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Synthesis of *C*-Aryl and *C*-Alkyl Glycosides Using Glycosyl Phosphates

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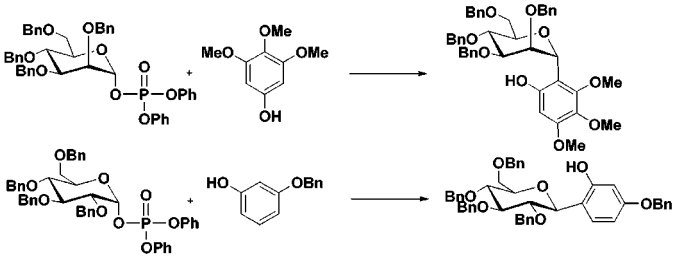
ABSTRACT



Mannosyl and glucosyl phosphate donors were successfully used in constructing *C*-aryl linkages common to many natural products via a Lewis acid induced Fries-like rearrangement. The rearrangement was stereo- and regiospecific, yielding only one *C*-glycoside product. *C*-Alkyl glycoside carbohydrate mimetics were generated by using silicon-derived *C*-nucleophiles and glycosyl phosphates.

C-Glycoside natural products such as bergenin and muscarine exhibit medicinally interesting properties, including antifungal and antitumorigenic responses.[1] Furthermore, *C*-glycoside analogues of biologically active carbohydrates are attractive pharmaceutical targets since they are not enzymatically degraded *in vivo*. Replacement of the exocyclic carbon−oxygen bond at the anomeric center with a carbon−carbon bond creates a hydrolytically stable carbohydrate mimetic with many possible biological applications.[2] For instance, examination of carbohydrate−protein interactions and cell-surface carbohydrate signaling is possible by conjugation of oligosaccharides to molecular probes through a *C*-alkyl glycoside tether.[3]

High-yielding and stereospecific methods for the preparation of *C*-glycosides have enabled the synthesis of many natural products and the construction of specific enzyme substrates. Several different approaches for the synthesis of *C*-glycosides have been explored previously.[1,4] The most common method for *C*-glycoside construction exploits the electrophilicity of the anomeric carbon by coupling nucleophiles to a glycosyl donor. Various leaving groups have been used as glycosyl donors in the electrophilic approach to preparing *C*-glycosides including anomeric acetates, trichloroacetimidates, thioglycosides, halides, and methyl glycosides.[1] Of interest to the work described here, anomeric phosphites were coupled to aromatic *C*-nucleophiles to yield *C*-aryl glycosides[5] and glycosyl phosphates were activated by SmI_2 to generate anomeric anions that were coupled with various electrophilic species.[6] Other approaches to *C*-glycoside formation involve the use of transition metal anomeric complexes, anomeric anions, sigmatropic rearrangements, and palladium-mediated couplings. Still, currently employed methodologies are often limited by long reaction times, poor stereoselectivity, the necessity for a large excess of activator, and low yields.

An indirect route to fashion *C*-aryl glycosidic linkages

(1) For a review, see: Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon: 1995; Vol. 13. Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: London, UK, 1995.

(2) Weatherman, R. V.; Mortell, K. H.; Chervenak, M.; Kiessling, L. L.; Toone, E. J. *Biochemistry* **1996**, *35*, 3619−3624.

(3) Bertozzi, C. R.; Bednarski, M. D. *J. Org. Chem.* **1991**, *56*, 4326−4329.

(4) Toshima, K.; Matsuo, G.; Ishizuka, T.; Ushiki, Y.; Nakata, M.; Matsumura, S. *J. Org. Chem.* **1998**, *63*, 2307−2313.

(5) Lin, C.-C.; Shimazaki, M.; Heck, M.-P.; Aoki, S.; Wang, R.; Kimura, T.; Ritzen, H.; Takayama, S.; Wu, S.-H.; Weitz-Schmidt, G.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 6826−6840.

(6) Hung, S.-C.; Wong, C.-H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2671−2674.

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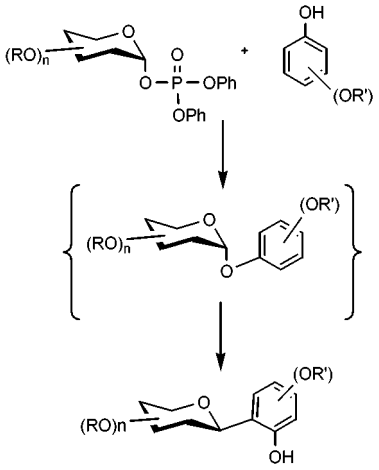
involves the initial installation of an *O*-glycosidic linkage followed by a Fries-like *O*-to-*C* rearrangement (Scheme 1).

Scheme 1. *O*-to-*C* Rearrangement with Glycosyl Phosphates



A glycosyl donor is activated to generate an electrophilic anomeric species that couples to an aromatic phenol to afford an *O*-glycoside. The initial *O*-glycoside then rearranges to the *C*-aryl bond under Lewis acidic conditions. Various aromatic systems, such as naphthol, methoxy phenol, and resorcinol derivatives, have been used in this approach. This rearrangement had been evaluated previously in the glucose series with glycosyl trichloroacetimidates[7] and fluorides.[8] The *O*-to-*C* conversion exclusively afforded the sterically favored *β*-*C*-aryl glucoside product.

The construction of *C*-alkyl glycosides can be achieved by the coupling of a carbon nucleophile, most commonly a silicon-based nucleophile, and a glycosyl donor. The anomeric stereochemistry of these *C*-alkyl glycosides is strongly dependent on the nature of the nucleophile. Generally, formation of the thermodynamically more stable α-glycosides predominates.

Here we present a new method for the synthesis of *C*-glycosides using glycosyl phosphates as the anomeric leaving group. We recently reported the one-pot synthesis of glycosyl phosphates from glycals and demonstrated their utility in the rapid and efficient formation of *O*- glycosidic linkages in solution and on solid support.[9,10] On the basis of our previous success with phosphate donors in creating *O*-glycosides, we sought to expand their use to the synthesis of *C*-glycosidic linkages.

Mannosyl donors had not previously been employed in the formation of aryl bonds via the *O*-to-*C* rearrangement pathway; thus the effect of the axial C2 substituent on the stereochemistry of this rearrangement had not been investigated. To evaluate the Fries-like rearrangement in the

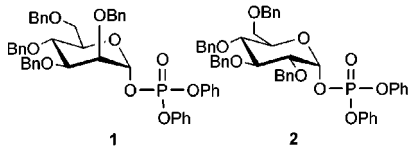
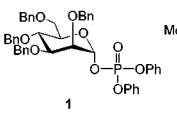
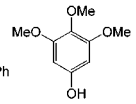
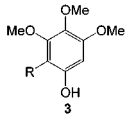
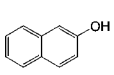
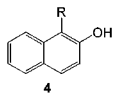
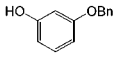
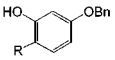


Figure 1. Glycosyl phosphates **1** and **2**.

synthesis of *C*-aryl mannosides, phosphate **1**[6] (Figure 1) was prepared. Donor **1** was activated with trimethylsilyl trifluoromethanesulfonate (TMSOTf) at 0 °C in the presence of electron-rich phenolic acceptors. Coupling of phosphate **1** with 3,4,5-trimethoxyphenol afforded exclusively the α-*C*-linked glycoside **3** in just 30 min (Table 1). The rearrangement occurred even at low temperatures (−15 °C) and did not allow for the isolation of any *O*-glycoside product. The aromatic phenol was varied to explore the scope of the *O*-to-*C* conversion with mannosyl phosphates. Using phosphate **1**, the α-*C*-mannosides of 2-naphthol and 3-benzyloxyphenol (**4** and **5**) were synthesized in excellent yield. *O*-Mannosides were obtained exclusively with less nucleophilic aromatic systems, such as 3-acetoxy phenol.

Table 1. *O*-to-*C* Rearrangement with Phosphate **1**[a]

donor	acceptor	*C*-glycoside product	yield *C*-glycoside (α:β)	yield *O*-glycoside (α:β)
			85% (1:0)	0%
			79% (1:0)	0%
			82% (1:0)	0%

[a] Conditions: 1 equiv of phosphate, 1.2 equiv of acceptor, and 1.2 equiv of TMSOTf in CH_2Cl_2 at 0 °C.

Several natural products, including gilvocarcin M and castacrenin B, contain a *C*-aryl glucosyl fragment. Given the success with mannosyl phosphate **1**, the construction of *C*-aryl linkages via an *O*-to-*C* rearrangement with glucosyl phosphate **2**[11] (Figure 1) was investigated. Coupling of 3,4,5-trimethoxyphenol and **2** afforded α-*O*-glycoside **6** (Figure 2) in 79% yield in 15 min. The rearrangement to the *β*-*C*-aryl linkage (**9**, Table 2) required a longer (>3 h) reaction time.

In expanding this methodology to other phenols, 2-naphthol and 3-benzyloxyresorcinol were used as aromatic

(7) Mahling, J.-A.; Schmidt, R. R. *Synthesis* **1993**, 325−328.
(8) Matsumoto, T.; Hosoya, T.; Suzuki, K. *Synlett* **1991**, 709−711.
(9) Plante, O. J.; Andrade, R. B.; Seeberger, P. H. *Org. Lett.* **1999**, *1*, 211−214.
(10) Andrade, R. B.; Plante, O. J.; Melean, L. G.; Seeberger, P. H. *Org. Lett.* **1999**, *1*, 1811−1814.
(11) Hashimoto, S.; Honda, T.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1989**, 685−687.

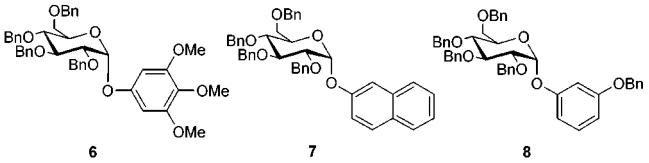
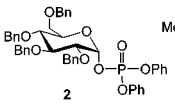
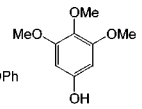
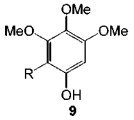
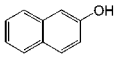
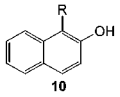
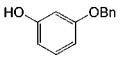
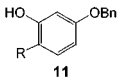


Figure 2. *O*-Glycosides.

nucleophiles. The *O*-glycoside products (**7** and **8**) were isolated after 15 min at 0 °C, and *C*-glycosides (**10**[7] and **11**)

Table 2. *O*-to-*C* Rearrangement with Phosphate **2**[a]

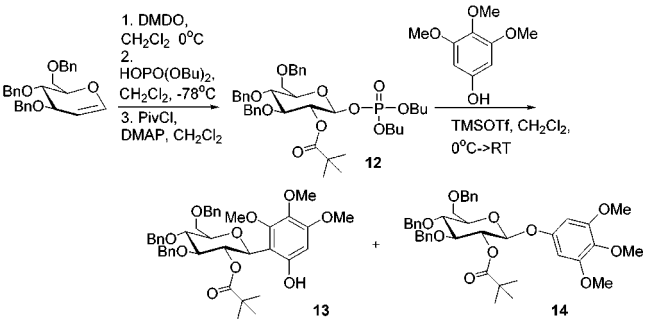
donor	acceptor	*C*-glycoside product	yield *C*-glycoside (α:β)	yield *O*-glycoside (α:β)
			57% (0:1)	13% (1:0)
			60% (0:1)	9% (1:0)
			62% (0:1)	trace

[a] Conditions: 1 equiv of phosphate, 1.2 equiv of acceptor, and 1.2 equiv of TMSOTf in CH_2Cl_2 at 0 °C → rt.

were obtained after longer reaction times. In all cases, the rearrangement was completely stereospecific, yielding exclusively the *β*-*C*-aryl linkage. Interestingly, *O*-glycoside products were obtained in trace amounts even after extended reaction times (>3 h), indicating that the *O*-to-*C* conversion did not reach completion. Furthermore, *O*-glucosides could be exclusively formed with less nucleophilic aromatic systems, as was observed with mannosyl phosphate **1**.

To investigate the effect of electron-withdrawing protecting groups on the *O*-to-*C* rearrangement, phosphate **12**[9] containing a C2-ester (Scheme 2) was synthesized from the corresponding glycal. Coupling of **12** to 3,4,5-trimethoxyphenol was accomplished in 12 h by TMSOTf activation to afford *C*-glycoside **13** and *O*-glycoside **14** in 21% and 35% yield, respectively. The conversion required extended reaction times (12 h) to obtain the desired product in modest yield. *C*-Glycoside **13**[12] provides access to bergenin-like structures (Figure 3)[13] since the difficult linkage to the aromatic system is installed from readily available educts.

Scheme 2 *O*-to-*C* Rearrangement with Phosphate **12**



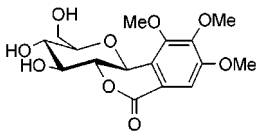
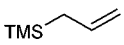
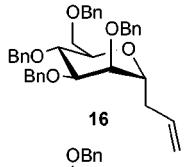
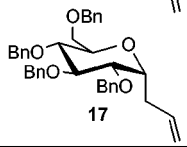
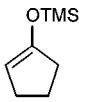
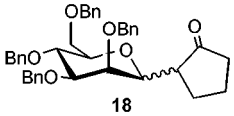
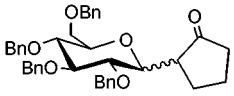


Figure 3. 8,10-Di-*O*-methylbergenin.

C-Alkyl glycosides are useful carbohydrate mimetics, commonly employed as enzyme inhibitors. The formation of various *C*-alkyl glycosides was evaluated with phosphates **1** and **2** (Table 3). Mannosyl phosphate **1** was activated with

Table 3. Synthesis of *C*-Alkyl Glycosides from **1** and **2**

donor	acceptor	yield	product
1		93%	 **16**
2		55%	 **17**
1		84%	 **18**
2		68%	 **19**

TMSOTf and coupled to allyl trimethylsilane to provide α-allyl glycoside **16**[14] in excellent yield (93%). Allyl glycoside **16** has previously served as a handle for studying mannose-binding lectins.[4]

Coupling of **1** to the cyclopentanone-derived trimethylsilyl enol ether afforded **18** as a mixture of diastereomers in 84%

(12) Schmidt, R. R.; Effenberger, G. *Carbohydr. Res.* **1987**, *171*, 59−79.
(13) Hay, J. E.; Haynes, L. J. *J. Chem. Soc.* **1958**, 2231−2238.
(14) Hosomi, A.; Sakata, Y.; Sakurai, H. *Carbohydr. Res.* **1987**, *171*, 223−232.

yield. Other silyl enol ethers can be employed in a similar fashion to construct different *C*-alkyl derivatives. Phosphate **2** was activated with TMSOTf at 0 °C in the presence of allyltrimethylsilane to afford the α-allyl glycoside **17**.[15]Donor **2** was coupled to the TMS enol ether, resulting in the formation of **19**[15] as a mixture of diastereomers.

In summary, we have demonstrated the use of glycosyl phosphates in the efficient synthesis of various *C*-aryl and *C*-alkyl glycosides. Mannosyl and glucosyl phosphates were successfully employed in a Lewis acid induced Fries-like rearrangement. Construction of *C*-aryl linkages present in natural products was easily accomplished by this rearrangement. Use of silicon-derived *C*-nucleophiles and glycosyl phosphate donors allowed for the generation of *C*-alkyl glycosides containing a handle for conjugation to proteins or molecular probes.

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Supporting Information Available: Detailed experimental procedures and compound characterization data, including ^{1}H, ^{13}C, and ^{31}P NMR data for all described compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0158462

(15) Hoffman, M. G.; Schmidt, R. R. *Liebigs. Ann. Chem.* **1985**, 2403−2419.