Expedient and Versatile Formation of Novel Amino-deoxy-ketoheptuloses

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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 ¹⁹F- 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-Dgluco/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 bishydroxylation⁹⁻¹² to give **2**, and azide insertion to **3**,¹³ led after hydrogenolysis to the desired 1-amino-keto-hept-2-ulose **4**.

(12) Noort, D.; Veenemann, G. H.; Boons, G. P. H.; van der Marel, G. A.; Mulder, G. J.; van Boom, J. H. *Synlett* **1990**, *4*, 205–206.

⁽¹⁾ Rai, R.; McAlexander, I.; Chang, C. W.-T. Org. Prep. Proced. Int. 2005, 37, 337–375.

⁽²⁾ Brimacombe, J. S. Angew. Chem., Int. Ed. 1971, 10, 236-248.

⁽³⁾ Stead, D. A. J. Chromatogr., B 2000, 747, 69–93.

⁽⁴⁾ Shahid, M. Anti-Infective Agents Med. Chem. 2007, 6, 107-117.

⁽⁵⁾ WHO 2011; Antimcrobial resistance. Fact sheet No. 194.

⁽⁶⁾ Waschke, D.; Thimm, J.; Thiem *Org. Lett.* 2011, *13*, 3628–3631.
(7) Leshch, Y.; Waschke, D.; Thimm, J.; Thiem, J. *Synthesis* 2011,

<sup>3871–3877.
(8)</sup> Waschke, D.; Thimm, J.; Leshch, Y.; Thiem, J.; Louchami, K.;

⁽⁸⁾ Waschke, D.; Thimm, J.; Lesnen, Y.; Thiem, J.; Louchami, K.; Malaisse W. Seven Carbon (C-7) Sugars Derivatives and Their Use. WO 2012016935 (A1) February. 09, 2012.

⁽⁹⁾ Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. J. Am. Chem. Soc. **1988**, 110, 1968–1970.

⁽¹⁰⁾ Kolb, H. C.; van Nieuwenhze, M. S.; Sharpless, K. B. Chem. Rev. 1994, 94, 2483–2547.

⁽¹¹⁾ Minato, M.; Yamamoto, K.; Tsuji, J. J. Org. Chem. 1990, 55, 766–768.

⁽¹³⁾ Lay, L.; Nicotra, F.; Panza, L.; Russo, G. Synlett 1995, 167–168.

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-Cnitro-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 water²⁴ afforded the hemiacetals 13 and 14. Further, oxidation to the lactones 15 and 16 and methylenation with

- (18) Litjens, R. E. J. N.; Leeuwenburgh, M. A.; Van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **2001**, *42*, 8693–8696.
- (19) Girard, C.; Miramon, M.-L.; de Solminihac, T.; Herscovici J. Carbohydr. Res. 2002, 337, 1796–1774.
- (20) Weinreb, S. M.; Demko, D. M.; Lessen, T. A. *Tetrahedron Lett.* **1986**, *27*, 2099–2102.
 - (21) Parker, K. A.; Mindt, T. L. Org. Lett. 2002, 4, 4265-4268
 - (22) Zhang, F.; Vasella, A. Carbohydr. Res. 2007, 342, 2546–2556.

- (24) Yamazaki, F.; Sato, S.; Nukada, T.; Ito, Y.; Ogawa, T. Carbohydr. Res. 1990, 201 (1), 31–50.
- (25) Zemplén, G. Ber. Dtsch. Chem. Ges. 1926, 59B, 1254-1266.

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-Obenzyl-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 water²⁷ afforded 1-azido-4,5,7-tri-O-benzyl-1,3dideoxy-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

⁽¹⁴⁾ Baumberger, F.; Beer, D.; Christen, M.; Prewo, R.; Vasella, A. *Helv. Chim. Acta* **1986**, *69*, 1191–1204.

⁽¹⁵⁾ Demchenko, A. V.; Pornsuriyasak, P.; de Meo, C. J. Chem. Educ. 2006, 83, 782–784.

⁽¹⁶⁾ Knapp, S.; Kukkola, P. J.; Sharma, S.; Murali Dhar, T. G.; Naughton, A. B. J. *J. Org. Chem.* **1990**, *55*, 5700–5710.

⁽¹⁷⁾ Popelová, A.; Kefurt, K.; Hlavácková, M.; Moravcová, J. Carbohydr. Res. 2005, 340, 161–166.

⁽²³⁾ Lensink, C. J. Organomet. Chem. 1998, 553, 387-392.

⁽²⁶⁾ Zemplén, G.; Pascu, E. Ber. Dtsch. Chem. Ges. 1929, 62B, 1613-1614.

⁽²⁷⁾ Suda, M.; Fukushima, A. *Tetrahedron Lett.* 1981, *22*, 759–762.
(28) Kamal, A.; Haider, Y.; Arkhtar, R.; Qureshi, A. A. *Pakistan J. Sci. Ind. Res* 1971, *14*, 63–67.

⁽²⁹⁾ Kamal, A.; Haider, Y.; Qureshi, A. A. Pakistan J. Sci. Ind. Res. 1971, 14, 68–70.

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-mannohept-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-deoxyhexoses (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 oxidation³¹ 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-a-D-glucohept-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-glucoheptulose 41 in 97% yield (Scheme 6).

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

⁽³⁰⁾ Chiara, J. L.; García, A.; Cristóbal-Lumbroso, G. J. Org. Chem. **2005**, 70, 4142–4151.

⁽³¹⁾ Hanessian, S.; Wong, D. H.-C.; Therien, M. Synthesis **1981**, 394-396.

⁽³²⁾ van Rheen, V.; Kelly, R. C.; Cha, D. Y. Tetrahedron Lett. 1976, 23, 1973–1976.

⁽³³⁾ Li, X.; Takahashi, H.; Ohtake, H.; Shiro, M.; Ikegami, S. *Tetrahedron* 2001, *57*, 8053–8066.

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



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



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.