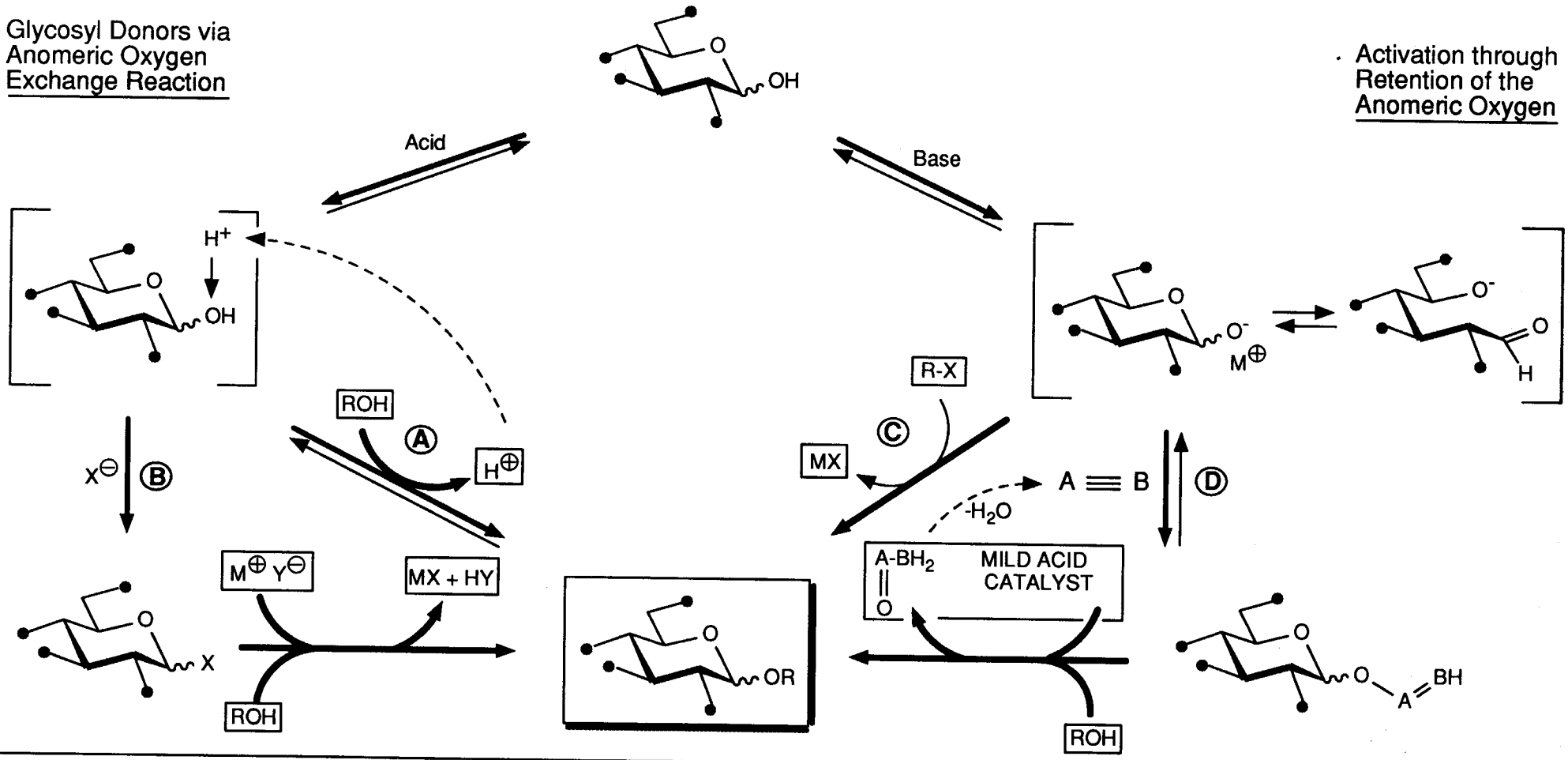
SYNTHESIS OF GLYCOSIDES AND SACCHARIDES

Glycosyl Donors via Anomeric Oxygen Exchange Reaction

Activation through Retention of the Anomeric Oxygen

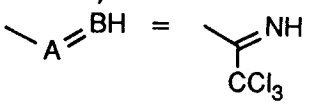


(A) Fischer - Helferich: (Acid Catalyzed Act.)

(B) Koenigs - Knorr : X = Cl, Br, (I) Activation
X = F-Activation
X = S-Activation

Glycosylation: "X-Philic" Promoter
(Generally: Heavy metal salts: Ag^{+}, Hg^{2+} etc)

(C) Anomeric O-Alkylation (Base Activation)

(D) Trichloroacetimidate Activation : 

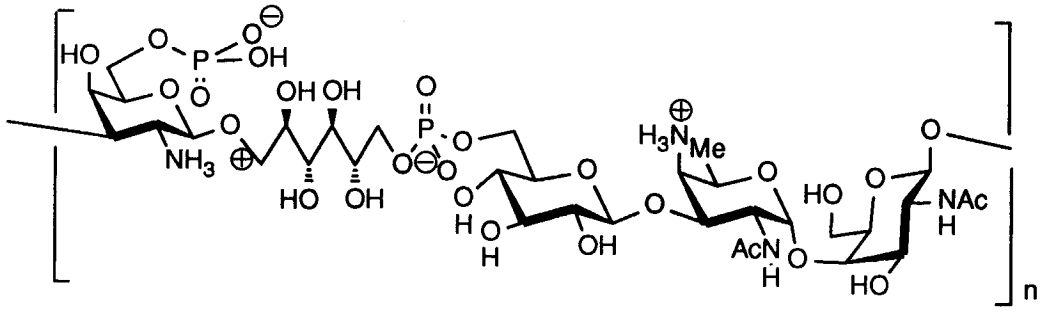
$PO(OR)_2$-, $P(OR)_2$-Activation

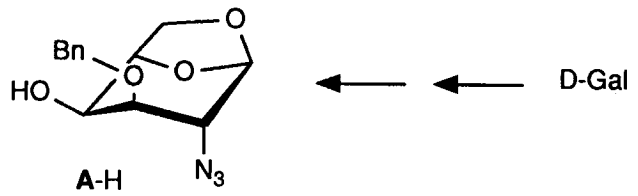
$SO_2(OR)$-, $SO(OR)$-, SO_2R-Activation

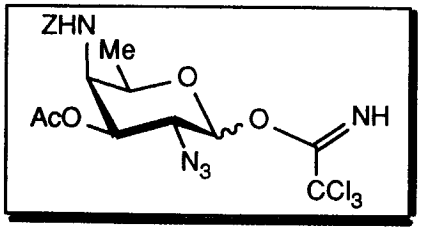
Glycosylation: Mild Acid Catalyst
(Generally: $BF_3 \cdot OEt_2$, TMSOTf, etc.)

SYNTHESIS OF THE [FucN$_2$α(1-4)GalN]-FRAGMENT OF THE REPEATING UNIT OF THE SUBCAPSULAR POLYSACCHARIDE C-SUBSTANCE FROM STREPTOCOCCUS PNEUMONIAE TYPE 1

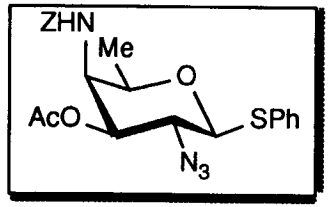
[P. Smid, J.H. van Boom, al. (1992)]



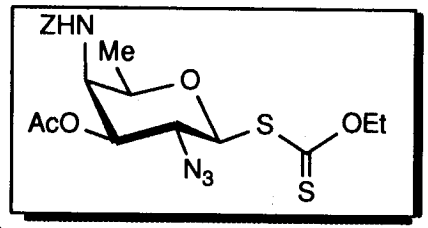




A-H, CH_2Cl_2, TMSOTf, -30°C (75 %)

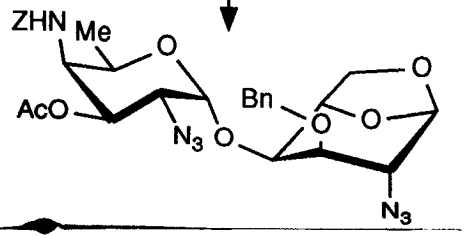


A-H, $Et_2O/C_2H_4Cl_2$, NIS/TfOH, RT (64 %)

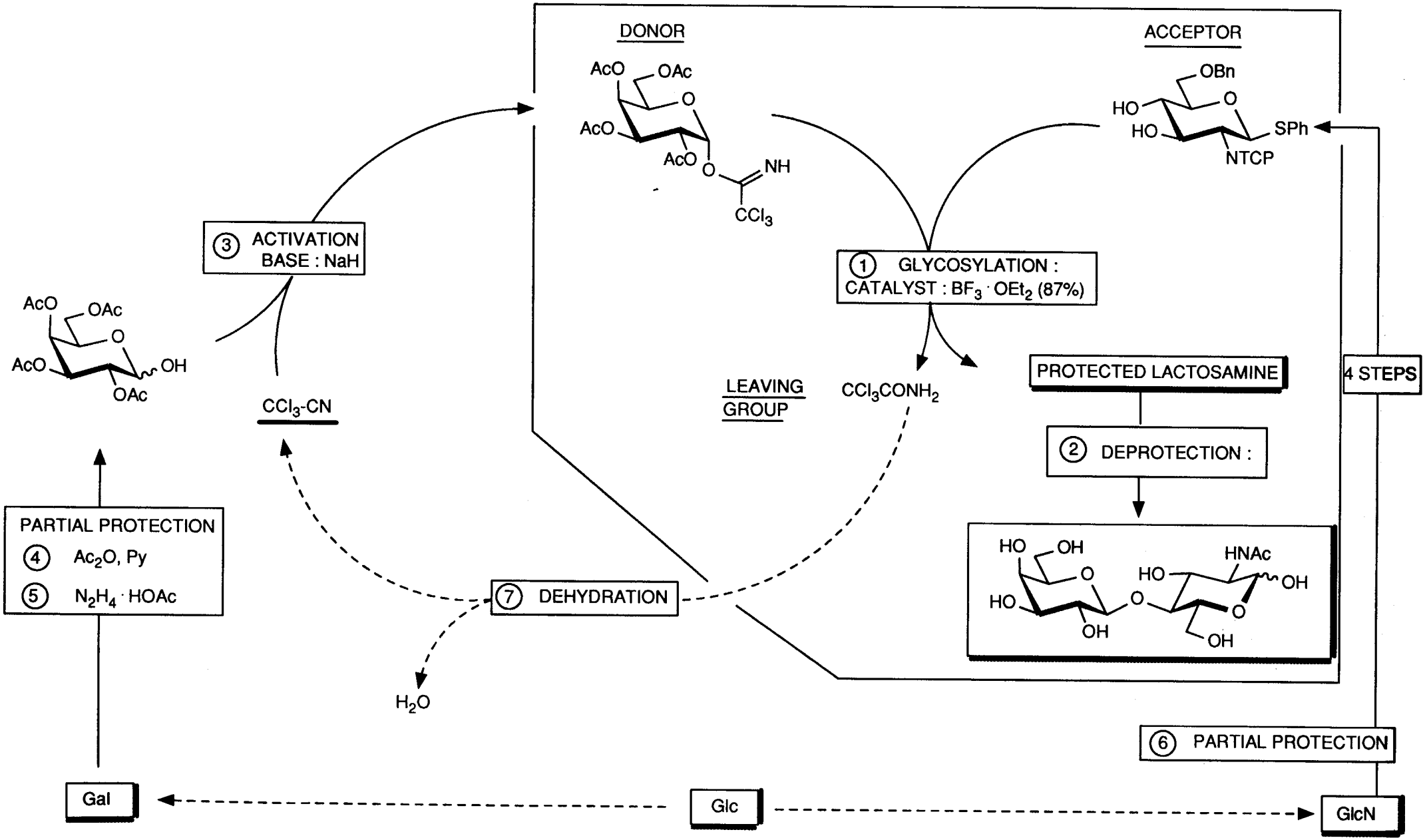


(a) **A**-H, $Et_2O/C_2H_4Cl_2$, NIS/TfOH, RT (16 %)

(b) **A**-H, CH_2Cl_2, $Cu(OTf)_2$, RT (23 %)

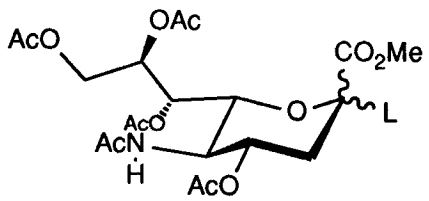


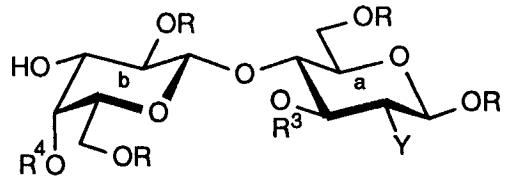
CHEMICAL SYNYTHESIS OF N-ACETYL-LACTOSAMINE



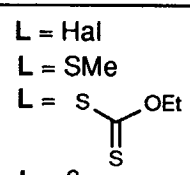
SYNTHESIS OF GANGLIOSIDES OF THE GANGLIO- AND LACTONEO-SERIES

Neu-Ac →



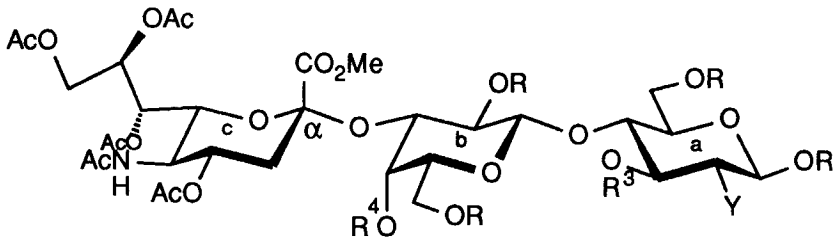


← LACTOSE

LEAVING GROUP: L = Hal
L = SMe
(L) L = 
L = ?

PROMOTER: HALOPHILIC
(P) THIOPHILIC
?

VARIATIONS: Y = OR, N_3
R^{3a} = R, Fucα(1-3)
R^{4b} = H,R,GalNβ(1-4),
Galβ(1-3)GalNβ(1-4)



← GM_1, GM_2

→ GM_3

PROBLEMS: YIELD
α/β-RATIO
PURIFICATION

SIALYL LEWIS X

R = Bn

SIALYL DONORS - ACCESSIBLE TO CATALYTIC ACTIVATION

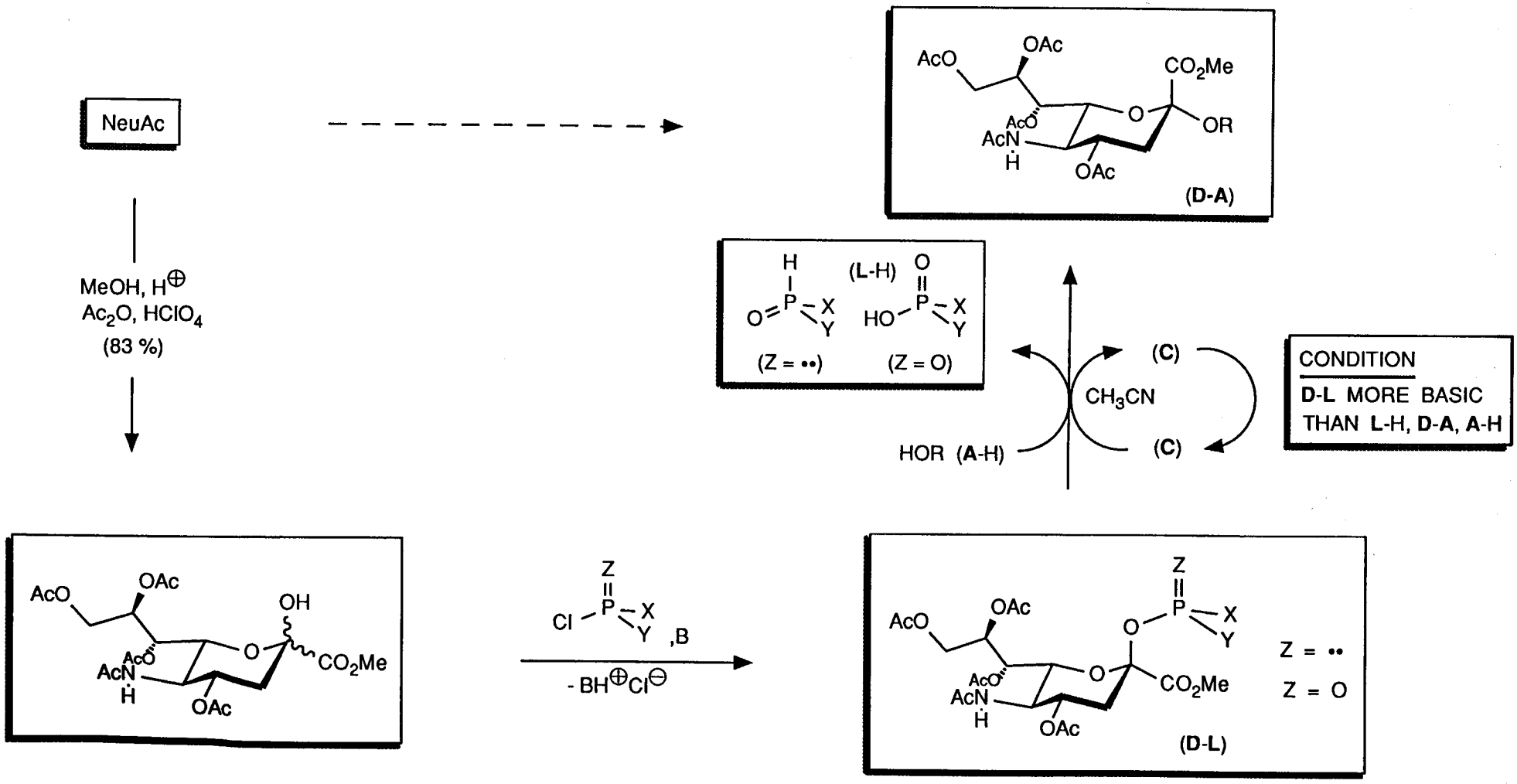
REQUIREMENTS

(1) CONVENIENT HIGHYIELDING SYNTHESIS OF THE DONOR

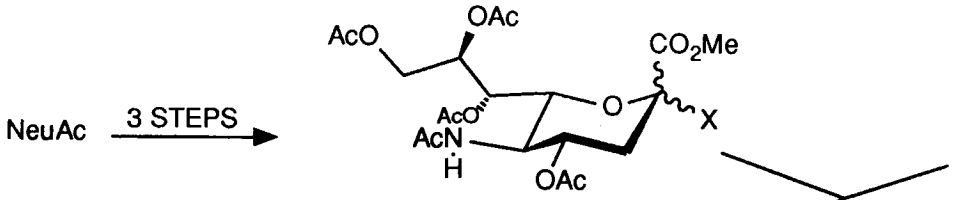
(2) CATALYTIC ACTIVATION BY SIMPLE MEANS (ACID/BASE)

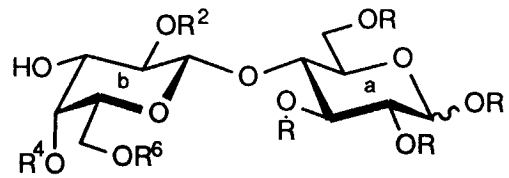
(3) HIGH YIELD IN THE GLYCOSYLATION STEP

(4) HIGH α-SELECTIVITY (α-FACE DIASTEREOSELECTION)



SYNTHESIS OF GM_3

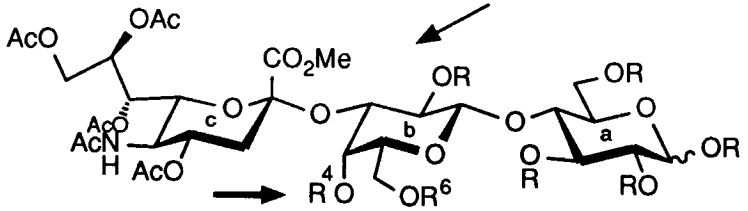


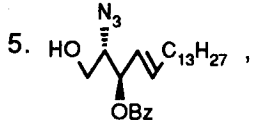


3 STEPS LACTOSE

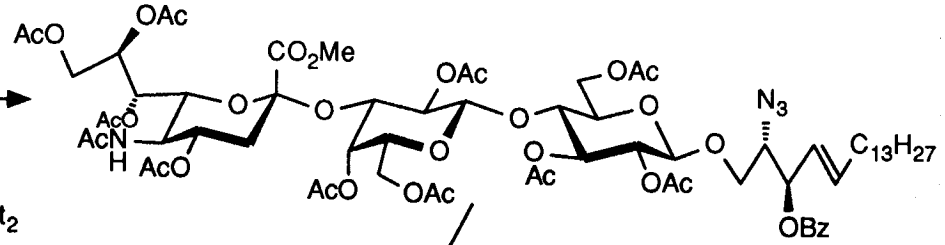
(R = Bn)

X	R^{2b}	R^{4b}	R^{6b}	D : A [eq]	PROMOTER	YIELD
SC(S)OEt	R	Ph-CH		1 : 1.5	NIS(2 eq), TfOH (0.2 eq)	24 %, α
$OP(OEt)_2$	R	Ph-CH		1 : 1.5	TMSOTf (0.1 eq)	38 %, α
SMe	R	H	Bn	1.6 : 1	NIS(2 eq), TfOH (0.2 eq)	50 %, α
$OP(OEt)_2$	R	H	Bn	1 : 1.5	TMSOTf (0.1 eq)	55 %, α
$OP(OEt)_2$	H	H	H	1 : 1.5	TMSOTf(0.1 eq)	75 %, α



1. Pd/C; H_2, MeOH (95%)
2. Ac_2O, Py (90%)
3. $N_2H_4 \cdot HOAc$, DMF (90%)
4. CCl_3CN, DBU (70%)
5. 

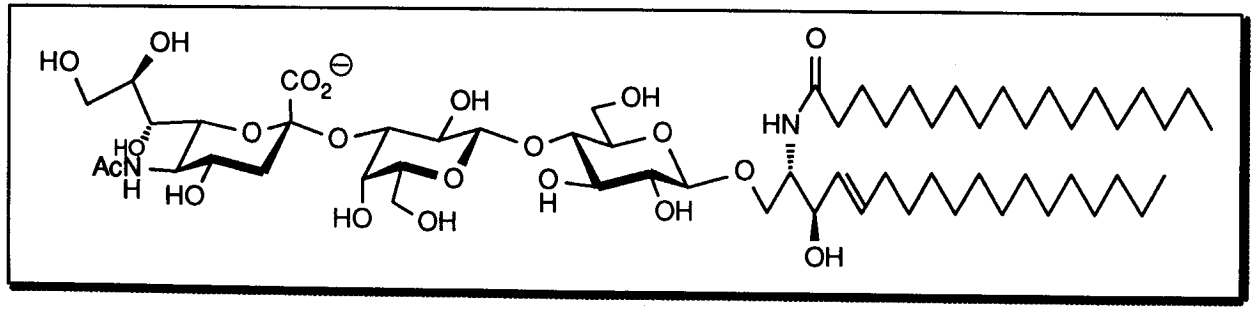
, $BF_3 \cdot OEt_2$ (65%)



R^{4b} = H, R^{6b} = Bn
R^{4b}, R^{6b} = PhCH
R^{4b} = R^{6b} = H

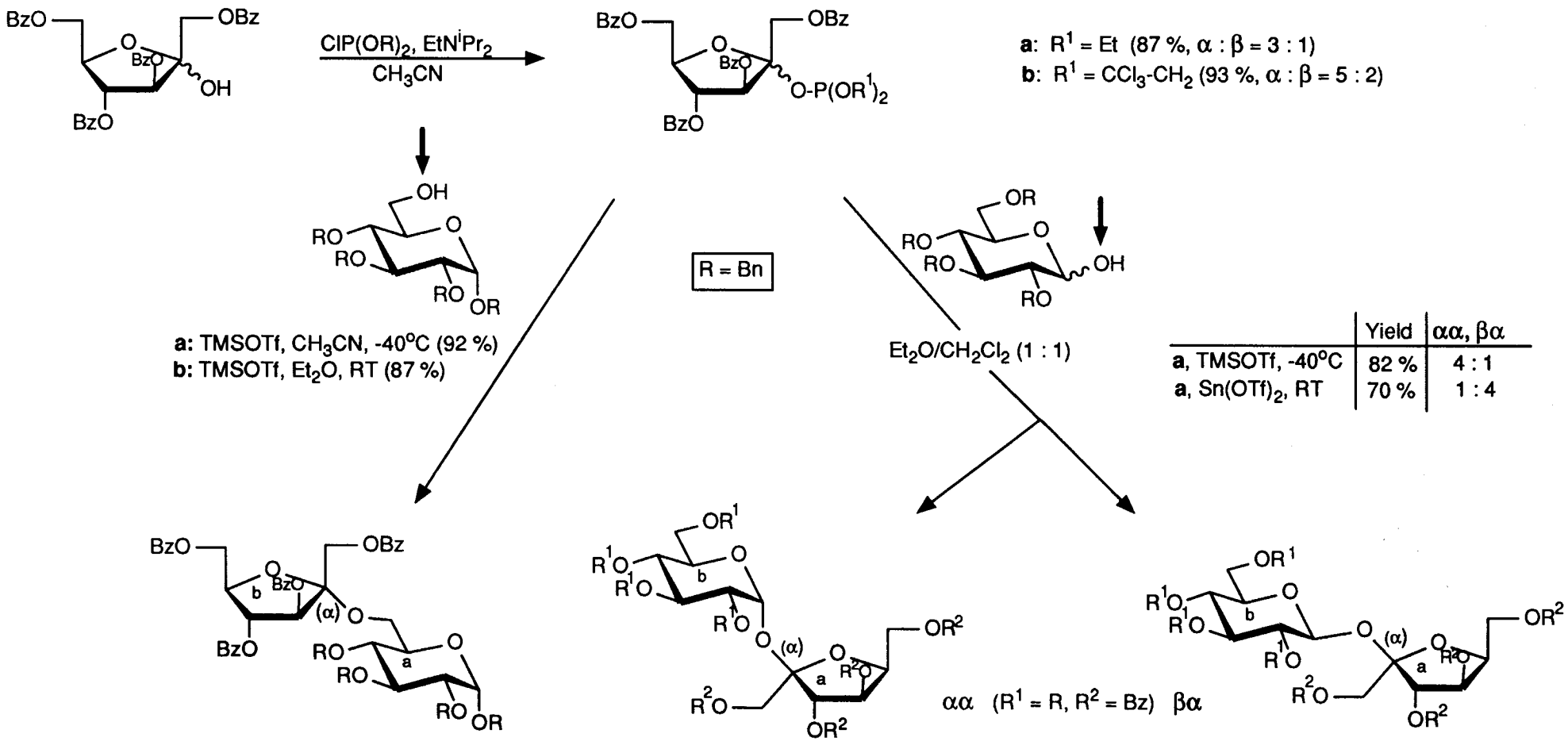
$NaCNBH_3$, HCl (90 %)
$H^{\oplus}$ (qu)

1. H_2S, Py/H_2O (95%)
2. $C_{17}H_{35}$ COOH, WSC, CH_2Cl_2 (60 %); NaOMe, MeOH (90%)



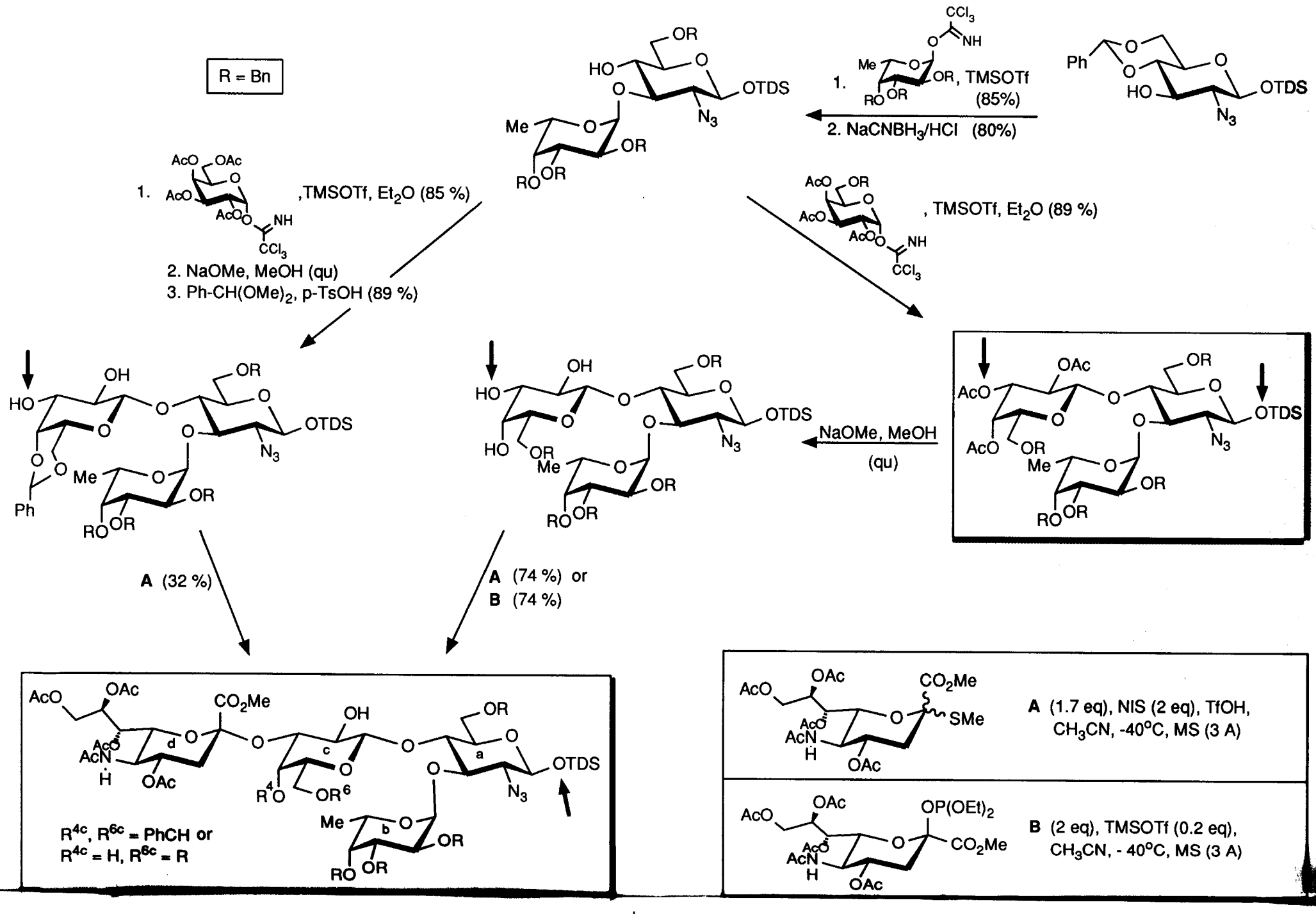
GM_1, GM_2

FRUCTOFURANOSYL PHOSPHITES AS GLYCOSYL DONORS



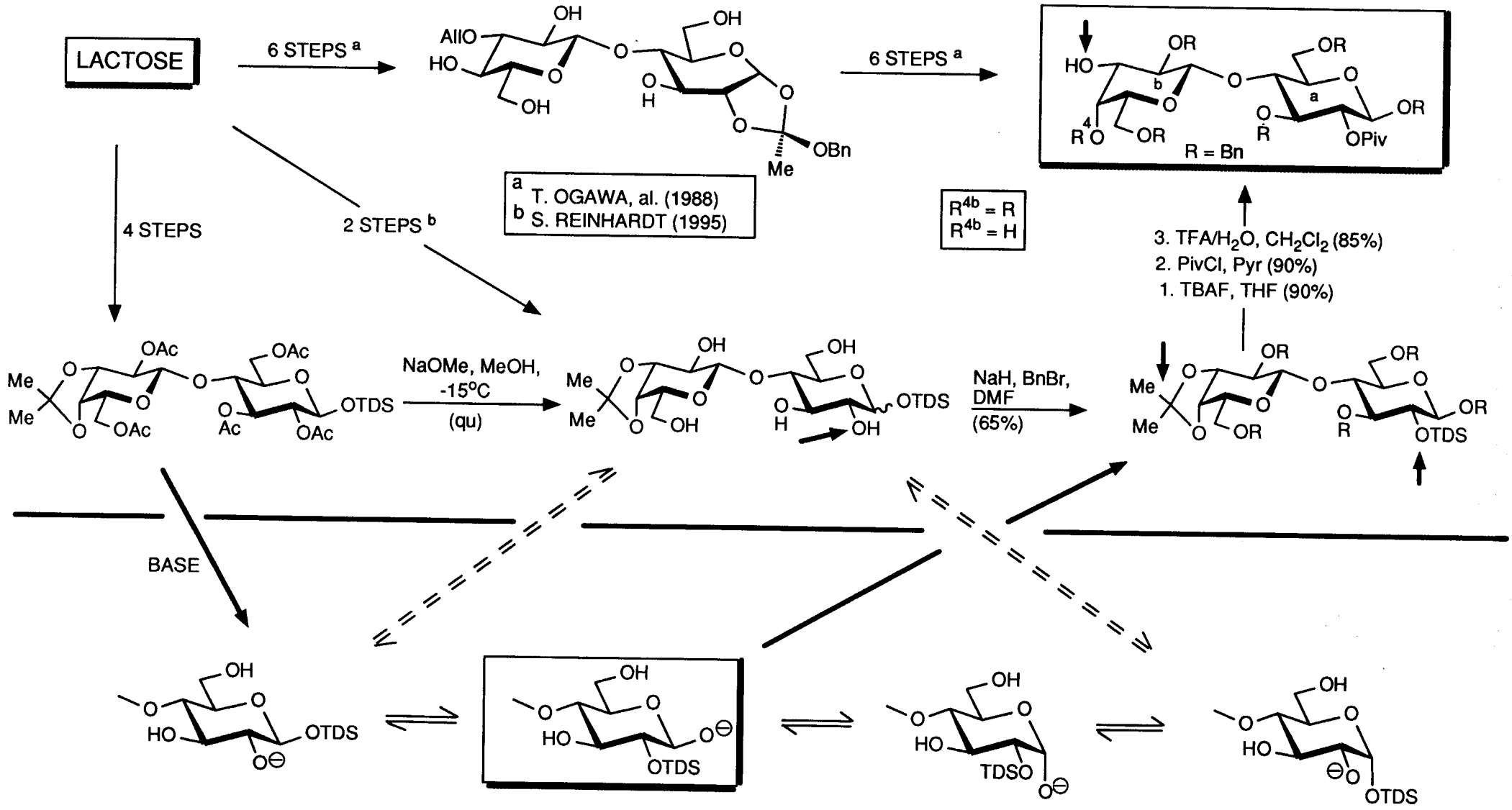
	Yield	αα, βα
a, TMSOTf, -40°C	82 %	4 : 1
a, $Sn(OTf)_2$, RT	70 %	1 : 4

SYNTHESIS OF A SIALYL MONOMER LEWIS X TETRASACCHARIDE BUILDING BLOCK

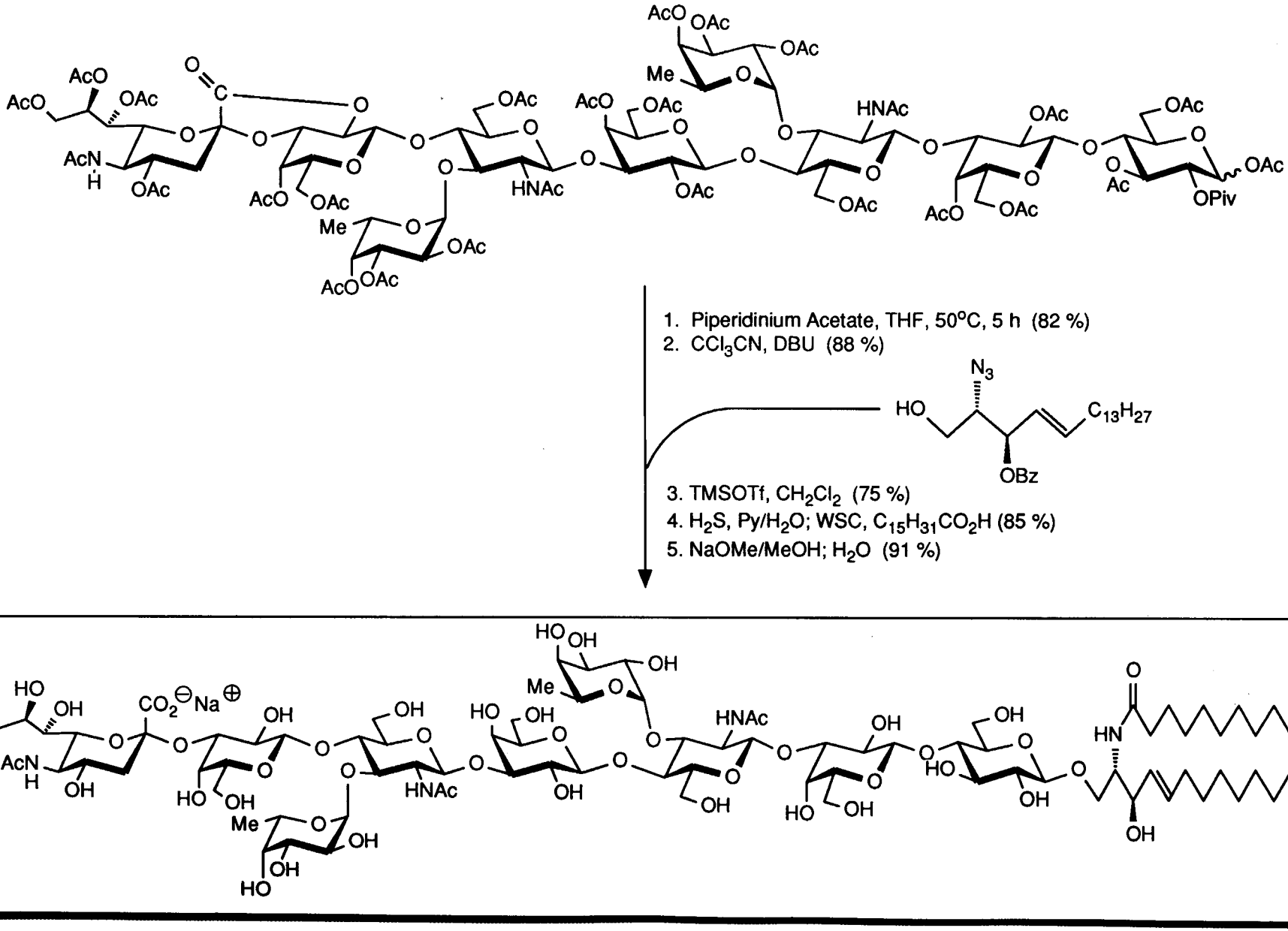


BASE CATALYZED (1-2)-O-SILYL GROUP MIGRATION

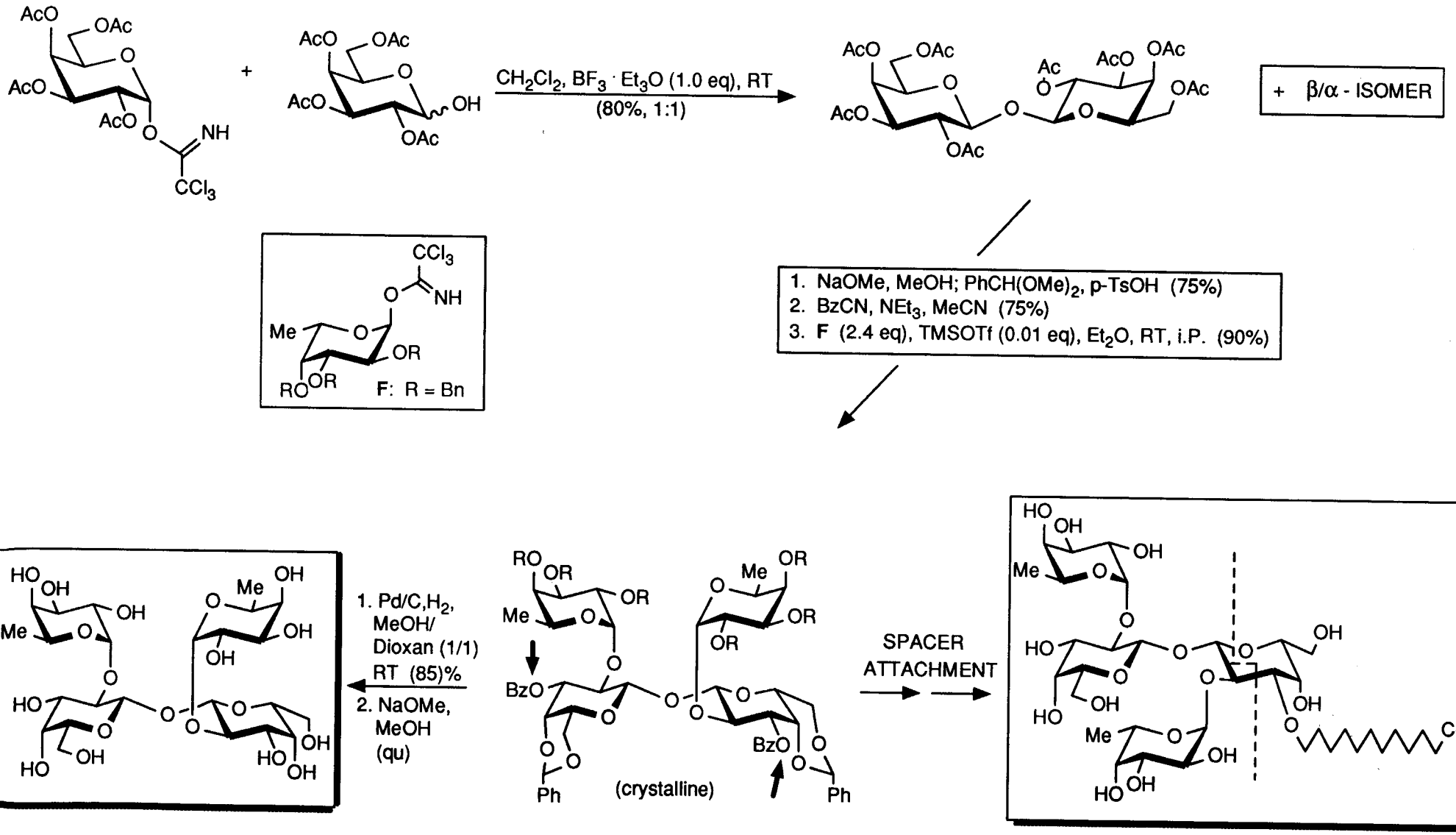
EFFICIENT SYNTHESIS OF A 3b,4b-O-UNPROTECTED 2a-O-PIVALOYL-LACTOSE BUILDING BLOCK



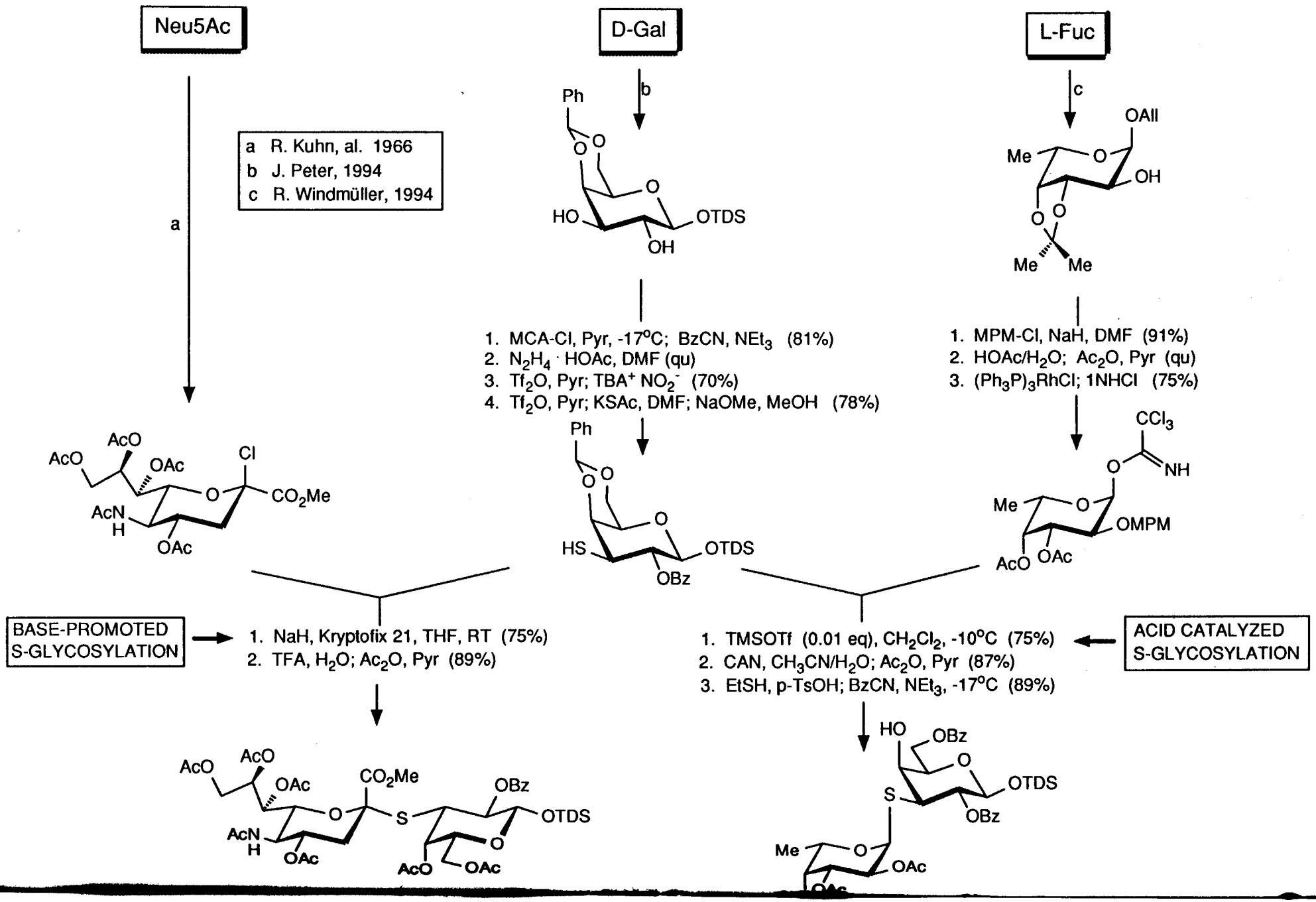
TOTAL SYNTHESIS OF THE SIALYL DIMER LEWIS X



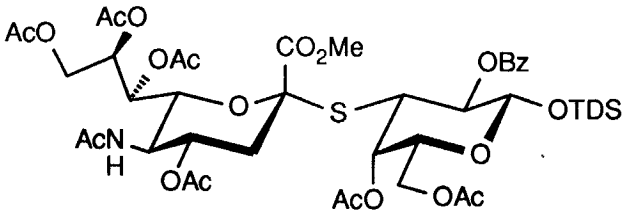
SYNTHESIS OF AN ANALOGUE AND OF A C_2-SYMMETRIC ANALOGUE OF LE^Y/Le^b EPITOPES



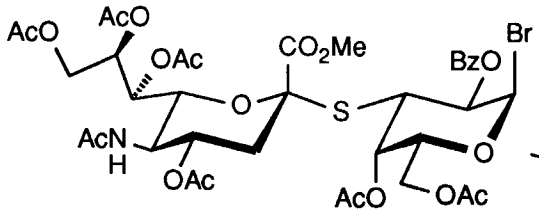
SYNTHESIS OF THE DISACCHARIDE BUILDING BLOCKS

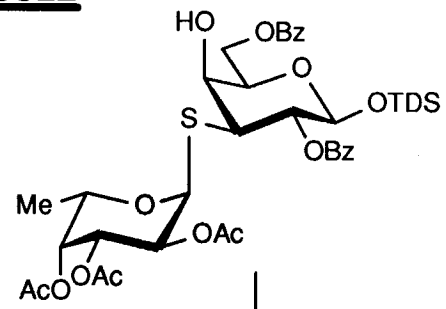


SYNTHESIS OF THE TARGET MOLECULE

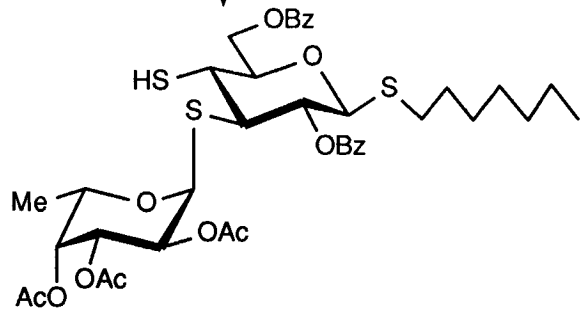


1. TBAF, THF, RT; Ac_2O, Pyr (90%)
2. HBr/HOAc, 0°C (95%)



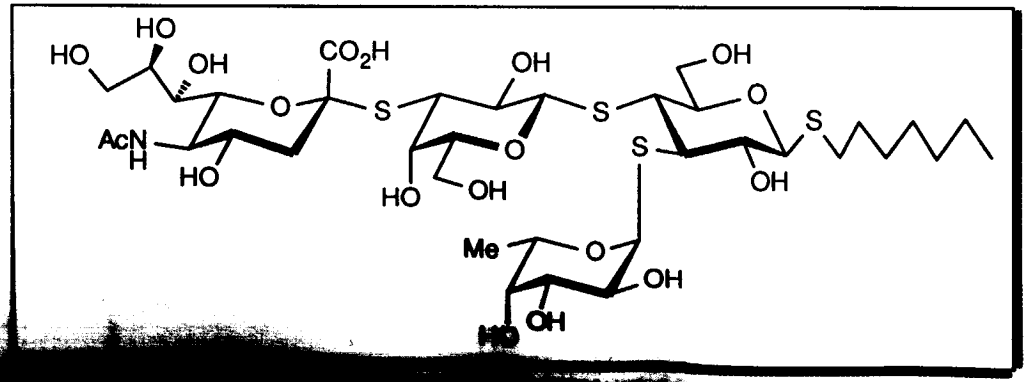


1. Tf_2O, Pyr, -17°C; KSAc, THF, RT (42%)
2. TBAF, THF, -20°C; CCl_3CN, DBU (91%)
3. HS-C_7H_{15}, $BF_3 \cdot OEt_2$ (73%) ← ACID CATALYZED S-GLYCOSYLATION
4. $N_2H_4 \cdot HOAc$, DMF (91%)

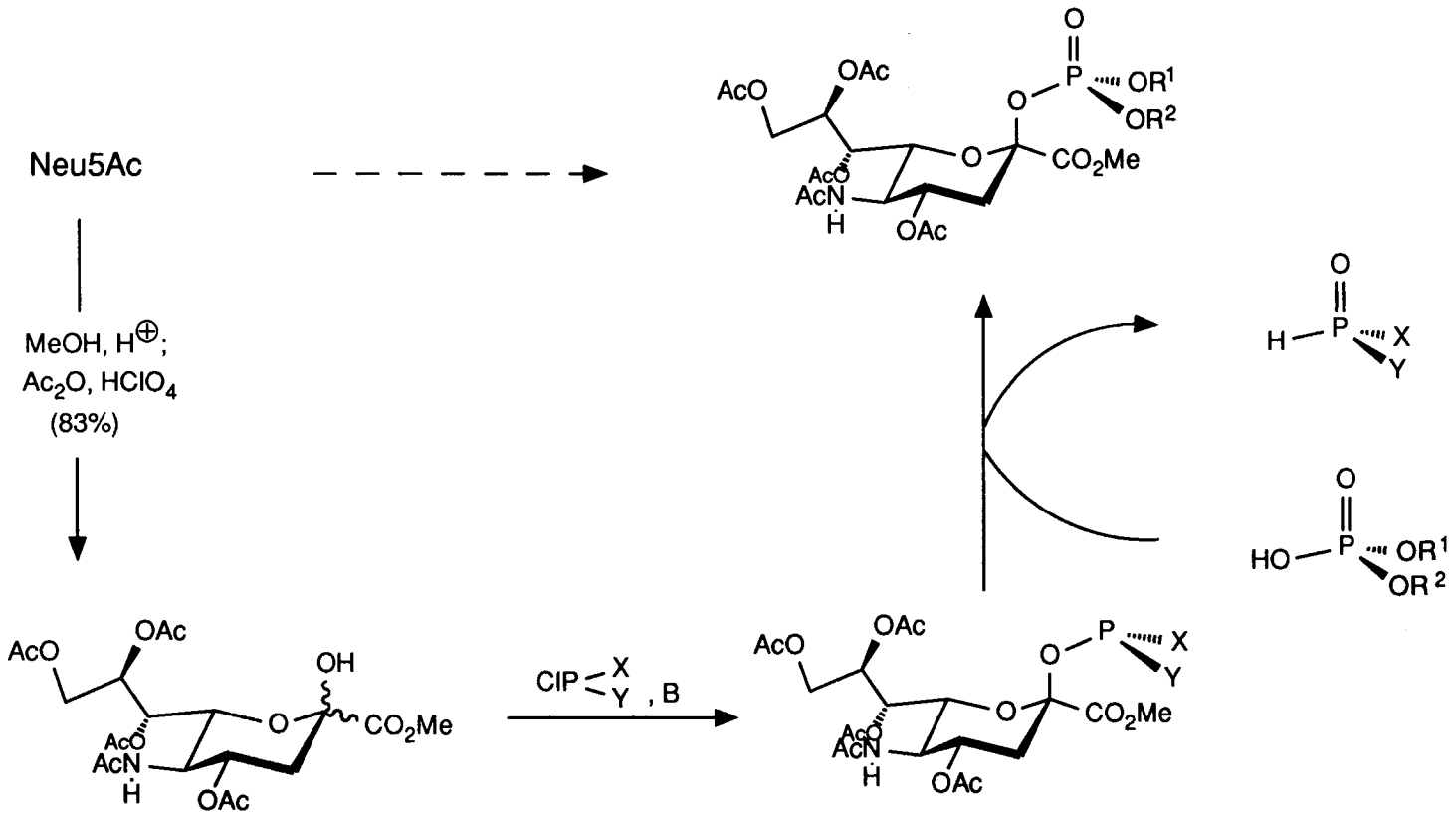


BASE-PROMOTED S-GLYCOSYLATION →

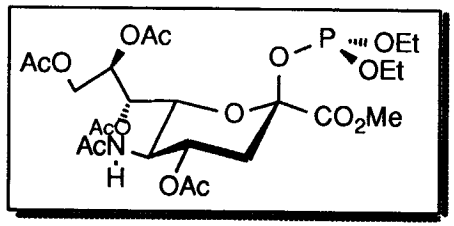
1. NaH, DMF, RT (70%)
2. NaOMe, MeOH; 0.2 N KOH (qu)



SIALYL PHOSPHITES AS DONORS FOR THE SYNTHESIS OF SIALYL PHOSPHATES



SYNTHESIS OF NATURAL CMP-Neu5Ac AND UMP-Neu5Ac

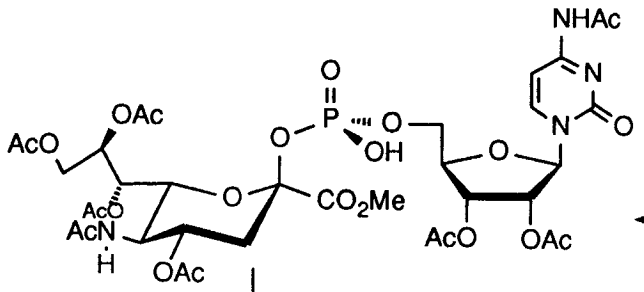


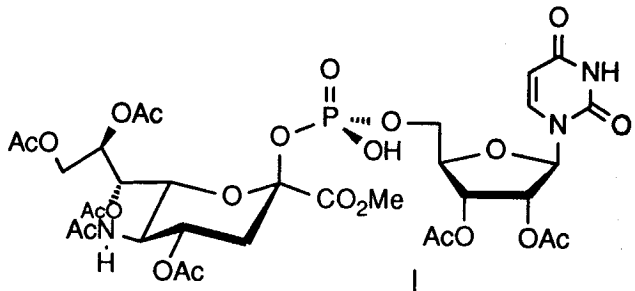
Tri-Ac-**CMP**

DMF : CH_3CN = 2 : 1
-20°C → r.t.
(50 %)

Di-Ac-**UMP**

DMF : CH_3CN = 1 : 2
-20°C → r.t.
(62 %)





Tri-Ac-**CMP**

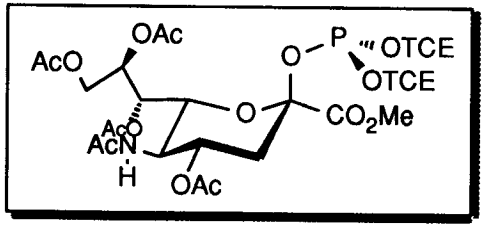
DMF : CH_3CN = 2 : 1
0°C → r.t., 5 d
(26 %)

Di-Ac-**UMP**

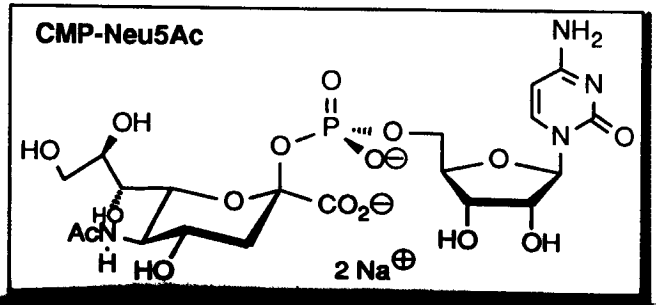
DMF : CH_3CN = 1 : 2
0°C → r.t., 4 d
(37 %)

NaOMe, MeOH;
NaOH, H_2O/MeOH
(68 %, crystals)

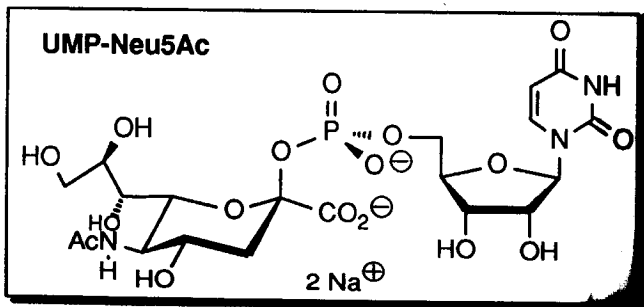
NaOMe, MeOH;
NaOH, H_2O, MeOH
(81 %)



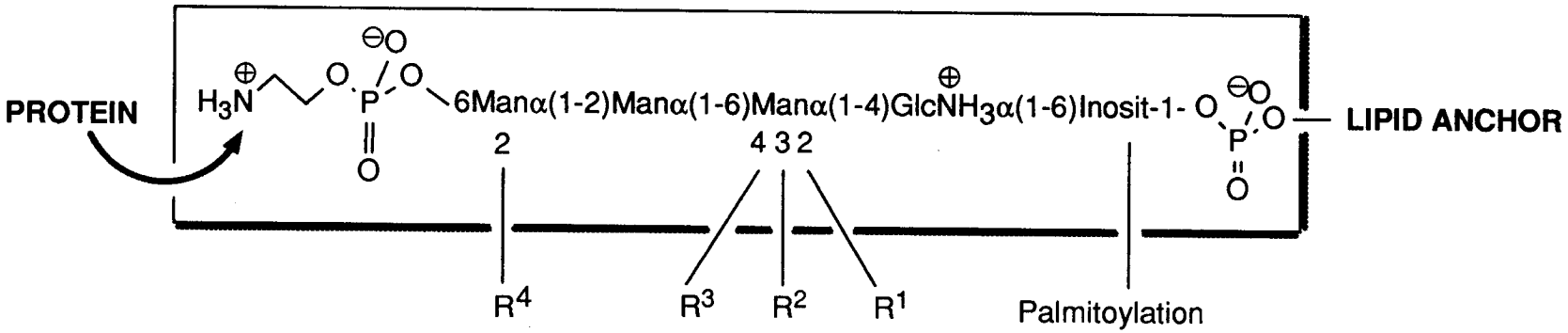
CMP-Neu5Ac



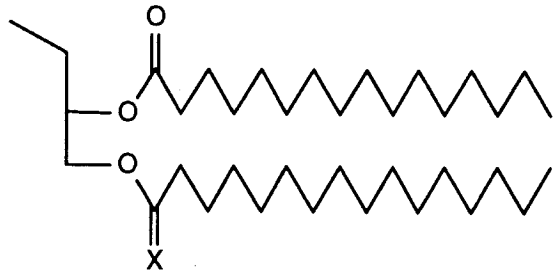
UMP-Neu5Ac



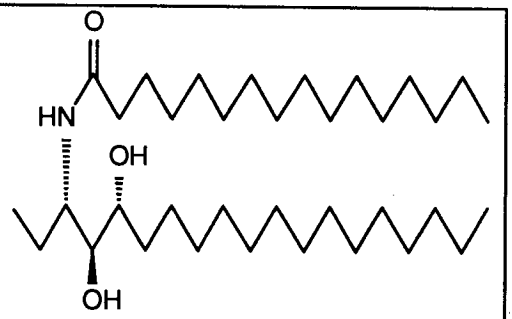
GENERAL STRUCTURE OF GPI-ANCHORS



LIPID ANCHOR:



or

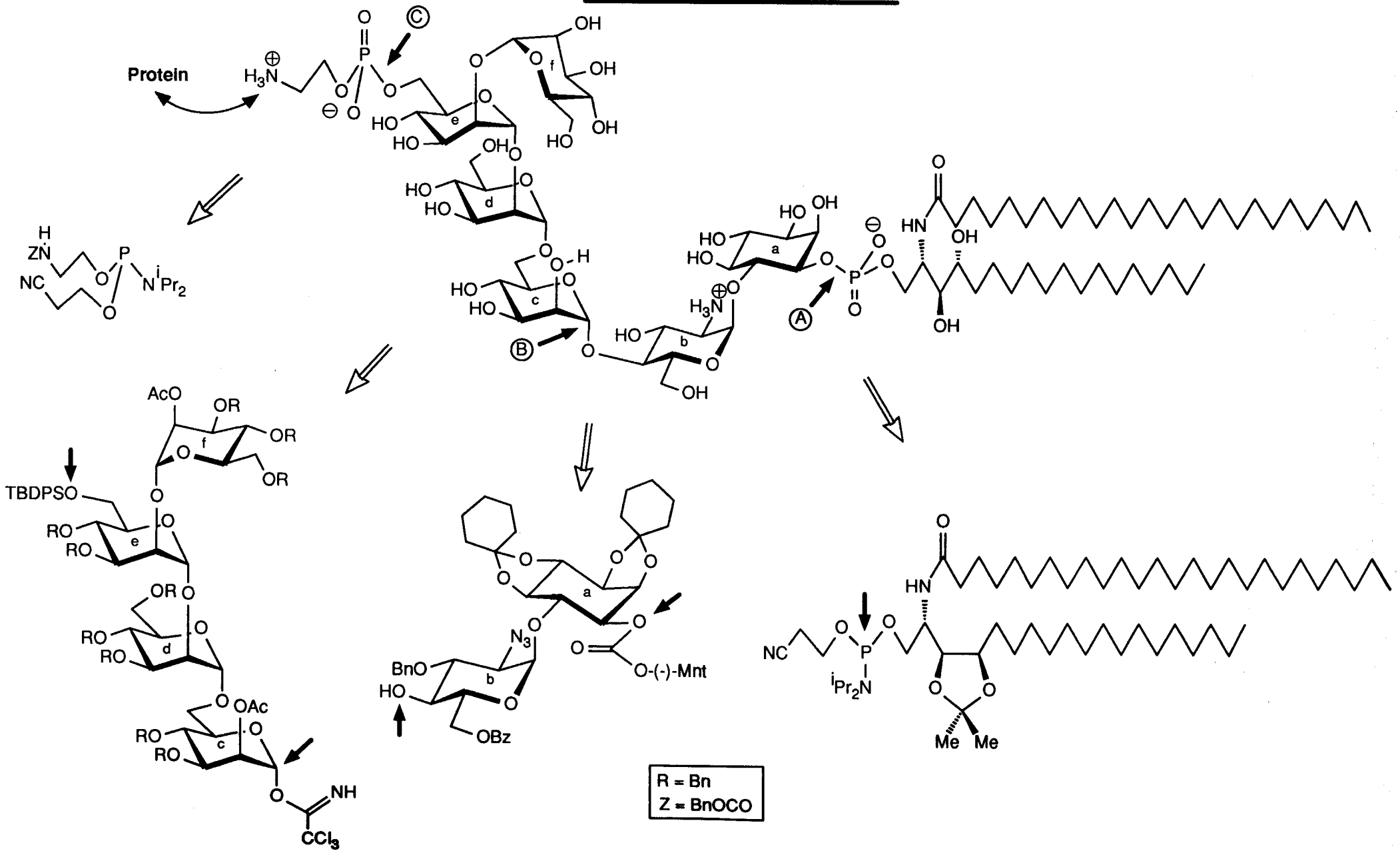


R^1 = ETHANOLAMINE PHOSPHATE

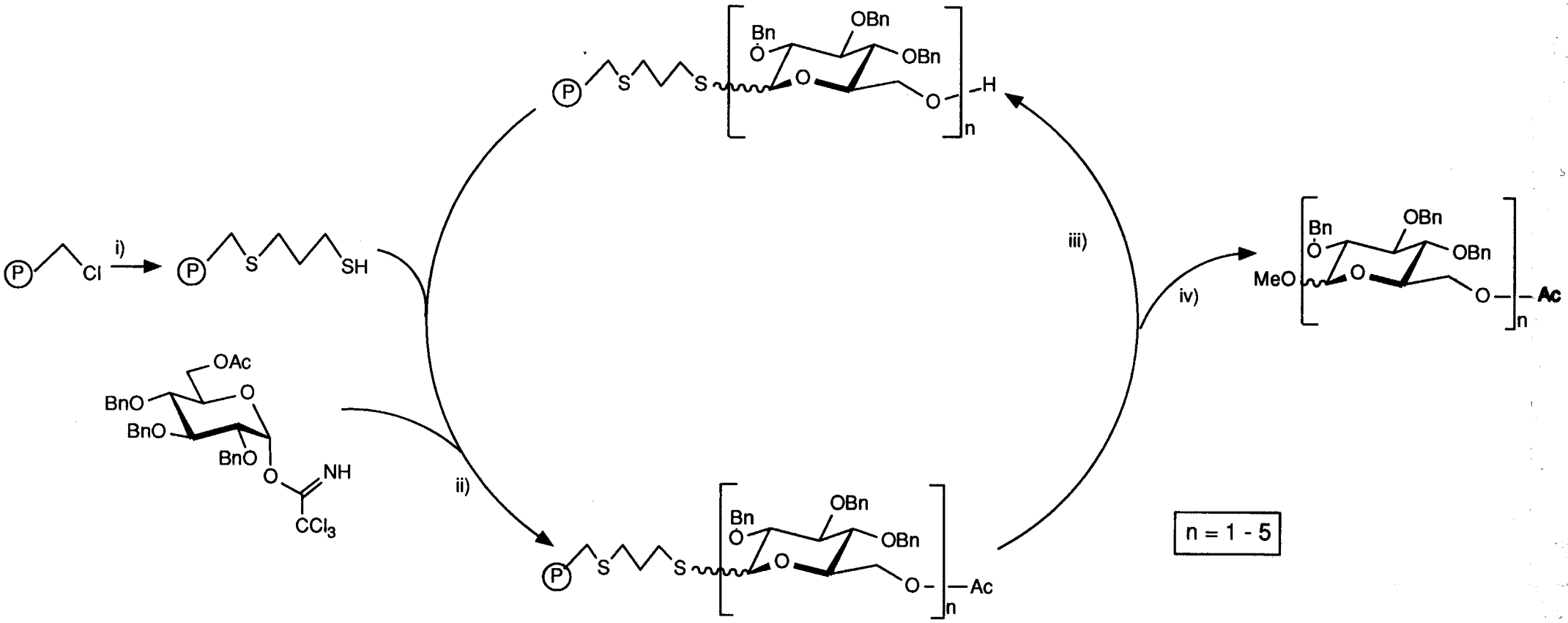
R^2 - R^4 = MONOSACCHARIDE OR OLIGOSACCHARIDE RESIDUES

GLYCOSYL-PHOSPHATIDYLINOSITOL MEMBRANE ANCHORS FROM SACCHAROMYCES CEREVISIAE

RETROSYNTHETIC ANALYSIS



NEW METHOD FOR THE SOLID PHASE SYNTHESIS OF OLIGOSACCHARIDES BASED ON THIOGLYCOSIDE LINKERS AND TRICHLOROACETIMIDATE DONORS



i) Propanedithiol (10 eq), DBU (2 eq), Tol, RT (→ 0.6 mmol/g)
ii) Trichloroacetimidate (3 eq), TMSOTf (0.2 eq), CH_2Cl_2, RT, 2 h (> 95 %, α: β ~ 1 : 1)
iii) **NaOMe, MeOH (0.5 M)/CH_2Cl_2 (1 : 9), RT, 2 h; 15-crown-5 (2 eq), CH_2Cl_2/MeOH, 20 : 1 (qu)**
iv) **DMTSB (2 eq), EtN^iPr_2 (2 eq), CH_2Cl_2/MeOH, 9 : 1 (qu)**