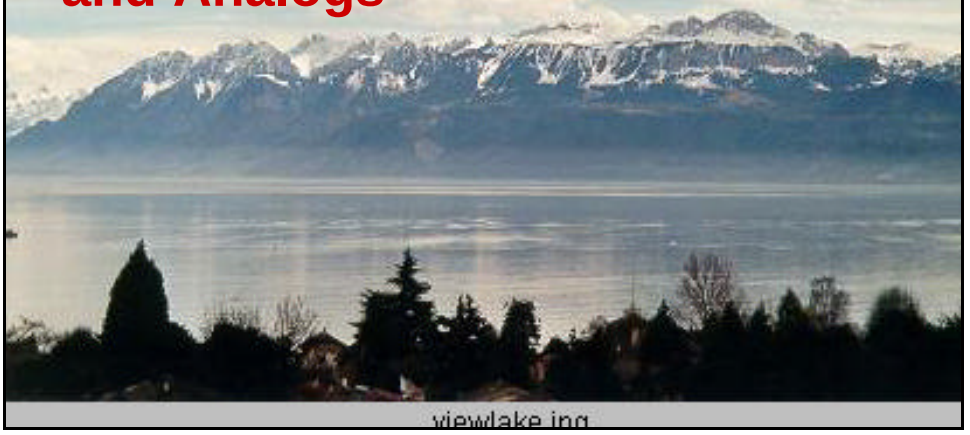
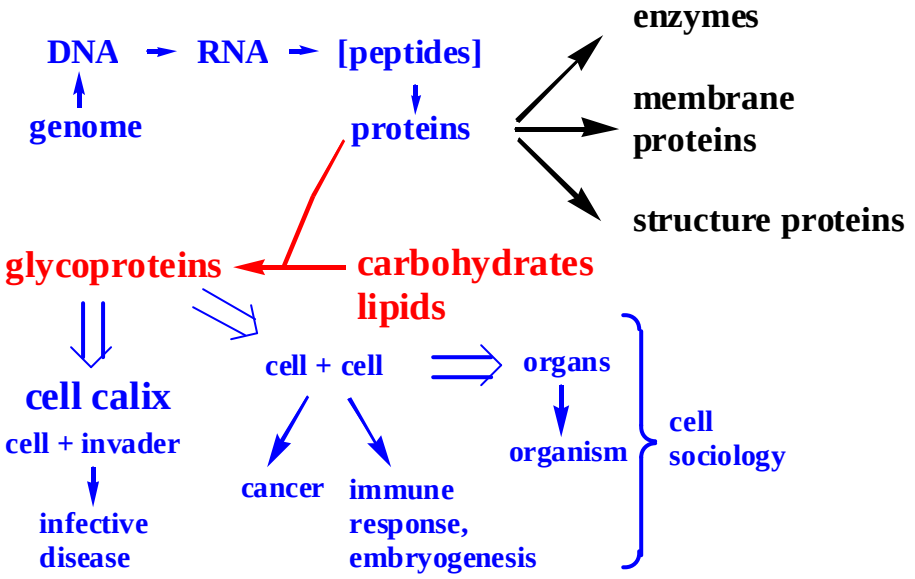
Glycomimetics: Why ? How ?

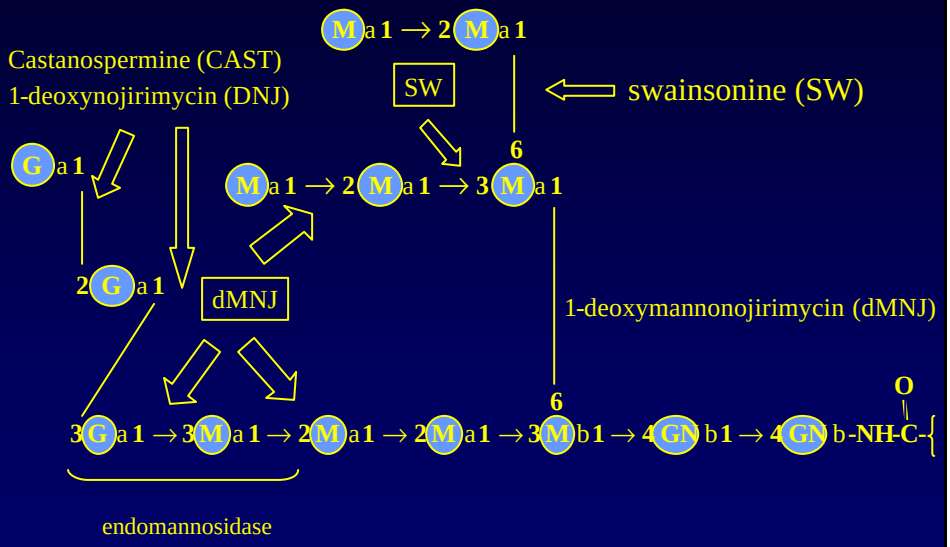
C-Disaccharides
Imino-C-disaccharides
and Analogs



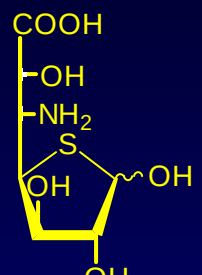
What you need to know to understand life: carbohydrate functions, glycosidation, etc.



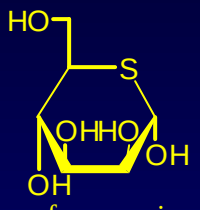
Glycoprotein Biosynthesis



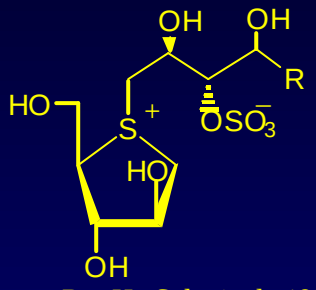
Natural Monothiosaccharides



in albomycin antibiotics, 1984

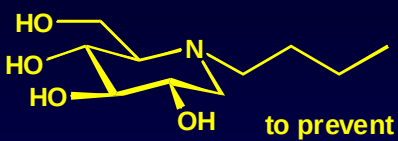


from marine sponge, 1987
1-deoxy-:
weak inhibitor of α-glucosidase



R = H : Salacinol, 1997
R = CH-CH-CH_2
OH OH OH
Kotalanol, 1998
(Indian medicine for diabetes)

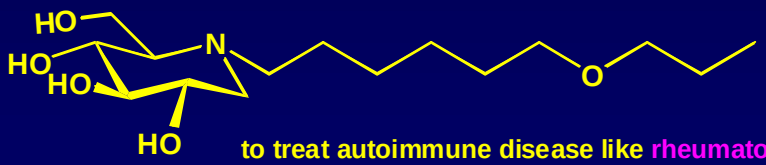
AZASUGARS AS POTENTIAL DRUGS



to treat human hepatitis B
cf.: Bock, T. M., et al. *Proc Nat Acad. Sci.* USA 1994, *91*, 2235

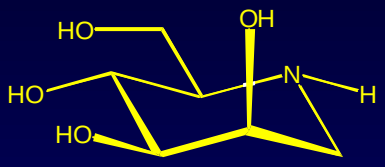
to prevent Tay-Sachs desease, reduces accumulation of glycosphingolipids in the brain
cf.: Platt, F. M. et al. *J. Biol. Chem.* 1997, *272*, 19365
Kolter, T. *Angew. Chem. I. E.* 1997, *36*, 1995

inhibits HIV entry
cf.: Fischer, P. B., et al. *J. Virology* 1996, *70*, 7153
Fenouillet, E., et al. *J. Virology* 1997, *231*, 89



to treat autoimmune disease like rheumatoid arthritis
cf.: van den Broek, L. A. et al. *J. Pharm. Pharmacology* 1996, *48*, 172

1-Deoxymannonojirimycin (dMN)



- α-mannosidase I inhibitor (Golgi)
- inhibition of α-mannosidase blocks processing of glycan[a)]

Unconjugates N-glycans $Man_3GlcNAc$ and $Man_3(Xyl)GlcNAc(Fuc)GlcNAc$ delay tomato ripening at 10 ng/g concentration
dMN inhibits their hydrolysis and delays tomato ripening[b)]

a) Vitale, A.; Zoppe, M.; Bollini, R. *Physiol. Plant.* **1989**, *89*, 1079
b) Yunovitz, H.; Gross, K. C. *J. Carbohydr. Chem.* **1995**, *14*, 653

SWAINSONINE

isolated from Swainsona canescens[1]
Swainsona procumbens[2]

® inhibits lysosomal acid a -mannosidase[3]
cytosolic a -mannosidase[3]
Golgi a -mannosidase II[4]
tumor cell invasion and metastasis[5]

® reduces the growth of human melanoma cells[6]

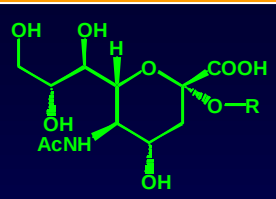
® stimulates lymphocyte proliferation[7]

® enhances natural killer cell activity in vivo leading to the inhibition of metastasis[8]

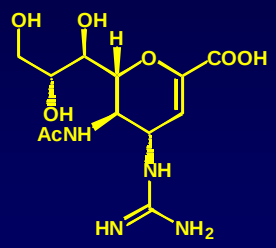
maximal daily oral dose: 300mg/kg[9]
(side effects: exema, anorexia, pains, fatigue)

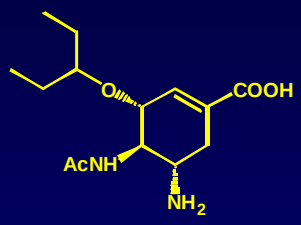
[1] Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Aust. J. Chem.* 1979, *32*, 2257
[2] Perrone, G. G.; Barrow, K. D.; McFarlane, I. J. *Bioorg. Med. Chem.* 1999, *7*, 831
[3] Dorling, P. R.; Huxtable, C. R.; Colegate, S. M. *Biochem.* 1980, *191*, 649
[4] Tulsiani, D. R. P.; Broquist, H. P.; James, L. F.; Touster, O. *Archiv. Biochem. Biophys.* 1984, *232*, 76
[5] Fernandes, B.; Sagman, M.; Demetrio, M.; Dennis, J. W. *Cancer Res.* 1991, *51*, 718
[6] Dennis, J. W.; Koch, K. Yousefi, S.; Vanderelst, I. *Ibid.* 1990, *50*, 1867
[7] Hino, M. et al. *J. Antibiotics* 1985, *38*, 926
[8] Humphries, M. J. et al. *Cancer Res.* 1988, *48*, 1410
[9] Goss, P. E. et al. *Clin. Can. Res.* 1997, *3*, 1077

Sialidase Inhibitors against Influenza Infection

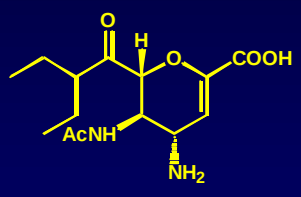


sialyl glycoside





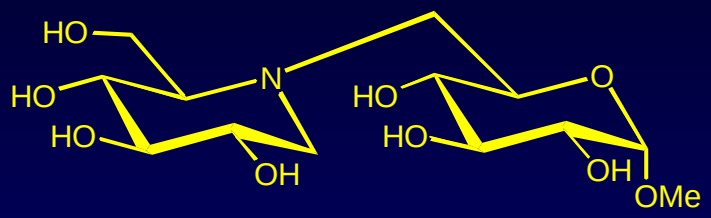
GS 4071
IC_{50}: 2 nM



(Glaxo-Wellcome)
2 nM

E.g.: Von Itzstein M., et al. *Nature (London)* **1993**, *363*, 418-423;
Kim, C. U., et al. *J. Am. Chem. Soc.* **1997**, *119*, 681-690; *J. Med. Chem.* **1998**, *41*, 2451-2460:
Smith, P. W., et al. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 601-604.

a-Glucosidase Inhibitor with long Duration of Action in Rats



MDL 73945 (Merrell Dow, Strasbourg)

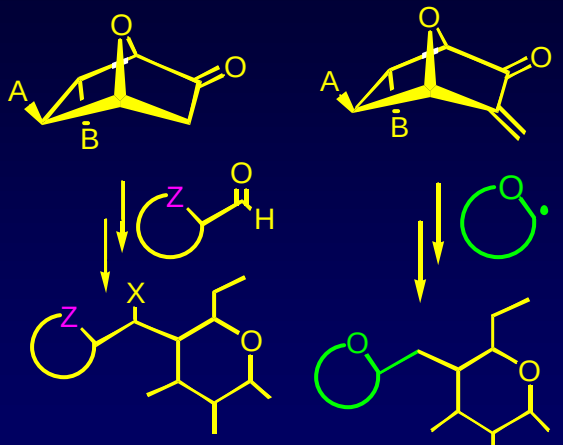
intestinal a-glucosidase inhibitor

reduces glycemic and insulin responses

to sugar load

K. M. Robinson , M. E. Begovic, M. E. Rhinehart, E. W. Heineke, J. B. Ducep, P. R. Kastner, F. N. Marshall, C. Danzin, *Diabetes* **1991**, *40*, 825-830

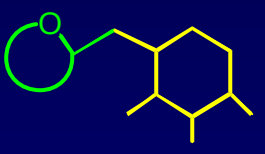
C-Disaccharides from 7-Oxanorbornenones (' Naked Sugars ')



High, predictable diastereoselectivities

1→2-C, 1→3-C, 1→4-C, 1→5-C

L- or D- nat. or unatural



a- or b- ; *p* or *f*

Z = O, NH, NR

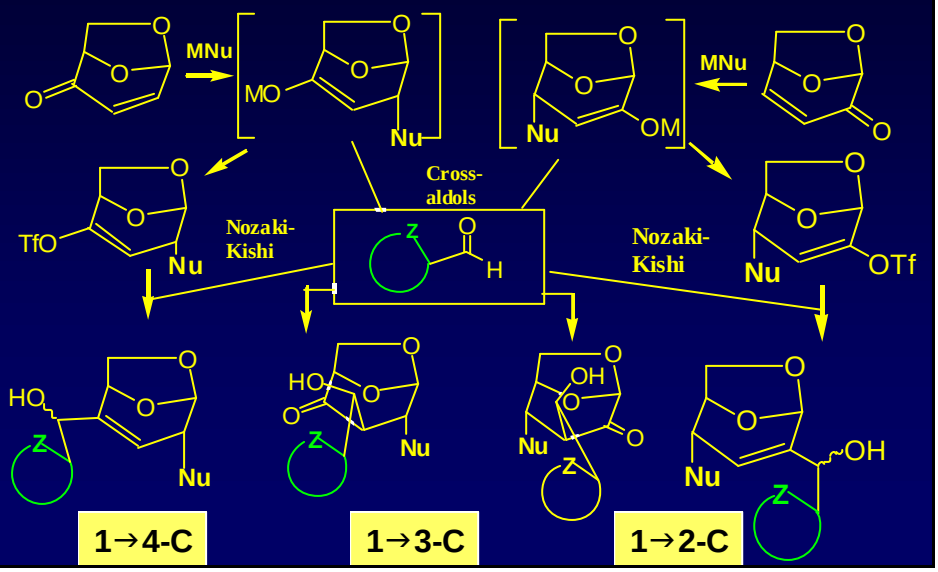
X = OH, F, H, etc.

a-D-Glc*p*, a-D-Man*p*

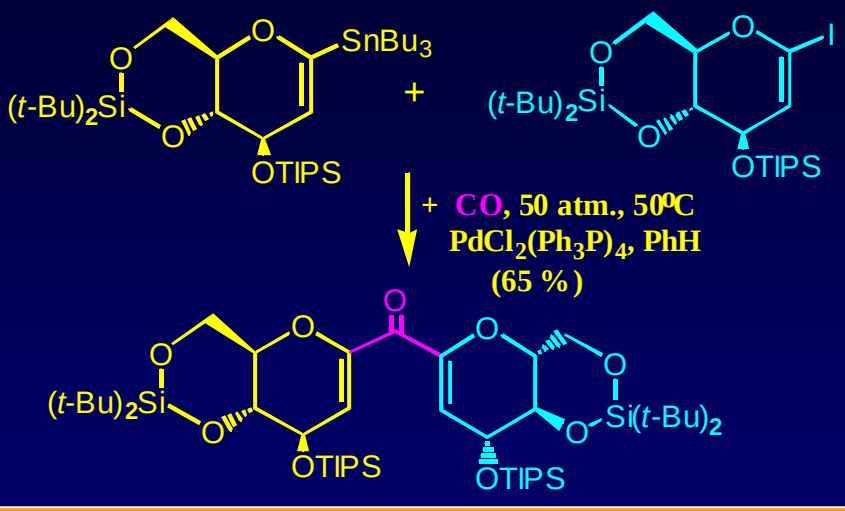
a-D-Gal*p*, a-L-Fuc*p*

C-glycosides of carbapyranoses

Combinatorial Approach: Isolevoglucosenone and Levoglucosenone as Templates

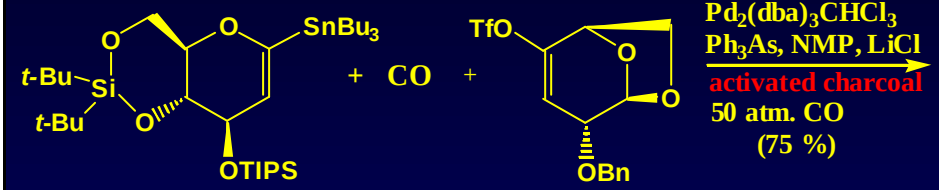


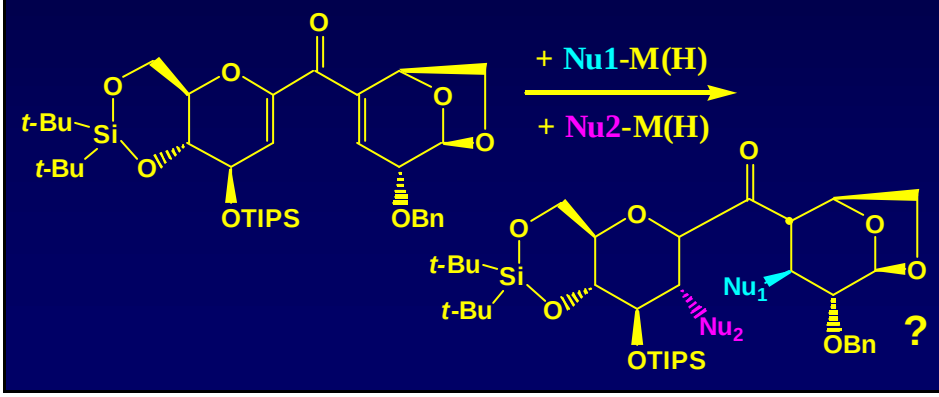
(1→1)-C-Disaccharides Carbonylative Stille Coupling

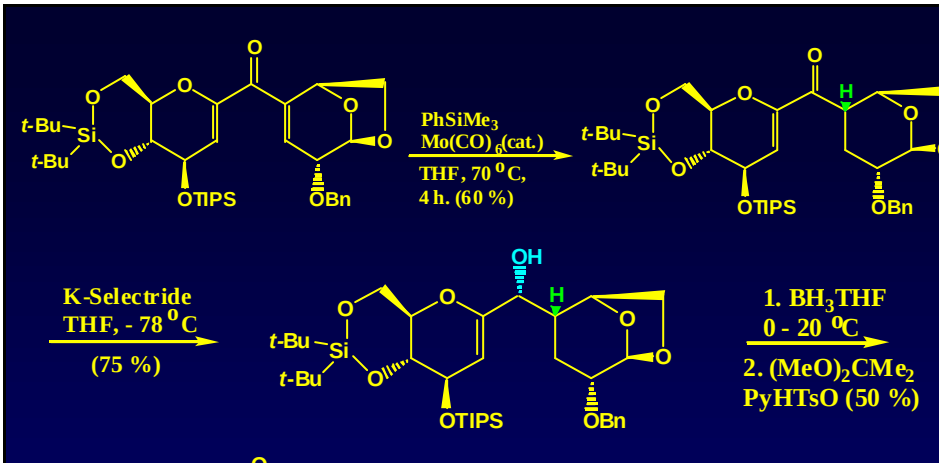


V.Jeanneret, L. Meerpoel, P. Vogel, *Tetrahedron Lett*. **1997**, *38*, 543

Library of C(1-4)disaccharides



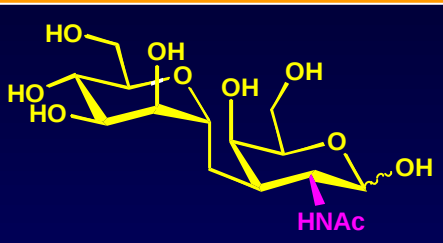




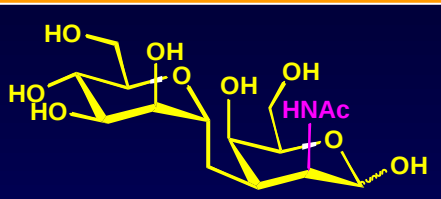
Peter Steunenberg

NEUTRAL (1→3)-C-DISACCHARIDES

Glycosidase and Glycosyltransferase inhibitors



a-D-Man*p*(1→3)CH_2-D-GalNAc



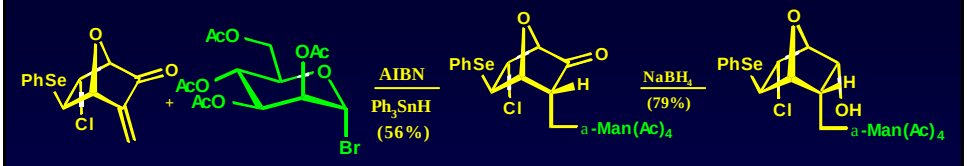
a-D-Manp(1→3)CH_2-D-TalNAc

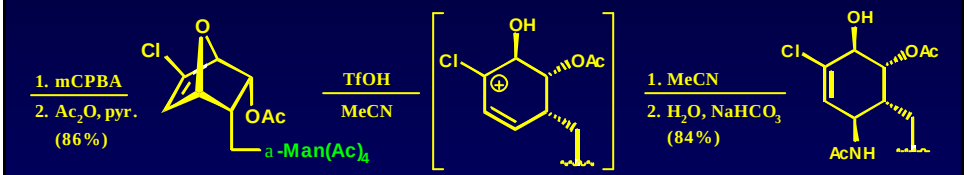
Inhibits several glycosidases
(b-galactosidase, jack bean, Ki = 7.5 mM)
and
human a-1,3-fucosyltransf. VI
with Ki = 120 mM

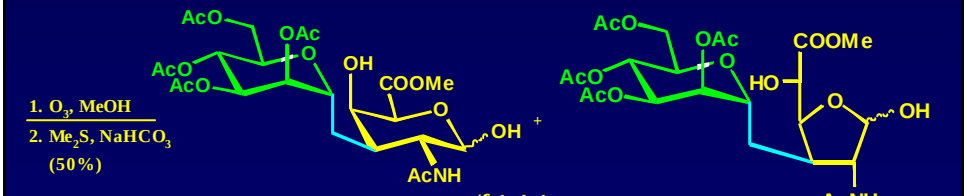
INACTIVE

C. Pasquarello, R. Demange, S. Picasso, E. Berger, M. Malissard, P. Vogel, ***J. Org. Chem.*** **2000, *65*,** 4251

GIESE'S RADICAL C-GLYCOSIDATION

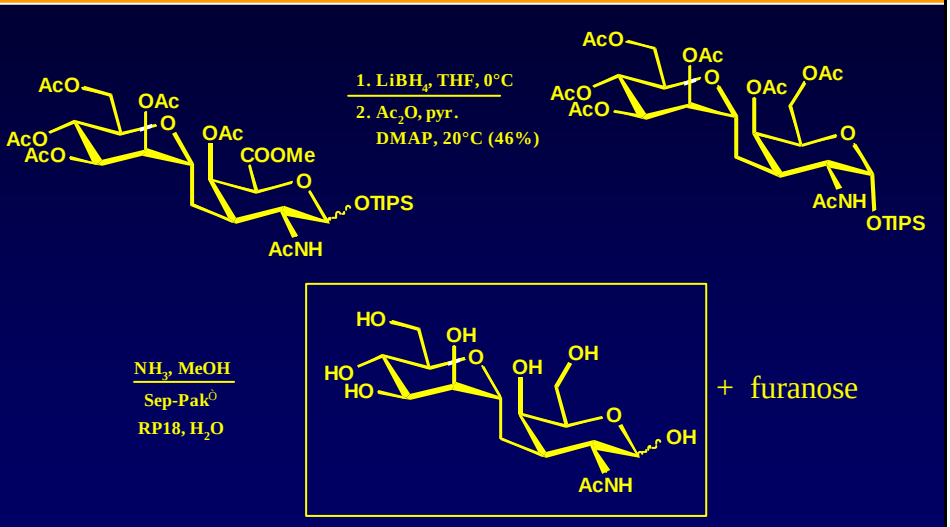






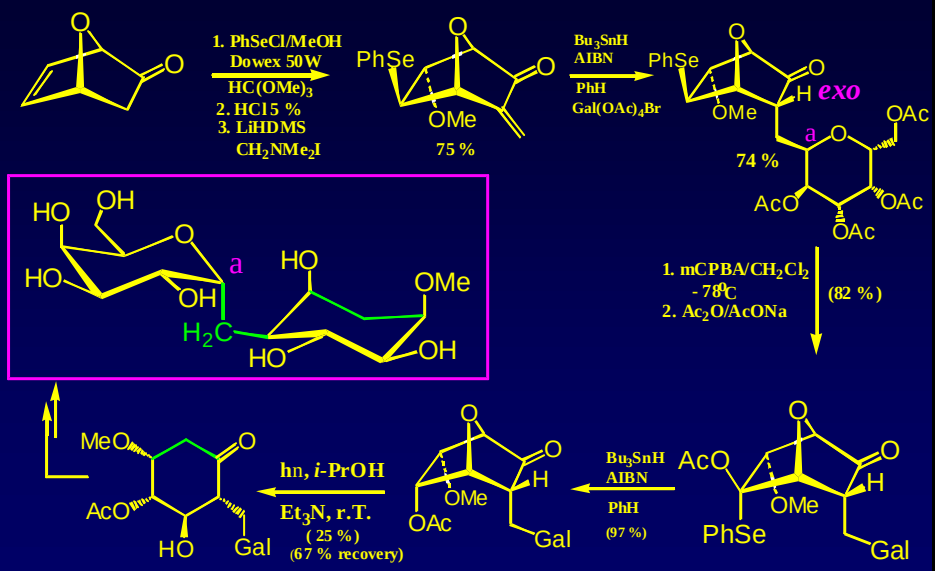
C. Pasquarello

α-D-Man*p*(1→3)CH_2-D-GalNAc



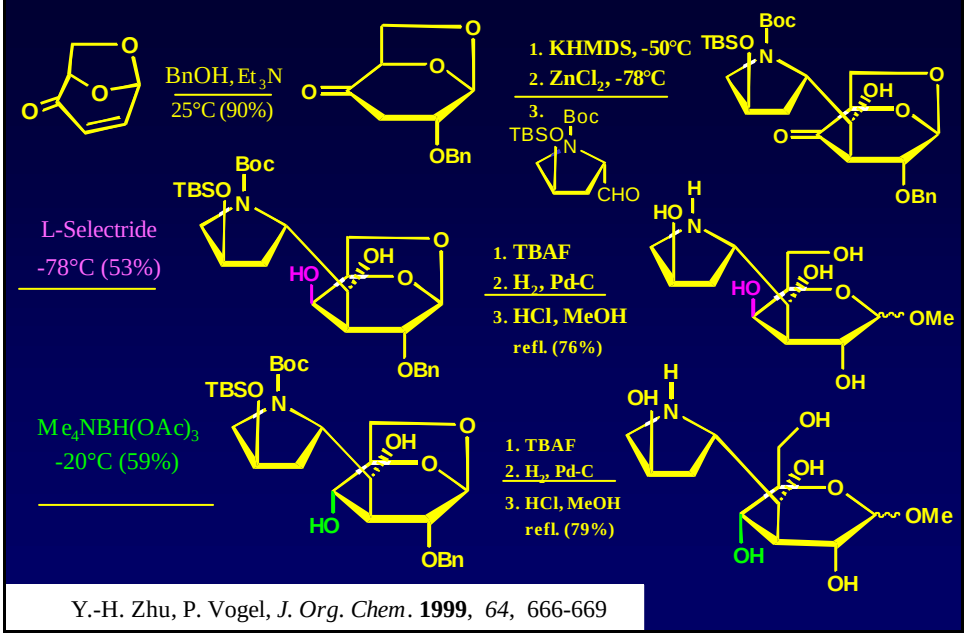
C. Pasquarello, S. Picasso, R.Demange, M. Malissard, E. G. Berger, P.Vogel, *J. Org. Chem.* **2000**, *65*, 4251

a -C-Galactopyranoside of a Carbapentopyranoside



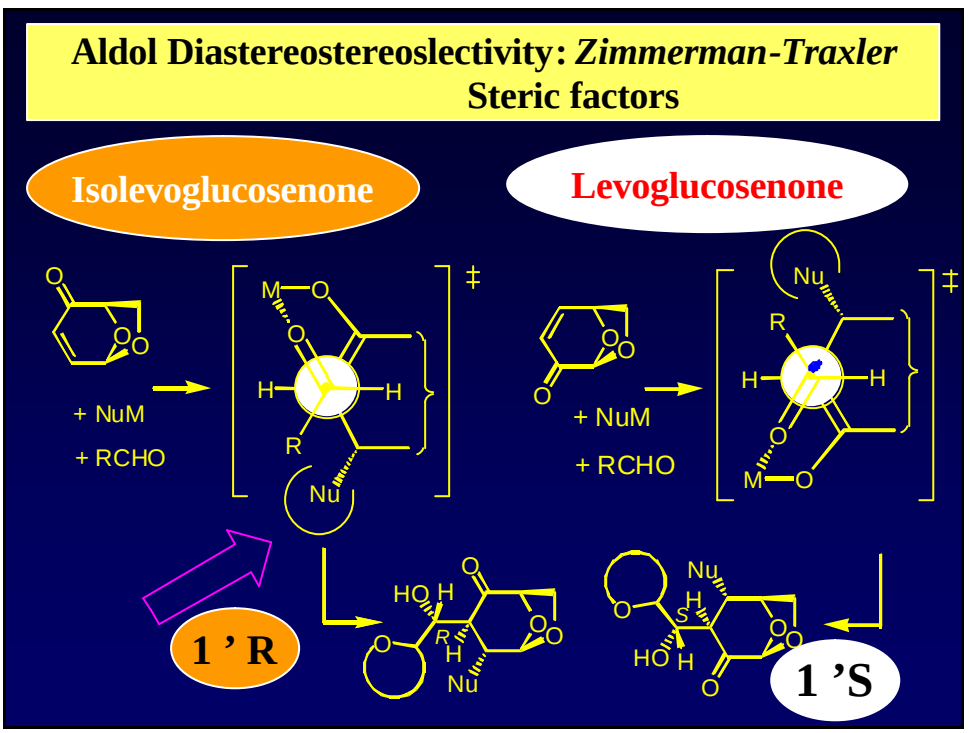
R. Ferritto, J. Cossy

(1→3)-C-LINKED IMINO-DISACCHARIDES

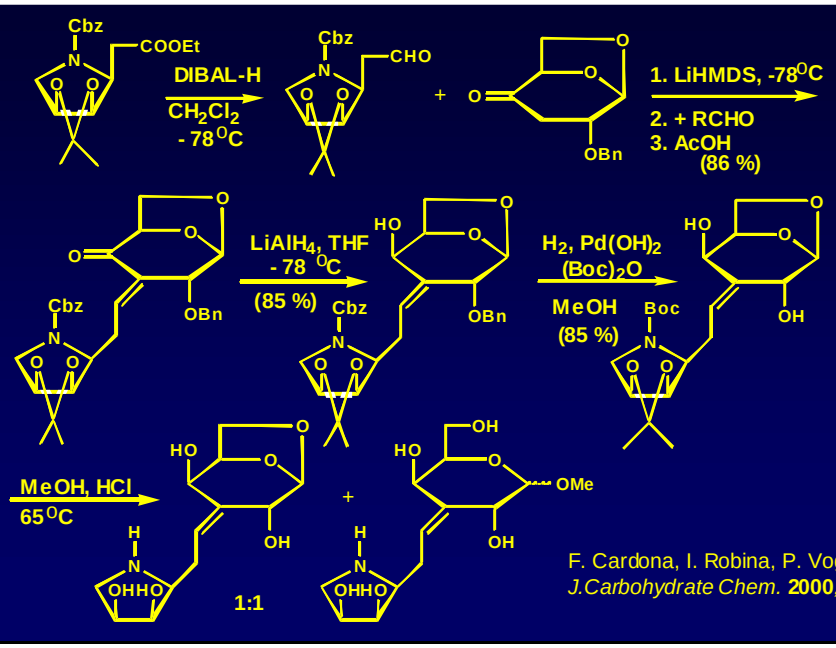


Y.-H. Zhu, P. Vogel, *J. Org. Chem*. **1999**, *64*, 666-669

Aldol Diastereostereoslectivity: *Zimmerman-Traxler* Steric factors

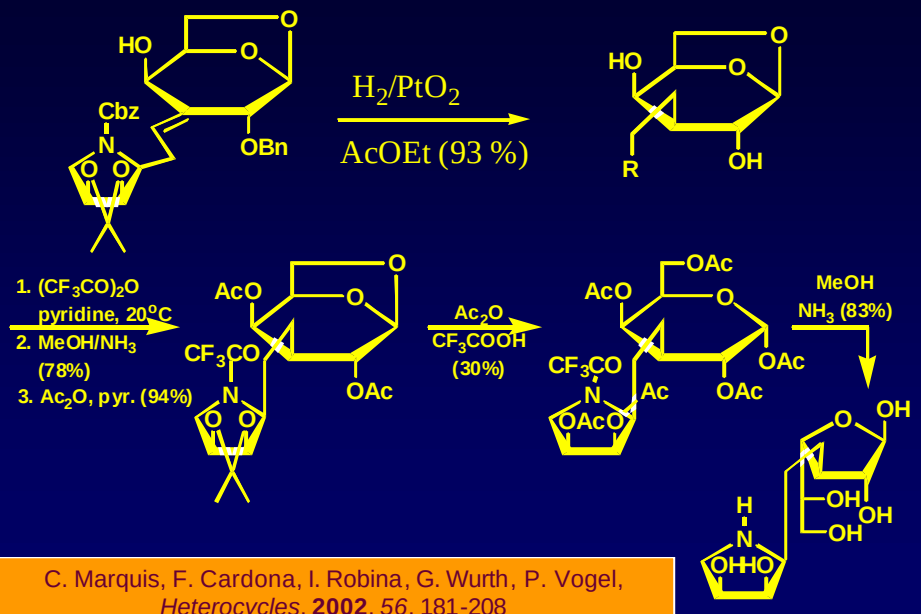


Homo-(1→3)-C-Linked Iminodisaccharides



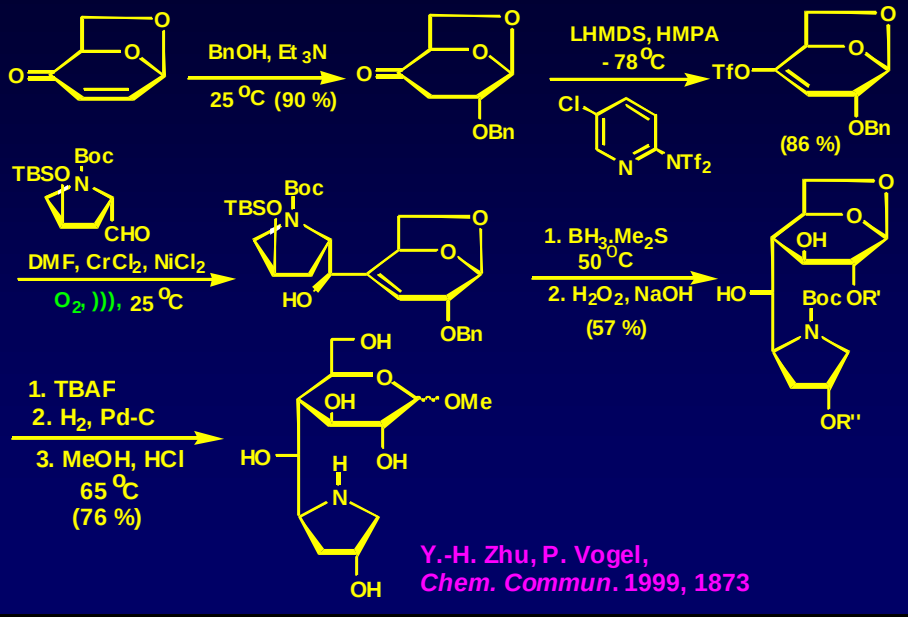
F. Cardona, I. Robina, P. Vogel,
J.Carbohydrate Chem. **2000**, *19*, 555

Homo(1→3)-C-linked Iminodisaccharide

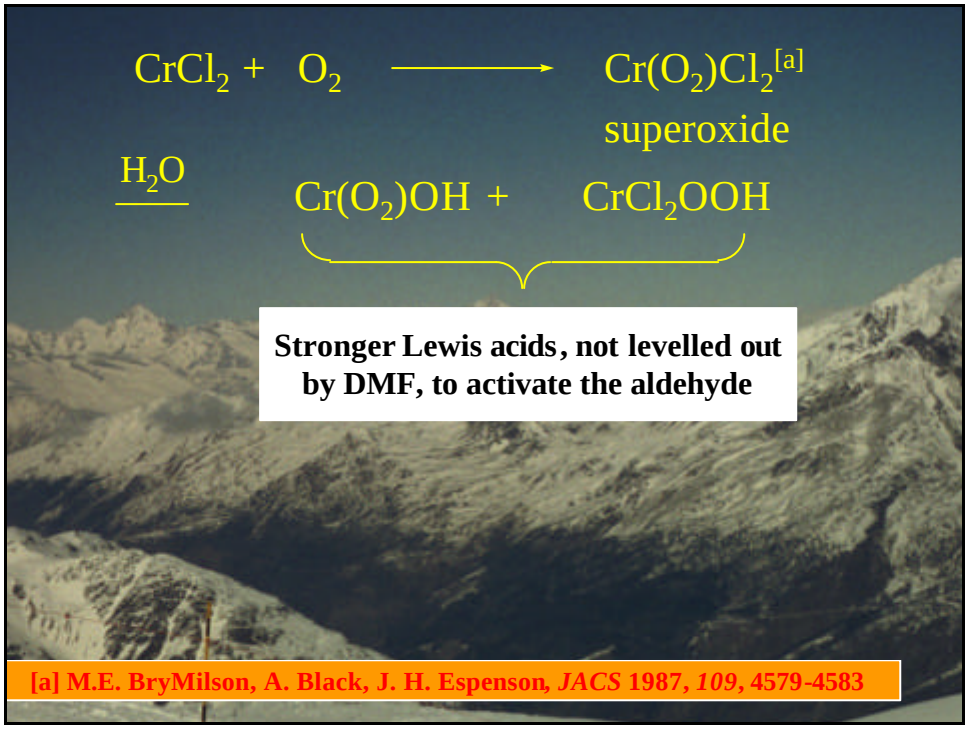


C. Marquis, F. Cardona, I. Robina, G. Wurth, P. Vogel,
Heterocycles, **2002**, *56*, 181-208

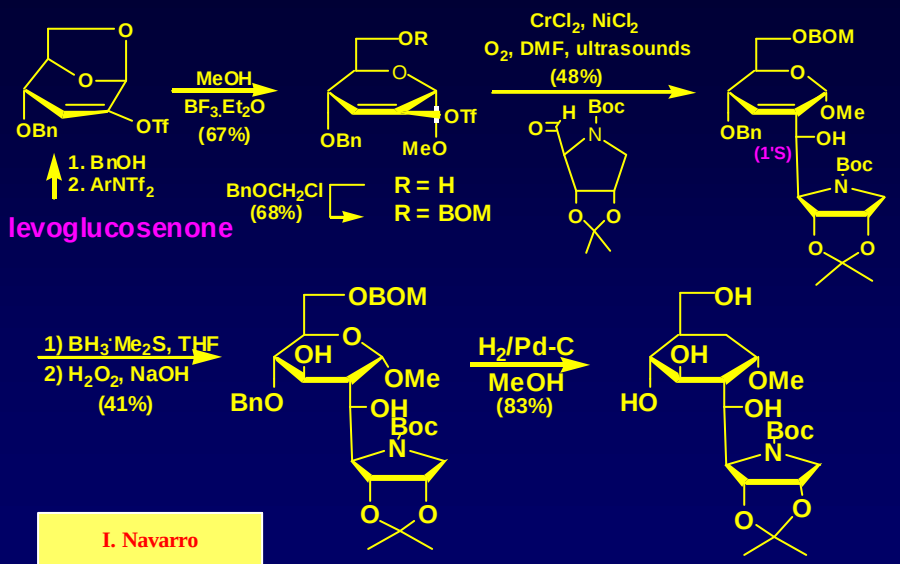
(1→4)-C-Linked Iminodisaccharides



Y.-H. Zhu, P. Vogel, *Chem. Commun*. 1999, 1873

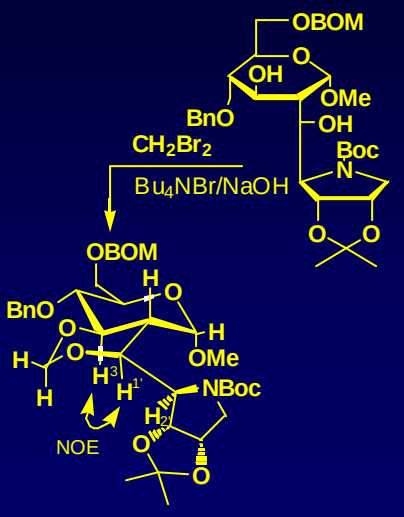


2,5-Dideoxy-2,5-imino-L-ribitol-1a,2-CH(OH)-D-Glc-OMe

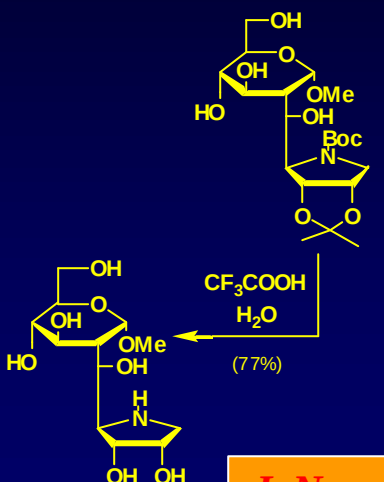


I. Navarro

Configuration of the (HO)CH linker

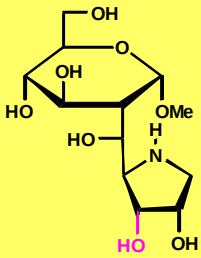


Deprotection



I. Navarro

GLYCOSIDASE INHIBITION



amyloglucosidase

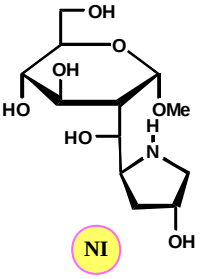
Rhizopus mold — IC_{50}: 65 µM; K_i: 145 µM (NC)

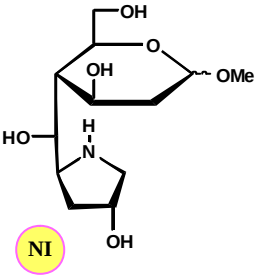
b **-glucosidase**

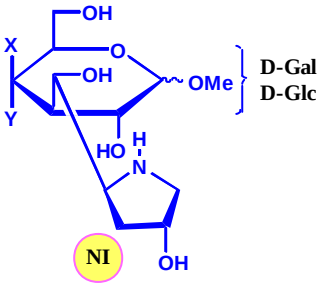
caldocellum saccharolyticum — IC_{50}: 260µM; K_i: 100 µM (M)

a **-mannosidase**

Jack bean — 39% (1 mM)







I. Navarro; R. Demange

X.-H. Zhu

Combinatorial Approach to Drug Discovery

1. Chemists prepare a large number of compounds (mixtures, arrays), (tagging, deconvolution, parallel synthesis)

2. Biologists evaluate their biological properties (high-through-put bioassays)

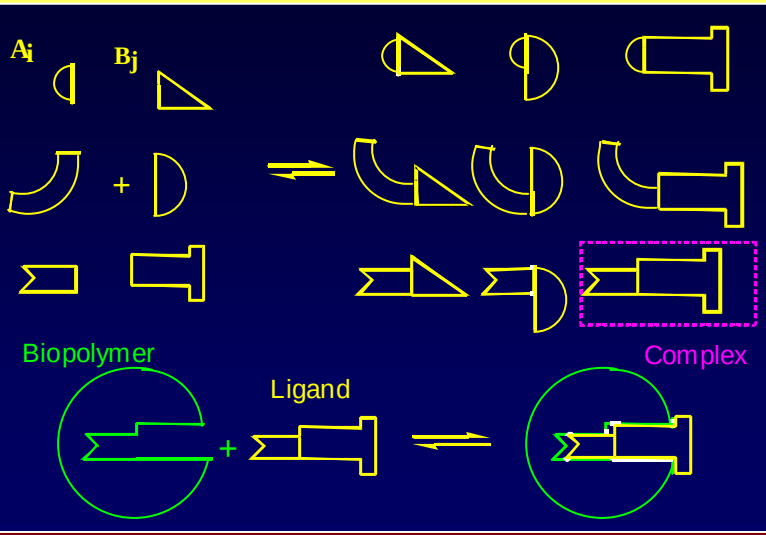
Combine both types of operations: adaptive chemistry; dynamic libraries

Mixtures of products equilibrating with simpler reactants: the enzyme, the receptor, the cell selects the best ligands

Sublibraries — Dynamic library

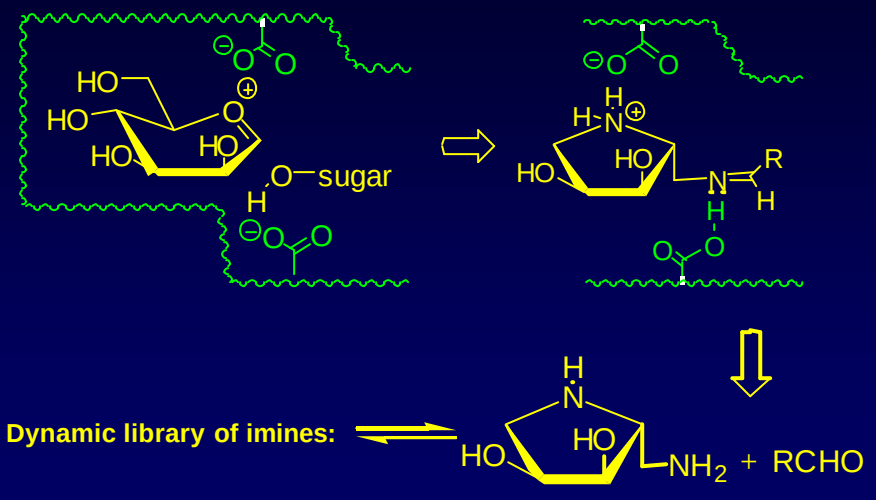
$$A_i + B_j \rightleftharpoons [A\text{-}B]_{ij} + \ldots\ldots$$

Dynamic Combinatorial Chemistry

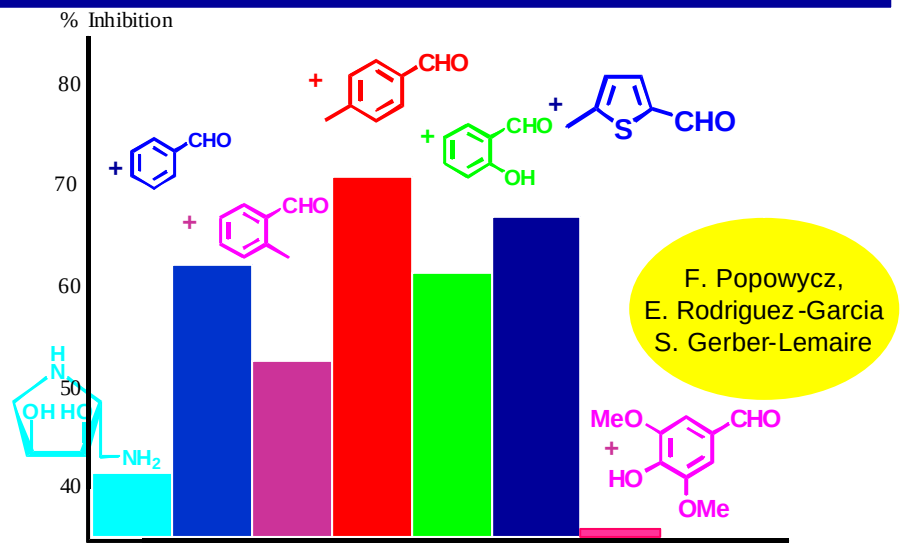


A. Ganesan, ***Angew. Chem. Int. Ed.*** **1998, *37*,** 2828
J.-M. Lehn, A. V. Eliseev, ***Science*** **2001, *291*,** 2331

Dynamic Library of Imines, α-Mannosidase Inhibitors

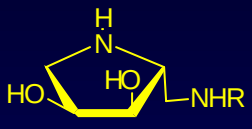


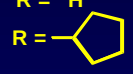
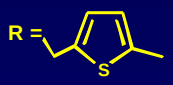
a-Mannosidase from almonds (0.03 U/ml)
$[diamine]_0 = [aldehyde]_0 = 0.5$ mM, pH = 5.0



F. Popowycz,
E. Rodriguez-Garcia
S. Gerber-Lemaire

b-Amino-imines models for 1,2-Diamine Inhibitors

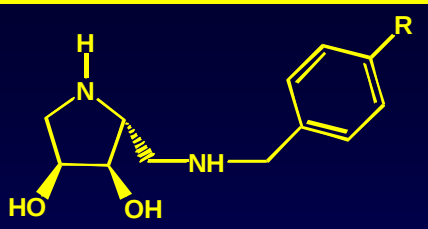


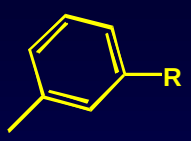
	Inhibition of a-Mannosidases (at 1 mM) from jack bean	from almonds
R = H	81 % (Ki: 53 mM)	51 %
R = 	60 %	53 %
$R = CH_2Ph$	92 % (7.5 mM)	69 % (Ki: 71 mM)
R = CH(COOH)Ph	NI	NI
R = 	98 % (3.6 mM)	86 % (18.5 mM)
$R = CH_2$ 	99 % (Ki: 2.5 mM)	82 % (Ki: 20 mM)

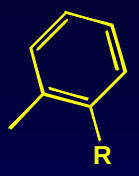
All competitive Inhibitors

F. Popowycz, S. Gerber-Lemaire, E. Rodriguez, R. Demange

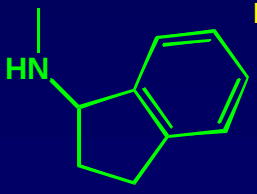
STRUCTURE-ACTIVITY







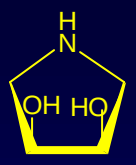
R =			
Me	3.0	10.1	10.6 mM
MeO	6.9	9.2	20.2
OH	4.9	8.4	
F	9.5	35.6	19.6
Cl	10.3	11.9	12.8
Br	8.5	10.1	11.2



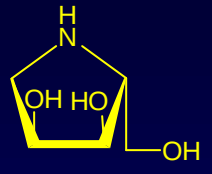
2.3 mM (C)

E. Rodriguez-Garcia
F. Popowycz
S. Gerber-Lemaire

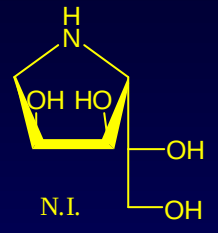
Inhibition of a-mannosidase from jack bean (at 1mM concentration)



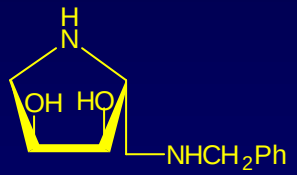
70 %



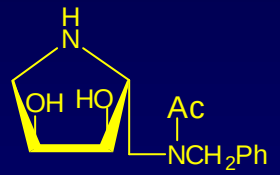
54 %



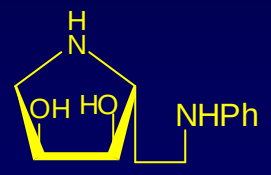
N.I.



92 % (Ki: 7.4 µm)



N.I.

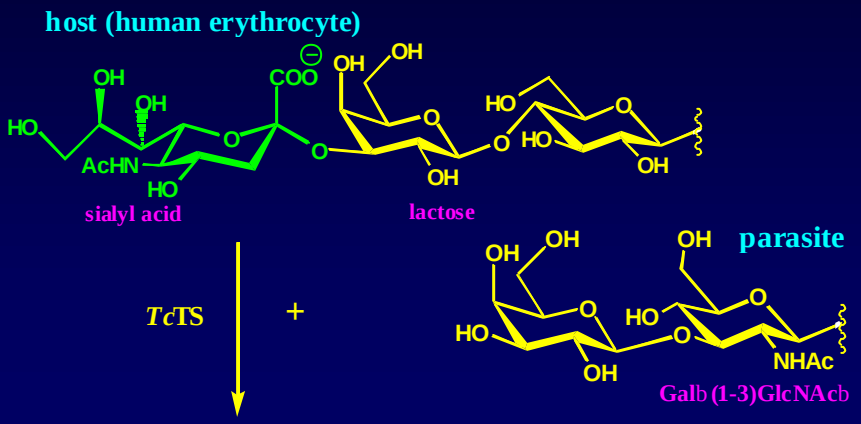


33 %

F. Popowycz, S. Gerber-Lemaire, R. Demange, E. Rodriguez-Garcia, A.T. Carmona, I. Robina, P. Vogel, *Biorg. Med. Chem. Lett.* **2001,** *11*, 2489

Chagas' disease

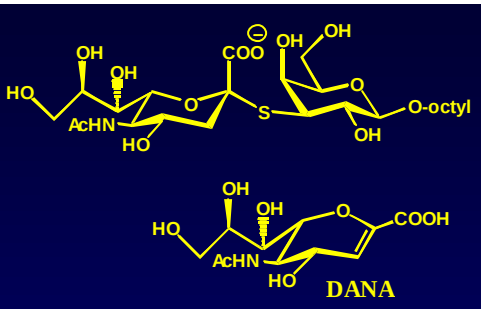
***Trypanosoma cruzi* is protected from anti-α-galactosyl antibodies by acquiring up to 107 sialic acid residues on its surface, a reaction catalysed by its unique trans-sialidase (*Tc*ST)**



Siaα(2-3)Galβ(1-3)GlcNAcβ (*Tc* surface)

Schenkman, *Cell*. **1991,** *65*, 117, Pereira-Chioccola, *J.Cell.Sc*. **2000,** *113*, 1299

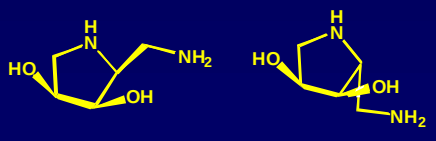
Trans-sialidase inhibition



Are not inhibitors of Trans-sialidase from Trypanosoma cruzi

Schenkman, S, et al., *Bioorg. Chem. Med. Lett*. **2001,***11*, 141

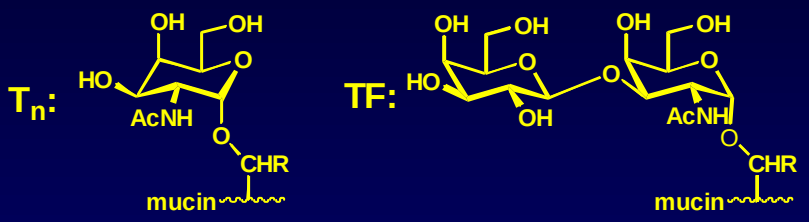
TcTS is inhibited by the sera of infected animals and Chaganic patients



Frasch,A.C.C. et al. *Infect.Immun.* **1994,** *62*, 5421; Pereira-Chioccola, V.L. et al. *Infect. Immun*. **1994,** *62*, **2973**

Tn and TF (Thomsen-Friedenreich) antigens are common in carcinoma malignancies (and prostate cancers)

Ref: Springer, G. F. *Science* 1984, *224*, 1198



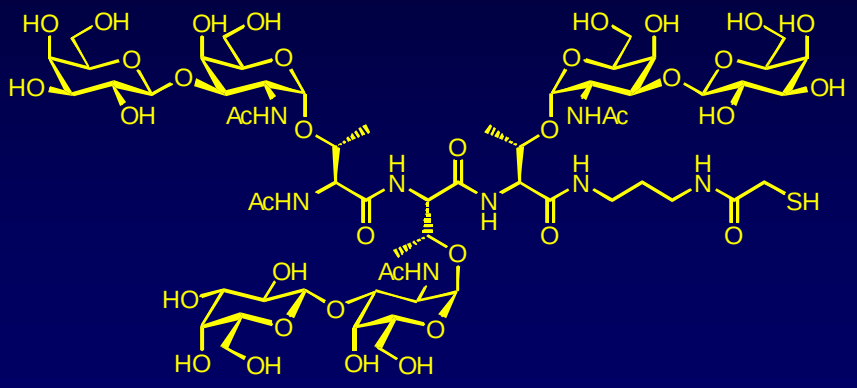
simple carbohydrate antigens in conjugate vaccines induce anti-cancer antibodies

Ref: MacLean, G. D.; Reddish, M. A.; Bowen-Yacyshyn, B. B.; Poppemo, S.; Longenecker, B. M. *Cancer Invest.* 1994, *12*, 46; Springer, G. F. *Clin. Rev. Oncogenesis* 1995, *6*, 57

THOMSEN-FRIEDENREICH ANTIGEN (T-Epitope)

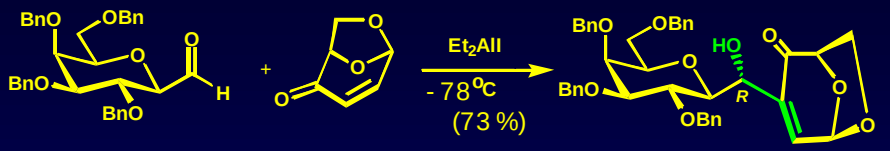
Anti-cancer immunogenicity of Galb (1→3)GalNAc: See e.g.: G. F. Springer, *Clin. Rev. Oncogenesis* 1995, *6*, 57

Candidate for anti-cancer vaccine

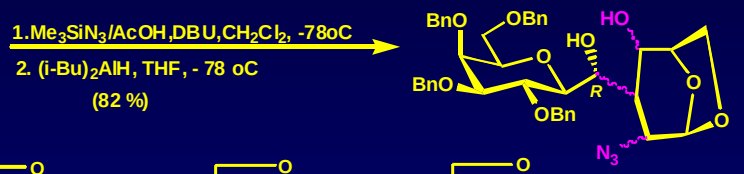


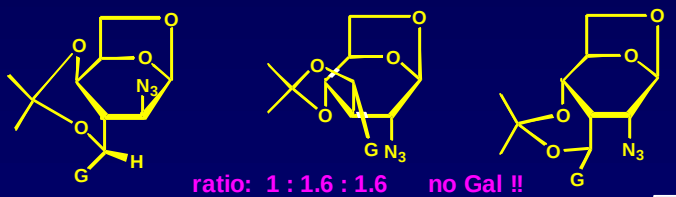
S. J. Danishefsky et al. *J. Am. Chem. Soc.* **1998**, *120*, 12 474

Toward Galb-C-GalNac



Method: Itoh,A,: Ozagawa,S.; Oshima,K.; Nozaki,H. *Bull.Chem.Soc.Jpn.* **1981**, *54*, 274

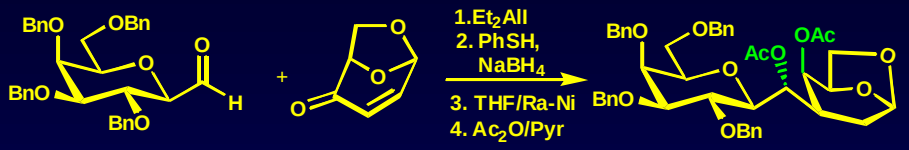


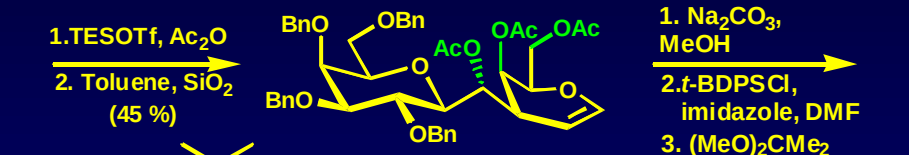


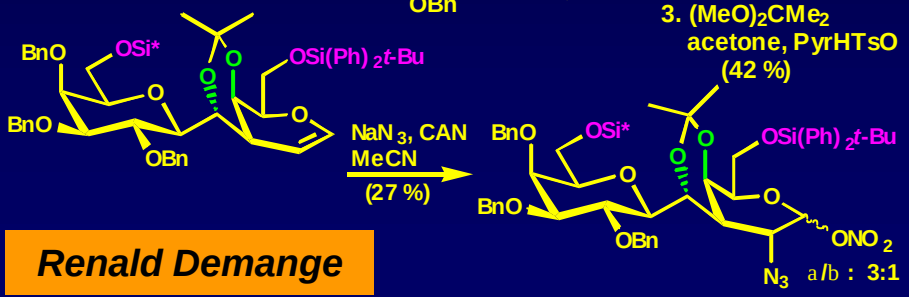
ratio: 1 : 1.6 : 1.6 no Gal !!

Raynald Demange

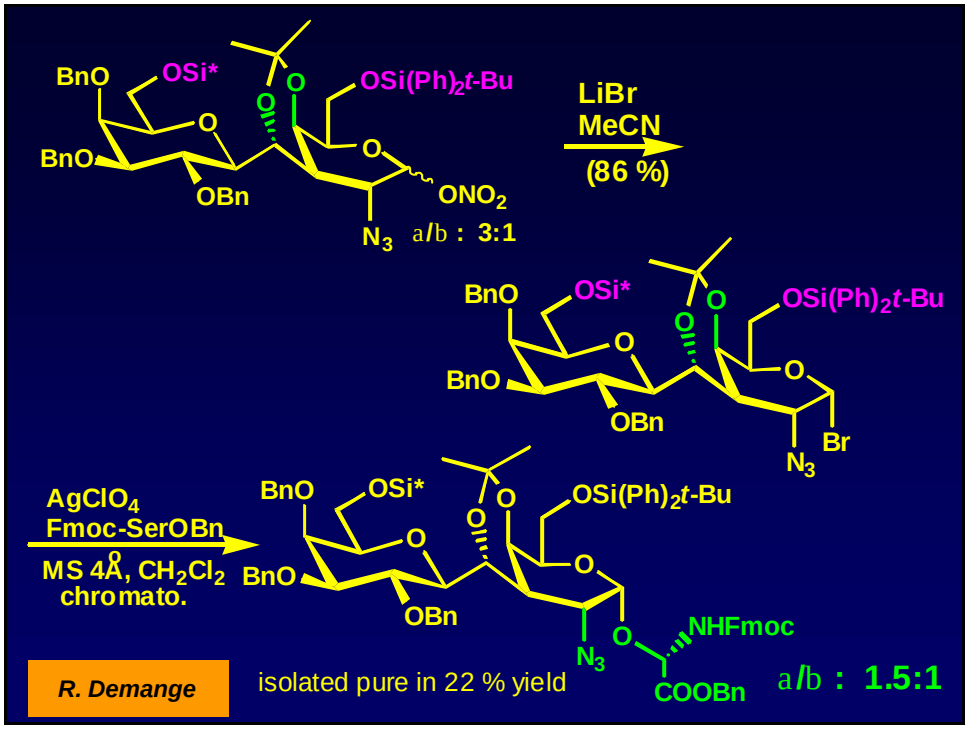
Change of protective groups



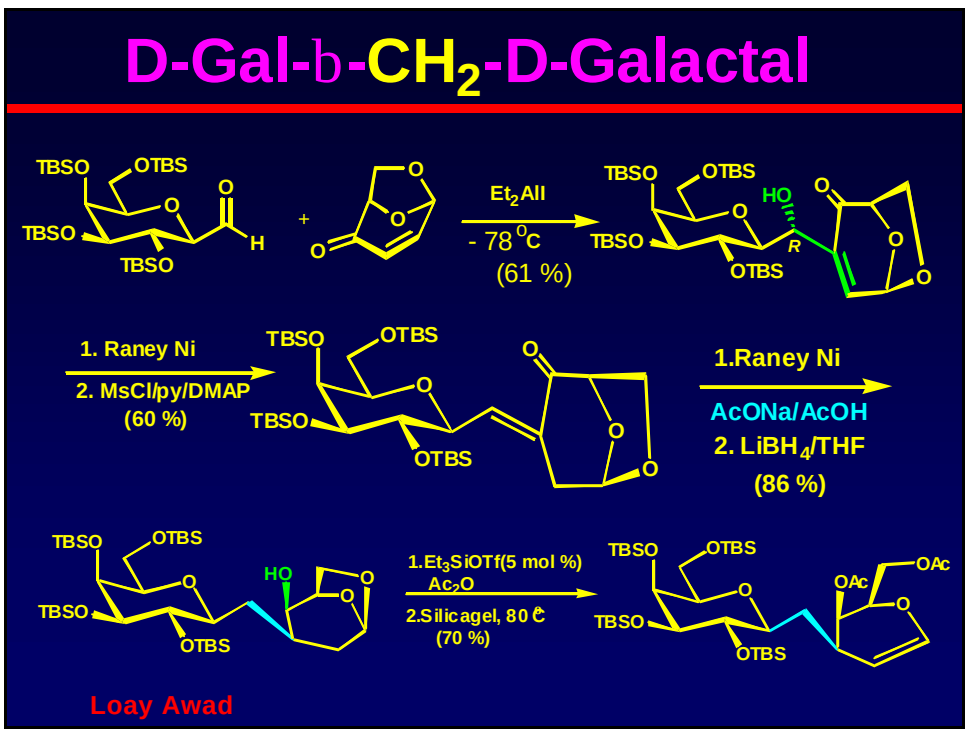




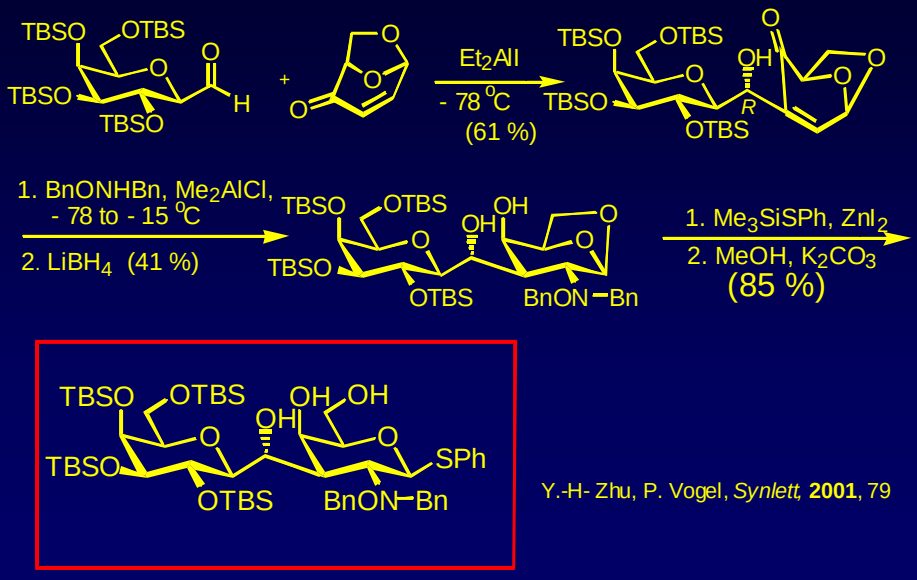
Renald Demange



D-Gal-b-CH_2-D-Galactal



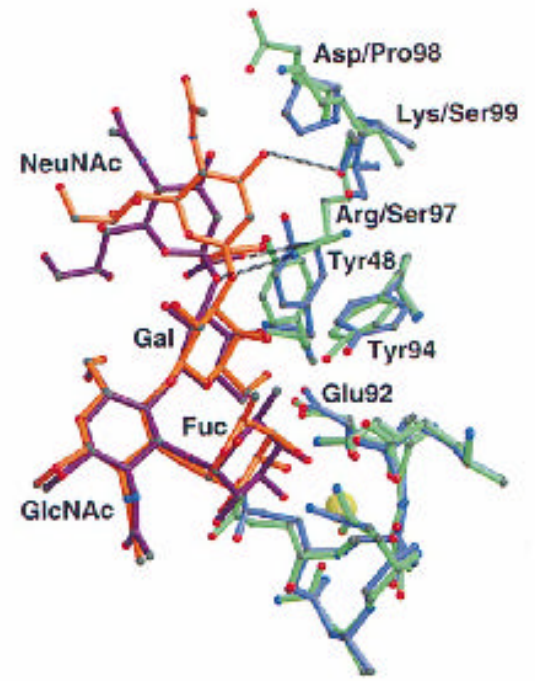
C-Analog of Thompsen-Friedenreich Epitope (T-Epitope)



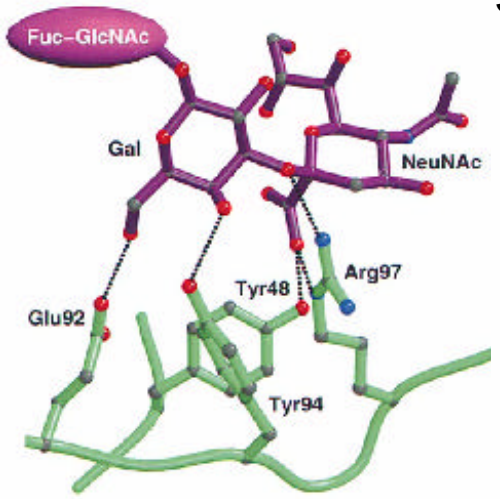
Y.-H- Zhu, P. Vogel, *Synlett,* **2001**, 79

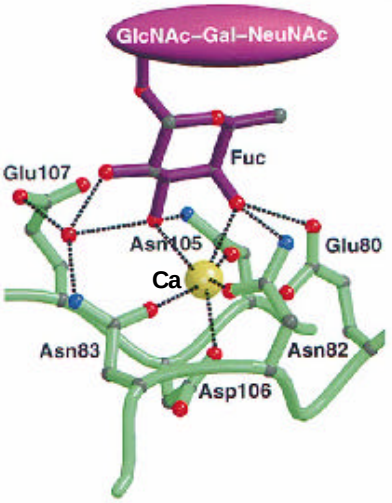
Recruitment and extravasation of leukocytes from blood stream

Perfusion injuries, stroke, rheumatoid arthritis, etc.



Sialyl Lewis X

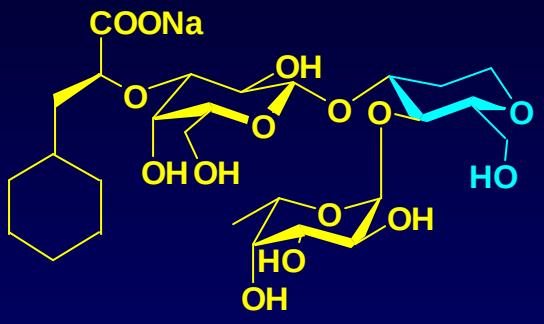




P-Selectin

Camphausen et al.

Sialyl Lewis^x : IC_{50}(E-Sel) = 1000 mM

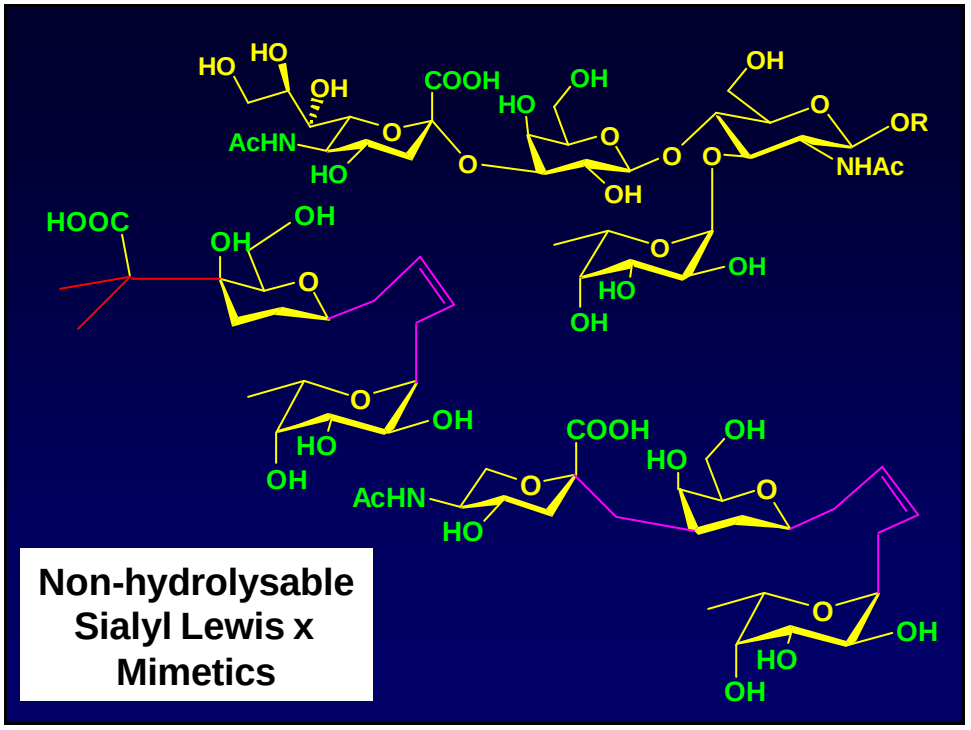


inactive

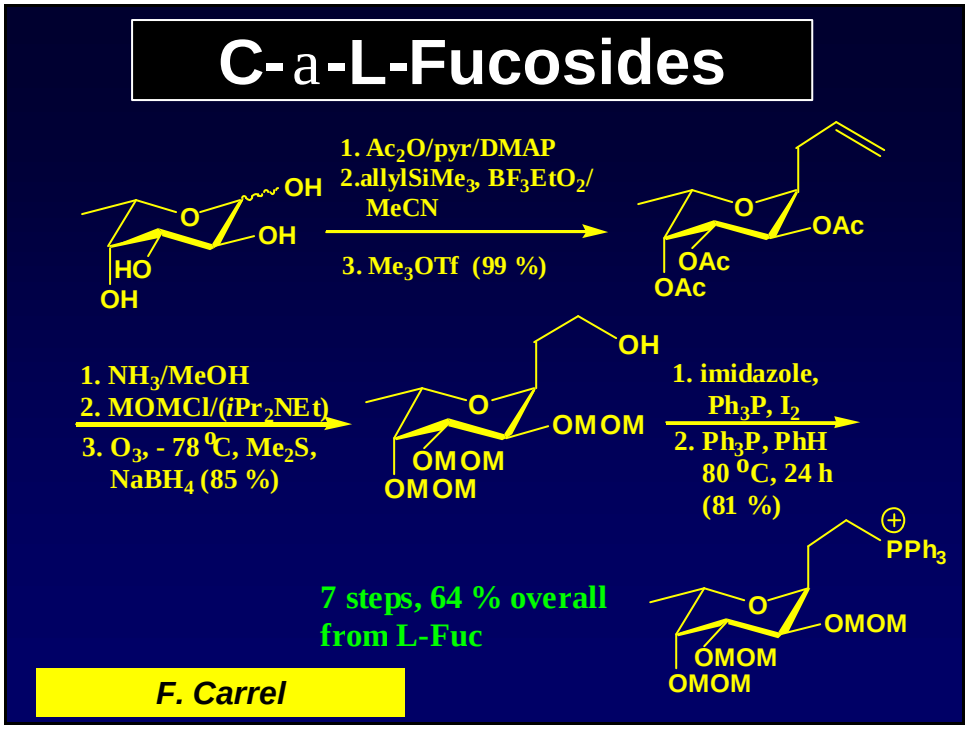
IC_{50}(E-Sel) = 36 mM

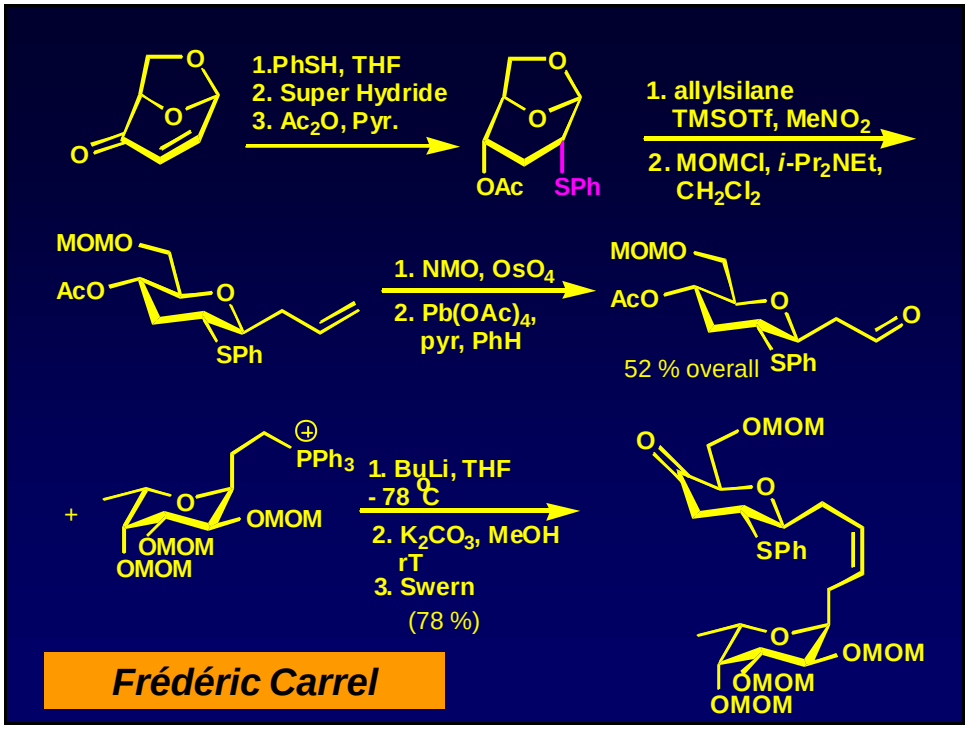
110 mM

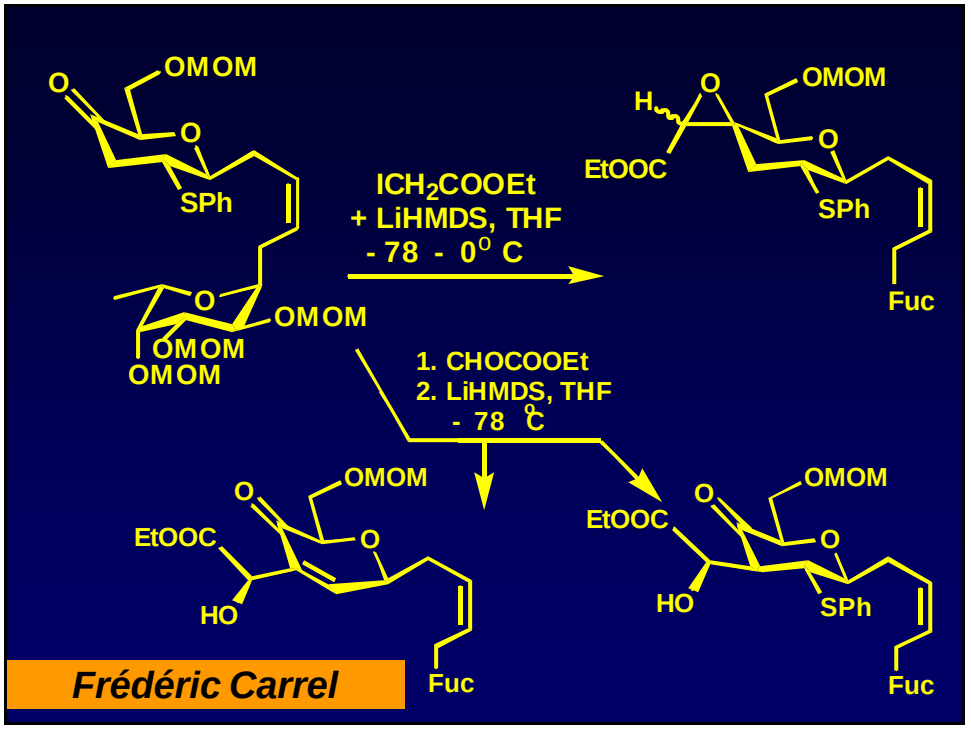
Thoma, G.; Kinzy, W.; Bruns, C.; Patton, J. T.; Magnani, J. L.; Bänteli, R. *J. Med. Chem*. 1999, *42*, 4909



C-a-L-Fucosides




1.PhSH, THF
2. Super Hydride
3. Ac2O, Pyr.
OAc
SPh
1. allylsilane
TMSOTf, MeNO2
2. MOMCl, i-Pr2NEt,
CH2Cl2
MOMO
AcO
SPh
1. NMO, OsO4
2. Pb(OAc)4,
pyr, PhH
52 % overall
PPh3
OMOM
1. BuLi, THF
- 78 °C
2. K2CO3, MeOH
rT
3. Swern
(78 %)
Frédéric Carrel


OMOM
SPh
ICH2COOEt
+ LiHMDS, THF
- 78 - 0° C
EtOOC
Fuc
1. CHOCOOEt
2. LiHMDS, THF
- 78 °C
HO
Frédéric Carrel

EPFL

Swiss Science Fondation
OFES, Bern (COST D13)
Socrates (Seville/Lausanne)
Fonds Herbette (Lausanne)
CSCS(ETHZ, Manno)

A. Baudat,
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V. Jeanneret,
L. Meerpoel,
C. Schaller,
C. Marquis,
S. Picasso,
C. Viodé,
F. Cardona,
R. Ferritto,
F. Carrel,
Y.-H. Zhu,
I. Navarro,
E. Rodriguez Garcia,
R. Demange,
F. Popowycz,
C. Pasquarello,
P. Steunenberg,
S. Berger-Lemaire,
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Collaborations:
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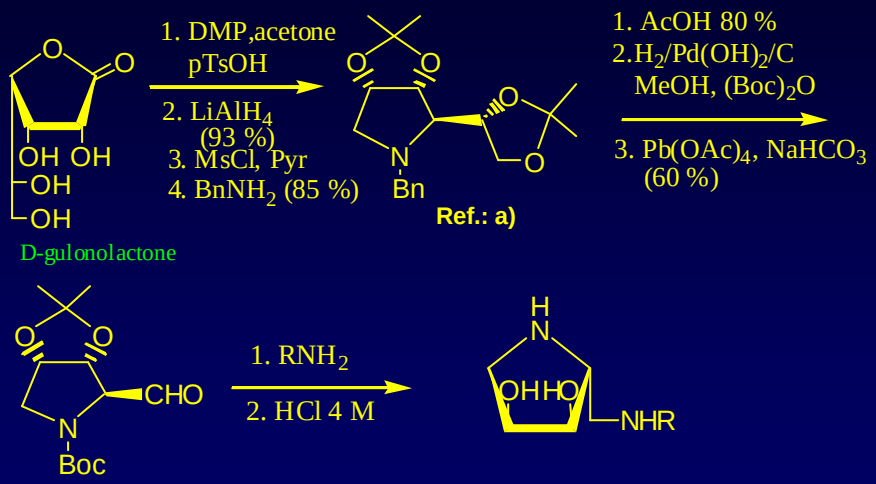
A. T. Carmona Asenjo
A. J. Moreno Vargas
J. Jimenez Barbero (Madrid)

E. Berger, M. Malissard (Zürich)

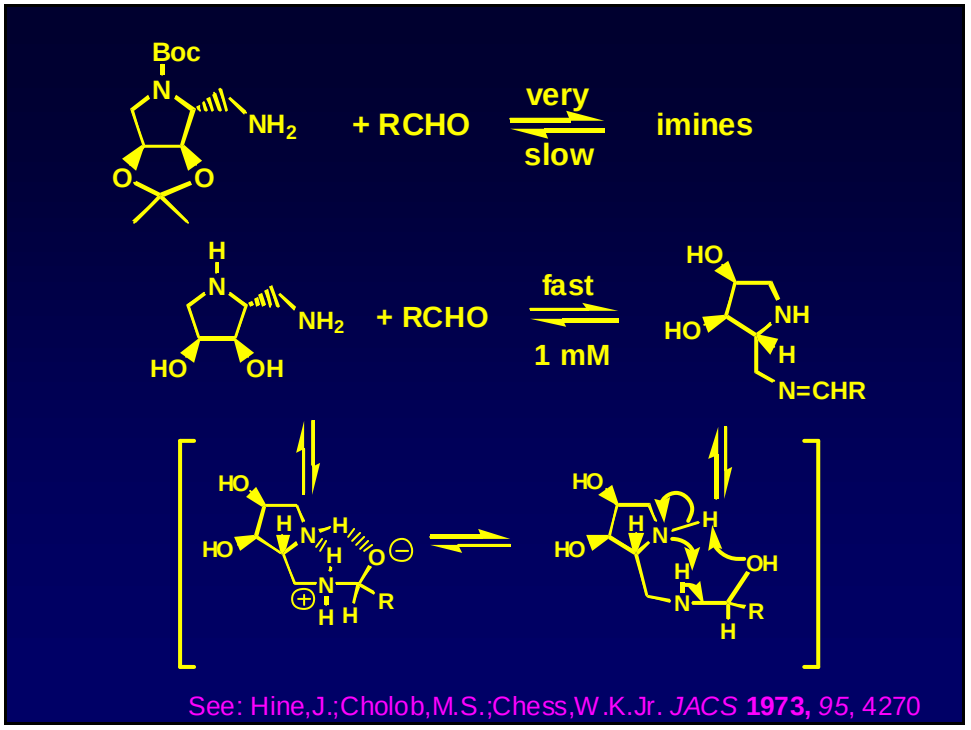
V. Kren (Prag)

Cost D13/0001/99: ***A. Dondoni, J. Fuentes, V. Jäger, J. Van Boom, V. Barberousse, A. Chollet, V.Kren, C. Nativi***

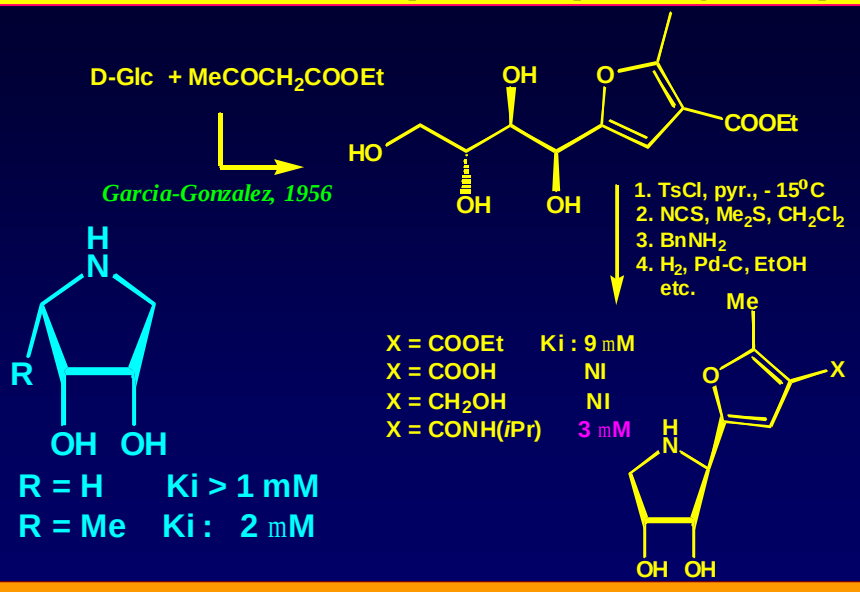
Synthesis of (2*R*,3*R*,4*S*)-pyrrolidine-3,4-diol Derivatives



a) G.W. J. Fleet, J. C. Son, D. St.C. Green, I. Cenci di Bello, B. Winchester, *Tetrahedron* **1988**, *44*, 2649

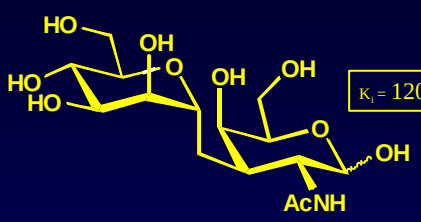


a-L-fucosidase (bov. epididymis)



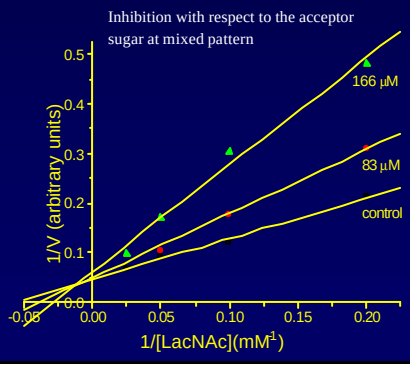
I.Robina,A.J.Moreno-Vargas, et al. *Bioorg.Med.Chem.Lett.*2001,*11*,2555

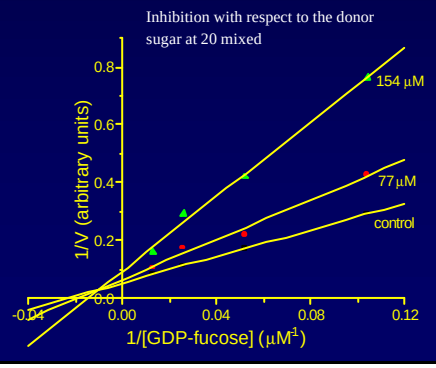
HUMAN α-1,3-FUCOSYLTRANSFERASE VI INHIBITION



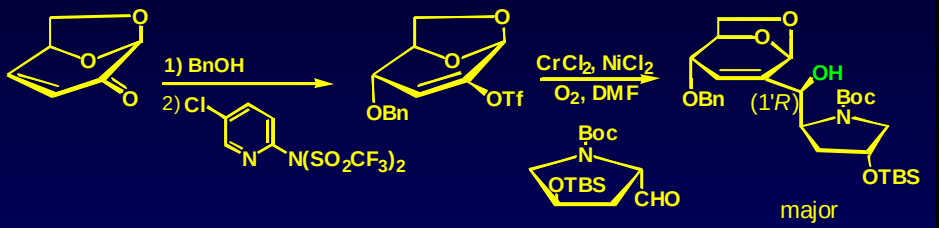
K_i = 120 μM

- mixed type of inhibition toward donor and acceptor
- the known inhibitor GDP does not synergize with the C-disaccharide
- GalNAc & Man(1→3)CH_2-TalNAc are not inhibitors

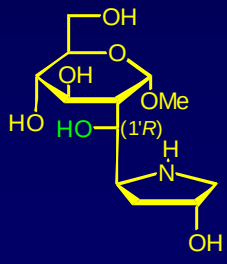




Imino-C(1→2)-disaccharides from levoglucosenone

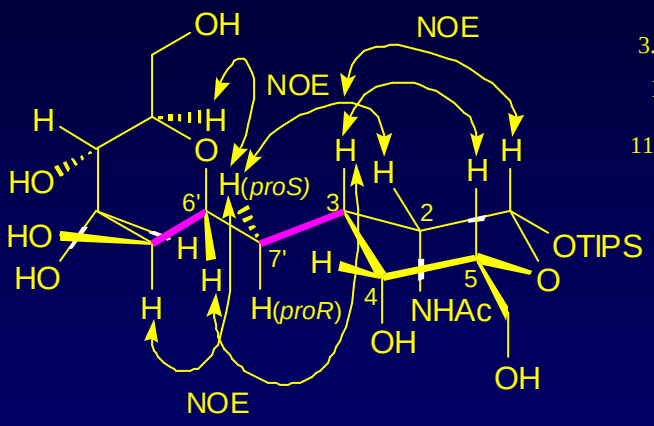


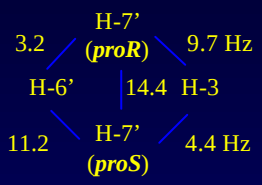
1) MeOH, TsOH
2) $BH_3{\cdot}Me_2S$, THF
3) H_2O_2, NaOH
4) MeOH, HCl
5) H_2, Pd-C, MeOH



Yao Hua Zhu

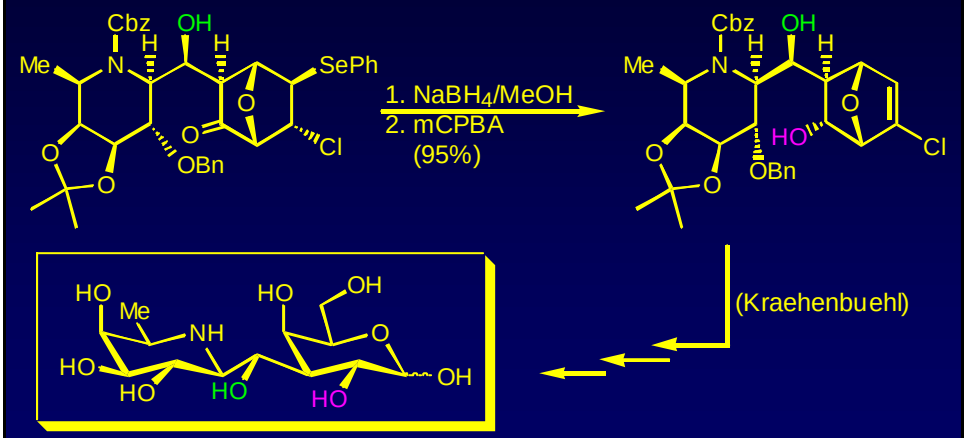
PREFERRED CONFORMATION OF α-D-Man*p*(1→3)CH_2-D-TalNAcTIPS



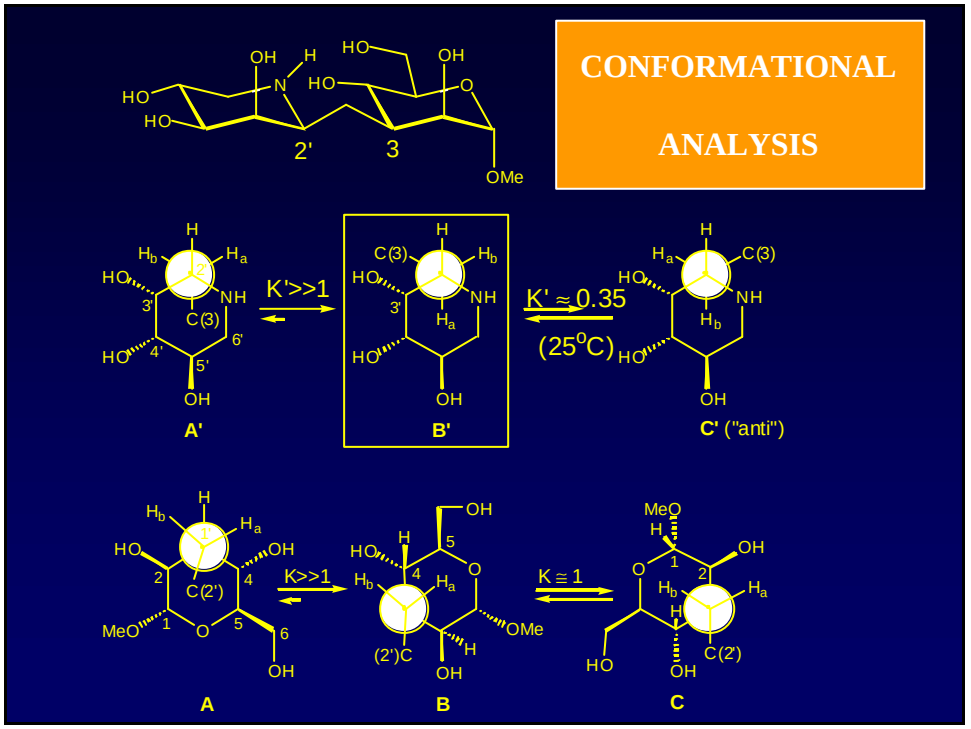


C. Pasquarello , S. Picasso, R. Demange, M. Malissard, E. G. Berger, P. Vogel, *J. Org. Chem.* **2000**, *65*, 4251

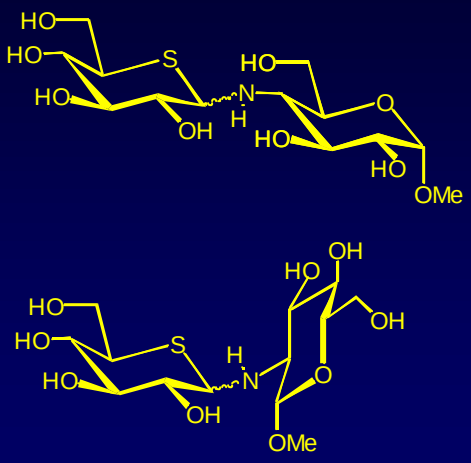
6-Deoxygalactonojirimycin b-C(1→3) Linked with D-Galactose



A. Baudat, P. Vogel, *J. Org. Chem.* 1997, *92*, 6251



Competitive Inhibitor of Maltose Binding by Glucoamylase G2

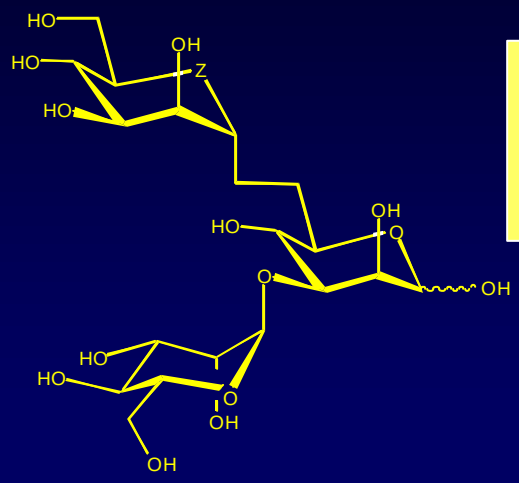


Methyl 5 ’-thio-4N-a -maltoside

Ki = 4 mM

J.S. Andrews, T. Weimar, T. P. Frandsen, B. Svensson, B. M. Pinto, *J. Am. Chem. Soc.* **1995**, *117*, 10799-10804

Binding with Concanavalin A



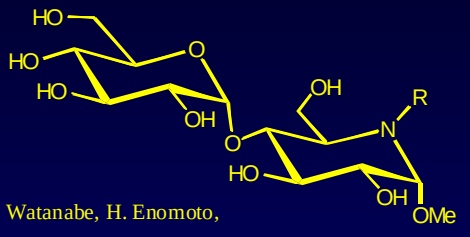
Z = O Kd = 198 mM

Z = S Kd = 31 mM

O. Tsuruta, H. Yuasa, S. Kurono, H. Hashimoto, *Bioorg, Med. Chem. Lett.* **1999**, *9*, 807

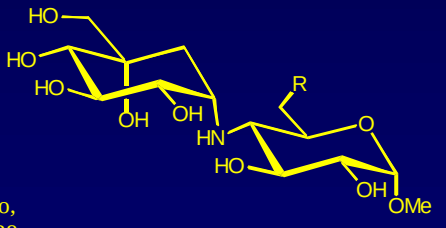
a-Glucosidase Inhibitors

Glucopyranosylmoranolines



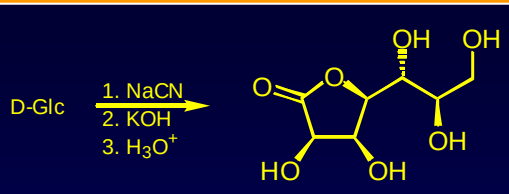
Y. Yoshikuni, Y. Ezure, T. Seto, K. Mori, K. Watanabe, H. Enomoto, *Chem. Pharm. Bull.* **1989**, *37*, 106-109

Valienamine and Derivatives

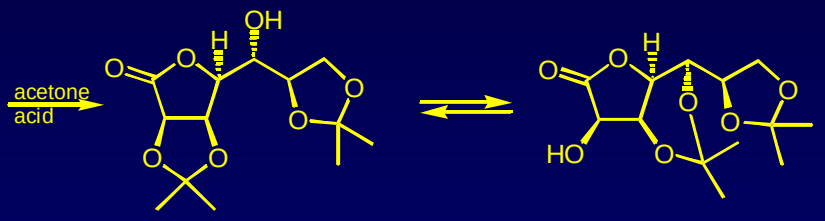


S. Hori, H. Fukase, T. Matsuo, N. Asano, K. Matsui, *J. Med. Chem.* **1986**, *29*, 1038

D-*glycero*-D-*gulo*-Heptano-1,4-lactone



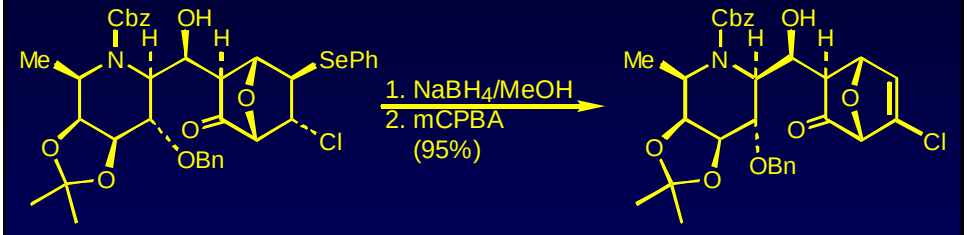
N. H. Richtmyer, *Methods Carb. Chem.* I (1962) 160

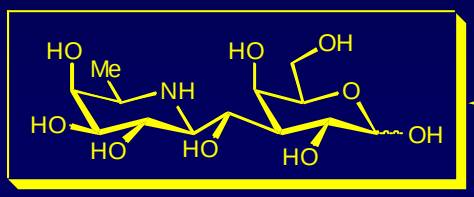


H_2SO_4, 20°C	**10%**	**80%[a)]**
H_3PO_4, $ZnCl_2$, 20°C	**0**	**66%[b)]**
TsOH	**14%**	**80%**

a) J. S. Brimacombe, *Carbohydr. Res.* **1966**, *2*, 341
b) T. K. M. Shing, H. C. Tsui, *JCS Chem. Commun.* **1992**, 432

The first branched Aza-C-disaccharide

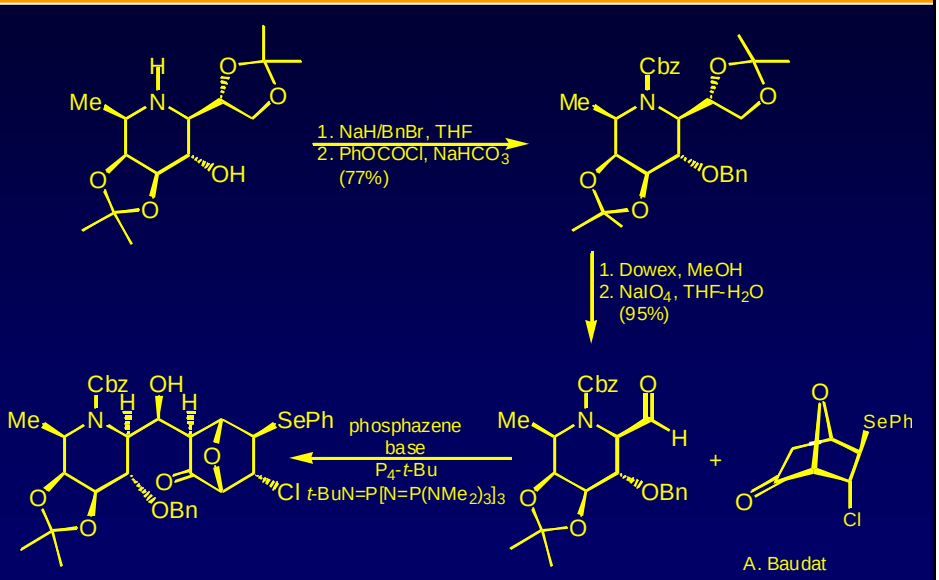




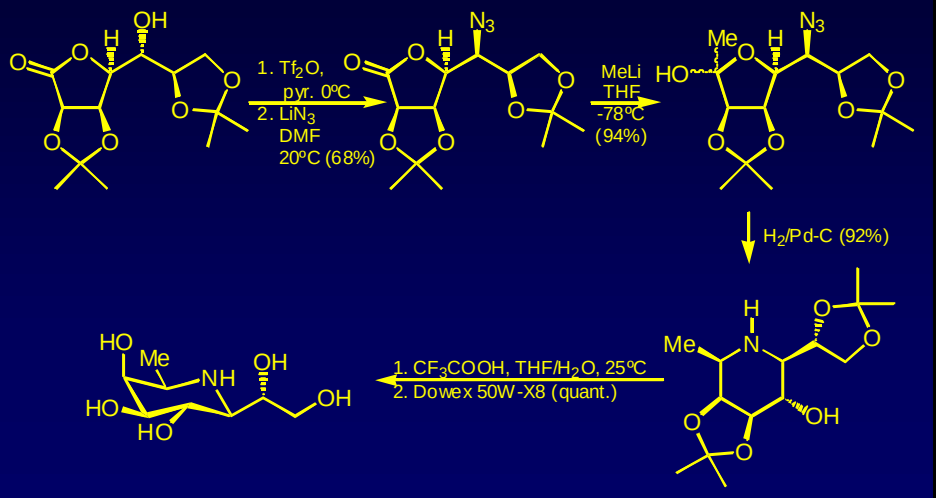
(Kraehenbuehl)

A. Baudat, P. Vogel, *J. Org. Chem.* 1997, *62*, 6252-6260

β-D-AzaGal-C-glycoside



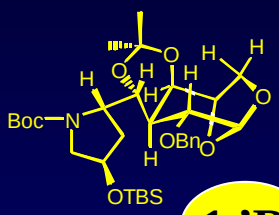
3,7,8-Trideoxy-3,7-imino-L-*galacto*-D-*threo*-octitol



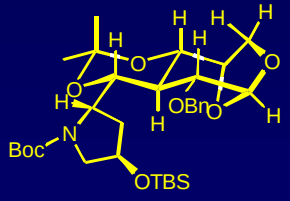
A. Baudat, S. Picasso, P. Vogel, *Carbohydrate Res.* 1996, *281*, 277-284

Configuration of the C-Disaccharides (NMR)

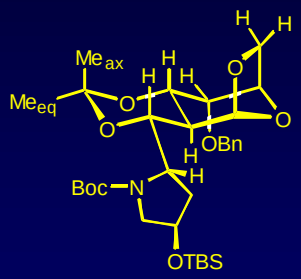
(1→3)-C



1 'R

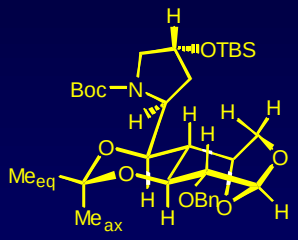


(1→2)-C



1 'R

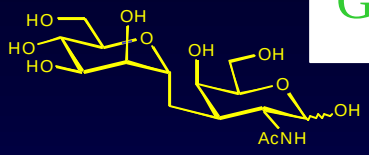
(1→4)-C



1 'R

Y.-H. Zhu, P. Vogel, *J. Org. Chem.* **1999**, *64*, 666
Chem. Commun. **1999**, 1873

Glycosidase Inhibition



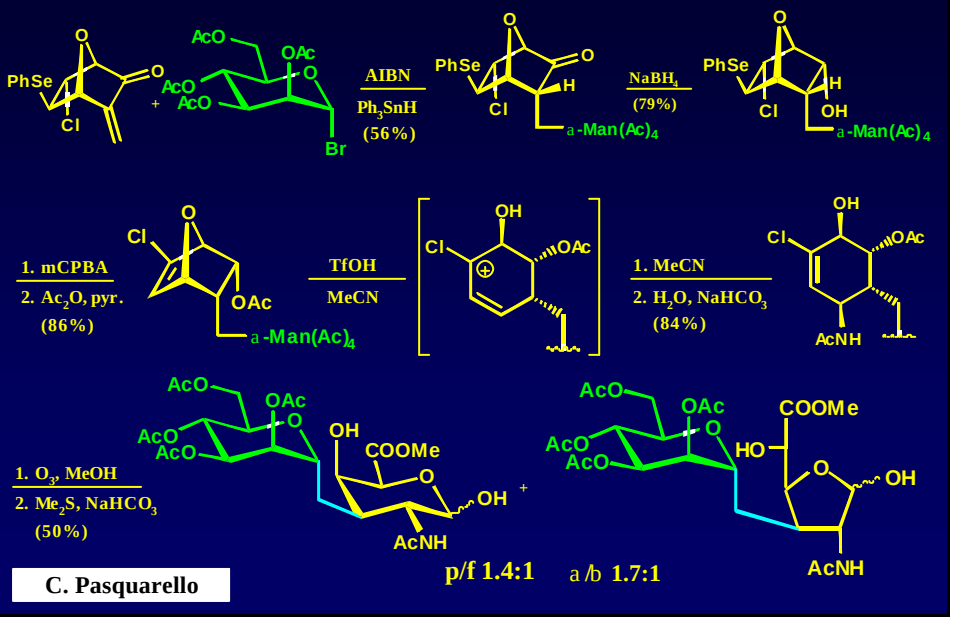
α-D-Manp-(1→3)CH_2-D-GalNAc (*p* and *f*)

	K_i:
α-L-fucosidase	
bovine epididymis	25 µM
human placenta	28 µM
α-galactosidase	
coffee beans	66 µM
Aspergillus niger	76 µM
Escherichia coli	39 µM
β-galactosidase	
jack beans	7.5 µM
Asperillus niger	-
α-glucosidase	
baker yeast	40 µM
rice	-
β-glucosidase	
almonds	-
caldocellum saccharolyticum	18 µM

	K_i:
α-mannosidase	
jack beans	-
almonds	-
β-mannosidase	
helix pomatia	-
β-xylosidase	
Asperillus niger	-
α-N-acetylgalactosaminidase	
chicken liver	-
β- N-acetylgalactosaminidase	
jack bean	-
bovine epididymis A	135 µM
bovine epididymis B	100 µM

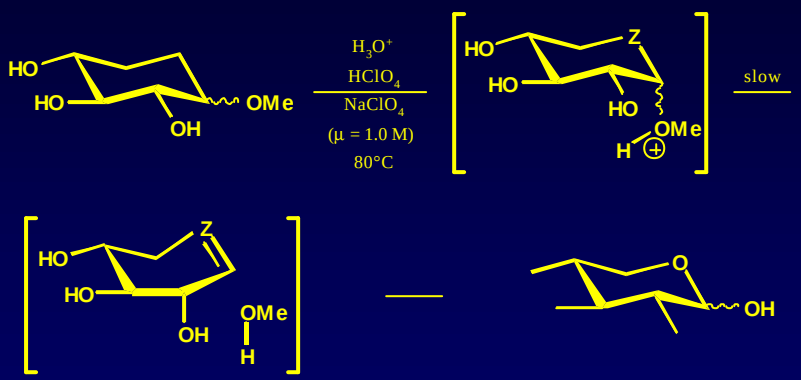
GalNAc does not inhibit these enzymes

GIESE'S RADICAL C-GLYCOSIDATION



C. Pasquarello

Kinetic Isotope Effects ⇒

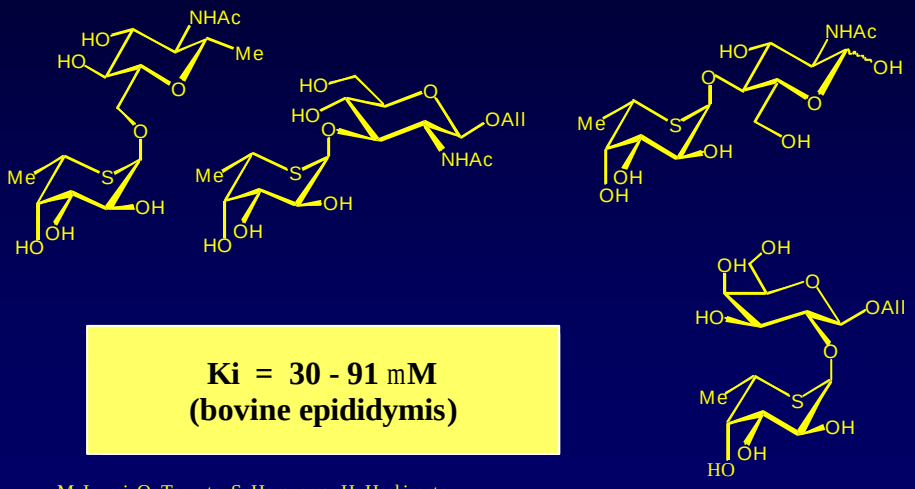


α-MeO k(S)/k(O) = 13.6

β-MeO k(S)/k(O) = 18.5

c.f: D. Idurugalla, A. J. Bennet, *J. Am. Chem.* **2001**, *123*, 10889-10898

α-L-Fucosidase Inhibition



Ki = 30 - 91 mM
(bovine epididymis)

M. Izumi, O. Tsuruta, S. Harayama, H, Hashimoto,
J. Org. Chem. **1997**, *62*, 992-998

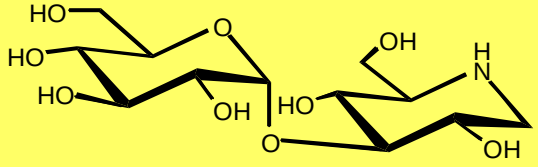
Continual formation of N-linked oligosaccharide still is observed in normal cells in the presence of a-glucosidase I, II and a-mannosidase I inhibitors such as the monosaccharide mimics:
castanospermine,
1-deoxynojirimycin,
1-deoxymannonojirimycin

[S. E. H. Moore, R. G. Spiro, *J. Biol. Chem.* 1990, *265*, 13104;
A. Tan, L. van den Broek, S. van Boeckel et al. *J. Biol. Chem.* 1991, *266*, 3571]

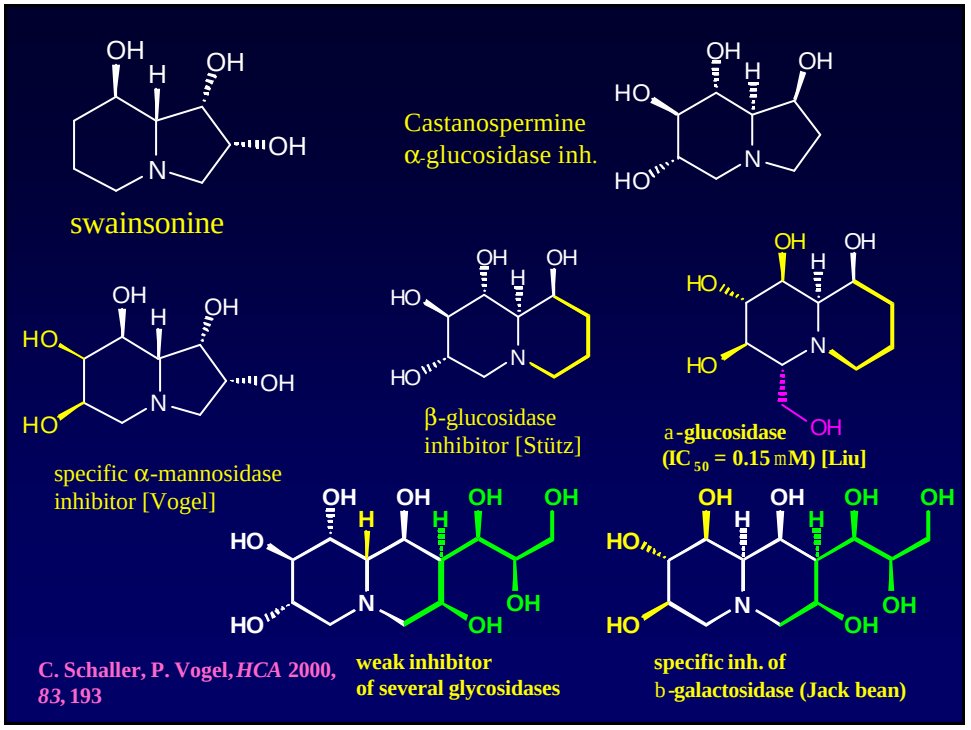
⇨ ***endo*-a-mannosidase in the Golgi system catalyses an alternative pathway of N-linked oligosaccharide biosynthesis**

[W. A. Lubas, R. G. Spiro, *J. Biol. Chem.* **1988**, *263*, 3990]

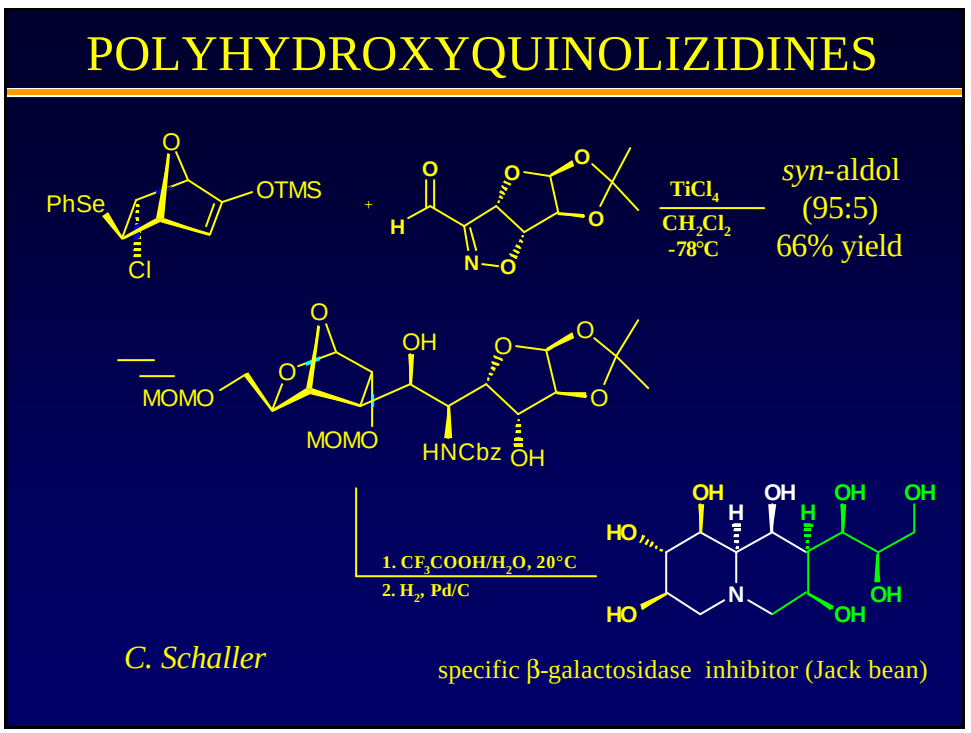
A disaccharide mimic is necessary as inhibitor, e.g.:



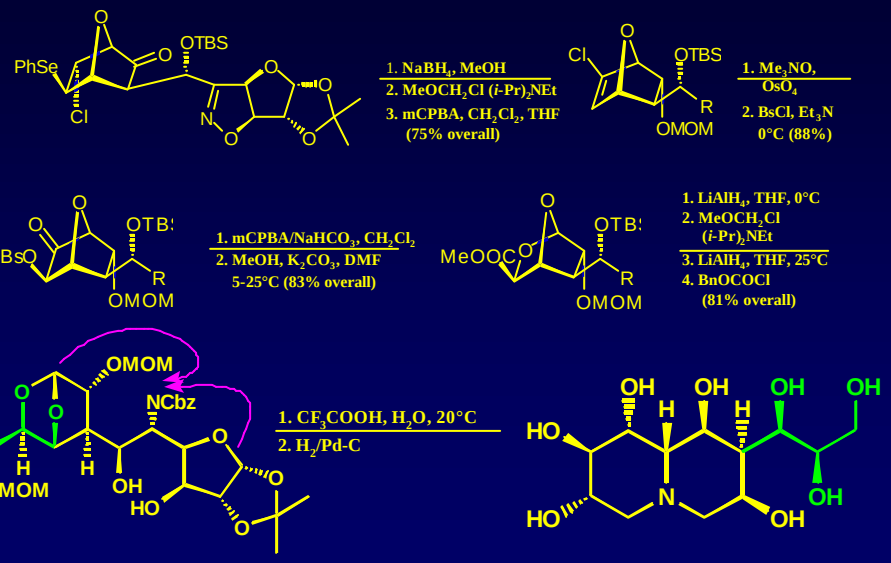
[U. Spohr, M. Bach, R. G. Spiro, *Can. J. Chem.* **1993**, *71*, 1919, 1928;
S. Hiraizumi, U. Spohr, R. G. Spiro, *J. Biol. Chem.* **1993**, *268*, 9927]



POLYHYDROXYQUINOLIZIDINES

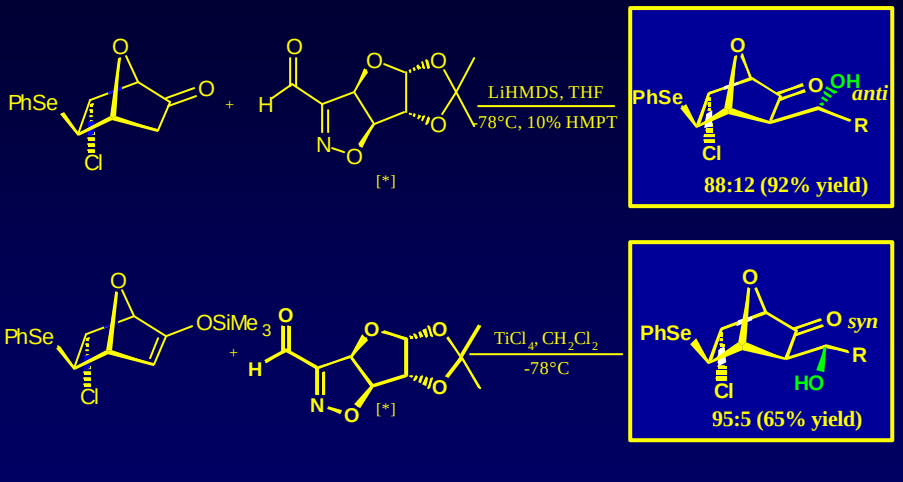


POLYHYDROXYQUINOLIZIDINES



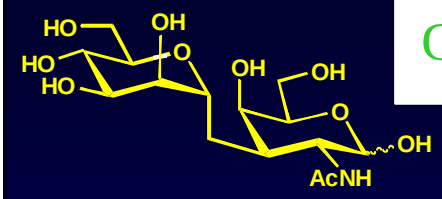
C. Schaller, P. Vogel, *Helv. Chim. Acta* **2000**, *83*, 193

Cross-Aldol Reactions



[*] C. Schaller, P. Vogel, V. Jäger *Carbohydr. Res.* **1998**, *314*, 25

Glycosidase Inhibition



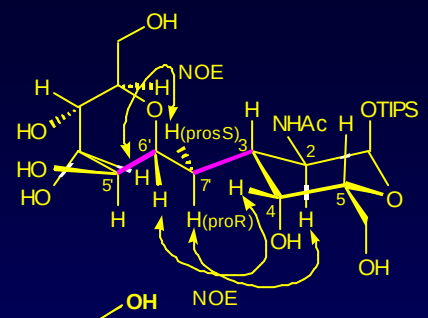
a -D-Manp-(1 ® 3)CH_2-D-GalNAc (*p* and *f*)

	K_i:
a -L-fucosidase	
bovine epididymis	25 m M
human placenta	28 m M
a -galactosidase	
coffee beans	66 m M
Aspergillus niger	76 m M
Escherichia coli	39 m M
b -galactosidase	
jack beans	7.5 m M
Asperillus niger	-
a -glucosidase	
baker yeast	40 m M
rice	-
b -glucosidase	
almonds	-
caldocellum saccharolyticum	18 m M

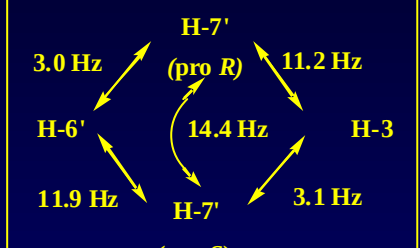
	K_i:
a -mannosidase	
jack beans	-
almonds	-
b -mannosidase	
helix pomatia	-
b -xylosidase	
Asperillus niger	-
a -N-acetylgalactosaminidase	
chicken liver	-
b - N-acetylgalactosaminidase	
jack bean	-
bovine epididymis A	135 m M
bovine epididymis B	100 m M

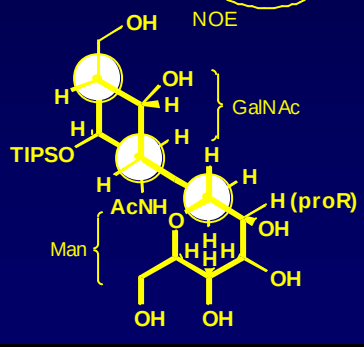
GalNAc does not inhibit these enzymes

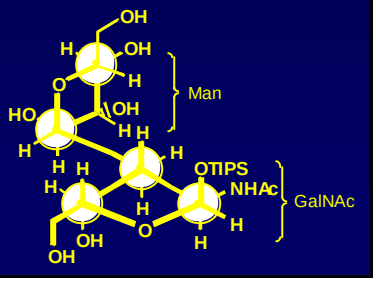
PREFERRED CONFORMATION OF α-D-Man*p*(1→3)CH_2-D-GalNAc*p*-TIPS

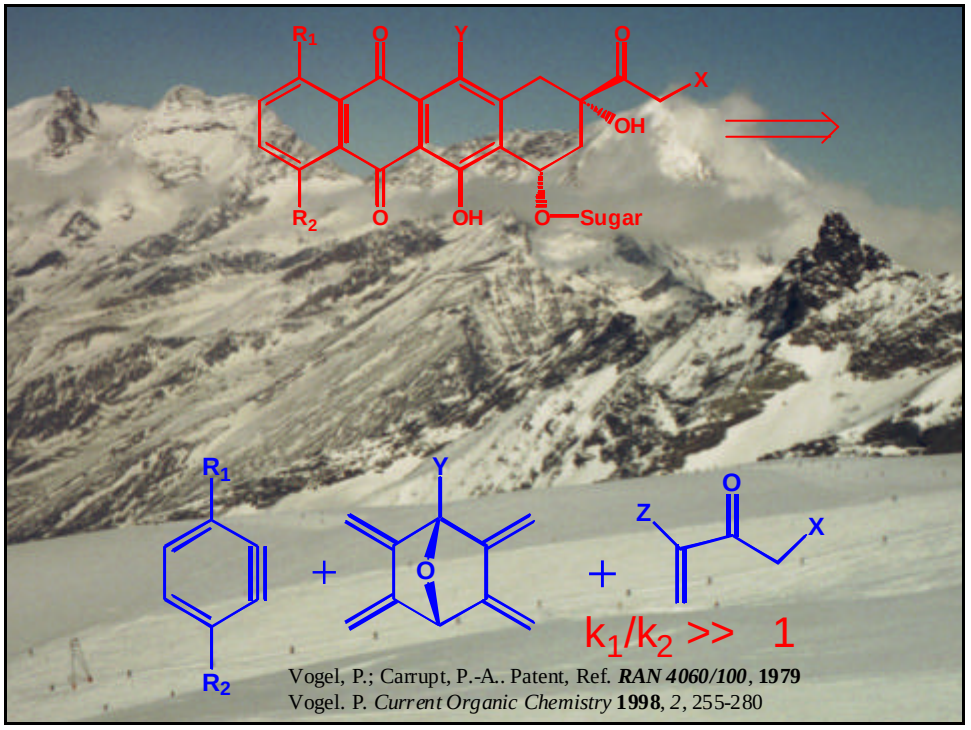


^{1}H-NMR (CD_3OD, -40 to + 60 ^{0}C)



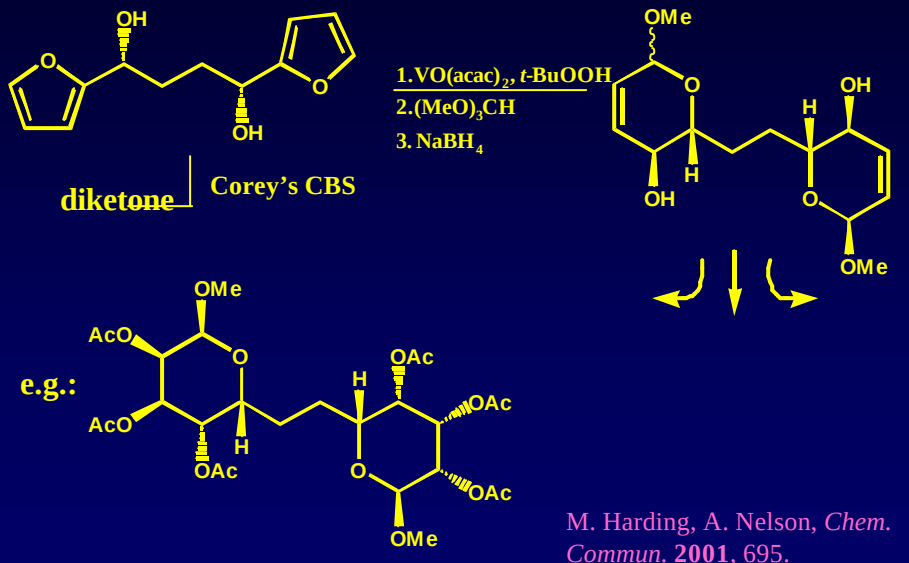






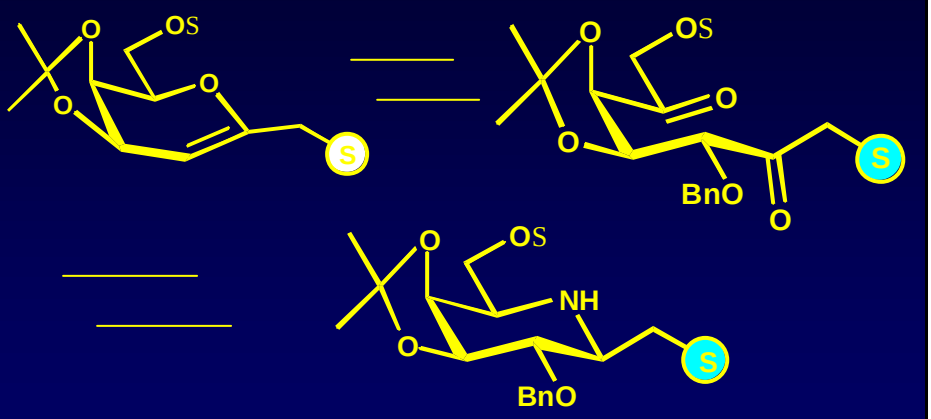
Vogel, P.; Carrupt, P.-A.. Patent, Ref. ***RAN 4060/100***, **1979**
Vogel. P. *Current Organic Chemistry* **1998**, *2*, 255-280

C(1 ® 6)-linked disaccharides



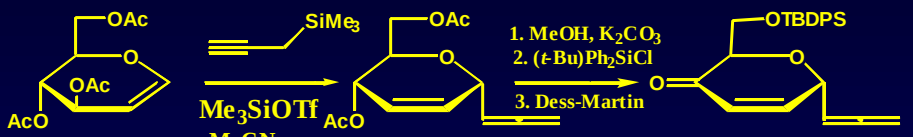
M. Harding, A. Nelson, *Chem. Commun*. **2001**, 695.

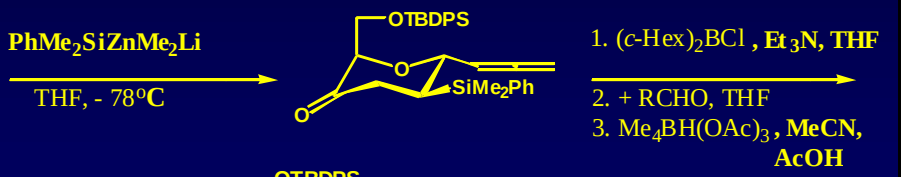
Aza-C-galacto disaccharides

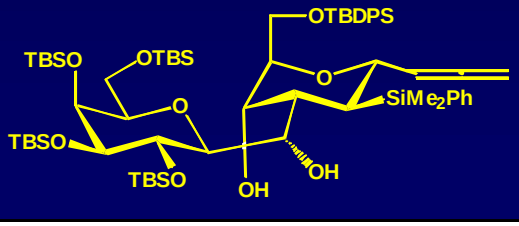


X. Cheng, G. Kumaran, D. R. Mootoo, *Chem. Commun.* 2001, 811

C-Glycosides of C-Disaccharides

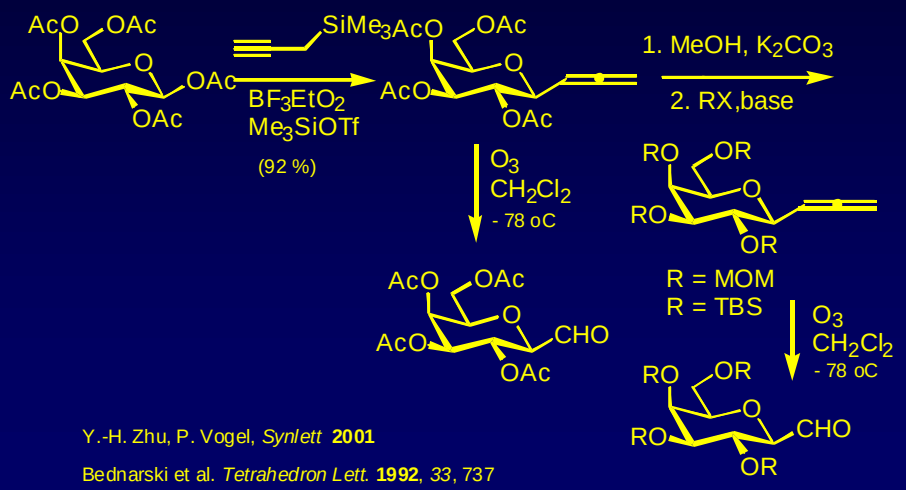






Y.-H. Zhu, P. Vogel, *Synlett*, **2001**,81

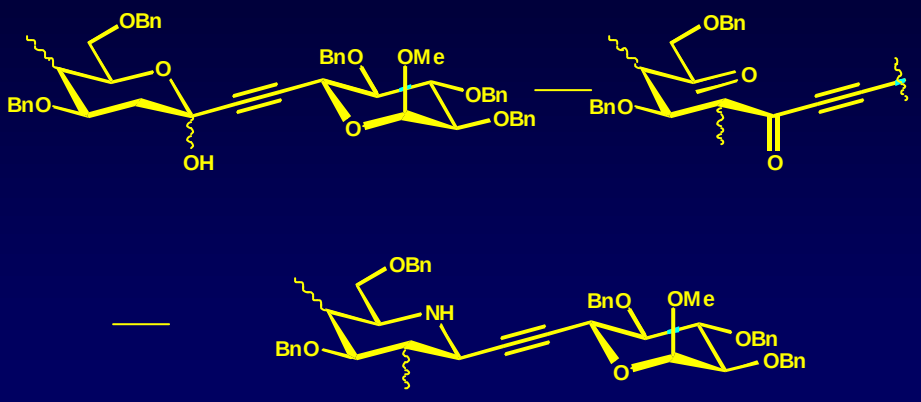
C-b-D-Galactopyranosylformaldehyde



Y.-H. Zhu, P. Vogel, *Synlett* **2001**

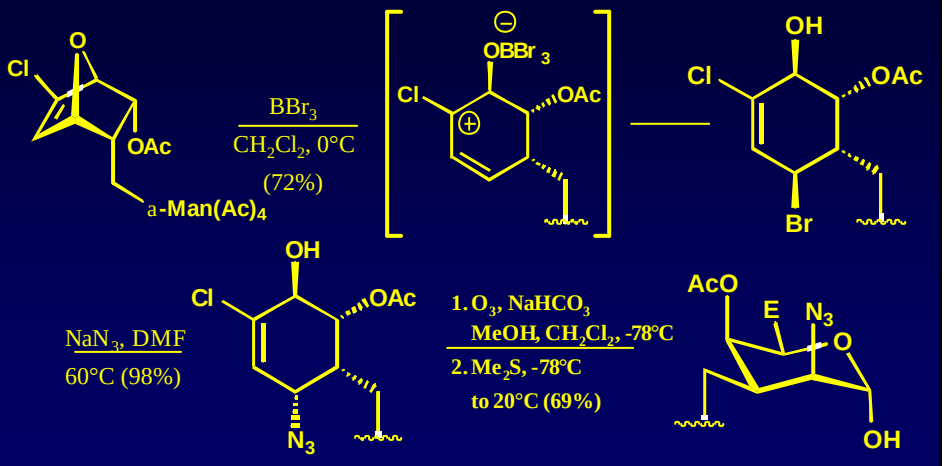
Bednarski et al. *Tetrahedron Lett.* **1992**, *33*, 737

Aza-C(1 ® 6)-Disaccharides



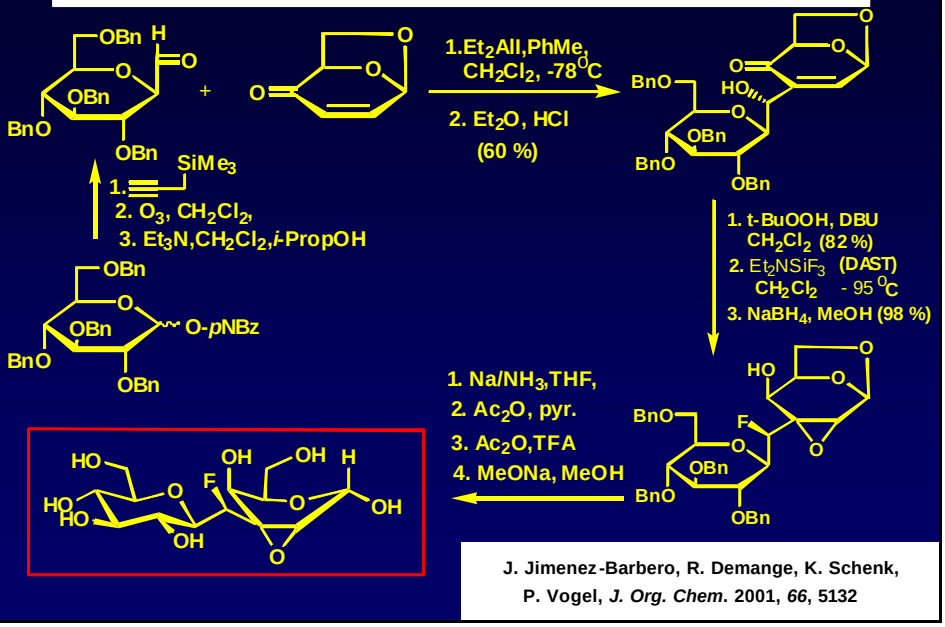
M. A. Leeuwenburgh, S. Picasso, H. S. Overkleeft, G. A. van der Marel, P. Vogel, J. H. van Boom, *Eur. J. Org. Chem.* **1999**, 1185

α-D-Man*p*(1→3)CH_2-D-TalNAc



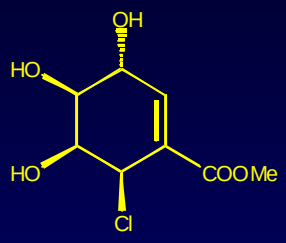
Carla Pasquarello

C(1→3)-C(F)-Linked Disaccharide

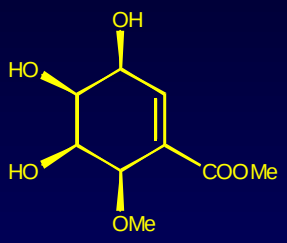


J. Jimenez-Barbero, R. Demange, K. Schenk, P. Vogel, *J. Org. Chem.* 2001, *66*, 5132

PERICOSINES A & B: ANTI-TUMOUR AGENTS



A

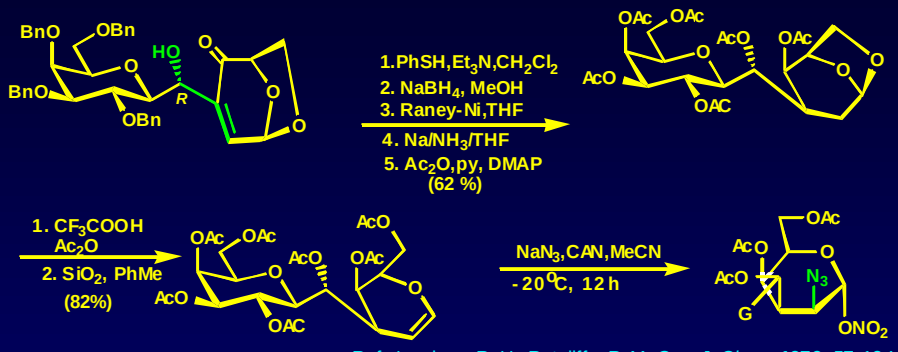


B

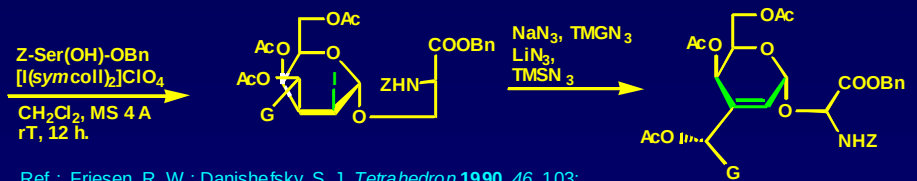
isolated from *Periconia byssoides*

***Ref*: A. Numata, M. Iritani, T. Yamada, K. Minoura, E. Matsumura, T. Yamori, T. Tsuruo, *Tetrahedron Lett*. 1997, *38*, 8215-8218**

D-Galβ-CH(OH)-D-GTalNAc-α-O-Ser



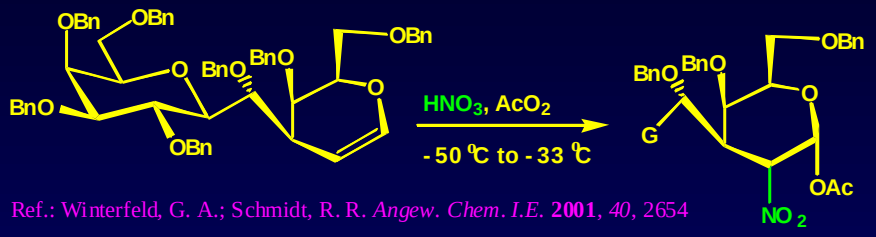
Ref.: Lemieux, R. U.; Ratcliffe, R. M. *Can. J. Chem.* **1979**, *57*, 1244



Ref.: Friesen, R. W.; Danishefsky, S. J. *Tetrahedron* **1990**, *46*, 103;
Kottenhahn, M.; Kessler, H. *Liebigs Ann, Chem*. **1991**, 727

R. Demange

Other attempts

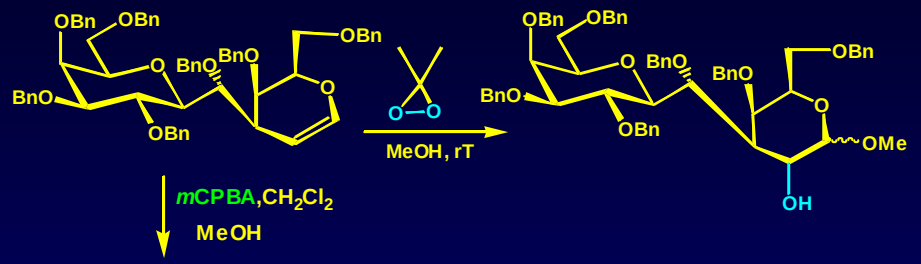


Ref.: Winterfeld, G. A.; Schmidt, R. R. *Angew. Chem. I.E.* **2001**, *40*, 2654

H-1: singulet
J(H-2-H-3): 2-3 Hz

Raynald Demange

Epoxidations of the galactal



R. Demange