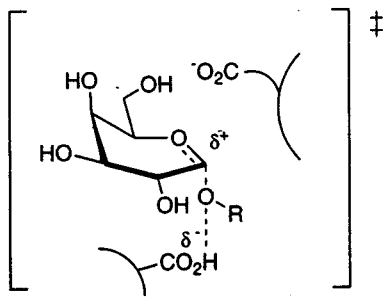


# **Design of Enzyme Inhibitor and Carbohydrates in Combinatorial Chemistry**

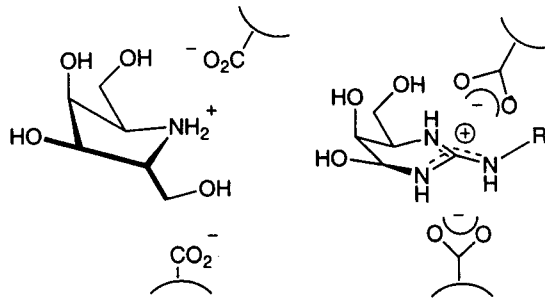
**Jin-Hyun Jeong**

**College of Pharmacy  
Laboratory of Glycoscience  
Kyunghee University**

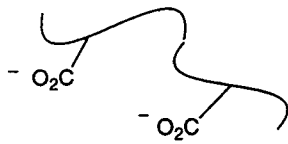
### Design of Transition-State Analog Inhibitors of Enzymes



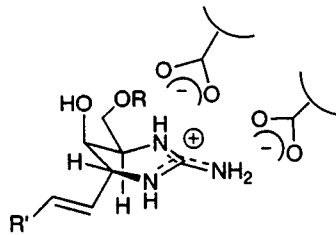
**$\alpha$ -Galactosidase**



**Inhibitors**

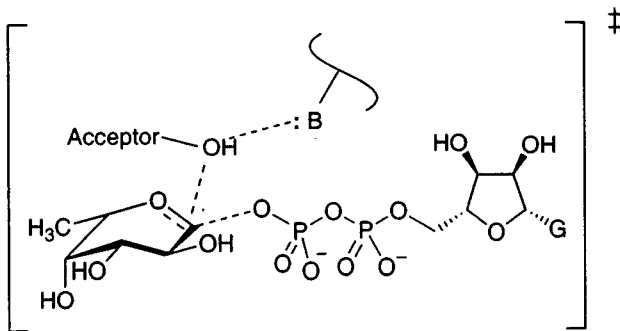


**HIV Protease**

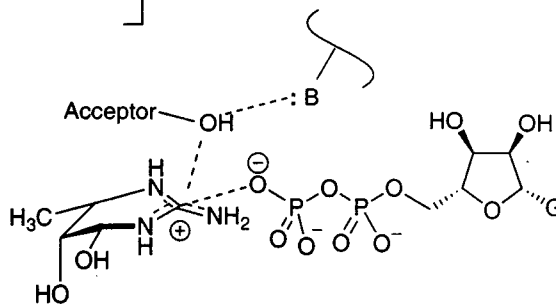


**Inhibitors**

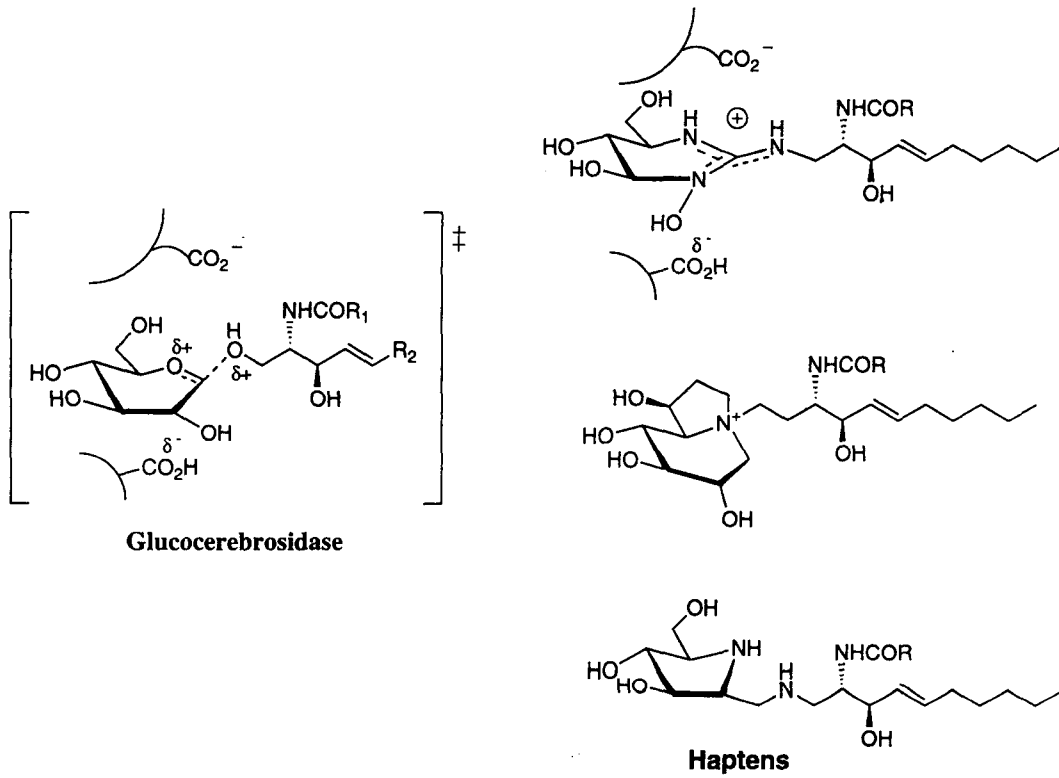
### Design of Transition-State Analog Inhibitors of Enzymes



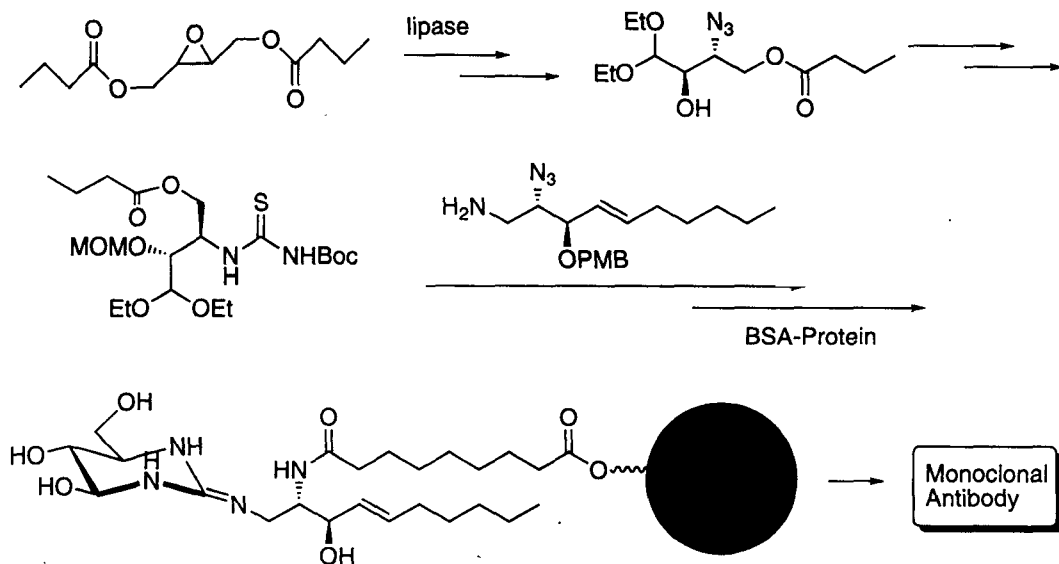
**$\alpha$ -Fucosyltransferase**



## Design of Haptens for the Treatment of Enzyme-Deficiency Diseases



## Design and Synthesis of Guanidino-Sugar for Gaucher Disease

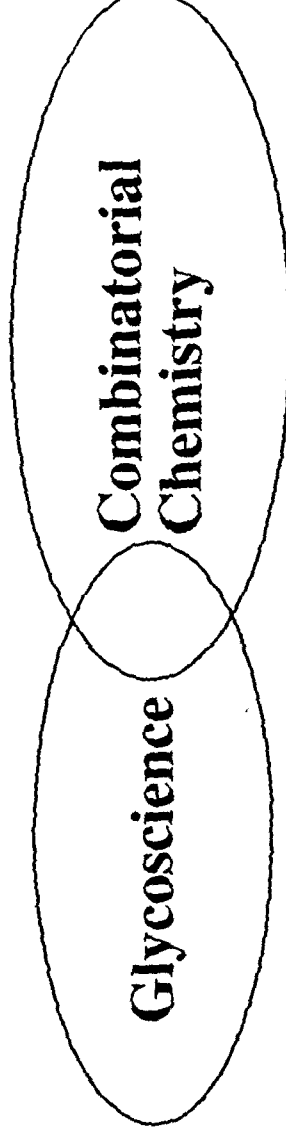


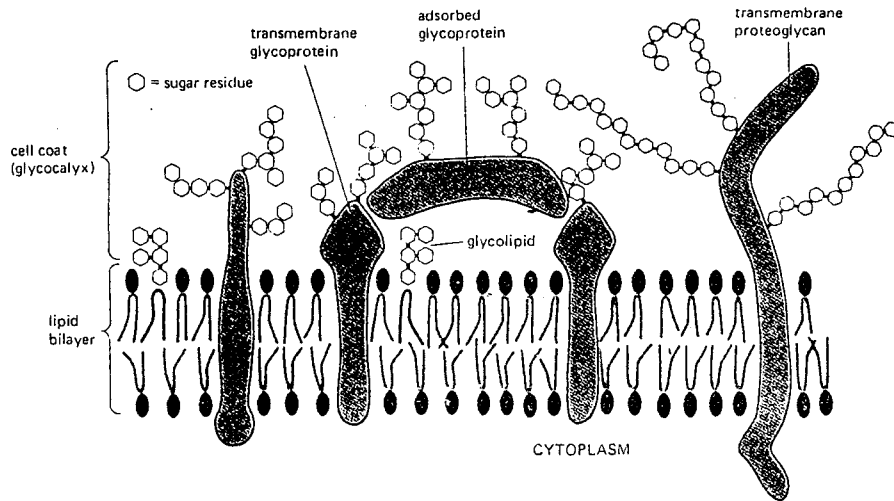
# **Carbohydrates as Drug Discovery Leads**

**How to discover and understand biologically-active oligosaccharide ligands**

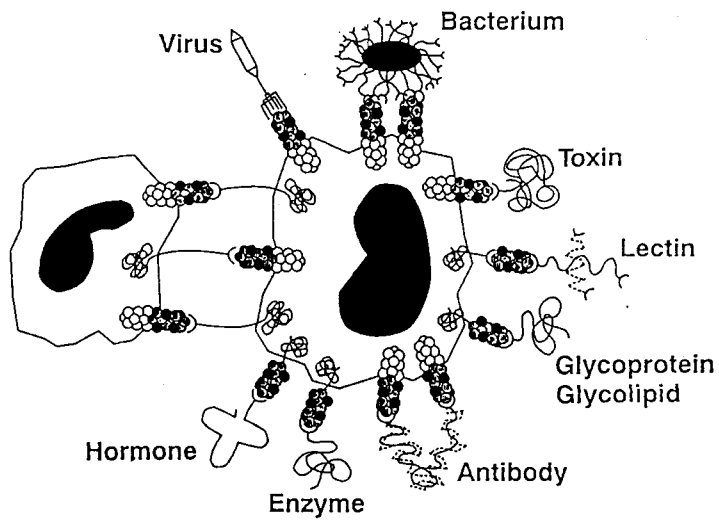
**How do carbohydrates influence the properties of the proteins and lipid membrane to which they are attached**

**How to enhance the binding affinity of such ligands once they are related**

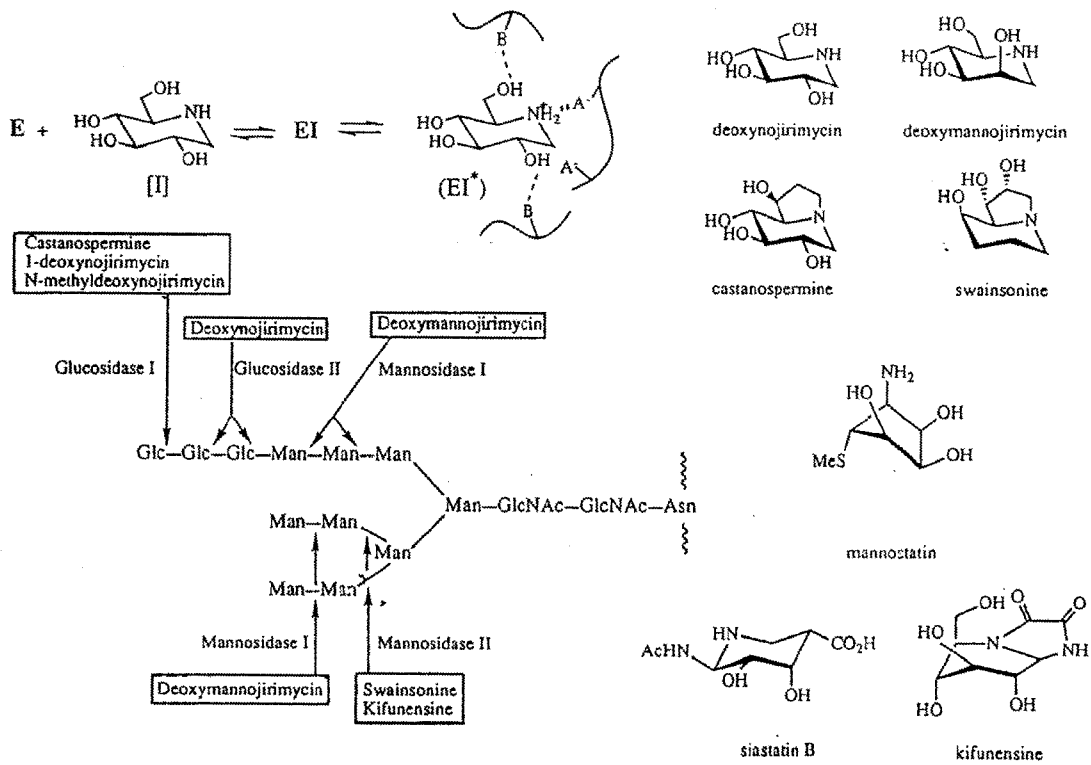
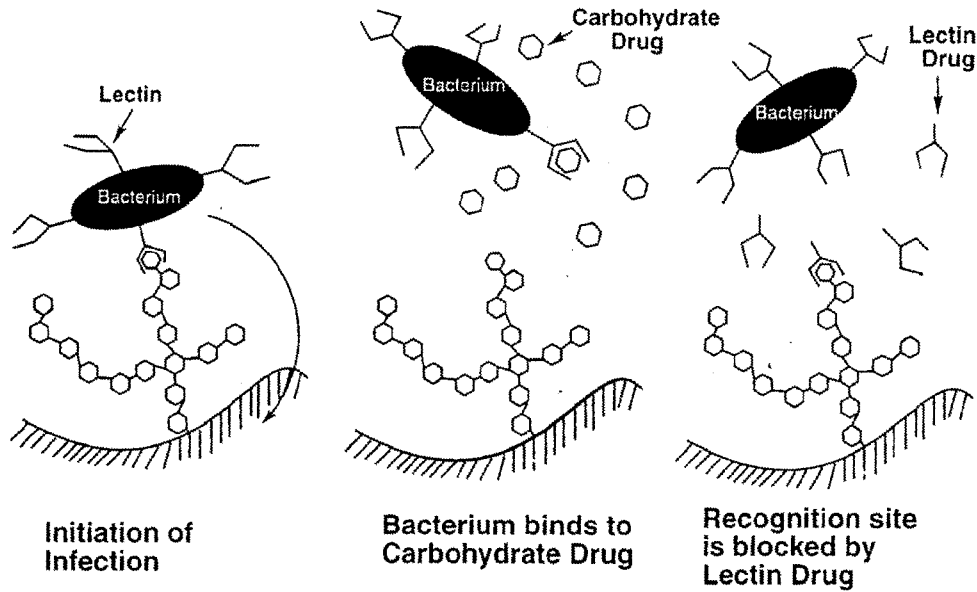




### Roles of Cell Surface Carbohydrate

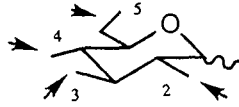


# Carbohydrate Drug and Lectin Drug

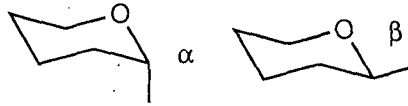


# Structure Diversity of Carbohydrates

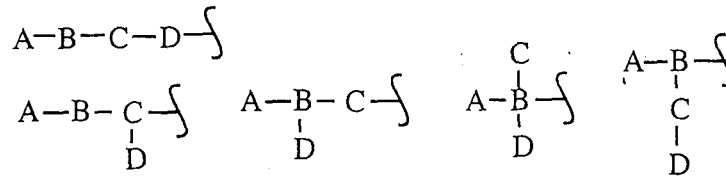
## 1. Regioselectivity



## 2. Anomer



## 3. Branching



## 4. Functionalization (sulfation or phosphorylation)

$$R \times A \times B \times F = \dots\dots\dots$$

## Comparison of isomeric possibilities for sequences of oligopeptides and oligosaccharides.

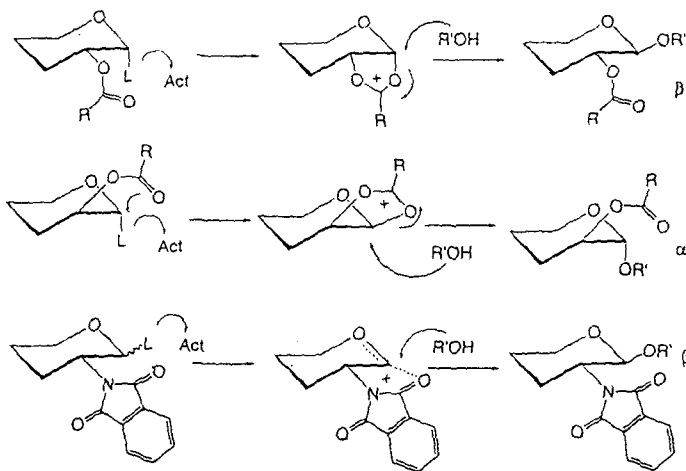
Oligomer	Composition	Number of possible Isomers	
		Oligopeptide	Oligosaccharide
Dimer	AA / AB	1 / 2	11 / 20
Trimer	AAA / ABC	1 / 6	120 / 720
Tetramer	AAAA / ABCD	1 / 24	1424 / 34560
Pentamer	AAAAA / ABCDE	1 / 120	17872 / 2144640

# Successful Glycosylation Reactions

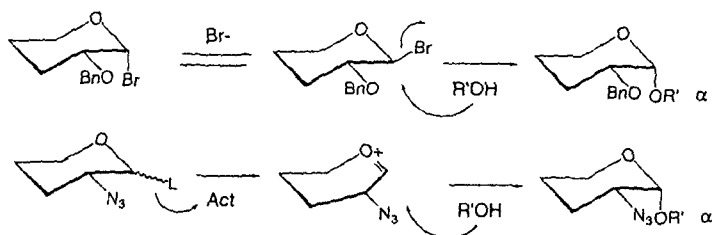
- **Regioselectivity**
  - **Stereoselectivity**
    1. Neighbouring Group Participation
    2. Solvent-assisted
    3. Insoluble Catalyst-assisted
    4. Special Condition for Sialoside
  - **for Combinatorial Chemistry**
- {  
Orthogonal Protection/Glycosylation Strategy  
Random Glycosylation Strategy



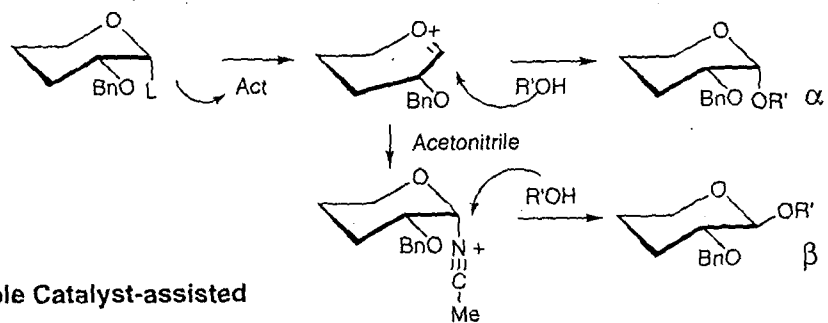
With NGP  
(1,2-trans)



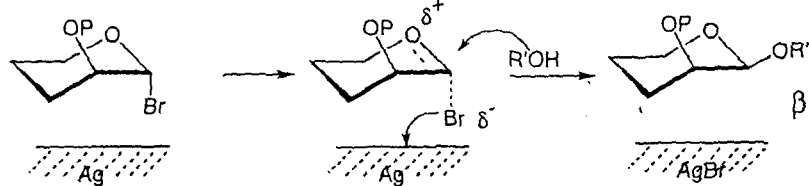
Without NGP  
(1,2-cis)



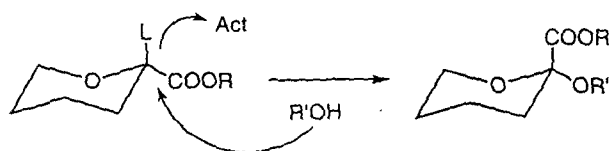
Solvent-assisted (1,2-trans)



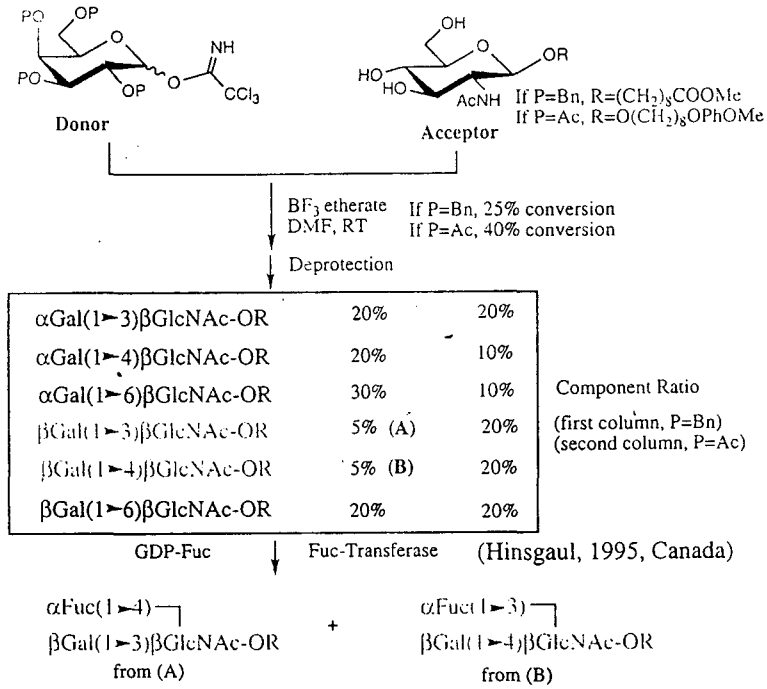
Insoluble Catalyst-assisted



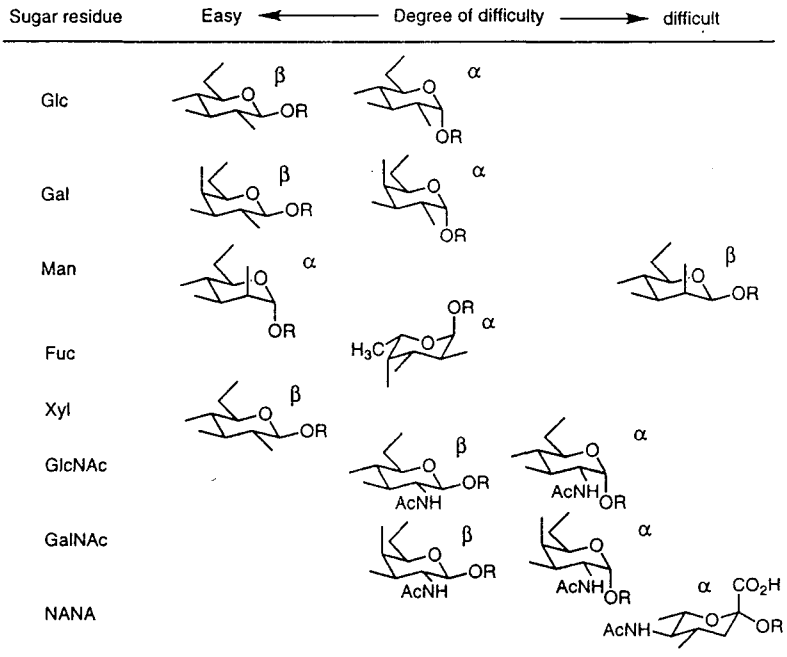
Special Condition for Sialosides



## Random Glycosylation

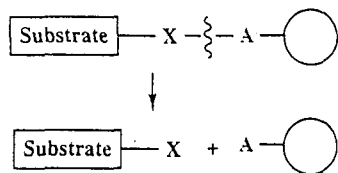


### Common mammalian glycosidic linkage and their relative ease of formation by chemical synthesis

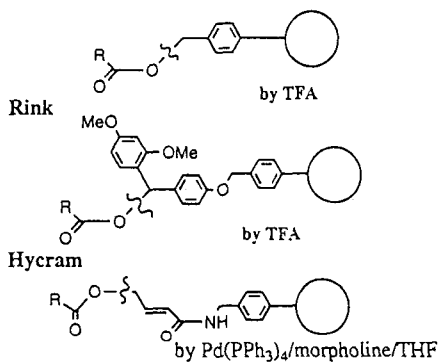


## Linker Design for Carbohydrate Synthesis

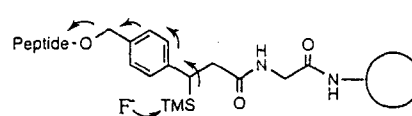
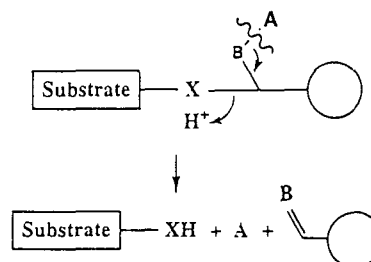
### Endo Cleavable Linker



### Merrifield/ Sheppard/ Wang



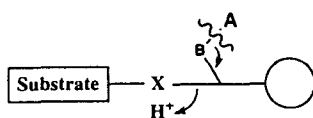
### Exo Cleavable Linker



Ramage TL 1992, 499. Chao JOC 1993, 2640.

## Enzyme-Cleavable Linkers

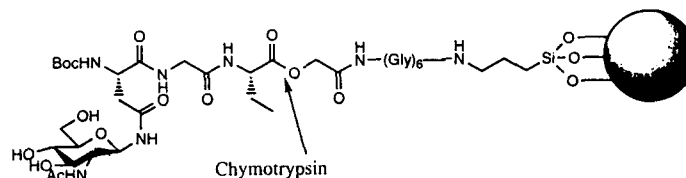
### Exo



A	B	Enzyme
PhCOOCO	NH or O	penicillin amidase
PhOCH <sub>2</sub> O	NH	SEM acylase
ClCH <sub>2</sub> CO	NH	acylase I
RCO	O	lipases
RCO	S	thioesterases
PO <sub>3</sub>	O	phosphatases
glycoside	O	glycosidases

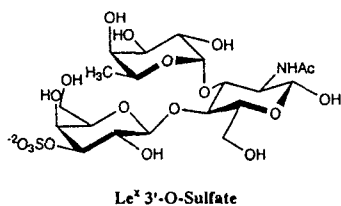
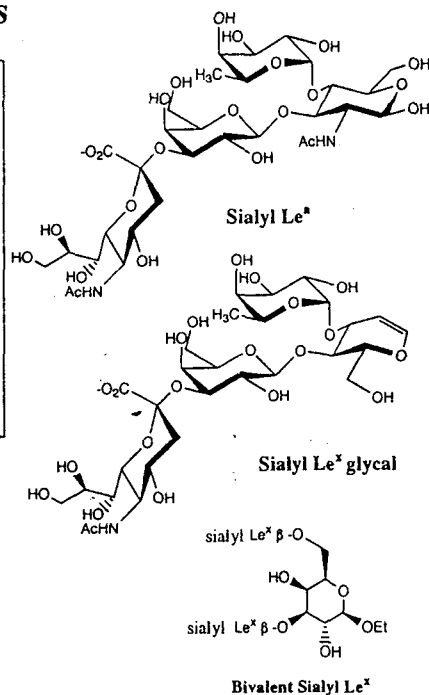
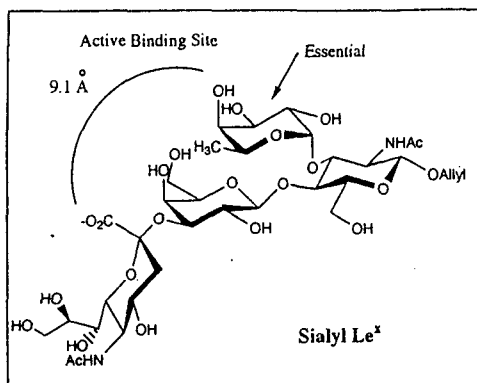
X = O, NH, S, CO<sub>2</sub>

### Endo

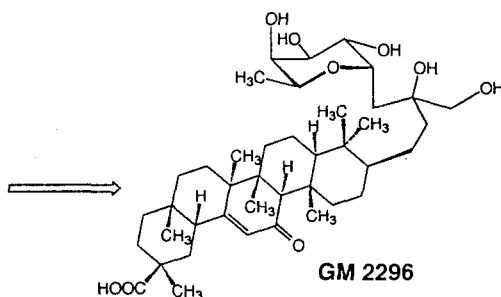
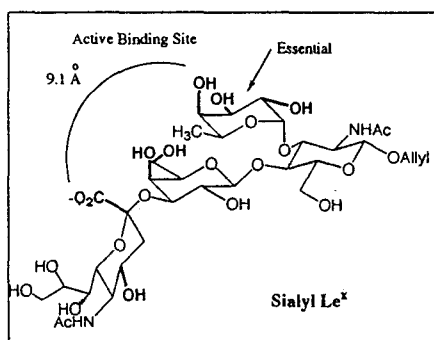


Wong, J. Am. Chem. Soc., 1994, 116, 1135.

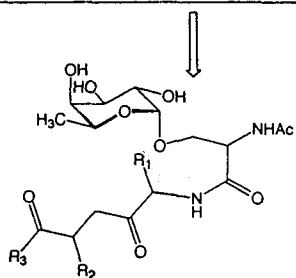
## SLe<sup>x</sup> Mimics



## Library Application and Pharmacophore Approach



Selectin IC<sub>50</sub> E (0.5 mM) L (5 μM) P (5 μM)

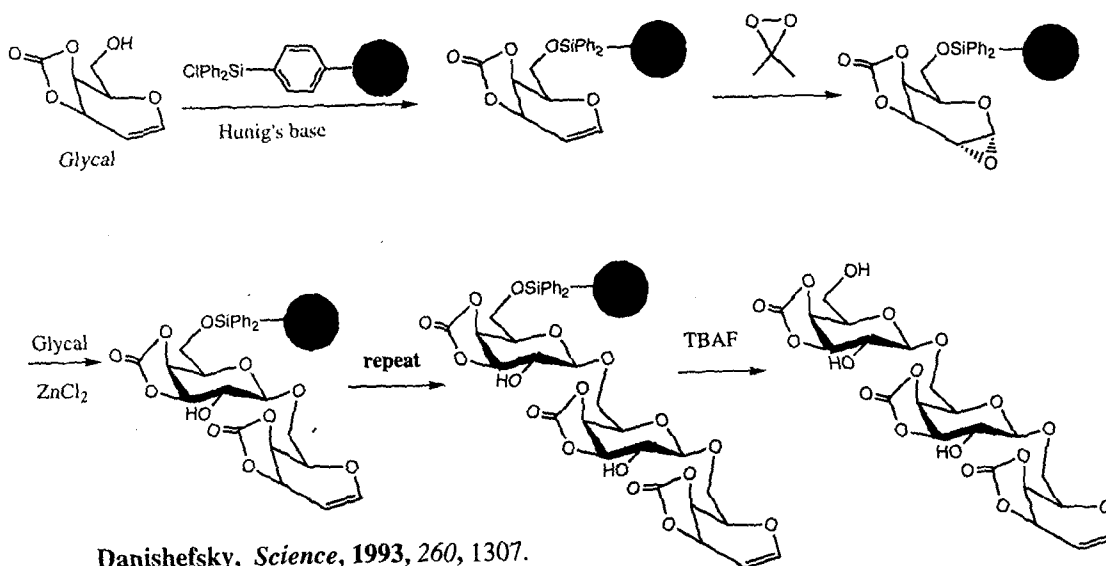


60 Compounds were prepared in mg amounts  
Tested in ELISA Assay for E-, L-, P-Selectin Assay

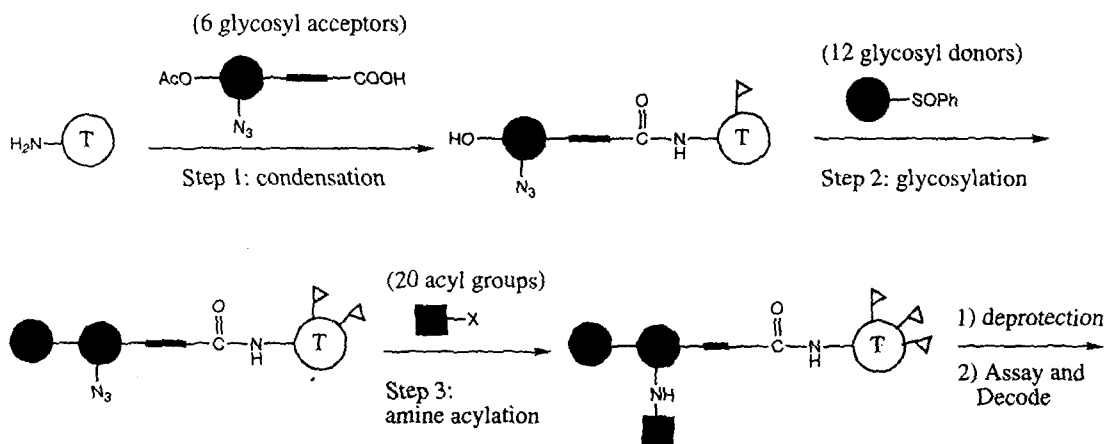
3 Active (< 1 mM) in inhibiting L-Selectin Binding  
4 Active (< 1 mM) in inhibiting P-Selectin Binding

J. H. Musser, Glycomed, 1995

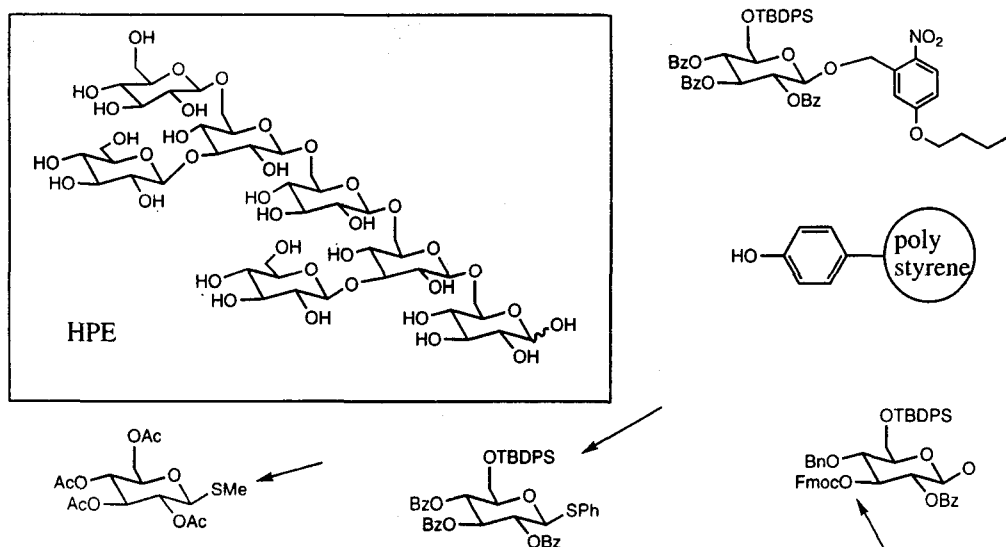
## Oligosaccharide Synthesis Using Glycals



## Di & Trisaccharide Synthesis and Screening with Chemical Coding on TentaGel resin

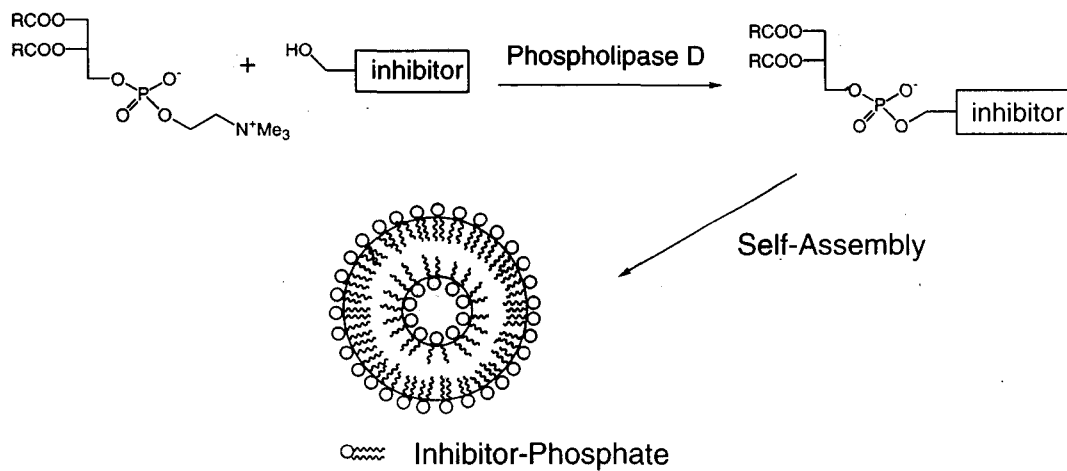


## Synthesis of Heptasaccharide Phytoalexin Elicitor (HPE)



Nicolaou, *J. Am. Chem. Soc.*, 1997, 119, 449.

## Enzymatic Synthesis of Phospholipid-Inhibitor Conjugates for Drug Delivery and Targeting



Wong, *J. Am. Chem. Soc.*, 1993, 115, 10487.

Glycoproteins와 Glycoconjugates의 생물학적 주요 역할

1) Recognition

세포-세포 (tight junction and adhesion)  
세포-박테리아, 바이러스, Toxins  
세포-Lectins (selectins)  
호르몬 (growth factor)  
항체 (면역 반응)  
Growth and Differentiation

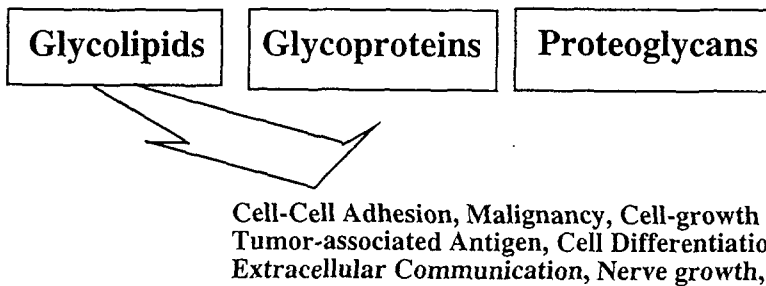
2) Communication

Tumor Markers (glycolipids)  
Tagging (silalyl timer, protein processing label)

3) Structural Elements

단백질의 folding 및 용해도와와의 연관  
세포막 電位 변화 (적혈구 세포)

**Glycoconjugates:**



Altered Ganglioside Biosynthesis is oncogenically transformed mosce cells. *Science* 1976, 194,906.

Differntiation Markers for Murine T Helper Lymphocyte. *Biochem.* 1992,31,12190.

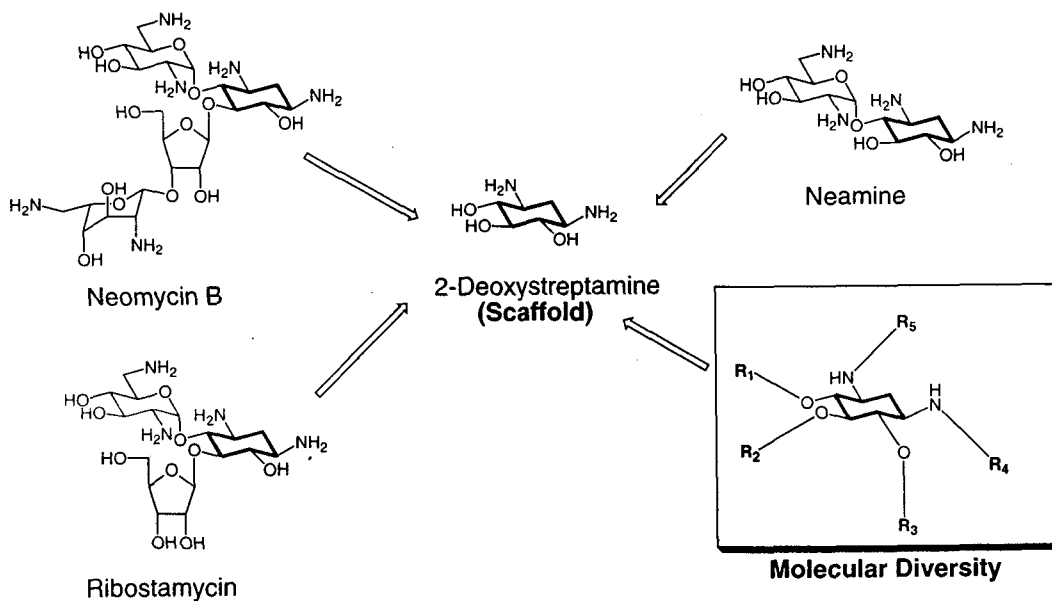
Neuronal and Embryonic Development, their roles in Adhesion Processes and Tumor Metasis.  
*Chem. Rev.* 1996, 96,683.

Onco-developmental Antigens. *Nature*, 1985,314,53.

Galactosyl Ceramide is an Essential Component of the Neural Receptor for human HIV-1 gp120  
*PNAS*, 1991,88,7131. *Science*, 1991,253,320.

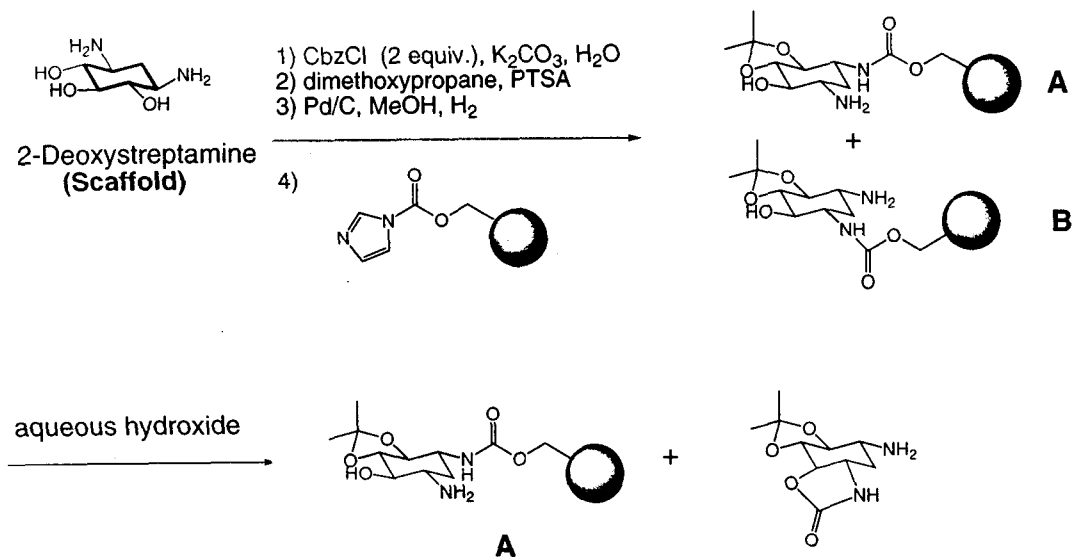
.....

## Development of RNA Target Drugs



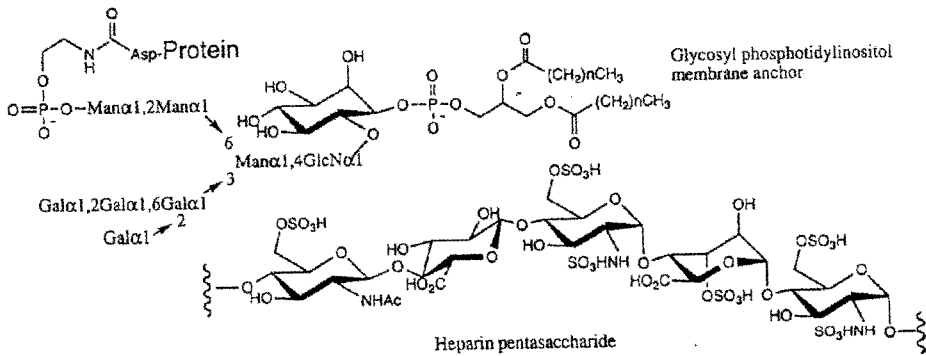
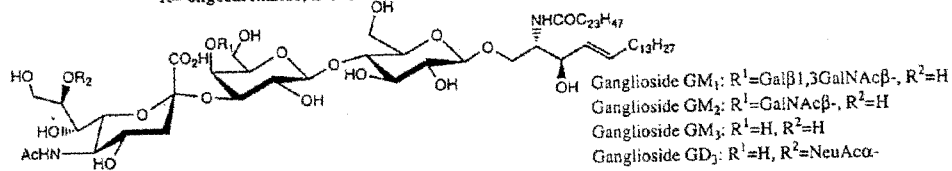
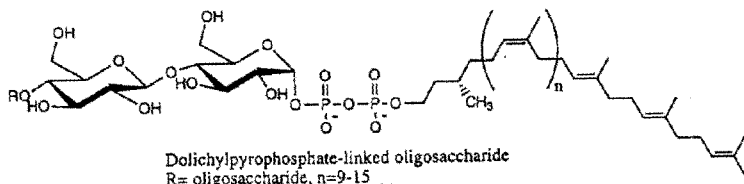
Wuonola, Scriptgen Pharm., Inc. 1996

## Regiochemical Control

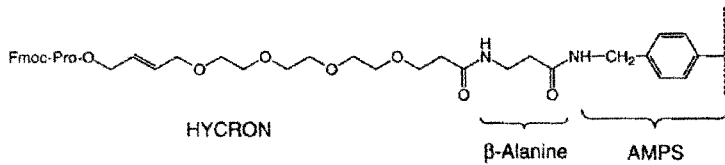


Wuonola, Scriptgen Pharm., Inc. 1996



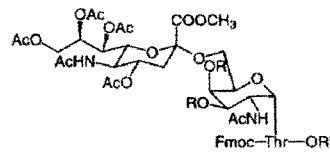


### Tumor-Associated Sialyl-T<sub>N</sub> Antigen Glycopeptide



- 1) morpholine, DMF (1/1)
- 2) Boc-Ala-OH, TBTU, HOBT, NMM, DMF
- 3) TFA, CH<sub>2</sub>Cl<sub>2</sub>
- 4) Hunig base, CH<sub>2</sub>Cl<sub>2</sub>

H-Ala-Pro-HYCRON-β-Ala-AMPS



3 steps for deprotection

Ac-Ala-Pro-Pro-Ala-His-Gly-Val-Thr-Ser-Ala-Pro-OH

Kunz, *Angew. Chem. Int. Ed. Engl.*, 1997, 36, 618.