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1 New Glycosylation Strategies for the Chemical Synthesis of Complex Oligosaccharides

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Abstract

This review discusses novel glycosylation strategies for the efficient chemical synthesis of complex oligosaccharide fragments related to the repeating units of plant and microbial polysaccharides. Special emphasis will be put on the glycodesilylation strategy and the application of intramolecular glycosylation sequences for the preparation of complex oligosaccharide structures containing pyruvated glycosyl moieties or glycosidic linkages which are difficult to be established otherwise.

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1. Introduction

Despite the great achievements carbohydrate chemistry has seen during the last decades, the chemical synthesis of complex bacterial saccharides and glycoconjugates of biological importance remains a quite difficult, sometimes even tedious task and certainly a challenging endeavour for a synthetic chemist. Nevertheless, the numerous specific biological functions complex carbohydrate structures are known to display with respect to subtle recognition phenomena, combined with the intrinsic difficulties encountered with obtaining sufficiently pure material from natural sources for studying those phenomena on a molecular basis downrightly hanker after the search for new and highly efficient synthetic methods for the chemical preparation of complex saccharides. Indeed, enormous effort toward new synthetic strategies in this respect has been made, and many of the long persisting pertinent problems of oligosaccharide synthesis could be solved in recent years.[1-10] But still, much room is left for the development of new efficient synthetic strategies for the chemical preparation of complex oligosaccharides, and in fact, some new and promising looking methodologies have also evolved in recent years.

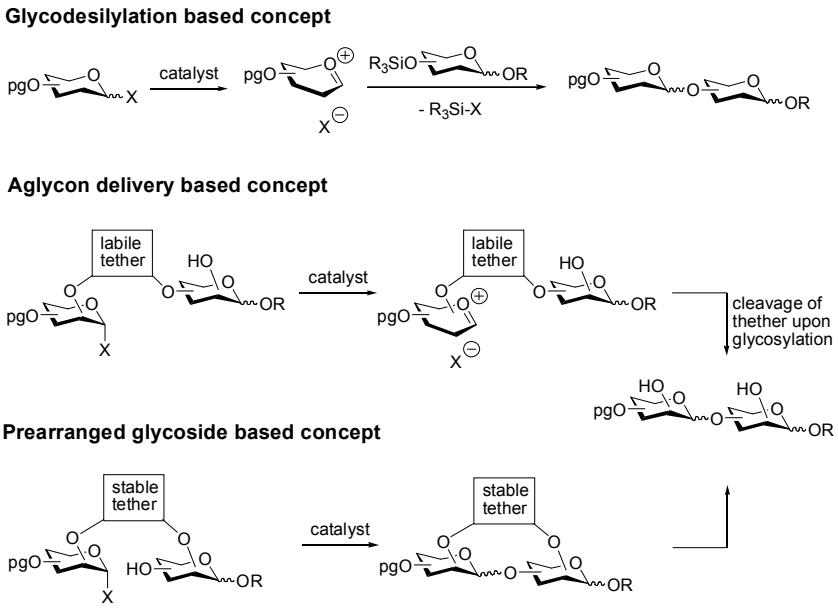


Figure 1. Glycodesilylation, aglycon delivery and prearranged glycoside based principles. X = leaving group, pg = protecting group, R = alkyl, aryl.

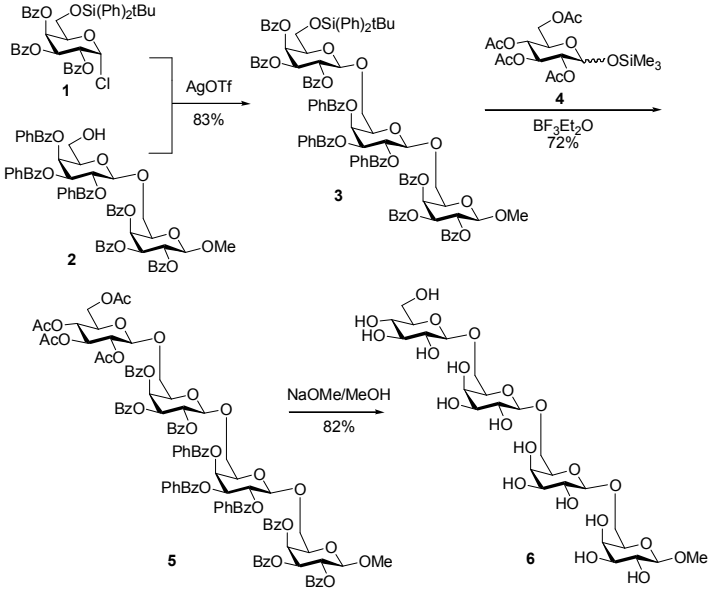
Here, emphasis with regard to oligosaccharide synthesis will be put on the glycosylation of silylated glycosyl acceptors using various glycosyl donors[11] ("glycodesilylation" based concept) and on intramolecular glycosylations using two different approaches, namely, the "intramolecular aglycon delivery" based concept and the "ring-closing glycosylation" or "prearranged glycoside" based concept.[12,13] (Fig. 1).

2. Glycodesilylation

In order to selectively alkylate a silylether with concomitant cleavage of the O-Si bond, attack of the ether oxygen by an electrophile is required. In the case of O-glycosidic bond formation, the attacking electrophile is usually a glycosyl cation generated from a suitable precursor like for example 1-O-silylated or 1-O-acylated glycoses or glycosyl fluorides and a Lewis acid. For 1-O-trimethylsilylated glycoses as the glycosyl donors, trimethylsilyltriflate (TMSTf)[14,15] and tin triflate (Sn(OTf)2)[16] have been used as the catalyst or promoter. The diastereoselectivity of these glycodesilylations follow the classical rules of Koenigs-Knorr reactions, *i.e.* 2-O-acyl protected glycosyl donors predominately afford β-glycosidic linkages whereas 2-O-benzyl protected donors give α-linkages depending on the solvent which is used for the glycosylation step. The method is also suitable to glycodesilylate glycosyl acceptors bearing the more stable *t*-butyldiphenylsilyl group. An example for the synthesis of a tetrasaccharide which was used for epitope mapping of a monoclonal antibody is shown in Scheme 1.[15]

According to this strategy, the silyl-protected galactosyl chloride **1** was coupled first in a classical AgOTf-promoted Koenigs-Knorr reaction with methyl digalactoside **2** to afford trisaccharide **3** in 83% yield. Next, the trisaccharide was glycodesilylated with 1-O-trimethylsilyl-glucose **4** using boron trifluoride as the catalyst to afford tetrasaccharide **5** in 72% yield. The latter was finally deprotected to give the tetrasaccharide **6**. This example shows that the glycodesilylation protocol can be efficiently combined with classical glycosylation methods.

1-O-Acyl protected glycoses have been activated for glycodesilylations of TMS-protected glycosyl acceptors with $GaCl_3/AgClO_4$,[17] TMSOTf[18] and $SnCl_4/Sn(OTf)_2$.[19] The latter catalyst was also used for furanosyl donors. A wide variety of TMS-protected alcohols and monosaccharide glycosides have been glycosylated using 1-O-acyl protected donors.[11] Several disaccharide structures often found in bacterial oligosaccharides have been prepared efficiently using 1-O-actyl protected glycosyl donors, namely Glc*p*-α(1,6)-Glc*p*, Glc*p*-α(1,4)-Glc*p*[17] and Rib*f*-α(1,6)-Glc*p*.[19] 1-O-Unprotected furanoses also have been successfully used as donors for glycosylations. Special Lewis acids are required for their activation though.[20,21]

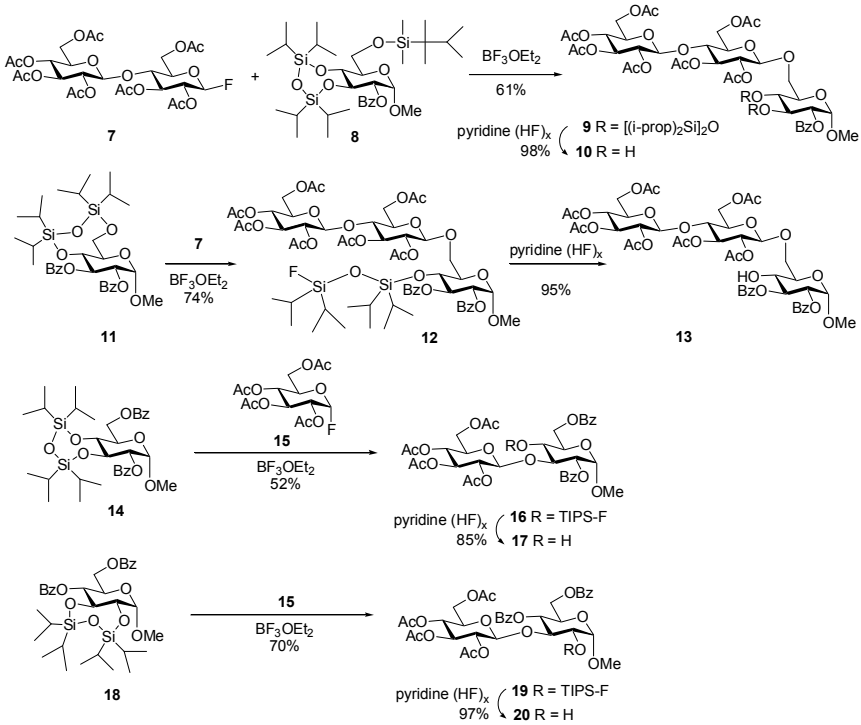


Scheme 1.

Glycosyl fluorides are the most often used glycosyl donors for glycodesilylation reactions. In general, glycosyl fluorides have gained considerable importance as donors in oligosaccharide synthesis since they are stable halogenoses which, in contrast to glycosyl chlorides, bromides and iodides, can be stored at room temperature, chromatographed and selectively protected, and also can be effectively activated with a wide variety of Lewis acids. Thus, glycosyl fluoride are ideal donors for oligosacchide synthesis in combination with other glycosyl donors like 1-thio-glycosides.[22-26] Similarly, glycosyl fluorides have been widely used for glycosylations of silylated glycosyl acceptors in combination with the following Lewis acids: SiF_4,[27] BF_3-etherate,[28-30] TiF_4,[31] TMSOTf,[31,32] and SnF_4.[31] Since during glycodesilylations a thermodynamically favored Si-F bond is formed, glycosyl fluorides react with silylethers faster than with alcohols.[28] However, the ease with which glycodesilylation occurs also strongly depends on the applied Lewis acid. Under heterogeneous catalysis with TiF_4, no significantly faster reaction was observed during glycosylation of silylethers and alcohols.[31] With SiF_4 as the catalyst, even a faster reaction of the corresponding alcohols was observed.[27] Likewise, the diastereoselectivity depends on the glycosyl fluoride, the catalyst, and most prominently, on the solvent. Glycosyl fluorides having an acyl group at position 2 react via neighbor group participation affording

mainly the corresponding β-glycosides. Glycosyl fluorides having a benzyl group at position 2 give rise to anomeric mixtures depending on the solvent. For example, 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl fluoride reacts with silylethers in acetonitrile to give almost exclusively the corresponding β-glucosides, whereas in diethylether, predominately α-glucosides are obtained while the anomeric selectivity of glycodesilylation is independent from the anomeric configuration of the fluoride.[27,31]

For oligosaccharide synthesis, glycodesilylation can be beneficially applied with regard to the disparate reactivities of different silyl protecting groups in the glycosyl acceptor. For example, it has been shown for 6-O-silylated hexa-O-benzoyl-amygdalin derivatives that the dimethylthexylsilyl group reacts significantly faster with acetofluoroglucose than the t-butyldimethylsilyl group.[30] Similarly, the bifunctional 1,1,3,3-tetraisopropyldisiloxane group reacts slower than the dimethylthexylsilyl group in glycodsilylations as outlined in Scheme 2.[33,34]



Scheme 2.

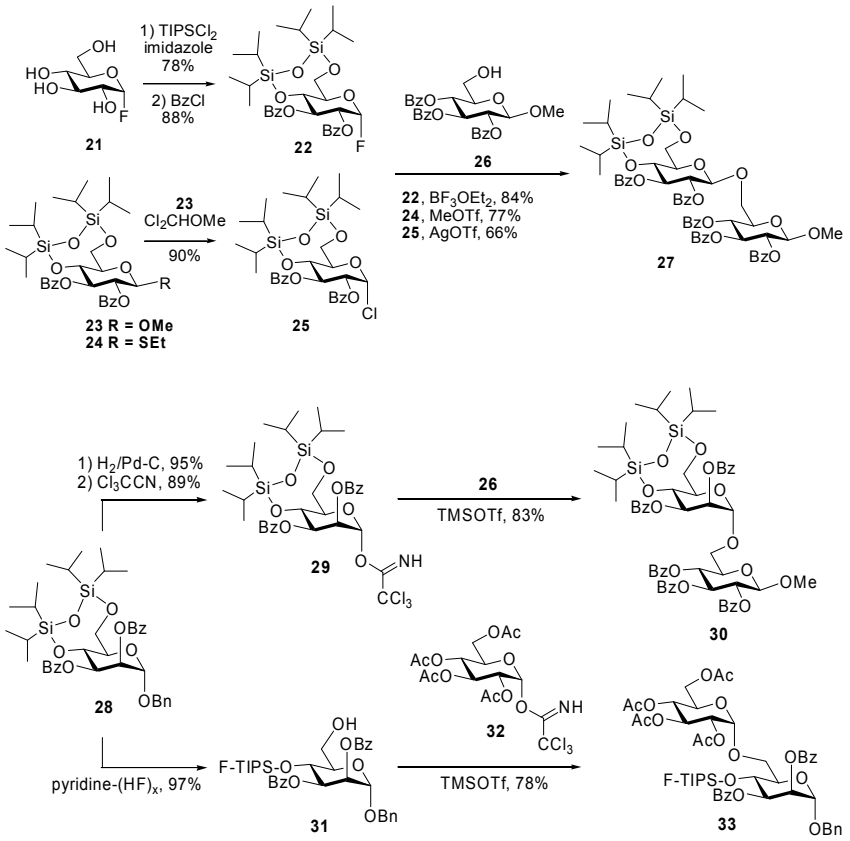
Cellobiosyl fluoride **7** selectively glycodesilylates the dimethylthexylsilylated position 6 beside the tetraisopropyldisiloxane (TIPS) protected positions 3 and 4 of glucoside 8 affording trisaccharide **9** in 61% yield. Next, the TIPS group in 9 can be selectively hydrolized with pyridine-HF complex to give the disaccharide acceptor 10 which can be further glycosylated at positions 3 and 4 of the α-glucoside moiety. A major advantage of the 1,1,3,3-tetraisopropyldisiloxane group is its ability to be regioselectively glycodesilylated with glycosyl fluorides (Scheme 2). For example, 4,6-*O*-TIPS protected glucoside **11** reacts smoothly with hepta-*O*-acetyl-cellobiosyl fluoride **7** under borontrifluoride catalysis to afford exclusively the 6-*O*-glycosylated trisaccharide **12** in 74% yield. The fluorodisiloxane group at position 4 can be easily removed by fluorodesilylation with Bu_4NF or HF-pyridine complex to give trisaccharide **13** which, in turn, can be further glycosylated at position 4.[33] Likewise, the 3,4-*O*-TIPS derivative **14** and the 2,3-*O*-TIPS derivative **18** afford the laminaribiosides **16** and **19**, which are converted into the corresponding disaccharide acceptors **17** and **20** upon cleavage of the remaining fluorodisiloxane groups.[34] Thus, a flexible regioselective glycosylation strategy results for the combination of the glycodesilylation protocol and the TIPS-protecting group.

The glycodesilylation based concept with TIPS-protected glycosides can be further expanded by a combination with other leaving groups for glycosyl donors. Surprisingly, glycosyl fluoride **21** itself can be 4,6-*O*-protected with TIPS to give the TIPS-protected donor **22** after benzoylation of the remaining hydroxyl groups. The latter donor **22** then reacts selectively with glycosyl acceptor **26** affording the gentiobioside **27** in 84% yield. No oligomerisation of the donor is observed under these conditions (Scheme 3).[33] Likewise, **27** can also be prepared from the chloride **25** which is obtained from the corresponding methyl glucoside **23**, or from the 1-thio-glucoside **24** upon adequate activation with either AgOTf or *N*-iodosuccinimide (NIS). TIPS-protected trichloroacetimidates are also suitable glycosyl donors as outlined in Scheme 3. Benzyl mannoside **28** can be easily converted into imidate **29** by a two step sequence first removing the aglycon followed by reaction with trichloroacetonitrile. Reaction of **29** with acceptor **26** then affords the TIPS-protected Man-α(1,6)-Glc disaccharide **30** in excellent yield.

Yet another useful extension of the glycodesilylation strategy which increases its flexibility even further is the selective ring opening of the TIPS group with HF-pyridine complex.[33] For example, **28** gives the mannosyl acceptor **31** in a virtually quantitative yield upon treatment HF-pyridine complex, which in turn, can get glycosylated under standard activating conditions with imidate **32** to afford disaccharide **33** (Scheme 3).

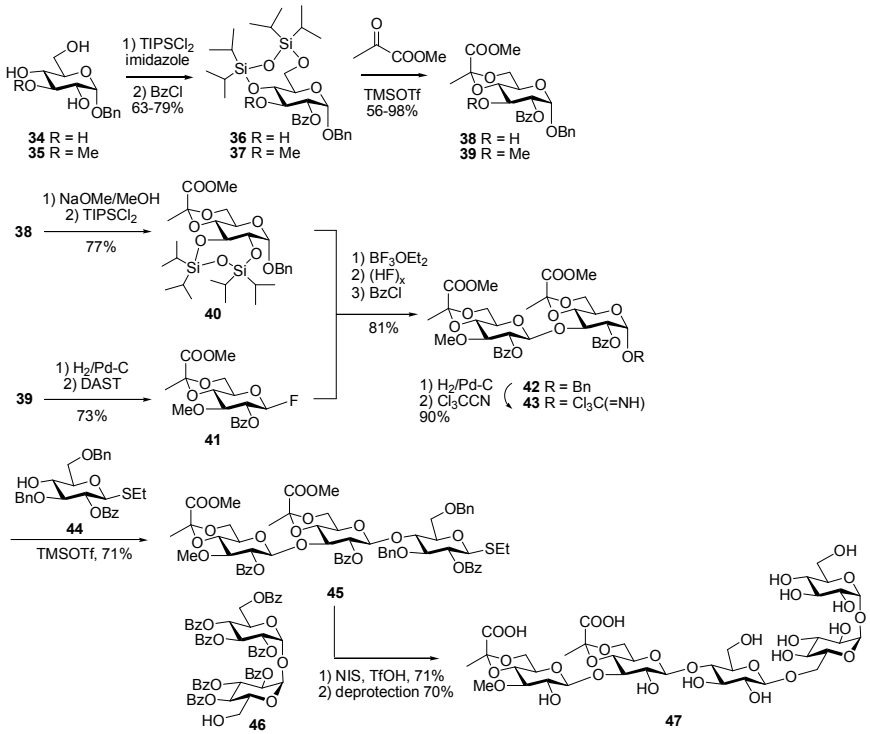
The flexible glycodesilylation protocol has been successfully applied to the chemical synthesis of pyruvated bacterial oligosaccharides. Pyruvic acetals,

i.e. 1-carboxyethylidene substituents, are among the most abundant non-carbohydrate groups found in various capsular polysaccharides and on the cell surface carbohydrate structures of higher organisms.[35,36] Although the concise biological function of the pyruvate acteal in bacterial saccharides is still unknown, it is thought that these acetal moieties modulate the specific interaction of the polysaccharides with protein receptors. Pyruvic acetals are also responsible for the gel-forming properties of some of these polysaccharides, like for instance Agar which contains a (*R*)-4,6-*O*-(1-carboxyethylidene)-β-D-galactosyl-(1→4)-3,6-anhydro-β-L-galactosyl repeating unit.[36] Pyruvic acetals are frequently found in capsular polysaccharides of *Rhizobium*, *Klebsiella*, *Steptococcus*, *Escherichia* and *Mycobacterium* species.[35]



Scheme 3.

Scheme 4 summarizes the chemical synthesis of the carbohydrate part of the *Mycobacterium smegmatis* pentasaccharide glycolipid.[37,38] First, the pyruvylated glucose monosaccharide building blocks **38** and **39** were prepared via Noyori-acetalisation of the suitably TIPS-protected glucosides **36** and **37**, starting from the benzyl glucosides **34** and **35**.[39] While the diastereo- and regioselective formation of the pyruvate acetals properly proceeded via the TIPS-protected glucosides **36** and **37**, more convenient direct acetalations of 4,6-unprotected glycosides with methyl pyruvate had been developed.[40-43]

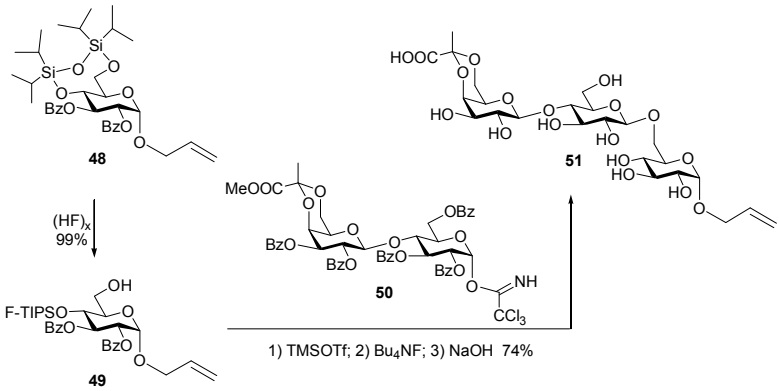


Scheme 4.

Next, a convergent blockwise glycosylation strategy based on the glycodesilylation protocol was realized as follwoes. Benzyl glucoside **38** was debenzoylated and TIPS protected to give monosaccharide **40** in 77% overall yield. On the other hand, glycoside **39** was sequentially converted into fluoride **41** by hydrogenolysis of the aglycon followed by fluorination with DAST. Coupling of **40** and **41** via borontrichloride catalyzed glycodesilylation at

position 3 of **40** proceeded smoothly. The intermediate disaccharide still containing the fluorodisiloxane group was not isolated, but instead, directly fluorodesilylated and rebenzoylated to afford **42** in 81% overall yield. Next, disaccharide block **42** was converted into the imidate **43** which was coupled with ethyl 1-thio-glycoside **44** to give the trisaccharide block **45** in 71% yield. Finally, the latter was condensed with partially protected trehalose **46** to afford the mycobacterium smegmatis pentasaccharide **47** after deprotection. The total synthesis of **47** is highly efficient and due to the glycodesilylation step superior to a classical stewise approach.

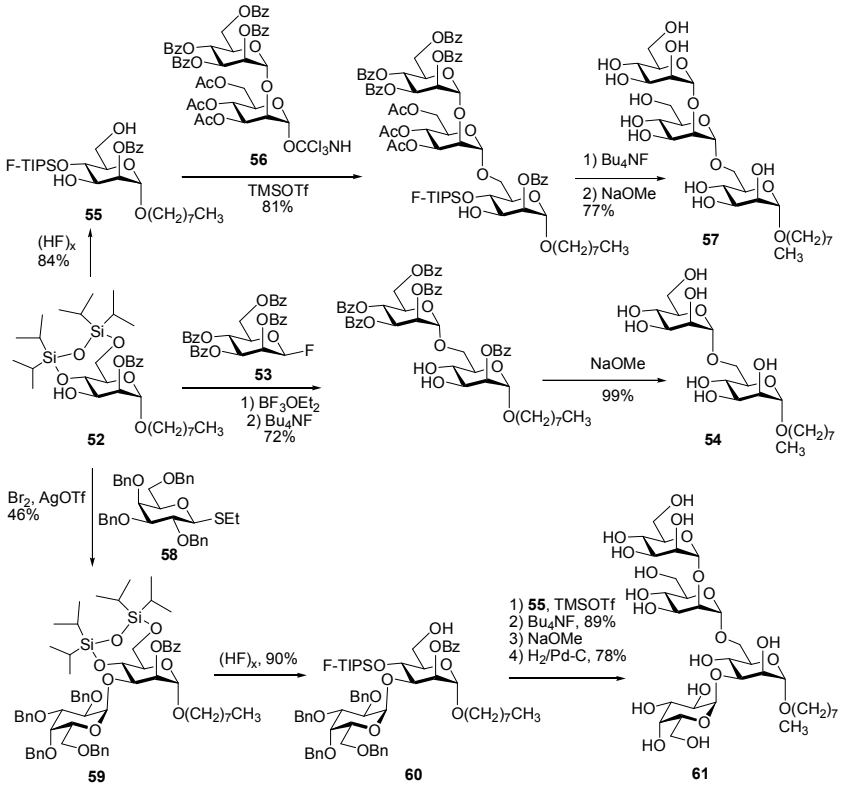
Scheme 5 summarizes the chemical synthesis of a pyruvated trisaccharide fragment related to the capsular polysaccharide of *Klebsiella* K26 applying the alternate glycodesilyation strategy via ring opening of a TIPS-protected glycoside.[44] First, the 4,6-O-TIPS protected allyl glucoside **48** was ring opened with HF-pyridine complex to give in a quantitative yield the ally glucoside acceptor **49**. Next, the latter was glycosylated with the pyruvated disaccharide imidate **50** to afford allyl trisaccharide **51** in 74% overall yield after final deprotection.



Scheme 5.

Another efficient application of the glycodesilylation strategy for the synthesis of di- through tetrasaccharide fragments related to the GPI anchor of *Trypanosoma brucei* is outlined in Scheme 6.[45,46] Once again, the three alternate glycodesilylation protocols were applied here, *i.e.* regioselective glycodesilylation of a TIPS-protected glycoside with a glycosyl fluoride, ring opening of the TIPS group followed by glycosylation of the obtained glycosyl acceptor with an imidate; chemoselective glycosylation of a TIPS-protected glycosyl acceptor with a 1-thio-glycoside. Specifically, octyl 4,6-*O*-TIPS

protected mannoside **52** was used for all three approaches as follows. First, regioselective glycosylation of **52** with fluoride **53** followed by desilylation of the intermediate afforded a disaccharide block in 72% overall yield which was finally deprotected to give the GPI anchor related disaccharide mannoside **54**.

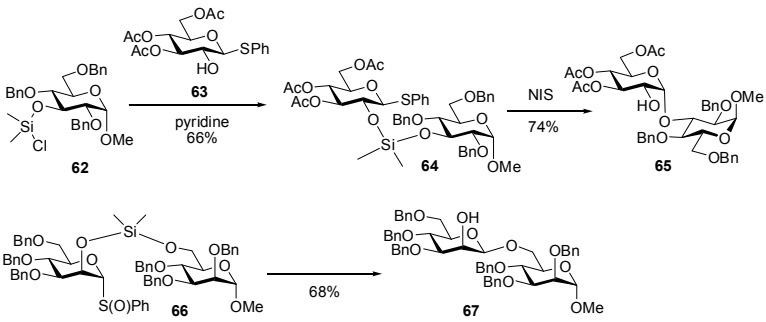


Scheme 6.

It is noteworthy that the glycodesilylation could be fine tuned to such an extent that no glycosylation of the hydroxyl in **52** occurred (*c.f.* the reaction of fluoride **22** with glycosyl acceptor **26** in Scheme 3). Second, starting material **52** was regioselectively ring opened to give mannosyl acceptor **55** which was smoothly glycosylated by imidate **56** to afford the corresponding trisaccharide in 81% yield. Finally, deprotection of the latter gave the GPI anchor related trisaccharide fragment **57**. Third, chemoselective galactosylation of the starting material **52** could be accomplished with ethyl 1-thio-galactoside **58** affording

the disaccharide block **59**. Once again, this example demonstrates the option to fine tune the glycosylation steps in glycodesilylation strategies so that alternatively the free hydroxyl or the TIPS group become glycosylated (*c.f.* the reaction of **52** with **53**). Next, the 4,6-*O*-TIPS group in **59** was opened to give the disaccharide acceptor **60** in 90% yield, which was successively glycosylated with disaccharide donor **56** followed by desilylation to afford the corresponding tetrasaccharide in 89% overall yield. Deprotection of the latter finally afforded the GPI anchor related octyl tetrasaccharide glycoside **61** in 78% yield. The GPI anchor fragments **54**, **57** and **61** were used to study the biological glycosylation pattern of *Trypanosome brucei*.[45,46]

The glycodesilylation strategy can also be applied to intramolecular glycosylations as outlined in Scheme 7. Here, a glycosyl acceptor like glucoside **62** is first linked to a glycosyl donor like **63** via a dimethylsilylene tether to give saccharide **64**. Intramolecular glycosylation of the latter selectively affords the α-linked disaccharide **65**. Similarly, the thethered saccharide **66** affords β-mannosyl disaccharide **67** upon intramolecular glycodesilylation.[47,48] Applications of intramolecular glycosylations for the chemical synthesis of complex oligosaccharides will be discussed in the following chapter.



Scheme 7.

3. Intramolecular Glycosylation

Like glycodesilylation (see above), the concept of intramolecularization of glycosylation reactions must still be regarded as a special strategy for the construction of complex oligosaccharides which is only applied to synthetic problems which are difficult to solve by classical techniques for oligosaccharide synthesis. Nevertheless, considerable knowledge about the principles governing the selelctivity of intramolecular glycosylations has accumulated over the last decade.[12,13,49] In this chapter, applications of the

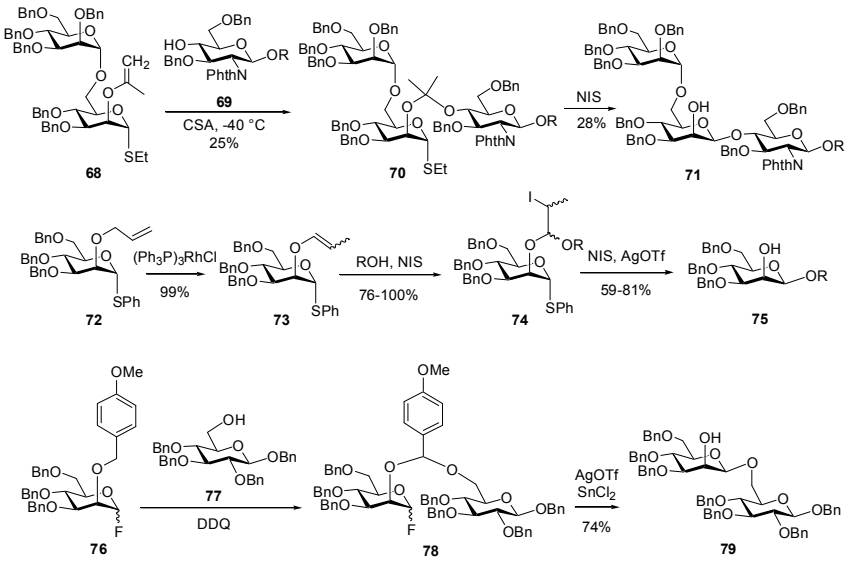
intramolecular glycosylation strategy to the chemical synthesis of complex oligosaccharide structures will be reviewed. In this context, only the intramolecular aglycon delivery based concept (IAD) and the prearranged glycoside based concept (see Figure 1) have found considerable applications in oligosaccharide synthesis so far, while other similar concepts like the leaving group based concept in which the aglycon is first attached to the anomeric center of a glycosyl donor through a labile tether have not.[49] Likewise, only one specific approach of the IAD based concept has found applications in oligosaccharide synthesis so far, *i.e.* tethering glycosyl donor and glycosyl acceptor through acetal tethers.

3.1 Intramolecuar Glycosylation via Acetal-Tethers

The IAD based concept was originally developed by Barresi and Hindsgaul in 1991 for solving the eminent and at that time still persisting problems encountered during the stereoselective formation of β-mannosidic bonds.[50-52] Starting from a suitable 2-O-(2-propenyl)-1-thio-α-D-mannopyranoside donor which is easily accessible from the corresponding 2-O-acetyl derivative with Tebbe reagent, acid-catalyzed acetalisation with a suitable glycosyl acceptors first affords a tethered glycoside in which glycosyl donor and acceptor are linked via an acetal tether. Next, activation of the donor with NIS results in cleavage of the acetal tether with concomitant formation of the glycosidic bond to give exclusively the corresponding β-linked disaccharide. A major drawback of the IAD based concept, however, is the rather low yield when this concept is applied to the synthesis of more complex oligosaccharides where the acetalisation as well as the glycosylation step proceed sluggishly as outlined in Scheme 8.[52]

Acid-catalyzed acetalization of 2-O-(2-propenyl)-1-thio-glycoside disaccharide **68** with glucosamine **69** gave the acetal-tethered saccharide **70** in only 25% yield, and intramolecular glycosylation of the latter also proceeded rather ineffectively to afford the desired trisaccharide **71** in 28% yield only although solely the β-mannosidic linkage was formed. Recently, two more efficient approaches for the IAD based concept which circumvent such problems have been presented by Fairbanks[53-56] and Ito and Ogawa.[57-59] In Fairbanks approach, a 2-O-allyl-glycoside donor is first isomerized into a 2-O-(2-propenyl)-glycoside, *c.f.* **72**→**73**, Scheme 8. Next, a glycosyl acceptor is linked to the vinylether moiety of the donor through a iodoacetalation step to give the tethered glycoside **74** in good yield. Finally, the latter affords the saccharide, here β-mannoside **75**, upon activation of the donor. An advantage of this protocol is that the acetalisation and the intramolecular glycosylation steps can be performed with the same reagent, *i.e.* I_2, AgOTf. Solely the

solvent needs to get changed from dichloromethane for the acetalation step to acetonitrile for the glycosylation step.[53]



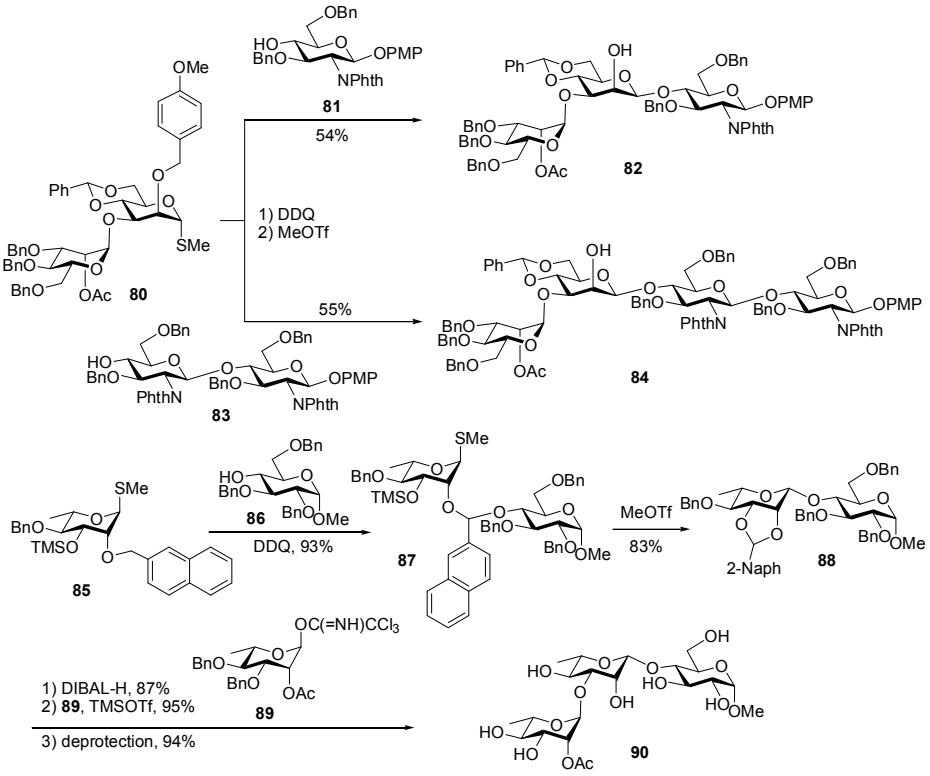
Scheme 8.

Ito and Ogawa's *p*-methoxyphenylmethyl tether can be generated from a *p*-methoxyphenyl group (PMP) of a 1-thio-glycoside **76** by oxidation with DDQ in the presence of the respective glycosyl acceptor **77** (Scheme 8). Thus, tethered glycosides **78** was very conveniently accessible in high yield, and even did not need to get isolated or purified for the next glycosylation step.[57] Upon activation of the donor moiety, the saccharide **79** could be very efficiently constructed. This approach is also compatible to 1-thio-glycoside donors, opening up a very flexible strategy for the synthesis of complex oligosaccharides containing glycosidic linkages which are not easily established by classical glycosylation procedures.[60-62] Furthermore, the IAD based concept via *p*-methoxybenzylidene acetals is also suitable for polymer-supported syntheses of disaccharides where a suitable *p*-allyloxybenzyl group at position 2 of a 1-thio-mannosyl donor is first converted into a PEG-modified benzyl group which allows for the convenient isolation of the intermediate tethered glycosides.[63] The synthesis of β-D-fructofuranosides is yet another useful application of this concept.[64-66] The latter 1,2-cis glycosidic linkage is as difficult to establish as in the case of β-mannosides. In an elegant synthesis

of α-D-fucofuranose-containing disaccharides, Plusquellec used the IAD concept via *p*-methoxybenzylidene acetals in combination with a glycosylation protocol via pentenyl glycosides. Here, even the intermediate NIS-adduct could be isolated.[66]

According to the IAD based concept via *p*-methoxybenzylidene acetals, various oligosaccharides of biological importance have been synthesized and will be discussed briefly in the following.

In a series of papers, Ito et al. have successfully applied the IAD based concept via *p*-methoxybenzylidene acetals to the efficient synthesis of oligosaccharides related to the core region of Asn-linked glycans (Scheme 9).[61,62,67-69] For example, starting from the 2-*p*-methoxybenzyl protected disaccharide **80**, sequencial thethering and intramolecular glycosylation with glucosamine derivative **81** followed by deprotection of the protecting groups afforded the trisaccharide **82** with exclusive β-selectivity.



Scheme 9.

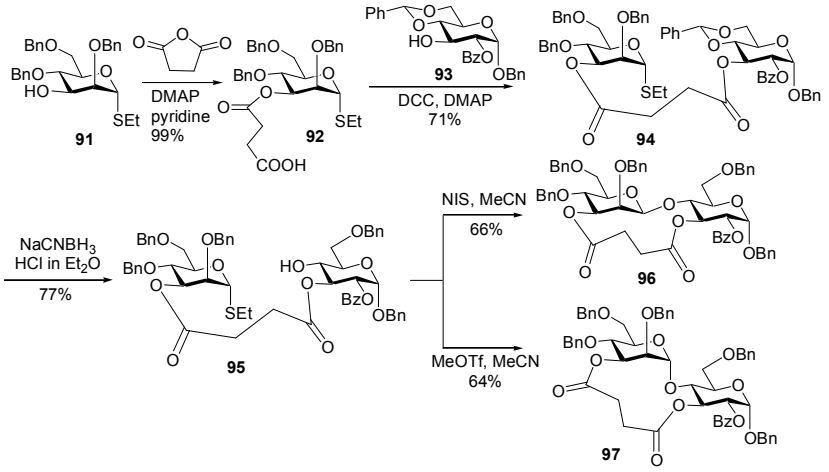
Likewise, IAD with disaccharide **83** gave the related tetrasaccharide **84** in a good overall yield. Recently, this promising approach for the efficient construction of β-mannosidic linkages in oligosaccharide synthesis has been expanded to the preparation of β-rhamosyl moieties containg saccharides using 2-naphthylmethyl ethers instead of the *p*-methoxybenzyl group for the intermediate tethering. For example, treatment of methyl 1-thio-L-rhamnoside **85** and glucoside **86** with DDQ gave first the tethered saccharide **87** in a virtually quantitative yield. Next, treatment of the latter with MeOTf resulted in the exclusive formation of the β-rhamnosidic linkage with concurrent desilylation of the TMS-group to give the acetal-protected disaccharide **88** in 83% yield. Regioselective reductive ring opening of the 2-naphthylacetal with DIBAL-H followed by rhamnosylation of the intermediate disaccharide acceptor with imidate **89** and final deprotection afforded the trisaccharide **90** which is related to a glycan from *S. natans*.[70]

The IAD based concept via benzylidene acetals has also been applied to the efficient and selective synthesis of asymmetric substituted trehalose-lipids found as abundant metabolites in the cell wall of *Mycobacterium tuberculosis*.[71,72] The IAD based concept via silylene tethers has not been applied to the synthesis of complex oligosaccharide structures yet, but a series of mono and disaccharide building blocks useful for classical oligosaccharide synthesis have been prepared by IAD via silylene tethers.[73-79]

3.2 Intramolecular Glycosylation via Prearranged Glycosides

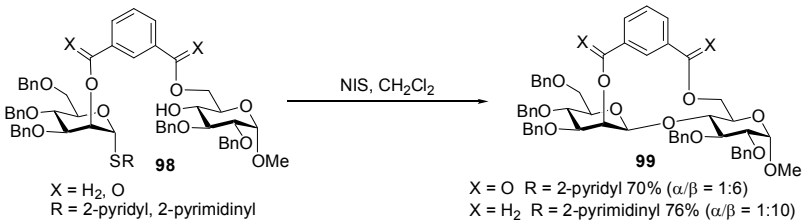
In contrast to the IAD based concepts for intramolecular glycosylations, the prearranged glycoside based concept is a truly intramolecular glycosylation where cyclic saccharide derivatives are formed upon the glycosylation step (see Figure 1). In this approach, the regio- and stereoselectivity of the glycosylation step is mainly governed by the nature of the tether linking glycosyl donor and acceptor prior to the glycosylation step, and the positions to which the tether is attached in the donor and acceptor moieties.[12,13,49] The rigidness of the tether also strongly influences the outcome of the intramolecular glycosylation step,[80,81] as does the activation procedure used for the formation of the glycosidic bond.[82] The principle for the prearranged glycoside based concept for the synthesis of oligosaccharides is outlined in Schemes 10 and 11. For instance, the 1-thio-glycosyl donor **91** is first succinylated with succinic anhydride followed by esterification of **92** with the glucoside acceptor **93** to give the tethered glycoside **94**. Next, the benzylidene group in the acceptor moiety of **94** is regioselectively opened to give prearranged glycoside **95**. Treatment of the latter with NIS in acetonitrile affords solely the tethered β-linked disaccharide **96**, while activation with

MeOTf in acetonitrile results in an inverted anomeric selectivity giving solely the corresponding α-linked disaccharide **97** (Scheme 10).[82]



Scheme 10.

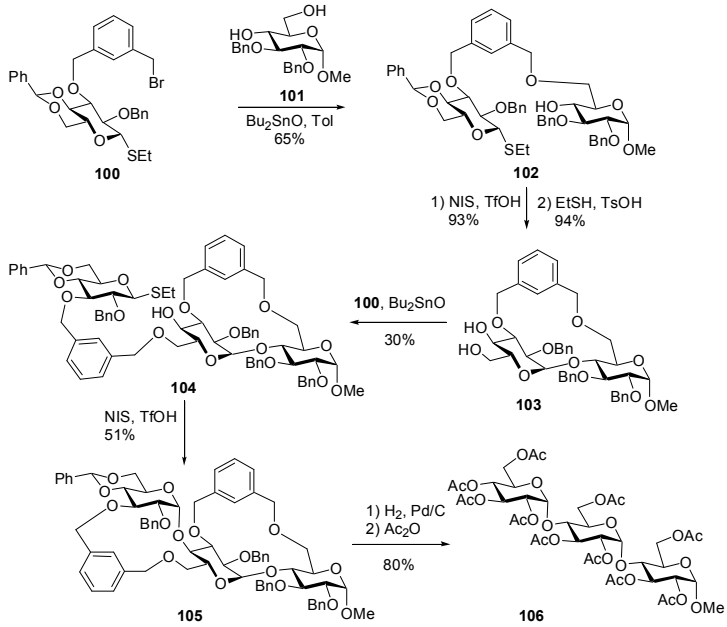
Similarly, the anomeric selectivity during ring closing glycosylation of the tethered glycosides **98** affording disaccharides **99** strongly depends on the rigidity of the tether (Scheme 11).[80,81]



Scheme 11.

The prearranged glycoside based concept fort he synthis of oligosaccharide also allows for a reiterative intramolecular glycosylation strategy as outlined in Scheme 12.[83-85] First, the protected ethyl 1-thio-glucosyl donor **100** containing a m-xylylene tether was condensed with the glucosyl acceptor **101** to give the first prearranged glycoside **102** in 65% yield. Intramolecular glycosylation of **102** and removal of the benzylidene group in the resulting disaccharide affords the tethered α-linked disaccharide acceptor

103 in a virtually quantitative yield. Second, alkylation of **103** with donor **100** was reiterated to afford **104** which gave the tethered trisaccharide **105** upon the second intramolecular glycosylation step. Final deprotection and reacetylation afforded trisaccharide **106**.[84]

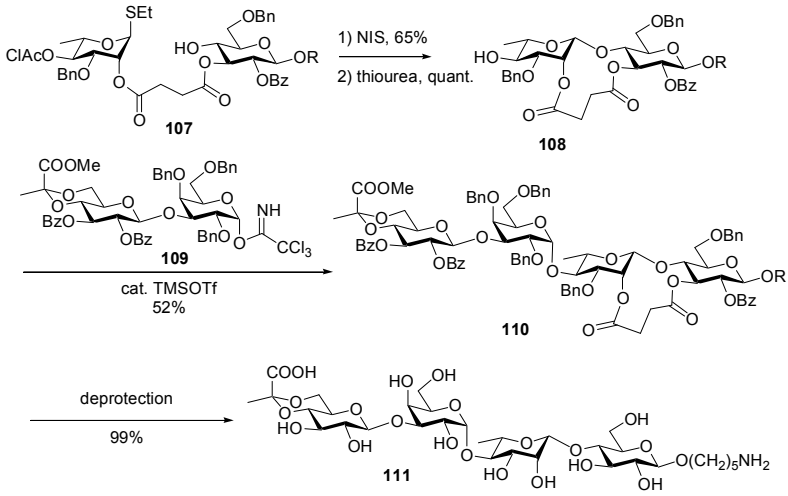


Scheme 12.

In the following, some applications of the prearranged glycoside based concept to the synthesis of bacterial oligosaccharides will be presented. Although only a few examples have been published so far, a vast number of di- and trisaccharides which are useful as building blocks for classical oligosaccharide synthesis have been prepared using this approach.[49]

Scheme 13 summarizes the efficient synthesis of an aminopentyl tetrasaccharide fragment related to the capsular polysaccharide of *Streptococcus pneumonia* type 27, which can be used for the preparation of an artificial vaccine against pneumonia in infants.[86,87] The repeating unit of the capsular polysaccharide contains a β-L-rhamnosyl residue which was established via the prearranged glycoside based concept as follows. First, the succinyl tethered diglycoside **107** was prepared from suitable precursors as outlined in Scheme 10. As the temporary protecting group for position 4 of the rhamnose moiety a chloroacetyl group was chosen. Other temporary protecting

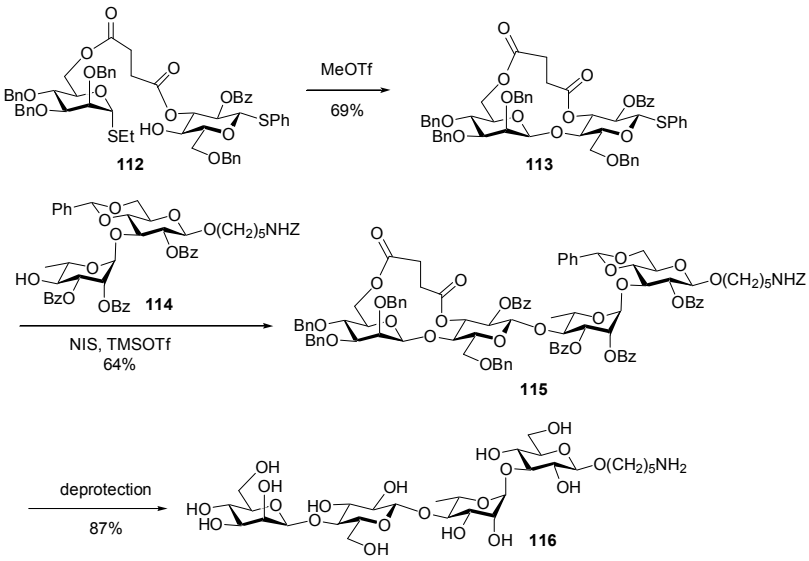
groups resulted in lower yields during the intramolecular glycosylation step.[86] Treatment of **107** with NIS followed by removal of the chloraacetyl group afforded the tethered disaccharide acceptor **108** in 65% yield. Next, the latter was condensed with the pyruvylated disaccharide trichloroacetimidate **109** to give the tetrasaccharide **110** in 52% yield. Final deprotection of **110** yielded the aminopentyl tetrasacchide **111** in a virtually quantitative yield.



Scheme 13.

The prearranged glycoside based concept for the synthesis of complex oligosaccharides can also be combined with classical glycosylation strategies as outlined in Scheme 14 for the synthesis of a tetrasaccharide 5-aminopentyl glycoside related to the exopolysaccharide of *Arthrobacter sp*.[88] Here, the strategy of armed and disarmed glycosyl donors was efficiently combined with an intramolecular glycosylation step for the construction of the β-mannosidic bond in the repeating unit of the *Arthrobacter* exopolysaccharide. Once again, the succinyl tethered diglycoside **112** was first prepared from the corresponding monosaccharides. Thus, **112** displayed an armed ethyl 1-thio-mannosyl donor and a disarmed phenyl 1-thio-glucosyl donor which also functioned as acceptor for the intramolecular glycosylation step. Activation of the mannose donor in the prearranged glycoside **112** with methyl triflate selectively gave the β-linked disaccharide **113** in 69% yield. No reaction of the phenylthio group could be detected. Next, disaccharide donor **113** was activated with NIS and coupled to the disaccharide acceptor **114** to afford the tetrasaccharide **115** in 64% yield. Finally, tetrasaccharide 5-aminopentyl

glycoside **116** related to the exopolysaccharide of *Arthrobacter sp.* was obtained upon deprotection of **115**.

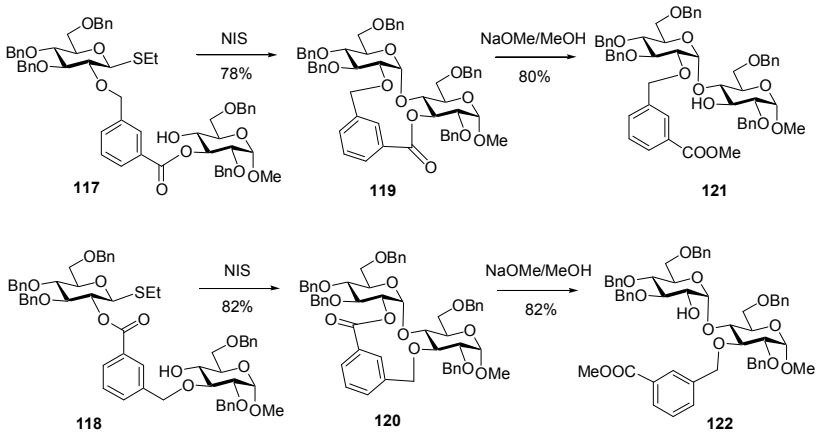


Scheme 14.

Yet another useful extension of the prearranged glycoside based concept for the preparation of complex oligosaccharides are asymmetric tethers which allow for a regioselective ring opening of the linker in the disaccharide building block. For instance, hydroxycarbonylbenzyl linkers as shown in Scheme 15 can either be attached to the glycosyl donor or the glycosyl acceptor part, resulting in a tethered disaccharide after intramolecular glycosylation which can be regioselectively opened to give two different disaccharide acceptors.[89] For example, the isomeric tethered diglycosides **117** and **118**, both prepared from the same monosaccharides and methyl *m*-bromomethylbenzoate, afford the isomerically tethered maltobiosides **119** and **120** upon intramolecular glycosylation with NIS. Saponification of the tethers then afford the disaccharide acceptor **121** and **122** which can be elongated further either at position 3 or 2'.[89] A similar approach via asymmetric tethers had been published by Schmidt at al.[85] Thus, highly flexible synthetic strategies for the preparation of oligosaccharides can be established.

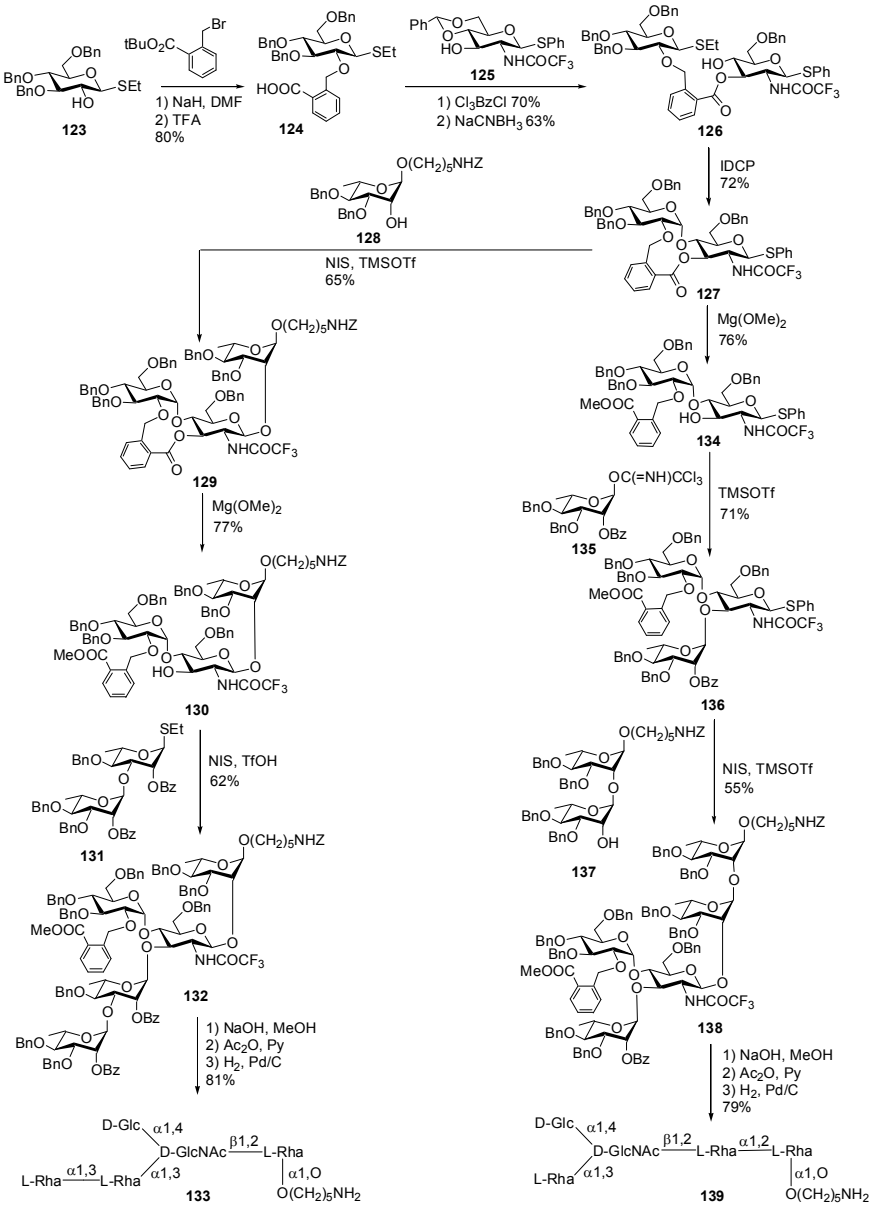
An application of the latter strategy using asymmetric tethers for the preparation of two pentasaccharides related to the repeating unit of the exopolysaccharide of *Shigella sp.* is shown in Scheme 16.[90] Starting from the

glycosyl donor **123**, alkylation with *t*-butyl *o*-bromomethyl benzoate followed by ester hydrolysis gave donor **124** which was condensed with the thio-glycoside **125** to afford the tethered diglycoside **126** after regioselective benzylidene ring opening. Once again, the armed-disarmed strategy could be applied to **126** since the ethylthio group could be selectively activated beside the phenylthio group (*c.f.* Scheme 14).



Scheme 15.

Thus, activation of **126** with iodoniumdicollidineperchlorate (IDCP) resulted in a clean ring closing glycosylation affording the disaccharide phenyl 1-thio-glycoside **127** in 72% yield. Next, the latter was coupled to rhamnoside **128** upon activation with NIS to give the trisaccharide **129**. Saponification of the asymmetric tether in **129** afforded trisaccharide acceptor **130** which was finally glycosylated with disaccharide donor **131** to afford the pentasaccharide **132**. Deprotection of the latter gave the final pentasaccharide **133** in 81% yield. On the other hand, the asymmetric tether in **127** was first saponified to afford the disaccharide acceptor **134**, glycosylation of which with imidate **135** gave the trisaccharide donor **136** in 71% yield. Next, condensation of **136** with the disaccharide acceptor **137** gave the isomeric pentasaccharide **138** which again, was deprotected to afford the free pentasaccharide **139**. Both pentasaccharides **133** and **139** represent isomeric repeating units of the exopolysaccharide of *Shigella sp*., and are efficiently accessible from **127** by the application of a combination of the prearranged glycoside based concept with asymmetric tethers and the strategy of armed and disarmed glycosyl donors.


123
1) NaH, DMF
2) TFA
80%
124
125
1) Cl3BzCl 70%
2) NaCNBH3 63%
126
IDCP
72%
128
NIS, TMSOTf
65%
127
Mg(OMe)2
76%
134
129
Mg(OMe)2
77%
OC(=NH)CCl3
TMSOTf
71%
135
130
136
131
NIS, TfOH
62%
NIS, TMSOTf
55%
137
132
138
1) NaOH, MeOH
2) Ac2O, Py
3) H2, Pd/C
81%
1) NaOH, MeOH
2) Ac2O, Py
3) H2, Pd/C
79%
D-Glc
D-GlcNAc
L-Rha
133
139

Scheme 16.

This example shows nicely once again how the powerful combination of different synthetic strategies opens up new and efficient ways to prepare complex oligosaccharides

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