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Addition of Lithiated *C*-Nucleophiles to 2,3-*O*-Isopropylidene-D-erythronolactone: Stereoselective Formation of a Furanose *C*-Disaccharide

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Abstract: Addition of PhLi and lithiated dithianes to 2,3-*O*-isopropylidene-D-erythronolactone affords lactols, which are reduced with Et_3SiH to the corresponding *C*-glycosides, the structures of two of which have been solved by X-ray diffraction. The use of a D-ribose-derived lithiated dithiane nucleophile in this chemistry allows for the convenient construction of a furanose *C*-disaccharide.

The chemical synthesis of carbohydrate mimics (*glycomimetics*) is driven by the needs of glycobiology since compounds such as iminosugars and *C*-glycosides are valuable tools for the study of carbohydrate-associated proteins.[1] The *C*-glycosides are compounds in which a methylene group replaces the exocyclic oxygen of the *O*-glycoside to be mimicked, and this substitution endows the mimic with the ability to withstand enzymatic hydrolysis and thus serve as a stable substitute for the *O*-glycoside.[2] There is continued debate about the actual efficacy of *C*-glycoside mimetics since there are no anomeric effects (either *endo* or *exo*) in play and there may be significant differences in their preferred conformations versus the *O*-glycosides;[3] however, there is evidence that *C*-glycosides are capable of binding to proteins such as glycosyl hydrolases, glycosyl transferases, and lectins.[4]

Many routes to *C*-glycosides have been developed[2] and the applications to *C*-disaccharides and *C*-oligosaccharides are important extensions.[4] We are interested in the application of dithioacetal chemistry to the creation of the crucial C−C bond between the "nonreducing" end of a *C*-disaccharide and the "aglycon" portion. With the growing interest in furanose-based oligosaccharides as components of, for example, bacterial cell walls[5] we chose to investigate the synthesis of a furanose *C*-disaccharide. As shown in Figure 1, the coupling of a dithiane nucleophile with an electrophilic sugar lactone, followed by removal of −SPh groups and reduction of the resultant lactol, should provide an efficient protocol for *C*-disaccharide synthesis. Addition of organometallic reagents,[6] including lithiated dithiane nucleophiles,[7] to carbohydrate-derived lactones is a well-known route to *C*-glycosidic compounds and the reduction of lactols is usually stereoselective. The work of Dondoni and colleagues[2c,d] is of particular value here in which sugar lactones were coupled with lithiated heterocycles.[8] The lactol intermediates from these reactions may be reduced stereoselectively, for example via their acetates, en route to *C*-glycosides.[8b] Questions of stereocontrol are of interest in the addition step and of paramount importance in the reduction step for the present synthesis to be useful. Here we detail the application of this approach to the simple furanose *C*-disaccharide **1**, as well as evidence from X-ray diffraction for the stereochemical course of the synthetic steps.

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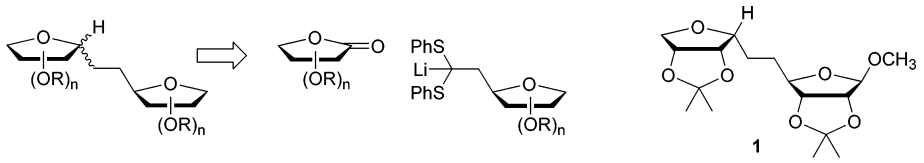
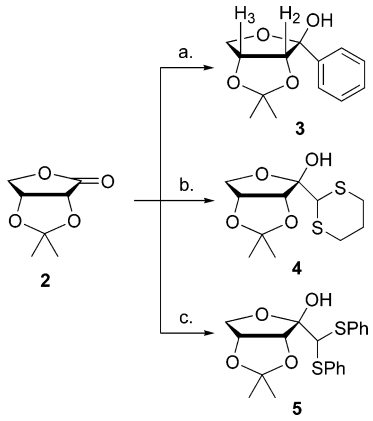


FIGURE 1. Possible disconnection for *C*-disaccharide synthesis and the target compound (**1**).

SCHEME 1[a]



[a] Reagents and conditions: (a) PhLi, THF, −78 °C, then aq NH_4Cl. (b) 2-Lithio-1,3-dithiane, THF, −78 °C, then aq NH_4Cl. (c) $(PhS)_2CHLi$, THF, −78 °C, then aq NH_4Cl.

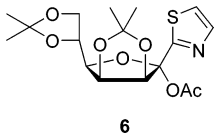
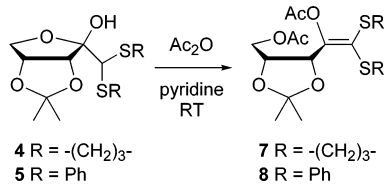


FIGURE 2. D-Mannofuranose-derived lactol acetate **6**.

We chose to begin our studies toward *C*-disaccharide **1** by adding phenyllithium to commercially available 2,3-*O*-isopropylidene-D-erythronolactone (**2**) to learn about the stereochemical preferences of a ketol formed from this system and the possibility of stereoselectivity in the subsequent ketol reduction. Thus, treatment of **2** with PhLi at −78 °C resulted in the clean formation of a single product, **3** (Scheme 1), as a solid in 86% yield. The stereochemical identity of **3** is not obvious from its NMR spectra and is assumed to be the *β*-anomer by comparison with a similar compound produced by Dondoni and colleagues from 2,3;5,6-di-*O*-isopropylidene-D-mannofuranolactone[8b] that was found to equilibrate with its α-anomer in solution. The anomeric D-mannofuranosyl lactols in that case were trapped as the respective acetates and the identity of the thermodynamic α-anomer (**6**) was proven by X-ray crystallography.[8b] In the present work compound **3** does not apparently undergo measurable anomerization and is assumed to be the thermodynamic lactol with the anomeric OH and O-2 of the furanose ring trans as in the closely related **6** (Figure 2).

We next moved to lithiated dithianes as the nucleophile and found that reaction of lactone **2** with 2-lithio-1,3-dithiane gave a 5:1 inseparable mixture of two compounds as a syrup in 77% yield based on 1,3-dithiane. It was found that using an excess of lactone led to the cleanest product mixtures and since the ^{13}C NMR spectrum of the syrup contained no carbonyl signal the ring-closed lactols **4** are most likely formed. Upon purification

SCHEME 2



by chromatography and drying under vacuum the residue, which originally contained α- and *β*-lactols, solidified and was found to now only be one anomer. Although the orientation of the dithiane group relative to the furanose ring could not be determined directly from NMR data it is reasonable to assume that the major lactol is the anomer with the OH and the ring O-2 trans to each other. With the less expensive $(PhS)_2CHLi$ as the nucleophile, lactone **2** reacted cleanly to afford one lactol product, isolated as a colorless syrup in 83% yield, thought to be the *β*-anomer **5**. Again the stereochemical identity of **5** is not certain.

It is the reasonable to assume that the *β*-lactols **3**, **4**, and **5** are the thermodynamic products of addition to lactone **2**; however, we investigated the addition of lithiated dithianes to lactone **2** further by attempting to form acetates of the lactol products. Quenching the reaction mixtures with Ac_2O would possibly allow for the trapping of α- and *β*-lactols before the mixture reached equilibrium and then the use of chemical shifts from the acetate ^{13}C spectra to aid in designating anomeric configuration as has been used previously.[9] First, when lactols **4** and **5** were isolated by aqueous workup, and then subjected to standard acetylation conditions with Ac_2O and pyridine, the only products isolated proved to be the acetylated ketene dithioacetals **7** and **8**, formed in 98% and 85% yields, respectively (Scheme 2). These compounds must arise from ring opening of the lactols under the reaction conditions and enolization at C-1 and C-2 followed by acetylation. The isolation of **8** proved useful in subsequent experiments in which the reaction between $(PhS)_2CHLi$ and lactone **2** was quenched at different time intervals with Ac_2O in an attempt to trap any intermediate lactol alkoxides. When the reaction mixtures were quenched at low temperature after 5 min, 30 min, and 1 h, ^1H NMR spectra of the crude material showed at least three components in each, one of which could be positively identified as the enol diacetate **8**. When the reaction mixture was allowed to warm to room temperature over 2 h and then quenched with Ac_2O, **8** proved to be the main component of the mixture. We were unable to resolve these mixtures adequately for absolute confirmation of structure of each component and so the acetylation experiments were not useful in ascertaining

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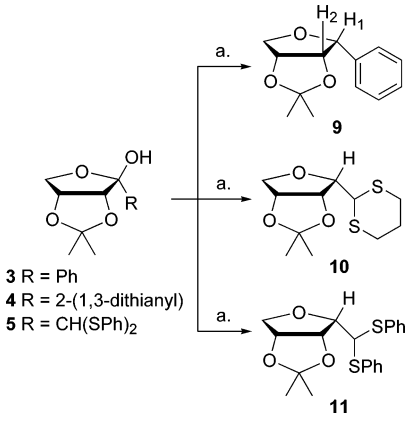
SCHEME 3[a]



[a] Reagents and conditions: (a) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, -78 °C.

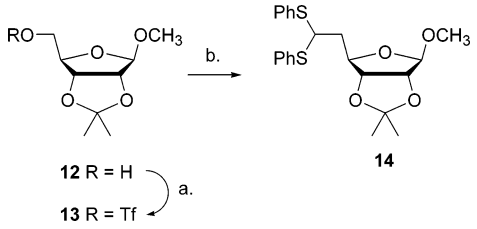
the exact structure of the lactols. That the acetylation of the 1,3-dithianyl lactols **4** gave only one diacetate (**7**) is evidence that the two components of that lactol mixture are most likely epimers.

To learn if reduction of lactols **3**−**5** would be stereoselective, each was treated with Et_3SiH and $BF_3{\cdot}OEt_2$ at low temperature. Reduction of **3** resulted in the formation of two compounds in approximately 3:1 ratio, the major one of which (**9**, 33% yield, Scheme 3) was isolated cleanly by chromatography and then crystallized in a form suitable for analysis by X-ray. The structure[10] clearly shows the major reduction compound to be the stereoisomer that arises from delivery of the hydride from above the furanose ring, presumably to avoid steric interaction of Et_3SiH with the bulky isopropylidene group below the ring. The ^1H signal assignments for **9** were proven from a COSY spectrum and the coupling constant for H-1 to H-2 (numbering shown in **9**, Scheme 3) was found to be ∼3.7 Hz. Comparing the rest of the spectrum to that of the precursor **3** revealed a general upfield shift of the signals for H-2, H-3, H-4, and H-4′, as would be expected for replacement of OH with H.

Reduction of lactol **4** under the same conditions generated one major *C*-glycoside (**10**) in 84% yield, which was isolated cleanly by chromatography and crystallized for X-ray analysis. As with phenyl *C*-glycoside **9**, compound **10** was found to have the exocyclic group orientated cis to O-2 of the furanose, a consequence of hydride delivery from above the sugar ring. The X-ray structure of **10** clearly shows this orientation.[10] The reduction of lactol **5** with Et_3SiH and $BF_3{\cdot}OEt_2$ produced an inseparable mixture of two compounds in a 2 to 1 ratio and in 82% yield. The structure of the major component was thought to be **11**. Since the lactols reduced here gave mainly "cis" *C*-glycosides, in which the exocylic substituent (Ph in **9**; −2-(1,3-dithianyl) in **10**; $-CH(SPh)_2$ in **11**) and O-2 of the furanose ring are cis to each other, it was expected that application of this chemistry in the synthesis of *C*-disaccharide **1** would result in a similar stereochemical outcome.

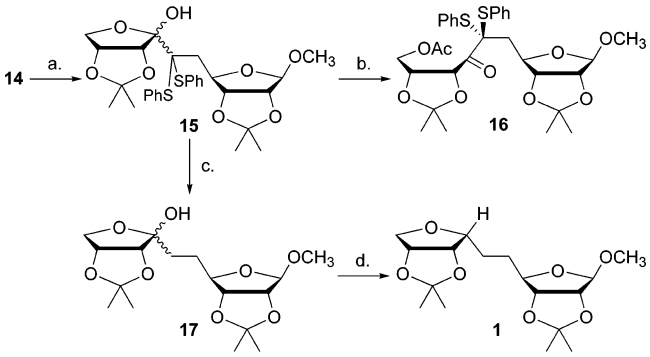
Methyl 2,3-*O*-isopropylidene *β*-D-ribofuranoside (**12**, Scheme 4) was chosen as the precursor for the sugar-

SCHEME 4[a]



[a] Reagents and conditions: (a) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2. (b) $(PhS)_2CHLi$, THF, −78 °C.

SCHEME 5[a]



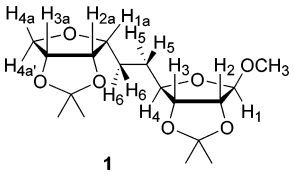
[a] Reagents and conditions: (a) *n*-BuLi, THF, −78 °C, then 3 equiv of **2**. (b) Ac_2O, pyridine. (c) Raney Ni, EtOH, H_2O, rt. (d) Et_3SiH, $BF_3{\cdot}OEt_2$, -78 °C.

derived dithiane nucleophile since this compound is available in only one step from D-ribose on large scale[11] and has only O-5 unprotected and thus available for manipulation. Activating **12** as the triflate **13** (92% yield) allowed for smooth displacement with $LiCH(SPh)_2$ to afford dithioacetal **14** in 63% yield as a syrup (Scheme 4). When **14** was deprotonated with *n*-BuLi and treated with lactone **2** at low temperature (Scheme 5) it was found that the yield of the coupling product **15** could be maximized by using an excess of the lactone with the ketol subsequently being isolated in 77% yield by chromatography. ^1H and ^{13}C NMR showed the product to be a mixture of at least two compounds with a carbonyl signal at 195 ppm revealing that some of the open chain ketone was present. When the crude reaction mixture was acetylated after workup with Ac_2O in pyridine, the only acetate formed proved to be the acyclic ketone **16**, which was isolated as a colorless syrup in 87% yield.

As with the simple lactols **3**−**5** above, we were unable to trap **15** as a closed-ring acetate that would have been suitable for reduction and we had difficulty trying to reduce **15** directly with Et_3SiH and $BF_3{\cdot}OEt_2$, ending up instead with a complex mixture of products. We therefore chose to remove the SPh groups first using Raney nickel, and lactol **17** was isolated as a syrup that contained two components in ∼4:1 ratio. Since there was no carbonyl signal present in the ^{13}C spectrum, the two compounds are thought to be α- and *β*-lactols with the latter being major for reasons detailed earlier. With **17** in hand it was straightforward to reduce the lactol, which was gratifyingly found to occur with a high degree of stereocontrol

(10) X-ray structures of compounds **9** and **10** are found in the Supporting Information.

(11) Leonard, N. J.; Carraway, K. L. *J. Heterocycl. Chem.* **1966**, *3*, 485−489.



1

FIGURE 3. Numbering scheme for *C*-glycoside **1**.

to afford the *C*-disaccharide **1** in 51% isolated yield. A NOESY spectrum of **1** (see Supporting Information) was complicated by the signals for H_{1a} and H_{4a} (see Figure 3 for numbering scheme) overlapping in the 1-D proton spectrum. The structure of **1** as a "cis" 1,2-*C*-glycoside follows from the stereochemical course of the earlier reductions to form *C*-glycosides **9** and **10**.

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Supporting Information Available: Experimental details for all new compounds; ^{1}H and ^{13}C NMR spectra for compounds **1**, **3**, **4**, **5**, **7**, **8**, **9**, **10**, **11**, **14**, **15**, **16**, **17**; COSY and NOESY spectra for compound **1**; X-ray structures of compounds **9** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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