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HF-Induced Intramolecular *C*-Arylation and *C*-Alkylation/Fluorination of 2-Aminoglycopyranoses

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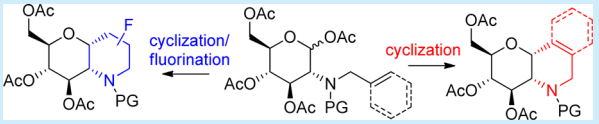
Supporting Information

ABSTRACT: Internal *C*-aryl and *C*-alkyl glycosides derived from 2-aminoglycopyranoses have been synthesized, exploiting a HF-mediated stereoselective intramolecular glycosylation. These conditions are compatible with acetate protecting groups and allow introduction of aromatics with various electronic distributions at the anomeric position. This strategy also provides straightforward entry to original fluorinated sugar−azacycle hybrids via a tandem internal *C*-glycosylation/fluorination reaction starting from 2-*N*-allyl/propargyl glycopyranoses. All cyclizations proceed in a 1,2-*cis* stereocontrolled manner.



C-Aryl glycosides[1] are natural products isolated from plants or microorganisms that demonstrate a vast array of important biological activities.[2] Among these, internal *C*-aryl glycosides, which have been found as ingredients in folk medicines,[3] encompass an enzymatically and chemically robust pseudoanomeric C−C bond and a conformationally locked aglycon moiety.[4] Internal *C*-aryl glycosides are also naturally occurring[5] and constitute a valuable stereocontrolled entry to *C*-aryl glycosides.[6] Their synthesis usually involves an intramolecular Friedel−Crafts reaction as the key step. Various Lewis acids and glycosyl donors bearing different protecting groups and anomeric leaving groups have been screened to optimize this process that is able to incorporate either a furanose[7] or a pyranose sugar unit (Figure 1).[8] To date, this methodology is limited to 2-*O*-aryl glycosides with electron-rich aromatics bearing OH, $SiMe_3$, CH_3, or OCH_3 substituents because of the inherent low electrophilicity[9] of the electrophilic sugar-derived intermediate. In this context, synthesis of unprecedented congeners is of interest as it may eventuate in the discovery of lead compounds having novel biological activities and pharmaceutical value. Exploiting the unique reactivity of organic compounds in superacid, we report herein a general and straightforward access to rare[10] internal 2-*N*-*C*-aryl and *C*-alkyl (fluorinated) glycosides derived from 2-glycopyranosylamines (Figure 1).

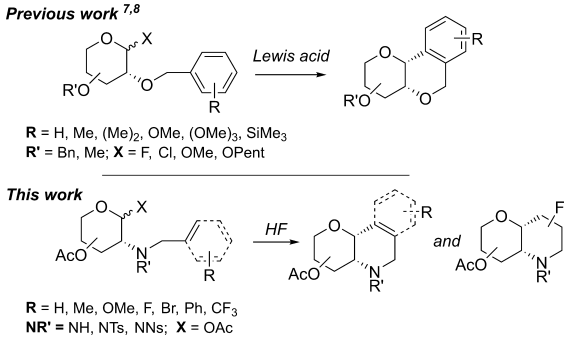


Figure 1. Previously developed methodologies from 2-*O*-aryl glycosides and the one disclosed herein from 2-*N*-aryl/alkyl glycosides to access internal *C*-aryl glycosides and fluorinated sugar−azacycle hybrids.

In marked contrast to acids, superacids[11] can generate polycationic superelectrophilic species[12] able to react with poor nucleophiles such as deactivated arenes.[13,14] Applied to carbohydrates, it could allow rapid anomeric arylation in a stereocontrolled manner through an intramolecular aglycon delivery provided the arene is already present in the glycosyl donor. We have previously identified the acetyl as the protecting group of choice when applying superacid conditions to carbohydrates.[15]

As a first approach, the reactivity of the peracetylated *N*-benzyl-β-D-2-aminoglucopyranose **1a** was examined, and several superacids were screened (Table 1). HF/SbF_5 failed to trigger the intramolecular *C*-arylation, even after modulating the acidity of the medium (Table 1, entries 1 and 2).[16] Satisfyingly, treatment of **1a** with neat liquid HF afforded the desired tricyclic product **2a** (41%) along with the fluorinated derivative **3a** (Table 1, entry 4).[17] Increasing the reaction time failed to improve the yield of **2a**. Use of neat CF_3SO_3H was unsuccessful (Table 1, entries 5 and 6). Protonation of the 2-amino group by HF, thus deactivating the anomeric position, might be responsible for the observed low conversion. This forced us to protect the secondary amine as its *N*-tosyl derivative to afford compound **1b**. Gratifyingly, upon HF treatment, **1b** led exclusively to the formation of the desired product **2b** (Table 1

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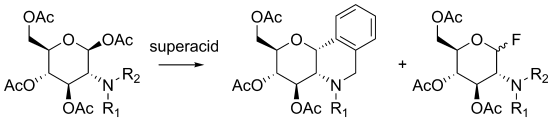
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Intramolecular C-Arylation of 2-Aminoglucosides



entry	substrate	conditions (superacid/ temp (°C) /time)	product ratio[c] 1/2/3	yield of 2a/ 2b[d] (%)
1	1a	HF/SbF_5[a]/−20/2 h	e	f
2	1a	HF/SbF_5[b]/−20/2 h	e	f
3	1a	neat HF/−20/2 h	1/3/1	f
4	1a	neat HF/−20/24 h	0[g]/3/1	41
5	1a	neat HF/−20/48 h	0[g]/3/1	37
6	1a	neat TfOH/0/1.5 h	e	f
7	1b	neat HF/−20/0.5 h	0/1/0	80
8	1b	neat HF/−40/15 min	0/1/0	88

[a]HF/SbF_5 (mol % SbF_5 = 21.6). [b]HF/SbF_5 (mol % SbF_5 = 13.8). [c]Ratio determined by ^1H NMR analysis of the reaction crude. [d]Yield obtained after purification by flash column chromatography. [e]Complex mixture. [f]Not determined. [g]Traces of starting material were detected.

entry 7). Finally, performing the reaction at −40 °C for 15 min proved beneficial and produced **2b** in excellent 88% yield (Table 1, entry 8).

The structure of **2b** was firmly established by X-ray crystallography (CCDC no. 1492103) and confirmed a 1,2-*cis* arrangement imposed by the stereochemistry of C-2 bearing the nitrogen-containing nucleophile (Figure 2). These results

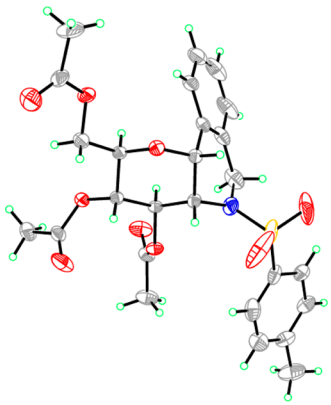


Figure 2. ORTEP drawing of compound **2b**.

demonstrate the ability of HF to activate the anomeric leaving group presumably leading to the formation of a transient glycosyl cation that is next trapped by the aromatic ring.

To define the scope of this process, the optimized cyclization conditions were applied to a range of 2-*N*-aryl glycosides, incorporating aromatics with various electronic distributions. These compounds were readily prepared by an *N*-sulfonylation/*N*-alkylation or reductive amination/*N*-sulfonylation synthetic strategy starting from commercially available 2-aminoglycosides (Figure 3).[18] In most cases, the cyclization proceeded smoothly, leading to exclusive formation of the 1,2 *syn* adducts. The inductively activated naphthalene-substituted derivative **1c** was converted to its cyclic counterpart **2c** in almost quantitative yield. The cyclization also readily took place with a methoxybenzyl substituent (products **2d**,**e**). For synthetic purposes, we switched to the *N*-nosyl derivatives

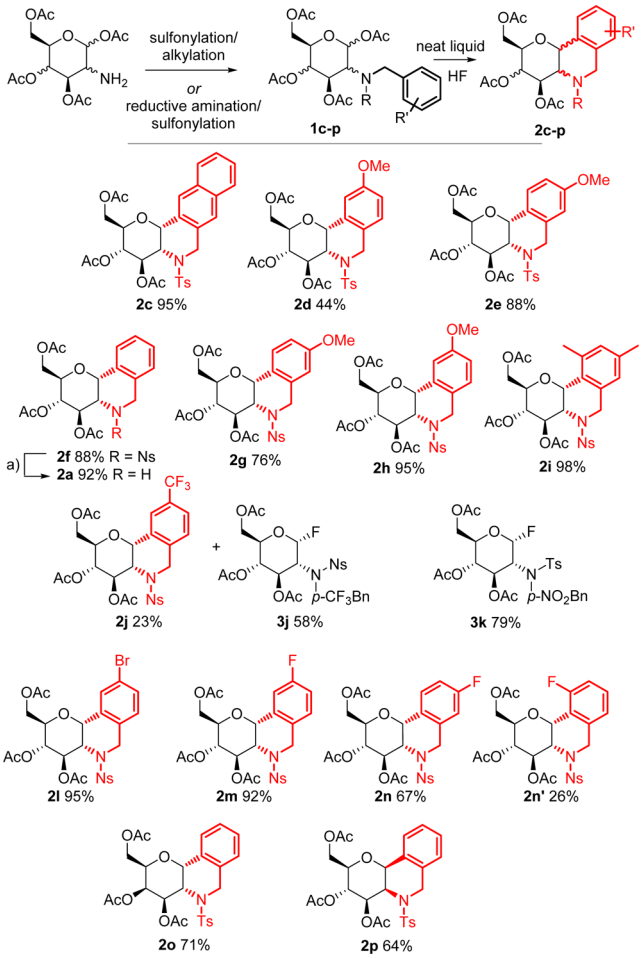


Figure 3. Scope of the HF-mediated cyclization applied to 2-*N*-benzylaminoglycosides. (a) $PhSH/K_2CO_3$, DMF.

which uneventfully afforded the internal *C*-aryl glucosides **2f**−**i** in high 76−98% yields. The convenient removal of the nosyl group was illustrated by the synthesis of the tetrahydroquinoline **2a** from **2f** by treatment with thiophenolate (92%).[19] We then moved to more electronically challenging aromatics bearing a Br, F, CF_3, or NO_2 substituent. Gratifyingly, along with the fluorosugar **3j**, we were able to isolate the trifluoromethyl derivative **2j** albeit in low yield (23%), a result that illustrates the superelectrophilic character of the transient glycosyl cation trapped by poor nucleophiles. The limit of this methodology was reached with the deactivated *p*-nitrophenyl derivative **1k** (*N*-tosyl) that only afforded the fluorosugar **3k** with no trace of the internal *C*-aryl glycoside (Figure 3).

Haloaromatics **1l**−**n** also cyclized efficiently to afford tricycles **2l**−**n**′ in excellent yields. Starting from monosaccharide **1n** bearing a fluorine atom in *meta* position on the aromatic ring, two internal *C*-aryl glycosides **2n** and **2n**′ were isolated, accounting for the low steric demand of the fluorine atom allowing rotation of the aromatic ring around the $C_{Ar}-C_N$ linkage. The generality of our approach regarding the glycosyl donor configuration was confirmed by briefly examining the D-*galacto*- **1o** and D-*manno*-configured **1p** derivatives that respectively furnished the corresponding internal *C*-aryl glycosides **2o** and **2p** in good yields (Figure 3).

Concerning the mechanism of this reaction, the isolation of the 1-fluoro sugars **3j** and **3k** and the identification of the remaining acetic acid by NMR analysis are in agreement with

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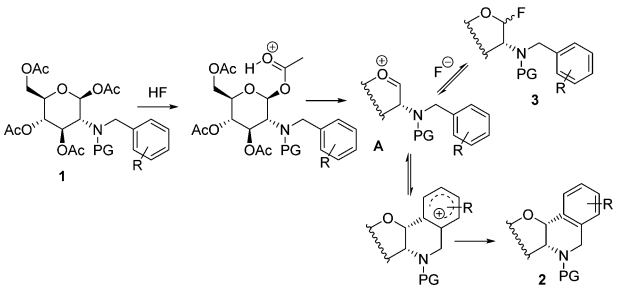
Org. Lett. XXXX, XXX, XXX−XXX

an activation of the anomeric acetate by protonation and the formation of the transient glycosyl oxocarbenium ion **A** in neat HF superacid (Scheme 1).[20] This oxocarbenium ion can then

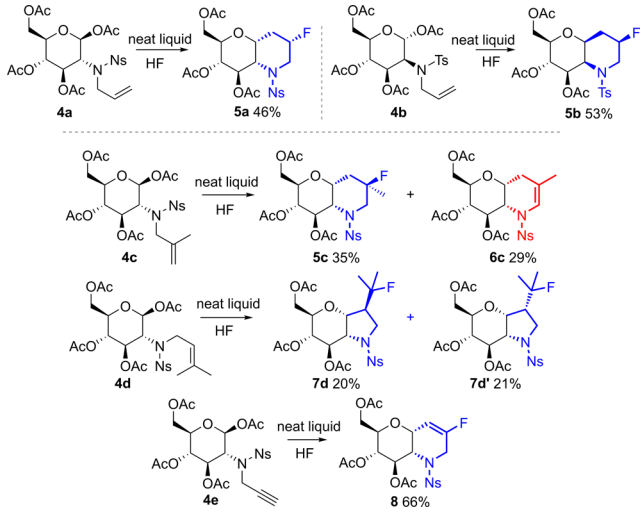
Scheme 1. Suggested Mechanism for the Generation of Fluorinated and *C*-Aryl Monosaccharides in HF Superacid



be fluorinated despite the weak nucleophilic character of the fluoride ions in these conditions.[21] Through activation of the resulting C−F bond, an equilibrium between the fluorinated product **3** and the cationic intermediate **A** can be postulated. The highly electrophilic character of this latter allows its subsequent and irreversible trapping by the arene to furnish the internal *C*-aryl glycoside **2**.

Extension of this strategy to 2-*N*-alkylglycosyl donors incorporating a C=C bond in the substituent at position 2 is worth investigating as it should provide original fused sugar-azacycle structures of biological and synthetic interest (Scheme 2).[22−24] Related 2-*O*-alkyl derivatives have been previously

Scheme 2. Cyclization/Fluorination Sequence Applied to 2-Aminoglycosides Bearing an Unsaturated Alkyl Chain at Position 2[a]



[a]Conditions: neat liquid HF, −40 or 0 °C, 1 h.

exploited by Crich in a cation-clock approach to decipher the chemical mannosylation mechanism.[25] Applying our optimized conditions to *N*-allyl-D-gluco- **4a** and -D-mannopyranose **4b** furnished the corresponding monofluorinated bicycles **5a** (46%) and **5b** (53%), respectively, exhibiting a 1,2-*cis* relationship.[26] In these derivatives, a stereodefined C−F bond β to the nitrogen atom was created, resulting from trapping of the transient cyclic cation by fluoride anions.[27−30] Noteworthy, performing the reaction at 0 °C was required in the mannopyranose series to go to completion demonstrating the singular reactivity of this monosaccharide.[18] Extension to substituted alkenes with compound **4c** bearing a methallyl group on the nitrogen produced the fluorinated product **5c** (35% yield) along with the elimination product **6c** (29% yield). Formation of the diastereomeric fluorinated pyrrolidines **7d** and **7d′** was observed starting from compound **4d**, as anticipated. The stereochemistry of compounds **5c**, **7d**, and **7d′** was determined by extensive NMR experiments.[18] Finally, the cyclization/fluorination process was applied to *N*-propargyl derivative **4e** to cleanly provide the fluoro olefin **8**.

In conclusion, we have explored the intramolecular Friedel−Crafts arylation of 2-aminoglycosides triggered by HF superacid, allowing the stereoselective delivery of a set of original internal 2-amino-*C*-aryl glycosides in the glucose, galactose, and mannose series. This reaction was extended further in the *N*-allyl and *N*-propargyl series to furnish fluorinated sugar−azacycle hybrids. These sugar-based polycyclic compounds with a central piperidine ring, amenable for further structural modification, are of interest in a medicinal chemistry context[31] in regard to the therapeutic potential of fluorine-containing molecules and sugar derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00003.

X-ray data for compound **2b** (CIF)

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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Org. Lett. XXXX, XXX, XXX−XXX