

# 3.2 Glycosyl Trichloroacetimidates

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## Abstract

In the first part of this review, the basic principles of chemical glycosylation reactions are discussed; this way the advantages of *O*-glycosyl trichloroacetimidates and related systems as glycosyl donors become obvious. Many new methods for the generation of *O*-glycosyl trichloroacetimidates and for their use as glycosyl donors have been introduced which are

compiled as well as their use in solid-phase oligosaccharide synthesis. The power of these glycosyl donors is demonstrated by their application in complex oligosaccharide and glycoconjugate synthesis, as outlined in the second part of this review. Recent applications in glycolipid, glycosyl amino acid and glycopeptide, nucleoside and nucleotide glycosidation, glycosaminoglycan, cell wall constituent, and GPI anchor synthesis, glycosylation of various natural products and their metabolites, and finally cyclooligosaccharide generation are compiled. In the last section, related glycosyl donors are briefly discussed.

### Abbreviations

<b>ADMB</b>	4-acetoxy-2,2-dimethylbutanoyl
<b>CAC</b>	chloroacetyl
<b>CDs</b>	cyclodextrins
<b>CSs</b>	chondroitin sulfates
<b>DBU</b>	1,8-diazabicyclo[5.4.0]undec-7-ene
<b>DDQ</b>	2,3-dichloro-5,6-dicyno-benzoquinone
<b>DMM</b>	<i>N</i> -dimethylmaleoyl
<b>DPM</b>	diphenylmethyl
<b>FGFs</b>	fibroblast growth factors
<b>Fmoc</b>	9-fluorenylmethyl carbamate
<b>GAGs</b>	glycosaminoglycans
<b>GPI</b>	glycosylphosphatidyl inositol
<b>HS</b>	heparan sulfate
<b>ILs</b>	ionic liquids
<b>IP</b>	inverse procedure
<b>IPG</b>	inositolphosphoglycan
<b>LTAs</b>	lipoteichoic acids
<b>MPEG</b>	mono-methyl polyethyleneglycol
<b>MPLC</b>	medium pressure liquid chromatography
<b>NAP</b>	naphthylmethyl
<b>PLL</b>	photolabile linker
<b>PNBP</b>	<i>p</i> -nitrobenzylpyridine
<b>PPTS</b>	pyridinium <i>p</i> -toluenesulfonate
<b>PTBD</b>	polymer-supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene
<b>PS-DBU</b>	polystyrene-supported DBU
<b>SPOS</b>	solid-phase oligosaccharide syntheses
<b>TBS</b>	<i>tert</i> -butyl-dimethylsilyl
<b>TMSOTf</b>	trimethylsilyl trifluoromethanesulfonate

## 1 Introduction

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The biological significance of oligosaccharides and glycoconjugates has stimulated many activities in carbohydrate chemistry. Most of these activities have been devoted to the development of methods for glycoside bond formation as the assembly of monosaccharide building

blocks to complex oligosaccharides and glycoconjugates is the most difficult task in this endeavor.

## 2 Glycosyl Donor Generation Through Anomeric-Oxygen Exchange Reactions

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For a long time the methods developed for glycosylation have essentially favored approaches which require for glycosyl donor generation an *anomeric oxygen exchange reaction* on the half-acetal moiety of pyranoses and furanoses [► *Fig. 1*, methods (A) and (B)] [1,2,3,4]. The *Fischer–Helferich method* (A), as a direct acid-catalyzed anomeric-oxygen replacement reaction has been very successfully applied to the synthesis of simple alkyl glycosides. However, because of its reversibility, it is of limited usefulness in the synthesis of complex oligosaccharides and glycoconjugates. For this endeavor, irreversible methods are required, which can be attained by preactivation of the anomeric center by introducing good leaving groups which can be released by leaving group specific promoters or—even better—by catalytic amounts of an activator.

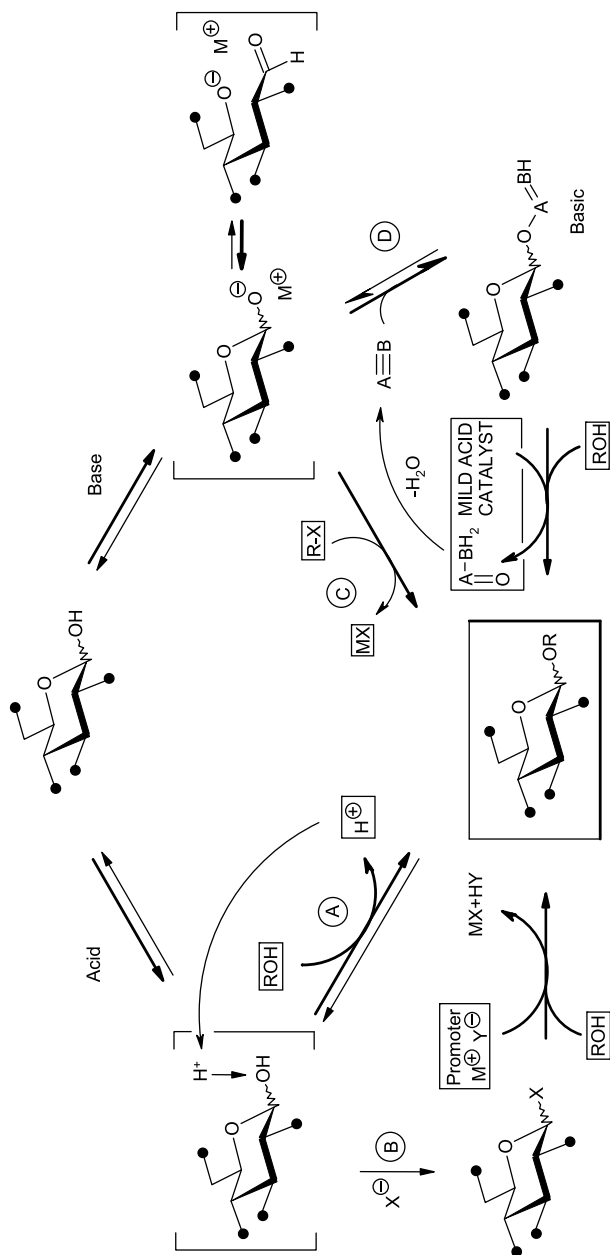
The best-known of these methods is the *Koenigs–Knorr method* (B) in which the anomeric hydroxy group is replaced by chlorine or bromine. Thus, an  $\alpha$ -halogen-ether is generated which in the glycosylation step can be readily activated by halophilic promoters frequently incorrectly termed “catalyst.” Generally, from one up to four equivalents of heavy metal salts are employed resulting in an irreversible transfer of the glycosyl donor moiety to the acceptor. On the basis of this general method many valuable techniques for the synthesis of complex oligosaccharides and glycoconjugates have been introduced which have been extensively reviewed. However, the obvious limitations of this method were the reason for the search for alternative methods [1,2,3,4,5,6,7].

Therefore, other anomeric oxygen exchange reactions closely related to the *Koenigs–Knorr method* have been extensively investigated. Particularly, the introduction of fluorine and alkyl- and arylthio groups as leaving groups gained great interest because these groups also tolerate manipulations of orthogonal protecting groups. Differences in thio leaving group tendencies (in combination with the “armed”/“disarmed” principle) could be even employed for one-pot consecutive glycosylations leading to more or less pure oligosaccharide products. However, the basic drawbacks of the *Koenigs–Knorr method* are also associated with these promoter systems. For instance, the large amounts of promoter required (and often additional reagents) limit their usefulness particularly in large-scale oligosaccharide and glycoconjugate synthesis.

## 3 Direct Anomeric Oxygen Alkylation

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For more than a century glycosylations were essentially based on methods where the anomeric carbon of the sugar residue to be coupled served as the electrophile (the glycosyl donor) and the alcohol (the glycosyl acceptor) as the nucleophile [► *Fig. 1*, (A), (B)]. Alternatively, base-mediated deprotonation of the anomeric hydroxy group generating at first an anomeric



A **Fischer-Helferich:** (Acid catalyzed Act.)

B **Koenigs-Knorr:** X = Cl, Br, (I), Activation

X = F-Activation

X = S-R-Activation (+ Hetarylthio)

C **Anomeric O-Alkylation:** (Base Activation)

D **Trichloroacetimidate Activation:** A  $\equiv$  B =  $CCl_3-CN$

Related Systems (?):

$PO(OR)_2$ ,  $P(OR)_2$ -Activation

$SO_2(OR)$ ,  $SO(OR)$ ,  $SO_2R$ -Activation

**Glycosylation: "Mild Acid catalyst"**

(Generally:  $BF_3 \cdot OEt_2$ , TMSOTf, etc.)

**Glycosylation: "X-Phylic" Promoter**

(Generally: Heavy metal salts:  $Ag^+$ ,  $Hg^{2+}$ , etc.)

Figure 1

Synthesis of glycosides and saccharides

oxide structure from a pyranose or a furanose and then anomeric *O*-alkylation leading directly and irreversibly to glycosides should be also available [● Fig. 1, (C)]. Surprisingly, no studies employing this simple ‘anomeric *O*-alkylation method’ as termed by us [1,2,3,4], for the synthesis of complex glycosides and glycoconjugates had been reported before our work. Only a few scattered examples with simple alkylating agents, for instance, excess methyl iodide or dimethyl sulfate, have been found in the literature [1]. However, in our hands, direct anomeric *O*-alkylation of variously protected and totally unprotected sugars in the presence of a base and triflates or Michael acceptors, respectively, as alkylating agents has become a very convenient method for glycoside bond formation [8,9,10,11]. Base-promoted decomposition reactions, particularly of the acyclic form, were practically not observed. Often even high anomeric diastereocontrol was available. The high diastereocontrol in pyranoses is based on the enhanced nucleophilicity of equatorial oxygen atoms (due to steric effects and the stereoelectronic *kinetic anomeric effect*) [1,2,3,4] and on the higher stability of axial oxygen atom-derived products (due to the *thermodynamic anomeric effect*). Chelation effects can be also employed to design anomeric stereocontrol. The availability and to some extent the stability of the carbohydrate-derived alkylating agents precluded the general applicability of this simple method to the synthesis of complex oligosaccharides and glycoconjugates.

#### 4 Glycosyl Donor Generation Through Retention of the Anomeric Oxygen

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The requirements for an efficient glycosylation method are the following:

- high chemical and stereochemical yield,
- applicability to large-scale preparations, and
- avoidance of large amounts of waste materials, i. e. activation of the donor by catalytic amounts of reagent.

These demands were not met by any of the above-described methods for the synthesis of complex oligosaccharides and glycoconjugates. However, the general strategy for glycoside bond formation seems to be correct:

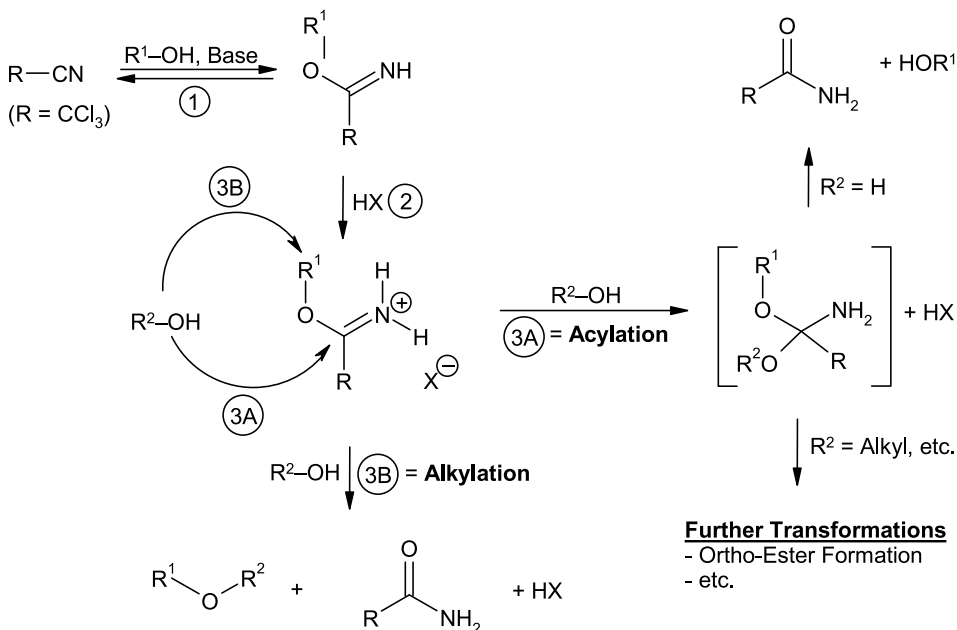
- The first step (*activation step*) should consist of an activation of the anomeric center under formation of a stable glycosyl donor—best by a catalyzed attachment of a leaving group to the anomeric hydroxy group.
- The second step (*glycosylation step*) should consist of a sterically uniform high-yielding glycosyl transfer to the glycosyl acceptor based on glycosyl donor activation with catalytic amounts of promoter, i. e. a catalyst. Obviously, this catalytic procedure has to be orthogonal to the glycosyl donor preparation procedure. Diastereocontrol in the glycosylation step may be derived from the anomeric configuration of the glycosyl donor (by inversion or retention), by anchimeric assistance, by the solvent influence, by thermodynamic and/or stereoelectronic effects, or by any other effects.

The experience with the direct anomeric *O*-alkylation exhibited that these demands can be fulfilled by a simple base-catalyzed anomeric *O*-transformation into a leaving group and

its acid-catalyzed activation in the glycosylation step. This approach should also satisfy the demand for simplicity in combination with efficiency which is decisive for general acceptance.

Obviously, for achieving stereocontrolled activation of the anomeric oxygen atom, the anomerization of the anomeric hydroxy group or the anomeric oxide ion, respectively, has to be considered. Thus, in a reversible activation process and with the help of kinetic and thermodynamic reaction control, possibly both activated anomers should be accessible. From these considerations it was concluded that suitable triple-bond systems  $A\equiv B$  (or compounds containing cumulative double bond systems  $A=B=C$ ) might be found that add pyranoses and furanoses under base catalysis directly and reversibly in a stereocontrolled manner [● Fig. 1, (D)].

Electron-deficient nitriles, such as for instance trichloroacetonitrile (and trifluoroacetonitrile [11]), are known to undergo direct and reversible, base-catalyzed addition of alcohols providing *O*-alkyl trichloroacetimidates (or *O*-alkyl trifluoroacetimidate, respectively) [1,12,13] [● Fig. 2, (1)]. This imidate synthesis has the advantage that the imidates can be isolated as stable adducts which are less sensitive to hydrolysis than the corresponding salts. On acid addition leading to imidate activation [● Fig. 2, (2)], hydrolysis with water ( $R^2-OH = H_2O$ ) is a fast reaction furnishing amide  $CCl_3-CO-NH_2$  and alcohol  $R^1-OH$  [● Fig. 2, (3A)]; mechanistically this is an acylative attack of the imidate at the nucleophile. With other nucleophiles, after acylation by the imidate, other transformations are possible, as for instance ortho-ester formation. However, the basic question is: are these activated imidates also good alkylating agents [● Fig. 2, (3B)] as required for being effective in glycosidation reactions? On consider-



■ **Figure 2**  
Trichloroacetimidate formation and its acid-catalyzed transformations

ation of the influence of the substituents R and R<sup>1</sup> on these two competing reactions an attack of R<sup>2</sup>-OH leads to the following expectations:

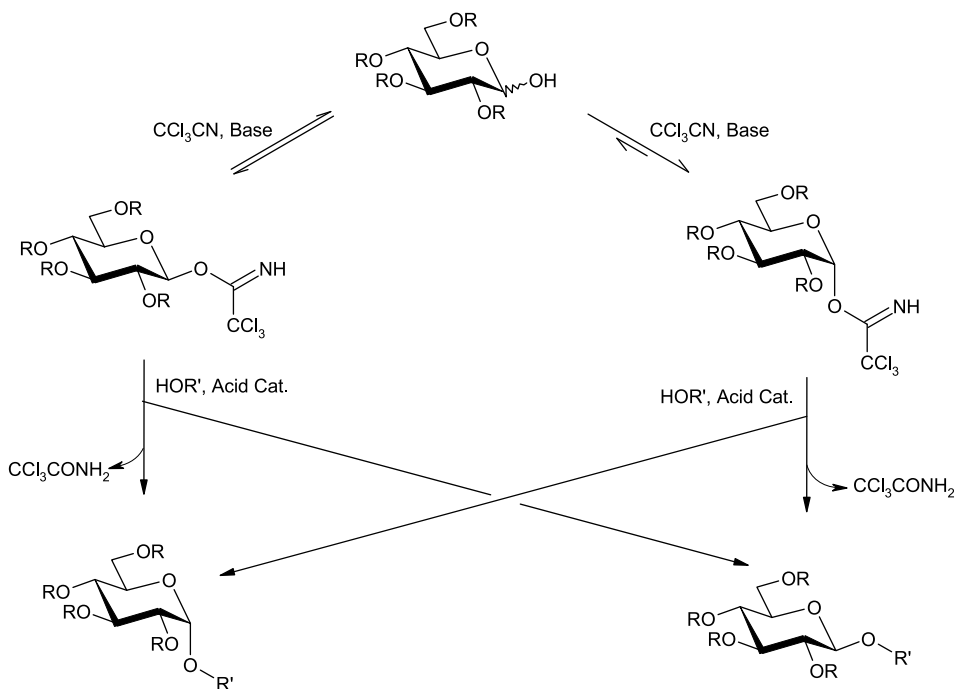
- Acylation [reaction (3A)] is supported by R being a small electron-withdrawing group, R<sup>1</sup> destabilizing carbenium ion formation.
- Alkylation [reaction (3B)] is supported by R being a sterically demanding electron-withdrawing group, R<sup>1</sup> supporting carbenium ion formation.

From these considerations it can be deduced that the bulky and strongly electron-withdrawing trichloromethyl group as R and the glycosyl group as R<sup>1</sup>, which through the  $\alpha$ -oxygen atom supports oxocarbenium ion formation at the anomeric center, should provide excellent alkylating agents; hence, *O*-glycosyl trichloroacetimidates should on acid activation exhibit excellent glycosyl donor properties.

As expected, on base-catalyzed addition of the anomeric hydroxy group to trichloroacetonitrile the *O*-glycosyl trichloroacetimidate is formed for which, due to the reversibility of the addition, the different nucleophilicities of the anomeric oxides, and the different thermodynamic stabilities of the *O*-glycosyl trichloroacetimidates, anomeric stereocontrol is possible. Thus, the weak base potassium carbonate could be employed for preferential or exclusive formation of the  $\beta$ -anomer and the strong base sodium hydride could be employed for the thermodynamically more stable  $\alpha$ -anomer (● Fig. 3). This stereocontrol could be successfully extended to S<sub>N</sub>2-type glycosidation reactions in solvents of low donicity and under low temperature conditions and particularly to glycosylations of O=X-OH nucleophiles with X being RC or R<sub>2</sub>P (see below). However, for many cases anomeric stereocontrol is based on other effects such as for instance neighboring group participation and/or steric effects, stereoelectronic effects, solvent participation effects, etc.

The experience with the *trichloroacetimidate method* exhibited that the demands on a new glycosylation methodology are fulfilled:

- (i) The *O*-glycosyl trichloroacetimidates are readily formed and generally stable under room temperature conditions. However, on acid catalysis they exhibit extraordinary high glycosyl donor properties.
- (ii) The release of nonbasic trichloroacetamide fulfills the criteria for acid catalysis: The acid is not consumed by the leaving group, therefore generally only catalytic amounts of (Lewis) acid are required (~0.001 to 0.1 equivalents).
- (iii) The released trichloroacetamide is also not acidic, therefore the acidity provided by the catalyst amount is maintained throughout the reaction course. Hence, negative effects of increasing acidity in the reaction mixture (found for instance for phosphate, sulfate, sulfonate leaving groups, ● Fig. 1, D) are avoided.
- (iv) Glycosidation is basically a condensation reaction. In this procedure, water is bound to trichloroacetonitrile under trichloroacetamide formation. Hence, drying agents are not required. Often molecular sieves are used in glycosidation reactions. Because they may affect the acidity of the reaction in an unpredictable fashion, their use is not even recommended in this method.
- (v) Trichloroacetamide can be removed from the reaction mixture and transformed back to trichloroacetonitrile, thus exhibiting the cost-effectiveness and ecofriendliness of this method in large-scale preparations.



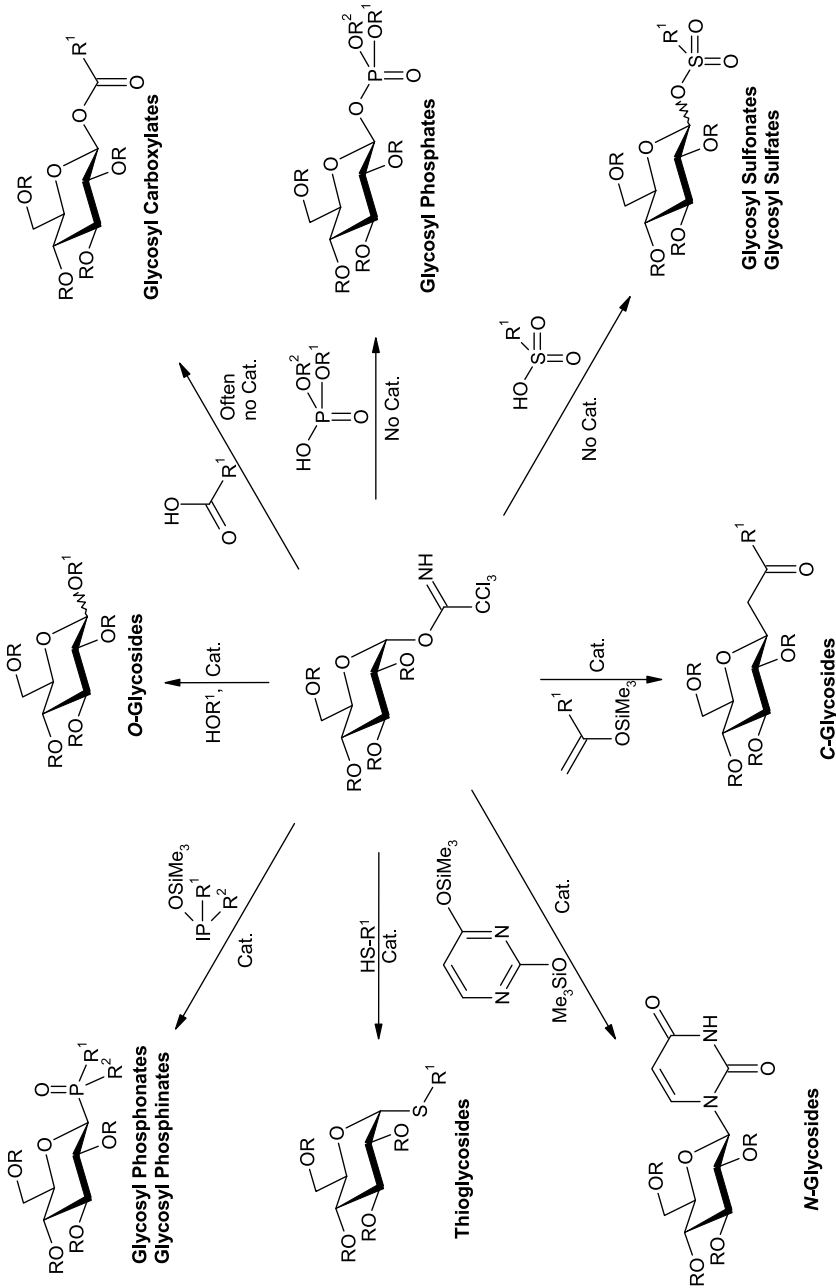
■ **Figure 3**  
***O*-Glycosyl trichloroacetimidate formation and acid-catalyzed glycosylation of acceptors HOR'**

(vi) Neither in the formation of the *O*-glycosyl trichloroacetimidates nor in the glycosidation reactions are equivalent or even higher amounts of salts produced—a disadvantage of most of the above-mentioned methods, particularly in large-scale preparations. Also, highly expensive sterically hindered bases are not required.

This discussion exhibits that *O*-glycosyl *N*-methyl-acetimidates, introduced by the Sinaÿ group [14,15], are poor glycosyl donors: they lack the strongly electron-withdrawing sterically demanding trichloromethyl group. Hence, they are rather better acylating agents than alkylating agents. In addition, their formation via *O*-glycosylation of *N*-methyl-acetamide with excess amounts of silver oxide is quite cumbersome.

These favorable aspects of *O*-glycosyl trichloroacetimidates led to their frequent use as glycosyl donors for various types of glycosyl acceptors such as nucleophiles (● Fig. 4). Besides hydroxy groups (of standard alcohols, phenols, sugars, etc.), also carboxylic acids, phosphorous acids, and sulfonic and sulfuric acids, respectively, were successfully employed as acceptors; due to the acidity of these acidic acceptors, generally catalysts are not required for the activation of the glycosyl donors and—presumably via an eight-membered transition state—often the inversion product at the anomeric center is generated. However, also various *C*-, *N*-, *S*-, and *P*-nucleophiles have been successfully glycosylated by *O*-glycosyl trichloroacetimidates [1,2].





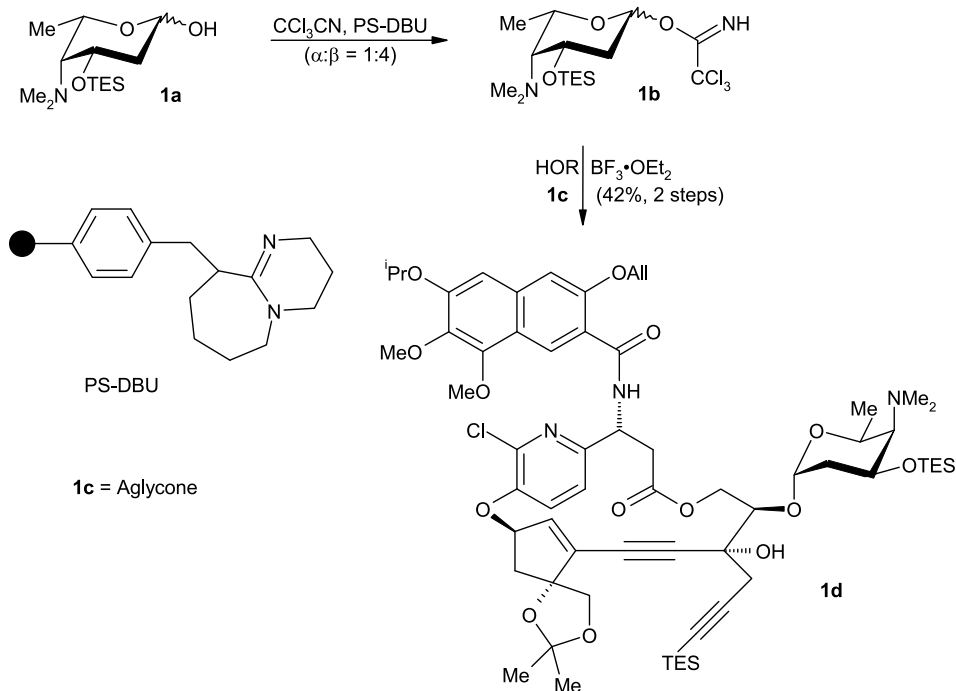
■ Figure 4  
Reaction of *O*-glycosyl trichloroacetimidates with *O*-, *C*-, *N*-, *S*-, and *P*-nucleophiles—activation by (Lewis)acid catalysis

## 4.1 Methodological Aspects

As outlined above, the anomeric hydroxy groups add under base catalysis readily to the electron-deficient nitrile group of trichloroacetonitrile to furnish generally via equilibration at the anomeric center *O*-glycosyl trichloroacetimidates. As bases mainly potassium carbonate, sodium hydride, DBU, and cesium carbonate are employed. Weak bases, such as for instance potassium carbonate, permit kinetic product control (formation of the equatorial product) whereas strong bases, as for instance sodium hydride, lead to the thermodynamically more stable product (generally the axially oriented trichloroacetimidate group). Because of convenience, DBU has become the most popular base, which also favors axial product formation. Therefore, polystyrene-supported DBU (PS-DBU) [16,17] and various other solid-supported nitrogen bases were successfully employed in this reaction as shown for the particularly difficult trichloroacetimidate formation of 4-dimethylamino-2,4,6-trideoxy sugar kedarasamine (**1a** → **1b**) and its use in the glycosylation of the ansamacrolide substructure (**1b** + **1c** → **1d**) of the kedarcidin chromophore (🔍 *Scheme 1*) [17]. Also Dowex 1-X8 OH<sup>-</sup> is a good catalyst for the trichloroacetimidate formation of a glucosamine derivative [18,19]. Polymer-supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene (PTBD) turned out to be a powerful catalyst for trichloroacetimidate formation as well [17,19]; this base catalyst in combination with Nafion<sup>®</sup>-SAC resin (a nanocomposite of Nafion<sup>®</sup> resin with porous silica) could be successfully employed in one-pot trichloroacetimidate formation and following glycosylation reactions [19].

*O*-Glycosyl trichloroacetimidates are quite stable under neutral but also under basic conditions. Hence, trichloroacetimidate formation is tolerated by standard *O*- and *N*-protecting groups, such as *O*-acyl, *O*-benzyl, *O*,*O*-alkylidene, *O*-silyl, *N*-acyl and *N*,*N*-diacyl, *N*-phthaloyl (Phth), *N*-dimethylmaleoyl (DMM), and the latent amino functionality azido. It is particularly worth mentioning that trichloroacetimidate formation is also tolerated by Fmoc-protected hydroxy groups; this group has become an important temporary protecting group which is orthogonal to other temporary protecting groups, thus permitting in oligosaccharide synthesis not only regioselective chain extension but also branching [20,21]. The useful 3-*O*-Fmoc-protected galactosyl donor **2d** can be readily prepared from compound **2a** via intermediates **2b** and **2c** (🔍 *Scheme 2*) [20]. Additional protecting groups have been recently probed particularly at 2-*O* in order to influence the stereochemical outcome, such as for instance the diphenylmethyl (DPM), the 9-fluorenyl (Fl) group [22], and the 4-acetoxy-2,2-dimethylbutanoyl (ADMB) group [23]. The ADMB group is a useful alternative to the pivaloyl group; it combines the strong 1,2-*trans*-selection in glycosylation reactions of the pivaloyl group with the ease of removal of more reactive acyl groups. Other important new groups are the *O*-trifluoroethylsulfonate group which could be successfully employed to release the sulfate group and the replacement of the 6-hydroxy group by a phenylthio group which is employed for uronate formation [25].

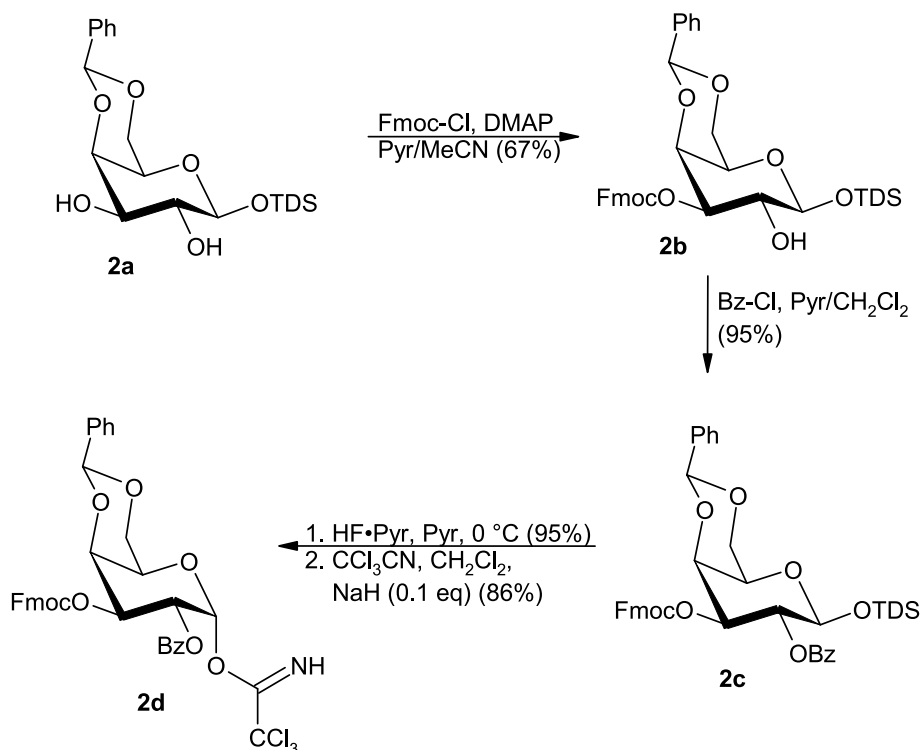
*O*-Glycosyl trichloroacetimidates are under acidic conditions very powerful glycosyl donors. Reaction with nonacidic nucleophiles is generally performed with catalytic amounts of Brønsted or Lewis acids. TMSOTf and BF<sub>3</sub>OEt<sub>2</sub> are the most frequently employed catalysts. TMSOTf is the catalyst of first choice and it is generally used in 0.001 to 0.1 equivalents based on the glycosyl donor. Commonly 1.0 to 1.5 equivalents of glycosyl acceptor are added. Dichloromethane is the solvent of first choice. Because of the high reactivity of *O*-glycosyl



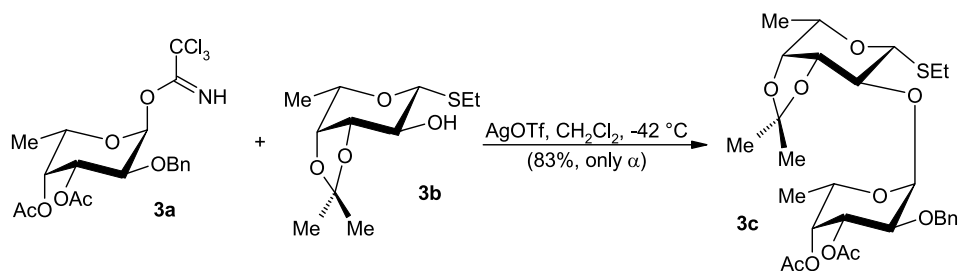
■ Scheme 1

trichloroacetimidates often reaction temperatures between 0 and  $-40^\circ\text{C}$  are selected. For highly sensitive glycosyl donors and for the anomeric stereocontrol many variations have been probed which are shortly summarized.

Numerous acid catalysts have been investigated. Brønsted acids, such as for instance *p*-TsOH and TfOH, can lead—as previously discussed [1,2,3,4,26]—to *O*-glycosyl sulfonates as reactive intermediates which are in most cases not the glycosyl donors but rather some type of glycosyl oxocarbenium ion intermediates ( $\text{S}_{\text{N}}1$ -type reactions). Similarly, pyridinium *p*-toluenesulfonate (PPTS) [27,28] and perchloric acid [29,30] are working as catalysts. Metal triflates such as AgOTf [31,32], Cu(OTf)<sub>2</sub> [33], Sn(OTf)<sub>2</sub> [34,35], Sm(OTf)<sub>3</sub> [36], and Yb(OTf)<sub>3</sub> [37], are particularly valuable in glycosylations with acid sensitive glycosyl donors and/or acceptors. On Cu(OTf)<sub>2</sub>-activation of various donors the trichloroacetimidates have proven to be the most potent glycosyl donors [33]. For instance, AgOTf has proven to be useful, as a catalyst for highly reactive deoxysugars such as glycosyl donors, as shown in ▶ Scheme 3 for the reaction of fucosyl donor **3a** with fucosyl acceptor **3b** giving the  $\alpha$ -oligosaccharide **3c** [32]. Sn(OTf)<sub>2</sub> permitted successful glycosylations of acid sensitive glycol derivatives as acceptors as shown for the synthesis of **4c** from **4a** and **4b** (▶ Scheme 4) [35]. Various other catalyst systems have proven to be useful such as for instance  $\text{HB}(\text{C}_6\text{F}_5)_4$  [29,30], *N*-acyl-sulfonamides, phenols [38], I<sub>2</sub> [39], I<sub>2</sub>/Et<sub>3</sub>SiH [40], and electrophilic carbonyl compounds [41], such as for instance chloral. Silica-supported perchloric acid [42,43], acid-washed molecular sieves (MS



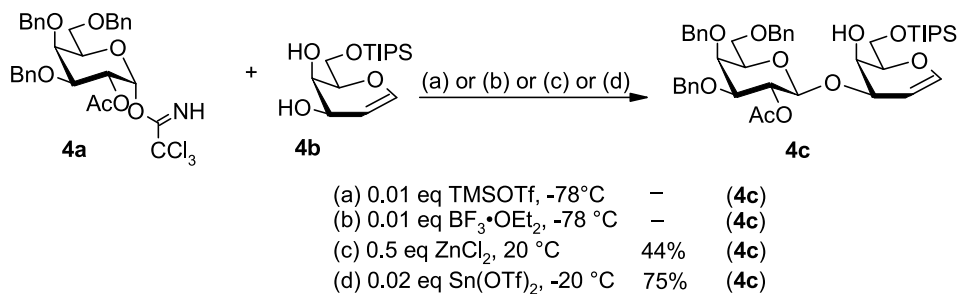
■ Scheme 2



■ Scheme 3

AW 300 [44], and Nafion<sup>®</sup>-SAC resin [19] (see above) are highly valuable solid-supported acid catalysts. This is nicely demonstrated in an avermectin B<sub>1a</sub> analog synthesis [43]: Rhamnosylation of intermediate **5b** with donor **5a** gave target molecule **5c** in quantitative yield (► Scheme 5).

The solvent of choice in the glycosylation reactions is dichloromethane. In combination with a solvent of low polarity and/or of low donicity (such as for instance cyclohexane, petroleum ether, etc.), BF<sub>3</sub>OEt<sub>2</sub> as a mild catalyst and at low temperature, S<sub>N</sub>2-type reactions could be



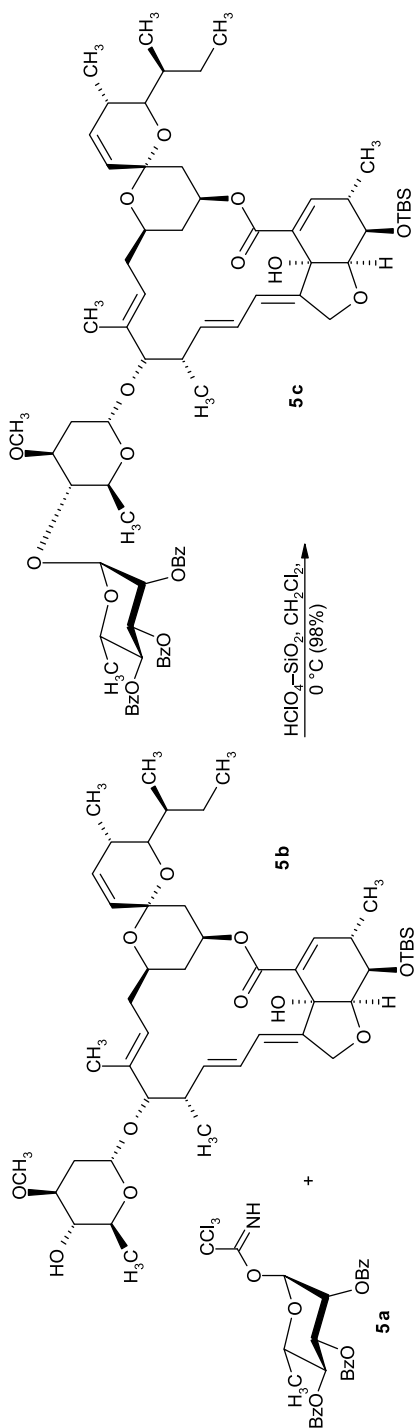
#### Scheme 4

carried out [1,2,3,4]. Solvents of high donicity (such as for instance ethers and nitriles) permit—based on the exo-anomeric effect—a different anomeric stereocontrol: As found and previously explained, in ethers at room temperature generally the axial product (for most cases the  $\alpha$ -product) is favored whereas in nitriles at low temperature, based on the nitrile effect, the equatorial product (for most cases the  $\beta$ -product) is preferentially or exclusively obtained [3,4,45,46]. Hence, solvent and temperature selection play also an important role in anomeric stereocontrol.

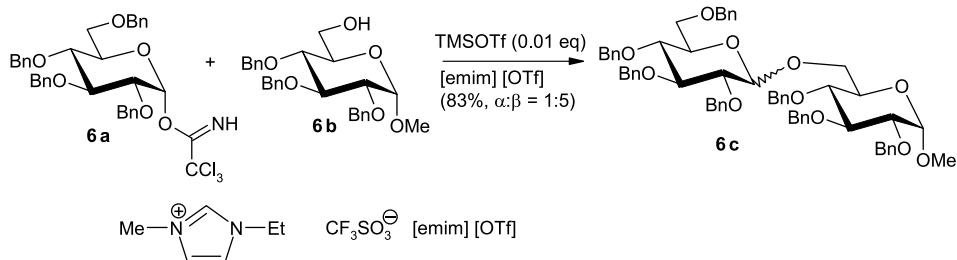
Another interesting solvent effect is associated with the application of the ‘inverse procedure’ (IP) which consists of the addition of the glycosyl donor to a mixture of acceptor and acid catalyst [47,48]. In this way, particularly with highly reactive glycosyl donors often dramatic glycosylation yield improvements could be obtained [49]. This result seems to be based on a cluster effect between the catalyst and acceptor molecules; hence, on penetration of the donor into this cluster, activation of the donor and following glycoside bond formation takes place within the cluster in a practically intramolecular fashion. Obviously, this effect is critically dependent on the acceptor type, the solvent, and the temperature; therefore it requires often some experimentation for its successful application.

A dramatic polarity increase of the solvent can be reached by adding  $\text{LiClO}_4$  to organic solvents (for instance, ether, dichloromethane, etc.) which enabled *O*-glycosyl trichloroacetimidate activation under essentially neutral conditions [50,51]. High polarity solvents are also ionic liquids (ILs) which have gained a lot of interest as solvents for organic reactions [52]. ILs have been probed in glycosylation reactions with *O*-glycosyl trichloroacetimidates and excellent glycosylation yields have been obtained (● Scheme 6; **6a** + **6b** → **6c**) [53]; for reactive systems again no acid activation is required [53]. Microwave heating has been employed for *O*-glycosyl trichloroacetimidate activation as well, furnishing glycosides in high yields [54]; however, presumably due to the temperature effects only modest anomeric stereocontrol was available.

Besides solvent, temperature, and (kinetic and thermodynamic) stereoelectronic effects, anchimeric assistance by neighboring acyl groups and/or by steric shielding is decisive for the anomeric stereocontrol [1,2,3,4,5,6,7,22]. This way 1,2-*trans*- ( $\beta$ -*gluco*,  $\alpha$ -*manno*) and 1,2-*cis*-type ( $\alpha$ -*gluco*) glycosides have been generally obtained at wish in good to excellent stereochemical yields. However, a 2-*O*-acyl group does not guarantee  $\beta$ -glucopyranoside or  $\alpha$ -mannopyranoside formation. Besides undesired ortho-ester formation, which can often be



► Scheme 5



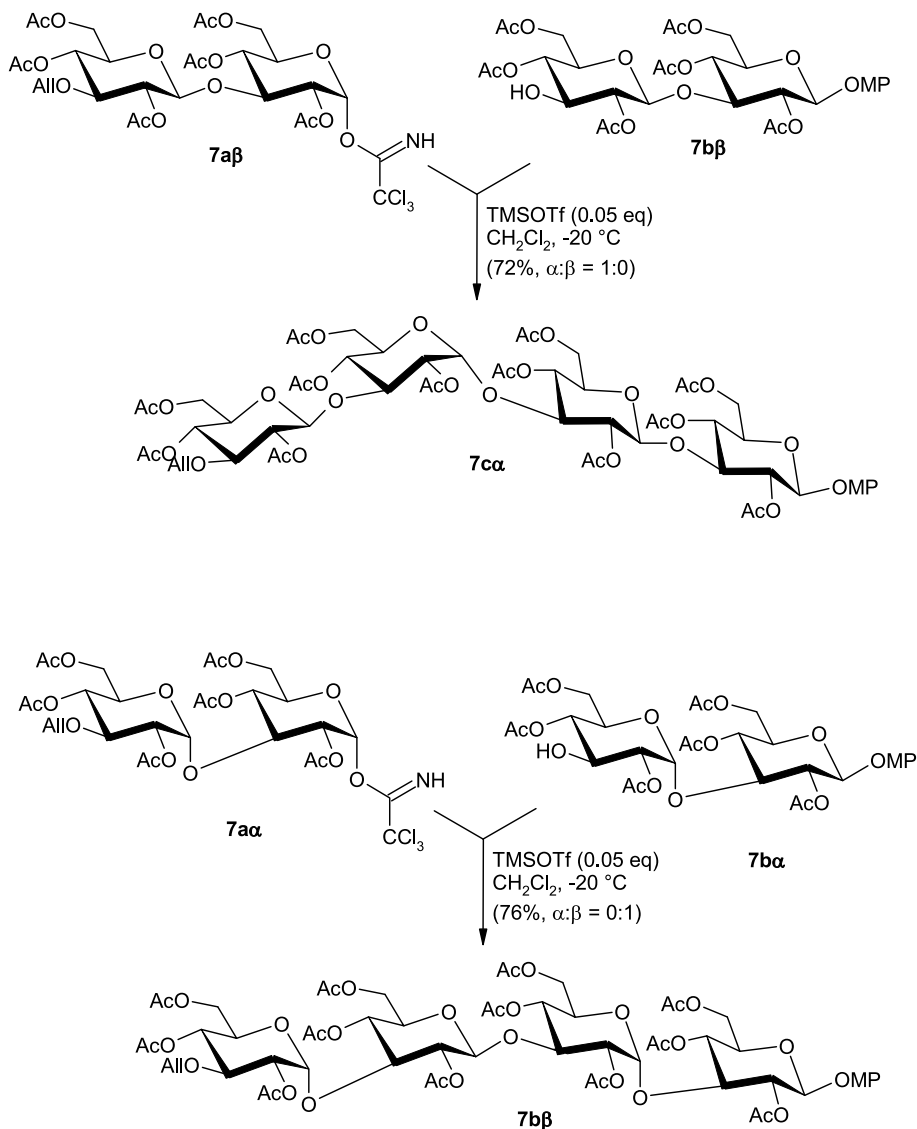
■ Scheme 6

overcome by using more catalyst or by varying the acyl group, once in a while still the  $\alpha$ -glucopyranoside or even some  $\beta$ -mannopyranoside, respectively, is obtained. Interesting cases of  $\alpha$ -linkage on attempted 2-*O*-acyl supported  $\beta$ (1–3)-glucan synthesis were recently reported which were explained by ‘remote control’ [55,56,57].  $7\mathbf{a}\beta + 7\mathbf{b}\beta$  gave  $7\mathbf{c}\alpha$  whereas  $7\mathbf{a}\alpha + 7\mathbf{b}\alpha$  gave  $7\mathbf{c}\beta$  (● Scheme 7). However, this problem could be readily overcome by employing the ADMB group [23]. The influence of the structure of the glycosyl acceptors on the anomeric stereocontrol has often been discussed and since the work of van Boeckel et al. [58,59] the potential importance of matched and mismatched donor-acceptor pairs on the stereochemical outcome of glycosylation reactions has become evident. Recent work on 2-azido-2-deoxyglucopyranosyl trichloroacetimidates exhibited that the structure of the glycosyl donor has generally the major influence [60].

Other anchimerically assisting groups at C-2, such as  $-\text{SPh}$ ,  $-\text{SePh}$ ,  $-\text{Br}$ , and  $-\text{I}$ , have been investigated [61,62]. Particularly worth mentioning is the work on equatorial iodo substitution of glucopyranosyl trichloroacetimidates which strongly favored 1,2-*trans*- i.e.  $\beta$ -glycosidation. This result could be due to generation of an iodonium intermediate or due to the steric demand of the iodo group, thus favoring a twist-boat type oxocarbenium ion intermediate which—as previously discussed in  $\beta$ -mannopyranoside synthesis (see below) [26]—for steric and stereo-electronic reasons favors nucleophilic attack from the  $\beta$ -side [63,64].

An interesting addition to the repertoire of anchimerically assisting groups is the chiral 1-phenyl-2-(phenylsulfonyl)ethyl group [65]. Coupled as (*S*)-isomer  $\mathbf{8a}$  to the 2-hydroxy group of the glucopyranosyl trichloroacetimidates with acceptor  $\mathbf{8b}$  1,2-*cis*- i.e.  $\alpha$ -glucopyranosides  $\mathbf{8c}$  have been obtained in excellent yields and stereoselectivities (● Scheme 8). The formation of a cyclic  $\beta$ -linked sulfonium ion intermediate  $\mathbf{8a}^*$ , having a *trans*-decalin type structure has been confirmed by NMR experiments. This intermediate seems to be preferentially or exclusively attacked by the nucleophile from the  $\alpha$ -side.

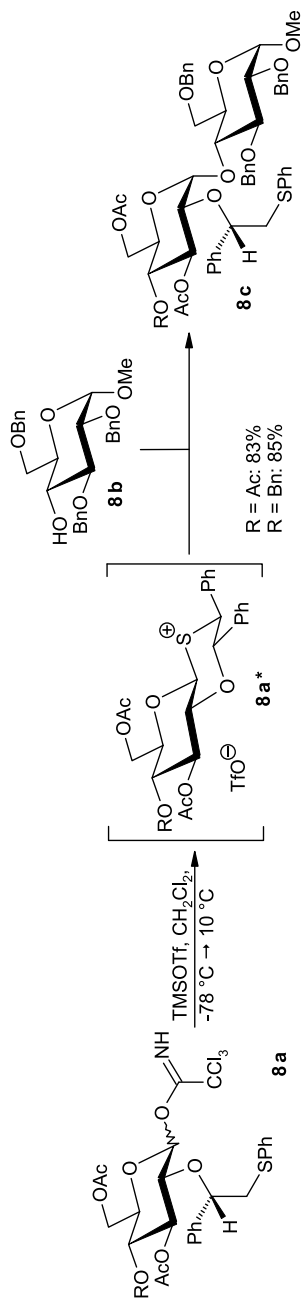
A particularly difficult problem is 1,2-*cis*- i.e.  $\beta$ -linkage formation in  $\beta$ -mannopyranoside synthesis. The presence of  $\beta$ -linked mannopyranosides in various natural products [66], particularly in the *N*-glycan core structure of glycoproteins [66,67], led to the search for efficient methodologies for generating this target structure. Investigation of mannopyranosyl donors with nonparticipating protecting groups and different leaving groups led in general mainly or exclusively to  $\alpha$ -products [1,66,67,68]. Several specific methods led to some success in this endeavor [69,70,71,72,73,74], however finally epimerization of  $\beta$ -glucopyranosides at 2-*O* [74,75,76,77,78,79] and intramolecular aglycone delivery [80,81,82,83,84] have led



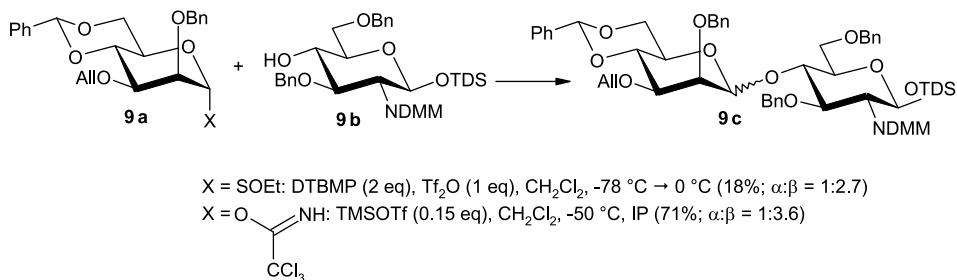
■ Scheme 7

to very successful results. Mannopyranosyl donors with diol *O*-protecting groups leading to ring annelation had already been investigated but again with limited success [85]. Therefore, it was a big surprise that 2,3-di-*O*-alkyl-4,6-*O*-benzylidene-protected mannopyranosyl sulfoxides as glycosyl donors gave preferentially  $\beta$ -products with various acceptors at low temperatures [86,87]. The same result is more conveniently obtained with the corresponding trichloroacetimidates as shown in **Scheme 9** with glycosyl donor **9a** furnishing with accep-





■ Scheme 8

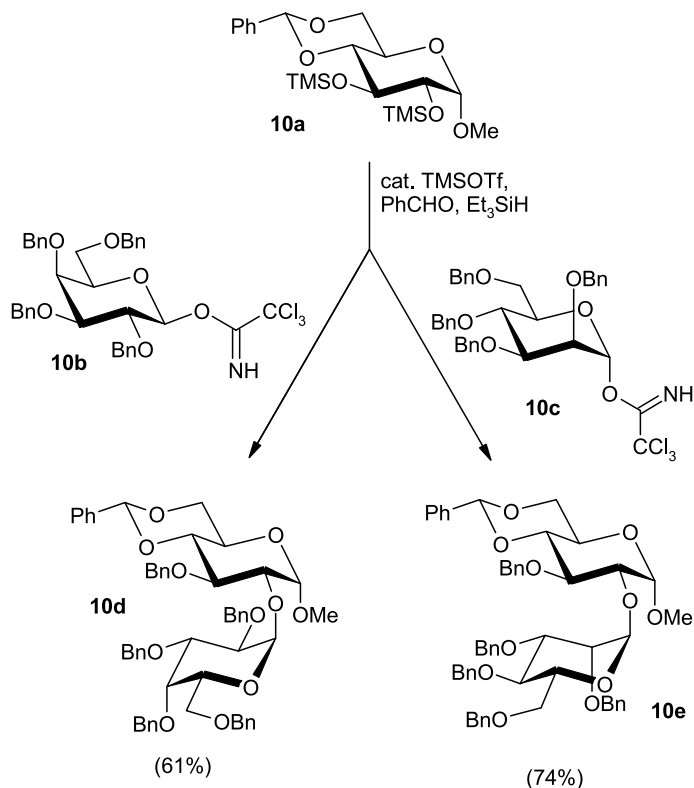


### Scheme 9

tor **9b** preferentially the  $\beta$ -disaccharide **9c** [26]. The results obtained on varying the reaction parameters were not compatible with the reaction mechanism proposed for sulfoxide activation, in which an  $\alpha$ -triflate intermediate is thought to play the decisive role [87]. Rather the anomeric stereocontrol is caused by a conformational effect enforced by the 4,6-*O*-benzylidene group on the pyranosyl ring, which favors the generation of a flattened twist-boat conformation as the intermediate. For stereoelectronic and steric reasons, this twist-boat intermediate will be preferentially attacked from the  $\beta$ -side, thus forming after equilibration the  ${}^4\text{C}_1$ -conformer of the  $\beta$ -mannopyranoside [26]. This mechanistic proposal is also confirmed by L-rhamnosylation reactions with bulky 3-*O*- and 4-*O*-protecting groups which enforce the  ${}^4\text{C}_1$ -conformation and this way favor  $\beta$ -L-rhamnoside formation [88]. On the basis of these mechanistic considerations,  $\beta$ -mannopyranoside formation should be facilitated by nonparticipating, strongly electron-withdrawing groups at the 2-*O* atom because generation of the twist-boat intermediate would gain from a strong dipole effect. This expectation could be confirmed [89].

Regioselectivity in glycosylation reactions is generally based on a sequence consisting first of regioselective functional group protection, making use of various principles, second glycosylation of the *O*-unprotected hydroxy group, and finally of *O*-deprotection. Direct regioselective glycosylation using the difference in reactivity of sugar hydroxy groups is of great interest as it often avoids cumbersome protection and deprotection steps. Many regioselective glycosylations of partly unprotected carbohydrate acceptors have been reported in the literature [1,2,3,4,5,6,7]. Generally, they make use of the higher reactivity of primary hydroxy groups over secondary hydroxy groups (particularly those in axial orientation) and the higher reactivity of equatorial 3-hydroxy groups, for instance in galacto- and glucopyranosides. This was again confirmed in the glycosylation of 4,6-*O*-benzylidene-glucopyranosides which gave with various glycosyl trichloroacetimidates as donors the (1–3)-linked disaccharides in very good yields [90]. Another interesting alternative is one-pot regioselective protection and following *O*-glycosylation with *O*-glycosyl trichloroacetimidates which, as shown in **Scheme 10** in the glycosylation of **10a** with donors **10b** and **10c** affording disaccharides **10d** and **10e**, respectively, makes use of this reactivity difference [91].

Separation of the target glycosides from the reaction mixture generally requires column chromatography purification. Alternatively, highly fluorinated compounds are readily separated from nonfluorinated compounds by a simple phase separation. Therefore, organic synthesis

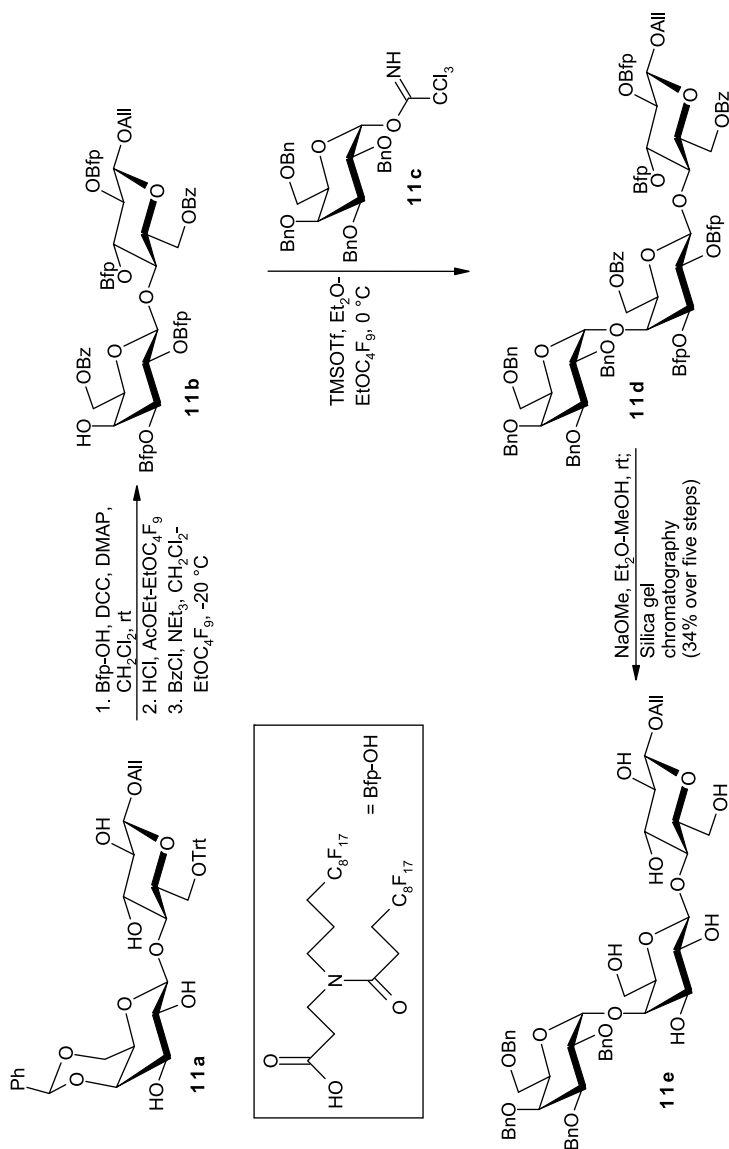


■ Scheme 10

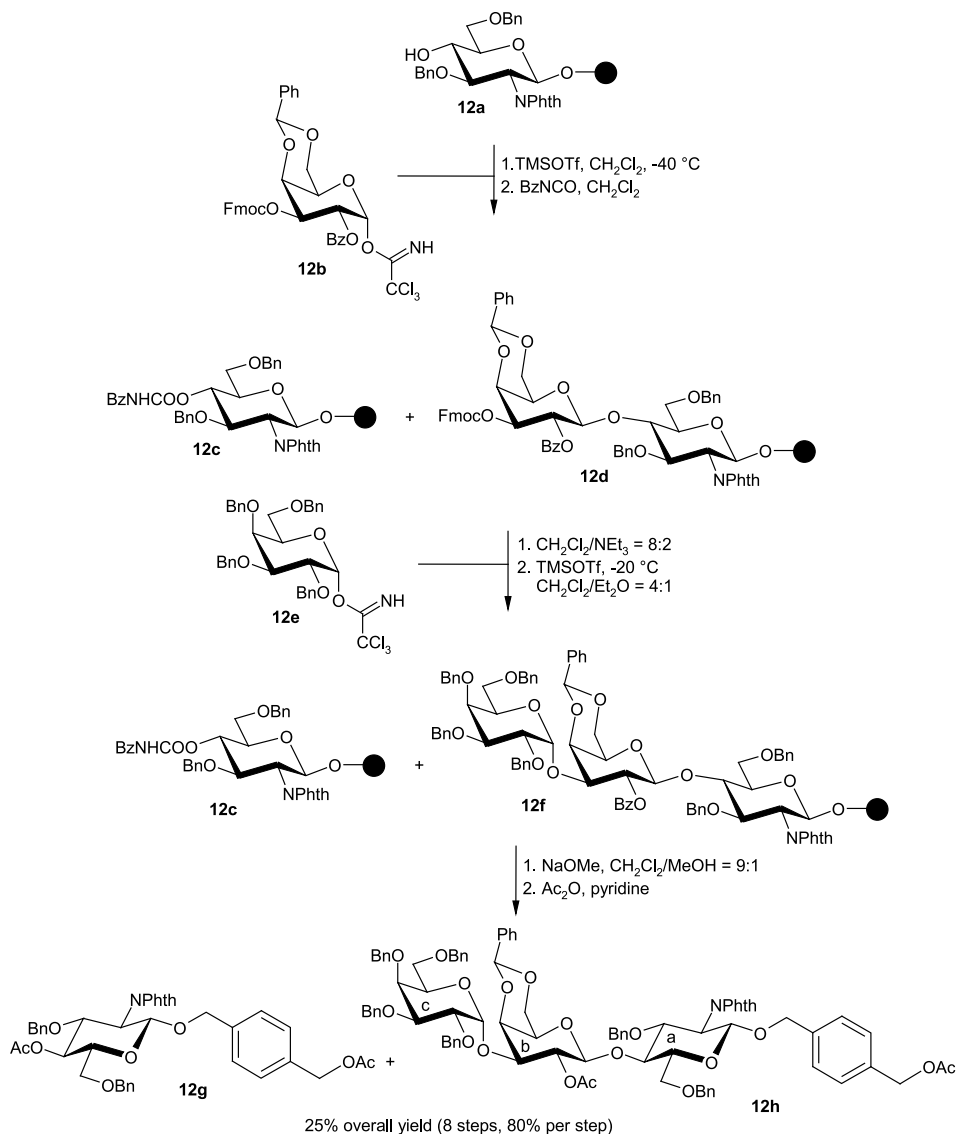
with substrates having fluorinated tags has become a valuable alternative to solid-phase synthesis (see below). This concept has been already applied to oligosaccharide synthesis [92]. On the basis of the novel fluorous acyl protecting group Bfp (**bis fluorous chain type propanoyl**) highly successful oligosaccharide syntheses could be performed [93], which were extended to the synthesis of globo-triasyl ceramide **11e** from lactoside **11a** as shown in ● Scheme 11 [94]. All fluorous intermediates (**11b** and **11d**) were extracted with FC-72 (perfluorohexane isomers) and an organic solvent (toluene or methanol) and were purified without silica gel chromatography. After removal of the Bfp groups by simple base-catalyzed methanolysis the pure allyl trisaccharide **11e** was obtained by only one silica gel column chromatography in 34% total yield after five steps (~81% per step).

## 4.2 Glycoside Synthesis on Polymer Supports

Successful solid-phase oligosaccharide syntheses (SPOS) have been developed by several research groups [95,96,97,98,99,100,101,102,103,104,105], which exhibit the inherent advantages over solution phase synthesis, such as (i) higher reaction yields due to the use



**Scheme 11**



■ Scheme 12

of excess building blocks, (ii) shorter reaction times for the completion of total syntheses, and (iii) convenient purification procedures by just washing the resin. In addition, methods to avoid undesired byproduct formation in the synthesis of the target molecules have been introduced [106,107,108,109], such as for instance capping procedures of unreacted intermediates (► Scheme 12) [108]. Low reactive acceptor **12a** after glycosylation with donor **12b** is capped with benzoyl isocyanate yielding **12c** and **12d**. Chain extension with **12e** (→ **12c** + **12f**) and cleavage led to readily separable **12g** and **12h**. So far, no generally accepted strategy has yet

appeared for the efficient construction of various complex oligosaccharides on polymer supports, thus limiting the commercialization of automated synthesizers. However, it seems that *O*-glycosyl trichloroacetimidates and the less reactive *O*-glycosyl phosphates have the potential to become the glycosyl donors of choice because the requirement of catalytic amounts of just one activator is a major advantage over the other glycosylation methods.

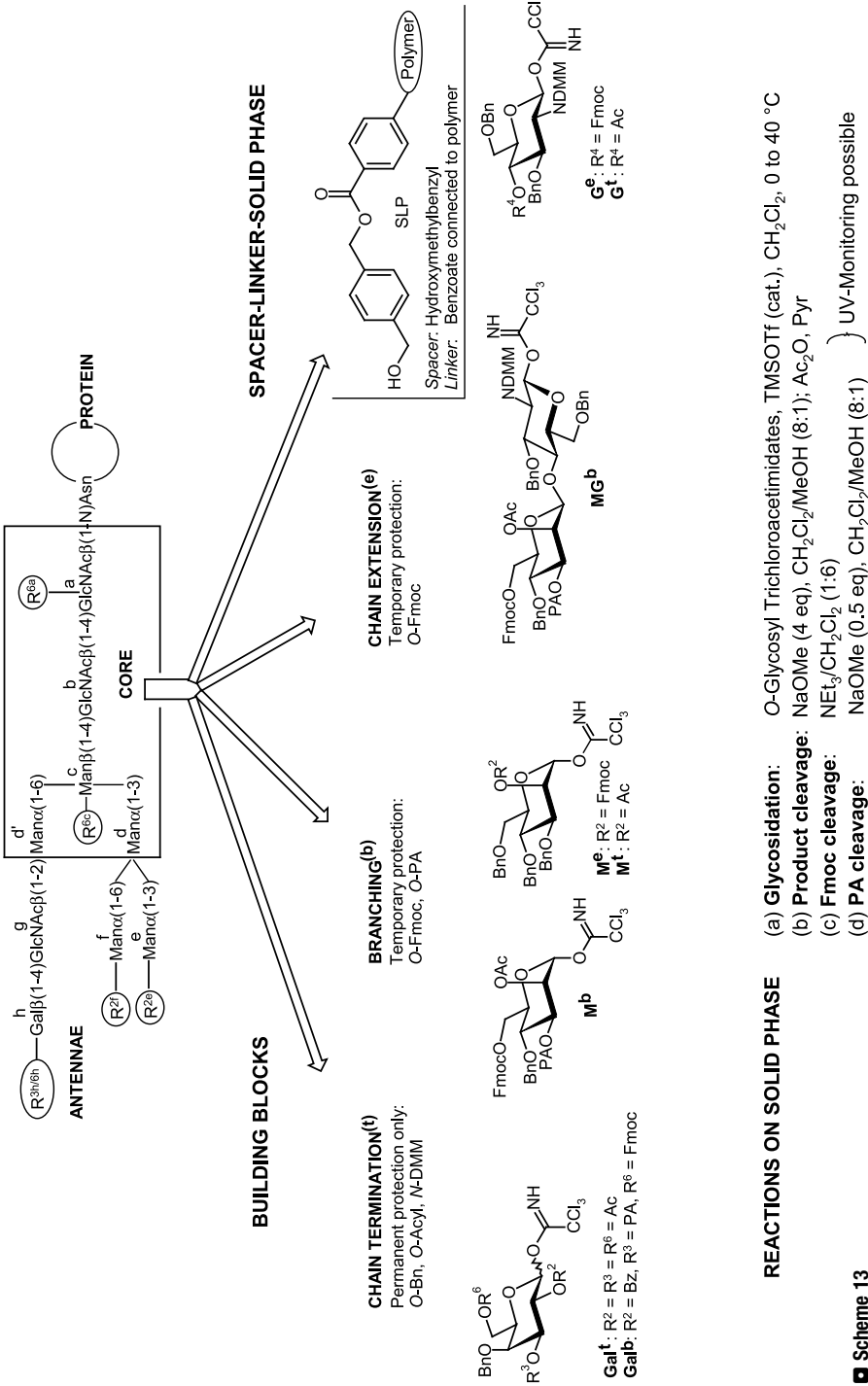
After various attempts of the Schmidt group with different linkers between solid support and the carbohydrate groups, such as for instance

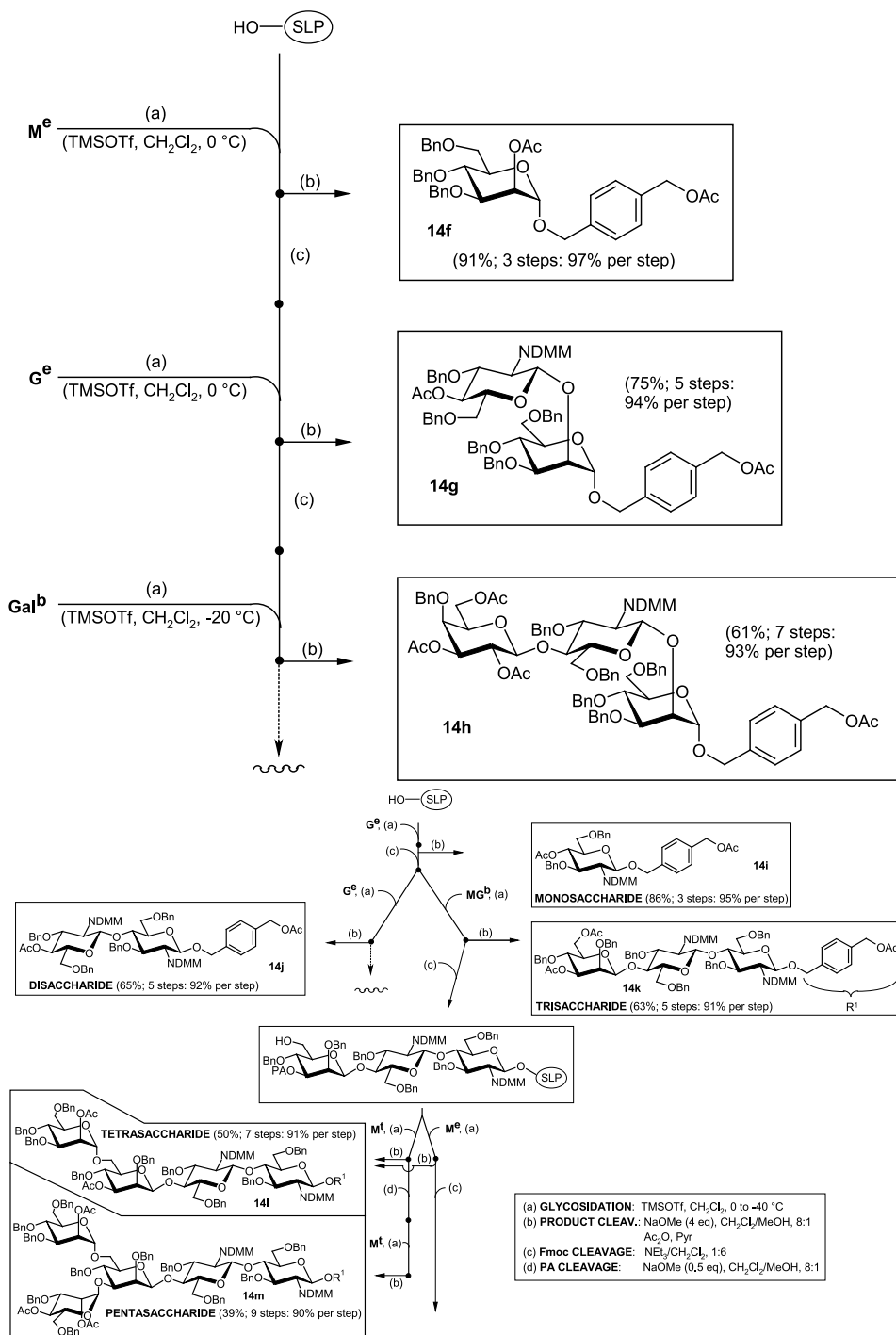
- thioglycosides and their cleavage by thiophilic reagents,
- silyl glycosides and their cleavage by fluorides,
- pentenyl-type glycosides and their cleavage by electrophilic reagents, and
- allyl-type glycosides and their cleavage by cross metathesis or by ring-closing metathesis, respectively [21,110,111],

finally the ester-based SPOS design was introduced which gave excellent results in chain extension and product cleavage from the resin [110,111]. However, to cope with complex oligosaccharide synthesis, besides the ester-linker and -spacer system, three types of glycosyl donor building blocks for controlled chain extension (suffix **e**), branching (suffix **b**), and chain termination (suffix **t**) are required. An efficient solution to these requirements for SPOS of a small library of *N*-glycans is exhibited in [Scheme 13](#) which shows the retrosynthesis to the required building blocks and the required reaction steps. A particularly important role played the selection of the *N*-protecting group for the glucosamine residue.

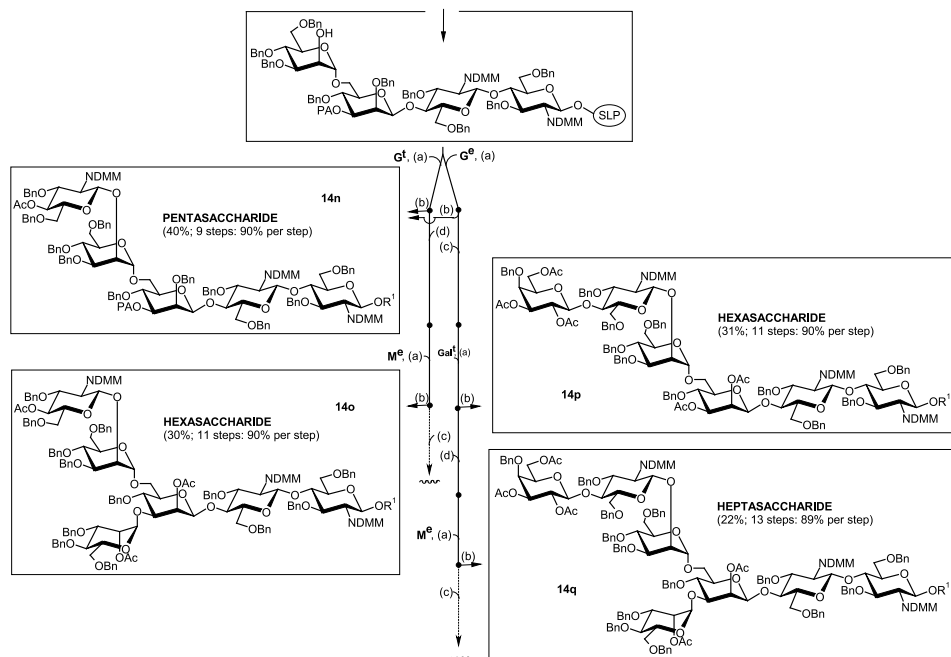
The ester-based SPOS methodology ([Scheme 13](#)) comprises (i) different types of esters, that is, the benzoate group as a linker and for chain termination and the Fmoc and PA (phenoxyacetyl) group as temporary protecting groups for chain extension and branching which can be chemoselectively cleaved (in the sequence Fmoc and then PA), (ii) the benzyl group for permanent *O*-protection and for the spacer between the anomeric center at the reducing end sugar, thus providing after final product cleavage from the resin a structurally defined target molecule, (iii) *O*-glycosyl trichloroacetimidates of type **e**, **b**, or **t** (for chain extension, branching, or termination) as powerful glycosyl donors, which can be readily activated by catalytic amounts of (Lewis) acid, and (iv) benzoic acid residues on the Merrifield resin for the linkage of the hydroxymethylbenzyl spacer. Hence, retrosynthesis of a typical *N*-glycan molecule containing the core pentasaccharide and some antennae leads to spacer-linker connected Merrifield resin SLP and to glycosyl donors **G<sup>e</sup>**, **G<sup>t</sup>**, **Gal<sup>t</sup>**, **Gal<sup>b</sup>**, **M<sup>b</sup>**, **M<sup>t</sup>**, and **MG<sup>b</sup>** which can be selectively converted into acceptors on resin (**e** and **b**-type donor building blocks). Thus, as indicated in [Scheme 13](#), only four simple procedures are required for successful SPOS: (a) glycosidation under TMSOTf catalysis; (b) product cleavage under transesterification conditions; (c) selective Fmoc cleavage under basic conditions; and (d) selective PA cleavage under milder transesterification conditions.

On the basis of this concept, as shown in [Scheme 14a–c](#), a small library of *N*-glycans (compounds **14a** to **14q**) was successfully synthesized: (i) The Merrifield resin as solid support exhibited excellent results during all stages of the assembly; (ii) all glycosylations, including those with *N*-DMM protected glycosyl donors, gave high yields; (iii) the methodology presented herein shows the desired versatility in terms of efficient chain extension and branching requiring only two standard (in one direction) orthogonal protecting







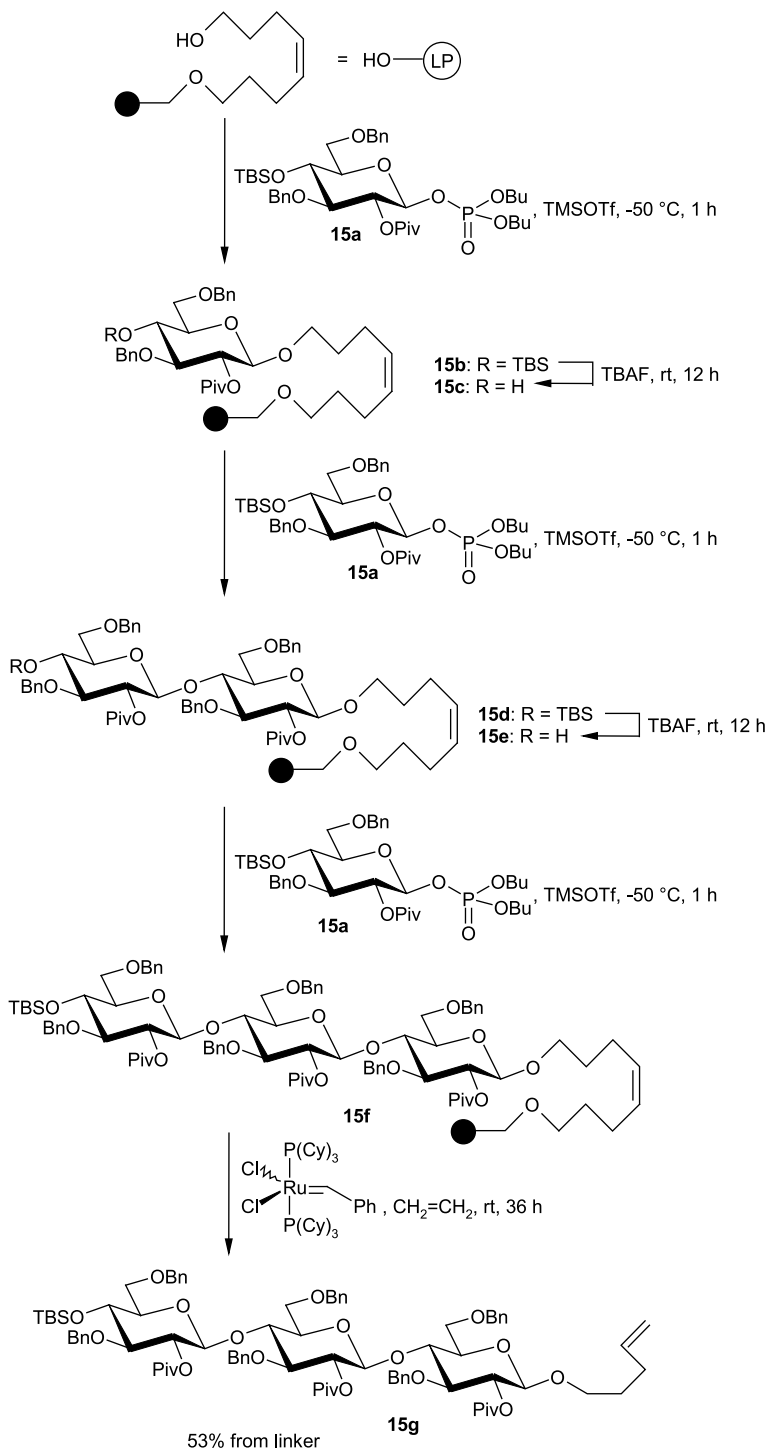


#### Scheme 14 (left page and above)

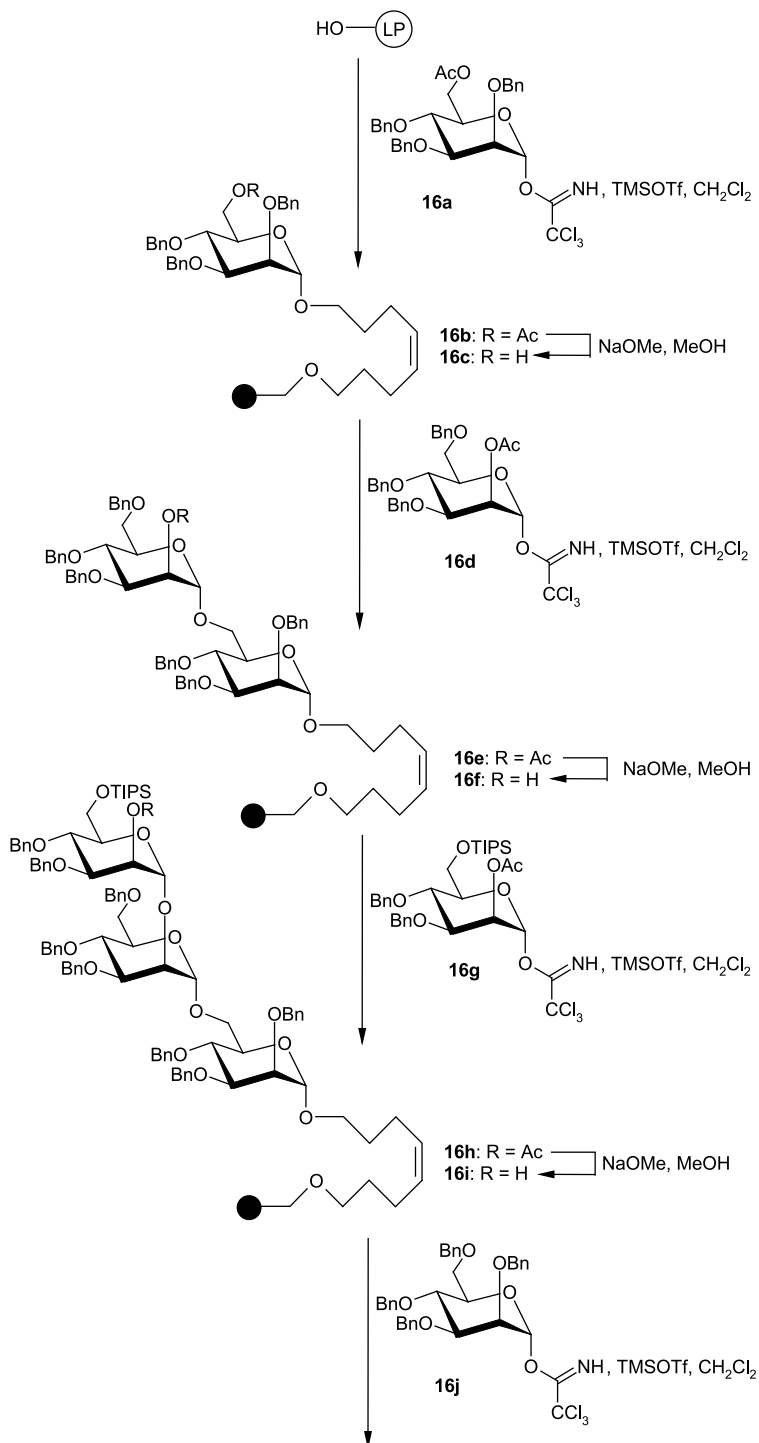
#### Solid phase synthesis of a small library of *N*-glycans: typical constituents

groups; (iv) cleavage of the product from the resin was feasible leading to stable 1-*O*-benzyl type products with only benzyl, DMM and, after acetylation, acetyl protection; (v) the crude products were already of high purity; therefore, standard silica gel chromatography and MPLC were sufficient for purification; (vi) yields of isolated products were high, ranging from 97% per step (after three steps) to 89% per step (after 13 steps) on solid-phase; (vii) the methodology is technically simple, thus lending itself available to automation.

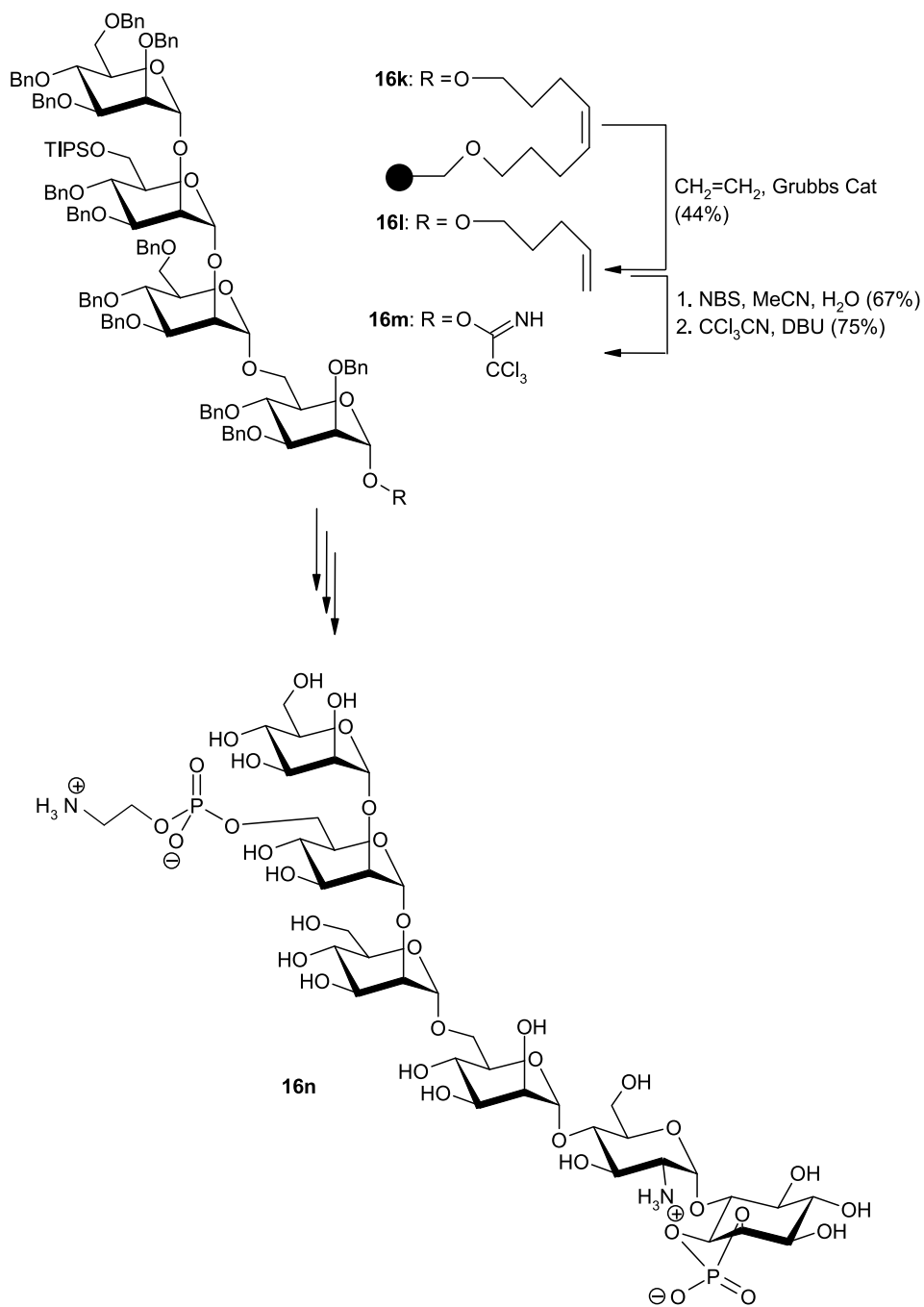
Very good SPOS results have also been obtained by the Seeberger group with *O*-glycosyl phosphates and *O*-glycosyl trichloroacetimidates, respectively, as glycosyl donors and (*Z*)-4-octene-1,8-diol as the linker between the Merrifield resin and the sugar residue. The linker was cleaved by cross-metathesis with ethylene, thus providing pentenyl glycosides as cleavage products (Schemes 15 and 16) [112]. **Scheme 15** shows the synthesis of pentenyl cellotriose **15g** with **15a** as the donor over seven steps with **15b–f** as intermediates in 53% overall yield. As a temporary protecting group in the glycosyl donor the TBS group in the 4-position was employed. The  $\beta$ -selectivity was supported by a 2-*O*-pivaloyl group. This method was also employed in an automated SPOS which was based on a modified peptide synthesizer and *O*-glycosyl trichloroacetimidates as glycosyl donors (**Scheme 16**) [96,113,114]. This way a glycosylphosphatidyl inositol (GPI) (**16n**) was synthesized which functions as a malarial toxin. Starting from three different *O*-glycosyl trichloroacetimidates (**16a, d, f**)



■ Scheme 15



Scheme 16



**Scheme 16**  
 (continued)

PNBP method  
Cac Detection

DisperseRed method  
NH<sub>2</sub>, OH Detection

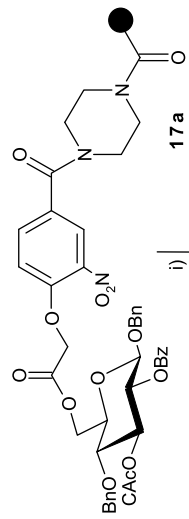
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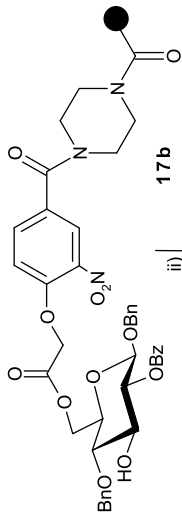
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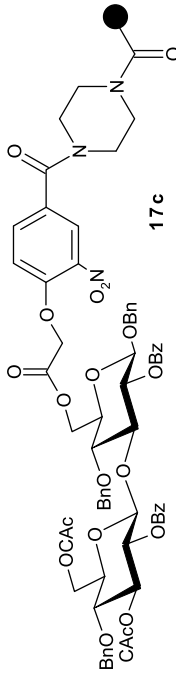
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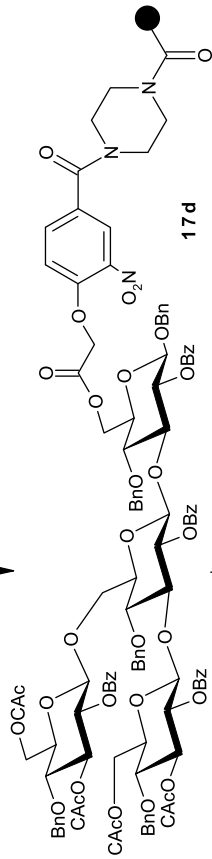
i)



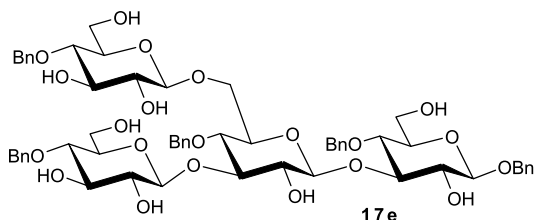
ii)



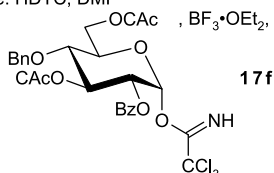
i), ii)



iii)



- i) (a) Capping:  $\text{Ac}_2\text{O}$ ,  $i\text{Pr}_2\text{NEt}$ ,  $\text{CH}_2\text{Cl}_2$   
 (b) CAc-Cleavage: HDTC, DMF  
 ii) Glycosylation:  $\text{BF}_3 \cdot \text{OEt}_2$ ,  $\text{CH}_2\text{Cl}_2$



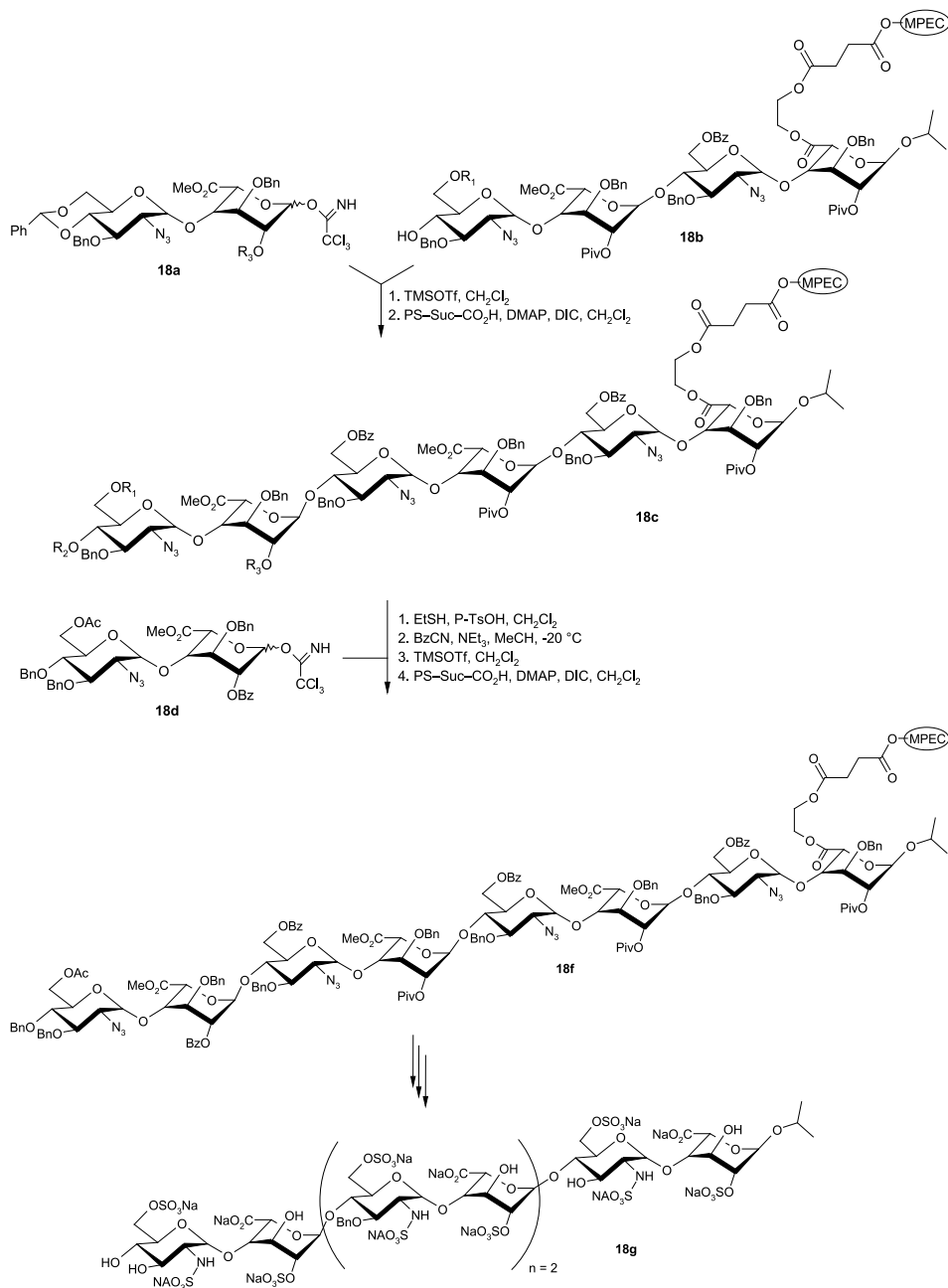
- iii) Cleavage from resin: NaOMe, MeOH, THF (30% overall yield)

### ■ Scheme 17 (continued)

having *O*-acetyl groups as temporary protection for chain extension and one per-*O*-benzylated *O*-mannopyranosyl trichloroacetimidate (**16j**) for chain termination a tetrasaccharide **16k** was obtained which was cleaved from the resin ( $\rightarrow$  **16l**) by cross metathesis. Transformation into a trichloroacetimidate **16m** and glycosylation of a pseudodisaccharide led after deprotection to the target molecule **16n**.

For the real-time monitoring of the glycosylation result by the Ito group sensitive color tests were introduced with *p*-nitrobenzylpyridine (PNBP), reacting with chloroacetyl (CAc) as the temporary protecting group under red color formation, and with cyanuric chloride-Disperse Red conjugate, which readily reacts with hydroxy or amino groups to give a red color on the resin [115]. This way, as shown in [Scheme 17](#), the repeating unit **17e** of the immuno-active oligosaccharide schizophyllan was synthesized based on a partly CAc-protected *O*-glycosyl trichloroacetimidate donor **17f** with **17a** as starting material and **17b** to **17d** as intermediates; the presence of the CAc groups could be readily monitored with PNBP and the presence or absence of hydroxy groups was monitored by the Disperse-Red method. As a linker to piperazine-modified TentaGel, a 2-nitrophenyloxyacetyl group [99] was employed that can be readily cleaved under transesterification conditions. This led also to loss of other ester protecting groups furnishing the target molecule **17f** in very good overall yield.

The synthesis of oligosaccharides on soluble supports has been further investigated as well. Particularly worth mentioning is the synthesis of heparin-like oligosaccharides on polyethylene glycol  $\omega$ -monomethyl ether (MPEG) resin with a succinoyl ester linker and *O*-glycosyl trichloroacetimidates as glycosyl donors [116,117]. A typical example is shown in [Scheme 18](#) [117]. After the glycosylation steps of **18a** with polymer bound **18b** and **18c** with **18d**, respectively, catalyzed by TMSOTf, a capping step was included in which unreacted MPEG-bound acceptor was captured onto the solid-phase of succinate-functionalized Merri-



■ Scheme 18

field resin (PS–Suc–CO<sub>2</sub>H) by a chemoselective ester formation ( $\rightarrow$  **18c** and **18f**). Alkaline hydrolysis released the octasaccharide from the resin and also all other ester groups were cleaved. By further known transformations [118] the octasaccharide fragment **18g**, containing the structural motif of the regular region of heparin, was obtained.

An interesting comparative study between solution phase synthesis and synthesis of the same oligosaccharides on MPEG as soluble support was carried out by the Furneaux group [119]. This study clearly reflected the incompatibility of MPEG as a soluble support with some common reagents, reaction conditions, and choice of standard protecting groups. Hence, the shortcomings associated with this support seem to outbalance the merits [119,120].

To avoid some limitations of PEGs, as for instance low loading, hyperbranched polyester such as Boltorn H40 and H50 have been successfully investigated in glycosylation reactions with *O*-glycosyl trichloroacetimidates [121]. For simple mono- and disaccharide synthesis optimization of the reaction conditions led to practically quantitative transformations.

## 5 Recent Applications of *O*-Glycosyl Trichloroacetimidates in Complex Oligosaccharide and Glycoconjugate Synthesis

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Several comprehensive reviews have been devoted to the use of *O*-glycosyl trichloroacetimidates in glycosylation reactions. In this overview, so far the basic principles of the glycosylation methods, the strengths of the *trichloroacetimidate method*, differences to other methods, and methodological variations have been discussed. In this chapter recent applications of this method in complex glycoconjugate synthesis will be highlighted.

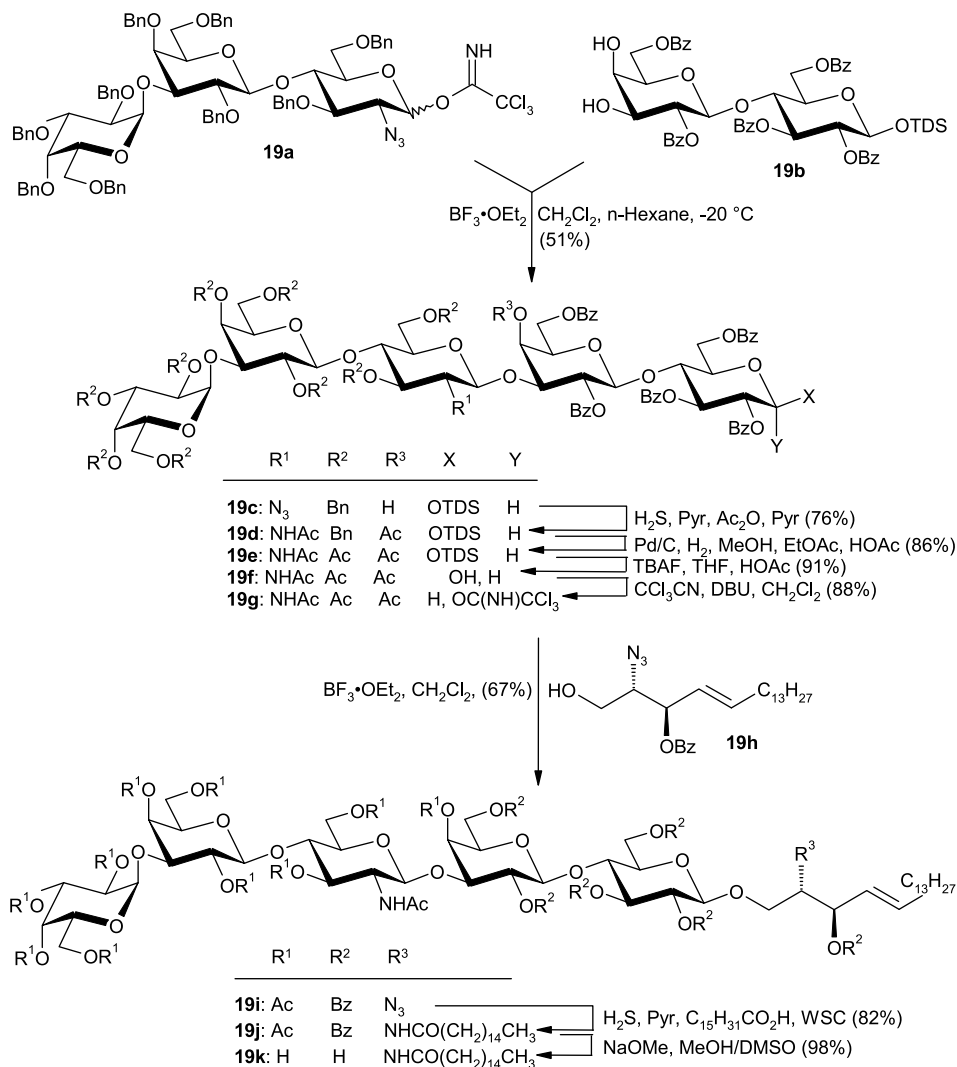
### 5.1 Glycolipids

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Glycosphingolipid synthesis has remained a target of great interest because of the biological importance of these compounds. Assembly of the sugar residues with *O*-glycosyl trichloroacetimidates as donors and attachment of the ceramide residue via the azidosphingosine *glycosylation procedure* [122,123] has become the method of choice. On the basis of this approach, aminodeoxy analogs of globotriosyl ceramide [124], globo- and isoglobotriosides bearing cinnamoylphenyl tags [125], and a quite practical globotriose synthesis [126], which is essentially based on *O*-acyl protection, have been carried out. An efficient glycosylation protocol for the attachment of an  $\alpha$ -linked galactosamine residue for asialo GM2 synthesis has been reported [127]. A novel ether-bridged GM3 lactone analog has been successfully prepared and used in antibody-based cancer therapy studies [128]. Also ganglioside GD3 was synthesized [129]; comparison with bovine-brain derived GD3 showed that the effects in GD3-triggered uncoupling of mitochondrial respiration and induction of apoptosis in oligodendrocytes are very similar. Also ganglioside mimics for binding studies with myelin-associated glycoprotein were prepared [130].

The *lacto*- and *neolacto*-series of glycosphingolipids also attracted further attention. The synthesis of the lacto-*N*-neotetraose and lacto-*N*-tetraose building blocks has been improved by using the *N*-dimethylmaleoyl protecting group [131]. A total synthesis of the natural antigen **19k** involved in a hyperacute rejection response to xenotransplants has been carried out as

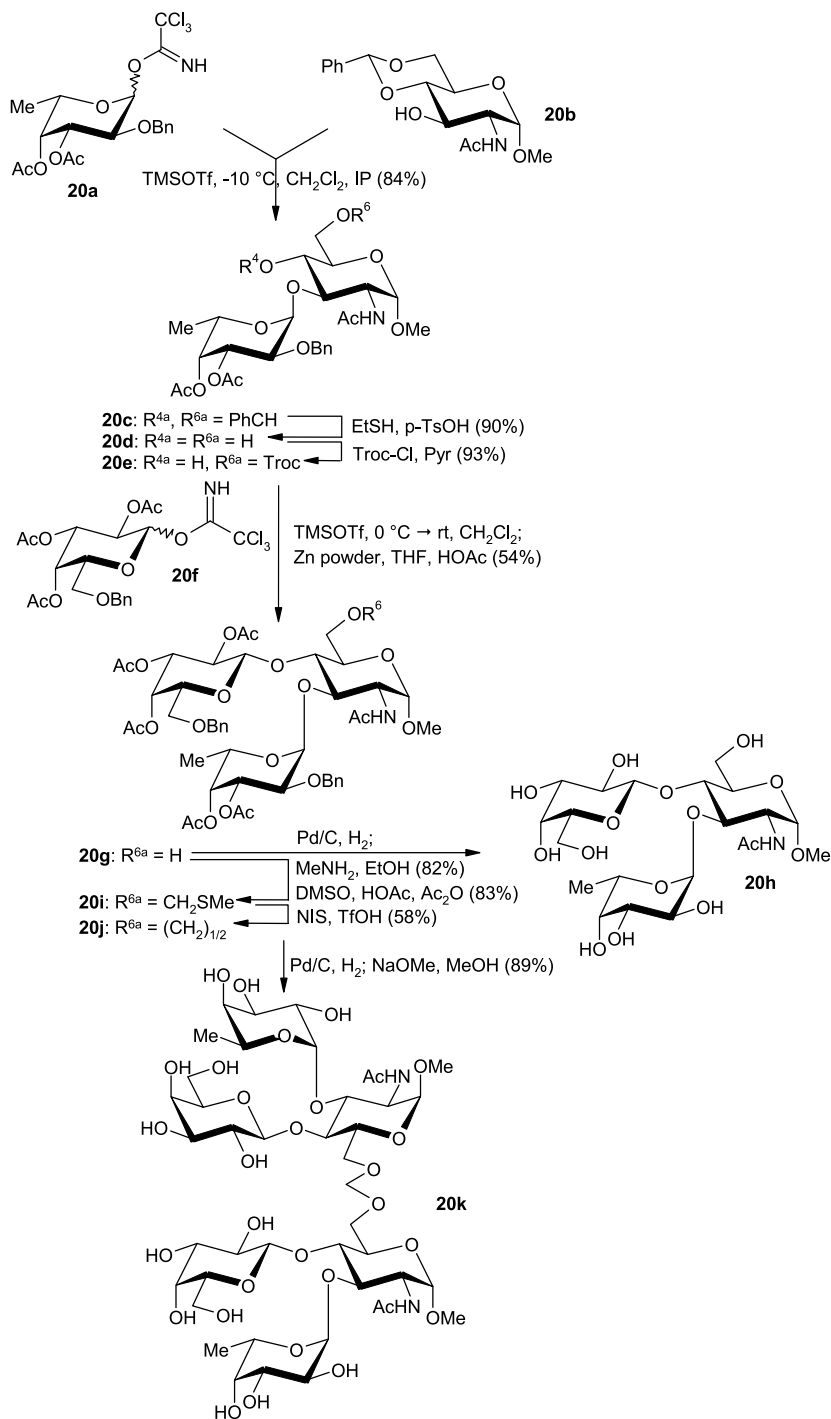




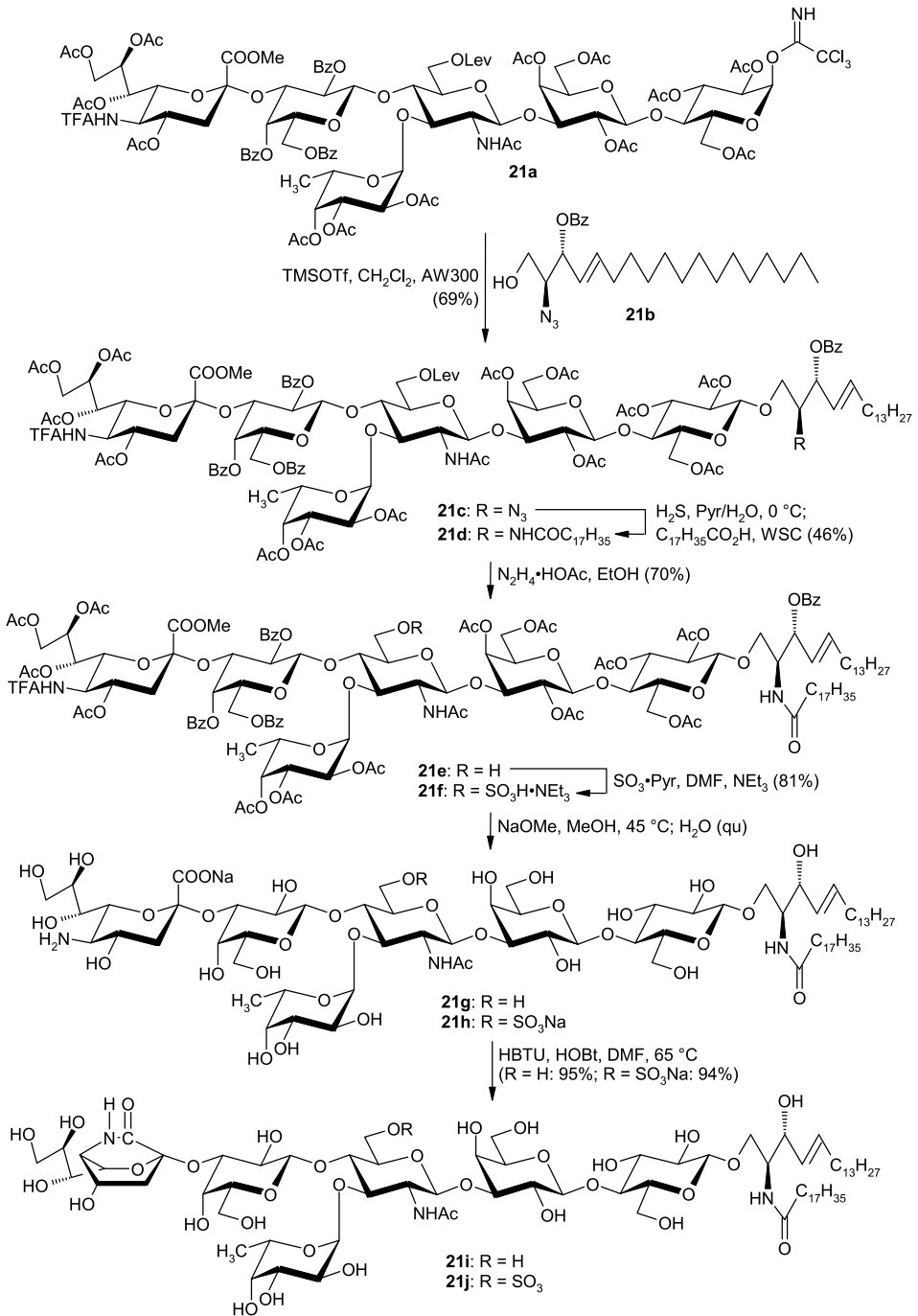
Scheme 19

shown in [Scheme 19](#) [132]. Glycosyl donor **19a**, also obtained via the *trichloroacetimidate method*, gave with acceptor **19b** pentasaccharide **19c**. Standard transformation via **19d**, **19e**, and **19f** led to pentasaccharide donor **19g**. Application of the *azidosphingosine glycosylation procedure* with **19h** as acceptor furnished **19i** which was transformed via **19j** into the target molecule **19k**.

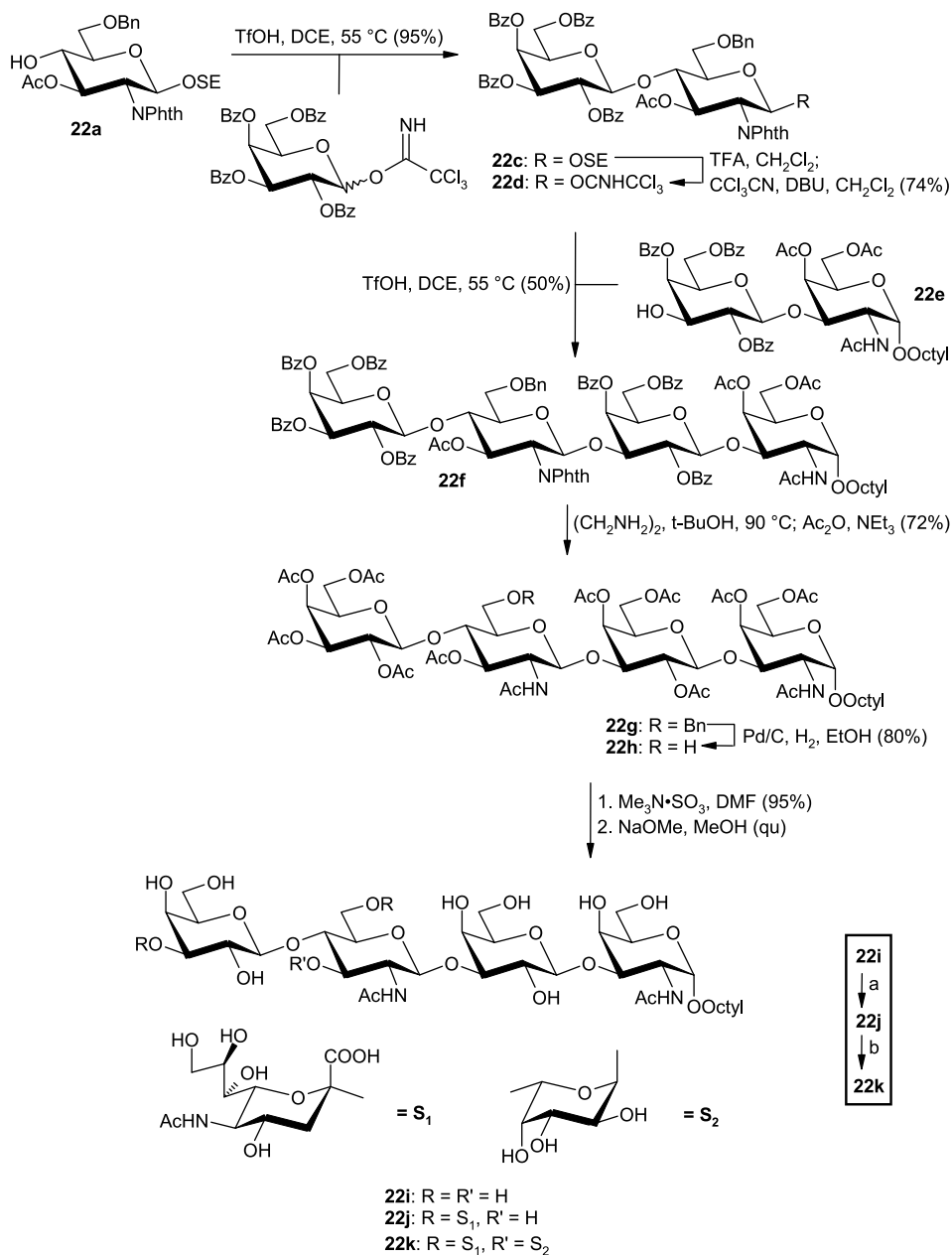
Further, for microdomain formation studies fluorescence labeled sialyl Lewis X [133], for cluster effect studies dimeric sialyl Lewis X [134], and for carbohydrate-carbohydrate recognition studies a dimer of Lewis X [135] were synthesized ([Scheme 20](#), **20k**). To this aim,



■ Scheme 20



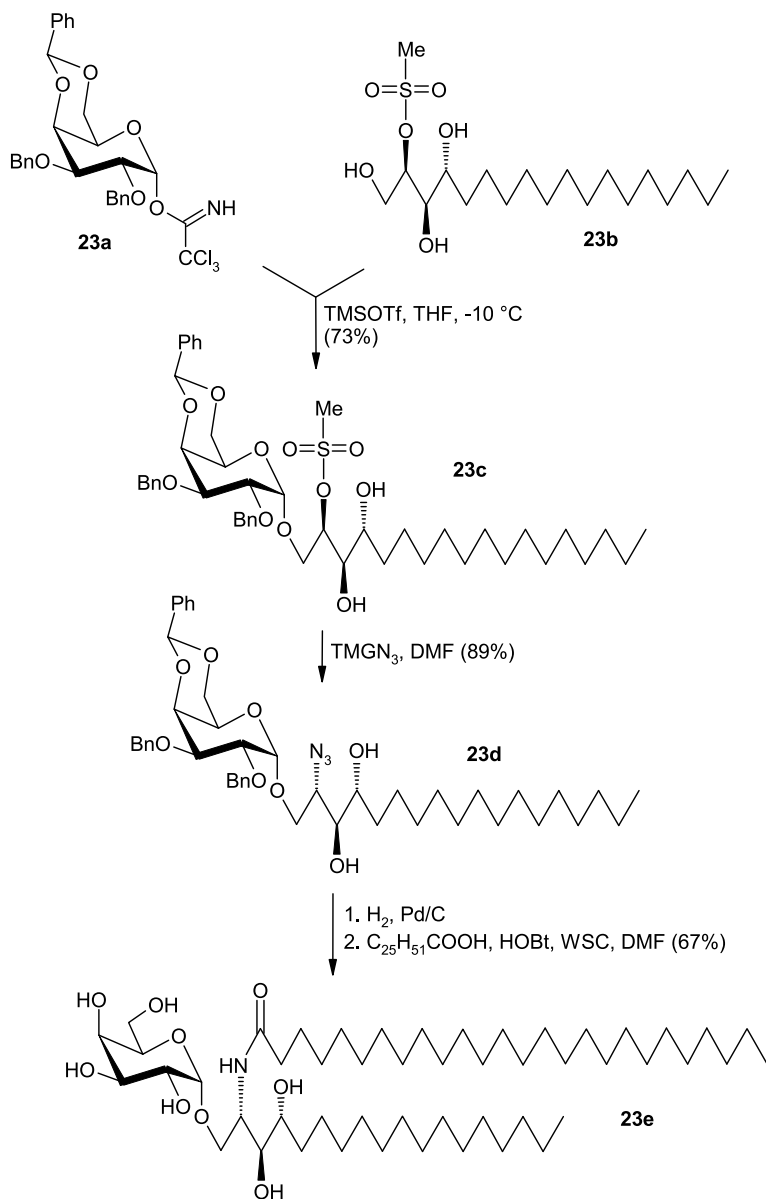
■ Scheme 21



■ Scheme 22

Reagents and conditions: (a) SAT(N), CMP-NANA, MOPS (pH 7.4), Triton S4, BSA, H<sub>2</sub>O, CIP, 55%; (b) FucT(V), GDP-Fuc, MnCl<sub>2</sub>, DTT, Tris-HCl (pH 7.4), qu

from building blocks **20a**, **20b**, and **20f** via intermediates **20c**, **d**, **e** protected Lewis X intermediate **20g** was obtained which gave monomer **20h**. For the dimerization, via **20i**, **j**, the target molecule **20k** was obtained. The synthesis of sialyl Lewis X containing glycolipids with different core structures [136] exhibited the importance of the spacer in selectin-binding



■ Scheme 23

studies [137]. Sulfated sialyl Lewis X variants, containing a lactamized sialyl residue, were obtained by the Kiso-Ishida group (● *Scheme 21*) [138]; these compounds were found to be potent antigenic determinants. Following the standard procedure **21a** and **21b** gave **21c**, which was transformed via **21d–h** into lactamized target molecules **21i** and **21j**. Also chemoenzymatic synthesis was successfully engaged in the synthesis of sulfated sialyl Lewis X connected to a core 1 mucin (T antigen) structure (● *Scheme 22*) [139]. From **22a, b** disaccharide **22c** was obtained, which was transformed into donor **22d** giving with acceptor **22e** tetrasaccharide **22f**. Partial deprotection ( $\rightarrow$  **22g, h**), regioselective sulfation and final deprotection gave **22i**; enzymatic sialylation and fucosylation led to target molecules **22j** and **22k**.

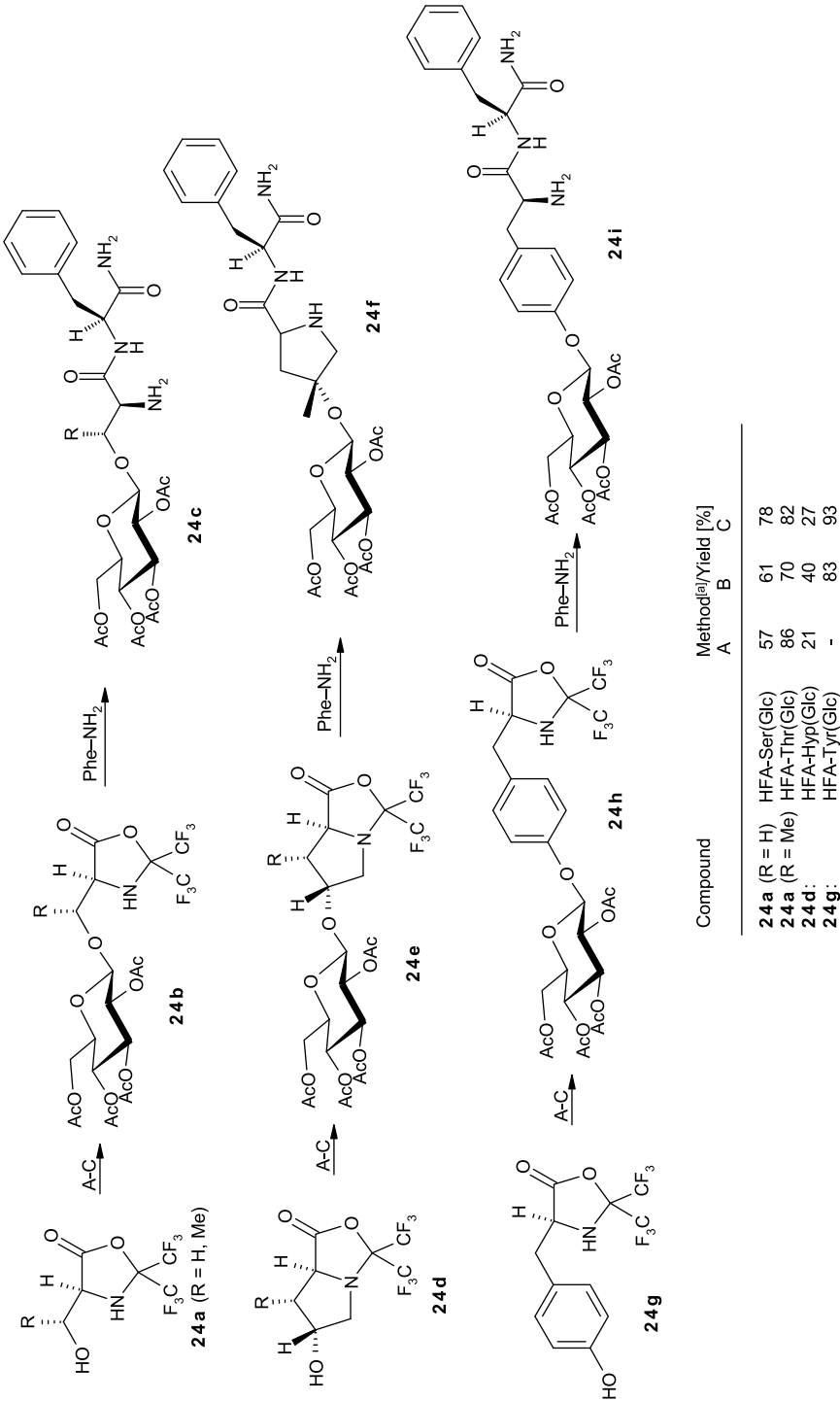
Some  $\alpha$ -galactosyl ceramides with a phytosphingosine residue, isolated from the marine sponge *Agelas mauritianus*, were found to possess strong in vivo activities against several murine tumor cells [140,141]. The synthesis of analogs exhibited that compound **23e** (● *Scheme 23*) is a potent candidate for clinical trials [142]; **23e** was also found to have immunostimulatory activity [143]. These findings promoted a great demand for this compound, therefore, several syntheses of **23e** and analogs have been reported [144]. The Schmidt group reported an efficient synthesis which is based on galactosyl trichloroacetimidate **23a** as donor and phytosphingosine derivative **23b** as acceptor which led to the  $\alpha$ -linked intermediate **23c**. Azide introduction ( $\rightarrow$  **23d**), hydrogenolysis of protecting groups and *N*-acylation furnished target molecule **23e** very efficiently.

Lipid-linked T and T<sub>n</sub> antigens [145] and glycosidated phosphoglycerolipids [146] were also synthesized based on *O*-glycosyl trichloroacetimidates donors. In a comparative study glucopyranosylation of methyl  $\omega$ -hydroxy-hexadecanoate with different glucosyl donors was carried out which demonstrated the advantageous properties of the trichloroacetimidate donor; this way the desired  $\beta$ -linked target molecule for biological studies was readily obtained [147]. 3,4,5-Tris(alkyloxy)benzyl glycosides were prepared with standard *O*-glycosyl trichloroacetimidates as donors [148]. The three lipid chains permitted the immobilization of these compounds on a hydrophobic surface and lectin affinity studies by surface plasmon resonance.

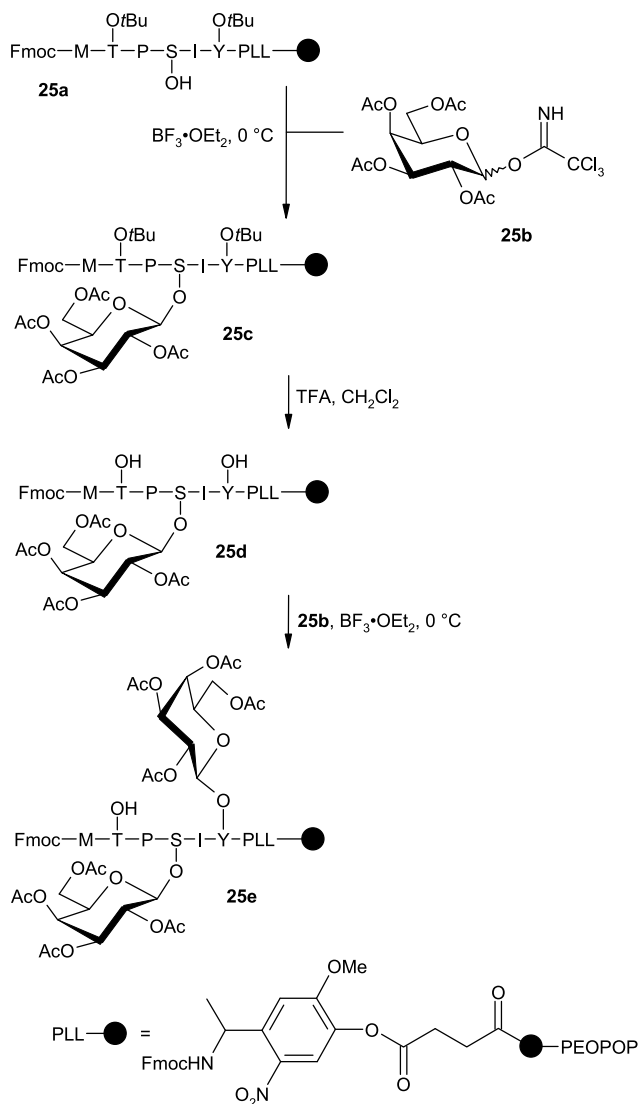
## 5.2 Glycosyl Amino Acids and Glycopeptides

The availability of *O*- or *N*-glycosyl amino acids as building blocks for glycopeptide or eventually glycoprotein synthesis is of great importance. Therefore, various synthetic methods have been reported [149,150]. Direct *O*-glycosylations of serine and threonine derivatives with *O*-glycosyl trichloroacetimidates as donors have been reported [151,152]. The straightforward hexafluoroacetone *O,N*-protection of Ser, Thr, Pyp, and Tyr gave generally the best results with trichloroacetimidate donors as shown in ● *Scheme 24* [153] on glucosylation of **24a, d, g** with per-*O*-acetylated glucopyranosyl donors affording **24b, e, h**. As this protection also leads to an activated carboxylate group, protecting group cleavage and peptide chain extension can be combined furnishing dipeptides **24c, f, i**.

The presence of the Glc $\alpha$ (1–2)Gal $\beta$ (1–O)Hyl moiety in collagen was reason to synthesize this building block [154]. Replacement of the  $\omega$ -amino group of Hyl by an azido group and protection of the  $\alpha$ -amino group by the Z group and the carboxylate group by a *t*-butyl group led cleanly to the target molecule after two glycosylation steps. Glycosylation of Fmoc-protected Ser, Hse, and Thr with T<sub>N</sub>, T, and ST-derived glycosyl donors were also success-



[a] Method A: Helferich variant of the Koenigs-Knorr reaction; method B: Procedure according to Paulsen; method C: Procedure according to Schmidt

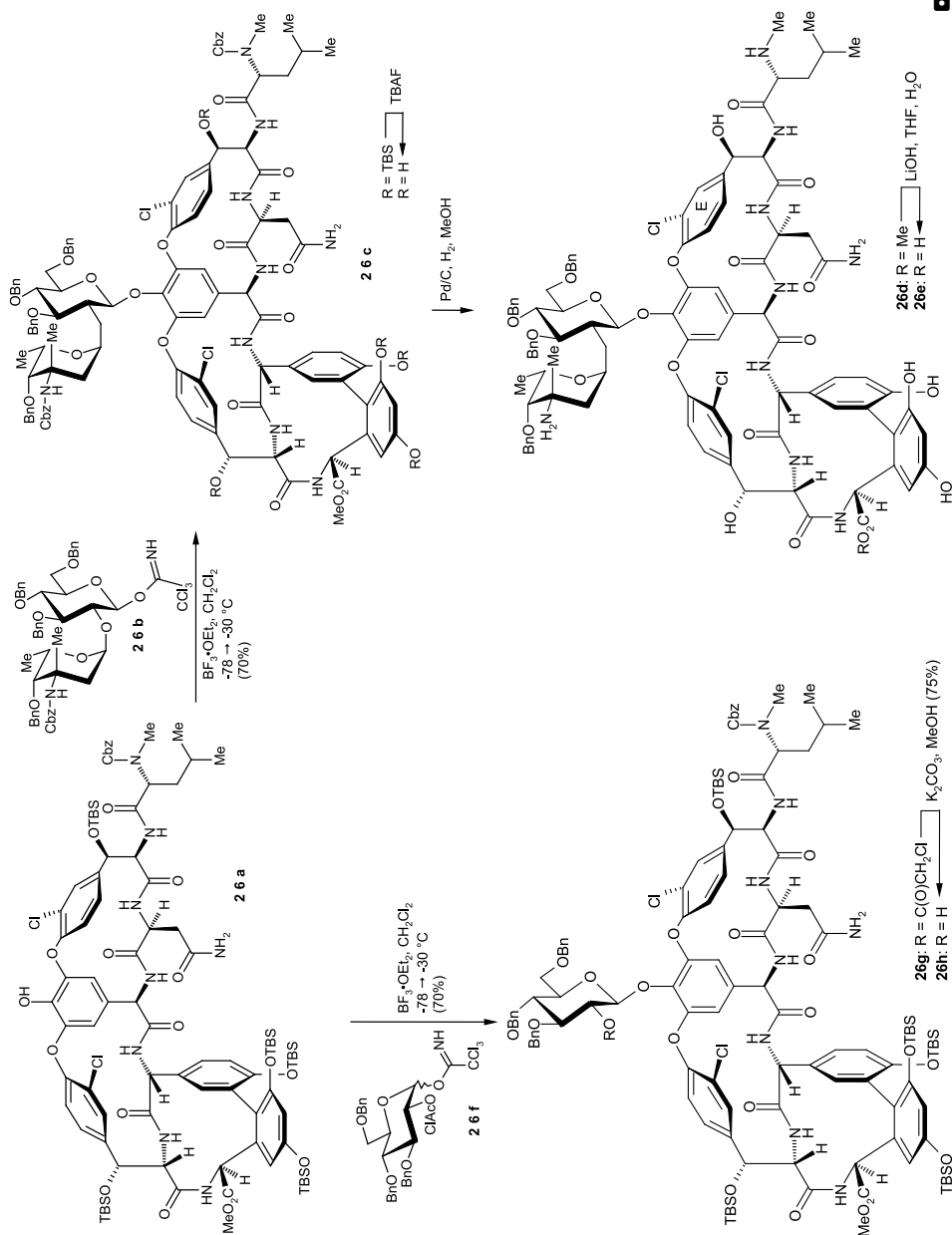


■ Scheme 25

fully carried out, partly by following known procedures [155,156]. Also an important Gal $\beta$  (1–4)GlcNAc $\beta$ (1–3)-L-Fuc moiety was prepared, which is part of *O*-linked chains of human clotting factor IX [157].

More demanding is direct glycosylation of peptides, which was so far not very successful because of solubility problems and side reactions with the functional groups [158,159,160]. The Meldal group expected that a solid-phase approach would suffer less from these drawbacks, therefore, they undertook a study with Ser, Thr, and Tyr containing hexapeptides, hav-

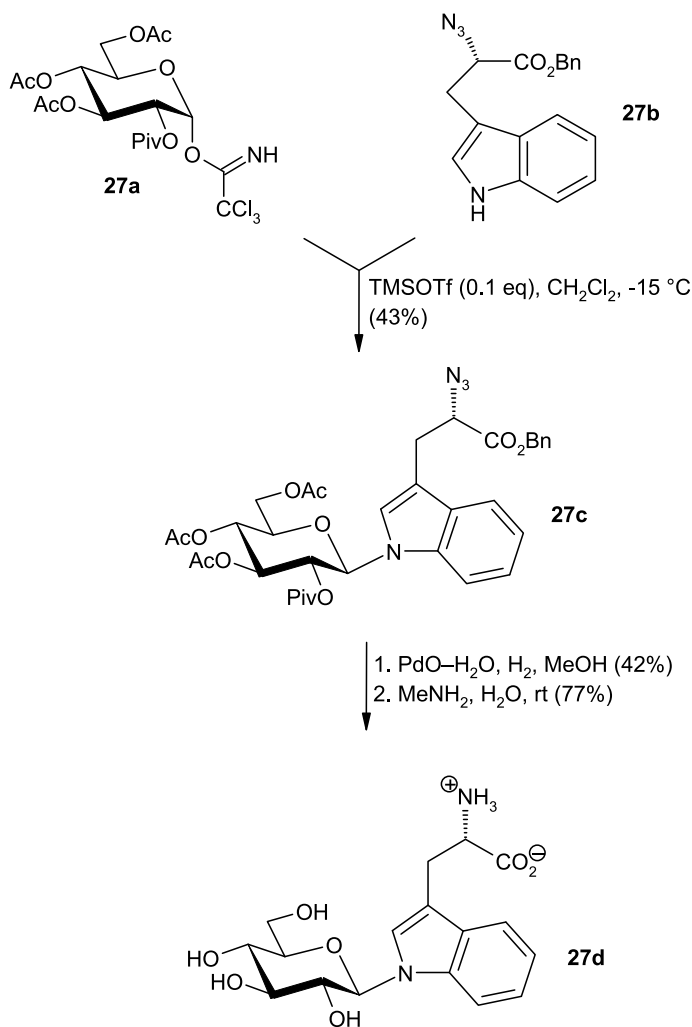




Scheme 26

ing no other functional side chains (!), leading to direct reaction in the order Tyr > Ser > Thr, as shown in **Scheme 25** [161]. The peptide was linked via a photolabile linker (PLL) to the resin ( $\rightarrow$  **25a**). Galactosylation with **25b** ( $\rightarrow$  **25c**), then *O*-deprotection ( $\rightarrow$  **25d**), and galactosylation with **25b** gave **25e**; threonine did not undergo reaction in this case.

A particularly interesting case is the glycosylation of the vancomycin aglycone to achieve the vancomycin total synthesis as successfully investigated by the Nicolaou group [162,163]. They obtained very good results on glycosylation of aglycone **26a** with glycosyl donors **26b** and **26g** affording intermediates **26c** and **26g** (**Scheme 26**), which were further transformed, thus furnishing via **26d** target molecule **26e**. Similarly, vancomycin analogs were prepared by



■ Scheme 27

the Wong group [164]; biological studies exhibited growth inhibition of vancomycin sensitive bacteria by several of these compounds.

*N*-Glycopeptides are generally obtained by treatment of reducing sugars with ammonium bicarbonate [165] or reduction of glycosyl azides [166] with activated aspartic acid. This way a heptasaccharide synthesized with *O*-glycosyl trichloroacetimidates as donors was linked to Asp [167,168,169,170]; further work along these lines was carried out [171]. Direct formation of the *N*-glycosidic linkage with Asn by chemical glycosylation is still an important task. An interesting method was investigated by Ito et al. [172] based on hydroxyamination of the Asp side chain and then glycosylation with a glycosyl donor. The results show, for standard glycosyl donors direct *N*-glycosylation is possible, however so far yields and anomeric stereoselection are not yet satisfactory.

A number of *C*- and *N*-linked tryptophan glycoconjugates were discovered as constituents of natural products [173,174,175,176]. Also tryptophan *N*-glucoside **27d** has been detected for which Unverzagt et al. [177] reported a successful synthesis (🔍 *Scheme 27*). With the help of 2-*O*-pivaloyl protection in glycosyl donor **27a** the undesired acetal formation could be overcome; thus with acceptor **27b** *N*-glucoside **27c** could be obtained and then transformed into target molecule **27d**.

### 5.3 Nucleoside and Nucleotide Glycosidation

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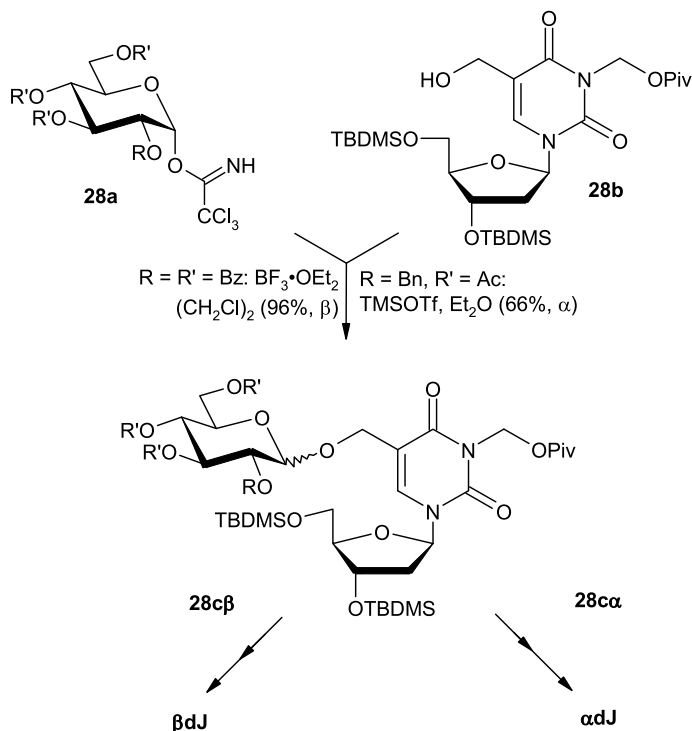
The presence of carbohydrate moieties in biomolecules influences many biological functions, thus also modulation of the functions of the aglycone. Therefore, studies have been undertaken to glycosylate nucleosides [178] and nucleotides [179]. Particularly interesting is the direct glycosylation of CPG-bound oligo-deoxynucleotides containing pyrimidine residues leading to reaction preferentially at the 5'-end.

The occurrence at 5-( $\beta$ -D-glucopyranosyloxymethyl)-2'-deoxyuridine ( $\beta$ dJ) in DNA, for instance of *Trypanosoma brucei* [180,181,182], led to the development of an efficient route for the synthesis of  $\beta$ dJ (🔍 *Scheme 28*) and its phosphoramidite as building blocks for DNA synthesis [183]. The synthesis was based on glycosyl donor **28a** ( $R=R'=Bz$ ) which gave with acceptor **28b** intermediate **28c $\beta$**  and after deprotection  $\beta$ dJ. Similarly, from **28a** ( $R=Bn$ ,  $R'=Ac$ ) and **28b**  $\alpha$ -linked **28c $\alpha$**  was obtained which led to  $\alpha$ dJ.

### 5.4 Synthesis of Glycosaminoglycans

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Glycosaminoglycans (GAGs) are bioactive oligosaccharides that are highly functionalized, linear, and anionically charged. Because of their complexity their chemical synthesis is a demanding task. The chondroitin sulfates (CSs) are a member of the GAG family. They are found in the extracellular matrix of connective tissues at the surface of many cells and in intracellular secretory granules [184,185]. They are linear heteroglycans built mainly from D-GlcA and GalNAc dimers which are  $\beta$ (1–3)-linked; chain extension employs a  $\beta$ (1–4)-linkage. In addition, the sugar residues are sulfated at various positions ( $\rightarrow$  A- E- and K-type CSs). Stereocontrolled shark cartilage CS (D-type) synthesis has been successfully carried out by Jacquinet et al. (🔍 *Scheme 29*) [186,187]. The GlcA building block **29a** possesses as temporary protecting group for chain extension at 4-*O* the chloroacetyl group, and for sulfation at 2-*O* the benzoyl

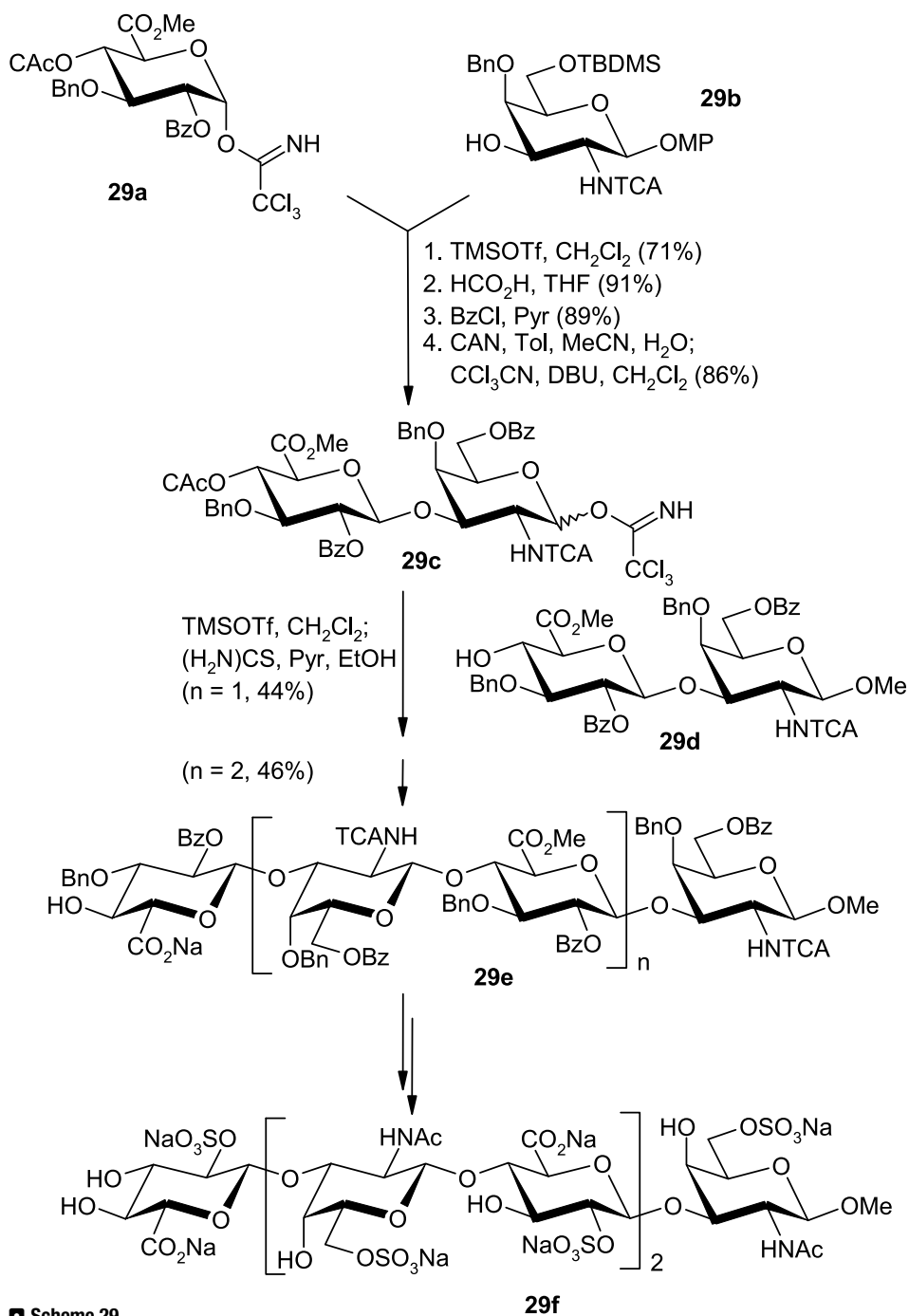


■ Scheme 28

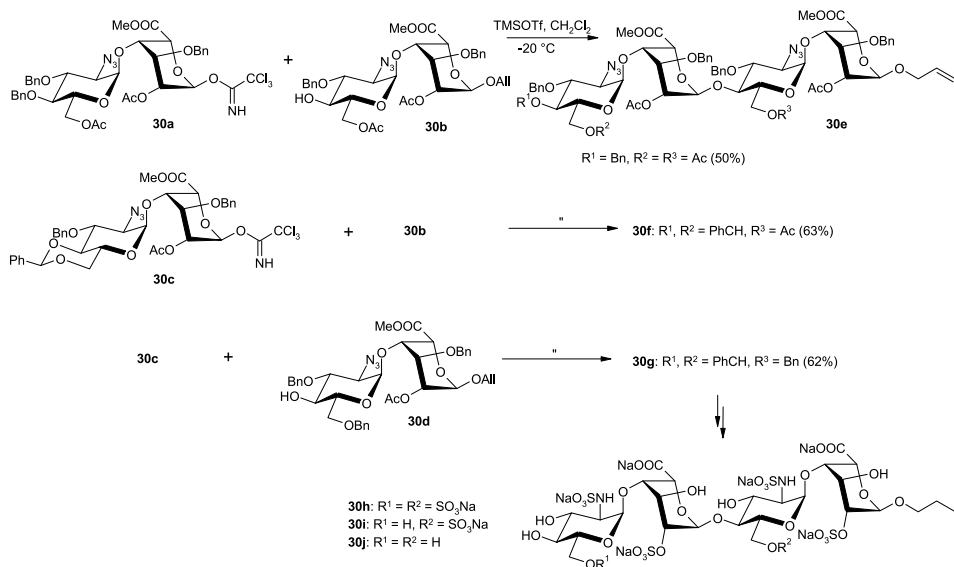
group. Similarly, the galactosamine residue **29b** carries for chain extension at 1-*O* an MP group and for sulfation at *O*-6 the TBDMS group; the amino group is protected by the trichloroacetyl group. Glycosylation and further transformations furnish donor **29c** which on chain extension with **29d** led to the tetrasaccharide **29e** ( $n = 1$ ) and higher oligomers which could be deprotected to yield, for instance, target molecule **29f**. On the basis of a similar strategy E-type CS was obtained which was found to stimulate neuronal outgrowth [188]. A hexameric E-type CS was also synthesized by Tamura et al. [189]; in this synthetic approach the amino group of the galactosamine residue was replaced by an azido group.

Hyaluronic acids possess a repeating unit consisting of GlcA  $\beta(1-3)$ -linked to GlcNAc; chain extension of this dimer employs a  $\beta(1-4)$ -linkage. The dimeric unit has been successfully synthesized based on GlcA trichloroacetimidate as the donor [190]. A trimer consisting of two GlcNAc residues and one GlcA residue was also successfully obtained [191]. In this synthesis design the carboxylate function was introduced at a late stage, after construction of the trisaccharide backbone.

Fibroblast growth factors (FGFs) display high binding affinities for GAGs [185,192,193,194,195] such as heparan sulfate (HS) and heparin. Heparin is a linear, heterogeneously sulfated, anionic polysaccharide composed of alternating L-iduronic acid and D-glucosamine residues which is found in almost all animal tissues. The biological roles of several members of the FGFs



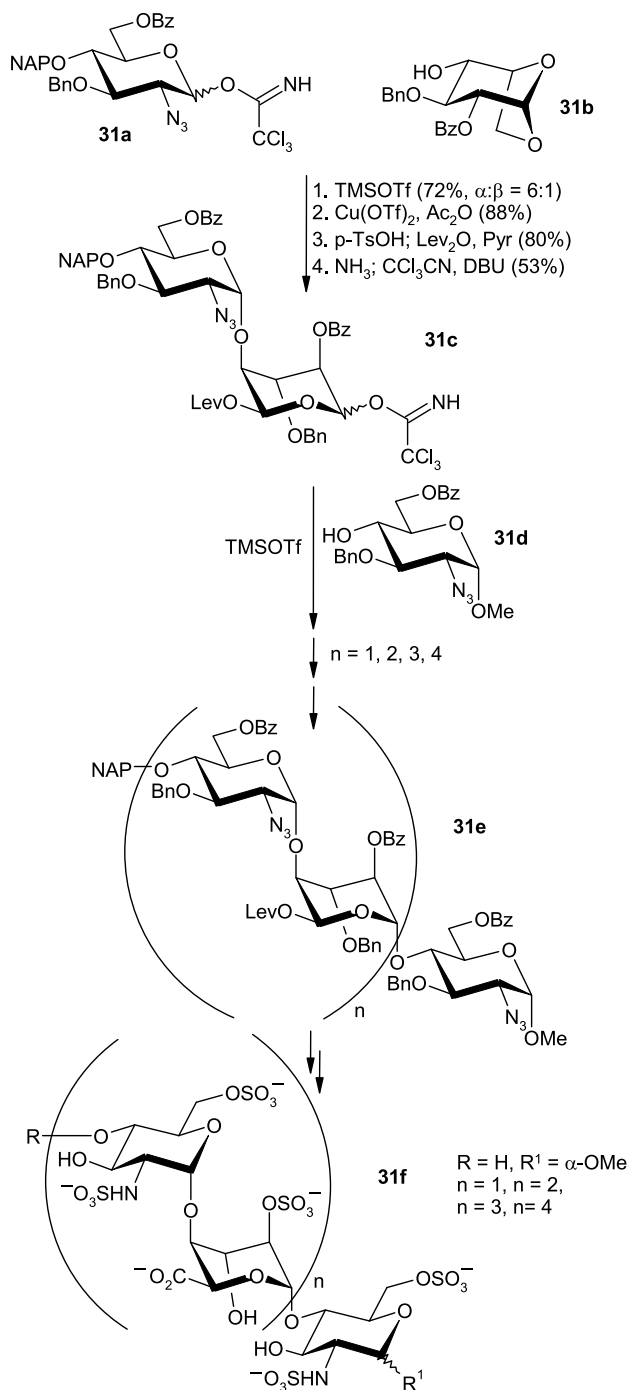
Scheme 29



### Scheme 30


have been extensively investigated [196,197], which also called for synthetic endeavors; they are still ongoing. The synthesis of a highly sulfated tetrasaccharide has been reported by Lay et al. (Scheme 30) [198]. It is based on a versatile  $\alpha(1-4)$ -linked GalN<sub>3</sub>-IdoA disaccharide building block from which four differently protected disaccharide acceptors and donors (30a–d) are obtained, thus leading to 30e, f, g. The deprotection scheme is shown for 30g, leading to target molecules 30h, i, j. An interesting study was also reported by Bonnaffé et al. [199]; for successful glycosylation a remote *N*-acetyl group had to be replaced by an azido group. Tri-, penta-, hepta-, and nonasaccharides of heparin have been synthesized by Hung et al. (Scheme 31) [200]. In this synthetic approach, the carboxylate function is again introduced at a late stage by oxidation of the hydroxymethyl group of the idose moiety. Glycosylation of Ido derivative 31b with donor 31a led via further transformations to disaccharide donor 31c which was chain extended with glucosamine acceptor 31d to yield 31e with  $n = 1$ . Further chain extension is based on 31c having naphthylmethyl (NAP) temporary protection; chemoselective NAP cleavage is readily performed with DDQ. Thus via the higher oligomers of 31e after deprotection target molecules 31f ( $n = 1, 2, 3, 4$ ) are obtained. Heparin-like oligosaccharide syntheses were also reported by Martin-Lomas et al. [201], by Seeberger et al. [202], and by Yu et al. [203]. The low reactivity of the axial 4-hydroxy group in the iduronate residue in the Seeberger approach led to trichloroacetimidate rearrangement because the donor and acceptor reactivity did not match.


Proteoglycans are other important glycoconjugates with various roles [204], such as lubrication and blood anticoagulation. Several proteoglycans possess a highly conserved tetrasaccharide linkage region joining a GAG to a core protein. This GlcA $\beta(1-3)$ Gal $\beta(1-3)$ Gal $\beta(1-4)$ Xyl $\beta(1-O)$ Me tetrasaccharide was also successfully synthesized based on the *trichloroacetimidate method* [205].



Scheme 31

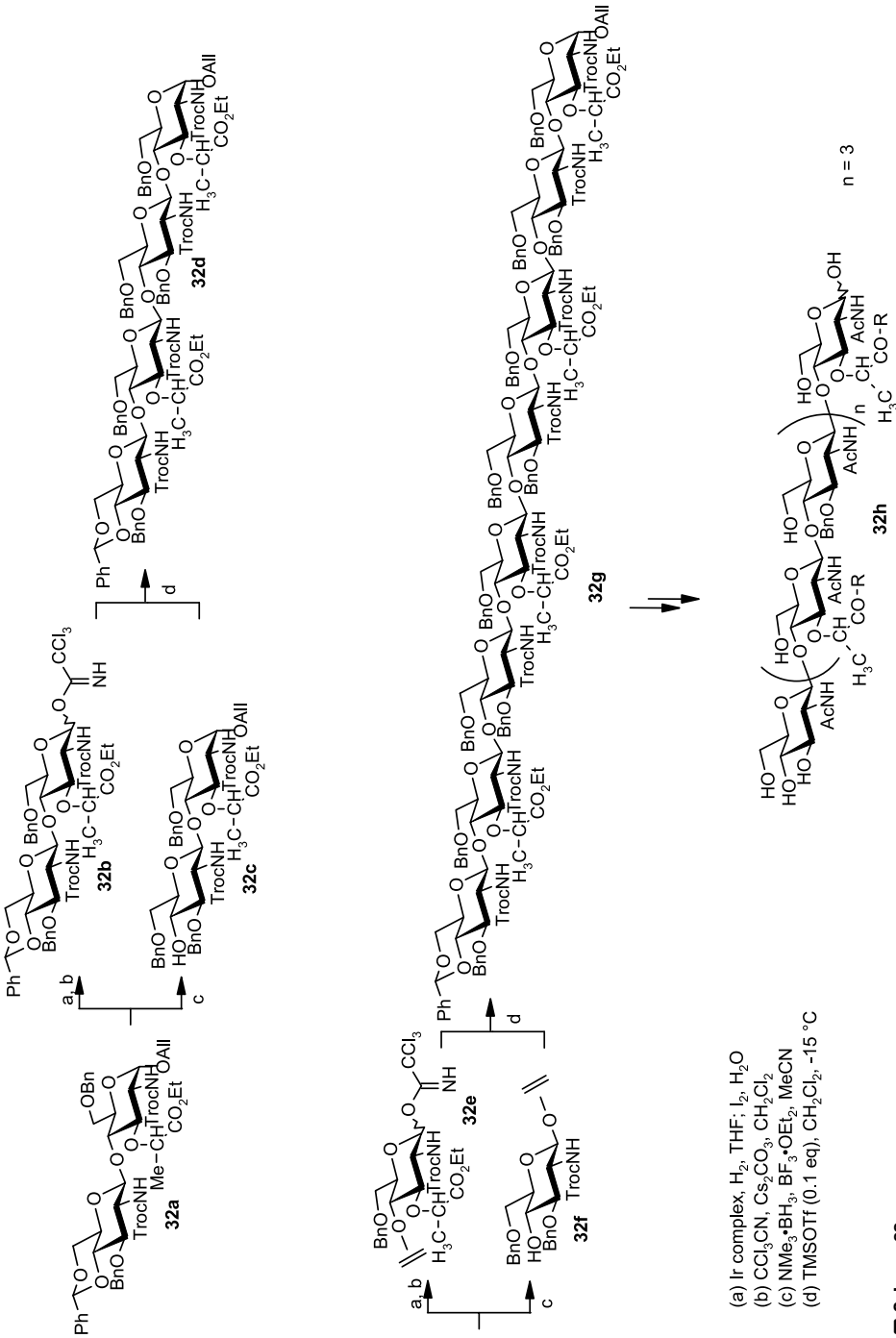
## 5.5 Cell Wall Constituents

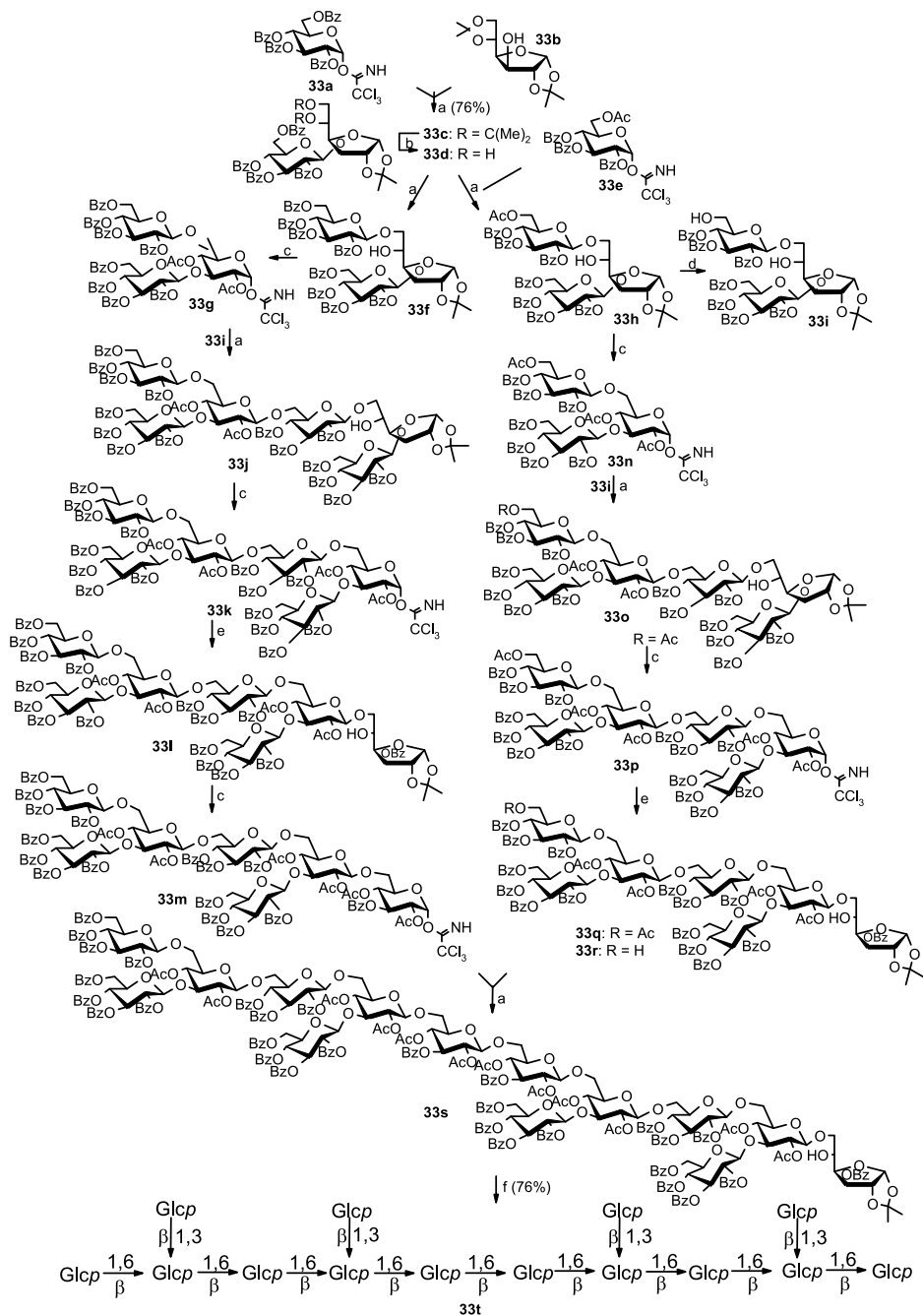
Bacterial cell wall peptidoglycan is known as a strong immunopotentiator which induces various mediators such as cytokines, prostaglandins, platelet activation factor, and NO, thus stimulating the immune system [206]. The receptor for peptidoglycans was shown to be TLR2 [207], the same as for lipoteichoic acids (LTAs) and lipoproteins. Therefore, the synthesis of peptidoglycan fragments is of continuing interest. Recently up to an octasaccharide fragment was obtained as shown in  Scheme 32 [208,209]. Starting material **32a** was transformed into donor **32b** and acceptor **32c** based on the temporary protection at *O*-1 with allyl and at *O*-4' with benzylidene. Glycosylation afforded tetrasaccharide **32d** which by similar transformation to **32e** and **32f** led to octasaccharide **32g** which could be deprotected to yield target molecule **32h**. This procedure of chain extension could be even extended to the hexadecasaccharide, however the Troc deprotection of this compound failed so far. To the octasaccharide **32h** also small peptides were attached via the lactate residue and the biological activity of the derived compounds was tested.

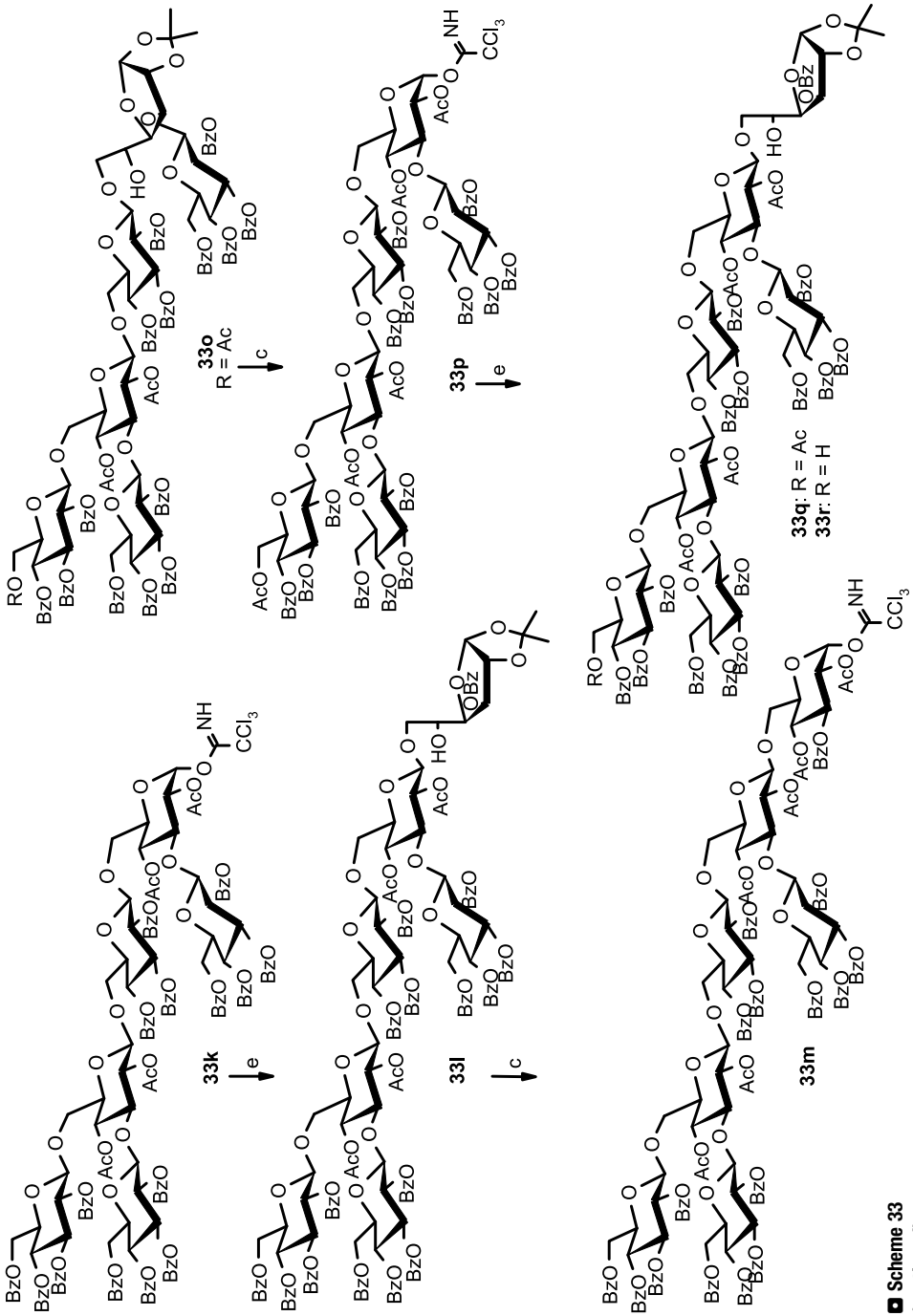
Many bacterial and fungal cell walls contain homo- and heteroglycans. The synthesis of fragments of these cell wall constituents has gained increasing interest in the last years. The  $\text{Man}\alpha(1-3)\text{Man}\alpha(1-2)\text{Man}\alpha(1-6)\text{Man}\alpha(1-2)\text{Man}$  heptasaccharide obtained by mild acetolysis from *C. glabrata* IFO 0622 has been successfully synthesized by Kong et al. [210]; they synthesized also a related sulfated pentasaccharide [211]. Also mannan repeating units of *Trichophyton mentagrophytes*, *T. rubrum* [212], *Saccharomyces cerevisiae* X 2180-1A [213], and *Candida kefyr* IFO 0586 [214] have been prepared. Another important class of glycans are  $\beta(1-3)$ - and  $\beta(1-6)$ -linked glucans which are frequently branched. Glucans consisting of  $\beta(1-3)$ -linked glucose residues having  $\beta(1-6)$ -linked branches have been found in many plants and fungi [215,216]. Since these glucans show antitumor activity, the synthesis of at least minimal structural units for biological activity studies has gained great interest [217]. Recently, several successful syntheses of such molecules have been reported mainly by Kong et al. [218,219,220,221,222,223]. Also a 2-branched  $\beta(1-3)$ -glucan was found and dimers of the trisaccharide repeating unit were prepared [224]. 3-Branched  $\beta(1-6)$ -linked glucans were found to be phytoalexin elicitors; they possess antitumor activities as well. A highly efficient synthesis of tetradecasaccharide **33t** was reported again by the Kong group [225] ( Scheme 33). The synthesis is based on readily available glucose-derived building blocks **33a**, **33b**, and **33e** and leads via disaccharides **33c** and **33d**, trisaccharides **33f-33i**, and **33n**, hexasaccharides **33j**, **k**, **o**, **p**, heptasaccharides **33l**, **m**, **q**, **r** to tetradecasaccharide **33s** which was deprotected to furnish target molecule **33t** in good overall yield. Such compounds were also prepared in large scale and with different aglycones [226,227,228].

Mannoglucan from *Microellabosperia grisea* possesses also high antitumor activity, therefore the repeating unit  $\{[\text{Glc}\alpha(1-3)][\text{Glc}\alpha(1-6)]\text{Glc}\beta(1-4)\text{Glc}\beta(1-4)\}_n$  has been synthesized via an efficient route [229].  $\beta(1-6)$ -Linked galactofuranosyl oligosaccharides are constituents of the cell wall of bacteria and fungi including some clinically significant pathogens [230,231,232]. The highly immunogenic arabinogalactans contain arabinofuranosyl and galactofuranosyl residues.  $\beta(1-6)$ -Linked galactofuranose oligomers, also found in the cell wall of the fungus *Fusarium*, exhibited in plants elicitor activity. Therefore, a  $\beta(1-6)$ -linked *O*-galactofuranosyl hexasaccharide was prepared based on the *trichloroacetimidate method* in high yield [233,234]. The Kong group also synthesized  $\alpha(1-5)$ -linked L-arabinofu-

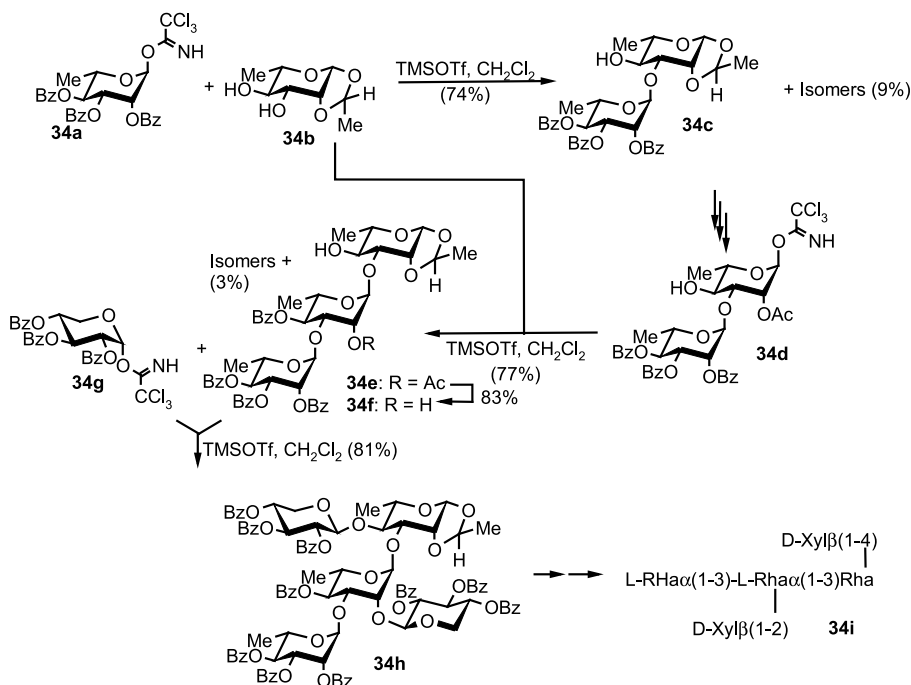








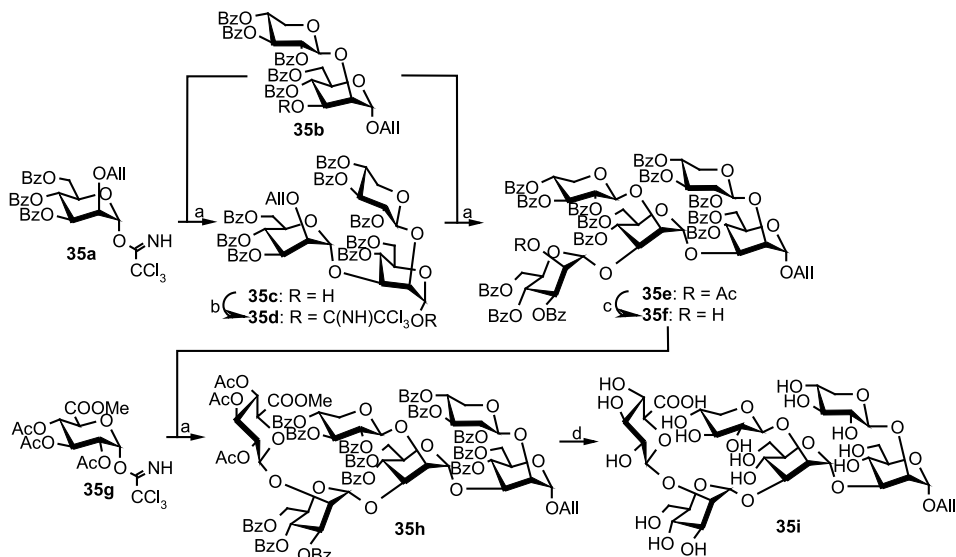
■ Scheme 33  
 (continued)



■ Scheme 34

ranosyl oligosaccharides up to the octamer based on related methodologies [235]. 2-*O*-Arabinofuranosylated  $\beta$ (1–6)-linked galactopyranosyl oligosaccharides, found in arabiogalactans, could be obtained also by Kong et al. [236] who also reported the successful synthesis of other arabinogalactan linkage types based on the *trichloroacetimidate method* [237,238,239,240]. Lipoarabinomannans have attracted great interest as well, because they are part of the cell surface oligosaccharide of mycobacterial species that cause many diseases, including tuberculosis and leprosy. The largest heteroglycan synthesis for this type of compound was recently reported in which the *trichloroacetimidate method* plays an important role [241].

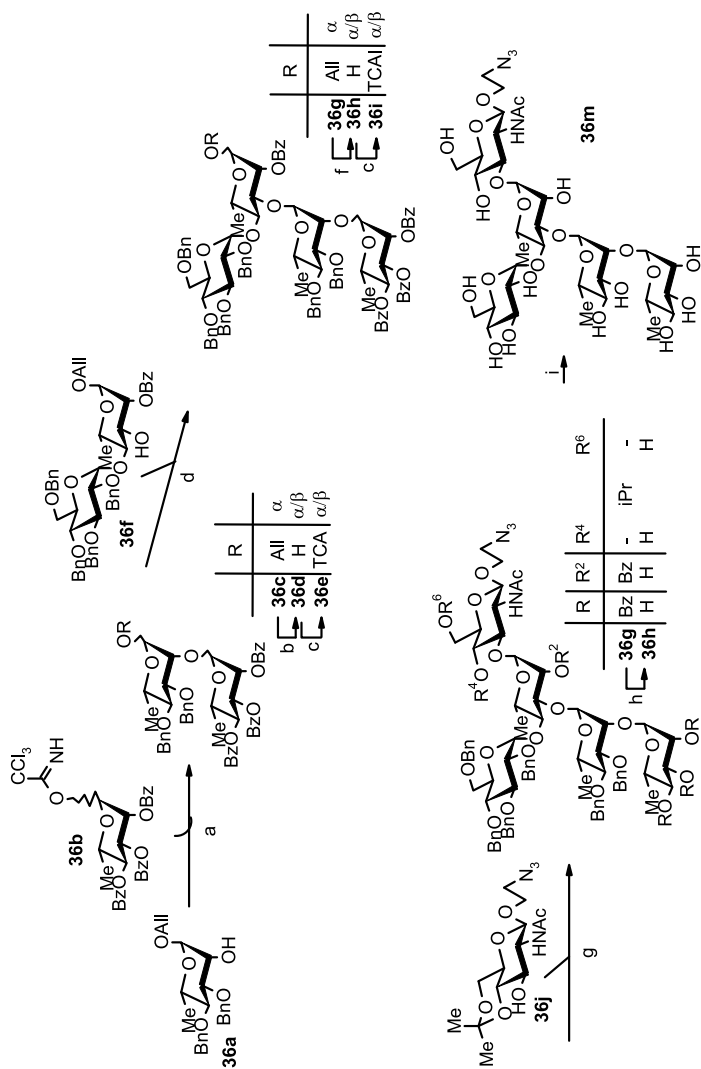
In algal cell wall polysaccharides  $\beta$ (1–3)-linked xylans were found. Fragments up to the hexamer were successfully synthesized [242]. The specific *O*-chain of the lipopolysaccharide of many bacteria contains repeating units composed of various sugar residues. Several of these repeating units or fragments thereof have been synthesized based on the *trichloroacetimidate method*. Rhamnosylated rhamnan [243], the D-Rhap $\alpha$ (1–3)[L-Xylp $\beta$ (1–2)]D-Rhap $\alpha$ (1–3)[L-Xylp $\beta$ (1–2)]D-Rha unit [244], (● Scheme 34, 34i), a more complex xyloarhamnan [245], a xylosylated GlcNAc rhamnan [246], a rhamnan with GlcNAc in the branch [247,248], the pentasaccharide D-Glc $\beta$ (1–2)-[D-Ribf $\beta$ (1–3)]L-Rhap $\alpha$ (1–3)L-Rhap $\alpha$ (1–3)L-Rhap $\alpha$ (1–2) L-Rhap [249], the glucurono xylomannan hexasaccharide repeating unit of *C. neoformans* serotype A (● Scheme 35) [250], a heptasaccharide fragment of *C. neoformans* serotype C [251], a repeating unit of *lactosillan* [252], the *Shigella flexneri* serotype 2a [253,254,255,256,257], and serotype 5a [258] have been efficiently obtained (● Scheme 36). The straight forward syn-



(a) TMSOTf,  $\text{CH}_2\text{Cl}_2$ ,  $-10^\circ\text{C} \rightarrow \text{rt}$  (dry); (b)  $\text{PdCl}_2$ , 90% acetic acid- $\text{NaOAc}$ , rt, 12 h; then  $\text{GI}_3\text{CN}$ , DBU,  $\text{CH}_2\text{Cl}_2$ , 2 h; (c) 2%  $\text{CH}_3\text{COCl}-\text{CH}_3\text{OH}$ ,  $0^\circ\text{C} \rightarrow \text{rt}$ ; (d) sat.  $\text{NH}_3-\text{MeOH}$ , rt, 36 h; then  $\text{H}_2\text{O}$ , rt, 5 h.


#### Scheme 35

thesis of heptasaccharide **34i** is outlined in [Scheme 34](#) [244]. Rhamnosyl donor **34a** readily reacts with rhamnose acceptor **34b** to give mainly disaccharide **34c** which is transformed into donor **34d**. Chain extension with **34b** leads to **34e** and then to acceptor **34f** which on reaction with xylosyl donor **34g** furnishes pentasaccharide **34h**; deprotection leads to target molecule **34i**. The hexasaccharide repeating unit synthesis of *C. neoformans* type A is outlined in [Scheme 35](#) [29]. Mannosyl donor **35a** reacts with acceptor **35b** to afford trisaccharide **35c** leading to donor **35d** which on reaction with **35b** gives pentasaccharide **35e** and acceptor **35f**. Glucuronidation with donor **35g** furnished hexasaccharide **35h** which gave on deprotection target molecule **35i**. The *Shigella flexneri* serotype 2a pentasaccharide fragment is outlined in [Scheme 36](#) [36]. Rhamnosyl donor **36b** and acceptor **36a** yield disaccharide **36c** which is transformed via **36d** into donor **36e**. On reaction with acceptor **36f** tetrasaccharide **36g** is obtained which is again transformed via **36h** into donor **36i**. Reaction with acceptor **36j** pentasaccharide **36k** is obtained which led to target molecule **36m** having an aminoethyl group at *O*-1 for glycoconjugate synthesis. Linkage to the PADRE sequence, acting as a universal T-cell epitope, was successfully performed and immunogenicity studies were carried out. Also successful investigations towards the synthesis of a tetrasaccharide rhamnogalacturanan related to an antiulcer pectic polysaccharide have been reported [259]. The *Neisseria* lipooligosaccharide contains two heptose residues within the conserved core structure; one heptose residue is 3,4-branched. On the basis of the *trichloroacetimidate method* a successful synthesis of a branched tetrasaccharide unit was successfully performed by Yamasaki et al. [260,261].



(a) cat. TMSOTf, Et<sub>2</sub>O, -70 °C → rt, 8 h; (b) i. cat. [Ir(COD)(PCH<sub>2</sub>(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>)<sub>2</sub>]+PF6<sup>-</sup>, THF, rt, 16 h, ii. HgO, HgBr<sub>2</sub>, acetone/water, rt, 1 h; (c) CCl<sub>3</sub>CN, DBU, CH<sub>2</sub>Cl<sub>2</sub>, rt, 2 h; (d) cat. TMSOTf, Et<sub>2</sub>O, -60 to -30 °C, 2 h; (f) i. cat. [Ir(COD)(PCH<sub>2</sub>(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>)<sub>2</sub>]+PF6<sup>-</sup>, THF, rt, 16 h, ii. HgO, HgCl<sub>2</sub>, acetone/water, rt, 1 h; (g) cat. TMSOTf, 4 Å-MS, CH<sub>2</sub>Cl<sub>2</sub>, rt, 3 h; (h) i. 50% aq. TFA, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 2 h; ii. cat. MeONa, MeOH, 55 °C; 2 h; (i) 10% Pd/C, 1 M aq. HCl, EtOH/EtOAc, rt, 2 h.

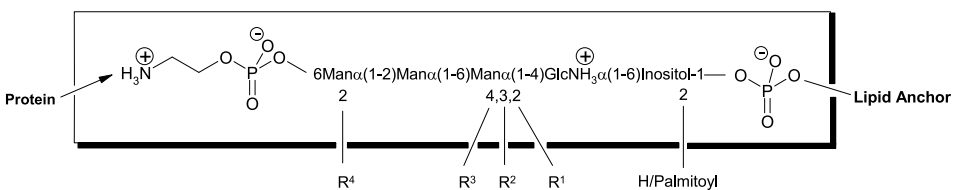
## 5.6 Synthesis of Glycosylphosphatidyl Inositol Anchors

Glycosylphosphatidyl inositol anchors constitute a class of glycolipids that link proteins and glycoproteins via their C-terminus to eukaryotic cell membranes. The first structure of a GPI anchor, that of *Trypanosoma brucei*, was published by Ferguson et al. [262]. Since then quite a few examples of GPI anchors were described, allowing the definition of the core structure depicted in  Scheme 37 [263].

The diversity within GPI anchors is mainly reflected in the location and nature of the branching groups of the glycan residue (R2, R3, R4). Additional ethanolamine phosphates (R1) seem to be specific for higher eukaryotes [264]. Concerning the lipid residue, many of the structures of GPI anchors contain a diacylglycerol moiety but alkylacylglycerol residues are not uncommon and ceramide structures have also been identified [263]. These modifications of the evolutionary conserved structure give rise to species-, stage-, and tissue-specific GPI structures.

The function of GPI anchors has been extensively discussed. A controversial aspect of GPI anchors is their ability to mediate signaling mechanisms or to function as second messengers, e. g. in insulin-mediated signal transduction processes [265]. Therefore, to perform biological studies elucidating the functions of GPI anchors, it seems to be an important objective to have access to structurally homogeneous GPI anchors and their derivatives. For the total synthesis of GPI anchors, a combination of lipid, phosphate, and oligosaccharide chemistry is required. A highly versatile strategy has been successfully followed for a ceramide-containing GPI anchor of yeast [266,267]. Similarly obtained were the acylglycerol-containing GPI anchors of *Trypanosoma brucei* [268,269] and *rat brain Thy-1* [270].

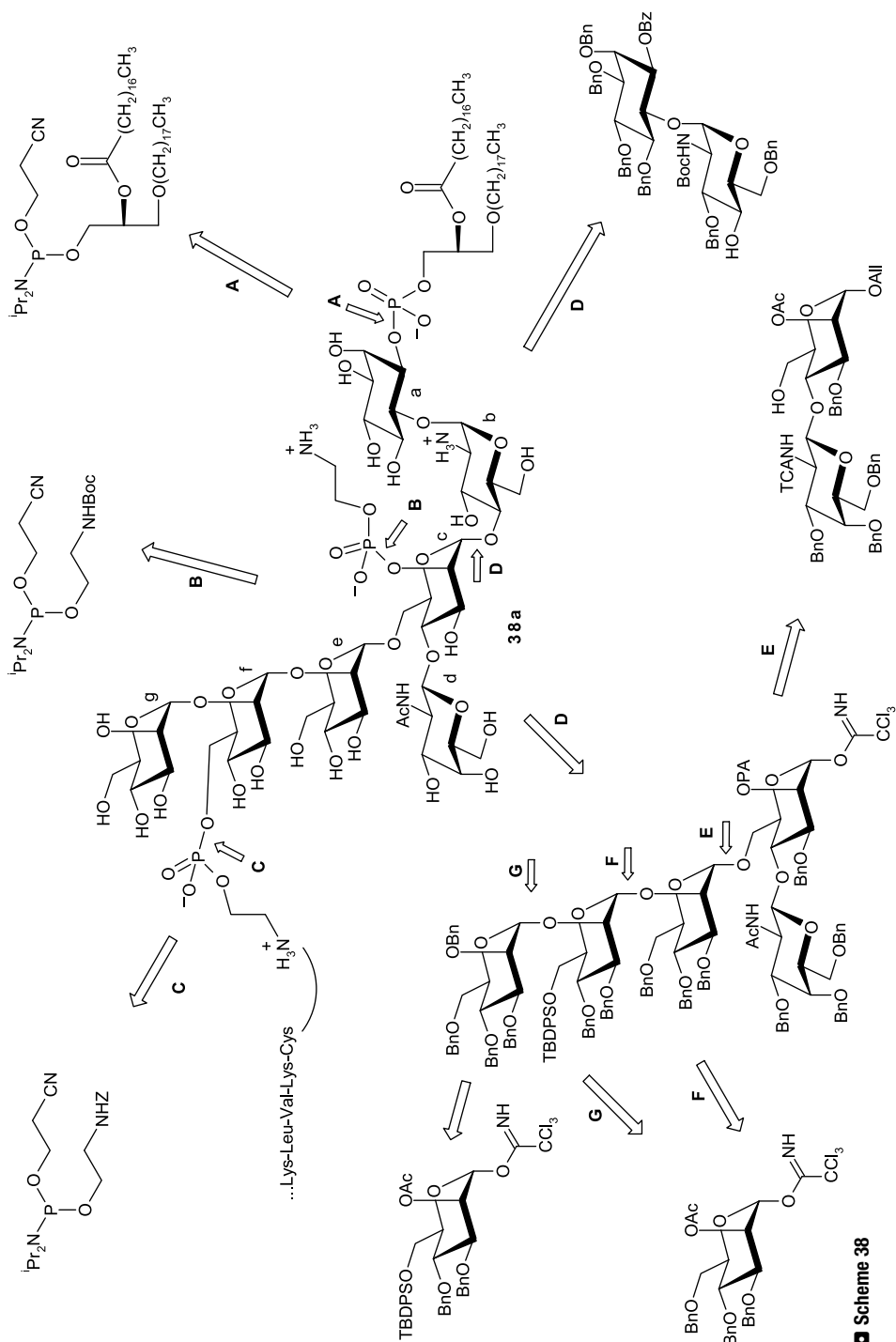
On the basis of earlier work [266,267], the development of a highly variable synthetic strategy, which is also applicable to the preparation of branched GPI anchors, was reported by Schmidt et al. [271,272]. This strategy allows also for the attachment of peptide or protein residues to the GPI anchor. The focus was on 4,6-branched mannose residues as there are sev-



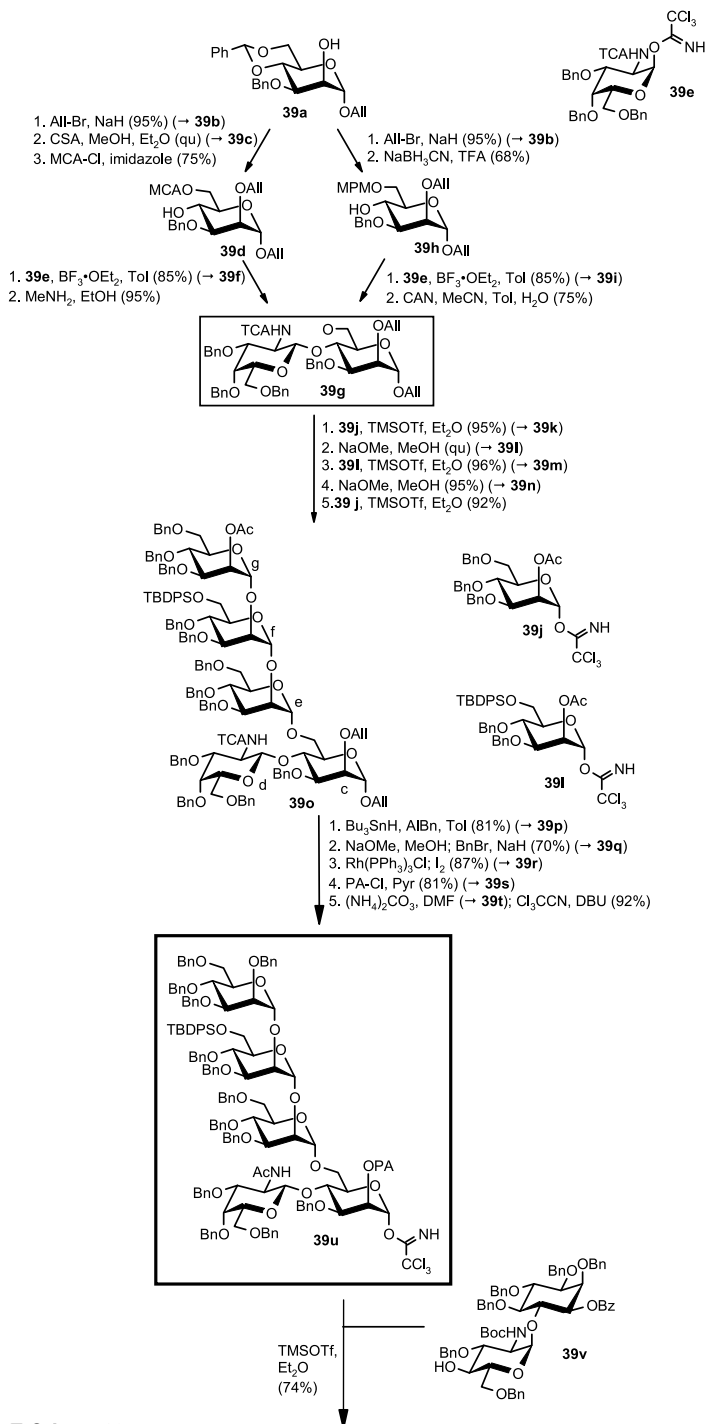
Natural Source	R <sup>4</sup>	R <sup>3</sup>	R <sup>2</sup>	R <sup>1</sup>	Lipid
<i>S. cerevisiae</i>	Man $\alpha$ (1-2)	H	H	H	Ceramide/DAG
<i>T. brucei</i> VSG	H	H	Gal <sub>2,4</sub> $\alpha$ (1-3)	H	DAG
<i>T. gondii</i> A	H	GalNAc $\beta$ (1-4)	H	H	DAG
<i>T. gondii</i> B	H	Glc $\alpha$ (1-4)GalNAc $\beta$ (1-4)	H	H	DAG
Rat brain <i>Thy-1</i>	Man $\alpha$ (1-2)	GalNAc $\beta$ (1-4)	H	EA-P	Acylalkylglycerol

### Scheme 37

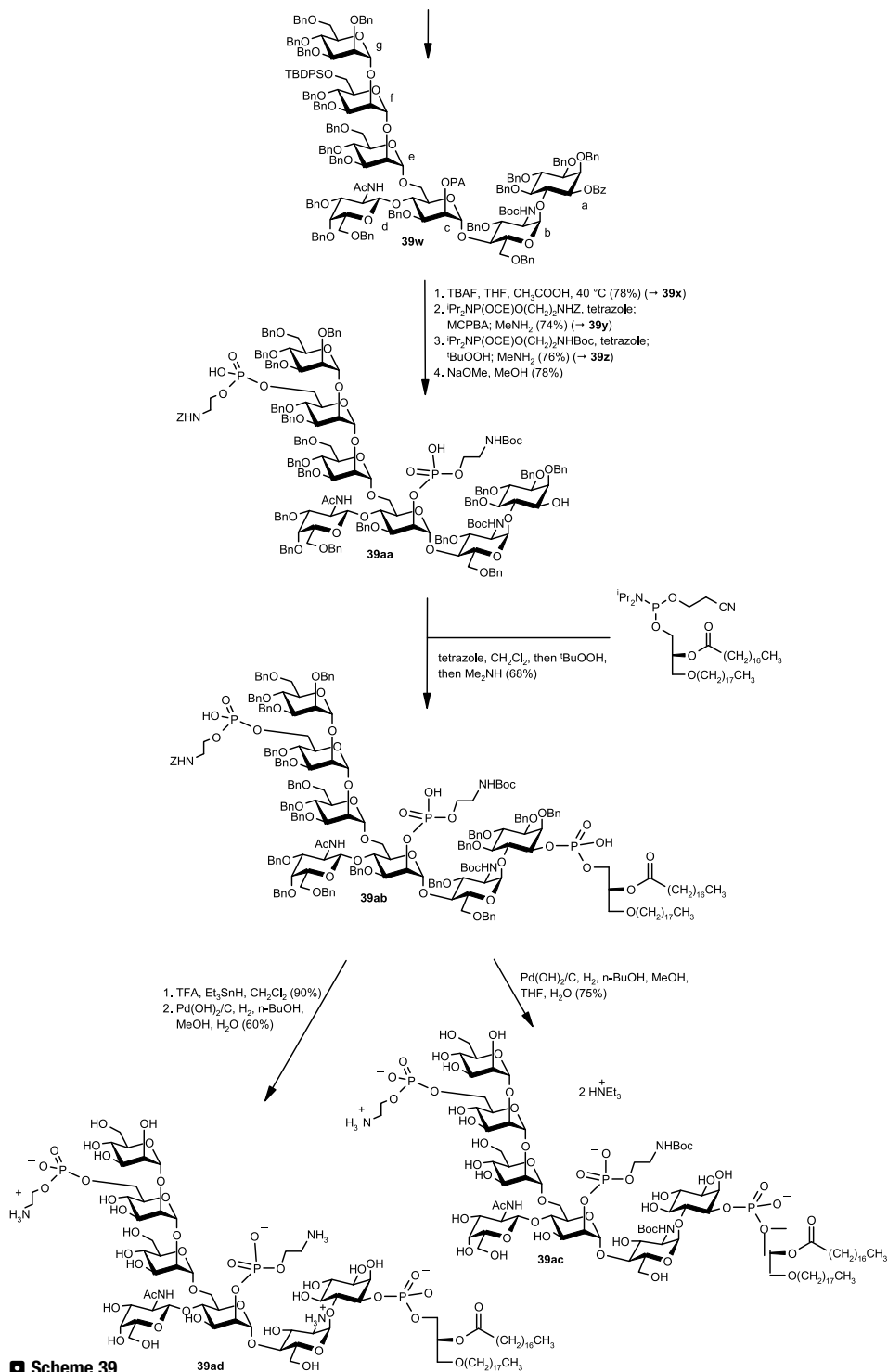
General structure of GPI anchors (EA, ethanolamine; P, phosphate; DAG, diacylglycerol)



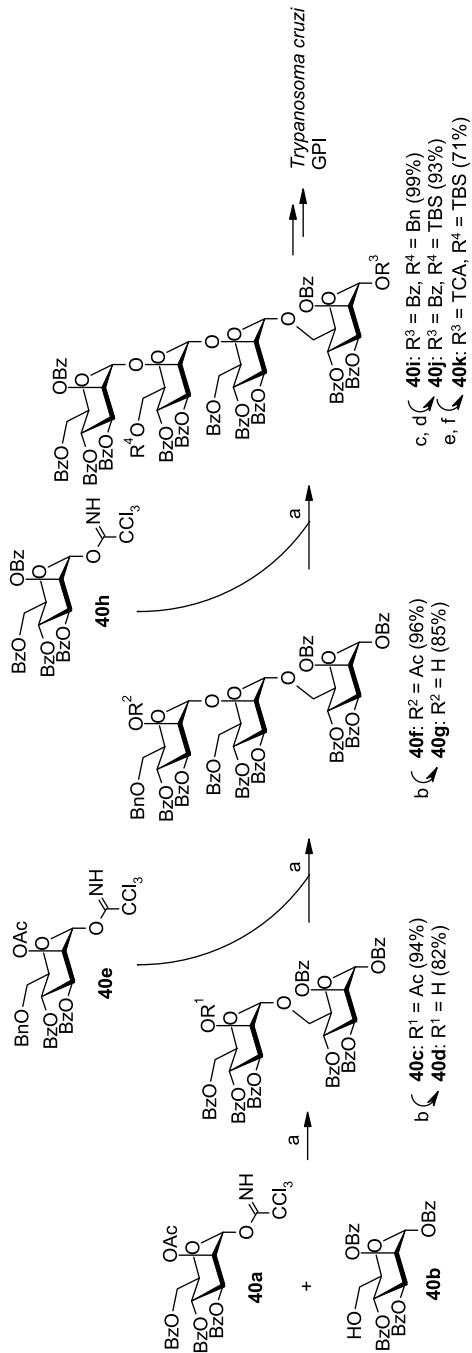




Scheme 39



**Scheme 39**  
 (continued)



Reagents: (a) TMSO<sub>2</sub>CF<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>; (b) 2% HCl, MeOH/CH<sub>2</sub>Cl<sub>2</sub>; (c) H<sub>2</sub>, Pd(OH)<sub>2</sub>/C, THF; (d) TBSO<sub>2</sub>CF<sub>3</sub>, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>; (e) NH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub> • HOAc, THF; (f) CCl<sub>3</sub>CN, Cs<sub>2</sub>CO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, Bn = benzyl, THF = tetrahydrofuran, TMS = trimethylsilyl.

**Scheme 40**

eral prominent examples in nature (► *Scheme 37*). Therefore, the fully phosphorylated GPI anchor of *Toxoplasma gondii* was prepared [271]. Also a new route to rat-brain Thy-1 [272] was developed which is outlined in ► *Scheme 38*, showing important disconnections and building blocks; it is totally based on trichloroacetimidate donors. Two efficient routes starting from mannosyl acceptor **39a** and glucosamine-derived donor **39e** leading to disaccharide **39g** were developed (● *Scheme 39*). With variously protected mannosyl donors **39j** and **39l**, chain extension to pentasaccharide **39o** could be efficiently performed. Transformation into donor **39n** and reaction with disaccharide acceptor **39v** led to pseudoheptasaccharide **39w**. Introduction of two orthogonally protected aminoethyl phosphate residues led to **39aa** to which the phospholipid was attached (→ **39ab**). Debenzylation afforded *N*-Boc-protected **39ac** which permits regioselective attachment of peptide residues to one aminoethylphosphate moiety and complete deprotection led to target molecule **39ad**. This way a highly variable concept for the synthesis of branched GPI anchors could be established. It is based on versatile building blocks which are readily accessible and provide the desired regio- and stereocontrol. The concept further allows for the regioselective attachment of peptides or proteins.

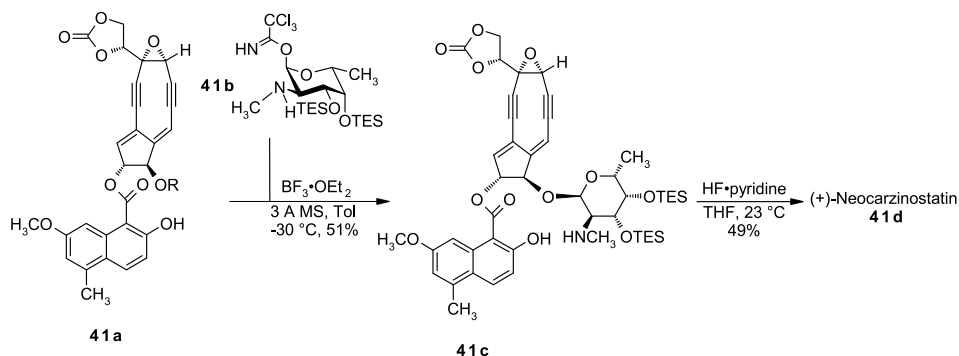
The synthesis of a partial structure of a branched pseudohexasaccharide of an inositolphosphoglycan (IPG) has been reported by Martin-Lomas et al. [273]. Linear oligosaccharides of GPIs were also synthesized based on the *trichloroacetimidate method* [274,275]. The GPI anchor of *Trypanosoma cruzi* containing an unsaturated fatty acid was obtained without any *O*-benzyl protection in the decisive intermediate (● *Scheme 40*) [276]. Acyl-protected donor **40a** and acyl-protected acceptor **40b** gave disaccharide **40c** which was transformed into acceptor **40d** which on reaction with donor **40e** gave trisaccharide **40f** and then acceptor **40g**. Glycosylation with **40h** led to tetrasaccharide **40i** which was transformed via **40j** into donor **40k**. From this compound the desired target molecule was prepared.

## 5.7 Glycosylation of Various Natural Products and Their Metabolites

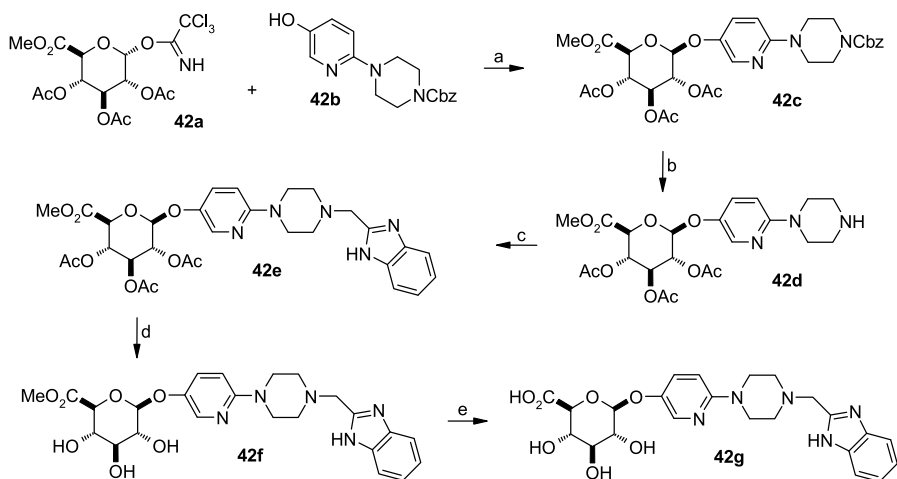
Many antibiotics are glycosylated, however the structural complexity of many antibiotics and their glycosylation is a demanding task. On the basis of the *trichloroacetimidate method* a successful synthesis of landamycin A hexasaccharide was reported [277]. Novobiocin was glycosylated with three different *O*-glycosyl trichloroacetimidates as donors at the 7-hydroxy group [278]. Also the quite sensitive (+)-Neo-carzinostatin aglycone **41a** (● *Scheme 41*) could be successfully glycosylated [279]. Reaction of **41a** with glycosyl donor **41b** furnished the desired glycoside **41c** in good yield which on deprotection afforded target molecule **41d**. Hydroquinone glycosylation leading to  $\alpha$ -arbutin was also performed [280]; this compound is an inhibitor of human tyrosinase and therefore of interest in the cosmetic industry.

Aminoglycoside antibiotics are of special interest as glycosylation targets. Interesting neomycin trisaccharide mimetics have been prepared by Boons et al. [281]. Glycosidase inhibitors have also been combined with additional carbohydrate residues in order to fine tune their biological properties. Thus, deoxynojirimycin has been combined with  $\beta(1-3)$ - and  $\beta(1-6)$ -linked glucan residues [282].

Many metabolites are glucuronidated, therefore the introduction of the glucuronic acid residue is a major task because of the low reactivity of the derived donors and their tendency to 4,5-elimination. Therefore, often compounds are first glycosidated and at a later stage of the



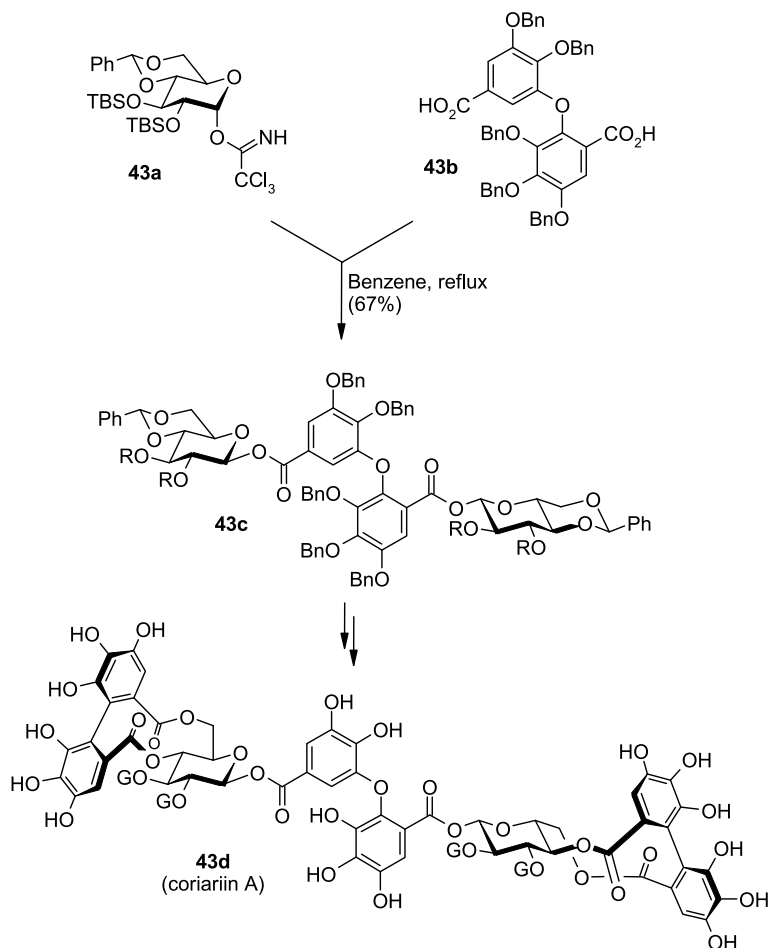
Scheme 41



(a) 2.0 eq 42a, 1.0 eq 42b,  $\text{BF}_3 \cdot \text{OEt}_2$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-60^\circ\text{C}$  → rt, 41 h, 75%; (b) 5% Pd/C,  $\text{H}_2$ , MeOH, rt, 83%; (c) (1) benzimidazolymethyl chloride,  $\text{NEt}_3$ , NMP,  $0^\circ\text{C}$  → rt, (2) EtOAc, rt, 62%; (d) 0.1 eq LiOH, MeOH,  $-10^\circ\text{C}$  → rt; (e) 1.9 eq LiOH, MeOH, rt; 2.0 eq AcOH,  $\text{H}_2\text{O}$ ,  $\text{CHCl}_3$  wash; Dowex hydroxide resin, filtration, wash, then  $\text{AcOH}_{\text{aq}}$ , 87%.

Scheme 42

synthesis the hydroxymethyl group is selectively oxidized to the carboxylate group. Excellent results in direct glucuronidation based on *O*-isobutyryl-protected trichloroacetimidate have been obtained by Scheinmann and Stachulski et al., who glucuronidated for instance an anti-estrogenic steroid [283,284] and morphine [285]. Also MS 209, a quinoline derivative exhibiting multidrug resistance in cancer therapy was directly glucuronidated based on an *O*-pivaloyl-protected donor [286]. 5-Hydroxypyridine derivative 42b (Scheme 42) which is part of ABT-724, a potent D4 dopamine receptor agonist, could be directly glucuronidated [287] leading to 42c. Further transformations via intermediates 42e and 42f gave the desired glycosylated metabolite 42g.

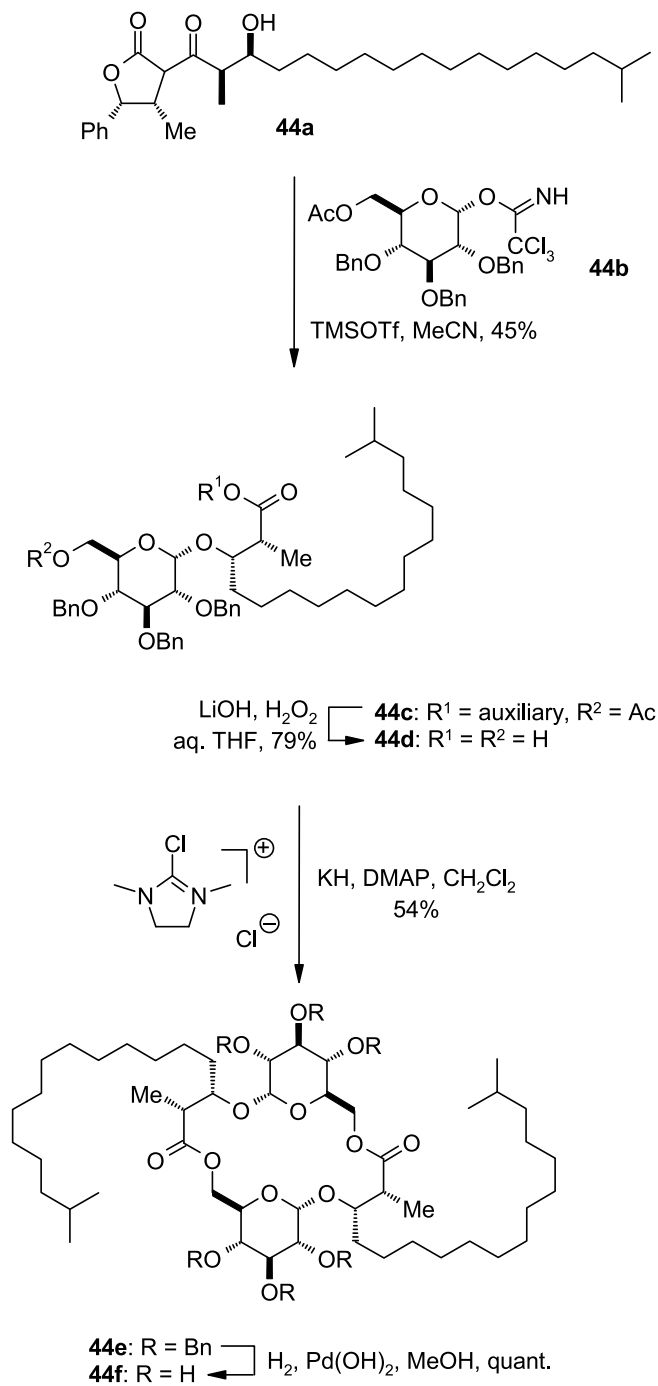


■ Scheme 43

Dihydroxyphenyl glycosides are a family of plant components. Some representatives have also been synthesized based on the *trichloroacetimidate method*, such as for instance the conandroside [288]. Other plant metabolites, such as for instance the ellagitannins, contain benzoyl groups at the anomeric oxygen. The derived coriariin A (**43d**, ● Scheme 43) was obtained as discussed above just by heating **43b** with glycosyl donor **43a**, leading to **43c**, which was transformed into target molecule **43d** [289]. Macrophyllloside D [290] and buprestin A [291] were similarly prepared.

*N*-Glycosylation of nitrogen-containing heterocycles has also been investigated. An interesting synthesis of *N*-indigoglycosides was undertaken which, as analogs of akashines, exhibit activity against various human tumor cell lines [292].

Unique glycolipids produced by plants are the resin glycosides for which the first synthesis was based on the *trichloroacetimidate method* [293,294]. Other members of this family have been



Scheme 44

prepared with the help of closely related trichloroacetimidate building blocks and a similar strategy, such as for instance for woodrosin I [295] and tricolorin F [296]. Structurally related, highly bioactive antiviral compounds, such as for instance cycloviracin B<sub>1</sub> or glucolipsin A were isolated and successfully synthesized [297,298,299]. The approach to the synthesis of glucolipsin A [299] is exhibited in **Scheme 44**. Glucosylation of fatty acid derivative **44a** with *O*-glycosyl trichloroacetimidate **44b** gave the desired glycoside **44c** in good yield. Ester hydrolysis ( $\rightarrow$  **44d**) and dimerization to **44e** and then hydrogenolysis of the *O*-benzyl groups led to target molecule **44f** which had physical data in accordance with the natural product (see [299]).

Saponins are steroid- or triterpenoid-based glycolipids which are found in terrestrial and marine plants. They possess various biological activities [300]. Several papers reported on successful glycosylations at the 3-hydroxy group [301,302,303,304,305,306]. When this hydroxy group is sterically hindered due to disubstitution at C-4, this glycosylation is a difficult task. However, with *O*-glycosyl trichloroacetimidate donors good yields and anomeric selectivities have also been obtained for this glycosylation step [307,308,309,310,311,312]. Particularly worth mentioning is the total synthesis of QS 21 A published by Gin et al. [25] where the decisive step is carried out with a trisaccharide donor.

Most carbohydrates contain ethane-1,2-diol fragments, therefore they were also successfully included into crown ether macrocycles [313]. Polyvalency of carbohydrates was studied based on dendrimeric structures which were generated on successful glycosylations of highly branched polyethylene glycol units [314].

## 5.8 Cyclooligosaccharides

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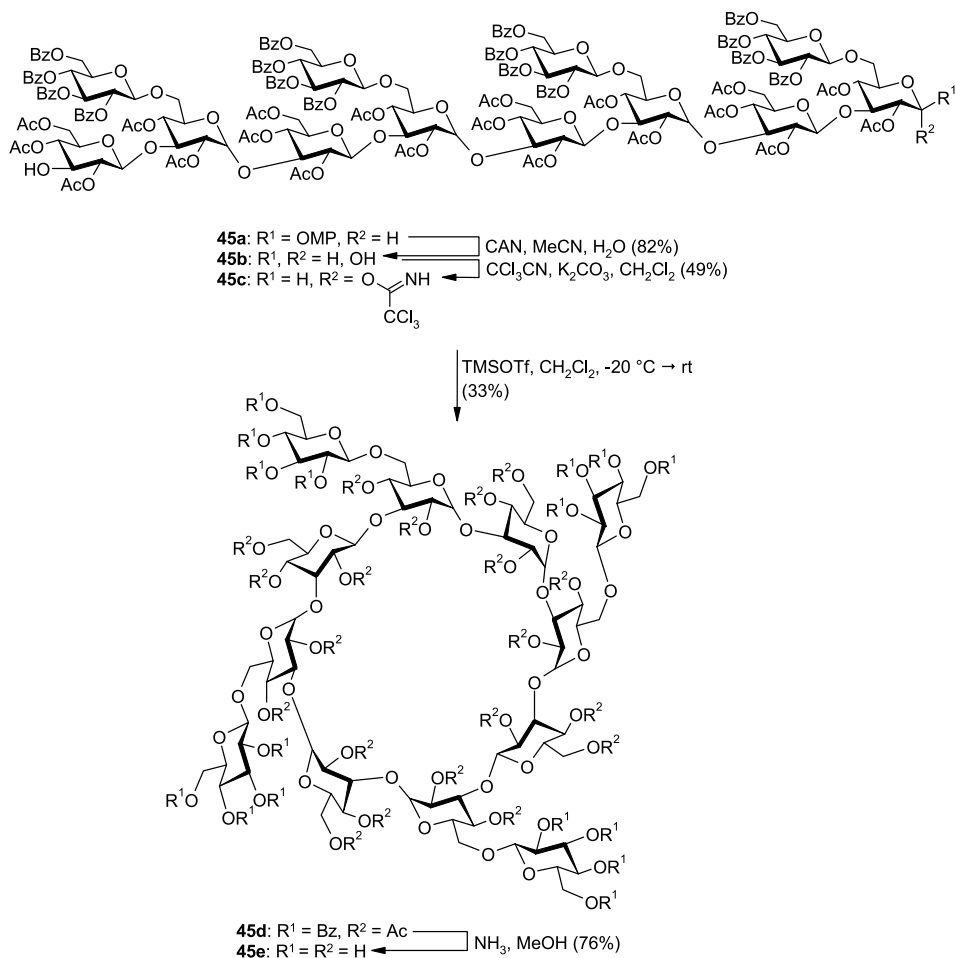
Cyclodextrins (CDs) have gained a lot of interest because they provide useful cavities for the generation of inclusion complexes. Therefore, branched CDs and CDs with various carbohydrate residues have been synthetic targets. The *trichloroacetimidate method* was successfully employed to reach such goals. Mannosyl, galactosyl, lactosyl, and the Gal $\beta$ (1-4')-lactosyl residues were selectively introduced at *O*-6 of  $\beta$ - and  $\gamma$ -CD, respectively [315,316]. Also building blocks for oligomannoside attachment to CDs were prepared [317]. Most remarkable is the synthesis of a *O*-6 branched cyclo(1-3)-glucohexaose and octaose [318,319]. The ring closure of the prepared nona- and dodecasaccharide worked extremely well based on *O*-glycosyl trichloroacetimidate donors (**Scheme 45**) [5]. Dodecasaccharide **45a** was transformed via **45b** into trichloroacetimidate **45c** having a 3-hydroxy group at the nonreducing end. Acid-catalyzed activation led to CD derivative **45d** which gave after deacylation target molecule **45e**.

## 5.9 C-Glycoside Synthesis

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The synthesis of "C-glycosides" has been of great interest [320]. C-Glycosylation of electron-rich compounds with *O*-glycosyl trichloroacetimidates continues to be a method of choice. This work is not discussed here in detail. A few references give an entry to the work in this field [321,322,323,324].





■ Scheme 45

## 5.10 *O*-Glycosyl Trichloroacetimidates of *N,O*- and *S,O*-Halfacetals

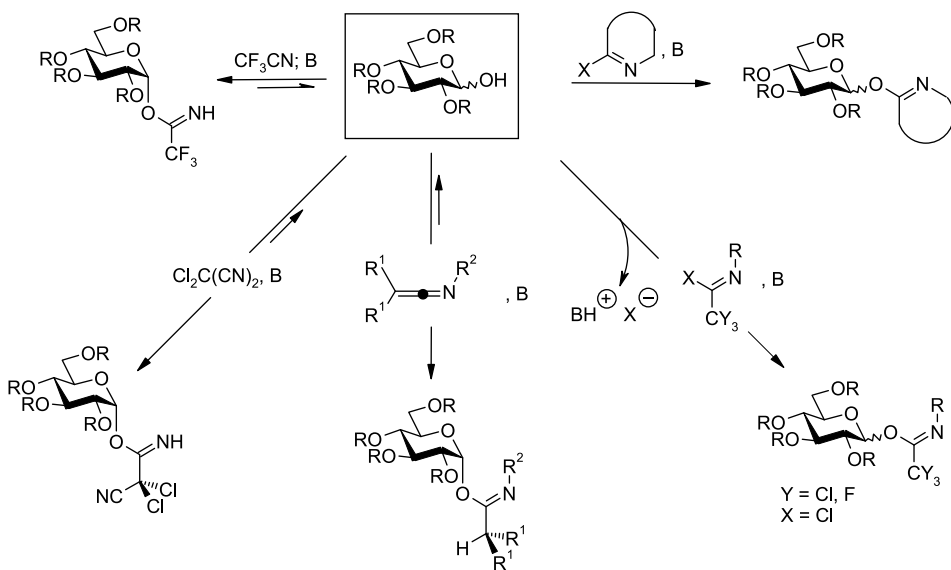
Not only *O,O*-halfacetals but also *N,O*- and *S,O*-halfacetals have successfully been transformed into trichloroacetimidate derivatives [325,326]. Thus carbohydrates with sulfur in the ring have been successfully transformed into *O*-glycosyl trichloroacetimidates and employed in glycosylation reactions by M. Hashimoto et al. [327,328] and by H. Hashimoto et al. [329,330]. Thy glycosyl donors could be readily obtained by base-catalyzed trichloroacetone nitrile addition to the anomeric hydroxy group and glycosylation yields under standard conditions were generally very good.

## 6 Related Activation Systems

*O*-Glycosyl trichloroacetimidates have become popular because they are easily available, powerful glycosyl donors. Therefore, investigations were undertaken to provide glycosyl donors which follow the principle of *O*-glycosyl trichloroacetimidate formation and activation. A short outline of this work is attached here.

Already previously trifluoroacetonitrile has been investigated for the generation of glycosyl donors [12,331]. However, because trifluoroacetonitrile is a gas, its use is not as convenient as the use of trichloroacetonitrile. In addition, preliminary glycosylation results were inferior to those obtained with *O*-glycosyl trichloroacetimidates. Much more promising were studies with dichloromalonitrile which is a suitable reagent for the base-catalyzed generation of *O*-glycosyl dichloro-cyanoacetimidates [332,333]. These compounds exhibited glycosyl donor properties closely related to those of *O*-glycosyl trichloroacetimidates (Scheme 46). A further important class of compounds is ketene imines, which should readily lead to *O*-glycosyl imidates. However, so far only a few examples were investigated [12,13,330], therefore, the potential of these compounds has not been elucidated yet.

Another interesting class of compounds are imide halides having electron-withdrawing carbon substituents and their heterocyclic equivalents. After some earlier work [12,334,335,336,337,338], recently imide halides have gained increased interest and excellent glycosylation results have been reported [45,339,340]. However, these systems have the disadvantage of furnishing equimolar amounts of salt on glycosyl donor generation. Additionally, glycosyl donor generation is not reversible, therefore  $\alpha/\beta$ -stereocontrol is more difficult or even impossible. Hence, matching or even surpassing the properties of *O*-glycosyl trichloroacetimidates remains a demanding task.



Scheme 46

## 7 Conclusions

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The requirement for efficient glycosylation methods, as outlined at the beginning of this chapter, namely convenient diastereocontrolled anomeric *O*-activation (first step) and subsequent efficient diastereocontrolled glycosylation promoted by catalytic amounts of a promoter (second step) are essentially completely fulfilled by the *trichloroacetimidate method*. In terms of reactivity and applicability toward different acceptors, the *O*-glycosyl trichloroacetimidates have generally proven to be outstanding glycosyl donors, which resemble in various respects the nucleoside diphosphate sugar derivatives used by nature as glycosyl donors. Thus, base-catalyzed generation of *O*-glycosyl trichloroacetimidates followed by acid-catalyzed glycosylation have become a very competitive alternative to other methods mainly requiring anomeric oxygen exchange reactions for glycosyl donor generation and at least equimolar amounts of a promoter system for the glycosylation step. Hence, the *trichloroacetimidate method* can readily be adapted for large-scale preparations. Recently, related activation systems have attracted increasing interest, thus widening the scope of this glycosylation method.

## Acknowledgement

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