NEIGHBOURING GROUP DIRECTION IN ASYMMETRIC GLYCOSYLATION

TREBALL DE FI DE GRAU

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Nottingham, May 2015

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ACKNOWLEDGEMENTS

I would like to express my gratitude to all people who have helped me during my project. But, especially to my supervisor, Laurence Grey for his motivation, patience and for all the time that he has spent helping and advising me.

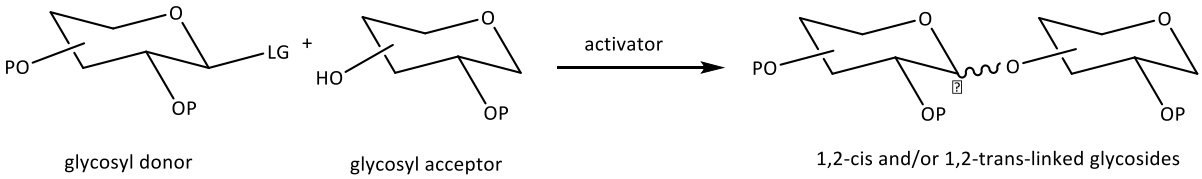
I would also like to gratefully thank Dr Raymond Leslie who has brought me this opportunity and their constant interest in my work.

Finally, I would like to thank my family and friends, for the constant support in all moments.

CONTENTS

Abstract

The stereoselective *cis*-glycosyde linkage still remain as a difficult task although the significant improvements in the last two decades. One of the best methods to get the stereoselective *cis*-glycosyde linkage is by Intramolecular Aglycone Delivery (IAD).[1] This project proposes the IAD strategies to form the donor with the newest 2-naphthylmethyl (NAP) tether to goal the stereospecific 1,2-*cis* linkages.[2]



1. INTRODUCTION

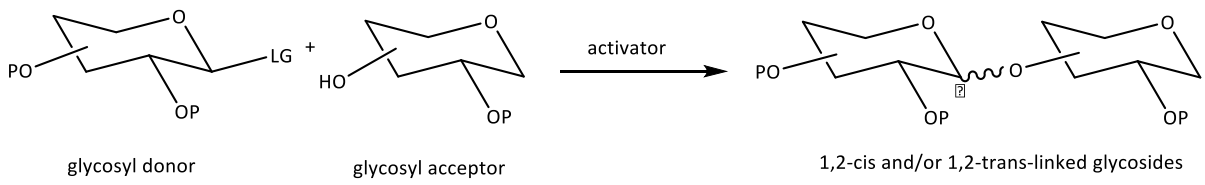
1.1 Area of development

This project has taken place in NTU Clifton campus of Nottingham. Specifically at the School of Science and Technology where my tutor, Dr Raymond Leslie, is researching about 'Neighbouring Group Direction' as a method for stereoselective glycosylation. My supervisor was Laurence Grey who is doing his PhD in the Leslie's group, focused on a novel approach to intramolecular aglycone delivery.

1.2 Antecedents

Carbohydrates are the natural compounds more abundant on the Earth. As a result they are involved in many cellular processes such as bacterial infections and development and growth of tumours. The medicine would be further improved if we could rely on the detailed knowledge of the structure, conformation and properties of carbohydrates molecules. Although significant improvements of glycoside and oligosaccharide synthesis a variety of synthetic targets containing glycosidic linkages cannot yet be directly accessed.[3]

All the cellular recognition processes invariably rely on the monosaccharides in the polysaccharides chain units are joined via glycosidic bonds.[4] These linkages are formed by a glycosylation reaction, most commonly a promoter-assisted nucleophilic displacement of the leaving group (LG) of the glycosyl donor with the hydroxyl moiety of the glycosyl acceptor. Other functional groups on both the donor and the acceptor are temporarily masked with protecting groups (P). These reactions are most commonly performed in the presence of an activator: promoter or catalyst (scheme 1). As the new glycosidic linkage creates a chirality center, particular care has to be taken with regard to the stereoselectivity.

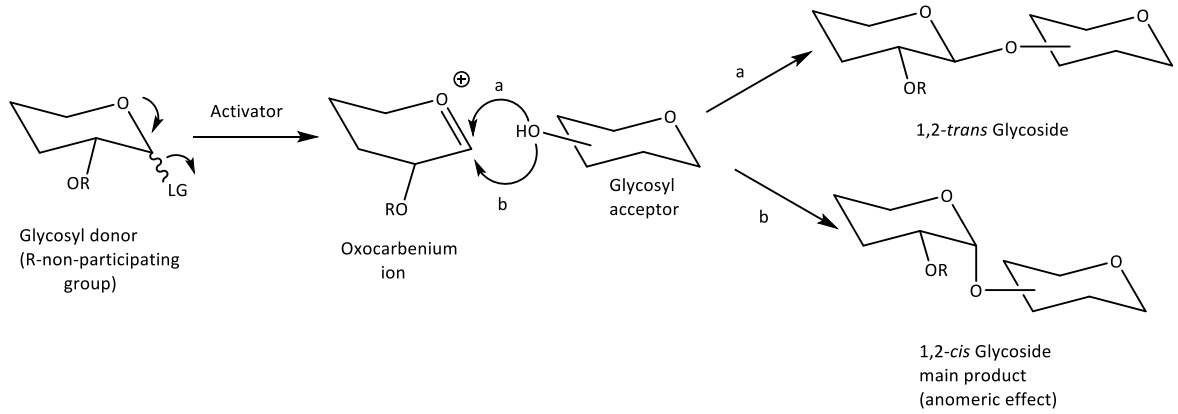


Scheme 1. General Glycosylation reaction.

Recently, many developments in the area of chemical glycosylation still remain compromised when applied the stereoselective synthesis of difficult glycosidic linkages, specially 1,2-*cis* glycosides. In spite of the considerable progress in this field, no universal method for the synthesis of these linkages has yet emerged.

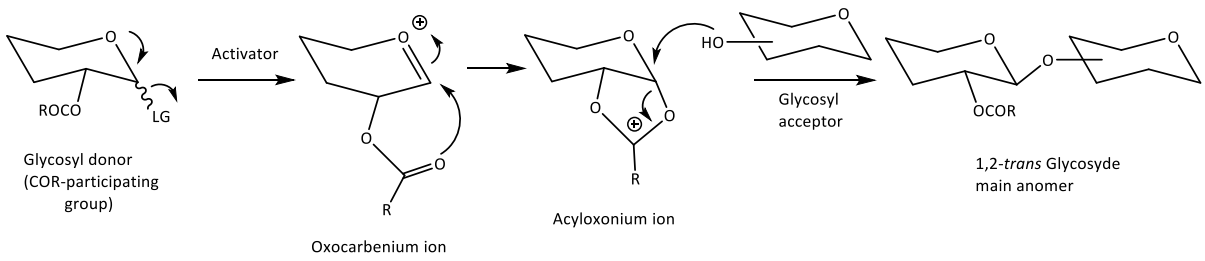
1.2.1 General reaction mechanism

The glycosylation reaction involves nucleophilic displacement at the anomeric center.[3] As the reaction takes place at the secondary carbon atom with the use of weak nucleophiles (sugar acceptors), it often follows a unimolecular S_N1 mechanism. The only possibility to intramolecularly stabilize glycosyl cation formed from the gycosyl donor bearing a non-participating group (generally benzyl group) is by resonance from O5 that results in oxocarbenium ion (Scheme 2). The nucleophilic attack would be almost equally possible from either top (*trans*, β) or the bottom face (*cis*, α) of the ring. However, the α-product is thermodynamically favoured because of the so-called anomeric effect (explained in the next point).



Scheme 2. Non-Participating Neighbouring groups.

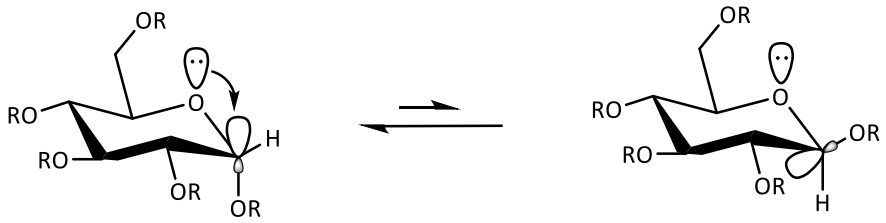
1,2-*trans* Glycosidic linkage can be stereoselectively formed with the use of a neighbouring participating group, generally an acyl moiety. These glycosylations proceed via a bicyclic intermediate, acyloxonium (Scheme 3), formed as a result of the activator-assisted departure of the leaving group followed by the intramolecular stabilization of the glycosyl cation. In this case, the attack of a nucleophile (alcohol, glycosyl acceptor) is only possible from the top face of the ring, therefore allowing stereoselective formation of a 1,2-*trans* glycoside.



Scheme 3. Participating Neighbouring groups.

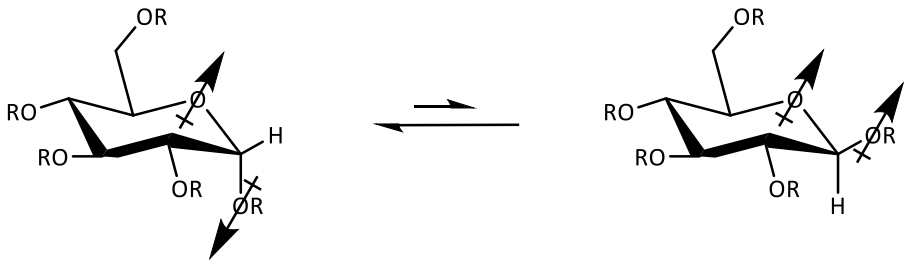
1.2.2 Anomeric effect

The anomeric effect is defined as the preference of electronegative substituent of the glycosyl donor to be axially rather equatorially oriented in opposition to the steric effect, which normally leads to a preference for the equatorial conformation.[5] There are two main theories that explaining this effect. The most common 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 (scheme 4).[4]



Scheme 4. The hyperconjugation- anomeric effect.

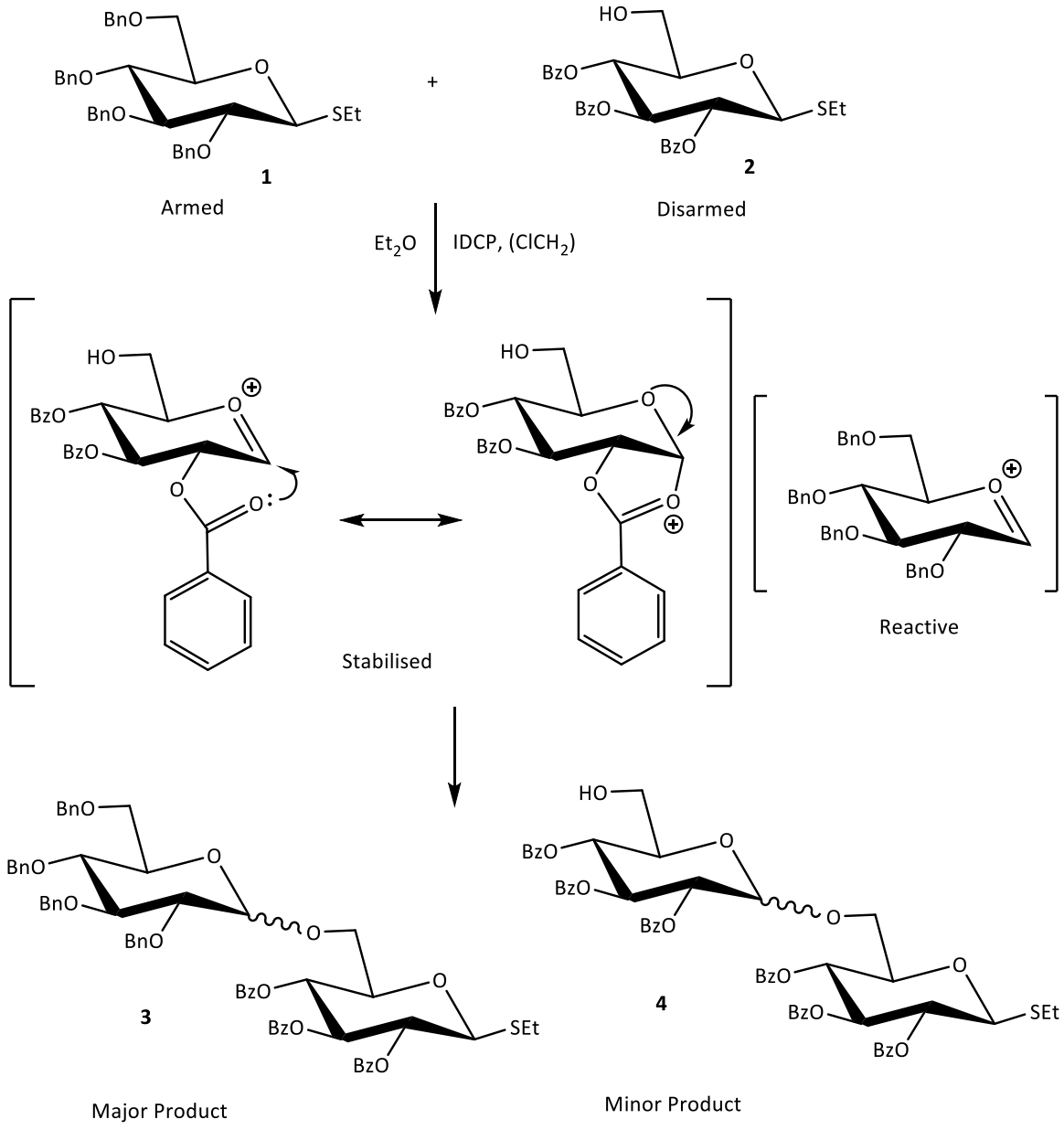
The complementary theory proposes that orbital repulsion as a result of dipole alignment disfavours the equatorial β-configuration (scheme 5). Therefore, the axial α-configuration is more favoured because the dipoles are opposed.[6]



Scheme 5. The dipole alignment- anomeric effect.

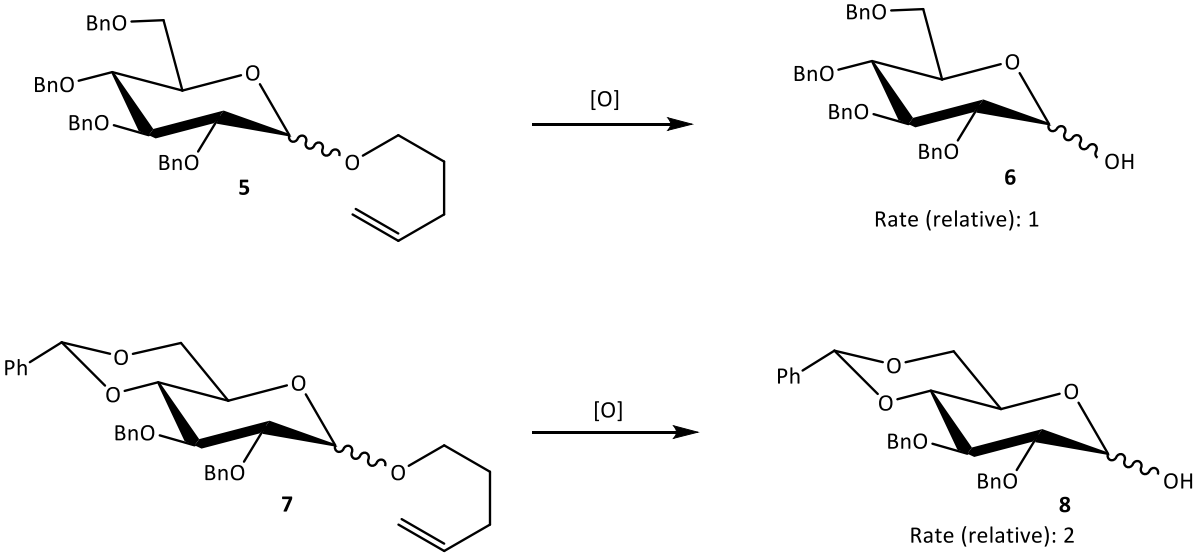
1.2.3 Armed -disarmed effect

One important factor that effects glycoside bond formation is the armed – disarmed effect. This outcome is a consequence that protecting groups have on the oxocarbenium ion transition state. It can be disseminated into two types, torsional and electronic. Scheme 6 outlines the electronic effect,[3] whereby the oxocarbenium ion is stabilised by ester protecting groups. The reaction is between an ether protected glycoside donor **1**, and an ester protected acceptor-donor **2**. The accepting of the ether protected glycoside(**1**) with the ester protected(**2**) proceeds magnitudes faster than with the self-accepting ester donor.



Scheme 6. The electronic armed-disarmed effect.

The other way to disarm a glycoside is through causing torsional strain.[7] In the formation of the anomeric oxocarbenium ion, the carbohydrate assumes a half chair conformation. It is possible to increase the energy of this conformational change through cyclic protecting groups, such as the 4,6-O-benzylidene (**7**) or an acetenide (Scheme 7).



Scheme 7. The torsional armed-disarmed effect on hydrolysis rate.

2. OBJECTIVES

The present study is aimed at synthesize a donor able to form the selective 1,2-*cis*-glycoside bond efficiently via participation of a neighbouring group functionality.

The following objectives, which have pursued, begin for purposes of personal knowledge and then, the goals of this work:

- To immerse in the world of carbohydrates, especially in the glycoside reactions.
- To look in depth into scientific research of new and more efficient donor for the synthesis of disaccharides or oligosaccharides in high yields and produce fewer by-products.
- To know the limits and the range of applicability of this donor.

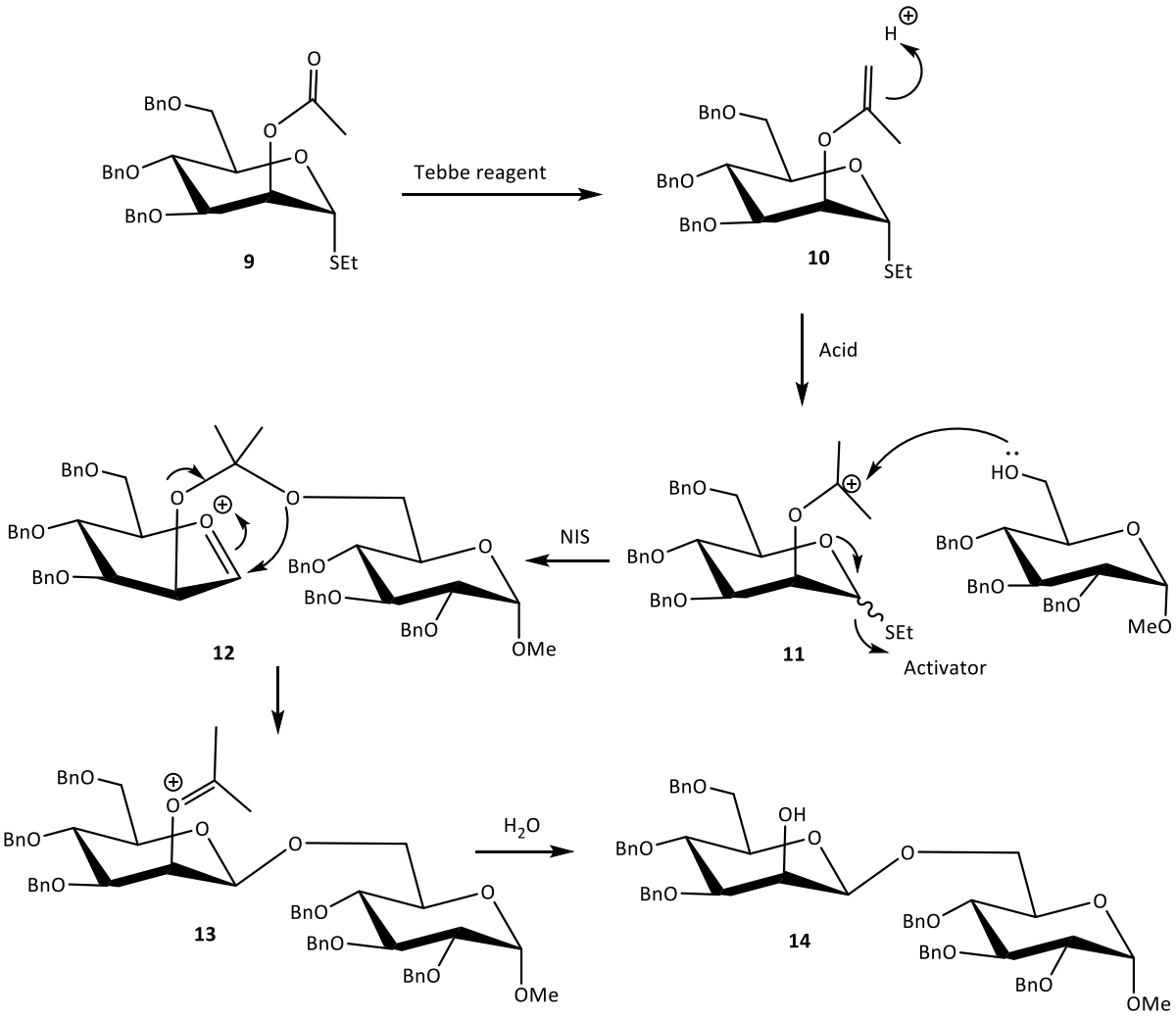
3. BASIS

3.1 Intramolecular Aglycon Delivery

The intramolecular aglycon delivery (IAD) concept for intramolecular glycosylations has gained significant applications for oligosaccharide synthesis. Originally developed for the highly stereoselective synthesis of β-mannosidic linkages, still an imminent problem in saccharide synthesis and later extended to other glycoside syntheses.[1] IAD is a particular type of intramolecular glycosylation strategy, wherein the glycosyl acceptor is temporarily appended to the 2-hydroxyl group of a glycosyl donor through a short linker. The first so-called 'tethering' step, that is the linking of donor and acceptor, is followed by the activation of the glycosyl donor, which subsequently furnishes the 1,2-*cis* glycoside in a completely setereoselective fashion .[8]

3.1.1 Acetal tethering

The first example for this concept was presented by Barresi and Hindsgaul in 1991 and it was then fully published in 1994.[3] Their research provides a backbone to which further research in stereoselective glycoside delivery systems could rapidly proceed. Their method uses a carbon tethering system (scheme 8) and proceeds via NIS – acid activation of C2 glycosidic isopropylene **10** to form an isopropyl oxocarbenium ion **11**, to which the glycoside acceptor will bind, and then migrate to the anomeric position upon hydrolysis to yield **14**.[1]

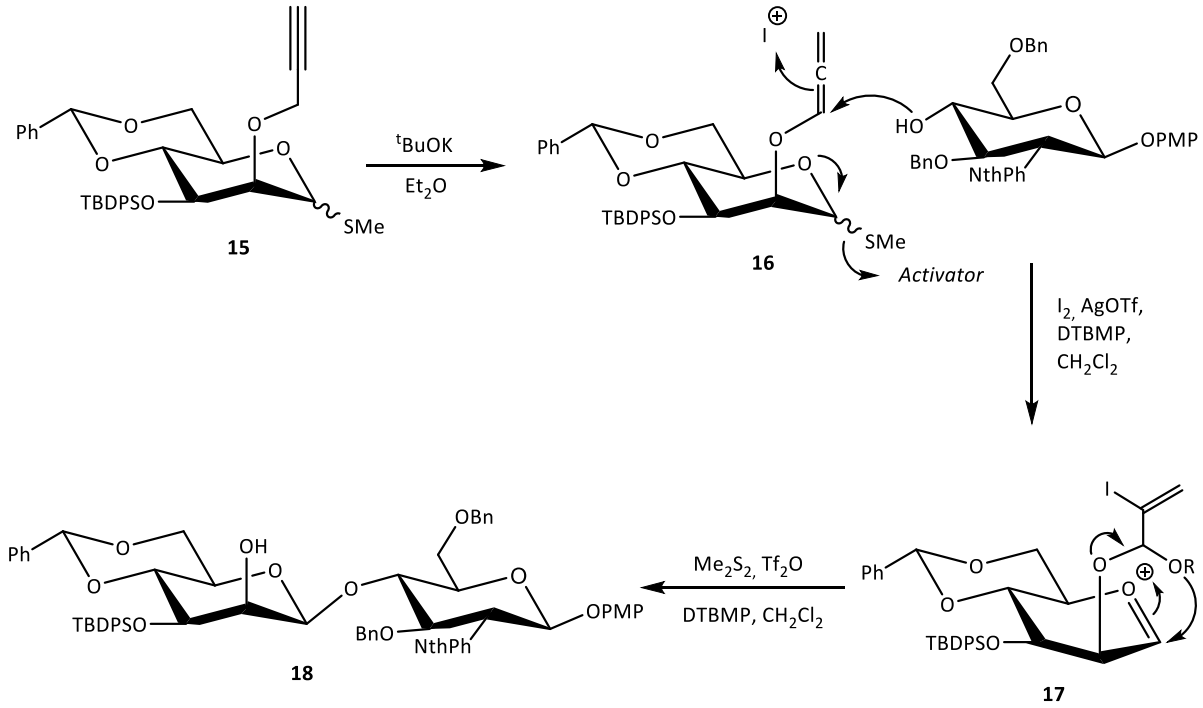


Scheme 8. Barresi and Hindsgaul intramolecular aglycone delivery.

They reported complete anomeric selectivity, and optimised the reaction to achieve yields up to 77%. However, the major drawback are rather low yields when this concept is applied to the synthesis of more complex oligosaccharides, where both the acetalization step and the IAD glycosylation proceed in less than 30% yield owing to side reactions.[2, 9, 10, 11]

3.1.2 Iodonium tethering

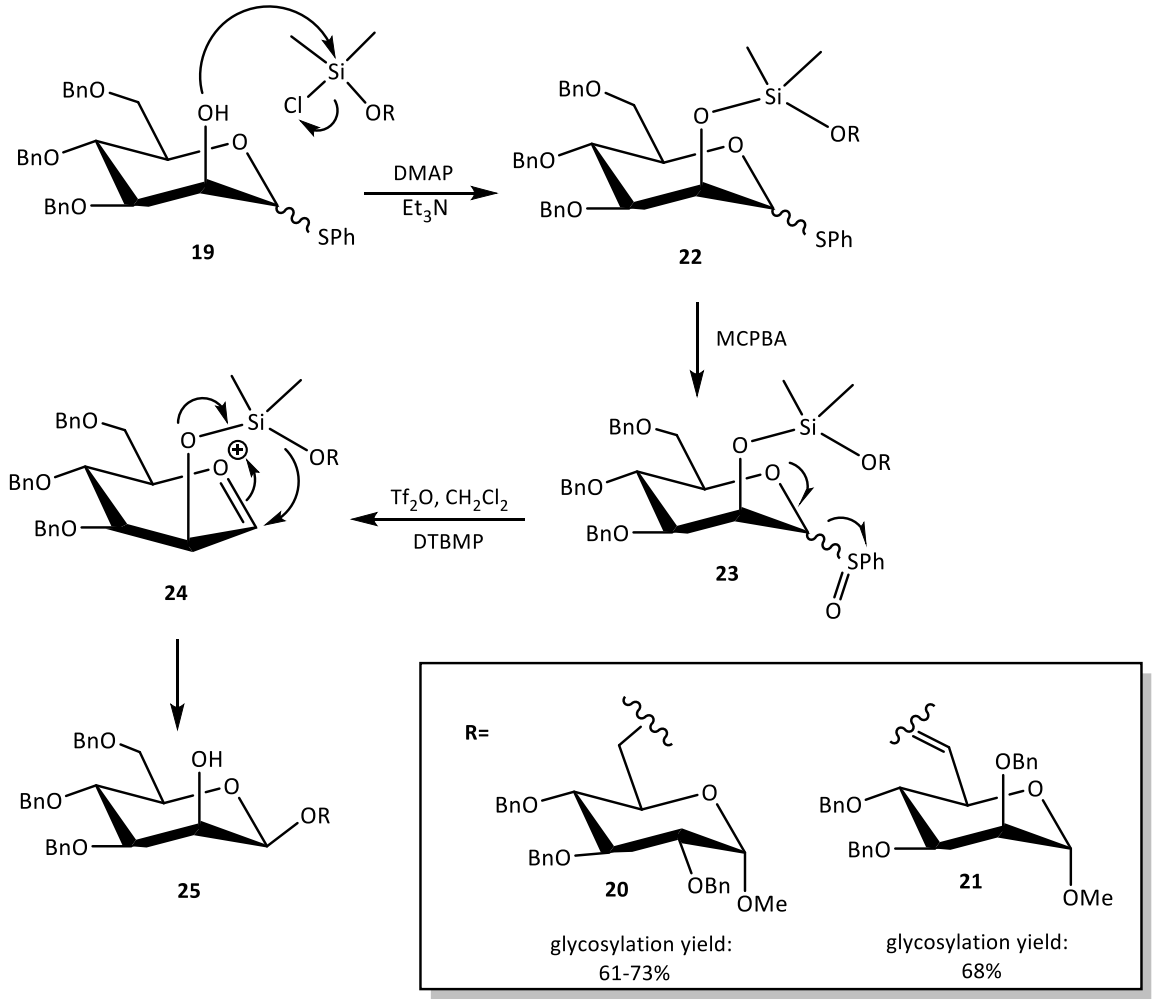
Fairbanks has developed a notable carbon tethering aglycone delivery system that circumvents the above-mentioned problems and allows for the efficient preparation of complex oligosaccharides (scheme 9). Their method,[8] of propargyl mediated intramolecular alglycone delivery, proceeds via basic treatment of the glycosidic C2 propargyl group **15**, to form the allene **16**. Treatment with iodine, silver triflate, 2,6-di-tert-butyl-4-methylpyridine and the glycoside acceptor gave the tethered dimer **17**. Finally activation of the anomeric leaving group allows migration of the glycoside acceptor to the anomeric position to yield **18**. They reported complete stereoselectivity, with a yield of 81%.[12]



Scheme 9. Propargyl mediated intramolecular aglycone delivery.

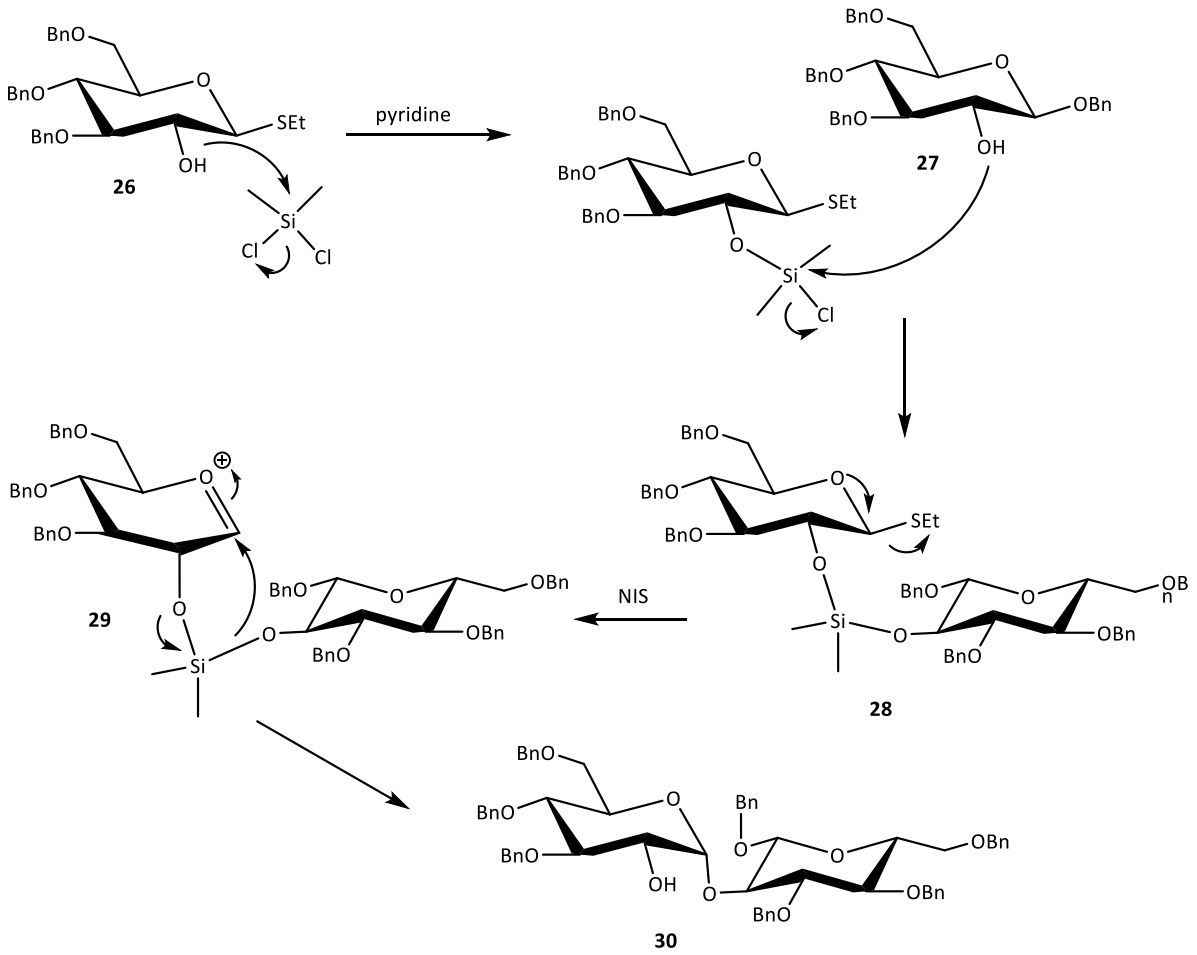
3.1.3 Silicon tethering

Stork developed an intramolecular delivery system that implemented a silicon tether (scheme 10). [13] This reaction proceeds via temporary silyl tether that is generated between **19** and **20** or **21** to give tethered dimer **22**. Oxidation of the thioether leaving group to yield sulphoxide **23** allowed the oxocarbenium ion formation to self-activate with departure of the leaving group to give via **24**, the temporary silyl tether is then cleaved with an aqueous work up to yield **25**. [14]



Scheme 10. Intramolecular aglycone delivery via temporary dimethyl silyl tether.

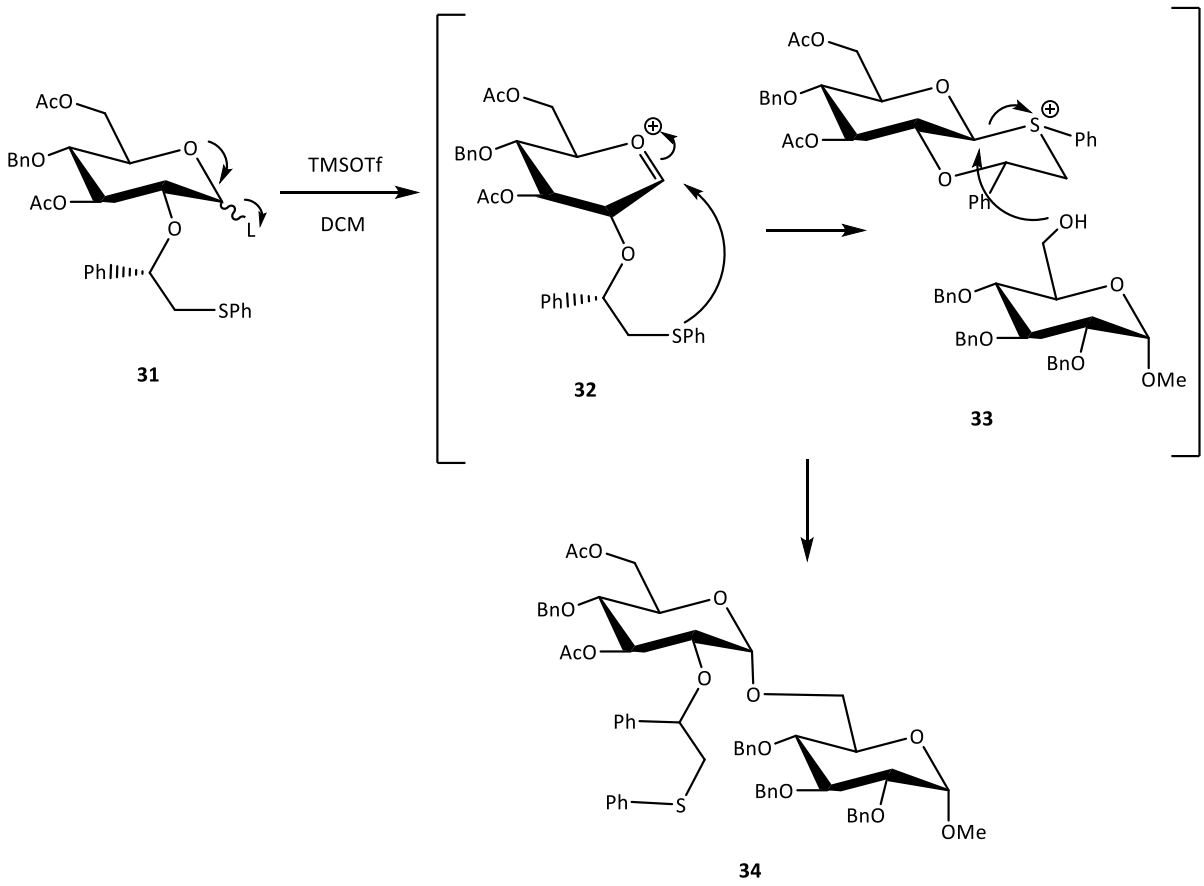
The silyl acetal-based IAD approach was also studied by Bols,[2] who reported the synthesis of 1,2-*cis*-α-glucoside (scheme 11). Further study clarified its practicality in the synthesis of α-glucoside **30** structure. Donor **26** with acceptor **27** gave this product through corresponding mixed acetal **28**. Glycosylation was achieved with full stereoselection, yields up to 45%.



Scheme 11. IAD through dimethylsilaketal-tethered intermediate.

3.1.4 Sulphur tethering

Boon published a method in which C2 group can be manipulated to interact with the oxocarbenium ion, and give rise to the *cis* anomer.[15] Interestingly, this reaction proceeds via a *trans* decalin intermediate **33**, that then allows attack by the glycoside acceptor resulting in *cis* orientation **34** relative to the C2 group (scheme 12):

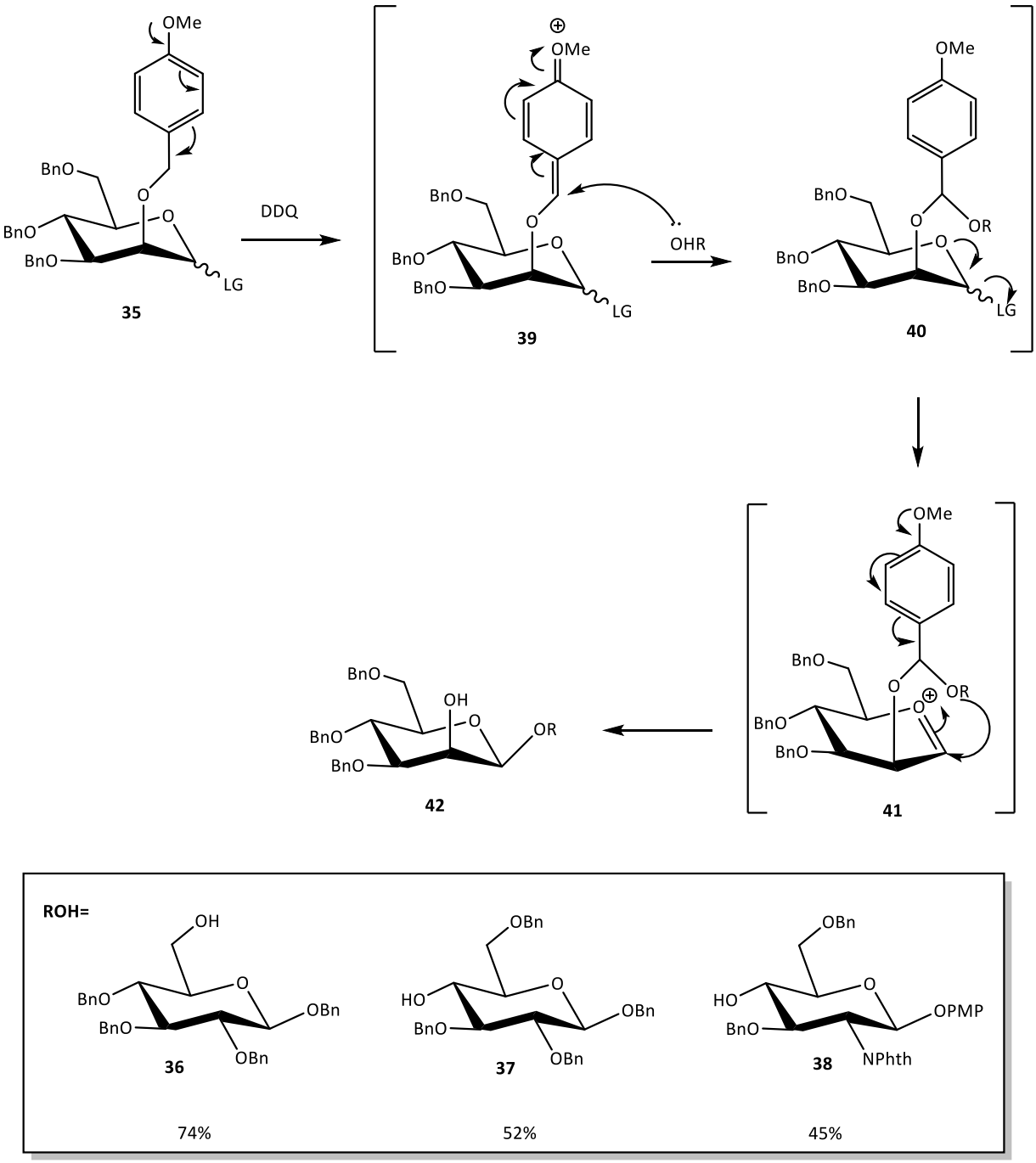


Scheme 12. Glycosylation via a substituted *trans* decalin intermediate.

The S-chirality of the C2 group guides the phenyl group to occupy an equatorial position, meaning the temporary sulphur bond is allocated a β orientation. Thus the attack from the acceptor has to proceed in the α orientation, providing the 1,2-*cis* glycoside **34**.

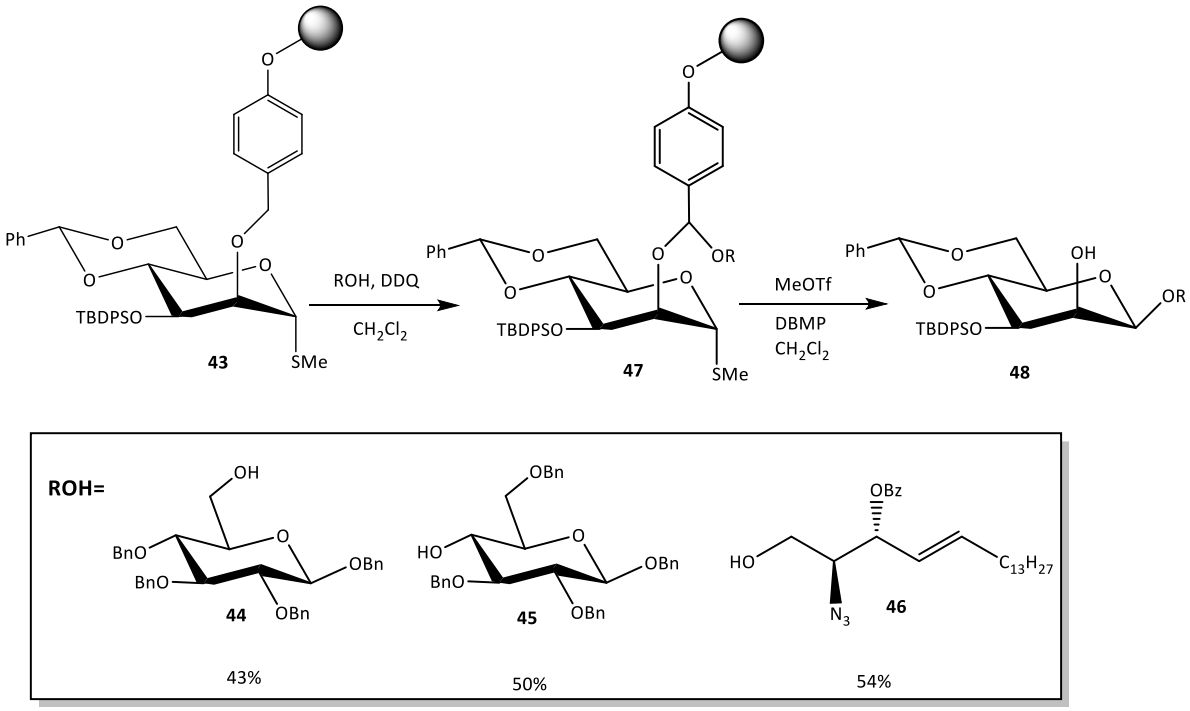
3.1.5 Oxidative tethering

Ito and Ogawa proposed a method of aglycone delivery in the synthesis of β mannosyls that substituting the aliphatic tether used by Hindsgaul and Fairbanks by an aromatic tether that circumvents the difficulties encountered during acetal formation.[3] Ogawa's *p*-methoxyphenylmethyl tether can be generated from a *p*-methoxyphenyl group (PMB) by oxidation with DDQ in the presence of the respective glycosyl acceptor. Thus, tethered glycosides are very conveniently accessible in high yield. Another significant improvement is the fact that the intermediate tethered glycosides do not need to get isolated but, instead, can directly get converted into the corresponding saccharides (scheme 13).



Scheme 13. IAD via *p*-methoxybenzylidene acetals.

The IAD concept via *p*-methoxybenzylidene acetals was also shown to be suitable for polymer-supported syntheses of disaccharides (scheme 14).[16] A suitable *p*-allyloxybenzyl group at position C2 of a 1-thio-mannosyl donor is first converted into a PEG-modified benzyl group that allows for the convenient isolation of the intermediate glycosides.



Scheme 14. Polymer-supported synthesis via IAD.

4. EXPERIMENTAL DESCRIPTION

4.1 Material, reagents and equipment

All the reactions were performed from oven dried glassware and metal ware. The solvents where dried from clean activated molecular sieves for 14-16 hours before hand. Solvents, silica and other reagents/reactants were ordered as >98% pure from either Sigma Aldrich, Fisher Scientific, Alfa Aesar, Acros Organics or TCl Chemicals. Solvent evaporation was performed under Buchi Rotor Vap vacuum stills. Distillation processes were performed under high vacuum through a quick fit – assembled vacuum still from oven dried clean glassware. NMR analysis was obtained from a JEOL Delta2 Nuclear Magnetic Resonance spectrometer and BRUKER Nuclear Magnetic Resonance spectrometer, using deuterated chloroform as solvent. TLC was from fisher scientific brand Silica – glass plates. Flash column chromatography was performed via direct application of the compound, as a solution onto the column. The solid phase was prepared off column as a silica gel, made with the mobile phase determined from TLC analysis. All reactions that involved heating where warmed under a condenser, and the reactions that involved stirring where stirred at a steady rate with a magnetic stirrer bar. All procedures were carried out under a nitrogen atmosphere. Procedures that occurred under this project were supervised and COSHH's where taken with compliance to HR regulations.

4.2 Synthesis

4.2.1 Donor

In approaching the neighbouring group direction method proposed above, the first thing we had to do is propose a glycoside to synthesise.[17] Figure 1 shows the proposed glycoside donor and a suitable tethering system (X).

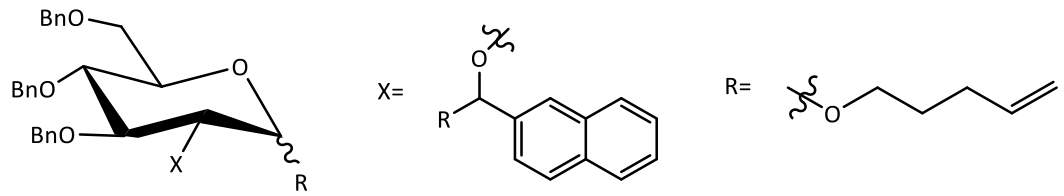
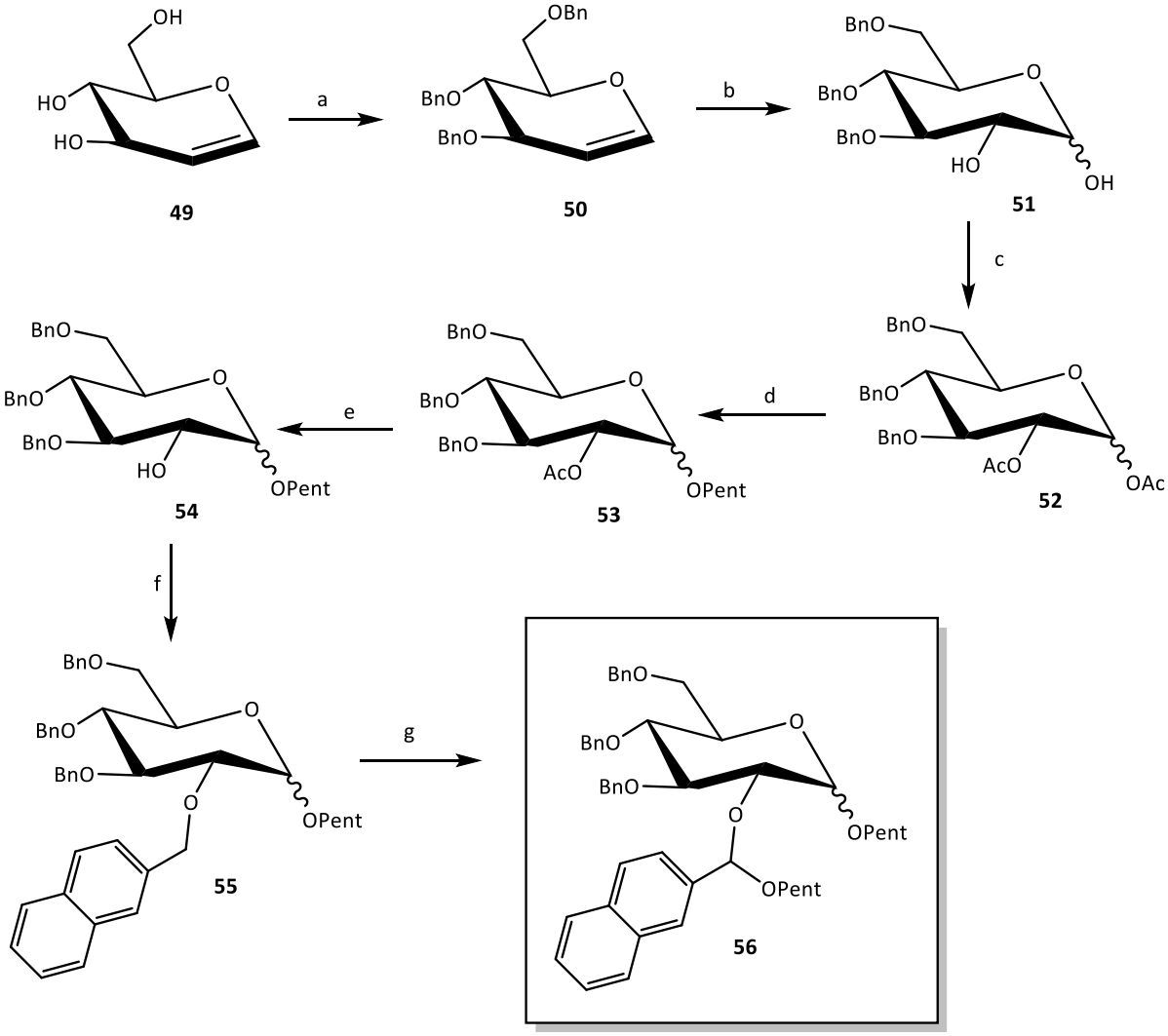


Figure 1. 3,4-bis(benzyloxy)-2-(benzyloxy)methyl-5-(naphthalen-2-yl)(pent-4-en-1-yloxy)methoxy)-6-(pent-4-en-1-yloxy)tetrahydroglucopyranoide.

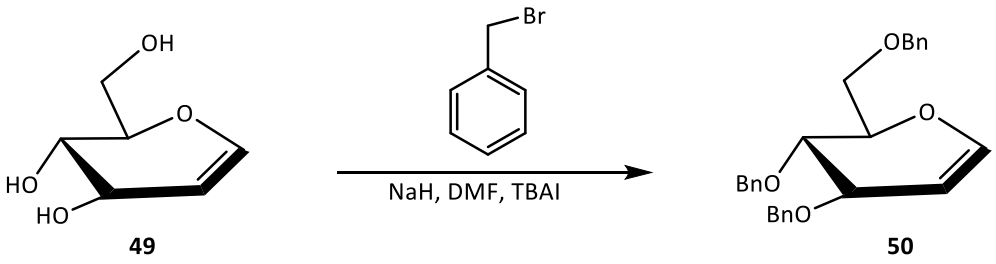
This tethering system is used because the 2-napthylmethyl (NAP) group ether has been gradually gaining popularity as a hydroxyl protective group in natural product synthesis. It is similar to PMB ether in that it is removable under oxidative conditions. Therefore, we think that the NAP group gives the resonance enough to make more stable introducing the acceptor.

Synthesis of this gluco donor is known[18] and we could utilise this for our studies following the scheme 15.



Scheme 15. a) BnBr, NaH, n-Bu_4NI, DMF, 0ºC- R.T., 24hrs. b) OsO_4, NMO, Acetone, H_2O - R.T, 24 hrs. c) AcO_2, DCM, py, 0ºC – R.T., 16 hrs. d) 4-penten-1-ol, $Sn(IV)Cl_4$, DCM, 0ºC – R.T. 48 hrs. e) MeOH, MeONa, 0ºC – R.T., 5hrs. f) NAP, NaH, n-Bu_4NI, DMF, 0ºC- R.T., 24hrs. g) 4-penten-1-ol, DDQ, DCM, 0ºC – R.T., 5hrs.

Step a

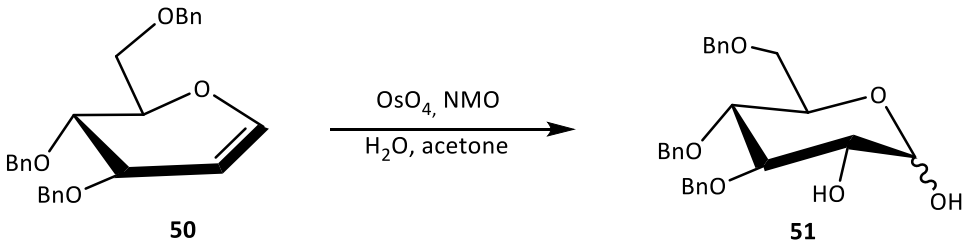


49 **50**

Scheme 16. Step a of the donor synthesis.

D-glucal **49** (3.233g, 0.022mol) was dissolved in 15ml of DMF at 0ºC. Benzyl bromide (8.684mL, 0.0726mol, 3.3 eq.) and tetra-n-Butyl Ammonium Iodide (1.2g) were added and dissolved. This was cannulated onto NaH (2.9g, 0.0726mol, 3.3 eq. 60% dispersal in mineral oil.). The reaction was stirred for 16 hours and allowed to warm to room temperature. The reaction was quenched with water (100mL), and extracted with Et_2O (3 x 150 mL). The combined organic phases were then washed with water (2 x 150 mL) and brine (150 mL). It was then dried over $MgSO_4$ and concentrated. The resulting yellow oil was purified with the solvent (80% propan-2-ol/20% hexane) and filtered under vacuum to obtained white crystals of benzyl ether **50** (7.27g 82%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33 (Ar m 15H), 6.43 (d 1H, J= 6.08 Hz), 4.88 (dd 1H, J=6.08,Hz), 4.85 (s 1H), 4.65 (m 5H), 4.22 (d 1H, J= 5.48 Hz), 4.06 (m 1H), 3.80 (m 3H).

Step b

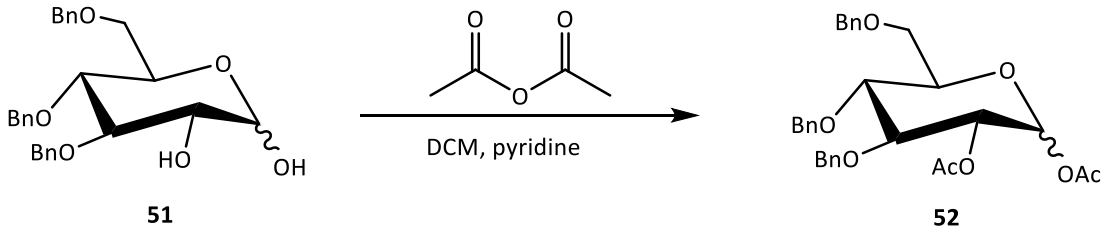


50 **51**

Scheme 17. Step b of the donor synthesis.

Benzyl ether **50** (7.27g, 0.018mol) was dissolved in 100mL of acetone at room temperature. NMO (2.56g, 0.022mol, 1.126 eq.), water (50mL) and OsO_4 (3.8mL, 100mg/250mL t-butyl alcohol) were added and the reaction was stirred for 16 hours at room temperature. The reaction was washed with water (100mL), and extracted with EtOAc (3 x 100mL). The combined organic phases were then washed with water (2 x 100mL) and brine (100mL). The aqueous phase was disposed of as heavy metal waste. The organic phase was then dried over $MgSO_4$ and concentrated. The resulting was a brown oil of diol **51** (7.65g 97%). ^{1}H NMR ($CDCl_3$, 400MHz) δ 7.32 (Ar m 15H), 5.23 (t 1H, J= 3.64 Hz), 4.86 (m 2H), 4.56 (m 7H), 4.12 (dd 1H, J= 7.2 Hz), 3.79 (m 3H), 3.67 (m 1H).

Step c

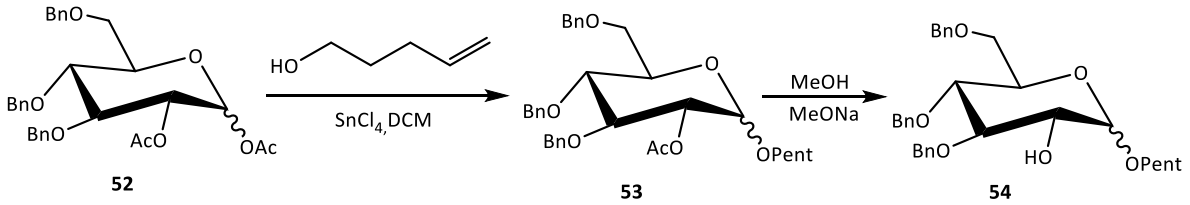


51 52

Scheme 18. Step c of the donor synthesis.

Diol **51** (7.65g, 0.017mol) was mixed with DCM (20mL) at room temperature. Acetic anhydride (6.37mL, 0.067mol, 3.5eq.) and pyridine (3.7mL) were added and the reaction was stirred for 16 hours at room temperature. The reaction was quenched with copper sulphate 10% (150mL), and extracted with EtOAc (3 x 150 mL). The combined organic phases were washed twice with water (2 x 150mL) and once with brine (150mL). The organic phase was dried with $MgSO_4$ and concentrated to afford crude yellow oil of acetate **52** (8.72g 88%). ^{1}H NMR ($CDCl_3$, 300MHz) δ 7.35 (Ar m 15H), 6.3 (d 3H, J= 3Hz), 5.15 (m 1H), 4.83 (m 6H), 3.84 (m 3H), 2.16 (m 3H), 1.96 (d 3H, J=9Hz).

One pot step d & e



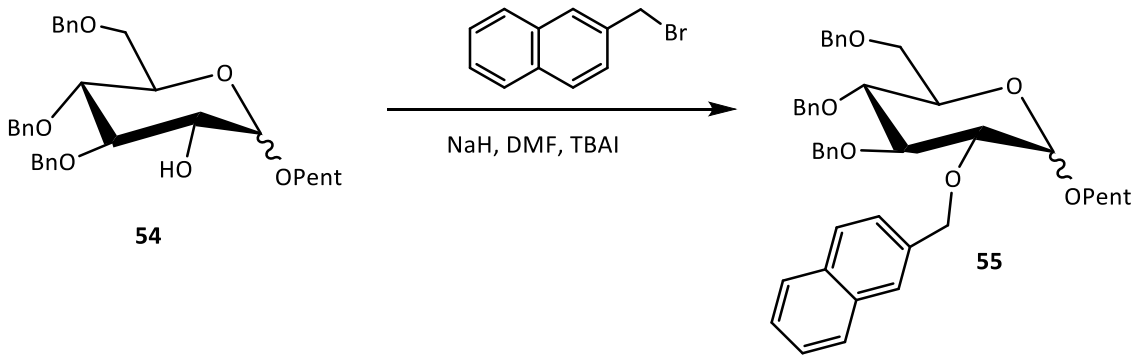
52 53 54

Scheme 19. Step d & e of the donor synthesis.

Acetate **52** (8.72g, 0.017mol) was dissolved 30mL of DCM at 0ºC. 4-pentan-1-ol (17.45mL) and $SnCl_4$ (23.25mL, 2molar solution in DCM) were added; the reaction was stirred and allowed to warm to room temperature. The reaction was stirred for 2 days, and further $SnCl_4$ (23.25mL, 2 molar solution in DCM) was added every 24 hours. The reaction was quenched with HCl (100mL), and extracted with DCM (3 x 100mL). The combined organic phases were then washed with water (2 x 100mL) and brine (100mL). It was then dried over $MgSO_4$ and concentrated. The resulting yellow oil **53** was dissolved 200mL of methanol at 0ºC. NaOMe (2mL, 25%w.t. solution in Methanol) was added and the reaction was stirred and allowed to warm to room temperature. The reaction was stirred for 16 hours. The reaction was washed with water (100mL) and extracted with EtOAc (3 x 100mL). The combined organic phases were then washed with water (2 x 100mL) and brine (100mL). It was then dried over $MgSO_4$ and concentrated. The resulting yellow oil was purified via silica gel chromatography using a 10% EtOAc in hexanes where it was separate α (colourless oil) from β (white

solid). Isolated yield of α **54** (1.01g 12%) with ^{1}H NMR ($CDCl_3$, 400MHz) δ 7.33 (Ar m 15H), 5.83 (m 1H), 5.29 (s 1H), 4.85 (d 2H, J=11.68Hz), 4.60 (m 3H), 4.11 (m 2H), 3.73 (m 6H), 2.36 (m 6H), 1.27 (m 2H). Isolated yield of β **54** (1.96g 23%) with ^{1}H NMR ($CDCl_3$, 400MHz) δ 7.33 (Ar m 15H), 5.81 (m 1H), 5.27 (s 1H), 4.94 (m 6H), 4.62 (d 2H, J= 0.6Hz), 4.52 (m 1H), 3.77 (m 6H), 3.48 (m 1H), 1.74 (m 2H), 1.26 (s 2H), 0.88 (m 1H).

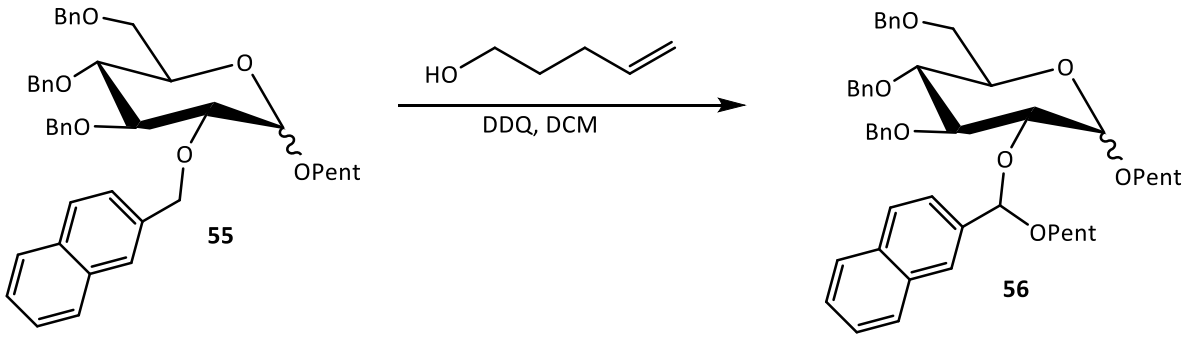
Step f



Scheme 20. Step f of the donor synthesis.

α-anomer **54** (1.01g 2mmol) was dissolved in 5mL of DMF at 0ºC. 2-(Bromomethyl)naphthalene (0.49g, 2.2mmol, 1.1 eq.) and TBAI (500mg) were added and dissolved. This was cannulated onto NaH (96mg, 2.4mmol, 1.2 eq. 60% dispersal in mineral oil). The reaction was stirred for 16 hours and allowed to warm to room temperature. The reaction was quenched with water (100mL), and extracted with Et_2O (3 x 100 mL). The combined organic phases were washed with water (2 x 100 mL) and brine (100 mL). Then, it was then dried over $MgSO_4$ and concentrated. The resulting yellow oil was purified via silica gel chromatography using 15% EtOAc in hexanes to afford **55** as a white solid (0.71g 58%).^{1}H NMR ($CDCl_3$, 300MHz) δ 7.76 (m 4H), 7.47 (m 3H), 7.34 (Ar m 15H), 5.78 (m 2H), 4.72 (m 7H), 4.36 (m 3H), 3.91 (m 1H), 3.38 (m 7H), 2.17 (s 2H), 1.19 (m 2H). The β-anomer **55** was obtained by the same way as colourless-yellow oil (1.46g 55%).^{1}H NMR ($CDCl_3$, 400MHz) δ 7.80 (m 4H), 7.52 (m 3H), 7.30 (Ar m 15H), 5.82 (m 2H), 5.04 (m 10H), 4.01 (t 1H J=9.28Hz), 3.62 (m 2H), 3.43 (m 5H), 1.75 (m 2H), 1.26 (m 2H).

Step g

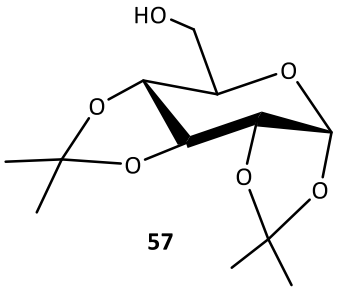


Scheme 21. The last step of the donor synthesis.

α-anomer **53** (0.71g 1.1mmol) was dissolved in 10mL of DCM at 0ºC. 4-penten-1-ol (0.14mL, 1.32mmol, 1.2 eq.), powdered 4Å molecules sieves activated (500mg) and DDQ (0.30g, 1.32mmol, 1.2 eq.) were added and dissolved. The reaction was stirred for 5 hours and allowed to warm to room temperature. The reaction was filtered with celite under vacuum. The reaction was quenched with 10% $NaCO_3$ (100 mL) and extracted with DCM (3 x 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. The resulting yellow oil was purified via silica gel chromatography using 10% EtOAc in hexanes to afford **54** as a brown oil (164mg 21%). ^{1}H NMR ($CDCl_3$, 400MHz) δ 7.94 (m 4H), 7.38 (m 3H), 7.33 (Ar m 15H), 6.05 (d 1H, J= 1.96Hz), 5.81 (m 2H), 5.30 (m 2H), 5.04 (m 6H), 4.6 (m 2H), 3.93 (m 1H), 3.59 (m 9H), 2.30 (m 5H), 1.74 (m 4H). The β-anomer **54** was obtained by the same way a white solid (88mg 18%).^{1}H NMR ($CDCl_3$, 400MHz) δ 7.83 (m 4H), 7.54 (m 3H), 7.26 (Ar m 15H), 5.84 (m 3H), 4.97 (m 8H), 4.51 (m 2H), 4.02 (m 9H), 2.18 (m 4H), 1.56 (m 4H), 1.26 (s 1H), 0.90 (m 1H).

4.2.2 Acceptor

The glycosylation reaction require a glycoside acceptor to test the glycosylation technique, and monitor the α:β selectivity. Figure 2 presents the acceptor that it was utilised for our glycosylation reaction.



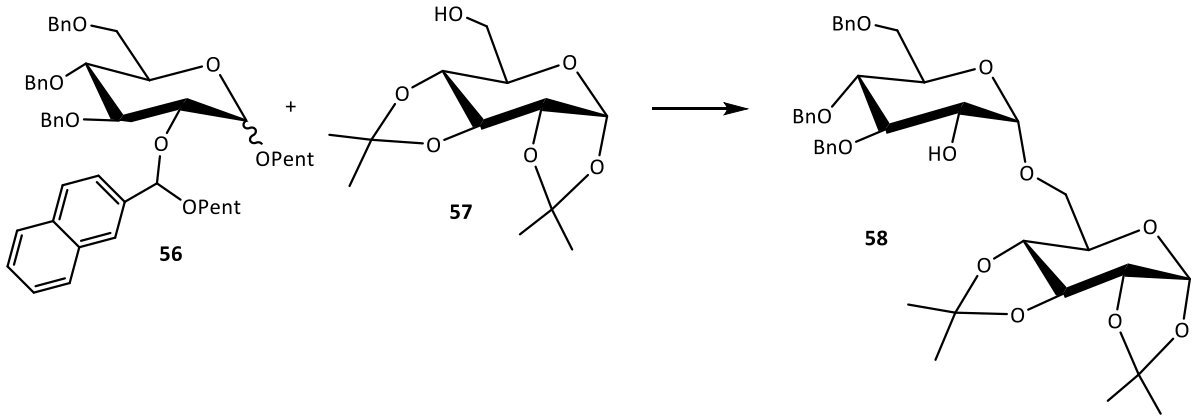
57

Figure 2. 1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose acceptor.

This reagent it was pursuased from Sigma Aldrich with 97% of purity to do the glycosylation reaction. ^{1}H NMR ($CDCl_3$, 400MHz) δ 4.61 (d 1H), 4.35 (dd 2H, J= 2.4, 18.96 Hz), 3.88 (m 3H), 2.20 (d 1H, J= 3.08 Hz), 1.67 (s 1H), 1.54 (3s 12H).

4.2.3 Disaccharide

Once we had the donor and the acceptor we could do the glycosylation reaction to obtain the disaccharide (scheme 22). We utilised the α-donor **56**, so we obtained the α-dissacharide **58**.



Scheme 22. Synthesis of the α-disaccharide.

α-donor **56** (134mg, 0.184mmol) was dissolved in 8mL of DCM at 0ºC. The acceptor **55** (60mg, 0.23mmol, 1.2 eq.) and NIS (89mg, 0.40mmol, 2.2 eq.) were added and dissolved. Powdered 4Å molecules sieves activated (300mg) and TMSTF (0.07mL, 0.0387mmol, 2.2 eq.) were added and the reaction was stirred for 2 hours and allowed to warm to room temperature. DCM (20mL) was added and the mixture was filtered. The filtrate was washed with saturated $NaHCO_3$ (50mL), saturated $Na_2S_2O_3$ (50mL) and water (50mL). The combined organic phases were dried over $MgSO_4$ and concentrated. The resulting yellow solid was purified via silica gel chromatography using 10% EtOAc in hexanes gradient to 100% EtOAc. The disaccharide **58** was afford as yellow oil (47mg 37%). ^{1}H

NMR ($CDCl_3$, 400MHz) δ 7.33 (Ar m 15H), 5.36 (m 1H), 4.85 (m 1H), 4.52 (m 1H), 3.69 (m 12H), 2.98 (m 1H), 2.32 (m 1H), 2.02 (m 1H), 1.60 (m 1H), 1.30 (m 12H), 0.94 (m 2H).

5. RESULTS & DISCUSSION

Regarding to the synthesis of the donor, the first steps have been very gratefully because they were obtained in good yields. When the separation of α and β anomers was required, the yields decreased considerably due to this difficulty, especially in the last step. We assume that the last step should be optimized due to the high amount of by products obtained, as well as the consumption of the start material was not complete (figure 3).

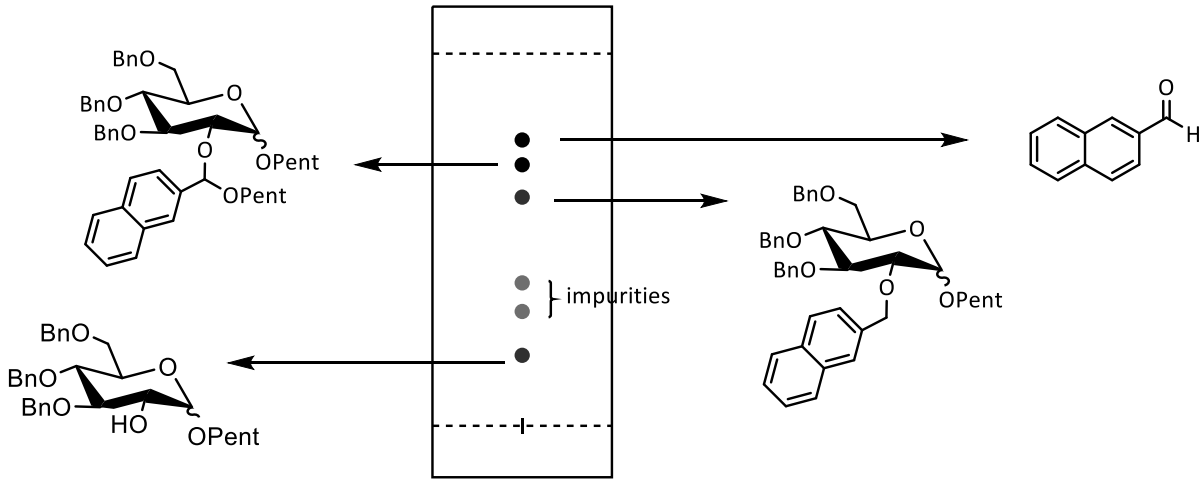


Figure 3. TLC plate of the last step of the donor using as solvent EtOAC/hexane (25/75) of the crude reaction.

Concerning the synthesis of the disaccharide, although we got the desired product, the reaction should also be optimized due to the high amount of impurities (figure 4).

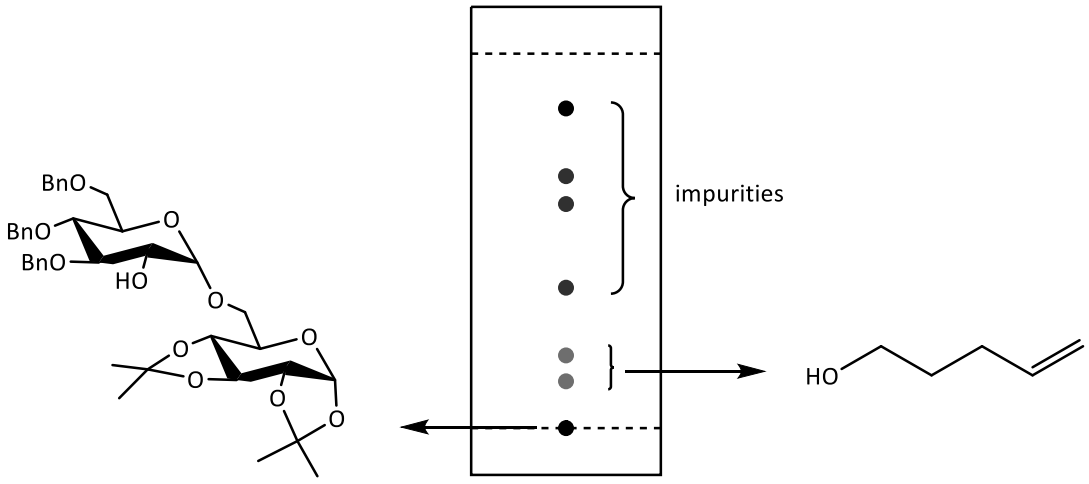
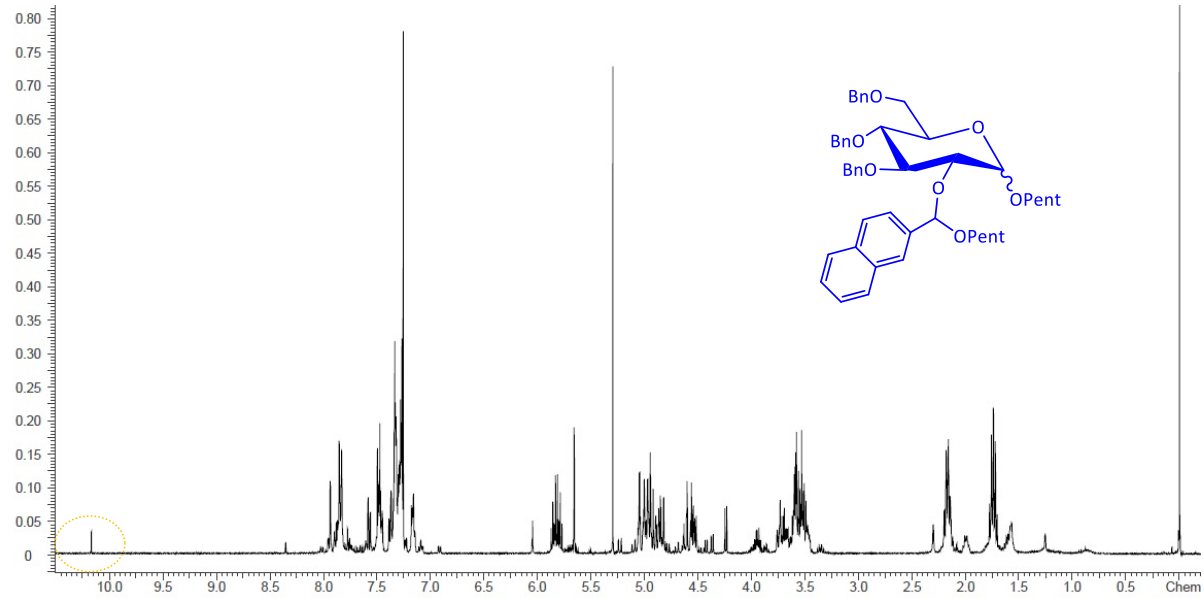


Figure 4. TLC plate of the disaccharide reaction using as solvent EtOAc/hexane (25:75) of the crude reaction.

5.1 Characterization

5.1.1 Donor

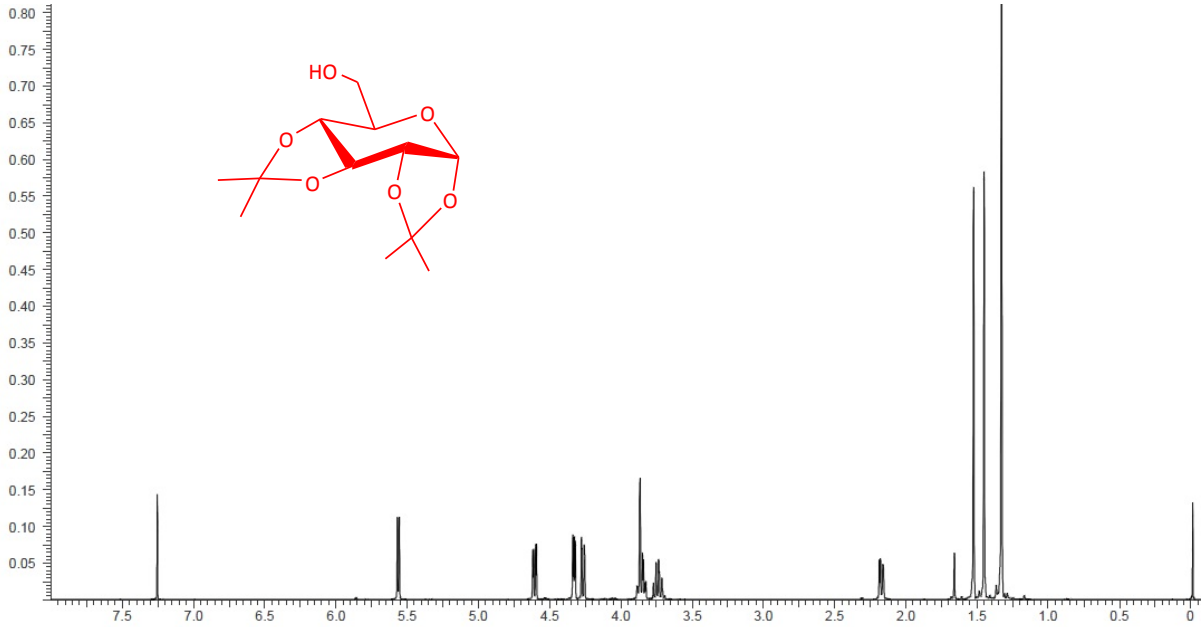
It can be seen in the spectrum 1 that there are all the peaks expected from the α-donor, but there are also some impurities because the peak at 10.3ppm could shows the presence of the 2-naphthaldehyde which it couldn't be separated via silica gel chromatography from our product. We tried to remove the 2-naphthaldehyde by adding in the solution some DCM and a little of ethylenediamine polymer-bound. The mixture was stirred during 10 min and then was filtered and concentrated. Unfortunately, we obtained the same spectrum. Likewise, The presence of the 2-naphthaldehyde confirm that the reaction has taken place, so we got the desired product.



Spectrum 1. ^{1}H NMR of α-donor.

5.1.2 Acceptor

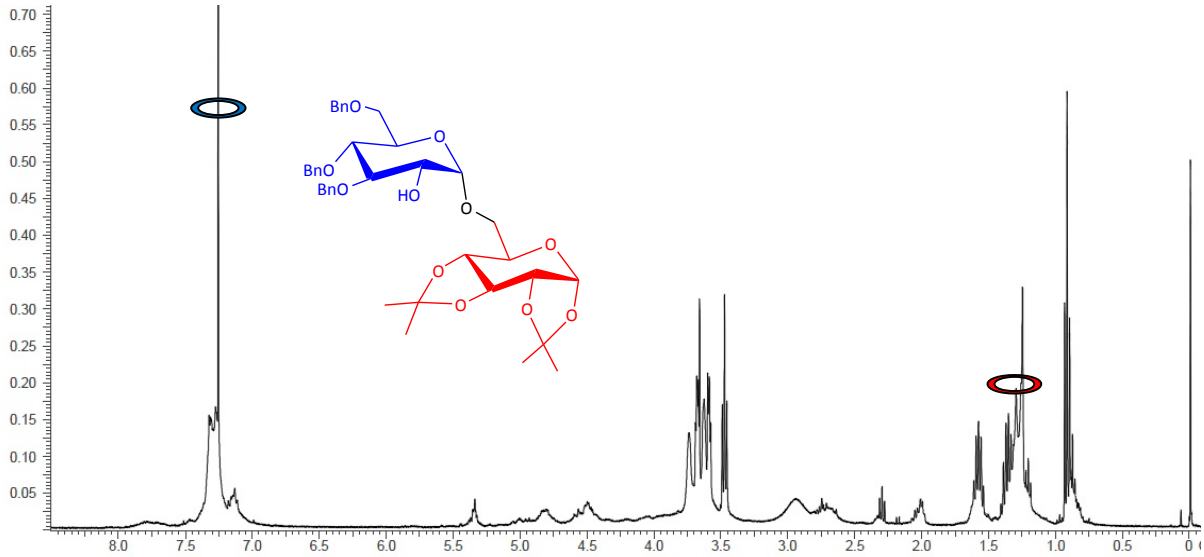
It can be seen in the spectrum 2 that all the peaks expected from the acceptor are present. However, the peaks at 7.2 and 5.5ppm don't belong to the acceptor. These peaks belong to the solvent residual peaks.



Spectrum 2. ^{1}H NMR of acceptor.

5.1.3 Disaccharide

It can be seen in the spectrum 3 that there are a lot of impurities which makes its interpretation not easy. However, it is possible to observe that the coupling is done because the essential peaks of the both donor and acceptor are present in the spectrum. One set of these peaks at 7.3ppm, shows the presence of 15 protons from the aromatic protective group (BnO) of the donor. The other important set of peaks is at 1.3ppm, and shows the 12 protons from the methyl group of the acceptor.



Spectrum 3. ^{1}H NMR the crude reaction of the α-disaccharide synthesis.

6. CONCLUSIONS & PERSPECTIVES

Even I haven't obtained very good yields in the last step of the donor and in the disaccharide synthesis, I'm proud of this work because I have done one donor that could be able to synthesise *cis*-disaccharides, which was the aim of this project.

In addition, this project has been also useful for me to increase my knowledge about carbohydrates and its specific organic chemistry. Moreover, the new experience to work in another country and with new people has been very challenging.

The future research would consists on the purification of the donor synthesized and optimized their synthesis. It would be also important to find the donor limits in order to know if it is a good donor or not. One way to check that is doing the reaction with different acceptors to know if it is sensitive to steric effects increasing the alcohol (secondary alcohols, and disaccharide alcohols) and then see if it cause significant decreases in the yield or not.

7. REFERENCES

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