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Highly Efficient Synthesis of Ketoheptoses

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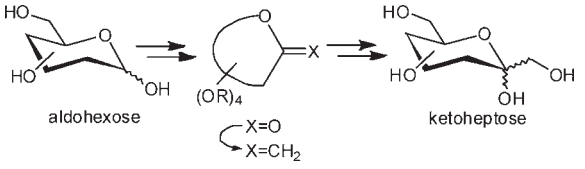
ABSTRACT



A reliable, facile, high overall yielding and diastereoselective synthesis of ketoheptoses was developed and applied for preparation of the two most diabetogenic ketoheptoses as well as in a modified version for the synthesis of kamusol.

Ketoheptoses are rare seven carbon sugars with a number of interesting pharmacological properties. Previously it was demonstrated that injection of D-*manno*-heptulose (**1**) leads to a serious increase in blood glucose levels by inhibition of the glucose metabolism *in vitro* and *in vivo*.[1a−d] In a survey of eight ketoheptoses only D-*manno*-heptulose (**1**) and D-*gluco*-heptulose (**2**) showed significant diabetogenic properties.[2] Due to their ability to increase blood glucose levels and inhibit glucose metabolism, they are of particular pharmacological interest as potential therapeutics for hypoglycemia[3] or cancer.[4,5]

D-*manno*-Heptulose (**1**) was first extracted and obtained in rather low yields from avocado in 1917.[6] A number of earlier synthetic approaches focusing on the synthesis of **1** were developed. These involved the Lobry−de Bruyn transformation,[7a] condensation of D-arabinose with 2-nitroethanolate,[7b] the oxidation of volemitol,[7c] and a chain elongation using a Grignard reaction,[7d] by Wittig reaction[7e] or iodomethyllithium.[7f] Synthesis of a wider range of ketoheptoses was achieved by Kiliani−Fischer synthesis[2] or aldol condensation.[7g] All of these multistep syntheses resulted in the formation of diastereomeric mixtures with yields typically below 25%.

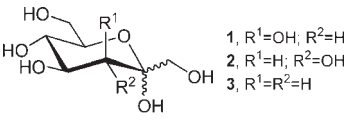


Figure 1. Synthesized ketoheptoses **1**−**3**.

A novel and universally applicable synthetic access to ketoheptoses starting from the corresponding aldohexose is reported. This synthetic route was exploited for the preparation of the two most diabetogenic ketoheptoses, D-*manno*-heptulose (**1**) and D-*gluco*-heptulose (**2**) (Figure 1). Preparation involves seven synthetic steps without any epimerization or time-consuming purification (Schemes 1, 2). Using this novel method, ketoheptoses were obtained in overall yields of 56% (**1** and **2**).

By a slight modification of this synthetic route, the natural product kamusol (**3**), one of several metabolites from *Aspergillus sulphureus*,[8a,b] was prepared and thus the

(1) (a) Roe, J. H.; Hudson, C. S. *J. Biol. Chem.* **1936**, *112*, 443–449. (b) Simon, E.; Kraicer, P. F. *Arch. Biochem. Biophys.* **1957**, *69*, 592–601. (c) Paulsen, E. P.; Richenderfer, L.; Winick, P. *Nature* **1967**, *214*, 276–277. (d) Coore, H. G.; Randle, P. J. *Biochem. J.* **1964**, *91*, 56–59.

(2) Nelkin, W. *Acta Physiol. Hung.* **1970**, *38*, 401–404.

(3) Paulsen, E. P. *Ann. N.Y. Acad. Sci.* **1968**, *150*, 455–456.

(4) Board, M.; Colquhoun, A.; Newsholme, E. A. *Cancer Res.* **1995**, *55*, 3278–3285.

(5) Malaisse, W. J. *Diabetologia* **2001**, *44*, 393–406.

(6) La Forge, F. B. *J. Biol. Chem.* **1917**, *28*, 511–522.

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(8) (a) Kamal, A.; Haider, Y.; Arkhtar, R.; Qureshi, A. A. *Pakistan J. Sci. Ind. Res.* **1971**, *14*, 63–67. (b) Kamal, A.; Haider, Y.; Qureshi, A. A. *Pakistan J. Sci. Ind. Res.* **1971**, *14*, 68–70.

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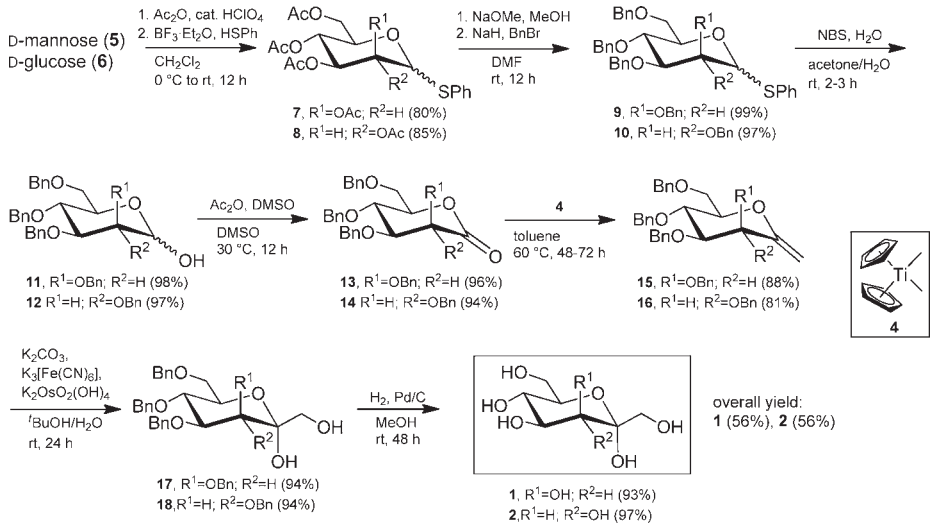
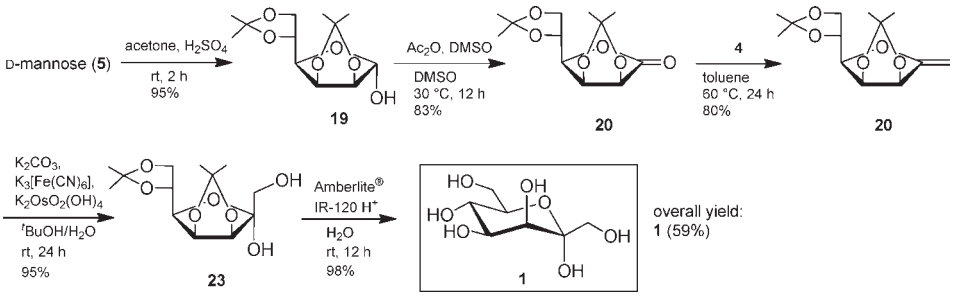
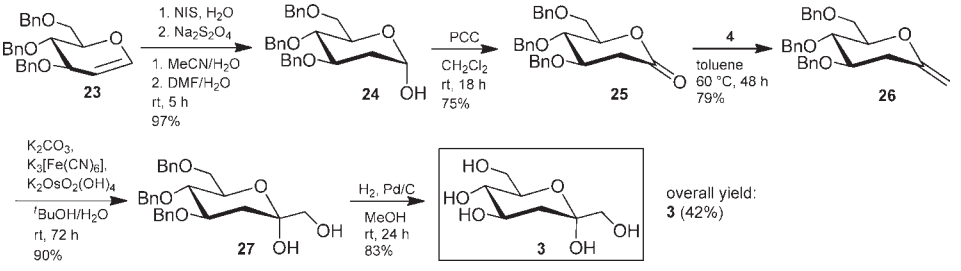
Scheme 1. Synthesis of Ketoheptoses **1** and **2**



Scheme 2. Alternative Route to D-*manno*-Heptulose (**1**)



Scheme 3. Synthesis of Kamusol (**3**)



only existing synthetic access[9] (reported 10%) to **3** significantly improved [42% in a five step synthesis (Scheme 3)].

The key step of the synthetic route is the methylenation of a sugar lactone to an exocyclic enol ether using the Petasis reagent (**4**).[10,11a,11b] Compared to alternative

(10) Example reaction protocol: Under argon and exclusion of light, compound **13** (5.28 mmol) was dissolved in anhydrous toluene (80 mL) and compound **4** (11.1 mmol) was added. The reaction mixture was heated to 60 °C and stirred for 3 d in the dark. Then the solvent was removed in vacuum, and the crude product was purified by column chromatography (petroleum ether/ethyl acetate 15:1) to obtain **15** (4.66 mmol, 88%) as a slightly yellow oil.

(11) (a) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392–6394. (b) Csuk, R.; Glänzer, B. I. *Tetrahedron* **1991**, *47*, 1655–1664.

(12) Clauss, K.; Bestian, H. *Liebigs Ann.* **1962**, *654*, 8–19.

(13) (a) Zemplén, G. *Ber. Dtsch. Chem. Ges.* **1926**, *59B*, 1254–1266. (b) Zemplén, G.; Pacsu, E. *Ber. Dtsch. Chem. Ges.* **1929**, *62B*, 1613–1614.

methylenating agents such as Tebbe's reagent and Grubbs' titanacyclobutanes, the Petasis reagent (**4**) has a number of advantages. Easily accessible from titanocene dichloride[12] and much easier to handle due to lower sensitivity to moisture and air, it also tolerates higher reaction temperatures and this results in enhanced yields.

Typically, the synthetic route starts from an aldohexose to reach the corresponding ketoheptose within seven steps. D-Glucose (**6**) and D-mannose (**5**) were peracetylated and glycosylated in a one-pot procedure to give phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside (**7**, 80%) and phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**8**, 85%), and both were purified by crystallization. Following deacetylation under Zemplén conditions[13a,b] by subsequent perbenzylation, phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-mannopyranoside (**9**, 97%) and phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (**10**, 95%) were obtained (full synthetic scheme in the Supporting Information). Then, thioglycosides **9** and **10** were hydrolyzed using NIS in water/acetone to give the hemiacetals 2,3,4,6-tetra-*O*-benzyl-D-mannopyranose (**11**, 98%) and 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**12**, 97%).[14] Afterward these were oxidized to the related lactones 2,3,4,6-tetra-*O*-benzyl-D-mannono-1,5-lactone (**13**, 96%) and 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone (**14**, 94%).[15] Starting from **5** and **6** the lactones could be obtained in four steps with overall yields of 73% (**13**) and 77% (**14**).

By methylenation of **13** and **14** using the Petasis reagent **4** the exocyclic enol ethers 2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-mannohept-1-enitol (**15,** 88%) and 2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-glucohept-1-enitol **16** (81%) could be obtained.

The following Sharpless dihydroxylation gave 3,4,5,7-tetra-*O*-benzyl-α-D-*glycero*-D-*lyxo*-hept-2-ulopyranose (**17**, 94%) and 3,4,5,7-tetra-*O*-benzyl-α-D-*glycero*-D-*xylo*-hept-2-ulopyranose (**18**, 94%).[16a−c] Interestingly only the α-configured products (confirmed by NOESY experiments) were isolated from the reaction mixture in both cases. As known from literature neither **1** nor **2** shows mutarotation,[2] and a corresponding effect seems to be true for **17** and **18**.

In the final step, **17** and **18** were hydrogenated to give the desired ketoheptoses **1** (93%) and **2** (97%). Again only the α-anomers were isolated after chromatography in both cases. NMR spectra recorded in aqueous solution showed the presence of a single diastereomer for **1** and **2**, and no traces of furanoses were detected. Additionally, the optical rotation in aqueous solution remained constant for two days. The α-configuration of **1** was also confirmed by X-ray structure (Figure 2).

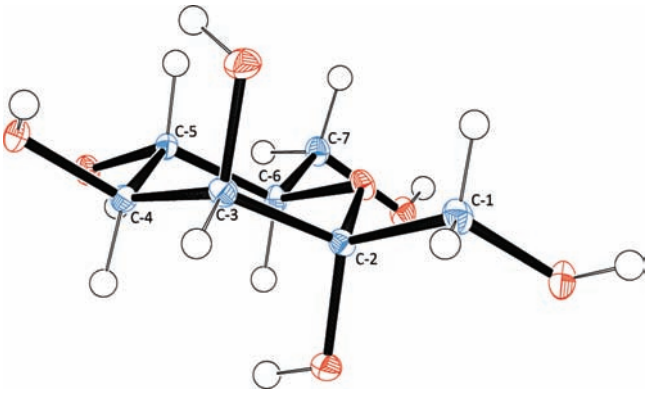


Figure 2. X-ray structure of **1**; red (O); blue (C); white (H).

By application of this synthetic route, the ketoheptoses **1** and **2** were obtained in total yields of 56% (**1**) and 56% (**2**) starting from **5** and **6**. As none of the reaction steps involves epimerization or the formation of significant amounts of byproducts, workup and purification are usually easy and done by crystallization or flash chromatography. All reactions could be performed in scale up to 10 g and gave reproducibly good yields.

Since D-mannose (**5**) can form a suitable diisopropylidene derivative, an alternative route for the preparation of **1** was developed. After preparation of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (**19**, 95%)[17] only the α-anomer was isolated, purified by crystallization. The α-configuration was also confirmed by X-ray structure. The following oxidation gave 2,3:5,6-di-*O*-isopropylidene-α-D-mannono-1,4-lactone (**20**, 83%) after crystallization.

By methylenation of **20**, 2,5-anhydro-1-deoxy-3,4:6,7-di-*O*-isopropylidene-D-mannohept-1-enitol (**21**, 80%) was obtained in good yield.

This compound was dihydroxylated to give 3,4:6,7-di-*O*-isopropylidene-α-D-*glycero*-D-*lyxo*-hept-2-ulofuranose (**22**, 95%), and again only the α-anomer (NOESY experiments) was isolated. Cleavage of the acetals was performed in aqueous solution using Amberlite IR-120 H^+ to give **1** (98%).

In comparison to the first method (Scheme 1), this furanose route is shorter and the workup is less elaborate, since the first two compounds can be easily crystallized even in large scale, and this results in a higher overall yield of **1** (59%).

The presented synthetic route was modified for the preparation of the natural product kamusol (**3**), which was isolated as one of several metabolites from the fungus *Aspergillus sulphureus*.[8a,b] Starting with 3,4,6-tri-*O*-benzyl-D-glucal (**23**), which in turn is easily prepared from **6** (Scheme 3), first the preparation of 3,4,6-

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(15) Albright, J. D.; Goldman, L. *J. Am. Chem. Soc.* **1965**, *87*, 4214–4216.
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tri-*O*-benzyl-2-deoxy-α-D-glucose (**24**, 97%) in a simple one-pot procedure was performed.[18] The standard oxidation procedure using Ac_2O and DMSO was unsuitable for the preparation of 3,4,6-tri-*O*-benzyl-2-deoxy-D-glucono-1,5-lactone (**25**) since the acetate anion formed during the reaction progress acts as a base and promotes deprotonation of the C−H acidic protons at C-2 leading to the formation of significant amounts of the α,β-unsaturated lactone. As a consequence the less basic PCC was used for oxidation of **24** to give **25** in a 75% yield.

Methylenation of **25** with **4** led to 2,6-anhydro-1,3-dideoxy-4,5,7-tri-*O*-benzyl-D-glucohept-1-enitol (**26**, 79%). Further, the exocyclic enol ether **26** was dihydroxylated to give 3-deoxy-4,5,7-tri-*O*-benzyl-α-D-*glycero*-D-*xylo*-hept-2-ulo-pyranose (**27**) in 90% yield. Once more only the α-anomer of **27** was isolated as confirmed by NOESY experiments. In the final step compound **27** was hydrogenated to give **3** in 81% yield.

This method allowed the preparation of **3** starting from **23** in a total of five steps and an overall yield of 42%. The previously reported synthesis of **3** started from 2,3-di-*O*-formyl-D-erythrose and also required five steps;[9] however, in only 10% yield overall yield a diastereomeric mixture could be prepared.

In conclusion, a versatile synthetic access to ketoheptoses was established. Starting from an aldohexose, the corresponding ketoheptose can be reached within seven steps usually with high yields for the individual steps. The utility of this method was tested by the preparation of D-*manno*-heptulose (**1**) and D-*gluco*-heptulose (**2**) from D-mannose (**5**) and D-glucose (**6**). Overall yields for the preparation of **1** and **2** (both 56%) were much higher than those reported in previous work.[7a−f] Another advantage of the reported method is the versatility. In contrast to earlier studies, which focused mainly on the synthesis of **1**, a variety of ketoheptoses can be prepared.

Furthermore the synthetic route was modified for the synthesis of the natural product kamusol (**3**), and the reported synthesis[9] of **3** improved in terms of stereoselectivity and yield, enhancing the previously reported overall yield of 10% in a five step synthesis to 42%.

The presented synthetic route additionally allows access to novel ketoheptose derivatives. Further derivatization of **1**, **2**, and **3** as well as future applications are under study and will be reported in due course.

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Supporting Information Available. General experimental procedure for preparation of **1**, **2**, and **3** with full spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.