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# A Convergent Strategy for the Synthesis of β-Carba-galacto-disaccharides

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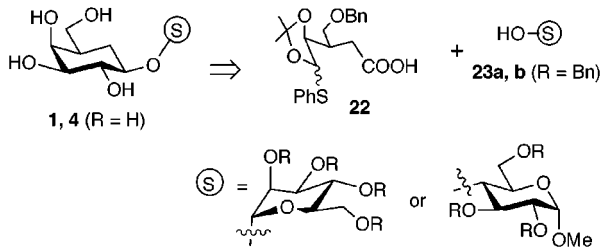
## ABSTRACT




**A convergent strategy for the synthesis of β-carba-galacto-disaccharides is illustrated by the preparation of 1 and 4, from a central "glycone" component 22, and the corresponding "aglycone" segments, monosaccharide alcohols, 23a or 23b. The key step is the formation of the carbasugar ring via an oxocarbenium ion–enol ether cyclization**

Glycomimetic molecules have attracted considerable interest as biochemical probes and potential therapeutic agents.[1] Analogues that have limited structural modifications relative to the native carbohydrate are of relevance to the systematic dissection of mechanistic pathways.[2] The notion that the oxygens of the acetal linkages are generally intimately involved in carbohydrate-receptor interactions has led to interest in acetal analogues. Structures in which the endocyclic or the exocyclic oxygen of the acetal linkage is replaced by a methylene residue are especially common.[3−5] These carba and *C*-glycosides (e.g., **1** and **2**, respectively, Figure 1) are expected to exhibit steric and conformational features similar to those of the parent *O*-glycoside **3** but would be stable to chemical and enzymic hydrolysis.[6]

*C*-glycoside/carbasugar analogue pairs of a given *O*-glycoside could be valuable for the evaluation of the relative importance of the individual acetal oxygens in carbohydrate mechanisms.[7] We have been interested in the synthesis of disaccharide mimetics because of their potential to provide information regarding substrate specificity.[8] A number of

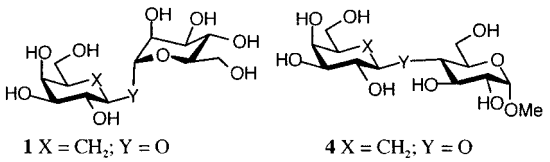



**Figure 1.** Acetal analogues of disaccharides.

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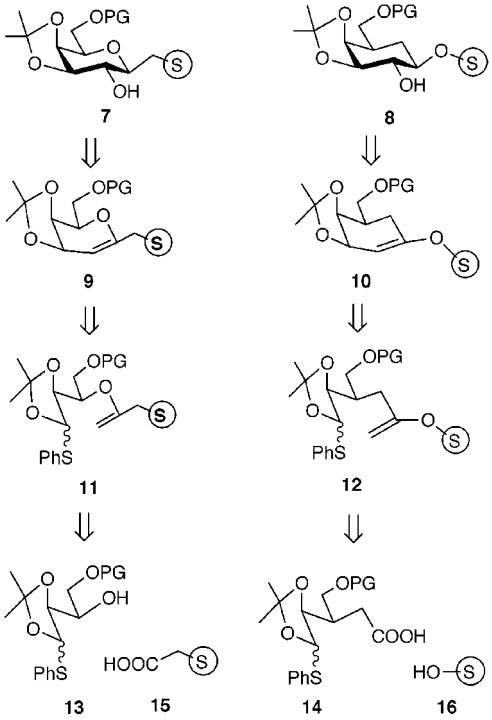
convergent methodologies have been developed for the synthesis of *C*-disaccharides.[4] By comparison the synthesis of carba-disaccharides are not as well explored. The most common strategy utilizes the coupling of an epoxysugar or epoxycyclitol with an alcohol partner.[3b−d,9] However syntheses of the epoxide components are not trivial, coupling yields are low when secondary alcohols are used, and the overall procedures are lengthy.

We have shown that 1-thio-1,2-*O*-isopropylidene acetals (TIAs, e.g., **13**) provide a convergent entry to *C*-galactodisaccharides.[10] Thus esterification of TIA alcohol **13** and a saccharide acid **15**, followed by Tebbe olefination of the resulting ester, provides an enol ether **11**. An oxo-carbenium ion-alkene cyclization on **11** leads to the C1-substituted glycal **9**, which is converted to the $\beta$-*C*-galactoside **7**. We envisaged synthesis of the corresponding carba analogue **8** by juxtaposing the location of the alcohol and acid residues in the *C*-glycoside precursors. Accordingly, TIA acid **14** and saccharide alcohol **16** may be transformed in two steps to the enol ether **12**. Notwithstanding the position of the olefin in the cyclization product, the enol ether **10** would be expected to give under conditions of hydroboration−oxidation, the $\beta$-carbo-galactoside **8**. Herein is described the application of this methodology to the synthesis of **1** and **4**, analogues of a sialyl Lewis X mimetic and methyl lactoside, respectively.[11]

**Scheme 1**




The TIA-acid **22** corresponding to the glycone component was obtained from the C-branched pyranoside **18**, which has been previously prepared in four steps from D-lyxose **17** by Keck and co-workers.[12] Sodium ammonia reduction of the benzyl ether in **18** provided the lactol **19**. Treatment of **19** with diiodosobenzene diacetate (DIB) according to the Suarez methodology for fragmentation of anomeric alkoxy radicals led to a mixture of 1,2-*O*-isopropylidene acetates **20** in 96% yield.[13] It was important that this reaction be carried out under high dilution conditions. Lower yields of products resulting from an intramolecular iodoetherification reaction of the alkene appeared to be significant when the reaction was carried out at high concentrations.[14] Acetal exchange on **20** with thiophenol, followed by basic hydrolysis of the crude product and benzylation of the resulting alcohol, provided **21** as an approximately 4:1 mixture of acetals in 70% overall yield from **20**.[15] Ozonolysis of **21** and $NaClO_2$ oxidation[16] of the derived aldehyde led to a mixture of TIA acids **22**.

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(15) The TIA mixture **21** was inseparable by chromatography and used without separation in the next step. The subsequent acid **22** and the ester and enol ether derivatives of **22** showed similar mixture ratios. That the origin of the mixture was at the acetal carbon was confirmed by the formation of a single glycal product in the subsequent oxocarbenium ion cyclizations.

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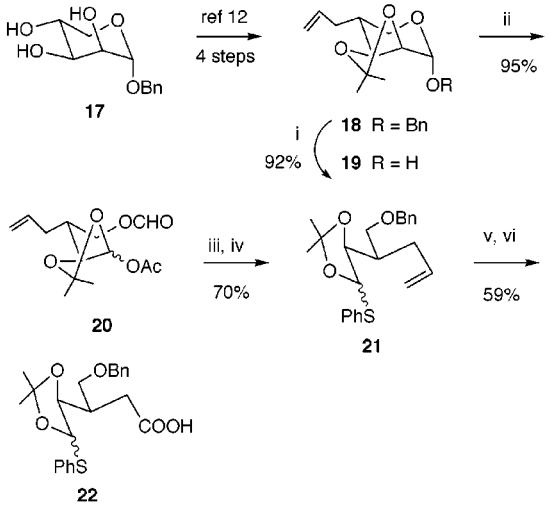
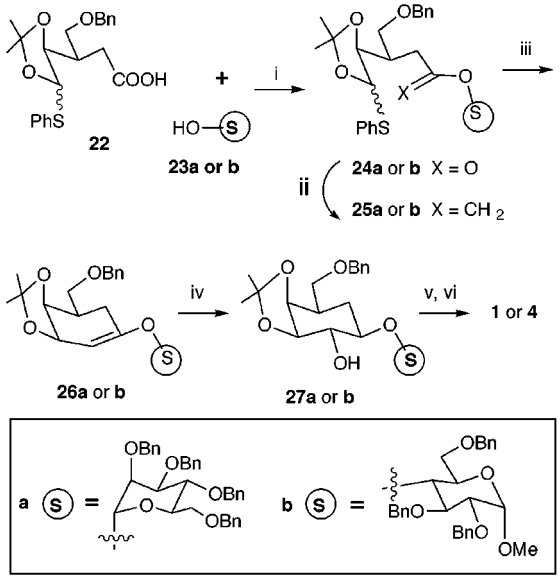
**Scheme 2**[a]




[a] (i) Na, $NH_3$, THF; (ii) DIB, $I_2$, cyclohexane (0.04 M); (iii) PhSH, $BF_3{\cdot}OEt_2$, −78 °C then NaOMe, MeOH; (iv) NaH, BnBr, $Bu_4NI$, DMF; (v) $O_3$, $MeOH/CH_2Cl_2$, −78 °C then $Ph_3P$; (vi) $NaClO_2$, $CH_3CN$, 2-methyl-2-butene.

**Scheme 3**[a]




[a] (i) DCC, DMAP, PhH; (ii) Tebbe; (iii) MeOTf, DTBMP, $CH_2Cl_2$ (iv) $BH_3{\cdot}Me_2S$ then $Na_2O_2$; (v) MeOH, HCl; (vi) Pd/C EtOH, HCOOH **1**, **4** (both 72% over two steps).

DCC-mediated esterification[17] of the known manno and gluco alcohol components **23a**[18] and **23b**[19] with 1.2 equiv of acid **22** led to esters **24a** and **24b** in approximately 80% yield in both cases. Ester mixture **24b** was found to be a single α-anomer with respect to the mannose linkage, as determined from the H−H and C−H coupling constants ($J_{H1,H2} = 2$, $J_{C1H1} = 175$ Hz).[15,20] Tebbe olefination[21] of **24a** and **24b** gave the corresponding enol ethers **25a** and **25b** in 80% and 86% yields, respectively. The enol ethers were stable to purification on silica gel.

Activation of **25a** and **25b** with methyl triflate in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) led to the cyclic enol ethers **26a** and **26b** in yields of 64% and 75%, respectively. In neither case was any of the regioisomeric alkene product detected. Treatment of **26a** and **26b** with $BH_3{\cdot}Me_2S$ provided the carbadisaccharides **27a** and **27b** in respective yields of 72% and 78%. The observed *J* values for the acetate derivatives of **27a** and **27b** ($J_{1,2} = 10.0$ and 10.5, $J_{2,3} = 8.0$ and 8.5, $J_{3,4} = 4.0$ and 3.5, $J_{4,5} = 4.0$ and 3.5 Hz, respectively) were in close agreement with those for related 3,4-*O*-isopropylidene-*β*-*O*-galactosides.[22] In addition, for the manno acetate derivative NOEs between H5 and H1 and H5 and H3 were clearly discernible. The deprotected carbadisaccharides **1** and **4** were obtained in good yield from **27a** and **27b** over two straightforward operations involving hydrolysis of the acetonide and hydrogenolysis of the benzyl ethers.

The alcohol component **16** for the carbadisaccharide methodology is the identical compound that would normally be used as the glycosyl acceptor in the synthesis of the parent *β*-*O*-galactoside and is also the precursor for the acid aglycone component **15** in our earlier synthesis of *β*-*C*-galactosides (Scheme 2). The TIA methodology therefore provides a general protocol for conversion of a given glycosyl acceptor **16** to either its *β*-*C*-galactoside **8** or *β*-carbagalactoside **7**. In both the *C*-glycoside and carbasugar synthesis the key "glycone"−"aglycone" coupling step is an esterification reaction. The reliability of this segment coupling reaction should allow for the general synthesis of *β*-galacto mimetics with a high degree of complexity in the aglycone segment.

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**Supporting Information Available:** $^1H$ and $^{13}C$ NMR and HRMS data for **1**, **4**, **22**, **27a**, and **27b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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