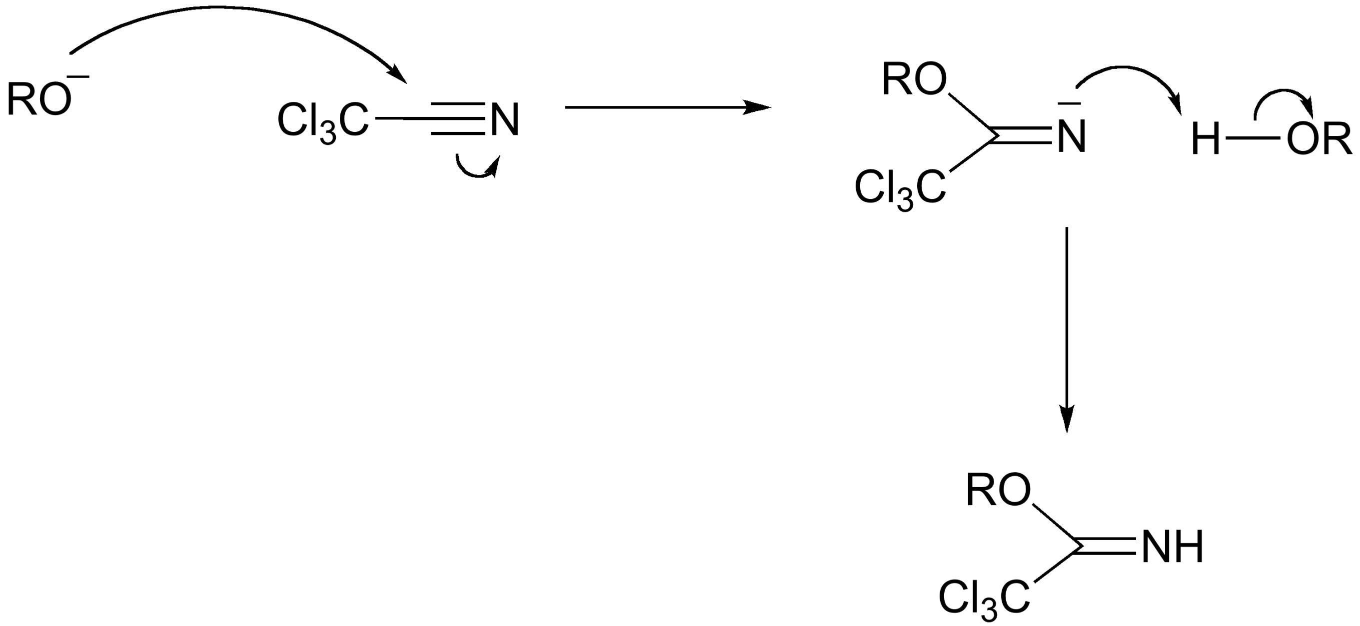
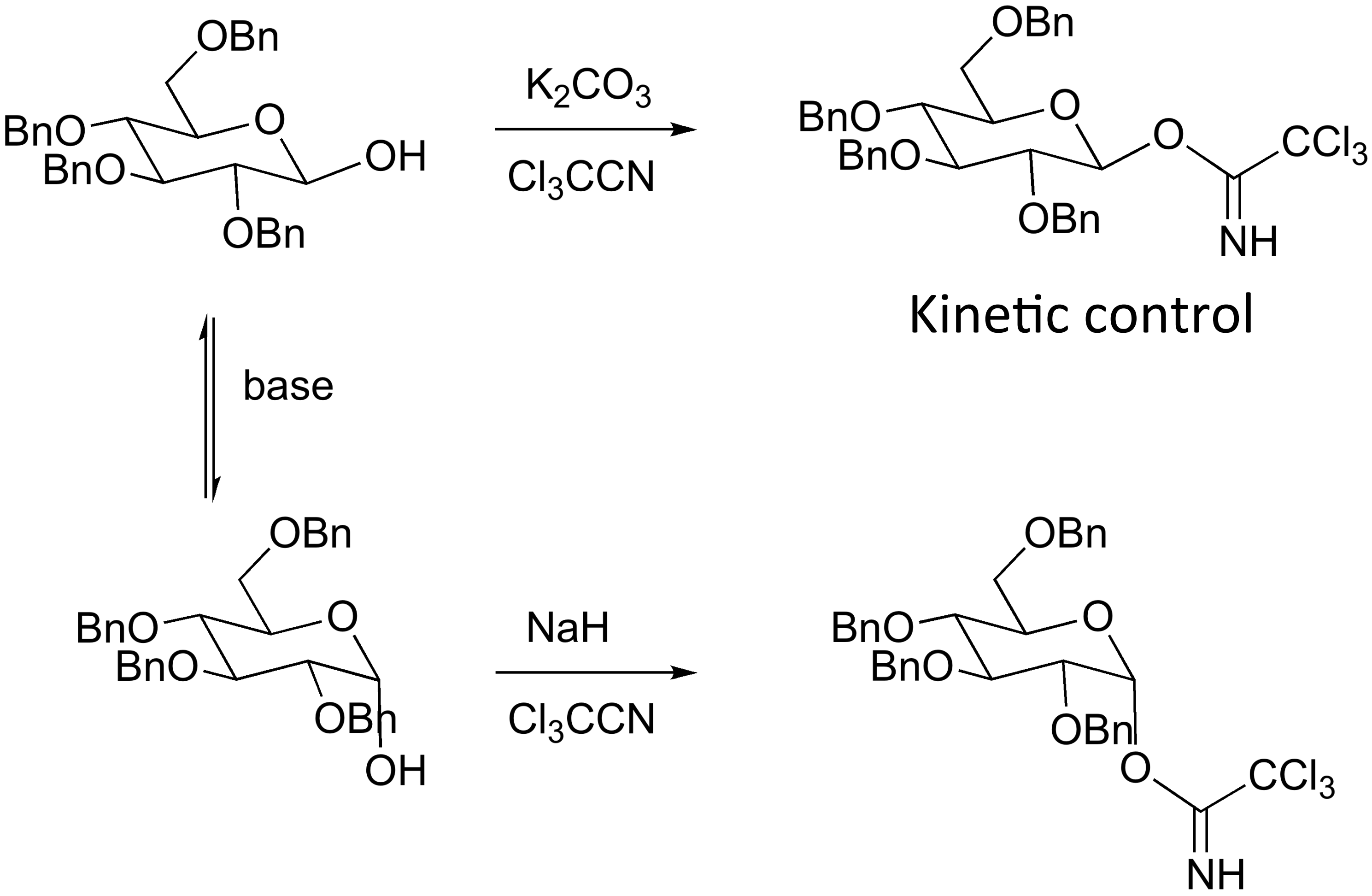
# 9.1 Chemical disaccharide formation -2

# 3.5 Trichloroacetimidates

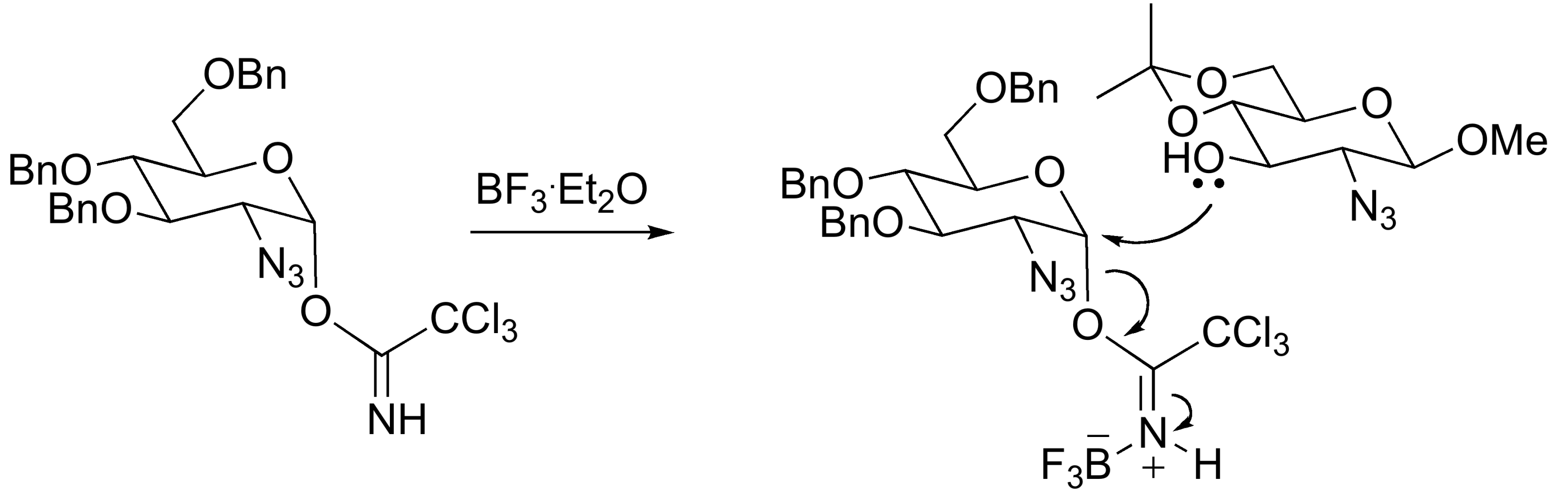


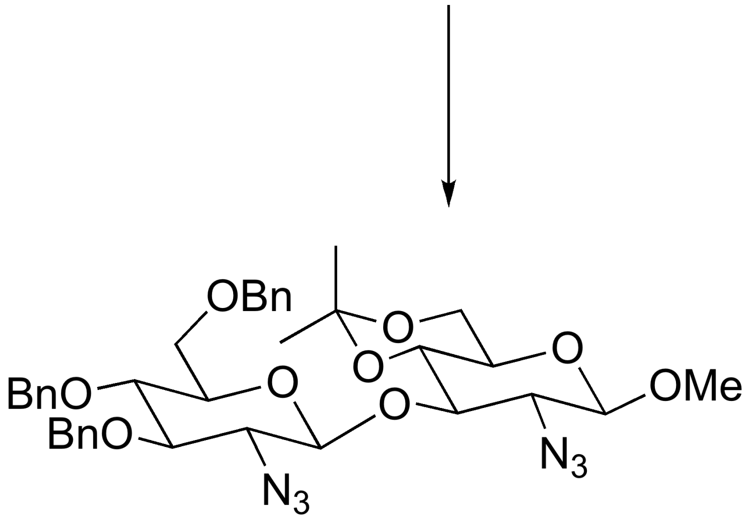
Similarity between anomeric trichloroacetimidate formation and the acetylation rxns, either the $\alpha$- or $\beta$-anomeric acetates could be formed preferentially under different rxn conditions



Kinetic control

Thermodynamic control



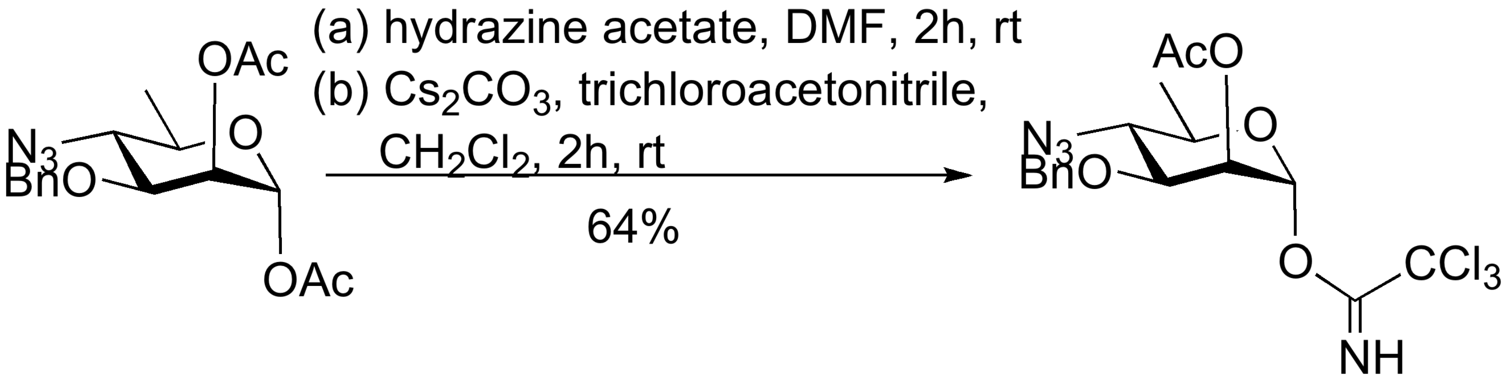


Non-neighbouring group participation

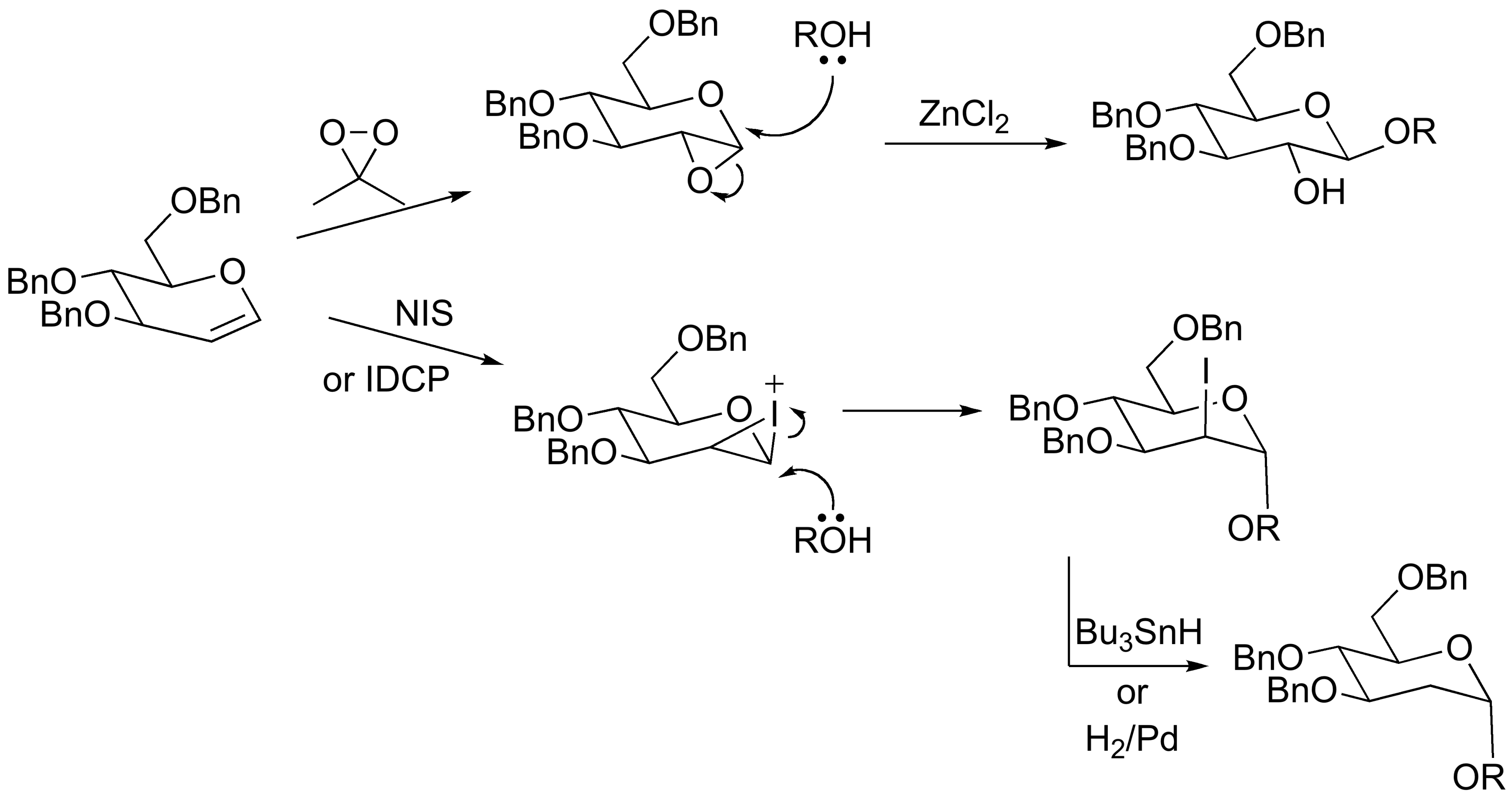
$S_N2$ type rxn

Inversion of configuration

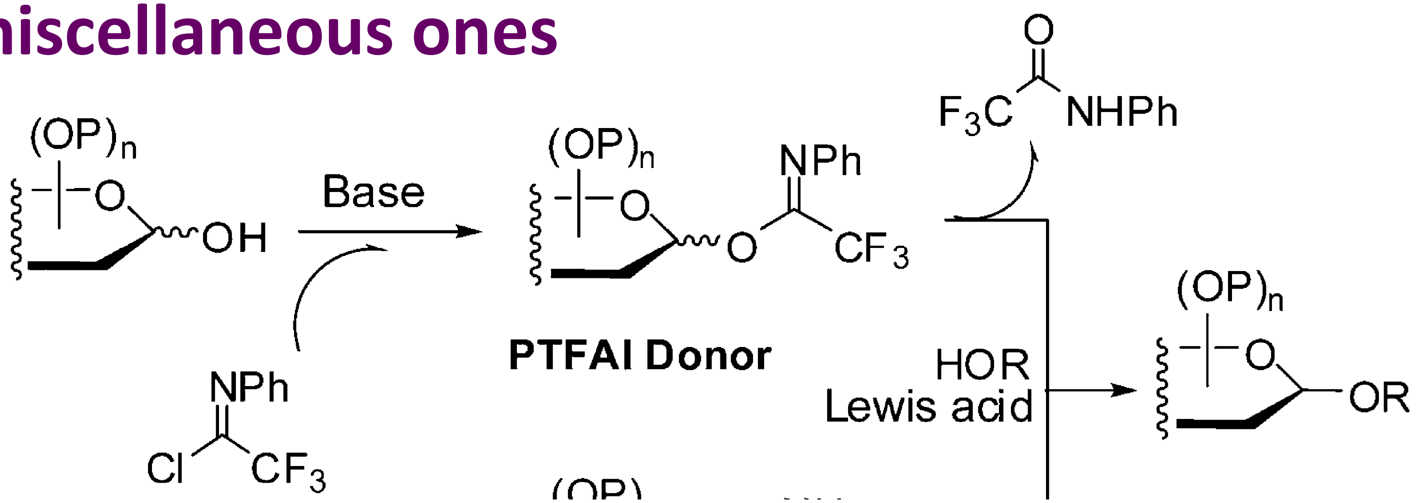
Neighbouring group participation SN1 rxn

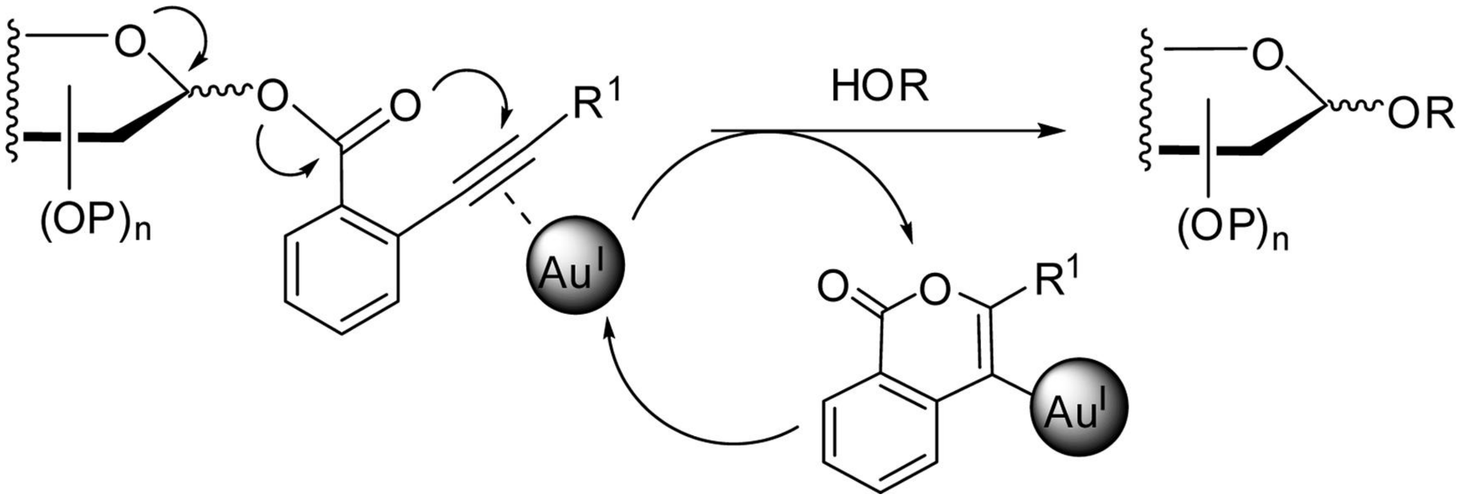

OAc
N3
BnO
O
OAc
(a) hydrazine acetate, DMF, 2h, rt
(b) Cs2CO3, trichloroacetonitrile,
CH2Cl2, 2h, rt
64%
AcO
N3
BnO
O
O
CCl3
NH

# 3.6 Glycals



# 3.7 miscellaneous ones



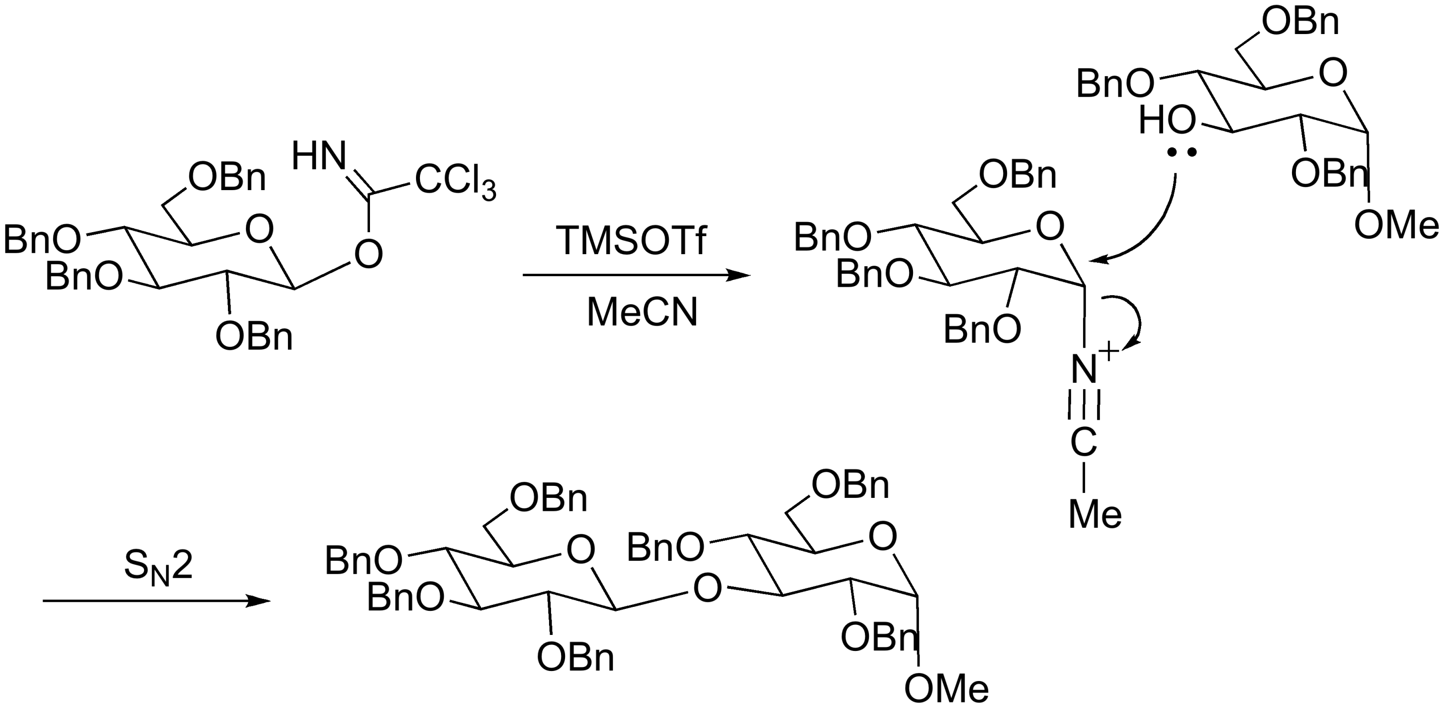


B. Yu, Acc. Chem. Res. 2012 doi 10.1021/ar200296m

# 4 Control of stereochemistry

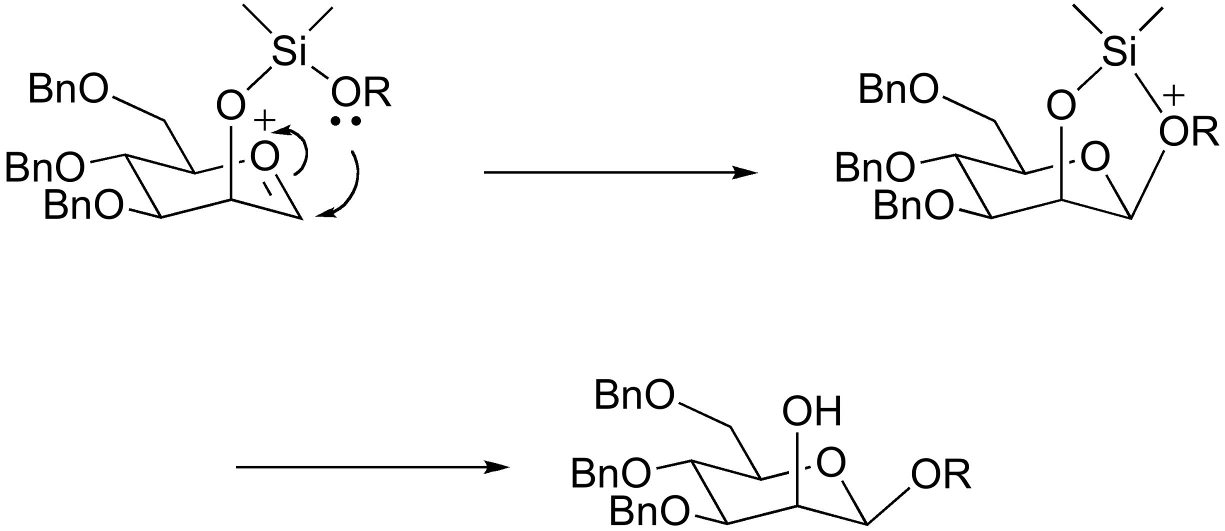
## 4.1 Neighbouring group participation

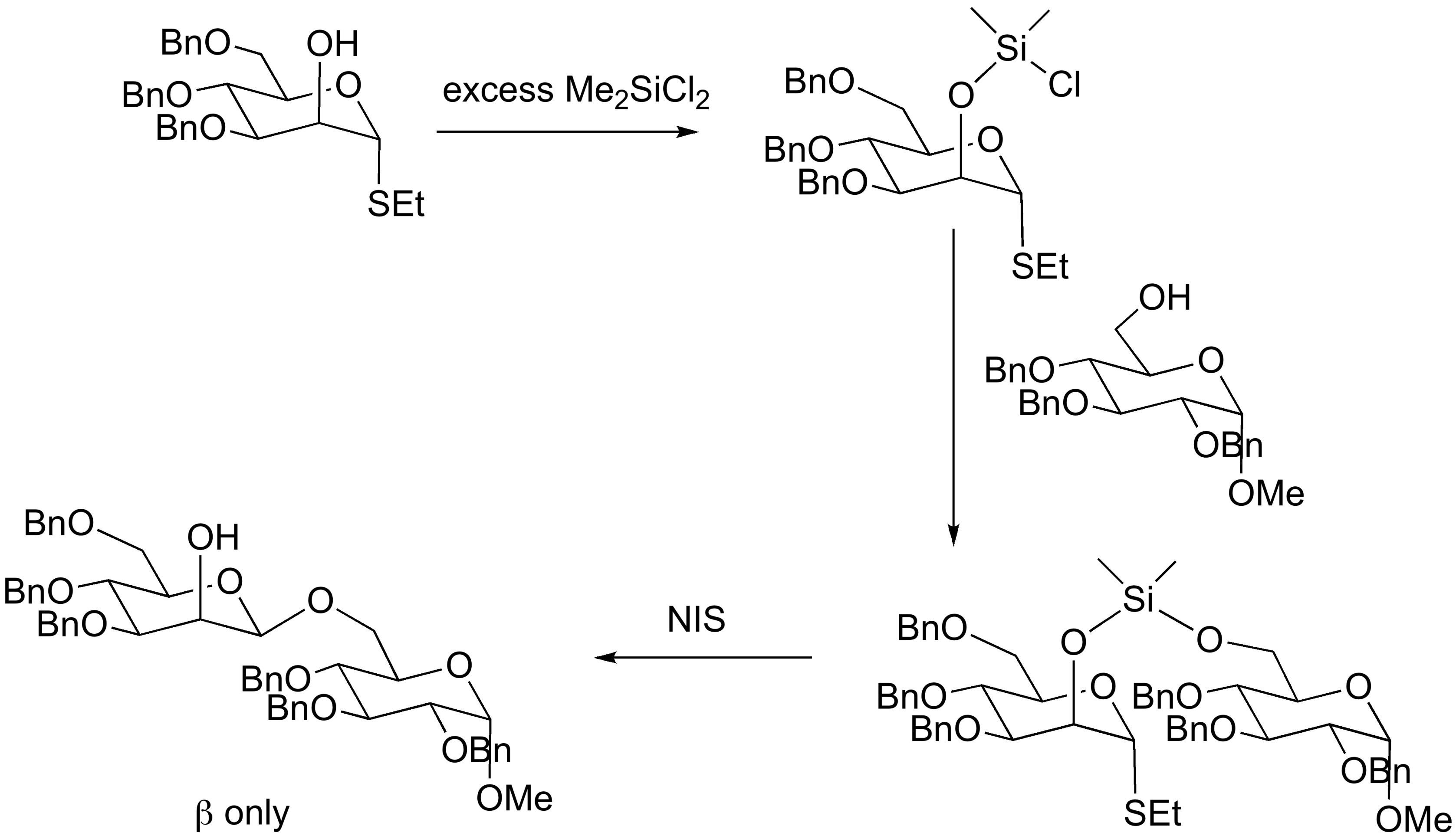
## 4.2 Solvent



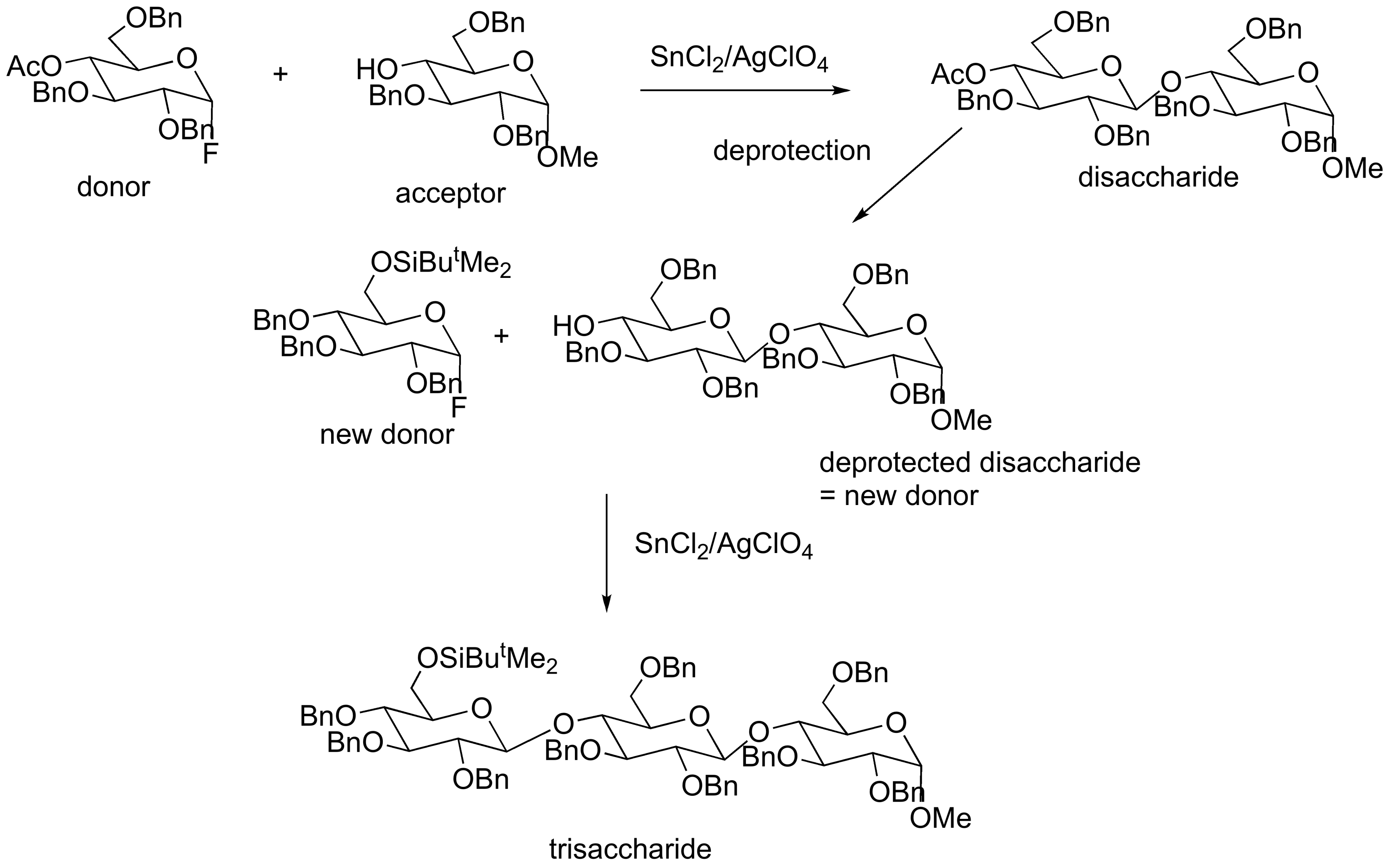
α:β = 24:1

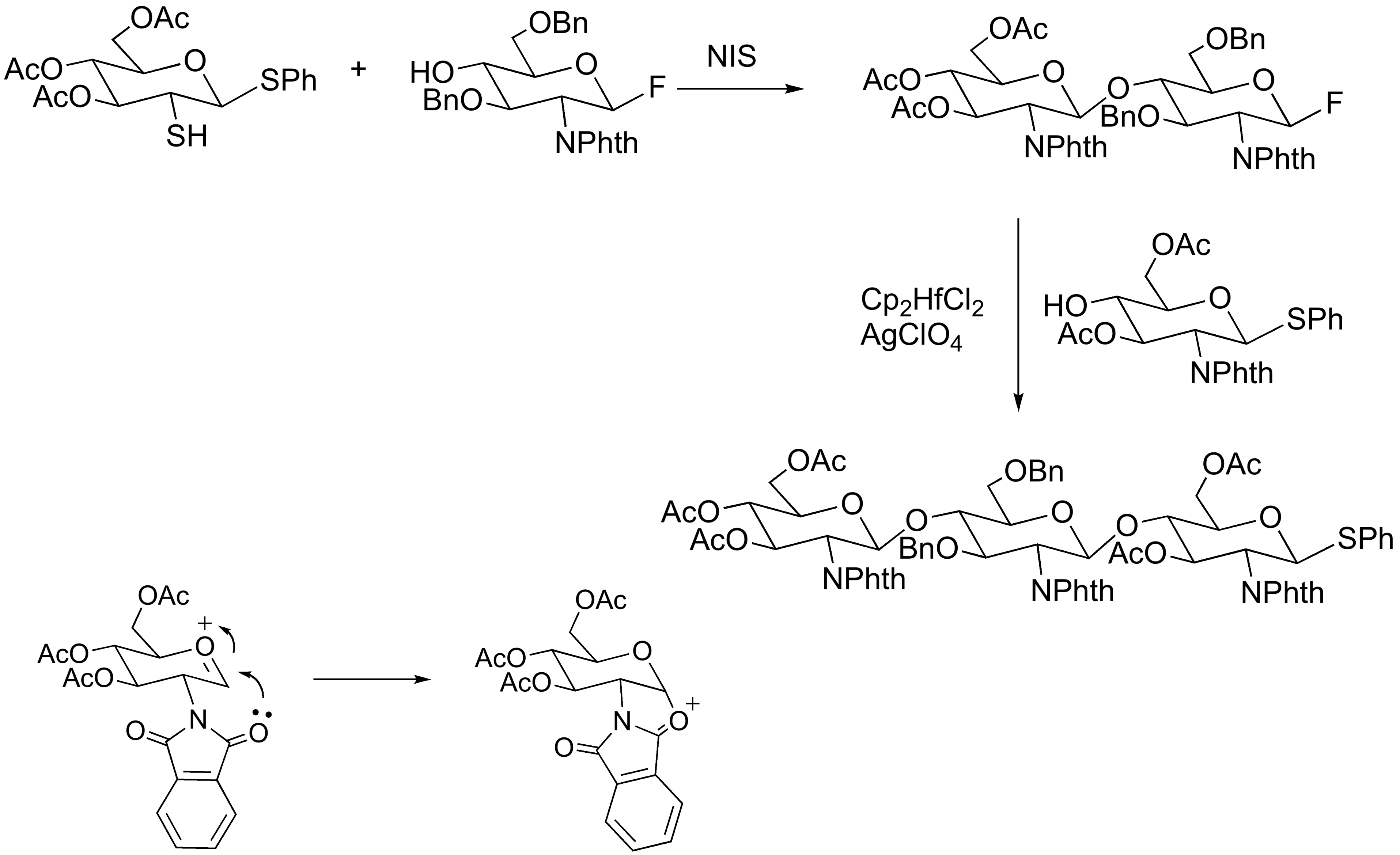
# 4.3 Molecular tethering ---- intramolecular aglycon delivery (IAD)




excess Me$_2$SiCl$_2$
NIS
β only

# 5 Oligosaccharide synthesis




OAc
AcO
AcO
O
SPh
SH
+
OBn
HO
BnO
O
F
NPhth
NIS
OAc
AcO
AcO
O
O
OBn
O
F
BnO
NPhth
NPhth
$Cp_2HfCl_2$
$AgClO_4$
OAc
HO
AcO
O
SPh
NPhth
OAc
AcO
AcO
O
O
OBn
O
BnO
O
OAc
O
AcO
SPh
NPhth
NPhth
NPhth
OAc
AcO
AcO
O
+
N
O
O
OAc
AcO
AcO
O
N
O
+
O

# 6 Solid phase synthesis

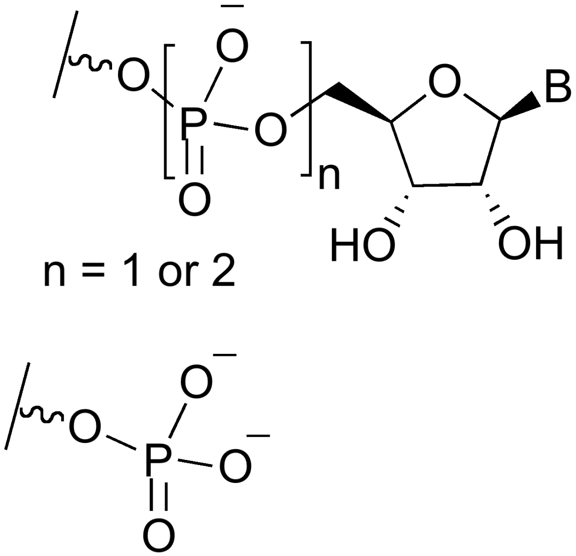
# 9.2 Enzymatic disaccharide formation

## 1 Tackling the problems of chemical disaccharide formation

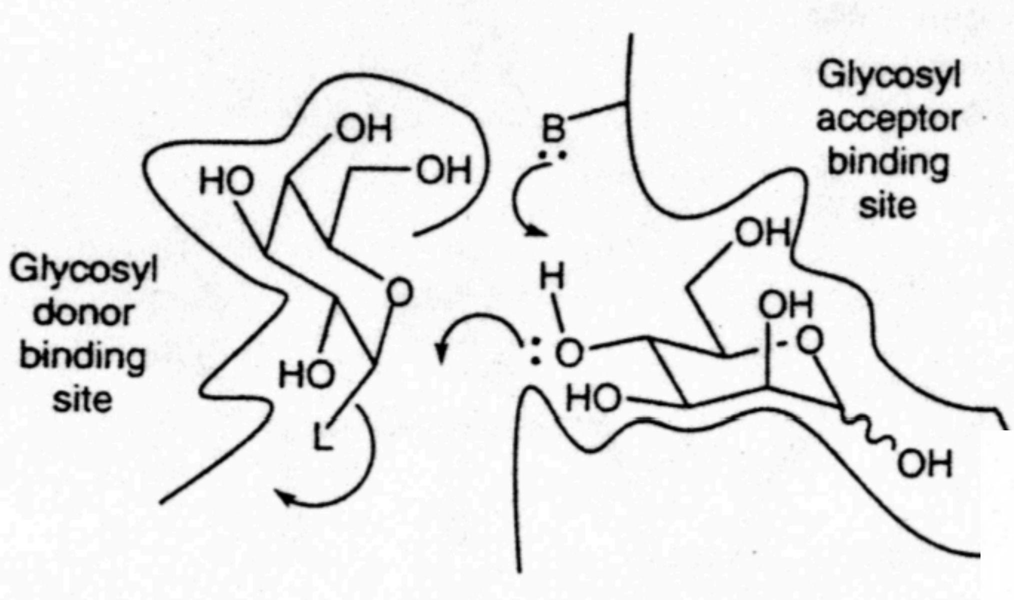
## 2 Glycosyltransferases and glycosidases

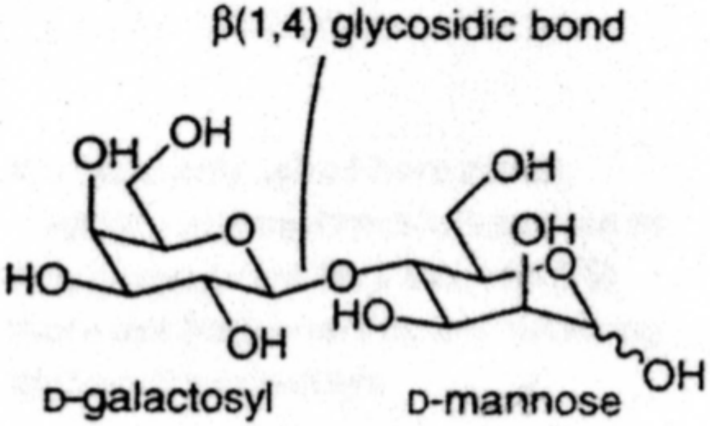
## 3 The mechanism of action of carbohydrate processing enzymes

LG =



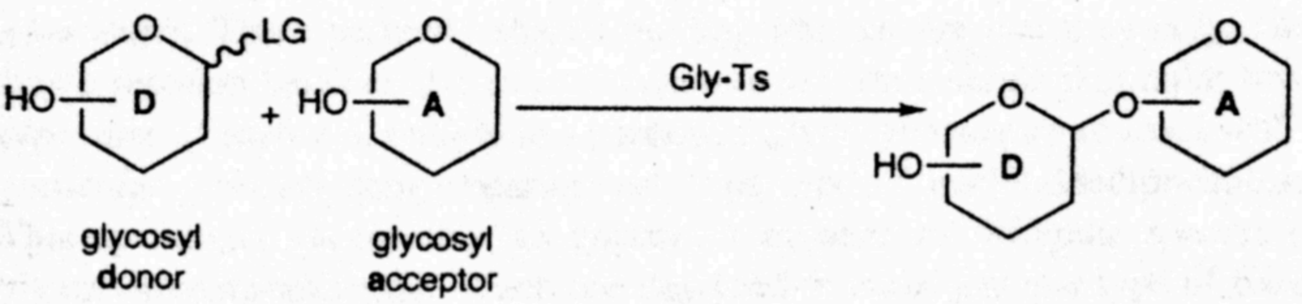
# 3 The mechanism of action of carbohydrate processing enzymes

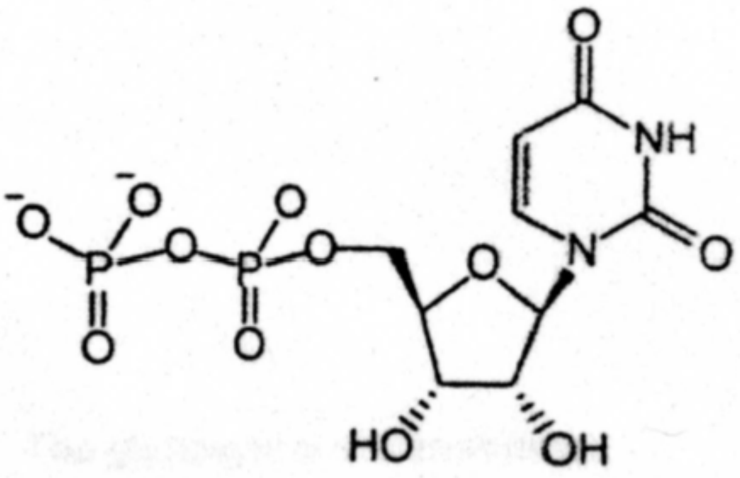




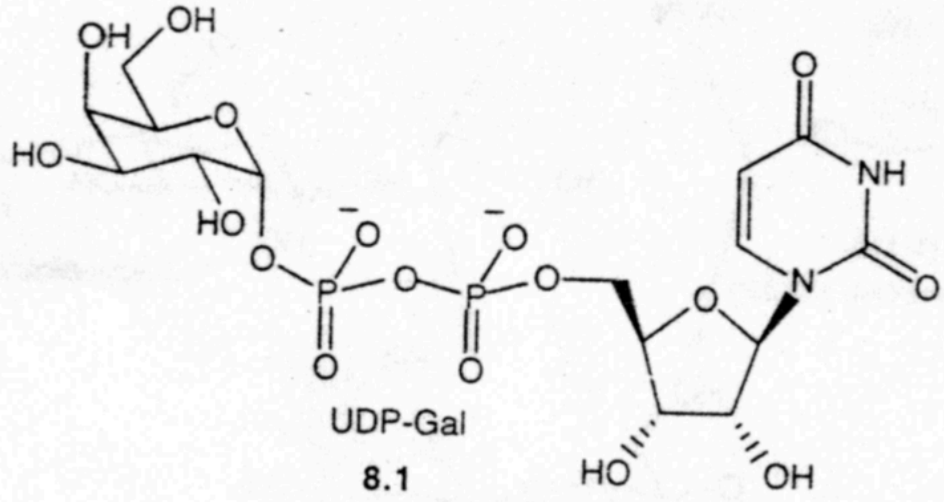
4-*O*-(β-D-galactopyranosyl)-D-mannopyranose

# 4 Glycosyltransferases



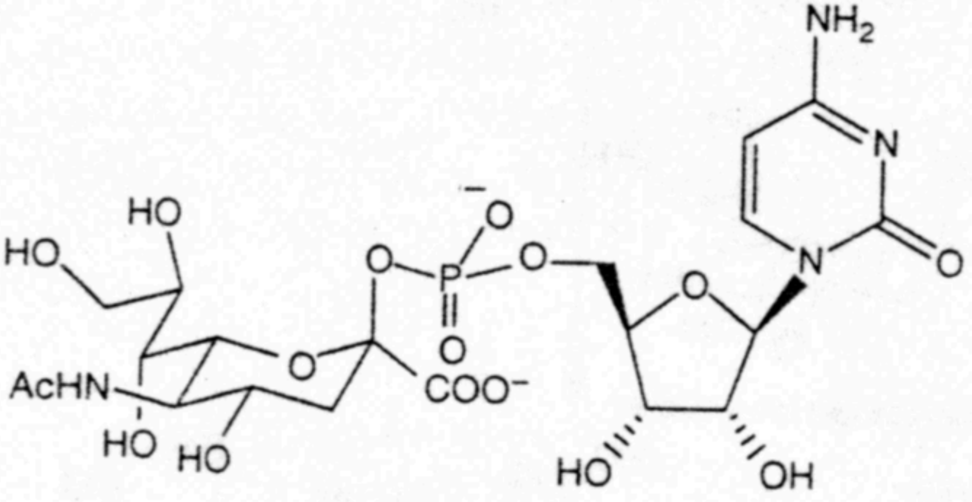


uridine diphosphate—a nucleotide

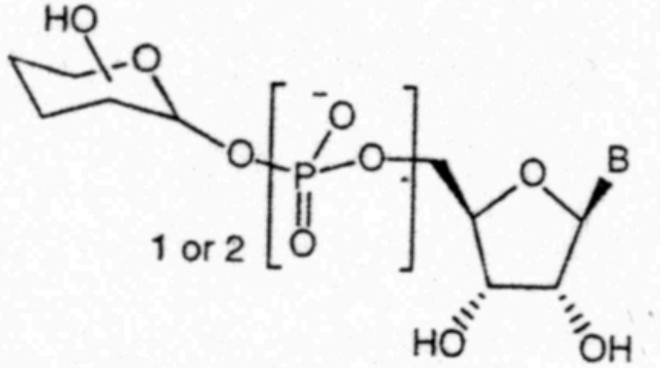


UDP-Gal

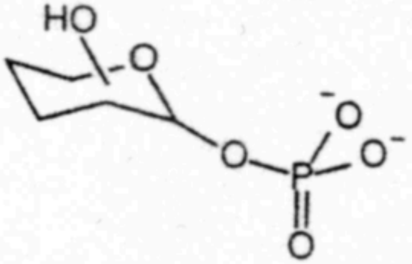
**8.1**



CMP-sialic acid

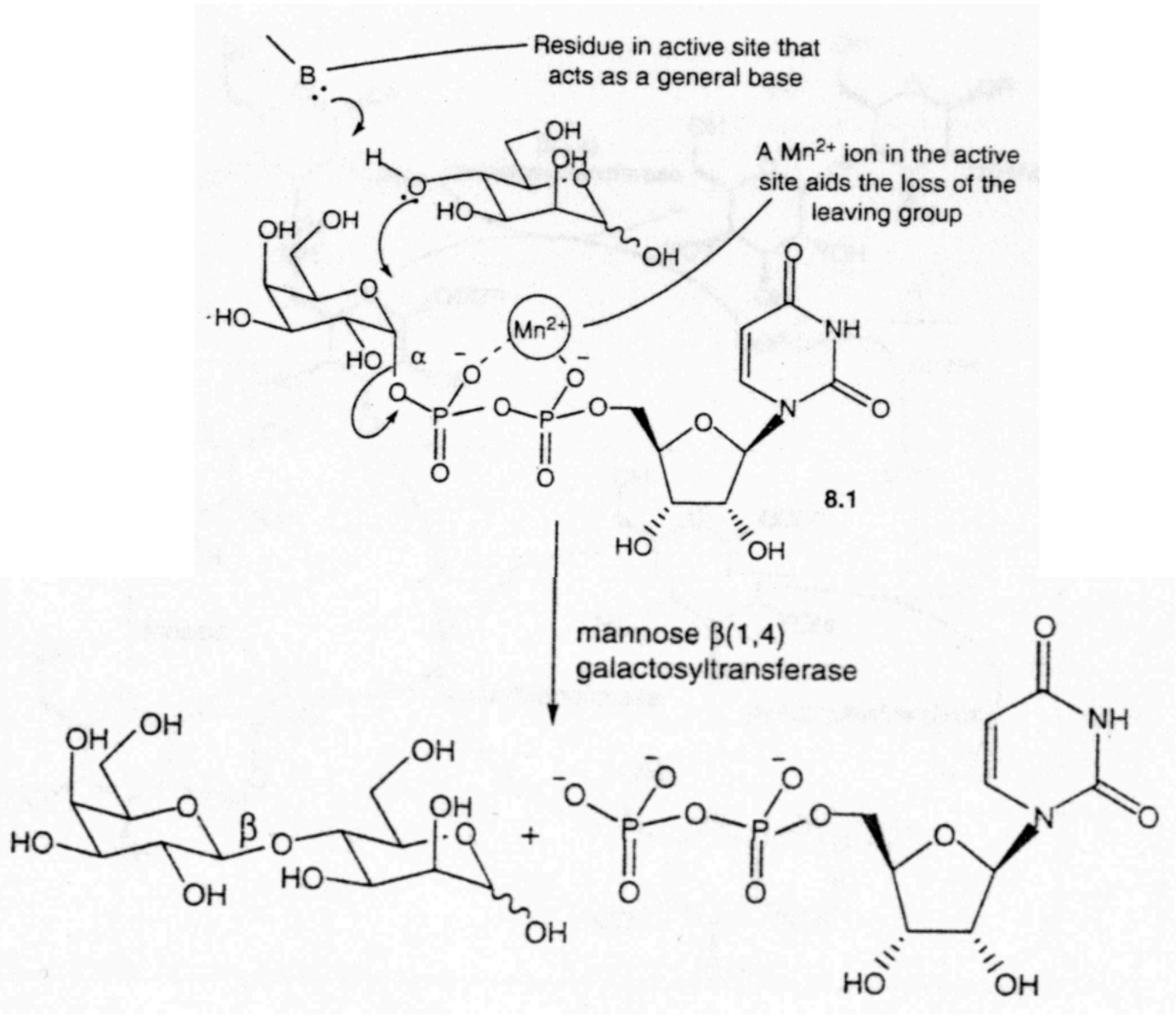


**8.3**



**8.4**

where B = appropriate purine or pyrimidine base of A, C, T, G, U.

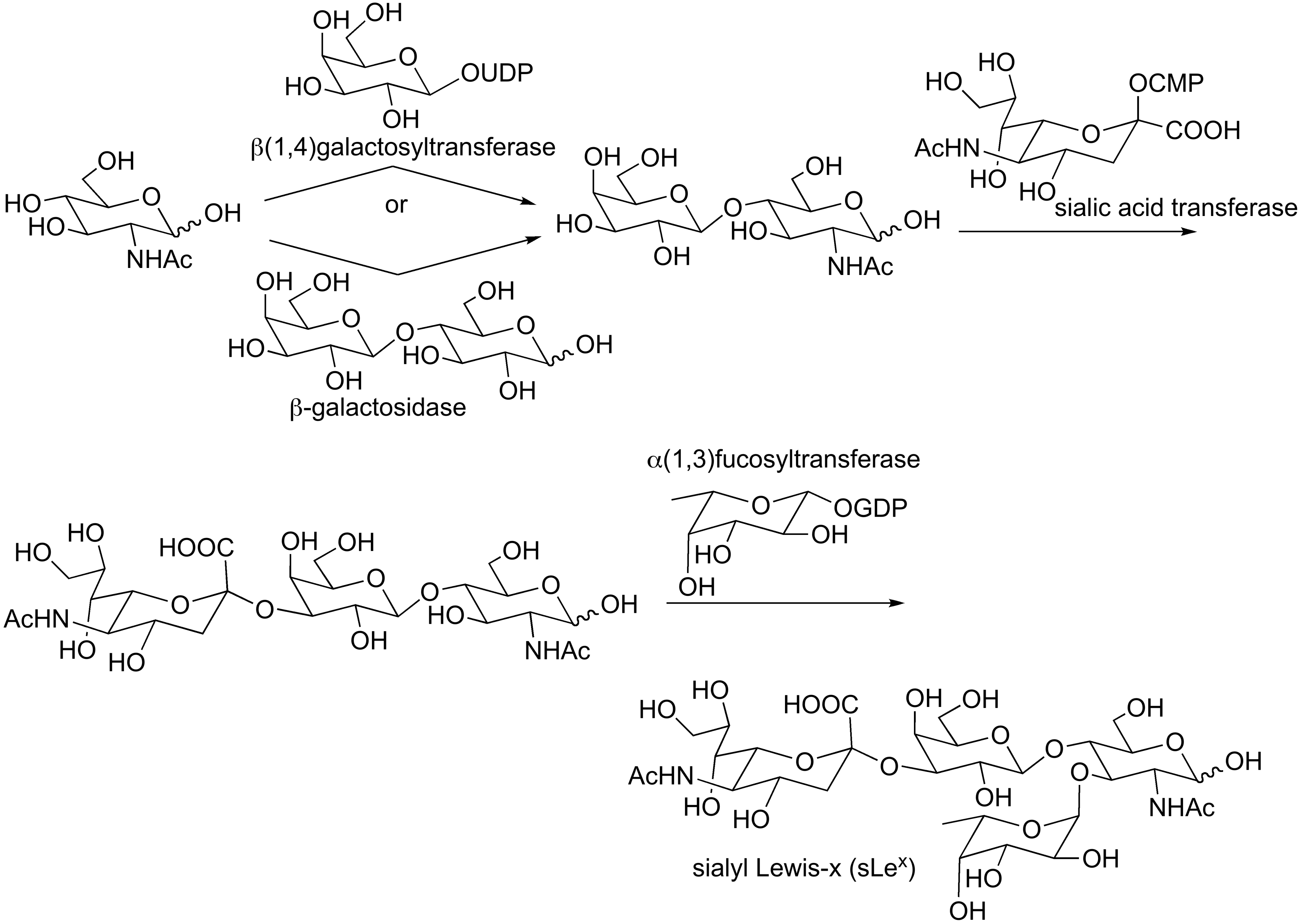


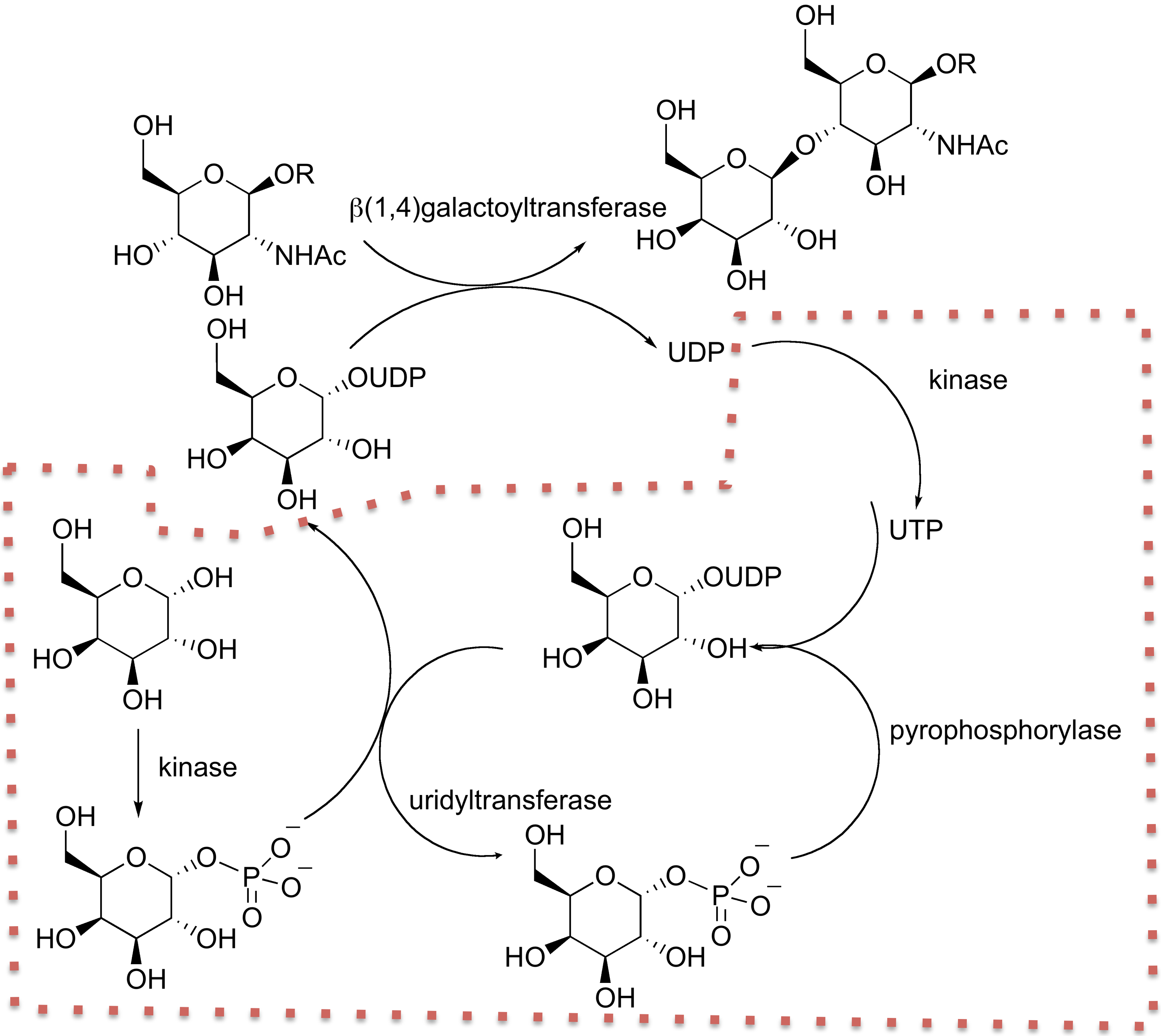
Residue in active site that acts as a general base

A $Mn^{2+}$ ion in the active site aids the loss of the leaving group

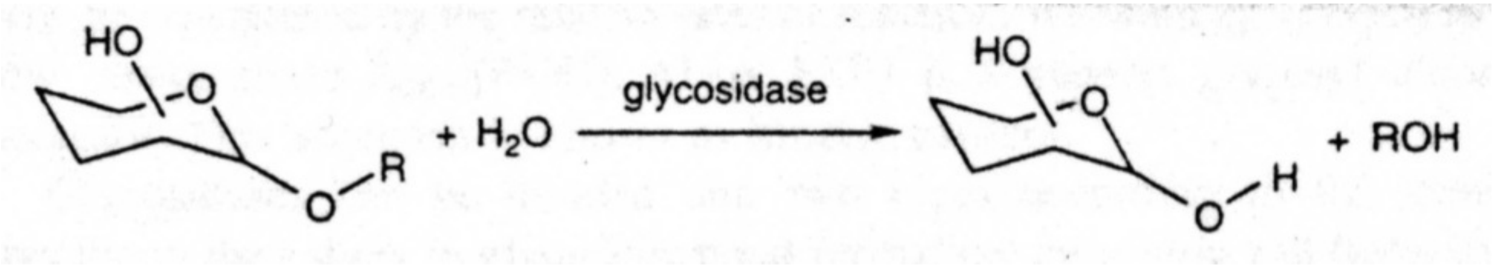
8.1

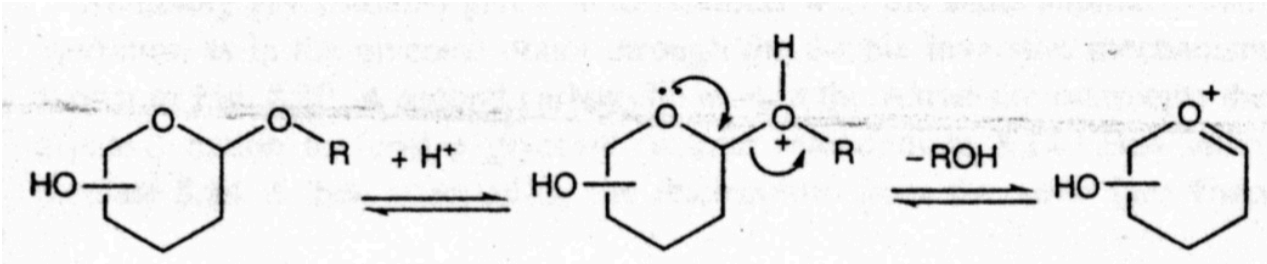
mannose β(1,4) galactosyltransferase

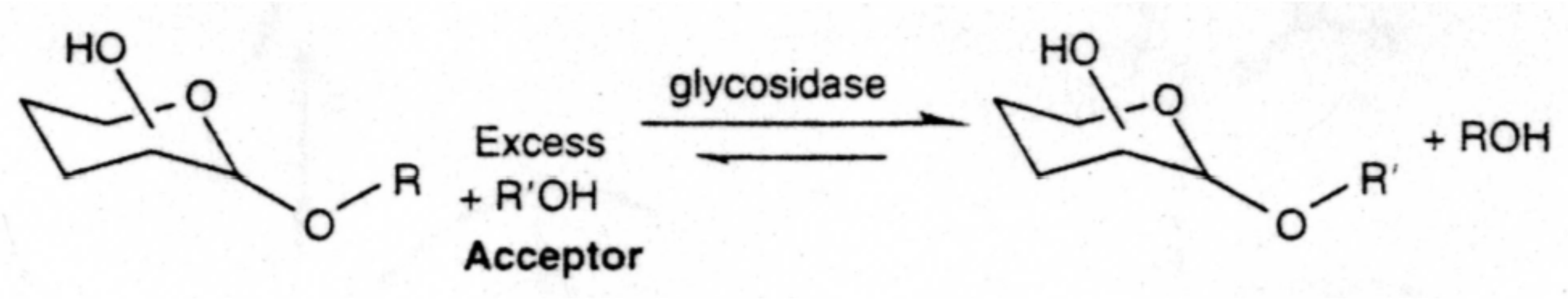

β(1,4)galactosyltransferase
OUDP
or
β-galactosidase
sialic acid transferase
OCMP
COOH
AcHN
NHAc
HOOC
α(1,3)fucosyltransferase
OGDP
sialyl Lewis-x (sLe$^x$)

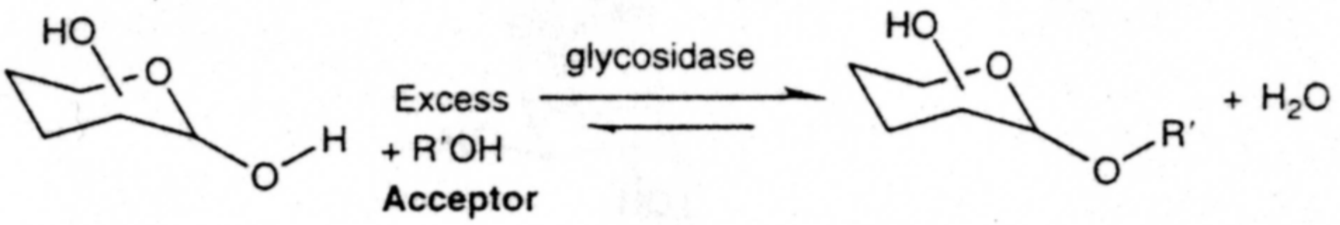

β(1,4)galactoyltransferase
UDP
kinase
UTP
pyrophosphorylase
kinase
uridyltransferase
OR
NHAc
OUDP
OH
HO

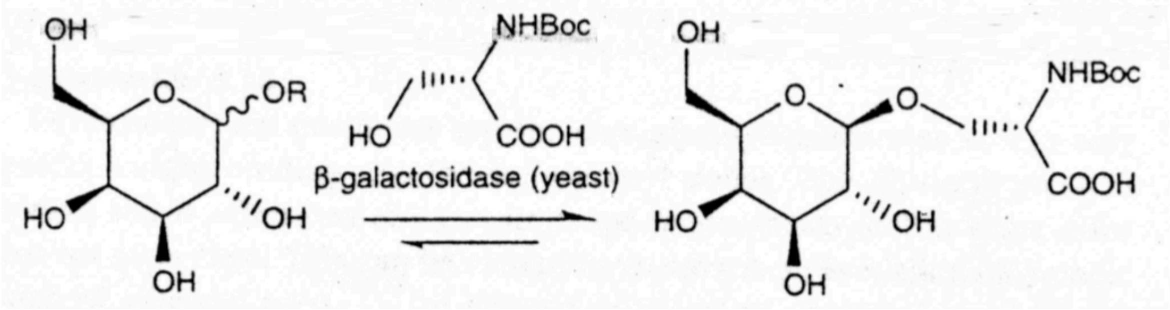
# 5 Glycosidases

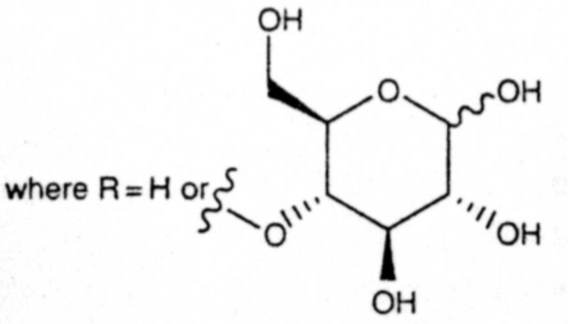


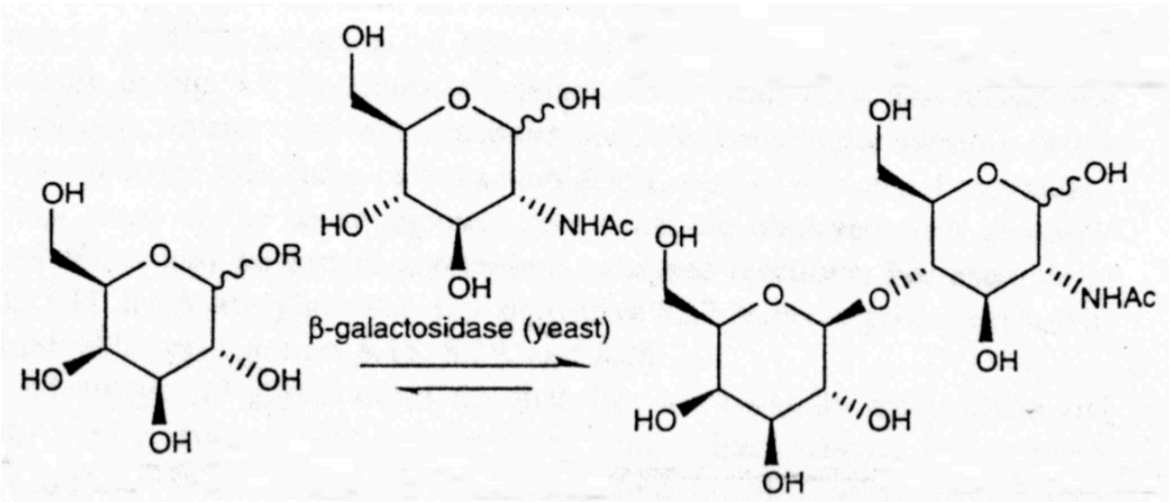


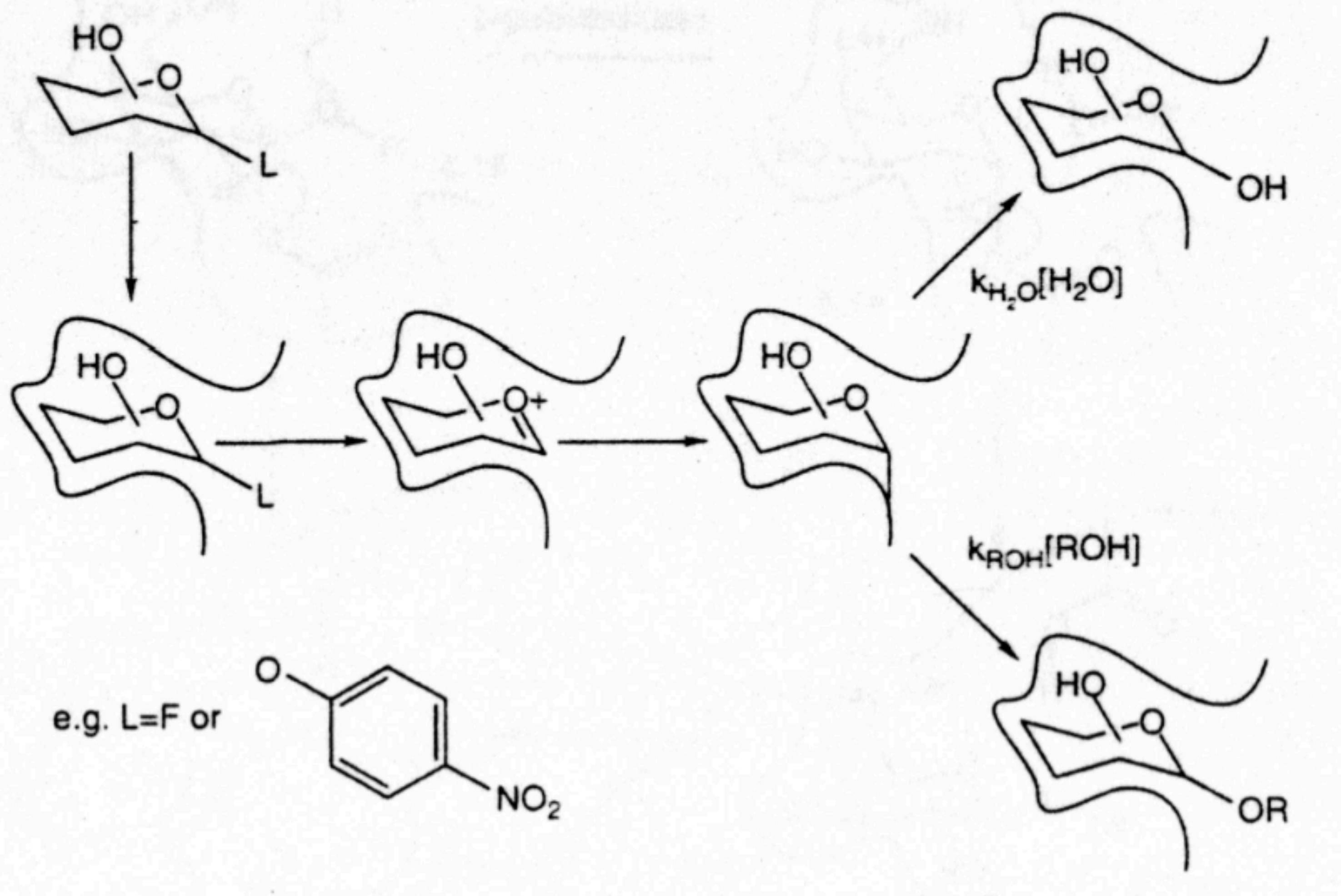


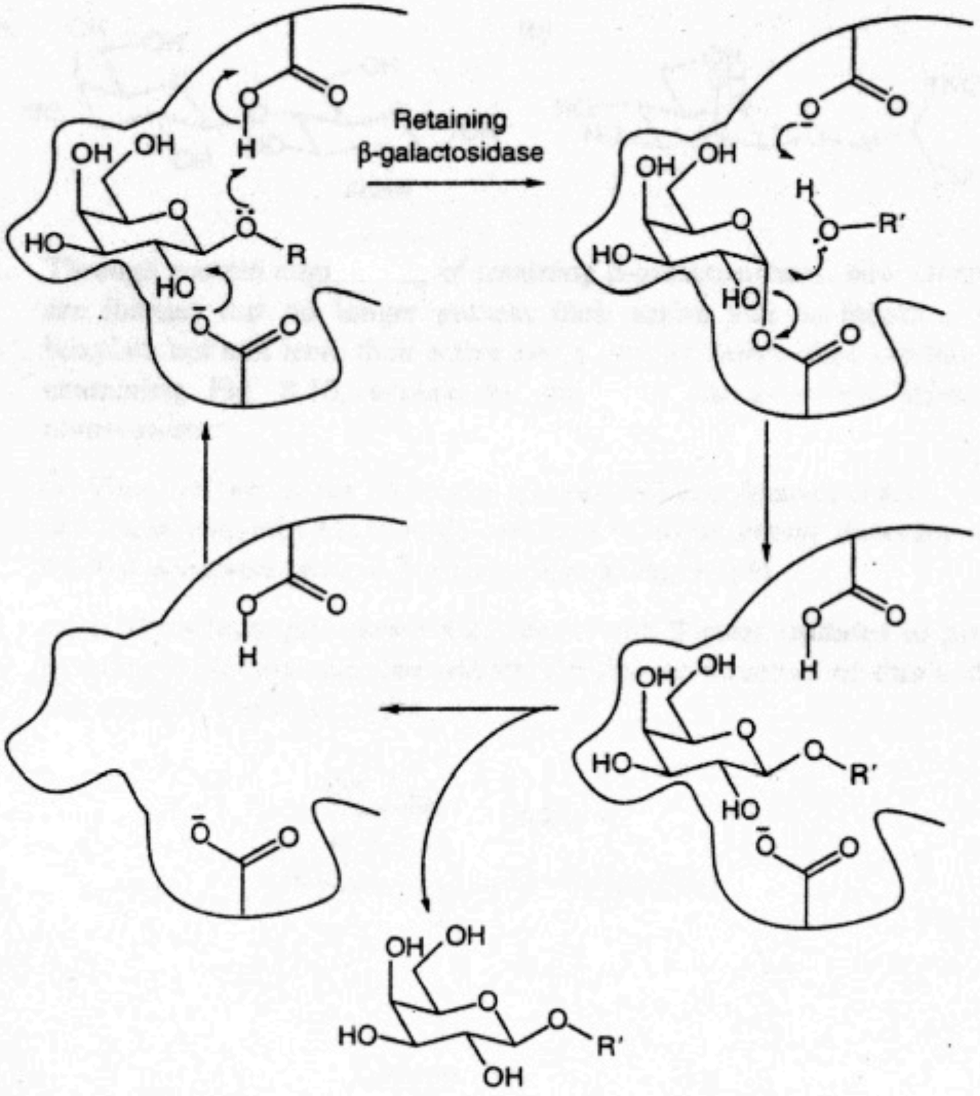

HO
O
O
H
Excess
+ R'OH
Acceptor
glycosidase
HO
O
O
R'
+ H₂O

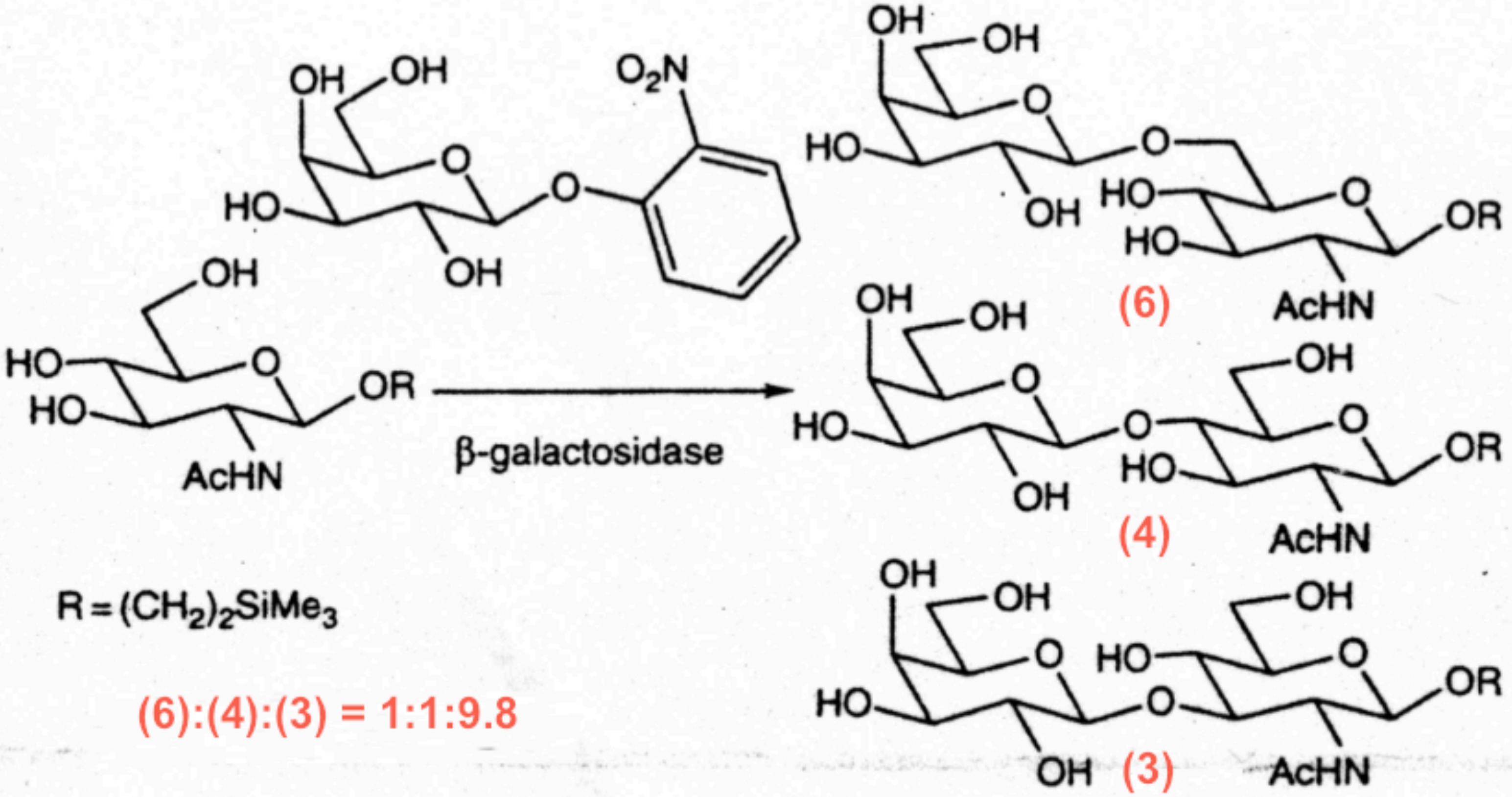

OH
O
OR
HO
OH
OH
NHBoc
HO
COOH
β-galactosidase (yeast)
OH
O
O
NHBoc
COOH
HO
OH
OH


where R = H or
OH
O
OH
O
OH
OH


OH
O
OR
HO
OH
OH
OH
O
OH
HO
NHAc
OH
β-galactosidase (yeast)
OH
O
OH
NHAc
OH
OH
O
O
HO
OH
OH


HO
O
L
O+
OH
$k_{H_2O}[H_2O]$
$k_{ROH}[ROH]$
OR
e.g. L=F or
O
$NO_2$


Retaining
β-galactosidase
OH
OH
HO
HO
O
R
R′
H
O



$R = (CH_2)_2SiMe_3$

**(6):(4):(3) = 1:1:9.8**

# 6 Glycosidases *vs* glycosyltransferases

| | Glycosyltransferases | Glycosidases |
|---|---|---|
| Efficiency in disaccharide synthesis | Usually > 80% | Often ~40% |
| Specificity | For the glycosyl donor, glycosyl acceptor and the nucleotide leaving group | Only for the glycosyl donor and sometimes partially for the glycosyl acceptor |
| Ease of use | Need buffers, correct glycosyl donor, hard to isolate | Very robust, tolerant of conditions, easier to isolate |

# 7 chemoenzymatic synthesis

## 7.1 advantage

## 7.2 example one: one-pot three-enzymatic approach to synthesis sialic acid

## 7.3 example two: heparin

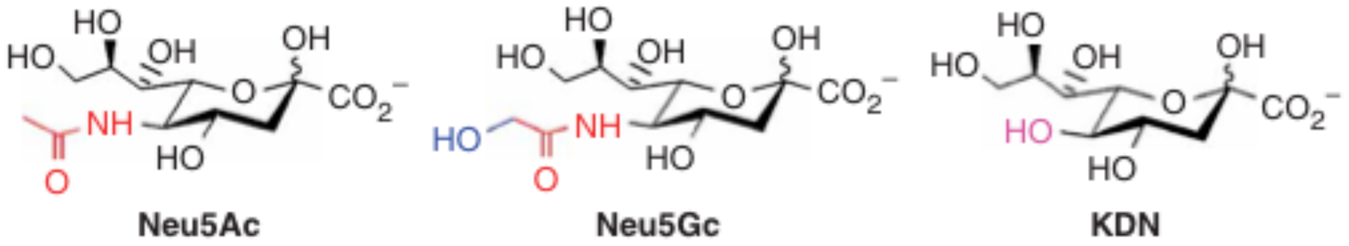


**Figure 1** | Three basic forms of naturally occurring sialic acids: Neu5Ac, Neu5Gc and KDN.

X. Chen, Nature Protocols 2006, 1, 2485
Robert J. Linhardt, Science 2011, 334, 498