Recent developments in chemical oligosaccharide synthesis

GEERT-JAN BOONS

The School of Chemistry, The University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

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1 Introduction

Glycoconjugates are the most functionally and structurally diverse molecules in nature and it is now well established that protein- and lipid-bound saccharides play essential roles in many molecular processes impacting on eukaryotic biology and disease.[1] Examples of such processes include fertilisation, embryogenesis, neuronal development, hormone activities, the proliferation of cells and their organisation into specific tissues. Remarkable changes in the cell-surface carbohydrates occur with tumour progression, which appear to be intimately associated with the dreaded state of metastasis.[2] Furthermore, carbohydrates are capable of inducing a protective antibody response and this immunological reaction is a major contributor to the survival of the organism during infection.[3] Oligosaccharides have also been found to control the development and defence mechanisms of plants.[4] The increased appreciation of the role of carbohydrates in the biological and pharmaceutical sciences has resulted in a revival of interest in carbohydrate chemistry.

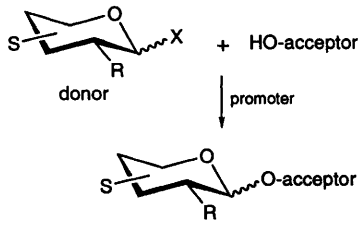
The chemical synthesis of oligosaccharides is much more complicated than the synthesis of other biopolymers such as peptides and nucleic acids. The difficulties in the preparation of complex oligosaccharides are a result of a greater number of possibilities for the combination of monomeric units to form oligosaccharides. In addition, the glycosidic linkages have to be introduced stereospecifically (α:β selectivity). To date, there are no general applicable methods or strategies for oligosaccharide synthesis and consequently the preparation of these molecules is very time consuming. Nevertheless, contemporary carbohydrate chemistry makes it now possible to execute complex multi-step synthetic sequences that give oligosaccharides consisting of as many as 20 monosaccharide units.[5] The preparation of oligosaccharides of this size is only possible when each synthetic step in the assembly of the oligosaccharide is high yielding and, furthermore, the formation of each glycosidic linkage is highly stereoselective. Apart from this, the assembly of the monomeric units should be highly convergent.

This review describes the recent advances in chemical oligosaccharide synthesis. In the first part, methods for stereoselective glycosylation are reviewed and the scope and limitations are mentioned (Section 2). Next, the glycosylation of 3-deoxy-2-keto-ulo(pyranosyl)onates and 2-deoxy sugars are discussed (Sections 3 and 4). In Sections 5–8, examples of convergent oligosaccharide synthesis are presented and new glycosylation strategies for the facile preparation of saccharide building blocks are discussed. Finally, recent advances in solid supported oligosaccharide synthesis are summarised (Section 9).

2 Methods for stereoselective glycosylation

2.1 Glycosidic bond synthesis

Inter-glycosidic bond formation is generally achieved by condensing a fully protected glycosyl donor, which bears a leaving group at its anomeric centre, with a suitably protected glycosyl acceptor that contains often only one free hydroxy group (**Scheme 1**).[6,7] Traditionally,[6a] the most widely used glycosylation methods utilised anomeric halide derivatives of carbohydrates as glycosyl donors. However, these compounds often suffer from instability and require relatively drastic conditions for their preparation. The introduction of the



Factors that influence the α:β ratio in glycosylations
1. Substituent R: participating *vs.* non-participating
2. Orientation of substituent R: equatorial *vs.* axial
3. Type of substituents (S) in donor and acceptor
4. Type of leaving group (X)
5. Type of promoter
6. Solvent
7. Temperature
8. Pressure

Scheme 1

orthoester[8] and imidate[9] procedures was the first attempt to find alternatives to the glycosyl halide methodologies. Since these original disclosures, many other leaving groups at the anomeric centre have been reported (**Figure 1**).[6j] However, of these glycosyl donors, the anomeric fluorides, trichloroacetimidates and thioglycosides have been applied most widely. These compounds can be prepared under mild conditions, are sufficiently stable to be purified and stored for a considerable period of time, and undergo glycosylations under mild conditions. By selecting the appropriate reaction conditions, high yields and good $\alpha:\beta$ ratios can be obtained.

The anomeric linkages can be classified according to the relative and absolute configuration at C-1 and C-2 (**Figure 2**) and they are: the 1,2-*cis*- and 1,2-*trans*-2-D-glycero series (allo-, gluco-, gulo- and galactopyranosides) and the 1,2-*cis*- and 1,2-*trans*-2-L-glycero series (altro-, manno-, ido- and talo-galactopyranosides). Apart form these types, some miscellaneous glycosidic linkages can also be identified including: 2-deoxyglycosides and 3-deoxy-2-keto-ulo(pyranosylic) acids.

The stereoselective introduction of the glycosidic linkage is one of the most challenging aspects in oligosaccharide synthesis. The nature of the protecting group at C-2 of the glycosyl donor is a major determinant of the anomeric selectivity. A protecting group at C-2 which can perform neighbouring group participation during glycosylation will give 1,2-*trans* glycosidic linkages. On the other hand, when a non-assisting functionality is present at C-2 then the reaction conditions (*e.g.* solvent, temperature, promoter) will determine the anomeric selectivity. Also the constitution of the glycosyl donor and acceptor (*e.g.* type of saccharide, leaving group at the anomeric centre, protection and substitution pattern) have a major effect on the $\alpha:\beta$ selectivity.

2.2 Neighbouring group assisted procedures

The most reliable method for the introduction of 1,2-*trans*-glycosidic linkages is based on

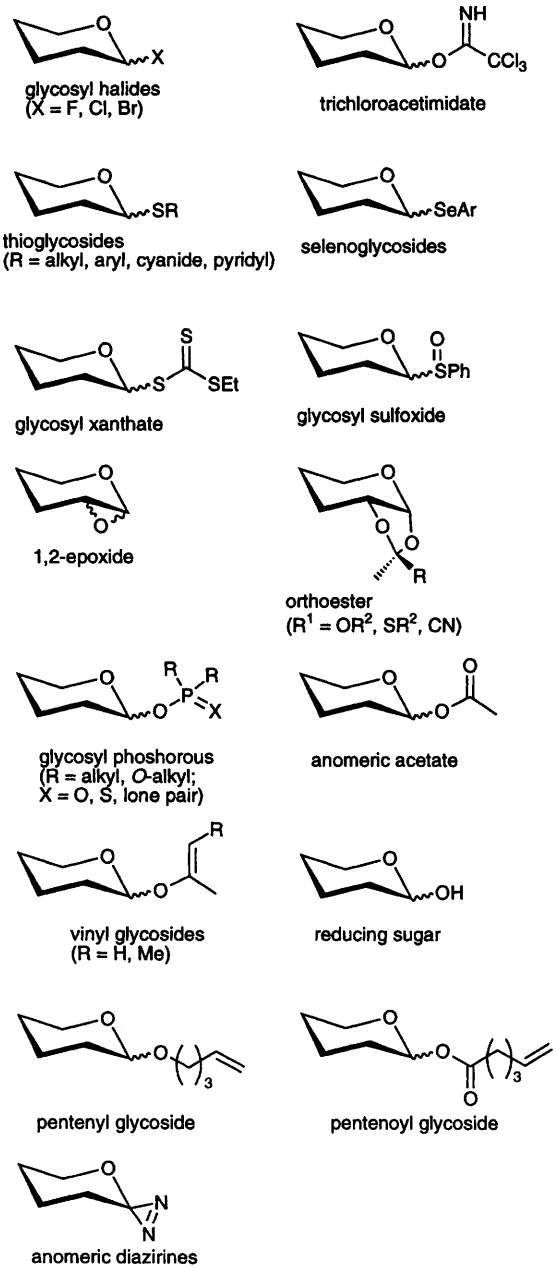


Figure 1

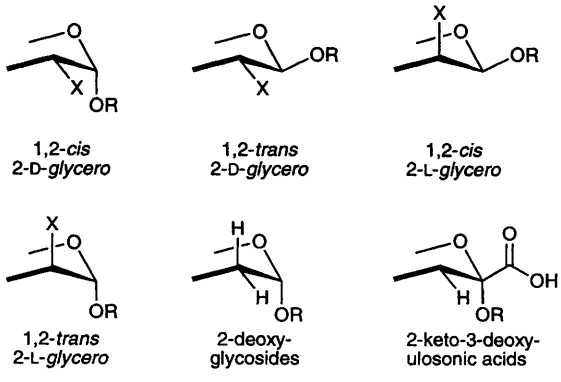
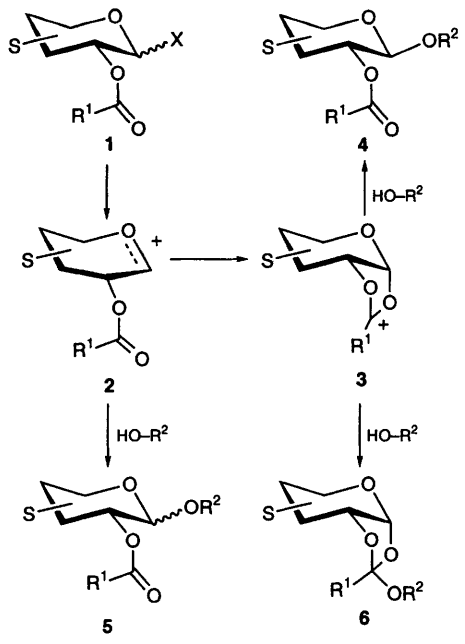


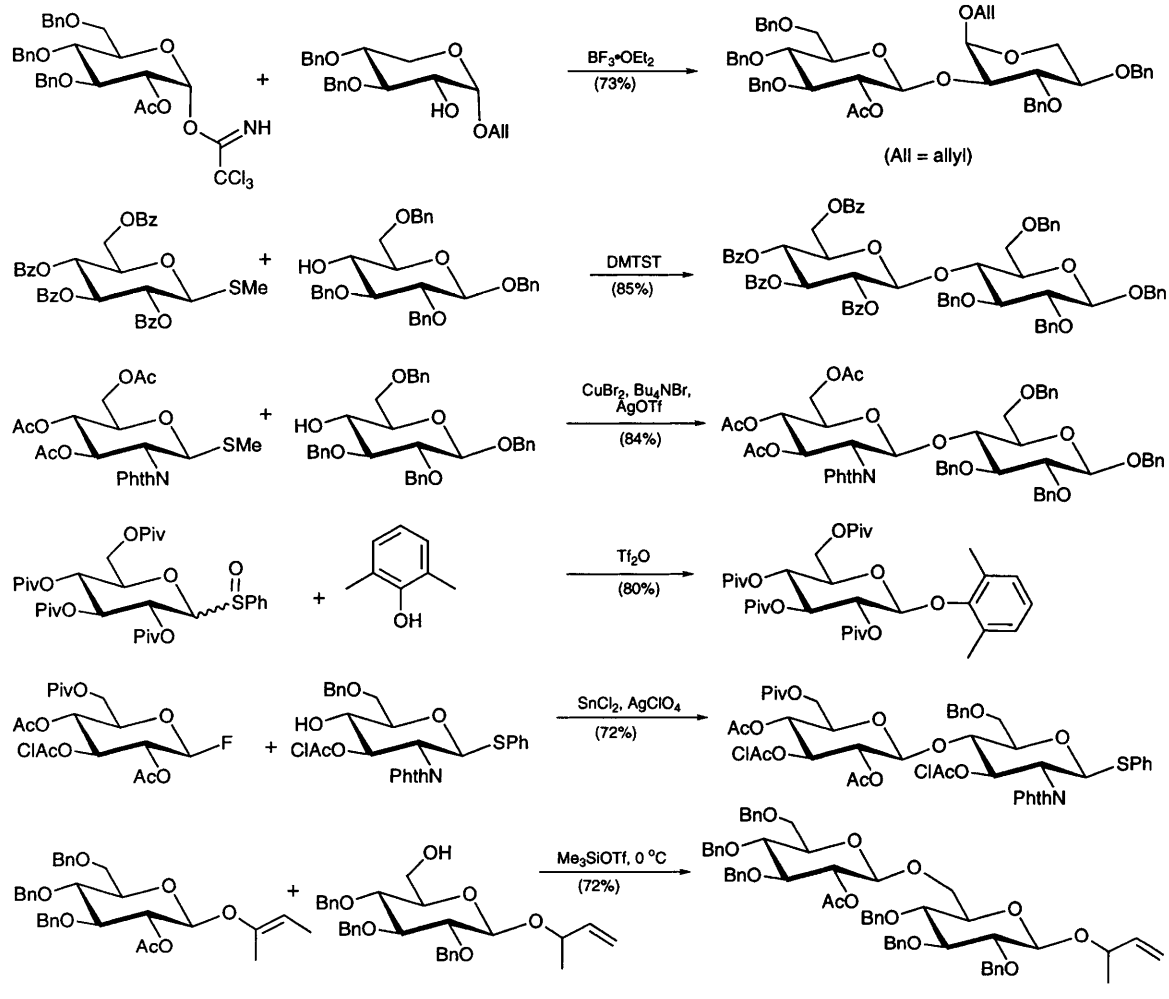
Figure 2

neighbouring group participation of a 2-*O*-acyl functionality. The principle of this approach is schematically illustrated in **Scheme 2**. Thus, activation of the anomeric centre of **1** results in the formation of an oxonium ion **2**. Subsequent neighbouring group participation of the 2-*O*-acetyl protecting group leads to a more stable acetoxonium ion **3**. Attack of an alcohol at the anomeric centre results in the formation of a 1,2-*trans*-glycoside **4**. Thus, in the case of glucosyl-type donors, β-linked products will be obtained and mannosides will give α-glycosides. The neighbouring group assisted glycosylation procedures are compatible with many different anomeric leaving groups and representative examples are depicted in **Scheme 3**.

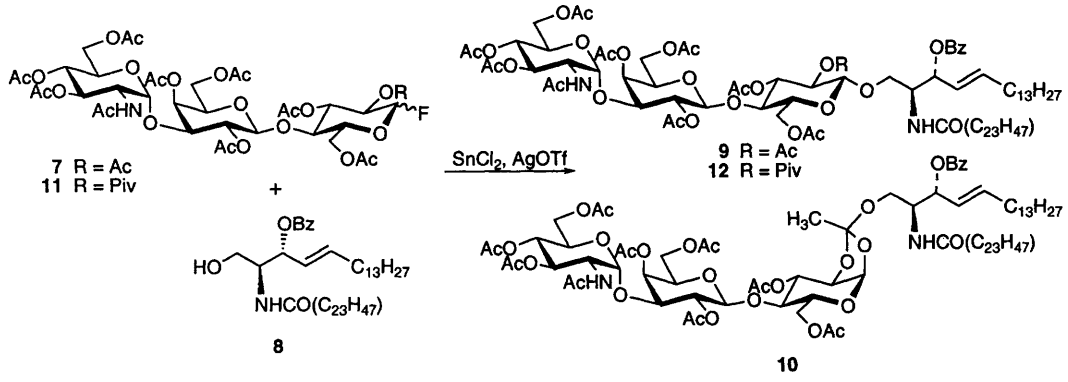
In some glycosylations, the alcohol will attack at the C-2 position of the dioxolane ring of **3** resulting in the formation of an undesired orthoester **6** (**Scheme 2**). For example, reaction of the glycosyl donor **7** with acceptor **8** gave only traces of coupling product **9** and a significant amount of orthoester **10** was isolated (**Scheme 4**).[10] However, glycoconjugate **12** was isolated in a respectable 77% yield when glycosyl donor **11** was used. In this donor, the 2-*O*-



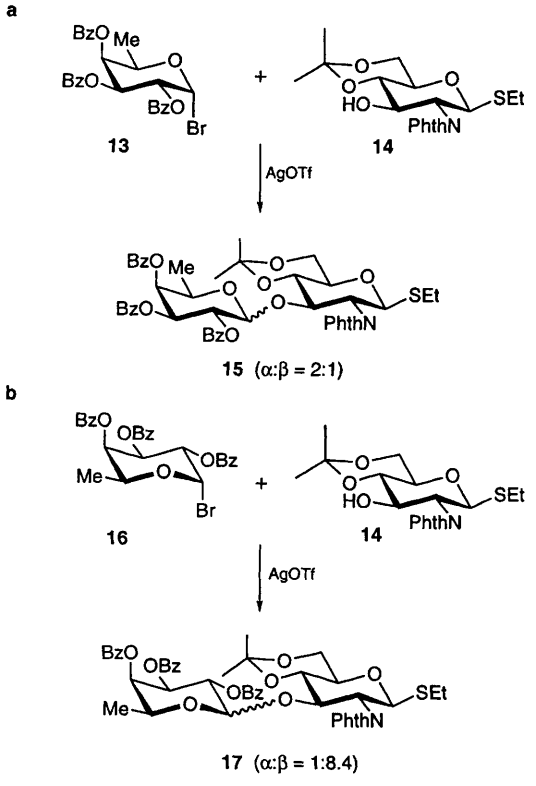
Scheme 2



Scheme 3



Scheme 4



Scheme 5

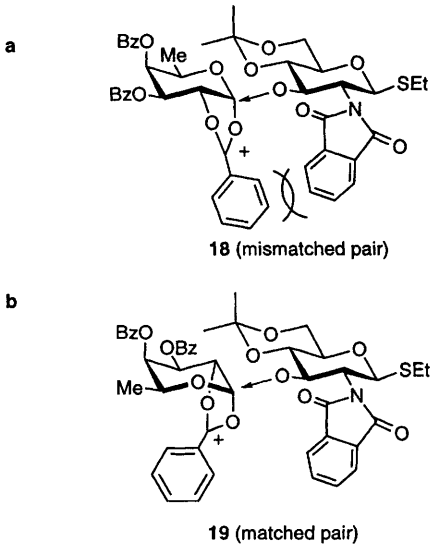


Figure 3

acetyl protecting group has been replaced by a pivaloyl functionality. The increase in yield was explained as follows: the orthoester formation is disfavoured by the presence of the bulky *tert*-butyl group adjacent to the electrophilic carbon atom enhancing attack at the anomeric centre. A similar effect can be achieved by benzoyl protecting groups.

In some cases, the glycosylation may also proceed *via* the oxonium ion **2** to give mixtures of anomers **5** (**Scheme 2**). For example, van Boeckel and co-workers showed[11] that coupling of bromide **13** with acceptor **14** in the presence of silver trifluoromethane sulfonate at −50 °C gave the dimer **15** with modest anomeric selectivity of $\alpha:\beta = 2:1$ (**Scheme 5a**). Thus, although the participating benzoyl group present at C-2 of the glycosyl donor **13** should direct β-glycosidic bond formation, mainly the α-linked product was obtained. It was reasoned that the transition state leading to the β-glycoside **18** was strongly disfavoured (mismatched pair) by severe steric hindrance (**Figure 3a**). It was anticipated that the use of glycosyl donor **16** with opposite chirality should give a different stereochemical outcome (double stereodifferentiation). Indeed, coupling of **16** with **14** under identical conditions afforded predominantly the β-linked dimer **17** ($\alpha:\beta = 1:8.4$) (**Scheme 5b**). Computer modelling studies showed that in this case the transition state leading to the β-product **19** is more favoured (matched pair, **Figure 3b**).

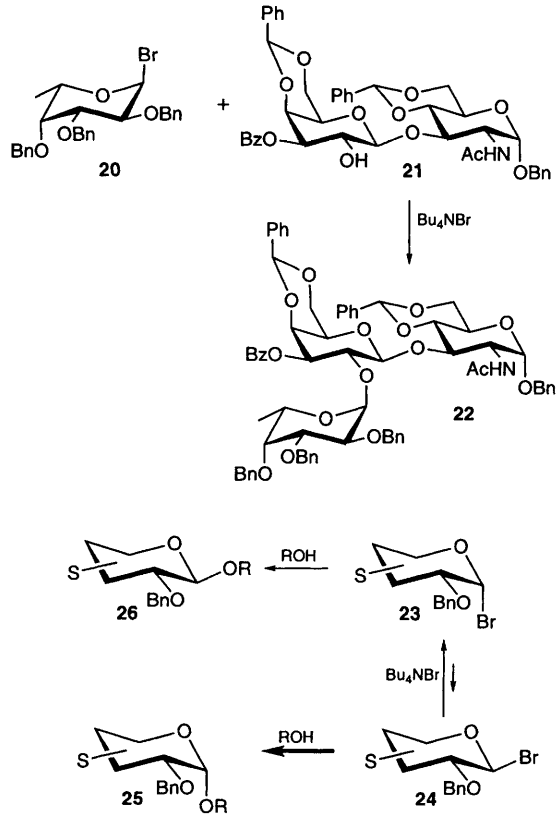
In general, when in glycosylations unexpected $\alpha:\beta$ ratios or very low yields are obtained then unfavourable steric hindrance in the transition state should be considered. These unfavourable interactions may be reduced using sterically less demanding protecting groups.

2.3 *In-situ* anomerisation

A major breakthrough in α-glycosidic bond synthesis came with the introduction of the *in situ* anomerisation procedure. This approach requires

glycosyl donors with a non-participating protecting group at C-2. Lemieux and co-workers described[12] that coupling of bromide **20** with glycosyl acceptor **21** in the presence of tetrabutylammonium bromide gave trisaccharide **22** mainly as the α-anomer (**Scheme 6**). The stereochemical outcome of this reaction was explained by the Curtin–Hammett principle.[13] Thus, in this type of reaction, the tetrabutylammonium bromide catalyses the equilibration between the α- and β-halides **23** and **24**. This equilibrium is shifted strongly towards the α-bromide **23** since this compound is stabilised by the anomeric effect. However, the energy barrier for nucleophilic attack by an alcohol is lower for the β-halide **24**. Therefore, glycosylation will take place from this intermediate and mainly α-glycosides **25** will be formed. However, an important requirement of this reaction is that the rate of equilibration is much faster than that of glycosylation. Furthermore, it is essential that the glycosylation is performed in a solvent of low polarity. In polar solvents, the reaction will proceed *via* an oxycarbonium ion and the anomeric selectivity will be reduced. Tetraalkylammonium halides react only with very reactive glycosyl halides. More reactive activators are required for more demanding glycosylations and nowadays a whole range of activators with different reactivities are available.[6j]

High α-anomeric selectivities have been obtained with other anomeric leaving groups. For example,



Scheme 6

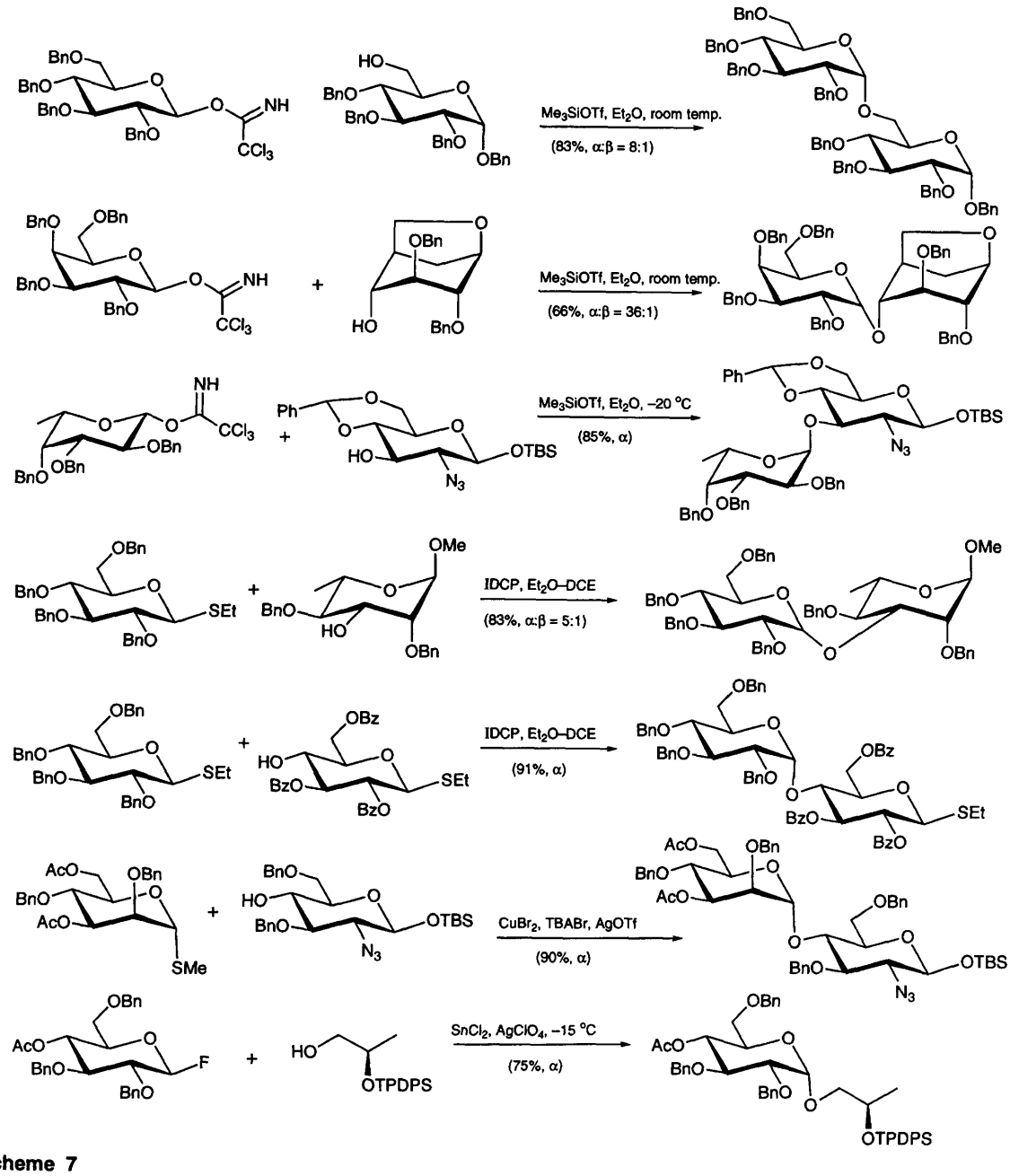
trimethylsilyl triflate mediated couplings of perbenzylated trichloroacetimidates at low temperature give in many cases excellent α-selectivities. Some examples have been reported in which thioglycosides and glycosyl fluorides also give high α-selectivities (**Scheme 7**). It has to be noted that the reaction mechanisms of these glycosylations have been less well studied. However, it is reasonable to assume that they proceed *via* an *in situ* anomerisation process.

As mentioned above, it is very important that the equilibration between the two ion pairs is faster than the glycosylation and many different parameters affect this requirement (see Scheme 2). Often many different reaction conditions have to be examined in order to obtain satisfactory results. Also small changes in the constitution of the glycosyl donor or acceptor may have a dramatic effect on the stereochemical outcome of a glycosylation.

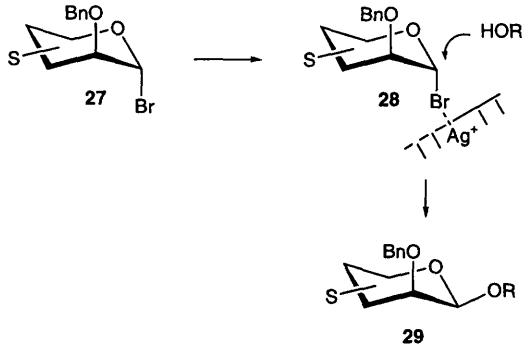
2.4 Glycosylation with inversion of configuration

The *in situ* anomerisation procedure requires a fast equilibrium between an α- and β-ion pair. On the other hand, some glycosylation procedures are based on preventing this pre-equilibration and, hence, glycosylation will proceed *via* inversion of configuration. For example, glycosylation of α-halides **27** in the presence of an insoluble silver salt results mainly in β-glycoside formation **29**.[14] In this case, anomerisation of the halide is restricted because of lack of nucleophiles in the reaction mixture and therefore the reaction will proceed with inversion of configuration. A schematic illustration of the reaction mechanism is depicted in **Scheme 8**. Silver silicate and silver silicate-aluminate have often been applied as the heterogeneous catalyst. These catalysts have proven to be valuable in the preparation of β-linked mannosides which cannot be prepared by neighbouring group participation or *in situ* anomerisation.

The presence of an non-participating substituent on C-2 is an important requirement for a glycosylation using a heterogenous catalyst. However, van Boeckel and co-workers have shown[15] that the nature of the substituents at C-3, C-4 and C-6 also have a major effect on the anomeric ratios of the coupling products. As can be seen in **Scheme 9**, reaction of **30** with **31** gave dimer **32** as an mixture of anomers. However, when the acetyl group at C-3 was replaced by a benzyl group (**33**) then the dimer **34** was isolated mainly as the β-anomer. Reaction of a glycosyl donor having a trichloroacetyl group at C-3 (**35**) with **31** yielded dimer **36** as an anomeric mixture. When glycosyl donors with a 4-*O*-acyl group, **37** and **39**, were used high levels of β-products, **38** and **40**, were obtained. Surprisingly, a glycosyl donor having a 4-*O*-alkyl group (**41**) gave **42** with lower levels of anomeric selectivity. Thus, these results indicate that an acyl group at C-3 decreases and at C-4 increases the β-selectivity. These observations were explained as

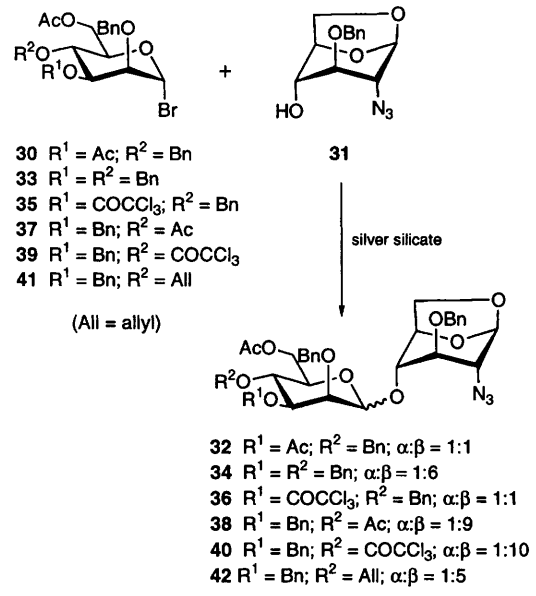


Scheme 7



Scheme 8

follows: anomeric mixtures will be obtained when the glycosylation proceeds *via* an oxonium ion and such an intermediate will be formed when the positive charge at the anomeric centre is well stabilised. A lone pair of the oxygen atom of the 4-*O*-acyl group can interact through bonds with the p(O) ring orbital. Thus, this interaction is stronger than expected with inductive effects only, and the electron withdrawing 4-*O*-acyl substituent suppresses oxy carbonium ion formation. Through-bond interactions are only significant when a succession of *trans*-bridges is available. Therefore, a 3-*O*-acyl group can interact only with the anomeric centre *via* inductive effects. Thus, destabilisation of



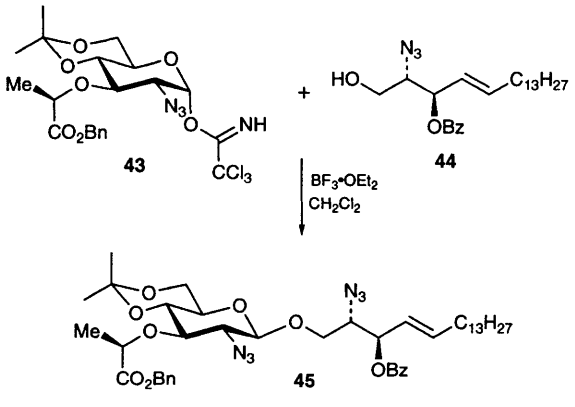
Scheme 9

an oxonium ion is less profound and hence more α-product will be obtained.

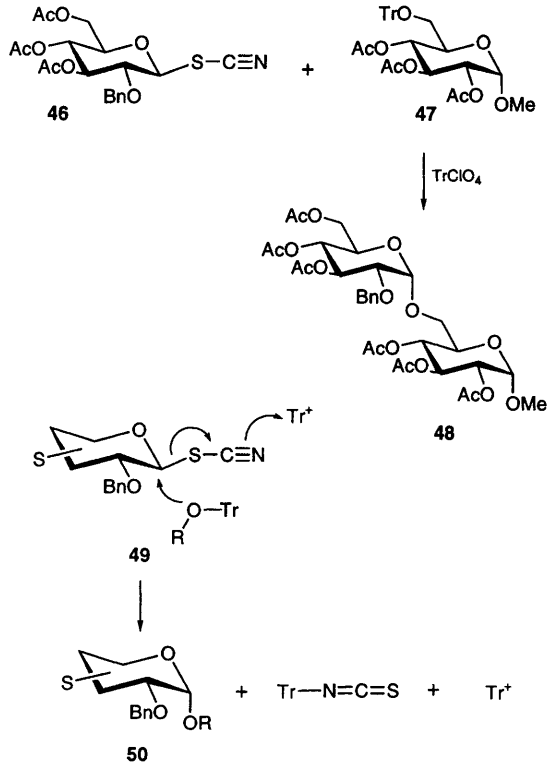
β-Mannosides have also been prepared by direct substitution of an 1-*O*-tosyl-α-mannoglycosyl donor.[16] However, this method has not been applied widely in oligosaccharide synthesis.

Glycosylations may also proceed *via* inversion of configuration when performed in an apolar solvent and activated by a mild promotor. Schmidt and co-workers showed[17] that $BF_3 \cdot Et_2O$ mediated glycosylation of α-glucosyl and α-galactosyl trichloroacetimidate donors in dichloromethane or mixtures of dichloromethane–hexane give mainly β-glycosides. For example, $BF_3 \cdot Et_2O$ mediated coupling of **43** with **44** in dichloromethane at −20 °C gave dimer **45** mainly as the β-anomer (**Scheme 10**).

Kochetkov and co-workers have reported[18] an efficient approach for the synthesis of 1,2-*cis*-pyranosides employing 1,2-*trans*-glycosyl thiocyanates as glycosyl donors and tritylated sugar



Scheme 10

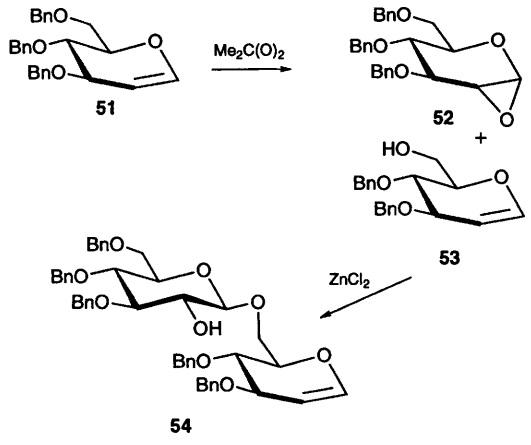


Scheme 11

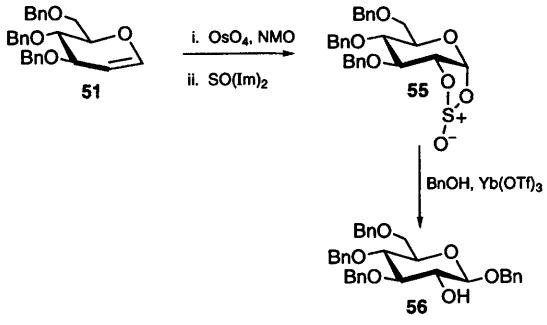
derivatives as glycosyl acceptors. For example, coupling of **46** with tritylated saccharide **47** gave dimer **48** as the α-anomer (**Scheme 11**). This coupling reaction is initiated by the reaction of the nitrogen atom of the thiocyanate **49** with a trityl cation with simultaneous nucleophilic attack by the oxygen atom of the trityl protected sugar alcohol at the anomeric centre to give an α-glycoside **50**. It appears that this reaction proceeds by clean S_N2 inversion at the anomeric centre.

The substitution pattern of a glycosyl donor may also prevent *in situ* anomerisation and under appropriate conditions glycosylation will take place *via* S_N2 substitution. For example, Danishefsky and co-workers have shown[19] that reaction of a 1,2-*cis* epoxide **52**, obtained by epoxidation of a glucal **51** with dimethyldioxirane, with a sugar alcohol **53** in the presence of $ZnCl_2$ gives stereoselectively a 1,2-*trans* glycosidic linked product **54** (**Scheme 12**). However, van Boom and co-workers reported[20] that $ZnCl_2$ mediated glycosylation of 1,2-epoxides derived from galactal gives mixtures of anomers. Thus, in these cases, the reaction proceeds *via* a S_N1 mechanism.

Recently, Kiessling and co-workers used 1,2-cyclic sulfites as glycosyl donors.[21] They argued that these compounds are more easily accessible and less labile than the corresponding epoxides and, hence, more appropriate glycosyl donors. Thus, osmylation of glucal **51** proceeded with high diastereofacial selectivity (19:1) to give a 1,2-diol in high yield (91%) which upon treatment with thionyl



Scheme 12



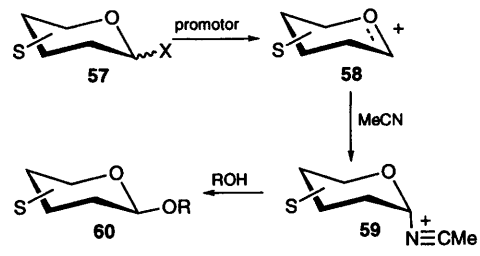
Scheme 13

imidazolide stereospecifically gave the 1,2-*cis* cyclic sulfite **55** (**Scheme 13**). Exposure of **55** to lanthanide(III) triflate and reaction with benzyl alcohol resulted mainly in the formation of 1,2-*trans* glucoside **56** (10:1). It has not been reported whether 1,2-cyclic sulfites also give acceptable results with sugar alcohols as glycosyl acceptors.

2.5 Solvent participation

The stereochemistry of a glycosylation can also be controlled by a participating solvent.[22] The most marked example is the use of acetonitrile which in many cases leads to the formation of an equatorial glycosidic bond.[23] Several groups have independently proposed[24] that this reaction proceeds *via* an α-nitrilium ion **59** which is generated under S_N1 conditions (**Scheme 14**). Nucleophilic substitution of the nitrilium ion by an alcohol will lead to β-glycosidic bond formation (**60**). An important requirement for the reaction is the absence of a participating functionality at C-2.

It has been shown that different types of glycosyl donors (*e.g.* trichloroacetimidates, fluorides, phosphates and pentenyl-, vinyl- and thio-glycosides) feature the ability to form the highly reactive nitrilium intermediates. As can be seen



Scheme 14

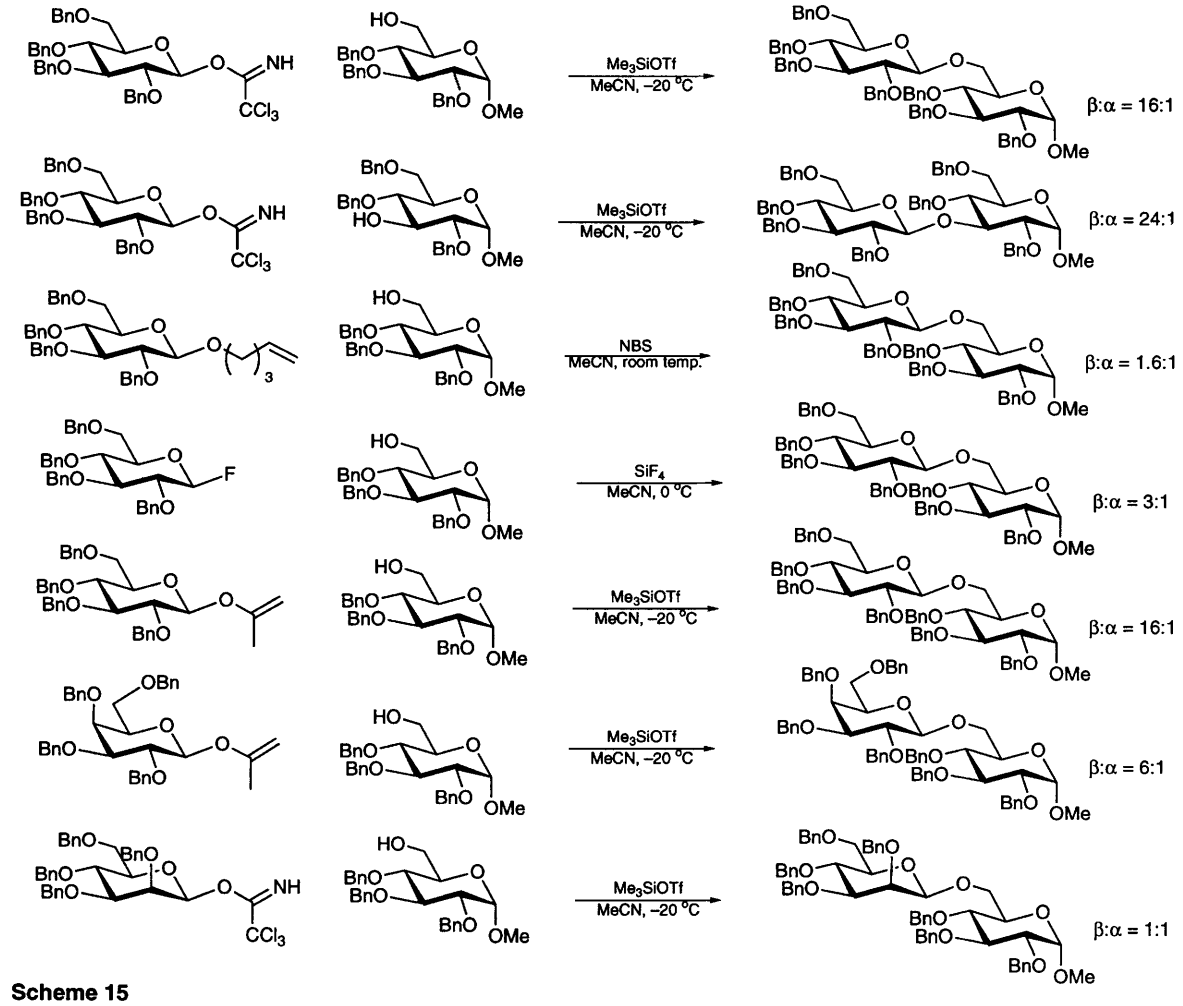
from **Scheme 15**, the highest β-selectivities are obtained with reactive alcohols at low reaction temperatures. Unfortunately, mannosides give poor anomeric selectivities under these conditions.

2.6 Intramolecular aglycon delivery

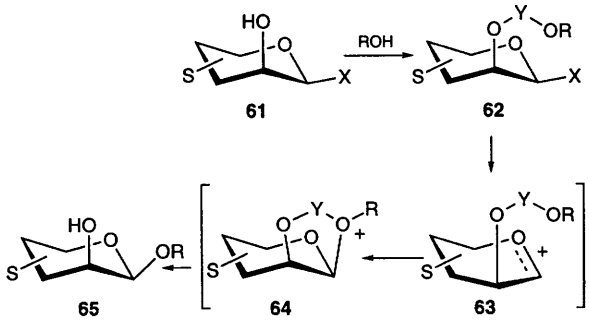
Recently, Stork[25] and Hindsgaul[26] reported independently the preparation of β-mannosides in a highly stereoselective manner by an intramolecular aglycon delivery approach. In this approach, the sugar alcohol (ROH) is first linked *via* an acetal or silicon tether (Y = CH_2 or $SiMe_2$, respectively) to the C-2 position of a mannosyl donor and subsequent activation of the anomeric centre of this adduct **62** forces the aglycon to be delivered from the β-face of the glycosyl donor (**Scheme 16**).

A silicon tether could easily be introduced as is shown in **Scheme 17**. Compound **66** was first converted to the corresponding chlorodimethyl silyl ether and subsequent reaction with **67** gave the tethered compound **68**. Oxidation of the phenylsulfanyl group of **68** yielded phenyl sulfoxide **69** which on activation by the method of Kahne resulted in the selective formation of β-mannoside **70** in a 61% overall yield.

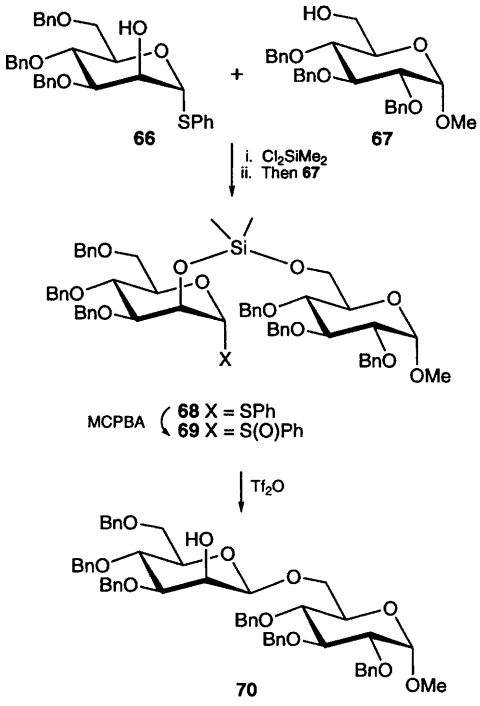
The acetal tethered compound **72** could easily be prepared by treatment of equimolar amounts of **71** with **67** in the presence of a catalytic amount of acid (**Scheme 18**). Reaction of **72** with *N*-iodosuccinimide (NIS) in dichloromethane resulted in the formation of β-linked disaccharide **70** in 61% overall yield. In this reaction, no α-linked disaccharide could be detected. It is of interest to note that when this reaction was performed in the presence of methanol, no methyl glycoside was obtained. This experiment indicates that the glycosylation proceeds *via* a concerted reaction and not a free anomeric carbocation. Recently, Ogawa and co-workers showed[27] that an intramolecular acetal can also be introduced by treatment of a mixture of a mannoside, having a methoxybenzyl protecting group at C-2 and an alcohol with DDQ. Intramolecular aglycon delivery has also been used for the preparation of 1,2-*cis*-glucosides.[28] Furthermore, glycosyl acceptors have also been tethered *via* the hydroxy groups C-4 and C-6.[29] However, in these cases the anomeric ratios in the glycosylations were rather disappointing.



Scheme 15



Scheme 16

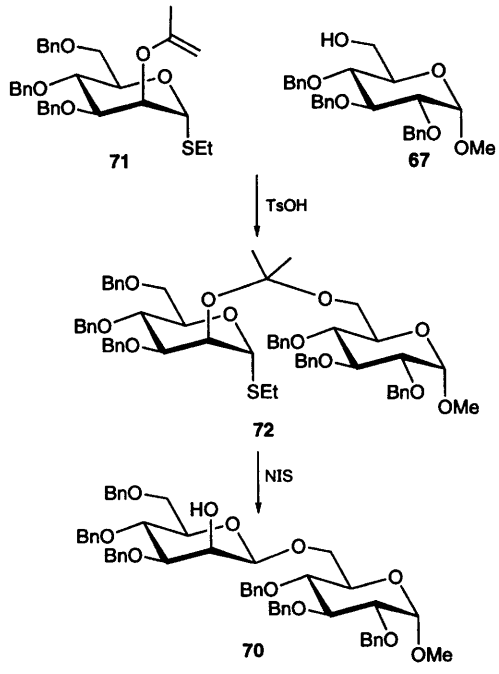


Scheme 17

3 Glycosylation of 3-deoxy-2-ulopyranosonates (3-deoxy 2-ketoaldonic acids)

The above discussed methods for stereoselective glycosylations are mainly applicable to aldoses with a substituent at C-2. However, there are other types of glycosides, the preparation of which requires special consideration.

N-Acetyl-α-neuraminic acid (Neu5Ac) is a cyclic ketoaldonic acid which frequently terminates oligosaccharide chains of glycoproteins and



Scheme 18

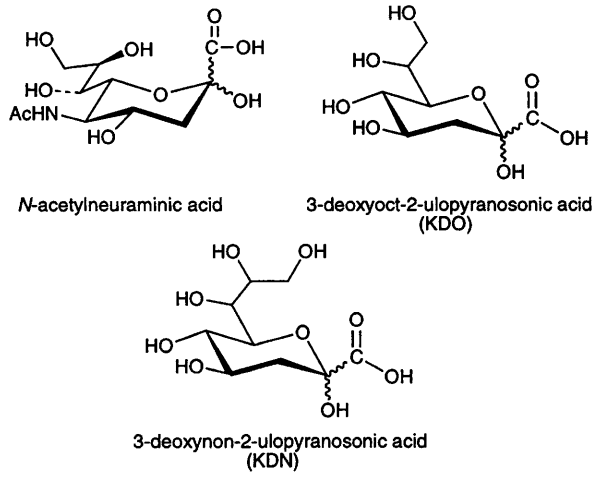
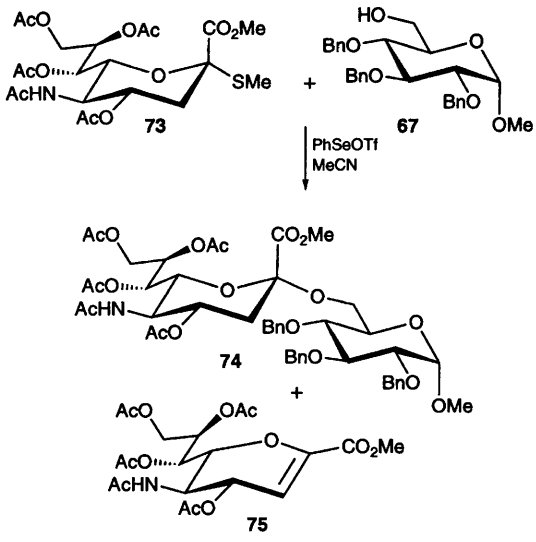


Figure 4 Some important cyclic ketoaldonic acids

glycolipids of cell membranes and plays vital roles in their biological activities (**Figure 4**).[1,2] The use of derivatives of Neu5Ac as glycosyl donors is complicated by the fact that no C-3 functionality is present to direct the stereochemical outcome of the glycosylations. Furthermore, the electron withdrawing carboxylic acid at the anomeric centre makes these derivatives prone to undergo elimination. Finally, the glycosylation of Neu5Ac has to be performed at a tertiary oxy carbonium ion.

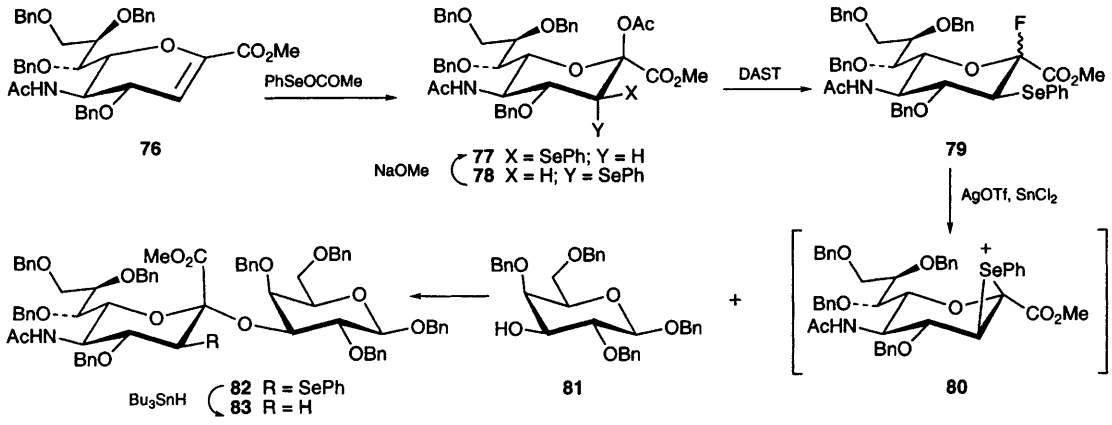
Silver or mercury salt promoted activation of bromides and chlorides of *N,O*-acylated neuraminic acid esters gives, particularly with secondary sugar hydroxy groups as acceptors, only modest yields of the desired α-linked coupling products.[30] Recently, thioglycosides of neuraminic acid derivatives have been used as sialyl donors.[31] These compounds are



Scheme 19

readily available, stable under many different chemical conditions but undergo glycosylation in the presence of a thiophilic reagent [*N*-iodosuccinimide (NIS), dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST) or phenyl selenyl triflate (PhSeOTf)]. For example, PhSeOTf mediated coupling of **73** with **67** in acetonitrile gave mainly the α-linked product **74** ($\alpha:\beta = 82:18$) in a 78% yield (**Scheme 19**). The β-product predominated when the glycosylation was performed in dichloromethane (63%, $\alpha:\beta = 16:84$). Apart from the coupling products glycal **75** was also isolated. Recently, effective sialylations have been reported using phosphites[32] or xanthates[33] as the anomeric leaving group. It is important to note that the anomeric phosphite group can be activated by catalytic amounts of promoter.

Some indirect glycosylation methods have been described which take advantage of a temporary stereocontrolling functionality at C-3 of Neu5Ac.[34] For example, Ogawa and co-workers employed glycosyl donors such as **79** and it was expected that during glycosylation an intermediate episelenium ion **80** would be formed, nucleophilic substitution of which should lead to α-glycosides (**Scheme 20**). Essential for this strategy is the steroselective introduction of a C-3β substituent. The synthesis of **79** was started from the readily available 2,3-dehydro derivative **76**. Thus, reaction of **76** with phenylselenyl acetate afforded a mixture of **77** and **78** in which the axial adduct predominated over the equatorial one. Treatment of this mixture of compounds with sodium methoxide resulted in epimerisation at C-3 (**77**:**78** = 2:1). The epimers could easily be separated by silica gel column chromatography to afford pure **77**. The undesired epimer **78** could be equilibrated to a mixture of **77** and **78**. Treatment of **77** with DAST afforded the glycosyl donor **79**. Silver triflate/tin(II) chloride mediated glycosylation in carbon tetrachloride with the secondary sugar alcohol **81** gave clean formation



Scheme 20

of α-linked product **82**. Finally, the phenylselenyl group could easily be removed by reduction with tributyl tin hydride to give the desired disaccharide **83**. Despite the fact that this method provides a reliable approach for the preparation of α-sialic acid derivatives, it is hampered by the fact that the synthetic sequence is rather laborious.

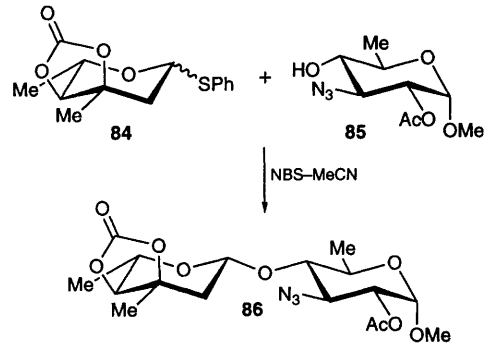
It is important to note that efficient enzymatic methods have been developed for the glycosylation of sialic acid.[35]

Other important 3-deoxy-2-ulopyranosonic acids are KDO and KDN (**Figure 4**). The glycosylation of these compounds is hampered by the same difficulties as for Neu5Ac, but for these compounds no enzymatic approaches have been described yet.

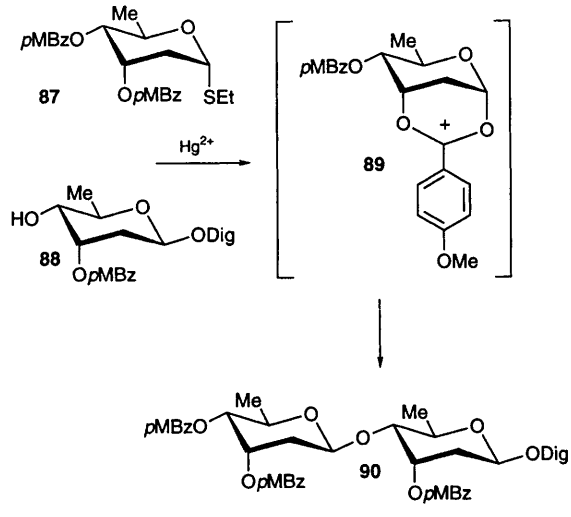
4 Formation of 2-deoxy glycosidic linkages

The macrolides, anthracyclines, cardiac glycosides and aureolic acids are important classes of glycosylated compounds which share the same feature; *i.e.* they contain 2,6-dideoxy glycosides. The introduction of a 2-deoxy α:β-glycosidic linkage requires special considerations since the absence of a functionality at C-2 excludes neighbouring group assisted glycosylation procedures and furthermore enhances the lability of the corresponding glycosyl donors.[36] 2-Deoxy glycosyl halides have been employed in glycosidic bond synthesis; however, yields and stereochemical outcomes were often rather disappointing.[36] The increased stability, ease of preparation and excellent reactivity of 2-deoxy thioalkyl (or thiophenyl) glycosyl donors makes them an ideal choice to be used as glycosyl donors.[37]

For example, it has been reported that reaction of thioglycoside **84** with **85** in acetonitrile in the presence of NBS gave disaccharide **86** in a good yield with high β-selectivity (72%, α:β = 1/9) (**Scheme 21**). In this case, the β-selectivity probably arises from a solvent effect (participation of acetonitrile). On the other hand, Wiesner and co-workers used a participating 3-*O*-*p*-methoxybenzoyl protecting group to obtain β-selectivity (**Scheme 22**).[38] Thus, mercury-ion assisted glycosylation of **87** gave high levels of



Scheme 21



*p*MBz = *para*-methoxybenzyl

Scheme 22

β-selectivity and it was assumed that this glycosylation proceeds *via* intermediate **89**. However, Binkley and co-workers suggested that neighbouring group participation of a C-3 acetoxy functionality is not a major determinant of stereochemical outcome of this type of

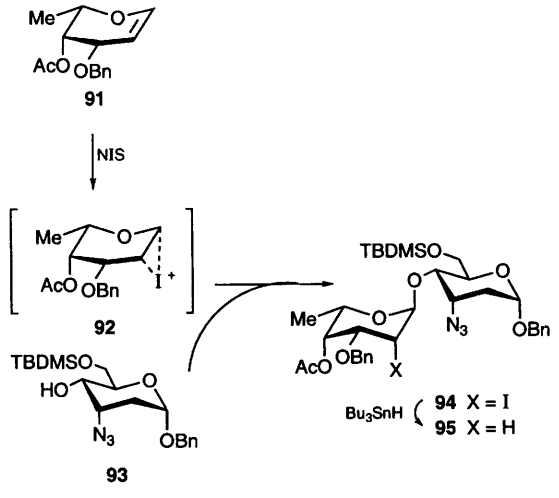
glycosylation.[39] Thiem and co-workers showed[40] that *S*-(2-deoxyglycosyl) phosphorodithioates are also relatively stable donors for 2-deoxy-glycosyl preparation.

Other reliable approaches are based on the use of a temporary directional functionality at C-2.[41] For example, treatment of glucal **91** with NIS as an electrophile leads to the formation of intermediate **92** which is favoured by an inverse anomeric effect (**Scheme 23**). Nucleophilic attack by **93** from the opposite side provided the α-glycosidic linked dimer **94**. The iodo derivative could be reduced with tributyl tin hydride to give the corresponding 2-deoxy glycoside **95**.

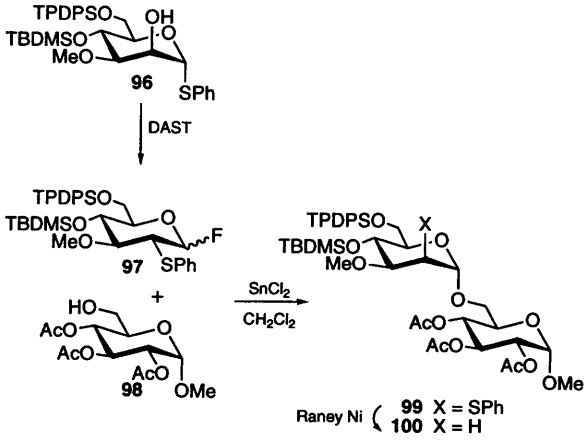
Recently, it was observed that treatment of various 2-hydroxy sugars with diethylaminosulfur trifluoride (DAST) resulted in a stereoselective 1,2-migration.[42] For example, treatment of **96** with DAST gave the glycosyl fluoride **97** as mixture of anomers. Compound **97** could be used as a glycosyl donor and, depending on the solvent, α- and β-glycosides could be prepared (**Scheme 24**). The thiophenyl group of a coupling product **99** could be removed by reduction with Raney Ni to afford a corresponding 2-deoxy glycoside **100**.

A similar type of migration was observed when a thioglycoside having a phenoxythiocarbonyl ester on C-2 was activated with iodonium ions.[43] For example, treatment of a mixture of **101(a** or **b)** and **104** with NIS/TfOH gave the formation of 1,2-*trans* β-glucoside **105** (**a** or **b**) (**Scheme 25**). The reaction proceeds probably *via* the intermediate **102** (**a** or **b**) and **103** (**a** or **b**) which are formed after iodonium ion activation of the phenoxythiocarbonyl ester of **101** (**a** or **b**). It was noted that the glycosylation with an SEt glycosyl donor is more effective then for the SPh donor (85% and 75% respectively). However, it is well known that Raney nickel mediated desulfurisation of the SEt derivative **105a** is less facile (50%, 5 d) than of SPh derivative **105b** (81%, 2 h). When in this reaction a glucose-type of glycosyl donor is used then α-linked 2-deoxy glycosides can be obtained.

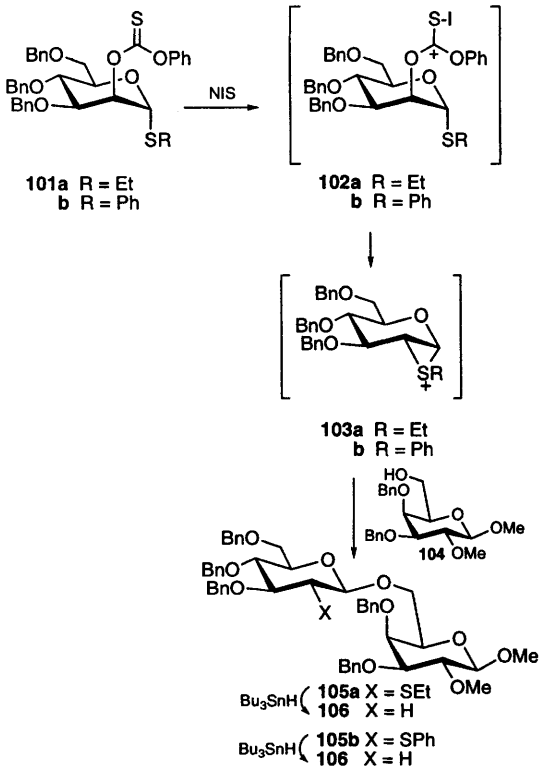
Toshiba and co-workers have designed conformationally rigid glycosyl donors which possess a thioether bridge between the C-2 and C-6 position and these compounds have been used for the stereoselective synthesis of 2,6-dideoxy glycosides (**Scheme 26**).[44] Chemoselective activation of the anomeric thiophenyl moiety of **107** with NIS/TMSOTf and reaction with the hydroxy group of **108** gave mainly formation of the α-linked dimer **109** in high yield (89%). The chemoselectivity of this reaction is based on the greater reactivity of the 2,6-anhydro-2-thio glycosyl donor **107** compared to that of the 2,6-anhydrosulfenyl sugar **108** (for



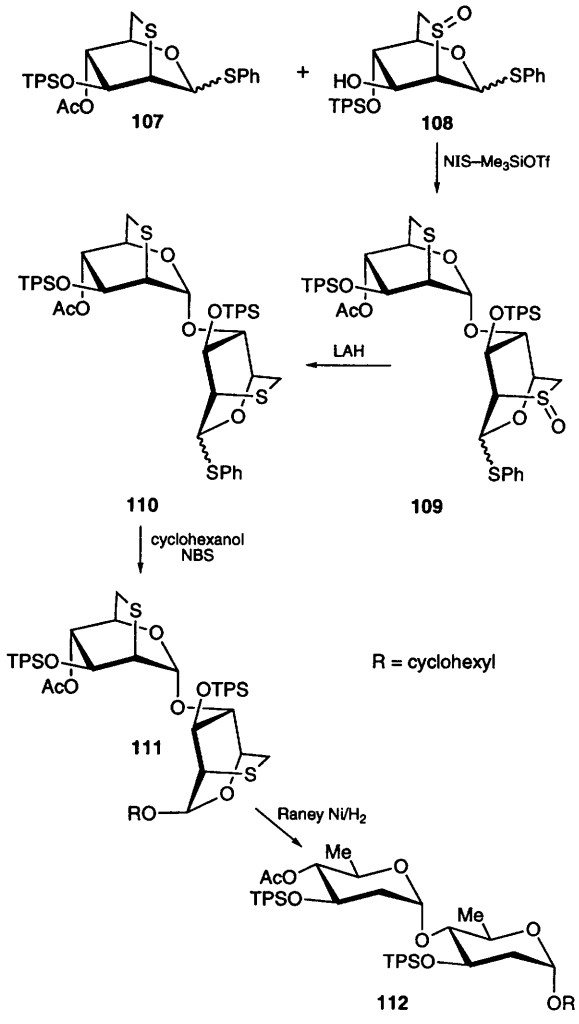
Scheme 23



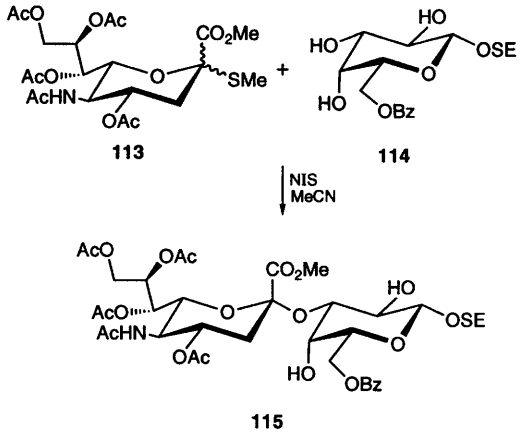
Scheme 24



Scheme 25



Scheme 26



Scheme 27

chemoselective glycosylations see paragraph 7). The sulfoxide moiety of **109** was reduced with lithium aluminium hydride to afford **110** which was glycosylated with cyclohexanol to yield **111**. Finally, reductive cleavage of the thioethers of **111** gave the 2,6-dideoxy glycoside **112**.

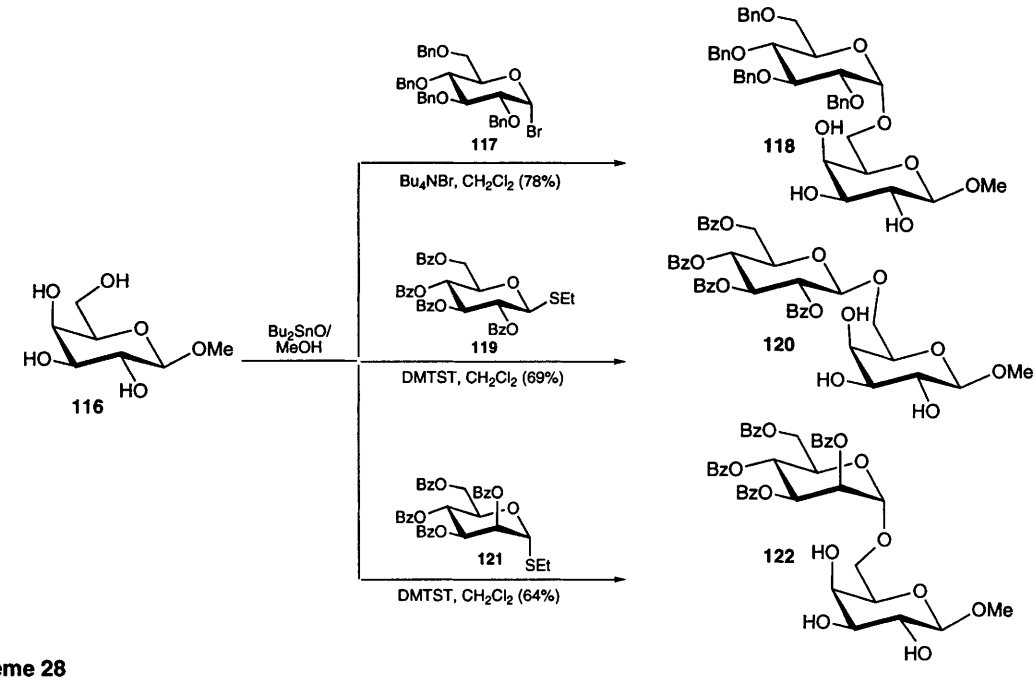
In an interesting approach to glycosides of 2-deoxy sugars, Giese and co-workers reported[45] that treatment of a 2-*O*-phosphoryl bromide and a sugar alcohol with Bu_3SnH under conditions of photochemical initiation gave the corresponding 2-deoxy glycoside. In this reaction, the phosphoryl bromide rearranges to give a 2-deoxy derivative which undergoes glycosylation. The anomeric ratios in this approach were disappointing.

5 Regioselective glycosylations

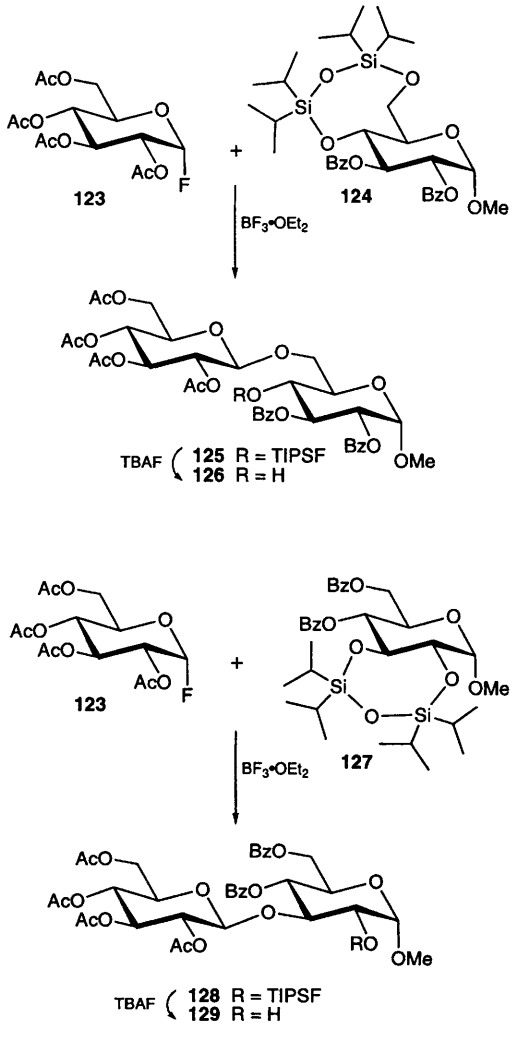
In most glycosylations, the glycosyl acceptor contains only one free hydroxy group. However, when two or more hydroxy groups differ significantly in reactivity then a regioselective glycosylation can be considered. For example, iodonium ion promoted glycosylation of the thioglycoside **113** derived from neuraminic acid with triol **114** in acetonitrile gave dimer **115** in a 61% yield, exclusively as the α-anomer (**Scheme 27**).[46] The regioselectivity of this reaction is due to the greater reactivity of the equatorial alcohol compared to the axial hydroxy group. Furthermore, a C-2 hydroxy group has generally a lower nucleophilicity due to the electron withdrawing effect of the anomeric centre. It is of interest to note that the yield of this reaction is significantly higher than when performed on a galactosyl acceptor having only a free C-3 hydroxy group. It should also be realised that the procedures for the preparation of glycosyl acceptors having several free hydroxyls are often easier to conduct and, hence, may offer shorter routes to oligosaccharides.

Recently, Garegg and co-workers reported[47] that glycosidation of the tin acetal of unprotected methyl galactoside gave regioselectively 1,6 linked dimers in yields of 44–81% (**Scheme 28**). For example, the main product obtained when methyl β-D-galactopyranoside **116** was treated first with dibutyltin oxide and then reacted with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide **117** in the presence of tetrabutylammonium bromide was the α-linked dimer **118** in a 78% yield. Glycosidation of the same stannylene derivative with thioglycosides **119** and **121** in the presence of dimethyl-(methylthio)sulfonium triflate (DMTST) as the thiophilic promotor gave the 1,6 linked products **120** and **122**, respectively. Owing to the participating group at C-2, the products had the expected β-configuration. No orthoester formation was observed in these reactions. Furthermore, when the reactions were performed in the absence of stannylene activation, no reaction products or mixtures of oligomers were obtained.

Ziegler and co-workers have found[48] that 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl (TIPS) protected glycosides can be regioselectively glycosylated by glycosyl fluorides using $BF_3 \cdot OEt_2$ as the promoter (**Scheme 29**). For example, treatment of **124** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl



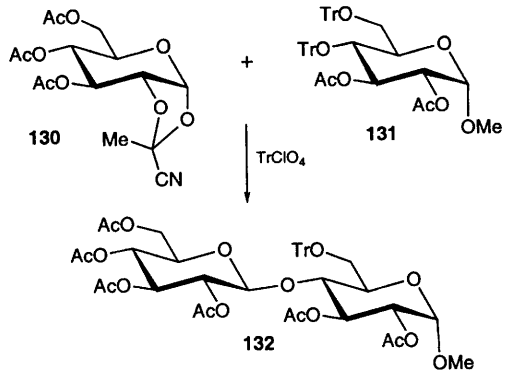
Scheme 28



Scheme 29

fluoride **123** in the presence a catalytic amount of $BF_3 \cdot OEt_2$ in dichloromethane resulted exclusively in glycosylation at the C-6 position to give the β-linked disaccharide **125** in a 71% yield. Apart from the dimer, a small amount of the partial hydrolysed monomer was isolated. Thus, in this reaction the BF_3 hydrolyses partially the silyl diether as well as activates the anomeric fluoride. The silyl group at C-4 of dimer **125** could easily be removed by treatment with a catalytic amount tetrabutylammonium fluoride to give **126**. When the 2,3-TIPS-protected methyl glycoside **127** was treated with **123** in the presence of $BF_3 \cdot Et_2O$ the corresponding laminaribioside **128** was solely formed. On the other hand, predominantly C-2 glycosylation was observed when methyl 4,6-*O*-benzylidene-α-D-glucopyranoside was coupled under various conditions with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide. Thus, in the latter example, the TIPS-protecting group completely reverses the regioselectivity. This observation was explained by the fact that the C-2 position of **127** is sterically very congested forcing the glycosylation to take place at the C-3 position.

Recently, Kochetkov and coworkers reported[49] an other approach to invert expected regioselectivity (**Scheme 30**). They showed that mainly the 1,4-linked disaccharide **132** was formed when the cyanoethylidene glycosyl donor **130** was coupled with the di-tritylated glycosyl acceptor **131** in the presence of a catalytic amount of $TrClO_4$. The opposite reactivity of primary and secondary trityl ethers in comparison with the corresponding alcohols could be explained by the formation of an earlier transition state upon glycosylation of trityl ethers compared to that of alcohols. Thus, in such a glycosylation the electron density at the oxygen atom and not steric factors determines the regioselectivity.



Scheme 30

6 Convergent block synthesis

Oligosaccharides can be prepared by a linear glycosylation strategy or by block synthesis. In a linear glycosylation strategy, monomeric glycosyl donors are added to a growing saccharide chain. Such an approach is less efficient than when oligosaccharide building blocks are used as glycosyl donors and acceptors (convergent approach). Glycosyl bromides have been used in block synthesis; however, results were often rather disappointing especially with labile bromides.[50]

Nowadays a variety of glycosyl donors are available which can be prepared under mild conditions, are sufficiently stable to be purified and stored for a considerable period of time, undergo glycosylations under mild conditions, and by selecting the appropriate reaction conditions give high yields and good $\alpha:\beta$ ratios. These features allow the preparation of oligosaccharides by efficient block syntheses.

The favourable properties of the trichloroacetimidate methodology have been exploited in the block synthesis of the prominent tumour associated dimeric antigen Lewis X (Le^X).[51] The retrosynthetic strategy is depicted in **Figure 5**. In order to make efficient use of common building blocks, it was decided to disconnect the octasaccharide into two trimeric units and a lactoside residue. The trisaccharide was further disconnected into a fucose and a lactosamine moiety and the latter was readily available from lactose. Thus, the strategy was designed in such a manner that optimal use could be made of the cheaply available disaccharide lactose. In such an approach, the number of glycosylation steps is considerably reduced. The key building blocks for the preparation of the target compound **I** were **133**, **134** and **135**.

The azido-lactose building block **134** was prepared by azidonitration of lactal, followed by selective protection. The selectively protected lactoside **135** was readily available from lactose *via* a sophisticated protecting group interconversion strategy. α-Fucosylation of acceptor **134** with the very reactive fucosyl donor **133**, under 'inverted procedure' conditions,[52] gave trisaccharide **136** in a 89% yield (**Scheme 31**). The trisaccharide **136** was converted into the required glycosyl donor **137** and acceptor **138**. Thus, removal of the TBDMS protecting group of **136** with TBAF and treatment of the resulting lactol with trichloroacetonitrile in the presence of DBU afforded trichloroacetimidate **137** in a good overall yield. On the other hand, cleavage of the isopropylidene moiety of **136** under mild acidic conditions furnished **138**.

Coupling of glycosyl donor **137** with acceptor **138** in the presence of $BF_3 \cdot Et_2O$ as catalyst gave the hexasaccharide **139** in a 78% yield. In the latter reaction, the higher acceptor reactivity of the equatorial 3-OH group with respect to the axial 4-OH was exploited. The synthesis of octasaccharide **142** required the repetition of the above described strategy, *i.e.* conversion of the anomeric TBDMS group into a trichloroacetimidate functionality (**139**→**141**) and coupling of the trichloroacetimidate **141** with lactoside unit **135** (64%). Finally, target molecule **I** was obtained by reduction of the azido group of **142**, followed by acetylation of the amino group and hydrogenation under acidic conditions. Using a similar approach, spacers containing dimeric and trimeric Lewis X antigens have been synthesised.[51e]

The described glycosylation strategy is highly convergent and makes optimal use of the common trisaccharide **136**. Furthermore, efficient use was made of the commercially available dimer lactose. Finally, the trichloroacetimidates could be prepared

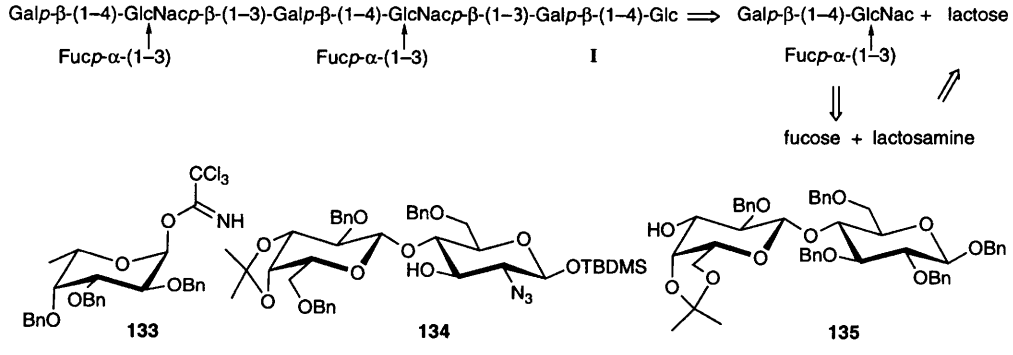
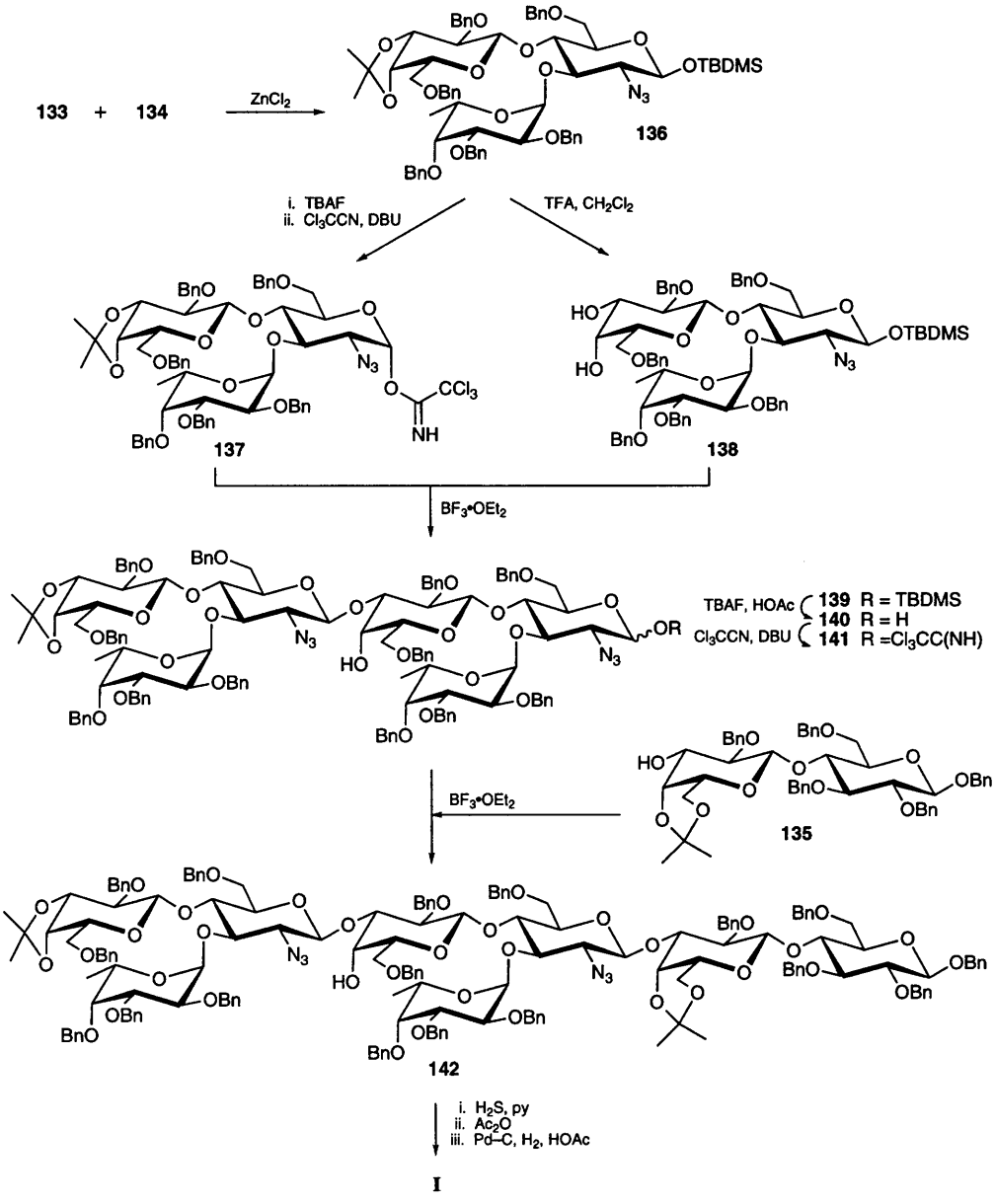


Figure 5

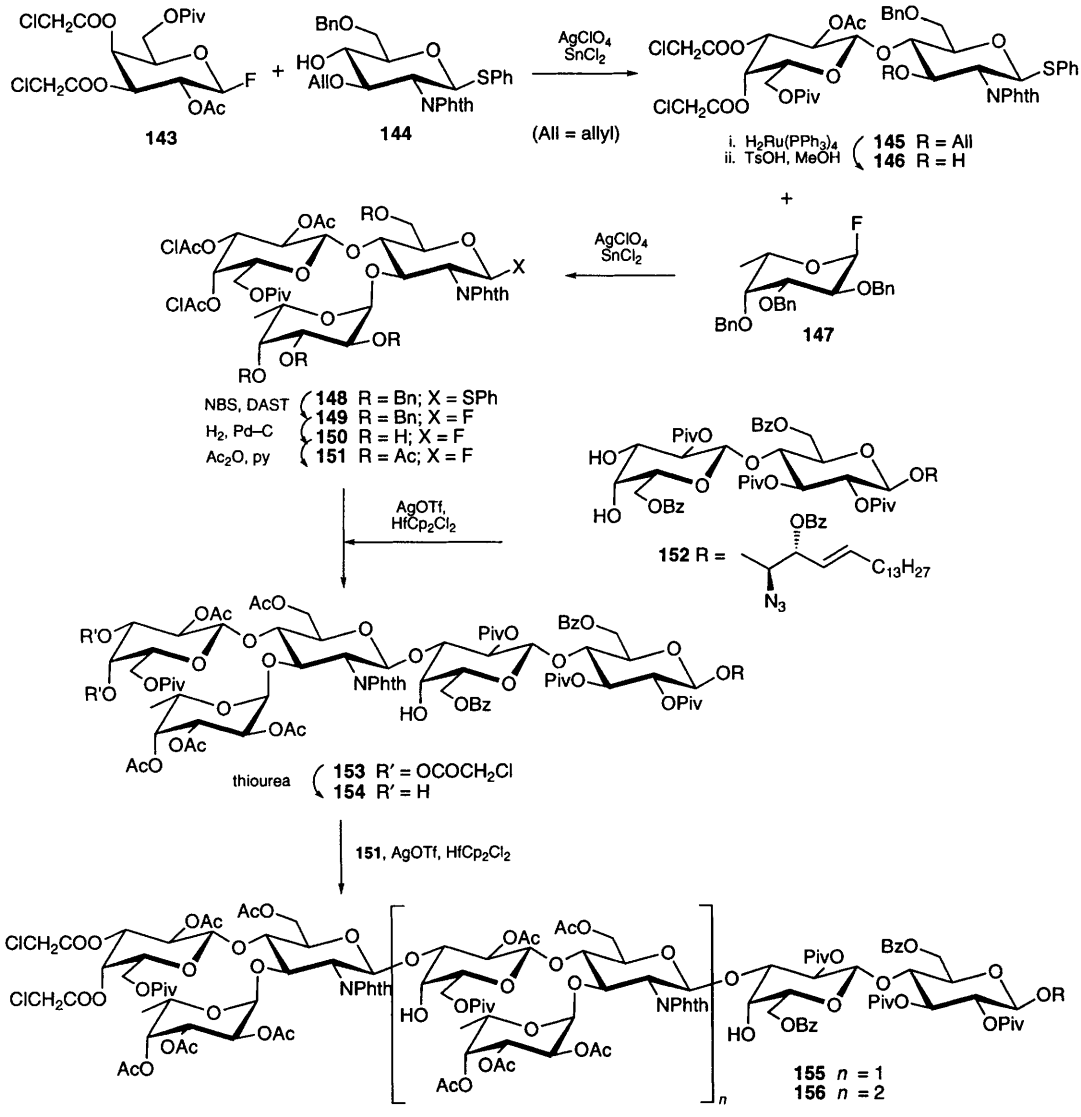


Scheme 31

in high yield and these donors behaved very well in the glycosylation reactions (high yields and anomeric selectivities). The latter point requires some attention. It should be realised that some types of glycosidic linkages can be constructed rather easily whereas others impose great difficulties. In planning a synthetic scheme, the disconnections should be chosen in such a way that the block assembly will not impose problems. Furthermore, difficult glycosylations should be performed in an early stage of the synthesis.

Nicolaou and co-workers have prepared[53] a trimeric Le^x antigen exploiting the favourable properties of anomeric phenylthio groups (**Scheme 32**). As in the approach of Schmidt and co-workers, the target molecule is disconnected into a common trisaccharide (**151**) and a lactoside building block (**152**). In this case, the trisaccharide intermediate is assembled from monomers, **143**, **144** and **147**. Furthermore, the building blocks are assembled in a different order. Thus, coupling of **143** with **144** in the presence of silver perchlorate and tin(II) chloride gave stereospecifically the β-glycoside **145** in a 72% yield. Selective removal of the allyl protecting group of **145** furnished glycosyl acceptor **146** which was coupled with the fully benzylated fucosyl fluoride **147** to yield trisaccharide **148** in a 87% yield. Thioglycoside **148** was converted into a glycosyl fluoride **149** by treatment with *N*-bromosuccinimide (NBS) and DAST which was followed by a protecting group exchange to give glycosyl donor **151** in a 84% overall yield.

Coupling of **151** with lactoside **152** in the presence of silver triflate (AgOTf) and $HfCp_2Cl_2$

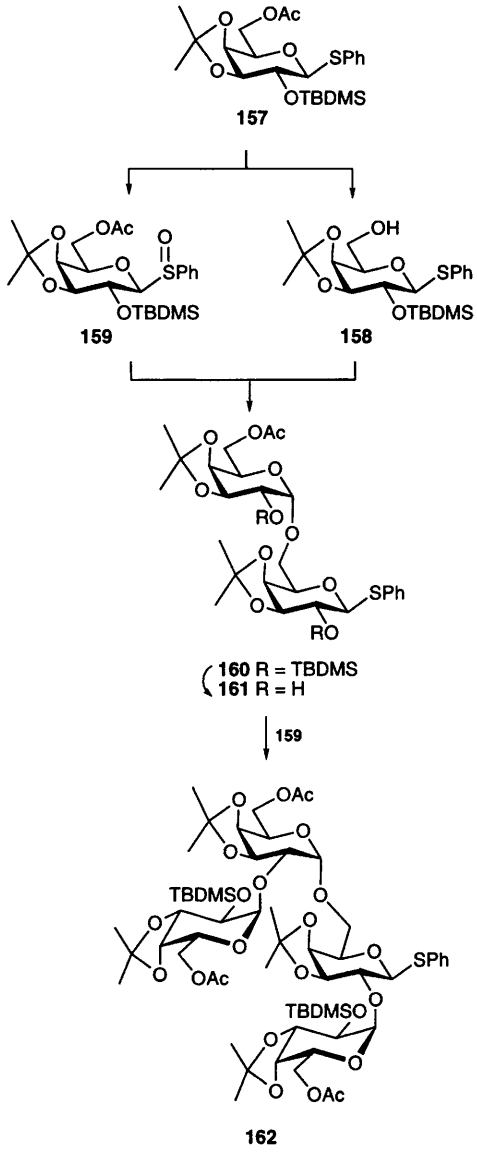


Scheme 32

occurred regioselectively at the more reactive 3-position to give stereoselectively the pentasaccharide **153** (91%). The chloroacetyl groups of **153** were removed by treatment with thiourea and two reiterations of the coupling and deprotection procedure led to the isolation of undecasaccharide **156**. Compound **156** was deprotected to yield the desired trimeric Le^X antigen. This described strategy is highly convergent and minimises the number of manipulations which have to be executed at the oligosaccharide stage. Attractive features of the strategy are: (i) the stability of thioglycosides under many different chemical conditions, (ii) the ease of activation of thioglycosides by conversion into glycosyl fluorides, (iii) the high efficiency of glycosyl fluorides in glycosidic bond formation and, (iv) the excellent behaviour of thioglycosides as glycosyl acceptors. Apart from these synthetic approaches, several alternative synthetic routes for Le^X have been reported.[54]

Martin-Lomas and co-workers reported[55] a highly convergent approach for the preparation of the fully protected tetragalactoside moiety of the GPI anchor of *Trypanosome brucei*. In this approach the tetrasaccharide **162** was prepared from the common building block **157** (**Scheme 33**). Thus, the common building block **157** could be converted into the glycosyl acceptor **158** by base-mediated removal of the acetyl protecting group. Treatment of **157** with MCPBA gave the anomeric sulfoxide **159** which was coupled under the conditions described by Kahne to give dimer **160** (78%, $\alpha:\beta = 86:14$). Dimer **160** was converted into the glycosyl acceptor **161** which was coupled with **159** to give the tetrasaccharide **162**. The phenylthio group of **162** could be oxidised to the corresponding anomeric sulfoxide and is ready for further glycosylation.

In the examples discussed above only one type of anomeric leaving group has been used. However, for the successful preparation of complex oligo-



Scheme 33

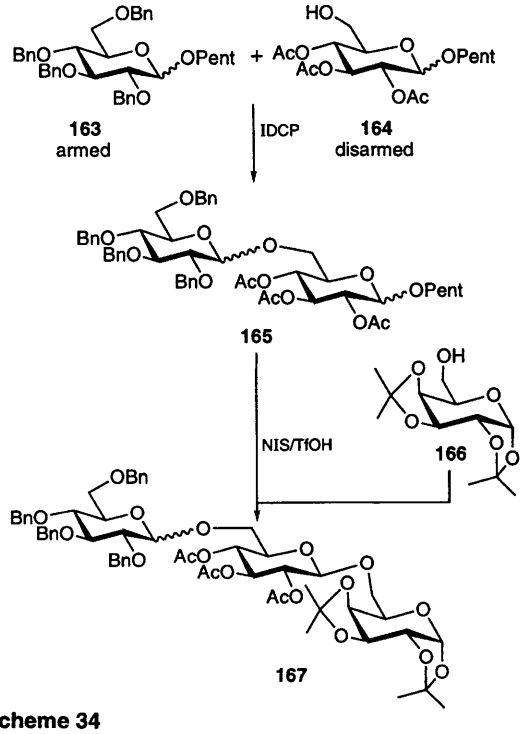
saccharides, a range of different leaving groups often need to be examined.

7 Chemoselective glycosylations

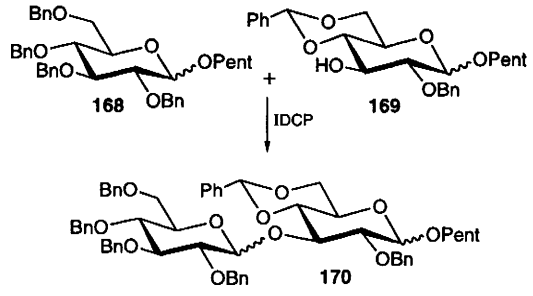
An important requirement of convergent oligosaccharide synthesis is ease of accessibility of oligosaccharide building blocks. Fraser-Reid and co-workers have introduced[6h,56] a chemoselective glycosylation (armed-disarmed glycosylation strategy) which allows the preparation of this type of unit with a minimum of protecting group manipulations. They have shown that pentenyl glycosides having a C-2 ether protecting group can be coupled chemoselectively to C-2 benzoylated pentenyl glycosides. The chemoselectivity relies on the fact that an electron withdrawing C-2 ester deactivates (disarms) and an electron donating C-2 ether activates (arms) the anomeric centre.

Thus, coupling of armed donor **163** with disarmed acceptor **164**, in the presence of the mild activator iodonium di-collidine perchlorate (IDCP), gave the dimer **165** as an anomeric mixture in a yield of 62% (**Scheme 34**). Next, the disarmed dimer **165** could be further glycosylated with acceptor **166**, using the more powerful activating system *N*-iodo-succinimide–catalytic triflic acid (NIS–TfOH) to yield the trisaccharide **167** (60%). Thus, this chemoselective glycosylation approach allows the preparation of a trisaccharide without a single protecting group manipulation between the glycosylations. The C-2 acyl protecting group of compound **165** performs neighbouring group participation in the glycosylation and therefore only a 1,2-*trans* linked product will be formed. When a 1,2-*cis* glycosidic linkage is required, the acyl group has to be replaced by an ether type protecting group, hence introducing additional manipulations at the oligosaccharide stage.

It has also been found that cyclic acetals reduce the reactivity of pentenyl glycosides.[57] This deactivating effect is large enough to allow a chemoselective glycosylation of benzylated pentenyl glycosyl donor **168** with cyclic acetal protected glycosyl acceptor **169** to give dimer **170** as an anomeric mixture in a modest 52% yield (**Scheme 35**). It should be noted that compound **170** has a non-participating C-2 benzyl functionality and coupling of **170** with a glycosyl acceptor will allow the introduction of an α-glycosidic linkage. Deactivation by cyclic acetals reflects presumably the torsial strain inflicted upon the developing cyclic oxy carbonium ion, the planarity of which is opposed by the cyclic protecting group. The pentenyl methodology has been applied to the preparation of several complex oligosaccharides.[58]

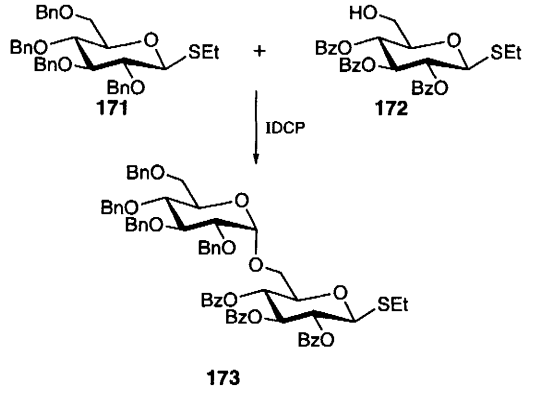


Scheme 34



Scheme 35

Chemoselective glycosylations have also been developed for other types of glycosides. Van Boom and co-workers showed[59] that, similar to pentenyl glycosides, the reactivity of thioglycosides towards iodonium cations can be modulated by the choice of protecting groups and it was found that a C-2 ether group activates and a C-2 ester deactivates the sulfur atom at the anomeric centre. Thus, iodonium cation mediated coupling of **171** with **172** gave disaccharide **173** mainly as the α-anomer in a 84% yield (**Scheme 36**). In addition, it was established

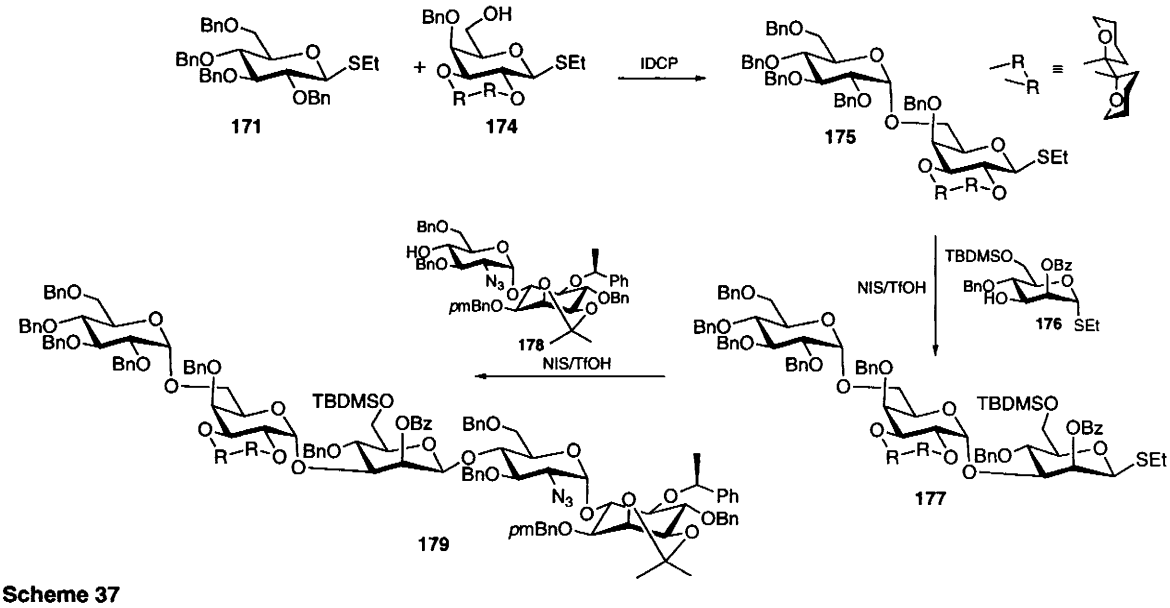


Scheme 36

that a disarmed thioglycoside (*e.g.* **173**) could be readily activated with the strong thiophilic promotor NIS/TfOH. It was also found that thioglycosides are more reactive than analogous pentenyl glycosides and give often better α-selectivities. In this case, the chemoselective glycosylation approach was rationalised as follows: the electron density on the anomeric sulfur atom in a 2-*O*-acyl ethyl thioglycoside is decreased, due to the inductive effect of the electron withdrawing ester functionality at C-2 and as a result, the nucleophilic complexation of the anomeric thio group with iodonium ions decreases and the thioglycoside can be regarded as disarmed with respect to an armed 2-*O*-alkyl thioglycoside.[59d]

Ley and co-workers proposed[60] that the armed–disarmed glycosylation strategy could gain versatility by tuning the glycosyl donor leaving group ability further. They described that a dispiroketal protecting group (R–R) has a marked effect on the reactivity of the anomeric centre and it was found that a dispiroketal protected thioglycoside (*e.g.* **174**, **Scheme 37**) has a reactivity between an armed C-2 alkylated thioglycoside (*e.g.* **171**) and a disarmed C-2 acyl thioglycoside (*e.g.* **176**). The three levels of anomeric reactivity were exploited in the preparation of a protected pentasaccharide unit common to the variant surface glycoprotein of *Trypanosome brucei*. Thus, iodonium dicollidine perchlorate mediated chemoselective glycosylation of glycosyl donor **171** with dispiroketal protected acceptor **174** gave disaccharide **175** in an excellent yield (82%, $\alpha:\beta = 5:2$). Further chemoselective glycosylation of the torsially deactivated donor **175** with electronically deactivated acceptor **176** in the presence of the more powerful activator NIS–TfOH gave trisaccharide **177** in 63% yield as one isomer. Finally, the pseudo-pentasaccharide **179** was obtained by condensation of glycosyl donor **177** with glycosyl acceptor **178**.

In the armed–disarmed glycosylation approach, the leaving group ability is controlled by protecting

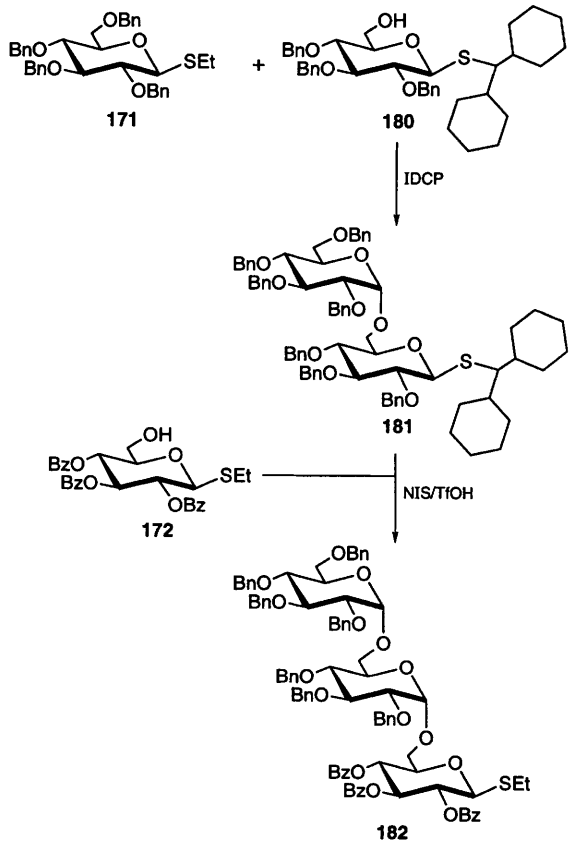


Scheme 37

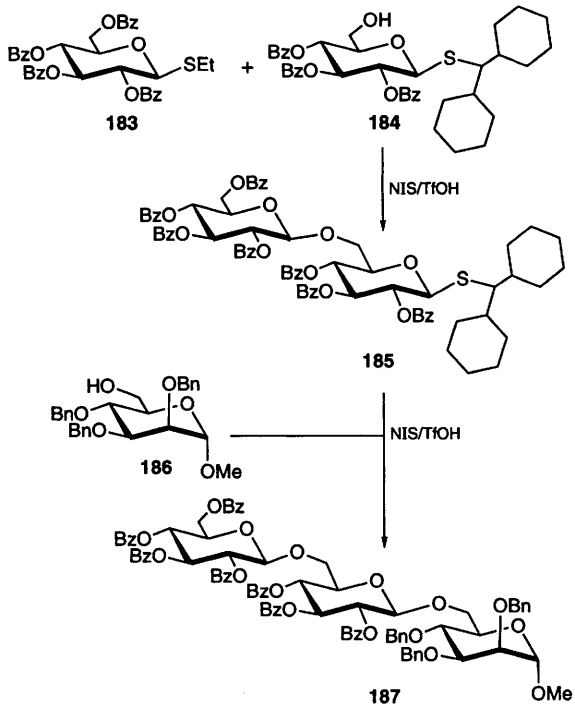
groups (ether–dispiroketal–ester). It may, however, be advantageous to control the anomeric reactivity by means of modifying the leaving group itself. Boons and co-workers showed[61] that the bulkiness of the anomeric thio group has a marked effect on glycosyl reactivity whereby a new range of differentially reactive coupling substrates could be produced (**Schemes 38** and **39**).

Thus, IDCP mediated chemoselective glycosylation of glycosyl donor **171** with glycosyl acceptor **180** gave the disaccharide **181** in an excellent yield of 79% as one anomer. Further chemoselective coupling of sterically deactivated donor **181** with the electronically deactivated glycosyl acceptor **172** in the presence of the more powerful promoter system NIS–TfOH gave trisaccharide **182** in a 82% yield. In both coupling reactions, no self-condensed or polymeric products were detected. These experiments show that the reactivity of a C-2 benzylated dicyclohexylmethyl thioglycoside is of an order of magnitude *between* the reactivities of ethyl thioglycosides having a fully armed ether and disarmed ester protecting group on C-2.

The new method to control the anomeric leaving group mobility allowed the generation of glycosyl donors or acceptors with new reactivities. It was envisaged that the sterically and electronically deactivated glycosyl acceptor **184** should have a lower reactivity than the electronically deactivated



Scheme 38

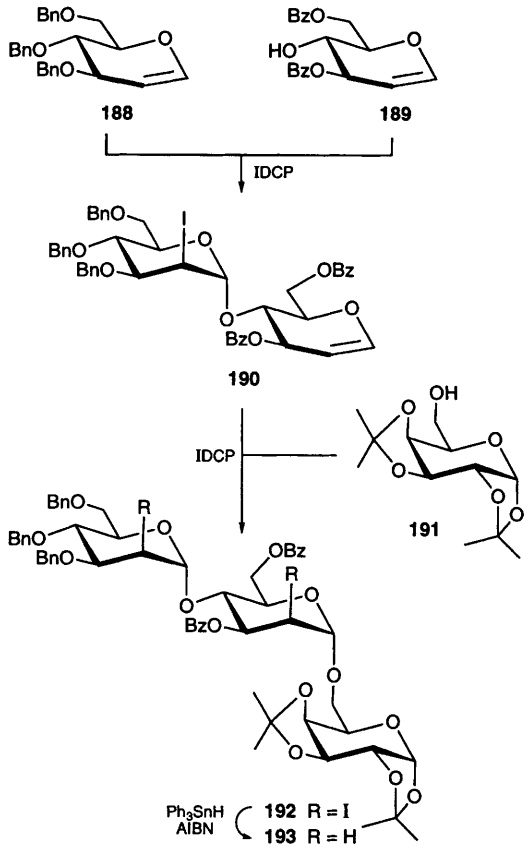


Scheme 39

glycosyl donor **183** (**Scheme 39**). Indeed, coupling of glycosyl donor **183** with glycosyl acceptor **184** in the presence of NIS–TfOH gave dimer **185** in a 61% yield. Glycosyl donor **185** was coupled with **186** in the presence of NIS–TfOH and trisaccharide **187** was isolated in a good yield. The latter reaction demonstrated that a sterically and electronically deactivated substrate is still a suitable glycosyl donor. This glycosylation approach offers the largest number of reactivity levels published to date.

Investigations by Danishefsky and co-workers have revealed[62] that chemoselective activation is also applicable to glycals and this methodology opened the way for the efficient preparation of 2-deoxy containing oligosaccharides (**Scheme 40**). Thus, IDCP mediated chemoselective oxidative coupling of ether protected glycal **188** with the partly acylated glycal **189** stereoselectively gave the disaccharide **190** in 58% yield. The dimer **190** could also be activated with IDCP and reaction with glycosyl acceptor **191** yielded trimer **192** (79%). Radical mediated dehalogenation of **192** afforded the 2-deoxy glucoside containing trisaccharide **193** (94%). In another strategy,[63] glycals were activated by epoxidation followed by stereoselective condensation with a partly protected glycal. After protection of the 2-hydroxy group, this procedure could be repeated.

The chemoselective glycosylations described in this section allow the facile preparation of di-, tri- and tetra-saccharides. These saccharides can be used in a convergent block synthesis of larger oligosaccharides. Often the monomeric units required for the preparation of the building block can be synthesised from a common unit. It should



Scheme 40

be noted also that other glycosylation strategies (*e.g* latent-active[64] and orthogonal[65] glycosylations) have been developed which allow efficient preparation of oligosaccharide building blocks.

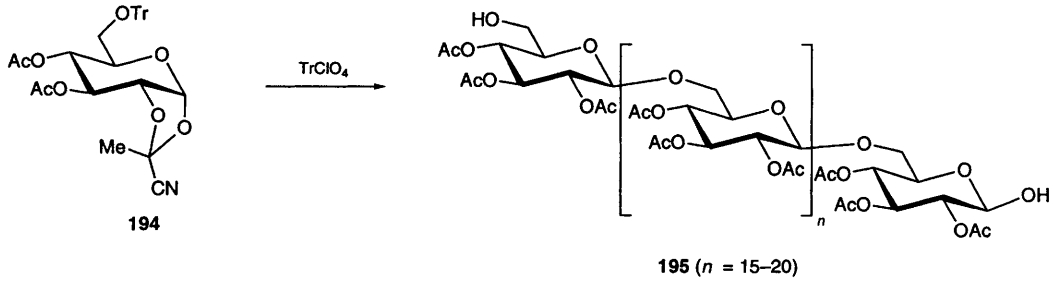
8 Polycondensations and one-pot multi-step glycosylations

The glycosylations discussed above utilise a fully protected glycosyl donor which is condensed with an appropriately protected glycosyl acceptor to give a well defined product. On the other hand, the use of a glycosyl donor having a reactive alcohol or ether functionality will result in polymerisation.[66] For example, when an *O*-trityl ether (Tr) and a cyanoethylidene group are present in the same molecule (*e.g.* **194**) then under glycosylation conditions polymerisation will take place. For example, treatment of 3,4-di-*O*-acetyl-1,2-*O*-cyanoethylidene-6-*O*-trityl-α-D-glucopyranoside (**194**) with a catalytic amount of tritylium perchlorate (10–20 mol%) resulted in polycondensation giving **195**. The reaction gave compounds with a molecular weight of approximately 3000–4000 (**Scheme 41**). It has been found that for some reactions an increase in the degree of polymerisation can be obtained by applying high pressure. It should be mentioned that also other substrates have been used in this type of polymerisation reaction.

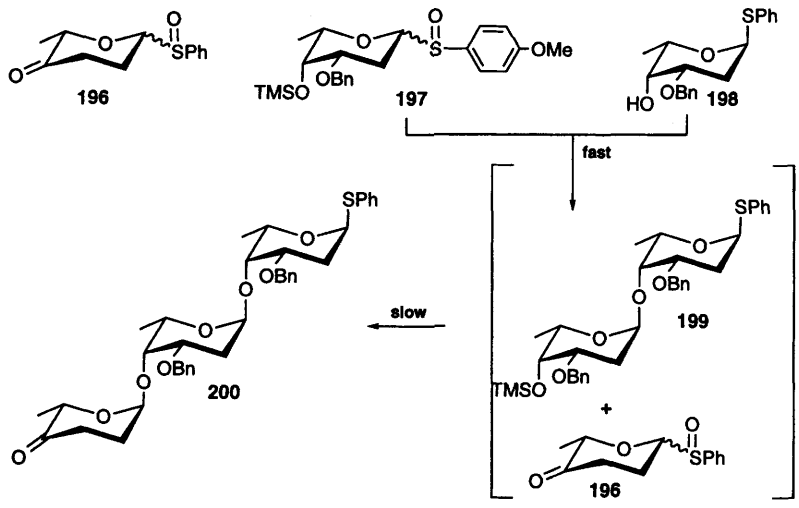
Recently, more controlled methods for sequential glycosylations have been reported. Kahne and co-workers described[67] a glycosylation method that is based on activation of anomeric sulfoxides with triflic anhydride (Tf_2O) or triflic acid (TfOH). Mechanistic studies revealed that the rate limiting step in this reaction is triflation of the sulfoxide; therefore the reactivity of the glycosyl donor could be influenced by the substituent in the *para* position of the phenyl ring and the following reactivity order was established OMe > H > NO_2. The reactivity difference between a *p*-methoxyphenyl sulfonyl donor and an unsubstituted phenylsulfonyl glycosyl acceptor is large enough to permit selective activation. In addition, silyl ethers are good glycosyl acceptors when catalytic triflic acid is the activating agent but react more slowly than a corresponding alcohol.

These features opened the way for a one-pot synthesis of a trisaccharide **200** from a mixture of monosaccharides **196**, **197** and **198** (**Scheme 42**).[68] Thus, treatment of this mixture with triflic acid resulted in the formation of trisaccharide **200** in a 25% yield. No other trisaccharides were isolated and the only other coupling product was dimer **199**.

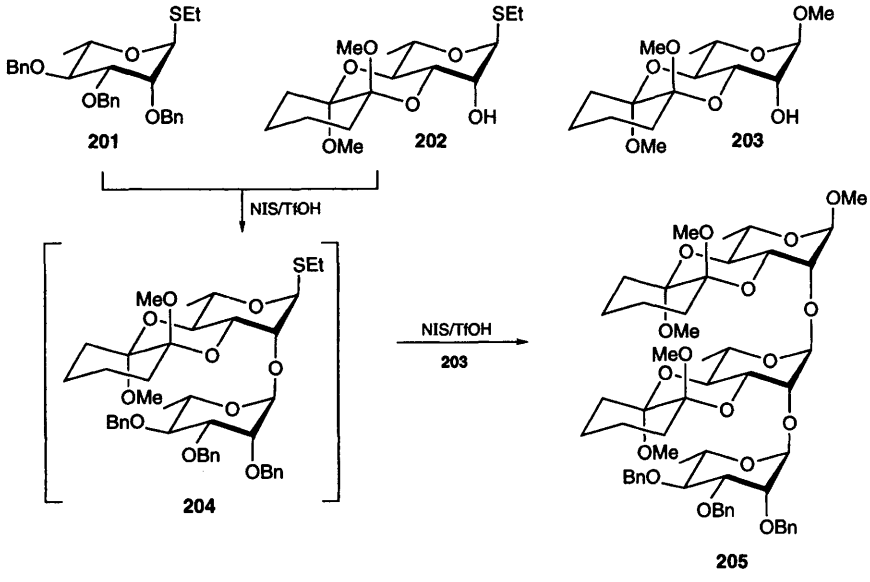
The products of the reaction indicate that the glycosylation takes place in a sequential manner. First, the most reactive *p*-methoxyphenylsulfenyl glycoside **197** was activated and reacts with alcohol **198** and not with the silyl ether **197**. In the second stage of the reaction, the less reactive silyl ether of disaccharide **199** reacts with the less reactive sulfoxide **196** to give trisaccharide **200**. The phenylthio group of trisaccharide **200** could be oxidised to a sulfoxide which was used in a subsequent glycosylation. The obtained trisaccharide



Scheme 41



Scheme 42



Scheme 43

is part of the natural product ciclumycin 0 and despite the relatively low yield of the coupling reactions, this methodology provides a very efficient route for this compound. It has, however, to be proven whether this methodology is applicable to a wide ranger of glycosyl donors and acceptors.

Ley and co-workers reported[69] a facile one-pot two-step synthesis of a trisaccharide unit **205** which is derived from the common polysaccharide antigen of a group B *Streptococci.* The trisaccharide was assembled from the benzylated rhamnoside **201** and the cyclohexane-1,2-diacetal (CDA) protected rhamnosides **202** and **203** (**Scheme 43**). The preparation of **205** is based on the armed–disarmed glycosylation strategy and exploits the fact that the activated thioglycoside **201** is more reactive than the torsially deactivated CDA protected rhamnoside **202**. Thus, NIS–TfOH mediated chemoselective coupling of **201** with **202** gave dimer **204**. Next, the second acceptor **203** was added to the reaction mixture and the disaccharide **204** could be activated by the addition of another equivalent of NIS and a catalytic amount of triflic acid to afford the trisaccharide **205** in an excellent overall yield of 62%. It is of interest to note that a stepwise preparation of **205** resulted in a lower overall yield. This glycosylation approach was also employed for the preparation of a tetramannoside.

Recently, one-pot multi-step glycosylations have been reported in which glycosyl donors and acceptors having different types of anomeric groups were used.[70]

The described glycosylation strategies allow the construction of several glycosidic linkages by a one-

pot procedure. It should, however, be realised that this type of reaction will give only satisfactory results when all the glycosylations are high yielding and highly diastereoselective. For example, it is generally known that rhamnoside donors often give very high α-selectivities. Furthermore, by exploiting neighbouring group participation it is easy to form 1,2-*trans*-glycosides. Other type of glycosidic linkages may impose problems.

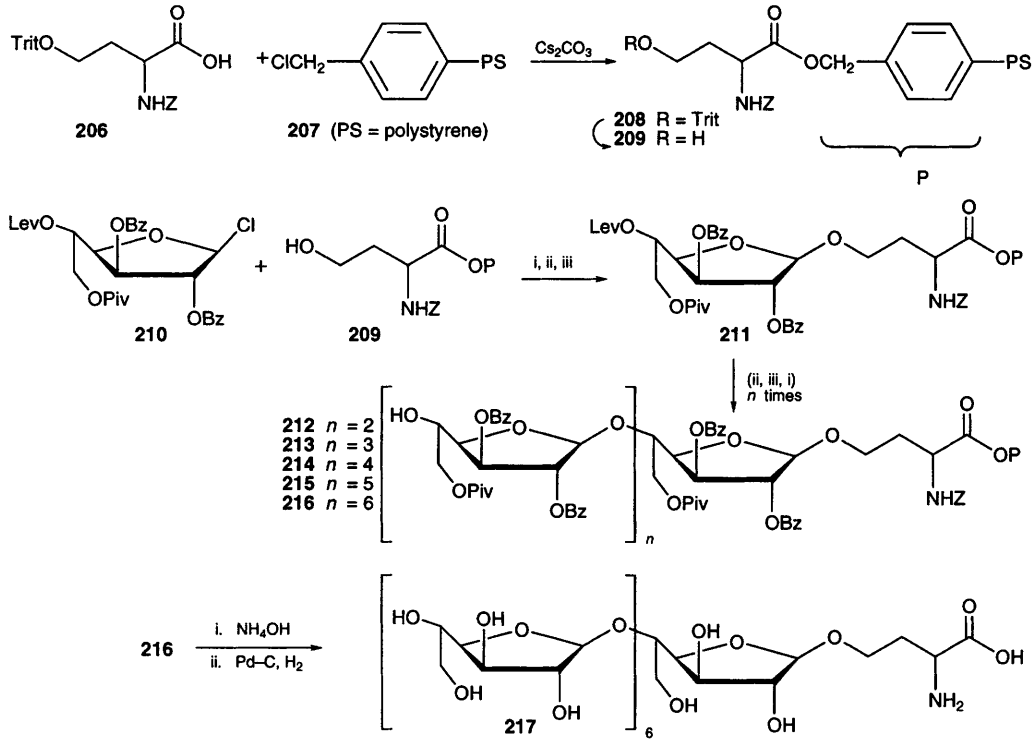
9 Solid-phase oligosaccharide synthesis

Inspired by the success of solid-phase peptide and oligonucleotide syntheses, in the early seventies several research groups attempted to develop methods for solid supported oligosaccharide synthesis.[71] However, since no powerful methods for glycosidic bond formation were available, the success of these methods were limited and only simple di- and tri-saccharides could be obtained.

In 1987, van Boom and co-workers reported[72] the solid supported synthesis of a D-galactofuranosyl heptamer. The synthetic approach which was followed is illustrated in **Scheme 44**. The selectively protected L-homoserine **206** was linked to the Merrifield polymer chloromethyl polystyrene (PS = polystyrene) **207** to give the derivatised polymer **208**. The loading capacity of the polymer was 0.5 mmol g^{-1} resin. Acid hydrolysis of the trityl group of **208** gave **209** and coupling of the chloride **210** with the immobilised **209** under Koenigs–Knorr conditions afforded the polymer linked homoserine glycoside **211**. It was observed that the coupling reaction had not gone to completion and to limit the formation of shorter fragments, the unreacted hydroxy groups were capped by treatment with acetic anhydride in the presence of pyridine and *N*,*N*-dimethylaminopyridine (DMAP). Elongation of **211** was performed as follows: the levulinoyl (Lev) group of **211** was removed by treatment with a hydrazine–pyridine–acetic acid mixture, the released alcohol was coupled with chloride **210** and the unreacted hydroxy groups were capped by acetylation. After repeating this procedure five times ($n = 6$), the heptasaccharide **216** was released from the resin by basic hydrolysis. Under these conditions also the benzoyl and pivaloyl (Piv) protecting groups were removed. Finally, cleavage of the benzyloxycarbonyl (Z) group by hydrogenolysis over Pd–C gave **217** in an overall yield of 23%.

Kahne and co-workers described[73] the solid supported synthesis of oligosaccharides using anomeric sulfoxides as donors.

In the procedures of van Boom and Kahne, the anomeric centre of a saccharide is linked to the solid support and glycosyl donors are added to the growing chain. Recently, Danishefsky reported[74] an inverse approach in which the incoming sugars are glycosyl acceptors. The basic strategy involves



Reagents: (i) $Hg(CN)_2$, $HgBr_2$, **144**; (ii) Ac_2O, pyridine, DMAP; (iii) NH_2NH_2, HOAc, pyridine
Z = benzyloxycarbonyl; Lev = levulinoyl; Piv = pivaloyl

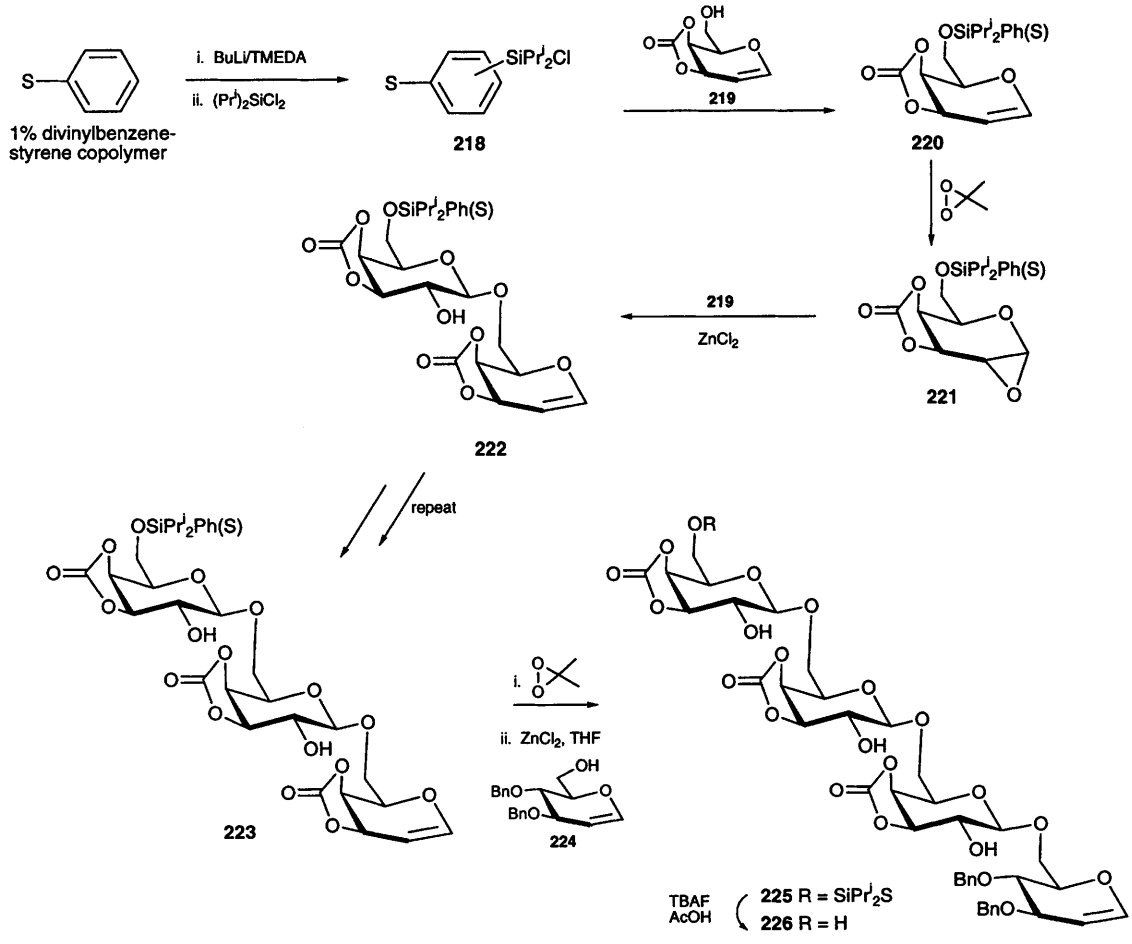
Scheme 44

attachment of a glycal to a polymer support, followed by epoxidation to provide a 1,2-anhydro-derivative. This polymer-bound glycosyl donor is then treated with a solution of a protected glycal, acting as a glycosyl acceptor, to give a polymer-bound disaccharide. Reiteration of this reaction sequence provides larger oligosaccharides which ultimately are retrieved from the support (**Scheme 45**).

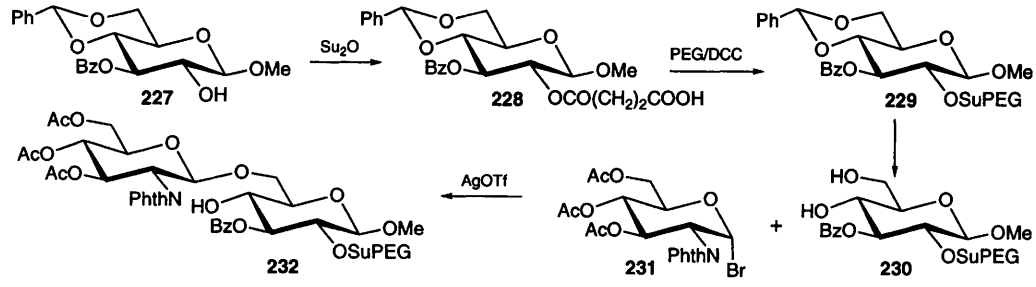
A commercially available 1% divinylbenzene–styrene copolymer was employed and the glycal was attached to this resin using a diisopropylsilyl ether linker. Such a linker is stable under the employed reaction conditions but can be cleaved by fluoride ion treatment. In previous studies a diphenyl-dichlorosilane linker was used; however, it was shown that this linker was inferior to the diisopropylsilyl linker.[74b]

Lithiation of the copolymer followed by quenching with diisopropyldichlorosilane provided **218**. The silylated polymer was reacted with a solution of galactal **219** in dichloromethane and Hünig's base to give the corresponding dialkylsilyl linked polymer construct **220**. The loading of the solid support was 0.9 mmol g^{-1} resin. The double bond of the polymer bound glycal **220** was activated by epoxidation with 3,3-dimethyldioxirane and the epoxide **221**, thus obtained, was reacted with a tetrahydrofuran solution of **219** in the presence of $ZnCl_2$ to give the polymer bound dimer **222**. The glycosidation procedure required a 6–10 fold excess of solution based glycosyl acceptor and 2–3 equivalents of promoter. However, in some reactions less acceptor and shorter reaction times have been applied. It should also be noted that no glycosylation at the 2-position was observed.

Twice repetition of this two-step procedure (epoxidation, glycosylation) provided a polymer bound tetrasaccharide **225** which was released from the solid support by treatment with tetrabutyl-ammonium fluoride (TBAF). The method allowed the preparation of the tetrasaccharide **226** in a 74% overall yield. An advantageous aspect of this solid supported approach is that no capping step is required because any unreacted epoxide will hydrolyse in the washing procedure. On the other hand, in the case of a very difficult glycosylation step, most of the solid supported linked glycosyl donor may decompose lowering the overall yield. In the procedures of van Boom and Kahne, excess of donor can be used to achieve acceptable yields in difficult glycosylation reactions.



Scheme 45



Scheme 46

The rate of reactions on a solid support are generally reduced compared to solution based methods. Krepinsky and co-workers addressed this problem by a polymer-supported solution synthesis of oligosaccharides (**Scheme 46**).[75] This strategy is based on the fact that a polyethylene glycol polymer supported saccharide is soluble under conditions of glycosylation but insoluble during work-up. Poly(ethylene glycol) monomethyl ether (PEG) was coupled through a succinic (Su) ester linkage to a carbohydrate hydroxy group. When PEG is bound to a carbohydrate, a glycosylation reaction can be driven to completion by repeated addition of the glycosylating agent. For example, in the silver ion mediated coupling of **230** with **231** to give **232**, several portions of the bromide were added until the reaction had gone to completion. The progress of the glycosylation could be monitored by NMR spectroscopy. After the reaction had finished, the PEG-bound product was precipitated by the addition of diethyl ether. Subsequently, the crude polymer was recrystallised from ethanol and after drying was used in the next synthetic step. The PEG-succinimide linkage could be cleaved by DBU-catalysed methanolysis in dichloromethane.

Recently, PEG was bound to the anomeric centre of a saccharide *via* an α,α'-dioxyxylyl glycoside.[76] This linkage is stable under many chemical conditions including glycosylation but can be cleaved by hydrogenolysis. The PEG-based methodology has been used for the preparation of a heptaglucoside having phyto-alexin elicitor activity[77a] and other oligosaccharides.[77b–d]

The polymer support based glycosylation methods eliminate time-consuming work-up procedures and purification steps. However, despite recent advances, only relatively simple oligosaccharides have been prepared by these methods and the glycosidic linkages of these oligosaccharide were 1,2-*trans* linked.

10 Concluding remarks

Nowadays a range of glycosyl donors, such as trichloroacetimidates, thioglycosides and fluorides, can be prepared by standard procedures and these compounds have a reasonable shelf-live and can be used confidently in glycosylations. Several methods have been developed to control the anomeric selectivity of glycosylation reactions. These approaches are in many cases unreliable and often modest $\alpha:\beta$ selectivities are obtained. It should be realised that often many reaction conditions need to be examined to achieve acceptable results. Nevertheless, contemporary carbohydrate chemistry makes it now possible to execute multistep synthetic sequences that give complex oligosaccharides. Convergent strategies have been developed which make efficient use of common building blocks. In this respect, chemoselective glycosylations allow the preparation of saccharide building blocks without extensive protecting group manipulations.

Several polymer support based glycosylation methods have been reported. However, only relatively simple oligosaccharides have been prepared by these methods and the glycosidic linkages of these oligosaccharide were often 1,2-*trans* linked. Problems associated with basic glycosylation methodology need first to be addressed before solid oligosaccharide synthesis can be introduced as a general method. An attractive alternative for solid-phase oligosaccharide synthesis may be one-pot multi-step glycosylations. This type of methodology allows each glycosylation step to be monitored but reduces time-consuming work-up and purification steps.

In order to overcome problems associated with chemically based methods, combined enzymatic approaches have been developed. In such an approach, glycosidic linkages which are very difficult to introduce chemically are introduced enzymatically and *vice versa*. The latter approach has proven to be extremely valuable for the introduction of neuramic acid units in an oligosaccharide. It should be realised that the number of enzymes available to perform these transformations are limited.

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