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1,5-α-D-Mannoseptanosides, Ring-Size Isomers That Are Impervious to α-Mannosidase-Catalyzed Hydrolysis

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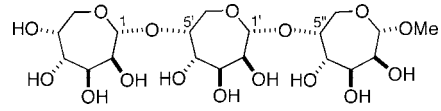
ABSTRACT



1,5-D-Mannoseptanosyl di- and trisaccharide ring-size isomers of the corresponding mannopyranosyl oligosaccharides have been prepared. Remarkably, these compounds show no inhibition of the α-mannosidase-catalyzed hydrolysis of *p*-nitrophenyl-α-D-mannopyranoside.

Seven-membered ring (septanose) oligosaccharides are unknown in nature, as the thermodynamic preference of five- and six-membered furanose and pyranose rings dominate the structural motifs of natural sugars and their glycoconjugates.[1] However, seven-membered ring sugars can be produced using methods that utilize selective protective group transformations of secondary alcohols of hexose sugars[2,3] or by rearrangements of appropriately protected furanoside derivatives.[4] Peczuh and co-workers have recently provided considerable insights into other methods for preparation of several stereoisomers of septanose carbohydrates.[5]

Our laboratory has initiated a program to explore the chemical, physical, and biological properties of the seven-membered ring isomers of naturally occurring carbohydrate structures, with particular emphasis on septanosyl isomers of D-manno and D-gluco stereochemistry. Notwithstanding the differences in hydroxyl positions for septanosides, we anticipate that the biocompatibility of these substrates will be quite high, as potential enzymatic or non-enzymatic glycosidic hydrolysis will yield the biologically innocuous hexose sugar. Furthermore, the absence of primary hydroxyl groups and conformational differences for the seven-membered ring isomer may result in novel enzymatic reactivity or stability, which may be harnessed in applications of septanose oligosaccharides as biomaterials or components for drug delivery.[6]

Our interest in this area began in 2004 when we reported the synthesis of septanose (seven-membered ring) glycals via alkynol cycloisomerization.[7] The regioselectivity for septanose glycal formation was dependent on a cyclic protective group between adjacent alcohols (acetonide or benzylidene acetal), but each diastereomer favored the septanose glycal. Our initial synthesis of the alkynyl diol substrates involved a one-carbon homologation of aldehyde

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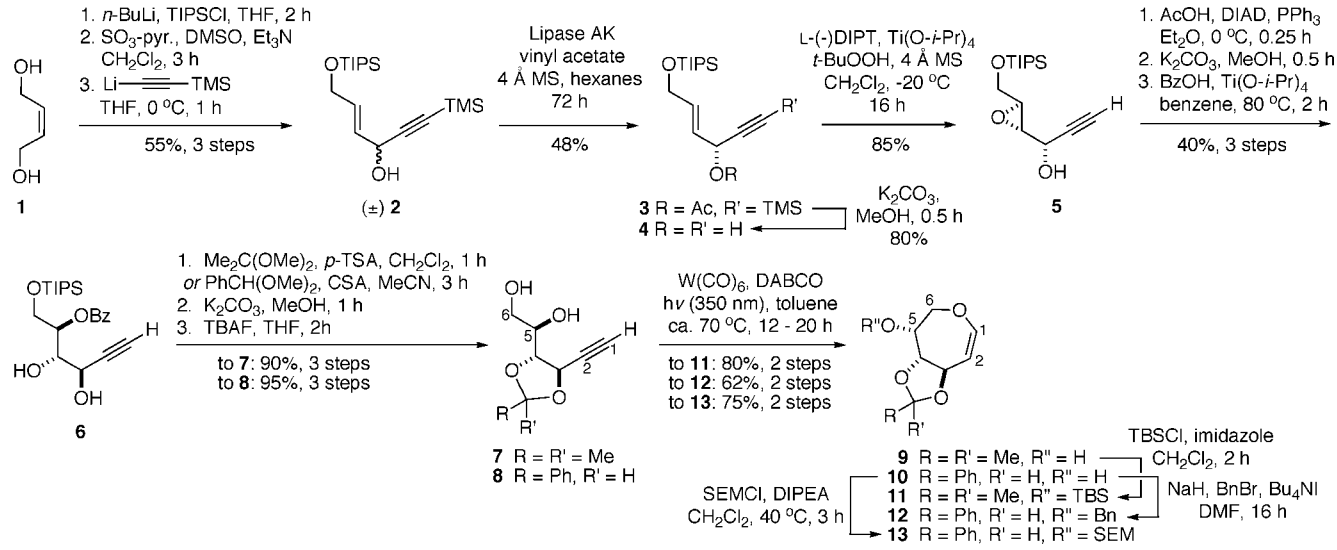
Scheme 1. Synthesis of D-Arabinoseptanose Glycals **9**−**13**



to alkyne[8] of an appropriately protected pentose. Unfortunately, preparation of the alkynol substrate for the D-arabino glycal (precursor to D-manno- and D-glucoseptanosides) was much more difficult than for the other three diastereomers. We now report asymmetric syntheses of the alkynyl diols **7** and **8** that provide gram-scale quantities of the D-arabinoseptanose glycals, while offering flexibility in protective group patterns. Key features of this synthesis include the lipase-catalyzed enzymatic resolution of (±)-**2** (Scheme 1),[9] which was more easily conducted on multigram scale than enantioselective alkynylation[10] or Sharpless kinetic resolution of (±)-**2**.[11] From compound **4**, the chiral secondary alcohols were introduced with Sharpless epoxidation[12] to **5**, followed by Mitsunobu inversion[13] and Ti(O-*i*-Pr$_4$)-promoted regioselective addition of benzoic acid[14] to alkynyl diol **6**. After introduction of the required cyclic protective group as acetonide **7** or as benzylidene acetal **8**, tungsten-catalyzed alkynol cycloisomerization[15] provided the respective septanose glycals **9** and **10**, which were isolated after protection of the 5-hydroxyl as the glycals **11**−**13**.[16]

Our original intention was to functionalize the glycal by dimethyldioxirane (DMDO) epoxidation, followed by nucleophilic addition at C1. Unfortunately, epoxidation of acetonide glycal **11** was not stereoselective. Moreover, basic methanolysis of the mixture of epoxides afforded a 1:1 mixture of the D-glucoseptanosyl epoxide **14** and the methanol addition product **15** arising from the D-mannoseptanosyl epoxide (Scheme 2). The epoxide **14** was remarkably stable to a variety of nucleophilic addition conditions. On the other hand, the reaction of **12** with DMDO resulted in a complex mixture, consistent with competitive oxidation of the benzylidene acetal.[17] Thus reductive cleavage of the benzylidene acetals **12** and **13** was followed by O-benzylation to afford the septanose glycals **17** and **18** in excellent yield. DMDO epoxidations of glycals **17** and **18** were stereoselective, so that addition of sodium methoxide to the epoxide intermediate **19** provided the partially protected D-mannoseptanoside **20**, whereas lithium thiophenoxide addition resulted in the formation of thioglycosides **22**−**23**. Thus epoxidation occurred *cis* to the allylic C3 benzyloxy substituent but *trans* to both C4 and C5 substituents, consistent with observations in several six-membered ring glycals.[18] The protective group manipulations of **20** to **21** and **22**−**23** to **24**−**25** were straightforward, other than the observation that deprotection of the trimethylsilylethoxymethyl (SEM) group to the free C5-alcohol of methyl α-mannoseptanoside acceptor synthon **21** was possible only with DMPU solvent in conjunction with molecular sieves.[19,20]

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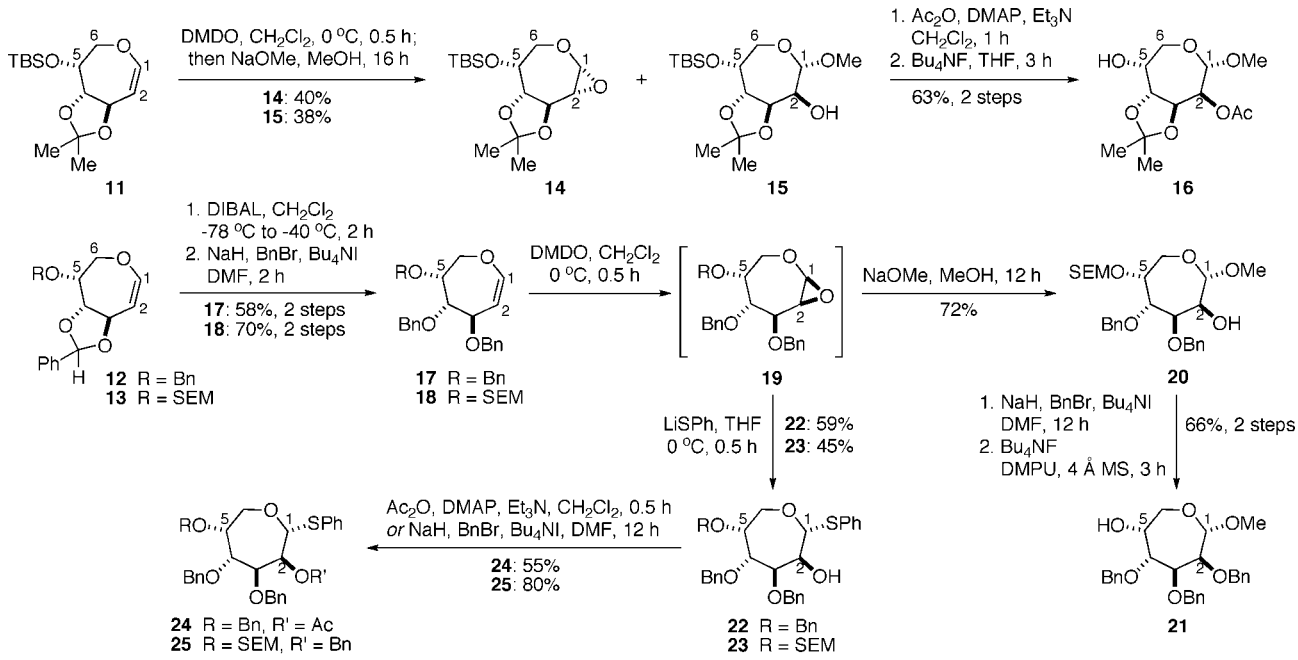
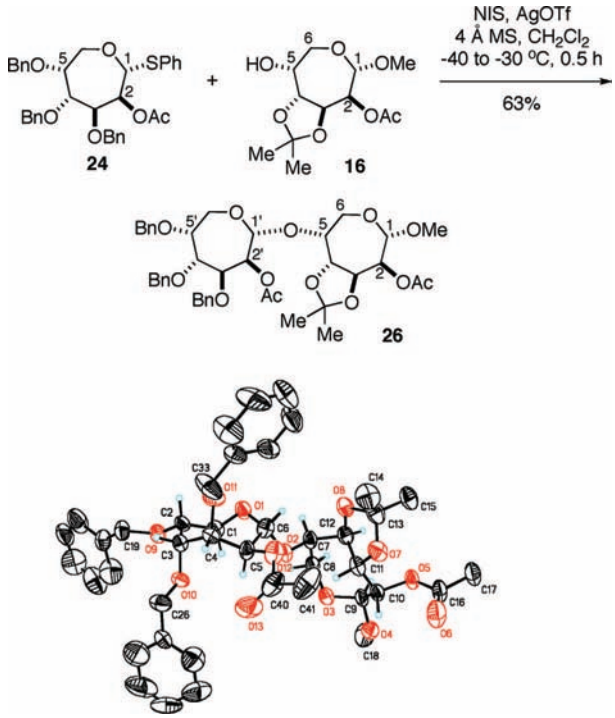
(20) (a) The stereochemistry of septanoside **25** was confirmed by conversion into the known α-1,6-diacetyl-2,3,4-tri-*O*-benzyl-D-mannopyranose,[20b] in three steps: (1) TFA, CH_2Cl_2; (2) NBS, H_2O, THF; (3) Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2. (b) Tennant-Eyles, R. J.; Davis, B. G.; Fairbanks, A. J. *Tetrahedron: Asymmetry* **2000**, *11*, 231.

Scheme 2. Preparation of Various D-Mannoseptanoside Derivatives



Encouraged by Peczuh's report of glycosylations of other septanose thioglycosides,[5e] we first studied the glycosylation of septanoside acceptor synthon **16** with the thioglycoside donor synthon **24**. This transformation provided fully protected disaccharide **26** (Scheme 3), for which the crystal structure confirmed the stereochemical assignments for the compounds arising from epoxidation and ring-opening products **15** and **19**. A more practical combination of O5-SEM-protected thioglycoside **25** with C5-alcohol **21** provided the disaccharide **27** (Scheme 4), again with *alpha* stereoselectivity despite the absence of a participating group at C2. After removal of the SEM protective group, disaccharide alcohol **28** was glycosylated again with **25** to provide trisaccharide **29**. Each mannoseptanoside was fully deprotected by global debenzylation via $Pd(OH)_2$/C-catalyzed hydrogenolysis. The crude polyols **31** and **32** were purified by forming the peracetate derivatives and silica gel chromatography, followed by ammoniacal methanolysis, whereas the trisaccharide **33** was obtained analytically pure without further purification.

Scheme 3. Synthesis and Crystal Structure of Disaccharide **26**



Although the seven-membered ring isomers of the naturally occurring pyranosides exhibit substantially different arrangements of the hydroxyls, including the incorporation of the primary C6 carbon into the ring, we still wondered if the common arrangement of hydroxyls at C2, C3, and C4 would be sufficient for **31**−**33** to serve as substrates for glycosidase hydrolysis. Thus we evaluated the jack bean α-mannosidase-catalyzed hydrolysis of *p*-nitrophenyl α-D-mannopyranoside (PNP-Man) in the presence of varying concentrations of α-mannoseptanosides **31**−**33** (Table 1).[21] Remarkably, none of our mannoseptanosides showed significant inhibition of PNP-Man hydrolysis, suggesting that these seven-membered ring-size isomers did not interact with the matched enzyme for α-mannopyranoside hydrolysis. Given the different conformations of mannoseptanosides and mannopyranosides, future enzyme inhibition studies might

Scheme 4. Iterative Glycosylation Synthesis of D-Mannopyranosyl Di- and Trisaccharides

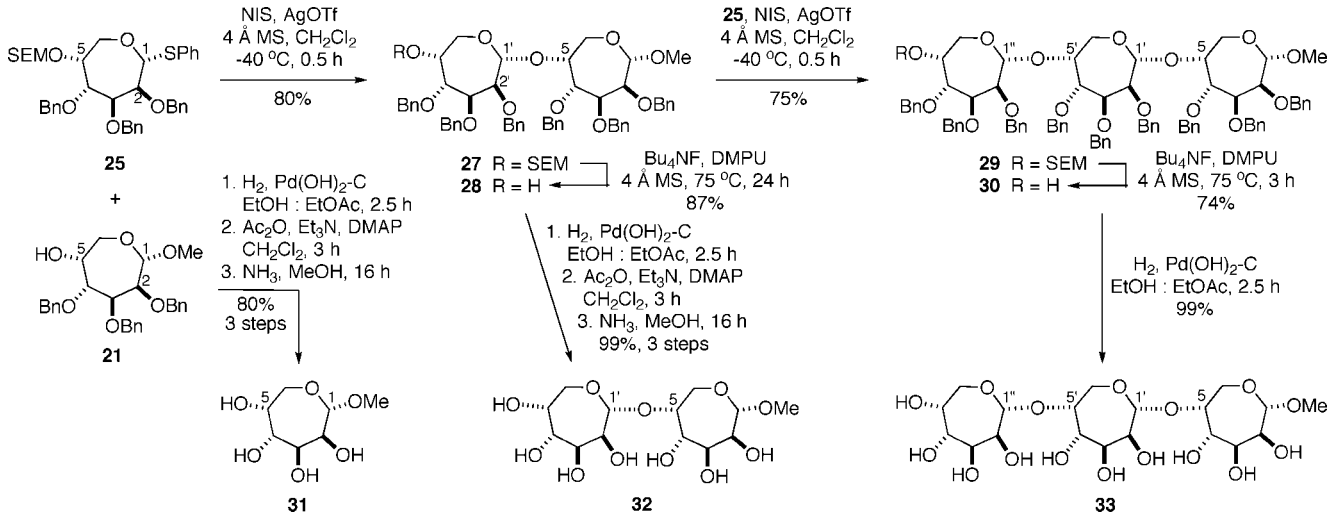


Table 1. Kinetic Parameters for *p*-Nitrophenyl Mannopyranoside (PNP-Man) Hydrolysis by α-Mannosidase in the Absence and Presence of Septanosyl Oligosaccharides **31**−**33**[a]

	control[b]	0.75 mM **31**	6.0 mM **31**	0.75 mM **32**	6.0 mM **32**	0.75 mM **33**	6.0 mM **33**
K_m (mM)	3.8 ± 0.5	3.1 ± 0.3	3.6 ± 0.3	2.7 ± 0.2	4.3 ± 0.4	2.1 ± 0.2	2.4 ± 0.3
K_{cat} (s^{-1})	44 ± 1	38 ± 1	41 ± 1	45 ± 1	41 ± 1	44 ± 1	46 ± 2

[a] Inhibition of jack bean α-mannosidase-catalyzed hydrolysis of PNP-Man (0−30 mM) in the absence of mannoseptanosides (control) or in the presence of 0.75 or 6.0 mM mannoseptanosides **31**, **32**, and **33**. [b] The literature reports K_m values for jack bean α-mannosidase-catalyzed hydrolysis of PNP-Man ranging from 2.5 to 4.67 mM (ref 21a,b).

benefit from testing additional members of the glycosidase family, in order to cover a broader range of substrate specificity.

In conclusion, tungsten-catalyzed cycloisomerizations of alkynyl alcohols have ultimately permitted access to a unique family of non-natural septanosyl oligosaccharide ring-size isomers of α-mannopyranosides. As the 1,5-linked D-mannoseptanosyl di- and trisaccharides have not previously been reported in the literature, the demonstration of this glycosylation strategy involving more complex glycosyl acceptors and donors is an important achievement toward future applications of this concept to the synthesis of long-chain oligoseptanosides via larger fragment coupling strategies.

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Supporting Information Available: Detailed experimental procedures and characterization for all synthetic compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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