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Disiloxane-Protected 2-Deoxyribonolactone as an Efficient Precursor to 1,2-Dideoxy-1-β-aryl-D-ribofuranoses

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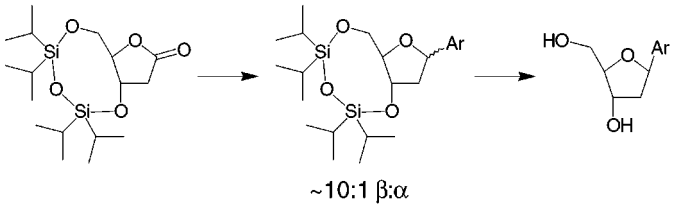
ABSTRACT



Aryl C-nucleosides are analogues of natural nucleosides where the bases have been replaced with aromatic moieties. Work herein describes the highly stereoselective syntheses of non-hydrogen-bonding carbocyclic derivatives using a disiloxane-protected 2-deoxy-D-ribono-1,4-lactone as a stable and readily accessible starting material. Unlike the bis(TBDMS)-protected congener, this compound enables the use of sterically congested *ortho*-substituted aryllithium reagents in the initial addition reaction.

There has been much interest in the synthesis of nucleoside derivatives bearing carbocyclic aromatic moieties in the place of the nucleobases. Aryl C-nucleosides maintain the ability for aromatic stacking while relinquishing their hydrogen-bonding potentials. Due to these characteristics, such molecules have been studied as potential universal bases[1] and as non-hydrogen-bonding isosteres of natural bases.[2] Moreover, there is much potential for the use of such nucleoside replacements in the design of novel base pairs involving hydrophobic interactions and shape complementarity.[3]

Despite the relatively straightforward structures of these compounds, efficient methods for the synthesis of simple aryl C-nucleosides are scarce. The key synthetic issue is the incorporation of the aryl moiety in the β-configuration, which mimics the anomeric stereochemistry of natural nucleosides. The most common method for the synthesis of these compounds involves the reaction of diarylcadmium reagents with 1,2-dideoxy-3,5-di-*O*-*p*-toluoyl-α-1-chloro-D-ribofuranose.[4] Unexpectedly, these substitution reactions do not proceed with inversion but yield the α-anomers as the major products in moderate yields.[4] The α-anomers can be equilibrated under acidic conditions to mixtures favoring the β-anomers, providing moderate yields of the desired compounds.[4]

The lack of stereochemical control in the addition reaction and the limited stability of the key chlorofuranoside[5] intermediate prompted this laboratory to explore alternative routes to aryl C-nucleosides. Recently, we reported a method for the synthesis of 1,2-dideoxy-β-1-phenyl-D-ribofuranose

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(4) (a) Ren, R. X.-F.; Chaudhuri, N. C.; Paris, P. L.; Rumney, S.; Kool, E. T. *J. Am. Chem. Soc.* **1996**, *118*, 7671. (b) Guckian, K. M.; Schweitzer, B. A.; Ren, R. X.-F.; Sheils, C. J.; Paris, P. L.; Tahmassebi, D. C.; Kool, E. T. *J. Am. Chem. Soc.* **1996**, *118*, 8182. (c) Chaudhuri, N. C.; Ren, R. X.-F.; Kool, E. T. *Synlett* **1997**, 341.

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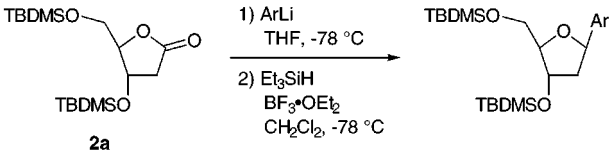
(**1a**) based upon the addition of phenyllithium to a protected 2-deoxy-D-ribono-1,4-lactone followed by stereoselective reduction of the resulting hemiketal.[6] This result demonstrated that approaches used for syntheses of aryl ribofuranoses[7] could be applied to the efficient and stereoselective synthesis of a β-aryl 2-deoxyribofuranose. Significantly, this method utilizes an easily prepared, shelf-stable precursor. The modification of this methodology to produce a general synthesis of other aryl C-nucleosides is reported in this Letter.

Initial efforts focused on the addition of several aryllithium reagents to the 3,5-di-*O*-TBDMS ether of 2-deoxy-D-ribono-1,4-lactone (**2a**) used previously (Scheme 1).[6] Unexpectedly,

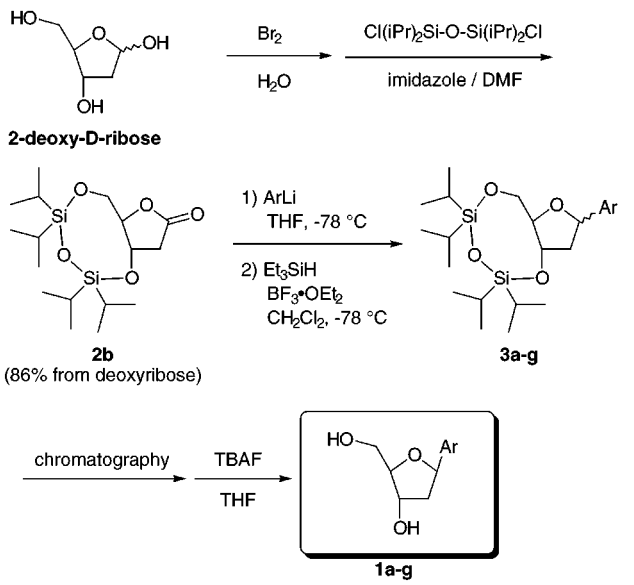
Scheme 1



this reaction proved to be very sensitive to substitution on the aryllithium reagent. For example, reactions of **2a** with 4-tolyllithium, 3-tolyllithium, or 2-naphthyllithium followed by treatment with $Et_3SiH/BF_3{\cdot}OEt_2$ produced significantly diminished yields of the C-nucleosides (10, 8, and 16%, respectively). Aryllithiums with substitution adjacent to the carbanion (2-tolyllithium and 1-naphthyllithium) produced none of the desired product. Because the desired C-nucleosides and unreacted starting material were the only products isolated, it appeared that the addition of the aryllithium reagent was the problematic step. It was postulated that the *O*-protecting groups hindered the approach of the aryllithium reagents toward the lactone carbonyl carbon. Although these groups appear remote to the reactive site, the trajectory of the aryllithium reagent must bring it directly over the furanose ring during the course of the reaction. It appears likely that the TBDMS groups are large enough to sterically hinder this approach. One possible means to reduce the steric influence of these groups is to restrict their motion by imposing a cyclic structure. The bifunctional disiloxane protecting group introduced by Markiewicz[8] is suitable for this purpose, and the cyclic 5′,3′-disiloxane derivatives of nucleosides are well-known compounds. Synthesis of the required deoxyribonolactone disiloxane (**2b**) was accomplished in two steps (Scheme 2). First, oxidation of 2-deoxy-D-ribose by aqueous bromine generates the corresponding 2-deoxy-D-ribono-1,4-lactone. Reaction of this crude product with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane and imidazole produces the protected 2-deoxy-D-ribono-1,4-lactone in excellent overall yields (≥85%) on a multigram scale.

Conversion of the 2-deoxy-D-ribono-1,4-lactone to the aryl C-nucleosides was attempted using the procedure previously

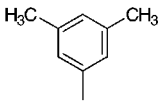
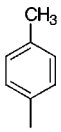
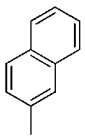
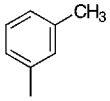
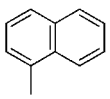
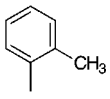
Scheme 2



employed by this laboratory.[6] Thus, aryllithium reagents were added to a solution of lactone **2b** at −78 °C (Scheme 2). The reaction was maintained at low temperature for an hour, when it was quenched. The crude products, which presumably include both diastereomeric hemiketals and the keto alcohols, were treated at −78 °C with Et_3SiH in the presence of a strong Lewis acid. This produces the corresponding C-nucleosides **3a**−**g** in higher yields than were observed with the TBDMS-protected starting material. Moreover, the reaction proved less sensitive to the nature of the aryllithium reagent, producing moderate yields of products even with sterically hindered reagents such as 1-naphthyllithium and 2-tolyllithium (Table 1).

One drawback to the use of the disiloxane protecting group is the observed formation of some of the α-diastereomer.

Table 1. Yields and β:α Ratios of **3a**−**g** from the Reaction of ArLi with **2b** Followed by Reduction with $Et_3SiH/BF_3{\cdot}OEt_2$

Ar	Total Yield (β:α)	Ar	Total Yield (β:α)
	**3a** 56% (11:1)		**3e** 34% (11:1)
	**3b** 24% (28:1)		**3f** 38% (10:1)
	**3c** 35% (15:1)		**3g** 34% (11:1)
	**3d** 17% (6.5:1)		

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(7) (a) Matulic-Adamic, J.; Beigelman, L.; Portmann, S.; Egli, M.; Usman, N. *J. Org. Chem.* **1996**, *61*, 3909. (b) Matulic-Adamic, J.; Beigelman, L. *Tetrahedron Lett.* **1997**, *38*, 203. (c) Matulic-Adamic, J.; Beigelman, L. *Tetrahedron Lett.* **1997**, *38*, 1669.
(8) Markiewicz, W. T. *J. Chem. Res, Synop.* **1979**, 24.

The β/α ratios (determined by ^{1}H NMR spectroscopy) were generally about 10:1 (Table 1), and the anomers can be separated by flash column chromatography. The configurations of the β-anomers of **3a**−**g** were confirmed by NOE experiments (data not shown). The stereochemical control of these reactions probably arises from a kinetic preference for attack of hydride upon the α-face of the C-1 carbocation, producing the β-aryl C-nucleoside. Loss of some stereocontrol indicates that the cyclic disiloxane group is affecting the conformational preferences of the carbocation intermediate.

Conversion of disiloxanes **3a**−**g** into the unblocked C-nucleosides **1a**−**g** can be readily accomplished using tetrabutylammonium fluoride in THF. All compounds produced spectroscopic data consistent with the assigned structures or that agreed with data previously reported by others[1,4a] (see Supporting Information). Overall, this route represents an efficient method for the syntheses of 1,2-dideoxy-1-β-aryl-D-ribofuranoses. The reaction sequence described herein utilizes a stable intermediate that can be converted in moderate yields and excellent stereoselectivities into the desired aryl C-nucleosides. The use of other organolithium reagents in this protocol is currently being explored.

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Supporting Information Available: Preparative procedures and spectroscopic data for **2a**, **3a**−**g**, and **1a**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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