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Synthesis of *C*-Septanosides from Pyranoses via Vinyl Addition and Electrophilic Cyclization

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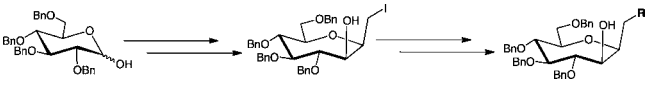
ABSTRACT



A two-step synthesis of *C*-septanosides from pyranoses is reported. Vinyl addition to tetra-*O*-benzyl D-glucose, D-galactose, and D-mannose gave the corresponding allylic alcohols. Electrophilic cyclization followed by treatment with iodine gave iodomethyl *C*-septanosides suitable for substitution reactions. The cyclizations were diastereoselective, giving *cis*-1,2 configured *C*-septanosides. Selectivity is rationalized through a model for electrophilic additions that invokes the conformation of the allylic system. This new approach should be generally applicable to the synthesis of a variety of *C*-septanosides.

Compounds containing a seven-membered ring such as polyhydroxylated azepanes and septanose carbohydrates have received considerable attention over the past decade as potential "non-natural" surrogates for pyranoses in a number of biochemical settings.[1] In one example, a polyhydroxylated azepane designed to mimic the stereochemistry and functional groups of *N*-acetyl glucosamine inhibited a human *O*-GlcNAcase.[2] A number of other reports have detailed the inhibition of glycosidases using azepanes and related compounds.[3] With respect to septanosides, we have demonstrated that methyl β-septanosides can bind competitively into the pyranose binding pocket of Concanavalin A, a plant lectin that normally recognizes α-mannosides.[4] Nitrophenyl septanosides have been used as substrates of naturally occurring α- and β-glycosidases, but the k_{cat} and K_M values suggested that they were relatively poor substrates.[5] It may be that septanosides will be poor substrates for glycosidases in general and therefore able to evade degradation in cellular contexts. Under acidic conditions, however, we have observed that hydrolysis of septanosides is more facile than for pyranosides.[6] This presumably owes to the lower stability of seven-membered rings in comparison to six-membered rings.[7] If septanosides are more susceptible to acid hydrolysis, then, access to *C*-glycosides will be important to their application in biological contexts. *C*-Glycosides are analogs of pyranoses that take up conformations that are very similar to the corresponding sugars and have similar protein-binding profiles.[8] By design, they are also resistant to both enzymatic and acidic hydrolysis by virtue of the fact that the glycosidic C−O linkage has been replaced with a C−C bond.[9]

To that end, we anticipated that *C*-septanosides could be prepared via electrophilic cyclization of the appropriate enitols. The approach has been used to synthesize *C*-pyranosides; in this case, the sequence involves

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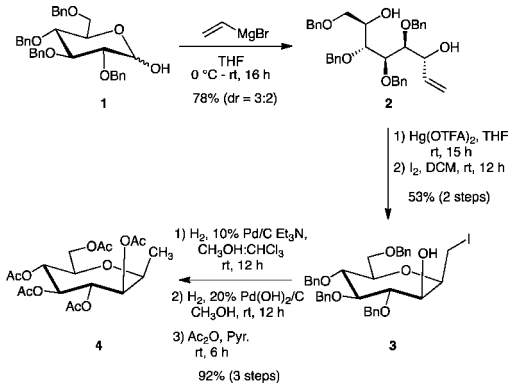
Scheme 1. Synthesis of *C*-Septanoside **4** via Vinylation and Electrophilic Cyclization



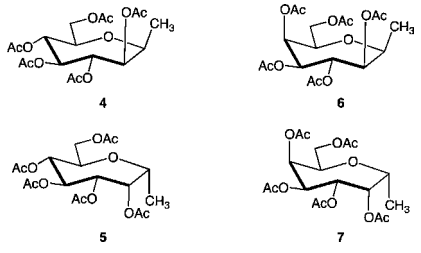
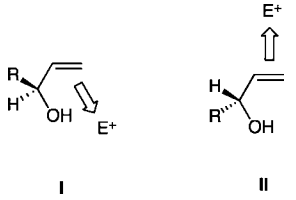


Figure 1. Products (**4**–**7**) of vinylation–cyclization sequence in the D-gluco and D-galacto series.

generation of the enitol by Wittig olefination of a pyranose[10] or vinyl addition to a pentose followed by Hg^{2+} cyclization.[11] This strategy was originally utilized to stereoselectively prepare α-D-*C*-glucopyranose derivatives and later other, rarer *C*-glycosyl compounds. Since then, it has been used to prepare numerous biologically active *C*-glycosyl derivatives.[12] The key question to us (Scheme 1) was whether the cyclization of species such as **2** to form a seven-membered ring would be favored over other reactions (e.g., intermolecular etherification, intramolecular attack of a benzyl ether, etc.). There is ample literature precedent for the addition of vinyl Grignards to aldohexoses.[13] Cyclization using Hg^{2+} as an electrophile would give an alkyl mercury species that could be converted to the corresponding iodomethyl compound. This, in turn, could be used as an electrophile for the preparation of a variety of *C*-septanoside conjugates.

Our implementation of the strategy is illustrated using tetra-*O*-benzyl-D-glucose **1** in Scheme 1. Addition of vinyl magnesium bromide to **1** gave a 3:2 mixture of diastereomeric allylic alcohols (78% combined yield). In our hands, the yield and selectivity of the addition were slightly lower than has been reported;[12,14] the procedure was sufficient enough, however, to obtain material for the subsequent reactions without optimization. The major isomer, **2**, was treated with $Hg(OTFA)_2$ in THF followed by I_2 in DCM. The product of the two-step process, to our delight, was iodomethyl compound **3** which was obtained in 53% yield over the two steps. At this stage, the stereochemistry of the newly created stereocenter at C2 (glycosidic numbering) was uncertain. To facilitate characterization of the stereochemistry of the new compound, we chose to dehalogenate the iodomethyl group and also to convert the benzyl protecting groups to acetates via hydrogenation and acetylation, which gave *C*-septanoside **4** in 92% yield. The ^{13}C and, importantly, ^{1}H NMR spectra for **4** were simpler to interpret in comparison to **3**. Diagnostic cross-peaks in the NOESY spectrum of **4** ($CDCl_3$) between H1–H2, H1–H4, and H1–H6 were considered diagnostic for the *cis*-1,2 "β" configuration shown in Scheme 1. Additionally, the low $^{3}J_{H1,H2}$ coupling (3.3 Hz) constant also supported the *cis* configuration of protons at the C1 and C2 positions. The minor isomer of vinyl addition to glucose, which is epimeric at the allylic alcohol carbon relative to **2**, was subjected to the same reaction sequence; analysis of NMR spectra of the product, as had been done for characterization of **4** previously, led to assignment of *cis*-1,2 *C*-septanoside **5** as the structure (Figure 1).[15] Through the same set of reactions, tetra-*O*-benzyl-D-galactose was converted to **6** and **7**, respectively.[12,16] Moreover, our structural assignment of **4**–**7** was fortified by the inside alkoxy model for that rationalizes stereoselectivity for additions to chiral allylic systems.[17,18]



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Stereoselectivity in the cyclization reaction is linked to the absolute configuration at the allylic carbon. The π-bond is nucleophilic when it is coplanar with the C–O bond of the allylic carbon (e.g., **I** or **II**) because, in this conformation, its electron density is localized on the π-bond itself rather than delocalized into the σ^* of the C–O bond.[16,17]

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(15) Cyclization products en route to and including **5** have ~10% inseparable impurity which we have tentatively been assigned as the 1,2-*trans* product. More details are in the Supporting Information.

(16) The Supporting Information contains details on the synthesis of compounds **5**–**7**.

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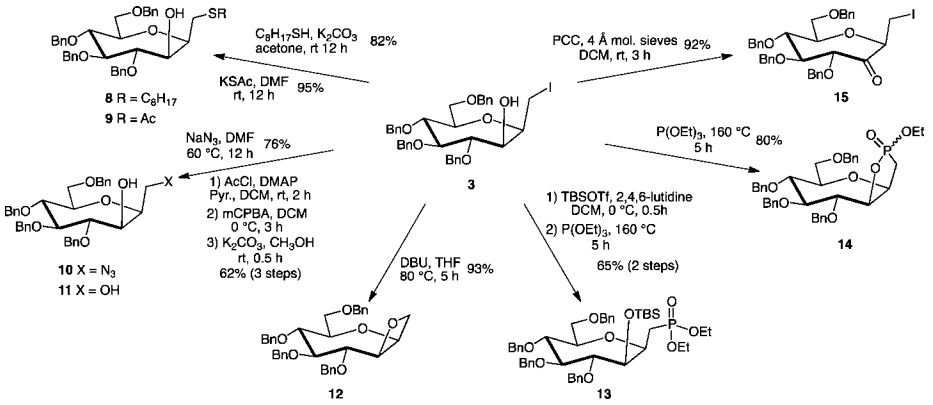
Scheme 2. Reactions Utilizing the Iodomethyl Group of *C*-Septanoside **3**



From here, attack on the electrophile occurs *syn* to the allylic hydrogen to give a π-complex. Hehre et al. have commented that, for intramolecular reactions, attack is on the Hg^{2+} olefin π-complex and not onto the onium ion itself. Attack on this complex by the pendant hydroxyl group leads to the cyclized product. Our structural assignment of *cis*-1,2 *C*-septanosides **4**–**7**, based on NMR spectra, corresponds with the inside alkoxy model. The model has been used to rationalize several related cyclization reactions.[11b,19]

An attractive feature of the synthesis is that its product contains an alkyl iodide that can be enlisted for subsequent reactions. Scheme 2 collects a number of examples using the reactive alkyl iodide unit of *C*-septanoside **3**. Substitution by nucleophiles such as octane thiol, thioacetate, and azide produced compounds **8**–**10** in 82%, 95%, and 76% yields, respectively.[20] A mild procedure for conversion of alkyl iodides to alcohols[21] was used to convert **3** to diol **11** in 62% yield over three steps. The C2 hydroxyl group was protected as the acetate in this sequence to avoid formation of the oxetane in the hydroxylation reaction. Overall, oxetane formation was relatively facile as in the conversion of **3** to **12** in the presence of DBU (93%). Arbuzov reactions under two different circumstances were also explored. Protection of the C2 hydroxyl group as the TBS ether followed by phosphonate formation gave **13** (65% yield over two steps).[21] Alternatively, if the C2 hydroxyl group was left unprotected, attack by triethyl phosphite gave cyclic phosphonate **14** in 80% yield as a mixture of diastereomers that are epimeric at the phosphorus atom.[22] Finally, oxidation of the C2 hydroxyl group using PCC provided ketone **15** in 92% yield.[23] Interestingly, elimination of HI from **15** to give the conjugated enone was unsuccessful when using either collidine or DBU as a base (vide infra).

A more complex distribution of products was obtained when tetra-*O*-benzyl mannose was the starting material for the synthesis (Scheme 3). Addition of vinyl magnesium bromide to tetra-*O*-benzyl-mannose resulted in an inseparable mixture (3:2) of diastereomeric allylic alcohols **16** (72%). The mixture was put under the cyclization reaction conditions with the expectation that, based on the results of the previous substrates, each of the allylic alcohols would give its corresponding *C*-septanoside. Instead, the reaction ended up giving three different products, only one of which was a *C*-septanoside.

The major product of the cyclization, **17**, was isolated in 43% yield and followed a reaction course similar to the other septanosides. The other two products arose from different pathways, however. It was apparent from the ^{1}H NMR spectra of **18** and **19** that a benzyl group had been lost from these compounds over the course of the reaction. This observation suggested they cyclized via a nucleophilic benzyl ether oxygen, which has several precedents.[12,24,25] As was done previously, the assignment of structures **17**–**19** was made by inference from a collection of NMR spectra of the corresponding acetyl protected compounds **20**–**22**. The key spectral data used to assign a structure for **20** were NOESY crosspeaks between H1–H2 and H1–H5. Analysis of ^{1}H, COSY, NOESY, HSQC, and HMBC spectra for **21** ($CDCl_3$) provided compelling evidence for its structure. A NOESY correlation between H1–H4 was one key data point as well as HMBC correlations for acetyl carbonyls to C2, C3, and C5–C7 but not to C4. Formation of the five-membered ring using a benzyl ether oxygen as a nucleophile has been utilized extensively in the formation of highly substituted tetrahydrofurans.

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(20) (a) Sulfide formation: Paterson, E.; Griffin, F. K.; Alcaraz, M. L.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2002**, 1323–1336. (b) Thioacetate: Centrone, C. A.; Lowary, T. L. *Bioorg. Med. Chem.* **2004**, *12*, 5495–5503.

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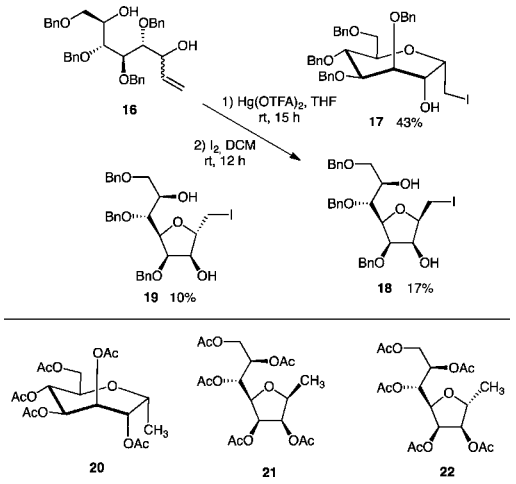
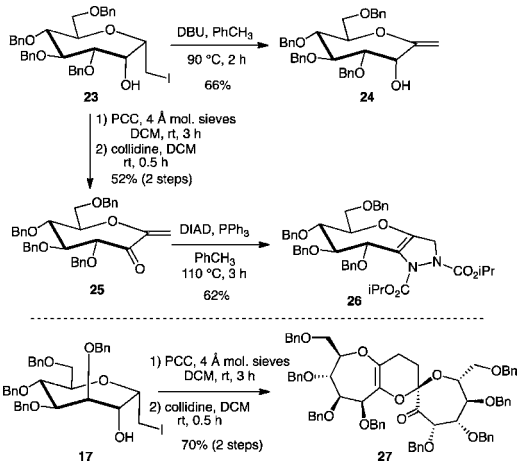
Scheme 3. Cyclization Products of Allylic Alcohol **16**



Scheme 4. Reactions of the α-*C*-Septanosides



The inherent nucleophilicity of the ether oxygen and the favorable kinetics for the formation of five-membered rings are consistent with this assignment. HMBC data for **22** also showed that the C4 hydroxy group was not acetylated which prompted us to assign the structure as a substituted tetrahydrofuran. The spectra for **22** were distinct from those of **21** but nonetheless similar. Based on these observations we have tentatively assigned the last cyclization product as the *trans*-1,2 isomer **22**.

We have also observed some interesting differences in the outcomes of reactions of α- and *β*-*C*-septanosides. In the glucose series, for example, treatment of *β*-*C*-septanoside **3** with DBU in THF gave oxetane **12** (Scheme 2). Treatment of the α-diastereomer **23**, on the other hand, gave exoglycal **24** in 66% yield (Scheme 4). One argument[26] to rationalize these observations is based on the ability of the C2 hydroxyl to form a H-bond with the C3 benzyloxy group in **23** but not in **3**. Maintenance of the H-bond may make it difficult to deprotonate and thereby favor the elimination reaction to form **24**. Oxidation of the C2 hydroxyl of **3** gave ketone **15**, but when the subsequent elimination of HI across the C1-iodomethyl bond was attempted no reaction occurred. In contrast, PCC oxidation and collidine elimination of **23** gave enone **25** in 52% yield over two steps (Scheme 4). Successful elimination based on the opposite stereochemistry at C1 was consistent with different outcomes in DBU elimination of **3** and **23**. Formation of enone **25** was unexpected because previous work had shown that such compounds usually undergo facile cycloaddition reactions. Specifically, we and others have reported homodimerizations or *in situ* trapping of these enones with dienophiles.[22,27] Oxidation and elimination starting from **17**, for example, provided dimeric cycloaddition product **27** in 70% yield. We noted that **25** decomposed over time but it also could be intercepted if used soon after its preparation. We trapped it via a Huisgen addition reaction to form dihydropyrazole **26** (62%) as shown Scheme 4.[28] This result suggests that enone **25** and related compounds may be starting materials for a variety of additional reactions and underscores their potential for application as *C*-glycoside analogs of septanose carbohydrates.

The method for the diastereoselective synthesis of *C*-septanosides described here benefits from its utilization of readily available starting materials and the ability to create a variety of derivatives from the cyclization products. We have demonstrated the route using benzyl protected D-glucose, D-galactose, and D-mannose, but the route is likely amenable to a greater number of pyranoses; this is important because we and others have observed that, in the appropriate contexts, septanoses can be used as surrogates for pyranose sugars. Also, the new *C*-septanosides should be significantly more stable toward hydrolysis in comparison to *O*-septanosides. Attack by nucleophiles on the iodomethyl group that arises via the cyclization provided a variety of functionalized *C*-septanosides (e.g., **10**–**14**). The cyclization products can also undergo other reactions such as dimerization or addition reactions of enones such as **25**. Our current efforts are aimed at utilizing the new addition and cyclization method for the synthesis of *C*-septanoside analogs to be tested for their ability to bind target proteins.

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

The authors declare no competing financial interest.

(26) A figure and comments on the difference in reactivity of **3** and **23** are in the Supporting Information.

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