3.4 *O*-Glycosyl Donors

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Abstract

O-Glycosyl donors, despite being one of the last successful donors to appear, have developed themselves into a burgeoning class of glycosyl donors. They can be classified in two main types: *O*-alkyl and *O*-aryl (or hetaryl) glycosyl donors. They share, however, many characteristics, they can be (1) synthesized from aldoses, either by modified Fisher glycosidation (*O*-alkyl) or by nucleophilic aromatic substitution (*O*-aryl or *O*-hetaryl), (2) stable to diverse chemical manipulations, (3) directly used for saccharide coupling, and (4) chemoselectively activated. Among these, *n*-pentenyl glycosides stand apart. They were the first *O*-alkyl glycosyl donors to be described and have paved the way to many conceptual developments in oligosaccharide synthesis. The development of the chemoselectivity-based "armed-disarmed" approach for saccharide coupling, including its stereoelectronic or torsional variants, now extended to other kinds of glycosyl donors, was first recognized in *n*-pentenyl glycosides. The chemical manipulation of the anomeric substituent in the glycosyl donor to induce reactivity differences between related species (sidetracking) was also introduced in *n*-pentenyl glycosides. An evolution of this concept, the "latent-active" strategy for glycosyl couplings, first described in thioglycosyl donors (vide infra), has been elegantly applied to *O*-glycosyl donors. Thus, allyl and vinyl glycosides, 2-(benzyloxycarbonyl)benzyl (BCB) glycosides and 2′-carboxybenzyl (CB) glycosides are useful "latent-active" glycosyl pairs. Finally, unprotect-

ed 3-methoxy-2-pyridyl (MOP) glycosides have been used in glycosylation processes with moderate success.

Keywords

2′-carboxybenzyl (CB) glycosides; 3-methoxy-2-pyridyl glycosides; Armed–disarmed; DISAL glycosyl donors; Halonium ion transfer; Latent-active glycosylation; *n*-Pentenyl glycosides; *O*-heteroaryl glycosyl donors; Oligosaccharide synthesis; Vinyl glycosides

Abbreviations

BCB	2-(benzyloxycarbonyl)benzyl
CAN	cerium ammonium nitrate
CB	2′-carboxybenzyl
DAST	(diethylamino)-sulfur trifluoride
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DISAL	a dinitrosalicylic acid glycoside derivative
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DTBMP	di-*tert*-butylmethylpyridine
IDCP	iodonium di-*sym*-collidine perchlorate
MOP	3-methoxy-2-pyridyl
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMP	1-methylpyrrolidin-2-one
NPG	*n*-pentenyl glycosides
NPhth	*N*-phthaloyl
NPOE	*n*-pentenyl orthoester
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
TBAF	tetra-*n*-butylammonium bromide
TBAI	tetra-*n*-butylammonium iodide
TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
TESOTf	triethylsilyl trifluoromethanesulfonate
Tf_2O	trifluoromethanesulfonic anhydride
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TPSOTf	*tert*-butyldiphenylsilyl trifluoromethane sulfonate
Troc	*N*-trichloroethoxycarbonyl
TTCP	*N*-tetrachlorophthaloyl

1 Introduction

From the early days, chemists involved in chemical glycosylation have been trying to develop successful glycosyl donors. In general, the characteristics of a successful glycosyl donor might

include: (*a*) preparation under mild reaction conditions, (*b*) selective activation by reagents that would not interfere with the protecting and functional groups present in the donor and the glycosyl acceptor, and (*c*) good reactivity [1,2,3,4]. More recently, the advent of convergent block synthesis to tackle complex oligosaccharide preparations have also demanded that glycosyl donor building blocks (*d*) are sufficiently stable to be purified and stored for considerable periods of time, and (*e*) are resistant towards a wide range of reaction conditions [5,6,7,8,9]. According to this, *O*-glycosyl donors (the topic of this chapter), because of their remarkable "shelf-life" and stability (conditions *d*, *e*) will be attractive candidates for oligosaccharide block synthesis, provided that conditions *a*, *b*, and *c* are also met.

A chronology, displayed in ● *Fig. 1*, highlights the relatively recent arrival of *O*-glycosyl donors to the assortment of relevant glycosyl donors. In fact, the first *O*-alkyl glycosyl donor (*n*-pentenyl glycoside) [10], was introduced more than a century after the first glycosylation was described (synthesis of aryl glycosides from glycosyl chlorides) [11].

This late arrival is understandable on the basis of the outline in ● *Scheme 1a*, which makes it obvious that in situ transformation of one alkyl glycoside donor into a disaccharide (or into another alkyl glycoside) could be problematic. The acidic conditions normally used to cleave alkyl glycosides (**1**), generating oxocarbenium ion **2**, could tamper with the newly formed intersaccharidic linkage in **3**, notwithstanding the liberation of alkanol that might compete for glycosylation with the sought glycosyl acceptor, thus regenerating **1** (● *Scheme 1b*). The successful implementation of the strategy represented in ● *Scheme 1a* would imply that: (*a*) the alkanols have to be released under a non-nucleophilic form, and (*b*) the newly formed glycosidic linkage must be compatible with the promoter employed.

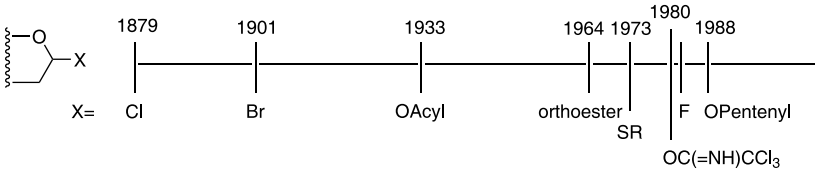
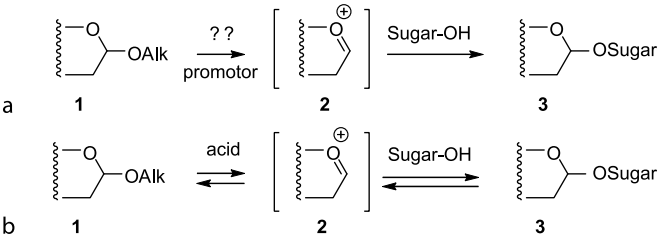


Figure 1
Chronology of selected glycosyl donors



Scheme 1
***O*-Alkyl-glycosyl donors in glycosylation**

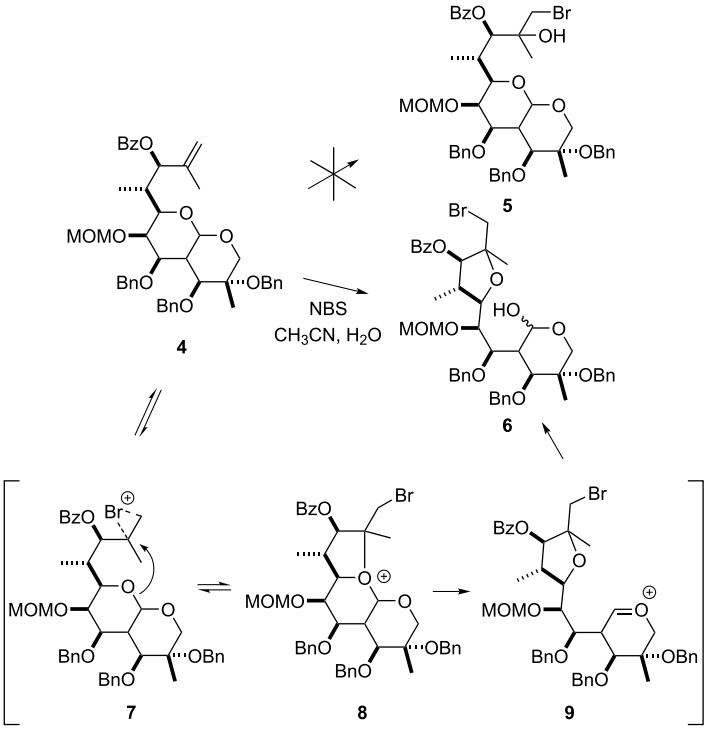
2 *n*-Pentenyl Glycosides

2.1 Introduction

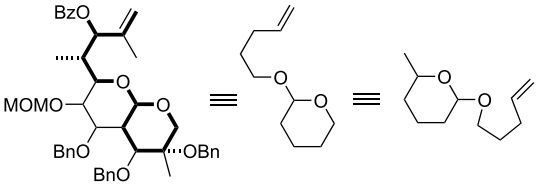
2.1.1 The Origin of *n*-Pentenyl Glycosides (NPGs)

The discovery of *n*-pentenyl glycosides (NPGs) [12], was derived from an observation made by Mootoo and Fraser-Reid in a completely unrelated project [13]. Attempted formation of bromohydrin **5** by reaction of **4** with NBS in 1% aqueous acetonitrile led, instead to bromomethyl tetrahydrofuran **6** (● *Scheme 2*) [14]. To rationalize this transformation (**4**→**6**), the authors invoked a 5-*exo*-cyclization [15] of the pyranosidic oxygen in **7** leading to cationic intermediate **8**, and thence to oxocarbenium ion **9**, that upon capture of H_2O led to hemiacetal **6**. The overall result of the process had been a, nonhydrolytic, electrophilic unravelling of the glycosidic-type bond in **4**.

The overlap between structures **4** and **10** permitted the authors to design structure **11**, as a candidate for testing electrophilic deprotection at the anomeric center of a pyranose (● *Scheme 3*). It has now become clear, 20 years after this observation, that the correlation shown in ● *Scheme 3* led to a breakthrough in glycoside synthesis.



Scheme 2
The origin of *n*-pentenyl glycosides



4 **10** **11**

Scheme 3
The design of *n*-pentenyl glycosides

2.1.2 Chemoselective Liberation of the Anomeric Group in NPGs

To test the validity of their assumption, Mootoo and Fraser-Reid prepared NPGs **12**–**18** and treated them with NBS in 1% aqueous acetonitrile [16]. Their results, summarized in ❯ *Table 1*, showed that differently substituted NPGs could be chemoselectively liberated at the anomeric center to yield hemiacetals **19**–**24**. Furthermore, benzylidene, silyl, p-methoxybenzyl (PMB), ethoxyethyl, and allyl protecting groups proved to be compatible with the conditions employed in the deprotection of the anomeric pent-4-enyl group. Diol **18**, however, furnished a complex reaction mixture probably related to competing glycosylation processes, vide infra.

2.2 NPGs as Glycosyl Donors

To test the potential of NPGs as glycosyl donors, Fraser-Reid et al. first examined the reaction of compound **12** with NBS in MeCN-MeOH [10]. The reaction took place in 3 h, at room temperature yielding methyl glucoside **25** in 85% yield as a 1:3 (α:β) anomeric mixture (❯ *Table 2*, entry i). The utilization of iodonium di-*sym*-collidine perchlorate (IDCP) [17] as a promoter resulted in a faster reaction (0.5 h), which maintained the previous anomeric mixture (❯ *Table 2*, entry ii). The use of a 4:1 mixture of Et_2O-CH_2Cl_2 as solvent, to favor α-glucoside formation while solubilizing IDCP, resulted in a 3:1 (α:β) anomeric mixture of **25** (❯ *Table 2*, entry iii). When CH_2Cl_2 was used as a solvent a 1.2:1 (α:β) anomeric mixture was obtained.

NPGs were next tested in the elaboration of disaccharides by glycosylation of monosaccharide acceptors. Gluco- (**12**), *manno*- (**26**), and 2-deoxy- (**27**) NPGs reacted with sterically demanding methyl glucoside **28**, to give disaccharides **29**–**31** (❯ *Table 3*). Gluco-derivatives gave the best α versus β solvent dependence, MeCN favoring β, and Et_2O favoring α (the same trend as noted for MeOH, ❯ *Table 2*). For the *manno*- and 2-deoxy donors **26** and **27**, no consistent pattern of solvent dependence was noticed. 2-Deoxy-donor **27**, gave appreciable α-selectivities with secondary acceptors (❯ *Table 3*, entries vii–ix). MeCN gave the lowest overall yield of disaccharide products (❯ *Table 3*, entries i, iv, vii). Reactions of 2-deoxy NPG **27** (❯ *Table 3*, entries vii–ix) were generally much faster than those of either **12** or **26**, an observation that parallels the observed trends in acid lability of the three donors (❯ *Table 3*, entries i–vi). With Et_2O as solvent, reactions with primary alcohol acceptors displayed more stereoselectivity than reactions with secondary hydroxyl acceptors.

Table 1
Oxidative hydrolysis of some NPGs with NBS in 1% aqueous acetonitrile

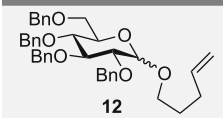
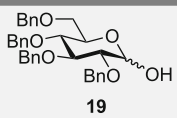
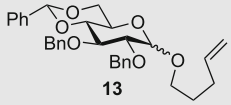
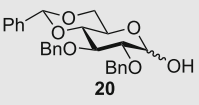
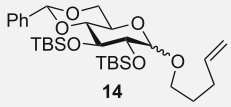
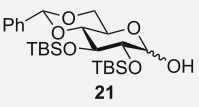
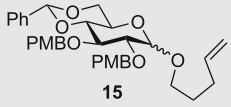
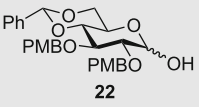
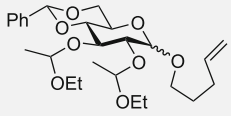
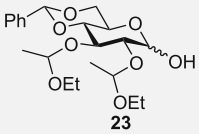
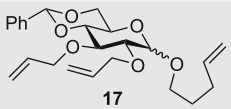
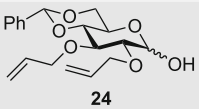
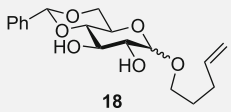
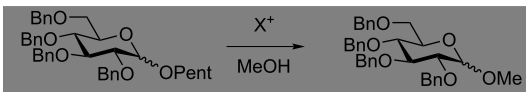
Substrate	Product	Yield (%)
 **12**	 **19**	85
 **13**	 **20**	70
 **14**	 **21**	90
 **15**	 **22**	68
 **16**	 **23**	63
 **17**	 **24**	72
 **18**	complex mixture	

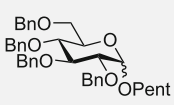
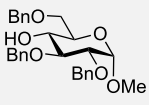
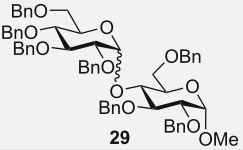
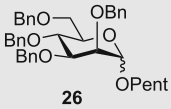
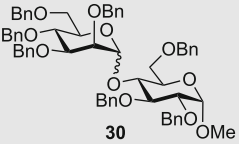
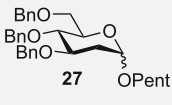
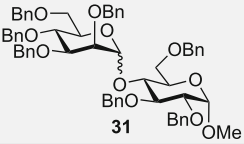
Table 2
Reaction of NPG 12 with methanol in the presence of halonium ions



12 **25**

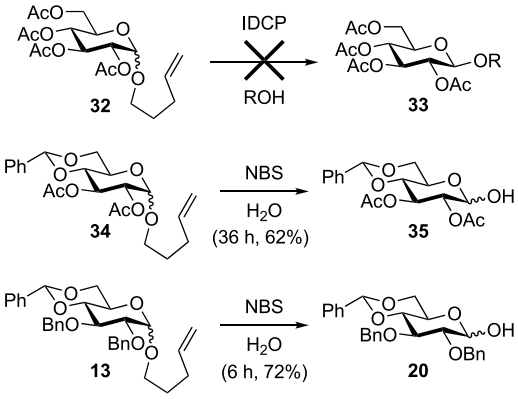
Entry	Promoter	Time (h)	Solvent	α:β	Yield (%)
I	NBS	3	MeCN	1:3	85
ii	$I(collidine)_2ClO_4$	0,5	MeCN	1:3	75
iii	$I(collidine)_2ClO_4$	0,5	CH_2Cl_2	1.2:1	85
iv	$I(collidine)_2ClO_4$	24	CH_2Cl_2-Et_2O	3:1	75

Table 3
Direct elaboration of NPGs into disaccharides on treatment with IDCP

Entry	NPG	Acceptor	Time (h)	Solvent α:β	Product	Yield (%)
i	 **12**	 **28**	1–2	MeCN 1:2	 **29**	20
ii	12	28	1–2	CH_2Cl_2 1.2:1	29	75
iii	12	28	16–24	Et_2O/CH_2Cl_2 3:1	29	95
iv	 **26**	28	2–5	MeCN 6:1	 **30**	36
v	26	28	2–5	CH_2Cl_2 9:1	30	76
vi	26	28	24	Et_2O/CH_2Cl_2 α only	30	92
vii	 **27**	28	0,5	MeCN 7:3	 **31**	51
viii	27	28	0,5	CH_2Cl_2 4:1	31	57
ix	27	28	4–6	Et_2O/CH_2Cl_2 4:1	31	61

2.2.1 Acyl-Substituted NPG Donors

The results in *Table 3* made it clear that the use of different solvents to induce (α versus β) stereoselectivity in glycosyl couplings of NPGs was only moderately successful, generally leading to anomeric mixtures [10]. As it has been established, good stereocontrol in the formation of 1,2-*trans* glycosidic linkages can be conveniently obtained with the assistance of a neighboring participating group, generally an acyl moiety [18]. In this context, Fraser-Reid and co-workers examined the glycosylation of NPG **32** for the preparation of 1,2-*trans* glycoside **33** (*Scheme 4*). Unfortunately, the reaction did not lead to glycoside **33**, but to compounds resulting from addition across the terminal double bond of the pent-4-enyl moiety. Along this line, the authors had previously noticed that hydrolysis of acyl derivative **34** was considerably slower than that of **13** [16]. These results paralleled previous observations by Paulsen [1] on the deactivating effect of esters versus ether protecting groups upon differently substituted glycosyl halides. These observations, however, according to the state-of-the-art in glycosylation in 1988, only meant that acyl-NPGs would not be useful as glycosyl donors.



[a] The reaction was stopped at 50% conversion, the yield is based on recovered **34**.

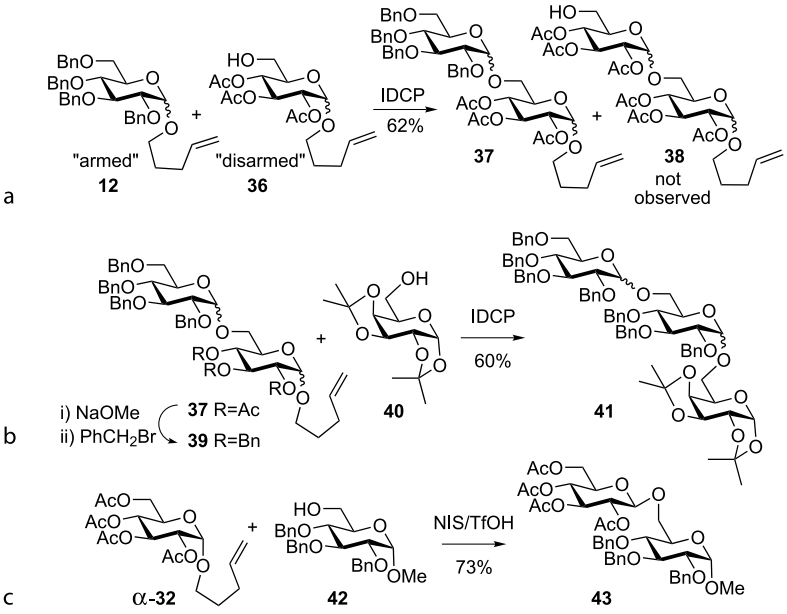
Scheme 4
Reaction of acylated NPGs with halonium ions

2.3 *Armed–Disarmed* Strategy for Glycosyl Coupling

Fraser-Reid and co-workers, however, anticipated that the difference in reactivity found in differently substituted NPGs could be applied in a chemoselective protocol for glycosyl coupling [19]. The activated and the deactivated NPGs were termed "armed sugar" and "disarmed sugar", respectively. Thus, as illustrated in *Scheme 5a*, coupling of **12** and **36**, mediated by IDCP afforded a 62% yield of disaccharide **37** [19]. Therefore, the acyl groups of **36** indeed "disarmed" the NPG, thereby ensuring that **12** served as the only glycosyl donor. No evidence for a hexaacetyl disaccharide **38**, arising from self-condensation of **12** was found, nor of further reaction of (disarmed) disaccharide **37** with the acceptor **36**.

The chemoselective coupling, however, is not the only quality of the armed-disarmed strategy for glycosyl assembly. An additional aspect of this strategy is the ability to "rearm" disarmed glycosyl donors for further glycosyl coupling. Thus, "disarmed" **37** was converted to "armed" disaccharide **39**, (by replacing the acetyl groups with benzyl substituents) which could then glycosylate galacto- derivative **40**, to yield trisaccharide **41**, in 60% yield (*Scheme 5b*). An alternative way of "rearming" NPGs by increasing the potency of the promoter used for glycosylation was also introduced by the same authors [20]. According to that, an iodonium ion generated in situ from NIS and TfOH was able to promote the coupling of "disarmed" pent-4-enyl glycosides (e. g. α-**32**, *Scheme 5c*) with acceptors to give 1,2-*trans* disaccharides, e. g. **43**, via neighboring group participation [18].

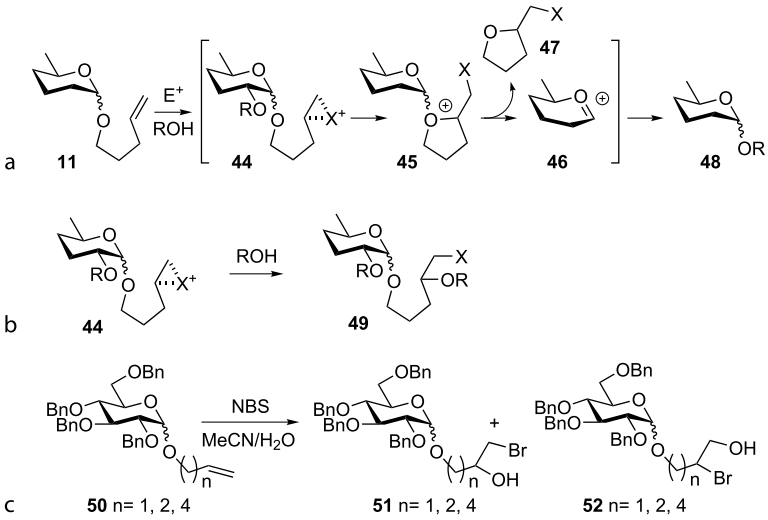
The armed-disarmed concept takes advantage of reactivity differences induced by the ring substituents on the anomeric leaving group and, although originally described for NPG donors, it has been extended to various types of glycosyl donors. These include thioglycosides [21,22], glycals [23], glycosyl fluorides [24], selenoglycosides [25], glycosyl phosphoroamidates [26,27], glycosyl thioformimidates [28,29,30], and *S*-benzoxazolyl glycosides [31,32,33].



Scheme 5
Armed-disarmed strategy for chemoselective glycosyl couplings

2.3.1 Mechanistic Aspects of the Oxidative Hydrolysis of NPGs

The currently accepted mechanism for the reaction of NPGs (e. g. **11**) with halonium ions is outlined in *Scheme 6a*. The oxygen in the acetal function participates in a favored 5-*exo-tet* ring opening of an intermediate cyclic halonium ion, **44** [15]. The ensuing furanilium ion **45**, evolves by splitting off a non-nucleophilic halotetrahydrofuran **47** [34], thus leading to oxocarbenium ion **46**, that can trap the nucleophile (ROH). The overall result is the cleavage of the acetal moiety with the formation of a new glycosyl derivative, **48**. Madsen and Fraser-Reid have demonstrated that even when the system NIS/TESOTf [20] is used to promote the cleavage of NPGs, the reaction is not acid catalyzed but still halonium ion catalyzed [35].
In this connection, the question of why the reaction of an NPG in the presence of water leads to an aldose **48** (R=H), rather than to a halohydrin **49** (R=H) was raised (*Scheme 6b*). In fact, the successful cleavage observed for NPGs rests on two issues: (*a*) the concentration of nucleophile (water in the case of hydrolysis), and (*b*) the rate of the 5-*exo-tet* cyclization, **44**→**45**. Pertinent to question *a* the intramolecular reaction **44**→**45**, is preferred to the bimolecular reaction with water leading to a halohydrin, **44**→**49**, under the conditions used by the authors. An increase in the concentration of water would enhance the rate of the bimolecular reaction, without affecting the intramolecular process. Indeed added water led to the formation of bromohydrin **49** (R=H) [36]. Related to the second issue, Rodebaugh and Fraser-Reid examined the same reaction with allyl, butenyl, and hexenyl glycosides **50** ($n = 1, 2, 4$), differing on the rate of cyclization compared to NPGs [37,38]. They found that, unlike NPGs, they all gave rise to isomeric halohydrins **51** and **52**, upon treatment with NBS in aqueous MeCN (*Scheme 6c*).



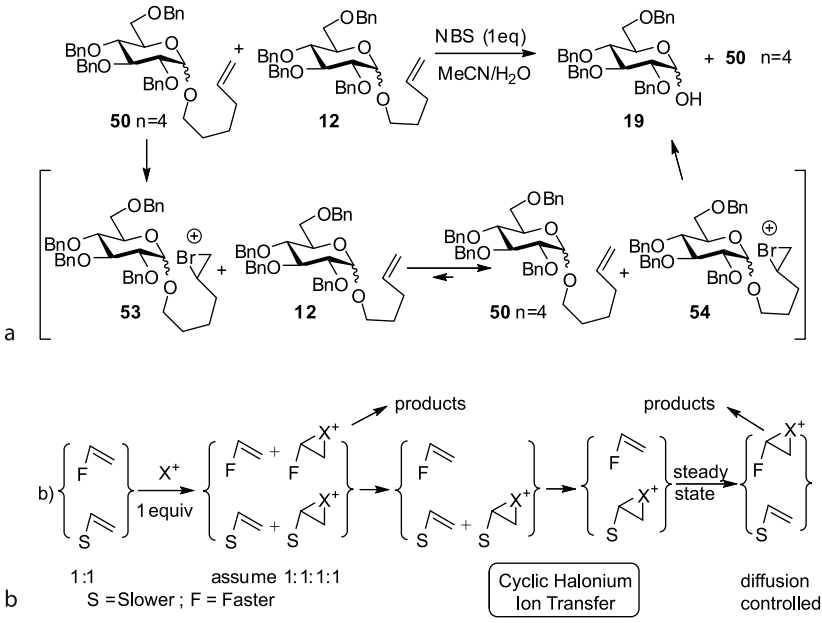
Scheme 6
Oxidative cleavage of NPGs

2.3.2 Evidence for Intermolecular Halonium-Ion Transfer

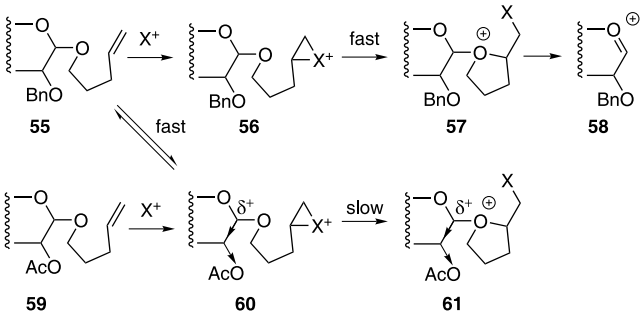
In a related experiment, hexenyl glycoside **50** ($n = 4$), that has been found to react 2.3-times slower than NPG **12** [37,38], was made to compete with **12** for 1 equiv. of NBS. The hexenyl glycoside **50** ($n = 4$) was recovered unchanged together with hemiacetal **19**, arising from the hydrolysis of **12** (*Scheme 7a*). Rodebaugh and Fraser-Reid proved that this phenomenon was due to a diffusion-controlled intermolecular halonium-ion transfer (a similar process has been previously noted by Brown and co-workers for "sterically encumbered olefins" [39]). Accordingly, bromonium species **53**, obtained by irreversible reaction of **50** with NBS [37,38], would undergo a fast bromonium ion transfer to NPG **12** leading to halonium **54** (i. e. **44**, *Scheme 6a*) which will undergo a fast transformation to **19**. The general process, a classic example of Le Chatelier's principle, is represented in *Scheme 7b*. When two alkenes are made to compete for one equivalent of halonium ion X^+, a steady-state regime can be envisaged whereby the faster (F) (e. g. NPG **12**) reacts completely, and the slower (S) (e. g. **50**, $n = 4$) is recovered completely.

2.3.3 Intermolecular Halonium-Ion Transfer: A Key Factor in the Implementation of the Armed-Disarmed Protocol

This intermolecular halonium ion transfer had indeed been postulated earlier as the key factor to account for the absence of self-coupling product **38**, when armed and disarmed NPGs, **12** and **36** respectively, were made to compete for one equivalent of NBS (*Scheme 5a*). The observed 6-fold difference in the hydrolysis rates of **36** and **12** should have resulted in the presence of **38**, in at least 10% [40]. Irreversible reaction of NPGs **55** and **59** with NBS leads to halonium ions **56** and **60**, respectively (*Scheme 8*). The transfer of halonium (e. g. **60**→**55**) is reversible and rapid compared with the subsequent steps leading to glycoside formation



Scheme 7
Intermolecular halonium-ion transfer



Scheme 8
Halonium ion transfer: a key factor in armed-disarmed couplings

(**56**→**57**→**58**). By corollary, the inherent reactivity of the glycosyl donors is thus revealed in the final product distribution. If the acceptor functionality is located in the less reactive component, selective glycosylations take place leading to a specific disaccharide.

2.3.4 Torsional Disarming of NPGs

Fraser-Reid and co-workers found that widely used cyclic acetals also affected anomeric reactivity [41]. They showed that these reactivity differences could be applied to an armed-

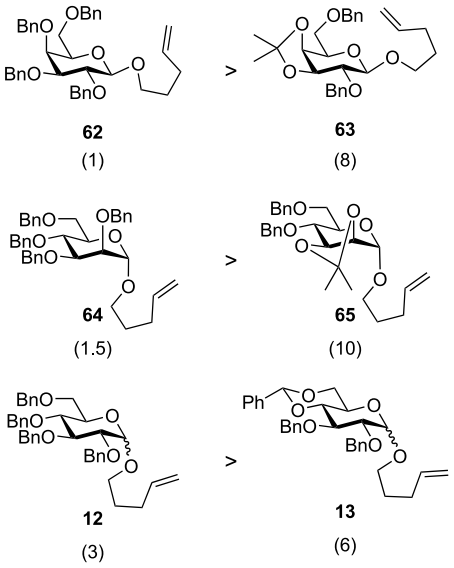
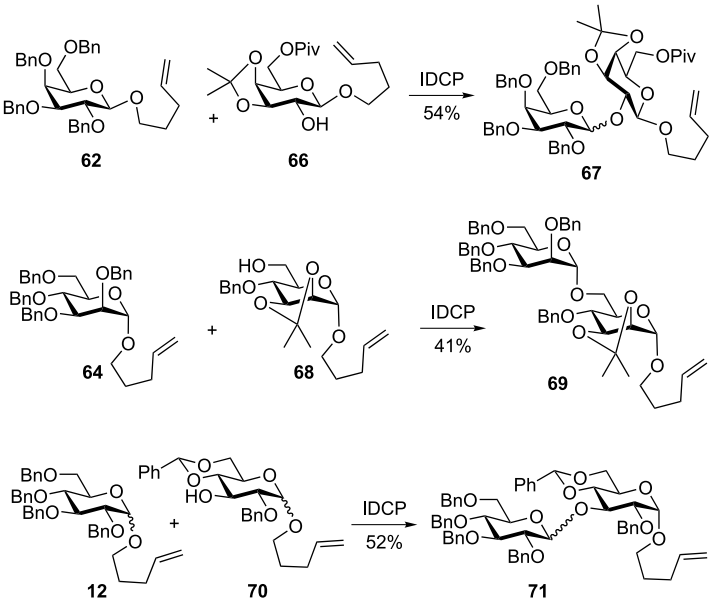


Figure 2
Relative rates of oxidative hydrolysis for acetal-protected NPGs

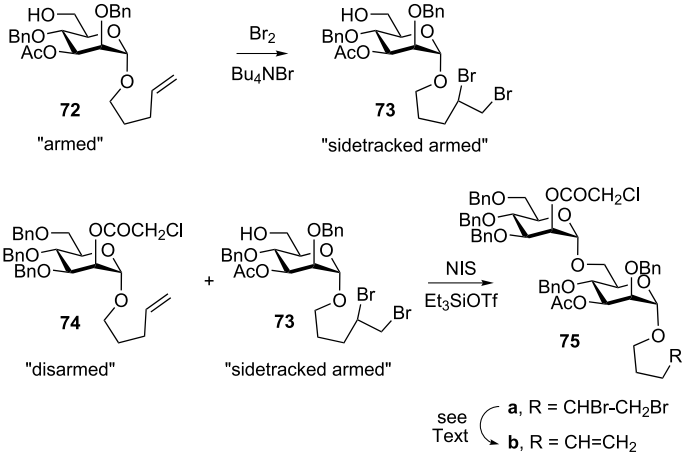
disarmed protocol based on torsional, rather that electronic, effects. The measured experimental relative rates of oxidative hydrolysis for some pairs of *galacto*- (**62**, **63**), *manno*- (**64**, **65**), and *gluco*- (**12**, **13**), acetalated and nonacetalated NPGs are displayed in *Fig. 2*. From these data, the authors were able to design the successful armed-disarmed couplings shown in *Scheme 9*. These reactivity differences were ascribed to the fact that *trans*-fused protection restricts the molecule from ring flexibility, thereby making it increasingly difficult to reach a half-chair transition state from a chair ground state.

2.3.5 Sidetracking of NPGs: A Reversal for the Armed-Disarmed Strategy

In the armed-disarmed protocol, the reactivity differences induced by the ring substituents upon the anomeric center were exploited for chemoselective couplings. In these protocols, the more reactive "armed" NPG always glycosylates the "disarmed" NPG. On the basis of chemical manipulation of the pent-4-enyl moiety, rather than the ring substituents, Fraser-Reid and co-workers showed that "disarmed" NPGs could be used to glycosylate "armed" NPGs [40]. Treatment of NPG **72** with bromine and tetra-*n*-butylammonium bromide (TBAF), in a bimolecular reaction (e. g. **44**→**48**, *Scheme 6b*) yielded dibromoderivative (*Scheme 10*) **73**. Glycosylation of the latter with "disarmed" **74**, under the agency of NIS/TESOTf, yielded disaccharide **75a**, which could be transformed to the pentenyl disaccharide **75b**. Several methods proved to be successful for the restoration of the double bond from the dibromoderivative including, (a) Zn/TBAI in sonicating EtOH, (b) NaI in methyl ethyl ketone, and (c) SmI_2 in THF [42]. The choice of the reagent will vary with the



Scheme 9
Armed-disarmed couplings based on torsional effects



Scheme 10
Sidetracking of NPGs in saccharide synthesis

reactivity of the substrate, as well as the protecting groups thereon. More recently, a milder brominating system, the combination of $CuBr_2$ and LiBr in MeCN:THF (3:1), has been used to brominate *n*-pentenyl glycosides containing *O*-benzyl, *O*-*p*-methoxybenzyl, *N*-phthaloyl, and *N*-tetrachlorophthaloyl protecting groups [43].

2.4 Conversion of NPGs to Other Glycosyl Donors

NPGs have been converted into different glycosyl donors.

2.4.1 Conversion to Glycosyl Bromides

Konradsson and Fraser-Reid [44] reported the conversion of NPGs into glycosyl bromides, e. g. **76**, by treatment of the corresponding pentenyl glycoside with a dilute dichloromethane solution of bromine, conditions that favor unimolecular reaction. The reaction was shown to be compatible with acetals, benzyl, silyl, and allyl protecting groups in the NPG (● *Scheme 11a*).

2.4.2 Conversion to Glycosyl Phosphates

Pale and Whitesides [45] described the synthesis of glycosyl phosphates **77** [46,47], by reaction of dibenzyl phosphate with NPG **12**, with the use of either IDCP or NBS as promoters. The authors noted the influence of the solvent (MeCN, Et_2O, CH_2Cl_2) and the promoter in the α/β selectivity of the glycosyl phosphates formed (● *Scheme 11b*).

2.4.3 Conversion to Glycosyl Fluorides

Clausen and Madsen [48] reported the transformation of NPG **78** into glycosyl fluoride **79** by treatment with NBS and (diethylamino)-sulfur trifluoride (DAST) (● *Scheme 11c*).
López et al. [49] described the preparation of glycosyl fluorides **80**, by reaction of NPGs with bis(pyridinium) iodonium (I) tetrafluoroborate (IPy_2BF_4) in the presence of tetrafluoroboric acid (● *Scheme 11d*). The process was compatible with the presence of silyl and benzyl groups in the NPG.

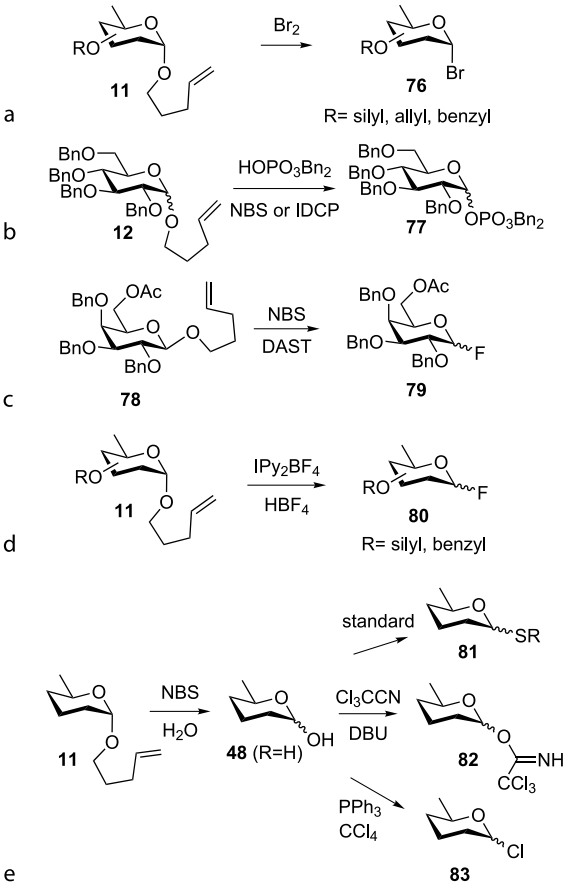
2.4.4 Chemoselective Liberation Followed by Anomeric Activation

The ability to chemoselectively deprotect pent-4-enyl glycosides opens an avenue for a two-step transformation of NPGs into different glycosyl donors. In this context, NPGs can be transformed [50] into thioglycosides **81** [51,52,53], glycosyl trichloroacetimidates **82** [54], and glycosyl chlorides **83** [55] (● *Scheme 11e*).

2.5 NPGs in the Stereocontrolled Assembly of α- and β- Glycoproteins

2.5.1 Pyranosylacetonitrilium Ions from NPGs

Ratcliffe and Fraser-Reid found that acetonitrile was able to trap glycosyl oxocarbenium ions (e. g. **46**), arising from NPGs, to give acetonitrilium ions, e. g. **84** (● *Scheme 12a*) [56]. The latter reacted with water to produce intermediate **85** that evolves to α-amide **86**, in a Ritter-type reaction [57] (● *Scheme 12a*).
This transformation was significant from a mechanistic standpoint. The formation of the α-acetonitrilium ion was not expected on the basis of the reverse anomeric effect (originally defined as the tendency of positively charged substituents at C-1 of a pyranose ring to adopt the equatorial orientation [58]). The authors, however, unambiguously established the α-orientation of

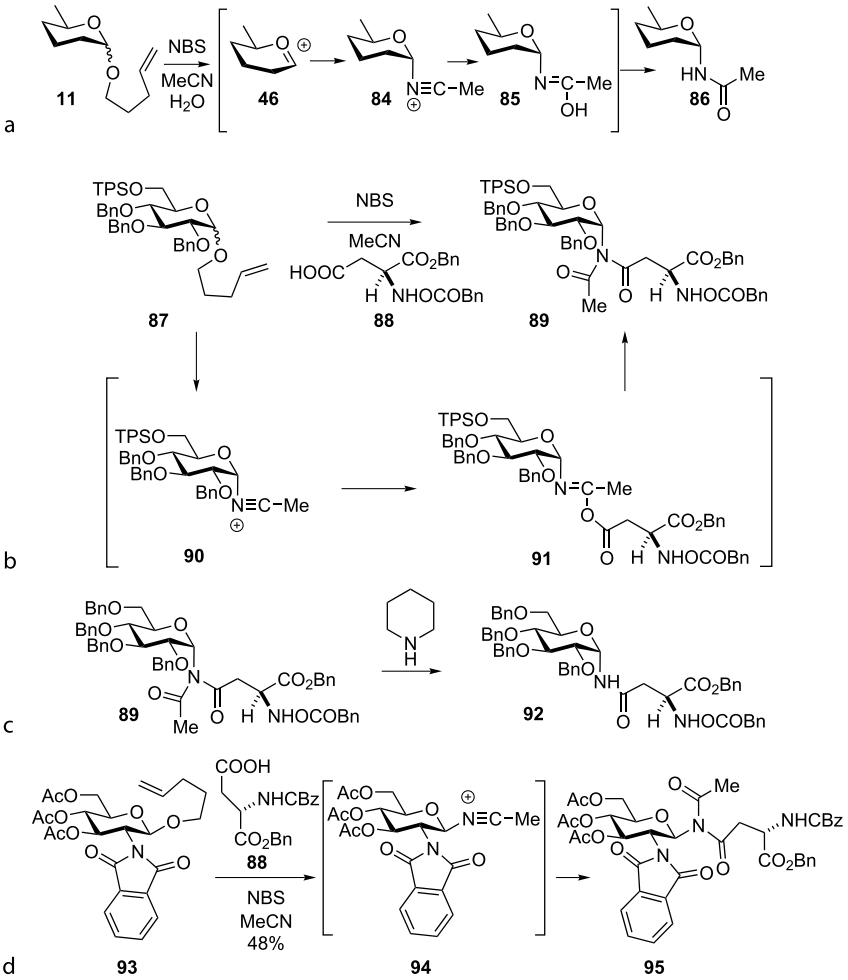


Scheme 11
Conversion of NPGs into different glycosyl donors

the amide and explained this result assuming the formation of the kinetically favored α-D-glucopyranosylacetonitrilium ion, **84** [59].

2.5.2 Synthesis of *N*-α-Linked Glycoproteins from Pyranosylacetonitrilium Ions

The synthetic value of the above-mentioned transformation was considerably enhanced when a carboxylic acid, rather than water, was used to trap the pyranosylacetonitrilium ion (*Scheme 12b*) [59]. Reaction of **87** with aspartic acid derivative **88**, in dry acetonitrile containing NBS, led to α-imide **89** in 61% yield [60,61]. The acetonitrilium ion **90** was trapped by carboxylic acid **88**, to give an imidic anhydride **91**, which rearranged in situ to give the *N*,*N*-diacyl derivative **89**. The route to 2-acetamido-1-*N*-(L-aspart-4-oyl)-2-deoxy-β-D-glycopyranosyl-amine **92**, was completed by selective *N*-deacetylation of **89** with piperidine (*Scheme 12c*) [59].



Scheme 12
Reactions of pyranosylacetonitrilium ions arising from NPGs

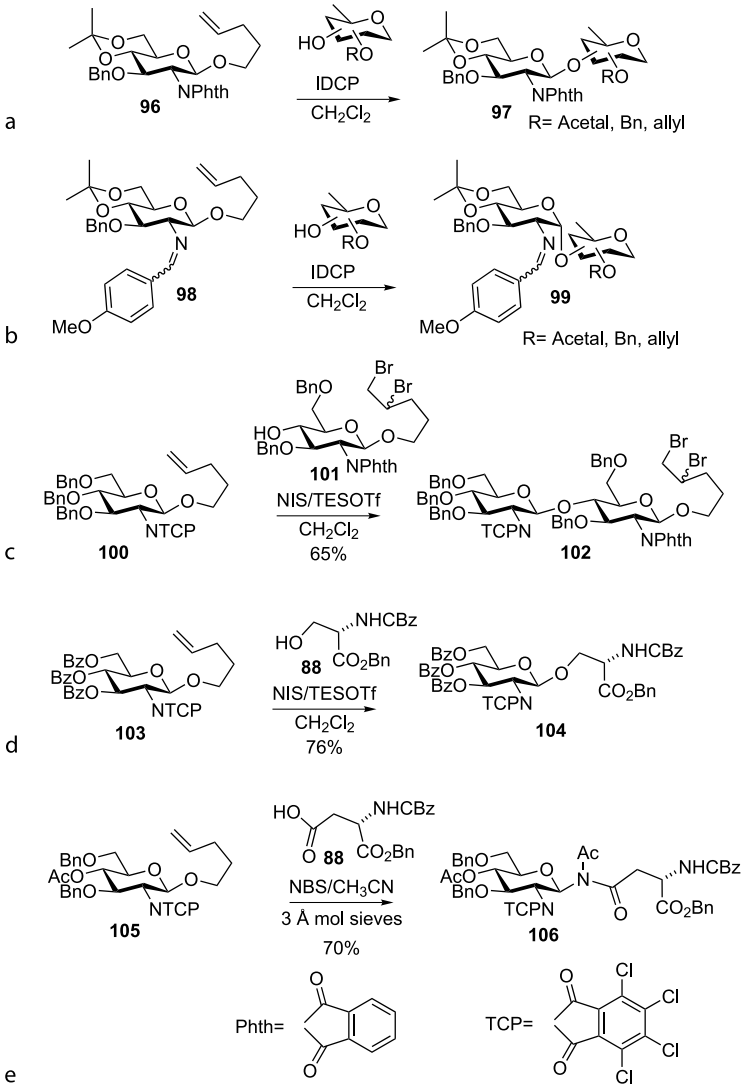
2.5.3 Synthesis of *N*-β-Linked Glycoproteins from Pyranosylacetonitrilium Ions

More interestingly, the presence of a neighboring participating group at C2 induces the formation of β-nitrilium ion intermediates, e. g. **94** (*Scheme 12d*), thus paving the way to β-linked glycoproteins [62]. Accordingly, phthalimido NPG **93**, reacted with aspartic acid derivative **88**, in acetonitrile using NBS as promoter, via the β-nitrilium intermediate **94**, to give the β-asparagine-linked product **95** in 48% yield.

More recently, this method has been elaborated in a three-component-reaction (NPG, acetonitrile, carboxylic acid) route to *N*-glycosylamines [63].

2.6 *n*-Pentenyl 2-Amino-2-Deoxy Glycoside Derivatives as Glycosyl Donors

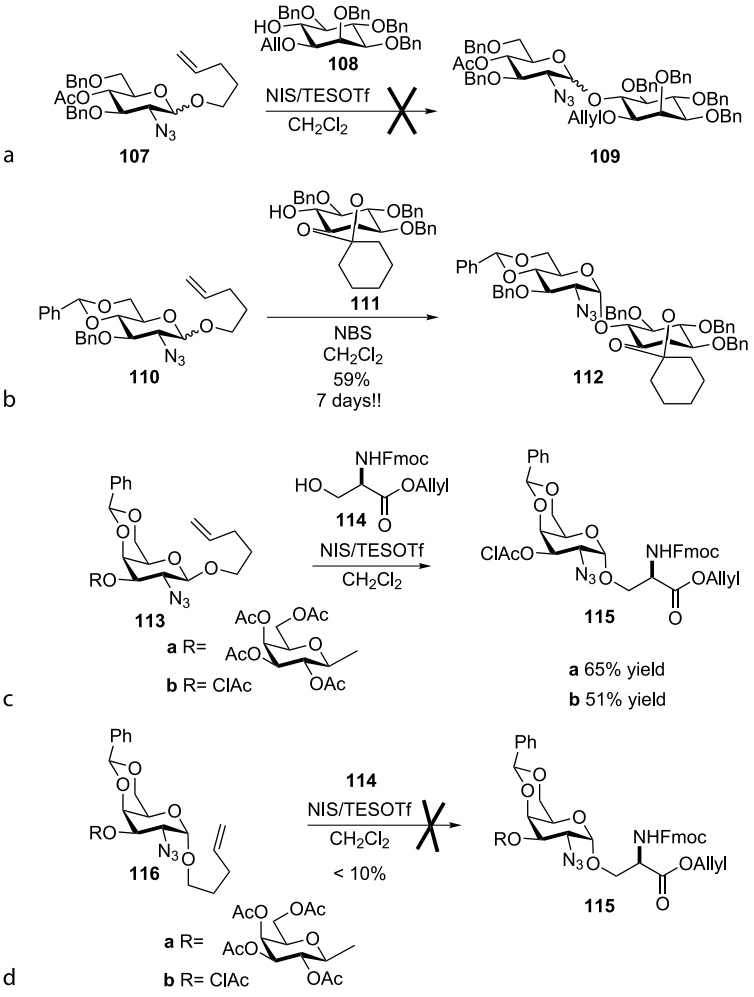
Several pent-4-enyl 2-amino-2-deoxy glycoside derivatives were evaluated as glycosyl donors for the synthesis of 2-amino-2-deoxy oligosaccharides [64]. 2-Deoxy-2-phthalimido **96**, and 2-anisylimino-2-deoxy-D-glucopyranosides **98**, underwent IDCP-induced coupling with



Scheme 13
Glycoside formation from pent-4-enyl 2-amino-2-deoxy glycosides

a variety of sugar alcohols to give β and α disaccharides **97** and **99**, respectively, in moderate to good yields (● *Scheme 13a,b*) [65,66]. 2-Deoxy-2-*N*-tetrachlorophthaloyl NPGs, e. g. **100**, **103**, [67,68,69] are useful donors for the stereocontrolled access to 1,2-*trans* glycosides as exemplified in ● *Scheme 13c,d*. Good yields of disaccharide **102**, and aminoacid **104** were obtained by the use of NIS/TESOTf as promoter. β-*N*-Linked glycopeptide **106** was prepared by treatment of **105** with acid **88** in dry MeCN containing NBS (● *Scheme 13e*).

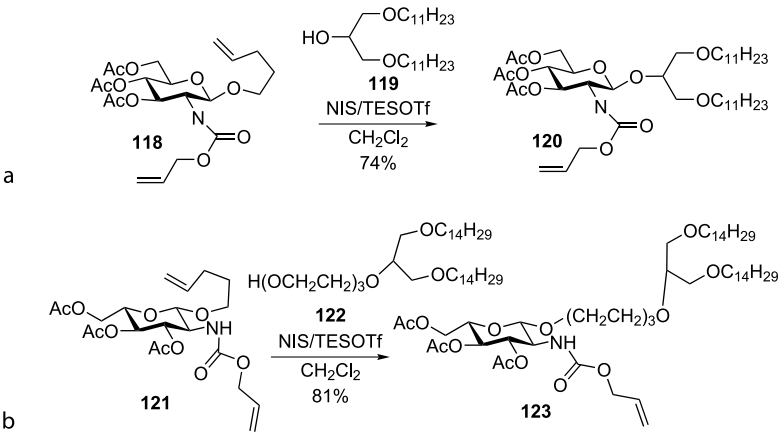
Controversial results have been reported when 2-deoxy-2-azido NPGs were used as glycosyl donors (● *Scheme 14*). Fraser-Reid and co-workers reported that **107** failed to give pseudo-disaccharide **109** upon reaction with acceptor **108** under the agency of NIS/TESOTf



Scheme 14
Glycoside formation from pent-4-enyl 2-deoxy-2-azido NPGs

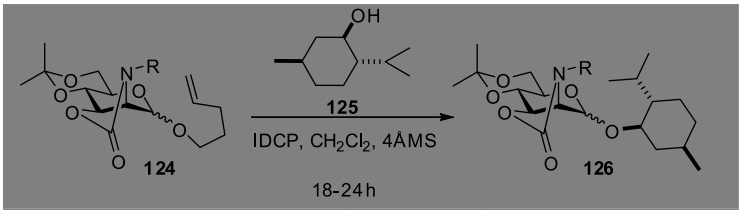
(Scheme 14*a*) [70]. By contrast, good results were obtained with the benzylidenated derivative **110** (Scheme 14*b*). The authors ascribed this result to the conformational constraint imposed by the benzylidene ring, in keeping with their precedents [41].

Svarovsky and Barchi [71] observed a striking reactivity difference between pent-4-enyl β- and α-2-azido-2-deoxy galactosides **113** and **116**, respectively (Scheme 14*c*-X). Thus, where-



Scheme 15
Pent-4-enyl 2-allyloxycarbonyl-2-deoxy-D- and L-glucopyranosides

Table 4
Glycosidation of (−)-menthol (125) by oxazolidinone protected NPGs, 124



Entry	Oxazolidinone	R[a]	IDCP (equiv)	α:β	Yield (%)
i	α	H	2	4:1	53
ii	β	H	2	5:1	24
iii	α	CBz	4	α only	71
iv	β	CBz	4	α only	4
v	α	TCBoc	4	α only	41
vi	α	Troc	4	α only	50
vii	α	Boc	4	α only	63

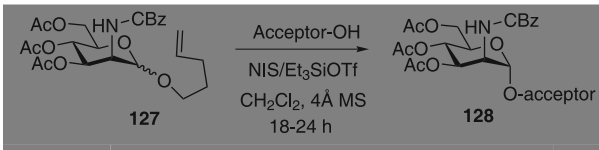
[a] CBz = (benzyloxy)carbonyl, TCBoc = (2,2,2-trichloro-1,1-dimethylethoxy)carbonyl, Troc = (2,2,2-trichlroethoxy)carbonyl, Boc = *tert*-butoxycarbonyl

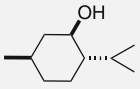
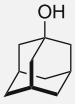
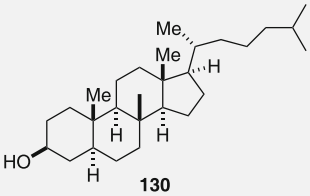
as β-NPGs **113a** and **113b** reacted with serine derivative **114** to give the sought α-glycosyl aminoacids **115a,b**, with complete stereocontrol, the corresponding α-anomers **116a,b** gave very poor yields of **115a,b** (< 10%) and much slower reaction rates.

Fraser-Reid's group advanced the synperiplanar lone-pair hypothesis (SLPH), to account for the fact that β-D-glycopyranosides hydrolyze ≈2–3 times faster [72] than the corresponding α-anomers [73]. This theory advocates that as the reaction progresses synperiplanar lone-pair interactions in the energetically accessible half-chair conformation of the β-anomer are equivalent to the antiperiplanar interactions in the half-chair of the α-anomer (antiperiplanar lone pair hypothesis, ALPH) [74]. On the other hand, the torsional effects associated with the conformational restraint imposed by the presence of the benzylidene ring might enhance this β/α reactivity difference to the point that the α-anomer hardly reacts [75].

2-Allyloxycarbonylamino-2-deoxy D- and L-glucopyranosides **118** and **121**, respectively, have been reported by Lafont and Boullanger [76], to successfully glycosylate 10-tetradecyloxymethyl-3,6,9,12-tetraoxahexacosanol (**119**) and 1,3-bis(undecyloxy)propan-2-ol (**122**), in the course on their studies on neoglycolipids for monolayers (*Scheme 15*). In this case, the chemoselectivity in the reaction of the anomeric pent-4-enyl moiety in the presence of the

Table 5
Stereocontrolled glycosylation using *N*-CBz NPG donor 127



Entry	Donor	Acceptor-OH	α:β	Yield (%)
				
i	α	**125**	α only	63
ii	β	125	α only	60
				
iii	α	**129**	α only	66
iv	β	129	α only	60
				
v	α	**130**	α only	68
vi	β	130	α only	63

[a] CBz = (benzyloxy)carbonyl

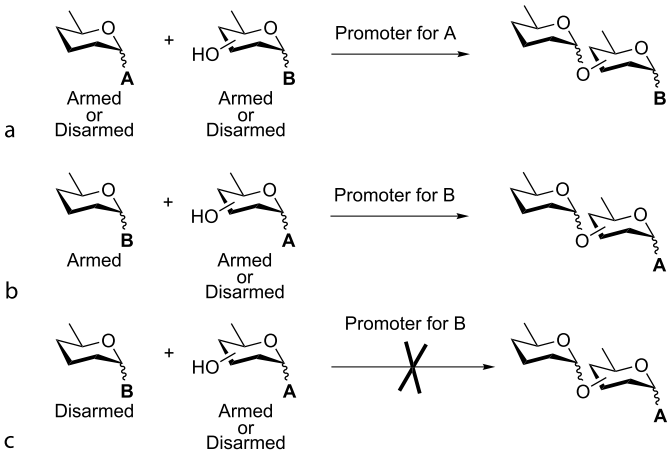
allyloxycarbonyl group is noteworthy. Related *n*-pentenoyl derivatives have been reported as efficient protecting groups for amines by its mild deprotection with iodine in THF-water [77]. Rojas and co-workers [78] described a novel synthetic route to α-linked 2-deoxy-2-mannosamine derivatives, which involved a stereocontrolled glycosidation step of NPG oxazolidinones (e. g. **124**, ❯ *Table 4*) and *N*-CBz NPGs (e. g. **127**, ❯ *Table 5*). The authors found a striking difference in reactivity between α- and β-anomers of oxazolidinones **124**. α-NPG oxazolidinones served as highly stereoselective donors (❯ *Table 4*, entries iii, v–vii), whereas the β-anomer was nearly inert (❯ *Table 4*, entries ii, iv). However, regioselective *N*-CBz oxazolidinone ring opening to **127**, prior to glycosylation permitted elaboration of either NPG anomer to the desired α-Man-NCBz products **128** (❯ *Table 5*).

2.7 Semi-Orthogonal Couplings of NPGs

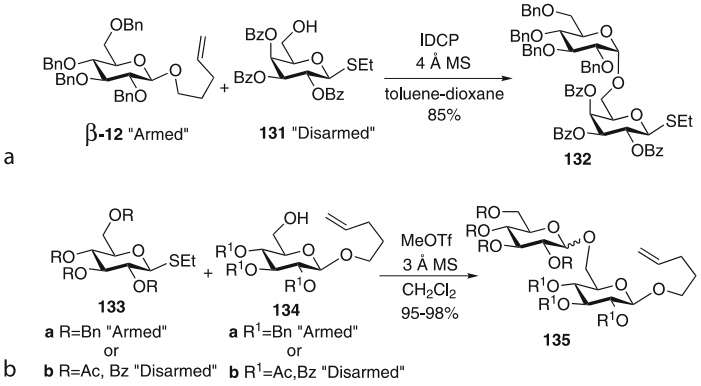
The term "semi-orthogonality" between glycosyl donors (e. g. **A** and **B**, ❯ *Scheme 16*) was introduced by Demchenko [79]. It indicates that whereas selective activation of armed and disarmed glycosyl donor **A** can be effected in the presence of either armed or disarmed donor **B** (❯ *Scheme 16a*), the opposite is not feasible. Thus, in semi-orthogonal donors, the selective activation of disarmed glycosyl donor **B** in the presence of glycosyl donor **A** can not be accomplished (❯ *Scheme 16c*).

2.7.1 Semi-Orthogonality of *O*-Pentenyl and *S*-Ethyl Glycosides

Demchenko and De Meo found conditions for the selective activation of NPGs and ethyl 1-thioglycosides (❯ *Scheme 17*) [79]. They demonstrated that armed NPGs (e. g. β-**12**)



Scheme 16
Semi-orthogonality of glycosyl donors

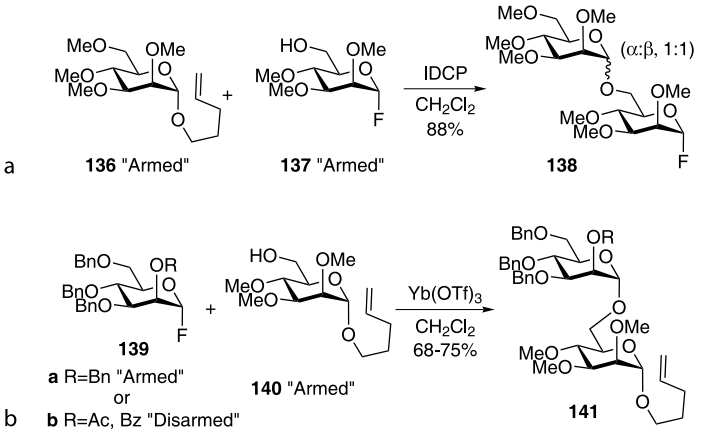


Scheme 17
Semi-orthogonality of *O*-pentenyl and *S*-ethyl-glycosides

could be activated in the presence of thioglycosides (e. g. **131**) with IDCP as the promoter (*Scheme 17a*). On the other hand, the use of methyl triflate (MeOTf) permitted the activation of disarmed thioglycosides (e. g. **133b**) in the presence of armed or disarmed NPGs, **134** (*Scheme 17b*).

2.7.2 Semi-Orthogonality of NPGs and Glycosyl Fluorides

López et al. reported the selective activation of armed NPGs (e. g. **136**) in the presence of armed glycosyl fluorides (e. g. **137**) on treatment with IDCP (*Scheme 18a*) [49]. On the other hand, armed and disarmed glycosyl fluorides **139**, could be activated in the presence of armed NPGs (e. g. **140**) on treatment with ytterbium triflate ($Yb(OTf)_3$) (*Scheme 18b*).

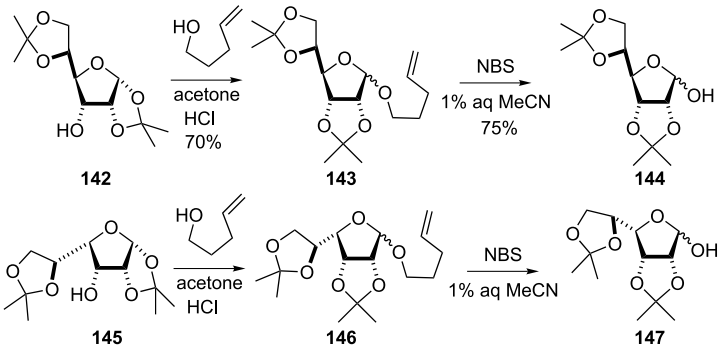


Scheme 18
Semi-orthogonality of NPGs and glycosyl fluorides

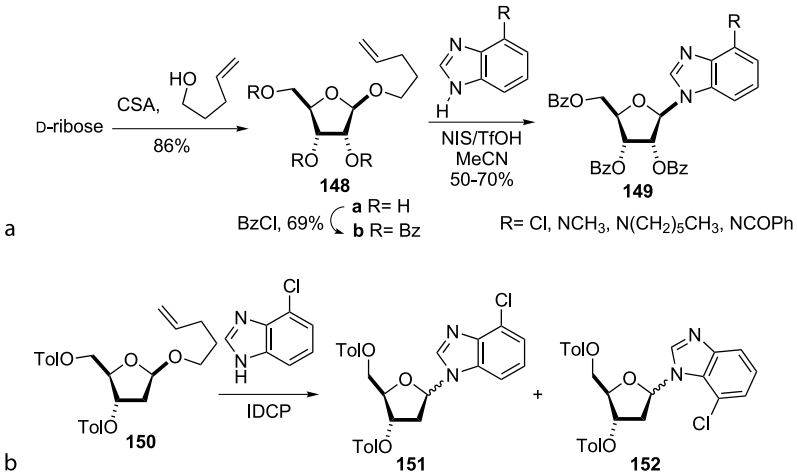
2.8 *n*-Pentenyl Furanoside Donors

2.8.1 Chemoselective Deprotection of the Anomeric Center

Unlike *n*-pentenyl pyranosides, the corresponding furanosides have attracted comparatively little attention. Sharma and Rao reported the preparation of *n*-pentenyl D-allo-, and D-gulo-furanosides **143** and **146**, respectively (*Scheme 19*) [55]. They made use of an efficient acid-induced rearrangement of diacetonides **142** and **145**, in the presence of *n*-pentenyl alcohol. The ensuing pent-4-enyl diacetonides **143** and **146**, were chemoselectively cleaved to hemiacetals **144** and **147**.



Scheme 19
Pent-4-enyl furanosides from D-allose and D-gulose diacetonides



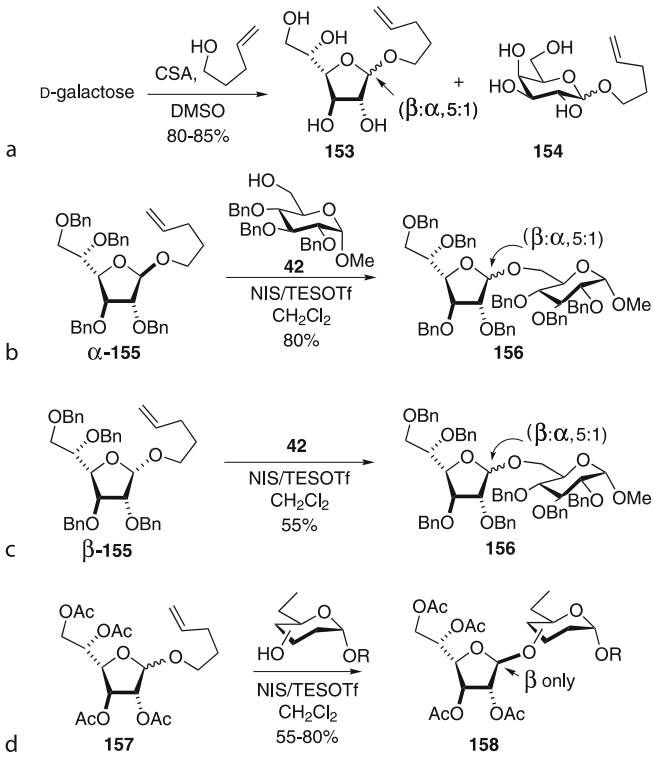
Scheme 20
Pentenyl ribofuranosides in the synthesis of purine nucleosides

2.8.2 Application to the Synthesis of Nucleosides

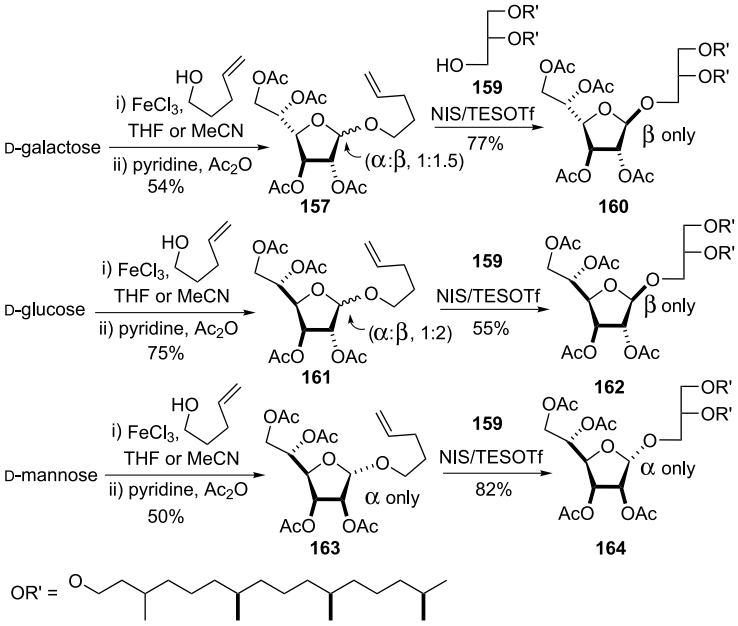
Chapeau and Marnett developed a synthetic route to purine nucleosides from *n*-pentenyl ribosides (Scheme 20) [80]. The authors used a Fischer glycosylation of D-ribose with 4-pentenol to produce pent-4-enyl β-D-erythro-pentofuranoside **148a**, in 86% yield. Reaction of the latter with benzoyl chloride produced their glycosyl donor **148b**, in 69% yield. Addition of TfOH to acetonitrile solutions containing **148b**, the selected purine, and NIS, resulted in a rapid coupling to form the desired nucleosides **149**, in a stereocontrolled manner with yields ranging from 50 to 70% (Scheme 20a). The absence of an acyl group at *O*2 in 2-deoxy NPG **150**, enhanced its reactivity to iodonium sources so IDCP could be used as the promoter. Thus, reaction of **150** with 6-chloropurine in acetonitrile was neither regio- nor stereo-selective, yielding four coupling products **151**α,β and **152**α,β, in similar amounts (Scheme 20b).

2.8.3 *n*-Pentenyl Furanosides as Glycosyl Donors

Arasappan and Fraser-Reid described the preparation of *n*-pentenyl galactofuranosides and evaluated their prospects as glycosyl donors (Scheme 21) [81]. Fischer glycosidation of D-galactose under kinetic conditions using *n*-pentenyl alcohol and DMSO as co-solvent [82]



Scheme 21
Pentenyl galactofuranosides



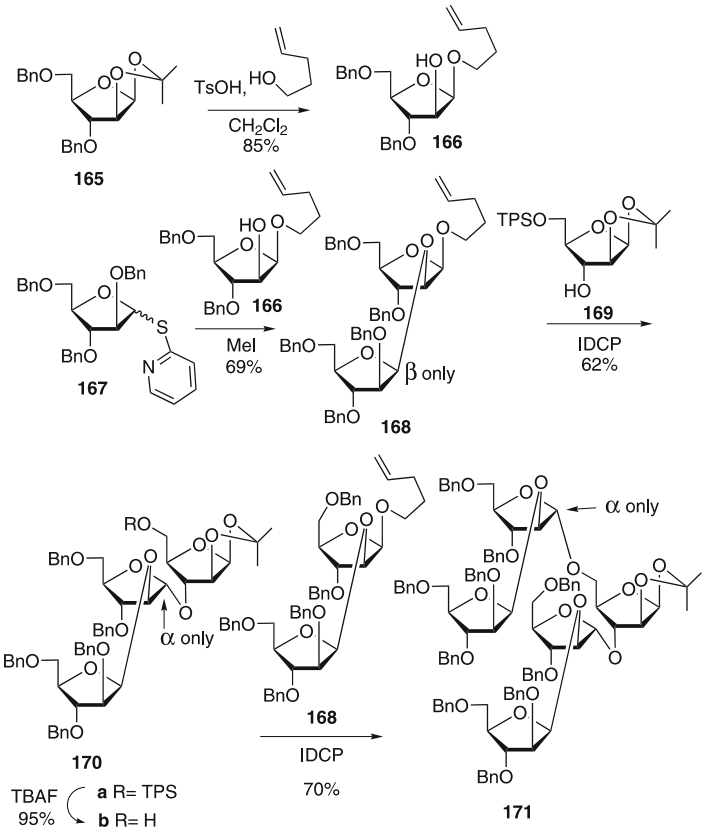
Scheme 22
Synthesis of archaeol glycolipid analogues from pent-4-enyl furanosides

afforded an anomeric α/β (1:3) mixture of *n*-pentenyl galactofuranosides **153**, (≈80–85% yield), contaminated with small amounts of the corresponding *n*-pentenyl galactopyranosides, **154** (*Scheme 21a*). Glycosylation with α- or β- pentenyl glycosides **155** was irrelevant to the product β/α ratio, both favoring the β-furanoside β-**156** (*Scheme 21b,c*). Reactions with donors α- or β-**157** resulted in the β-linkage product **158**, exclusively (saccharide acceptors with free hydroxyl groups at C-2, C-4, and C-6 were assayed), presumably due to the neighboring group participation of the C-2 ester functionality (*Scheme 21d*).

Plusquellec and co-workers reported an improved method for the preparation of *n*-pentenyl furanosides [83] based on their previously described use of $FeCl_3$ as a catalyst in Fischer-type glycosylations [84]. Accordingly, D-glucose, D-galactose, and D-mannose upon treatment with $FeCl_3$ and *n*-pentenyl alcohol followed by in situ acetylation, yielded pent-4-enyl D-gluco-, D-galacto-, and D-mannofuranoside derivatives **157**, **161**, and **163**, respectively in yields ranging from 50 to 75%. Glycosylation of glycerol diether **159** with these donors, promoted by NIS/TESOTf yielded glycolipids **160**, **162**, and **164** in high yields and with excellent 1,2-*trans* stereoselectivity (*Scheme 22*).

2.8.4 *n*-Pentenyl Arabinofuranosides in the Assembly of Oligoarabinans of *Mycobacterium tuberculosis*

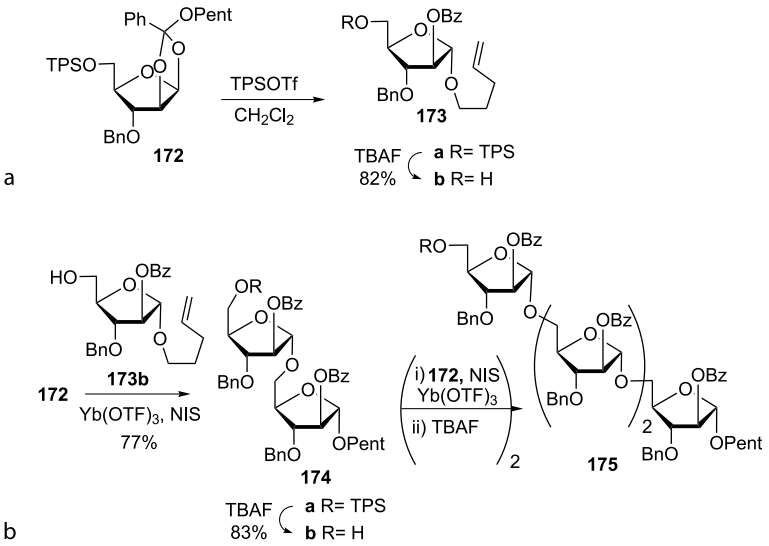
Recent interest in oligoarabinans, have been triggered by their presence in the lipoarabinomannan polysaccharide component of the cell wall complex of mycobacteria [85]. Several research groups have employed *n*-pentenyl arabinofuranosides in their approaches to oligoarabinans.



Scheme 23
Synthesis of a pentaarabinofuranosyl structure motif of *Mycobacterium tuberculosis*

n-Pentenyl β-D-arabinofuranoside **166**, readily prepared from **165**, was employed as acceptor/donor in Gurjar's approach to arabinosyl pentasaccharide **171** (*Scheme 23*) [86]. Accordingly, **166** was glycosylated with *S*-(2-pyridyl)-1-thiofuranose **167** to yield, in a stereoselective manner, β-disaccharide **168**. The latter, itself a pentenyl donor, was then used as a glycosyl donor in two glycosylation events. First, IDCP-promoted glycosylation of silyl derivative **169** yielded trisaccharide **170a** in 62% yield, and in a stereocontrolled manner. Desilylation of **170a** furnished **170b**, which then functioned as the acceptor in the second IDCP-induced glycosylation with **168** to produce pentasaccharide **171**.

More recent studies by Fraser-Reid's group, have focused on the use of NPOEs both as arabinofuranosyl donors, and as convenient starting materials for the preparation of *n*-pentenyl arabinofuranosyl acceptors [87]. TPSOTf-induced rearrangement of NPOE **172**, followed by desilylation afforded pentenyl glycoside **173b** (*Scheme 24*). Glycosylation of pentenyl glycoside **173b** with NPOE **172** was carried out using NIS/Yb(OTf)$_3$, a chemospecific promoter for NPOEs [88,89]. Iteration of the sequence permitted the preparation of the α-1,5-linked arabinan segment of the complex lipoarabinomanan cell wall array of *Mycobacterium tuberculosis*, **175**.



Scheme 24
NPOEs in the synthesis of arabinofuranosyl donors

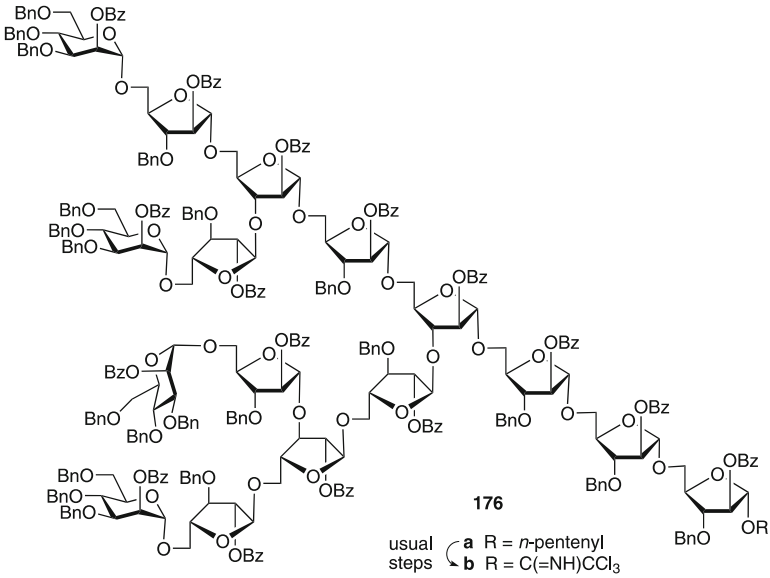


Figure 3
Mannose-capped multibranched dodecafuranoarabinan of *Mycobacterium* species

The potency of this strategy relies ultimately in the sturdiness, and yet the possibility for chemoselective cleavage, of pentenyl arabinofuranosides (e. g. **175**) [90]. Its value has been demonstrated recently with the synthesis of the pentenyl glycoside of mannose-capped dode-

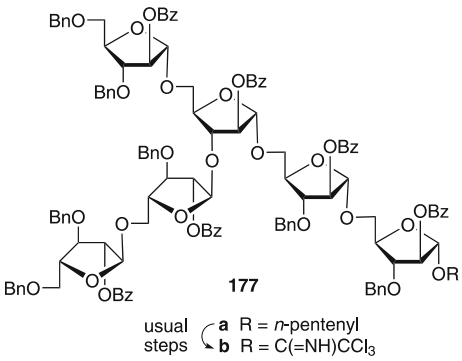
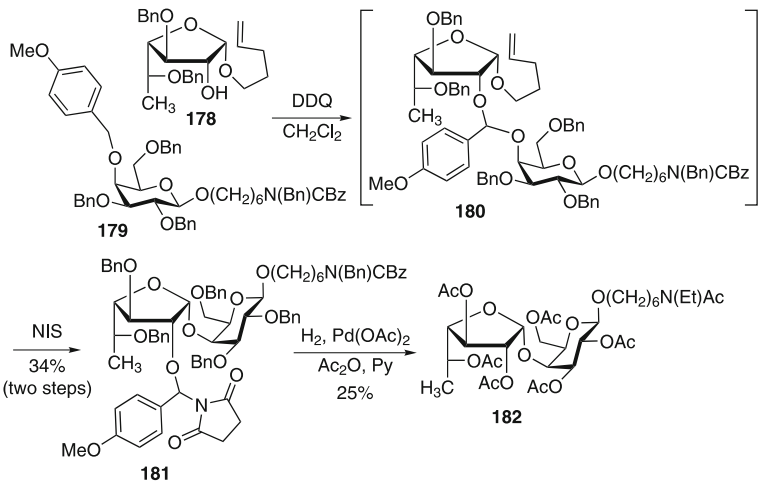


Figure 4
Multibranched hexafuranoarabinan of *Mycobacterium* species

cafuranoarabinan of *Mycobacterium* species, **176a** (*Fig. 3*). The final NPG→trichloroacetimidate transformation (**176a**→**176b**) made possible the coupling of this arabinan segment to an oligomannan acceptor, thus resulting in the synthesis of the largest heterooligosaccharide to date, a 28-mer arabinomannan [91].

n-Pentenyl arabinofuranosides have also been used by Seeberger and co-workers in the final stages of their synthesis of a 12-mer component of *Mycobacterium tuberculosis* [92]. *n*-Pentenyl arabinan hexasaccharide **177a**, was transformed to the corresponding trichloroacetimidate **177b** and coupled with a mannan hexasaccharide acceptor to yield the sought arabinomannan dodecasaccharide (*Fig. 4*).



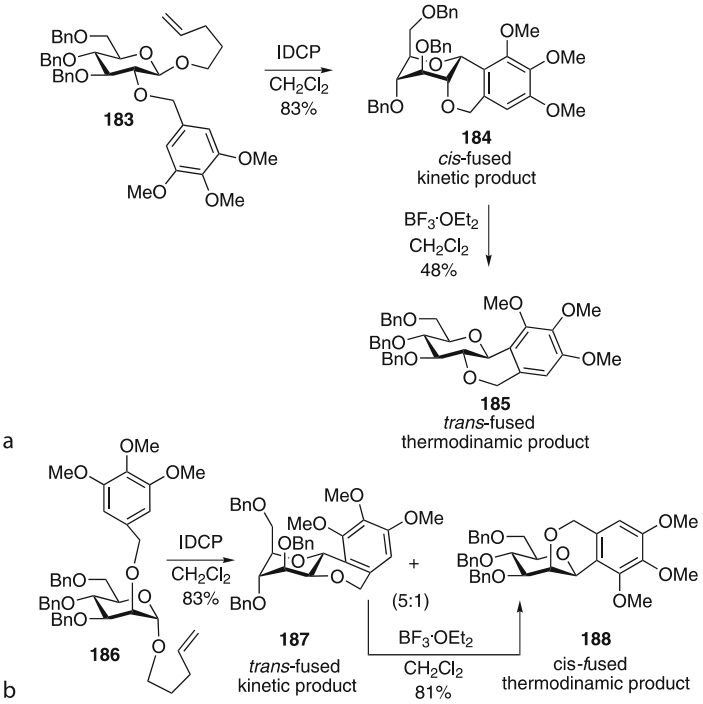
Scheme 25
NPGs as glycosyl donors in intramolecular aglycon delivery

2.8.5 Intramolecular Aglycon Delivery from *n*-Pentenyl Glycofuranosides

An approach to α-D-fucofuranosyl glycosides that makes use of the intramolecular aglycon delivery (IMAD) [93,94,95,96] starting from an *n*-pentenyl fucofuranoside has been described (*Scheme 25*) [97]. *n*-Pentenyl fucofuranoside **178** bearing a free 2-OH group was attached to a 4-*O*-PMB-protected galactopyranoside **179**, upon treatment of the mixture with DDQ. The unstable tethered compound **180**, could be activated with NIS, in the absence of even catalytic amounts of acid, to undergo an efficient *p*-methoxybenzyl-assisted aglycon delivery [95] leading to the desired glycoside **181**. The unusual structure **181**, resulting from quenching of the benzylic cation with *N*-succinimide, was then processed to α-D-fucofuranoside **182**.

2.8.6 Intramolecular *C*-Glycosylation of NPGs

The intramolecular *C*-glycosylation of NPGs has been studied by Martin's group in the course of their approaches to bergenin [98] and related natural products [99,100]. The treatment of pentenyl β-D-glucopyranose **183** with IDCP promoted an internal, Friedel–Crafts type, *C*-arylation reaction in excellent yield (*Scheme 26a*). The resulting product was exclusively the kinetically favored, *cis*-fused tricyclic system **184**. Treatment of the latter with an oxophilic Lewis acid ($BF_3{\cdot}OEt_2$) led to the *trans*-fused (β-linked) **185**. On the contrary, analogous reac-



Scheme 26
Intramolecular *C*-glycosylation of NPGs

tion of α-D-mannopyranoside **186** led to a mixture of *trans*- and *cis*-fused compounds **187**, and **188** (5:1), where the major *trans*-fused (α-linked) product **187**, was this time the kinetic product (*Scheme 26b*). Treatment of the latter with $BF_3{\cdot}OEt_2$ promoted the epimerization to the, more stable, 1,2-*cis* epimer **188**, in 81% yield.

2.8.7 NPGs of *N*-Acetylneuraminic Acids (Neu5Ac)

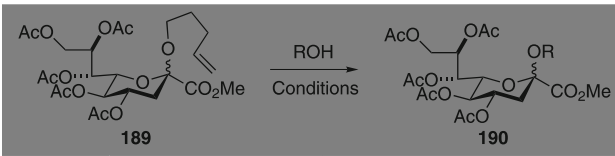
One report describing *O*-sialylation of 4-pentenyl glycosides of Neu5OAc, e. g. **189**, has appeared (*Table 6*) [101]. Good α/β selectivity (11:1) was attained in the glycosylation of primary acceptor **40** in MeCN using NIS/TfOH as the promoter (*Table 6*, entry i), however, with the secondary acceptor **191** the α/β selectivity dropped to 4:1 (entry iii). The use of Et_2O as solvent produced a 1:1 mixture of anomers (entry ii).

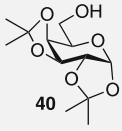
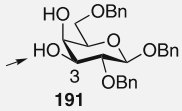
2.8.8 NPGs of L-Iduronic Acid as Glycosyl Donors

In their studies on heparin/heparin sulfate, and dermatan sulfate, Petitou, Sinaÿ and co-workers found that *n*-pentenyl glycosides of L-Iduronic acid, e. g. **192**, were efficient glycosyl donors [102]. In contrast, the corresponding thioglycosides, and glycosyl fluorides did not give the expected disaccharides. Reaction of *n*-pentenyl glycosyl donors **192** (α or β) with acceptors **194**–**197** (*Table 7*) was carried out in CH_2Cl_2 with NIS/TfOH to furnish the corresponding α-disaccharides **193**, in good yields.

More recently, Reichardt and Martín-Lomas have evaluated *n*-pentenyl glycosides of glucosamine $\alpha 1 \rightarrow 4$L-iduronic acid disaccharide, as substrates for autocondensation in their approach to heparin oligosaccharide fragments. However, the NIS used as promoter, being

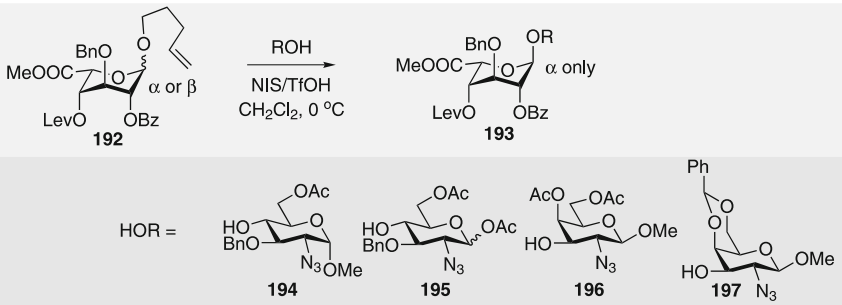
Table 6
***n*-Pentenyl glycosides of Neu5Ac in glycosylation**



Entry	ROH	Conditions	Yield (%) (α:β)
i	 40	NIS/TfOH MeCN, −40 °C	60 (11:1)
ii	40	NIS/TfOH Et_2O, −40 °C	33 (1:1)
iii	 191	NIS/TfOH MeCN, −40 °C	37[a] (4:1)

[a] The glycosylation is regioselective at *O*-3

Table 7
***n*-Pentenyl glycosides of L-iduronic acids as glycosyl donors**



Yields of disaccharide	80% from α-192 83% from β-192	75% from α-192 77% from β-192	72% from α-192	90% from α-192

itself a nucleophile, competes with the acceptor disaccharide in the polycondensation process, which results in fast chain-reaction termination and a low yield and degree of polymerization [103].

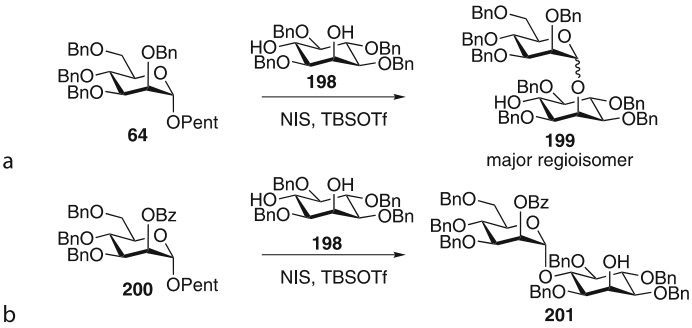
2.9 NPGs in Regioselective Couplings

The synthesis of branched saccharides by multiple glycosylations onto a central monosaccharide normally requires the use of orthogonal protecting groups in the acceptor. In this context, regioselective glycosylation of diols or polyols would ease the number of protection-deprotection steps in these synthetic protocols.

2.9.1 The Role of the *O*-2 Substituent in Regioselective Couplings

In their studies on *myo*-inositol glycosylation, Fraser-Reid and co-workers made the observations summarized in ❯ *Scheme 27* [104]. In the hope of achieving selective glycosidation of the equatorial-OH, they treated diol **198** with the armed *n*-pentenyl donor **64** (❯ *Scheme 27a*). However, the major product was the mixture of α/β glycosides **199** from glycosidation at the axial-OH (❯ *Scheme 27a*). In order to improve α anomeric stereoselectivity they selected the corresponding disarmed NPG **200**, as the donor (❯ *Scheme 27b*). Surprisingly, the only product obtained was the disaccharide **201** from glycosidation at the equatorial-OH.

In a series of subsequent papers Fraser-Reid and co-workers confirmed these discrepancies, and showed that the *O*-2 substituent in glycosyl donors, besides its recognized role for stereocontrol, exerts a profound influence in eliciting regioselective glycosyl couplings [105,106,107]. In most cases, 2-*O*-acyl NPGs and NPOEs shared the same regiopreferences, which were usually different from the ones displayed by 2-*O*-alkyl NPGs. The regiopreferences of the former were generally more pronounced or even exclusive.

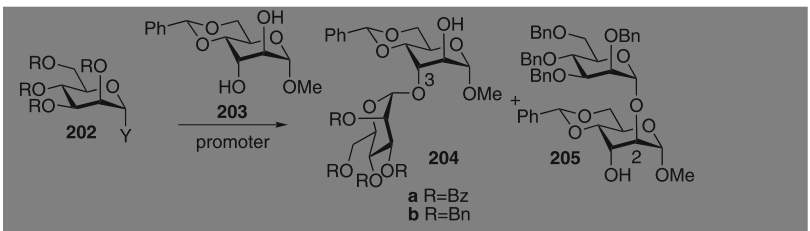


Scheme 27
Influence of the *O*-2 protecting group in regioselective glycosylations

2.9.2 Reciprocal Donor Acceptor Selectivity (RDAS)

The influence of the *O*-2 substituent in regioselective couplings is not limited to pentenyl glycoside donors. Thioglycoside and trichloroacetimidate donors have shown the same tendency [108]. The glycosylation of allose diol **203** with donors **64** and **202a–f** (*Table 8*) illustrates this point. NPOE **202a** (that shows the same regiopreferences as disarmed NPGS), disarmed thiomannoside **202c**, and disarmed trichloroacetimidate **202e**, exhibited the same preference for the *O*3 of allose acceptor **203** (*Table 8*, entries i, iii, v). On the contrary, armed donors **64**, **202c**, and **202e** furnished a 2:1 mixture of disaccharides **204b** and **205**. The above-mentioned examples indicate that each donor expresses preference for one of the diol–OHs in the acceptor and vice versa. The authors coined the term *Reciprocal Donor Acceptor Selectivity* (RDAS) [109] to account for these findings.

Table 8
Influence of the *O*-2 substituent in the regioselective coupling of various glycosyl donors with allose diol 203



Entry	Donor (202)	Promoter (Temp °C)	Products (ratio 03:02)	Yield %
i	a Y=orthoester; R=Bz	NIS/BF_3·Et_2O −30	204a only	92
ii	64 Y=OPent; R=Bn	NIS/BF_3·Et_2O −30	204b + 205 (2:1)	37
iii	b Y=SPh; R=Bz	NIS/BF_3·Et_2O −30	204a only	58
iv	c Y=SPh; R=Bn	NIS/BF_3·Et_2O −30	204b + 205 (2:1)	66
v	d Y=OC(NH)CCl_3; R=Bz	BF_3·Et_2O −78	204a only	65
vi	e Y=OC(NH)CCl_3; R=Bn	BF_3·Et_2O −78	204b + 205 (2:1)	54

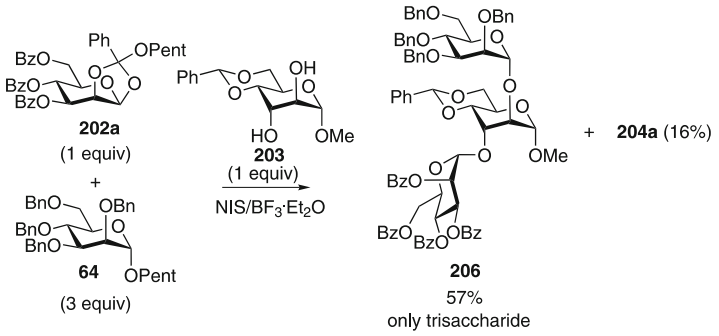
2.9.3 In Situ Double Differential Glycosylations of Two Donors with One Acceptor

The practical utility of this concept was further demonstrated when diol acceptor **203**, NPOE **202a**, and armed-NPG **64** were treated with NIS/BF_3·Et_2O to give one single trisaccharide **206**, in 57% yield (● *Scheme 28*) [110]. It seemed that in the formation of the trisaccharide the regiopreferences of the NPOE **202a** and the armed NPG **64**, displayed in ● *Table 8*, have been followed.

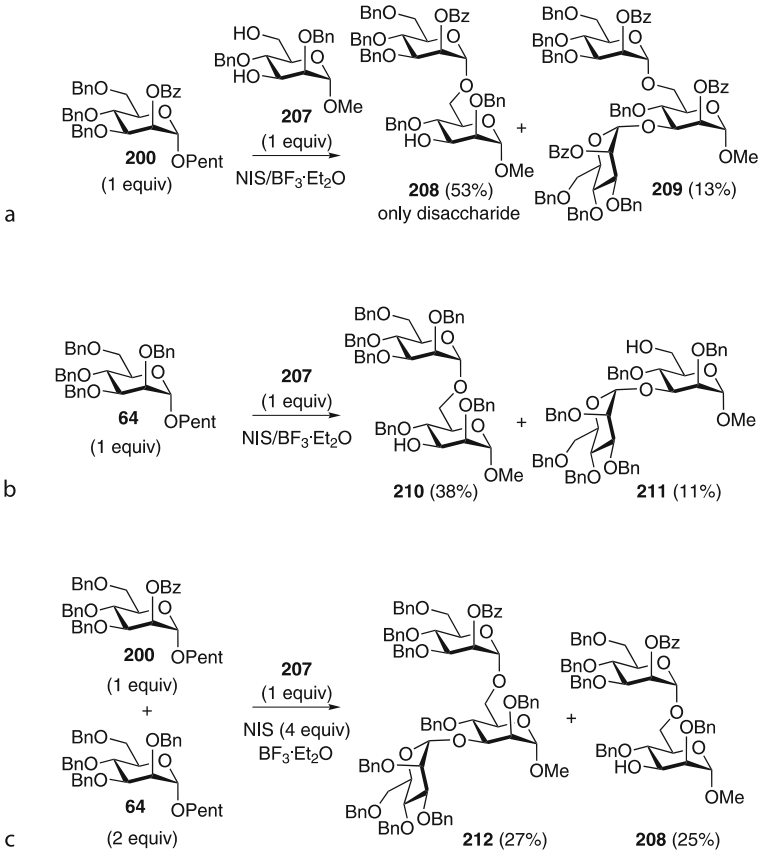
Analogously, the regiopreferences (RDAS) of disarmed NPG **200**, and armed NPG **64** vis a vis mannose diol **207**, were evaluated (● *Scheme 29a,b*). With the disarmed donor **200** mannosylation occurred at the (C6)-OH only to give **208** in 53% yield, and also the symmetrical trisaccharide **209** in 13% yield, but with no evidence for the dimannan resulting from glycosylation of the (C3)-OH (● *Scheme 29a*). By contrast, the armed donor **64** gave a 38% yield of the *O*-6 product, **210**, but also 11% of the *O*3 regioisomer **211** (● *Scheme 29b*). Analysis of these results according to conventional wisdom, dictates that the preference of both donors, **200** and **64**, for the primary −OH was to be expected [1] but raised the question of the possible outcome of a three-components double glycosylation when **200** and **64** compete for diol **207**. Previous calculations had shown that the relative reactivity of these donors (k_{64}/k_{200}) is 3.2 [111]. Hence, it was expected that *O*6 mannosylation by the armed donor, **64**, would predominate in any trimannan produced. Surprisingly, a single trimannan **212**, in which the *less* reactive donor **200** ended up at *O*6 was obtained, even in the presence of 2 equiv. of the "*more reactive*" **64**.

2.10 The Origin of Regioselectivity in Three-Component Couplings

In searching for the origin of the regioselectivity observed in the formation of trisaccharides **206** and **212** (● *Scheme 28* and ● *Scheme 29*) several factors were considered. The reactions in ● *Scheme 28* and ● *Scheme 29c* were carried out with excess NIS promoter, conditions under which the intermolecular halonium ion transfer (responsible for the armed-disarmed effect) is not operative. A study of the three types of *n*-pentenyl donors indicated that their relative reactivities were in the order NPOE > armed > disarmed (e. g. **202a** > **64** > **200**) [111]. Therefore, the most and the least reactive donors have "chosen" their preferred −OH in the final trisac-



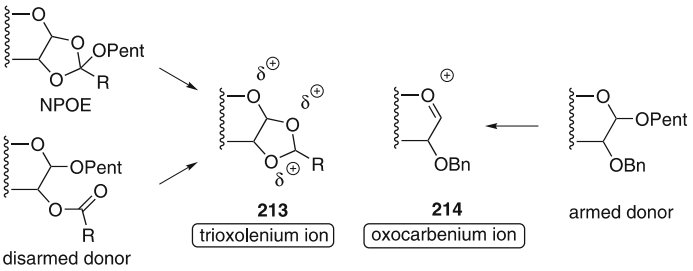
Scheme 28
In situ three-component double differential glycosylation of two donors and one diol acceptor



Scheme 29
In situ three-component double differential glycosylation of two donors and one diol acceptor

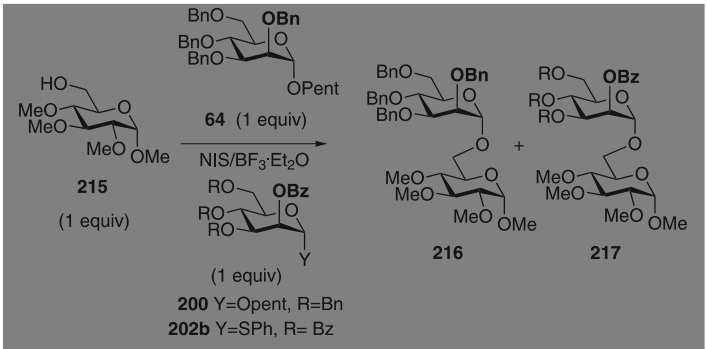
charide. On the other hand, the most and the least reactive donors give rise to the highly delocalized, more stable intermediate **213**, while the armed donor gives the less stable oxocarbenium ion **214** (*Scheme 30*) [112]. The conclusion was that in *competitive* glycosylations the more *stable* donor/intermediate (not the most *reactive* donor) controls regioselectivity, resulting in the formation of the single trisaccharides **206** and **212** and the single disaccharides **204a** and **208**.

In order to confirm this assumption the authors performed the experiments in *Table 9* [113]. Equimolar amounts of armed and disarmed donors **64**, and **200** or **202b** were allowed to compete for one equivalent of acceptor **215** under the agency of NIS. When one equivalent of NIS was used the major product obtained was that of glycosylation of armed NPG **216**, thus in agreement with a process of intermolecular halonium transfer and preferred reaction of the more reactive donor (*Table 9*, entries i, iii). When the amount of NIS was increased to three equivalents, the observed ratio of compounds **216** and **217** indicated enhanced coupling of the disarmed donor (*Table 9*, entries ii, iv), thus in agreement with the proposed rationalization for the regiopreferences observed in the three-component reactions.



Scheme 30
Reactive intermediates from different glycosyl donors

Table 9
Competition studies on the glycosylation of acceptor 215 in the presence of glycosyl donors (64 and 200 or 202b) with variable amounts of NIS



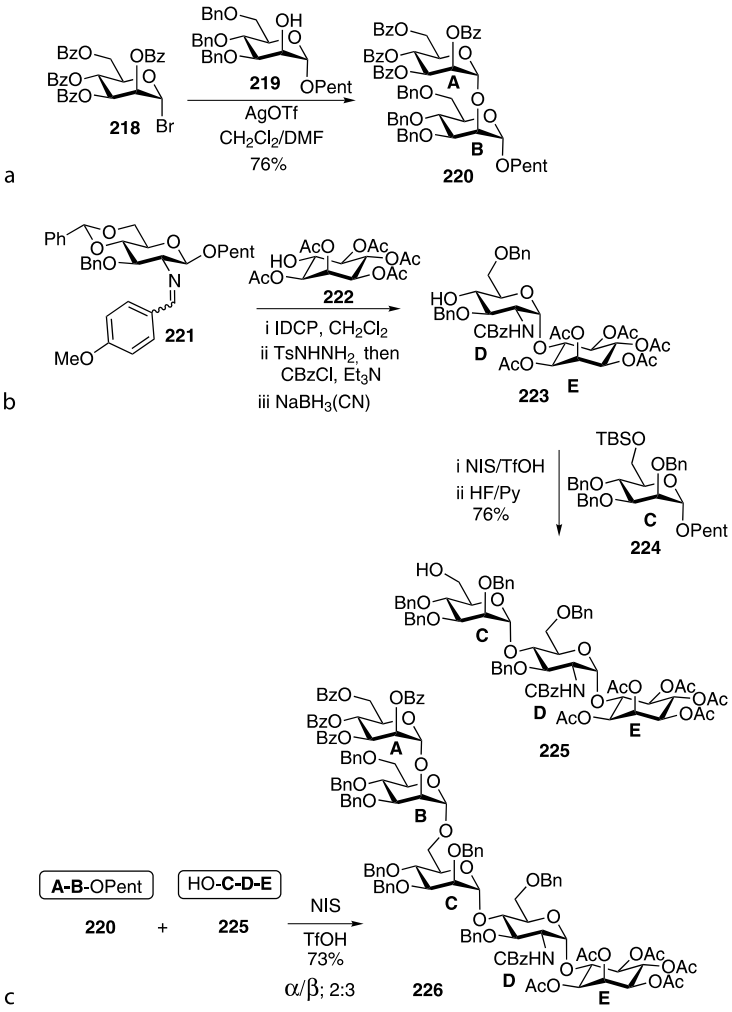
Entry	Donors		NIS	Product ratio		Yield
	armed/disarmed		(equiv)	216	217	(%)
i	64	200	1	2	1.1	57
ii	64	200	3	1.1	1	69
iii	64	202b	1	1	0	52
iv	64	202b	3	1	2.2	83

2.11 NPGs in Oligosaccharide Synthesis

Since their discovery, the unique properties of NPGs have allowed the preparation of several oligosaccharides. The pentenyl moiety may be installed early in the synthetic sequence and can survive many types of protecting group manipulations. Some selected syntheses of oligosaccharides are briefly discussed below.

2.11.1 The Pentasaccharide Core of the Protein Membrane Anchor Found in *Trypanosoma brucei*

Fraser-Reid and co-workers described a block (i. e., convergent), and a linear approach to the title compound, **226** (*Scheme 31*) [114]. The convergent approach, outlined in *Scheme 31*,



Scheme 31
The pentasaccharide core of the protein membrane anchor of *Trypanosoma brucei*

makes use of the stereocontrolled glycosylation of inositol derivative **222** with 2-deoxy-2-imino NPG **221** (*Scheme 31b*). Protecting group manipulations led to acceptor **223** that was glycosylated with NPG **224**, to furnish, after desilylation, the acceptor **CDE** block, **225**. The donor counterpart **220**, had been readily prepared by Koenigs–Knorr [115] coupling of NPG **219** with glycosyl bromide **218** (*Scheme 31a*). Finally, coupling of fragments AB (**220**) and CDE (**225**) promoted by NIS/TfOH led to pentasaccharide **226**, in 73% as an α/β (2:3) mixture (*Scheme 31c*).

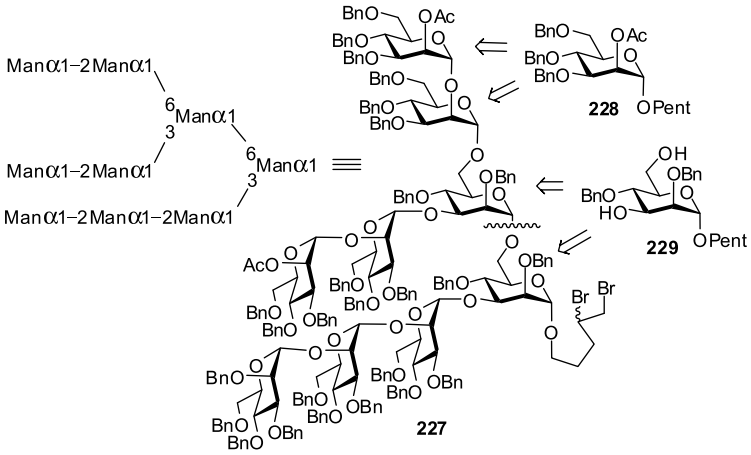
2.11.2 The Nonamannan Component of High Mannose Glycoproteins

The concise approach to nonamannan **227** (› *Scheme 32*), was greatly simplified with the sidetracking of NPGs [116,117] that allows the same NPG synthon to function as glycosyl donor or as glycosyl acceptor.

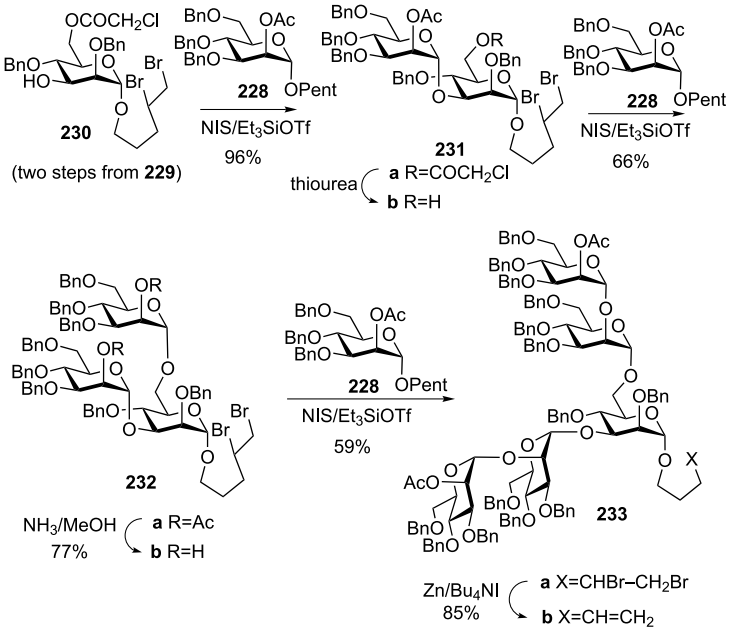
In the retrosynthesis of **227**, the authors identified three types of elements depending on the number of sugar units attached to them. Two components carried sugars at *O*3 and *O*6, four held substituents at *O*2, and the last three had no monosaccharides attached. According to that, the nonasaccharide target could be correlated with only two mannopyranose precursors **228** and **229**, since synthon **228** could be used to access the last two kinds of sugars. The approach featured the final link of a pentasaccharide donor with a tetrasaccharide acceptor, as outlined in › *Scheme 32*.

The synthesis of pentasaccharide donor **233** started with the mannosylation of sidetracked NPG **230** with disarmed NPG donor **228** (› *Scheme 33*). The ensuing, stereoselectively formed disaccharide **231a**, after unveiling of its C6-OH, underwent a second mannosylation with **228**. Removal of the acetates in **232a** with NH_3/MeOH led to diol trisaccharide **232b**, which was bis-mannosylated with **228** to give pentasaccharide **233a** in 59% yield. Regeneration of the pentenyl moiety in sidetracked **233a**, with Zn/nBu_4NI, granted access to pentasaccharide NPG donor, **233b**.

The lowest antenna of **227** was built from **234** (› *Scheme 34*). By taking advantage of the sidetracking concept, compound **228** could be used as a glycosyl donor or, after dibromination and deacetylation as the glycosyl acceptor **234**, thereby facilitating the rapid assembly of trisaccharide fragment **235**. Thus, coupling of **234** and **228** afforded the expected disaccharide in 73% yield, deacetylation and additional coupling with **228** led to trisaccharide **235a** in 62% yield. The latter was transformed in glycosyl donor **235b** by reductive elimination, and coupled with **230** to give sidetracked tetrasaccharide **236a**. Dechloroacetylation of the latter led to **236b** that was glycosylated by pentasaccharide donor **233b** to give nonasaccharide **227** in 57% yield.



Scheme 32
The nonamannan component of high mannose glycoproteins

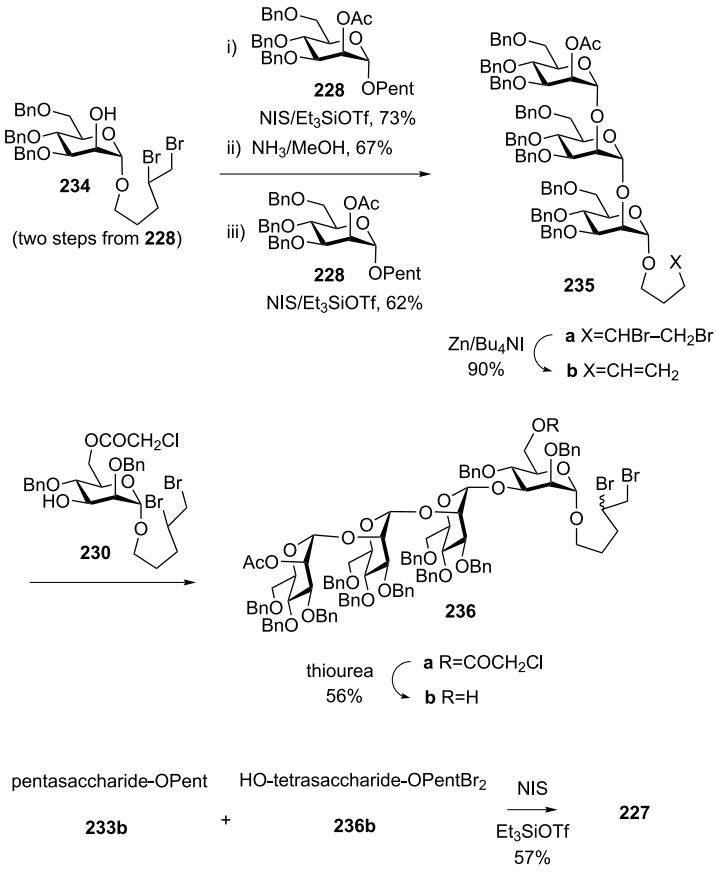


Scheme 33
Convergent synthesis of nonamannan 227. Synthesis of the pentasaccharide donor 233

2.11.3 Synthesis of NodRf-III (C18:1) (MeFuc)

Nodulation factors comprise a family of unique oligosaccharides composed substantially of glucosamine (2-amino-2-deoxy-D-glucose) units that are *N*-acylated with acetic acid and fatty acids residues, the latter residing at the nonreducing terminus [118]. The block synthesis of NodRf-III (C18:1) (MeFuc) **237**, a nod factor produced by *Rhizobium fredii*, is an illustrative example of the chemistry developed around 2-amino-2-deoxy-NPGs (*Scheme 35*) [119]. The key elements in this stereocontrolled synthesis are: (a) the use of the TCP protecting group, which provides a facile method for *N*-differentiation in the glucosamine oligomer, (b) the assistance of the sidetracking methodology, (c) a solvent-assisted stereoselective α-fucosylation, (d) a β-selective, neighboring group assisted, glycosidation, and (e) the use of $FeCl_3$ for late-stage debenzylation of the oligosaccharide moiety [120,121]. In the retrosynthesis (*Scheme 35*), the authors selected a TCP as protecting group for the nitrogen atom that would bear the unique fatty acid, while the repeating unit would be a 2-deoxy-2-*N*-phthaloyl NPG capable of acting as a glycosyl donor (e. g. **238**). The reducing end retron was identified with benzyl glycoside **239**.

The disaccharide acceptor **239** was prepared in 85% yield by coupling (NIS/TESOTf) of acceptor **241** with *n*-pentenyl fucoside **240** in Et_2O:CH_2Cl_2, (5:1) (*Scheme 36*). The disaccharide donor **238** was assembled in 71% by coupling of NPG **242** with sidetracked acceptor **243** (NIS/TESOTf), followed by reinstating of the pent-4-enyl moiety from the dibromo pentenyl residue in **244**. Final coupling (NIS/TESOTf) of donor **238** with acceptor **239** yielded

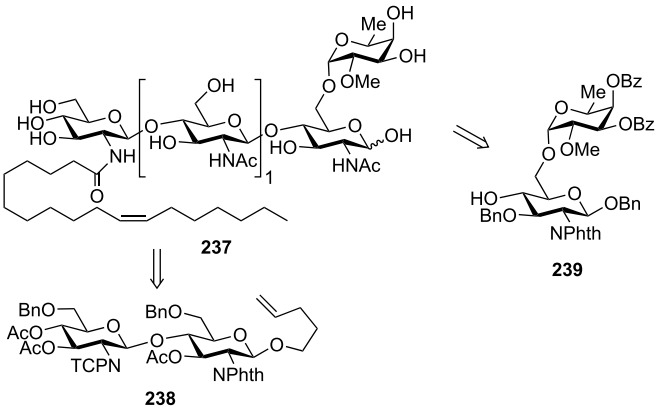


Scheme 34
Convergent synthesis of nonamannan 227. Synthesis of the tetrasaccharide acceptor 236b and final assembly

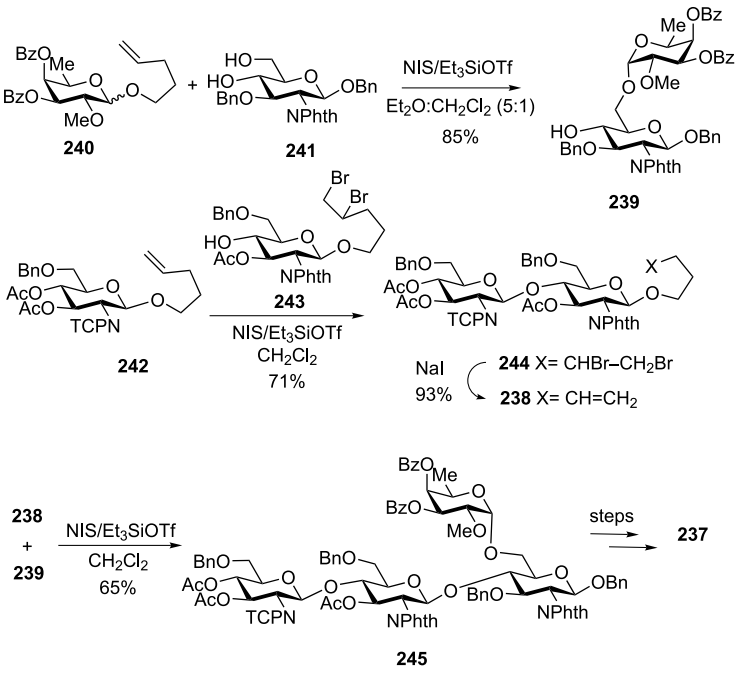
tetrasaccharide **245** in 65% yield. The final stages in the preparation of **237** involved: (i) $FeCl_3$ debenzylation, (ii) silylation of the resulting free –OHs, (iii) deprotection of the TCP and condensation with an activated fatty acid, (iv) removal of the phthalimido protecting groups, and (v) acylation, saponification, and desilylation.

2.11.4 Synthesis of Phosphorylated Rat Brain Thy-1 Glycosylphosphatidylinositol Anchor

Glycosylphosphatidylinositol (GPI) membrane anchors constitute a class of glycolipids that covalently link certain proteins to cell and virion surfaces [122,123]. A boost in their chemistry occurred in 1988 when Ferguson et al. reported the first covalent structure of a member of this family [124,125]. The first synthesis of a fully phosphorylated GPI, compound **246** (*Fig. 5*), was accomplished by Fraser-Reid's group based entirely on NPG chemistry [126,127,128,129,130].



Scheme 35
Retrosynthesis of nodulation factor NodRf-III (C18:1) (MeFuc)



Scheme 36
Synthesis of nodulation factor NodRf-III (C18:1) (MeFuc)

The retrosynthetic analysis dictated a heptasaccharide **251**, with all free hydroxyls in the final product benzylated, and the three sites of phosphorylation all differentially protected, so that all three can be manipulated separately for maximal flexibility. The free amine of glucosamine is protected as an azide, which can be taken through multiple transformations and will only be unmasked at the end of the synthesis (*Scheme 37*). The heptasaccharide is in turn put

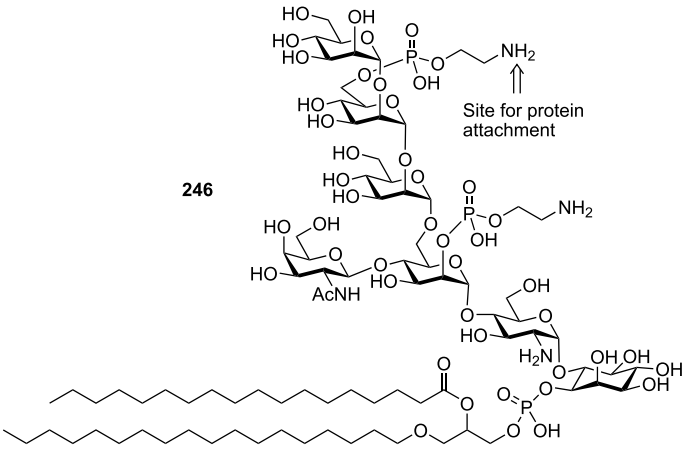
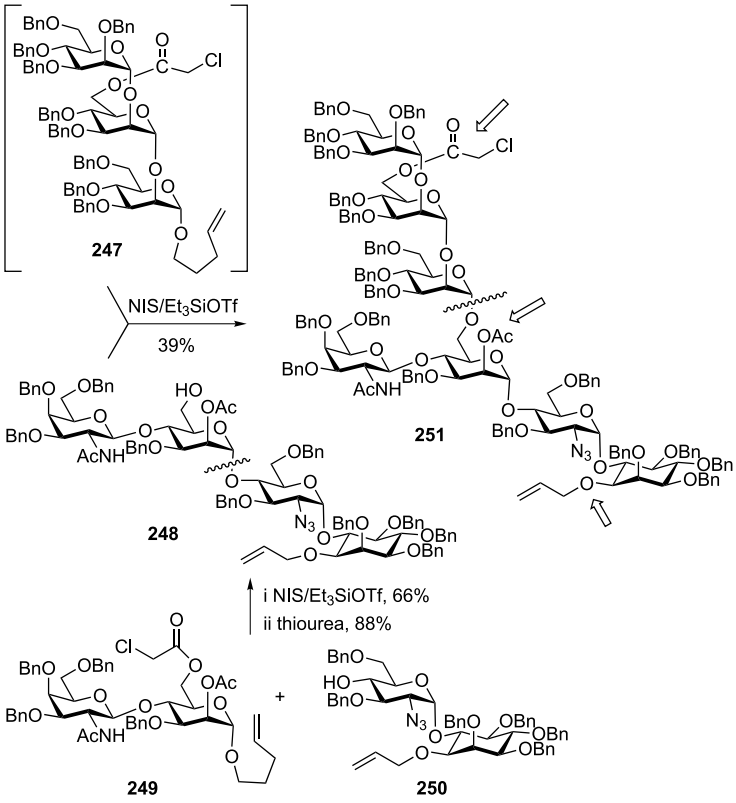
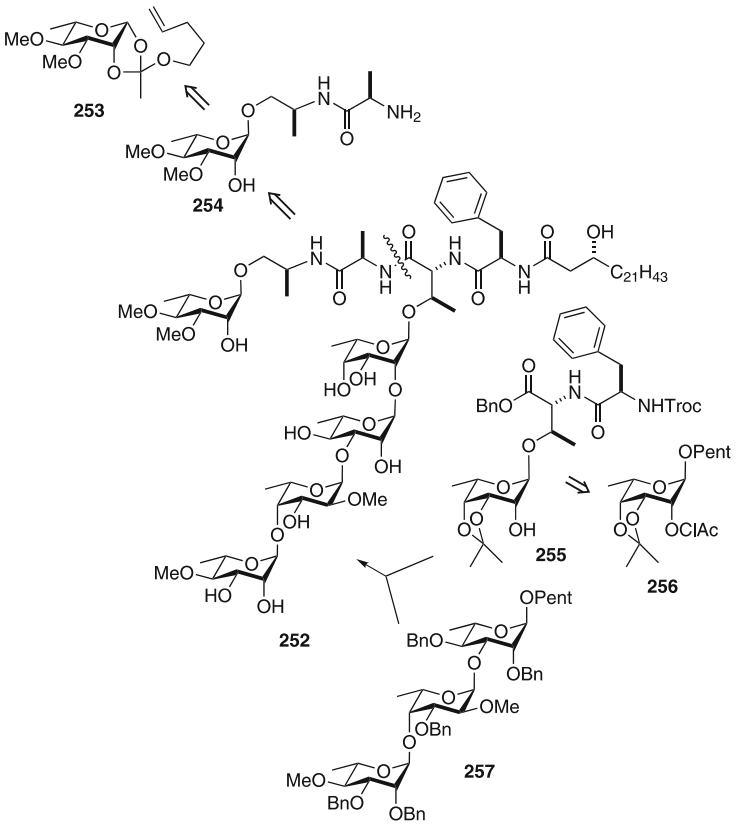


Figure 5
Rat brain Thy-1 GPI anchor 1, 246



Scheme 37
Synthesis of rat brain Thy-1 GPI anchor 1



Scheme 38
Synthesis of the glycopeptidolipid of *Micobacterium avium* Serovar 4, 252

together in three portions, a galatosaminylmannose **249** being coupled to azidoglucosylinositol **250** and then a trimannose, **247**, being coupled to that moiety. Coupling of glycosyl donor **249** with the disaccharide acceptor **250** was carried out with NIS/TESOTf to give α-linked tetrasaccharide **248** in 66% yield. Notably, the allyl protecting group survived the treatment with NIS. The *O*6 of the mannose residue was deprotected by removal of the chloroacetate moiety with thiourea and glycosylated with pentenyl trimannoside **247** to give the fully protected heptasaccharide **251** in 39% yield. The three positions (marked with arrows) were then deprotected and phosphorylated according to the following sequence: dechloroacetylation with thiourea, saponification of the acetate with methoxide, and deallylation with $PdCl_2$. Complete debenzylation, then culminated the synthesis of **246**.

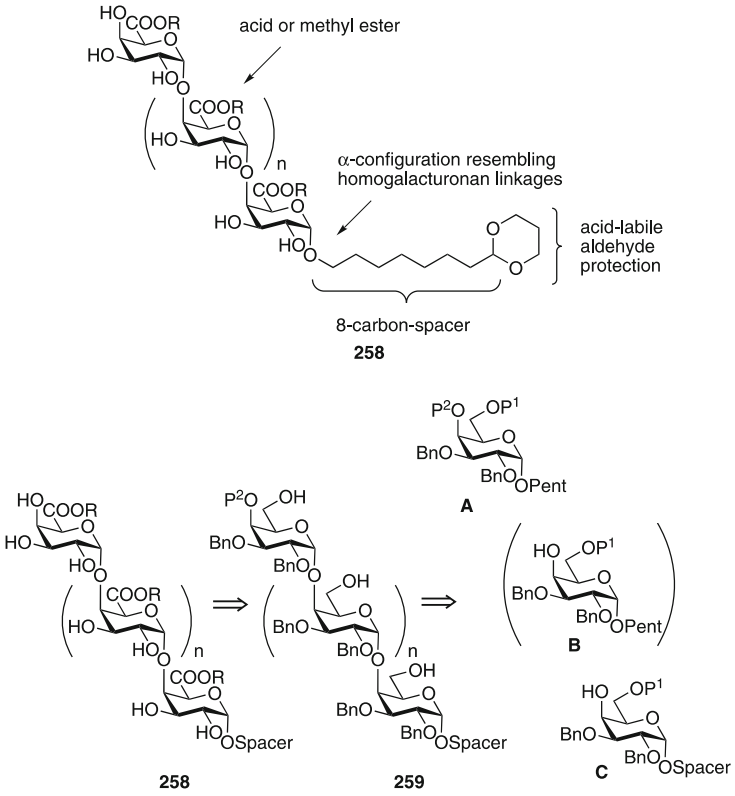
2.11.5 Synthesis of the Glycopeptidolipid of *Micobacterium avium* Serovar 4

Heidelberg and Martin described the first synthesis of the "polar mycoside C" **252** (*Scheme 38*) [131]. The synthesis was based on the disconnection of the final structure into three saccharidic building blocks, an L-rhamnosyl pseudodipeptide **254**, a 6-deoxy-L-talosyl

dipeptide **255**, and a pentenyl trisaccharide donor **257**. The key steps were the creation of the glycosidic linkage between the trisaccharide donor **257**, and the 6-deoxy-L-talose unit **255** (IDCP, 60% yield), and the final coupling of the two glycopeptide fragments. Other pentenyl mediated couplings were the glycosylation of orthoester **253** leading to **254** (NIS/TMSOTf, 81%) and the stereoselective α-coupling of disarmed NPG **256** to give glycodipeptide **255** (NIS/TMSOTf, 70%).

2.11.6 Synthesis of Oligogalacturonates Based on NPGs

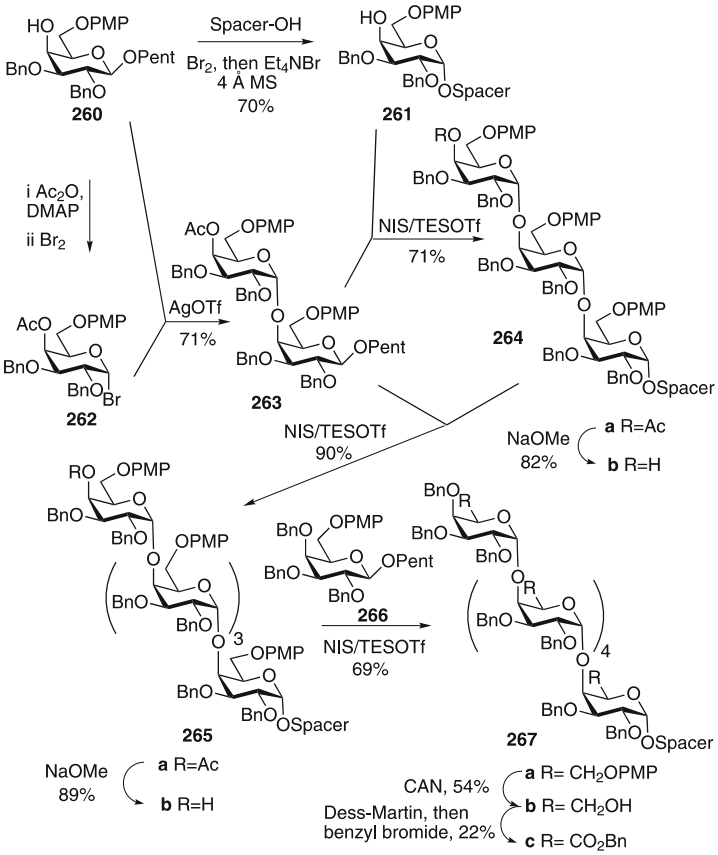
Madsen and co-workers described a concise approach to oligogalacturonates (e. g. **258**, ● *Scheme 39*) conjugated to bovine serum albumin (BSA) based on NPGs. They synthesized several oligogalacturonates, which were linked to the BSA by reductive amination via an aldehyde spacer at the reducing end (● *Scheme 39*) [48,132,133]. Their strategy called for two orthogonal protecting groups (P^1 and P^2), and three different monomeric building blocks: a spacer galactoside **C** to serve as glycosyl acceptor for the reducing end, and two glycosyl donors **A** and **B**, the former for the nonreducing end and the latter for the galacturonic



■ Scheme 39
Retrosynthesis of oligogalacturonates for conjugation to bovine serum albumin

repeating unit. *p*-Methoxyphenyl (PMP) and acetyl groups were used as protecting groups. The methodology was then based on the repeated coupling of galactose donors onto galactose acceptors followed by deprotection at *O*6, as in **259**, which permitted the oxidation of these primary positions to either the carboxylic acids or methyl esters.

The attaching of the spacer to galactose (i. e. **261**, building block **C**) was carried out by glycosylation, under Lemieux conditions [134], of a glycosyl bromide readily obtained from NPG, **260** (*Scheme 40*). Coupling of NPG **260** with galactosyl bromide **262** (AgOTf, 71%) led to pentenyl disaccharide **263** that glycosylated acceptor **261** (NIS/TESOTf, 71%) to give trisaccharide **264a**. Deprotection of the latter to **264b**, and glycosylation with glycosyl donor **263** (NIS/TESOTf, 90%) led to pentasaccharide **265a**. Glycosyl assembly to hexasaccharide **267**, included the glycosylation of pentenyl donor **266** with acceptor **265b** (NIS/TESOTf, 69%), obtained by NaOMe treatment of **265a**. The final stages of the synthesis included CAN-mediated deprotection of the *p*-methoxyphenyl groups, Dess–Martin oxidation and esterification.



Scheme 40
Synthesis of oligogalacturonates

2.11.7 Miscellaneous

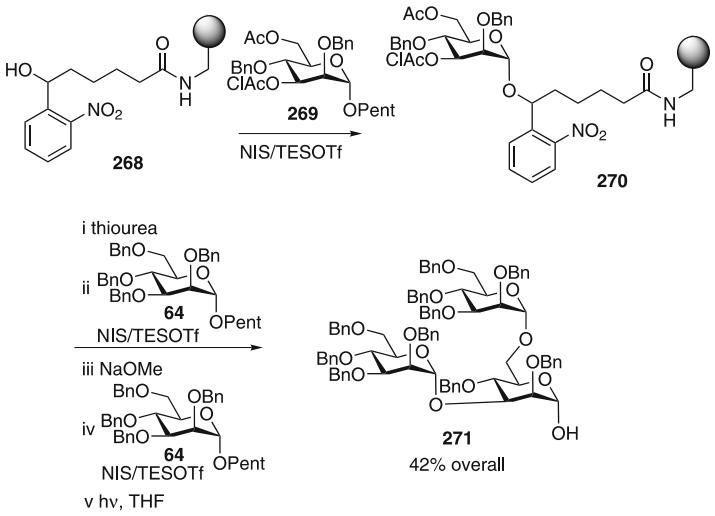
Arasappan and Fraser-Reid reported an NPG-based methodology for the stereoselective construction of the tetrasaccharyl cap portion of Leishmania Lipophosphoglycan [135].
Kuzuhara and co-workers have reported the use of a NPG disaccharidic synthon as the chain elongating unit in the synthesis of amphiphilic chitopentaose and chitoheptaose derivatives [136].
Toshida and co-workers have described the synthesis of a set of di- and tri-sulfated galabioses by using an *n*-pentenyl galactoside donor and IDCP as the catalyst [137].

2.12 NPGs in Solid-Phase Oligosaccharide Synthesis

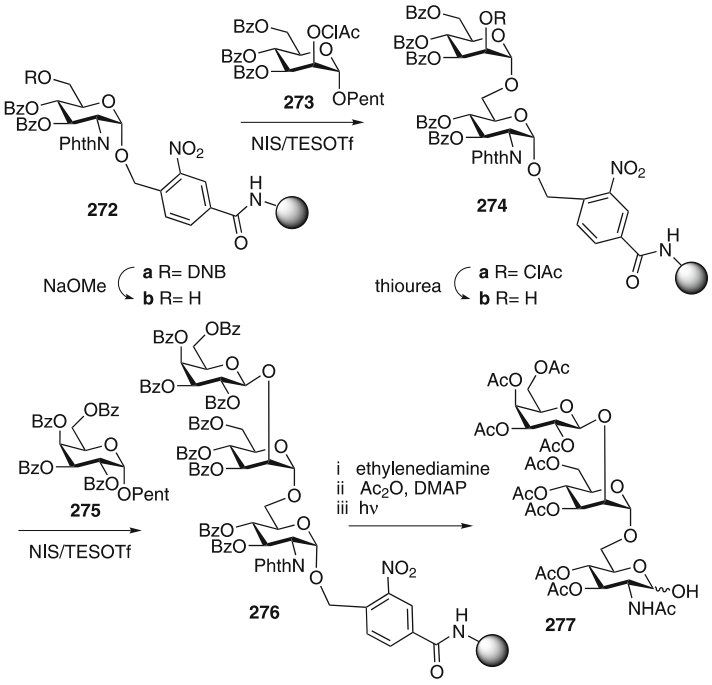
Solid-phase oligosaccharide synthesis has received considerable attention in the last years [138]. Some of the approaches that involve NPGs are discussed below.

2.12.1 Glycosylation of Supported Alcohol Acceptors with NPG Donors

Fraser-Reid and co-workers designed a photolabile *o*-nitrobenzylic linker **268**, which was used in the synthesis of a branched trimannan oligosaccharide **271** (*Scheme 41*) [139]. Differentially protected NPG **269** was coupled to the resin via linker **268**. Selective removal of the C6 chloroacetyl and C3 acetyl groups, followed each by mannosylation (NIS/TESOTf) with NPG **64**, afforded trimannan **271**, in 42% overall yield after photolytic cleavage.
In a related approach, Fraser-Reid and co-workers used Chiron's polystyrene-grafted "crowns" with Rich's photocleavable o-nitrobenzyl linker [140] and NPG donors in the synthesis of trisaccharide **277** (*Scheme 42*) [141]. After attachment of the first aminoglucosyl moiety to



Scheme 41
NPGs in solid-phase oligosaccharide synthesis

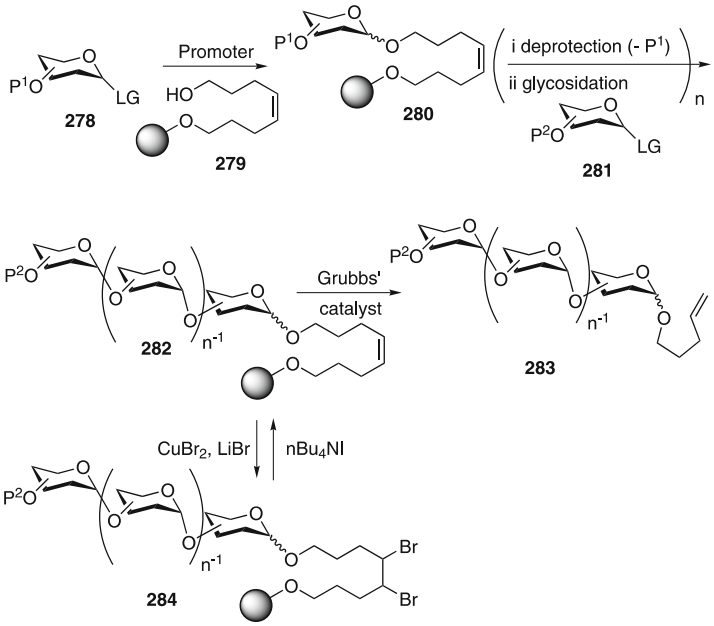


Scheme 42
NPGs in solid-phase oligosaccharide synthesis

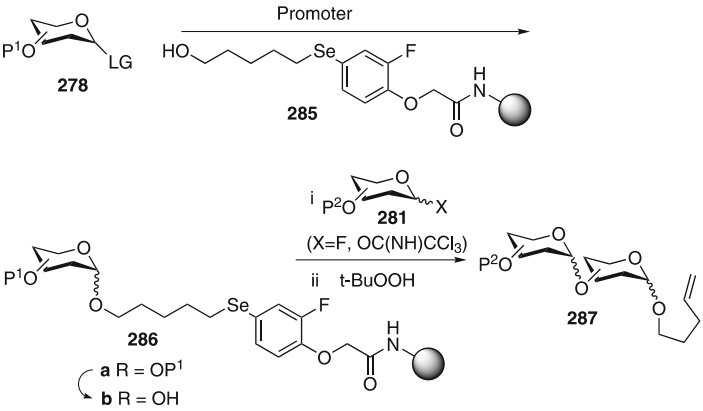
the linker, via its corresponding NPG, the C6 dinitrobenzoyl (DNB) group was removed to give **272b**. Coupling with mannose donor **273**, deprotection of the *O*2 chloroacetyl group, and galactosylation with NPG **275** furnished trisaccharide **276**. Global deprotection followed by peracetylation and photolytic cleavage from the solid support provided trisaccharide **277**.

2.12.2 Pentenyl Glycoside-Based Linkers

Seeberger and co-workers developed a new linker concept in solid-phase oligosaccharide synthesis. They designed a new NPG-based linker that upon deprotection rendered an oligosaccharide NPG suitable for further glycosylations in fragment couplings (*Scheme 43*) [142]. The first carbohydrate moiety (e. g. **278**) was connected via a glycosidic bond to octenediol-functionalized Merrifield's resin, **279**. Resins with loadings of up to 0.65 mmol/g were obtained and employed in oligosaccharide synthesis. Glycosylation events can now take place in deprotected saccharide **280** to yield oligosaccharide **282**. The octenediol linker was then cleaved by olefin cross metathesis using Grubbs' catalyst under an atmosphere of ethylene to afford fully protected oligosaccharides in the form of NPGs, e. g. **283**. A further refinement of this strategy is that it can be made compatible with glycosyl donors that require electrophiles as activators by sidetracking the linker to the corresponding dibromooctane derivative (e. g. **284**) [143]. Seeberger and co-workers have illustrated the potency of this strategy with several oligosaccharide syntheses [144,145,146,147].



Scheme 43
Seeberger's NPG-based linkers for oligosaccharide synthesis



Scheme 44
A fluorinated selenide linker for solid-phase synthesis of NPGs

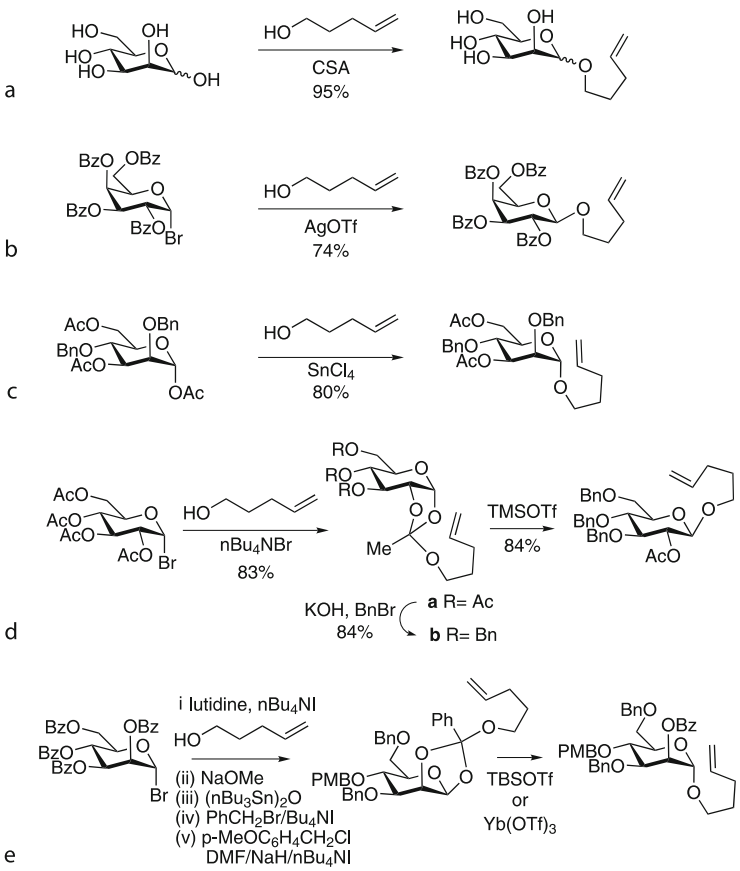
Mogemark et al. described a fluorinated selenide linker **285**, for solid-phase synthesis of NPGs (*Scheme 44*) [148]. The resin-bound linker could be glycosylated both with trichloroacetimidates and glycosyl fluorides to give anchored saccharides, e. g. **286**, that can be submitted to glycosylation once deprotected. After oxidation to a selenoxide with t-BuOOH the linker undergoes β-elimination upon heating, and releases the NPG **287**, in excellent yield.

2.13 Miscellaneous Uses of NPGs

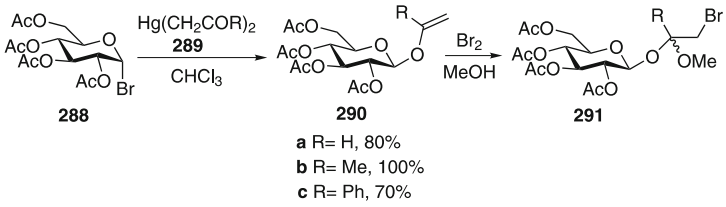
The versatility of NPGs has been further enhanced by chemical modifications of the pent-4-enyl moiety itself. In this context, the pentenyl moiety has been transformed in many spacer functionalities [149,150], used as a handle to incorporate amino-acid moieties [151,152,153,154], used as a monomer in copolymerization strategies [155,156,157], used in the formation of dendrimers [158], and converted to dimeric and trimeric structures for multivalent presentations [159,160]. These applications fall beyond the scope of this chapter.

2.14 Preparation of NPGs

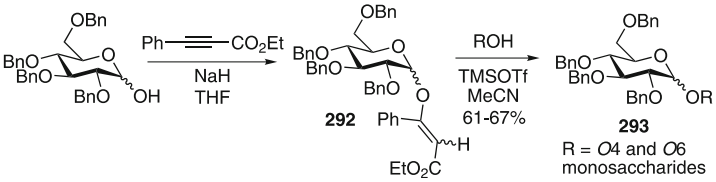
NPGs, being normal *O*-glycosides, can be readily obtained by application of the standard procedures for preparing such derivatives [12]. They can be obtained by Fischer glycosida-



Scheme 45
Methods for the preparation of NPGs



Scheme 46
Synthesis of 1′-substituted vinyl glucosides



Scheme 47
Synthesis of 1′-substituted vinyl glycosides

tion (*Scheme 45a*) [82,161,162]. An obvious advantage of this procedure is that the *n*-pentenyl group can be installed right at the outset of the synthesis; however, the formation of α/β anomers might sometimes be a drawback. Use of the Koenigs–Knorr coupling [115] permits the stereocontrolled preparation of NPGs (*Scheme 45b*). $SnCl_4$ facilitates the formation of NPGs from acetyl mannosides (*Scheme 45c*) [117]. The most useful method for the preparation of NPGs is, arguably, the acid-catalyzed rearrangement of NPOEs, prepared under Lemieux–Morgan conditions (*Scheme 45d,e*) [163]. This method permits the stereoselective synthesis of NPGs with different protecting groups [50,164]. Rousseau and Martin described the rearrangement of acetyl NPOEs with TMSOTf (*Scheme 45d*) [99], and Fraser-Reid and co-workers have used TBSOTf [165] or ytterbium triflate [166] to rearrange benzoyl-substituted NPOEs (*Scheme 45e*).

3 Enol Ether-Type Glycosides

3.1 Early Contributions

De Raadt and Ferrier were the first to report the preparation and attempted glycosylation of 1′-substituted-vinyl glycosides [167]. Reaction of tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**288**) with bis(acetonyl)mercury derivatives **289a–c** in refluxing chloroform afforded vinyl-, isopropenyl-, and styryl-β-D-glucosides **290a–c** in excellent yields (*Scheme 46*). However, when **290a–c** were each treated with either NBS or bromine/$AgClO_4$ in the presence of methanol no glycosides were formed, the products in each case being mixed stereoisomers of the glycosyl acetals **291a–c**.

Schmidt and co-workers described the preparation of vinyl glucosides **292** from the reaction of tetra-*O*-benzyl glucose with ethyl phenyl propiolate under the agency of sodium hydride

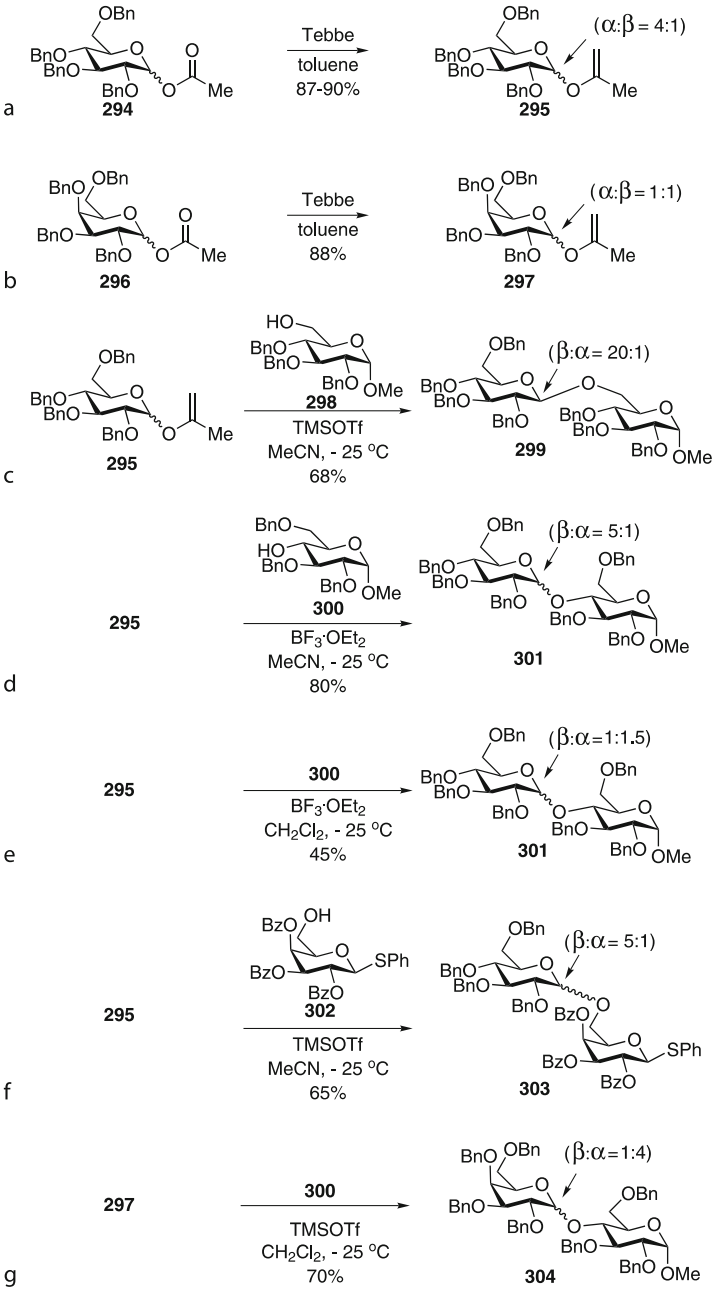
(Scheme 47) [168]. The reaction of **292**, as an anomeric mixture, with various acceptors was examined in acetonitrile at −40 °C in the presence of TMSOTf as catalyst. Reaction of **2** with 6-OH and 4-OH methyl glucosides as acceptors gave the corresponding disaccharides in 61 and 67% yield and as 85:15 and 75:25 β/α mixtures, respectively. Similar results were obtained for tetra-*O*-benzyl galactose.

3.2 Isopropenyl Glycosides

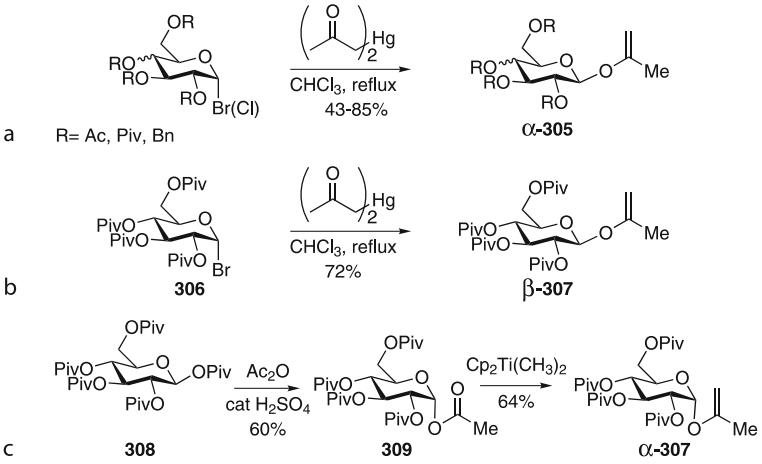
Sinaÿ and co-workers described the synthesis of isopropenyl glycosides [169] by reaction of the corresponding anomeric acetates with the Tebbe reagent [170]. Reaction of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**294**) with a solution of Tebbe reagent in toluene gave the isopropenyl glycosides **295**, in 87–90% yields (Scheme 48*a*). Likewise, isopropenyl galactoside **297** ($\alpha:\beta \approx 1:1$) was prepared from the corresponding acetate **296** by Tebbe methylenation in 88% yield (Scheme 48*b*). Treatment of **295** ($\alpha:\beta = 4:1$) in MeCN at −25 °C with the primary hydroxyl acceptor **298**, in the presence of TMSOTf gave the disaccharides **299** (68%) with an excellent β-selectivity (20:1) (Scheme 48*c*). The condensation of **295** with the secondary alcohol **300** in MeCN at −25 °C in the presence of $BF_3{\cdot}Et_2O$ afforded the disaccharide **301** in good yield, albeit with reduced stereoselectivity ($\beta:\alpha = 5:1$) (Scheme 48*d*). When the same glycosylation was carried out in CH_2Cl_2 instead of MeCN the disaccharide **301** was obtained in limited yield (Scheme 48*e*). The successful glycosylation of phenyl 1-thio-glycoside **302** with **295** in the presence of TMSOTf illustrates the usefulness of isopropenyl glycosides in the synthesis of thiophenyl disaccharides (e. g. **303**, Scheme 48*f*). The authors found no significant variations on yield or stereoselectivity by the use of either mainly α or mainly β isopropenyl derivatives. The best results for galactosylation were achieved in CH_2Cl_2 with TMSOTf as promoter (Scheme 48*g*).

Chenault and co-workers reported the use of *O*-isopropenyl glycosides bearing ester protecting groups [171,172]. These compounds are stable at room temperature and can be readily purified by column chromatography on silicagel, moreover their glycosylation would proceed to give β-glycosides via neighboring group participation. The reaction of bis(acetonyl)mercury [173] with glycopyranosyl halides proved to be a good method for the preparation of isopropenyl β-glycopyranosides (e. g. **305**, Scheme 49*a*). The authors described routes to *O*-isopropenyl 2,3,4,6-tetra-*O*-pivaloyl-α, and β-D-glucopyranosides **α-307** and **β-307**, respectively. Reaction of 2,3,4,6-tetra-*O*-pivaloyl-α-D-glucopyranosyl bromide (**306**) with diacetonyl mercury led to **β-307** (Scheme 49*b*), whereas regioselective methylidenation [174] of **309** (prepared stereoselectively by acid-catalyzed exchange of the anomeric pivaloyloxy group of penta-*O*-pivaloyl-β-D-glucopyranose, **308**) generated **α-307** as the only product (Scheme 49*c*). The β-isomer, however, exhibited greater shelf life than the latter.

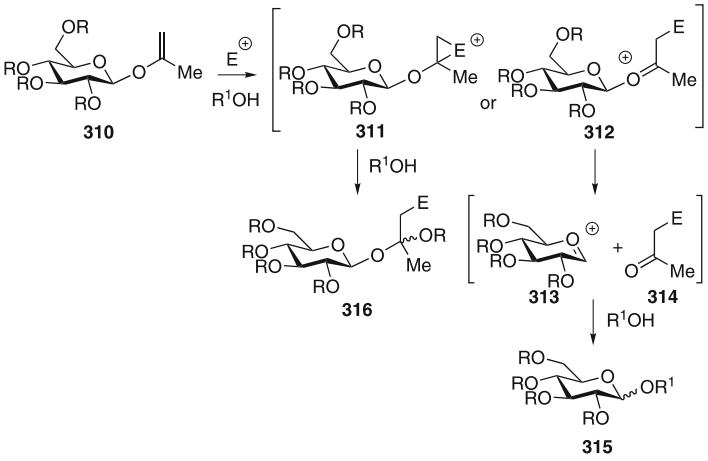
On the basis of the reaction of NPGs with electrophiles, Chenault et al. considered the possible activation of isopropenyl glycosides with electrophiles. The mechanism of activation was expected to involve initial capture of the electrophile (E^+) by the vinyl ether double bond of **310** leading to the formation of cation **311** or **312** (Scheme 50). Collapse of **311** or **312** to form glycosyl oxocarbenium ion **313** and acetone derivative **314** would be followed by nucleophilic attack on **313** to generate glycoside **315**. An alternative reaction would involve direct nucleophilic attack on **311** or **312** to generate the addition product **316**.



Scheme 48
Synthesis and glycosylation reactions of isopropenyl glycosides

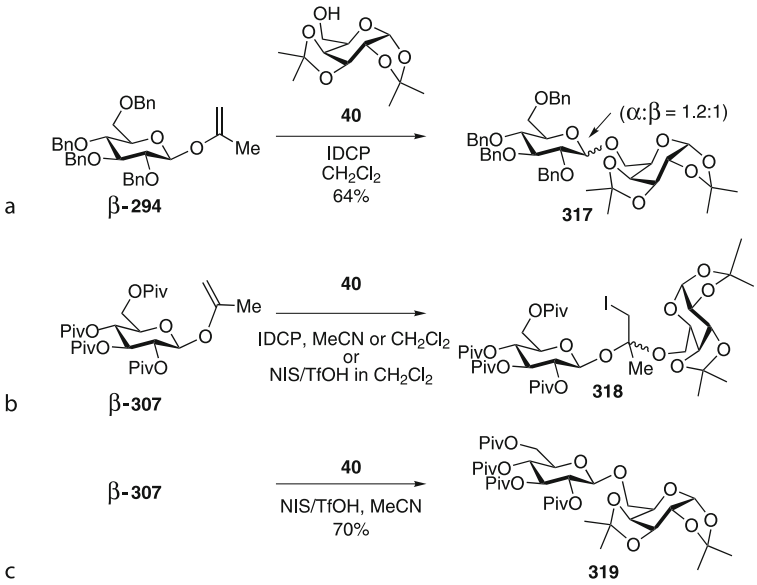


Scheme 49
Synthesis of pivaloyl isopropenyl glycosides



Scheme 50
Activation of isopropenyl glycopyranosides

The authors found that "armed" and "disarmed" isopropenyl glycosides displayed different behavior towards electrophiles (*Scheme 51*). Armed isopropenyl glycoside ***β*-294**, glycosylated acceptor **40** to give disaccharide **317** under the agency of IDCP, a relatively weak electrophile, in a nonpolar solvent (CH_2Cl_2) (*Scheme 51a*). On the other hand, disarmed glycoside ***β*-307**, led under the same conditions to the electrophilic addition product **318**. Use of a more potent electrophile (NIS/TfOH) in CH_2Cl_2 also resulted in the formation of the addition product **318** (*Scheme 51b*). However, NIS/TfOH in more polar MeCN successfully promoted the glycosidic coupling (*Scheme 51c*). Apparently, the relatively electron-releasing ethereal protecting groups lower the energy barrier to oxocarbenium ion formation from



Scheme 51
Reaction of armed and disarmed isopropenyl glycopyranosides

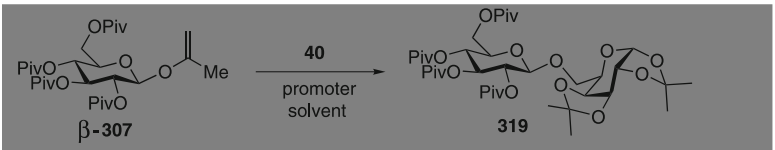
armed ***β*-294** relative to that from disarmed glycoside ***β*-307**. In general, factors which favor the formation of the glycosyl oxocarbenium ion (strong electrophile, polar solvent, electron-releasing protecting groups on the glycosyl donor) lead to transglycosylation. Factors which retard the formation of the glycosyl cation (weak electrophile, nonpolar solvent, electron-withdrawing protecting groups on the glycosyl donor) lead to addition across the isopropenyl ether double bond.

The ability of various electrophiles to promote transglycosylation of disarmed isopropenyl glycosides is outlined in *Table 10*. NIS/TfOH, TMSOTf, and Tf_2O in MeCN, all led to the formation of disaccharide **319** in good yield (*Table 10*, entries i–iii). Reactions were carried out at 0 °C and were complete within 2–5 min. With silver triflate (AgOTf) the reaction was slower and gave a lower yield of disaccharide **319** (*Table 10*, entry iv). When TfOH, NIS, or NBS were used alone ***β*-307** failed to react and the glycosyl donor was recovered unchanged (*Table 10*, entries vi, viii). Thus, neither NIS/TfOH, TMSOTf, Tf_2O, nor AgOTf seem to activate isopropenyl glycosides by acting as a source of TfOH. Dimethyl(methylthio)-sulfonium triflate (DMTST) was the only promoter that led exclusively to the formation of disaccharide **319** from ***β*-307** when CH_2Cl_2 was used as the solvent.

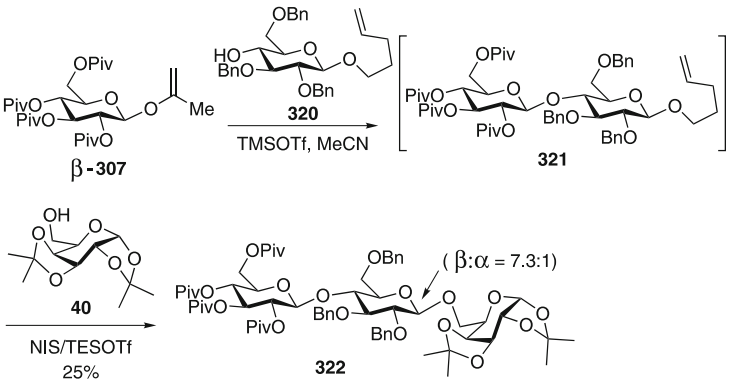
In terms of glycosyl donors, either ***α*-307** or ***β*-307** gave the same results in terms of yields. Likewise, isopropenyl galactopyranosides reacted in a similar manner to glucopyranosides. Acylated isopropenyl donors gave lower yields than pivaloyl analogs, presumably because of complications due to orthoester formation [175].

Isopropenyl glycosides could be activated selectively in the presence of armed NPGs, and that allowed a one-pot synthesis of trisaccharide **322** involving the successive glycosyl coupling of a vinyl glycoside ***β*-307**, and an NPG, **321** (*Scheme 52*).

Table 10
Evaluation of promoters for transglycosylation of β-307



Entry	Promoter	Solvent	Yield
i	NIS/TfOH	MeCN	70%
ii	TMSOTf	MeCN	69%
iii	Tf_2O	MeCN	65%
iv	silver triflate	MeCN	24% (24h)
v	DMTST	CH_2Cl_2	48%
vi	TfOH	MeCN	no reaction
vii	trimethylsilyl iodide	MeCN	no reaction
viii	NIS or NBS	MeCN	no reaction



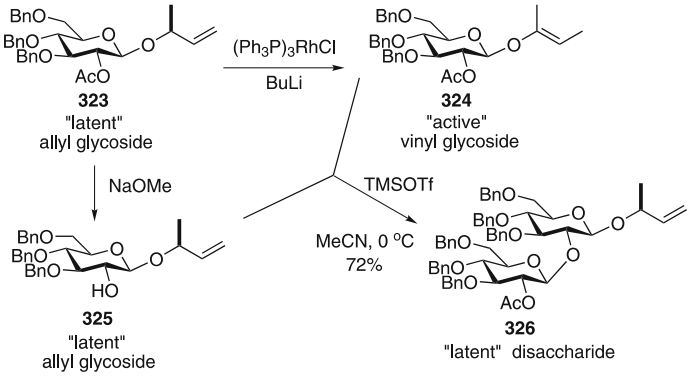
Scheme 52
One-pot synthesis of trisaccharide 322

3.3 3-Butene-2-yl Glycosides as Precursors for Vinyl Glycosides

Boons and co-workers introduced stable allyl glycosides (e. g. **323**, *Scheme 53*), which are converted to the enol ether-type glycosides **324**, prior to glycosylation [176].

3.3.1 Latent-Active Glycosylation Strategy

The allyl glycoside **323**, can be considered a "latent" [177] form of a glycosyl donor which can be efficiently isomerized to the "active" vinyl glycoside, **324**. The isomerization reaction was performed by a rhodium catalyst obtained by treating the Wilkinson's catalyst, $(Ph_3)P_3RhCl$,

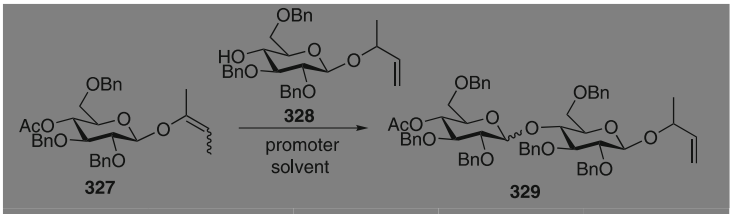


Scheme 53
Vinyl glycoside-based latent-active strategy for glycosyl coupling

with BuLi [178]. Base labile functionalities in the molecule are compatible with these isomerization conditions [179]. The "active" vinyl glycoside **324**, undergoes Lewis acid-catalyzed glycosylation reactions with "latent" allyl glycoside **325**, to give "latent" disaccharide **326** (*Scheme 53*). Unlike isopropenyl glycosides, which require stoichiometric amounts of Lewis acids for activation [169], the reaction of Boons' vinyl glycosides only demands catalytic amounts of TMSOTf. The higher reactivity of the substituted vinyl glycoside was ascribed to the additional methyl substituent of the vinyl moiety that makes the double bond more electron rich. Although racemic 3-buten-2-ol could be used for the preparation of **323** without affecting its reactivity, the use of diastereomeric allyl glycosides can be avoided with the use of optically pure 3-buten-2-ol, easily obtainable in multigram amounts.

The use of neighboring participating groups permits the formation of 1,2-*trans* glycosides (e. g. **326**, *Scheme 53*). The choice of solvent and, to some extent, the choice of activator, was used to control the α/β ratio in glycosyl donors without participating groups at *O*2. TMSOTf-

Table 11
Effect of the solvent and promotor in α/β selectivity

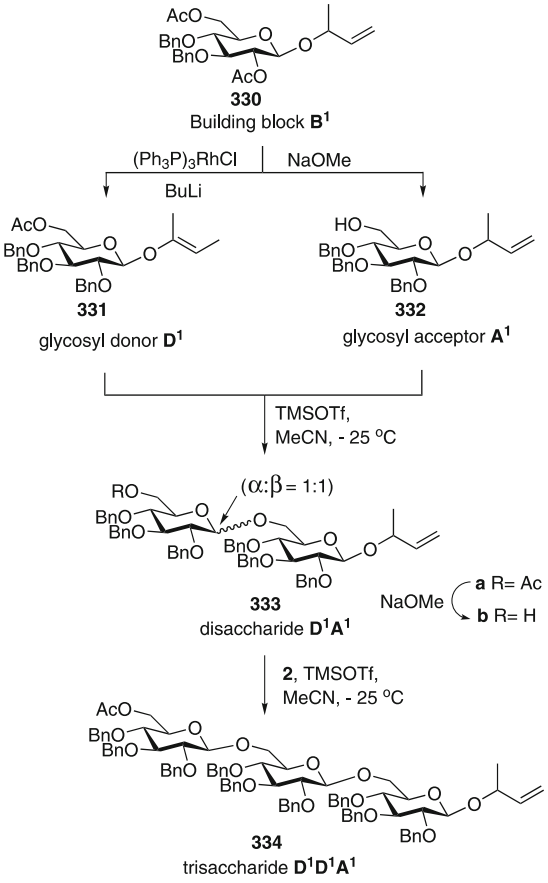


Entry	Promoter	Solvent	α/β ratio	Yield
i	TMSOTf	MeCN	1:8	78%
ii	TMSOTf	CH_2Cl_2	1.5:1	69%
iii	$BF_3{\cdot}OEt_2$	Et_2O	1.5:1	69%
iv	NIS/TfOH	Et_2O/dichloroeth	3:1	73%

promoted condensation of **327** with **328** in MeCN gave disaccharide **329** as the β-anomer mainly (α/β = 1:8) (*Table 11*, entry i). An improved α-selectivity was obtained (73%, α/β = 3:1) when the coupling was performed in ether/dichloroethane (*Table 11*, entry iv).

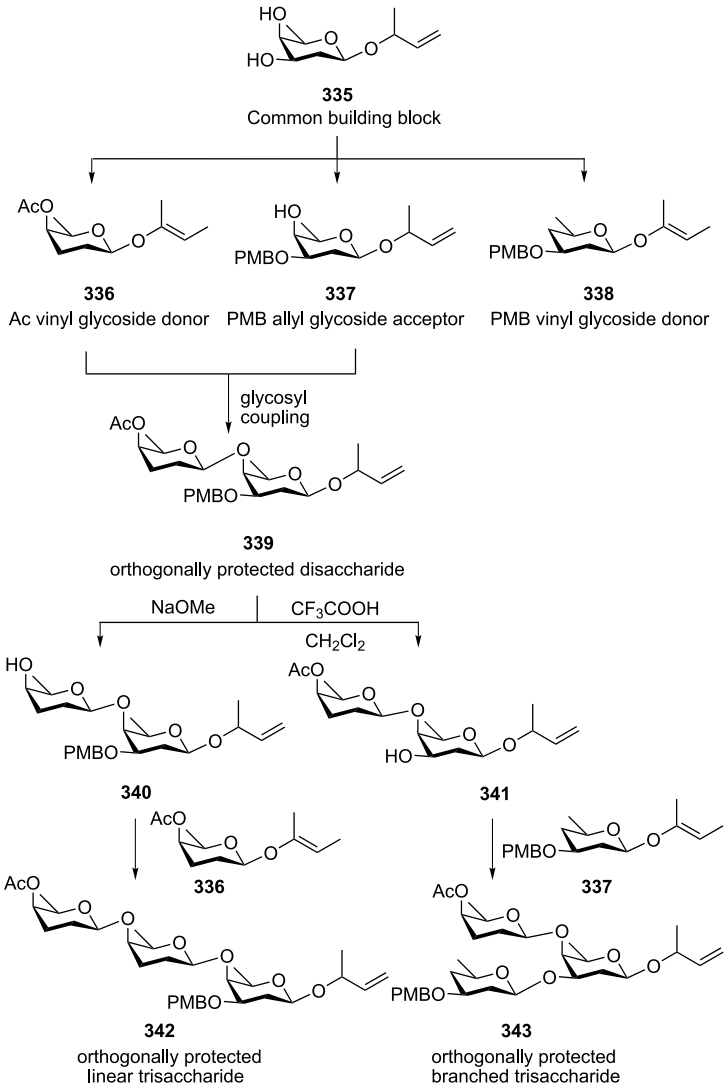
3.3.2 Preparation of Trisaccharide Libraries

Linear Trisaccharide Libraries Boons et al. described an approach to combinatorial synthesis of trisaccharide libraries based on their latent-active glycosylation strategy [180]. One major building block, **330** (i. e. $\mathbf{B}^1$, *Scheme 54*) can be converted into a glycosyl donor **331** (i. e. $\mathbf{D}^1$) and a glycosyl acceptor **332** (i. e. $\mathbf{A}^1$). Coupling of compounds **331** and **332** gives disaccharide **333a** in excellent yield (the anomeric ratio can be greatly influenced by changes in the temperature: α/β = 1:20 at low temperature; α/β = 1:1 at ambient temperature). The latter can be converted into a glycosyl acceptor **333b** (i. e. $\mathbf{D}^1\mathbf{A}^1$) by removing the acetyl protecting



Scheme 54
Preparation of linear trisaccharide libraries

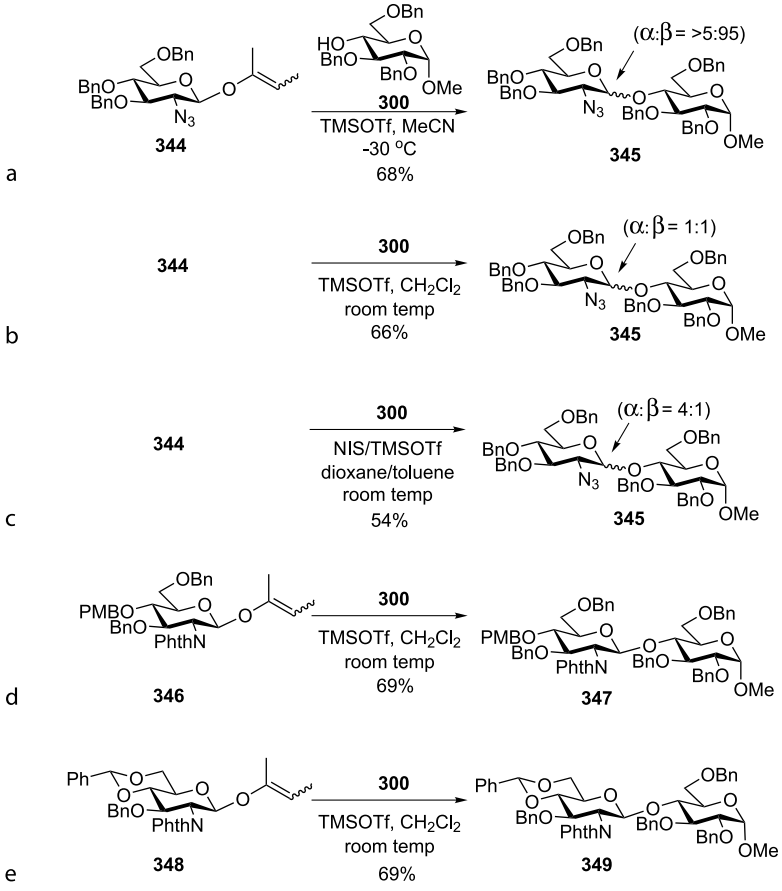
group and into a glycosyl donor by isomerizing the allyl moiety. These compounds can be used in oligosaccharide synthesis, as outlined in *Scheme 54*, for example by coupling **333b** with **332** to give trisaccharide **334** (i. e. $\mathbf{D}^1\mathbf{D}^1\mathbf{A}^1$). Application of this strategy to four allyl building blocks ($\mathbf{B}^{1\rightarrow4}$) would lead to four vinyl glycosyl donors ($\mathbf{D}^{1\rightarrow4}$) and four allyl glycosyl acceptors ($\mathbf{A}^{1\rightarrow4}$). Individual glycosylations of each donor with each acceptor will furnish 16 disaccharides ($\mathbf{D}^{1\rightarrow4}\mathbf{A}^{1\rightarrow4}$) (if glycosylations are stereoselective, or 32 disaccharides if conditions are met for 1:1 anomeric selectivity). Next, the disaccharides can be mixed, and removal



Scheme 55
Preparation of branched trisaccharide libraries

of the acetyl groups will give an assortment of acceptors. The pool of compounds can be split, and in combinatorial steps each pool of glycosyl acceptors can be coupled with a particular glycosyl donor ($\mathbf{D}^{1\rightarrow4}$) resulting in four libraries of 32 (or 64, as above) trisaccharides each.

Branched Trisaccharide Libraries Biologically important oligosaccharides often contain more complex features such as branching points and further functional groups. In this context, Boons and co-workers, using the latent-active strategy, designed a synthetic method to create orthogonally protected saccharides (acetyl and p-methoxybenzyl groups were used as orthogonal protecting groups) that could be easily further derivatized [181]. Thus, a common allyl glycoside building block (e. g. **335**, ❯ *Scheme 55*) can be converted to two vinyl glycoside donors bearing orthogonal protecting groups (e. g. **336** and **338**), and to an allyl glycosyl acceptor **337**, bearing one free hydroxyl and one selectively removable PMB ether. The latter will be coupled with donor **336** bearing an acetyl protecting group to give an orthogonally



Scheme 56
3-Buten-2-yl derivatives for the synthesis of amino sugar containing disaccharides

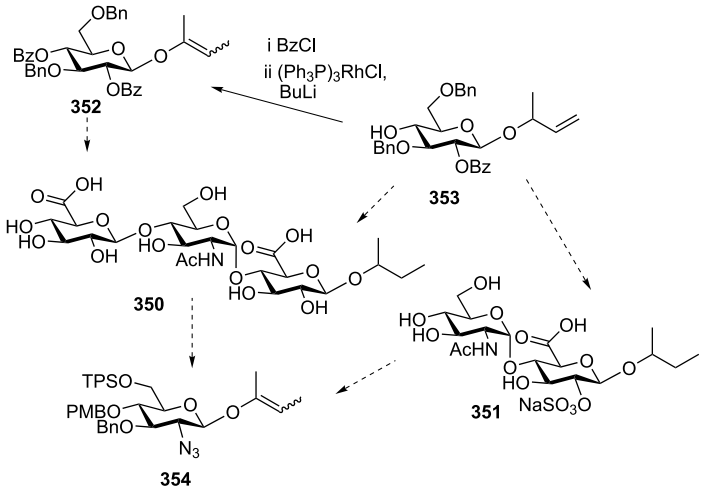
protected disaccharide, **339**. Compound **339** can be elaborated into linear or branched trisaccharides **342** and **343**. Thus, deprotection of the acetyl group in **339**, and glycosylation with vinyl donor **336** will yield linear trisaccharide **342**, whereas removal of the PMB group and coupling with **337** will produce orthogonally protected branched trisaccharide **343**.

3.3.3 3-Buten-2-yl 2-amino-2-deoxy Glycosides as Glycosyl Donors

Boons and co-workers studied the use of 3-buten-2-yl 2-azido-2-deoxy, and 2-deoxy-2-phthalimido glycosides, as building blocks for the preparation of sugar containing oligosaccharides [182]. Vinyl glycoside donors **344**, **346**, and **348**, were uneventfully prepared by isomerization of the corresponding 3-buten-2-yl glycosides with $(Ph_3)P_3RhCl/BuLi$ in yields exceeding 90%. Several glycosyl acceptors were used in the study, although representative data in ❯ *Scheme 56* refer solely to acceptor **300**. The glycosylation with azido donor **344**, in MeCN using TMSOTf as the promoter at −30 °C, proceeded with high β-selectivity (❯ *Scheme 56a*), whereas NIS/TMSOTf in a dioxane/toluene mixture gave good α-selectivities (❯ *Scheme 56c*). 2-Buten-2-yl 2-deoxy-2-phthalimido glycosides **346** and **348** reacted in CH_2Cl_2 in the presence of a catalytic amount of TMSOTf to give only the β-linked disaccharides **347** and **349**, respectively.

3.3.4 An Approach for Heparin Synthesis Based on 3-Buten-2-yl Glycosides

Haller and Boons described an approach fully based on 3-buten-2-yl glycosides for the synthesis of trisaccharide **350** and sulfated disaccharide **351** (❯ *Scheme 57*) [183]. In their strategy the glucuronic acid moieties were introduced at a late stage of the synthetic sequence by selective oxidation of primary hydroxyl groups with TEMPO and NaOCl. “Latent” allyl glycoside **353** functioned as an acceptor for the reducing end in compounds **350** and **351**, and was also transformed to “active” vinyl glycoside **352**, for the nonreducing unit of **350**. The 2-aceta-



Scheme 57
3-Buten-2-yl derivatives for the synthesis of amino sugar containing oligosaccharides

mido-2-deoxy unit in **350**, was retrosynthetically correlated with 2-azido-2-deoxy glycosyl donor **354**.

3.3.5 Conversion of 2-Buten-2-yl Glycosides to Other Glycosyl Donors

Treatment of "active" vinyl glycosides with NIS/TMSOTf in CH_2Cl_2 in the presence of dibenzyl phosphate gives good yield of glycosyl phosphates [184].
2-Buten-2-yl glycosides can also be transformed to glycosyl fluorides and trichloroacetimidates by hydrolysis to the corresponding hemiacetal (HgO, $HgBr_2$, aq. acetone) followed by standard treatment (CCl_3CN, DBU, CH_2Cl_2 or DAST, THF, respectively) [183].

3.3.6 Synthesis of 3-Buten-2-yl Glycosides

Being normal alkyl glycopyranosides, 3-buten-2-yl glycosides can be prepared by standard glycosylation methods, as previously mentioned for NPGs.

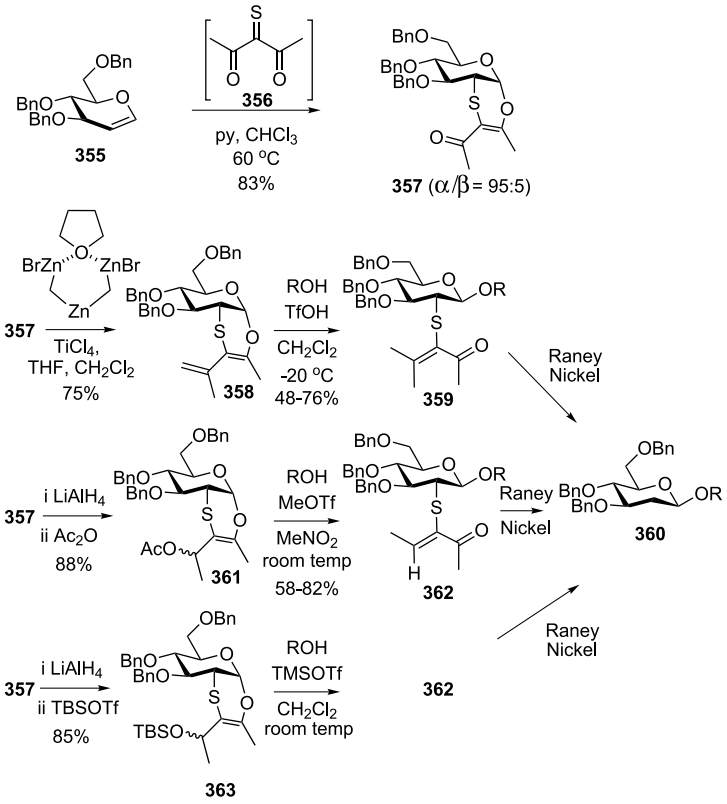
3.4 Oxathiines: Vinyl Glycosyl Donors for the Synthesis of 2-Deoxy Glycosides

Cycloadduct **357**, readily available by cycloaddition of tri-*O*-benyzl glucal (**355**) with the electron-poor 3-thioxopentane-2,4-dione (**356**) [185] has been used by two research groups as precursor glycosyl for vinyl glycosyl donors **358**, **361**, and **363** (◉ *Scheme 58*). Franck and co-workers showed that glycoside **358**, prepared by methylenation of **357**, underwent β-selective glycosylation with a variety of glycosyl acceptors in the presence of TfOH to give glycosides **359**, in good yields [186]. Moreover, Raney nickel desulfurization of **359** granted access to 2-deoxy-glycosides **360** [187]. Capozzi and co-workers reported that acetyl [188], and silyl [189] derivatives **361** and **363**, also functioned as glycosyl donors in reactions catalyzed by MeOTf in nitromethane and TMSOTf in CH_2Cl_2, respectively. The timing in the quenching of the reactions is crucial for obtaining completely selective β-glycosylations, and prolonged reaction times led to α/β anomeric mixtures. The total β-stereoselectivity of the coupling was ascribed by Capozzi and co-workers to an S_N2 type reaction (**361**→**362**, ◉ *Scheme 59*) that induces β-stereospecific glycosylation [188]. The observed subsequent α/β–equilibration presumably proceeds through an oxonium intermediate **364** (◉ *Scheme 59*).

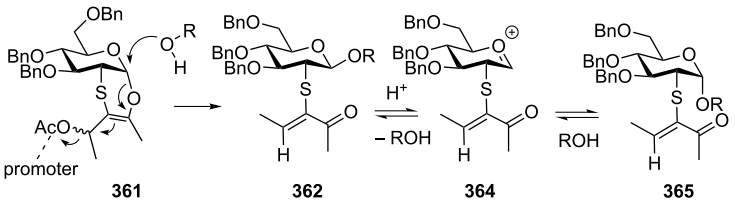
4 DISAL Glycosyl Donors

4.1 Synthesis and Glycosylation Reactions

Petersen and Jensen reasoned that glycosides of phenols (e. g. **366**) carrying sufficiently electron-withdrawing substituents could possibly serve as *O*-glycosyl donors under neutral or mildly basic conditions (◉ *Scheme 60*) [190,191]. Carbohydrate hemiacetals have been used as nucleophiles in aromatic substitutions using activated fluoroarenes [192,193]. Accordingly, glycosides of methyl 2-hydroxy-3,5-dinitrobenzoate (DISAL, a *DI*nitro*SAL*icylic acid derivative), e. g. **367** (◉ *Scheme 61*), and methyl 4-hydroxy-3,5-dinitrobenzoate (*para*-isomer)



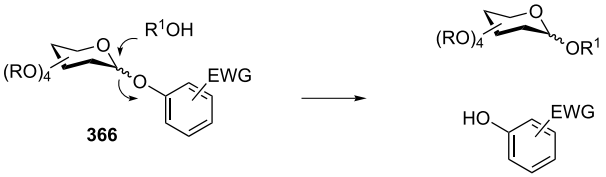
Scheme 58
Oxathiines: vinyl glycoside donors for the synthesis of 2-deoxy glycosides



Scheme 59
Stereocontrol in the formation of 2-deoxy glycosides from oxathiines

were prepared by reaction of carbohydrate hemiacetals with the corresponding activated fluoroarenes in the presence of a base. The use of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) gave an α/β ratio similar to the starting 1-OH, i. e. predominantly α. In contrast, the formation of β-DISAL donors was favored using 1,4-dimethylpiperazine as base. The fluoroarenes were prepared by nitration of 2-fluoro- or 4-fluoro-benzoic acid.

The preparation of disaccharides, from benzyl-protected DISAL donors (e. g. **367**, ◉ *Scheme 61*), was best carried out in 1-methylpyrrolidin-2-one (NMP), a high polar, aprotic solvent,



Scheme 60
Glycosides of phenols with electron-withdrawing substituents as glycosyl donors

at 40 °C, in the absence of Lewis acids (*Scheme 61a,b*). The fact that glycosylations also occurred in the presence of base (e. g. Et_3N, 2,6-lutidine) indicated that the glycosylations were not auto-catalytically promoted by the released phenol. Under these conditions, galactose derivative **40** was glycosylated with DISAL donor **367** (1.5 equiv.) to give disaccharide **368** in 90% yield (α/β = 2.4:1). Glycosylation of a secondary hydroxyl group with DISAL donor **367** required increasing the temperature to 60 °C, and resulted in the formation of disaccharide **370** as the α-glycoside in 74% yield (*Scheme 61b*). The *para*-glycosyl donor, (vide supra) also proved effective in analogous glycosylations.

Unlike benzyl-protected DISAL donors, benzoyl-protected donors, e. g. **371**, did not give the expected glycosides under these neutral conditions, in part due to trapping of intermediates as the orthoesters (*Scheme 61c*). Lewis acids, such as $BF_3{\cdot}Et_2O$ or TMSOTf, activated the acylated DISAL donor **367**, albeit diisopropylidene acceptors **40** and **369** were not stable in the reaction media [194]. More robust benzyl-protected acceptors were glycosylated with alkylated and acylated DISAL donors in the presence of $BF_3{\cdot}Et_2O$ to give disaccharides **372** and **373** in 82 and 46% yield, respectively (*Scheme 61d,e*). Interestingly, $LiClO_4$ was found to be an efficient additive for activation of DISAL donors in nonpolar solvents, giving significantly higher yields of disaccharides than $BF_3{\cdot}Et_2O$ (*Scheme 61f*). Acylated DISAL donor **371** did not give good yield of disaccharides when reacting with secondary hydroxyl acceptors (*Scheme 61g*). More recently, Jensen and co-workers have shown that high-temperature glycosylation of DISAL donors using precise microwave heating results in improved yield of disaccharides (*Scheme 61h*) [195].

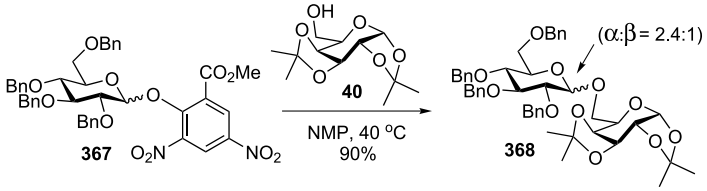
4.2 DISAL Donors in Solid-Phase Synthesis

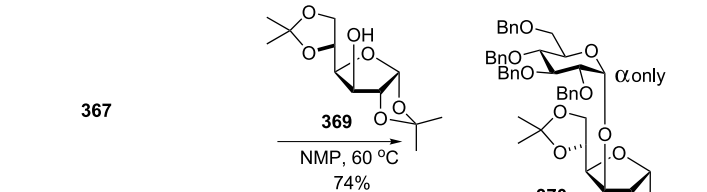
This approach was extended to solid-phase glycosylation of D-glucosamine derivatives anchored by the 2-amino group through a Backbone Amide Linker to a solid support [196].

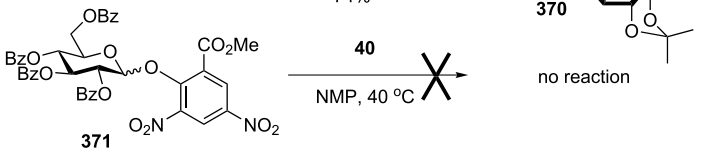
4.3 Intramolecular Glycosylation Approach to the Synthesis of 1,4-Linked Disaccharides

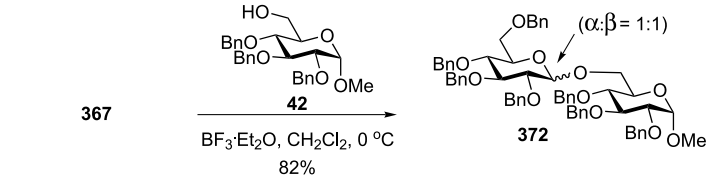
The DISAL donor concept was developed further to allow intramolecular glycosylations [197]. The glycosyl donor and acceptor were linked through the DISAL leaving group positioned to facilitate intramolecular glycosyl transfer to 4-OH by a 1,9-glycosyl shift (*Scheme 62a*).

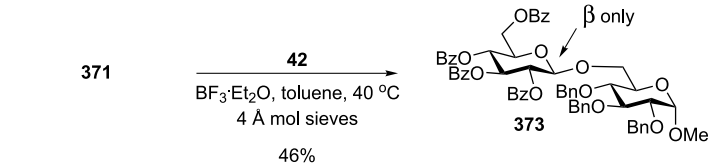
Scheme 61
Glycosylation with DISAL glycosyl donors

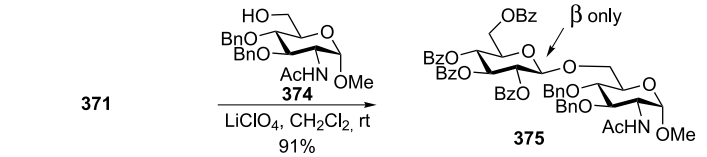
a

OBn
BnO
BnO
BnO
O
CO2Me
O2N
NO2
367
OH
40
NMP, 40 °C
90%
OBn
(α:β = 2.4:1)
368

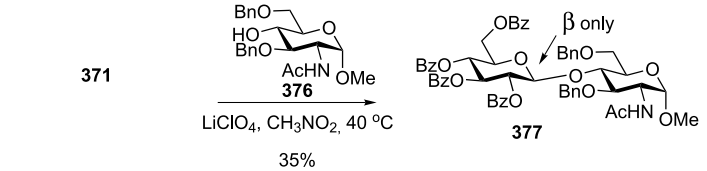
b

367
OH
369
NMP, 60 °C
74%
BnO
BnO
BnO
BnO
α only
370

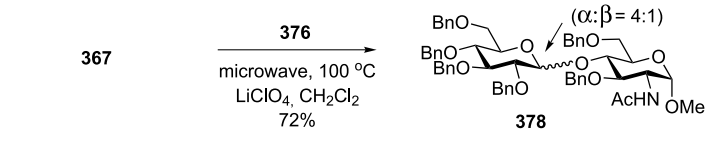
c

OBz
BzO
BzO
BzO
CO2Me
O2N
NO2
371
40
NMP, 40 °C
no reaction

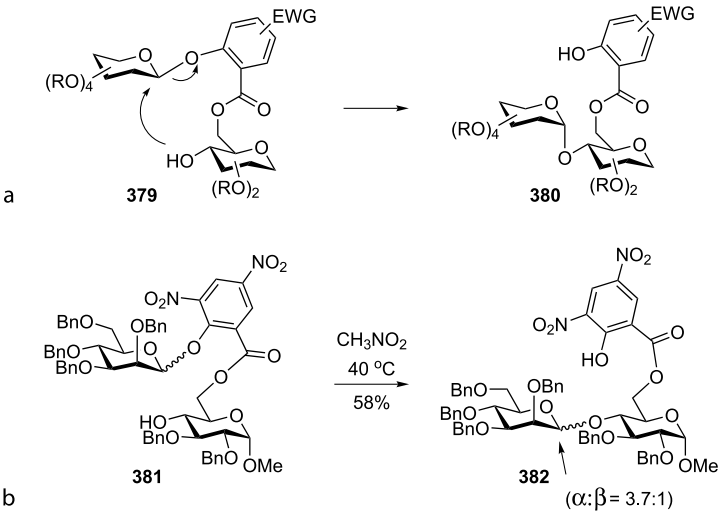
d

367
HO
BnO
BnO
BnO
OMe
42
BF3·Et2O, CH2Cl2, 0 °C
82%
OBn
(α:β = 1:1)
372

e

371
42
BF3·Et2O, toluene, 40 °C
4 Å mol sieves
46%
OBz
β only
373

f

371
HO
BnO
BnO
AcHN
OMe
374
LiClO4, CH2Cl2, rt
91%
OBz
β only
375

g

371
BnO
HO
BnO
AcHN
OMe
376
LiClO4, CH3NO2, 40 °C
35%
OBz
β only
377

h

367
376
microwave, 100 °C
LiClO4, CH2Cl2
72%
BnO
(α:β = 4:1)
AcHN
OMe
378



Scheme 62
DISAL-Based intramolecular glycosylation approach to 1,4-linked disaccharides

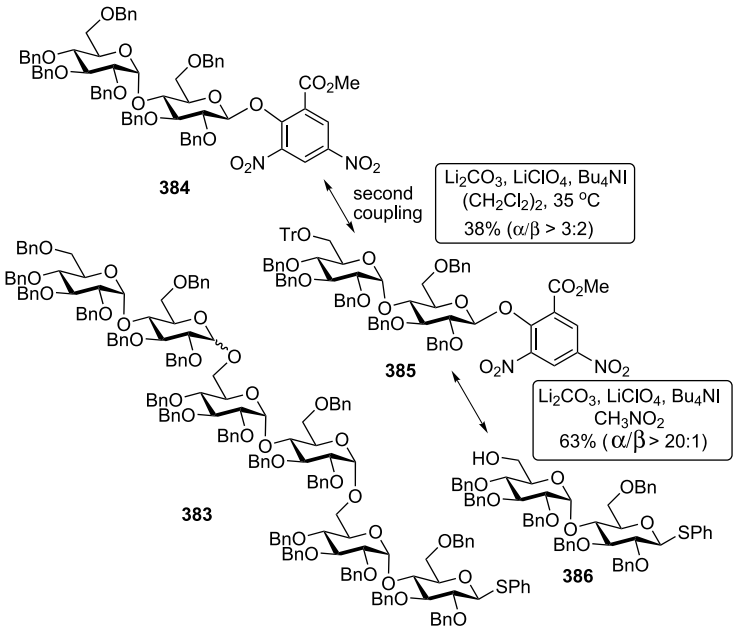
The tethered glycoside **381** underwent intramolecular transglycosylation to form the 1,4-linked mannoside **382** as an anomeric mixture (α/β = 3.7:1) in moderate yield (*Scheme 62b*).

4.4 Application of DISAL Donors to Oligosaccharide Synthesis

Jensen and co-workers reported the synthesis of hexasaccharide **383**, a starch-related hexasaccharide (*Scheme 63*) [198]. Their approach was based on the use of DISAL disaccharides **384** and **385**, readily obtained from the corresponding disaccharide hemiacetals, for sequential glycosylations. Glycosylation of phenyl 1-thio disaccharide **386** with DISAL donor **385** took place with good yield and excellent α-selectivity in CH_3NO_2 in the presence $LiClO_4$ and Li_2CO_3. The trityl group that have survived the coupling, was next removed and the ensuing tetrasaccharide glycosylated with DISAL donor **384** ($LiClO_4$, Li_2CO_3, $(CH_2Cl_2)_2$, 35 °C, 38% yield, α/β = 3:2).
DISAL donors have also been used in the preparation of phenazine natural products and analogs [199].

4.5 2-Deoxy-2-amino Derivatives as DISAL Donors

Jensen and co-workers evaluated the behavior of different glucosamine-derived DISAL donors in glycosylation reactions [200]. *N*-tetrachlorophthaloyl (TCP), *N*-trifluoroacetyl (TFAc), and *N*-trichloroethoxycarbonyl (Troc) DISAL donors **387**, **388**, and **389** and **390**, respectively, were prepared from the corresponding hemiacetals (*Fig. 6*). Glycosylation of cyclohexanol, in NMP at 60 °C, with these donors took place with yields ranging from 35 to 76%. The *N*-TCP protected donor **387**, was the least reactive. *N*-Troc protected donors **389** and **390**, gave the highest glycosylation yields with monosaccharides (63–71% yield), although they displayed



Scheme 63
Synthesis of hexasaccharide 383 based on DISAL donors

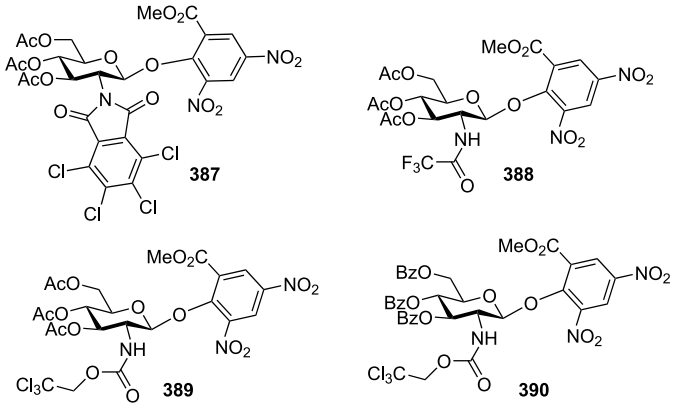
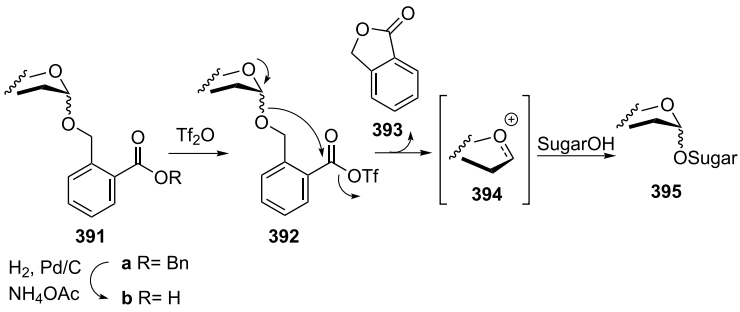


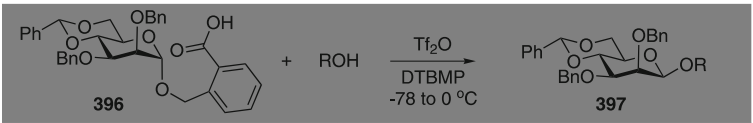
Figure 6
Glucosamine-derived DISAL donors

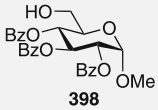
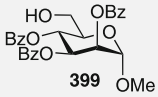
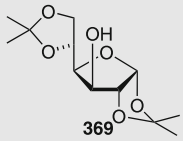
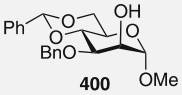
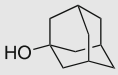
lower selectivities with primary hydroxyl acceptors (α/β ratio, from 1:1 to 1:7). A secondary hydroxyl acceptor was glycosylated with *N*-Troc DISAL donor **389** under microwave heating (130 °C, CH_3NO_2, $LiClO_4$) to give the corresponding disaccharide in 38% yield (β-anomer only). *N*-TFAc DISAL donor **388** gave even lower yields on coupling reactions with primary hydroxyl acceptors (35–45%) although β-disaccharides were obtained exclusively.



Scheme 64
2′-Carboxybenzyl (CB) glycosides

Table 12
***β*-Mannopyranosylation with 2′-carboxybenzyl glycosides**



Entry	Glycosyl acceptor (ROH)	Solvent	β/α ratio	Yield (%)
i	 **398**	CH_2Cl_2	β only	91
ii	389	toluene	20:1	95
iii	 **399**	CH_2Cl_2	β only	91
iv	 **369**	CH_2Cl_2	> 20:1	91
v	 **400**	CH_2Cl_2	17:1	96
vi	 **129**	CH_2Cl_2	> 20:1	90

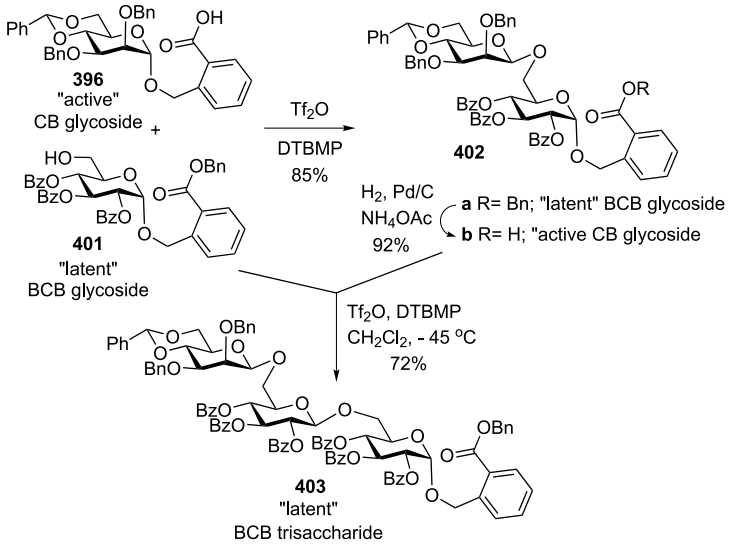
5 2′-Carboxybenzyl (CB) Glycosides

Kim and co-workers introduced a novel type of *O*-glycosyl donor, the 2′-carboxybenzyl (CB) glycoside **391b**, readily available by selective hydrogenolysis of the benzyl ester functionality

of 2-(benzyloxycarbonyl)benzyl (BCB) glycosides, **391a** [201,202,203]. Lactonization of the glycosyl triflate **392**, which was derived from the CB glycoside **391b**, is the driving force for the facile generation of the oxocarbenium ion **394** (◉ *Scheme 64*). Reaction of **394** with the glycosyl acceptor (Sugar–OH) would give the desired saccharide **395**. In the course of the transformation, a non-nucleophilic phthalide **393** is extruded. Treatment of CB glycosides with Tf_2O in the presence of di-tert-butylmethylpyridine (DTBMP) at −78 °C and subsequent addition of the glycosyl acceptor afforded the expected disaccharides in excellent yields.

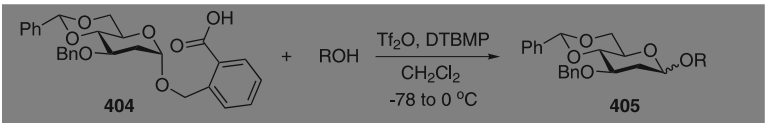
5.1 β-D-Mannosylation Employing 2′-Carboxybenzyl Glycosyl Donors

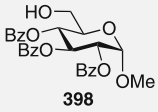
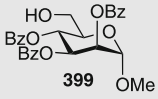
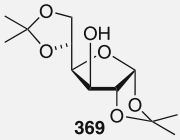
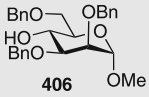
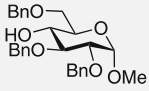
The stereospecific formation of β-mannopyranosyl linkages is a challenging task in oligosaccharide synthesis [204]. Crich and co-workers found that 4,6-*O*-benzylidene-protected glycosyl sulfoxides or thioglycosides are useful donors in the construction of β-mannopyranosyl linkages [205,206,207,208,209]. Kim and co-workers have shown that CB glycosides with a 4,6-benzylidene group can also be applied for stereoselective β-mannopyranosylation. Glycosylations of primary alcohol acceptors, **398** and **399**, in CH_2Cl_2 were completed in 1 h at −78 °C to afford only β-mannosides in high yields (◉ *Table 12* entries i, iii). Toluene was also found to be a good solvent (◉ *Table 12*, entry ii). This high β-selective mannosylation was also achieved with secondary alcohols, e. g. **369**, **400**, and with hindered tertiary alcohol **129** (◉ *Table 12*, entries iv–vi). Glucosyl CB donors possessing the 4,6-benzylidene group gave high yields of α-glucosides.



Scheme 65
2′-Carboxybenzyl glycoside-based "latent-active" strategy for glycosyl coupling

Table 13
***β*-Selective glycosylation of secondary hydroxyl acceptors**



Entry	Glycosyl acceptor (ROH)	α/β ratio	Yield (%)
i	 **398**	1:1	92
ii	 **399**	1:1.2	80
iii	 **369**	1:10	76
iv	 **406**	1:10	78
v	 **300**	*β* only	72

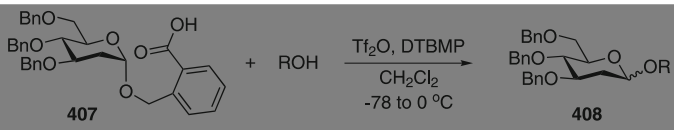
5.2 Latent-Active Glycosylation Strategy

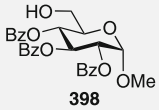
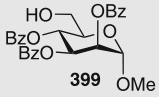
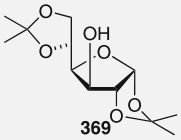
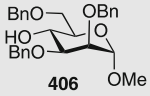
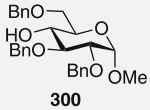
A remarkable feature of 2′-carboxybenzyl glycosides (e. g. **391b**, ➤ *Scheme 64*) is that they can be used as a latent-active pair, together with their synthetic precursors 2-(benzyloxycarbonyl)benzyl (BCB) glycosides (e. g. **391a**, ➤ *Scheme 64*). The successful mannosylation of "latent" BCB-glycoside **401** with "active" CB glycoside **396**, to give disaccharide **402a** indicated that a sequential glycosylation strategy for oligosaccharide synthesis would be possible (➤ *Scheme 65*). Thus, BCB disaccharide **402a** was readily converted into the active CB disaccharide **402b** by selective hydrogenolysis (92%, in the presence of benzyl and benzylidene groups), which upon treatment with Tf_2O/DTBMP glycosylated the latent BCB glycoside **401** to yield trisaccharide **403** in 72% yield.

5.3 Stereoselective Construction of 2-Deoxyglycosyl Linkages

Kim and co-workers have developed a highly *α*- and *β*- stereoselective (dual stereoselective) [210] method for the synthesis of 2-deoxyglycosides by employing CB 2-deoxyglycosides as glycosyl donors. Glycosylation of the 4,6-*O*-benzylidene-protected glycosyl donor

Table 14
α-Selective glycosylation of secondary hydroxyl acceptors



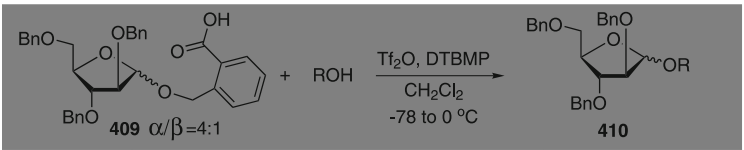
Entry	Glycosyl acceptor (ROH)	β/α ratio	Yield (%)
i	 **398**	1:1	98
ii	 **399**	1:1.2	93
iii	 **369**	α only	91
iv	 **406**	α only	91
v	 **300**	α only	88

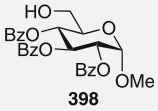
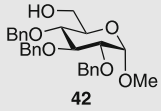
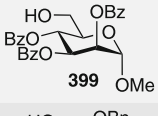
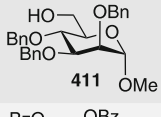
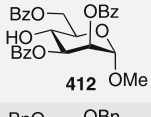
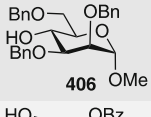
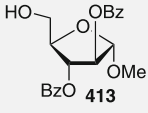
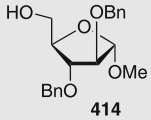
404 with secondary alcohols afforded predominantly β-glycosides (*Table 13*, entries iii–v). Complete reversal of the stereoselectivity, from β to α, was observed in the glycosylation of secondary alcohols with benzyl-protected glycosyl donor **406** (*Table 14*, entries iii–v). On the other hand, glycosylation of primary hydroxyl acceptors with both donors did not show appreciable stereoselectivity (*Table 13* and *Table 14*, entries i, ii). The authors suggested that the secondary hydroxyl acceptors formed β-disaccharides by S_N2-like displacement of an α-triflate favored in 4,6-*O*-benzylidene derivatives, as previously mentioned in the formation of β-mannosides of 4,6-*O*-benzylidene derivatives. No or poor β-selectivity in the reaction of **404** with primary alcohols was interpreted assuming that the more reactive primary alcohols reacted both with the α-triflate and an oxocarbenium ion.

5.4 2′-Carboxybenzyl Furanosyl Donors. Acceptor-Dependent Stereoselective β-D-Arabinofuranosylation

Kim and co-workers reported recently that CB tribenzyl-D-arabino furanoside **409** (easily available from methyl tribenzyl-D-arabinofuranoside) could be efficiently applied in stereos-

Table 15
β-Selective arabinofuranosylation of acyl-protected acceptors



Entry	Glycosyl acceptor (ROH)	β/α ratio	Yield β/α ratio (%)
i	 **398**	99:1	97
ii	 **42**	7:1	95
iii	 **399**	β only	95
iv	 **411**	4:1	95
v	 **412**	20:1	86
vi	 **406**	4:1	95
vii	 **413**	β only	92
viii	 **414**	2.2:1	95

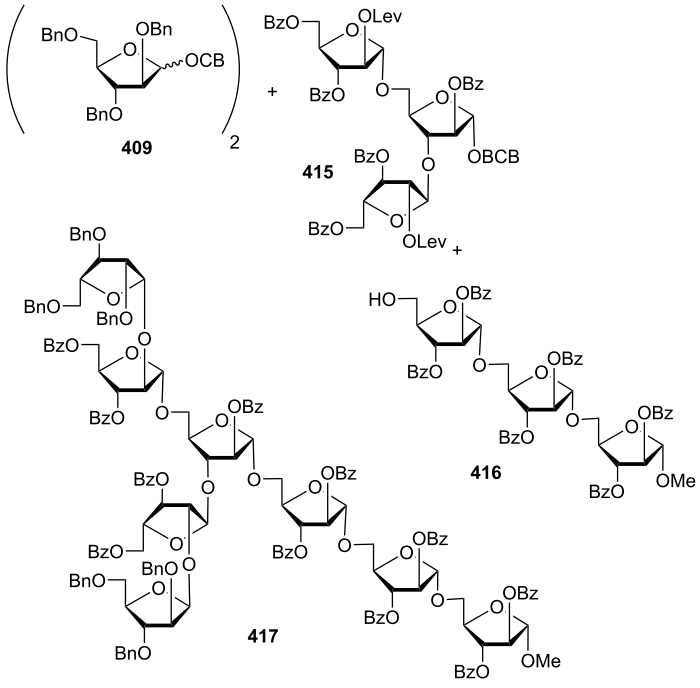
elective β-arabinofuranosylation processes [211]. They found that the presence of acyl-protective groups on the glycosyl acceptors was essential for attaining β-stereoselective glycosyl couplings. Thus, reaction of donor **409** with acceptor **398** having benzoyl-protective groups afforded a β-disaccharide almost exclusively (β/α = 99:1) in 97% yield (*Table 15*, entry i), while the same reaction with acceptor **42** having benzyl-protective groups gave a mixture of α- and β-disaccharides (β/α = 7:1) (*Table 15*, entry ii). Further examples in *Table 15*

clearly showed that the protective groups in the acceptors, regardless of pyranoses or furanoses and of primary alcohols or secondary alcohols, were the crucial factor for the outcome of the stereochemistry in glycosylations with **409**. This observed stereoselectivity was also donor dependent, since glycosylation with 2-benzyl-3,5-dibenzoyl CB arabinofuranoside was not as stereoselective [211].

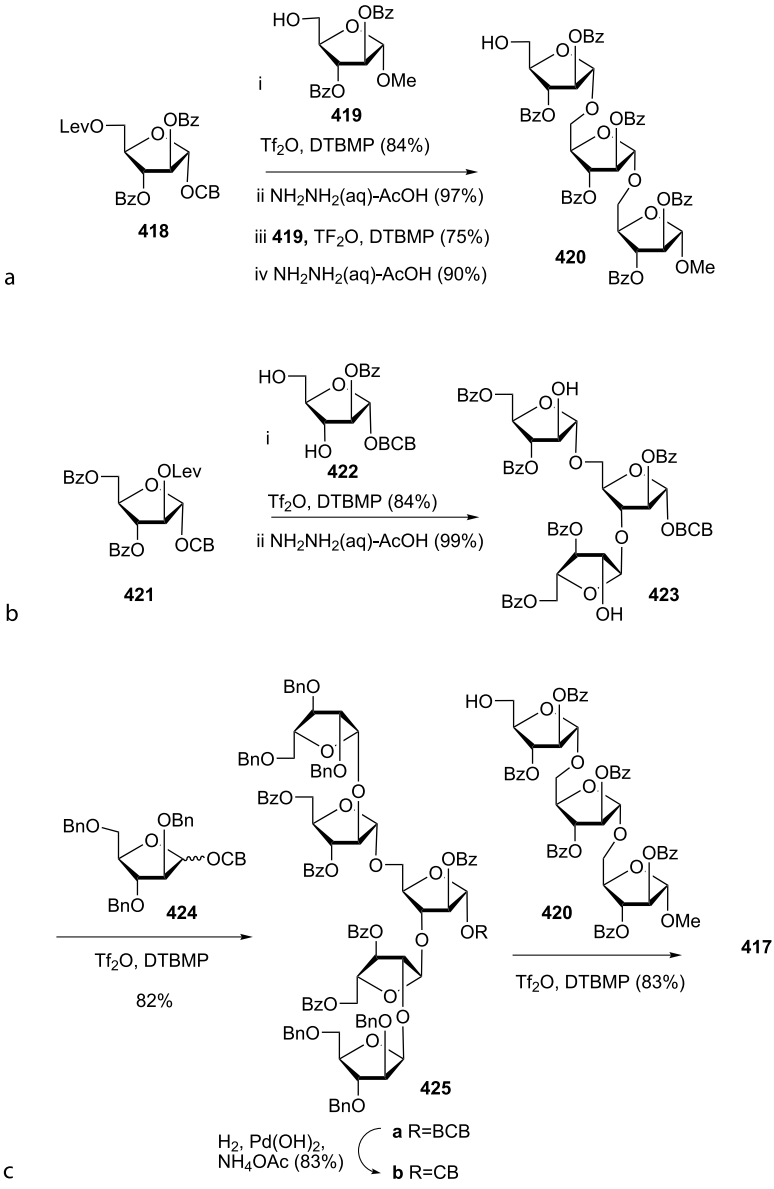
5.4.1 Synthesis of an Octaarabinofuranoside Based on Stereoselective β-D-Arabinofuranosylation

The authors applied this acceptor-dependent β-arabinofuranosylation method to the synthesis of octaarabinofuranoside **417**. Their retrosynthesis of compound **417** led to three components, a linear methyl trisaccharide **416**, a branched BCB trisaccharide **415**, and to CB furanosyl donor **409**. Levulinyl protective groups were chosen in fragments **415** and **416** for selective deprotection prior to furanosyl coupling (*Scheme 66*). Three arabinose building blocks were used in the assembly.

Arabinofuranosyl donor **418** glycosylated acceptor **419**, to yield after levulinyl-deprotection and repetitive glycosylation with **419**, the linear trisaccharide **420** (*Scheme 67a*). Coupling of latent BCB donor **422**, with active CB donor **421**, led after deprotection of the levulinyl groups to diol **423** (*Scheme 67b*). The crucial double β-arabinofuranosylation of diol **423**



Scheme 66
Retrosynthesis of octaarabinose 417. A component of lipoarabinomannan in mycobacterial cell wall

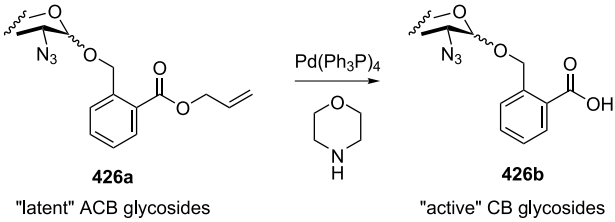


Scheme 67
Synthesis of octaarabinose 417

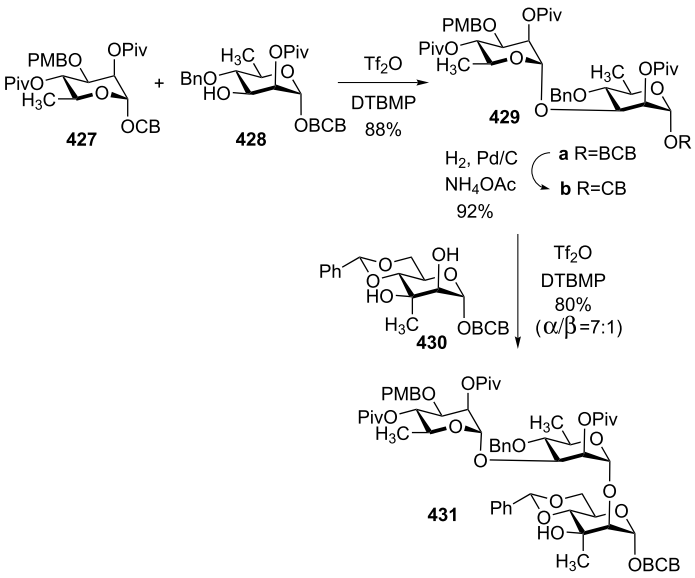
with 3.7 equiv. of the arabinofuranosyl donor **424**, paved the way to pentaarabinofuranoside **425a** (82% yield) with complete β-selectivity. The latent BCB arabinofuranoside **425a** was converted into the active CB arabinoside **425b**. Finally, coupling of the latter with triarabinofuranosyl acceptor **420**, afforded octaarabinofuranoside **417**, in 83% yield.

5.5 2′-(Allyloxycarbonyl)benzyl (ACB) Glycosides: New "Latent" Donor for the Preparation of "Active" 2-Azido-2-deoxy BC Glycosyl Donors

Kim and co-workers introduced 2′-(allyloxycarbonyl)benzyl (ACB) glycosides, e. g. **426a**, as new "latent" glycosyl donors for 2-azido-2-deoxy-glucosides [212]. Introduction of the new ACB group in the place of the previously used BCB group was necessary because the azide functionality at C-2 was also reduced during the conversion of the BCB group into the CB group under the normally used hydrogenolysis conditions (Pd/C, H_2, NH_4OAc, MeOH). 2-Azido-2-deoxy ACB glycosides could be converted into active CB glycosyl donors (e. g. **426b**, ➤ *Scheme 68*) without affecting the azide functionality on treatment with a catalytic amount of $Pd(Ph_3P)_4$ in the presence of morpholine [213].



Scheme 68
2′(Allyloxycarbonyl)benzyl (ACB) glycosides



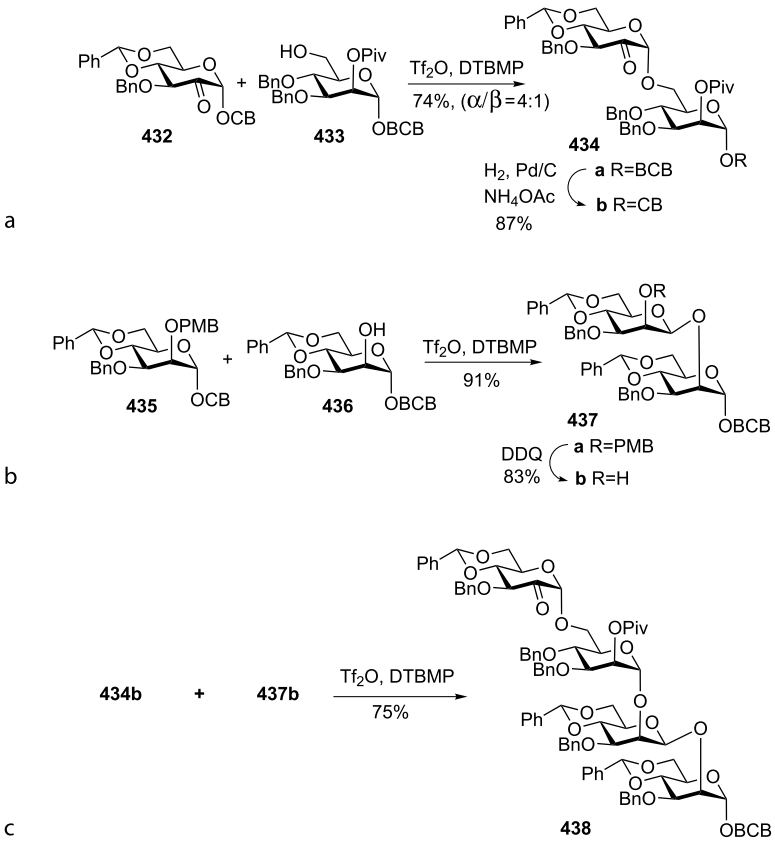
Scheme 69
Synthesis of trisaccharide 431

5.6 Synthesis of Oligosaccharides Based on BC Glycosyl Donors

The CB glycoside methodology by means of the "latent" BCB (or ACB) glycoside and the "active" CB glycoside has proved itself as a reliable method for the synthesis of complex oligosaccharides.

5.6.1 Synthesis of Trisaccharide 431, the Repeat Unit of the *O*-Antigen Polysaccharide from Danish *Helicobacter pylori* Strains

Kim and co-workers synthesized the repeat unit of the *O*-antigen polysaccharide from Danish *Helicobacter pylori* strains, **431** (Scheme 69) [214]. Coupling of donor CB L-rhamnoside **427** and acceptor BCB D-rhamnoside **428** gave α-disaccharide **429a** in 88% yield. Selective hydrogenolysis of "latent" BCB disaccharide afforded "active" CB disaccharide **429b** in



432 **433** **434** **435** **436** **437** **438**

Scheme 70
Synthesis of tetrasaccharide 438

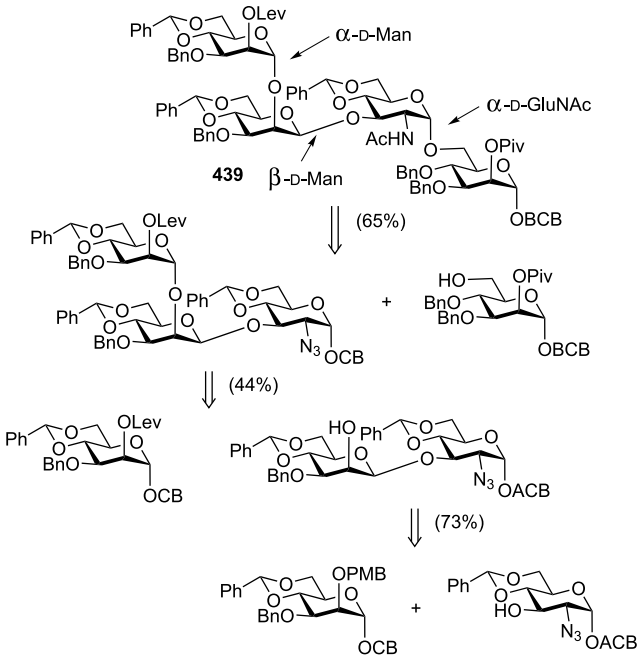
92% yield. Finally, glycosylation of 3-*C*-methyl mannoside, **430**, with **429b** yielded the target α-trisaccharide **431**, along with its β-anomer in 7:1 ratio in 80% yield. A result that indicated that neighboring group participation is operative in CB glycosides.

5.6.2 Synthesis of Tetrasaccharide 438

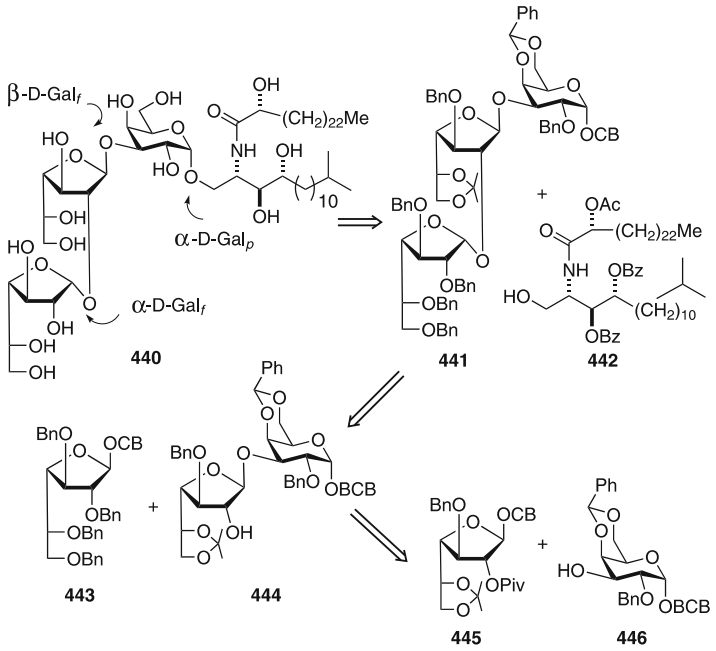
The CB methodology was also applied to the synthesis of protected tetrasaccharide **438**, an analogue of the tetrasaccharide repeat unit of the *O*-antigen polysaccharide from the *E. coli* lipopolysaccharide (*Scheme 70*) [215]. Coupling of "latent" BCB acceptor **433** with "active" CB glycosyl donor **432** gave a mixture of α-disaccharide **434a** along with its β-isomer (4:1) in 74% yield (*Scheme 70a*). Glycosylation of acceptor **436** with donor **435** gave β-mannoside **437a**, that after removal of the PMB protecting group led to **437b** (*Scheme 70b*). Finally, coupling of the latter with active donor **434b**, prepared from latent **434a**, yielded tetrasaccharide **438**, in 75% yield (*Scheme 70c*).

5.6.3 Synthesis of Tetrasaccharide Repeat Unit from *E. coli* O77

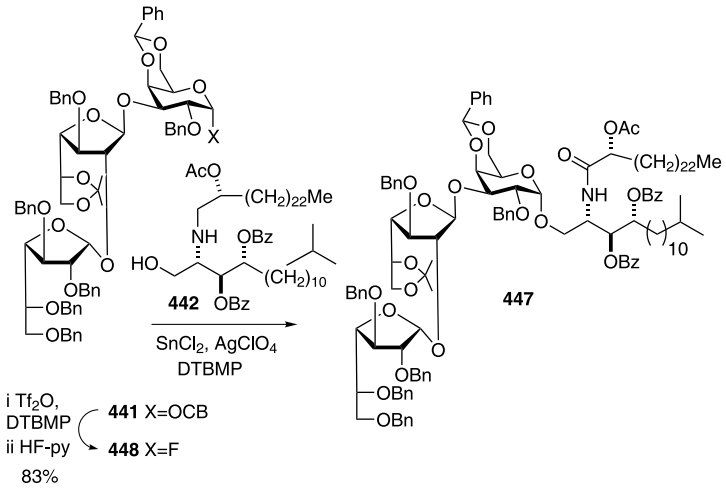
A route to a tetrasaccharide **439** was reported, which made use of the previously mentioned "latent" 2′-(allyloxycarbonyl)benzyl (ACB) glycosides in combination with "latent" and "active" BCB and CB glycosides, respectively [212]. The retrosynthesis is outlined in



Scheme 71
Retrosynthesis of tetrasaccharide 439



Scheme 72
Retrosynthesis of Agelagalastatin 440



Scheme 73
Transformation of CB glycoside 441 into glycosyl fluoride 448 and final coupling of Agelagalastatin

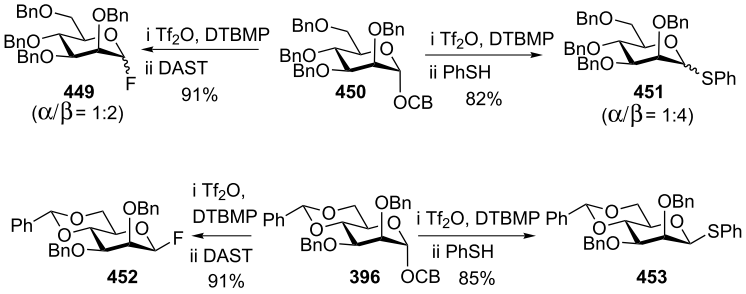
Scheme 71. All glycosyl couplings were based on the "latent-active" methodology, and all were stereoselective. A slightly modified synthesis of **439** has been reported including one CB mediated coupling [216].

5.6.4 Total Synthesis of Agelagalastatin

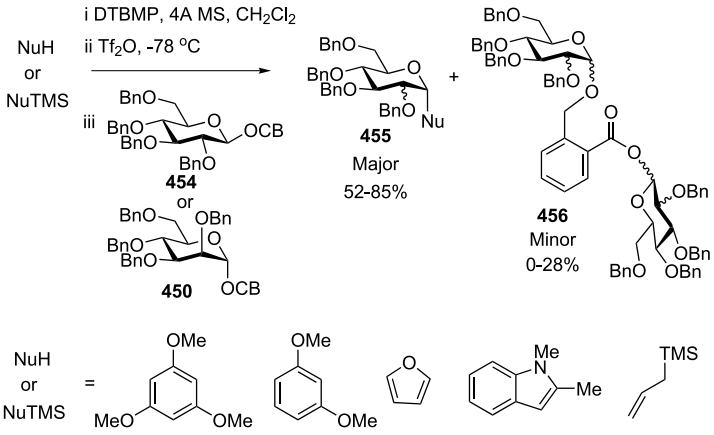
The total synthesis of agelagalastatin, an antineoplastic glycosphingolipid, has been described by Kim and co-workers [217]. The retrosynthesis, outlined in *Scheme 72*, involved a β-D-galactofuranosylation, an α-D-galactofuranosylation, and a final α-D-galactopyranosylation. The β-D-galactofuranosylation was achieved in 79% yield via neighboring group participation of the pivaloyl group at *O*2 in compound **445**. The α-D-galactofuranosylation to **441**, took place with 91% yield with a nonparticipant benzyl group at *O*2 in donor **443**. The final α-D-galactopyranosylation (*Scheme 73*) was carried out with CB trisaccharide donor **441** furnishing compound **447** in 77% yield as a 1.4:1 (α/β) mixture of saccharides. The efficiency of this coupling was improved by conversion of the CB trisaccharide donor to glycosyl fluoride **448**. Treatment of **441** with TF_2O/DTBMP followed by HF-pyridine, as a source of fluoride, yielded glycosyl fluoride **448**. The glycosylation of acceptor **442** with glycosyl fluoride **448**, then gave the target protected agelagalastatin **447**, in 72% yield as the pure α-isomer.

5.7 Conversion of 2′-Carboxybenzyl Glycosides into Other Glycosyl Donors

CB glycosides have been converted to phenyl 1-thio glycosides and glycosyl fluorides in one-pot operations [218]. Thus, treatment of CB glycosyl donors with TF_2O/DTBMP in CH_2Cl_2 at −78 °C for 10 min followed by addition of PhSH furnished thioglycosides, e. g. **451**, **453** (*Scheme 74*), whereas treatment with DAST or HF-pyridine (see *Scheme 73*) yielded the corresponding glycosyl fluorides, e. g. **449**, **452** (*Scheme 74*). The high β-selectivity observed in the formation of glycosyl fluoride **452** and thioglycoside **453** from 4,6-*O*-benzylidenemannopyranoside **396** was ascribed to the presence of a highly reactive 4,6-*O*-benzylidenemannopyranosyl α-triflate, in keeping with previously mentioned findings.



Scheme 74
Conversion of CB glycosides to glycosyl fluorides and thiophenyl glycosides



Scheme 75
CB glycosides in the synthesis of α-*C*-glycosides

5.8 2′-Carboxybenzyl Glycosides as Glycosyl Donors for *C*-Glycosylation

Glycosylation of various glycosyl acceptors (NuH or NuTMS, *Scheme 75*) with *manno*- and *gluco*- CB glycosyl donors **450** and **454**, respectively afforded α-*C*-glycosides **455**, exclusively or predominantly in good yields [218]. Experimentally these reactions were carried out by addition of the donor to a solution of the acceptor, DTBMP, and Tf_2O in CH_2Cl_2 at −78 °C. These modified conditions led to increased yields of *C*-glycosides and minimized the amount of self-condensed esters **456**.

6 *O*-Heteroaryl Glycosyl Donors

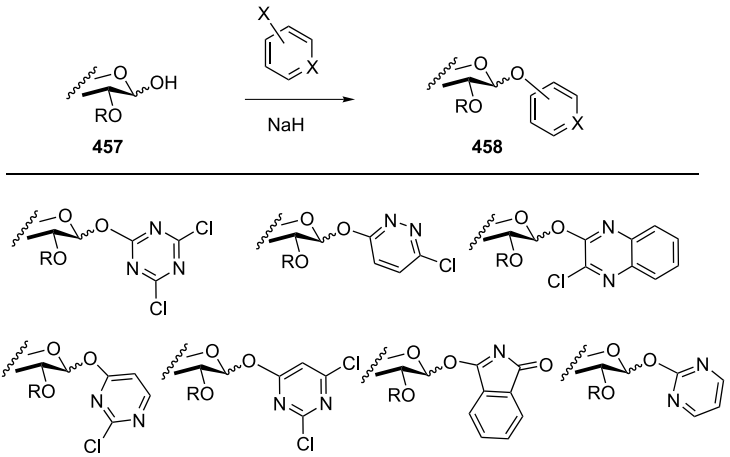
Glycosides of some heterocycles have also been investigated as glycosyl donors.

6.1 2-Pyridyl 2,3,4,6-tetra-*O*-benzyl-D-glucosides

The first example, reported by Nikolaev and Kochetkov [219], dealt with the use of 2-pyridyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucoside in glycosylation. This heteroaryl glycoside was prepared by glycosylation of 2(1H)-pyridinone by the corresponding sugar chloride, and was activated by electrophiles, such as MeOTf and $Et_3O{\cdot}BF_4$, to give mixtures of *cis*- and *trans*-glycosides.

6.2 *O*-Hetaryl Glycosides by Schmidt's Group

Schmidt and co-workers [168,220,221] reported the preparation, and use in glycosylation reactions of several *O*-hetaryl glycosides, e. g. **458**, conveniently prepared by anomeric



Scheme 76
***O*-Hetaryl glycosides synthesized by Schmidt's group**

O-hetarylation of hexoses, e. g. **457**, with the corresponding electron-deficient heteroaromatic/heterocyclic systems (*Scheme 76*). The best results in terms of glycosylation were obtained with tetrafluoropyridyl glycosides **460** and **462**, obtained by reaction of hexoses **459** and **461** with 2,3,4,5,6-pentafluoro pyridine (*Scheme 77a,b*). Under TMSOTf catalysis, in CH_2Cl_2 at room temperature, they furnished the corresponding α- and β-disaccharides **463** and **464** in 98 and 74% yield, respectively (*Scheme 77c,d*).

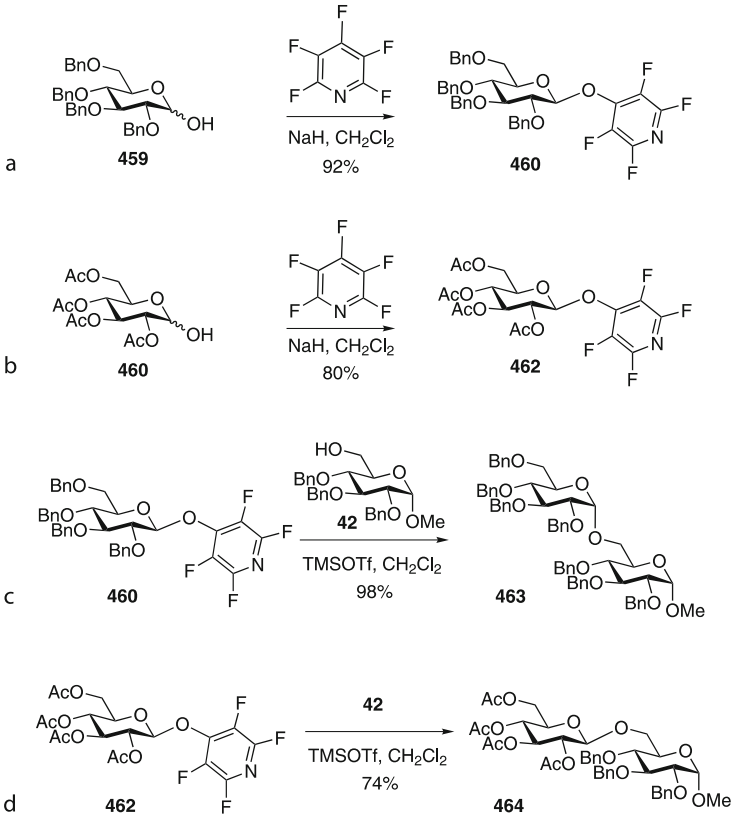
6.3 3-Methoxy-2-pyridyl (MOP) Glycosides

On the basis of the concept of remote activation [222], first applied to pyridine thioglycosides [223], Hanessian and co-workers introduced 3-methoxy-2-pyridyl (MOP) glycosides [224,225]. They first reported the usefulness of ribofuranosyl MOP donor **465** in the coupling with silylated pyrimidine bases, by activation with TMSOTf, to give 1,2-*cis* nucleosides, **466**, with high selectivity (*Scheme 78*) [226]. These glycosides react in MeOTf-, $Cu(OTf)_2$-, TfOH-, or $Yb(OTf)_3$-promoted reactions to give disaccharides [227].

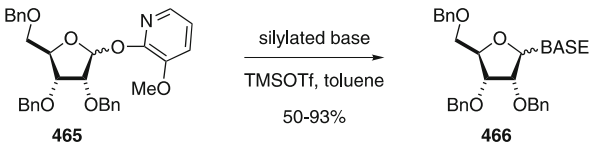
6.3.1 Coupling of Unprotected MOP Glycosyl Donors

Interestingly, unprotected MOP glycosides could also be used as donors. In fact, when using an excess of glycosyl acceptor (≈10 equiv.), disaccharides are obtained in reasonable yields, as illustrated in *Scheme 79*.

It was also found that introduction of any protecting group on the unprotected MOP glycosyl donors resulted in a significant decrease of the reactivity. This deactivation was considerable when *p*-fluorobenzoates (FBz) were used as protecting groups, and it was applied to the synthesis of disaccharides, and to iterative oligosaccharide synthesis (*Scheme 80*).



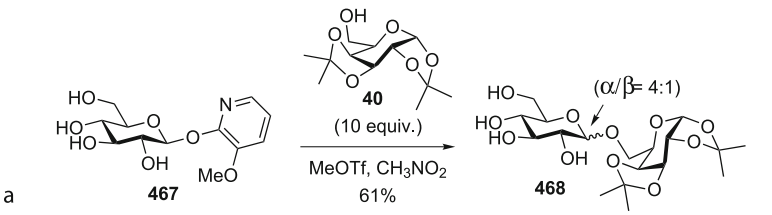
Scheme 77
2,3,5,6-Tetrafluoro-4-(2,3,4,6-tetra-*O*-acetyl or *O*-benzyl-β-D-glucopyranosyloxy) pyridine as glycosyl donors

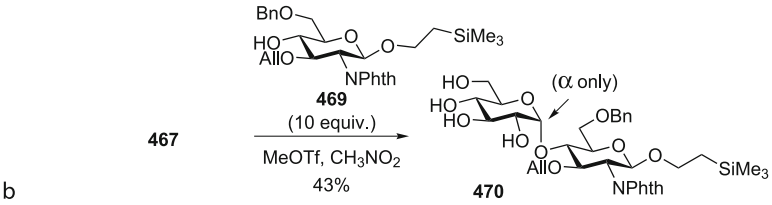


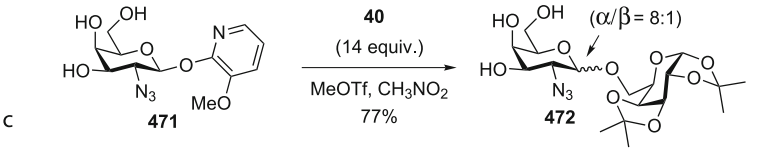
Scheme 78
MOP Ribofuranosyl donors in the synthesis of 1,2-*cis* furanosyl nucleosides

6.3.2 Esterification and Phosphorylation of Unprotected MOP Glycosides

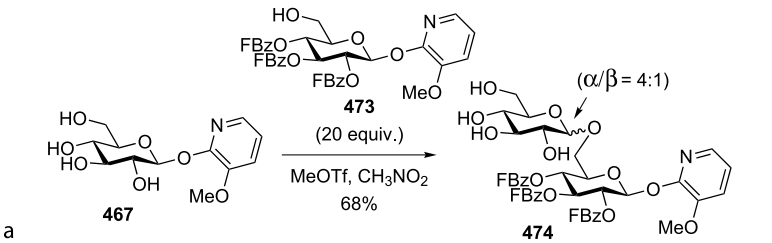
MOP glycosyl donors have been used in stereocontrolled esterification and phosphorylation, leading to glycosyl 1,2-*cis*-1-carboxylates or glycosyl 1,2-*cis*-glycosyl-1-phosphates in one step. Treatment of MOP donor **475** in acetonitrile or DMP with an excess (20–200 equiv.) of a carboxylic acid under anhydrous conditions led to the corresponding D-glycosyl carboxylate **477**, in excellent yields [228]. Moreover, treatment of 6-*O*-tert-butyldiphenylsilyl MOP donor **478** with only 1.5 equiv. of the corresponding carboxylic acid in CH_2Cl_2 resulted in the formation of 1,2-*cis*-glycosyl carboxylate **479** (*Scheme 81a*). Treatment of β-D-galactopyranosyl, and 2-azido-2-deoxy-α-D-galactopyranosyl MOP donors **475** and **471**, respectively with

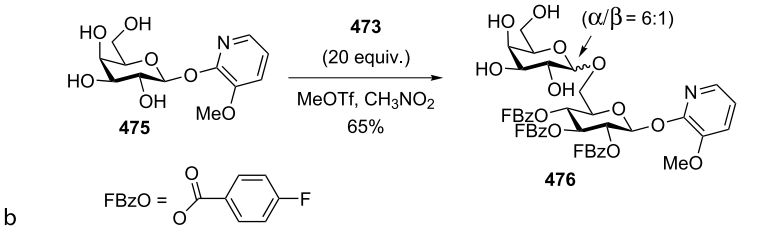




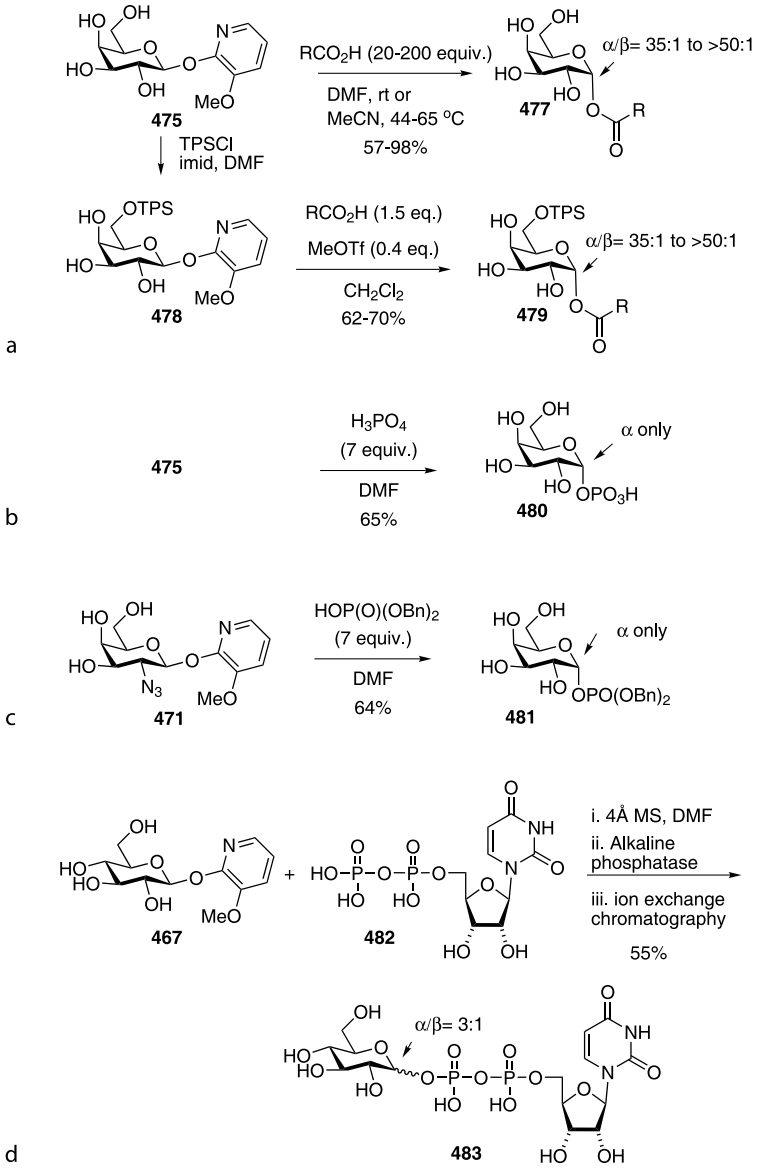


Scheme 79
Disaccharide synthesis with unprotected MOP donors





Scheme 80
Selective activation of unprotected- versus protected-MOP glycosides



Scheme 81
Stereocontrolled synthesis of glycosyl 1-carboxylates and 1-phosphates

7 equiv. of phosphoric acid or dibenzyl phosphate in DMF led to the corresponding α-glycosyl phosphates **480** and **481**, respectively. The same donors are also capable of transferring glucopyranosyl (e. g. **467**, *Scheme 81d*) and galactopyranosyl units to UDP-free acid **482**, to afford the corresponding uridine 5′ diphosphosugars (e. g. **483**) in one step [229].

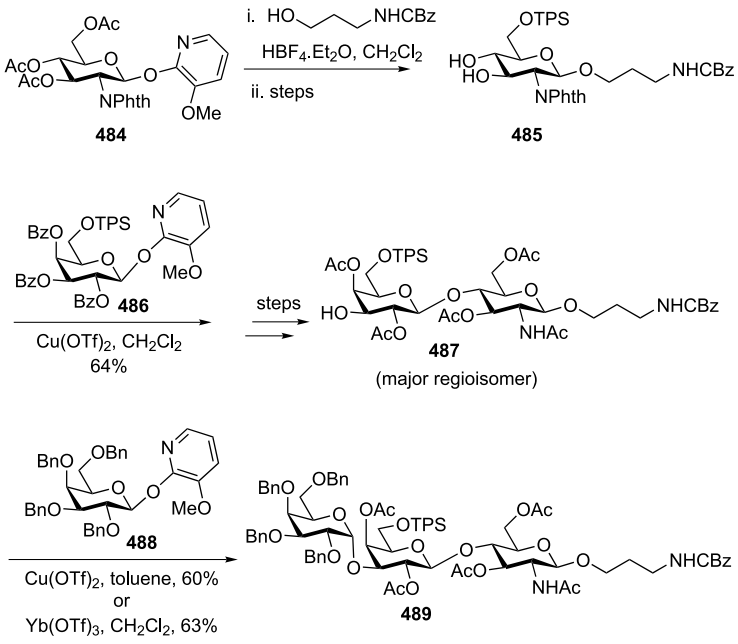
6.3.3 MOP Glycosides in Oligosaccharide Synthesis

A solid-phase oligosaccharide synthesis based on the MOP donor/acceptor methodology was developed by Hanessian and co-workers [224]. Thus, an *O*-unprotected polymer-phase bound MOP donor is coupled with an excess of a partially esterified MOP acceptor. Selective removal of the ester (or related protecting groups) from the new saccharides generates a new *O*-unprotected MOP donor to engage in a subsequent iteration.

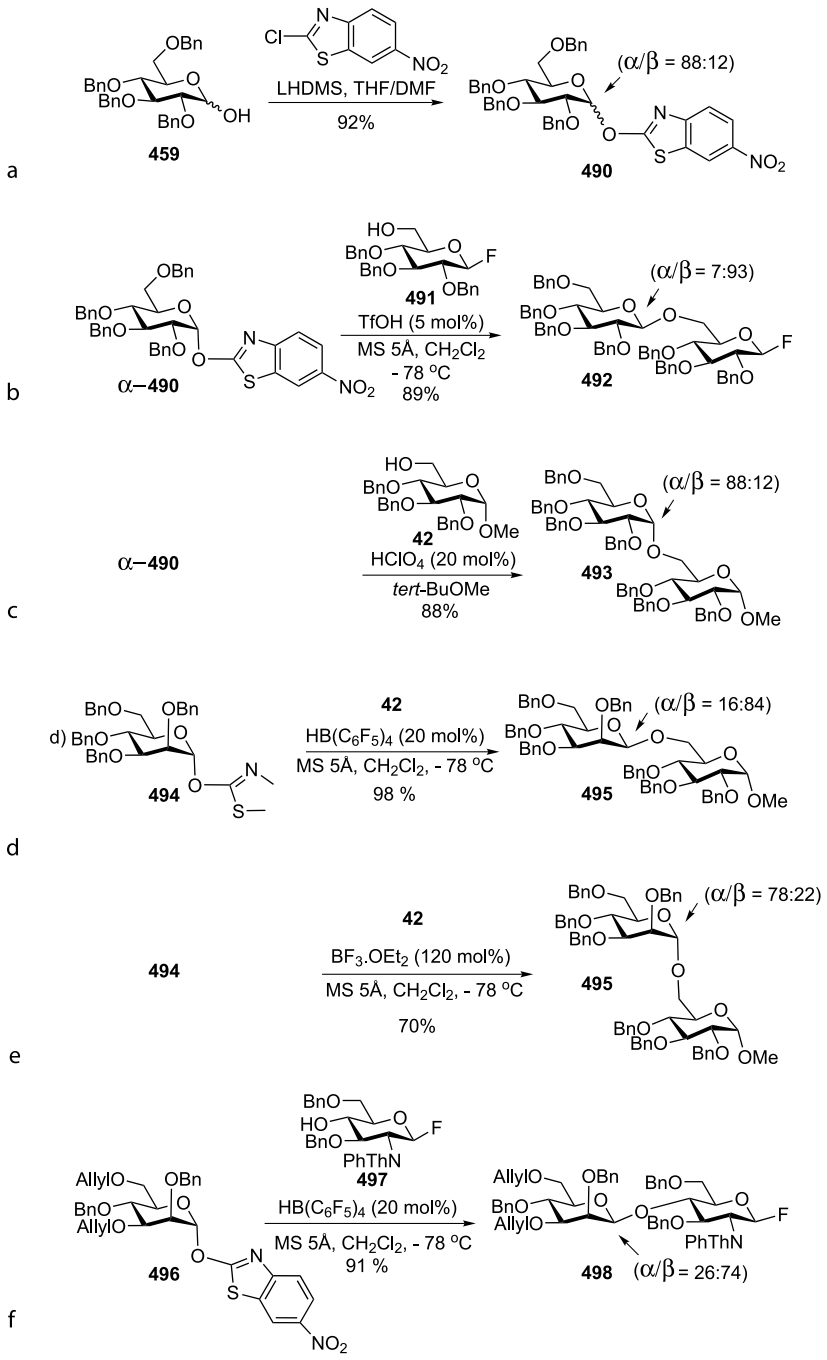
Hanessian and co-workers also illustrated the usefulness of the MOP methodology with some syntheses of oligosaccharides [230,231]. They reported a concise synthesis of a Galα1→3Galβ1→4GlcNAcOR trisaccharide **489**, outlined in ❯ *Scheme 82* [232]. Treatment of MOP donor **484** with 3-benzyloxycarbonylamino 1-propanol in the presence of $HBF_4{\cdot}Et_2O$ in CH_2Cl_2 led to the expected β-glycoside **485**. Protecting group manipulation and glycosylation with MOP galactopyranosyl **486** in the presence of $Cu(TfO)_2$ as activator gave the intended β-disaccharide **487**. Final glycosylation of **487** with β-galacto MOP donor **488** ($Cu(OTf)_2$) or $Yb(OTf)_3$, as promoters) led to protected trisaccharide **489**.

6.4 6-Nitro-2-benzothiazolyl Glycosides

Mukaiyama et al. described glycosyl 6-nitro-2-benzothiazoates (e. g. **490**) as useful glycosyl donors [233]. They are prepared by reaction of glycose derived hemiacetals (e. g. **459**) with 2-chloro-6-nitro-2-benzothiazoate (❯ *Scheme 83a*). The purified α-isomer **α-490**, react-



❯ Scheme 82
Synthesis of a trisaccharide using MOP glycosyl donors



Scheme 83
Glycosyl 6-nitro-2-benzothiazoate as a glycosyl donor

ed with primary hydroxyl acceptors in the presence of catalytic TfOH at −78 °C to give mainly β-glucosides, e. g. **492** (Scheme 83*b*). Although, a highly stereoselective α-glucosylation (α/β = 88:12) was carried out in high yield using 20 mol% of $HClO_4$ in *tert*-BuOMe (Scheme 83*c*). 6-Nitro-2-benzothiazolyl α-mannosides (e. g. **494**) effected stereoselective β-mannosylation with several glycosyl acceptors [234,235]. The highest β-stereoselectivity was achieved when tetrakis(pentafluorophenyl)boric acid [$HB(C_6F_5)_4$] [236] was employed as catalyst (Scheme 83*d*). $BF_3{\cdot}Et_2O$, a weaker Lewis acid, showed a reversed stereoselectivity [237] (Scheme 83*e*). The β-selective coupling was employed by Mukaiyama and co-workers in the formation of the β-Man(1→4)GlcN linkage, e. g. **498**, that exists in *N*-linked glycans (Scheme 83*f*) [238,239].

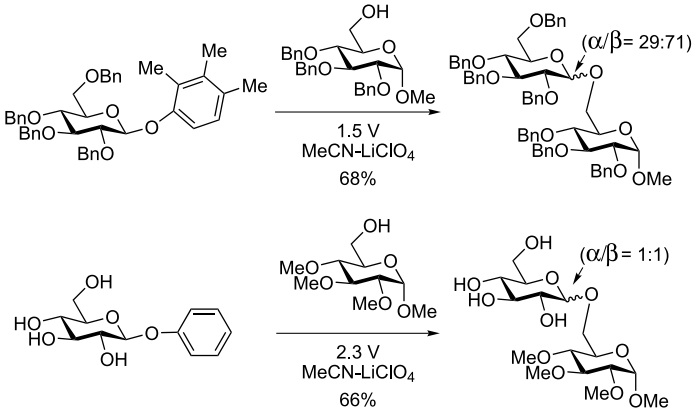
7 Miscellaneous *O*-Glycosyl Donors

Noyori and Kurimoto [240] described that hydroxyl-protected and -unprotected glycosyl aryloxides reacted with alcohols under mild electrolytic conditions to give the corresponding glycosides. They hypothesized that the glycosylation reaction proceeded via oxocarbenium ion intermediates generated from the radical cation of the easily oxidizable aryloxy substrate (Scheme 84).

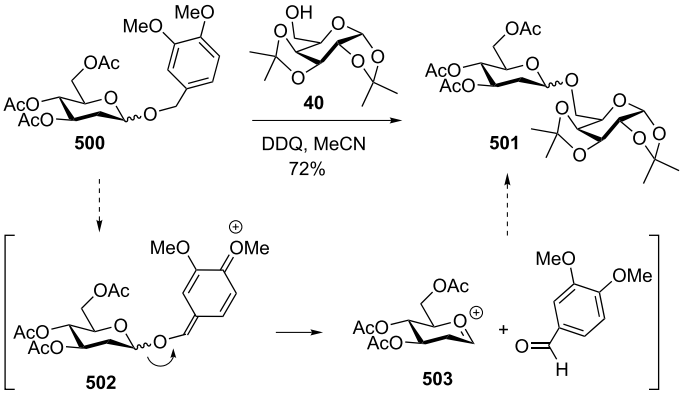
A combination of trimethylsilyl bromide and zinc triflate promoted the glycosylation of benzyl-, isopropyl-, and methyl glycosides with several glycosyl acceptors in moderate to good yields [241,242].

2-Deoxyglycosides, e. g. **501**, were obtained by DDQ oxidation of 3,4-dimethoxybenzyl glycosides **500**, in MeCN in the presence of primary, secondary, and tertiary alcohols (Scheme 85) [243].

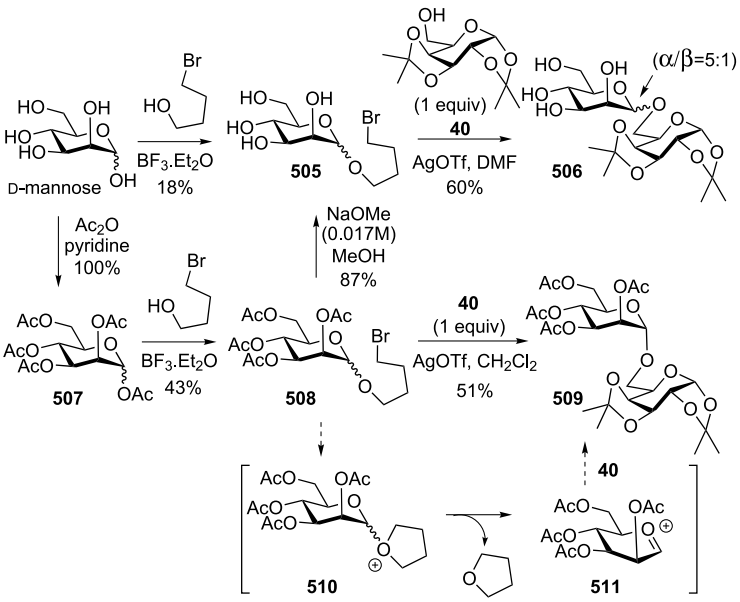
Davis and co-workers [244] examined the self-activating properties of unprotected and acetylated bromobutyl glycosides **505** and **508**, respectively (Scheme 86). These readily available compounds reacted with galactose acceptor **40** (1 equiv.) in the presence of a halophilic Lewis



Scheme 84
Electrochemical glycosylation of glycosyl aryloxides



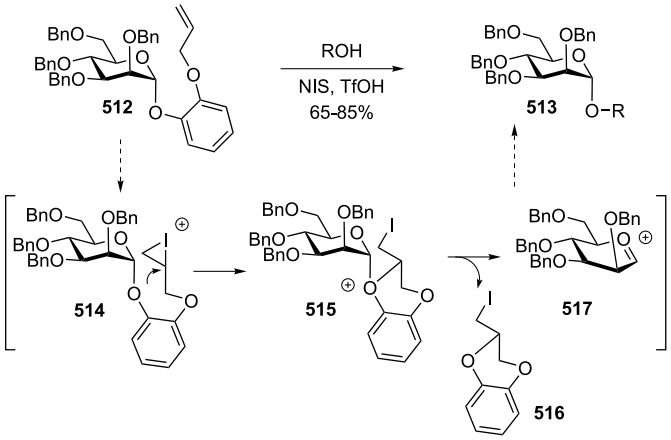
Scheme 85
3,4-Dimethoxybenzyl 2-deoxy glycosides as glycosyl donors



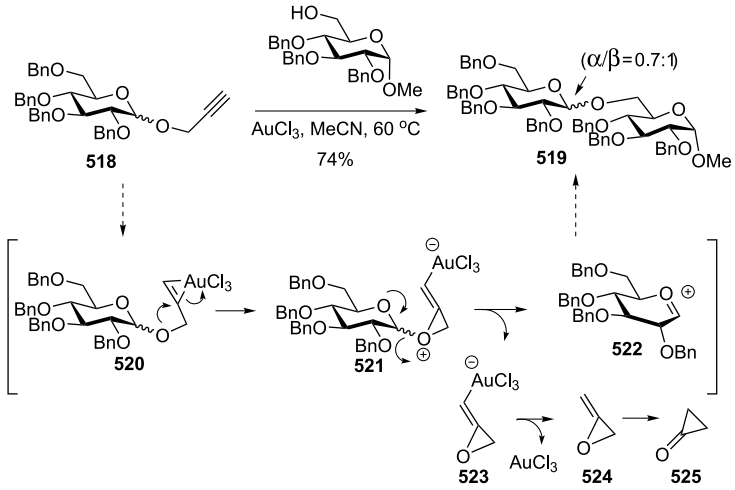
Scheme 86
Bromobutyl glycosides as glycosyl donors

acid promoter (AgOTg) to give disaccharides **506** and **509** in moderate yields. The suggested reaction pathway involved a spontaneous, or acid, triggered, 5-*exo-tet* cyclization of the bromobutyl glycoside, e. g. **508→510**, to form an anomeric furanosyl cation **510**, which would evolve to give non-nucleophilic volatile tetrahydrofuran, and oxocarbenium ion **511**. The latter will then react with acceptor **40** to furnish the disaccharide.

Hung and co-workers have reported on the use of 2-allyloxyphenyl mannoside **512** as a useful glycosyl donor [245]. Mannoside **512** reacted in the presence of NIS/TfOH in CH_2Cl_2 at room



Scheme 87
2-Allyloxyphenyl mannosides as glycosyl donors



Scheme 88
Propargyl glycosides as glycosyl donors

temperature, with a series of primary and secondary hydroxyl acceptors to give α-mannosides, e. g. **513**, in good yields (*Scheme 87*). The proposed mechanism for the formation of the oxocarbenium ion **517**, outlined in *Scheme 87*, implies a 6-*exo-tet* cyclization on halonium ion **514**, and the ejection of the non-nucleophilic species **516**.

Hotha and Kashyap have identified propargyl glycosides **518**, as new glycosyl donors (*Scheme 88*) [246,247]. Various aglycones, including primary and secondary alcohols, reacted with propargyl glycosides in the presence of 3 mol% of $AuCl_3$ in MeCN at 60 °C, to give α/β-mixtures of glycosides and disaccharides in good yields. The α,β-ratio of the

transglycosylation products was found to be independent of the anomeric ratio of the donor. per-*O*-Acylated propargyl glycosides did not give transglycosylation products. A possible reaction pathway to the generation of an intermediate oxocarbenium ion, based on the alkynophilicity of gold catalysts, was advanced by the authors (› *Scheme 88*). Coordination of $AuCl_3$ to the glycosyl donor **518** would be followed by formation of the cyclopropyl gold carbene intermediate (**520**) that could evolve to intermediate **521**, which would lead to oxocarbenium ion **522**, and alkenyl gold complex **523**. The latter upon protodemetalation will generate $AuCl_3$ and cyclopropanone **525** via intermediate **524**.

Acknowledgements

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