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ANOMERIC-OXYGEN ACTIVATION FOR GLYCOSIDE SYNTHESIS: THE TRICHLOROACETIMIDATE METHOD

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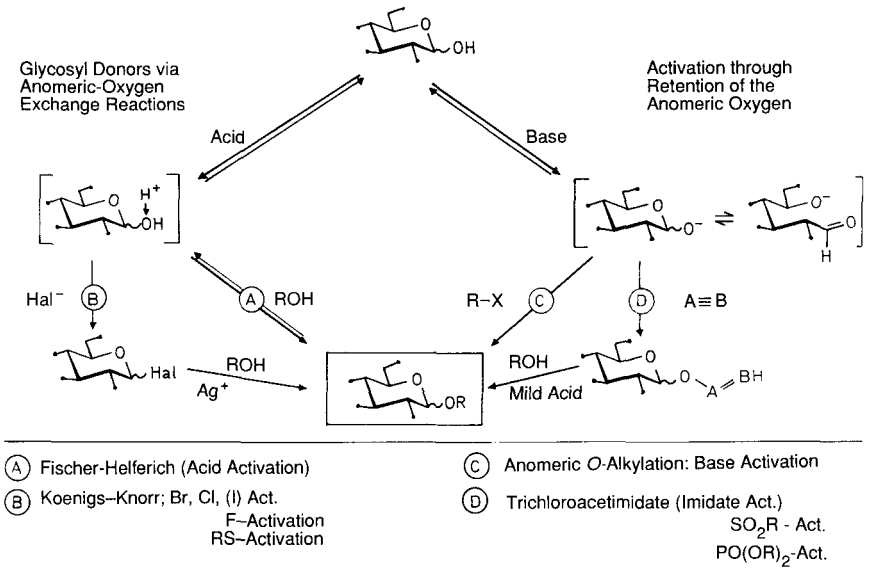
I. GENERAL INTRODUCTION TO GLYCOSIDE SYNTHESIS: ACTIVATION THROUGH ANOMERIC OXYGEN-EXCHANGE REACTIONS

The biological significance of glycoconjugates has stimulated much synthetic activity in glycoside synthesis in the past years (1–7). These efforts were initially concentrated mainly on improvements of the well-known Koenigs–Knorr method (8), introduced in 1901, which requires an *exchange of the anomeric hydroxyl group* by *bromine* or *chlorine* as the first step (generation of the glycosyl-group donor). The second step involves glycosyl-group transfer to the glycosyl acceptor in the presence of a heavy metal ion promoter (Scheme 1, path B). Although this is the basis of a very valuable methodology that has been reviewed extensively (4,5,7), several inherent disadvantages make the Koenigs–Knorr method often experimentally demanding and certainly not very suitable for large-scale preparations. For instance, the requirement of at least equimolar amounts of the heavy metal salt promoter, often incorrectly termed "catalyst," is a limiting factor (1–3). Therefore, alternative methods are of interest.

Other anomeric-oxygen exchange reactions have been recently investigated quite extensively. Closely related to the Koenigs–Knorr method is the introduction of *fluorine as the leaving group* (Scheme 1, path B) (6,9–13). Because of the difference in halophilicity of this element as compared with bromine and chlorine, additional promoter systems besides silver salts were found useful as activators for glycosylation reactions (14–16). However,



SCHEME 1.—Synthesis of Glycosides and Saccharides.

because of the generally lower donor properties of glycosyl fluorides (17) these intermediates have not yet gained wide application in the synthesis of complex glycoconjugates.

Thioglycosides, where the anomeric oxygen atom is replaced by an alkyl or arylthio group, have recently attracted considerable attention as glycosyl donors (Scheme 1, path B) (5,18,19). They offer sufficient temporary protection of the anomeric center and present several alternative possibilities for regioselective activation to generate glycosyl donor properties. Earlier methods for activation include mainly mercury(II), copper(II), and lead(II) salts (20–28). However, besides the requirement of generally more than equimolar amounts of heavy metal salts, relatively low glycosyl-donor properties were experienced with these systems. This problem was partly overcome by the use of heterocyclic thioglycosides (21,23,25–27). In addition to metal salts, bromonium and chloronium ions are also highly thiophilic and thus provide with counter-ions of bromide and chloride, respectively, the corresponding glycosyl halides for a subsequent Koenigs–Knorr type of reaction (18,19,29). If the counter-ion of the halonium ion is a poor nucleophile (for instance, succinimide from *N*-bromosuccinimide), then direct reaction with alcohols as competing nucleophiles is favored and thus leads to *O*-glycosides. However, low α,β selectivities are frequently obtained for nonneighboring

group-assisted reactions (23,30). Formation of sulfonium ions from thioglycosides by the action of methyl triflate was also successfully applied to *O*-glycoside bond-formation (31 – 34). Disadvantages of this method include the low α,β selectivity observed for nonparticipating 2-*O*-protective groups, the health hazard of methyl triflate, and the formation of methylation products in other side reactions. The recently introduced activator dimethyl(methylthio)sulfonium triflate (DMTST) proved to be highly thiophilic and gives rise to faster glycosylation than does methyl triflate (35). However, again, with nonparticipating groups the α,β selectivity is usually low (32). Radical activation of thioglycosides has also been recently reported, providing similar results in terms of yield and diastereoselectivity (36).

The Fischer – Helferich method, as a direct anomeric-oxygen replacement reaction (Scheme 1, path A), has been very successfully applied for syntheses of simple alkyl glycosides. However, because of its reversibility, it has not gained general importance in the synthesis of complex oligosaccharides and glycoconjugates (1).

II. Anomeric-Oxygen Activation: Anomeric *O*-Alkylation

1. Introduction

The requirements for glycoside syntheses, high chemical and stereochemical yield, and applicability to large-scale preparations were not effectively met by any of the methods just described. However, it seems that the general strategy for glycoside synthesis is reasonable:

(*i*) The first step should consist of a sterically uniform activation of the anomeric center with formation of a stable glycosyl donor having either the α or the β configuration;

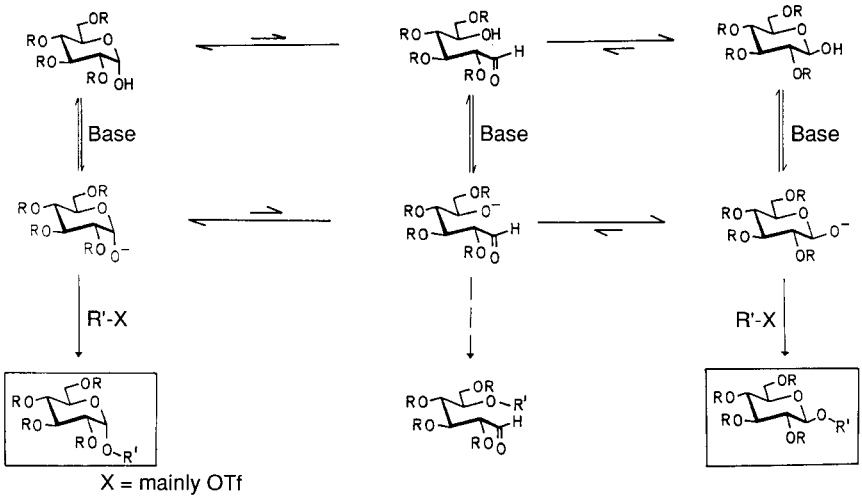
(*ii*) The second step should consist of a catalyzed, sterically uniform, irreversible glycosyl transfer to the acceptor, proceeding with either retention or inversion of configuration at the anomeric center in high chemical yield and without affecting other bonds.

Only simple means meeting these requirements will lead to a generally acceptable and useful methodology. Therefore, besides acid activation (Scheme 1, paths A and B), the simplest form of activation would be base activation generating first an anomeric alkoxide structure of a pyranose or furanose (Scheme 1, paths C and D). This approach is especially tempting because Nature has a similar approach for generating glycosyl donors, namely glycosyl phosphate formation [see Section IV.2 and Ref. (17)].

2. Anomeric *O*-Alkylation

The direct *O*-alkylation of the anomeric center (Scheme 1, path C) by treatment of furanoses and pyranoses with base and then with simple alkylating agents, for instance an excess of methyl iodide or dimethyl sulfate, has long been known (1,3). Surprisingly, no studies employing this simple method for syntheses of more-complex glycosides and saccharides have been reported prior to our work (1,37,38).

In the beginning, direct anomeric *O*-alkylation seemed very unlikely to fulfill all of the requirements for glycoside and saccharide synthesis. Even when all remaining functional groups (generally hydroxyl groups) are blocked by protecting groups, the ring–chain tautomerism between the anomeric forms and the open-chain form (Scheme 2) already gives three



SCHEME 2. — 1-*O*-Alkylation and 1-*O*-Acylation (Irreversible Reactions).

possible sites for attack of the alkylating agent. In addition, base-catalyzed elimination in the open-chain form of the sugar could be a destructive side-reaction. Therefore, the yield, the regioselectivity, and the stereoselectivity of such direct anomeric *O*-alkylation would not generally be expected to be outstanding. In any event, the process should be governed at least by the following factors:

(*i*) the stability of the deprotonated species;
(*ii*) the ring–chain tautomeric equilibrium and its dynamics; and
(*iii*) the relative reactivities (nucleophilicities) of the three *O*-deprotonated species.

Because of the irreversibility of the *O*-alkylation reaction, kinetic regio- and stereo-control is required for selective product-formation. Therefore, selective formation of either α or β product seemed to be unattainable.

The first experiments with iodide derivatives of carbohydrates revealed that better alkylating agents are required (37). However, excellent reactivity with corresponding trifluoromethanesulfonates (triflates) was observed, providing, for instance, with 2,3-*O*-isopropylidene-D-ribose and derivatives, depending on the reaction conditions, very high yields of either α- and β-linked disaccharides (37). Surprisingly, even partial *O*-protection or, as recently discovered, *O*-nonprotection was compatible with this reaction (39–44). The stereocontrol could be effected by intramolecular metal-ion complexation, by steric effects, and by taking advantage of the increased nucleophilicity of the equatorial anomeric oxide over the axial anomeric oxide [kinetic anomeric effect (45,46)]. This method could even be employed in selective formation of α-glycosides of Kdo (47,48). Thus, the direct anomeric *O*-alkylation constitutes an especially simple procedure for glycoside and saccharide synthesis, giving generally high yields and diastereoselectivities. The limitation to primary triflates was a major drawback for the general use of this *anomeric* O-*alkylation* in glycoside synthesis. However, this problem was recently overcome, at least in part, by modifying the reaction conditions (49).

III. Anomeric-Oxygen Activation: The Trichloroacetimidate Method

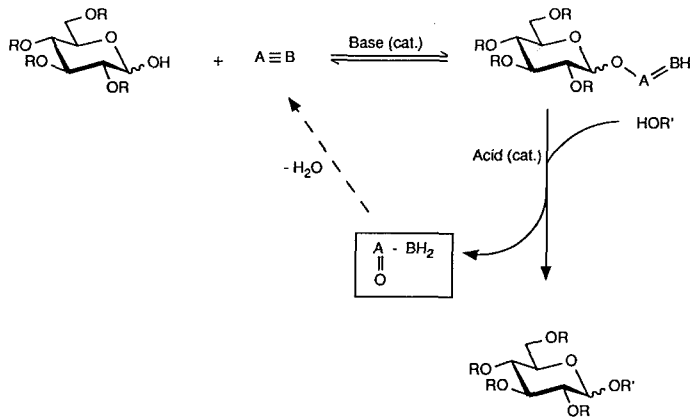
1. Formation of *O*-Glycosyl Trichloroacetimidates

Aside from direct anomeric *O*-alkylation (Scheme 1, path C), base-catalyzed transformation of the anomeric oxygen atom into a good leaving-group (Scheme 1, path D) should be easily readily effected. Therefore, it is not surprising that several approaches have been directed toward this goal, as will be discussed later (Section IV). However, stable and concomitantly reactive intermediates were never obtained for the separate anomers. Obviously, for achievement of stereocontrolled activation of the anomeric oxygen atom, the anomerization of the anomeric hydroxyl group or the anomeric oxide ion, respectively, has to be considered (Scheme 2). Thus, in a reversible activation process and with the help of kinetic and thermodynamic reaction-control, possibly both activated anomers should be accessible.

These considerations led us to the conclusion 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, because of reversibility, in a stereocontrolled manner (Scheme 1, path D) (1 – 3); thus, both activated anomers may be obtainable at will. However, the instability of open-chain aldehydic intermediates in basic media and the insufficient or undifferentiated reactivities of the α- and β-anomeric oxides lowered the expectations for stereocontrolled anomeric *O*-activations along these lines.

The desired formation of stable anomeric *O*-activated intermediates via base catalysis requires a different catalytic system for reactivity in the subsequent glycosylation step. Therefore, after base-promoted trapping of anomeric *O*-activated intermediates (first step), mild acid treatment in the presence of acceptors, leading to the formation of glycosides (namely, acetals and derivatives) in an irreversible manner (second step), would constitute the simple means of catalysis desired for a new and efficient glycosylation method. These demands have to be considered in the selection of A≡B (or A=B=C). Thus, the stable intermediates obtained in the first step have to exhibit by appropriate choice of the centers A and B (or A, B, and C) good glycosyl-donor properties in the presence of strictly catalytic amounts of acid. The water liberated upon glycoside formation is then transferred in two separate steps to the activating agent A≡B (or A=B=C), thus providing the driving force for the glycosylation reaction (Scheme 3). This concept fulfills



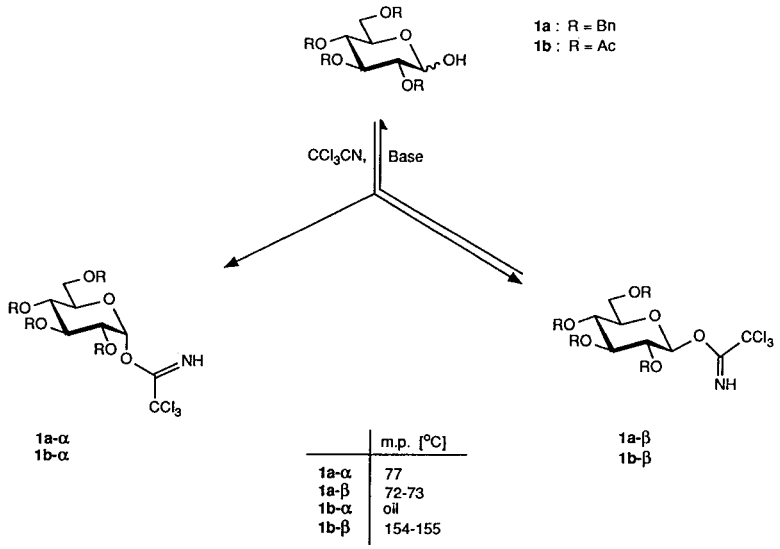
SCHEME 3. —Steps in the Glycosylation Reaction.

the requirements just given for an efficient glycosylation methodology: truly catalytic amounts of a simple base (first step) and of a simple acid (second step) are required for anomeric *O*-activation and promotion of the glycosylation, respectively; liberated water will not compete with the glycosyl acceptor for the glycosyl donor because it is concomitantly chemically bound

to the activating species A≡B (or A=B=C); and thus, reversibility in the first and irreversibility in the second step provide important means for controlling the yield and stereochemistry of the anomeric *O*-activated intermediate and of glycoside-bond formation. The *trichloroacetimidate method* developed by us, and recent contributions from other laboratories to this methodology, have proved the validity of this concept (1–3).

Electron-deficient nitriles, such as for instance trichloroacetonitrile and trifluoroacetonitrile (A≡B: A = N; B = $CCCl_3$, CCF_3), are known to undergo direct and reversible, base-catalyzed addition of alcohols providing *O*-alkyl trichloroacetimidates (1,50). This imidate synthesis has the advantage that the free imidates can be isolated as stable adducts, which are less sensitive to hydrolysis than their corresponding salts.

A detailed study of the addition of trichloroacetonitrile to 2,3,4,6-tetra-*O*-benzyl-D-glucose (**1a**, Scheme 4) revealed (1–3,45) that, from the equatorial



	m.p. [°C]
1a-α	77
1a-β	72-73
1b-α	oil
1b-β	154-155

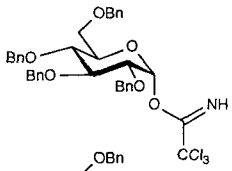
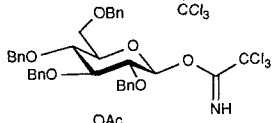
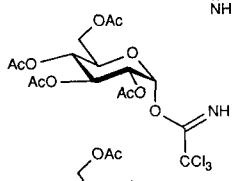
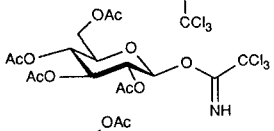
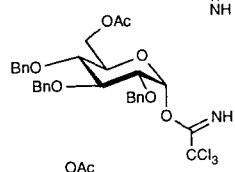
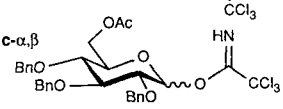
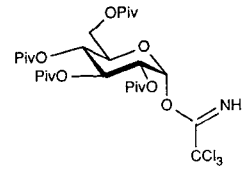
SCHEME 4. — Addition of CCl_3CN at the Anomeric Position.

1-oxide ion, the β-trichloroacetimidate **1a**-β is generated preferentially or even exclusively in a very rapid and reversible addition-reaction (Schemes 2 and 3). However, this product anomerizes in a slow, base-catalyzed reaction (via retroreaction, anomerization of the 1-oxide ion, and renewed trichloroacetonitrile addition) to the α-trichloroacetimidate **1a**-α having the electron-withdrawing 1-substituent in an axial disposition, as favored by the

thermodynamically operating anomeric effect. Thus, with different bases [for instance K_2CO_3, Cs_2CO_3 and NaH or 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU)] both *O*-activated anomers may be isolated in pure form and in high yields via kinetic and thermodynamic reaction-control. Both anomers are commonly thermally stable and may be stored easily. A similar result was

TABLE I

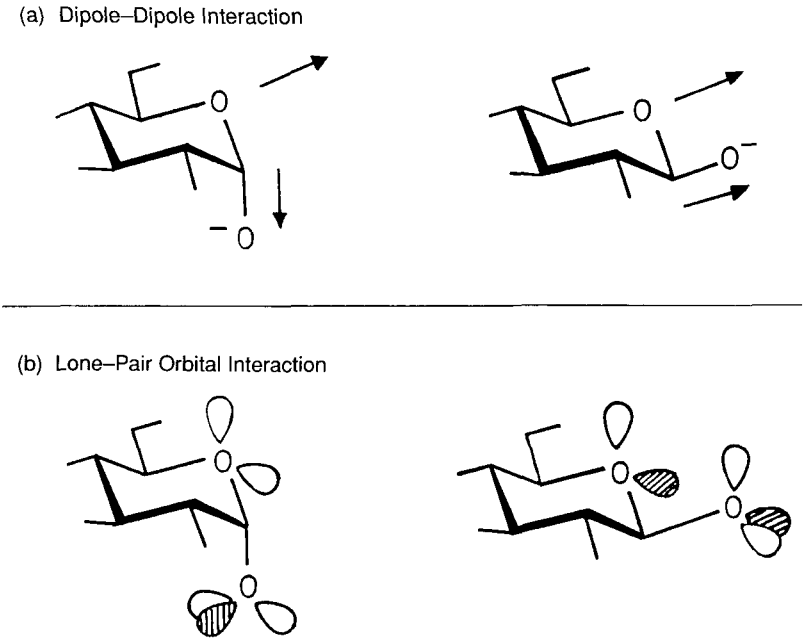
Synthesis of Trichloroacetimidates of D-Glucose

	Compound[a]	Reaction conditions	Anomeric config. (α:β)	Yield (%)	Ref.
1a-α		CH_2Cl_2, NaH, CCl_3CN, room temp.	1:0	78	65,66
1a-β		CH_2Cl_2, K_2CO_3, CCl_3CN, room temp.	0:1	90	46,67,68
1b-α		CH_2Cl_2, K_2CO_3, CCl_3CN, 48 h, room temp.	1:0	98	66
1b-β		CH_2Cl_2, K_2CO_3, CCl_3CN, 2 h room temp.	0:1	78	46
1c-α		CH_2Cl_2, NaH, CCl_3CN, room temp.	1:0	90	58a,61
1c-α,β		CH_2Cl_2, K_2CO_3, CCl_3CN, 6 h, room temp.	1:3	74	58a
1d-α		CH_2Cl_2, NaH, CCl_3CN, 1.5 h, room temp.	1:0	60	69,70

[a] Bn, benzyl; Piv, pivaloyl; Ac, acetyl.

obtained for the less reactive *O*-acetyl derivative **1b** of D-glucose, providing trichloroacetimidates **1b**-α and **1b**-β, respectively (see Table I).

The higher nucleophilicity of the β-oxide ion may be attributed to a steric factor in combination with a kinetically effective stereoelectronic effect that results from repulsions of lone electron pairs, dipole effects, or both (Scheme 5) (45,46). This effect should be more pronounced in anomeric β-oxide ions



SCHEME 5.—Enhanced Nucleophilicity of β-Oxides (Kinetic Anomeric Effect).

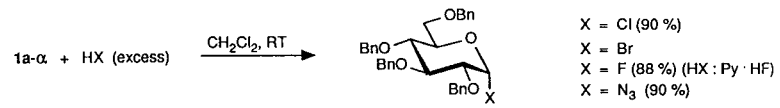
than in β-pyranosides because of the difference in the number of oxygen lone-pair orbitals and the difference in their relative energies. In addition, this *kinetic anomeric effect* should be particularly efficient in the β-mannopyranosyl oxide ion, where the thermodynamic anomeric effect, favoring the α-anomer, is also stronger. This expectation could be experimentally confirmed in the irreversible anomeric *O*-alkylation of mannopyranose, which leads in nonpolar solvents preferentially to β-glycoside formation (see references in Section II.2). However, in the reversible trichloroacetimidate formation, the stronger thermodynamic anomeric effect results in much faster generation of the α-trichloroacetimidate, and therefore trapping of the β-species becomes much more difficult. Thus, a distinction between the thermodynamic and the kinetic anomeric effect could be experimentally verified.

The stereoselective anomeric *O*-activation of carbohydrates and their derivatives via *O*-glycosyl trichloroacetimidate formation is capable of extension to all important hexopyranoses (Glc, Gal, Man, Fuc, Rha, Qui, GlcN, GalN), hexofuranoses, pentopyranoses, and pentofuranoses, as well as to glucuronic acid, galacturonic acid, and muramic acid; to 2-deoxy-*arabino*-hexose derivatives; and to many di-, tri-, and oligo-saccharides (see Section III.3). It commonly provides stable compounds in a stereocontrolled manner. Thus, the requirements put forward for the first step, namely, efficient stereocontrolled formation of stable glycosyl donors, are fulfilled (see Section II.1).

Ultimately the significance of the *O*-glycosyl trichloroacetimidates must be based solely on their glycosylation potential under mild acidic catalysis. This potential has indeed been confirmed overwhelmingly in various laboratories and is presented in comprehensive detail in this article.

2. Reaction with Brønsted Acids

The trichloroacetimidate method for glycoside synthesis extended its versatility right at the outset (51,52a) by exhibiting an especially smooth reaction of *O*-(glycosyl)trichloroacetimidates with Brønsted acids. Without the addition of any catalyst, simple Brønsted acids are able to substitute the trichloroacetimidate group at room temperature in high yields, as shown (17) for **1a**-α in Scheme 6. Because of anomerization of possible β products

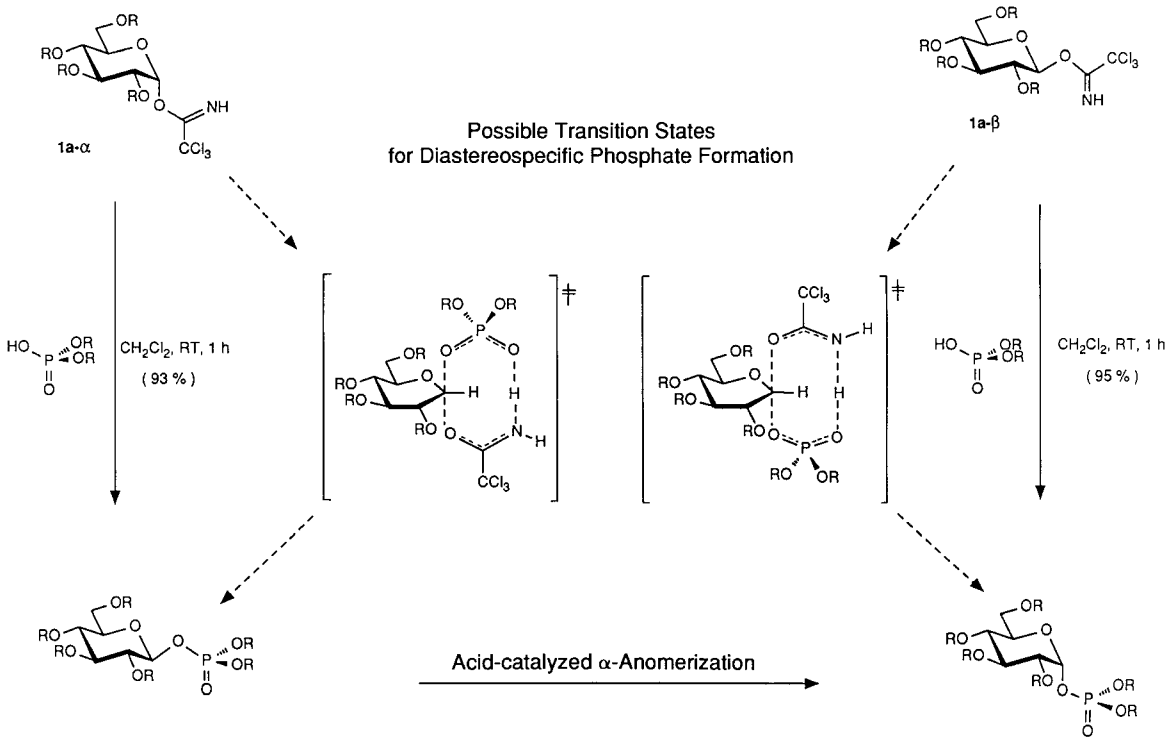


SCHEME 6. — Substitution of the Trichloroacetimidate Group by Simple Brønsted Acids.

formed at the beginning of the reaction, only α products are finally isolated in these instances.

Carboxylic acids, being weaker acids, react with **1a**-α with inversion of configuration at the anomeric center to yield β-*O*-acyl compounds (1,53). This mild and convenient method for 1-*O*-acylation of carbohydrates is also useful for pharmacological drug modification (54) or for the resolution of carboxylic acids (53).

Accordingly, phosphoric acid mono- and di-esters permit uncatalyzed glycosyl transfer from *O*-(glycosyl)trichloroacetimidates (52a,55–57,58a,58b). The reaction is thus very useful in the synthesis of glycophospholipids (1,55), which are important constituents of cell membranes (1). Commonly, direct phosphorylation at the anomeric hydroxyl group leads to



SCHEME 7. — Reaction of α- and β-Trichloroacetimidates with Dibenzyl Hydrogenphosphate.

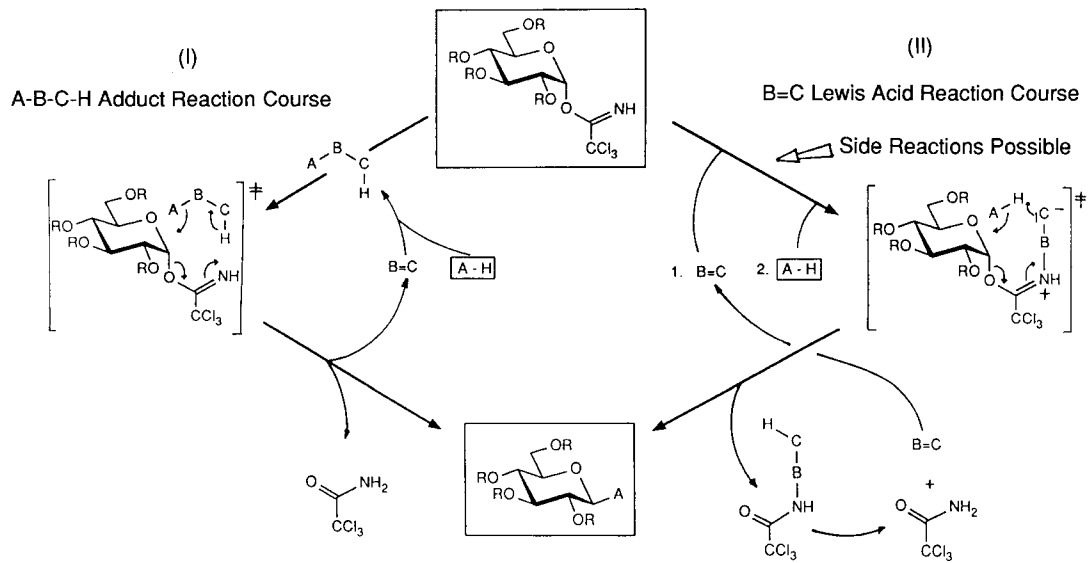
low α,β-selectivity. However, with the *O*-(glycosyl)trichloroacetimidates, a high α or β selectivity is observed and anomerization proceeds only in the presence of strong acids. Therefore, the generation of cyclic transition-states was proposed (56) (Scheme 7), which results in an SN2 type of configurational inversion. Calculations on the basic structures of the α- and β-trichloroacetimidates, respectively, exhibit ground-state conformational preference for conformers that support the intermediate generation of these cyclic transition states. Presumably, the cyclic transition-state is not a planar ring of eight atoms, because the calculated dihedral angles of the ground states deviate considerably from such a possibility, but rather resembles a chairlike transition-state with two long bonds constituting the O · · · C · · · O and N · · · H · · · O connections.

Thus, all systems having related A=B—C—H geometry may react via the cyclic transition-state proposed for phosphoric acid derivatives and therefore exhibit high diastereoselectivity. Accordingly, in addition to the carboxylic acids and the phosphoric acids already mentioned, phosphonic (59) and phosphinic acids (59), monoalkylsulfuric acid (56,60), and even α-pyridone (17,56) exhibit the same reaction behavior. However, the 2-pyridyl β-glycoside thus obtained from **1a**-α is subsequently transformed via the same kind of pyridone attack into the corresponding 2-pyridyl α-glycoside (17,61). This finding may also explain anomerization to the thermodynamically more stable product in formation of glycosyl phosphates (56).

Further development of this idea led to the proposal (56) that reactive B=C groups, for instance carbonyl systems, would be able to activate alcohol acceptors AH by generating a related A—B—C—H intermediate (Scheme 8, path I). It seemed that chloral might act as a catalyst along these lines. However, it turned out that the rate of decay in the transition state is too low in all systems tested thus far. Therefore, the carbonyl compound is more or less a substitute for a Lewis acid catalyst, as indicated in Scheme 8, path II. The high reactivity and diastereoselectivity in chloral-catalyzed reactions is attributable to the nitriles used as solvents in these reactions [see Section III.3.**b** and Ref. (62)].

3. Alcohols and Sugars as *O*-Nucleophiles

a. Introduction. — The synthesis of oligosaccharides is characterized, because of the various connections, anomeric configuration, and branching, by a much larger number of possibilities for coupling than that of other natural biopolymers, such as peptides or proteins, and ribo- or deoxy-ribonucleotides. Comparison of the number of possible isomers with those of the corresponding peptides and nucleotides impressively illustrates this point as indicated earlier (1). The wide structural variety renders sugars and, in par-



SCHEME 8.—Mechanistic Alternatives for A—H Glycosylation with B=C Catalysts.

ticular oligosaccharides, ideal as carriers of biological information, encoding considerably more information per building block than proteins and nucleic acids.

This great structural variety, however, complicates the specific biosynthesis of complex oligosaccharides. In general, the formation of each saccharide linkage requires specific enzymes ("one linkage — more than one enzyme"); and thus, in comparison with the enzymic synthesis of proteins and nucleic acids, much more effort is needed.

The chemical synthesis of oligosaccharides is also more complicated than the synthesis of other biopolymers, because the construction of each individual oligosaccharide poses a new challenge, requiring a knowledge of methods, together with experience and experimental skill. Thus, there are no universal methods available neither for biological *in vivo* nor for chemical *in vitro* syntheses.

In synthesis of a disaccharide, two polyfunctional sugar components must be specifically linked. Therefore, the reactivity and the disastereoselectivity of the glycosyl-donor species and the regioselectivity (that is, differentiation of the reactivities) at the glycosyl-acceptor species are important prerequisites for success. Protection strategies and suitable procedures for activation of the anomeric carbon atom are required; in addition, the coupling step must occur diastereoselectively with respect to formation of an α or β linkage. The high glycosylation potential of variously protected *O*-glycosyl trichloroacetimidates, their excellent α/β diastereoselectivity generally found, and their high regioselectivity often observed with partially *O*-protected sugar acceptors will be documented here.

b. *O*-Glucosyl Trichloroacetimidates as Donors. — D-Glucose (63,64) plays a central role in the formation of plant polysaccharides (for instance, such homoglycans as cellulose and starch). Also, the heteroglycan repeating-units of many bacterial, plant, and animal polysaccharides contain glucose in α- and β-glycosidic linkage. As a constituent of the oligosaccharide moieties of glycosphingolipids and glycoproteins, D-glucose is less frequently encountered. Glycosphingolipids contain D-glucose in the core region, where it is β-glycosidically linked to ceramide. In N-glycoproteins, α-linked D-glucose is a terminating signal in the biosynthesis of the complex oligosaccharide chains; fully developed glycoproteins do not contain glucose.

The synthesis and application of *O*-glucosyl trichloroacetimidates is focused on *O*-benzyl- and *O*-acetyl protected derivatives (1,52a) because these two protective groups have proven to be the most valuable in glycoside synthesis. Representative examples of trichloroacetimidate formation are collected in Table I (**1a–1d**). As already outlined (Section III.1), the glucosyl trichloroacetimidates are obtained in high yields and the diastereoselectivi-

ties observed for the base-catalyzed addition of the 1-*O*-unprotected glucose derivatives to the electron-poor trichloroacetonitrile are remarkable, thus providing α- and β-glucosyl trichloroacetimidates, respectively, depending mainly on the reaction conditions. The reaction conditions have not yet been optimized in all examples described here and in subsequent sections; this is partly attributable to the fact that α,β-mixtures can be tolerated in glycosylation reactions when neighboring-group participation controls the diastereoselectivity in glycoside-bond formation.

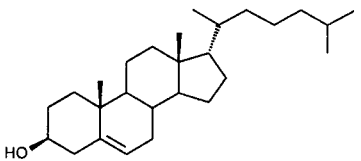
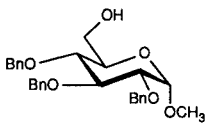
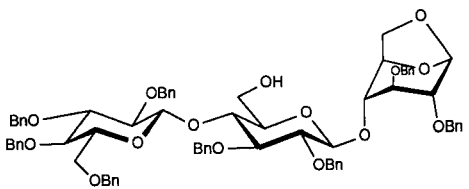
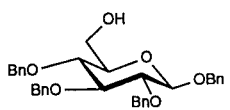
For reaction as *O*-nucleophiles with *O*-glycosyl trichloroacetimidates, alcohol components generally require the presence of an acid catalyst (1–3). Boron trifluoride etherate ($BF_3 \cdot OEt_2$) at $-40°C$ to room temperature in dichloromethane or dichloromethane–*n*-hexane as solvents and trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) at $-80°C$ to room temperature in ether or acetonitrile, respectively, as solvents have proved to be eminently suitable (52a,62). This is exemplified by the reactions of **1a**-α and **1a**-β with various acceptors (Tables II and III). It should be noted that the results reported in the tables generally have not been optimized. Obviously, even at low temperatures, **1a**-α exhibits high glycosyl-donor activity, thus providing generally the β-products in high yields and diastereoselectivities (Table II, reactions with **2A–2M**). The reaction of **2E** exhibits that the (much less reactive) thioglycosides are not affected; therefore the products obtained may be used immediately for further glycosylations. However, glycosylation of **2E** with the corresponding glucosyl fluoride as donor was not successful. The low diastereoselectivity found (71) for the reaction with acceptor **2D** is rather unexpected. It may be due to the use of trifluoromethanesulfonic acid as catalyst, which as a Brønsted acid should interfere differently with the donor **1a**-α. *O*-Acyl-protected acceptors **2J** and **2K**, having *O*-acetyl protection vicinal to the accepting hydroxyl group, proved to be less reactive, and lower α,β selectivities were found in their glycosylation with **1a**-α. *O*-Acetyl protective groups at other positions did not affect the convenient β-glycoside formation.

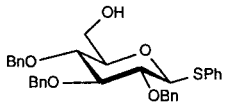
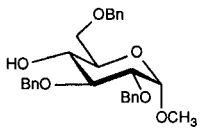
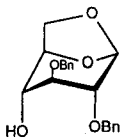
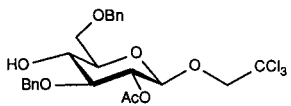
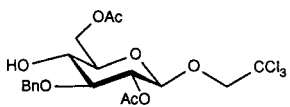
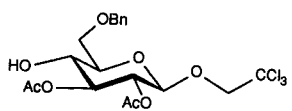
Thus far, α-glucopyranoside formation has not been extensively investigated (67) because this connection is less frequently found in glycoconjugates. However, it was observed that, with β-trichloroacetimidate **1a**-β as donor, stronger catalyst systems, as for instance Me_3SiOTf, favor formation of the thermodynamically more-stable product, especially when the reactions are performed in ethers as solvents (Table III; reactions with **3A, 2G,** and **2F**) (67).

The influence of solvents in glycosylation reactions has been observed and discussed extensively already (1,4,74). For instance, the participation of ethers, when anomeric leaving-groups are removed under SN1-type conditions, results [because of the reverse anomeric effect (75,76)] in the genera-

TABLE II

Reaction of the Benzyl-Protected Glucosyltrichloroacetimidate 1a-α with *O*-Nucleophiles

	Glycosyl acceptor	Reaction conditions	Anomeric configuration (α:β)	Yield (%)	Reference
2A		CH_2Cl_2, $BF_3 \cdot OEt_2$, $-18°C$, 2.5 h	1:13	78	51,52a
2B		CH_2Cl_2, $BF_3 \cdot OEt_2$, $-40°C$, 2 h	1:19	85	51,52a
		CH_3CN, Me_3SiOTf, $-40°C$, 20 min	1:16	89	62
		CH_3CH_2CN, Me_3SiOTf, $-40°C$, 20 min	1:16	83	62
		CH_3CH_2CN, Me_3SiOTf, $-80°C$, 15 min	1:16	74	62
2C		CH_2Cl_2, $BF_3 \cdot OEt_2$, $-35°C$	1:6	70	65
2D		CH_2Cl_2, CF_3SO_3H, $-20°C$	1.2:1	86	71

2E		CH_2Cl_2–*n*-hexane, $BF_3 \cdot OEt_2$, −10°C, 3 h	0:1	80	72
2F		CH_2Cl_2, $BF_3 \cdot OEt_2$, −30°C, 2.5 h	1:4	81	51,52a
		CH_3CH_2CN, Me_3SiOTf, −80°C, 10 min	1:19	81	62
2G		CH_2Cl_2, $BF_3 \cdot OEt_2$, −38°C, 1.5 h	1:10	90	71
2H		CH_2Cl_2, $BF_3 \cdot OEt_2$, MS 4 Å, −70°C	0:1	96	73
2I		CH_2Cl_2, $BF_3 \cdot OEt_2$, MS 4 Å, −70°C	0:1	94	71
2J		CH_2Cl_2, $BF_3 \cdot OEt_2$, MS 4 Å, −70°C	1:2.5	46	73

(continues)

TABLE II *(continued)*

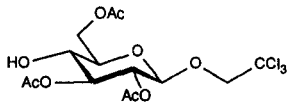
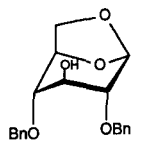
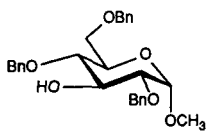
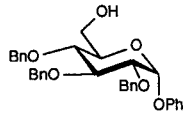
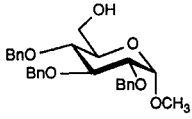
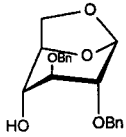
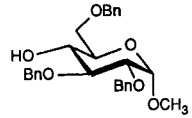
	Glycosyl acceptor	Reaction conditions	Anomeric configuration (α:β)	Yield (%)	Reference
2K		CH_2Cl_2, $BF_3 \cdot OEt_2$, MS 4 Å, −70°C	1.8:1	45	73
2L		CH_2Cl_2, $BF_3 \cdot OEt_2$, −35°C, 3.5 h	0:1	32	51,52a
2M		CH_3CH_2CN, Me_3SiOTf, −80°C, 10 min	1:24	72	62

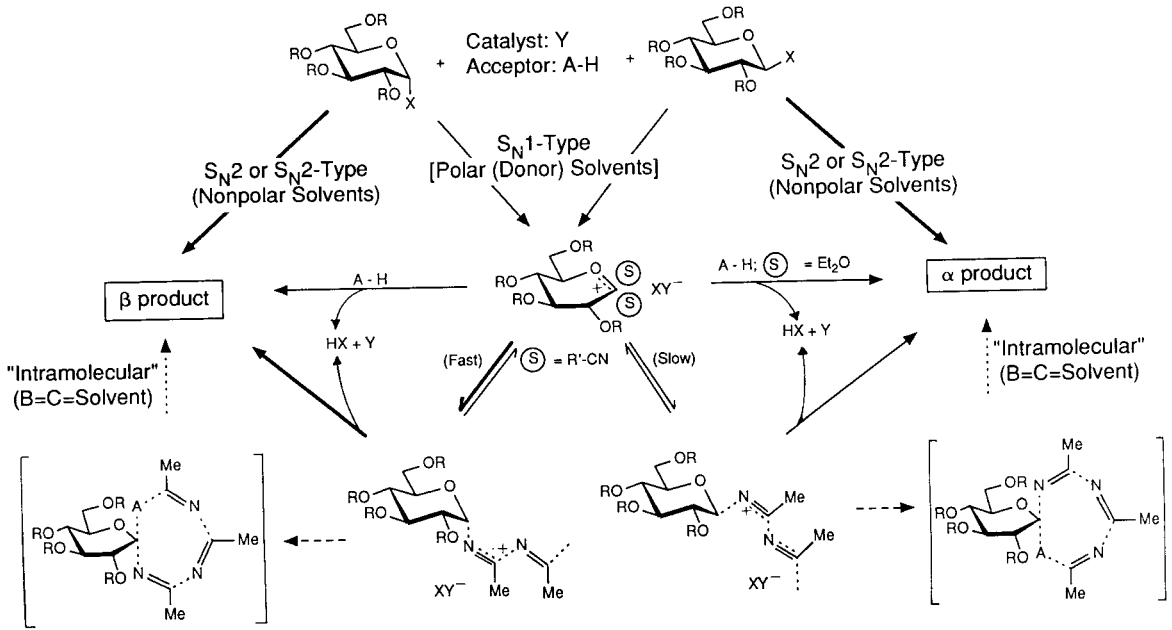
TABLE III

Reaction of the Benzyl-Protected Glucosyl Trichloroacetimidate 1a-β with *O*-Nucleophiles

	Acceptor	Reaction conditions	Anomeric configuration (α:β)	Yield (%)	Reference
3A		Et_2O, Me_3SiOTf, room temp., 2 h	8:1	85	67
		Et_2O, Me_3SiOTf, $-10°C$, 1.25 h	5:1	89	67
2B		CH_3CH_2CN, Me_3SiOTf, $-80°C$, 20 min	1:24	74	62
2G		Et_2O, Me_3SiOTf, room temp., 5 h	3:1	95	67
2F		Et_2O, Me_3SiOTf, room temp., 6 h	3:1	72	67

tion of equatorial oxonium ions (β configuration in D-glucopyranose); these favor via invertive attack of the acceptor the formation of the thermodynamically more-stable axial products (α configuration in D-glucopyranose) (Scheme 9).

The dramatic effect of nitriles as participating solvents in glycosylation reactions was first observed in *O*-glycosylations with *O*-glucosyl trichloracetimidates (51,53). This effect demonstrated that, independent of the configuration of the glucosyl donor, in the presence of a strong catalyst and at low temperatures, β-glucopyranoside formation is favored (see Tables II and III; reactions with **2B**, **2F**, and **2M**). The explanation (Scheme 9) that fast kinetic α-nitrilium–nitrile–conjugate formation providing the β-product precedes formation of the thermodynamically more-stable β-nitrilium–nitrile–conjugate, which then could also furnish α products as previously observed (77), was supported by several findings. Excellent leaving-group abilities even at low temperatures are required for the application of this methodology, and therefore, aside from trichloroacetimidates, not all leaving groups can be used in this highly useful reaction (78).



SCHEME 9.—Glycosylation Reaction Courses.

From these results there emerges a general picture of the reaction of trichloroacetimidate donors that is summarized in Scheme 9. In nonpolar solvents and with $BF_3 \cdot OEt_2$ as catalyst at temperatures as low as possible SN2 (or presumably it is better to say SN2-type) reactions (via a tight ion-pair) take place. With stronger catalysts, as for instance Me_3SiOTf, a highly reactive carbenium-ion intermediate that favors kinetic attack from the α face is generated. However, with ethers and the result of reverse anomeric attack, fast transformation into a β-face shielded intermediate takes place, leading to formation of the α product; whereas with nitriles, on account of conjugate formation, α-face shielding remains efficient. A cyclic eight-membered transition state, leading to intramolecular glycoside-bond formation as shown in Scheme 9 may be hypothesized to explain the high reactivity and selectivity.

Oligosacharides as donors bearing glucose at the reducing end and having at least nonparticipating 2-*O*-protection provided essentially the same results (Table IV) (66,79). For instance, trichloroacetimidate formation with NaH as base gave the donors **4a,b** in high yields and with high α-selectivity (65). Their reaction with acceptor **2G** furnished, under $BF_3 \cdot OEt_2$ catalysis at low temperatures, exclusively β products (65). Consideration of recent findings (see foregoing) should lead to improved yields in these reactions (62).

The reaction of glucosyl trichloroacetimidates permitting neighboring-group participation through 2-*O*-acyl protection [see for instance, the trichloroacetimidates **1b**-α,β (Table I)] exhibits generally clean β-product formation regardless of the configuration of the starting material (1) (Table V). However, the examples clearly show that the donor reactivity is lowered by acyl protection. Therefore, good yields are still attainable with reactive acceptors, but not as readily for acceptors of low reactivity. However, with Me_3SiOTf as catalyst, very promising results even for less reactive acceptors were obtained (see Table V). In the Koenigs–Knorr reaction, orthoester formation was found to be a major drawback in these kinds of reactions (4). The mildly acidic nature of the trichloroacetimidate method decreases the problem of orthoester formation, thus leading to greatly improved glycosidation yields.

Because of the presence of a C=C double bond in the sphingosine moiety, *O*-acyl protected glucosyl donors received general attention in the synthesis of glycosphingolipids (GSL). As a consequence of the many problems encountered with direct glucosylation of ceramides, employing all known glycosylation procedures, the introduction of the "azidosphingosine glycosylation" methodology, namely, glucosylation of azidosphingosine (70,84–95) (for instance, compounds **6A–6D**, Table VI) and then attachment of the fatty acyl group to the amino group liberated from the azido function, led to

TABLE IV

Reaction of Glucosyl Trichloroacetimidates of Oligosaccharides with the Nucleophile 2G

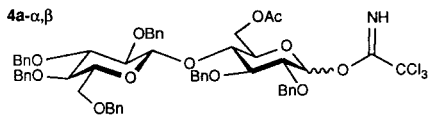
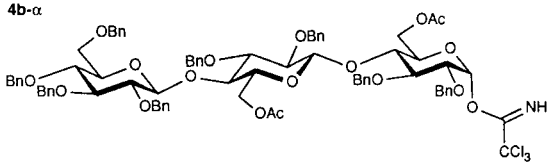
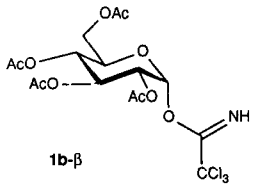
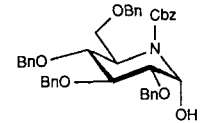
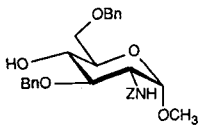
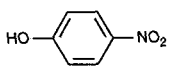
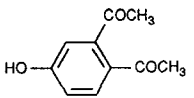
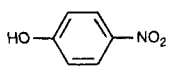
Glycosyl donor	Trichloroacetimidate formation	Reaction conditions	Anomeric configuration ($\alpha:\beta$)	Yield (%)	Reference
4a-α,β 	CH_2Cl_2, NaH, CCl_3CN, room temp., 93%, $\alpha:\beta$ 11:1	CH_2Cl_2, $BF_3 \cdot OEt_2$, −40°C, 2 h	0:1	57	65
4b-α 	CH_2Cl_2, NaH, CCl_3CN, room temp., 5 h; 96%	CH_2Cl_2, $BF_3 \cdot OEt_2$, −35°C, 5 h	0:1	40	65

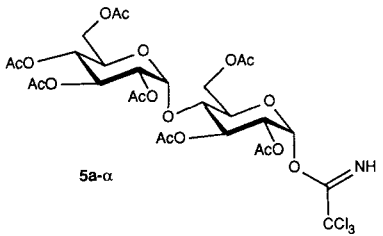
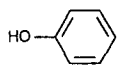
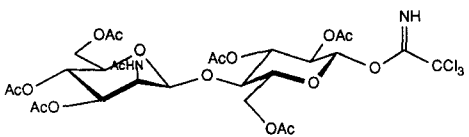
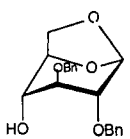
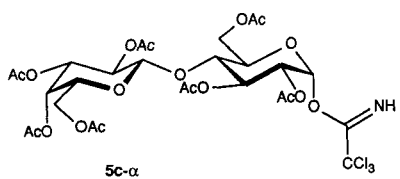
TABLE V

Glycosides and Saccharides from Acetylated Glucosyl Trichloroacetimidates

Glycosyl donor	Glycosyl acceptor[a]	Reaction conditions	Anomeric configuration (α:β)	Yield (%)	Reference
 **1b-β**	 **5A**	CH_2Cl_2, $BF_3 \cdot OEt_2$, $-30°C$	0:1	85	80
	 **5B**	CH_2Cl_2, $BF_3 \cdot OEt_2$, MS 4 Å, $-20°C$	0:1	25	81
	 **5C**	CH_2Cl_2, $BF_3 \cdot OEt_2$, room temp., 2 h	0:1	67	51,52a
1b-β	 **5D**	CH_2Cl_2, $BF_3 \cdot OEt_2$, room temp., 2 h	0:1	74	51,52a
	 **5C**	CH_2Cl_2, $BF_3 \cdot OEt_2$, room temp., 45 min	0:1	64	51, 52a

(continues)

TABLE V *(continued)*

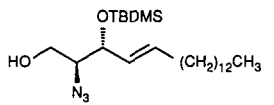
Glycosyl donor	Glycosyl acceptor[a]	Reaction conditions	Anomeric configuration ($\alpha:\beta$)	Yield (%)	Reference
 5a-α	 5E	CH_2Cl_2, $BF_3 \cdot OEt_2$, room temp.	0:1	78	51
 5b-α	 2G	CH_2Cl_2, Me_3SiOTf, −20°C, 45 min	0:1	81	82
 5c-α	$HOCH_2COOCH_3$ (5F)	CH_2Cl_2, Me_3SiOTf, −15°C, 30 min	0:1	65	83
	$HO(CH_2)_3COOCH_3$ (5G)	CH_2Cl_2, Me_3SiOTf, −15°C, 30 min	0:1	73	83
	$HO(CH_2)_8COOCH_3$ (5H)	CH_2Cl_2, Me_3SiOTf, −15°C, 30 min	0:1	72	83
	$HOCH_2COOCH_2Ph$ (5I)	CH_2Cl_2, Me_3SiOTf, −15°C, 30 min	0:1	71	83
	$HO(CH_2)_3COOCH_2Ph$ (5J)	CH_2Cl_2, Me_3SiOTf, −15°C, 30 min	0:1	67	83

[a] Cbz, Z, benzyloxycarbonyl.

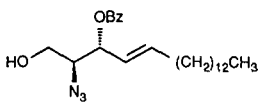
TABLE VI

Glycosylation of Azidosphingosine Derivatives with Trichloroacetimidates

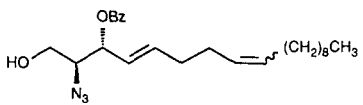
Glycosyl acceptor[a]

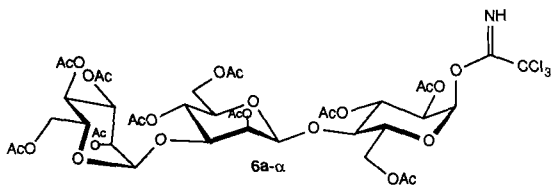
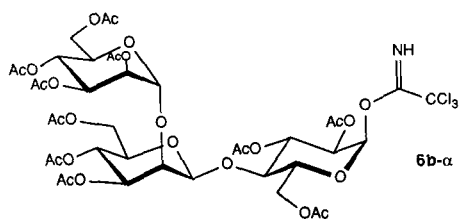


6A



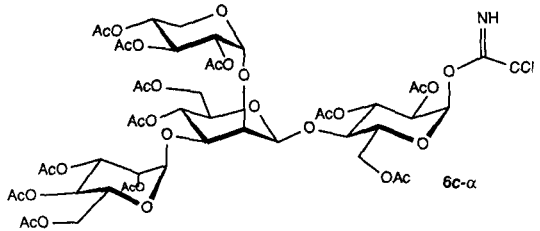
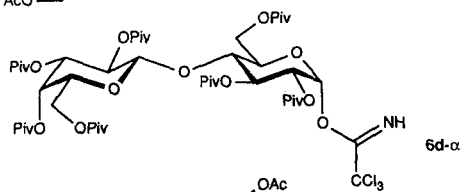
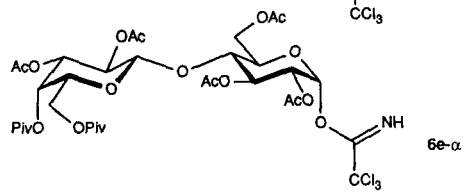
6B

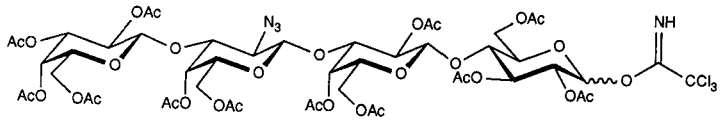


Glycosyl donor	Reaction conditions[b]		Reference
1b-α	Trichloroacetimidate:	See Table I	86
	Glycosylation:	**6C**, CH_2Cl_2, $BF_3 \cdot OEt_2$; 80% β	
1b-α	Trichloroacetimidate:	See Table I	87
	Glycosylation:	**6D**	
1d-α	Trichloroacetimidate:	See Table I	84
	Glycosylation:	**6B**, CH_2Cl_2, $BF_3 \cdot OEt_2$, room temp.; 94% β	
 **6a-α**	Trichloroacetimidate:	CH_2Cl_2, CCl_3CN, DBU; 88% α	91
	Glycosylation:	**6A**, CH_2Cl_2, Me_3SiOTf; 51% β	
 **6b-α**	Trichloroacetimidate:	CH_2Cl_2, CCl_3CN, DBU; 97% α	91
	Glycosylation:	**6A**, CH_2Cl_2, $BF_3 \cdot OEt_2$; 32% β	

(continues)

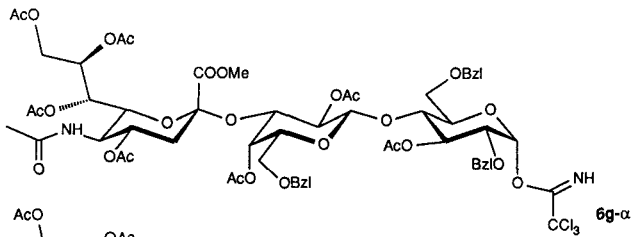
TABLE VI *(continued)*

Glycosyl donor	Reaction conditions[b]		Reference
 6c-α	Trichloroacetimidate:	$(CH_2Cl_2)_2$, CCl_3CN, DBU, −20°C; 88% α	91
	Glycosylation:	**6A**, CH_2Cl_2, Me_3SiOTf; 64% β **6B**, CH_2Cl_2, Me_3SiOTf; 68% β	
 6d-α	Trichloroacetimidate:	CH_2Cl_2, NaH, CCl_3CN, room temp.; 52% α	84,85
	Glycosylation:	**6B**, CH_2Cl_2, $BF_3 \cdot OEt_2$; 87% β	
 6e-α	Trichloroacetimidate:	CH_2Cl_2, NaH, CCl_3CN; 66% α	85
	Glycosylation:	**6B**, CH_2Cl_2, $BF_3 \cdot OEt_2$; 78% β	



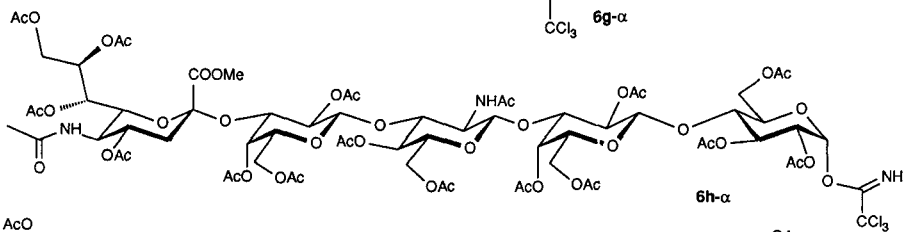
6f-α,β

Trichloroacetimidate:	CH_2Cl_2, NaH, CCl_3CN; 92%, $\alpha:\beta$ 4:1	92
Glycosylation:	**6B**, CH_2Cl_2–*n*-hexane, BF_3OEt_2; 71% β	



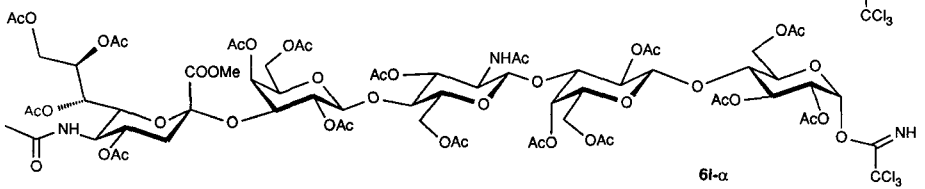
6g-α

Trichloroacetimidate:	CH_2Cl_2, CCl_3CN, 0°C, 2 h; 94% α	93
Glycosylation:	**6B**, CH_2Cl_2, $BF_3 \cdot OEt_2$, 0°C, 4 h; 92% β	93



6h-α

Trichloroacetimidate:	CH_2Cl_2, CCl_3CN, DBU, 0°C; 88% α	94
Glycosylation:	**6B**, CH_2Cl_2, $BF_3 \cdot OEt_2$, 0°C, 8 h; 56% β	94

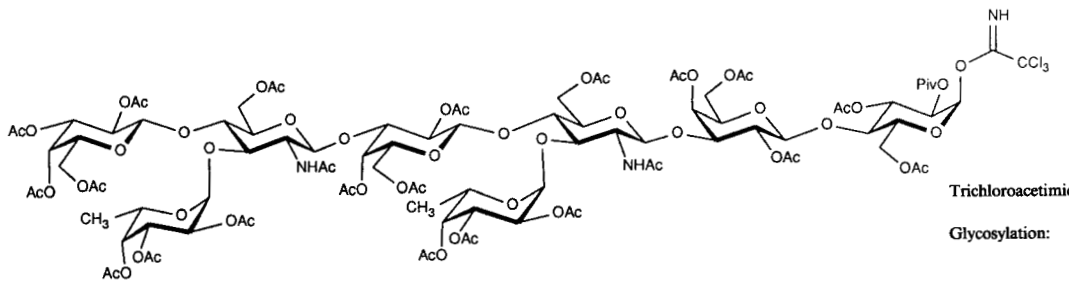
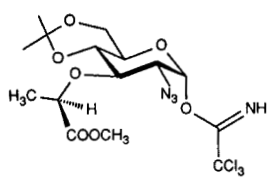


6i-α

Trichloroacetimidate:	CH_2Cl_2, CCl_3CN, DBU; 87% α	94
Glycosylation:	**6B**, CH_2Cl_2, $BF_3 \cdot OEt_2$; 42% β	94

(continues)

TABLE VI *(continued)*

Glycosyl donor	Reaction conditions[b]		Reference
 **6j-α**	Trichloroacetimidate:	CH_2Cl_2, CCl_3CN, DBU; 87% α	96
	Glycosylation:	**6B**, CH_2Cl_2, Me_3SiOTf (0.01 eq.), room temp.; 75% β	96
 **6k-α**	Trichloroacetimidate:	CH_2Cl_2, NaH, CCl_3CN; 90% α	57
	Glycosylation:	**6B**, CH_2Cl, $BF_3 \cdot OEt_2$, −20°C; 85% β	97

[a] TBDMS, *tert*-butyldimethylsilyl.
[b] DBU, 1,8-diazabicyclo[5,4,0]undec-7-ene.

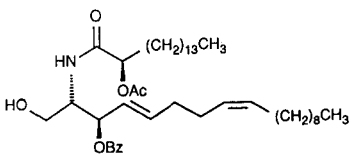
a major breakthrough in GSL synthesis. This is demonstrated in Table VI, which includes representative examples of this development. Thus, not only were simple glycosyl and lactosyl derivatives made readily accessible, but all major glycosphingolipid series were successfully synthesized, including gangliosides that contain neuraminic acid. The importance of tumor-associated antigens of glycosphingolipid nature also created interest in several L-fucose-containing glycosphingolipids, for instance, the Lewis X (Le^X) and Lewis Y (Le^Y) antigens. The acid sensitivity of the fucosyl anomeric bond generally requires special attention in glycoside-bond formation. However, it turned out that these *O*-acetyl protected donors did not cause any problems under the required reaction conditions. On account of the high acceptor reactivity of the azidosphingosines, orthoester formation as a side reaction was encountered for the first time (85). In many instances a slightly higher catalyst concentration readily overcomes this problem. The problem may also be solved with the help of 2-*O*-acyl-protective groups, which for steric (2-*O*-pivaloyl) or electronic (2-*O*-benzoyl) reasons do not undergo orthoester formation as readily as do 2-*O*-acetyl groups (70,85).

As just discussed, "ceramide glycosylation" seemed to cause major problems when the Koenigs–Knorr method was used (84). However, *O*-acetyl protected glycosyl trichloroacetimidate donors also provided acceptable yields with glucosyl or the lactosyl trichloroacetimidates (Table VII) (84,98–108). For higher oligosaccharide donors the results were unsatisfactory. However, again by attaching the bulky 2-*O*-pivaloyl group to the glucose moiety, this drawback may be overcome (84,101), a result which reinforces the search for further improvements in this most active field.

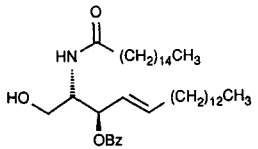
c. *O*-Galactosyl Trichloroacetimidates as Donors. — D-Galactose (63,64) is a constituent of complex glycosphingolipids and glycoproteins, where it plays an important role. It is found as a terminal or subterminal building block in a variety of different connections. In glycosphingolipids, galactose is part of the lactosyl ceramide core-structure. Terminal and subterminal β-(1 → 4)-connection to 2-acetamido-2-deoxy-D-glucose (*N*-acetylglucosamine) leads to the *N*-acetyllactosamine moiety, which is preferentially represented in the *lacto* and the *neolacto* series. The α-(1 → 4) and α-(1 → 3) connection determines the *gala, globo,* and *isoglobo* series. In glycoproteins, terminal galactose is a signal of the Ashwell receptor, whose function consists in the binding of galactosylated glycoproteins in the liver. In the asparagine-connected glycan residues of N-glycoproteins, galactose is mainly found in *N*-acetyllactosamine, whereas in the serine- or threonine-connected *O*-glycoproteins, galactose is preferentially β-(1 → 3)-linked to 2-acetamido-2-deoxy-D-galactose (*N*-acetylgalactosamine). This connection is also met in the *ganglio* and the *isoganglio* series of glycosphingolipids.

TABLE VII

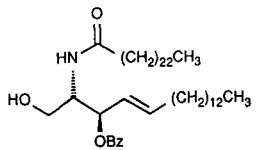
Glycosylation of Ceramides by Trichloroacetimidates



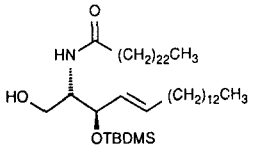
7A



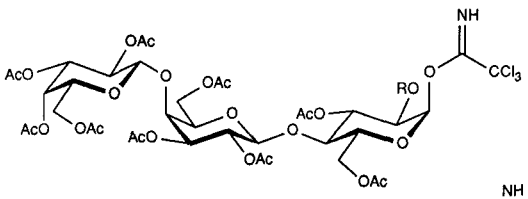
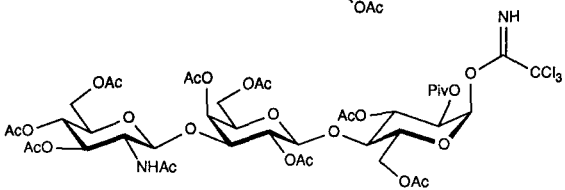
7B

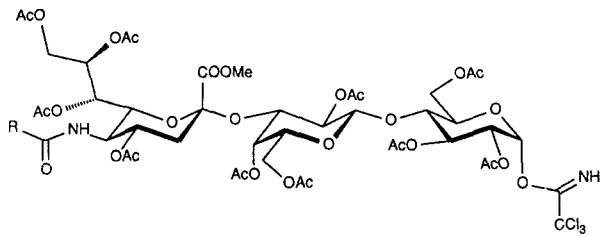


7C

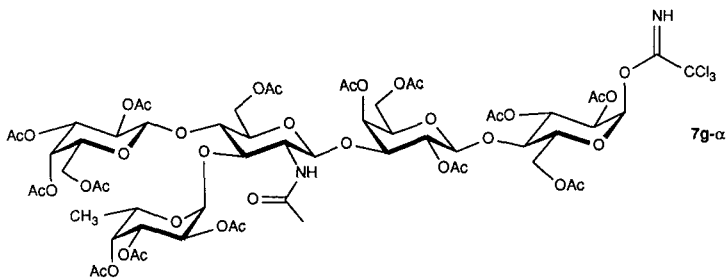


7D

Glycosyl donor	Trichloroacetimidate formation[a]	Glycosylation conditions	Yield (%)	Reference
1b-α	See Table I	7A, CH_2Cl_2, $BF_3 \cdot OEt_2$	57	86
1b-α	See Table I	7B, CH_2Cl_2, $BF_3 \cdot OEt_2$, room temp.	70	98
	**7a-α**: R = Ac; CCl_3CN, DBU; 79%	7C	13	100
	7b-α: R = Piv; 52%	7C, Me_3SiOTf	66	101
	7c-α: R = TMP	7D, Me_3SiOTf	27	102
	**7d-α**: 83% α	7C, Me_3SiOTf	37	101



7e-α: R = CH_3; CCl_3CN, DBU; 92%	**7D**, $BF_3 \cdot OEt_2$, $(CH_2Cl_2)_2$	52	103
7f-α: R = CH_2OAc; CCl_3CN, DBU; 76%	**7D**, $BF_3 \cdot OEt_2$, $(CH_2Cl_2)_2$	58	103

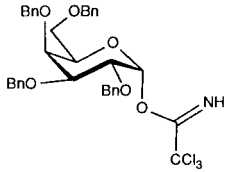
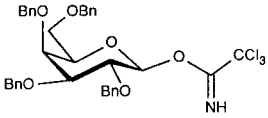
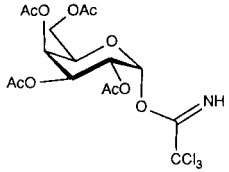
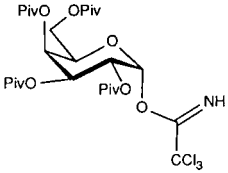
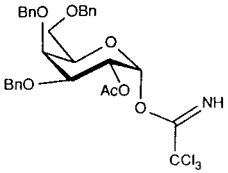
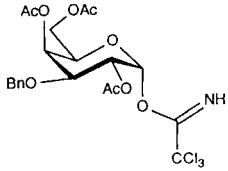


7g-α	**7g-α**	**7C**, $BF_3 \cdot OEt_2$	7	104

[a] TMP, 2,4,6-trimethylbenzoyl.

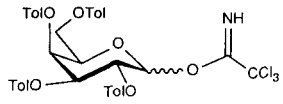
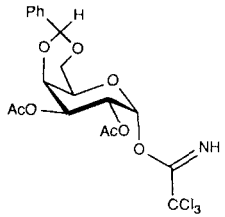
TABLE VIII

Synthesis of Trichloroacetimidates of D-Galactose[a]

	Trichloroacetimidate	Reaction conditions	Yield (%)	Reference
8a-α		CCl_3CN, CH_2Cl_2, NaH, room temp.	83	46
8a-β		CCl_3CN, CH_2Cl_2, K_2CO_3, room temp.	84	67,68
8b-α		CCl_3CN, CH_2Cl_2, Na, room temp.	39 α + 45 β	66,104,109
8c-α		CCl_3CN, CH_2Cl_2, NaH, room temp., 1.5 h	60	85
8d-α		CCl_3CN, CH_2Cl_2, DBU	80	110
8e-α		CCl_3CN, CH_2Cl_2, DBU, −5°C	71	111

(continues)

TABLE VIII *(continued)*

	Trichloroacetimidate	Reaction conditions	Yield (%)	Reference
8f-α		CCl_3CN, CH_2Cl_2, NaH, MS 4 Å, 0°C, 2 h	76	112
8g-α		CCl_3CN, CH_2Cl_2, NaH, room temp.	77	113

[a] Tol, Toluyl; DBU, 1,8-diazabicyclo[5,4,0]undec-7-ene.

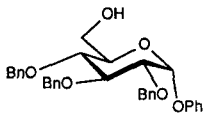
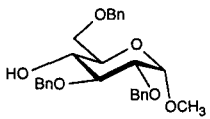
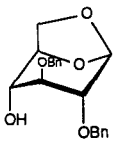
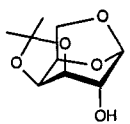
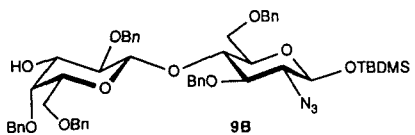
1-*O*-Unprotected galactose derivatives may be readily transformed into the trichloroacetimidates **8a–8g,** as shown in Table VIII. Again, as demonstrated for the *O*-benzyl-protected compounds **8a,** either the α-trichloroacetimidate **8a**-α or the β-trichloroacetimidate **8a**-β may be obtained highly selectively, depending on the base used for the catalysis of the addition to the trichloroacetonitrile.

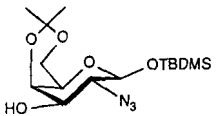
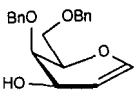
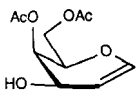
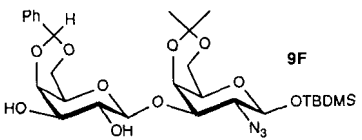
Galactosylation with the *O*-benzyl-protected donors **8a**-α and **8a**-β (Table IX) shows that conditions can be found for invertive product-formation in high yields. Thus, from **8a**-β in ether, preferentially α products were formed, and from **8a**-β in the rather nonpolar solvent-mixture dichloromethane–*n*-hexane, mainly the β product was obtained. The higher tendency of galactosyl donors to effect α-glycoside bond-formation compared with the corresponding glucosyl donors is well established in the literature (4) and is also observed here. This may be attributed to the generally higher reactivity of the galactosyl donor and to the axial 4-substituent.

2-*O*-Acyl-protected galactosyl donors readily provide β products. The reactivity may be increased by having partial *O*-benzyl protection, as exhibited (110,111) with donors **8d**-α and **8e**-α (Table X). The examples permit very successful 2-*O*-, 3-*O*-, and 4-*O*-connections, respectively. The high-yielding synthesis of the β-Gal-(1 → 3)-GalNAc building-blocks [**8f**-α + **10H,** Table X (112), and **8a**-α + **9C,** Table IX (115)] furnishes a convenient access to *O*-glycoprotein moieties; for instance, selective removal of the 1-*O*-Bu^{t}Me$_2$Si protective group in the **8a–9C** β-product (Table IX) and subsequent β-trichloroacetimidate formation leads to the desired β-Gal-

TABLE IX

Glycosidation with Benzylated Galactosyl Trichloroacetimidates[a]

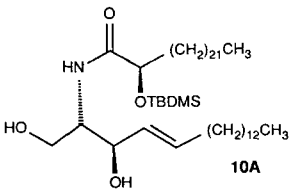
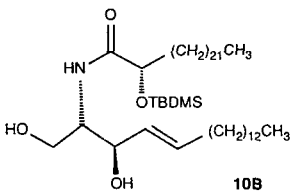
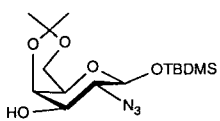
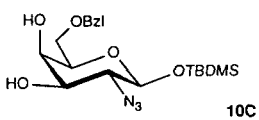
Trichloroacetimidate	Glycosyl acceptor	Reaction conditions	Yield (%)	Anomeric configuration (α:β)	Reference
8a-β	 **3A**	$(C_2H_5)_2O$, TBDMSOTf, room temp., 0.75 h	75	5:1	67
8a-β	 **2F**	$(C_2H_5)_2O$, Me_3SiOTf, room temp., 5 h	65	8:1	67
8a-β	 **2G**	$(C_2H_5)_2O$, Me_3SiOTf, room temp., 1 h	66	36:1	67
8a-β	 **9A**	$(C_2H_5)_2O$, Me_3SiOTf, room temp., 3.5 h	77	8:1	67
8a-β	 **9B**	$(C_2H_5)_2O$, Me_3SiOTf, $-20°C$	75	1:0	114

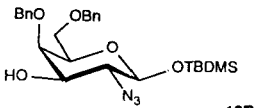
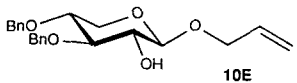
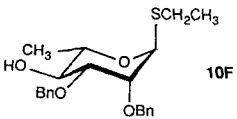
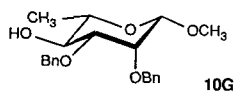
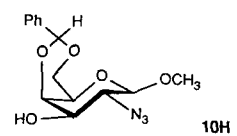
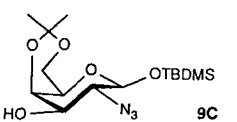
8a-α		**9C**	CH_2Cl_2–*n*-hexane, $BF_3 \cdot OEt_2$	84	1:7	115
8a-α		**9D**	CH_2Cl_2–*n*-hexane, Me_3SiOTf, −25°C	80	1:4	116
8a-α			CH_3CH_2CN, Me_3SiOTf, −40°C	75	0:1	72
8a-α		**9E**	CH_2Cl_2–*n*-hexane, $BF_3 \cdot OEt_2$, −25°C	83	1:3	72
8a-α		**9F**	CH_2Cl_2–*n*-hexane, Me_3SiOTf, −30°C, 2 h	49	1:0 (2-0)	117

[a] TBDMS, *tert*-butyldimethylsilyl.

TABLE X

Glycosylation with Acetylated Galactopyranosyl Trichloroacetimidates[a]

Trichloro-acetimidate	Glycosyl acceptor	Reaction conditions	Yield (%)	Anomeric configuration (α:β)	Reference
8b-α	 **10A**	$CHCl_3$, $BF_3 \cdot OEt_2$, MS 3 Å	33	0:1	118
8b-α	 **10B**	$CHCl_3$, $BF_3 \cdot OEt_2$, MS 4 Å	31	0:1	118
8b-α	 **9C**	CH_2Cl_2–*n*-hexane, $BF_3 \cdot OEt_2$, room temp., 1 h	67	0:1	117
8b-α	 **10C**	CH_2Cl_2–*n*-hexane, $BF_3 \cdot OEt_2$, −20°C, 2 h	69	0:1 (3-0)	117

8b-α	 **10D**	CH_2Cl_2–*n*-hexane, $BF_3 \cdot OEt_2$, −20°C, 2 h	65	0:1	117
8d-α	 **10E**	CH_2Cl_2, $BF_3 \cdot OEt_2$, MS 4 Å	73	0:1	110
8e-α	 **10F**	CH_2Cl_2, Me_3SiOTf, MS 4 Å, −30°C, 20 min	81	0:1	111
8e-α	 **10G**	CH_2Cl_2, Me_3SiOTf, MS 4 Å, −30°C, 10 min	87	0:1	111
8f-α	 **10H**	CH_2Cl_2, Me_3SiOTf, 10°C, 15 min	93	0:1	112
8g-α	 **9C**	CH_2Cl_2–*n*-hexane, $BF_3 \cdot OEt_2$, room temp., 1 h	75	0:1	113

[a] TBDMS, *tert*-butyldimethylsilyl.

(1 → 3)-α-GalNAc-(1 → O)-Ser glycopeptide moiety (115). The reaction of **8e**-α with thioglycoside (111) **10F** demonstrates again that a thio group at the anomeric position is compatible with application of the trichloroacetimidate method.

Among the gangliosides, G_M4 [α-NeuAc-(2 → 3)-β-Gal-(1 → O)-Cer] has a relatively simple chemical structure. It has been detected in human and chicken brain and also (119) as a major ganglioside of mouse erythrocytes, chicken-embryonic liver, and egg yolk. With the help of the azidosphingosine glycosylation it has been synthesized very efficiently from the neuraminic acid-containing galactosyl donor **11a**-β (Table XI) (120–122). Similarly the thio isomer was obtained from **11b**-β and (120,123) the positional isomer from **11c**-α.

d. *O*-Mannopyranosyl Trichloroacetimidates as Donors. — D-Mannose (63,64) is less frequently encountered in glycosphingolipids (only in the *arthro* series); however, it is generally a constituent of N-glycoproteins: a central α-Man-(1 → 6) [α-Man-(1 → 3)]Man trisaccharide moiety, which is β-(1 → 4)-connected to a chitobiose unit, is part of the core structure.

Mannopyranosyl trichloroacetimidates that have been synthesized are compiled in Table XII. Because of the stronger anomeric effect (1,45,75), α-trichloroacetimidate formation is much faster than observed for corresponding glucose and galactose derivatives, and therefore the α-trichloroacetimidates were generally isolated thus far. This was not regarded as a disadvantage because α-mannopyranoside formation, for instance from **12a**-α, should be readily achieved because of the stronger anomeric effect under thermodynamic reaction control. The examples in Table XIII show that this is indeed the case; selective α-product formation was observed even with $BF_3 \cdot OEt_2$ as catalyst. However, clean β-product formation from the α anomer **12a**-α under invertive conditions has not yet been achieved (51). Even the nitrile effect, as found recently, led to only partial success in this endeavor (62) (Table XIII). The ready formation of the α-mannopyranosyl linkage is also true for the 2-*O*-glycosylated *O*-mannopyranosyl trichloroacetimidates **14a**-α–**14e**-α (Table XIV). Use of Me_3SiOTf as catalyst would be presumably superior in these reactions.

2-*O*-Acyl protection should lead, as a consequence of neighboring-group participation and the anomeric effect, exclusively to α products. This has been proved in many experiments (Table XV); with Me_3SiOTf as catalyst excellent yields could be obtained in cases where all other methods essentially failed (129). It could be shown that at least some of the reactions proceed via rapid orthoester formation (129), and this intermediate then rearranges under Me_3SiOTf catalysis to the desired reaction product.

TABLE XI

Glycosylation of Trichloroacetimidates of D-Galactose with Sphingosine Derivative 6B

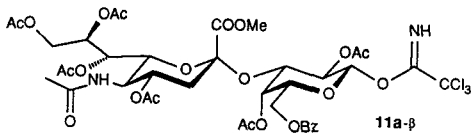
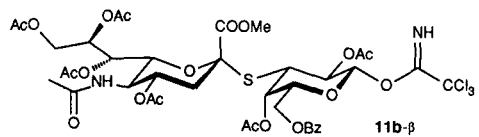
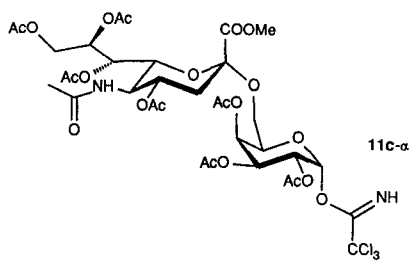
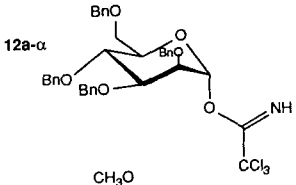
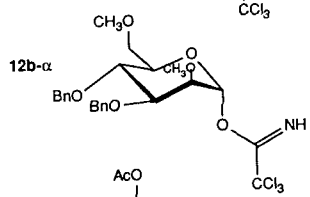
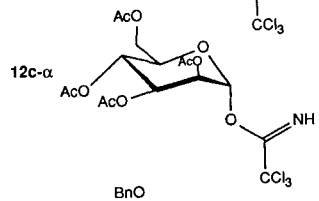
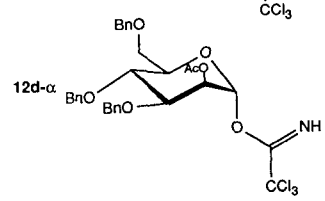
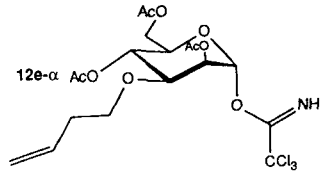
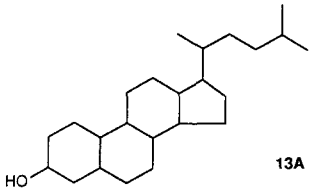
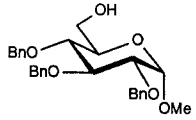
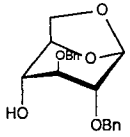
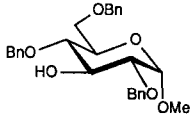
Glycosyl donor	Trichloroacetimidate formation	Reaction conditions	Yield (%)	Reference
8c-α	See Table VIII	CH_2Cl_2, BF_3OEt_2, room temp.	96 β	85
 **11a-β**	CH_2Cl_2, CCl_3CN, DBU, 0°C, 2 h; 79–93%, α:β 1:8	CH_2Cl_2, BF_3OEt_2, 0°C	82 β	120,121,122
 **11b-β**	CH_2Cl_2, CCl_3CN, NaH, 0°C; α:β 0:1, 85%	CH_2Cl_2, BF_3OEt_2, 0°C	70 β	123
 **11c-α**	CH_2Cl_2, CCl_3CN; α:β 11:1	CH_2Cl_2, BF_3OEt_2	78 β	120

TABLE XII
Trichloroacetimidates of D-Mannose

Trichloroacetimidate	Reaction conditions	Anomeric config. (α:β)	Yield (%)	Ref.
12a-α 	CH_2Cl_2, CCl_3CN, NaH, room temp., 0.5 h	1:0	99	46,124
12b-α 	CCl_3CN, NaH	1:0	46	125
12c-α 	CH_2Cl_2, CCl_3CN, NaH, 0°C–room temp., 20 min	1:0	n.n.	91,126
12d-α 	$(ClCH_2)_2$, CCl_3CN, DBU −5°C	1:0	98	127,128
12e-α 	CH_2Cl_2, CCl_3CN, K_2CO_3, **1α**	1:0	86	129

e. Trichloroacetimidates of Glucosamine Derivatives as Glycosyl Donors.—2-Acetamido-2-deoxy-D-glucose (*N*-acetylglucosamine) (63,64, 119) is an important constituent of all glycoconjugates. In the glycan chains of N-glycoproteins it is part of the core and of the glycan side-chains. In glycosphingolipids of the *lacto* and the *lactoneo* series, it is the main constituent. In proteoglycans, in bacterial lipopolysaccharides, in the murein of

TABLE XIII
Reactions with Mannosyl Trichloroacetimidate 12a-α

Acceptor		Reaction conditions	Anomeric config. (α:β)	Yield (%)	Ref.
	13A	CH_2Cl_2, $BF_3 \cdot OEt_2$, −15°C, 2 h	5:1	83	51
		CH_2Cl_2, $BF_3 \cdot OEt_2$, 20°C, 5.5 h	1:0	73	51
	2B	CH_2Cl_2, $BF_3 \cdot OEt_2$, 20°C, 20 h	1:0	68	51
		CH_3CH_2CN, Me_3SiOTf, −80°C, 20 min	1:1	77	62
		CH_3CH_2CN–*n*-hexane (1:4), Me_3SiOTf, −80°C, 20 min	3:2	70	62
	2G	CH_2Cl_2, $BF_3 \cdot OEt_2$, 20°C, 4 h	1:0	66	51
	2M	CH_3CH_2CN, Me_3SiOTf, −80°C, 10 min	1:1	71	62

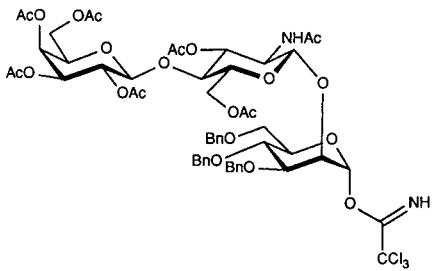
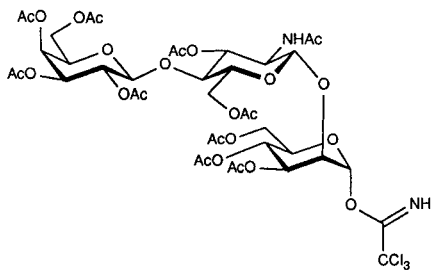
bacterial cell-walls, and as a polycondensation product in chitin it has wide distribution. In *N*-deacetylated form as free glucosamine it was identified as a constituent of glycosylphosphatidylinositols, which are membrane anchors for cell-surface glycoproteins (136).

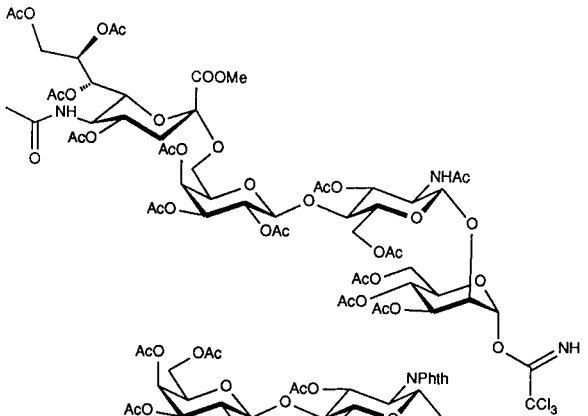
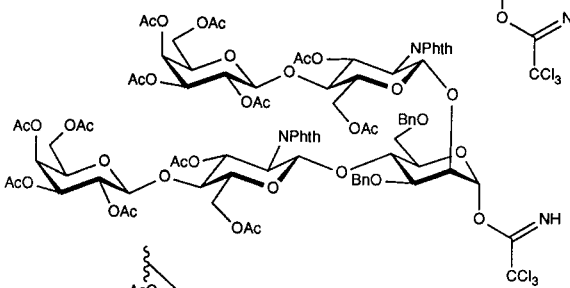
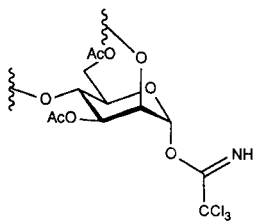
This wide distribution is accompanied by a variety of different linkages, as compiled in Table XVI. Obviously, β-connection is generally favored.

(*i*) Glucosamine Donors.—The great number of trichloroacetimidates synthesized thus far underlines the fact that compounds displaying high reactivity and high diastereocontrol are required for the great variety of

TABLE XIV

Glycosides and Saccharides from Mannosyl Trichloroacetimidates

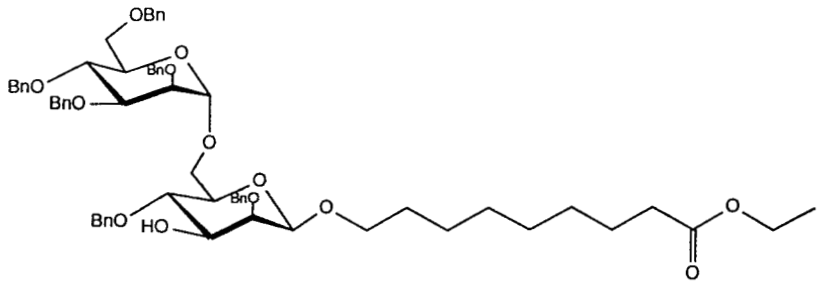
Trichloroacetimidate[a]	Trichloroacetimidate formation	Reaction conditions	Reference
14a 	CH_2Cl_2, CCl_3CN, NaH; 95% α	**14A**, $BF_3 \cdot OEt_2$, MS 4 Å; 45% α	130,131
14b 	CH_2Cl_2, CCl_3CN, DBU, 0°C, 30 min; 87% α	**14B**; 10% α **14C**, BF_3OEt_2, CH_2Cl_2; 60% α **14D**, $BF_3 \cdot OEt_2$; 53% α-(1 → 6) **14G**; 58% α	133,134

14c		$(CH_2Cl)_2$, CCl_3CN, DBU; 85% α	**14E**, $BF_3 \cdot OEt_2$, MS 4 Å, −10°C; 48%, α-(1 → 6)	132
14d		CH_2Cl_2, CCl_3CN, NaH; 92% α	**14F**, $BF_3 \cdot OEt_2$; 66%, $\alpha:\beta$ 1:1 **14A**, $BF_3 \cdot OEt_2$; 11%, $\alpha:\beta$ 2.3:1	126,130
14e		$(CH_2Cl)_2$, CCl_3CN, DBU, 0–20°C; 99% α	**14F**, $BF_3 \cdot OEt_2$; 52%, $\alpha:\beta$ 1:0	130

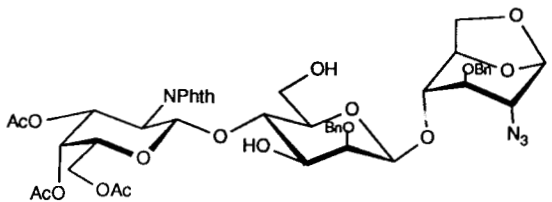
[a] MCA, monochloroacetyl.

(continues)

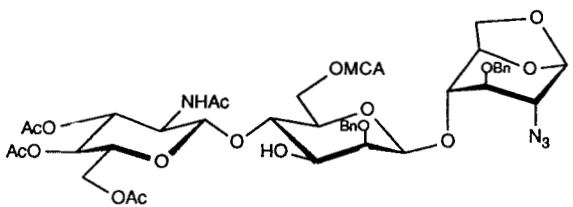
TABLE XIV *(continued)*



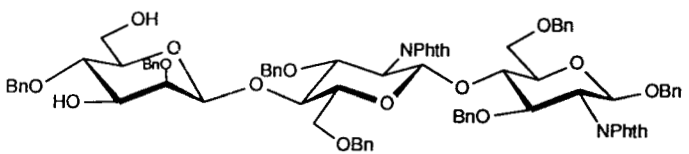
14A



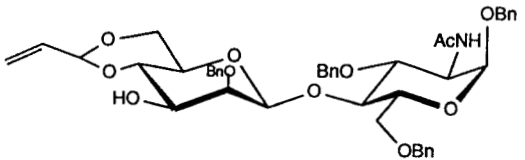
14D



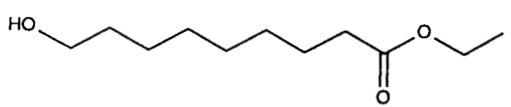
14B



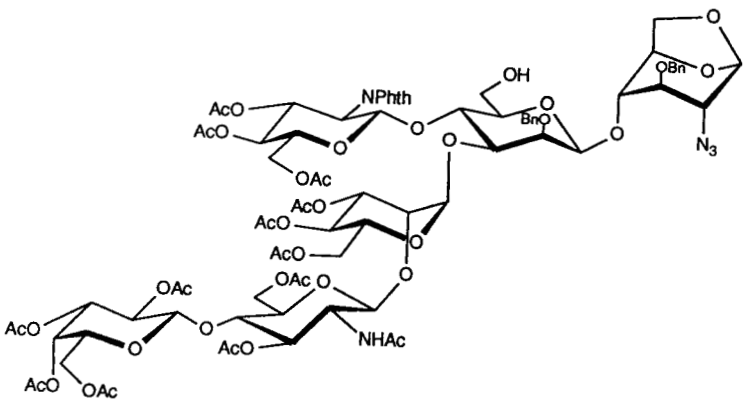
14E


OBn
AcNH
BnO
BnO
HO
O
O
O
O
O
O
OBn

14C


HO
O
O

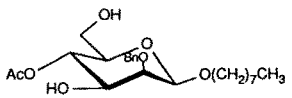
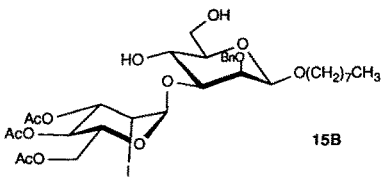
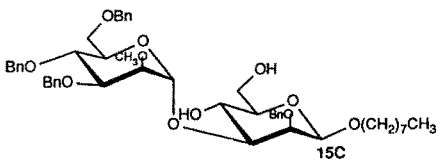
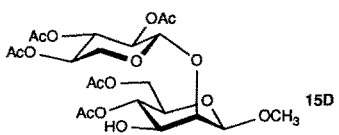
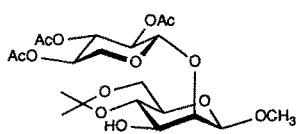
14F


AcO
AcO
NPhth
OAc
OH
BnO
O
O
O
OBn
O
N3
AcO
AcO
AcO
OAc
OAc
O
AcO
AcO
OAc
NHAc
AcO
OAc

14G

TABLE XV

Glycosylation of Acetylated Trichloroacetimidates of D-Mannose

Trichloro-acetimidate	Glycosyl acceptor	Reaction conditions	Yield (%)	Reference
12c-α	 **15A**	CH_2Cl_2, Me_3SiOTf, MS 3 Å, −10°C, 10 min	59 α-(1 → 6)	135
12c-α	 **15B**	CH_2Cl_2, Me_3SiOTf, MS 3 Å, −20°C, 20 min	60 α-(1 → 6)	135
12c-α	 **15C**	CH_2Cl_2, $BF_3 \cdot OEt_2$, MS 3 Å, room temp., 1 h	56 α-(1 → 6)	135
12c-α	 **15D**	CH_2Cl_2, Me_3SiOTf, MS 4 Å, −30°C, 10 min	88 α	127
12c-α	 **15E**	CH_2Cl_2, Me_3SiOTf, −30°C, 10 min	92 α	126

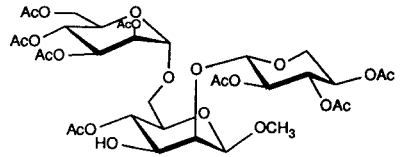
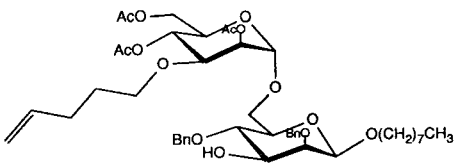
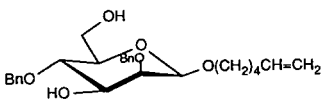
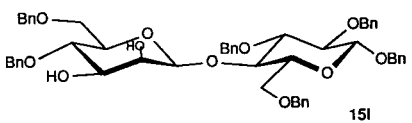
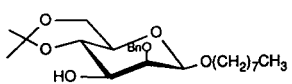
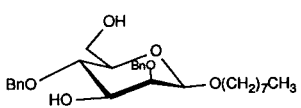
12c-α	 **15F**	CH_2Cl_2, Me_3SiOTf, MS 4 Å, −30°C, 10 min	94 α	126
12c-α	 **15G**	CH_2Cl_2, Me_3SiOTf, MS 3 Å, room temp., 30 min	75 α	135
12c-α	 **15H**	CH_2Cl_2, Me_3SiOTf, **12c-α** (2.3 eq.), MS 3 Å, room temp.	86 α-(1 → 3) α-(1 → 6) trisaccharide	135
12c-α	 **15I**	n.n.	90 α 3-*O*/2-*O* 1 : 3	91
12c-α	 **15J**	CH_2Cl_2, Me_3SiOTf, MS 3 Å, room temp., 10 min	87 α	135
12c-α	 **15K**	CH_2Cl_2, Me_3SiOTf, MS 3 Å, −10°C, 10 min	82 α-(1 → 6)	135

TABLE XVI
Naturally Occurring Glycosidic Linkages of *N*-Acetylglucosamine

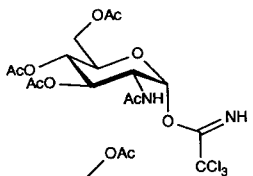
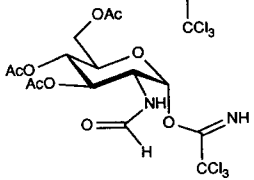
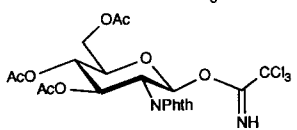
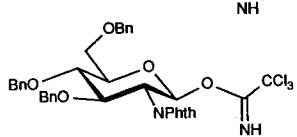
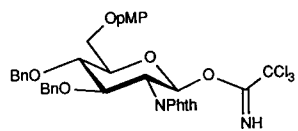
Glycosidic linkage	Acceptor	Occurrence
β-(1 → 4)	GlcNAc	Chitobiose core structure of N-glycoproteins
β-(1 → 4)	MurAc	Part of murein of Gram-negative bacteria
β-(1 → 6)	GlcNAc	Disaccharide unit of lipid A (as in *Salmonella minnesota*)
β-(1 → 6)	GalNAc	Part of core structures of the O-glycoproteins
β-(1 → 3)	GalNAc	
β-(1 → 3)	Gal	*lacto*- and *neolacto*-series of glycosphingolipids
β-(1 → 6)	Gal	
β-(1 → 3)	Man	*artho*-series of glycosphingolipids
α-(1 → 6)	GlcA	Phosphoglycosphingolipids of tobacco leaves
β-(1 → 2)	Man	Phosphoglycosphingolipids

glycoside bond-formation processes encountered. Compounds capable of neighboring-group participation through *N*-acyl or *N*-phthaloyl groups (Table XVII) are readily obtained from glucosamine. Presumably on account of the size of the *N*-phthaloyl group, only β-trichloroacetimidates (**17c**-β–**17f**-β) were obtained (139–144). However, for the *N*-acyl-protected compounds **17a**-α and **17b**-α it could be shown that the glycosylation reaction proceeds via intermediate oxazolines (137); therefore, an advantage for application of the trichloroacetimidate procedure could not be established in these cases. The *N*-phthaloyl-protected trichloroacetimidates permitted an enormous improvement in terms of yield and diastereoselectivity. However, the removal of the *N*-substituent from the glycosides sometimes caused problems. Therefore, 2-azido-2-deoxyglucose derivatives, readily obtained from glucals via the azidonitration methodology of Lemieux and Ratcliffe (152), seemed to be ideal; various trichloroacetimidates were accordingly prepared (Table XVII). Careful investigation of trichloroacetimidate (**17g**) formation (145) led again to conditions for the selective formation of both anomers. Also noteworthy is the selective formation (149) of the 4-*O*-unprotected trichloroacetimidate **17i**-β. Because the azido group is considered a nonparticipating group, it remained to be shown that the α-trichloroacetimidates can be transformed cleanly into β-glycosides under SN2-type conditions.

Experiments (137,137a) with the *N*-phthaloyl-protected donor **17c**-β showed excellent glycosyl-donor properties, as indicated in Table XVIII. Various galactose- and galactosamine-derived acceptors underwent successful reaction. The *O*-benzyl-*N*-phthaloyl-protected donors **17d,e,** and **f** showed comparable properties (141,143).

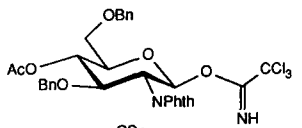
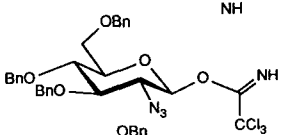
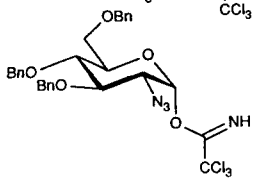
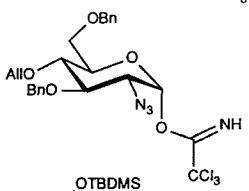
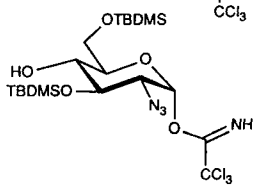
TABLE XVII

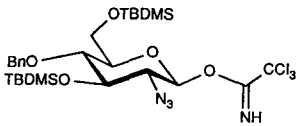
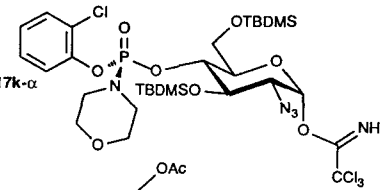
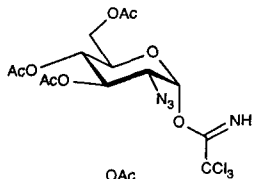
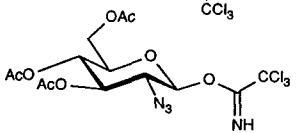
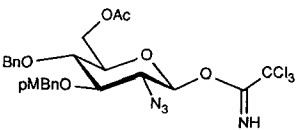
Synthesis of Trichloroacetimidates of D-Glucosamine

Trichloroacetimidate[a]	Reaction conditions	Anomeric configuration (α:β)	Yield (%)	Reference
17a-α 	CH_2Cl_2, CCl_3CN, NaH	1:0	74	137,137a
17b-α 	CH_2Cl_2, CCl_3CN, DBU, MS 4 Å, 0°C, 30 min	1:0	95	138,139
17c-β 	CCl_3CN, NaH	0:1	73	139,140
17d-β 	$(ClCH_2)_2$, CCl_3CN, DBU, 0°C, 16 h	0:1	92	141,142
17e-β 	CH_2Cl_2, CCl_3CN, DBU, 0°C, 2 h	0:1	99	143,144

(continues)

TABLE XVII *(continued)*

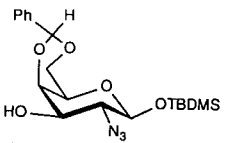
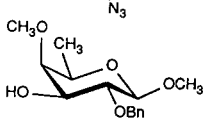
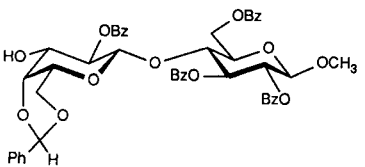
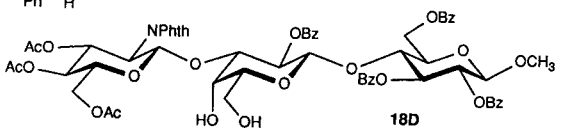
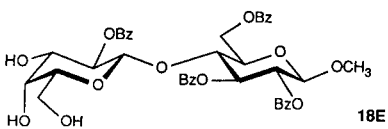
Trichloroacetimidate[a]	Reaction conditions	Anomeric configuration (α:β)	Yield (%)	Reference
17f-β 	$(ClCH_2)_2$, CCl_3CN, DBU, −5°C	0:1	81	141,142
17g-β 	CH_2Cl_2, CCl_3CN, K_2CO_3, 20°C, 4 h	0:1	90	145
17g-α 	DME, CCl_3CN, NaH, 0°C	4:1	98	53
	CH_2Cl_2, CCl_3CN, NaH, room temp.	1:0	75	54,55
17h-β 	CH_2Cl_2, CCl_3CN, NaH, 0°C, 12 h	1:0	75	148
17i-α 	CH_2Cl_2, CCl_3CN, NaH, room temp.	1:0	98	149

17j-β		CH_2Cl_2, CCl_3CN, K_2CO_3, room temp., 4 h	0:1	66[b]	149
17k-α		CH_2Cl_2, CCl_3CN, K_2CO_3–NaH, room temp., 4.5 h	1:0	66[b]	150
17l-α		CH_2Cl_2, CCl_3CN, NaH, room temp., 1 h	1:0	44[b]	137,147
17m-β		CH_2Cl_2, CCl_3CN, K_2CO_3, room temp., 6 h	1:2	75[b]	137
17n-β		CH_2Cl_2, CCl_3CN, K_2CO_3	0:1	n.n.	151

[a] pMP, *p*-methoxyphenyl; pMBn, *p*-methoxybenzyl; DME, 1,2-dimethoxyethane; TBDMS, *tert*-butyldimethylsilyl.
[b] From an epimeric mixture.

TABLE XVIII

Reaction of 2-*N*-Phthaloyl Trichloroacetimidate 17c-β with Nucleophiles

Glycosyl acceptor	Reaction conditions	Anomeric configuration (α:β)	Yield (%)	Reference
CH_3OH **(18A)**	$BF_3 \cdot OEt_2$, −30°C	0:1	65	140
 **10H**	$BF_3 \cdot OEt_2$, −20°C	0:1	70	140
 **18B**	Me_3SiOTf, −70°C, 5 min	0:1	93	138, 153
 **18C**	$BF_3 \cdot OEt_2$, −20°C	0:1	71	139
 **18D**	Me_3SiOTf, 0°C, 15 min	0:1	68	139
 **18E**	Me_3SiOTf, 5°C	0:1 3,6-di-*O*-glycosylation	75	139

The corresponding 2-azido derivatives revealed surprisingly similar results: high reactivity was combined with extraordinary β selectivity. Table XIX lists many important glycoside-bond formation reactions (145) with the *O*-benzyl-protected glycosyl donor **17g**-α. Only the reaction with the sterically hindered muramic acid acceptor **19E** led, in the presence of Me_3SiOTf, to partial α-product formation (57); however, this problem could be readily overcome by replacing the bulky Bu^tMe_2Si protective group by the benzyl group, as shown (148) for **19F**. Remarkable also are the reactions (149) of acceptor **17i**-β with the partially protected acceptors **19B** and **19G**: regioselective reaction at the 6-position and clean β-product formation was observed. The high tendency for β-product formation with the α-trichloroacetimidate derivatives of azidoglucose as donors is also because of the fact that the solubility of the compounds permits the use of the rather nonpolar solvent-mixture dichlormethane–*n*-hexane, which favors SN2-type reactions in the presence of $BF_3 \cdot OEt_2$ as catalyst and low temperatures.

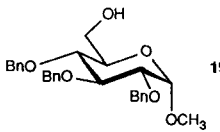
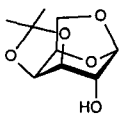
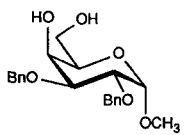
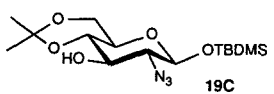
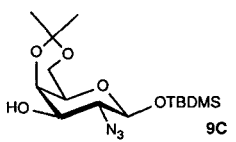
An interesting example showing that α-product formation may be readily achieved by the use of a β-trichloroacetimidate and Me_3SiOTf as catalyst is shown in Table XX: compounds **17n**-β + **20A** furnish exclusively the α-glycoside in high yield (151).

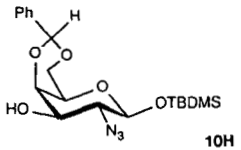
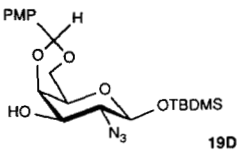
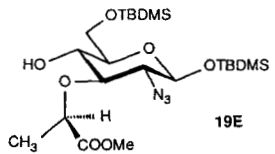
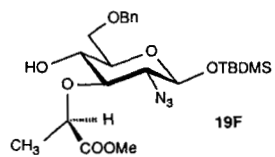
***(ii)* Lactosamine Donors.**—The general importance of lactosamine in glycosphingolipid and glycopeptide synthesis is because of the frequent occurrence of this building block (119). For instance, the branching of the pentasaccharide core of N-glycoproteins is determined by the connection with *N*-acetyllactosamine, which may occur in β-(1 → 3) linkage in long chains. In *O*-glycoproteins, *N*-acetyllactosamine is part of the core of mucin-type oligosaccharides. Likewise, the core structure of the glycosphingolipids of the *lactoneo* series is determined by *N*-acetyllactosamine.

The connection of these naturally occurring lactosamine units determines the protective-group pattern of the required building blocks. The general occurrence of the β linkage permits again the use of *N*-phthaloyl protection; however, azidolactose (155), readily obtained from lactal, also should be very useful as a consequence of the advantages of this group already discussed. Both of these types of trichloroacetimidates, having different protective groups, have been very successfully prepared, as indicated in Table XXI. Again, as just discussed, with *N*-phthaloyl protection exclusively β-trichloroacetimidates **21a**-β–**21e**-β were obtained (130,139,140,143,144,156–159). Both isomers may be selectively generated from the azidolactose derivatives, as shown (137, 160) for **21j**. With sodium hydride as the base, α-trichloroacetimidates are obtained in very high yields. Some of these com-

TABLE XIX

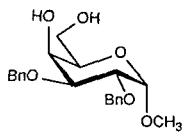
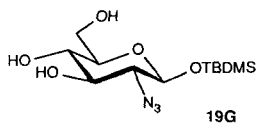
Reaction of 2-Azido-2-deoxyglucopyranosyl Trichloroacetimidates with Nucleophiles

Trichloro-acetimidate	Glycosyl acceptor[a]	Reaction conditions	Anomeric configuration (α:β)	Yield (%)	Reference
17g-α	 **19A**	CH_2Cl_2–*n*-hexane, Me_3SiOTf, −50°C, 10 min	0:1	60	146
17g-α	 **9A**	CH_2Cl_2–*n*-hexane, $BF_3 \cdot OEt_2$, −30°C, 20 h	0:1	80	146
17g-α	 **19B**	CH_2Cl_2–*n*-hexane, $BF_3 \cdot OEt_2$, −15°C	0:1	80	150
17g-α	 **19C**	CH_2Cl_2–*n*-hexane, $BF_3 \cdot OEt_2$, −20°C, 3 h	0:1	92	145
17g-α	 **9C**	CH_2Cl_2–*n*-hexane, $BF_3 \cdot OEt_2$, −15°C, 2 h	0:1	90	154

17g-α	 **10H**	CH_2Cl_2–*n*-hexane, $BF_3 \cdot OEt_2$, −18°C, 3 h	0:1	60	154
17g-α	 **19D**	CH_2Cl_2–*n*-hexane, $BF_3 \cdot OEt_2$, −15°C, 6 h	0:1	70	154
17g-α	 **19E**	CH_2Cl_2–*n*-hexane, Me_3SiOTf, −15°C, 5 h	1:1.6	90	57
17g-α	 **19F**	CH_2Cl_2–*n*-hexane, BF_3OEt_2, −20°C, 8 h	0:1	78	148

(continues)

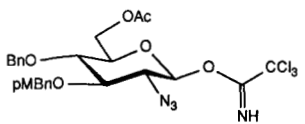
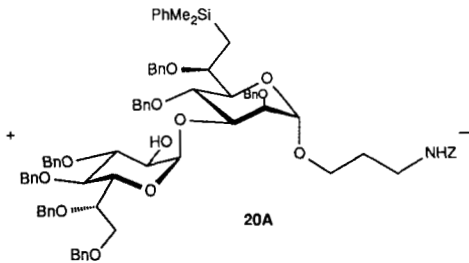
TABLE XIX *(continued)*

Trichloro-acetimidate	Glycosyl acceptor[a]	Reaction conditions	Anomeric configuration (α:β)	Yield (%)	Reference
17i-β	 **19B**	CH_2Cl_2–*n*-hexane, BF_3OEt_2	0:1	85	149
	 **19G**	CH_2Cl_2–*n*-hexane, $BF_3 \cdot OEt_2$	0:1 β-(1 → 6)	50	149

[a] pMP, *p*-methoxyphenyl; TBDMS, *tert*-butyldimethylsilyl.

TABLE XX

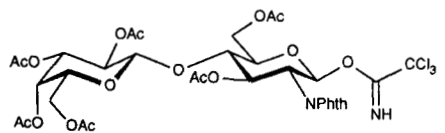
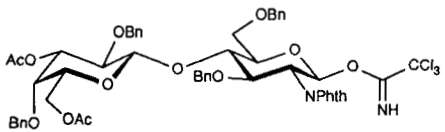
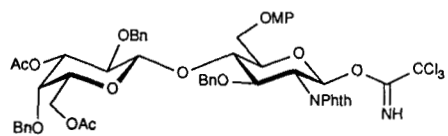
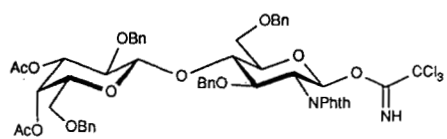
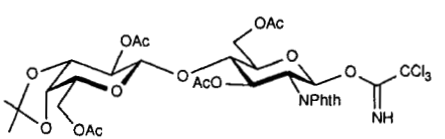
α-Selective Glycosidation of a β-Trichloroacetimidate[a]

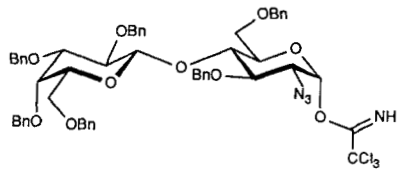
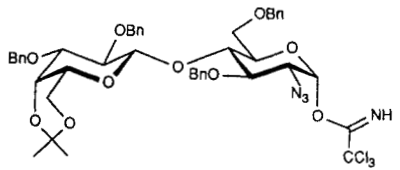
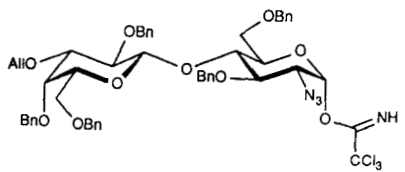
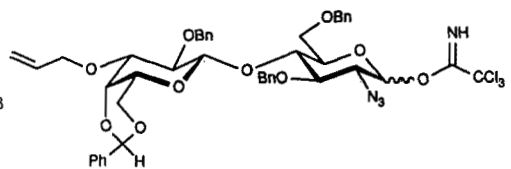
Reactants		Products
 17n-β	+  20A	TMSOTf, CH_2Cl_2 → 92 %, α/β 1 : 0[151]

[a] pMBn, *p*-methoxybenzyl.

TABLE XXI

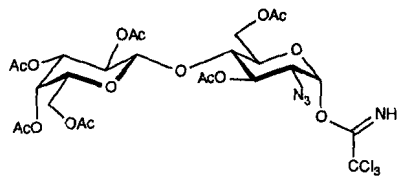
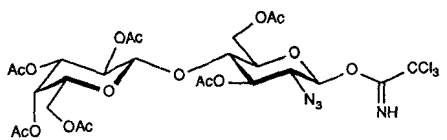
Synthesis of Trichloroacetimidates of *N*-Acetyllactosamine

Trichloroacetimidate	Reaction conditions	Anomeric configuration (α:β)	Yield (%)	Reference
21a-β 	CH_2Cl_2, CCl_3CN, NaH	0:1	72	130,139,140,156
21b-β 	CH_2Cl_2, CCl_3CN, DBU	0:1	92	157
21c-β 	CH_2Cl_2, CCl_3CN, DBU, 0°C, 3.5 h	0:1	87	143,114
21d-β 	CH_2Cl_2, CCl_3CN, DBU	0:1	72	158
21e-β 	CH_2Cl_2, CCl_3CN, K_2CO_3	0:1	66	159

21f-α		CH_2Cl_2, CCl_3CN, NaH	1:0	54[a]	115
21g-α		CH_2Cl_2, CCl_3CN, NaH, room temp., 2.5 h	4:1	82	155
21h-α		CH_2Cl_2, CCl_3CN, NaH, room temp.	4:1	80	114,155
21l-α/β		CH_2Cl_2, CCl_3CN, NaH, room temp., 3 h	4.3:1	70	155

(continues)

TABLE XXI *(continued)*

	Trichloroacetimidate	Reaction conditions	Anomeric configuration (α:β)	Yield (%)	Reference
21j-α		CH_2Cl_2, CCl_3CN, NaH	9:1	53[a]	137,160
21j-β		CH_2Cl_2, CCl_3CN, K_2CO_3	1:5	64[a]	137

[a] From epimeric mixture.

pounds are already suitable for further connections in the 3-,3′-, 4′-, and 6′-positions (114,115,137,155,160).

Several glycosylation reactions with *N*-phthaloyl-protected donor (140) **21a**-β have been very successfully performed, as indicated in Table XXII. The β-selectivities and the yields are generally very good. The reaction (130) with **22C** demonstrates that dilactosaminylation can also be successfully achieved. The reaction of the 3′,4-*O*-unprotected *O*-benzyl-lactose derivative (157) **22D** led, contrary to the generally observed higher reactivity of the 3′-position, to reaction at both positions. This problem could be overcome by employing the *O*-acyl protected lactosamine derivative **23A** (Table XXIII). With donor **21e**-β, Veyrières *et al.* (159) obtained tetrasaccharide **23B** in high yield. This reaction could be repeated with the derived tetrasaccharides **23c** as donor and **23D** as acceptor, thus leading to the corresponding octasaccharide in good yield.

As already observed for azidoglucose-derived donors, glycosylations with azidolactose-derived donors (**21f**-α–**21j**-α, Table XXIV) also exhibited high reactivity and β selectivity (92,114,115,154,161,162). With these results in hand, excellent preconditions for successful syntheses of the Le^x and Le^y antigens have been presented (164,165). Representative examples for the decisive glycoside-bond formations are compiled in Table XXV. Comparison of the results of *N*-phthaloyl protection and of the azido group does not exhibit advantages for the use of *N*-phthaloyl derivatives.

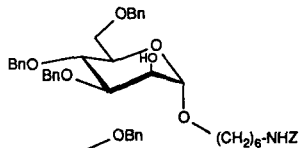
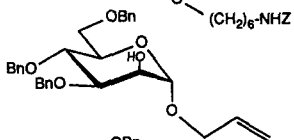
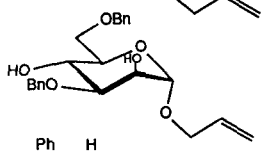
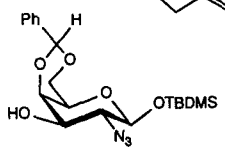
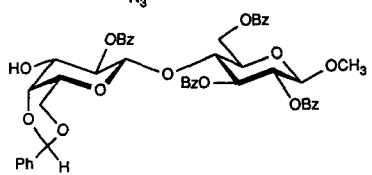
***(iii)* Chitobiose Donors.**—Only a few trichloroacetimidate-based chitobiose donors have been synthesized thus far, as indicated in Table XXVI. Their reaction with benzyl alcohol as acceptor demonstrates the potential usefulness of these donors in glycosylation reactions.

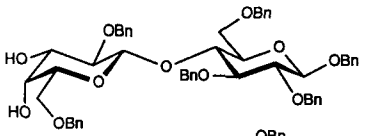
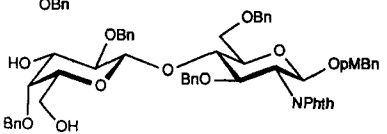
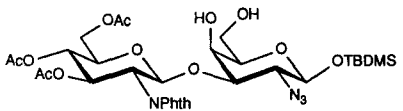
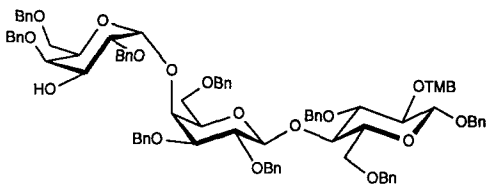
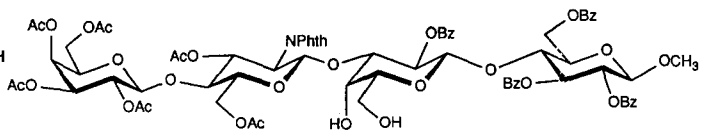
***(iv)* Muramic Acid as Donor.**—The cell-wall peptidoglycan of bacteria has a β-(1 → 4)-linked glycan chain, consisting of alternating 2-acetamido-2-deoxy-D-glucose and *N*-acylmuramic acid residues that are cross-linked by a peptide chain. The resulting peptidoglycan network (murein) and its fragments exhibit marked immunostimulatory and antitumor properties. The minimal structure for activity, the so-called Freund's complete adjuvant, is a "muramoyl dipeptide" (MDP). Many investigations have been directed toward the synthesis of derivatives of MDP, including glycosides and oligosaccharides; the attachment of lipophilic groups is of special interest because of their potential in combined chemotherapy and immunotherapy (166,167).

The transformation of azidoglucose derivatives into muramic acid precursors enabled the formation of trichloroacetimidates as muramic acid donors that could be very successfully employed in glycoside bond-forma-

TABLE XXII

Reaction of 2-*N*-Phthaloyl-2-deoxytrichloroacetimidate 21a-β with Nucleophiles[a]

	Glycosyl acceptor	Reaction conditions	Anomeric configuration (α:β)	Yield (%)	Reference
22A		CH_2Cl_2, $BF_3 \cdot OEt_2$, $-8°C$, 3.5 h	0:1	69	156
22B		$(CH_2Cl)_2$, $BF_3 \cdot OEt_2$	0:1	73	132
22C		$(CH_2Cl)_2$, MS 4 Å, $BF_3 \cdot OEt_2$, $-15°C$	0:1	73 β-(1 → 3,6)	130
10H		CH_2Cl_2, $BF_3 \cdot OEt_2$, $-20°C$	0:1	67	140
18C		$BF_3 \cdot OEt_2$, $-20°C$	0:1	75	139

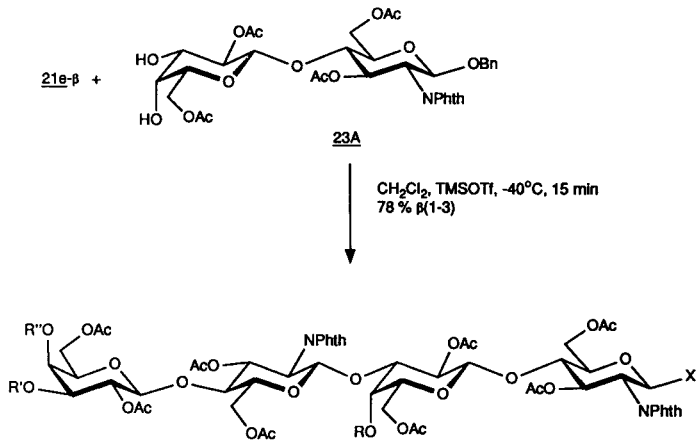
22D		n.n.	0:1 β-(1:3′) β-(1:4′) 2:1	88	157
22E		$(CH_2Cl)_2$, $BF_3 \cdot OEt_2$ (2.0 eq.), room temp.	0:1	87	157
22F		$BF_3 \cdot OEt_2$, −20°C	0:1	71	140
22G		$(CH_2Cl)_2$, $BF_3 \cdot OEt_2$	0:1	22	102
22H		Me_3SiOTf, −20°C	0:1 β-(1 → 6)	80	139

[a] Z, benzyloxycarbonyl; pMBn, *p*-methoxybenzyl; TBDMS, *tert*-butyldimethylsilyl; TMB, 2,4,6-trimethylbenzoyl.

TABLE XXIII

Synthesis of Oligomers of Lactosamine (Ref. 159)

Reactions and products



23B R = H, X = OBn, R', R'' = $=C(CH_3)_2$
23c R = Ac, X = $OC(=NH)CCl_3$, R', R'' = $=C(CH_3)_2$
23D R = Ac, X = OBn, R', R'' = H

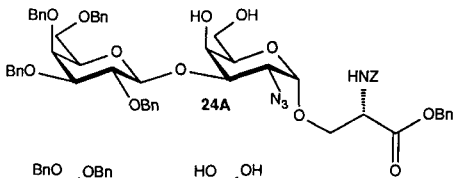
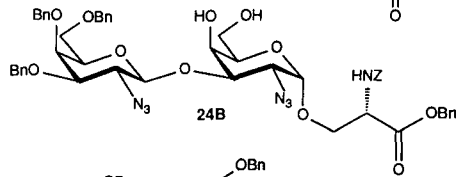
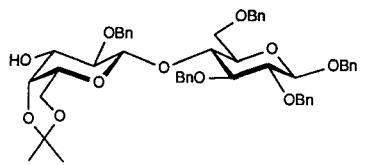
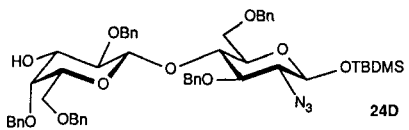
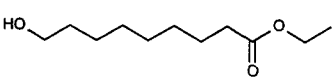
tion. Table XXVII shows that α- and β-trichloroacetimidates **27a**-α and -β may be obtained directly and also that disaccharide donors were successfully prepared. These compounds can be used for selective β- and α-glycoside bond-formations (57,97).

f. Trichloroacetimidates of Galactosamine Derivatives as Glycosyl Donors. — 2-Acetamido-2-deoxy-D-galactose (*N*-acetylgalactosamine) (63, 64) is a constituent of the core structure of mucin-type oligosaccharides; it is α-*O*-connected to serine and threonine. The derived *O*-glycoproteins constitute, along with the N-glycoproteins, a major class of glycoconjugates. In glycosphingolipids, *N*-acetylgalactosamine is mainly encountered in the *globo, isoglobo,* and *ganglio* series. Representative examples of these connections are compiled in Table XXVIII. Obviously, β-(1 → 3)-, β-(1 → 4)-, and α-(1 → 3)-connections are most important and therefore *N*-phthaloyl protection is not appropriate for the production of versatile donors.

Table XXIX demonstrates that various protective-group patterns are compatible with trichloroacetimidate formation, and not only α but also β derivatives may be generated highly selectively, as for instance **29b**-β (149)

TABLE XXIV

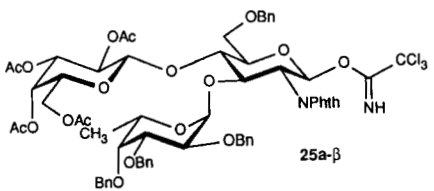
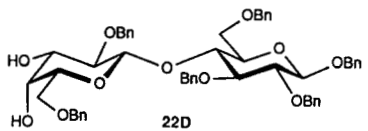
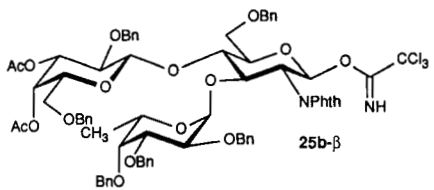
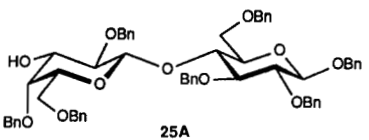
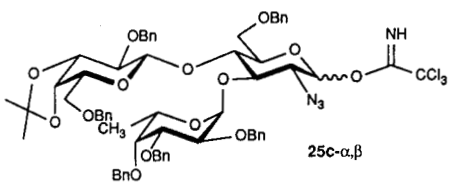
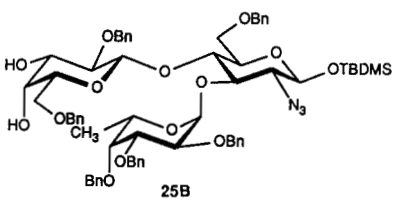
Reaction of 2-Azido-2-deoxytrichloroacetimidates of Lactosamine with Nucleophiles

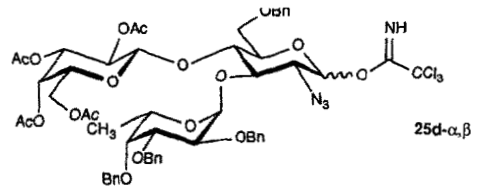
Trichloro-acetimidate	Glycosyl acceptor[a]	Reaction conditions	Yield (%)	Reference
21f-α	 **24A**	CH_2Cl_2–*n*-hexane, $BF_3 \cdot OEt_2$, −15°C	81 β-(1 → 6)	115
21f-α	 **24B**	CH_2Cl_2–*n*-hexane, $BF_3 \cdot OEt_2$	80 β-(1 → 6)	154
21g-α	 **24C**	CH_2Cl_2–*n*-hexane, $BF_3 \cdot OEt_2$, MS 4 Å, −25°C	84 β	92
21h-α	 **24D**	CH_2Cl_2–*n*-hexane, Me_3SiOTf, −20°C, 1 h	72 β	114
21i-α	 **14F**	CH_2Cl_2–*n*-hexane, $BF_3 \cdot OEt_2$, −15°C	65 β	162

[a] Z, benzyloxycarbonyl; TBDMS, *tert*-butyldimethylsilyl.

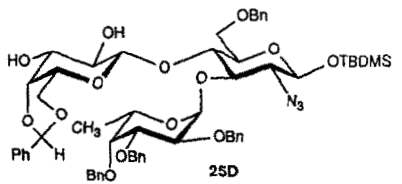
TABLE XXV

Synthesis of Oligosaccharides with Le^x Determinants

Glycosyl donor	Glycosyl acceptor
 **25a-β**	 **22D**
	Trichloroacetimidate Formation: CH_2Cl_2, CCl_3CN, DBU; 67 % Glycosylation Conditions: $(CH_2Cl)_2$, BF_3OEt_2; 67 % β (1-3)[104]
 **25b-β**	 **25A**
	Trichloroacetimidate Formation: n. n. Glycosylation Conditions: $(CH_2Cl)_2$, BF_3OEt_2; 52 % β[163]
 **25c-α,β**	 **25B**
	Trichloroacetimidate Formation: CH_2Cl_2, CCl_3CN, DBU, 5 h, room temp.; 94 %, α : β 5 : 1 Glycosylation Conditions: CH_2Cl_2/n-hexane (1 : 1), MS 4 Å, -25°C, BF_3OEt_2; 81 % β[184]

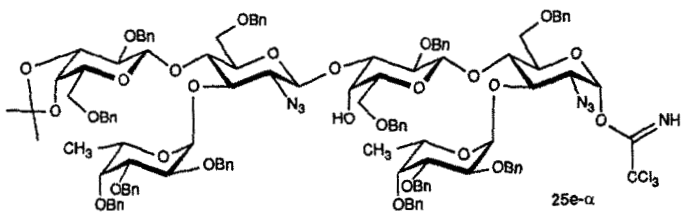


25d-α,β

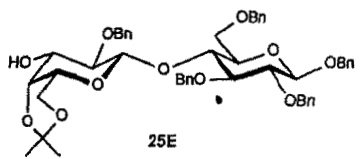


25D

Glycosylation Conditions: CH_3CN, TMSOTf (0.01 eq), -40°C; 80 % β[62,165]



25e-α



25E

Trichloroacetimidate Formation: CH_2Cl_2, CCl_3CN, DBU; 73 % α[164]
Glycosylation Conditions: CH_2Cl_2/*n*-hexane (1:1), -25°C, MS 4 Å, BF_3OEt_2; 52 % β[154]

(continues)

TABLE XXV *(continued)*

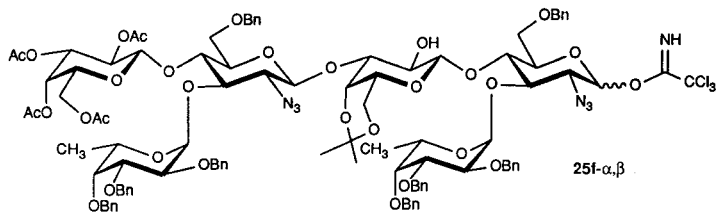
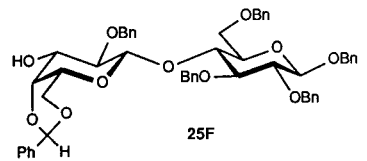
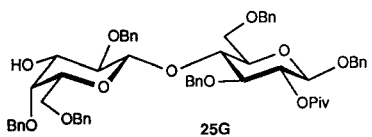
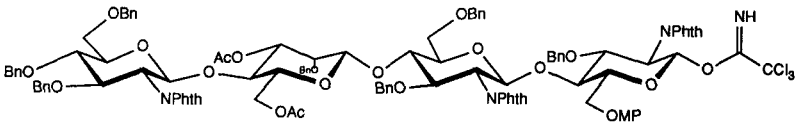
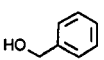
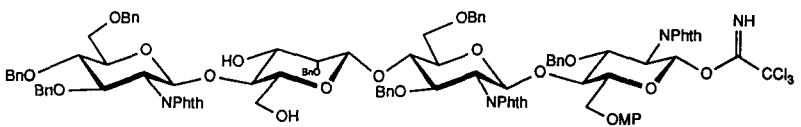
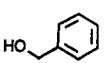
Glycosyl donor	Glycosyl acceptor
 **25f-α,β**	 **25F**
	Glycosylation Conditions: CH_3CN, TMSOTf, (0.02 eq.), -40°C; 80 % β[165]
	 **25G**
	Glycosylation Conditions: CH_3CN, TMSOTf, (0.02 eq.), -40°C; 74 % β[165]

TABLE XXVI

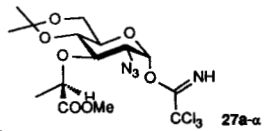
Glycosylation of Chitobiose Derivatives

Glycosyl donor[a]	Trichloroacetimidate formation	Glycosyl acceptor	Glycosylation conditions	References
 **26a-β**	CCl_3CN, DBU $(ClCH_2)_2$, −5°C, Ar; 96%	 **26A**	$(ClCH_2)_2$, $BF_3 \cdot OEt_2$, −20°C, Ar; 87% (two steps)	127
 **26b-β**	CCl_3CN, DBU −55°C, 30 min; 78.6%	 **26A**	$(ClCH_2)_2$, $BF_3 \cdot OEt_2$, −23°C, Ar; 84%	127,142

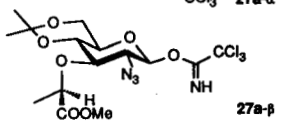
[a] MP, *p*-methoxyphenyl.

TABLE XXVII

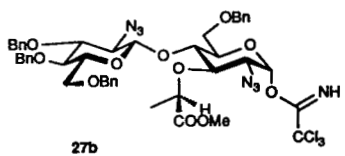
Synthesis of Glycosides of Muramic Acid



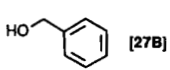
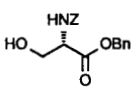
CH_2Cl_2, CCl_3CN, NaH, 40°C; 90% (Ref 57)



CH_2Cl_2, CH_2Cl_2, K_2CO_3, room temp.; 86% (Refs. 57,97)



CH_2Cl_2, K_2CO_3/NaH, CCl_3CN, room temp., 8 h 75%, $\alpha:\beta$ 6:1 (Ref. 148)

Glycosyl donor	Glycosyl acceptor	Reaction conditions	Yield (%)	Anomeric configuration ($\alpha:\beta$)	Reference
27a-α	 [27A]	CH_2Cl_2, room temp., 3 h	60	0:1	57
27a-α	 [27B]	CH_2Cl_2, −20°C, Me_3SiOTf, 4 h	70	1:0	57
		CH_2Cl_2, −20°C, Me_3SiOTf	71	3:1	57

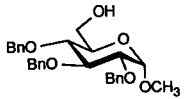
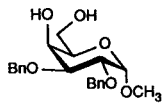
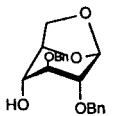
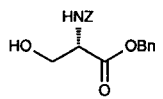
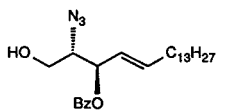
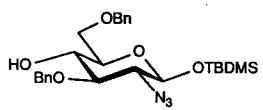
27a-α		CH_2Cl_2–*n*-hexane −10°C, $BF_3 \cdot OEt_2$, 3 h	92	0:1	57
27a-α		CH_2Cl_2–*n*-hexane −10°C, $BF_3 \cdot OEt_2$, 30 min	80	0:1	57
27a-α		CH_2Cl_2–*n*-hexane −5°C, $BF_3 \cdot OEt_2$, 6 h	80	1:4	57
27a-β		Et_2O, MS 4 Å, N_2, −20°C, 2 h, Me_3SiOTf	91	1:0	97
27a-β		CH_2Cl_2, MS 4 Å, 3 h, $BF_3 \cdot OEt_2$	85	0:1	97
27a-α		CH_2Cl_2, $BF_3 \cdot OEt_2$, room temp., 14 h	38	0:1	97

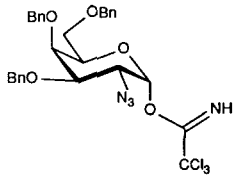
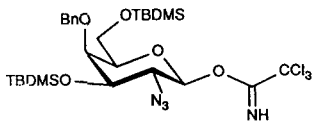
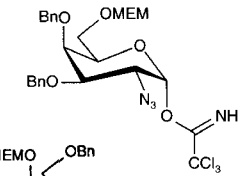
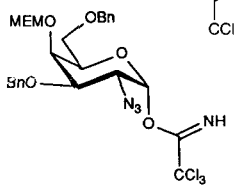
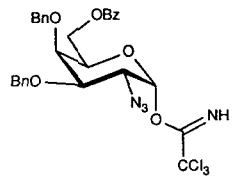
TABLE XXVIII

Structures of *N*-Acetylgalactosamine-Containing Glycosphingolipids

Gala-Series	
α-GalNAc-(1 → 3)-β-GalNAc-(1 → 3)-α-Gal-(1 → 4)-β-Gal-(1 → O)-Cer	
Globo-Series	
β-GalNAc-(1 → 3)-α-Gal-(1 → 4)-β-Gal-(1 → 4)-β-Glc-(1 → O)-Cer	Globotetranosylceramide
α-GalNAc-(1 → 3)-β-GalNAc-(1 → 3)-α-Gal-(1 → 4)-β-Gal-(1 → 4)-β-Glc-(1 → O)-Cer	Forssman antigen
β-Gal-(1 → 3)-β-GalNAc-(1 → 3)-α-Gal-(1 → 4)-β-Gal-(1 → 4)-β-Glc-(1 → O)Cer	Globopentaosylceramide
Isoglobo-Series	
β-GalNAc-(1 → 3)-α-Gal-(1 → 3)-β-Gal-(1 → 4)-β-Glc-(1 → O)-Cer	Isoglobotetraosylceramide
Ganglio-Series	
β-GalNAc-(1 → 4)-β-Gal-(1 → 4)-β-Glc-(1 → 0)-Cer	Gangliotriaosylceramide
β-Gal-(1 → 3)-β-GalNAc-(1 → 4)-β-Gal-(1 → 4)-β-Glc-(1 → O)-Cer	Gangliotetraosylceramide
Lacto-Series	
α-GalNAc-(1 → 3)-β-Gal-(1 → 3)-β-GlcNAc-(1 → 3)-β-Glc-(1 → 4)-β-Glc-(1 → O)-Cer 2 ↑ α1Fuc	
Arthro-Series	
β-GalNAc-(1 → 4)-β-GlcNAc-(1 → 3)-β.-Man-(1 → 4)-β-Glc-(1 → O)-Cer	
α-GalNAc-(1 → 4)-β-GalNAc-(1 → 4)-β-GlcNAc-(1 → 3)-β-Man-(1 → 4)-β-Glc-(1 → O)-Cer	
Phosphoglycosphingolipids	
4-OMe-β-Gal-(1 → 3)-β-GalNAc-(1 → 3)-α-Fuc-(1 → 4)-β-GlcNAc-(1 → 2)-Man	(Fragment)

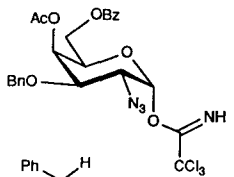
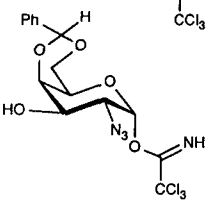
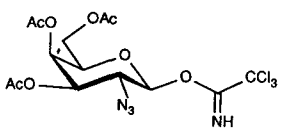
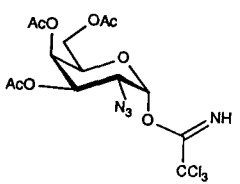
TABLE XXIX

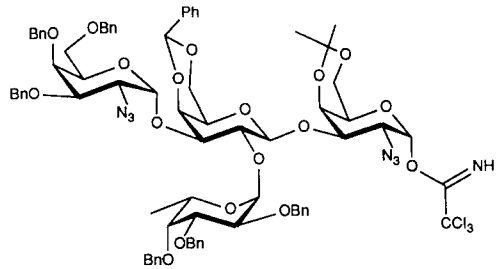
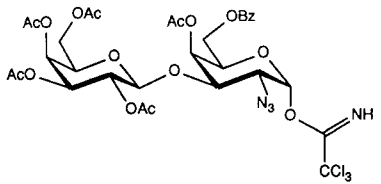
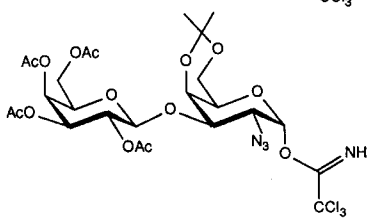
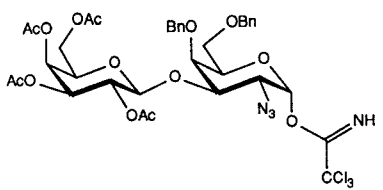
Synthesis of Trichloroacetimidates of *N*-Acetylgalactosamine

Trichloroacetimidate	Reaction conditions	Yield (%)	Anomeric configuration (α:β)	Reference
29a-α 	CH_2Cl_2, CCl_3CN, NaH, 1 h	68	1:0	137
29b-β 	CH_2Cl_2, CCl_3CN, K_2CO_3	88	0:1	149
29c-α,β 	$(CH_2Cl)_2$, CCl_3CN, DBU room temp., 3 h	85 (α/β 3:1)	3:1	169
29d-α 	$(CH_2Cl)_2$, CCl_3CN, DBU, room temp., 2 h	81	1:0	169
29e-α 	$(CH_2Cl)_2$, CCl_3CN, DBU, room temp.	79	1:0	169

(continues)

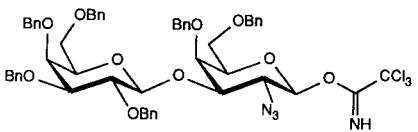
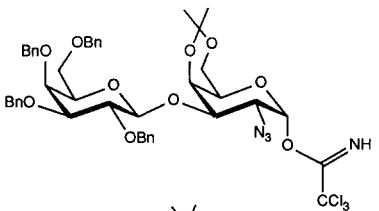
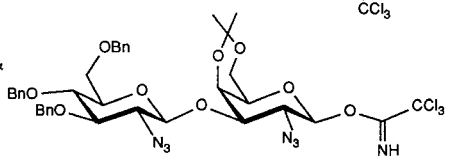
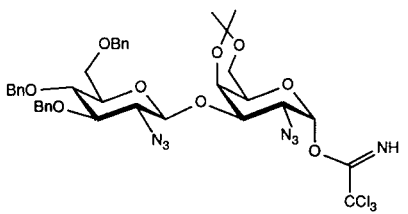
TABLE XXIX *(continued)*

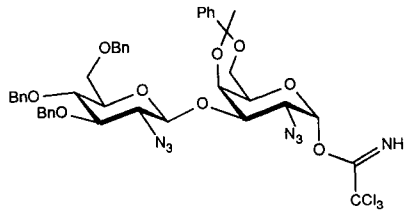
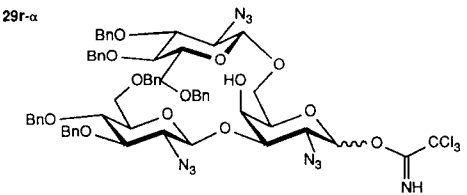
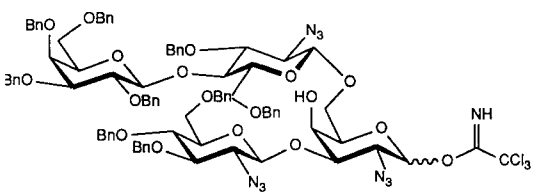
Trichloroacetimidate	Reaction conditions	Yield (%)	Anomeric configuration (α:β)	Reference
29f-α 	$(CH_2Cl)_2$, CCl_3CN, DBU, room temp., 2.5 h	81	1:0	169
29g-α 	DME, CCl_3CN, NaH, 2 h	64	1:0	137
29h-β 	CH_2Cl_2, CCl_3CN, K_2CO_3, 6 h	51[a]	0:1[a]	137,116,170
29h-α 	CH_2Cl_2, CCl_3CN, NaH, 1 h	63[a]	1:0[a]	137

29l-α		CCl_3CN, CH_2Cl_2, DBU, room temp.	84	1:0	113
29j-α		CCl_3CN, CH_2Cl_2, DBU	60	1:0	117
29k-α		CCl_3CN, CH_2Cl_2, DBU, room temp.	88	1:0	117
29l-α		CCl_3CN, CH_2Cl_2, DBU, room temp.	72	1:0	117

(continues)

TABLE XXIX *(continued)*

Trichloroacetimidate	Reaction conditions	Yield (%)	Anomeric configuration (α:β)	Reference
29m-β 	CCl_3CN, CH_2Cl_2, K_2CO_3 room temp.	70	0:1	116
29n-α 	CH_2Cl_2, CCl_3CN, K_2CO_3/NaH, room temp., 6 h	95	1:0	150
29o-α 	CH_2Cl_2, CCl_3CN, K_2CO_3	76	0:1	150
29p-α 	CH_2Cl_2, CCl_3CN, NaH, room temp.	75	1:0	150

29q-α		CH_2Cl_2, CCl_3CN, NaH, room temp.	84	1:0	150
29r-α		CH_2Cl_2, CCl_3CN, K_2CO_3, room temp., 4 h	56	1:2	150
29s-α,β		CH_2Cl_2, CCl_3CN, K_2CO_3, room temp., 4 h	71	1:3	150

[a] From epimeric mixture.

and **29i-β** (113). Useful building blocks for efficient oligosaccharide syntheses are thus readily accessible. Trichloroacetimidates **29b-i** (116, 137,149,169,170) are versatile building blocks for 3,6-branched core-structures of mucin-type oligosaccharides. The selective formation of compound (137) **29g-α** from the corresponding 1,3-*O*-unprotected azido-galactose derivative demonstrates again that only partial *O*-protection may be required, because the anomeric hydroxylic group is more reactive toward trichloroacetonitrile under basic conditions than the other hydroxyl groups. This aspect, which could decrease the number of protection and deprotection steps, has not yet been fully considered in the planning of complex of oligosaccharide syntheses.

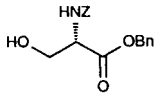
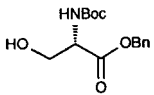
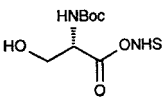
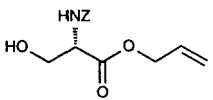
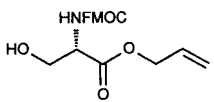
The first glycosylation experiments were carried out with donor (149) **29b-β**, which with Me_3SiOTf as catalyst exhibited high α selectivities; with the α-trichloroacetimidates (169) **29d–f** and $BF_3 \cdot OEt_2$ as catalyst in the nonpolar solvent toluene, excellent β selectivities were observed. In more recent glycosylations the α-connection to serine played a prominent role. Typical results with monosaccharide and oligosaccharide donors having azidogalactose at the reducing end vary (Table XXX). As expected, reactions with α-trichloroacetimidates, employing $BF_3 \cdot OEt_2$ as catalyst, are not α selective. Obviously, β-trichloroacetimidates and Me_3SiOTf at low temperatures are of advantage for attaining high α selectivity, as indicated in the reaction of donors **29b, g, h, m,** and **p,** and serine and threonine acceptors **30A–E.**

g. Trichloroacetimidates of Mannosamine Derivatives as Glycosyl Donors. — The relatively rare occurrence of 2-acetamido-2-deoxy-D-mannose in Nature has consequently drawn little attention to its glycosylation reactions. The azido derivatives **31a-α** and **3b-α** (Table XXXI) have been successfully prepared. Reaction of **31b-α** has been successfully employed for phosphonate formation.

h. Trichloroacetimidates of 6-Deoxyhexoses: Fucose, Rhamnose, and Quinovose. — (*i*) *O*-Fucopyranosyl trichloracetimidates: Inverse Procedure for Glycosylation. — L-Fucose is an important constituent of glycosphingolipids. Because most of the tumor-associated blood-group glycosphingolipids have been found to contain α-connected L-fucose, for instance Le^x and Le^y, α-fucosylation constitutes an important task in glycosphingolipid synthesis (174). To this aim, the tri-*O*-benzylfucosyl donor (175,176) **32a** (Table XXXII) has been prepared in high yield. Reaction with galactose acceptors led, with Me_3SiOTf as catalyst in ether, to high yields of H-disaccharide (174), the determinant of blood group O. With the (less reactive) lactosamine derivatives as acceptors, lower yields were observed mainly because of de-

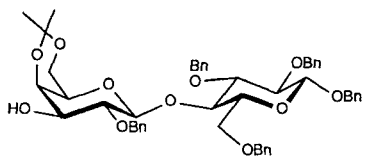
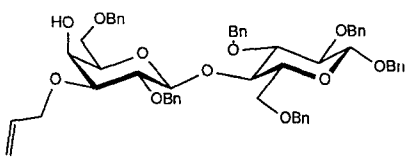
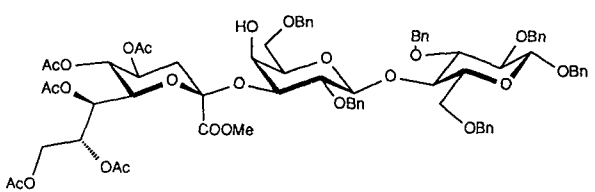
TABLE XXX

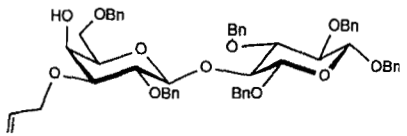
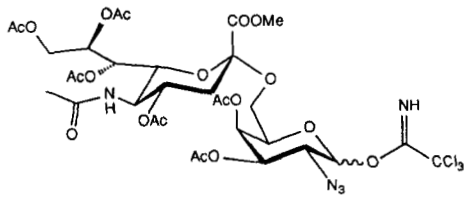
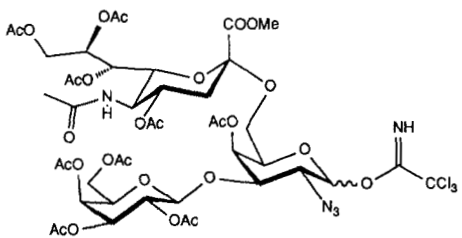
Glycosylation with Galactosamine Trichloroacetimidates

Trichloroacetimidate	Glycosyl acceptor		Reaction conditions	Yield (%)	Anomeric configuration (α:β)	Reference
29b-β		**30A**	CH_2Cl_2, Me_3SiOTf, $-20°C$, 30 min	81	4:1	116,150
29g-α		**30A**	CH_2Cl_2, Me_3SiOTf, $-20°C$	43	1:0	137
29h-α		**30A**	CH_2Cl_2, Me_3SiOTf, $-15°C$	81	5:1	171
29h-β		**30A**	CH_2Cl_2–*n*-hexane, $-30°C$, Me_3SiOTf	86	1:0	116
29h-β		**30B**	CH_2Cl_2–*n*-hexane, $-30°C$, Me_3SiOTf	55	1:0	116
29h-β		**30C**	CH_2Cl_2–*n*-hexane, $-30°C$, Me_3SiOTf	60	1:0	116
29h-β		**30D**	CH_2Cl_2–*n*-hexane, $-30°C$, Me_3SiOTf	80	1:0	116
29h-β		**30E**	CH_2Cl_2–*n*-hexane, $-30°C$, Me_3SiOTf	78	1:0	116

(continues)

TABLE XXX *(continued)*

Trichloroacetimidate	Glycosyl acceptor		Reaction conditions	Yield (%)	Anomeric configuration (α:β)	Reference
29m-β		**30A**	CH_2Cl_2–*n*-hexane, −20°C, Me_3SiOTf	85	1:0	116
29n-α		**30A**	CH_2Cl_2, Me_3SiOTf, −30°C	86	2:1	115
29p-α		**30A**	CH_2Cl_2, Me_3SiOTf, −20°C	88	1:0	154
29i-α		**30F**	CH_2Cl_2, *n*-hexane, $ZnCl_2$. OEt_2, room temp., 15 h	81	1:1,2	113
29j-α		**30G**	CH_3CN, Me_3SiOTf, −40°C, 15 min	46	0:1	117
29j-α		**30H**	CH_3CN, Me_3SiOTf, −40°C, 15 min	38	0:1	117

29l-α		**30l**	CH_3CN, Me_3SiOTf, $-40°C$, 15 min	53	0:1	117
30a-α,β		**30A**	$(CH_2Cl)_2$, Me_3SiOTf, $-15°C$	82	3:2	172
30b-α,β		**30A**	$(CH_2Cl)_2$, Me_3SiOTf, MS 4 Å, $-15°C$	48	1:2	173

(continues)

TABLE XXX *(continued)*

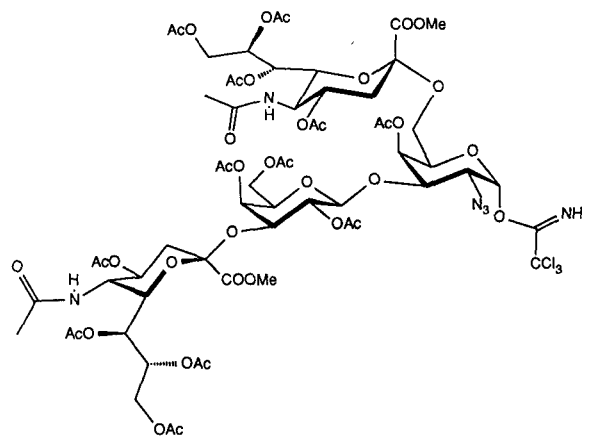
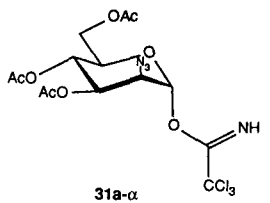
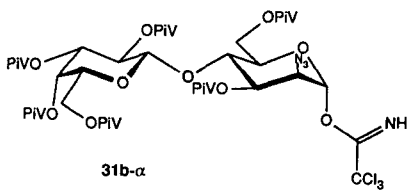
Trichloroacetimidate	Glycosyl acceptor	Reaction conditions	Yield (%)	Anomeric configuration (α:β)	Reference
30c-α		**30A** $(CH_2Cl)_2$, $BF_3 \cdot OEt_2$, MS 4 Å, −15°C 30 min	n.n.	1:2.7	121

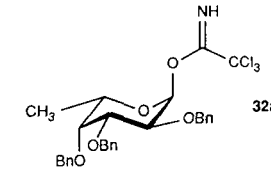
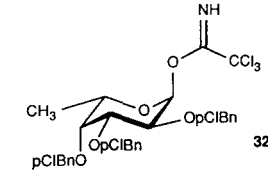
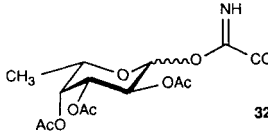
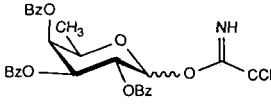
TABLE XXXI

Glycosylation of Trichloroacetimidates of 2-Azido-2-deoxy-D-mannose Derivatives

Trichloroacetimidate	Glycosyl acceptor	Reaction conditions	Reference
 **31a-α**	$P(OCH_3)_3$ **31A**	Trichloroacetimidate formation: CH_2Cl_2, CCl_3CN, NaH, room temp. Glycosylation: CH_2Cl_2, Me_3SiOTf; 58%, $\alpha:\beta$ 6:1	147
 **31b-α**	$HO-\overset{\overset{O}{\|}}{P}(OBn)_2$ **31B**	Trichloroacetimidate formation: CH_2Cl_2, CCl_3CN, NaH; 60% α[a] Glycosylation: CH_2Cl_2, $BF_3 \cdot OEt_2$, $-10°C$; 61%	150

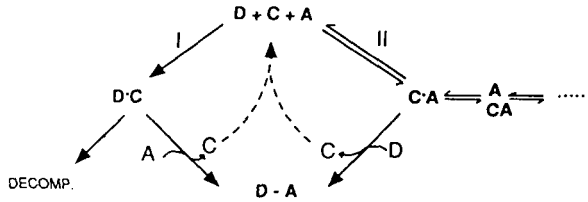
[a] From epimeric mixture.

TABLE XXXII
Synthesis of Trichloroacetimidates of Fucose

Compound	Reaction conditions	Yield (%)	Anomeric configuration (α:β)	Reference
 **32a**	CH_2Cl_2, CCl_3CN, K_2CO_3, room temp.	50	1:0	175,58b
	CH_2Cl_2, CCl_3CN, DBU, room temp.	65	1:0	162
 **32b**	CH_2Cl_2, CCl_3CN, DBU, room temp.	79	1:0	162
 **32c**	CH_2Cl_2, CCl_3CN, NaH, room temp.	71	1:0	58b
	CH_3CN, CCl_3CN, K_2CO_3, room temp.	76	2:3	58b
 **32d**	CCl_3CN, K_2CO_3	90	1:1	178

composition of the highly reactive fucosyl donor **32a** under the reaction conditions. Therefore, an alternative reaction procedure is required.

Glycosylations and also fucosylations are generally carried out as a formally termolecular reaction of donor (D), acceptor (A), and promotor or catalyst (C) (depending on the amount required) (1,4). Because of differences in the affinities, the reaction course is expected to be first DC interaction, followed by interaction of the DC complex with A (Scheme 10, reaction course I). Obviously, for this sequence of interactions, donors and acceptors with matching reactivities are required. Therefore, acceptor and donor reactivities are often varied by changing the protective-group pattern and, in addition, the donor reactivity is varied by the selection of leaving groups and



SCHEME 10. — Postulated Reaction Courses.

catalysts (1,4). However, this strategy is less successful for very reactive glycosyl donors, which may decompose in the presence of the catalyst while awaiting reaction with the acceptor. Therefore, complexation of acceptor A with the catalyst C prior to interaction with the donor D (Scheme 10, reaction course II) should overcome this problem.

The efficiency of this approach could be demonstrated in α-fucosylation with donor **32a** and the acceptors **19C** and **33A - D** (Table XXXIII). Thus, with the help of this inverse procedure, the versatile building blocks for syntheses of the Le^a, Le^x, Le^y, and H antigen determinants are readily accessible (176). Presumably, this procedure may become of general importance when reactive glycosylating agents are employed. Alternatively, the reactivity of the fucosyl donor could be decreased, as has been recently proven very successfully (177).

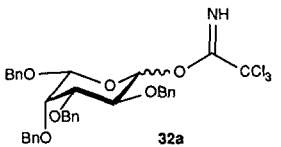
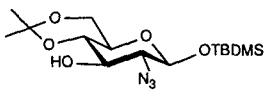
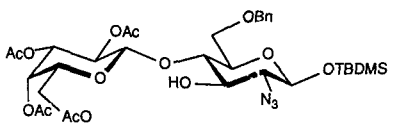
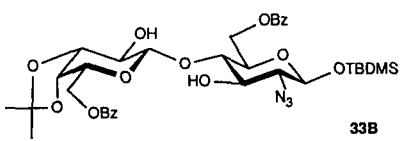
Acyl-protected fucosyl donors have also been generated very successfully (Table XXXII) (58b). Their reaction with acceptors led via neighboring-group participation to β products (58b,178).

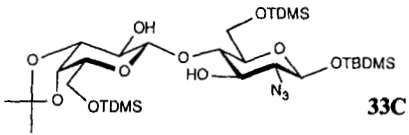
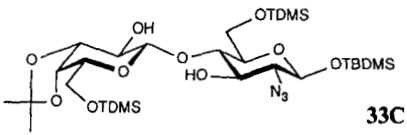
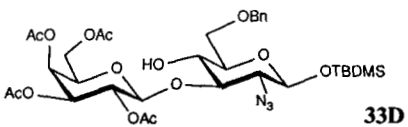
***(ii)* O-Rhamnopyranosyl Trichloroacetimidates.** — Rhamnosides are mainly found in plant heteroglycans (63,64). Some rather preliminary investigations have been carried out with rhamnose derivatives. The trichloroacetimidates obtained as rhamnopyranosyl donors are listed (124,178 - 181) in Table XXXIV. Their structural similarity to mannose explains the ready formation of α-glycosidic bonds.

***(iii)* O-Quinovopyranosyl Trichloroacetimidates.** — Quinovosides (6-deoxyglucosides) are found, for instance, as constituents of many saponins, which are composed of a carbohydrate portion attached to an aglycon that is a complex steroid in asterosaponins (182). Their dramatic biological effects have provided a motivation for structure elucidation and also for synthesis (183). The trichloroacetimidate donors **35a-d** prepared are listed in Table XXXV. They have been successfully used in oligosaccharide synthesis. Likewise, a 6-sulfoquinovosyl trichloroacetimidate has been successfully prepared (58a).

TABLE XXXIII

Reaction of Trichloroacetimidates of L-Fucose with *O*-Nucleophiles

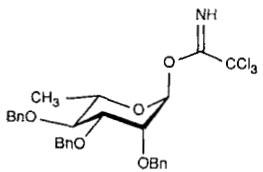
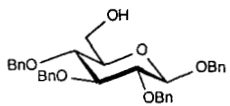
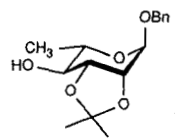
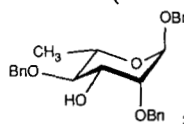
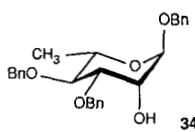
Glycosyl donor	Glycosyl acceptor[a]	Reaction conditions	Yield (%)	Reference
 **32a**	 **19C**	$(C_2H_5)_2O$, Me_3SiOTf (0.01 eq.), room temp., IP	85	165
32a	 **33A**	$(C_2H_5)_2O$, Me_3SiOTf (0.01 eq.), room temp., IP	78	165
32a	 **33B**	CH_2Cl_2, Me_3SiOTf (0.02 eq.), room temp., IP, 1.5 eq. **32a**	72 (3-*O*)	177
		CH_2Cl_2, Me_3OTf (0.02 eq.), room temp., IP, 4 eq. **32a**	71 (3,2′ di-*O*)	177

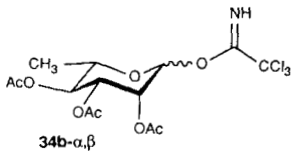
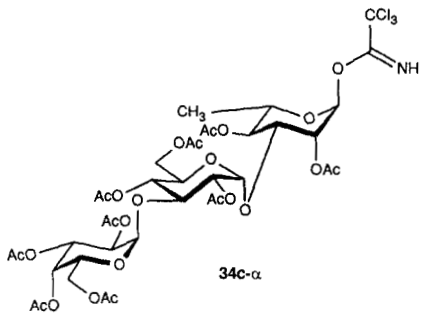
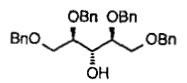
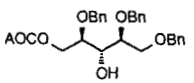
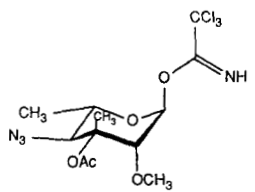
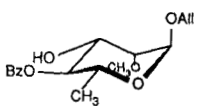
32a	 **33C**	$(C_2H_5)_2O$, Me_3SiOTf, −15°C → 0°C, 10 eq. **32a**	90 (3,2′ di-*O*)	162
32b	 **33C**	$(C_2H_5)_2O$, Me_3SiOTf, −20°C 11 h, 8 eq. **32b**	71 (3,2′ di-*O*)	162
32a	 **33D**	$(C_2H_5)_2O$, Me_3SiOTf (0.01 eq.), room temp., IP	78	176

[a] TBDMS, *tert*-butyldimethylsilyl; TDMS, dimethyl-(2,3-dimethyl-2-butyl)silyl.

TABLE XXXIV

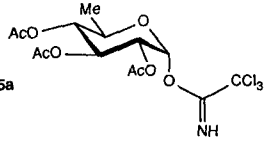
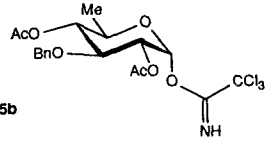
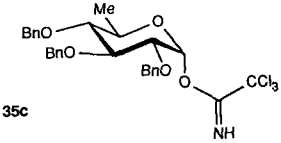
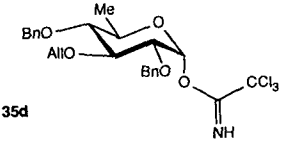
Glycosylation of L-Rhamnopyranosyl Derivatives

Glycosyl donor	Trichloroacetimidate formation	Glycosyl acceptor[a]	Reaction conditions	Reference
 **34a-α**	CCl_3CN, NaH, CH_2Cl_2, room temp., 30 min; 85%	 **34A**	CH_2Cl_2, *p*-TsOH; 86% α	124
		 **34B**	CH_2Cl_2, *p*-TsOH; 96% α	124
		 **34C**	CH_2Cl_2, *p*-TsOH; 82% α	124
		 **34D**	CH_2Cl_2, *p*-TsOH; 70% α	124

 **34b-α,β**	CH_2Cl_2, CCl_3CN, K_2CO_3	n.n.		178
 **34c-α**	CH_2Cl_2, CCl_3CN, DBU, room temp., 1 h; 81%	 **34E**	CH_2Cl_2, Me_3SiOTf, $-30°C$, 5 min; 90%	179
		 **34F**	CH_2Cl_2, Me_3SiOTf, $-30°C$, 20 min; 75%	180
 **34d-α**	CCl_3CN, DBU, CH_2Cl_2, room temp., 20 min; 97%	 **34G**	$BF_3 \cdot OEt_2$ (1.25 eq.), CH_2Cl_2, MS 4 Å, Ar, 12 h; 90% α	180

[a]AOC, allyloxycarbonyl.

TABLE XXXV
Synthesis of Trichloroacetimidates of D-Quinovose

Glycosyl donor[a]	Reaction conditions	Yield (%)	Anomeric configuration (α:β)	Reference
 35a	CH_2Cl_2, CCl_3CN, DBU, room temp.	92	1:0	183
 35b	CH_2Cl_2, CCl_3CN, DBU, room temp.	90	1:0	183
 35c	CH_2Cl_2, CCl_3CN, DBU, room temp.	84	6:1	183
 35d	CH_2Cl_2, CCl_3CN, DBU, room temp.	88	1:0	183

[a] All, allyl.

i. Trichloroacetimidates of 2-Deoxyhexoses: 2-Deoxy-D-*arabino*-hexose.—The presence of the 2-deoxy-β-D-*arabino*-hexopyranoside ("2-deoxy-β-D-glucopyranoside") moiety in natural products has stimulated various approaches for the selective synthesis of this glycosidic bond (184–189). A temporary 2-phenylthio group as a neighboring group, generating an episulfonium-ion intermediate during glycoside-bond formation, seems to be advantageous because it is also readily removable by hydrogenation, affording the desired 2-deoxy sugar (188,189). Successful application of the trichloroacetimidate method to this problem required (*i*) a convenient synthesis of a 2-*S*-phenyl-2-thio-D-glucose derivative, subsequently (*ii*) a stable α-trichloroacetimidate, and finally (*iii*) high diastereoselection in the glyco-

syl transfer. This could be accomplished starting from tri-*O*-benzyl-D-glucal, as shown in Table XXXVI (190). The 2-phenylthio-substituted trichloroacetimidate **36**-α was readily obtained and it exhibited extraordinarily high reactivity; reactions with different acceptors were fast even at temperatures as low as $-95\,^{\circ}C$, affording preferentially β-glycosides **36a–d** in high yields. Transformation into the desired 2-deoxy derivatives **36A–D** was readily achieved by treatment with Raney nickel (190).

Obviously, extension of this methodology to other 2-deoxy sugars and also to selective formation of α-glycoside bonds with 2-deoxy sugars should be feasible. The extension of this methodology to 3-deoxy-2-glyculosonates (for instance, Neu5Ac) is under investigation.

j. Trichloroacetimidates of Glucuronic Acid. — D-Glucosiduronate (glucuronide) formation is an important means for detoxification in mammals and leads to soluble conjugates that can be excreted via the urine. Glycosides of D-glucuronic acid occur also in many microbial, plant, and animal polysaccharides (for instance, in heparin) (191). Glycoside-bond formation with the help of trichloroacetimidates has been accomplished quite successfully (169,192,193). To this aim, donors **37a–c** have been synthesized from the 1-*O*-unprotected derivatives in high yields (Table XXXVII). Representative examples of their reaction with various acceptors are compiled in Table XXXVIII.

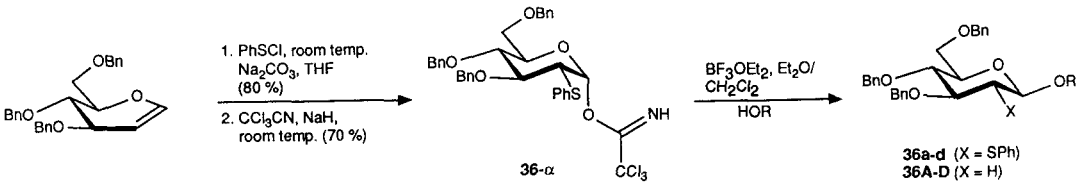
k. Trichloroacetimidates of Pentoses. — Thus far, there has been relatively little activity in the application of the trichloroacetimidate method to formation of pentopyranosides and pentofuranosides (46,183,194–199). The reported examples exhibit results similar to those already discussed, and thus special limitations are not expected.

l. Reactions of *O*-Glycosyl Trichloroacetimidates with N-, S-, C-, and P-Acceptors. — Only a few studies with N-nucleophiles have been performed. Hydrazoic acid, as a strong acid, reacts with *O*-glycosyl trichloroacetimidates and readily gives the thermodynamically most stable glycosyl azide without any additional catalyst (53) (Scheme 6). Nitrogen heterocycles require an acid catalyst for reaction; thus, bis-(trimethylsilylated) uracil and thymine gave, with trichloroacetimidate **1a**-α, exclusively the β-linked nucleosides at room temperature with boron trifluoride etherate as catalyst (1,53,200). Reactions in nitriles as solvent lead during workup to trapping of nitrilium adducts (53,78).

The strong interest in 1-thioaldoses and 1-thioglycosides (66,201) as a consequence of their recent use as anomeric protecting-groups, and concomitantly for glycosyl transfer with the help of thiophilic activators, led to

TABLE XXXVI

Synthesis of 2-Deoxy-β-D-*arabino*-hexopyranosides



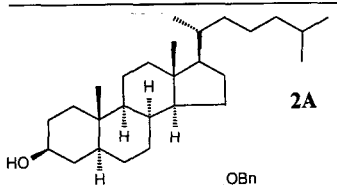
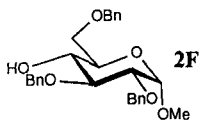
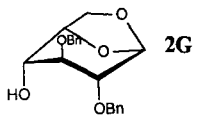
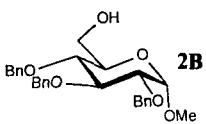
Glycosyl acceptor	Reaction conditions		Yield (%)	Anomeric configuration (α:β)	Reference
 **2A**	20°C, 1 h	**36a**	90	8:1	190
 **2F**	−40°C, 15 min	**36b**	90	1:0	190
 **2G**	−60°C, 15 min	**36c**	85	3:1	190
 **2B**	−95°C, 15 min	**36d**	83	1:0	190

TABLE XXXVII
Synthesis of Trichloroacetimidates of D-Glucuronate

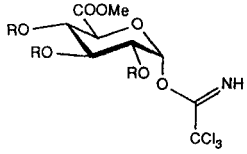
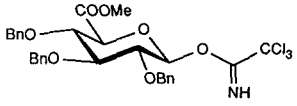
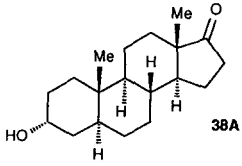
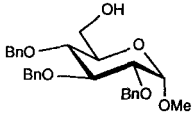
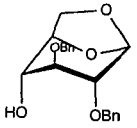
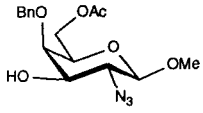
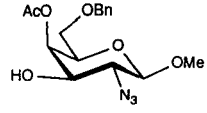
Compound		Reaction conditions
	**37a** (R = Bn)	NaH, CCl_3CN, CH_2Cl_2, 15 min (98%) (Ref. 192)
	37b (R = Ac)	DBU, CCl_3CN, $(CH_2Cl)_2$, 1 h (92%) (Refs. 169,193)
	**37c**	K_2CO_3, CCl_3CN, CH_2Cl_2, 8 h (73%) (Ref. 193)

TABLE XXXVIII
Synthesis of β-D-Glucosiduronates

Donor	Acceptor	Reaction conditions	Yield (%)	Anomeric configuration (α:β)	Reference
37a	 **38A**	CH_2Cl_2, $BF_3 \cdot OEt_2$, −25°C, 2 h	88	0:1	192
37a	 **2B**	CH_2Cl_2, $BF_3 \cdot OEt_2$, −30°C, 2 h	88	0:1	192
37a	 **2G**	CH_2Cl_2, $BF_3 \cdot OEt_2$, −30°C, 2 h	82	0:1	192
37b	 **38B**	Toluene, Me_3SiOTf, −20°C	75	0:1	169
37b	 **38C**	Toluene, Me_3SiOTf −20°C	72	0:1	169

the study of the reactivity of *O*-glycosyl trichloroacetimidates in the glycosylation of S-nucleophiles (66). In the examples investigated employing *O*-acyl- and *O*-benzyl protected donors, generally high reactivity was observed. Surprisingly, with the *O*-benzyl protected trichloroacetimidate **1a**-α in the presence of boron trifluoride etherate as catalyst, 1-thioglycosides of the α configuration are obtained exclusively. Because the anomeric effect in alkyl 1-thioglycosides supposedly corresponds approximately to that in alkyl glycosides (202,203), under the reaction conditions kinetically controlled β-product formation was expected; under thermodynamic control, both anomers should be formed. Obviously, glycosyl transfer to the S-nucleophiles in these cases occurs by a different mechanism. It was assumed, that, as in SNi reactions, the configuration is retained by intramolecular reaction via a tight ion-pair (66). Thiocarboxylic acids react again without the addition of any acidic catalyst to provide 1-*S*-acetyl-1-thio sugars (66,68).

The great interest in *C*-glycosyl compounds is reflected in the extensive research in this field (204). Successful investigations with *O*-glycosyl trichloroacetimidates as glycosyl donors and phenol ethers (199,207,208), silyl enol ethers (205,206), trimethylsilyl cyanide (205,206), and allyltrimethylsilane (206) as C-acceptors underline the wide scope of these highly reactive glycosyl donors.

The biological importance of glycosyl phosphates prompted interest in the synthesis of glycosyl phosphates as structural analogues (209,210). Excellent examples for their synthesis were contributed by the reaction of trichloroacetimidates **17l**-α, **29a**-α, and **39a**-α with trimethyl phosphite in presence of Me_3SiOTf as catalyst (211) (Table XXXIX). Attack at phosphorus and subsequent *O*-demethylation led in a Michaelis–Arbuzov type of reaction to the desired products. Obviously, various other elements or their derivatives are conceivable as glycosyl acceptors. These may react either directly as strong acids (as for instance hydrogen halides, see Scheme 6) or as good nucleophiles react in the presence of a catalyst with the highly reactive *O*-glycosyl trichloroacetimidates as donors.

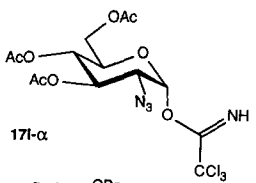
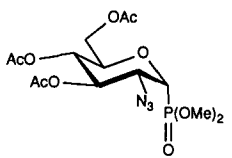
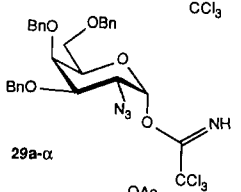
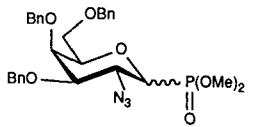
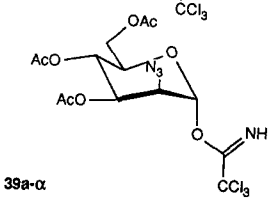
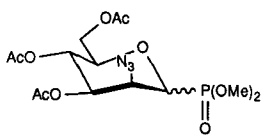
IV. Other Anomeric-oxygen Activation Methods

1. Other Glycosyl Imidates, Glycosyl Carboxylates, and Glycosyl Sulfonates

Base-catalyzed addition of glycosyl oxides for anomeric *O*-activation has been extended meanwhile to trifluoroacetonitrile (see Scheme 9), to dichloroacetonitrile, to 1-aryl-1,1-dichloroacetonitriles, and to ketene imines (46,51,52). Also 2-(glycosyloxy)-pyridine and -pyrimidine derivatives were readily prepared from the corresponding 2-halo precursors (78). However,

TABLE XXXIX

Reaction of *O*-Glycosyl Trichloroacetimidates with $P(OMe)_3$

Donor	Reaction conditions	Product	Yield (%)	Anomeric configuration (α:β)	Reference
 17l-α	CH_2Cl_2, room temp. 1 h, Me_3SiOTf		76	1:0	211
 29a-α	CH_2Cl_2, room temp. 1 h, Me_3SiOTf		64	1:1	211
 39a-α	CH_2Cl_2, room temp. 1 h, Me_3SiOTf		59	6:1	211

none of the imidate donors thus obtained seems to exceed the *O*-glycosyl trichloroacetimidates in terms of ease of formation, stability, and reactivity.

Acetimidate formation with *N*-methylacetamide and acylated glycosyl halides according to Sinaÿ *et al* (212,213), using three equivalents of silver oxide as an activator, leads neither to particularly stable nor to reactive donors. Any other developments along these lines have already been summarized in previous reviews (1,3). The same is mainly true for anomeric *O*-activations via 1-*O*-acylation (1,214), including orthoester (1) formation, 1-*O*-alkylation (1,215) and -silylation (1), and 1-*O*-sulfonylation (1).

2. Glycosyl Phosphates and Related Systems

One of the most important direct nucleophilic substitutions at activated carbon atoms carried out in nature is enzymic *O*- and *N*-glycosyl bond-formation at the anomeric carbon atom (216). At this activated position, the leaving groups are phosphates, pyrophosphates, and their nucleoside and lipid ester derivatives, which are biosynthesized via anomeric *O*-phosphorylation reactions. *In vitro* anomeric *O*-phosphorylation readily furnishes dialkyl or diaryl glycosyl phosphates (217). These also exhibit, in inert solvents in the presence of boron trifluoride etherate or Me_3SiOTf as catalysts, good glycosyl donor properties comparable to those of glycosyl fluorides and sulfides, respectively, as reported elsewhere (17). However, with A=B—C—H systems as acceptors (see Section III.2), where a catalyst is not required, their reactivity is similar to that of the very reactive trichloroacetimidate donors, as indicated by competition experiments (17). Thus, contrary to a recent statement (218), not only *in vivo* but also *in vitro* nucleophilic substitution at activated carbon atoms, as exemplified by the anomeric center, can be efficiently performed with glycosyl phosphates. This was recently demonstrated not only for glycosyl phosphates but also for such derivatives related to imidates as O—P (=X)Y_2, where X = O and Y = NMe_2, X = O and Y = Ph, X = S and Y = OMe, and X = NTs and Y = Ph (219–223).

V. Conclusions

The requirements for new glycosylation methods outlined at the beginning of this chapter, namely convenient diastereocontrolled anomeric *O*-activation (first step) and subsequent efficient diasterecontrolled glycosylation promoted by genuinely catalytic amounts of a catalyst (second step), are essentially completely fulfilled by the *trichloroacetimidate method.* This is clearly shown by the many examples and references given in this article. In terms of stability, reactivity, and applicability toward different acceptors, the

O-glycosyl trichloroacetimidates have generally proven to be outstanding glycosyl donors, which resemble in various respects the natural nucleoside diphosphate sugar derivatives as glycosyl donors. Thus, base-catalyzed generation of *O*-glycosyl trichloroacetimidates and ensuing acid-catalyzed glycosylation have become a very competitive alternative to direct, often uncontrolled acid-catalyzed transformation of sugars into glycosides (Fischer–Helferich method) or to glycosyl halide and glycosyl sulfide formation for the activation step, which requires at least equimolar amounts of a promoter system for the glycosylation step (Koenigs–Knorr method and variations). In addition, the trichloroacetimidate method may be readily adapted for large-scale preparations.

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