Chapter 2
O-glycoside Formation

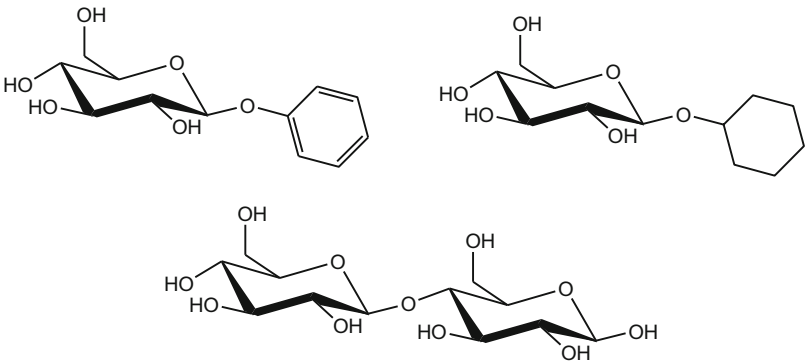
2.1 General Methods

When a monosaccharide (or a sugar fragment of any size) is condensed with either an aliphatic or aromatic alcohol, or another sugar moiety through oxygen, a glycoside bond is formed. General examples of *O*-glycosides are shown in Scheme 2.1.

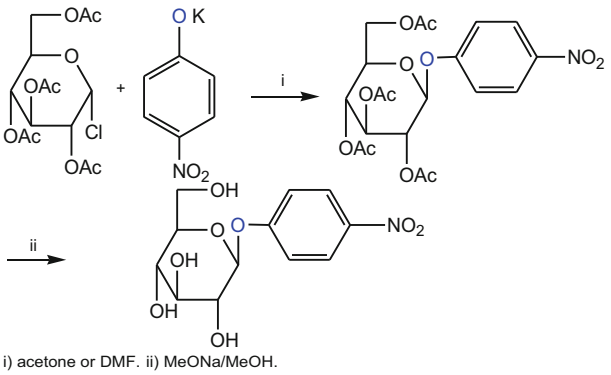
The most common coupling reaction methodologies used for preparing the vast majority of *O*-glycosides known thus far are as follows: [1]

Michael reaction
Fischer reaction
Koenigs–Knorr reaction
Helferich reaction
Fusion method
Imidate reaction
Glycal reaction
Sulfur reaction
Armed–disarmed approach
Unprotected anomeric carbon
Unprotected glycosylations
Miscellaneous leaving groups
Solid phase approach

M. Brito-Arias, *Synthesis and Characterization of Glycosides*,
DOI 10.1007/978-3-319-32310-7_2

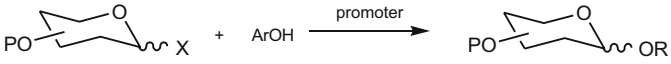


Scheme 2.1 Examples of *O*-glycosides



Scheme 2.2 Synthesis of paranitrophenyl-β-D-glucopyranosyl tetraacetate

2.1.1 Michael Reaction



Promoter	Conditions
NaH	THF
K_2CO_3, NaOH	Acetone

This pioneering methodology for *O*-glycosylation consists of the condensation reaction between 2,3,4,6-tetraacetyl-α-D-glucopyranosyl chloride and potassium phenoxide to generate the acetylated derivate that undergoes basic hydrolysis to give phenyl-β-D-glucopyranoside (Scheme 2.2). Since its original methodology, some modifications have been introduced especially for aromatic glycosides.

Some of the main features associated with this methodology are:

Preserves the pyranose or furanose ring
Drives the addition of the aromatic aglycon to the anomeric position
Uses protecting groups which are easily removed in basic medium
Produces exclusively the β-*O*-glycoside as a result of neighboring group participation

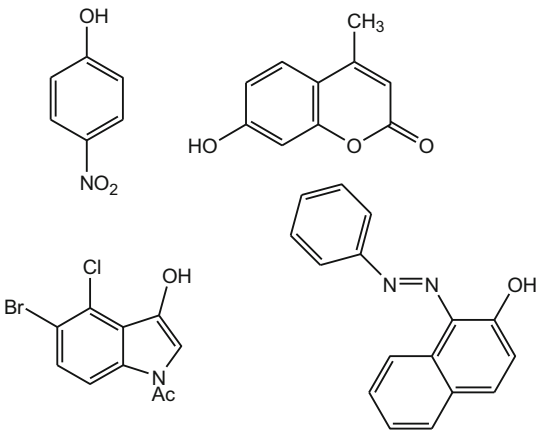
This reaction has been employed for the preparation of *O*-glycosides that are used as substrates for detection and measurement of enzymatic activity of most of the known glycosidases.

Using this methodology, several chromophores have been attached to most of the common monosaccharides. After *O*-glycoside cleavage by the enzyme, the release of the chromophore will indicate the sites and eventually will quantify the enzymatic activity. Some of the chromophores currently used for these purposes are represented in Scheme 2.3.

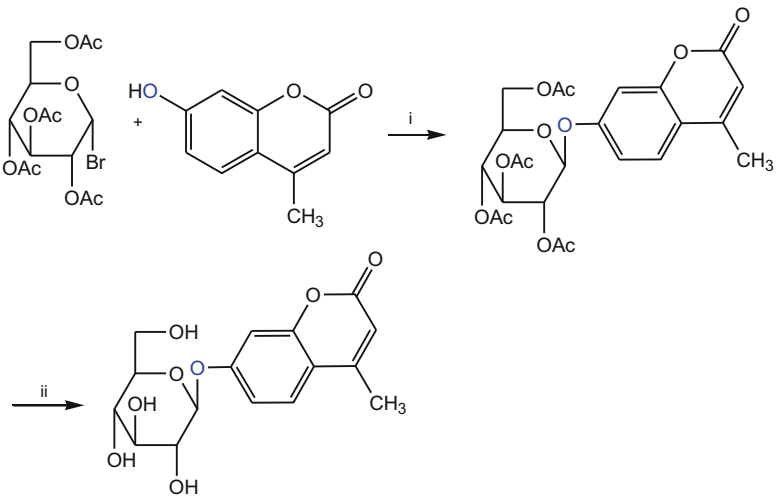
The highly fluorescent *O*-glycoside substrate 7-hydroxy-4-methylcoumarin-β-D-glucopyranose is prepared by condensation between acetobromoglucose and 4-methylumbelliferone in the presence of potassium carbonate in acetone. The intermediate is deacetylated under basic conditions to form umbelliferyl β-D-glucopyranoside (Scheme 2.4).

Anderson and Leaback [2] were able to prepare 5-bromo indoxyl-β-D-*N*-acetylglucopyranoside, a histochemical substrate for enzymatic detection of chitinase by condensing 3,4,6-triacetyl-β-D-*N*-acetylglucopyranoside chloride with 5-bromo-hydroxy-*N* acetyl indole at 0 °C under nitrogen atmosphere (Scheme 2.5).

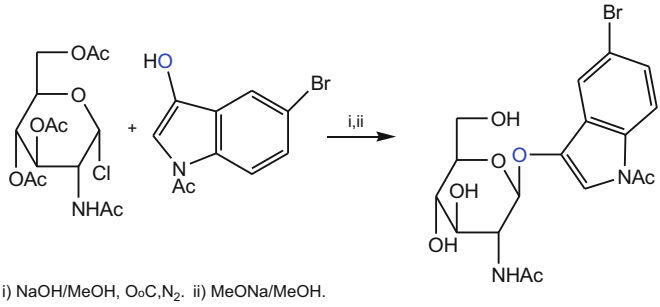
An alternative method for preparing the indoxyl glycosides was described more recently consisting in the coupling reaction between fucosyl bromide donor and indoxylic acid allyl ester under basic medium providing the *O*-glycosides in 84 % yield as β-anomer. This protocol was extended in the synthesis of sialic acid indoxyl glycosides (Scheme 2.6) [3].



Scheme 2.3 *O*-glycoside chromophores used for enzymatic detection

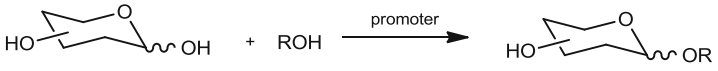


Scheme 2.4 Michael approach for preparation umbelliferyl-*O*-glycoside



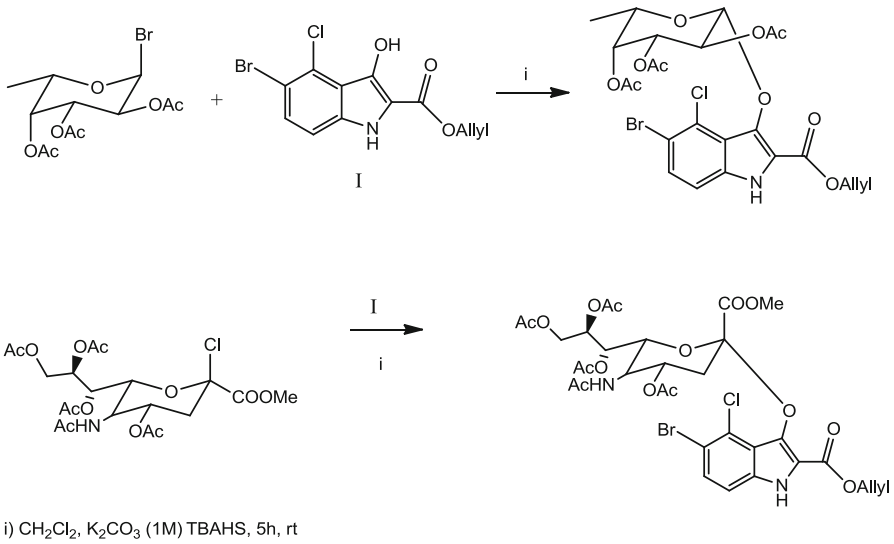
Scheme 2.5 Synthesis of indole *O*-glycoside derivative

2.1.2 Fischer Reaction



Promoter	Conditions
HCl gas	CH_2Cl_2, r.t.
pTsOH	CH_2Cl_2, r.t.

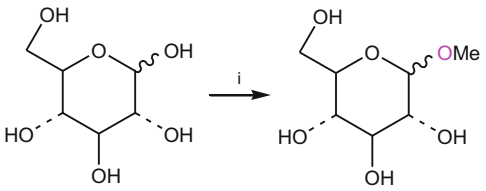
This straightforward strategy is used specially for the preparation of simple *O*-glycosides and the advantage of this methodology is that it does not require the use of protecting groups and simply by combining the free sugar with an alcohol



i) CH_2Cl_2, K_2CO_3 (1M) TBAHS, 5h, rt

Scheme 2.6 Alternative method for preparing the indoxyl glycosides

Scheme 2.7 Fischer *O*-glycoside reaction



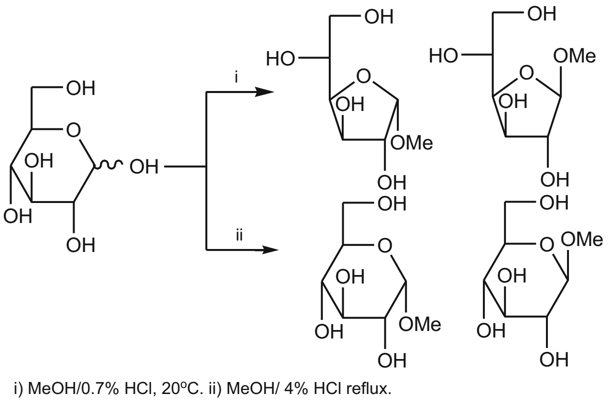
i) MeOH-HCl(g).

under acidic condition we furnish the corresponding *O*-glycoside. However, contrary to the previous method, this procedure is not stereo selective and therefore it provides a mixture of anomers. Also it has been found satisfactory only for small aliphatic alcohols (Scheme 2.7).

The addition of a controlled stream of dry HCl during a period of around 10 min at room temperature generally is the condition of choice. However, the use of Lewis acid, ion exchange resin and more recently triflic acid have been also reported providing good yields [4].

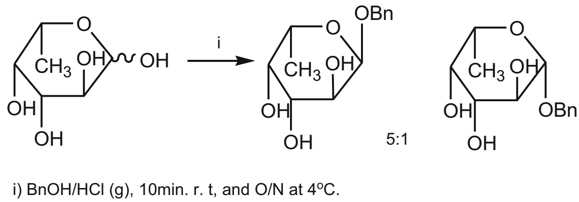
It is worth mentioning that besides the main product, a mixture of isomers has been detected, suggesting that a rather complex mechanism is involved. It is also seen that the amount of these isomers depends importantly on the condition reactions employed (Scheme 2.8).

The Fischer methodology has been applied successfully for the synthesis of benzyl *O*-glycosides. L-Fucose was converted into benzyl fucopyranoside [5] by treatment with benzyl alcohol under saturation with HCl at 0 °C, to furnish the α and β anomers (ratio 5:1) in 80 % yield (Scheme 2.9).

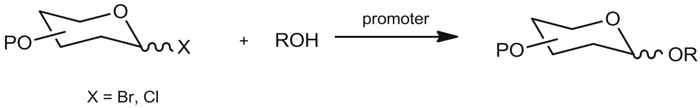


Scheme 2.8 Fischer *O*-glycoside isomers

Scheme 2.9 Fischer conditions for preparation of benzyl L-fucose

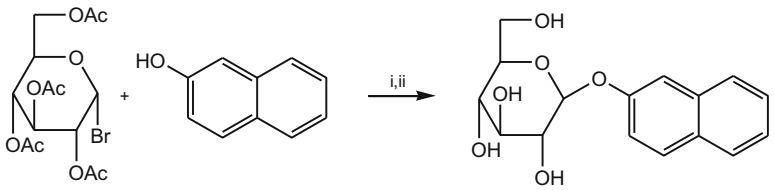


2.1.3 Koenigs–Knorr Reaction



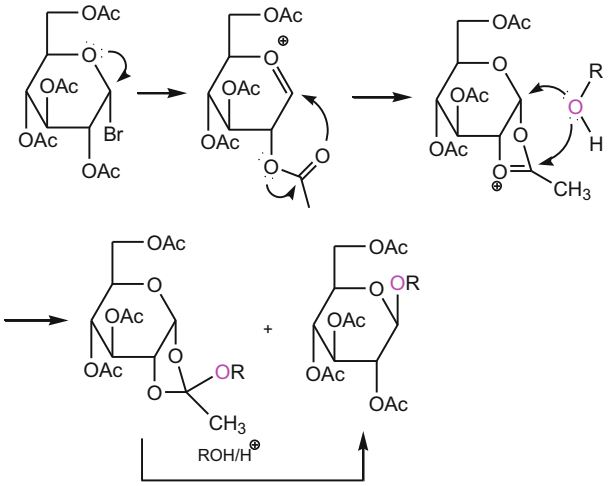
Promoter	Conditions
Ag_2CO_3	PhH, drierite (drying agent), I_2
Ag_2O	s-collidine (acid scavenger).
	CH_2Cl_2, 23 °C, borinic ester, ref. [6]
$AgNO_3$	HgO (acid scavenger)
$AgClO_4$	Ag_2ClO_3 (acid scavenger), THF or toluene, r.t.
AgOTf	CH_2Cl_2, r.t.
Silver silicate	CH_2Cl_2, 4 Å MS, −60 °C ref. [7]

This reaction reported in 1901 is still one of the most useful reactions for preparing a wide variety of *O*-glycosides [8]. It is useful for coupling reactions with either alkyl or aromatic alcohols as well as for coupling between sugars. The methodology requires silver salts as catalyst and among them the oxide, carbonate, nitrate, and



i) Ag_2O or Ag_2CO_3/PhH, drierite, I_2. ii) MeONa/MeOH.

Scheme 2.10 Koenigs–Knorr reaction

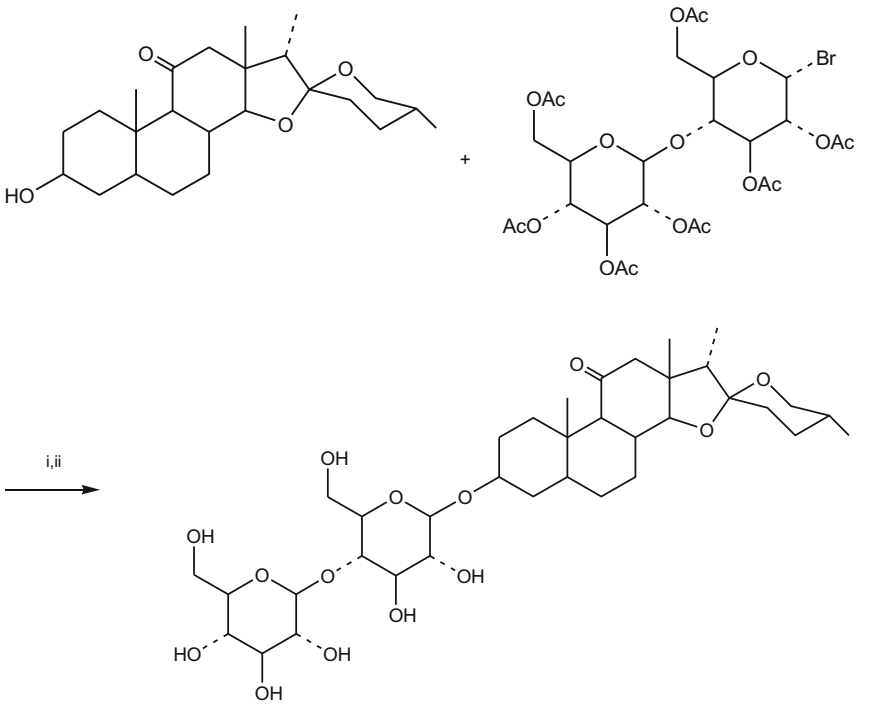


Scheme 2.11 Proposed mechanism for Koenigs–Knorr glycosidic reaction

triflate silver salts are the most commonly employed (Scheme 2.10). Also a drying agent such as calcium sulfate (drierite), calcium chloride, or molecular sieves is recommended. Improved yields are obtained with iodide, vigorous stirring, and protection against light during the course of the reaction.

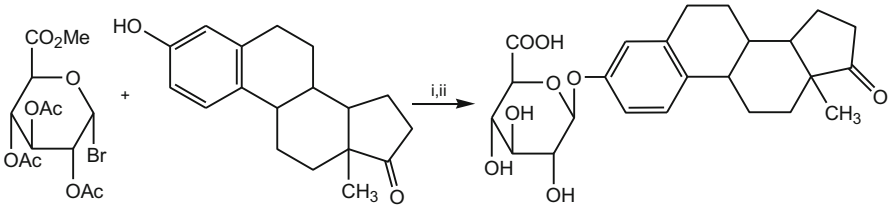
The stereochemistry observed is 1,2 trans type in most of the cases reported, as a consequence of neighboring group participation. When the protecting group is acetate at C (2), there is an intra molecular nucleophilic displacement of the leaving group, generating an orthoester [9]. This intermediate is responsible for the incorporation of the alcohol on the β-position (Scheme 2.11). Only until recently a method for preparing 1,2-cis glycosides has been developed involving the use of (1S)-phenyl-2-(phenylsulfanyl)ethyl moiety at C-2 of a glycosyl donor to give a quasi-stable anomeric sulfonium ion. The sulfonium ion is formed as a trans-decalin ring system. Displacement of the sulfonium ion by a hydroxyl leads to the stereoselective formation of α-glycosides [10].

This versatile methodology can be applied for preparation of alky, aryl, and oligosaccharide *O*-glycosides. A steroidal glycoside cholesterol absorption inhibitor



i) ZnF_2,CH_3CN. ii) NaOMe

Scheme 2.12 Synthesis of steroidal glycoside



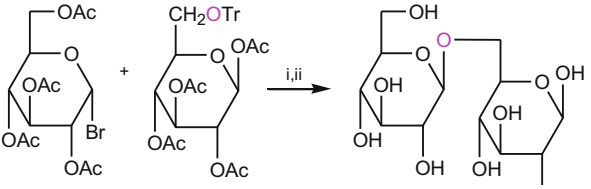
i) Cd_2CO_3. ii) MeONa/MeOH

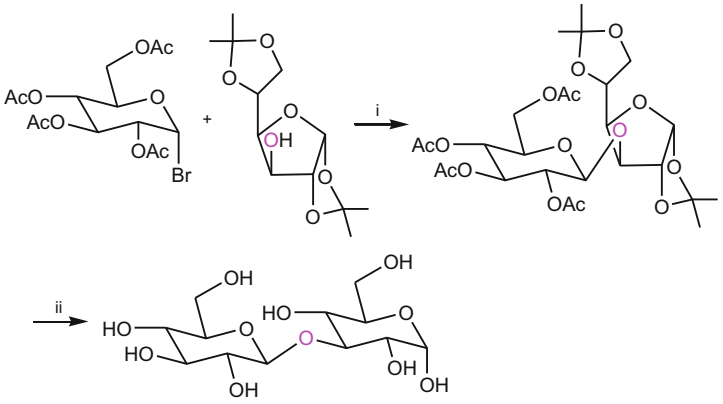
Scheme 2.13 Synthesis of a steroidal *O*-glycoside

was prepared by condensation between acetobromocellobiose and (3β,5α, 25R)-3-hydroxyspirostan-11-one with anhydrous ZnF_2 as catalyst in acetonitrile to provide the steroidal glycoside in 93 % yield (Scheme 2.12) [11].

The steroidal glycoside estrone-β-D-glucuronide was prepared by condensation between methyl tri-*O*-glucopyranosylbromide uronate and estrone, employing cadmium instead of silver carbonate (Scheme 2.13) [12]. For recent developments for the synthesis of *O*-glucuronides [13].

Scheme 2.14 Synthesis of gentobiose





Scheme 2.15 Synthesis of laminaribiose

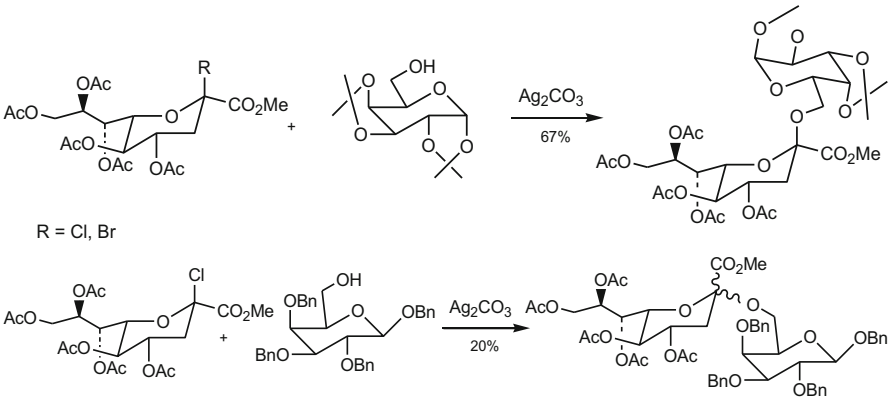
The syntheses of various disaccharides have been reported under Koenigs-Knorr conditions. Gentobiose octaacetate was prepared through condensation of acetobromoglucose with 1,2,3,4-tetra-*O*-acetyl-*O*-trityl-β-D-glucopyranose in nitromethane using silver perchlorate as catalyst (Scheme 2.14) [14].

Bächli and Percival [15] reported the synthesis of laminaribiose by reacting 1,2,5,6-diisopropylidenglucose with acetobromoglucose in the presence of silver carbonate, iodine, and drierite to produce an acetonide intermediate which upon treatment with oxalic acid and sodium methoxide furnished the 1,3-disaccharide (Scheme 2.15).

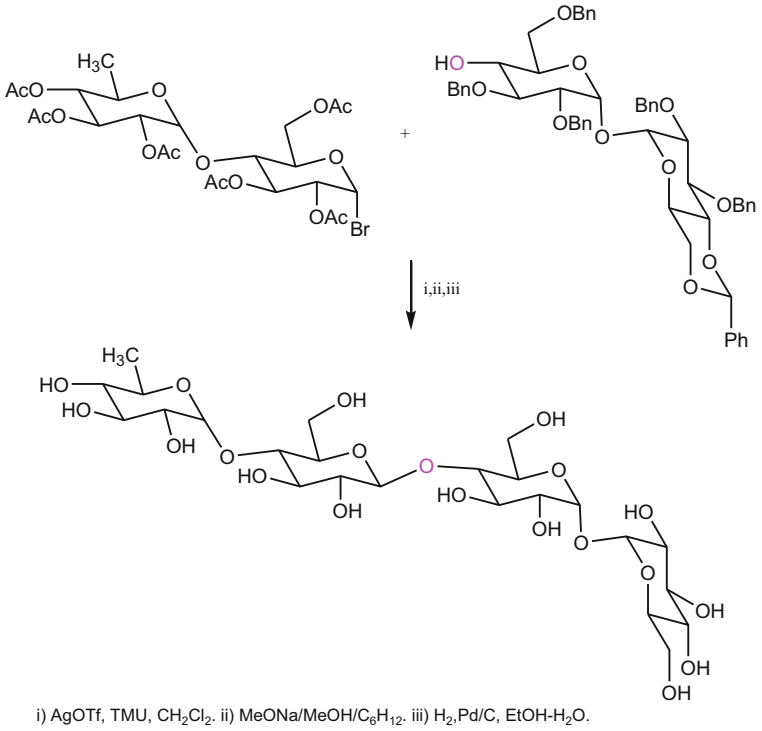
The synthesis of various disaccharides containing *N*-acetylneuraminic acid (Neu5Ac) was achieved by using acetochloro and acetobromo neuraminic acids as glycosyl donors with active glycosyl acceptors under Ag_2CO_3-promoted reactions conditions (Scheme 2.16) [16, 17].

These conditions are also suitable for preparing short oligosaccharides such as the one presented in Scheme 2.17. The donor sugar acetobromogentobiose is coupled to the acceptor intermediate using silver triflate as glycosidation catalyst [18].

Total synthesis of bleomycin group antibiotic has been achieved by Katano and Hecht [19]. Thus, glycoside coupling reaction of protected disaccharide glycosyl donor with histidine derivative using silver triflate as glycoside promoter provided bleomycin key intermediate in 21 % (Scheme 2.18).

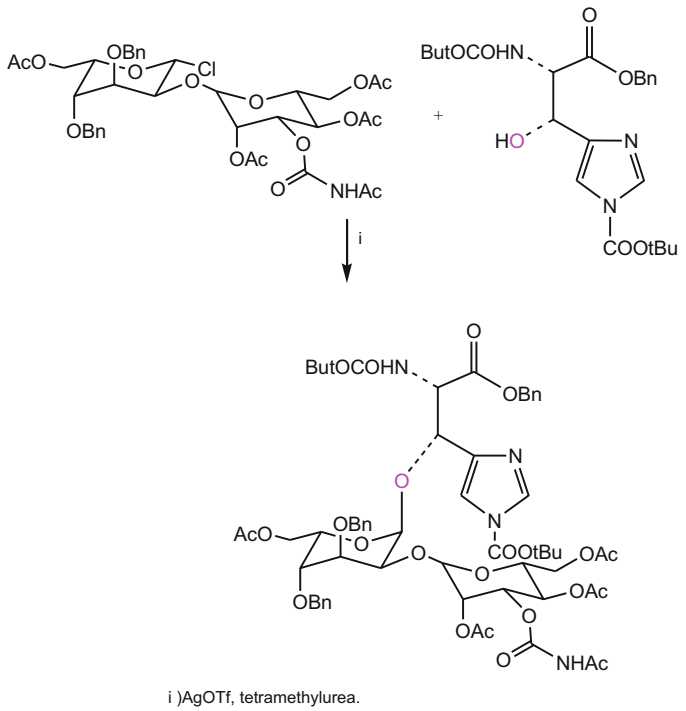


Scheme 2.16 Silver carbonate promoted synthesis of Neu5Ac(2→6) disaccharides

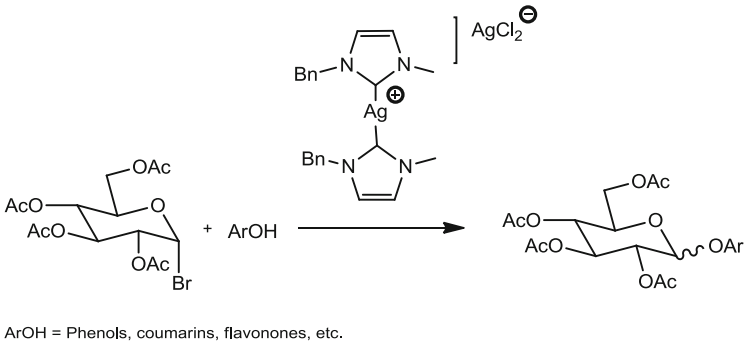


Scheme 2.17 Synthesis of tetrasaccharide

O-glycosidation reactions promoted via silver N-heterocyclic carbene complexes formed in situ in ionic liquids have been implemented. Good to excellent yields were obtained using Ag–NHC complexes derived from imidazolium halide salts to promote the glycosidation reaction (Scheme 2.19) [20].

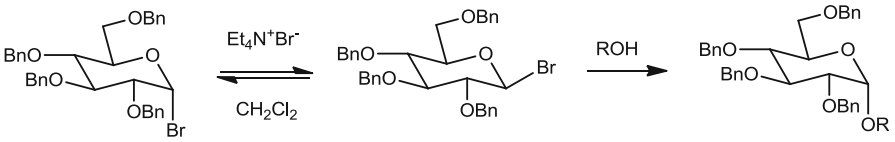


Scheme 2.18 Glycosylation reaction for preparation of bleomycin precursor



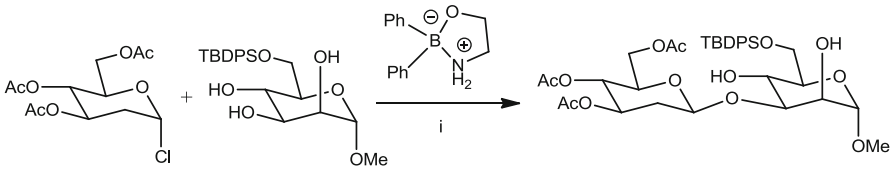
Scheme 2.19 O-glycosidation reactions promoted via silver N-heterocyclic carbene complexes

On the other hand it has been found that 1,2-cis glycosides can be synthesized from α-glycosyl bromide with aliphatic alcohols in the presence of tetraethylammonium bromide, under mild conditions reporting high yields. The α-stereoselectivity can be explained by an equilibrium between the glycosyl bromide promoted by the tetraethylammonium bromide and the nucleophilic attack on the oxonium ion generated during the interconversion (Scheme 2.20) [21].



R = Me, iPr, t-Bu-

Scheme 2.20 Preparation of α-glycosyl bromide with aliphatic alcohols in the presence of tetraethylammonium bromide

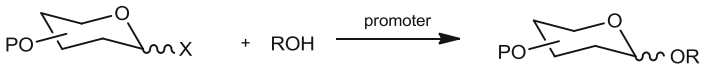


i) Ag_2O, CH_2Cl_2

Scheme 2.21 Glycosylation reaction in the presence of silver oxide and borinic acid derived catalyst

Deoxy aceto chloro glucose has been also used as glycosyl donors under silver oxide conditions providing disaccharides in high yields. Moreover, the use of borinic acid derived catalyst enhance the regioselective and β-selective reactions with acceptors having unprotected cis-1,2- and 1,3-diol groups (Scheme 2.21) [22].

2.1.4 Helferich Reaction

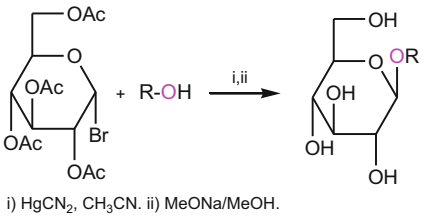


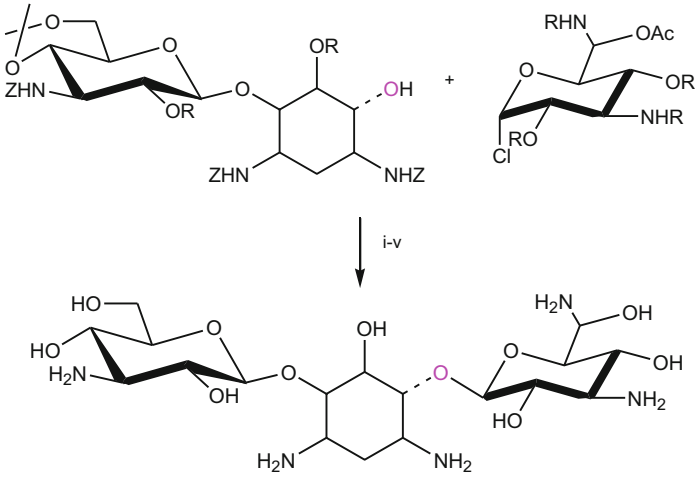
X = Br, Cl

Promoter	Conditions
$Hg(CN)_2$	CH_3CN
$HgBr_2$	CH_3CN
HgI_2	CH_3CN
ZnI_2	MS, CH_2Cl_2

This methodology is considered a modification of the previous one, and the main change being the use of mercury and zinc salts instead of silver. Also more polar solvents are used such as acetonitrile or nitromethane (Scheme 2.22). The yields reported for this reaction are up to 70 %, or higher; however, a mixture of anomers is often observed.

Scheme 2.22 Helferich general reaction



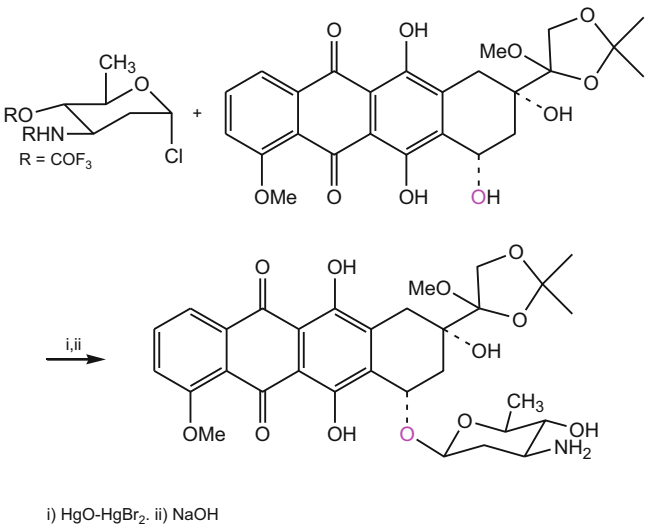


Scheme 2.23 Synthesis of a kanamycin A derivative

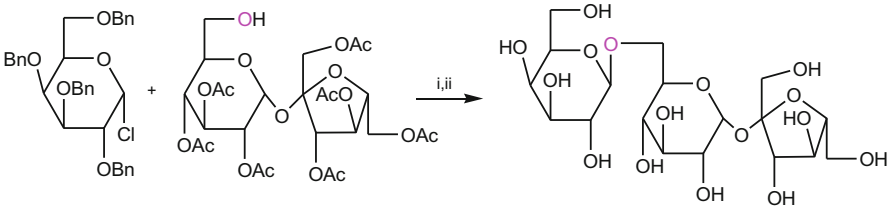
By following this strategy, Umezawa et al. [23, 159, 160] prepared kanamycin A by condensing 6-*O*-[2-*O*-benzyl-3-(benzyloxycarbonylamino)-3-deoxy-4,6-*O*-isopropylidene-α-D-glucopyranosyl]-*N*,*N*′-di(benzoyloxycarbonyl)-2-deoxyestreptamine, as glycosyl acceptor with 2,3,4-tri-*O*-benzyl-6-(*N*-benzylacetamido)-6-deoxy-α-D-glycopyranosyl chloride, as glycosyl donor. The catalyst employed was mercury (II) cyanide (Scheme 2.23).

The antitumoral *O*-glycoside epirubicine was prepared under Helferich conditions [24] using the acetonide form of adriamycinone and 2,3,6-trideoxy-3-trifluoroacetamido-4-*O*-trifluoroacetyl-α-L-arabinohexopyranosyl chloride, and a mixture of mercury (II) oxide and bromide as shown in Scheme 2.24.

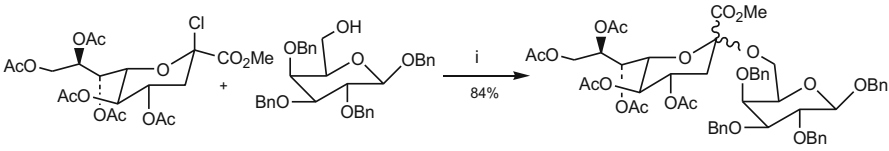
Other coupling reactions between sugars under Helferich conditions have been as well described [25]. For example the case of trisaccharide raffinose prepared by condensation between tetra-*O*-benzyl-α-D-galactopyranosyl chloride as donor and 2,3,4,1′,3′,4′,6′-hepta-*O*-acetyl sucrose as acceptor (Scheme 2.25).



Scheme 2.24 Synthesis of epirubicin



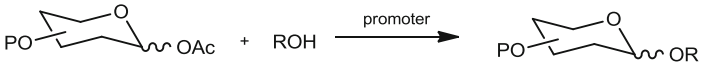
Scheme 2.25 Synthesis of raffinose derivative



Scheme 2.26 Helferich conditions for the preparation of sialic disaccharide

Helferich conditions have been used for preparing disaccharides containing Neu5Ac(2→6)Gal and Glc in good yields, although with low stereocontrol (α:β 3:4) (Scheme 2.26).

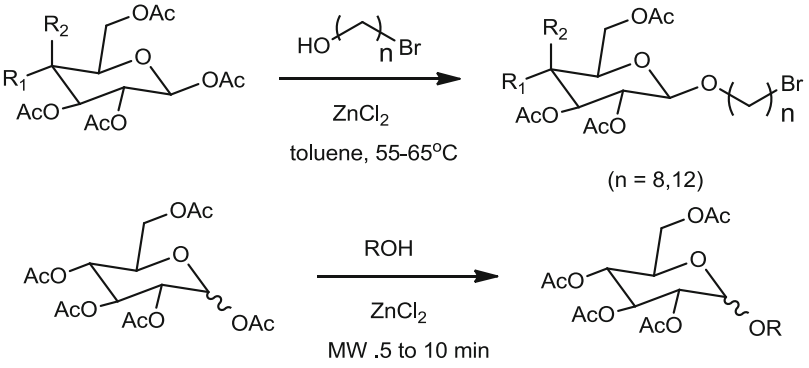
2.1.5 *Acetate Donors*

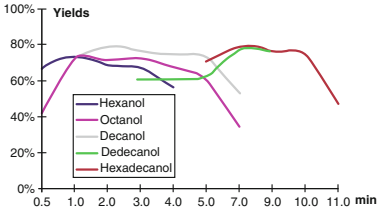


Promoter	Conditions
$ZnCl_2$	Heat, or MW
$ZnCl_2$	120 °C
$SnCl_4$	5–10 °C
TsOH	120 °C

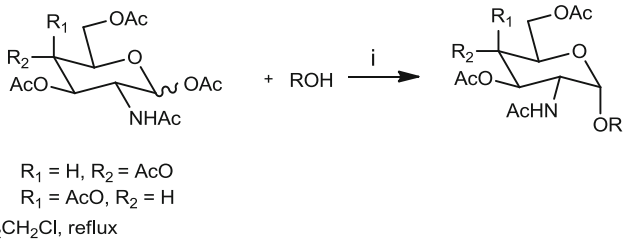
This method has been used for preparing long chain and aromatic glycosides under different acid promoters such as $ZnCl_2$, $SnCl_4$, $FeCl_3$, TsOH, or zeolite. Particularly the use of $ZnCl_2$ as promoter has been successfully utilized to attach long chain alcohol to peracetate saccharides with moderate heating or microwave conditions to produce amphipathic glycosides in moderate to good yields as mainly the 1,2-*trans*-glycosides or as a mixture of anomers (Scheme 2.27) [26, 27].

A one-step procedure for the preparation of α-*O*-glycosamine pentaacetylated glycosides with yields up to 70 % and high α-stereoselectivity was achieved by condensation between commercially available D-glycosamine pentaacetates and fluorogenic coumarins, substituted phenols, and protected serine acceptors under ferric chloride conditions (Scheme 2.28) [28].



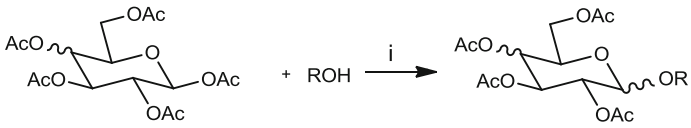


Scheme 2.27 Preparation of long chain and aromatic glycosides under different acid promoters



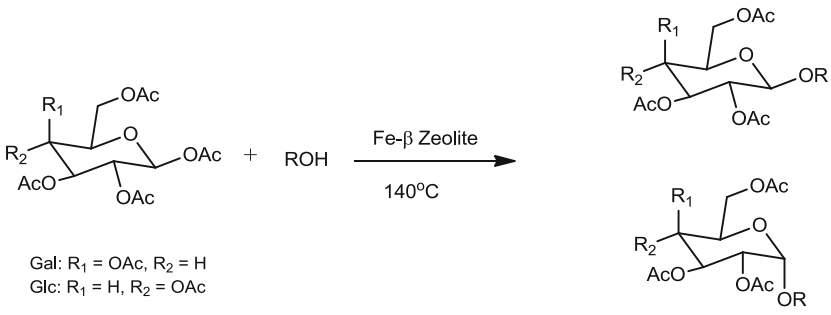
R_1 = H, R_2 = AcO
R_1 = AcO, R_2 = H
i) $FeCl_3$, $ClCH_2CH_2Cl$, reflux

Scheme 2.28 Preparation of α-*O*-glycosamine pentaacetylated glycosides



i) $SnCl_4$+CF_3CO_2Ag or $SnCl_4$

Scheme 2.29 O-glycosidation protocol under $SnCl_4$ or silver triflate an $SnCl_4$ conditions



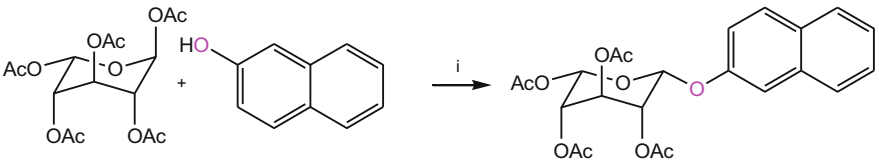
Gal: R_1 = OAc, R_2 = H
Glc: R_1 = H, R_2 = OAc
ROH = Cetyl alcohol, dodecyl alcohol, octanol, 2-ethylhexanol

Scheme 2.30 Heterogeneous catalysts for the preparations of alkyl glycosides

Another simple method for *O*-glycosidation under $SnCl_4$ or silver triflate an $SnCl_4$ is described reporting high yields as a mixture of anomers depending on the as bulkiness, presence of electron-withdrawing groups or polyethoxy motifs (Scheme 2.29) [29].

The application of zeolites as heterogeneous catalysts for the preparations of alkyl glycosides is an alternative method due to the acid strength and larger pore openings and channel intersections. Thus, the Fe-β zeolite gave the maximum yield of 63 % of cetyl galactopyranoside as a mixture of anomers (Scheme 2.30) [30].

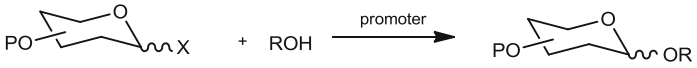
This methodology has been also useful to synthesize 1-naphthyl 2,3,4,6-tetra-*O*-acetyl-α,β-L-idopyranoside by mixing 1,2,3,4,6-penta-O-acetyl-α-L-idopyranose, 1-naphthol, zinc chloride and heating up to 120 °C during 1 h (Scheme 2.31) [31].



i) $ZnCl_2$,120ºC, 1h.

Scheme 2.31 Preparation of naphthyl *O*-glycosides with peracetylated sugars with naphthols under $ZnCl_2$ catalyst

2.1.6 *Imidate Reaction*



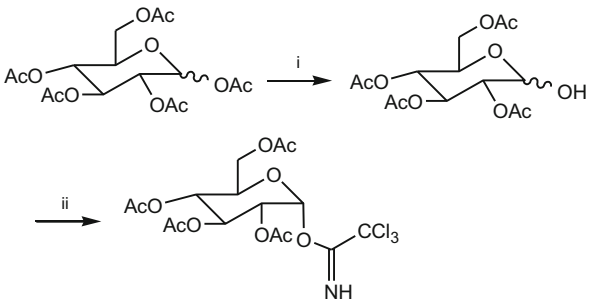
X = $OC(NH)CCl_3$

X = $OC(NPh)CF_3$

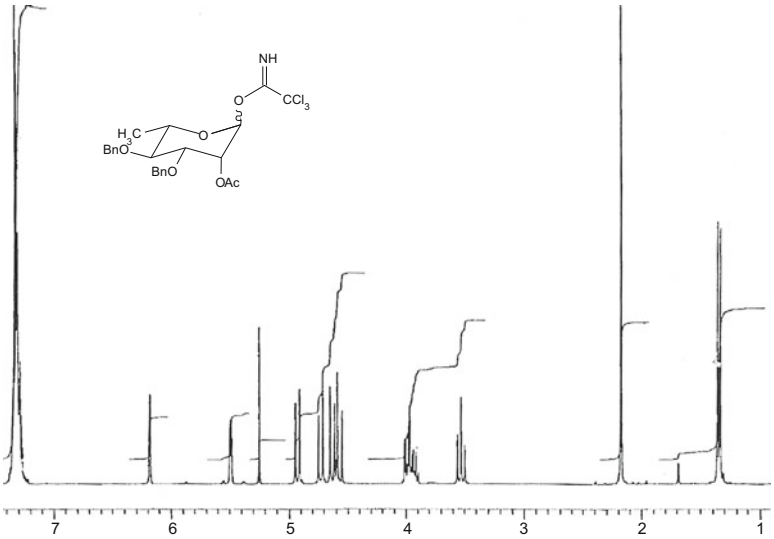
Imidate	Promoter	Conditions
$OC(NH)CCl_3$	AgOTf	CH_2Cl_2, 0 °C → r.t.
$OC(NH)CCl_3$	TMSOTf	CH_2Cl_2 or MeCN, 0 °C
$OC(NH)CCl_3$	BF_3-OEt_2	CH_2Cl_2 or MeCN, −20 °C
$OC(NH)CCl_3$	NaH	CH_2Cl_2
$OC(NH)CCl_3$	$PhBF_2$	CH_2Cl_2, −78 °C, ref. [32]
$OC(NH)CCl_3$	Chiral Brønsted acid catalyst	toluene ref. [33]
$OC(NH)CCl_3$	2 mol% $Pd(PhCN)_2Cl_2$, 4 mol% AgOTf	CH_2Cl_2, −78 °C, ref. [34]
$OC(NPh)CF_3$	TBSOTf	4 Å MS, toluene, −40 °C

This protocol is attributed to Schmidt and coworkers [35, 161] who introduced trichloroacetimidate as a good leaving group for preparation of *O*-glycosides. A significant number of simple and complex *O*-glycosides involving the imidate coupling reaction have been described. This strategy involves the use of trichloroacetonitrile that in the presence of a base is incorporated on the anomeric hydroxyl group to generate trichloroacetimidate (Scheme 2.32). It should be noted that the resulting imidate derivative is air sensitive and should be used in coupling reactions immediately following preparation. Imidate formation might be spectroscopically detected by ^{1}H NMR through a signal appearing down field at 6.2 ppm [36].

Once the imidate if formed, it can be subjected to nucleophilic attack to provide the corresponding *S*-, *N*-, *C*-, or *O*-glycoside, depending on the chosen nucleophile. The use of a catalyst such as $BF_3.OEt_2$, TMSOTf, or AgOTf is necessary to carry out the reaction to completion (Scheme 2.33). Although the unquestionable applicability of this approach, an undesirable side reaction has been encountered with glycosyl trichloroacetimidates in the presence of Lewis acid catalysis via the Chapman rearrangement [35, 161].



i) Bn-NH_2, HCl, THF. or NH_2NH_2 ii) Cl_3CN, $CsCO_3/CH_2Cl_2$, r.t.

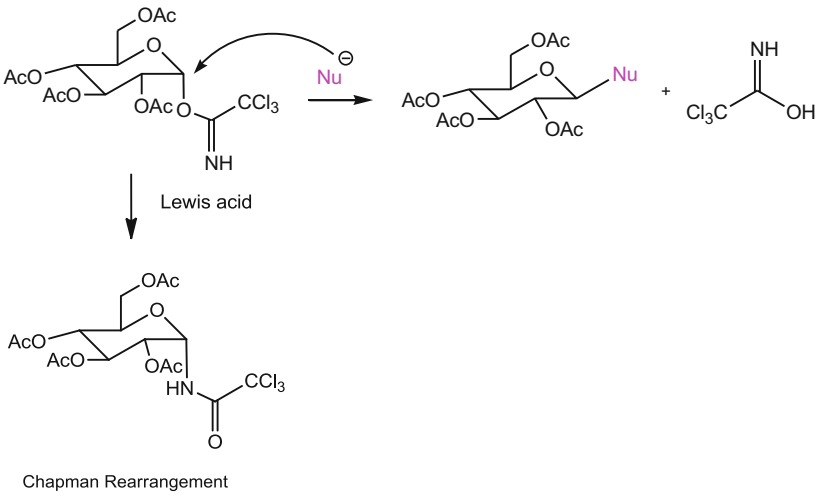


Scheme 2.32 Preparation of glycosyl imidate and ^{1}H NMR of imidate rhamnosyl derivative

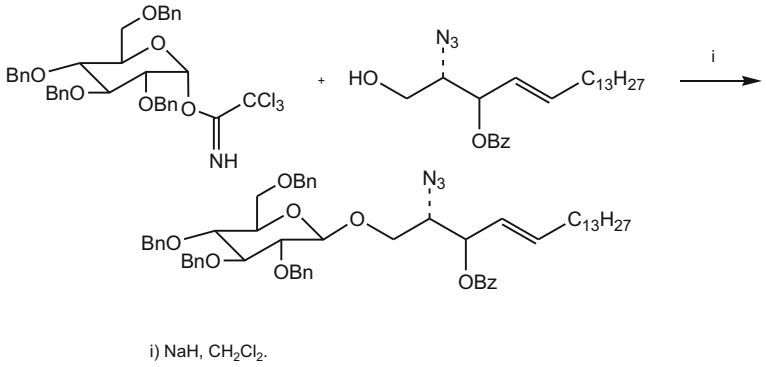
Hasegawa et al. [37] has prepared the ganglioside shown in Scheme 2.34 using 2,3,4,6-tetrabenzylglucopyranosyl-α-acetimidate with the lipophilic alcohol, to generate a ganglioside.

The total synthesis of calicheamicin α and dynemicin A has been described by Danishefsky's group [38], and involves glycosylation of calicheamicinone congener with the complex glycosyl imidate using $BF_3.OEt_2$ as Lewis acid catalyst (Scheme 2.35).

Naturally occurring herbicides known as tricolorin A, F and G were isolated from the plant *Ipomoea tricolor* and since then synthesized involving glycoside coupling reactions. The first total synthesis of tricolorin A was performed by Larson and Heathcock [39], involving three coupling reactions steps with imidate intermediates used as glycosyl donors (Scheme 2.36). The lactonization key step for the preparation of the synthesized tricolorins has been achieved either under macrolactonization



Scheme 2.33 Nucleophilic displacement of imidate leaving group

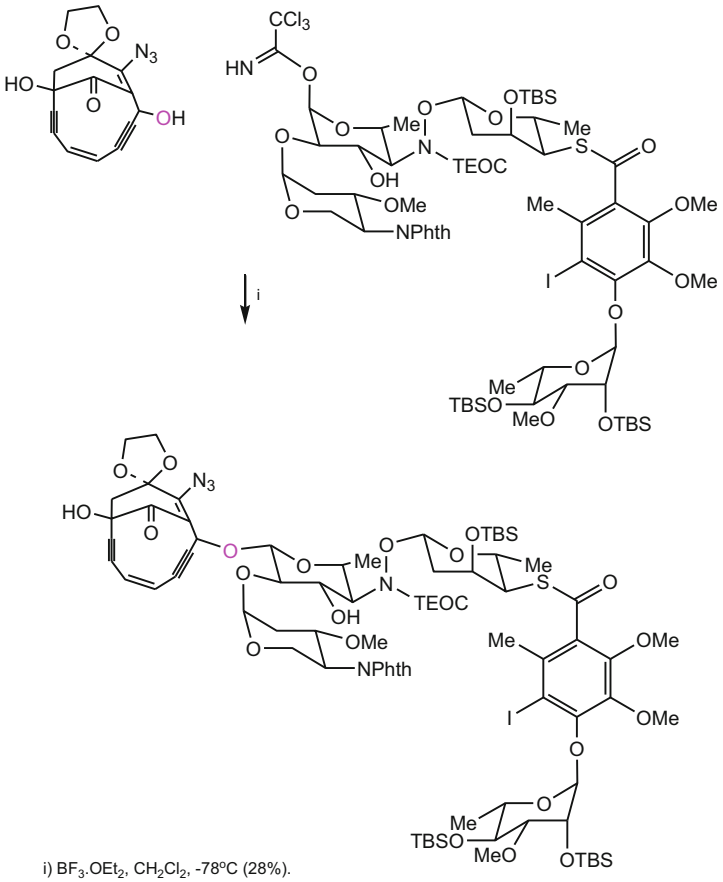


Scheme 2.34 Coupling reaction for the preparation of ganglioside

conditions reported by Yamaguchi [40, 41] and also under ring closure methathesis conditions [36].

Another hetero-trisaccharide resin glycoside of jalapinolic acid known as tricolorin F has been synthesized involving coupling reactions with imidates as glycosyl donors. In this way disaccharide and trisaccharide were prepared sequentially. The resulting tricoloric acid C derivative was deprotected and subjected to lactonization under Yamaguchi conditions to produce protected macrolactone. Final removal of acetonide and benzyl protecting groups provided Tricolorin F (Scheme 2.37) [41].

A convergent approach for obtaining a tumoral antigen fragment of Lewis^x has been developed by Boons et al. [42, 162] Condensation of the imidate glycosyl donor and the trisaccharide glycosyl acceptor provided the hexasaccharide, which

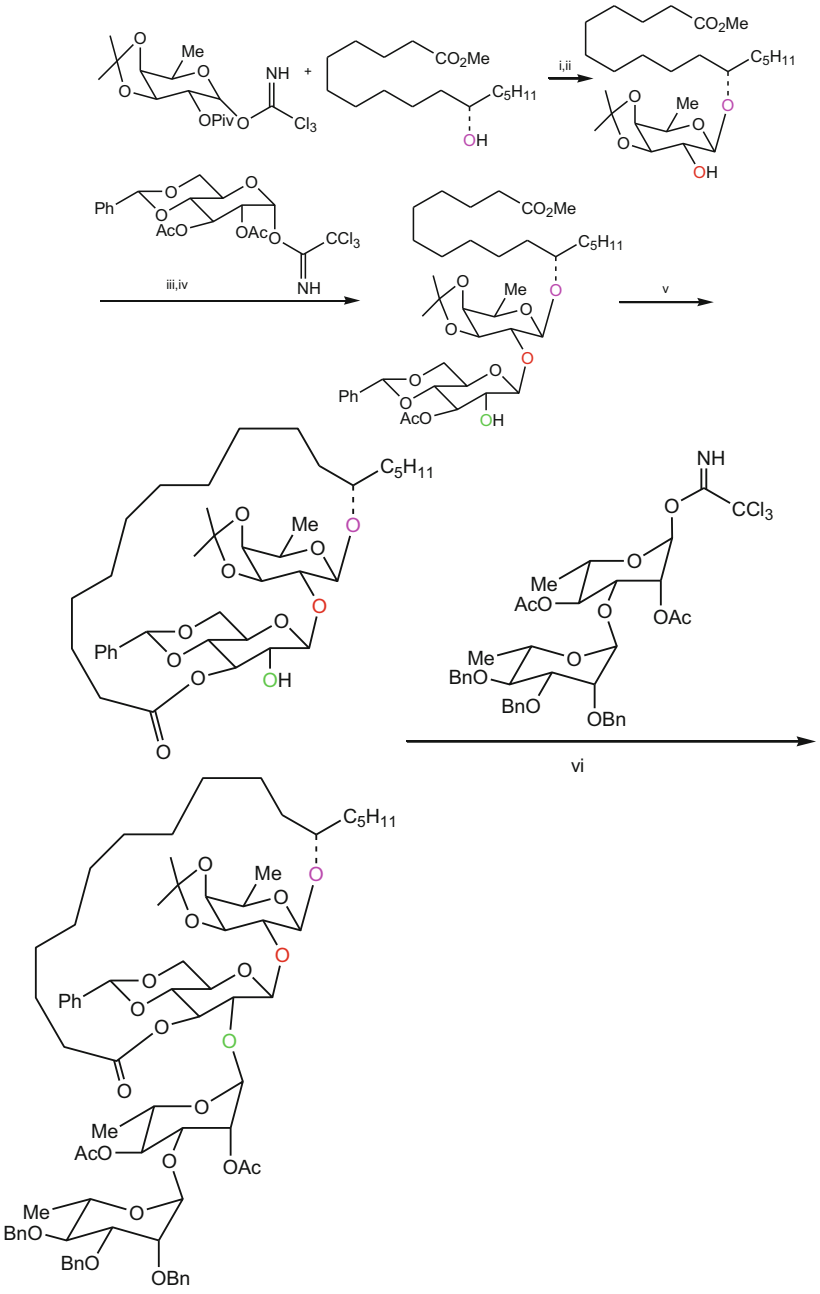


Scheme 2.35 Glycosylation of calicheamicinone congener

was further allowed to react with trichloroacetimidate to generate a hexasaccharide glycosyl donor. The final coupling reaction with the disaccharide using $BF_3.OEt_2$, furnished the tumoral fragment Lewis^X (Scheme 2.38).

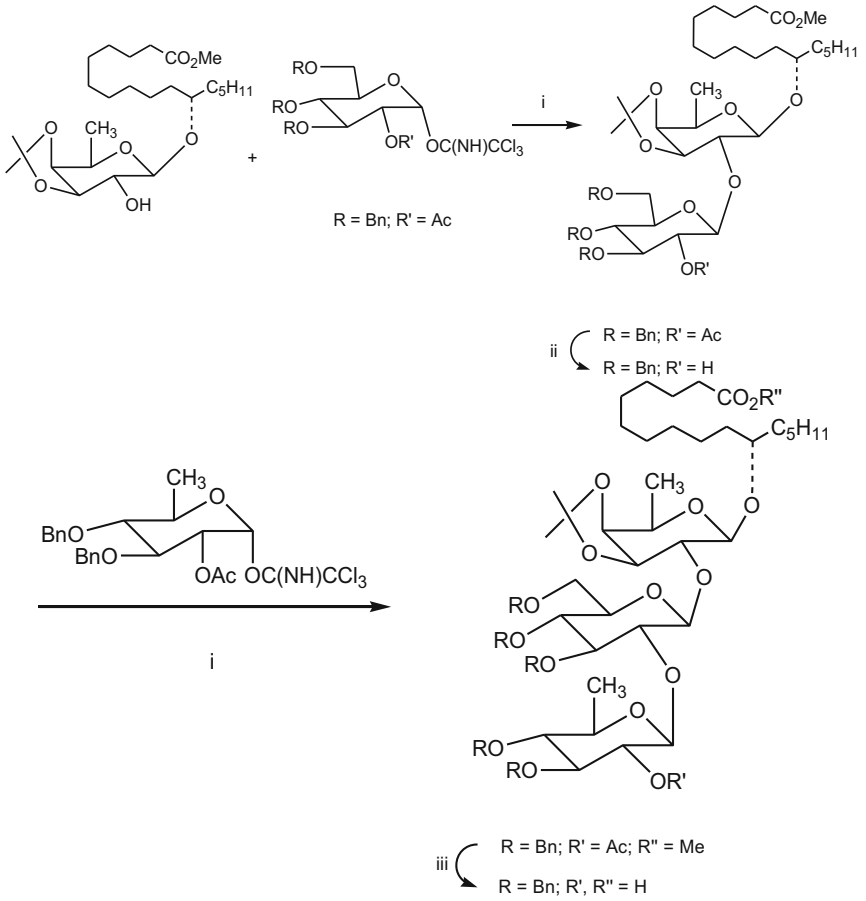
Selectins (E, P, and L) are mammalian C-type lectins involved in the recognition process between blood cells or cancer cells and vascular endothelium. L-selectins plays a key role in the initial cell-adhesive phenomena during the inflammatory process, whereas E-selectins binds strongly to sialyl Lewis^A and Lewis^X [43, 44, 163–165]. It has been found that the tetrasaccharide sialyl Lewis^X is the recognition molecule and the preparation of sialyl Lewis^X confirmed the hypothesis that sulfation increase the affinity for L-selectins [45]. The chemical synthesis of 3e- and 6e-monosulfated and 3e,6e-disulfated Lewis^X pentasaccharides has been prepared according to the Scheme 2.39.

Likewise, thioaryl donors can also be suitably converted to acetimidates for performing glycoside coupling reactions. This is the case of arabinosyl thio derivative



i) AgOTf, CH_2Cl_2. ii) MeONa/MeOH. iii) AgOTf, CH_2Cl_2. iv) a) MeONa/MeOH. b) 1eq. Ac_2O, DMAP, CH_2Cl_2, Et_3N. v) a) LiOH, THF, H_2O. b) 2,4,6-trichlorobenzoyl chloride, Et_3N, MAP, benzene. vi) AgOTf, CH_2Cl_2.

Scheme 2.36 Synthesis of tricolorin A precursor

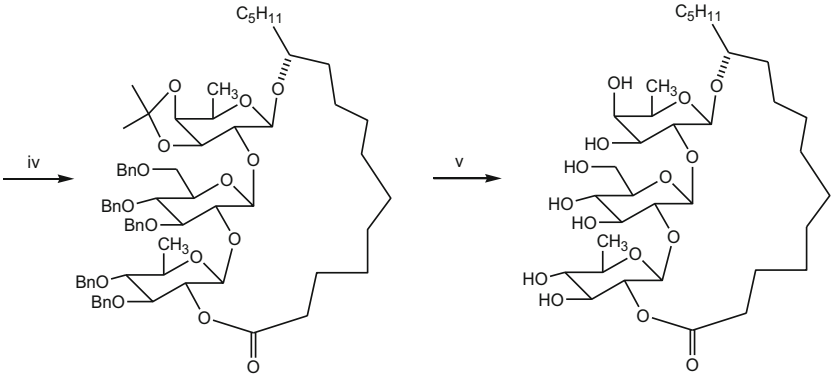


Scheme 2.37 Synthesis of tricolorin F

which is deprotected under NBS-pyridine conditions forming the lactol in 80 % yield as a mixture of anomers (2:1). Treatment with NaH, followed by addition of Cl_3CCN provided the desired trichloroacetimidate intermediate. This strategy has been successfully applied in the syntheses of cytotoxic marine natural products eleutherobin (Scheme 2.40) [46].

Fluorogenic aglycones such as 4-methylumbelliferyl have been attached to peracetylated imidates providing the alpha anomer only when TMSOTf was used as promoter at −20 °C (Scheme 2.41). The resulting glycoside was further used for preparing a 4-MU α-T-anitgen [47].

In order to understand the α-stereoselectivity the authors proposed that the imidates in the presence of TMSOTf generate an oxocarbenium triflate ion pair which in turn will accept the nucleophilic attack, favoring an alpha glycoside formation due to the extra stability arising from through-space electrostatic interaction between the axially disposed C-4 acetyl function and ring oxygen atom of the corresponding α-glycosyl oxonium ion (Scheme 2.42).



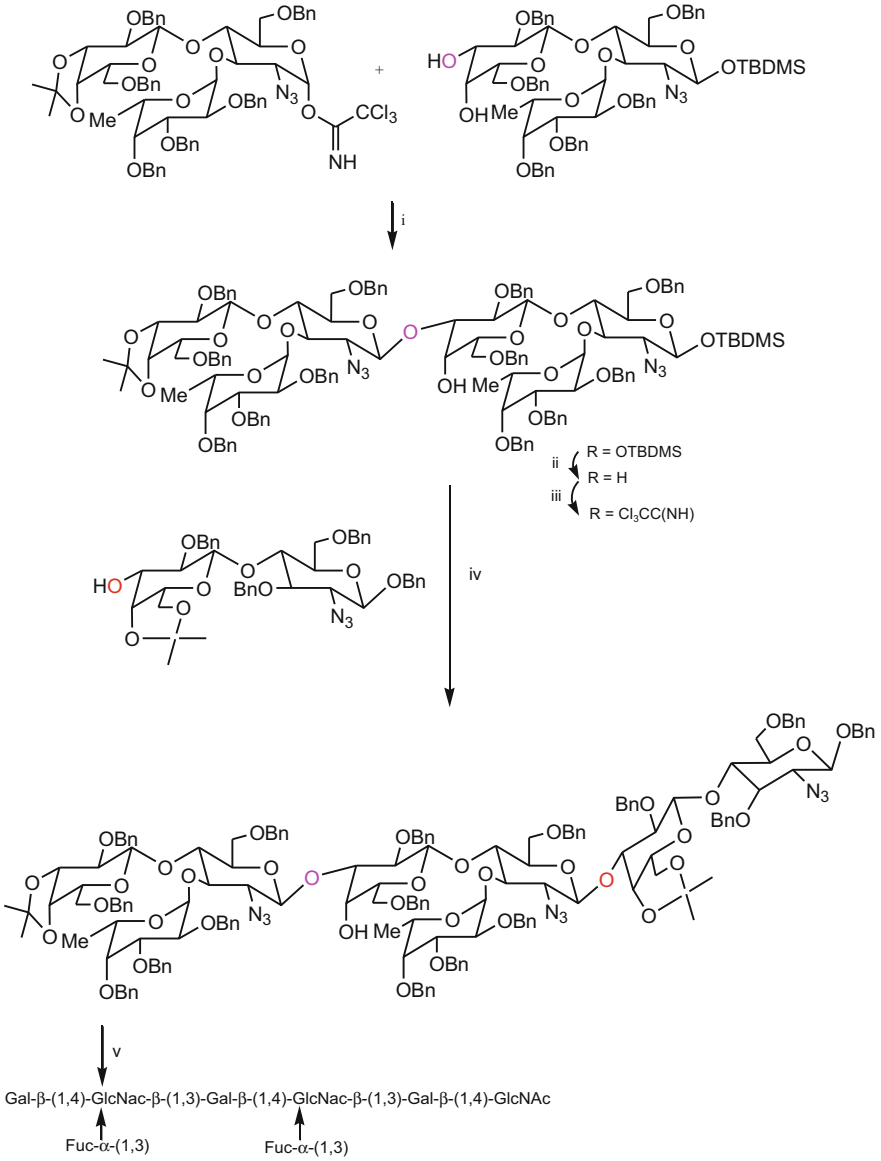
i) $BF_3.Et_2O$, CH_2Cl_2, -20°C, 1 h; (ii) NaOMe, MeOH, 6h, rt. iii) KOH, MeOH-H_2O, 4 h, reflux. iv) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, PhH. v) 10% HCl-MeOH, $Pd(OH)_2$-C 10%, MeOH.

Scheme 2.37 (continued)

Another approach leading to the preparation of amino acid glycosides with enhanced α-stereoselectivity was described involving trichloroacetimidate donors with non-participating protecting groups with protected amino acids using the heterogeneous catalyst, $HClO_4$–SiO_2, reporting high yields (Scheme 2.43) [48].

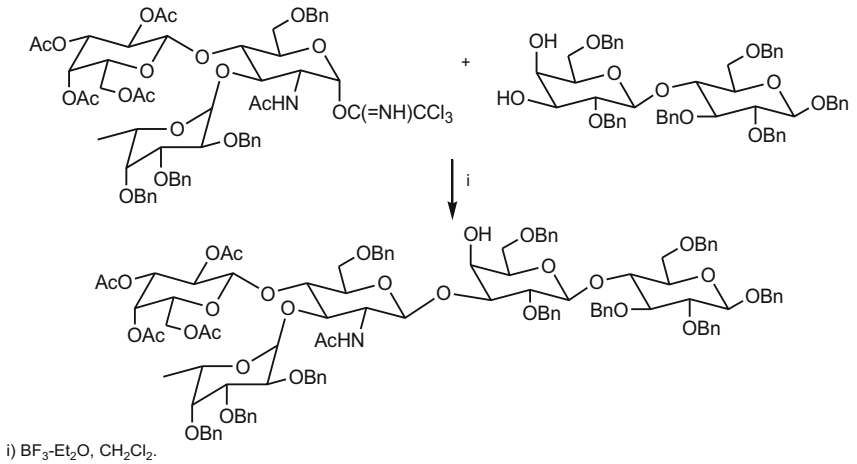
An additional utility of trichloroacetimidates as leaving group is its ability to be transformed to ureas with α-stereoselectivity via nickel-catalyzed [1,3]-rearrangement and subsequent treatment with secondary amines under the conditions described in Scheme 2.44 [49].

Another approach involving imidates was assayed with trifluoroacetimidate as leaving group and a disaccharide acceptor, using CH_2Cl_2 as solvent and TBSOTf as the promoter. Under these conditions different α:β ratios were observed, however by lowering the temperature from −20 °C to −40 °C and improved α:β ratio was obtained while keeping the good yields (Scheme 2.45) [50].



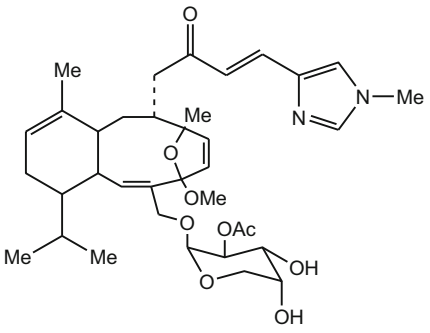
i) $BF_3.OEt_2$, CH_2Cl_2. ii) TBAF, AcOH. iii) Cl_3CCN, DBU. iv) $BF_3.OEt_2$, CH_2Cl_2.
v) a) AcOH. b) H_2, Pd-C.

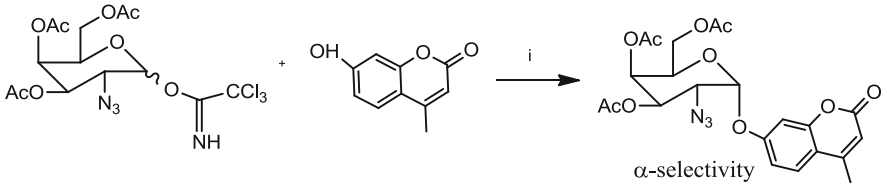
Scheme 2.38 Convergent synthesis of Lewis^X fragment



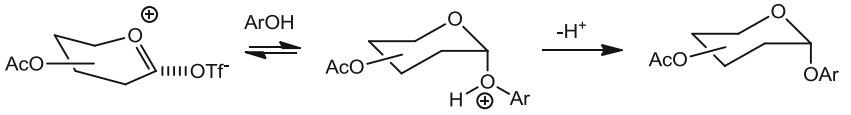
Scheme 2.39 Coupling reaction for the preparation of Lewis^X pentasaccharide intermediate

Scheme 2.40 Cytotoxic marine glycoside eleutherobin

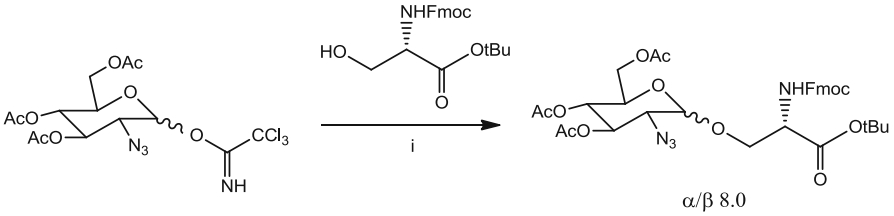




Scheme 2.41 Synthesis of α-4-methylumbelliferyl glycosides

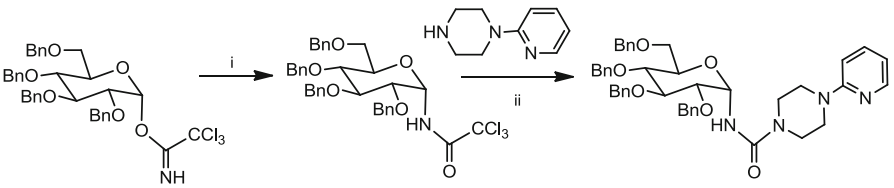


Scheme 2.42 Proposed oxocarbenium triflate ion intermediates leading to α-stereoselectivity



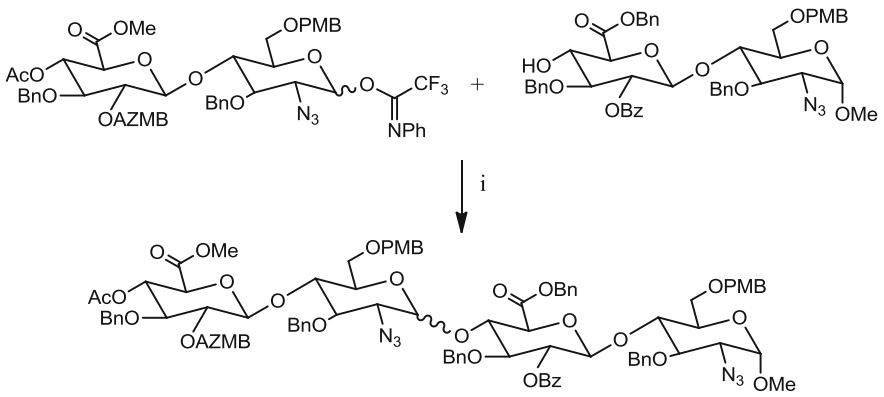
i) $HClO_4$-SiO_2, CH_2Cl_2-dioxane, 0°C

Scheme 2.43 Preparation of α-amino acid glycosides from imidates



i) $Ni(dppe)Cl_2$, AgOTf, CH_2Cl_2, 25°C. ii) Cs_2CO_3, DMF

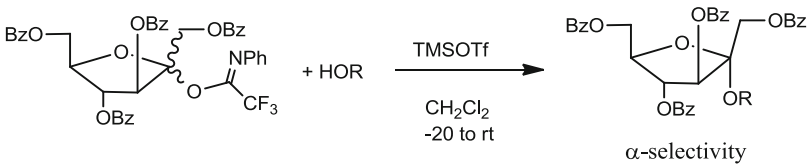
Scheme 2.44 Preparation of glycosyl ureas from imidates



i) TBSOTf,4 Å MS, toluene, -40 °C, 71%

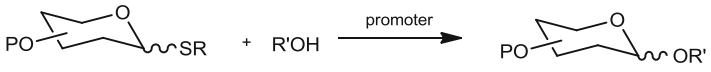
Scheme 2.45 Synthesis of tetrasaccharides from phenyl trifluoroacetimidate as glycosyl donor

Likewise, fructofuranosides having *N*-phenyl trifluoroacetimidate as leaving group formed α-*O*-glycosides for different aglycons such as admantanol, protected sugars, phenols, and flavonoids, when TMSOTf is used as promoter at low temperature (Scheme 2.46) [51].



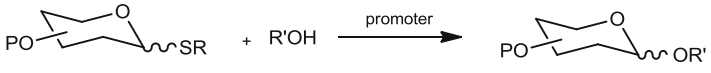
Scheme 2.46 Preparation of fructofuranosyl glycosides from *N*-phenyl trifluoroacetimidate as leaving group

2.1.7 Sulfur Reaction



R = Me, Et

Promoter	Conditions
NIS-TfOH	0 °C → r.t.
$HgCl_2$	CH_2Cl_2 or MeCN, 0 °C
$CuBr_2$-Bu_4NBr-AgOTf	CH_2Cl_2 or MeCN, −20 °C
MeOTf	Et_2O, r.t.
MeSOTf	Et_2O, r.t.
AgOTf-Br_2	CH_2Cl_2
DMTST	MeCN, −15 °C
NBS-TfOH	EtCN, −78 °C

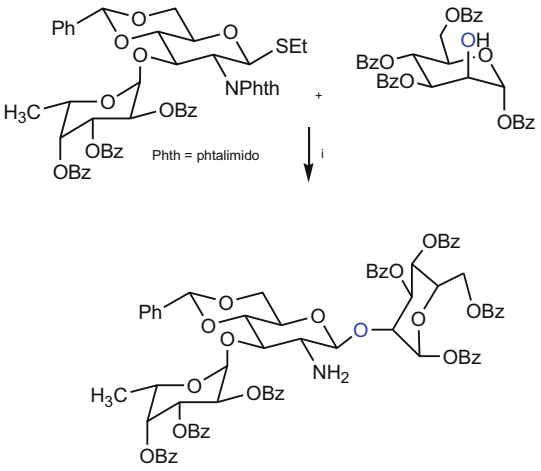


R = Ph, Tol

Promoter	Conditions
NIS/TfOH	MeCN
NBS	CH_2Cl_2, r.t.
BSP	CH_2Cl_2, MS, r.t
DMTST	CH_2Cl_2
MeOTf	CH_2Cl_2
MeSOTf	CH_2Cl_2
(a) Ph_2SO, Tf_2O (b) TBAI	CH_2Cl_2, MS, −78 °C, ref. [52]
NIS, AgOTf	CH_2Cl_2, MS, −45 °C ref. [53]

Thioglycosides are useful glycosyl donors widely used in the preparation of *O*-glycosides. An example of their applicability for the preparation of saccharide synthesis is represented in Scheme 2.47. Thus, the synthesis of trisaccharide intermediate was obtained by combining the thioglycoside donor with a monosaccharide

Scheme 2.47 Thioglycoside coupling reaction for preparation of a trisaccharide intermediate



i) $CF_3SO_3CH_3$, Et_2O, MS, rt. ii) a) NH_2-NH_2.H_2O, EtOH reflux. b) Ac_2O, Py

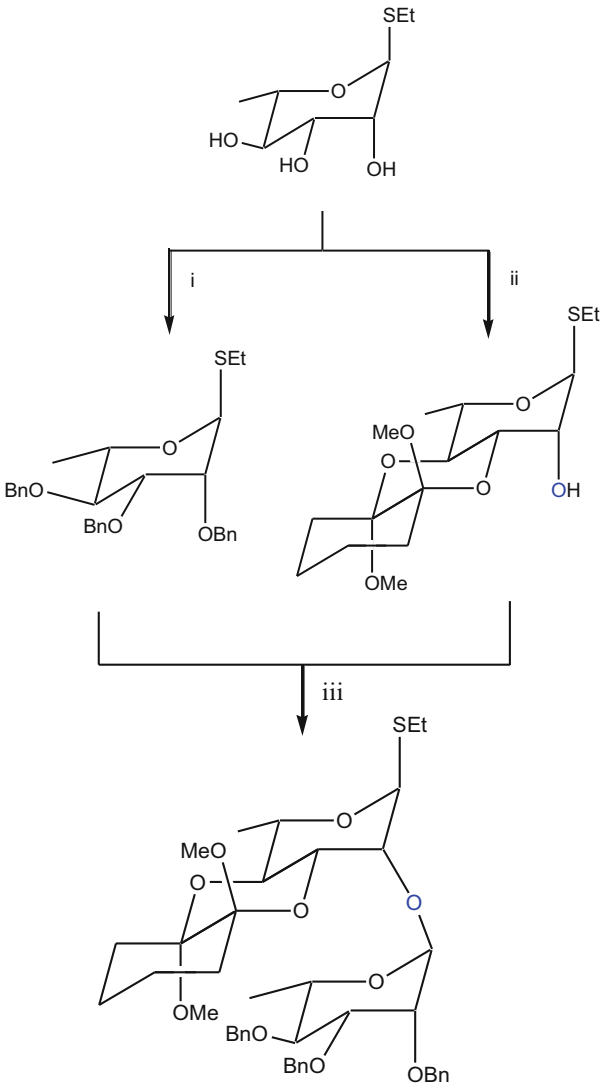
acceptor in the presence of methyltriflate, to provide the target trisaccharide in 72 % yield [54].

A convergent synthesis of the trisaccharide unit belonging to an antigen polysaccharide from streptococcus has been performed by Ley and Priepke [55]. In this approach rhamnosylalkylsulfur was used as the glycosyl donor, and cyclohexane-1,2-diacetal as the protecting group (Scheme 2.48).

Thioalkyl donors are also useful derivatives for the preparation of biologically important natural sugars known as sialic acids [23, 159, 160]. An efficient procedure for introducing thioalkyl groups as leaving groups involves the conversion of acetate into thiomethyl by treatment with methylthiotrimethylsilane in the presence of TMS-triflate. *O*-glycosylation reaction proceeds between the thioglycosylsialic donor and a glycosyl acceptor (bearing an -OH group available), using a catalyst such as *N*-iodosuccinimide-TfOH as promoter (Scheme 2.49) [56].

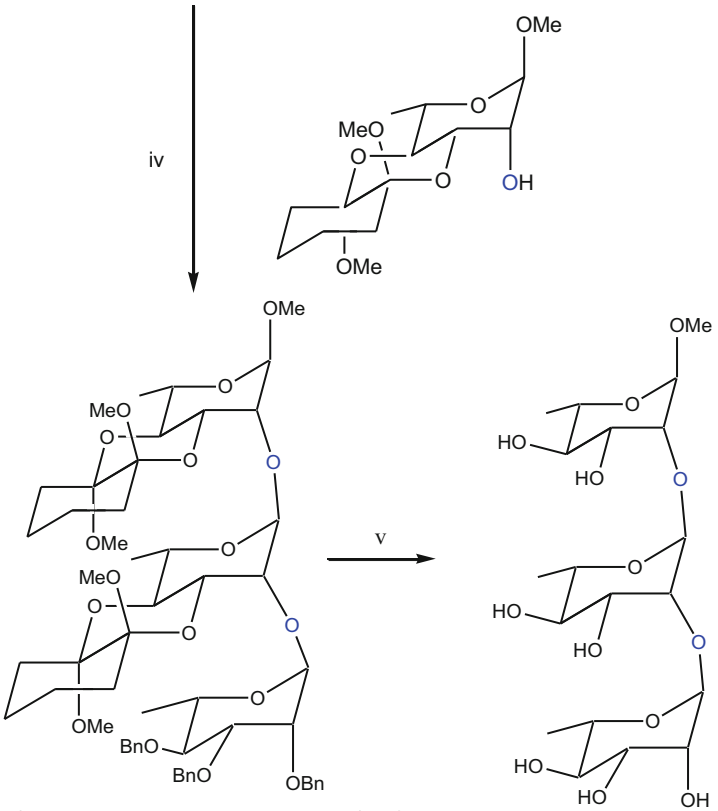
The synthesis of aryl 2-deoxy-D-glycopyranosides from 2-deoxy-1-thioglycosides and differently substituted phenols and naphthols under *N*-iodosuccinimide/triflic acid conditions is reported. The analysis of the reaction mixtures was followed by HPLC technique showing that the α-anomers are the major product (Scheme 2.50) [57].

2-thiophenyl glycosides were used as glycosyl donor for preparing complex oligosaccharides containing sialyl moieties. A remarkable convergent approach was described for preparing a sialyl octasaccharide consisting in the initial glycosidic reaction between 2-thiophenyl Neu5Ac donor and trisaccharide intermediate to produce the expected tetrasaccharide in 45 % having an α(2 → 6)-linkage. The resulting tetrasaccharide was coupled with dimeric sialyl donor to yield hexasaccharide in 42 %. Acetal hydrolysis was followed by coupling reaction with Neu5Acα(2 → 3) GalSMe donor to give the octasaccharide in 85 % yield (Scheme 2.51) [58].



Scheme 2.48 Synthesis of an antigen polysaccharide fragment

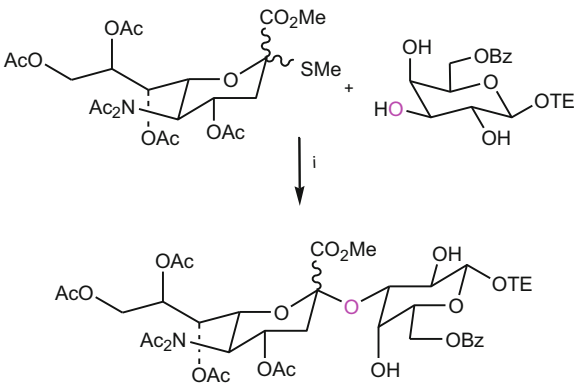
Crich and Li [59] introduced the use of 1-(Benezenesulfinyl)piperidine/triflic anhydride as promoter conditions for preparing *O*-glycosides from thioglycoside donors. These conditions were applied for preparing Salmonella type E1 core trisaccharide (Scheme 2.52). This method has been adopted as an alternative approach known as "iterative or preactivation" glycosylation which consist in treatment of the thioglycoside with 1-benzenesulfinyl piperidine (BSP) or morpholine analog (BSM) and triflic anhydride at low temperature, and the resulting "glycosyl triflate"



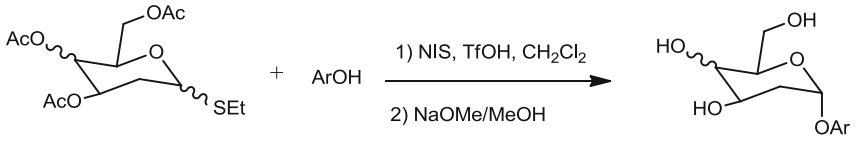
i) BnBr, NaH, DMF. ii) 1,1,2,2-tetramethoxycyclohexane. iii) IDCP, 4ÅMS. iv) NIS. v) AcOH-H_2O. vi) H_2,Pd/C, EtOH.

Scheme 2.48 (continued)

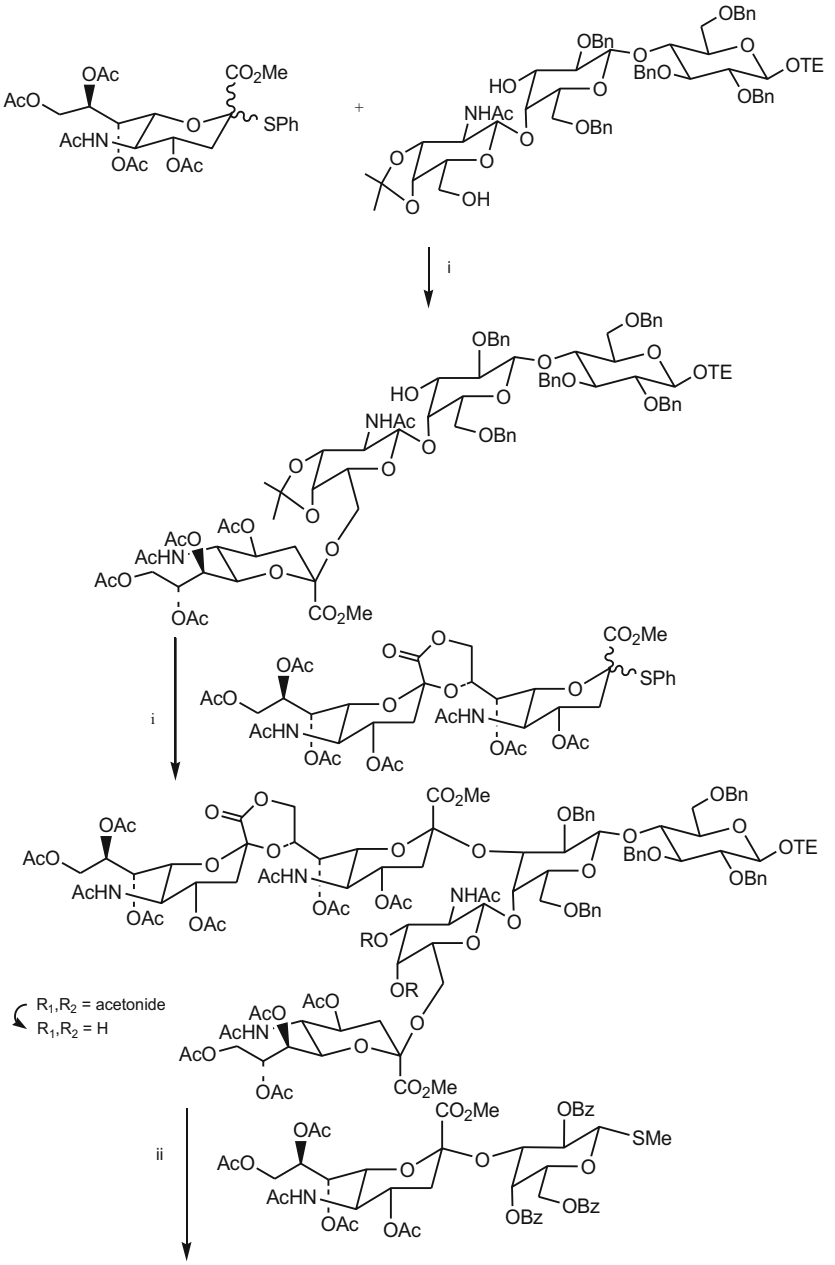
Scheme 2.49 Thioalkyl donor for the preparation of sialic acids



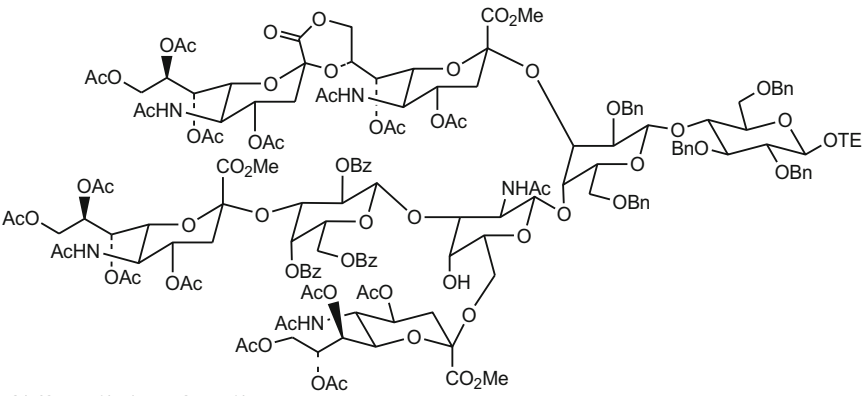
i) NIS/TfOH, MeCN, -40°C.



Scheme 2.50 Synthesis of aryl 2-deoxy-D-glycopyranosides from 2-deoxy-1-thioglycosides

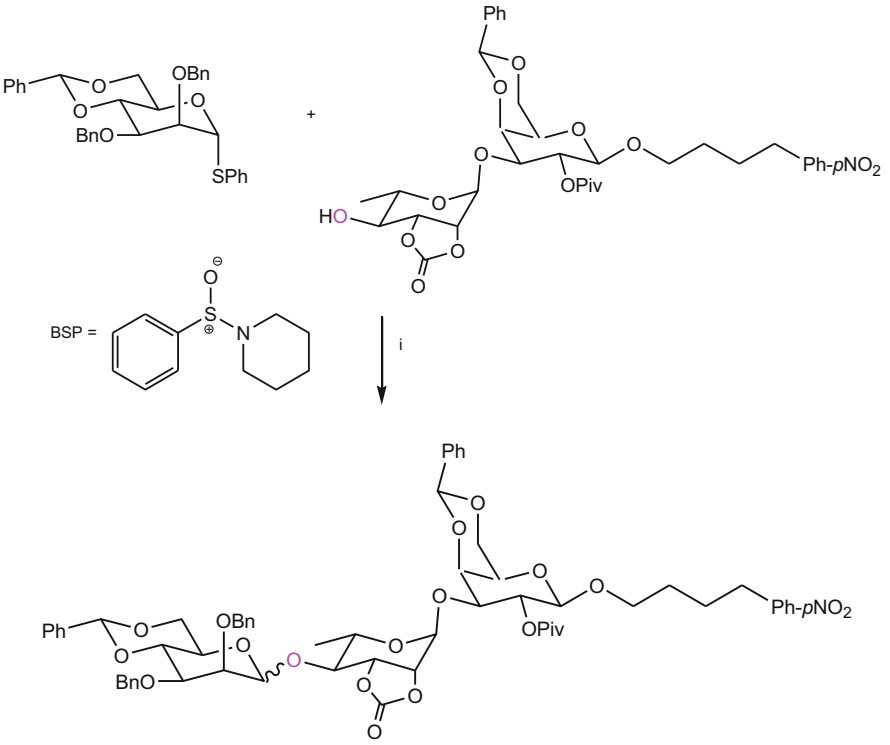


Scheme 2.51 Convergent synthesis of sialyl oligosaccharide



i) NIS/TfOH, 45%. ii) DMTST, 85%.

Scheme 2.51 (continued)



i) a) BSP, m.s., CH_2Cl_2, r.t. b) Tf_2O, -60°C to 0°C 1h.

Scheme 2.52 Preparation of Salmonella type E_1 core trisaccharide under BSP-Tf_2O conditions

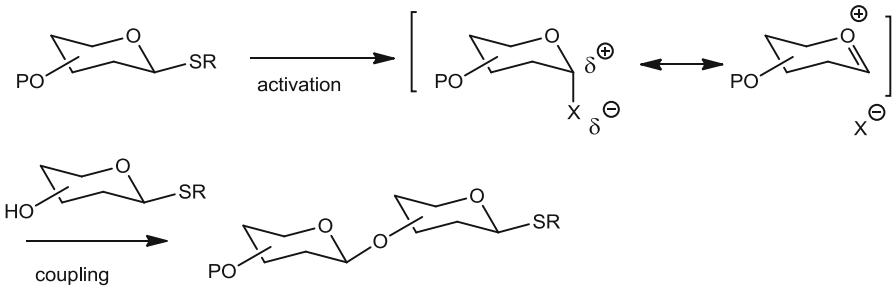
intermediate treated with a thioglycosides acceptor having a free alcohol suitable for attachment [60].

This method has been extended as an alternative approach known as "iterative or preactivation" glycosylation which consist in the treatment of the thioglycoside with 1-benzenesulfinyl piperidine (BSP) or morpholine analog (BSM) and triflic anhydride at low temperature, and the resulting "glycosyl triflate" intermediate treated with a thioglycosides acceptor having a free alcohol suitable for coupling reaction (Scheme 2.53) [60, 61].

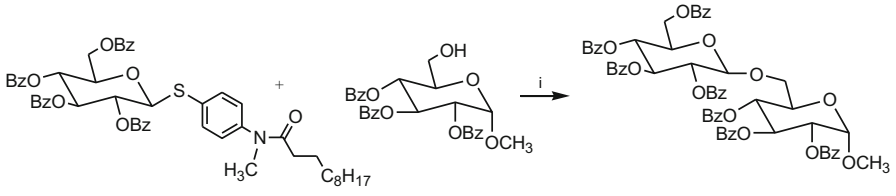
Highly fluorinated thiols have been developed and used as donors in the preparation of disaccharides. The reactivity of these novel fluorinated thiols were examined using different acceptors. Thus, disaccharide formation under glycosidic conditions provided the disaccharides in high yields (Scheme 2.54) [62].

Thioglycosides have been used as donor models for glycosylations with imidazolium-based ionic liquids promoters under *N*-iodosuccinimide conditions. Thus it was observed that tetra-*O*-benzyl-1-thio-β-D-glucopyranoside as donor and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose as glycoside acceptor gave the disaccharide in almost 1:1 α/β ratio in 84 % yield. This methodology claims to have the ability of recycling the ionic liquid promoter which make it attractive as a cost effective protocol (Scheme 2.55) [63].

An study using protected thio gluco and galactoside bearing and acetate group at 6-position was conducted to determine the influence of solvent in the stereoselectivity of the glycosylation reaction with small and reactive acceptors has been carried

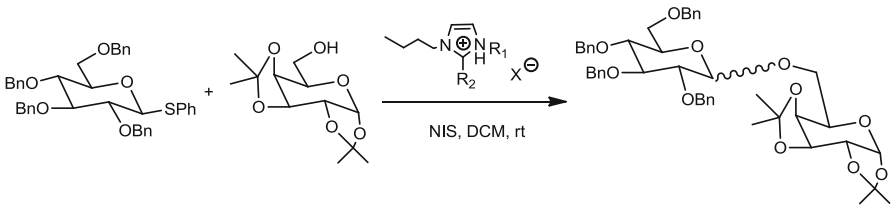


Scheme 2.53 Iterative or preactivation protocol

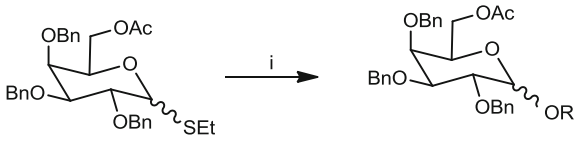


i) NIS (2eq.), AgOTf (0.2eq.), CH_2Cl_2.

Scheme 2.54 Highly fluorinated thiols glycosyl donor for glycosidation

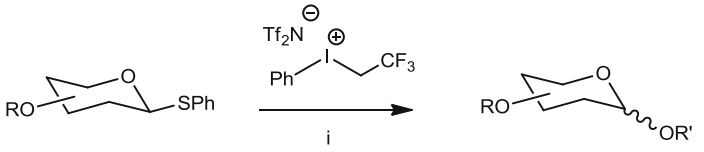


Scheme 2.55 glycosylations with imidazolium-based ionic liquids promoters under *N*-iodosuccinimide



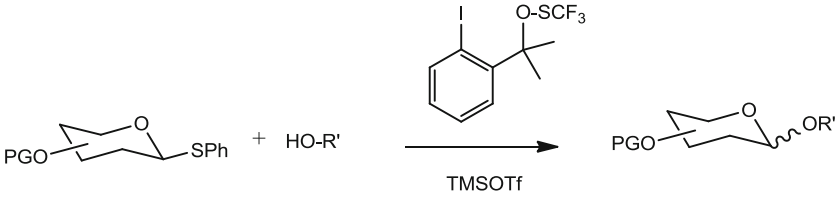
i) NIS, TfOH, MS, Et_2O, -60°C

Scheme 2.56 α-stereoselectivity under NIS/TfOH activation



i) R'OH, TTBP, CH_2Cl_2, rt

Scheme 2.57 *O*-glycoside formation with an air- and water-stable iodonium salt

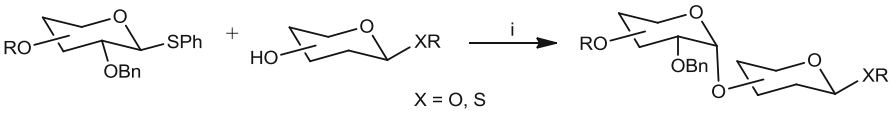


Scheme 2.58 O-glycosylation under thioperoxide-TMSOTf conditions

out, observing a high α-stereoselectivity when using NIS/TfOH as activator and ethyl ether as the solvent at −60 °C. Other solvents did not improve the *α*/*β* ratio, although yields were high (Scheme 2.56) [64].

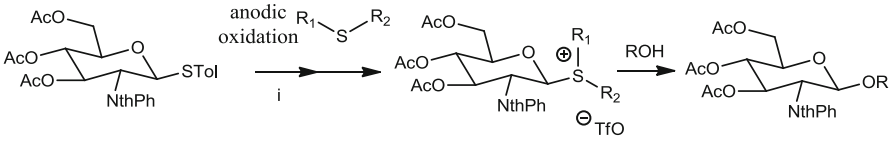
Fully substituted and deoxy thioglycoside donors were converted to cholesterol and disaccharide *O*-glycosides by reaction with an air- and water-stable iodonium salt phenyl(trifluoroethyl)-iodonium triflimide as an activator for glycosylation reporting 68–97 % yield as a mixture of isomers (Scheme 2.57) [65].

Thioperoxide in combination with trimethylsilyl trifluoromethanesulfonate (TMSOTf) was designed as thioglycosides activators as it can be seen in the *O*-glycoside synthesis of disaccharides reporting high yields and β stereoselectivity or as a mixture of anomers (Scheme 2.58) [66].



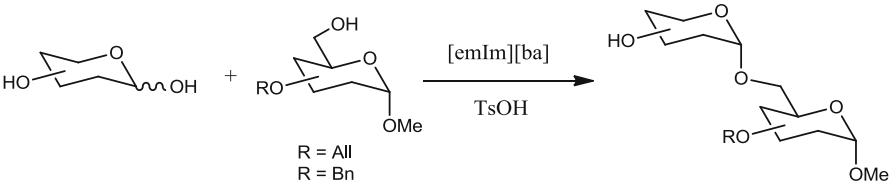
i) Ph_2SO, Tf_2O, N-methylmaleimide ii) BuN^+I^-

Scheme 2.59 1,2-Cis glycosylation under Ph_2SO/Tf_2O conditions



i) Bu_4NOTf, CH_2Cl_2, -78%°C

Scheme 2.60 O-glycosylation method via electrochemically generated glycosyl triflate



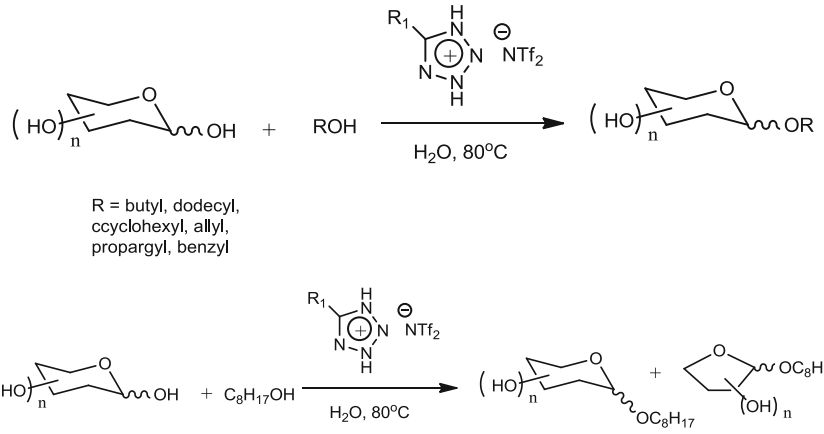
Scheme 2.61 Unprotected glycosylation in the presence of acidified liquid ion solvents

Another report for preparing 1,2-cis-R-glycosides from thioglycosyl donors without directing groups involved activating conditions of Ph_2SO/Tf_2O at low temperature. It was observed that the use of tetrabutylammonium iodide (TBAI) and *N*-methylmaleimide leds to a increase of yield accompanied by high 1,2-cis stereoselectivity (Scheme 2.59) [67].

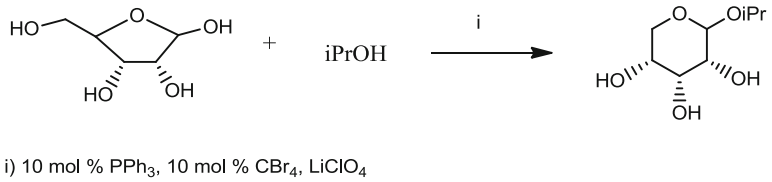
Toluylglycoside was chosen as a glycosyl donor for preparing glycosyl sulfonium ions, via electrochemically generated glycosyl triflate, which in turn served for preparing β-disaccharides from moderate to good yields depending on the temperature at which glycosylation was performed (Scheme 2.60) [68].

2.1.8 Unprotected Glycosylations

Attempts for preparing straight glycosylations using unprotected sugars with a variety of aglycons such as aliphatic, aromatic and other sugars have been implemented in the presence of different promoters. For instance simple benzyl glycosides and disaccharides of glucose, mannose and *N*-acetylgalactosamine were obtained in 1-ethyl-3-methylimidazolium benzoate with Amberlite IR-120 (H+) resin or *p*-toluenesulfonic acid as promoters in modest yields (Scheme 2.61) [69].



Scheme 2.62 Unprotected glycosylation in the presence of Brønsted acid ionic liquids (BAILs)

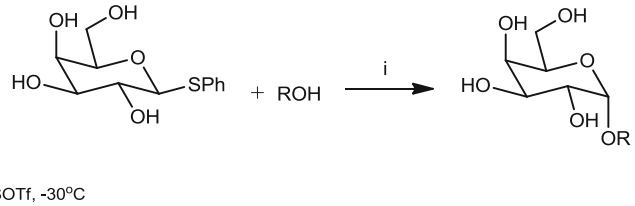


Scheme 2.63 Unprotected glycosylation via the Apple reaction

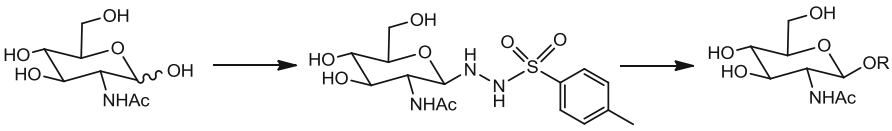
Brønsted acid ionic liquids (BAILs) have been designed as promoters for glycosylations of unprotected sugars due to their ability to adjust solubility properties by different cation–anion combinations. Under these conditions the yields reported range from 19 to 67 depending on the alcohol assayed, providing mainly the α-anomer. It has been observed that the reaction between different aldose monosaccharides and octanol produces a mixture of pyranosides and furanosides as a mixture of anomers (Scheme 2.62) [70].

Glycosylation of unprotected ribose with a variety of alcohols, have been carried out by following a variation of the Apple reaction which substitute a hydroxyl group by a bromine in situ, under triphenylphosphine and tetrabromomethane conditions. An improvement in the reaction was observed when lithium perchlorate was used in arabinose, xylose, and lyxose providing good yields although the glycosides were obtained in the pyranoid form with different α/β ratios (Scheme 2.63) [71].

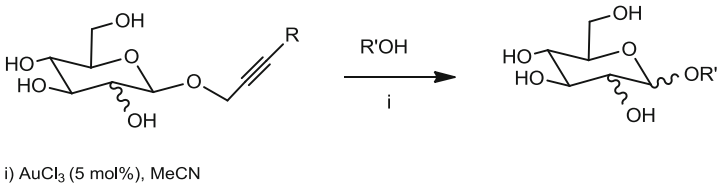
Previously this group was able to prepare isopropyl glycosides by direct glycosylation reaction of unprotected riboside with isopropanol in the presence of mandelic acid and titanium tert-butoxide [72]. On the other hand, Meng et al. [73] reported the 1,2-cis-alkyl glycosidation protocol with unprotected phenyl 1-thioglycosyl donors with a variety of alcohol acceptors under the activation of *N*-iodosuccinimide–trimethylsilyl triflate (although other Lewis acids such as TfOH or $BF_3.OEt_2$ provide good yields). The desired product was obtained in 75–76% yields and with high α stereoselectivity (Scheme 2.64).



Scheme 2.64 Unprotected glycosylation with unprotected phenyl 1-thioglycosyl donors



Scheme 2.65 Unprotected glycosylation by using *p*-toluenesulfonylhydrazide as donor



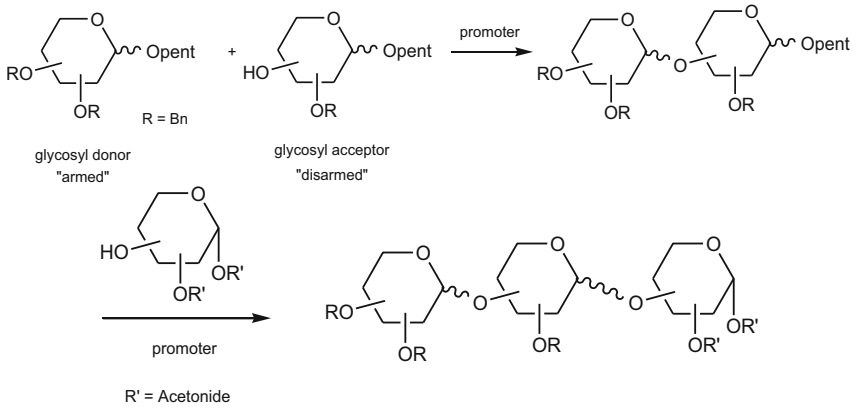
Scheme 2.66 Unprotected glycosylation from 2-butynyl glycosyl donors in the presence of gold (III) activation

Another protecting group free glycosidations was proposed by using *p*-toluenesulfonylhydrazide as leaving group followed by coupling reaction with alcohols in the presence of NBS in DMF at room temperature, providing the *O*-glycoside in good yields 70–87 % mainly as a β-isomer (Scheme 2.65) [74].

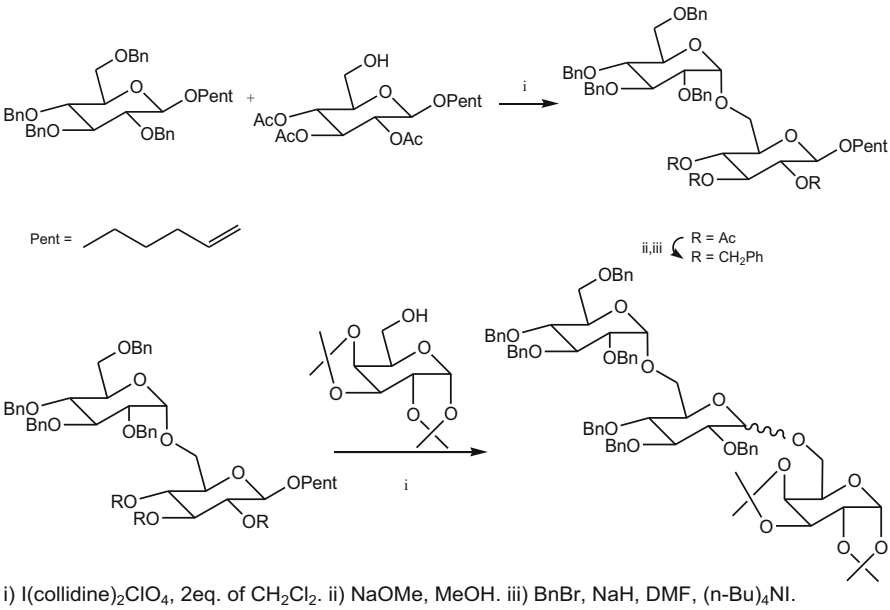
Gold (III) activation of unprotected glycosyl donors bearing 2-butynyl as leaving group has been used in combination with primary alcohols and protected saccharides as acceptors, providing the corresponding *O*-glycosides as a mixture of anomers in moderate yields (Scheme 2.66) [75].

2.1.9 Armed–Disarmed Method

This versatile approach has been attributed to Mootoo and Fraiser-Reid [76], and considers the use of a glycosyl donor in the classical sense coined with the term "armed saccharide" (because the reducing end is armed for further coupling reaction), and an acceptor in this case "disarmed saccharide" which contains both a free alcohol and a leaving group sufficiently resistant for the ongoing coupling reaction. The resulting disaccharide now becomes and armed disaccharide which in turn is



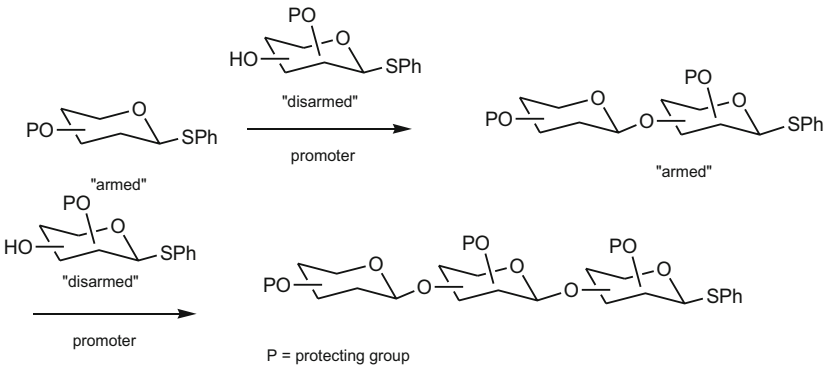
Scheme 2.67 General scheme for the armed–disarmed approach



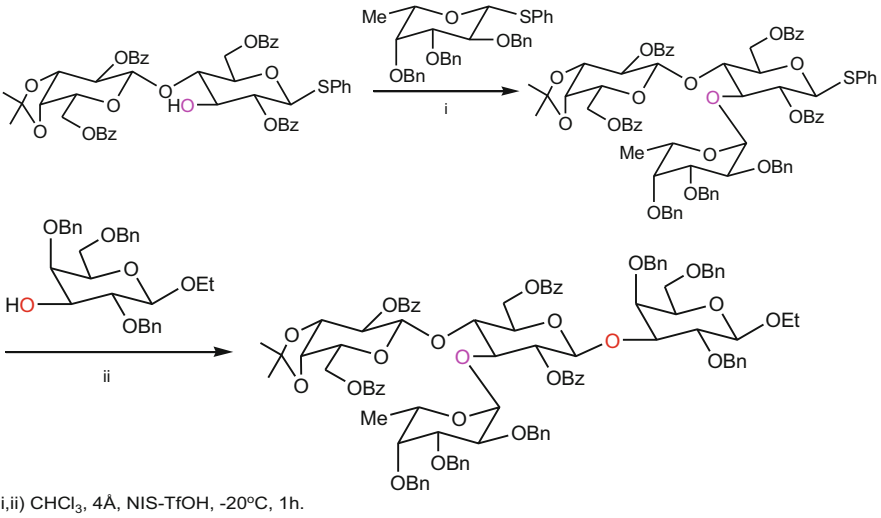
Scheme 2.68 Armed–disarmed approach

reacted with another glycosyl acceptor or disarmed sugar to produce the oligosaccharide chain elongation (Scheme 2.67).

This method was first implemented in the preparation of 1–6 linked trisaccharide shown in Scheme 2.68. As it can be observed the disarmed sugar intermediates function as glycosyl acceptor bearing the hydroxyl group at position 6 available for establishing a glycosidic linkage with the armed unit.



Scheme 2.69 General scheme of the armed–disarmed approach with thioglycosyl sugars

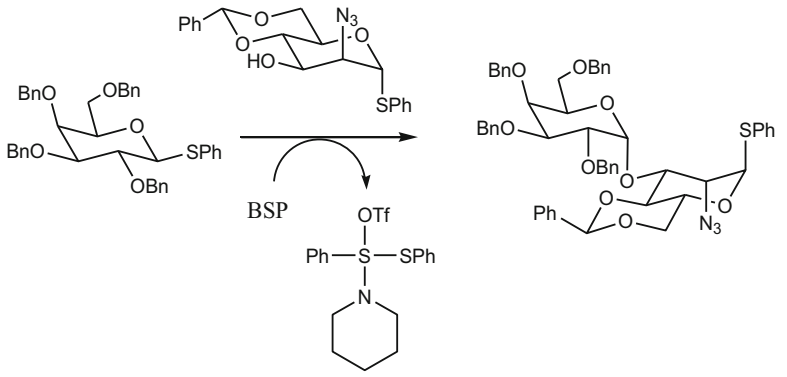


Scheme 2.70 Preparation of Lewis^x tetrasaccharide using armed–disarmed coupling method

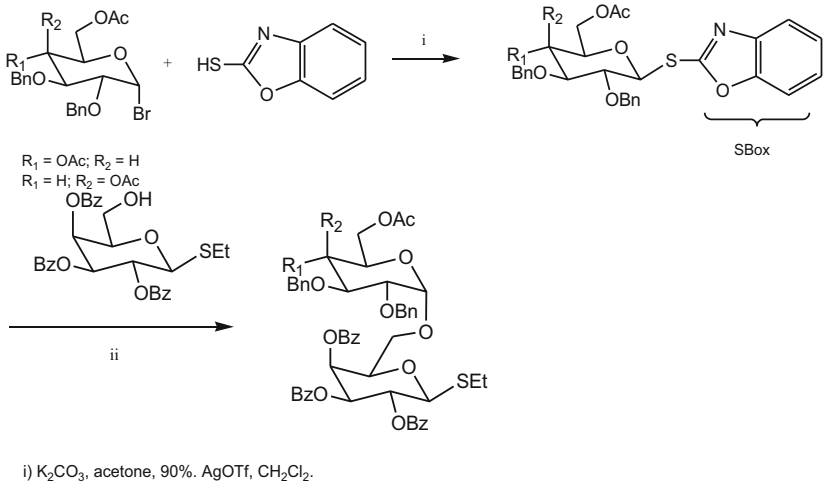
Despite the usefulness of pentenyl as protecting group, clear preference in the use of thioglycoside donors as armed and disarmed donors is often observed (Scheme 2.69) [77].

This concept was applied successfully in the stereocontrolled synthesis of Le^x oligosaccharide derivatives by using two glycosylation steps as described by Yoshida et al. [78]. The first coupling between "armed" thiophenyl fucopyranosyl derivative and "disarmed" thiophenyl lactose derivative under NIS-TfOH conditions provided trisacccharide which was subjected without purification to second condensation with different acceptors, one of which is indicated in Scheme 2.70.

The construction of α-linked mannoside disaccharide was achieved under the armed–disarmed approach by using armed thiogalactoside donor activated by BSP/Tf_2O and condensed with disarmed thiomannoazide intermediate bearing a



Scheme 2.71 Synthesis of α-linked mannosyl disaccharide following an armed–disarmed strategy

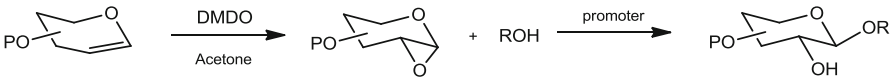


Scheme 2.72 Armed–disarmed synthesis using S-benzoxazol (SBox) as disarmed glycosyl donor

free hydroxyl group. Addition of triethyl phosphate prior to the aqueous work up led to the generation of the expected α-linked disaccharide in 74 % (Scheme 2.71) [77].

Recently S-benzoxazol thio glycoside (SBox) was synthesized and introduced as alternative glycosyl donor for preparing disaccharides under the armed–disarmed approach. Thus, the SBox glycosyl donor was used as armed donor and condensed with disarmed thioglycoside to provide the target disaccharide (Scheme 2.72) [79].

2.1.10 Glycal Reaction



Promoter	Conditions
$ZnCl_2$	THF

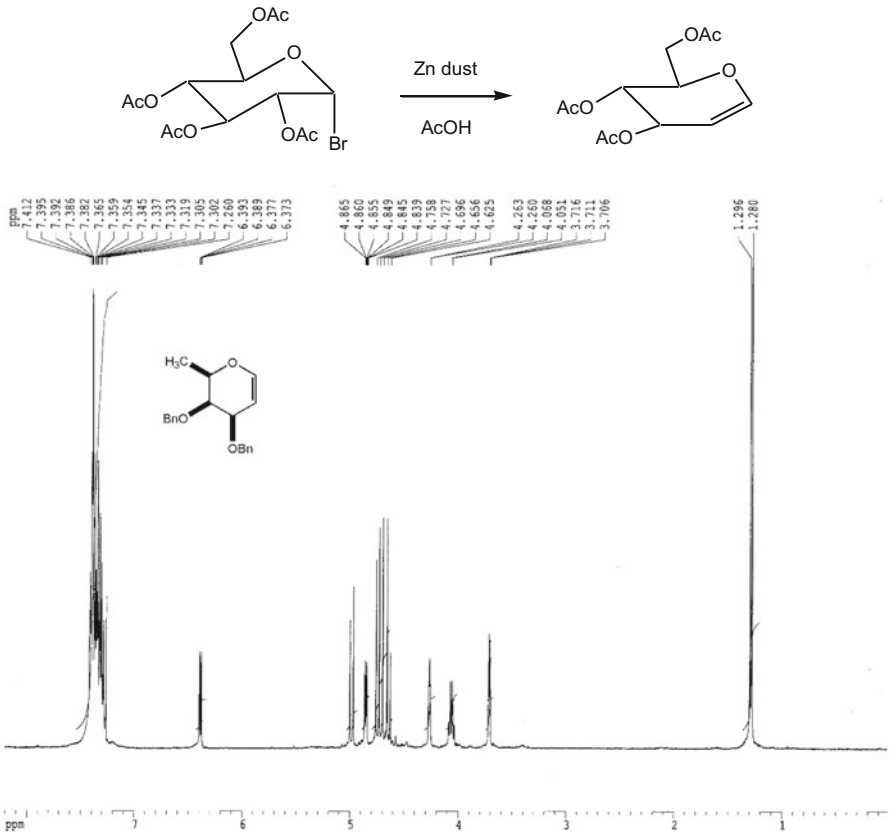
The glycals are unsaturated sugars with a double bond located between C1 and C2. These useful intermediates were discovered by Fischer and Zach in 1913 [80] and their utility in the preparation of building blocks for oligosaccharide synthesis is increasingly important. Different routes for the preparation of triacetyl glucals have been examined by Fraser-Reid et al. [81], involving the Ferrier rearrangement. Moreover, a suitable one-pot preparation of glucals has been more recently described, starting from reducing sugars by Shull et al. [82] The general procedure for preparing these valuable intermediates is based on the reductive removal of a halogen and neighboring acetate group through the use of zinc in acetic acid (Scheme 2.73). The completion of this reaction can be followed by ^{1}H NMR, where the presence of a signal around 6.3 ppm as double of double with $J_{1,2}=6.2$ Hz, $J_{1,3}=0.3$ Hz is expected for H-1, and a multiple shifted upfield for H-2.

More recently the use of alternative catalysts such as titanium complex, Li/NH_3, Sodium, Cr (II) and vitamin B-12 as catalysts has been described as improved method, for preparing especially acid sensitive glycals.

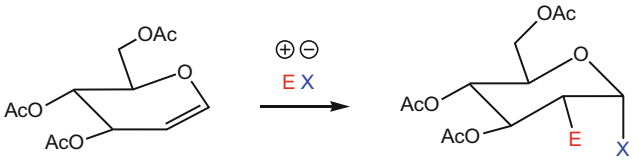
As for any double bond, these unsaturated sugars may undergo electrophilic addition, which takes place at the C2 position leaving a positive charge at C1, which instantly reacts with the conjugate base. This reaction is particularly useful for the preparation of 2-deoxypyranosides (Scheme 2.74).

A more extended application for glycoside bond formation has been developed recently. Such strategies consist of the conversion of glycals into Brigl's epoxide, and then further treatment with nucleophiles to effect ring opening. The oxidation of the double bond has been successfully achieved with dimethyl dioxirane (DMDO) in acetone (Scheme 2.75).

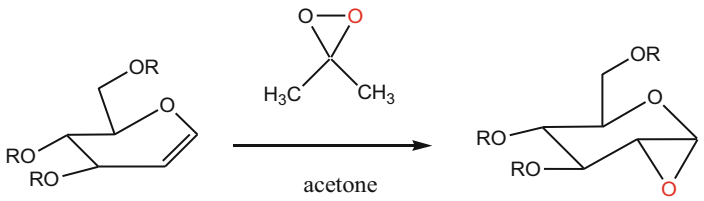
The standard procedure for generation of DMDO was developed by Murray and Jeyaraman [83], and optimized by Adam et al. [84]. Such procedure involves the use of potassium monoperoxysulfate as oxidizing agent, and the reaction conditions require temperatures below 15 °C and efficient stirring. The DMDO–acetone solution generated must be immediately distilled under moderate vacuum. The concentrations of DMDO are in the order of 0.09–0.11 M (5 %), and it is used as acetone solution. The transformation of the glycal to the epoxide can be verified by ^{1}H NMR, where it is observed the disappearance of the signal at 6.3 ppm for H-1 double bond, and it is expected the presence of a signal at 5.0, as double for H-1 and at 3.1 as double of double for H-2 (Scheme 2.76).



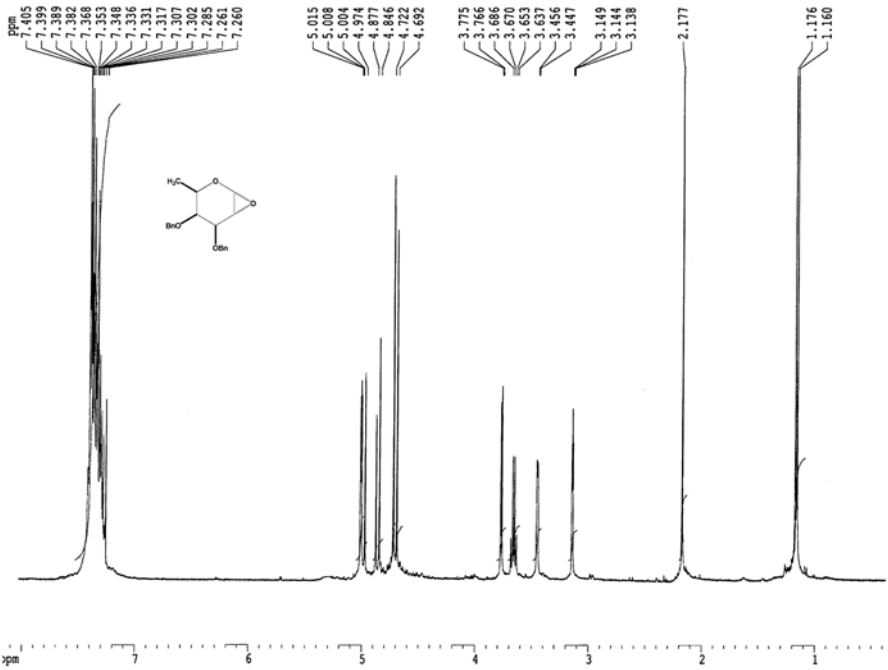
Scheme 2.73 Fischer–Sachs glucal and ^{1}H NMR of benzylfucopyranosyl glycal



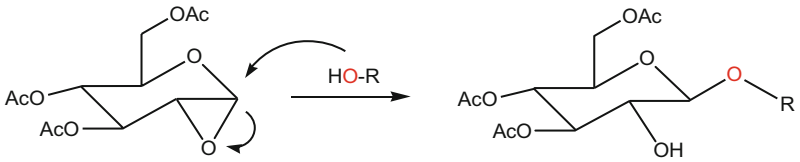
Scheme 2.74 Electrophilic addition



Scheme 2.75 Brigl epoxide formation



Scheme 2.76 ^{1}H NMR spectra of 1,2-anhydro-3,4-di-*O*-benzyl-α-D-fucopyranose (and traces of acetone)

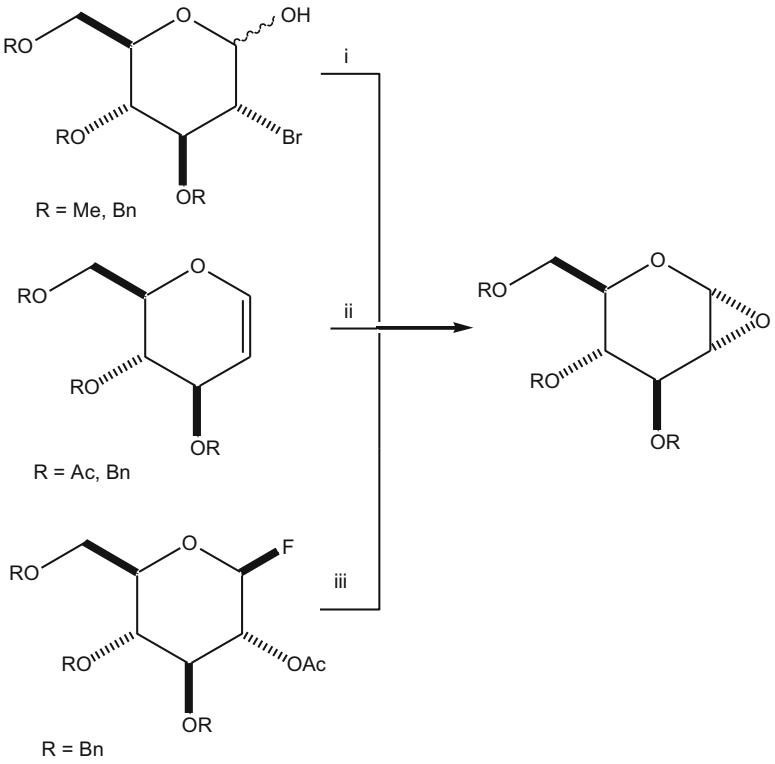


Scheme 2.77 Ring opening for β-glycoside formation

The stereo selectivity of epoxide formation is protecting group dependent, observing in the case of acetate protecting group a mixture of epoxide anomers, and preferentially the α-anomers if the protecting groups are benzyl, or methyl groups (α:β ratio 20:1). As expected, the epoxide ring opening by nucleophiles occurs with inversion of configuration, providing β-glycosides exclusively (Scheme 2.77).

Likewise, alternative epoxide conditions from glycals have been assayed besides DMDO treatment. Among them, cyclization of a bromohydrin [85], *m*-chloroperoxybenzoic acid-potassium fluoride complex oxidation of the glycal [86], and potassium tertbutoxide oxidation of fluoride glycosyl donor [87] has been described (Scheme 2.78).

The potential of 1,2-anhydro sugars as glycosyl donor for the preparation of β-linked saccharides was established by Halcomb and Danishefsky [88] and such

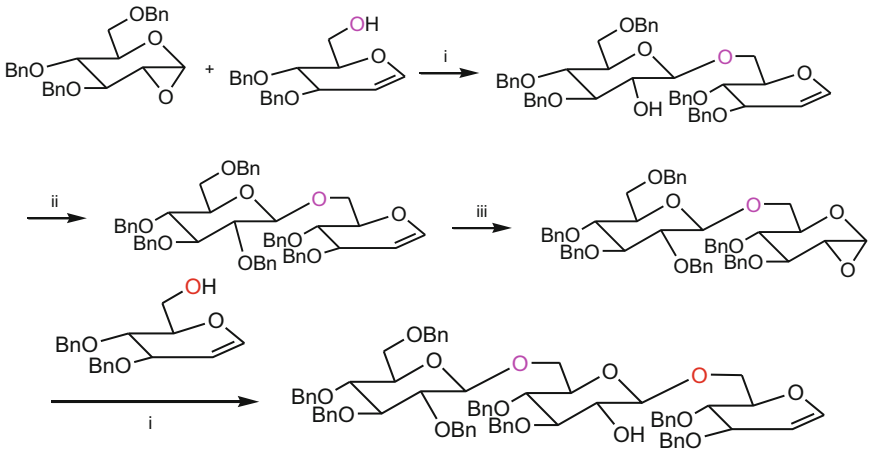


Scheme 2.78 Alternative glycal-epoxidations

strategy consist in the treatment of the glucal having available a hydroxyl group at position 6, with the sugar epoxide under Lewis acid conditions ($ZnCl_2$) at low temperature. The resulting glucal disaccharide generated as a single coupling product was further converted to the epoxide which eventually lead to the next coupling reaction with another glucal acceptor (Scheme 2.79).

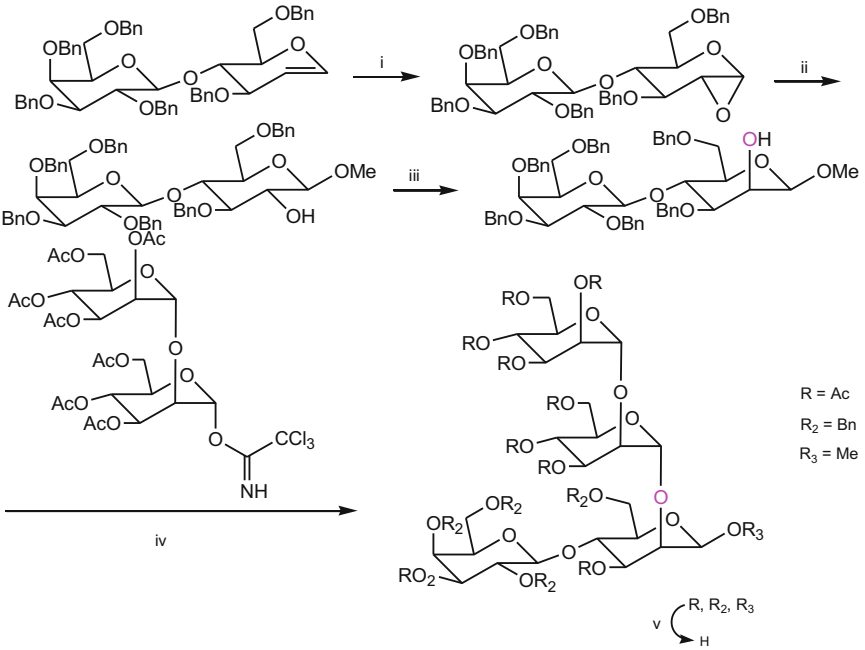
The tetrasaccharide Cap Domain of the antigenic lipophosphoglycan of *Leishmania donovani* has been prepared under the glycal approach by Upreti and Vishwakarma [89]. Thus, the preparation of the hexa-*O*-benzyl-lactal under standard procedures was followed by oxirane formation with dimethyl dioxirane to generate the corresponding oxirane. Methanolysis ring opening and gluco → manno conversion generated the disaccharide intermediate. This was coupled to the mannobiose donor to produce the tetrasaccharide, which after deprotection lead to the tetrasaccharide Cap domain (Scheme 2.80).

Brigl's epoxide has been exploited successfully for the preparation of glycosylated peptides such as collagen type II derived glycosides carrying β-Gal and αGlc-1,2-βGal side chains [90, 166]. Galactosyl glycal is reacted with DMDO–acetone



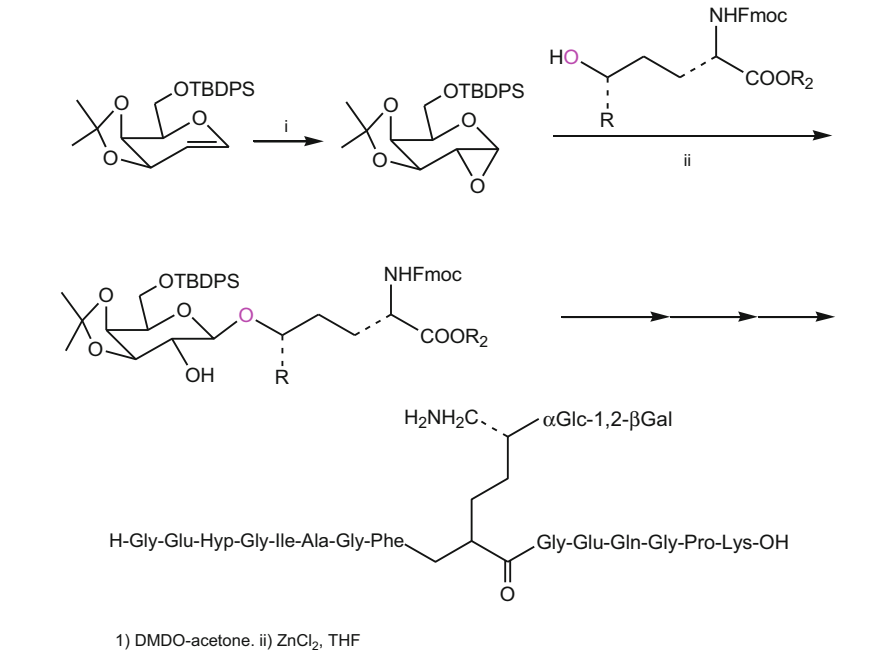
i) $ZnCl_2$/THF, -78ºC to r.t. ii) NaH, BnBr. iii) DMDO-acetone.

Scheme 2.79 Epoxide glycal as glycosyl donors

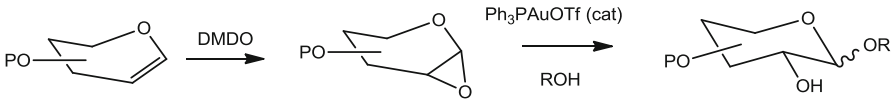


i) DMDO,CH_2Cl_2, 0ºC, 2h. ii) MeOH, rt, 4h. iii) a) $(COCl)_2$, DMSO, CH_2Cl_2, -78ºC. b) $NaBH_4$, rt, 4h.
iv) TMSOTf, CH_2Cl_2, -30ºC, 45min. v) a) $Pd(OH)_2$, H_2,4h. b) NaOMe, MeOH. c) Ac_2O/AcOH/H_2SO_4.

Scheme 2.80 Synthesis of a tetrasaccharide using an epoxide disaccharide as glycosyl donor



Scheme 2.81 Amino acids glycosidation



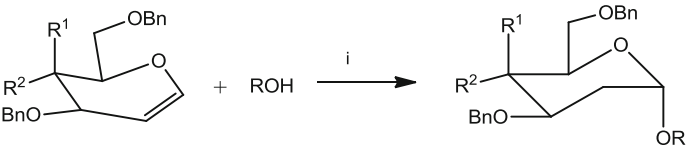
Scheme 2.82 O-glycosylation from anhydro glycals promoted by gold complex

solution and the resulting epoxide reacted with hydroxylysine and $ZnCl_2$ as promoter (Scheme 2.81). General procedures for preparation of glycosidic bond of glycopeptides can be reviewed in the comprehensive study reported by Kunz [91].

A Gold (I)-catalyzed glycosidation approach was developed by reaction of anhydro glycals with protected sugar acceptors or cholesterol, using as promoter $Ph_3PAuNTf_2$ producing the glycosylation product as a mixture of anomers in moderate to good yields (Scheme 2.82) [92].

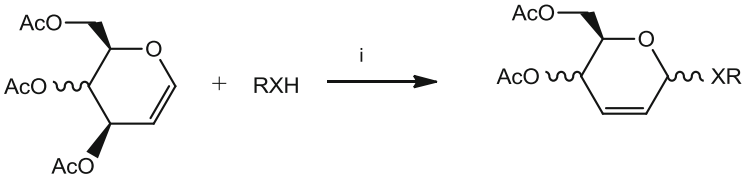
Glycals can lead to 2-deoxy-*O*-glycosides by treatment of protected D-glucal and D-galactal with the alcohol in the presence of trimethylsilyl iodide and triphenylphosphine to produce the *O*-glycoside favoring the α-selectivity (Scheme 2.83) [93].

Likewise the preparation of unsaturated *O*- and *S*-glycosides can be accomplished properly by glycosidic reaction of glycal triacetate with alcohol or thiol under erbium triflate-catalysis, observing that in dry CH_3NO_2 during 2 h the higher yields of the Ferrier product (90 %) mainly as the α-isomer (Scheme 2.84) [94].



R^1 = OBn, R^2 = H
R^1 = H, R^2 = OBn
i) TMSI-PPh_3, DCM

Scheme 2.83 Preparation of 2-deoxy-*O*-glycosides from glycals promoted by TMSI-PPh_3

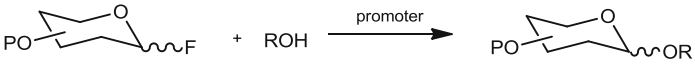


R = alkyl, aryl; X = O, S
i) $Er(OTf)_3$, dry CH_3NO_2, 2h

Scheme 2.84 Preparation of unsaturated *O*- and *S*-glycosides under erbium triflate-catalysis

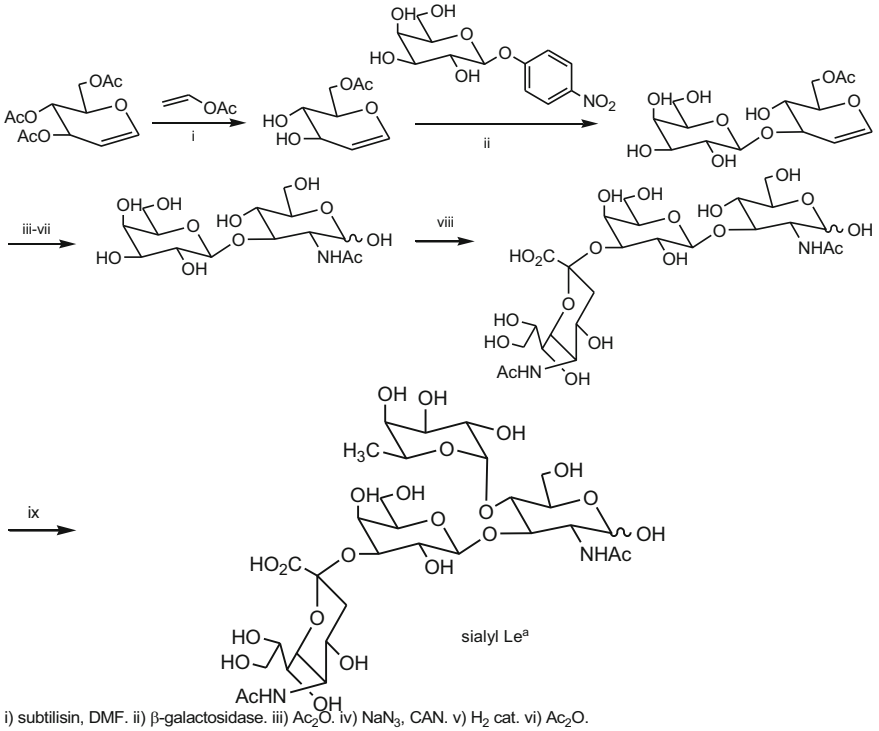
This methodology has been extended for the preparation of E-selectin ligand tetrasaccharide sialyl Lewis^X (SLe^x), which is located at the terminus of glycolipids present on the surface of neutrophils. The chemoenzymatic sequence consisted in the reaction of the 6-acetylated glucal with β-galactosidase transferase to produce disaccharide which was subjected to further transformations according to the pathway presented in Scheme 2.55 (Scheme 2.85) [95].

2.1.11 *Fluorine Reaction*



Promoter	Conditions
$SnCl_2$-$AgClO_4$	Et_2O, −15 → r.t.
Cp_2HfCl_2-AgOTf	CH_2Cl_2, −25 °C
$SnCl_2$-AgOTf	CH_2Cl_2, 0 °C

Fluorine is considered a poor leaving group, and its use for glycoside bond formation has been more restricted than chlorine and bromine, although display higher thermal and chemical stability. Nonetheless several *O*-glycoside synthesis involving



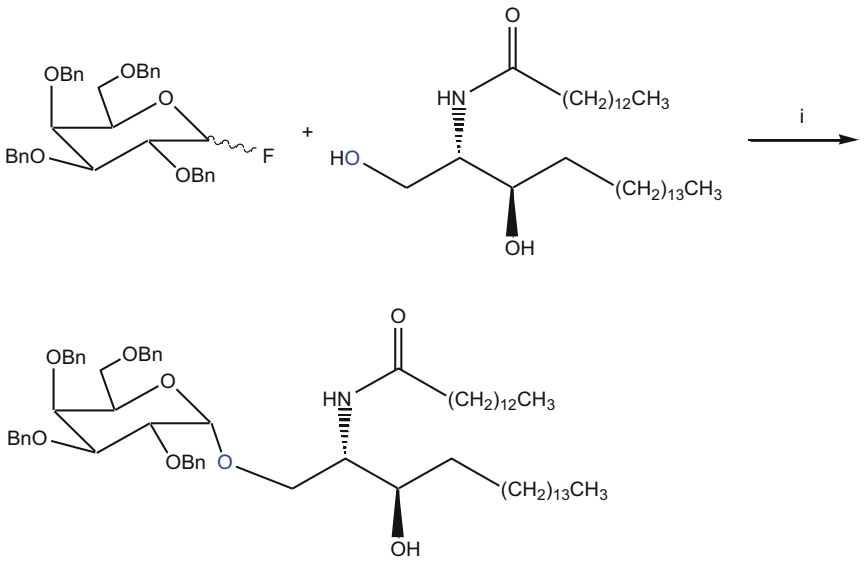
Scheme 2.85 Chemoenzymatic synthesis of tetrasaccharide sialyl Le^a

glycosyl donors with fluorine as leaving group has been described, specially for the preparation of α-*O*-glycosides with high stereoselectivity [96].

Based in the use of fluorine glycosyl donors, the synthesis of the marine algae α-agelaspines was carried out through the condensation of perbenzylated galactopyranosyl fluorine as anomeric mixture with the long chain alcohol in the presence of a mixture of $SnCl_2$ and $AgClO_4$ as catalyst (Scheme 2.86) [97].

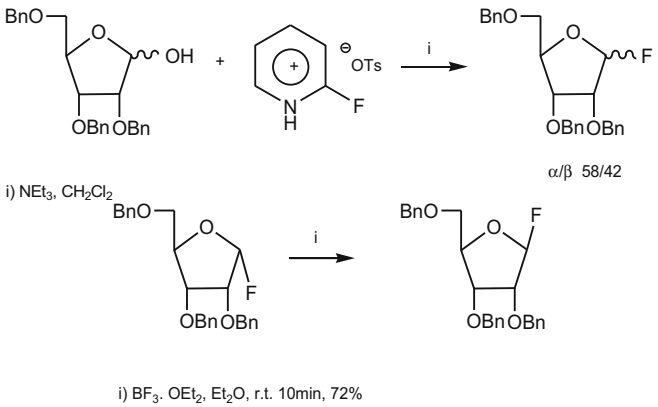
A general procedure for the preparation of ribofuranosyl fluorides and their use as glycosyl donors for *O*-glycosylation with α-stereocontrol was developed by Mukaiyama et al. [98], and consist in the conversion of 2,3,5-tri-*O*-benzyl-D--ribofuranoside that react under mild conditions with 2-fluoro-1-methylpyridinium tosylate at room temperature to give an anomeric mixture (α:β 58:42) in 84 % yield. These two fluorines could be either separate or interconverted by treating the α-anomer with boron trifluoride etherate in ether at room temperature (Scheme 2.87).

It has been observed that the glycosylation reaction between the glycosyl fluorine and different alcohols under Lewis acid conditions provides mainly α-riboglucosides in high yield as it is shown in Scheme 2.88



i) $SnCl_2$, $AgClO_4$/THF. ii) H_2, Pd-$BaSO_4$/THF.

Scheme 2.86 Fluorine monosaccharide as glycosyl donor

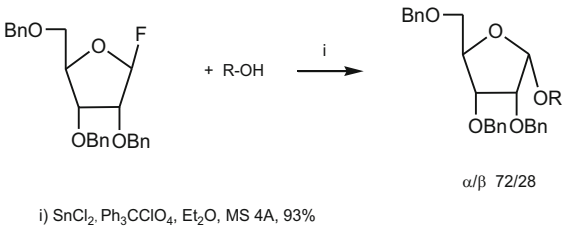


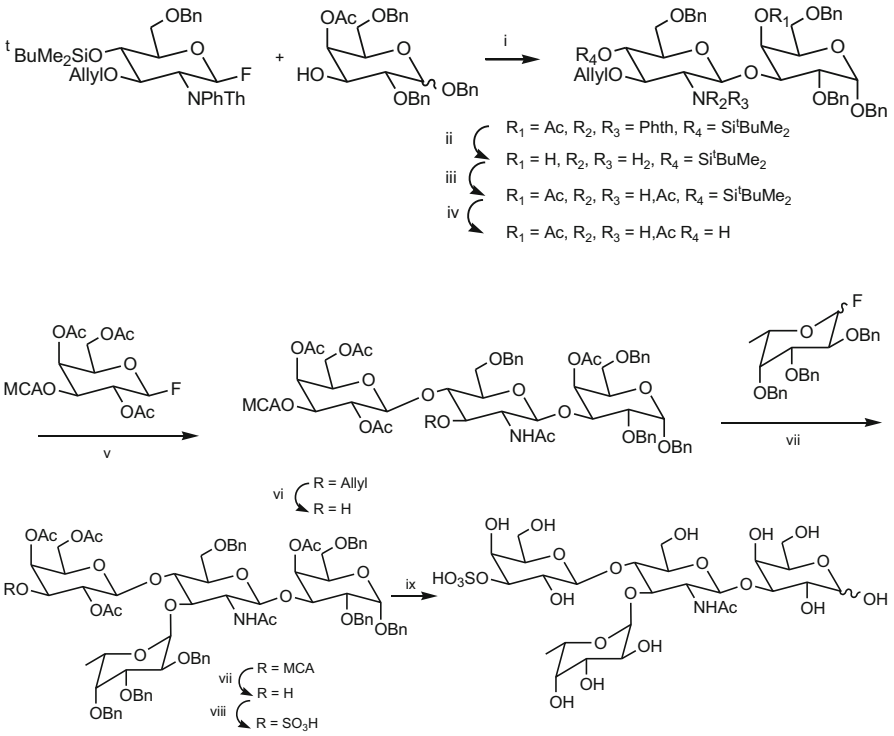
i) BF_3. OEt_2, Et_2O, r.t. 10min, 72%

Scheme 2.87 The Mukaiyama protocol for preparation of ribofuranosyl fluoride

Sulfated Le^x and Le^a-type oligosaccharide selectin ligands were synthetically prepared as described below. Thus, glycosyl donor and acceptor were condensed under Mukaiyama conditions ($AgClO_4$-$SnCl_2$) to form the β-glycoside in 90 % yield. The sulfated tetrasaccharide was formed by reaction of tetrasaccharide acceptor with SO_3.NM_3 complex in anhydrous pyridine (Scheme 2.89) [99].

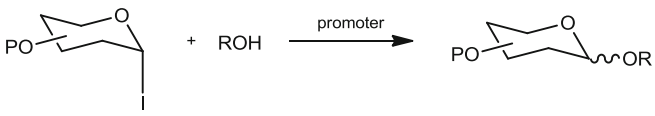
Scheme 2.88
N-glycosylation reaction using ribofuranosyl fluorine





Scheme 2.89 Total synthesis of sulfated Le^x

2.1.12 Iodine Reaction



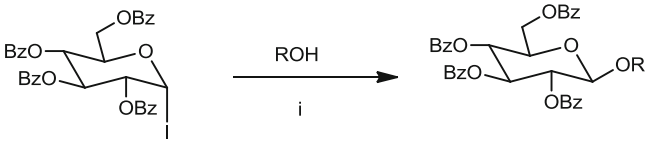
Promoter	Conditions
NBS (1.2), TMSOTf (0.4), TMU (0.2)	5 °C to rt, 4 h
$ZnCl_2$ (1.4)	rt, 12 h

Promoter	Conditions
NBS (1.2), Cu(OTf)2 (0.12)	5 °C to rt, 28 h
Bu_4NI	DIPEA, PhH, 4 Å MS
NIS, I_2, TMSOTf	3 Å MS, DCE

Glycosyl iodides have been increasingly adopted as glycosyl donors for the synthesis of *O*-, *S*, and *C* glycosides, on one side because of the introduction of suitable reagents for iodination such as iodotrimethylsilane (Me_3SiI), and hexamethyldisilane (HMDS) with molecular iodine, and on the other because of the feasibility for generating either α and β glycosides (Scheme 2.90) [100].

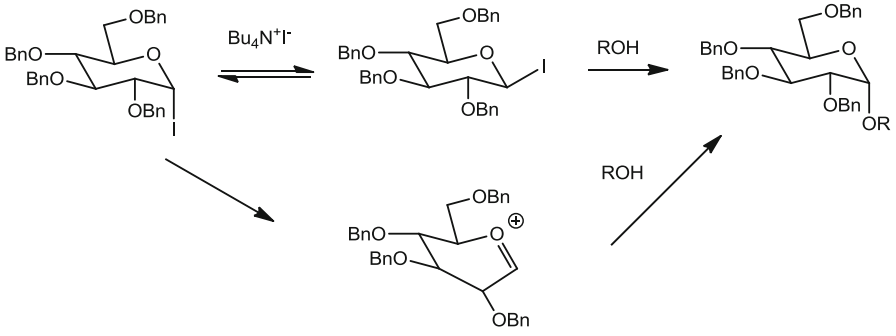
In general the stereocontrol on glycosylations depends on a combination of factors mainly the protecting group at C-2 position, the nature of the leaving group and the promoter conditions. It is well accepted that there are two possible mechanism S_N1-like and S_N2-like which define the final *α*/*β* ratio or the major anomer produced. Usually the intermediate oxacarbenium ion has poor stereochemical control, because it can be attacked from both the α- and β-side while in the S_N2-type the protected glycosyl donor is activated by an electrophile and the leaving group is displaced by the nucleophile being in this case the sugar acceptor or any other aglycone (Scheme 2.91) [101–103].

The nature of the aglycones linked to glycosyl iodide donors are diverse and among them morphine, uridine diphosphate, and steroidal alcohols have been glycosylated with promoters such as and Bu_4NF, NBS-I_2-TMSOTf (Scheme 2.92) [104–108].

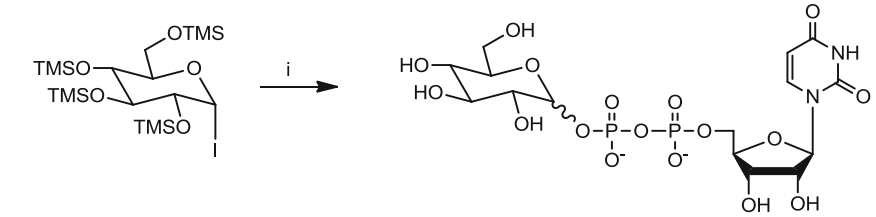


i) NBS with ZnI_2 (cat)

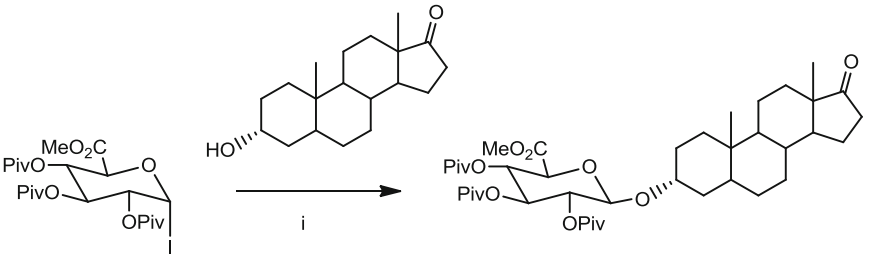
Scheme 2.90 O-glycosylation from protected glycosyl iodides under NBS-ZnI_2 conditions



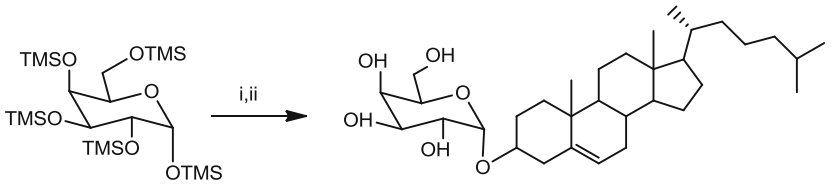
Scheme 2.91 Schematic representation of α-glycosylation stereocontrol involving glycosyl iodides



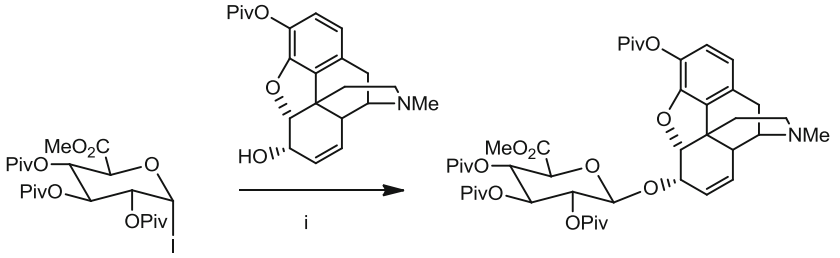
i) UDP(Bu_4N. ii) Bu_4NF, III) alkaline phosphatase



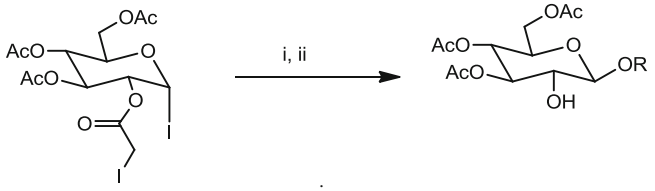
i) NBS, I_2, TMSOTf, 3 A MS, DCE



i) Cholesterol, TBAI (3 eq), DIPEA, 4 A MS, CH_2Cl_2, rt, 2d. ii) Dowex 50, MeOH



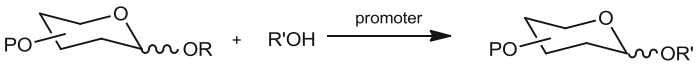
i) CH_2Cl_2, I_2, 4A MS



i) ROH, AgOTf. ii) thiourea

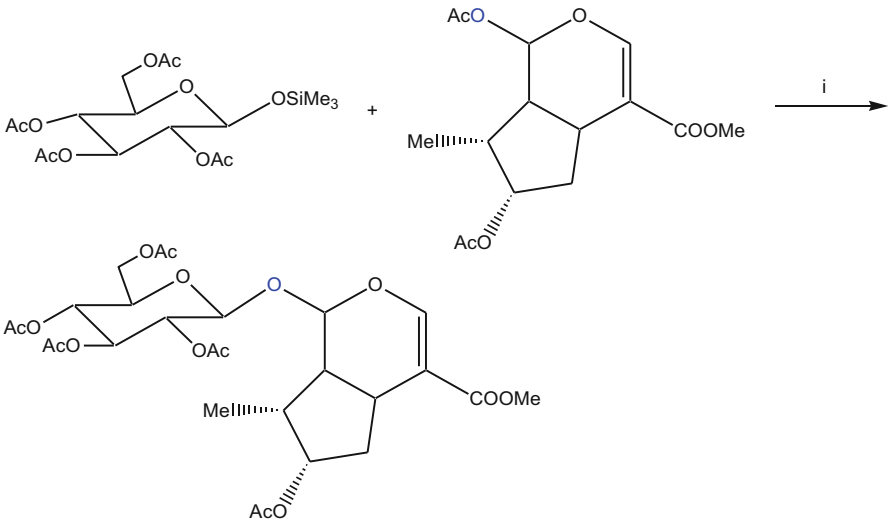
Scheme 2.92 Example of *O*-glycosylations from glycosyl iodides in the presence of different promoters

2.1.13 Silyl Reaction



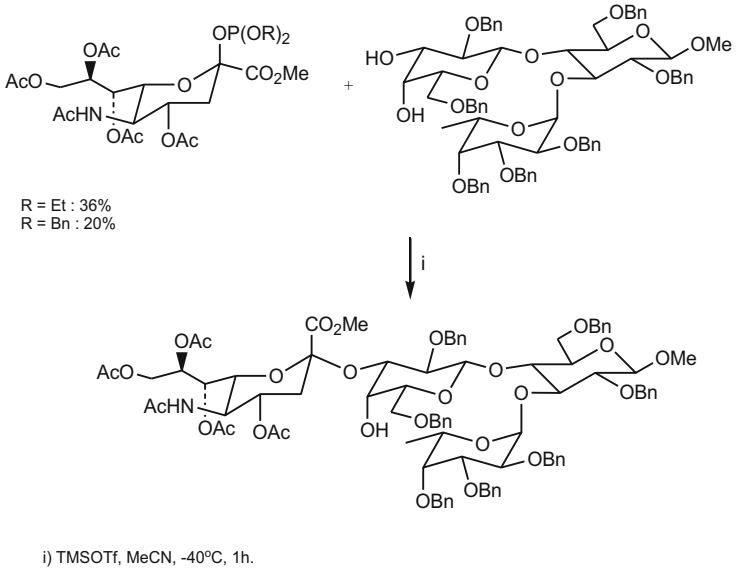
R	Promoter	Conditions
Me_3Si	TMSOTf or $BF_3.Et_2O$	CH_2Cl_2, −5 °C
$^tBuMe_2Si$	TMSOTf	CH_2Cl_2–acetone, −35 °C

Silyl groups are best known as versatile protecting groups, and their use as leaving groups for glycoside bond formation has been more limited. An example of glycoside formation involving a silyl group as leaving group is reported for the preparation of luganol *O*-glycoside [109]. In this work, the glycosyl donor is combined with luganine in the presence of trimethylsilyltriflate at low temperature (Scheme 2.93). It is worth mentioning that stereoselectivity is dependent on C-2 neighboring group participation. When acetate is the C-2 protecting group, the β-anomer is obtained, while if the protecting group is benzyl, the α-anomer is preferred.



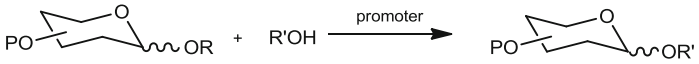
i) $TfOSiMe_3$, -40°C.

Scheme 2.93 Sialyl derivatives as glycosyl donors



Scheme 2.94 Phosphorous glycosyl donors for oligosaccharide synthesis

2.1.14 Phosphate Reaction

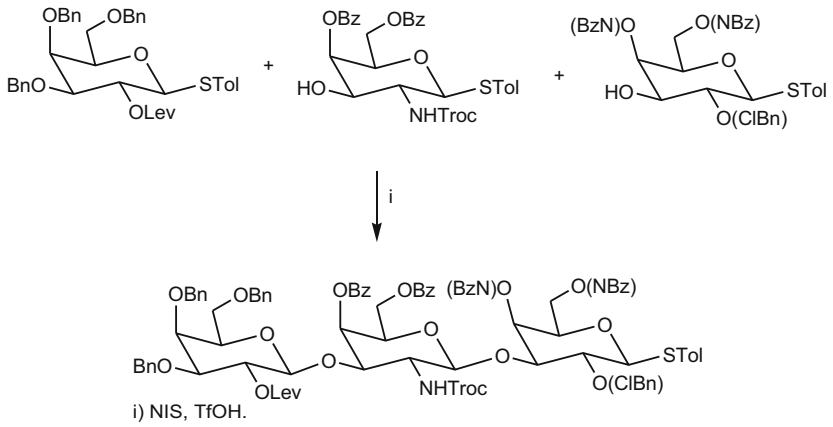


R	Promoter	Conditions
$P(=O)(OPh)_2$	TMSOTf	CH_2Cl_2, –5 °C
$P(=S)(Me)_2$	$TrClO_4$	
$P(=O)(NMe_2)_2$	TMSOTf	CH_3CN, –40 °C
$P(=NTs)(NMe_2)_2$	BF_3-Et_2O	CH_2Cl_2

Phosphorous glycosyl donors are another option for preparing oligosaccharides. These donors have been used for the preparation of sialyl oligosaccharides however the yield reported were moderate. This is the case of the preparation of sialyl tetrasaccharide derivative which was carried out by condensation between sialyl phosphate and trisaccharide acceptor under TMSOTf as catalyst (Scheme 2.94) [110, 111].

2.1.15 Pool Strategy

This term applies to define a one-step reaction used to build up two β-linkages simultaneously from three sugar intermediates [112]. This approach has been described for the preparation of the glycosyl ceramide Globo H hexasaccharide



Scheme 2.95 One-pot reaction for two β-linkages formation

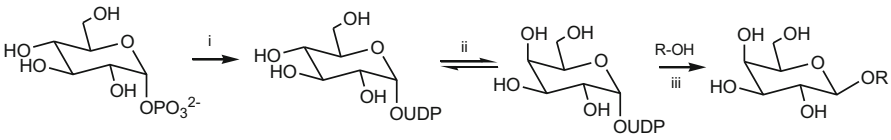
identified as an antigen on prostate and breast cancer cells. The synthesis consisted in the initial synthesis of the trisaccharide building block from the one-pot reaction of the three suitable sugar intermediates under *N*-iodosuccinimide and triflic acid conditions in 67 % yield (Scheme 2.95).

2.1.16 Enzymatic Approach

Enzymes in organic chemistry has become an essential tool for the synthesis of important target molecules and in many cases they are considered the first choice specially for those key steps involving stereospecifically controlled reaction conditions. In general enzymes are considered efficient catalysts which perform the desired transformation under mild conditions with high selectivity and specificity, usually avoiding epimerization, racemization and rearrangements processes. Besides there is a current need of developing economical and environment friendly processes for synthesis. However still some aspects needs close attention in order to fulfill thoroughly the requirements specially for high scale production. Thus, many enzymes are unstable, high cost, difficult to handle, and requires expensive cofactors.

Glycosyltransferases are important enzymes involved in essential processes related to oligosaccharide biosynthesis and they have found also very useful as biocatalyst for the chemoenzymatic synthesis of interesting oligosaccharides and nucleotides [113, 114]. They have been classified as Leloir if they are involved in the biosynthesis of most of N- and O-linked glycoproteins in mammalians, and require monophosphates and diphosphates as glycosyl donors, and non-Leloir enzymes which utilize sugar phosphates as substrates.

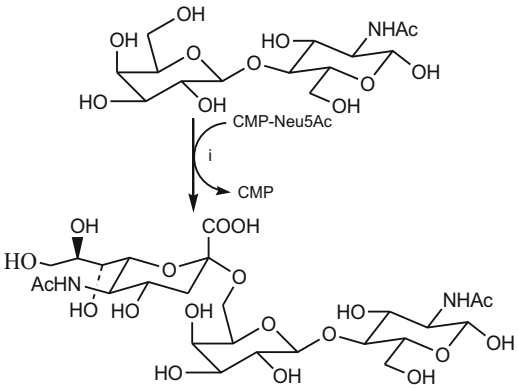
Glycosylations with galactosyltransferases can be performed through the use of glucose-1-phosphate as donor. A general sequence consists in the conversion by using UDP-Glc pyrophosphorylase to give UDP-glucose. Epimerization with UDP-glucose epimerase forms UDP-galactose which is used for glycosylation with galactosyltransferase (Scheme 2.96) [115].



i) UTP,UDP-Glcpyrophosphorylase. ii) UDP-Glc4-epimerase. iii) Gal transferase.

Scheme 2.96 Glycosylation with galactosyltransferases

Scheme 2.97 Synthesis of sialyl trisaccharide mediated by sialyl glycosyltransferase



i) α-(2-6)-sialyltransferase

The use of phosphorylase enzymes emerge as a potentially useful enzymatic tool for glycosylation, and an array of these enzymes such as glucan, sucrose, glucosyl glycerol, laminaribiose, nigerose, and maltose phosphorylases, have been isolated and identified from different microorganisms and considered for synthesis even at industrial scale synthesis [116].

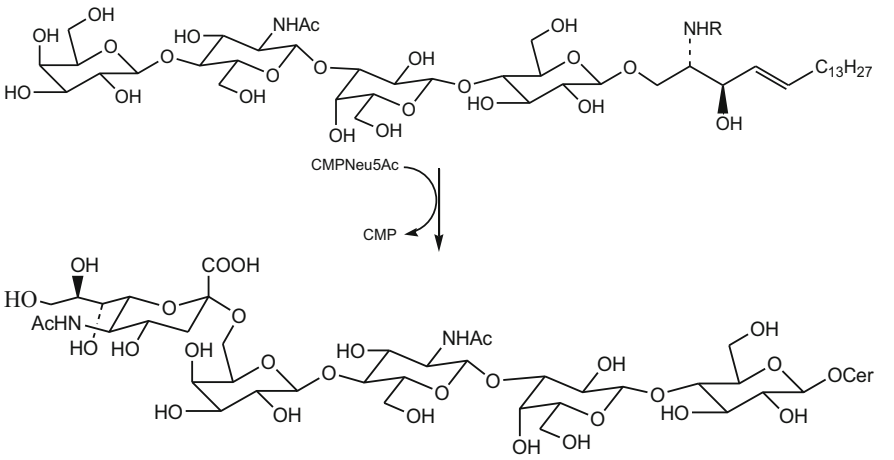
Several chemoenzymatic synthesis of α(2→6) and α(2→3)-oligosaccharides have been reported through the use of sialyltransferases for glycosidic coupling reactions. One described approach involves the in situ regeneration of CMP-Neu5Ac, requiring catalytic amount of CMP-Neu5Ac (Scheme 2.97) [117].

Sialyltransferases also proved to be efficient biocatalysts in the preparation of gangliosides, being involved in (2→6) linkage formation between the tetrasaccharide ceramide and CMP-Neu5Ac (Scheme 2.98) [118].

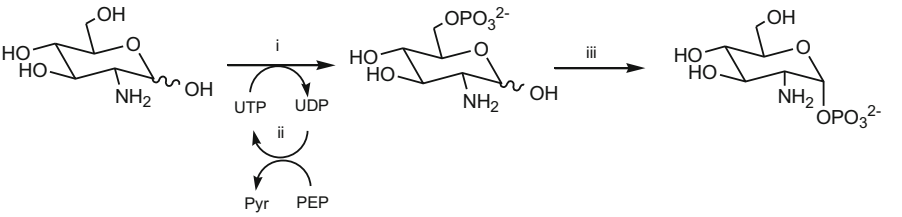
Glucosamine may be enzymatically transformed to glucosamine 6-phosphate by treatment with hexokinase from yeast, and ultimately to glucosamine 1-phosphate by the action of phosphoglucomutase (Scheme 2.99) [119].

UDP-glucuronic acid was prepared from UDP glucose by the action of UDP-Glc dehydrogenase along with NAD. This cofactor was regenerated with lactate dehydrogenase in the presence of pyruvate (Scheme 2.100) [120].

CMP-N-acetylneuraminic acid has been prepared form CTP and NeuAc under catalysis by CMP-NeuAc synthetase. In a cascade representation, it is observed that CTP is synthesized from CMP with adenylate kinase and pyruvate kinase (Scheme 2.101) [121].

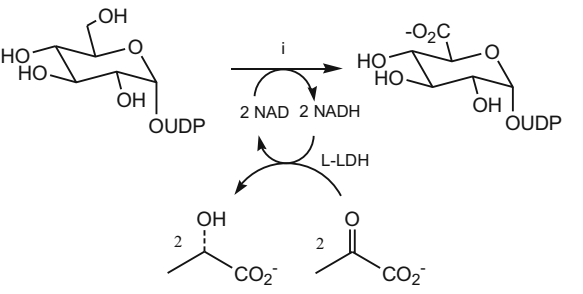


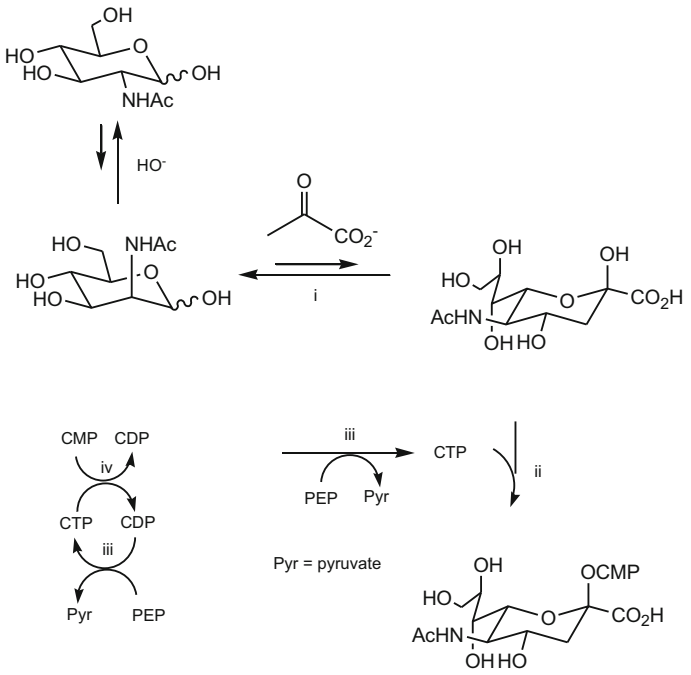
Scheme 2.98 Enzymatic synthesis of ganglioside



Scheme 2.99 Enzymatic preparation of glucosamine 6- and 1-phosphate

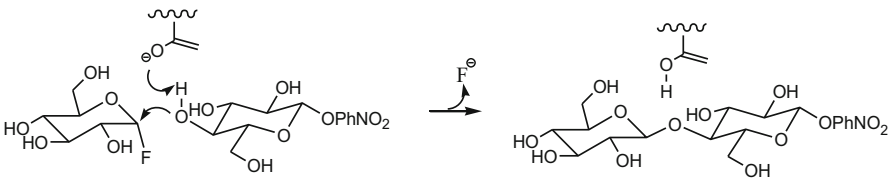
Scheme 2.100 Enzymatic preparation of UDP-glucuronide





i) UDP-NeuAc aldolase. ii) CMP-NeuAc synthetase. iii) pyruvate kinase. iv) adenylate kinase.

Scheme 2.101 Synthesis of CMP-N-acetylneuraminic acid

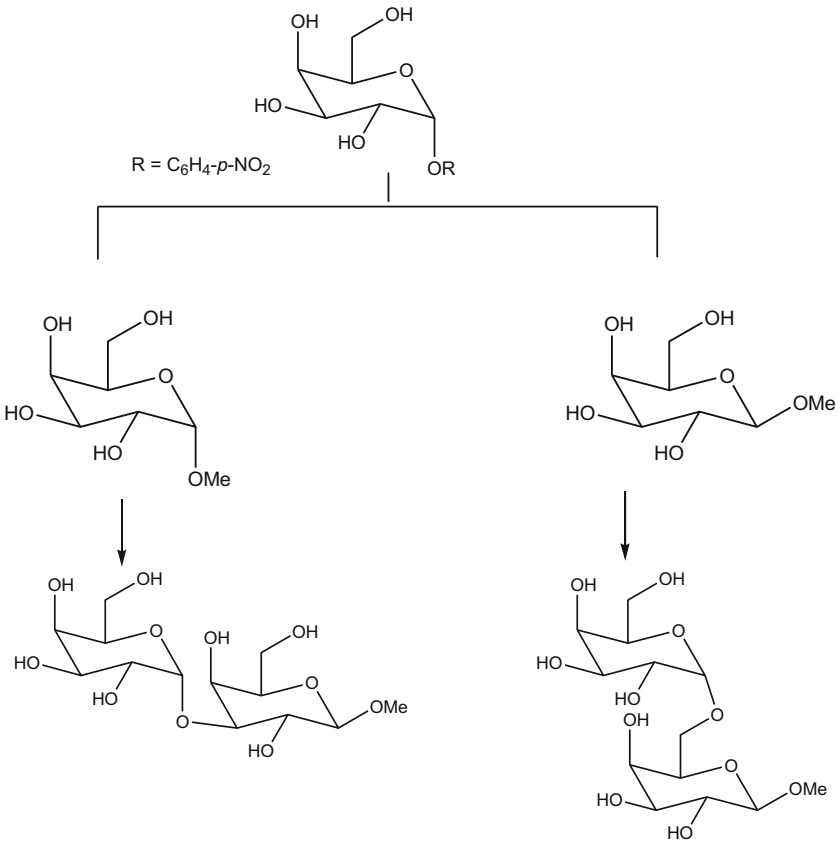


Scheme 2.102 Glycosynthase-catalyzed oligosaccharide synthesis

2.1.16.1 Enzymatic Synthesis of Oligosaccharides

Mutated glycosidase also known as glycosynthase AbgGlu358Ala in combination with activated glycosyl donors and suitable acceptors can generate synthetic oligosaccharides. Thus, for this transformation the conditions selected were α-glycosyl fluoride as glycosyl donor and *p*-nitrophenyl as glycosyl acceptor in the presence of ammonium bicarbonate buffer. The proposed mechanism of glycosynthase-catalyzed reaction is illustrated in Scheme 2.102 [122].

The Regioselective preparation of α-1,3 and α-1,6 disaccharides by using α-glycosidase as biocatalyst has been described. Thus, by combining

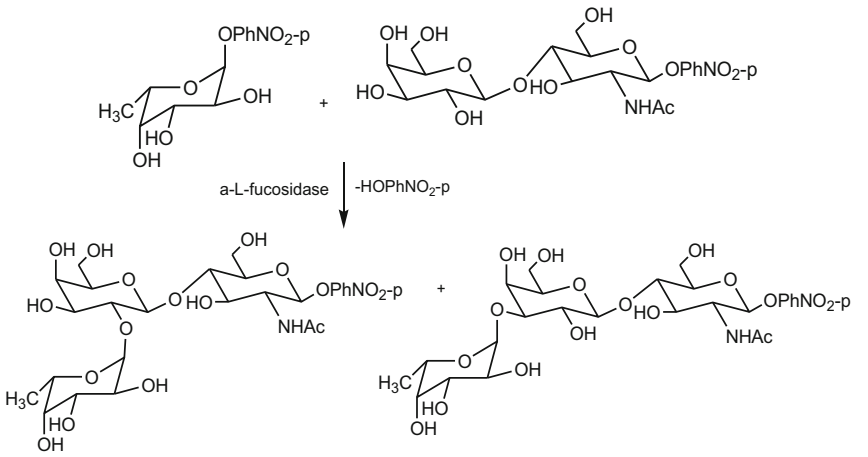


Scheme 2.103 Example of microbial catalyzed coupling reaction

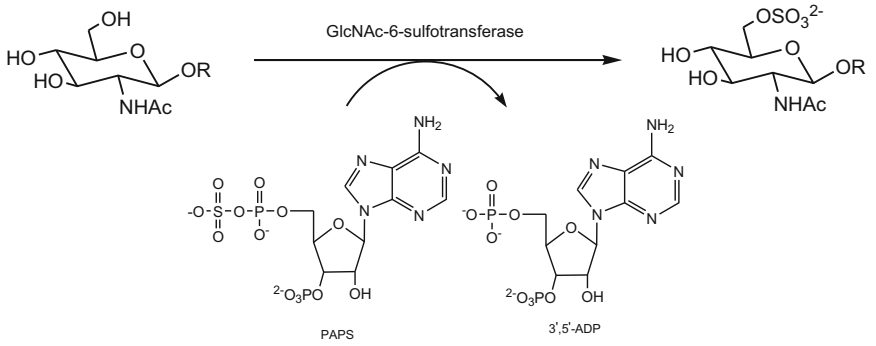
p-nitrophenyl-α-galactose functioning as glycosyl donor, with the glycosyl acceptor methoxygalactose, the expected 1,3- and 1,6-disaccharide were obtained in the form of α- and β-anomers (Scheme 2.103) [123].

A transglycosylation reaction mediated by α-L-fucosidase from *Alcaligenes* sp. was performed by combination of *p*-nitrophenylglycosides donors, with different acceptors such as *N*-acetylglucosamine, lactose, D-GlcNAc, and D-Glc, providing the corresponding *p*-nitrophenyl glycosides of disaccharides and trisaccharides containing a (1 → 2)-, (1 → 3)-, (1 → 4)-, or (1 → 6)-linked to the α-L-fucosyl group. In the general procedure illustrated in Scheme 2.76 the *p*-nitrophenyl fucoside donor was combined with *p*-nitrophenyl lactosamine acceptor, being incubated with α-L-fucosidase at 50 °C to produce the 2- and 3-linked trisaccharides (Scheme 2.104) [124].

Sulfotransferases provides a versatile method for the preparation of glycoside sulfates. A recent report describes the use of 3′-phosphoadenosine-5′-phosphosulfate (PAPS), and GlcNAc-6-sulfotransferase as catalyst (Scheme 2.105) [125].



Scheme 2.104 Transglycosylation reaction for the preparation of 2- and 3-linked trisaccharides

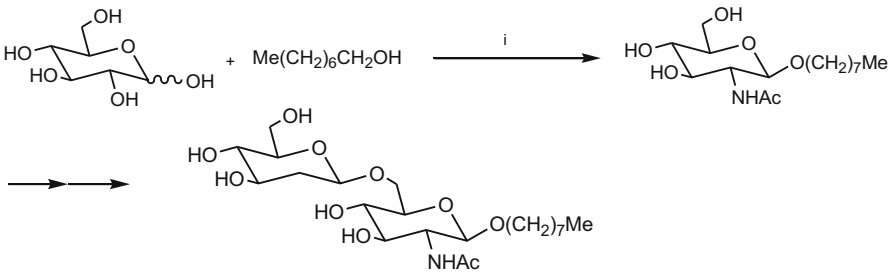


Scheme 2.105 Transfer of the sulfuryl group from PAPS to the glycoside

A chemoenzymatic synthesis of rhodiooctanoside isolated from Chinese medicines was described. The synthesis was carried out by direct β-glucosidation between 1,8-octanediol and D-glucose using immobilized β-glucosidase from almonds with the synthetic propolymer ENTP-4000 to generate the glycoside in 58 % yield (Scheme 2.106) [126].

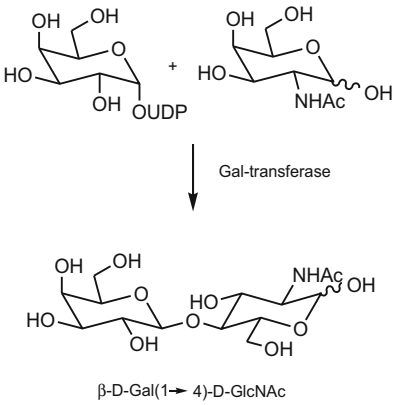
Lactosamine was prepared using and enzymatic approach consisting in the preparation of UDP glucose and condensation with *N*-acetyl glucosamine (GlcNAc) in the presence of galactosyl transferase (Scheme 2.107) [127].

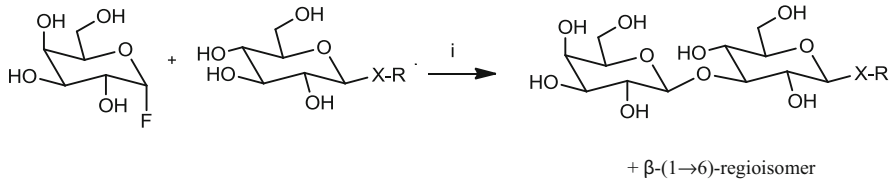
Unprotected glycosyl fluorides also have been used as donors for the enzymatic synthesis of disaccharides. For instance, glycosynthase and glycosidase mutants obtained from *Thermotoga maritima* and *Thermus thermophilus* have been used effectively for the regioselective synthesis of disaccharides (1 → 3) in higher of 80 % yield (Scheme 2.108) [128].



Scheme 2.106 Chemoenzymatic synthesis of rhodiooctanoside

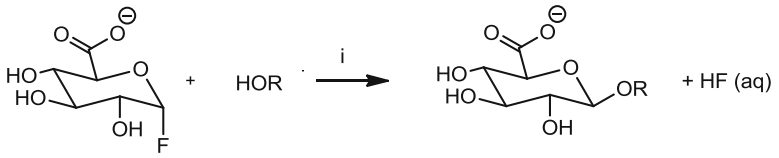
Scheme 2.107 Enzymatic synthesis of lactosamine





Scheme 2.108 Enzymatic glycosylation from unprotected glycosyl fluorides

Another example of enzymatic glycosylation using unprotected fluorides donors was achieved by using α-D-glucuronyl fluoride with engineered *Escherichia coli* glucuronylsynthase, providing β-glucuronides in moderated to good yield depending on the alcohol acceptor employed (Scheme 2.109) [129].



i) glucuronylsynthase phosphate buffer, pH 7.5

Scheme 2.109 Enzymatic glycosylation from unprotected glycosyl fluorides

2.1.17 Solid Phase Methodology

Perhaps what remains as the most challenging task for sugar chemistry is the synthesis of complex oligosaccharides such as that found in bacterial membranes or wall cells, and that are usually in the form of glycopeptides. Different types of monosaccharides can be present as constitutive parts such as glucose, galactose, mannose, *N*-acetylglucosamine, sialic acid and L-fucose. Also, the order of linkage and stereoselectivity between them is rarely conserved.

The different nature, stereoselectivity and linkage sequence have been a formidable obstacle for the development of general procedures of the type used for peptides and oligonucleotides which can be prepared on machine synthesizers with high efficiency.

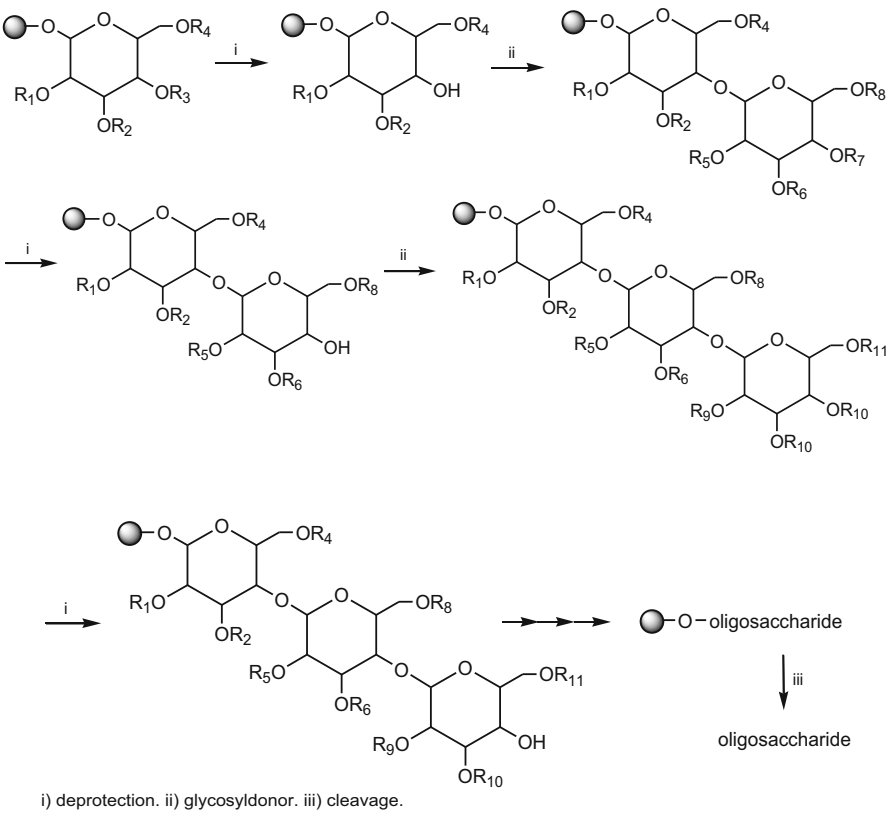
The main advantage of the solid phase methodology is the coupling of sugar units to the resin, which allows easy washing away of the non reacted reagents, avoiding tedious purifications steps.

Nonetheless despite the difficulties, interesting progress has been made for preparing oligosaccharides [130, 167, 168], and glycopeptides [131], suggesting that in the solid phase technology for complex sugars will be affordable.

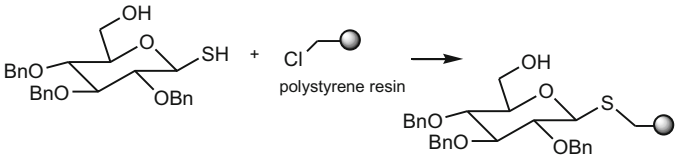
The solid phase approach involves three elements namely the glycosyl donor, glycosyl acceptor and the resin which is properly activated with a group susceptible for attachment either with the glycosyl donor or acceptor depending on the strategy of choice. Although it appears obvious, it is important to remain that the linkage between the resin and the sugar should be easily cleaved under compatible conditions for the glycoside bond.

According to a comprehensive review [132], the synthetic strategies are classified into: (a) donor-bound, (b) acceptor-bound, and (c) bidirectional Strategies.

One general approach involves the initial attachment of a glycosyl donor (halides, trichloroacetimidate, sulfoxides, phosphate (one is repeated), thio, allyl and glycals) to the resin (polystyrene-base). The attached sugar is selectively deprotected depending on the required position (1,2- 1,3- 1,4- 1,6-), transforming the resin–sugar complex in a sugar acceptor which will be coupled to the next glycosyl donor to produce a second linkage. By repeating this sequence an elongated chain is obtained. The final release and full deprotection will produce the free oligosaccharide (Scheme 2.110) [133].



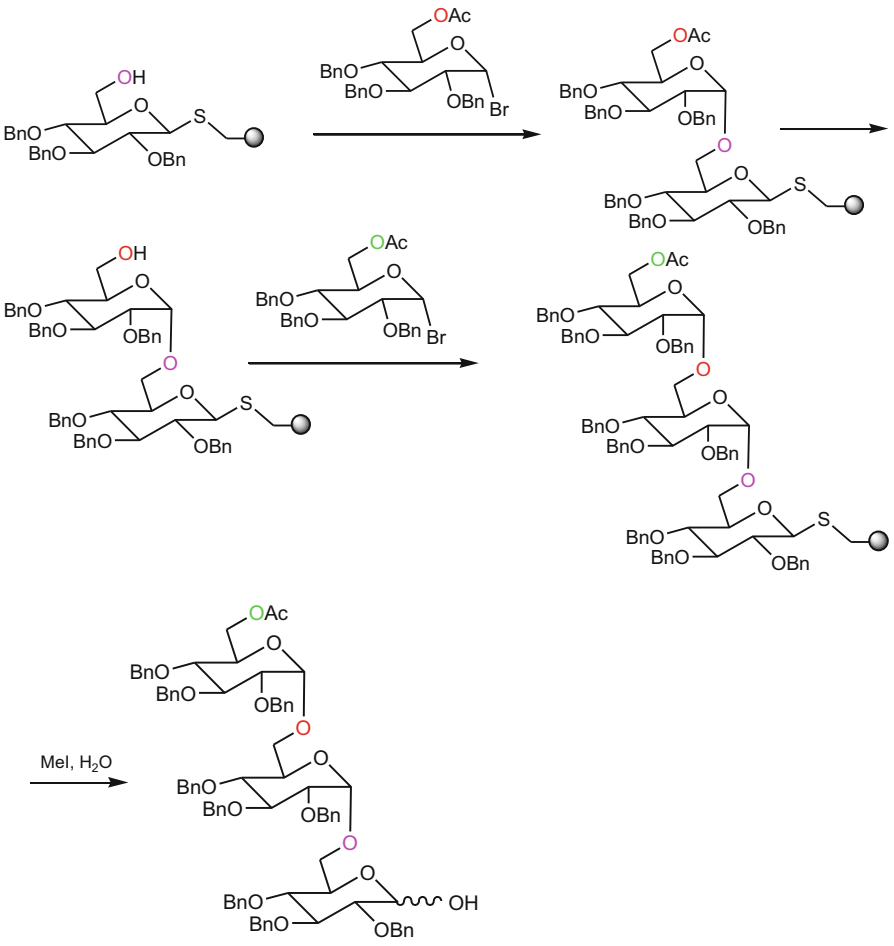
Scheme 2.110 General scheme for solid-phase oligosaccharide synthesis 1,4-linkage case



Scheme 2.111 Example of donor bound strategy for solid-phase glycosylation reactions

An example of the donor bound strategy is the bounding of sulfur glycoside to polystyrene resin to form a sulfur linkage between the donor and the resin (Scheme 2.111). Suitable hydroxyl group from the donor will serve as linkage site with de next sugar unit for chain elongation.

It should be noted that the glycosyl donor also contains a position available for the linkage with the next sugar. In other words the glycosyl donor once attached to the resin becomes a glycosyl acceptor, as can be seen for the next coupling sequence (Scheme 2.112) [132].

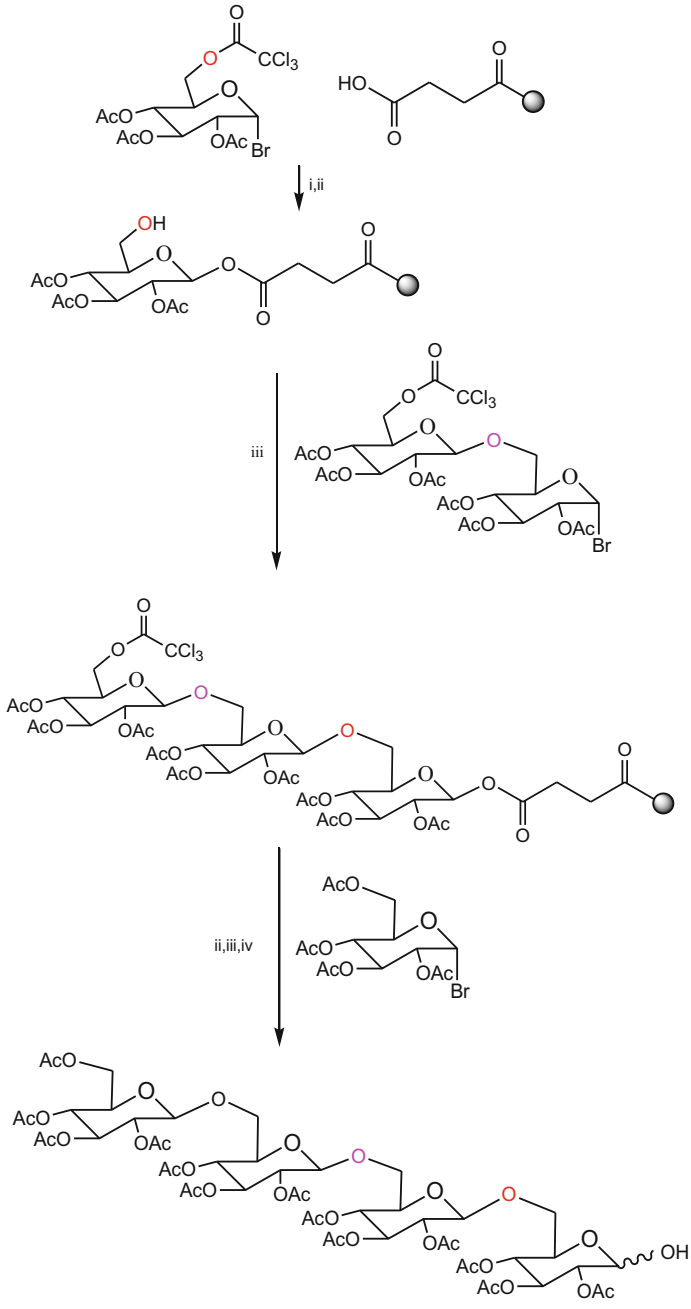


Scheme 2.112 Sulfur mediated solid-phase coupling reaction

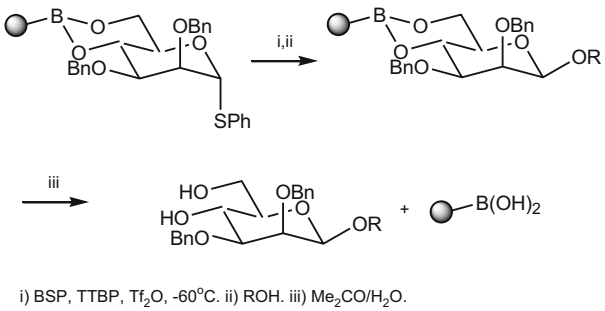
The synthesis of β-(1 → 6) gentotetraose was accomplished by using a benzoyl propionate as resin linker. The glycosyl donor chosen was acetobromoglucose functionalized with trichloroacetate group as a temporary protecting group at position 5. Glycosylation reactions were effected under Helferich conditions and cleavage from resin was performed with hydrazinium acetate (Scheme 2.113).

Polymer solid phase has been also exploited successfully by Crich et al. [134], for the synthesis of sensitive β-mannosides, using a variation of sulfhoxide method, consisting in the transformation of sulfoxide to triflic group as leaving group. The subsequent addition of alcohol acceptor to the donor attached to the Wang resin will result in the glycoside β-mannoside formation (Scheme 2.114).

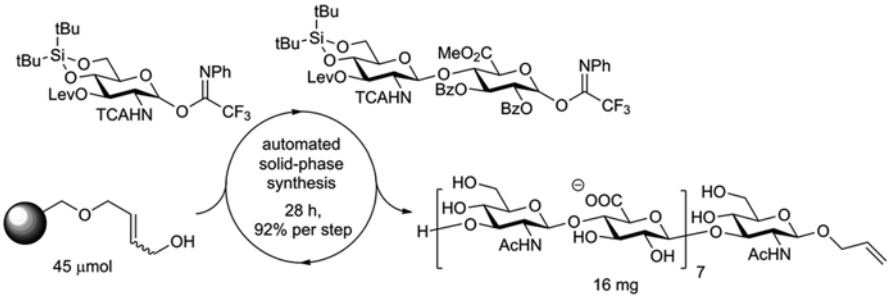
The *N*-phenyl trifluoroacetimidate donor was incorporated as a building block for solid-phase assembly as described in Scheme 2.115, starting from the coupling



Scheme 2.113 Solid-phase coupling promoted by Helferich conditions



Scheme 2.114 Solid-phase synthesis of β-mannoside glycoside

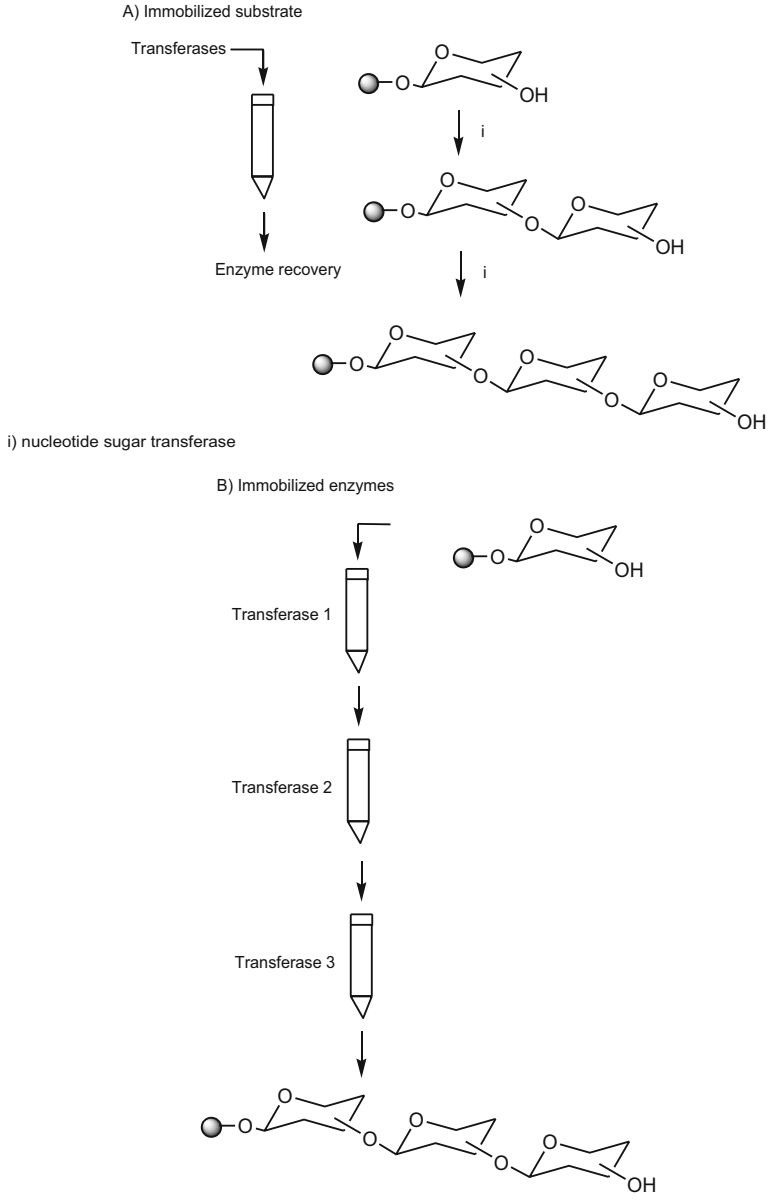


Scheme 2.115 Solid-phase assembly by using *N*-phenyl trifluoroacetimidate donors

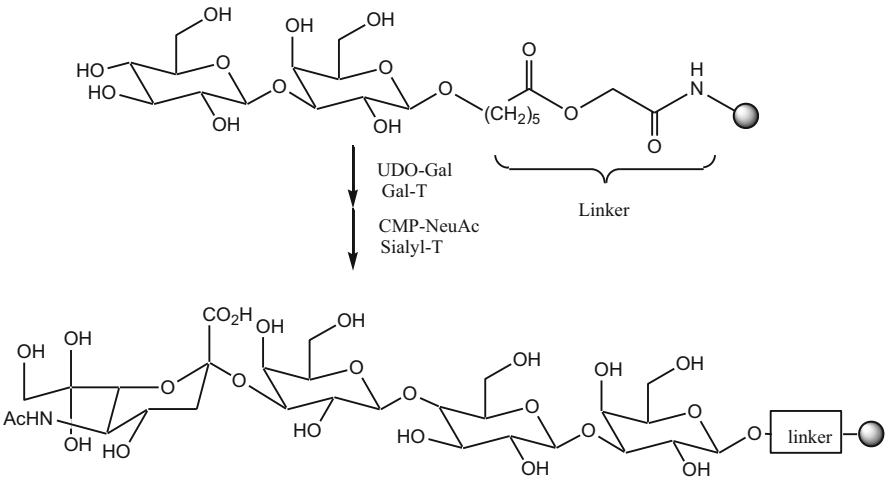
with a resin under TfOH conditions, and subsequent condensation with S-phenylglucuronic acid, to furnish dimer which was transformed into imidate donor until reaching a building block at multigram scale (Scheme 2.115) [135].

The enzymatic solid-phase oligosaccharide synthesis relies mainly by the use of glycosyltransferases, glycosidases, and glycosynthases. By taking advantage on their high stereoselectivity and regioselectivity, various oligosaccharides and glycopeptides have been prepared usually under mild conditions without the need of using protecting groups. Unfortunately the enzymatic approach is still in some cases unaffordable due to its high cost for large scale processes, lower yields provided and their limited capability for recognizing a broad range of sugars specially those not common. Two general approaches have been proposed for the preparation of oligosaccharides through the solid-phase approach (Scheme 2.116) [136].

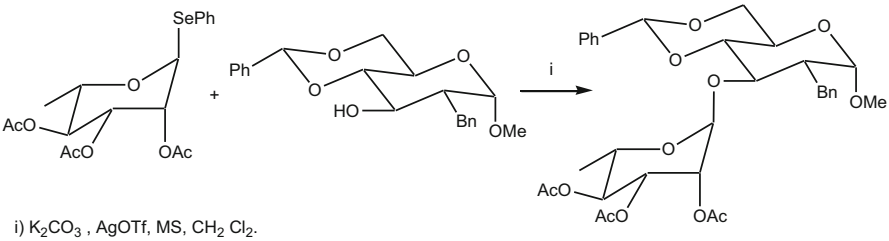
A solid-phase enzymatic approach for extending the oligosaccharide chain was described by Gijsen et al. [136] in which a disaccharide-linker fragment attached to a resin was coupled with the glycosyltransferases UDP-galactose and CMP-NeuAc in the presence of galactosyltransferases and sialyltransferase as enzymatic catalyst. Final treatment with hydrazine was used to release the tetrasaccharide from the solid support (Scheme 2.117).



Scheme 2.116 Two general approaches for immobilized solid-phase oligosaccharide synthesis



Scheme 2.117 Enzymatic-solid phase glycosylation reaction



Scheme 2.118 Phenylselenosugars as glycosyl donors

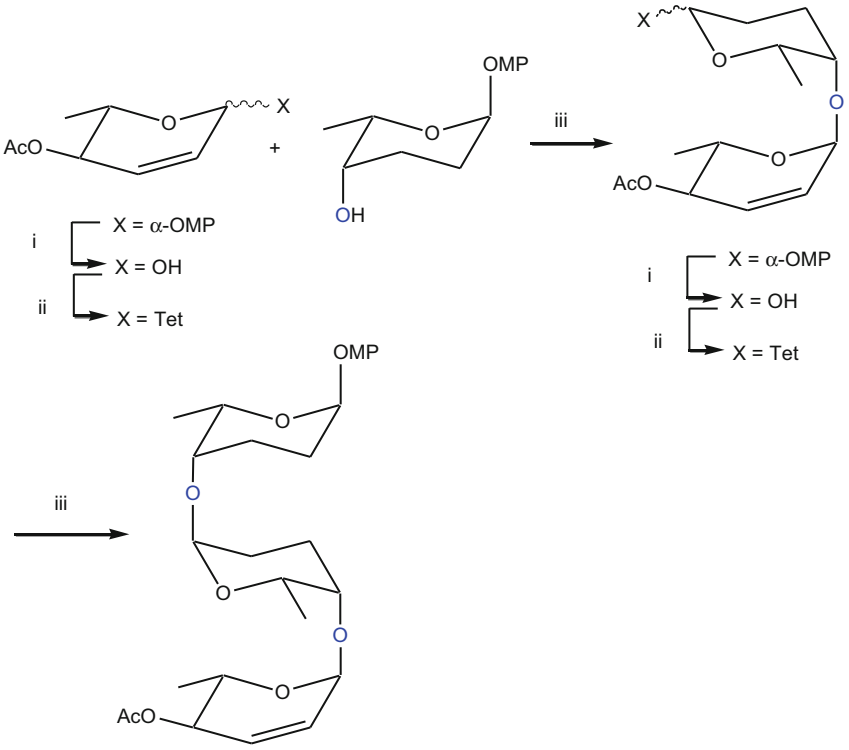
2.1.18 Miscellaneous Glycosylations

2.1.18.1 Selenosyl Donors

The use of selenoglycosides as glycosyl donors and acceptor in glycosylation reactions has also been described by Metha and Pinto [137]. A typical glycosidation procedure with phenylselenoglycoside donors involves the glycosyl acceptor, 4-Å molecular sieves, silver triflate, and potassium carbonate in dichloromethane (Scheme 2.118).

2.1.18.2 Tetrazol as Leaving Group

Tetrazol has also been tested as a leaving group for the preparation of an antibiotic fragment [138]. A coupling reaction with the methoxyphenyl glycosyl acceptor was catalyzed with $(Me_3)_3OBF_4$ as shown in Scheme 2.119.



i) CAN. ii) 1H-tetrazole. iii) $(CH_3)_3OBF_4$, MS.

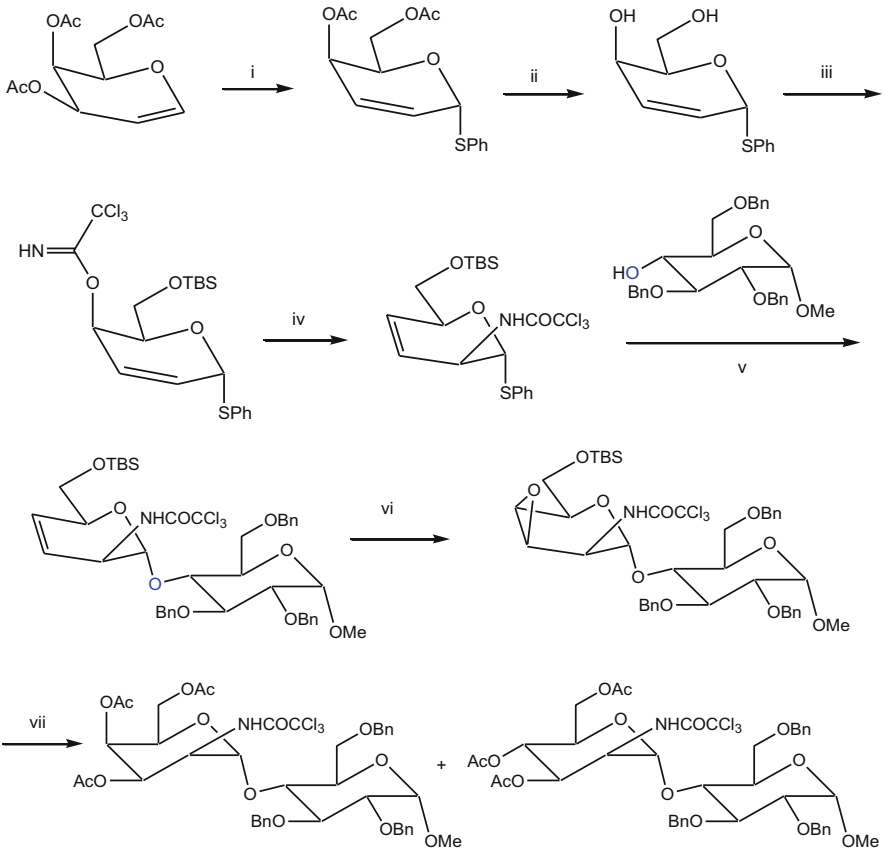
Scheme 2.119 The use of tetrazol as a leaving group

2.1.18.3 Sigmatropic Glyosylations

2-aminodisaccharides were obtained by an elegant [3,3] sigmatropic rearrangement, by Takeda et al. [139] The addition of thiophenol to an unsaturated C-1 in the presence of Lewis acid, was followed by a sigmatropic rearrangement with an imidate group which migrates from C-4 to C-2. Disaccharide formation was catalyzed with $Pd(CH_3CN)_2$-AgOTf complex in dichloromethane (Scheme 2.120).

2.1.18.4 Zinc Promoted Glycosylation

The total synthesis of the cyclic glycolipid arthrobacilin A, a cell growth inhibitor was achieved by Garcia and Nizhikawa [140], under zinc *p-tert*-butylbenzoate salt as glycoside catalyst, obtaining the β-galactoside glycoside in 73 % along with α-isomer in 27 % (Scheme 2.121).



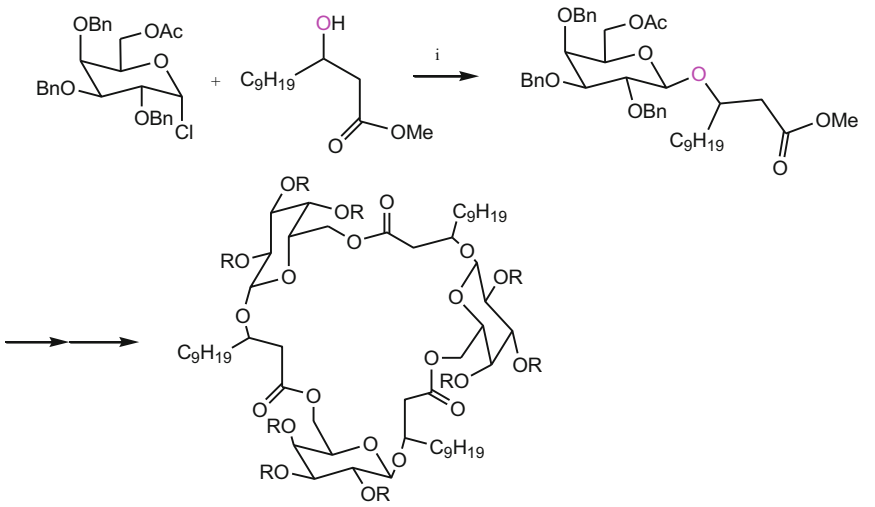
i) PhSH, $SnCl_4/CH_2Cl_2$ .ii) MeONa/MeOH. iii) a) TBSCl-imidazol/CH_2Cl_2. b) Cl_3CCN-NaH/CH_2Cl_2. iv) xylene, reflux. v) $Pd(CH_3CN)_2$-AgOTf,MS 4A/CH_2Cl_2 . vi) m-CPBA/CH_2Cl_2 . viii) Ac_2O-AcOH/ $BF_3.OEt_2$.

Scheme 2.120 Sigmatropic rearrangement

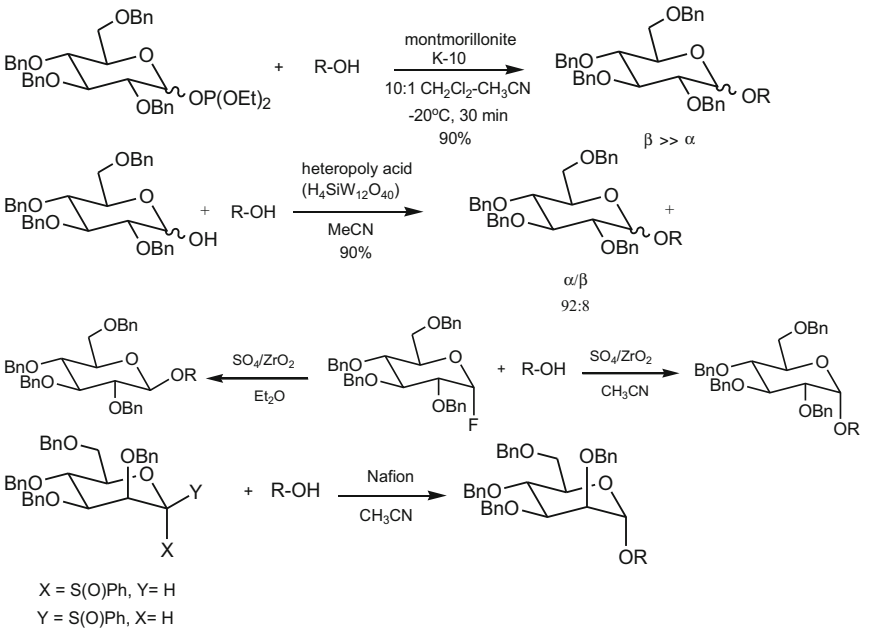
2.1.18.5 Heterogenous Catalysis

Stereocontrolled α- and β-glycosylations by using environmentally benign heterogenous catalyst has been developed as a novel approach for stereoselective formation of β-*O*-glycosidic linkages. Polymeric materials such as montmorillonite K-10 [141], heteropoly acid ($H_4SiW_{12}O_{40}$) [142], sulfated zirconia (SO_4/ZrO_2) [143], and perfluorinated solid-supported sulfonic acids (Nafion resins) [144] have been assayed successfully providing series of stereocontrolled *O*-glycosides in high yield (Scheme 2.122).

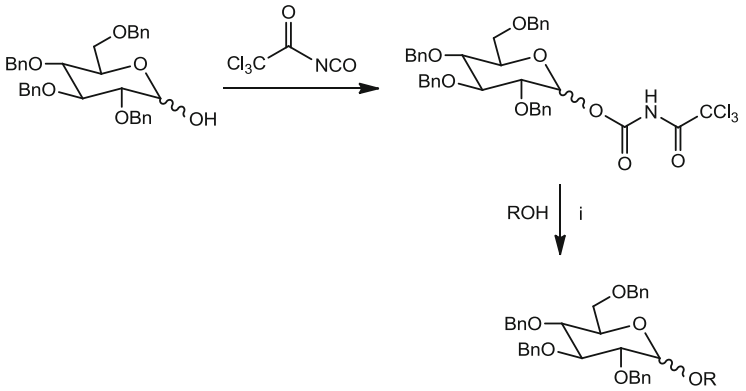
Glycosyl *N*-trichloroacetylcarbamate obtained from reaction of tetrabenzyl glucopyranoside hemiacetals with trichloroacetyl isocyanate was used as glycosyl



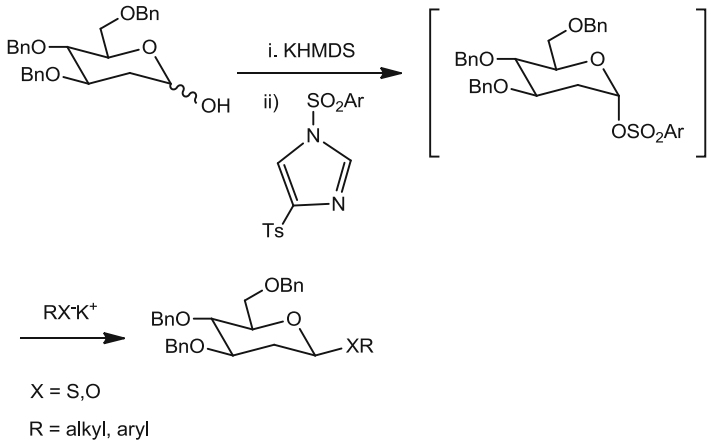
Scheme 2.121 Glycosylation reaction for preparation of arthrobacilin A



Scheme 2.122 Stereocontrolled O-glycosidations using heterogeneous polymeric materials



Scheme 2.123 O-glycosylation via *N*-trichloroacetylcarbamate

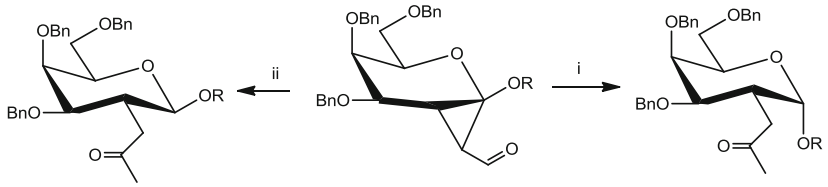


Scheme 2.124 Preparation of β-glycosides via glycosyl sulfonate formation

donors. Various Lewis acids were tested for α-selective glycosylation observing that the promoters TMSOTf and $TMSClO_4$ yield the best results (Scheme 2.123) [145].

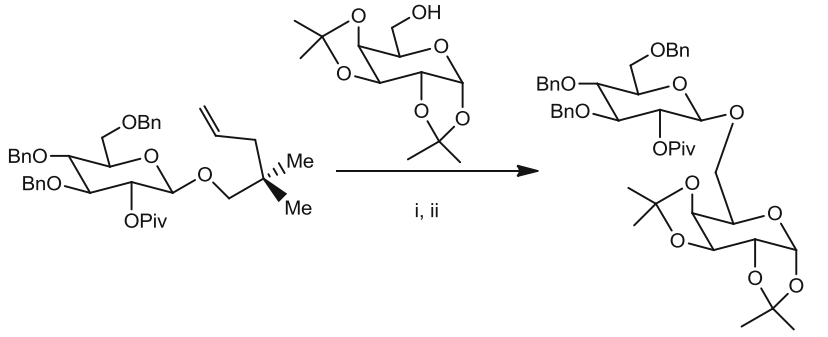
N-Sulfonyl imidazole has been used as activating agent for preparing 2-deoxy monosaccharides through deprotonation of the anomeric hydroxyl group with KHMDS at low temperature. Further reaction with *N*-sulfonyl imidazole resulted in the glycosyl sulfonates intermediate generated in situ which was finally reacted with the desired nucleophile to produce the β-glycoside in moderate to good yields (Scheme 2.124) [146, 147].

On the other hand 1,2-cyclopropaneacetylated sugar has been proposed as glycosyl donors for O-glycosylations, allowing stereoselective control depending on the catalyst employed. Thus, β-anomeric products were obtained with $BF_3.OEt_2$ as catalyst, whereas TMSOTf-catalyzed glycosylation prefers the α-anomeric products (Scheme 2.125).



i) TMSOTf, ROH, CH_2Cl_2, MS, 0°C to rt. ii) $BF_3.Et_2O$, ROH, CH_2Cl_2, MS, -20°C to rt

Scheme 2.125 Stereocontrolled glycosylations from 1,2-cyclopropaneacetylated sugar as glycosyl donors



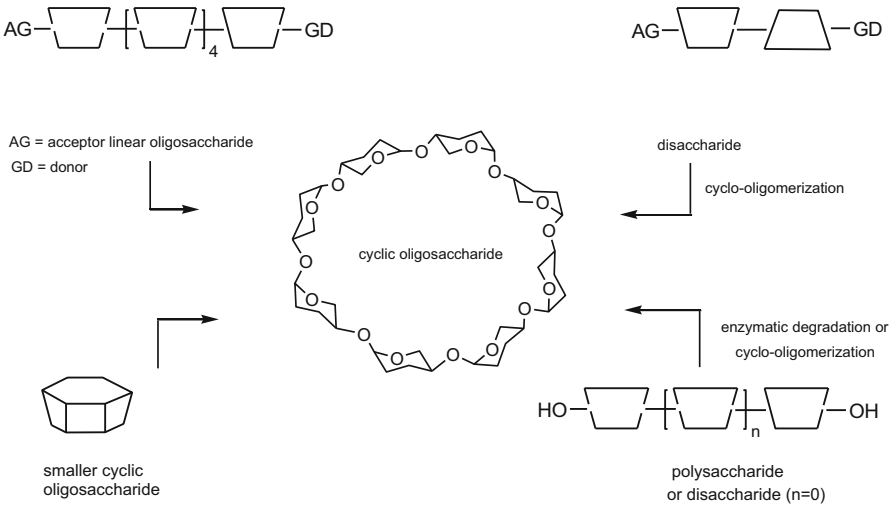
i) ROH, NBS, TESOTf (cat.), CH_2Cl_2, -78°C, 1h

Scheme 2.126 Preparation of protected β-1,6 disaccharide form Gem-dimethyl 4-*n*-pentenyl glycosides

Gem-dimethyl 4-*n*-pentenyl glycosides were proposed as glycosyl donors for glycosylation and hydrolysis of the anomeric carbon when using NBS as the sole stoichiometric activator with yield reported around 80 % mainly with β selectivity (Scheme 2.126) [148].

2.1.19 Cyclic Oligosaccharides

The synthesis of cyclic oligosaccharides involves the preparation of linear saccharides which ultimately are joined together to form a cyclic macromolecule. There are two main approaches proposed based on the cycloglycosylation step. The first involves the preparation of a long chain having and each end the donor and acceptor functionalities that will be interconnected through a glycosidic bond at a final step, and the second involving the polycondensation of smallest repeating unit called "saccharide monomers." It has been observed that the latter strategy is considered less laborious; however, it produces cyclic oligomers of different size since under these conditions the ring formation step is not controllable.



Scheme 2.127 The four suggested approaches to the synthesis of cyclic oligosaccharides

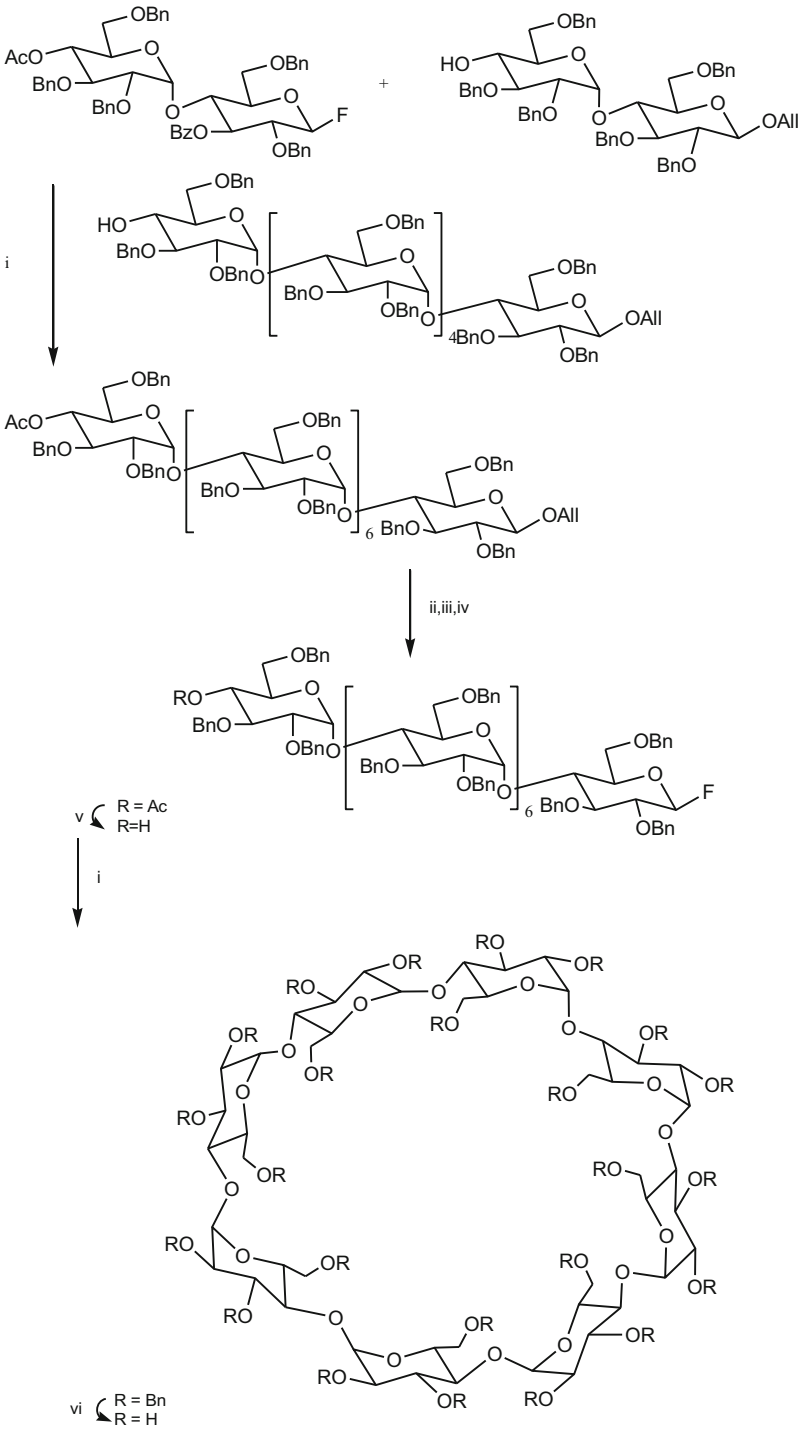
The chemical synthesis of cyclic oligosaccharides has been mainly driven to obtain cyclic (1 → 4)-linked oligopyranosides, however (1 → 3), and (1 → 6) linked cycloforms are also described. In the case of (1 → 2)-linked oligosaccharides, the ring closure require about 17 or more glucopyranoside residues because (1 → 2)-linkage composed of pyranoside connected by one equatorial and one axial bond assumes rigid conformations and cannot cyclize [149].

The pioneering total synthesis of cyclic oligosaccharide α-Cyclodextrin was carried out by Ogawa's group in 1985 [150] and since then alternative chemical or enzymatic methodologies appeared for preparing cyclic oligosaccharides. Nowadays the industrial production of cyclodextrins relies on the enzymatic conversion of prehydrolyzed starch into a mixture of cyclic and acyclic oligomers.

A full report about cyclic oligosaccharides [150] proposes four approaches to the synthesis of cyclic oligosaccharides developed during the last 10 years. (1) the stepwise preparation of a linear precursor that is subjected to cycloglycosylation; (2) the one-pot polycondensation/cycloglycosylation of a small "oligosaccharide monomer" typically, a disaccharide or trisaccharide that can yield a range of macrocycles of different sizes; (3) the enzyme-assisted synthesis of natural or unnatural cyclic oligosaccharides; (4) the ring opening of cyclodextrins followed by oligosaccharide chain elongation and cycloglycosylation (Scheme 2.127).

Despite the significant advances observed in cyclic oligosaccharide synthesis, their preparation is time consuming, producing the target compounds with low regioselective and stereoselective in low yields. The total synthesis of α-CD and γ-CD was described according to Scheme 2.128 [151, 152].

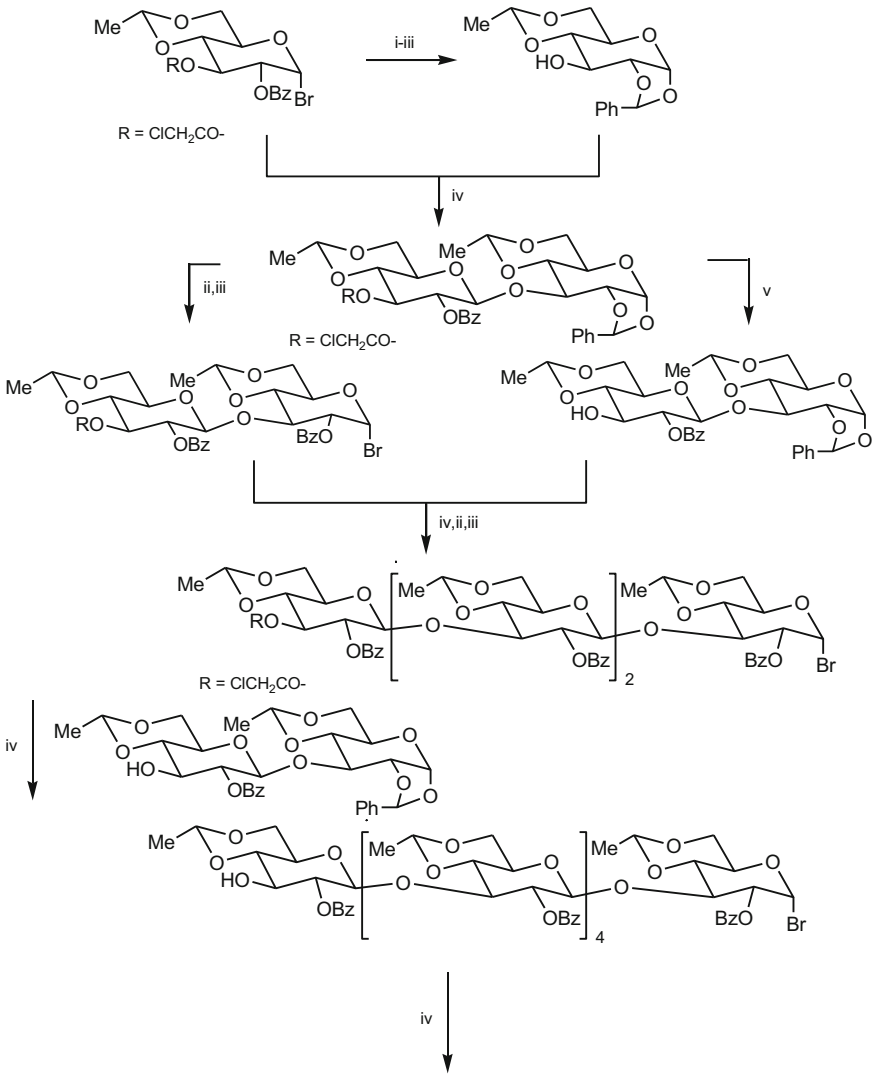
In 1990, the chemical synthesis of β-(1 → 3) linked hexasaccharide was reported. The chemical approach involved the glycosidic reaction between benzylidene acceptor and protected glycosyl bromide as glycosyl donor, under silver triflate-promoter conditions. As it can be seen in Scheme 2.89, the construction of



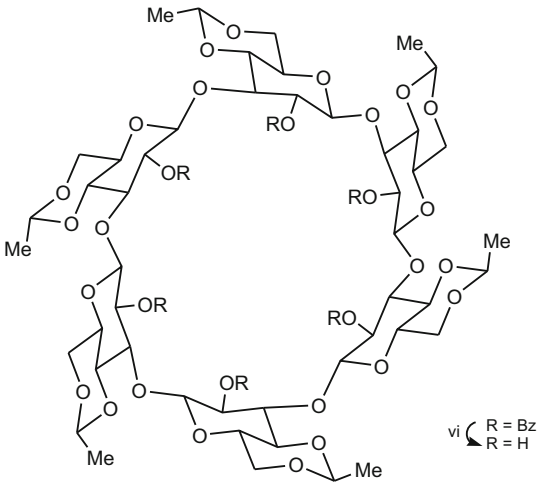
Scheme 2.128 Chemical synthesis of cyclic α(1 → 4)-oligosaccharide γ-CD

the linear oligosaccharide and its final cycloglycosylation was performed by using glycosyl bromides which were prepared by photolytic brominolysis of 1,2-*O*-benzylidene glucose with $BrCCl_3$ (Scheme 2.129) [153].

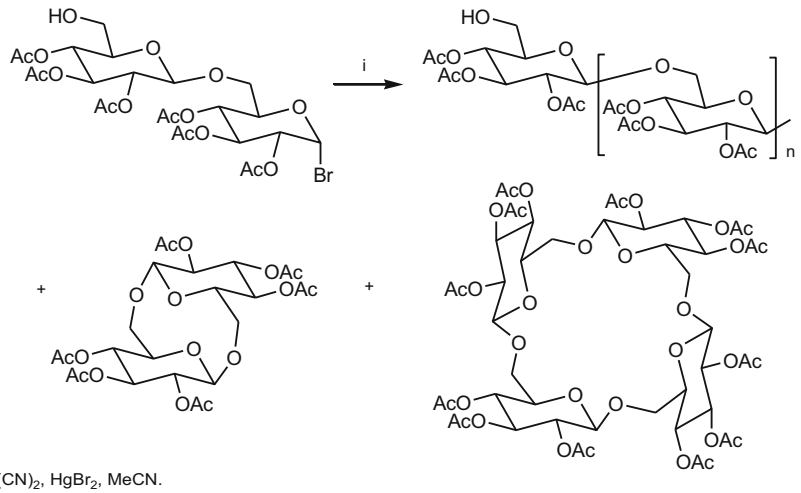
The formation of (1→6)-glycopyranosidic linkages might produce cyclic disaccharides, trisaccharides, and tetrasaccharides. An early synthesis of β-(1→6)-glucopyranan under Helferich conditions, generated along with the linear oligomer, a cyclic disaccharide and tetrasaccharide in 12% and 6% respectively (Scheme 2.130) [154].



Scheme 2.129 Synthesis of cyclic β-(1→3)-linked oligosaccharide

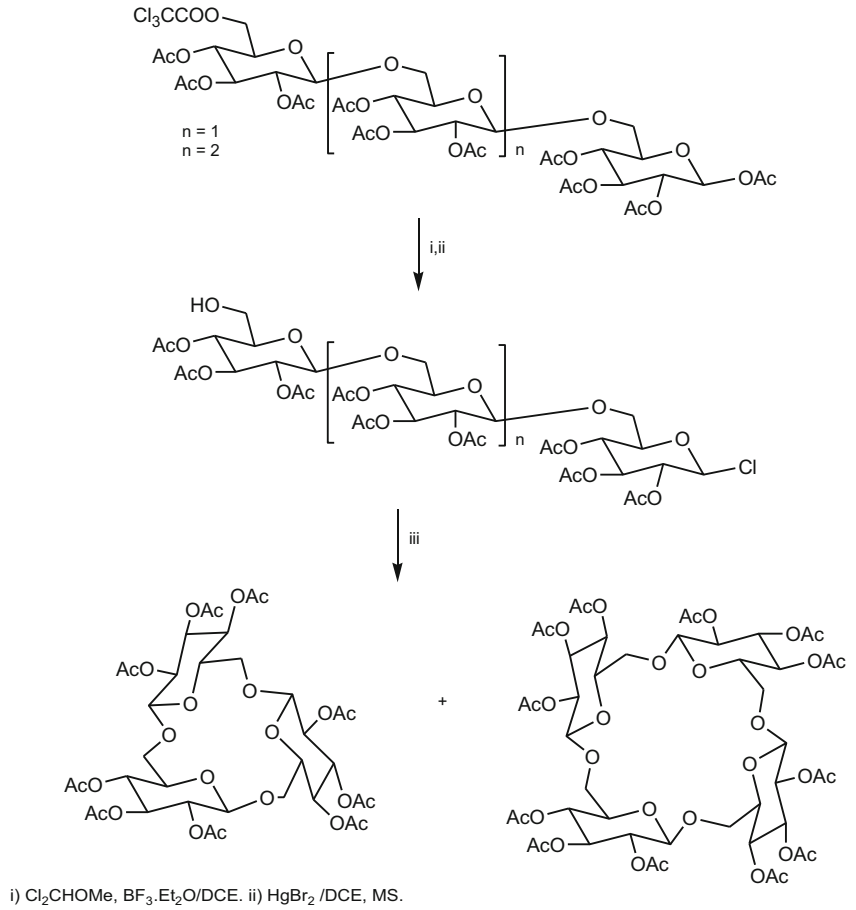


Scheme 2.129 (continued)



Scheme 2.130 Preparation of linear, and cyclic β(1 → 6) disaccharides and tetrasaccharides

An improved synthesis of cyclotetraoside was described by the same group 10 years later, consisting in the preparation from the peracetylated tetrasaccharide into the tetrasaccharide derivative having both the acceptor and the donor components. The final cyclization was performed under Helferich conditions providing a mixture of trisaccharide and tetrasaccharide in 22 % and 25 % yield respectively (Scheme 2.131) [118, 155].

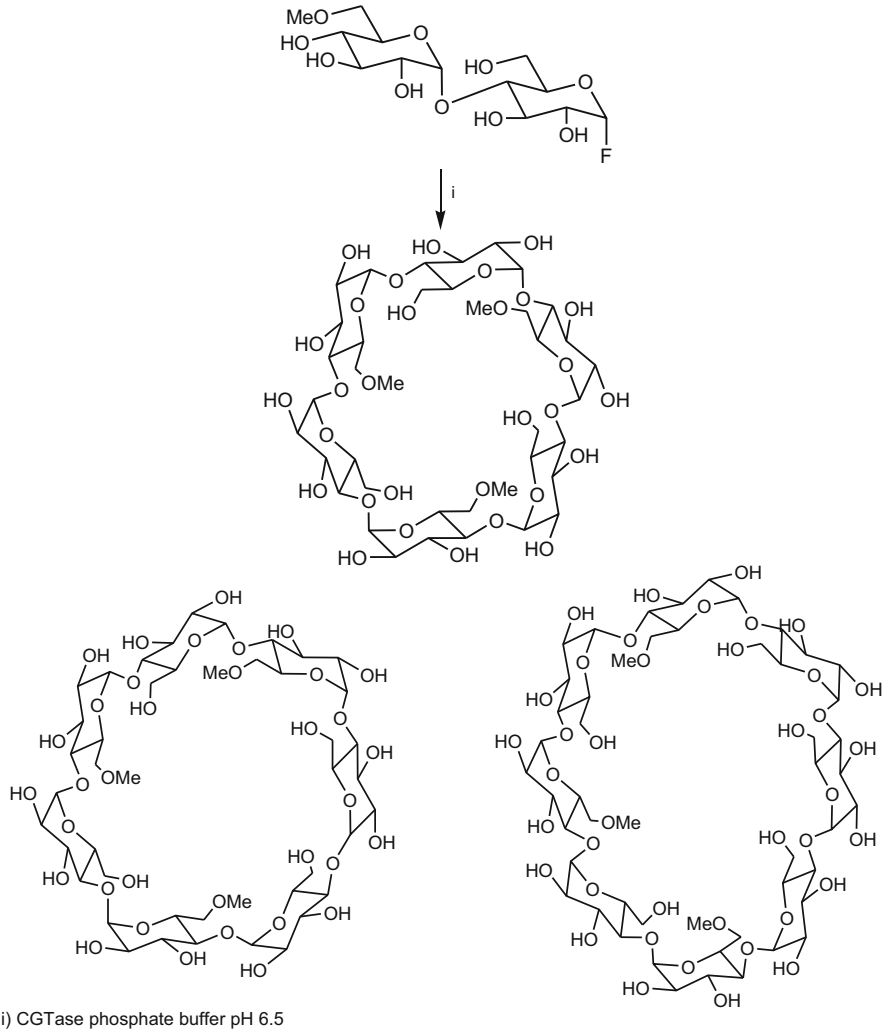


Scheme 2.131 Improved synthesis of cyclic β(1 → 6) trisaccharides and tetrasaccharides

2.1.19.1 Chemoenzymatic and Enzymatic Synthesis

The use of enzyme is as mentioned for many *O*- or *N*-glycosides the parallel possibility for preparing cyclic oligosaccharides. The limitation continue to be the availability and affordability; however, some enzymes such as glycosidases and cycloglycosyltransferases (CGTases) which are involved in the preparation of cyclodextrins from starch and other α-(1 → 4)-glucans are accessible and more versatile [155].

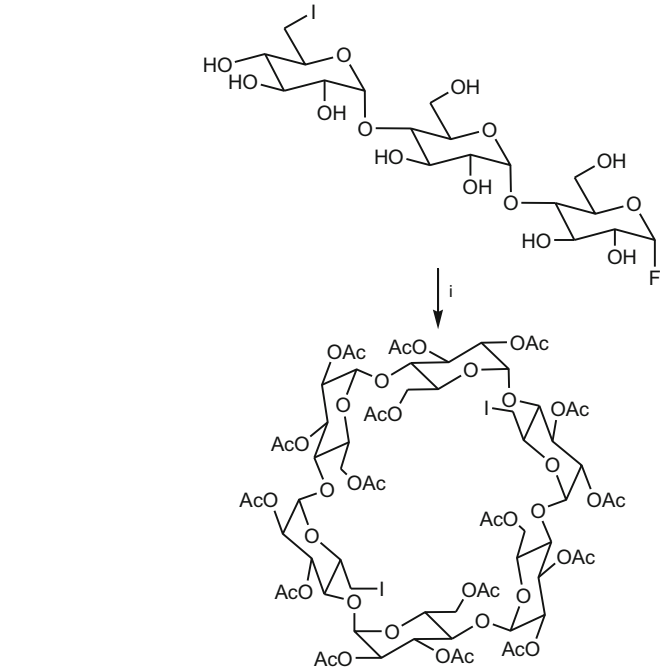
The feasibility of the chemoenzymatic approach was established in the preparation of cyclic β(1 → 4) hexasaccharides, heptasaccharides, and octasaccharides, from 6-*O*-methylmaltosyl fluoride when incubated with CGTase. Thus, a mixture of 6^{I}, 6^{III}, 6^{V}-tri-*O*-methyl-α-CD (42 %), 6^{I}, 6^{III}, 6^{V}-tetra-*O*-methyl-γ-CD (16 %) and in less proportion 6^{I}, 6^{III}, 6^{V}-tri-*O*-methyl-β-CD were obtained (Scheme 2.132) [136, 156].



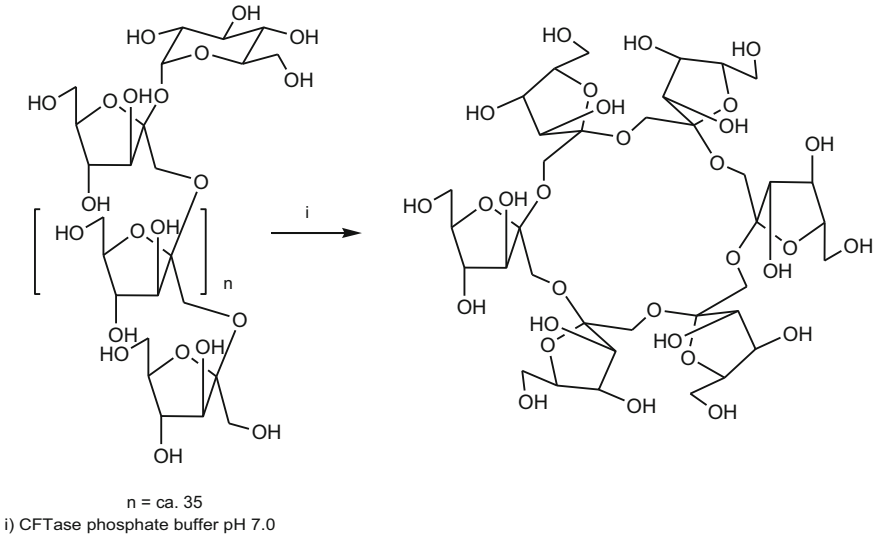
Scheme 2.132 Synthesis of 6^{I}, 6^{III}, 6^{V}-tri-*O*-methyl-α-CD, 6^{I}, 6^{III}, 6^{V}-tetra-*O*-methyl-γ-CD and 6^{I}, 6^{III}, 6^{V}-tri-*O*-methyl-β-CD

Furthermore, under the same conditions it was possible to prepare from the maltotriosyl fluoride the cyclic α(1 → 4) hexasaccharide (6^{I}, 6^{II}-dideoxy-6^{I},6^{II}-diiodo-α-CD) in 38 % (Scheme 2.133) [118, 157].

An alternative option for the enzymatic preparation of cyclic oligosaccharides besides CGTases is glycosidases which exerts its action on polysaccharides. This possibility is exploited in the preparation of cyclic fructins by conversion of β-(1 → 2)-fructofuranan by bacterial fructotransferases isolated from *Bacillus circulans* (Scheme 2.134) [158].

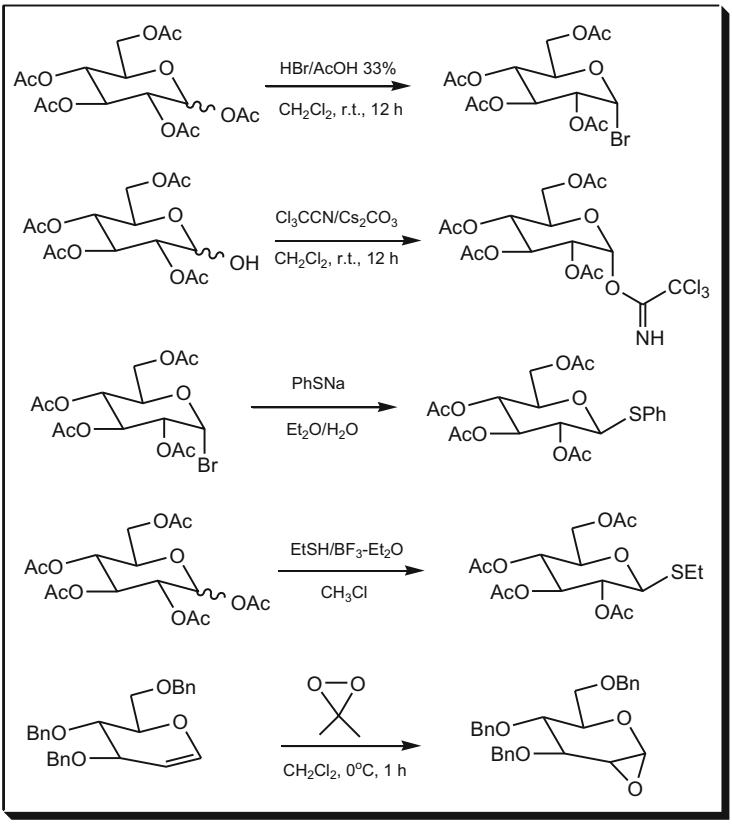


Scheme 2.133 Enzymatic synthesis of 6^{I}, 6^{II}-dideoxy-6^{I},6^{II}-diiodo-α-CD



Scheme 2.134 Enzymatic synthesis of cycloinulooligosaccharides

2.1.19.2 Summary for Preparing Conventional Glycosyl Donors



References

1. Toshima K, Tatsuta K (1993) Recent progress in O-glycosylation methods and its application to natural product synthesis. Chem Rev 93:1503–1531
2. Anderson FB, Leaback DH (1961) Substrates for the histochemical localization of some glycosidases. Tetrahedron 12:236–239
3. Böttcher S, Hederos M, Champion E, Dekany G, Thiem J (2013) Novel efficient routes to indoxyl glycosides for monitoring glycosidase activities. Org Lett 15:3766–3769
4. Wessel HP (1988) Use of trifluoromethanesulfonic acid in fischer glycosylations. J Carbohydr Chem 7:263–268
5. Shearly YF, O'Dell CA, Amett G (1987) Synthesis and antiviral evaluation of carbocyclic analogs of 2-amino-6-substituted-purine 3′-deoxyribofuranosides. J Med Chem 30:1090–1094
6. Beale TM, Taylor MS (2013) Synthesis of cardiac glycoside analogs by catalyst-controlled, regioselective glycosylation of digitoxin. Org Lett 15:1358–1361
7. Kaneko M, Herzon SB (2014) Scope and limitations of 2-deoxy- and 2,6-dideoxyglycosyl bromides as donors for the synthesis of β-2-deoxy- and β-2,6-dideoxyglycosides. Org Lett 16:2776–2779

8. Koenigs W, Knorr E (1901) Ueber einige derivate des traubenzuckers und der galactose. Ber Deutsch Chem Gesell 34:957–981
9. Igarashi K (1977) Advances in carbohydrate chemistry and biochemistry. Adv Carbohydr Chem Biochem 34:243–283
10. Kim J-H, Yang H, Park J, Boons G-J (2005) A general strategy for stereoselective glycosylations. J Am Chem Soc 127:12090–12097
11. De Ninno MP, McCarthy PA, Duplatiel KC, Eller C, Etienne JB, Zawistowski MP, Bangerter FW, Chandler CE, Morehouse LA, Sugarman ED, Wilkins RW, Woody HA, Zaccaro LM (1997) Steroidal glycoside cholesterol absorption inhibitors. J Med Chem 40:2547–2554
12. Conrow RB, Bernstein S (1971) Steroid conjugates. VI. Improved Koenigs--Knorr synthesis of aryl glucuronides using cadmium carbonate, a new and effective catalyst. J Org Chem 36:863–870
13. Stachulski AV, Jenkins GH (1998) The synthesis of O-glucuronides. Nat Prod Rep 15:173–186
14. Bredereck A, Wagner A, Kuhn H, Ott H (1960) Oligosaccharidsynthesen II. Synthesen von di- und trisacchariden des gentiobiosetyps. Ber Deutsch Chem Gesell 93:1201–1206
15. Bächli P, Percival EG (1952) The synthesis of laminaribiose and proof of its identity with laminaribiose isolated from laminarin. J Chem Soc 224:1243–1246
16. Khorlin AY, Privalova IM, Bystrova IB (1971) Synthesis of N-acetylneuraminyl-(2 → 3)- and - (2 → 6)-hexoses. Carbohydr Res 19:272–275
17. Paulsen H, Tietz H (1982) Synthesis of trisaccharide moieties from n-acetylneuraminic acid and n- acetyllactosamine. Angew Chem Int Ed 21:927–928
18. Wessel HP, Iberg N, Trumtel M, Viaud MC (1996) Selectively deoxygenated sulfated tetrasaccharides as probes for the investigation of smooth muscle cell antiproliferative activity. Bioorg Med Chem Lett 6:27–32
19. Katano K, An H, Aoyagi Y, Overhand M, Sucheck SJ, Stevens WC Jr, Hess CD, Zhou X, Hecht SM (1998) Total synthesis of bleomycin group antibiotics. The total synthesis of bleomycin demethyl A2, bleomycin A2 and decarbamoyl bleomycin demethyl A2. J Am Chem Soc 120:11285–11296
20. Talisman IJ, Kumar V, Razzaghy J, Malhotra SV (2011) O-Glycosidation reactions promoted by in situ generated silver N-heterocyclic carbenes in ionic liquids. Carbohydr Res 346:883–890
21. Lemieux RU, Hendriks KB, Stick RV, James K (1975) Halide ion catalyzed glycosidation reactions. Syntheses of α-linked disaccharides. J Am Chem Soc 97:4056–4062
22. Thomas M, Beale TM, Moon PJ, Taylor S (2014) Organoboron-catalyzed regio- and stereoselective formation of β-2-deoxyglycosidic linkages. Org Lett 16:3604–3607
23. Umezawa S, Koto S, Tatsuta K, Hineno H, Nishimura Y, Tsumura T (1969) Studies of aminosugars. XXI. The total synthesis of kanamycin C. Bull Chem Soc Jpn 42:529–533
24. Roth HJ, Kleeman A (1988) Pharmaceutical chemistry: drug synthesis, vol 1. Ellis Horwood Ltd., Chichester
25. Suami T, Otake T, Nishimura T, Ikeda Y (1973) Synthesis of raffinose and an isomer. Carbohydr Res 26:234–239
26. Murakami T, Hirono R, Sato Y, Furusawa K (2007) Efficient synthesis of ω-mercaptoalkyl 1,2-trans-glycosides from sugar peracetates. Carbohydr Res 342:1009–1020
27. Ferlin N, Duchet L, Kovensky J, Grand E (2008) Microwave-assisted synthesis of long-chain alkyl glucopyranosides. Carbohydr Res 343:2819–2821
28. Wei G, Lv X, Du Y (2008) $FeCl_3$-catalyzed α-glycosidation of glycosamine pentaacetates. Carbohydr Res 343:3096–3099
29. Xue JL, Cecioni S, He L, Vidal S, Praly J-P (2009) Variations on the SnCl4 and CF3CO2Ag-promoted glycosidation of sugar acetates: a direct, versatile and apparently simple method with either α or β stereocontrol. Carbohydr Res 344:1646–1653
30. Aich U, Loganathan D (2007) Zeolite-catalyzed Helferich-type glycosylation of long-chain alcohols. Synthesis of acetylated alkyl 1,2-trans glycopyranosides and alkyl 1,2-cis C2-hydroxy-glycopyranosides. Carbohydr Res 342:704–719

31. Bagget N, Samra AK, Smithson A (1983) Synthesis of some aryl 2,3,4,6-tetra-O-acetyl-l--idopyranosides and of 4-methylcoumarin-7-yl α-l-idopyranosiduronic acid. Carbohydr Res 124:63–74
32. Kumar A, Kumar V, Dere RT, Schmidt RR (2011) Glycoside bond formation via acid-base catalysis. Org Lett 13:3612–3615
33. Cox DJ, Smith MD, Fairbanks AJ (2010) Glycosylation catalyzed by a chiral Brønsted acid. Org Lett 12:1452–1455
34. Mensah EA, Azzarelli JM, Nguyen HM (2009) Palladium-controlled β-selective glycosylation in the absence of the C(2)-ester participatory group. J Org Chem 74:1650–1657
35. Schmidt RR (1986) New methods for the synthesis of glycosides and oligosaccharides—are there alternatives to the Koenigs-Knorr method? Angew Chem Int Ed 25:212–235
36. Fürstner A, Müller T (1999) Efficient total syntheses of resin glycosides and analogues by ring-closing olefin metathesis. J Am Chem Soc 121:7814–7821
37. Hasegawa A, Fushimi K, Ishida H, Kiso M (1993) Synthesis of saialyl Lewis analogs containing azidoalkyl groups at the reducing end. J Carbohydr Chem 12:1203–1216
38. Danishefsky S, Shair MD (1996) Observations in the chemistry and biology of cyclic enediyne antibiotics - total syntheses of calicheamicin gamma(i)(1) and dynemicin-a. J Org Chem 16:16–44
39. Larson DP, Heathcock CH (1997) The total synthesis of tricolorin A. J Org Chem 62:8406–8418
40. Lu SF, O'Yang OO, Guo ZW, Yu B, Hui YZ (1997) Total synthesis of tricolorin A. J Org Chem 62:8400–8405
41. Brito-Arias M, Pereda-Miranda R, Heathcock CH (2004) Synthesis of tricolorin F. J Org Chem 69:4567–4570
42. Boons GJ, Isles S (1996) Vinyl glycosides in oligosaccharide synthesis. 2. The use of allyl and vinyl glycosides in oligosaccharide synthesis. J Org Chem 61:4262–4264
43. Komba S, Galustian H, Ishida H, Feizi T, Kannagi R, Kiso M (1999) The first total synthesis of 6-Sulfo-de-N-acetylsialyl Lewis^{x} ganglioside: a superior ligand for human L-selectin. Angew Chem Int Ed 38:1131–1133
44. Koenig A, Jain R, Vig R, Norgard-Sumnicht KE, Matta KL, Varki A (1997) Selectin inhibition: synthesis and evaluation of novel sialylated, sulfated and fucosylated oligosaccharides, including the major capping group of GlyCAM-1. Glycobiology 7:79–93
45. Lubineau A, Alais J, Lemoine R (2000) Synthesis of 3e- and 6e-monosulfated and 3e,6e-disulfated Lewis^{x} pentasaccharides, candidate ligands for human L-selectin. J Carbohydr Chem 19:151–169
46. Nicolaou KC, Ohshima T, van Delft FL, Vourloumis D, Xu JY, Pfefferkorn J, Kim S (1998) Total synthesis of eleutherobin and eleuthosides A and B. J Am Chem Soc 120:8674–8680
47. Chang S-S, Lin C-C, Li Y-K, Mong K-KT (2009) A straightforward α-selective aromatic glycosylation and its application for stereospecific synthesis of 4-methylumbelliferyl α-T-antigen. Carbohydr Res 344:432–438
48. Ludek O, Gu W, Gildersleeve JC (2010) Activation of glycosyl trichloroacetimidates with perchloric acid on silica (HClO4–SiO2) provides enhanced α-selectivity. Carbohydr Res 345:2074–2078
49. Park NH, Nguyen HM (2009) Stereoselective rearrangement of trichloroacetimidates: application to the synthesis of r-glycosyl ureas. Org Lett 11:2433–2436
50. Chen J, Zhou Y, Chen C, Xu W, Yu B (2008) Synthesis of a tetrasaccharide substrate of heparanase. Carbohydr Res 343:2853–2862
51. Lian G, Gao Q, Lin F (2008) Synthesis of fructofuranosides: efficient glycosylation with N-phenyltrifluoroacetimidate as the leaving group. Carbohydr Res 343:2992–2996
52. Chu A-HA, Nguyen SH, Sisel JA, Minciunescu A, Bennett CS (2013) Selective synthesis of 1,2-cis-α-glycosides without directing groups. Application to iterative oligosaccharide synthesis. Org Lett 15:2566–2569
53. Imamura A, Lowary T (2010) β-Selective arabinofuranosylation using a 2,3-O-xylylene-protected donor. Org Lett 12:3686–3689

54. Lonn H (1985) Synthesis of a tetra- and a nona-saccharide which contain α-l-fucopyranosyl groups and are part of the complex type of carbohydrate moiety of glycoproteins. Carbohydr Res 139:115–121
55. Ley SV, Priepke HWM (1994) A facile one-pot synthesis of a trisaccharide unit from the common polysaccharide antigen of group B streptococci using cyclohexane-1, 2-diacetal (CDA) protected rhamnosides. Angew Chem Int Ed 33:2292–2294
56. Boons G-J, Demchenko AV (2000) Recent advances in O-sialylation. Chem Rev 100: 4539–4566
57. Paul S, Jayaraman N (2007) Synthesis of aryl-2-deoxy-d-lyxo/arabino-hexopyranosides from 2-deoxy-1-thioglycosides. Carbohydr Res 342:1305–1314
58. Hotta K, Ishida H, Kiso M, Hasegawa A (1995) Synthetic studies on sialoglycoconjugates 66: first total synthesis of a cholinergic neuron-specific ganglioside GQ1bα1. J Carbohydr Chem 14:491–506
59. Crich D, Li H (2000) Synthesis of the Salmonella type E(1) core trisaccharide as a probe for the generality of 1-(benzenesulfinyl)piperidine/triflic anhydride combination for glycosidic bond formation from thioglycosides. J Org Chem 67:4640–4646
60. Lu Y-S, Li Q, Zhang X-S, Ye L-H (2010) Highly direct α-selective glycosylations of 3,4-O-carbonate-protected 2-deoxy- and 2,6-dideoxythioglycosides by preactivation protocol. Org Lett 10:3445–3448
61. Yamago S, Yamada T, Maruyama T, Yoshida J-i (2004) Iterative glycosylation of 2-deoxy-2-aminothioglycosides and its application to the combinatorial synthesis of linear oligoglucosamines. Angew Chem Int Ed 43:2145–2148
62. Jing Y, Huang X (2004) Fluorous thiols in oligosaccharide synthesis. Tetrahedron Lett 45:4615–4618
63. Galan MC, Jouvin K, Alvarez-Dorta D (2010) Scope and limitations of imidazolium-based ionic liquids as room temperature glycosylation promoters. Carbohydr Res 345:45–49
64. Eva C, Lourenço EC, Ventura MR (2011) The synthesis of compatible solute analogues—solvent effects on selective glycosylation. Carbohydr Res 346:163–168
65. Chu A-H, Minciunescu A, Montanari V, Kumar K, Bennett CS (2014) An air- and water-stable iodonium salt promoter for facile thioglycoside activation. Org Lett 16:1780–1782
66. He H, Zhu X (2014) Thioperoxide-mediated activation of thioglycoside donors. Org Lett 16:3102–3105
67. Chu AA, Nguyen SH, Sisel JA, Minciunescu A, Bennett CS (2013) Selective synthesis of 1,2-cis-R-glycosides without directing groups. Application to iterative oligosaccharide synthesis. Org Lett 15:2566–2569
68. Nokami T, Nozaki Y, Saigusa Y, Shibuya A, Manabe S, Ito Y, Yoshida J-i (2011) Glycosyl sulfonium ions as storable intermediates for glycosylations. Org Lett 13:1544–1547
69. Park TJ, Weïwer M, Yuan X, Baytas SN, Munoz EM, Murugesan S, Linhardt RJ (2007) Glycosylation in room temperature ionic liquid using unprotected and unactivated donors. Carbohydr Res 342:614–620
70. Delacroix S, Bonnet J-P, Courty M, Postel D, Van Nhien AN (2013) Glycosylation mediated—BAIL in aqueous solution. Carbohydr Res 381:12–18
71. Schmalisch S, Mahrwald R (2013) Organocatalyzed direct glycosylation of unprotected and unactivated carbohydrates. Org Lett 15:5854–5857
72. Pfaffe M, Mahrwald R (2012) Direct glycosylation of unprotected and unactivated carbohydrates under mild conditions. Org Lett 14:792–795
73. Meng B, Zhu Z, Baker DC (2014) 1,2-cis Alkyl glycosides: straightforward glycosylation from unprotected 1-thioglycosyl donors. Org Biomol Chem 28:5182–5191
74. Gudmundsdottir AV, Nitz M (2008) Protecting group free glycosidations using p-toluenesulfonohydrazide donors. Org Lett 10:3461–3463
75. Mamidyala SK, Finn MG (2009) Glycosylation using unprotected alkynyl donors. J Org Chem 74:8417–8420
76. Mootoo DR, Konradsson P, Udodong U, Fraser-Reid B (1988) Synthesis of the tetrasaccharide motif and its structural analog corresponding to the lipopolysaccharide of Escherichia coli O75. J Am Chem Soc 110:5583–5584

77. Codee JDC, Litjens REJN, den Heeten R, Overkleeft HS, van Boom JN, van der Marel GA (2003) Ph2SO/Tf2O: a powerful promotor system in chemoselective glycosylations using thioglycosides. Org Lett 5:1519–1522
78. Yoshida M, Kiyoi T, Tsukida T, Kondo H (1998) One-pot synthesis of Lewis^X oligosaccharide derivatives using armed-disarmed coupling method. J Carbohydr Chem 17:673–681
79. Demchenko AV, Malysheva NN, De Meo C (2003) S-Benzoxazolyl (SBox) glycosides as novel, versatile glycosyl donors for stereoselective 1,2-cis glycosylation. Org Lett 5:455–458
80. Fischer E, Zach K (1913) Sitz Ber Kgl preuss Akad Wiss 16:311
81. Freiser-Reid B, Kelly DR, Tulshian DB, Ravi PS (1983) Routes from "Triacetyl Glucal" to 6-deoxy-hex-2-enopyranosides. J Carbohydr Chem 2:105–114
82. Shull BK, Wu Z, Koreeda M (1996) A convenient, highly efficient one-pot preparation of peracetylated glycals from reducing sugars. J Carbohydr Chem 15:955–964
83. Murray RW, Jeyaraman R (1985) Dioxiranes - synthesis and reactions of methyldioxiranes. J Org Chem 50:2847–2853
84. Adam W, Bialas J, Hadjiarapoglou L (1991) A convenient preparation of acetone solutions of dimethyldioxirane. Chem Ber 124:2377–2378
85. Marzabadi CH, Spilling CD (1993) Stereoselective glucal epoxide formation. J Org Chem 58:3761–3766
86. Belluci G, Catelani G, Chiappe C, D'Andrea F (1994) A simple and highly diastereoselective preparation of glycal epoxides using the MCPBA-KF complex. Tetrahedron Lett 35:8433–8436
87. Du Y, Kong F (1995) Stereoselective glycosylation of fully benzylated 1,2- and 1,3-anhydrosugar-pyranose with protected serine methyl ester. J Carbohydr Chem 14:341–352
88. Halcomb RL, Danishefsky SJ (1989) On the direct epoxidation of glycals: application of a reiterative strategy for the synthesis of β-linked oligosaccharides. J Am Chem Soc 111:6661–6666
89. Upreti M, Ruhela D, Vishwakarma RA (2000) Synthesis of the tetrasaccharide cap domain of the antigenic cell surface Lipophosphoglycan of Leishmania donovani parasite. Tetrahedron 56:6577–6584
90. Broddefalk J, Bergquist KE, Kihlberg J (1996) Preparation of a glycopeptide analogue of type II collagen—use of acid labile protective groups for carbohydrate moieties in solid phase synthesis of O-linked glycopeptides. Tetrahedron Lett 37:3011–3014
91. Kunz H (1987) Synthesis of glycopeptides, partial structures of biological recognition components [New Synthetic Methods (67)]. Angew Chem Int Ed Engl 26:294–308
92. Li Y, Tang P, Chen Y, Yu B (2008) Gold(I)-catalyzed glycosidation of 1,2-anhydrosugars. J Org Chem 73:4323–4325
93. Cui X-K, Zhong M, Meng X-B, Li Z-J (2012) The synthesis of 2-deoxy-α-d-glycosides from D-glycals catalyzed by TMSI and PPh_3. Carbohydr Res 358:19–22
94. Procopio A, Dalpozzo R, De Nino A, Maiuolo L, Nardi M, Oliverio M, Russo B (2007) A facile Er(OTf)3-catalyzed synthesis of 2,3-unsaturated O- and S-glycosides. Carbohydr Res 342:2125–2131
95. Wong CH, Ichikawa Y, Krach T, Gautheron-Le Narvor C, Dumas DP, Look GC (1991) Probing the acceptor specificity of beta-1,4-galactosyltransferase for the development of enzymatic synthesis of novel oligosaccharides. J Am Chem Soc 113:8137–8145
96. Shimizu M, Togo H, Yokohama M (1998) Chemistry of glycosyl fluorides. Synthesis 6:799–822
97. Morita M, Natori T, Akimoto K, Osawa T, Fukushima H, Koezuka Y (1995) Synthesis of a-, b-monoglycosylceramides and four diastereomers of an a-galactosylceramide. Bioorg Med Chem Lett 5:699–701
98. Mukaiyama T, Hashimoto Y, Shoda S (1983) Stereoselective synthesis of 1,2-cis-glycofuranosides using glycofuranosyl fluorides. Chem Lett 12:935–938
99. Nicolaou KC, Bockovich NJ, Carcanague DR (1993) Total synthesis of sulfated Lex and Lea-type oligosaccharide selectin ligands. J Am Chem Soc 115:8843–8844
100. Murakami T, Sato Y, Shibakami M (2008) Stereoselective glycosylations using benzoylated glucosyl halides with inexpensive promoters. Carbohydr Res 343:1297–1308

101. Walvoort MTC, Dinkelaar J, van den Bos LJ, Lodder G, Overkleeft HS, Codée JDC, van der Marel GA (2010) The impact of oxocarbenium ion conformers on the stereochemical outcome of glycosylations. Carbohydr Res 345:1252–1263
102. Bohé L, Crich D (2015) A propos of glycosyl cations and the mechanism of chemical glycosylation; the current state of the art. Carbohydr Res 403:48–59
103. Meloncelli P, Martin AD, Lowary TL (2009) Glycosyl iodides. History and recent advances. Carbohydr Res 344:1110–1122
104. Uchiyama T, Hindsgaul OJ (1998) Rapid conversion of unprotected galactose. J Carbohydr Chem 17:1181–1190
105. Harding JR, King CD, Perrie JA, Sinnott D, Stachulski A (2005) Glucuronidation of steroidal alcohols using iodosugar and imidate donors V. Org Biomol Chem 3:1501–1507
106. Kulkarni SS, Gervay-Hague J (2008) Two-step synthesis of the immunogenic bacterial glycolipid BbGL1. Org Lett 10:4739–4742
107. Bickley J, Cottrell JA, Ferguson JR, Field RA, Harding JR, Hughes DL, Kartha KPR, Law JL, Schienmann F, Stachulski A (2003) Preparation, X-ray structure and reactivity of a stable glycosyl iodide. Chem Commun 1266–1267
108. Ko Y-J, Shim S-B, Shin J-H (2009) Facile synthesis of 2-O-iodoacetyl protected glycosyl iodides: useful precursors of 1 → 2-linked 1,2-trans-glycosides. Org Lett 11:609–612
109. Tietze LF, Fischer R (1983) Stereoselective synthesis of iridoid glycosides. Angew Chem Int Ed Engl 22:888
110. Coteron JM, Singh K, Asensio JL, Domingues-Dalda M, Fernandez-Mayoralis A, Jimenez-Barbero J, Martin-Lomas M (1995) Oligosaccharides structurally related to E-selectin ligands are inhibitors of neural cell division: synthesis, conformational analysis, and biological activity. J Org Chem 60:1502–1519
111. Hanashima S, Tomiya T, Ishikawa D, Akai S, Sato K (2009) Sialylation using N-glycolylneuraminyl phosphite donors to synthesize Neu5Gc-containing glycans. Carbohydr Res 344:959–965
112. Burkhart F, Zhang Z, Wacowich-Sgarbi S, Wong CH (2001) Synthesis of the globo H hexasaccharide using the programmable reactivity-based one-pot strategy. Angew Chem Int Ed 40:1274–1277
113. Nilsson KG (1987) A simple strategy for changing the regioselectivity of glycosidase-catalysed formation of disaccharides. Carbohydr Res 167:95–103
114. Freeman GA, Shauer SR, Rideout JL, Short SA (1995) 2-Amino-9-(3-azido-2,3-dideoxy-beta-d-erythro-pentofuranosyl)-6-substitute d-9H-purines. Synthesis and anti-HIV activity. Bioorg Med Chem 3:447–458
115. Simon ES, Grabowski S, Whitesides GM (1990) Convenient synthesis of cytidine 5′-triphosphate, guanosine 5′-triphosphate, and uridine 5′-triphosphate and their use in the preparation of UDP-glucose, UDP-glucuronic acid, and GDP-mannose. J Org Chem 55:1834–1841
116. O'Neill EC, Field RA (2015) Enzymatic synthesis using glycoside phosphorylases. Carbohydr Res 403:23–37
117. Ichikawa Y, Shen GJ, Wong C-H (1991) Enzyme-catalyzed synthesis of sialyl oligosaccharide with in situ regeneration of CMP-sialic acid. J Am Chem Soc 113:4698–4700
118. Gaudino JJ, Paulson JC (1994) A novel and efficient synthesis of neolacto series gangliosides 3′-nLM1 and 6′-nLM1. J Am Chem Soc 116:1149–1150
119. Heidlas JE, Lees WJ, Pale P, Whitesides GM (1992) Gram-scale synthesis of uridine 5′-diphospho-N-acetylglucosamine: comparison of enzymic and chemical routes. J Org Chem 57:146–151
120. Toone EJ, Simon ES, Whitesides GM (1991) Enzymatic synthesis of uridine 5′-diphosphoglucuronic acid on a gram scale. J Org Chem 56:5603–5606
121. Liu JLC, Shen G-J, Ichikawa Y, Rutan JF, Zapata G, Vann WF, Wong C-H (1992) Overproduction of CMP-sialic acid synthetase for organic synthesis. J Am Chem Soc 114:3901–3910
122. Mackenzie LFQ, Wang Q, Warren RAJ, Whiters SG (1998) Glycosynthases: mutant glycosidases for oligosaccharide synthesis. J Am Chem Soc 120:5583–5584
123. Drueckhammer DG, Hennen WJ, Pederson RL, Barbas CF III, Gautheron CM, Krach T, Wong C-H (1991) Enzyme catalysis in synthetic carbohydrate chemistry. Synthesis 1991:499–525

124. Zeng X, Murata T, Usui T (2003) Glycosidase-catalyzed synthesis of fucosyl di- and trisaccharide derivatives using α-l-fucosidase from Alcaligenes sp. J Carbohydr Chem 22:309–316
125. Cook BN, Bhakta S, Biegel T, Bowman KG, Armstrong JI, Hemmerich S, Bertozzi CR (2000) Differential carbohydrate recognition of two GlcNAc-6-sulfotransferases with possible roles in L-selectin ligand biosynthesis. J Am Chem Soc 122:8612–8622
126. Akita H, Kawahara E, Kato K (2004) Chemoenzymatic synthesis of rhodiooctanoside isolated from Chinese medicines, rhodiolae radix. Tetrahedron Asymmetry 15:1623–1629
127. Wong CH, Halcomb RL, Ichikawa Y, Kajimoto T (1995) Enzymes in organic synthesis: application to the problems of carbohydrate recognition (Part 2). Angew Chem Int Ed 34:521–546
128. Marton Z, Tran V, Tellier C, Dion M, Drone J, Rabiller C (2008) Engineering of glucoside acceptors for the regioselective synthesis of β-(1 → 3)-disaccharides with glycosynthases. Carbohydr Res 343:2939–2946
129. Wilkinson SM, Liew CW, Mackay JP, Salleh HM, Withers SG, McLeod MD (2008) Escherichia coli glucuronylsynthase: an engineered enzyme for the synthesis of β-glucuronides. Org Lett 10:1585–1588
130. Nicolaou KC, Watanabe N, Li J, Pastor J, Winssinger N (1998) Solid-phase synthesis of oligosaccharides: construction of a dodecasaccharide. Angew Chem Int Ed 37:1559–1561
131. Mitchell SA, Pratt MR, Hruby UJ, Polt R (2001) Solid-phase synthesis of O-linked glycopeptide analogues of enkephalin. J Org Chem 66:2327–2342
132. Seeberger PH, Haase WC (2000) Solid-phase oligosaccharide synthesis and combinatorial carbohydrate libraries. Chem Rev 100:4349–4394
133. Sears P, Wong CH (2001) Toward automated synthesis of oligosaccharides and glycoproteins. Science 291:2344–2350
134. Crich D, Smith M (2002) Solid-phase synthesis of β-mannosides. J Am Chem Soc 124:8867–8869
135. Walvoort MTC, Volbeda AG, Reintjens NRM, van den Elst H, Plante OJ, Overkleeft HS, van der Marel GA, Codée JDC (2012) Automated solid-phase synthesis of hyaluronan oligosaccharides. Org Lett 14:3776–3779
136. Gijsen HJM, Qiao L, Fitz W, Wong CH (1996) Recent advances in the chemoenzymatic synthesis of carbohydrates and carbohydrate mimetics. Chem Rev 96:443–474
137. Metha S, Pinto MB (1993) Phenylselenoglycosides as novel, versatile glycosyl donors and acceptors in oligosaccharide synthesis. J Org Chem 58:3269–3276
138. Sobti A, Kim K, Solikowski GA (1996) Application of glycosyltetrazoles in oligosaccharide synthesis - assembly of the c3 trisaccharide component of the antibiotic PI-080. J Org Chem 61:6–7
139. Takeda K, Kaji E, Nakamura H, Akiyama A, Konda A, Mizuno Y, Takayanagi H, Harigaya Y (1996) Synthesis of 2-amino-2-deoxy-d-hexopyranoside-containing disaccharides involving glycosylation and [3,3] sigmatropic rearrangement. Synthesis 1996:341–348
140. Garcia DM, Yamada H, Hatakeyama S, Nishikawa M (1994) Total synthesis of arthrobacilin A. Tetrahedron Lett 35:3325–3328
141. Nagai H, Matsumura S, Toshima K (2002) Environmentally benign and stereoselective formation of β-O-glycosidic linkages using benzyl-protected glucopyranosyl phosphite and montmorillonite K-10. Tetrahedron Lett 43:847–850
142. Toshima K, Nakai H, Matsumura S (1999) Novel dehydrative glycosidations of 1-hydroxy sugars using a heteropoly acid. Synlett 9:1420–1422
143. Toshima K, Kasumi K, Matsumura S (1999) Novel stereocontrolled glycosidations of 2-deoxyglucopyranosyl fluoride using a heterogeneous solid acid, sulfated zirconia (SO4/ZrO2). Synlett 6:813–815
144. Oikawa M, Tanaka T, Fukuda N, Kusumoto S (2004) One-pot preparation and activation of glycosyl trichloroacetimidates: operationally simple glycosylation induced by combined use of solid-supported, reactivity-opposing reagents. Tetrahedron Lett 45:4039–4042
145. Shirahata T, Matsuo J-i, Teruya S, Hirata N, Kurimoto T, Akimoto N, Sunazuka T, Kaji E, Ōmura S (2010) Improved catalytic and stereoselective glycosylation with glycosyl N-trichloroacetylcarbamate: application to various 1-hydroxy sugars. Carbohydr Res 345:740–749

146. Issa JP, Lloyd D, Steliotes E, Bennett CS (2013) Reagent controlled β-specific dehydrative glycosylation reactions with 2-deoxy-sugars. Org Lett 15:4170–4173
147. Tian Q, Xu L, Ma X, Zou W, Shao H (2010) Stereoselective synthesis of 2-C-acetonyl-2-deoxy-d-galactosides using 1,2-cyclopropaneacetylated sugar as novel glycosyl donor. Org Lett 12:540–543
148. Fortin M, Kaplan J, Pham K, Kirk S, Andrade RB (2009) gem-Dimethyl 4-pentenyl glycosides: novel glycosylating agents and anomeric protecting groups. Org Lett 11:3594–3597
149. Gattuso G, Nepogodiev SA, Stoddart JF (1998) Synthetic cyclic oligosaccharides. Chem Rev 98:1919–1958
150. Ogawa T, Takahashi Y (1985) Synthesis of α-Neu5Acp-(2→3)-d-Gal and α-Neu5Acp-(2→3)-β-d-Galp-(1→4)-d-Glc. Carbohydr Res 138:C5–C9
151. Takahashi Y, Ogawa T (1987) Total synthesis of cyclomaltooctaose and an isomer of cyclomaltohexaose, cyclo{→6)-[α-d-Glcp-(1→4)]5-α-d-Glcp-(1-}O. Carbohydr Res 169:127–149
152. Collins PM, Ali MH (1990) A new cycloglucohexaose derivative the chemical synthesis of Cyclo{→3-[β-D-Glcp-(1→3)-]5-D-Glcp(1→)}. Tetrahedron Lett 31:4517–4520
153. Bassieux D, Gagnaire D, Vignon M (1977) Étude par R.M.N.-13C et -1h du (1→6)-β-d-glucane et des oligosaccharides linéaires et cycliques correspondants. Carbohydr Res 56:19–33
154. Excoffier G, Paillet M, Vignon M (1985) Cyclic (1→6)-β-d-glucopyranose oligomers: synthesis of cyclogentiotriose and cyclogentiotetraose peracetates. Carbohydr Res 135:C10–C11
155. Nakamura N (1994) Methods Carbohydr Chem 10:269
156. Cottaz S, Apparu C, Driguez H (1991) Chemoenzymatic approach to the preparation of regioselectively modified cyclodextrins. The substrate specificity of the enzyme cyclodextrin glucosyltransferase (CGTase). J Chem Soc Perkin 1: 2235–2241
157. Apparu Ch, Driguez H, Williamson G, Svensson B (1995) Chemoenzymatic synthesis of 6 '-S-α-D-glucopyranosyl- 6-thiomaltooligosaccharides: their binding to Aspergillus niger glucoamylase G1 and its starchbinding domain Carbohydrate Research 277: 313-320
158. Kamakura M, Uchiyama T (1993) Reactions catalyzed by cycloinulo-oligosaccharide fructanotransferase. Biosci Biotechnol Biochem 57:343
159. Hanessian S, Tremblay M, Swayze EE (2003) Tobramycin analogues with C-5 aminoalkyl ether chains intended to mimic rings III and IV of paromomycin. Tetrahedron 59:983–993
160. Tanaka H, Nishida Y, Furuta Y, Kobayashi K (2002) A convenient synthetic pathway for multivalent assembly of aminoglycoside antibiotics starting from amikacin. Bioorg Med Chem Lett 12:1723–1726
161. Schmidt RR, Kinzy W (1994) Anomeric-oxygen activation for glycoside synthesis: the trichloroacetimidate method. Adv Carbohydr Chem Biochem 50:21–123
162. Boons G-J (1996) Contemp Org Synth 3:173–200
163. Zhang Y, Brodsky A, Sinay P (1998) Synthesis of mono-, di- and trisulfated Lewis^x trisaccharides. Tetrahedron Asymmetry 9:2451–2464
164. Hasegawa A, Ito K, Ishida H, Kiso M (1995) Synthetic studies on sialoglycoconjugates 70: synthesis of sialyl and sulfo Lewis^x analogs containing a ceramide or 2-(Tetradecyl)hexadecyl residue. J Carbohydr Chem 14:353–368
165. Sanders WJ, Gordon EJ, Dwir O, Beck PJ, Alon R, Kiessling LL (1999) Inhibition of L-selectin-mediated leukocyte rolling by synthetic glycoprotein mimics. J Biol Chem 274:5271–5278
166. Broddefalk J, Bäcklund J, Almqvist F, Johansson M, Holmdahl R, Kilhberg J (1998) T cells recognize a glycopeptide derived from type II collagen in a model for rheumatoid arthritis. J Am Chem Soc 120:7676–7683
167. Nicolaou KC, Winssinger N, Pastor J, De Roose F (1997) A general and highly efficient solid phase synthesis of oligosaccharides. Total synthesis of a heptasaccharide phytoalexin elicitor (HPE). J Am Chem Soc 119:449–450
168. Wong CH, Ye XS, Zhang Z (1998) Assembly of oligosaccharide libraries with a designed building block and an efficient orthogonal protection–deprotection strategy. J Am Chem Soc 120:7137–7138