2
O-Glycoside Formation

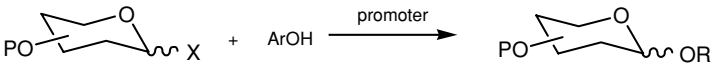
2.1 General Methods

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

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

The Michael reaction
The Fischer reaction
The Koenigs-Knorr reaction
The Helferich reaction
The Fusion method
The Imidate reaction
The Sulfur reaction
The armed-disarmed approach
The Glycal reaction
The Miscellaneous leaving groups
The solid-phase approach

2.1.1 The Michael Reaction



P = protecting group
X = Br, Cl

Promoter	Conditions
NaH	THF
K_2CO_3, NaOH	acetone

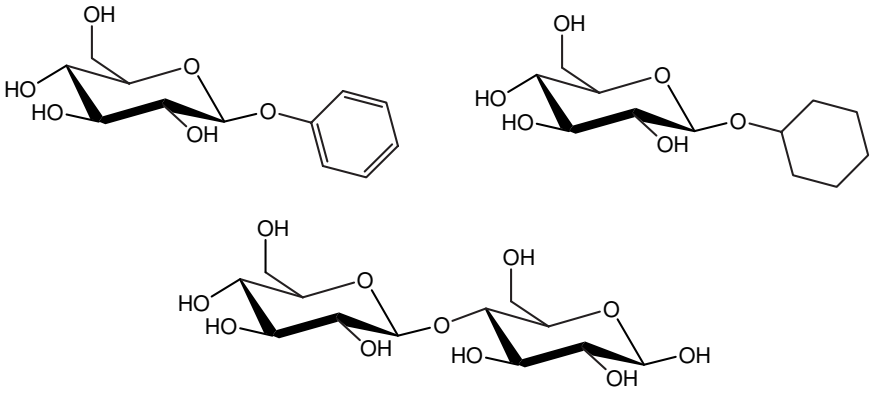
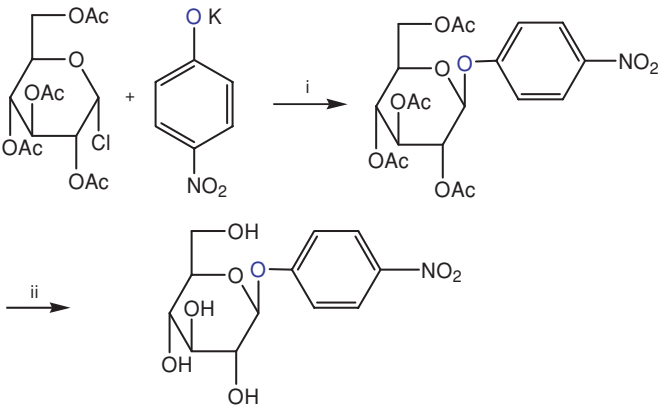


FIGURE 2.1. Examples of *O*-glycosides.

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 (Figure 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



i) acetone or DMF. ii) MeONa/MeOH.

FIGURE 2.2. Synthesis of paranitrophenyl-β-D-glucopyranosyl tetraacetate.

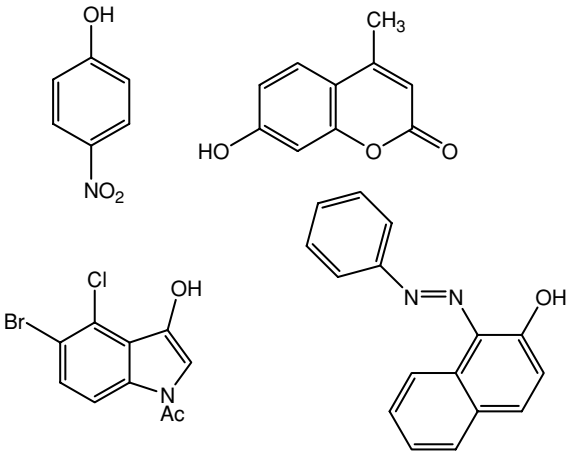


FIGURE 2.3. *O*-glycoside chromophores used for enzymatic detection.

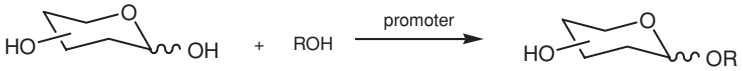
This reaction has been employed for the preparation of *O*-glycosides that are used as substrates for detection and measurement of enzymatic activity of most of the known glycosidases.

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 Figure 2.3.

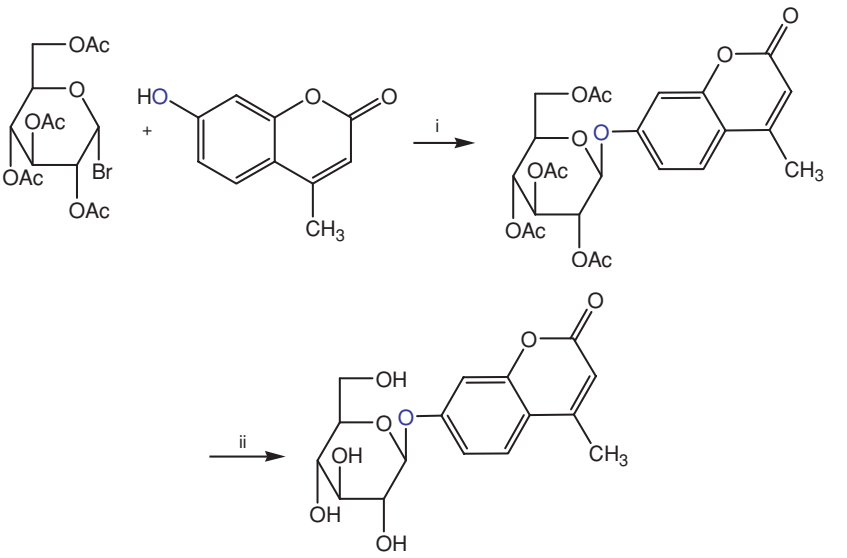
The highly fluorescent O-glycoside substrate 7-hydroxy-4-methylcoumarin-β-D-glucopyranose is prepared by condensation between acetobromoglucose with 4-methylumbelliferone in the presence of potassium carbonate in acetone. The intermediate is deacetylated under basic conditions to afford umbelliferyl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

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

2.1.2 *The Fischer Reaction*



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

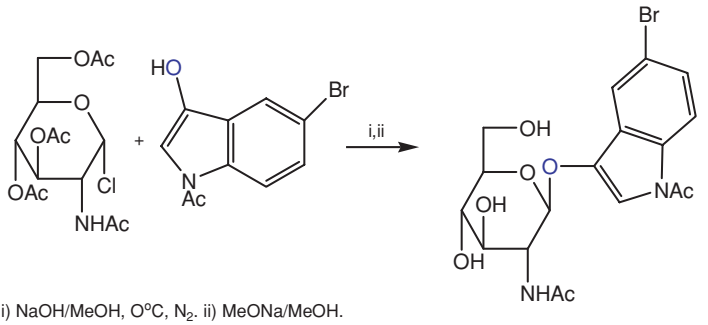


i) K_2CO_3/acetone. ii) MeONa/MeOH.

FIGURE 2.4. Michael approach for preparation umbellyferyl-*O*-glycoside.

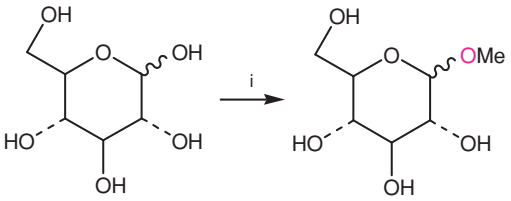
This straightforward strategy is used specially for the preparation of simple *O*-glycosides. The advantage of this methodology is that it does not require the use of protecting groups and simply by combining the free sugar with an alcohol under acidic condition we furnish the corresponding *O*-glycoside. 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 (Figure 2.6).

The addition of a controlled stream of dry HCl during a period of around 10 min at room temperature generally are the conditions of choice. However, the use



i) NaOH/MeOH, O°C, N_2. ii) MeONa/MeOH.

FIGURE 2.5. Synthesis of indole *O*-glycoside derivative.



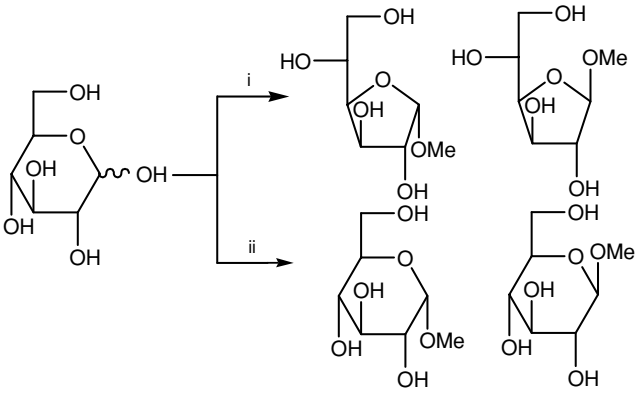
i) MeOH-HCl(g).

FIGURE 2.6. The Fischer *O*-glycoside reaction.

of Lewis acid, ion exchange resin, and more recently triflic acid have been also reported providing good yields.[3]

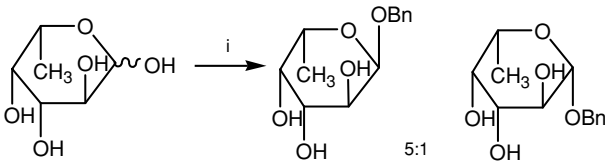
It is worth mentioning that besides the main product, a mixture of isomers has been detected, suggesting that a rather complex mechanism is involved. It is also seen that the amount of these isomers depends importantly on the condition reactions employed (Figure 2.7).

The Fischer methodology has been applied successfully for the synthesis of benzyl *O*-glycosides. L-Fucose was converted into benzyl fucopyranoside[4] 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 (Figure 2.8).



i) MeOH/ 0.7% HCl, 20°C. ii) MeOH/ 4% HCl reflux.

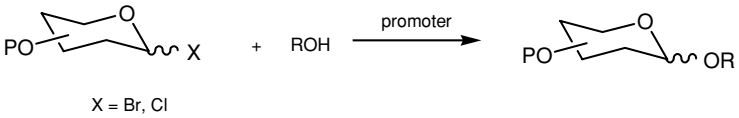
FIGURE 2.7. The Fischer *O*-glycoside isomers.



i) BnOH/HCl (g), 10 min. r.t, and O/N at 4°C.

FIGURE 2.8. Fischer conditions for preparation of Benzyl L-fucose.

2.1.3 *The Koenigs-Knorr Reaction*



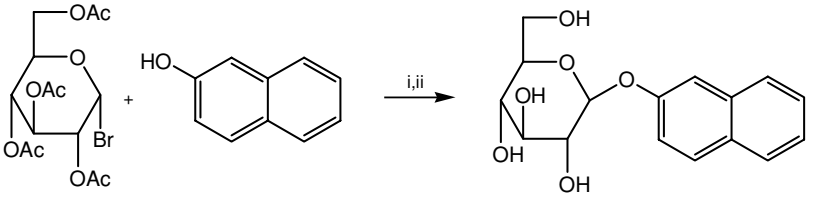
X = Br, Cl

Promoter	Conditions
Ag_2CO_3	PhH, drierite (drying agent), I_2
Ag_2O	s-collidine (acid scavender)
$AgNO_3$	HgO (acid scavender)
$AgClO_4$	Ag_2ClO_3 (acid scavender), THF or toluene, r.t.
AgOTf	CH_2Cl_2, r.t.

This reaction reported in 1901 is still one of the most useful reactions for preparing a wide variety of *O*-glycosides.[5] 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 triflate silver salts are the most commonly employed (Figure 2.9). 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 intramolecular nucleophilic displacement of the leaving group, generating an orthoester.[6] This intermediate is responsible for the incorporation of the alcohol on the β-position (Figure 2.10). 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.[7]

This versatile methodology can be applied for preparation of alky, aryl, and oligosaccharide *O*-glycosides. A steroidal glycoside cholesterol absorption inhibitor was prepared by condensation between acetobromocellobiose and (3β,5α,



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

FIGURE 2.9. The Koenigs-Knorr reaction.

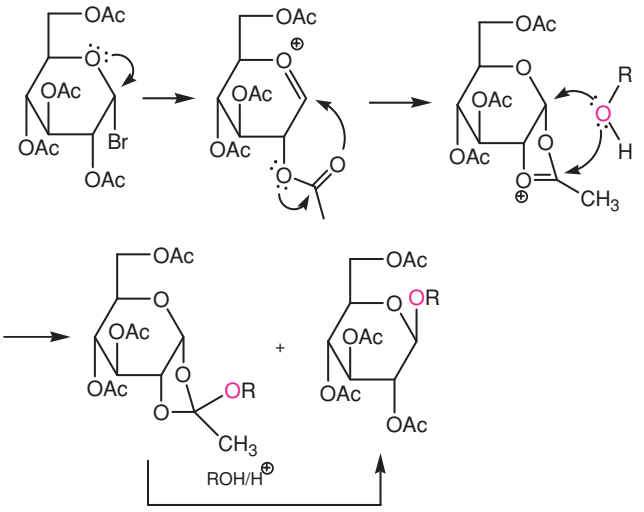


FIGURE 2.10. Proposed mechanism for the Koenigs-Knorr glycosidic reaction.

25R)-3-hydroxyspirostan-11-one with anhydrous ZnF_2 as catalyst in acetonitrile to provide the steroidal glycoside in 93% yield (Figure 2.11).[8]

The steroidal glycoside Estrone-β-D-glucuronide was prepared by condensation between Methyl tri-*O*-glucopyranosylbromide uronate with estrone, employing cadmium instead of silver carbonate (Figure 2.12).[9] A comprehensive study about methods for the preparation of diverse *O*-glucuronides has been described.[10]

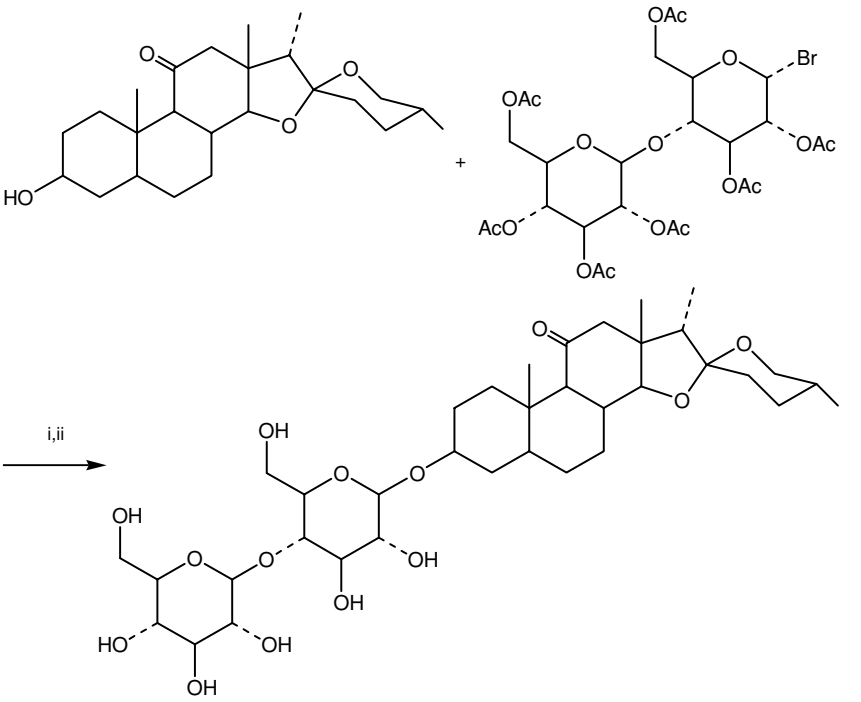
The syntheses of various disaccharides have been reported under Koenigs-Knorr conditions. Gentobiose octaacetate was prepared through condensation of acetobromoglucose with 1,2,3,4-Tetra-*O*-acetyl-*O*-Trityl-β-D-glucopyranose in nitromethane using silver perchlorate as catalyst (Figure 2.13).[11]

Bächli and Percival[12] 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 (Figure 2.14).

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 (Figure 2.15).[13,14]

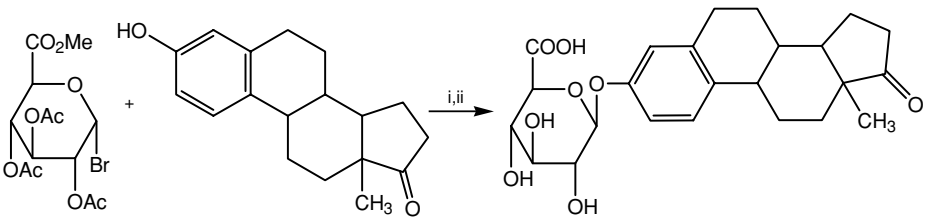
These conditions are also suitable for preparing short oligosaccharides such as the one presented in Figure 2.16. The donor sugar acetobromogentobiose is coupled to the acceptor intermediate using silver triflate as glycosidation catalyst.[15]

Total synthesis of Bleomycin group antibiotic has been achieved by Katano and Hecht.[16] Thus, glycoside coupling reaction of protected disaccharide glycosyl donor with histidine derivative using silver triflate as glycoside promoter provided Bleomycin key intermediate in 21% (Figure 2.17).



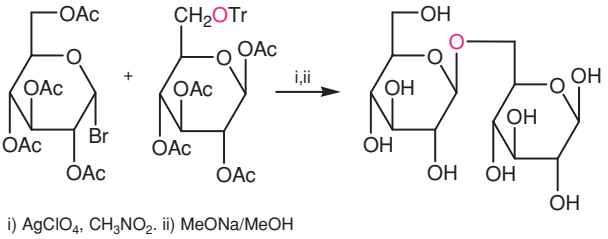
i) ZnF_2, CH_3CN. ii) NaOMe

FIGURE 2.11. Synthesis of steroidal glycoside.



i) Cd_2CO_3. ii) MeONa/MeOH

FIGURE 2.12. Synthesis of a steroidal *O*-glycoside.



i) $AgClO_4$, CH_3NO_2. ii) MeONa/MeOH

FIGURE 2.13. Synthesis of gentobiose.

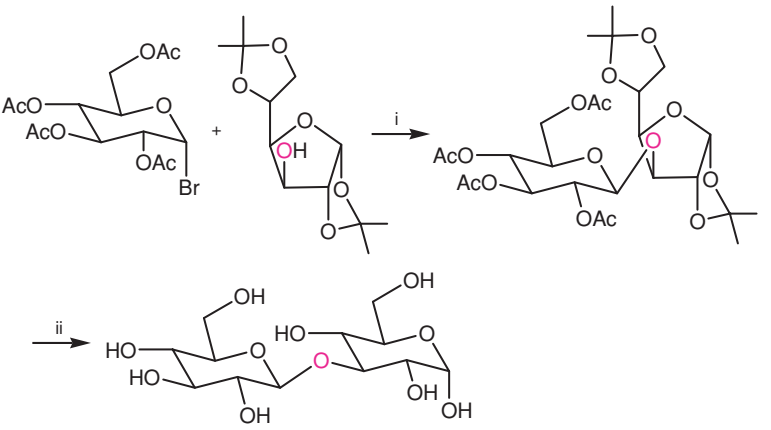


FIGURE 2.14. Synthesis of laminaribiose.

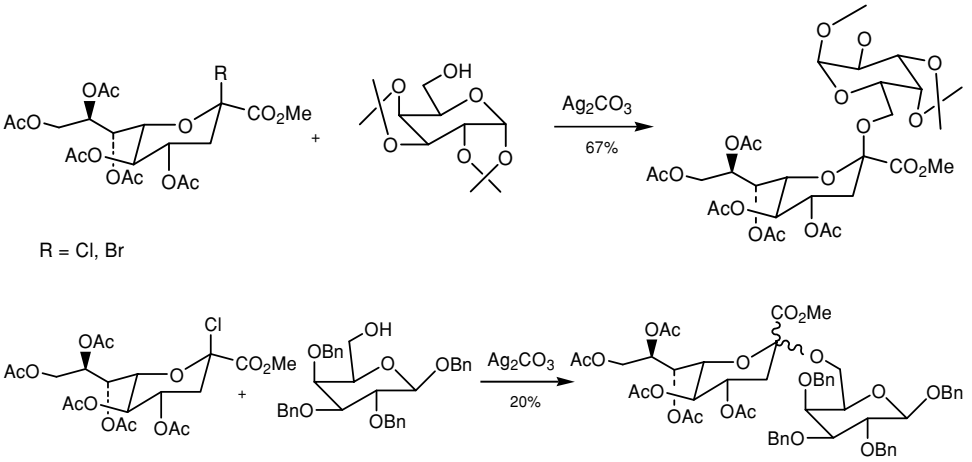
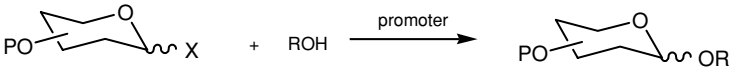


FIGURE 2.15. Silver carbonate promoted synthesis of Neu5Ac(2→6) disaccharides.

2.1.4 *The Helferich Reaction*



Promoter	Conditions
$Hg(CN)_2$	CH_3CN
$HgBr_2$	CH_3CN
HgI_2	CH_3CN

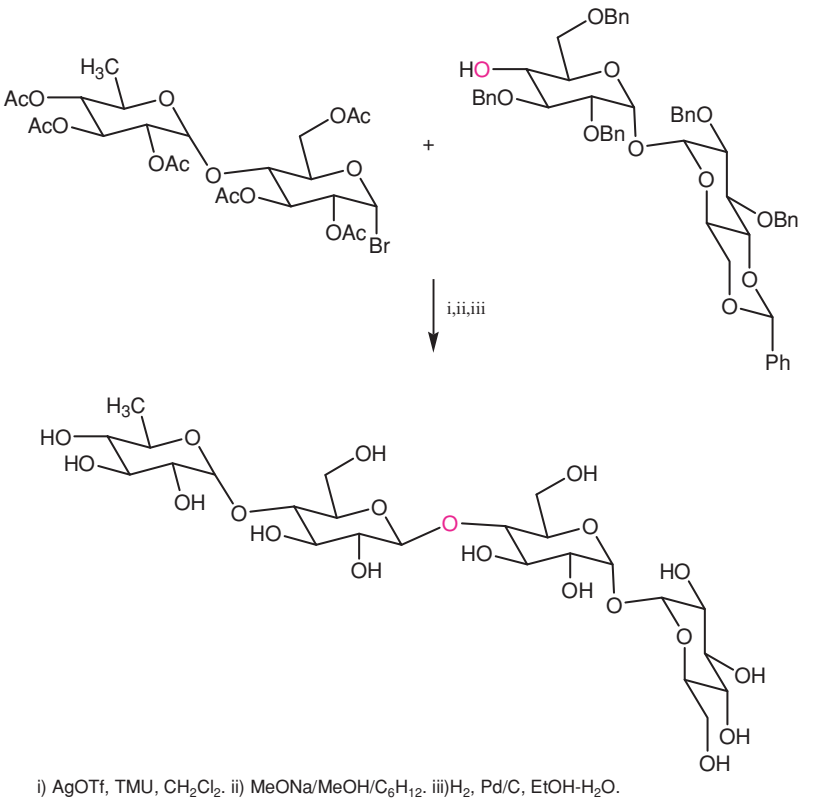


FIGURE 2.16. Synthesis of tetrasaccharide.

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 (Figure 2.18). The yields reported for this reaction are up to 70%, or higher. However, a mixture of anomers is often observed.

By following this strategy, Umezawa et al.[17] had prepared kanamacin A by condensing 6-*O*-[2-*O*-benzyl-3-(benzyloxycarbonylamino)-3-deoxi-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-deoxi-α-D-glycopyranosyl chloride, as glycosyl donor. The catalyst employed was mercury (II) cyanide (Figure 2.19).

The antitumoral *O*-glycoside Epirubicine was prepared under Helferich conditions[18] using the acetonide form of Adriamicinone and 2,3,6-trideoxi-3-trifluoroacetamido-4-O-trifluoroacetyl-α-L-arabinohexopyranosyl chloride, and a mixture of mercury (II) oxide and bromide as shown in Figure 2.20.

Other coupling reactions between sugars under Helferich conditions have been as well described.[19] For example, the case of trisaccharide Rafinose prepared by

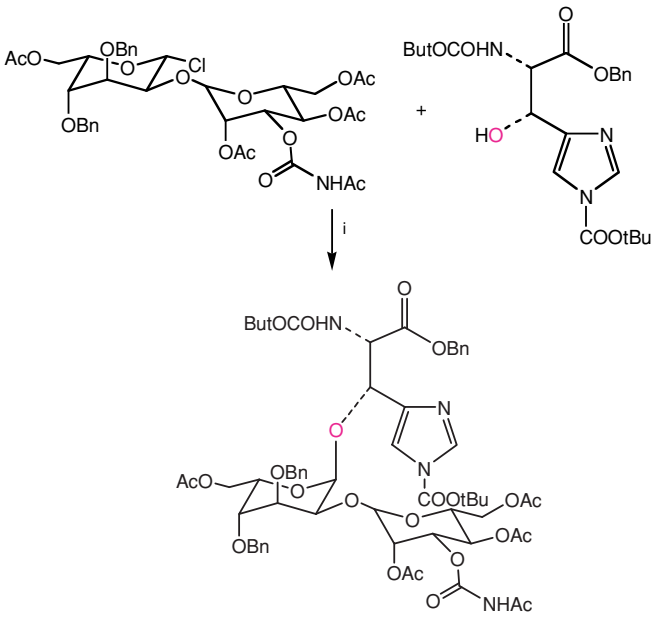


FIGURE 2.17. Glycosilation reaction for preparation of Bleomycin precursor.

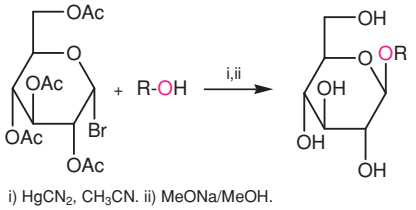
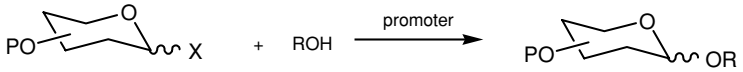


FIGURE 2.18. The Helferich general reaction.

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 (Figure 2.21).

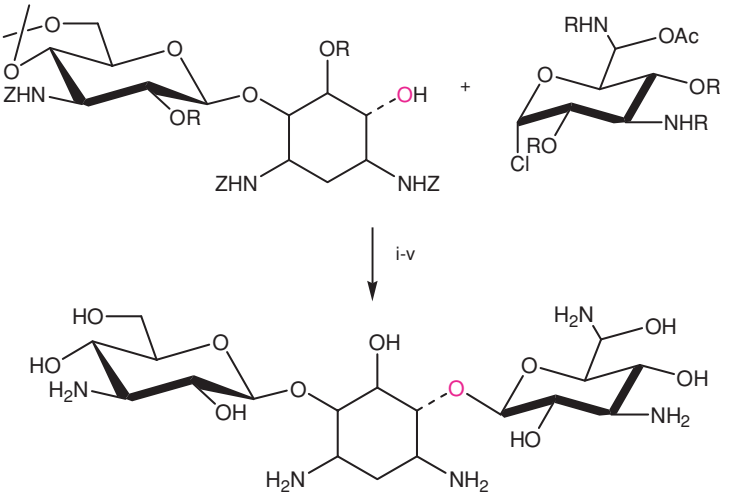
Helferich conditions have been used for preparing disaccharides containing Neu5Ac(2→6)Gal and Glc in good yields, although with low stereocontrol (α:β 3:4) (Figure 2.22).

2.1.5 The Fusion Reaction



X = OAc

Promoter	Conditions
$ZnCl_2$	120°C
TsOH	120°C

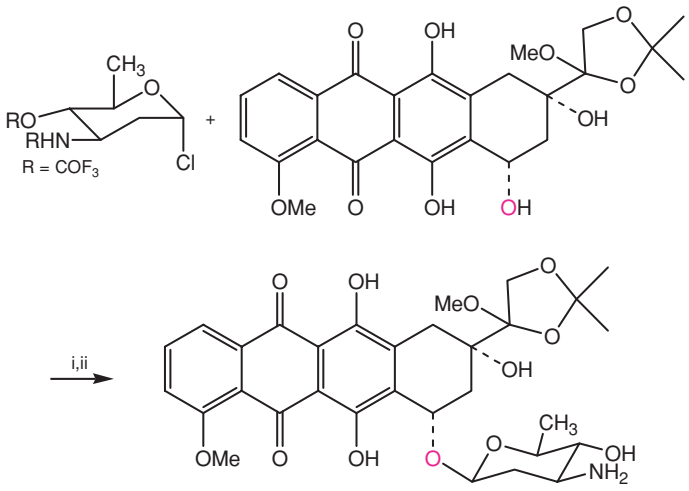


Z = $PhCH_2COO$-

R = $PhCH_2$-

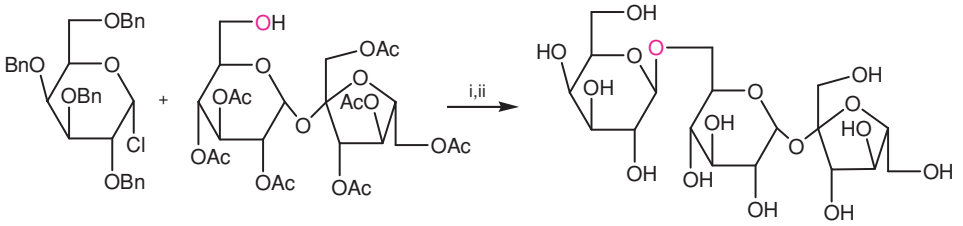
i) $Hg(II)CN_2$, $CaSO_4$/dioxane, PhH. ii) MeONa/MeOH. iii) AcOH. iv) H_2, Pd-C.

FIGURE 2.19. Synthesis of a kanamacin A derivative.



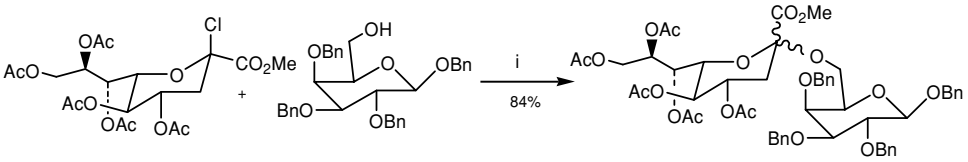
i) HgO-$HgBr_2$. ii) NaOH

FIGURE 2.20. Synthesis of Epirubicine.



i) $Hg(II)CN_2$, $CaSO_4$, PhH. ii) MeONa/MeOH. iii) H_2, Pd-C.

FIGURE 2.21. Synthesis of Rafinose derivative.



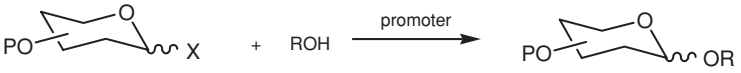
i) $Hg(CN)_2/HgBr_2$ (3:1)

FIGURE 2.22. Helferich conditions for the preparation of sialic disaccharide.

This is a process that is mainly used for preparing aromatic glycosides, and generally consists of the reaction between the sugar, having a leaving group either as acetate or bromide with a phenolic aglycon, under Lewis acid conditions, at temperatures above 100°C.

This methodology has been 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*-acety1-α-L-idopyranose, 1-naphthol, zinc chloride and heating up to 120°C during 1h. Also aromatic S-glycosides could be effectively prepared under the fusion method. Thiophenol 2,3,4,6-tetraacetyl glucopyranose was prepared as a mixture of anomers (40:60, α:β) when thiophenol was combined with ZnO or $ZnCO_3$ and then refluxed with acetobromoglucose in CH_2Cl_2 (Figure 2.23)[20].

2.1.6 *The Imidate Reaction*



X = $OC(NH)CCl_3$

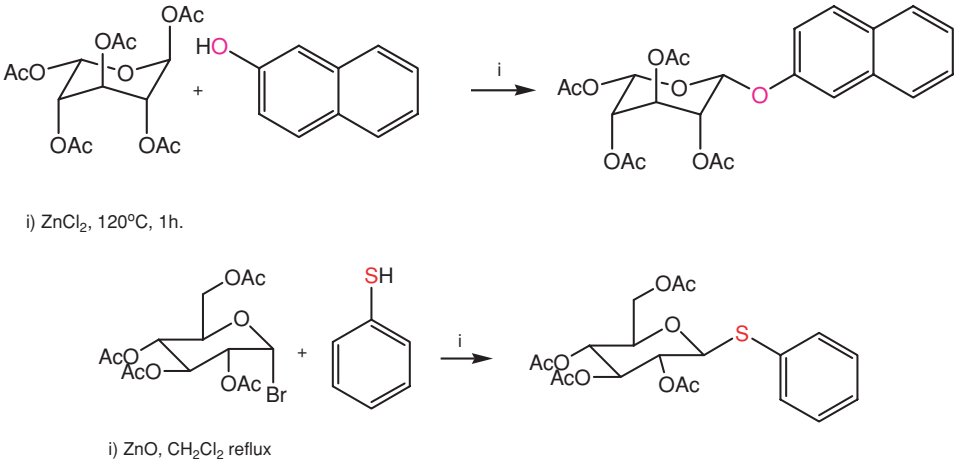


FIGURE 2.23. Naphtyl *O*-glycosides and Phenyl S-glycosides.

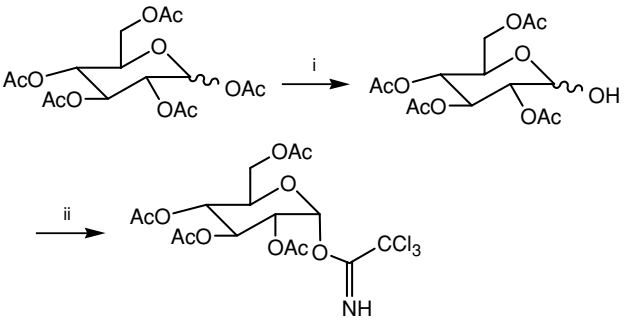
Promoter	Conditions
AgOTf	CH_2Cl_2, 0°C→r.t.
TMSOTf	CH_2Cl_2 or MeCN 0°C
BF_3-OEt_2	CH_2Cl_2 or MeCN, −20°C
NaH	CH_2Cl_2

This is a more recent procedure attributed to Schmidt and coworkers[21a–c] 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 (Figure 2.24). 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.[22]

Once the imidate is 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 (Figure 2.25). 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.[21b–c]

Hasegawa et al.[23] have prepared the ganglioside shown in Figure 2.26 using 2,3,4,6-tetrabenzylglucopyranosyl-α-acetimidate with the liphophilic alcohol, to generate a ganglioside.

The total synthesis of calicheamicin α and dynemicin A has been described by Danishefsky's group,[24] and involves glycosilation of calicheamicinone congener



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

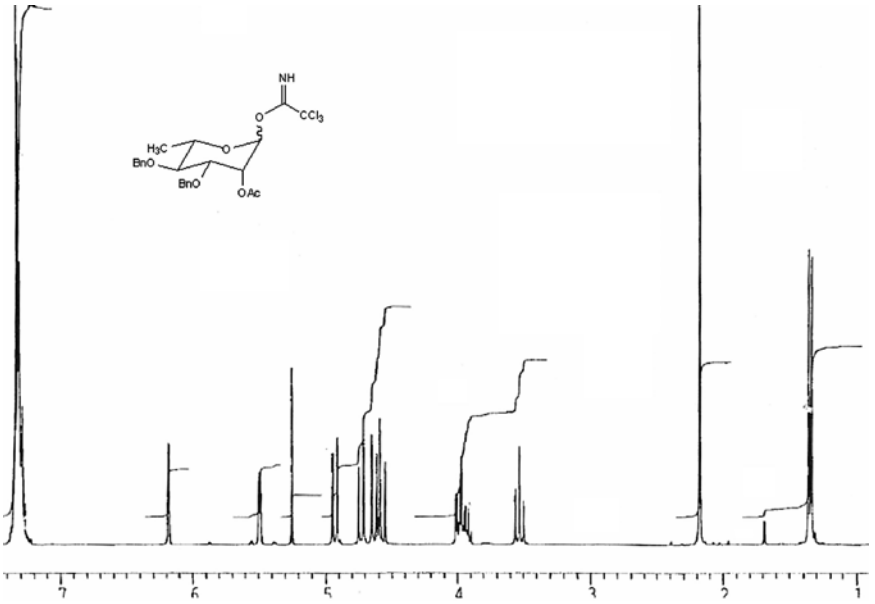


FIGURE 2.24. Preparation of glycosyl imidate and ^{1}H NMR of imidate ramnosyl derivative.

with the complex glycosyl imidate using $BF_3.OEt_2$ as Lewis acid catalyst (Figure 2.27).

Naturally occurring herbicides known as tricolorin A, F, and G were isolated from the plant *Ipomea tricolor* and since then synthesized involving glycoside coupling reactions. The first total synthesis of tricolorin A was performed by Larson and Heathcock,[25] involving three coupling reactions steps with imidate intermediates used as glycosyl donors (Figure 2.28). The lactonization key step for the preparation of the synthesized tricolorins has been achieved either under macrolactonization conditions reported by Yamaguchi[26,27] and also under ring clousure methathesis conditions.[22]

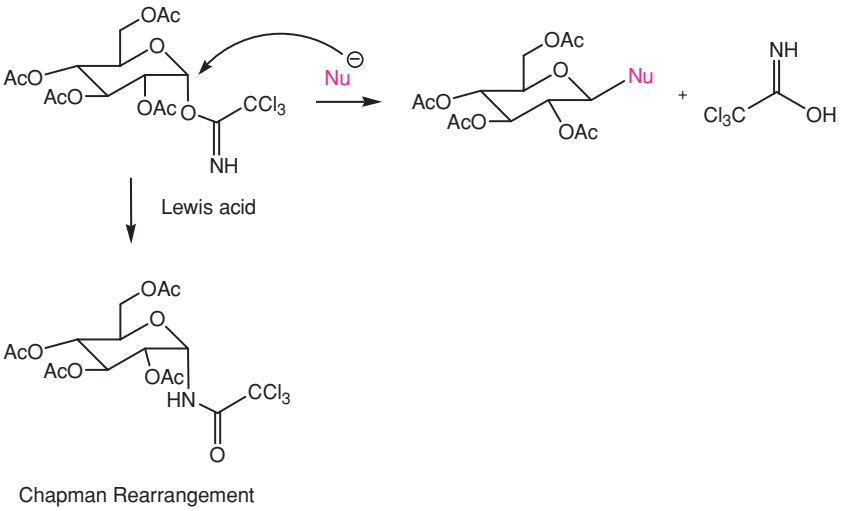


FIGURE 2.25. Nucleophilic displacement of imidate leaving group.

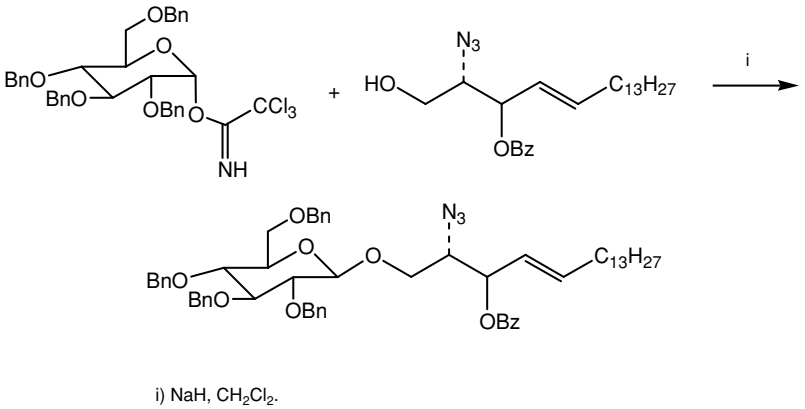


FIGURE 2.26. Coupling reaction for the preparation of ganglioside.

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 (Figure 2.29).[27]

A convergent approach for obtaining a tumoral antigen fragment of Lewis X has been developed by Boons et al.[28] Condensation of the imidate glycosyl donor and the trisaccharide glycosyl acceptor provided the hexasaccharide, which was

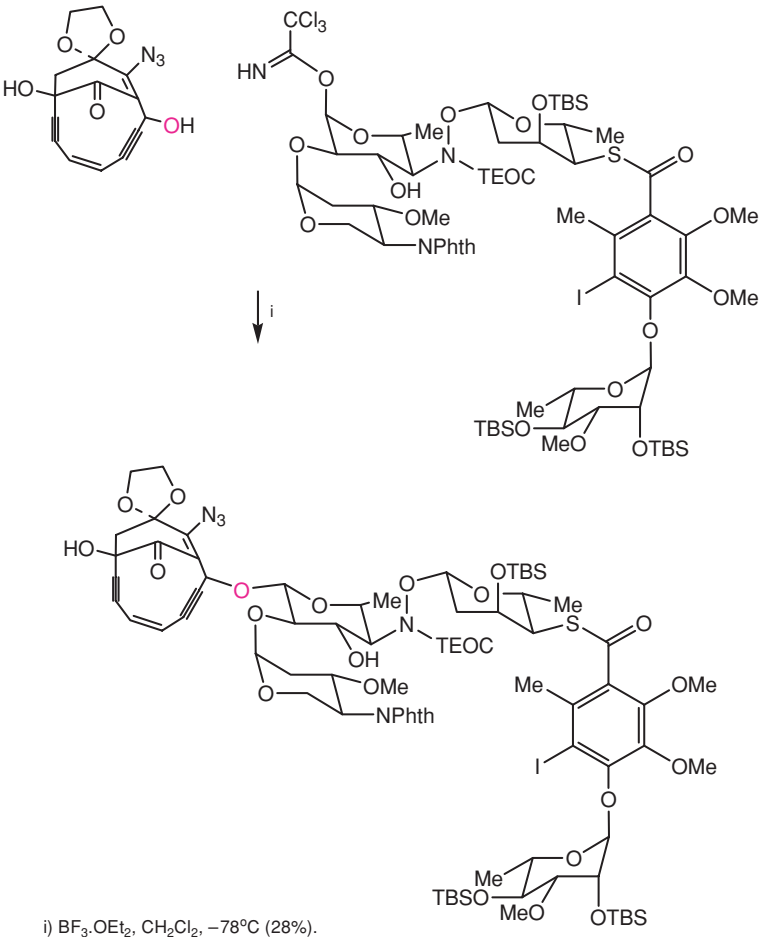
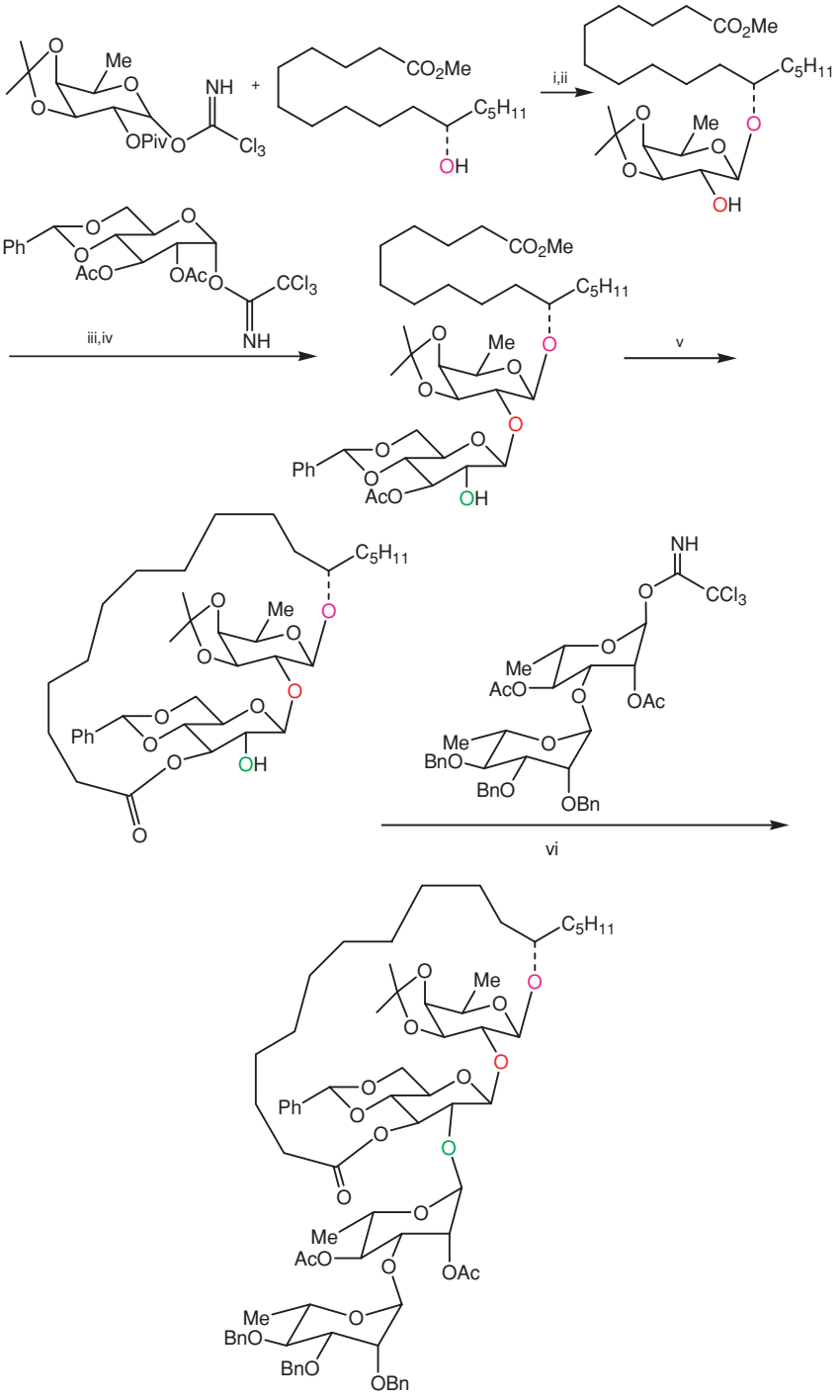


FIGURE 2.27. Glycosylation of calicheamicinone congener.

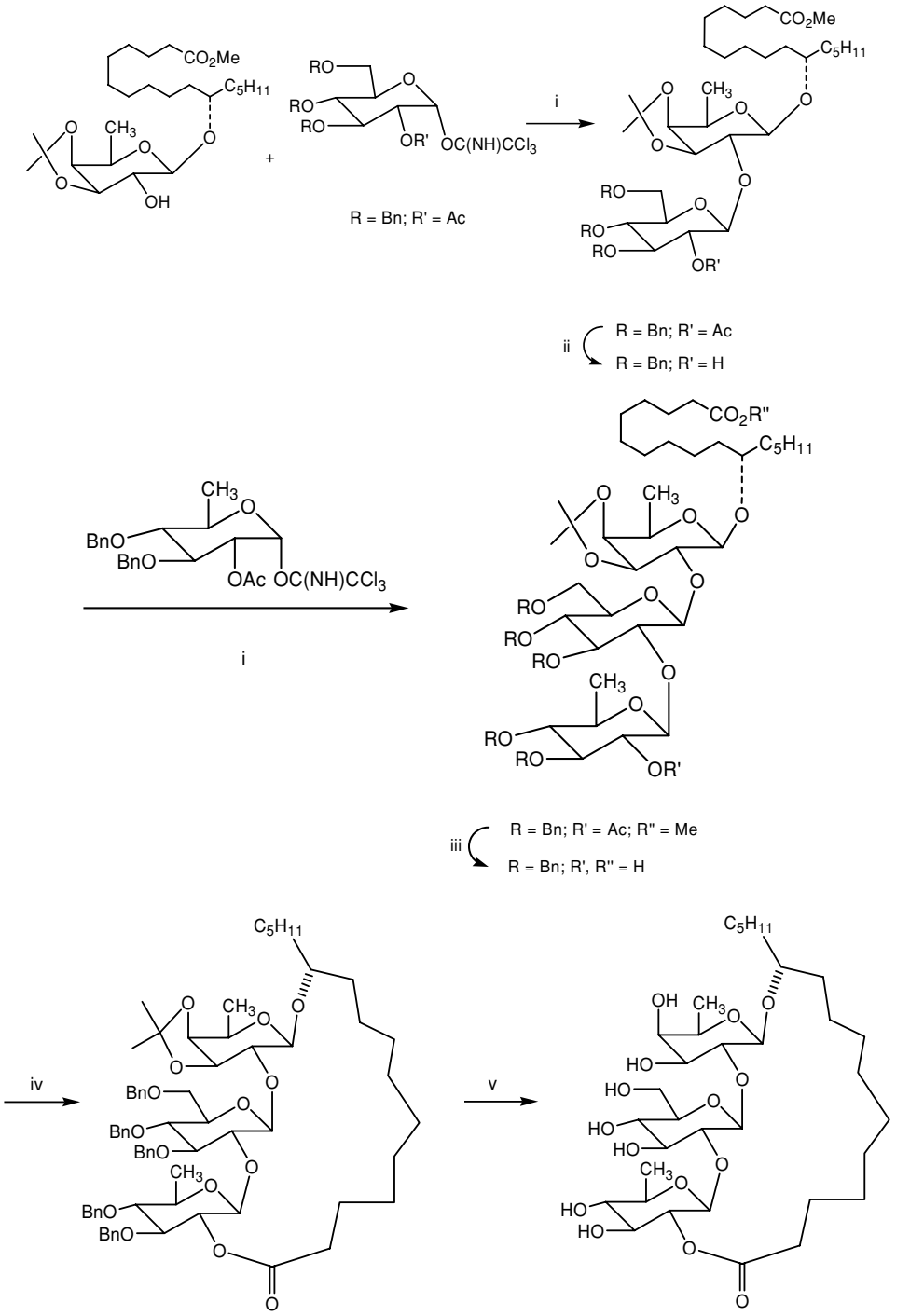
further allowed to react with trichloroacetimidate to generate a hexasaccharide glycosyl donor. The final coupling reaction with the disaccharide using $BF_3.OEt_2$, furnished the tumoral fragment Lewis X (Figure 2.30).

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 play a key role in the initial cell-adhesive phenomena during the inflammatory process, whereas E-selectins bind strongly to sialyl Lewis a and x.[29,30] 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.[31] The chemical synthesis of 3e- and 6e-monosulfated and 3e,6e- disulfated Lewis x pentasacharides has been prepared according to Figure 2.31.



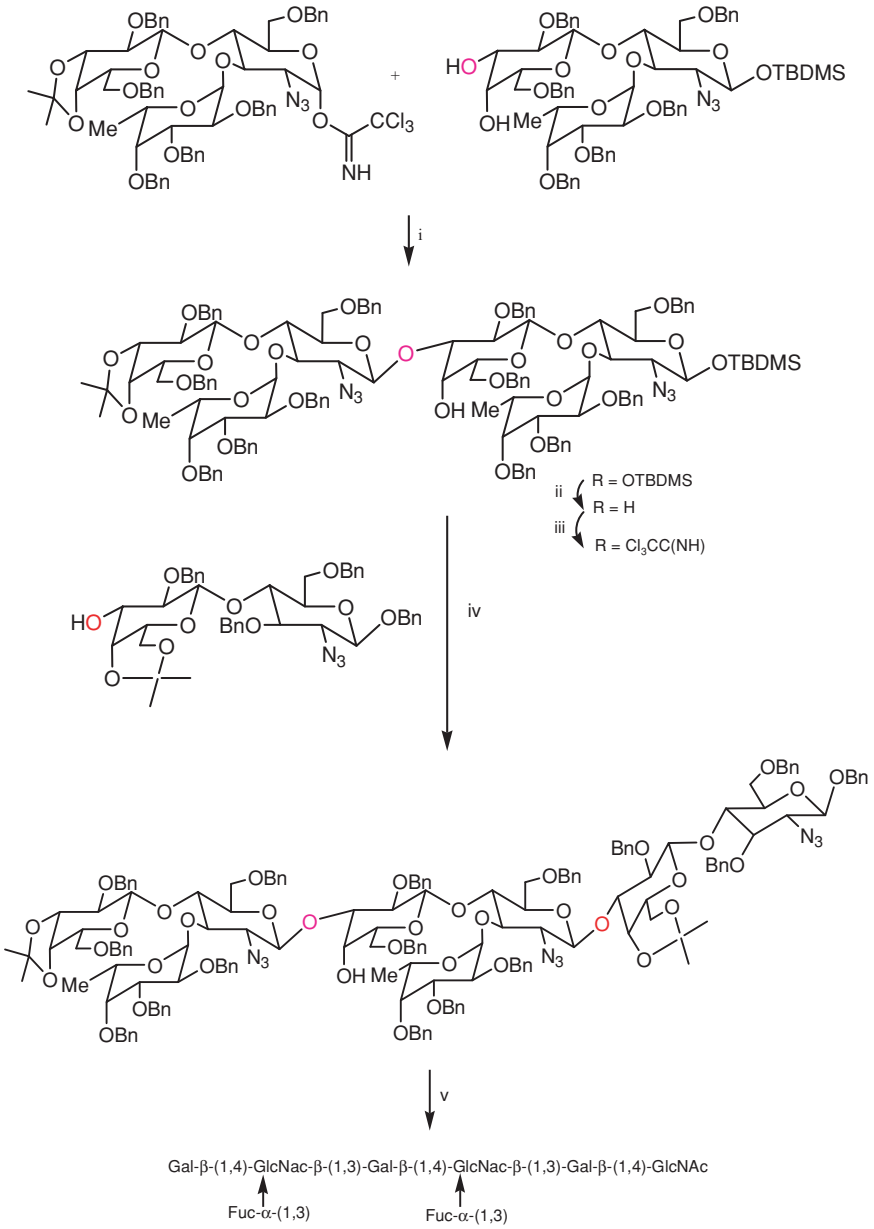
i) AgOTf, CH_2Cl_2. ii) MeONa/MeOH. iii) AgOTf, CH_2Cl_2. iv) a)MeONa/MeOH. b) 1 eq. Ac_2O, DMAP, CH_2Cl_2, Et_3N. v) a) LiOH, THF, H_2O. b) 2,4,6-trichlorobenzoyl chloride, Et_3N, MAP, benzene. vi) AgOTf, CH_2Cl_2.

FIGURE 2.28. Synthesis of tricolorin A precursor.



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.

FIGURE 2.29. Synthesis of Tricolorin F.



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.

FIGURE 2.30. Covergent synthesis of Lewis X fragment.

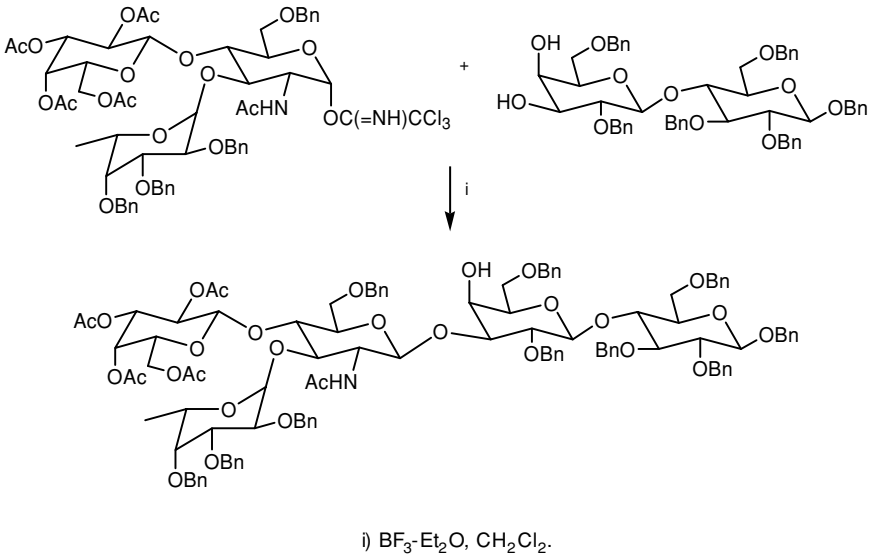
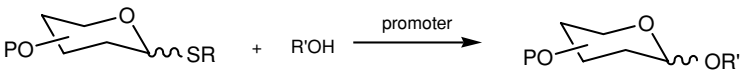


FIGURE 2.31. Coupling reaction for the preparation of Lewis x pentasaccharide intermediate.

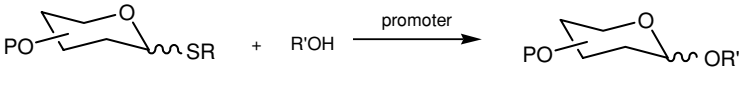
Likewise, thioaryl donors can also be suitably converted to acetimidates for performing glycoside coupling reactions. This is the case of arabinosyl thio derivative, which is deprotected under NBS-pyridine conditions affording the lactol in 80% yield as a mixture of anomers (2:1). Treatment with NaH, followed by addition of Cl_3CCN, provided the desired trichloroacetimidate intermediate. This strategy has been succesfully applied in the syntheses of cytotoxic marine natural products Eleutherobin (Figure 2.32).[32]

2.1.7 The 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

Promoter	Conditions
NBS	CH_2Cl_2, r.t.
BSP	CH_2Cl_2, MS, r.t
DMTST	
MeOTf	
MeSOTf	

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 Figure 2.33. Thus, the synthesis of trisaccharide intermediate was obtained by combining the thioglycoside donor with a monosaccharide acceptor in the presence of methyltriflate, to provide the target trisaccharide in 72% yield.[33]

A convergent synthesis of the trisaccharide unit belonging to an antigen polysaccharide from streptococcus has been performed by Ley and Priepke.[34] In this approach ramnosylalkylsulfur was used as the glycosyl donor, and cyclohexane-1,2-diacetal as the protecting group (Figure 2.34).

Thioalkyl donor are also useful derivatives for the preparation of biologically important natural sugars known as Sialic acids.[23] 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*-glycosilation reaction proceeds between the thioglycosylsialic donor with a glycosyl acceptor (bearing an -OH group available), using a catalyst such as N-iodosuccinimide-TfOH as promotor (Figure 2.35).

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

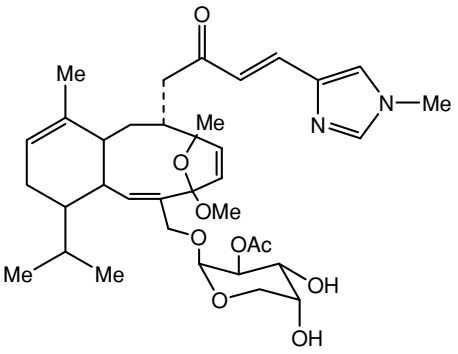
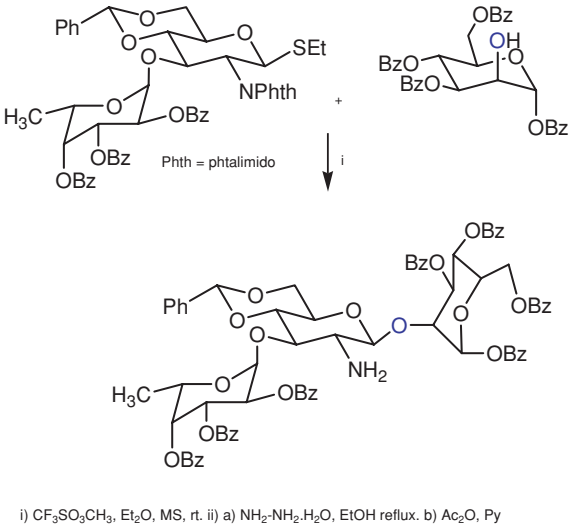


FIGURE 2.32. Citotoxic marine glycoside Eleutherobin.



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

FIGURE 2.33. Thioglicoside coupling reaction for preparation of a trisaccharide intermediate.

initial glycosidic reaction between 2-thiophenyl Neu5Ac donor with trisaccharide intermediate to produce the expected tetrasaccharide in 45% having an $\alpha(2\rightarrow6)$-linkage. The resulting tetrasaccharide was coupled with dimeric sialyl donor to yield hexasaccharide in 42%. Acetal hydrolysis was followed by coupling reaction

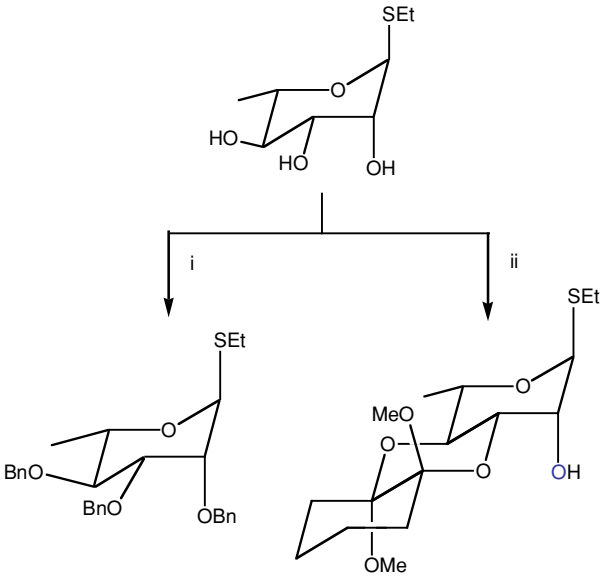
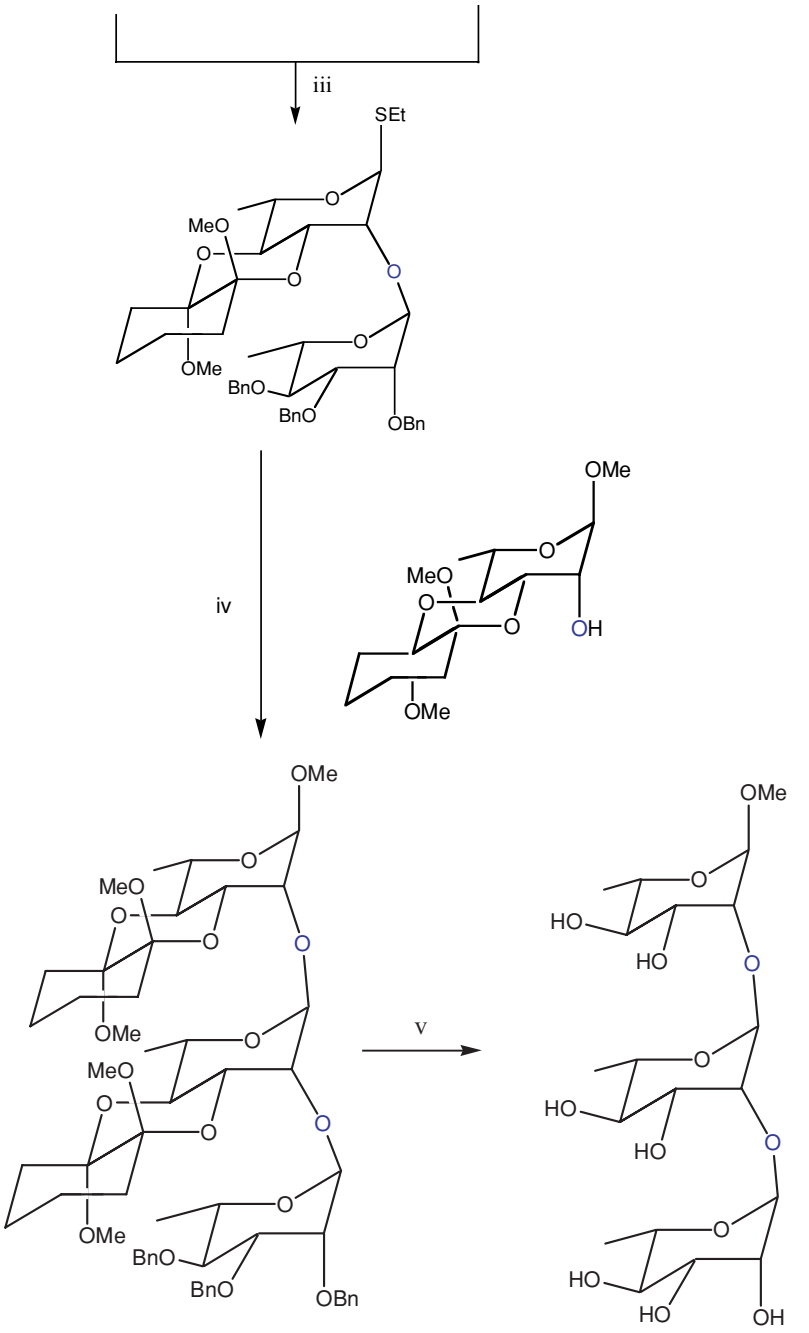


FIGURE 2.34. Synthesis of an antigen polysaccharide fragment.



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

FIGURE 2.34. (*Continued*)

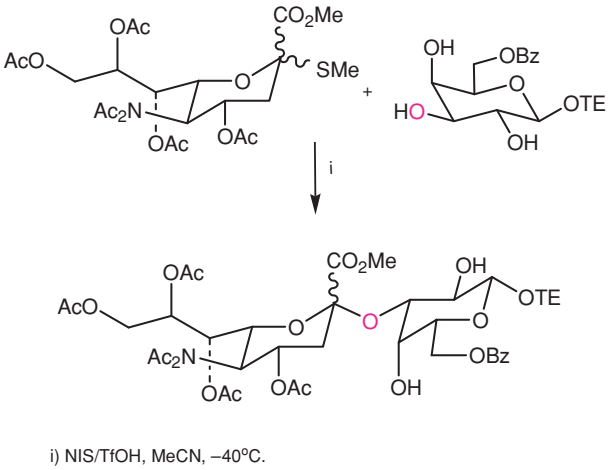


FIGURE 2.35. Thioalkyl donor for the preparation of sialic acids.

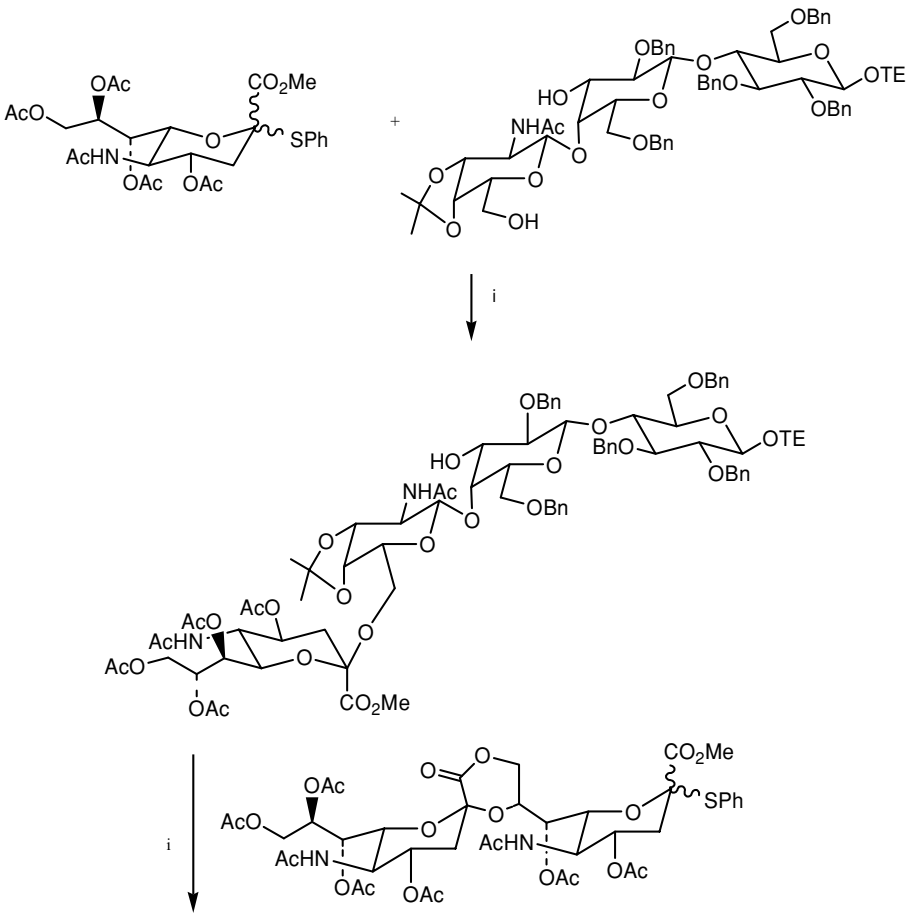


FIGURE 2.36. Convergent synthesis of sialyl oligosaccharide.

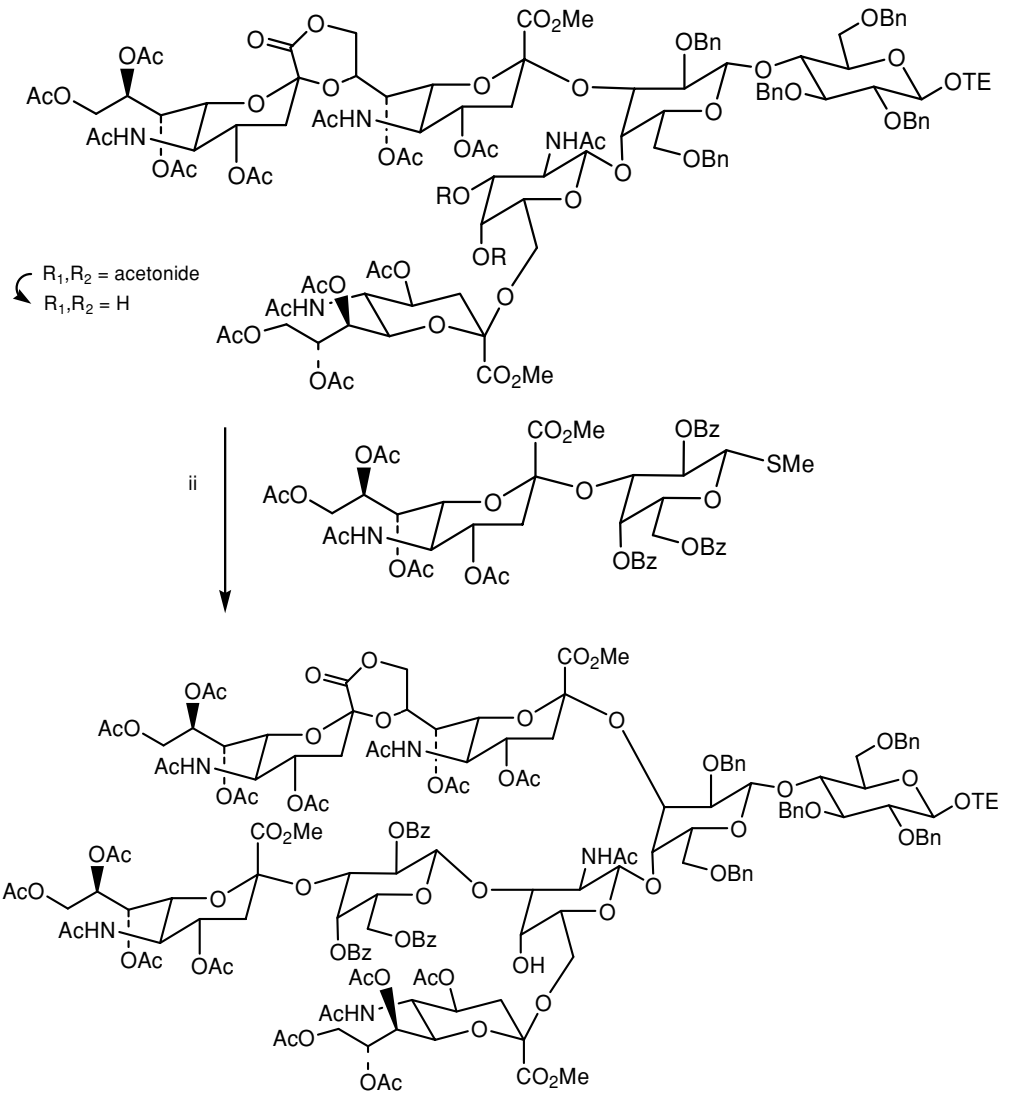
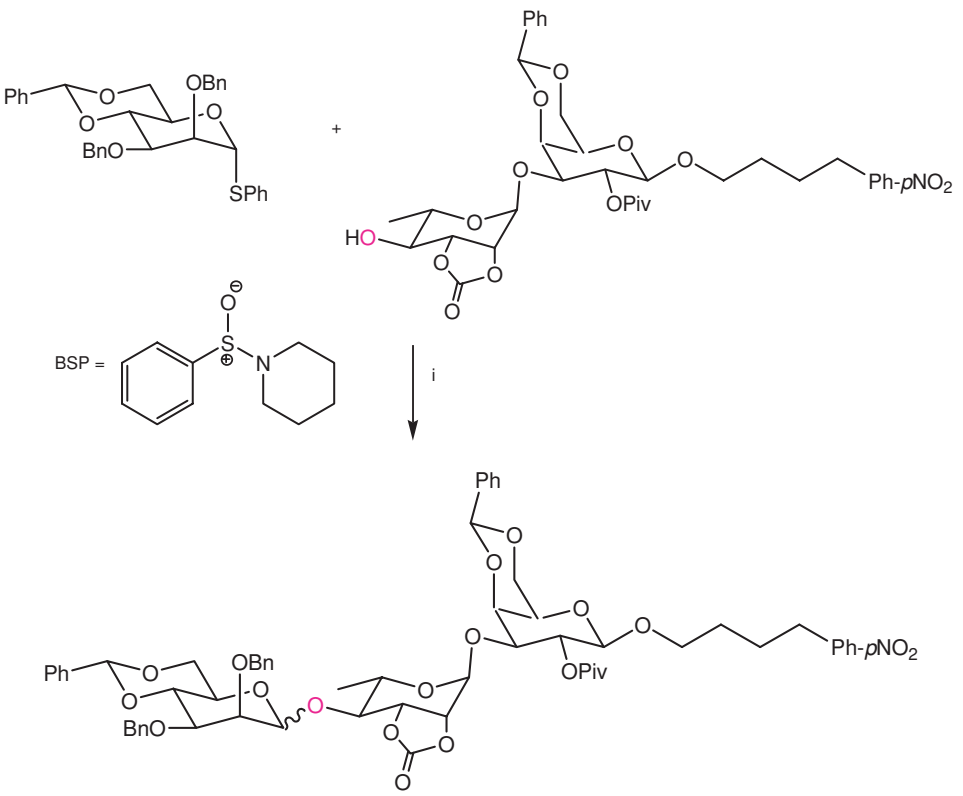


FIGURE 2.36. (*continued*)

with Neu5Acα(2→3)GalSMe donor to give the octasaccharide in 85% yield (Figure 2.36).[35]

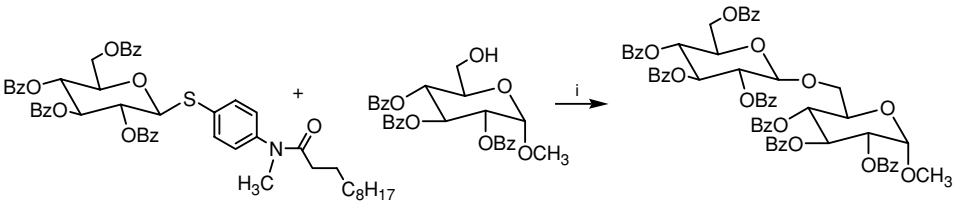
Crich and Li[36] introduced the use of 1-(Benezenesulfinyl)piperidine/triflic anhydride as promoter conditions for preparing *O*-glycosides from thioglycoside donors. These conditions were applied for preparing Salmonella-type E1 core trisaccharide (Figure 2.37).



i) a) BSP, m.s., CH_2Cl_2, r.t. b) Tf_2O, –60ºC to 0ºC 1h.

FIGURE 2.37. Preparation of Salmonella-type E_1 core trisaccharide under BSP-Tf_2O conditions.

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 (Figure 2.38).[37]



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

FIGURE 2.38. Highly fluorinated thiols glycosyl donor for glycosidation.

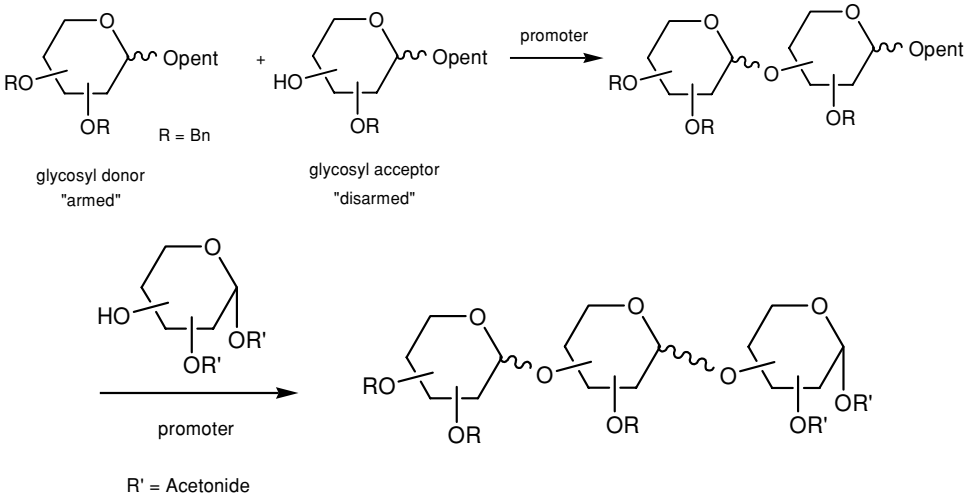


FIGURE 2.39. General scheme for the armed-disarmed approach.

2.1.8 *The Armed-Disarmed Method*

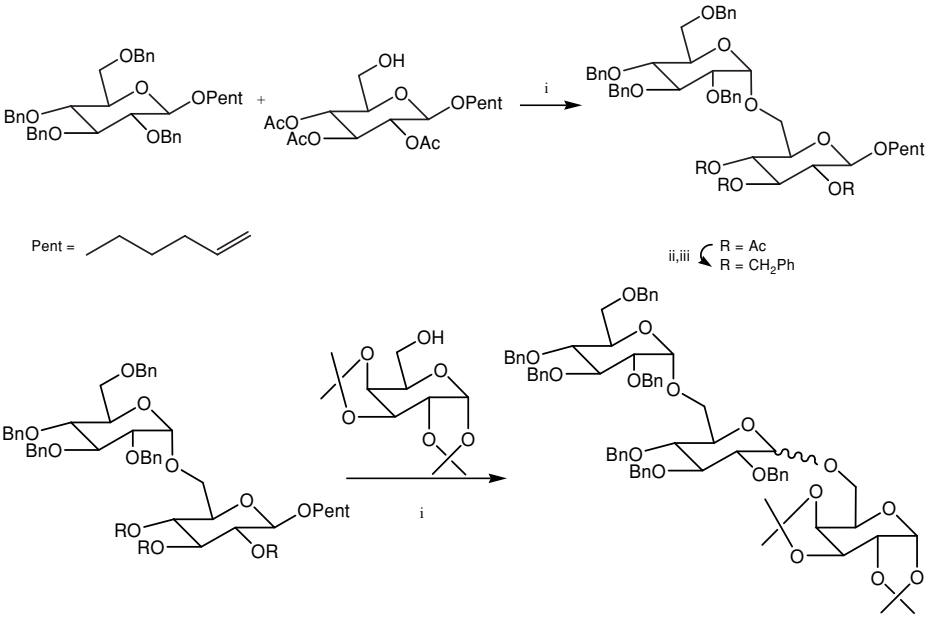
This versatile approach has been attributed to Mootoo and Fraiser-Reid,[38] and considers the use of a glycosyl donor in the classical sense coined with the term "armed saccharide" (because the reducing end is armed for further coupling reaction), and an acceptor, in this case "disarmed saccharide," which contains both a free alcohol and a leaving group sufficiently resistant for the ongoing coupling reaction. The resulting disaccharide now becomes an armed disaccharide, which in turn is reacted with another glycosyl acceptor or disarmed sugar to produce the oligosaccharide chain elongation (Figure 2.39).

This method was first implemented in the preparation of 1-6 linked trisaccharide shown in Figure 2.40. As one can see, 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.

Despite the usefulness of pentenyl as protecting group, clear preference in the use of thioglycoside donors as armed and disarmed donors is often observed (Figure 2.41).[39]

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.[40] The first coupling between "armed" thiophenyl fucopyranosyl derivative with "disarmed" thiophenyl lactose derivative under NIS-TfOH conditions provided trisaccharide, which was subjected without purification to second condensation with different acceptors, one of which is indicated in Figure 2.42.

The construction of α-linked mannoside disaccharide was achieved under the armed-disarmed approach by using armed thiogalactoside donor activated



i) I(collidine)$_2$ClO$_4$, 2 eq. of CH_2Cl_2. ii) NaOMe, MeOH. iii) BnBr, NaH, DMF, (n-Bu)$_4$NI.

FIGURE 2.40. The armed-disarmed approach.

by BSP/Tf_2O and condensed with disarmed thiomannoazide intermediate bearing a 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% (Figure 2.43).[39]

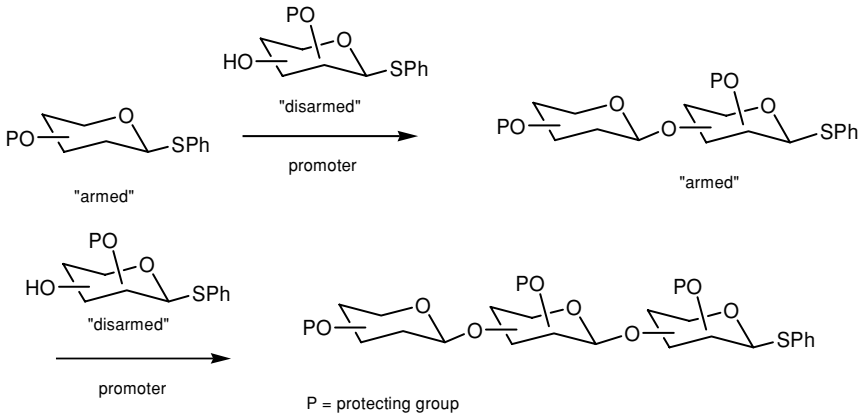


FIGURE 2.41. The general scheme of the armed-disarmed approach with thioglycosyl sugars.

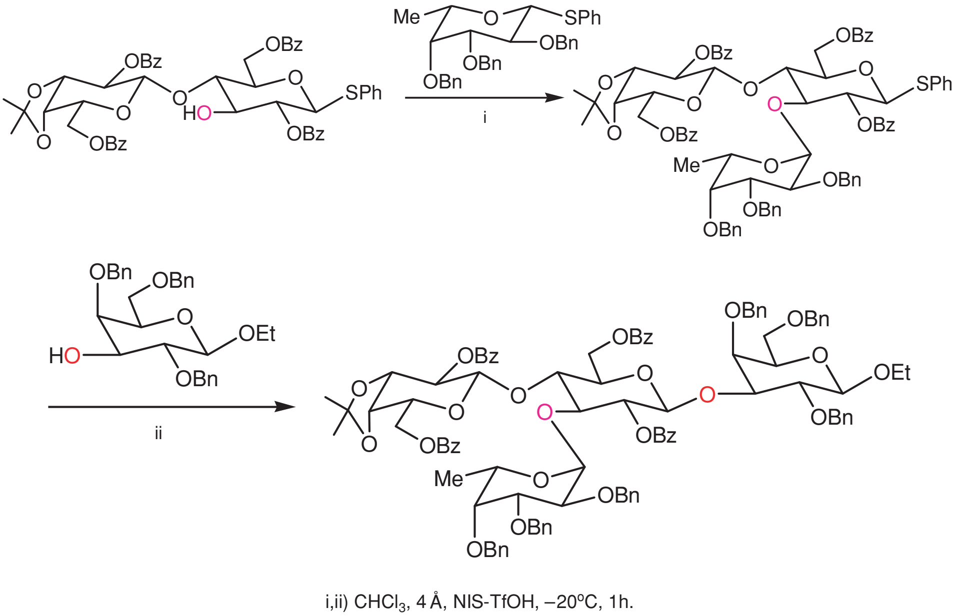


FIGURE 2.42. Preparation of Lewis X tetrasaccharide using armed-disarmed coupling method.

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 (Figure 2.44).[41]

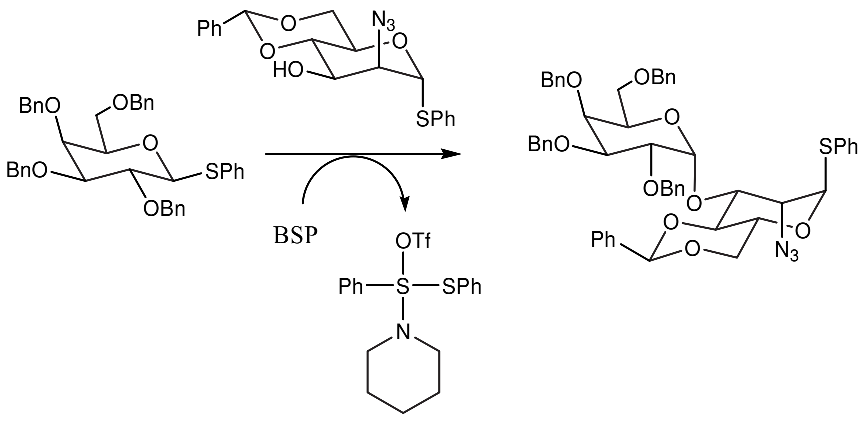


FIGURE 2.43. Synthesis of α-linked mannosyl disaccharide following an armed-disarmed strategy.

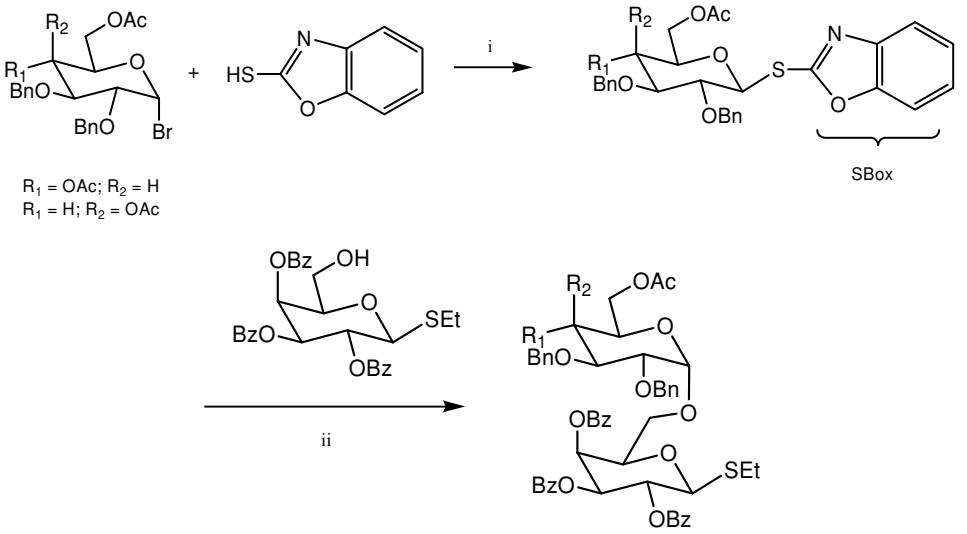
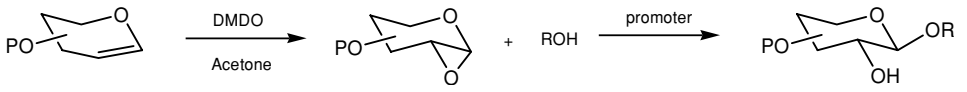


FIGURE 2.44. Armed-disarmed synthesis using S-benzoxazol (SBox) as disarmed glycosyl donor.

2.1.9 The 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[42] and their utility in the preparation of building blocks for oligosaccharide synthesis is increasingly important. Different routes for the preparation of triacetyl glycals have been examined by Fraser-Reid et al.,[43] involving the Ferrier rearrangement. Moreover, a suitable one-pot preparation of glycals has been more recently described, starting from reducing sugars by Shull et al.[44] 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 (Figure 2.45). 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.

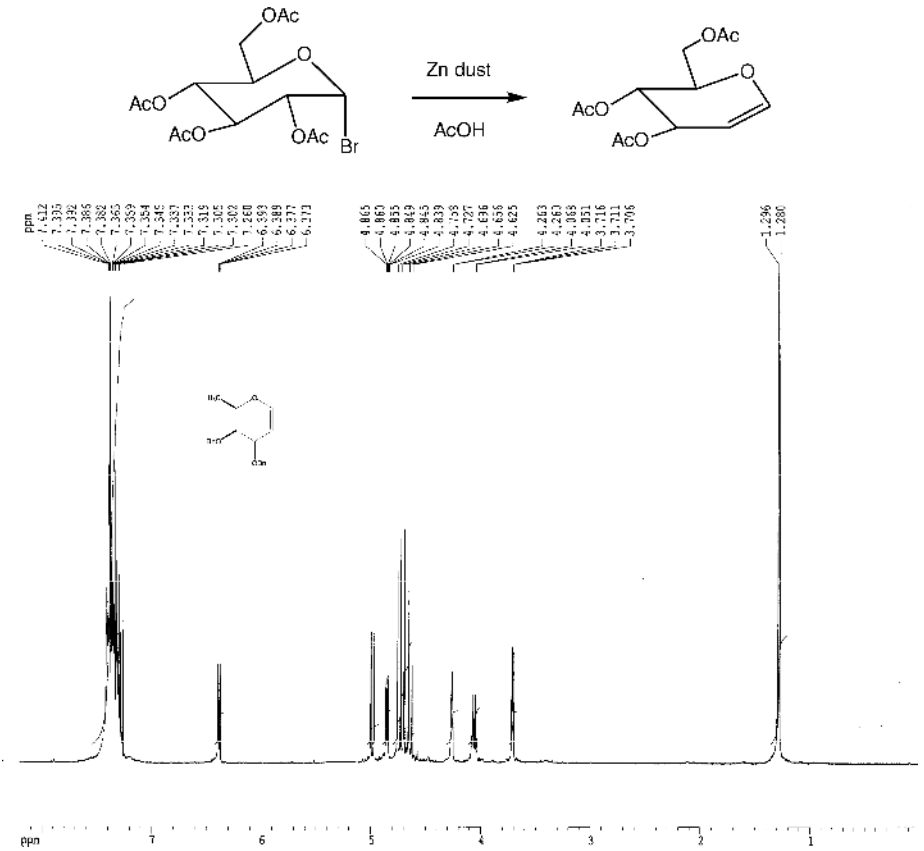


FIGURE 2.45. The Fischer-Sachs glucal and ^{1}H NMR of benzylfucopyranosyl glycal.

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 (Figure 2.46).

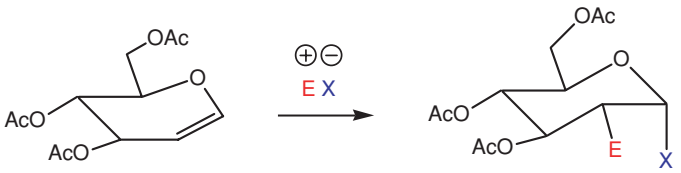


FIGURE 2.46. Electrophilic addition.

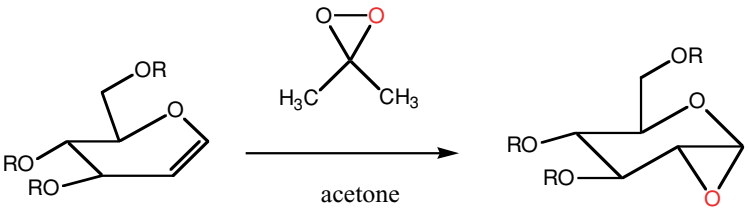


FIGURE 2.47. The Brigl epoxide formation.

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 (Figure 2.47).

The standard procedure for generation of DMDO was developed by Murray and Jeyaraman[45] and optimized by Adam et al.[46] Such procedure involves the use of potassium monoperoxysulfate as oxidative acetone agent, and the reaction conditions require temperatures below 15°C, an 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}HNMR, where the disappearance of the signal at 6.3 ppm for H-1 double bond is observed, 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 (Figure 2.48).

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 (Figure 2.49).

Likewise, alternative epoxide conditions from glycals have been assayed besides DMDO treatment. Among them, cyclization of a bromohydrin,[47] *m*-chloroperoxybenzoic acid-potassium fluoride complex oxidation of the glycal,[48] and potassium tertbutoxide oxidation of fluoride glycosyl donor[49] has been described (Figure 2.50).

The potential of 1,2-anhydro sugars as glycosyl donor for the preparation of β-linked saccharides was established by Halcomb and Danishefsky[50] and such 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 led to the next coupling reaction with another glucal acceptor (Figure 2.51).

The tetrasaccharide Cap domain of the antigenic lipophosphoglycan of *Leishmania donovani* has been prepared under the glycal approach by Upreti and Vishwakarma.[51] Thus, the preparation of the hexa-*O*-benzyl-lactal under stardard

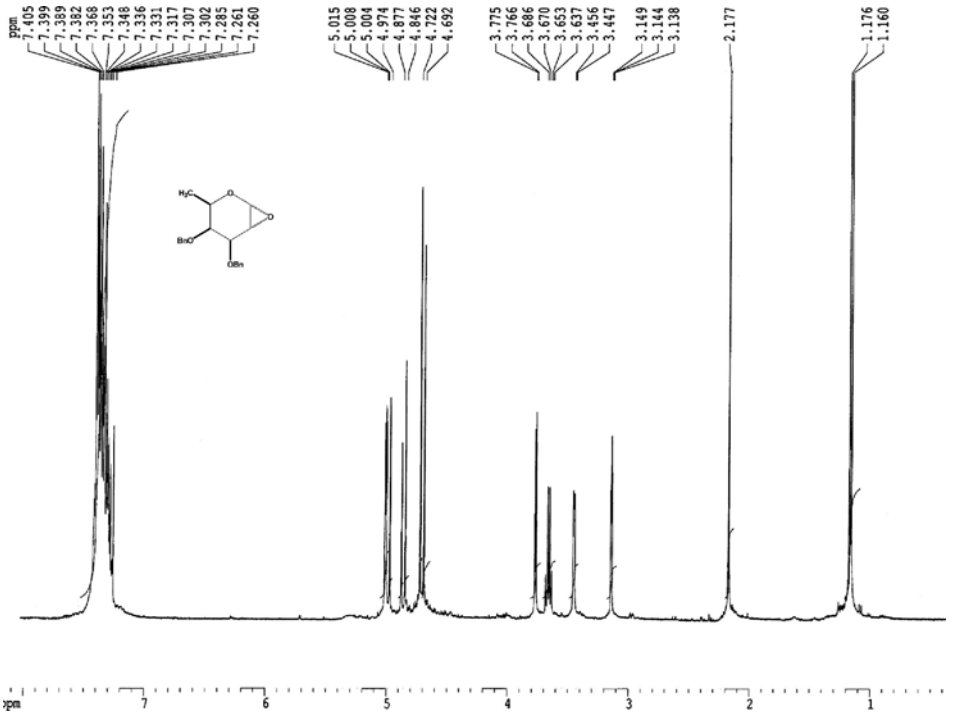


FIGURE 2.48. ^{1}H NMR spectra of 1,2-anhydro-3,4-di-*O*-benzyl-α-D-fucopyranose (and traces of acetone).

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 deprotecction led to the tetrasaccharide Cap domain (Figure 2.52).

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.[52] Galactosyl glycal is reacted with DMDO-acetone solution and the resulting epoxide reacted with hydroxylysine and $ZnCl_2$ as promoter (Figure 2.53). General procedures for preparation of glycosidic bond of glycopeptides can be reviewed in the comprehensive study reported by Kunz.[53]

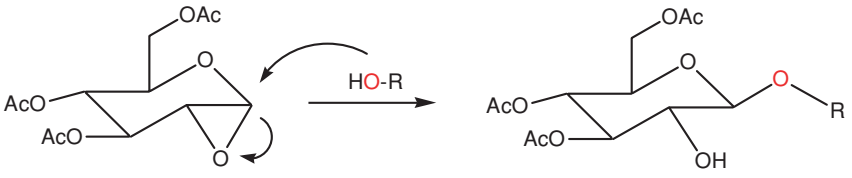
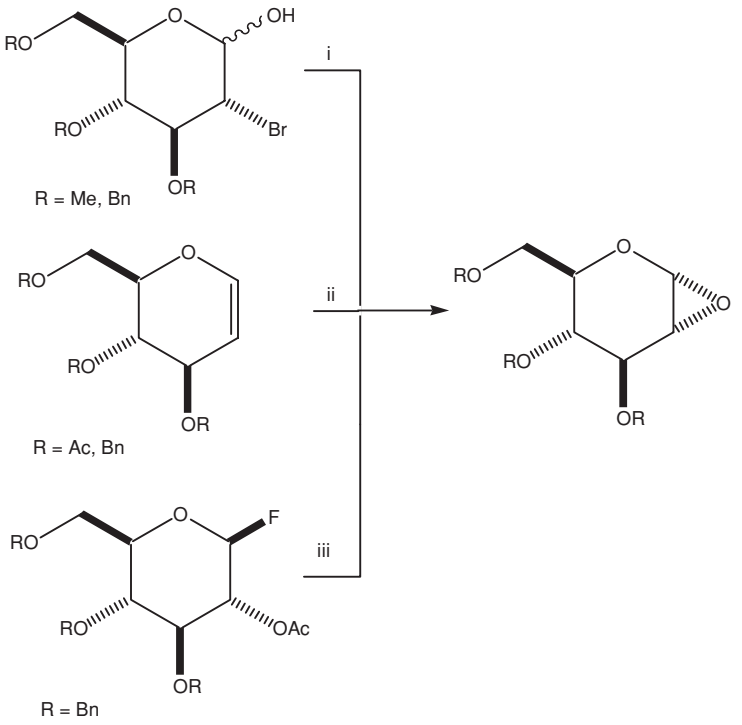
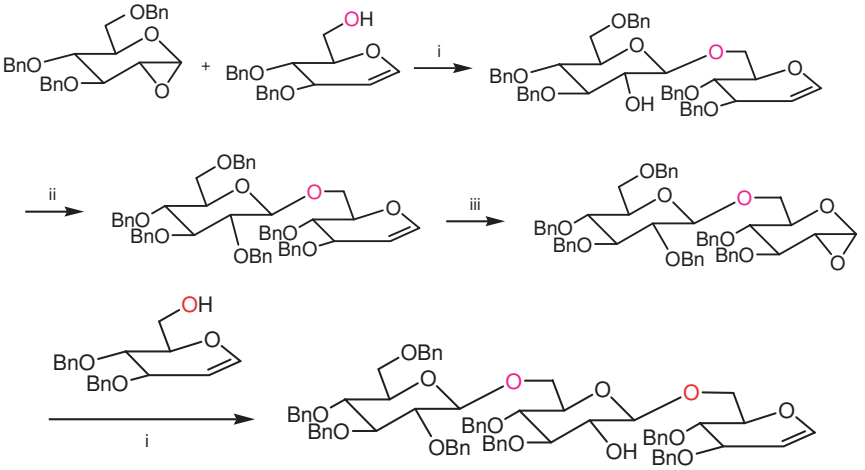


FIGURE 2.49. Ring opening for β-glycoside formation.



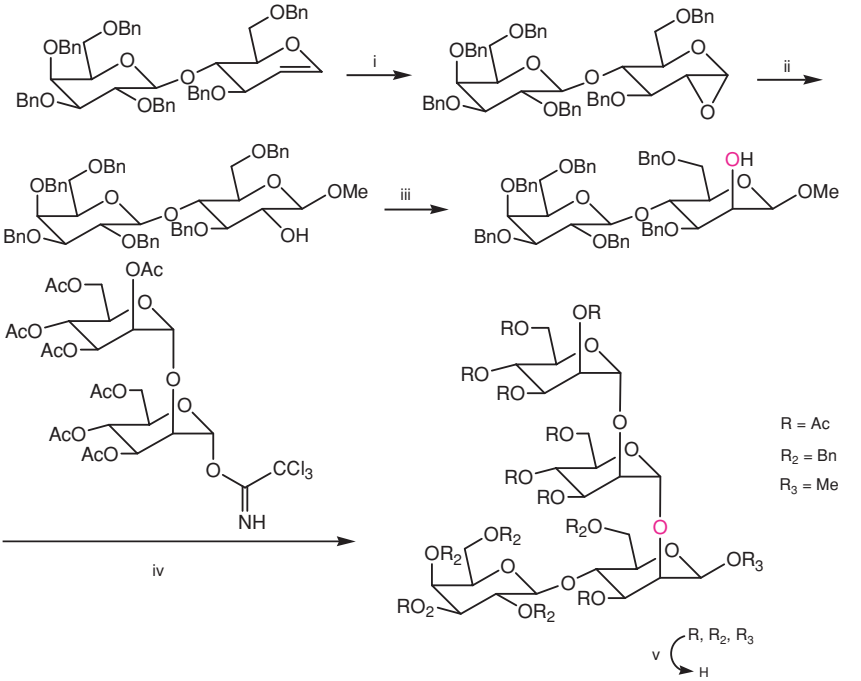
i) KH or, KHMDS, 18-crown-6, –70°C. ii) MCPBA-KF, CH_2Cl_2, r.t. iii) t-BuOK, THF.

FIGURE 2.50. Alternative glycal-epoxidations.



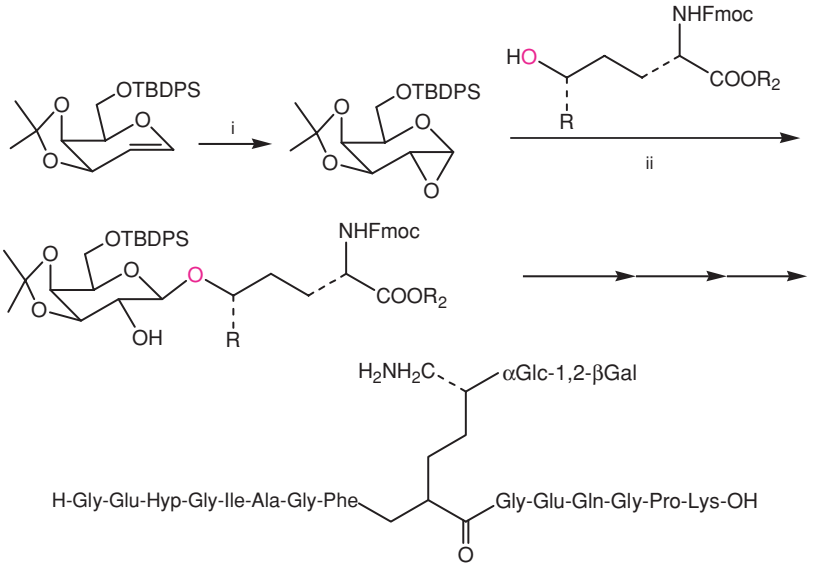
i) $ZnCl_2$/THF, –78°C to r.t. ii) NaH, BnBr. iii) DMDO-acetone.

FIGURE 2.51. Epoxide glycal as glycosil 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, 45 min. v)a) $Pd(OH)_2$, H_2, 4h. b) NaOMe, MeOH. c) Ac_2O/AcOH/H_2SO_4.

FIGURE 2.52. Synthesis of a tetrasacharide using an epoxide disaccacharide as glycosyl donor.



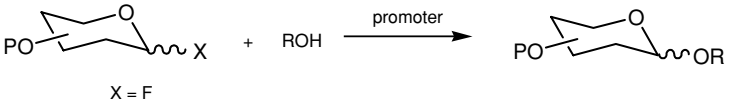
1) DMDO-acetone. ii) $ZnCl_2$, THF

FIGURE 2.53. Amino acids glycosidation.

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 Figure 2.54.[54]

2.1.10 Miscellaneous Leaving Groups

2.1.10.1 Fluoride Glycosyl Donors



Ppromoter	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

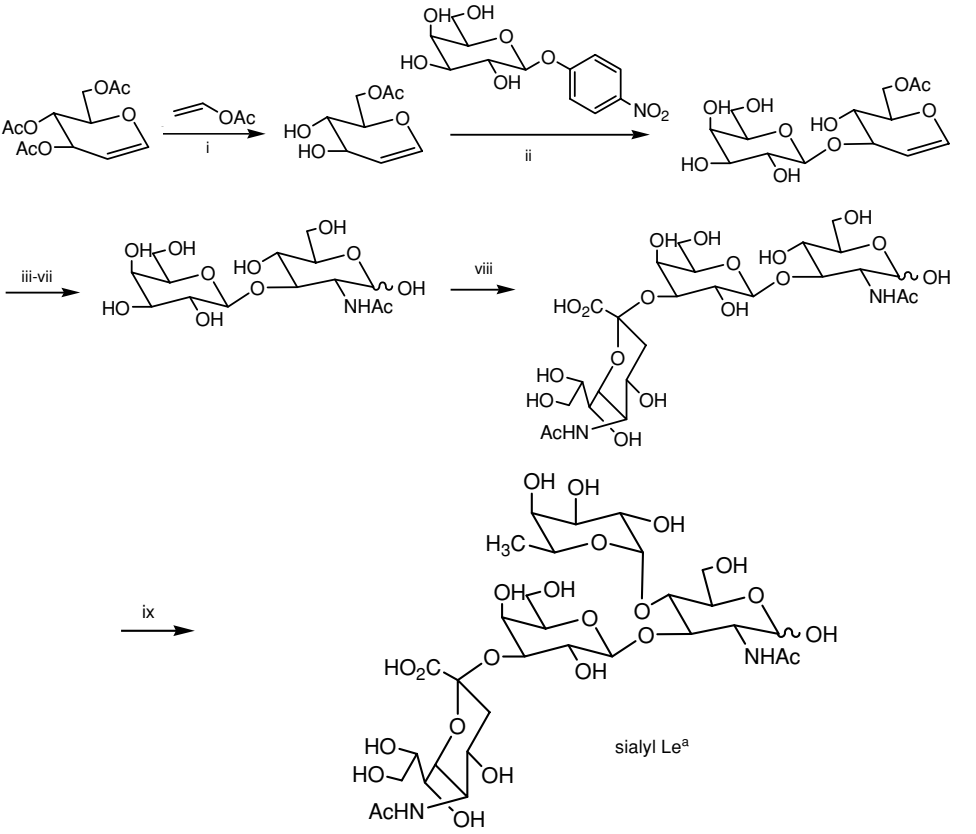
Fluorine is considered a poor leaving group, and its use for glycoside bond formation has been more restricted than chlorine and bromine, although display higher thermal and chemical stability. Nonetheless several *O*-glycoside synthesis involving glycosyl donors with fluorine as leaving group has been described, specially for the preparation of α-*O*-glycosides with high stereoselectivity.[55]

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 $SnCl_2$-$AgClO_4$ as catalyst (Figure 2.55).[56]

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.,[57] and consists of 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 (Figure 2.56).

It has been observed that the glycosylation reaction between the glycosyl fluorine with different alcohols under Lewis acid conditions provides mainly α-riboglucosides in high yield as it is shown in Figure 2.57.

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

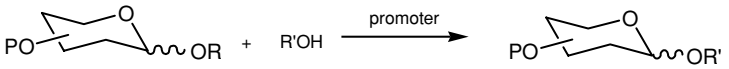


i) subtilisin, DMF. ii) β-galactosidase. iii) Ac_2O. iv) NaN_3, CAN. v) H_2 cat. vi) Ac_2O. vii) saponification. viii) α2-3SiaT, CMP-NeuAc. ix) α1-3/4 FucT, GDP-Fuc.

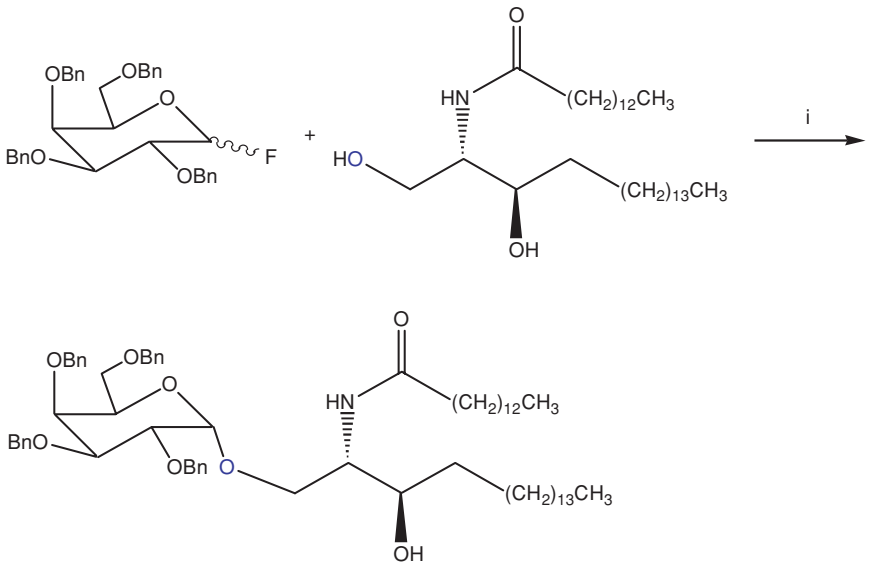
FIGURE 2.54. Chemoenzymatic synthesis of tetrasaccharide sialyl Le^a.

β-glycoside in 90% yield. The sulphated tetrasaccharide was formed by reaction of tetrasaccharide acceptor with $SO_3.NM_3$ complex in anhydrous pyridine (Figure 2.58).[58]

2.1.10.2 Silyl Glycosyl Donors



R	Promoter	Conditions
Me_3 Si	TMSOTf or $BF_3.Et_2O$	CH_2Cl_2, −5°C
$^tBuMe_2Si$	TMSOTf	CH_2Cl_2-acetone, −35°C



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

FIGURE 2.55. Fluorine monosaccharide as glycosyl donor.

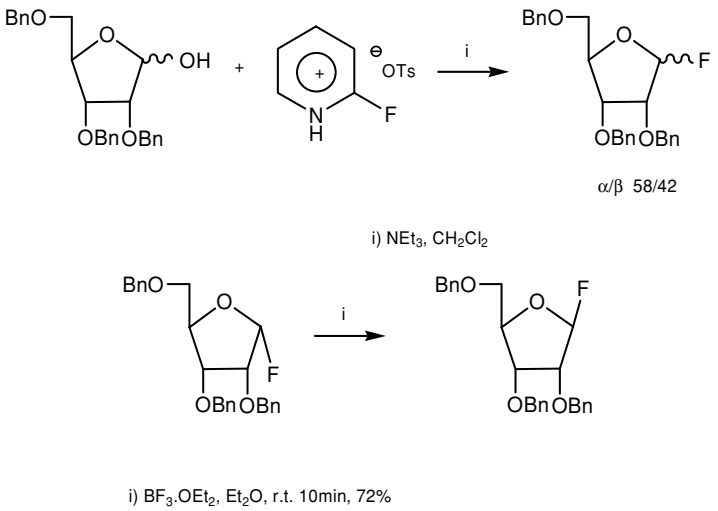


FIGURE 2.56. The Mukaiyama protocol for preparation of ribofuranosyl fluoride.

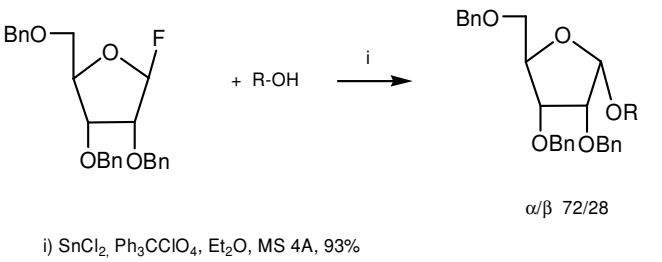


FIGURE 2.57. N-glycosylation reaction using ribofuranosyl fluorine.

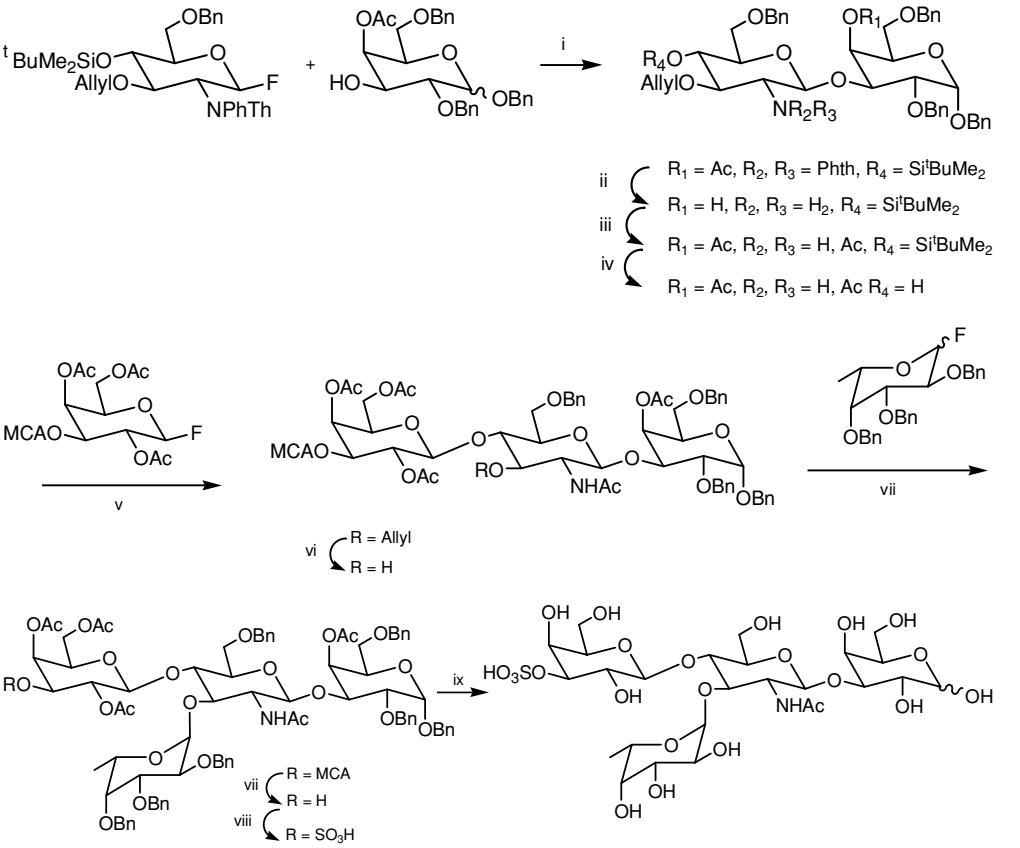
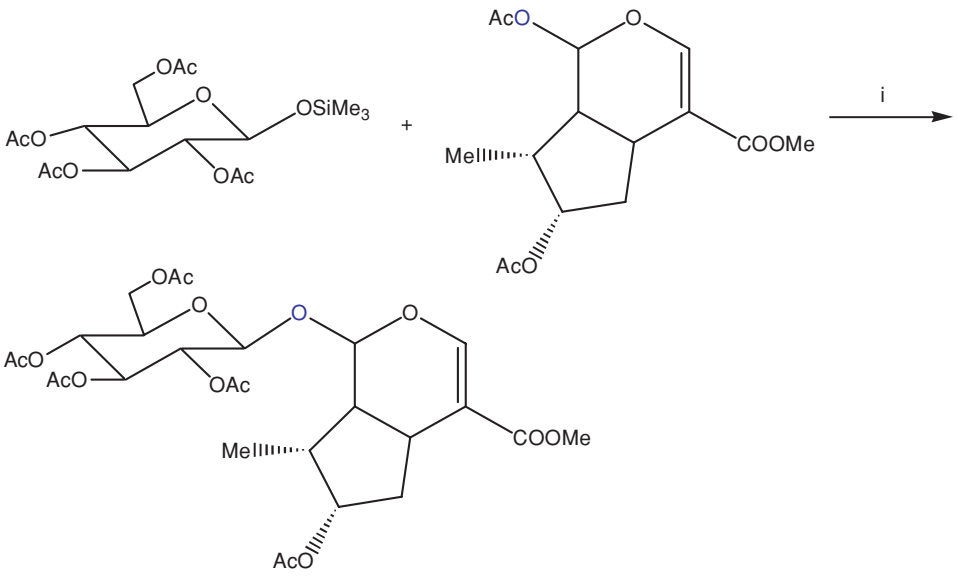


FIGURE 2.58. Total synthesis of sulphated Le^x.



i) $TfOSiMe_3$, -40^oC.

FIGURE 2.59. Silyl derivatives as glycosyl donors.

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.[59] In this work, the glycosyl donor is combined with luganine in the presence of trimethylsilyltriflate at low temperature (Figure 2.59). 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.

The use of selenoglycosides as glycosyl donors and acceptor in glycosilation reactions has also been described by Metha and Pinto.[60] A typical glycosidation procedure with phenylselenoglycoside donors involves the glycosyl acceptor, 4-Å molecular sieves, silver triflate, and potassium carbonate in dichloromethane (Figure 2.60).

Tetrazol has also been tested as a leaving group for the preparation of an antibiotic fragment.[61] A coupling reaction with the methoxyphenyl glycosyl acceptor was catalyzed with $(Me_3)_3OBF_4$as shown in Figure 2.61.

2-Aminodisaccharides were obtained by an elegant [3,3] sigmatropic rearrangement, by Takeda et al.[62] 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 that migrates from C-4 to C-2. Disaccharide formation was catalyzed with $Pd(CH_3CN)_2$-AgOTf complex in dichloromethane (Figure 2.62).

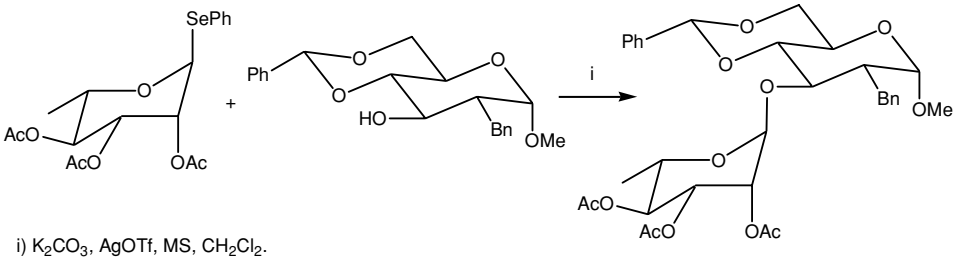


FIGURE 2.60. Phenylselenosugars as glycosyl donors.

The total synthesis of the cyclic glycolipid Arthrobacilin A, a cell growth inhibitor was achieved by Garcia and Nizhikawa,[63] under zinc *p-tert*-butylbenzoate salt as glycoside catalyst, obtaining the β-galactoside glycoside in 73% along with α-isomer in 27% (Figure 2.63).

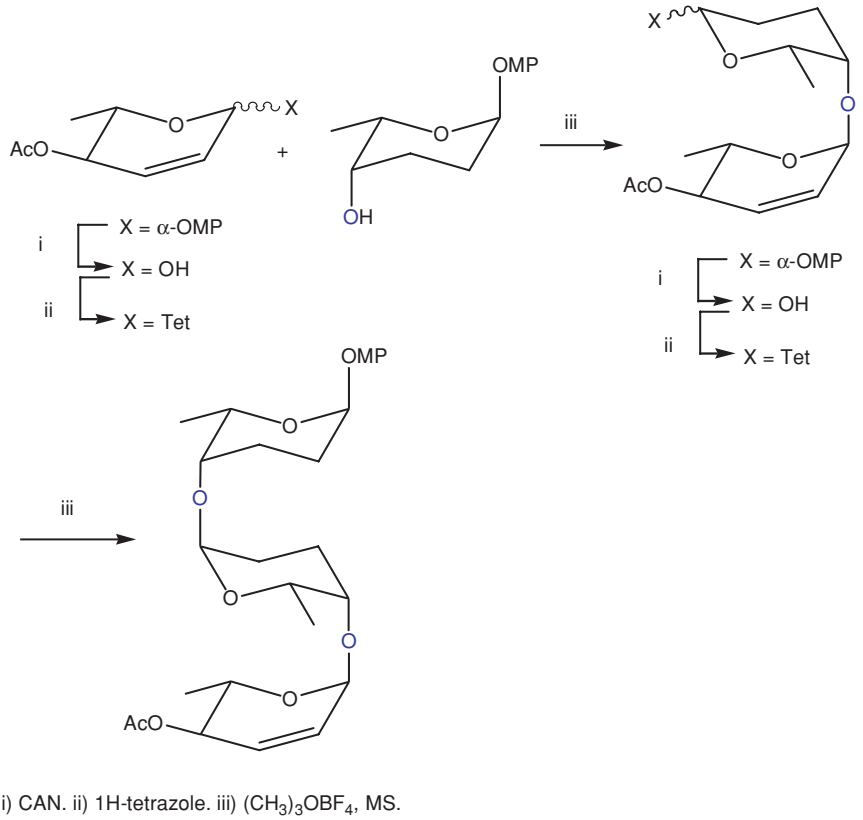
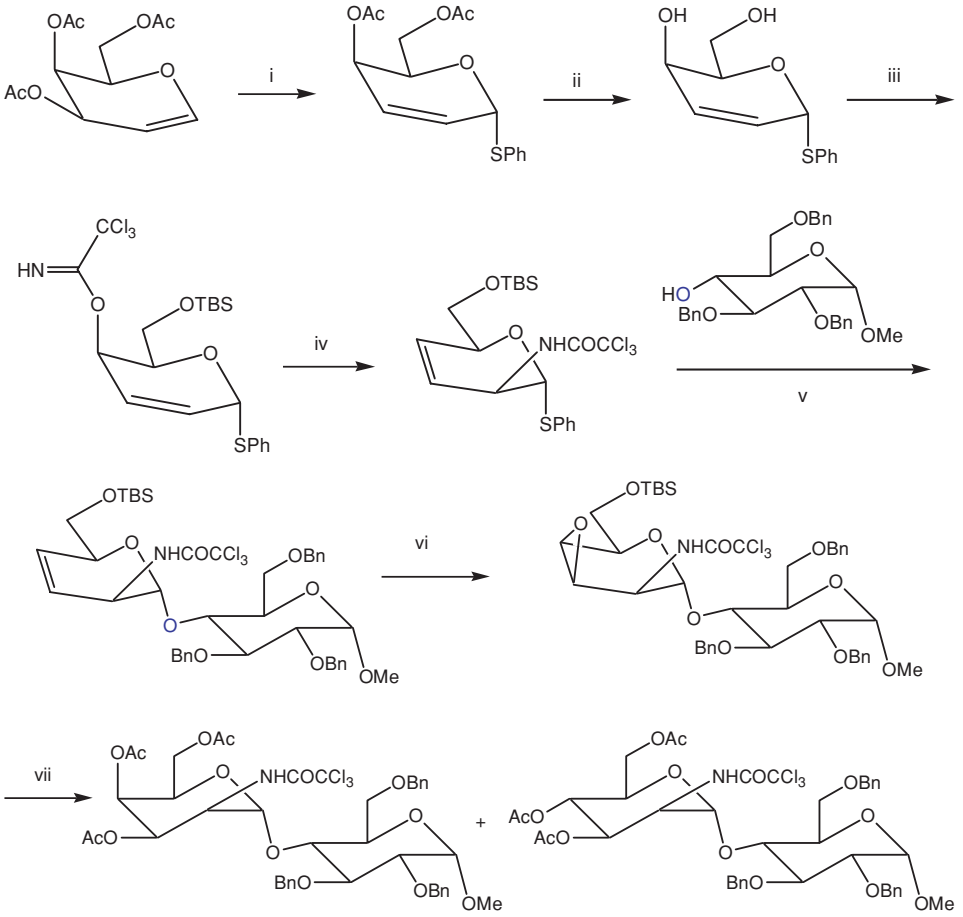


FIGURE 2.61. The use of tetrazol as a leaving group.



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/$BF_3.OEt_2$.

FIGURE 2.62. Sigmatropic rearrangement.

2.1.10.3 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,[64] heteropoly acid ($H_4SiW_{12}O_{40}$),[65] sulphated zirconia (SO_4/ZrO_2),[66] and perfluorinated solid-supported sulfonic acids (Nafion resins)[67] have been assayed successfully providing series of stereocontrolled *O*-glycosides in high yield (Figure 2.64).

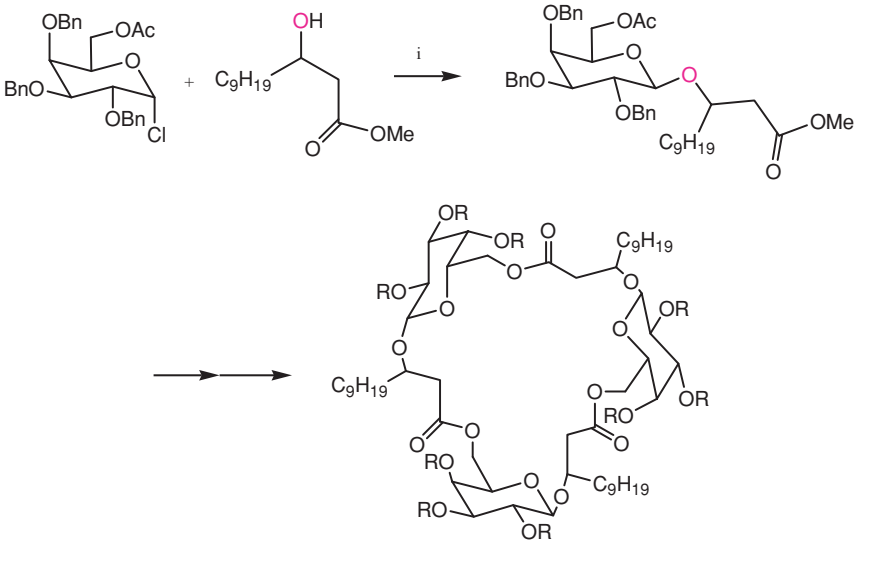


FIGURE 2.63. Glycosylation reaction for preparation of Arthrobacilin A.

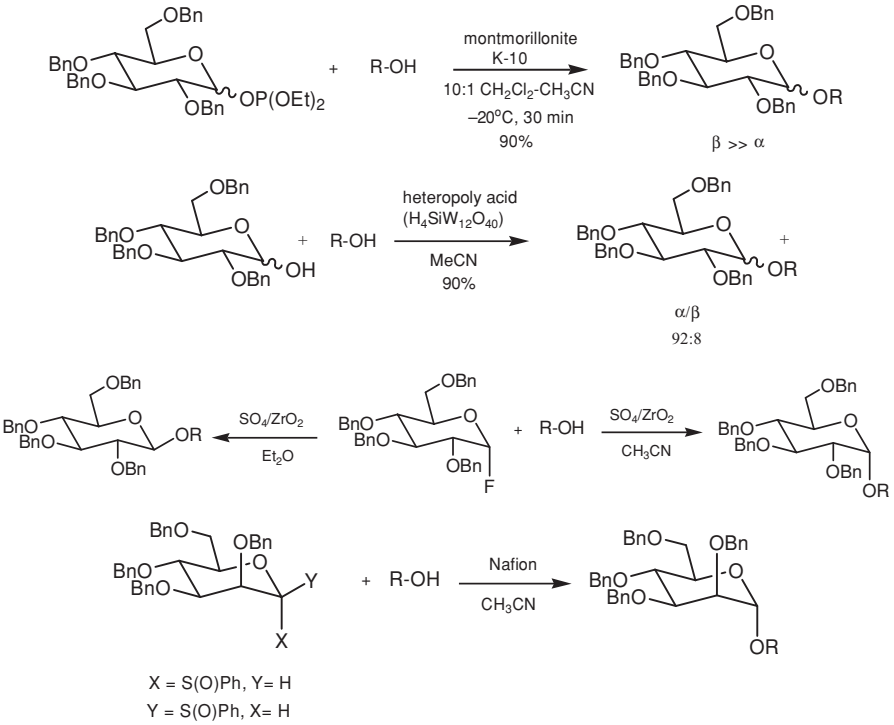


FIGURE 2.64. Stereocontrolled *O*-glycosidations using heterogeneous polymeric materials.

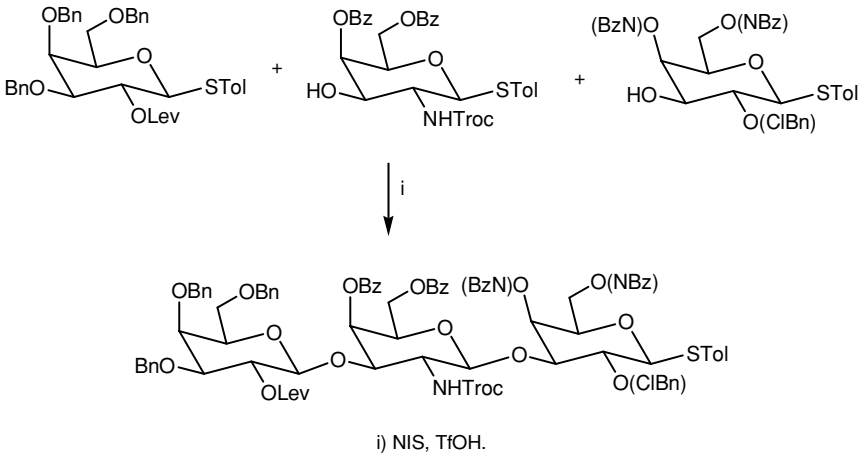
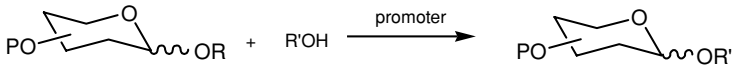


FIGURE 2.65. One-pot reaction for two β-linkages formation.

2.1.10.4 The Pool Strategy

This term applies to define a one-step reaction used to build up two β-linkages simultaneously from 3 sugar intermediates.[68] This approach has been described for the preparation of the glycosyl ceramide Globo H hexasaccharide 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 3 suitable sugar intermediates under N-iodosuccinimide and triflic acid conditions in 67% yield (Figure 2.65).

2.1.10.5 Phosphate Glycosyl Donors



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

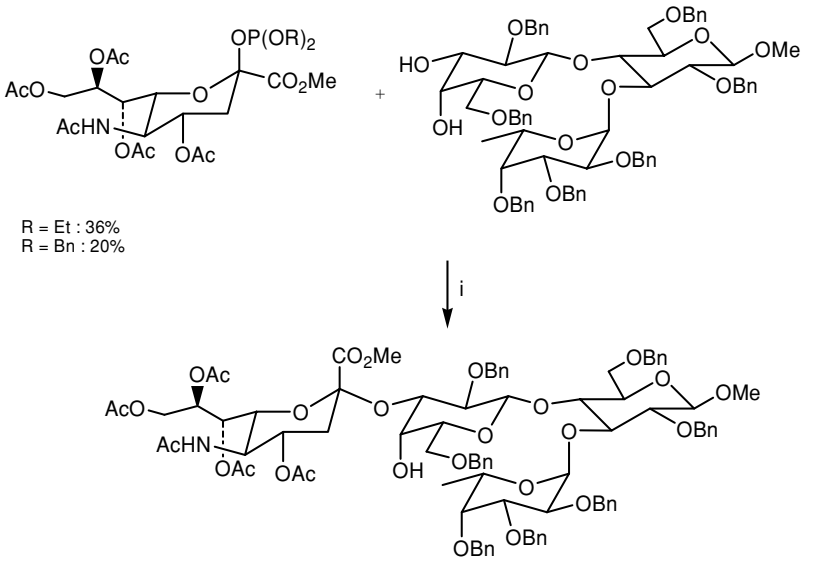


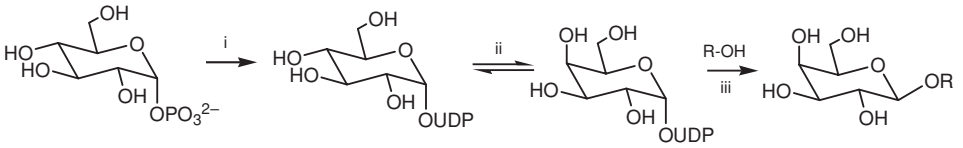
FIGURE 2.66. Phosphorous glycosyl donors for oligosaccharide synthesis.

between sialyl phosphite with trisaccharide acceptor under TMSOTf as catalyst (Figure 2.66).[69]

2.1.11 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, especially for those key steps involving stereospecifically controlled reaction conditions. In general, enzymes are considered efficient catalysts that 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 environmentally friendly processes for synthesis. However, some aspects still need close attention in order to fulfill thoroughly the requirements especially for high-scale production. Thus, many enzymes are unstable, high cost, difficult to handle, and require expensive cofactors.

Glycosyltransferases are important enzymes involved in essential processes related to oligosaccharide biosynthesis, and they have been found also very useful as biocatalyst for the chemoenzymatic synthesis of interesting oligosaccharides



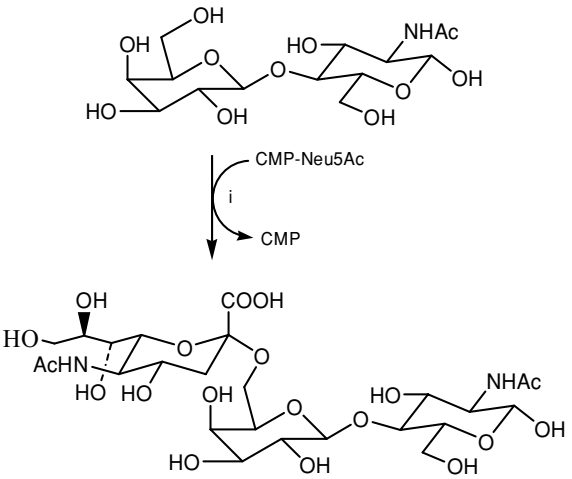
i) UTP, UDP-Glc pyrophosphorylase. ii) UDP-Glc 4-epimerase. iii) Gal transferase.

FIGURE 2.67. Glycosylation with galactosyltransferases.

and nucleotides.[70,71] They have been classified as Leloir if they are involved in the biosynthesis of most of N- and O-linked glycoproteins in mammalians, and requires mono- 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 affords UDP-galactose, which is used for glycosylation with galactosyltransferase (Figure 2.67).[72]

Several chemoenzymatic synthesis of $\alpha(2\rightarrow6)$ and $\alpha(2\rightarrow3)$-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 (Figure 2.68).[73]



i) α-(2-6)-sialyltransferase

FIGURE 2.68. Synthesis of silayl trisaccharide mediated by silayl glycosiltransferase.

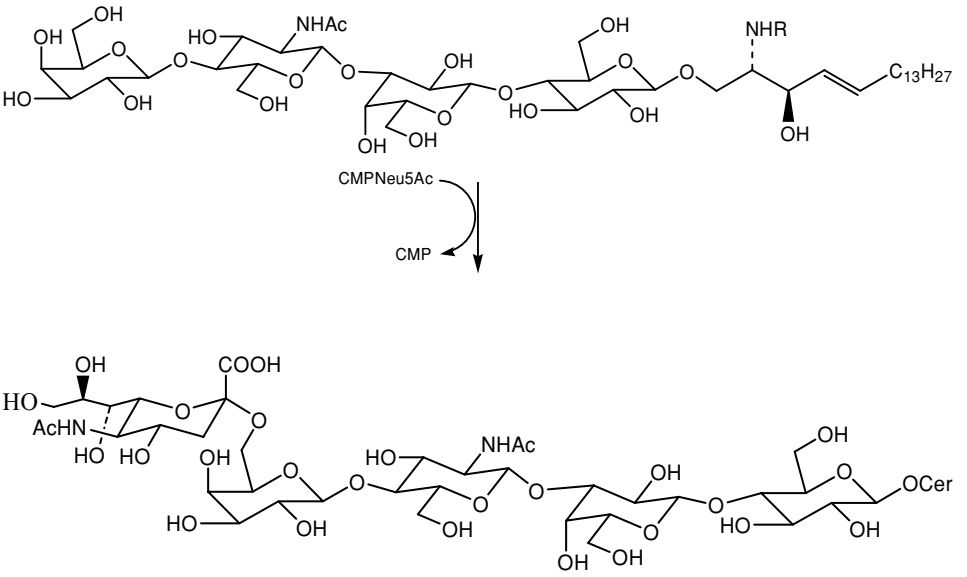


FIGURE 2.69. Enzymatic synthesis of ganglioside.

Sialyltransferases also proved to be efficient biocatalysts in the preparation of gangliosides, being involved in (2→6) linkage formation between the tetrasaccharide ceramide with CMP-Neu5Ac (Figure 2.69).[74]

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 (Figure 2.70).[75]

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 piruvate (Figure 2.71).[76]

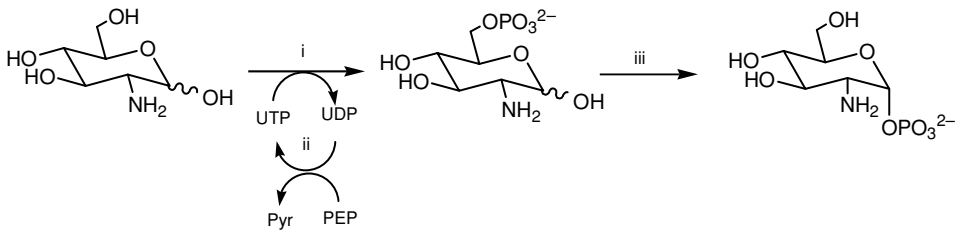
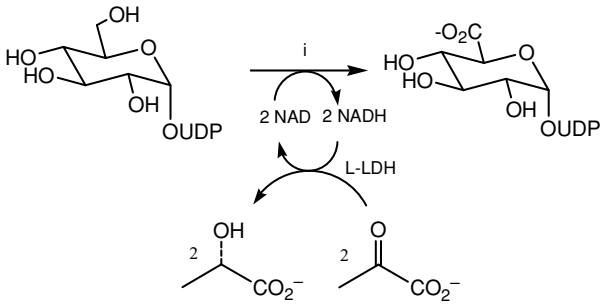


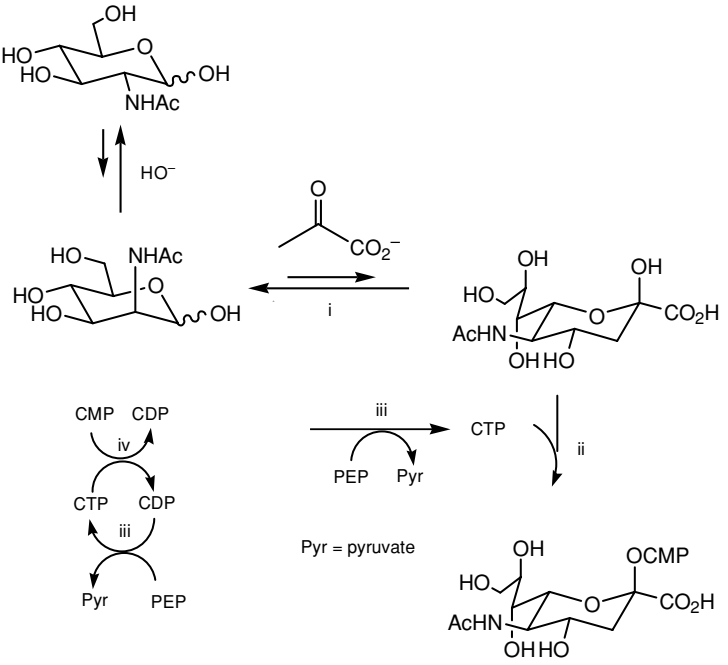
FIGURE 2.70. Enzymatic preparation of glucosamine 6- and 1-phosphate.



i) UDP-Glc dehydrogenase

FIGURE 2.71. Enzymatic preparation of UDP-glucuronide.

CMP-N-acetylneuraminic acid has been prepared from 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 (Figure 2.72).[77]



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

FIGURE 2.72. Synthesis of CMP-N-acetylneuraminic acid.

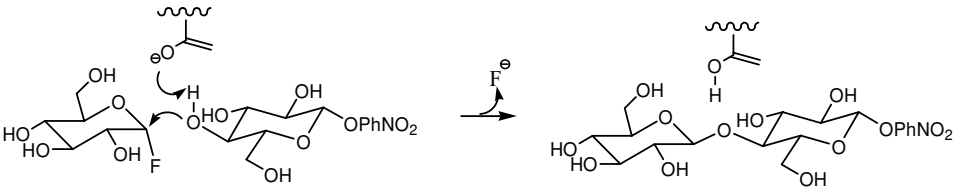


FIGURE 2.73. Glycosynthase-catalyzed oligosaccharide synthesis.

2.1.11.1 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 Figure 2.73.[78]

The Regioselective preparation of α-1,3 and α-1,6 disaccharides by using α-glycosidase as biocatalyst has been described. Thus, by combining *p*-nitrophenyl-α-galactose functioning as glycosyl donor, with the glycosyl acceptor methoxy-galactose, the expected 1,3- and 1,6-disaccharides were obtained in the form of α- and β- anomers (Figure 2.74).[79]

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 di- 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 Figure 2.75 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.[80]

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 (Figure 2.76).[81]

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 (Figure 2.77).[82]

Lactosamine was prepared using an enzymatic approach consisting in the preparation of UDP glucose and condensation with N-acetyl glucosamine (GlcNAc) in the presence of galactosyl transferase (Figure 2.78).[83]

2.1.12 The Solid-Phase Methodology

Perhaps what remains the most challenging task for sugar chemistry is the synthesis of complex oligosaccharides such as those found in bacterial membranes or

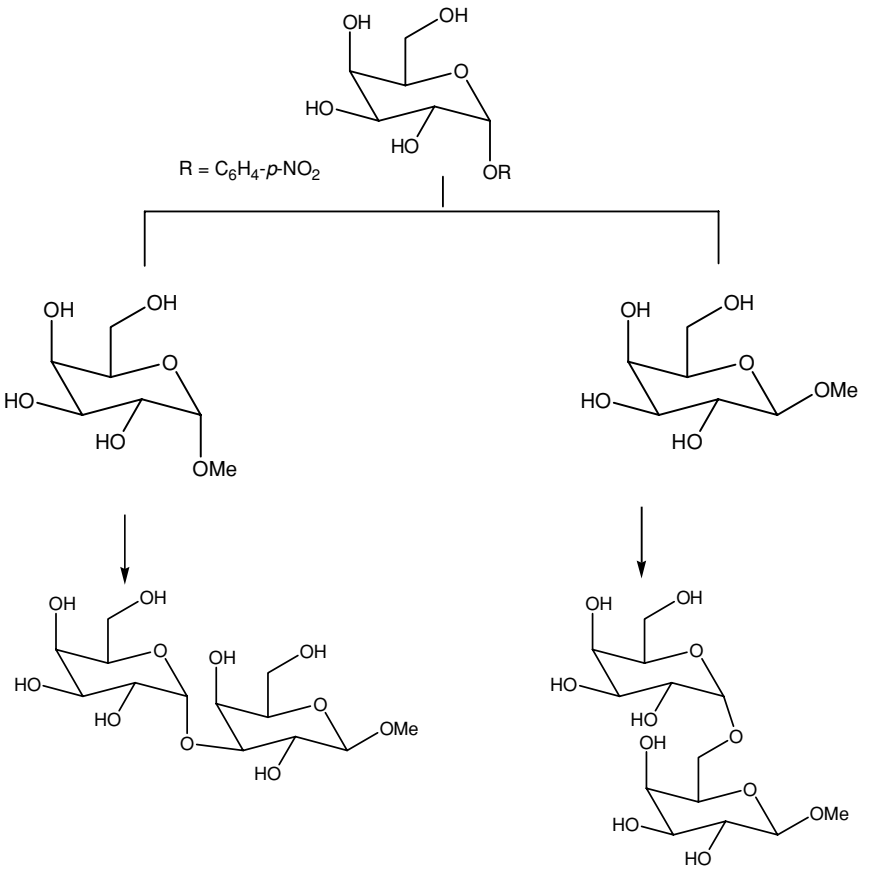


FIGURE 2.74. Example of microbial catalyzed coupling reaction.

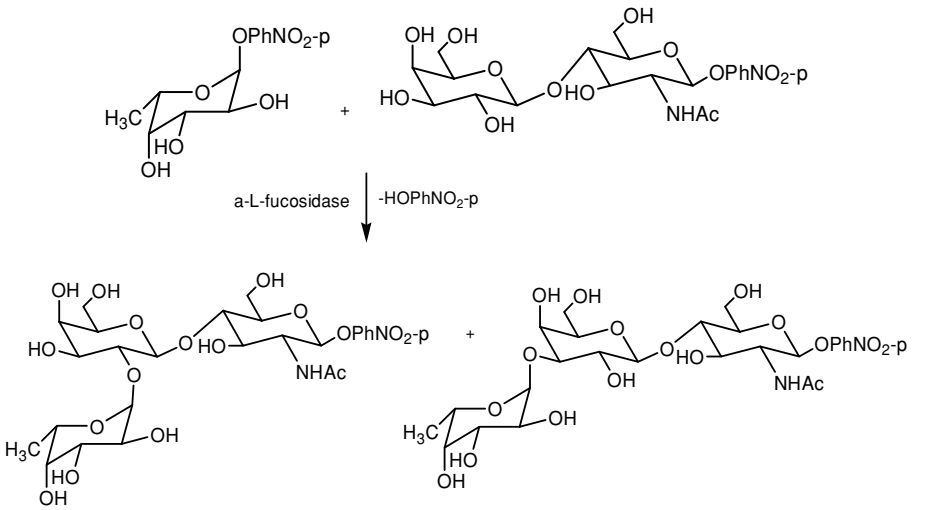


FIGURE 2.75. Transglycosylation reaction for the preparation of 2- and 3-linked trisaccharides.

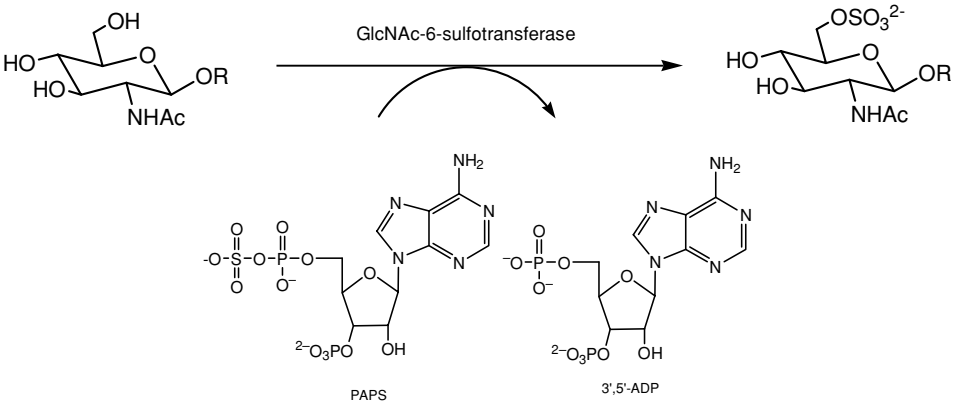


FIGURE 2.76. Transfer of the sulfuryl group from PAPS to the glycoside.

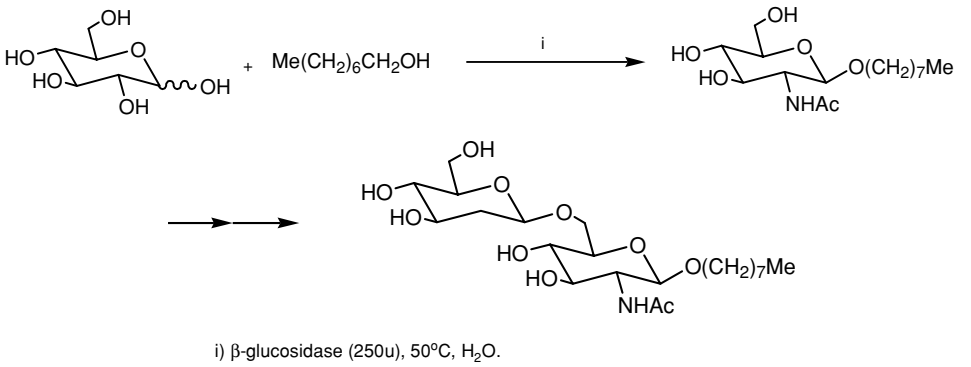


FIGURE 2.77. Chemoenzymatic synthesis of rhodiooctanoside.

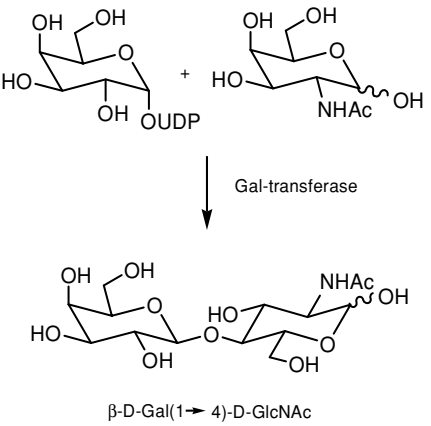


FIGURE 2.78. Enzymatic synthesis of lactosamine.

wall cells and are usually in the form of glycopeptides. Different types of monosaccharides can be present as constitutive parts such as glucose, galactose, mannose, N-acetylglucosamine, silaic 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 nonreacted reagents, avoiding tedious purifications steps.

Nonetheless, despite the difficulties, interesting progress has been made for preparing oligosaccharides[84a] and glycopeptides,[84b] 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,[85] the synthetic strategies are classified by (a) Donor-bound, (b) Acceptor-bound, and (c) Bidirectional Strategies.

One general approach involves the initial attachment of a glycosyl donor (halides, trichcloroacetimidate, sulfoxides, phosphates, phosphates, thio and pentenyl and glycols) 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 (Figure 2.79).[86]

An example of the donor-bound strategy is the bounding of sulfur glycoside to polistyrene resin to form a sulfur linkage between the donor and the resin (Figure 2.80). 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 (Figure 2.81).[85]

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 (Figure 2.82).

Polymer solid phase has been also exploited successfully by Crich et al,[87] 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

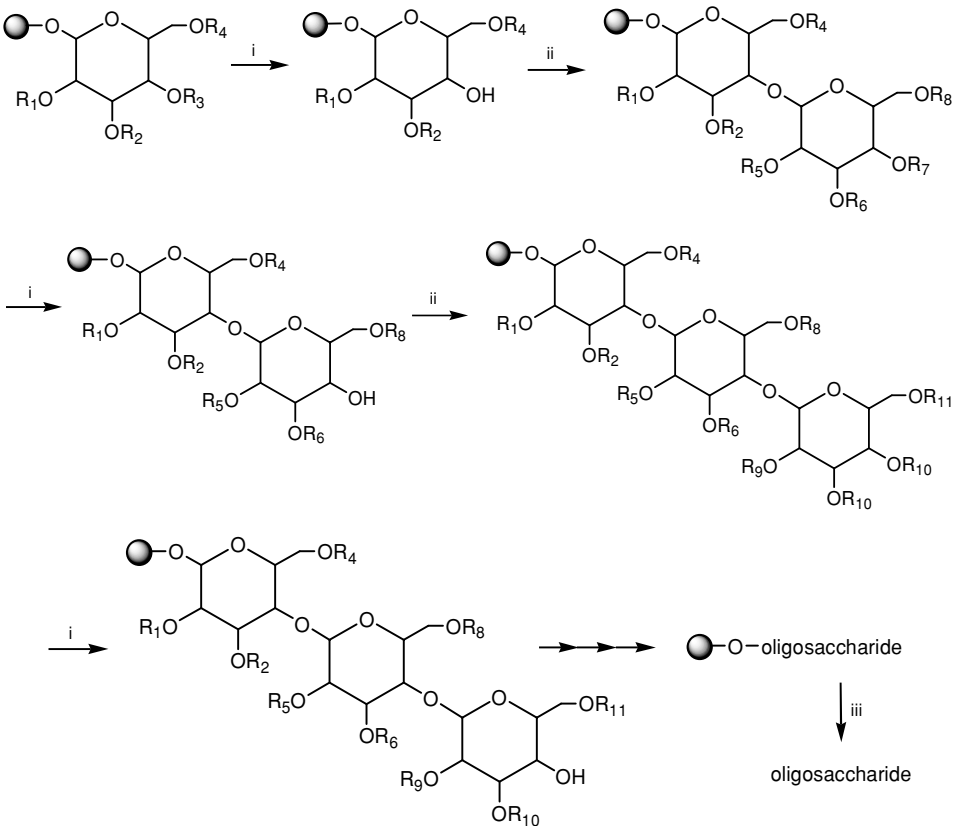


FIGURE 2.79. General scheme for solid-phase oligosaccharide synthesis 1,4-linkage case.

subsequent addition of alcohol acceptor to the donor attached to the Wang resin will result in the glycoside β-mannoside formation (Figure 2.83).

The enzymatic solid-phase oligosaccharide synthesis relies mainly by the use of glycosyltransferases, glycosidases and glycosynthases. By taking advantage on their high stereo- 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

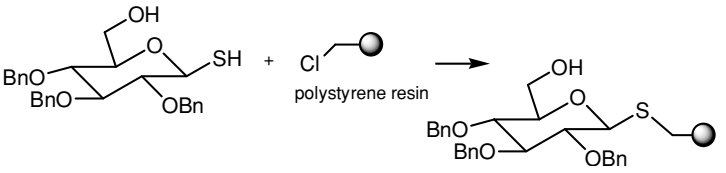


FIGURE 2.80. Example of donor-bound strategy for solid-phase glycosilation reactions.

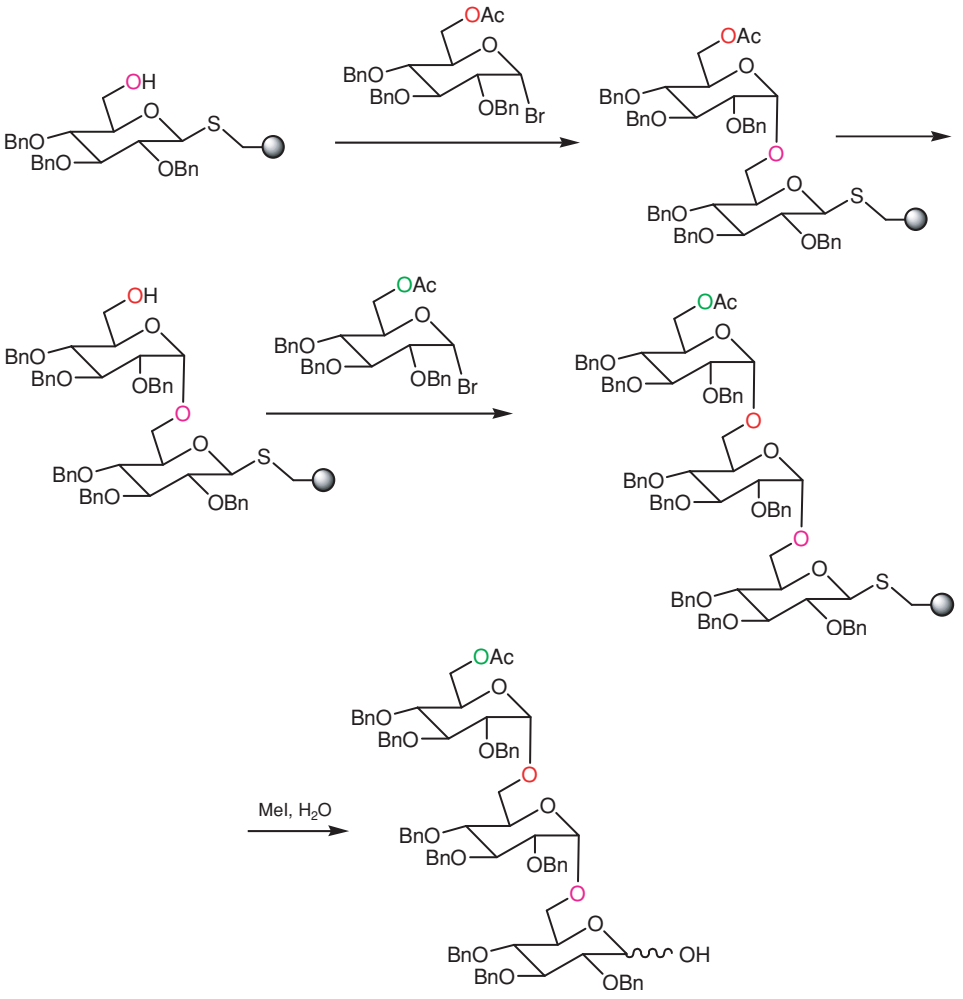
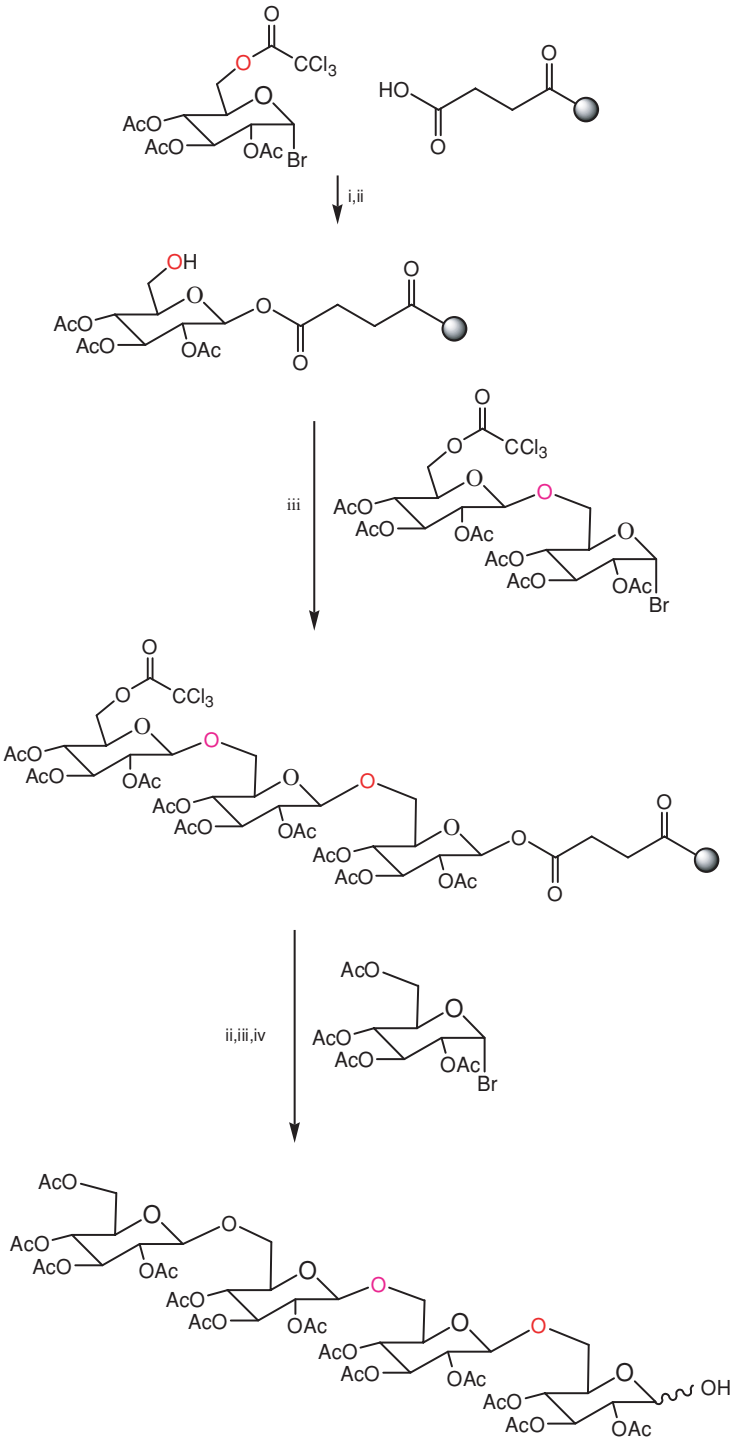


FIGURE 2.81. Sulfur mediated solid-phase coupling reaction.

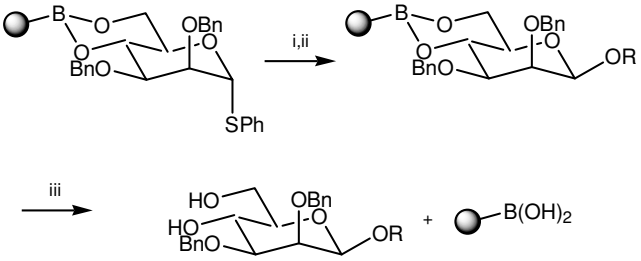
unaffordable due its high cost for large-scale processes, lower yields provided, and their limited capability for recognizing a broad range of sugars, especially those not common. Two general approaches have been proposed for the preparation of oligosaccharides through the solid-phase approach (Figure 2.84).[88]

A solid-phase enzymatic approach for extending the oligosaccharide chain was described by Gijsen et al.[88] in which a disaccharide-linker fragment attached to a resin was coupled with the glycosyltransferases UDP-galactose and CMP-NeuAc in the presence of galacosyltransferases and Sialyltransferase as enzymatic catalyst. Final treatment with hydrazine was used to release the tetrasaccharide from the solid support (Figure 2.85).



i) TBABr, 35°C. ii) MeOH, Py. iii) $Hg(CN)_2$, 30°C. iv) hydrazinium acetate 50°C.

FIGURE 2.82. Solid-phase coupling promoted by Helferich conditions.



i) BSP, TTBP, Tf_2O, –60°C. ii) ROH. iii) Me_2CO/H_2O.

FIGURE 2.83. Solid-phase synthesis of β-mannoside glycoside.

2.2 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 at 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 later strategy is considered less laborious however produce cyclic oligomers of different size since under these conditions the ring formation step is not controllable.

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 requires 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.[89]

The pioneering total synthesis of cyclic oligosaccharide α-Cyclodextrin was carried out by Ogawa's group in 1985,[89] 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[90] 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 di-, or trisaccharide that can yield a range of macrocycles of different sizes;
3. the enzyme-assisted synthesis of natural or unnatural cyclic oligosaccharides;

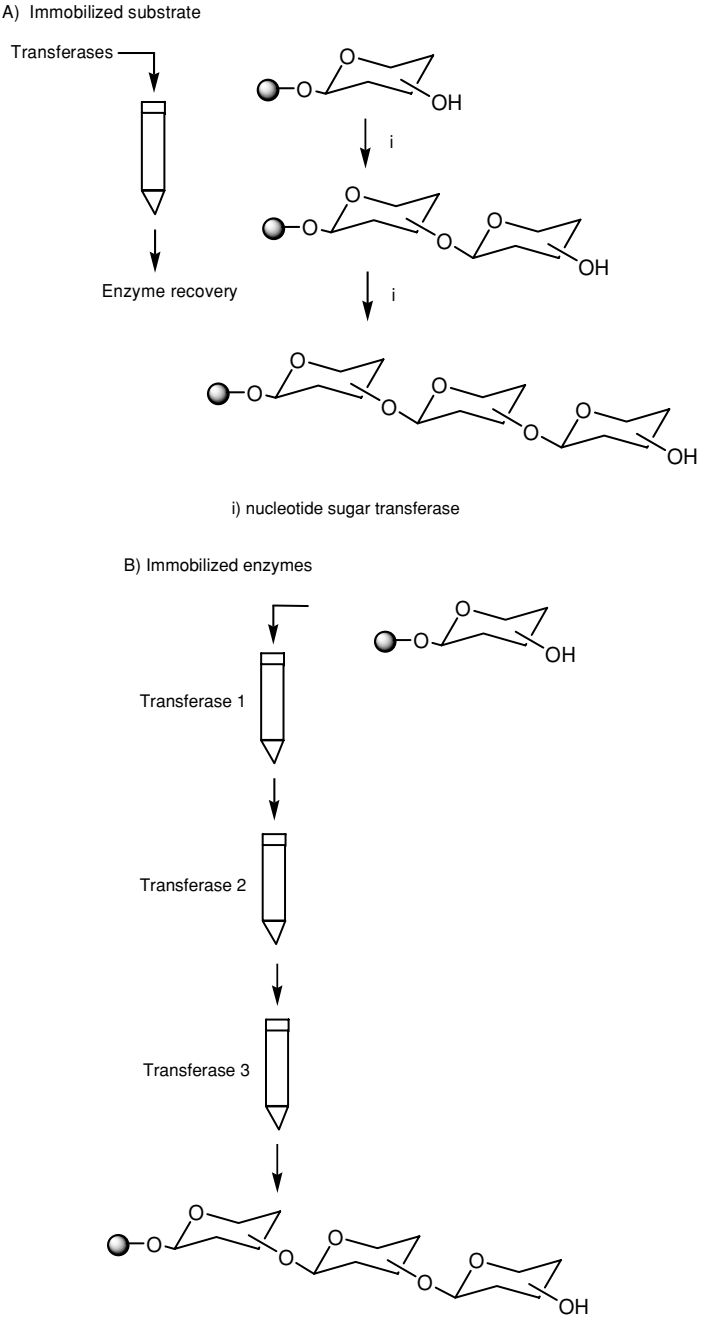


FIGURE 2.84. Two general approaches for immobilized solid-phase oligosaccharide synthesis.

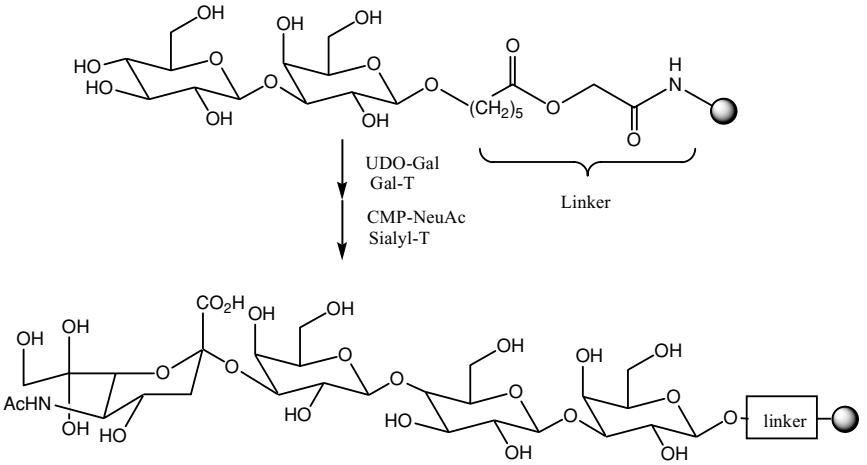


FIGURE 2.85. Enzymatic-solid phase glycosylation reaction.

4. the ring opening of cyclodextrins followed by oligosaccharide chain elongation and cycloglycosylation (Figure 2.86).

Despite the significant advances observed in cyclic oligosaccharide synthesis, their preparation is time-consuming, producing the target compounds with low regio- and stereoselective in low yields. The total synthesis of α-CD and γ-CD was described according to Figure 2.87.[91,92]

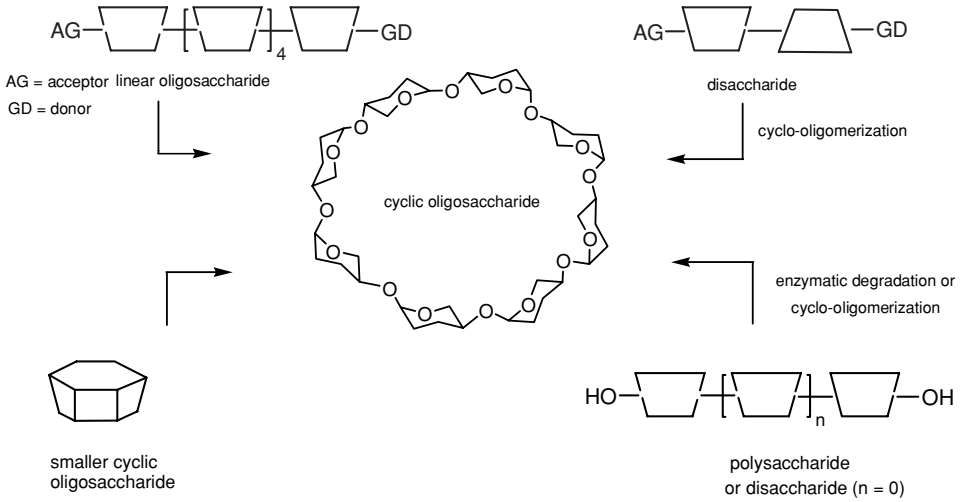


FIGURE 2.86. The four suggested approaches to the synthesis of cyclic oligosaccharides.

In 1990 it was reported the chemical synthesis of β-(1→3) linked hexasaccharide. The chemical approach involved the glycosidic reaction between benzylidene acceptor and protected glucosyl bromide as glycosyl donor, under silver triflate-promoter conditions. As can be seen in Figure 2.88, the construction of 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 $BrCCl_3$(Figure 2.88).[93]

The formation of (1→6)-glycopyranosidic linkages might produce cyclic di-tri- and tetrasaccharides. An early synthesis of β-(1→6)-glucopyranan under Helferich conditions, generated along with the linear oligomer, a cyclic di- and tetrasaccharide in 12 and 6%, respectively (Figure 2.89).[94]

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 tri- and tetrasaccharide in 22% and 25% yield, respectively (Figure 2.90).[95]

2.2.1 *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 continues to be

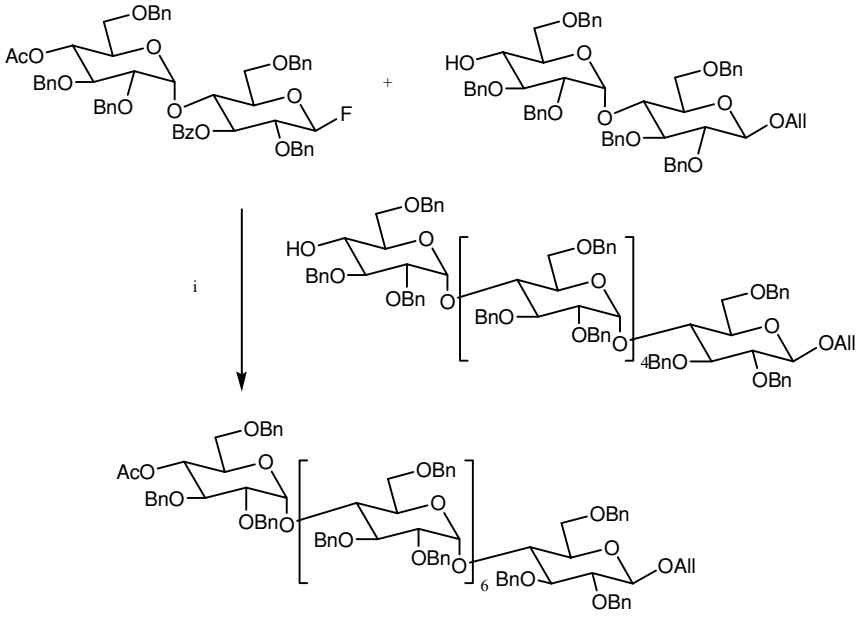
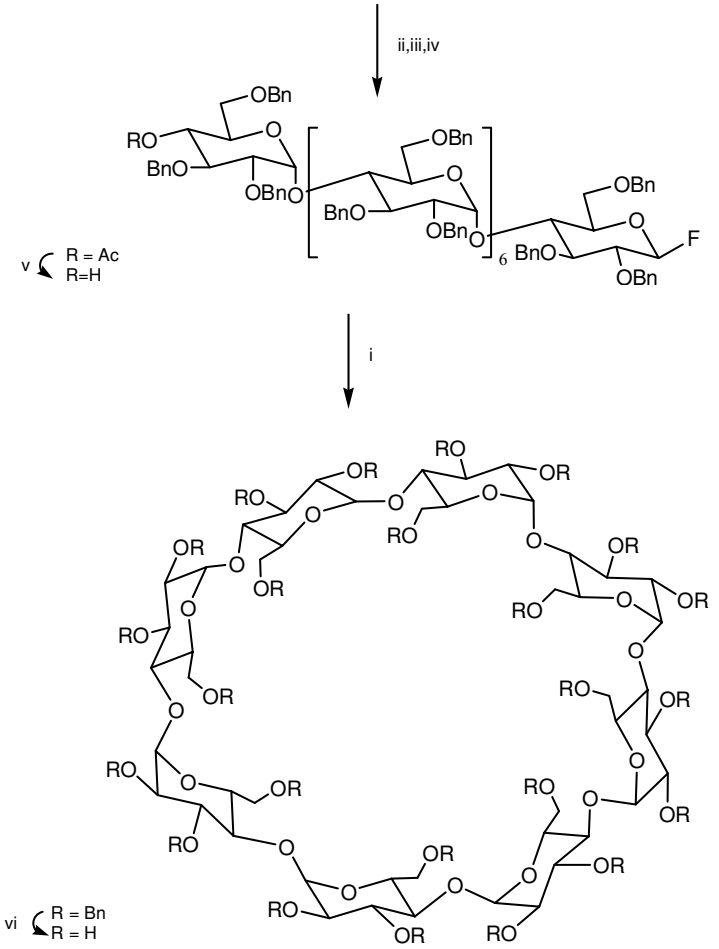


FIGURE 2.87. Chemical synthesis of cyclic α(1→4)-oligosaccharide γ-CD.



i) $SnCl_2$/AgOTf. ii) $PdCl_2$/AcOH. iii) SO_2Cl_2/DMF. iv) AgF/MeCN. v) NaOMe/MeOH/THF. vi) H_2, Pd-C, THF-MeOH/H_2O.

FIGURE 2.87. (*continued*)

the availability and affordability, however. Some enzymes such as glycosidases and cycloglycosyltransferases (CGTases) that are involved in the preparation of cyclodextrins from starch and other α-(1→4)-glucans are accessible and more versatile.[95]

The feasibility of the chemoenzymatic approach was established in the preparation of cyclic β(1→4) hexa-, hepta- 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 was obtained (Figure 2.91).[96]

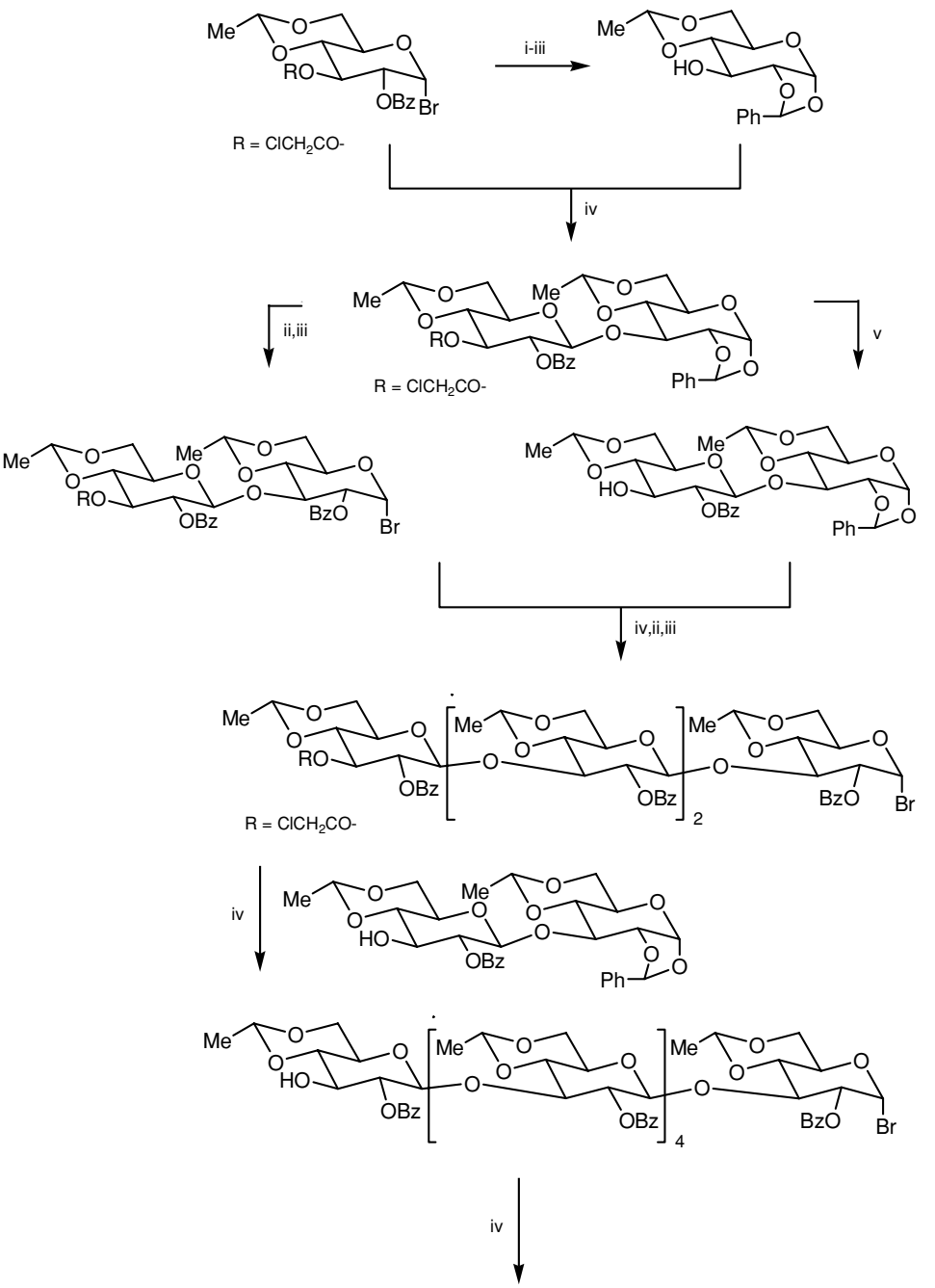


FIGURE 2.88. Synthesis of cyclic β-(1→3)-linked oligosaccharide.

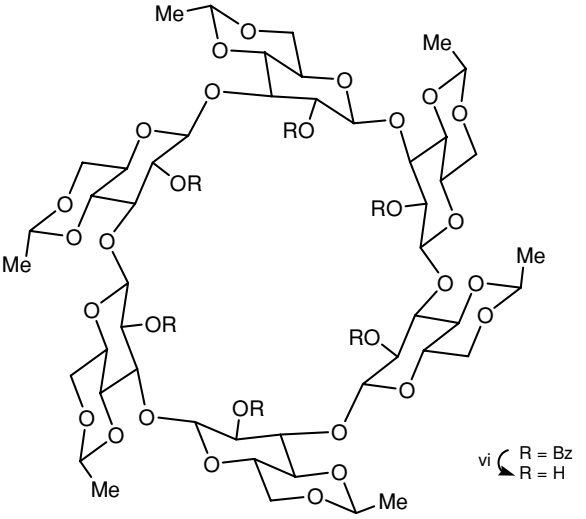


FIGURE 2.88. (*continued*)

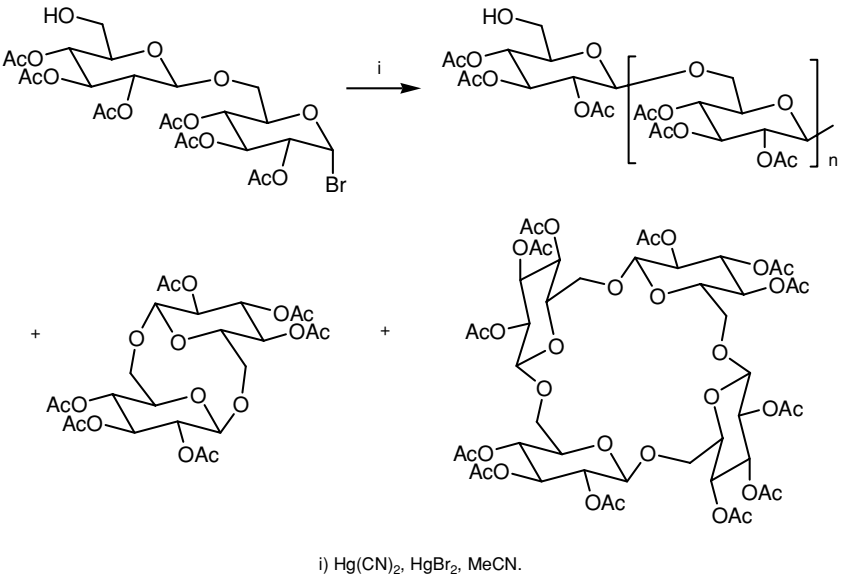
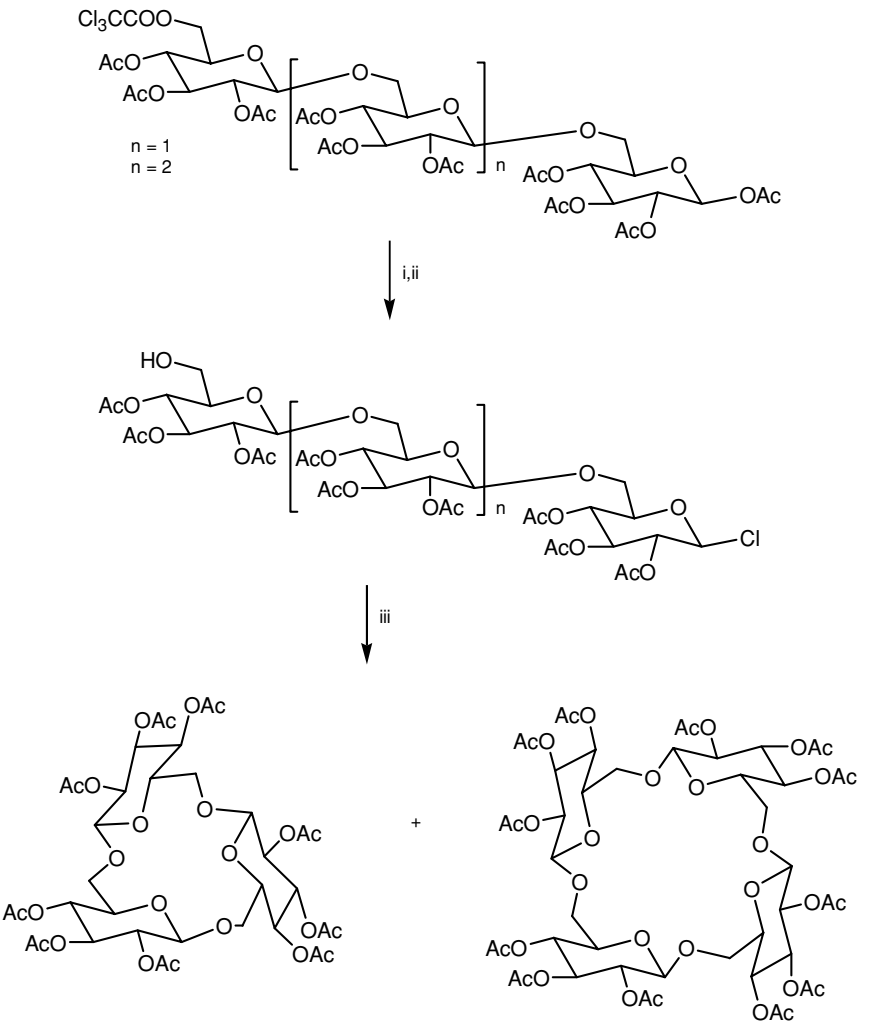


FIGURE 2.89. Preparation of linear and cyclic β(1→6) di- and tetrasaccharides.



i) Cl_2CHOMe, $BF_3.Et_2O$/DCE. ii) $HgBr_2$/DCE, MS.

FIGURE 2.90. Improved synthesis of cyclic β(1→6) tri- and tetrasacharides.

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% (Figure 2.92).[97]

An alternative option for the enzymatic preparation of cyclic oligosaccharides besides CGTases are glycosidases, which exert their action on polysaccharides. This possibility was exploited in the preparation of cyclic fructins by conversion of β-(1→2)-fructofuranan by bacterial fructotransferases isolated from *Bacillus circulans* (Figure 2.93).[98]

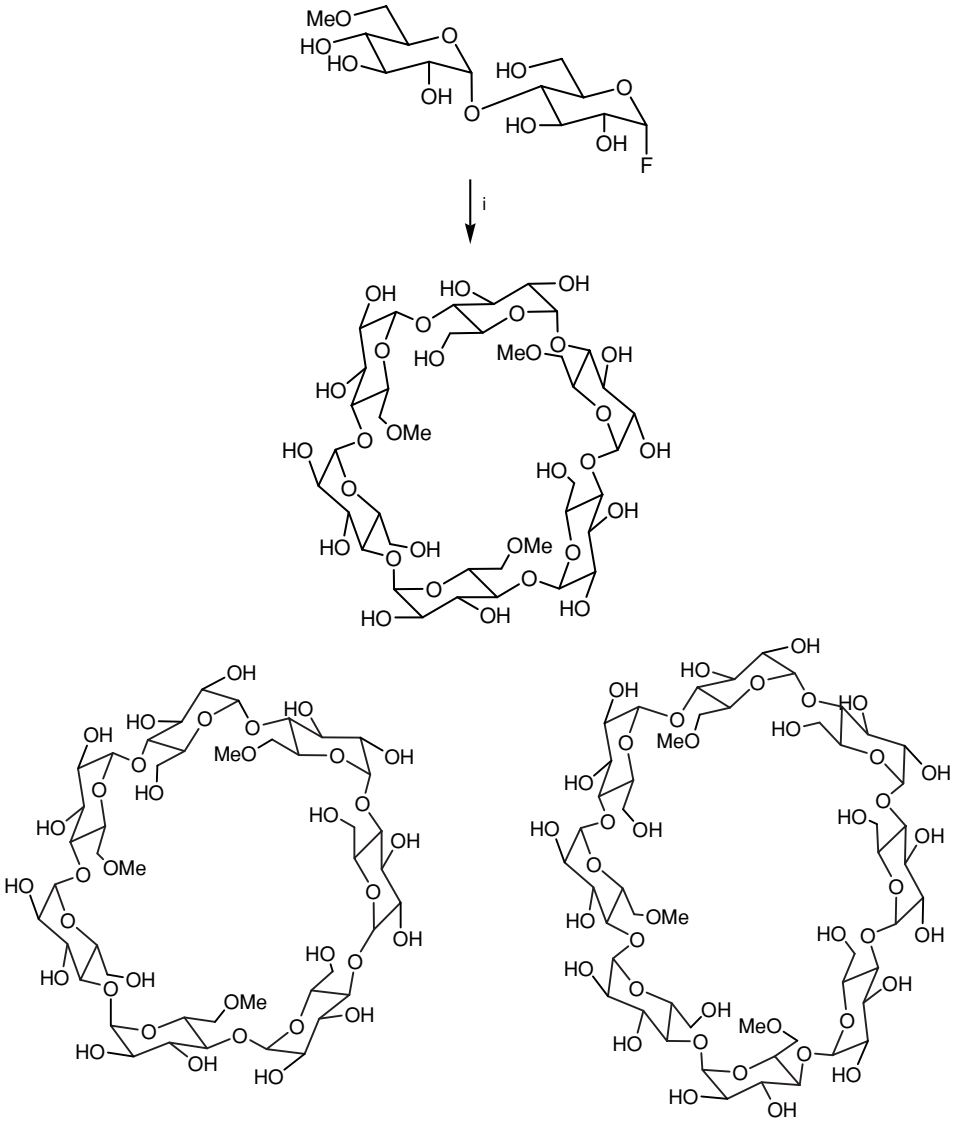


FIGURE 2.91. Synthesis of of 6^{I}, 6^{III}, 6^{V}-tri-O-methyl-α-CD, 6^{I}, 6^{III}, 6^{V}-tetra-O-methyl-γ-CD and 6^{I}, 6^{III}, 6^{V}-tri-O-methyl-β-CD.

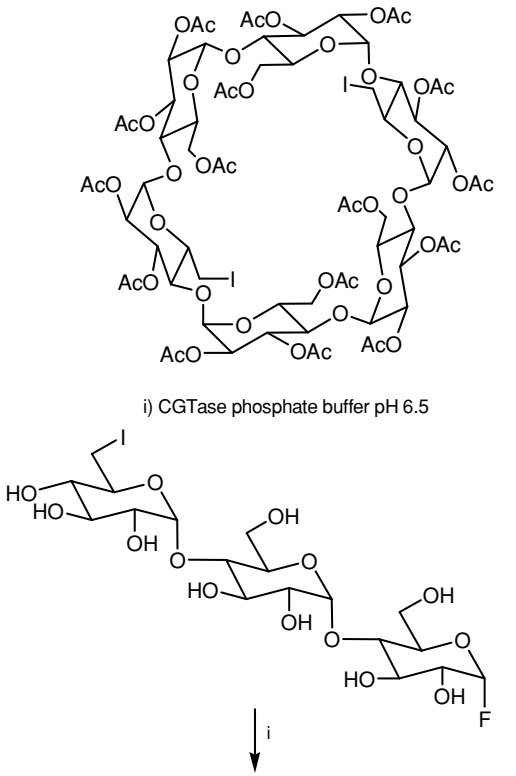


FIGURE 2.92. Enzymatic synthesis of 6^{I}, 6^{II}-dideoxy-6^{I},6^{II}-diiodo-α-CD.

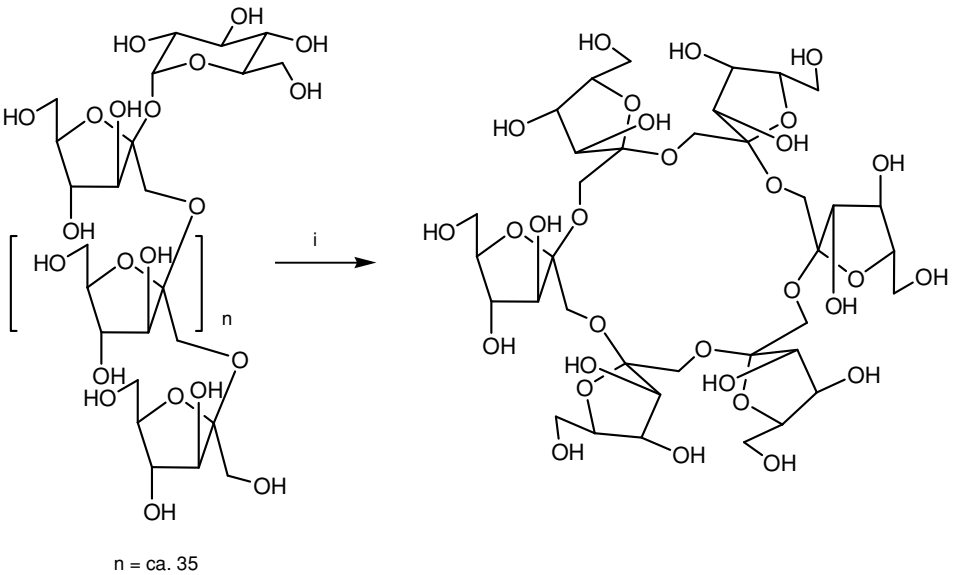
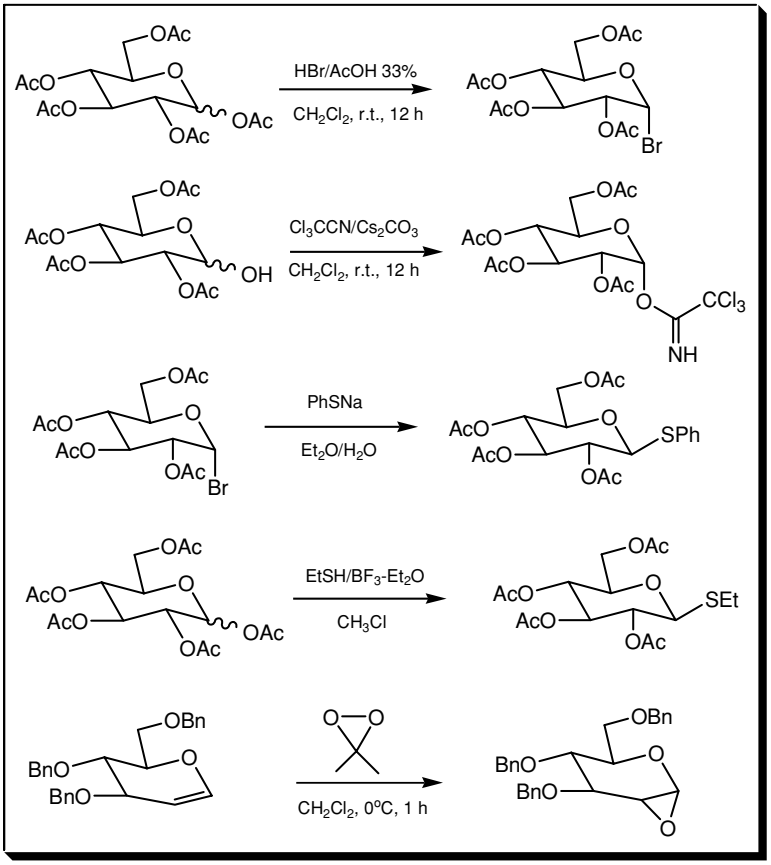


FIGURE 2.93. Enzymatic synthesis of cycloinulooligosaccharides.

Summary of Preparation of the Main Glycosyl Donors



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