Reviews

New protecting groups in the synthesis of oligosaccharides*

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The review is focused on new hydroxy and amino protecting groups in carbohydrate chemistry developed or gained popularity over the last 15 years. Representative examples for the protecting group manipulations are given.

Key words: protecting groups, oligosaccharides, carbohydrates, glycosylation.

Introduction

Protecting groups play a key role in the synthesis of complex naturally occurring substances.[1] To a large extent, this concerns oligosaccharides "constructed" from carbohydrate monomer units containing up to five hydroxy groups often in combination with amino and carboxyl functions.[2] These functional groups are differentiated during oligosaccharide synthesis by careful choice of orthogonal sets of protecting groups. Although protecting groups are introduced into the molecule to temporarily mask a particular functional group, but they can also affect the reactivity of the carbohydrate moiety, *i.e.*, stereochemical outcome and yield of glycosylation.[3] Moreover, protecting groups changing overall hydrophilicity/lipophilicity of the products, their solubility and ability to crystallize can often expedite separation/purification steps.[4,5]

To date, several reviews on protecting groups in carbohydrate chemistry have been published.[3,6] Herein, we are focused on novel protecting groups (developed during last 15 years or gained popularity within this period) from the viewpoint of the current breadth of application in the synthesis of oligosaccharides. Therefore, each section describes the protecting groups starting from the most commonly used and continuing to the less popular ones.

1. Hydroxy protecting groups

1.1. Protecting groups with minimized sterical effect

It is well known[3] that the bulkiness of a protecting group is of critical importance for stereochemical out-

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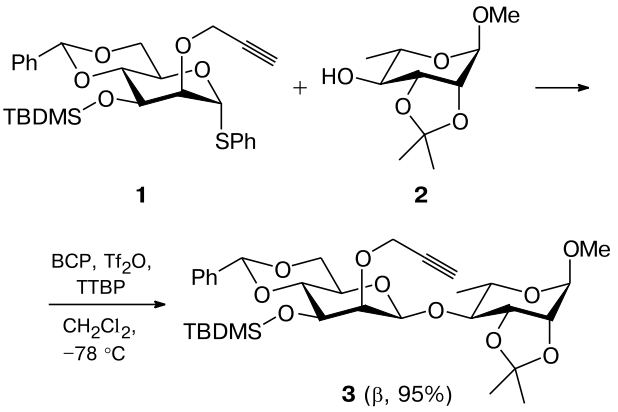
come of glycosylations. This is true not only for the protecting groups with large steric bulk but also for the groups with steric bulk lower than that of the conventional protecting groups. For example, 2,3-*O*-benzylated 4,6-*O*-benzylidene protected mannosyl donors were found to be β-selective but replacement of one of the benzyl groups with more bulky TBDMS group or other monosaccharide residue resulted in the significant decrease in selectivity.[7,8]

To overcome the poor selectivity of mannosyl donors bearing bulky substituents, various propargyl ethers as protecting groups were suggested.[9,10] Thus, unsubstituted propargyl group noticeably reduced steric buttressing from the bulky silyl protecting group at O(3) of donor **1**: glycosylation of rhamnose derivative **2** led selectively to β-(1→4)-disaccharide **3** (Scheme 1).[9] The protecting group was introduced using propargyl bromide and NaH in DMF at 0 °C. Deprotection was accomplished in two steps: 1) Bu^{t}OK, THF, ~20 °C; 2) OsO_4 as a catalyst, *N*-methylmorpholine *N*-oxide, acetone/H_2O, ~20 °C.

Scheme 1



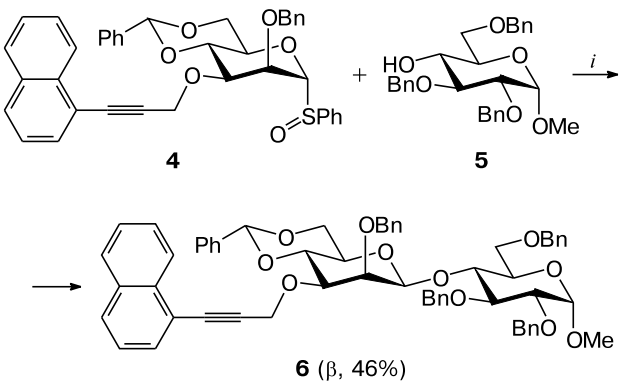
TBDMS is Bu^{t}Me$_2$Si, BSP is 1-benzenesulfenylpiperidine, TTBP is 2,4,6-tri-*tert*-butylpyrimidine.

Since the removal of propargyl protection required two steps, more readily cleavable protecting groups were developed, *e.g.*, 1-naphthylpropargyl[11] and 4-trifluoromethylbenzenepropargyl[10] ethers. Although these protecting groups are formally more bulky due to the presence of the substituents, they do not impair steric environment by virtue of the geometry and location of the —C≡C— moiety.

1-Naphthylpropargyl protecting group at O(3) orthogonal to other protecting groups of glycosyl donor **4** was used for the synthesis of disaccharide **6** (Scheme 2)[11] as a sterically minimal alternative to TBDMS ether. Protection was achieved by 1-naphthylpropargyl bromide and NaH in DMF at 0 °C; the protected derivative was cleaved by treatment with DDQ in CH_2Cl_2/H_2O at ~20 °C.

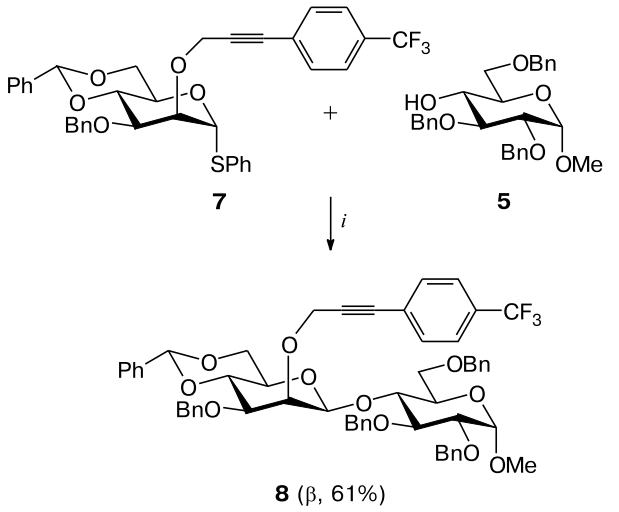
4-Trifluoromethylbenzenepropargyl group at the O(2) atom was used similarly in the synthesis of disaccharide **8** (Scheme 3).[10] Protecting group was introduced by treatment with 4-trifluoromethylbenzenepropargyl bromide and NaH in DMF at 0 °C. Deprotection was performed with lithium naphthalenide in THF at −70 °C.

Scheme 2



i. Tf_2O, TTBP, CH_2Cl_2, −78 °C, oct-1-ene.

Scheme 3



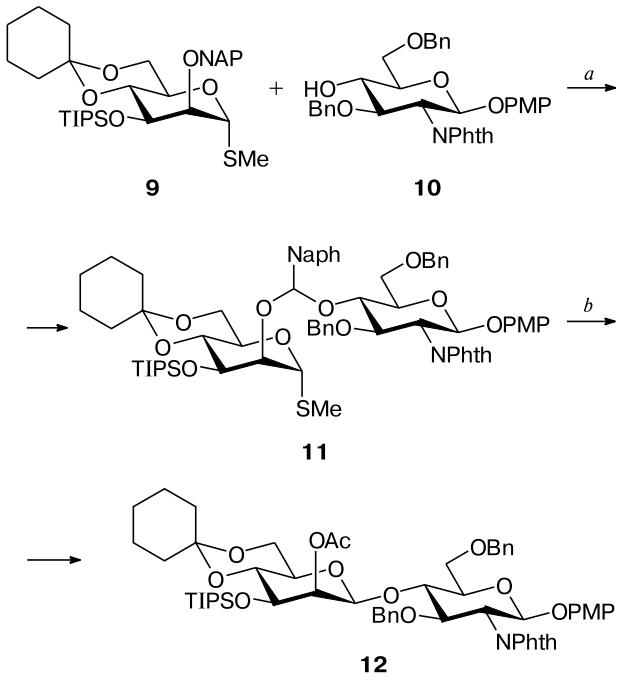
i. BSP, Tf_2O, TTBP.

1.2. Protecting groups for intramolecular aglycon delivery

2-Naphthylmethyl (NAP) protection similarly to conventional 4-methoxybenzyl protecting group was found to be very successful in realization of the protecting group-mediated intramolecular aglycon delivery (IAD), the approach developed for the stereoselective synthesis of 1,2-*cis* glycosides.[12] Thus, 2-*O*-naphthylmethyl-protected mannosyl donor **9** reacted with mannosyl acceptor **10** upon oxidative activation to give mixed acetal **11** (Scheme 4). Subsequent activation of thioglycoside moiety initiated the

rearrangement of mixed acetal moiety into the target β-mannopyranoside **12**. This strategy was successfully applied for construction of 1,2-*cis* glycosidic bonds of β-mannopyranosides, β-arabinofuranosides, α-glucopyranosides, and β-rhamnopyranosides.[13,14]

Scheme 4



NAP is 2-naphthylmethyl, TIPS is Pr^i_3Si, Naph is naphthalen-2-yl, PMP is 4-$MeOC_6H_4$, Phth is phthaloyl.

Reagents and conditions: *a*. DDQ, molecular sieves 4 Å, $(CH_2Cl)_2$, ~20 °C (99%, one isomer); *b*. 1) MeOTf, 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), $(CH_2Cl)_2$, ~20 °C; 2) Ac_2O, pyridine (90%, β-disaccharide only).

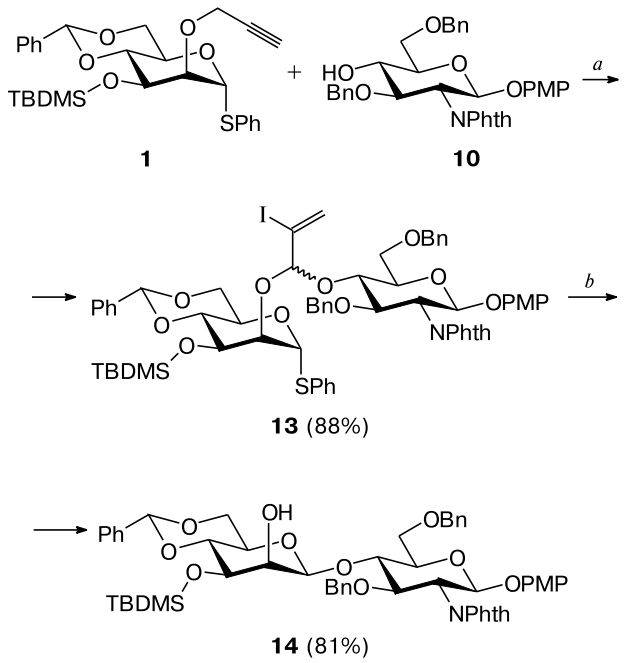
Recently,[15] Liu and co-workers developed a new protocol for selective cleavage of 2-naphthylmethyl ether with pyridinium hydrofluoride in toluene at room temperature. Benzyl ether survived under these conditions.

Propargyl group at the O(2) can also be utilized within the IAD concept. For instance, isomerization of the 2-*O*-propargyl group of thiomannoside **1** to allene followed by reaction with compound **10** gave mixed acetal **13**, which further stereoselectively transformed to the target disaccharide **14** (Scheme 5).[16]

1.3. Conformation-constraining protecting groups

Control stereoselectivity in the synthesis of oligosaccharides can be achieved adopting conformation-constraining protecting groups. *i.e.*, cyclic bifunctional protecting groups including benzylidene and bisacetal protecting systems, carbonyl (carbonate and oxazolidinone),

Scheme 5



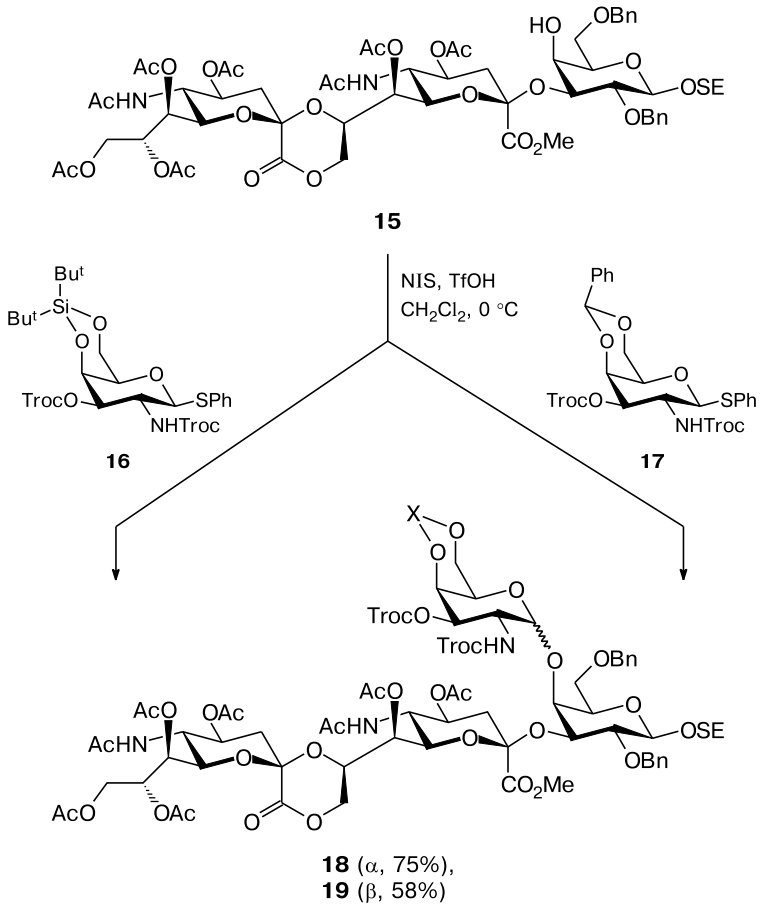
Reagents and conditions: *a*. 1) $KOBu^t$, Et_2O (66%); 2) I_2, AgOTf, DTBMP, CH_2Cl_2, −78 °C; *b*. Me_2S_2, Tf_2O, DTBMP, CH_2Cl_2, 0 °C.

and cyclic silyl groups. These protecting groups can restrict the flexibility of the sugar ring favoring a certain conformation of the intermediate thus making one of its sides more accessible for attack.[2,17]

Di-*tert*-butylsilylene (DTBS) protecting group was introduced as more acid resistant than isopropylidene and benzylidene groups.[18,19] The DTBS also attracts attention due to its α-directing effect in the reaction of oligosaccharide **15** with glycosyl donor **16** despite the presence of participating acyl substituents (Troc (2,2,2-trichloroethoxycarbonyl), Bz, Phth (phthaloyl)) at O(2). This result is opposite to the direction of the similar reaction involving galactosyl donor **17** bearing benzylidene group (Scheme 6). According to the authors, the most likely reason for such unusual reaction direction is the steric effect of the *tert*-butyl groups, which was indirectly confirmed by X-ray diffraction (XRD) analysis. The XRD study of compound **16** revealed that equatorial *tert*-butyl group is positioned close to anomeric center. The DTBS group was introduced using $Bu^t_2SiCl_2$, *N*-hydroxybenzotriazole (HOBt) in pyridine at 95 °C, deprotection was achieved by treatment with Bu_4NF in THF at 0 °C.

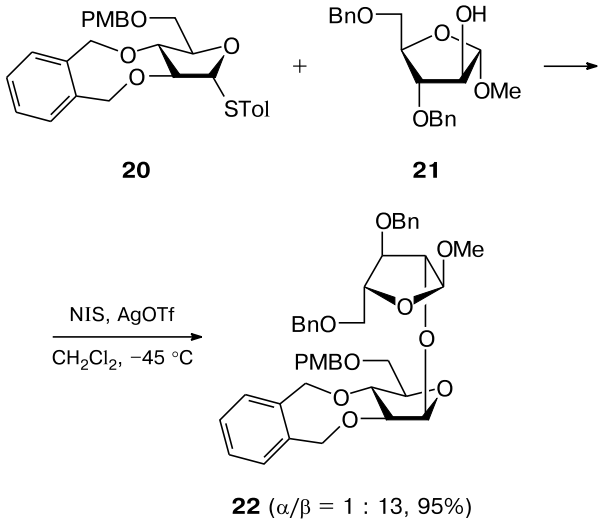
Xylylene protecting group is the other example of the conformation-constraining protecting group. Xylylene protection was employed in the β-stereoselective synthesis of arabinofuranoside **22** (a fragment of lipoarabinomannan from the *Mycobacterium tuberculosis* cell wall) from thioglycoside **20** and arabinose derivative **21** (Scheme 7).[20]

Scheme 6



X = Bu^t_2Si (**18**), CHPh (**19**); SE = $CH_2CH_2SiMe_3$; Troc = $Cl_3CH_2CH_2OC(=O)$

Scheme 7



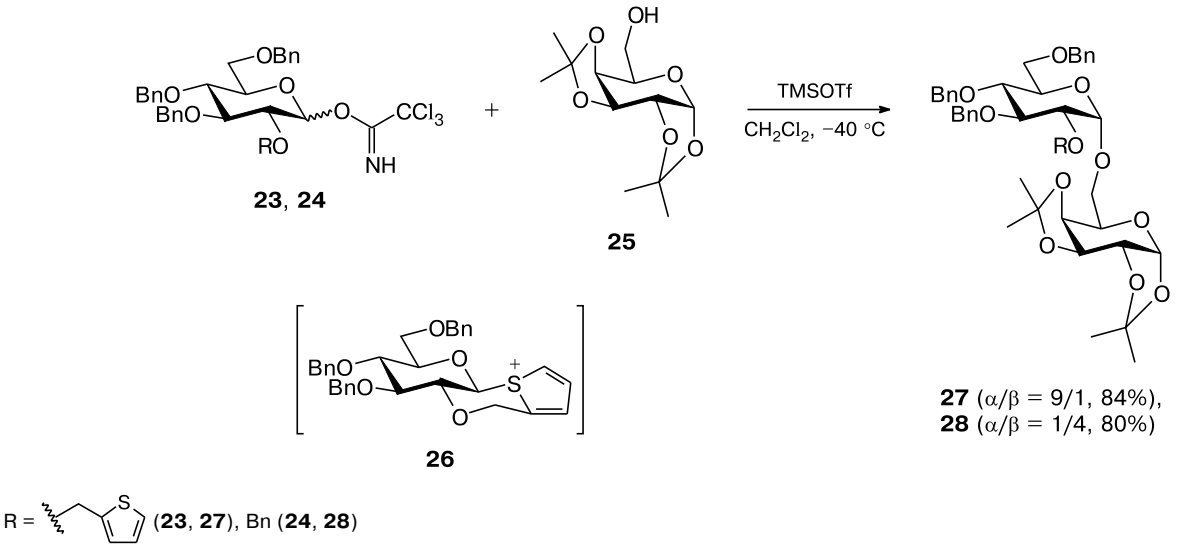
PMB is 4-$MeOC_6H_4CH_2$.

It was found[20] that good β-selectivity can be achieved only in the presence of the 5-*O*-PMB protecting group. Introduction of the xylylene group was accomplished with α,α′-dibromo-*o*-xylene and NaH in DMF at 0 °C, the protected derivative was cleaved with H_2, Pd/C, EtOH/THF at ~20 °C.

1.4. Hetarylmethyl and hetarylcarbonyl protecting groups

The hetarylmethyl groups neighboring an anomeric center are able to participate in glycosylation giving bicyclic positively charged intermediates undergoing selective ring opening upon nucleophilic attack with glycosyl acceptor.[21,22] Such neighboring participation is characteristic of the thiophen-2-ylmethyl group used for protection of glycosyl donor **23** (Scheme 8)[21] in the reaction with compound **25**. Cox and Faibanks suggested formation of transient intermediate thiophenium ion **26** α-directing the nucleophile and thus noticeably increasing α-stereoselectivity as compared with benzyl-protected derivative **24**.

Scheme 8

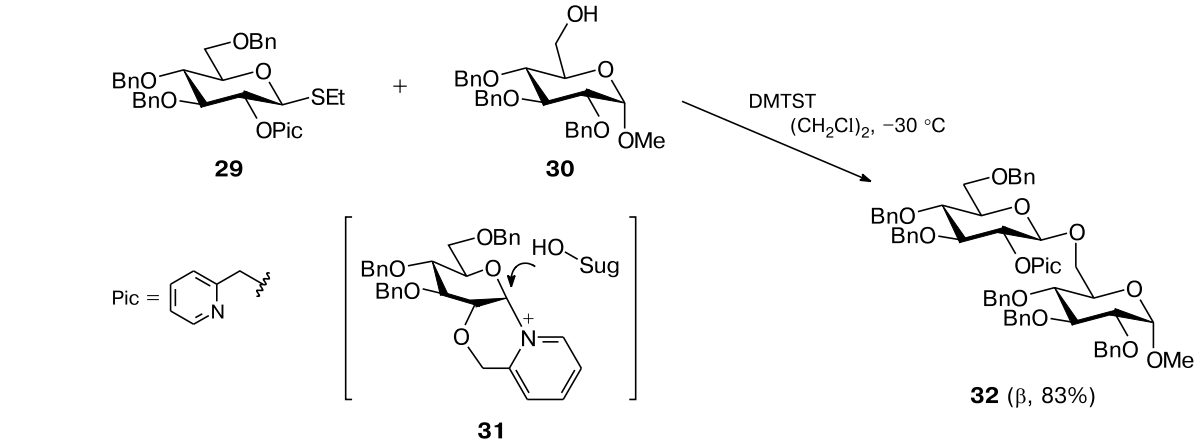


No detailed explanation of a preferred formation of α-isomer **26** was given. The protecting group was introduced using 2-bromomethylthiophene and NaH in DMF at 0 °C, removal was not described.

In contrast to the above-described *cis*-directing effect of the sulfur-containing group, a 2-picolyl (Pic) group of thioglycoside **29** was found to be *trans*-directing (Scheme 9). It was shown[23] that in this case glycosylation proceeded *via* predominant formation of 1,2-*cis*-bicyclic intermediate **31** further undergoing ring opening with glycosyl acceptor **30** to give selectively 1,2-*trans* glycoside **32**. Introduction of the protecting groups was achieved with PicBr and NaH in DMF at −25 °C and removal was accomplished with H_2, Pd/C in EtOH/AcOEt at ~20 °C.

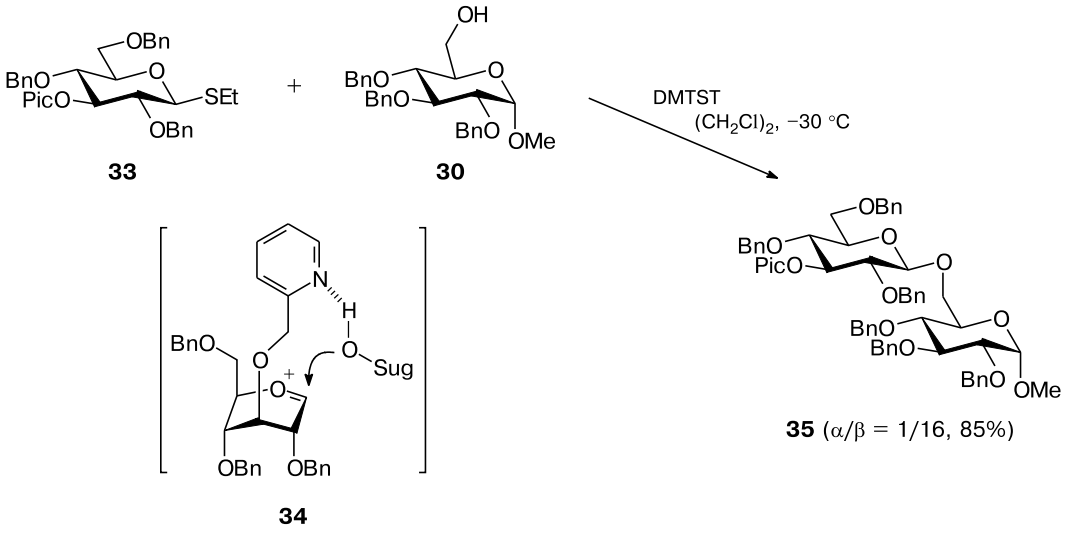
High stereoselectivity of glycosylation was also provided by the picolyl group at remote position to the anomeric carbon. For instance, the O(3) protected thioglycoside **33** reacted with glycosyl acceptor **30** (Scheme 10)[23] to yield disaccharide **35** with anomeric ratio α/β = 1/16. In this case, predominant β-glycosylation was explained by the intramolecular H-bond formation between glycosyl donor and glycosyl acceptor similarly to intermediate **34** providing facial selectivity for the attack of the glycosyl donor. It should be noted that no exact confirmation of this putative mechanism was given. However, much lower stereoselectivity in the reactions involving the corresponding trimethylsilyl-protected glycosyl acceptors unable to H-bond formation supports the mechanism of stereocontrol proposed by Demchenko and co-workers.

Scheme 9



DMTST is dimethyl(methylthio)sulfonium triflate.

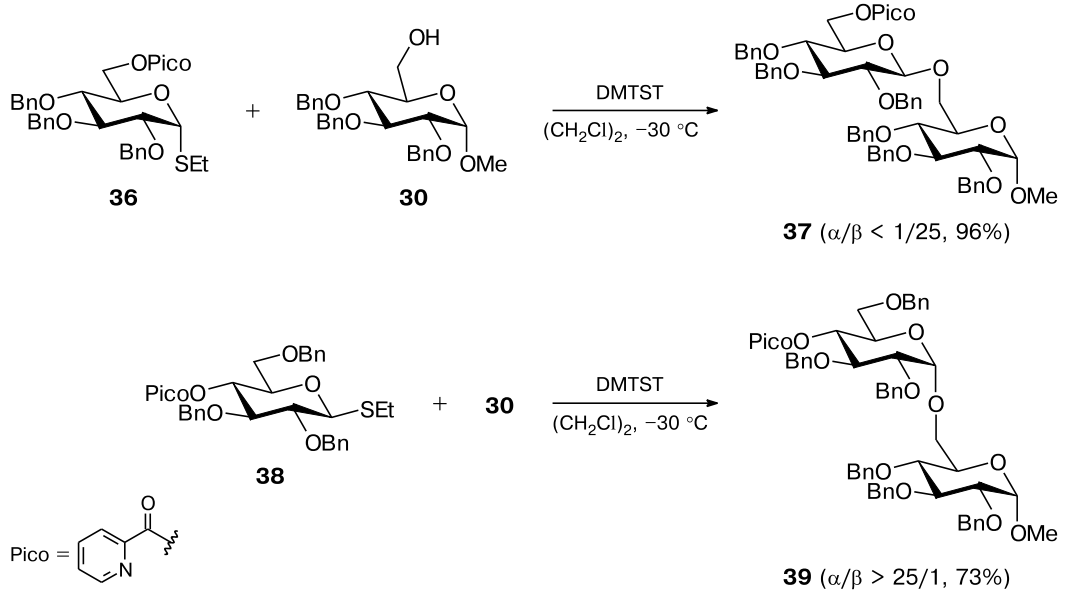
Scheme 10



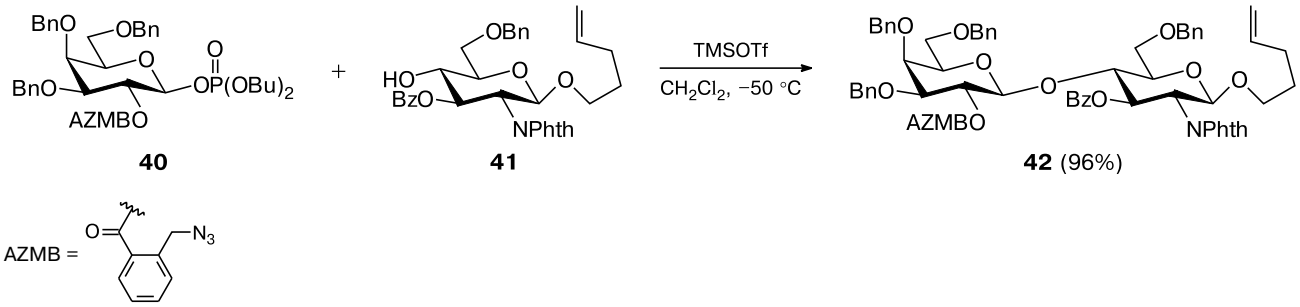
Further study of the protecting group influence on stereochemistry of glycosylation revealed that the closely related pycoloyl (Pico) protecting group at the O(6) position of glycosyl donor provided even higher stereoselectivity in glycosylation.[23,24] When the Pico group was placed at the O(4) position, glycosylation showed reversal stereoselectivity giving predominantly α-isomer. The effect of the remote pycoloyl group on stereoselectivity of glycosylation was demonstrated in the reactions of thioglycosides **36** and **38** with glycosyl donor **30** (Scheme 11)[23]: the α/β anomeric ratios were <1/25 for disaccharide **37** and >25/1 for disaccharide **39**. The protecting group was introduced employing PicoOH, DCC, and DMAP in CH_2Cl_2 at ~20 °C, cleavage was effected using $Cu(OAc)_2$, MeOH, CH_2Cl_2 at ~20 °C.[25]

Coordination chemistry approach was attempted to enhance stereoselectivity of glycosylation: the reaction involved platinum complexes of carbohydrates protected with pycolyl or related groups. However, the reaction gave worse stereoselectivity than in the case of pycoloyl protection. The O(6)-protected glycosyl donor provided the best results: the anomeric ratio in target disaccharide was α/β = 9.4/1.[26]

Scheme 11



Scheme 12



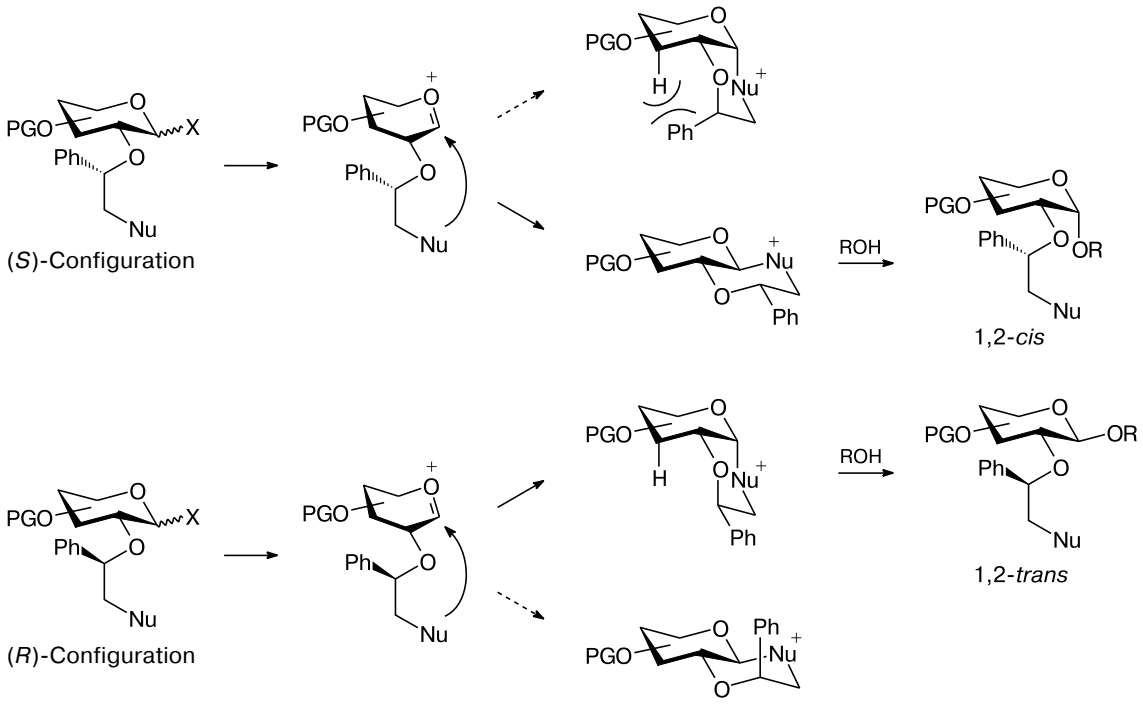
1.5. 2-(Azidomethyl)benzoyl protecting group

2-(Azidomethyl)benzoyl (AZMB) protecting group is mainly of interest as a stereodirecting group closely related to Bz protecting group, which can be selectively removed under relatively mild conditions. The AZMB protection was used in the synthesis of H-type II pentasaccharide.[27] The AZMB protecting group was found to be stable in glycosylation (Scheme 12) of glucosamine derivative **41** with galactosyl donor **40** selectively yielding β-disaccharide. This group is compatible with a wide variety of hydroxy and amino protecting groups, *e.g.*, All, Lev (levulinoyl), PMB, and TIPS. The AZMB and Bz groups represent an excellent pair of orthogonal protecting groups. Introduction of the AZMB protecting group was achieved with AZMBCl and DMAP in CH_2Cl_2 at ~20 °C; the removal conditions were PBu_3, THF/H_2O at ~20 °C.

1.6. Chiral auxiliary groups

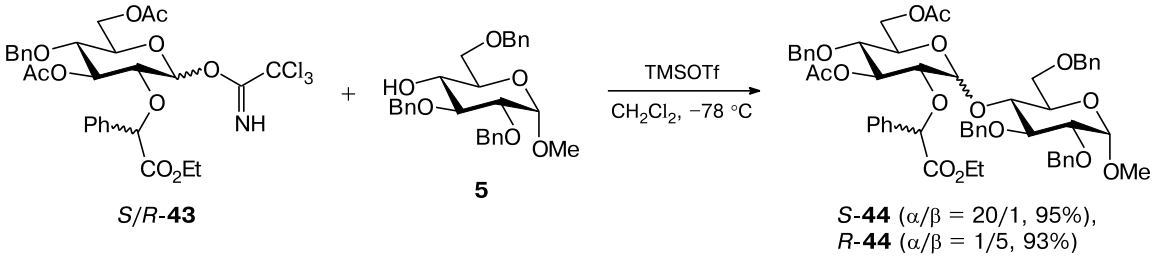
Boons and co-workers described[28,29] a novel glycosylation strategy, in which a chiral auxiliary substituted with a nucleophilic (Nu) fragment and positioned at the O(2) of glycosyl donor controls the stereochemical outcome of glycosylation (Scheme 13). Upon formation of an oxacarbenium ion, the participation of the Nu substituent led to formation of either *cis*- or *trans*-decalin system depending on the configuration of chiral auxiliary at the O(2). The auxiliary with *S*-stereochemistry due to favored equatorial position of the phenyl group in bicyclic intermediate

Scheme 13

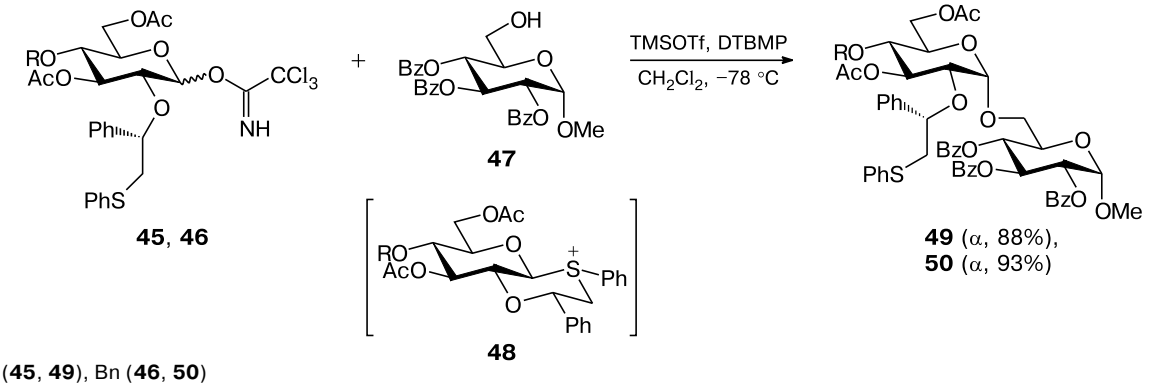


PG is protecting group; Nu is nucleophile.

Scheme 14



Scheme 15



R = Ac (**45**, **49**), Bn (**46**, **50**)

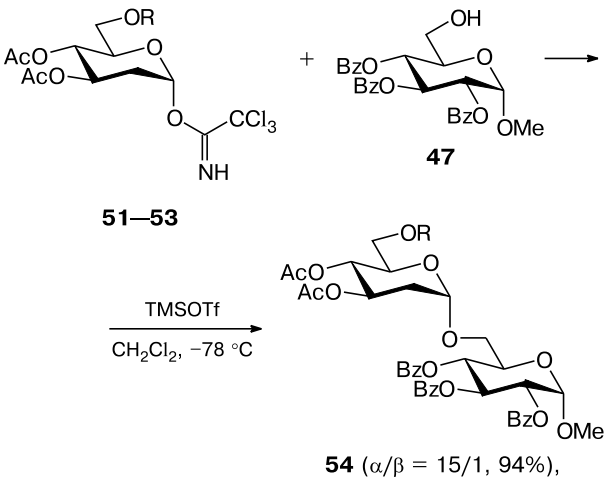
led to preferred formation of the *trans*-decalin intermediate undergoing further ring opening with an external nucleophile ROH to give 1,2-*cis* glycoside. The auxiliary at the O(2) position with the *R*-configuration favored formation of 1,2-*trans* glycoside *via cis*-decalin intermediate.

1-(Ethoxycarbonyl)benzyl group was the first chiral auxiliary explored.[28,29] Thus, glycosylation of glucose derivative **5** with glycosyl donor **43** bearing *S*-ethoxycarbonylbenzyl auxiliary resulted in disaccharide *S*-**44** with high α-anomeric selectivity. In contrast, glycosylation involving glycosyl donor **43** with auxiliary with *R*-configuration showed a reversal anomeric selectivity and mainly yielded β-linked disaccharide *R*-**44** (Scheme 14). Auxiliary was introduced with ethyl mandelate in toluene in the presence of $BF_3 \cdot Et_2O$ and molecular sieves 4 Å at ~20 °C; the auxiliary can be removed by reduction with either H_2, Pd/C at ~20 °C or Na, NH_3 at −78 °C.

One of the most efficient chiral auxiliaries of a new generation is (1*S*)-phenyl-2-phenylthioethyl auxiliary.[30] Upon TMSOTf-activation of glycosyl donors **45** and **46** (Scheme 15), this auxiliary provided quasi-stable sulfonium ions **48** having *trans*-decalin structure. Subsequent nucleophilic substitution involving different glycosyl acceptors, *e.g.*, **47**, led exclusively to α-glucosides (for instance, **49** and **50**) and α-galactosides. Utility of the suggested approach was demonstrated by the synthesis of Galα1-3Galβ1-4GlcNAc trisaccharide. The auxiliary can be introduced using (1*S*)-phenyl-2-phenylthioethyl acetate in CH_2Cl_2 in the presence of $BF_3 \cdot Et_2O$ at 0 °C and removed by treatment with $BF_3 \cdot Et_2O$ in Ac_2O at 0 °C.

Later,[31] it was shown that 2-deoxyglycosyl donor **51** bearing (1*S*)-phenyl-2-phenylthioethyl moiety at the O(6) position can be successfully employed for the synthesis of α-linked glycoside **54** (Scheme 16).

Scheme 16



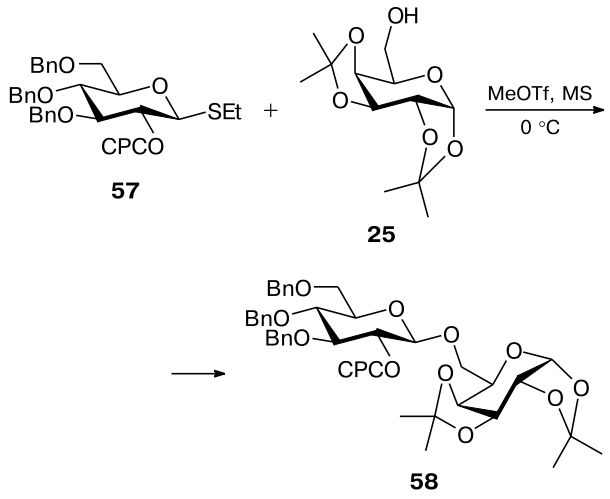
R = (*S*)-CH(Ph)CH_2SPh (**51**, **54**), Bn (**52**, **55**), Ac (**53**, **56**)

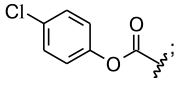
It should be noted that this chiral auxiliary found application in solid-phase synthesis of a biologically important branched α-glucans.[32]

1.7. 4-Chlorophenoxycarbonyl protecting group

4-Chlorophenoxycarbonyl (CPC) protecting group attracts attention first of all as a participating group that can be selectively removed under relatively mild conditions comparing with other carbonates.[33] The CPC group is orthogonal to a wide range of common protecting groups, *i.e.*, Bz, Piv (pivaloyl), TIPS, Lev, All, and PMB. The CPC group is stable under conditions employed for glycosylation of derivative **25** with thioglycoside **57** affording β-disaccharide **58** in good yield (Scheme 17). The CPC derivative was prepared by the reaction with 4-cholophenyl chloroformate in the presence of DMAP at ~20 °C, it was cleaved by treatment with LiOH, H_2O_2, THF/H_2O at 0 °C.

Scheme 17

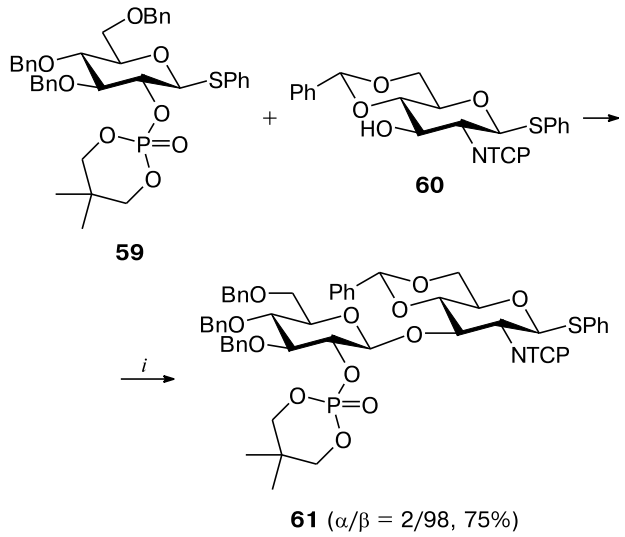


CPC =  ; MS is molecular sieves 4 Å.

1.8. Dialkyl oxyphosphoryl protecting group

It was recently shown[34] that dialkyl oxyphosphoryl group at the O(2) position is a stereodirecting group for glycosylation providing 1,2-*trans* glycosides (Scheme 18). Glycosylation of thioglycoside acceptor **60** with thioglycoside donor **59** under pre-activation conditions led stereoselectively to product **61** in good yield. The protecting group was introduced using 2,2-dimethyltrimethylene phosphorochloridate and NaH in THF at ~20 °C, the phosphate was cleaved by NaOH (10 equiv.), EtOH/H_2O at 60 °C.

Scheme 18



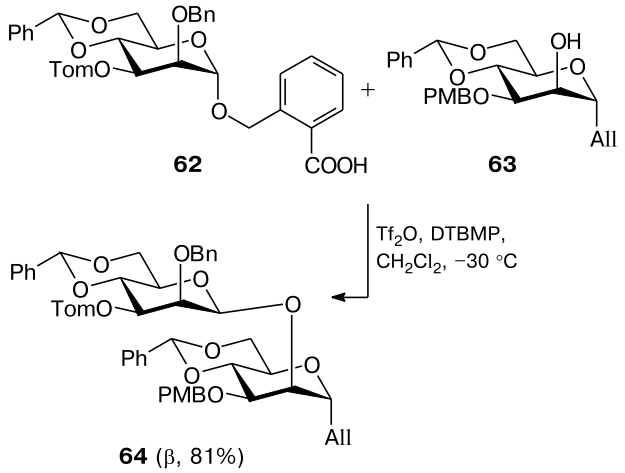
TCP is tetrachlorophthaloyl.

i. BSP, Tf_2O, TTBP, CH_2Cl_2, –60 °C.

1.9. Triisopropylsilyloxymethyl protecting group

Steric strain at the O(3) position in mannosylation can be reduced not only using sterically minimal protecting groups but also "shifting" bulky silyl substituent from the mannose moiety to oxymethylene fragment. The successful example of this approach is the application of triisopropylsilyloxymethyl (Tom) protection (Scheme 19)[35] in the synthesis of disaccharide **64** from mannosyl donor **62** and mannose derivative **63**. Protection was effected by Bu_2SnCl_2, Pr^i_2EtN, $(CH_2Cl)_2$ followed by TomCl; cleavage was performed with Bu_4NF, THF/H_2O at ~20 °C.

Scheme 19

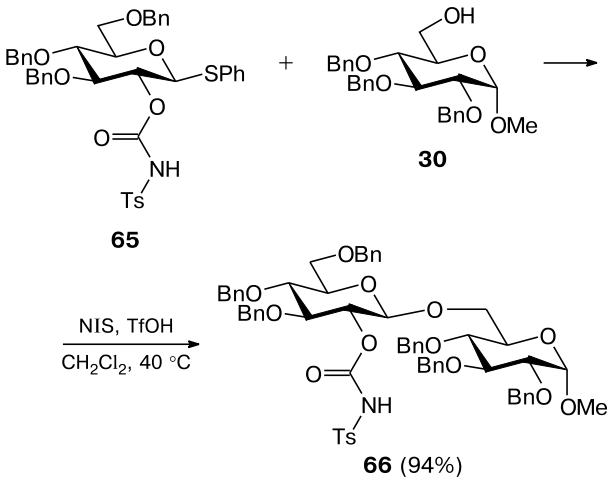


Tom is $Pr^i_3SiOCH_2$; PMB is 4-$MeOC_6H_4CH_2$.

1.10. Sulfonylcarbamoyl protecting group

The sulfonylcarbamoyl protecting group in contrast to typical protecting groups is stable under harsh basic conditions (*e.g.*, in the presence of NaOMe/MeOH) existing in the relatively inert deprotonated form and is labile under mild basic conditions.[36] This protecting group is compatible with other common protecting groups and efficiently controls anomeric selectivity. Thus, reaction of thioglycoside **65** and glucose derivative **30** provided disaccharide **66** in good yield (Scheme 20). The sulfonylcarbamoyl protecting group forms orthogonal pairs with Bz, TBDPS, and Bn groups. The protecting group was introduced by 4-toluenesulfonyl isocyanate in THF at ~20 °C; the protected derivative was cleaved with pyridine/H_2O (7 : 3) at 40 °C.

Scheme 20



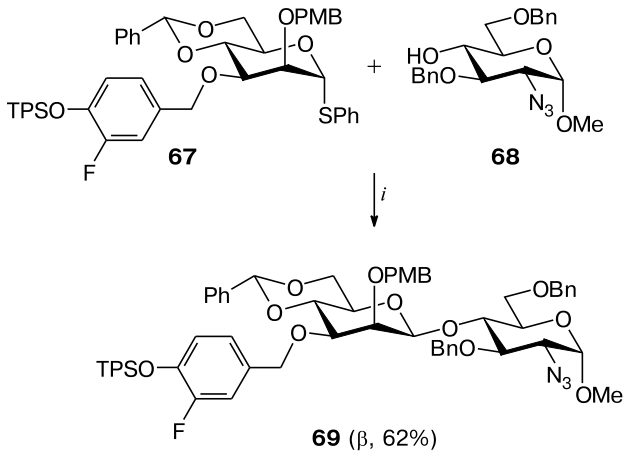
1.11. 4-(tert-Butyldiphenylsilyloxy)-3-fluorobenzyl protecting group

4-(*tert*-Butyldiphenylsilyloxy)-3-fluorobenzyl group was first used in the synthesis of β-mannosides as a new benzyl-ether type protecting group labile in the presence of the fluoride ion (Scheme 21).[37] Protected thioglycoside **67** reacted with glycosyl acceptor **68** to give disaccharide **69**. The protected derivative was prepared by the reaction with 4-TPSO-3-fluorobenzyl bromide and NaH in DMF at 0 °C and was cleaved with Bu_4NF in THF under microwave irradiation.

1.12. Sulfonyl-containing protecting groups

The (methanesulfonyl)ethoxymethyl (Msem) group was developed as a sterically minimal protecting group labile under basic conditions that provides high β-selectivity in mannosylation (Scheme 22).[38] For instance, the protected mannose thioglycoside **70** reacted with derivative **71** furnishing disaccharide **72**. Conditions for introduction of the Msem groups were as follows: 1) Bu_2SnO, refluxing toluene; 2) MsemCl, CsF, Bu_4NBr, toluene, ~20 °C. Removal of the Msem was achieved using Bu_4NF, piperidine in THF at ~20 °C.

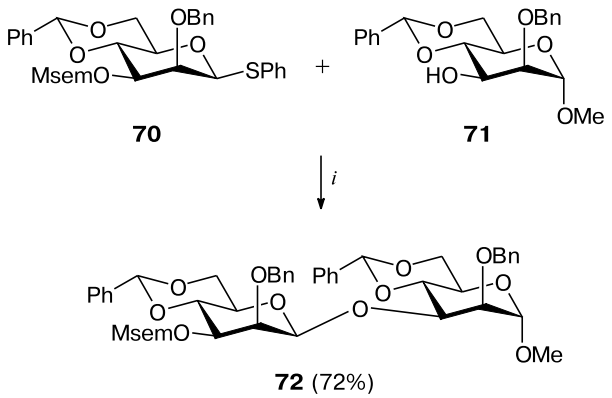
Scheme 21



TPS is Bu^tPh_2Si.

i. BSP, Tf_2O, TTBP, CH_2Cl_2, −60 °C, oct-1-ene.

Scheme 22



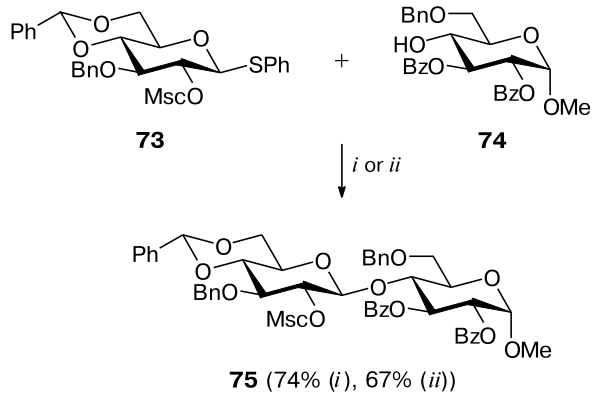
Msem is $MeS(=O)_2CH_2CH_2OCH_2$.

i. Ph_2SO, Tf_2O, TTBP, CH_2Cl_2, −78 °C.

The methanesulfonylethoxycarbonyl (Msc) group has found application as an anchimeric participating protecting group providing high stereoselectivity and preventing orthoester formation (Scheme 23).[39] For example, the protected thioglycoside **73** reacted with glucose derivative **74** under various glycosylation conditions to give disaccharide **75** in moderate to good yields. The Msc protecting

group was introduced using MscCl and pyridine at 0 °C and was removed by treatment with either DBU in DMF or Bu_4NF in THF at ~20 °C.

Scheme 23



75 (74% (*i*), 67% (*ii*))

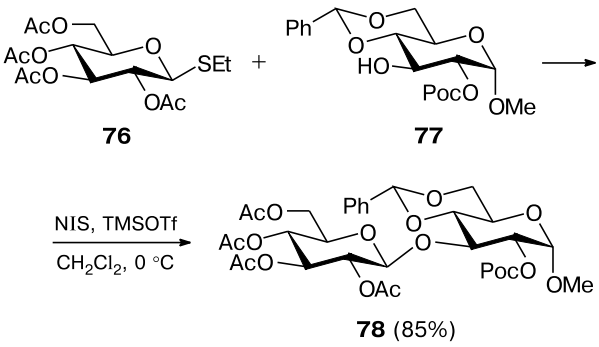
Msc is $MeS(=O)_2CH_2CH_2OC(=O)$.

i. NIS, TMSOTf, CH_2Cl_2, –40 °C;
ii. Ph_2SO, Tf_2O, TTBP, CH_2Cl_2, –60 °C.

1.13. Propargyloxycarbonyl protecting group for glycosyl acceptors

The propargyloxycarbonyl (Poc) group was specially developed for protection of the hydroxy functions in the glycosyl acceptors. The Poc group is orthogonal to a wide range of traditional protecting group, *e.g.*, Cbz (benzyloxycarbonyl), Alloc (allyloxycarbonyl), Lev, Ac, Bn, and Bnd (benzylidene). The Poc group can be readily removed under neutral conditions by treatment with tetrathiomolybdate.[40] This protecting group was employed (Scheme 24) in glycosylation of substituted glucose derivative **77** with glycosyl donor **76** to yield disaccharide **78**. The Poc group was introduced using PocCl and TMEDA in CH_2Cl_2 at –78 °C, the removal was effected with $(BuNEt_3)_2MoS_4$ in MeCN at ~20 °C.

Scheme 24



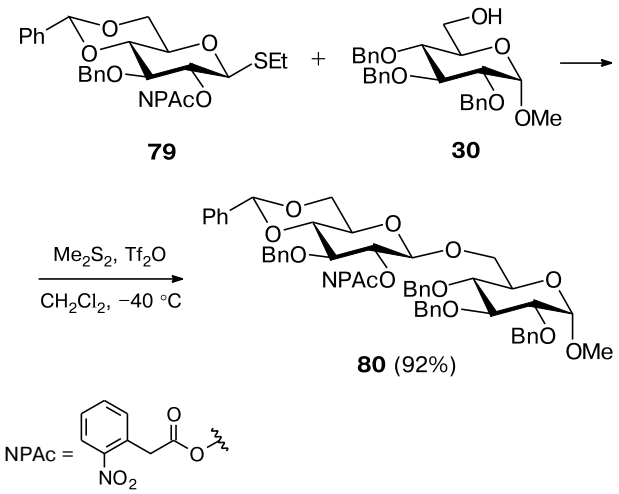
78 (85%)

Poc is $CH{\equiv}CCH_2OC(=O)$—.

1.14. 2-Nitrophenylacetyl protecting group

2-Nitrophenylacetyl (NPAc) protecting group is an efficient participating group well suited for stereocontrolled synthesis of 1,2-*trans* glycosides.[41] Thus, the reaction of the protected thioglycoside **79** and glucose derivative **30** afforded disaccharide **80** in high yield (Scheme 25). The NPAc group is orthogonal to a wide variety of protecting groups commonly used in carbohydrate chemistry (TBDMS, Lev, Fmoc (9-fluorenylmethoxycarbonyl), Nap, PMB, and Bz). The conditions employed for the introduction of the NPAc group are either NPAcCl (or $NPAc_2O$), pyridine, 0 °C or NPAcOH, DCC, DMAP (or DEAD), CH_2Cl_2, ~20 °C. The cleavage was achieved using Zn and NH_4Cl in refluxing MeOH.

Scheme 25



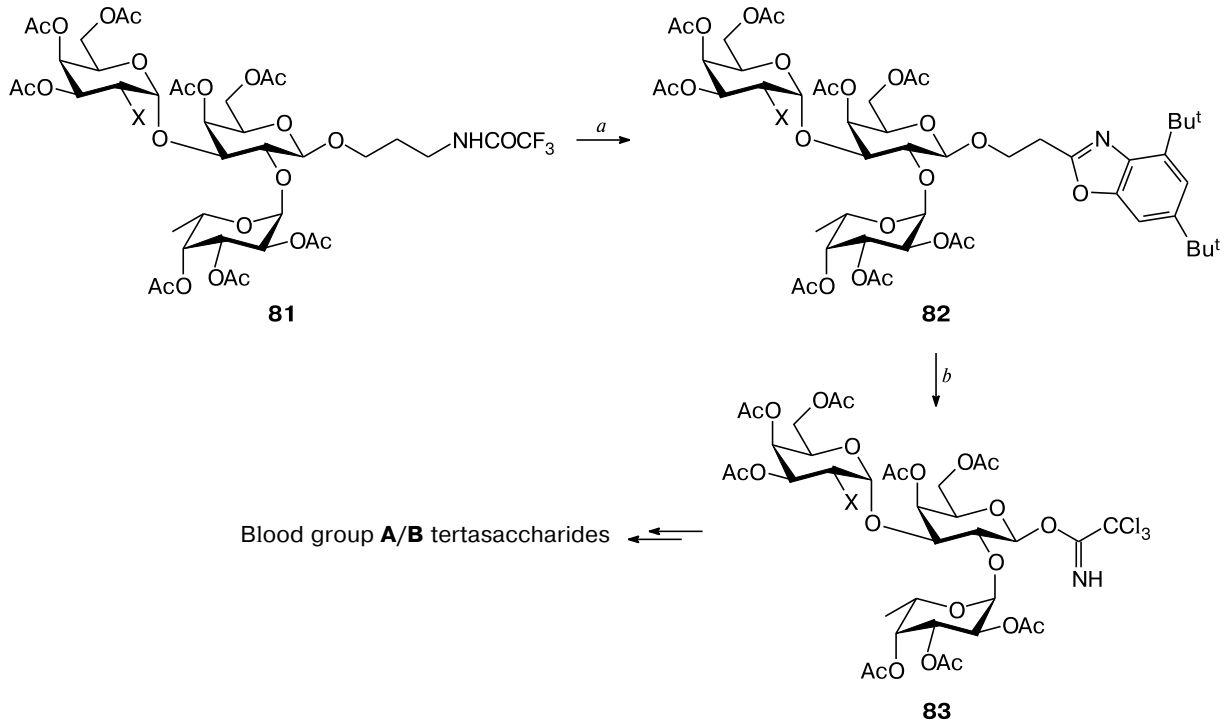
80 (92%)

1.15. Protected spacer groups

The special type of the protecting groups at O(1) are the groups able to play a role of spacers. Among them, *N*-trifluoroacetyl-3-aminopropyl group attracts special attention. On the one hand, this group can be removed allowing transformation of trisaccharide **81** *via* intermediate benzoxazole **82** to active glycosyl donor **83** used further in the synthesis of blood group tetrasaccharides **A** and **B** (Scheme 26).[42–44] On the other hand, trifluoroacetyl cleavage converted this group into the $OCH_2CH_2CH_2NH_2$ spacer-arm, which is a valuable and popular group in glycobiology in the past two decades.

Another example of the protected spacer group is 4-(2-chloroethoxy)phenyl group combining the best properties

Scheme 26

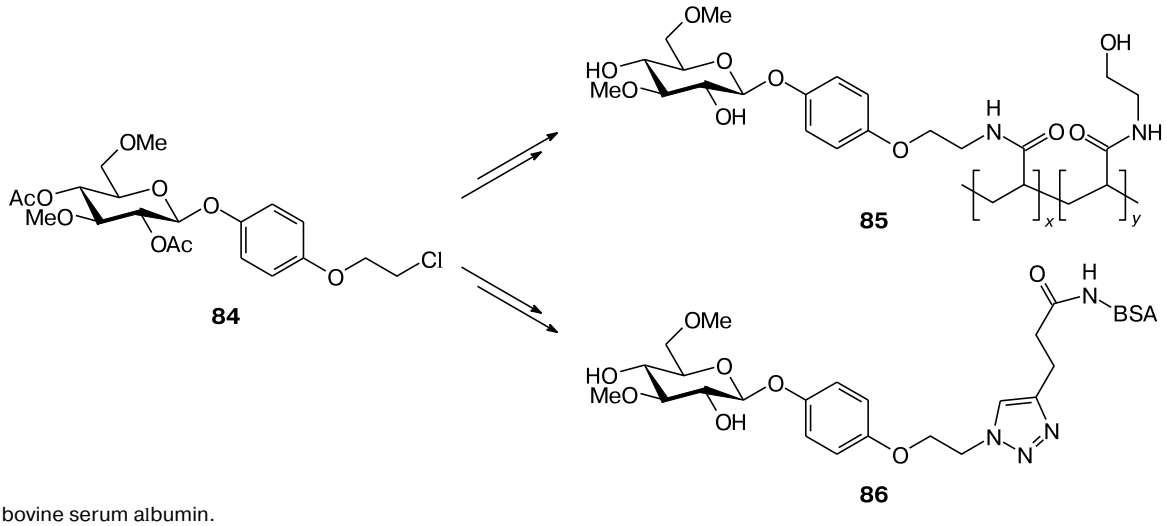


X = NHAc (**A**) or OH/OAc (**B**)

Reagents and conditions: *a*. 1) NaOMe, MeOH; 2) NaOH, H_2O; 3) 3,5-di-*tert*-butyl-1,2-benzoquinone, MeOH; 4) $(COOH)_2 \cdot 2H_2O$ (pH 4); 5) Ac_2O/pyridine. *b*. 1) NaOAc, Ac_2O—AcOH (1 : 1), 100 °C; 2) $N_2H_4 \cdot HOAc$, DMF, 50 °C; 3) Cl_3CCN, DBU, CH_2Cl_2.

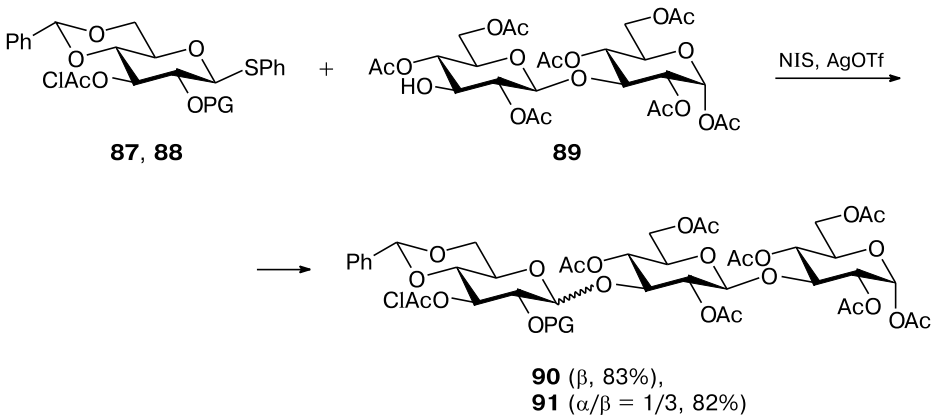
of readily removable 4-methoxyphenyl group and easily functionalizable 2-chloroethyl group.[45,46a,b] Thus, the chlorine atom of derivative **84** can be readily replaced with azido group followed by transformation into amino function. This transformation sequence was employed in the synthesis of glycoconjugates of 3,6-di-*O*-methylglucose **85** and **86** (Scheme 27), the terminal units of a specific glycolipid from *Mycobacterium leprae*. The protecting group can

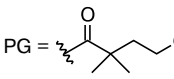
Scheme 27



BSA is bovine serum albumin.

Scheme 28



PG =  (**87**, **90**), Piv (**88**, **91**)

be readily removed under oxidative conditions similarly to 4-methoxyphenyl protecting group.[46a] The protecting group was introduced by treatment of 2,4-di-*O*-acetyl-3,6-di-*O*-methyl-α-D-glucopyranosyl bromide with 4-$HOC_6H_4O(CH_2)_2Cl$ in the presence of Cs_2CO_3 in MeCN and was cleaved with cerium ammonium nitrate in $MeCN/H_2O$ (5 : 1) at 0 °C.

1.16. Other functionalized classical protecting groups

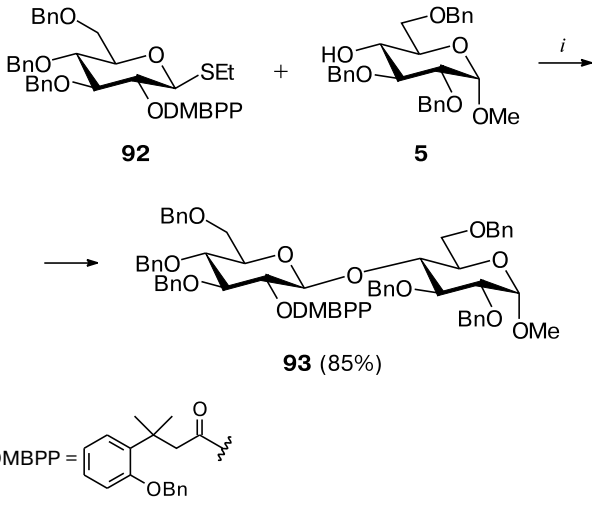
A number of participating acyl groups (*O*-acetyl, *O*-chloroacetyl, *O*-benzoyl, and *O*-pivaloyl) are extensively used for the construction of 1,2-*trans* glycosidic linkages. However, glycosylation in the presence of these protecting groups often gives cyclic orthoesters instead of isomeric target 1,2-*trans* glycosides. Moreover, the deprotection conditions are often too harsh. Recently, several novel protecting groups of acyl-type lacking above-mentioned drawbacks have been developed.

4-Acetoxy-2,2-dimethylbutanoyl ester was suggested as an analog of the pivaloyl protecting group. It enables the stereoselective synthesis of β-glucopyranosides and can be removed under mild conditions.[47] Methanolysis used for cleavage initiates intramolecular lactonization followed by the dimethyl butyrolactone elimination.

An example would be the glycosylation (Scheme 28) of disaccharide **89** with glycosyl donor **87** showing higher β-selectivity than in the case of the pivaloyl-protected glycosyl donor **88**. The protected derivative was prepared using 4-acetoxy-2,2-dimethylbutanoyl chloride in pyridine at 0 °C, deprotection was performed by treatment with DBU in MeOH at ~20 °C.

3-(2-Benzyloxyphenyl)-3,3-dimethylpropanoyl (DMBPP) group was developed as a participating protecting group enabling stereoselective synthesis of β-glucopyranosides and α-mannopyranosides. Similar to benzyl ester, the DMBPP group can be removed by hydrogenolysis under neutral conditions. The possibilities of this protecting group was demonstrated by the reaction of protected thioglycoside **92** with glucose derivative **5** (Scheme 29).[48] Introduction of the DMBPP ester was achieved using DMBPPOH, 1,1′-carbonyldiimidazole, and DBU in MeCN at 60 °C, the removal was carried out with Pd/C, H_2, MeOH/AcOEt at ~20 °C.

Scheme 29



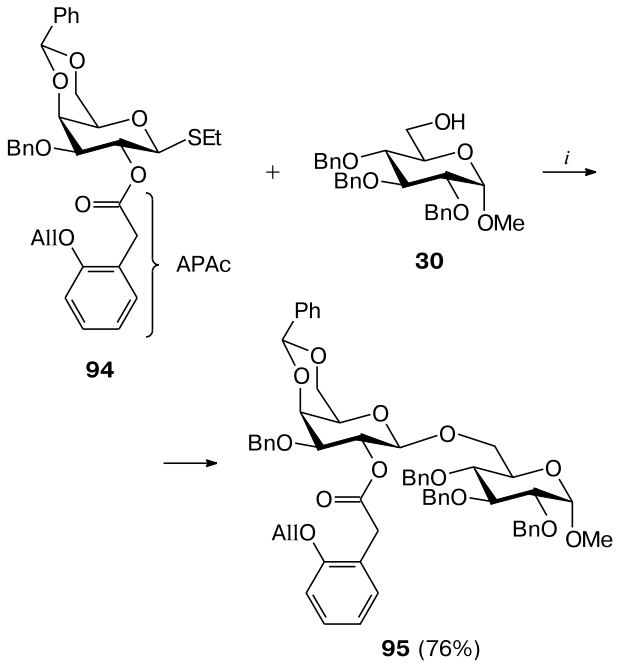
DMBPP =

i. NIS, TfOH, CH_2Cl_2, –40 °C.

(2-Allyloxyphenyl)acetyl (APAc) group is the other example of functionalized protecting group that can be removed under milder conditions than those required for the removal of related traditional protecting groups. It can be cleaved by treatment with $Pd(PPh_3)_4$ in ethanol—water

under reflux.[49] The APAc group being orthogonal to Ac and Lev groups is well suited for stereoselective glycosylation giving exclusively 1,2-*trans* products. The successful example is the reaction of thioglycoside **94** and glucose derivative **30** to give disaccharide **95** in good yield (Scheme 30). The APAc protecting group was introduced using APAcOH, DCC, and DMAP in CH_2Cl_2; deprotection was achieved using $Pd(PPh_3)_4$ and proton sponge in refluxing $EtOH/H_2O$.

Scheme 30



i. NIS, TMSOTf, CH_2Cl_2.

2. Amino protecting groups

Several novel protecting groups for the nitrogen atom of 2-amino-2-deoxysugars have been described.

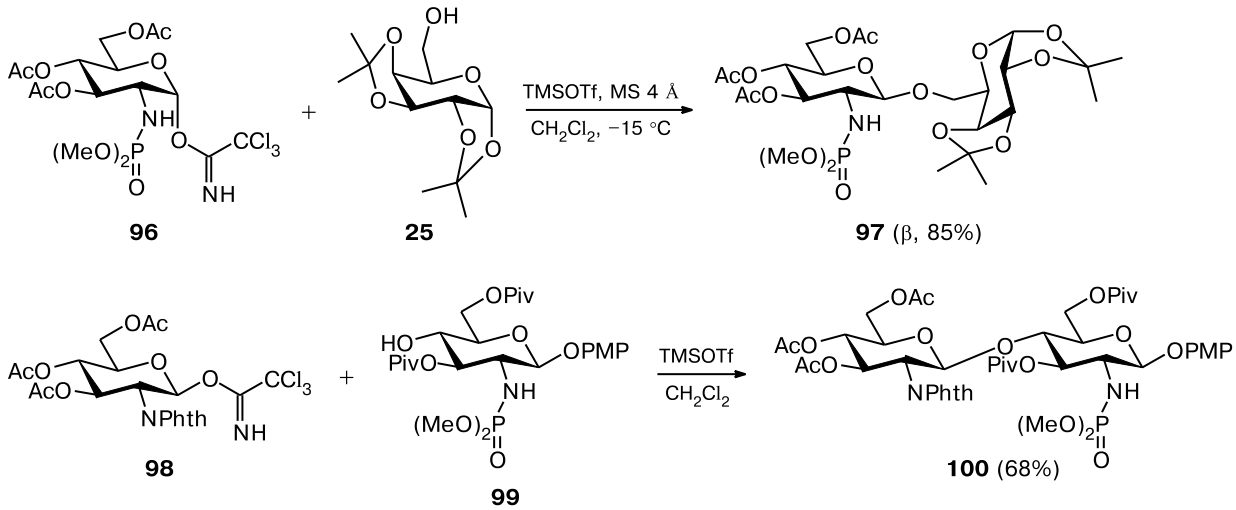
2.1. N-Dimethoxyphosphoryl protecting group

N-Dimethoxyphosphoryl protecting group was used in the synthesis of different β-glucosaminides (Scheme 31),[50,51] *e.g.*, in the synthesis of **97** (as a participating group on glycosyl donor, reaction **96** + **25**) and **100** (as a protecting group on glycosyl acceptor, reaction **98** + **99**). This protecting group is stable under ordinary basic and acidic conditions and can be either removed by hydrolysis under harsh conditions or transformed directly to acetyl group. This group did not show particular advantages as compared with the conventional protecting groups. For introduction of this protecting group, the following conditions were employed: 1) $(MeO)_2POCl$, DMAP, Et_3N, CH_2Cl_2, 0 °C; 2) NH_3, THF/MeOH, 0 °C; removal was achieved by the use of NaOH or hydrazine, or AcCl in the presence of DMAP in pyridine under reflux.

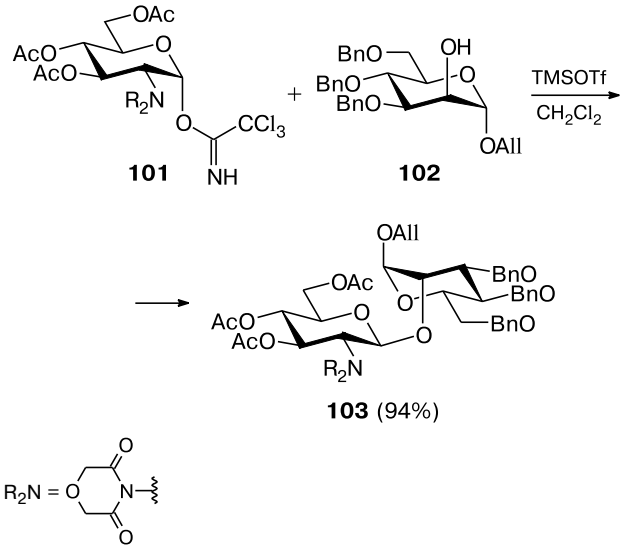
2.2. Diglycolyl protecting group

Diglycolyl protecting group shows pronounced anchimeric assistance providing high yields of target products of glycosylation.[52] An example is the reaction of the protected activated glucosamine **101** with mannose derivative **102** to afford disaccharide **103** in high yield (Scheme 32). The protecting group was introduced by treatment with diglycolic anhydride, pyridine, and Ac_2O at ~20 °C and cleaved using KOH in refluxing EtOH.

Scheme 31



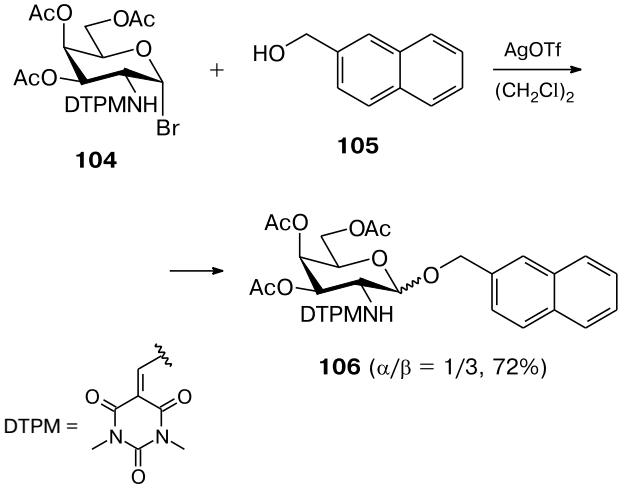
Scheme 32



2.3. [1,3-Dimethyl-2,4,6-(1H,3H,5H)-trioxypyrimidin-5-ylidene]methyl protecting group

[1,3-Dimethyl-2,4,6-(1*H*,3*H*,5*H*)-trioxypyrimidin-5-ylidene]methyl (DTPM) group was developed as an amine participating protecting group for aminosugars.[53] The advantage of the DTPM group is the relatively mild protection/deprotection conditions; however, it provides low stereoselectivity in the reactions of the protected carbohydrates with model alcohols. For example, galactosyl bromide **104** reacted with naphthylmethyl alcohol **105** to give a mixture of α- and β-**106** in high yield but with anomeric ratio of only 1 : 3 (Scheme 33). Conditions for protection are $DTPMNMe_2$, MeOH, ~20 °C, for removal are NH_3, H_2O, 100 °C.

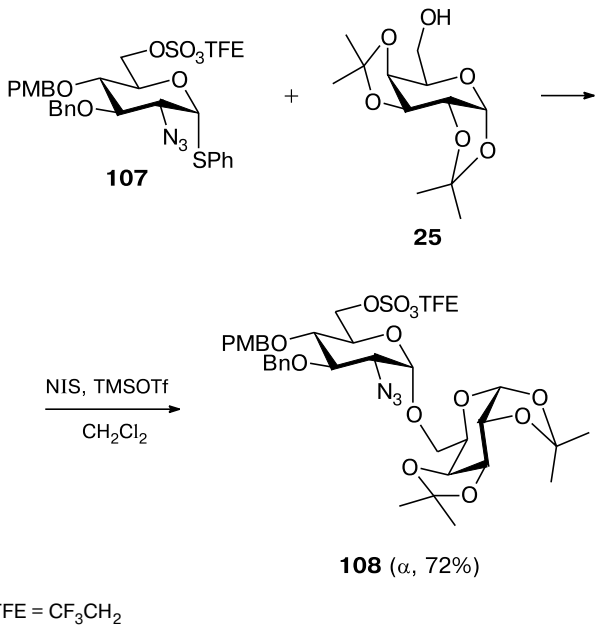
Scheme 33



3. *O*-Sulfo protecting groups

Protection of the *O*-sulfo groups is important in the synthesis of glycosaminoglycans. The *O*-sulfo moieties of carbohydrates are routinely protected with 2,2,2-trifluoroethyl (TFE) group.[54] Thus, glycosylation of compound **25** with glycosyl donor **107** proceeded under mild conditions to give exclusively α-linked disaccharide **108** (Scheme 34). The group is stable to organic acids and catalytic hydrogenation.[55] The TFE ester was formed by treatment of the sulfo derivative with 2,2,2-trifluorodiazoethane in MeCN in the presence of citric acid.[55] Recently, an alternative protocol for the preparation of TFE-protected sulfates was reported. The procedure allows direct introduction of the TFE-protected sulfo group onto the hydroxy group of carbohydrate. The transformation was achieved using sulfuryl imidazolium salts readily available from trifluoroethyl sulfonyl chloride and imidazoles.[56] The TFE protecting groups can be removed using either $KOBu^t$ in Bu^tOH[54,55] or NaN_3 in DMF at 70 °C.[56]

Scheme 34



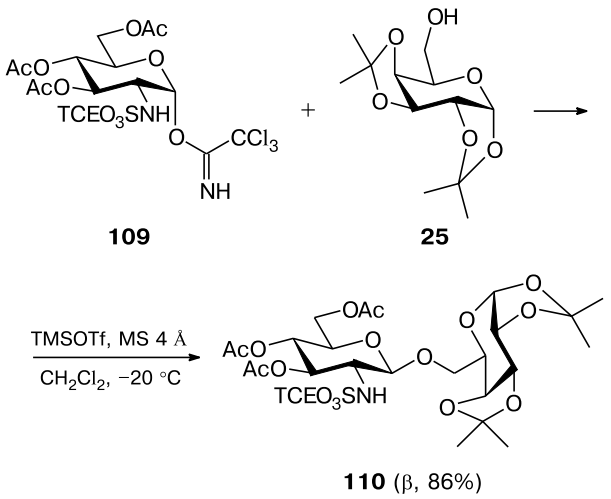
4. *N*-Sulfo protecting groups

2,2,2-Trichloroethyl (TCE) group was found to be a valuable protecting group for *N*-sulfo groups. 2,2,2-Trichloroethoxysulfonyl group is stable to potassium carbonate in methanol and can be introduced under conditions used for sulfamide synthesis ($CCl_3CH_2OSO_2Cl$, Et_3N, DMAP, DMF, 0 °C). It is readily removable with zinc in methanol in the presence of ammonium chloride at

~20 °C affording glucosamine *N*-sulfate sodium salts in ~90% yields.[57]

Chen and Yu reported[57] several examples of the reactions of the protected glucosamine **109** with different glycosyl acceptors, *e.g.*, **25**. In all cases, the only glycosylation products were β-glucosides in 76—92% yields (Scheme 35).

Scheme 35



110 (β, 86%)

TCE = CCl_3CH_2

Conclusion

The protecting groups play a very important role in chemical synthesis of carbohydrates. First of all, they dramatically affect stereoselectivity of glycosylation. New protecting groups with improved features allow development of novel glycosylation protocols that cannot be implemented with current protecting group strategy.

Among protecting groups described in the present review, conformation-constraining groups form an outstanding family of the protecting groups. Such groups as Bu^t_2Si and chiral auxiliaries developed by Boons and co-workers[28,29] representing the most successful recent findings serve for realization of the hardest tasks of oligosaccharide synthesis, selective construction of 1,2-*cis* glycoside linkage. We also like to emphasize the extension in the family of 1,2-*trans* directing participating-type protecting groups now including α-picolyl, α-picoloyl, and dialkyl oxyphosphoryl groups differing from common acyl protecting groups by different nucleophilic properties and protection/deprotection conditions. Among acyl protecting groups, 4-nitrophenylacetyl and sulfonylcarbamoyl groups should be specially noted, since being simple protecting groups they form good orthogonal systems with a wide variety of the conventional protecting groups.

It should be noted that the most of the described in the present review protecting groups are applied not only for the model reactions but also in the practical synthesis. However, now only some of these protecting groups, *e.g.*, α-picoloyl and Bu^t_2Si groups, have found applications in the syntheses of both their developers and other researches.

The lack of attention to the protection of *O*- and *N*-sulfate derivatives of glycosyl donors and acceptors also should be underlined. To date, the *O*- and *N*-sulfo protecting groups are in great demand in glycobiology due to growing interest in glycosaminoglycans and glycoconjugates. Development of efficient protecting strategy for these functions is likely to be a major challenge faced by synthetic carbohydrate chemists for the coming decades.

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