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Umpolung Strategy for the Synthesis of 2-Deoxy-*C*-aryl Glycosides: A Serendipitous, Efficient Route for *C*-Furanoside Analogues†

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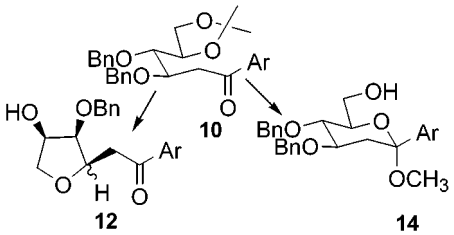
ABSTRACT



2-Deoxy-*C*-aryl glycosides are potential synthetic targets as they form a very vital moiety of several biologically active natural products. This paper describes a synthetic route using an umpolung strategy, which has not been explored till date. Our synthetic endeavor led to a versatile intermediate aryl ketone 10, which has paved the way for two important classes of *C*-glycosides, viz., *C*-alkyl furanosides 12 and methyl 2-deoxy-*C*-aryl pyranosides 14.

The *C*-aryl glycosides, part of the general *C*-glycoside[1] family, are carbohydrates with an aromatic ring directly attached to the anomeric carbon. Due to a strong C−C bond at the anomeric center, they are endowed with an inherent ability to withstand enzymatic and chemical hydrolysis.[2] These compounds therefore constitute an important class of biologically active natural products.[3] The class 2-deoxy-*C*-aryl glycosides, in particular, constitutes a common structural feature of several groups of antitumor antibiotics such as the angucyclines,[4] pluramycin,[5] gilvocarcins,[6] and the vineomycins.[7] Hence, they have become a vital subject of synthetic interest[8] to practicing carbohydrate chemists. The synthesis of *C*-aryl glycosides can be broadly classified as (1) activation of the anomeric center either as an electrophilic oxonium ion or as a nucleophilic carbanion followed by reaction with the corresponding aromatic equivalents,[8,9] (2) transition metal mediated cross-coupling between suitably functionalized glycosyl and aromatic coupling partners,[10] (3) cycloaddition between aromatic aldehydes and activated dienes,[11] and (4) benzannulation strategies based on as-

† Dedicated to Professor K. K. Balasubramanian and Professor B. Viswanathan (both from IIT-M, Chennai).

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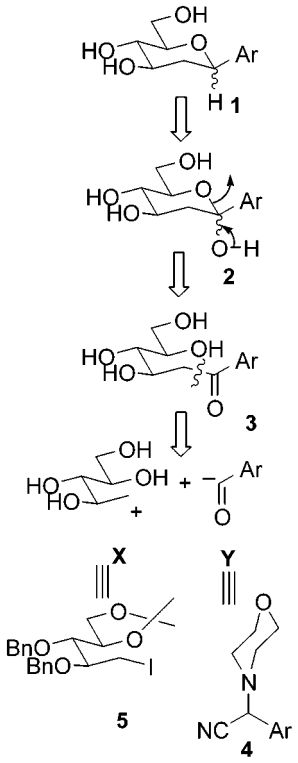
sembling the glycosylated aromatic ring from suitably functionalized carbohydrate precursors.[12]

The retrosynthetic analysis depicted in Scheme 1 invokes the use of an umpolung strategy. The route based on the

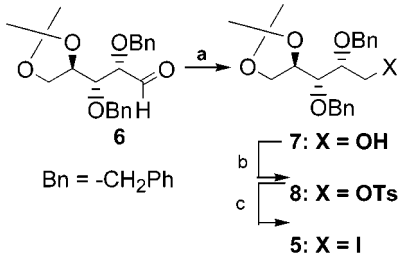
Scheme 1. Retrosynthetic Approach for 2-Deoxy-*C*-aryl Glycoside



umpolung strategy has never been explored in the literature for the synthesis of 2-deoxy-*C*-aryl glycosides **1**. The hemiketal **2**, a potential precursor for **1** should be readily amenable from the aryl ketones **3**. The strategy appeared to be extremely attractive, as there is no dearth of acyl anion equivalents in the literature.[13] From the plethora of reagents available for the acyl anion synthon **Y**, we were attracted by the less frequently used α-aminonitriles **4**, due to the simplicity and convenience involved in their preparation on a multigram scale.[14] Also, unlike alkylations of other acyl anion equivalents, which require much stronger bases, stringent dry conditions, and low temperatures, alkylation of α-aminonitriles are conveniently carried out at room temperature.[15] The arabino-configured electrophilic synthon **X** should be available from a suitably protected D-arabinose derivative.

The ready accessibility of the differentially protected sugar aldehyde **6**[16] (Scheme 2) from D-arabinose paved the way

Scheme 2. Synthesis of Electrophile **5**[a]

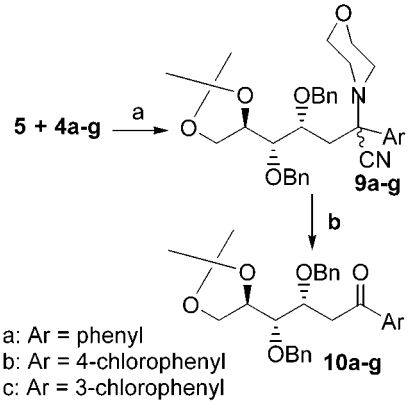


[a] Reagents: (a) $NaBH_4$, CH_3OH, 0 °C, 15 min, 83%. (b) *para*-TsCl, Et_3N, $CHCl_3$, catalytic DMAP, 24 h, 27 °C, 80%. (c) NaI, $NaHCO_3$, $(CH_3)_2CO$, 60 °C, 75%.

for the required iodo derivative **5** as a synthetic equivalent for the five-carbon electrophilic synthon **X**. Reduction of the aldehyde **6** with sodium borohydride afforded the alcohol **7** in 70% yield, which was activated as the tosylate **8** and converted to the iodide **5** in 75% yield by reaction with NaI in acetone.

The α-aminonitriles **4a**−**g** underwent clean alkylation with the iodo compound **5**, affording the alkylated products **9a**−**g** as diastereoisomeric mixtures in 75−77% yields (Scheme 3). The progress of the reaction could be easily seen by the

Scheme 3. Successful Alkylation of Aryl Acyl Anion Equivalent[a]



[a] Reagents: (a) NaH, Dry DMF, 1 h, 27 °C. (b) $CuSO_4 \cdot 5H_2O$, CH_3OH:H_2O, 5−6 h, 60 °C.

gradual decrease of the deep yellow color of the carbanion after addition of the electrophile. Without any purification, the alkylated products **9a**−**g** were directly subjected to hydrolysis using $CuSO_4 \cdot 5H_2O$ in aqueous methanol at 60

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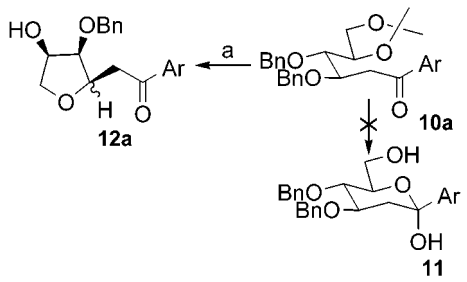
°C.[17] Clean unmasking of the keto functionality occurred to furnish the aryl ketones[18] **10a**−**g** in 68−70% yields.

Since hydrolysis of the terminal isopropylidene ketal protection in aryl ketones **10a**−**g**, under mild aqueous acidic conditions, should in principle give the 2-deoxy-*C*-aryl glycosides as hemiketals **11** (Scheme 4), compound **10a** as

Scheme 4. Serendipity Leading to the Formation of *C*-Alkyl Furanosides[a]



[a] Reagent: (a) 0.02 N H_2SO_4 in CH_3CN.

a representative example was subjected to reaction with 0.02 N sulfuric acid in acetonitrile. Interestingly, the isolated compound in 77% yield, strikingly revealed a characteristic carbonyl functionality (δ_C = 197.25 ppm in ^{13}C NMR and a strong band at ν = 1680 cm^{-1} in IR spectrum). ^1H NMR further indicated the presence of only one benzyloxy group (δ_H = 4.41 and 4.76 ppm, each d, 2H, J = 11.72 Hz). On the basis of the spectral evidence, the isolated compound was found to be **12a**[19] (Scheme 4).

The structure and the absolute configuration of the various stereogenic centers in compound **12a** were confirmed by performing extensive NMR experiments. Assignment of all

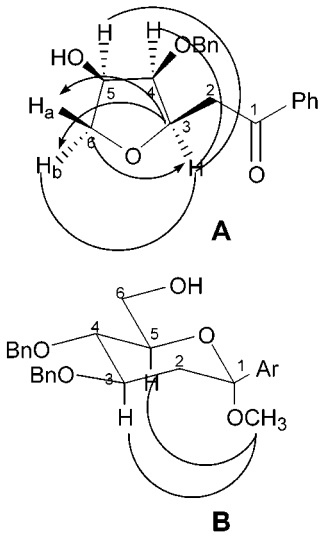
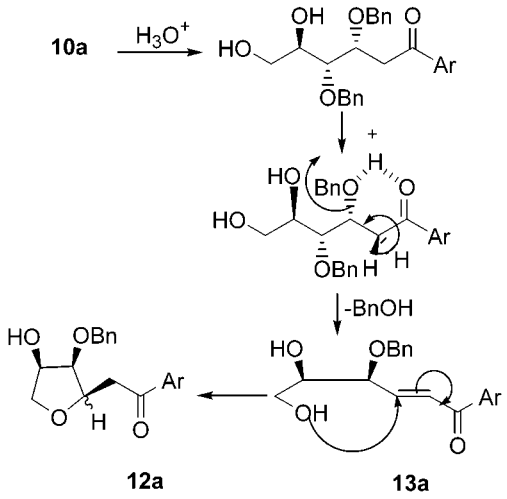


Figure 1. (A) Significant HMBC (→) and NOE observed in ROESY (↔) for **12a**. (B) Significant NOE observed in the ROESY for **14a**.

the proton signals in the molecule were perfomed by double-quantum-filtered correlation spectroscopy (DQF-COSY). All the carbons in the molecule were unambiguously correlated to the proton signals by performing a heteronuclear multiple-quantum coherence (HMQC) experiment. The presence of an ether bridge between C-3 and C-6 was confirmed from a heteronuclear multiple-bond correlation (HMBC) spectrum, which clearly indicated a ^3J correlation between C-3 and H-6a, H-6b as well as between C-6 and H-3 (Figure 1, A). Finally, rotating frame Overhauser spectroscopy (ROESY) revealed a strong NOE for H−C (3)/H−C(5) and H−C(3)/H−C(4), thereby locating all the substituents on the same side of the molecule. Since the stereochemistry at C-4 and C-5 is fixed, the orientation of the alkyl chain at C-3 must be β.

The mechanistic rationale for the formation of **12a** is also easily discernible (Scheme 5). Effective chelation of a proton

Scheme 5. Mechanism for the Formation of **12a**



between the oxygen atoms of the carbonyl group and β-benzyloxy group promotes a facile β-elimination leading to a potential Michael acceptor **13a**. A facile intramolecular Michael reaction from the more exposed face of the double bond explains the formation of the product **12a** with dominant β-selectivity. The generality for the formation of *C*-alkyl furanosides **12a**−**g** from **10a**−**g**, under 0.02 N H_2SO_4 in acetonitrile, was reproduced in good yields and β-selectivity as shown in Table 1.

To exclude the formation of the Michael acceptor **13a** either prior to or after the ketal hydrolysis, it became imperative to use nonacidic conditions for the removal of the isopropylidene ketal protection in **10a**. With the precedence that a dilute solution of iodine in methanol[20] has been

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(18) These aryl ketones were not stable; therefore, they were immediately used for subsequent reactions.

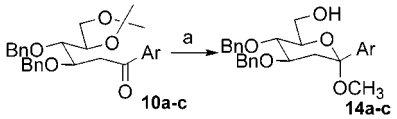
Table 1. Formation of *C*-Alkyl Furanosides from **10a**−**g** with a Solution of 0.02 N H_2SO_4 in Acetonitrile in 1.5 h

entry	product	% yield[a]	α:β ratio[b]
1	**12a**	77	1:10
2	**12b**	78	1:10.3
3	**12c**	76	1:8
4	**12d**	75	1:5.7
5	**12e**	72	1:10
6	**12f**	80	1:10
7	**12g**	70	1:1

[a] Isolated yields. [b] Calculated from ^{1}H NMR spectra.

used for deprotection of isopropylidene ketals, ketone **10a** was treated with a 1% solution of I_2 in methanol (Scheme 6). To our satisfaction, a clean reaction ensued furnishing

Scheme 6. Synthesis of Methyl 2-Deoxy-*C*-aryl Glucopyranosides[a]



a: Ar = phenyl
b: Ar = 4-chlorophenyl
c: Ar = 3,4,5-trimethoxyphenyl

[a] Reagents: (a) 1% I_2 in CH_3OH, 8 h, 27 °C, 76−80%.

the required 2-deoxy-*C*-aryl glucopyranoside as the methyl α-D-glucopyranoside derivative **14a** in 76% yield. Unambiguous assignments of all the proton signals in compound **14a** were performed by a DQF-COSY experiment. All the carbons in the molecule were unambiguously correlated to the proton signals by performing HMQC experiments. A ROESY correlation (Figure 1, B) revealed an Overhauser enhancement peak for OCH_3−C(1)/H−C(3) and OCH_3−C(1)/H−C(5), clearly placing all these substituents on the same side of the ring. Since the OCH_3 is located α, the orientation of the aryl moiety at C-1 was confirmed to be β. The formation of the pyranoside product[21] under 1% I_2/methanol solution conditions was further confirmed and generalized by two more examples, **14b** and **14c**, as depicted in Scheme 6.

In conclusion, our synthetic studies toward 2-deoxy-*C*-aryl glycosides, by an umpolung strategy that has not been reported to date, has led to versatile intermediate, aromatic ketones. These ketones provide both the pyranoside and furanoside analogues in good yields and stereoselectivity by a mere change in the deisopropylidenation conditions.

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Supporting Information Available: Characterization data for compounds **5**, **7**, **12a**−**g**, and **14a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) There is only one report for synthesis of this furanoside analogue by a Claisen condensation of methyl ketones with sugar lactones. Both the yields and stereoselectivity are poor in this work; see: Csuk, R.; Kuhn, M.; Strohl, D. *Tetrahedron* **1997**, *53*, 1311−1322.

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(21) Methyl ketosides have been conveniently deoxygenated to aryl glycosides: Shiozaki, M. *J. Org. Chem*. **1991**, *56*, 528−532.