Regioselective Acylation of Pyranoses

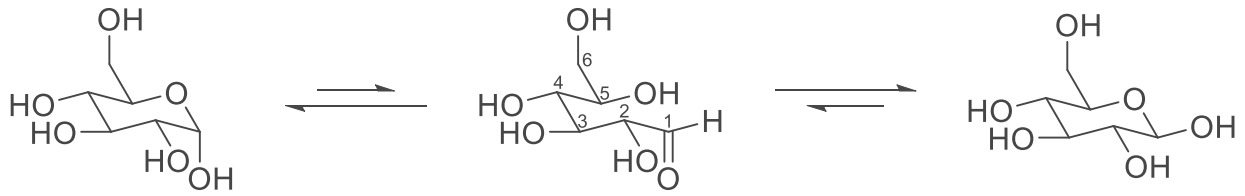
3th November 2017

Alexander Seitz

Institute of Organic Chemistry
Justus-Liebig University
35392 Giessen, Germany

Pyranoses

- 6-membered ring with 5 *C* and 1 *O*
- OH-group at one of the *O* neighboured C‘s (e.g. hemiacetal)

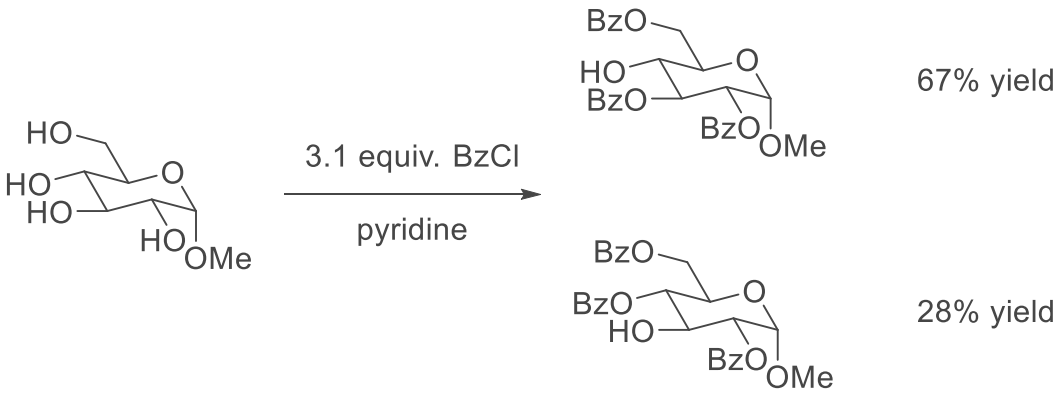


36% 0.02% 64%

- β-anomer is favored because OH is equatorial
- Fixation of anomeric center *via* protection

P. Y. Bruice: *Organische Chemie.* 5., aktualisierte Auflage; R. T. Morrison; R. N. Boyd, *Organic Chemistry*, 2nd Edition; J. Lehmann: *Kohlenhydrate. Chemie und Biologie.* 2., neu bearb. und erw. Auflage.

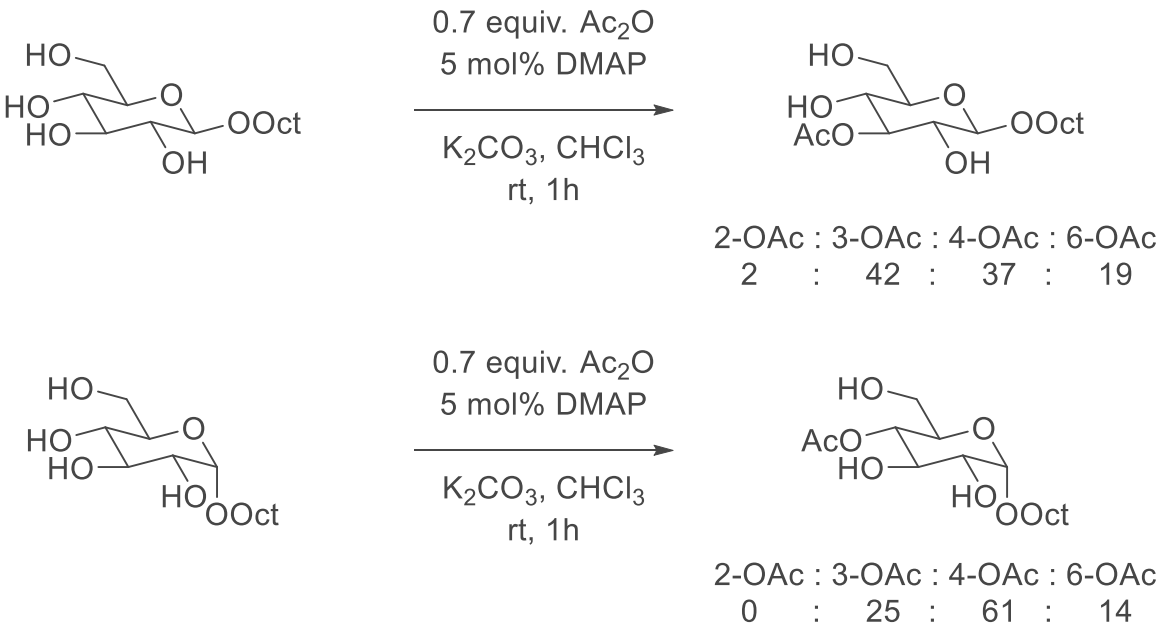
- Benzoylation used to rank reactivity by Richardson and Williams



- 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-galactopyranosie: 2-OH > 3-OH > 4-OH

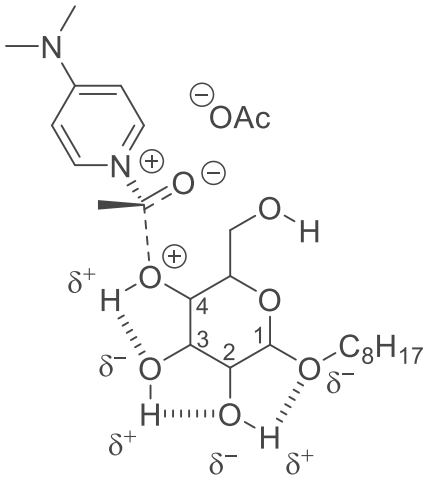
J. Lawandi, S. Rocheleau, N. Moitessier, *Tetrahedron* **2016**, *72*, 6283-6319; A. C. Richardson, J. M. Williams, *Chem. Comm.* **1965**; 104-105, J. M. Williams, A. C. Richardson, *Tetrahedron* **1967**, *23*, 1369-1378.

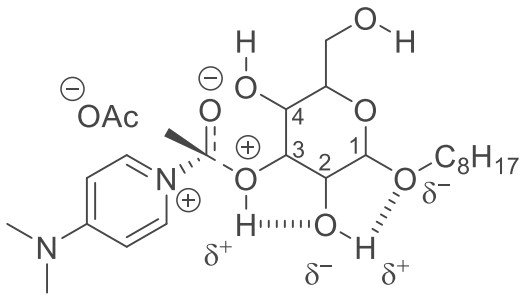
- 1999 DMAP was first used as a catalyst
- Change of reactivity could be observed

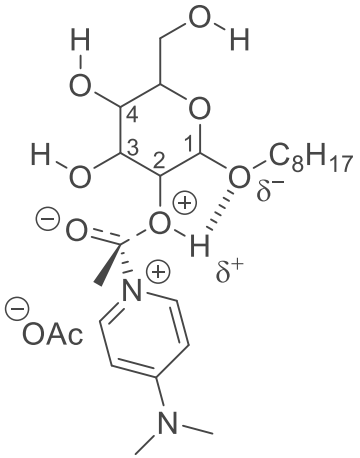


T. Kurahashi, T. Mizutani, J. I. Yoshida, *J. Chem. Soc. Perkin Trans. 1* **1999** ,465-473; W. Muramatsu, T. Kawabata, *Tetrahedron Lett.* **2007**, *48*, 5031-5033.

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



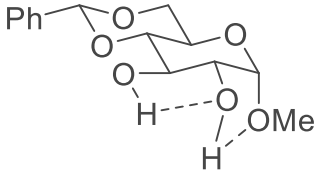


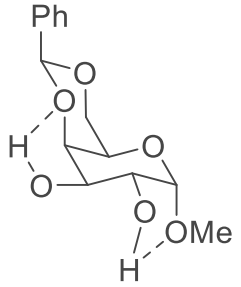


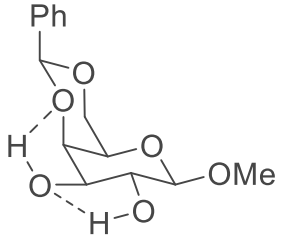
T. Kurahashi, T. Mizutani, J. I. Yoshida, *J. Chem. Soc. Perkin Trans. 1* **1999** ,465-473; W. Muramatsu, T. Kawabata, *Tetrahedron Lett.* **2007**, *48*, 5031-5033.

Hydrogen bond network in pyranoses

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

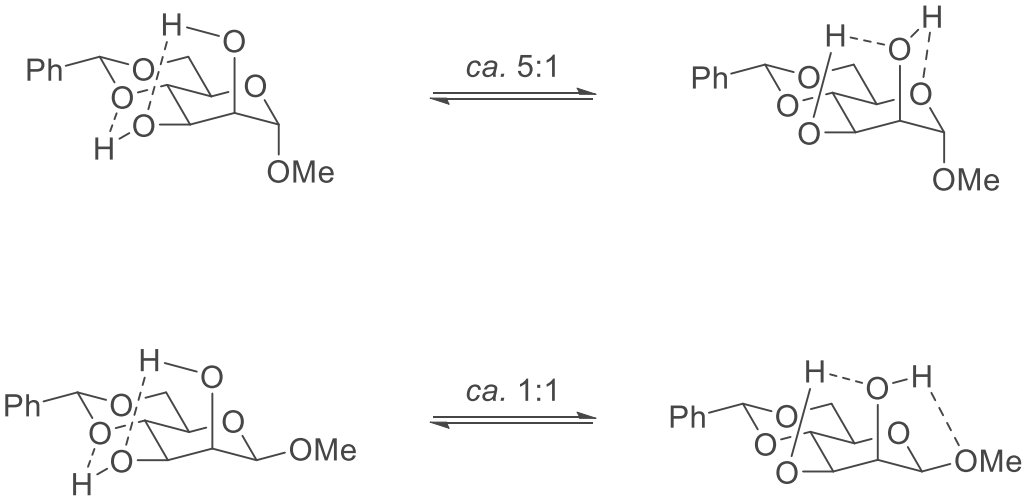






J. Lawandi, S. Rocheleau, N. Moitessier, *Tetrahedron* **2016**, *72*, 6283-6319, P. R. Muddasani, E. Bozó, B. Bernet, A. Vasella, *Helv. Chim. Acta* **1994**, *77*, 257-290.

Hydrogen bond network in pyranoses



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

J. Lawandi, S. Rocheleau, N. Moitessier, *Tetrahedron* **2016**, *72*, 6283-6319, P. R. Muddasani, E. Bozó, B. Bernet, A. Vasella, *Helv. Chim. Acta* **1994**, *77*, 257-290; R. C. Wende, *New Frontiers in Peptide Catalysis* **2016**.

Acylation of methyl 4,6-*O*-benzylidene-α-D-pyranosides

- Review of Lawandi *et al*. 2016

- Focus on acylation of methyl 4,6-*O*-benzylidene-α-D-pyranosides

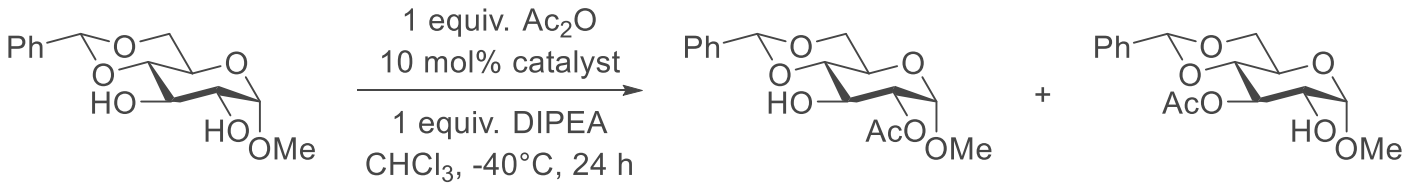
- Lipases catalyze acetylation with very high selectivity (up to 100%) and very high yields (up to 95%)

- Most catalysts/additives are only working with one of the pyranoses

J. Lawandi, S. Rocheleau, N. Moitessier, *Tetrahedron* **2016**, *72*, 6283-6319, 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.

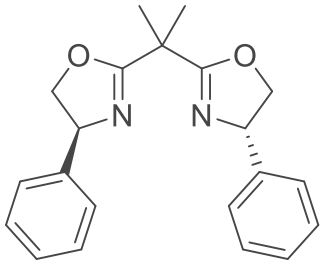
Acylation of methyl 4,6-*O*-benzylidene-α-D-pyranosides

- Allen and Miller used $CuCl_2$ and a PhBOX ligand



$CuCl_2$(R)-PhBOX:	1.8	1
$CuCl_2$(S)-PhBOX:	1.6	1

- With Acetylchloride higher regioselecitivies
  - (*R*)-catalyst: 2-*O*/3-*O* (7.0:1.0)
  - (*S*)-catalyst: 2-*O*/3-*O* (1.0:4.5)

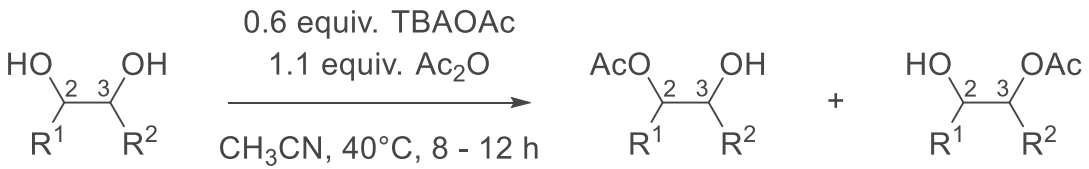


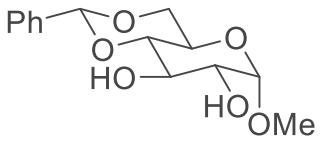
(S),(S)-PhBOX

C. L. Allen, S. J. Miller, *Org. Lett.* **2013**, *15* , 6178-6181, J. I. García, G. Jiménez-Osés, V. Martínez-Merio, J. A. Mayoral, E. Pires, I. Villalba, *Chem. Eur. J.* **2007**, *13*, 4064-4073.

Acylation of methyl 4,6-*O*-benzylidene-α-D-pyranosides

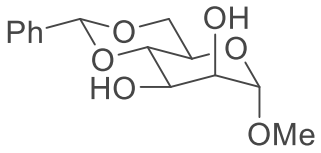
- Zhou *et al*. used TBAOAc as catalyst





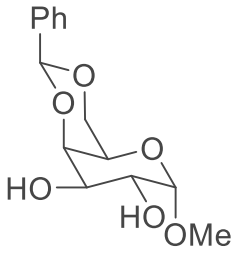
88%

0%



50%

50%



0%

90%

Y. Zhou, M. Rahm, B. Wu, X. Zhang, B. Ren, H. Dong, *J. Org. Chem.* **2013**, *78*, 11618-11622.

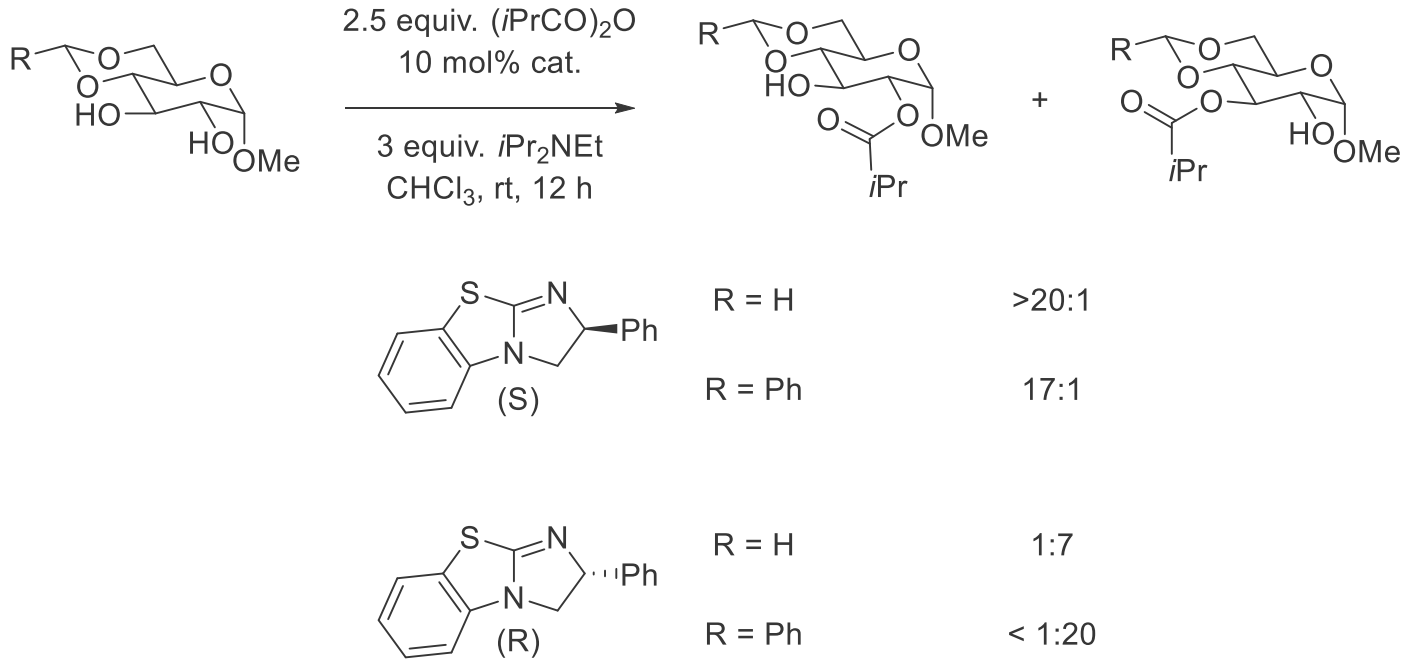
Overview acetylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside

Catalyst	Product ratio			Conversion [%]
pyridine	3-29	32-42	6-26	77-93
DMAP	45-49	55-51	-	40-65
Et_3N	80	5	15	-
NaO*t*Bu, EtOAc	48	52	-	76
$ZnCl_2$, pyridine	53	13	23	90
Ag_2O, KI, AcCl	15	81	-	-
cat. TBAOAc, $Me_2Si(OMe)_2$	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, *Carbohyd. 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.

Acylation of methyl 4,6-*O*-benzylidene-α-D-pyranosides

- Xiao *et al*. could inverse regioselectivity

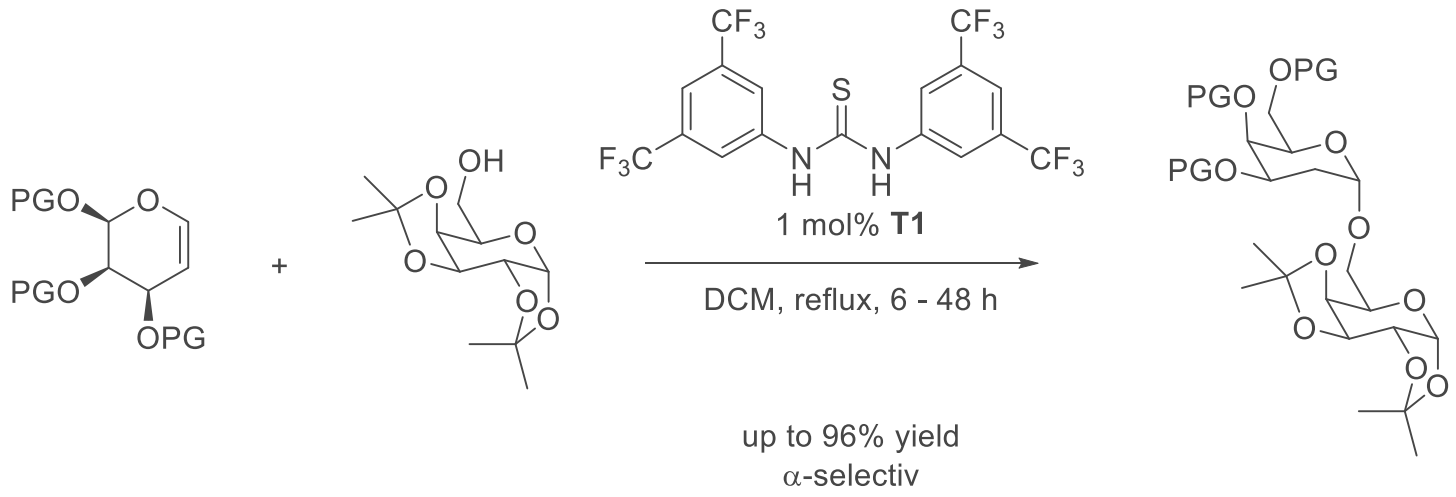


- No selectivity for β-anomer

G. Xiao, G. A. Cintron-Rosado, D. A. Glazier, B.-m. Xi, C. Liu, P. Liu, W. Tang, *J. Am. Chem. Soc.* **2017**, *139*, 4346-4349.

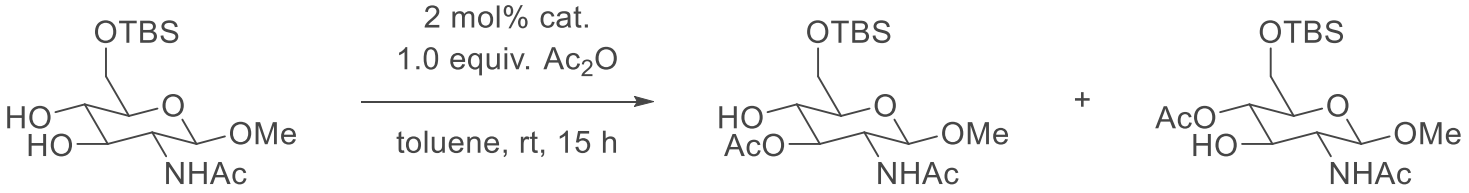
Motivation

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



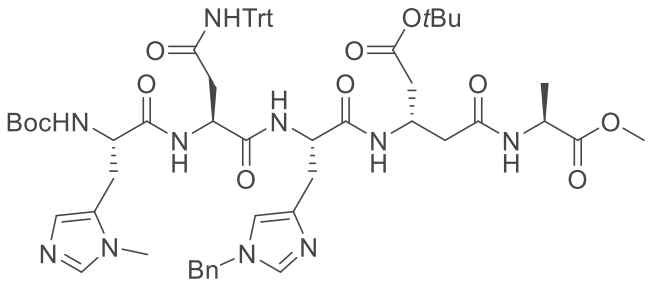
E. I. Balmond, D. M. Coe, M. C. Galan, E. M. McGarrigle, *Angew. Chem. Int. Ed.* **2012**, *51*, 9152–9155; R. C. Wende, *New Frontiers in Peptide Catalysis* **2016**.

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

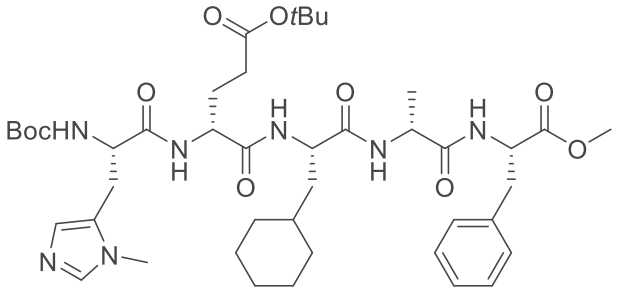


1 **2**

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



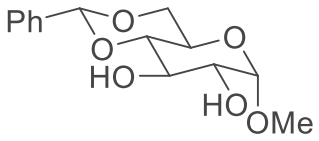
4



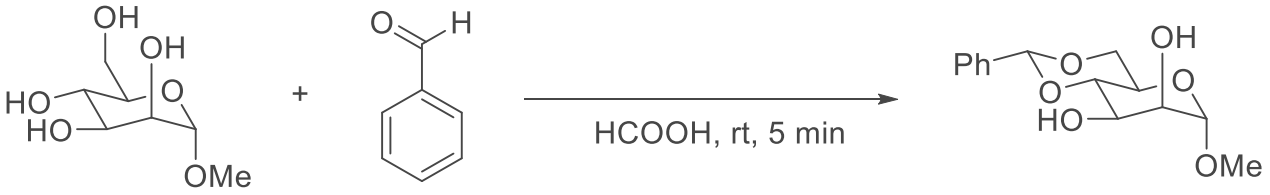
3

K. S. Griswold, S. J. Miller, *Tetrahedron* **2003**, *59*, 8869–8875; R. C. Wende, *New Frontiers in Peptide Catalysis* **2016**.

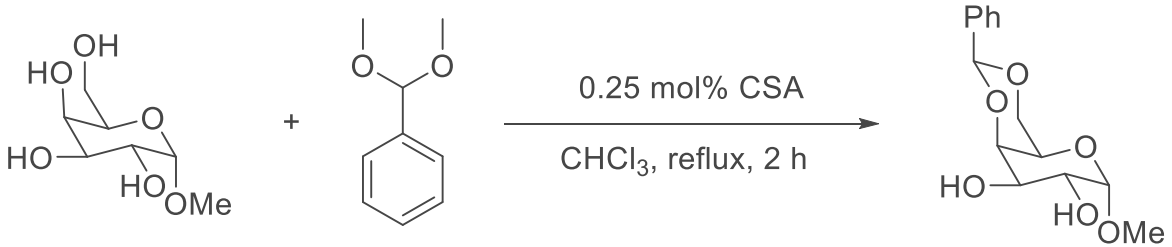
Protection of Methyl-D-pyranoses



25g/102€
Sigma Aldrich



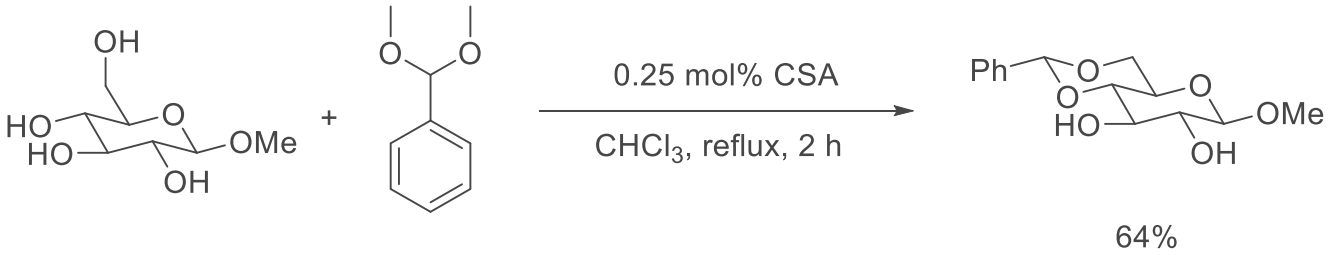
30%



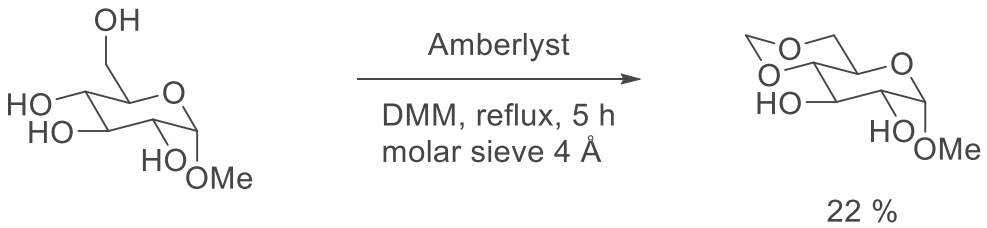
90%

T. Tewson, M. Soderlind, *J. Carbohyd. Chem.* **1985**, *4*, 529-543; J. Buchanan, J. Schwarz, *J. Chem. Soc (Resumed)* **1962**, 4770-4777; R. Raju, B. F. Castillo, S. K. Richardson, M. Thakur, R. Severins, M. Kronenberg, A. R. Howell, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4122-4125.

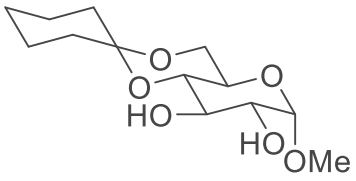
Protection of Methyl-D-pyranoses



64%



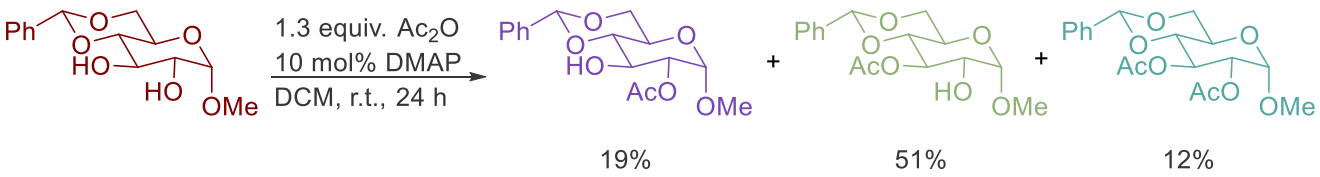
22 %

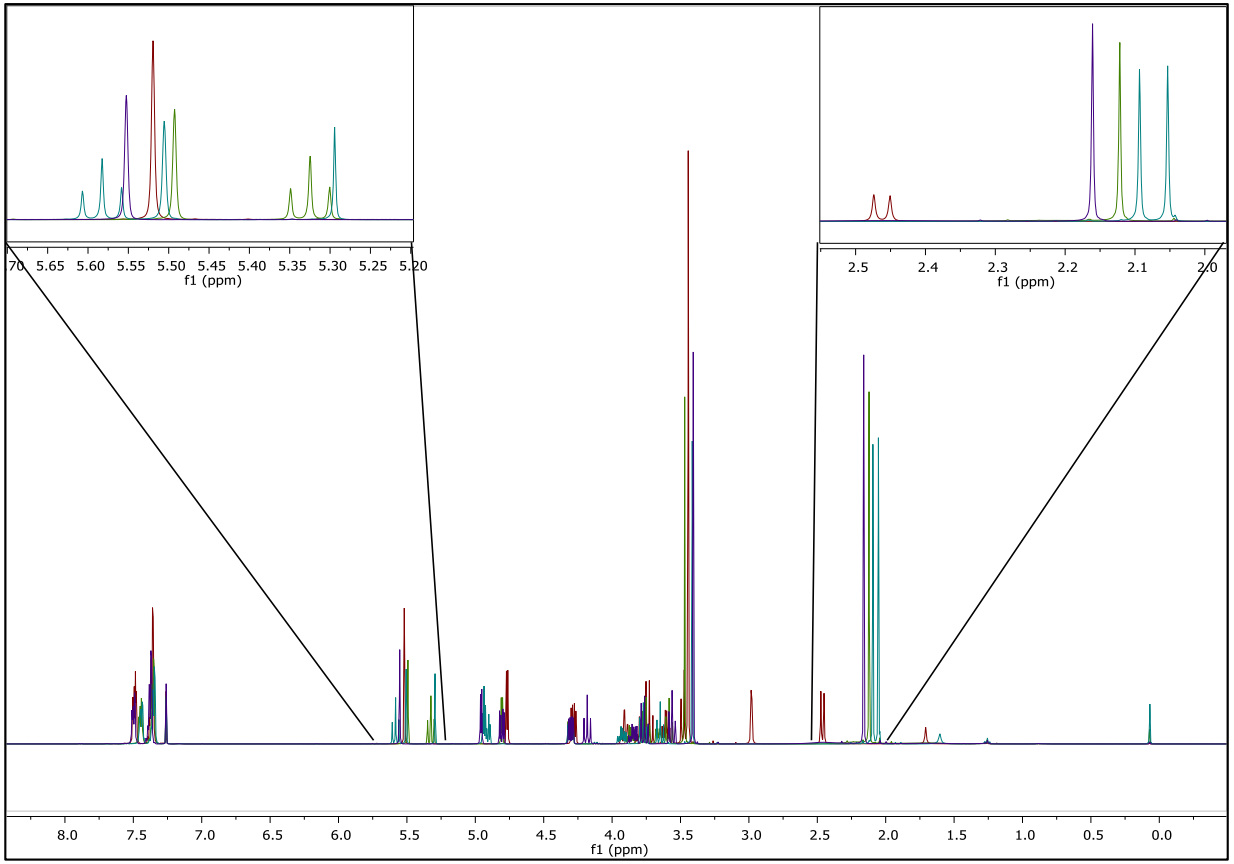


McGarrigle's group

R. Raju, B. F. Castillo, S. K. Richardson, M. Thakur, R. Severins, M. Kronenberg, A. R. Howell, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4122-4125; R. Nouguier, V. Mignon, J.-L. Gras, *Carbohydr. Res*. **1995**, *277*, 339-345.

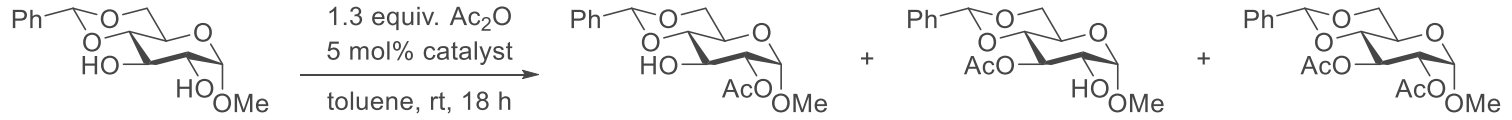
Acetylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside

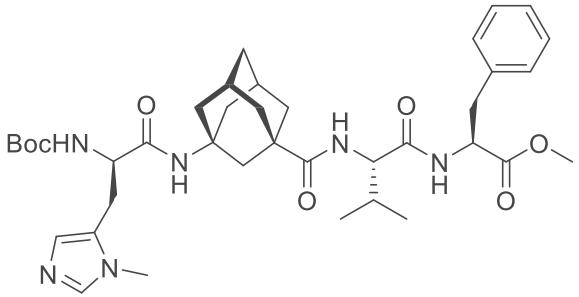
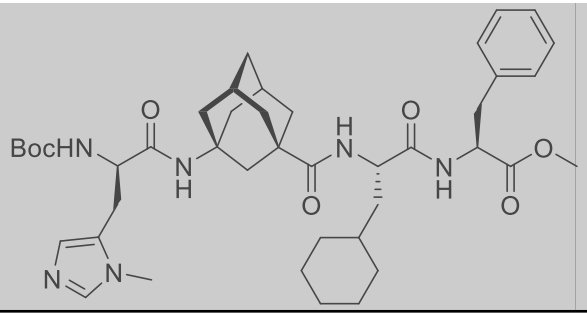




R. C. Wende, *New Frontiers in Peptide Catalysis* **2016**.

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

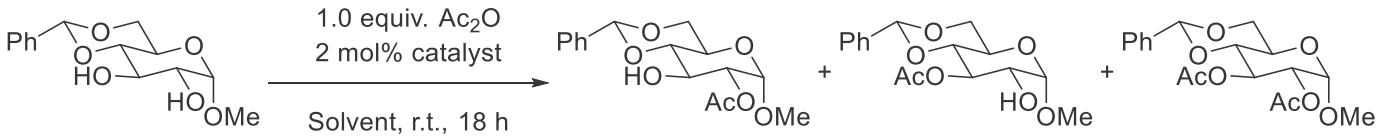


Catalyst	Product ratio			Conversion [%]
NMI (10mol%)	23	71	5	87
Et_3N (9 equiv., DCM)	70	–	30	75 (yield)
	85 88	9 11	6 1	>95 (0 °C) 88[a]
	67	22	11	>95

[a]18 mL toluene, 2 mol% catalyst and 1.0 equiv. acetic anhydride were used.

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

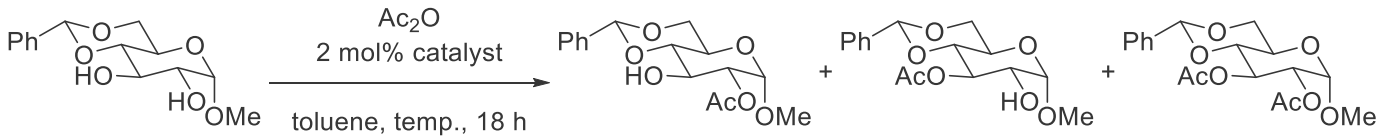
Solvent Screening

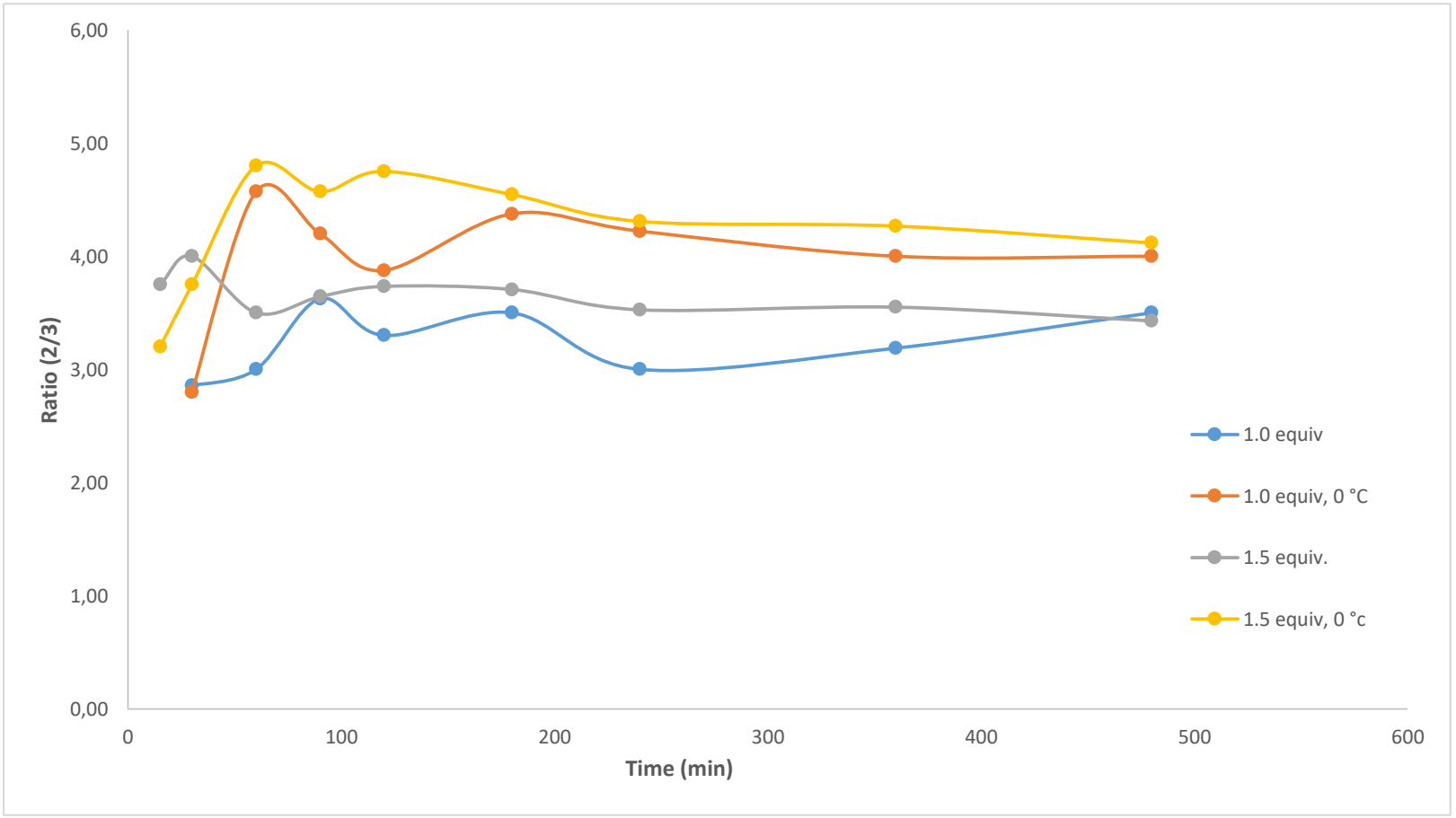


Solvent	Product ratio			Conversion [%]
Acetonitrile	68	29	3	25
Chloroform	72	25	3	18
Toluene	88	11	1	88[a]
Chlorobenzene	74	22	4	91
1,1,1,3,3,3-hexafluoro-2-propanol	73	27	0	30
α, α, α- trifluorotoluene	72	22	6	94

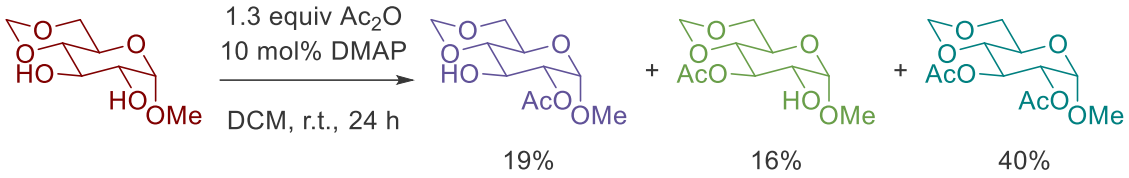
[a]18 mL toluene

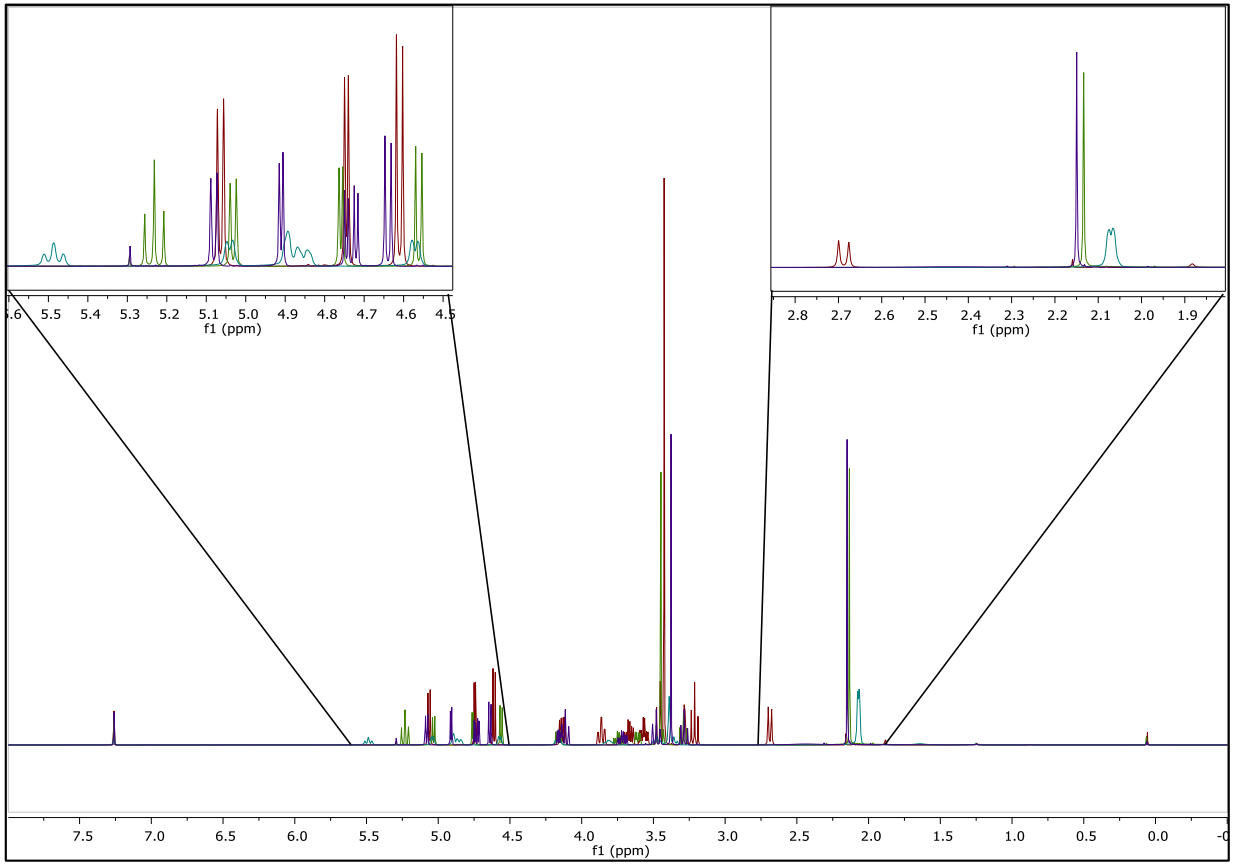
Kinetics


Ac2O
2 mol% catalyst
toluene, temp., 18 h
Ph
HO
OMe
AcO
+

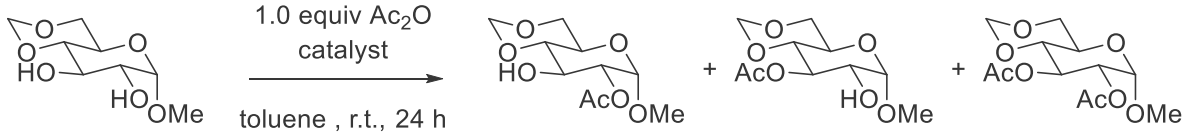

6,00
5,00
4,00
3,00
2,00
1,00
0,00
Ratio (2/3)
0
100
200
300
400
500
600
Time (min)
1.0 equiv
1.0 equiv, 0 °C
1.5 equiv.
1.5 equiv, 0 °c

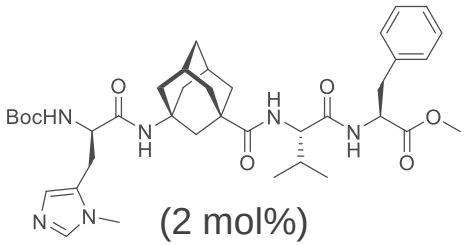
Acetylation of methyl 4,6-*O*-methylidene-α-D-glucopyranoside



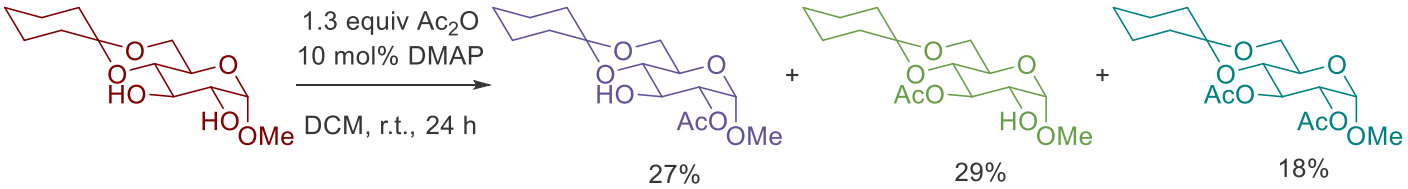


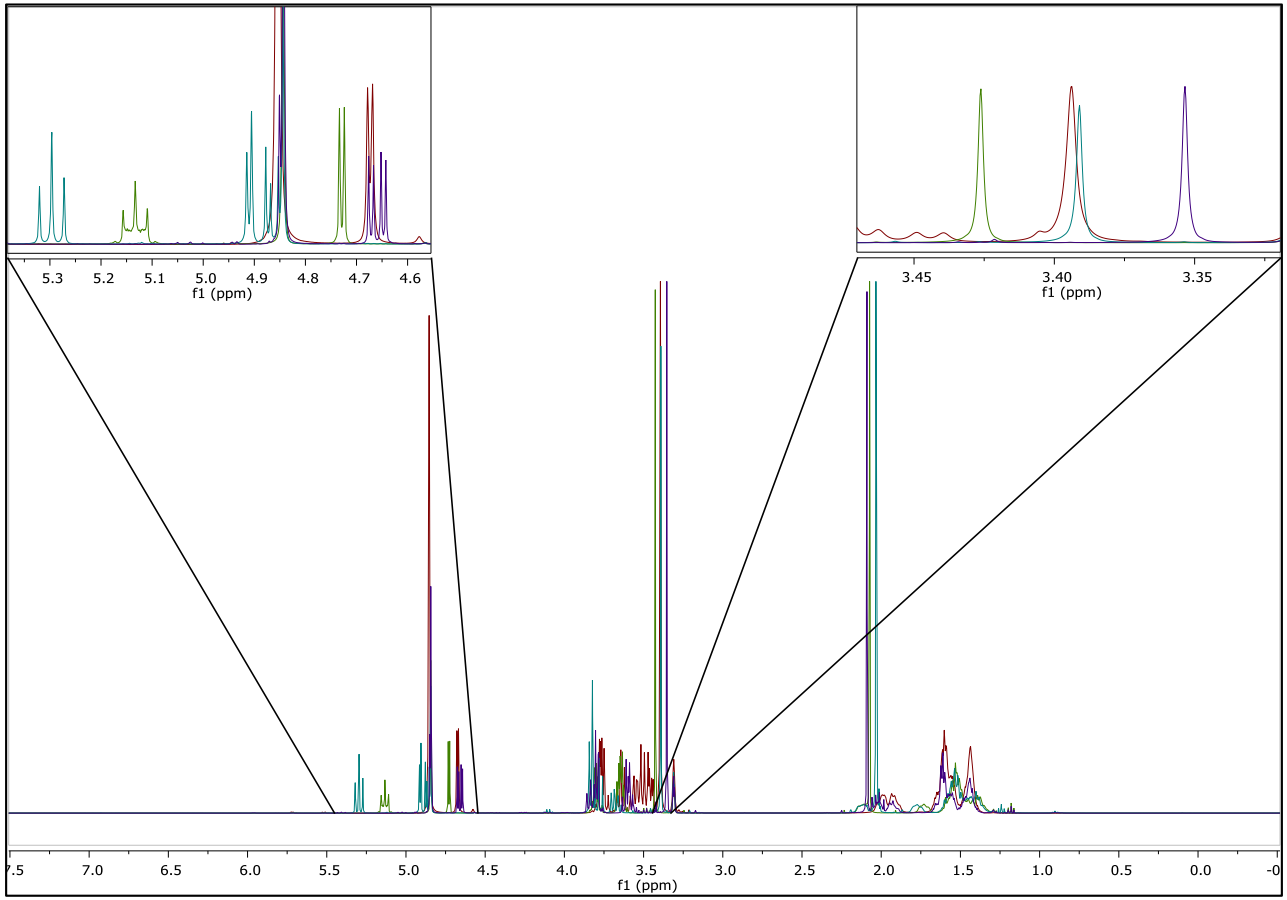
Acetylation of methyl 4,6-*O*-methylidene-α-D-glucopyranoside



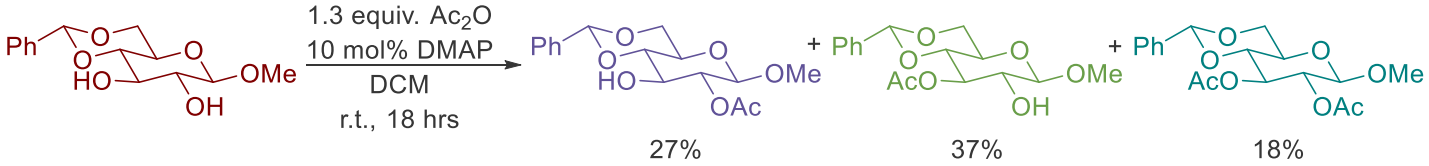
Catalyst	Product ratio			Conversion [%]
NMI (10 mol%)	39	57	4	58
DMAP (10 mol%)	35	47	18	>95
 (2 mol%)	76	20	4	>95

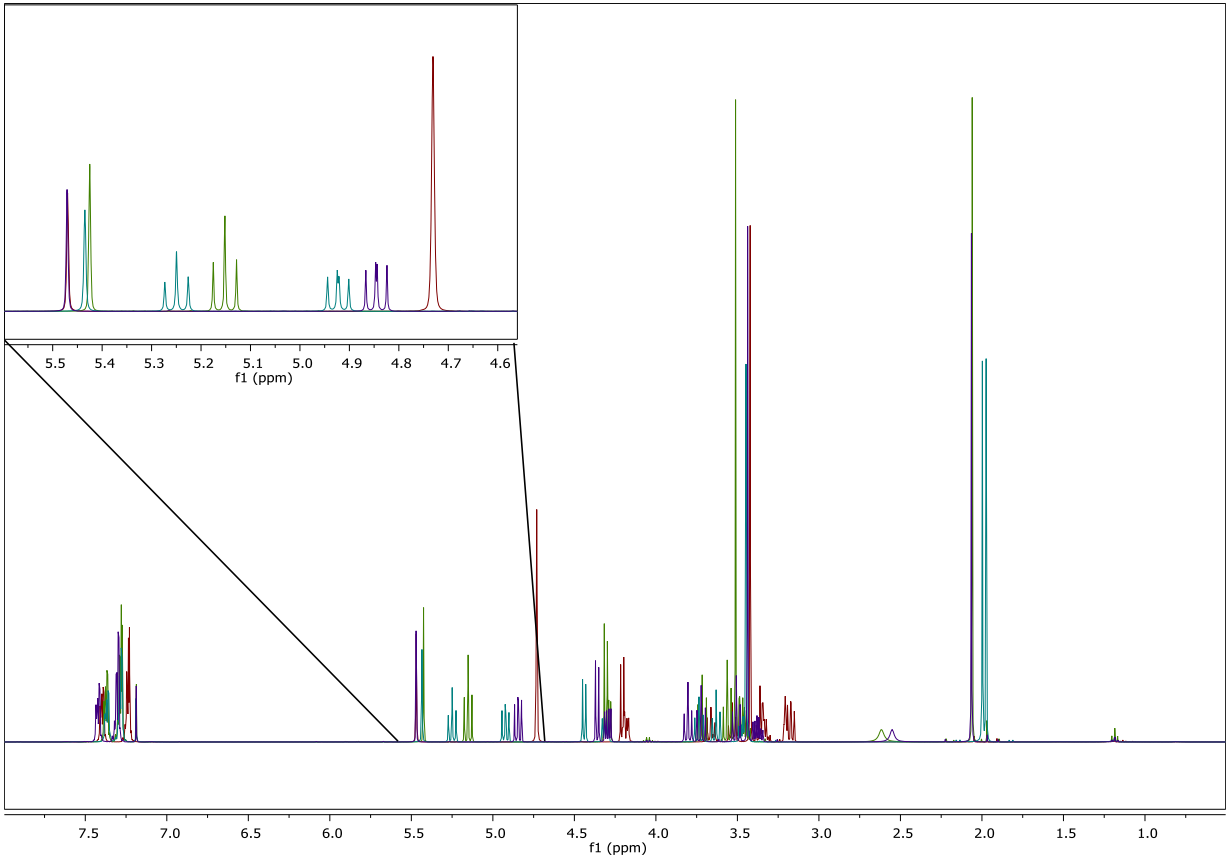
Acetylation of methyl 4,6-*O*-methylidene-α-D-glucopyranoside



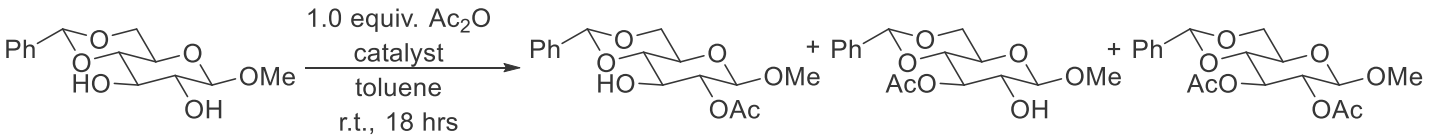


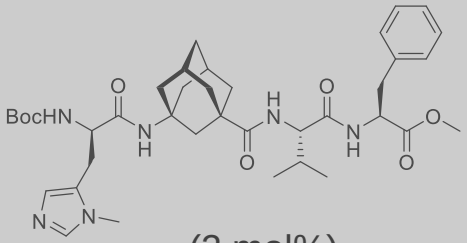
Acetylation of methyl 4,6-*O*-benzylidene-β-D-glucopyranoside



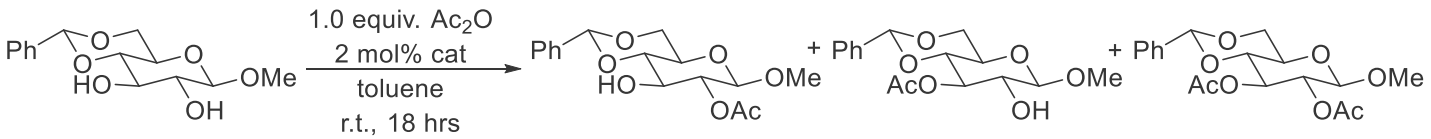


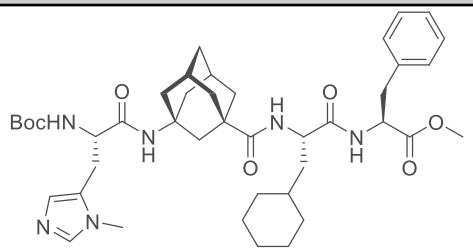
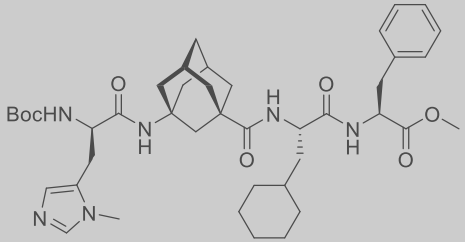
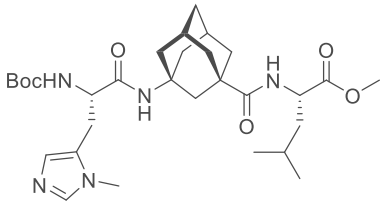
Acetylation of methyl 4,6-*O*-benzylidene-β-D-glucopyranoside



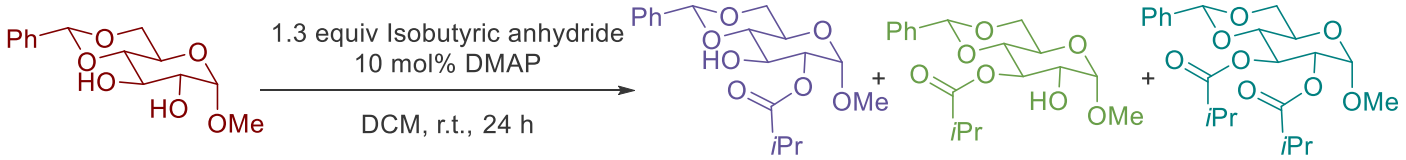
Catalyst	Product ratio			Conversion [%]
NMI (10 mol%)	20	55	25	32
DMAP (10 mol%)	18	35	47	78
Et_3N (9 equiv.)	34	62	4	83
 (2 mol%)	38	49	13	52

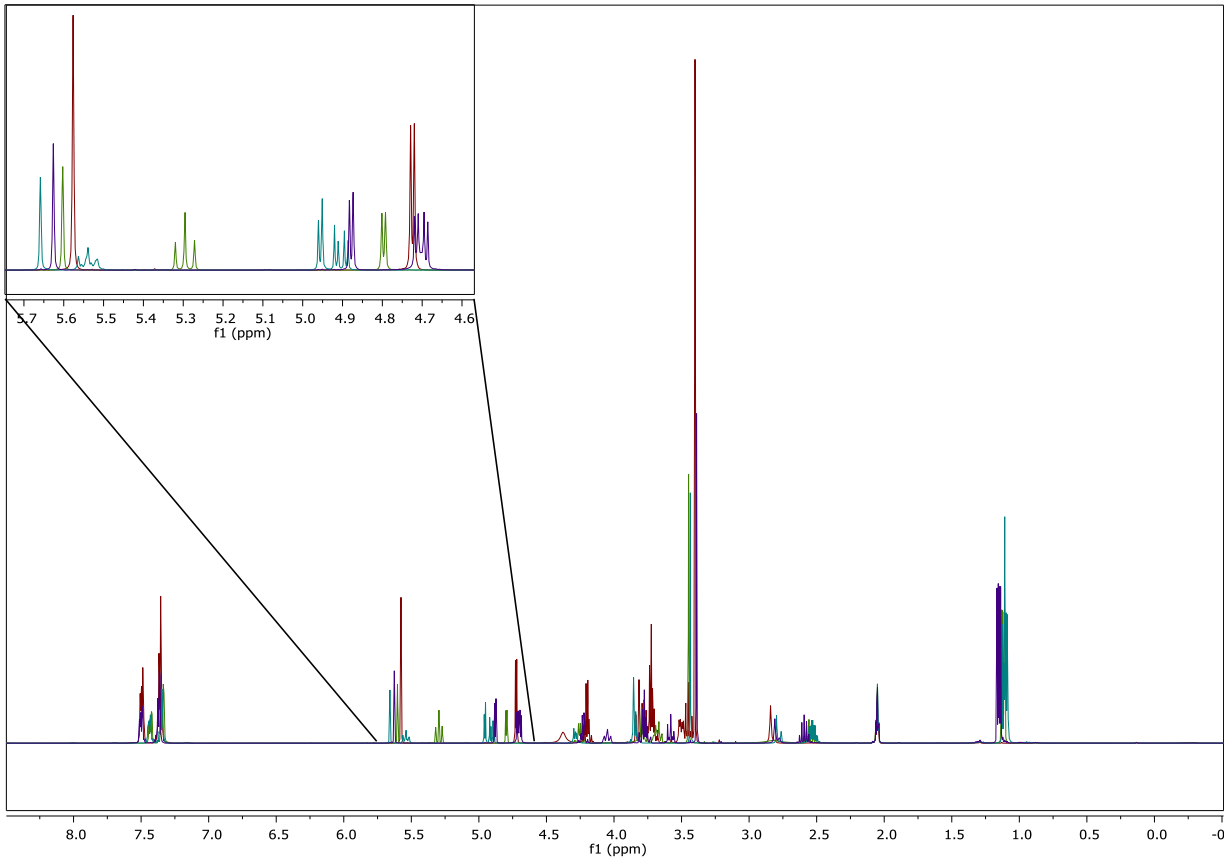
Acetylation of methyl 4,6-*O*-benzylidene-β-D-glucopyranoside



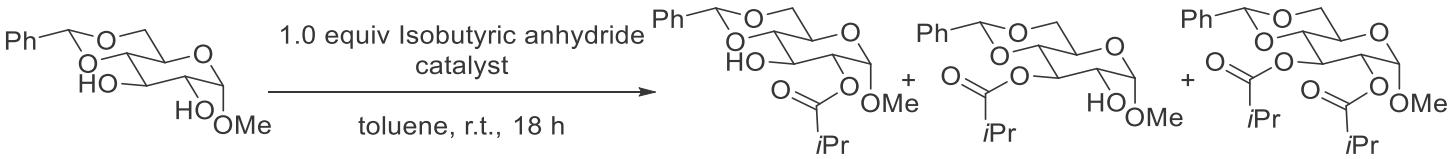
Catalyst	Product ratio			Conversion [%]
	28	39	33	75
	35	54	11	51
	26	62	12	36

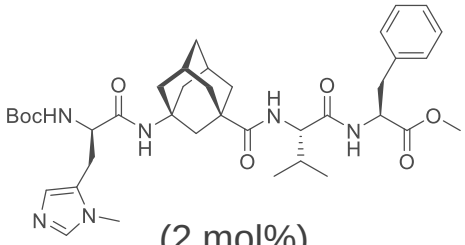
Acylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside



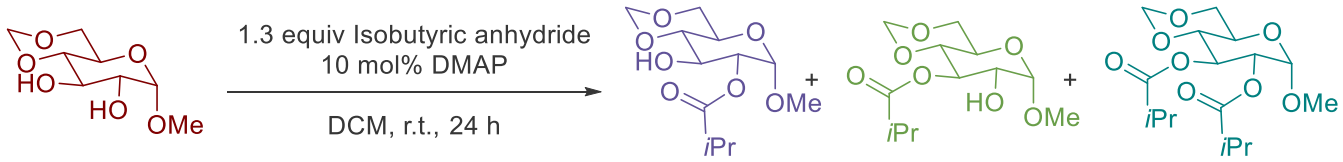


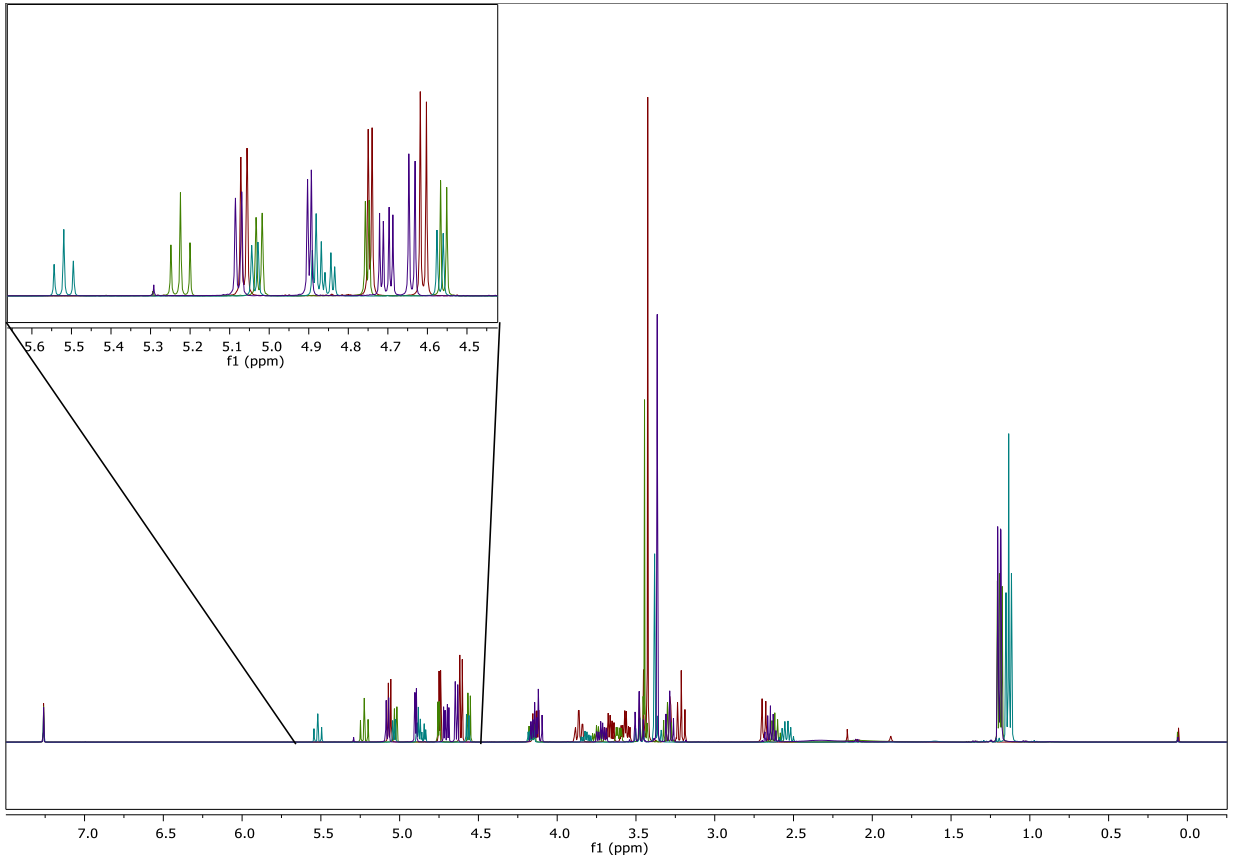
Acylation of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside



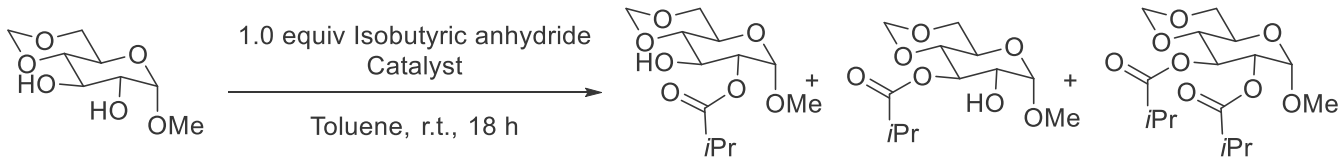
Catalyst	Product ratio			Conversion [%]
NMI (10 mol%)	31	66	3	71
DMAP (10 mol%)	36	55	9	96
 (2 mol%)	85	12	3	89

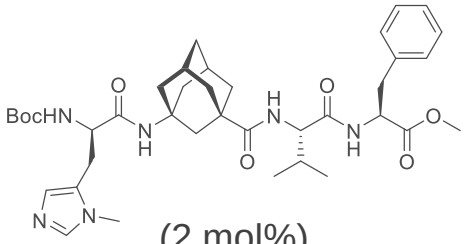
Acylation of methyl 4,6-*O*-methylidene-α-D-glucopyranoside



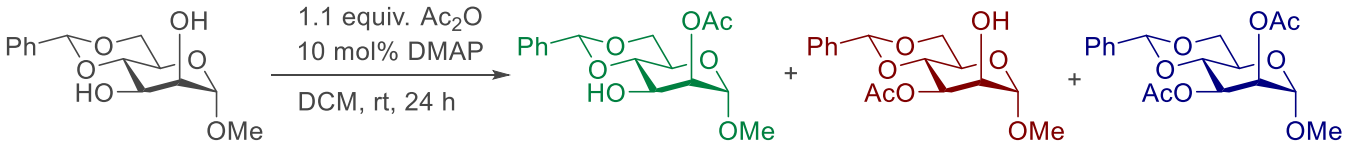


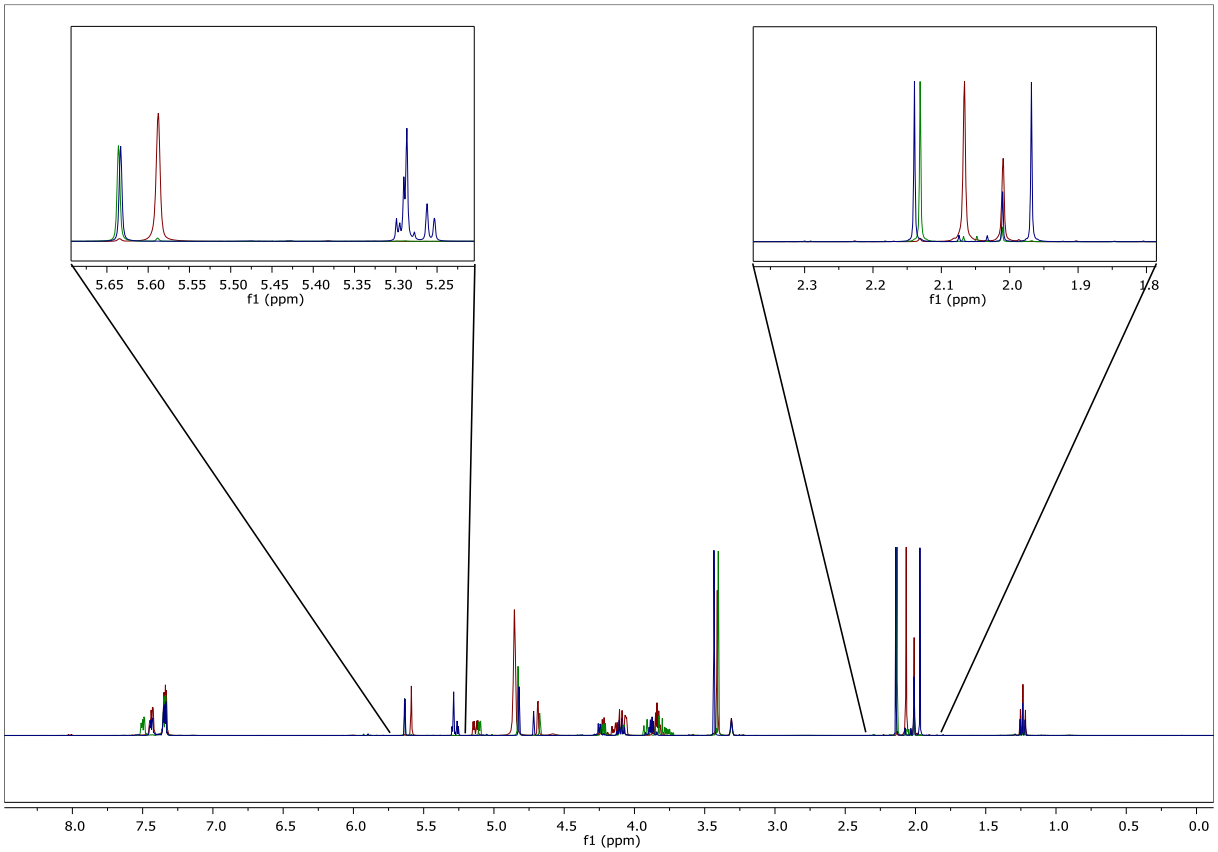
Acylation of methyl 4,6-*O*-methylidene-α-D-glucopyranoside



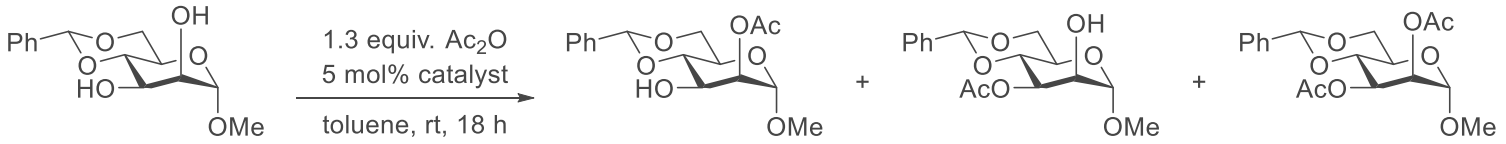
Catalyst	Product ratio			Conversion [%]
NMI (10 mol%)	49	46	5	54
DMAP (10 mol%)	53	35	12	91
 (2 mol%)	87	9	4	91

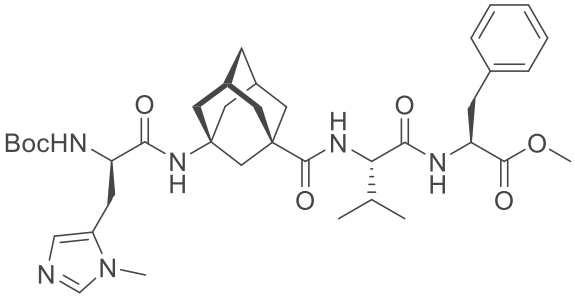
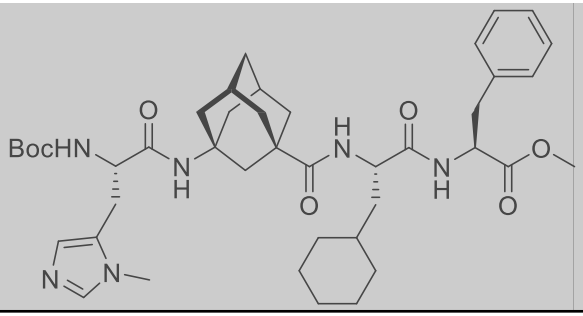
Acetylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside



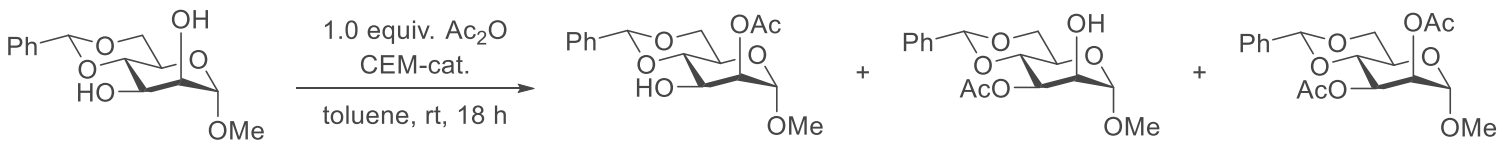


Acetylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside



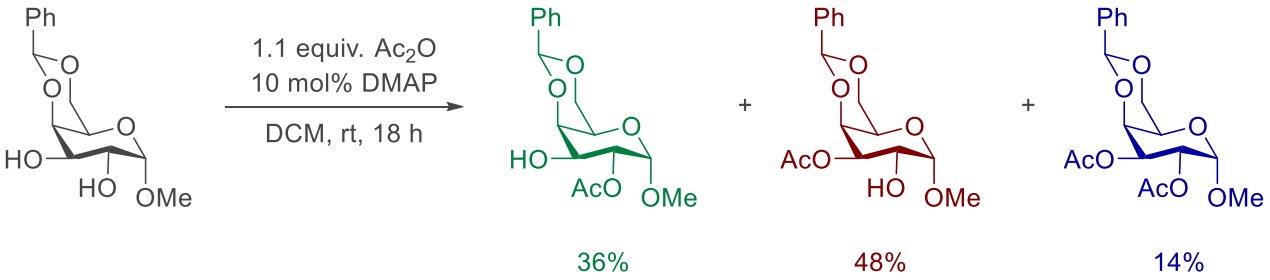
Catalyst	Product ratio			Conversion [%]
NMI (10mol%)	6	75	19	73
Et_3N (9 equiv., DCM)	45	55	–	34
	30	52	18	83
	57	5	38	>95

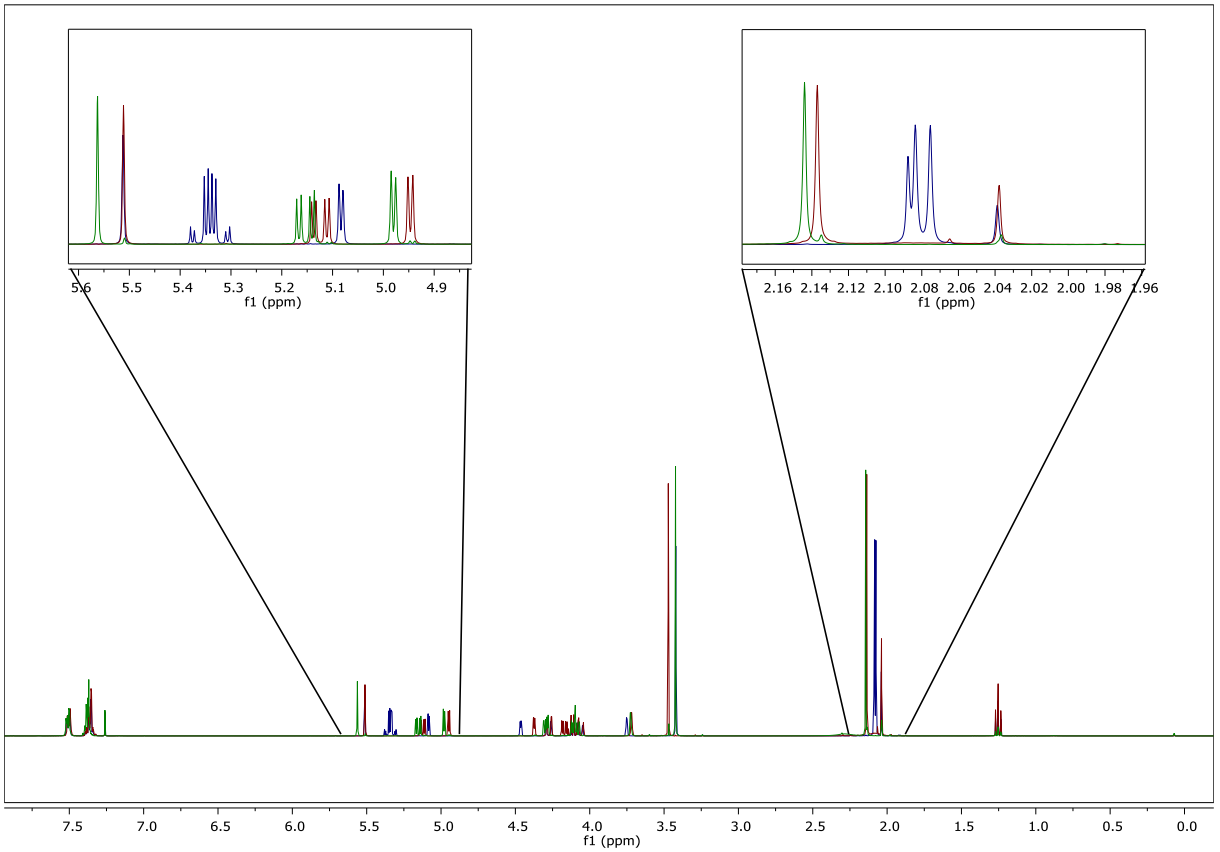
Acetylation of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside



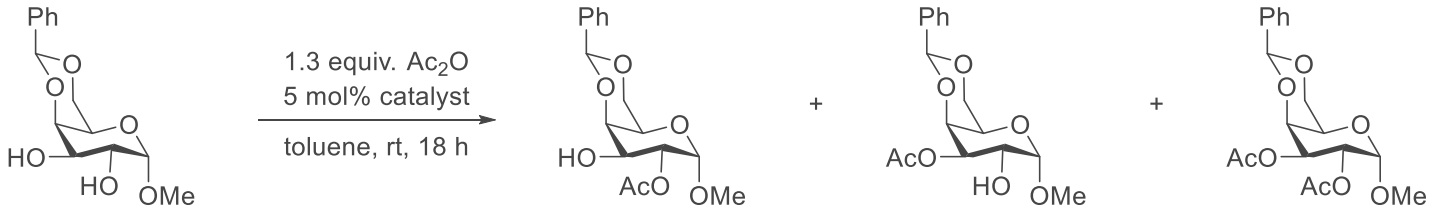
Catalyst [mol%]	Concentration [mmol/mL]	Product ratio			Conversion [%]
10	0.01	77	6	17	80
5	0.01	81	5	14	85
2	0.01	81	5	14	85
1	0.01	81	5	14	85
2	0.005	82	7	11	87
2	0.05	74	7	19	76

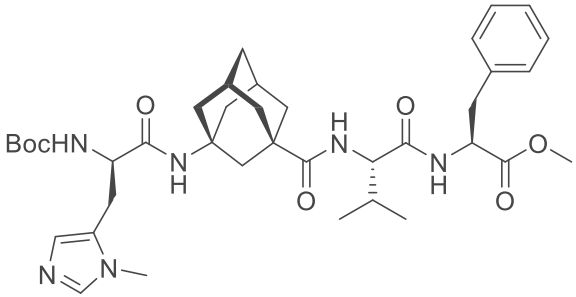
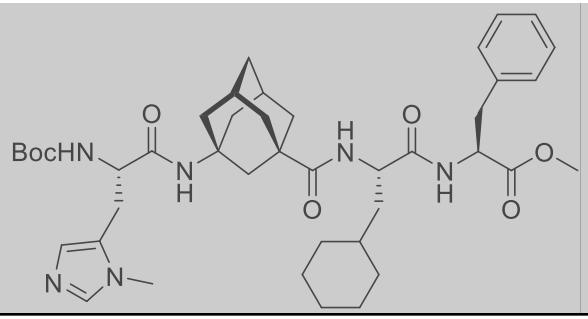
Acetylation of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside



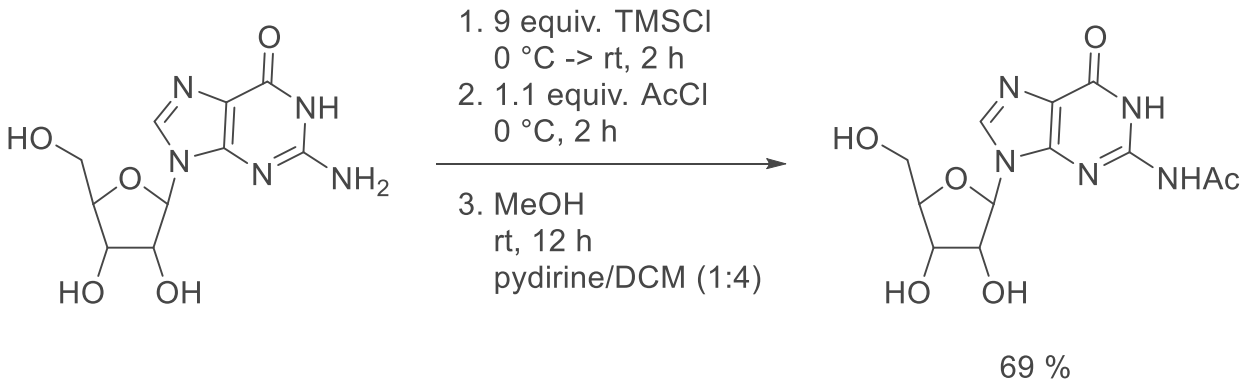


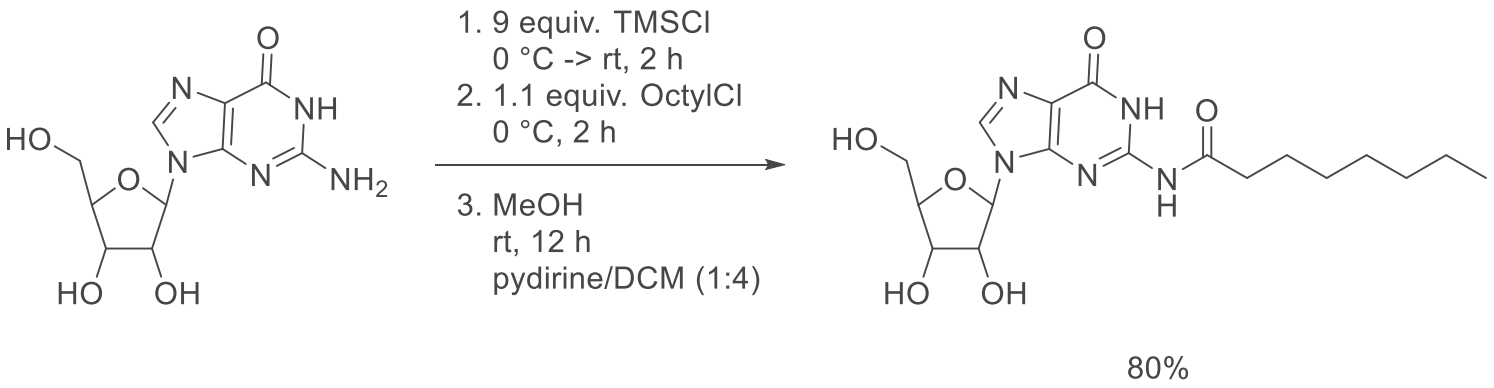
Acetylation of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside



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

Protection of other Carbohydrates





Y. Fan, B. L. Gaffney, R. A. Jones, *Org. Lett.* **2004**, *6*, 2555-2557.

Summary

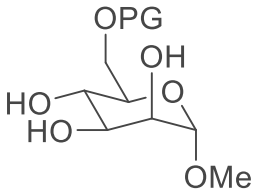
- Inversion of intrinsic reactivity for
  - methyl 4,6-*O*-protected-α-D-glucopyranoside
  - methyl 4,6-*O*-benzylidene-α-D-mannopyranoside

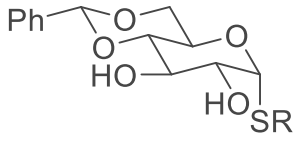
- Influence of anomeric center high for glucopyranoside

- No catalyst for galactopyranoside found yet

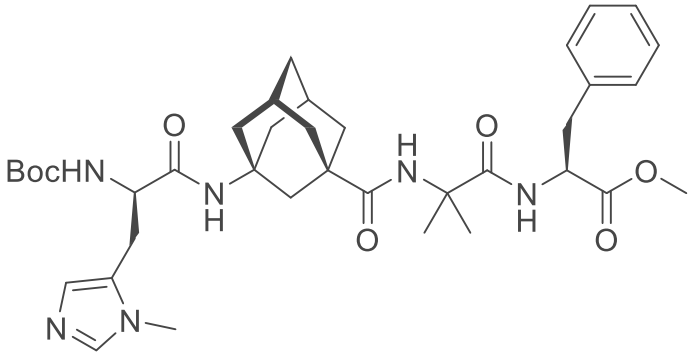
- Guanosin-derivaties poor solubility

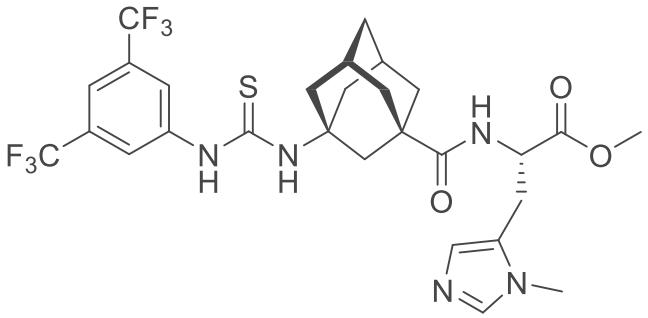
- Desing of experiments (almost finished)
- More carbohydrates



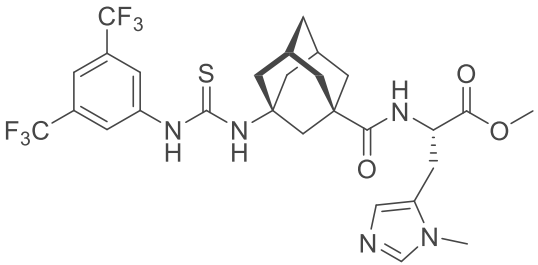


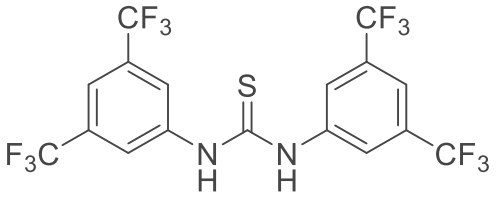
- Catalyst library



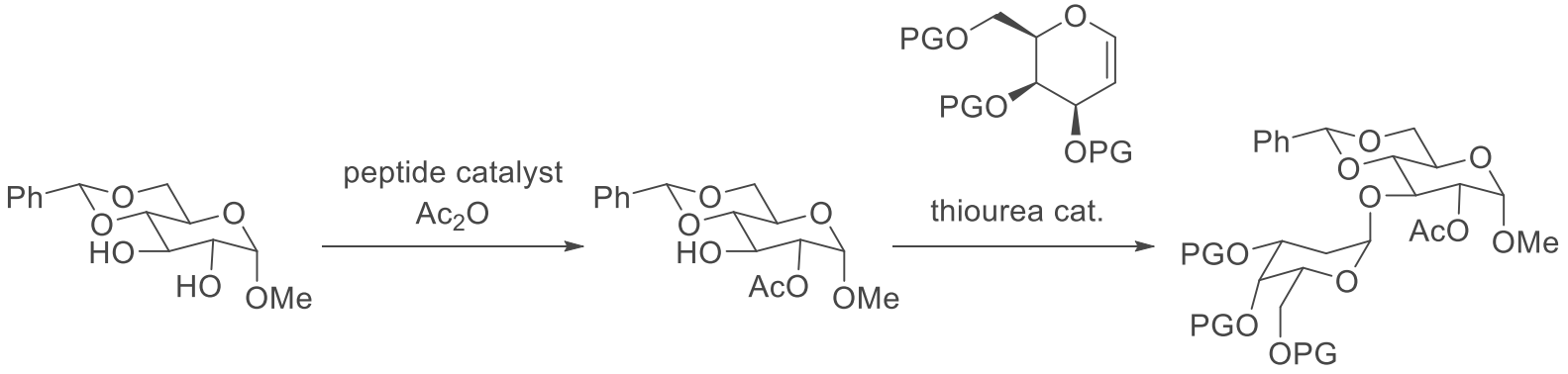


- Glycsoylation with the formed 2-acetylated products





- Is multicatalysis possible ?



E. I. Balmond, D. M. Coe, M. C. Galan, E. M. McGarrigle, *Ang. Chem. Int. Ed.* **2012**, *51*, 9152-9155.

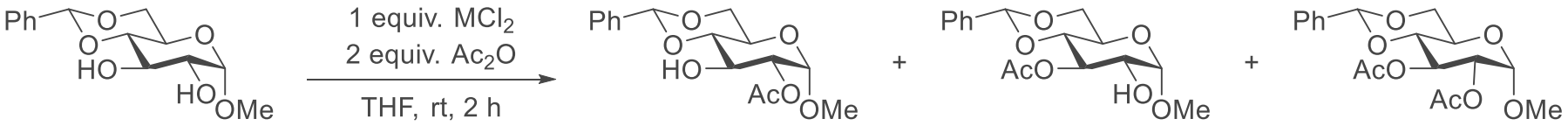
Acknowledgment

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

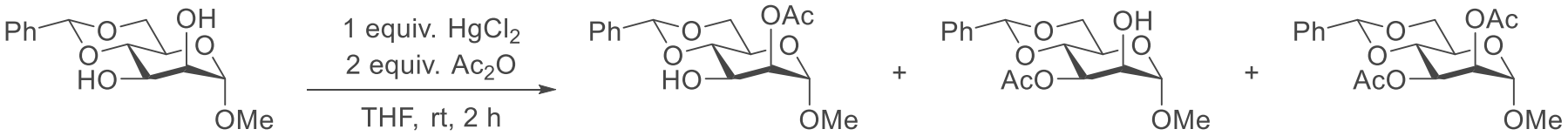
Thank you for your attention!

Acylation of methyl 4,6-*O*-benzylidene-α-D-pyranosides

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



Cu:	82%	-	18%
Hg:	15%	80%	5%



38%	21%	41%

R. Eby, K. T. Webster, C. Schuerch, *Carbohydr. Res.* **1984**, *129*, 111-120.