

Asymmetric Control of the Diastereoselectivity of Glycosylation

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Abstract

Diastereoselective control of glycosylation still remains a difficult task.¹ Therefore, new glycosylation methods using asymmetric catalysis were developed to control the diastereoselectivity. Two systems were developed and each focused on a separate type of glycosyl donor. In the first system, glycosyl halides were subjected to reaction conditions inspired by Hamilton *et al.*, who effectively had controlled the substitution of a racemic chloroamine by an alcohol.² Asymmetric control of glycosylation was achieved through this adapted catalytic system. Both enantiomers of the catalyst ((R) and (S) TRIP) generally displayed β -selectivity with tertiary butyl methyl ether (TBME) as the solvent allowing almost exclusive formation of the β -anomer (Figure 1). However, low and inconsistent yields were obtained.

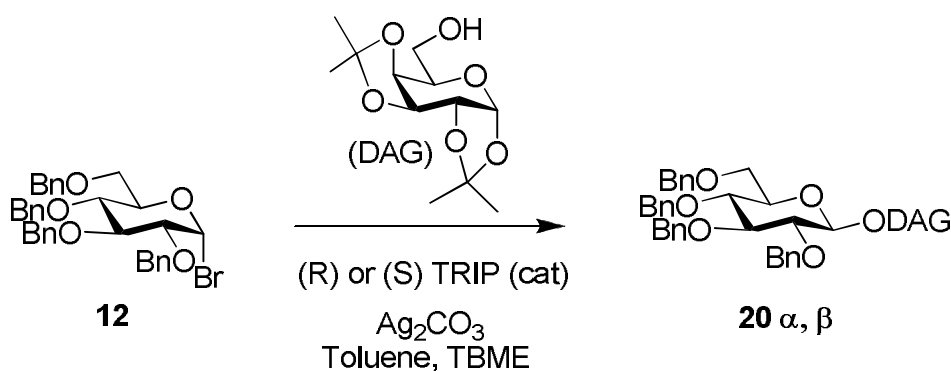


Figure 1 : Asymmetric control of a glycosyl halide displaying β selectivity

The second system proposed the use of the same phosphoric acid catalyst (TRIP) to catalyze the glycosylation of glycols. However, this was ineffective as the catalyst was not a strong

enough Brønsted acid. These studies then led to the development of two new chiral catalysts which then promoted the glycosylation of glycols, along with the formation of an undesired side product (Figure 2). Attempts were made to reduce the formation of the side product but unfortunately this proved unsuccessful. The diastereoselective outcome displayed between the different catalysts in separate trials was negligible, but the principles developed in this study should lead to the further development of new chiral catalysts for the glycosylation of glycols.

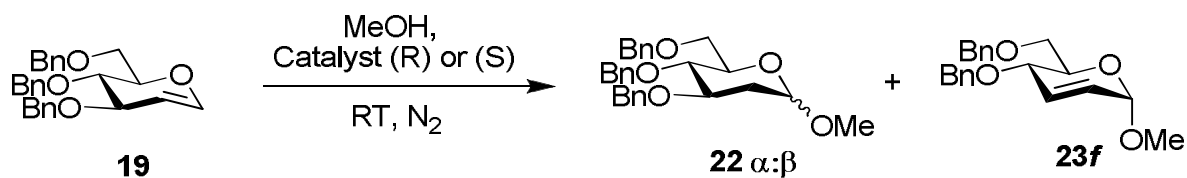


Figure 2 : The glycosylation of glycols

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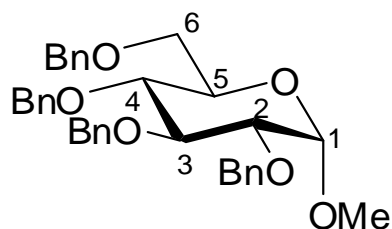
Abbreviations

Ac	acetyl
AgOTf	silver triflate
Ar	aryl
at	apparent triplet
BATC	benzyl ammonium triethyl chloride
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Bz	benzoyl
c	concentration g/100ml
cat.	catalytic amounts
cm	centimetre
CSA	D-(+)-camphorsulfonic acid
d	doublet
DAG	diacetone galactose and 1,2:3,4-di- <i>O</i> -isopropylidene- α -D-galactopyranoside
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
dm	decimetre
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DNA	deoxyribonucleic acid
dt	doublet of triplets
E1	elimination 1 st order
ee	enantiomeric excess
eqv	equivalent
ESI	electrospray ionisation
Et ₃ N	triethylamine
FT IR	fourier transform infrared spectroscopy
g	gram (s)

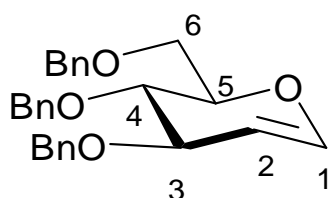
HPLC	high-performance liquid chromatography
hr	hour(s)
HRMS	high resolution mass spectrometry
HSAB	hard soft acid base theory
Inc.	including
Int.	intermediate
iPr	isopropyl
<i>J</i>	coupling constant
LG	leaving group
lit.	literature
m	multiplet
m.p	melting point
m/z	mass to charge ratio
mbar	millibar
Me	methyl
mg	milligram(s)
min	minute(s)
mL	milliliter(s)
NBS	n-bromosuccinimide
NMR	nuclear magnetic resonance
ppm	parts per million
RT	room temperature
s	singlet
S _N 1	substitution nucleophilic 1st order
S _N 2	substitution nucleophilic 2 nd order
t	triplet
t.l.c	thin layer chromatography
TBME	tertiary butyl-methyl ether
TMSI	tetramethylsilane iodide
TRIP (S/R)	(S/R)-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diylhydrogenphosphate
v/v	volume per volume
v _{max}	adsorption maxima

Explanatory note

The carbohydrates and derivatives in this thesis are numbered in accordance with carbohydrate conventions as outlined in 1997.[†] The two protons on C6 for hexose sugars are labelled H-6 and H-6'.



Methyl 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranoside



3,4,6-Tri-*O*-benzyl-D-glucal

[†] *Carbohydr. Res.*, **1997**, 297, 1 - 92

Chapter 1: Introduction

1.1 Summary

The aim of the studies detailed in this thesis was to develop new glycosylation methods, employing asymmetric catalysis to control diastereoselectivity. The introduction will include a discussion of how glycosidic bonds are formed, and other methods by which diastereoselective control may be achieved. Examples of current research in asymmetric catalysis will be given and how these principles could be applied to a carbohydrate system will be explained.

1.2 Importance of Carbohydrates

Carbohydrates are ubiquitous metabolites found in abundance throughout nature.^{3,4} As a result they are involved in many different cellular processes ranging from acting as an energy source (e.g. glucose), through to fertilisation and other cellular recognition processes.^{5,6} All of these recognition processes invariably rely on the monosaccharides in the polysaccharide chain to have defined stereochemistry and regiochemistry, and if required the same specificity with a biological macromolecule. For example, amylose and cellulose are both polysaccharides comprised of glucose monomers joined by 1,4 linkages (Figure 3). However, the stereochemistry of these linkages defines their cellular role.

Amylose is joined through kinetically labile α -linkages to form a helix like structure making it an ideal energy reserve, whereas, cellulose is joined through robust β -linkages to form a linear chain making it an ideal structural material.^{7,8}

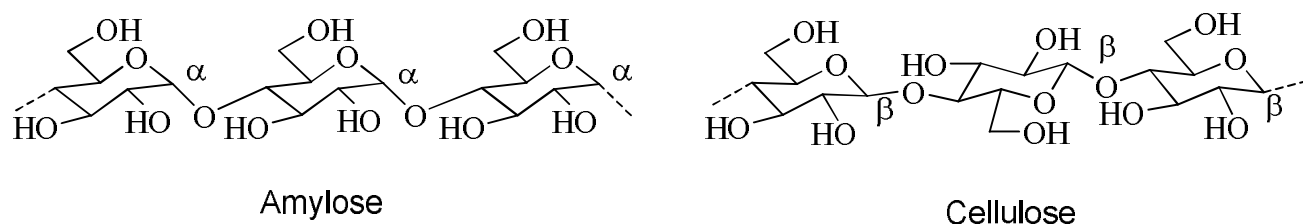


Figure 3: Amylose & Cellulose

1.3 Formation of the Glycosidic Bond

Glycosidic bond formation occurs when a glycosyl donor (R-X or glycal) is reacted with a glycosyl acceptor (any suitable nucleophile). Glycosyl donors are electrophiles typically capable of forming a resonance stabilised cationic intermediate, often called a glycosyl cation. This thesis investigates two routes for formation of such a cationic intermediate (Figure 4). The first route uses activation of glycosyl halides (R-X) which can undergo a S_N1 type reaction where the halide (X) departs from the anomeric center forming the cationic intermediate.⁹ The second route uses glycals which can undergo protonation of the double bond to form a cationic intermediate in a reverse E1 process.¹⁰

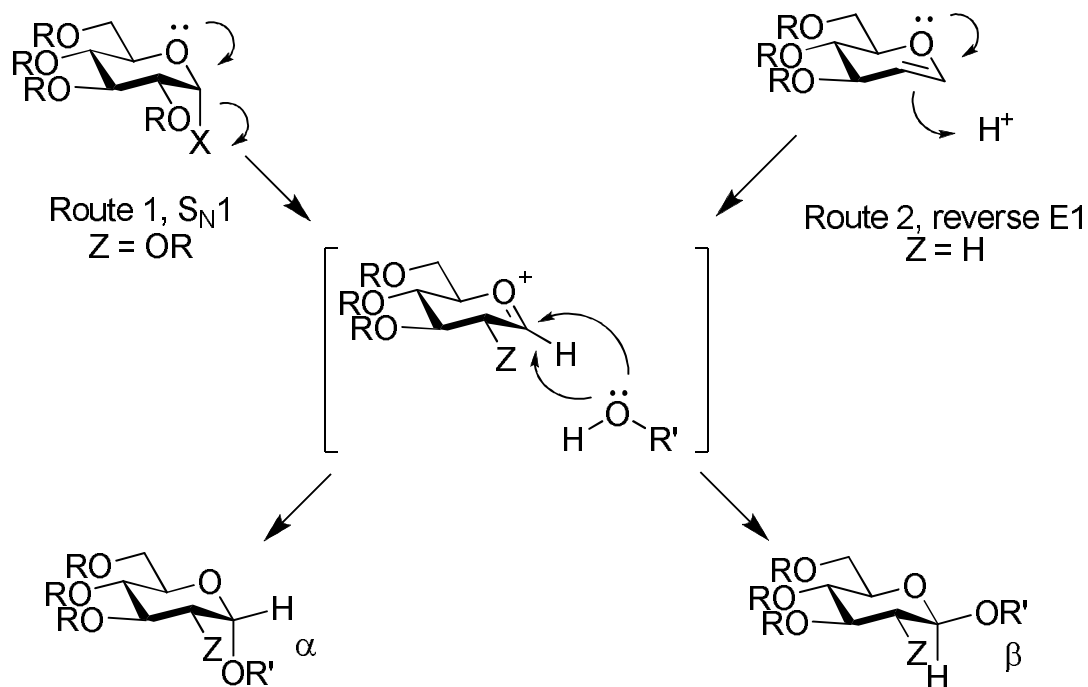


Figure 4 : Glycosidic bond formation

The cationic intermediate on either face is susceptible to nucleophilic attack by a glycosyl acceptor forming either an α or β -glycosidic bond. The proportion of each anomer formed is influenced by four major factors, the anomeric effect, neighbouring group participation, steric effects and solvent effects.

1.4 The Anomeric Effect

The anomeric effect is a stereoelectronic effect at the anomeric centre of the glycosyl donor favouring an axial α -configuration (Figure 5). In a comparative cyclohexane system the most favoured position for a substituent attached to the ring is an equatorial position as this would be expected under normal thermodynamic considerations. However, a number of

theories explaining these differences have been developed. The most popular explanation is the hyperconjugation between one of the lone pairs of electrons belonging to the rings oxygen orbital (n) with the anti-bonding orbital (σ^*) of the anomeric C-O bond.¹¹

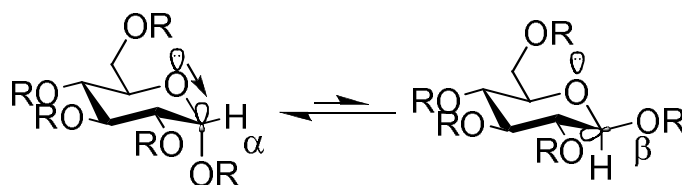


Figure 5: Anomeric effect - Hyperconjugation

A second complementary theory proposes that orbital repulsion as a result of dipole alignment disfavours the equatorial β -conformation (Figure 6).¹² In contrast, the axial α -configuration is more favoured as the dipoles are roughly opposed.

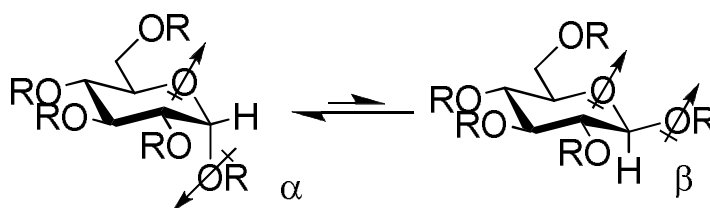


Figure 6 : Anomeric effect – Dipole alignment

1.5 Neighbouring Group Participation

Several strategies can be employed to control the diastereoselectivity of glycosylation. One of the most common and effective is neighbouring group participation.¹³ Diastereoselective control gained is strongly dependent on protecting groups, more specifically the protecting group of the C2 hydroxyl. If the C2 hydroxyl is protected as an ester (e.g. acetyl or benzoyl) it may cyclise during the formation of the cationic intermediate acting as an internal Lewis base. In this specific example the formation of this 5-membered ring then blocks nucleophilic attack from the α -position only allowing a S_N2 type reaction to proceed affording a β -glycosidic bond (Figure 7).

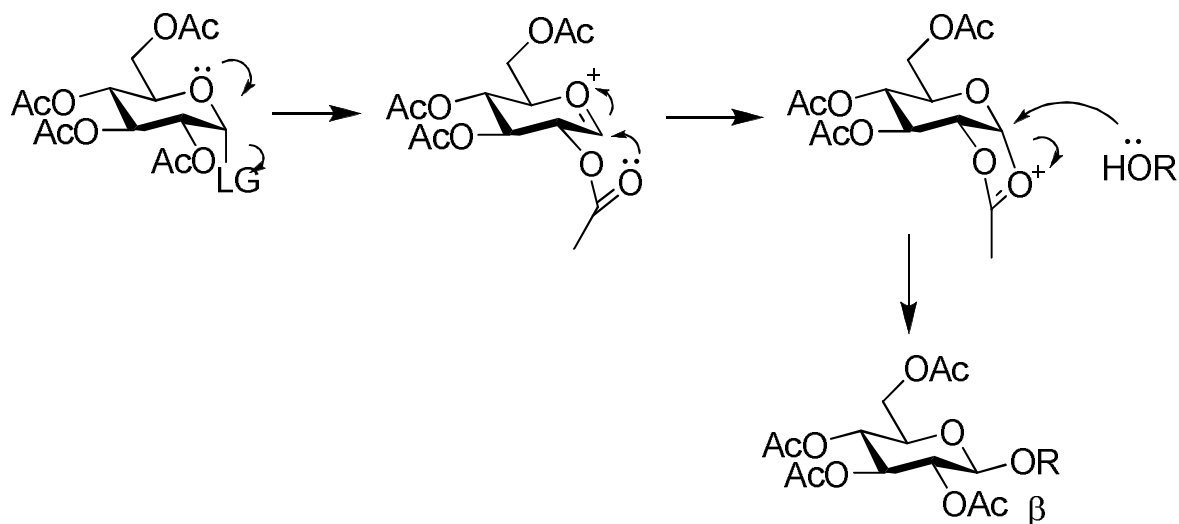


Figure 7 : Neighbouring Group Participation

Neighbouring group participation only allows the formation of 1,2 trans linkages. This is a limitation and new methodology needs to be adapted to control the diastereoselectivity regardless of the configuration at the C2 hydroxyl.

1.6 Solvent Effects

Another factor affecting the diastereoselectivity of glycosylation is the nature of the solvent used.⁹ Some solvents participate in glycosylation by interacting with the cationic intermediate. The most well known two are diethyl ether (Et₂O) and acetonitrile (MeCN). Diethyl ether interacts through the lone pair of electrons on the oxygen pairing through a β -configuration with the cationic intermediate, possibly due to its large steric size.¹⁴ In comparison acetonitrile is sterically smaller and therefore, pairs through the lone pair of electrons on its nitrogen forming an α -nitrilium ion.¹⁴ Subsequent substitution of the cationic intermediates then proceeds by a S_N2 mechanism to afford the respective α or β -glycosidic bond selectively (Figure 8).

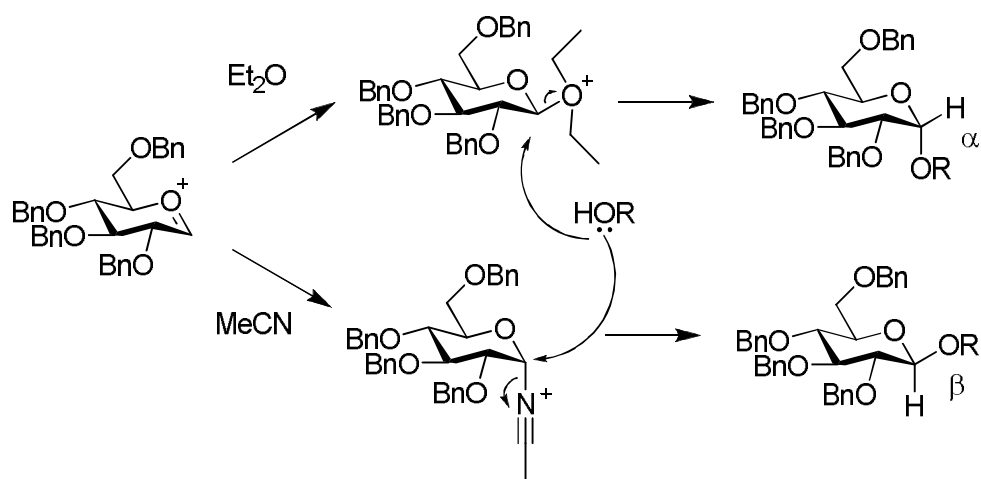


Figure 8: Solvent control of diastereoselectivity of glycosylation

1.7 Asymmetric Catalysis

Asymmetric catalysis is a long standing technique employed by synthetic chemists to produce enantio-enriched products. The enrichment comes from the introduction of chiral catalysts to increase the enantioselectivity of the reaction. Recent developments using chiral acid base catalysis rely upon tight ion pairing *in situ*. This may be accomplished by the use of lower temperatures and non polar solvents to decrease the distance at which the cation and anion can be stabilised. However, one of the oldest examples comes from 1904, when Mackwald used a chiral alkaloid brucine to enantioselectively decarboxylate a malonic acid derivative (Figure 9).¹⁵

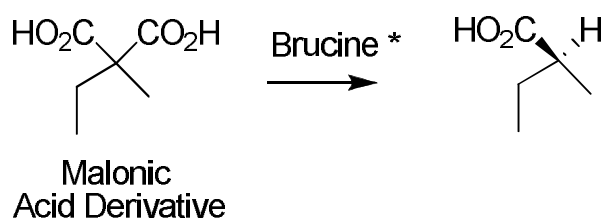


Figure 9 : Marckwalds decarboxylation

Since then interest in asymmetric catalysis has led to the development of new organic and inorganic chiral catalysts. A more modern example comes from Noyori, who with Knowles and Sharpless won the Nobel Prize in 2001 for their work on asymmetric catalysis.^{16,17} Noyori used a C_2 symmetric ruthenium catalyst to stereoselectively reduce a ketone to an alcohol with high selectivity (82% ee) and high yields (100%, Figure 10).¹⁸

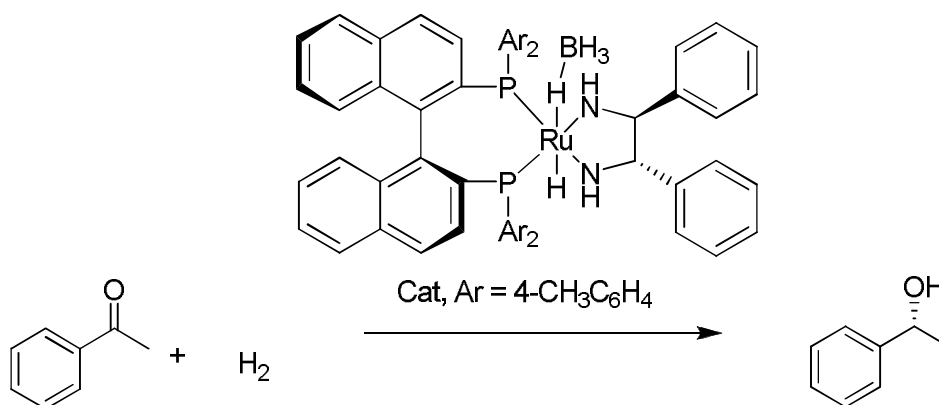


Figure 10 : Noyori's stereoselective reduction

1.8 Previous BINOL based phosphoric catalysts

Another C_2 symmetrical molecule of interest for asymmetric catalysis is 1,1'-bi-2-naphthol (BINOL).¹⁹ This molecule has been exploited due to its ability to coordinate with metal complexes and the ability to attach various functional groups onto the central hydroxyls.²⁰ One of the most successful organic catalysts made from BINOL is (R/S)-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (R/S-TRIP, Figure 11). This catalyst incorporates a phosphoric acid and sterically large side groups attached to the BINOL backbone. The sterically large side groups are usually thought to have a great influence over the stereoselectivity of a reaction.²¹

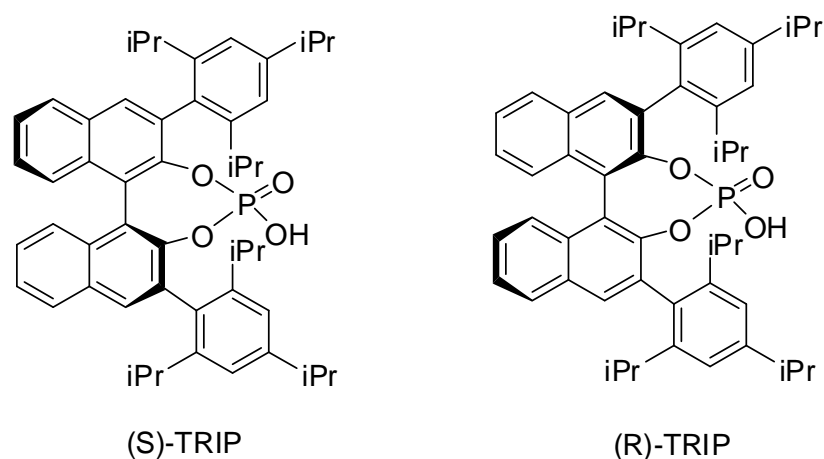


Figure 11: (S/R)-3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (S/R-TRIP)

A recent example of this catalyst's use was by Hamilton *et al.*² who used catalytic amounts of (S)-TRIP to stereoselectivity control the substitution of a racemic chloroamine by an alcohol (Figure 12). The reaction was successful in giving high yields (84%) and high selectivity (94% ee). It was therefore thought, that a similar catalytic system using glycosyl halides would be of interest.

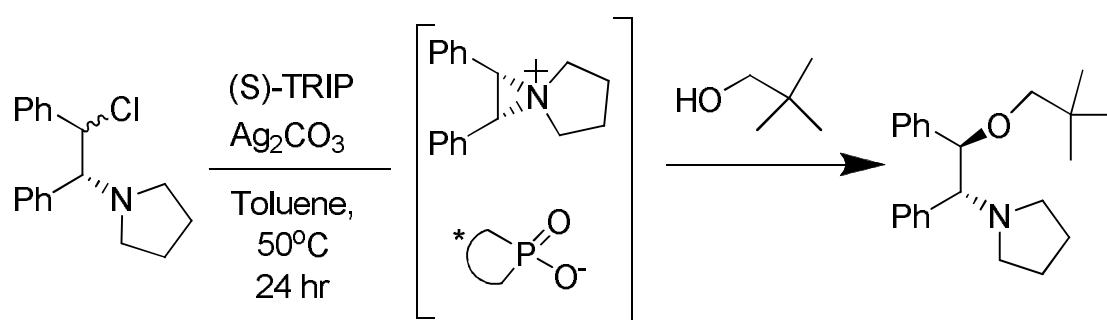


Figure 12: Hamilton's stereoselective nucleophilic substitution of alcohol to a racemic chloroamine²

1.9 Asymmetric Catalysis of Glycosylation

Asymmetric catalysis of glycosylation is a relatively new area of research.²² The most relevant research in this area was completed by D. J Cox, a previous member of the Fairbanks research group.¹ The system included a catalyst structurally similar to TRIP with a trichloroacetimidate glycosyl donor (Figure 13). The system was found to be high yielding (80%+) and β -selective though more so for the (S) enantiomer than (R) enantiomer.¹ This research promoted further support for the planned use of TRIP as an asymmetric catalyst in a similar glycosyl halide system. However, the ultimate objective for the diastereoselective

control of glycosylation would be when one enantiomer gives high α -selectivity and the other enantiomer gives high β -selectivity.

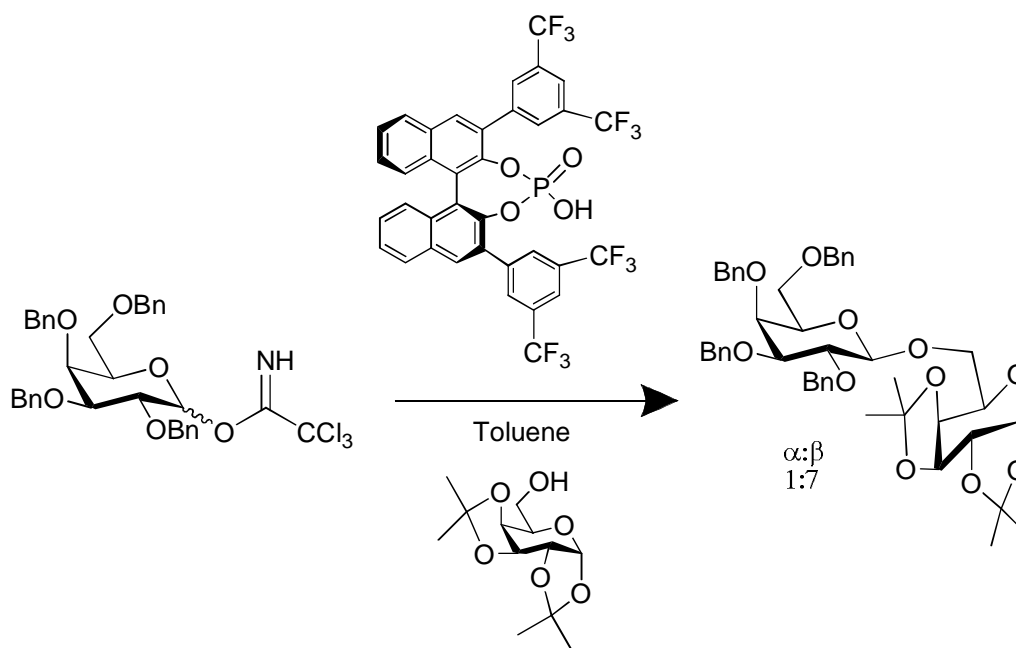


Figure 13: Asymmetric catalysis of glycosylation¹

1.10 Proposed development of Catalytic Systems

The first phase of development involved the synthesis of numerous glycosyl acceptors and donors. The next phase focused on the development of two separate catalytic systems targeted at the asymmetric control of glycosylation. The first catalytic system mimicked Hamilton's reaction conditions that were used to asymmetrically control the substitution of a racemic chloroamine by an alcohol (Figure 12).² The major change made to this system was the replacement of the chloroamine with a glycosyl halide (Figure 14). The second

catalytic system involved the use of TRIP to asymmetrically control the glycosylation of glycols (Figure 15). TRIP would be used as a chiral Brønsted acid to protonate the double bond allowing subsequent glycosylation. The primary objectives of these systems were to optimise the reaction conditions, to improve stereoselectivity and to suppress the formation of possible side-products. The final stage of development focused on the synthesis of new chiral catalysts that may in future allow asymmetric control of either catalytic system.

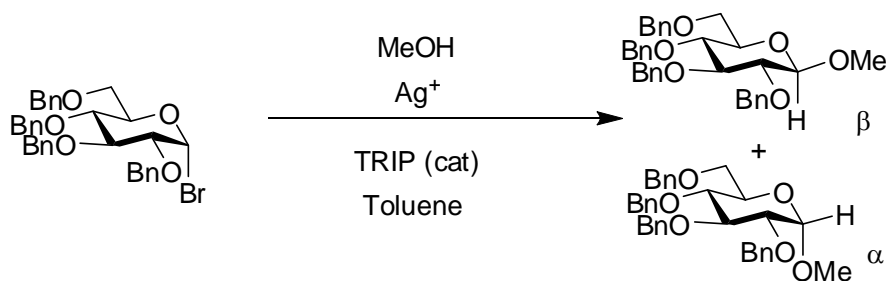


Figure 14 : General glycosyl halide glycosylation

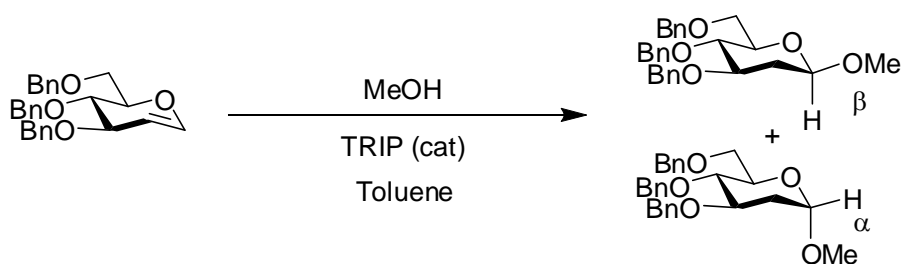


Figure 15 : General glycol glycosylation

Chapter 2: Results and Discussion

2.1 Synthesis of Glycosyl Acceptors & Donors

2.1.1 Synthesis of Glycosyl Acceptors

Three different glycosyl acceptors (**4**, **5**, **8**) were synthesised from methyl α -D-glucopyranoside **1** using different protecting group manipulations (Figure 16). Each of these glycosyl acceptors differed by the regiochemistry of the free hydroxyl (**4** and **5**) and also the protecting groups on the other hydroxyls (**4** and **8**). This was in order to investigate if the formation of the glycosidic bond could be influenced.

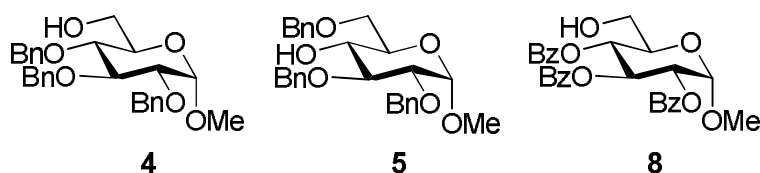


Figure 16 : Glycosyl acceptors

Retrosynthetic analysis revealed a common intermediate for the synthesis of glycosyl acceptors **4** and **5**. The first step was a benzylidene protection of the C4 and C6 hydroxyls, followed by a benzyl protection of the C2 and C3 hydroxyls. The last step differed as different hydroxyl groups needed to be revealed. Therefore, two different regioselective reduction reactions were employed to afford glycosyl acceptors **4** and **5** (Figure 17).

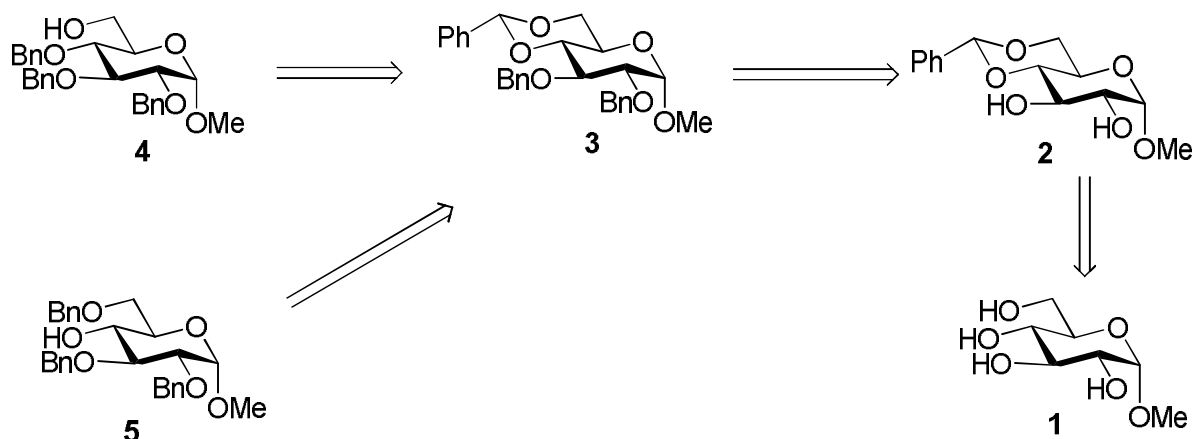


Figure 17: Retrosynthetic analysis for glycosyl acceptors **4** and **5**

The first manipulation involved the regioselective protection of the C4 and C6 hydroxyls *via* a benzylidene protecting group (Figure 18).²³ This regioselectivity is observed as the thermodynamically favourable double chair conformation is adopted upon protection. As a result of this protection methanol is displaced as a side product and is removed *in situ* to drive the reaction towards the benzylidene glucopyranoside **2**.

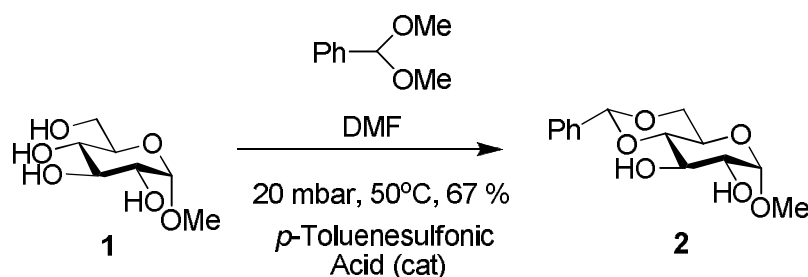


Figure 18 : Benzylidene protection of methyl α-D-glucopyranoside **1**

The remaining two free hydroxyls of the benzylidene protected glucopyranoside **2** were protected using benzyl bromide in a Williamson ether synthesis to afford a fully protected glucopyranoside **3** (Figure 19).²⁴ The moderate yield obtained may have been a result of the low reactivity of the C3 hydroxyl due to the steric hindrance of the benzylidene protecting group.

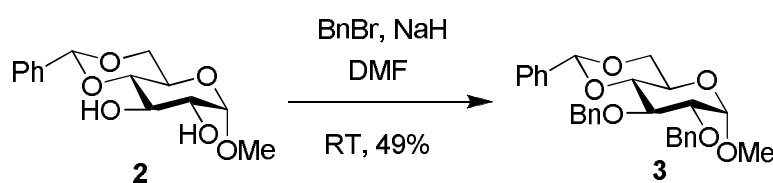


Figure 19 : Benzyl protection of the benzylidene glucopyranoside **2**

Regioselective reductive cleavage of the benzylidene allowed selective formation of either glycosyl acceptors **4** or **5** as desired (Figure 20).^{25,26} Both deprotections used a Lewis acid (AlCl_3 or $\text{BF}_3 \cdot \text{OEt}_2$) and a hydride source (LiAlH_4 or Et_3SiH). The Lewis acid is thought to be the main aspect controlling the regioselectivity. It has been proposed that it coordinates to OH-4 or OH-6 directing the regioselective reduction reaction to afford the respective glycosyl acceptors (**4**, **5**).²⁷

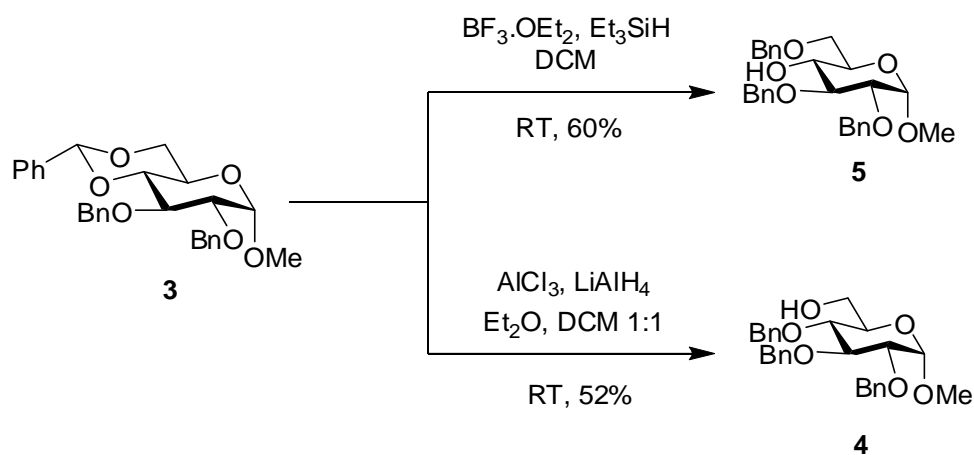


Figure 20: Regioselective reduction to afford glycosyl acceptors **4** and **5**

It was proposed that glycosyl acceptor **8** could initially be synthesised using a regioselective trityl protection of methyl α -D-glucopyranoside **1**. Then benzoyl protection of all the remaining free hydroxyl groups and a mild acid treatment to remove the trityl protecting group (Figure 21).

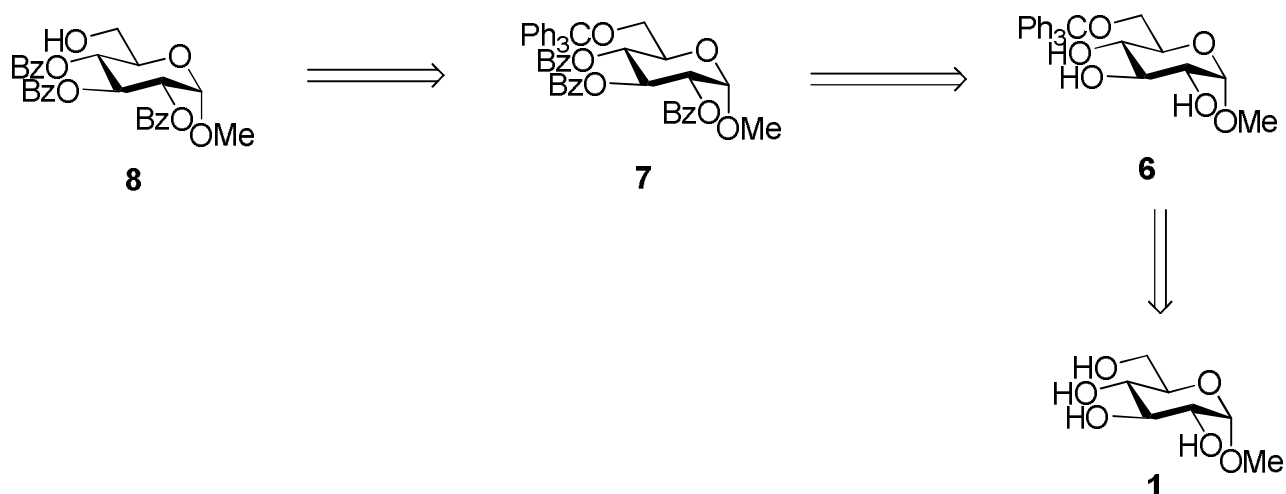


Figure 21: Retrosynthetic analysis for glycosyl acceptor **8**

The first manipulation used the large steric bulk of the trityl protecting group to regioselectively protect the 1° hydroxyl at C6 affording the tritylated glucopyranoside **6** in a good yield (Figure 22).²⁸

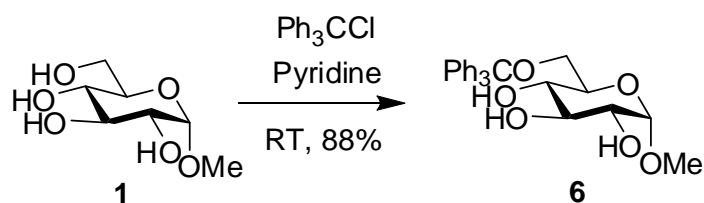


Figure 22 : Trityl protection of methyl α -D-glucopyranoside **1**

The remaining hydroxyls of the tritylated glucopyranoside **6** were protected as benzoyl esters. This reaction used the solvent pyridine as a nucleophilic catalyst along with benzoyl chloride to afford the fully protected glucopyranoside **7** in a moderate yield (Figure 23).

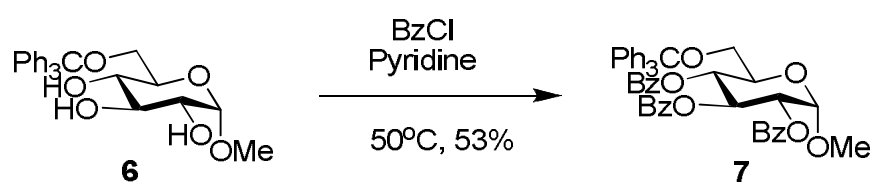


Figure 23 : Benzoyl protection of the tritylated glucopyranoside **6**

The trityl group was then removed by the use of an aqueous acid. However, the benzoyl protecting groups are also acid sensitive and can hydrolyse under similar conditions. The traditional method of trityl deprotection uses 80% aqueous acetic acid at 50°C.²⁹ However,

these conditions proved ineffective as the starting material was recovered and a new method was required (Figure 24).

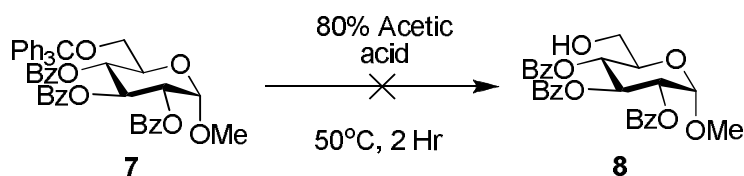


Figure 24 : Attempted trityl deprotection

Ding *et al.*³⁰ have reported an alternative deprotecting method using FeCl₃·6H₂O as a moderate acid to selectively deprotect the trityl protecting group affording glycosyl acceptor **8** (Figure 25). However, only a moderate yield was obtained, possibly due to the deprotection of the benzoyl protecting groups as indicated by t.l.c.

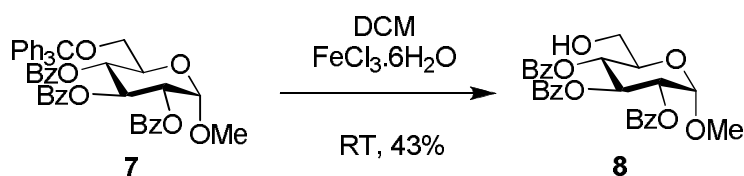


Figure 25 : Trityl deprotection affording glycosyl acceptor **8**

2.1.2 Synthesis of Glycosyl Donors - Glycosyl Halides

Glycosyl halides are amongst the most useful glycosyl donors.³¹ As a result of their utility, three glycosyl halides were synthesised from methyl α -D-glucopyranoside **1** to investigate their differences in reactivity (Figure 26).

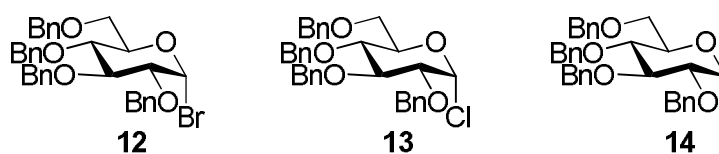


Figure 26 : Glycosyl Donors

Retrosynthetic analysis revealed a generic pathway in which the halogenated glycosyl donors (**12**, **13**, **14**) may be synthesised. Initially methyl α -D-glucopyranoside **1** could be benzyl protected followed by an acid catalysed hydrolysis of the anomeric centre. Finally treatment with oxalyl bromide or oxalyl chloride would then afford the respective glycosyl donors (**12** & **13**, Figure 27).³² An acetylation after the hydrolysis and then treatment with TMSI could then afford the glycosyl iodide **14** (Figure 27).

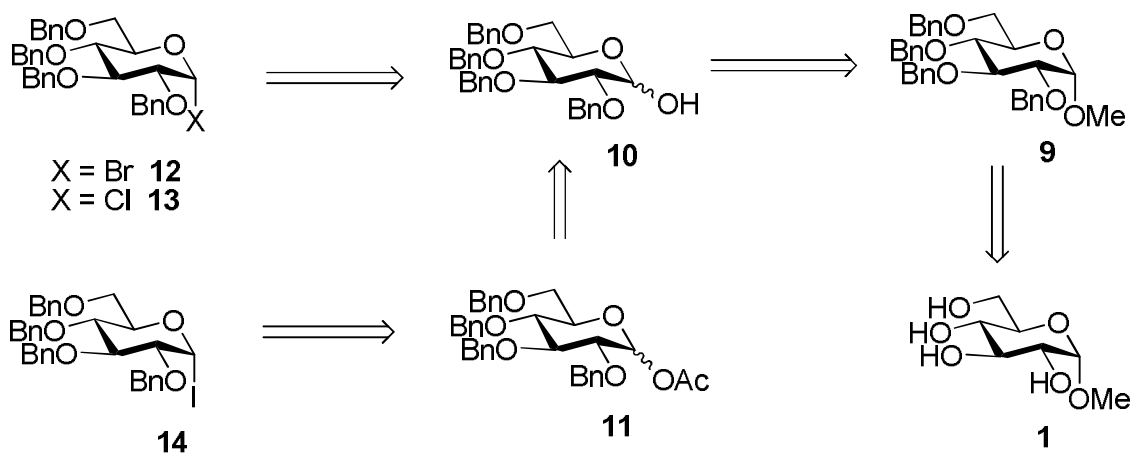


Figure 27 : Retrosynthetic analysis for Glycosyl Donors **12**, **13**, **14**

Benzyl protection of methyl α -D-glucopyranoside **1** used a Williamson ether synthesis with benzyl bromide to afford the fully protected glucopyranoside **9** in a good yield (Figure 28).³²

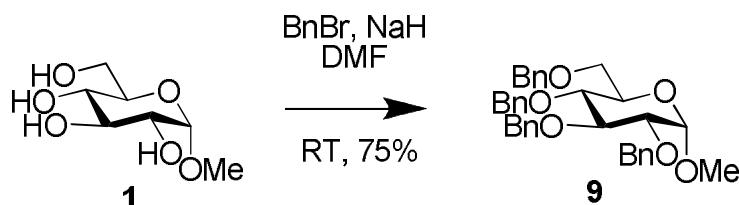


Figure 28 : Benzyl protection of methyl α -D-glucopyranoside **1**

Acid catalysed hydrolysis of the fully protected glucopyranoside **9** afforded the hydrolysed counterpart **10** in modest yield (Figure 29).³² A modest yield was always obtained as leaving the reaction on for a longer period of time would lead to decomposition of the target product, affording a black carbonised sludge.

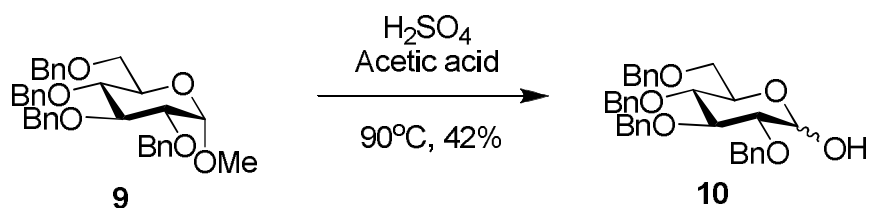


Figure 29 : Acid catalysed hydrolysis of the anomeric centre

Bromination of the hydrolysed glucopyranoside **10** was one of the most difficult steps in the synthesis (Figure 30). This was due to the brominated glucopyranosides **12** lability to undergo hydrolysis at room temperature and also during flash column chromatography. Therefore it could not be purified and had to be used in its crude state. Oxalyl bromide proved to be the most effective reagent although sometimes inconsistent in the bromination.³³ This resulted in large amounts of starting material at times being detected by ^1H NMR spectroscopy.

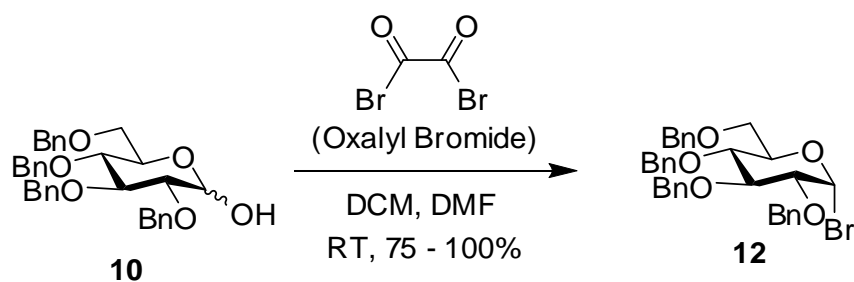


Figure 30 : Bromination of the anomeric centre

Other generic brominating methods using NBS were attempted. However, t.l.c indicated no consumption of the starting material **10**, therefore these methods were discarded (Figure 31).

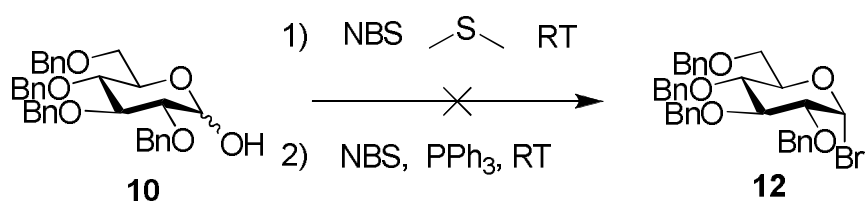


Figure 31 : Attempted Brominations using NBS

Chlorination of the anomeric centre was much simpler as the greater inherent stability of the glycosyl chloride **13** allowed purification of the product by flash column chromatography. This reaction was completed in similar fashion as the bromination with oxalyl chloride replacing oxalyl bromide as the halogenating reagent (Figure 32).³⁴

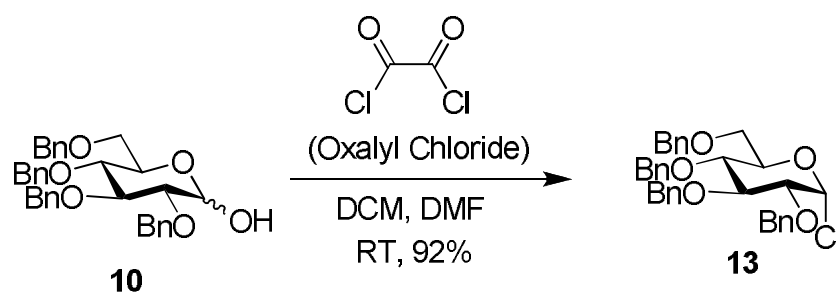


Figure 32 : Chlorination of the anomeric centre

Acetylation of the anomeric centre was a straightforward reaction using acetyl chloride with pyridine as the nucleophilic catalyst in DCM to afford the acetylated glucopyranoside **11** in good yield (Figure 33).³⁵

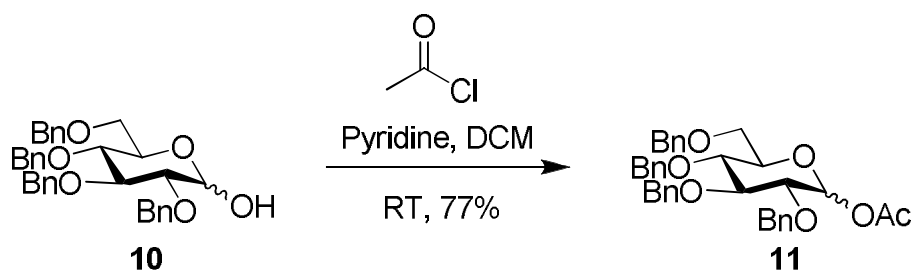


Figure 33 : Acetylation of the anomeric centre

Treatment of the acetylated glucopyranoside **11** with iodine to form the glycosyl iodide **14** proved difficult as **14** rapidly reacted with atmospheric water to form the hydrolysed counterpart **10**. For this reason, the glycosyl iodide **14** was concentrated *in vacuo* after treatment with TMSI and was used immediately for the catalytic trials (Figure 34).³⁵

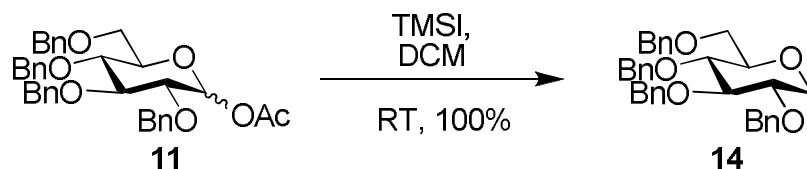


Figure 34 : Synthesis of the glycosyl iodide **14**

2.1.3 Synthesis of Glycosyl Donors - Glycals

The second type of glycosyl donors, glycals, contain a double bond between C1 and C2 (Figure 35). This important feature allows glycals to undergo Brønsted acid catalysed glycosylation to afford the desired 2-deoxy glycosides.

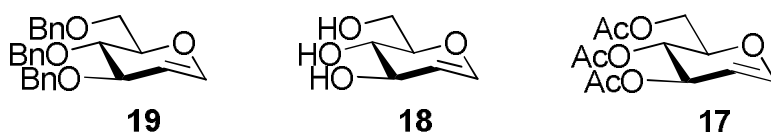


Figure 35 : Glycals

Retrosynthetic analysis revealed a straightforward scheme involving protection, deprotection, bromination and a reductive elimination to synthesise the benzyl protected glucal **19** (Figure 36).

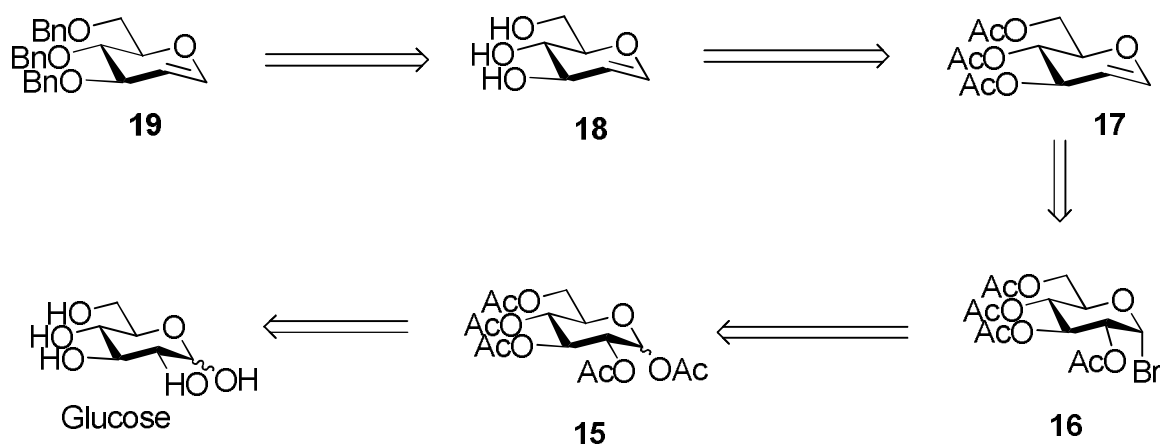


Figure 36 : Retrosynthetic analysis for glycals

Acetylation of glucose using acetic anhydride (Ac_2O) and an electrophilic iodine catalyst then afforded the acetylated glucopyranoside **15** in a good yield as predominantly the α -anomer (Figure 37).

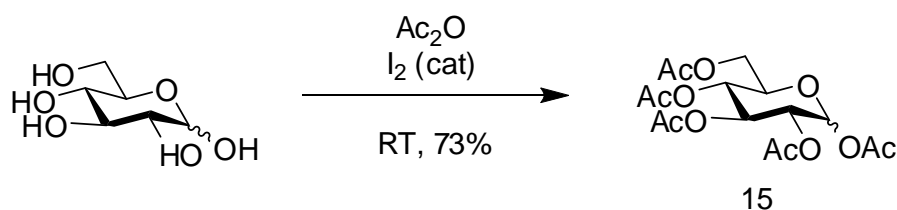


Figure 37 : Acetylation of glucose

Bromination of the acetylated glucopyranoside **15** using hydrogen bromide (HBr) in acetic acid afforded the brominated glucopyranoside **16** in a good yield (Figure 38).³⁶ Lower levels of hydrolysis were observed for this brominated glucopyranoside **16** when compared to the benzyl protected equivalent **12**. This decrease in hydrolysis was a direct result of disarming the protecting groups used. Benzyl protecting groups are electron donating allowing them to stabilise the cationic intermediate giving increased reactivity. In comparison, acetyl protecting groups are electron withdrawing and cause destabilisation of the cationic intermediate resulting in decreased reactivity.³⁷

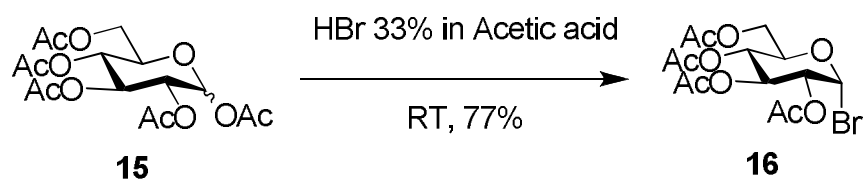


Figure 38 : Bromination of the acetylated glucopyranoside **15**

Reductive elimination of the glycosyl bromide **16** used activated zinc as a Lewis base to form the acetylated glycal **17** in a good yield (Figure 39).³⁸

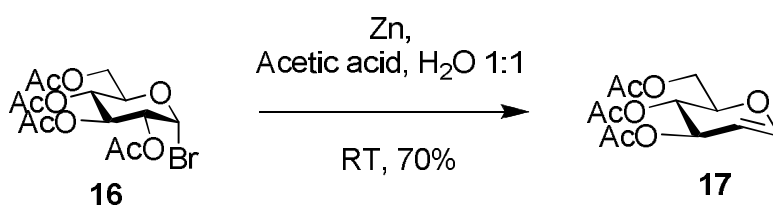


Figure 39 : Reductive elimination of the glycosyl bromide **16**

A Zemplén deacetylation of the acetylated glycal **16**, involved the formation of sodium methoxide *in situ* to rapidly afford D-glucal **17** (20 min, Figure 40).³⁹

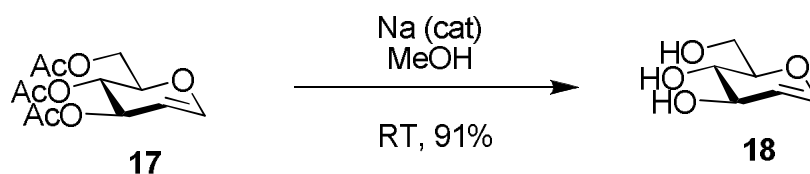


Figure 40 : Deacetylation of the acetylated glycal **17**

Benzylation of D-glucal **18** proved a difficult reaction as consistently poor yields were obtained (Figure 41). This was possibly due to the use of crude rather than purified starting material. However, the benzyl protecting groups were the most desired as they were the most likely protecting group to suppress possible side products.

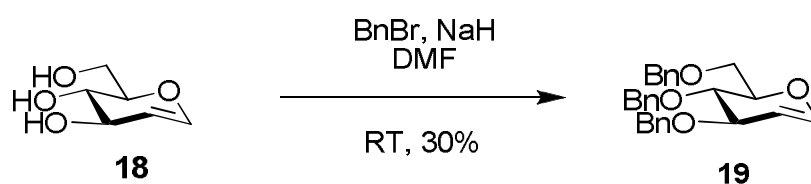


Figure 41 : Benzylation of D-Glucal **18**

2.2 Glycosyl Halide Trials

2.2.1 Synthetic strategy

Recently Hamilton *et al.*² reported a catalytic system, in which an insoluble achiral silver activator was used in combination with a chiral Brønsted acid to enantioselectively control the substitution of a racemic chloroamine by an alcohol (Figure 12). The ability to use the cheaper achiral silver activator in conjunction with an expensive chiral Brønsted acid meant that stoichiometric amounts of the expensive Brønsted acid were not required making the process cheaper. The proposed mechanism '*chiral anion phase transfer catalysis*' was thought to progress through three key phases, phase transfer, halide extraction and nucleophilic addition (Figure 42). This was an attractive prospect to apply to a glycosylation

reaction and therefore formed the basis of the catalytic trials. The anomer ratio of the glycosides produced were measured by ^1H NMR integration using previously characterised compounds.⁴⁰

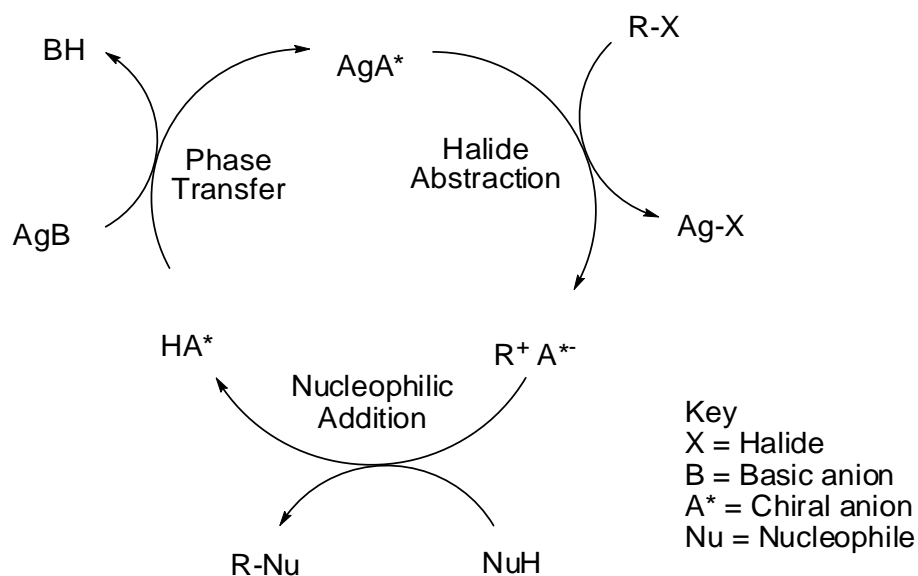


Figure 42 : Hamilton's 'chiral anion phase transfer catalysis'²

2.2.2 Initial Trials

Reaction conditions similar to Hamilton's were tested first to determine if the diastereoselectivity could be controlled in a carbohydrate system.² High temperatures and toluene were used along with the glycosyl chloride **13**, diacetone galactose and (R)-TRIP (Figure 43).

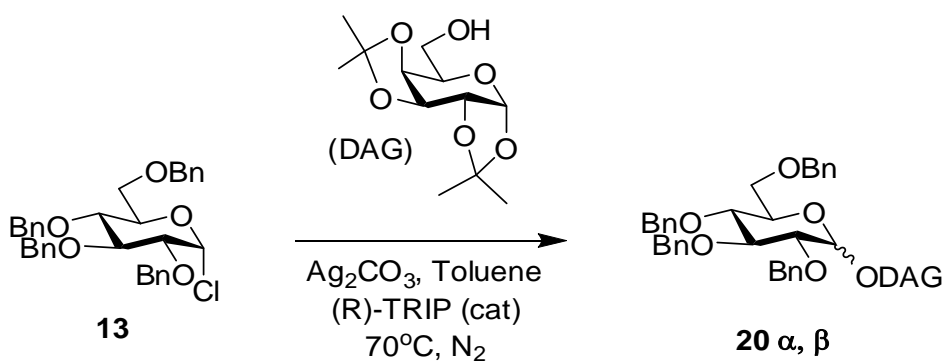


Figure 43 : Catalyst Trials – Hamilton’s conditions

Hamilton’s general conditions gave a low yield with a long reaction time. Also, no difference in diastereoselectivity was observed between the trial and the control. Therefore, further development of the system was required (Table 1). As a precaution all reactions were UV protected by aluminium foil as decomposition of the silver salt occurs readily in light.

Table 1 : Catalyst Trials – Hamilton’s conditions

Trial	Glycosyl Donor	Glycosyl Acceptor	Silver Activator	Solvent	Catalyst	Time (Days)	Yield (%)	α	β
1	R-Cl (13)	DAG	Ag ₂ CO ₃	Toluene	-	3	28	0.46	1
2	R-Cl (13)	DAG	Ag ₂ CO ₃	Toluene	5% R TRIP	3	18	0.47	1

2.2.3 Optimisation Phase

The optimisation phase was designed with stepwise manipulations to determine the optimal reaction conditions (Figure 44). These conditions involved systematic variation of the glycosyl donors and acceptors, the silver activators, and the reaction solvents.

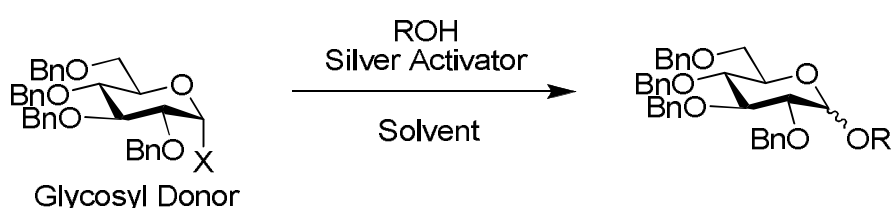


Figure 44 : Catalyst Trials – General conditions

Variation of the glycosyl halides was the first aspect of the reaction conditions to be investigated (Table 2). Three glycosyl halides (**12**, **13**, **14**) were investigated with silver triflate in DCM. However, only the glycosyl bromide **12** and glycosyl chloride **13** afforded the target products (**20 α** , **20 β**). The glycosyl iodide **14** afforded multiple unidentifiable products and therefore was no longer used. The glycosyl bromide **12** was preferred over the glycosyl chloride **13** as it reacted more rapidly and gave a higher yield.

Table 2 : Optimisation Phase - Glycosyl Donor

Trial	Glycosyl Donor	Glycosyl Acceptor	Silver Activator	Solvent	Time (Min)	Yield (%)	α	β
3	R-Br (12)	DAG	AgOTf	DCM	30	61	1.08	1
4	R-Cl (13)	DAG	AgOTf	DCM	45	39	0.85	1
5	R-I (14)	DAG	AgOTf	DCM	90	Failed	-	-

The second variable to be investigated was the glycosyl acceptor (Table 3). It was planned that the precious glycosyl acceptors (**4**, **5**, **8**) synthesised earlier would be used once the catalytic system had been optimised. Therefore, methanol and diacetone galactose were selected in their place to optimise the system as they were readily available. Diacetone galactose was preferred over methanol as it generally gave a higher yield.

Table 3 : Optimisation Phase - Glycosyl Acceptor

Trial	Glycosyl Donor	Glycosyl Acceptor	Silver Activator	Solvent	Time (Min)	Yield (%)	α	β
3	R-Br (12)	DAG	AgOTf	DCM	30	61	1.08	1
6	R-Br (12)	MeOH	AgOTf	DCM	30	46	0.9	1

Silver salts are important to the reaction conditions as they act as stoichiometric activators. The insolubility of the silver salt is important as an achiral counter anion would compete with the chiral counter anion for ion pairing with the cationic intermediate. As a result, this would affect any possible diastereoselectivity of glycosylation. Silver triflate is a highly soluble silver salt therefore its use led to a rapid and non-diastereoselective (**21** α :**21** β , 0.9:1, Table 4, Trial 6) reaction due to the large amounts of achiral counter anion. The less soluble silver carbonate was also trialled and led to a slower reaction in which some diastereoselectivity was observed (**21** α :**21** β 0.55:1, Table 4, Trial 7). As a result of the low solubility, silver carbonate was selected for the catalytic trials.

Table 4 : Optimisation Phase - Silver Activator

Trial	Glycosyl Donor	Glycosyl Acceptor	Silver Activator	Solvent	Time (Hrs)	Yield (%)	α	β
6	R-Br (12)	MeOH	AgOTf	DCM	0.5	46	0.9	1
7	R-Br (12)	MeOH	Ag₂CO₃	DCM	17	40	0.55	1

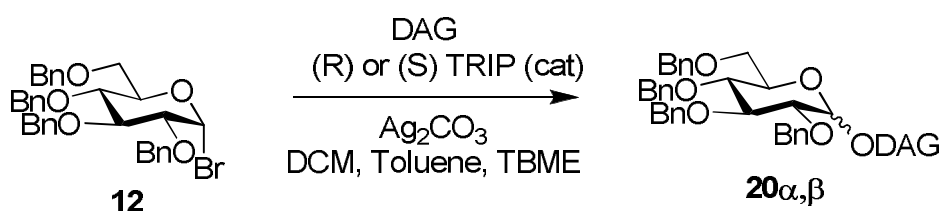
Solvents are a highly critical component of the reaction conditions as they can play a major role in the control of diastereoselectivity. Two factors influencing the diastereoselectivity were addressed when selecting the solvents. The first factor was the requirement that the solvent was not able to interact with the cationic intermediate. The reason being, if the solvent did interact with the cationic intermediate it would skew any possible diastereoselectivity of glycosylation. The second factor was pre-emptive and addressed the polarity of the solvent as this would have a large influence on ion pairing *in situ*, and ultimately affect the ability of the catalyst to control the diastereoselectivity of the reaction. Toluene and DCM were the two solvents selected initially but TBME was also selected at a later point in time when Reisman *et al.*²² reported promising results with a similar catalytic system. It was observed that in DCM a β -anomer was favoured (**20 α :20 β** 0.36:1, Table 5, Trial 8). Whereas, the use of either toluene or TBME both gave non selective reactions (**20 α :20 β** ~1:1, Table 5, Trials 9, 10). The polarity of the solvents had a major effect on the rate of the reaction. DCM, a non polar solvent, displayed a quicker reaction time of 3 days, whereas the two non polar solvents, toluene and TBME, took longer at 4 and 7 days respectively (Table 5). This observation may be due to the more polar solvent, DCM, facilitating easier formation of ions *in situ* thus resulting in lower activation energy and a faster reaction. Different yields were also observed as DCM gained a moderate yield (56%) with toluene and TBME both gaining low yields (28 & 36 %). However, the lower yields cannot be explained by the differences in polarity.

Table 5 : Optimisation Phase - Solvent

Trial	Glycosyl Donor	Glycosyl Acceptor	Silver Activator	Solvent	Time (Days)	Yield (%)	α	β
8	R-Br (12)	DAG	Ag ₂ CO ₃	DCM	3	56	0.36	1
9	R-Br (12)	DAG	Ag ₂ CO ₃	Toluene	4	28	0.94	1
10	R-Br (12)	DAG	Ag ₂ CO ₃	TBME	7	36	1.09	1

2.2.4 Catalytic Trials

Studies conducted during the optimisation phase suggested that the best conditions for the catalytic trials would be the use of the glycosyl bromide **12** with diacetone galactose and silver carbonate (Figure 45). The solvents were changed with the catalytic trials because of their large influence over the diastereoselectivity of glycosylation.

**Figure 45** : Optimal conditions for the glycosyl halide catalytic trials

The first system investigated the use of TRIP in DCM. A reaction using (R)-TRIP in DCM proved to be unique, as an increase in α -selectivity was observed (**20 α :20 β** , 0.92:1, Table 6, Trial 11). Its counterpart (S)-TRIP in DCM unfortunately, displayed no effective selectivity (**20 α :20 β** 0.33:1, Table 6, Trial 12) as compared to the control reaction (**20 α :20 β** 0.36:1,

Table 6, Trial 8). Therefore, the DCM trials did not prove conclusively that the diastereoselective outcome of glycosylation was dependent upon the catalyst.

The second system was to trial TRIP in the non-polar solvent, toluene. (R)-TRIP and (S)-TRIP in toluene both displayed β -selectivity (R - **20 α :20 β** , 0.46:1; S - **20 α :20 β** , 0.28:1, Table 6, Trial 13, 14) with (S)-TRIP displaying a further preference of this selectivity.

The last system used TRIP in TBME as a result of Reisman's work with a similar system.²² (R)-TRIP and (S)-TRIP in TBME both displayed extensive β -selectivity (R - **20 α :20 β** , 0.06:1; S - **20 α :20 β** , 0.04:1, Table 6, Trial 15, 16). Therefore, the toluene and TBME catalytic trials did prove that the diastereoselective outcome of these glycosylation were dependent on the catalyst. However, low yields were obtained possibly due to the hydrolysis of the glycosyl bromide **12**. It was these inconsistent and low yields throughout the catalytic trials that helped to decide upon abandonment of the glycosyl halide system.

Table 6 : Glycosyl halide catalytic trials

Trial	Glycosyl Donor	Glycosyl Acceptor	Silver Activator	Solvent	Catalyst	Time (Days)	Yield (%)	α	β
8	R-Br (12)	DAG	Ag ₂ CO ₃	DCM	-	3	56	0.36	1
9	R-Br (12)	DAG	Ag ₂ CO ₃	Toluene	-	4	28	0.94	1
10	R-Br (12)	DAG	Ag ₂ CO ₃	TBME	-	7	36	1.09	1
11	R-Br (12)	DAG	Ag ₂ CO ₃	DCM	5% R TRIP	3	10	0.92	1
12	R-Br (12)	DAG	Ag ₂ CO ₃	DCM	5% S TRIP	3	16	0.33	1
13	R-Br (12)	DAG	Ag ₂ CO ₃	Toluene	5% R TRIP	4	45	0.46	1
14	R-Br (12)	DAG	Ag ₂ CO ₃	Toluene	5% S TRIP	4	23	0.28	1
15	R-Br (12)	DAG	Ag ₂ CO ₃	TBME	5% R TRIP	7	12	0.06	1
16	R-Br (12)	DAG	Ag ₂ CO ₃	TBME	5% S TRIP	7	6	0.04	1

2.3 Glycal Trials

2.3.1 Synthetic strategy

Glycals normally undergo achiral Brønsted acid catalysed glycosylation to afford 2-deoxy-glycosides.⁴³ However, our approach was to introduce chiral Brønsted acids to control the diastereoselectivity of glycosylation. The chiral Brønsted acid TRIP which was used in the previous trials was selected again as it displayed some diastereoselective control over glycosylation. Other reaction conditions were selected to optimise any possible diastereoselectivity. These included the use of a non polar solvent with low temperatures as it would encourage tight ion pairing. The benzylated glycal **19** was also selected as the protecting groups on the glycal were the most likely to suppress any side products. The

anomer ratio of the glycosides produced was measured by ^1H NMR integration using previously characterised compounds.^{41,42,43,44}

2.3.2 Initial Trials

TRIP was initially trialled to investigate its ability to act as a Brønsted acid catalyst and catalyse the glycosylation of glycols. The first reaction conditions trialled used a low temperature and a non polar solvent toluene. Unfortunately these conditions proved unsuccessful. Systematic modifications were made to the system in order to promote glycosylation. These modifications included raising the temperature, increasing the catalyst loading and the use of a more polar solvent. However, all the modifications proved ineffective in promoting any reaction and so TRIP was abandoned as a potential acid catalyst (Figure 46).

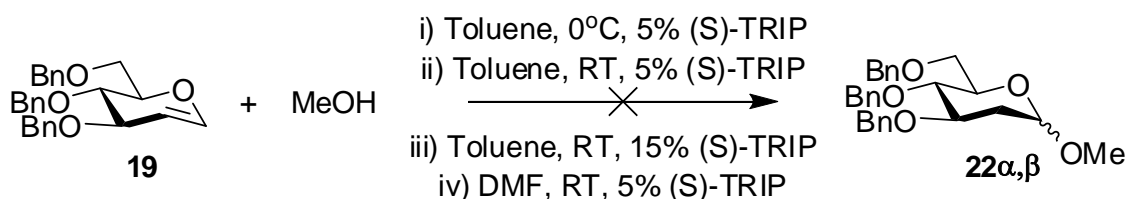


Figure 46 : Attempted TRIP catalysed glycosylation of glycols

The next phase was to trial the reaction with a more acidic catalyst. Camphorsulfonic acid (CSA, pK_a -2) was chosen as a replacement for TRIP (pK_a 2) and was found to catalyse the

reaction, indicating that the acidity of the catalyst was important (Figure 47). The disadvantage to using the stronger acid was the formation of the Ferrier side product **23f**.

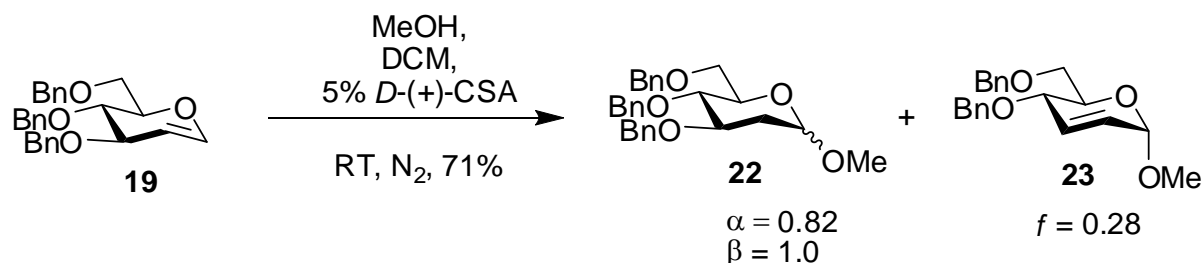


Figure 47 : CSA catalysed glycosylation of glycols

2.3.3 The Ferrier Reaction

A Ferrier product can be produced during a Brønsted or Lewis acid catalysed glycosylation of a glycol.¹⁰ This rearrangement involves a double bond migration and a simultaneous nucleophilic substitution. The rearrangement was first pioneered by Ferrier in the late 1960's when he used tri-*O*-acetyl-D-glucal with a Lewis acid (BF₃·OEt₂) to make a 2,3 unsaturated glycoside as an anomeric mixture (Figure 48).⁴⁵

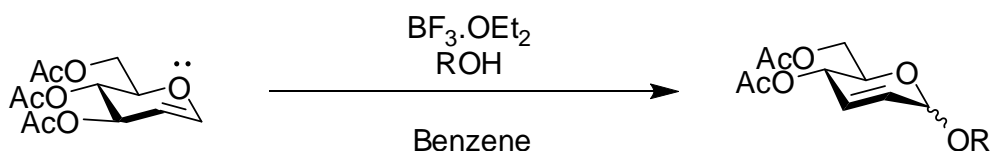


Figure 48 : Lewis acid-catalyzed Ferrier rearrangement of tri-*O*-acetyl-D-glucal

Several attempts to explain the competition between the Ferrier rearrangement and glycosylation have been made using HSAB theory.⁴⁶ These explanations suggest that a hard Brønsted acid coordinates to the oxygen at C3 enabling it to act as a leaving group and favouring the Ferrier rearrangement. However, a softer Brønsted acid (e.g. $\text{PPh}_3\cdot\text{HBr}$) coordinates to the softer anomeric center stabilising the cationic intermediate and favouring glycosylation (Figure 49).⁴⁶

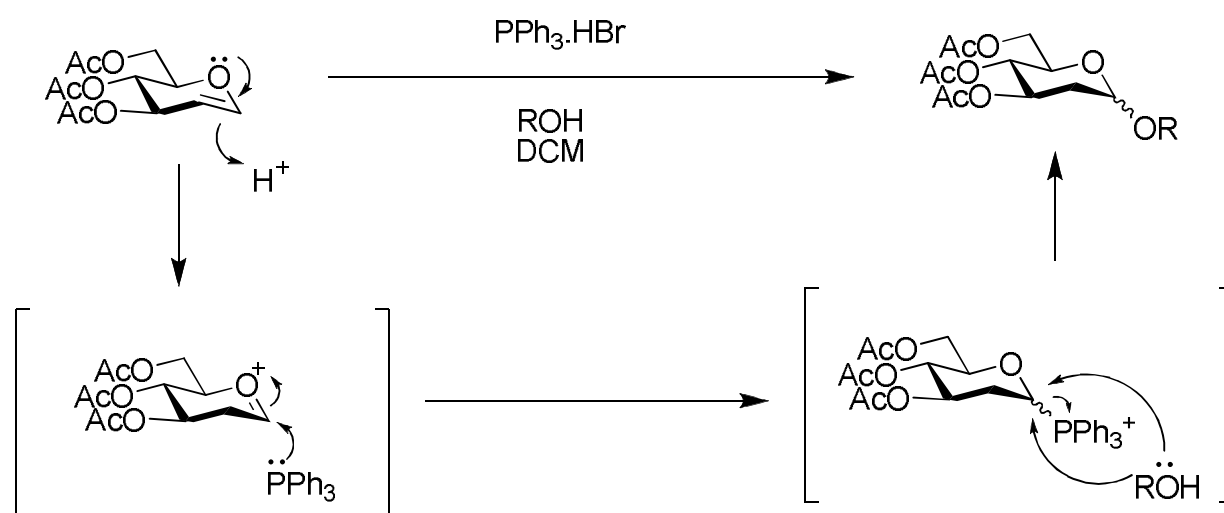


Figure 49 : Soft Brønsted acid catalysed glycosylation of a glycal

The Ferrier process observed in the CSA trial differed slightly to the traditional Ferrier rearrangement as it exclusively produced the α anomer. This $\text{S}_{\text{N}}2'$ reaction involves inversion and a double bond migration in a single step across two bonds (Figure 50).⁴⁷ The α -selective Ferrier rearrangement has also been observed in other situations.^{10,42,41}

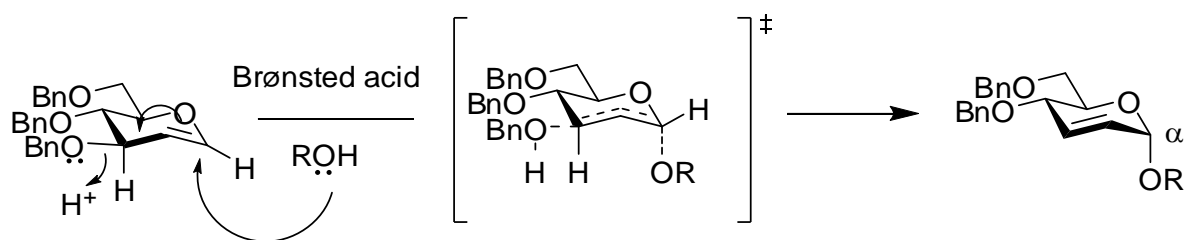


Figure 50 : S_N2' Ferrier rearrangement resulting in α -selectivity

2.3.4 Development of a new catalyst

Cheon *et al.*²¹ have recently reported the development of a new series of stronger Brønsted acid catalysts which contain a BINOL backbone with a strong triflamide acid attached to the central phosphorus. These catalysts would be ideal to apply to a glycal system as the use of CSA proved that a stronger Brønsted acid was required to promote glycosylation. A model system was proposed to test the ability of the triflamide acid to glycosylate. However, the model catalyst did not incorporate large hydrophobic side groups attached to the aromatic backbone. These large side groups are often thought to be important in controlling the stereoselectivity of reactions.²¹ Initially catechol replaced BINOL as the aromatic backbone because it was less expensive.

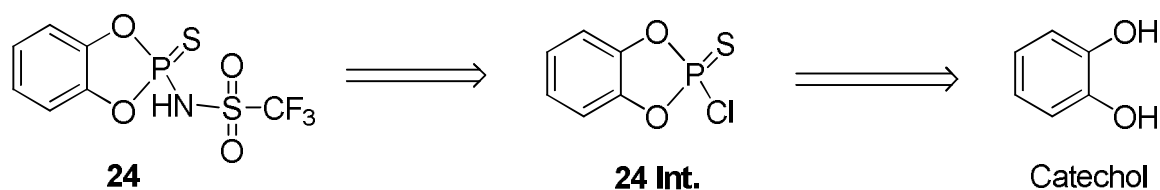


Figure 51 : Retrosynthetic analysis of the proposed catechol catalyst

Retrosynthetic analysis followed Cheon's general synthesis. Firstly, PSCl₃ was added to the aromatic backbone resulting in a phosphoric intermediate to which the triflamide was attached (Figure 51).

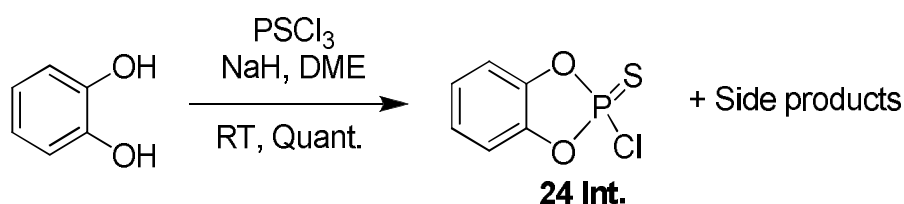


Figure 52 : Synthesis of Catechol catalyst

The first step followed Cheon's general method, and appeared straightforward as it used PSCl₃ with NaH in DME at RT. However the addition of PSCl₃ yielded the target product as well as a number of side products as demonstrated by ³¹P NMR (δ ppm 57, 38, 14) and mass spectrometry (m/z 226, 289, 340) (Figure 52).²¹ These side products could have been formed by dimerisation of the multiple catechol rings. Therefore, an alternative method was required.

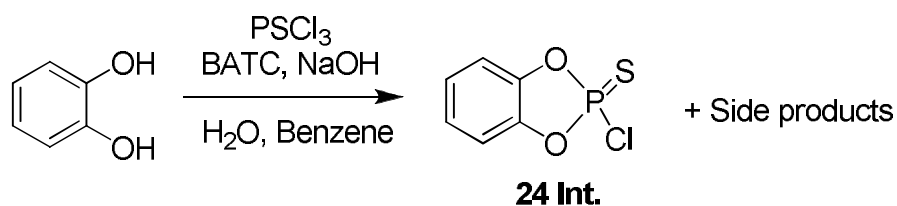


Figure 53 : Kumara's Phase transfer catalysis

Another method was investigated using Kumara *et al's* phase transfer catalysis (Figure 53).⁴⁸ The system had two phases between which benzyl ammonium triethyl chloride (BATC) would transfer, enabling deprotonation of the hydroxyls and therefore the attachment of PSCl_3 to catechol. This method produced the target product along with an impurity as determined by ^{31}P NMR (δ ppm 57, 37). Therefore, the catechol system was abandoned favouring direct use of racemic BINOL with the same retrosynthetic plan.

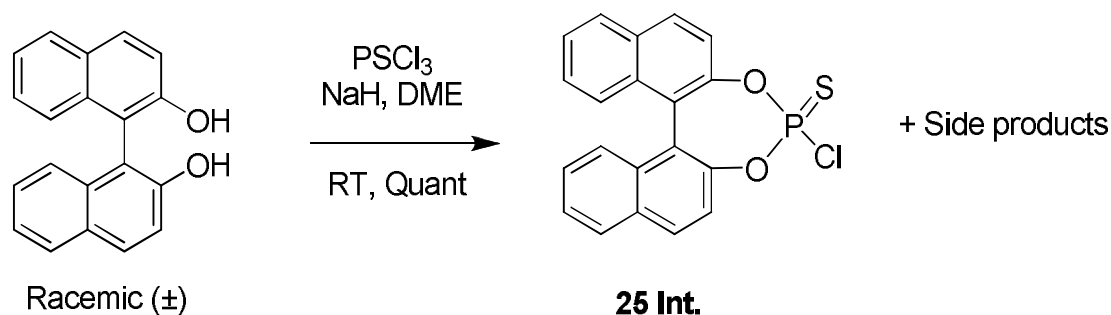


Figure 54 : Cheon's general synthesis first step

Cheon's general synthesis of the triflamide catalyst was followed.²¹ However, difficulty was encountered again with the first step forming the target intermediate and multiple

unidentifiable products as demonstrated by ^{31}P NMR (δ ppm 74, 67, 66, 53) (Figure 54).²¹

Therefore another method was sought.

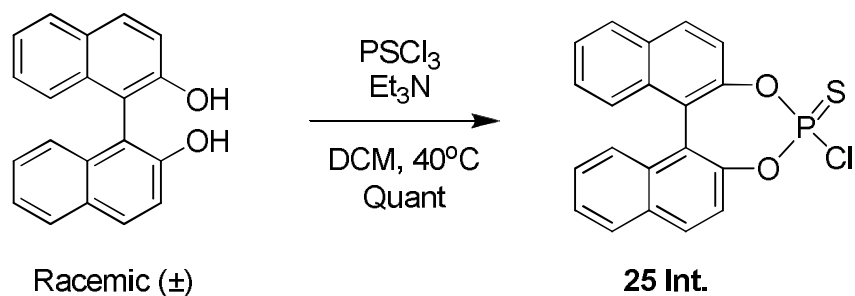


Figure 55 : Gong's general synthesis

Gong *et al.*⁴⁹ have reported an alternative synthesis utilising a weaker base triethylamine (Et_3N) in DCM (Figure 55). This method allowed a clean and quantitative conversion of BINOL into compound **25**'s intermediate. ^{31}P NMR (δ ppm 74) was then used to confirm the clean addition of PSCl_3 to the BINOL backbone.

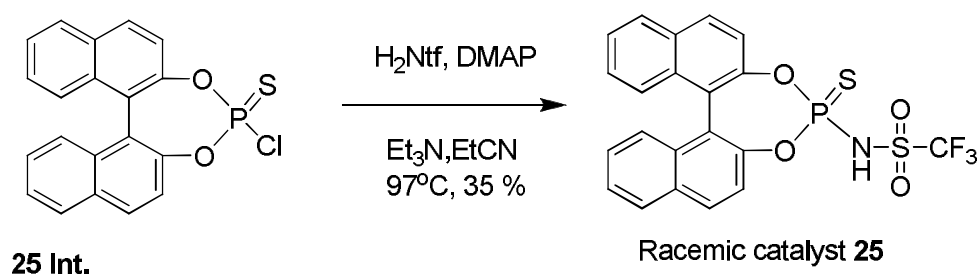


Figure 56 : Cheon's second catalyst step

The final step of the synthesis followed Cheon's general method.²¹ This used triflamide and a nucleophilic catalyst DMAP with triethylamine in propionitrile refluxing (Figure 56).²¹ This final step afforded the desired racemic catalyst **25** in a low yield (~35%). ¹⁹F NMR (δ ppm - 77.63) spectroscopy was then used to demonstrate the attachment of the triflamide to the intermediate. The enantiopure catalysts (**26(R)** & **27(S)**) were then synthesised using the same methods to afford similar yields.

2.3.5 Catalytic Trials

Initial catalytic trials tested the racemic catalyst to investigate its ability to catalyse the glycosylation of glycols. The catalyst was successful as a proof of concept, but it unfortunately produced a large amount of the α selective Ferrier side product (Figure 57). The reaction gave a moderate yield (57%) which required 2 days to complete.

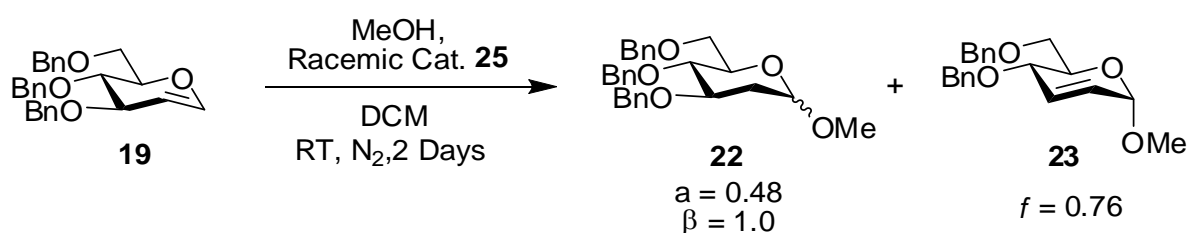


Figure 57 : Initial glycol glycosylation conditions

Development of the catalytic trials then focused on the use of the enantiopure catalysts (**26(R)** & **27(S)**) to determine if the diastereoselectivity of glycosylation could be influenced

(Table 7, Trial 17, 18). However, no diastereoselectivity was observed but a shortened reaction time was displayed when comparing the enantiopure catalysts (**26(R)** & **27(S)**) to the racemic catalyst (**25**). No plausible explanations apart from impurities in the racemic catalyst would be able to explain this difference. The objective of the catalytic trials shifted upon formation of the Ferrier side product as a diastereoselective glycosylation would be nullified if a side product was present. Therefore, various reaction conditions were trialled to decrease the amount of Ferrier side product produced (Table 7).

Table 7 : Reaction conditions targeted at the removal of ferrier side product

Trial	Solvent	Catalyst	Time	Yield	α	β	f	Temperature	Ferrier percentage (%)
17	DCM	10% (R)	4hrs	81	0.52	1	0.65	RT	30
18	DCM	10% (S)	4hrs	78	0.46	1	0.96	RT	40
19	Toluene	10% (S)	1 day	84	0.51	1	0.44	RT	23
20	Toluene	10% (R)	1 day	83	0.56	1	0.46	RT	23
21	Toluene	10% (S)	4 days	67	0.49	1	0.26	0°C	14
22	Toluene	3% (S)	2 days	69	0.59	1	0.35	RT	18
23	Toluene	3% (S)	7 days	37	0.53	1	0.24	0°C	13

Tight ion pairing between the glycal and catalyst *in situ* was believed to be the key in reducing the amount of the Ferrier rearrangement. Therefore, the first variable to be changed in order to remove the Ferrier side product **23f** was the solvent; DCM was replaced by the less polar toluene to increase ion pairing. This decreased the percentage of the Ferrier product from 30% and 40% to 23% respectively. The next key changes were a decrease in temperature to increase tight ion pairing and a reduction of catalyst loading was used. Both modifications had a positive impact on decreasing the percentage of Ferrier product formed from 23% to 14% and 18% respectively, but both modifications decreased the product yield. Finally these modifications were combined in an attempt to remove the

Ferrier rearrangement completely. However, the percentage of Ferrier product could only be decreased to 13% with a low yield. No diastereoselectivity of glycosylation between the enantiopure catalysts was observed as the stereochemistry of the target product **22** remained consistent throughout the trials ($22\alpha:22\beta$ ~0.5:1, Table 7). As each change was made to decrease the percentage of Ferrier product formed, the reaction time was lengthened.

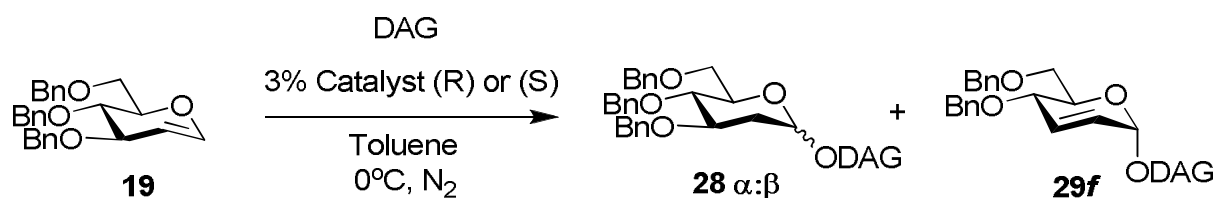


Figure 58 : Optimal conditions to remove the Ferrier side product with DAG

The optimal conditions for the suppression of the Ferrier side product were then trialled with another glycosyl acceptor, diacetone galactose, to determine if the larger steric size had an effect on the diastereoselectivity of glycosylation and the percentage of Ferrier side product formed (Figure 58).

Table 8 : Optimal conditions to remove the Ferrier side product with DAG

Trial	Solvent	Catalyst	Time		α	β	f	Temperature	Ferrier percentage (%)
			(Days)	Yield					
24	Toluene	3% (S)	7	26	1.03	1	0.02	0°C	1
25	Toluene	3% (R)	7	29	1.36	1	0.35	0°C	12

There was no significant difference seen in the diastereoselectivity of the target products ($28\alpha:28\beta$ ~1:1, Table 8, Trial 24, 25). However, there was a significant difference in the amounts of Ferrier side product produced with the (S) catalyst only producing 1% side product $29f$ compared to the (R) catalyst which produced 12% side product 29 (Table 8, Trial 24, 25).

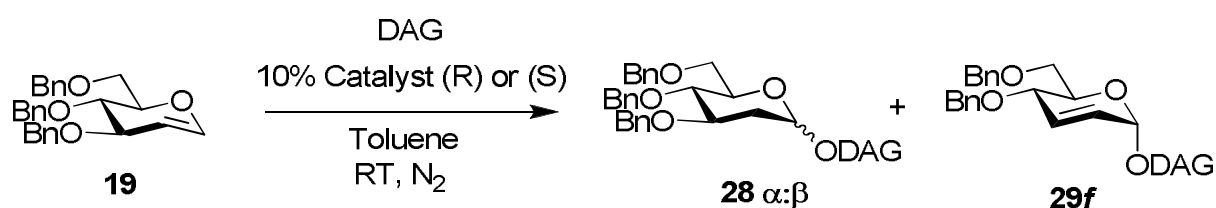


Figure 59 : Highest yielding conditions with DAG

The last trial took the highest yielding conditions and paired diacetone galactose with both versions of the catalyst to determine if the diastereoselectivity of glycosylation could be influenced (Figure 59).

Table 9 : Highest yielding conditions with DAG

Trial	Solvent	Catalyst	Time (Days)	Yield	α	β	f	Temperature	Ferrier Percentage (%)
26	Toluene	10% S	2	78	2.05	1	0.65	RT	17
27	Toluene	10% R	2	82	2.26	1	0.55	RT	14

Unfortunately, the highest yielding conditions displayed no diastereoselectivity of glycosylation between the two catalysts ($28\alpha:28\beta$ ~2:1, Table 9).

Chapter 3: Conclusion

3.1 Summary

In conclusion, the two glycosyl systems investigated produced mixed results. The first system using glycosyl halides with catalytic amounts of TRIP did demonstrate asymmetric control of glycosylation as a β -diastereoselective reaction was observed. However, there was an exception with (R) TRIP in DCM, displaying an α -diastereoselective reaction. These trials were plagued by inconsistent and low yields, primarily due to the unstable nature of the glycosyl bromide **12**. Therefore, this study was eventually abandoned in favour of developing a more promising glycal system.

The second system using glycals proved more successful with the synthesis of a new chiral Brønsted acid. This acid then allowed the glycosylation of glycals where TRIP had failed previously. The new chiral Brønsted acid was synthesised from previously known methods affording a low yield over two steps (~30%).^{21,49} The success was short lived as formation of the Ferrier side product then contaminated the trials. Attempts were then made to decrease the percentage of this side product but ultimately proved unsuccessful as it could only be consistently decreased to 13%. No diastereoselectivity of glycosylation was observed between the two enantiopure catalysts. Therefore, the development ceased. Unfortunately, none of the glycosyl acceptors synthesised earlier were required as the catalytic systems failed early in development.

3.2 Future Development

Future development will target the synthesis of new chiral Brønsted acids to further investigate the glycosylation of glycols. These Brønsted acids will be designed with fewer oxygen atoms around the acid which will allow for the coordination of the acid to the anomeric centre, hopefully eliminating the Ferrier rearrangement and allowing a diastereoselective reaction.

Chapter 4: Experimental

4.1 General Experimental

Reaction conditions: All reactions, unless otherwise stated, were performed under N₂ at RT.

Molecular sieves 3Å were crushed and microwave activated (6 x 30 sec on high). **Solvents**

and Reagents: All chemicals were purchased from Sigma Aldrich (inc. methyl α -D-glucopyranoside **1**). Anhydrous toluene and DCM were obtained by distillation over calcium

hydride under N₂. All the other solvents and reagents supplied (analytic or HPLC grade) were used without further purification. 'Petrol' refers to the fraction of light petroleum ether

boiling in the range of 40 - 60°C. **Chromatography:** Thin layer chromatography (t.l.c.) was performed on Merck Kieselgel 60F254 pre-coated aluminium-backed plates. Visualisation of

the plates was achieved using a u.v. lamp ($\lambda_{\text{max}} = 254 \text{ nm}$) and ammonium molybdate (5% in 2M H₂SO₄). Flash chromatography was performed using Silica 60 230-400 mesh. **Melting**

Points: Melting points were recorded on an Electrothermal IA6304 melting point block.

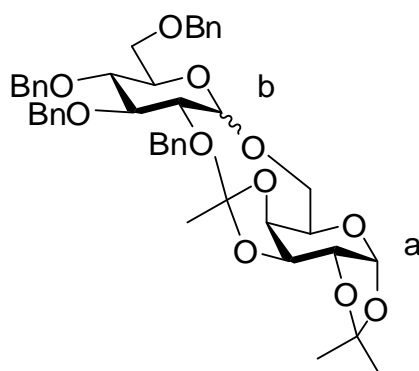
Optical Rotations: Optical rotations were measured on a Perkin-Elmer 341 polarimeter with a path length of 1 dm. Concentrations are given in g/100 mL. **Infrared Spectroscopy:**

Infrared spectra were recorded on a Perkin Elmer LR64912c FT IR spectrophotometer using a thin film prepared on a sodium chloride plate. Peaks are given in cm⁻¹. Only characteristic

peaks are quoted. **Mass Spectrometry:** High-resolution mass spectra were recorded on a Bruker MaXis 3G with electrospray ionisation (ESI⁺ or ESI⁻). **NMR Spectroscopy:** Proton

nuclear magnetic resonance spectra (δH) were recorded on a Varian INOVA 300 (300 MHz) or a Varian VNMR 500 (500 MHz) spectrometer and were calibrated according to the

chemical shift of residual protons in the deuterated solvent stated. ^{13}C NMR spectra (δC) were recorded on a Varian VNMR 500 (125 MHz) spectrometer and were calibrated according to the chemical shift of the deuterated solvent stated. ^{31}P NMR spectra (δP) were recorded on a Varian INOVA 300 (121 MHz) spectrometer and were calibrated to 85% H_2PO_4 in the deuterated solvent stated. ^{19}F NMR spectra (δF) were recorded on a Varian INOVA 300 (282 MHz) spectrometer and were calibrated against CFCl_3 . All chemical shifts are quoted in ppm and coupling constants (J) in Hz. The abbreviations used to denote multiplicities can be found in the abbreviations section. All disaccharides were labelled in a systematic method with remainder of the glycosyl acceptor being labelled 'a' and the glycosyl donor labelled 'b'.

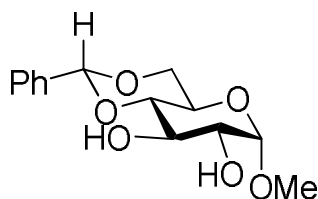


2,3,4,6-Tetra-*O*-benzyl- α/β -D-glucopyranosyl-(1 \rightarrow 6)-methyl-2,3,4-tri-*O*-benzyl- α -D-glucopyranoside **20**

4.2 Experimental Methods

Glycosyl Acceptors

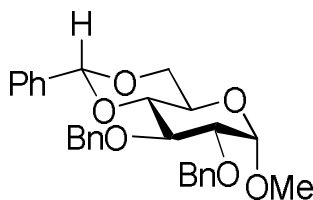
Methyl 4,6-*O*-benzylidene- α -D-glucopyranoside **2**



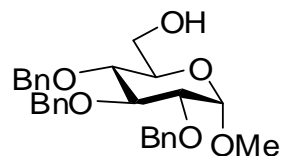
Methyl α -D-glucopyranoside **1** (9.97 g, 51.4 mmol) was dissolved in anhydrous DMF (40 mL) with *p*-toluenesulfonic acid (0.034 g, 0.17 mmol) and α,α -dimethoxytoluene (7.6 mL, 50.7 mmol). The reaction mixture was placed on a rotary evaporator (20 mbar) at 60°C for 1 hour after which a short path evaporation adaptor was fitted and the temperature was increased to 100°C until all the DMF had evaporated. Once the DMF was evaporated, t.l.c (ethyl acetate) indicated the consumption of the starting material (R_f 0.0) and the formation of a major product (R_f 0.6). Saturated aqueous sodium bicarbonate (20 mL) was added to the reaction mixture, which was then concentrated *in vacuo* at 100°C until it was finely dispersed. The resulting solid was then dried overnight on phosphorous pentaoxide *in vacuo*. The sample was then recrystallised from propanol to give methyl 4,6-*O*-benzylidene- α -D-glucopyranoside **2** (9.84 g, 67 %) as a white solid. m.p. 195°C [lit. 195°C]⁵⁰; $[\alpha]_D^{20}$ +105 (*c*, 1.0 in CHCl₃) [lit. $[\alpha]_D^{20}$ +105 (*c*, 1.0 in CHCl₃)]⁵⁰; ¹H NMR (500 MHz, CDCl₃) δ ppm 3.42 - 3.83 (5H, m, H-2, H-3, H-5, H-6, H-6'), 3.51 (3H, s, OMe), 4.32 (1H, dd, $J_{3,4}$ 8.9 Hz, $J_{4,5}$ 3.4 Hz,

H-4), 4.85 (1H, d, $J_{1,2}$ 3.8 Hz, H-1), 5.58 (1H, s, Ar-CH), 7.39 - 7.43 (3H, m, Ar-H), 7.51 - 7.54 (2H, m, Ar-H).

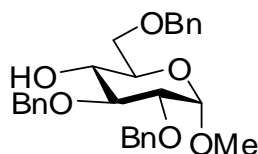
Methyl 4,6-*O*-benzylidene-2,3-di-*O*-benzyl- α -D-glucopyranoside **3**



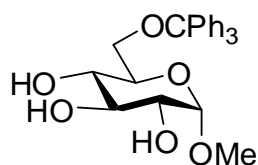
Methyl 4,6-*O*-benzylidene- α -D-glucopyranoside **2** (8.87 g, 31.4 mmol) was dissolved in DMF (150 mL). NaH (60% dispersion in mineral oil, 4.15 g, 172.92 mmol) was then added at 0°C under N₂. After 30 minutes benzyl bromide (9.3 mL, 78.6 mmol) was added to the reaction and was allowed to warm to RT. After 23 hours t.l.c (petrol: ethyl acetate, 3:1) indicated the consumption of the starting material (R_f 0.0) and the formation of a major product (R_f 0.4). The reaction was then quenched by careful addition of methanol (10 mL), and then diluted in petrol: ethyl acetate (3:1, 200 mL), washed with water (100 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol: ethyl acetate, 3:1) to give methyl 4,6-*O*-benzylidene-2,3-di-*O*-benzyl- α -D-glucopyranoside **3** (7.1 g, 49 %) as a colourless oil. $[\alpha]_D^{20}$ -27.3 (*c*, 1.0 in CHCl₃) [lit. $[\alpha]_D^{20}$ -31.2 (*c*, 1.0 in CHCl₃)]⁵¹; ¹H NMR (500 MHz, CDCl₃) δ ppm 3.45 (3H, s, OMe), 3.65 (1H, m, H-6'), 3.78 (1H, m, H-5), 4.09 (1H, m, H-6), 4.30 (1H, dd, $J_{3,4}$ 9.9, $J_{4,5}$ 4.5 Hz, H-4), 4.60 (1H, d, $J_{1,2}$ 3.7 Hz, H-1), 4.72 (1H, dd, $J_{2,3}$ 11.3, $J_{3,4}$ 9.9 Hz, H-3), 4.86 (1H, dd, $J_{1,2}$ 3.7, $J_{2,3}$ 11.3 Hz, H-2), 4.88 (2H, d, $J_{a,b}$ 12.1 Hz, OCH₂Ph), 4.94 (2H, d, $J_{a,b}$ 11.3 Hz, OCH₂Ph), 5.60 (1H, s, Ar-CH), 7.30 - 7.55 (15H, m, Ar-H)

Methyl 2,3,4-tri-O-benzyl- α -D-glucopyranoside 4

Methyl 4,6-*O*-benzylidene-2,3-di-*O*-benzyl- α -D-glucopyranoside **3** (1.32 g, 2.85 mmol) was dissolved in a mixture of diethyl ether and DCM (1:1, 60 mL). Lithium aluminium hydride (1.3 g, 34.28 mmol) was then added in small portions under N₂ at RT. A suspension of AlCl₃ (3.8 g, 28.5 mmol) in diethyl ether (30 mL) was subsequently added to the reaction. After 3 hours t.l.c (petrol: ethyl acetate, 1:1) indicated the consumption of the starting material (R_f 0.68) and the formation of a single major product (R_f 0.36). The reaction was quenched by the addition of ethyl acetate (30 mL) and water (50 mL) forming a precipitate which was filtered. The filtrate was further diluted with diethyl ether (100 mL), washed with water (2 x 100 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The product was purified by flash chromatography (petrol: ethyl acetate, 1:1) to give methyl 2,3,4-tri-*O*-benzyl- α -D-glucopyranoside **4** (0.7 g, 52 %) as a colourless oil. $[\alpha]_D^{20} +23.5$ (*c*, 1.0 in CHCl₃) [lit. $[\alpha]_D^{20} +19.20$ (*c*, 1.0 in CHCl₃)]⁵²; ¹H NMR (500 MHz, CDCl₃) δ ppm 2.09 (1H, at, *J* 6.4 Hz, OH), 3.41 (3H, s, OCH₃), 3.53 (1H, m, H-5), 3.67 - 3.76 (2H, m, H-6, H-6'), 3.79 - 3.84 (3H, m, H-2, H-3, H-4), 4.61 (1H, d, *J*_{1,2} 3.5 Hz, H-1), 4.67 - 4.73 (4H, m, OCH₂Ph), 4.83 (1H, d, *J*_{a,b} 11.3 Hz, OCH₂Ph), 5.02 (1H, d, *J*_{a,b} 10.8 Hz, OCH₂Ph), 7.28 - 7.39 (15H, m, Ar-H)

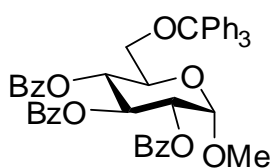
Methyl 2,3,6-tri-*O*-benzyl- α -D-glucopyranoside 5

Methyl 4,6-*O*-benzylidene-2,3-di-*O*-benzyl- α -D-glucopyranoside **3** (5.5 g, 11.9 mmol) was stirred at 0°C under N₂ in DCM (100 mL), at which point Et₃SiH (0.63 g, 142.85 mmol) and BF₃·OEt₂ (3.1 mL, 23.8 mmol) were added slowly to the reaction mixture. The reaction mixture was then allowed to warm to RT. After 3 hours t.l.c (petrol: ethyl acetate, 2:1) indicated the consumption of the starting material (R_f 0.49) and the formation of a major product (R_f 0.31). The reaction was then quenched by the addition of wet DCM (100 mL). The organic mixture was then washed with saturated aqueous sodium bicarbonate (2 x 100 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol: ethyl acetate, 2:1) to give methyl 2,3,6-tri-*O*-benzyl- α -D-glucopyranoside **5** (3.3 g, 60 %) as a colourless oil. [α]_D²⁰ +13.6 (*c*, 1.0 in CHCl₃) [lit. [α]_D²⁰ +13.4 (*c*, 1.0 in CHCl₃)]⁵²; ¹H NMR (500 MHz, CDCl₃) δ ppm 3.43 (3H, s, OMe), 3.56 (1H, dd, *J*_{1,2} 3.6, *J*_{2,3} 11.5 Hz, H-2), 3.60 - 3.86 (5H, m, H-3, H-4, H-5, H-6, H-6'), 4.56 - 4.84 (6H, m, OCH₂Ph), 4.68 (1H, d, *J*_{1,2} 3.6 Hz, H-1), 7.30 - 7.42 (15H, m, Ar-H)

Methyl 6-*O*-trityl- α -D-glucopyranoside 6

Chlorotriphenylmethane (15.7 g, 56.65 mmol) and DMAP (0.15 g, 1.28 mmol) were added to a solution of methyl α -D-glucopyranoside **1** (5.0 g, 25.75 mmol) in pyridine (100 mL). The reaction was stirred at RT under N_2 for 1 hour at which point t.l.c (ethyl acetate: methanol, 9:1) indicated the consumption of the starting material (R_f 0.16) and the formation of a major product (R_f 0.56). The reaction mixture was then concentrated *in vacuo* to a quarter of its original volume, partitioned between DCM (300 mL) and saturated aqueous ammonium chloride (200 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was recrystallised from ethanol to give methyl 6-O-trityl- α -D-glucopyranoside **6** (9.92 g, 88 %) as a pale orange crystalline solid. m.p. 141°C [lit. 144°C]⁵⁰; $[\alpha]_D^{20} +53.2$ (c, 1.0 in $CHCl_3$) [lit. $[\alpha]_D^{20} +59.4$ (c, 1.0 in $CHCl_3$)]⁵⁰; 1H NMR (500 MHz, $CDCl_3$) δ ppm 3.37 - 3.43 (2H, m, H-6, H-6'), 3.44 (3H, s, OCH_3), 3.50 - 3.56 (2H, m, H-2, H-4), 3.65 - 3.70 (2H, m, H-3, H-5), 4.78 (1H, d, $J_{1,2}$ 4.2 Hz, H-1), 7.22 - 7.34 (15H, m, 15 x Ar-H).

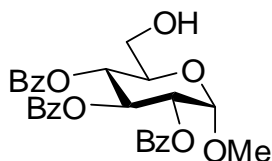
Methyl 2,3,4-tri-O-benzoyl-6-O-trityl- α -D-glucopyranoside **7**



Benzoyl chloride (11 mL, 91.0 mmol) was added to a mixture of methyl 6-O-trityl- α -D-glucopyranoside **6** (9.92 g, 22.7 mmol) in pyridine (60 mL). The reaction was stirred for a further 24 hours at which point t.l.c (petrol: ethyl acetate, 3:1) indicated consumption of the starting material (R_f 0.1) and the formation of a new major product (R_f 0.4). The reaction mixture was diluted with DCM (100 mL), washed with water (2 x 100 mL), sodium bicarbonate (2 x 100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*.

The residue was purified by flash chromatography (petrol: ethyl acetate, 3:1) to give methyl 2,3,4-tri-*O*-benzoyl-6-*O*-trityl- α -D-glucopyranoside **7** (8.54 g, 53 %) as a white solid. m.p. 121°C (petrol/ethyl acetate); $[\alpha]_D^{20} +30.11$ (*c*, 1.0 in CHCl₃) [lit. $[\alpha]_D^{20} +45.7$ (*c*, 1.0 in CHCl₃)]⁵³; ¹H NMR (500 MHz, CDCl₃) δ ppm 3.31 (2H, m, H-6, H-6'), 3.53 (3H, s, OCH₃), 4.19 (1H, dt, *J*_{4,5} 10.2, *J*_{5,6} 4.2, *J*_{5,6'} 4.2 Hz, H-5), 5.27 - 5.32 (2H, m, H-1, H-2), 5.55 (1H, t, *J* 9.6 Hz, H-4), 6.08 (1H, t, *J* 9.6 Hz, H-3), 7.08 - 7.54 (24H, m, Ar-H), 7.73 (2H, d, *J* 8.7 Hz, Ar-H), 7.86 (2H, d, *J* 8.4 Hz, Ar-H), 7.99 (2H, d, *J* 8.4 Hz, Ar-H).

Methyl 2,3,4-tri-*O*-benzoyl-*O*- α -D-glucopyranoside **8**

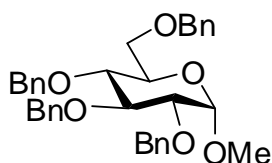


FeCl₃·6H₂O (6.50 g, 24.19 mmol) was added to the solution of methyl 2,3,4-tri-*O*-benzoyl-6-*O*-trityl- α -D-glucopyranoside **7** (8.54 g, 12.09 mmol) in DCM (50 mL) and the reaction was stirred at RT under N₂. After 1 hour t.l.c (petrol: ethyl acetate, 2:1) indicated the consumption of the starting material (*R*_f 0.6) and showed the formation of a major product (*R*_f 0.3). The solution was further diluted in DCM (300 mL), washed with water (2 x 100 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was then purified by flash chromatography (petrol: ethyl acetate, 2:1) to afford methyl 2,3,4-tri-*O*-benzoyl-*O*- α -D-glucopyranoside **8** (2.49 g, 43 %) as a white solid. m.p. 134°C (petrol) [lit. 133.5°C]⁵⁴; $[\alpha]_D^{20} +52.7$ (*c*, 1.0 in CHCl₃) [lit. $[\alpha]_D^{20} +51.3$ (*c*, 1.0 in CHCl₃)]⁵⁴; ¹H NMR (500 MHz, CDCl₃) δ ppm 2.75 (1H, brs, OH), 3.51 (3H, s, OCH₃), 3.79 (1H, m, H-6), 4.03 (1H, m, H-6'), 4.15 (1H, m, H-5), 5.28 (1H, d, *J*_{1,2} 3.8 Hz, H-1), 5.31 (1H, dd, *J*_{1,2} 3.8, *J*_{2,3} 9.6 Hz, H-2), 5.54 (1H, dd, *J*_{3,4} 9.8, *J*_{4,5}

9.8 Hz, H-4), 6.27 (1H, dd, $J_{2,3}$ 9.6, $J_{3,4}$ 9.8 Hz, H-3), 7.30 - 7.58 (9H, m, Ar-H), 7.90 (2H, d, J 7.3 Hz, Ar-H), 8.01 (4H, d, J 7.5 Hz, Ar-H)

Glycosyl Donors

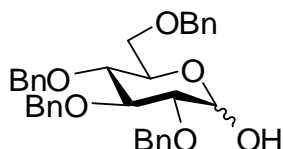
Methyl 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranoside **9**



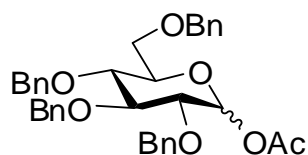
Methyl α -D-glucopyranoside **1** (2.0 g, 10.29 mmol) was dissolved in DMF (50 mL), and NaH (60% dispersion in mineral oil, 1.5 g, 61.79 mmol) was added at 0°C under N₂. After 30 minutes benzyl bromide (7.54 mL, 61.79 mmol) was added and the reaction was allowed to warm to RT. After 23 hours t.l.c (petrol: ethyl acetate, 3:1) indicated the consumption of the starting material (R_f 0.0) and the formation of a major product (R_f 0.6). The reaction mixture was quenched by the careful addition of methanol (10 mL), and was partitioned between DCM (100 mL) and water (100 mL). The organic layer was subsequently washed with water (2 x 100 mL), brine (50 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol: ethyl acetate, 6:1) to give methyl 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranoside **9** (4.31 g, 75 %) as an orange oil. $[\alpha]_D^{20} +16.7$ (c, 1.0 in CHCl₃) [lit. $[\alpha]_D^{20} +19.3$ (c, 1.0 in CHCl₃)]³²; ¹H NMR (500 MHz, CDCl₃) δ ppm 3.38 (3 H, s, OMe), 3.57 (1H, dd, $J_{1,2}$ 3.4, $J_{2,3}$ 9.7 Hz, H-2), 3.61 - 3.68 (2H, m, H-4, H-6), 3.70 - 3.80 (2H, m, H-5, H-6'), 3.99 (1H, at, $J_{2,3}$ 9.3, $J_{3,4}$ 9.2 Hz, H-3), 4.44 - 4.53 (2H, m, OCH₂Ph), 4.56 - 4.72 (2H,

m, H-1, OCH₂Ph), 4.64 (1H, d, $J_{1,2}$ 3.6 Hz, H-1) 4.77 - 4.89 (3H, m, OCH₂Ph), 4.98 (1H, d, $J_{a,b}$ 10.6 Hz, OCH₂Ph), 7.08 - 7.43 (18H, m, Ar-H)

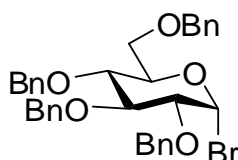
2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose **10**



Methyl 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranoside **9** (11.45 g, 20.64 mmol) was dissolved in glacial acetic acid (250 mL) and the mixture was heated to 90°C while stirring, after which sulphuric acid (2 M, 62.5 mL) was added. After 2 more hours' sulphuric acid (2 M, 62.5 mL) was added and the reaction mixture stirred further at 90°C. After 21 hours t.l.c (petrol: ethyl acetate, 4:1) indicated the consumption of the starting material (R_f 0.4) and the formation of a major product (R_f 0.1). Water (100 mL) was added to the reaction and the mixture was cooled to 0°C at which point a white precipitate formed. The precipitate was then filtered and washed with wet methanol (80% V/V) to give 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **10** (4.7 g, 42 %) ³² as a white solid being a mixture of diastereoisomers (α : β 1:1) ¹H NMR (500 MHz, CDCl₃) δ ppm 3.42 (1H, m, H-2 β), 3.51 - 3.75 (9H, m, H-2 α , H-4 α , H-6 α , H-6' α , H-3 β , H-4 β , H-5 β , H-6 β , H-6' β), 3.98 (1H, t, J 9.4 Hz, H-3 α), 4.05 (1H, ddd, $J_{4,5}$ 10.1, $J_{5,6}$ 3.8, $J_{5,6'}$ 2.1 Hz, H-5 α), 4.45 - 5.00 (17H, m, H-1 β , 4 x OCH₂Ph), 5.24 (2H, d, $J_{1,2}$ 3.3 Hz, H-1 α), 7.06 - 7.54 (40H, m, 20 x Ar-H α , 20 x Ar-H β)

1-O-Acetyl-2,3,4,6-tetra-O-benzyl-D-glucopyranoside 11

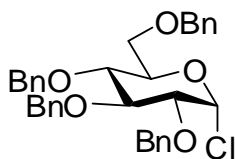
Acetyl chloride (0.05 mL, 0.74 mmol) was added to 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **10** (0.1 g, 0.18 mmol) which was dissolved in DCM (2 mL) and pyridine (0.07 mL, 0.93 mmol) at 0°C, and the reaction was allowed to warm to RT. After 2.5 hours t.l.c (petrol: ethyl acetate, 4:1) indicated the consumption of the starting material (R_f 0.1) and the formation of a major product (R_f 0.4). The reaction mixture was then diluted with DCM (10 mL) and partitioned against sulphuric acid (2M, 20 mL), brine (20 mL) and concentrated *in vacuo*. The residue was then purified by flash column chromatography (petrol: ethyl acetate, 4:1) to afford 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside **11** (103 mg, 77 %) ³⁵ being a mixture of isomers (α : β , 5:1). ¹H NMR (500 MHz, CDCl₃) δ ppm 2.10 (3H, s, OMe β), 2.18 (3H, s, OMe α), 3.65 - 3.96 (12H, m, H-2 α , H-3 α , H-4 α , H-5 α , H-6 α , H-6' α , H-2 β , H-3 β , H-4 β , H-5 β , H-6 β , H-6' β), 4.47 - 5.05 (16H, m, 4 x OCH₂Ph α , 4 x OCH₂Ph β), 5.61 (1H, d, $J_{1,2}$ 8.1 Hz, H-1 β), 6.36 (1H, d, $J_{1,2}$ 3.7 Hz, H-1 α), 7.17 - 7.34 (40H, m, 20 x Ar-H α , 20 x Ar-H β)

2,3,4,6-Tetra-O-benzyl- α -D-glucopyranose bromide 12

Oxalyl bromide (0.021 mL, 0.23 mmol) was added dropwise to a solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **10** (97 mg, 0.18 mmol) in DCM (1.25 mL) and DMF (0.06 mL) at RT.

The reaction mixture was left for 1 hour after which point t.l.c (petrol: ethyl acetate, 3:1) indicated the consumption of some of the starting material (R_f 0.1) and the formation of a major product (R_f 0.6). The reaction mixture was then washed with ice cold water (3 x 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford crude 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranose bromide **12** (100.6 mg, 95 %) ³² as an orange oil. ^1H NMR (500 MHz, CDCl_3) δ ppm 3.54 (1H, dd, $J_{1,2}$ 3.7 $J_{2,3}$ 9.2 Hz, H-2), 3.65 (1H, dd, $J_{5,6}$ 1.8, $J_{5,6'}$ 11.0 Hz, H-5), 3.69 - 3.83 (3H, m, H-4, H-6, H-6'), 4.04 (1H, at, $J_{2,3}$ 9.2, $J_{3,4}$ 9.2 Hz, H-3), 4.42 - 5.02 (8H, m, 4 x OCH_2Ph), 6.43 (1H, d, $J_{1,2}$ 3.6 Hz, H-1), 7.09 - 7.42 (20H, m, 20 x Ar-H)

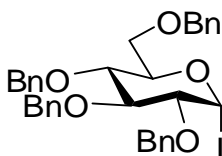
2,3,4,6-Tetra-*O*-benzyl- α -D-glucopyranose chloride **13**



Oxalyl chloride (0.31 mL, 3.70 mmol) was added dropwise to a solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **10** (500 mg, 0.92 mmol) in DCM (6 mL) and DMF (0.3 mL) at RT. The reaction mixture was stirred overnight at which point t.l.c (petrol: ethyl acetate, 3:1) indicated the consumption of most of the starting material (R_f 0.1) and the formation of a new major product (R_f 0.5). The reaction mixture was then washed with ice cold water (3 x 10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol: ethyl acetate, 3:1) to afford 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranose chloride **13** (473.6 mg, 92 %) as a colourless oil. $[\alpha]_D^{20} +97$ (c , 1.5 in CHCl_3) [lit. $[\alpha]_D^{20} +96$ (c , 1.5 in CHCl_3)] ⁵⁵; ^1H NMR (500 MHz, CDCl_3) δ ppm 3.65 (1H, dd, $J_{1,2}$ 3.7, $J_{2,3}$ 10.8 Hz, H-2), 3.70 - 3.81 (1H, m, H-6), 3.99- 4.20 (3H, m, H-4, H-5, H-6'), 4.44 - 4.54 (1H, m,

H-3), 4.59 - 4.98 (8H, m, 4 x OCH₂Ph), 6.07 (1H, d, $J_{1,2}$ 3.7 Hz, H-1), 7.08 - 7.46 (20H, m, 20 x Ar-H)

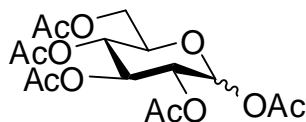
2,3,4,6-Tetra-*O*-benzyl- α -D-glucopyranose iodide **14**



Trimethylsilyl iodide (0.03 mL, 0.22 mmol) was added dropwise to a solution of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside **11** (92 mg, 0.16 mmol) in DCM (1.6 mL) at 0°C. The reaction mixture was allowed to warm to RT and was stirred for an additional 45 minutes. After 45 minutes the reaction mixture was concentrated *in vacuo* to afford crude 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranose iodide **14**³⁵ which was used in the next step without further purification.

Glycols

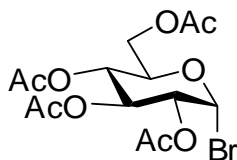
1,2,3,4,6-Penta-*O*-acetyl-D-glucopyranoside **15**



D-Glucose (15 g, 83.26 mmol) was added portion-wise to a stirred mixture of acetic anhydride (75 mL) and iodine (0.61 g, 2.44 mmol) over 30 minutes. The solution was then

left stirring for 23 hours at which time t.l.c (petrol: ethyl acetate, 1:1) indicated the consumption of the starting material (R_f 0.0) and the formation of a single product (R_f 0.4). The reaction mixture was then poured into an ice-cold saturated aqueous sodium thiosulphate solution (250 mL) causing the desired product to precipitate. The solution was then filtered to give crude 1,2,3,4,6-penta-*O*-acetyl- α -D-glucopyranoside **15** (24 g, 73 %) ⁵⁶ as a white solid being predominantly the α -anomer. ¹H NMR (500 MHz, CDCl₃) δ ppm δ 2.01, 2.02, 2.04, 2.09, 2.18 (15H, 5 x s, 5 x CH₃), 4.08 - 4.13 (2H, m, H-5, H-6), 4.25 - 4.27 (1H, dd, J 12.4 Hz H-6'), 5.08 - 5.16 (2H, m, H-2, H-4), 5.47 (1H, at, J 9.9 Hz, H-3), 6.32 (1H, d, $J_{1,2}$ 3.7 Hz, H-1)

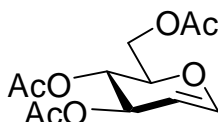
2,3,4,6-Tetra-*O*-acetyl- α -D-glucopyranosyl bromide **16**



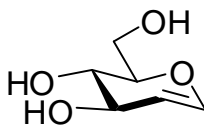
1,2,3,4,6-Penta-*O*-acetyl-D-glucopyranoside **15** (21.29 g, 55.5 mmol) was added portion-wise to a solution of hydrogen bromide in acetic acid (33%, 35 mL) at 0°C. The mixture was stirred for an hour under N₂ at which time t.l.c (petrol: ethyl acetate, 1:1) indicated consumption of the starting material (R_f 0.4) and the formation of a major product (R_f 0.7). The reaction was quenched with ice-cold water (250 mL), extracted with DCM (2 x 200 mL) and the combined organic layers were then washed with saturated aqueous sodium bicarbonate (2 x 200 mL), dried (MgSO₄), filtered and concentrated *in vacuo* to give crude 2,3,4,6-tetra-*O*-acetyl- α -D-glucopyranosyl bromide **16** (17.51 g, 77 %) ⁵⁶ as an oil. ¹H NMR (500 MHz, CDCl₃) δ ppm 2.04, 2.05, 2.06, 2.07, (12H, 4 x s, 4 x CH₃), 4.11 - 4.16 (1H, dd, $J_{5,6}$

1.7, $J_{6,6'}$ 10.5 Hz, H-6), 4.29 - 4.36 (2H, m, H-5, H-6'), 4.85 (1H, dd, $J_{1,2}$ 3.9, $J_{2,3}$ 10.1 Hz, H-2), 5.16 (1H, at, J 9.8 Hz, H-4), 5.56 (1H, at, J 9.8 Hz, H-3), 6.61 (1H, d, $J_{1,2}$ 3.9 Hz, H-1).

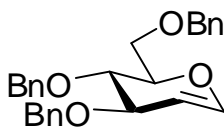
3,4,6-Tri-*O*-acetyl-D-glucal **17**



Previous to the reaction zinc filings (24.6 g, 376 mmol) were activated in a solution of 10% aqueous hydrochloric acid (100 mL), filtered, washed with water (20 mL) and acetone (20 mL). The activated zinc filings were then added to 2,3,4,6-tetra-*O*-acetyl- α -D-glucopyranosyl bromide **16** (14 g, 34.2 mmol) in a mixture of acetic acid (40 mL) and water (40 mL) under N_2 . After 1.5 hours t.l.c (petrol: ethyl acetate, 1:1) indicated consumption of the starting material (R_f 0.7) and formation of a single product (R_f 0.8). The reaction mixture was filtered and the filtrate washed with DCM (3 x 100 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (2 x 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude 3,4,6-tri-*O*-acetyl-D-glucal **17** (6.56 g, 70 %) ⁵⁶ as a white solid. 1H NMR (500 MHz, $CDCl_3$) δ ppm 2.05, 2.08, 2.10 (9H, 3 x s, 3 x CH_3), 4.19 (1H, m, H-6), 4.22 - 4.27 (1H, m, H-5), 4.40 (1H, m, H-6'), 4.84 (1H, dd, $J_{1,2}$ 6.2, $J_{2,3}$ 3.3 Hz, H-2), 5.22 (1H, dd, $J_{3,4}$ 7.5, $J_{4,5}$ 5.8 Hz, H-4), 5.33 - 5.37 (1H, m, H-3), 6.46 (1H, dd, $J_{1,2}$ 6.1 Hz, H-1)

D-Glucal 18

A solution of sodium methoxide was prepared by dissolving sodium (20 mg, 1.07 mmol) in methanol (20 mL). This was slowly added to crude 3,4,6-tri-*O*-acetyl-D-glucal **17** (5.5 g, 20.19 mmol) in methanol (80 mL) and the reaction was stirred at 0°C under N₂. After 20 minutes t.l.c (petrol: ethyl acetate, 1:1) indicated consumption of the starting material (R_f 0.8) and formation of a single product (R_f 0.0). The reaction mixture was then concentrated *in vacuo* to a quarter its original volume, stirred with silica gel (5 g) and filtered through a silica plug. The filtrate was concentrated *in vacuo* and to give crude D-glucal **18** (2.7 g, 91 %) ⁵⁶ as a white solid. ¹H NMR (500 MHz, CD₃OD) δ ppm 3.58 (1H, dd, *J*_{3,4} 7.1, *J*_{4,5} 9.5 Hz, H-4), 3.72 - 3.82 (2H, m, H-5, H-6), 3.90 (1H, dd, *J*_{5,6'} 2.5, *J*_{6,6'} 12.0 Hz, H-6'), 4.11 - 4.14 (1H, m, H-3), 4.70 (1H, dd, *J*_{1,2} 6.0, *J*_{2,3} 2.3 Hz, H-2), 6.36 (1H, dd, *J*_{1,2} 6.1 Hz, H-1)

3,4,6-Tri-*O*-benzyl-D-glucal 19

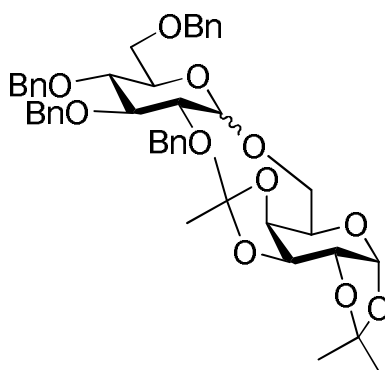
Crude D-glucal **18** (2.7 g, 18.45 mmol) was dissolved in anhydrous DMF (80 mL) and stirred at 0°C under N₂. To the solution NaH (60% in mineral oil, 1.7 g, 73.8 mmol) then benzyl bromide (9 mL, 73.8 mmol) were added and allowed to warm to RT. After 17 hours t.l.c (petrol: ethyl acetate, 1:1) then indicated the consumption of the starting material (R_f 0.0) and the formation of a major product (R_f 0.7). The reaction was then quenched by the

careful addition of methanol (10 mL) and concentrated *in vacuo*. The residue was then dissolved in diethyl ether (400 mL), washed with water (2 x 250 mL) and brine (2 x 250 mL). The combined aqueous extracts were also extracted with diethyl ether (100 mL). All the combined organic extracts were then dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol: ethyl acetate, 6:1) to give 3,4,6-tri-*O*-benzyl-D-glucal **19** (2.36 g, 30 %) as a white crystalline solid. m.p. 51.0°C (petrol:ethyl acetate) [lit. 53-54°C]⁵⁷; [α]_D²⁰ -2.0 (c, 1.0 in CHCl₃) [lit. [α]_D²⁰ -2.0 (c, 1.0 in CHCl₃)]⁵⁷; ¹H NMR (500 MHz, CDCl₃) δ ppm 3.74 - 3.87 (3H, m, H-4, H-6, H-6'), 4.04 - 4.09 (1H, m, H-5), 4.20 - 4.22 (1H, m, H-3), 4.54 - 4.84 (6H, m, 3 x OCH₂Ph), 4.87 (1H, dd, *J*_{1,2} 6.1 Hz, *J*_{2,3} 2.7 Hz, H-2), 6.41 (1H, d, *J*_{1,2} 6.1 Hz, H-1), 7.23 - 7.37 (15H, m, 15 x Ar-H).

General Glycosylation A – Non catalysed

A solution containing the glycosyl halide (1 eqv) and glycosyl acceptor (2 eqv) in anhydrous solvent were added to a flame dried round bottom flask. This flask was wrapped in aluminium foil and molecular sieves were added at RT. After stirring for 30 minutes the silver activator was added. The reaction was monitored via t.l.c until the glycosyl donor was consumed at which point the reaction was diluted with DCM (10 mL) and washed with H₂O (10 mL), brine (10 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The mixture was then purified by flash chromatography to afford the respective glycoside.

Trial 1 - 2,3,4,6-Tetra-*O*-benzyl- α/β -D-glucopyranosyl-(1 \rightarrow 6)-methyl-2,3,4-tri-*O*-benzyl- α -D-glucopyranoside **20**



Following *general glycosylation A* 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranose chloride **13** (186.8 mg, 0.33 mmol) and 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranoside (174 mg, 0.66 mmol) were dissolved in anhydrous toluene (3 mL) at 70°C. After 30 minutes of stirring silver carbonate (49.6 mg, 0.18 mmol) was added to the reaction mixture. T.l.c (petrol: ethyl acetate, 4:1) then indicated the consumption of the glycosyl chloride **13** (R_f 0.77) and the formation of two products (R_f 0.40, 0.37) after 3 days. The reaction mixture was washed then purified by flash chromatography (petrol: ethyl acetate, 4:1) to afford 2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranosyl-(1 \rightarrow 6)-methyl-2,3,4-tri-*O*-benzyl- α -D-glucopyranoside **20** (70.1 mg, 28 %) as a diastereomeric mixture ($\alpha:\beta$, 0.46: 1.0).⁴⁰ **20 α**) ^1H NMR (500 MHz, CDCl_3) δ ppm 1.32 (6H, s, 2 x CH_3), 1.46 (3H, s, CH_3), 1.54 (3H, s, CH_3), 3.59 (1H, dd, $J_{1,2}$ 4.0, $J_{2,3}$ 9.7 Hz, H-2b), 3.65 (1H, dd, $J_{5,6'}$ 1.7, $J_{6,6'}$ 10.3 Hz, H-6'b), 3.69 (1H, t, J 9.7 Hz, H-4b), 3.73 - 3.80 (3H, m, H-6a, H-6'a, H-6b), 3.83 (1H, m, H-5b), 3.99 (1H, t, J 9.7 Hz, H-3b), 4.05 (1H, m, H-5a), 4.32 (1H, dd, $J_{1,2}$ 5.2, $J_{2,3}$ 2.3 Hz, H-2a), 4.36 (1H, dd, $J_{3,4}$ 8.0, $J_{4,5}$ 2.3 Hz, H-4a), 4.47 - 4.98 (9H, m, H-3a, 4 x OCH_2Ph), 5.00 (1H, d, $J_{1,2}$ 4.0 Hz, H-1b), 5.52 (1H, d, $J_{1,2}$ 5.2 Hz, H-1a), 7.13 - 7.38 (20H, m, Ar-H) ; **20 β**) ^1H NMR (500 MHz, CDCl_3) δ ppm 1.31 (6H, s, 2 x CH_3), 1.45 (3H, s, CH_3),

1.50 (3H, s, CH₃), 3.44 - 3.48 (2H, m, H-2b, H-5b), 3.59 - 3.65 (2H, m, H-3b, H-4b), 3.67 - 3.75 (3H, m, H-6a, H-6b, H-6'b), 4.09 (1H, m, H-5a), 4.16 (1H, dd, $J_{5,6}$ 3.4, $J_{6,6'}$ 10.3 Hz, H-6b), 4.24 (1H, dd, $J_{3,4}$ 8.0, $J_{4,5}$ 2.3 Hz, H-4a), 4.32 (1H, dd, $J_{1,2}$ 5.2, $J_{2,3}$ 2.3 Hz, H-2a), 4.45 (1H, d, $J_{1,2}$ 8.0 Hz, H-1b), 4.50 - 5.05 (9H, m, H-3, 4 x OCH₂Ph), 5.57 (1H, d, $J_{1,2}$ 5.2 Hz, H-1a), 7.12 - 7.43 (20H, m, Ar-H)

Trial 3

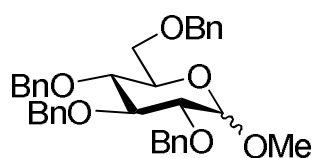
Following *general glycosylation A* 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranose bromide **12** (126 mg, 0.21 mmol) and 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranoside (108 mg, 0.42 mmol) were dissolved in anhydrous DCM (3 mL). After 30 minutes of stirring silver triflate (79 mg, 0.31 mmol) was added to the reaction mixture. T.l.c (petrol: ethyl acetate, 4:1) then indicated the consumption of the glycosyl bromide **12** (R_f 0.58) and the formation of two products (R_f 0.40, 0.37) after 30 minutes. The reaction mixture was washed then purified by flash chromatography (petrol: ethyl acetate, 4:1) to afford 2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranosyl-(1 \rightarrow 6)-methyl-2,3,4-tri-*O*-benzyl- α -D-glucopyranoside **20** (98.6 mg, 61 %) as a diastereomeric mixture (α : β , 1.08: 1.0).

Trial 4

Following *general glycosylation A* 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranose chloride **13** (134 mg, 0.24 mmol) and 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranoside (124 mg, 0.48 mmol) were dissolved in anhydrous DCM (3 mL). After 30 minutes of stirring silver triflate

(83 mg, 0.33 mmol) was added to the reaction mixture. T.l.c (petrol: ethyl acetate, 4:1) then indicated the consumption of the glycosyl chloride **13** (R_f 0.77) and the formation of two products (R_f 0.40, 0.37) after 45 minutes. The reaction mixture was washed then purified by flash chromatography (petrol: ethyl acetate, 4:1) to afford 2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranosyl-(1 \rightarrow 6)-methyl-2,3,4-tri-*O*-benzyl- α -D-glucopyranoside **20** (71 mg, 39 %) as a diastereomeric mixture (α : β , 0.85: 1.0).

Trial 6 - Methyl 2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranoside **21**



Following *general glycosylation A* 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranose bromide **12** (98 mg, 0.16 mmol) and MeOH (0.014 mL, 0.32 mmol) were dissolved in anhydrous DCM (3 mL). After 30 minutes of stirring silver triflate (61 mg, 0.24 mmol) was added to the reaction mixture. T.l.c (petrol: ethyl acetate, 4:1) then indicated the consumption of the glycosyl bromide **12** (R_f 0.58) and the formation of two products (R_f 0.37, 0.33) after 30 minutes. The reaction mixture was washed then purified by flash chromatography (petrol: ethyl acetate, 4:1) to afford methyl 2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranoside **21** (40.6 mg, 46 %) as a diastereomeric mixture (α : β , 0.9: 1.0).⁴⁰ **21 α**) $^1\text{H NMR}$ (500 MHz, CDCl_3) δ ppm $^1\text{H NMR}$ (500 MHz, CDCl_3) δ ppm 3.38 (3H, s, OMe), 3.57 (1H, dd, $J_{1,2}$ 3.5 $J_{2,3}$ 9.7 Hz, H-2), 3.61 - 3.68 (2H, m, H-4, H-6), 3.70 - 3.80 (2H, m, H-5, H-6'), 3.99 (1H, t, $J_{2,3}$ 9.4 Hz, H-3), 4.44 - 4.53 (2H, m, OCH_2Ph), 4.56 - 4.72 (3H, m, H-1, OCH_2Ph), 4.77 - 4.89 (3H, m, OCH_2Ph), 4.98 (1H, d, $J_{a,b}$ 10.6 Hz, OCH_2Ph), 7.08 - 7.43 (18H, m, Ar-H); **21 β**) $^1\text{H NMR}$ (500 MHz, CDCl_3) δ ppm $^1\text{H NMR}$ (500

MHz, CDCl₃) δ ppm 3.42 - 3.48 (2H, m, H-2, H-5), 3.55 (3H, s, OMe), 3.60 - 3.71 (3H, m, H-3, H-4, H-6), 3.76 (1H, m, H-6'), 4.32 (1H, d, $J_{1,2}$ 7.5 Hz, H-1), 4.53 - 4.93 (8H, m, 4 x OCH₂Ph), 7.14 - 7.36 (20H, m, Ar-H)

Trial 7

Following *general glycosylation A* 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranose bromide **12** (83 mg, 0.13 mmol) and MeOH (0.010 mL, 0.26 mmol) were dissolved in anhydrous DCM (3 mL). After 30 minutes of stirring silver carbonate (36 mg, 0.13 mmol) was added to the reaction mixture. T.l.c (petrol: ethyl acetate, 4:1) then indicated the consumption of the glycosyl bromide **12** (R_f 0.58) and the formation of two products (R_f 0.37, 0.33) after 17 hours. The reaction mixture was washed then purified by flash chromatography (petrol: ethyl acetate, 4:1) to afford methyl 2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranoside **21** (28.7 mg, 40 %) as a diastereomeric mixture ($\alpha:\beta$, 0.55: 1.0)

Trial 8

Following *general glycosylation A* 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranose bromide **12** (67 mg, 0.11 mmol) and 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranoside (59.2 mg, 0.23 mmol) were dissolved in anhydrous DCM (3 mL). After 30 minutes of stirring silver carbonate (18 mg, 0.06 mmol) was added to the reaction mixture. T.l.c (petrol: ethyl acetate, 4:1) then indicated the consumption of the glycosyl bromide **12** (R_f 0.58) and the

formation of two products (R_f 0.40, 0.37) after 3 days. The reaction mixture was washed then purified by flash chromatography (petrol: ethyl acetate, 4:1) to afford 2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranosyl-(1 \rightarrow 6)-methyl-2,3,4-tri-*O*-benzyl- α -D-glucopyranoside **20** (49.1 mg, 56 %) as a diastereomeric mixture (α : β , 0.39: 1.0).

Trial 9

Following *general glycosylation A* 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranose bromide **12** (50 mg, 0.08 mmol) and 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranoside (44 mg, 0.17 mmol) were dissolved in anhydrous toluene (3 mL). After 30 minutes of stirring silver carbonate (14 mg, 0.05 mmol) was added to the reaction mixture. T.l.c (petrol: ethyl acetate, 4:1) then indicated the consumption of the glycosyl bromide **12** (R_f 0.58) and the formation of two products (R_f 0.40, 0.37) after 4 days. The reaction mixture was washed then purified by flash chromatography (petrol: ethyl acetate, 4:1) to afford 2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranosyl-(1 \rightarrow 6)-methyl-2,3,4-tri-*O*-benzyl- α -D-glucopyranoside **20** (17.2 mg, 28 %) as a diastereomeric mixture (α : β , 0.94: 1.0).

Trial 10

Following *general glycosylation A* 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranose bromide **12** (36 mg, 0.06 mmol) and 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranoside (31.2 mg, 0.12 mmol) were dissolved in anhydrous tertiary butyl methyl ether (3 mL). After 30 minutes of stirring silver carbonate (8.2 mg, 0.03 mmol) was added to the reaction mixture. T.l.c

(petrol: ethyl acetate, 4:1) then indicated the consumption of the glycosyl bromide **12** (R_f 0.58) and the formation of two products (R_f 0.40, 0.37) after 7 days. The reaction mixture was washed then purified by flash chromatography (petrol: ethyl acetate, 4:1) to afford 2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranosyl-(1 \rightarrow 6)-methyl-2,3,4-tri-*O*-benzyl- α -D-glucopyranoside **20** (27 mg, 36 %) as a diastereomeric mixture ($\alpha:\beta$, 1.09: 1.0).

General Glycosylation B – Catalysed

A solution containing the glycosyl donor (1 eqv) and glycosyl acceptor (2 eqv) in anhydrous solvent was added to a flame dried round bottom flask. This flask was wrapped in aluminium foil and molecular sieves were added at RT. After stirring for 30 minutes, (R) or (S) TRIP and the silver carbonate (0.6 eqv, 1.2 effective) were added to the reaction mixture. The reaction was monitored via t.l.c until the glycosyl donor was consumed at which point the reaction was diluted with DCM (10 mL) and washed with sodium bicarbonate (10 mL), H₂O (10 mL), brine (10 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The mixture was then purified by flash chromatography to afford the respective glycoside.

Trial 2

Following *general glycosylation B* 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranose chloride **13** (184.5 mg, 0.33 mmol) and 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranoside (171.9 mg, 0.66 mmol) were dissolved in anhydrous toluene (3 mL) at 70°C. After 30 minutes stirring

(R)-TRIP (12.4 mg, 0.18 mmol) and silver carbonate (54.5 mg, 0.20 mmol) were added to the reaction mixture. T.l.c (petrol: ethyl acetate, 4:1) then indicated the consumption of the glycosyl chloride **13** (R_f 0.77) and the formation of two products (R_f 0.40, 0.37) after 3 days. The reaction mixture was washed then purified by flash chromatography (petrol: ethyl acetate, 4:1) to afford 2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranosyl-(1 \rightarrow 6)-methyl-2,3,4-tri-*O*-benzyl- α -D-glucopyranoside **20** (46 mg, 18 %) as a diastereomeric mixture ($\alpha:\beta$, 0.47: 1.0)

Trial 11

Following *general glycosylation B* 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranose bromide **12** (52.9 mg, 0.09 mmol) and 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranoside (46.8 mg, 0.18 mmol) were dissolved in anhydrous DCM (3 mL). After 30 minutes stirring (R)-TRIP (3 mg, 0.004 mmol) and silver carbonate (13 mg, 0.05 mmol) were added to the reaction mixture. T.l.c (petrol: ethyl acetate, 4:1) then indicated the consumption of the glycosyl bromide **12** (R_f 0.58) and the formation of two products (R_f 0.40, 0.37) after 3 days. The reaction mixture was washed then purified by flash chromatography (petrol: ethyl acetate, 4:1) to afford 2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranosyl-(1 \rightarrow 6)-methyl-2,3,4-tri-*O*-benzyl- α -D-glucopyranoside **20** (6.1 mg, 10 %) as a diastereomeric mixture ($\alpha:\beta$, 0.92: 1.0).

Trial 12

Following *general glycosylation B* 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranose bromide **12** (52.9 mg, 0.09 mmol) and 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranoside (46.8 mg, 0.18

mmol) were dissolved in anhydrous DCM (3 mL). After 30 minutes stirring (S)-TRIP (3 mg, 0.004 mmol) and silver carbonate (14 mg, 0.05 mmol) were added to the reaction mixture. T.l.c (petrol: ethyl acetate, 4:1) then indicated the consumption of the glycosyl bromide **12** (R_f 0.58) and the formation of two products (R_f 0.40, 0.37) after 3 days. The reaction mixture was washed then purified by flash chromatography (petrol: ethyl acetate, 4:1) to afford 2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranosyl-(1 \rightarrow 6)-methyl-2,3,4-tri-*O*-benzyl- α -D-glucopyranoside **20** (29.6 mg, 16 %) as a diastereomeric mixture (α : β , 0.33: 1.0).

Trial 13

Following *general glycosylation B* 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranose bromide **12** (50 mg, 0.08 mmol) and 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranoside (44.2 mg, 0.17 mmol) were dissolved in anhydrous toluene (3 mL). After 30 minutes stirring (R)-TRIP (3 mg, 0.004 mmol) and silver carbonate (14 mg, 0.05 mmol) were added to the reaction mixture. T.l.c (petrol: ethyl acetate, 4:1) then indicated the consumption of the glycosyl bromide **12** (R_f 0.58) and the formation of two products (R_f 0.40, 0.37) after 4 days. The reaction mixture was washed then purified by flash chromatography (petrol: ethyl acetate, 4:1) to afford 2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranosyl-(1 \rightarrow 6)-methyl-2,3,4-tri-*O*-benzyl- α -D-glucopyranoside **20** (27.8 mg, 45 %) as a diastereomeric mixture (α : β , 0.46: 1.0).

Trial 14

Following *general glycosylation B* 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranose bromide **12** (123.4 mg, 0.21 mmol) and 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranoside (109.2 mg, 0.42 mmol) were dissolved in anhydrous toluene (5 mL). After 30 minutes stirring (S)-TRIP (7.9 mg, 0.01 mmol) and silver carbonate (34.7 mg, 0.13 mmol) were added to the reaction mixture. T.l.c (petrol: ethyl acetate, 4:1) then indicated the consumption of the glycosyl bromide **12** (R_f 0.58) and the formation of two products (R_f 0.40, 0.37) after 4 days. The reaction mixture was washed then purified by flash chromatography (petrol: ethyl acetate, 4:1) to afford 2,3,4,6-tetra-*O*-benzyl- α/β -D-glucopyranosyl-(1 \rightarrow 6)-methyl-2,3,4-tri-*O*-benzyl- α -D-glucopyranoside **20** (38.1 mg, 23 %) as a diastereomeric mixture (α : β , 0.28: 1.0).

Trial 15

Following *general glycosylation B* 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranose bromide **12** (59.5 mg, 0.1 mmol) and 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranoside (52 mg, 0.2 mmol) were dissolved in anhydrous tertiary butyl methyl ether (3 mL). After 30 minutes stirring (R)-TRIP (3.7 mg, 0.005 mmol) and silver carbonate (16.5 mg, 0.06 mmol) were added to the reaction mixture. T.l.c (petrol: ethyl acetate, 4:1) then indicated the consumption of the glycosyl bromide **12** (R_f 0.58) and the formation of two products (R_f 0.40, 0.37) after 7 days. The reaction mixture was washed then purified by flash chromatography (petrol: ethyl acetate, 4:1) to afford 2,3,4,6-tetra-*O*-benzyl- α/β -D-

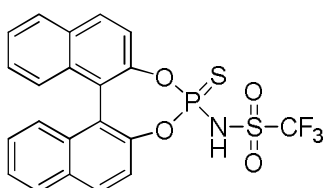
glucopyranosyl-(1→6)-methyl-2,3,4-tri-*O*-benzyl- α -D-glucopyranoside **20** (8.9 mg, 12 %) as a diastereomeric mixture (α : β , 0.06: 1.0).

Trial 16

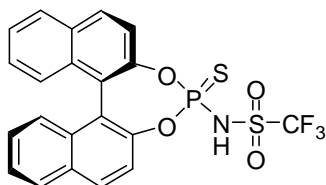
Following *general glycosylation B* 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranose bromide **12** (65.7 mg, 0.11 mmol) and 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranoside (57 mg, 0.22 mmol) were dissolved in anhydrous tertiary butyl methyl ether (3 mL). After 30 minutes stirring (S)-TRIP (4.1 mg, 0.006 mmol) and silver carbonate (18.4 mg, 0.07 mmol) were added to the reaction mixture. T.l.c (petrol: ethyl acetate, 4:1) then indicated the consumption the glycosyl bromide **12** (R_f 0.58) and the formation of two products (R_f 0.40, 0.37) after 7 days. The reaction mixture was washed then purified by flash chromatography (petrol: ethyl acetate, 4:1) to afford 2,3,4,6-tetra-*O*-benzyl- α / β -D-glucopyranosyl-(1→6)-methyl-2,3,4-tri-*O*-benzyl- α -D-glucopyranoside **20** (4.7 mg, 6 %) as a diastereomeric mixture (α : β , 0.04: 1.0).

Catalyst Synthesis

(\pm) {1,1'-binaphthalen-2,2'-yl}-*N*-triflyl-thiophosphoramidate **25**



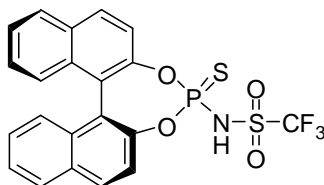
(±)-BINOL (0.5 g, 1.7 mmol) and triethylamine (0.53 mL, 2.25 mmol) were dissolved in DCM (5 mL) at 40°C. PSCl₃ (0.18 mL, 1.87 mmol) was then carefully added dropwise to the reaction mixture. After 4 hours t.l.c (petrol: ethyl acetate, 3:1) indicated the consumption of starting material (R_f 0.4) and formation of a single product (R_f 0.7). The reaction mixture was then partitioned between DCM (10 mL) and H₂O (10 mL). The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo* affording an intermediate product (694 mg, 1.7 mmol). A portion of the intermediate product (0.2 g, 0.47 mmol) was then dissolved in EtCN (10 mL) at 97°C. DMAP (5.7 mg, 0.047 mmol), NH₂Tf (142 mg, 0.95 mmol) and triethylamine (0.26 mL, 1.88 mmol) were then added to the reaction mixture. After 36 hours t.l.c (petrol: ethyl acetate, 1:2) indicated consumption of the starting material (R_f 0.9) and the formation of a product (R_f 0.2). The reaction was then quenched carefully with cold H₂O (10 mL), partitioned against ethyl acetate (10 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was then purified by flash chromatography (petrol: ethyl acetate, 1:2) to afford (±) {1,1'-binaphthalen-2,2'-yl}-*N*-triflyl-thiophosphoramidate **25** (52 mg, 34 %) as a brown foam-like solid. ν_{\max} (thin film/cm⁻¹) 3500 (w, NH); ¹H NMR (500 MHz, CDCl₃) δ ppm 7.34 - 7.47 (4H, m, Ar-H), 7.52 - 7.68 (4H, m, Ar-H), 7.98 - 8.20 (4H, m, Ar-H); ¹³C NMR (500 MHz, CDCl₃) δ ppm 121.4 (1C, q, *J* 90.7 Hz), 126.37 (2C), 127.15 (2C), 127.23 (2C), 127.30 (2C), 128.83 (2C), 131.62 (2C), 131.81 (2C), 132.12 (2C), 132.37 (1C), 132.51 (1C), 132.56 (2C); ¹⁹F NMR (300 MHz, CDCl₃) δ ppm -78.62; ³¹P NMR (300 MHz, CDCl₃) δ ppm 61.60; HRMS (ESI) Exact mass calculated for C₂₁H₁₂F₃NO₄PS₂ (M-1): 494 Found: 493.99

(R) {1,1'-binaphthalen-2,2'-yl}-N-triflyl-thiophosphoramidate 26

(R)-BINOL (0.2 g, 0.69 mmol) and triethylamine (0.21 mL, 1.57 mmol) were dissolved in DCM (2 mL) at 40°C. PSCl_3 (0.076 mL, 0.75 mmol) was then carefully added dropwise to the reaction mixture. After 4 hours t.l.c (petrol: ethyl acetate, 3:1) indicated the consumption of starting material (R_f 0.4) and formation of a single product (R_f 0.7). The reaction mixture was then partitioned between DCM (10 mL) and H_2O (10 mL). The organic layer was dried (MgSO_4), filtered and concentrated *in vacuo* affording an intermediate product (289 mg, 0.69 mmol) which was then dissolved in EtCN (10 mL) at 97°C. DMAP (8.4 mg, 0.069 mmol), NH_2Tf (205.6 mg, 1.38 mmol) and triethylamine (0.38 mL, 2.76 mmol) were then added to the reaction mixture. After 36 hours t.l.c (petrol: ethyl acetate, 1:2) indicated consumption of the starting material (R_f 0.9) and the formation of a product (R_f 0.2). The reaction was then quenched carefully with cold H_2O (10 mL), partitioned against ethyl acetate (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was then purified by flash chromatography (petrol: ethyl acetate, 1:2) to afford (R) {1,1'-binaphthalen-2,2'-yl}-N-triflyl-thiophosphoramidate **26** (115.3 mg, 34 %) as a brown foam-like solid. $[\alpha]_D^{20}$ -184.4 (*c*, 1.0 in CHCl_3); ν_{max} (thin film/ cm^{-1}) 3500 (w, NH); ^1H NMR (500 MHz, CDCl_3) δ ppm 7.34 - 7.47 (4H, m, Ar-H), 7.52 - 7.68 (4H, m, Ar-H), 7.98 - 8.20 (4H, m, Ar-H); ^{13}C NMR (500 MHz, CDCl_3) δ ppm 121.4 (1C, q, J 90.7 Hz), 126.37 (2C), 127.15 (2C), 127.23 (2C), 127.30 (2C), 128.83 (2C), 131.62 (2C), 131.81 (2C), 132.12 (2C), 132.37 (1C), 132.51 (1C), 132.56 (2C); ^{19}F NMR (300

MHz, CDCl₃) δ ppm -76.56; ³¹P NMR (300 MHz, CDCl₃) δ ppm 60.42; HRMS (ESI) Exact mass calculated for C₂₁H₁₂F₃NO₄PS₂ (M-1): 494 Found: 493.99

(S) {1,1'-binaphthalen-2,2'-yl}-N-triflyl-thiophosphoramidate 27



(S)-BINOL (0.2 g, 0.69 mmol) and triethylamine (0.21 mL, 1.57 mmol) were dissolved in DCM (2mL) at 40°C. PSCl₃ (0.076 mL, 0.75 mmol) was then carefully added dropwise to the reaction mixture. After 4 hours t.l.c (petrol: ethyl acetate, 3:1) indicated the consumption of starting material (R_f 0.4) and formation of a single product (R_f 0.7). The reaction mixture was then partitioned between DCM (10 mL) and H₂O (10 mL). The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo* affording an intermediate product (289 mg, 0.69 mmol) which was then dissolved in EtCN (10 mL) at 97°C. DMAP (8.4 mg, 0.069 mmol), NH₂Tf (205.6 mg, 1.38 mmol) and triethylamine (0.38 mL, 2.76 mmol) were then added to the reaction mixture. After 36 hours t.l.c (petrol: ethyl acetate, 1:2) indicated consumption of the starting material (R_f 0.9) and the formation of a product (R_f 0.2). The reaction was then quenched carefully with cold H₂O (10 mL), partitioned against ethyl acetate (10 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was then purified by flash chromatography (petrol:ethyl acetate, 1:2) to afford (S) {1,1'-binaphthalen-2,2'-yl}-N-triflyl-thiophosphoramidate **27** (135.7 mg, 39 %) as a brown foam-like solid. $[\alpha]_D^{20}$ +187.8 (c, 1.0 in CHCl₃); ν_{\max} (thin film/cm⁻¹) 3500 (w, NH); ¹H NMR (500 MHz, CDCl₃) δ ppm 7.30 - 7.44 (4H,

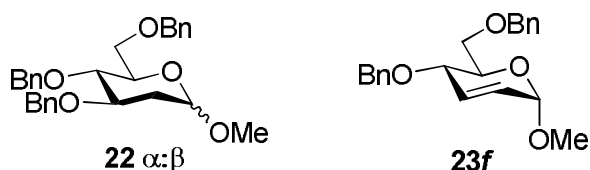
m, Ar-H), 7.47 - 7.64 (4H, m, Ar-H), 7.90 - 8.10 (4H, m, Ar-H); ^{13}C NMR (500 MHz, CDCl_3) δ ppm 121.4 (1C, q, J 90.7 Hz), 126.37 (2C), 127.15 (2C), 127.23 (2C), 127.30 (2C), 128.83 (2C), 131.62 (2C), 131.81 (2C), 132.12 (2C), 132.37 (1C), 132.51 (1C), 132.56 (2C); ^{19}F NMR (300 MHz, CDCl_3) δ ppm -77.63; ^{31}P NMR (300 MHz, CDCl_3) δ ppm -63.47; HRMS (ESI) Exact mass calculated for $\text{C}_{21}\text{H}_{12}\text{F}_3\text{NO}_4\text{PS}_2$ (M-1): 494 Found: 493.99

Glycal Catalyst Trials

General Glycosylation C - Glycals

A solution of 3,4,6-tri-*O*-benzyl-D-glucal **19** (1 eqv) and the glycosyl acceptor (3 eqv) in anhydrous solvent (3 mL) were added to a flame dried round bottom flask. The catalyst (CSA, \pm , R, S) was then added to the reaction mixture at RT. The reaction was monitored via t.l.c until 3,4,6-tri-*O*-benzyl-D-glucal **19** was consumed at which point the reaction was diluted with DCM (10 mL) and washed with saturated sodium bicarbonate solution (10 mL), H_2O (10 mL) and brine (10 mL). The mixture was then dried (MgSO_4), filtered, concentrated *in vacuo* and purified by flash chromatography to afford the respective glycoside.

Trial 17 - Methyl 3,4,6- tri-*O*-benzyl-2-deoxy-D-arabino-hexopyranose (**22** α : β) & Methyl 4,6-di-*O*-benzyl-2,3-dideoxy-D-erythro-hex-2-enopyranoside (**23f**)



Following *general glycosylation C* 3,4,6-tri-*O*-benzyl-D-glucal **19** (0.1 g, 0.23 mmol) and MeOH (0.029mL, 0.71 mmol) were dissolved in anhydrous DCM (3mL). (R) {1,1'-binaphthalen-2,2'-yl}-*N*-triflyl-thiophosphoramidate **26** (11.3 mg, 0.023 mmol) was then added to the reaction mixture at RT. After 4 hours t.l.c (ether: petrol, 3:7) indicated the consumption of 3,4,6-tri-*O*-benzyl-D-glucal **19** (R_f 0.54) and the formation of two products (R_f 0.35, 0.33). The reaction mixture was washed then purified by flash chromatography (ether: petrol, 3:7) to afford methyl 3,4,6-tri-*O*-benzyl-2-deoxy-D-arabino-hexopyranose (**22** α : β)^{44,43} and methyl 4,6-di-*O*-benzyl-2,3-dideoxy-D-erythro-hex-2-enopyranoside (**23f**)⁴¹ as an inseparable mixture (83.7 mg, 81 %, α : β :*f*, 0.52:1.00:0.65) ; **22** α) ¹H NMR (500 MHz, CDCl₃) δ ppm 1.73 (1H, ddd, $J_{1,2}$ 3.5, $J_{2,3}$ 12.2, $J_{2,2'}$ 12.2 Hz, H-2), 2.29 (1H, dd, $J_{2,2'}$ 13, $J_{2,3}$ 5.0 Hz, H-2'), 3.32 (3H, s, OMe), 3.63 - 3.79 (4H, m, H-3, H-4, H-6, H-6'), 3.97 (1H, ddd, $J_{4,5}$ 11.4, $J_{5,6}$ 8.5, $J_{5,6'}$ 5 Hz, H-5), 4.64 (1H, d, $J_{1,2}$ 3.7Hz, H-1), 4.52 - 4.90 (6H, m, 3 x OCH₂Ph), 7.27 - 7.37 (15H, m, Ar-H); **22** β) ¹H NMR (500 MHz, CDCl₃) δ ppm 1.64 (1H, dd, $J_{2,3}$ 11.0, $J_{2,2'}$ 12.3 Hz, H-2), 2.34 (1H, ddd, $J_{1,2}$ 1.0, $J_{2,2'}$ 12.3, $J_{2,3}$ 5 Hz, H-2'), 3.51 (3H, s, OMe), 3.60 - 3.79 (4H, m, H-3, H-4, H-6, H-6'), 3.97 (1H, ddd, $J_{4,5}$ 11.4, $J_{5,6}$ 8.5, $J_{5,6'}$ 5 Hz, H-5), 4.63 (1H, d, $J_{1,2}$ 3.6Hz, H-1), 4.52 - 4.90 (6H, m, 3 x OCH₂Ph), 7.27 - 7.37 (15H, m, Ar-H); **23f**) ¹H NMR (500 MHz, CDCl₃) δ ppm 3.44 (3H, s, OMe), 3.77 - 3.70 (2H, m, H-6, H-6'), 3.93 (1H, dt, J 9.3, 3.0 Hz, H-

5), 4.16 (1H, d, $J_{4,5}$ 9.3 Hz, H-4), 4.44 - 4.65 (4H, m, 2 x OCH₂Ph), 4.91 (1H, s, H-1), 5.76 (1H, d, $J_{2,3}$ 10.2 Hz, H-3), 6.06 (1H, d, $J_{2,3}$ 10.2 Hz, H-2), 7.22 - 7.34 (10H, m, Ar-H)

Trial 18

Following *general glycosylation C* 3,4,6-tri-*O*-benzyl-D-glucal **19** (0.1 g, 0.23 mmol) and MeOH (0.029mL, 0.71 mmol) were dissolved in anhydrous DCM (3mL). (S) {1,1'-binaphthalen-2,2'-yl}-*N*-triflyl-thiophosphoramidate **27** (11.3 mg, 0.023 mmol) was then added to the reaction mixture at RT. After 4 hours t.l.c (ether: petrol, 3:7) indicated the consumption of 3,4,6-tri-*O*-benzyl-D-glucal **19** (R_f 0.54) and the formation of two products (R_f 0.35, 0.33). The reaction mixture was washed then purified by flash chromatography (ether: petrol, 3:7) to afford methyl 3,4,6-tri-*O*-benzyl-2-deoxy-D-arabino-hexopyranose (**22 α : β**) and methyl 4,6-di-*O*-benzyl-2,3-dideoxy-D-erythro-hex-2-enopyranoside (**23f**) as an inseparable mixture (80.1 mg, 78 %, α : β :*f*, 0.46:1.0:0.96)

Trial 19

Following *general glycosylation C* 3,4,6-tri-*O*-benzyl-D-glucal **19** (0.1 g, 0.23 mmol) and MeOH (0.029mL, 0.71 mmol) were dissolved in anhydrous toluene (3mL). (S) {1,1'-binaphthalen-2,2'-yl}-*N*-triflyl-thiophosphoramidate **27** (11.3 mg, 0.023 mmol) was then added to the reaction mixture at RT. After 1 day t.l.c (ether: petrol, 3:7) indicated the consumption of 3,4,6-tri-*O*-benzyl-D-glucal **19** (R_f 0.54) and the formation of two products (R_f 0.35, 0.33). The reaction mixture was washed then purified by flash chromatography (ether: petrol, 3:7) to afford methyl 3,4,6-tri-*O*-benzyl-2-deoxy-D-arabino-hexopyranose

(**22** α : β) and methyl 4,6-di-*O*-benzyl-2,3-dideoxy-D-erythro-hex-2-enopyranoside (**23f**) as an inseparable mixture (98.1 mg, 84 %, α : β :*f*, 0.51:1.0:0.44)

Trial 20

Following *general glycosylation C* 3,4,6-tri-*O*-benzyl-D-glucal **19** (0.1 g, 0.23 mmol) and MeOH (0.029mL, 0.71 mmol) were dissolved in anhydrous toluene (3mL). (R) {1,1'-binaphthalen-2,2'-yl}-*N*-triflyl-thiophosphoramidate **26** (11.3 mg, 0.023 mmol) was then added to the reaction mixture at RT. After 1 day t.l.c (ether: petrol, 3:7) indicated the consumption of 3,4,6-tri-*O*-benzyl-D-glucal **19** (R_f 0.54) and the formation of two products (R_f 0.35, 0.33). The reaction mixture was washed then purified by flash chromatography (ether: petrol, 3:7) to afford methyl 3,4,6-tri-*O*-benzyl-2-deoxy-D-arabino-hexopyranose (**22** α : β) and methyl 4,6-di-*O*-benzyl-2,3-dideoxy-D-erythro-hex-2-enopyranoside (**23f**) as an inseparable mixture (93.4 mg, 83 %, α : β :*f*, 0.56:1.0:0.46)

Trial 21

Following *general glycosylation C* 3,4,6-tri-*O*-benzyl-D-glucal **19** (0.1 g, 0.23 mmol) and MeOH (0.029mL, 0.71 mmol) were dissolved in anhydrous toluene (3mL). (S) {1,1'-binaphthalen-2,2'-yl}-*N*-triflyl-thiophosphoramidate **27** (11.3 mg, 0.023 mmol) was then added to the reaction mixture at 0°C. After 4 days t.l.c (ether: petrol, 3:7) indicated the consumption of 3,4,6-tri-*O*-benzyl-D-glucal **19** (R_f 0.54) and the formation of two products (R_f 0.35, 0.33). The reaction mixture was washed then purified by flash chromatography (ether: petrol, 3:7) to afford methyl 3,4,6-tri-*O*-benzyl-2-deoxy-D-arabino-hexopyranose

(**22** α : β) and methyl 4,6-di-*O*-benzyl-2,3-dideoxy-D-erythro-hex-2-enopyranoside (**23f**) as an inseparable mixture (70.1 mg, 67 %, α : β :*f*, 0.49:1.0:0.26)

Trial 22

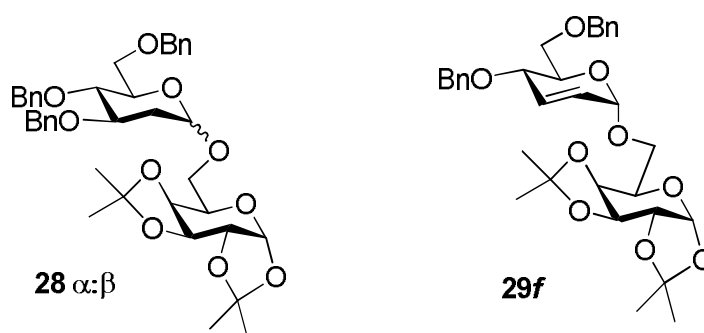
Following *general glycosylation C* 3,4,6-tri-*O*-benzyl-D-glucal **19** (0.1 g, 0.23 mmol) and MeOH (0.029mL, 0.71 mmol) were then dissolved in anhydrous toluene (3mL). (S) {1,1'-binaphthalen-2,2'-yl}-*N*-triflyl-thiophosphoramidate **27** (3.4 mg, 0.006 mmol) was then added to the reaction mixture at RT. After 2 days t.l.c (ether: petrol, 3:7) indicated the consumption of 3,4,6-tri-*O*-benzyl-D-glucal **19** (R_f 0.54) and the formation of two products (R_f 0.35, 0.33). The reaction mixture was washed then purified by flash chromatography (ether: petrol, 3:7) to afford methyl 3,4,6-tri-*O*-benzyl-2-deoxy-D-arabino-hexopyranose (**22** α : β) and methyl 4,6-di-*O*-benzyl-2,3-dideoxy-D-erythro-hex-2-enopyranoside (**23f**) as an inseparable mixture (71.6 mg, 69 %, α : β :*f*, 0.59:1.0:0.35)

Trial 23

Following *general glycosylation C* 3,4,6-tri-*O*-benzyl-D-glucal **19** (0.1 g, 0.23 mmol) and MeOH (0.029mL, 0.71 mmol) were then dissolved in anhydrous toluene (3mL). (S) {1,1'-binaphthalen-2,2'-yl}-*N*-triflyl-thiophosphoramidate **27** (3.4 mg, 0.006 mmol) was then added to the reaction mixture at 0°C. After 7 days t.l.c (ether: petrol, 3:7) indicated the consumption of 3,4,6-tri-*O*-benzyl-D-glucal **19** (R_f 0.54) and the formation of two products (R_f 0.35, 0.33). The reaction mixture was washed then purified by flash chromatography (ether: petrol, 3:7) to afford methyl 3,4,6-tri-*O*-benzyl-2-deoxy-D-arabino-hexopyranose

(**22** α : β) and methyl 4,6-di-*O*-benzyl-2,3-dideoxy-D-erythro-hex-2-enopyranoside (**23f**) as an inseparable mixture (38.4 mg, 37 %, α : β :*f*, 0.53:1.0:0.24)

Trial 24 - 3,4,6-tri-*O*-benzyl-2-deoxy- α / β -D-arabino-hexopyranosyl-(1 \rightarrow 6)-1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranose (**28** α : β) and 4,6-di-*O*-benzyl-2,3-dideoxy- α -D-erythro-hex-2-enopyranosyl-(1 \rightarrow 6)-1,2:3,4-di-*O*-isopropylidene-D-galactopyranoside (**29f**)



Following *general glycosylation C* 3,4,6-tri-*O*-benzyl-D-glucal **19** (0.1 g, 0.23 mmol) and 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranoside (179 mg, 0.69 mmol) were dissolved in anhydrous toluene (3mL). (S) {1,1'-binaphthalen-2,2'-yl}-*N*-triflyl-thiophosphoramidate **27** (3.4 mg, 0.006 mmol) was then added to the reaction mixture at 0°C. After 7 days t.l.c (petrol: ethyl acetate, 3:1) indicated the consumption of 3,4,6-tri-*O*-benzyl-D-glucal **19** (R_f 0.54) and the formation of two products (R_f 0.40, 0.43). The reaction mixture was washed then purified by flash chromatography (petrol: ethyl acetate, 3:1) to afford 3,4,6-tri-*O*-benzyl-2-deoxy- α / β -D-arabino-hexopyranosyl-(1 \rightarrow 6)-1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranose (**28** α : β)⁴² and 4,6-di-*O*-benzyl-2,3-dideoxy- α -D-erythro-hex-2-enopyranosyl-(1 \rightarrow 6)-1,2:3,4-di-*O*-isopropylidene-D-galactopyranoside (**29f**)⁴¹ as an inseparable mixture (39.5 mg, 26 %, α : β :*f*, 1.03:1.0:0.02) **28** α) ¹H NMR (500 MHz, CDCl₃) δ ppm 1.33 (3H, s, CH₃), 1.34 (3H, s, CH₃), 1.43 (3H, s, CH₃), 1.52 (3H, s, CH₃), 1.73 (1H, m, H-

2_{axb}), 2.33 (1H, m, H-2_{eqb}), 3.49 - 3.84 (6H, m, H-6a, H-6'a, H-4b, H-5b, H-6b, H-6'b), 3.91 - 4.05 (2H, m, H-5a, H-3b), 4.22 (1H, dd, $J_{3a,4a}$ 8.1, $J_{4a,5a}$ 1.6 Hz, H-4a), 4.31 (1H, dd, $J_{1a,2a}$ 5.0, $J_{2a,3a}$ 2.4 Hz, H-2a), 4.46 - 4.71 (6H, m, H-3a, 2.5 x OCH₂Ph), 4.88 (1H, d, $J_{a,b}$ 10.7 Hz, 0.5 x OCH₂Ph), 5.02 (1H, d, $J_{2axb,1b}$ 3.6 Hz, H-1b), 5.51 (1H, d, $J_{1a,2a}$ 4.8 Hz, H-1a), 7.14 - 7.37 (15H, m, Ar-H); **28 β**) ¹H NMR (500 MHz, CDCl₃) δ ppm 1.33 (3H, s, CH₃), 1.34 (3H, s, CH₃), 1.43 (3H, s, CH₃), 1.55 (3H, s, CH₃), 1.63 - 1.71 (1H, m, H-2_{eqb}), 2.47 (1H, m, H-2_{axb}), 3.49 - 3.84 (6H, m, H-6a, H-6'a, H-4b, H-5b, H-6b, H-6'b), 3.55 (1H, d, $J_{1,2}$ 9.6 Hz, H-1b), 3.91 - 4.05 (2H, m, H-5a, H-3b), 4.22 (1H, dd, $J_{3a,4a}$ 8.1, $J_{4a,5a}$ 1.6 Hz, H-4a), 4.31 (1H, dd, $J_{1a,2a}$ 5.0, $J_{2a,3a}$ 2.4 Hz, H-2a), 4.46 - 4.71 (6H, m, H-3a, 2.5 x OCH₂Ph), 4.91 (1H, d, $J_{a,b}$ 10.8 Hz, 0.5 x OCH₂Ph), 5.56 (1H, d, $J_{1a,2a}$ 4.8 Hz, H-1a) 7.14 - 7.37 (15H, m, Ar-H); **29 α**) ¹H NMR (500 MHz, CDCl₃) δ ppm 1.32 (3H, s), 1.33 (3H, s), 1.43 (3H, s), 1.51 (3H, s), 3.66 - 3.94 (5H, m), 4.02 (1H, t, J 6.9 Hz), 4.21 - 4.31 (2H, m), 4.42 (1H, d, J 11.4 Hz), 4.48 (1H, d, J 12.3 Hz), 4.57 - 4.60 (2H, m), 4.66 (1H, d, J 12.3 Hz), 5.09 (1H, s), 5.51 (1H, d, J 5.1 Hz), 5.78 (1H, d, $J_{2,3}$ 10.2 Hz, H-3b), 6.06 (1H, d, $J_{2,3}$ 10.2 Hz, H-2b), 7.21 - 7.34 (10H, m, Ar-H)

Trial 25

Following *general glycosylation C* 3,4,6-tri-*O*-benzyl-D-glucal **19** (0.1 g, 0.23 mmol) and 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranoside (179 mg, 0.69 mmol) were dissolved in anhydrous toluene (3mL). (R) {1,1'-binaphthalen-2,2'-yl}-*N*-triflyl-thiophosphoramidate **26** (3.4 mg, 0.006 mmol) was then added to the reaction mixture at 0°C. After 7 days t.l.c (petrol: ethyl acetate, 3:1) indicated the consumption of 3,4,6-tri-*O*-benzyl-D-glucal **19** (R_f 0.54) and the formation of two products (R_f 0.40, 0.43). The reaction mixture was washed then purified by flash chromatography (petrol: ethyl acetate, 3:1) to afford 3,4,6-tri-*O*-benzyl-2-

deoxy- α/β -D-arabino-hexopyranosyl-(1 \rightarrow 6)-1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranose (**28 $\alpha:\beta$**) and 4,6-di-*O*-benzyl-2,3-dideoxy- α -D-*erythro*-hex-2-enopyranosyl-(1 \rightarrow 6)-1,2:3,4-di-*O*-isopropylidene-D-galactopyranoside(**29*f***) as an inseparable mixture (43.6 mg, 29 %, $\alpha:\beta:f$, 1.36:1.0:0.35)

Trial 26

Following *general glycosylation C* 3,4,6-tri-*O*-benzyl-D-glucal **19** (0.1 g, 0.23 mmol) and 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranoside (179 mg, 0.69 mmol) were dissolved in anhydrous toluene (3mL). (S) {1,1'-binaphthalen-2,2'-yl}-*N*-triflyl-thiophosphoramidate **27** (11.3 mg, 0.023 mmol) was then added to the reaction mixture at RT. After 2 days t.l.c (petrol: ethyl acetate, 3:1) indicated the consumption of 3,4,6-tri-*O*-benzyl-D-glucal **19** (R_f 0.54) and the formation of two products (R_f 0.40, 0.43). The reaction mixture was washed then purified by flash chromatography (petrol: ethyl acetate, 3:1) to afford 3,4,6-tri-*O*-benzyl-2-deoxy- α/β -D-arabino-hexopyranosyl-(1 \rightarrow 6)-1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranose (**28 $\alpha:\beta$**) and 4,6-di-*O*-benzyl-2,3-dideoxy- α -D-*erythro*-hex-2-enopyranosyl-(1 \rightarrow 6)-1,2:3,4-di-*O*-isopropylidene-D-galactopyranoside (**29*f***) as an inseparable mixture (119.2 mg, 78 %, $\alpha:\beta:f$, 2.05:1.0:0.65)

Trial 27

Following *general glycosylation C* 3,4,6-tri-*O*-benzyl-D-glucal **19** (0.1 g, 0.23 mmol) and 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranoside (179 mg, 0.69 mmol) were dissolved in anhydrous toluene (3mL). (R) {1,1'-binaphthalen-2,2'-yl}-*N*-triflyl-thiophosphoramidate **26**

(11.3 mg, 0.023 mmol) was then added to the reaction mixture at RT. After 2 days t.l.c (petrol: ethyl acetate, 3:1) indicated the consumption of 3,4,6-tri-*O*-benzyl-D-glucal **19** (R_f 0.54) and the formation of two products (R_f 0.40, 0.43). The reaction mixture was washed then purified by flash chromatography (petrol: ethyl acetate, 3:1) to afford 3,4,6-tri-*O*-benzyl-2-deoxy- α/β -D-arabino-hexopyranosyl-(1 \rightarrow 6)-1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranose (**28 α : β**) and 4,6-di-*O*-benzyl-2,3-dideoxy- α -D-erythro-hex-2-enopyranosyl-(1 \rightarrow 6)-1,2:3,4-di-*O*-isopropylidene-D-galactopyranoside (**29 f**) as an inseparable mixture (126.2 mg, 82 %, α : β : f , 2.26:1.0:0.55)

Trial 28 – CSA Trial

Following *general glycosylation C* 3,4,6-tri-*O*-benzyl-D-glucal **19** (0.1 g, 0.23 mmol) and MeOH (0.03mL, 0.71 mmol) were dissolved in anhydrous DCM (3mL). *D*-(+)-camphorsulfonic acid (5.3mg, 0.02 mmol) was then added to the reaction mixture at RT. After 1 day t.l.c (ether: petrol, 3:7) indicated the consumption of 3,4,6-tri-*O*-benzyl-D-glucal **19** (R_f 0.5) and the formation of two products (R_f 0.35, 0.33). The reaction mixture was washed then purified by flash chromatography (ether: petrol, 3:7) to afford methyl 3,4,6- tri-*O*-benzyl-2-deoxy-D-arabino-hexopyranose (**22 α : β**) and methyl 4,6-di-*O*-benzyl-2,3-dideoxy- α -D-erythro-hex-2-enopyranoside (**23 f**) as an inseparable mixture (73.1 mg, 71 %, α : β : f , 0.82, 1.0, 0.28)

Trial 29 – Racemic catalyst

Following *general glycosylation C* 3,4,6-tri-*O*-benzyl-D-glucal **19** (0.1 g, 0.23 mmol) and MeOH (0.03mL, 0.71 mmol) were dissolved in anhydrous DCM (3mL). (±) {1,1'-binaphthalen-2,2'-yl}-*N*-triflyl-thiophosphoramidate **25** (11.3 mg, 0.023 mmol) was then added to the reaction mixture at RT. After 2 days t.l.c (ether: petrol, 3:7) indicated the consumption of 3,4,6-tri-*O*-benzyl-D-glucal **19** (R_f 0.5) and the formation of two products (R_f 0.35, 0.33). The reaction mixture was washed then purified by flash chromatography (ether: petrol, 3:7) to afford methyl 3,4,6- tri-*O*-benzyl-2-deoxy-D-arabino-hexopyranose (**22 α : β**) and methyl 4,6-di-*O*-benzyl-2,3-dideoxy- α -D-erythro-hex-2-enopyranoside (**23f**) as an inseparable mixture (73.1 mg, 57 %, α : β :*f*, 0.48, 1.0, 0.76).

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