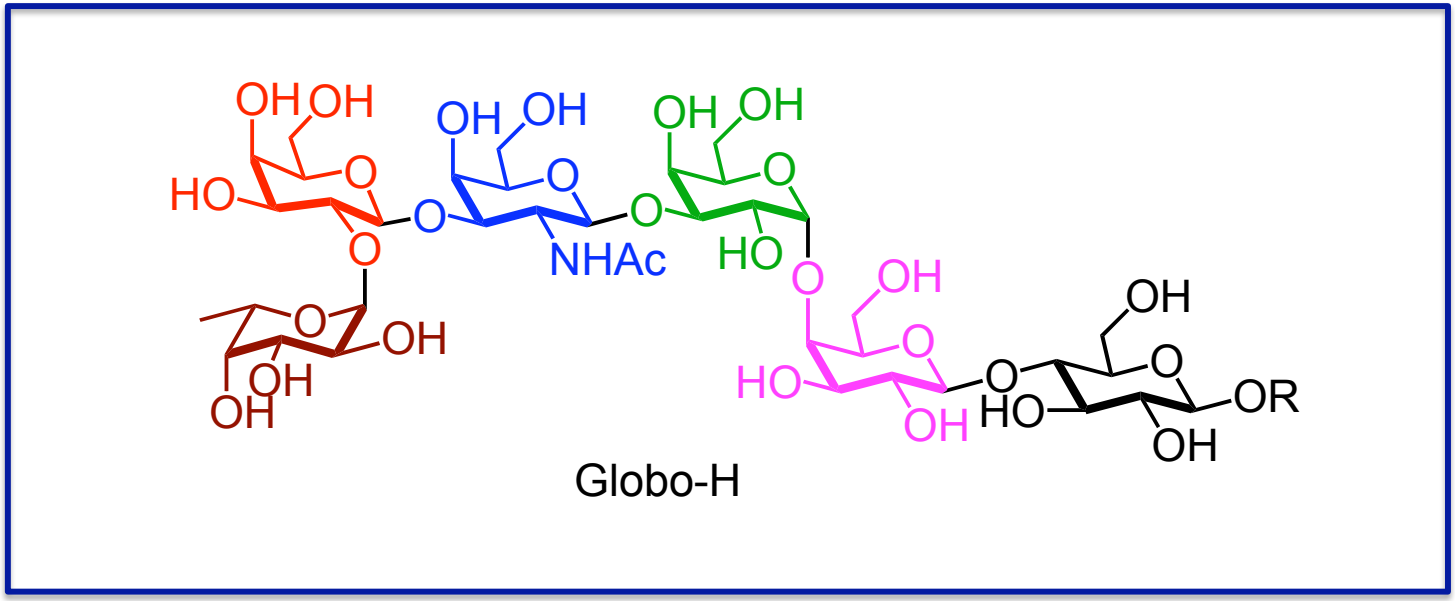
Development of Carbohydrate Based Anticancer Vaccine

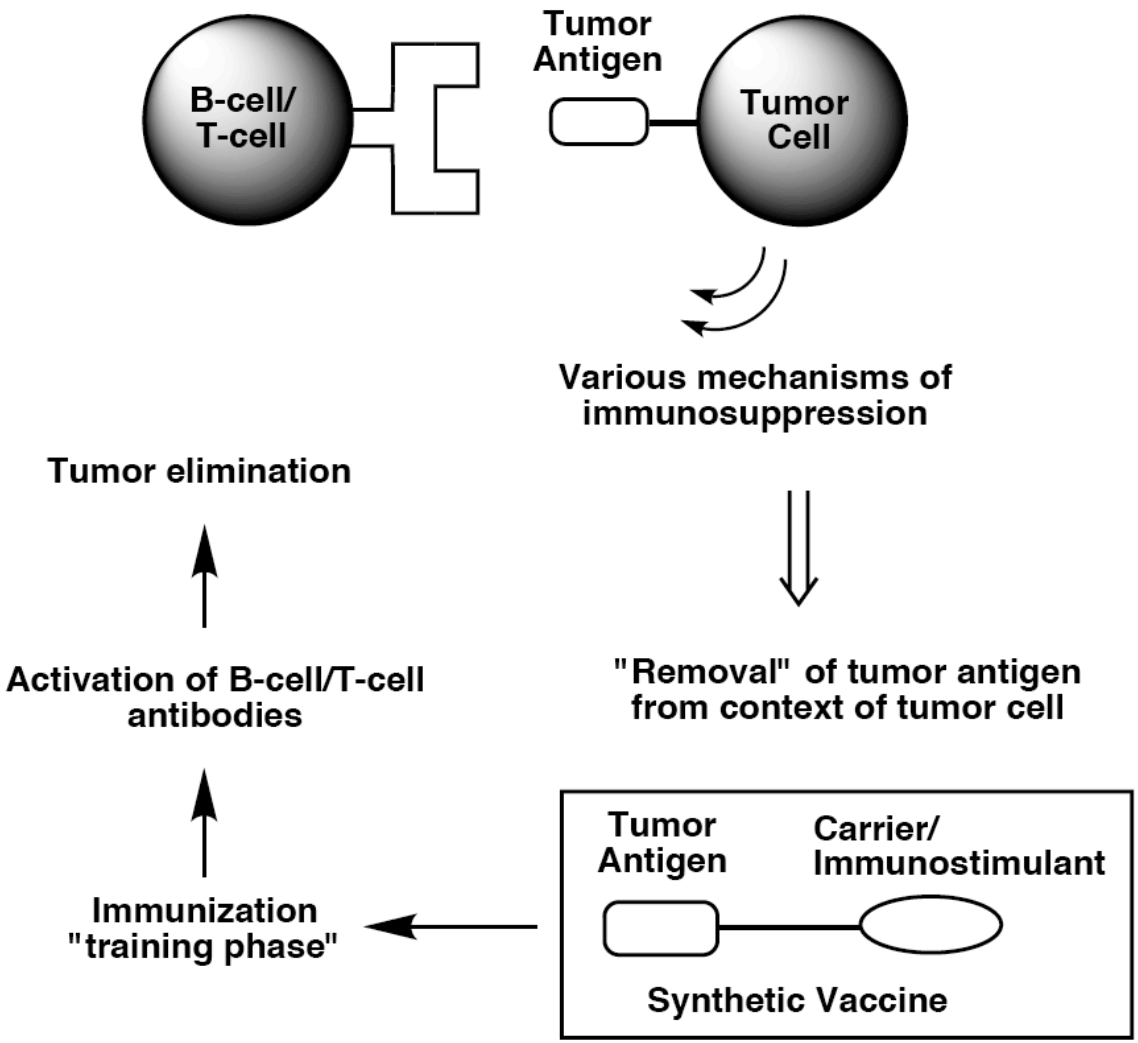


Globo-H

Munmun Mukherjee

Group Meeting

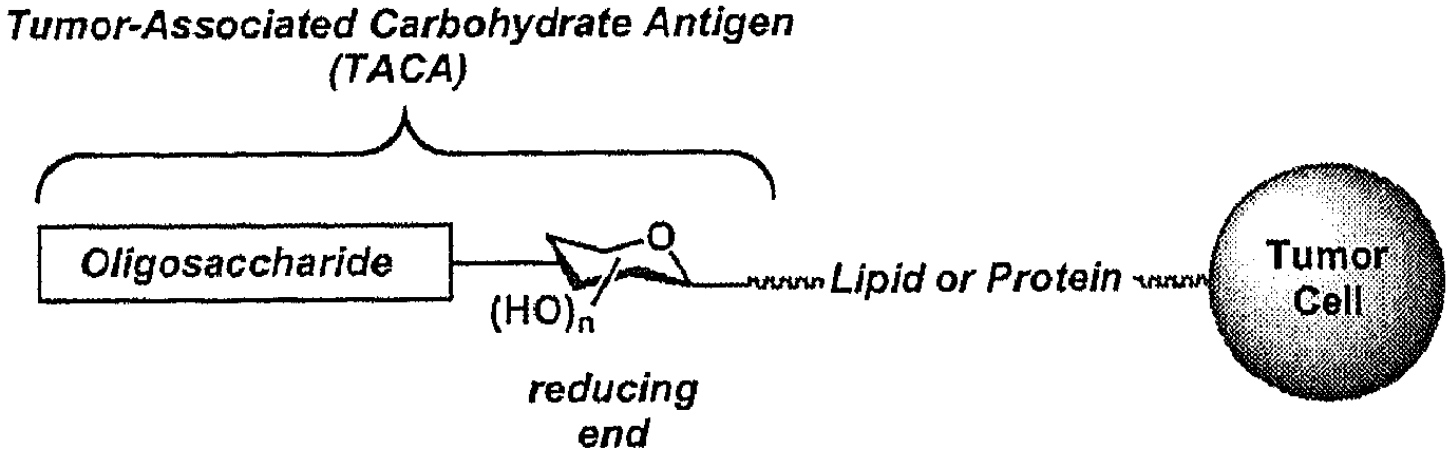
Strategy



Danishefsky, J. S, Allen, J. R, *Angew. Chem. Int. Ed*. **2000**, *39*, 836 - 863

Design of Carbohydrate-Based antitumor Vaccines

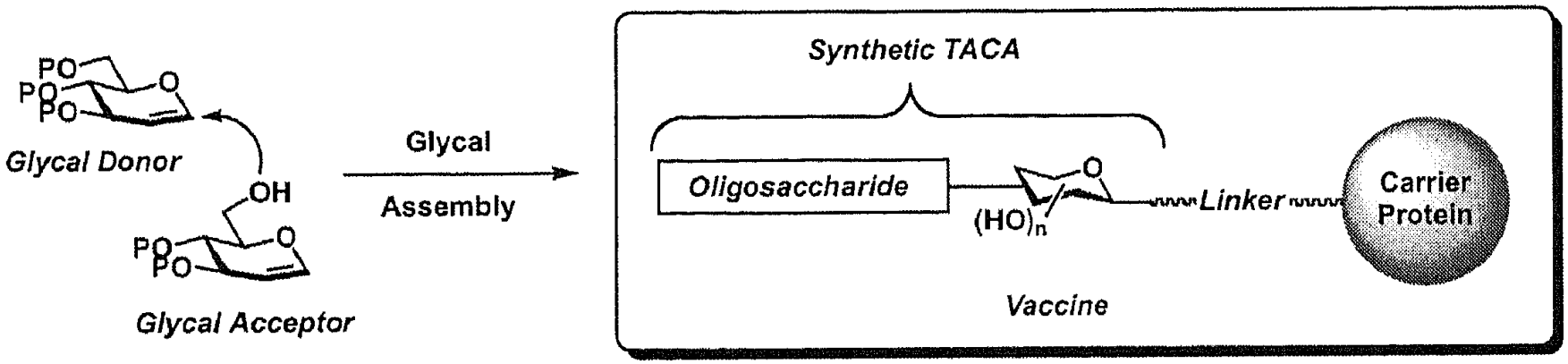
Cell-surface glycoproteins and glycolipids displaying tumor-associated carbohydrate antigen



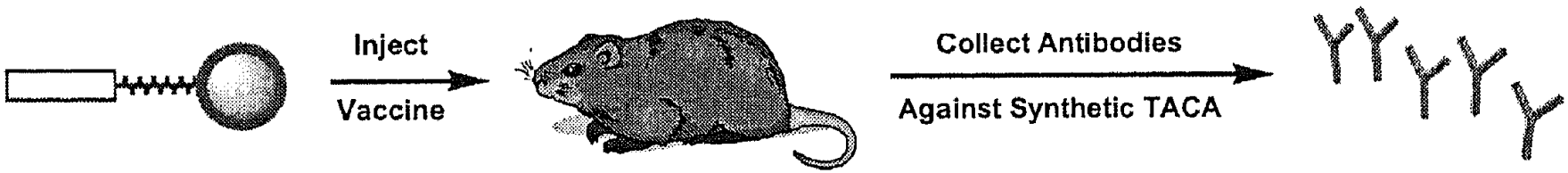
Malignantly transformed tumor cell exhibit abnormal cell surface glycosylation patter

Danishefsky, J. S, Rebecca, M. W.; Warren, D.J.; Querfelli, O. *Expert Rev. Vaccines* **2005**, *4*, 677

Design of Carbohydrate-Based antitumor Vaccines



Mimic the tumor cell surface : vaccine with one or more TACA

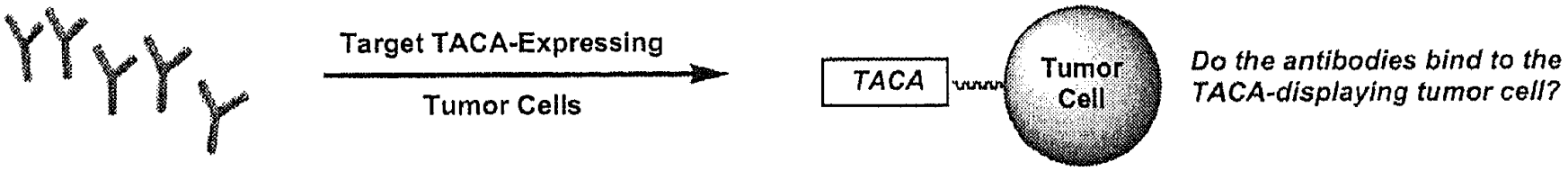


Induction of antibodies to synthetic TACA

Danishefsky, J. S, Rebecca, M. W.; Warren, D.J.; Querfelli, O. *Expert Rev. Vaccines* **2005**, *4*, 677

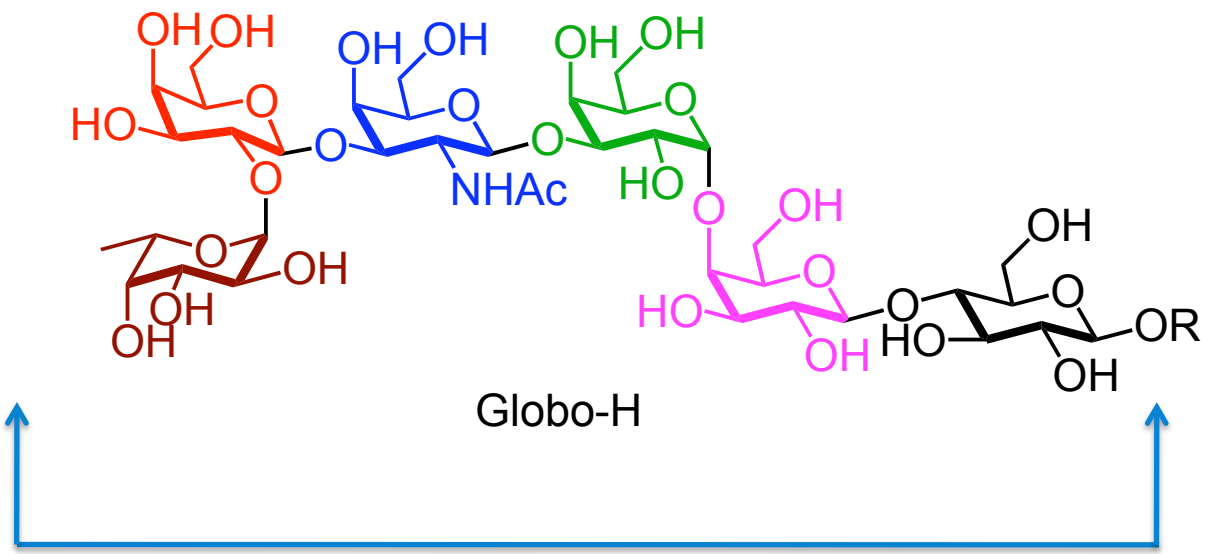
Design of Carbohydrate-Based antitumor Vaccines

Evaluation of reactivity of antibodies against cell-surface TACAs



Danishefsky, J. S, Rebecca, M. W.; Warren, D.J.; Querfelli, O. *Expert Rev. Vaccines* **2005**, *4*, 677

Monovalent Vaccines



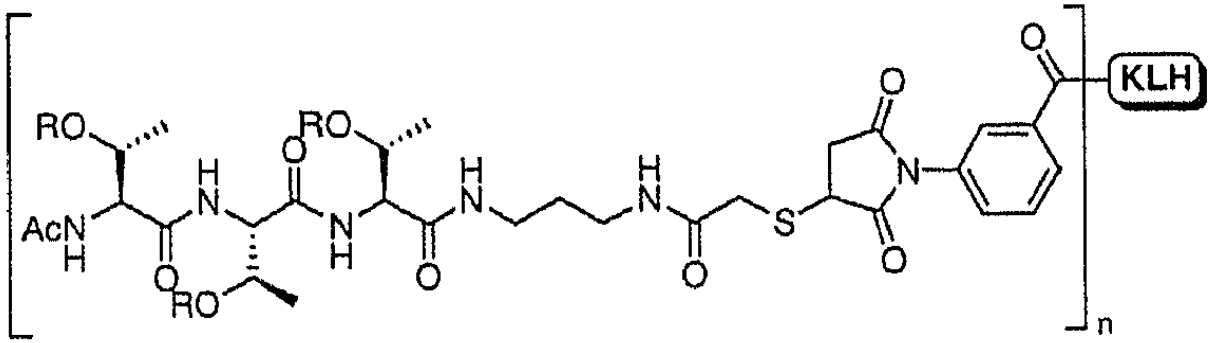
Isolated in submilligram quantities as a ceramide-linked glycolipid from the human breast cancer cell line MCF-7 by Hakomori *et al.*

Globo-H was also expressed in other types of carcinomas including colon, lung, ovary, small cell lung cancer, and prostest cancers

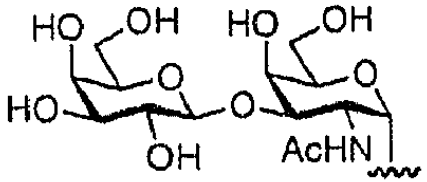
Galonic, P. D., Gin, Y. D., *Nature* **2007**, *446*, 1000

Monovalent Clustered Vaccines

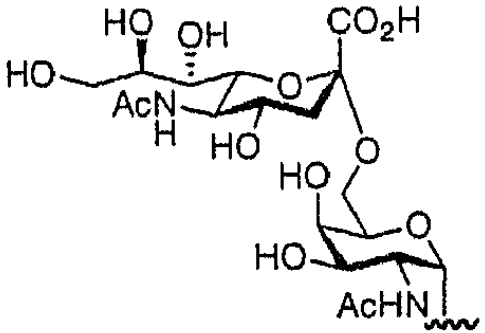
Exhibit enhanced levels of antibody induction in comparison with nonclustered congeners



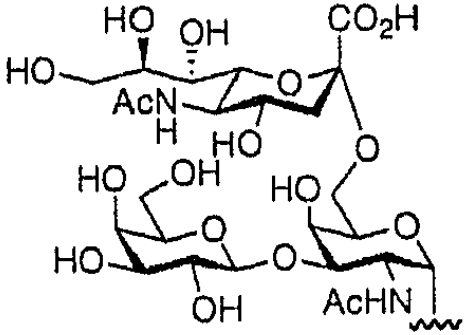
R =



TF(c)-MBS-KLH



STn(c)-MBS-KLH



2,6-STF-MBS-KLH

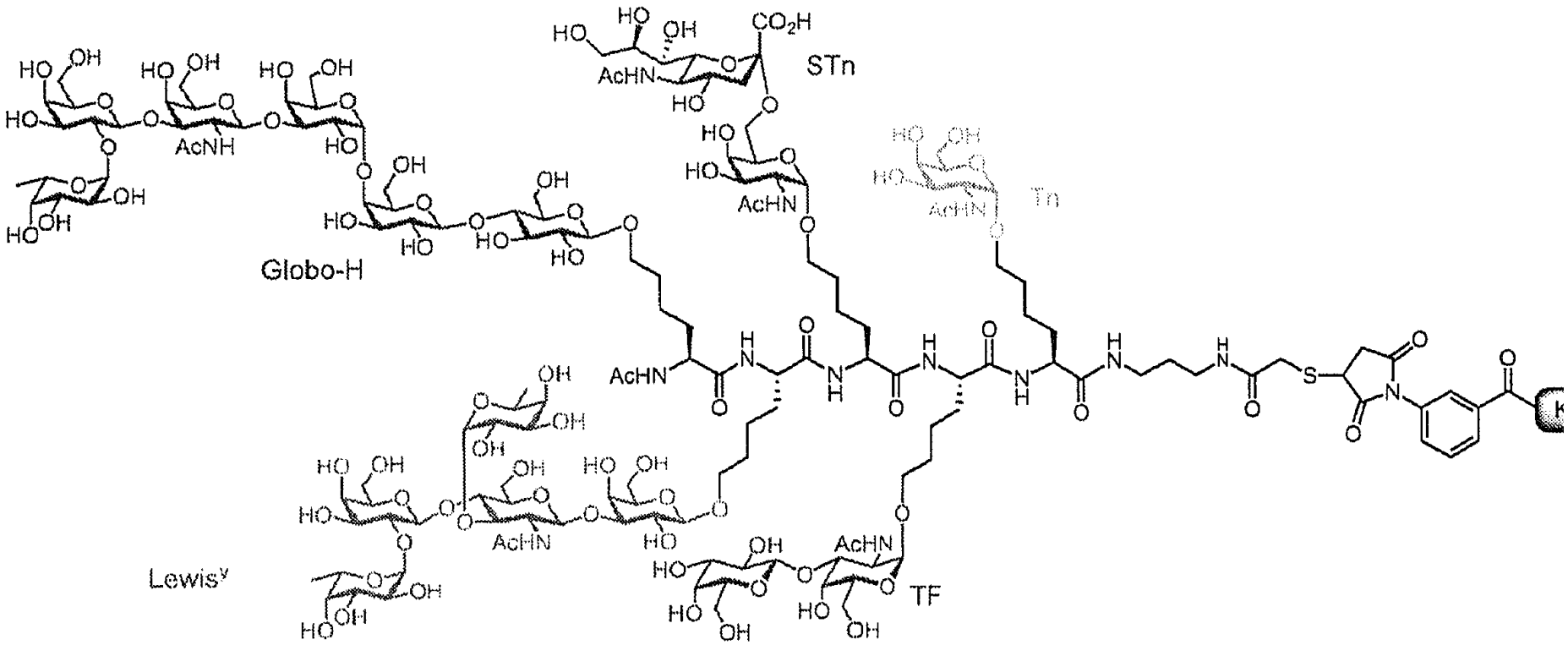
Clustering groups of antigens to single peptide backbone

Cassette method: galactose (Gal)NAc monosaccharide α-linked to amino acid

synthesis of oligosaccharide proceed with preexisting α-*O*-linkage

Danishefsky, J. S, Allen, J. R, *Angew. Chem. Int. Ed*. **2000**, *39*, 836

Unimolecular Multivalent Vaccines



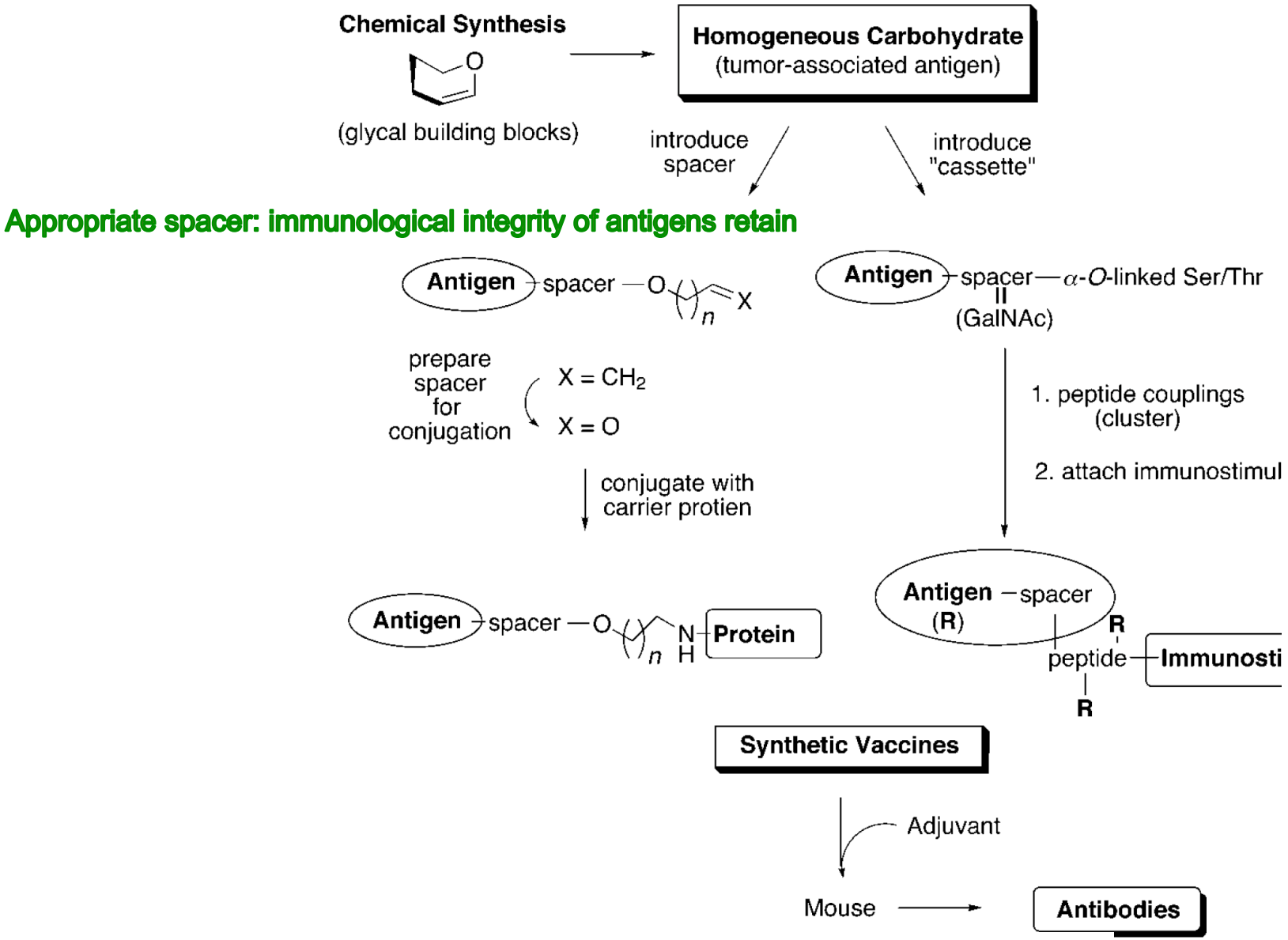
Unimolecular pentavalent vaccine: mimic heterogeneity

Each antigens except Le^y induced formation of IgM and IgG antibodies.

second generation pentavalent construct involve replacement of Le^y antigen.

Danishefsky, J. S, Rebecca, M. W.; Warren, D.J.; Querfelli, O. *Expert Rev. Vaccines* **2005**, *4*, 677

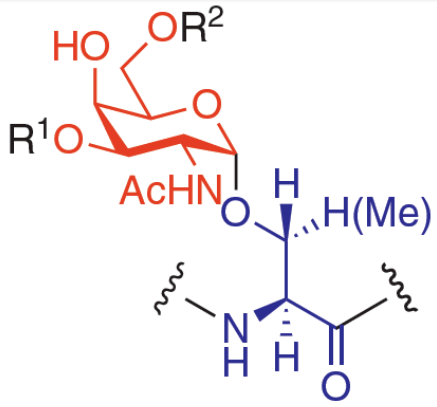
General approach to synthetic Carbohydrate Vaccines



Danishefsky, J. S, Allen, J. R, *Angew. Chem. Int. Ed*. **2000**, *39*, 836 - 863

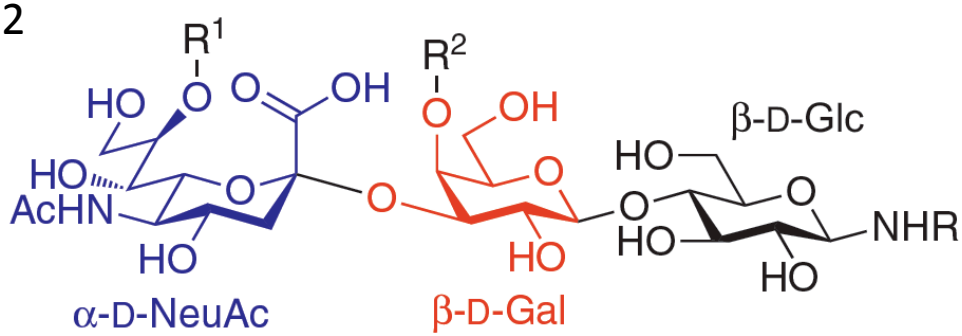
Some Antigens in Cancer cell

1



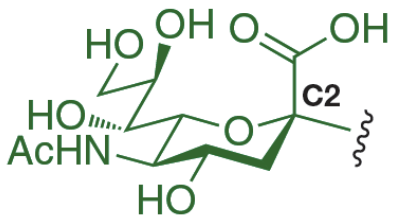
GalNAcα1-*O*-Ser/Thr linkage

2

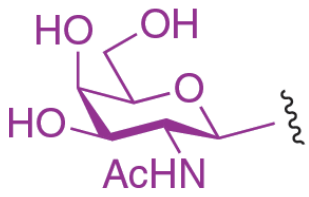


α-D-NeuAc β-D-Gal

T_N	R^1 = H; R^2 = H
T	R^1 = β-D-Gal; R^2 = H
ST_N	R^1 = H; R^2 = α-D-NeuAc
2,6-ST	R^1 = β-D-Gal; R^2 = α-D-NeuAc
GM2	R^1 = H; R^2 = β-D-GalNAc
GD3	R^1 = α-D-NeuAc; R^2 = H
GD2	R^1 = α-D-NeuAc; R^2 = β-D-GalNAc



α-D-NeuAc



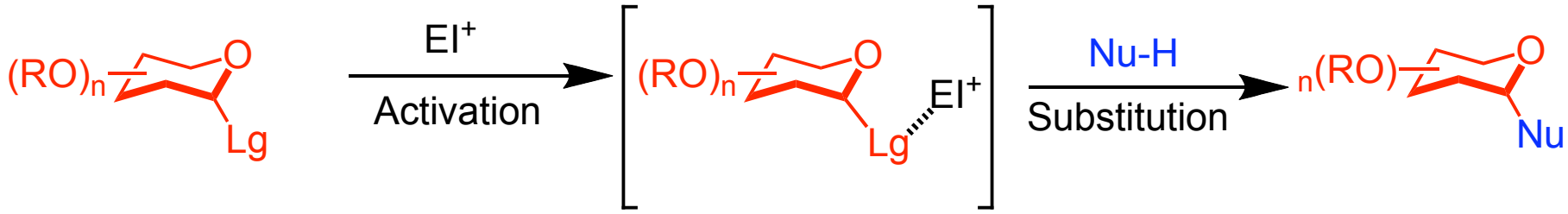
β-D-GalNAc

3. Globo-H

Galonic, P. D., Gin, Y. D., *Nature* **2007**, *446*, 1000

Glycosylation Strategy

Acetal exchange



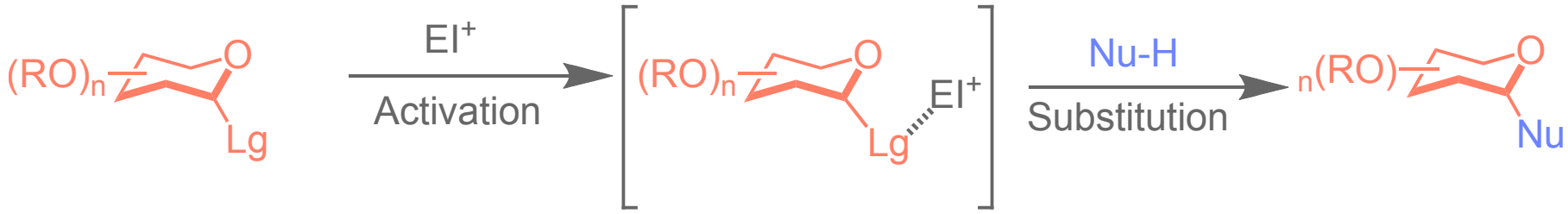
Protected glycosyl donor

Lg = X, Allyl, OH, SR_2

Nu-H :nucleophilic gycosyl acceptor

Glycosylation Strategy

Acetal exchange

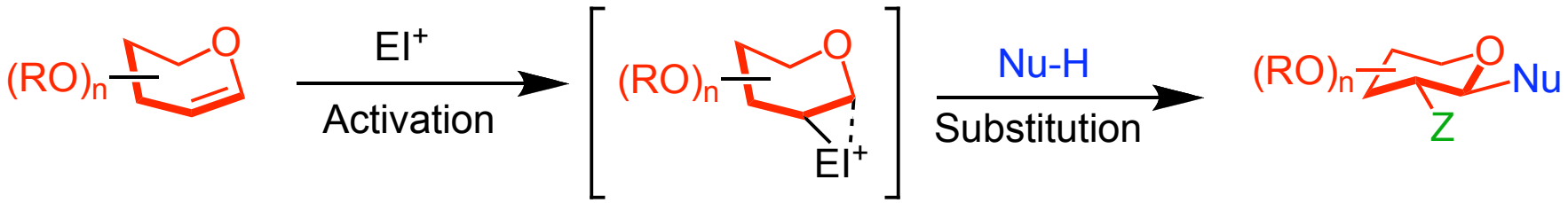


Protected glycosyl donor

Lg = X, Allyl, OH, SR_2

Nu-H :nucleophilic gycosyl acceptor

Glycal oxidation



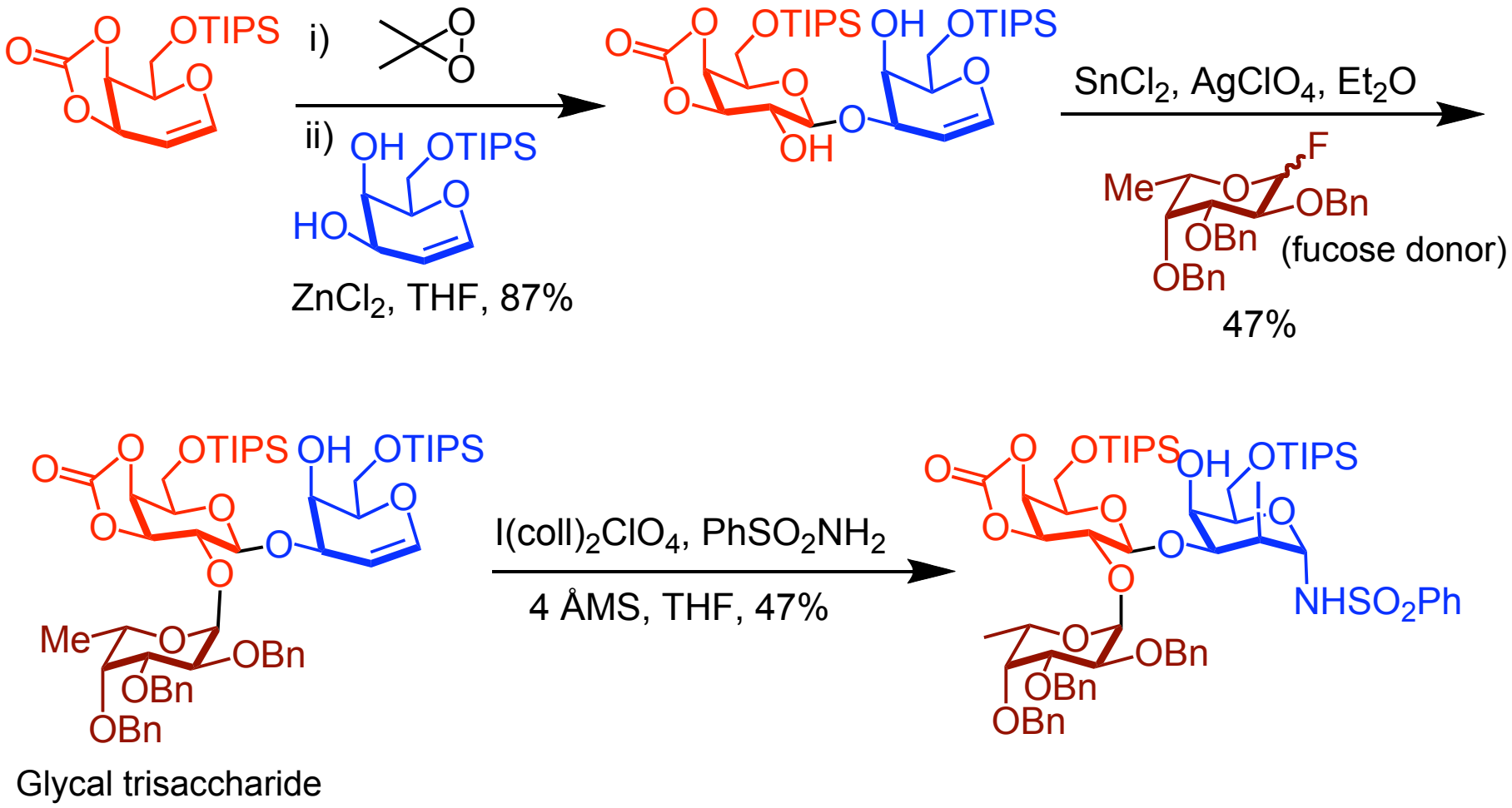
Dehydrated glycosyl donor

EI = DMDO, $PhI(O_2CR)_2$, I^+(electrophilic oxidant)

Nu-H :nucleophilic gycosyl acceptor

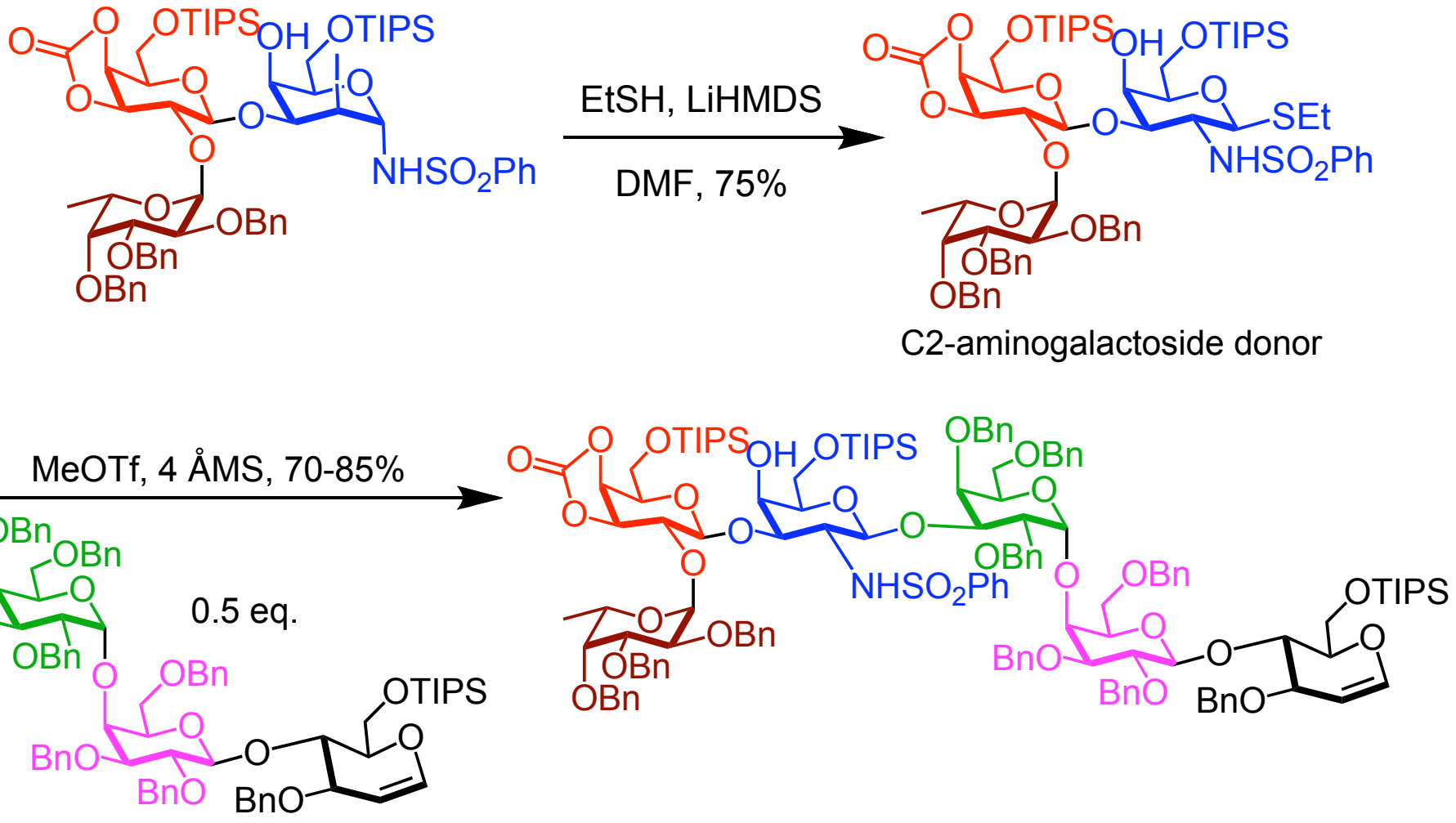
Galonic, P. D., Gin, Y. D., *Nature* **2007**, *446*, 1000-1007

First Total Synthesis of Globo-H



Bilodeau,M.T.; Park,T.K.; Hu, S.; Randolph,J.T.; Danishefsky, S.J.; Livingston, P.O.; Zhang,S. *J. Am. Chem. Soc.* **1995**, *117,* 7840

First Total Synthesis of Globo-H

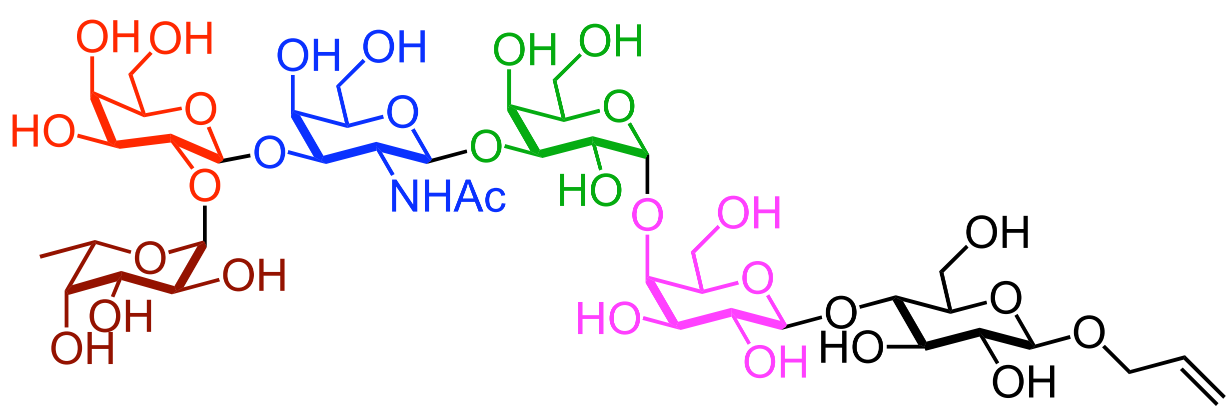


Bilodeau,M.T.; Park,T.K.; Hu, S.; Randolph,J.T.; Danishefsky, S.J.; Livingston, P.O.; Zhang,S. *J. Am. Chem. Soc.* **1995**, *117,* 7840

First Total Synthesis of Globo-H

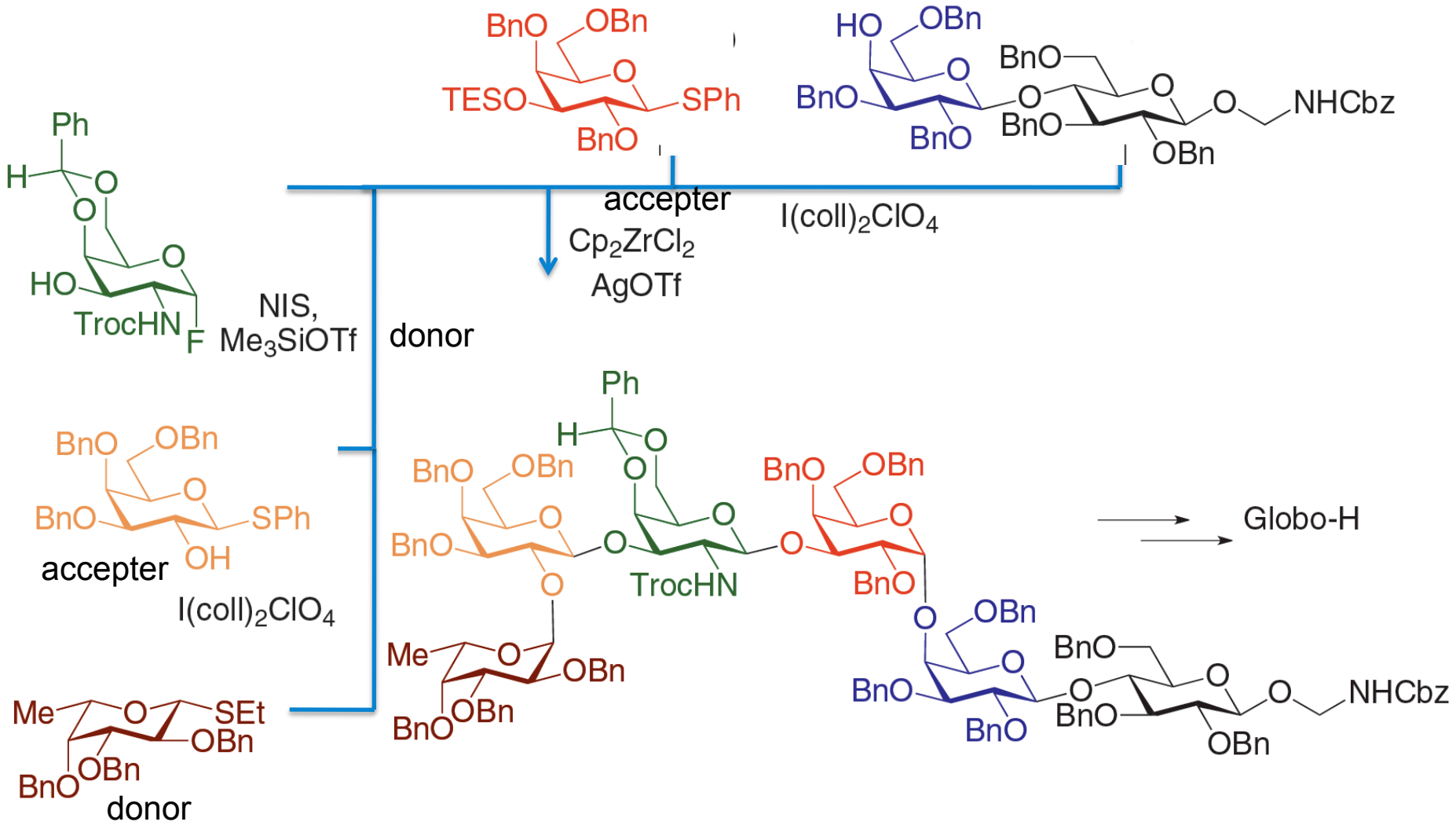
a) TBAF, THF, 94%
b) (i) Na, NH_3, THF
(ii) Ac_2O, TEA, THF
DMAP, 85%

c) (i) DMDO, DCM
(ii) Allyl Alcohol, 66%
d) NaOMe, MeOH, >99%



Bilodeau,M.T.; Park,T.K.; Hu, S.; Randolph,J.T.; Danishefsky, S.J.; Livingston, P.O.; Zhang,S. *J. Am. Chem. Soc.* **1995***, 117,* 7840

Orthogonal Glycosylation Strategy

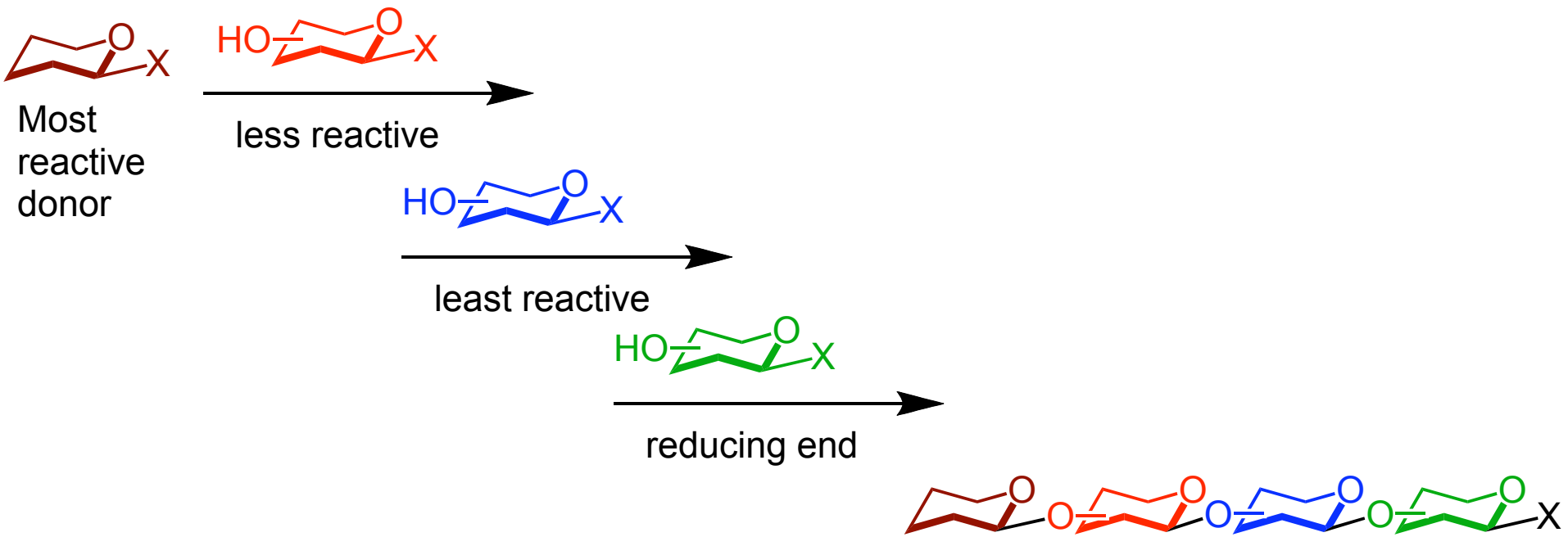


Tong Zhu, T.; Boons, G.J. *Angew. Chem. Int. Ed*. **1999**, *38*, 3495

Galonic, P. D., Gin, Y. D., *Nature* **2007**, *446*, 1000

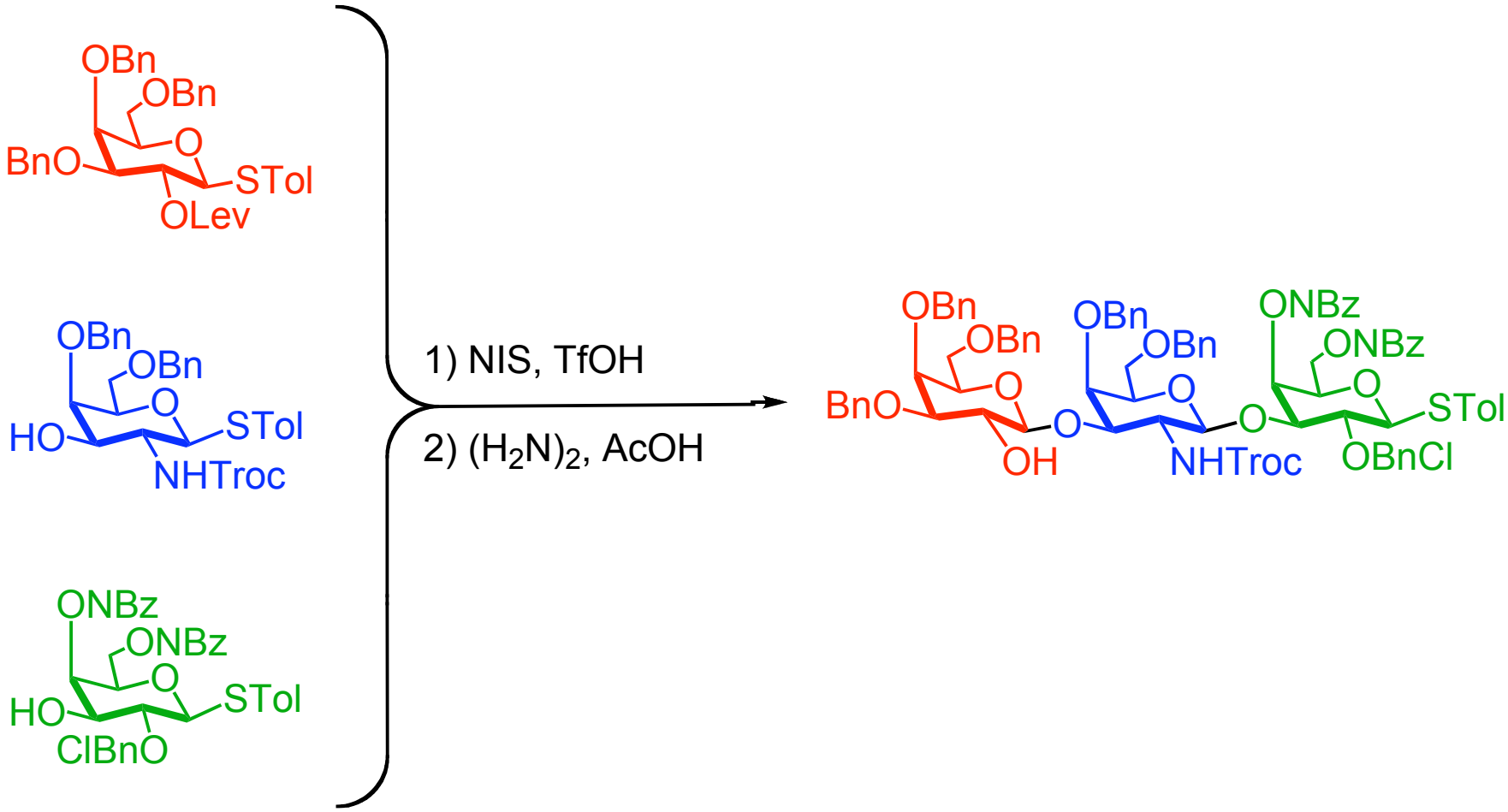
One-Pot Synthesis Strategy

1. Relative reactivity of various glycerides donors
2. Choice of protecting group



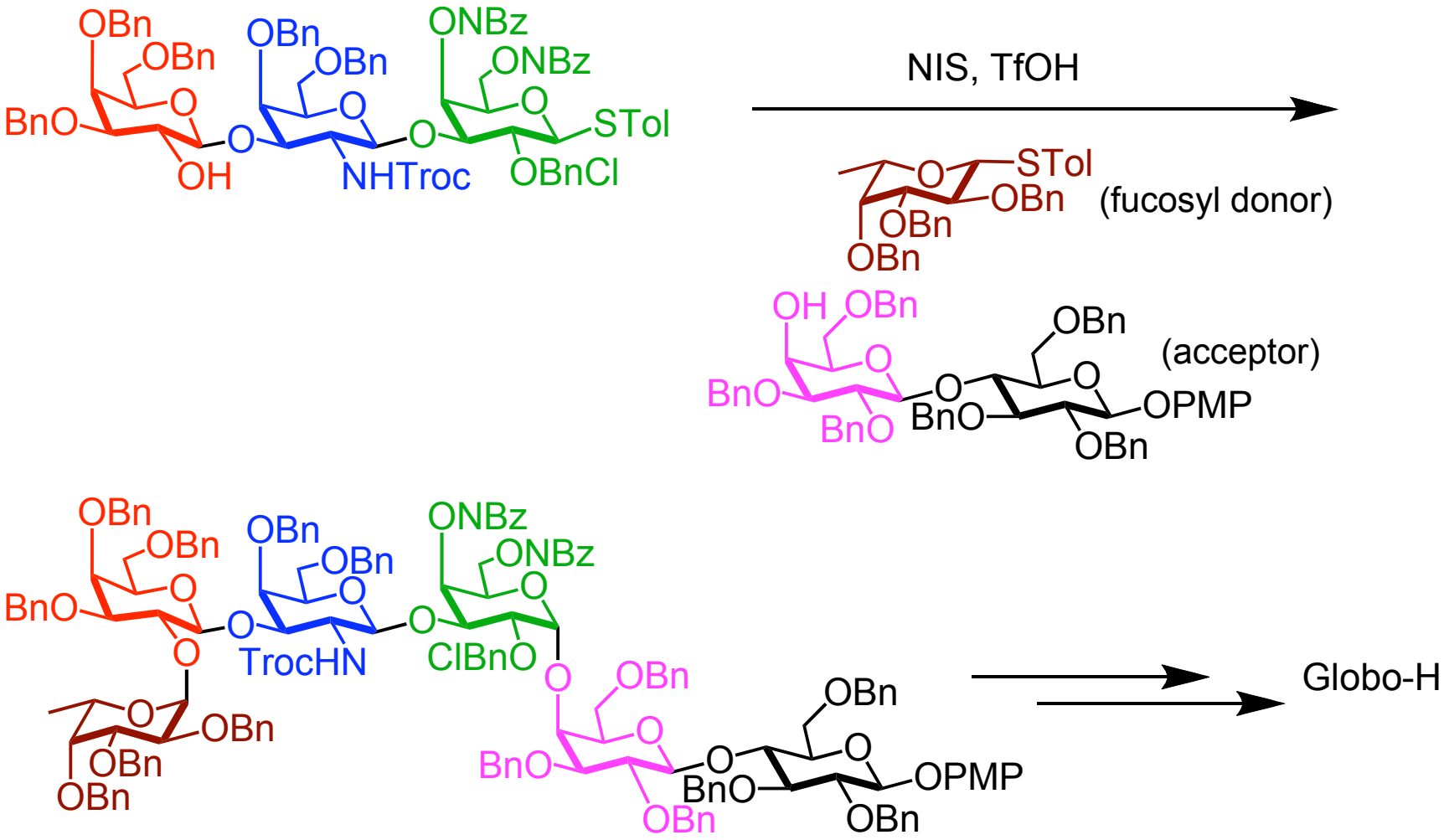
Douglas, N. L., Ley, S. V., Lucking, U. ; Warriner, S. L. *J. Chem. Soc. Perkin Trans. I* **1998**, *1,* 51

One-Pot Synthesis



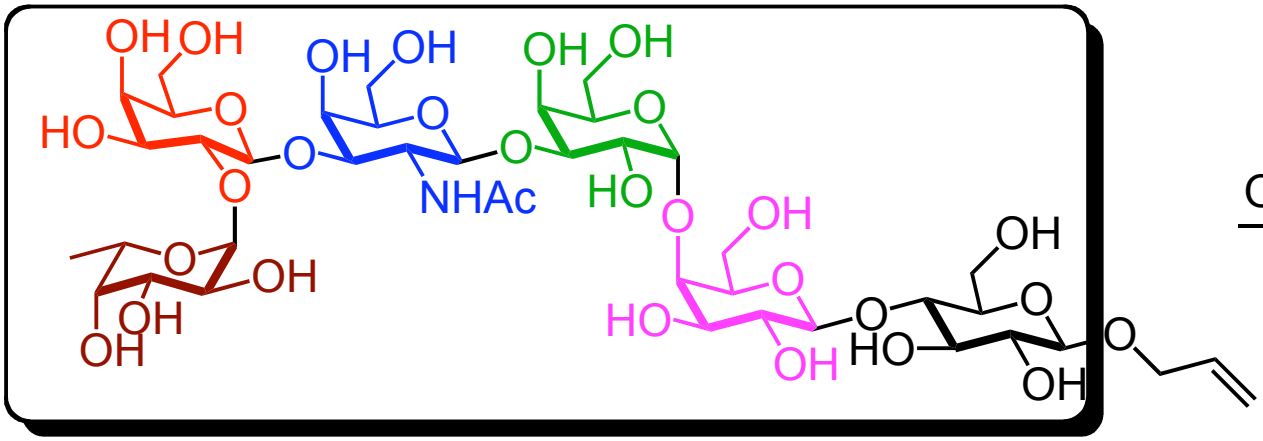
Burkhart, F., Zhang, Z., Wacowich-Sgarbi, S.; Wong, C.-H. *Angew. Chem.Int. Ed.* **2001***, 40,* 1274

One-Pot Synthesis

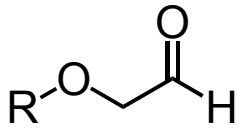


Burkhart, F., Zhang, Z., Wacowich-Sgarbi, S.; Wong, C.-H. *Angew. Chem.Int. Ed.* **2001**, *40,* 1274

End Game

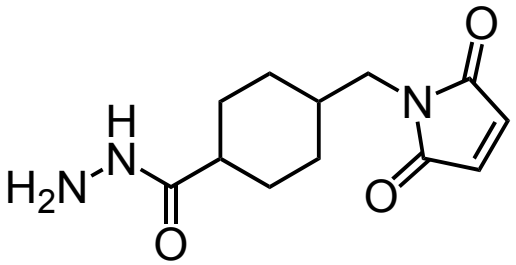


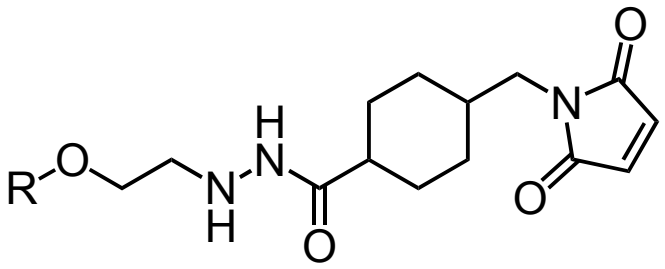
Ozonolysis



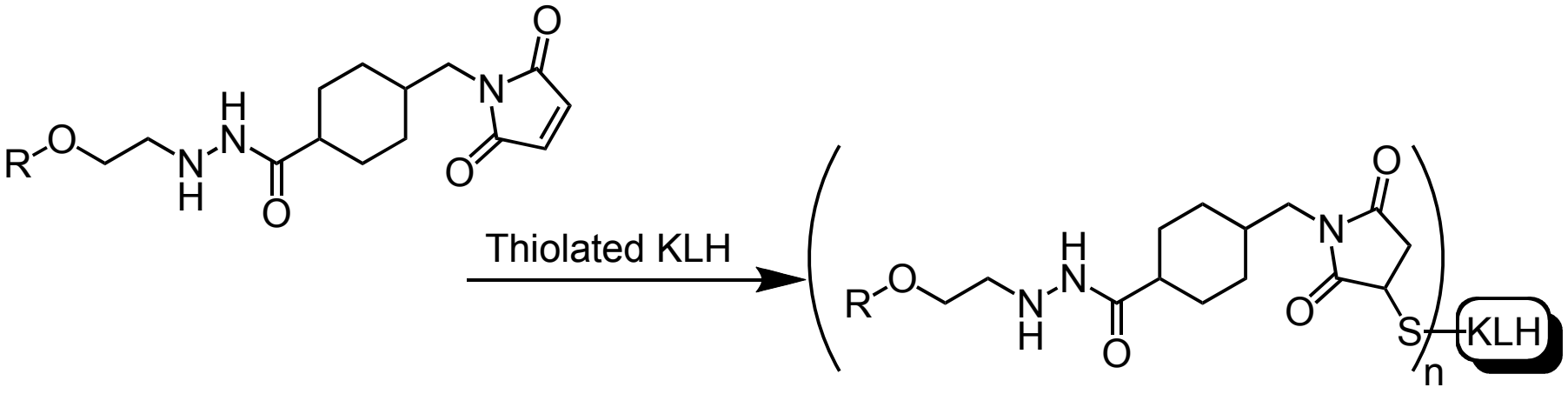
 = R

$NaCNBH_3$





End Game



Final Vaccine

Conclusion

Organic syntheis ,a powerful tool in getting complex carbohydrate antigens, potential targets for cancer immunotherapy.

investigation of some antigens (Globo-H, ST_N, T_N, T) relies on chemical synthesis

Recently prepared pentavalent neoglycoeptide (to mimic heterogenity) have shown encouraging antibody response

"Methodological building upon the principles of our science leads to the magic of synthesis –with its unique capability to prepare molecules of virtually any shape and juxtaposition of functional groups. Creative synthesis is the indispensable talent that the chemist will bring to the many exciting struggles and opportunities in the future." – *Samuel Danishefsky*

Future Direction