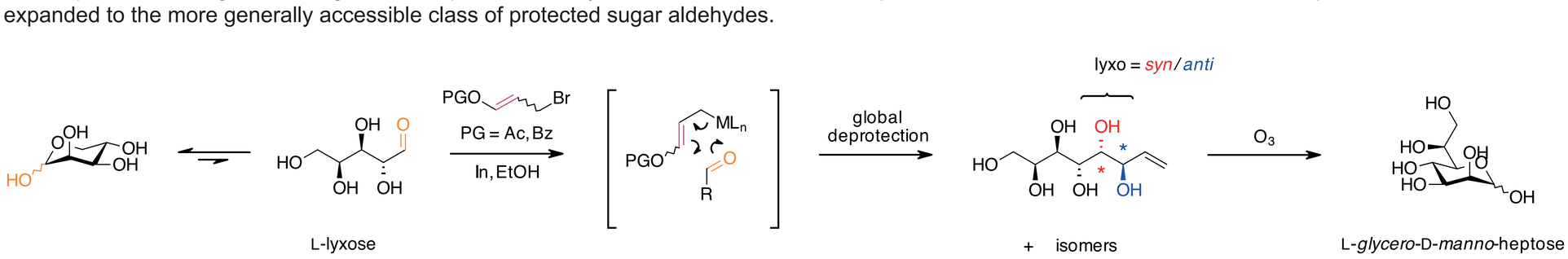
Indium Mediated Acyloxyallylation of Sugar Aldehydes

Lara Maltrovsky, Nina Biedermann, Markus Draskovits, Christian Stanetty*

Institute of Applied Synthetic Chemistry, TU Wien, Getreidemarkt 9,1060 Vienna, Austria

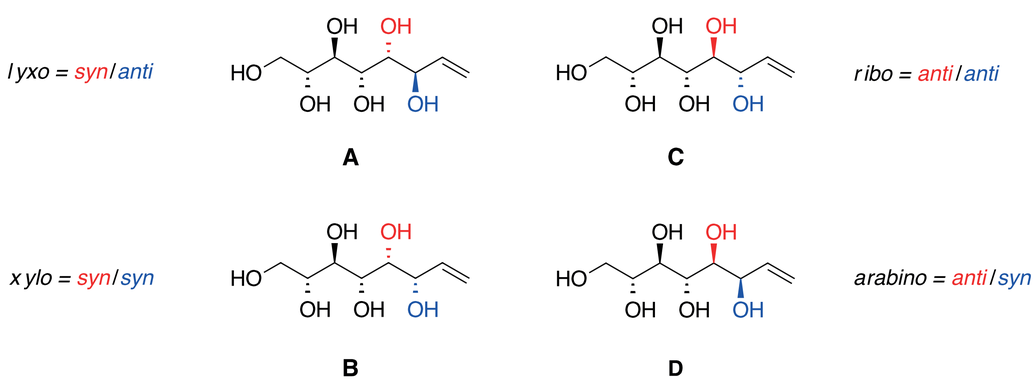
State of the Art: Indium Mediated Acyloxyallylation (IMA) of (Un)protected Aldoses

The indium mediated acyloxyallylation of aldoses was introduced by Madsen *et al.* in 2005 and constitutes a useful tool for the elongation of reducing sugars by two carbon atoms (upon ozonolysis).[1] While the studied transformation can lead to four different diastereomers, the mainly observed isomer was the product with *lyxo*-configuration, representing a *syn*-orientation in respect to the former 2-OH-group and an *anti*-addition to the aldehyde. The latter had been expected[2], however, the predominant *syn*-orientation in regard to the former C2-stereocenter is a specific feature for reducing sugars as starting materials and was exploited in our case study towards bacterial L-*glycero*-D-*manno* heptose at scale.[3] Following up, we engaged in an in-depth methodological investigation of unprotected L-erythrose and D-threose and a protected version thereof which furnished a pronounced diastereodivergence.[4] This study is now expanded to the more generally accessible class of protected sugar aldehydes.



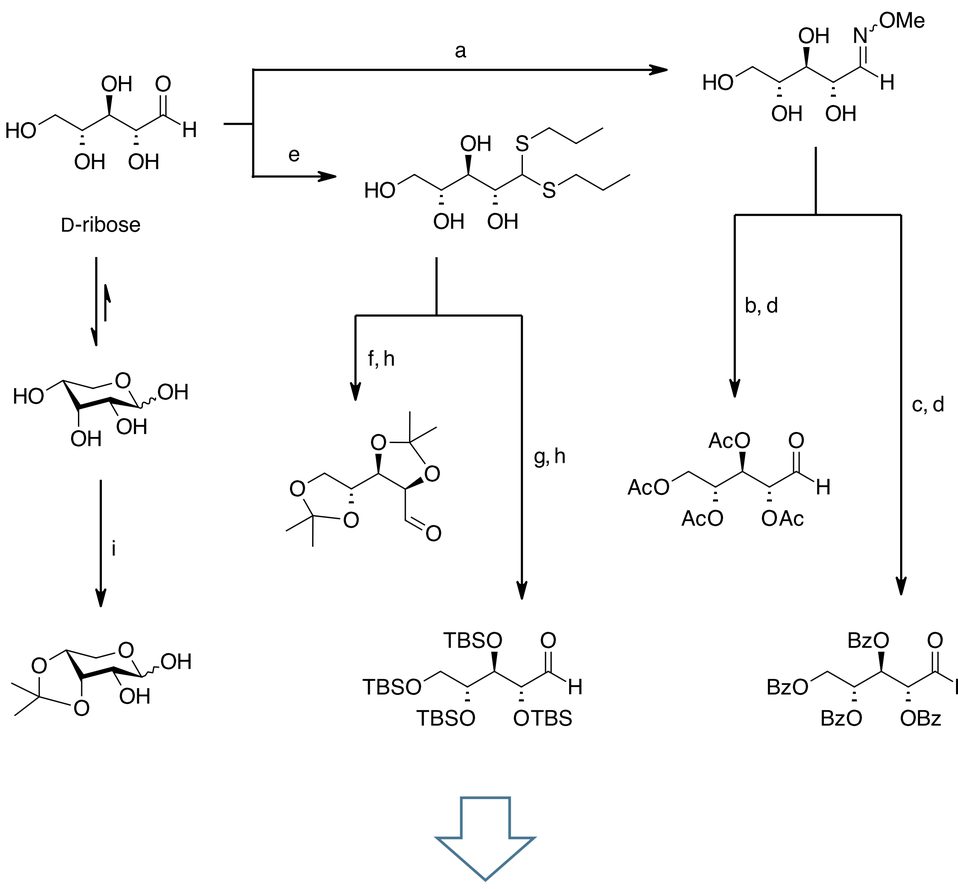
Products of the IMA

Due to the introduction of two new stereocenters during the indium mediated elongation reaction for ribose the following four different diastereomers can be formed:



Synthesis of Protected Sugar Aldehydes

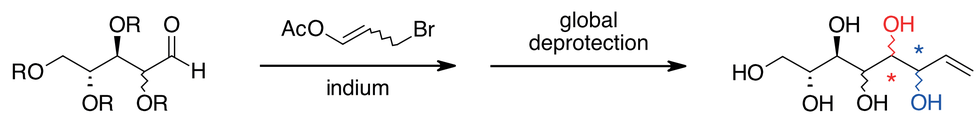
We chose protected sugar aldehydes as substrates as they can be synthesized from all sugars alike and selected ribose as stereochemical pattern for our initial screening. Selected examples were transferred to arabinose later on. The different derivatives were afterwards subjected to the indium mediated acyloxyallylation to investigate the influence of a variety of commonly used protecting groups onto the diastereoselectivity.



Reagents and conditions: (a) $NH_2OMe{\cdot}HCl$, pyridine, rt; (b) Ac_2O, DMAP, pyridine, rt; (c) BzCl, pyridine, rt; (d) O_3, DCM, DMS, -80 °C to rt; (e) C_3H_8S, conc. HCl, 0 °C to rt; (f) DMP, *p*-TsOH, acetone, rt; (g) TBDMS triflate, 2,6-lutidine, dry DCM, 0 °C to rt; (h) I_2, $NaHCO_3$, acetone/water, rt; (i) DMP, Amberlyst® 15(H), DMF, rt.

IMA of Protected Sugar Aldehydes

The goal of the project was the investigation of the diastereomeric ratio of the formed products in respect to the used protecting group. The diastereomeric ratios were determined from the ^{1}H-NMR spectra of the obtained product mixtures upon complete deprotection.



protecting group	starting material	**A** *syn/anti*	**B** *syn/syn*	**C** *anti/anti*	**D** *anti/syn*
-	ribose	**58%**	35%	7%	-
	arabinose	**74%**	23%	3%	-
3,4-acetonide	ribose	**60%**	24%	10%	6%
	arabinose	**58%**	19%	23%	-
2,3; 4,5-acetonide	ribose	14%	16%	**53%**	17%
	arabinose	36%	10%	53%	-
acetate	ribose	14%	15%	**32%**	**39%**
benzoate	ribose	17%	15%	**30%**	**38%**
TBS	ribose	22%	22%	27%	29%

Compound **A** with *lyxo*-configuration (*syn*/*anti*) was found to be the main isomer for D-ribose and also 3,4-*O*-isopropylidene-D-ribose, probably due to the chelation with the OH-group on C2. In contrary, full protection of the reducing sugar led to a shift towards formation of enitols **C** and **D** which show *ribo*- (*anti*/*anti*) and *arabino*-configuration (*anti*/*syn*), respectively. The same trends could be observed when using D-arabinose and arabinose derivatives as starting materials. However, of the used protecting groups only the acetonide protection of D-ribose delivers a reasonable opposing selectivity of the elongation reaction towards a major product with *ribo*-configuration.

Conclusion and Outlook

We have successfully prepared a family of *ribo*-configured protected sugar aldehydes and subjected them to the indium mediated acyloxyallylation. Within our investigation we found diastereodivergence depending on whether the starting materials (2-OH) did bear protecting groups or not. The effect of different protecting groups was examined and a protection *via* acetonides was found to be most suitable to shift the reaction outcome towards an *anti*/*anti*-configured product. In addition, we also applied the indium mediated acyloxyallylation to arabinose and arabinose derivatives to confirm that our findings are independent of the configuration of the starting material. The experiments showed that the trends can be transferred likewise to sugar aldehydes with ‚*threo*'-configuration.

The successful application of the reaction on protected aldoses is encouraging and we hope that our findings help to promote a more frequent consideration of the indium mediated acyloxyallylation as a suitable synthetic solution for a two-carbon elongation within and even beyond the scope of carbohydrate chemistry.

1. Palmelund, A.; Madsen, R., Chain Elongation of Aldoses by Indium-Mediated Coupling with 3-Bromopropenyl Esters, *J. Org. Chem.* 2005, 70, 8248-8251.
2. Lombardo, M.; Morganti, S.; Trombini, C., 3-Bromopropenyl Esters in Organic Synthesis: Indium- and Zinc-Mediated Entries to Alk-1-ene-3,4-diols, *J. Org. Chem.* 2003, 68, 997-1006.
3. Stanetty, C.; Baxendale, I., Large-Scale Synthesis of Crystalline 1,2,3,4,6,7-Hexa-*O*-acetyl-L-*glycero*-alpha-D-*manno*-heptopyranose, *Eur. J. Org. Chem.* 2015, 2718-2726.
4. Draskovits, M.; Stanetty, C.; Baxendale, I.; Mihovilovic, M., Indium- and Zinc-mediated Acyloxyallylation of Protected and Unprotected Aldotetroses, *J. Org. Chem.* 2018, 83, 2647-2659.