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Strategies in Oligosaccharide Synthesis

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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 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 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. To date, there are no general applicable methods or strategies for oligosaccharide synthesis and consequently the preparation of oligosaccharides 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. The preparation of oligosaccharides of this size is only

possible when a synthetic strategy is highly convergent.[5] In such a glycosylation strategy, most of the synthetic effort is directed towards the preparation of the monomeric glycosyl donors and acceptors. The assembly of these units to an oligomer should involve a minimum number of synthetic steps and each reaction step should proceed with high stereoselectivity and high yield. Furthermore, an efficient synthetic strategy should make optimal use of common intermediates and oligosaccharide building blocks.

This review describes the recent advances in the development of efficient strategies for oligosaccharide synthesis and a selected number of illustrative examples will be discussed. In the first part linear and convergent block syntheses of oligosaccharides will be discussed. In the second part, new glycosylation strategies for the facile preparation of saccharide building blocks will be described. Next, recent advances in solid supported oligosaccharide synthesis will be summarised and in the final part enzyme mediated preparations will briefly be discussed.

2. Linear glycosylation strategies

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 hydroxyl group.[6,7] Traditionally,[6a] the most widely used methods utilise 1-bromide or 1-chloride derivatives of carbohydrates as glycosyl donors and by careful selection of the reaction conditions and type of protection, both α- and β-glycosidic linkages can be prepared with high stereoselectivity. It should, however, be noted that 1-halo glycosides often suffer from instability and require relatively drastic conditions for their preparation. These unfavourable features impose a glycosylation strategy in which monomeric glycosyl donors have to be added to a growing saccharide chain and, hence, such a linear synthetic strategy is less convergent and less efficient. Glycosyl bromides have been used in block synthesis, however, results were often rather disappointing especially with rather labile bromides.[8]

3. Convergent block synthesis

The introduction of the ortho-ester[9] and imidate[10] procedures were the first attempts to find alternatives to the glycosyl halide methodologies. Since then, many other leaving groups for the anomeric centre have been reported.[6j] However, from these glycosyl donors, the fluorides, trichloroacetimidates, and thioglycosides have been applied most widely in glycosidic bond synthesis. These anomeric leaving groups can be introduced under mild reaction conditions and are sufficiently stable to be purified and stored for a considerable period of time. Furthermore, they can undergo glycosylations under mild conditions and by selecting the appropriate reaction conditions, high yields and good α/β ratios can often been obtained. These favourable features allow the use of these glycosyl donors in elegant block syntheses.

The favourable properties of the trichloroacetimidate methodology were exploited in the block synthesis of the prominent tumour associated antigen Lewis X (Le^x).[11] The retrosynthetic strategy is depicted in **Figure 1**. 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 **1**, **2** and **3** (**Figure 1**).

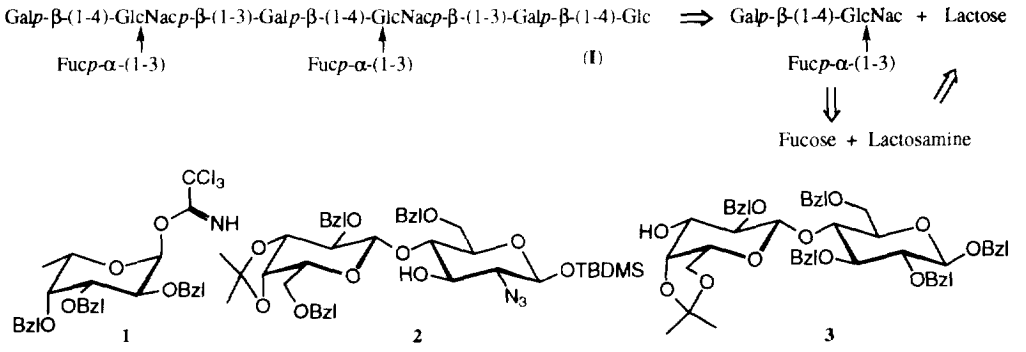
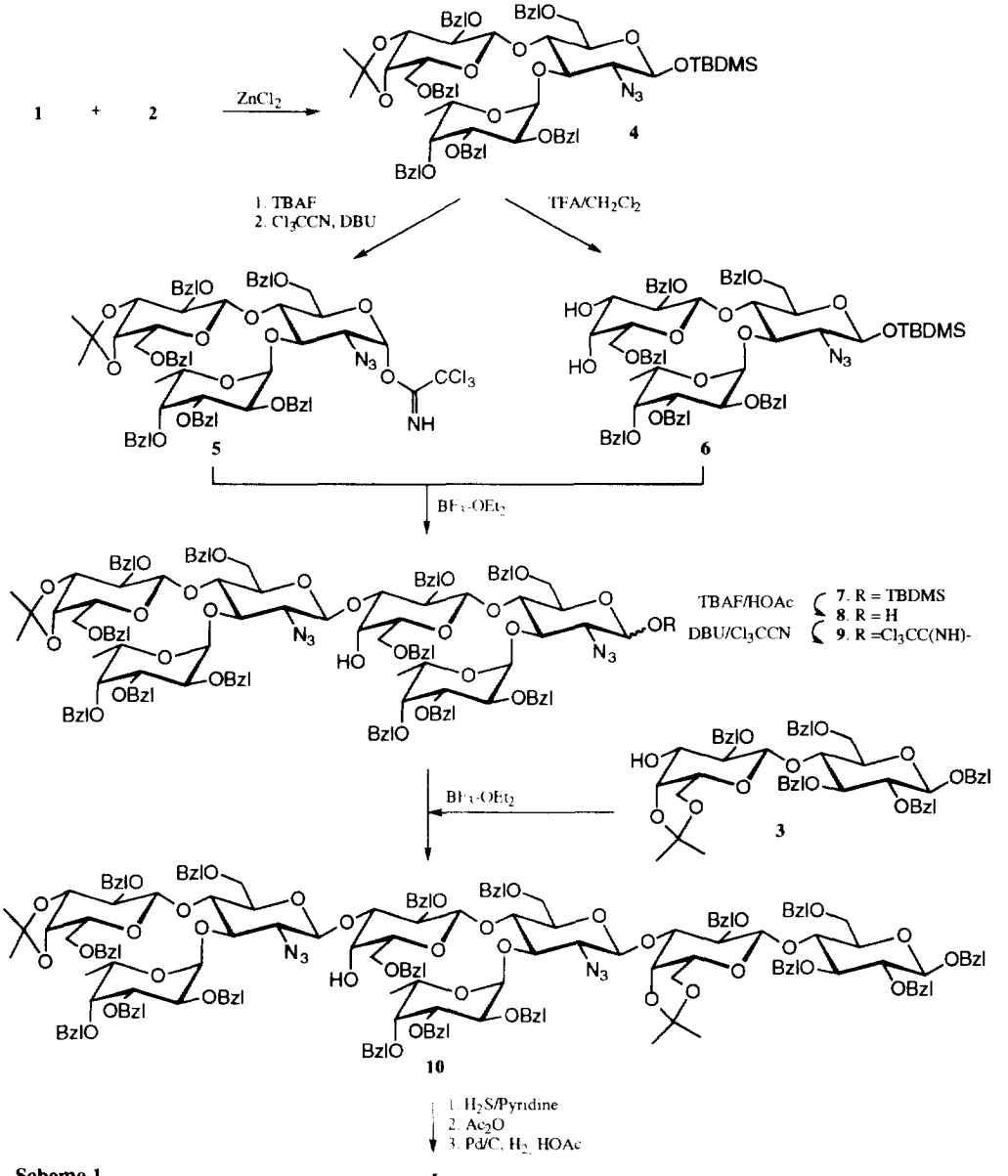


Figure 1

The azido-lactose building block **2** was prepared by azidonitration of lactal, followed by selective protection. The selectively protected lactoside **3** was readily available from lactose *via* a sophisticated protecting group inter-conversion strategy. α-Fucosylation of acceptor **2** with the very reactive fucosyl donor **1**, under "inverted procedure" conditions,[12] gave trimer **4** in a 89% yield (**Scheme 1**). The trisaccharide **4** was converted into the required glycosyl donor **5** and acceptor **6**. Thus, removal of the TBDMS protecting group of **4** with TBAF and treatment of the resulting lactol with trichloroacetonitrile in the presence of DBU afforded trichloroacetimidate **5** in a good overall yield. On the other hand, cleavage of the isopropylidene moiety of **4** under mild acidic conditions furnished **6**. Coupling of glycosyl donor **5** with acceptor **6** in the presence of BF_3-Et_2O as catalyst gave the hexasaccharide **7** 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 **10** required the repetition of the above described methodology, *i.e.* conversion of the anomeric TBDMS group into a trichloroacetimidate functionality (**7**→**9**) and coupling of the trichloroacetimidate **9** with lactoside unit **3** (64%). Finally, target molecule **I** was obtained by reduction of the azido group of **10**, followed by acetylation of the amino group and hydrogenation under acidic conditions. Using a similar approach, a spacer containing dimeric Lewis X antigen has also been described.[11e] Furthermore, several alternative synthetic routes for Le^x have been reported.[13]

The described glycosylation strategy is highly convergent and makes optimal use of the common trisaccharide **4**. Furthermore, efficient use was made of the commercially available dimer lactose and, finally, the trichloroacetimidates could be prepared in high yield and these donors behaved very well in the glycosylation reactions (high yields and high 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. For example, it is rather straightforward to obtain stereoselectively 1,2-trans glycosidic linkages by exploiting neighbouring group participation of a C-2 acyl protecting group. On the other hand, attempts to prepare selectively 1,2-cis glycosidic linkages often result in anomeric mixtures, and the formation of a β-mannoside linkage is notoriously difficult. 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. In this respect, earlier work of Paulsen[14] and Schmidt,[15] had shown that azido-glucosyl donors undergo glycosylation reactions in high yield and both α- and β-glycosidic linkages can be obtained. Therefore, this type of glycosyl donor proved to be very useful in the block assembly of compound **I** (**Scheme 1**).

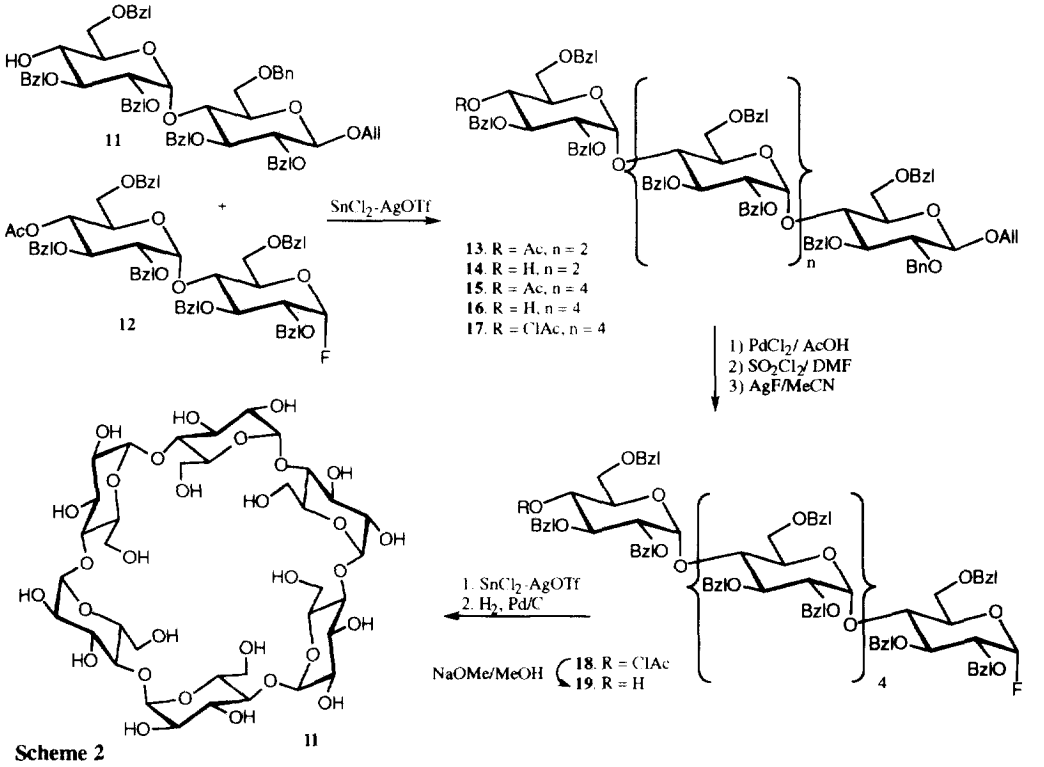


Scheme 1

A highly convergent synthesis of α-cyclodextrin (**II**) has been reported[16] by Ogawa *et al.* The synthetic strategy was based on macro-cyclisation of the D-glucohexaose derivative **19** which could be assembled from **11** and **12** (**Scheme 2**). Furthermore, the starting materials **11** and **12** were readily available from a common maltoside building block. Thus, coupling of **11** with **12** according to a procedure of Mukaiyama *et al.* afforded a 79% yield (α/β = 1.8/1) of the glucotetraose **13**. Deacetylation of **13** gave **14** which was coupled with **12** to yield hexamer **15** (65%, α/β = 1/2). The acetyl functionality of **15** was replaced by a

chloroacetyl protecting group (→**17**) and the anomeric allyl group of **16** was removed and a fluoride (→**18**) was introduced. Finally, base mediated cleavage of the monochloroacetyl group of **18** gave **19**, macrocyclisation of which afforded **II** (yield 22%). The introduction of a chloroacetyl protecting group was required because of the chemical instability of anomeric fluorides. It should be noted that despite efficient use was made of a common building block, the overall yield of **II** was rather disappointing. This result was mainly due to modest anomeric selectivities in the glycosylation reactions.

An organic synthetic approach allows the preparation of completely unnatural cyclodextrins and Mori *et al.* reported[17] the preparation of the α-1,4-linked cyclomannohexaose. Interestingly, the cyclisation step in this total synthesis was achieved in a much higher yield (64%) than in the analogous reaction leading to the natural product (21%). Recently,[18] the synthesis of an unnatural cyclodextrin containing five glucopyranoside units was reported. In an alternative strategy,[19] the easily available 6'-*O*-trityl-β-D-maltoside heptaacetate was reacted with $SnCl_4$ and this reaction yielded, apart from a mixture of linear oligosaccharides, hexa-, octa- and deca-cyclogentiomaltodextrins (20-30%).



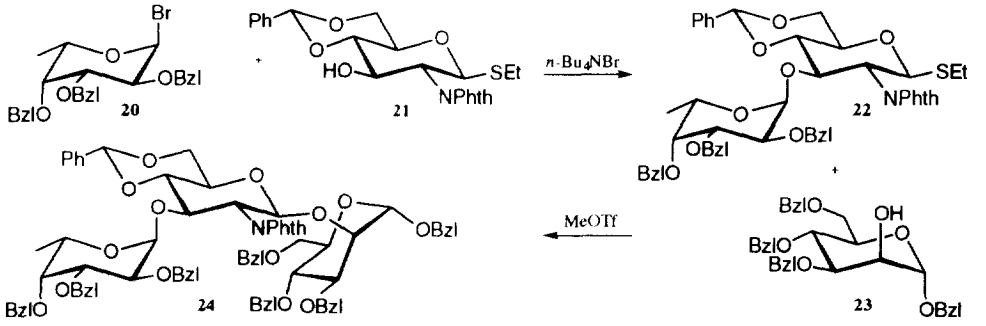
Scheme 2

4. Selective and two-stage activation and orthogonal glycosylation strategies

Not withstanding the attractive features of the above mentioned block synthesis, the conversion of a common building block into a glycosyl donor requires several manipulations at the anomeric centre presenting a drawback (*e.g.* removal of anomeric protecting group followed by introduction of a leaving group) which is especially undesirable when performed on larger fragments. In addition, the number of anomeric protecting groups is limited. The possibility of epimerisation at C-2 of a 1-hydroxyl intermediate should not be

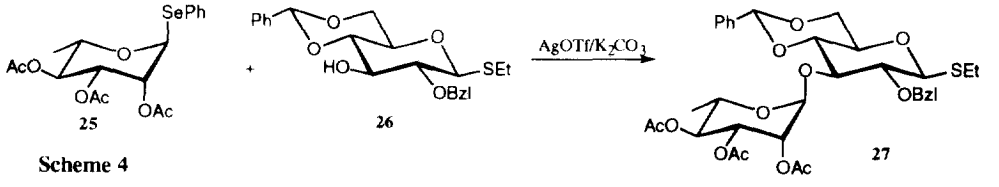
excluded.[20] Ideally, the anomeric substituent of an oligosaccharide building block should be sufficiently stable to withstand protecting group manipulations (*i.e.* acts as a protecting group), but also have an adequate reactivity to permit its use as a glycosyl donor (*i.e.* acts as leaving group). Furthermore, if these substituents are stable to conditions required to activate other types of leaving groups than they may also be used as glycosyl acceptors. Thioglycosides[6i] and n-pentenyl glycosides[6h] possess these features. They are stable under many different chemical conditions but can readily be activated and used as donors in glycosidic bond synthesis.

Lönn *et al.* exploited the favourable properties of thioglycosides in an elegant preparation of a trisaccharide[21] and a heptasaccharide[22] which are part of the complex type of carbohydrate moiety of glycoproteins (**Scheme 3**). The strategy is based on the fact that a bromide can selectively be activated in the presence of a thioglycoside. Thus, tetra-*n*-butylammonium bromide mediated coupling of the thioglycoside **21** with fucopyranosyl bromide **20** gave disaccharide **22** in a 81% yield. The disaccharide **22** was used subsequently in the next glycosylation reaction and coupled with glycosyl acceptor **23** in the presence of methyl triflate to give trimer **24**. Apart from the trimer **24**, the formation of elimination and *O*-methylated products were observed. A similar strategy was applied for the synthesis of a branched heptasaccharide having phyto-alexin-elicitor activity.[23] Since the report of Lönn, many other activators for thioglycosides have been reported[6i,j] and these reagents are more reactive and prevent *O*-alkylation and elimination.

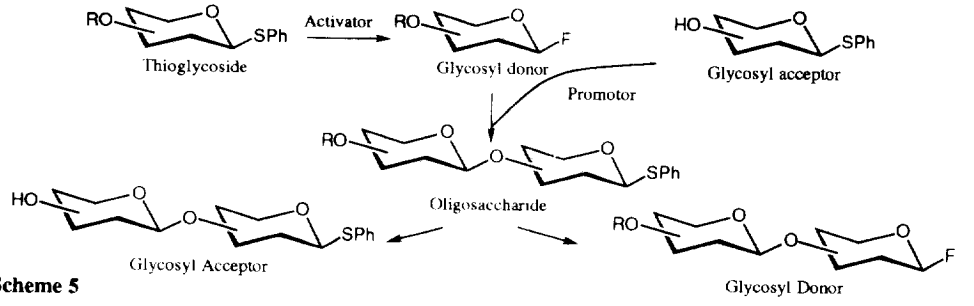


Scheme 3

Recently, Pinto *et al.* showed[24] that selenoglycosyl donors can be coupled with ethylthioglycosyl acceptors (**Scheme 4**). It was observed that a selenoglycoside can be activated with silver triflate in the presence of an inorganic base (K_2CO_3). On the other hand, thioglycosides are stable under these conditions. Thus, treatment of a mixture of selenoglycoside **25** and thioglycoside **26** in the presence of silver triflate gave disaccharide **27** in a 85% yield. In a subsequent glycosylation reaction, the anomeric thio group of **27** can be activated with a thiophilic reagent.

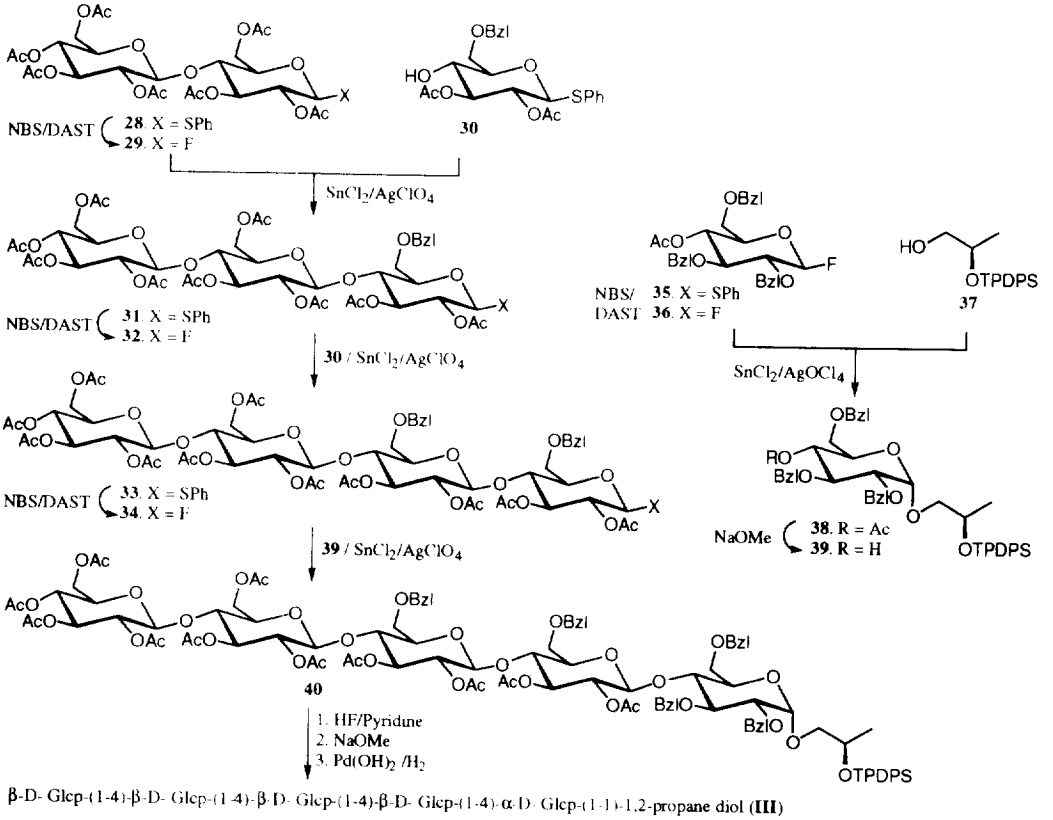


Scheme 4



Scheme 5

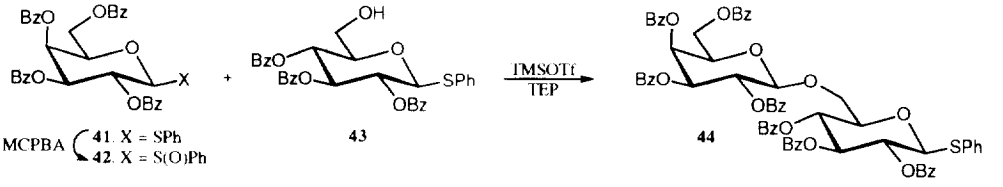
Nicolaou *et al.* have described[6f] a two-stage glycosylation strategy, the essence of which is outlined in **Scheme 5**. Thus, a thioglycoside can be converted into a glycosyl fluoride donor and this donor can be coupled with a thioglycosyl acceptor. The procedure can now be repeated by conversion of the anomeric thio group of the oligosaccharide into an anomeric fluoride which can be used in a further coupling reaction. This glycosylation strategy has been exploited[25] in the preparation of *Rhynchosporides* **(III)** and the key reactions are depicted in **Scheme 6**.



Scheme 6

Activation of **28** with NBS and DAST gave fluoride **29** (85%) which was coupled with thioglycosyl acceptor **30** to give trisaccharide **31** (75%). The anomeric thiol group of **31** was again converted into a fluoride (→**32**, 85%) which was subsequently used in a glycosylation with the common acceptor **30** to give tetramer **33** (75%). This procedure could be repeated and in the final glycosylation, glycosyl donor **34** was coupled with **39** to give the pentasaccharide **40** (72%). Deblocking of **40** furnished the desired pentameric *Rhynchosporides* **III**. The two-stage activation strategy has also been exploited[26,27] in the preparation of di- and trimeric Le^x and Globotriaosylceramide. This two-stage glycosylation 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 mainly 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, (iv) the excellent behaviour of thioglycosides as glycosyl acceptors.

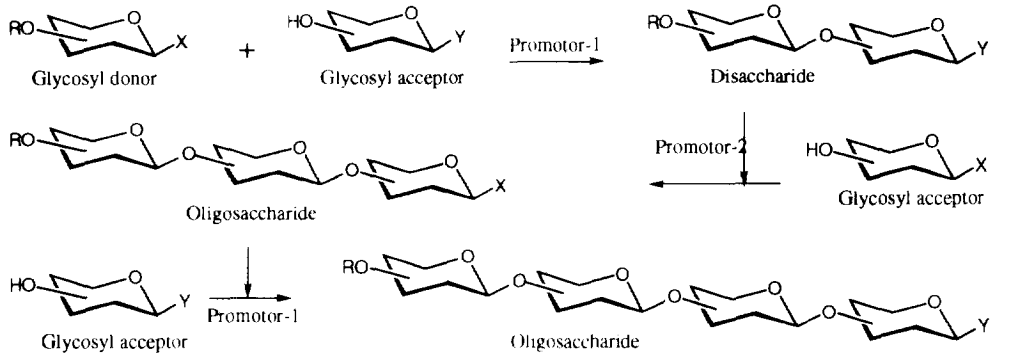
Recently,[28] another two-stage activation strategy was reported which employed anomeric sulfoxides as donor and thioglycosides as acceptor molecules. The approach is based on the fact that anomeric sulfoxides can be activated by Lewis acids and that thioglycosides are stable under these conditions. Furthermore, anomeric sulfoxides can readily be prepared by oxidation of thioglycosides. For example (**Scheme 7**), phenylsulfenyl glycoside **42** could readily be obtained by oxidation of thioglycoside **41** with *m*-chloroperbenzoic acid (MCPBA) and coupling of **42** with **43** in the presence of triethyl phosphite (TEP) and TMSOTf gave dimer **44** in an acceptable yield (64%). It is of interest to note that in the absence of TEP, no glycosylation product was obtained. The TEP was required to trap the transiently formed phenylsulphenyl ester which may activate acceptor **43** resulting in the formation of a 1,6-anhydro derivative.



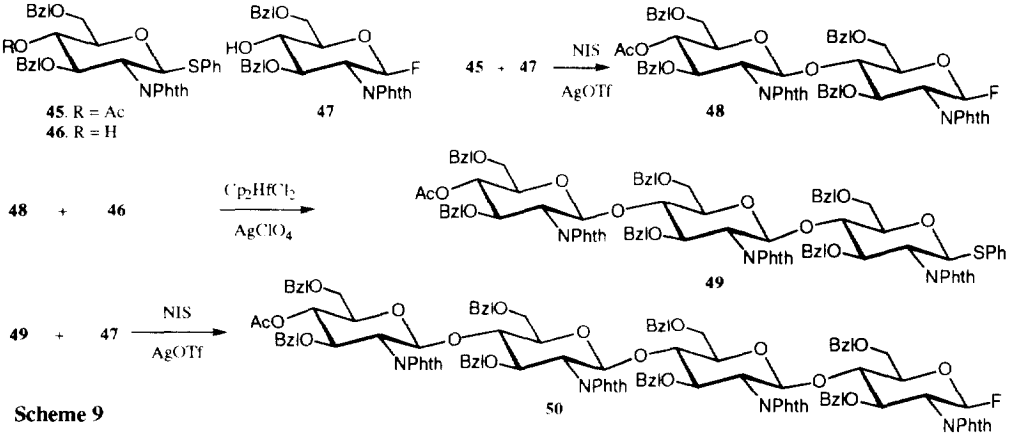
Scheme 7

An orthogonal glycosylation strategy in which manipulations at the oligosaccharide stage are further reduced was proposed[29] by Ogawa *et al.* In this approach, two anomeric groups (X and Y) are used which both act as anomeric protecting group as well as leaving group and a schematic representation of this approach is depicted in **Scheme 8**.

The orthogonal glycosylation strategy exploits the fact that a thioglycoside (X) can be activated without affecting an anomeric fluoride (Y) and *visa versa* and the feasibility of this methodology was demonstrated by the preparation of the pentasaccharide **50** (**Scheme 9**). Compound **50** was assembled from the monomers **45**, **46** and **47** which were readily available from a common precursor. Thus, coupling of **45** with **47** in the presence of the promotor NIS/AgOTf gave dimer **48** in a 85% yield and subsequent Cp_2HfCl_2-$AgClO_4$ mediated coupling of this dimer (**48**) with thiophenyl acceptor **46** afforded trimer **49** (72%). The procedure could be repeated to give tetramer **50** and this compound was used in a block synthesis to give a heptasaccharide.



Scheme 8

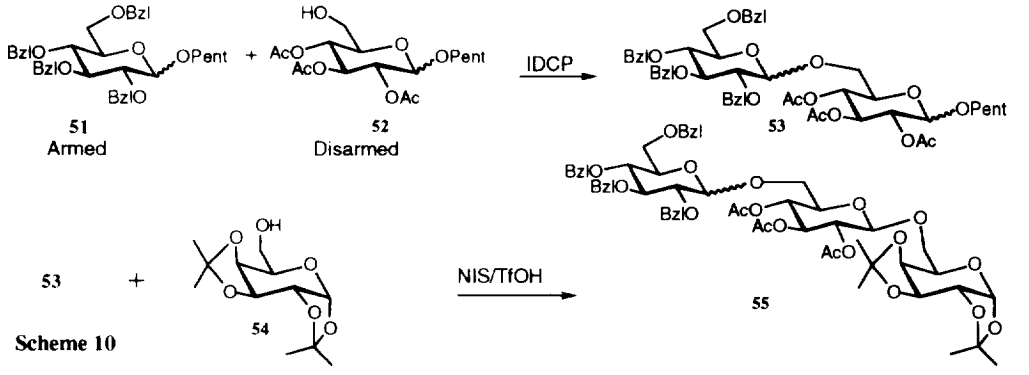


Scheme 9

5. Chemoselective glycosylation reactions

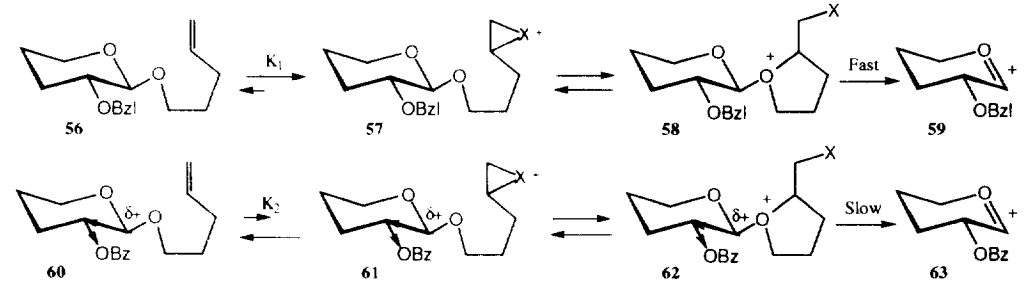
The orthogonal glycosylation strategy relies on the orthogonal properties of two different anomeric groups. Fraser-Reid *et al.* have introduced[6f,30] a chemoselective glycosylation strategy (armed - disarmed glycosylation strategy) in which a C-2 ether protected pentenyl glycoside can be coupled chemoselectively to a benzoylated pentenyl glycoside. Thus, in this strategy only one type of anomeric group is required. The chemoselective glycosylation relies on the fact that C-2 esters deactivate (disarm) and C-2 ethers activate (arm) the anomeric centre.

For example, coupling of armed donor **51** with disarmed acceptor **52**, in the presence of the mild activator iodonium di-collidine perchlorate (IDCP), gave the dimer **53** as an anomeric mixture in a yield of 62% (**Scheme 10**). Next, the disarmed dimer **53** could be further glycosylated, with for example acceptor **54**, using the more powerful activating system *N*-iodosuccinimide/catalytic triflic acid (NIS/TfOH) to yield the trisaccharide **55** (60%).



Scheme 10

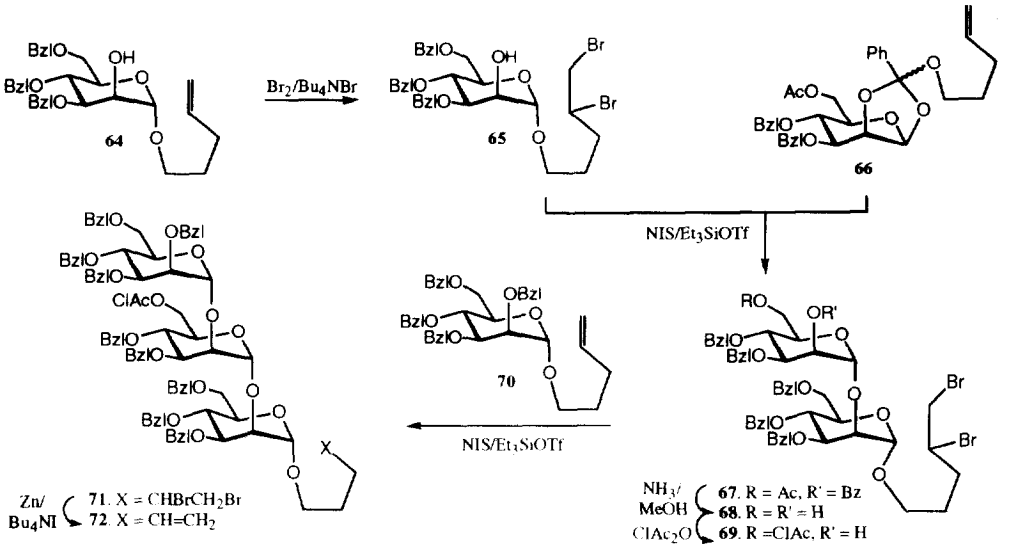
The difference in reactivity between alkylated and acylated pentenyl glycosides was rationalised as follows[31] (**Scheme 11**): intermediates **61** and **62** are destabilised by the contiguous partial (δ+) and full (+) charges, and hence the formation of intermediates **61** and **62** are disfavoured. However, **56** does not suffer impartial destabilisation and will go forward to give the reactive intermediate **59**. On the other hand, the difference in reaction rate between **56** and **60** may also be explained by a difference in nucleophilicity of the exocyclic anomeric oxygen atom. The effect of protecting groups upon anomeric reactivity has been known[32] for many years, however, Fraser-Reid *et al.* were the first to exploit this effect in chemoselective glycosylation reactions.



Scheme 11

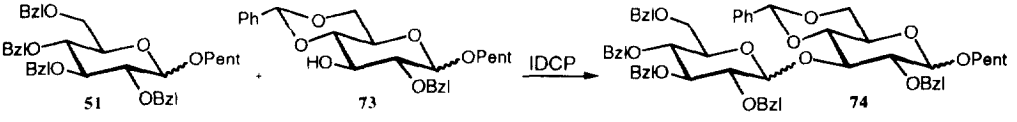
The C-2 acyl protecting group of compound **53** (**Scheme 10**) will perform neighbouring group participation in the glycosylation and in this reaction only a 1,2-trans linked product will be formed. When a 1,2-cis glycosidic linkage is required, the acyl group has to be replaced by an ether type protecting group, hence, introducing additional manipulations at the oligosaccharide stage.

In an alternative strategy (**Scheme 12**),[33] pentenyl orthoester **66** was coupled with 4,5-dibromopentanyl glycoside **65** to give disaccharide **67** (78%). Compound **65** could easily be obtained by treatment of pentenyl glycoside **64** with bromine in the presence of tetra-*n*-butyl ammonium bromide (86%). Disaccharide **67** was converted into glycosyl acceptor **69** which was coupled with **70** to afford trisaccharide **71** (75%), the 4,5-dibromopentanyl of which was converted into a pentenyl glycoside by reductive debromination (→**72**). This methodology allows the coupling of two electronically activated compounds, *e.g.* **69** and **70**, and trisaccharide **72** was used in a block synthesis of a GPI anchor.[34]



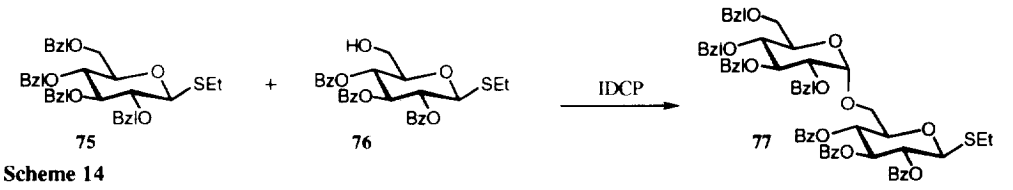
Scheme 12

It has also been found that cyclic acetals reduce the reactivity of pentenyl glycosides.[35] This deactivating effect is large enough to allow a chemoselective glycosylation of benzylated pentenyl glycosyl donor **51** with cyclic acetal protected glycosyl acceptor **73** to give a dimer **74** as an anomeric mixture in a modest 52% yield (**Scheme 13**). Deactivation by cyclic acetals reflects presumably the torsial strain inflicted upon the developing cyclic oxo-carbonium ion, the planarity of which is opposed by the cyclic protecting group.



Scheme 13

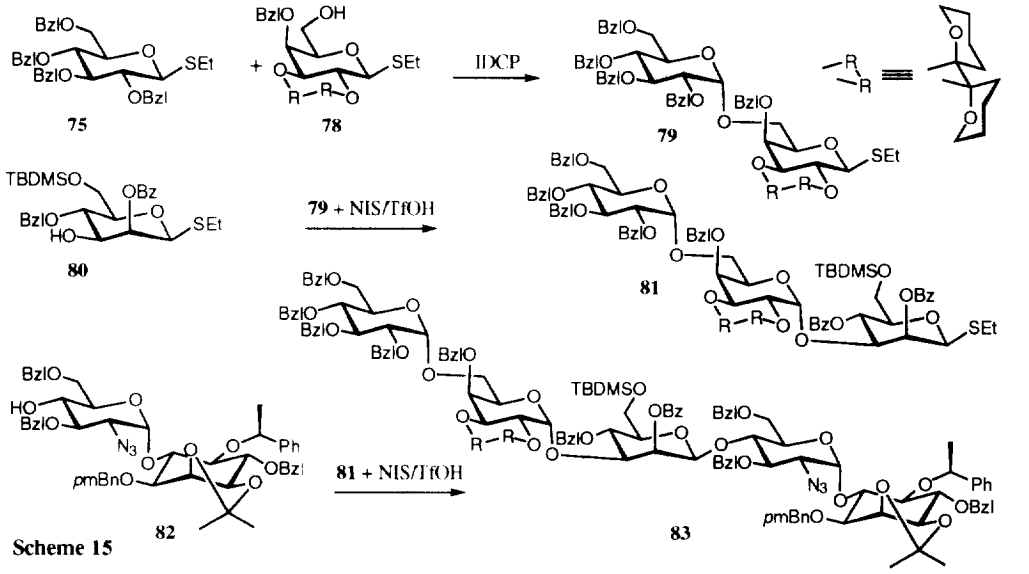
Chemoselective glycosylations have also been developed for other types of glycosides. Van Boom *et al.* showed[36] that similar to pentenyl glycosides, the reactivity of thioglycosides towards iodonium cations can be modulated by the choice of protecting groups and it was found that a C-2 ether group activates and a C-2 ester deactivates the anomeric centre. Thus, iodonium cation mediated coupling of **75** with **76** gave disaccharide **77** mainly as the α-anomer in a 84% yield (**Scheme 14**). In addition, it was established that a disarmed thioglycoside (*e.g.* **76**) could be readily activated with the strong thiophilic promotor NIS/TfOH. It was also found that thioglycosides are more reactive then 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 ethylthio glycoside 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 thioglycosides.[36d]



75 76 77

Scheme 14

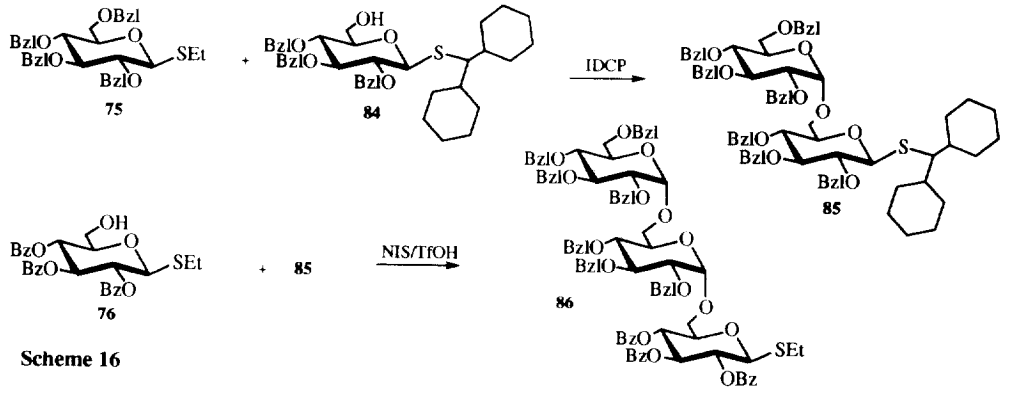
Ley *et al.* proposed[37] that the armed-disarmed glycosylation strategy could gain versatility by tuning the glycosyl donor leaving group ability further. They described that a dispiroketal protecting group (R-R) has a marked effect on the reactivity of the anomeric centre and it was found that a dispiroketal protected thioglycoside (*e.g.* **78**, **Scheme 15**) has a reactivity between an armed C-2 alkylated thioglycoside (*e.g.* **75**) and a disarmed C-2 acyl thioglycoside (*e.g.* **80**). The three levels of anomeric reactivity were exploited in the preparation of a protected pentasaccharide unit common to the variant surface glycoprotein of *Trypanosoma brucei* (**Scheme 15**). Thus, iodonium dicollidine perchlorate mediated chemoselective glycosylation of glycosyl donor **75** with dispiroketal protected acceptor **78** gave disaccharide **79** in an excellent yield (82%, α/β = 5/2). Further chemoselective glycosylation of the torsially deactivated donor **79** with electronically deactivated acceptor **80** in the presence of the more powerful activator NIS/TfOH gave a 63% yield of trisaccharide **81** as one isomer. Finally, the pseudo-pentasaccharide **83** was obtained by condensation of glycosyl donor **81** with glycosyl acceptor **82**.



75 78 79 80 81 82 83

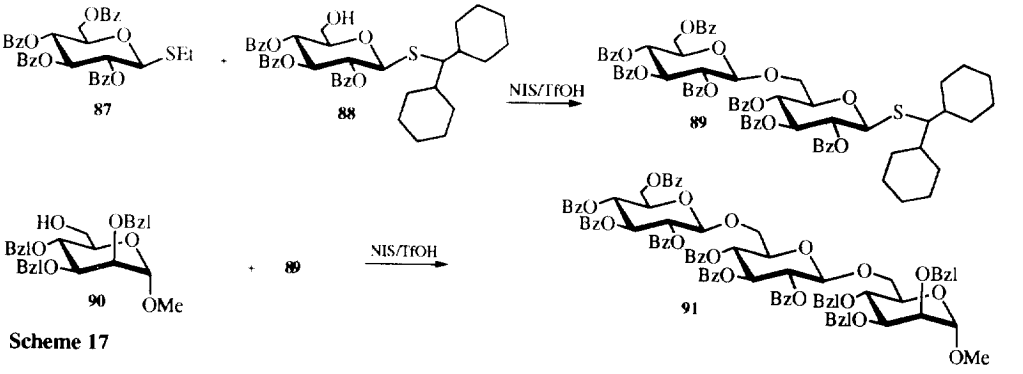
Scheme 15

In the armed-disarmed glycosylation approach, the leaving group ability is controlled by protecting groups (ether/dispiroketal/ester). It may, however, be advantageous to control the anomeric reactivity by means of modifying the leaving group itself. Boons *et al.* showed[38] 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 (**Scheme 16** and **17**).



Scheme 16

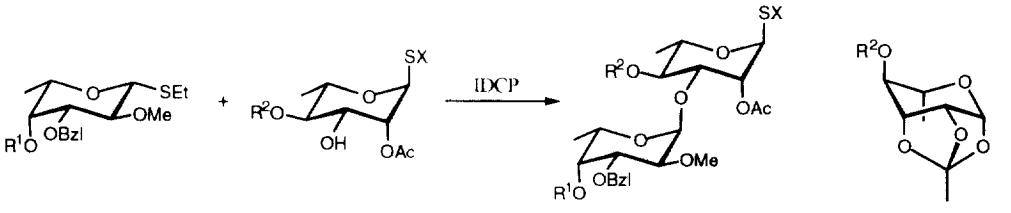
Thus, IDCP mediated chemoselective glycosylation of glycosyl donor **75** with glycosyl acceptor **84** gave disaccharide **85** in an excellent yield of 79% as one anomer. Further chemoselective coupling of sterically deactivated donor **85** with the electronically deactivated glycosyl acceptor **76** in the presence of the more powerful promoter system NIS/TfOH gave trisaccharide **86** 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 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 **88** should have a lower reactivity than the electronically deactivated glycosyl donor **87** (**Scheme 17**). Indeed, coupling of glycosyl donor **87** with glycosyl acceptor **88** in the presence of NIS/TfOH gave dimer **89** in a 61% yield. Glycosyl donor **89** was coupled with **90** in the presence of NIS/TfOH and trisaccharide **91** was isolated in a good yield. The latter reaction demonstrated that a sterically and electronically deactivated substrate is still a suitable glycosyl donor.



Scheme 17

In summary, the reactivity of thioglycosides can be controlled by the nature of protecting groups and the size of the anomeric leaving moiety. However, other subtle features of thioglycosides may contribute to their reactivity. The disaccharide unit **97** was required for the preparation of a tetrasaccharide derived from the

glycopeptidolipid of *Mycobacterium avium* serotype 4 and it was envisaged that this disaccharide could be obtained by chemoselective coupling of a thioglycoside donor bearing a C-2 ether group with a thioglycoside acceptor having a C-2 ester group (**Scheme 18**).[39] However, coupling of **92** with **94** gave disaccharide **97** in a disappointing 57% yield and orthoester **101** was obtained as the main side product. Thus, the C-2 ester protected 6-deoxy thioglycoside **94** is readily activated by IDCP to give **101** and therefore can not be regarded as a truly electronically deactivated glycosyl acceptor. This observation was not surprising because it is generally known that 6-deoxy glycosides are much more reactive than their 6-hydroxy counter parts. In order to suppress ortho-ester formation, the less reactive acceptor **95** (the 4-benzoate group has a deactivating effect) was condensed with donor **92** and the disaccharide **98** was now isolated in a good yield but with poor diastereoselectivity. The lack of diastereoselectivity was attributed to the very high reactivity of **92**. It was expected that the reactivity of **92** could be reduced by the replacement of the allyl group with a chloroacetyl group. However, coupling of **93** with **95** gave dimer **99** mainly as the α-anomer but again a substantial amount of ortho-ester (**102**) was formed. It was anticipated that the formation of the required dimer could be improved further without effecting the stereoselectivity by replacing the SEt by a SPh in the acceptor (phenyl thioglycosides are less reactive than ethyl thioglycosides). Indeed, coupling of **93** with **96** gave dimer **100** in good yield as virtually one anomer. A similar glycosylation strategy was adopted for the preparation of a common inner core trisaccharide fragment corresponding to the cell-wall of *Mycobacterium kansasii*.[40]



92. R^1 = All
93. R^1 = ClAc

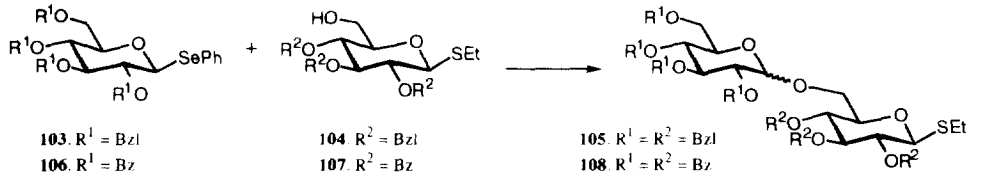
94. R^2 = Bzl, X = Et
95. R^2 = Bz, X = Et
96. R^2 = Bz, X = Ph

97. R^1 = All, R^2 = Bzl, X = Et
98. R^1 = All, R^2 = Bz, X = Et
99. R^1 = ClAc, R^2 = Bz, X = Et
100. R^1 = ClAc, R^2 = Bz, X = Ph

101. R^2 = Bzl
102. R^2 = Bz

Scheme 18

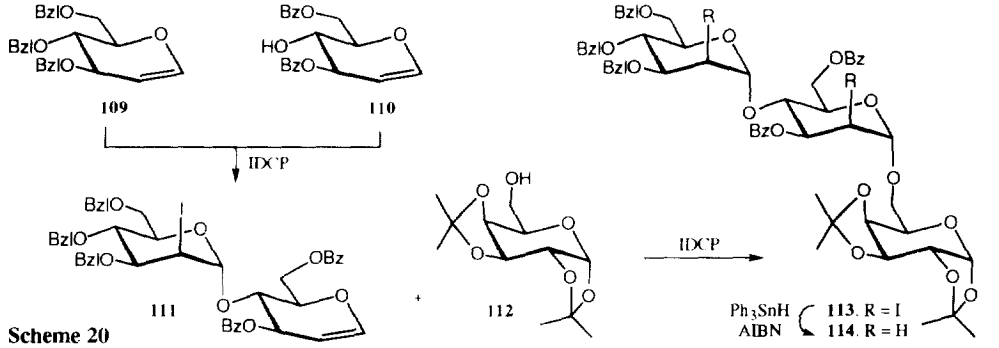
In the previous section, it was described that selenoglycosides can be activated under conditions which do not effect thioglycosides and this observation was exploited in a selective glycosylation strategy. Recently,[41] it was shown that both seleno- and thioglycosides can be activated with NIS/TfOH and it was observed that under these conditions selenoglycosides are much more reactive than their ethylthio counterparts (**Scheme 19**). This observation opened the way to condense chemoselectively the fully benzylated phenyl selenyl glycoside **103** with the partially benzylated ethyl 1-thioglycoside **104** using IDCP as promoter to yield predominantly an α-linked disaccharide **105** (79%, α/β = 3/1). On the other hand, NIS/TfOH-mediated glycosylation of a fully benzoylated phenyl thioglycoside **106** with a partially benzoylated thioglycoside **107** gave the β-linked disaccharide **108** in an excellent 79% yield. The iodonium-ion assisted activation of selenoglycosides was applied in the preparation of a tetrameric saccharide fragment corresponding to the repeating unit of *Proteus vulgaris* strain 5/43.[42]



Scheme 19

Investigations by Danishefsky *et al.* have revealed[43] that chemoselective activation is also applicable to glycals and this methodology opened the way for the efficient preparation of 2-deoxy containing oligosaccharides (**Scheme 20**). Thus, IDCP mediated chemoselective oxidative coupling of ether protected glycal **109** with the partly acylated glycal **110** gave stereoselectively disaccharide **111** in a 58% yield. The dimer **111** could also be activated with IDCP and reaction with glycosyl acceptor **112** yielded trimer **113** (79%). Radical mediated dehalogenation of **113** afforded the 2-deoxy-glucoside containing trisaccharide **114** (94%). In another strategy,[44] glycals were activated by epoxidation followed by stereoselective condensation with a partly protected glycal. After protection of the 2-hydroxyl group, this procedure could be repeated.

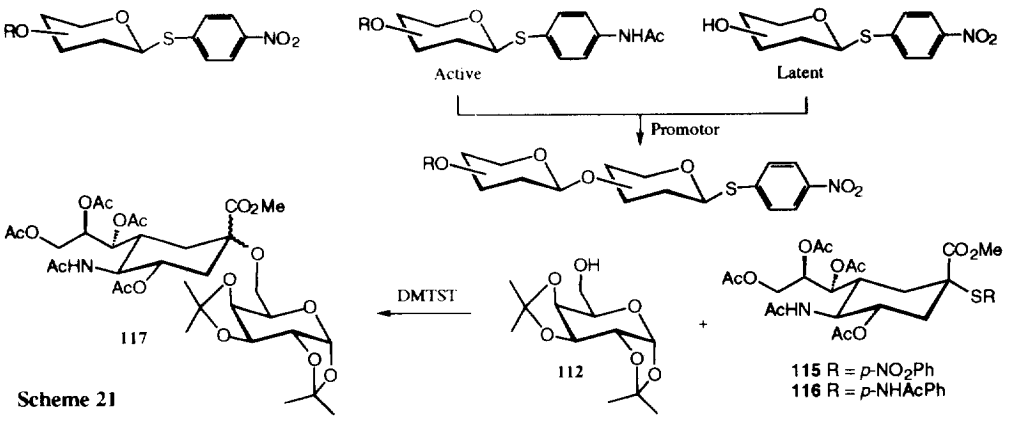
The developments described in this section allow the facile preparation of di-, tri- and tetra-saccharides. These saccharides can be used in a convergent block synthesis of larger oligosaccharides. Often the monomeric units required for the preparation of the building block can be synthesised from a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



Scheme 20

6. Latent-active glycosylation strategies

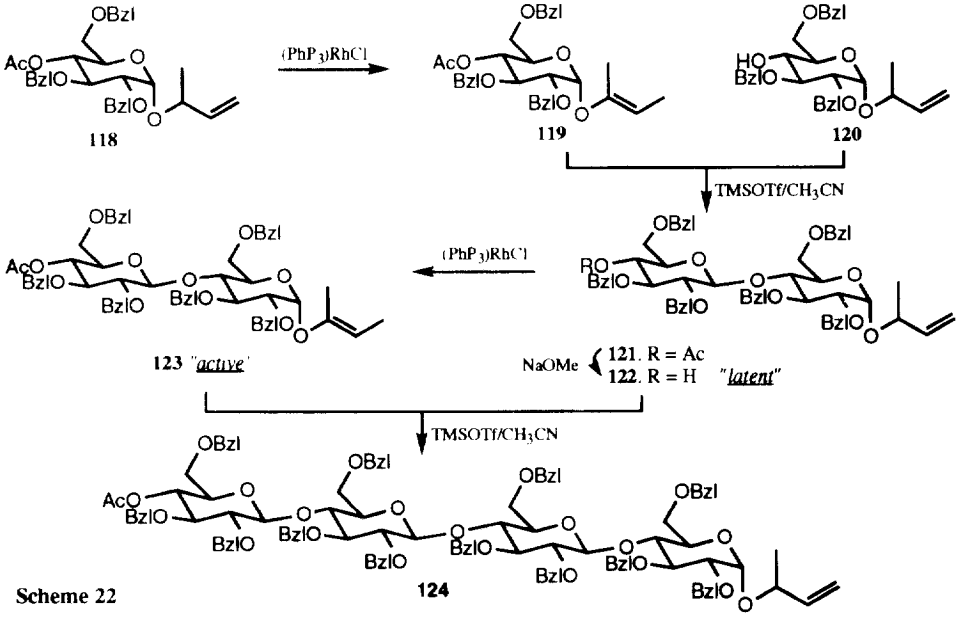
Recently,[45] a latent-active concept for the convergent syntheses of oligosaccharide was proposed. In such a strategy, a stable anomeric group can be converted into a good leaving group by a simple chemical interconversion. It was anticipated that *p*-nitrophenyl thioglycosides are inert towards thiophilic reagents but the electron withdrawing nitro-substituent should be easily convertible into an electron donating *N*-acetyl group (latent→active) and it should be possible to condense this "active" thioglycoside with a "latent" *p*-nitrophenyl thioglycoside. Next, the nitrophenyl substituent of the obtained condensed product can be activated by a repetition of this procedure (**Scheme 21**). Roy *et al.* showed[45] that treatment of nitrophenylthio sialoside **115** and alcohol **112** in the presence of DMTST gave no product formation. Reduction of the nitro-group with $SnCl_2$ followed by acetylation of the amino group gave *N*-acetyl phenyl



Scheme 21

sialoside **116** which was condensed with **112** in the presence of DMTST to give an anomeric mixture of disaccharides (**117**) in a good yield (81%, α/β = 3/1). Unfortunately, it was demonstrated[46] that iodonium-ion mediated condensation of a 4-*N*-acetylamino thioglycopyranosides with 4-nitrophenyl thioglycopyranosides gave disaccharides in modest yields.

A novel approach based on a similar type of glycosylation reaction has been developed.[47] This glycosylation strategy is based on the fact that a substituted allyl glycoside can be isomerised to a 2-isobutenyl glycoside which, in turn, may undergo a Lewis acid-promoted glycosylation reaction. For example (**Scheme 22**), isomerisation of the substituted anomeric allyl ether of **118**, using Wilkinson catalyst, gave the substituted vinyl glycoside **119** which, in turn, was used in a TMSOTf promoted glycosylation reaction with substituted allyl glycoside **120** to give the β-linked dimer **121** in an excellent yield (89%, α/β = 1/20).

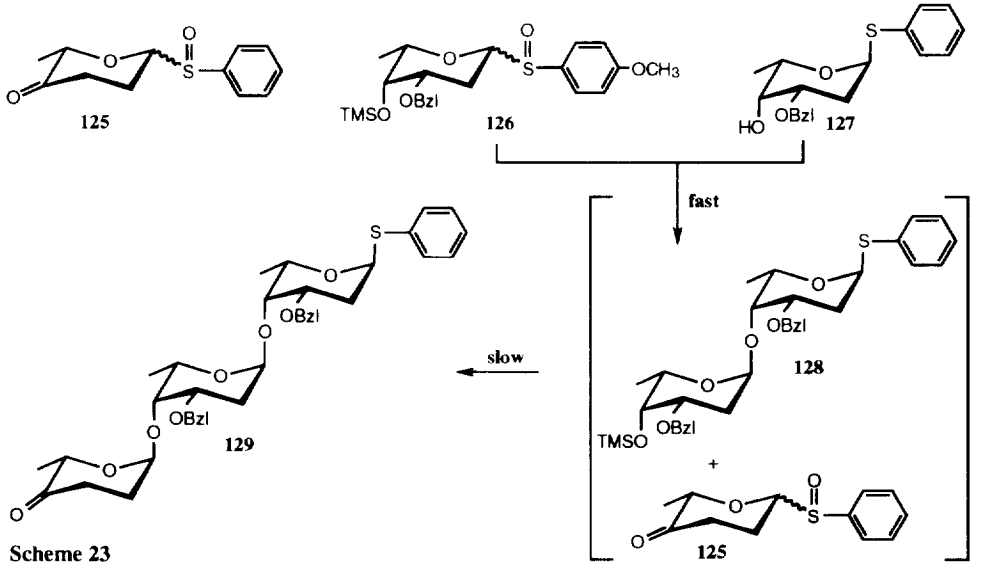


Scheme 22

Dimer **121** could be converted into a glycosyl donor **123** (latent→ active) and glycosyl acceptor **122**. Coupling of **122** with **123** gave tetramer **124** in a 83% yield (α/β = 1/8). This latent-active glycosylation strategy provides a facile approach to prepare building blocks which can be used for convergent oligosaccharide synthesis.

7. One-pot multi-step glycosylations

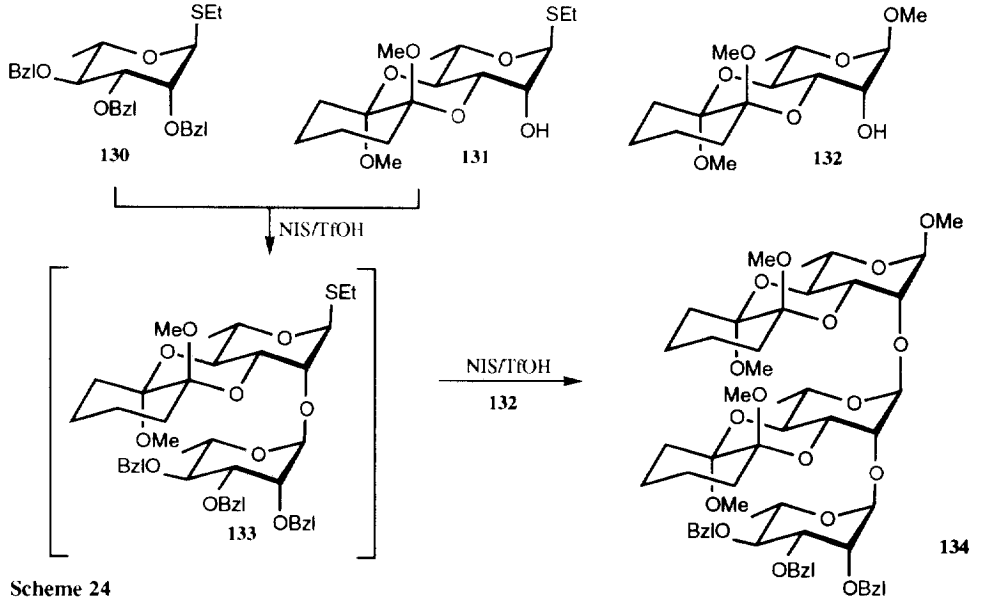
Recently, several methods have been reported to perform sequential glycosylations as a one-pot procedure. Kahne *et al.* described[48] a glycosylation method that is based on activation of anomeric sulfoxides with triflic anhydride (Tf_2O) or triflic acid (TfOH). Mechanistic studies revealed that the 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 **129** from a mixture of monosaccharides **125**, **126** and **127** (**Scheme 23**).[49] Thus, treatment of this mixture with triflic acid resulted in the formation of trisaccharide **129** in a 25% yield. No other trisaccharides were isolated and the only other coupling product was dimer **128**. The products of the reaction indicate that the glycosylation takes place in a sequential manner. First, the most reactive *p*-methoxyphenylsulfenyl glycoside **126** was activated and reacts with alcohol **127** and not with the silyl ether **126**. In the second stage of the reaction, the less reactive silyl ether of disaccharide **128** reacts with the less reactive sulfoxide **125** to give trisaccharide **129**.



Scheme 23

The phenylthio group of **129** could be oxidised to a sulfoxide which was used in a subsequent glycosylation. The obtained trisaccharide 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.

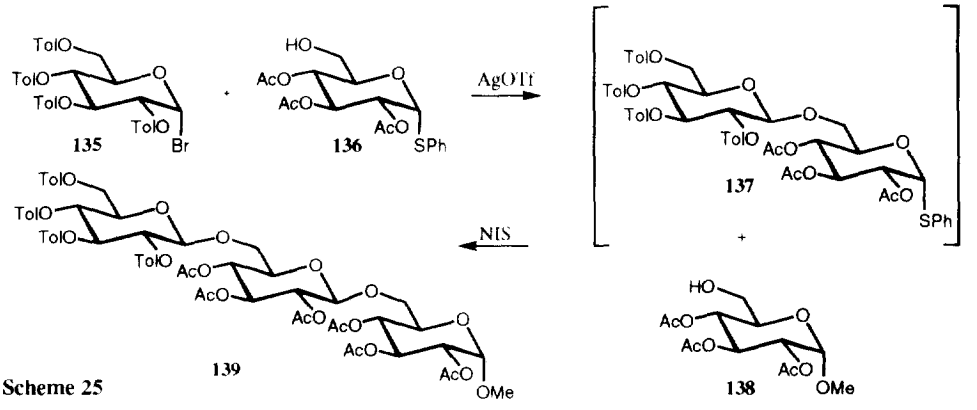
Ley *et al.* reported[50] a facile one-pot two-step synthesis of a trisaccharide unit (**134**) which is derived from the common polysaccharide antigen of a group B *Streptococci*. The trisaccharide was assembled from the benzylated rhamnoside **130** and the cyclohexane-1,2-diacetal (CDA) protected rhamnosides **131** and **132** (**Scheme 24**). The preparation of **134** is based on the armed-disarmed glycosylation strategy and exploits the fact that the activated thioglycoside **130** is more reactive than the torsially deactivated CDA protected rhamnoside **131**. Thus, NIS/TfOH mediated chemoselective coupling of **130** with **131** gave dimer **133**. Next, the second acceptor **132** was added to the reaction mixture and the disaccharide **133** could be activated by the addition of another equivalent of NIS and a catalytic amount of triflic acid to afford the trisaccharide **134** in an excellent overall yield of 62%. It is of interest to note that a stepwise preparation of **134** resulted in a lower overall yield.



Scheme 24

Takahashi described[51] a similar one-pot two-step glycosylation but now the difference in reactivity between glycosyl donor and acceptors was accomplished by the use of two types of anomeric leaving groups with different reactivities (**Scheme 25**). Thus, glycosyl bromide **135** could be coupled with thioglycoside **136** in the presence of silver triflate to give dimer **137**. While the anomeric phenyl thio-groups in **136** and **137** are stable to silver triflate (AgOTf), addition of both the second activator (NIS) and the glycosyl acceptor **138** promoted the selective activation of glycosyl donor **137**, resulting in the formation of trisaccharide **139** (84% overall yield). In this example, the stereochemical outcome of the two glycosylation reactions was

controlled by the neighbouring group participation of the 2-*O*-toluoyl (Tol) and acetyl protecting groups (see **Scheme 25**). A similar one-pot two-step glycosylation procedure was used for the preparation of an elicitor-active hexaglycoside and in this case the difference in reactivity between a trichloroacetimidate and thioglycoside was exploited.[52]



Scheme 25

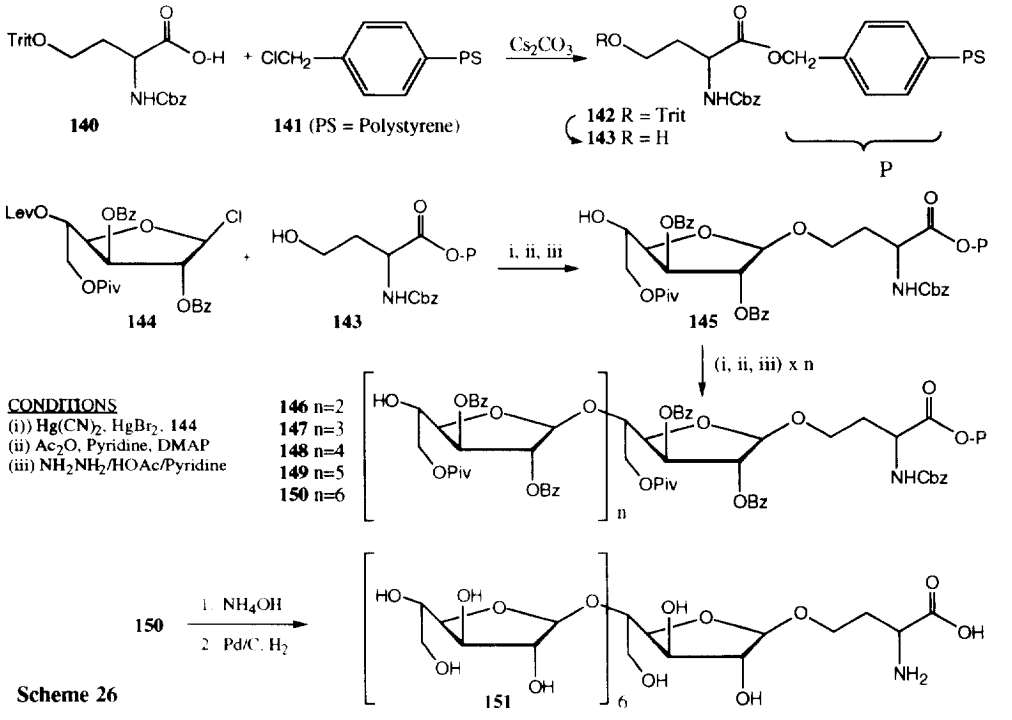
The described glycosylation strategies allow the construction of several glycosidic linkages by a one-pot procedure. It should, however, be realised that this type of reactions will give only satisfactory results when the glycosylations are highly diastereoselective. For example, it is generally known that rhamnosides donors give often very high α-selectivities (**Scheme 24**). Furthermore, by exploiting neighbouring group participation it is easy to form 1,2-trans glycosides (**Scheme 25**). Other type of glycosidic linkages may impose problems.

8. 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.[53] However, since no powerful methods for glycosidic bond formation were available, the success of these methods were limited and only simple di- and trisaccharides could be obtained. In 1987, van Boom *et al.* reported[54] the solid supported synthesis of a D-galactofuranosyl heptamer. The synthetic approach which was followed is illustrated in **Scheme 26**. The selectively protected L-homoserine **140** was linked to the Merrifield polymer chloromethyl polystyrene (PS = polystyrene) **141** to give the derivatised polymer **142**. The loading capacity of the polymer was 0.5 mmol/g resin. Acid hydrolysis of the trityl group of **142** gave **143** and coupling of the chloride **144** with the immobilised **143** under Koenigs-Knorr conditions afforded the homoserine glycoside **145**. It was observed that the coupling reaction had not gone to completion and to limit the formation of shorter fragments, the unreacted hydroxyl groups were capped by treatment with acetic anhydride in the presence of pyridine and *N,N*-dimethylaminopyridine (DMAP). Elongation of **145** was performed as follows: the levulinoyl (Lev) group of **145** was removed by treatment with a hydrazine/pyridine/acetic acid mixture and the released alcohol was coupled with chloride **144** and the unreacted hydroxyl groups were capped by acetylation. After repeating this procedure five times (n=6), the heptasaccharide **150** was released from the resin by basic hydrolysis. Under these conditions also the

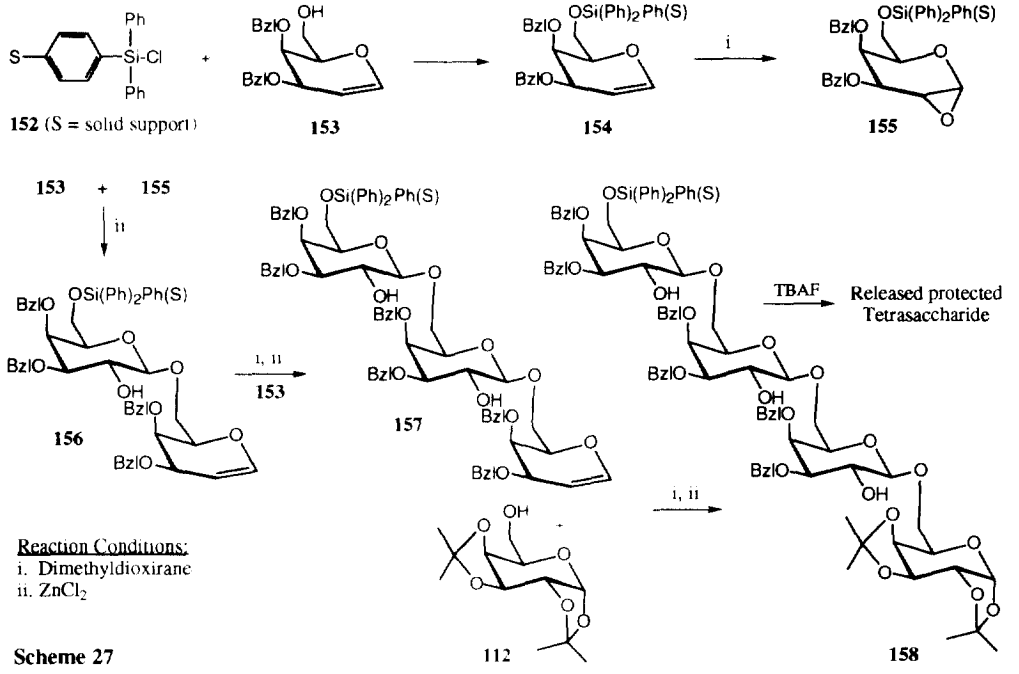
benzoyl and pivaloyl (Piv) protecting groups were removed. Finally, cleavage of the benzyloxycarbonyl (CBz) group by hydrogenolysis over Pd/C gave **151** in an overall yield of 23%.

Kahne *et al.* described[55] the solid supported synthesis of oligosaccharides using anomeric sulfoxides as donors.



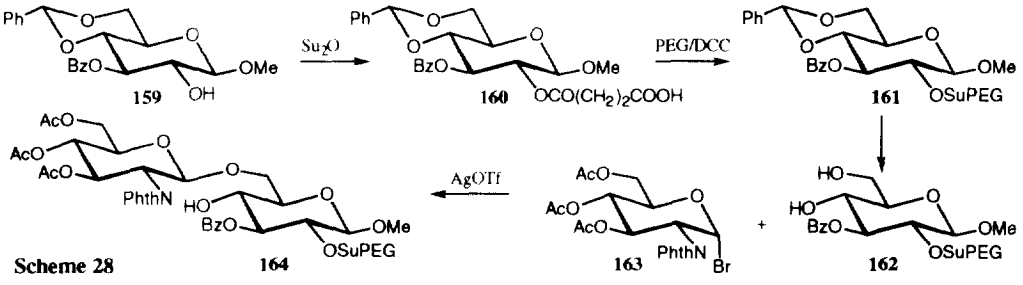
Scheme 26

In both procedures (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 [56] an inverse approach using the incoming sugars as glycosyl acceptor. The synthesis of an oligosaccharide is initiated by attaching a suitably protected glycal (**153**) to a solid support (polystyrene) (**152**). The double bond of the glycal (**154**) is then activated by epoxidation (→**155**) and glycosidation occurs between a solution-based glycal acceptor (**153**) and the epoxide linked to the solid support (**Scheme 27**). The last sugar (**112**) can be introduced as a non-glycal to terminate the process and the oligosaccharide (**158**) can be released from the solid support by tetra-*n*-butylammonium fluoride (TBAF) treatment. This method allowed the preparation of a tetrasaccharide in a 32% overall yield. An advantageous aspect of the technique 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 minimise lowering of the yield in difficult glycosylation reactions.



Scheme 27

The rate of reactions on a solid support are generally reduced compared to solution based methods. Krepinsky *et al.* addressed this problem by polymer-supported solution synthesis of oligosaccharides (**Scheme 28**).[57] This strategy is based on the fact that a polyethylene polymer supported saccharide is soluble under conditions of glycosylation but insoluble during the work-up procedure. Poly(ethylene glycol)mono methyl ether (PEG) was coupled through a succinic (Su) ester linkage to a carbohydrate hydroxyl group. When PEG is bound to a carbohydrate, a glycosylation reaction can be driven to completion by repeated addition of the glycosylation agent. For example, in the silver ion mediated coupling of **162** with **163** to give **164**, 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.



Scheme 28

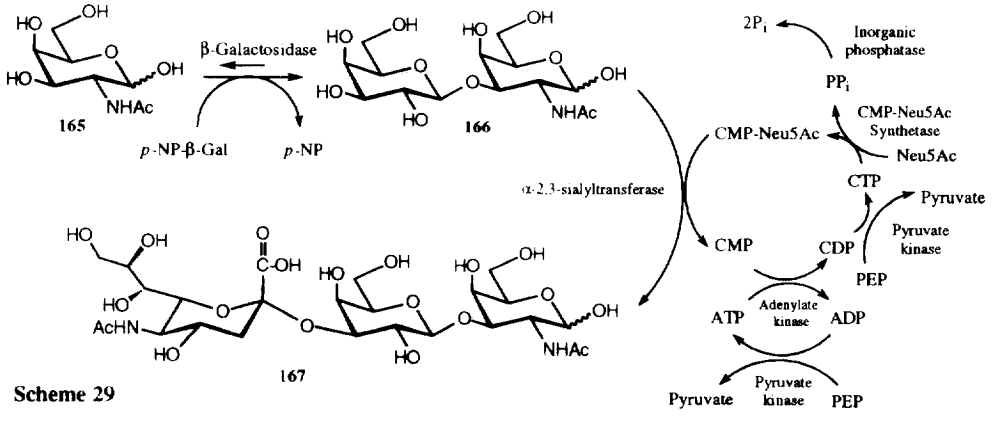
Recently, PEG was bound to the anomeric centre of a saccharide *via* an α,α'-dioxyxylyl glycoside.[58] This linkage is stable under many chemical conditions including glycosylation but can be cleaved by hydrogenolysis. The PEG-based methodology has been used for the preparation of a heptaglucoside having phyto-alexin-elicitor activity [59a] and other oligosaccharides.[59b-d]

The polymer supported 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.

9. Enzymatic and semi-synthetic glycosylation strategies

The need for increasingly efficient methods for oligosaccharide synthesis has stimulated the development of enzymatic methods and two basic approaches are available.[60] In the first approach, glycosyltransferases and sugar nucleotide diphosphate are used for glycosidic bond formation. This method is very powerful especially when the sugar nucleotides are regenerated *in situ*. The enzymatic methods bypasses the need for protecting groups since the enzymes control both the regio- and stereoselectivity of glycosylation. It should, however, be realised that the number of available glycosyl transferases is still very limited. On the other hand, the reverse hydrolytic activity of glycosidases can be exploited in glycosidic bond formation. This method allows the preparation of several disaccharides.

Recently, a combined sequential use of a glycosidase together with a glycosyl transferase and a co-factor regeneration was used for the preparation of Sialyl T-antigen **167**.[61] Thus, the enzyme β-galactosidase catalysis the coupling reaction between *N*-acetyl galactosamine and *p*-nitrophenyl β-D-galactopyranoside (**165**, *p*-NP-Gal) to give the dimer **166**. Compound **166** is a substrate for the enzyme α-2,3 sialyltransferase and reaction with CMP-Neu5Ac gave the sialyl T-antigen **167** in an isolated yield of 36% (26 mg product was obtained). The released cytosine monophosphate (CMP) was regenerated according the process depicted in **Scheme 29**. It is important to note that reverse hydrolysis of disaccharide intermediate **166** is blocked by the glycosyltransferese mediated conversion into the trisaccharide **167** and this compound is no longer a substrate for this enzyme.



Scheme 29

In order to overcome problems associated with chemically and enzymatically based methods, combined approaches have been developed.[62] In such an approach, glycosidic linkages which are very difficult to introduce chemically are introduced enzymatically and *visa versa*. The latter approach has proven to be extremely valuable for the introduction of neuramic acid units in an oligosaccharide.

Enzymatic oligosaccharide synthesis has also been performed on solid supports.[63]

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