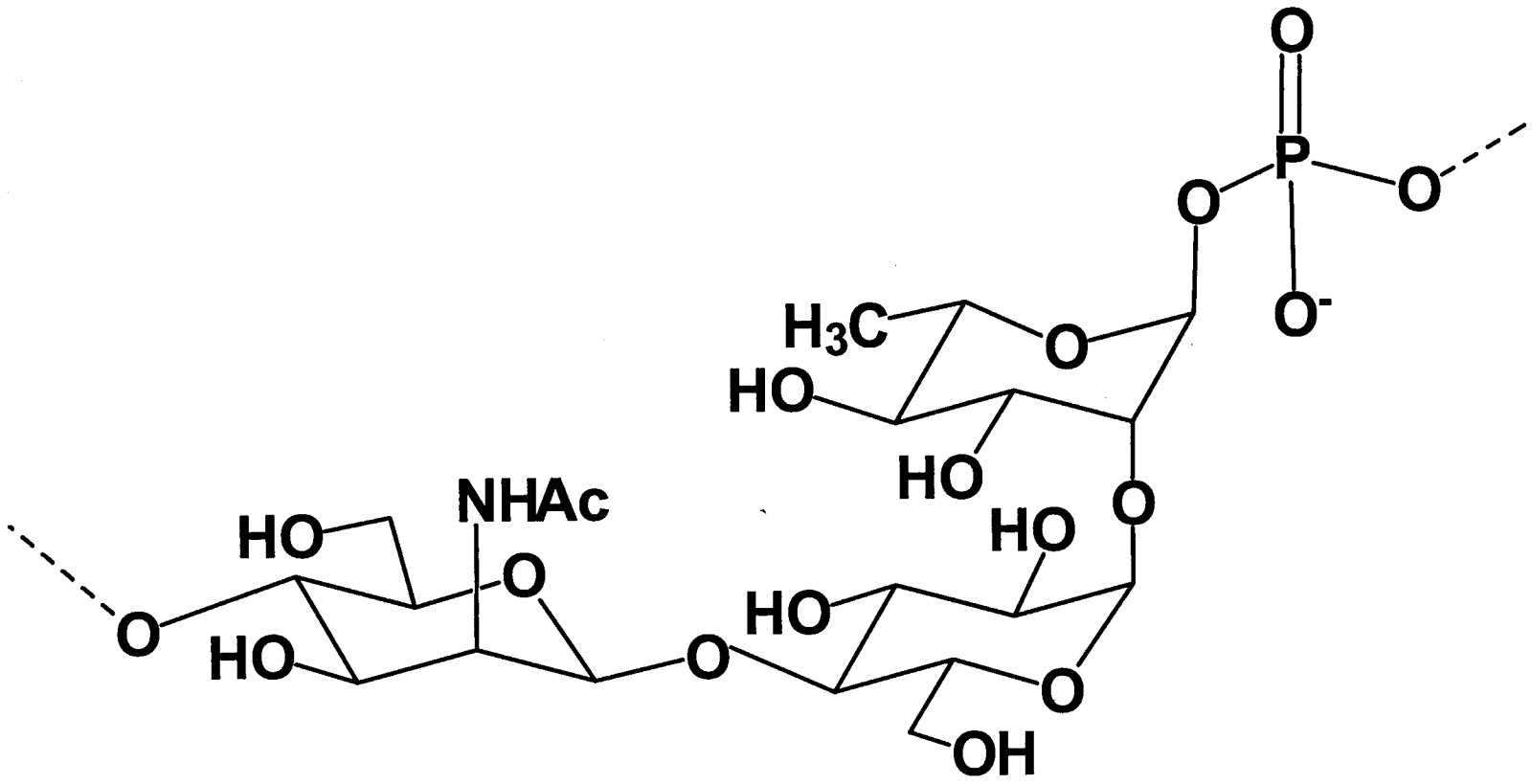
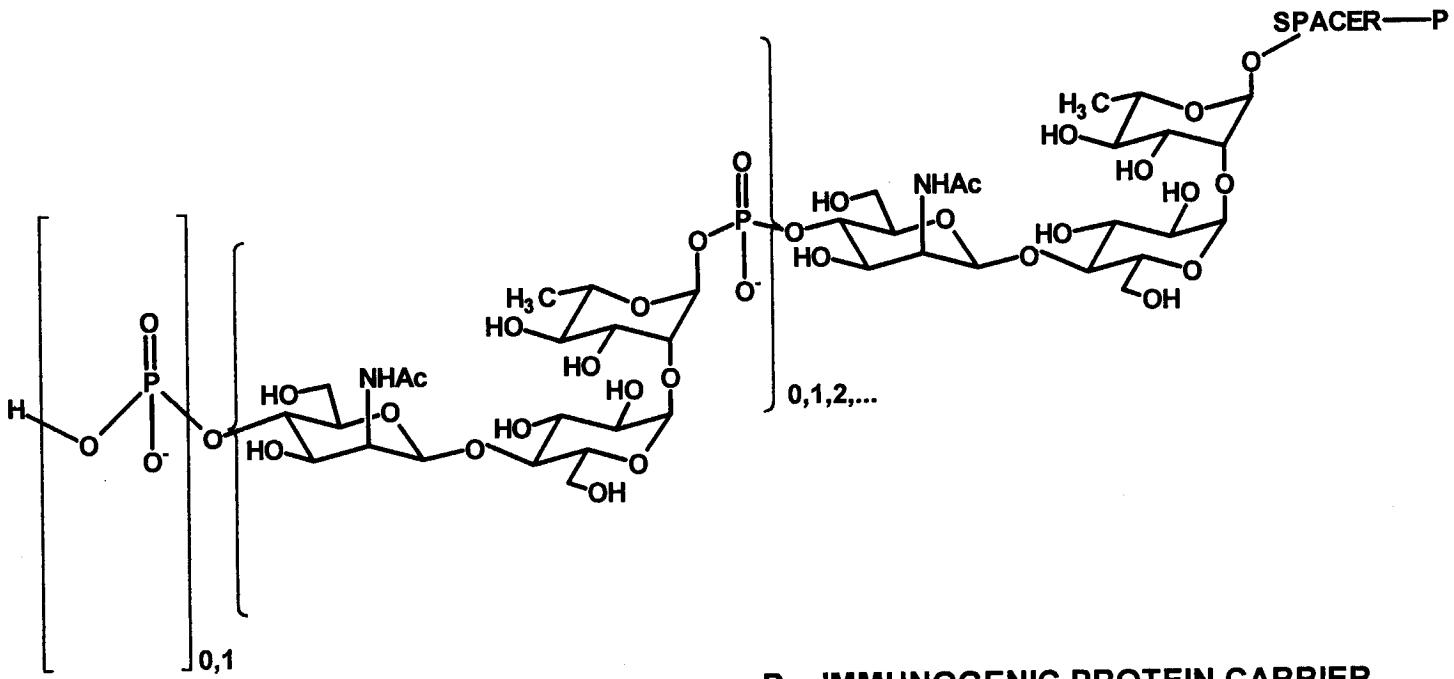
Streptococcus pneumoniae 19F repeating unit

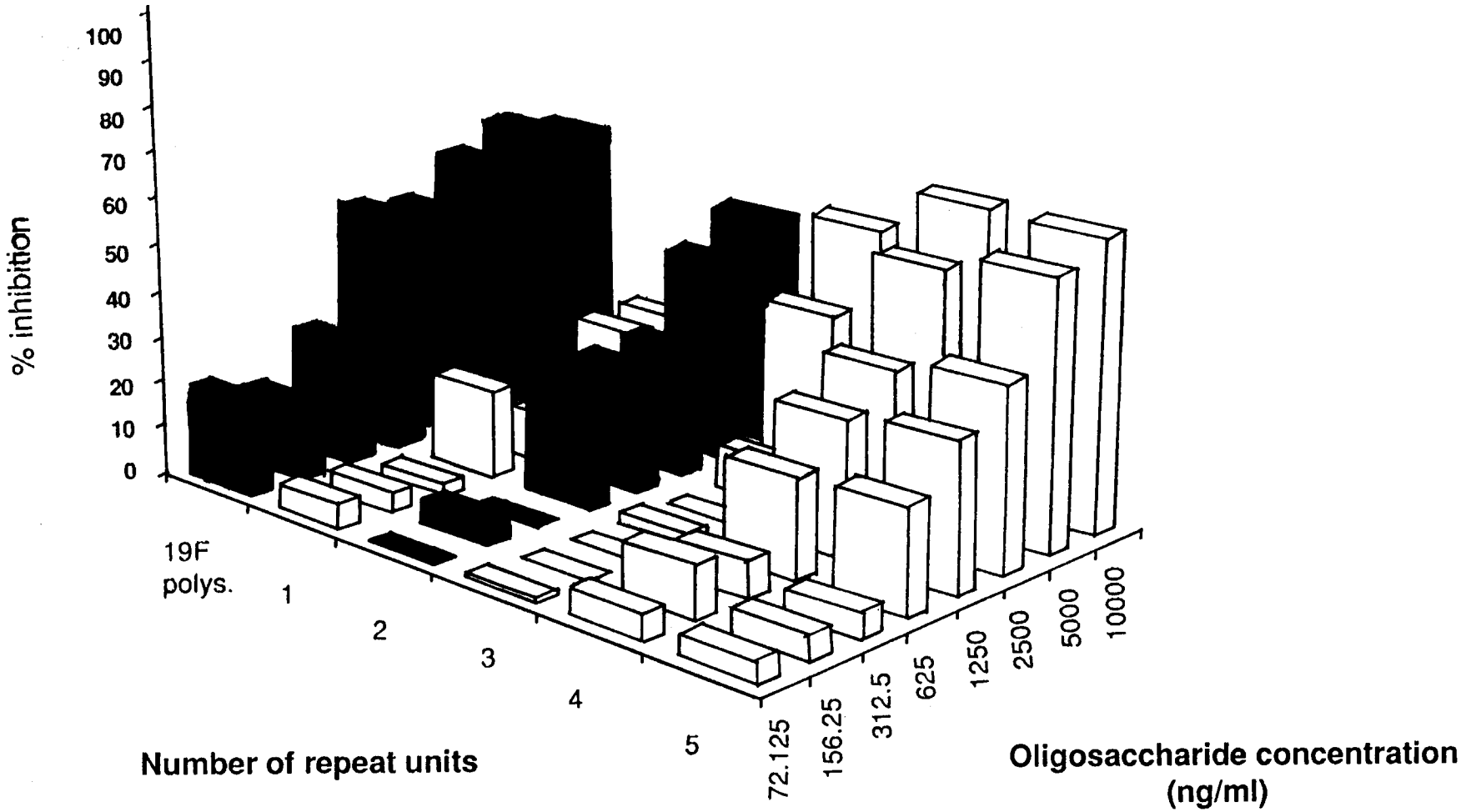


MODEL OF VACCINE AGAINST STREPTOCOCCUS PNEUMONIAE 19F

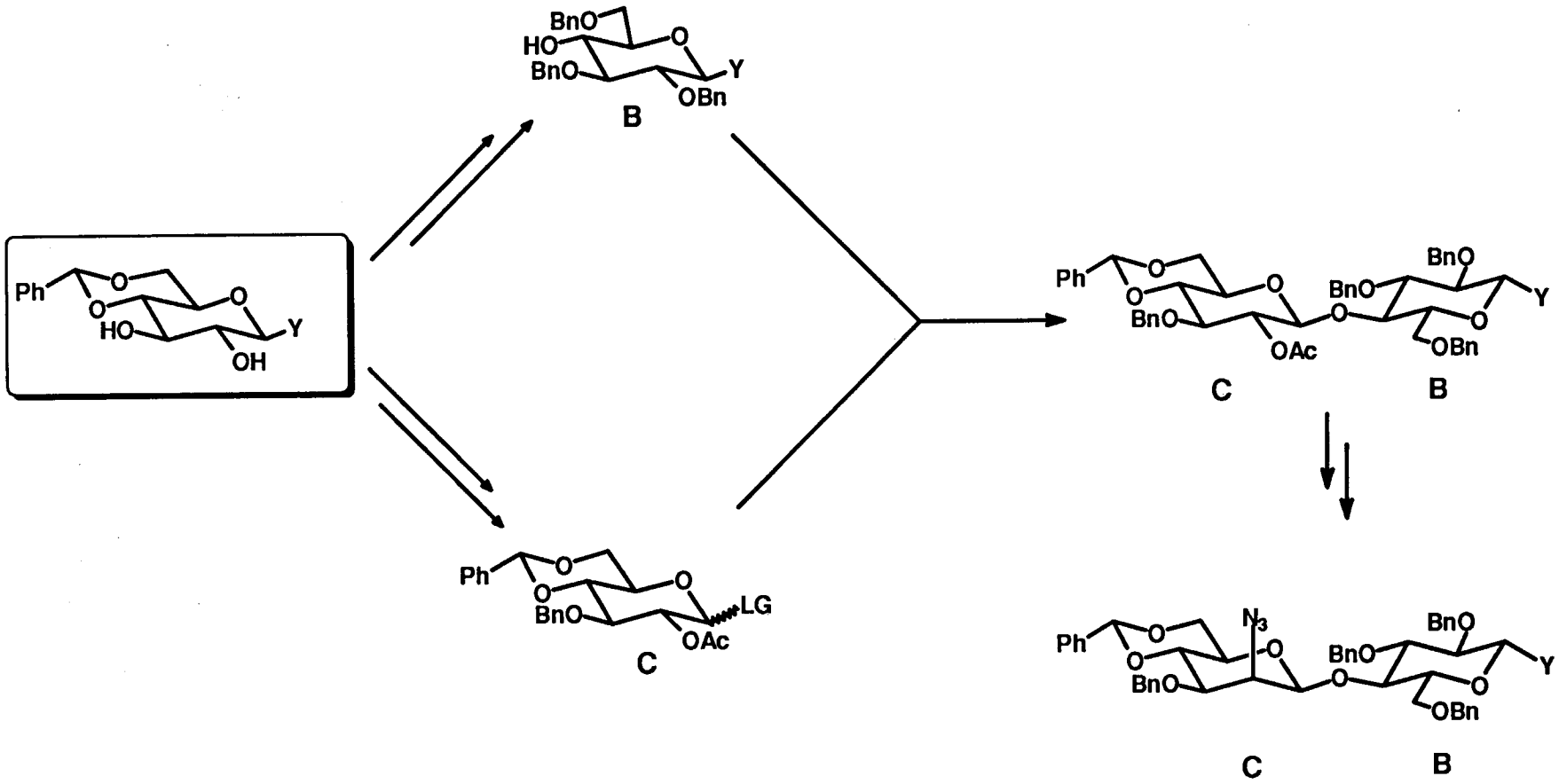


P = IMMUNOGENIC PROTEIN CARRIER

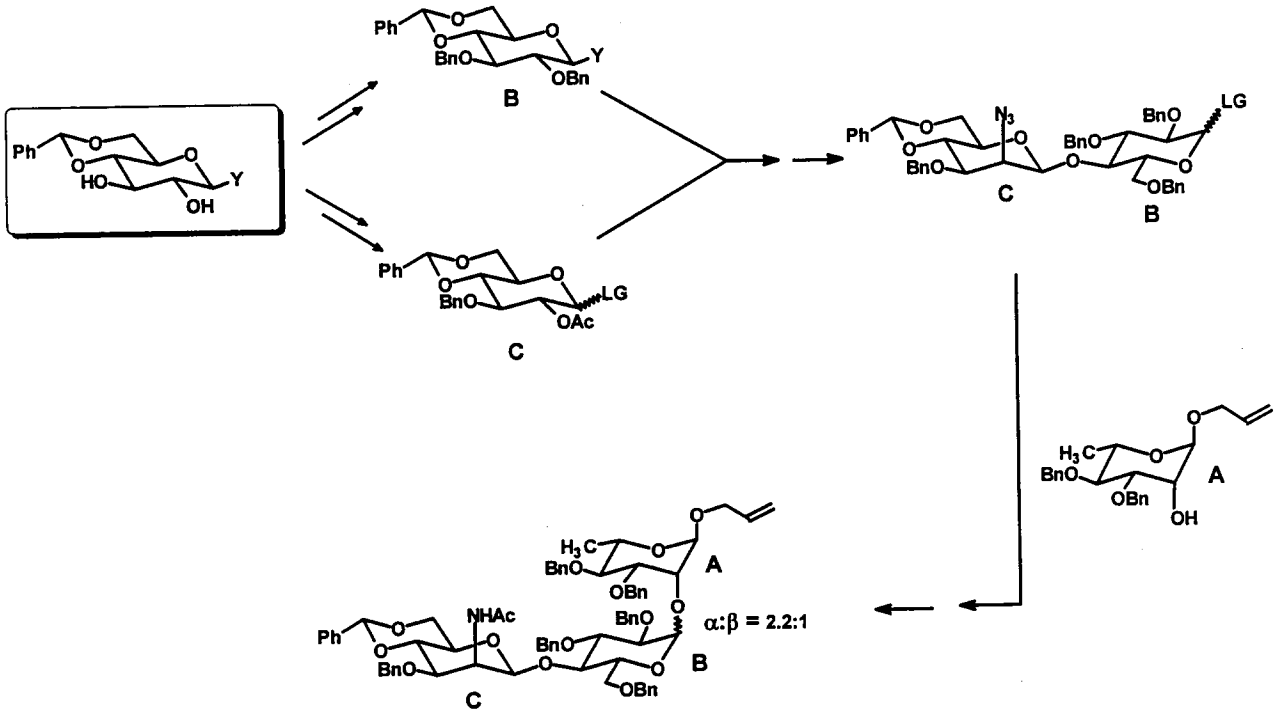
Inhibition of anti-19F polysaccharide antibody response by different oligosaccharides



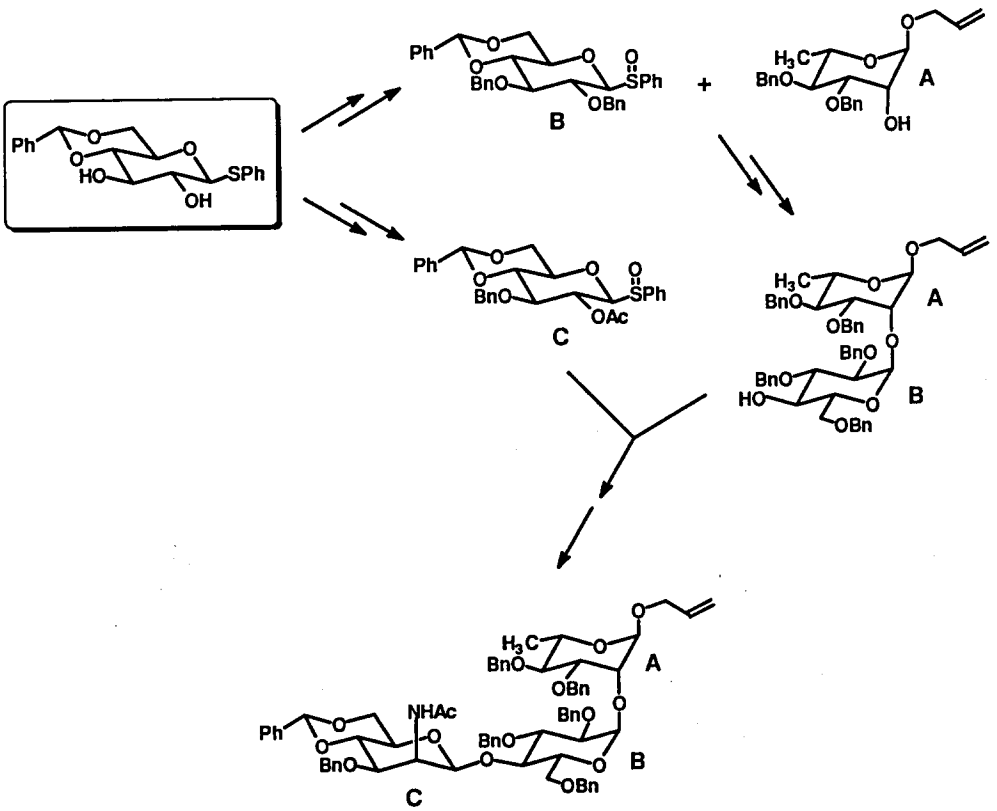
C3TAINING β-MANNOSAMINE SYSTEM



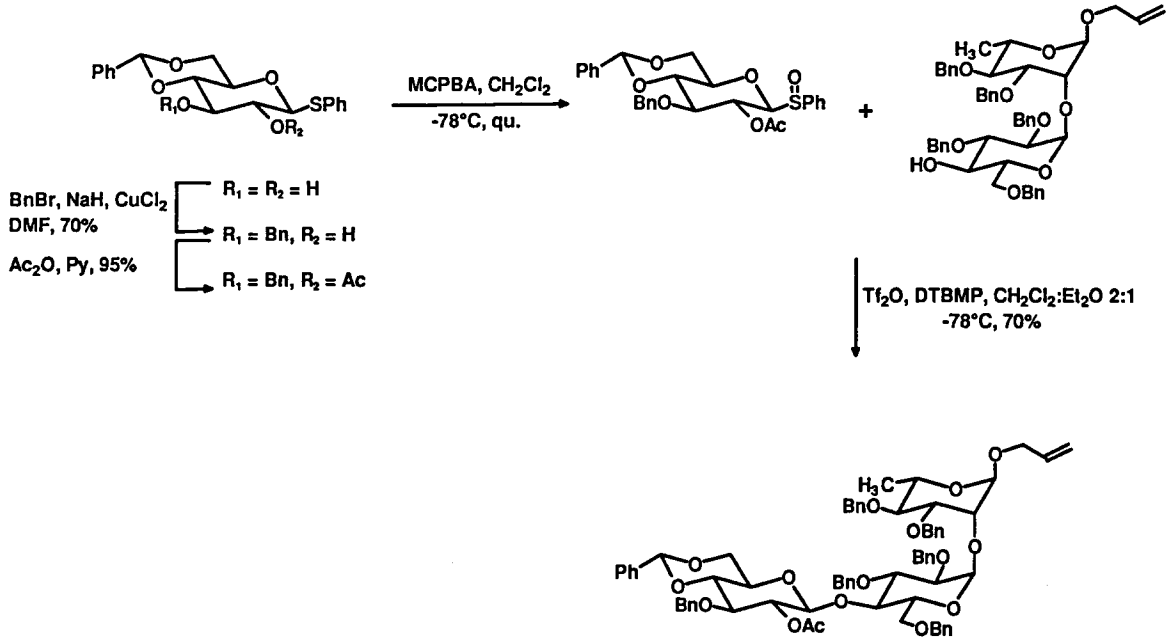
SCHEME C - B - A



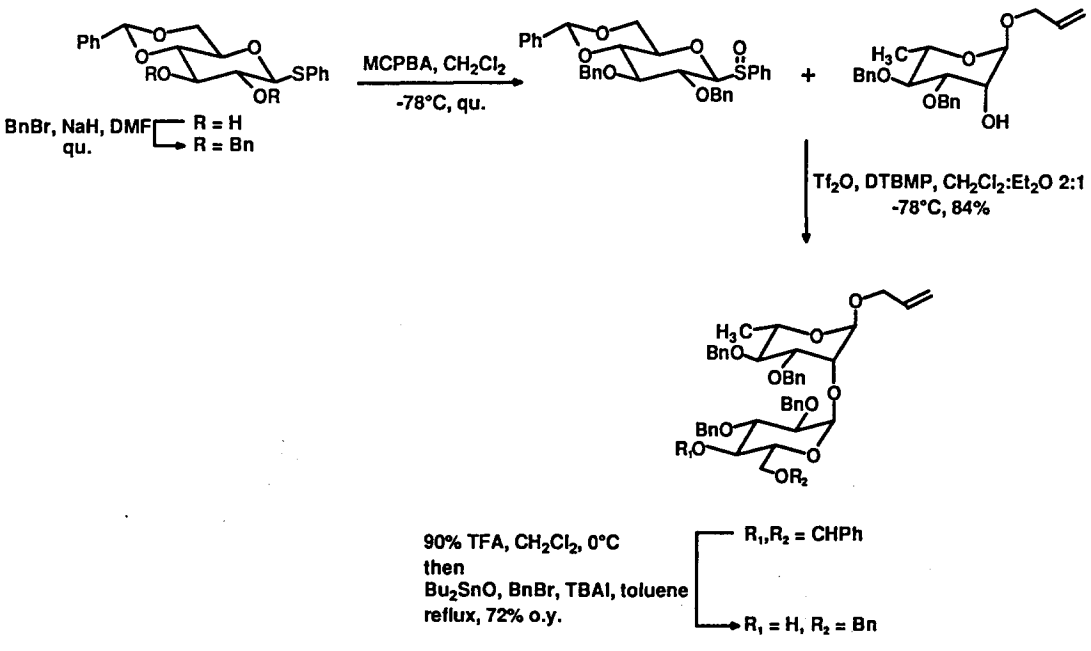
SCHEME B - A - C



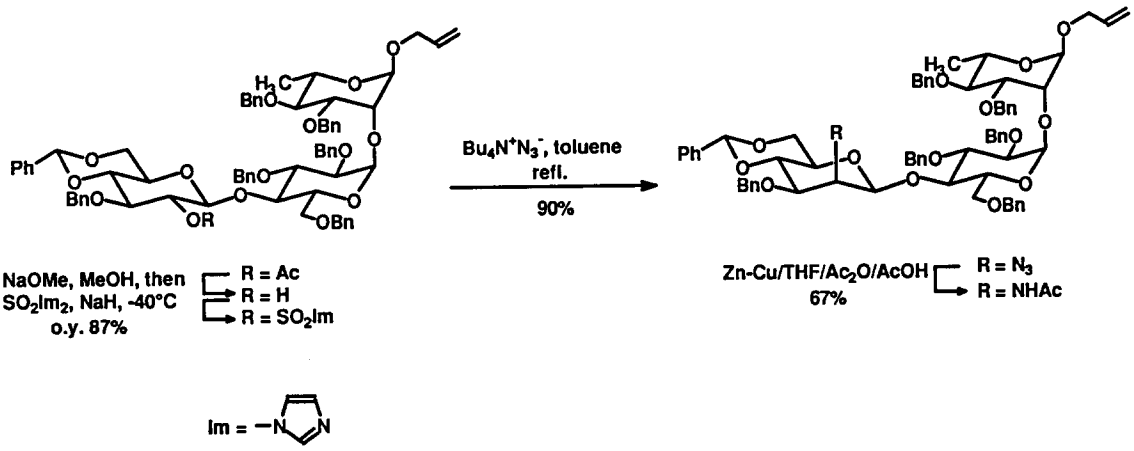
SYNTHESIS OF A - B - C / D - E - F



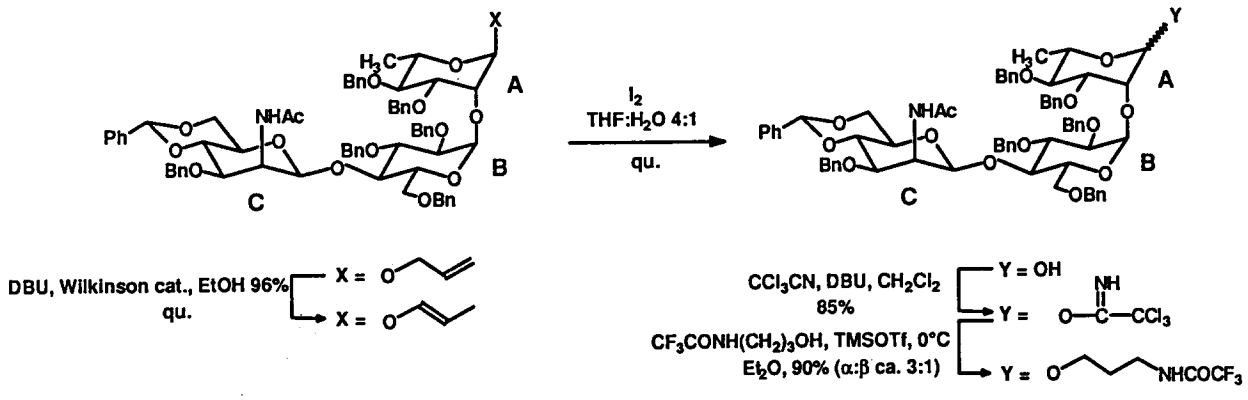
SYNTHESIS OF A - B / D - E



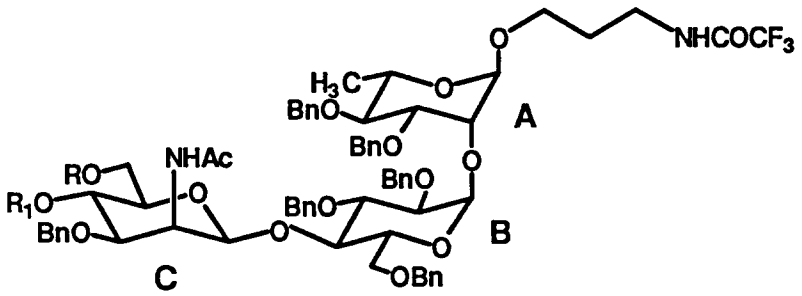
INVERSION GLUCOSE → MANNOSAMINE



SYNTHESIS OF ABC-SPACER



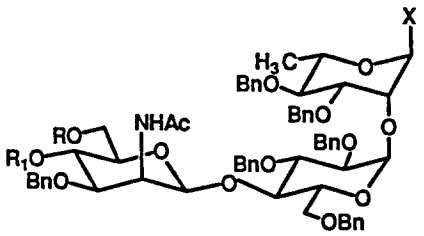
SYNTHESIS OF ABC-SPACER



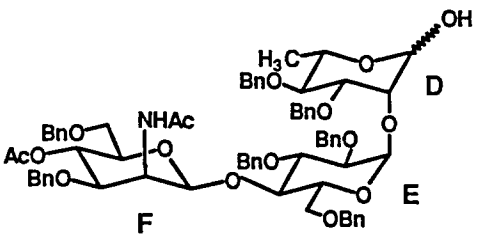
90% TFA, CH_2Cl_2, 0°C
then
Bu_2SnO, BnBr, TBAI, toluene
reflux, 67% o.y.

- R, R_1 = CHPh
- R = R_1 = H
- R = Bn; R_1 = H

SYNTHESIS OF D-E-F



I_2
THF:H_2O 4:1
82%



0% TFA, CH_2Cl_2, 0°C
hen
Bu_2SnO, BnBr, TBAI,
oluene reflux, 81% o.y.

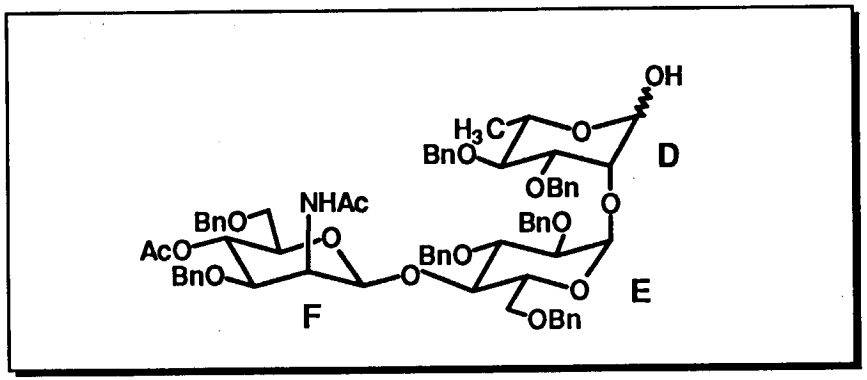
Ac_2O, Py, 96%

DBU, Wilkinson cat.,
EtOH 96%, qu.

- R, R_1 = CHPh ; X = O
- R = R_1 = H ; X = O
- R = Bn; R_1 = H ; X = O
- R = Bn; R_1 = Ac ; X = O
- R = Bn; R_1 = Ac ; X = O

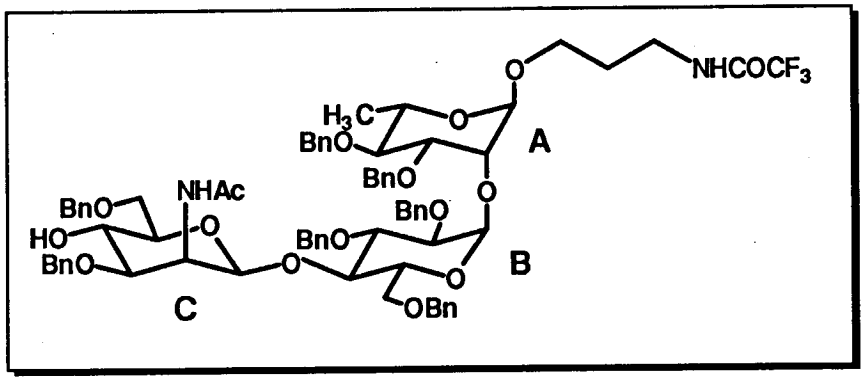
PHOSPHODIESTER BRIDGE: SYNTHETIC APPROACHES

R_1OH =



1) R_1OH → R_1—O—P(H)(=O)—OH $\xrightarrow{R_2OH}$ R_1—O—P(H)(=O)—O—R_2

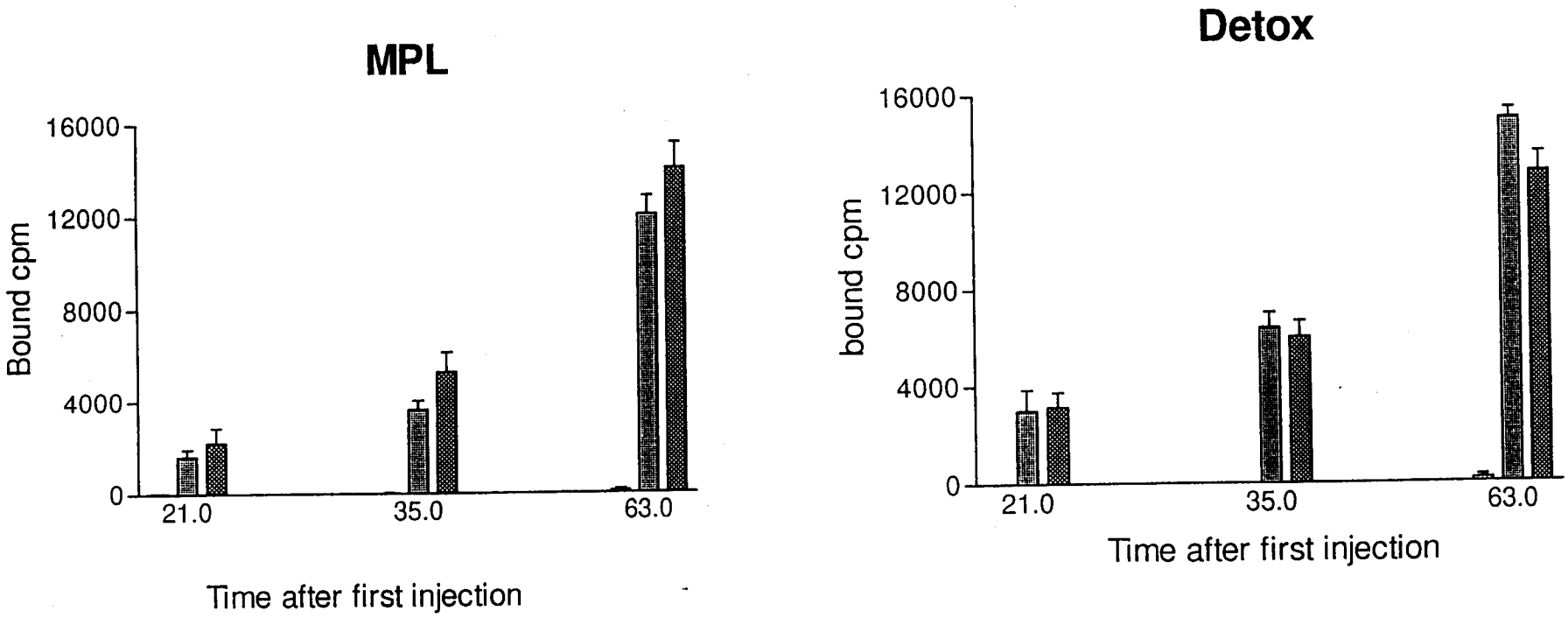
R_2OH =



2) R_2OH → R_2—O—P(H)(=O)—OH $\xrightarrow{R_1OH}$ R_2—O—P(H)(=O)—O—R_1

Activity of the glycoconjugate *in vivo*

(tetrasaccharide-KLH injected to mice CB 6F1)



VACCINATION PROTOCOL

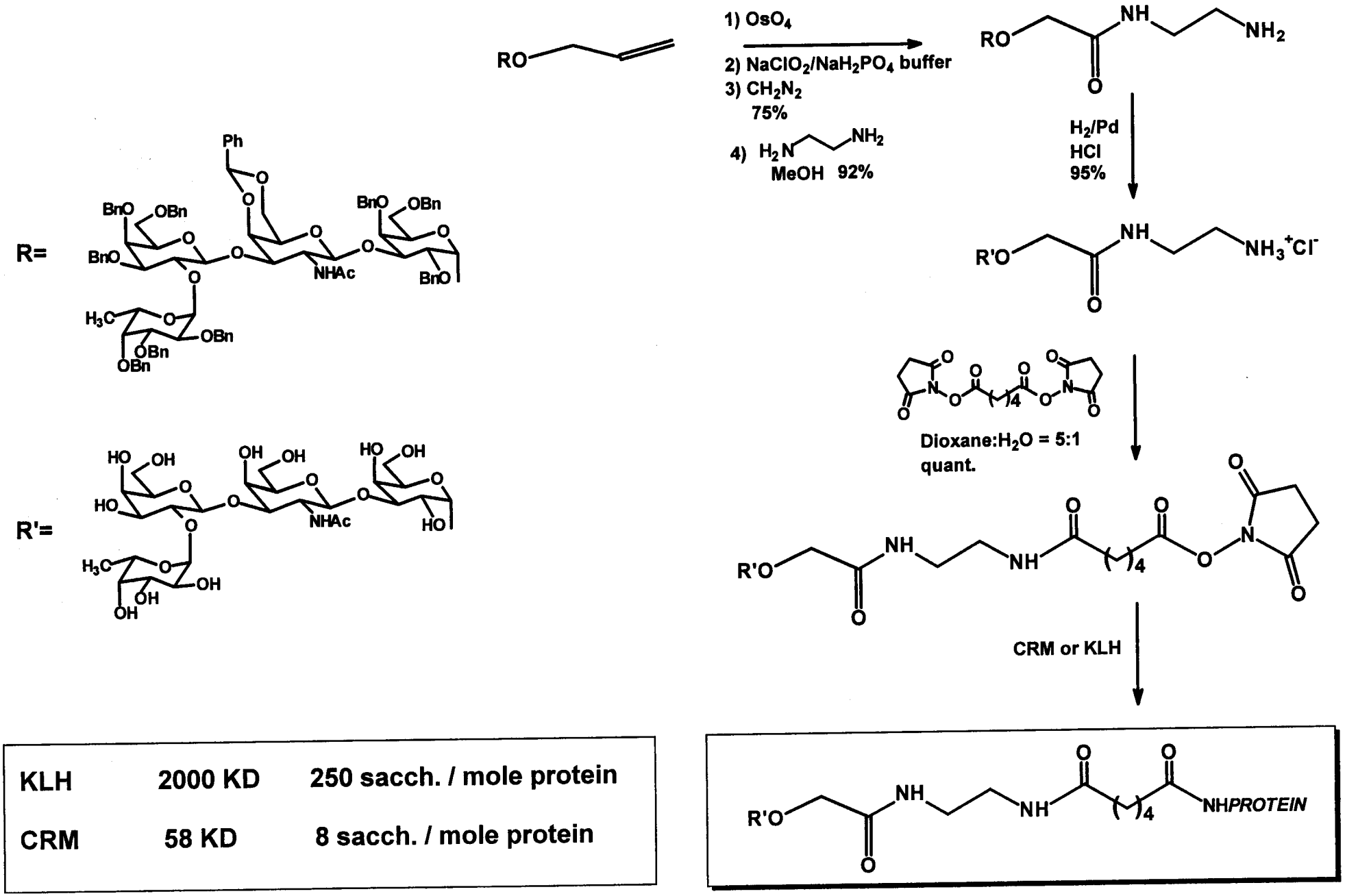
MICE CB6 F1

SUBCUTANEOUS INJECTION
2 X 100 µl

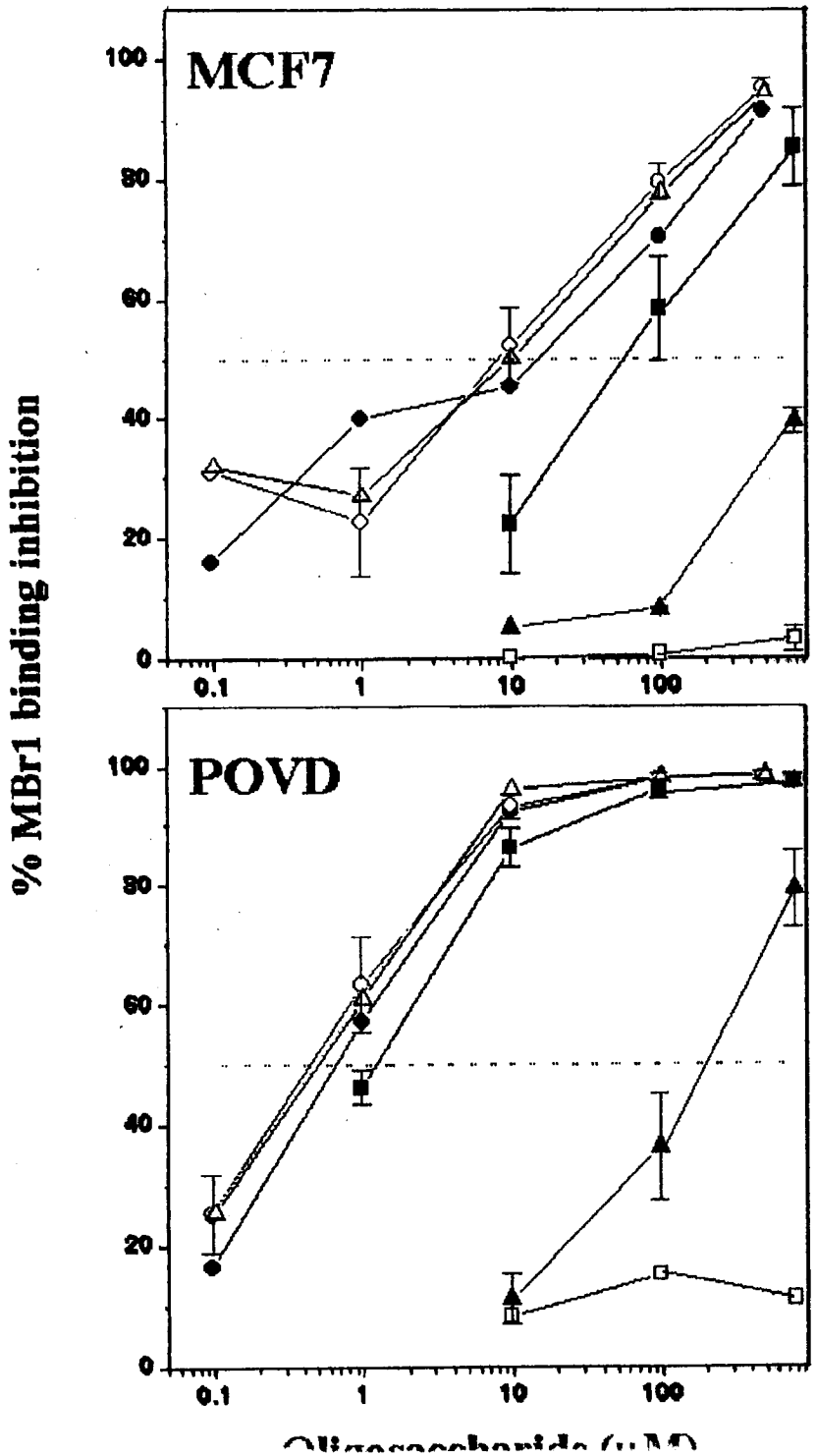
Injection	days	sera collection
1°→	0	←t_0
2°→	+15	
	+21	←t_1
3°→	+28	
	+35	←t_2
boost →	+50	
	} 56-62	←t_3

cellular response

SYNTHESIS OF GLYCOCONJUGATES OF *C-D-E-F*



KLH	2000 KD	250 sacch. / mole protein
CRM	58 KD	8 sacch. / mole protein



● 1. ABCDEF Fucα(1→2)-Galβ(1→3)-GalNAcβ(1→3)-Galα(1→4)-Galβ(1→4)-Glcβ-O-allyl

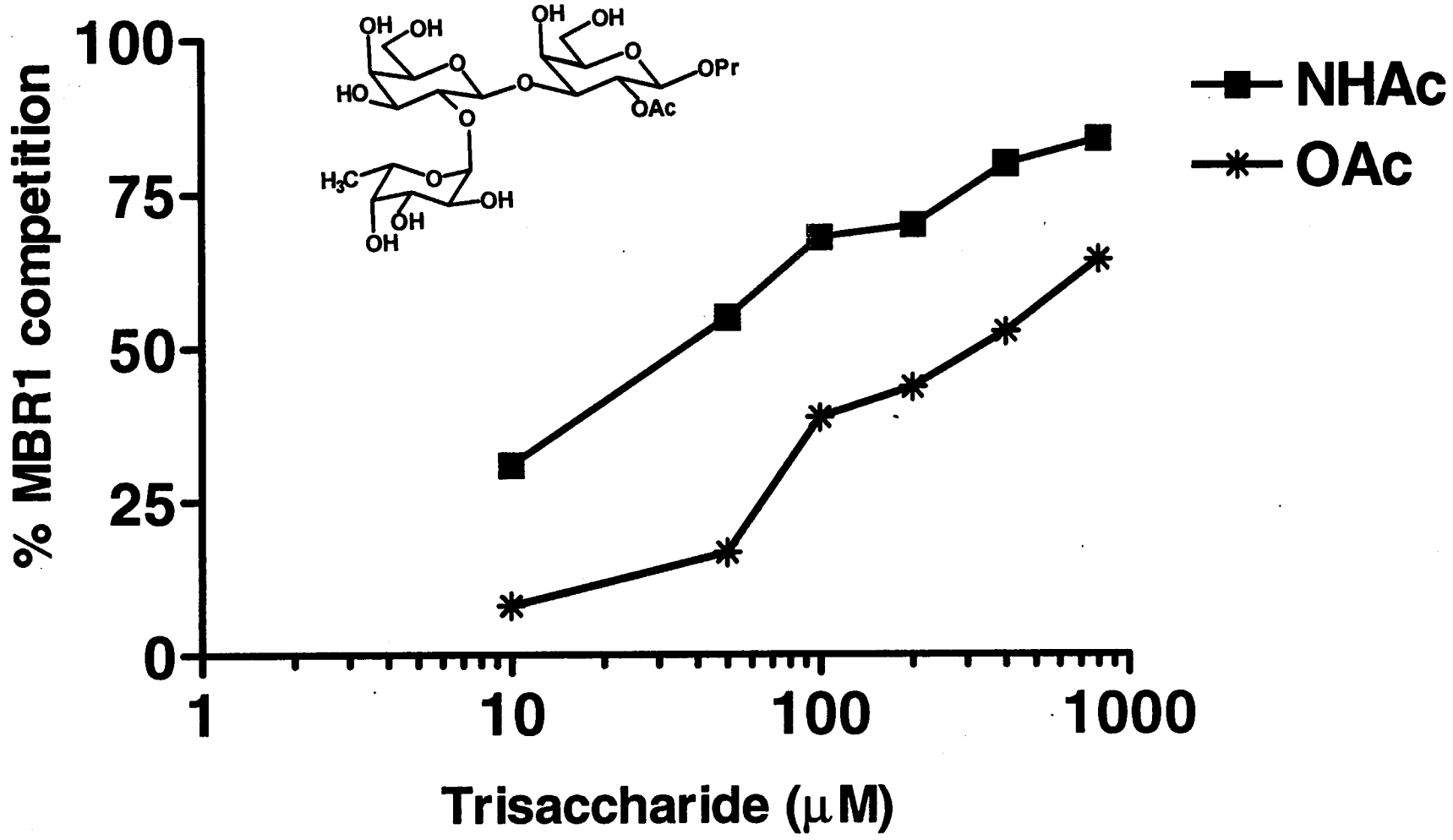
■ 2. DEF Fucα(1→2)-Galβ(1→3)-GalNAcβ-O-propyl

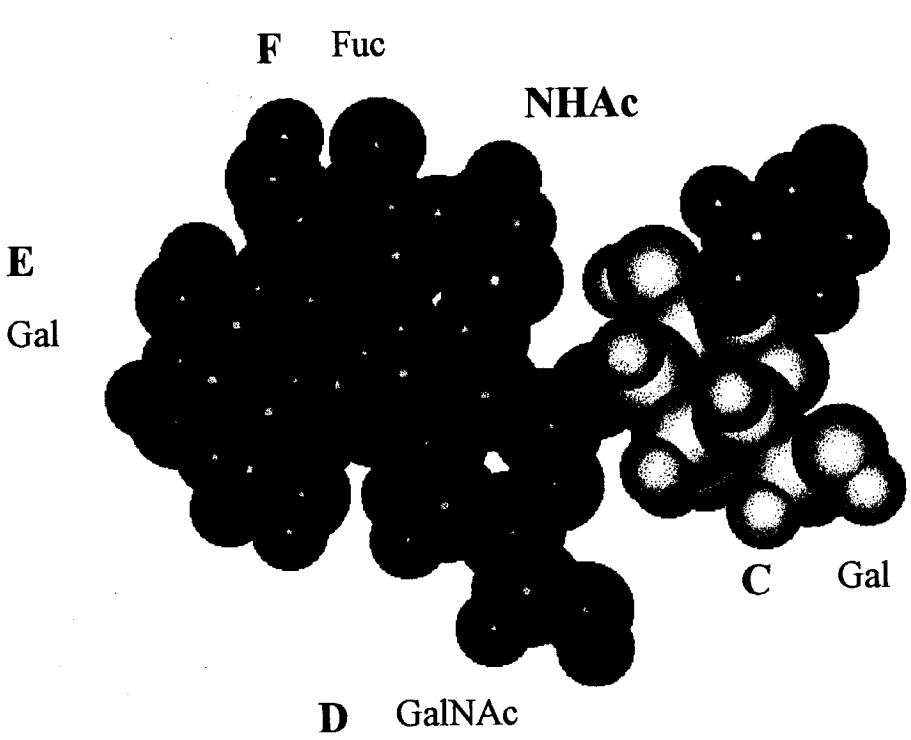
▲ 3. α DEF Fucα(1→2)-Galα(1→3)-GalNAcβ-O-propyl

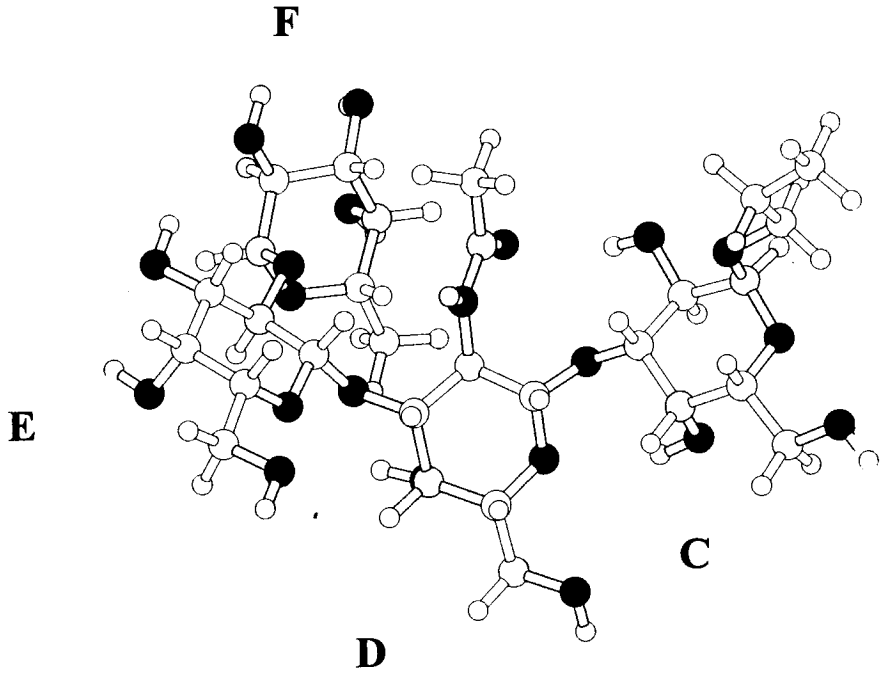
○ 4. CDEF Fucα(1→2)-Galβ(1→3)-GalNAcβ(1→3)-Galα-O-propyl

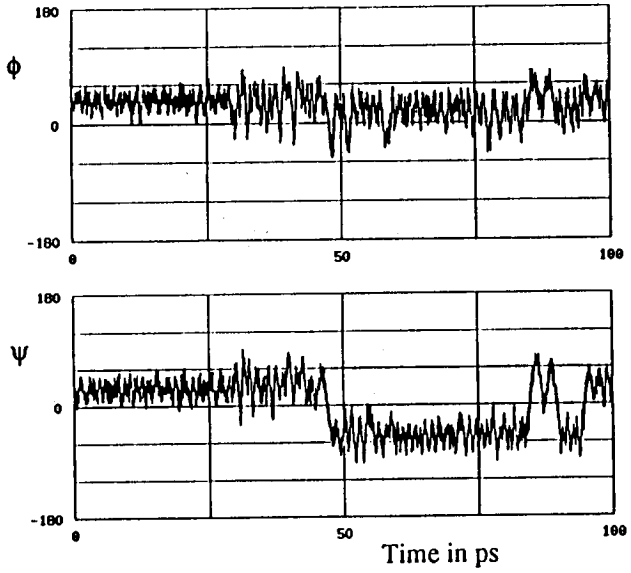
△ 5. β CDEF Fucα(1→2)-Galβ(1→3)-GalNAcβ(1→3)-Galβ-O-propyl

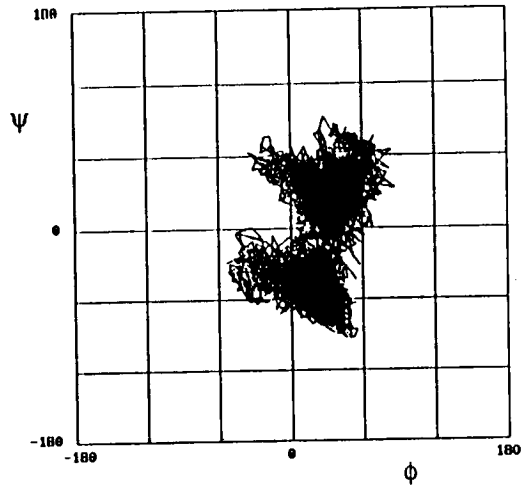
□ 6. CDE Galβ(1→3)-GalNAcβ(1→3)-Galα-O-propyl

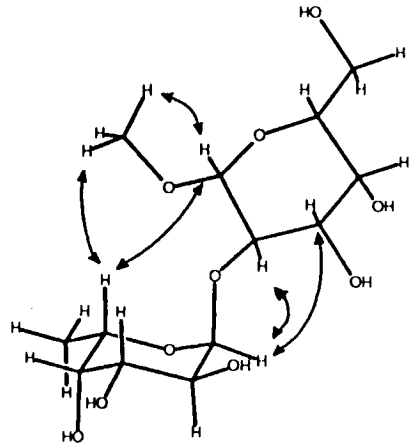

% MBR1 competition
100
75
50
25
0
1
10
100
1000
Trisaccharide (μM)
NHAc
OAc
OH
OH
HO
O
OPr
OAc
H3C
OH


F Fuc
NHAc
E
Gal
C Gal
D GalNAc


F
E
C
D

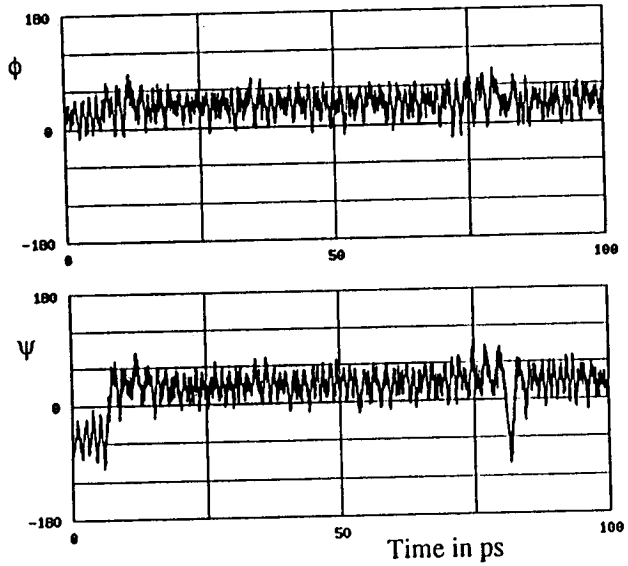


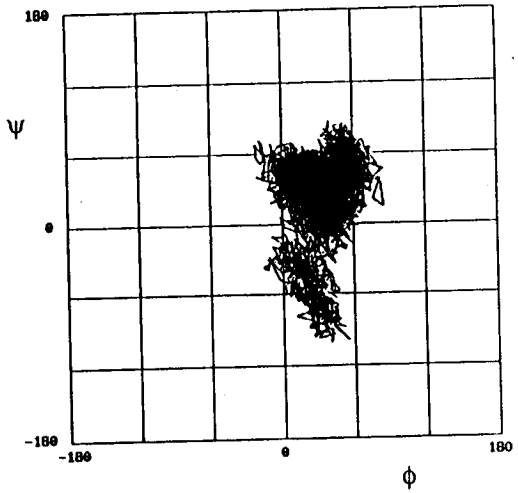


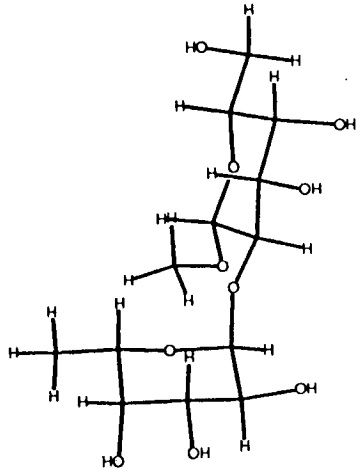


A

ϕ 36° **ψ 23°**

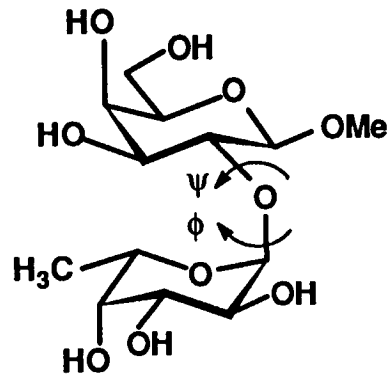






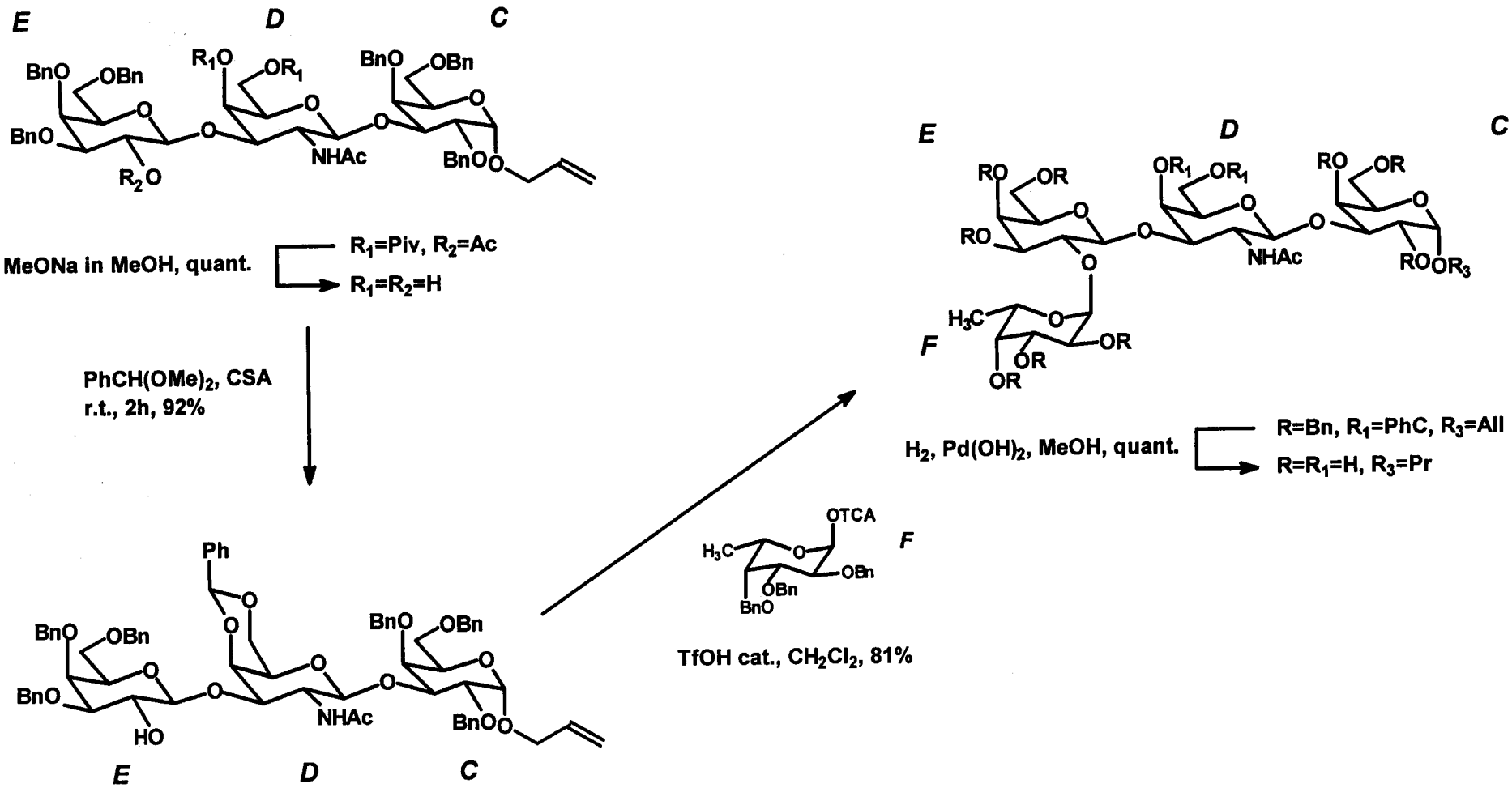
B

ϕ 26° **ψ -58°**

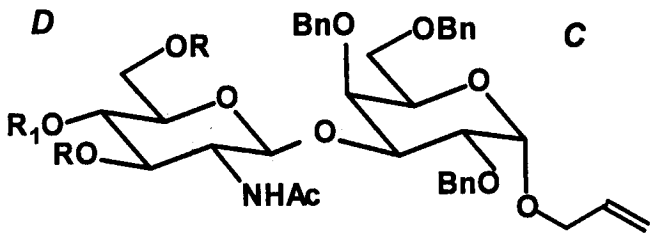


	ϕ/ψ (degrees)	E_{rel} (Kcal/mol)	Equil. percentage
A	36/23	0.47	30.9
B	26/-58	0.00	68.3
C	21/173	2.67	0.8
D	46/-147	4.75	<0.1

SYNTHESIS OF *C-D-E-F*



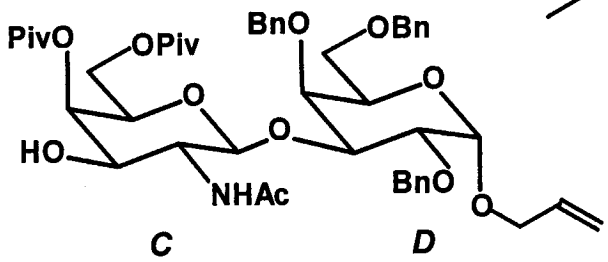
SECOND SYNTHESIS OF *C-D-E*

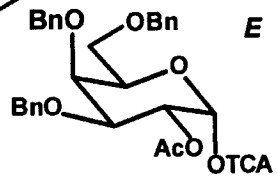


MeONa in MeOH quant. R=R$_1$=Ac → R=R$_1$=H

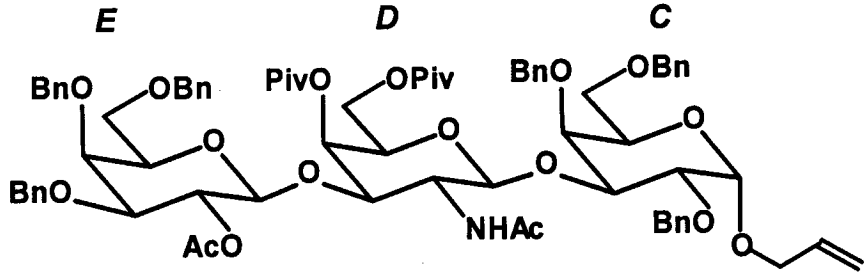
PivCl, CH_2Cl_2:py=1:1, 78% → R=Piv, R$_1$=H

CH_2Cl_2, py, Tf_2O
Then H_2O
79%

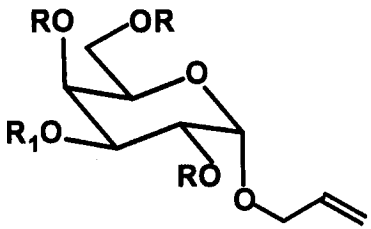




TfOH, CH_2Cl_2
84%



SYNTHESIS OF *C-D*



Bu_2SnO, benzene, reflux 24h
then $Bu_4N^+Br^-$, MPMCl 80%

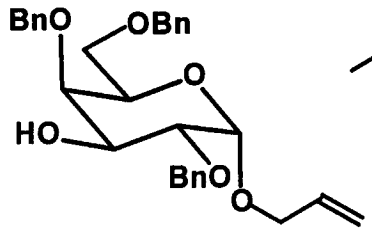
$R=R_1=H$

$R=H, R_1=PMB$

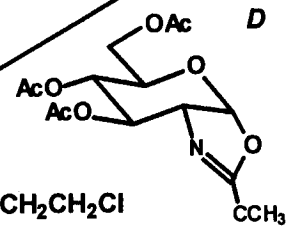
BnBr, NaH, THF
83%

$R=Bn, R_1=PMB$

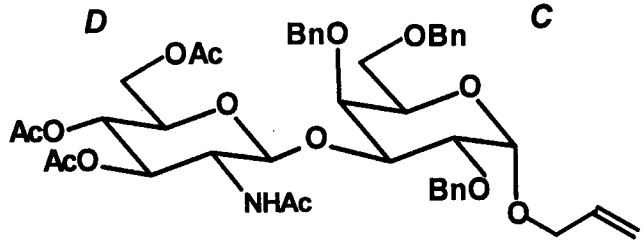
DDQ, CH_2Cl_2:H_2O=20:1
72%



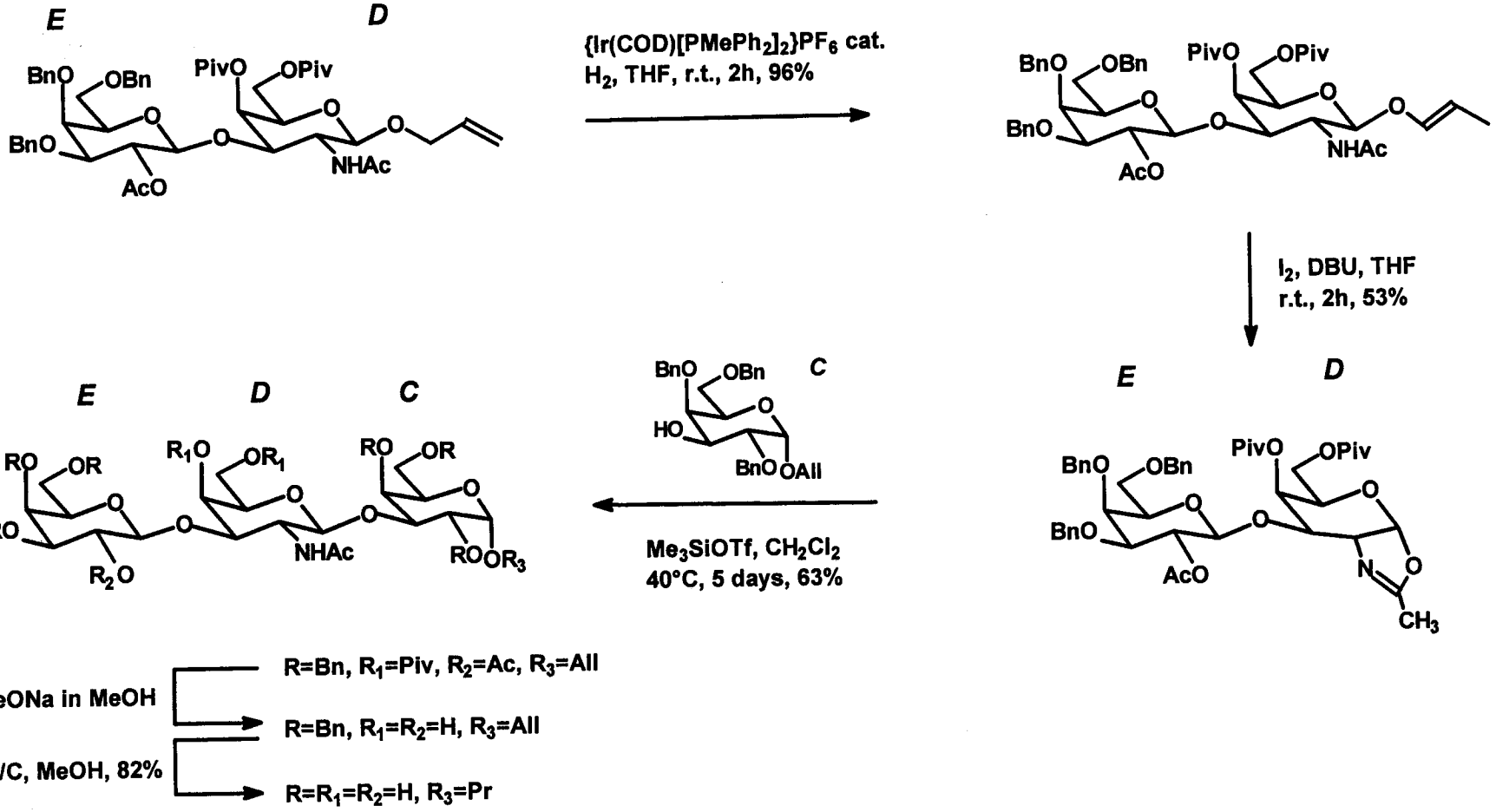
C



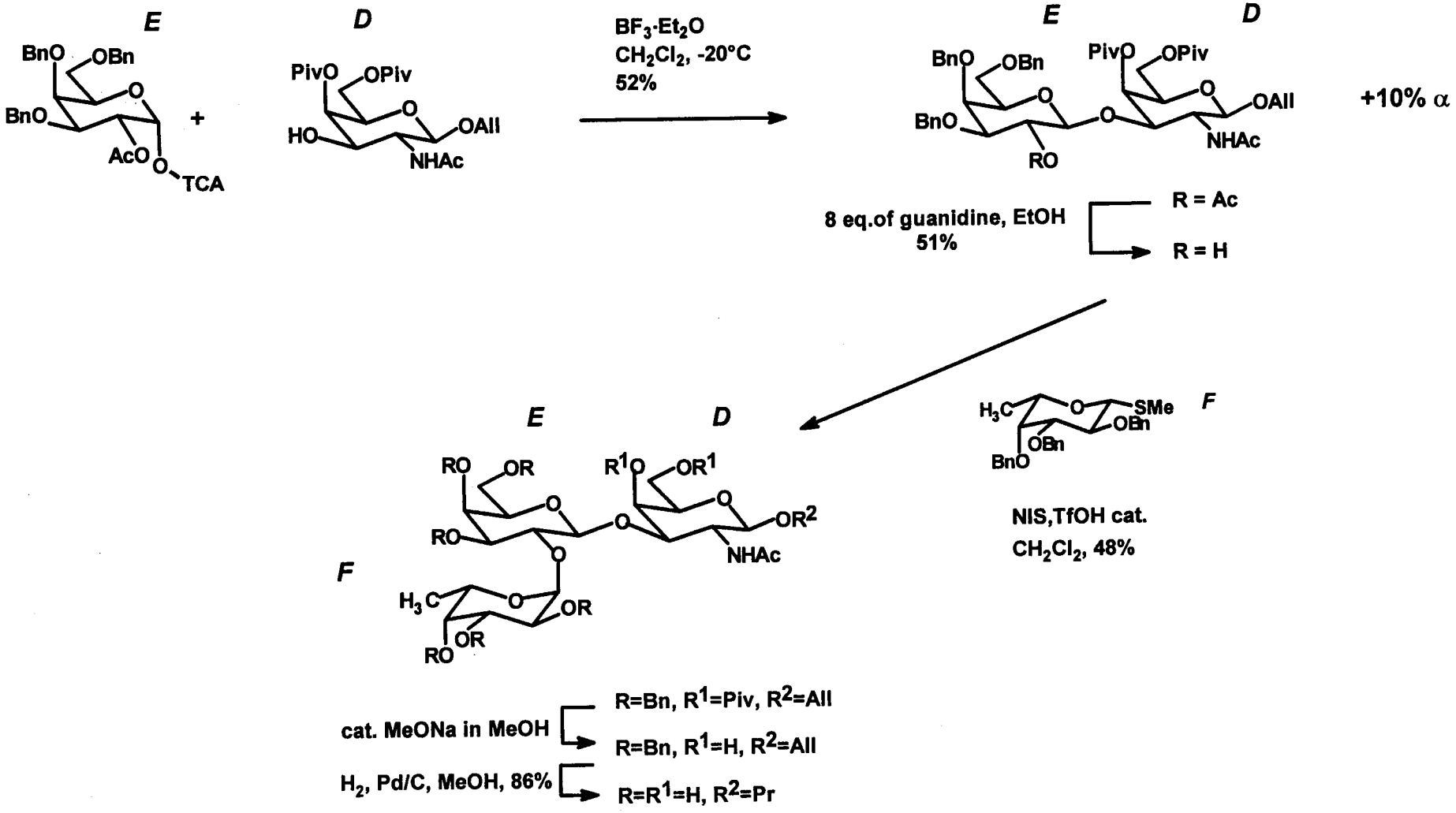
TfOH, $ClCH_2CH_2Cl$
70%



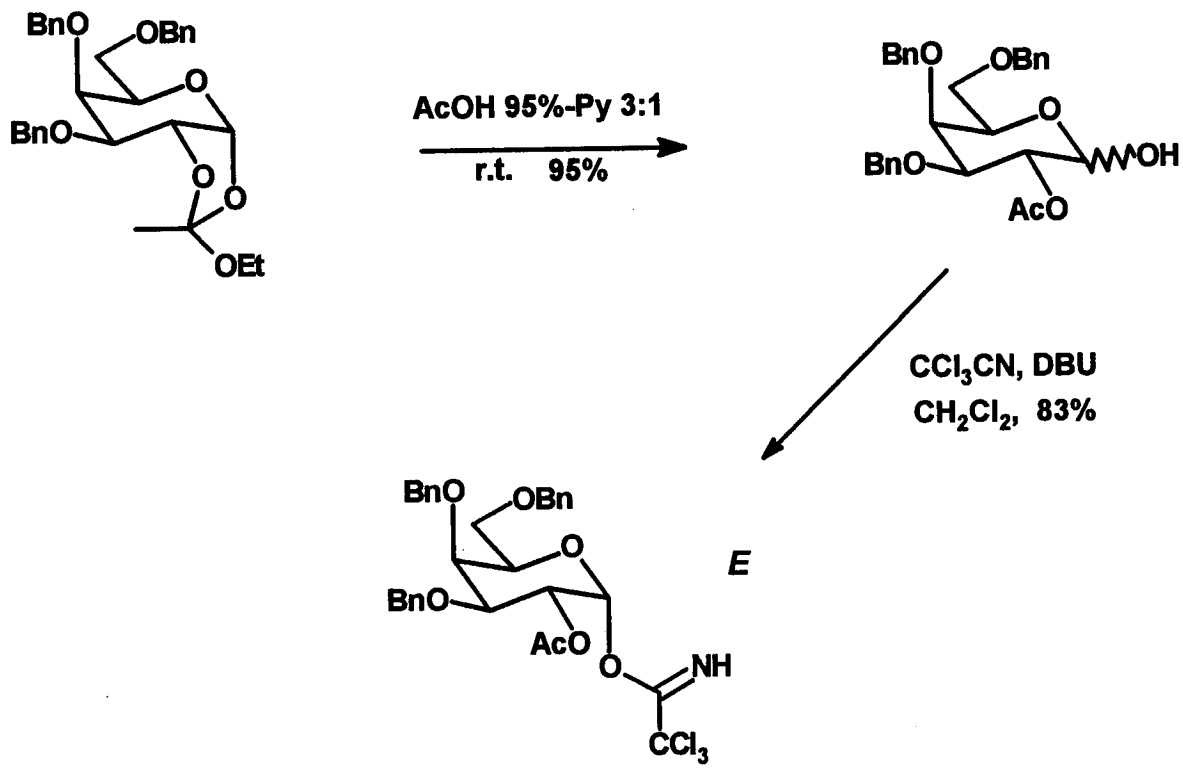
FIRST SYNTHESIS OF *C-D-E*



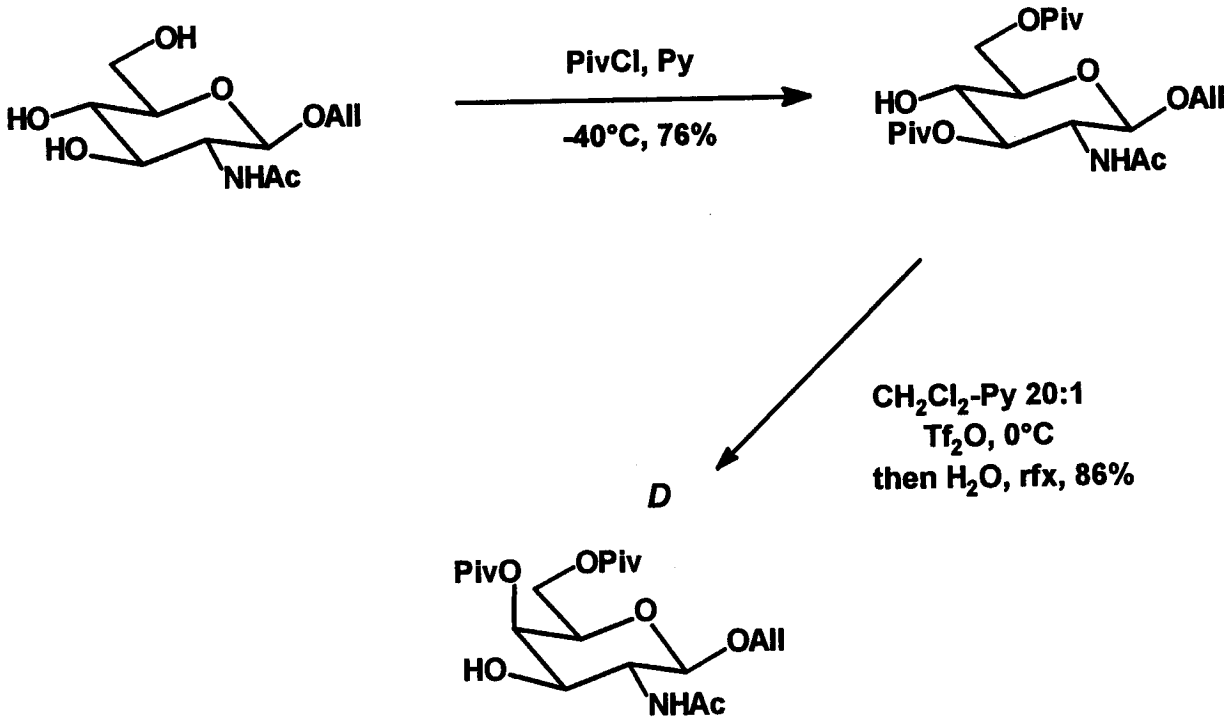
SYNTHESIS OF *D-E-F*



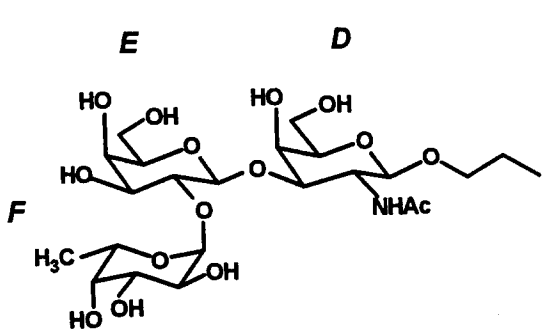
BUILDING BLOCK *E*

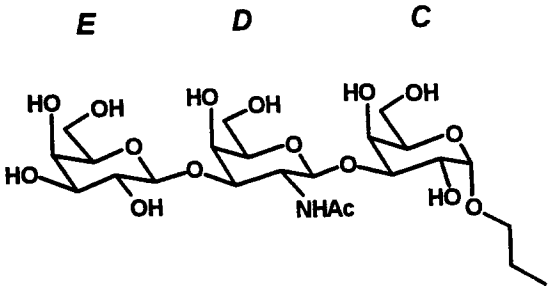


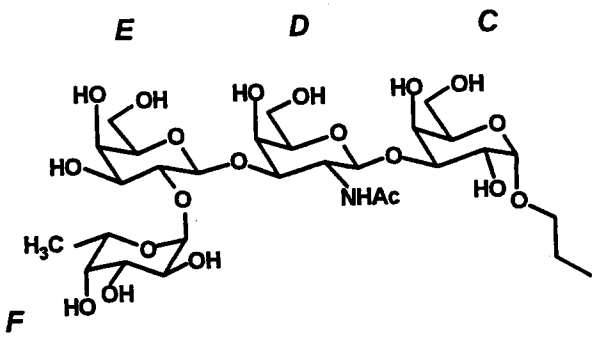
BUILDING BLOCK *D*

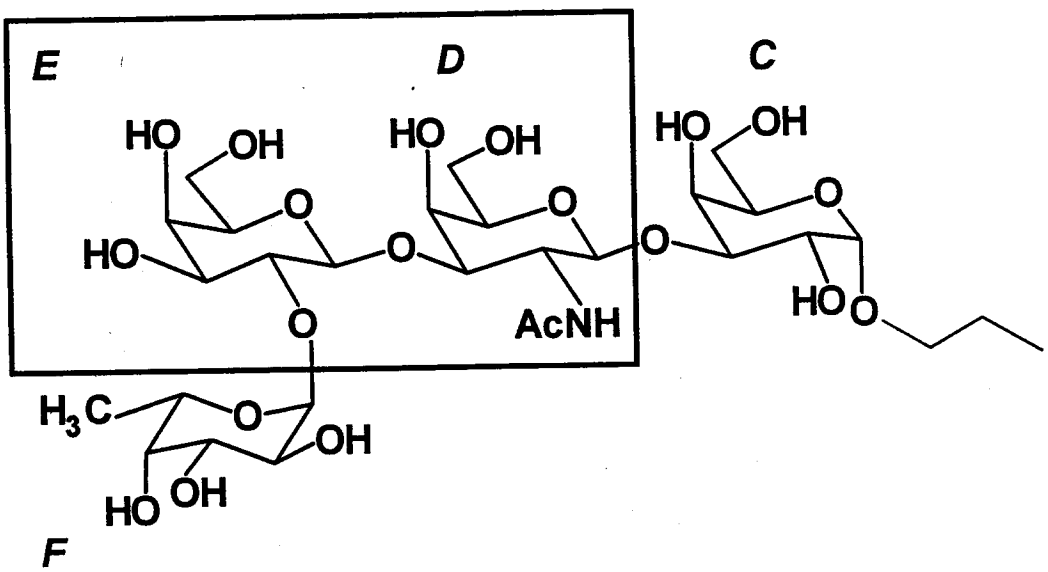


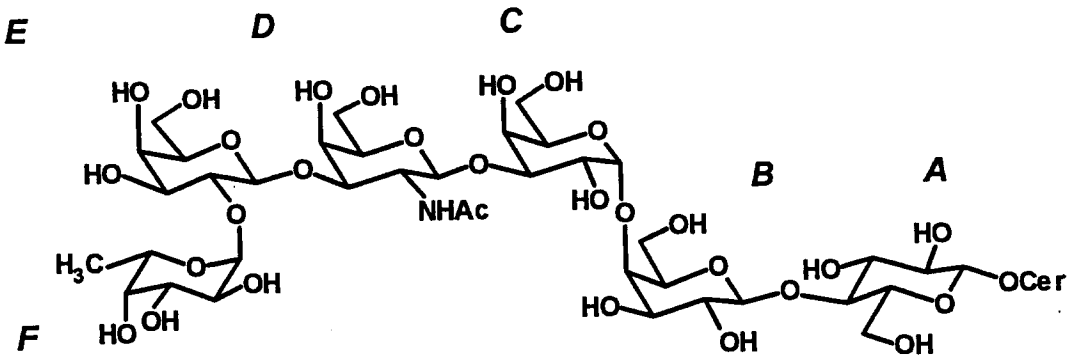
SYNTHETIC TARGETS

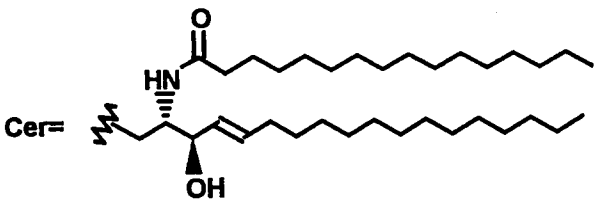




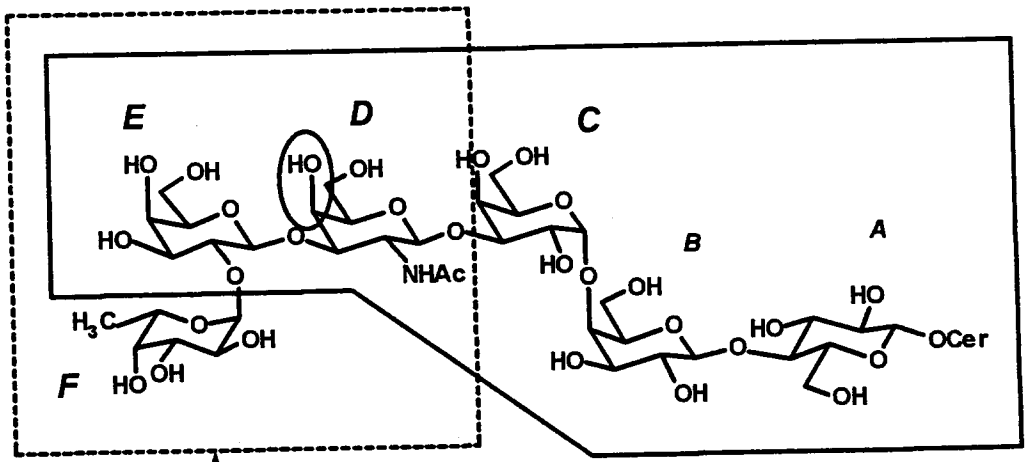








Globo-H



β-Gal(1→3)-βGalNAc(1→4)-βGal(1→4)-Glc

α-Fuc(1→4)

SYNTHESIS OF THE PROTECTED SPACER CONTAINING DIMER OF THE TRISACCHARIDE REPEATING UNIT OF 19F