

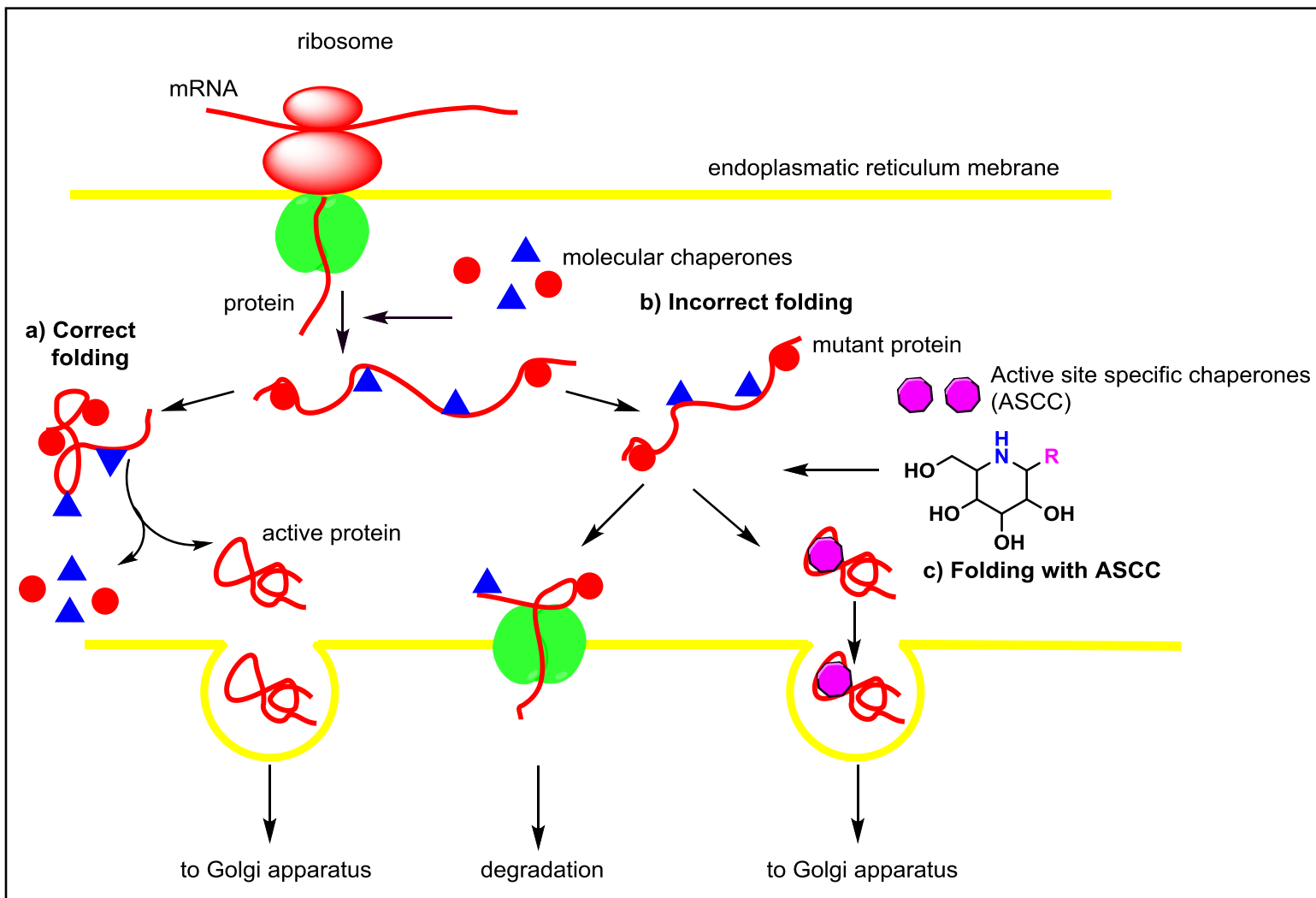
Diversity Oriented Synthesis of Iminoalditol Building Blocks for Glycoprobes

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Lysosomal Storage Diseases (LSD)

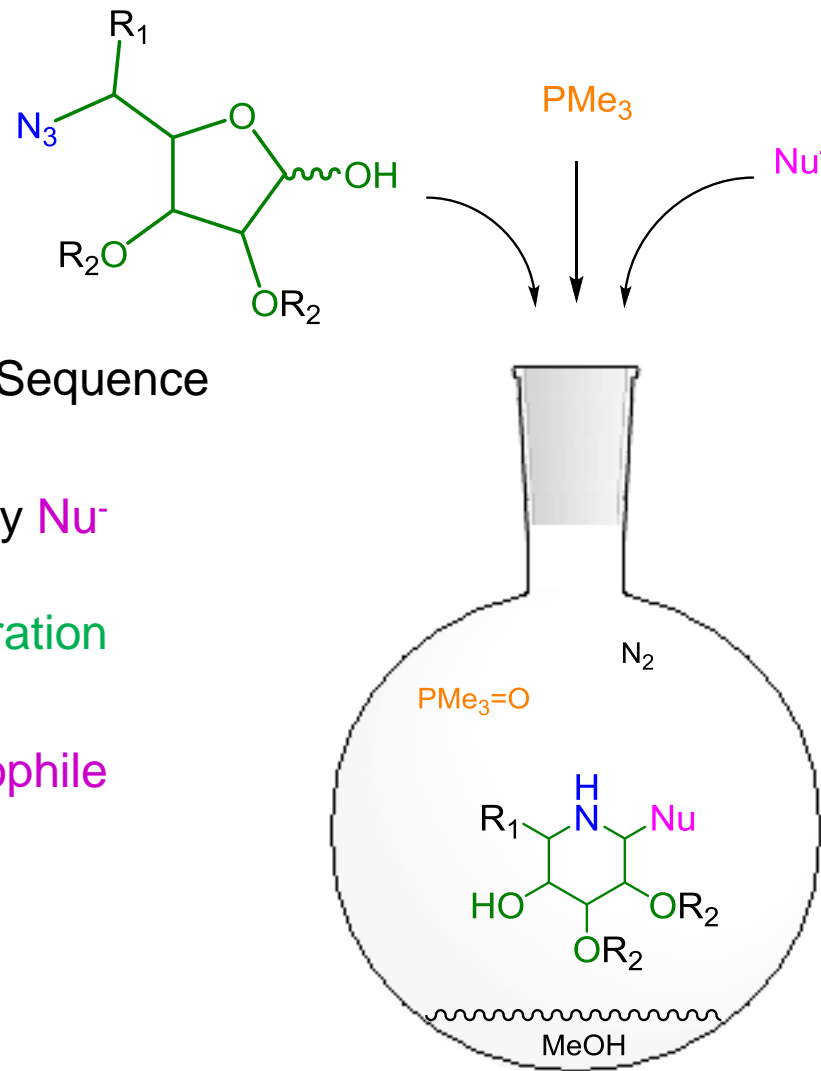
- Enzymatic disfunction of the degradation of macromolecules such as Glycosphingolipids, Proteins, Lipids, Glycogen, Glycoproteins
- Genetical disorders of lysosomal acidic glycosyl hydrolases.
- Misfolding of the enzyme leads to its clearance

LSD	Malfunctioning Enzyme	Accumulated Substrate
Pompe	α -Glucosidase	Glykogen
Gaucher	β -Glucocerebrosidase	Glucosylceramide
Fabry	α -Galactosidase A	Globotriaosylceramid
Sandhoff	β -Hexosaminidase B	GM2-Gangliosides



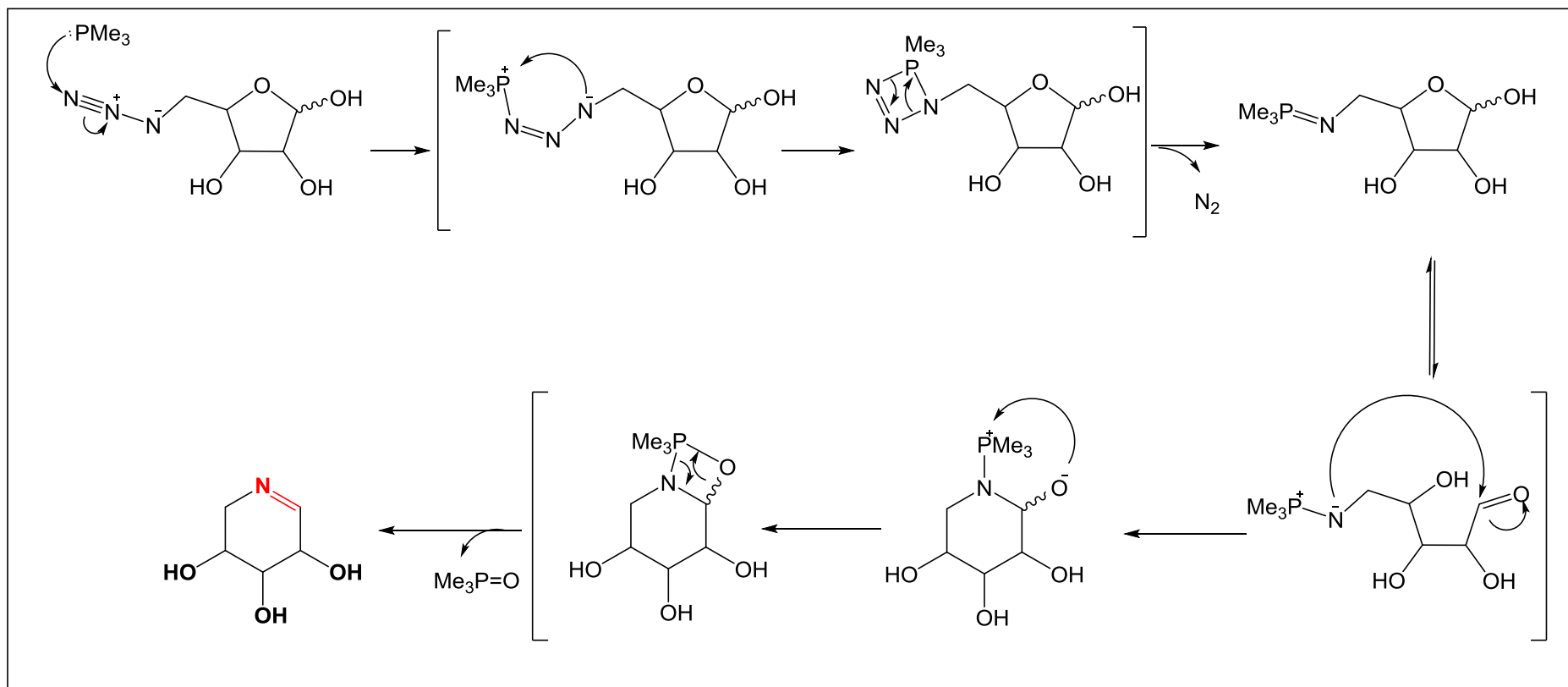
Wrodnigg, T.M.; Stütz, A.E. *Curr. Enz. Inhib.* **2012**, *8*, 1-53

Tandem One-Pot Approach



- Staudinger/aza-Wittig Reaction Sequence
- Iminium intermediate attacked by Nu^-
- Diversity point A: Sugar configuration
- Diversity point B: Type of nucleophile
- R_2 can be substituent of choice
- $R_1 = H; CH_2OH$

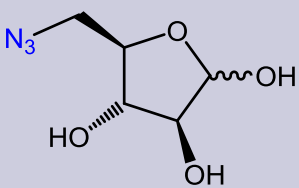
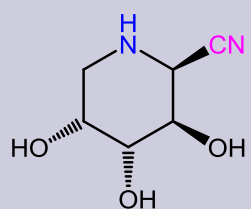
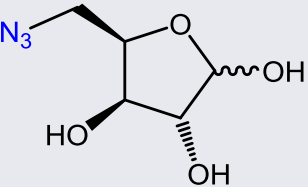
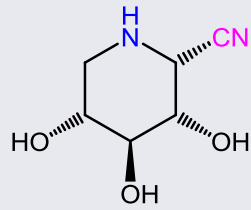
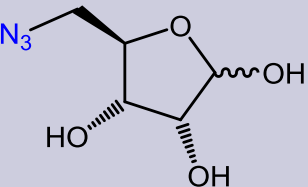
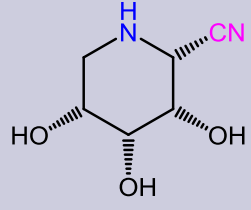
Staudinger/aza-Wittig Reaction Mechanism



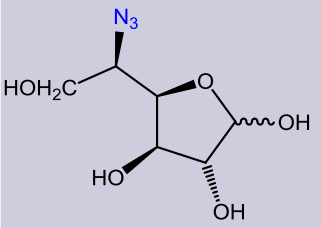
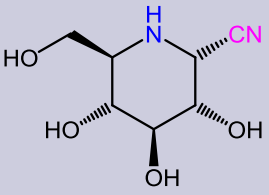
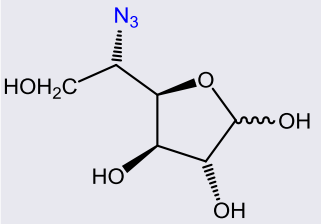
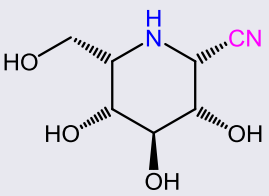
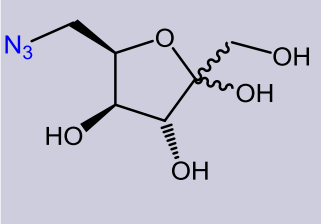
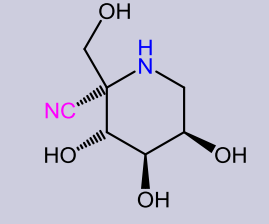
Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; de los Santos, J. *Tetrahedron* **2007**, 63, 523-575

Diversity point A: Sugar configuration I

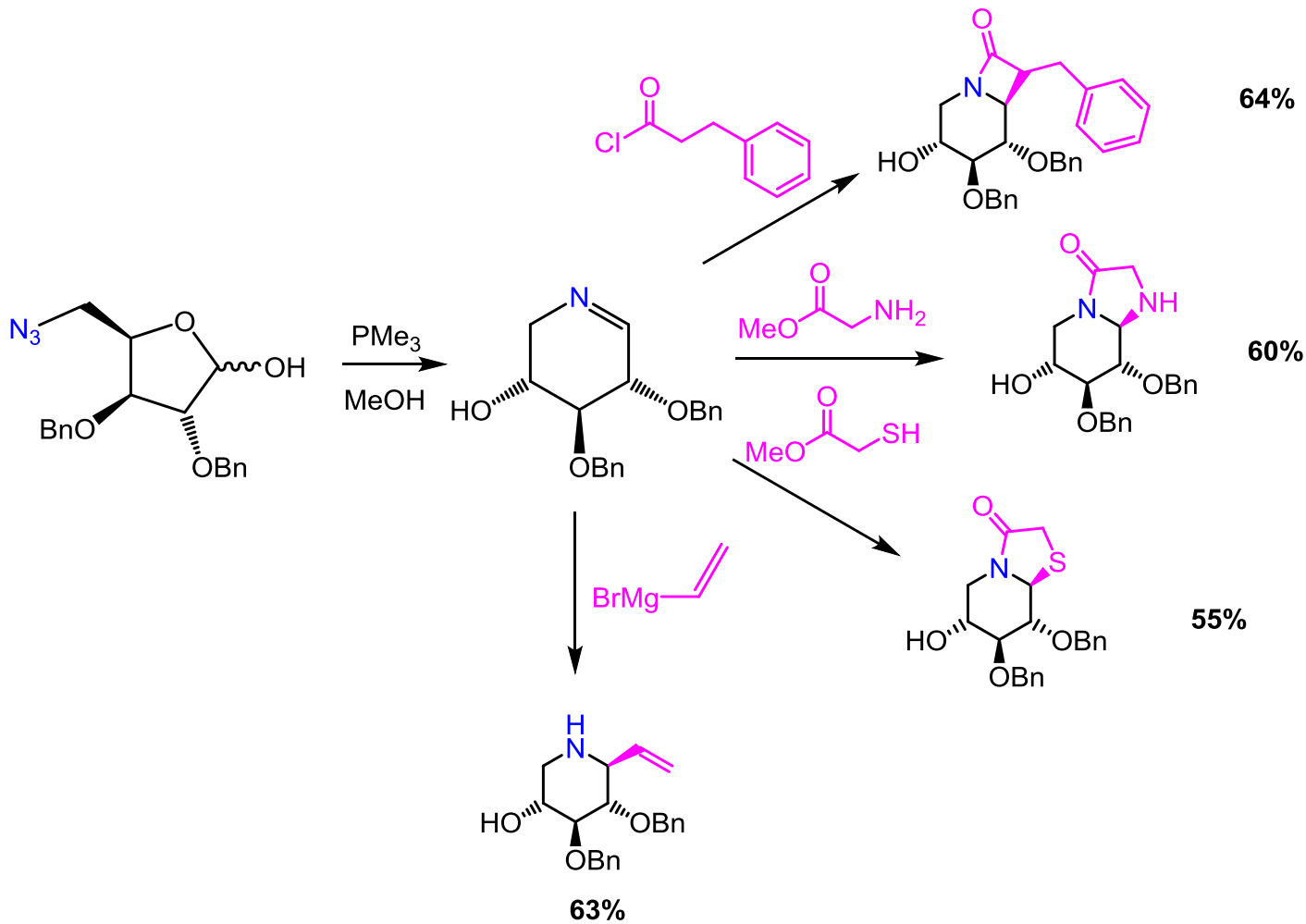
- Model nucleophile: **NaCN**

Substrate	Product	Yield	HR-MS [g/mol]	Optical Rotation
		80 %	158,0705	-52,3° (1g/100ml) MeOH
		99%	158,0702	+36,9° (0,945g/100ml) H ₂ O
		95%	to be measured	-28,2° (1,01g/100ml) H ₂ O

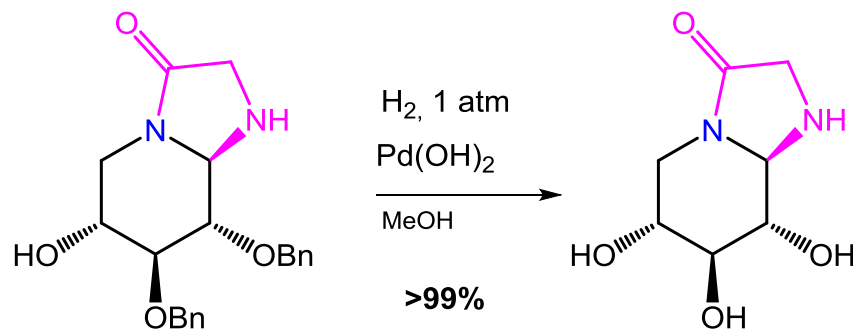
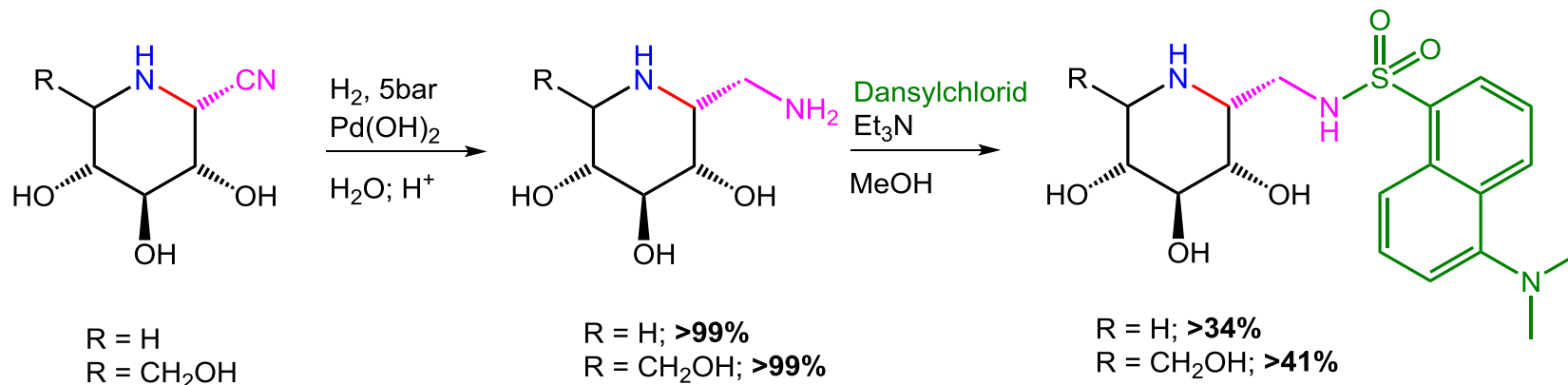
Diversity Point A: Sugar configuration II

Substrate	Product	Yield	HR-MS [g/mol]	Optical Rotation
		95%	188.0815	+67,6° (0,95g/100ml)MeOH
		41%	to be measured	-24,6° (1,35g/100ml)MeOH
		39%	to be measured	to be measured

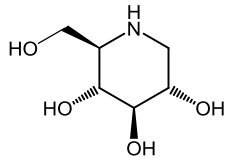
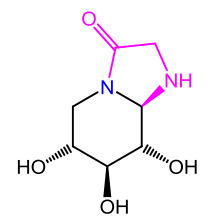
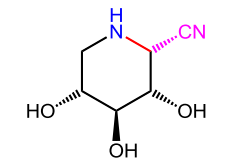
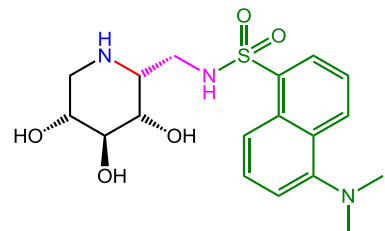
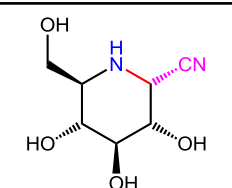
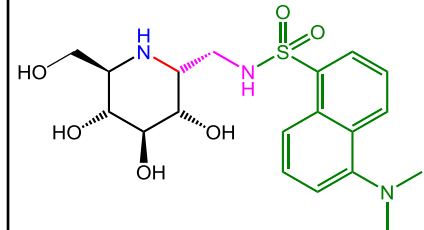
Diversity Point B: Type of Nucleophile



Preparation of Glycoprobes



Biological activity of compounds

Compound	K_i (μM) human lysosomal β -Glu	Compound	K_i (μM) human lysosomal β -Glu
	79a		N.I.
	34b		0,0075^b
	716b		178

^a Saul, R. *et.al. Arch.Biochem.Biophys.* **221**; 593-597.

^b Zoidl, M.; Müller, B.; Torvisco, A.; Tysoe, C.; Benazza, M.; Siriwardena, A.; Withers, S.G.; Wrodnigg, T.M. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2777-2780.

Conclusion

Advantages:

- + Quick and easy methodology to produce C-glycosyl type iminoalditol building blocks.
- + Tolerates every substrate and nucleophile tested so far.

Challenges:

- Phosphine compound is poisonous.
- Purification of unprotected products is challenging.

Outlook

- **Optimisation of the yields of the follow up chemistry.**

- **Application as - glycoside processing enzyme inhibitors**
 - **pharmacological chaperones**
 - **glycoprobes**

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