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Facile synthesis of *C*-aryl glycals from sugar-derived lactones

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Abstract—A general entry to C(1) aryl-substituted glycals from the corresponding sugar lactones is described. This approach features one-pot access to aryl glycals. A variety of aryllithium reagents can be used and the method is compatible with various 2-deoxysugar lactones.

1. Introduction

C-Alkyl and aryl glycosides are important synthetic targets owing to their significant biological activities as antibiotic and anticancer agents.[1] In order to address problems associated with the synthesis of these natural products,[2] we developed a general entry to the major classes of *C*-aryl glycosides.[3] The strategy features the ring opening of cycloadducts that are obtained by the Diels–Alder reaction of substituted benzynes with glycosyl furans. Having established the basic elements of the approach, we then became interested in applying it to the synthesis of natural and non-natural *C*-aryl glycosides. In this context, we encountered a need for a facile and efficient route to *C*-aryl glycals, especially those derived from furans.

Owing to their obvious importance, a number of procedures for preparing *C*-aryl glycals have been recorded, including cross-coupling reactions of glycal derivatives,[4] ring closing metatheses of dienes,[5,6] and addition–eliminations of sugar lactones.[7] However, all of these methods are subject to one or more limitations. For example, approaches to *C*-aryl glycals based on palladium-catalyzed cross-couplings of 1-iodoglycals or 1-metallated glycals are restricted because routes to the requisite glycal precursors are not general. Techniques involving ring closing metathesis suffer from the requirement of high catalyst loadings to obtain products in useful yields. The route to *C*-aryl glycals comprising the addition of aryl Grignard reagents to 2-deoxysugar lactones, followed by dehydration of the intermediate hemiketals requires the use of large excesses of Martin's sulfurane. Because of the cost of this reagent, this approach is impractical when larger quantities of material are required. In view of the limitations of the aforementioned methods, we set to the task of developing a more general procedure for the synthesis of *C*-aryl glycals from readily available materials, and we now wish to report these findings.

Of the existing methods for preparing *C*-aryl glycals, we found the method of Sulikowski to be particularly appealing,[7] because it employed readily available sugar lactones as the starting materials. We thus used this procedure as a starting point for our investigations. For example, addition of 2-furyllithium to sugar lactone **1** proceeded smoothly, but we found that the hemiacetal addition product **3** existed primarily in the open form **4** at room temperature in $CDCl_3$ (Scheme 1). Although this equilibrium is well known, it did not appear to interfere in previously reported reductive processes to form *C*-aryl glycosides.[3,7] However, when we treated this mixture with Martin's sulfurane according to the two-pot procedure of Sulikowski and co-workers,[7] the desired glycal **5** was obtained in only 32% yield. We were unable to optimize the procedure further.

It then occurred to us that difficulties with the aforementioned ring-chain tautomerism might be avoided if the intermediate lithium alkoxide of the hemiketal **3** could be trapped in situ to give a derivative that would undergo facile elimination to give the desired

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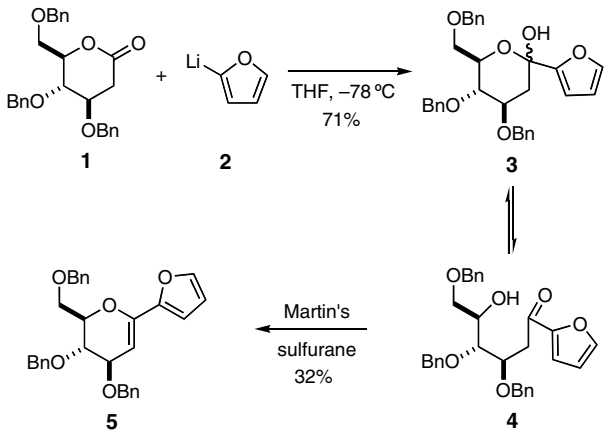
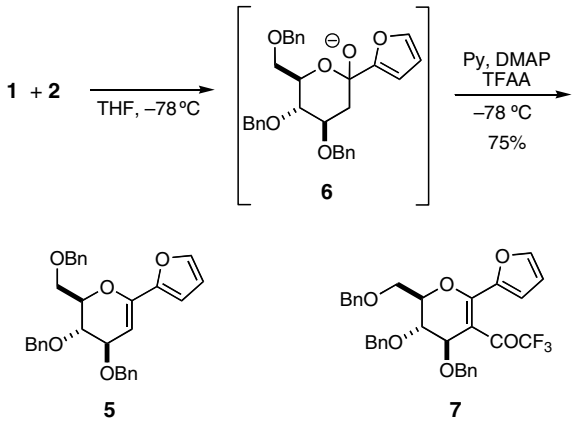


Scheme 1.

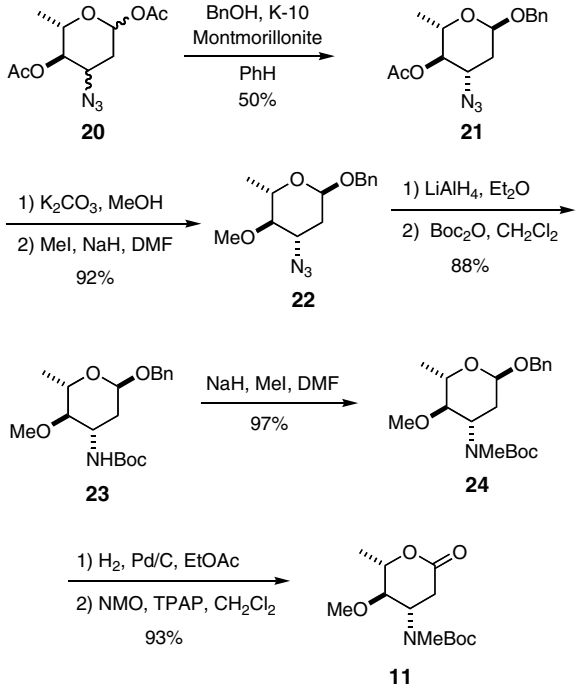
glycal **5**. Thus, following addition of **2** to **1**, the alkoxide **6** was treated at −78 °C with a mixture of pyridine, 4-*N*,*N*-dimethylaminopyridine (DMAP), and trifluoroacetic anhydride (TFAA) to furnish the furylglucal **5** in very good yield (Scheme 2). If a large excess of TFAA was present, acylation of the glycal enol ether ensued,[8] affording the α-furyl-β-trifluroacetoxyglucal **7** as a significant by-product (22% yield). Indeed, when **5** was treated with an excess of TFAA in the presence of pyridine and DMAP, **7** was isolated in 63% yield. Several experiments were conducted to see whether other electrophilic trapping agents might prove superior to TFAA. However, use of acetic anhydride (Ac_2O), methanesulfonyl chloride (MsCl), and triflic anhydride (Tf_2O) furnished **5** in significantly reduced yields (12–32%).



Scheme 2.

Having optimized the procedure for the preparation of **5**,[9] we explored the generality of the method using a variety of aryllithium reagents and the known sugar lactones **1**,[10] **8**[11], **9**,[12] and **10**.[11] Lactones **1**, **8**, **9**, and **10** were prepared from the corresponding commercially available peracetoxy glycals. The acetoxy groups were first removed by saponification, and the hydroxyl groups were then globally protected as benzyl (or methyl) ethers.

Use of pyridinium chlorochromate (PCC)[10,12] to oxidize these glycals to lactones was somewhat capricious in our hands, and we found a two-step procedure to be more efficient. In the event, hydration of the glycals in the presence of $PPh_3{\cdot}HBr$[13] and subsequent oxidation of the intermediate lactols with TPAP[14] gave the desired sugar lactones. The amino lactone **11** was synthesized from the known azide **20**,[15] in good overall yield according to the sequence of reactions depicted in Scheme 3.

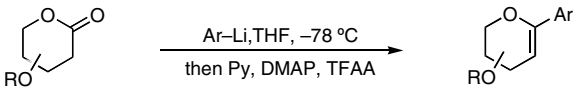


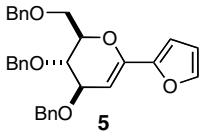
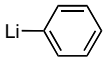
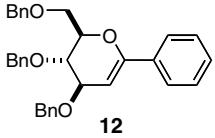
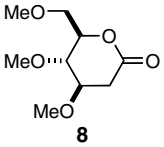
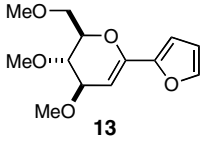
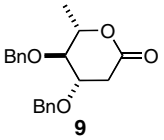
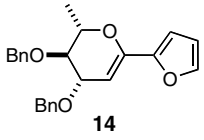
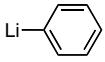
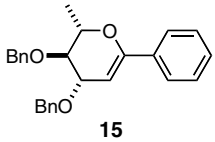
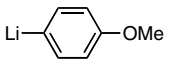
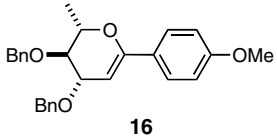
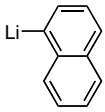
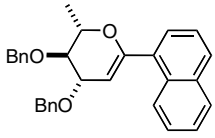
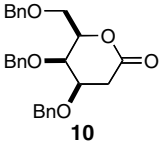
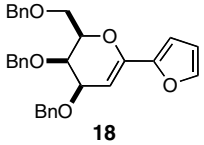
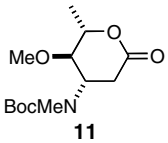
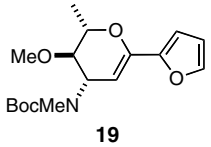
Scheme 3.

Generally good to excellent yields of aryl glycals were obtained using a variety of aryllithiums and sugar lactones (Table 1). The yield of the aryl glycal seems to be directly related to the nature of the starting sugar. For example, *C*-aryl rhamnals were invariably formed in the best yields (Table 1, entries 4–7). The 6-deoxy aminoglycal was also formed in excellent yield (entry 9). On the other hand, the formation of *C*-aryl galactals proved to be somewhat problematic (Table 1, entry 8), and significant quantities of the corresponding acyclic δ-hydroxy ketone were consistently isolated. It thus appears that trapping of the alkoxide generated by addition of an aryllithium reagent to 2-deoxy galactose lactone **10** is slow relative to collapse of the hemiacetal alkoxide to give the open chain δ-hydroxy ketone. All attempts to improve the yield by varying the temperature, time, and equivalents of TFAA were unsuccessful.

In summary, we have developed a general and efficient method for the synthesis of *C*-aryl glycals from the corresponding 2-deoxysugar lactones in a one-pot operation.

Table 1. Preparation of *C*-aryl glycals from sugar lactones[9]



Entry	Lactone	Ar–Li	Product[a]	Yield[b]
1	**1**		 **5**	75%[c]
2	**1**		 **12**	76%
3	 **8**		 **13**	75%
4	 **9**		 **14**	92%
5	**9**		 **15**	91%
6	**9**		 **16**	86%
7	**9**		 **17**	95%
8	 **10**		 **18**	31%
9	 **11**		 **19**	92%

[a] Products obtained were >95% pure by ^{1}H NMR.
[b] Reported yield for 0.2 mmol scale reaction, except for entry 9 (0.8 mmol scale).
[c] Reaction also performed on 8.3 mmol scale in 71% yield.

A number of aryllithium reagents and sugar-derived lactones have been shown to be compatible with the procedure, so it should be of general utility in the carbohydrate field.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.02.150.

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