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AN IMPROVED ROUTE TO 1,2-DIDEOXY-β-1-PHENYL-D-RIBOFURANOSE

Uthai Wichai and Stephen A. Woski*

Department of Chemistry and Coalition for Biomolecular Products

Box 870336, The University of Alabama, Tuscaloosa, AL 35487-0336, U.S.A.

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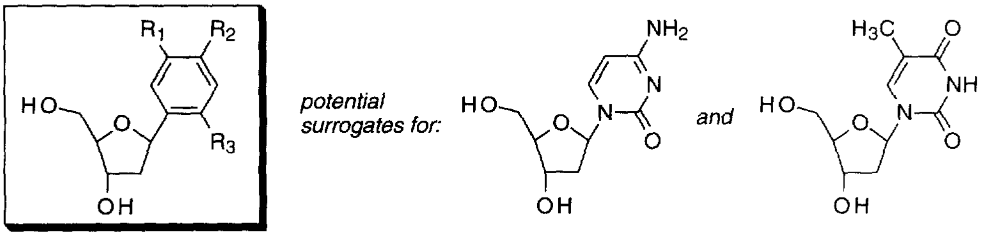
Abstract: An efficient synthesis of the aryl nucleoside analogue 1,2-dideoxy-β-1-phenyl-D-ribofuranose (**1**) is described. This route utilizes the addition of phenyllithium to a protected 2-deoxyribonolactone followed by reduction with triethylsilane/boron trifluoride etherate to selectively produce the β-anomer. Deprotection yields the desired aryl C-nucleoside in 27% overall yield from 2-deoxy-D-ribose.

Recently, there has been much interest in the synthesis of nucleoside derivatives bearing carbocyclic aromatic moieties at the anomeric position. Aryl C-nucleosides of this type can approximate the sizes and shapes of natural nucleosides. For example, phenyl C-nucleosides can serve as replacements for natural pyrimidine nucleosides. Moreover, the aryl C-nucleosides maintain the ability for aromatic stacking while relinquishing their hydrogen bonding potential. Due to these characteristics, these molecules have been studied as potential universal bases[1] and as nonhydrogen bonding isosteres of natural bases.[2]



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 control of the anomeric stereochemistry. Because the bases in natural nucleosides are found only in the β-configuration, selective formation of this anomer in aryl C-nucleosides is most desirable. Previously, the most successful method for 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 (the so-called chlorosugar).[3] Unexpectedly, this substitution reaction does not proceed with inversion but yields the α-anomers as the major products in moderate yields.[3] This compound can be equilibrated under acidic conditions to a mixture favoring the β-anomer (β/α from 2.5:1 to 4:1).[3] However, this extra step only provides a moderate yield of the desired compound.[3] Furthermore, while the use of the chlorosugar is well established, a limited shelf-life (~2 weeks) makes this compound a less than ideal intermediate.[4]

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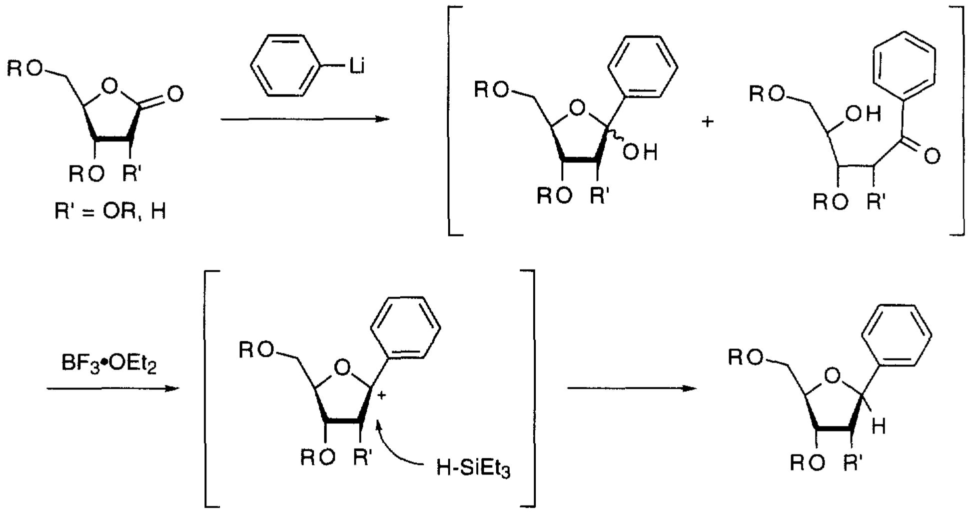
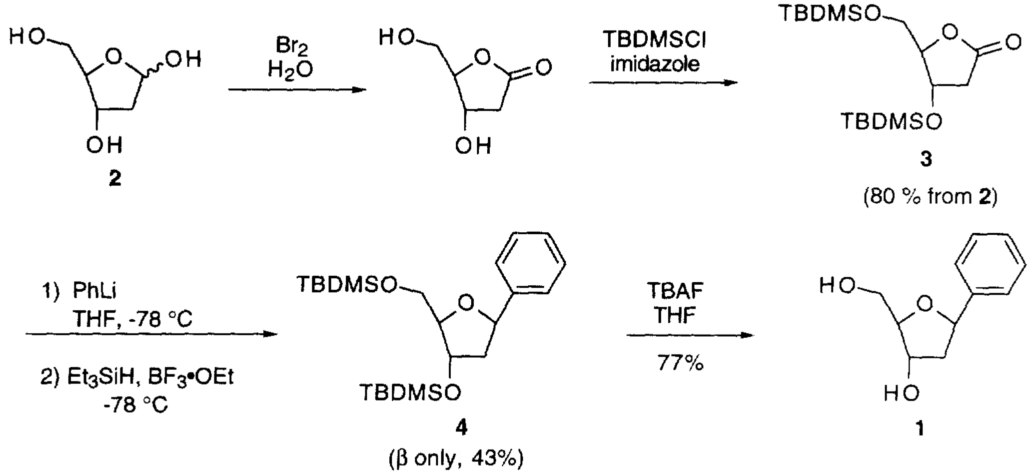
Herein, we describe a different synthetic approach toward carbocyclic aryl C-nucleosides, and we report its application to the synthesis of the simplest of these compounds, 1,2-dideoxy-β-1-phenyl-D-ribofuranose (**1**) (Scheme 1). This method utilizes the addition of an aryl organometallic reagent to a protected 2-deoxy-D-ribono-1,4-lactone. Reduction of the resulting mixture of products under Lewis acidic conditions using a silane as a hydride source should produce the desired deoxyribofuranose system. Notably, this approach has recently been applied by Matulic-Adamic, Beigelman, and coworkers[5] to the syntheses of aryl C-nucleosides of ribose in moderate to poor yields with complete β-stereoselectivity. However, at the outset it was not clear that this method could be successfully extended to the deoxyribose series. The key issue was whether the stereoselectivity would be maintained in the absence of a 2'-substituent. Presumably, this reaction proceeds through a 1'-carbocation intermediate with delivery of the hydride from the α-face. The α-2'-substituent could assist the approach of the silane from the more hindered face by control of the conformation of the ribofuranosyl ring or by direct interaction with the silicon center. Furthermore, this method has only been applied in relatively few cases,[5] so its scope is not yet known. Nevertheless, encouraged by observations in this laboratory that acid-promoted S_N1-type additions to 2-deoxyribofuranosyl cations generally occur from the α-face,[6] it seemed reasonable to examine the applicability of this scheme for the synthesis of β-aryl C-2'-deoxynucleosides.

Scheme 1



The key intermediate in this proposed route, a protected 2-deoxy-D-ribono-1,4-lactone, was synthesized from commercially available 2-deoxy-D-ribose (**2**). Thus, oxidation using aqueous bromine[7] and treatment of the crude product with *tert*-butyldimethylsilyl chloride (TBDMS-Cl)/imidazole[8] produced the desired 2-deoxyribonolactone **3** in 80% overall yield as a stable solid (Scheme 2). A THF solution of **3** was treated with phenyllithium, yielding a complex mixture of addition products and unreacted starting material. Treatment of the crude mixture with triethylsilane in the presence of BF_3•OEt_2 produced the desired product **4**.[9] Analysis

Scheme 2

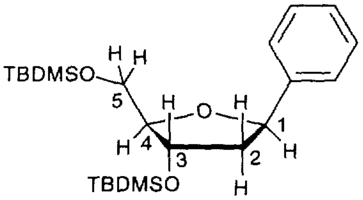


of the ^1H NMR spectrum[9] and NOE data (Table 1) support the assignment of this compound as the β-anomer. None of the α-anomer was detected; however, a significant amount of ribonolactone and trace amounts of a partially desilylated product were found.

It has been determined that the optimal reaction conditions require the maintenance of low temperature (-78 °C) for both the phenyllithium addition and the $Et_3SiH/BF_3 \cdot OEt_2$ reduction steps.[10] Under these conditions the yield of chromatographically purified product was 43% for the two steps; additionally, 10% of the starting material was recovered. A number of conditions were explored to drive the addition reaction to completion. It was found that even in the presence of a large excess of phenyllithium, unreacted ribonolactone was recovered. Warming the reaction mixture to 0 °C or room temperature did not result in the complete consumption of the starting lactone, but did lead to greatly reduced yields of the product. Similarly, altering the order of addition, changing the solvent to diethyl ether, or adding cosolvents such as 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) did not improve the results. Interestingly, other organometallic species such as phenylmagnesium bromide and phenylcerium dichloride did not show any reaction with the lactone.

The synthesis of the target aryl C-nucleoside was concluded by removal of the silyl protecting groups

Table 1: NOE data for 3,5-di-*O*-*tert*-butyldimethylsilyl-1,2-dideoxy-β-1-phenyl-D-ribofuranose (4)



	NOE enhancement					
Irradiation	H-1	H-2β	H-2α	H-3	H-4	H-5
H-1	------		3%		1.8%	
H-2β	2%	------	12.5%	4.8%		1%
H-2α	5.2%	12%	------	1.1%		
H-3		4%	1%	------	2.5%	1%
H-4	1.9%			2%	------	1.5%

using tetrabutylammonium fluoride (TBAF), producing **1** in 77% yield.[11] Overall, the synthesis of **1** from 2-deoxyribose requires five steps, only three of which require chromatography. The overall yield is 27%, and this could be further increased by recycling the recovered ribonolactone intermediate. This route constitutes an improvement over existing methods for the synthesis of **1** in terms of efficiency and selectivity. Moreover, the key intermediate, deoxyribonolactone **3**, is a stable and easily handed compound. Efforts are currently underway to extend this methodology to the syntheses of other aryl C-deoxynucleosides.

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References and Notes

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9. ^{1}H NMR for **4** (360 MHz, $CDCl_3$): δ 7.39–7.23 (m, 5H, Ar), 5.16 (dd, 1H, *J* = 10.3, 5.3 Hz, H-1), 4.44 (m, 1H, H-3), 3.98 (m, 1H, H-4), 3.78 (dd, 1H, *J* = 10.6, 3.7 Hz, H-5), 3.60 (dd, 1H, *J* = 10.6, 6.0 Hz, H-5), 2.13 (ddd, 1H, *J* = 12.7, 5.4, 1.4 Hz, H-2α), 1.93 (m, 1H, H-2β), 0.93 (s, 18H), 0.11 (s, 6H), 0.10 (s, 6H). ^{13}C NMR (90.7 MHz, $CDCl_3$): δ 142.3, 128.2, 127.3, 126.0, 88.0, 80.0, 74.4, 63.8, 44.2, 25.9, 25.8, 18.3, 18.0, 4.7, 4.6, 3.9.
10. Optimized procedure for synthesis of 3,5-di-*O*-*tert*-butyldimethylsilyl-1,2-dideoxy-β-1-phenyl-D-ribofuranose (**4**): A solution of **3** (1.02 g, 2.83 mmol) in 10 mL of anhydrous THF was cooled to -78 °C, and phenyllithium (1.13 M solution in hexane 3.49 mL, 3.94 mmol, 1.39 equiv) was added dropwise. The reaction mixture was stirred at -78 °C for 1 h; then the reaction was quenched by the addition of saturated aqueous NH_4Cl. The resulting mixture was extracted with ether, and the combined extracts were washed with water and brine, dried over anhydrous sodium sulfate, and filtered. Evaporation under reduced pressure afforded an oil which was dissolved in anhydrous CH_2Cl_2 (10 mL) and cooled to -78 °C. Et_3SiH (0.90 mL, 5.6 mmol, 2.0 equiv) was added to the solution, followed by the dropwise addition of $BF_3{\bullet}OEt_2$ (0.69 mL, 5.6 mmol, 2.0 equiv). The mixture was stirred at -78 °C for 6 hours and quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with ethyl ether, and the combined extracts were washed with saturated aqueous $NaHCO_3$, water, and brine. The organic phase was dried over anhydrous sodium sulfate and filtered, and the filtrate was evaporated under reduced pressure to afford crude product as an oil. Silica gel column chromatography (toluene, R_f = 0.51) afforded 0.514 g of **4** as pale-yellow oil (43 % from **3**).
11. The ^{1}H NMR spectrum of this material matched that reported by Millican and coworkers (Ref. 1). These workers unequivocally confirmed the β anomeric stereochemistry of their immediate synthetic precursor to **1** (the 3,5-di-*O*-toluoyl derivative) by X-ray crystallography (Gunning, J.; Neidle, S.; Millican, T. A.; Eaton, M. A. W.; Mock, G. A.; Mann, J. *Acta Cryst.* **1985**, *C41*, 720.).