

Regioselective Acetylation of Carbohydrates

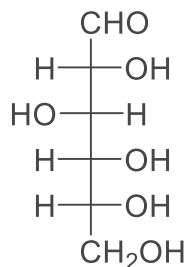
16th December 2016

Alexander Seitz

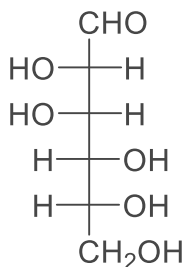
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Justus-Liebig University
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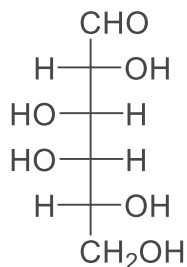
- Carbohydrates with molecular formula $C_6H_{12}O_6$
- Differentiation in aldoses and ketoses
- 16 Different stereoisomers for aldoses
- Most important are D-Glucose, D-Mannose and D-Galactose



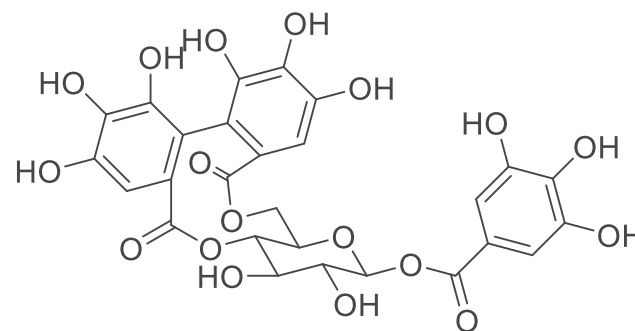
D-Glucose



D-Mannose



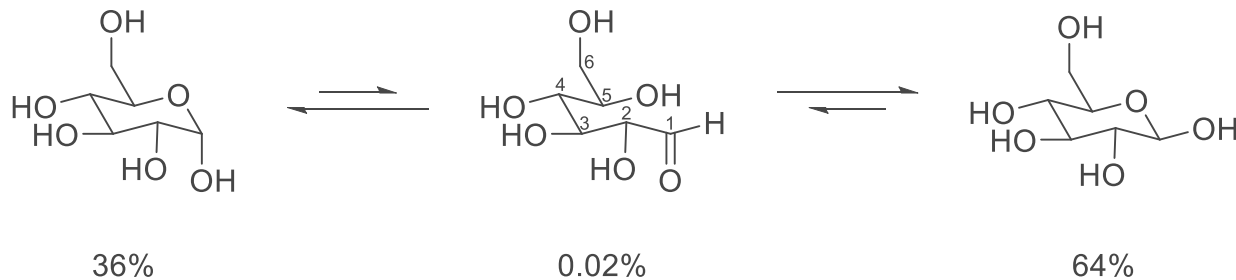
D-Galactose



strictinin



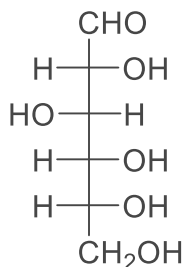
- Numbering of carbons starts at the most oxidized C
- Open-chained form is disfavored in solution



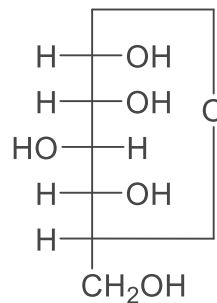
- β -anomer is favored because OH is equatorial



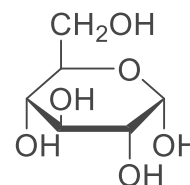
- Lot of possibilities to draw/display hexoses



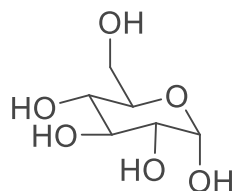
Fischer projection



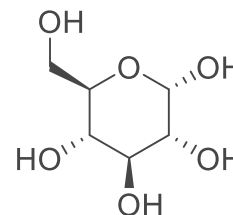
Tollens projection



Haworth projection



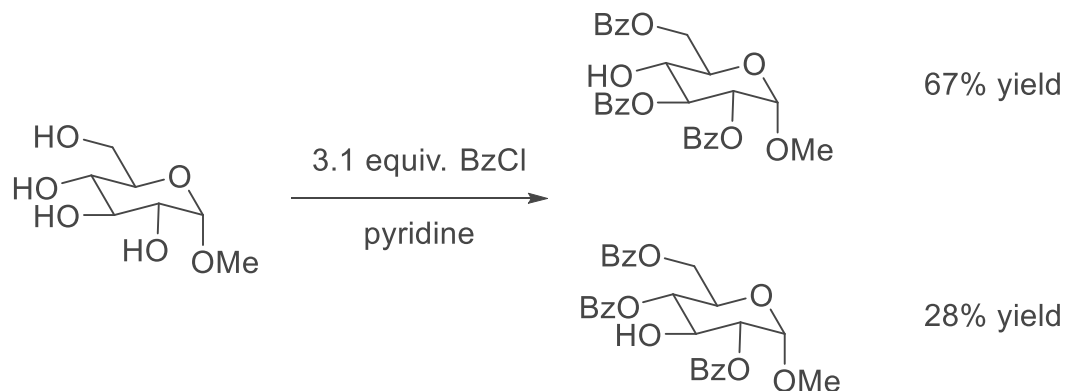
chair projection



stereochemical view



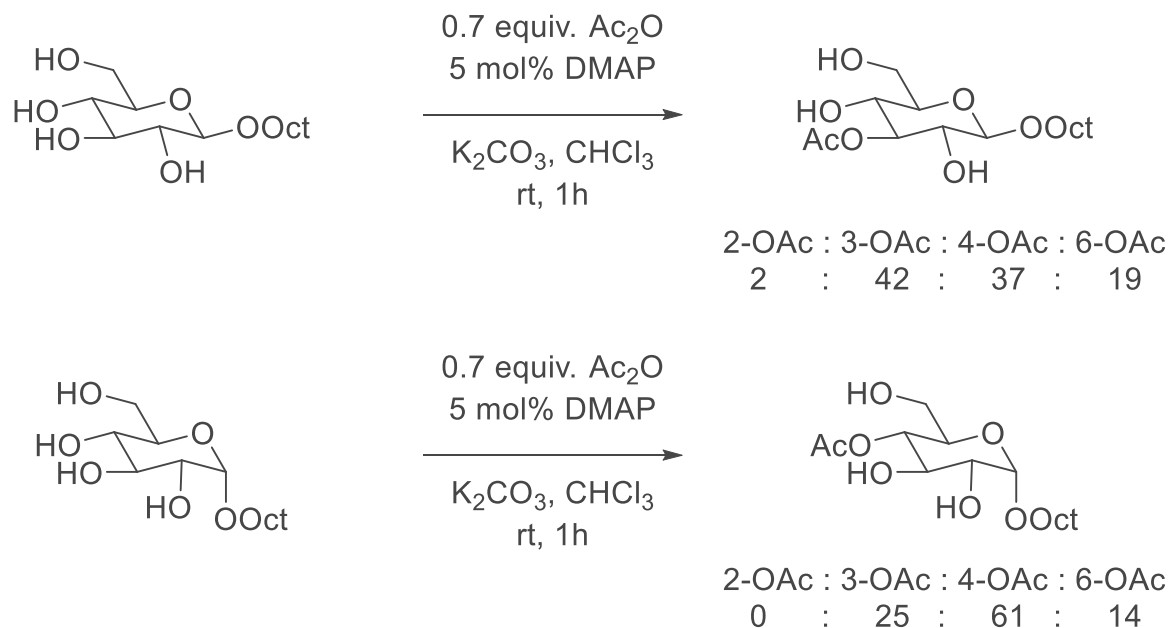
- Benzoylation used to rank reactivity by Richardson and Williams



- In all investigated sugars the 6-position reacts first
 - methyl α -D-glucopyranoside: 2-OH > 3-OH > 4-OH
 - methyl α -D-mannopyranoside: 3-OH > 2-OH > 4-OH
 - methyl α -D-galactopyranoside: 2-OH > 3-OH > 4-OH

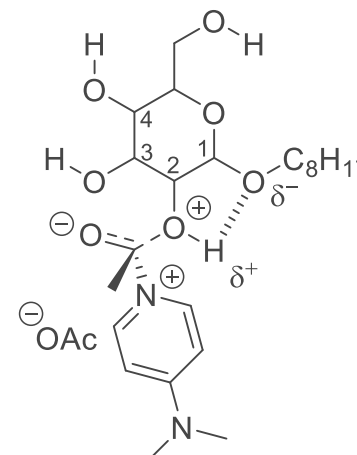
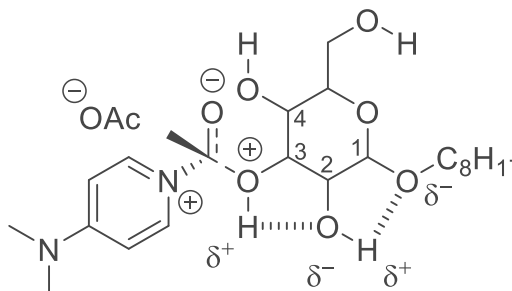
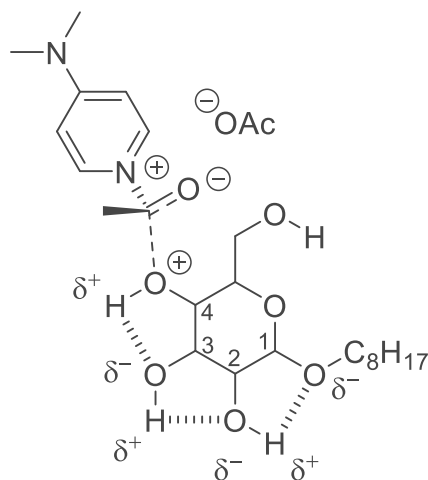


- 1999 DMAP was first used as a catalyst
- Change of reactivity could be observed



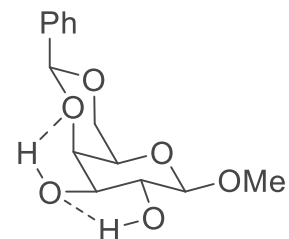
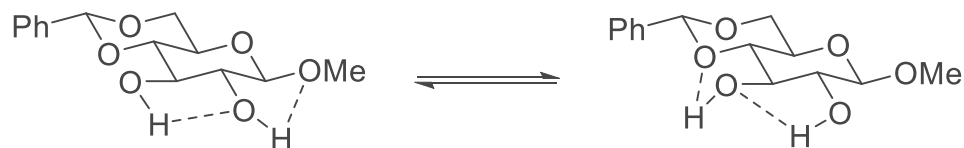
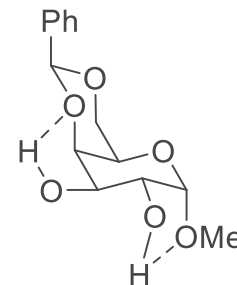
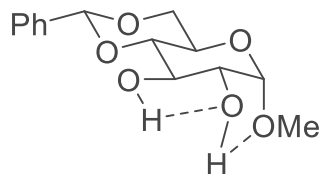


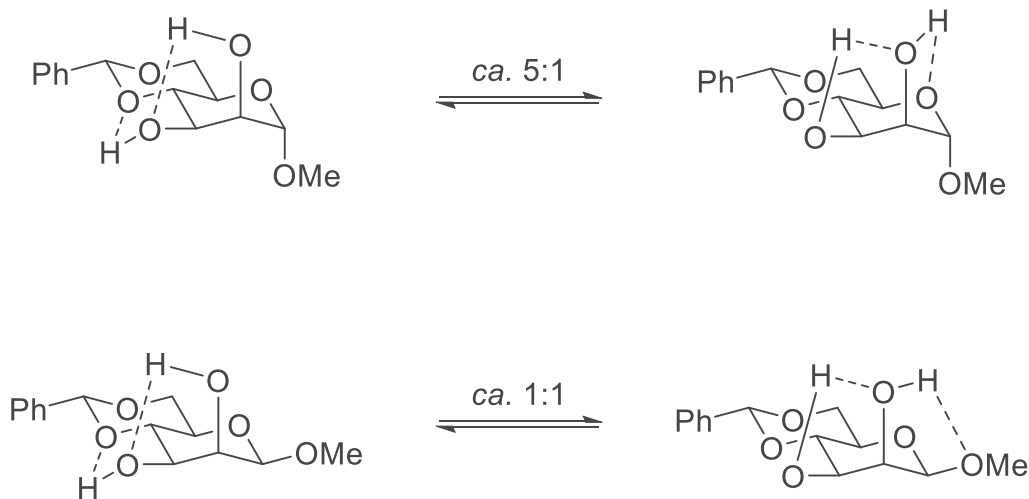
- Comparable results for mannoside and galactoside
- Delocalization of positive charge *via* hydrogen bond network





- IR (in DCM or DCE) and NMR (in CDCl_3) studies
- Network has influence on acidity of the hydroxyl-groups





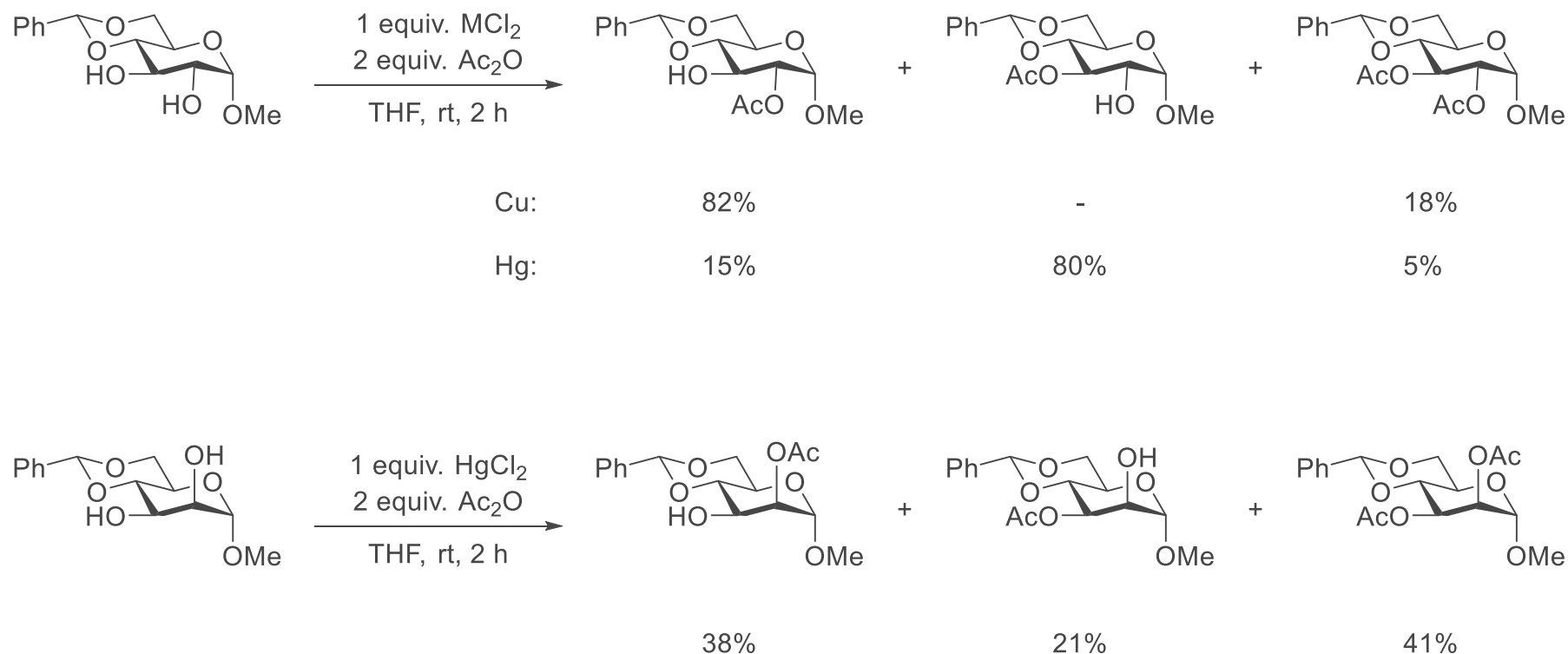
- Reactivity of Carbohydrates also depends on
 - Reactants
 - Protecting groups
 - Solvent



- Review of Lawandi *et al.* 2016
- Focus on acylation of methyl 4,6-*O*-benzylidene- α -D-pyranosides
- Lipases catalyze acetylation with very high selectivity (up to 100%) and very high yields (up to 95%)
- Most catalysts/additives are only working with one of the pyranoses

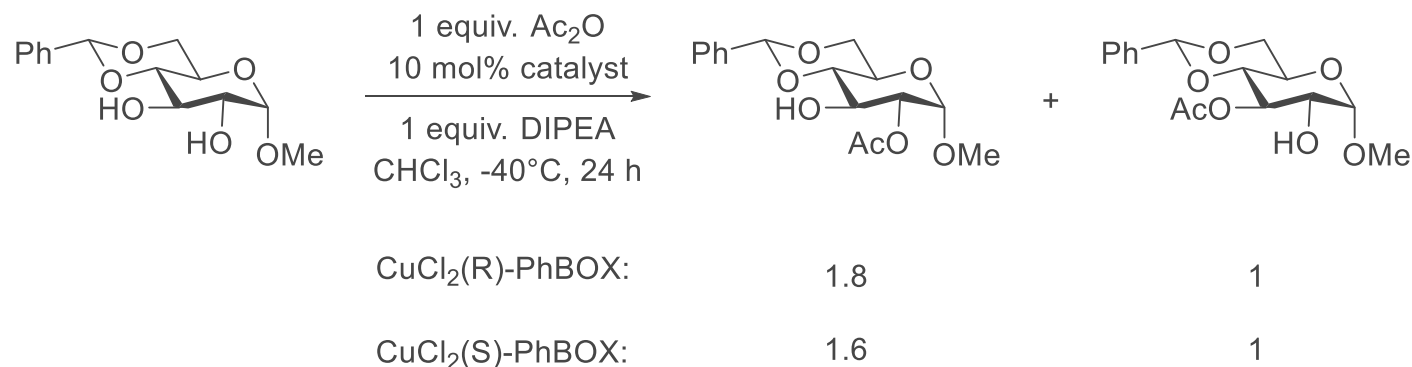


- 1984 Eby *et al.* used HgCl_2 and CuCl_2



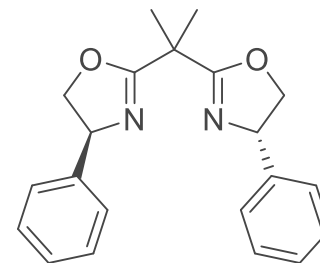


- Allen and Miller used CuCl_2 and a PhBOX ligand



- With Acetylchloride higher regioselectivities

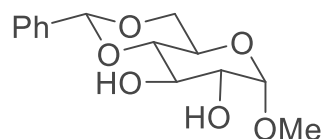
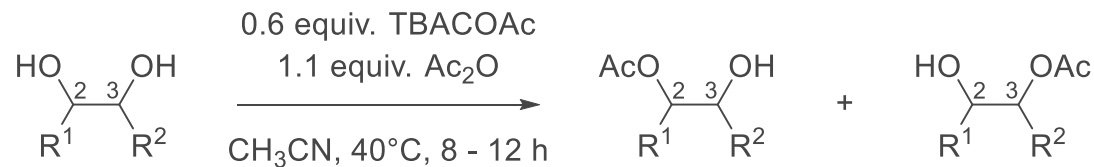
- (*R*)-catalyst: 2-O/3-O (7.0:1.0)
- (*S*)-catalyst: 2-O/3-O (1.0:4.5)



(*S*),(*S*)-PhBOX

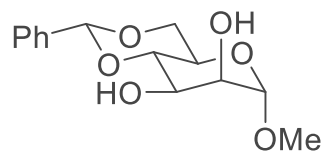


- Zhou *et al.* used TBAOAc as catalyst



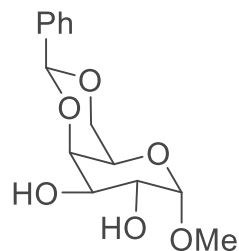
88%

0%



50%

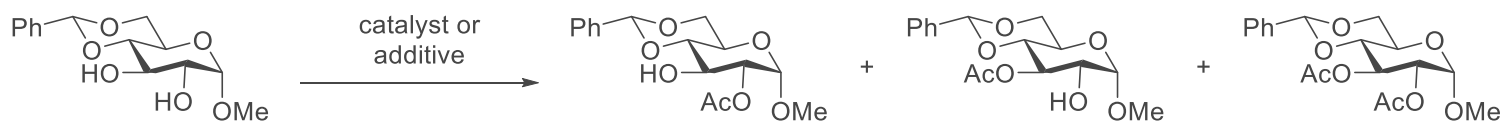
50%



0%

90%

Overview acetylation of methyl 4,6-O-benzylidene- α -D-glucopyranoside

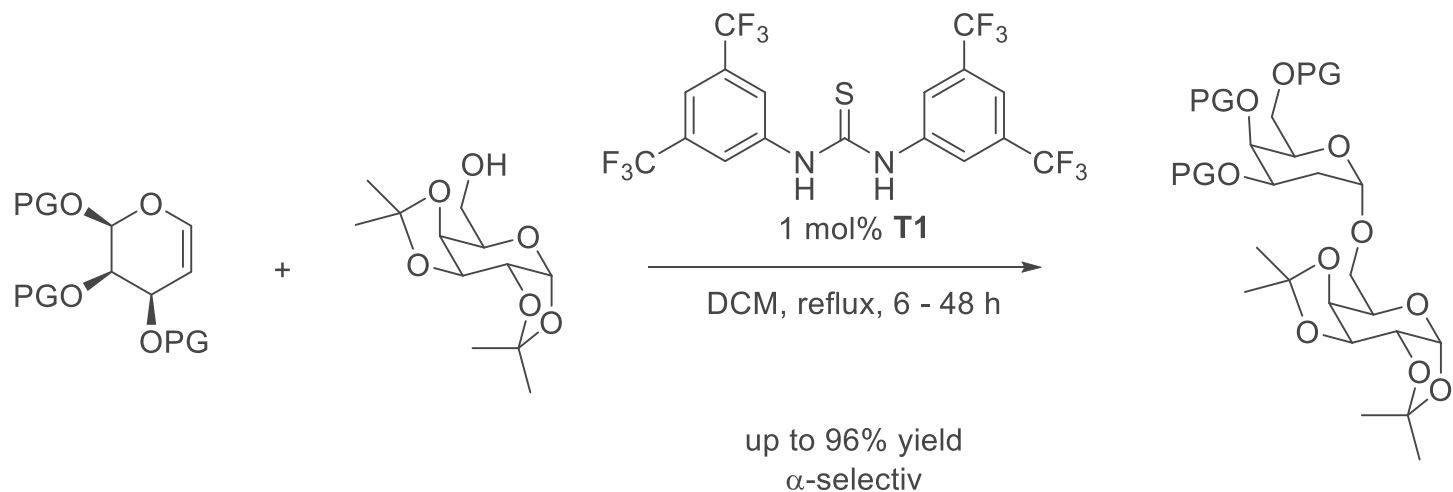


Catalyst	Product ratio			Conversion [%]
pyridine	3-29	32-42	6-26	77-93
DMAP	45-49	55-51	-	40-65
Et ₃ N	80	5	15	-
NaOtBu, EtOAc	48	52	-	76
ZnCl ₂ , pyridine	53	13	23	90
Ag ₂ O, KI, AcCl	15	81	-	-
cat. TBAOAc, Me ₂ Si(OMe) ₂	65	-	-	-
lipases	up to 100	-	-	up to 95

N. Moitessier, P. Englebienne, Y. Chapleur, *Tetrahedron* **2005**, 61, 6839–6853; R. W. Jeanloz, D. A. Jeanloz, *J. Am. Chem. Soc.* **1957**, 79, 2579–2583; S. Hanessian, M. Kagotani, *Carbohydr. Res.* **1990**, 202, 67–79; X.-A. Lu, C.-H. Chou, C.-C. Wang, S.-C. Hung, *Synlett* **2003**, 1364–1366; X. Liu, B. Becker, M. A. Cooper, *Aust. J. Chem.* **2014**, 67, 679–683; Y. Zhou, O. Ramström, H. Dong, *Chem. Commun.* **2012**, 48, 5370–5372; M. J. Chinn, G. Lacazio, D. G. Spackman, N. J. Turner, S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1* **1992**, 661–662; L. Panza, M. Luisetti, E. Crociati, S. Riva, *J. Carbohydr. Chem.* **1993**, 12, 125–130.

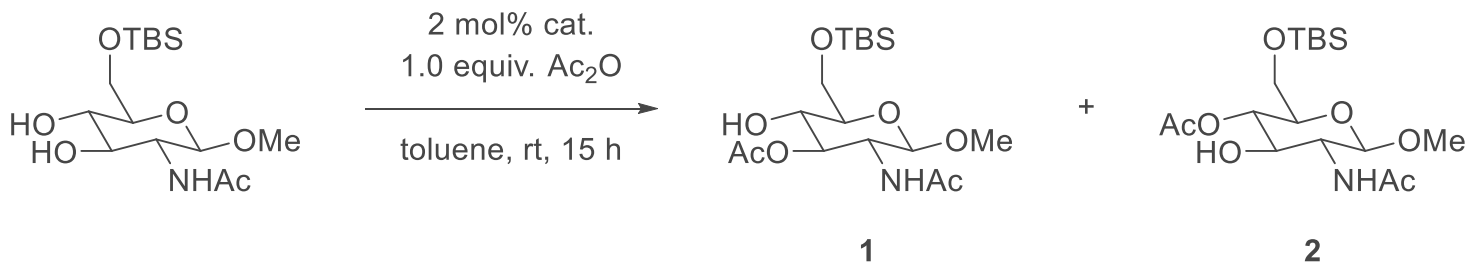


- Develop a multistep catalysis sequence with our groups catalysts
- McGarrigle showed selective glycosylation of galactals with T1

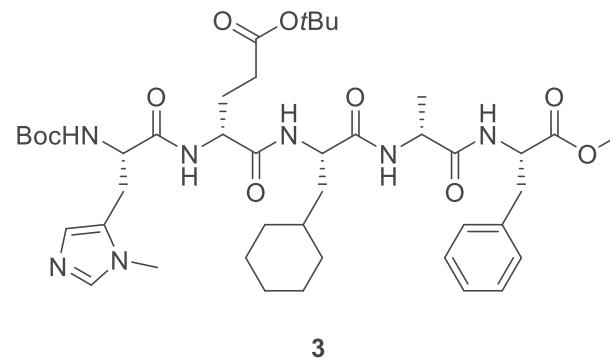
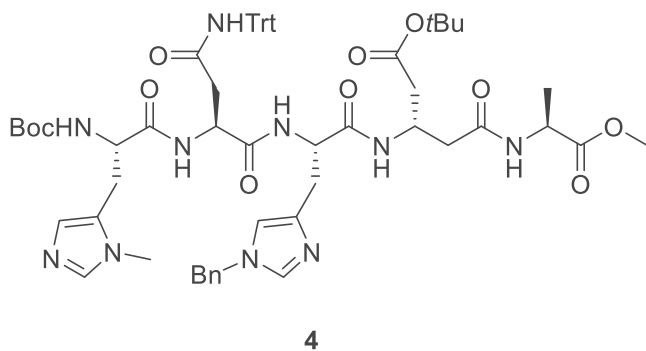


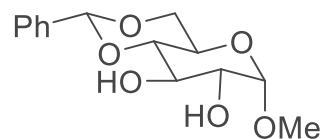


- Miller *et al.* 2003: peptide catalyzed acylation

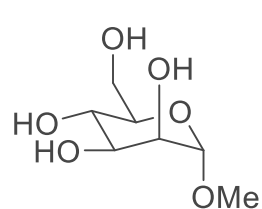


Catalyst	1	2	DiAc	C [%]
NMI	50	22	28	86
3	97	3	0	88
4	53	47	0	80

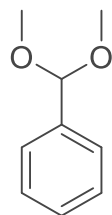




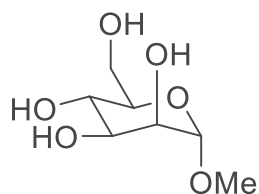
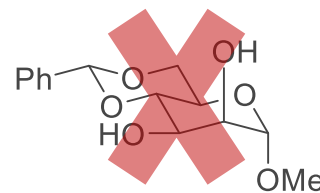
25g/102€
Sigma Aldrich



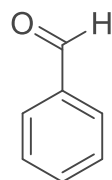
+



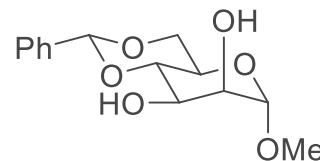
1 mol% pTsOH
DMF, rt, 48h



+

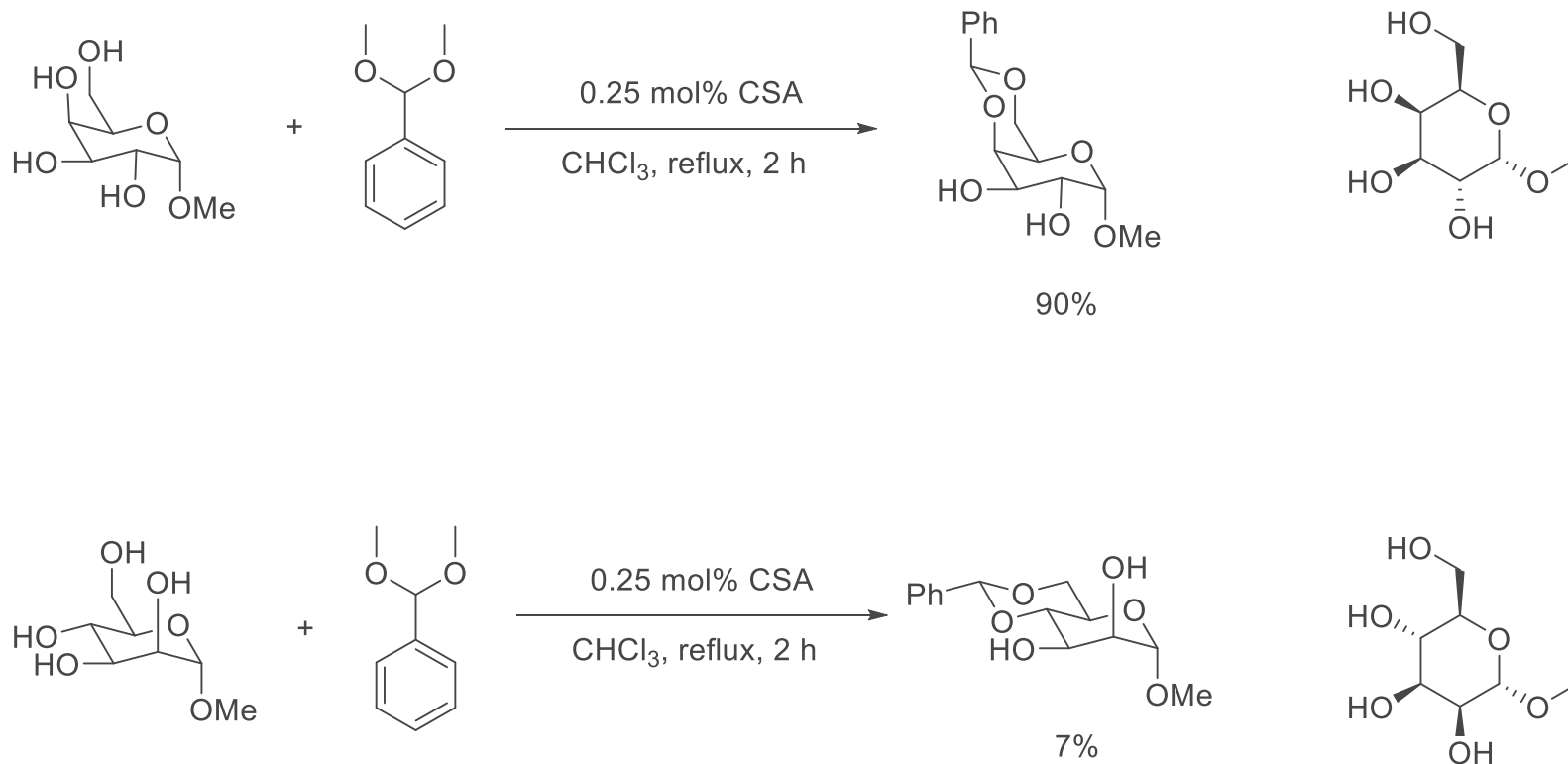


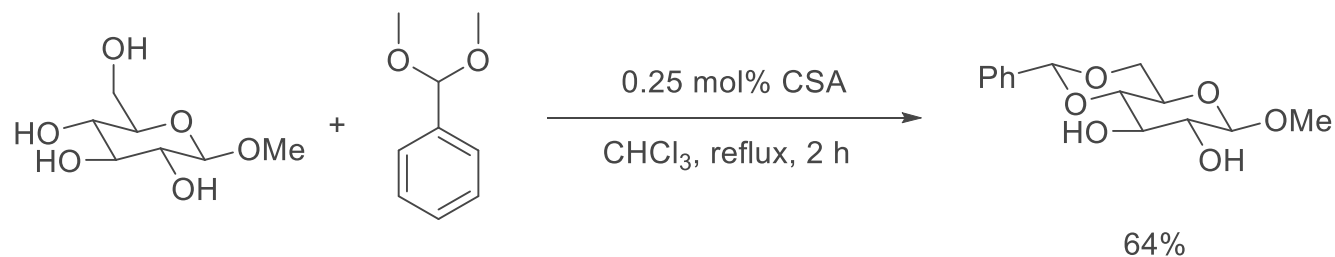
HCOOH, rt, 5 min



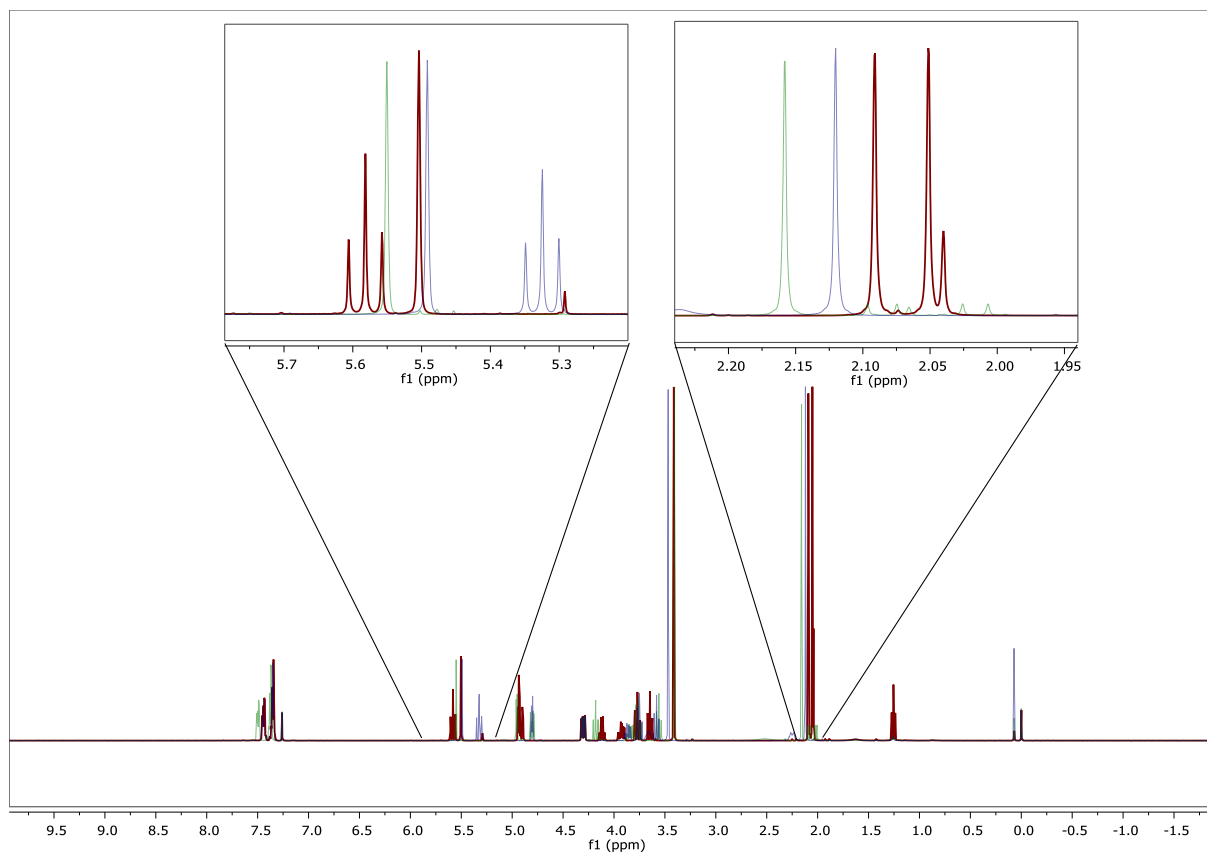
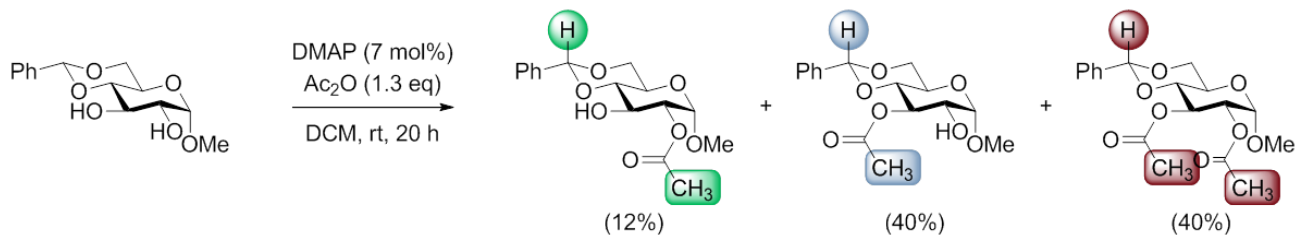
30%

NMR in Methanol-d⁴ !!!

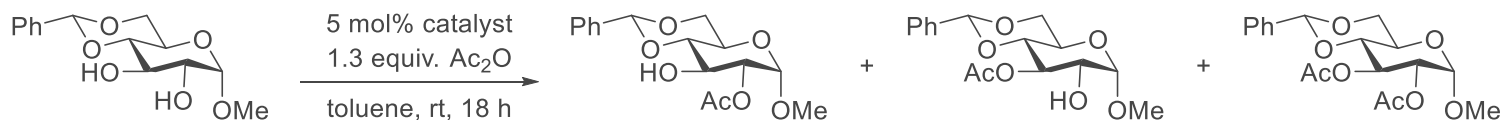




Acetylation of methyl 4,6-O-benzylidene- α -D-glucopyranoside



Acetylation of methyl 4,6-O-benzylidene- α -D-glucopyranoside

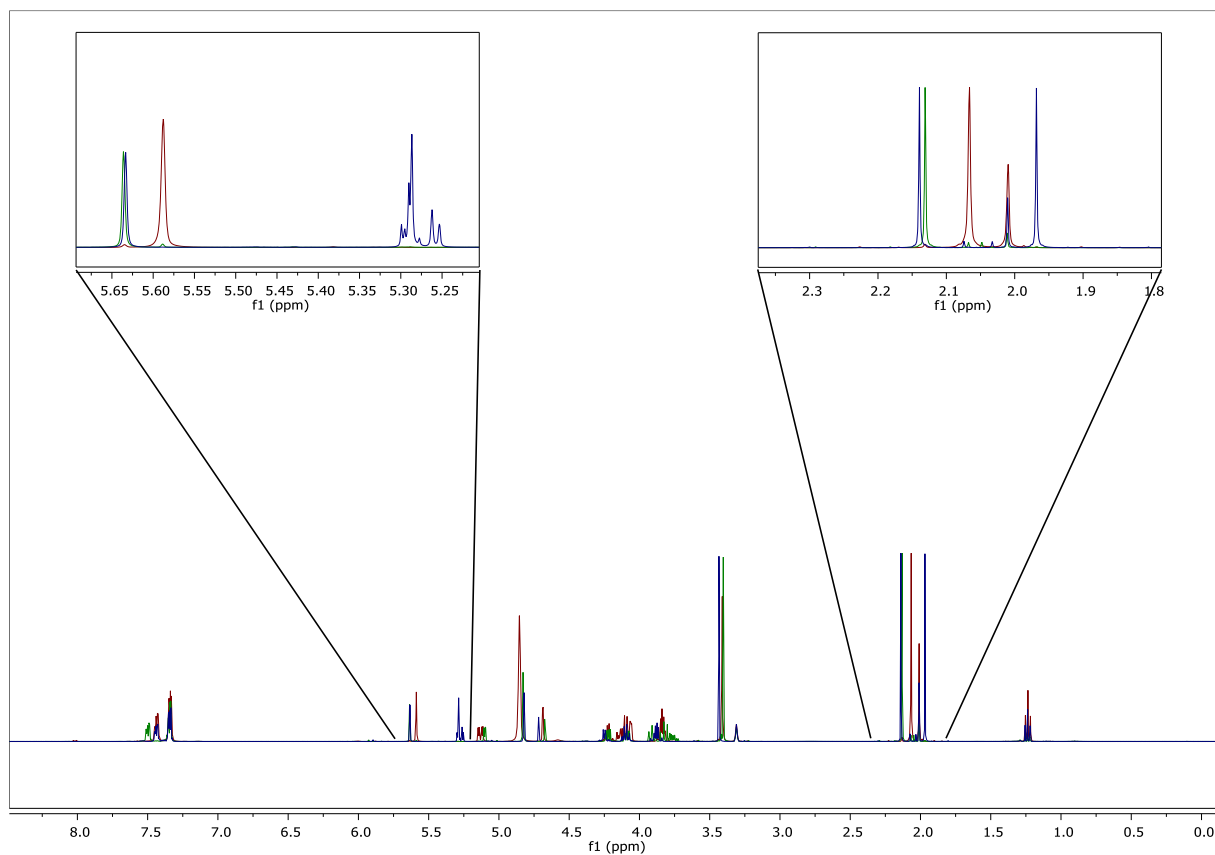
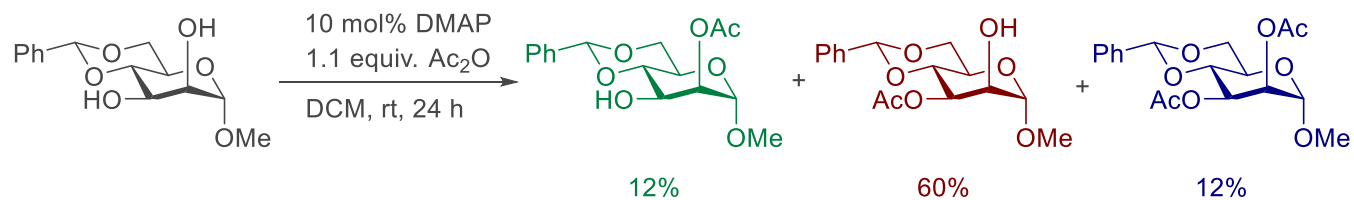


Catalyst	Product ratio			Conversion [%]
NMI (10mol%)	23	71	5	87
Et_3N (9 equiv., DCM)	70	—	30	75 (yield)
	85	9	6	>95 (0 °C)
	88	11	1	88 ^a
	67	22	11	>95

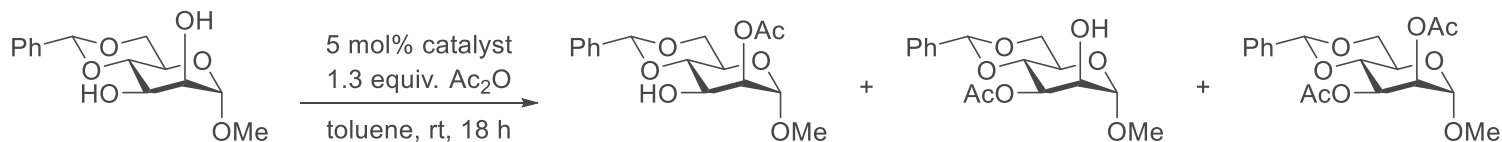
^a18 mL toluene, 2 mol% catalyst and 1.0 equiv. acetic anhydride were used.

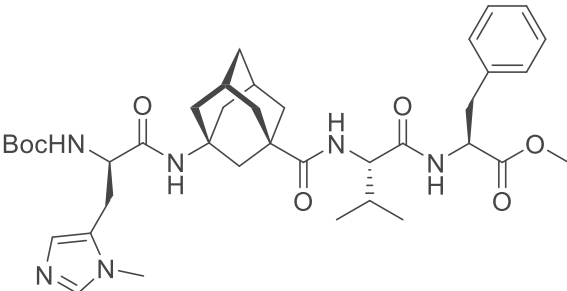
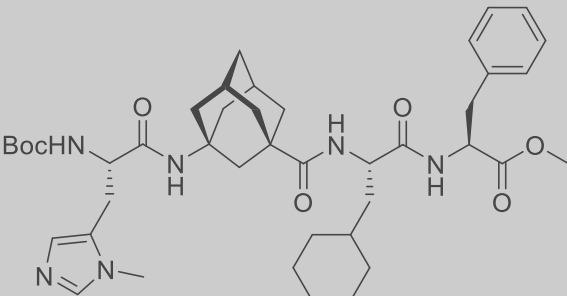
* R. C. Wende, *New Frontiers in Peptide Catalysis* **2016**.

Acetylation of methyl 4,6-O-benzylidene- α -D-mannopyranoside

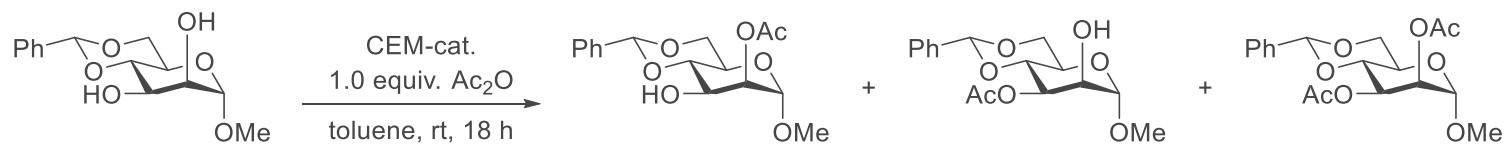


Acetylation of methyl 4,6-O-benzylidene- α -D-mannopyranoside



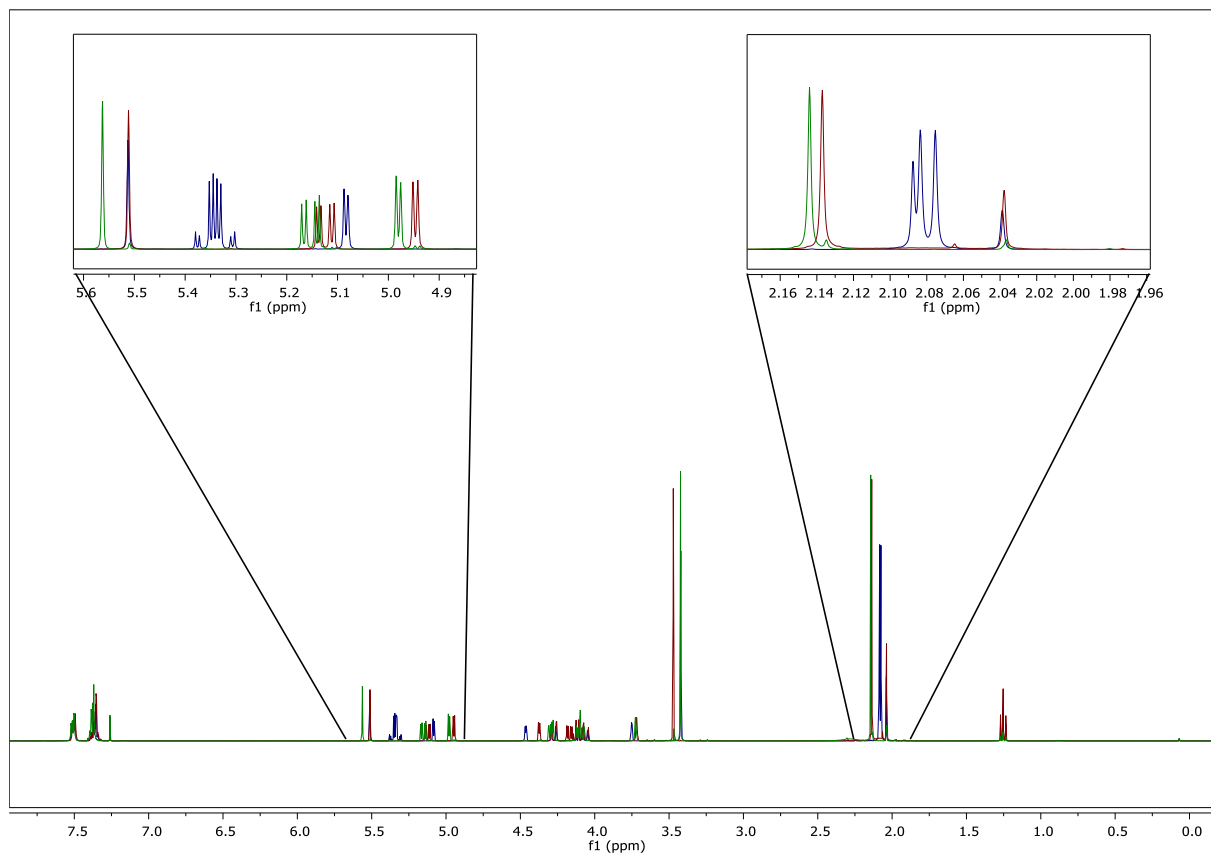
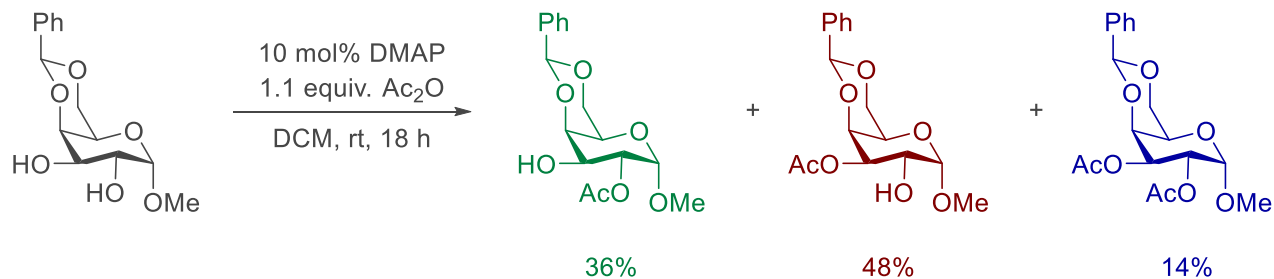
Catalyst	Product ratio			Conversion [%]
NMI (10mol%)	6	75	19	73
Et_3N (9 equiv., DCM)	45	55	—	34
	30	52	18	83
	57	5	38	>95

Acetylation of methyl 4,6-O-benzylidene- α -D-mannopyranoside

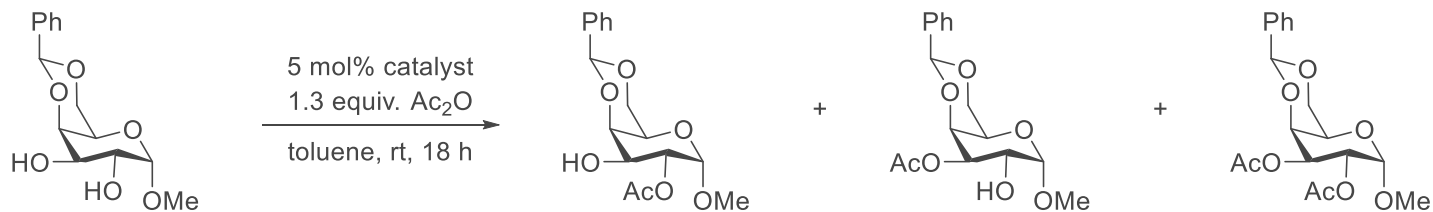


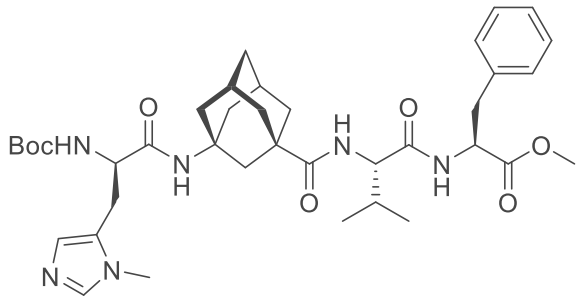
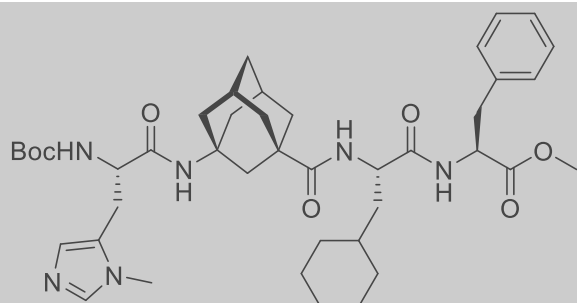
Catalyst [mol%]	Concentration [mmol/mL]	Product ratio			Conversion [%]
10	0.01	77	6	17	80
5	0.01	81	5	14	85
2	0.01	81	5	14	85
1	0.01	81	5	14	85
2	0.005	82	7	11	87
2	0.02	-	-	-	-
2	0.05	74	7	19	76

Acetylation of methyl 4,6-O-benzylidene- α -D-galactopyranoside

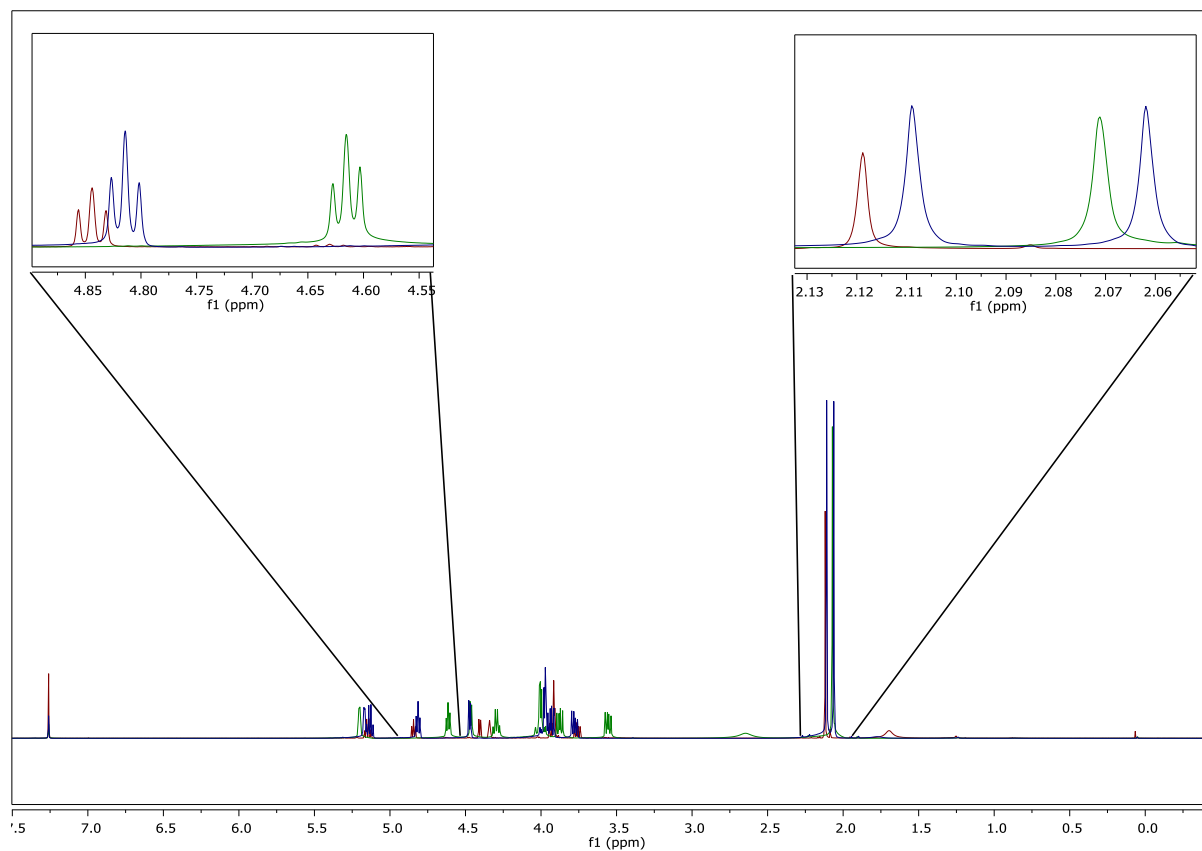
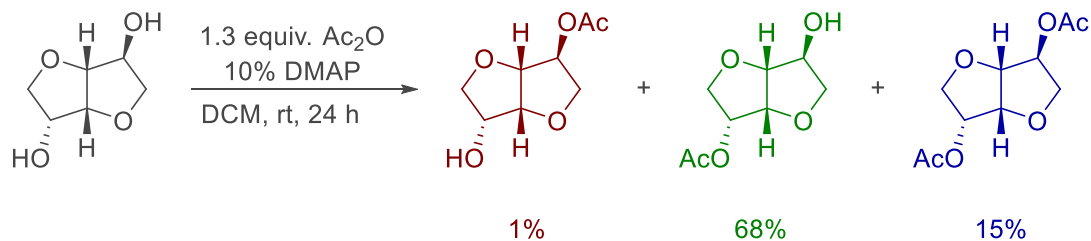


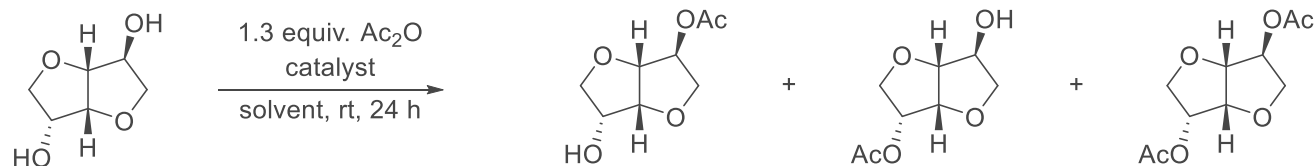
Acetylation of methyl 4,6-O-benzylidene- α -D-galactopyranoside



Catalyst	Product ratio			Conversion [%]
NMI (10mol%)	40	55	5	63
DMAP (10mol%)	34	42	24	>95
	26	69	6	95
	24	72	4	90

Acetylation of D-Isosorbide

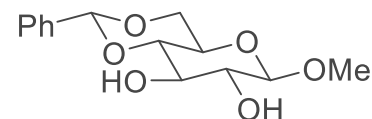
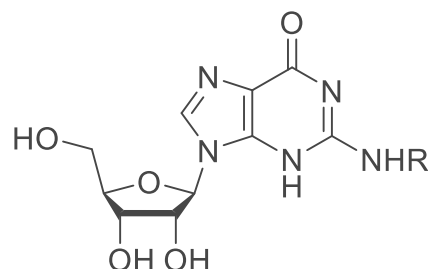
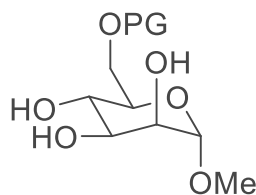




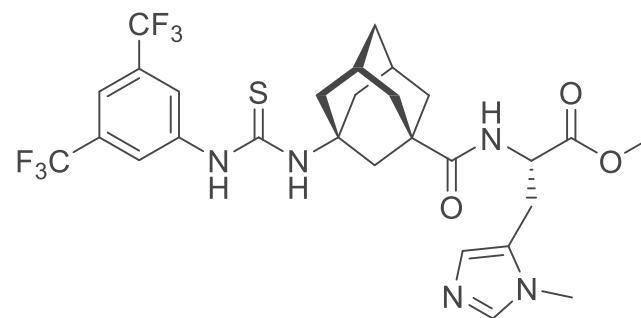
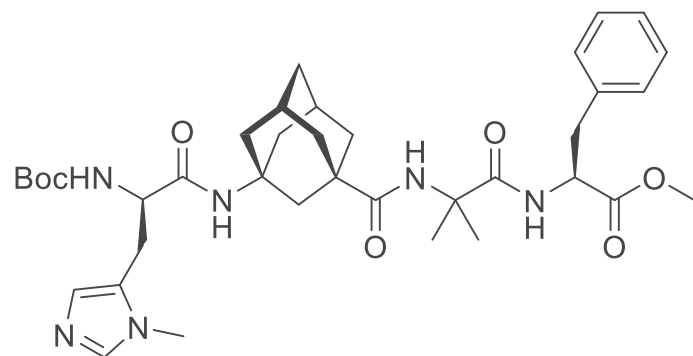
Catalyst	Solvent	Product ratio			Conversion [%]
NMI (10mol%)	toluene	-	88	12	>95
DMAP (5mol%)	toluene	-	71	29	>95
DMAP (5mol%)	DCM	-	79	21	>95



- More carbohydrates

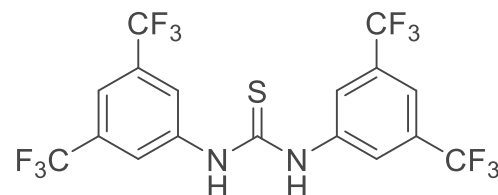
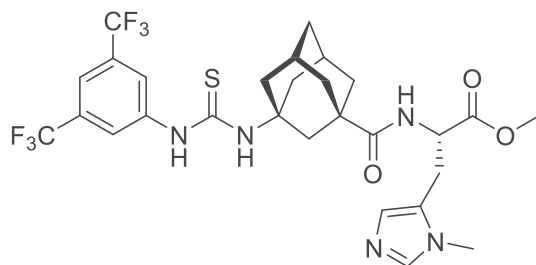


- Optimization of reaction conditions
- Catalyst library

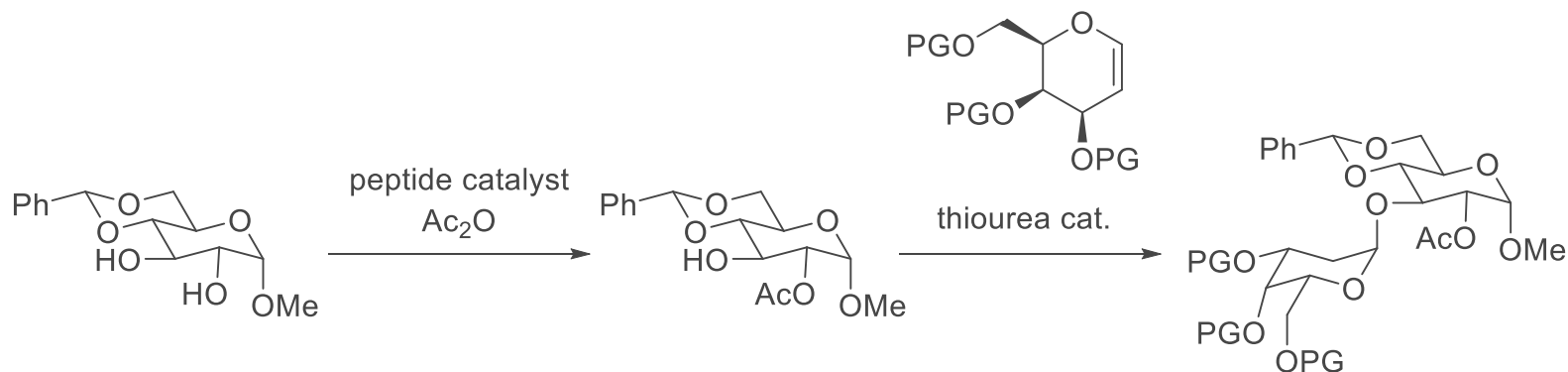




- Glycosylation with the formed 2-acetylated products



- Is multicatalysis possible ?





- Prof. Peter R. Schreiner
- Raffi
- Philipp, Michi, Sascha, Markus and Cesare
- JPB, Eschi and Dominik
- Analytical department
- PRS-Group





Thank you for your attention!

