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Expedient and Versatile Formation of Novel Amino-deoxy-ketoheptuloses

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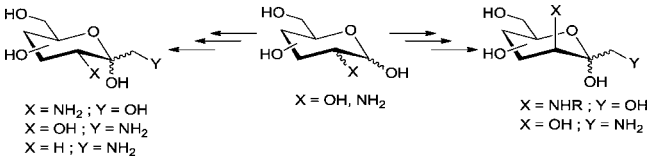
ABSTRACT



Novel monoketoheptuloses have been synthesized employing an amination step in a *pre*- and/or *post*-C1 chain elongation using a Petasis reagent by starting from aldohexoses or aldohexosamines. A series of *gluco* and *manno* configured 1-/3-deoxy-1-/3-amino-ketohept-2-uloses could be obtained.

Deoxy sugars and deoxy aminosugars are ubiquitously present in plants, fungi, and bacteria. Further, they constitute structurally relevant parts of the *LPS* lipopolysaccharides as well as *EPS* extracellular polysaccharides and are found as secondary metabolites displaying antibiotic activity. Their biosynthesis is mainly by transamination, and under physiological conditions ionized amines are responsible for their pharmacokinetic properties by inducing inter- and intramolecular electrostatic interactions. The ability of aminosugars to display bacteriocidal activity has been synthetically exploited and resulted in potent amino glycose antibiotics and antiviral agents.[1,2] Amino glycosides are preferably used to combat infections due to Gram-negative bacteria, such as e.g. *Pseudomonas*, *Acinetobacter*, and *Enterobacter* species.[3,4] Their mode of action is concentration dependent and primarily based on impairing bacterial protein synthesis through binding to prokaryotic ribosomes. However, new bacteriocidal derivatives are desired due to growing resistance effects by aminoglycoside modifying enzymes (AME, ~60 known) expressed by resistant bacteria.[5]

The present work describes syntheses of novel amino deoxy-ketoheptuloses to be considered as a novel class of potent bacteriocidal and antiviral aminoglycoside targets. Recently, we reported on efficient syntheses of rare ketoheptuloses and regioisomeric fluorinated ^{19}F- ketoheptuloses.[6−8] The use of methylene exoglycals allows for versatile access to regiospecific positions and facile introduction of various functionalities.

Our focus was on the synthesis of 1- and 3-amino-D-*gluco*/*manno*-hept-2-uloses, since primary and secondary mono- and diamino functions are common structural themes in aminoglycosides such as kanamycin, tobramycin, and gentamicin.[4]

Starting from D-glucose the exocyclic glycal **1** was accessible in seven steps (Scheme 1).[6−8] Subsequent Sharpless bishydroxylation[9−12] to give **2**, and azide insertion to **3**,[13] led after hydrogenolysis to the desired 1-amino-keto-hept-2-ulose **4**.

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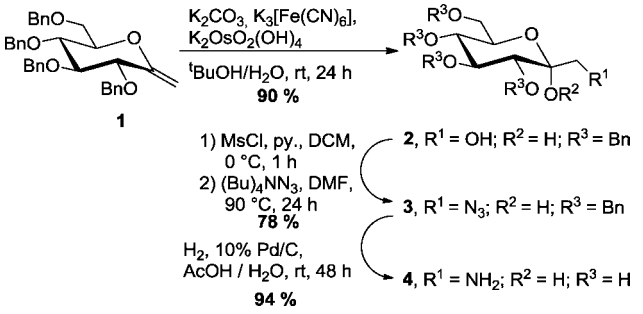
Scheme 1. *N*-Insertion *Post-C1 Elongation* from Aldohexoses: Synthesis of 1-Deoxy-1-amino-D-*gluco*-hept-2-ulose **4**

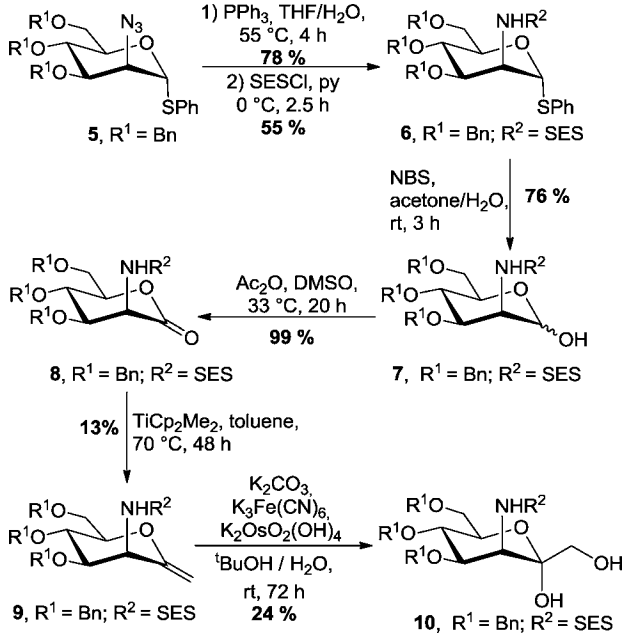


It was shown that stereoselective β-addition to 1-C-nitro-glycals allows for syntheses of 3-azido-keto-heptuloses. However access to 1-C-nitro-glycals, handling, and overall reaction efficiency were disadvantageous.[14]

Synthesis of 3-amino-ketoheptuloses was initially performed by *N*-insertion prior to C1 elongation, using azide **5**, which was obtained in six steps from methyl α-D-glucopyranoside.[15−19] Its reduction and protection by 2-trimethylsilylethanesulfonyl (SES)[20] afforded **6**. By using pyridine as both solvent and base[21] the yield of this step could be increased to 55%. Hydrolysis of **6** with NBS in aqueous acetone to give **7**, followed by oxidation with acetic anhydride and DMSO,[22] afforded lactone **8**. Apparently, due to interactions between the titanium reagent and the amine function,[23] the methylenation of **8** using Petasis reagent gave **9** in low yields. Further bishydroxylation of **9** afforded the amino derivative **10** (Scheme 2). The syntheses of 3-amino-3-deoxy-D-*gluco*/*manno*-hept-2-uloses were therefore attempted in a corresponding fashion by introducing the azido functionality at a later stage starting from the tribenzyl orthoesters **11** and **12**, which can be obtained in five steps from D-mannose or D-glucose, respectively (Scheme 3).

Ring opening of the orthoesters **11** and **12** in acetic acid and water[24] afforded the hemiacetals **13** and **14**. Further, oxidation to the lactones **15** and **16** and methylenation with

Scheme 2. *N*-Insertion *prior to C1 Elongation* from Aldohexoses: Synthesis of 3-Deoxy-3-amino-D-*manno*-heptulose Derivative **10**



Petasis reagent gave the 3-*O*-acetylated exocyclic glycals **17** and **18**, respectively. After deacetylation under Zemplén conditions[25,26] and subsequent bishydroxylation 4,5,7-tri-*O*-benzyl-*manno*-hept-2-ulopyranose **19** and 4,5,7-tri-*O*-benzyl-*gluco*-hept-2-ulopyranose **20** were obtained. Then **19** and **20** were transformed into the 1,2-isopropylidene derivatives **21** and **22**. These were then transferred into their corresponding 3-azido derivatives, using nucleophilic substitution with triflic anhydride and tetrabutylammonium azide. The configuration at C-3 was inverted during this step to give the azido derivatives **23** and **24**. In the case of the *manno* derivative **21** substitution gave the *gluco* component **23** and the byproduct **25** due to elimination. Correspondingly, the *gluco* derivative **22** was converted into the 3-azido *manno* derivative **24**, which by selective hydrogenation in pyridine gave the *manno* amine **26**. However, deacetylation of exocyclic glucal **17** followed by mesylation to **27** and subsequent substitution by azide led to the unexpected rearrangement product 2,6-anhydro-1-azido-4,5,7-tri-*O*-benzyl-1,3-dideoxy-D-*arabino*-hept-2-enitol **28** (Scheme 4). Hydrolysis of **28** in trifluoroacetic acid and water[27] afforded 1-azido-4,5,7-tri-*O*-benzyl-1,3-dideoxy-α-D-*arabino*-hept-2-ulopyranose **29**, which could be easily hydrogenated to give amine **30**, the 1-amino derivative of the natural product Kamusol found in fungus *Aspergillus sulphureus*.[28,29]

Sharpless dihydroxylation of **28** gave 1-azido-4,5,7-tri-*O*-benzyl-1-deoxy-α-D-*gluco*-hept-2-ulopyranose **31**. Only the

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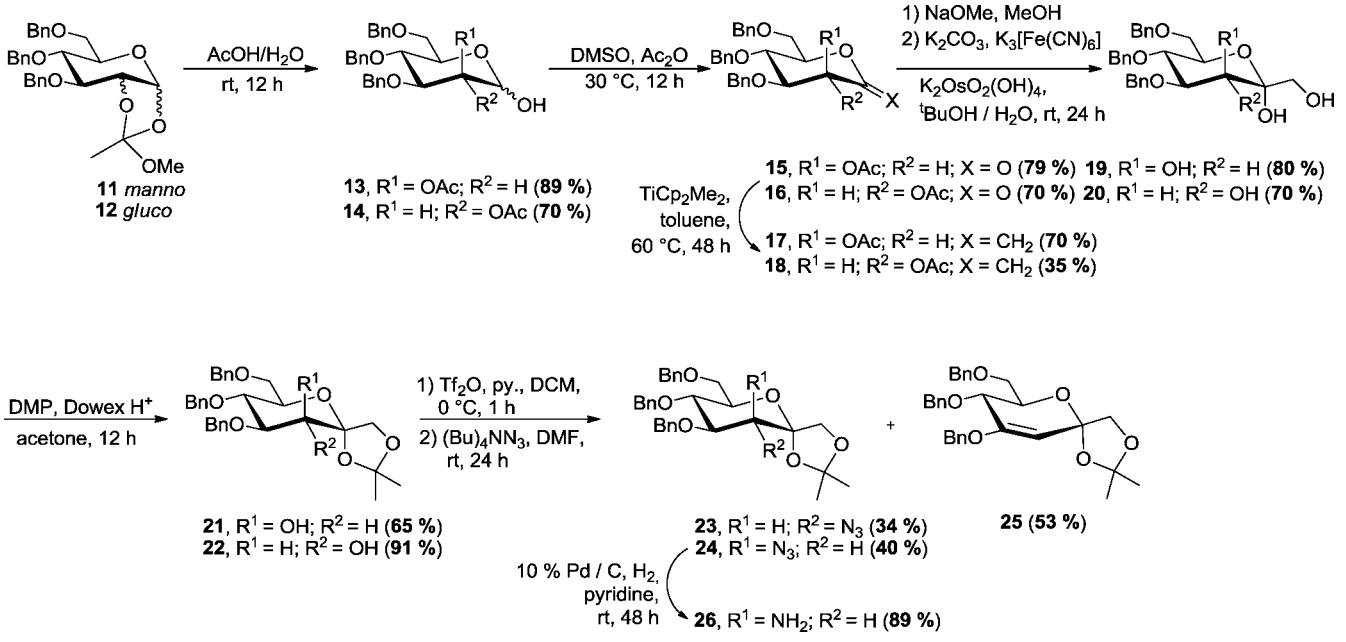
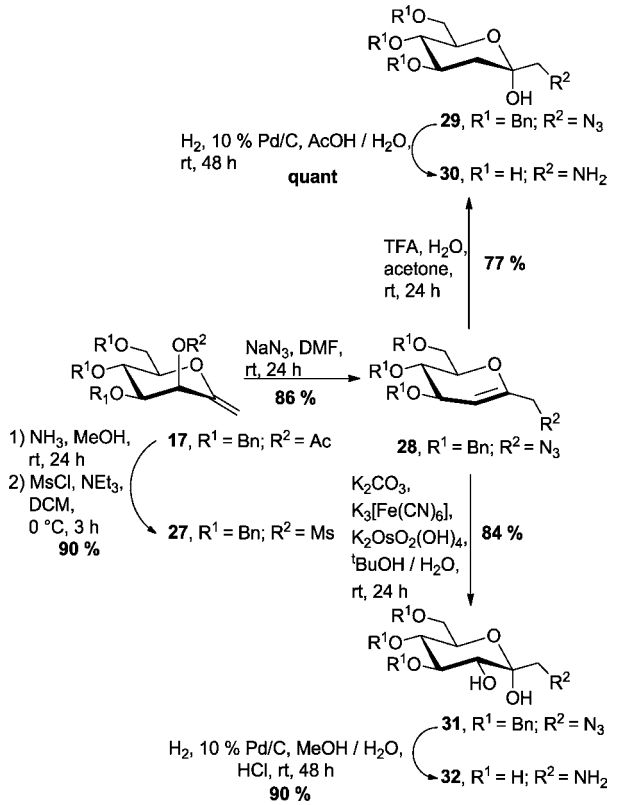
Scheme 3. Syntheses of 3-Amino-3-deoxy-D-*gluco*/*manno*-hept-2-uloses



Scheme 4. Synthesis and Functionalization of 1-Azido-4,5,7-tri-*O*-benzyl-1-deoxy-α-D-*gluco*-2-ulopyranose **31**



α-anomer of **31** was isolated as confirmed by NOESY experiments. Subsequent hydrogenation gave 1-amino-1-deoxy-α-D-*gluco*-hept-2-ulopyranose hydrochloride **32** in 90% yield.

Since sulfonamide protection for the 3-amino-D-*manno*-hept-2-ulose series was unsuitable due to complexation with Petasis reagent, a suitable protecting group for the 2-amino group had to be found starting from the 2-amino-2-deoxy-hexoses (Scheme 2). The phthalimido protection was chosen. However, this was considered risky since the two carbonyl groups could well be methylenated. The 3-phthalimido exocyclic enol ether **35** was nevertheless obtained from the known protected D-glucosamine derivative **33**[30] by oxidation[31] to lactone **34** and subsequent olefination (Scheme 5). Following Upjohn dihydroxylation[12,32,33] the diol **36** was isolated in 79% yield. The α-configuration was confirmed by NOESY experiments. In the final step, **36** was deprotected and hydrogenated to give the desired amino compound **37**. In addition acetylation of amine **38**, which was formed from **35** by cleavage of phthalimide, led to the *N*-acetyl derivate **39**. This compound was dihydroxylated to give 3-acetamido-4,5,7-tri-*O*-benzyl-3-deoxy-α-D-*gluco*-hept-2-ulopyranose **40** in 88% yield. Again, according to NOESY experiments only the α-anomer was isolated. Finally, hydrogenation of **40** afforded 3-*N*-acetyl-D-*gluco*-heptulose **41** in 97% yield (Scheme 6).

In summary, a variety of versatile synthetic routes to complex amino-deoxy-D-heptuloses and their intermediates

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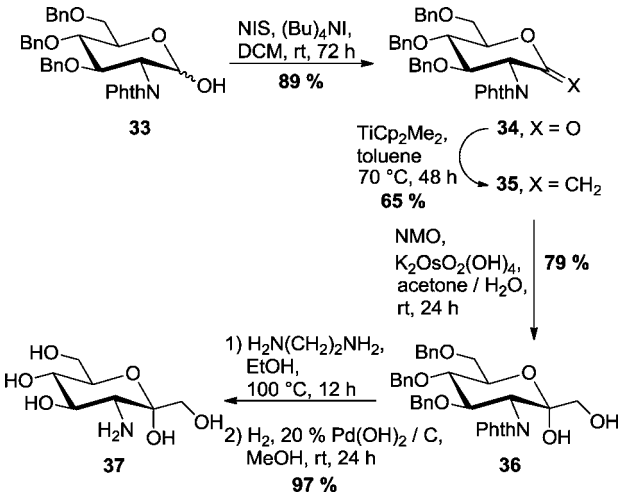
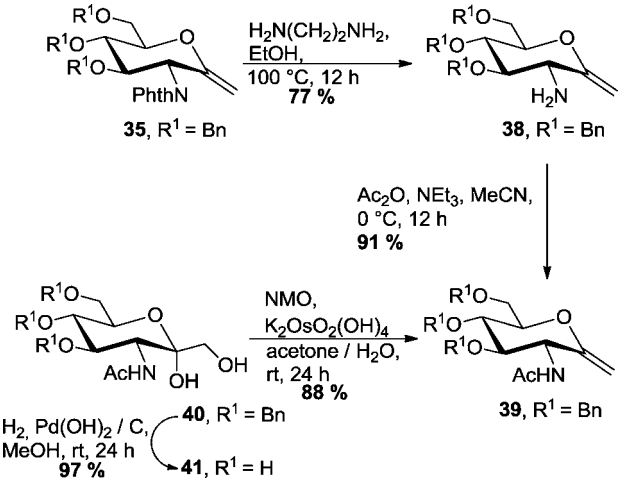
Scheme 5. Alternative Synthesis of 3-Amino-3-deoxy-D-*gluco*-hept-2-ulose **37**



Scheme 6. Synthesis of 3-*N*-Acetyl-D-*gluco*-heptulose **41**



have been established. Starting from monosaccharides, a C-1 extension via heptenitols allows for regiospecific transformations. The introduction of amine was achieved by the conversion of the hydroxyl group into a suitable leaving group followed by nucleophilic attack by azide. Unexpectedly, nucleophilic substitution of **27** led to the rearrangement product **28**, which was easily converted into the 1-amino derivative of kamusol. Additionally, Sharpless dihydroxylation of **28** with subsequent hydrogenolysis gave the 1-amino derivative of D-*gluco*-heptulose.

In conclusion, these versatile synthetic approaches allow access to a variety of amino-deoxy-ketoheptuloses. These represent useful structures for formation of novel amino glycoside targets which will be reported in due course.

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Supporting Information Available. Experimental procedures for preparation of all novel compounds with full spectroscopic data. This material is free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.