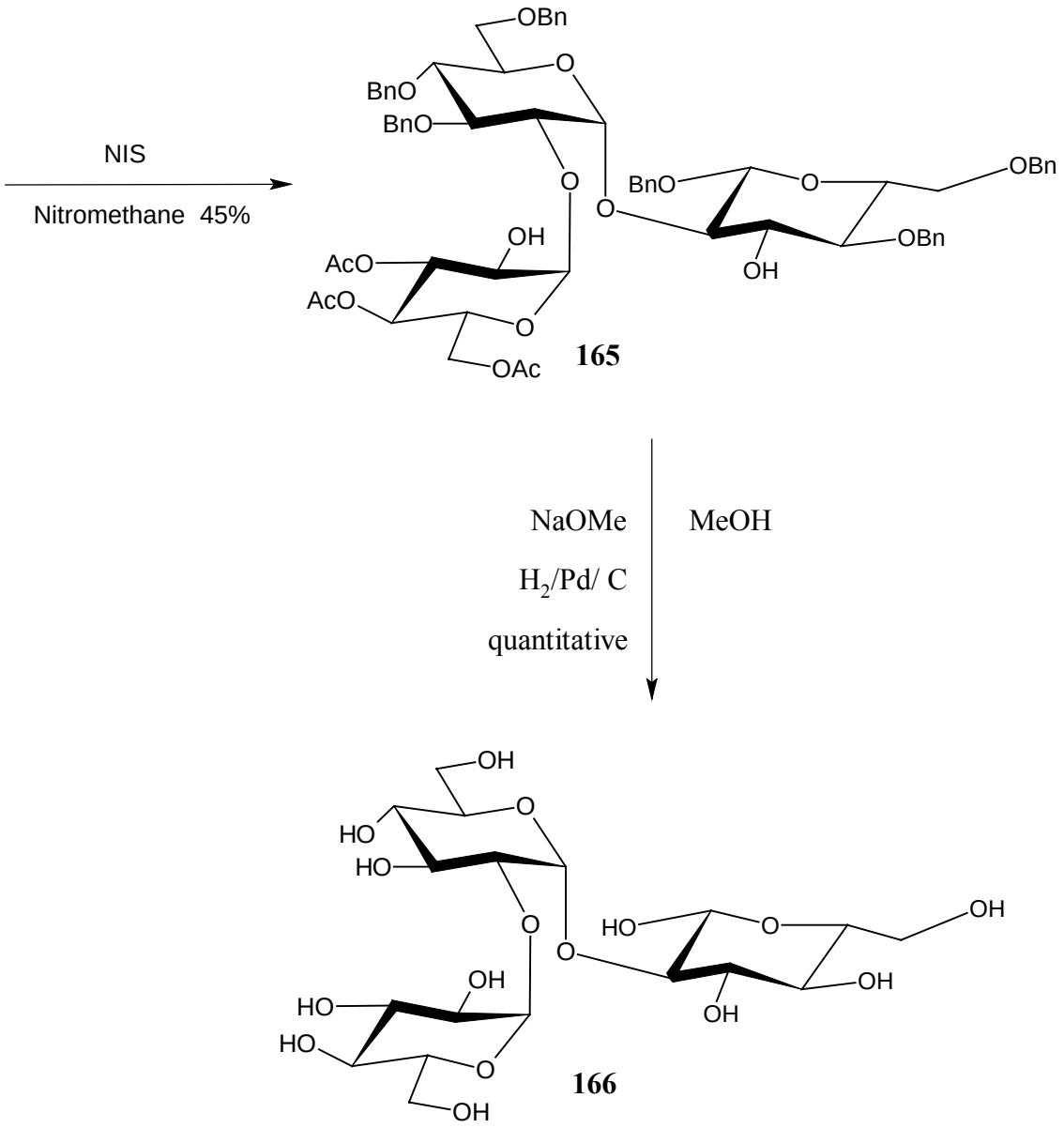
159

Me_2SiCl_2

pyridine 82%



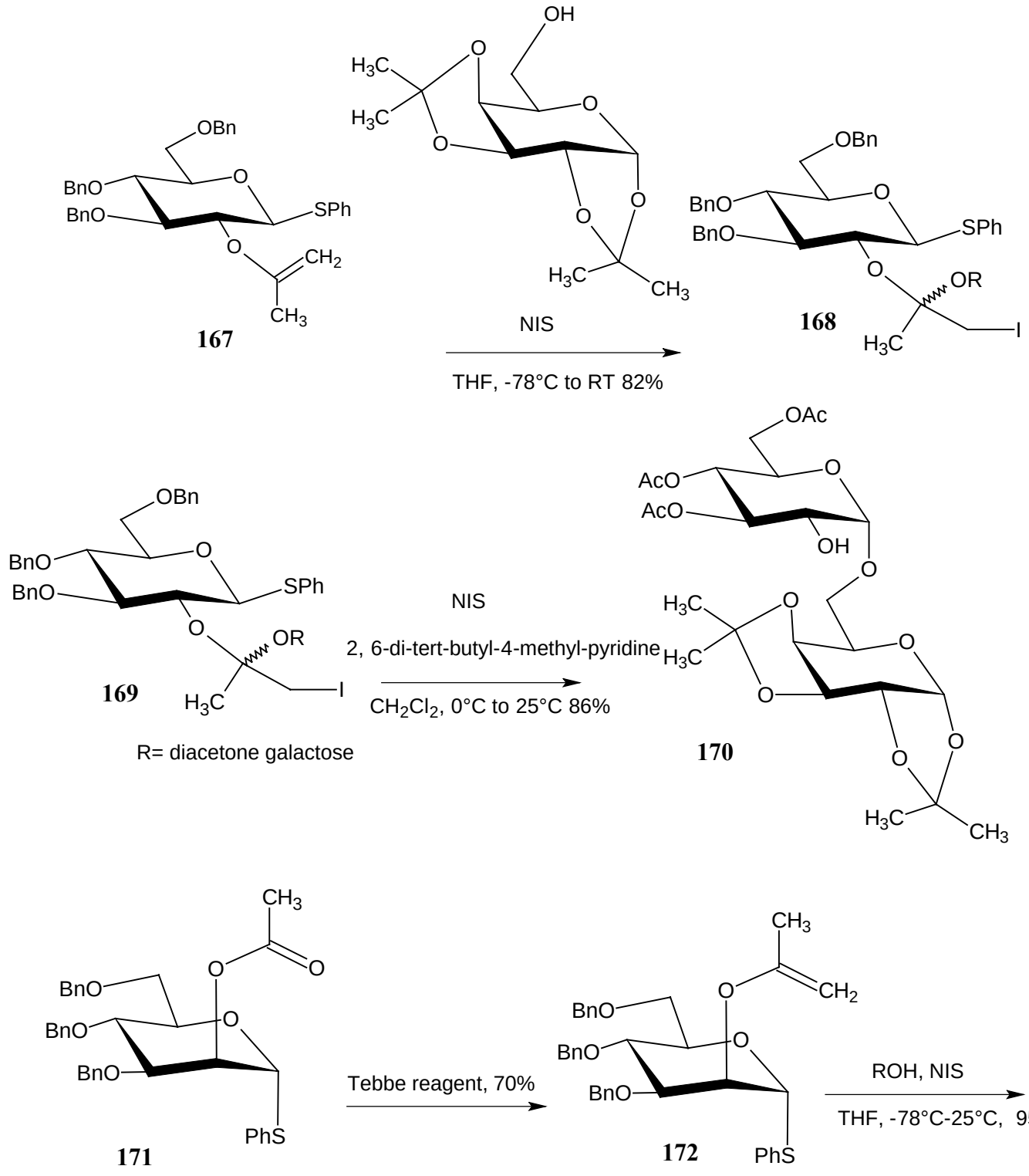
164

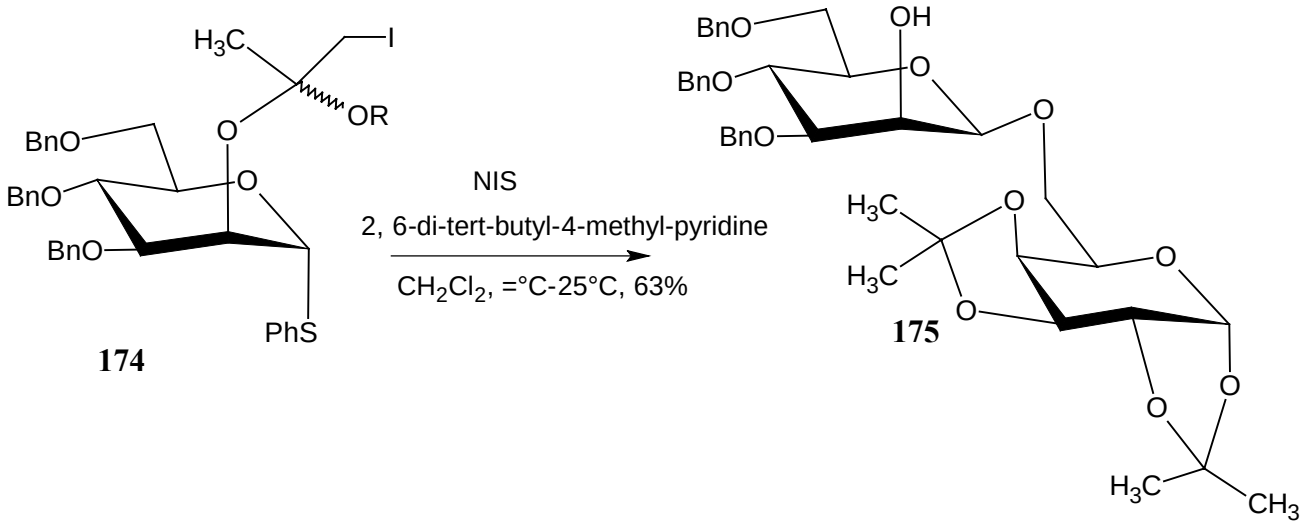


A new and modification of the "Intramolecular Aglycon Delivery" method was introduced by Fairbanks *et al.*[43] with the NIS-mediated Hindsgaul type Intramolecular Aglycon Delivery for the stereoselective synthesis of α-glucosides and ß-mannosides. In an example here when when starting with a glucose donor **162** and reaction with NIS and a diacetone galactose acceptor **168** produced the mixed acetal **169** in 82% yield followed by glycosylation with NIS, in the presence of di-tert-butyl-4-methy pyridine in dichlorome thane at 0°C to 25°C which afforded 86% yield of the α-D-disaccharide **170**. A similar set of reactions were performed with in the the analogous *manno* derivative **171**. The mannose donor enol ether **172** was prepared from the α-D-thioglycoside **171** through Tebbe reagent with a respectable 70% yield. Reaction of **172** with NIS and deacetone galactose **171** furnished the mixed iodoacetal **173** in an exellent 95%

yield. Finally glycosylation reactiion again with NIS (5equiv.excess) in the presence of 2,6,-di-tert-butyl-4-methyl-pyridine in dichloromethane (0°C-25°C) gave 63% yield of only ß-mannoside products **175**. When cyclohexanol was used as acceptor, of a quantitative yield of ß-mannoside was achieved. Reactions are described below in the following. (Scheme **41**.)

Scheme 41.

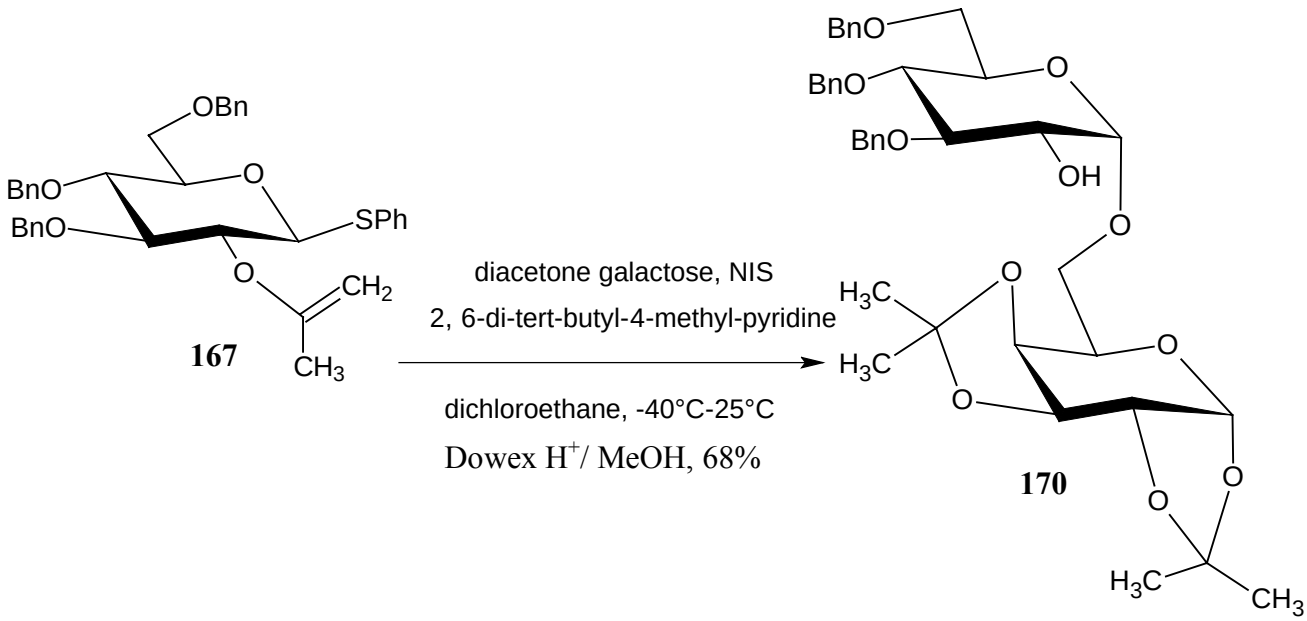




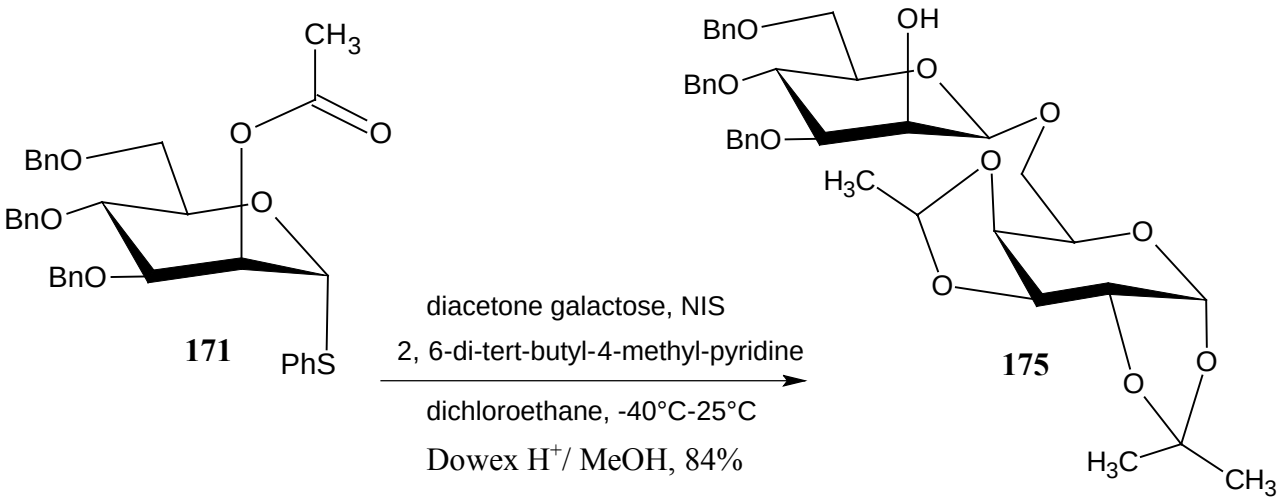
174 **175**

Spurred by these successes, investigations then turned to a potential one-pot approach[43] to effect both, the tethering and glycosidation reaction in a single step. In screening solvents to produce a clean high-yielding reactions was the choice of dichloroethane satisfying. Starting from both glucose enolether **167** and mannose enolether **171**, the one-pot reaction with diacetone galactose, NIS, 2,6-di-tert-butyl-4-methyl-pyridine at in dichloroethane at -40°C to room temperature, then Dowex H^+/methanol gave the α disaccharide **170** in a good yield of 68% for the former, and a significant 84% yield of ß-mannoside **175** for the latter.
(See scheme **42**) .

Scheme 42.



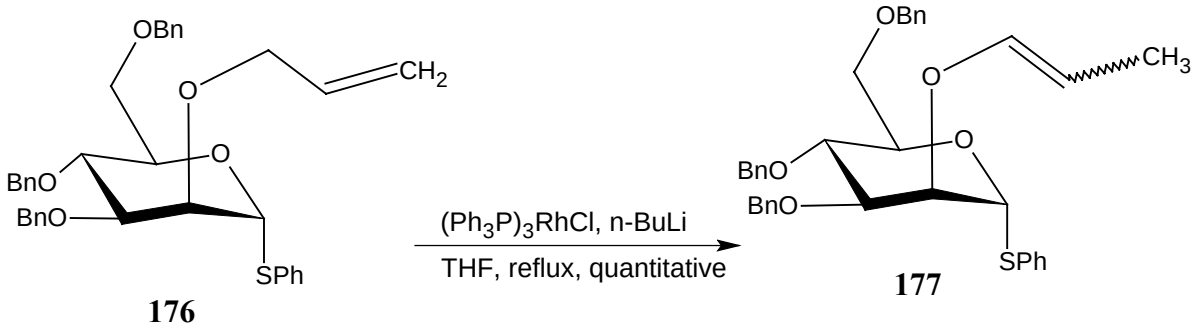
167 **170**

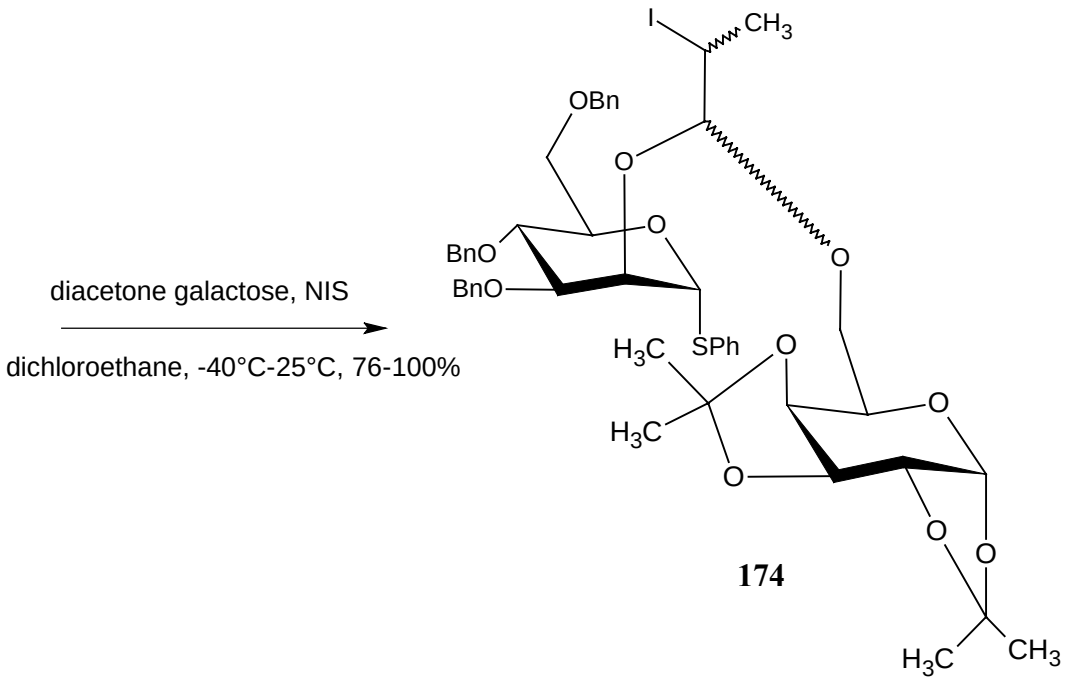


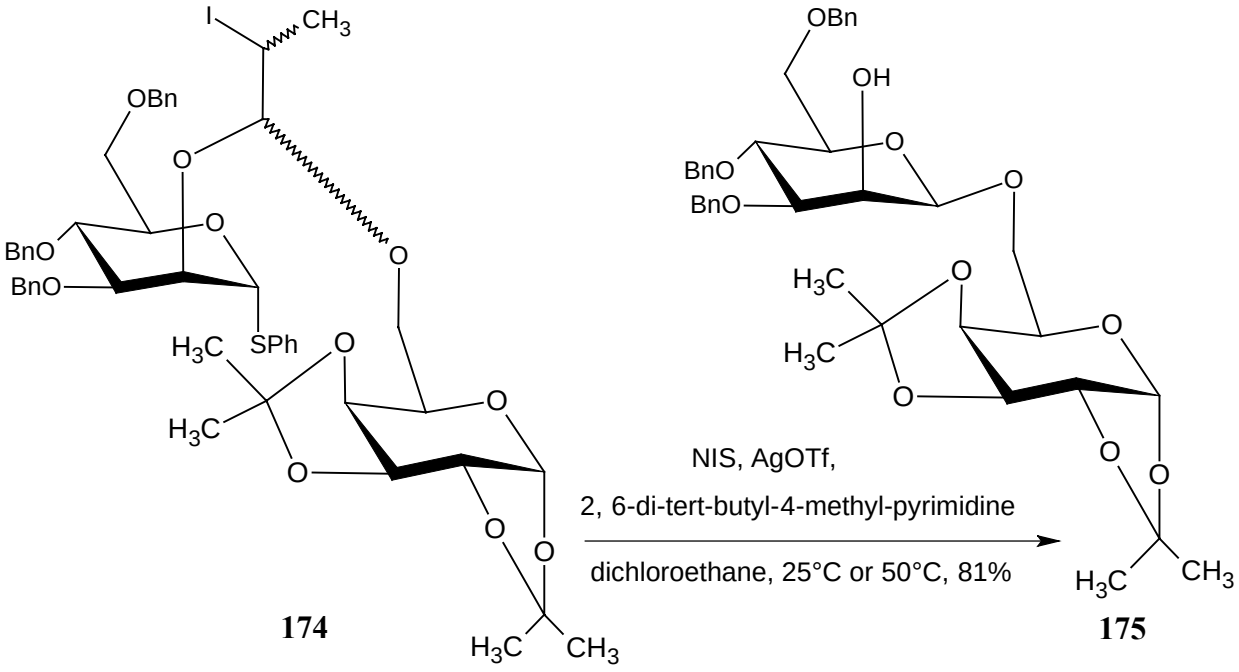
With the success of this procedure, they have demonstrated that N-iodosuccinimide can be used to effect both tethering and glycosydation steps implicit in the Hindsgaul mixed ketal approach to 1,2-*cis*- glycosides, and this methodology allows stereoselective sythesis of α-glycosides as well as ß-mannosides.

Fairbanks and coworkers reported another modification of the Hindsgaul type of Intramolecular Aglycon Delivery[44] by using 2-O-allyl protected thioglycosides donors as means of tethering with an acceptor. By means of theWilkinson's catalyst, isomerization leading to a vinyl ether ether was obtained in quantitative yield, which was subjected to reaction with NIS and an an acceptor to the desired tethered disaccharide, followed by glycosilation as effected in their former procedures. As donors available were a benzylated mannoside thioglycoside **176** which was isomerized by a combination of Wilkinson reagent and n-butyllithium, which proceeded efficiently to yield the enol ether **177.** Mediated tethering with NIS and an acceptor diacetone-galactose **168** furnished **174** in almost quantitative yield of mixed acetals, then glycosylation of **174** with NIS in dichloroethane at -40°C-25°C afforded 81% yield of only ß- mannoside **175**. (Scheme **43**) .

Scheme 43.



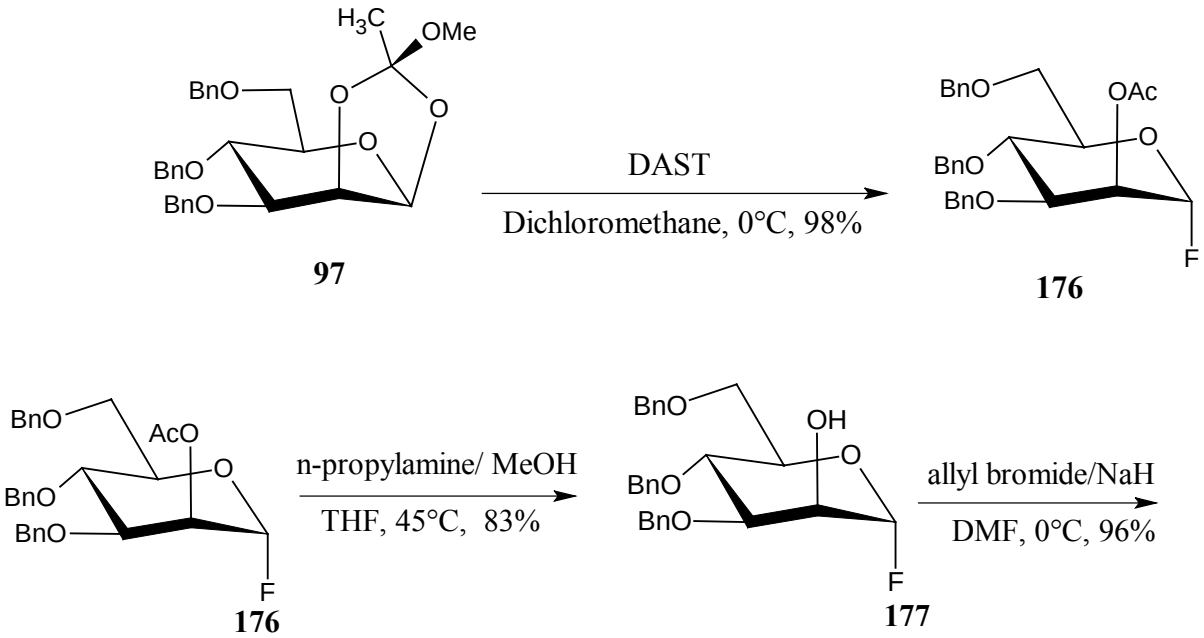




This methodology with the 2-O-allyl protected glycosyl donors may thus be employed for the synthesis of various *cic*-1,2 glycosides and ß-mannosides in good to exellent yields. Noteworthy is the efficient isomerization of the allyl group which reveals superior to the often messy Tebbe methylation reaction. In addition , the use of excess glycosyl donor allows the tethering and glycosylation to be conducted in a single reaction vessel, thus obviating the sensitive handling of mixed acetal intermediates.

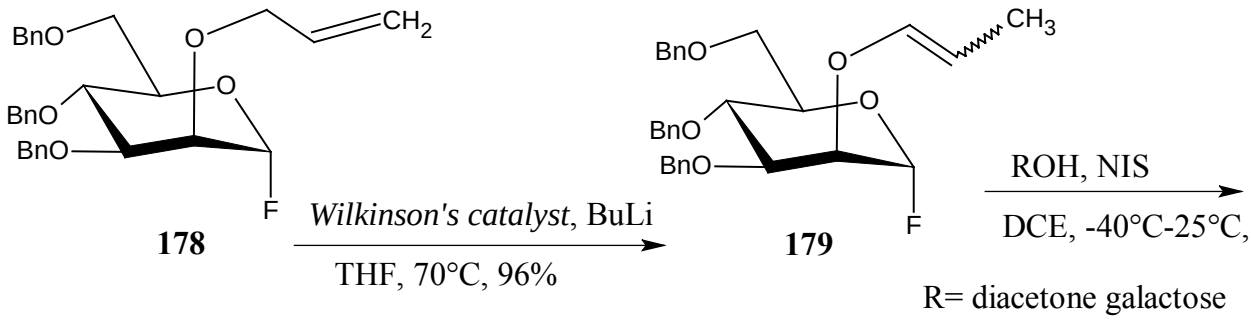
Inspiring themselves with the same methodology, a particular interest was focused on glycosyl fluorides[45,46],mannose and galactose. Glycosylfluorides bearing 2-O-allyl protecting groups were prepared. Reaction of the glycosyl orthoester **97** with DAST gave the 2-O-acetated-α-D-glycosyl fluoride **176** in 98%yield. Deacetylation of **176** with n-propylamine in methanol furnished quantitative yield of **177** and finally reprotection ofthe OH-2 by treatment with allyl bromide and sodium hydride in DMF yielded the desired donor **178**. (Scheme **44**)

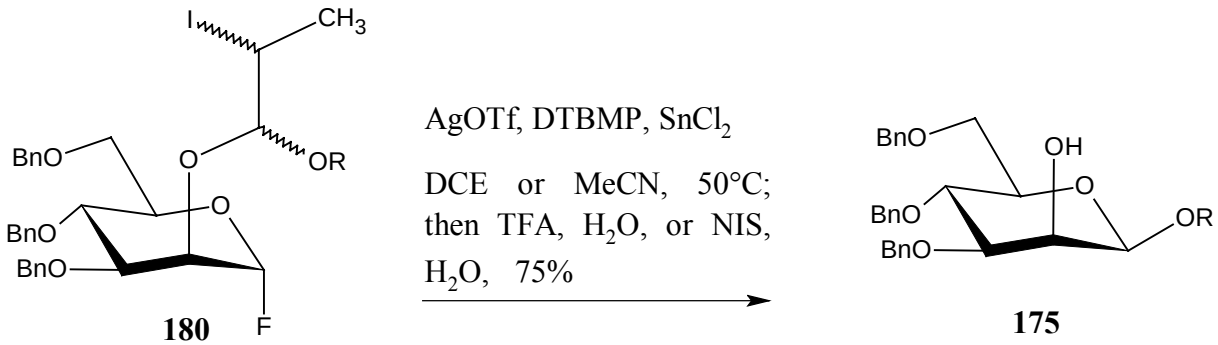
Scheme 44.

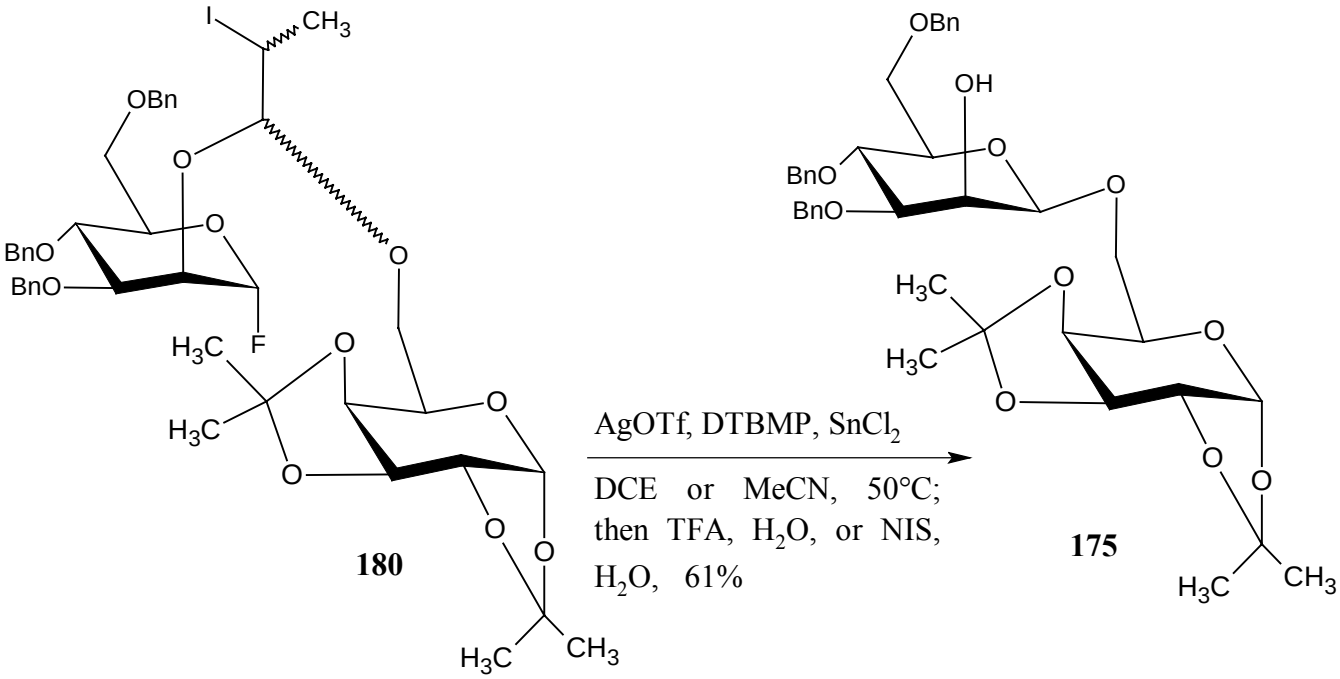


Isomerization of **178** furnished the isomerized product **179** in quantitative yield 96%. The following step was the formation of the mixed enolether **180** by reaction with NIS, ROH, in dichloroethane at -45°C to -25°C where R is diacetone galactose in 98% yield and finally intramolecular glycosylation reaction with silvertriflate,2,6-di-tert-butyl-methylpyridine in dichloroethane or acetonitrile at 50°C yield 61% of the ß-dissachride **175** with the mannosyl derivative as donor. (Scheme **44**).

Scheme 44.

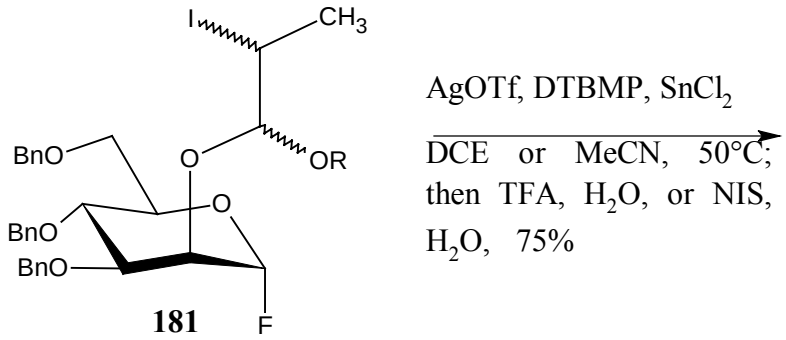


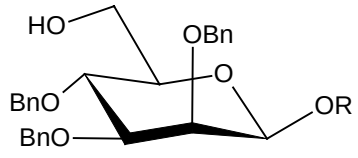




Another very successful accomplishment of this method was the intramolecular glycosylation reaction was achieved with a tribenzylated galactose acceptor toward the obtention of the mannosyl dissacharide in 75% yield of **183** with the same reagents and conditions. (See below scheme **45**.)

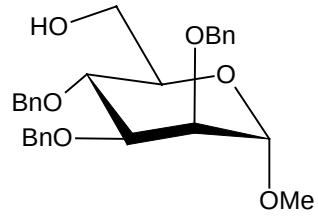
Scheme 45.

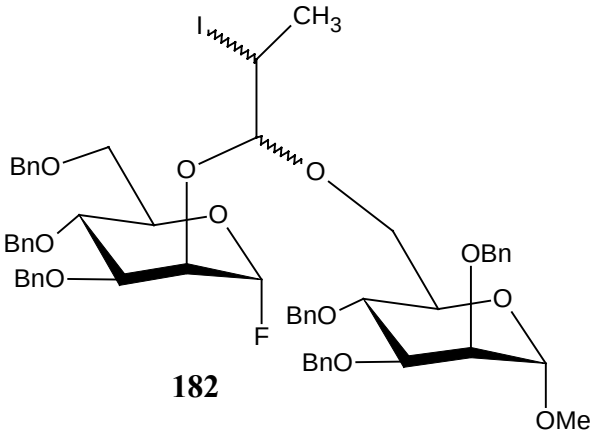




183

when R=

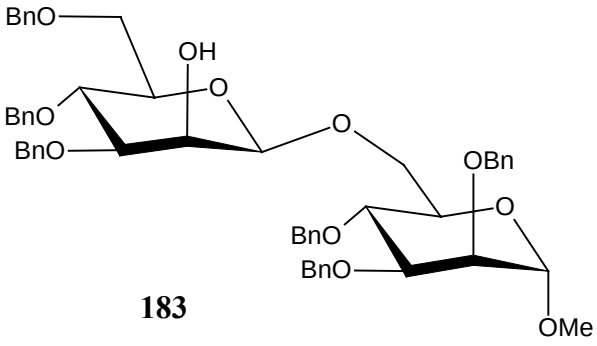




182

AgOTf, DTBMP, $SnCl_2$

DCE or MeCN, 50°C; then TFA, H_2O, or NIS, H_2O, 75%



183

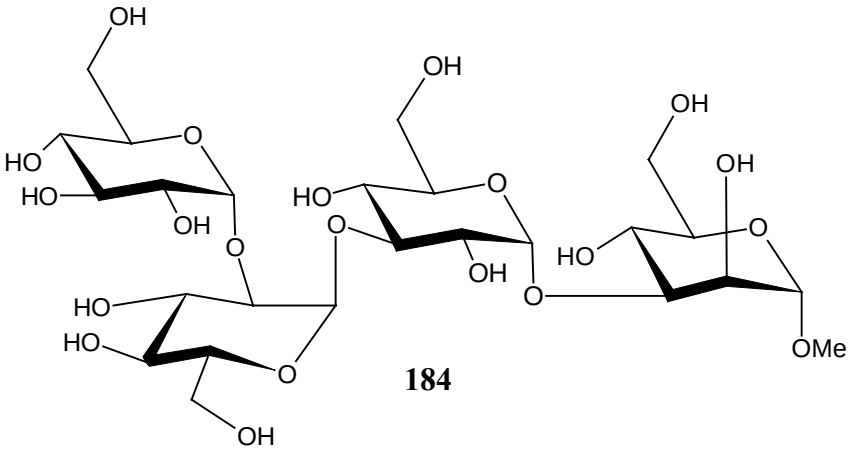
This methodology present two features worthy to mention. The first being that the efficiency of glycosylation is solvent dependant. Fairbanks and cowokers had observed whereas the glycosylation of manno mixed acetals was slow in acetonitrile and occured at the same time as the partial hydrolysis of the tether, the same experiment carried out in dichloroethane as solvent proceeded very quickly and without hydrolysis.

The second important feature noteworthy of consideration is the formation of side products by nucleophilic trapping of the oxonium ion produced subsequently to the intramolecular glycosylation reaction. In earlier experiments with thioglycosides, byproducts were observed after glycosylation were identified as mixed acetals. These presumably arose from trapping of the oxonium ion produced subsequent to the glycosylation reaction byan external alcohol acting as a nucleophile. In thioglycoside cases, treatment of the crude reaction mixture

treated with tifluoroacetic acid (*TFA*) during work-up resulted in the hydrolysis of any such acetals and in the increased yield of disired 1,2-*cis*- glycoside.

Fairbanks *et al.* extended the Allyl-Mediated Intramolecular Aglycon Delivery involving glycosyl fluorides to the synthesis of oligosaccharides[47]. One example is a tetrasaccharide **184** (**Fig. 7**) which represents to the glucose-terminated arm of the $GLc_3Man_9GLcNAc_2$, tetrasaccharide, which is the oligosaccharide structure transferred to certain asparagine residues of nascent glycoproteins(tripeptide sequence, AsnXxxSer,where Xxx Pro) by the enzyme oligosaccharyl transferase (OST) during the glycoprotein biosynthesis. Using glycosyl fluorides they have been able to complete the tetrasaccharide synthesis via an iterative allyl IAD aproach.

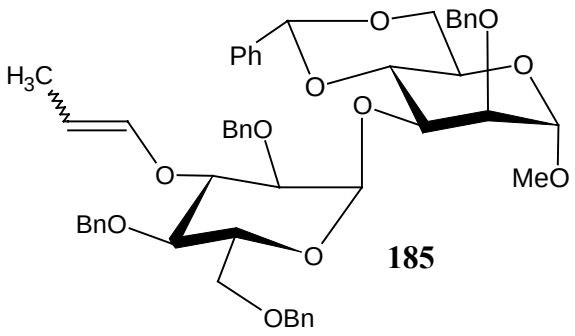
Fig 7.



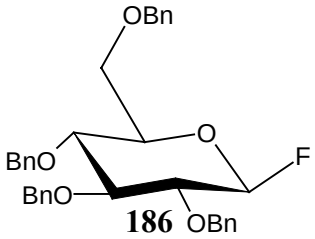
184

Starting with a 3-O-allylic protetected disaccharide **185**, and reaction with an ß-D-tribenzylated glucosylfluoride **186** acceptor, iodine, silvertriflate, in the presence of 2,6-di-tert-butyl-4-methylpyridine, in dichloromethane at -78°C -25°C, gave the iodoacetal tethered trisaccharide **187** in 78% yield. Glycosylation reaction with tin (II) chloride, silver triflate, DTBMP, in dichloroethane at 65°C furnished the α-D- trisacchatride **188** in 40% yield. For the formation of **190**, the tethered tetrasaccharide,was obtained in 78% yield from the reaction with an isomerized protected 2-O-allyl- ß-D-glucosyl fluoride acceptor **189**, as in the first reaction step. Glycosylation with the same reaction patterns as for the obtention of the trisaccharide **188** afforded the protected α-D-tetrasaccharide **191** in 25% yield. Finally the full deprotection of the trisaccharide by hydrogenation, with palladium(II) diacetate lead to **184** with quantitative yield. (See scheme **46**).

Scheme46



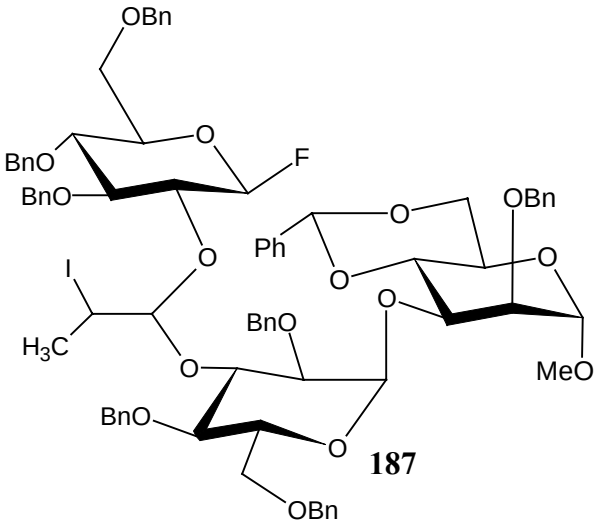
185



186

I_2, AgOTf,DTBMP

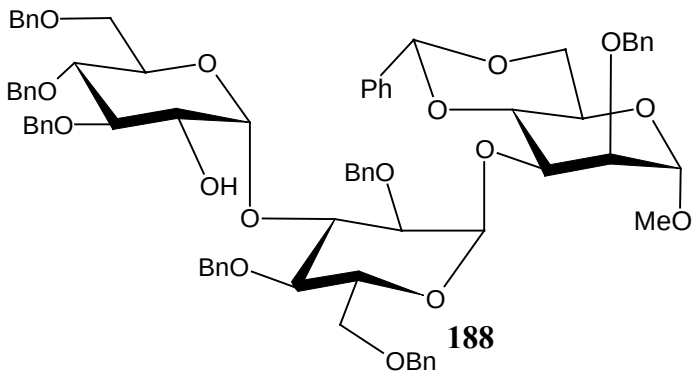
CH_2Cl_2 - 78°C- 25°C, 78%



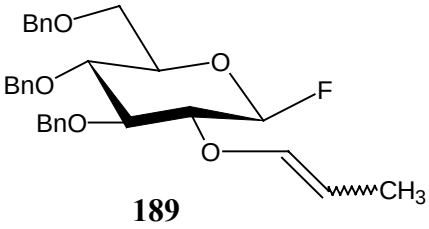
187

$SnCl_2$, AgOTf,DTBMP

dichloroethane 65°C, 40%



188

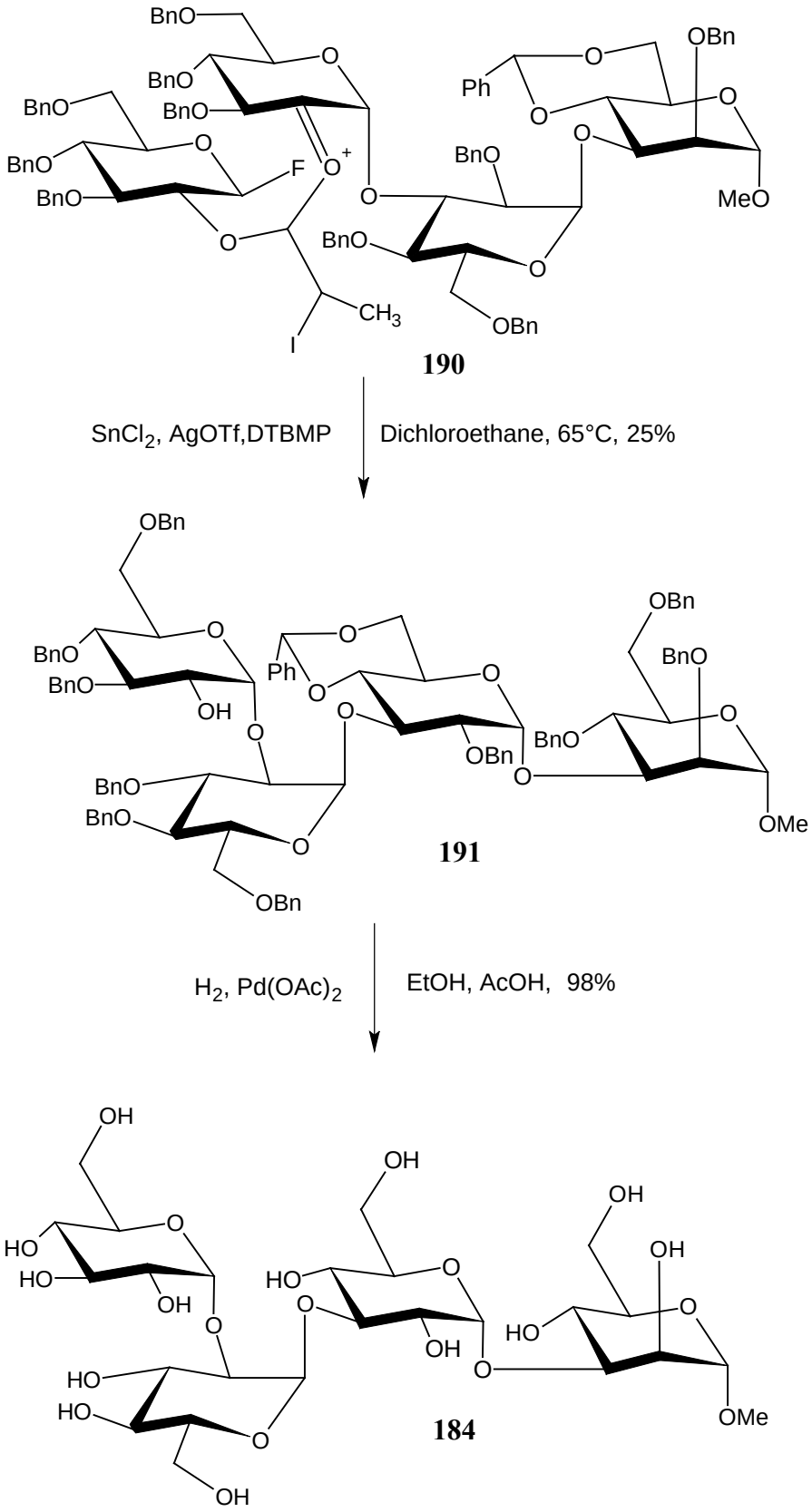


189

I_2, AgOTf,DTBMP

CH_2Cl_2 - 78°C- 25°C, 78%

Scheme 46.


BnO
OBn
Ph
MeO
F
CH3
I
190
SnCl2, AgOTf,DTBMP
Dichloroethane, 65°C, 25%
OH
191
H2, Pd(OAc)2
EtOH, AcOH, 98%
184
OMe

Glycosyl fluorides have been demonstrated to be exellent glycosyl donors for the ally mediated IAD approach to 1,2-*cis*- glycosides . Moreover the tethering and stereospecific intramolecular glycosylation may be achieved for a variety of primay and secondary carbohydrate alcohols Particularly, the use of glycosyl fluorides presents the advantage that, the tethering efficiency can be increased in the case of bulky secondary carbohydrate alcohols with extended reaction times. Comparatively with the original approaches of *Stork* and *Hindsgaul*, this method reveals superior in terms simplicity of application and yield, and can therefore be considered as complementary to the *Ogawa PMB* approach. Despite of more efficiency of the tethering in the *PMB* system, the allyl system presents the advantagee that threre is no requirement for cyclic 4,6-protection of the glycosyl donor for the obtention of good yields in the glycosylation step and that the technique is also applicable for he formation of α-glico linkages.

CHAPTER III

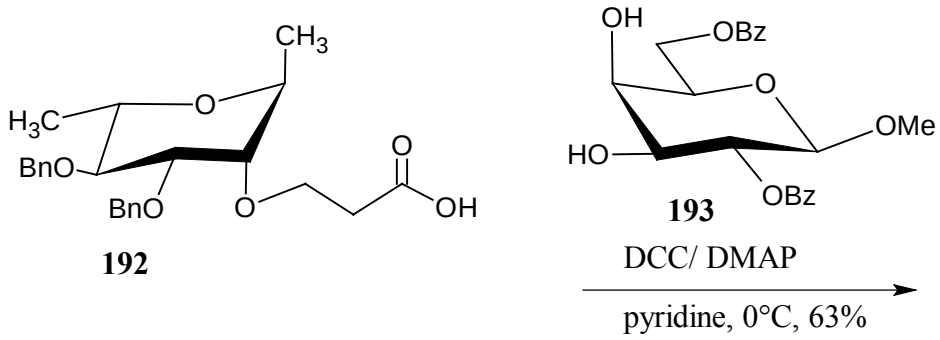
SPACER-MEDIATED

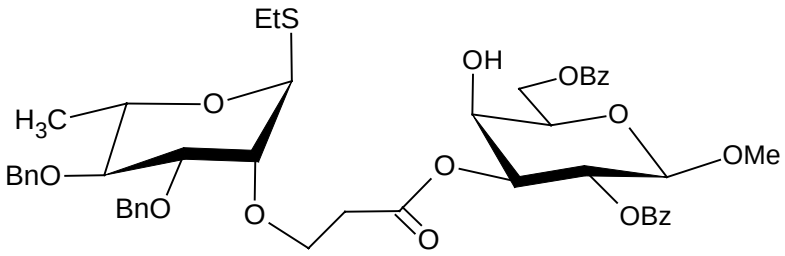
LINKAGE VIA NONREACTING CENTERS

Spacer-mediated Linkage via Nonreactiong Centers

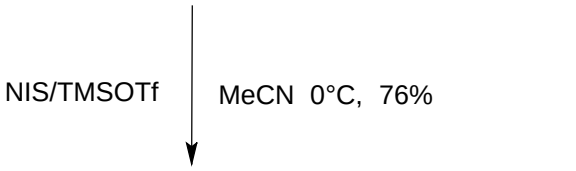
The succinyl and malonyl spacer were investigated by Ziegler and coworkers [49,50,51,52,53,54] in the aim to produce attachement of a glycosyl donor to a less reactive acceptor, bringing a prearranged position toward enforcement of highly stereoselective glycosylation.
Because of stereoselective and steric reasons, glycosylation reaction implying D-mannosides, L-Rhamnoside yielded preferentially α-glycoside. The synthesis of ß-mannosides and ß-L-rhamnosides, are regarded as one of the most challenging task in saccharide synthesis. Many approaches applied toward the synthesis of ß-mannosides revealed inapplicable for the formation of ß-L-rhamnosides. In an elegant synthetic methodology, Ziegler *et al.* adopted the malonyl and pthaloyl ester spacer to tether a benzylated gluco, galacto, and rhamnoglycoside, in order to afford ß-L rhamnoglycosidic bond. In addition, they reported the in fluence of the bridging spacer attached at various positions of the donor and acceptor to reach anomeric selectivity.
Selected as donor, was ethyl-1-thio- 3,4-diO-benzoylated 2-O succinyl-α-D-rhamnopyranose **192**. Selective coupling reaction with methyl-2,6-di-O benzoyl-α-D-galactopyranose **193** with DCC, DMAP, in pyridine furnished the tethered disaccharide in 63% yield.
Intramolecular glycosylation with NIS/TMSOTf in acetonitrile yielded 76% of only α-glycosidic bond of the disaccharide **195**. In galactosylation the anomeric selectivity is controlled by matched and mismatched of the galactosyl intermediate cation with glycosyl acceptor.
Here the rhamnosyl residue approaches the front side and favours the formation of only α (1-4) glycosydic bond, no ß-anomer was observed. (Scheme **47**.)

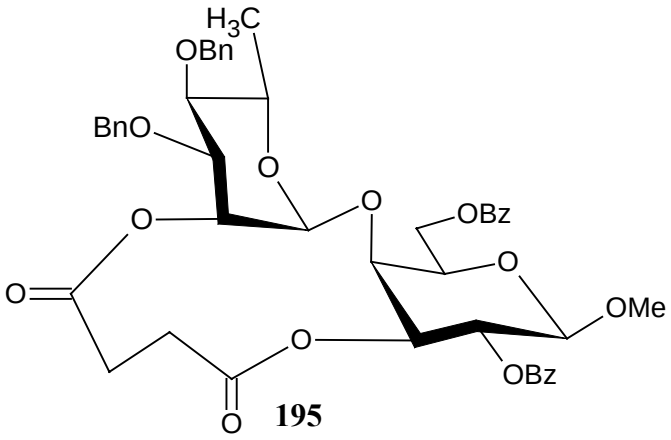
Scheme 47.





194

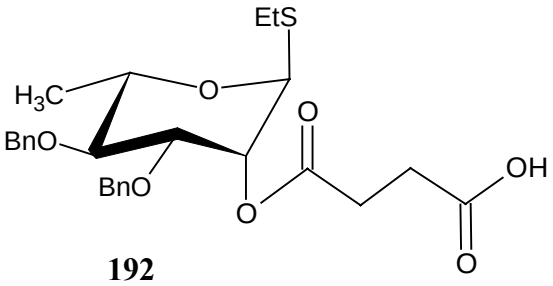




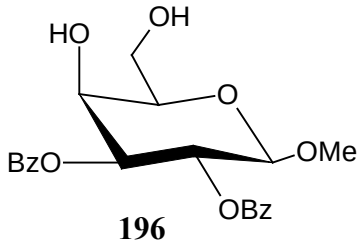
195

Introduction of the succinyl tehther by regioselectve condensation to galactose's 6th position, Gave the preaaranged bridged dissacharide **197**. Than, initiation with NIS/TMSOTf in acetonitrile at 0°C afforded an α/ß 1:1 mixture of **198** and **199**.In an attempt to demonstrate the possibility of influencing the anomeric selectivity, 1,6-di-O-benzyl-2-O-benzoyl-α-D-gluco pyranoside was the choice of replacement as acceptor for the galactoside. Initiation of the new succinylated bridged disaccharide with NIS/TMSOTf in acetonitrile at 0°Cfurnished 74% yield of the disaccharide with an α /ß ratio 14/60, thus predominatly ß-anomer. (Scheme **48**.)

Scheme 48



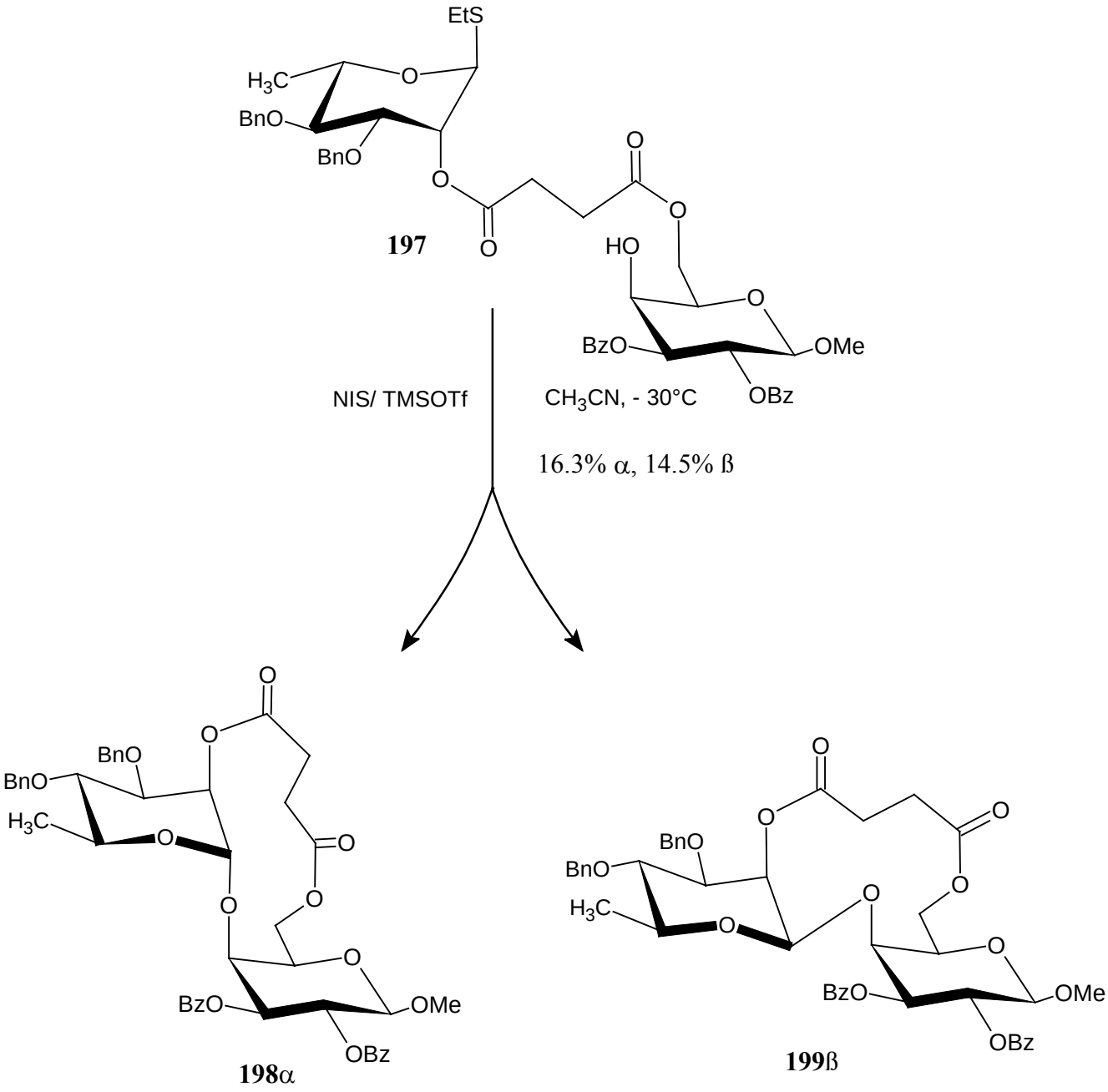
192



196

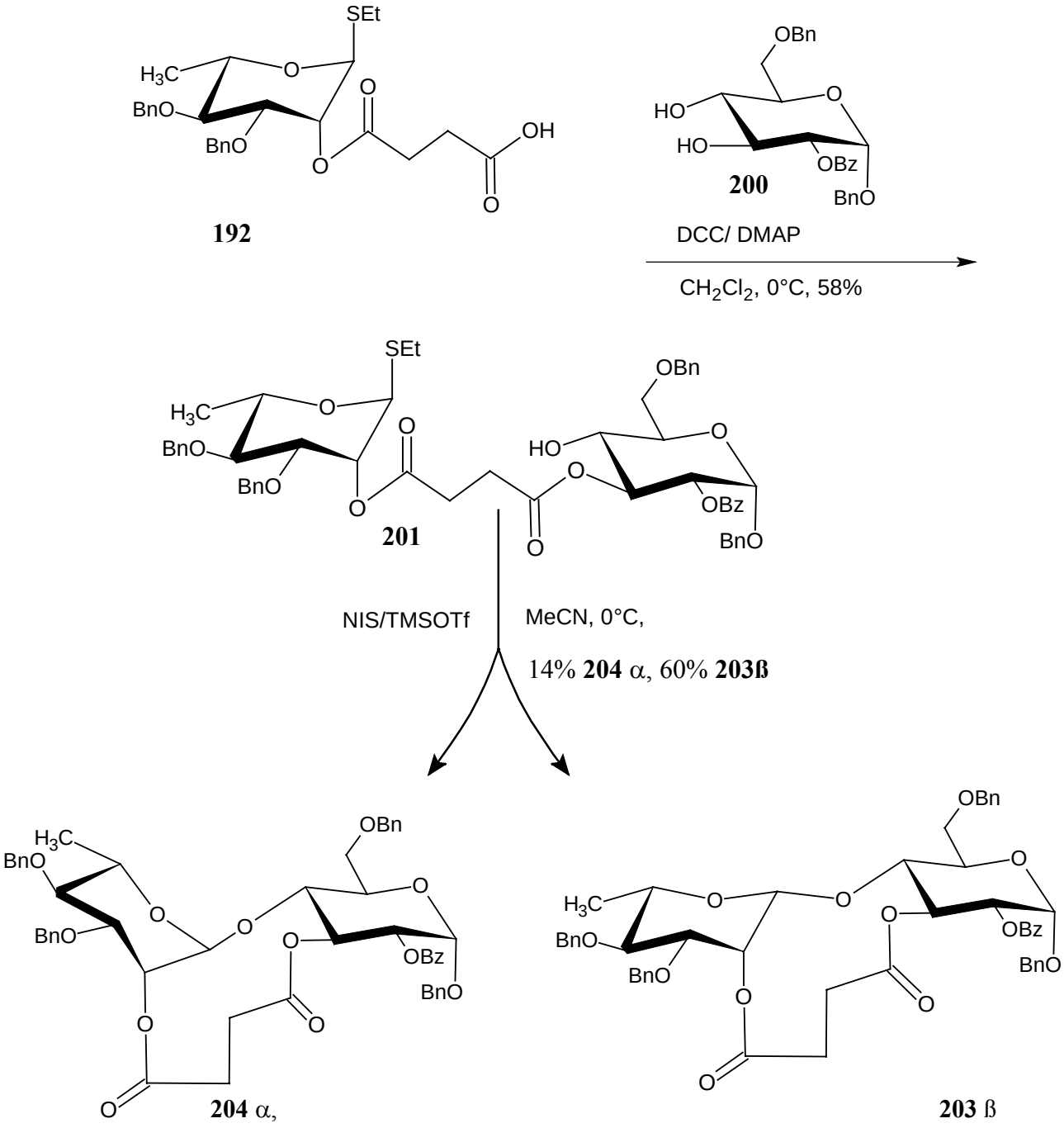
DCC/DMAP (cat)

CH_2Cl_2 0°C , 75%



In an attempt to demonstrate the the possibility of influencing anomeric selectivity of the intramolecular glycosylation *via* " prearranged" glycosides,the galactose donor was replaced by 1,6-di-O-benzyl-2-O-benzoyl-α-D-glucopyranoside acceptor **215**, which was tethered regioselectively at it's 3-O-position with the rhamnoside donor. Initiation with NIS/TMSOTf, in acetonitrile at 0°C afforded an overall yield of 74%, with an α/ ß ration of 14/60, 14% **204 α**, 60%, **203 ß**. This, than resulted to a mismatched case. (Scheme **49**)

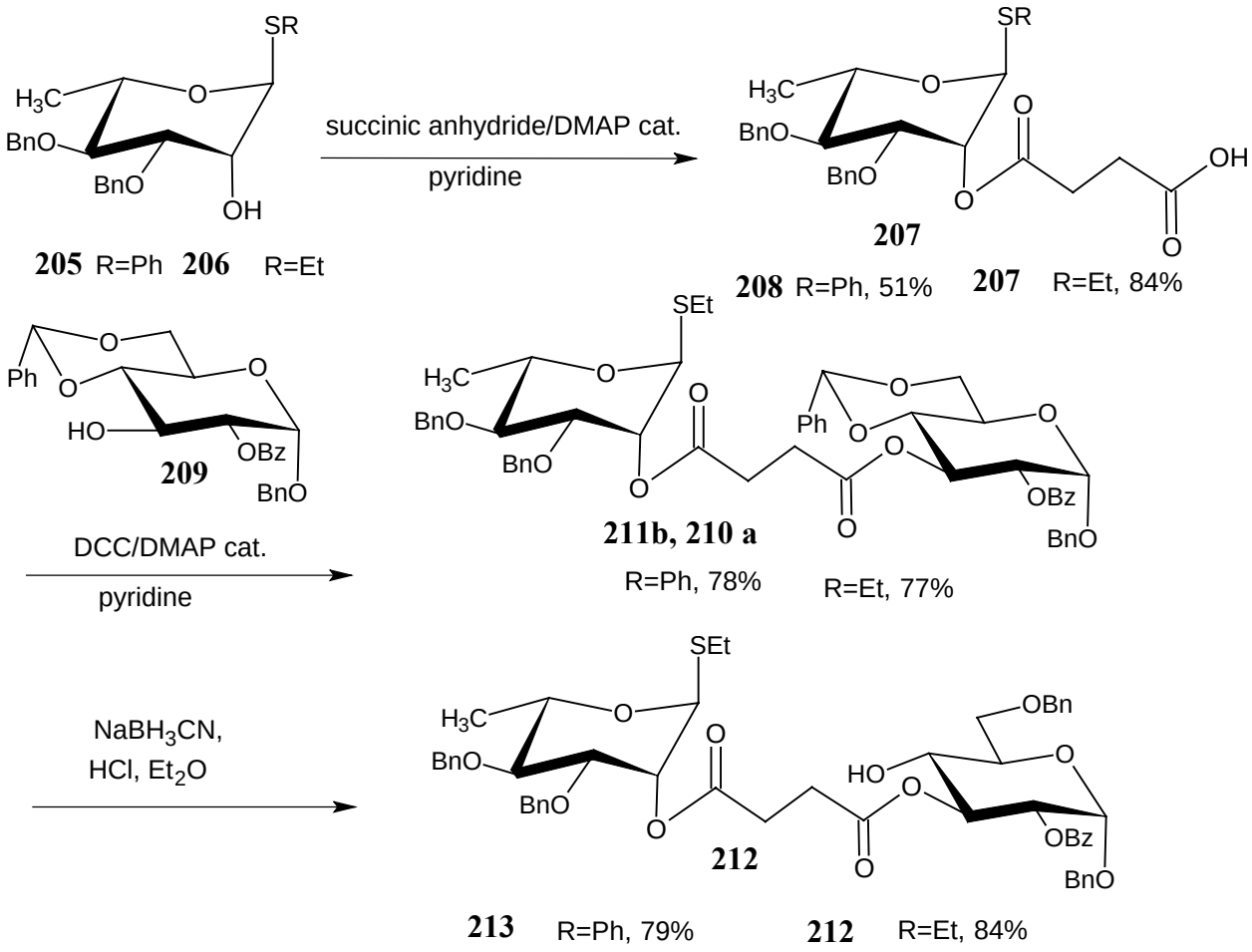
Scheme 49.

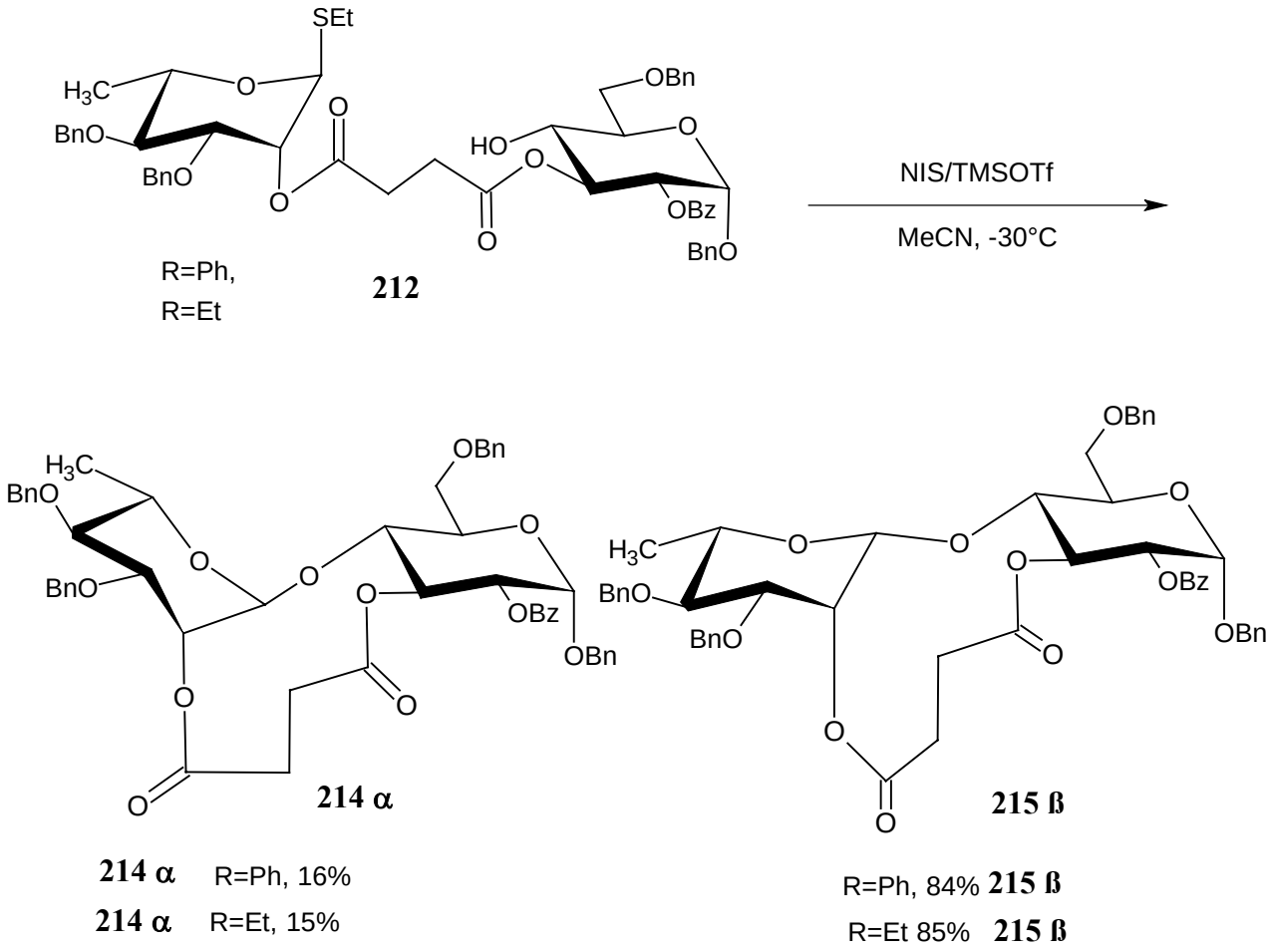


The same concept was extended by Ziegler et *al*[49,50,51] for the synthesis of L-Rh.ß(1-4)Glc disaccharide[50]. The importance of this type of glycosidic bond lies in it's common occurence in many bacterial capsular polysaccharides of *Streptococcus pneumonia* type XXVII. The prearranged glycoside contains a dibenzylated l-Rhamnoside donor liked to the 3-O position of a α-D-

glucoside acceptor via a succinyl ester tether.Starting with di-O- benzyl-α-L-rhamnopyranoside **206**, and condensation with succinicanhydride in presence of DMAP in pyridine afforded the succinylated derivatives **207**,**208**. Next was their condensation with DCC/DMAP with benzyl-2-O- benzoyl-4,6-di-O-benzylidene α-D-glucopyranoside **209** formed the 3,2-succinyl bridged saccharides **210 a, 211 b**, which were regioselectively opened with $NaBH_3CN$ to give compounds **212 a, 213 b**. Intramolecular glycosylation with NIS/TMSOTf in acetonitrile at -30°C with the phenyl-1-thio derivative gave an exellent 90% yield of disaccharide **215** with α/ß ratio 16:84. With the ethyl-1-thio derivative glycosylation was effected at room temperature with only NIS at 14.10^5kPa pressure furnishing a 58%yield of **214** with an α/ß ratio of 15/85. (Scheme **50**.)

Scheme 50.





The best ß-anomeric outcomes were obtain with acetonitrile as solvents. Results are summarized in the below table.

Table 7.

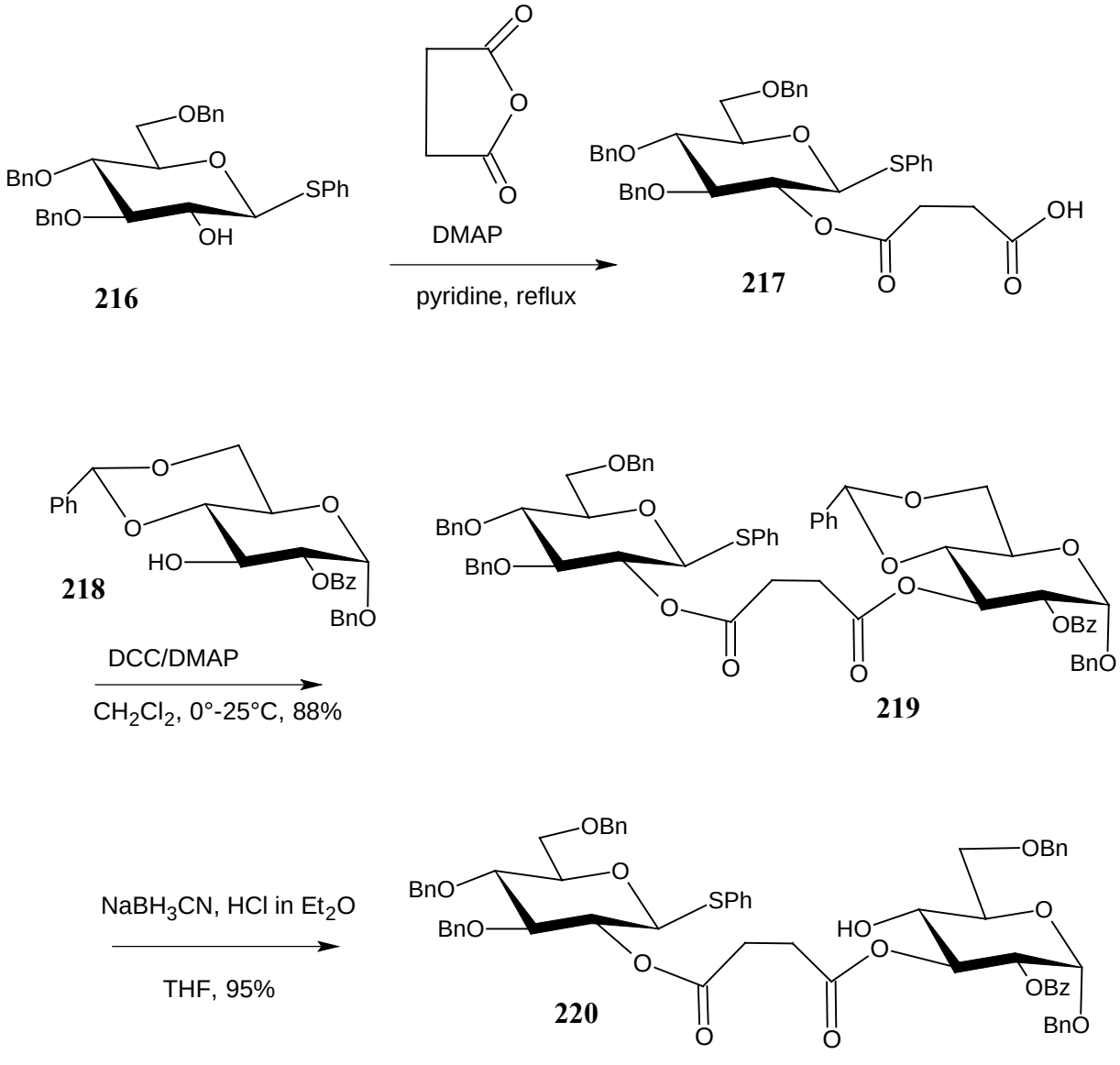
Bridged disaccharide	Solvent	Coupling conditions	Time	Temp (C°)	Product yield	α/ß ratio
R=ethyl	MeCN	NIS	14h	25	**215** (74%)	18/82
R=ethyl	MeCN	NIS/14.10^5 kPa	24h	25	**215** (58%)	15/85
R=Phenyl	MeCN	NIS/TMSOTf	10min.	-30	**215** (90%)	16/84

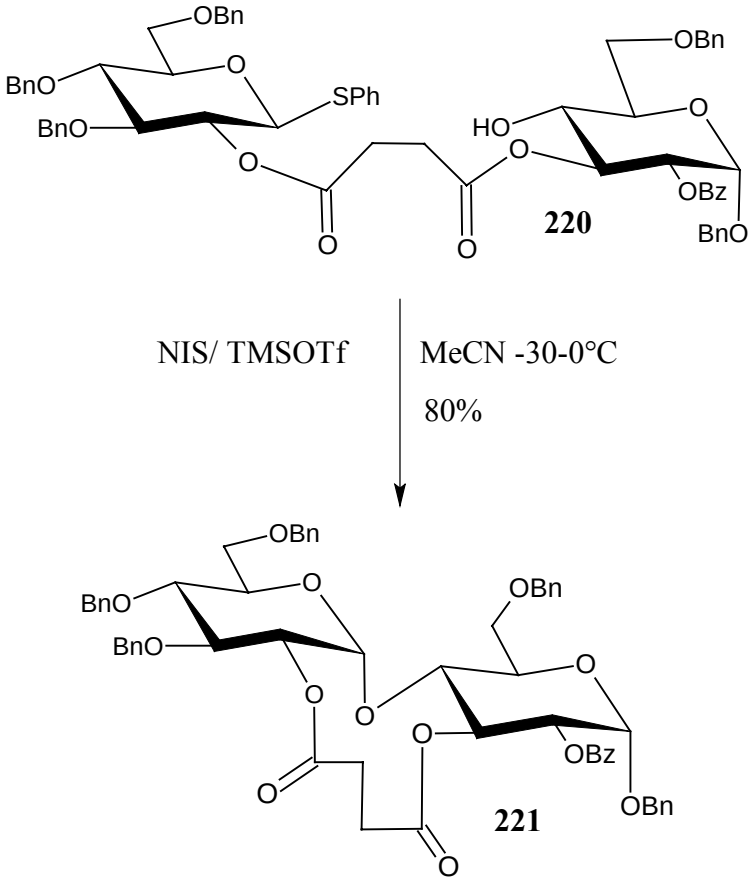
The intramolecular glycosylation via prearranged glycosides as presented from these results enable this efficient synthesis of ß-rhamnosides which are usually obtained with great difficulty by conventional glycosylation method, and also allowed access to high L-Rh-ß(1-4)Gluc content. Furthermore, less reactive alcohols could be glycosylated in high yield by this

glycosylation method through succinyl ester tether.

The suitability of this method was further demonstrated for the synthesis of 1,2 cis- configurated α-glycosides and α-galactosides[50]. As glycosyl donor was phenyl 3.4,6-tri-O- benzyl-1-thio- ß-D-glucopyranoside **216** chosen, succinyated ,and linked with benzyl 2-O-benzoyl-4,6-O-benzylidene-α-D-glucopyranose **218** as acceptor, to form the bridged disaccharide **219** in 88% yield. Selective partial cleavage of the benzylidene with $NaBH_3CN$ HCl in Et_2O, THF gave quantitative yield of prearranged glycoside **220**. Initiation with NIS TMSOTf in acetonitrile at-30-0°C afforded 80% yield of solely α disaccharide product **221**. (Scheme **51**)

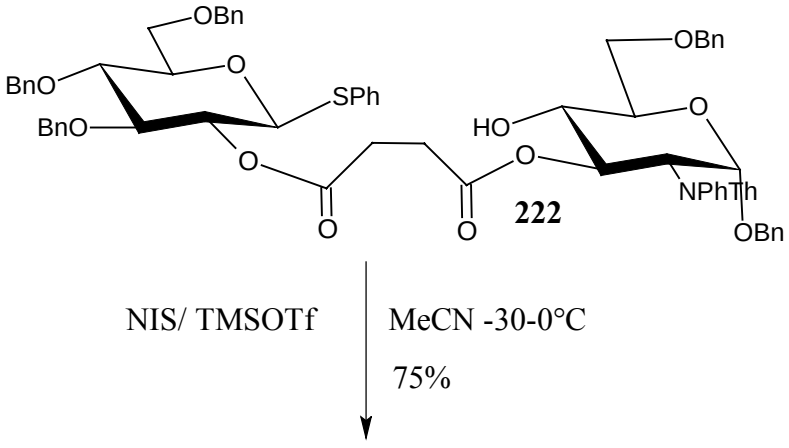
Scheme 51.

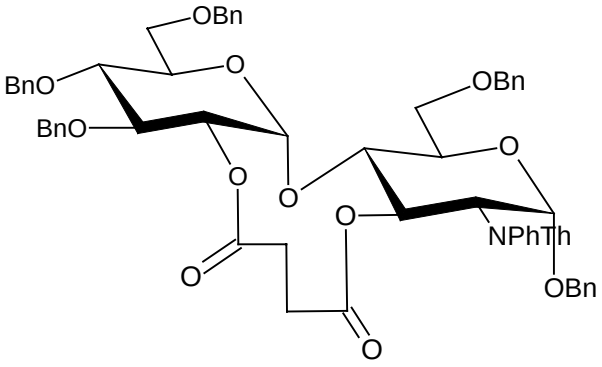




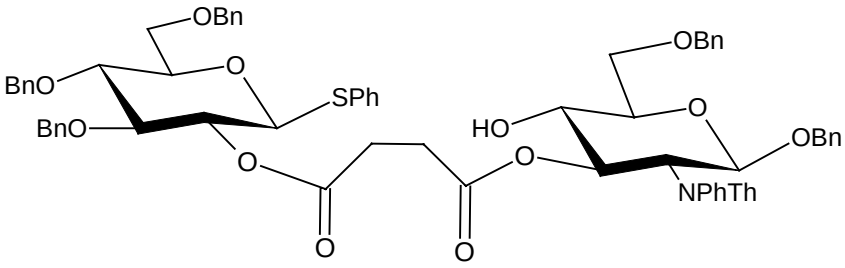
With α and ß-D- 2-phtalic protected glucosamine **222** were chosen as acceptor, intramolecular glycosylation initiated in the same conditions and solvent also afforded α(1-4) disaccharides with 75% of **223** for the former and 40% yield of **225** for the latter. With a 2-aceta glucosamine **226** as acceptor no intramolecular glycosylation occured due to the presence of acetimo group and the known nucleophilicity of position 4 in 2-acetimo- 3-O-acetyl-2-deoxy-glucopyranoside. (Scheme **52**).

Scheme 52.





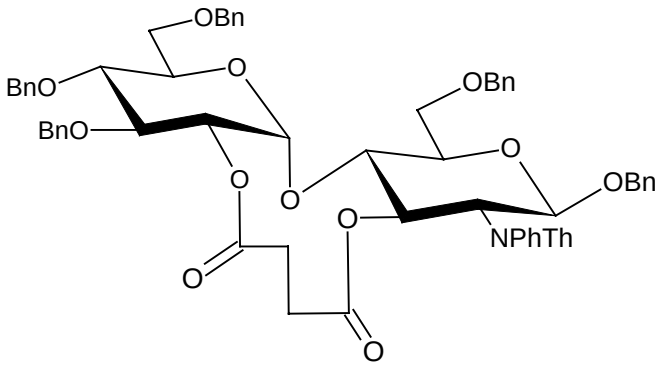
223



224

NIS/ TMSOTf MeCN -30-0°C

40%

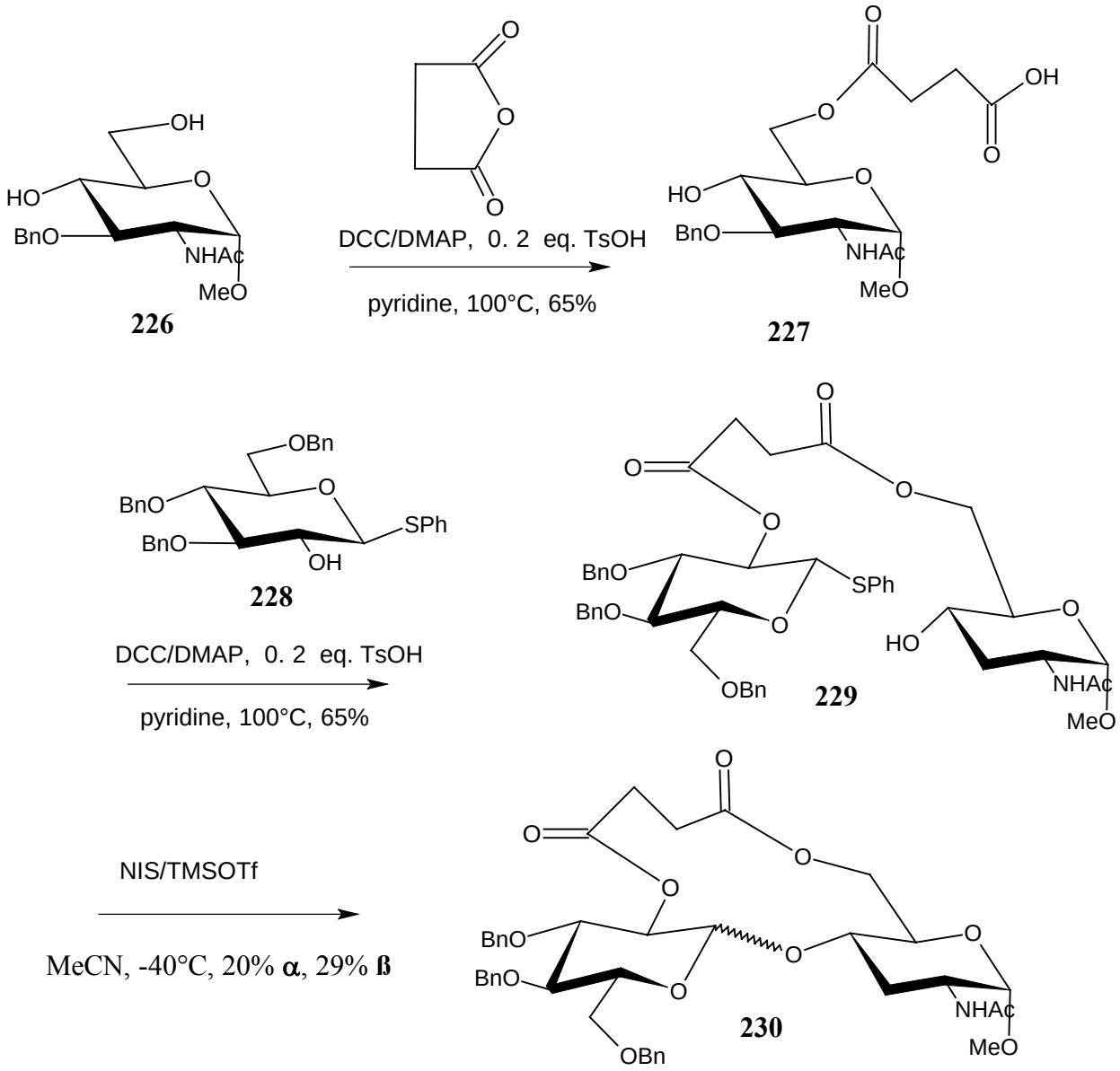


225

In order to verify that the relative configuration of the succinyl linked tethered donor and acceptor play an essential role for diastereoselectivity , the donor moiety **228** was linked to position 6 of the acceptor of methyl 2-acetimo-3-O-benzyl-2-deoxy-α-D-glucopyranoside **226**. The intermediate prearranged bridged disaccharide **229** exhibited an inverse relative configuration in comparison with the former bridged disaccharides and should afford higher ß-content. In fact, glycosylation gave an α/ß 40/60 with somewhat lower yield of 49% of **230** due to the formation of the

less favoured 12-membered ring compared to the former linked disaccharides with 11-membered rings.(Scheme **53**).

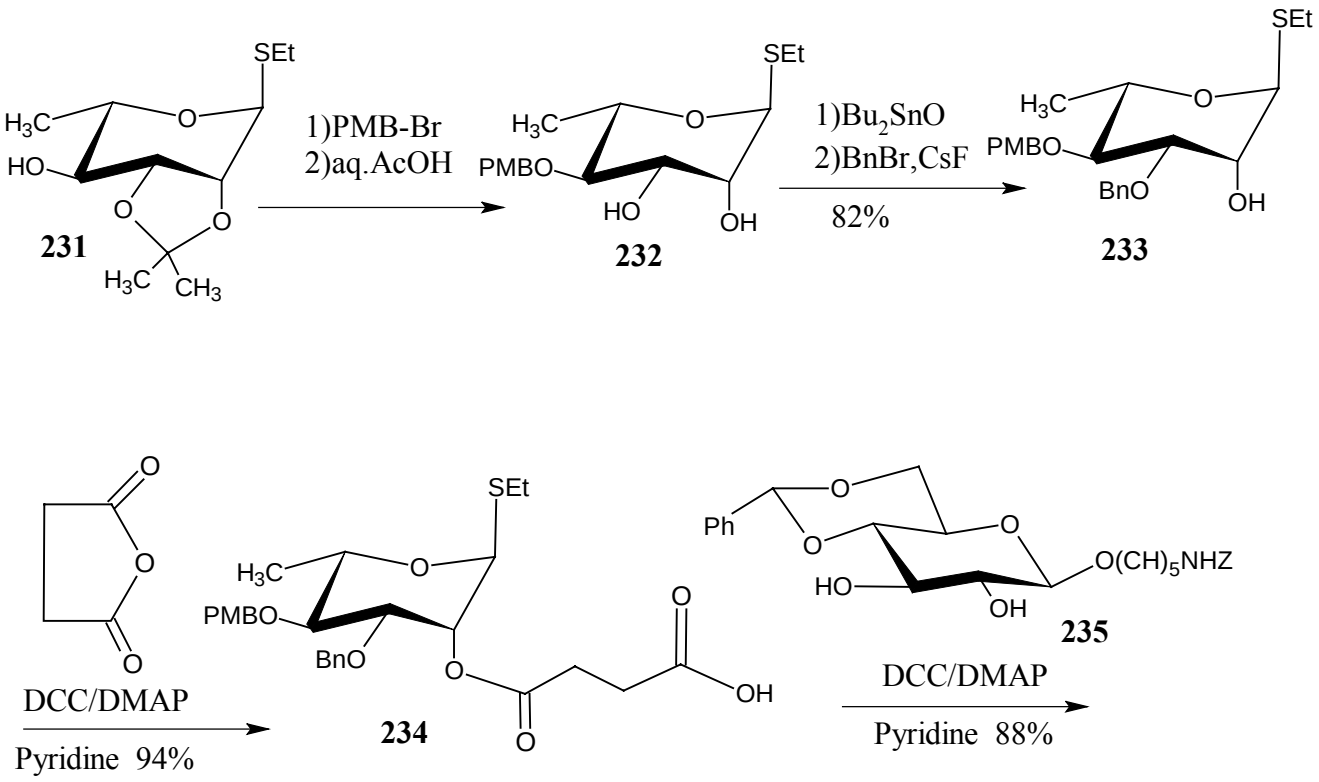
Scheme 53.

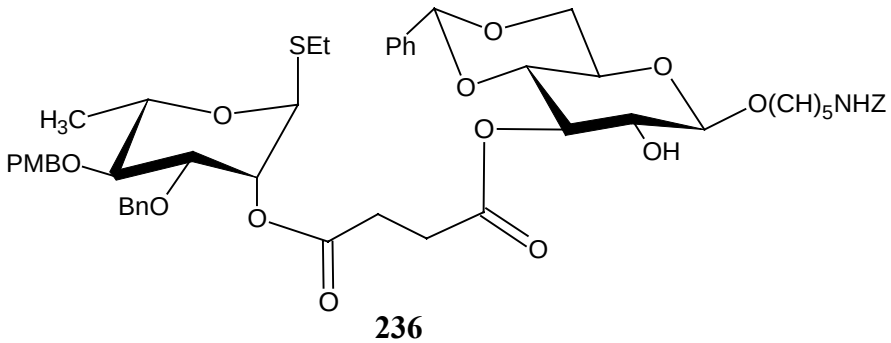


The prearranged glycoside concept was applied by Ziegler and coworkers[51] toward the synthesis of a tetrasaccharide fragment related to the capsular polysaccharide of *Streptococus pneuminiae* Type 27 that bears the L-Rh-ß(1-4)Gluc unit. Using a ethyl-2,3-O-isopropylidene -1-thio-α-L-rhamnopyranoside **231** as donor and reaction protection of the 4-OH with para-methoxy benzyl chloride, and cleavage of the acetal with aqueous acidic acid gave the diol **232.** Regioelective 3-O-benzylation with dibutyl tin oxide with benzylbromide yielded 82% of compound **233**. Next the succinyl spacer was introduced in 94% yield into position 2

by acylation of **233** with succinicanhydride to afford **234**, which was condensed by aid DCC/ DMAP with the glucose acceptor **235** to give the prearranged tethered disaccharide **236** in 88% yield. Compound **236** was selectively debenzylated with DDQ in quantitative yield of **237** and followed with reprotection of the 4-OH of the rhammoside donor by chloroacetylation afforded **238** with 94%. Reductive opening of the benzylidene acetal proceeded smoothly to firnish the desired alcohol **239** with 75% yield. Submission of **239** to intramolecular glycosylation with NIS in acetonitrile afforded the prearranged disaccharide **241** α, **240 ß** in 65% overall yield with an α/ ß ratio 10/55, thus predominantly the desired Rh-ß(1-4)Gluc. Deprotection of the dichloroacetyl group with thiourea gave the desired alcohol **242** which was submitted to glycosylation reaction with the disaccharide **254** imidate donor to afford the tetrasaccharide **255** in 37% yield. Debenzoylation with Zempflen reagent followed by cleavage of the tether with aqueous NaOH, and debenzylation by hydrogenation furnished the partially unprotected tetrasaccharide **257** in quantitative yield. (Scheme **54**, **55**).

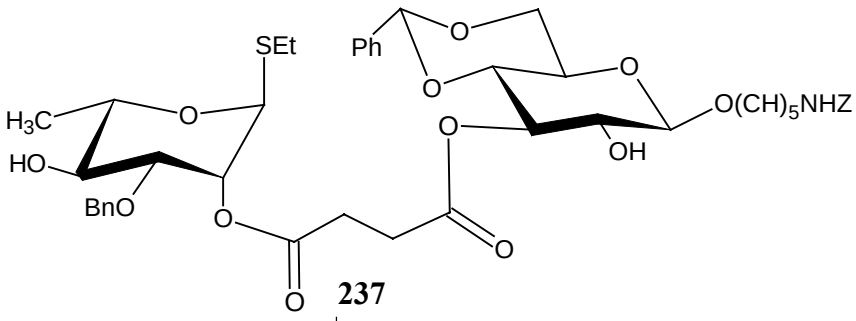
Scheme 54.





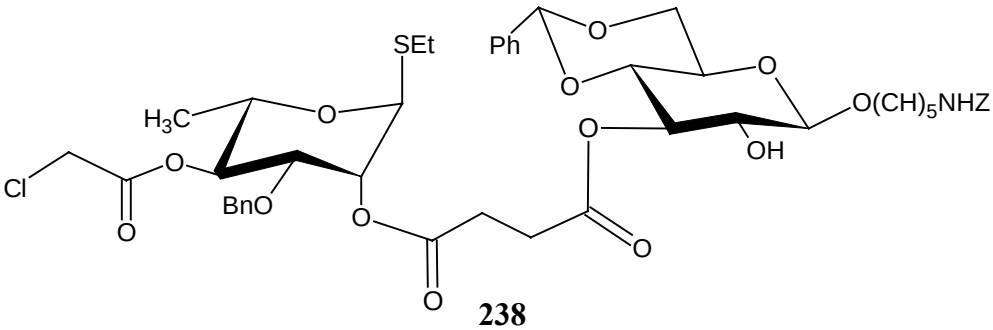
236

DDQ CH_2Cl_2/ H_2O 98%

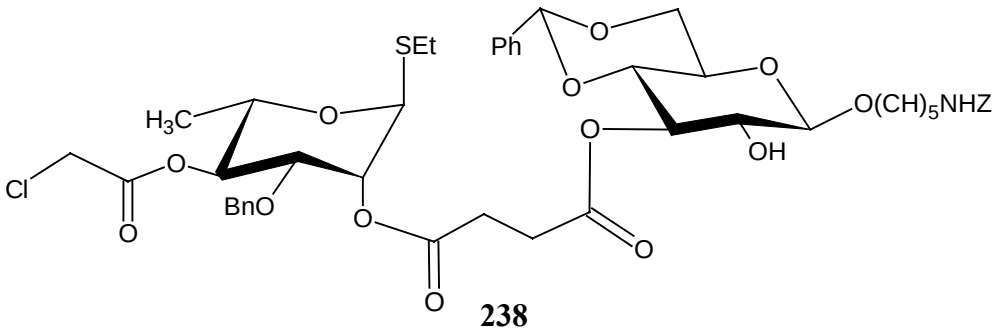


237

$(ClCH_2CO)_2$ 94%



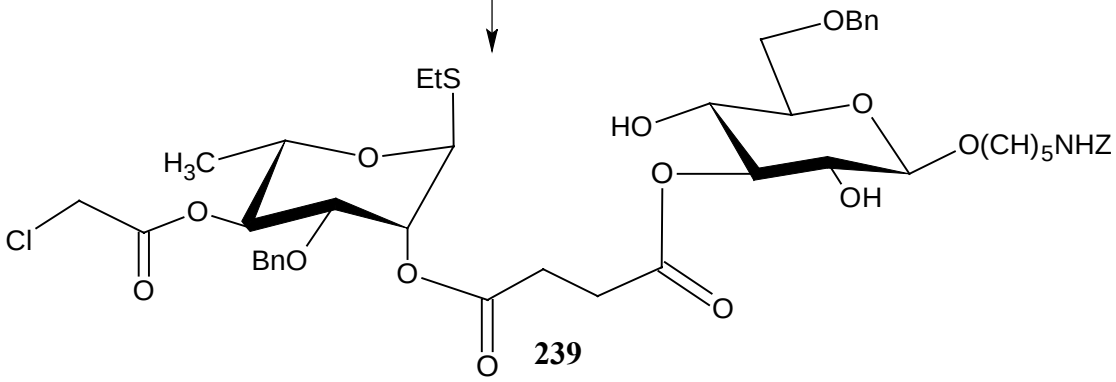
238



238

$NaBH_3CN$, HCl THF

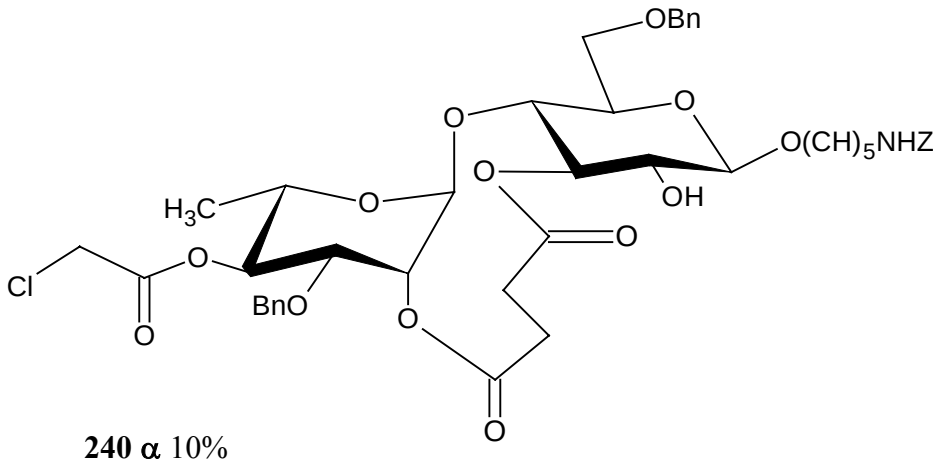
75%



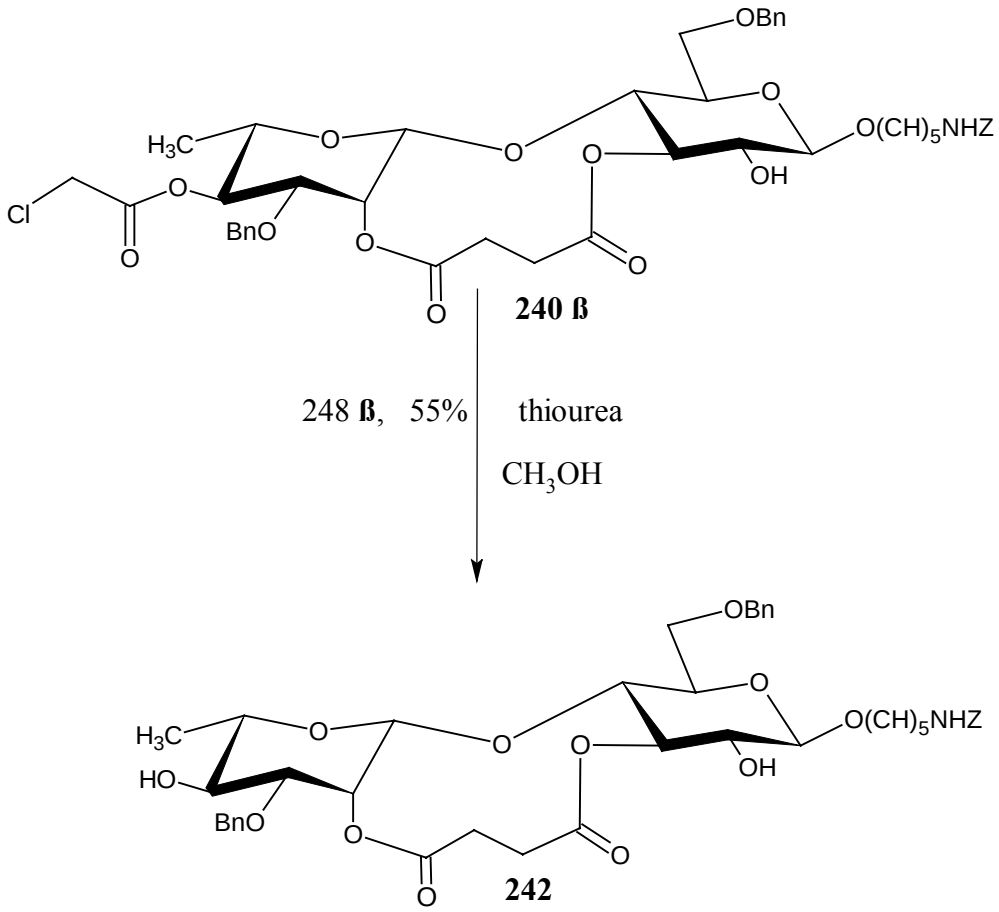
239

NIS acetonitrile

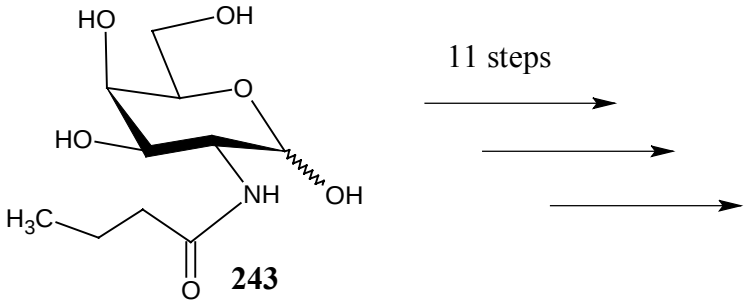
65% overall

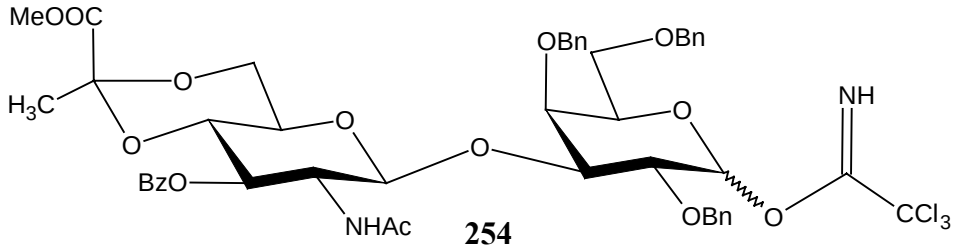


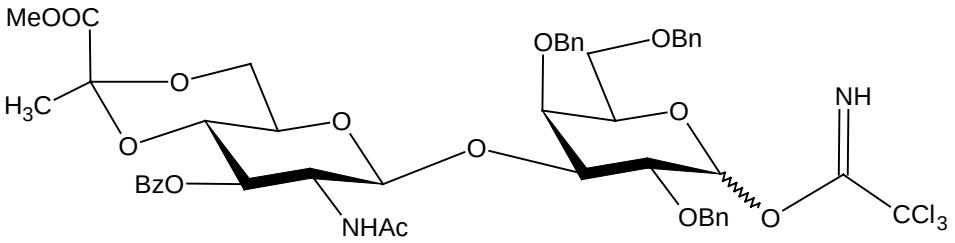
240 α 10%


OBn
O
O(CH)5NHZ
H3C
O
O
OH
Cl
O
BnO
O
O
O
O
240 ß
248 ß, 55%
thiourea
CH3OH
OBn
O
O(CH)5NHZ
H3C
O
O
OH
HO
BnO
O
O
O
242

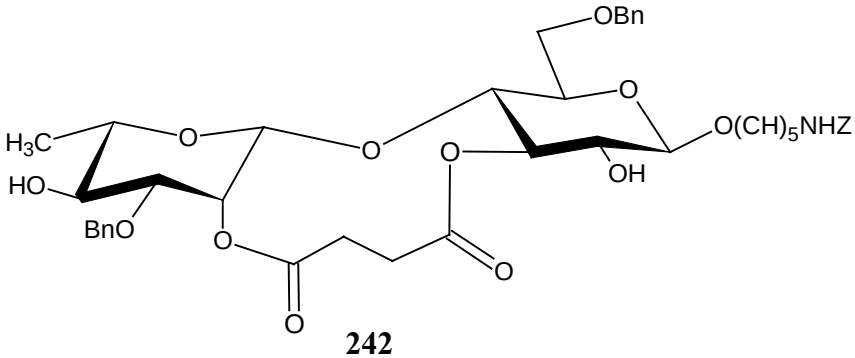
Scheme 55.


HO
OH
O
HO
NH
OH
H3C
O
243
11 steps


MeOOC
O
H3C
O
O
BzO
NHAc
O
OBn
OBn
O
OBn
NH
O
CCl3
254



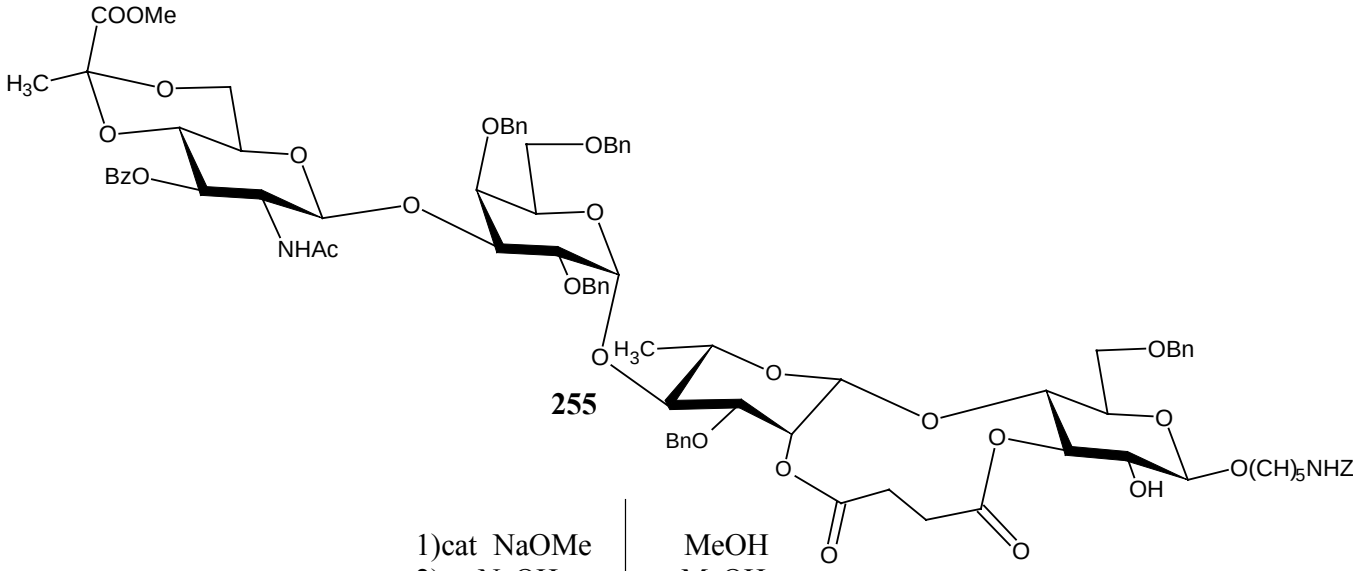
254



242

TMSOTf CH_2Cl_2

37%

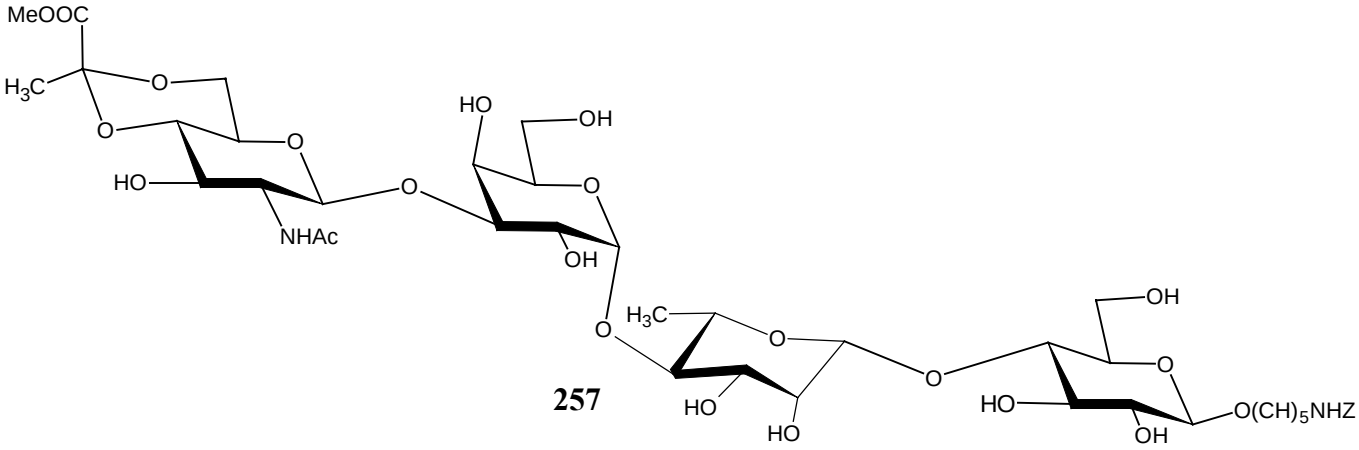


255

1)cat NaOMe MeOH

2)aq.NaOH, aq. MeOH

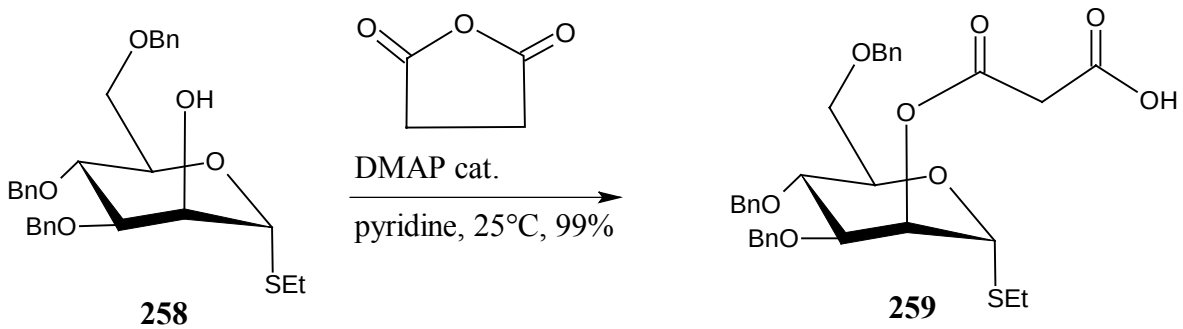
3)H_2/ $Pd(OH)_2$ 99%



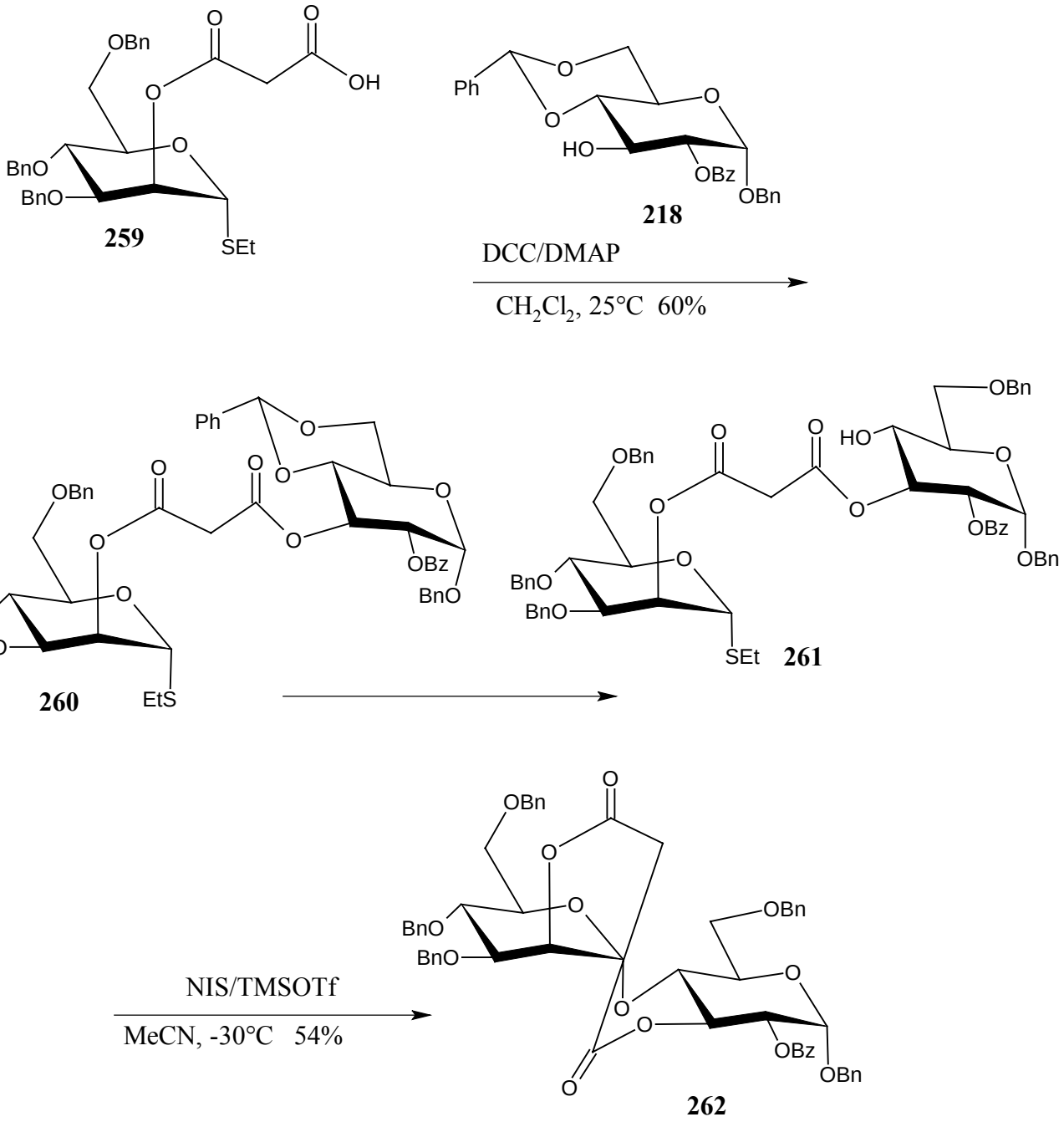
257

The performance of this method was investigated for the synthesis of α- and ß-mannosides Especially of Manß(1-4)Glc derivatives. In one case, Ziegler et *al* [52]. studied the anomeric selectivity during intramolecular mannosylation involving succinyl bridged glycosides. [53] Herein, a tribenzylated succinylated ethyl 1- thio-α-D-mannoside **259** was chosen as donor. Condensation reaction with 1-O-benzyl-,2-O-benzoyl- 4,6-O-benzylidene-α-D-glucopyranoside **218** yielded the succinylated bridged disaccharide **260** at 60%.Treatment of the latter with $NaBH_3CN$ and etheral HCL in THF, afforded 87% yield of the 4-O-alcohol **261**. Intramolecular glycosylation effected with NIS/TMSOTf in acetonitrile gave exclusively α(1-4) mannosylation, thus disaccharide **262** in 54% yield. (Scheme **56**).

Scheme 56.

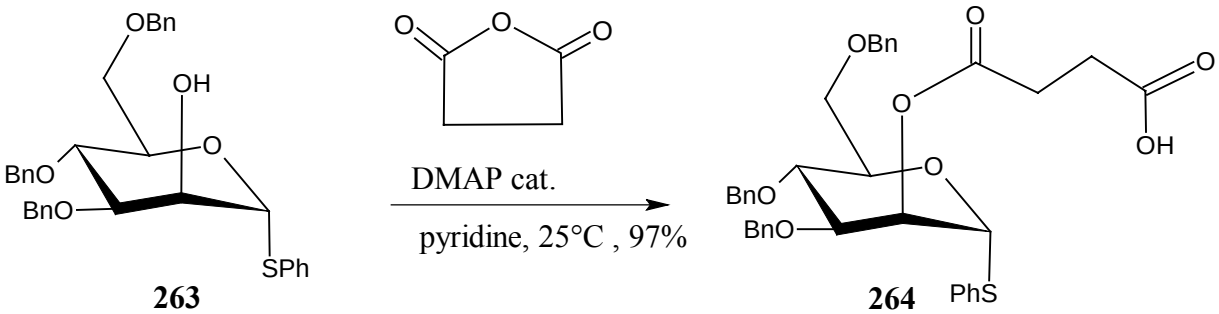


258 **259**

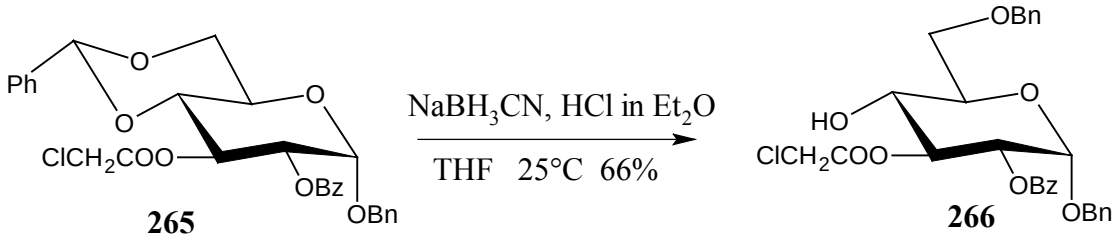


When the ring forming glycosylation from a (1-4) selective mannosylation was inverted to a (1-3) selective, an increase in the ß-content was observed since the relative stereochemistry of the donor-acceptor interaction were reversed. This was achieved by changing the position of the succinyl spacer to the 3-O of glucosyl acceptor **265** to its 4-O **266**. With the same reactions as the obtention of the succinylated bridged disaccharide **267** was achieved. Intramolecular glycosy lation with NIS/TMSOTf at -30°C afforded 50% **269** α and 26% **270** ß, thus the desired increased ß-glycoside. (Scheme **57**)

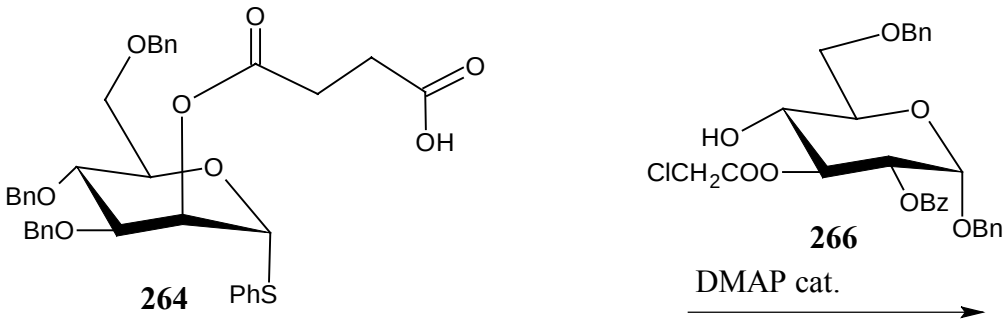
Scheme 57.



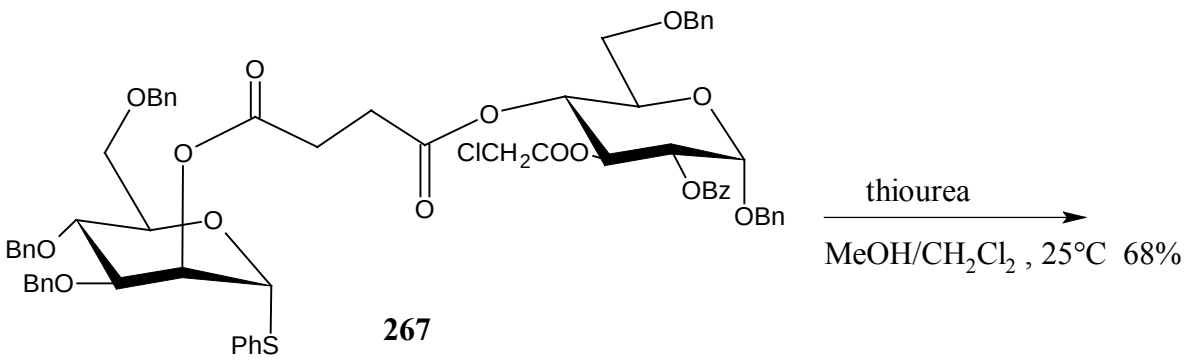
263 **264**



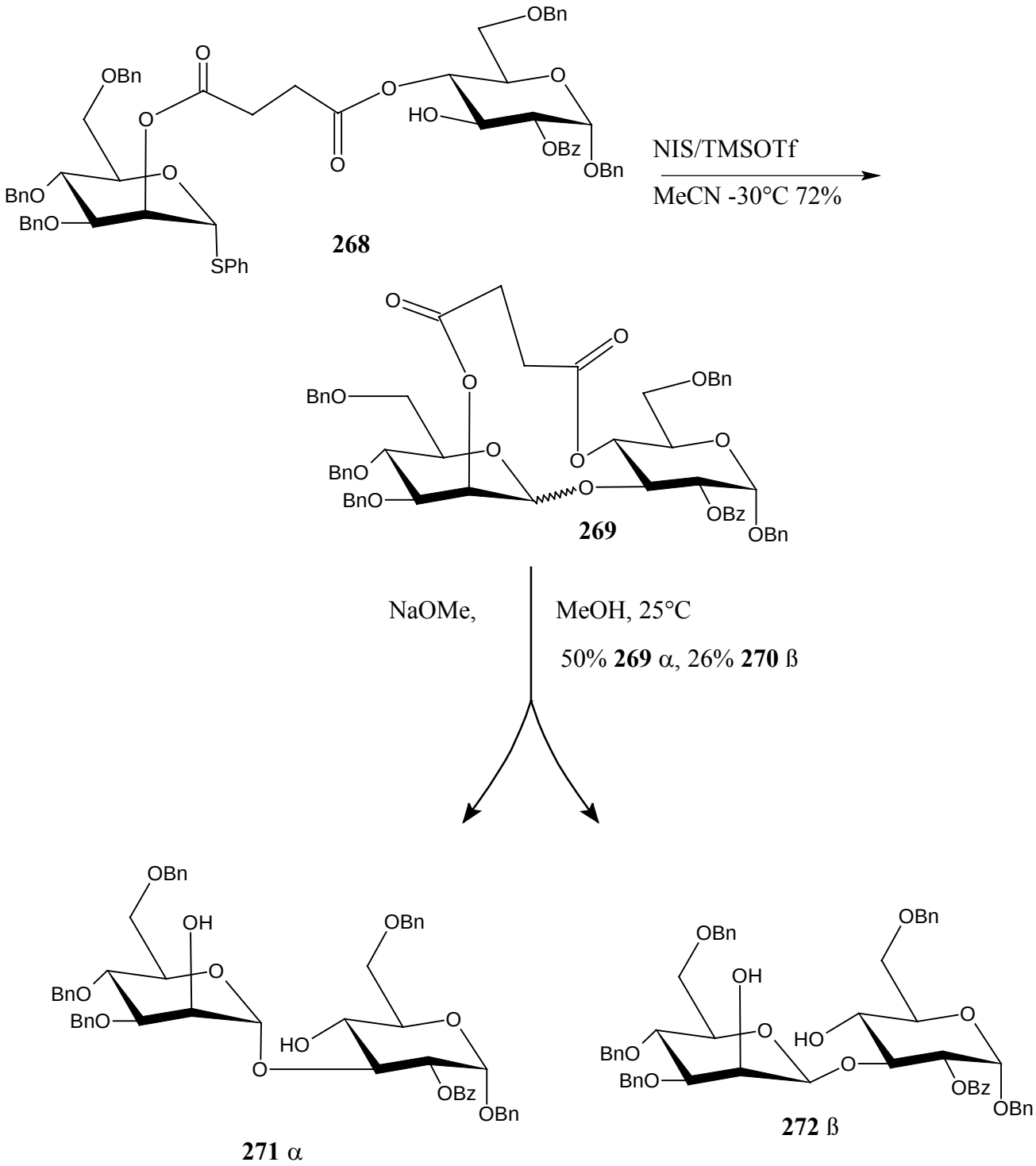
265 **266**



264 **266**

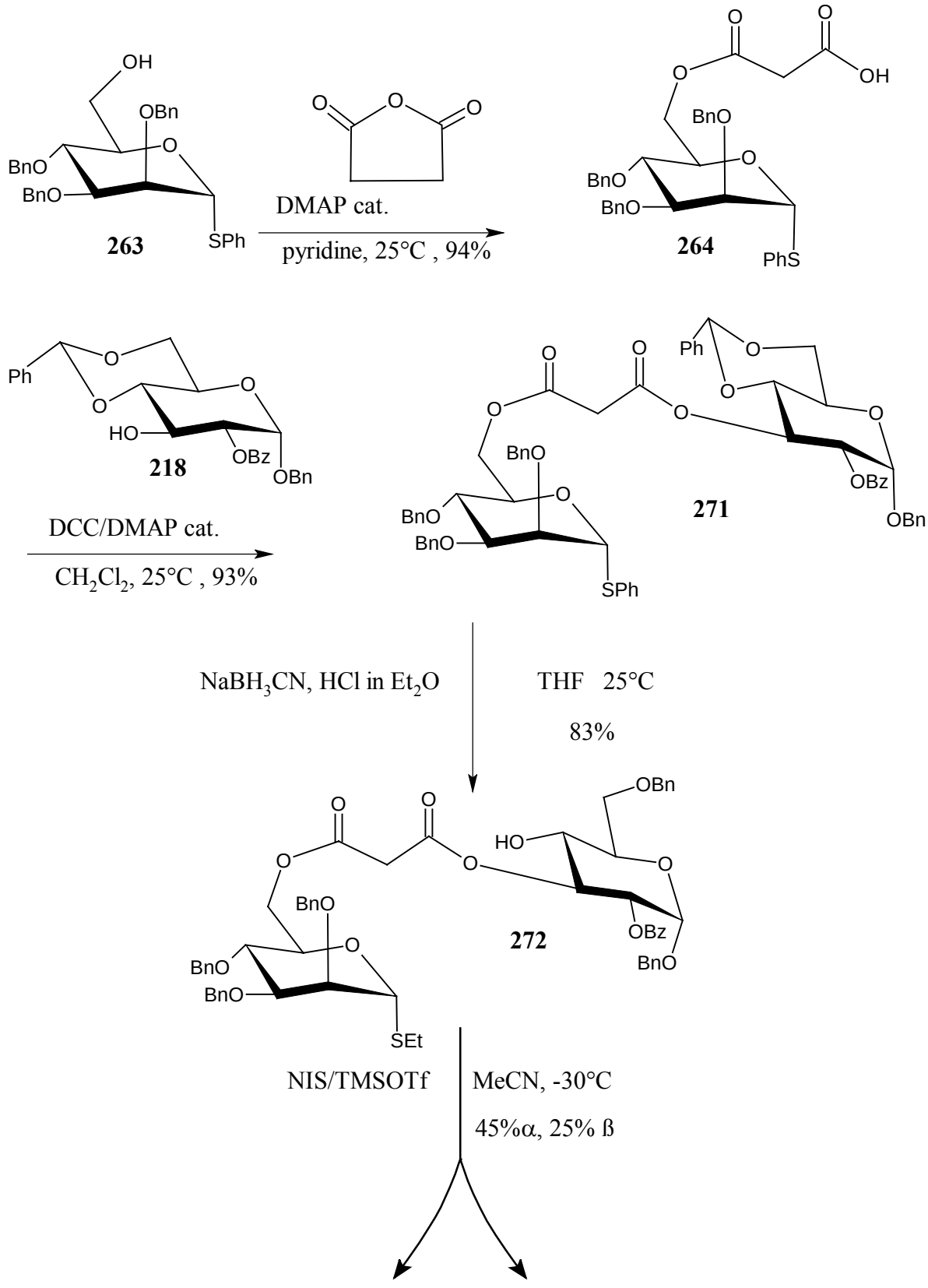


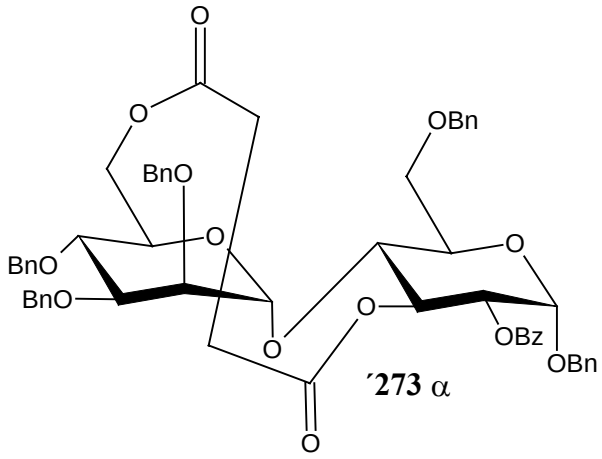
267



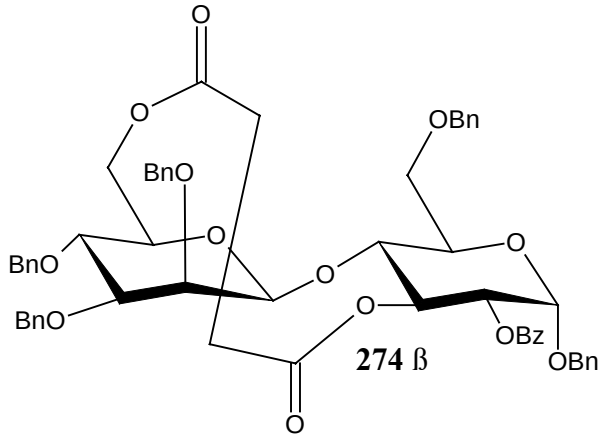
Similarly, the position change of the succinyl bridge from 2-O to 6-O of mannosyl donor to 3-O of glucosyl acceptor **218** inverted the stereochemistry of the prearranged glycoside bridge **272** and intramolecular glycosylation in the same conditions and solvent yielded 70% overall that is 40%of α and 25%ß thus an increase in the ß(1-4) ratio content desired (Scheme **58**).

Scheme 58.


OH
OBn
BnO
BnO
O
SPh
263
DMAP cat.
pyridine, 25°C , 94%
O
O
OH
BnO
PhS
264
Ph
HO
OBz
OBn
218
DCC/DMAP cat.
CH2Cl2, 25°C , 93%
271
NaBH3CN, HCl in Et2O
THF 25°C
83%
272
NIS/TMSOTf
MeCN, -30°C
45%α, 25% ß
SEt



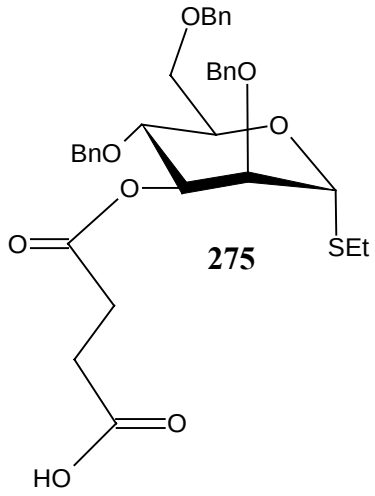
´**273** α



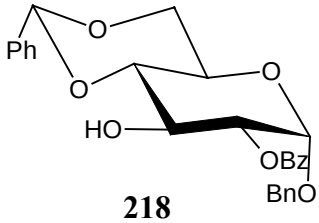
274 ß

The results successfully obtained from the preceeding above investigations presented for manno lysation *via* prearranged glycosides give an alternative to construct ß-mannosidic linkages. Indeed, further investigations using succinyl tethers were conducted by Ziegler and Lemanski[53] toward the synthesis of ß-man (1-4) gluc. A succinilated tribenzylated ethyl-1-thio-α-D- mannopyranoside **275** was the chosen candidate as donor and linked to benzyl-1-O-2-O-benzoyl- 4,6-O-benzylidene-α-D-glucopyranose **218** acceptor by condensation with the aid of DCC/DMAP in dichloromethane in 71% yield of **276** . Selective cleavage of benzylidene group with $NaBH_3CN$ gave the desired succinylated bridge alcohol **277** in 77% yield. Activation with NIS/trifluoromethane sulfonate in acetonitrile at 25°C afforded 64% yield of solely ß-(1-4) linked disaccharide **278 ß** . Compound **277** was subjected to glycosylation reaction with NIS/TMSOTf in acetonitrile at –30°C in to yield solely 64% of the same ß(1.4) linked disaccharide **278** . However activation with MeOTf in acetonitrile at 25°C afforded 77% yield of the α (1-4) linked disaccharide **279.** Deprotection of both disaccharides **278** and **279** with Zemplen reagent NaOMe in MeOH and benzoylation reaction in pyrideine at 25°C yielded 76% of the partially benzoylated disaccharide **282** for the former and 77% of **283** for the latter. (Scheme **59**).

Scheme 59



275

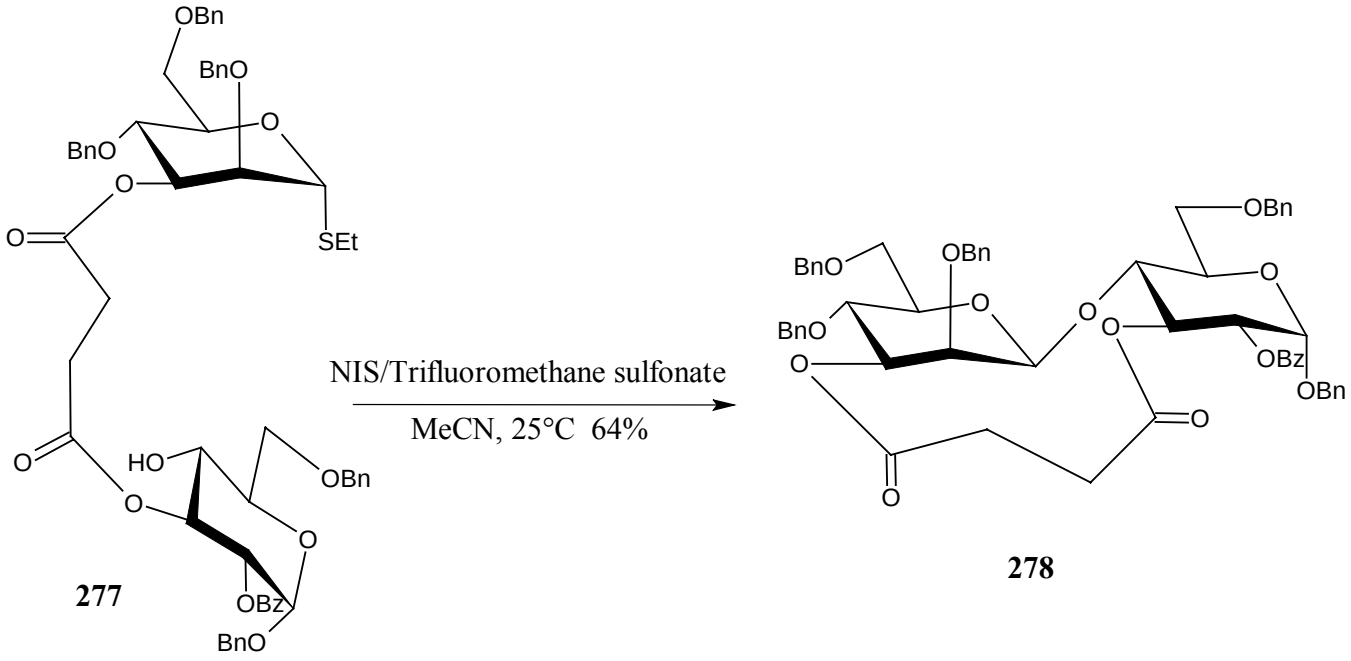


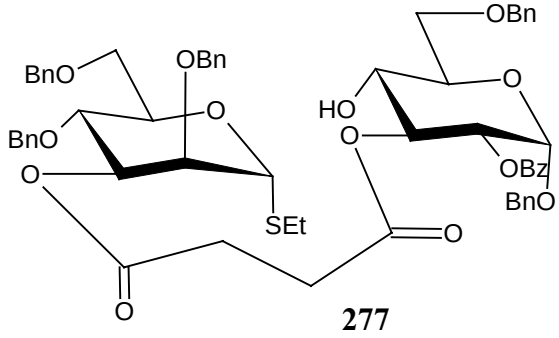
218

1)DCC/DMAP/CH_2Cl_2, 25°C 71% of **276**

2)$NaBH_3CN$, HCl in Et_2O

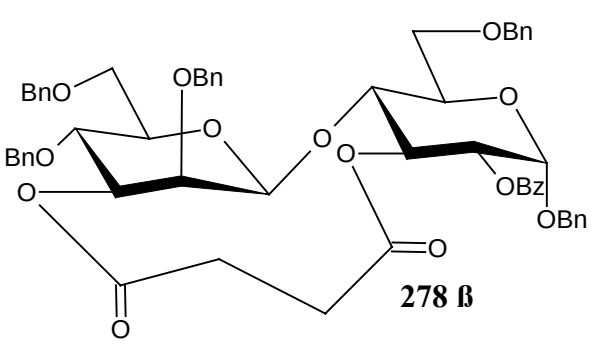
THF 0°C, 77%



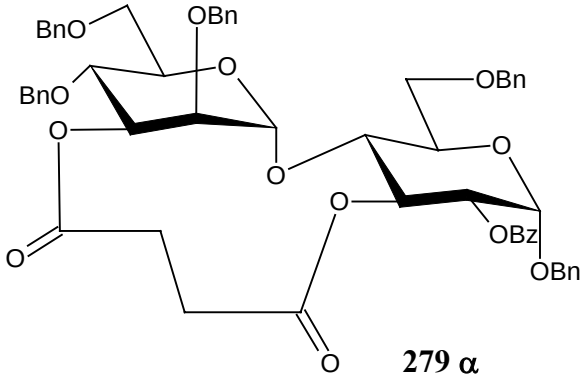


NIS/ trifluoromethanesulfonate
MeCN -30°C, 64% **278 ß**

MeOTf
MeCN, 25°C, 77%, **279α**



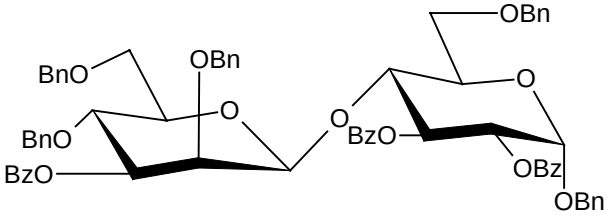
278 ß



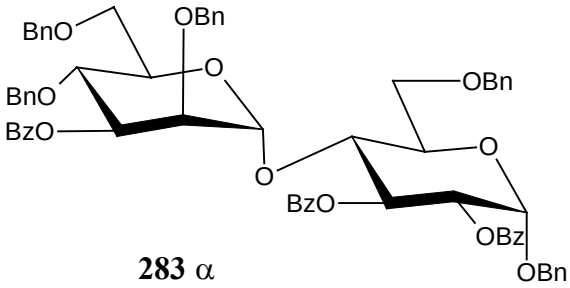
279 α

1)NaOMe, MeOH
2) BzCl pyridine,25°C, 76%

1)NaOMe, MeOH
2) BzCl pyridine,25°C, 77%



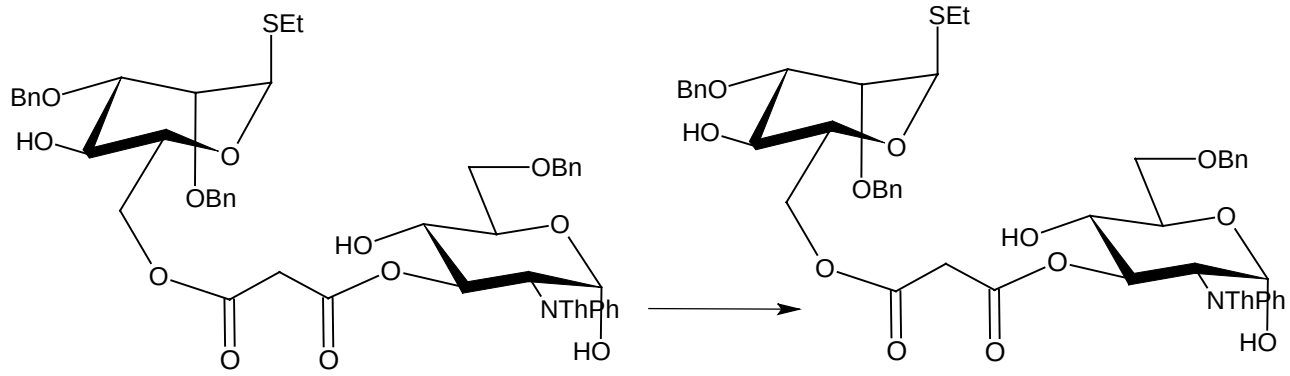
282 ß



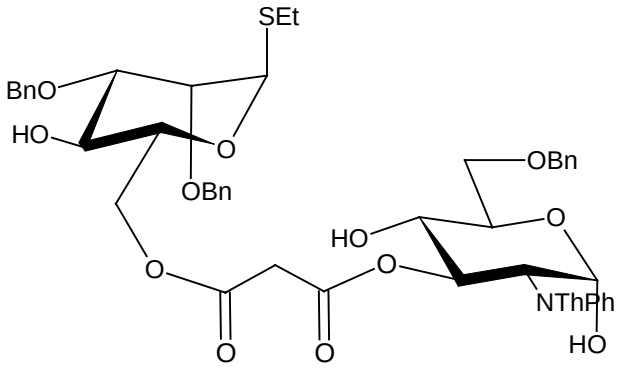
283 α

However, by replacing the succinyl bridge with a shorter malonyl tether, from 6-O position of mannosyl donor to 3-O position of glucosamine acceptor to give the tethered malonylated disaccharid **284** , and intramolecular glycosylation with NIS or MeOTf in the same conditions furnished 51% yield of **285** for the former and 50% yield of **286** for the latter both with 100% of man ß(1-4) glucosamine linkage, thus complete stereoselectivity. With a galactoside derivative as acceptor, positioning the malonyl tether from 6-O of mannosyl donor to 6-O- of galactosyl acceptor **287** bearing the free 4-OH and activation with NIS and MeOTf, as in the above cited conditions afforded 50% of man. ß(1-4) gal **288** and 55% yield of 100% man ß(1-4) gal disaccharide **289** . Replacement of malonyl spacer by a succinyl of the in the same positions **290**, and initiation with MeOTf furnished 53% yield of disaccharide **291** with complete stereoselectivy, thus 100% ß. (Scheme **60**).

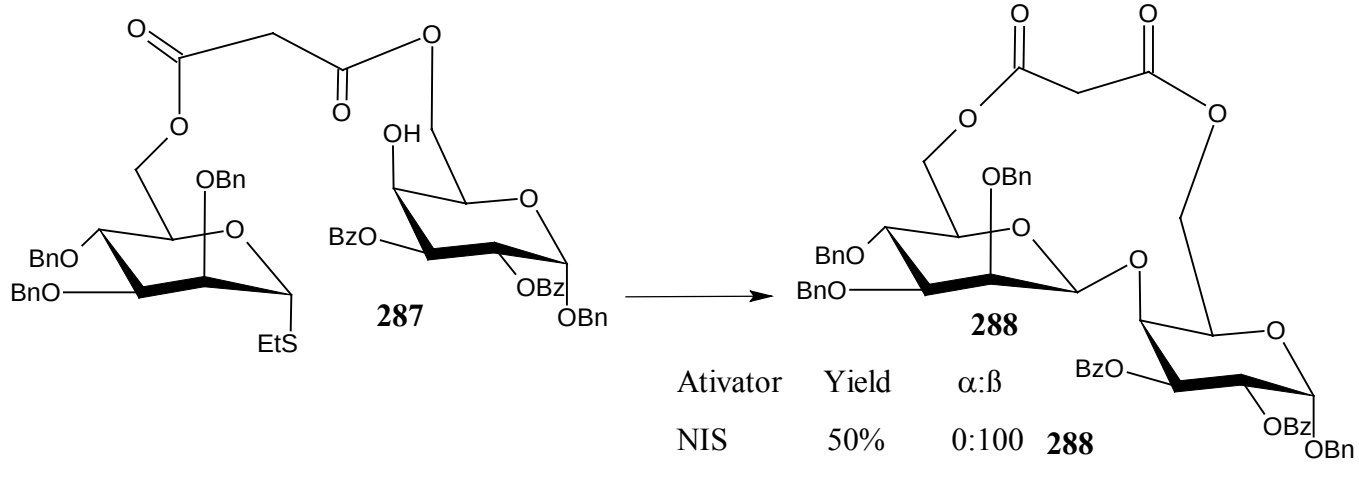
Scheme 60.



284

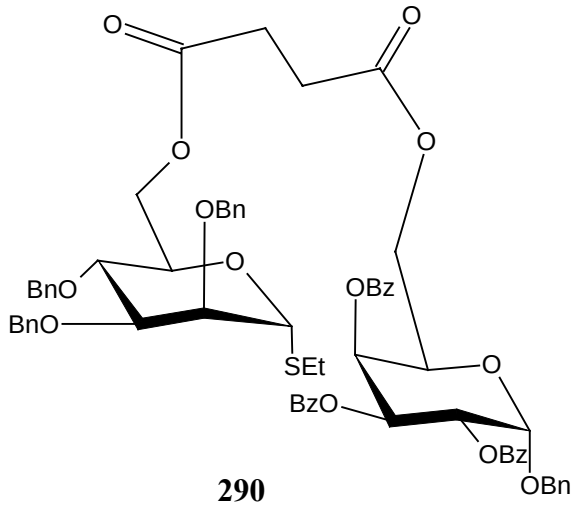


Ativator	Yield	α:ß	
NIS	50%	0:100	**285**
MeOTf	55%	0:100	**286**

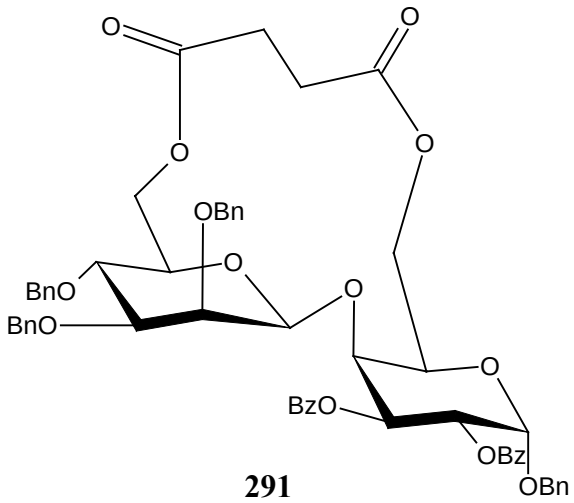


287 **288**

Ativator	Yield	α:ß	
NIS	50%	0:100	**288**
MeOTf	55%	0:100	**289**



290

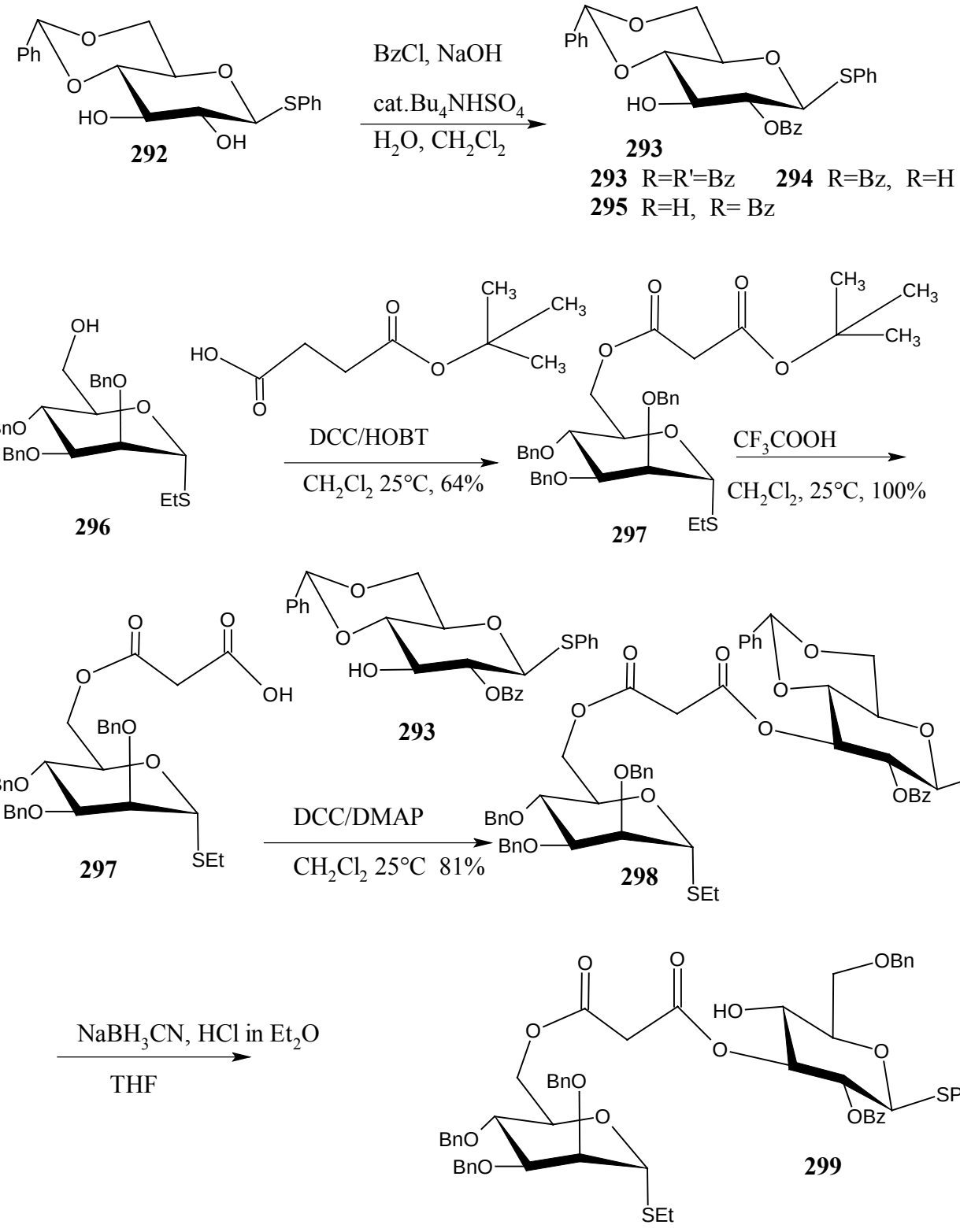


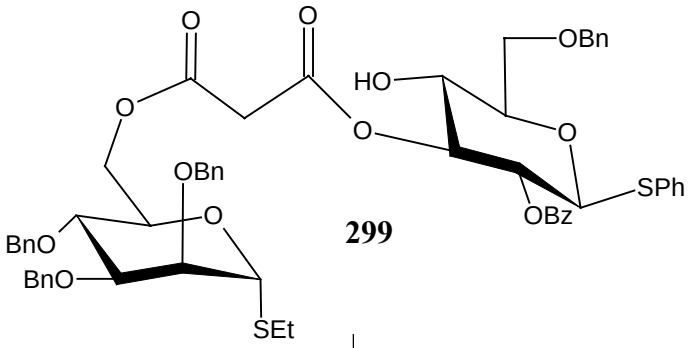
291

Activator	Yield	α:ß
MeOTf	53%	0:100

The use of succinyl and malonyl ester tether prooved to be efficient and applicable for the synthesis of more complex carbohydrates that bear the important ß-mannoside moieties. The prearranged glycoside methodology [54] was sucessfully aplied to the synthesis of a tetra-saccharide unit of Arthrobacter exopolysaccharides. The bacterial genius *Arthrobacter* is a bacterial genius responsible for severe endophthalmitis,different forms of kryptogenic poly-arthrisis, and menengitis. Starting from the known phenyl 4,6-O-benzylidene-1-thio-ß-D-glucopyranose **292**, a benzoylation reaction through transfer phase catalysis afforded the desired 2-O- benzoyate **293** product with 54% yield. Next objective was the obtention of the succinylated tribenzylated mannosyl donor **297** through condensation with a tert-butyl monoprotected malonic acid and ethyl-1-thio-2,3,4-tri-O-benzyl-α-D-mannopy ranoside **296** with 64% yield. Cleavage of the tert-butyl group by trifluoroacetic acid afforded quantitative yield of the mannosyl malonate **297** . Linkage of the 2-O- benzoylated glucoside **293** with **293** through condensation with aid of DCC/DMAP gave tethered disaccharide **298** in 81% yield, subsequently opened with $NaBH_3CN$ furnished the desired tethered disaccharide **299** in 71% yield. Intramolecular glycosylation of **299** by activation with MeOTf successfully generated the ß-linkage mannosyl moiety **300** in 69% yield. The coupling of the latter **300** disaccharide with the other disaccharide **308** by activation with NIS/TMSOTf at –70°C in dichloromethane furnished the tetrasaccharide **309** in 64% yield. Final deprotection with NaOMe in MeOH,and hydrogenation in the presence of $Pd(OH)_2$ at room temperature yielded 87% of the desired tetrasaccharide 5-aminopentyl **311**. (Scheme **61**, **62**)

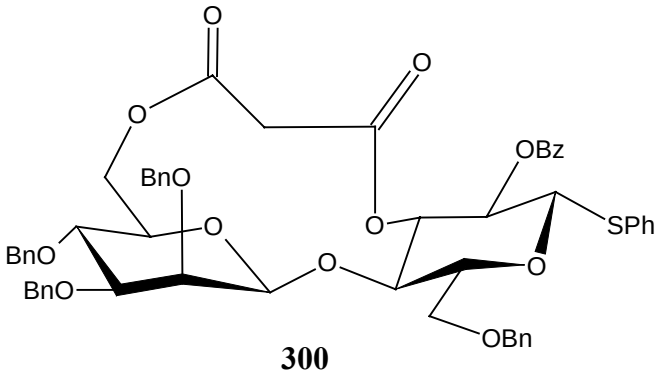
Scheme 61.


BzCl, NaOH
cat.Bu4NHSO4
H2O, CH2Cl2
292
293
293 R=R'=Bz 294 R=Bz, R=H
295 R=H, R= Bz
DCC/HOBT
CH2Cl2 25°C, 64%
CF3COOH
CH2Cl2, 25°C, 100%
296
297
DCC/DMAP
CH2Cl2 25°C 81%
298
NaBH3CN, HCl in Et2O
THF
299



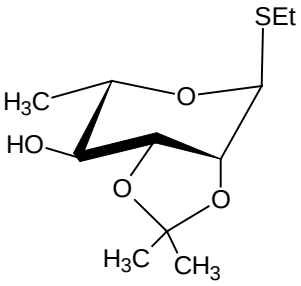
299

MeOTf MeCN, 25°C, 69%



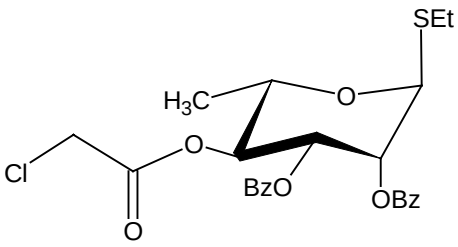
300

Scheme 62.

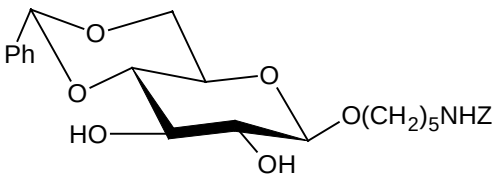


231

4 steps



304

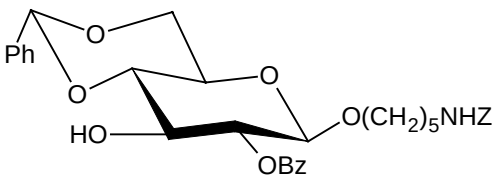


235

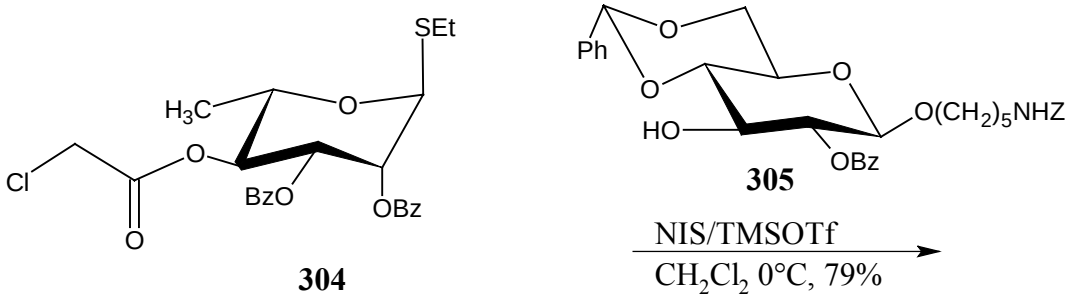
BnBr,NaOH

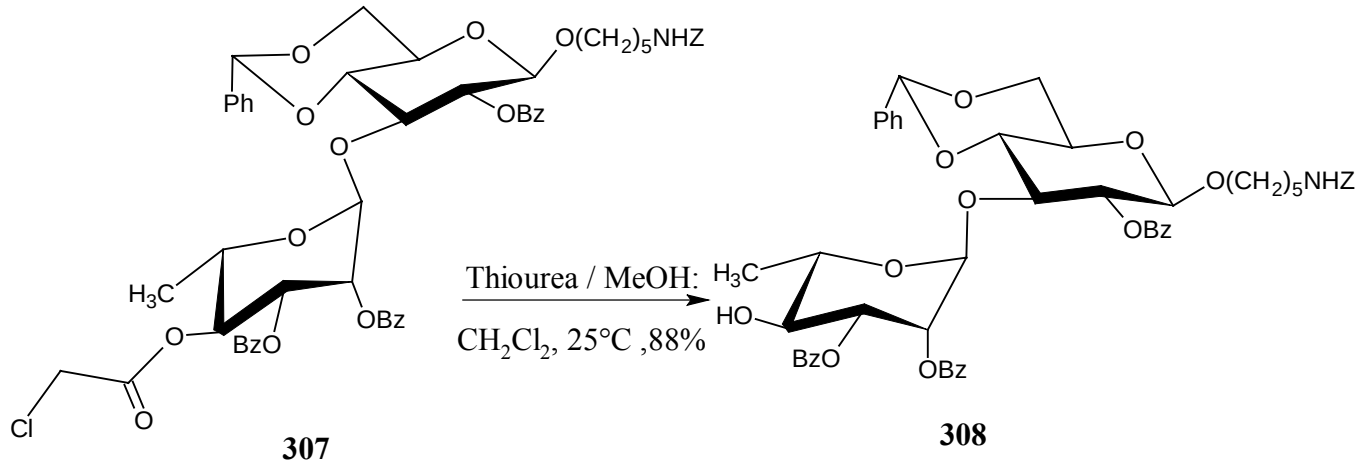
cat.Bu_4NHSO_4

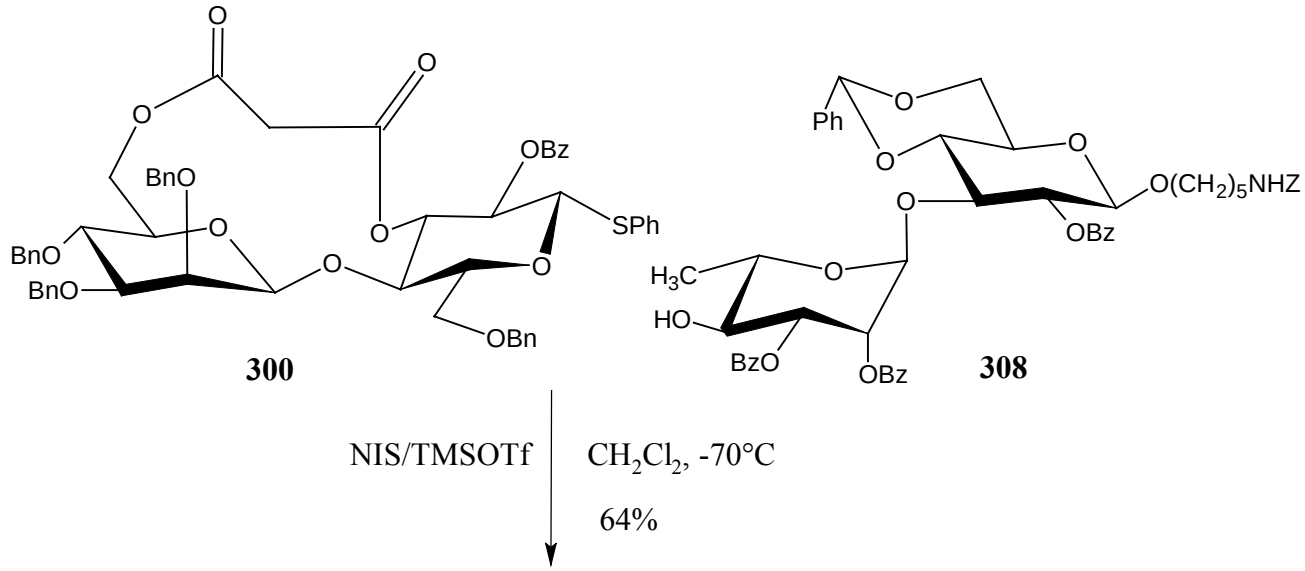
H_2O, CH_2Cl_2

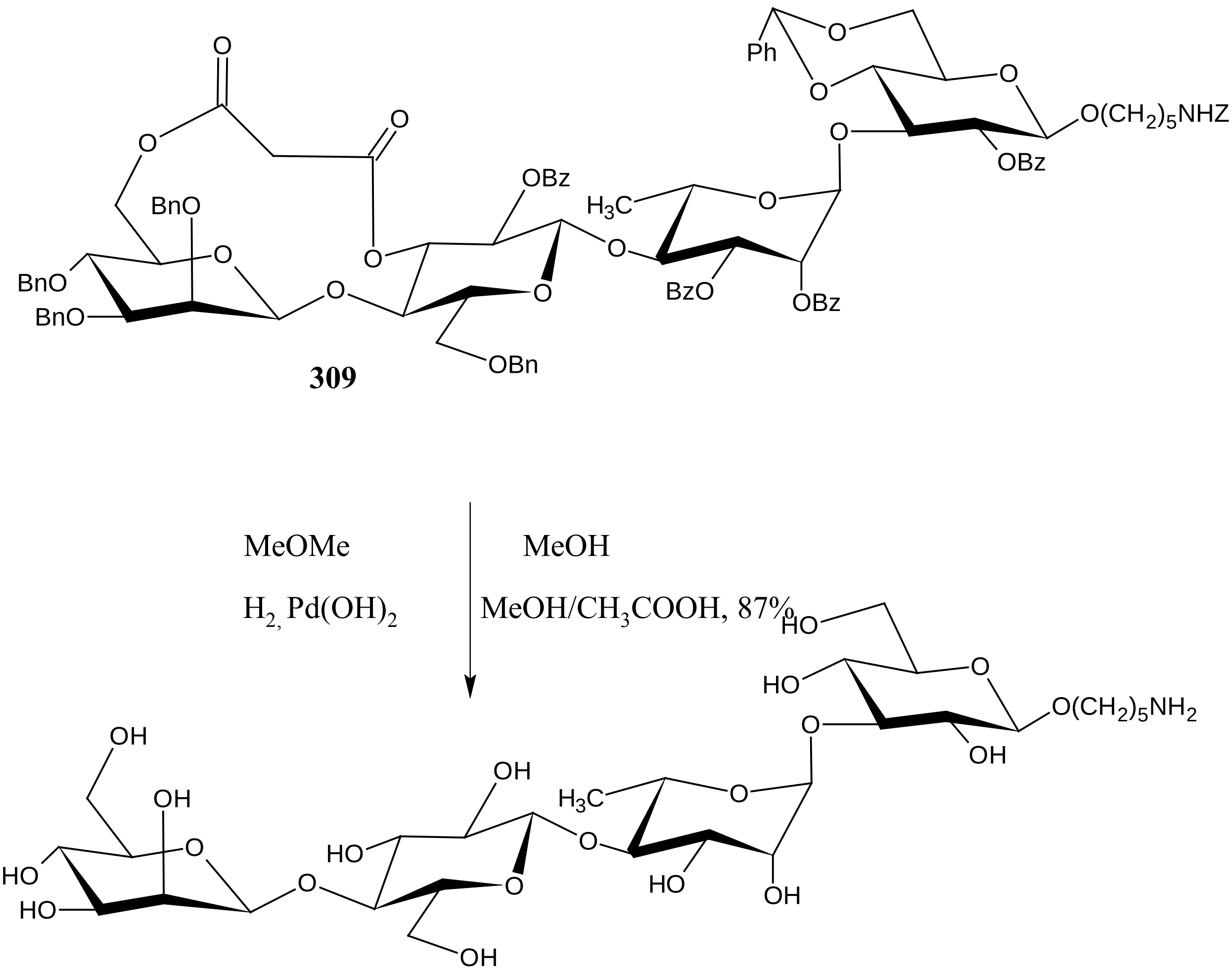


305


SEt
H3C
O
Cl
O
BzO
OBz
O
304
Ph
O
O
O
HO
O(CH2)5NHZ
OBz
305
NIS/TMSOTf
CH2Cl2 0°C, 79%


O
Ph
O
O
O(CH2)5NHZ
OBz
O
H3C
O
O
BzO
OBz
Cl
O
307
Thiourea / MeOH:
CH2Cl2, 25°C ,88%
Ph
O
O
O
O(CH2)5NHZ
OBz
H3C
O
HO
BzO
OBz
308


O
O
O
O
BnO
OBz
O
O
SPh
BnO
O
BnO
O
O
OBn
300
Ph
O
O
O
O(CH2)5NHZ
O
OBz
H3C
O
HO
BzO
OBz
308
NIS/TMSOTf
CH2Cl2, -70°C
64%



309

311

The efficient construction of ß-mannosyl containing disaccharide block reveals its usefullness through this concept for the synthesis of higher saccharides consisting of the ß-man(1-4) gluc moieties in good overall yield.

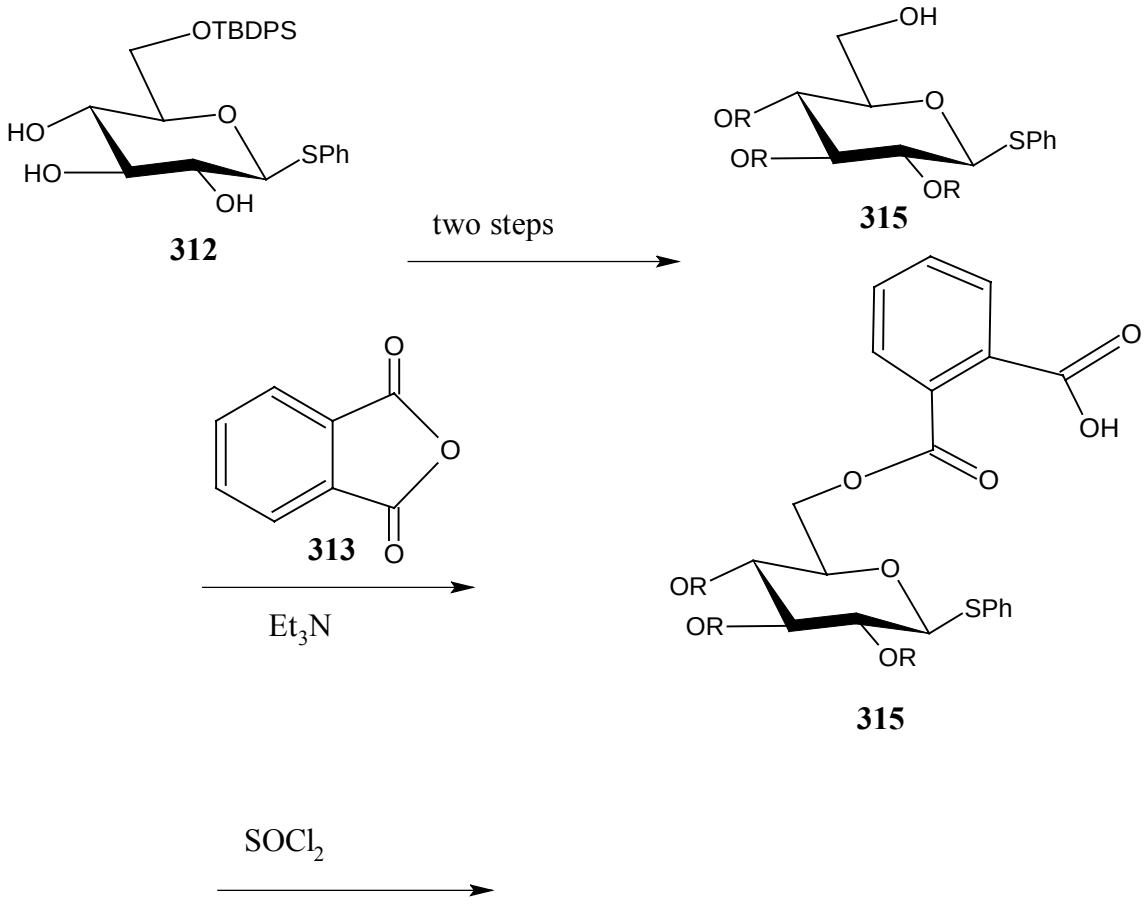
Other ester tethers such as phtaloyl and isopthaloyl linker(55) were conceived by Valverde *et al.* to investigate the intramolecular regioselective glycosylation. They introduced a novel strategy for glycosidic bond formation "Template Directed Cyclo-Glycosylation Reaction."

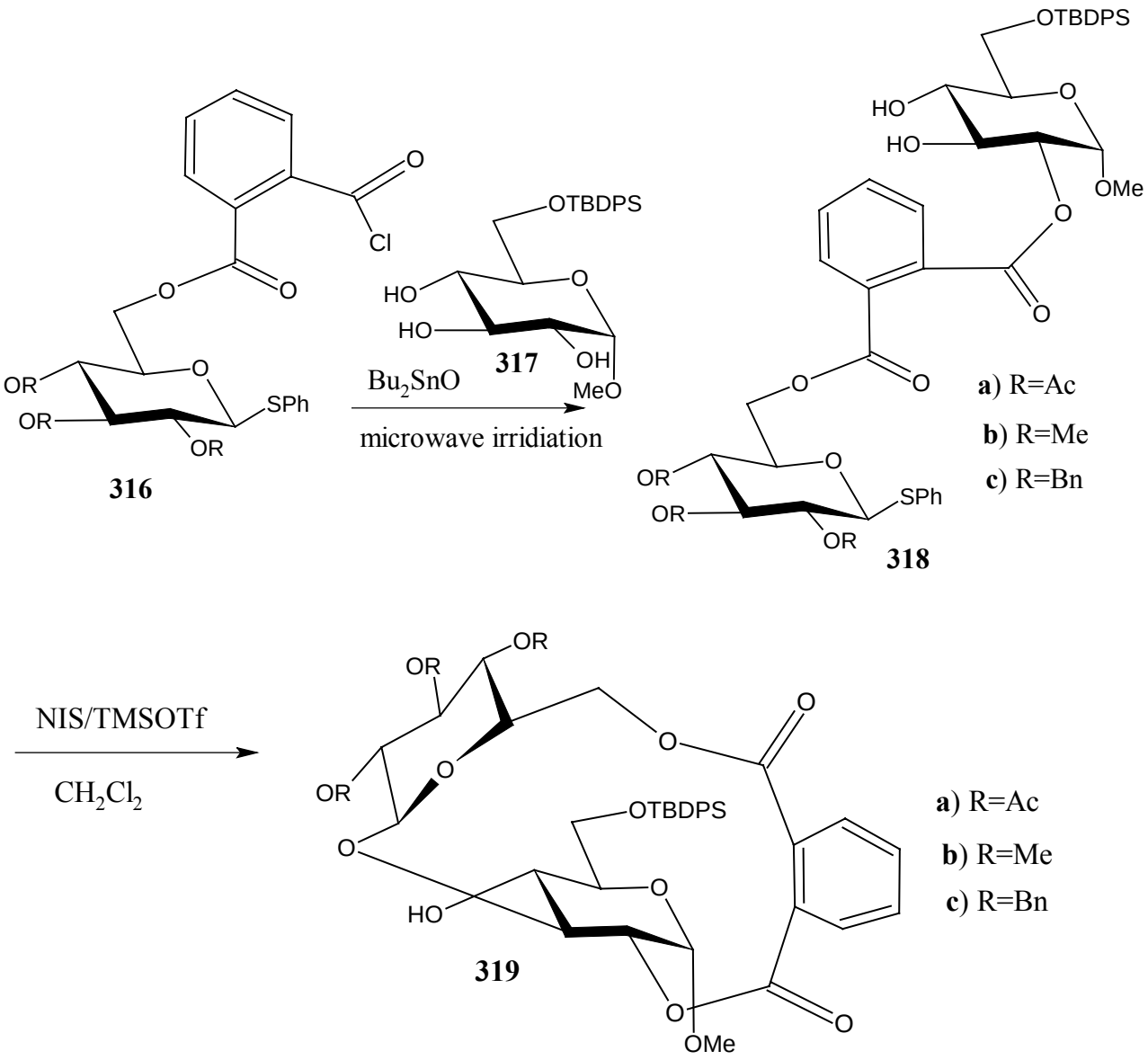
In this methodology, a donor is covalently attached to an acceptor through a suitable bifunctional spacer. The tethered disaccharide consist of two hydroxyl free groups which when creation of glycosydic bond occurs,it provide a certain discrimination between them. In implementing such an approach they hypothesized that the regio -and-stereo-selectivity in the formation of the glycosydic bond will be the results of geometrical restrictions in the transition state

affecting: (*a*) the size of the macrocyle (regioselectivity), and (*b*) the relative orientation in the approach of oxonium ion and the hydroxy group(stereoselectivity or α:ß selectivity).

This novel strategy was applied for the synthesis of glucodisaccharide in which the phthaloyl has been anchored at O-6 and O-2 of glycosyl donor **325** and acceptor **325** respectively. Reaction of **312** with phthalic anhydride **313** yielded the the aromatic esters **315** which upon activation with thionyl chloride to give **316** and then were regioselectively coupled with the glycosyl donor **317** by use of dibutyl stannylidene acetal under microwave irradiation at the O-2 position produced the mixed phthalic esters **318** . Macrocylic glycosylation with NIS/TfOH at 25°C in dichloromethane afforded cyclo adducts **319** regioselectively at 3-O position, with an anomeric outcome of almost exclusively ß-glycosidic bond. Modification of protecting groups on the glycosyl donor from participating acetate to nonparticipating ethers (methyl,benzyl) lead to virtually the same stereochemical results.
Exellent regioselectivity was achieved with almost 100% anomeric outcome, ß glycoside. (Scheme **63**).

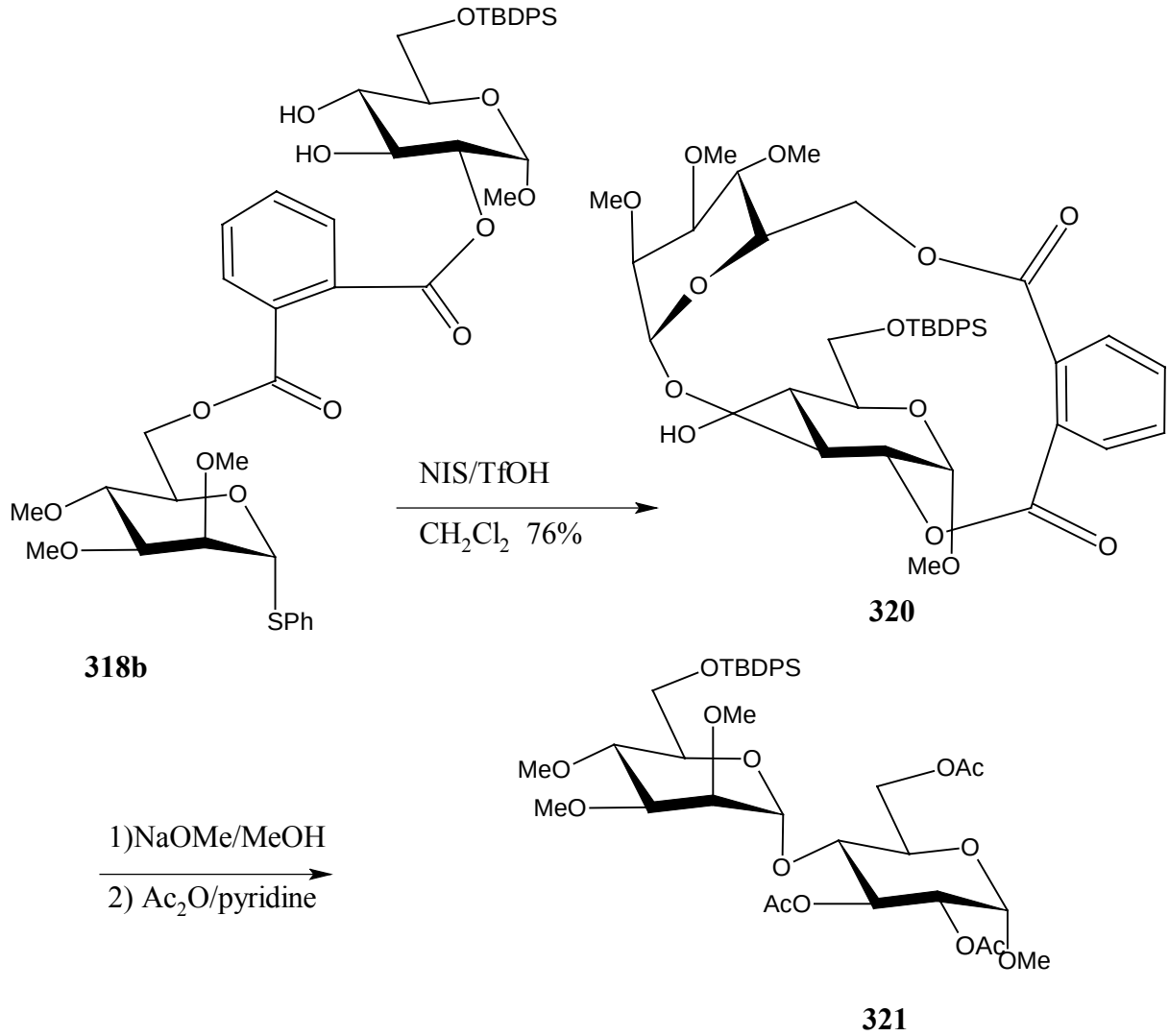
Scheme 63.





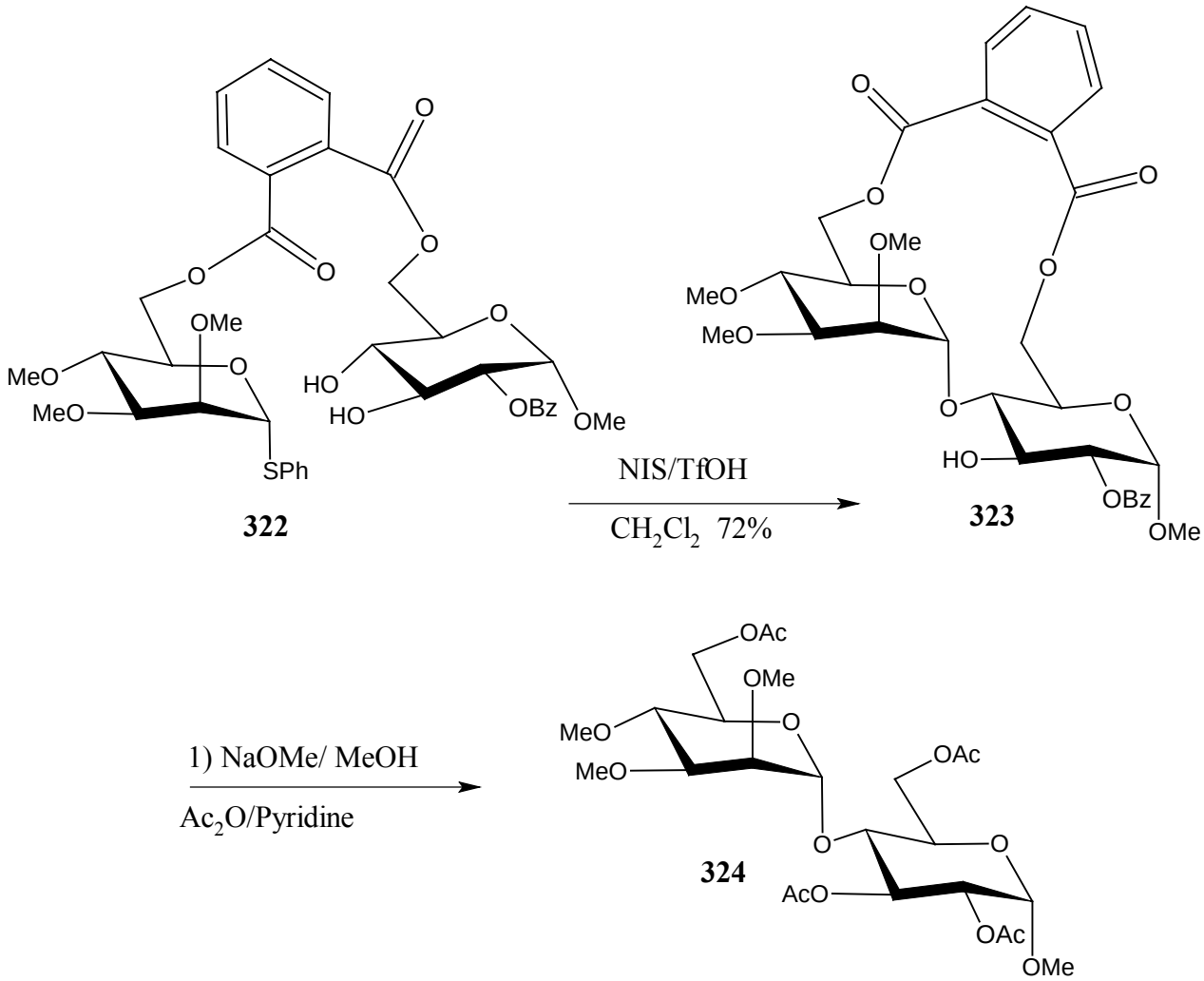
Valverde and coworkers embarked on further investigations with the same spacer in varying the anchoring sites of the spacer. Here, reaction temperature exerted a remarkable effect on the regio and stereoselectivity of intramolecular macrocyclic glycosylation reactions[56] . The aim The aim was to disclose how TDCG strategy is amenable to regio and stereochemical control upon changes in *a*) the topographic orientation of the anchoring hydroxyl groups fro the template and *b*) on reaction temperature. As donor was phenyl-1-thio-2,3,4-tri-O-methyl-α- manopyranoside chosen and anchored from its 6-O to 2'-O of a 6-O silylated α-D-glucopyranoside with its free 3' and 4'OH for regiochemical control in glycoside formation. Macrocyclic glycosylation of **318 b** with NIS/TfOH in dichloromethane to remarkably give 3'α-glycoside **320**. Cleavage of the tether with NaOMe in methanol and acetylation furnished the disaccharide **321**. (Scheme **64**)

Scheme 64.

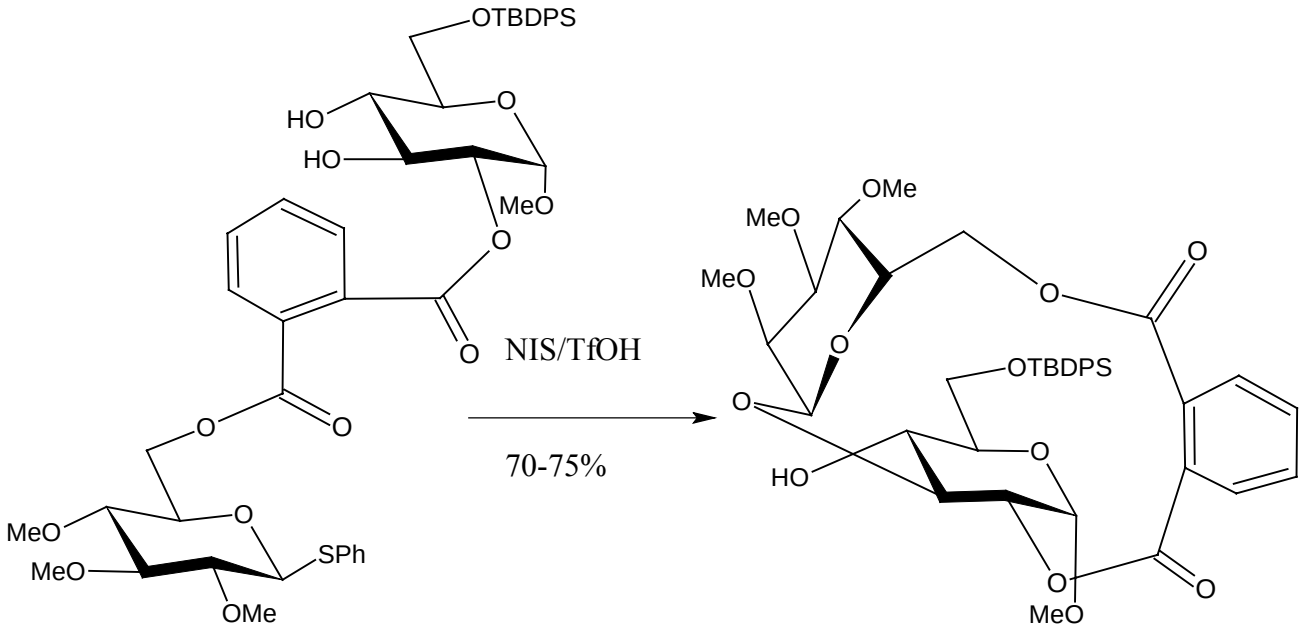


Variation in the position of pthalicester tether to positon 6OH of the mannose donor to 6'O (**322**) of glucose acceptor and glycosylation with NIS/TfOH in dichloromethane afforded only the regioisomeric 4'α-glycoside **323.** Cleavage of the tether with NaOMe followed by acetylation afforded the disaccharide **324** (Scheme **65**).

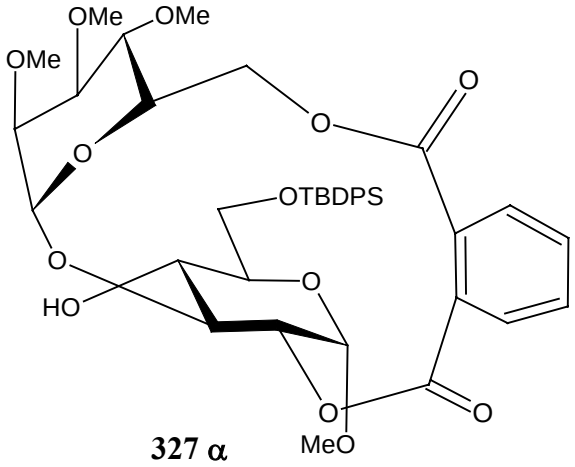
Scheme 65.



The affect of temperature on the stereoselectivity of glycosylation became than the main center of attention. Starting with anchored bridged disaccharide similar to the first example **325** but with a ß-phenyl-1-thio, macrocyclisation reaction activated by NIS/TfOH at different temperatures, 0°C,-20°C,-50°C,-78°C.The anomeric outcomes **327, 326** α/ß were 1:1, 1.2:1, 1,3:1 and 5.5:1 for the latter which illustrate the best result for ß-anomer obtention.(Scheme **66**)



325 **326 ß**



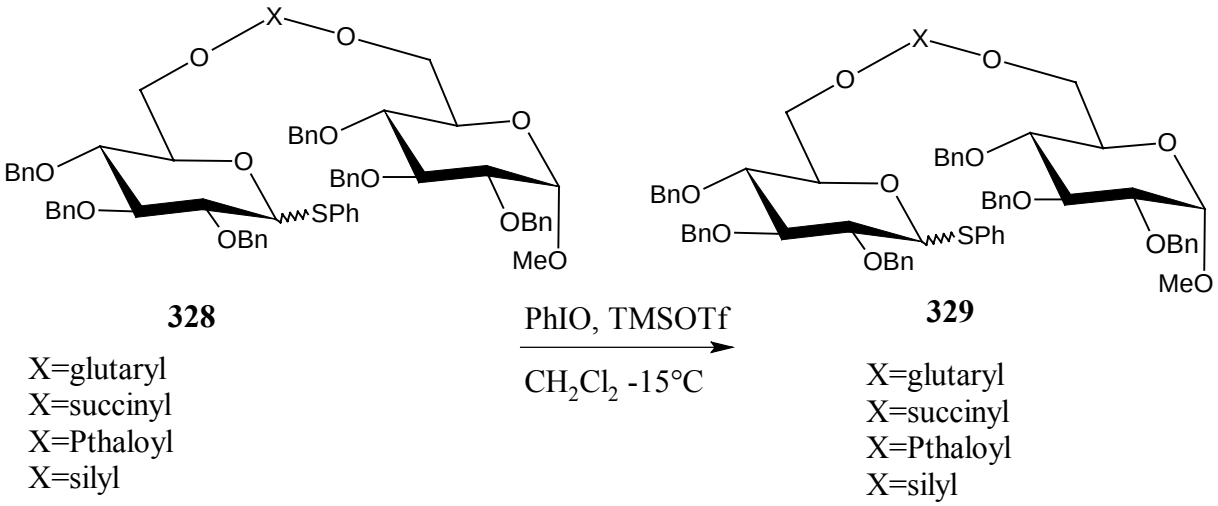
327 α

The results obtained from TDCG, lead to show that a change in the topographic orientation of hydroxyl groups by changing the anchoring site exerted an effect on the tran sition state for the glycosylation and resulted to an interesting change in regiochemistry in where mannosyl donors were involved. With glucosyl donors, the tendency in regioselectivity was less pronounced. At low temperature, the ß-cycloglycosylation product was largely preponderant.

The influence of different flexible spacers on the stereoselectivity of intramolecular glycosylation was investigated by Schoichi Kusumoto et *al.*[57] Among the tethers used, were phtaloyl, succinyl glutaryl,and silyl, as molecular clamp to link the glycosyl donor and accep for.

Glycosylation of these different bridged disaccharides initiated with PhIO,TMSOTf,was effected for an eventual comparison of anomeric outcome. (Scheme **67**, Table **8**).

Scheme 67.



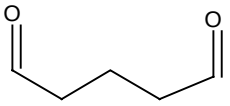
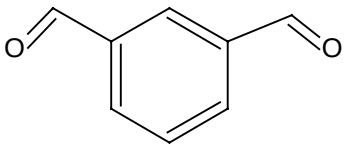
328

X=glutaryl
X=succinyl
X=Pthaloyl
X=silyl

329

X=glutaryl
X=succinyl
X=Pthaloyl
X=silyl

Table 8.

Entry	Linker	solvent	Time	yield	α/ ß
328		CH_2Cl_2	10min	37%	89:11
329		CH_2Cl_2	10min	67%	93:7
330		CH_2Cl_2	10min	86%	99:1
331		Et_2O	15h	46%	99:1
332		CH_3CN	30min	83%	28:72
333	 Si ($^tBu)_2$	CH_2Cl_2	20 min	82%	15:85
334	"	Et_2 O	30min	70%	2:98
335	"	CH_3CN	30min	77%	3:97

Solvent effect was also investigated on glycosylation of with dichloromethane, diethylether, and acetonitrile. With dichloromethane, and diethylether, high α-selectivity was promoted in the case of entries 1 to 4, with glutaryl, succinyl, and phthaloyl used as linkers, the best results being illustrated with phthaloyl linker (entry 2 and 3) with an anomeric outcome α/ß 93:7 for the former and 99:1 for the latter. In the case of entry 5, the solvent effect of acetonitrile dominated over the effect of molecular clamp. ß-selectivity was effected by the use of silyl linker.Glycosylation proceeded smoothly to afford ß-glucoside with all three solvents. Interestingly, with diethyether the highly promoted ß-glycosylation suggest that Et_2O is kinetically attached to the oxocarbenium ion intermediate from the α-face and the proximal acceptor attacks from the ß-face

Molecular clamps orient a facile stereocontrolled glycosylations. Phthaloyl and silyl bridged linking donors to acceptors a their 6-positions afforded high α and ß-selectivity during glycosylation. The above investigations show that anomeric selectivity is controlled by the length, rigidity, and structural features of linkers. This method reveals usefull for oligosaccharide synthesis.

Rigid Spacer Concept

The Rigid Spacer concept was introduced by Smith and coworkers [58,59] in order to obtain close proximity between a glycosyl donor and acceptor. This approach leads to a stucturally rigid array which enforces regio and diastereoselective glycosylation formally under construction of large rings (14 and 15 membered rings.) The extention of the concept of face-regioselective glycosydic bond formation requires a rigid spacer,which due to a geometrical constraint leads to stereocontrol of the reaction. As an example the xylene moiety was chosen by easily preparing αα-bromoxylene from nucleophylic substitution.

An explanation of the mechanism issued from this concept is illustrated in the below figure.

The first step involves the attachement of glycosyl donor to acceptor via a xylene rigid spacer In the acceptor, any cyclic1,3 or 1,2 threo or erythro diol arrangement position of the acceptor's hydroxyl toward the donor will allow for attachement of the spacer and will provide the desired hydroxyl group. Glycosylation occurs on the α or ß-face of the oxocarbonium ion thus resulting to an anomeric outcome.

This design keeps reacting centers at a proper distance to enforce the desired diastereoselection of the glycosylation step via a macrocyclic formation of a 14 or 15 membered ring from which products can be liberated.(Scheme **68**, Fig. **9**)

Scheme 68.

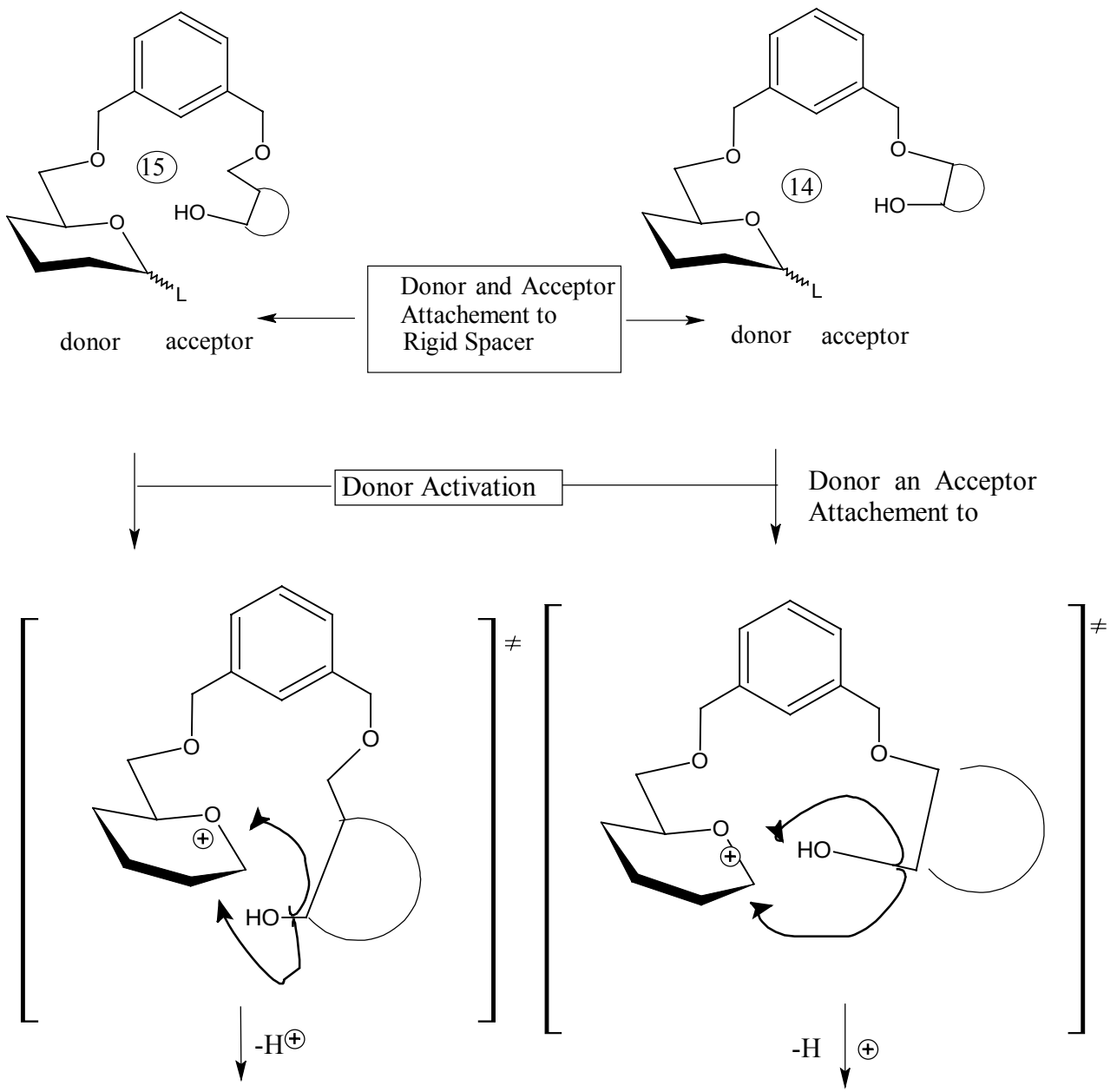
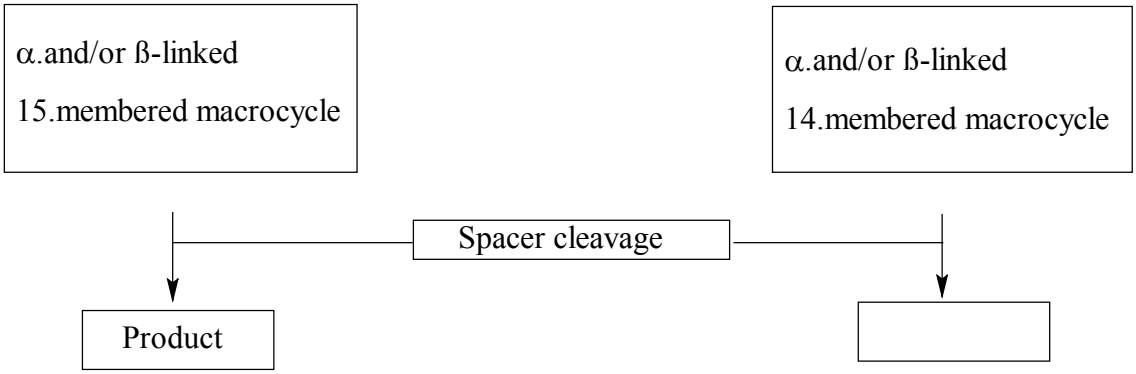
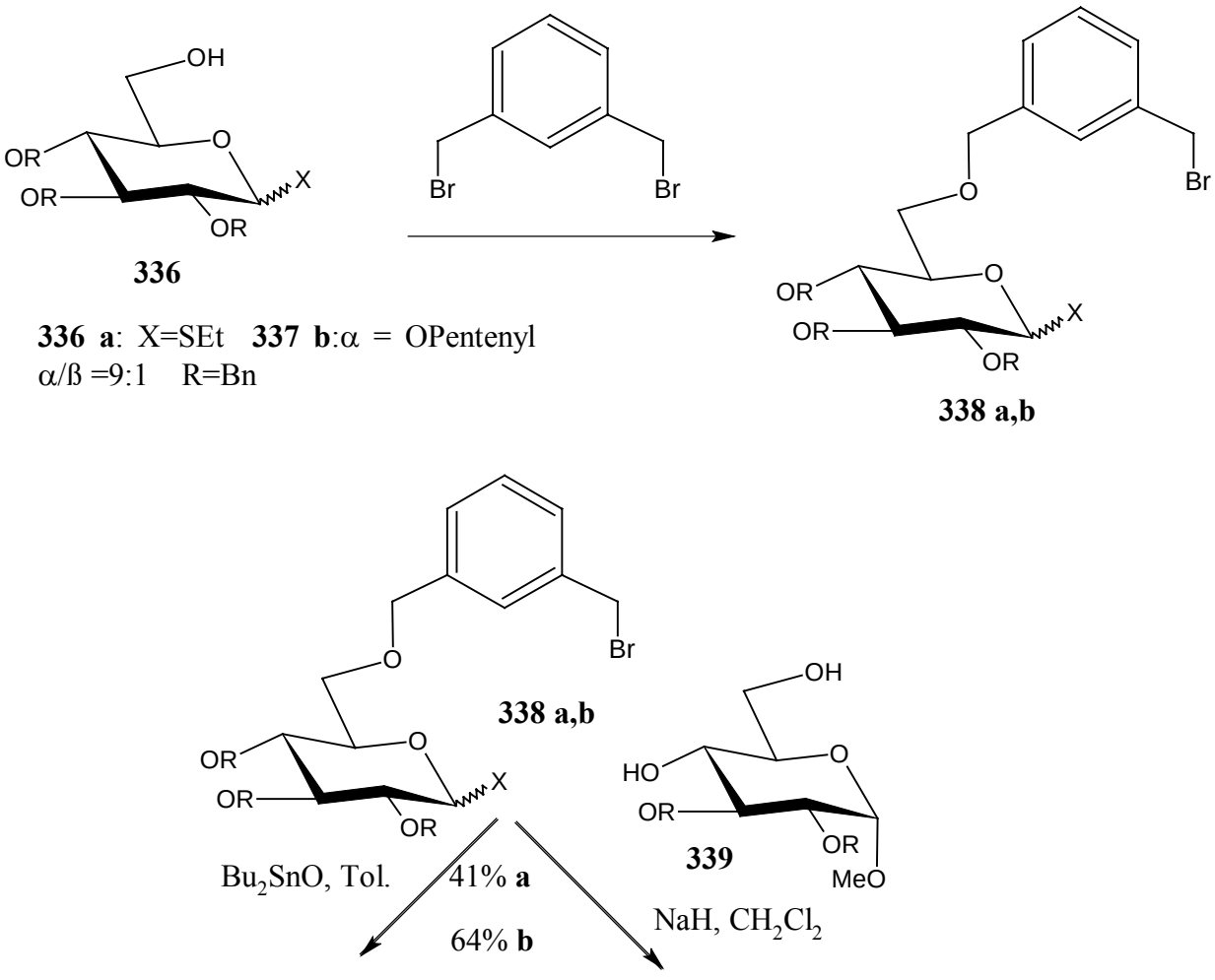


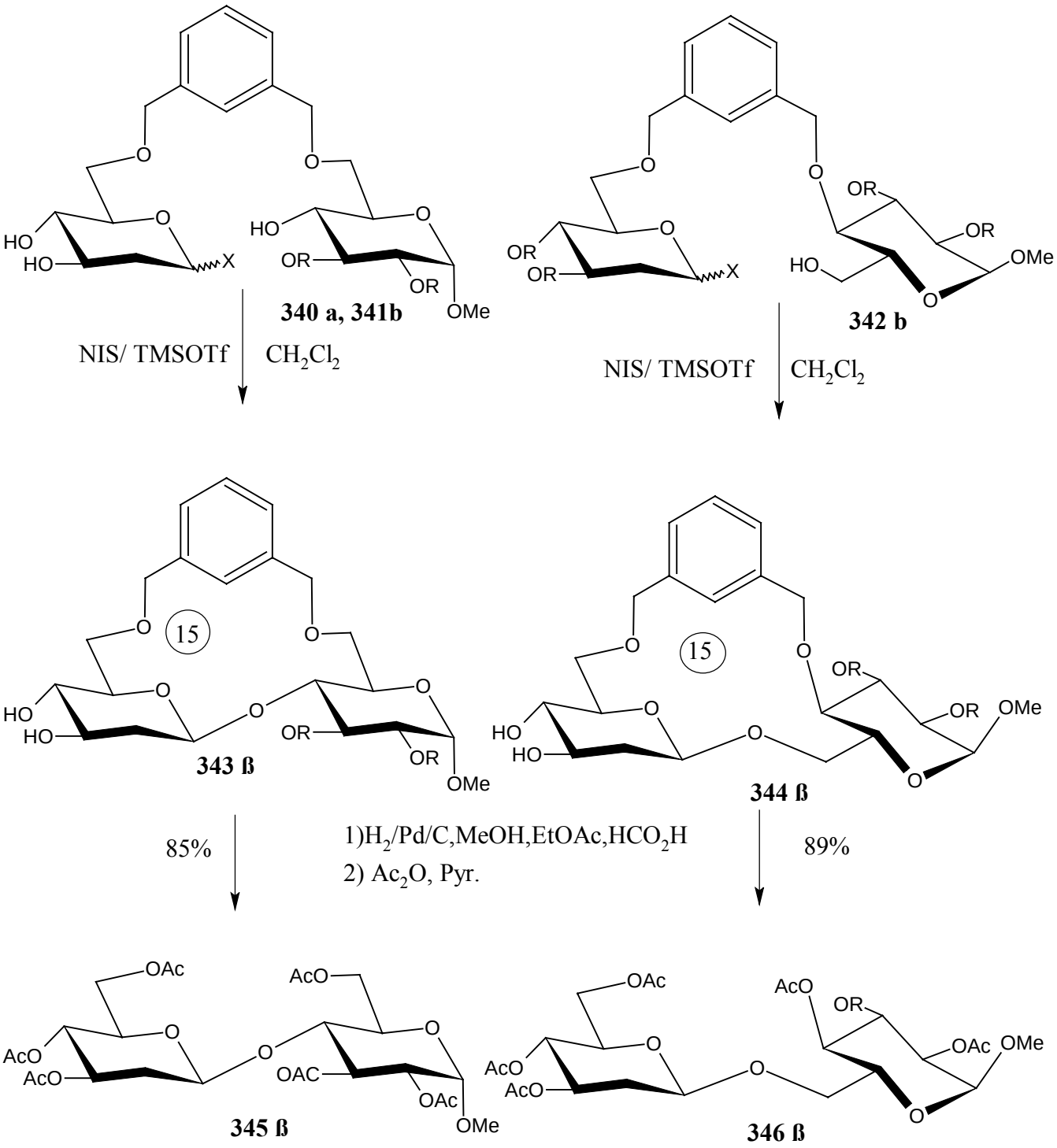
Fig 9.



The rationalisation of this concept was applied to the synthesis of a glucose disaccharide in which ethyl-1-thio-2,3,4-tri-O-benzyl α-D-methoxy glucopyranoside donor **336** is linked to an acceptor, methyl-2,3,-di-O-benzyl-α-D-glucopyranoside **339** through xylene rigid spacer. First step is the reaction between the tribenzylated glucosyl donor **336** with αα dibromoxylene in the presence of NaH,15-crown-5, in dichloromethane to give **338 a,b**. The next step involved two different routes in the aim of obtaining two xylenated bridged disaccharides. Reaction of **338 a,b** with dibutyltin oxide and the 4,6-O-unprotected glucosyl acceptor of configuration (5,4-L *threo*) **339** in the presence of tetrabutylamoniumiodide afforded the 6a6b-O-liked intermediate **340 a,b** 41% **340 a**, 64% **341 b**. Correspondingly the same reaction conducted in th presence of NaH in DMF with the 4,6-O-unprotected glucopyranose (L-*threo*) yielded the 4a,6b-O-linked intermediate **342 b**. Activation of **340 a** with NIS/ TMSOTf in dichloromethane at room temperature afforded the 15 membered ring **343** ß as the only anomeric product. A similar anomeric outcome with **342 b** when treated with NIS/TMSOTf in toluene at room temperature which afforded the 15 membered ring ß(1-6) **344** ß in 72% yield. Hydrogenolytic O-debenzylation and than O-deacetylation of both **343** ß and **344** ß gave cellobiose **345** ß for the former and **346**ß for the latter. (Scheme **69**).

Scheme 69.

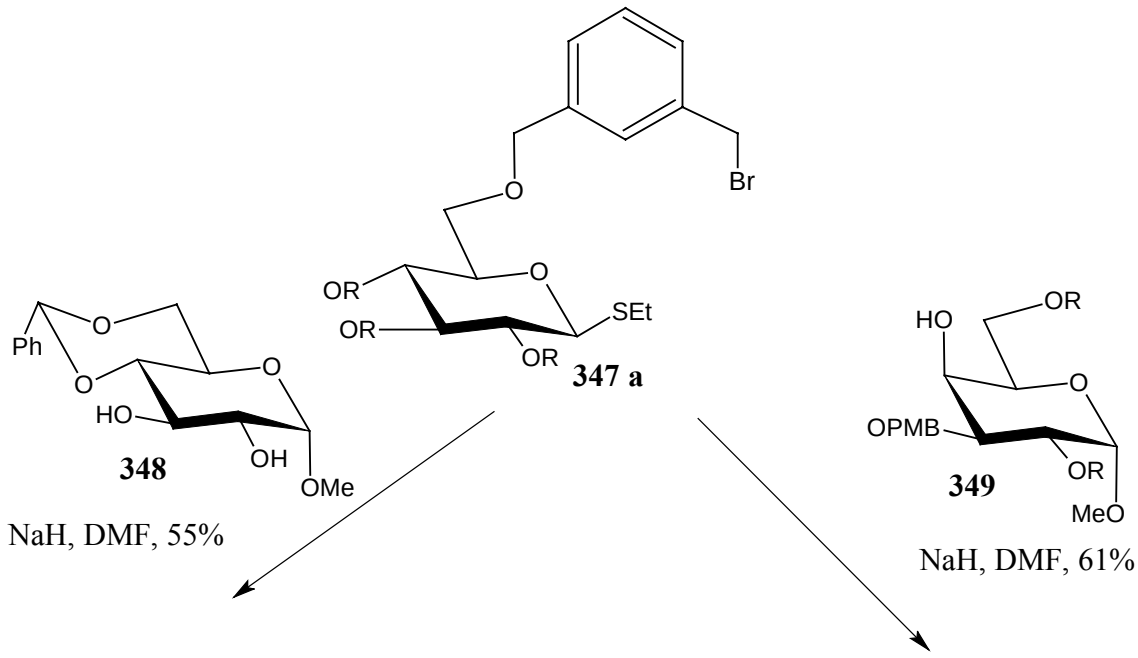


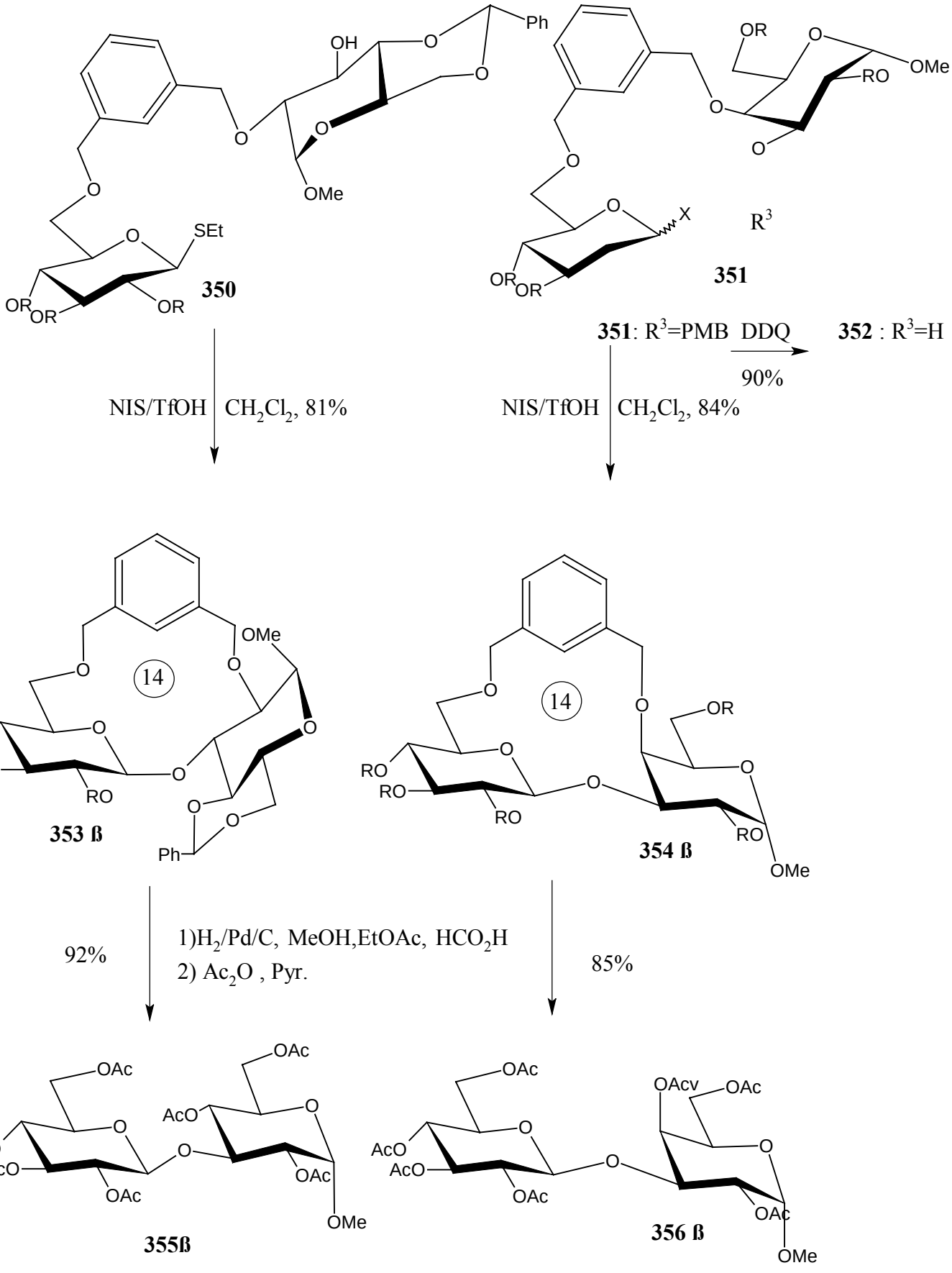


Conclusively,only ß-face selective ring closure to a 15 membered ring is observed foe a system system containing m-xylene residue as rigid spacer,ß-face attachement of the donor with L-threo-1,3- diol arrangement in the acceptor moiety.

Ring closure to a 14-membered ring was envisaged to further limit the conformational space of the donor and/or acceptor moiety and to favor intramolecular reaction course. Herein, the xylene rigid spacer was chosen in oder to generate a 14 membered ring. Treatment of the bromoxylene tribenzylated glucosyl **347 a** with 4,6-O-benzylidene 2,3-O-unprotected α-D-unprotected glycosyl acceptor **348** in the presence of NaH, in DMF resulted to 55% yield of 6ß 2 (2,3-L- *threo*) arranged bridge disaccharide **350**. Glycosylation under standard conditions furnished the 14 membered macrocyclic ß(1-3) disaccharide **352**ß in 81% yield. Correspondingly, the same reaction of **347a** with 4-O-unprotected galactose acceptor **349** in the presence of NaH, in DMF, afforded the 4a-O-linked intermediate **351** followed by deprotection of the para-methoxybenzyl group with DDQ in dichloromethane produced the 3a-O-unprotected **352** with a 6ß/4(4,3-L-*erythro*)- arranged configuration. Glycosylation of **350** and **352** under standard condition gave the only ß-14 membered ring disaccharides **353**,**354** in 81% an 84% yield. Hydrolytic O-debenzylation and acetylation of **353** ß und **354** ß yielded both acetylated disaccha rides **355** ß und **356** ß. (Scheme **70**).

Scheme 70.

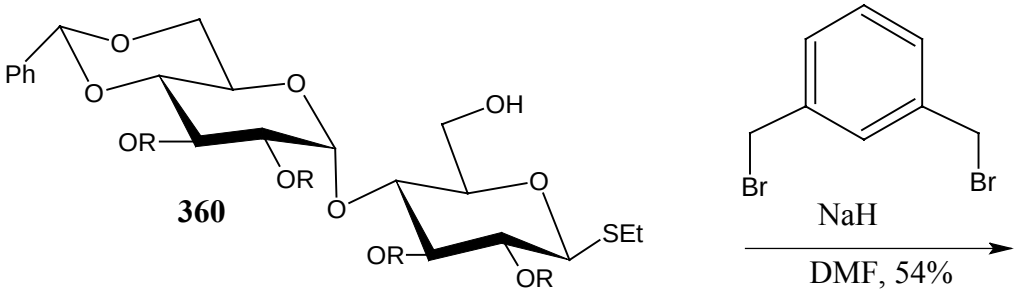



Ph
OH
O
OMe
SEt
OR
OR
OR
350
X
R3
351
351: R3=PMB DDQ
352 : R3=H
90%
NIS/TfOH CH2Cl2, 81%
NIS/TfOH CH2Cl2, 84%
14
RO
353 ß
354 ß
92%
1)H2/Pd/C, MeOH,EtOAc, HCO2H
2) Ac2O , Pyr.
85%
AcO
OAc
355ß
OAcv
356 ß

The rigid *m*-xylene spacer lead to the realisation of highly faced-selective and efficient intramolecular glycoside bond formation. in the high yield formation of 14-membered ring, intermolecular cular glycosylation only plays a very minor role. As exhibited, further potential for this intramolecular reaction is available by a further limitation of the conformational space of the glycosyl donor and acceptor moiety. Formal inversion of the relative sterochemical attachement of the donor and accetor moiety yields either α or β-glycosides, as desired.

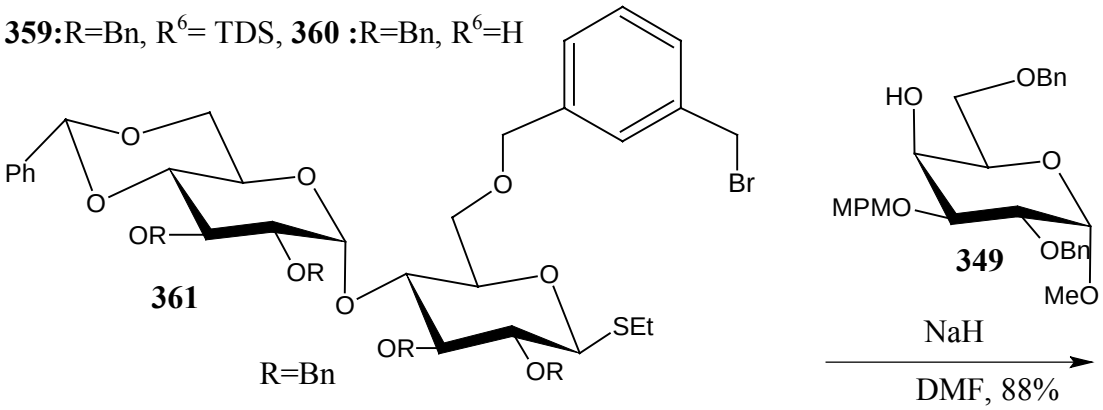
The performance of the rigid spacer concept was demonstrated in the synthesis of higher sac charide derivatives[60] by linking disaccharide donor to a mono or disaccharide acceptor.
A benzylated maltose thioglycoside **360** was selected as donor and tethered with αα' dibromo-xylene with 54% yield of **361**. The second ligation performed with a 4-O-unprotected bezylated galactose acceptor **349** afforded the 4 (4,3-L-erythro)-linked trisaccharide **362** in 88% yield. Selective debenzylation with DDQ in CH_2Cl_2 yielded the desired alcohol **363**. Glycosylaton of **363** under standard conditions NIS/TfOH in dichloromethane yielded 82% of the ß(1-3) trisac charide **364** exclusively. (Scheme **71**)

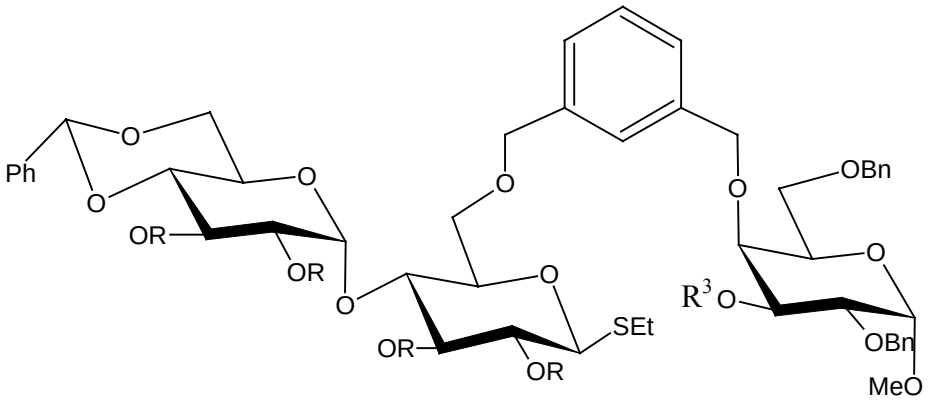
Scheme 71.



357: R=R^6= H **358 :**R=H, R^6=TDS

359:R=Bn, R^6= TDS, **360 :**R=Bn, R^6=H

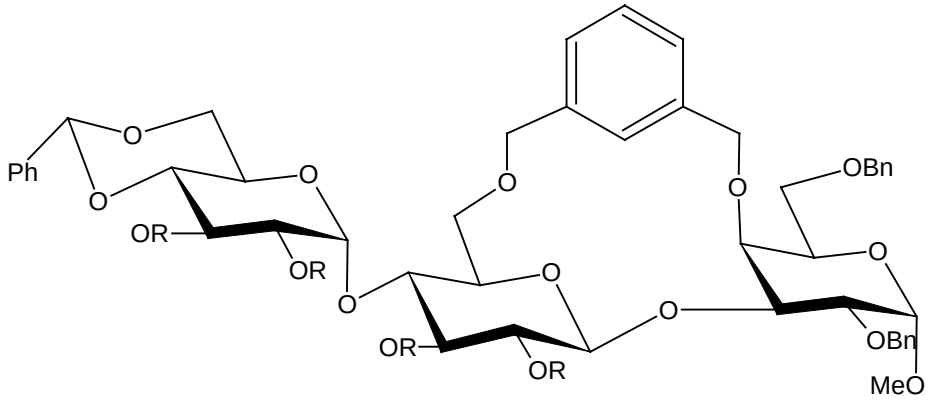




362: R=Bn, R^3= MPM DDQ **363**: R=Bn , R^3= H

CH_2Cl_2

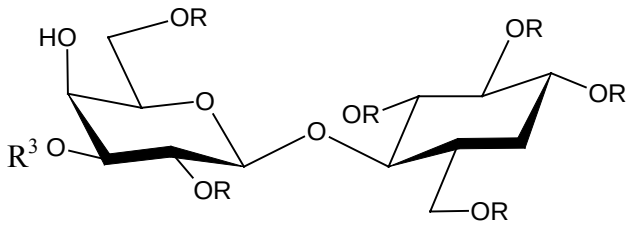
NIS/TfOH CH_2Cl_2 , 82%



364 ß R=Bn

This methodology was succesfully applied in the synthesis of a tetrasaccharide that contains the ß(1-3) glycosidic bond frequently found in nature. Here a 3b-O-unprotected lactose was chosen as acceptor. Linkage with the partially xylenated maltose donor **361** in the presence of NaH resulted to the xylenated bridged tetrasaccharide **367** in 51% yield. Prior to the obtention of **367**, the 3b-O-protected acceptor **366** had to be produced. The knowned 3b,4b-O-unprotected lactose **365** as selectively treated with para-methoxybenzyl chloride in the presence of dibutyltin oxide to afford the **366** 3-O- MPM-protected derivative in 84% yield. (Scheme **72**.) The bridged xylenated terasaccharide **367** containing the 3-OMPM- group was deprotected with DDQ to furnish the desired 3-O- alcohol **368**. Glycosylation by activation with NIS/ TfOH in dichloromethane resulted only in ß(1-3) linkage between the maltoside and lactosyl residue, thus the tetrasaccharide **369** in 78% yield. (Scheme **72**).

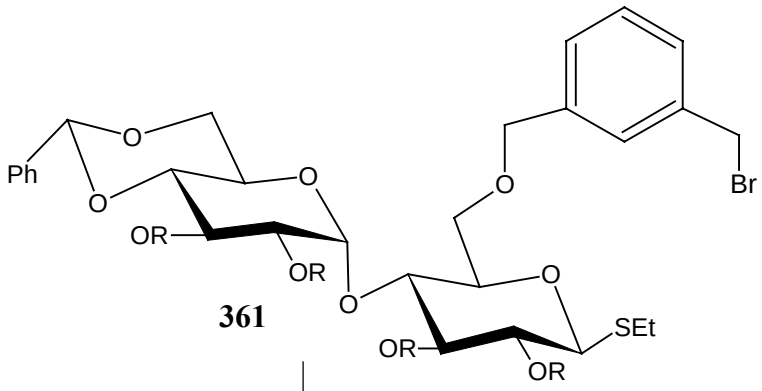
Scheme 72.



365: R=Bn, R^3=H

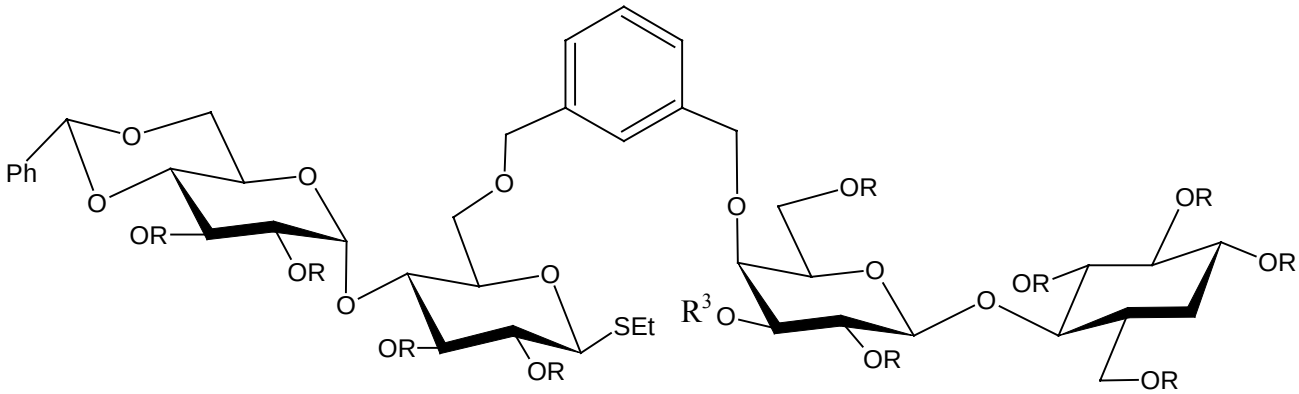
366:R=Bn, R^3=MPM

MPM-Cl, Bu_2SnO,Tol (84%)

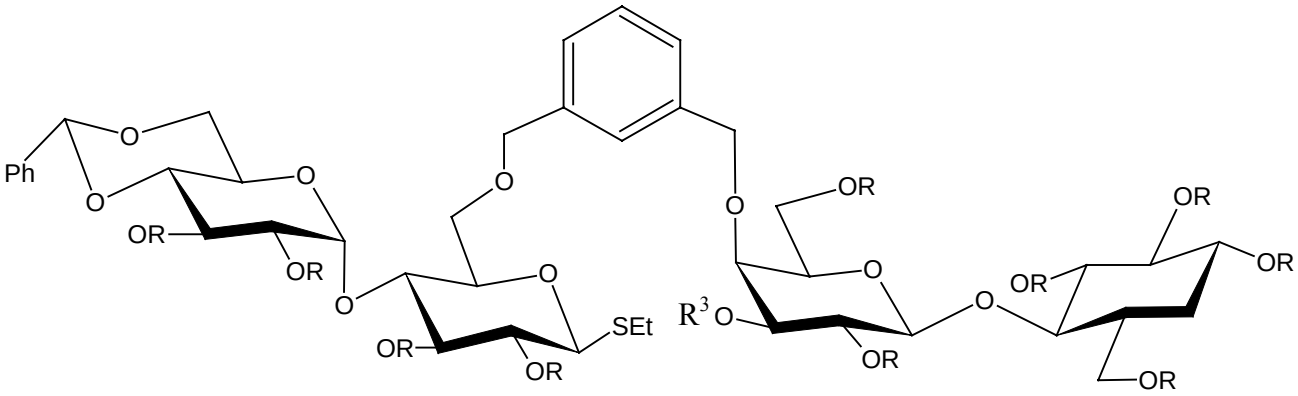


361

NaH DMF , 51%



367 R=Bn R^3= MPM

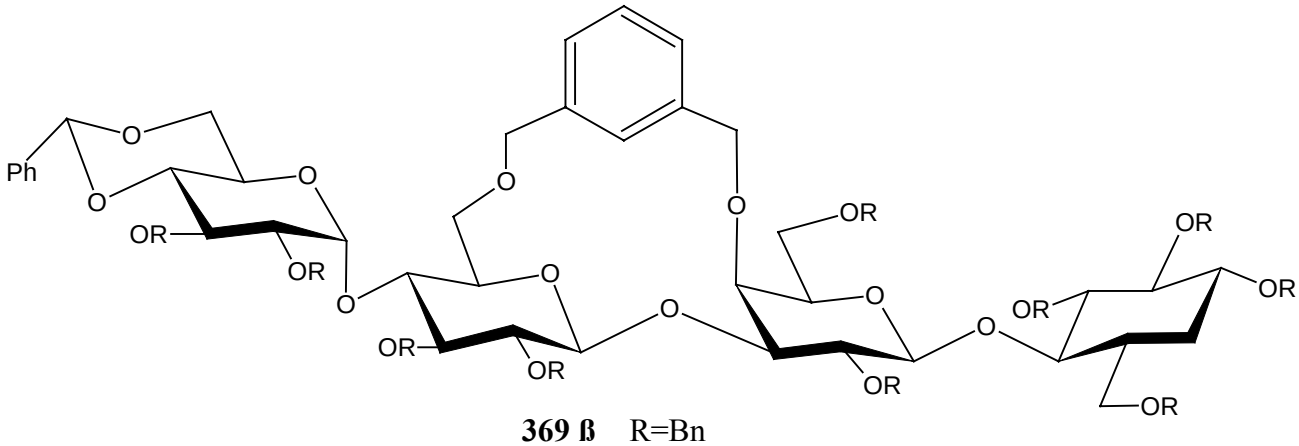


367: R=Bn, R^3=MPM

368: R=Bn, R^3= H

DDQ, CH_2Cl_2, 91%

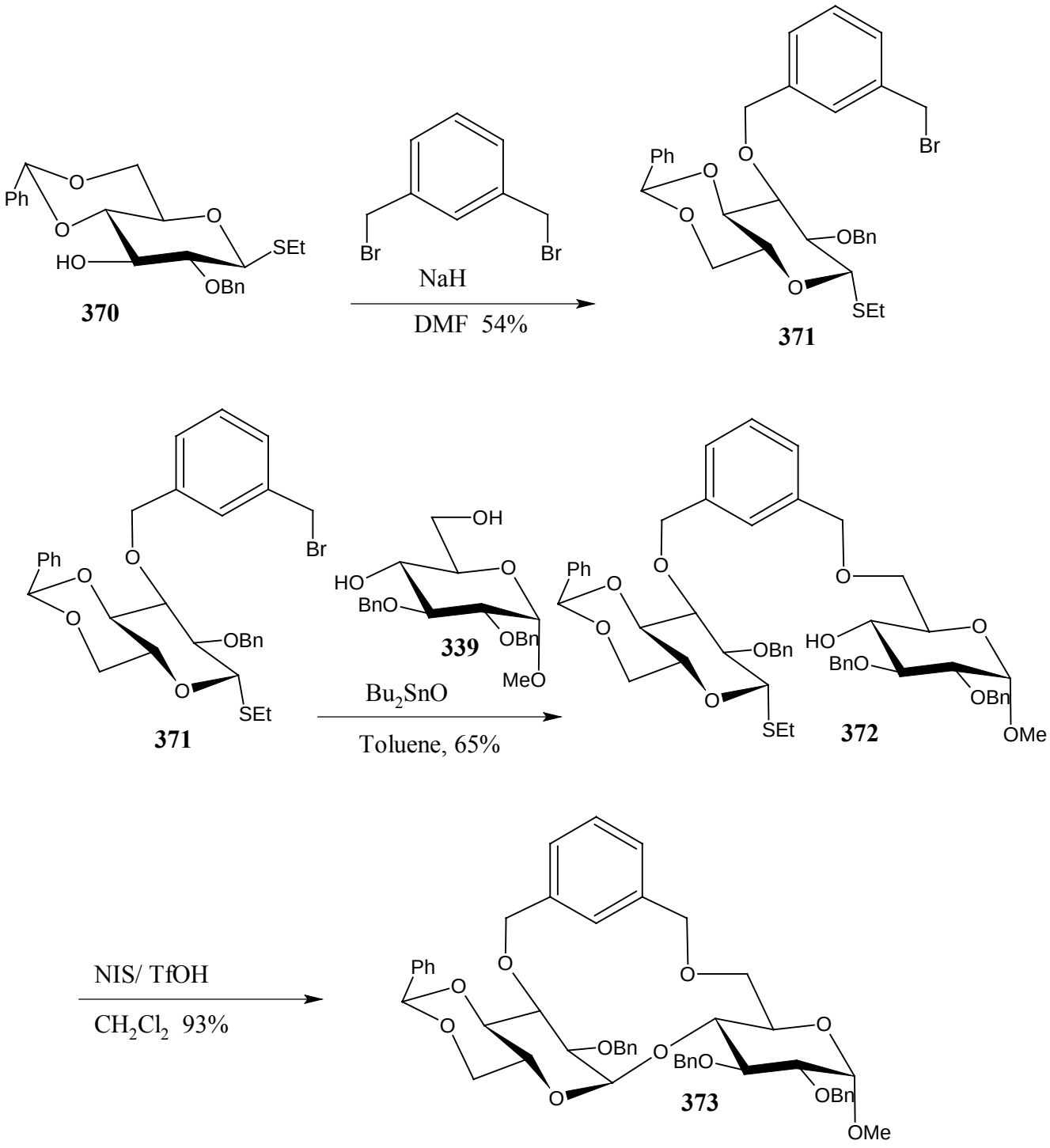
NIS/TfOH CH_2Cl_2, 78%



369 ß R=Bn

The great success in the generation of ß(1-3) tri and tetrasaccharide prompted further investigation toward the obtention of α(1-4) linkage, in which α(1-4) glucosyl di- and trisac charide. As donor of choice was the ethyl-1-thio-4,6-O-bezylidene-2-O benzyl-α-D-glucopy ranoside **370** which was ligated to αα' dibromoxylene to yield **371**. Further selective 6-O-linkage with a 4,6 di-O- unprotected dibenzylated glucose **339** acceptor in the presence of dibutyltin oxide gave the bridged disaccharide **372**. Activation with NIS/TfOH in dichloromethane furnished the α (1-4) disaccharide **373** in 93% yield. (Scheme **73**)

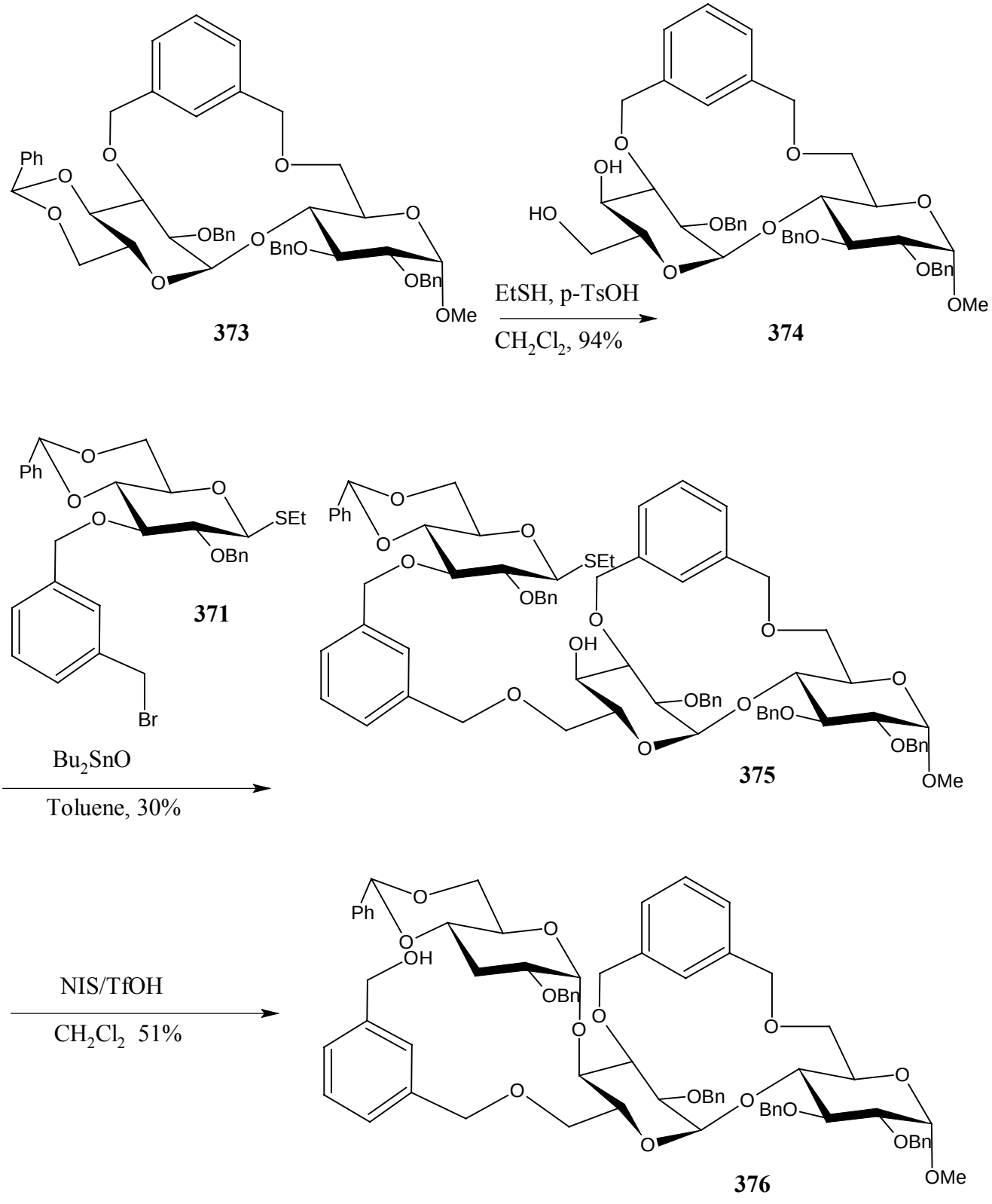
Scheme 73.

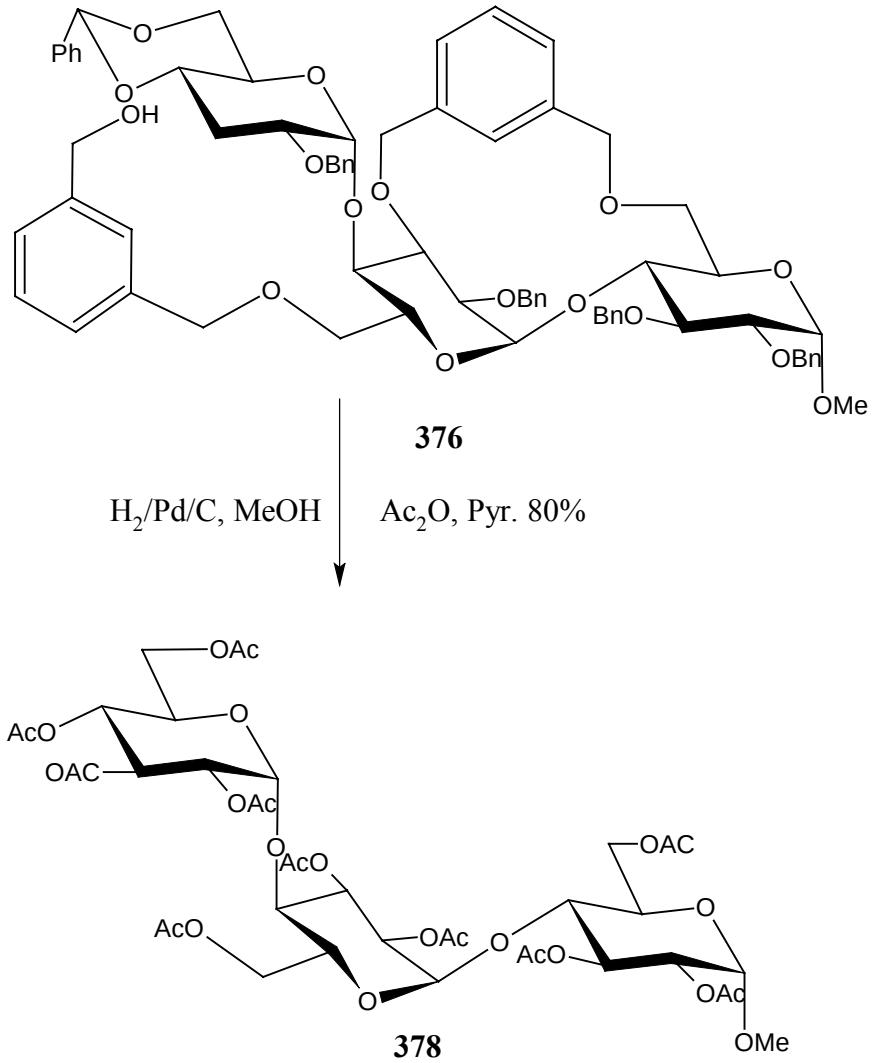


The next step toward the synthesis of α(1-4) trisaccharide involves the selective opening of the the benzylidene group in **373** with ethanethiol, and para-toluosulfonic acid to the diol **374**, than the selective 6-O-ligation of **374** with compound **371** in the presence of dibutyltin oxide to afford the ligated trisaccharide **375**. Glycosylation reaction under the same conditions furnished the α(1-4) trisaccharide **376** in 51% yield. Hydrogenolytic O-debenzylation, to **388** followed by

acetylation finally furnished the fully acetylated α(1-4) trisaccharide in **389** 80% yield. (Scheme**74**)

Scheme 74.





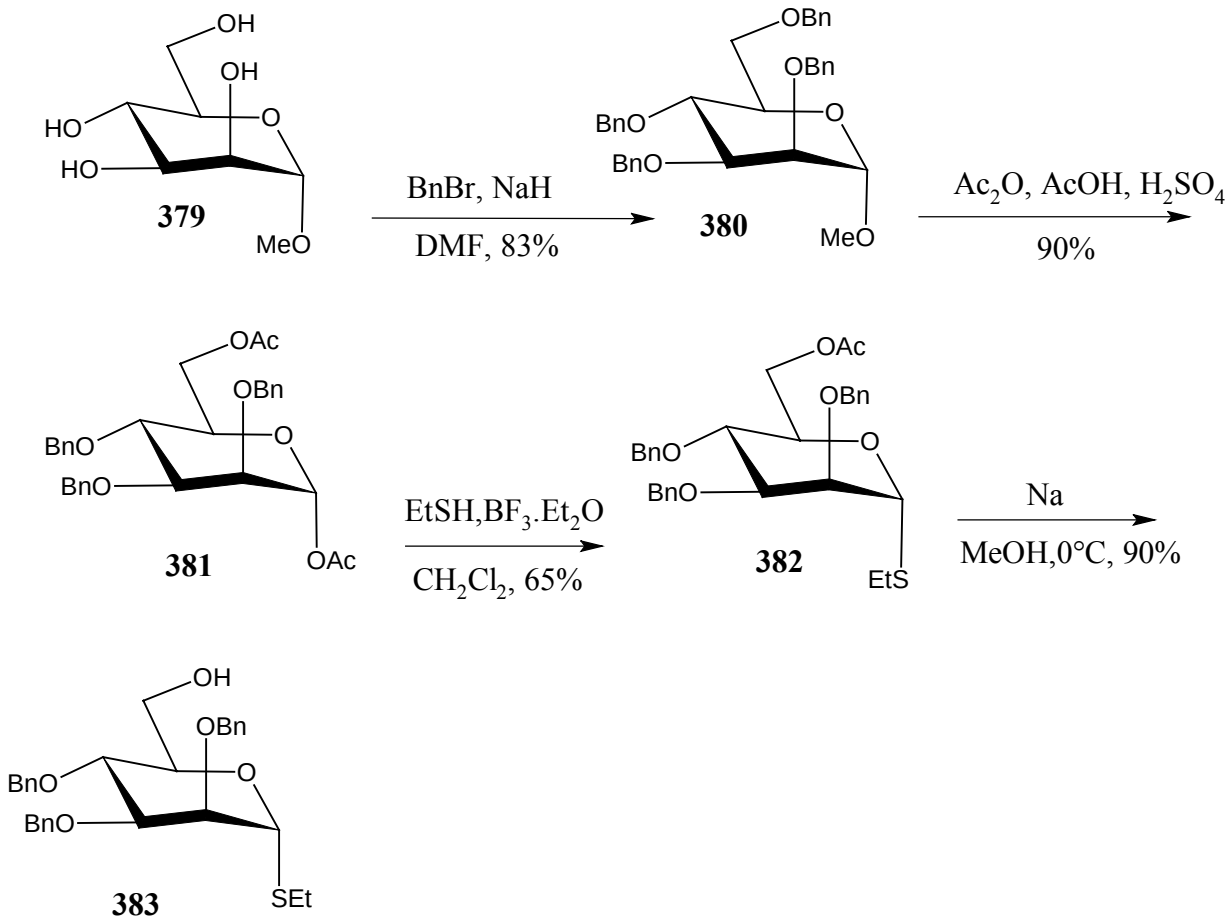
The rigid spacer concept prooved from all above results to be a successful method in it's extention toward tri- and tetrasaccharide synthesis. With the proper configuration only ß or α glycosydic linkage were highly stereoselectively generated. Moreover, the xylene spacer in the presence of benzyl group, and benzyledene group can fully removed by hydrogenolysis.

A completely different intramolecular glycosylation's approach was described by Anthony Fairbanks [60,61] and coworkers by using peptide spacers between donors and acceptors.
Besides reaching regio-and stereoselective glycosydic linkage, the particularly attractive feature of this approach allows the indirect use of existing automated method for solid phase for oligosaccharide construction

For initial studies, an ethyl-1-thio-2,3,4-tri-O-benzyl-α-D-mannopyranoside and methy-O-2,3, 4,-tri-O-para-methoxybenzyl-α-D-mannopyranoside were chosen as donor and acceptor for the latter. (Scheme **72**)

Starting from mannopyranoside **379**, benzylation with NaH, benzylbromide, in DMF gave the tetrabenzylated mannopyranoside **380** in 83% yield followed by acidic cleavage of with acetic acid, and sulfuric acid, than acetylation with acetic anhydride and base furnished **381** at 90% yield. Thiation of the latter with ethanethiol, borontrifluoride etherate yielded 65% of the ethyl mannopyranosyl thioglycoside **382.** Zemplen acetyl deprotection of **382** afforded the disired free 5-OH tetrabenzylated mannopyranosyl thioglycoside **383** with 90% yield. (Scheme **75**.)

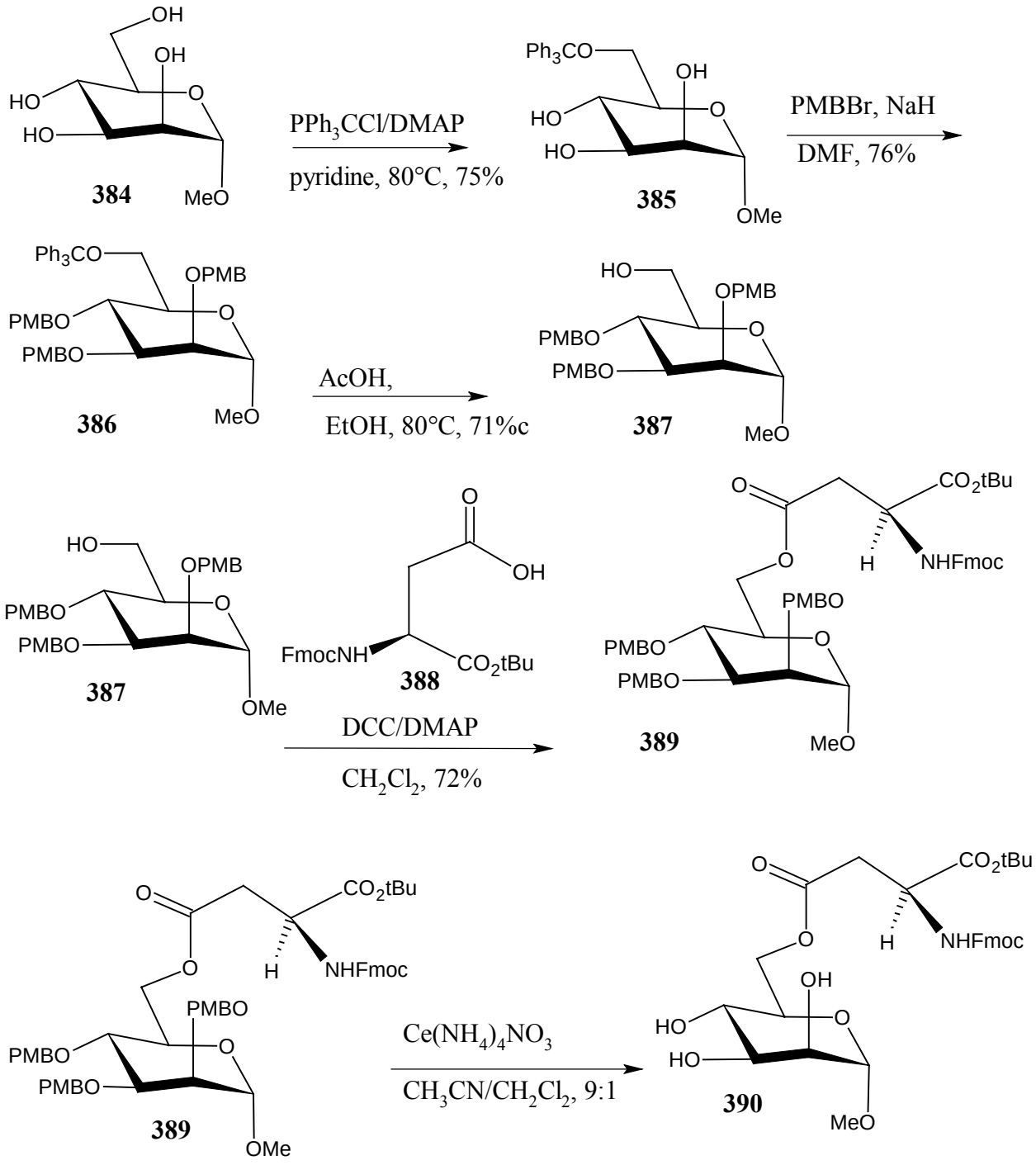
Scheme 75.

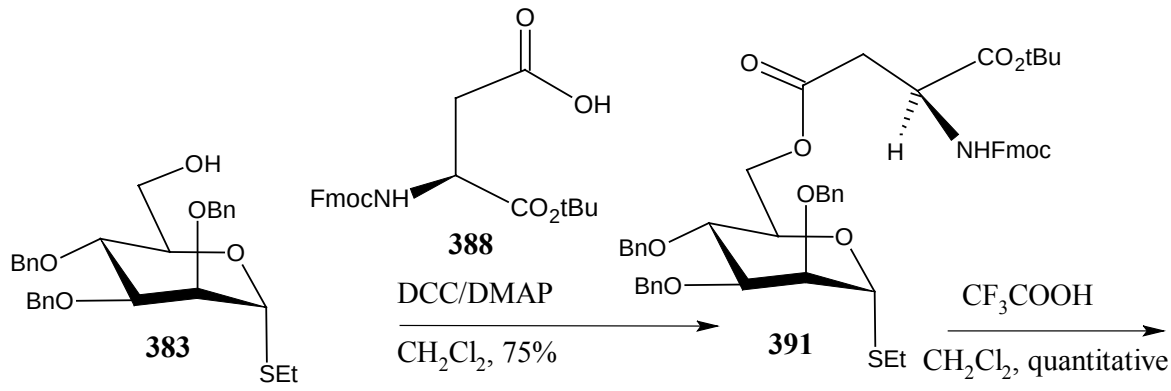


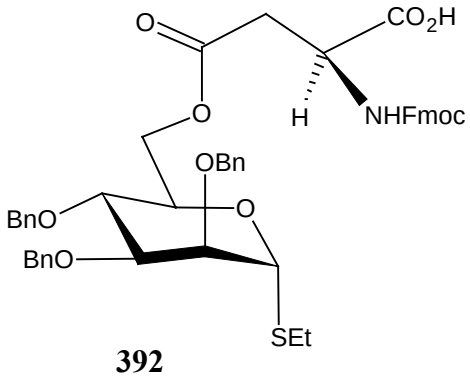
The acceptor was synthesized by tritylation of mannopyranoside **384** with trityl chloride, DMAP in pyridine at 75% yield of **385**, followed by para-methoxybenzylation reaction to a 76% yield of the para-methoxytribenzylated product **386.** Detritylation with acetic acid in etha nol furnished the 5-OH mannopyranoside product **387**. The next step was the peptide elaboration of donor **394** and acceptor **397**. Esterification reaction of acceptor **387** with the Fmoc protected aspartic amino acid **388** in the presence of DCC/DMAP in dichloromethane afforded 75 % yield of **389**. Deprotection of the para-methoxybenzyl group with cerium ammonium nitrate yielded

the triol mannopyranoside acceptor **390** at 80% yield. The donor mannopyranoside **383** was subjected to peptide elaboration by same reactions to the glycopeptide **391** and finally Boc-deprotection with trifluoroacetic acid furnished quantitative yield of the free carboxlic acid glycopeptide **392**. (Scheme **76**).

Scheme 76.







The aspartate liked mannosyl acceptor **392** was coupled to a serires of aminoacids. The peptide formation was achieved through two step coupling of **392**, this involves Fmoc group removal group removal of **390** with piperidine and subsequent EEDQ coupling with required Fmoc aminoacid. Once the desired intermediate amino acid has been added, the peptide sequence was completed by Fmoc deprotection and EEDQ mediated coupling to the aspatate -linked donor **392.** This allow constructions of peptide brigded disaccharides **394** and use for glycosylation reactions Glycosylation activated by NIS/ TfOH furnished the following anomeric outcomes **395 to 407** (**a to f**) in the yields described in (Scheme **77** , table **9.)**

Scheme 77.

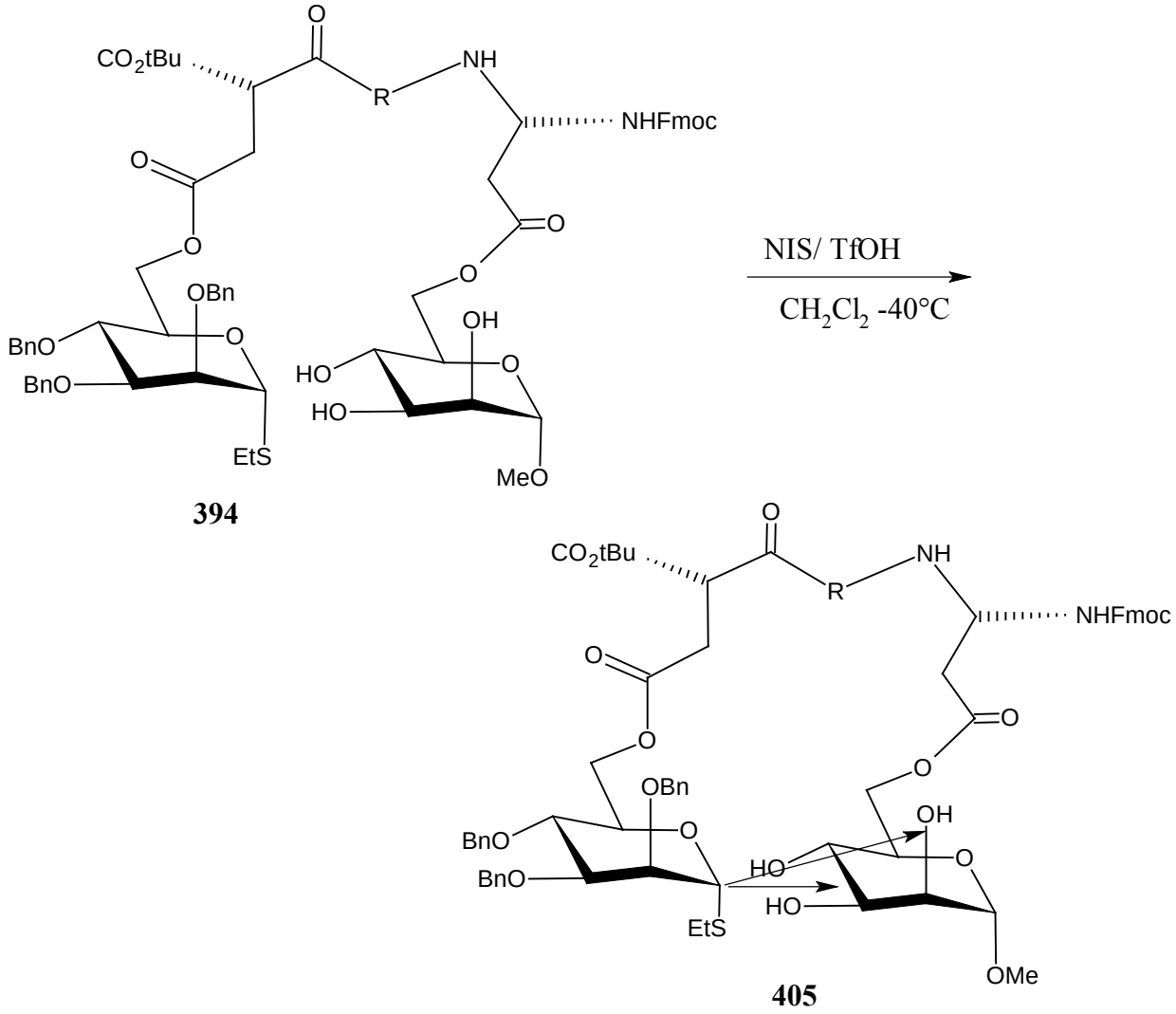

CO2tBu
O
R
NH
NHFmoc
O
O
O
O
OBn
BnO
O
BnO
EtS
OH
HO
O
HO
MeO
NIS/ TfOH
CH2Cl2 -40°C
394
CO2tBu
O
R
NH
NHFmoc
O
O
O
O
OBn
BnO
O
BnO
EtS
OH
HO
O
HO
OMe
405

Table 9.

Peptide	Total yield of Glycosylation reactions	Distribution and Yields of Major Products of Glycosylation	Yields of acetylated Disaccharides
a) Bu^t AspAspFmoc	59%	α(1-3) 11% ß(1-3) 23% ß(1-2) 13%	α(1-3) 60% ß(1-3) 78% ß(1-2) 54%
b) Bu^tAspGlyAspFmoc	41%	α(1-3) 21% ß(1-3) 20%	α(1-3) 58% ß(1-3) 77%
c) Bu^tAscpAlaAspFmoc	43%	α(1–3) 20% ß(1-3) 23%	α(1-3) 56% ß(1-3) 59%
d) Bu^tAspPheAspFmoc	44%	α(1-3) 13% ß(1-3) 18%	α(1-3) 58% ß(1-3) 71%
e) Bu^t AspAsnAspFmoc	43%	ß(1-3) 20%	ß(1-3) 63%
f) Bu^tAspProAspFmoc	49%	ß(1-2) 16% ß(1-3) 19% α(1-2) 14%	ß(1-2) 73% ß(1-3) 62% α(1-2) 79%

CHAPTER IV

INTRAMOLECULAR GLYCOSYLATION VIA

SUCCINYLAMIDE ALKYL SPACER

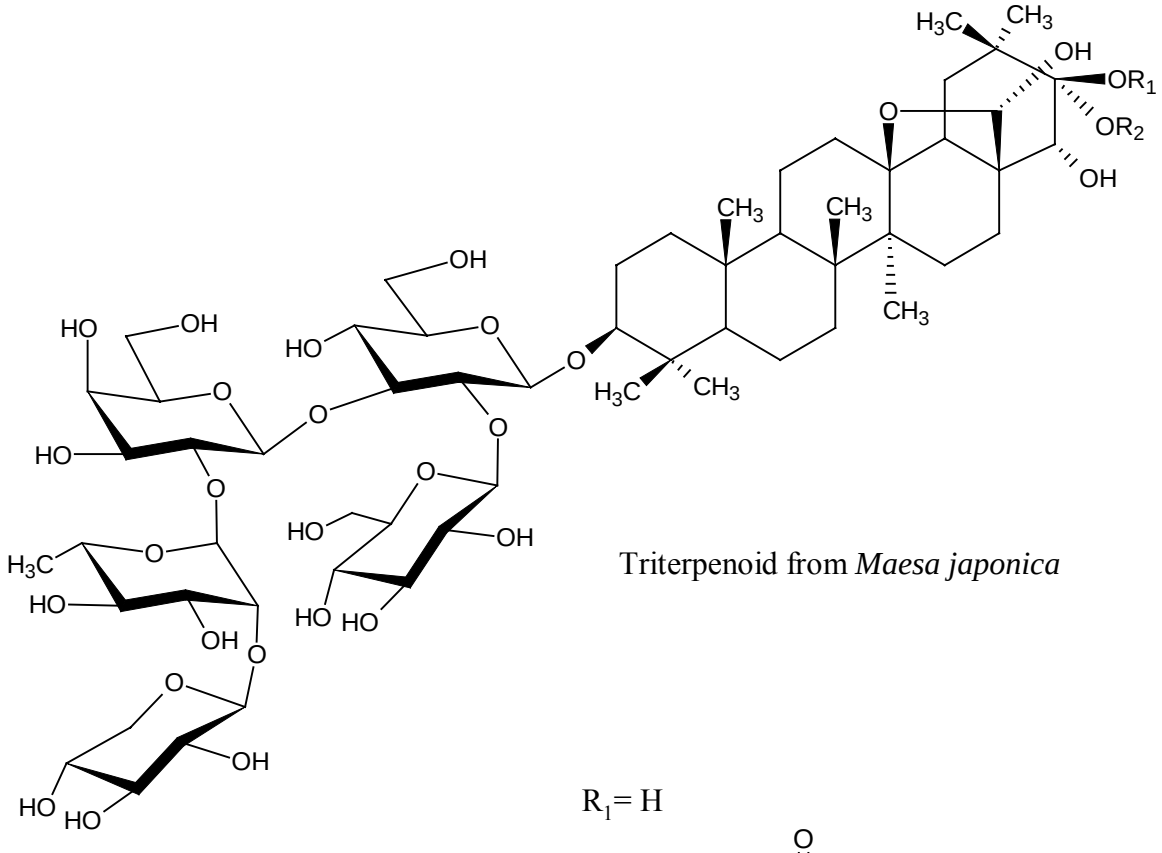
AND

MOLECULAR MODELLING

Considering the previously known intramolecular glycosylations methodologies reported, significant advances have been achieved in regio and stereoselective glycosylation. Among these are, the synthesis of ß-mannoside by Hindsgaul and Baresi, via the mixed isopropyldene acetal tethers. Ogawa and coworkers have elegantly developed the para- methoxybenzylacetal approach by using solid phase to synthesize tetrasaccharides involving the construction of ß-mannosides in high yield and in, regio-and stereoselectivity. Later Oscarson and Krog Jensen succesfully achieved the construction of one of the most difficult glycosydic linkage, ß- fructopyranoside via para-methoxybenzyl mixed acetal tether. Ziegler and coworkers have elegantly prepared ß-mannosides and ß-D Rham.(1-4) Gluc linkages by introducing the prearranged glycosides through succinyl and malonyl bridges in very high yield and exellent regio- and stereoselectiviy. Smith *et al.* designed the rigid spacer concept in creating close proximity through a xylene moiety thus, enforcing intramolecular glycosylation to obtain high anomeric outcome of ß or α glycosides.
As an additional approach, our objective is to add to these above mentioned efforts by endeavoring toward the formation of another important glycosidic linkage, the ß(1-3) by intramolecular glycosylation between donor and glucose acceptor.
The glycosidic bond ß(1-3) between galactose and glucose occurs frequently in some glyco conjugates such as Saponins[63] (see fig **10** next page). Saponins are glycosides found in many plants. Their name originated from the soapword " *'Saponaria*". These saponins consist of a saccharide or polysaccharide backbone linked to a polycyclic aglycon, either a choline steroid or a triterpenoid. Saponins have been used as sneezing powders and cough syrups to facilitate expectorations and as diuretics. Alfalfa saponins have the potential of reducing serum cholesterol in humans by preventing reabsorption after excretion in the bile. The ß(1-3) linkage of galaxies and glucose also occur in some Sialyl Lewis L^x [7,8,9] and in gangliosides[1,2], however between galactose and glucosamine, a derivative of glucose (see strucures in fig **2** and **4** pages 3 and 5). Therefore, the importance of this glycosidic bond type sparkled us to investigate a stereo- and regioselective synthesis. We have chosen to construct a succinylamidealkyl spacer, in which the amide moiety confer to the linker a certain flexibility that enhances its spacial conformation. Such a property exert an influence in the capacity of the succinylamidealkyl spacer to orient and prearange both the galactosyl donor and glucosyl acceptor in an ideal position in which one of the two free hydroxyl could undergo a discrimination such that only one of both is submitted to glycosylation. This can be termed a stereo and regioselective intramolecular glycosylation, since one position or region of the glucosyl acceptor is screened to engender a ß- glycosidic bond at position 3 preferentially to an α or ß at position 2.
In devising our synthetic strategy, we investigated the ideal functional group that could best enhance intramolecular glycosylation, that means the creation of a glycosyl donor containing the best suitable electron rich protecting group, and another glycosyl donor bearing a poorer electron

rich protecting group that also Among the diverse pool of electon donating groups chosen, the para-methoxybenzyl, and benzyl were presented as best candidates. The former is richer in electron due to the presence of methoxy groups which reveals that it is problematic because of its sensitivity to the glycosilation activator NIS (N-iodosuccinimide).

Fig10.



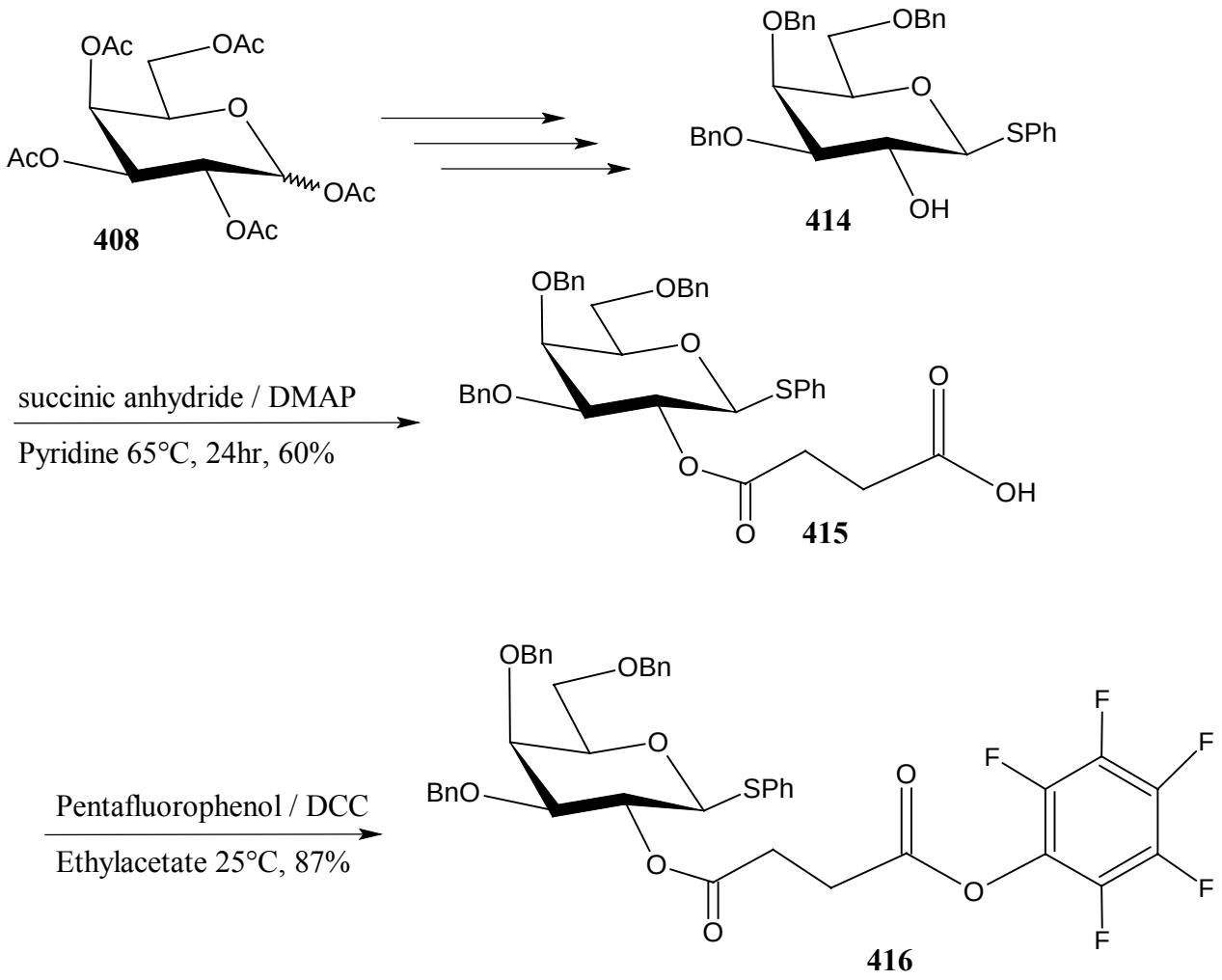
Triterpenoid from *Maesa japonica*

R_1= H

R_2=

During glycosylation the NIS causes the cleavage of the methoxy group on a sugar that bears para-methoxybenzyl group, and considerably decreases the yield of product. Contrarily, the benzyl group reveals complete inertness towards the NIS activator, therefore a much better choice. As main target, we opted to synthesize a phenyl-1-thio-3,4,6-tri-O-benzyl-ß-D- galactopyranosyl donor **415**. The starting material prior to this latter was a seven step synthesized phenyl-1-thio-3,4,6,-tri-*O*-benzyl-ß-D-galactopyranoside **414** which contained a free 2-OH group. Condensation of **414** with succinic anhydride, in the presence of a catalytical amount of DMAP, in acetonitrile at 65°C overnight, furnished 60% yield of the 2-*O*- succinylated ß-D-galactopyranoside **415**. Compound **415** was reacted with pentaflurophenol in the presence of DCC, in ethyl acetate at 0°C to yield 87 % of the 2-*O*- succinylated pentafluorophenol ester galactothioglycoside **416**. (See scheme **78**.)

Scheme 78.



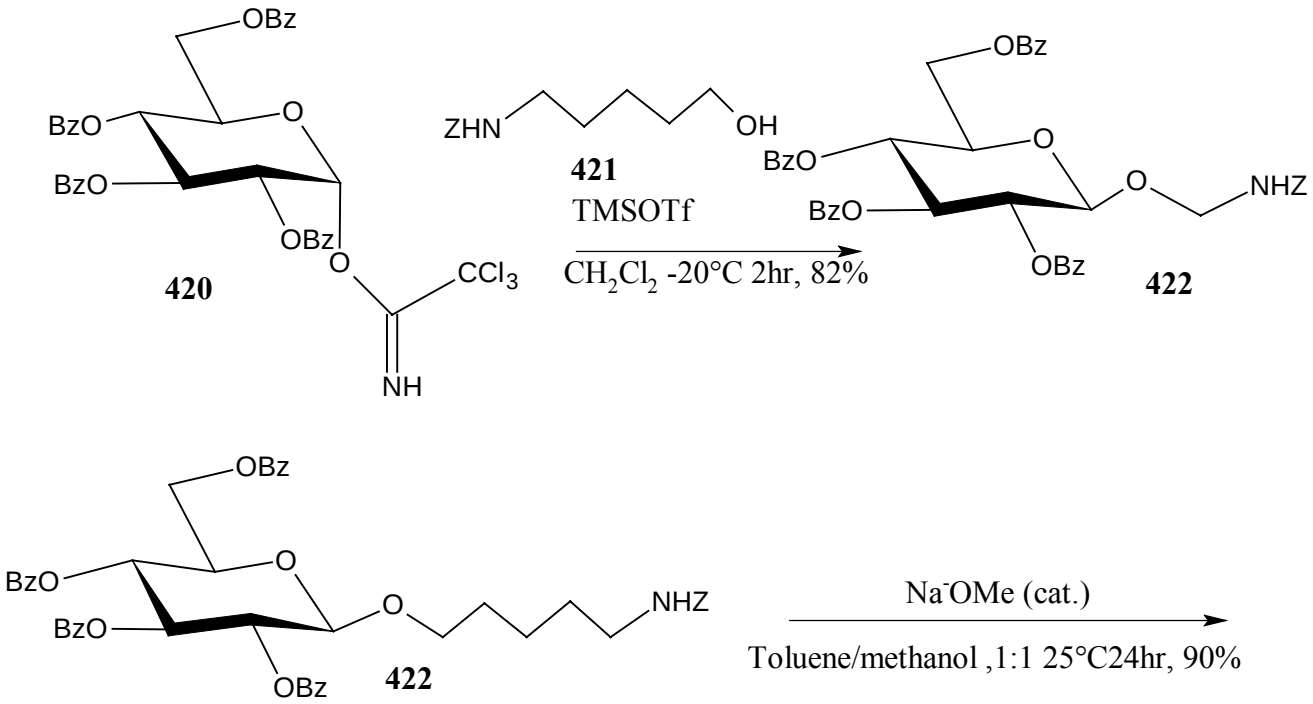
Our following goal was the synthesis of glucose aceptor that bears an aminopentyl spacer and a could enable a coupling reaction with the succinylated pentafluorophenol ester ß-D galacto-pyranosyl thioglycoside **416** towards the preparation of the succinylamidepentyl disaccharide. This required the glycosylation reaction between a glucose donor and Z-aminopentanol spacer. Among the possible glucose acceptor investigated were the tetraacetylated α-D-glucopyranosyl bromide, **438** a phenyl-1-thio-teraacetylated ß-D-glucopyranoside, and a tetrabenzoylated α,ß- D-glucopyranosylimidate **420**. The first consists of a glycosylation with Z-aminopentanol **421** by the Helferich reaction, that is the use of $Hg(CN)_2$, and $HgBr_2$ as catalyst in acetonitrile. However the prior synthesis of this compound effected in our group gave maximum 30% yield. The second option with the phenyl 1-thio-tetraaetylated ß-D-glucosyl with the same spacer In the presence of NIS, as activator and TMSOTf as catalyst, furnished 48% yielf of the desired glycosylated product. Both of these method were disregarded by us in favor of the tetrabenzoy-lated glucosyl imidate **417**. Glycosylation of the latter with Z-aminopentanol **421** using TMSOTf

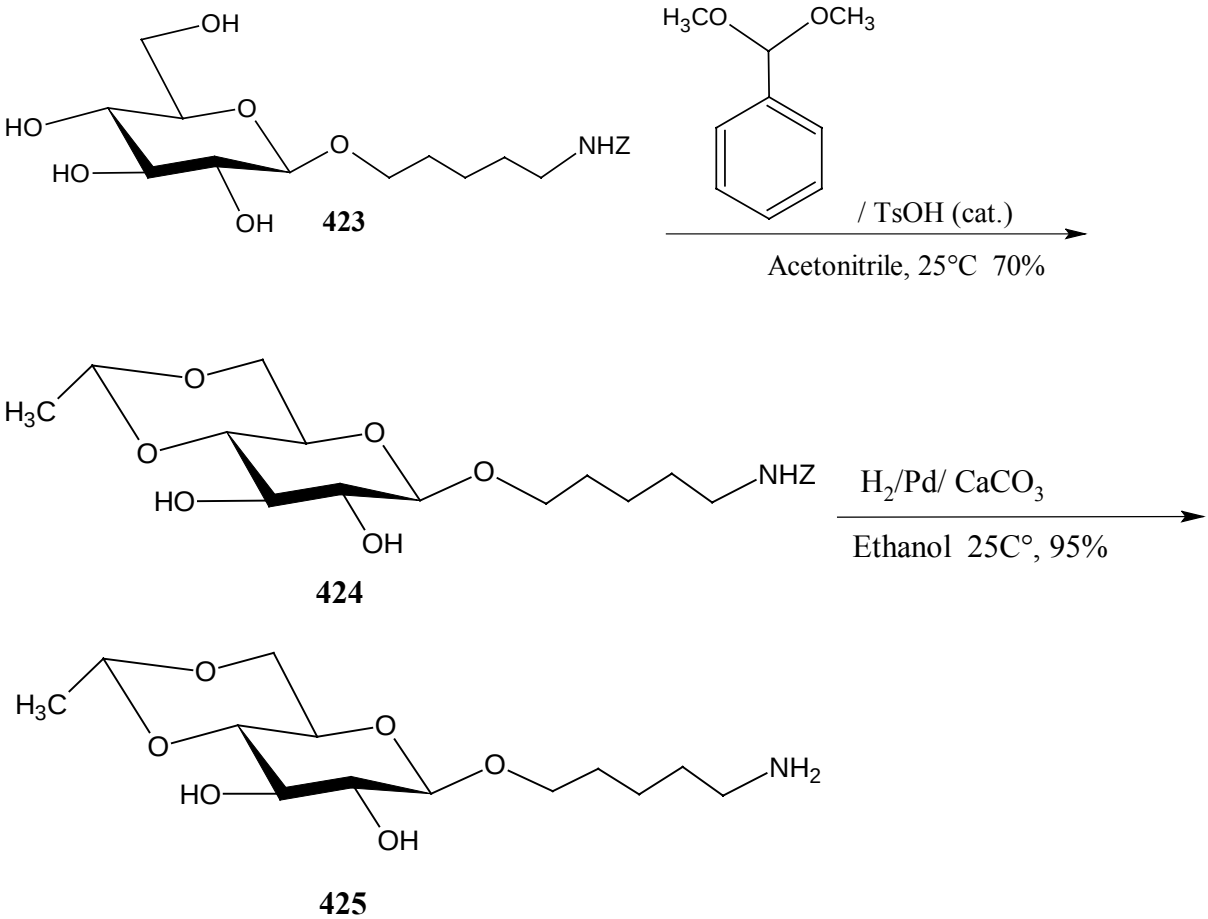
as catalyst, funished 82% of the desired Z-aminopentyl tetrabenzoylated ß-D glucoside **422**. Debenzoylation with the Zemplen reagent 1M NaOMe in methanol afforded 90% yield of the tetraol **423**. With the unprotected Z-aminopentyl- ß-D- glucopyranosyl **423** on hand, we set our aim in selecting a protecting group for the 4,6-O-position that would liberate the unprotected 2-OH and 3-OH on the acceptor. In the pool of available 4,6-O-protecting group we judged compatible to choose a benzylidene group because of its stability. As a second choice was the silyl group, however its lability in acidic and basic conditions became a drawback to its eventual utility.

Benzylidenation reaction of the glucosyl tetra - ol **423** with benzaldehyde dimethy acetal and a catalytic amount of TsOH in acetonitrile at room temperature yielded 70% of the 4,6-O-bezylidinated glucosyl acceptor **424** after recrystallisation.

Next came one of pivotal and delicate step, the generation of a free amine. We have herein two functional groups not necessarily orthogonal in many conditions, the benzylidene, and Z group. Both groups resist in basic conditions, but not in acidic medium. Moreover many hydrogenation catalyst result in their cleavage. Despite this puzzling challenge, hydrogenation offered more hope, due to the choices among catalysts. We engaged ourselves in opting for a hydrogenation in the presence of Lindlar's catalyst in ethanol for the *Z* group deprotection of **424**. After three to four hours time, TLC, revealed complete comsumption of starting material. The hydrogenation reaction furnished 90% yield of the product **425**. (Scheme **79**).

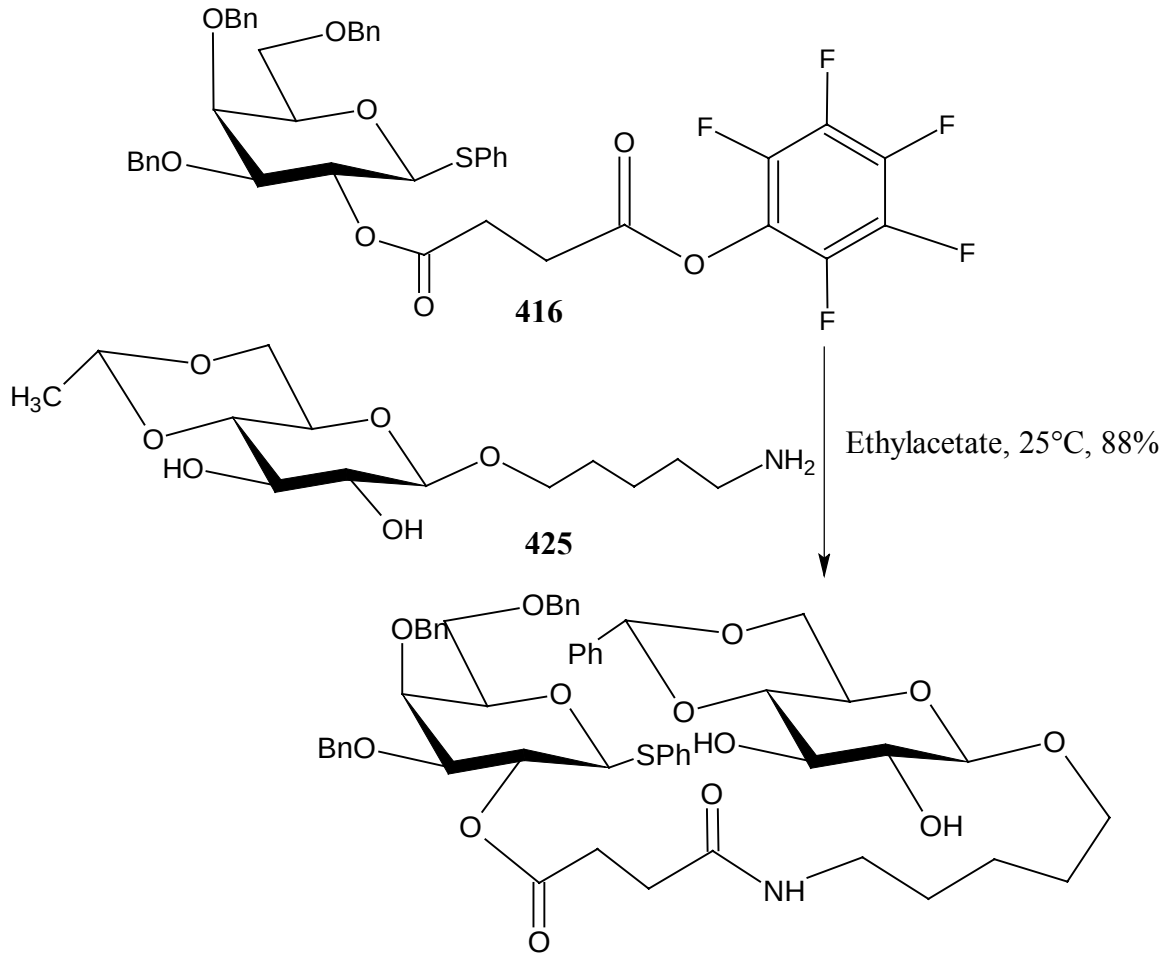
Scheme 79.





A small portion of the free amine **422** 2.08 mmol excess was directly subjected to coupling reaction with the succinilated pentafluorophenolester galactothioglycoside **416** . A direct NMR analysis by ^{13}C and ^{1}H showed formation of the amide moiety at 171. ppm for the former, and 5.8 ppm for proton NMR. In addition, the NMR study confirmed well the presence of the benzylidene group, at 101.ppm in the ^{13}C- NMR and 5.5 ppm in the ^{1}H-NMR, thus evidence of complete tolerance to hydrogenation with Lindlar's catalyst of product **422**. The amine **422** was obtained in 90% yield (Scheme **80**.) Coupling reaction with all the remaining galactose thioglycoside donor **416** and glusose acceptor **422** under the same conditions afforded 88% yield of the succinylamidepentyl disaccharide **423** after recrystal-lisation in acetone/hexane (1:3). This compound **423** presents an off white amorphous solid aspect. (Scheme **81.**) This compliments the reason of our choice for the succinylated pentafluorophenol ester tribenzylated ß-D-galactothioglycoside for the coupling reaction.

Scheme 80.



During the course of the reaction, we observed gradual precipitation of the tethered product, **426** which indicate the insolubility of this compound in ethyl acetate while the penta fluorophenol by product remained soluble in the solvent.

This occurence brought an advantage stemming from the fact that only an easy seperation by suction filtration of the insoluble tethered product was necessary from the filtrate containing pentafluorophenol by product, thus leaving only the desired product to recrystallise. In addition, the pentafluorophenol bearing five of the most electonegative element makes it an exellent leaving group when subjected to the amine's nucleophilic attack, therefore smoothly ejectable and giving easy formation of the amide. (See reaction scheme in fig. **80**).

This coupled reaction engendered a succinylamide pentyl disaccharide **426** with the glucose acceptor protected at position 4,6-*O*- with a free 3-OH, and 2-OH to be subjected to intramolecular glycosylation to examine which of the two will be discriminated and the one undergoing glycosylation. Previously mindful of the insolubility of this compound in ethylacetate,we set to carry out a solubility assay of this compound. Our observation confirmed its insolubility in

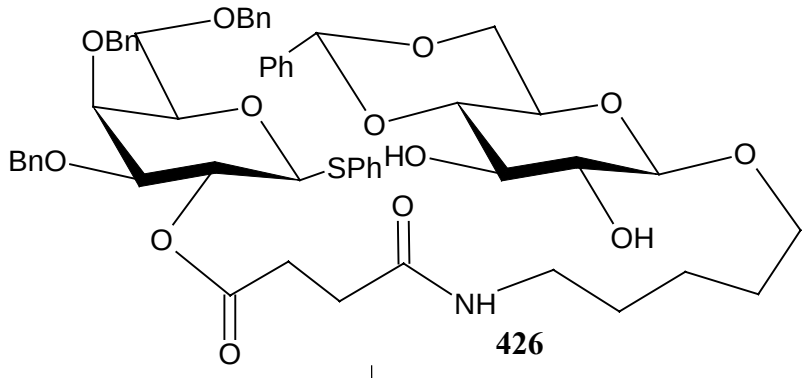
glycosylation solvents such as diethyl ether, toluene ,cold acetonitrile, a challenging task as to an eventual glycosylation reaction.Gratifyingly, dichloromethane and a mixture of dichloromethane:acetonitrile (1:1) at 25°C and a low temperature until -10°C alleviated our concern in completely solubilising the tethered disaccharide.

With a portion of the tethered product **426** , we embarked on the pivotal step of intramolecular glycosylation in a solvent mixture of dichloromethane/acetonitrile (1:1), with NIS as activator, TMSOTf as catalyst at a temperature range -5°C to 5°C for thirty to forty minutes . Monitoring the reaction by TLC, confirmed complete disappearance of starting material Chromatography of the crude product mixture with an eluent system toluene/acetone 4:1 for the isomer's seperation resulted in a low 20% overall yield due to the crytallisation of these product on the column. Another intramolecular glycosylation reaction was carried out with a more subtantial portion of the linked disaccharide in the same conditions and solvent mixture dichloromethane:acetonitrile 1:1. Verification by TLC revealed complete consumption of starting material . After conducting a thorough solubility assay for the crude product, to our delight the eluent mixture of dichloromethane/ acetone 6:1 completly showed completely dissolved this latter. In addition a TLC in this solvent mixture showed an ideal Rf for the seperation of the isomers. Indeed, the chromatography of the crude product with this eluent was very successful, allowing a smooth seperation of the isomers, and furnishing a 56% overall yield, that is 50% of the main fraction **427** and 6% of the the minor product **428**. Enthusiastically, we pursued an intensive NMR study with ^{1}H-NMR, ^{13}C-NMR, and 2D-NMR. The ^{13}C-NMR analysis confirmed intramolecular glycosylation for the first and main fraction, with 103.17 ppm for (C-1) galactose and 103.03 ppm for (C-1) glucose. Focusing on which hydroxyl 2-OH or 3-OH was subjected to glycosylation, that is the regio and stereoselectivity of the glycosylation reaction, we conducted for the main fraction **424** a 2-D NMR analysis with the help of High Molecular Bond Correlation (HMBC), C-H coupling ^{2}J to ^{5}J. Gratifyingly, the analysis confirmed a direct correlation between (H-1) galactose 4.61 ppm with (C-3) glucose 82.90 ppm, indicating that the 3-OH glucose was favored for glycosylation with glucose and 2-OH glucose discriminated. Concerning the minor product **425**, ^{13}C-NMR also showed intramolecular glycosylation with (C-1) galactose of 96.55 ppm that is an α glycosidic bond , and 101.79 ppm for (C-1) of the glucose acceptor. The conducted 2D -NMR analysis with HMBC revealed a direct ^{3}J correlation between (H-1) gal, 5.07 ppm with (C-3) gluc, 77.69 ppm, thus an α (1-3) glycosidic bond. The observation of a complete discrimination against the 2-OH and a real selectivity for the 3-OH of the glucose acceptor toward its glycosylation with galactose donor, thus forming the cyclic disaccharide was very interesting and surprising.

For the observed selectivity, we suggest that the succinylamidepentyl spacer enabled the

orientation and prearrangement of both sugars such as to enforce glycosylation stereo and regioseletively. (Reaction depicted below in scheme **81**).

Scheme 81.

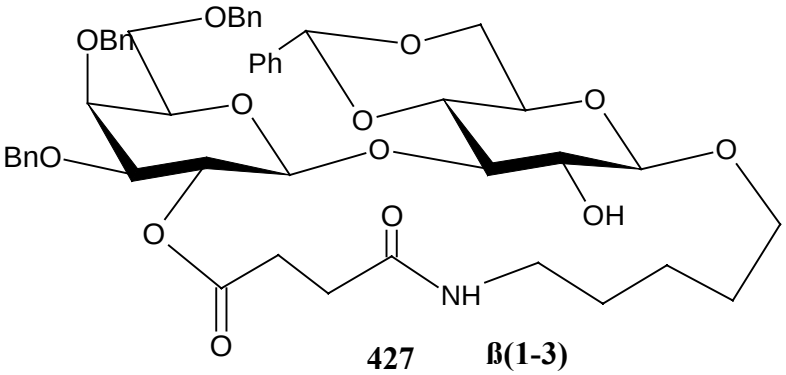


426

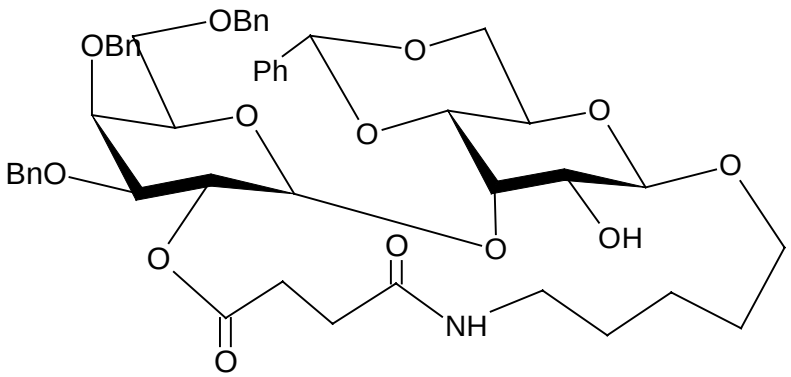
NIS/ TMSOTf

CH_2Cl_2/ CH_3CN

-5°C -0°C, 56%



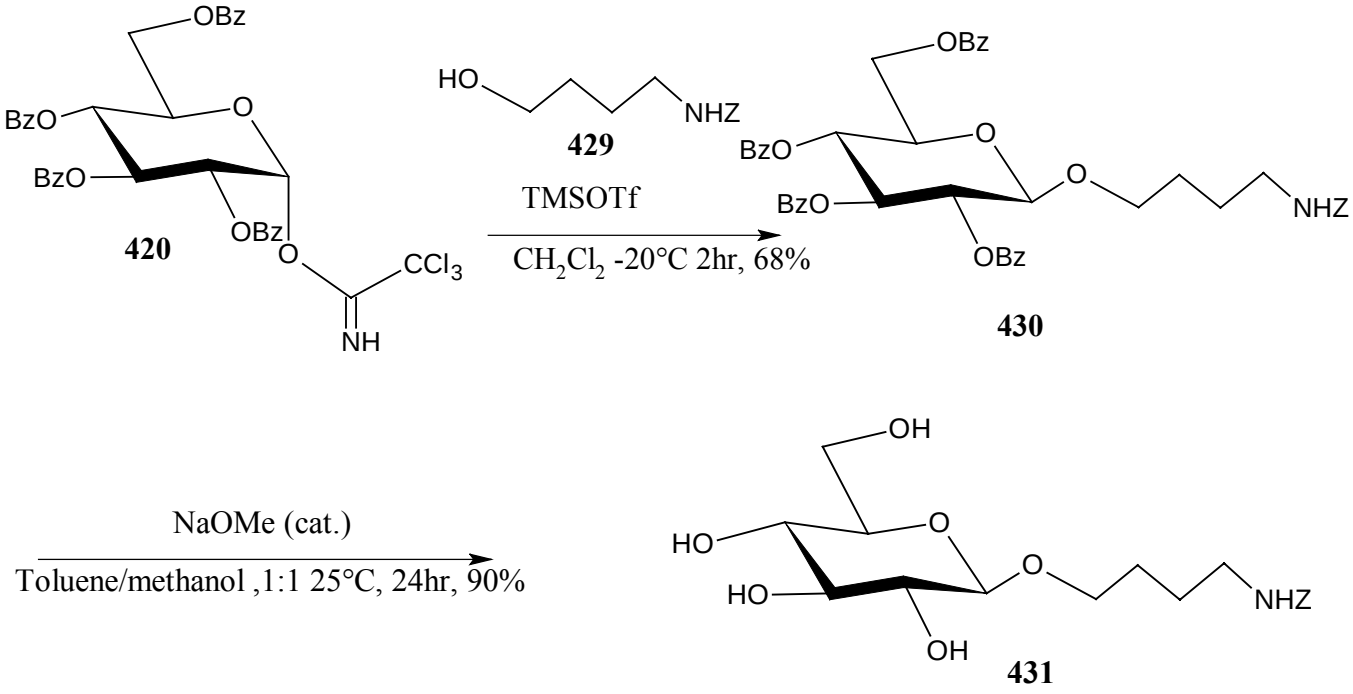
427 **ß(1-3)**

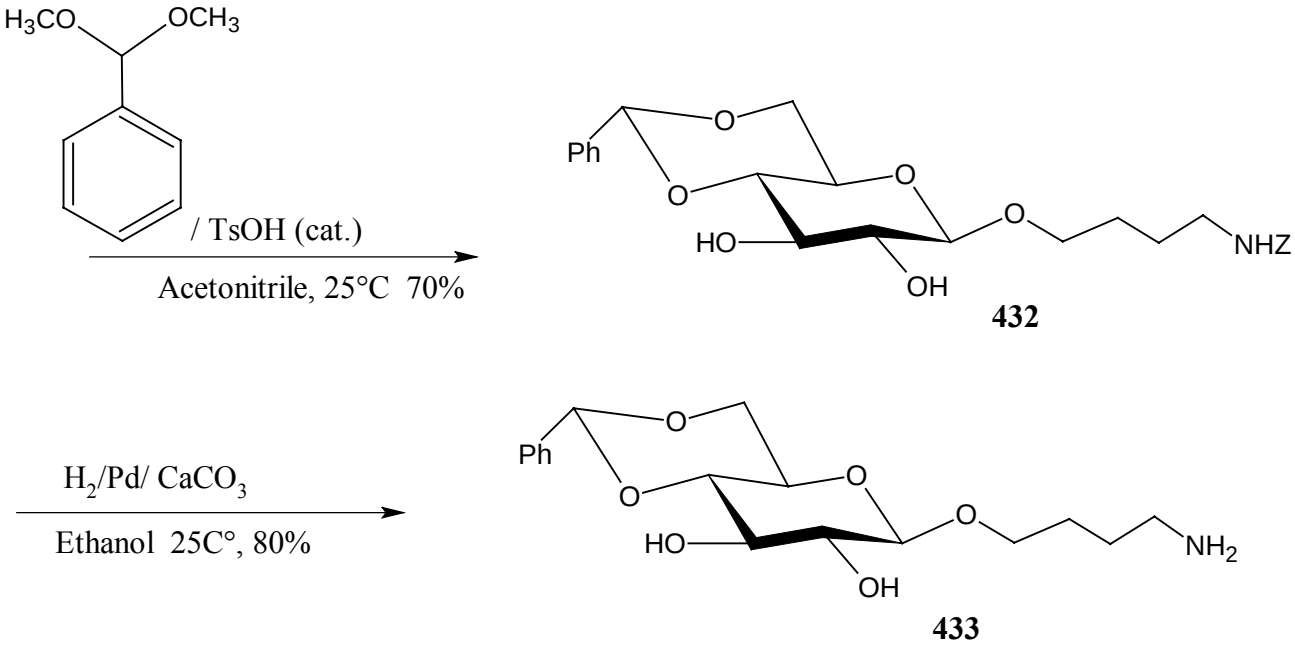


428 **α (1-3)**

The importance of this result motivate us to focus our observation with a gradually more constrained spacer and test if the intramolecular glycosylation would result a different outcome. We strived toward the synthesis of a new glucose acceptor that bears a shorter spacer, a *Z*-aminobutanol **429**. Mindfull of the previous good yield results with the tetrabenzoyl α/ß-D-glucopyranosylimidate **420** , we proceeded to a glycosylation reaction with *Z*-aminobutanol **429** in dry dichloromethane, at -20°C, with TMSOTf catalyst. A satisfactory 68% yield of a clear oily product was **430** obtained from this reaction Analysis from NMR and confirmed formation of the ß anomer at 101.34 ppm for ^{13} C-NMR and 4.78 ppm the well apparent doublet at 4.78-4.80 ppm for proton NMR. Debenzoylation with the Zemplen reagent 1M MeONa, in touene/ methanol 1:1 afforded 90% yield of the deprotected *Z*-aminobutyl ß-D-glucopyranoside **431**. Benzylenidation reaction of **431** , with benzaldehyde dimethyl acetal, and a catalytical amount of TsOH, furnished 66% yield of the desired product **432** after direct recrytallisation. Confident of our previous success for the *Z*-group deprotection we proceeded with the same hydrodenation reaction with Lindlar's catalyst which smoothly furnished 80% of the free amine **433**. (See scheme **82**).

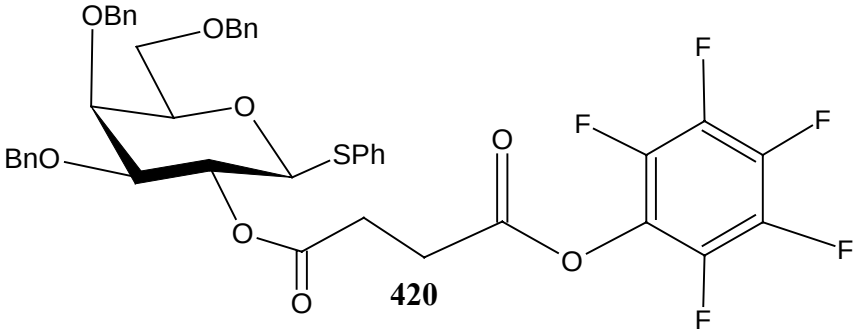
Scheme 82.



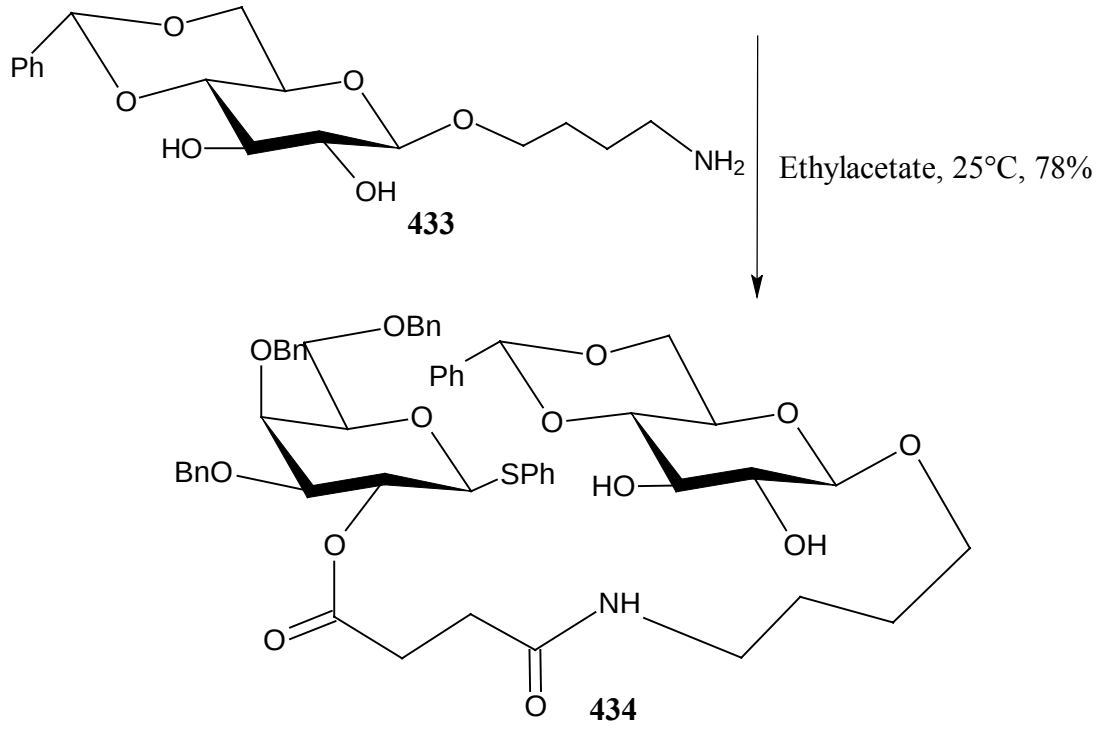


The free aminobutyl 4,6-O- benzylidinated ß-D- glucosyl **430** underwent direct coupling reaction with the pentafluorophenoleste tribenzylated ß-D- galactothioglycoside **416** in ethyl acetate at 25°C to give 78% yield of the tethered disaccharide **431**. Noteworthy to observe during the course of this coupling reaction, was the same insolulibility behavior diplayed by this tethered compound through it's gradual precipitation in ethyl acetate. Filtration by suction allowed seperation of the tethered disaccharide from the pentafluorophenol by product soluble in the solvent filtrate, thus bringing the evidence of the elegance and simplicity of the choice of this coupling method. The bridged disaccharide presented an aspect of an off-white amorphous solid easily recrystallised with aceton/hexane 1:3. The formation of amide and presence of the benzylidene group was well confirmed by NMR with 6.07-6.04 ppm in ^{1}H, 171.71 ppm in ^{13}C spectra for the former and, 5.47 ppm , 101.80 ppm for the latter.(See reaction scheme **83**).

Scheme 83.



420



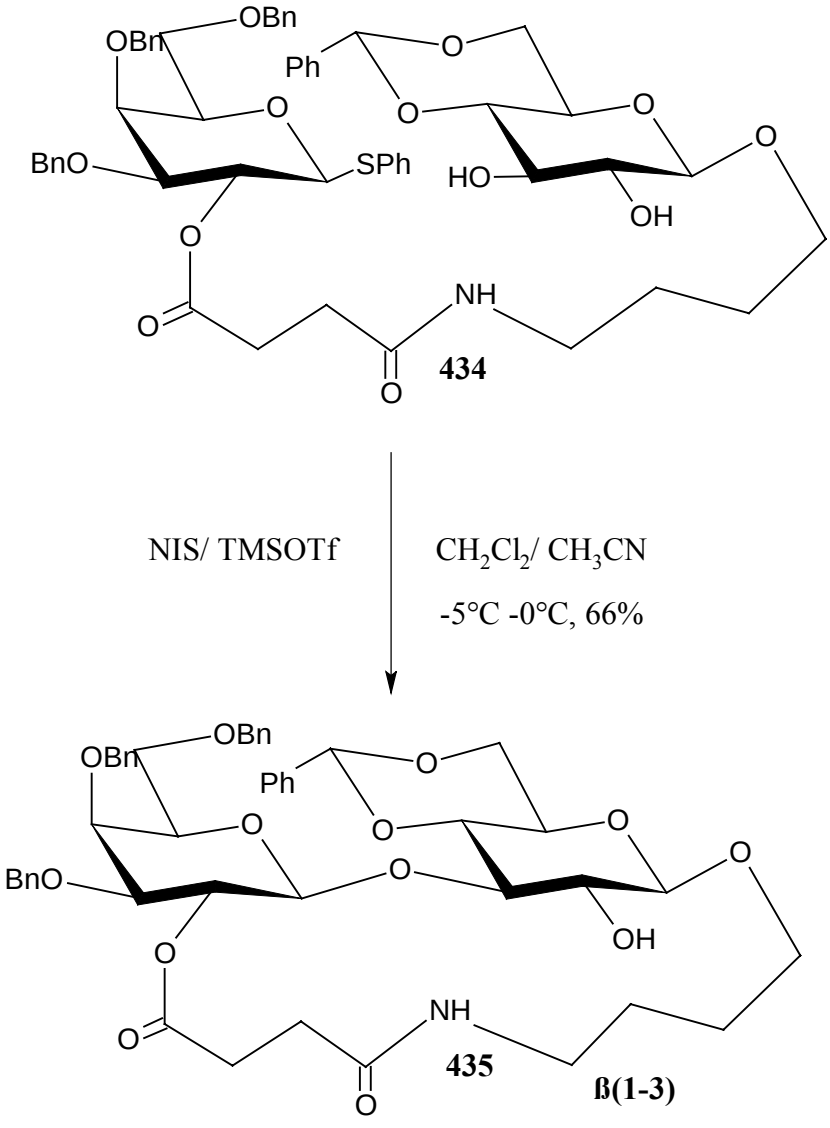
Intramolecular glycosylation of (432)

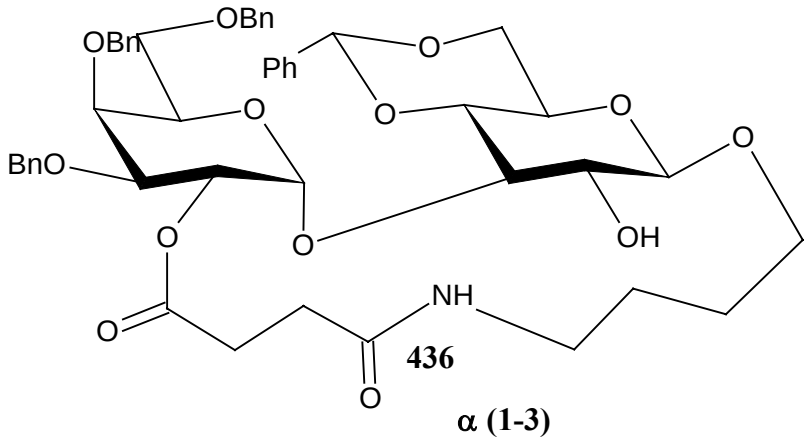
Based on solubility experience with the previous tethered disccharide **423**, compound **431** was subjected to a careful solubility test results showed the same behavior of this product as the first former as to its insolubility in glycosylation solvents, diethyl ether, toluene,cold acetonitrile. To our satisfaction, full solubility occured in dichloromethane, nomal to cold tenperature, and in a mixture dichloromethane: acetonitrile 1:1 from 25°C to -10°C.
Consequently the solvent mixture dichloromethane: acetonitrile became as in the first attempt the best candidate for glycosylation reaction. This succinylamidebutyl bridged disaccharide **434** underwent intramolecular glycosylation in this solvent mixture from 0°- to -5°C, activated by NIS and using TMSOTf as catalyst. The reaction was followed by TLC which revealed complete consumption of starting material after 30 to 40 minutes time. We then faced the additional challenge of finding an eluent that both can dissolve the crude product mixture and allow an easy seperation of isomers wizh a reasonable R_f. Gratifyingly, the solvent system dichloromethane:acetone: toluene 4:1:1 accomplished this task. Chromatography of the crude product in this eluent mixture smoothly allowed the easy seperation of both isomers, and the obtention of 66% overall yield of **435** and **436**. Intramolecular glycosylation was confirmed from carbon and proton NMR, with values of 102.85 (C-1) galacose 4.75-

4.73 ppm for ^{1}H-NMR, 102.71 (C-1) glucose, 4.60 ppm ^{1}H thus a ß anomer for the main fraction **435**. Concerning the minor fraction **436**, the values of 94.68 ppm (C-1) galactose, 5.72-5.71 ppm (H-1) galactose confirmed α anomer.We conducted a further 2D-NMR with HMBC which gave a direct correlation ^{3}J between (C-1) gal,102.77 ppm and (H-3) gluc 3.73 ppm and (H-1) gal 4.75 ppm with (C-3) gluc., 82.62 ppm, which showed a ß(1-3) anomeric outcome for the major fraction **435**. Investigation by HMBC for the minor product **436** confirmed direct correlation between (C-1) gal, 94.71 ppm with (H-3) gluc.3.60 ppm, therefore an α(1-3) glycosydic linkage.

The intramolecular glycosylation of the succinylamide butyl tethered disaccharide afforded 58% yield of ß (1-3) as predominant product **422** and 8% yield of α (1-3) as minor product **423** , thus a ß/α ratio of 7:1. (See scheme **84**).

Scheme 84.





436

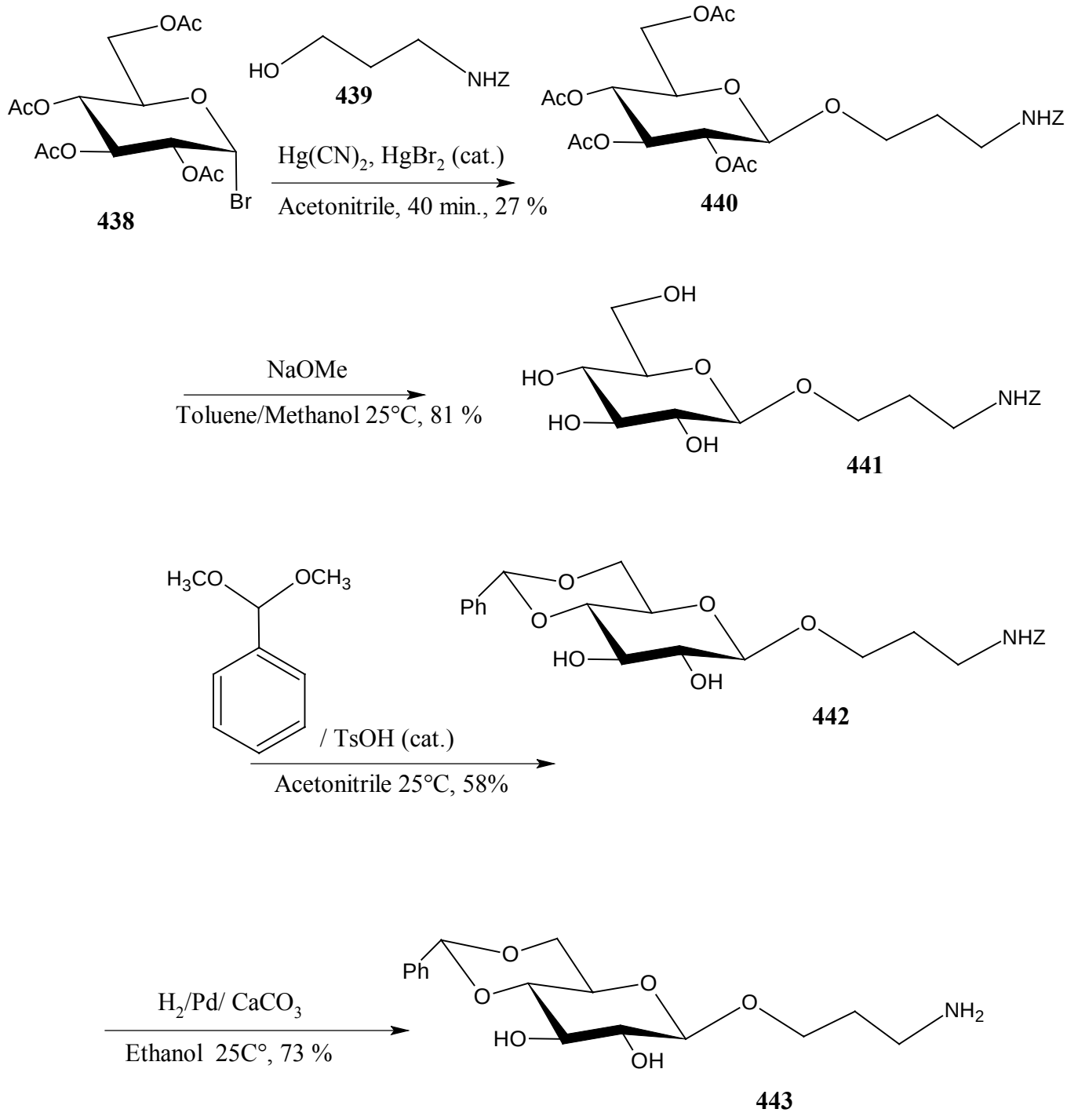
α (1-3)

These promising results prompted our motivation to further constrain the tether,and led to the following questions; can a satisfying glycosylation reaction yield of ß(1-3) be achievable with a succinylamide propyl disaccharide? Additionally, can an anomeric outcome result where only the 2-OH of the glucose acceptor becomes glycosylated? We adventured toward the objective to perform another intramocular glycosylation with an even constrained spacer by choosing *Z*-aminopropanol. The first task was to devise a glycosylation between a glucose donor and *Z*-aminopropanol . Scanning the possible choices of glucose donors, we opted to use the same tetrabenzoylated α,ß-D-glucopyranosylimidate **420**. Glycosylation with *Z*-aminopropanol **439** in dry dichlioromethane with TMSOTf catalyst gave no product but instead, rearrangement of the imidate. This stems from the fact that the proximity of the NHZ and OH group in the Z-aminopropanol structure engender hydrogen bonding beween these two group, thus a nucleophilicity decrease in reactivity toward activation of the imidate. Glycosylation with a tetraacetylared ß-D-glucopyranosyl thioglycoside and Z-aminopropanol with NIS and TMSOTf would also fail to furnish a desired product due to the same explained above occurence. We than centered our attention on the Helferich reaction by glycosylating tetraacetylated α-D-glucopyranosylbromide **438** with Z-aminopropanol **439** in the presence of $Hg(CN)_2$, and $HgBr_2$ as catalyst which afforded 27% yield of a clear oily product **440**. An investigation using ^{13}C and ^{1}H-NMR revealed the presence of a ß-D- glycosydic linkage with 100.61 ppm (C-1) for the former and 4.51-4.49 ppm the doublet for the glycosyl proton.

Despite this modest yield, we were just satisfied with at least having the Z-aminopropyl tetra-O-acetylated ß-D-glucopyranosy **440** on hand. Deacetylation reaction in basic conditions with 1 M sodium methanolate in toluene/methanol 1:1 gave 81% yield the tetraol **441** which was imme diately submitted to benzylidenation reaction with benzaldehydedimethylacetal and using p-TsOH as catalyst in acetonitrile 25°C to afford 58% yield of the benzylidinated product **442**.

Confident on the feasibility of the Z-group deprotection through hydrogenation with Lindlar's catalyst, this effected reaction successfully furnished 73% of the free amine **443**. (Reaction scheme **85**).

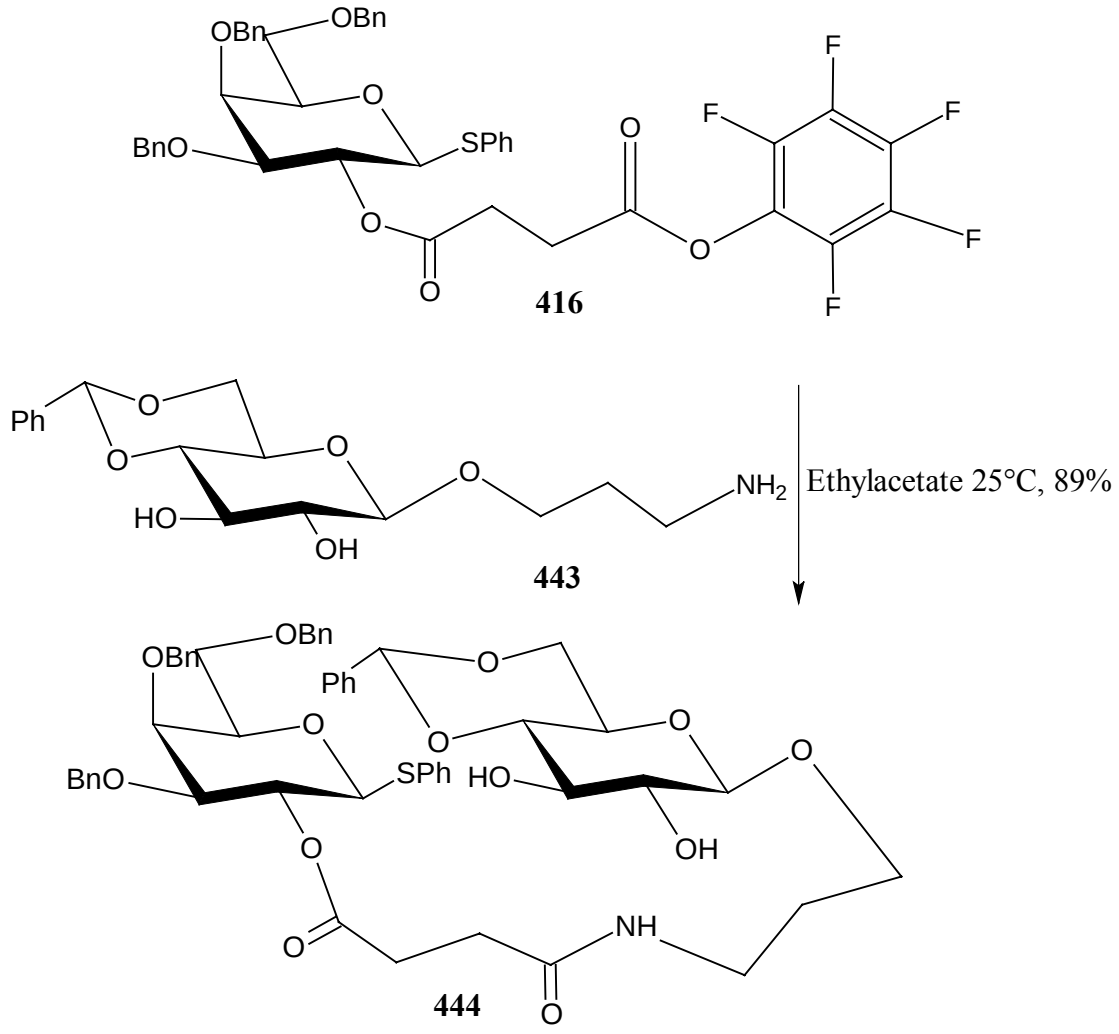
Scheme 85.



COUPLING REACTION

With the free amine **443** we embarked on the coupling reaction as previously with the succinylated pentafluorophenol ester tribenzylated ß-galactothioglycoside **416** in ethyl acetate at 25°C, to obtain 89% of the succinylamide propyl tethered disaccharide **444**. As previously the biged disaccharide precipitate gradually until end of the reaction. Its insolubility in ethyl acetate allowed easy separation from the pentafluorophenol by product though suction filtration. Investigation through NMR revealed the presence of amide formation with peak values of 171.78 ppm for ^{13} C and a broad singlet at 6.35 ppm for ^{1}H-NMR for this tethered white amorphous disaccharide. (See below reaction scheme **86**).

Scheme 86.



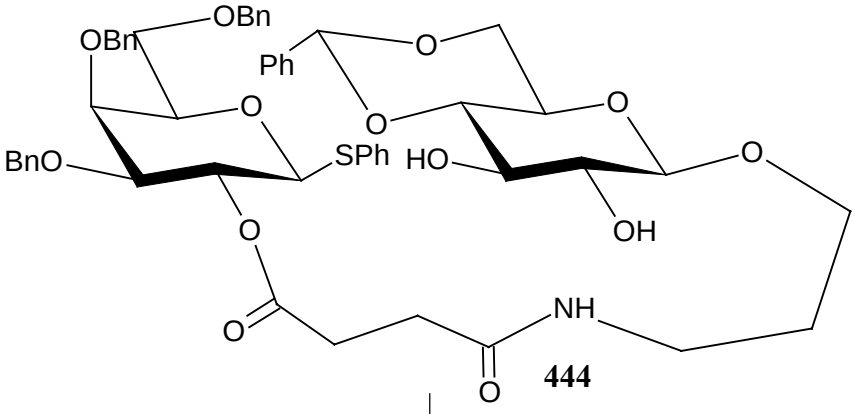
Intramolecular Glycosylation

After satisfactory obtention of the succinylamidepropyl tethered disaccharide **444**, came the final endeavor, the intramolecular glycosylation. A systematic solubility assay of the bridged disaccharide in several solvents, revealed again full dissolution of this compound in a cold mixture of dichloromethane/acetonitrile 1:1 from 25°C to -10°C. Intramamolcular glycosylation activated by NIS, TMSOTf as catalyst in the same solvent mixture at -5 to 5°C afforded 73% overall yield, with TLC showing complete dissappearance of starting material. The crude product mixture posed the same irritating insolubility challenge to overcome as to an eventual chromatographic seperation of the isomers. A recourse to an eluent system mixture predominantly dichloromethane that is CH_2Cl_2/acetone/toluene 4:1:0.5, fully solubilized the crude product and presented on TLC a reasonable Rf for the seperation of the isomers.

The chromatographic seperation of the isomers yielded 57% of the main fraction **445** and 15.61% of an unseperable mixture **446** but predominantly the second isomer.

A detailed NMR study of the main fraction ^{1}H and ^{13}C- NMR confirmed intramolecular glycosylation with the peak of 102.73 ppm (C-1)galactose, 102.19 ppm (C-1)gluc in ^{13}C-NMR spectra, and 4.74-4.72 ppm, a doublet (H-1) for galactose, 4.59-4.57 ppm (H-1) for glucose in the ^{1}H-NMR spectra. To detect which hydroxyl 3-OH, or 2-OH glycosylised with the galactose donor, a further analysis with 2D-NMR, HMBC, became of all importance. Astoundingly, we could draw a direct ^{3}J C-H correlation between C-3 glucose 82.30 ppm and (H-1) galactose 4.74 ppm, thus a ß(1-3) glycosidic bond for the main fraction **445**. For the minor product **446** we were able to draw a direct correlation between (C-1) glucose 95.45 ppm, and (H-3) glucose 3.56 ppm thus an α (1-3) glycosidic linkage. Moreover there is a correlation between the (H-3) glucose 3.56 ppm and the (C-1) galactose 103.70 ppm, thus a mixture of α(1-3) and ß(1-3) anomeric outcome as by product. This provided a direct response to our question and revealed complete choice for 3-OH toward glycosylation with the galaxies donor part, and full discrimination against the 2-OH glucose. The anomeric ratio outcome was ß/α 4:1. (See reaction scheme **87**).

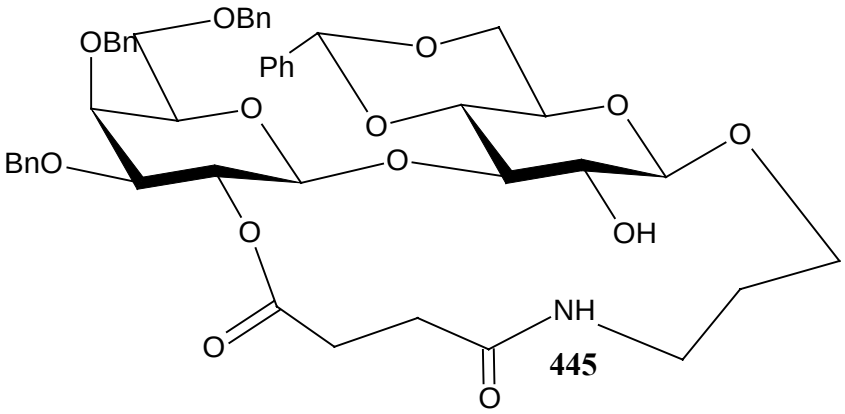
Scheme 87.



444

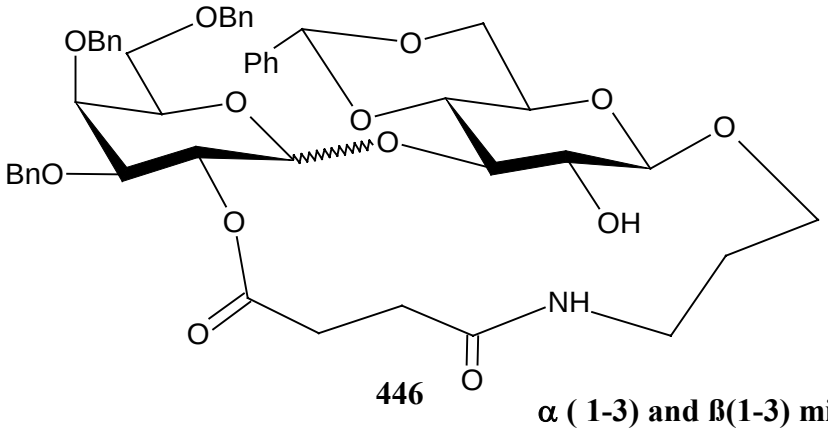
NIS/ TMSOTf CH_2Cl_2/ CH_3CN

-5°C -0°C, 73%



445

ß (1-3)



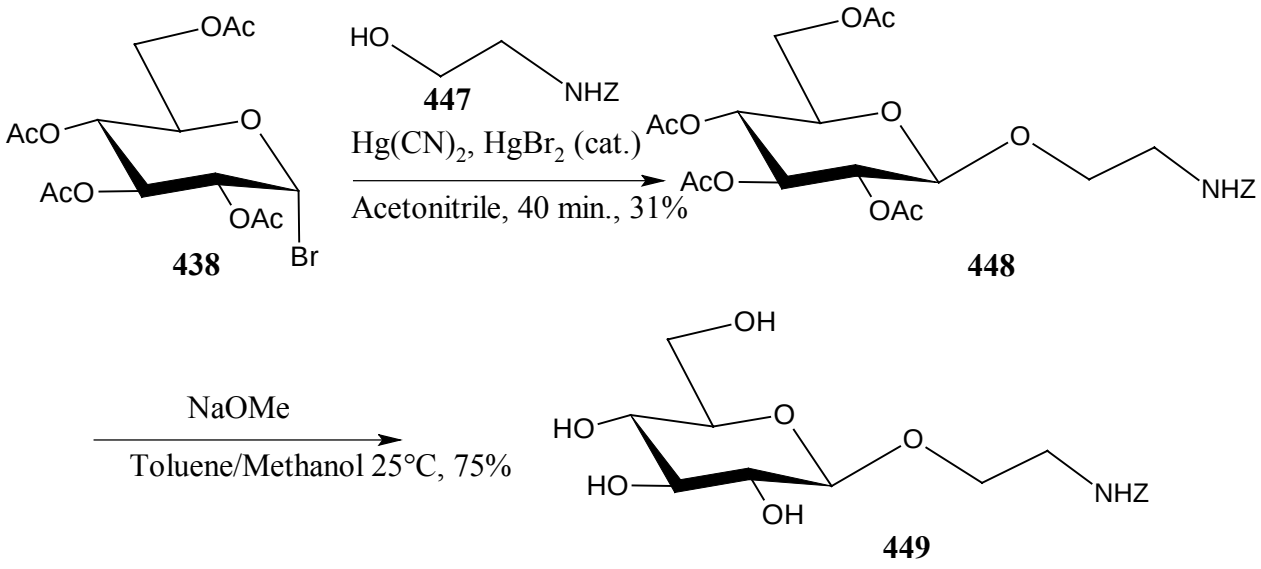
446

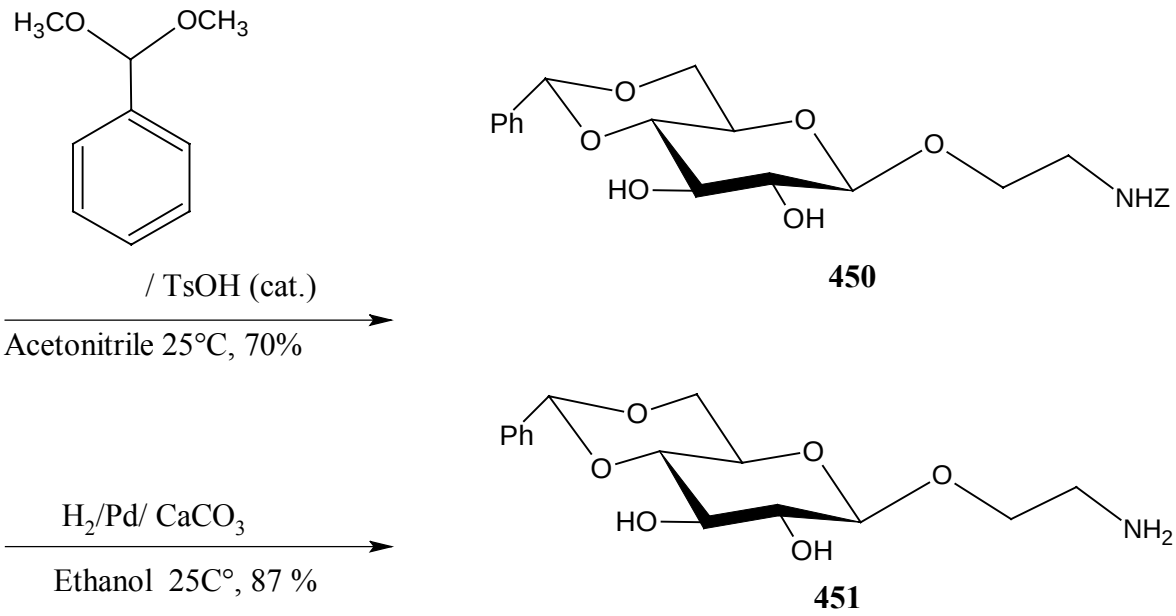
α (1-3) and ß(1-3) mixture

Case of the ethyl spacer

Mindful of the previous astounding result, we focused our attention on the smallest spacer with the idea of detecting a predominant 2-OH glycosylation. We then set for the synthesis of a *Z*-aminoethyl ß-D-glucopyranosyl acceptor. In reasoning about the non-ocurence of the glycosylated product formation between the tetrabenzoylated glucoimidate and the *Z*-aminopropanol due to hydrogen bonding between the NHZ and OH that decrease its nucleophilicity and reactivity, we had anticipated the same problematic behavior with *Z*-aminoethanol **447**, and omitted this reaction. We proceeded directly through a glycosylation reaction between the tetraacetylated α-D-glucopyranosyl bromide **438** with $Hg(CN)_2$ and $Hg(Br)_2$ as a catalyst in acetonitrile 25°C which successfully furnished 31% of the ß-D-glucopyranosyl acceptor **448** as a clear oil product after chromatography. Investigation through ^{13}C and ^{1}H-NMR gave evidence of the ß glycosydic bond formation with 101.04 ppm (C-1) and doublet at 4.49-4.57 ppm for (H-1). Deacetylation with 1M NaOMe in methanol/toluene 1:1 afforded 75% of the unprotected glucosyl **449**, which was directly reacted with benzaldehyde dimethyl acetal and TsOH as catalyst yielded the desired benzylidenated product **450**. Selective Z-deprotection through hydrogenation reaction afforded 83% yield of the free amine **451**. **(**Scheme **88**).

Scheme 88.

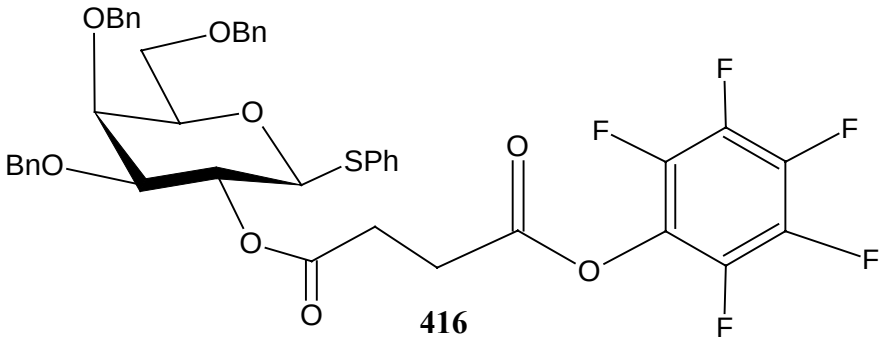




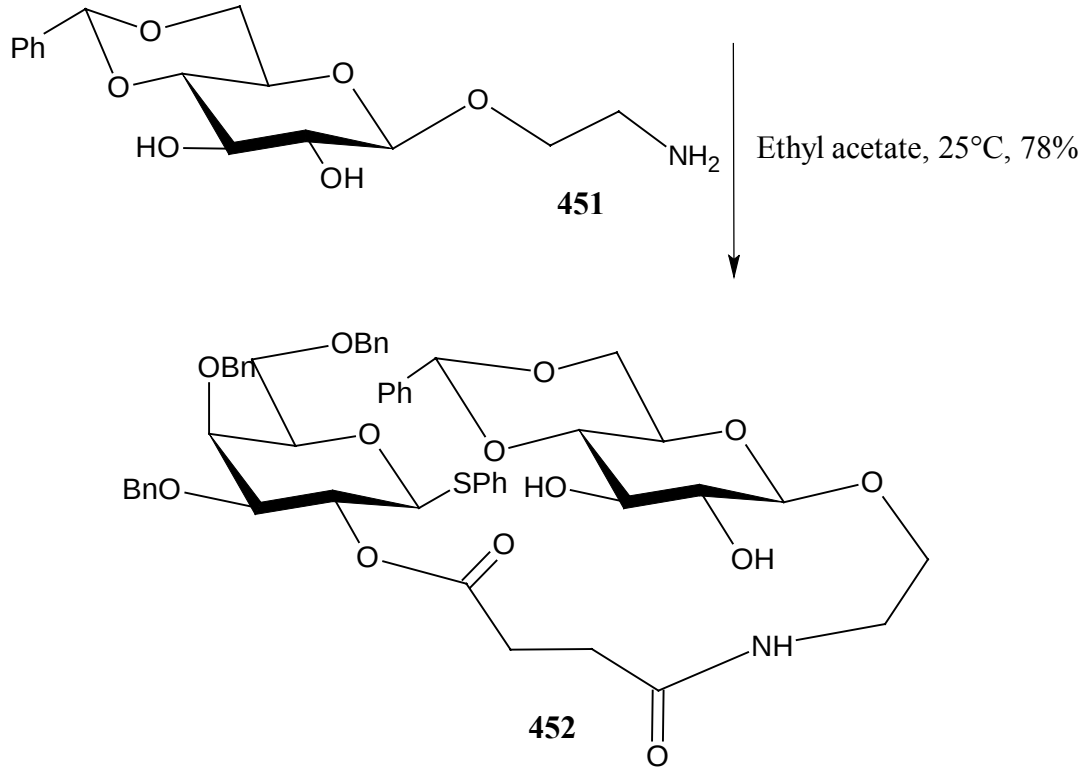
Coupling Reaction

We proceeded directly toward the coupling reaction of the aminoethyl 4,6-O-benzylidene ß-D-glucosyl **451** with the galactosylthioglycoside pentafluorophenol ester **416** in ethyl acetate at 25°C. We observed gradual precipitation of the tethered product during the reaction's course. Separation of the insoluble bridged disaccharide from pentafluorophenol by product through suction filtration and recrystallisation with acetone-hexane yielded 83% of the succinylamide ethyl disaccharide **452** as a white amorphous solid. A ^{13}C- NMR analysis showed the presence of amide and benzylidene group at values of 171.87 ppm for the amide and 101.85 for the benzylidene. The proton NMR gave values of 6.63 ppm as broad singulet for amide and a sharp singulet for benzylidene at 5.49 ppm. (See reaction scheme **89**).

Scheme 89.



416



451

452

Intramolecular Glycosylation

Before setting for the glycosylation reaction we investigated the solubility of the tethered product by screening different solvents. The only remaining choice was again the solvent mixture of dichloromethane/acetonitrile 1:1. Through intramolecular glycosylation of the succinyl amide ethyl disaccharide **452** in this solvent mixture at -5°C to 5°C activated by NIS and TMSOTf as catalyst we obtained after work-up a colored crude product. The insolubility of this crude mixture obliged us in having recourse in deploying additional efforts toward selecting an eluent that satisfied the solubility and seperation conditions. Finally, the eluent system mixture of CH_2Cl_2/acetone/ toluene 4:1:0.5 brought fulfilled these conditions, by completly dissolving of the crude mixture , and TLC in the same system gave an ideal Rf for the seperation of the isomers. The chromatography allowed easy seperation of the isomers, and gave us the two fractions with a 72.60% overall yield.

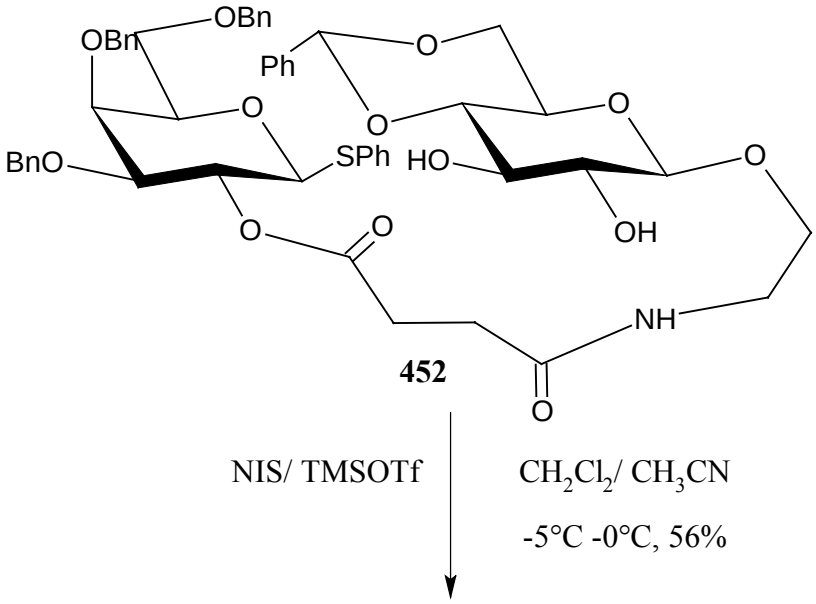
We pursued an NMR analysis of the main and minor fraction, which enabled the conclusion of an intramolecular glycosylation through values of 97.23 ppm (C-1) gal 99.94 ppm (C-1) gluc, thus an α glycosidic bond as revealed by ^{13}C-NMR for the major product **453**. For the minor **454**

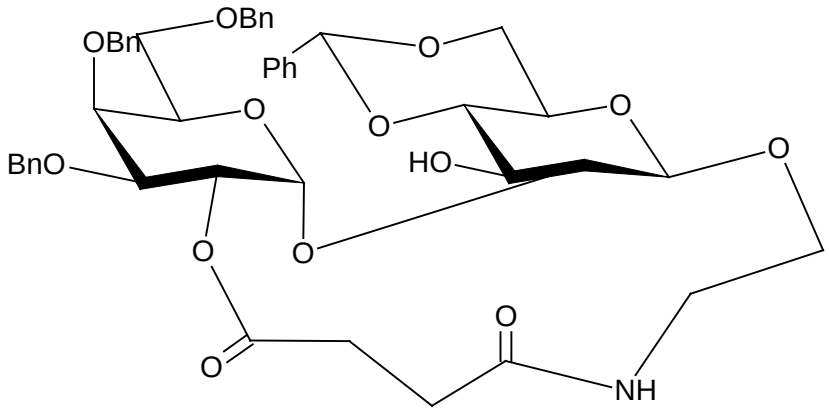
product the ^{13}C-NMR gave values of 97.16 ppm for (C-1) gal, 99.80 ppm for (C-1) gluc. therefore another α glycosydic linkage.These NMR datas left the conclusion of a 2-OH α glycosylation and a 3-OH α glycosylation. An extention 2D-NMR study with HMBC for the main fraction confirmed direct ^{3}J correlation between (C-1) gal. 97.25 ppm and (H-2) gluc. 3.78 ppm for product **453** thus an α(1-2) glycosydic bond. This answered directly our question by confirming this time an overall choice for the 2-OH to be glycosylated.

For the minor product **454**, analysis with HMBC shows direct ^{3}J correlation between (C-1) gal. 97.30 ppm and (H-3) gluc. 3.84 ppm. thus an α(1-3) glycosydic bond. (See scheme **90**)
With this successful methodology, we have achieved our goal, in constraining the spacer that that regio-and stereoselectively subjected 2-OH of the glucose spacer to glycosylation preferentially to the 3-OH, therefore emulating the elegance of our strategy.
Indeed, the full potential of our synthethic methodology has been harnessed, and allowed to fully outsmart the the stereo and regioselective chimereas.

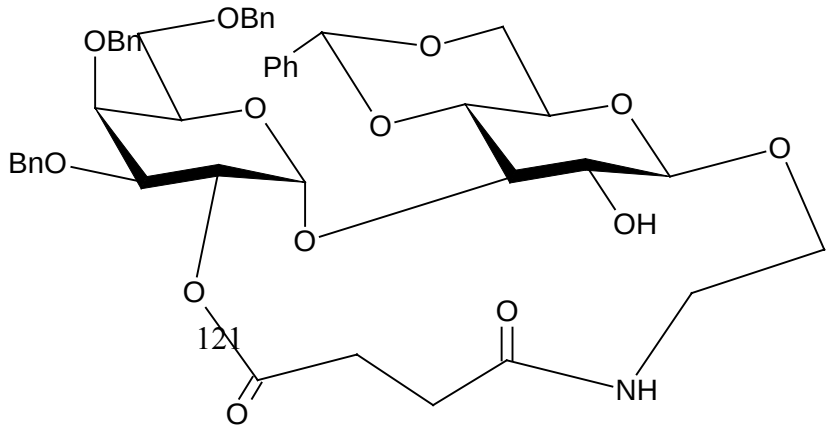
From the mentioned sucessfully obtained results of our inverstigations regarding the intramolecular glycosylations,one can now establish the difference between the different succinyl-amide alkyl linkers. The first succinylamide pentyl and butyl spacers linking galactose donor and glucose acceptor produced the best regio- and steroselectiviy with a ß/α glycosylation ratio of 8:1 for the former and 7:1 for the latter.

Scheme 90.





453 **α (1-2)**

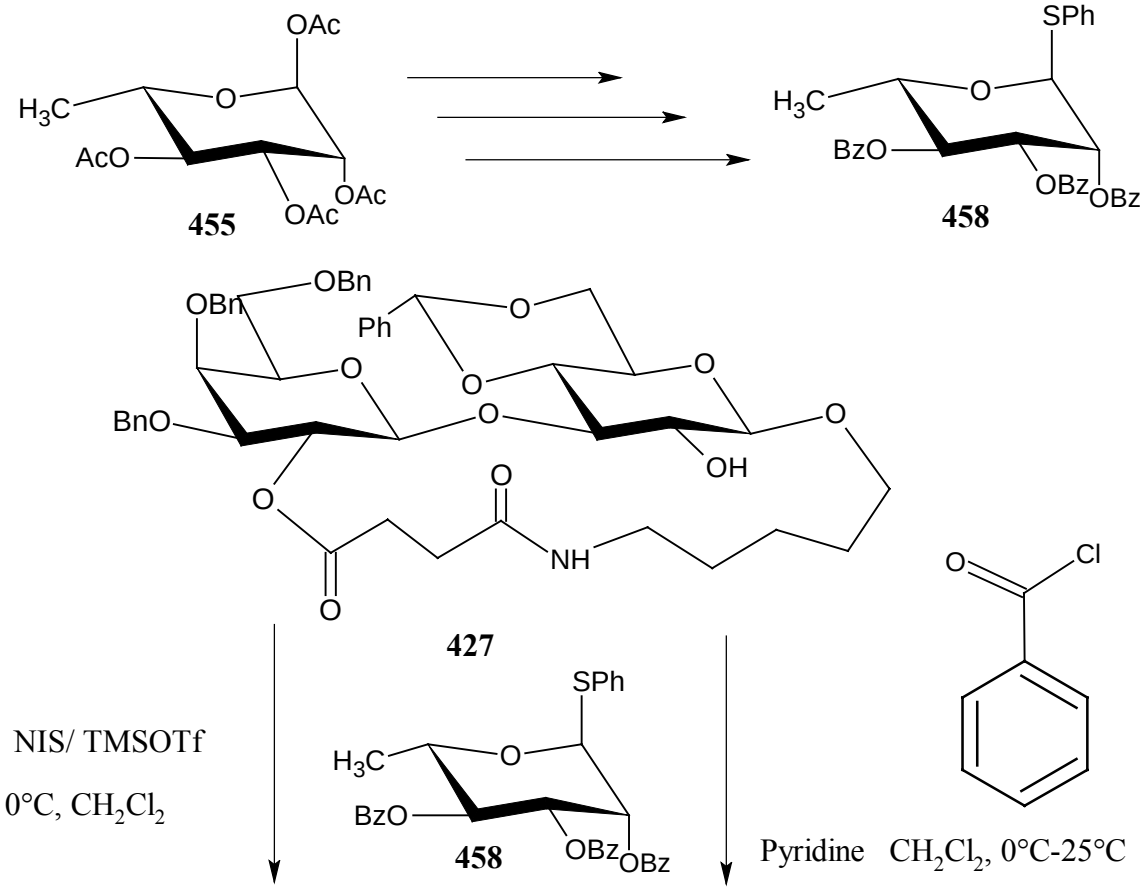


454 **α (1-3)**

The succinylamide propyl spacer brought a quantitatively a higher percentage yield of ß-anomer, howerver a lower ß/α ratio with that is 4:1 but nevertheless good stereo and regio-selectivity. With succinylamideethyl spacer, only α products were achieavable wich prefe-rentially brought the 2-OH of glucose accptor to glycosylation over the 3-OH with the ratio α (1-2)/ α (1-3) of 4:1.The first two longer spacers display much more flexibility as to better spacially prearrange the 3-OH hydroxyl such as to enforce glycosylation of the latter.
One of the important factor not to omit is the solvent's role. We have here a mixture of CH_2Cl_2/ acetonitrile 1:1. During the reaction there is formation of acylium carbocation that is nucleo-phylically attacked by acetonitrile and induced an upper attack of the nearly best spacially prearranged hydroxyl of glucose acceptor to glycolyse and afford the *n*-membered cyclised disaccharide.

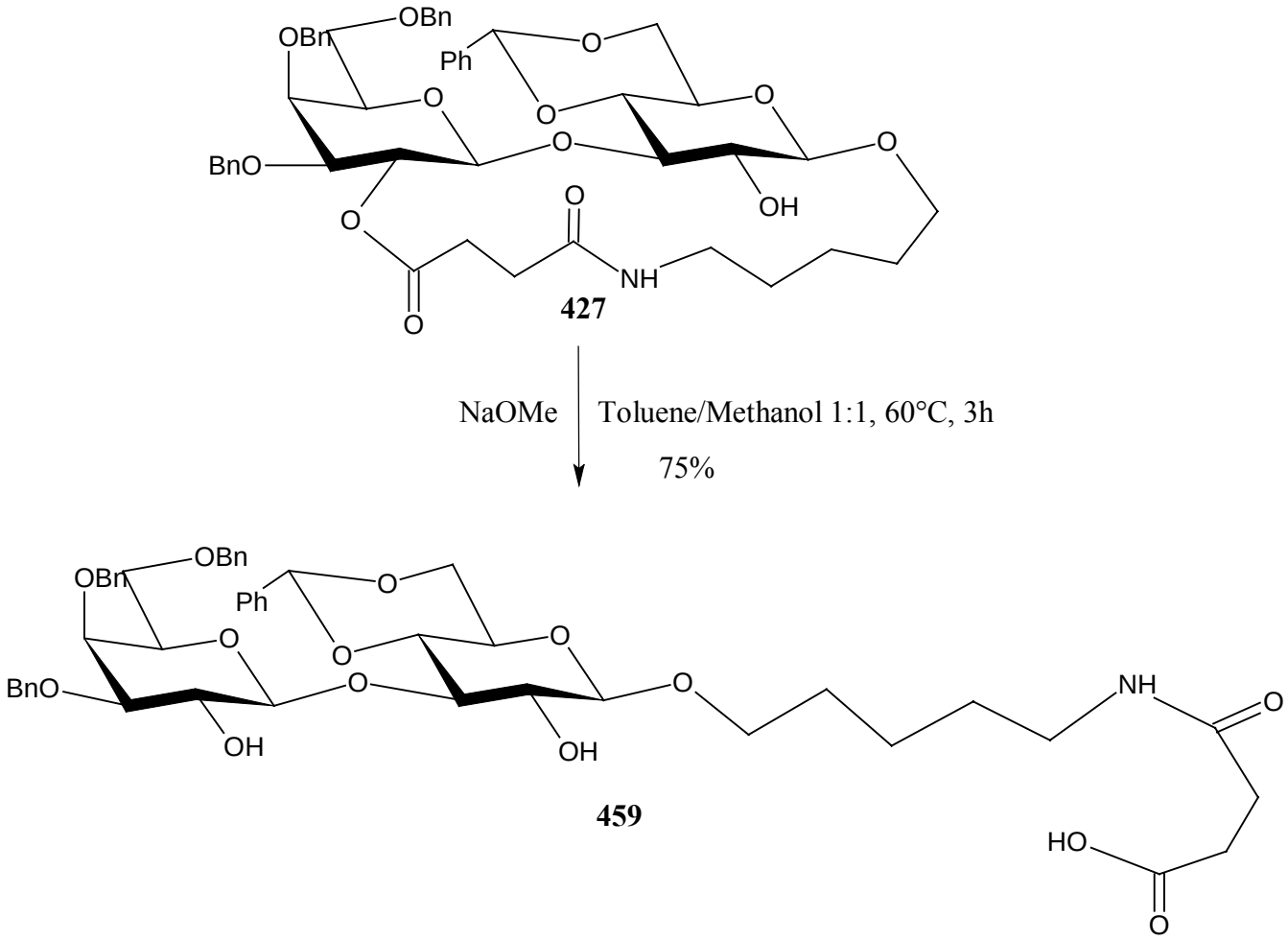
When observing the structural architecture of all these succinylamidealkyl disaccharides, it is noteworthy to bring answers to the following questions. How reactive is the embedded 2-OH of glucose acceptor, and how spacious are the cavities of the 18,17,16,and 15 membered cycle
as to allow an evenual glycosylation, benzoylation? How could higher saccharides be constructed from these cyclic disaacharides?
To find a response to these questions we focused on the glycosylation of the first succinylamide pentyl disaccharide **427** with a prepared 2,3,4-tri-O-benzoyl-α-(L)-rhamnopyranoside **458** activated by NIS and TMSOTf as catalyst at 0°C in dry dichloromethane . After two hours the reaction was followed by TLC which revealed no fromation of the trisaccharide. The reaction was run overnight at room temperature and the TLC still showded absolutely no reaction. Through chromatography in CH_2Cl_2 6:1, we were able to recuperate the unreacted ß-D-cyclic dissacharide **427**, and reacted it with benzoyl chloride in pyridine overnight and TLC also showed no reaction. (See reaction scheme **91**).

Scheme 91.



The impossibility of glycosylating, and benzoylation of the embedded 2-OH of the glucose acceptor led us to reconsider in opening the macrocylic heterocyle of compound **427** originating from the intramolecular glycosylation. The heterocyclic macrocycle consist of an ester group that can be cleaved, a gateway toward opening the ring in basic conditions. Reaction of compound **427** with 5.4 M MeONa in a mixture toluene/acetone at 60°C for three hours yielded 90% yield of the open pentylamidesuccinylcarboxylic acid **459**. The cleavage of te bridge had occured with the formation the carboxylic acid **459**. This is well confirmed by ^{1}H and ^{23}C-NMR (See scheme **92**) To delve for more productive answers to our above mentioned questions, we opted toward exploiting a X-ray crystallography to view the architectural aspect of the cyclic disaccharides major and minor product. Unfortunately such attempt was unfeasable due to the amorphous aspect of the solids, the crystal being to small did not allow this investigation. We then oriented our study toward the molecular modelling.

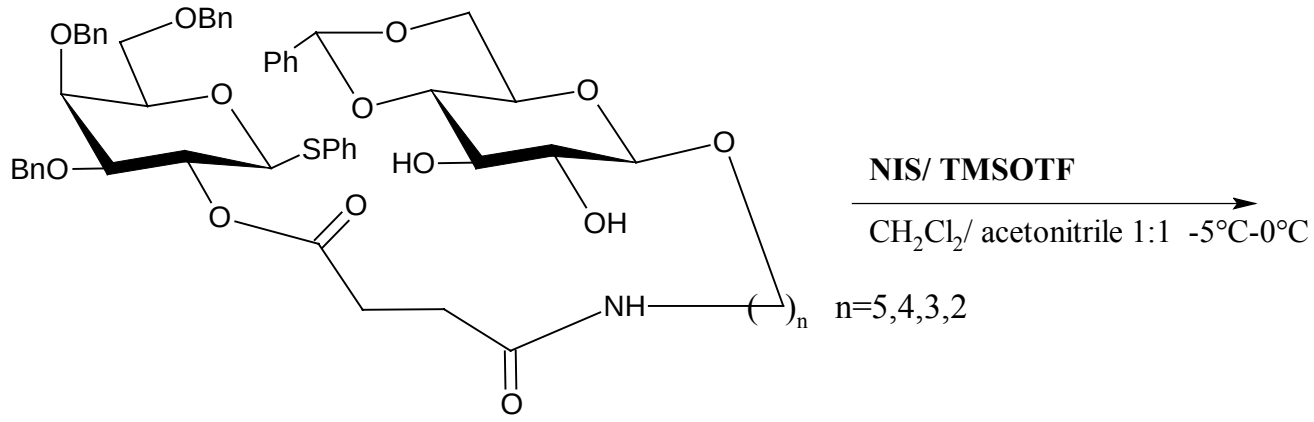
Scheme 92.

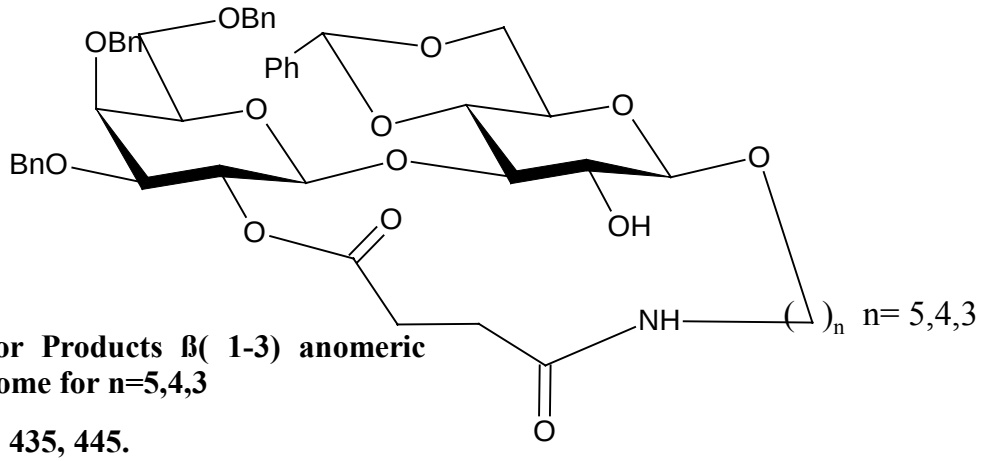


Study and analysis was conducted on the intramolecular glycosylation products by building building molecular models using the molecular modelling suite (1,2) Moloc. The cyclization junction was modeled and energy minimized in a recently reparamatized version of the MAB force field. Observation from this study shows bifurcated hydrogen bonding between the free 2-OH of the glucose donor part of the disaccharide with the peptide and ester moiety of the spacer. This factor decrease considerably the nucleophilic character of this embedded 2-OH in the ring thus no reactivity for a possible glycosylation. Additionally, the cavity of the ring formed from intramolecular glycosylation does not have the reasonable size to cage the rhamnopyranoside sugar. An eventual benzoylation of this embedded 2-OH gave no possible reaction.

As a recapitulation, all intramolecular glycosylation reactions have been carried out under argon atmosphere activate by NIS and TMSOTf in a solvent mixture dichloromethane/acetonitrile 1:1 at a temperature range -5°C - 0°C for thirty to fourty minutes time range. In these conditions all yield have been maximized.
Here we have prearranged tethered succinylamide alkyl disaccharides of gradually varied spacer length n=5,4,3,2. We have succeeded in effecting a regio-and stereoselective glycosylation between a tribenzylated galactose donor and a glucose acceptor bearing a free 2-OH and 3-OH group. These succinylamide alkyl spacer prearranges both the galactothioglycoside donor and the the 4,6-O-benzylidene glucoside donor such as one hydroxyl group, the 2-OH or the 3-OH is selectively chosen for an eventual selective glycosylation and the other hydroxyl remains fully discriminated. In the first three cases, the 3-OH has been fully selected for glycosylation. The last case with the more constrained smaller spacer singularises itself with a selective glycosylation of the embedded 2-OH. Results are summarized in the below reaction scheme **93** and table **11**

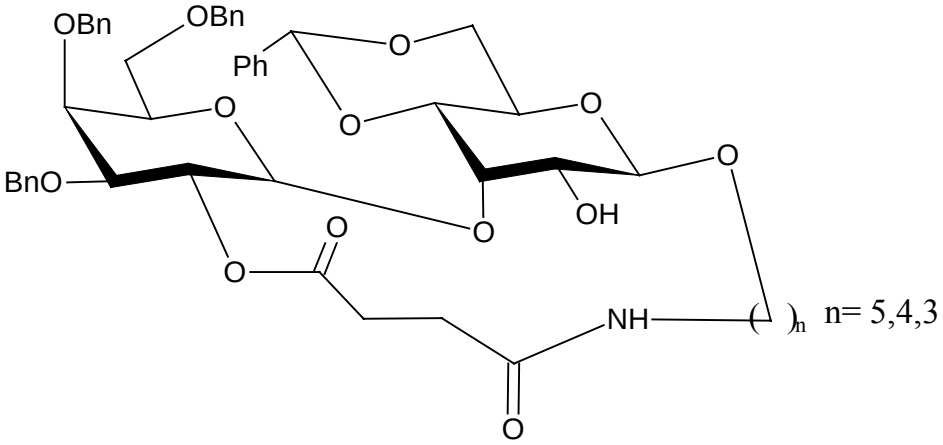
Scheme 93.





Major Products ß(1-3) anomeric outcome for n=5,4,3

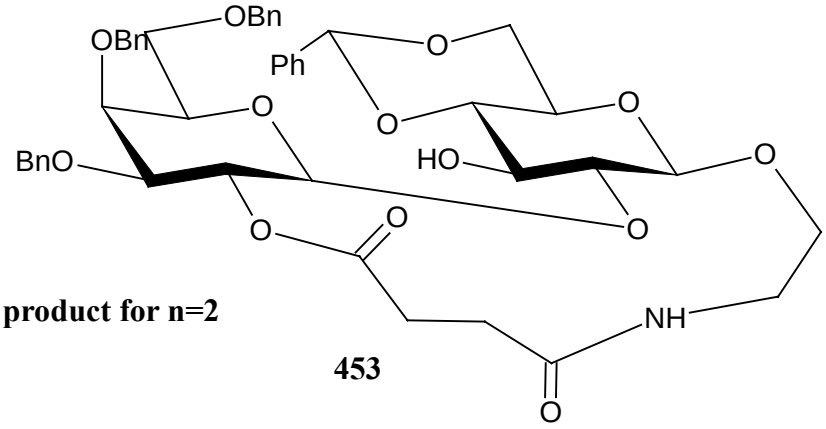
427, 435, 445.



Minor Products, α (1-3) anomeric outcome for n=5,4,3,2
428, 436, 446, 454

Case of the Succinylamide Alkyl Spacer

The case of the succinyl amide ethyl spacer distinguished itself with its constraint caracter in affording a major product of α (1-2) where the embedded 2-OH has been favored for glycosylation over the more accessible 3-OH. (See the below structure).



Major product for n=2

453

The intramolecular glycosylation percentage yields and results are summarized at the following table **11**.

PERCENTAGE YIELDS AND

STEREO-REGIOSELECTIVITY OUTCOMES

SPACER	*ALKYL*	*% YIELD*	*ß-GLYCOSYDIC BOND*	*α-GLYCOSYDIC BOND*	*ß/α*
n=5	*pentyl*	*56%*	*50% ß (1-3)*	*6% α (1-3)*	*8:1*
n=4	*butyl*	*66%*	*58% ß (1-3)*	*8% α (1-3)*	*7:1*
n=3	*propyl*	*73%*	*58% ß (1-3)*	*15% mixture*	*4:1*
n=2	*ethyl*	*72%*	*none*	*59% α (1-2)* *13% α (1-3)*	

Molecular Modelling

Molecular models of the intramolecular glycosylation products were built by using the molecular models using the molecular modelling suite Moloc (1.2). The cyclisation junction was modeled and energy minimized in a recently reparamatized version of the MAB force field. Observation from this study shows bifurcated hydrogen bonding between the free 2-OH of the glucose donor part of the disaccharide with the peptide and ester moiety of the spacer. This factor decrease considerably the nucleophilic character of this embedded 2-OH in the ring thus no reactivity for a possible glycosylation. It is than expected, that the 2-OH buried within the ring is less reactive and hence difficult to acetylate or benzoylate, perhaps just accessible for methylation. Additionally, the cavity of the ring from compounds **427,435,445,454**, formed from intramolecular glycosylation does not have the reasonable size to cage the rhamnopyranoside sugar, even a benzoyl group This molecular modelling investigation reveals itself fully concordant with the experimental analysis as to the non possibility of glycosylation, benzoylation.
More surprising is the role of our protecting group's choice, which to our surprise confirms strong aromatic triad stacking between the 4,6-O- benzyledene of the glucose acceptor and the 4-O and 6-O benzyl group of the adjacent galactose donor residue.

Aromatic π–π stacking [98,100] are attractive interactions that occurs between aromatic ring. Attracive interactions control such diverse phenomenon as the vertical base-base interactions which stabilize the double helecal structure of DNA, the intercalation of drugd into DNA, the packing of aromatic molecules in crystals, the tertiary structurein proteins, the conformational preferences of binding properties of polyaromatic macocyles, as well the stereo-and regioselective outcomes in organic reactions.[113,114,115]
There are two general types of π-stacking : face-to-face and edge-to- face.
Face-to-face interactions are responsible for the slippery feel ogf graphite, useful for lubricant properties. Similar π-stacking interactions between aryl rings of nucleobase pairs also stabilizes the DNA double helix. In the molecular modelling pictures of our intramolecular glycosylation products, we observe exactly the same effect, where the benzyl and benzyledene group are well placed faca-to face to one another. (See fig.**19**)
Edge-to-face interactions may be regarded as weak forms of hydrogen bonds between the slightly electron deficient hydrogen atoms of one aromatic ring and the electron π- cloud of another. Edge-to-face interactions are responsible for the characteristic herring bone packing in the crystals structures of a range of small aromatic hydrocarbons including benzene.
(See fig. **20**)

Fig. 19

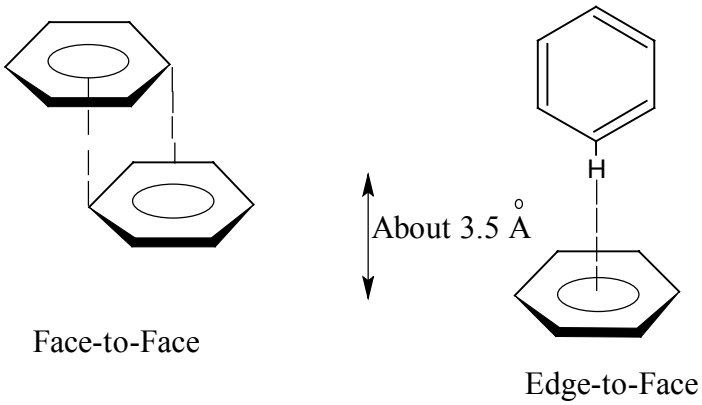
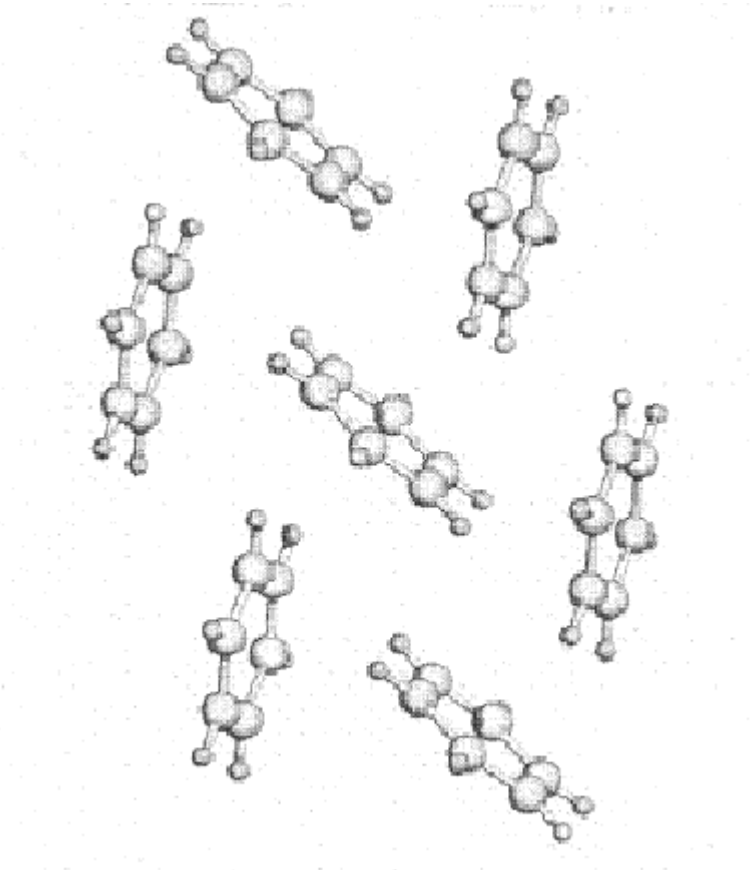


Fig. 20

Structure of benzene showing herrigbone motif arising from edge-to- face interactions



Our molecular modelling analysis revealed to us, that the strong aromatic triad stackings interactions between the 4,6-O-benzyledene group of the glucose acceptor and the the 4-and 6-O-benzylether groups of the adjacent galactose donor residue, determines the regio-and the stereochemistry of the intramolecular glycosylation products.

The first figure (fig.**11**) obtained from the molecular modelling illustrates a model of the disaccharide **427** without the tether and shows the degree of aromatic stacking. The following model picture (fig.**12**), shows the entire ß(1-3) main cyclisation product architecture of **427** with a clear view of the aromatic stacking at a near distance of the glycosidic center and the spacial orientation of the methylene consisting the succinylamide pentyl spacer. In another figure, a superposition of the ß(1-3) cyclisation product was performed and illustrates that the aromatic stacking occurs in all cases, and allows a view of the spacial arrangement of the different sized spacers.
(See fig. **13,14,15,16,17**).

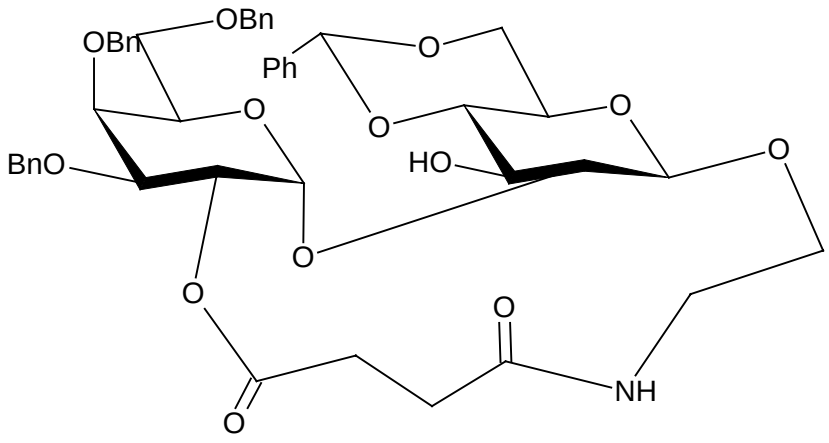
The above mentioned study concords exactly with all our experimental and NMR analysis.

One more question crossed our reasoning; what role does the solvent mixture plays on the aromatic stacking's phenomena?

The solvent mixture of dichloromethane/acetonitrile 1:1 utilized in the intramolecular glycosylation reactions do play an essential role. These solvents are polar aprotic, therefore they allow a maximun aromatic stacking occurence. This stems from the fact that these substances do not intercalate with the aromatic benzyl and benzyledene group, thus facilitates these aromatic protecting groups to stack among themselves with a maximun sponteneity. In contrast, if toluene was used as glycosylation solvent, it would intercalate by stacking with the benzylether and benzylidene groups. The molecular modelling investigation informs us about this very good choic of solvent mixture, and its importance for the intramolecular glycosylation reactions.

CASE OF SUCCINYLAMIDE ETHYL SPACER

Fig. 18



The molecular modelling investigations for the case of the succinyl amide ethyl **453** spacer confirms such interesting and surprising results that requires a separate discussion.

The first information that we obtained from the above mentioned study about the succinyl-amide ethyl spacer reveals that, the regio-and stereoselectivty leading to the for- mation of α(1-2) glycosydic linkage as major product **453**, results from an exergonic reaction and, the strong aromatic stacking.

During the course of the reaction, the thiophenyl group is rapidly expulsed from the glycosidic center generating the acylium intermediate. This can further be approached by the more accessible 3-OH in a strainfree process, whereas the more buried 2-OH is attacked by the acylium ion only when constrained through the shorter chain length.

Furthermore, the molecular modelling studies effected for observed regio-and stereochemistry of intramolecular glycosylation product (**453**) show the occurence of an alternative conformation with two aromatic diad stackings interactions and, two intramolecular hydrogen bonding (bifurcated hydrogen bond) which is significantly (7.0 kcal/mole) more stable than the ß(1-3)-products with two successive stackings and surprisigly one intramolecular hydrogen ß-turn-like hydrogen bond. Note

Noteworthy of observation are the stacking between the 6-O-benzyl protecting group of the galactose donor and the 4,6-O-benzyledene of the glucose acceptor. Their orientation present itself in a way to allow the 3-OH to form a bifurcated hydrogen bonding with the oxygen of the benzyl group with a 269 Angstroms distance, and a 276 Angstroms distance hydrogen bonding with the ring oxygen of of the galactose donor. This is an extraanular hydrogen bonding.

Inside the macrocylic 14 ring size, a strong intramolecular or intraannular hydrogen bonding (283 Angstroms) is produced between the NH of the peptide moiety and the succinyl oxygen and , a weaker on (397 Angstroms) with the glycosydic oxygen, thus enforcing a beta-turn type. (See fig. **15**,**16**,**17**.)

These ß-turn are observed on the surface of protein and in polypeptide constituting of aromatic or constrained aminoacids. Turns are segments between secondary stuctural elements and are defined as sites in a polypeptide where the peptidic chain reverses its overall direction. compared to helices or sheets, turns are the only regular secondary structures which consist of nonrepeating backbone torsional angles.

The ß-turns have been hypothesized to be involved in process of peptide hormones, recognition recognition of phospotyrosine containing peptides, signal peptidase action, receptor internali-sation signals, and glycosylation process.

Turns are classified into conformation type dependency on valuesof four backbone torsional angles (ϕ_1 ,ψ_1,ϕ_2,ψ_2) shown at (fig. **20**) .

Fig. 11

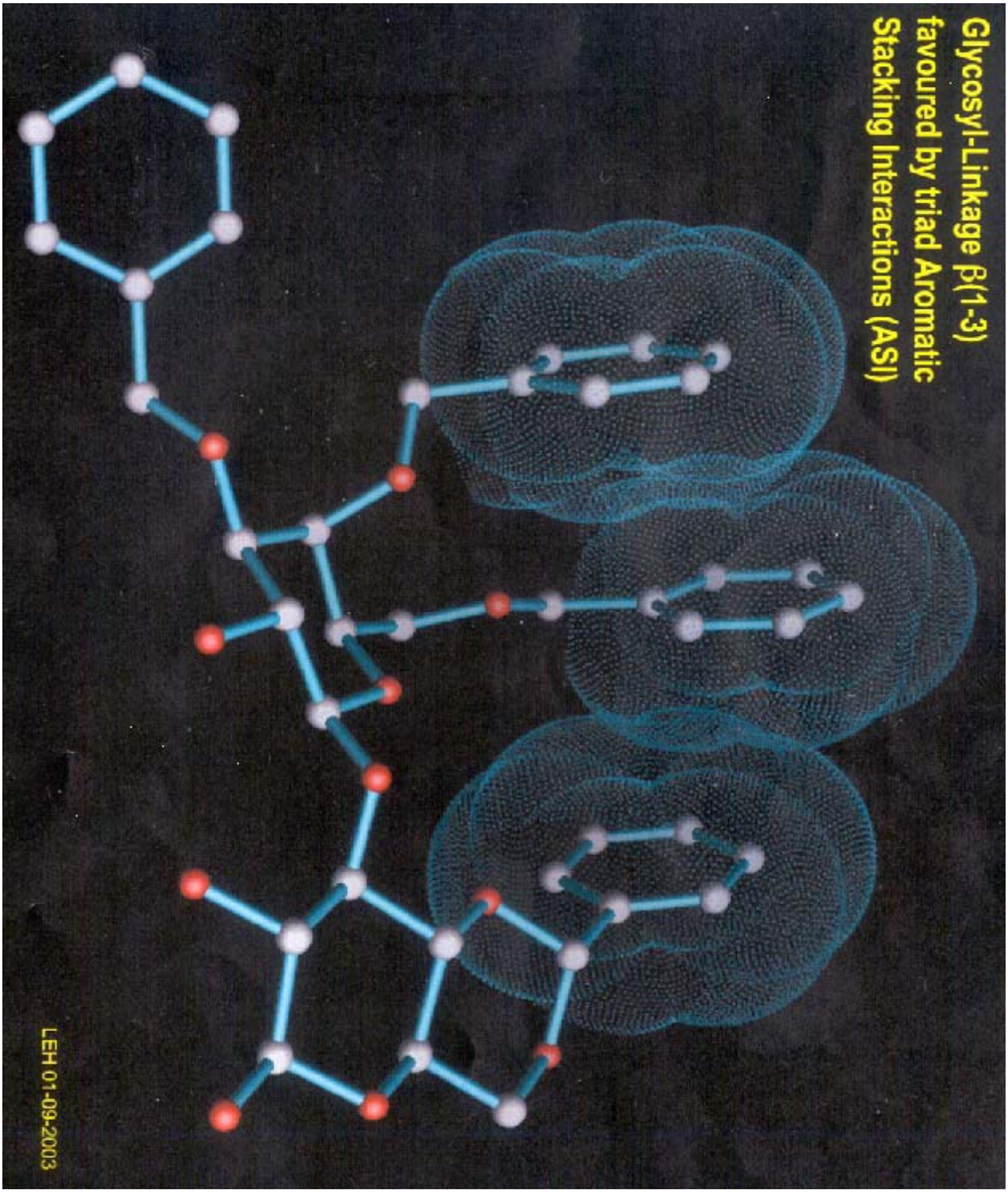

Glycosyl-Linkage β(1-3)
favoured by triad Aromatic
Stacking Interactions (ASI)
LEH 01-09-2003

Fig. 12

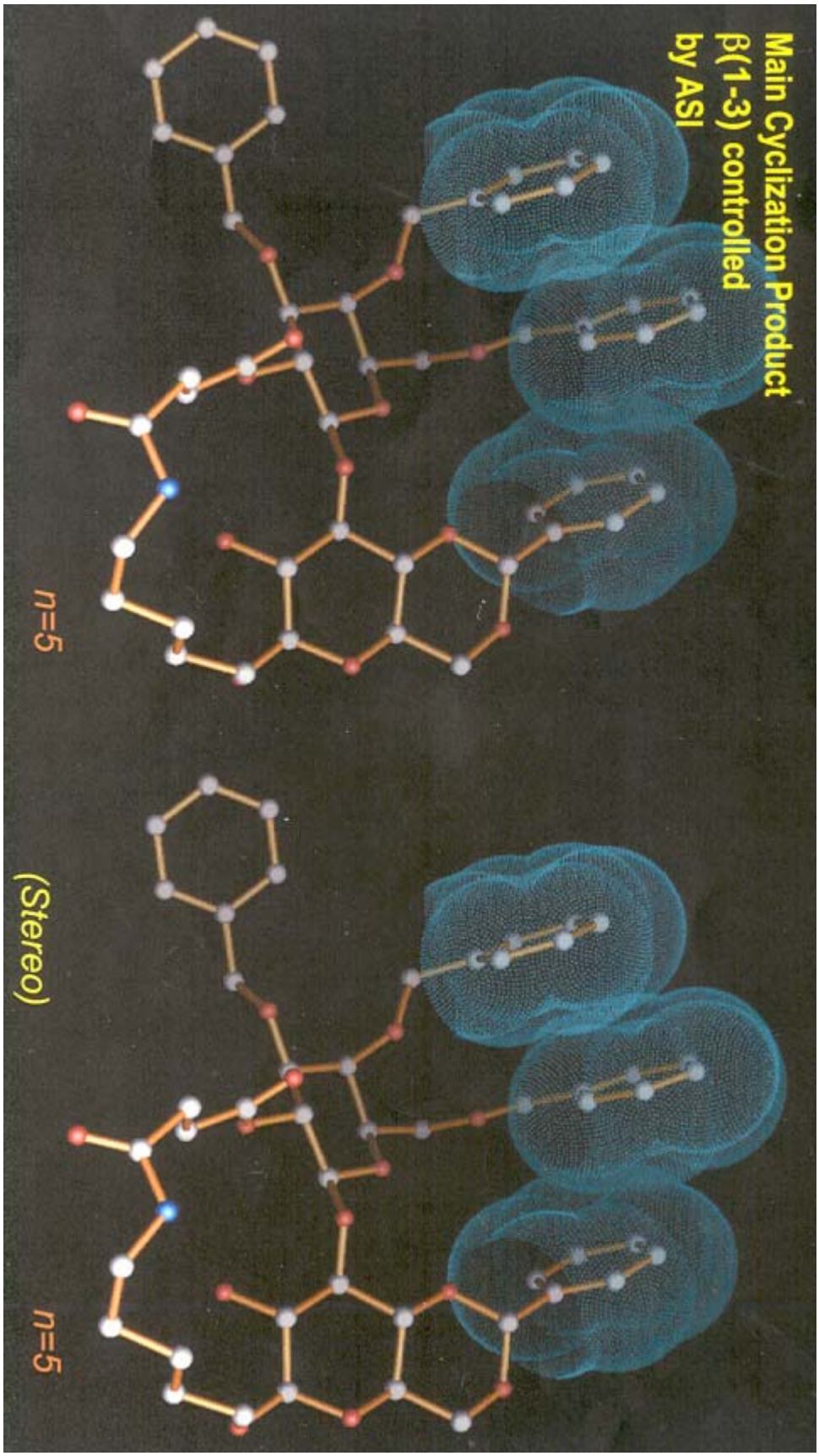

Main Cyclization Product
β(1-3) controlled
by ASI
n=5
(Stereo)
n=5

Fig. 13

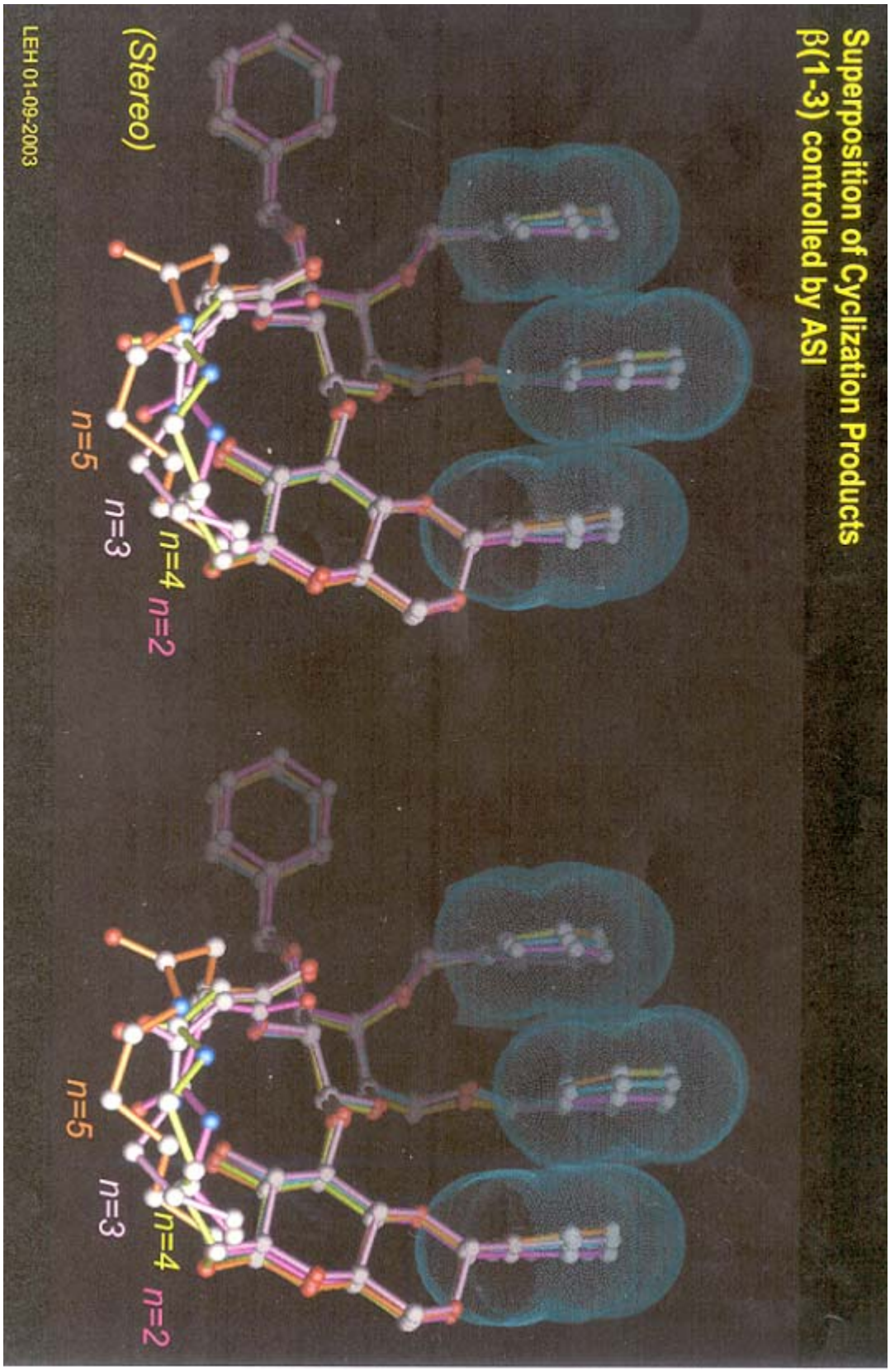

Superposition of Cyclization Products
β(1-3) controlled by ASI
(Stereo)
n=5
n=3
n=4
n=2
n=5
n=3
n=4
n=2
LEH 01-09-2003

Fig. 14

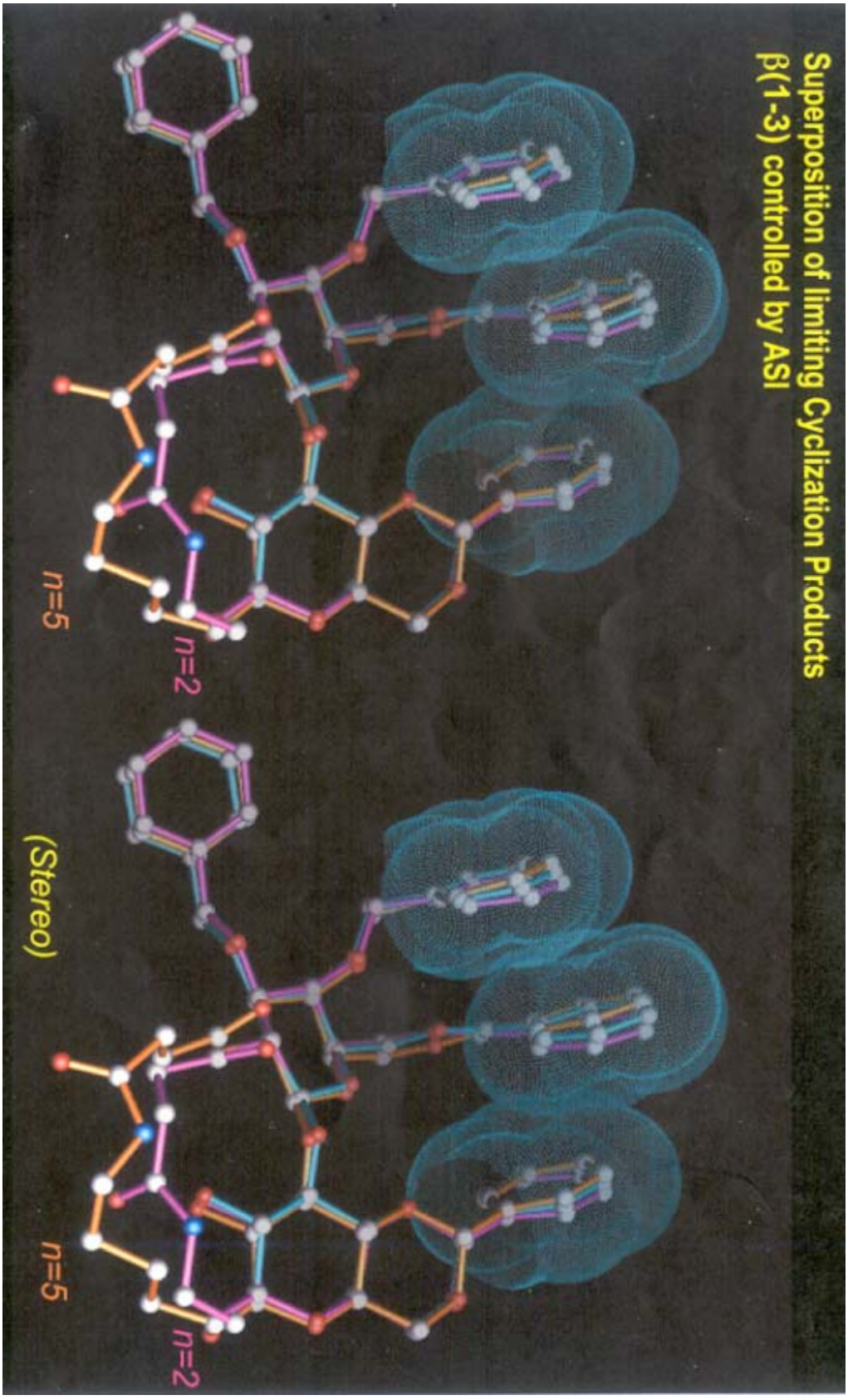

Superposition of limiting Cyclization Products
β(1-3) controlled by ASI
n=5
n=2
(Stereo)
n=5
n=2

Fig. 15

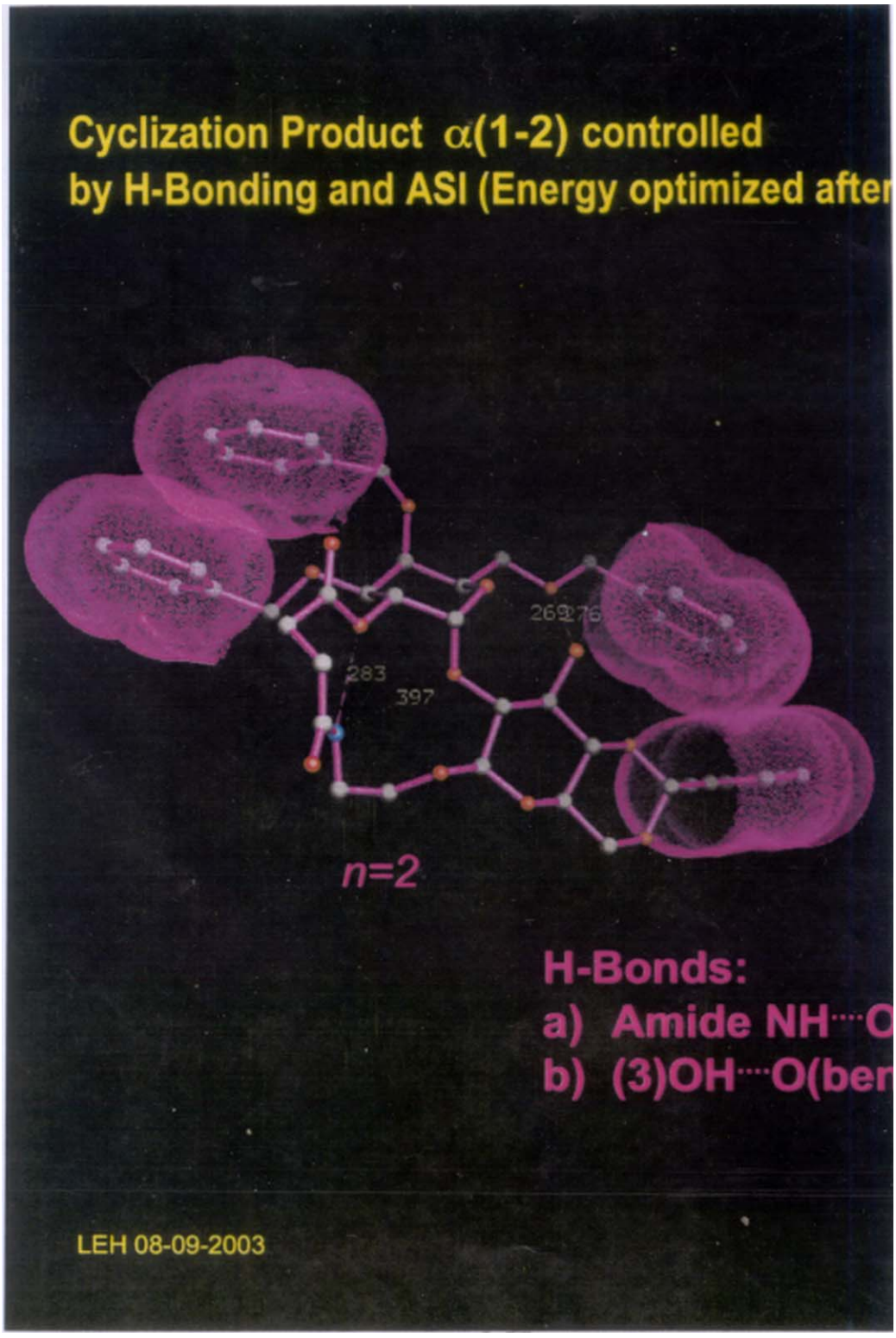

Cyclization Product α(1-2) controlled
by H-Bonding and ASI (Energy optimized after
269
276
283
397
n=2
H-Bonds:
a) Amide NH····O
b) (3)OH····O(ben
LEH 08-09-2003

Fig. 16

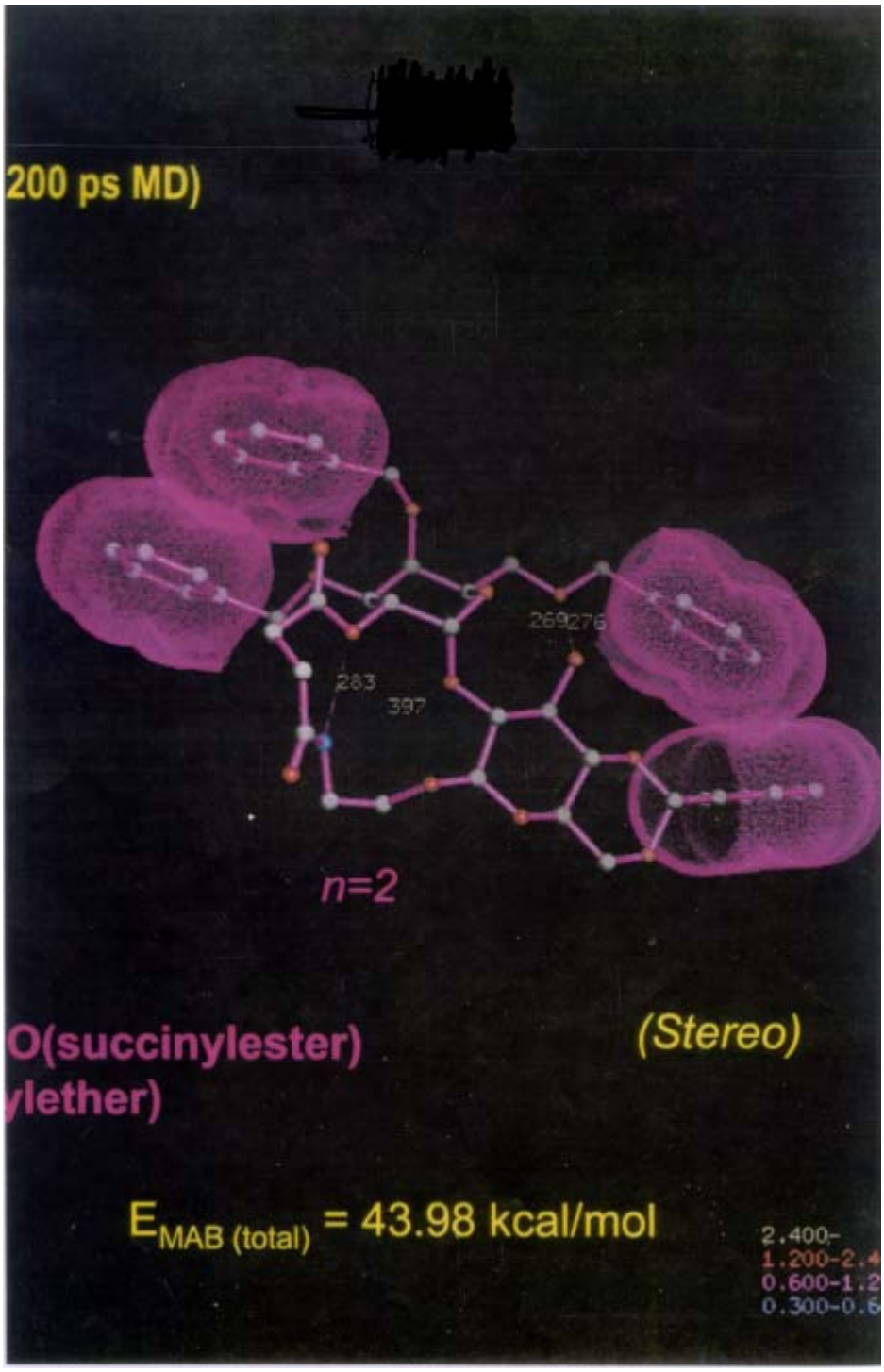
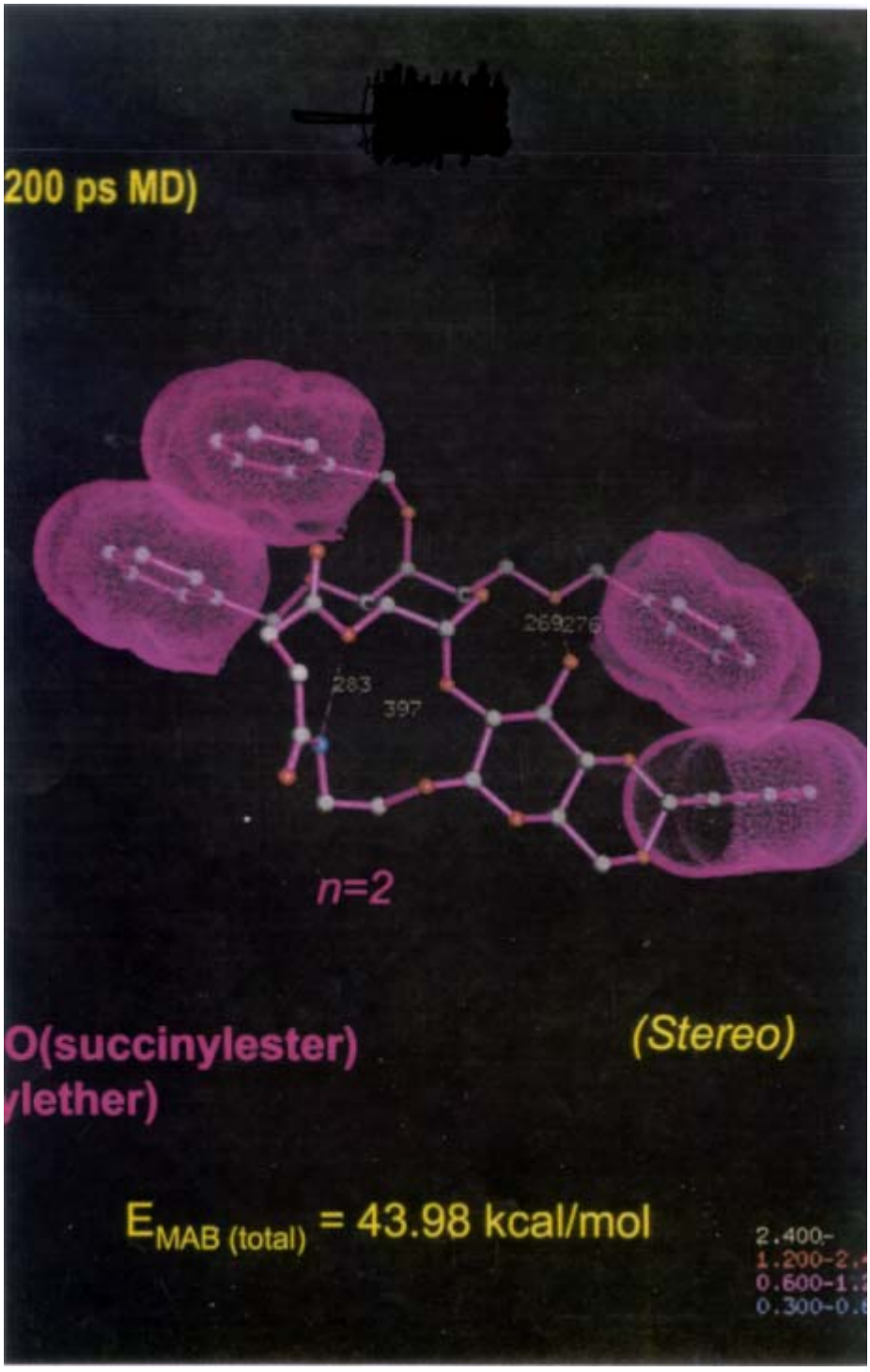

200 ps MD)
269
276
283
397
n=2
O(succinylester)
ylether)
(Stereo)
E MAB (total) = 43.98 kcal/mol
2.400-
1.200-2.4
0.600-1.2
0.300-0.6

Fig. 17


200 ps MD)
283
397
n=2
O(succinylester)
ylether)
(Stereo)
E MAB (total) = 43.98 kcal/mol
2.400-
1.200-2.
0.600-1.
0.300-0.

The backbone torsional angles refer to rotations about the N-C_α bond (ϕ) and C_α- C' bond (ψ). A second criterium is the $\alpha\ C_1 \rightarrow \alpha\ C_{i+3}$ distance which must be shorter than 7 Angstroms (fig. **21**). Very typical for β-turn motifs is a H-bond between the the carbonyl group at position ***i*** and the amide residue ***i*+3**.

Fig. 20

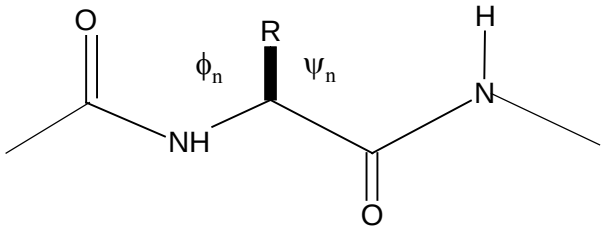
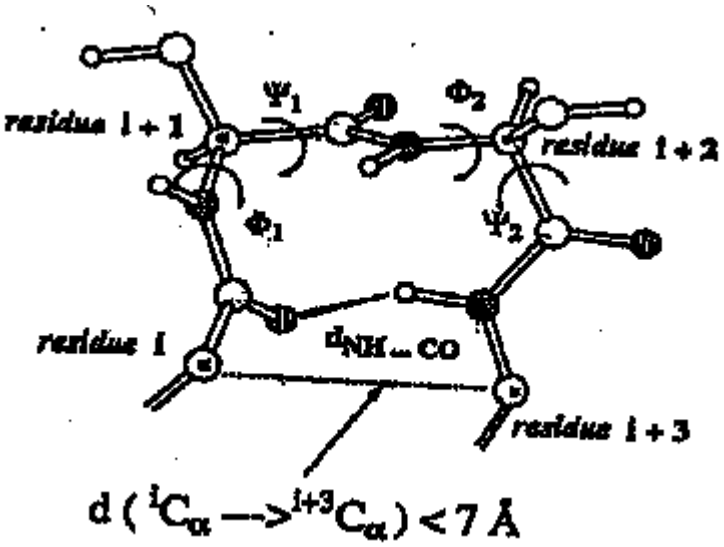


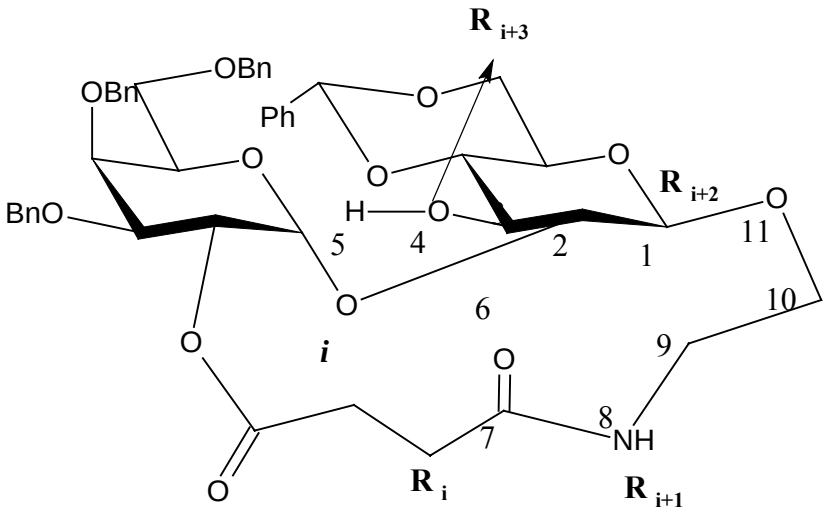
Fig. 21



Viewing the below structure (fig.**22**) of the intramolecular glycosylation with the succinyl-amide ethyl spacer, a similar comparison seems possible due to the fact that the 3-OH at a position ***i*** hydrogen bonded with the carbonyl of the amide moiety at distance of 10 atoms that is ***i*+3** residue.The NH of the amide structure make a hydrogen bond with he 3-OH of the disaccharide by 9 atoms distance which corresponds to 3 residues that is, a ***i*+3**, which is ideal for the occurence of a ß-turn motif. The bifurcated hydrogen[105,106] bonding occurs then in a 10 membered ring resembling a 3_{10}- helix. This type of helix is the only principal structure that occurs in globular proteins. The 3_{10}-helix [103, 105, 107] is a right-handed helix with three residues per turn. this structure has been reviewed by Tonlio and Benedetti.[105, 106] The backbone dihedral angles of a right-handed 3_{10}-helix (ϕ= -60° and ψ = -30°)

are similar to α-helix (ϕ = -62° and ψ = - 41°). In a recent structural analysis of 57 proteins of known structure revealed at 3.4% of the residues involved in a 3_{10} helix. The hydrogen bonding network in a 3_{10} is not optimal. 3_{10} helices are therefore, energetically slightly than the corresponding α-helices, although there is no dissallowed conformational region between them. Synthetic peptides can adopt a 3_{10} helix when a $C_{\alpha,\alpha}$– disubstituted amino acid such as α-amino-isobutylic acid (Aib) makes up more than 50% of their sequences.

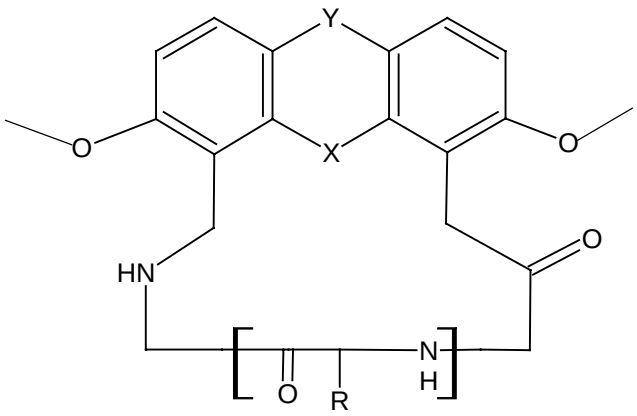
Fig. 22



ROLE OF THE SUGAR DISACCHARIDE

Our molecular modelling investigation led to consider us the role of the sugar disaccharide back-bone in the bifurcated hydrogen bonding which engenders an intramolecular ß-turn.
It has been investigate and shown that some synthesized di-and-tricyclic organic compounds have been used as templates to stabilise and enhance ß-turn. Daniel Obrecht and John A. Robinson[107.108,109,110] utilized tricyclic xanthene, phenoxazine,phenothiazine derived tempates that ha been shown to stabilize ß-turns. The structures are illustrated in the below (**Fig.**. **23**).

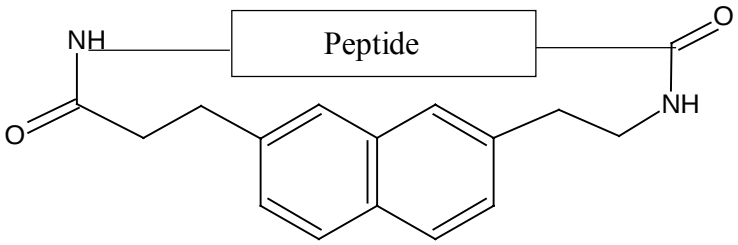
Fig. 23

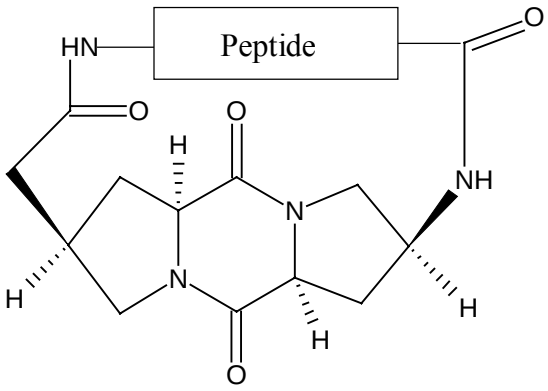


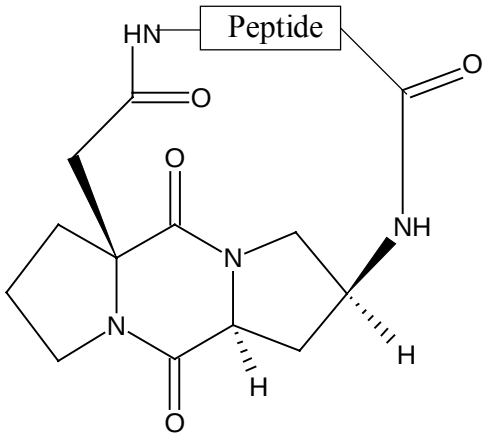
X=O, Y=C $(CH_3)_2$ xanthenes

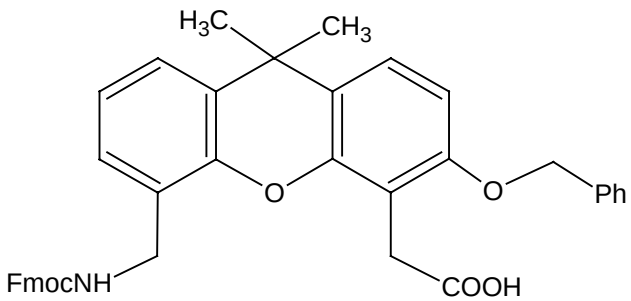
X=O, Y=NCH_3 phenoxazines

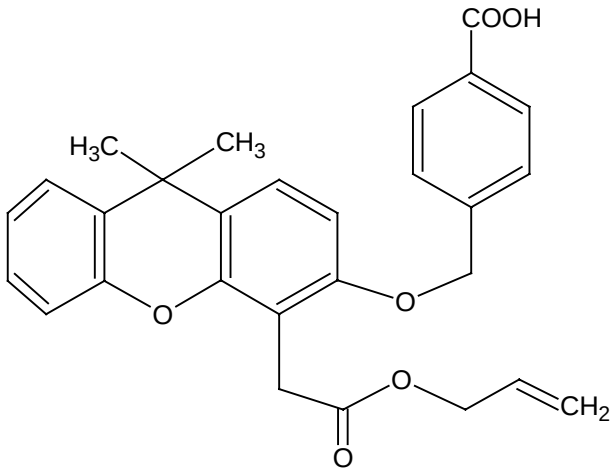
X=S, Y=NCH_3 phenothiazines







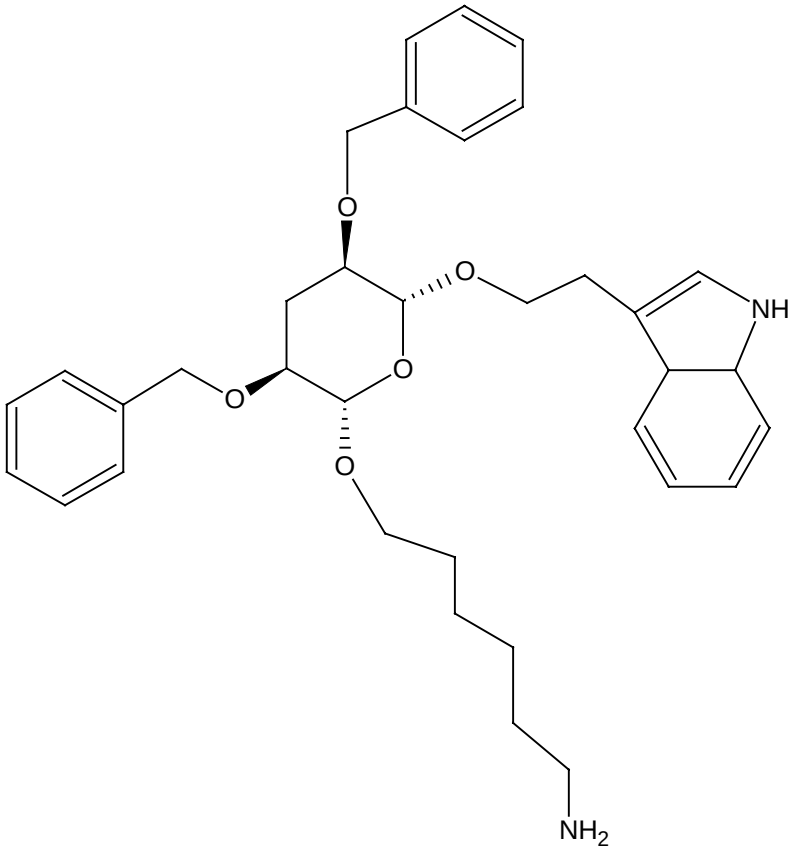




Unsimmetrical stabilizing Templates

Hirschman *et al.*[103,111,112] recently reported the synthesis of Somastatin (SRIF) analogues that contains a glucopyranose ring as a rigid template. The glucopyranose templates provides a hydrotycally stable framework which organises side chains fonctionalities essential for binding the somastatin receptor. (Fig. **24**).

Fig. 24



All of the cyclic structures illustrated above are templates that stabilize ß-turns in attached peptides for *n*=2 and 4. From our molecular modelling analysis, we agreably discovered that the disaccharide of our intramolecular glycosylation product **46** for the smaller spacer, also functions similarly like the above mentioned structures as a rigid template that stabilizes the single ß-turn. Furthermore, the disaccharide serves as an intraanular and extrannular bifurcated hydrogen bond donor.the succinylamide being a constrained tether allows a stabilization of the ß-turn.

A ß-turn like formation could probably also occur in other intramolecular glycosylation products with the longer spacers (n=4,5) with a di-or tripeptide moiety. Hence, the presence of more peptide moieties necessary for the occurence of a ß-turn like structure probably varies with the length of the spacer.

ADVANTAGE OF THE SUCCINYLAMIDE ALKYL SPACER IN INTRAMOLECULAR GLYCOSYLATION.

The use of the succinylamide alkyl spacer as spacer's choice for intramolecular glycosylation present the advantage that the reaction is completely intramolecular with no intermolecular reaction products detected. Furthermore, these spacers reveal a certain flexibility that prearranges the glucose acceptor and galactose donor toward a specific orientation which enforces the intramolecular glycosylation at a specific regio-and stereoselectively.

The surprising aspect of the intramolecular glycosylation are the structure of the products themselves, especially the benzyl protecting and benzylidene protecting groups with orient the regio- and stereoselectivity of the reaction through strong aromatic stacking triads for the pentyl, butyl, and propyl spacers, and strong aromatic stacking diads for the product containing the ethyl spacer. Therefore the protecting groups beared by the galactose donor and glucose acceptor play a major role in the anomeric outcome of the reaction. (See molecular models **11** to **17**.)

The mixture of solvents of the intramolecular reaction presents the advantage of favoring a maximum aromatic stacking due to their non-intercalation with the aromatic protecting groups.

The last intramolecular glycosylation product with the succinylamide ethyl spacer shows the interesting character of containing a constrained tether contituting a C_{10} ring in which a ß-turn occurs. Another amazing part of its structure is the dissacharide sugar moiety that serves as an intraanular bifurcated hydrogen bond donor and as a template that stabilizes a ß-turn like stucture resembling a 3_{10} -helix found frequently in globular protein. The disaccharide sugar funtions also as a bifurcated extraannular hydrogen bond donor, flanking the 6-OH benzyl group to strongly stack with the 4,6-O-benzylidene protecting group of the glucose acceptor, thus a dyad aromatic stacking. (See molecular models in fig. **16**,**17**)

Another main advantage of this methodology is the cleavage of the succinyl ester part of the tether in the products by mild conditions that furnishes the opened chained **459** disaccharide with 2-OH free on the galactose's donor and the other on the glucose acceptor. The next step is the conversion of the carboxylic acid of the chain to a methyl ester, which can be achieved through reaction with DCC and methanol . Than comes of selective benzoylation one of these 2-OHs, most likely on the side of the galactose donor, thus allowing the eventual glycosylation of the free 2-OH of the glucose acceptor with another protected sugar.

Furthermore, the opened tethered disaccharide that bears a carboxylic group herein, can be converted to a methyl ester acid and than further to a pentafluorophenol ester which opens the aim toward a couplage with a polypeptide or bind a protein.

Noteworthy to account for, is the benzylidene protecting group on the glucose acceptor part that can be submitted to selective cleavage, furnishing a free hydroxyl group either on the 4-O- or 5-O position of the glucose acceptor to be further glycosylated with another sugar, thus convertion of the carbohydrate moiety to a more complexed saccharide.
This practical and flexible methodology leads to the applicability of higher saccharides synthesis. Despite the significant contributions achieved through all of these various methods of intramolecular glycosylation and "intramolecular aglycon delivery", this method remains classifiable as one of a novel synthetic methodology in carbohydrate chemistry. It opens bright perspectives for the obtention and formation of other important glycosidic linkages present in many natural compounds.

EXPERIMENTAL PART

5. Experimental Part

Instrumentation

NMR-Spectrum

^{1}H-NMR-Spectrum: Bruker Avance 400 (400 MHz)

Bruker AMX 600 (600 MHz)

^{13}C-NMR-Spectrum: Bruker Avance 400 (400 MHz)

Bruker Avance 600 (600 MHz)

The chemical shifts were measured utilizing tetramethysilane (TMS) as internal standard solvent and δ-measued in ppm . The main solvent mixture utilised is chloroform-d_6 and trimethylsilane ($CDCl_3$-d_6-TMS). Coupling constants were recorded in Hertz.

Other solvent used was deuterium dimethyl sulfoxide (DMSO-d_6).

Datas are reported as follow: chemical shift

s: singlet	m: multiplet
b: bright signal	dd: double doublet
d: doublet	ddd: triple doublet
t: triplet	dt: double triplet
q: quadruplet	dq : double quadruplet
quint: quintuplet	tt: triple triplet

Optical rotations were measured by 20°C on a Perkin Elmer Polarimeter 241

High Resolution Mass Spectroscopy were recorded on the Mass spectrometer MAT 711.

Melting points were measured on Büchi Apparatus, Modell SMP-20 with Silicon bath

Analytical thin layer chromatography (TLC) was performed on Silicagel-Polygram SIL G plates (Macherey & Nagel). The compounds were visualizesd by UV_{254} light and the chromatography plates were sprayed by 5% sulfuric acid in ethanol solution .

Preparative Column chromatography was performed using silica gel (40-63 μm) (Macherey & Nagel).

All solvents were distilled and dried according to literature methods.

Sensitive reactions were carried out under argon atmosphere with dried absolute solvents

Reagents and Materials

Acetonitrile, absolute (Fluka, Agross), Acetic anhydride, Aminopentanol (Fluka), Aminobutanol (Acros), Aminopropanol (Acros), Aminoethanol (Acros), Benzylbromide (Fluka), Benzyloxychloroformate (Fluka), Benzaldehydedimethylacetal (Fluka),Benzoyl chloride (Fluka), Borontrifluoride etherate (Fluka, calcium carbonate, 4- (Dimethyl-amino) pyridine, D(+) Glucose (Fluka, Acros), D(+) Galactose (Fluka, Acros), Hydrobromic acid in 33% acetic acid, (Fluka), Ion exchange (Dowex 50Wx 8 H^+ Form), Lutidine, (Fluka) L (-) Rhamnose, (Fluka), Molecular Sieve 3 and 4Å (Roth), Mercuric (II) bromide, (Fluka, Acros), Mercuric(II) cyanide, (Fluka,Acros) *N,N'*-Dicycohexylcarbodiimide (Fluka, Merk), N-Iodosuccinic (Fluka), Paladium on calciumcarbonate (Lindlar's catalyst), (Fluka) Potassium carbonate (dried), Sodium acetate, (dried, Baker), Sodium hydride (Fluka), Succinic anhydride (Fluka), Thiophenol (Fluka), Trifluoromethanesulfonatetrimethylsilylester, (Fluka), Triethyamine, (Fluka), Trichloroacetonitrile (Acros, Fluka).

Nomenclature of synthesized Compounds.

(408) Synthesis of 1,2,3,4,6-penta-O-acetyl-α/β-D-galactopyranoside

(409) Synthesis of 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosidebromide

(410) Synthesis of 3,4,6-tri-O-acetyl-1,2-O-methoxyethyldene-α-D-galactopyranoside**.**

(411) Synthesis of 1,2-di-O-methoxyethyldene-α-D-galactopyranoside.

(412) Synthesis of 1,2-O-(1-methoxyethylene)-3,4,6-tri-O-benzyl-α-D-galactopyranoside

(413) Synthesis of Phenyl-1-thio-2-O-acetyl-3,4,6-tri-O- benzyl-β-D-galactopyranoside

(414) Phenyl-1-thio-3,4,6-tri-O-benzyl-β-D- galactopyranose

(415) Phenyl-1-thio-3,4,6-tri-O-benzyl-2-O-(3-carbonylpropanoyl)-β-D-galactopyranoside

(416) Phenyl-1- thio- 3,4,6-tri-O-benzyl-2-O- (3-carbonylpropanoylpentafuorophenol ester)-β-D- galactopyranose

(417) Synthesis of 1,2,3,4,6-penta-O-benzoyl-β-D- glucopyranoside

(418) Synthesis of 2,3,4,6-tetra-O-benzoyl-α-D-glucopyranosylbromide

(419) Synthesis of 2,3,4,6-tetra-O-α/β- D-glucopyranoside

(420) Synthesis of 2,3,4,6-Tetra-O-benzoyl-α/β-D-glucopyranosyltrichloroacetimidate

(421) Synthesis of 5-Benzyloxycarbonylaminopentane-1-ol

(422) [5-N-(Benzyloxycarbonylamino)-pentyl]-2,3,4,6-tetra-O-benzoyl-β-D-glucopyranoside

(423) [5-(N- Benzyloxycarbonylamino)-pentyl]-β- D- glucopyranoside

(424) 5-N-(Benzyloxycarbonylamino)-pentyl]-4,6-O-benzylidene-β-D-glucopyranoside

(425) 5-Aminopentyl-4,6-O-benzylidene-β-D –glucopyranose

(426) Phenyl-1-thio-3,4,6-tri-O-benzyl-β-D-galactopyranose-(2-yloxycarbonyl-propanoyl aminopentyl)-4,6-O-benzylidene-β-D-glucopyranoside

(427) Synthesis of [3,4,6-tri-O-benzyl-ß-D-galactopyranoside- (1→3)-2-yl-oxy carbonyl-propanoylaminopentyl]-4,6-O-benzylidene-ß-D-glucopyranoside

(428) Synthesis of [Phenyl-1-thio-3,4,6-tri-O-benzyl-α-D-galactopyranoside-(1→3) 2-yl-oxycarbonyl-propanoylaminopentyl]-4,6-O-benzylidene-ß-D-glucopyranoside.

(427) Synthesis of [3,4,6-tri-O-benzyl-ß-D-galactopyranoside- (1→3)-2-yl-oxy carbonyl-propanoylaminopentyl]-4,6-O-benzylidene-ß-D-glucopyranoside

(428) Synthesis of [Phenyl-1-thio-3,4,6-tri-O-benzyl-α-D-galactopyranoside-(1→3) 2-yl-oxycarbonyl-propanoylaminopentyl]-4,6-O-benzylidene-ß-D-glucopyranoside.

(429) Synthesis of 4-Benzyloxycarbonylaminobutane-1-ol

(430) [5-N (Benzyloxycarbonylamino)-butyl]-2,3,4,6-tetra-O-benzoyl-β-D-glucopyranoside.

(431) [4-N-(Benzyloxycarbonyamino)-butyl]-β-D- glucopyranoside

(432) [4- N (Benzyloxycarbonylamino)-buty]l-4.6-O-benzylidene-β-D-glucopyranoside.

(433) 4-Aminobutyl-4,6-O-benzylidene-β-D- glucopyranoside

(434) [Phenyl-1-thio-3,4, 6-tri-O-benzyl-β-D-galactopyranoside -(2yloxycarbonyl propanoylaminobutyl)-4,6-O- benzylidene-β-D- glucopyranose] –

(435) Synthesis of [3,4,6-tri-O-benzyl-ß-D-galactopyranoside-(1→3)-(2-yl-oxycarbonyl propanoylaminobutyl] 4,6-O-benzylidene-ß-D-glucopyranoside.

(436) Synthesis of [3,4,6-tri-O-benzyl-α-D-galactopyranoside-(1→3)-(2-yl-oxycarbonyl propanoylaminobutyl] 4,6-O-benzylidene-ß-D-glucopyranoside.

(437) Synthesis of 1,2,3,4,6-penta-O-acetyl-α,β-D-glucopyranoside **.**

(438) Synthesis of 2,3,4,6-tetra-O-acetyl-(α)-D-glucopyranosylbromide.

(439) Synthesis of 3-Benzyloxycarbonylaminopropane-1-ol

(440) [3-N- (Benzyloxycarbonylamino)-propyl]- 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside

(441) [3-N-(Benzyloxycarbonylamino)-propyl]-β-D- glucopyranoside

(442) [3-N-(Benzyloxycarbonylamino)-propyl]-4,6-O-benzylidene-β-D-glucopyranoside

(443) 3-Aminopropyl-4,6-O-benzylidene-β-D- glucopyranoside.

(444) [Phenyl-1- thio-3,4,6-tri-O-benzyl-β-D-galactopyranose-(2yloxycarbonylpropanoyl aminopropyl-4,6-O-benzylidene-β-D-glucopyranose

(445) 3,4,6-tri-O-benzyl-ß-D-galactopyranoside- (1→3)- [2-yl-oxycarbonyl propanoyl aminpropyl]-4,6-O-benzylidene-ß-D-glucopyranoside)

(446) 3,4,6-tri-O-benzyl-α-D-galactopyranoside- (1→3)-[2-yl-oxycarbonyl propanoyl aminopropyl]-4,6-O-benzylidene-ß-D-glucopyranoside.

(447) Synthesis of 2-Benzyloxycarbonylaminoethanol**.**

(448) [2-N-(Benzyloxycarbonylamino)-ethyl]-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside

(449) [2-N-(Benzyloxycarbonylamino)-ethyl]-β-D-glucopyranoside**.**

(450) [2-N-(Benzyloxycarbonylamino)-ethyl-4,6-O-benzylidene-β-D-glucopyranoseide.

(451) 2-Aminoethyl-4,6-O-benzylidene-β-D-glucopyranoside.

(452) [Phenyl-1-thio-3,4,6-tri-O-benzyl-β-D-galactopyranose-(2-yloxycarbonyl propanoyl aminoethyl)-4,6-O-benzylidene-β-glucopyranoside]

(453) 3,4,6-tri-O.benzyl-α-D-galactopyranoside-(1→2)-[2-yloxy-carbonyl-propanoyl aminoethyl]-4,6-O-benzylidene-ß-D-glucopyranoside

(454) 3,4,6-tri-O.benzyl-α-D-galactopyranoside-(1→3)-[2-yloxy-carbonyl-propanoyl aminoethyl]-4,6-O-benzylidene-ß-D-glucopyranoside.

(455) 1,2,3,4-tetra-O-acetyl-α-L-rhamnopyranoside

(456) Phenyl 1-thio-2,3,4-tri-O-acetyl-α-L-rhamnopyranoside

(457) Phenyl 1-thio-α-L-rhamnopyranoside.

(458) Synthesis of phenyl-1-thio-2,3,4-tri-O-benzoyl-α-L-rhamnopyranoside

(459) Synthesis of 3,4,6-tri-O-benzyl-pentylamide-ethylcarboxylic acid-4,6-O-benzylidene -galactopyranoside-ß-D-(1-3)-glucopyranoside

Experimental Procedures

Synthesis of 1,2,3,4,6-penta-O-acetyl-α/β-D-galactopyranoside (408).[63]

To a stirring mixture of 375 ml (397.5 mmol) of acetic anhydride and 25 g (305 mmol), were added portion wise 50g, (277.50 mmol) of galactose. The reaction mixture was heated to 130°C until a clear solution is observed, following a further heating to 140°C for 15 minutes. The reaction is followed by TLC , toluene/acetone 6:1. The mixture is brought to room temperature diluted with 400 ml of dichloromethane and worked up with iced water, twice with cold saturated sodium hydrogen carbonate and again with iced water. The organic phase is dried on sodium sulphate, filtered and solvent removed in vacuo. The remaining acetic anhydride is removed azeotropically three times with ethanol, and toluene to a crude product which is than recrystalized in ethanol to an off- white crystalline product.

Percentage yield 76.30 g (230.60 mmol) 70%
melting point : 141-143°C

Synthesis of 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosidebromide (409). [73]

In a solution of 60g (150.70 mmol) of **1** dissolved in 130ml, were added slowly, drop wise 115.16 ml (647 mmol) of HBr in 33% acetic acid at 0°C. The solution mixture was brought to room temperature and stirred. When TLC control toluene/acetone reveals end of reaction, the solution is diluted in 150ml of dichloromethane and worked up with iced water, twice with saturated solution of sodium hydrogenocarbonate, and iced water. The organic phase was dried on sodium sulphate, filtered, and reduced in vacuo. The crude oily product was recrystallized in ether/hexane 1:1 to a white solid.

Percentage yield: 54.70g (128.10 ml), 85%
melting point: 83-85°C

Synthesis of 3,4,6-tri-O-acetyl-1,2-O-methoxyethyldene-α-D-galactopyranoside. (410) [64]

Compound **2** 54.70g (106.80 mmol) was dissolved in 200 ml dichloromethane and mixed with 35.30 ml, (26 mmol), 28.g of lutidine, and 31 ml, (975 mmol), 31.07g of absolute methanol and stirred overnight. When TLC, toluene/acetone 4:1 reveals end of the reaction, the mixture was worked up with iced water , saturated solution of sodium hydrogen carbonate, and water, than dried on sodium sulphate, filtered, and reduced in vacuo to an oily product (47g, 142.30 mmol) that was directly used for deacetylation reaction.

Synthesis of 1,2-di-O-methoxyethyldene-α-D-galactopyranoside. (411) [64,65]

In a solvent mixture of 200ml toluene/methanol 1:1 were dissolved the triacetylated ortho ester derivative **3**, (47g, 142.30 mmol) and a catalytically amount of 1M sodium methanolate were added until a ph of 12. the reaction was stirred 40 minutes at room temperature and its course verified by TLC, toluene/acetone 2:1. As the end of the reaction is shown by TLC,

the mixture is evaporated in vacuo to (32.61g, 138.80 mmol) of semi-solid product, that was directly used for benzylation reaction.

Synthesis of 1,2-O-(1-methoxyethylene)-3,4,6-tri-O-benzyl-α-D-galactopyranoside (412)[64]

A suspension of (19,87g, 829 mmol) of NaH in 60 ml DMF was cooled to 0°C. The deacetylated (α-D- glycoside orthoester **(4)** (32,61g ,138,8 mmol) was dissolved in 100 ml of DMF and were added dropwise to the suspension NaH followed by another dropwise addition of benzyl bromide (83,98 g ,490 mmol,59,13ml) and stirred at 25°C. The reaction is followed TLC, (toluene-acetone 8:1). When the end of the reaction is revealed by TLC, The mixture is cooled to 0°C and the excess of NaH is eliminated by careful addition of methanol, than brought up to room temperature, diluted in CH_2Cl_2 100 ml, worked up with water, followed by two more extractions with CH_2Cl_2, and worked up with a saturated solution of $NaHCO_3$ and water. It is than dried on $NaSO_4$ concentrated, and co-evaporated with toluene until total elimination of the remaining DMF. The crude oily product was recrystallised in diethylether-hexane 1:1. A white crystalline product (45g, 89 mmol) was obtained.

Percentage yield 64%
mp: 83-85°C

Synthesis of Phenyl-1-thio-2-O-acetyl-3,4,6-tri-O- benzyl-β-D-galactopyranoside (413) [82]

To a solution of **(5)** (27.00g, 53mmol) in 230ml of dried acetonitrile mixed with 800 mg, 2.4 mmol of $HgBr_2$ cooled to0°C, was added drowise (8.49g,77.18 mmol,7.90 ml) of thiophenol. The reaction mixture is raised to room temperature, heated to 60°C and stirred 24h. The reaction was controlled by TLC (petroleum ether-hexane 3:1). At the end of the reaction, the mixture is cooled down to 25°C, dissolved in CH_2Cl_2, and worked up with water, saturated solution of $NaHCO_3$, and water, dried on Na_2SO_4, filtered, and concentrated, to yield a oily product. The oil was than recrystallised in ethanol, to a white crystalline product.

Percentage yield 16,25g (27.80 mmol ; 52.4%)
mp: 106-108°C

^{1}H-NMR($CDCl_3$):δ=7.56-7.08 (aromatics), 5.45-5.40 (t,1H,$J_{1,2}$ = 9.85Hz , $J_{2,3}$ = 9.85 Hz, H-2), 4.95-4.92(d,1H, J(H_a,JH_b)= -11.62, Ha benzyl), 4.71-4.39(m,6H,H-1,CH_2Ph), 3.99-3.98 (d,1H, $J_{3,4}$ =2.78, H-4), 3.69-3.61(m,3H,H-5,6a,6b),3.57-3.54(dd,1H,$J_{3,4}$=2.78 Hz, $J_{2,3}$ = 2.78 Hz, H-3), 2.00(3H, s, CH_3).

^{13}C-NMR ($CDCl_3$) : δ =169.42 ($COOCH_3$),138.38-126.51(aromatics),86.59 (C1),81.37 (C-3),77.52(C-5),74.28 (C-4), 74.28,73.52,71.90 (CH_2Ph),72.70 (C-2), 69.61(C-6), 21.00 (CH_3).

Phenyl-1-thio-3,4,6-tri-O-benzyl-β-D- galactopyranoside (414). [65, 67]

The resulting product **(** 6**)** was dissolved in a solvent mixture toluene-methanol 1:160ml of each, and a catalytic amount of 1M MeONa was added until pH of 12. It is heated 2h30 min to reflux at 75°C. The reaction medium is cooled to 25°C and than neutralized

with Dowex 50W 8 H^+ ion exchange, filtered and evaporated in vacuo to give an oily product,which is recrystallised with ethylacetate/hexane, resulting to a colorless solid.

Percentage yield 11.50g, 22 mmol; 79.10%)
Melting point: 87-88°C

Phenyl-1-thio-3,4,6-tri-O-benzyl-2-O-(3-carbonylpropanoyl)-β-D-galactopyranoside (415) [64,67]

Phenyl-1-thio-3,4,6-tri-O-benzyl-β-D-galactopyranose **(414)**, (11.50g, 22 mmol) and (22g 220 mmol) succinicanhydride, and a catalytic amount of DMAP were dissolved in 270ml of distilled pyridine and heated to 65-70°C overnight. The reaction course was followed by TLC (toluene-acetone 6:1). The residue is cooled down to 25°C, and worked up with water, iced 1M HCl, followed by three extractions with 3x 100ml CH_2Cl_2, than twice with saturated solution $NaHCO_3$, than water. The organic layers were dried on Na_2SO_4 filtered concentrated and, coevaporated with toluene for elimination of the remaining pyridine. A raw dark-brown raw product is obtained, and purified by chromatography, eluting with toluene/actone/0.1% CH_3COOH to a white foamy product.

Percentage yield (8.30g, 13.28 mmol; 60.40%)
$[\alpha]_D$ = +12.5° (c=1, $CHCl_3$)

^{1}H-NMR ($CDCl_3$) : δ= 7.49-7.00 (aromatics), 5.38-5.33 (t,1H,$J_{1,2}$=9.85,$J_{2,3}$= 9.86), 4.87-4.84 (d,1H, J=-11.62, Ha, benzyl),4.60-4.32 (m,6H, H-1, CH_2Ph),3.90-3.87 (d,1H, $J_{3,4}$= 2.53, H-4), 3.62-3.48 (m,4H,H-5.6a,6b, H-3), 2.61-2.45, (m,4H,CH_2), 2.10 (s,3H, CH_3).

^{13} C-NMR ($CDCl_3$) : δ = 177,18 (COOH), 170.70 ($COOCH_3$),138.28-127.43 (aromatics), 86.53 (C-1), 81.33 (C-3), 77.57 (C-5), 74.30,73.57,72.03 (CH_2Ph), 72.77 (C-4), 70.13 (C-2),68.75(C-6),28.98-28.73 (CH_2).

Phenyl-1- thio- 3,4,6-tri-O-benzyl-2-O- (3-carbonyl-propanoylpentafuorophenol ester-β-D- galactopyranoide (416). [88]

Dicyclohexyl carbodiimide (2.74g,13.28 mmol) were added to a solution of **(415)** (8.30g, 13.28 mmol) mixed with, (2,44g,13.28 mmol) of pentafluorophenol in 120ml of ethyl acetate. The reaction must be carried out at 0°C.When TLC (toluene-acetone 8/1) reveals end of reaction, the mixture is warmed up to room temperature, concentrated, and recrystalized with ethanol/hexane. A white precipitate was obtained.

Percentage yield 9.30g (11.51mmol; 86.70%
mp: 75-77°C
$[\alpha]_D$ = +133 (c=1, $CHCl_3$)

HRMS m/z calculated for C_{43} H_{37} O_8 S F_5 Na
Calculated : (831.20270)
Found : (831.20503)

^{1}H-NMR ($CDCl_3$): δ= 7.48-7.18 (m,20H, H,aromatic), 5.47-5.43(t,1H,$J_{1,2}$=9.60,$J_{2,.3}$=9.85), 4.96-4.93, (d,1H, J=-11.62, H-2), 4.60-4.410, (m,6H,H-1,CH_2Ph), 4.01-4.00, (d, 1H, J= 2.78, H-4), 3.70-3.58 (m,4H, H-5,6a,6b, H-3, $J_{2,3}$=2.78,$J_{3,4}$=2.78), 2.98-2.95,(m,2H,CH_2) 2.79-2.61, (m,2H, CH_2).

^{13} C-NMR ($CDCl_3$): δ = 169.89-168.21,(COO),138.41-127.48,(C, aromatics), 86.39 (C-1), 81.50 (C-3), 77.64 (C-5), 74.42,73.62,72.06, (CH_2Ph), 72.86(C-4),70.40(C-2), 68.72 (C-6), 28.93,28.30 (CH_2).

Synthesis of 1,2,3,4,6-penta-O-benzoyl-β-D- glucopyranoside (417) [74]

To a solution of glucose monohydrate (40g, 222 mmol) , in pyridine (125ml, 1.55 mmol) and chloroform (200ml) cooled to 0°C, benzoylchloride (185ml,155 mmol) was added dropwise. The mixture is stirred and refluxed at 65°C for 1h. and is than brought to room temperature. The solution is diluted with 200ml of chloroform and worked up with ice water, 2N HCl (150ml) 2x saturated solution of $NaHCO_3$, and cold water. The organic phase was dried on Na_2SO_4, concentrated in vacuo, and re-crystallised in methanol.

Percentage yield (125g,183.3 mmol, 83%): mp= 180.5°C.

Synthesis of 2,3,4,6-tetra-O-benzoyl-α-D-glucopyranosylbromide (418).[73]

Compound **417** (45g, 63mmol),was dissolved in 150 ml of dichloromethane, and cooled to 0°C. A solution of HBr in 33% acetic acid, (36 ml, 204 mmol) was added drop wise and the mixture was stirred 90 minutes at room temperature.The workup was proceeded with iced water, 2x saturated solution of $NaHCO_3$, and iced water. The organic phase was dried on Na_2SO_4, reduced, and dried on vacuumpump to a colorless foam.

Percentage yield (34g, 50.30mmol, 80%)

Synthesis of 2,3,4,6-tetra-O-α/β- D-glucopyranose (419). [75,76,77,78]

A solution of **418** was prepared by dissolving (34g, 51.60 mmol) of it in 300 ml of acetone, and 43ml of water. Sodium iodide (1.00g) was added to catalyse the reaction, and the mixture was stirred overnight at 40°C. The solution was cooled to 25°C, and evaporated in vacuo to eliminate the acetone. The crude aqueous residue was diluted in 200 ml dichloro methane, worked up with water, saturated solution of $NaHCO_3$, sodium thiosulphate, and water. It was than dried on Na_2SO_4, concentrated, set under vacuum pump to give a white foam. One proceeded to the purification of the product by filtration through column chromatography with toluene-acetone 8:1. A pure white foam is obtained after a reset to vcuum pump.

Percentage yield (28.25g, 47.35mmole; 92%)

Synthesis of 2,3,4,6-Tetra-O-benzoyl-α/β-D-glucopyranosyltrichloroacetimidate (420). [78,80,81]

To a solution of **419**, (28.25g, 47.3 mmole), mixed with K_2CO_3 (32.60g, 235.94 mmole) diluted in 200 ml of dichloromethane, cooled to 0°C, are added dropwise(28.7ml, 41g, 284mmole) of trichloroacetonitrile and the mixture was stirred overnight. When TLC reveals end of reaction, the mixture was centrifuged to separate the K_2CO_3, concentrated in vacuo, and set under vacuumpump to give an off-white foam. The foamy product was purified through filtration on column chromatography toluene-acetone 16:1, and rest on vacuum pump. A pure white foam was obtained.

Percentage yield (29.70g, 40.08mmole; 85%).

^{1}H-NMR ($CDCl_3$): δ = 8.64-7.08 (m, H, aromatics), 6.77-6.76 (d,1H,$J_{1,2}$ = 3.79Hz, H-1), 6.23-6.16 (dd,1H, $J_{2,3}$ = 9.86 Hz, H-3), 5.93-5.89 (t,1H,$J_{3,4}$ = 9.09 Hz, $J_{4,5}$ = 9.10Hz, H-4), 5.75-5.67 (m,2H. H-6a,6b), 5.57-5.53(dd,1H, $J_{1,2}$ = 3.79 Hz,$J_{2,3}$ = 3.54 Hz, H-2), 4.60-4.55 (m,2H, H-6a, H-5) 4.49-4.39 (m,2H,H6b-H-5,H6a)

^{13}C-NMR ($CDCl_3$): δ = 166.02, 165.61, 165.37, 165.15, (COO), 160.48(-C=NH), 133.50-127.26 (Aromatics-C-Benzoyl), 95.82 (C-1, α-cuppling), 92.31(CCl_3),70.61 (C-3), 70.1 (C-5), 68.96 (C-2), 67.86 (C-4) 62.40 (C-6).

Synthesis of 5-Benzyloxycarbonylaminopentane-1-ol (421). [87]

In 400 ml of water are dissolved (25g, 242.40mmol) of Z-aminopentanol with, (50g, 471.70 mmol of Na_2CO_3) and cooled down to 0°C. Benzyl chloroformate (40.80g, 38 ml, 260.80 mmol) was added drop wise to the cold stirred solution over 0.5 h. The mixture was stirred at 0°C for 2 to 3h, brought up to room temperature and worked up twice with cold water. The organic layer was dried on $NaSO_4$, filtered, and concen trated to a colorless oil. The oily product was set under vacuum pump and, resulted to the formation of a white foam, which was than recrystallised in diethylether to yield a white solid.

Percentage yield (48.00g, 202.53mmol; 83.50%): mp 44-46°C.

[5.N-(Benzyloxycarbonylamino)-pentyl]-2,3,4,6-tetra-O-benzoyl-β-D-glucopyranoside (422) [80,81]

The α, ß-glucosyl imidate **420** (11g, 12.84 mmole) is mixed with Z-aminopentanol **421** (3.18g, 13.50 mmole) are submitted to argon atmosphere and, dissolved in 200ml absolute CH_2Cl_2. The mixture is cooled down to-20°C and, TMSOTf (246µl, 1.32 mmole) are added and the reaction mixture is stirred at-20°C until TLC, toluene-acetone 8:1 reveals the end of reaction. The reaction medium is neutralised with a few drops of pyridine, or triethyl amine, and diluted in 100ml CH_2Cl_2, worked up with water, saturated solution of $NaHCO_3$, and water. It is than dried on Na_2SO_4, filtered, concentrated, and chromatographed with (toluene-acetone 10:1) to give a colorless oily product.
Percentage yield 8.20g, (10.14 mmole) 78.20%

^{1}H-NMR ($CDCl_3$): δ = 8.06-7.83 (aromatic-Benzoyl-H), 7.57-7.18 (aromatics Phenyl-H), 5.94 5.89 (t,1H,J_{3-4}) =9.60Hz, $J_{4,5}$= 9.60Hz, H-4), 5.72-5.67 (t,1H, $J_{-2,3}$= 9.60Hz, H-3), 5.55-5.51 (dd, 1H, $J_{1,2}$=7.83 Hz, H-2), 5.09 (brs, 1H, NH), 4.84-4.82 (d,1H, $J_{1,2}$=7.83Hz),4.68-4.64(dd, 1H, $J_{6a,6b}$=12.06Hz,J_{-6a-5}= 3.28Hz, H-6a), 4.53-4.49 (dd, 1H, J_{5-6b} = 5.05Hz, H-6b), 4.18-4.14 (ddd,1H, $J_{4,5}$ = 8.84Hz, H-5),3.95-3.90 (dt.1H,O-CH_2), 3.56-3.51 (m,1H, CH_2),3.26-3.22 (m,1H, CH_2),2.97-2.93(m,1H, -CH_2NH-),1.94,1.67 (m,6H, -O-$(CH_2)_4$-NH-).

^{13}C-NMR ($CDCl_3$): δ = 166.08-164.97 (CO), 151.00 (CO), 133.36-127.98 (aromatics), 101.20, 133.36-127.97 (Aromatics- Benzoyl, aromatics- Phenyl), (C-1),72.77 (C-3), 72.10 (C-5), 71.84 (C-2), 69.88 (CH_2-Phenyl), 69.69 (C-4), 66.42 (OCH_2), 40.71 (-NH-CH_2-), 30.85,29.27,28.81,22.94, (CH_2).

Synthesis of [5-(N- Benzyloxycarbonylamino)-pentyl]-β- D-glucopyranoside (423) [65,82]

To a solution of **422**, (8.20g, 10.14mmole) in toluene:methanol 1:1 (120ml), were added at room temperature a catalytical amount of 1M sodium methoxide until pH reaches 13. The solution was stirred overnight, the reaction followed by TLC, (toluene-acetone 1:2). The reaction medium was neutralised with Dowex 50Wx 8 H^+ ion exchange, filtered and reduced in vacuo. An oily product was obtained and used immediately for benzylidination reaction.

Percentage yield (3.80g, 9.52mmole, 94%).

[5-N(Benzyloxycarbonylamino)-pentyl]-4,6-O-benzylidene-β-D-glucopyranoside (424) [79,80,81]

Benzaldehyde dimethylacetal (1.78g, 11.61mmole,1.77ml), and a catalytical amount of para-toluosulfonic acid (0.221g, 1.161mmole) were added to a solution of **423**, (3.80, 9.52 mmole), and the mixture stirred overnight. The reaction is controlled by TLC (toluene-acetone2:1), and the mixture is neutralised with a few drops of triethyamine. It is than diluted in 50ml of dichloromethane, poured in water , extraced twice with 70 ml of dichloromethane, and worked up with saturated solution of $NaHCO_3$, and water.The combined organic phase is dried in Na_2SO_4, filtered concentrated and the crude product is recrystallised with ethyl acetate/ hexane 1:3 to give a white solid compound.

Percentage yield (3.30g, 6.755 mmole) 71% mp: 113-115°C

^{1}H-NMR ($CDCl_3$) δ = 7.88-7.25 (H aromatics), 5.50 (s,1H,CHϕ),4.36-4.34 (d,1H, $J_{1,2}$ = 7.83,H-1), 4.33-4.29 (dd,1H, $J_{6a,6b}$= -10.50Hz, H-6a), 3.90-3.88 (t,1H,$J_{4,5}$ = 9.80Hz, H-4), 3.54-3.13 (2m, 4H, H-5,6b,OCH_2).

^{13}C-NMR ($CDCl_3$) δ = 136.98-126.25 (C aromatics), 103.20 (C-1),101.80 (CHϕ), 80.48, (C-4), 74.52 (C-2), 73.19 (C-3), 70.1(CH_2, Z),68.62 (C-6), 66.64 (OCH_2), 66.33 (C-5).

5-Aminopentyl-4,6-O-benzylidene-β-D –glucopyranoside (425) [83]

To a solution of **424** (1.563g, 3.20 mmole) dissoled in 60 ml of ethanol is added a catalytical amount of Lindlar's catalyst (Ba_2CO_3), and submitted to hydrogenation. The reaction is

followed by TLC acetone-toluene 3:1. When tlc reveals end of the reaction, the reactin medium is filtered on celite, and reduced in vacuo.

Percentage yield (1.00g, 2.91 mmole), 91% yield

[Phenyl-1-thio-3,4,6-tri-O-benzyl-β-D-galactopyranoside-(2-yloxycarbonyl-propanoyl aminopentyl)-4,6-O-benzylidene-β-D-glucopyranoside (426) [88]

Under argon atmosphere the amine β-D- glucopyranose acceptor (1.00g, 2.912 mmole), **425** and the β-D-galactose pentafluorophenolester **416** (1.133g,1.402 mmole) were mixed in 100ml ethylacetate. The mixture was stirred overnight and, during the course of reaction most of the product precipitated because of its low solubility in ethyl acetate. When TLC, (toluene/ acetone 2:1) reveals end of the reaction, the product precipitate was filtered by suction and, recrystalised from acetone/hexane 1:3). The filtrate was reduced in vacuo and the rest of the crude product was simply purified by filtration on column chromatography (CH_2Cl_2 acetone (3:1).

Percentage yield (1.20g, 1.23 mmole, 88%) mp:158-160°C
$[\alpha]_D$ = -11.2

HRMS m/z calculated for $C_{55}H_{63}NO_{13}SNa$
Calculated: 1000.3917 M+Na Found: 1000.3997

H-NMR (CDCl3), δ = 7.50-7.21 (H aromatics), 6.04-6.01 (t,1H,NH),5.52(s,1H, CHPh), 5.45-5.42 (1,1H,$J_{2,3}$ =9.81, $J_{3,4}$ =9.85, H-2_{gal}), 4.94-4.92(d, 1H,J=11.62(CH_2Ph) 4.67-4.37 (3m,8H, CH_2Ph, H-1), 4.35-4.32 (dd,1H,$J_{6a,6b}$=10.61, H-$6a_{glc}$), 4.31-4.21, (d,1H,$J_{1,2}$ =7.58, H-1_{glc}) 3.98-9.95 (d.1H. $J_{4,5}$ = 2.53, H-4gal), 3.83-3.39(3m,9H,H-3_{gal},H-5_{gal},H6a,$6b_{gal}$,H-2_{glc}, H-$3_{glc,}$H-4_{glc},H-5_{glc},H-$6b_{glc}$),3.31-3.13(2m,2H, CH_2O),2.73-2.58(m,3H,CH_2), 2.47-2.44 (t,2H,CH_2) 1.88-2.00,(m,2H,CH_2).

^{13}C-NMR ($CDCl_3$), δ = 172.02 (COO), 171.51 (CONH),138.24-126.21 (C aromatic), 86.71 (C-1_{gal}), 81.15 (C-4_{glc}),77.53 (C-5_{gal}),74.58 (CH_2Ph),74.32 (C-3_{glc}), 73.47 (CH_2Ph) 72.82 (C-4_{gal}), 72.03 (CH_2Ph), 70.13 (C-5_{glc}), 70.00(CH_2O), 68.64 (C-6_{glc}), 68.61 (C-6_{gal}) 66.27(C-5_{glc}).

Intramolecular Glycosylation NIS/TMSOTf

Synthesis of [3,4,6-tri-O-benzyl-ß-D-galactopyranoside-(1→3)-2-yl-oxycarbonyl-propanoyl aminopentyl]-4,6-O-benzylidene-ß-D-glucopyranoside. (427) [88,89,92]

Dichloromethane/acetonitrile 1:1 as solvent.

Compound **36 (**1.20g, 1.23 mmole) was set under argon atmosphere, dissolved in50 ml solvents dichloromethane and stirred for 10 minutes. An additional 50ml of acetonitrile was added to the medium, and cooled down to –5-10°C. At this temperature, the activator NIS (1.52g, 6.725 mmole) is added and the reaction left stirring 30minutes. When the end

of reaction is revealed by TLC (toluene/acetone 2:1), the medium is neutralised with a few drops of triethyl amine or pyridine, diluted in dichloromethane, washed with water, saturated solution of $NaHCO_3$, $Na_2S_2O_3$, and water. The organic phase is dried on Na_2SO_4, filtered, and concentrated in vacuo. The isomers are purified and separated by column chromatography toluene/ acetone 4:1.

Overall percentage yield 0.60g, 0.691 mmole)

Major product β(1-3) glycosidic bond **(427)**
Minor product α(1-3) glycosidic bond **(428)**

Glycosidic bond	mass in g	mmole	%yield	melting points	$[\alpha]_D$
Major product β(1-3)	0.54g	0.622	50%	225-228°C	-15
Minor product α(1-3)	0.053g	0.061	6%	170-172°C	-8.6

HRMS m/z calculated for $C_{49}H_{57}O_{13}N\,Na$
Calculated : 890.3809
Founded : 890.3727

HRMS for minor product m/z calculated for $C_{49}H_{57}O_{13}N\,Na$
Calculated: 890.3728
Founded : 890.3761

^{1}H-NMR ($CDCl_3$) δ = 7.47-7.21(m, H, aromatics), 5.84-5.82 (brs,1H, NH), 5.49 (s,1H,CHPh), 5.33-5.30 (t,1H, $J_{2,3}$ =7.94 Hz, $J_{3,4}$ =7.94 Hz, H-2_{gal}), 4.90-4.88 (d,1H, J= -11.74), CH_2Ph), 4.64-4,58 (m,3H, CH_2Ph, H-1_{gal}), 4.49-4.47 (d,1H, J = 12.12 Hz), 4.39-4.28 (m,5H,CH_2Ph, H-1_{glc}, H-$6a_{glc}$), 4.35-4.33 (d,1H, $J_{1,2}$ = 7.52 Hz, H-1_{glc}), 3.973-3.970 (d,1H, $J_{4,5}$ = 2.50), 3.74.3.34 (5m,11H, H-3_{gal}, 5_{gal},,$6a_{gal}$,$6b_{gal}$,H-2_{glc}, 3_{glc}, H-4_{glc}, 5_{glc},$6b_{glc}$, CH_2O), 2.87-2.74 (3m, 3H, CH_2), 2.40-2.35 (m,2H,CH_2), 1.78-1.39 (5m, 10H, CH_2).

^{13C}-NMR ($CDCl_3$), δ = 172.97 (COO), 172.27 (CONH), 138.63-126.00(C, aromatics), 103.17 (C-1_{gal}), 103.09 (C-1_{glc}), 100.65 (CHPh), 82.88 (C-3_{glc}), 79.95 (C-3_{gal}), 79.64 (C-4_{glc}), 74.54 (CH_2Ph), 73.86 (C-2_{glc}), 73.67 (C-2_{gal}), 73.57 (CH_2Ph), 73.10 (CH_2Ph), 72.52 (C-4_{gal}), 72.00 (C-5_{gal}), 69.40 (CH_2Ph), 68.65 (C-6_{gal}), 68.03 (C-6_{glc}), 66.06 (C-5_{glc}) 38.88 (CH_2COO),29.69 (CH_2CON), 29.7 , 29.05,27.13 (CH_2).

Synthesis of [3,4,6-tri-O-benzyl-α-D-galactopyranoside-(1→3)-2-yl-oxycarbonyl-propanoyl aminopentyl]-4,6-O-benzylidene-ß-D-glucopyranoside. (428) [88,89,92]

^{1}H-NMR ($CDCl_3$) δ = 7.49-7.09 (H, aromatics), 6.19-6.18 (brs,1H,NH) 5.49 (s,1H, CHPh), 5.34-5.30 (dd,1H,$H_{2,3}$ = 6.37 Hz, $J_{3,4}$ = 6.37 Hz, H-2_{gal}), 5.08-5.07 (d,1H, $J_{1,2}$= 6.04 Hz, H-1_{gal}), 4.87-4.83 (d,1H, J =11.64Hz, CH_2Ph), 4.66-4.60 (t,1H, J =10.40Hz, CH_2Ph), 4.49-4.43 (m,4H,CH_2Ph, H-1_{glc}), 4.32-4.28 (dd,1H,J_{6a6b} = 10.58 Hz, H-$6a_{glc}$), 3.95 (brs, 1H, H-4_{gal}), 3.82-3.37 (4m, 11H, H-3_{gal},5_{gal},$6a_{gal}$,$6b_{gal}$,H-2_{glc},3_{glc},4_{glc},5_{glc},$6b_{glc}$, CH_2O), 2.94-2.90 (m,1H, CH_2), 2.76-2.69 (m,1H, CH_2), 2.54-2.39 (m,2H, CH_2),2.25-2.20, (m, 1H, CH_2).

^{13}C-NMR ($CDCl_3$), δ = 171.60 (COO), 170.85 (CONH), 136.48-125.34 (C aromatics), 101.79 (C-1 $_{glc}$), 100.62 (CHPh), 96.55 (C-1_{gal}), 79.42 (C-3_{gal}), 77.68 (C-3_{glc}), 76.51 (C-4_{glc}), 73.28 (C-2), 73.04 (CH_2Ph), 72.47 (CH_2Ph), 71.96 (C-2_{glc}), 71.37 (C-4_{glc}), 71.29 (CH_2Ph), 70.60 (C-5_{gal}), 67.96 (C-6_{glc}), 67.69 (C-6_{gal}), 67.21 (C-5_{gal}), 64.86 (CH_2O), 37.62 (CH_2COO), 30.59 (CH_2), 29.34 (CH_2), 28.67,27,56 (CH_2).

Synthesis of 4-Benzyloxycarbonylaminobutane-1-ol (429). [87]

Aminobutane 1-ol (10g, 112.18 mmol) was dissolved in 125 ml of acetone/water 4:1 and Na_2CO3 (9.66g, 91.22 mmol) was added. The mixture was cooled to 0°C and (24 ml 29.05g, 170.28 mmol) of benzylchloroformate was added dropwise to the stirred cold solution. The medium was stirred for 3h, brought to room temperature and than filtered The partially aqueous organic filtrate, was dissolved in CH_2Cl_2 (100ml) and extracted with CH_2Cl_2. The combined organic phase was dried on Na_2SO4 reduced in vacuo, set to dryness on high vacuum pump to give a waxy solid. The waxy solid was recrystallized with diethyl ether to a white solid.

Percentage yield (20 g, 88 mmol: 78.50%) : mp= 78-81° C

[5-N (Benzyloxycarbonylamino)-butyl]-2,3,4,6-tetra-O-benzoyl-β-D-glucopyranoside (430). [80,81]

The tetra-benzoylated- α /β-D glucpyranose imidate **420** (5.07g,6.840mmole)and Z-amino butanol **429** (1.39g, 6.22 mmole) are dissolved in 100 ml of dichloromethane, cooled down to –10°C , and stirred 20miutes.To the cooled mixture whie stirring are added a catalytical

amount (0.138g,0.622 mmole) of TMSOTf. The reaction is followed by tlc (toluene/acetone 8:1). At the end of the reaction, the mixture is neutralised with a few drops of pyridine, or triethyl amine diluted in dichloromethane and, worked up with water, saturated aqueous NaHCO3 and water. The organic phase is dried on Na_2SO_4, filtered, reduced in vacuo and the crude oily product purified by chromatography toluene/acetone 10:1.

Percentage yield (3.80g, 4.668mmole; 68.24%) $[\alpha]_D$ = +13.20 (C=0.5, $CHCl_3$).

HRMS m/z caculated for $C_{46}H_{43}O_{12}N$ Na
Caculated: 824.263473
Founded : 824.268256

^{1}H-NMR ($CDCl_3$) δ = 8.02-7.13 (H aromatics), 5.92-5.87 (1,1H,$J_{4,5}$ = 9.85, H-4), 5.69-5.64 (t,1H,$J_{2,3}$ = 9.60, H-3), 5.53-5.48 (dd,1H, $J_{2,3}$ = 8.08, $J_{1,2}$ = 7.834, H-2), 4.80-4.78, (d, 1H,$J_{1.2}$ = 7.84, H-1), 4.67-4.63 (dd.1H, J_{6a-6b} = 12.00,H-6a) 4.50-4.45 (dd,1H,J_{5-6a}, = 12.13, H-6b), 4.32 (br,1h, NH), 4.14-4.10 (ddd,1H, $J_{4,5}$ = 9.10, H-5), 3.94-3.90 (m,1H, CH_2), 3.57-3.51 (m,1H, CH_2), 3.27-3.26 (m,1H, CH_2), 3.04-3.03 (m.2H,CH_2), 1.66-1.40 (6H,m, CH_2).

^{13} C-NMR ($CDCl_3$): δ = 166.13-156.33 (COO), 137.86-125.29 (C aromatics),101.34 (C-1), 78.80 (C-3), 72.23, (C-5), 71.94 (C-2), 69.82 (CH_2Ph), 69.73 (C-4), 66.46 (OCH_2), 63.04 (C-6), 40.38, 30.90(CH_2NH), 26.37,21.44 (CH_2 CO).

[4-N-(Benzyloxycarbonyamino)-butyl]-β-D- glucopyranoside (431). [65,82]

Compound **430** (3.80g, 4.67 mmole) is dissolved in 60 ml solvent mixture toluene/acetone 1:1 and, a catalytical amount of sodium methanolate 1M is added and is stirred overnight.When TLC toluene/acetone 1:2 reveals end of reaction . The reaction medium is neutralized with ion exchange Dowex H^+, filtered and reduced in vacuo to an oily product, that is directly used for benzylidenation reaction.

Percentage yield (1.80g, 4.54mmole, 97%)

[4- N (Benzyloxycarbonylamino)-buty]l-4,6-O-benzylidene-β-D-glucopyranoide (432). [83]

To the dibenzoylated glucose **431**(1.80g, 4.54 mmole) dissolved in 80 ml of acetonitrile, was added benzaldehyde dimethylacetal (0.85 g, 5.58 mmole,1.15ml), TsOH (0.106g 0.558 mmole), and the mixture stirred overnight at 25°C. The mixture was poured in water and extraced two or three times with dichloromethane. The combined organic layer was washed with $NaHCO_3$, water and concentrated. The residue was recrystallised from ethylacetate/hexane 1:1.
Percentage yield (1.65g, 3.48mmole, 77%) mp :68-70°C
$[\alpha]_D$ =-38.6 (c= 0.5, $CHCl_3$
HRMS : m/z calculated for $C_{25}H_{31}O_8NNa$
Calculated : 496.1947
Found : 496.2004

^{1}H-NMR ($CDCl_3$) δ = 5.51(s,1H,CHϕ), 5.09(s,2H,Zgroup), 4.39-4.37 (d,1H,$J_{1,2}$ = 7.83, H-1),4.34-4.30 (dd,1H,$J_{6a,6b}$ = 10.67, H-6a), 3.98-3.95 , 3.83-3.73 (2m,3H,H-5, H-2,H-4), 3.57-3.43 (2m,4H, H-3, H-6b,CH_2O), 3.26-3.24 (br,2H,CH_2),1.67-1.62 (m,4H, CH_2).

^{13}C-NMR ($CDCl_3$) δ = 156.62(COO),137-126.28 (C aromatics)103.37(C-1)101.82 (CHPh), 80.46(C-4), 74.56 (C-2), 73.17 (C-3), 70.08 (CH_2, Z) 68.64 (CH_2O), 66.7(C-6), 66.37 (C-5),40,59 (CH_2), 26.88,26.17 (CH_2).

4-Aminobutyl-4,6-O-benzylidene-β-D- glucopyranoside (433). [84]

Compound **432** (0.60g, 1.56mmole) is diluted in 30 ml of ethanol, followed by addition of a catalytical amount of Lindlar's catalyst, $Pd/BaCO_3$**.** The mixture is stirred five minutes, vacuumed, and submitted to hydrogenation at room temperature for 2h. After controlling the reaction by TLC, acetone/toluene 3:1. The solution was filtered on celite, and concentrated. The residue was directly used for couplage reaction with the galactose pentafluorophenol ester **416**.

Percentage yield, (0.41g,1.246 mmole, 80%)

[Phenyl-1-thio-3,4, 6-tri-O-benzyl-β-D-galactopyranoside – (2yloxycarbonyl propanoyl aminobutyl)-4,6-O-benzylidene-β-D-glucopyranoside] (434). [88]

To a solution of compound **433** (0.41g,1.246 mmole), under argon atmosphere is added (0.484g, 0.60 mmole) of the galactose pentafluorophenol ester **416** in 60 ml ethyl acetate and

the mixture is stirred overnight at 25°C and stirred overnight. During the course of the reaction most of the product precipitate due to its low solubility in ethyl acetate. The reaction is controlled by TLC (toluene-acetone 2:1), and the precipitate collected by suction filtration The partially dried precipitate is recrystallised from acetone/hexane 1:3. The filtrate containing the rest of soluble product is concentrated in vacuo, and purified by filtration on column chromatography (CH_2Cl_2/acetone 3:1).

Percentage yield (0.45g, 0.468 mmole, 78%) mp:156-158°C

HRMS m/z calculated for $C_{54}\,H_{61}\,O_{13}\,N\,S\,Na$
Calculated : 986.3761
Found : 986.3703

^{1}H-NMR ($CDCl_3$) δ= 7.45-7.16 (H aromatics), 6.07-6.04 (t,1H, NH), 5.47 (s, 1H, CHPh), 5.40-5.35 (t,1H, $J_{2,3}$ = 9.83 Hz, $J_{3,4}$ = 9.83 Hz, H-2), 4.90-4.87 (d,1H, J =11.62Hz , CH_2Ph), 4.62-4.46 (m,4H, CH_2Ph, H-1_{gal}), 4.41-4.31(m,3H, CH_2Ph, H-1_{glc}),4.28-4.24 (dd,1H, $J_{6a,6b}$= H-$6a_{glc}$), 3.92-3.90(d,1H, $J_{4,5}$ = 2.53Hz), 3.78-3.17 (3m,12H, H-3_{gal},5_{gal}, $6a_{gal}$, $6b_{gal}$, H-2_{glc}, 3_{glc}, 4_{glc}, 5_{glc},$6b_{glc}$, CH_2O), 2.68-2.53 (m,2H, CH_2), 2.42-2.39 (t,1H,CH_2) 1.63-1.50(m, 4H, CH_2).

^{13}C- NMR δ = 171.05 (COO),171.71 (CONH), 138.35-126.30 (C aromatics), 103.49 (C-1_{glc}), 101.80 (CHPh), 86.80 (C-1_{gal}), 81.20 (C-4_{gal}), 80.44 (C-4_{glc}),77.58 (C-5_{gal}), 74.64 (C-2_{gal}), 74.38 (CH_2Ph), 73.56 (CH_2Ph), 73.22 (C-4_{gal}), 72.83 (C-2_{glc}), 72.08 CH_2O) 70.18 (C-3_{glc}), 70.63 (C-6_{glc}), 68.69 (C-6_{gal}), 66.36 (C-5_{glc}), 39.12,31.31, 31.00,26.52, 26.01 (CH_2).

Synthesis of [3,4,6-tri-O-benzyl-ß-D-galactopyranoside-(1→3)-[2-yl-oxycarbonyl propanoylaminobutyl] 4,6-O-benzylidene-ß-D-glucopyranoside. (435)
[88,89,92]

Compound **434** (0.41g, 0.426 mmole) was submitted to argon atmosphere, dissolved in 30 ml of absolute dichloromethane, and stirred 10 minutes. An additional 30ml of absolute acetonitrile was added , stirred 5 minutes and cooled down to –5°C .To the cooled reaction medium was added (0.53g, 2.343mmole) of NIS , TMSOTf(42.40 ul , 0.2343 mmole) and the medium was stirred 30 to 40 minutes. The reaction was followed by TLC (toluene- acetone 2:1). When the end of reaction is revealed by TLC, the reaction medium was neutralised with few drops of triethyl amine or pyridine, dissolved in 50 ml of CH_2Cl_2 washed with water, saturated solution of $NaHCO_3$, saturated solution of $Na_2\,S_2\,O_3$, and water. The organic phase was dried on Na_2SO_4, filtered and reduced in vacuo. The crude products are purified and separated by column chromatography (CH_2Cl_2/ acetone/ toluene) 4:1:1.

Overall percentage yield (0.24g, 0.281mmole, 66%).

Main product β (1-3) glycosidic bond **(435)**
Minor product α (1-3) glycosidic bond **(436)**

Glycosidic bond	mass in g	mmole	% yield	melting points	$[\alpha]_D$
Main product β(1-3)	0.21	0.246	58%	210-212°C	-13
Minor product α(1-3)	0.04	0.035	8%	205-207°C	-23

HRMS m/z calculated for major product $C_{48}\ H_{55}\ O_{13}N\ Na$
Calculated 876.3571
Founded 876.3880

HRMS m/z calculated for minor product $C_{48}\ H_{55}\ O_{13}\ N\ Na$
Calculated : 876.3571
Found : 876.3897

^{1}H-NMR $CDCl_3$ (major product)

δ = 7.73- 7.23 (H, aromatics), 6.04-6.03 (brs, 1H, NH), 5.51 (s,1H, CHPh), 5.40-5.37 (dd,1H, $J_{2,3}$ =9.60Hz, $J_{3,4}$ = 9.86Hz, H-2_{gal}), 4.94-4.89 (d,1H, J = 11.63Hz, CH_2Ph), 4.75-4.73 (d,1H, $J_{1,2}$ = 7.83Hz, H-1_{gal}), 4.65-4.56 (3m, 8H. $3CH_2Ph$, H-1_{glc}, H-6a $_{glc}$), 3.98-3.978 (d,1H, $J_{4,5}$ = 3.28), 3.91 –3.38 (5m, 12H, H-$6a_{glc}$, H-3_{gal},5_{gal}, $6a_{gal}$,$6b_{gal}$, H-2_{glc}, $3_{glc,}$ 4_{glc}, 5_{glc}, $6b_{gl}$,, CH_2O), 3.07-3.04 (m,1H,CH_2), 2,79-2.65 (2m, 2H, CH_2),

^{13}C-NMR ($CDCl_3$), δ = 173.04 (COO), 172.33(CONH), 138.44-121.53 (C, aromatics), 102,78(C-1_{gal}), 102.64 (C-1_{glc}), 100.60 (CHPh), 82.56 (C-3_{glc}), 80.10 (C-3_{gal}), 79.79 (C-4_{glc}), 74.42 (CH_2Ph), 73.84 (C-4_{gal}), 73.52 (CH_2Ph), 72.66 (C-2_{gal}), 72.13 (C-2_{glc}), 71.81 (CH_2Ph) 68.55 (C-6_{gal}), 68.09 (C-6_{glc}), 67.71(CH_2O), 66.64 (C-5_{glc}) 26.30,29.56, 30.41,38.93 (CH_2).

Synthesis of [3,4,6-tri-O-benzyl-α-D-galactopyranoside-(1→3)-[2-yl-oxycarbonyl propanoylaminobutyl] 4,6-O-benzylidene-ß-D-glucopyranoside.(436)
[88,89,92]

^{1}H-NMR ($CDCl_3$) for minor product

δ = 7.48-7.24 (H, aromatics), 5.86-5.83 (brs, 1H, NH), 5.72-5.71(d,1H,$J_{1,2,}$ = 3.94Hz, H-1_{gal}), 5.41 (s,1H,CHPh), 5,24-5.21(d,1H, $J_{2,3}$ =10.62 Hz, $J_{3,4}$ = 11.02 Hz, H-2_{gal}), 4.91-4.89 (d, 1H, J =11.50 Hz CH_2Ph), 4.72-4.40 (3m, 8H, $3CH_2Ph$, H-1_{gal}), 4.31-4.27 (dd,1H,$J_{6a,6b}$ = 10.17 Hz, H-$6a_{glc}$), 4.00-3.99 (d,1H, $J_{4,5}$ = 4.86Hz, H-4_{gal}),

3.83-3.49 (3m, 11H, H-3_{gal}, 5_{gal}, $6a_{gal}$, $6b_{gal}$, H-2_{glc}, 3_{glc}, 4_{glc}, 5_{glc}, $6b_{glc}$ CH_2O), 3.06-2.97 (m,1H, CH_2), 2.83-2.79(brd, 1H, CH_2), 2.57-2.25 (3m,4H, CH_2),1.68-1.51 (2m, 8H, CH_2).

^{13}C-NMR ($CDCl_3$), 172.90(COO), 172.12 (CONH), 138.37-124.61 (C, aromatics), 103.98 (C-1_{glc}), 101.57 (CHPh), 94.68 (C-1_{gal}), 81.20 (C-3_{gal}), 75.65 (C-4_{glc}), 74.56 (CH_2Ph), 73.45 (C-3_{glc}), 72.82 (CH_2Ph), 72.59 (C-2_{glc}), 72.26 (CH_2Ph), 72.03(C-2_{gal}), 69.81 (C-6_{glc}) 69.26 (C-6_{gal}), 68.69 (CH_2O), 68.60 (C-5_{gal}), 65.50 (C-5_{glc}).

Synthesis of 1,2,3,4,6-penta-O-acetyl-α,β-D-glucopyranoside (437). [72]

In a mixture already containing 60g. (731.44 mmol) of dried sodiun acetate in 700ml of acetic anhydride, was added portion wise 100g. (555.44 mmol) of glucose and the mixture was heated at 80°C. The reaction was controlled by TLC (toluene- acetone 4:1) As the TLC reveals no remaining starting material, the mixture is cooled to room temperature and poured in a container of iced water and refrigerated overnight. One observes formation of white precipitate that is filtered by suction, washed cold water and ethanol, and dried in dessecator.

Percentage yield: 185g. (475.44 mmol), 65 %
mp: 129-131°C

Synthesis of 2,3,4,6-tetra-O-acetyl-(α)-D-glucopyranosylbromide (438). [73]

To 45g (115.30mmol) of α/β-D- glucose pentaacetate dissolved and cooled to 0°C in 100 ml of CH_2Cl_2 were added 78.3ml (496.0 mmol), 40.11gr, of HBr in 33% acetic acid . The mixture was stirred at room temperature. When control by TLC, (toluene/ acetone 6:1 shows end of reaction , the medium was diluted in 100ml of CH_2Cl_2, worked out with iced water, twice with iced cold saturated solution of sodium hydrogen carbonate, and iced water. The organic phase is dried on sodium sulphate, filtered, and reduced in vacuo. Recrystallization with diethyl ether and hexane 1:1 gave a white crystaline solid.

Percentage yield: 37,5gr (87.80 mmol), 76%
mp: 86°C-88°C

Synthesis of 3-Benzyloxycarbonylaminopropane-1-ol (439). (87)

In acetone –water 4:1 500ml, (20g, 266.70 mmol) of 3-aminopropananol, with sodium carbonate,(22g, 207.75 mmol) of were dissolved and cooled to 0°C. To the cooled stirred mixture, are added dropwise over 0.5h, (68.30g, 400.35 mmol, 56.44ml) of benzyl chloroformate .The mixture is stirred at 0°C for a further 2.5h. The solids are filtered and, the filtrate is diluted in 100ml CH_2Cl_2 and water, extracted with dichloromethane, dried on Na_2SO_4,filtered and reduced in vacuo. The residue was triturated with hexane to give white crystals.

Percentage yield: (42.50g, 198.47mmol, 74.4%): mp: 46-48°C.

[3-N- (Benzyloxycarbonylamino)-propyl]- 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (440). [82,87]

Under argon atmosphere (14g, 35.7mmole) of α-D-bromoglucopyranose **438**, (8.14g, 39.2 mmole), aminopropanol, **439** $Hg(CN)_2$ (9.90g,39.2 mmole) and a catalytical amount of $HgBr_2$ were mixed and dissolved in 70 ml absolute acetonitrile.The mixture was stirred until

control of the reaction by TLC (toluene-acetone 6:1) reveals end of the reaction. The mixture is dissolved in 100 ml of dichloromethane, and worked up with water, saturated solution of $NaHCO_3$, and water. The organic phase was dried on Na_2SO_4, filtered and concentrated. The crude product was purified by chromatography (toluene-acetone 8:1).

Percentage yield (7.80g, 13.78 mmole, 27%)
$[\alpha_D]$= -16 (C = 0.5, $CDCl_3$)

^{1}H-NMR ($CDCl_3$) δ = 7.36-6.99 (H aromatics), 5.23-5.18 (t,1H,$J_{3,4}$ = 9.60, H-3), 5.09-5.05 (1H, $J_{4,5}$ = 9.60, H-4), 5.01-4.97 (dd,1H,$J_{2,3}$ = 9.60), 4.51-4.49 (d,1H, $J_{1,2}$ = 7.84 H-1), 4.26-4.23 (dd,1H, $J_{6a,6b}$ = -12.20, H-6a), 4.17-4.14 8dd,1H, H-6b), 3.70-3.67 (ddd,$J_{5,6a}$ = 2,8 H-5), 3.36 (dm, 2H, CH_2O),

^{13} C-NMR ($CDCl_3$), δ = 170.69-169.4 (COO), 137.85-123.81 (C aromatics), 100.61 (C-1), 72.73 (C-3), 71.73 (C-5), 68.32 (C-4), 67.49 (C-6), 66.55 (CH_2, Z),64.61 (C-6),61.81 (CH_2O) 38.12 (CH_2N), 29.45 (CH_2), 21.44,20.68,20.58 (CH_3).

[3-N-(Benzyloxycarbonylamino)-propyl]-β-D- glucopyranoside (441). [65, 82]

To a solution of compound **440** (7.80g,13.78 mmole), in 80 ml toluene/methanol 1:1, was added a catalytical amount of sodium methanolate 1M until pH 12-13 and, the was stirred . When TLC acetone/toluene 1:1 reveal end of the reaction, the solution is neutralised with ion exchange H^+ Dowex 50Wx 8 filtered and reduced in vacuo. The product was directly used for benzylidenation reation.

Percentage yield (4.42g, 11.21mmole) 81.13%.

[3-N-(Benzyloxycarbonylamino)-propyl]-4,6-O-benzylidene-β-D-glucopyranoside (442). [83]

To compound **441** (4.42g, 11.21mmole) dissolved in 60-70 ml of acetonitrile, was added, benzaldehyde dimethyl acetal (2.10g, 13.79 mmole,2.08ml), TsOH,(0.26g, 1.379 mmole and the mixture was stirred overnight.At the end of reaction, the mixture was dissolved in water and extracted three times with dichloromethane (60mml). The combined organic phase was washed with saturated solution of $NaHCO_3$, water, dried on Na_2SO_4 and concentrated.

The crude product was recrystallised from ethylacetate/hexane.

Percentage yield (3.00g, 6.49 mmole, 58%) mp: 125-128°C
$[\alpha]_D$ =-40.6

HRMS: m/z calculated for $C_{24}H_{29}NO_8Na$
Calculated : 482.179077
Found : 482.186006

^{1}H-NMR ($CDCl_3$) δ = 7.91-7.17 (H aromatic), 5.52 (s,1H, CHPh), 5.20-5.18 (t,1H,NH) 5.10 (s,2H, CH_2, Z), 4.37-4.35 (d.1H,$J_{1,2}$ = 7.83 H-1), 4.33-4.31 (t,1H,$J_{4,5}$ = 4.5, H-4), 4.00-3.95 (m,2H, H-5, 6a), 3.83-3.73 8m,2H,H-2, OH), 3.62-3.40(3m, H6b, OH, H-3, CH_2O), 3.27-3.21 (CH_2), 1.92-1.68 (3m, 2H, CH_2).

^{13} C- NMR ($CDCl_3$) δ = 156.83 (NHCO), 137.00-127.00 (C aromatic), 103.26 (C-1), 101.8 (CHPh), 80.37 (C-4), 74.51 (C-2), 73.27 (C-3), 68.60 (CH_2, Z), 67.26 (OCH_2), 66.7 (C-6), 66.34 (C-5), 37.61 (CH_2NH), 29.63 (CH_2).

3-Aminopropyl-4,6-O-benzylidene-β-D- glucopyranoside (443). [84]

To a solution of **442** (0.84g, 1.83 mmole) in 40ml ethanol was added a catalytical amount of Lindlar's catalyst. The solution was vacuumed and sumitted to hydrogenation for 2 to 4 h. The reaction was controled by TLC (acetone/toluene 3:1). The solution was than filtered on celite, concentrated, and the product kept under argon for immediate reaction with the penta-fluorophenol ester galactose derivative **416**.

Percentage yield (0.43g, 1.33 mmole, 73%)

[Phenyl-1- thio-3,4,6-tri-O-benzyl-β-D-galactopyranoside-(2yloxycarbonylpropanoyl aminopropyl-4,6-O-benzylidene-β-D-glucopyranoside (444). [88]

To the β-D- amino glucose acceptor **443** (0.72g, 2.29 mmole) under argon atmosphere was added the β-D-galactose pentafluorophenolester **416** (0.89g,1.10 mmole),and the mixture was stirred overnight. The formed product precipitates during the course of the reaction,due to its low solubility in ethyl acetate. When TLC (toluene/acetone 2:1) reveals the end of the reaction, the precipitated product was filtered by suction and recrystallised from acetone/ hexane 1:3. The filtrate containing the remaining solubilised product was concentrated and the crude product was purified on column chromatography (CH_2Cl_2/ acetone 3:1).

Percentage yield (0.94g, 0.987 mmole, 89%) mp:120-122°C

$[\alpha]_D$ = -10 (c=0.5)
HRMS m/z calculated for $C_{53}H_{59}O_{13}NSNa$
Calculated : 972.3647
Found : 972.3604

^{1}H-NMR ($CDCl_3$) δ = 7.66-7.21 (H aromatics), 6.35 (brs,1H, NH), 5,5 (s, 1H CHPh) 5.43-5.38 (t,1H, $J_{2,3}$ = 9.60 Hz, $J_{3,4}$ = 9.87 Hz, H-2_{gal}), 4.93-4.90 (d,1H, J = 11.62, CH_2Ph), 4.65-4.51(m. 3H, CH_2Ph, H-1_{gal}), 4.44-4.35 (m,3H, CH_2Ph, H-1_{glc}), 4.32-4.28 (dd, 1H, $J_{6a,6b}$ =-10.36Hz , H-$6a_{glc}$), 3,94(brs,1H, H-4_{gal}) 3.79-3.22 (3m, 12H, H-3_{gal},5_{gal},$6a_{gal}$,$6b_{gal}$, H-2_{glc}, 3_{glc}, 4_{glc},5_{glc},$6a_{glc}$, $6b_{glc}$, CH_2O), 2.72-2.57 (m, 2H, CH_2), 1.76-1.74 (m, 2H, CH_2), 1.26-1.23 (t, 1H, CH_2).

^{13}C-NMR ($CDCl_3$), δ = 172.16 (COO), 171.78 (CONH), 138.31-126.28 (C,aromatics), 103.22 (C-1_{glc}), 101.78 (CHPh), 86.80 (C-1_{gal}), 81.10 (C-3_{gal}), 80.39 (C-4_{glc}), 77.60 (C-5_{gal}), 74.66 (C-2_{gal}), 74.37 (CH_2Ph), 73.52 (CH_2Ph), 73.40 (C-4_{gal}), 72.01 (CH_2Ph), 70.93 (C-2_{glc}), 70.22 (C-3_{glc}), 68.72 (C-6_{glc}), 68.64 (C-6_{gal}), 67.95 (CH_2O), 36.67 (CH_2), 31.29 (CH_2), 30.03,29.03 (CH_2).

Synthesis of [3,4,6-tri-O-benzyl-ß-D-galactopyranoside- (1→3)-[2-yl-oxycarbonyl propanoylaminpropyl]-4,6-O-benzylidene-ß-D-glucopyranoside. (445) [88,89,92]

Under argon atmosphere compound **444** (0.65g, 0.68 mmole) was dissolved in 35ml dichloromethane by slightly heating and stirred 10 minutes. An additional 35ml of

absolute acetonitrile was added ,stirred and cooled down to –5°C. At this temperature is (0.84g, 3.74 mmole) of NIS, and (65.67 ul,0.374 mmole) TMSOTf added and the cooled mixture stirred 20 minutes. As TLC (toluene/acetone 2:1) reveals end of reaction, the reaction mixture is neutralised with a few drops of triethyamine or pyridine and brought up to room temperature. The medium is diluted in 50 ml dichloromethane, washed with water, saturated solution of $NaHCO_3$, $Na_2S_2O_3$, and water. The organic phase is dried on Na_2SO_4, filtered and reduced in vacuo. The crude products and isomers are purified and separated by column chromatography (CH_2Cl_2/ toluene/ acetone 5:2:1)

Overall percentage yield (0.42g, 0.496 mmole, 73%) **445**, **446**

Glycodidic bond		mass in gr	mmole	%yield	melting point	$[\alpha]_D$
Main product	β(1-3)	0.33	0.390	57.30%	218-221°C	-11
Minor product	mixture α(1-3) and ß(1-3)	0.09	0.110	15.90%	190-192°C	-

HRMS (major product) m/z calculated for $C_{47}\ H_{53}\ O_{13}\ N\ Na$
Calculated : 862.3512
Found : 862.3145

^{1}H-NMR ($CDCl_3$) **445** : δ = 7.48-7.18 (H, aromatics), 5.96-5.94 (br d,1H, NH), 5.50 (s,1H, CHPh), 5.28-5.23 (dd,1H,$J_{2,3}$ = 7.58 Hz,$J_{3,4}$ = 7.83Hz, H-2_{gal}), 4.74-4.53 (2m,6H, H-1_{gal}, H-1_{glc}, CH_2Ph), 4.43-4.37 (t,2H,J = 11.85, CH_2Ph), 4.33-4.29 (dd,1H, $J_{6a,6b}$ = 10.36Hz, H-$6a_{glc}$), 3.985-3.979 (d,1H, J =2.52Hz, H-4_{gal}), 3.74-3.33 (4m, 11H, H-3_{gal},5_{gal},$6a_{gal}$,$6b_{gal}$,H-2_{glc},3_{glc},4_{glc},5_{glc},$6b_{glc}$,CH_2O), 3.04-2.87 (m,1H, CH_2), 2.88-2.80 (m,2H,CH_2), 2.43-2.34(m,2H,CH_2), 2.45-2.28(m,2H,CH_2).

^{13}C-NMR ($CDCl_3$), δ = 173.21(COO), 172.60 (CONH), 138.02-125.90 (C, aromatics), 102.73 (C-1_{gal}), 102.19 (C-1_{glc}), 100.27(CHPh), 82.30 (C-3_{glc}), 79.90 (C-3_{gal}), 78.72 (C-4_{glc}), 74.32 (CH_2Ph), 74.12 (C-2_{gal}), 73.60 (CH_2Ph), 73.09 (C-5_{gal}), 72.81 (C-4_{gal}) 72.27 (CH_2Ph), 70.75 (C-2_{glc}), 68.48(C-6_{glc}), 68.24(C-6_{gal}), 66.25 (C-5_{glc}),

Synthesis of [3,4,6-tri-O-benzyl-α/ß-D-galactopyranoside- (1→3)-[2-yl-oxycarbonyl propanoylaminpropyl]-4,6-O-benzylidene-ß-D-glucopyranoside. (446) [88,89,92]

^{1}H-NMR ($CDCl_3$) **446** δ = 7.48-7.16 (H, aromatics), 6.33 (brs, 1H, NH'), 6.31 (brs, 1H, NH), 5.51(s,1H, CHPh'), 5.50 (s,1H, CHPh), 5.43-5.42 (d,1H, $J_{1,2}$= 3.98 Hz, H-1_{gal}'), 5.41-5.40 (d,1H, $J_{1,2}$= 3.98 Hz), 5.29-5.24 (dd, 1H, $J_{2,3}$=9.73 Hz, $J_{3,4}$=10.18 Hz, H-2_{gal},) 4.92-4.90 (d, 1H, J=11.50Hz, CH_2Ph'), 474-4.67 (m,2H, CH_2Ph' CH_2Ph), 4.64-4.55 (m,3H, CH_2Ph', CH_2Ph), 4.52-4.37 (m, 3H, CH_2Ph', CH_2Ph, H-$1_{glc.}$), 4.34-4.28 (m,2H, H-$6a_{glc}$', H-$6a_{glc}$), 4.02-4.00(d,1H, $J_{4,5'}$ =1.77 Hz, H-4_{gal}'), 3.99-3.98 (d,1H, $J_{4,5}$= 1.75 Hz, H-4_{gal}), 3.79-3.52 (3m, 10H, H-3_{gal}, $5_{gal,}6a_{gal}6b_{gal}$, H-2_{glc},3_{glc},$4_{glc}5_{glc}$,$6b_{glc}$,OH_{glc}), 3.47-3.42 (m,CH_2), 3.38-3.16 (3m,3H, $3CH_2$),3.03-2.97 (1H, CH_2), 2.89-2.57 (3m,4H, CH_2), 2.46-2.23 (2m, CH_2).

^{13}C-NMR ($CDCl_3$) δ = 173.17 (COO'), 172.96 (COO), 172.88 (CONH'), 172.52 (CONH), 138.30-125.91 (C, aromatics), 103.73 (C-1'$_{gal}$), 102.73(C-1_{glc}'), 102.13 (C-1_{glc}), 101.61

(CHPh'), 100.26 (CHPh), 95.47 (C-1_{gal}), 82.32 (C-3'$_{glc}$), 80.90 (C-3_{glc}), 79.89 (C-4'$_{glc}$), 78.70 (C-4 $_{glc}$),77.30 (C-2'$_{gal}$), 76.60 (C-2_{gal}), 74.63 (CH_2Ph) 74.46 (CH_2Ph'), 74.39 (C-3_{gal}) 74.11 (C-3'$_{gal}$), 73.56 (CH_2Ph'), 73.48 (CH_2Ph), 73.08 (C-2_{glc}), 72.69 (CH_2Ph) 72.46(C-2'$_{glc}$), 72.22 (CH_2Ph') 71.50 (C-5_{gal}), 70.66 (C-5'$_{gal}$), 69.16 (CH_2O), 68.95 (C-6_{gal}), 68.60 (C-6'$_{gal}$), 68.52 (C-6'$_{glc}$), 68.24 (C-6), 66.26 (C-5'$_{glc}$), 65.86 (C-5_{glc}), 36.11 (CH_2'), 34.91 (CH_2), 32.00 (CH_2'), 31.44 (CH_2), 31.07 (CH_2'), 30.88 (CH_2'), 30.17 (CH_2), 29.65 (CH_2'), 28.71 (CH_2'), 28.66 (CH_2).

Synthesis of 2-Benzyloxycarbonylaminoethanol (447). [87]

In acetone-water 81/19 500ml, (20 g, 350 mmol, 19.60 ml), of amino ethanol with 84.80g, 67.27 mmol) Na_2SO_3 are dissolved and cooled to 0°C. To this cold solution mixture are at 0°C (83.90g, 491.80 mmol, 69.33 ml) benzyl chloroformate over 0.5h drop wise added. The mixture was stirred at 0°C for 2.5h. The solids were filtered and, the filtrate diluted in 100 ml CH_2Cl_2. It was taken in water, extracted with more CH_2Cl_2, dried on Na_2SO_4, filtered, and reduced in vacuo. The residue was recrystallized in hexane to give a white partly needle solid.
Percentage yield (36.75g, 188.33 mmol, 54%): mp: 50-52°C.

[2-N-(Benzyloxycarbonylamino)-ethyl]-2,3,4,6-tetra-O-acetyl-β-D- glucopyranoside (448). [82,87]

Under argon atmosphere were mixed 2,3,4,6-tetra-O-acetyl -α-D-bromoglucopyranose, (20g, 48.62 mmole) **438**, Z-aminoethanol **447** (10.44g, 53.49 mmole), $Hg(CN)_2$ (12.33g, 48.62 mmole), and a catalytical amount of $Hg(Br)_2$ in 80 ml of absolute acetonitrile,and stirred. At the end of reaction, when revealed by tlc, toluene/acetone 6:1, the mixture is diluted in 150 ml CH_2Cl_2, washed with water, saturated solution of $NaHCO_3$, and water. The organic phase is dried on Na_2SO_4, filtered, and concentrated. The crude oil product is purified by column chromatography toluene/acetone 8:1.

Percentage yield (8.00g, 15.23 mmole, 31%).
$[\alpha]_D$ 0 –14.2 (C = 0.5, $CHCl_3$)

HRMS m/z calculated for $C_{24}H_{31}NO_{12}$
Calculated : 525.18463
Found : 525.16126

^{1}H-NMR ($CDCl_3$) δ=7.44-7.06 (H aromatic), 5.22-5.17 (t,1H.$J_{2,3}$ =9.35,$J_{3,4}$ = 9.60, H-3), 5.10-5.04 (t, 1H, $J_{4,5}$ =8.34, H-4), 5.00-4.95 (dd,1H, $J_{2,3}$ =8.09H-2), 4.49-4.67 (d,1H, $J_{1,2}$ = 7.83 Hz, H-1), 4.25-4.20 (dd, 1H,$J_{6a,6b}$=-12.38, H-6a), 4.15-4.08 (dd,1H, H-6b), 3.86-3.83 (m,1H, CH_2O) –3.68-3.65 (m, 1H, H-5), 3.44-3.39 (m,1H, CH_2), 2.51(s,2H, CH_2Z,

^{13}C-NMR ($CDCl_3$) δ =171.22-169.44 (COOAc), 169.38 (COO, Z), 156.33 (NH CO), 137.85-128.13 (C,aromatic), 101.04 (C-1), 72.61 (C-3), 71.85 (C-5), 71.22 (C-2),69.53 (C-6), 68.23 (C-4), 66.72 (CH_2Z), 41.00 (CH_2).

[2-N-(Benzyloxycarbonylamino)-ethyl]-β-D-glucopyranoside (449). [65,82]

A catalytical amount of sodium methanolate 1M was added to compound **437** (8.00g, 15.23 mmole) dissolved in 70ml toluene/methanol 1:1.The solution was stirred at 25°C, and the reaction controled by tlc (acetone/toluene 3:1). The solution was neutralized with ion exchange Dowex 50Wx 8 H^+, filtered, and concentrated.

Percentage yield (4.00g, 11.19 mmole) 75%

[2-N-(Benzyloxycarbonylamino)-ethyl-4,6-O-benzylidene-β-D-glucopyranoside (450). [83]

Compound **449** (4.00g, 11.19 mmole) dissolved in 50ml of acetonitrile,is mixed with (1.72 ml,13.77mmole, 1.71 ml) of benzaldehyde dimethylacetal, a catalytic amount of TsOH, (0.26g, 1.377 mmole) and was stirred overnight at 25°C.When tlc toluene/acetone 2:1 reveals the end of reaction ,the mixture was neutralised with a few drops of triethyl amine, diluted in water and extraced 3x with 50 ml dichloromethane. The combined organic phase is washed with saturated solution of Na_2SO_4, water, and concentrated. The crude product was recrystalised from ethyl acetate/hexane 1:1.

Percentage yield (3.50g, 7.81 mmole) 70% mp: 137-139°C
$[\alpha]_D$ = -41 (C=0.5, $CHCl_3$).

^{1}H-NMR ($CDCl_3$) δ= 7.69-7.01(H aromatic), 5.65 (brs, 1H, NH), 5.50 (s,1H,CHPh), 5.10 (s,2H, CH_2Z), 4.36-4.34 (d,1H, $J_{1,2}$ = 7.33, H-1), 4.31-4.27 (dd,1H,$J_{6a,6b}$ = 10.36 H-6a), 3.91-3.67 (2m,4H,H-5,H-4 H-2,OH), 3.52-3.35 (2m,4H, H-3, H-6b, CH_2O), 2.06 (brm,2H, CH_2).

^{13}C-NMR ($CDCl_3$) δ = 156.88 (COO, Z), 136.95126.29 (C, aromatic), 103.40 (C-1), 101.82 (CHPh), 80.35 (C-4), 74.37 (C-2), 73.14 (C-3), 69.76 (CH_2Z), 68.53 (CH_2O), 66.87 (C-6), 66.30 (C-5), 41.00(CH_2).

2-Aminoethyl-4,6-O-benzylidene-β-D-glucopyranoside (451). [84]

To a solution of **450** (0.70g, 1.562 mmole), in 30ml ethanol was added a catalytical amount of Lindlar's catalyst, set under vacuum and submitted to hydrogenation, and stirred. The reaction is controlled by tlc (acetone/toluene 3:1). The solution is filtered on celite, and concentrated. The product is set under argon atmosphere for immediate reaction with the galactose pentafluorophenolester **416**.

Percentage yield (0.41g, 1.362 mmol, 87%)

[Phenyl-1-thio-3,4,6-tri-O-benzyl-β-D-galactopyranoside-(2-yloxycarbonyl propanoyl aminoethyl)-4,6-O-benzylidene-β-D-glucopyranoside] (452). [88]

To compound **451** (0.42g,1.362 mmole), dissolved in 40ml of ethyl acetate under argon atmosphere, were added (0.53g, 0.655 mmole) of the galactose pentafluorophenolester **416** and the reaction was stirred overnight. The product precipitates during the course of the reaction, because of its low solubility in ethylacetate. When control with tlc (toluene:acetone 2:1)

reveals end of the reaction, the precipitated product is filtered by suction and recystallised from (acetone/hexane 1:3). The filtrate containing the remaining soluble product is concentrated in vacuo, and the crude oily product purified by filtration on column chromatography (CH_2Cl_2-acetone 3:1).

Percentage yield (0.51g, 0.544mmole, 83%) mp = 165-168°C
$[\alpha]_D$ = -20

HRMS m/z calculated for $C_{52}\,H_{57}\,O_{13}\,N\,S\,Na$
Calculated : 958.3448
Found : 958.3517

^{1}H-NMR ($CDCl_3$) δ = 7.47-7.21 (H, aromatic), 6.63(brs, 1H, NH), 5,49(s, 1H, CHPh), 5.43-5.37 (t,1H, $J_{2,3}$ = 9.56 Hz, $J_{3,4}$ = 9.70 Hz, H-2_{gal}), 4.94-4.90(d,1H,J = 11.61Hz, CH_2Ph),

4.61-4.29 (m, 6H,CH_2Ph, H-1_{gal},H-1_{glc}, H-$6a_{glc}$), 3.94(brs, 1H, H-4_{gal}), 3.78-3.30 (3m, 12H, H-3_{gal},5_{gal},$6a_{gal}$,$6b_{,gal}$,H-2_{glc},3_{glc},4_{glc},5_{glc},$6a_{glc}6b_{glc,}$ CH_2O), 2.92-2.86(d,1H,CH_2), 2.67 (brs,1H, CH_2), 2.49-2.47 (d,1H,CH_2)

^{13} C-NMR ($CDCl_3$) δ = 172.08(COO), 171.87 (CONH), 138.38-126.34 (C, aromatics), 103.75 (C-1_{glc}), 101.85 (CHPh), 86.79 (C-1_{gal}), 81.21(C-3_{gal}), 80.40 (C-4_{glc}), 77.48(C-5_{gal}) 74.70 (C-2_{gal}), 74.38(CH_2Ph),73.57(CH_2Ph), 73.40 (C-4_{gal}), 72.88 ((C-2_{glc}), 72.15 (CH_2Ph),70.29 (CH_2O), 68.80 (C-6_{glc}), 68.63 (C-6_{gal}), 66.42 (C-5_{glc}), 39.44 (CH_2COO), 33.90 (CH_2COO), 24.93(CH_2).

Synthesis of [3,4,6-tri-O-benzyl-α-D-galactopyranoside-(1→2)-[2-yloxy-carbonyl-propanoylaminoethyl]-4,6-O-benzylidene-ß-D-glucopyranoside (453). [88,89,92]

Under argon atmosphere compound **(452)**, (0.44g, 0.468 mmole) is dissolved in 27ml absolute dichloromethane, slightly heated to facilitate the dissolution of the starting material, and stirred 10minutes. An additional 27 ml of dried acetonitrile was added to the dissolved starting material, and cooled down to –5°C. To the cooled suspension, was added, NIS (0.58g, 2.571 mmole), and TMSOTf (46.40 ul, 0.257 mmole) and the mixture was stirred 20 minutes.When the reaction followed by TLC (toluene/acetone 2:1 comes to end, the mixture is neutralised with few drops of triethyamine or pyridine, and brought up to room temperature. The mixture is diluted with 50ml of dichloro methane, worked up with water, saturated solution of Na_2HCO_3, $Na_2S_2O_3$, and water. The organic phase is dried on Na_2SO_4, filtered, and reduced in vacuo. The crude isomers are purified and seperated on column chromatography (CH_2Cl_2/toluene/ acetone 5:2:1).

Overall yield (0.28g, 0.340 mmole, 72.65%)

Glycosydic bond	mass in g	mmole	%yield	melting point	$[\alpha]_D$
Main product : α(1-2)	0.23g	0.277	59.13%	209-212°C	+6 (c=0.1)
Minor product: α(1-3)	0.050g	0.060	13.00%	148-150°C	+2 (c =0.1)

HRMS (major product) m/z calculated for C_{46} H_{51} O_{13} N Na
calculated : 848.3258
found : 848.3288

HRMS (minor product) m/z calculated for C_{46} H_{51} O_{13} N Na
Calculated : 848.3258
Found : 848.3205

^{1}H-NMR ($CDCl_3$) δ = 7.50-7.24 (H, aromatics), 6.36-6.33 (2 brd, 1H, NH), 5.54 (s,1H,CHPh), 5.52-5.46 (dd, 1H, $J_{2,3}$ = 9.73 Hz, $J_{3,4}$ = 9.73 Hz, H-2_{gal}), 4.88-4.80 (dd, 2H, CH_2Ph, H-1_{gal}), 4.63-4.55 (dd,2H, CH_2Ph) 4.46-4.40 (m,3H,CH_2Ph, H-1_{glc}), 4.35-4.29(m,3H, CH_2Ph, H-$6a_{glc}$), 3.98-3.94 (t,1H, $J_{2,3}$ =9.32 Hz, $J_{3,4}$ = 9.32 Hz, H-3_{gal}) 3.91-3.90 (d,1H, $J_{4,5}$ = 2.65Hz, H-4_{gal}), 3.84-3.36 (4m,12H, H-5_{gal}, $6a_{gal}$,$6b_{gal}$, H-2_{glc},3_{glc},4_{glc},5_{glc},$6b_{glc}$, CH_2O), 3.01-2.95 (m,1H,CH_2), 2.77-2.67 (m,1H,CH_2), 2.58-2.42 (2m,2H,CH_2), 2.27-2.22 (m,1H, CH_2).

^{13}C-NMR ($CDCl_3$) δ = 172.70 (COO), 172.10 (CONH), 137.86-126.48 (C, aromatics), 101.94 (CHPh), 99.94 (C-1_{glc}), 97.30 (C-1_{gal}), 81.00 (C-3_{glc}),80.53 (C-2_{glc}), 80.11 (C-4_{glc}), 74.41 (CH_2Ph), 74.09 (C-5_{gal}), 73.67 (CH_2Ph), 72.92 (CH_2Ph), 71.48 (C-4_{gal}), 70.94 (C-2_{gal}), 70.85 (C-3_{gal}), 68.63 (C-6_{glc}), 68.09 (C-6_{gal}), 67.00 (CH_2O), 65.84 (C-5_{glc}), 39.24 (CH_2), 31.9 (CH_2),31.73 (CH_2). 30.97 (CH_2)

Synthesis of [3,4,6-tri-O-benzyl-α-D-galactopyranoside-(1→3)-[2-yloxy-carbonyl-propanoylaminoethyl]-4,6-O-benzylidene-ß-D-glucopyranoside (454) [88,89,92]

^{1}H-NMR ($CDCl_3$), minor product **(454)**

δ = 7.50-7.25 (H,aromatics), 6.35-6.34 (brd,1H, NH), 5.54 (s,1H, CHPh), 5.52-5.47(t,1H, $J_{3,4}$ =9.09 Hz, H-2_{gal}), 4.89-4.86 (d,1H,J =11.87Hz, CH_2Ph), 4.82-4.81 (d,1H, $J_{1,2}$ = 7.83 Hz H-1_{gal}), 4.64-4.56 (dd, 2H, CH_2Ph), 4.47-4.41 (m,2H, CH_2Ph, H-1_{glc}), 4.34-4.30 (dd,1H,$J_{6a\text{-}H}$ = 13.14 Hz, $H_{6a\ glc}$-H), 3.99-3.95 (t,1H, $J_{3,4}$ = 8.84 Hz, H-3_{gal}), 3.92-3.297 (d,1H, $J_{4,5}$ = 1.52Hz, H-4_{gal}), 3.85-3.36 (4m,11H, H-2_{gal}, 5_{gal}, $6a_{gal}$, $6b_{gal}$, H-2_{glc}-OH, 3_{glc}, 4_{glc}, $5_{glc}6b_{glc,}CH_2O$), 3.02-2.95 (m,1H, CH_2O), 2.77-2.68 (m,1H, CH_2), 2.59-2.43 (m,2H,CH_2), 2.28-2-23 (m,1H, CH_2).

^{13}C-NMR ($CDCl_3$), δ = 172.58 (COO), 171.97 (CONH), 137.73-126.35 (C, aromatics), 101.81 (CHPh), 99.80 (C-1_{glc}), 97.16 (C-1_{gal}), 80.88 (C-3_{glc}), 80.38 (C-2_{glc}), 79.97(C-4_{glc}), 74.70 (C-5_{gal}), 74.28 (CH_2Ph), 73.94(CH_2Ph), 72.08 (CH_2Ph), 71.31 (C-4_{gal}), 70.80 (C-2_{gal}), 68.50 (C-6_{gal}), 67.95 (CH_2O), 66.89 (C-6_{glc}), 65.70 (C-5_{glc}), 39.11 CH_2), 31.82 (CH_2), 30.86 (CH_2). 31.60 (CH_2)

Synthesis of 1,2,3,4-tetra-O-acetyl-α-L-rhamnopyranoside (455).[111]

20gr (110mmol) of α/β-L-rhamnopyranose are dissolved in 75 ml (919 mmol), 72.74 g of pyridine by slightly heating with a heat gun. A flow of argon is circulated in the system and 75 ml (787.20 mmol) 81 g of acetic anhydride are added drop wise at 0°C to the dissolved starting material and stirred at the same temperature. The reaction is

controlled by TLC, toluene/ acetone 8:1. When the end of reaction is well revealed by TLC, the mixture is diluted in 100 ml of diethyl ether and worked out twice with 200ml of cold 1N HCL, saturated solution of sodium hydrogen carbonate , and water. The organic phase is dried on sodium sulphate, filtered, and reduced in vacuo to a clear oil product

Percentage yield : 29.87g, (89.92 mmol), 82%

Synthesis of phenyl 1-thio-2,3,4-tri-O-acetyl-α-L-rhamnopyranoside (456).[111]

Thiophenol (1.73g, 15.7 mmol) and $SnCl_4$ (2.6g, 10mmol) were added to a solution of L-rhamnose tetraacetate **455** (5 g , 14.27mmol) in 150ml of CH_2Cl_2 at 0°C. The mixture was stirred at 0°C for 4hr. It was than diluted in 200 ml Et_2O , washed with 2% HCL, 38ml, 2x 50ml of water and $NaHCO_3$ 2x 50 ml, and 50 ml of brine. The organic phase was dried on sodium sulphate, filtered ,and solvent removed in vacuo. The oily product was recrystallized in ether/hexane 1:1 to give a white solid.

Percentage yield : (3.493g , 8.72 mmol) 65.6%
mp: 116-118°C

Synthesis of phenyl 1-thio-α-L-rhamnopyranoside (457).[65,82,111]

A catalytic amount of 1M NaOMe was added to a solution of **456** (3.493g, 8.72 mmol) in a solvent mixture toluene/methanol 1:1 60ml and stirred 1hr at room temperature.

The TLC control toluene/acetone 1:2 revealed complete consumption of starting material. The medium was neutralised with ion exchange H^+, Dowex 50Wx 8. to pH 7, and reduced in vacuo, and (2.10gr, 8.20mmol) of oily product was obtained, which was immediately used for benzoylation reaction.

Percentage yield: (2.10g, 8.20 mmol), 94.10%

Synthesis of phenyl-1-thio-2,3,4-tri-O-benzoyl-α-L-rhamnopyranoside (458).[74]

Compound **51**, (2.10g, 8.20 mmol) was dissolved in 30 ml of dried CH_2Cl_2 and 14.55 g , 184 mmole ,15 ml of dried pyridine, and cooled to 0°C. To the cooled mixture were slowly added 5.53 g, 39.36 mmol, 4.57 ml of benzoylchloride. The reaction mixture was stirred overnight at 0°C. When TLC showed completion of the reaction, the mixture was diluted in 100ml of CH_2Cl_2 and washed with 100 ml of 1N HCL, twice with saturated aqueous $NaHCO_3$, and water. The organic phase was dried on sodium sulphate, filtered, and reduced in vacuo to a oily product that was chromatographed with toluene/acetone 30:1.

Percentage yield: 2.70 g , 5.074 mmol , 62%

Synthesis of 3,4,6-tri-O-benzyl-pentylamide-ethylcarboxylic acid-4,6-O- benzylidene - galactopyranoside-ß-D-(1-3)-glucopyranoside (459). [65,82,89]

Compound **427** (0.35g, 0.403 mmole), is dissolved in a solution mixture 20 ml toluene/ methanol 1:1 and heated to 5°C for dissolution stirred 10 minutes. A catalytical amount of 1M sodium NaOMe was added until the PH 12, and the solution was stirred overnight at 50°C. When TLC control toluene/methanol 2:1 shows no presence of starting material, the mixture was cooled to room temperature and neutralised with ion exchange H^+ Dowex 50W X 8 and evaporated in vacuo. The non-bridged disaccharide was filtered on column chromatography with an eluent toluene/methanol 3:1

Percentage yield: (0.30 g, 0.340 mmol), 84 %
mp: 183-185°C $[\alpha]_D$ = -16 (c= 0.1)

HRMS m/z calculated for C_{49} H_{59} O_{14} N
Calculated: 908.38153
Found : 908.38278

^{1}H-NMR ($CDCl_3$) δ = 7.49-7.23 (H-aromatics), 5.95-5.93 (d,1H, J=7.77Hz, H-1_{gal}, 5.63 (s,1H, CHPh), 4.87-4.86(d,1H, J=11.112Hz,CH_2Ph), 4.57-4.44 (m,3H,CH_2Ph, H-1_{glc}) 4.27-4.26 (brs,2H,NH), 4.08 ((brs,1H,H-4_{gal}),3.79-3.08 (4m, 17H,H-2_{gal},3gal,5gal,$6a_{gal}$, $6b_{gal}$ OH_{gal}, H-2_{glc}, 3_{glc} 4_{glc} ,5_{glc}, $6a_{glc}$, $6b_{glc}$,OH_{glc},CH_2O, CH_2), 2.41-2.35 (2d,2H,CH_2) 1.70-1.57 (3m, 6H, 3CH_2)

^{13}C-NMR (CDCl3) δ= 172.36 (CONH), 157.73(CO), 139.95-126.83 (C-aromatics), 105.78 (C-1_{gal}), 103.5 9 (C-1_{glc}), 100.39 (CHPh), 83.57 (C-3_{glc}), 82.53 (C-3_{gal}), 79.41 (C-4_{glc}) 74.99 (CH_2Ph), 74.60 (C-2_{gal}), 73.37 (C-2_{glc}), 73.29 (CH_2Ph), 72.44 (CH_2Ph), 71.20 (C-5_{gal}), 69.80(C-6_{gal}), 69.81 (C-6_{glc}), 67.91 (CH_2O),66.60 (C-5_{glc}). 34.27 (CH_2),31.92 (CH_2), 31.64 (CH_2), 29.79 (CH_2), 26.29 (CH_2),25.36(CH_2), 23.74 (CH_2).

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ZUSAMMENFASSUNG

Die Verknüpfung von Monosaccharidmlekülen mit spezifischer anomer Konfiguration stellt seit vielen Jahren eine der Herausforderungen der organischen Chemie dar. Problematisch bei Glykosylierunsreaktionen is vor allem die mangelde Regio- und Stereoselektivität (ungewünsche anomere Konfiguration). Ein Weg, diese Hindernisse zu überwinden, stellt die Strategie der intamolekularen Glycosylierung dar.

Hierbei wird win Donor d.h. ein Monosaccharid der reichelektronreiche Schutzgruppe trägt, mit einem Acceptor, ein monosacharid der electronarme Schutzgruppe enthält, die beiden durch eine Brücke verbunden sind.

Das Ziel dieser Methode besteht darin, die beiden Moleküle in raumlichen Nähe zu bringen, umso Regio- und Stereoselektivität zu erzwingen. Hierbei, lassen sich zwei Fälle unterscheiden. Im Fall iener labilen Brücke durch die Reaktion hindurch erhalten bleibt. Mit Hilfe dieser Synthesestrategie wurden in der Vergangenheit beachtliche Leistungen erzielt, wie z.B. die synthese von ß-Mannosiden, die β-Verknüpfung zwischen Fructofuranosiden und Glucodids-acceptoren sowie ein β (1-4)- Verknupftes Rhamnoglucosid, welche auf klassischen Wege nur schwer darstellbar sind.

Unsere Arbeit zielt auf die Darstellung einer β (1-3)- anomeren Verknüpfung eines Galaktose Donors und eines Glukose-Acceptor. Diese Verknüpfung tritt häufig in Naturstoffen wie wie Saponins und Sialyl-Lewis L^x, auf.

Das Hauptziel war die Durchführung einer intramolekularen Glycosylierung zwischen einem Tri-O-benzylierten β- Thiophenylgalaktose-Donor und einem durch eine Bersteinamid-Alkyl-Brücke verbunden 4,6-O-benzyliden-β-D-glucopyranosid-Acceptor, welcher sowohl an Position-2 als auch an Position-3 eine Hydroxyfunktion zur Reaktion zur Verfügung stellt.

Die Alkylkette der Brücke variiert dabei von n= 5 bis n= 2.

Die Succinylamid-Brücke weißt genügend Flexibilität auf, um Donor und Acceptor in raumliche Nähe zu bringen. Diese Brücke, auch Spacer genannt, zwingt die beiden Sacchariden in einer solche Orientierung, daß bei der Aktivierung des anomeren Zentrums des Donors eine der beiden Hydroxyl-gruppen des Acceptors reagieren kann. Die verbleibende Hydroxyl-Gruppen kann später dann für weitere Reaktionen verwendet werden.

Zuerst wurde eine siebenstuffige Synthese durchgeführt, welche den 3,4,6-Tri-O-benzylierten Galaktose-donor **414** mit einer freien OH-Gruppe am Position 2 lieferte. Die Veresterung mit Bersteinsäureanhydrid in Pyridin bei 65°C mir DMAP als Katalysator ergab in guter Ausbeute das 2-O-succinylierte Produkt **415**. Die Aktievierung der Carbonsäure mit Pentafluoro-phenol und DCC in Ethylacetat bei 0°C führte in 87%-iger Ausbeute zu Produkt **416**

(Scheme **93**). Die vier Aminoalkyl-4,6-O-benzyliden-ß-D- Glucopyranosid-Donoren **425,433,443,** und **451** wurden in jeweils fünfstufigen Synthesen dargestellt.

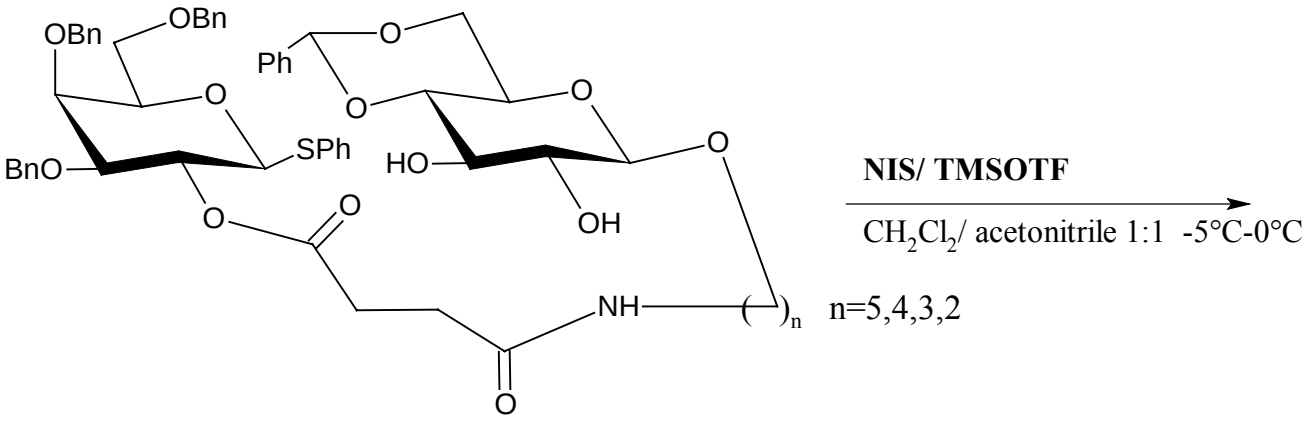
Synthese der Verbrückten Disacchariden

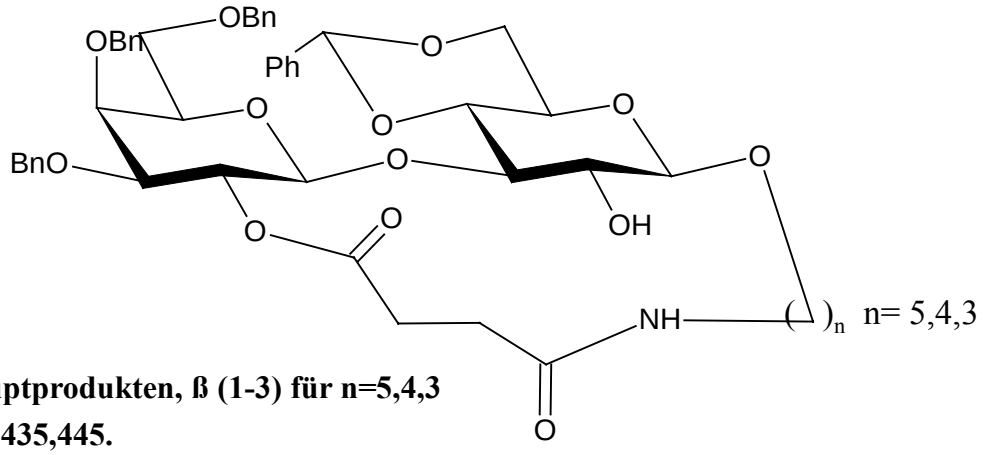
Zur Verbrückung der beiden Monosaccharidseinheiten, wurden der 2-O-succinoylierte Pentafluorophenolester ß-D-Galaktosethioglycosid donor **416** und die Aminoalkyl-4,6-O-ß-D-glucopyranosidsakzeptoren, **425**, **433**, **443**, **451**, durch eine Kupplungsreaktion in Ethylacetat, bei 25°C zu den voverbückten Disacchariden **426**, **433**, **443**, **451** in guten Ausbeute umgesetzt (Schema **80**,**83**, **86**,**89**, Seiten, **121**, **126**, **127**, **131**, **136**).

INTRAMOLEKULAR GLYCOSYLIERUNG

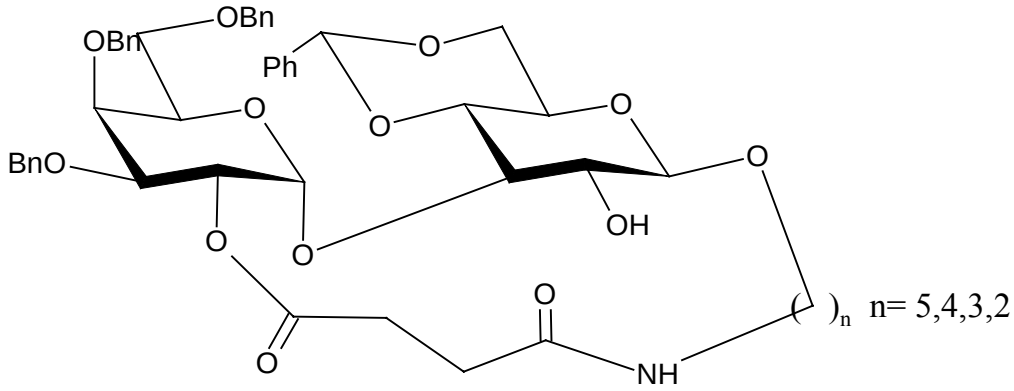
Die verschiedenen voverbrückten Disacchariden wurden einer intramolekularen Glycosielierung mit NIS-TMSOTf-Aktivierung in der Lösungsmittelsmischung dichloromethan/Acetonitril 1:1 im temperaturbereich 0°C- -5°C unterzogen (Scheme **93**). Die Ausbeuten und Anomers konfigurationen jeden die Versucht sind in der hierunten Tabelle **11** zuzammengefaßt.

Scheme 93.





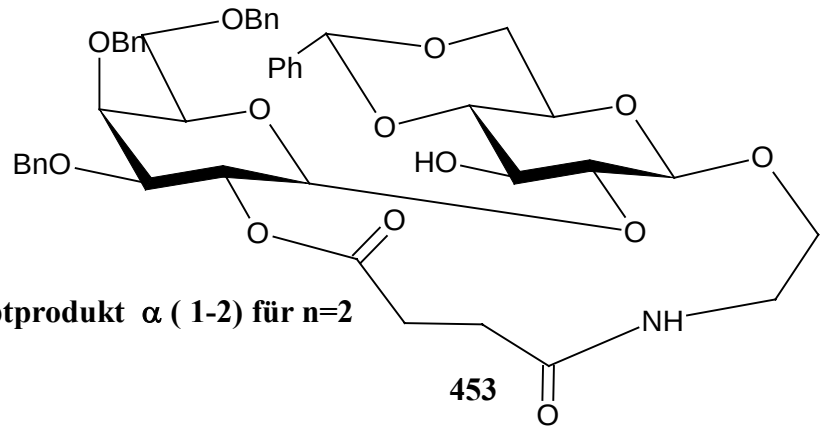
Hauptprodukten, ß (1-3) für n=5,4,3
427,435,445.



Nebenprodukten, α(1-3) für n=5,4,3,2
428,36,446,454

Fall der Succinylamidethyl Brücke

Die intramolekular Glycosylierung des Succinylamide ethyl Disaccharids, unterscheid sich von alle anderen Fälle mit einer α (1-2) Verknüpfung als Hauptprodukt, und wie anderen Fälle eine α (1-3) Veknüpfung als Nebenprodukt.



Hauptprodukt α (1-2) für n=2

453

AUSBEUTEN UND

STEREO -REGIOSELEKTIVITÄT RESULTATEN

Tabelle 11.

SPACER	*ALKYL*	*AUBEUTE*	*ß-GLYCOSYDIC*	*α-GLYCOSYDIC*	*ß/α*
n=5	***pentyl***	***56%***	***50% ß (1-3)***	***6% α (1-3)***	***8:1***
n=4	***butyl***	***66%***	***58% ß (1-3)***	***8% α (1-3)***	***7:1***
n=3	***propyl***	***73%***	***58% ß (1-3)***	***15% mixture***	***4:1***
n=2	***ethyl***	***72%***	***none***	***59% α (1-2)***	
				13% α (1-3)	

- Die Brücken mit n=1,2,3 lieferten ausschließlich ß (1,3)-Verknupfungen

  Verwendung der Brücke mit n=5 führte mit einem Anomerenverhätnis von α/ß= 1:8 zur best Regio-und-Stereoselektivität

  Die Brücke mit n=4 lieferte eine höhere Gesamtausbeute, auch eine sehr guten Stereoselekti-selektivität mit leicht geringen Anomerverhältnis (α:ß=1:4)

  Die Brücke mit n=3 lieferte die höchste Gesamtaubeute, mit deutlichen geringen aber akzeptabel Anomerenverhältnis (α/ß1:4).

  Die Brücke mit n=2 lieferte sowohl eine 1,2-als auch eine 1,3-Verknupfung mit α-1,2 als Hauptprodukt.

Zum Schluß, durch die Succinylamidealkyl vorverbrückten Disaccharide mit einer freien 2-OH und 3-OH zur Verfügung, bei der intramolecular Glycosylierung liefert von gut bis fair Gesamtsausbeute und Regio-Stereoselektivität.

Im Fall der Succinylamid-Ethylbrücke (n=2) wurde ein α (1-2) Verknüpfung als Hauptprodukt bevorzug, und α (1-3) als neben Produkt. Die kurze Brücke aufgrund ihrer eingesschränkten Beweglichkeit, zwingt die Glycosylierung in die schwere zugängliche 1,2-Position.

Außerdem, erhält man aus dem Molecular Modelling im Fall n=2 zwei starken aromatischen zweiwertigen Stapeleffekt zwischen Position 3 und 4-O-Benzylschutzgruppen des Galaktose donors. Das andere zweiwertigen Stapeleffekt liegt zwischen der 6-O- Benzylschutzgruppe des Galaktosdonors und der 4,6-O-Benzylidenschutzgruppe des Glukoseacceptors.

Zur Erklärung der vorliegenden Ergebnisse wurde Molecular modelling durchgeführt. Hier zeigt sich ein Triadstapeleffekt zwischen den drei aromatischen Schutzgruppen, die Benzyl- schutzgruppen des Galktosedonors an Position 4 und 6 und der 4,6-O-Benzylideneschutzgruppen des Glucoseacceptor. Außerdem erklärt das Molecular Modelling einen Lösungsmitteleinfluß. Nich-aromatischen Lösungsmittel wie Acetonitril und Dichloromethan unterstützen voll Stapelbildung, aromatische Lösungsmittel wie Benzol und Toluol vermindern die Stapelbildung durch Einlagerung.
Diesen aromatischen Stapeln sind in einer Weise positioniert daß der 3-OH eine Wasserstoffwechselwirkung mit dem Sauerstoffe der 6-O-Benzylethersgruppe und anderen mit dem Saurestoff des Galaktosedonor Ring, d.h. eine doppelten extraanular Wasserstoffwechsel- wirkung.
In der macrocyclischen 14-Ring, ist einen starken intramolecular oder intrannular Wasserstoffwechselwirkung zwischen der NH der Monopeptide und Saurstoffe der Succynylesters gruppe, und einer scwächere zwischen NH und Anomerensauerstoffe, d.h. intraanular dopplten Wasserstoffewechselwirkung. Von diesen doppelten Wasswestoffwechselwirkung hast sich eine ß-Turnsstruktur Type ausgelöst, die sich an der Fläcke von Proteinen und aromatischen Polypeptiden auftretten.

Im Fall der Succinylamid-Ethylbrücke (n=2) wurde ein α (1-2) Verknüpfung als Hauptprodukt bevorzug, und α (1-3) als neben Produkt. Die kurze Brücke aufgrund ihrer eingeschränkten Beweglichkeit, zwingt die Glycosylierung in die schwere zugängliche 1,2-Position.

Die aromatischen zweiwertigen Stapeln sie in einer Weise orientiert daß, eine Wasserstoffbrückenbindung zwischen der 3-OH der Glukoseacceptors und beiden, der 6-O- Benzylschutzgruppe und anomeren Saurestoffe des Galaktoseacceptors d.h. eine doppelten extraanularen Wasserstoffbrüke. In dem macrocyclischen 14-gliedrigen Ring, tritt sich eine starken Wasserstoffbrückenbindung zwischen der NH des Monopepetidebausteins und dem Wasserstoff der Succinylester des Rings auf. Es gibt zusätlichen Wasserstoffbrückenbindung zwischen

NH und dem glycosydischen Saurestoffe, d.h.doppelten intraanularen oder intramolekularen Wasserstoffbrücke. Desweiteren es entsteht von dieser doppelten Wasserstoffbrückenbindung eine ß-turn- Sruktur die sich analog zu aromatischen Polypeptiden, und Proteinen. Sämtliche theoretischen Ergebnisse stimmen mit unseren expreimentellen Daten überein.

Die Anwenderung unserer Synthesestrategie mit Succinylamid-alkylbrücken ermöglicht eine regio-und stereoselektive Glycosylierung zwischen einem Galaktosedonor und einem Glukose-acceptor der zwei OH-Funktionen an 2-und 3-Position hat. Hierbei wird auschliesßlich eine der beiden Hydroxylgruppe selektive glycosyliert, und die anderen discriminiert und frei bleibt.

Das Erfolg unserer Strategie, durch die Anwendung des Succinylamidalkyl Spacers ermöglicht eine selektiven Regio-stereo- intramolecularen Glycosylierung zwischen einem Galaktosid donor und Glycosidsakzeptor mit 3-OH, 2-OH Gruppe zur Verfügung. Die Auslösung unserer Methode zeigt eine völligen Discriminierung einer OH, und selektive Auswahl an der Hydroxylsgruppe für Glycosylierung.

Die Abspaltung der Succnylamidpentylsbrücke des cyclischen Disaccharids **425** mit beides mit Natriummethanolat lieferte der unverbrückten Disaccharid **451** mit der frein 2-OH Galaktosidsdonors un Glukoseakzeptors zur Verfügung und einer Carboxylsaüre Gruppe and der Kette.

Mit dem Produkt **451** am Hand, kannt einer höher Saccharid hergestellt werden.Esterifierung der Carbosäure mit DCC und Methanol, und dann, selektiven Benzoylierung der 2-OH des Galaktosidsdonors, Glycosylierung der 2-OH Gruppe des Glukosidsakzetors, selektiven Abspaltung der Benzylidenesgruppe und wieder Glycosylierung der OH Gruppe.

Andere synthetischen Perpektive, ist die Aktivierung der Carbosäure von Verbindung **451** mit Pentafluorophenol und DCC, für einner eventüellen Peptidekupplung, oder die Bindung einer Proteine. Hier beweise sich die Flexibilität und die Effizienz unsere Methode.

Mit dem so erhaltenen Produkt **459** können jetz höhen Sacchariden hergestellt werden, da die 2-OH Funktion der Galaktose selektive benzoyliert werden kann. An der Glukose kann anschließend die 2-OH glycosyliert werden, die Benzylidengruppe selektive abgespalt und die frei OH glycosyliert.
Es besteht weiterhin die Möglichkeit die Carbonsäurederivat des unverbrückten Disaccharids mit Pentafluorophenol und DCC eine Esterung durchzuführen für eine eventüellen

Pedptidkupplung. Die Carbonsäuredervat kann eine Protein binden die eine Aminesgruppe trägt. Hierdurch verdeut.licht sich die Eleganz, flexibilität und Effizienz unserer Methode.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. *Essential of Carbohydrate Chemistry and Biochemistry*, **1999**, Thisbe K.Lindhorst
2. *Comprehensive Natural Products Chemistry*, **1999**, Sir Derek Barton, Koji Nakanishi, Otto Meth. Cohn, Mario Pinto
3. *Carbohydrates*, Helen M. I. Osborn
4. *Glycoscience, Chemistry and Biology*, Vol III, Reid, B.-F.; Kunaki Tatsuta; Joachim Thiem.
5. *Carbohydrates in Chemistry and Biology*, Beat Ernrst, Gerdt W. Hart, Pierre Sinay.
6. *Carbohydrates in Chemistry and Biology*, Vol. 4, Beat Ernst, Gerdt W. Hart, Pierre Sinay.
7. Sharon, N.; Lis, H., *Eurp. J. Biochem.,* **1993**, *3*, 218
8. A. Vaki, *Glycobiol.*, **1993**, *3*, 97.
9. Dweck R.A., *Chem. Rev.*, **1996**, *3*, 97.
10. Hayes, B, K.; Hort, G. W., C*urr. Opin. Struct. Biol.*, **1994**, *4*, 692.
11. Liu, W.-J.;Ramachandran V.; Kay J, Kishimoto T.K., Cunnings R. D.; Mc Ever R.P. *J.Biol. Chem* ., **1998**, *273*, 7078.
12. Wilkins P.P.; Mc Ever P.P.; Cunnings R.D.; *J. Biol. Chem.***1996**, *271*,18732.
13. Ohno N; Yadomae T., Myazaki T., *Carbohydr. Res.* **1980**, *80*, 297-304.
14. Jennings H.J.; Rosell K.-G., Carlo D.J., *Can.J. Chem.* **1980**, *58*, 1069-1074
15. Jennings H.J.; *Adv. Carbohydr. Chem. Biochem.* **1983**, *41*, 155-208.
16. Kaji, E.; Lichtenthaler F.W.; Osa Y.; Takahashi E.; Matsui Zen S., *Chem Lett.*, **1992**, 707-710.
17. Bousquet E.; Khitri M.; Lay L.; Nicotra F.; Panza L.; Russo G., *Carbohydr. Res.*, **1998**, *311*, 171-181.
18. Inaba,S.,Yamada, M.; Yoshino, T.; Ishido,Y.*J.Am.Chem.Soc.***1973**,*95*,2062
19. Ishido, Y.;Inaba, S.;Yoshino, T.;Umezawa, H.*J.Chem.Soc.,Perkin Trans. 1*, **1977**, 1382.
20. Imori T.; Azumaya, I.; Shibazaki, T.; Ikegami, S. *Tetrahedron Lett.*, **1999**,*37*, 2267..
21. Azumaya, I.; Niwa, T.; Kotani, M.; Imori, T.; Ikegami, S., *Tetrahedron Lett.* **1999**, *40*, 4683
22. Scheffler, G.; Schmidt, R.R. *Tetrahedron Lett.* **1997**, *38*, 2943.
23. Behrendt, E,; Schmidt R.R. *Tetrahedron Lett.* **1993**, *34*, 6733
24. Mukai, C.; Itoh, T.; Hanakoa, M. *Tetrahedron Lett.* **1997**, *38*, 4595
25. Scheffler, G.; Schmidt, R.R. *J. Org.Chem.* **1999**, *64*,6733
26. Scheffler,G.; Behrendt, E.; Schmidt, R.R. *Eur.J.Org. Chem.* **2000**, 3527

27. Griedly, J.J.; Osborn, H.M.I. *J. Chem. Soc., Perkin Trans. I*, **2000**, 1471
28. Barresi, F.; Hindsgaul, O. *J.Am.Chem. Soc.* **1991**, *113*, 9376.
29. Barresi, F.; Hindsgaul, O. *Synlett*, **1992**, 759.
30. Barresi, F.; Hindsgaul, O. *Can. J. Chem.* **1994**, *72*, 1447.
31. Ito, Y.; Ohnishi, Y.; Ogawa, T.;Nakahara, Y. *Synlett*, **1998**, 1102
32. Lergenmüller, M.; Nukada, T.; Kuramochi, K.; Dan, A.; Ogawa, T.; Ito, Y. *Eurp. J. Org. Chem.* **1999**, 1367
33. Dan, A.; Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1995**, *36*, 7487.
34. Dan, A.; Ito. Y.; Ogawa, T. *J. Org. Chem.* **1995**, *60*, 4680.
35. Ito Y.;Ogawa, T. *J. Am. Soc.* **1997**, *119*, 5562.
36. Krog-Jensen C.; Oscarson, S. *J.Org. Chem.* **1996**,
37. Krog-Jensen C.; Oscarson S. *J.Org. Chem.* **1998**, *63*,1730.
38. Stork, G.; Kim, G.. *J.Am.Chem.Soc.* **1992**, *114*, 1087
39. Stork, G.; La Clair,J.J. *J.Am.Chem.Soc.* **1996**,*118*, 247
40. Bols, M.*J.Chem.Soc., Chem.Commun.* **1992**, 913.
41. Bols, M. *J. Chem.Soc. Chem. commun.* **1993**, 791.
42. Bols, M.*Acta Chem.Scand.* **1996**, *50*, 931.
43. Ennis S.C.; Fairbanks, A.J.; Tennant-Eyles, R-J.;Yeates, H.S., *Synlett*, **1999**, *9*, 1387.
44. Christopher Seward, M.P.; Cumpstey, I.;Aloui, M.;Ennis, S.C.; Redgrave, A.J.; Fairbanks, A.J.; *Chem.Com.* **2000**, 1409..
45. Cumptsey, I.;Fairbanks, A.J.; Redgrave, A.J. *Org. Lett.* **2001**, *3*, 2371.
46. Ennis, S.C.; Fairbanks, A.J.; Slinn, C.A.;Tennant-Eyles. R.J.; Yeates, H.S. *Tetrahedron*, **2001**, *57*, 4221.
47. Fairbanks, A.J., *Synlett*, **2003**, *13*, 1945.
48. Ziegler, T.; Lau, R. *Tetrahedron Lett.* **1995**, *36*, 1417.
49. Lau, R.; Schüler, G.;Schwanenberg, U.; Ziegler, T; *Liebigs Ann.* **1995**,
50. Ziegler, T.; Ritter A.; Hürttlen J. *Tetrahedron Lett.* **1997**, 38, 3715
51. Schüle, G.; Ziegler T. *Liebigs Ann.* **1996**, 1599
52. Ziegler T.; Lemanski, G.;Rakoczy, A. *Tetrahedron Lett.* **1995**, 36, 8972
53. Ziegler T.; Lemanski G.; *Angew. Chem.* **1998**, *110*, 3367; *Angew. Chem. Chem., Int. Ed. Engl.*, **1998**, *37*, 3129.
54. Ziegler T.; Lemanski G., *Eur.J.Org. Chem.* **2000**, 181.
55. Valverde S.; Gomez A.M.; Hernandez, A.; Herradón, B.; López J.C. *J. Chem. Soc.,Chem. Commun.* **1995**, 2005.
56. Valverde, S.; Gómez, A.; Herradón, B. *Terahedron Lett.* **1996**, *37*, 1105

57. Wakao, M,; Fikase, K,; Kusumoto, S. *Synlett.* **2000**, 22.

58. Huchel, U.; Schmidt, R.R., *Tetrahedron Lett.* **1998**, *39*, 7693

59. Müller, M.; Huchel, U.; Geyer, A.; Schmidt, R.R., *J.Org. Chem.*, **1999**, *64*, 6190-6201.

60. Müller, M.; Schmidt, R. R., *Eurp.J. Org.Chem.* **2001**, 2055-2066.

61. Tennant-Eyles, R. J.; Davis, B.G.; Fairbanks, J.A. *J.Chem. Soc., Chem Commun.* **1999**, 1037

62. Tennant- Eyles, R. J.; Fairbanks, J. A. *Tetrahedron Assym.* **2000**, *11*, 131

63. Koibe. K.,Kudo M., Jia Z., Nikaido T.,Ide. Y., Sakura T. *J. of Nat. Prod.* **1999**, *62*, 228-232.

64. Hansen R.G.; Rutter, W.J.;Krichevski, P. B*iochem. Prepar.*, **1955**, *4*, 1-2.

65. Bröder, W.; Kunz, H., *Carbohydr. Res.*, **1993**, *249*, 221

66. Zemplén, G.; Pascu, E., *Ber. dt. Chem.Ges.,* **1929**, *62*, 1613

67. De Pouilly P.; Chénedé, A.; Mallet, J.M; Sinay P., *Bull. Soc. Chim. Fr.*, **1993**, *130*, 256.

68. Ziegler, T.; Dettmann, R.; Ariffadhillah, Zettl, U., *J. Carbohydr. Chem.*, **1999**, *9*, 1079.

69. Kisfaludy,L.; Schön, I., *J.chem.Soc.,Chem.Commun.,* **1983**, 325.

70. Sakakiraba, S.; Inuaki, N., *Bull. Chem.Soc. Jpn.* **1964**, *37*, (8), 325-327.

71. Schön, I.;Szirtes, T.; Rill, A. Balogh, G.; Vadász Z.; Seprödi, J.; Teplàn, I; Chino,N.;Kumogaye, K.Y.; Sakakibara, S., *J. Chem. Soc. Perkin I.,*

72. **W**olfram, M.L.; Thomson, A. in ,, *Methods in Carbohydrate Chemistry, Vil.II,* (Hrsg. R.L. Whistler, J.N. BeMiller), **1963**, Academic Press, New York, S. 211.

73. Ravindranathan Kortha, K.P.; Jennings, H.J., *I.Carbohydr. Chem.*, **1990**, *9*, *9*, (5), 777-781.

74. Lichtenthaler, F.W., in ,, *Modern Synthethic Methods*", **1992**, ,, *Enantiopure building blocks from sugars and their utilisation in natural product synthesis"*

75. Mikamo, M., *Carbohydr. Res.*, **1989**, *191*, 150-153.

76. Itho, T.;Takamura, H.; Watanabe, K.; Araki, Y.; Ishido, Y., *Carbohydr. Res.* **1986**, *156*, 241-246.

77. Fiandor J.; Garciá- Lòpez, M.T.; de las Heras, F.G.;Mèndez- Castillòn, *Synthesis*, **1985**, 1121-1123.

78. Bien, F., *Dissertation*, Universität Stuttgart, **1997**.

79. Schmidt, R.R., *Angew. Chem.* **1986**, *98*,213-236; A*ngew. Chem., Int.Ed.Engl.* **1986**, *25*, 212-235.

80. Schmidt, R.R.; Kinzy, W., *Adv. Carbohydr. Res.* **1994**, *50*, 21-123.

81. Schmidt, R.R.; Castro-Palomino, J.C.; Retz, O. *Pure Appl. Chem.*, **1999**, *71*, 729-744.

82. Eckhardt, E.; Ziegler, T., *Carbohydr. Res.*, **1994**, *264*, 253-259.

83. Goto, F.; Ogawa, T., *Tetrahedron Lett.*, **1992**, *33*, 5099.

84. Sasaki, A.; Murahashi, N.; Yamaha, H.; Morikawa, A., *Biol. Pharm. Bull*, **1995**, *18*, 740-746.

85. Bodansky M.; Bodanszky, A, *the Practice of Peptide Synthesis,* Springer-Verlag, Berlin, Heidelberg, New York, Tokyo, **1984**.

86. Becker, F.G.O., Domschke, G., Fanghänel E., fischer M.,Gewald K., Meyer R., Pavel D,Schmidt H., Schvetlick K., *Organikum*, Deutcher Velrag der Wissenschaft, Berlin, **1990**, 16. Auflage, 288-298.

89. Lemanski, G., *Dissertation*, Universität zu Köln, **1999**. **1981**

87. Mallams A. K.,Morton, _James, B., Reichert, P., *J.Chem. Soc. Perkin Trans. I* ,

88. Chernyak, A. Ya., et. al., *Carbohydr. Res.* **1992**, *223*, 203-309.

90. Lemanski, G., *Diplomarbeit*, Universität Stuttgart, **1995**.

91. Höfle, G.; Steglich W.; Vorbrüggen, H., *Angew. Chem.* **1978**, *90*, 602-615.

92. Dettman, R., *Dissertation*, universität zu Köln, **2002**.

93. Demchenko, A.; Stauch, T.; Boons, G.-J., *Synlett*, **1997**, 818-820.

94. Boons, G.-J-; Zhu, T., *Synlett*, **1997**, 809-811.

95. Garegg, P.J., *Adv. Carbohydr. Chem. Biochem.*, **1997**, 179-205.

96. Fügedi, P.; Garegg, P.J.;Lönn, H.; Norberg, T., *Glycoconjugate J.* **1987**, *4*, 97-108.

97. Graham Jones, B.; Chapman Brant, J., *Synthesis*, **1995**, 475.

99. Jerry L. Atwood, Jonathan W. Steed, *Encyclopedia of Supramolecular Chemistry*, **2004**,

98. *Supramolecular Chemistry* **2000**, 26-28, Jonathan W. Steed, Jerry, L. Atwood

100. Castello, R. K.; Diederich, F.; Meyer, E.A., *Andew. Chem. Int. Engl. Ed.*, Vol.II, 1093-1099, 1551-1556.

2003, *42*, 1210.

101. William Jorgenson, L.; Severance Daniel, L., *J.Am. Chem.Soc.* **1990**, *112*, 4768.

102. Guckian Kevin, M.; Schweizer Barbara, A.; Ren Rex, X.-F.; Sheils Charles, J.; Thamassebi Deborah, C.; Kool Eric, T., *J. Am. Chem.Soc.* **2000**, *122*, 2213

103. *Comprehensive Supramolecular Chemistry*, **1996**, *4*, 204-239, Jerry L. Atwood, J. Eric D. Davies, David D. Mac Nicol, Fritz Vögtle, J.M. Lehn, Tonikozu Sasaki, Marya Liebermann.

104. Richardson J.S., *Nature*, **1977**, *268*, 495.

105. Toniolo, C.; Benedetti, B., *Trends in Biochem. Sci.,* **1991**, 130.

106. Toniolo, C., *CRC Crtit. Rev. Biochem.*, **1980**, *9*, 1-44.

107. Obrecht, D.; Altorfer, M.; Robinson, J.A., *Adv.in Med.Chem*., **1999**, *4*, 1-44.

108. Pfeifer Marc, E.; Linden A.; Robinson John, A., *Helv. Chim. Acta,* **1997**. *80*, 1513-1521.

109. Feigel, M., *J.Am. Chem. Soc.,* **1986**, *108*, 181-182.

110. Bisang Christian, Weber Christopher, Robinson John, A., *Helv. Chim. Acta*, **1996**, *79*, 1825-1838.

111. Hirchman Ralph, Nicolaou, K. C.; Pietranico Sherrie, M. Leaby, Ellen, Salvino, J.; Byron, A.; Cichy Maria, A.; Grant Poors, P.; Shakespear William, C.; Sprengeler Paul, A.; Hamley, P.; Smith Amos, B.; Reisine, T.; Raynor, K.; Maechler, L.; Donaldson, C.;Vale, W.; Freidiger Roger, M.; Cascieri Margaret, R.; Strader Catherine, D., *J. Am.Chem. Soc.*, **1993**, *115*, 12550-12568.

112. Hirschman R.; Yao, W.; Cascier Margaret, A.; Strader Catherine D.; Maechler, L.; Cichy-knight Maria, A.; Hynes, Jr., J.; Van Rijn Rachel, D.; Sprengeler Paul, A.; Smith Amos, B., *J. Med. Chem.*, **1996**, *39*, 2441-2448.

113. Lehmann C.; Mutter, M.; Kelle, M., *Synlett*, **1999**, 935-939

114. Ahn D.-R.; Egger A.;Lehmann C.; Pitsch S.; Leumann C.J., *Chem. Eur. J.* **2002**, *8/23*, 5312-5322.

115. Lehmann C.; Xu Y.- Z.; Christodoulou, C.; Gait M. J.; Van Meervelt, M., Moore, M., *Nucleosides & Nucleotides* **1991**, *10*, 1599-1614.

Meinen akademischen Lehrer waren die Professoren und Dozenten:

J. Baker, D. Berkowitz, R. Disch, G.W. Koeppel, G. Descotes, H. Charette, J. Périé, Sotiropoulos, A. Faucher, A. Laporterie, P. Tisnés, A. Lattes, M. Calmon, J. Satgé, M. Pasdeloup, P. de Loth, P. Poilblanc, M. Couret, P. Mauret, L.A. Aries, M.A. Klaebe P. Jouin, J. Martinez, Pr. Jacquier, H. Cristau, A. M. Lamazouère, L.A. Aries, P. Daunis, J. C. Rossi, G. Gosselin, J.C. Montero, M. Vert, M. Mutter, Th. Ziegler.