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# Diastereoselective Synthesis of β-Aryl-*C*-nucleosides from 1,2-Anhydrosugars

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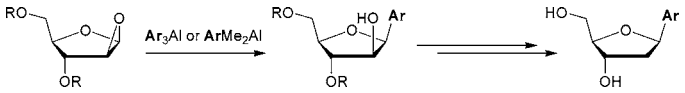
## ABSTRACT




**The cis opening of glycal epoxides with arylaluminum reagents provides strict stereocontrol in *C*-glycosylation. β-Aryl-*C*-2-deoxynucleosides are obtained from known glycals by an epoxidation–glycosylation–deoxygenation sequence.**

The replacement of nucleobases in oligodesoxynucleotides by designed surrogates is a frequently applied approach to confer new functions to DNA.[1−4] Aromatic base surrogates have been introduced with an aim to explore molecular interactions in DNA−DNA and DNA−protein recognition processes. For example, *C*-glycosidically linked aryl groups have allowed the role of hydrogen bonding and stacking to be discerned in DNA duplex formation.[5−12] Aromatic base surrogates can be accepted by DNA-polymerases and have thus been used to extend the genetic code.[5,6,13−15] We,[16] and others,[17−20] have incorporated polycyclic aromatic hydrocarbons as a means of studying the mechanism of DNA methylation and DNA repair. Interesting opportunities also are provided by fluorescent base surrogates which have utility as spectroscopic probes.[21]

Most studies have relied on the use of β-configured 1-*C*-aryl-2-deoxynucleotides, which mimic the anomeric stereochemistry of natural nucleosides. A crucial step in the synthesis of these building blocks is the β-selective incorporation of the aryl moiety.[22] The commonly used coupling of *O*-toluoyl-protected 1-chloro-2-deoxyriboside (Hoffer's chlorosugar)[23] with arylcadmium, arylmagnesium, arylzinc, or arylcopper reagents yields mixtures of anomers, with the less desired α-anomer as the major compound.[16,24,25] Sub-

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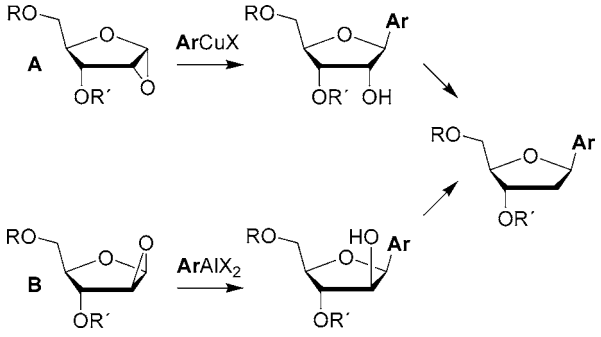
sequent acid-catalyzed anomerization reactions allow a shift in the anomeric ratio to provide the $\beta$-product in excess.[24,26] Friedel−Crafts alkylation of activated aromatic hydrocarbons using Lewis acids and methoxysugars as glycosyl donors provides direct access to predominantly $\beta$-*C*-aryl nucleosides.[27] In all of these syntheses, laborious separation from the α-anomers is still a necessity and, at times, a most challenging step. High $\beta$-selectivity has been reported for methods that draw upon the coupling of aryllithium reagents to benzyl- or disiloxane-protected 2-deoxyribonolactones.[7,12,28] Two subsequent stereodifferentiating reactions are combined in a reaction sequence that comprises palladium-catalyzed coupling of aryl iodides with glycals and reduction of the 3′-keto group.[29] We envisioned that the stereoselective opening of epoxides with arylmetal reagents should provide a more facile means of exerting strict stereocontrol in *C*-glycosylation reactions. The trans opening of 1,2-anhydroribose has been used for the preparation of nucleosides.[30] To our surprise, *C*-glycosylation with 1,2-anhydro furanoid sugars has not been described. In this paper, we present our study on the diastereoselective *C*-glycosylation with 1,2-anhydro sugars. It is shown that the coupling of arylaluminum reagents with 1,2-anhydroarabinose enables rapid and $\beta$-selective syntheses of 1′-*C*-aryl-2′-deoxynucleosides containing interesting aryl aglycons such as methylnaphthalenes and phenylnaphthalenes. It has been noted previously that glycosylation of heterocycles via glycal epoxide intermediates proceeds with high diastereoselectivity.[30] We reckoned that the trans-selective opening of 1,2-anhydroribose **A** with organocuprates followed by deoxygenation would provide the desired 1-*C*-aryl-2-deoxynucleoside in pure $\beta$-anomeric form (Scheme 1). As an alternative entry we considered the

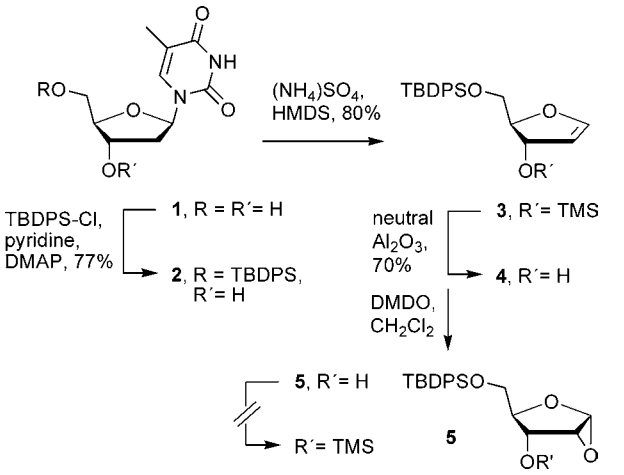
**Scheme 1.** Diastereoselective *C*-Glycosylation via 1,2-Anhydro Furanoid Sugars




cis-selective opening of the glycal epoxide **B** having the arabino configuration.

We first attempted the trans-selective opening of glycal epoxide **A** having the ribo configuration. The synthesis of a suitably protected 1,2-anhydroribose such as **A** (R = TBDPS, R′ = TMS) was required. The known 5-*O*-protected glycal **4** was synthesized from thymidine as described (Scheme 2).[31]

**Scheme 2.** Synthesis of Protected 1,2-Anhydroribose




The free 3-hydroxy group in **4** was necessary to achieve the desired selectivity in the epoxidation of the 1,2-double bond from the α-side to furnish 1,2-anhydroribose **5**. Next, the 3-hydroxyl group was protected in the presence of the epoxide **5**; this was required to render the 2′-hydroxy group, after epoxide opening, amenable to Barton deoxygenation. However, attempts to reinstall the 3-*O*-TMS ether in **5** were plagued by concomitant opening of the epoxide. After noticing the high reactivity of the glycal epoxide **5**, it was deemed important to avoid protecting group manipulations at this stage of the synthesis.

It was anticipated that a cis opening of the 1,2-anhydroarabinose **8** would allow the synthesis of aryl-$\beta$-*C*-arabinonucleosides **9** featuring an unprotected hydroxyl group at carbon-2 (Scheme 3).[31] The required epoxide **8** was obtained from the known glycal **7**[31] (prepared by a two-step synthesis from thymidine in 86%) by treatment with dimethyldioxirane (DMDO) in dichloromethane at 0 °C. Epoxidation of the fully protected glycal **7** occurred selectively from the $\beta$-side. The subsequent *C*-glycosylation reactions were explored using the naphthyl group as aglycon. Treatment of **8** with 1-naphthyllithium in the presence of aluminum trichloride conferred the desired cis opening. However, TLC analysis revealed the formation of various byproducts. Attempts to minimize decomposition by using $BF_3{\cdot}Et_2O$ for cis opening did not furnish the desired product **9**. The reaction of glycal epoxide **8** with trinaphthylaluminum, itself obtained from naphthyl Grignard reagent and aluminum trichloride, proceeded smoothly. The characteristic cross-peaks for H1′ and H4′ in the NOESY spectrum confirmed the $\beta$-configuration of 1-aryl-*C*-arabinonucleoside **9**. Best results were obtained by omitting the workup of **8** and by using thioanisole to quench excess DMDO. Under these conditions, 1-naphthyl-

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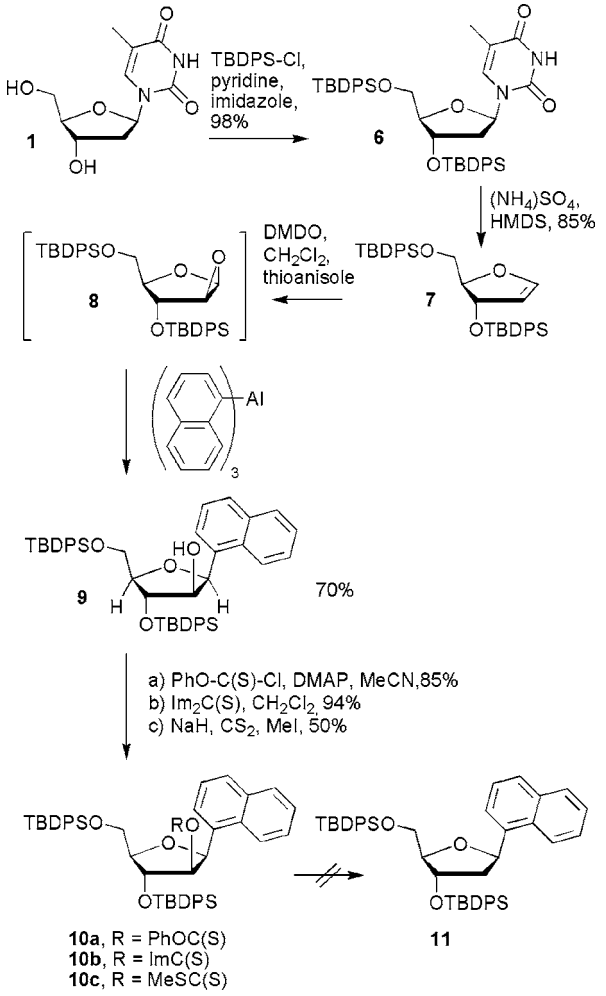
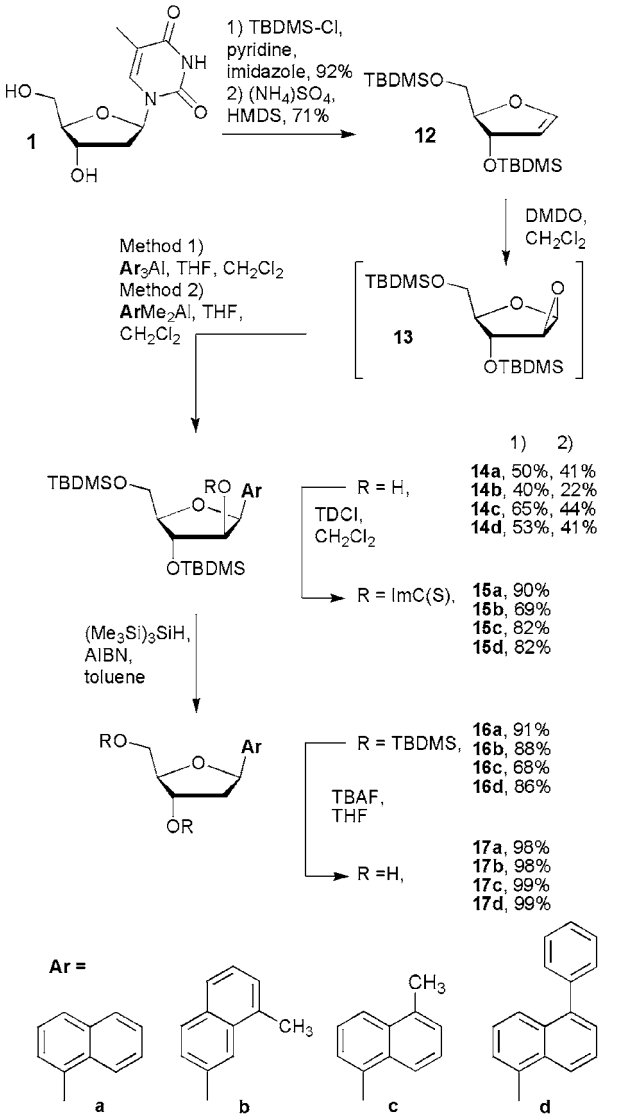
**Scheme 3.** Cis-Selective Opening of 1,2-Anhydroarabinose




**Scheme 4.** Synthesis of $\beta$-Aryl-*C*-nucleosides **17a**−**d**




$\beta$-*C*-arabinonucleoside **9** was afforded in 70% combined yield. The next step was the deoxygenation of the 2′-hydroxy group of the arabinonucleoside **9**. The phenylthionocarbonate **10a**, thiocarbonylimidazole **10b**, and methyl xanthate **10c** were synthesized. However, attempts to achieve the deoxygenation of **10a**−**c** by using tributyltinhydride or tris(trimethylsilyl)silane[32] as the reducing agent, and AIBN failed to deliver significant yields of desired product **11**.

We presumed that the deoxygenation was not successful due to the bulkiness of the two TBDPS groups and we reasoned that the use of *tert*-butyldimethylsilyl (TBDMS) protecting groups would provide less steric hindrance. To investigate this assumption, the TBDMS-protected glycal **12**[31] was prepared from thymidine. Epoxidation of **12** and cis opening of epoxide **13** with trinaphthylaluminum was performed as described for TBDPS-protected glycal **7**. The 1-naphthyl-$\beta$-*C*-arabinonucleoside **14a** was obtained in 50% yield from **12**. Importantly, the 3′,5′-*O*-TBDMS-protected arabinose derivative was amenable to deoxygenation. In the event, the 2′-hydroxyl group was allowed to react with thiocarbonyldiimidazole followed by treatment with tris(trimethylsilyl)silane and AIBN (Scheme 4). The two-step Barton deoxygenation[33] furnished the 2′-deoxynucleoside **16a** in 82% yield. Final desilylation was performed by treatment with tetrabutylammonium fluoride in tetrahydrofuran to afford fully deprotected 2′-deoxy-1′-$\beta$-naphthylnucleoside **17a**[8,24] in 98% yield.

After having secured synthetic access to the $\beta$-naphthyl-2′-deoxynucleoside **17a**, we explored the generality of the route. Within an ongoing project toward the use of bulky base surrogates as probes of enzymatic DNA methylation, we were in need of methyl- and phenylnaphthalene-based arylnucleosides **17b**−**d**. The required bromonaphthalenes **20b**−**d** were synthesized starting from 5- and 7-bromotetralones **18b**,**c** (Scheme 5).[34] The reaction with methylmagnesium chloride at 0 °C furnished alcohols **19b** and **19c** in

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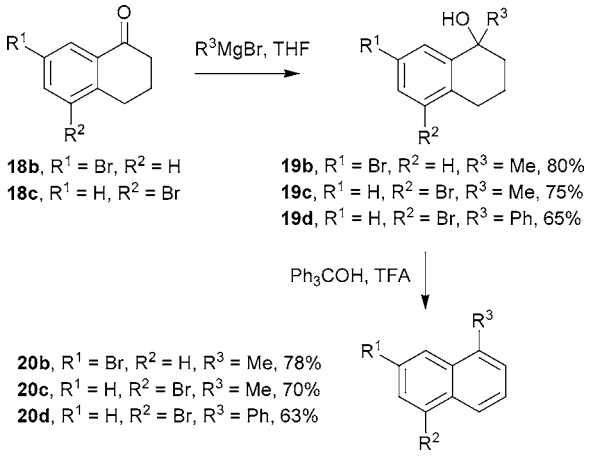
**Scheme 5.** Synthesis of Naphthalenes **20b−d**




80% and 75% yield, respectively. Subsequent treatment with TFA and triphenylmethanol delivered the corresponding bromonaphthalenes **20b** and **20c** in 78% and 70% yield. The preparation of 5-bromo-1-phenylnaphthalene **20d** was accomplished in 41% overall yield by exposing 5-bromotetralone **18c** to phenylmagnesium bromide followed by acid-mediated aromatization.

For the synthesis of the 2′-deoxy-1′-$\beta$-naphthylnucleosides **14b−d**, the bromonaphthalenes **20b−d** were converted to the corresponding trinaphthylaluminum reagents via Grignard intermediates. Sequential epoxidation of glycal **12** and cis-selective opening of glycal epoxide **13** proceeded with 40−65% combined yield. To reduce the amount of aryl equivalents in the organoaluminum reagent the use of dimethylnaphthylaluminum was investigated. In this case (method 2), the combined yield of the epoxidation-*C*-glycosylation sequence amounted to 41% for the naphthyl- and the phenylnaphthylnucleoside **14a** and **14d** and 44% and 22% for the methylnaphthylnucleosides **14c** and **14b**, respectively. Remarkably, the reaction still proceeded with exclusive cis selectivity, products from trans opening reactions were not detected. It was noticed that the use of dimethyl-1-(5-phenyl)-naphthenylaluminum led to the formation of minor amounts of two new easily separable products, arabinose dimer and trimer (see the Supporting Information). In progressing to the desired 2′-deoxynucleosides, the 2′-hydroxyl groups in arabinose derivatives **14b−d** were removed by means of the described two-step procedure. The deoxygenation at the TBDMS-protected arabinose again proceeded smoothly. Deprotection of the $\beta$-anomeric 2′-deoxyribose-*C*-nucleosides **16b−d** was performed by fluoride-mediated *O*-desilylation. Column chromatography furnished the unprotected aryl-*C*-nucleosides **17b−d** in excellent 98−99% yields.

A survey of the important methods for synthesis of $\beta$-aryl-*C*-nucleoside synthesis reveals that the shortest routes are provided by methods that lack diastereoselectivity in the *C*-glycosylation step. For example, the use of arylcadmium reagents[24] and Hoffer's chlorosugar[23] requires six steps in total to furnish $\beta$-aryl-*C*-nucleosides in up to 14% overall yield. The use of arylcopper reagents has allowed for improvements of the *C*-glycosylation step; however, the desired $\beta$-anomer still is formed as minor compound.[16] Predominant formation of $\beta$-products has been observed in Friedel−Crafts glycosylation chemistry, in which a Lewis acid induced the reaction of methoxy sugars with arenes to allow most rapid access, four steps in total, to aryl-*C*-nucleosides.[27] This route is restricted to electron-rich arenes (Hammett-Brown $\sigma^{+}_{arene} < -0{,}4$). In addition, the $\beta$-product still has to be separated from minor amounts of the α-anomer, which can be difficult. Diastereoselective *C*-glycosylation can be achieved by Heck-type couplings of arylpalladium species to glycals.[29] The yields that have been reported for the seven-step synthesis vary between 12 and 33%.[35,36] The reaction of *O*-benzyl-protected ribonolactone with aryllithium reagents and subsequent silane reduction also provides $\beta$-selectivity in aryl-2′-deoxynucleoside synthesis.[12] Aryl-*C*-nucleosides were obtained in 3% overall yield after 10 steps starting from commercially available ribose. The use of disiloxane-protected 2-ribonolactone allowed short syntheses of *C*-nucleosides in high yield with up to 83% diastereomeric excess.[28] The cis-opening of 1,2-anhydroarabinose by arylaluminum reagents described by us proceeds with exclusive $\beta$-selectivity and requires 7 steps, two of which (epoxidation-glycosylation and two-step Barton deoxygenation) can be performed consecutively without purification. Interestingly, aryl-*C*-nucleosides such as the 2′-deoxy-1′-*C*-phenylnaphthylnucleoside **17d** are obtained in up to 26% overall yield. The convenient protocol compares well to existing methods of aryl-*C*-nucleoside synthesis and avoids cumbersome steps such as iodoarene synthesis or separation of anomeric mixtures.

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**Supporting Information Available:** Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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