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## Accepted Article

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# Mild Palladium-Catalyzed Cyanation of Unprotected 2-Iodoglycals in Aqueous Media as Versatile Tool to Access Diverse *C2*-Glycoanalogues.

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**Abstract.** Access to unprotected 2-cyano-glycals *via* a mild palladium-catalyzed cyanation of protecting groups-free 2-iodoglycals in aqueous media has been developed. Diverse glycal substrates including disaccharide-type were successfully obtained in good to excellent yields. These unprotected 2-cyano-glycal scaffolds were successfully derivatized to different *C2*-glycoanalogues.

**Keywords:** unprotected glycosides; palladium catalysis; cyanation; aqueous media; 2-iodoglycals

## Introduction

The ubiquitous involvements of carbohydrate derivatives in biological responses has motivated the chemist community to develop synthetic tools to reach natural and unnatural analogues.[1] Design of unnatural mimics was largely explored in order to circumvent drawbacks of natural sugars. The main issue encountered by these biomolecules is related to their poor stability due to the sensitivity of natural C-O and C-N bonds. Enzymatically and chemically stable *C*-branched glycosides possessing an unnatural C-C bond were thus highly investigated.[2] Among the current synthetic routes to form C-C bonds on sugars, metal-catalyzed cross-couplings emerged as new powerful tools. In particular, during this last decade, 2-iodoglycal substrates attracted attention, due to their suitable reactivity in palladium-catalyzed processes. By this way, diverse *C2*-glycoanalogues were reached *via* classical Suzuki, Sonogashira, Heck, *etc*. cross-couplings. More recently, carbonylative reactions applied to 2-iodoglycals emerged (Scheme 1).[3] All these methodologies were carried out almost exclusively on *O*-protected iodoglycals (mostly acetylated or benzylated) except a single example of thiolation described by Messaoudi *et al.* on unprotected 2-iodo-D-glucal in organic media leading to moderate yield.[3h] Indeed, the use of unprotected carbohydrates as starting substrates raises many solubility and purification challenges as well as side reactivities due to the presence of numerous free hydroxyl groups.[4] Nevertheless, access to unprotected glycoanalogues in an acceptable scale is crucial for biological applications. Most of the current literature involving 2-iodoglycals does not deal with the deprotection of the obtained *C2*-glycals. However, deprotection may become challenging depending on the sensitivity of the introduced function. Indeed, per-acetylated sugars are usually deprotected in basic conditions,[5] which are incompatible with many functionalities. Similarly, hydrogenolysis, commonly used to remove benzyl protecting groups,[3i] could be deleterious in the presence of unsaturated functions. These limitations can constitute a dead end if the functional group introduced on the sugar reacts both with base and in the presence of hydrogen. One of the best example is certainly the nitrile group. However, nitrile is a particularly interesting functionality, which can be derivatized in many functions such as amide, carbonyl, tetrazole, amine, *etc.* Thus, *C2*-cyanoglycals appear to be potential versatile structures to access diverse glycoside derivatives. The first and only description of a procedure to synthesize such compounds in a protected version was by Hall *et al*. in 1973 using chlorosulfonyl isocyanate as cyanating reagent. This method was applied only on few examples in poor to modest yields.[6] Our strategy to reach these analogues was the opposite of the described literature on 2-iodoglycals. We decided to explore a new concept, to set the deprotection step before the introduction of the sensitive function (nitrile in our case). In consequence, this strategy required the development of both cyanation and subsequent derivatization steps on unprotected polar glycals (Scheme 1). Herein, we describe an access to diverse protecting groups-free *C2*-glycoanalogues *via* a key mild palladium-catalyzed cyanation reaction in aqueous media on unprotected 2-iodoglycals.

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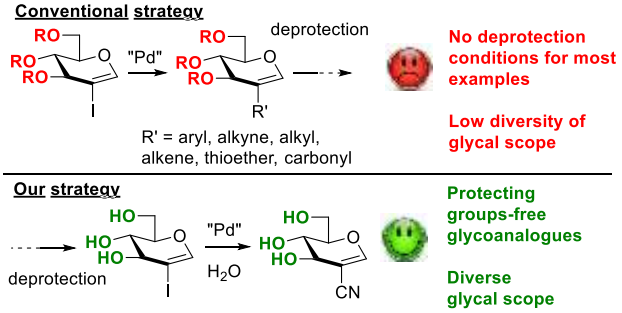
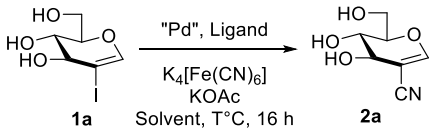



**Scheme 1**: Different strategies for palladium-catalyzed cross-couplings on 2-iodoglycals

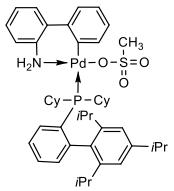
## Results and Discussion

The introduction of a nitrile group on aromatic substrates *via* palladium-catalyzed cross-coupling was largely explored in organic media[7] and was studied, to a lesser extent, in aqueous media at temperatures generally higher than 100°C.[8] In terms of cyanating reagent, our choice turned to a non-toxic, inexpensive cyanide source namely potassium ferrocyanide ($K_4[Fe(CN)_6]$). This reagent attracted more and more attention thanks to its non-hazardous properties and was already successfully used in many cyanation reactions.[7a] We started our methodology investigation on 2-iodo-D-glucal **1a**, obtained in two steps from the commercially available peracetylated D-glucal (Table 1, for detailed study see SI).[3g] Inspired by Buchwald cyanation conditions applied to aromatic compounds, **1a** was reacted in the presence of a palladium precatalyst, a ligand, a sub-stoichiometric amount of base and $K_4[Fe(CN)_6]$ in a mixture (1:1) of 1,4-dioxane/water at 100°C under argon atmosphere.[9] These conditions led to the formation of traces of the desired product **2a** (Table 1, entry 1). The use of *t*BuOH as organic co-solvent instead of 1,4-dioxane led to a good 62% yield in **2a** (Table 1, entry 2). Moreover, the solvent ratio of (1:1) appears to be crucial for the reactivity (Table 1, entries 3 and 4). Indeed, it was shown that cyanation reactions using $K_4[Fe(CN)_6]$ are optimal when cyanide anions are slowly delivered avoiding poisoning of the palladium complex.[8a] A decrease of the temperature to 75°C yielded **2a** in a good 72% (Table 1, entry 5). Unreactive argon atmosphere was also a crucial parameter since only 11% of **2a** were obtained under air atmosphere (Table 1, entry 6). Satisfyingly, we could halve both the amounts of precatalyst and ligand without significant loss of yield (Table 1, entry 7). On the other hand, only a slight excess of base compared to precatalyst amount is needed and furnished the best result yielding **2a** in an excellent 90% yield (85% isolated) (Table 1, entry 8). Indeed, the role of the base is assumed to be only the precatalyst activator. However, when the amounts of precatalyst, ligand and base were halved again, a modest yield of 44% was observed (Table 1, entry 9). The use of other couples of precatalysts/ligands was tested without any improvement (Table 1, entries 10-12). With the best conditions in hand (Table 1, entry 8), various unprotected 2-iodoglycals were engaged (Table 2). Several pyranoside glycal monosaccharides such as 2-iodo-D-galactal, 2-iodo-D-xylal as well as 2-iodo-L-rhamnal could be converted into their cyanated analogues in excellent yields (Table 2, **2b**, **2c**, **2d**).

**Table 1.** Optimization of the cyanation reaction on **1a**[a]




Pd-XPhos-G3 =




| Entry | T (°C) | Solvent (ratio) | Precatalyst (eq) | Ligand (eq) | KOAc (eq) | Yield (%)[b] |
|---|---|---|---|---|---|---|
| **1** | 100 | 1,4-dioxane/$H_2O$ (1/1) | Pd-XPhos-G3 (0.08) | XPhos (0.16) | 0.3 | Traces |
| **2** | 100 | *t*-BuOH/$H_2O$ (1/1) | Pd-XPhos-G3 (0.08) | XPhos (0.16) | 0.3 | 62[c] |
| **3** | 100 | *t*-BuOH/$H_2O$ (5/1) | Pd-XPhos-G3 (0.08) | XPhos (0.16) | 0.3 | 36 |
| **4** | 100 | *t*-BuOH/$H_2O$ (1/5) | Pd-XPhos-G3 (0.08) | XPhos (0.16) | 0.3 | 9 |
| **5** | 75 | *t*-BuOH/$H_2O$ (1/1) | Pd-XPhos-G3 (0.08) | XPhos (0.16) | 0.3 | 72 |
| **6** | 75 | *t*-BuOH/$H_2O$ (1/1) | Pd-XPhos-G3 (0.08) | XPhos (0.16) | 0.3 | 11[d] |
| **7** | 75 | *t*-BuOH/$H_2O$ (1/1) | Pd-XPhos-G3 (0.04) | XPhos (0.08) | 0.3 | 69 |
| **8** | **75** | ***t*-BuOH/$H_2O$ (1/1)** | **Pd-XPhos-G3 (0.04)** | **XPhos (0.08)** | **0.05** | **90[e]** |
| **9** | 75 | *t*-BuOH/$H_2O$ (1/1) | Pd-XPhos-G3 (0.02) | XPhos (0.04) | 0.025 | 44 |
| **10** | 75 | *t*-BuOH/$H_2O$ (1/1) | Pd-tBuXPhos-G3 (0.04) | *t*BuXPhos (0.08) | 0.05 | 35 |
| **11** | 75 | *t*-BuOH/$H_2O$ (1/1) | Pd-BrettPhos-G3 (0.04) | BrettPhos (0.08) | 0.05 | 55 |
| **12** | 75 | *t*-BuOH/$H_2O$ (1/1) | Pd-XantPhos-G3 (0.04) | XantPhos (0.08) | 0.05 | 45 |

[a] Conditions: **1** (0.165 mmol), $K_4[Fe(CN)_6]$ (0.4 equiv.), "Pd" (X equiv.), ligand (X equiv.), KOAc (X equiv.), organic solvent/$H_2O$ (0.760 mL), under Ar, T°C, 16h. [b] Determined by $^1H$ NMR using DMF as internal reference (see SI). [c] Corresponds to 56% isolated yield. [d] Under air atmosphere. [e] Corresponds to 85% isolated yield.

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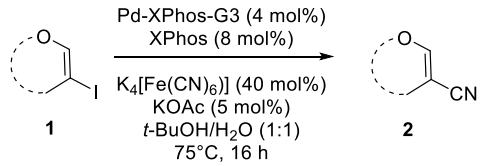
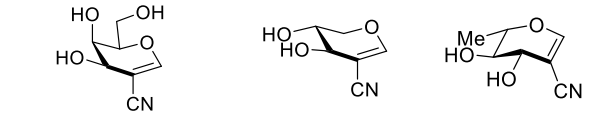
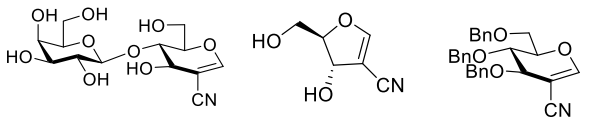
**Table 2**: Glycal scope[a]

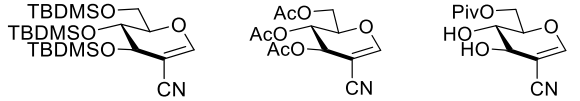


**2b** 92% **2c** 90% **2d** 100%



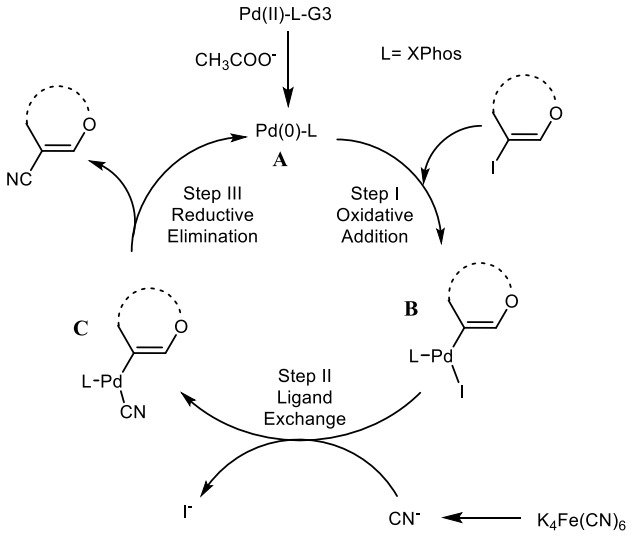
**2e** 83%[b] **2f** 76% (91%)[b] **2g** 51%[c] (65%)[b]



**2h** 44%[c] **2i** 0% **2j** 71%[d]

[a] Conditions: **2** (1 equiv.), $K_4[Fe(CN)_6]$ (0.4 equiv.), Pd-XPhos-G3 (4 mol%), XPhos (8 mol%), KOAc (5 mol%), *t*-BuOH/$H_2O$ (1:1), under Ar, 75°C, 16h. [b] 8 mol% of [Pd], 16 mol% of XPhos and 10 mol% of KOAc were used. [c] Reactions were performed at 130°C. [d] Reaction was performed at 90°C.

Glycal disaccharide (2-iodo-D-lactal) presenting six free hydroxyl groups required the use of 8 mol% of Pd-XPhos-G3, 16 mol% of ligand XPhos and 10 mol% of KOAc to obtain **2e** in an excellent 83% yield (32% in standard conditions). Furanoside 2-iodo-D-ribal led successfully to the desired product **2f** in good yield (76% in standard way, 91% when the amount of catalytic system is doubled). Protected 2-iodo-D-glucals (perbenzylated or persilylated) were also successfully engaged despite lower yields and required a higher reaction temperature (Table 2, **2g** and **2h**). These results can be explained by a lower solubility of protected glycals in the media but also by stereoelectronic effects. In case of peracetylated 2-iodo-D-glucal, only starting material or degradation was observed at temperatures between 75-130°C (Table 2, **2i**). This absence of reactivity could be correlated with the disarming effect of a fully ester protected sugar postulated in glycosylation reactions, which could reduce considerably the electron density of the double bond.[10] This hypothesis is supported by the fact that the presence of only one ester group on the primary hydroxyl group led to improved reactivity (Table 2, **2j**). The mechanism of the reaction is expected to proceed *via* a classical Pd(0)/Pd(II)-catalytic cycle (Scheme 2). At first, the active Pd(0)-XPhos species (**A**) is generated. Secondly, an oxidative addition of Pd(0) (step 1) to the glycal C-I bond occurs to form Pd(II) complex **B**. Slow dissociation of $K_4Fe(CN)_6$ produces cyanide anion, which forms complex **C** by ligand exchange. Finally, product **2** is obtained after reductive elimination with simultaneous reformation of Pd(0) species (**A**).




**Scheme 2:** Proposed cyanation mechanism.

This methodology is thus an easy access to protecting groups-free 2-cyano-glycals. These scaffolds are interesting frameworks, which might be derivatized to many *C2*-glycoside derivatives (Table 3). Under hydrogen atmosphere in the presence of supported palladium catalyst, **2a** was converted into **3a** where both nitrile and glycal double bond were reduced (Table 3, conditions A). Only one isomer was observed in $^1$H- and $^{13}$C-NMR and was isolated in 75% yield (Table 3, **3a**). The *C2-manno*-configuration of **3a** arising from an attack of $H_2$ by the less hindered face of the sugar, was assigned regarding both $^1$H-coupling constants and NOESY correlations (see SI). These conditions were applied successfully to **2d** furnishing **3b** in an excellent 83% yield as a single isomer with an axial $CH_2$-$NH_2$ group (Table 3, **3b**). The selective reduction of the nitrile group without affecting the double bond was achieved by using $NaBH_4$ reagent in the presence of a cobalt salt in aqueous media (Table 3, conditions B).[11] Both **2a** and **2c** could be transformed by this method into the corresponding amino-glycal **4** in moderate to good yields (Table 3, **4a** and **4b**). Compounds **3** and **4** are interesting platforms bearing a nucleophilic amine which can be used in peptide synthesis to reach original glycopeptide analogues. Nitriles **2a** and **2f** were then converted into their corresponding amide analogues **5a** and **5b** in good yields (Table 3, conditions C).[12] Heterocycles such as tetrazoles are also accessible from nitriles **2** by a cycloaddition reaction with sodium azide in good yields (Table 3, conditions D, **6a** and **6b**).[13] Finally, access to ketone derivatives from the 2-cyanoglycals **2** was possible by reaction with Grignard reagents,[14] exemplified on compounds **2a** and **2d** in very good yields (Table 3, **7a** and **7b**, conditions E). This method is complementary to our previous work dealing with carbonylative Suzuki-Miyaura cross-coupling on 2-iodoglycals which was applicable only for the synthesis of aryl and alkenylketones.[3l]

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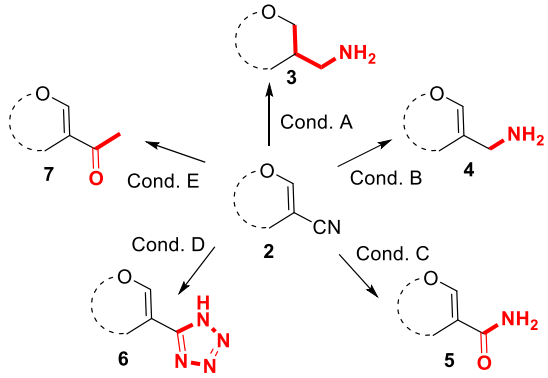
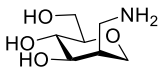
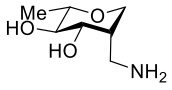
Nevertheless, in this last work we faced to deprotection issues due to the sensitivity of the ketone function.

**Table 3**: Access to diverse *C2*-glycoanalogues from **2**[a]

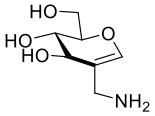


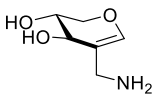
**3a,** 75%
(from **2a** cond. A)



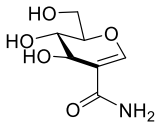
**3b,** 83%
(from **2d** cond. A)



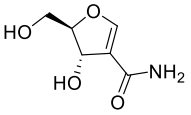
**4a,** 75%
(from **2a** cond. B)



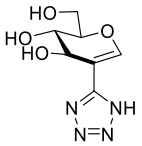
**4b,** 51%
(from **2c** cond. B)



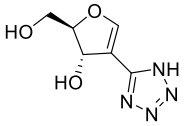
**5a,** 79%
(from **2a** cond. C)



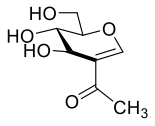
**5b,** 71%
(from **2f** cond. C)



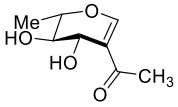
**6a,** 53%
(from **2a** cond. D)



**6b,** 47%
(from **2f** cond. D)



**7a,** 83%
(from **2a** cond. E)



**7b,** 81%
(from **2d** cond. E)

[a] Conditions: **A**: **2** (1 equiv.), $H_2$ (4 bar), $Pd(OH)_2/C$ (20 mol%), HCl 1M, *i*-PrOH, r.t., 18-72h. **B**: **2** (1 equiv.), $NaBH_4$ (4.1 equiv.) $CoCl_2.6H_2O$ (cat.), THF/$H_2O$ (2:1), 0°C to r.t., 2-6h. **C**: **2** (1 equiv.), CuI (2 equiv.), DBU (2 equiv.), $Cs_2CO_3$ (0.5 equiv.), $CH_3NO_2/H_2O$ (1:10), 100°C, 90 min. **D**: **2** (1 equiv.), $NaN_3$ (1.1 equiv.), CuI (0.2 equiv.), DMF, 100 °C, 18h. **E**: 1) **2** (1 equiv.), MeMgBr (6 equiv.), THF, 65°C, 18h; 2) HCl 1M, 65°C, 30 min.

## Conclusion

In summary, nitrile group was successfully introduced on unprotected 2-iodoglycals *via* a palladium-catalyzed process in aqueous media under mild conditions. D- or L-pyranoside-, D-furanoside-, and disaccharide- type iodoglycals could be converted into their cyanated derivatives in good to excellent yields. The reactivity of the nitrile group allowed the possibility to reach five protecting groups-free *C2*-glycoanalogue families possessing amine, amide, tetrazole or ketone functionalities. The development of a strategy setting the deprotection step at an early stage of a synthesis provides unprotected glycosides bearing a sensitive functionality in an easier way.

## Experimental Section

### General experimental methods

All chemical operations were carried out using standard sealed tubes. Acetonitrile was purified before use by distillation under an argon atmosphere. Tetrahydrofuran (THF) was distilled over Na/benzophenone under Ar. Other solvents were used without further purification. Commercially available chemicals were used as received unless otherwise stated. Pd-XantPhos-G3 was purchased from Sigma Aldrich, Pd-XPhos-G3, Pd-tBuXPhos-G3, Pd-BrettPhos- were synthesized from palladium dimer according to described procedure.[15] Reactions were monitored by thin-layer chromatography on silica gel plates (60 F254 aluminium sheets) which were rendered visible by ultraviolet and/or spraying with vanillin (15%) + sulfuric acid (2,5%) in EtOH followed by heating. $^1H$ NMR (400 MHz), $^{13}C$ NMR (100.5 MHz) were recorded at 298 K unless otherwise stated. Chemical shifts are given in ppm (δ) and are referenced to the internal solvent signal or to TMS used as an internal standard. Multiplicities are declared as follows: s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quadruplet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dt (doublet of triplet), m (multiplet). Coupling constants J are given in Hz. Infrared spectra (IR) were recorded on a FT-IR system using diamond window Dura SamplIR II, and the data are reported in reciprocal centimeters (cm−1) in the range 4000−600 cm−1. Optical rotations were measured on a polarimeter at 589 nm. [α] is expressed in deg•cm3•g−1•dm−1, and c is expressed in g/100 cm3. HRMS were determined on a TOF mass analyzer coupled with electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI).

### General experimental procedures

General procedure for iodination: To a stirred solution of peracetylated glycal in dry MeCN (3 mL per 1 mmol of 2-iodoglycal) at 80°C under argon were added NIS (1.2 eq) and $AgNO_3$ (0.2 eq) successively and stirred for 2 h. After consumption of starting material (TLC monitoring), the reaction mixture was filtrated on Celite®, washed with EtOAc and concentrated to give a crude product which was purified by silica gel column chromatography using indicated system.

General procedure for deacetylation: Peracetylated 2-iodoglycal was dissolved in methanol (6 mL per 1 mmol of 2-iodoglycal), then $K_2CO_3$ was added (0.1 eq). The resulting mixture was stirred at room temperature for 2 hours. After that time solvent was removed under vacuum. The crude was purified by flash chromatography using indicated system.

General procedure for cyanation with product isolation (C1): 2-Iodoglycal, $K_4Fe(CN)_6*3H_2O$ (0.4 eq), Pd-XPhos-G3 (0.04 eq), XPhos (0.08 eq), $CH_3COOK$ (0.05 eq) were added to a sealed tube. Then tBuOH (230 µL per 0.1 mmol of glycal iodide) and $H_2O$ (230 µL per 0.1 mmol of 2-iodoglycal) were added under argon. The resulting mixture was stirred at 75°C for 18 hours. After completion of the reaction, solvent was removed under vacuum, the crude was purified by flash chromatography using indicated system.

Procedure for condition screening cyanation with NMR yield determination (C2): The reaction was performed according to the procedure C1 starting from 2-iodoglucal (45 mg, 0.165 mmol). However, after quenching reaction, the mixture was filtered through a pad of Celite® and thoroughly washed several times with methanol. Volatiles were evaporated off then internal standard (DMF) was added (12.8 µL, 0.165 mmol) to the crude. To determine the yield analytical signals were integrated on $^1H$ NMR spectrum (7.99 ppm - DMF singlet set as reference which was compared with product's 7.29 ppm singlet signal (proton in anomeric position on the glycal double bond)).

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FULL PAPER

# Mild Palladium-Catalyzed Cyanation of Unprotected 2-Iodoglycals in Aqueous Media as Versatile Tool to Access Diverse *C2*-Glycoanalogues.

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