Intramolecular *O*-Glycoside Bond Formation

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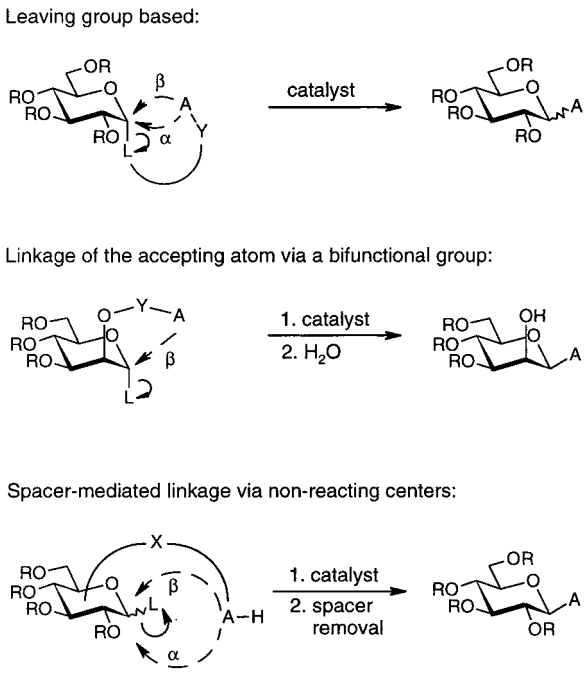
I. Introduction

Glycobiology has gained much attention in the last years because the oligosaccharide part of glycolipids, glycoproteins, and other glycoconjugates is responsible for their function in various biological processes, i.e., cell-growth regulation, cell differentiation, immunological response, metastasis, inflammation, and bacterial and viral infections.[1−12] The large number of possible oligosaccharide isomers is not only caused by the number of sugar monomers, but also by their stereo- (α- or β-configuration) and regioisomeric linkages (connection to the 2-OH, 3-OH, 4-OH, or 6-OH of hexopyranoses). Although a large number of synthetic methods for glycoside bond formation have been developed,[13−17] not all problems are well solved, i.e., the synthesis of some α-glycosides, of β-mannopyranosides, solid-phase and/or combinatorial synthesis.

Although the advantage of intramolecular reactions in stereo- and regioselectivity is well-known, for instance in Diels−Alder and many other reactions, only recently investigations have been reported to improve the stereo- or regioselectivity of glycosylation reactions via this approach. These can be divided into three classes of spacer-mediated linkages of the acceptor to the donor (Scheme 1).[18]

Scheme 1



Leaving group based intramolecular glycosylation: the glycosyl acceptor is attached to the leaving group of the glycosyl donor. Once the leaving group is released, the accepting atom is transferred to the anomeric carbon.

Linkage of the accepting atom via a bifunctional group: the accepting atom is attached via a bifunctional group to the glycosyl donor, generally to 2′-O. Once the leaving group is released, linkage to the accepting atom leads to cleavage of the bifunctional group in the same step or later during work up ("functional substituent based intramolecular glycosylation", "intramolecular or internal aglycon delivery", "temporary silicon connection method", "silicon-tethered intramolecular glycosylation").

Spacer-mediated linkage via nonreacting centers: the glycosyl acceptor is attached with a spacer at any functional substituent at any position to the glycosyl donor and contains generally one unprotected hydroxy group (or more) to be glycosylated ("rigid spacer concept", "intramolecular glycosylation of prearranged glycosides", "template directed cyclo-glycosy-

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Karl-Heinz Jung was born 1949 in Pforzheim (Germany). He studied chemistry at the University of Stuttgart, where he received his Diploma in 1974 and his Ph.D. degree in 1977. Then he joined the University of Konstanz and got a permanent position as a scientist in the group of Professor Dr. R. R. Schmidt. He works in field of the synthesis of riburonic acid derivatives, nucleosides, and nucleoside sugar diphosphates and has been a coauthor in several review articles and book chapters on glycoconjugates, glycosylation methods, and the synthesis of sphingosines.

Matthias Müller was born 1972 in Ellwangen (Germany). He studied chemistry at the Fachhochschule Aalen and University of Konstanz and is currently working on his doctoral thesis under the supervision of Professor Dr. R. R. Schmidt. His research is focused on new intramolecular glycosylation reactions.

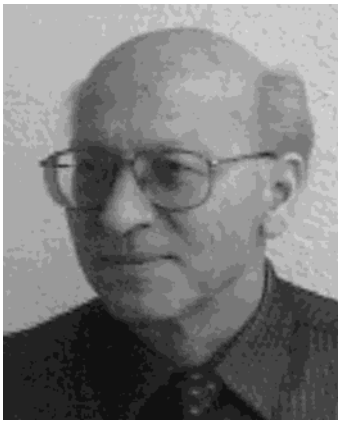
lation", "remote glycosylation"). The spacer remains in the molecule and has to be removed in a second step.

The following abbreviations are used throughout this review: Ac = acetyl, Bn = benzyl, Bz = benzoyl, DMTST = dimethyl(methylthio)sulfonium triflate, DTBP = 2,6-di-*tert*-butylpyridine, IDCP = iodonium collidine perchlorate, IDCT = iodonium collidine triflate, Mbn = 3-methoxybenzyl, MCPBA = *m*-chloroperbenzoic acid, MP = *p*-methoxyphenyl, MeOTf = methyl triflate, NIS = *N*-iodo succinimide, Ph = phenyl, TfO = triflate (trifluoromethanesulfonate), TPS = *tert*-butyldiphenylsilyl, TMS = trimethylsilyl, TMSOTf = trimethylsilyl triflate, Z = benzyloxycarbonyl.

II. Leaving Group Based Intramolecular Glycosylation

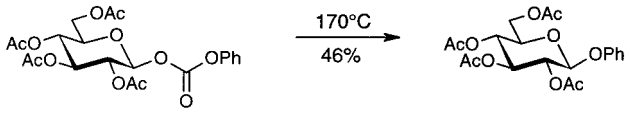
A. Decarboxylative Glycosylation

The first example of decarboxylative glycosylation was reported 1973 for the synthesis of phenyl β-D-



Richard R. Schmidt received his Ph.D. degree at the University of Stuttgart in 1962, where he worked under the guidance of Professor Gommper on push–pull-stabilized quinone methides. From 1965 to 1966 he had a postdoctoral fellowship with Professor Frank M. Huennekens at the Scripps Research Foundation in La Jolla, CA, on coenzyme B_{12} metabolism. He returned to Stuttgart and became Dozent and Associate Professor. Since 1975 he has been a Full Professor at the University of Konstanz; he has stayed there since 1975 and denied calls to other universities. His main research interests are devoted to carbanion chemistry, stereochemistry, cycloaddition reactions, chemistry of heterocycles, and natural products. In recent years his work has been mainly dedicated to carbohydrate and, in particular, glycoconjugate chemistry and their biological relevance.

Scheme 2



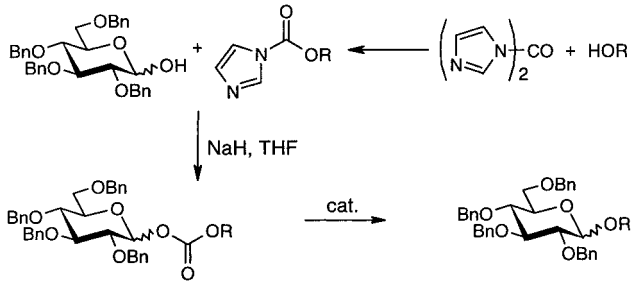
glucopyranoside (Scheme 2).[19] The method was also applied to the *N*-glycoside synthesis of purines and pyrimidines. Although the yields were moderate, the stereoselectivity was high, yielding exclusively β-anomers. Detailed investigations with other phenyl derivatives and optimized reaction conditions resulted in better yields.[20]

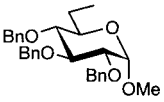
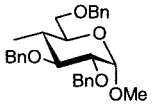
Many years later the decarboxylative glycosylation was applied to the synthesis of oligosaccharides under different reaction conditions, i.e., the use of Lewis acids and lower temperatures.[21,22] Coupling of a benzyl-protected glucose donor and an acceptor with carbonyldiimidazole and glycosylation with TMSOTf (Scheme 3) gave the Glcβ(1−6)Glc (entry 1) and Glcβ(1−4)Glc (entry 3) disaccharides with moderate stereoselectivity. Use of $SnCl_4/AgClO_4$ as promoter gave preferentially α-disaccharides (entries 2 and 4). The *O*-benzyl-protected galactose donor gave similar results. The investigation showed that the stereoselectivity was not affected by the anomeric configuration of the carbonate residue but was dependent on the catalyst/promotor and the solvent systems.

A better stereoselectivity was obtained with a *O*-benzoyl-protected glucose donor (Scheme 4).[23] Coupling with a 4-*O*-unprotected acceptor and treatment of the resulting carbonate with TMSOTf gave exclusively the β-disaccharide. The galactose or phthalimido-protected glucosamine donors and a 3-*O*- or 6-*O*-unprotected acceptor were also used for the synthesis of β-disaccharides with very good stereoselectivities.

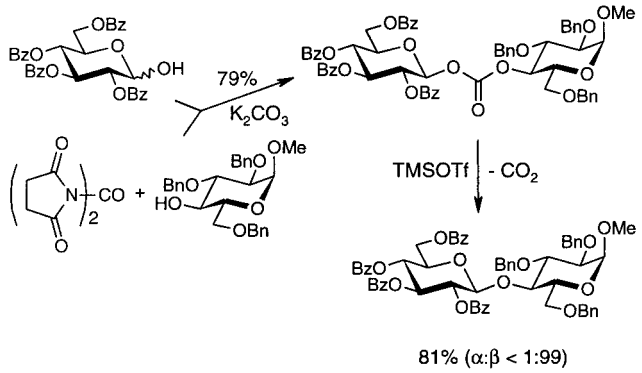
Because the stereoselectivities reported in Schemes 3 and 4 are similar to those obtained in intermolecu-

Scheme 3



entry	R	cat.	yield (α:β)
1		TMSOTf, mesitylene	78% (16:84)
2		$SnCl_4/AgClO_4$, Et_2O	82% (83:17)
3		TMSOTf, mesitylene	72% (37:63)
4		$SnCl_4/AgClO_4$, Et_2 O	62% (86:14)

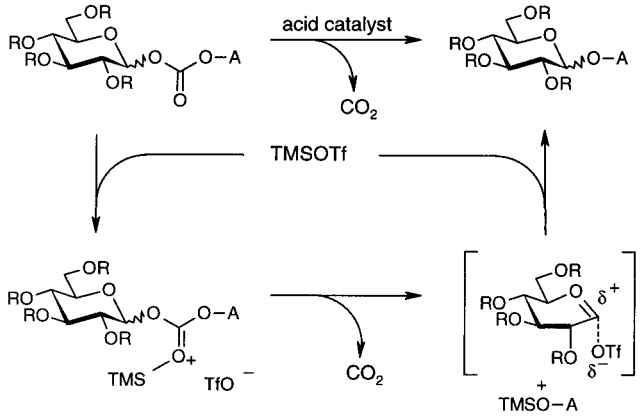
Scheme 4



lar glycosylation reactions, the decarboxylative glycosylation reaction was reinvestigated in order to decide between an intra- versus intermolecular reaction course (Scheme 5).[24] Competition experiments with the *O*-benzyl-protected carbonate **AC** and the *O*-(3-methylbenzyl)-protected *o*-bromobenzyl carbonate **BD** gave not only the products **ac** and **bd**, expected for an intramolecular reaction course, but all four products **ac**, **bc**, **ad**, and **bd**, typical for an intermolecular reaction course, were obtained. The investigations were performed with two Lewis acids, TMSOTf (entry 1) and $BF_3{\cdot}OEt_2$ (entry 2).

The presented investigations show that decarboxylative glycosylations are at least partially or even completely intermolecular processes. A possible reaction course proceeds via activation of the carbonyl oxygen and formation of the glycosyl cation intermediate (Scheme 6). The stereoselectivity of the product

Scheme 6

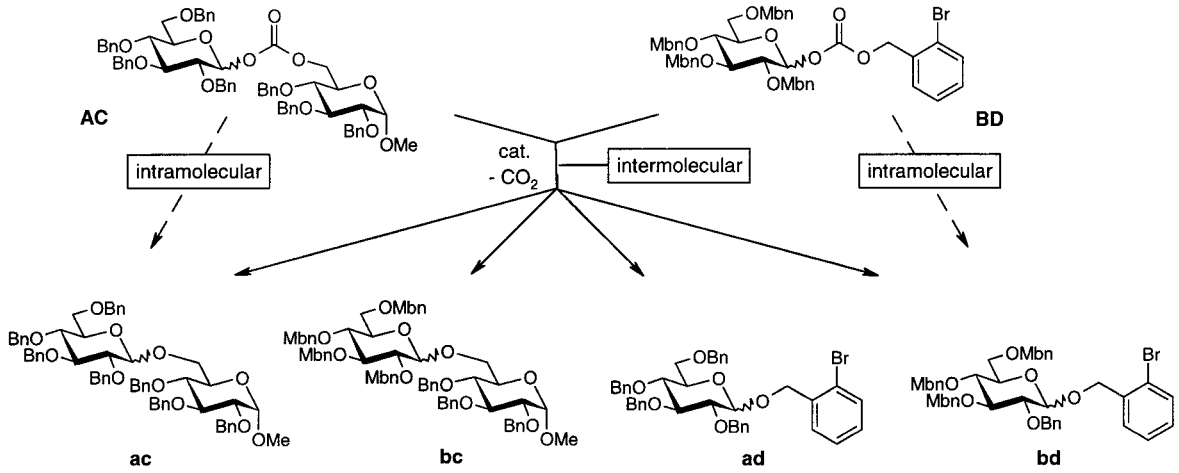


formation is influenced by the catalyst, the solvent (ether effect), and the protecting groups (participating neighboring group at 2-*O*).

B. Special Glycosyl Esters

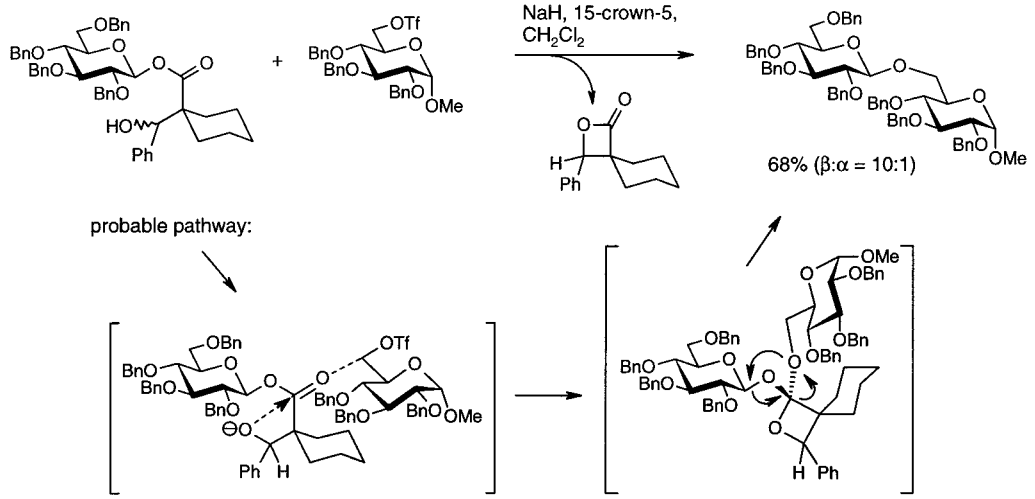
Because of these findings, other systems for intramolecular glycosylation reactions were investi-

Scheme 5



entry	cat.	yield ac		yield bc	yield ad		yield bd
1	TMSOTf, mesitylene	35%	(α:β=1:3.7)	35%	45%	(α:β=1:3.6)	45%
2	$BF_3{\cdot}Et_2O$, toluene	26%	(α:β=1.4:1)	13%	51%	(α:β=1:1)	22%

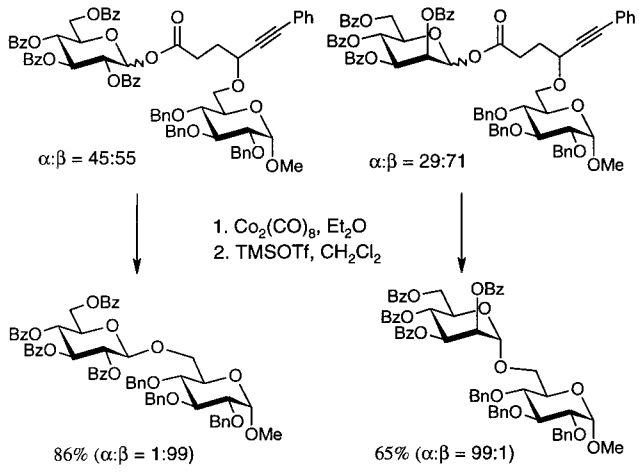
Scheme 7



gated. A new system with "in-situ tethering" of the acceptor was presented with a glycosyl β-hydroxyacetate moiety as donor (Scheme 7),[25] which can be easily prepared from the corresponding trichloracetimidate and cyclohexanecarboxylic acid followed by aldol reaction with benzaldehyde. Reaction with the acceptor, which has to be converted into its triflate derivative, gave, probably via an ortho ester intermediate, the β-disaccharide with high stereoselectivity (β:α = 10:1); thus, a remarkable result for a donor with a nonparticipating neighboring group at 2-*O* was gained. A similar ortho ester intermediate was previously proposed for the stereoselective formation of α-thioglycosides from α-trichloracetimidates.[26] The corresponding α-anomer of the donor presumably follows a different reaction pathway because a lower stereoselectivity was found (α:β = 2:1).

In another example a glucosyl hexynoate was used as donor (Scheme 8).[27] After activation by transfor-

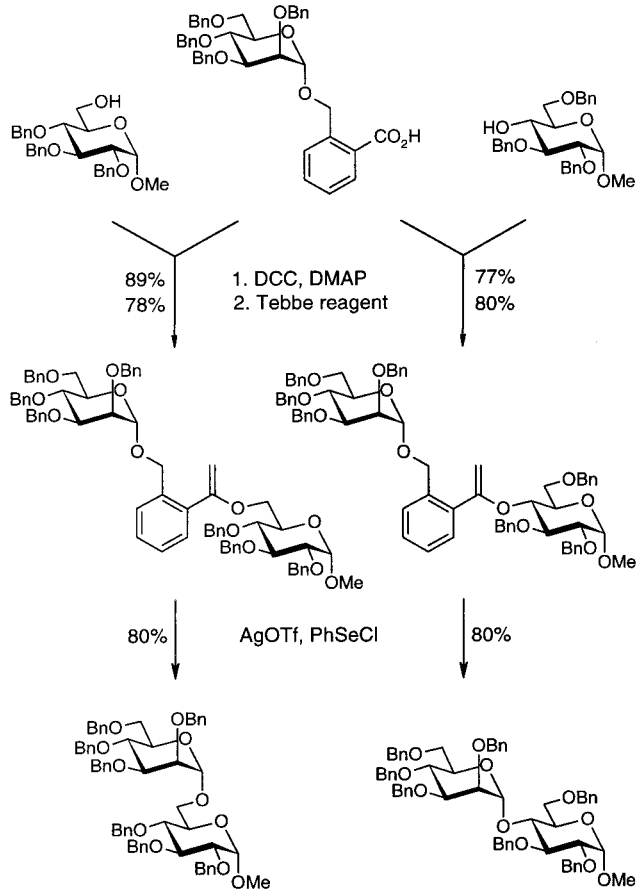
Scheme 8



mation into the dicobalthexacarbonyl complex, the acceptor moiety is released and transferred to the anomeric center to yield the β-glucoside with very high stereoselectivity (α:β = 1:99). Similarly, the corresponding mannosyl donor gave the corresponding α-mannoside. The selectivity is only high for glycosyl donor moieties with participating neighboring groups at 2-OH, whereas benzyl-protected donors gave results similar to those obtained for intermolecular glycosylations; therefore, the reaction course would have to be confirmed.

A pentenyl-type activation has also been introduced in order to study an intramolecular glycosylation approach (Scheme 9).[28] The 6-*O*- and 4-*O*-unprotected

Scheme 9



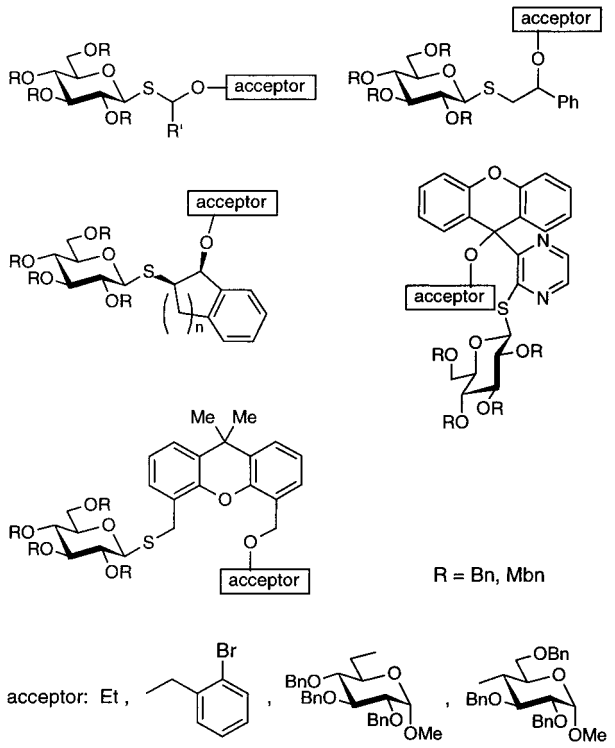
acceptors were used for ester formation with the 2-hydroxymethylbenzoic acid mannoside derivatives. Conversion into the benzo-annelated pentenyl glycosides with Tebbe reagent and glycosylation with AgOTf/PhSeCl yielded exclusively the α-mannosides.

The corresponding benzyl-protected glucosyl donors were also investigated with the same method; yet the resulting stereoselectivities (referring to the β-anomer) were low and practically independent of the configuration of the starting materials. Therefore, crossover experiments were performed, which confirmed an intermolecular reaction course.

C. Thioglycoside Approach

Several examples have been proposed using the thioglycoside activation method and having the acceptor connected to the leaving group (Scheme 10)

Scheme 10



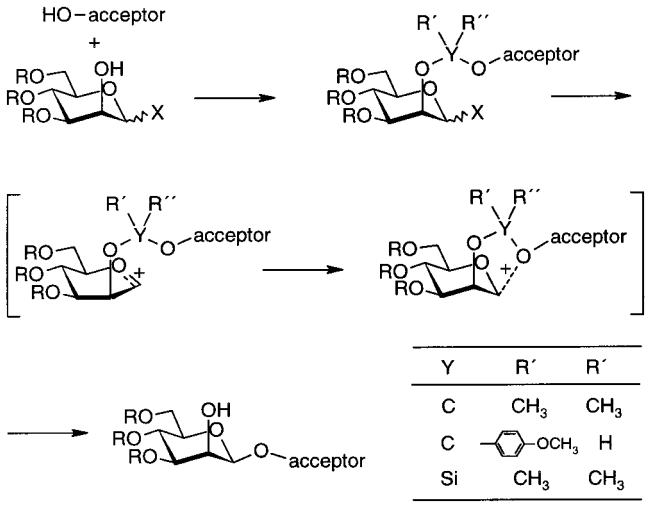
in order to enforce glycoside bond formation via an intramolecular (1,3)-, (1,4)-, (1,5)-, or (1,9)-shift.[29] Yet, glycosylation with the usual thiophilic promotor systems DMTST, MeOTf, or AgOTf gave the corresponding glycosides in good yields but with low stereoselectivity. Therefore, again competition experiments were performed verifying that an intermolecular reaction course is favored instead of an intramolecular (1,3)-, (1,4)-, (1,5)-, or (1,9)-shift.

III. Linkage of the Accepting Atom via a Bifunctional Group

The intramolecular glycosylation approach by "linkage of the accepting atom via a bifunctional group" ("intramolecular aglycon delivery", IAD) was originally developed for the synthesis of β-mannosides and later extended to the synthesis of other glycosides. The synthesis of the β-mannosidic linkage is a difficult task because the anomeric effect favors kinetically as well as thermodynamically the formation of the α-mannosides, and participating neighboring groups at 2-*O* also lead to α-mannosides (1,2-*trans*-configuration).[17,30]

The reaction sequence consists of two steps (Scheme 11). In the first step, the acceptor is attached via its

Scheme 11

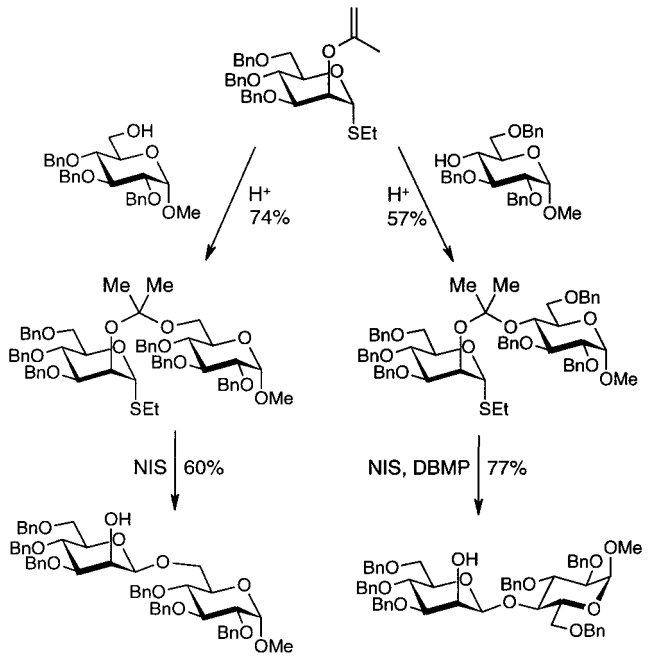


accepting atom to the unprotected hydroxy group of the donor via a bifunctional CR_2 or SiR_2 linker. In the second step, the leaving group is activated and attack of the anomeric center at the acceptor under cleavage of the linker in a stereocontrolled intramolecular process takes place. For high efficiency, both steps should work with high yields and the activation should be mild enough in order to prevent the cleavage of the linker prior to transfer of the acceptor to the anomeric center.

A. Isopropylidene Ketal-Tethered Acceptor

In the first example for this approach, an isopropylidene ketal was chosen as the bifunctional group for the attachment of the acceptor to the glycosyl donor (Scheme 12).[31,32] The 2-*O*-isopropenyl ether derivative of the mannosyl donor, which can be easily

Scheme 12



prepared from the 2-*O*-acetyl derivative with Tebbe reagent, was used for acid-catalyzed addition of the 6-*O*- or 4-*O*-unprotected acceptors to yield the corresponding isopropylidene ketal derivatives. Glycosylation by activation of the thioglycosides with NIS yielded exclusively the β-mannosides with good yields. The use of a phthalimido-protected glucosamine acceptor also gave high stereoselectivity but only moderate yields (step 1 55%, step 2 51%).

Extension of the method to di- and trisaccharide donors and disaccharide acceptors required for the synthesis of the core pentasaccharide unit of *N*-glycoproteins showed the limitations of the methodology.[33] Because ketal formation is unfavorable due to steric reasons, the yields dropped dramatically. The method even failed when sterically hindered disaccharide donors were used. The glycosylation steps worked with high stereoselectivity but with low product yields.

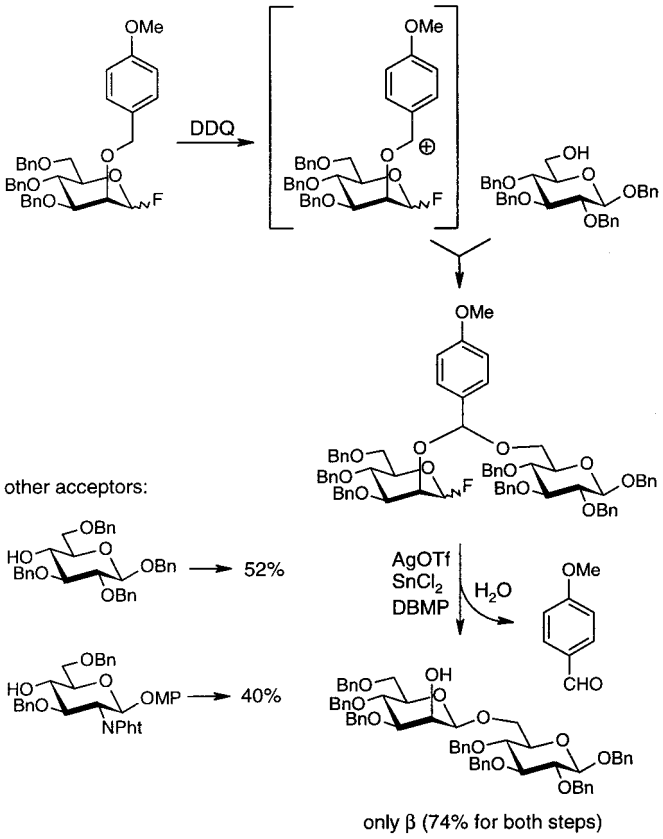
A modification of this method was recently reported in which the acid-catalyzed ketal formation was replaced by iodonium-initiated ketal or acetal formation.[34] From the 2-*O*-isopropenyl or propenyl glucose and mannose thioglycoside donors, several α-glucosides and β-mannosides were stereoselectively obtained in a one-pot reaction by tethering and activation with NIS. Besides some non-carbohydrate moieties, only 6-*O*-unprotected galactose, glucose, and mannose derivatives were used as acceptors. Investigations with carbohydrates containing more hindered secondary hydroxy groups are currently in progress.

B. Methoxybenzylidene Acetal-Tethered Acceptor

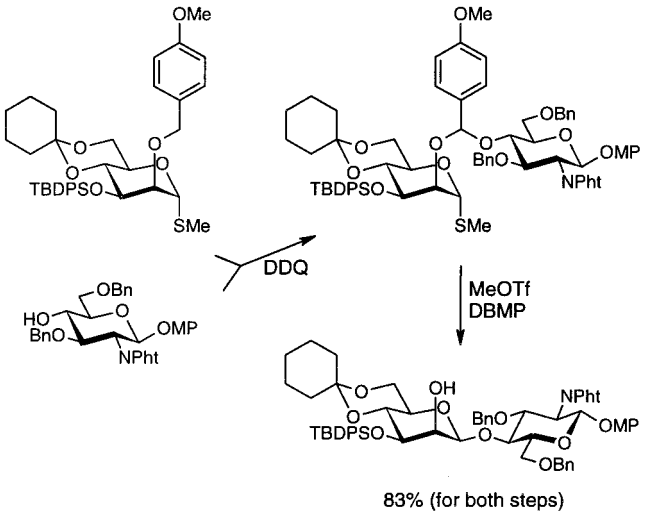
To avoid the unfavorable ketal formation, the methoxybenzylidene acetal was designed as a bifunctional group for the attachment of the acceptor to the glycosyl fluoride donor (Scheme 13).[35] Another advantage is that acetal formation was not achieved by an acid-catalyzed equilibrium reaction but via oxidation of a methoxybenzylidene group and addition of the acceptor to the methoxybenzylcarbenium ion intermediate. As a further advantage, purification of the acetal is not required; it can be used directly for the glycosylation step by activation of the glycosyl fluoride with $AgClO_4/SnCl_2$. The β-mannoside was exclusively obtained with a good overall yield (74% for both steps). The use of the 4-*O*-unprotected glucose or phthalimido-protected glucosamine acceptors gave again very high stereoselectivities but lower yields (52% and 40%), probably because glycosyl fluorides are not sufficiently reactive for the glycosylation of less reactive acceptors.

A real improvement was achieved with the help of thioglycoside donors (Scheme 14).[36,37] Fortunately, the thioglycoside is stable under the conditions (DDQ) of acetal formation with the acceptor. Now the mixed acetal could be subjected to intramolecular glycosylation with MeOTf as promotor to yield the Manβ-(1−4)GlcN disaccharide unit of the core pentasaccharide of *N*-glycoproteins in a remarkable yield of 83% (for both steps). The properly selected protective group pattern contributed much to the good result. From two possible diastereomers of the mixed acetal,

Scheme 13



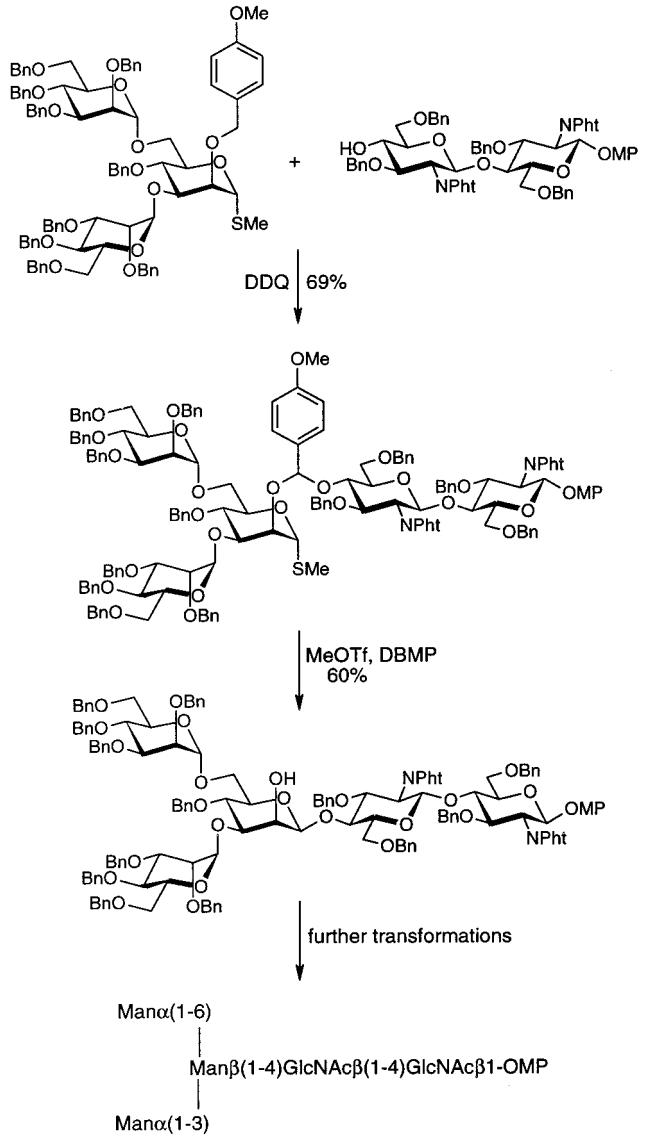
Scheme 14



generally only one isomer is formed (≥95% de). Nevertheless, investigations showed that both diastereomers, which were independently prepared via difficult routes, gave the same results (stereoselectivity and yield) in the intramolecular glycosylation step. In an intermolecular approach, β-mannosides were also prepared from glycosyl sulfoxides; as intermediates, α-glycosyl triflates were proposed.[38]

The high performance of the methoxybenzylidene acetal method enabled its use for the key step in the total synthesis of the core pentasaccharide unit of *N*-glycoproteins (Scheme 15).[39,40] In a highly convergent strategy, the required trisaccharide thioglycoside donor and the acceptor were coupled with DDQ.

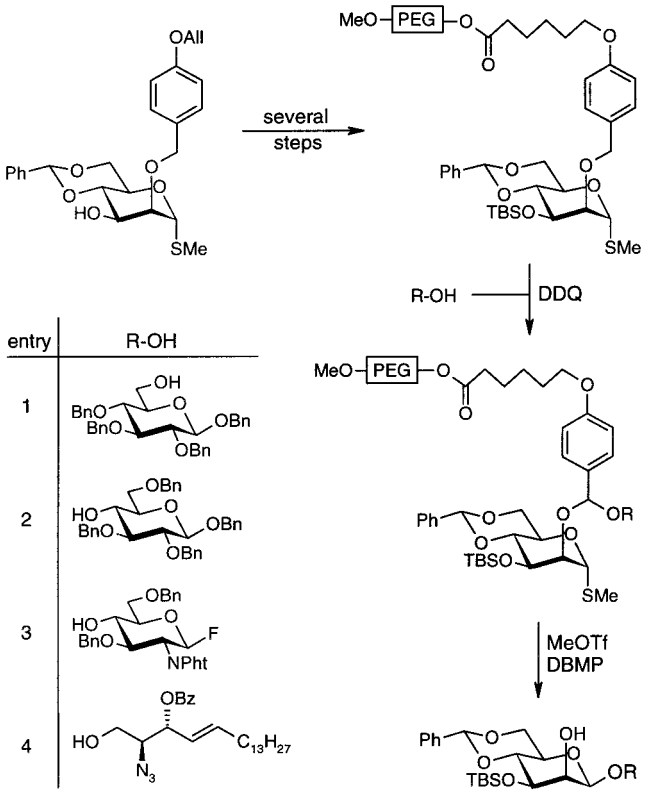
Scheme 15



The resulting mixed acetal was activated with MeOTf for the intramolecular glycosylation to yield exclusively the β-mannoside. After further transformations, the methoxyphenyl glycoside of the desired core pentasaccharide was obtained. A 6a-*O*-fucosylated pentasaccharide derivative[41] and a bisecting GlcNAc-containing hexasaccharide core unit of *N*-glycoproteins[42] were also prepared applying the methoxybenzylidene acetal method for the β-mannosylation step.

It was demonstrated that the methoxybenzylidene acetal method is also suitable in polymer-supported synthesis (Scheme 16).[43] The 2-*O*-allyloxybenzyl-protected thioglycoside donor was attached to the poly(ethylene glycol) support via several steps. The resulting polymer-linked donor was used in the usual way for the preparation of the mixed acetal with the acceptor. Compared with the conventional solution technique, the mixed acetal can be readily purified without column chromatography. In the second step the intramolecular glycosylation is accompanied by the cleavage of the product from the polymer support. Therefore, very pure β-mannoside products were obtained without further purification. Besides the 4-*O*- and 6-*O*-unprotected glucose acceptors (entry 1

Scheme 16



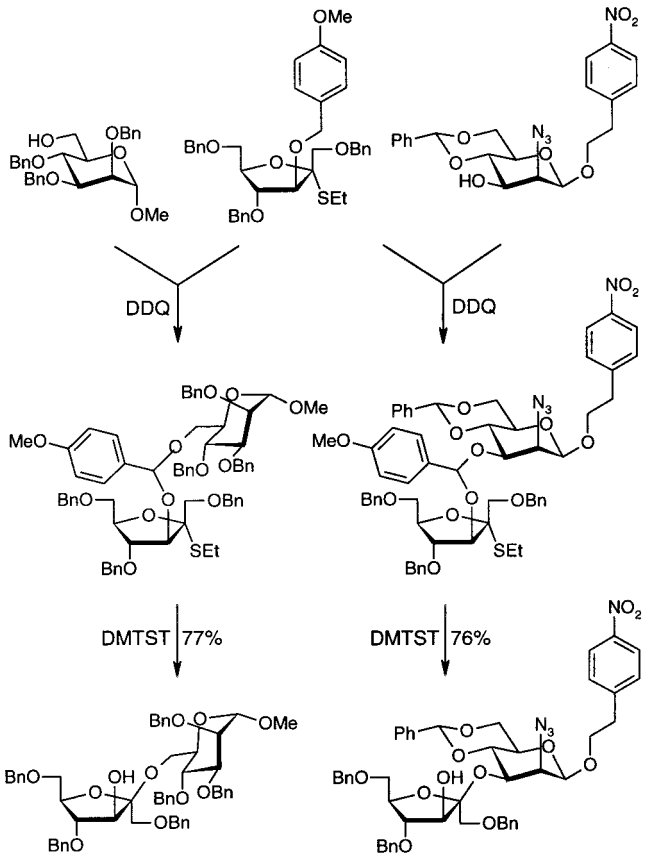
and 2), a phthalimido-protected glucosamine fluoride was also used as acceptor; thus, the resulting disaccharide fluoride (entry 3) can be used as donor for further glycosylations. Also, an azidosphingosine derivative (entry 4) was used as the acceptor. Though the yields (43−54%) are still lower than those obtained using the conventional solution technique, further studies concerning leaving group, promoter, solvent, protective group pattern, solid support, and linker should be performed in order to utilize the advantage of solid-phase or polymer-supported reaction techniques for intramolecular glycosylation reactions.

The performance of the methoxybenzylidene acetal method was also shown in the synthesis of β-D-fructofuranosides (Scheme 17);[44,45] this linkage is as difficult to synthesize as the β-mannoside linkage because of its 1,2-*cis*-configuration. The fructose thioglycoside donor and the mannose or azidomannose acceptors were coupled with DDQ. The resulting mixed acetals were activated with DMTST (or MeOTf, IDCP, IDCT) to yield stereoselectively the β-D-fructofuranosides (77% and 76% yield over two steps). The α-anomer was not found. Use of the α- or β-thioglycoside as donor showed no difference in the stereoselectivity of the reaction.

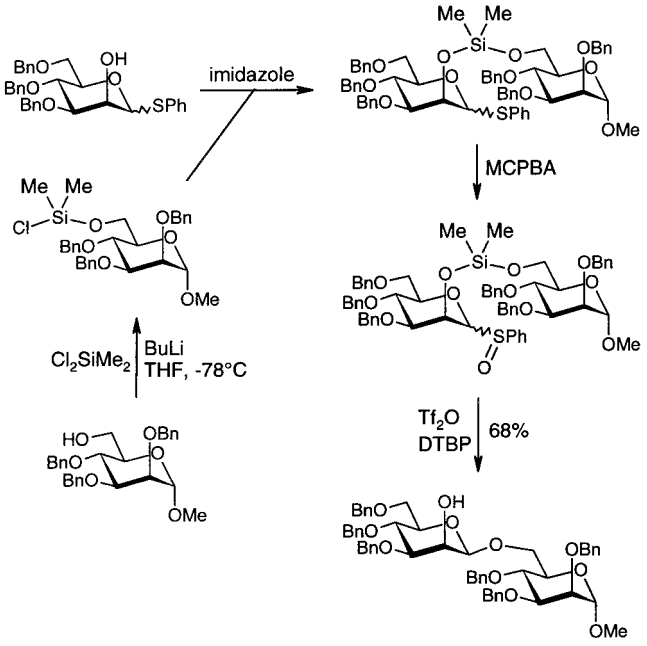
C. Silicon-Tethered Acceptor

In another approach to the synthesis of β-mannosides applying the "linkage of the accepting atom via a bifunctional group", a silicon-tethered acceptor was suggested (Scheme 18).[46] Reaction of the acceptor with dichlorodimethylsilane gave the chlorodimethylsilyl ether, which was coupled with the 6-*O*-unprotected thiomannoside acceptor. The resulting

Scheme 17



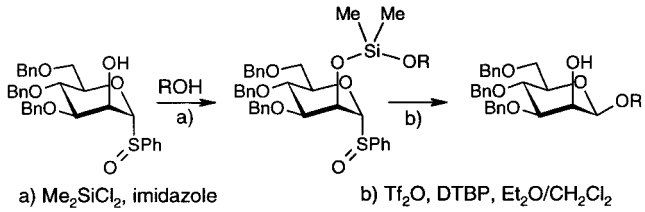
Scheme 18



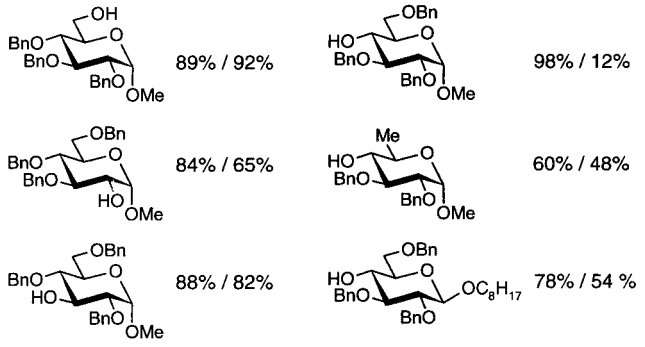
silicon-tethered "disaccharide" was used for intramolecular glycosylations applying sulfoxide activation. Oxidation with MCPBA and activation of the resulting sulfoxide with triflic anhydride gave exclusively the β-mannoside in good yield (68%). The use of the α- and β-thiomannoside gave the same results concerning stereoselectivity and yield.

Further improvement of the method concerning the preparation of the silicon-tethered "disaccharide" also enabled the use of secondary hydroxy groups in the acceptors (Scheme 19).[47] One-pot reaction of dichlo-

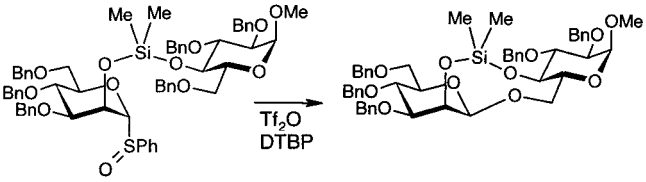
Scheme 19



ROH (acceptors):



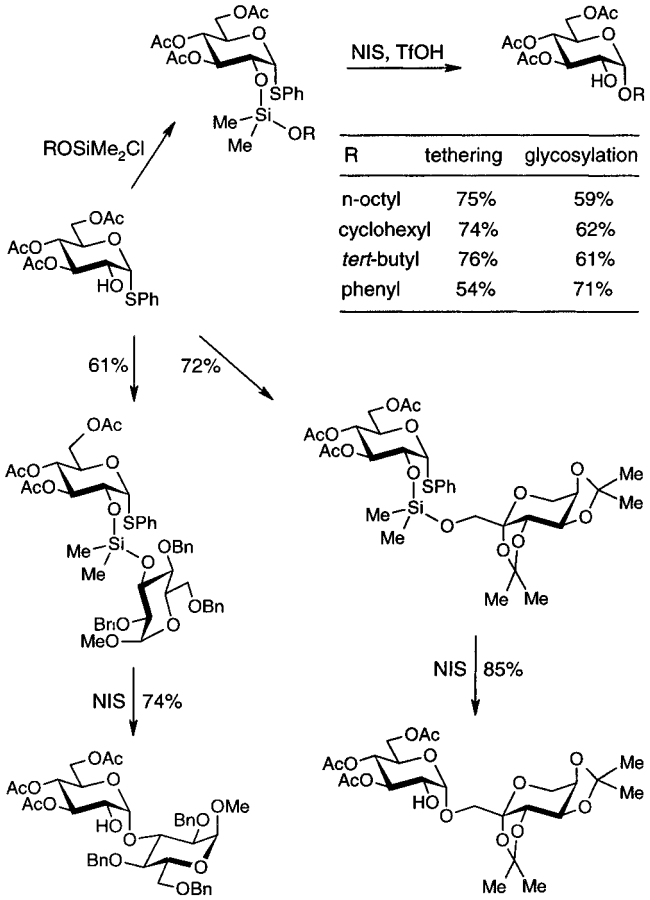
yields for tethering/glycosylation step



rodimethylsilane with the acceptor and the 2-*O*-unprotected mannose sulfoxide donor gave the desired silicon-tethered "disaccharide" directly, thus reducing the number of steps and avoiding isolation of the sensitive chlorodimethylsilyl ether intermediate. The reaction probably works because of the low reactivity of the 2-OH group of the mannosyl sulfoxide compared with the unprotected hydroxy group of the acceptor. Further processing, as described above, gave the β-mannoside disaccharides. The use of 6-*O*-, 2-*O*-, and 3-*O*-unprotected glucose acceptors gave very good yields (65−92%); 4-*O*-unprotected acceptors led only to moderate yields (12−54%). In the case of the 4-*O*-unprotected methyl-α-glucoside, only 12% of the expected disaccharide was obtained; instead, in the main reaction a glycosylation of the "spacer-mediated linkage via nonreacting centers" type was obtained. Glycosylation of the oxygen in the 6-position under loss of the benzyl group took place leading to a Manβ(1−6)Glc disaccharide (82%). A similar entropically favored process has been observed previously (see below, Scheme 42).[48]

The silicon-tethered acceptor approach was also extended to the synthesis of α-glucosides (Scheme 20),[49,50] which also belong to the difficult class of 1,2-*cis*-configurated glycosides. The 3,4,6-*O*-acetyl-protected 2-*O*-unprotected thioglycoside donor was coupled via silicon tethering with *n*-octanol, cyclohexanol, *tert*-butyl alcohol, and phenol. Intramolecu-

Scheme 20



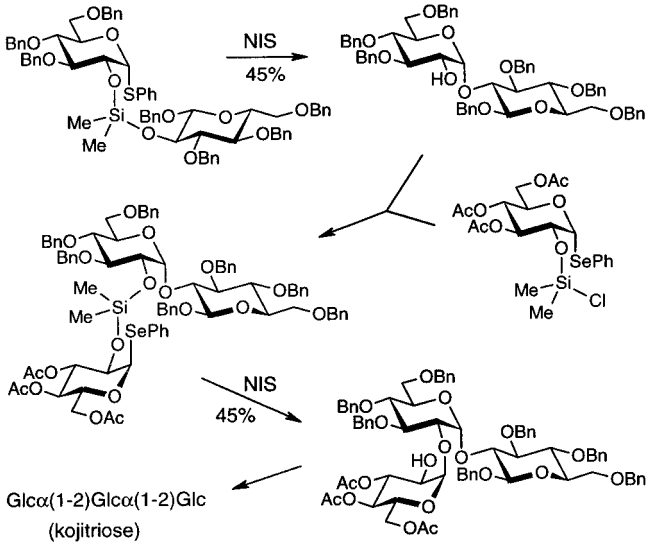
R	tethering	glycosylation
n-octyl	75%	59%
cyclohexyl	74%	62%
tert-butyl	76%	61%
phenyl	54%	71%

lar glycosylation was performed using the thioglycoside activation method with NIS/triflic acid as promotor. Thus, the α-glucosides were exclusively obtained in good yields (59−71%). Preparation of the silicon-tethered derivatives of the 3-*O*-unprotected glucose and 1-*O*-unprotected fructose derivatives and glycosylation in the same manner yielded the corresponding α-glucosides in very good yields (74% and 85%). Investigations with thiogalactosides as donors gave, again, good stereoselectivities but only poor yields, because of the appearance of competing side reactions.[51]

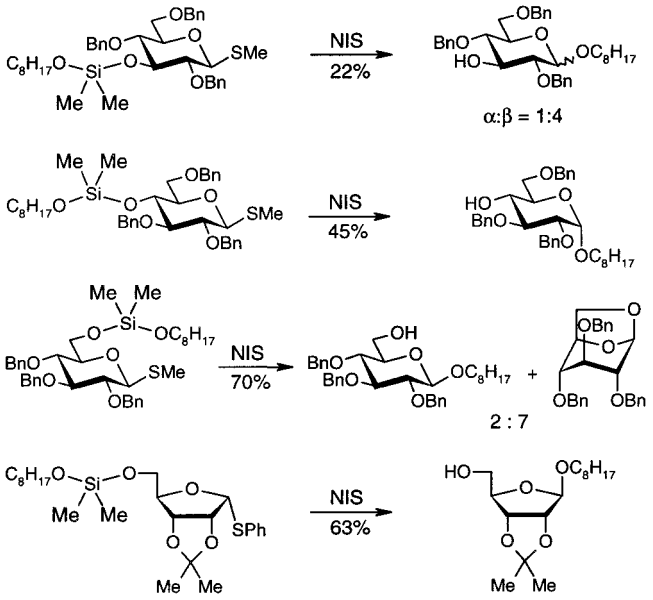
The performance of the silicon-tether method was shown in the synthesis of kojitriose (Scheme 21).[52] Intramolecular glycosylation of a silicon-tethered "diglucoside" with NIS gave the 2-*O*-unprotected Glcα(1−2)Glc derivative. This was subsequently subjected to the same sequence with a selenoglycoside as donor to yield via the silicon-tethered "trisaccharide" the protected trisaccharide and after deprotection the Glcα(1−2)Glcα(1−2)Glc trisaccharide (kojitriose). An approach to the synthesis of fructose failed.

The influence of the ring size of the transition state on the stereoselectivity was investigated by tethering the acceptor (*n*-octanol) to something other than the 2-OH group of the thioglycoside donor (Scheme 22).[53] Performing the intramolecular glycosylation step by activation of the thioglycoside with NIS, the 3-*O*-tethered derivative gave the *β*-glucoside with moderate stereoselectivity (α:*β* = 1:4) and low yield (22%), whereas the 4-*O*-tethered derivative gave exclusively the α-glucoside (45%). The 6-*O*-tethered derivative

Scheme 21



Scheme 22



gave, besides the expected *β*-glucoside, mainly the 1,6-anhydroglucose derivative, which is formed by transfer of the "wrong" oxygen from the silicon atom to the anomeric center. The use of the 5-*O*-tethered thioriboside as donor gave exclusively the *β*-riboside in 63% yield.

To confirm the intramolecularity in this approach, at least for reactions resulting in low stereoselectivities and/or low yields, competition experiments would be required (see section II and ref 24). To date, such experiments have not been reported.

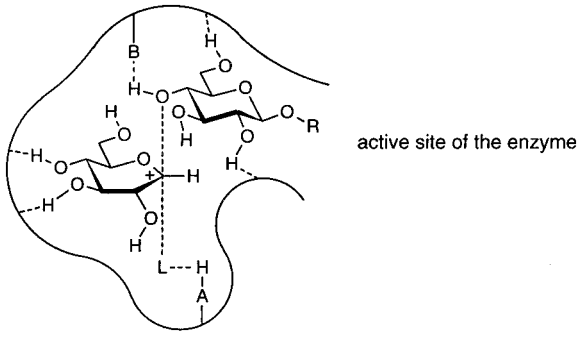
The use of silicon-tethered reactions in intramolecular glycosylations and other chemical reactions was reviewed some time ago.[54]

IV. Spacer-Mediated Linkage via Nonreacting Centers

Glycosyl transfer within the active site of an enzyme can be regarded as an intramolecular process in which the glycosyl donor and acceptor are held in

close proximity ensuring regio- and diastereoselective glycoside bond formation (Scheme 23).[18,24,55] To mimic

Scheme 23

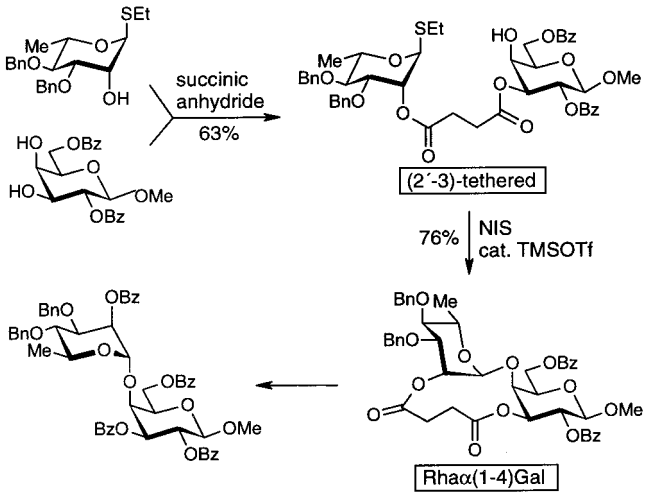


a similar process in vitro, the attachment of the acceptor to the donor by means of a spacer which is connected to nonreacting centers has been proposed. Particularly rigid spacers enforcing the proximity of the reacting centers should result in efficient glycosylation reactions.[18]

A. Succinyl and Malonyl Spacer

A succinyl spacer was investigated for the attachment of the donor and the acceptor in order to bring them in a "prearranged" position and enforce a highly stereoselective glycosylation (Scheme 24).[56] Obviously

Scheme 24

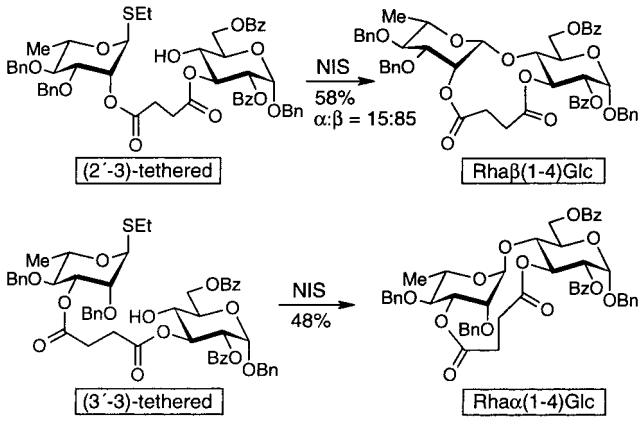


this approach provides a lot of conformational flexibility for the spacer-connected donor−acceptor pair, and the reaction centers are far from being "prearranged" for the exclusive formation of one product. Surprisingly, flexible succinyl and malonyl spacers led to some good results in terms of yield and/or stereocontrol.

Reaction of the 2-*O*-unprotected thiorhamnoside with succinic anhydride and then regioselective condensation with a 3-*O*- and 4-*O*-unprotected galactose acceptor gave the (2′−3)-succinyl-tethered glycoside precursor. Intramolecular glycosylation by activation of the thioglycoside with NIS yielded exclusively the α-rhamnoside in good yield (74%). As in most other examples (see below) with excess NIS as promoter, a catalytic amount of TMSOTf was added. The spacer has to be removed in a further step to obtain the L-Rhaα(1−4)Gal disaccharide derivative. The good stereoselectivity is presumably due to neighboring group participation of the 2′-*O*-succinyl group; a corresponding intermolecular approach gave the α-glycoside in 81% yield.

The described approach was investigated for the synthesis of the L-Rha*β*(1−4)Glc disaccharide (Scheme 25),[57] which is of interest because it occurs in many

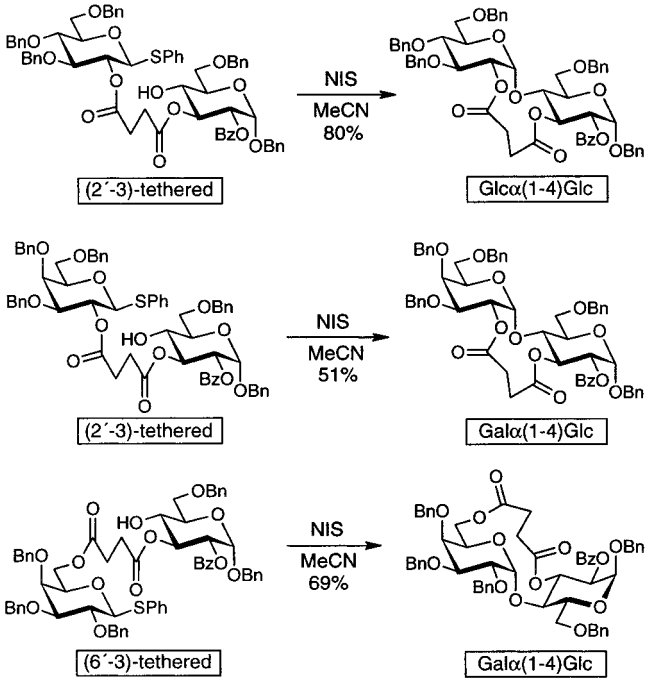
Scheme 25



bacterial capsular polysaccharides. The 4-*O*-unprotected "prearranged glycosides" were generally prepared by reaction of the donor with succinic anhydride, condensation with the 3-*O*-unprotected 4,6-*O*-benzylidene glucose derivative, and reductive benzylidene opening with $NaCNBH_3$/HCl. Intramolecular glycosylation of the (2′−3)-succinyl-tethered glycoside precursor with NIS/TMSOTf gave mainly the desired L-Rha*β*(1−4)Glc isomer (α:*β* = 15:85). A variation of the tether using phthaloyl or malonyl decreased the stereoselectivity (α:*β* ≈ 1:1). Application of the silicon-tethered approach failed totally (6%, α). The change of the tethering position using a (3′−3)-succinyl-tethered precursor gave exclusively the L-Rhaα(1−4)Glc disaccharide in 48% yield. The method was applied to the total synthesis of tetrasaccharide fragment related to the capsular polysaccharide of *streptococcus pneumoniae* type 27 in which the key step is the L-Rha*β*(1−4)Glc linkage.[58] The *β*-glucoside was obtained in 65% yield with good stereoselectivity (α:*β* = 16:84) despite the potential neighboring group participation of the 2′-*O*-succinyl group.

The suitability of the method for the synthesis of 1,2-*cis*-configurated glycosides was demonstrated for the synthesis of α-glucosides and α-galactosides (Scheme 26).[59,60] A (2′−3)-succinyl-tethered prearranged glycoside containing a 4-*O*-unprotected glucose moiety was prepared as described above and activated with NIS/TMSOTf to give exclusively the Glcα(1−4)Glc disaccharide (80%). The use of a phthalimido-protected glucosamine as acceptor gave practically the same result (75%, only α). In the synthesis of α-galactosides, the (2′−3)-succinyl-tethered precursor gave again a good stereoselectivity (only α) but only a modest yield (51%). However, intramolecular glycosylation of the (6′−3)-succinyl-tethered precursor gave exclusively the Galα(1−4)-Glc disaccharide in good yield (69%). These results

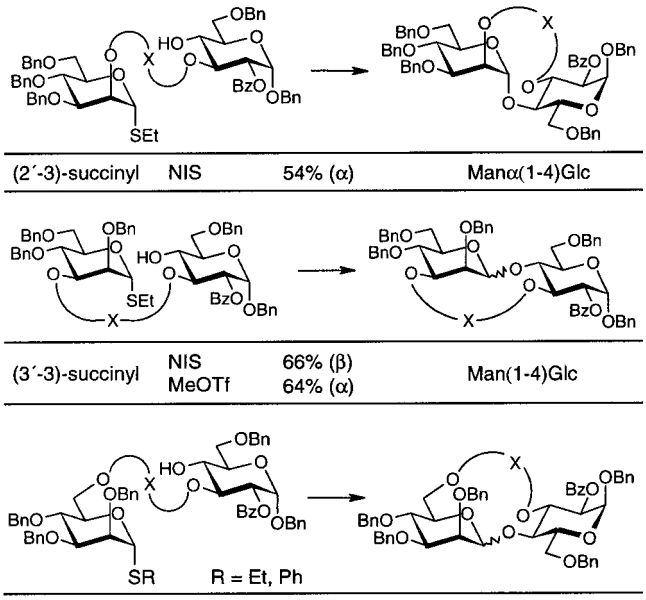
Scheme 26



showed again that in contrast to the intermolecular glycosylation reactions, participating neighboring groups and solvent effects play a minor role in stereocontrol; the major influence on stereoselectivity is exerted by the configurations of the donor and acceptor, by the attachment position and length of the spacer, and in some cases by the catalyst/promotor systems.

Finally, the performance of the method was investigated for the synthesis of α- and *β*-mannosides especially of Man*β*(1−4)Glc derivatives; as already discussed above, this is a very important test case in carbohydrate chemistry. Variation of the tethering position at the donor and the acceptor moiety, of the length of the tethering group, and of the activation method gave a large number of interesting results[61−63] which are summarized in Scheme 27. The (2′−3)-succinyl-tethered ethyl thioglycoside precursor containing 4-*O*-unprotected glucose as acceptor was prepared as described above and activated with NIS to give exclusively the Manα(1−4)Glc disaccharide (54%). Intramolecular glycosylation of the corresponding (3′−3)-succinyl-tethered precursor gave a surprising result. Use of NIS as promotor gave exclusively the Man*β*(1−4)Glc disaccharide (66%), whereas use of MeOTf gave highly stereoselectively the α-anomer (64%, only α). The strong dependence on the promotor system in this example could not really be explained. An approach with a (6′−3)-succinyl-tethered precursor gave nearly no stereoselectivity. However, much improvement was achieved by shortening the tethering group. Glycosylation of a (6′−3)-malonyl-tethered precursor with MeOTf gave the Man*β*(1−4)Glc disaccharide with good stereoselectivity (α:*β* = 8:92) and yield (79%). Even better selectivity was obtained for the corresponding phthalimido-protected glucosamine acceptor; the Man*β*(1−4)GlcNPht disaccharide, whose synthesis is usually the key step in the total synthesis of the core

Scheme 27



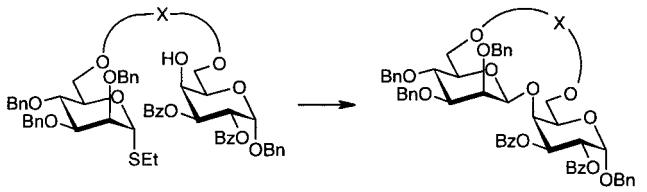
pentasaccharide of *N*-glycans, was isolated in an acceptable yield. The results of these (6′−3)-tethered examples are nearly independent of the promotor (NIS or MeOTf) used. Further shortening of the tethering group using the (6′−3)-oxalyl- and (6′−3)-carbonyl-tethered precursor gave no glycoside formation on activation with NIS or MeOTf. Applying the sulfoxide activation by oxidation of the phenyl thioglycosides with MCPBA and activation of the resulting sulfoxides with Tf_2O yielded exclusively the Manα-(1−4)Glc disaccharides.

The above results were applied to a (6′−3)-malonyl-tethered glycoside precursor for the *β*-mannosylation step in the total synthesis of the Man*β*(1−4)Glc*β*(1−4)Rhaα(1−3)Glc tetrasaccharide of *Arthrobacter sp.* CE−17.[64]

For the synthesis of Man*β*(1−4)Gal disaccharides, (6′−6)-tethered glycoside precursors were used also (Scheme 28).[62] The (6′−6)-succinyl and (6′−6)-malonyl-tethered derivatives gave exclusively the Man*β*-(1−4)Gal anomers independent of the employed promotor system (NIS or MeOTf).

The examples discussed above consider the best and most important applications of the described method. In contrast to the classical intermolecular glycosylation methods, the stereochemical results are less dependent on promotor system, solvent, or potential neighboring group participation but strongly

Scheme 28



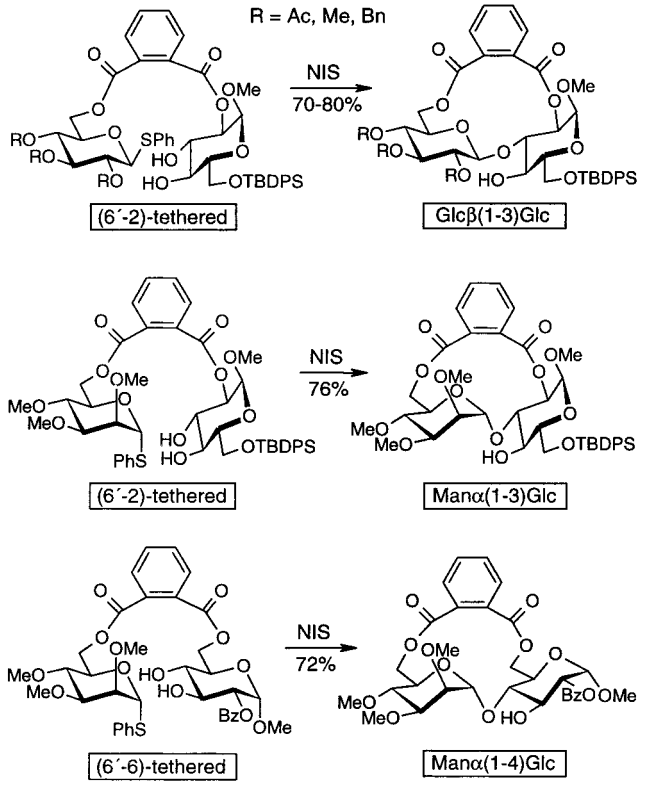
(6′-6)-succinyl	MeOTf	53% (β)	Manβ(1-4)Gal
(6′-6)-malonyl	NIS MeOTf	50% (β) 55% (β)	Manβ(1-4)Gal

dependent on tethering position of the spacer, the length of the spacer, and the configurations of the donor and the acceptor moiety within the "prearranged glycosides". Because the intramolecular glycosylation of the "prearranged glycosides" can be regarded as double-asymmetric induction, the influence of D- and L-glucose in the acceptor moiety was also investigated.[65] However, the prediction of the stereoselectivity still remains difficult and requires additional investigations.

B. Phthaloyl and Isophthaloyl Spacer

The "spacer-mediated linkage via nonreacting centers" concept was also employed for investigation of the regioselectivity of intramolecular glycosylation reactions using a phthaloyl spacer (Scheme 29).[66,67]

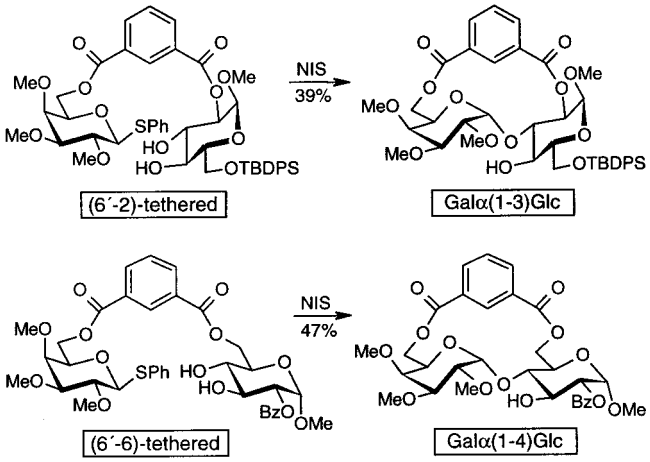
Scheme 29



The (6′−2)-phthaloyl-tethered glycoside precursor was prepared by reaction of the 6-*O*-unprotected donor with phthalic anhydride, conversion into the acid chloride, and then regioselective condensation with the acceptor using dibutyltin oxide. Intramolecular glycosylation by activation with NIS/TfOH regioselectively and stereoelectively yielded the Glcβ-(1−3)Glc disaccharide. The stereoselectivity was high with participating neighboring groups at the donor (R = Ac, only β) as well as with nonparticipating neighboring groups (R = Me, Bn, α:β < 15:85), but it was found that the regioselectivity was only high at low temperatures (−78 °C). Very good regio- and stereoselectivities were found for the mannosylation reactions. Intramolecular glycosylation of the (6′−2)-phthaloyl-tethered precursor gave exclusively the Manα(1−3)Glc disaccharide, whereas the (6′−6)-phthaloyl-tethered derivative gave the Manα(1−4) disaccharide.

Investigation of the same system with galactose as donor gave very low stereoselectivities. An improvement was very recently achieved by variation of the spacer to isophthaloyl (Scheme 30),[68] thus employing

Scheme 30

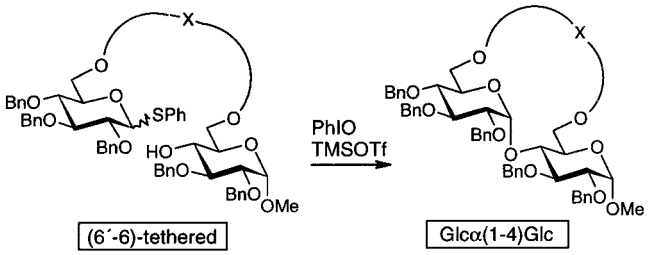


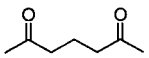
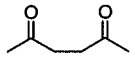
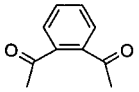
the "rigid spacer concept".[18] Intramolecular glycosylation of the (6′−2)-isophthaloyl-tethered glycosyl precursor with NIS/TfOH regio- and stereoselectively gave the Galα(1−3)Glc disaccharide, whereas processing the (6′−6)-isophthaloyl-tethered derivative in the same manner gave exclusively the Galα(1−4)-Glc disaccharide.

The influence of different mainly flexible spacers on the stereoselectivity of the intramolecular glycosylation was investigated (Scheme 31).[69] The (6′−6)-phthaloyl-tethered glycoside precursor (entry 3) gave the Glcα(1−4)Glc disaccharide with better stereoselectivity (α:β = 99:1) than the corresponding glutaryl- (entry 1) and succinyl-tethered derivatives (entry 2). A reversal of the stereoselectivity was observed for the corresponding silicon-tethered derivative (entry 4), which gave Glcβ(1−4)Glc disaccharide with high stereoselectivity (α:β = 3:97).

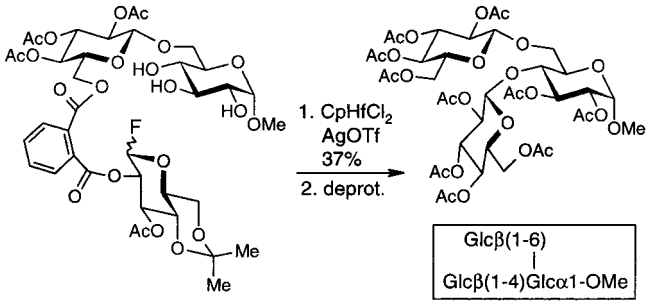
The phthaloyl spacer method was also applied to the synthesis of a branched trisaccharide leading to remote intramolecular glycosylation (Scheme 32).[70] A glycosyl fluoride donor phthaloyl tethered to the 6′-*O* position of a 2-*O*-, 3-O-, and 4-*O*-unprotected disaccharide was activated with $Cp_2HfCl_2/AgClO_4$ to give with low yield (37%) but high regio- and stereoselectivity exclusively the β(1−4)-linked trisaccharide. A related intermolecular experiment gave a mixture of the β(1−2)- and β(1−3)-isomers (21% and 11%) but not the β(1−4)-isomer.

Scheme 31



entry	linker (X)	yield	α/β
1		37%	89:11
2		67%	93:7
3		86%	99:1
4		77%	3:97

Scheme 32

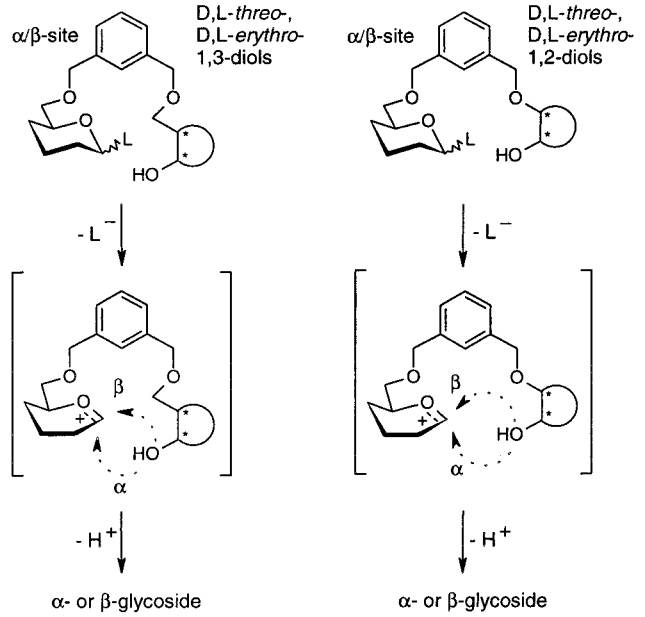


C. Rigid Spacer Concept

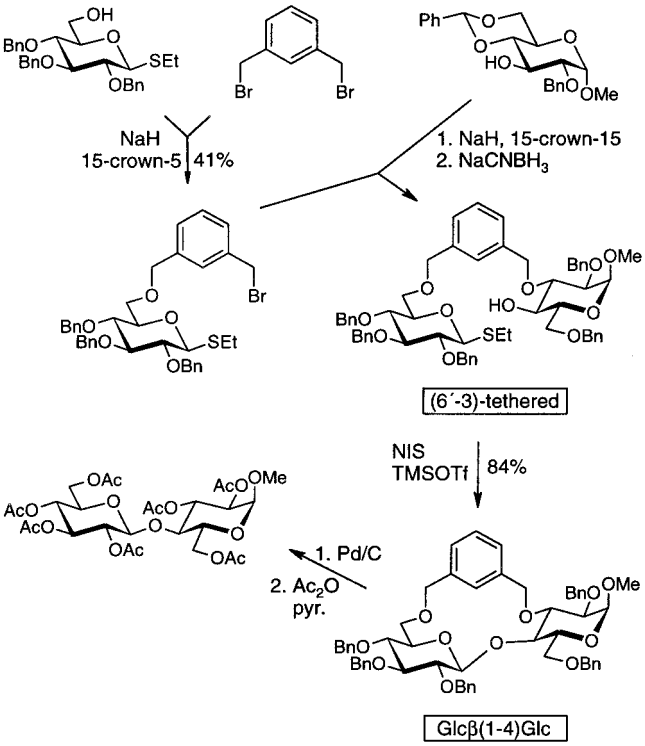
To obtain closer proximity between the glycosyl donor and acceptor, the rigid spacer concept was designed. As this leads to a structurally rigid array, a highly diastereoselective glycosylation formally under construction of a large ring should be enforced. As a powerful example for a rigid spacer, the *m*-xylylene moiety was chosen (Scheme 33).[18,55] Its ether linkage precludes any potential neighboring group participation. Thus, the stereoselectivity of the intramolecular glycosylation reaction should be controlled only by the relative orientation of the donor and the acceptor moiety by the tethering spacer. A major influence is exerted by the attachment site of the spacer at the donor (α- or *β*-site), by the configuration of the acceptor (D,L-*threo* or D,L-*erythro*) within the macrocyclic ring, and by the ring size.

The xylylene-tethered donor/acceptor moiety can be very easily prepared by nucleophilic substitution reactions with α,α′-dibromo-*m*-xylene (Scheme 34).[55] After attachment of the thioglycoside donor and the acceptor one after the other, the unprotected 4-OH group was obtained by regioselective 4,6-*O*-benzylidene opening with $NaCNBH_3$. Intramolecular glycosylation by activation with NIS/TMSOTf gave the Glc*β*(1−4)Glc disaccharide with very high stereoselectivity (only *β*) and yield (84%). The xylyene

Scheme 33



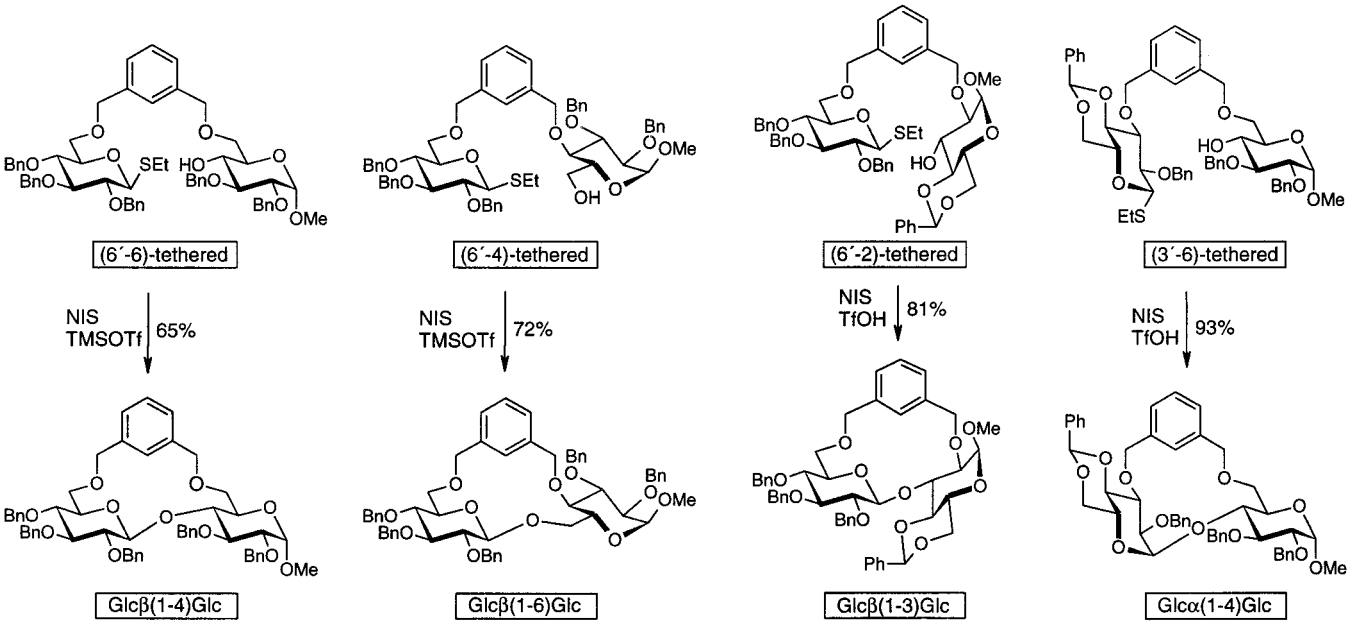
Scheme 34



spacer and the benzyl protecting groups can be removed in one step by catalytic hydrogenation.

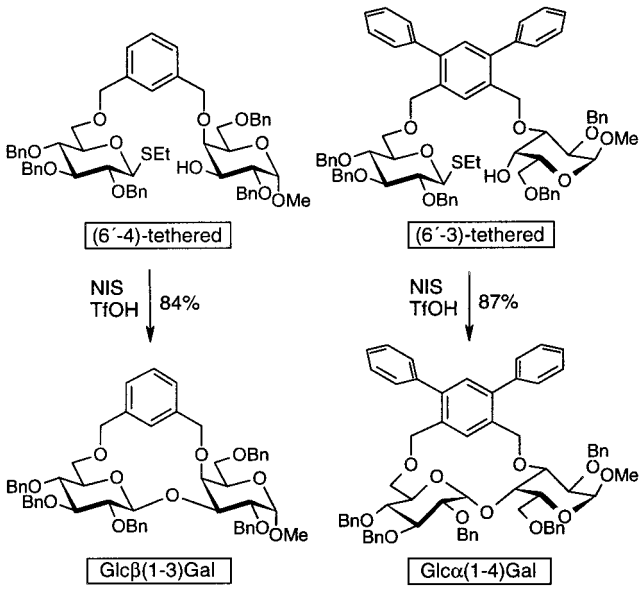
The high performance of the *m*-xylylene method was demonstrated for several other disaccharide linkages (Scheme 35).[18] The Glc*β*(1−4)Glc disaccharide was also prepared by intramolecular glycosylation from (6′−6)-tethered glycoside precursor, whereas the (6′−4)- and (6′−2)-tethered precursors were used for the preparation of the Glc*β*(1−6)Glc and the Glc*β*-(1−3)Glc disaccharides. All glycosides were formed with very high stereoselectivity (only *β*). The Glcα-(1−4)Glc disaccharide could be prepared from the (3′−6)-tethered precursor, again with very high stereoselectivity (only α) and yield (93%).

Scheme 35



The xylylene method was also applied to the use of galactose acceptors (Scheme 36).[18] Intramolecular

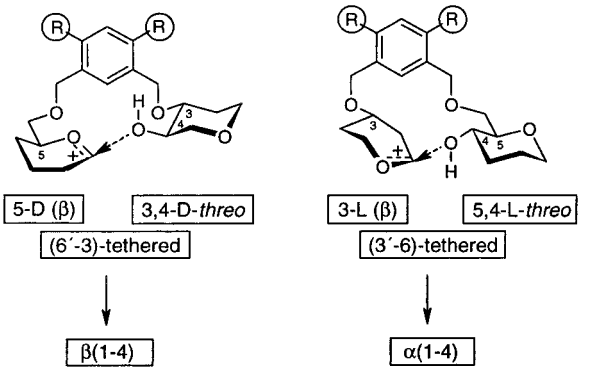
Scheme 36



glycosylation of the (6′−4)-tethered precursor with NIS/TfOH gave the Glcβ(1−3)Gal disaccharide. For the synthesis of the Glcα(1−4)Gal disaccharide, a diphenyl-substituted xylylene spacer for the (6′−3)-tethered precursor was used because the unsubstituted xylylene linker gave lower stereoselectivity (α:β = 3:1). Again, both examples worked with very high stereoselectivity (only β/only α) and yields (84%/87%).

The results show that the stereoselectivity of the glycosylation is controlled by the ring size (14- or 15-membered), by the configuration of the donor and of the two chiral centers of the acceptor (L-*threo*, L-*erythro*, D-*threo*, D-*erythro*) within the macrocyclic ring, and by the available conformational space (Scheme 37). Formal inversion of the relative stereochemistry within the donor and the acceptor moiety

Scheme 37



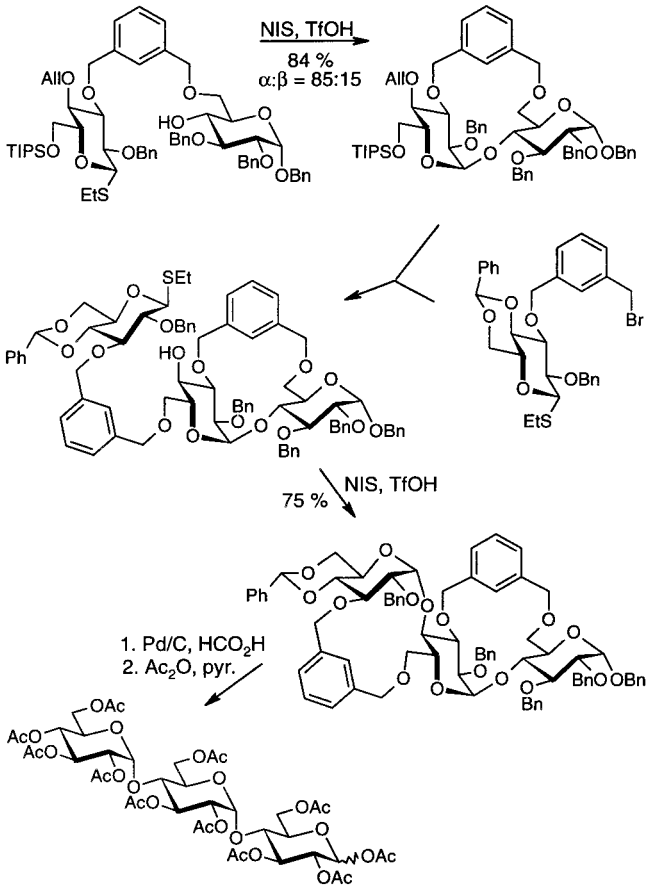
entry	tethering	donor config.	acceptor config.	ring size	linkage
1	6′-6	5-D (β)	5,4- L-*threo*	15	Glcβ(1-4)Glc
2	6′-4	5- D (β)	4,5- L-*threo*	15	Glcβ(1-6)Glc
3	6′-2	5- D (β)	2,3- L-*threo*	14	Glcβ(1-3)Glc
4	6′-4	5- D (β)	4,3- L-*erythro*	14	Glcβ(1-3)Gal
5	6′-3	5- D (β)	3,4- D-*threo*	14	Glcβ(1-4)Glc
6	6′-3	5- D (β)	3,4- D-*erythro*	14	Glcα(1-4)Gal
7	3′-6	3- L (β)	5,4- L-*threo*	14	Glcα(1-4)Glc

yields either α- or β-glycosides. Inversion of the relative stereochemistry of acceptor attachment can be obtained by changing the attachment site in an *erythro*-diol system or by choosing an enantiomeric *threo*-configurated arrangement. For stereochemically different donor attachment, formally two alternatives exist: either inversion of the configuration of the attachment site is performed, thus going from β-face to α-face attachment and vice versa, or the face of the attachment is retained. However, the attachment site is on the opposite half of the pyranose plane. For example, intramolecular glycosylation of the (6′−3)-tethered precursor possessing a 5-D-(β)-configuration at the donor and 3,4-D-*threo*-configu-

ration at the acceptor yields exclusively the $\beta(1-4)$ disaccharide (entry 5), whereas the (3′−6)-tethered precursor with 3−l (β)-configuration at the donor and 5,4-L-*threo*-configuration at the acceptor leads to the $\alpha(1-4)$ disaccharide (entry 7).

The performance of the rigid spacer concept was demonstrated in the synthesis of a trisaccharide derivative (Scheme 38).[71] A suitably protected (3′−6)-tethered precursor was employed for intramolecular glycosylation by activation with NIS/TfOH. The resulting α-disaccharide (84%, $\alpha:\beta = 85:15$) was used for the attachment of the next donor moiety, again via a (3′−6)-tether. After deprotection of the required hydroxy group in the acceptor moiety, the second intramolecular glycosylation step was performed by activation with NIS/TfOH to yield the trisaccharide derivative with good yield (75%) and stereoselectivity (only α). Deprotection and acetylation gave the acetylated Glcα(1−4)Glcα(1−4)Glc (maltotriose) derivative.

Scheme 38

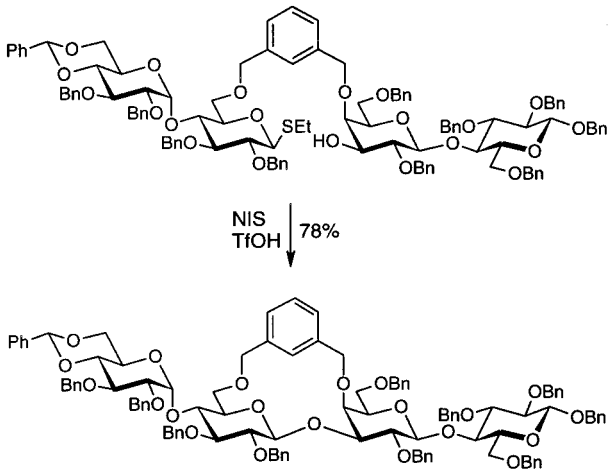


The rigid spacer concept was also investigated for the use of disaccharide donors and acceptors (Scheme 39).[71] Intramolecular glycosylation of a precursor containing a maltose donor and a lactose acceptor moiety by activation with NIS/TfOH gave the Glcα-(1−4)Glcβ(1−3)Galβ(1−4)Glc tetrasaccharide with good yield (78%) and stereoselectivity (only β).

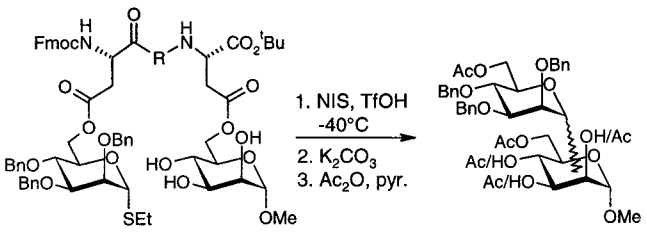
D. Peptide Spacer

A completely different spacer-based approach for intramolecular glycosylation was described by means of a peptide spacer (Scheme 40).[72] A thiomannoside donor and a 2′-*O*-, 3′-*O*-, and 4′-*O*-unprotected mannose acceptor were attached to the terminal asparagine moieties of some tri- and tetrapeptides in order to investigate the regio- and stereoselectivity of the intramolecular glycosylation activated by NIS/TfOH. In comparison to an intermolecular control experiment (entry 1), the Gly (entry 2) and Phe (entry 3) containing tripeptides and the tetrapeptide (entry 5) showed no $\beta(1-2)$-glycoside formation; with the Pro containing spacer (entry 4), no $\alpha(1-3)$-glycoside but instead $\alpha(1-2)$-glycoside was obtained.

Scheme 39



Scheme 40



entry	R	α(1-3)	β(1-3)	β(1-2)	α(1-2)
1	—	11	23	13	—
2	Gly	21	20	—	—
3	Phe	13	18	—	—
4	Pro	—	19	16	14
5	GlyGly	—	56	—	—

% yields

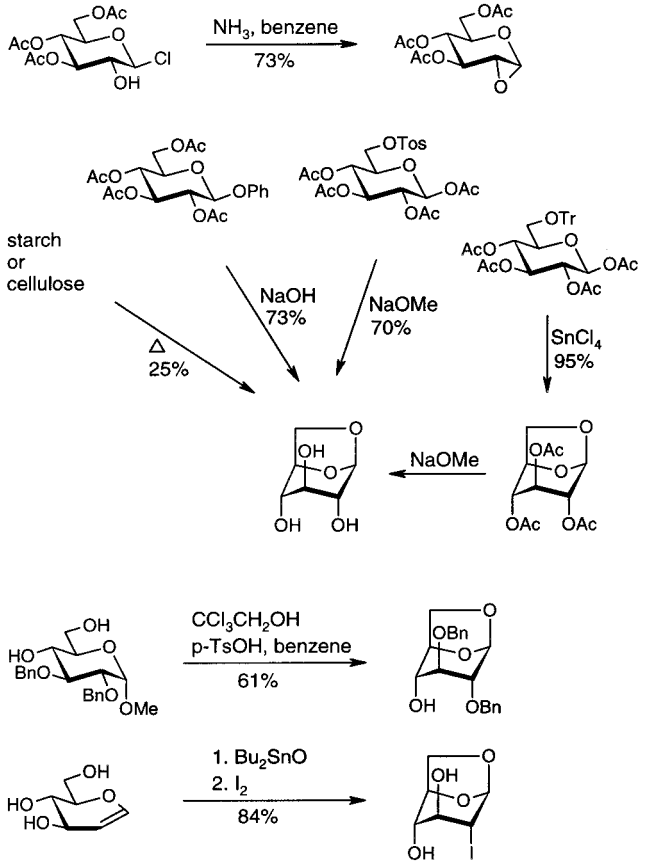
The aim of this peptide approach might be to perform highly stereoselective glycosylations on the solid phase after attaching the donor and acceptor by means of glycosylated amino acids in a suitable distance. Much further research work is still required in this approach.

V. Synthesis of Cyclic Glycosides

In this section, syntheses of glycosides are described which do not use intramolecular glycosylation as a means for achieving high stereoselectivity. Instead, the spacer remains in the product because it is part of the target molecule.

1,2-Anhydroglucose (Brigl's anhydride) and 1,6-anhydroglucose can be regarded as such glycosides. Their syntheses have been known for a long time (Scheme 41). 1,2-Anhydroglucose was prepared from

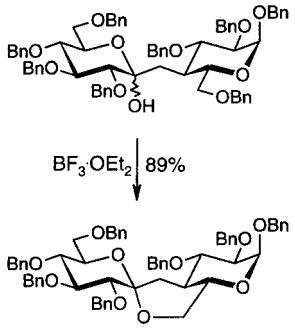
Scheme 41



2-*O*-unprotected glycosyl chloride by intramolecular nucleophilic substitution.[73] 1,6-Anhydroglucose can be prepared by pyrolysis of starch or cellulose[74] or by alkaline treatment of phenyl *β*-D-glucopyranoside,[75] of 6-*O*-tosyl glucose,[76] or of many other glucose derivatives. The reaction of 6-*O*-tosyl glucose is not really an intramolecular glycosylation because the glycosidic bond is not formed; instead, the 1-*O*/6-*C* bond is formed by intramolecular nucleophilic substitution (intramolecular anomeric *O*-alkylation).[15] In the best preparative method, the 6-*O*-trityl glucose derivative was treated with Lewis acids in order to obtain 1,6-anhydroglucose in very high yields ($SnCl_2$, 95%; $TiCl_4$, 92%).[77] In two recently reported methods, very mild conditions were applied. A methyl α-D-glucopyranoside derivative was treated with trichloroethanol and *p*-toluenesulfonic acid to yield the partially protected 1,6-anhydroglucose derivative which is well suited for further transformations.[78] Reaction of glucal first with dibutyltin oxide and then with iodine gave the 2-iodo-1,6-anhydroglucose derivative in very good yield (84%), which is an intermediate in the synthesis of 2-azido derivatives.[79]

An example with a disaccharide derivative involved in an intramolecular glycosylation reaction was also reported. A *C*-disaccharide containing a ketose moiety was treated with Lewis acid leading to an intramolecular glycosylation in nearly quantitative

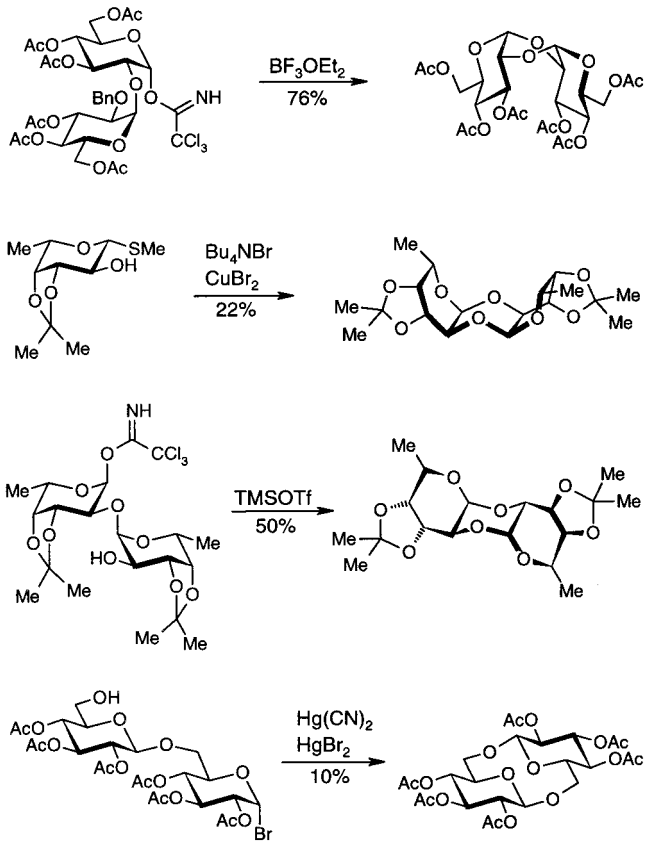
Scheme 42



yield (Scheme 42).[48] A leaving group at the anomeric center is not required because of the ease of carbonium ion formation (oxygen-stabilized tertiary carbon). Because of entropic reasons, the oxygen of the 6-*O*-benzyl group is sufficiently nucleophilic and the benzyl group is released during the glycosylation reaction. From two possible diastereomeric spiroketals, one isomer is exclusively formed.

In the synthesis of cyclodextrins and other cyclooligosaccharides, the intramolecular glycosylation is usually the key step. Several syntheses of cyclodisaccharides were reported (Scheme 43). A Glcα(1−2)-

Scheme 43

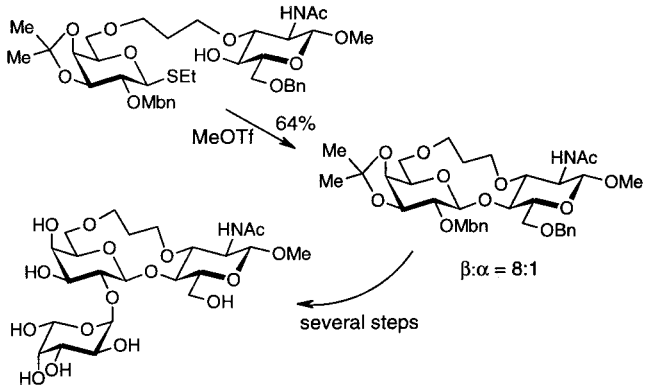


Glc (kojibiose) trichloroacetimidate derivative was treated with $BF_3{\cdot}OEt_2$ to yield cyclo-α(1−2)glucobioside (cyclokojibiose) in high yield (76%).[80] As already observed (see above, Scheme 42), the neighboring 2′-*O*-benzyl oxygen is a good nucleophile and the glycoside bond is formed under release of the benzyl group. X-ray studies showed that the glucopyranoside rings have a slightly distorted $^4C_1$ conforma-

tion and the central 1,4-dioxane ring has a boat conformation with the anomeric carbon in the bow positions. A similar cyclodisaccharide was prepared from a 2-*O*-unprotected L-fucose thioglycoside by activation with $Bu_4NBr/CuBr_2$.[81] Also, the cyclo-α-(1−2)-L-fucobioside could be obtained in modest yield (22%) together with some oligosaccharides. This molecule is very strained because all three rings have unfavorable twist−boat conformations. A 2′-*O*-unprotected D-Fucα(1−2)-L-Fuc trichloroacetimidate was used for intramolecular glycosylation with TMSOTf to yield a cyclodisaccharide which has an inversion center and is achiral because it consists of D-fucose and L-fucose. X-ray analysis showed that the central 1,4-dioxane ring has a chair conformation but that the two sugar rings have boat conformations.[81] Glycosylation of a 6′-*O*-unprotected Glcβ(1−6)Glc (gentobiose) derivative gave the cyclogentiobioside in only low yield (10%) together with the expected oligomers.[82] Energy calculations showed that the sugar rings should have twisted conformations due the ring strain in the central 10-membered ring.

Another type of disaccharide containing a longer bridge was prepared starting from a (6′−3)-tethered glycoside precursor (Scheme 44).[83] Intramolecular

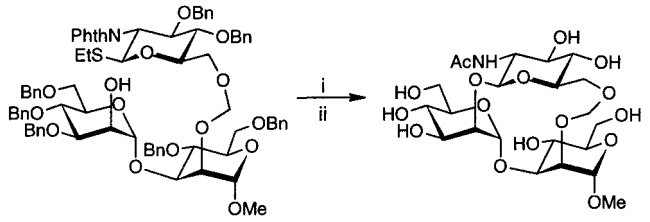
Scheme 44



glycosylation with MeOTf as promotor gave a Galβ-(1−4)GlcNAc derivative (64%, β:α =8:1), which was further processed for the synthesis of a H-type 2 blood-group trisaccharide derivative possessing a constrained, bioactive conformation.

The synthesis of a cyclic trisaccharide was described starting from a thioglycoside which was methylene-tethered to a disaccharide (Scheme 45).[84]

Scheme 45

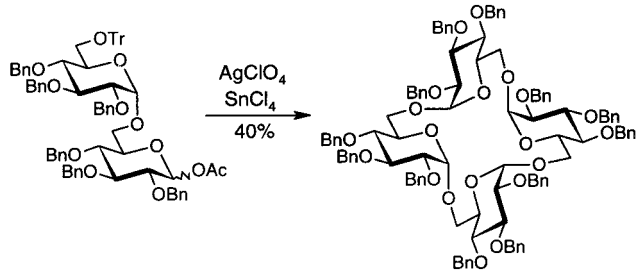


i) NIS/TMSOTf, 34%; ii) deprotection

Intramolecular glycosylation with NIS/TMSOTf yielded stereoselectively the β-glycoside (34%), thus providing a conformationally constrained GlcNAcβ-(1−2)Manα(1−3)Man trisaccharide which was designed for probing carbohydrate−protein interactions.

As an example for cyclotetrasaccharides, the synthesis of cycloisomaltotetraoside was described (Scheme 46).[85] As a precursor, a Glcα(1−6)Glc de-

Scheme 46



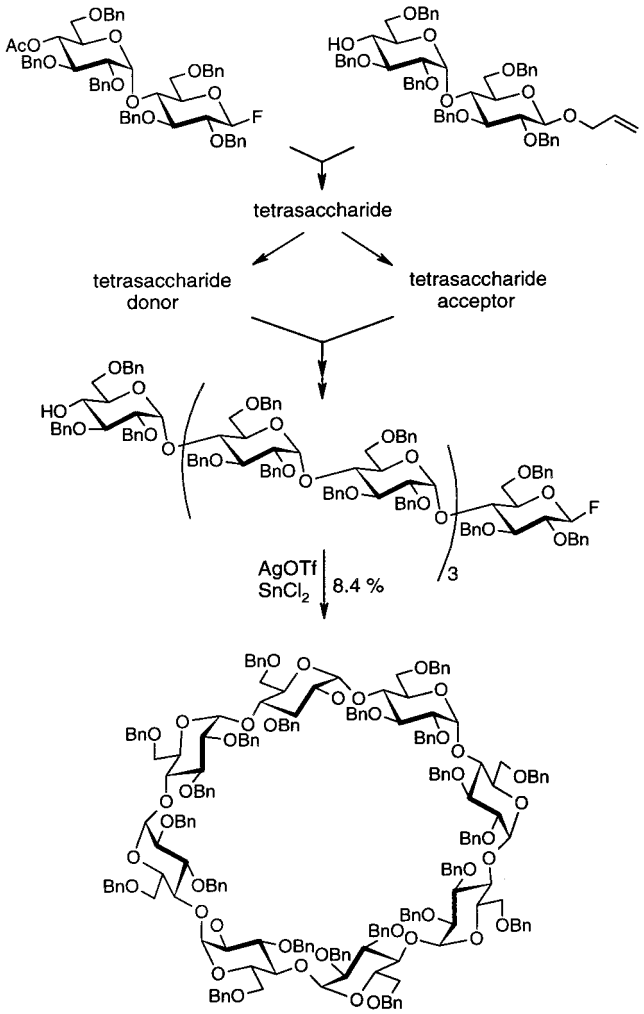
rivative was selected which contains a glycosyl acetate as a donor and a trityl-protected oxygen as an acceptor; the trityl group is released during the reaction course. Activation with $AgClO_4/SnCl_4$ gave, first, a linear condensation of two molecules leading to the corresponding tritylated tetrasaccharide; then an intramolecular glycosylation reaction takes place. The cycloisomaltotetraoside was stereoselectively obtained in 40% yield, and no cyclic di-, hexa-, or octasaccharide was detected. The cyclization versus oligomerization of the oligosaccharide chain is controlled by the concentration of the reaction mixture. The extension of this concept to the synthesis of cyclohexasaccharides was less successful.[86] From a trisaccharide precursor, a mixture of the desired cyclogentiohexaoside (12%), the cyclogentiotrioside (47%), and the β-connected cyclotrisaccharide (11%) was obtained.

The first total synthesis of cyclomaltooctaoside (γ-cyclodextrin) was described applying a strongly convergent strategy (Scheme 47).[87] Glcα(1−4)Glc (maltose) donor and acceptor derivatives were used as starting materials for the multistep synthesis of the linear octasaccharide containing the glucosyl fluoride moiety as a donor and the unprotected 4-OH group as an acceptor. Intramolecular glycosylation activated by $AgOTf/SnCl_2$ gave the cyclomaltooctaoside derivative in quite low yield (8.4%). The cyclomaltohexaoside (α-cyclodextrin) was prepared in 21% yield based on the same method.[88] With the help of the glycal activation method for the intramolecular glycosylation step, a cyclomaltohexaoside derivative was obtained in 48% yield.[89] By means of the thioglycoside activation method for the intramolecular glycosylation step and a modified protective group pattern, the cyclomaltopentaoside was prepared in 27% yield.[90]

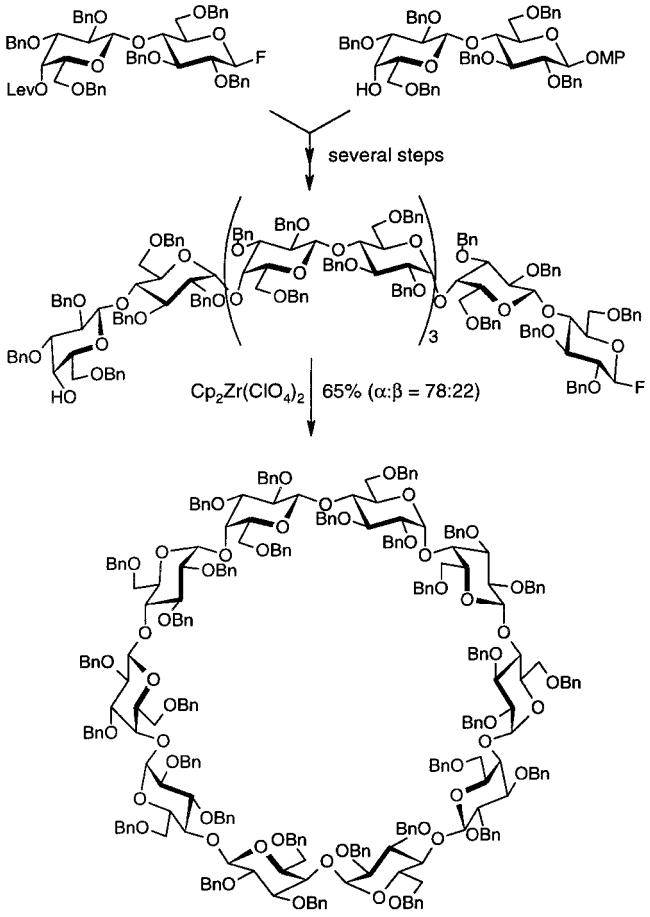
Accordingly, the *manno* isomer of α-cyclodextrin was prepared.[91] A α(1−4)-connected linear mannose hexasaccharide was used as a precursor for intramolecular glycosylation applying the thioglycoside activation method with phenylselenyl triflate as promotor. Thus, the cyclo-α(1−4)mannohexaoside derivative was exclusively obtained in remarkable 92% yield. The corresponding cyclo-α(1−4)mannopentaoside could be only obtained in very low yield.

To investigate the influence of the ring size and the number of axial bonds within the macrocycle on

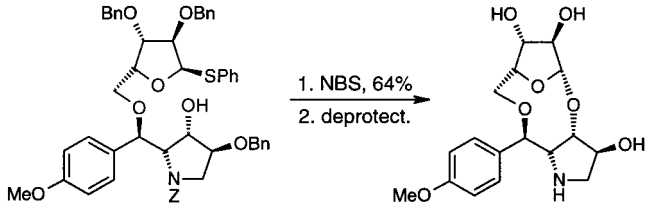
Scheme 47



Scheme 48



Scheme 49



the course of the intramolecular glycosylation, some cyclolactooligosaccharides were prepared (Scheme 48).[92] A lactose donor (fluoride) and acceptor were used for the synthesis of a linear lactodecasaccharide. Then, intramolecular glycosylation activated by $CpZr(ClO_4)_2$ yielded the cyclolactodecaoside derivative in good yield (65%) and acceptable stereoselectivity (α:β = 78:22). Better yields and stereoselectivities were obtained for the ring closure to the corresponding cyclolactooctaoside[92] (85%, only α) and cyclolactohexaoside[93] (74%, only α) derivatives. Attempts for cycloglycosylations with partially β-connected lactooligosaccharides failed.

Syntheses of compounds in which the macrocycle contains a sugar moiety together with non-carbohydrate parts were also described. For instance, a pyrrolidine derivative was connected with a xylose thioglycoside via an ether function. (Scheme 49).[94] Intramolecular glycosylation activated with NBS gave the nine-membered cyclic glycoside in 64% yield with very good stereoselectivity (only β). Deprotection gave AB3217-A, a novel anti-mite substance.

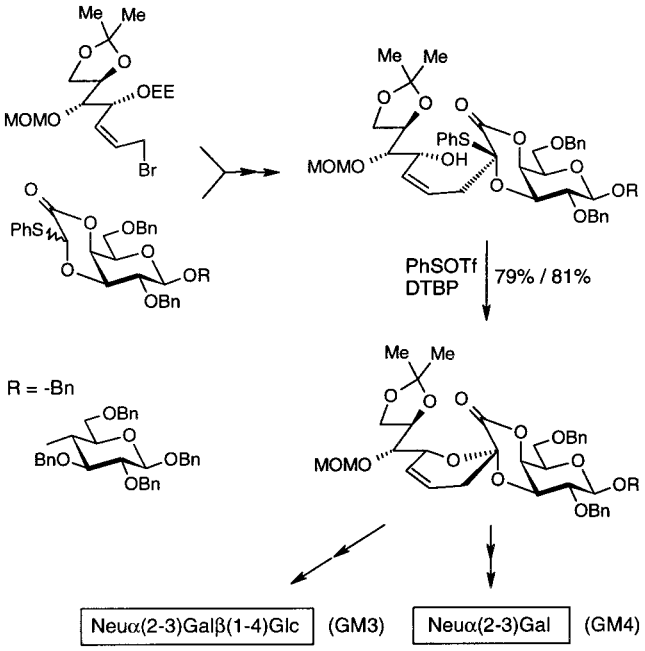
VI. A Unique Case Termed "Intramolecular Glycosidation"

Recently, a novel approach to the synthesis of α-sialyl glycosides was reported which combines the construction of the sialic acid and the formation of the α-glycosidic bond in an unusual manner (Scheme 50).[95] A C_2-fragment (later the C-1 and C-2 atoms of sialic acid) was attached to 3-*O* and 4-*O* of a galactose or lactose derivative. Formally the "glycosidic" bond was already formed in this step. Subsequently, the sialic acid chain is completed by an alkylation reaction with a carbohydrate-derived allyl bromide as C_7-fragment. After 6-*O* deprotection, intramolecular acetal formation was performed under activation with PhSOTf to give the α-sialoside precursors with good yields (79% and 81%) and stereoselectivities (α:β = 4:1 and 2.8:1). Further transformations led to the gangliosides GM3 and GM4. Formally, this approach is not an intramolecular glycosylation or glycosidation because the glycosidic bond to the acceptor is not formed in an intramolecular step.

VII. Conclusion

In the last 10 years, much effort has been devoted to the development of intramolecular glycosylation

Scheme 50



reactions in order to achieve high yields and stereoselectivities and/or in order to synthesize natural products or related compounds which contain macrocyclic glycosides. Good solutions have been presented for the formation of nearly all important glycosidic linkages, including β-mannopyranosides and α-glycosides.

Though the stereoselective formation of nearly all types of glycosides via intramolecular glycosylation reactions are at our disposal, very few applications to the synthesis of natural products, particularly glycoconjugates, have been reported hitherto. Most applications were reported from the authors who themselves developed the method. To obtain a similar acceptance for intramolecular glycosylation as for intermolecular methods, much effort is required in order to improve access to the required starting materials and to extend the method to the synthesis of complex glycoconjugates.

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