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Direct *C*-Glycosylation of Organotrifluoroborates with Glycosyl Fluorides and Its Application to the Total Synthesis of (+)-Varitriol

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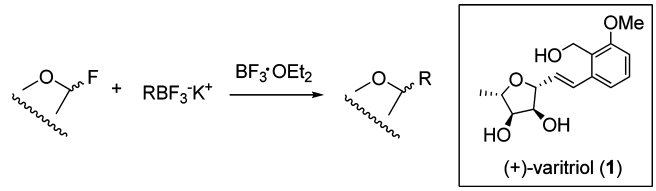
ABSTRACT



A mild, stereoselective, and quick approach to accessing alkynyl and alkenyl *C*-glycosides *via* $BF_3{\cdot}Et_2O$ promoted coupling of organotrifluoroborates and glycosyl fluorides is reported. The application of this method was further demonstrated by the concise and efficient total synthesis of (+)-varitriol in only seven steps.

Glycosylation reactions play a pivotal role in carbohydrate chemistry.[1] *O*-Glycosidic compounds are the most abundant and important among all types of glycosides, whereas *C*-glycosides have attracted considerable interest in carbohydrate, enzymatic, and metabolic chemistry over the past decades for their interesting structures and higher stability toward glycosidases and hydrolytic conditions.[2] Furthermore, *C*-glycosides are also widely found in natural products and synthetic pharmaceuticals such as (+)-varitriol (**1**),[3] (−)-aspergillide C (**2**),[4] *C*-mannosyltryptophan (*C*-man-trp, **3**),[5] and chaetiacandin (**4**) (Figure 1).[6] In addition, *C*-glycosides are useful chiral building blocks for the syntheses of natural products and pharmaceuticals.[7] Undoubtedly, these features have stimulated the development of successful strategies for the stereoselective construction of *C*-glycosides, and a plethora of methods have been reported over the past years.[8] Among the contemporary methods, direct attachment of carbon nucleophiles to sugar anomeric carbon presents significant achievements, especially the methods of capturing

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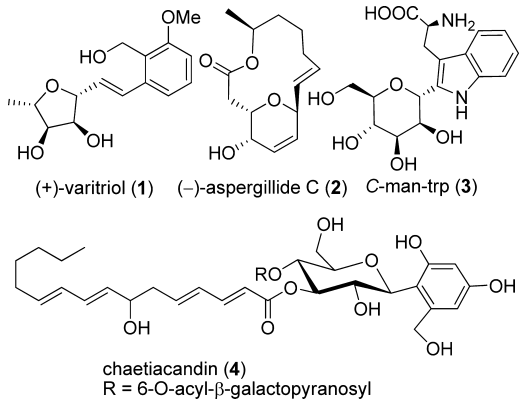


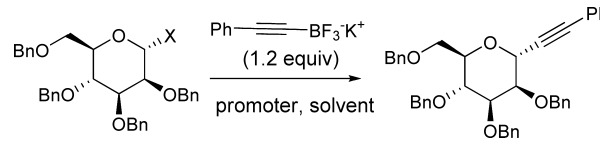
Figure 1. Naturally occurring *C*-glycosides.

the electrophilic oxocarbenium ion (which was generated by activation of the anomeric center with a Lewis acid or Brønsted acid) with a carbon nucleophile.[8a,9]

Organoboron compounds exhibit wide-ranging utilities in synthetic chemistry. As one of the most stable organoboron reagents, potassium organotrifluoroborates offer various advantages such as an easier preparation procedure and higher nucleophilicity, compared to relevant boronic acids and boronic esters. Based on their synthetic utility, they have become increasingly popular for C−C bond formation.[10] Recently, Stefani[9b] and Bode[11] have demonstrated the efficiency of nucleophilic addition reactions of potassium organotrifluoroborates with oxocarbenium ions. In connection with our continuous research interest in carbohydrate chemistry,[12] herein, we report a direct *C*-glycosylation method by coupling of potassium organotrifluoroborates with sugar oxocarbonium ions.

Our investigation began with the optimization of direct *C*-glycosylation of potassium phenylethynyltrifluoroborate (Table 1). To this end, benzylated mannose derivatives were chosen as glycosyl donors, because mannosylation without neighboring group participation usually exhibits excellent

Table 1. Optimization of Direct *C*-Glycosylation of Potassium Phenylethynyltrifluoroborate



	X	promoter (equiv)	temp(°C)	solvent	time(h)	yield(%)
1	OMe	BF_3·OEt_2 (2)	80	MeCN	24	–
2	OAc	BF_3·OEt_2 (2)	rt	MeCN	14	61
3	OAc	$TiCl_4$ (1.2)	rt	MeCN	12	11
4	OAc	$SnCl_4$ (1.2)	rt	MeCN	14	20
5	OAc	TMSOTf (1.2)	0	MeCN	2	43
6	OAc	$SiCl_4$ (1.2)	rt	MeCN	16	–
7	STol	BF_3·OEt_2 (2)	rt	MeCN	4	65
8	$OCNCl_3$	BF_3·OEt_2 (2)	rt	MeCN	1	81
9	**F**	**BF_3·OEt_2 (1.3)**	**rt**	**MeCN**	**0.3**	**94**
10	F	BF_3·OEt_2 (1.3)	rt	DCM	0.5	71
11	F	BF_3·OEt_2 (1.3)	rt	toluene	2	51

α-selectivity, which simplifies the isolation and characterization of the product. In addition, mannosylation also attracted significant interest in biological and medicinal chemistry.[13] Initially, methyl mannoside was subjected to the glycosylation reaction with BF_3·Et_2O as a Lewis acid (entry 1). However, no product was formed even under refluxing conditions due to the poor reactivity of an anomeric methoxy group. To our delight, the reaction with mannosyl acetate gave α-mannoside in 61% yield (entry 2). Further screening of Lewis acids such as $TiCl_4$, $SnCl_4$, $SiCl_4$, and TMSOTf revealed that BF_3·Et_2O produced the best result whereas TMSOTf gave moderate yields (entries 3−6). Furthermore, the efficiency of anomeric leaving groups was examined in the presence of BF_3·Et_2O (entries 7−9). Good leaving groups such as STol and trichloroacetimidate afforded better results than that of the acetate group; the reaction of mannosyl fluoride completed in the shortest reaction time with the highest yield (entry 9). Use of solvent other than MeCN gave diminished results (entries 10, 11).

With these optimal reaction conditions in hand, we continued to investigate the scope of the *C*-glycosylation coupling reaction. First, a series of potassium organotrifluoroborates were tested toward *C*-mannosylation (Figure 2). Among them, alkynyl-trifluoroborates possessing either aromatic or aliphatic substituents provided the desired products in good yields; even aliphatic alkynyltrifluoroborates with long chains gave the mannosylation product in good yields (**7aa**−**7ad**). Alkenyltrifluoroborates gave lower yields due to the reduced reactivity of the sp^2-hybridized bonds (**7ae**, **7af**). Unfortunately, preliminary efforts attempted to employ potassium alkyl- and aryl-trifluoroborates failed, in which the anomeric position was intramolecularly arylated by 2-OBn group instead.[14]

The versatility of the BF_3·OEt_2 promoted *C*-glycosylation protocol for other sugar fluorides was studied using potas-

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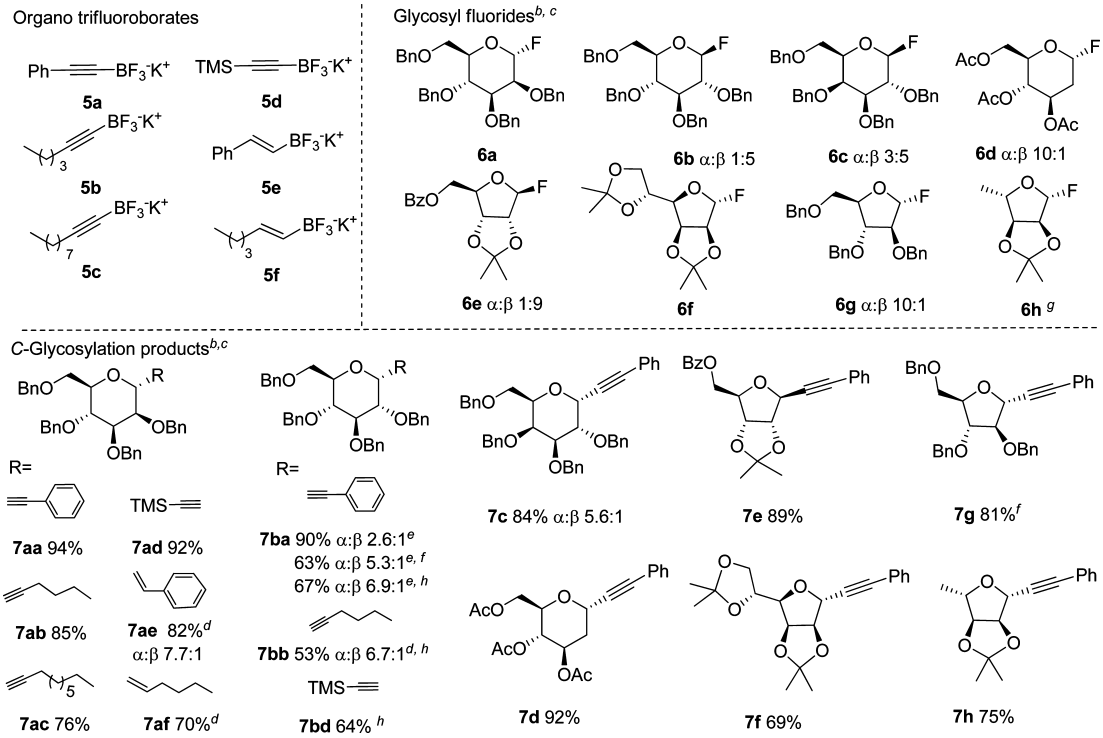

Figure 2. Direct *C*-glycosylation of organotrifluoroborates with glycosyl fluorides. (a) For the entire figure, unless otherwise noted, the reactions were carried out according to Procedure A. (b) Unless otherwise noted, only one anomer was observed as drawn; for those depicting an α,*β* ratio, the stereochemistry of the major isomer was shown as drawn. (c) Isolated yields are recorded above. Unless otherwise noted, α,*β* ratio was determmined by ^{1}HNMR. (d) Only *E* alkene was observed. (e) The α,*β* ratio was determined by HPLC. (f) Reaction was carried out according to Procedure B. (g) Unstable and decomposed quickly. (h) Reaction was carried out according to Procedure C. **Procedure A**: To a solution of glycosyl fluoride (0.2 mmol) and organo trifluoroborate (1.2 equiv) in acetonitrile (1 mL) was added BF_3•OEt_2 (1.3 equiv) at rt. The reaction was carried out at rt for 20 min. **Procedure B**: To a solution of glycosyl fluoride (0.2 mmol) and organo trifluoroborate (2.0 equiv) in acetonitrile (1 mL) was added BF_3•OEt_2 (2.2 equiv) at −40 °C. The reaction was carried out at −40 °C for 6 h. **Procedure C**: Premixing of BF_3•OEt_2 (2.2 equiv) and organo trifluoroborate (2.0 equiv) in acetonitrile (1 mL) followed by addition of glycosyl fluoride (0.2 mmol). The reaction was carried out at −40 °C for 6 h.

sium phenylacetylene trifluoroborate as the coupling partners. D-Galactosyl fluoride **6c** gave the desired product **7c** in good yield with high selectivity under the optimized conditions. 2-Deoxyglucosyl fluoride **6d** was also tolerated in this condition and gave the α-isomer **7d** in 92% yield as a single product. Extending the glycosylation method to furanose was also pursued. Unlike D-mannofuranosyl fluoride **6f** and D-arabinosyl fluoride **6g** which were able to generate the corresponding alkynyl sugar in good yields with exclusive α-selectivities (**7f**, **7g**), D-ribofuranosyl fluoride **6e** and L-furanosyl fluoride **6h** were considerably more *β*-selective (**7e**, **7h**). The diastereoselectivities for both furanose and pyranose have no correlation with their anomeric fluoride configuration, but rather, they depend on the conformation of the oxonium intermediates.[15]

Extending the *C*-glycosylation method to *C*-glucosylation was further studied. The reaction of glucosyl fluoride **6b** and trifluoroborate **5a** produced **7ba** in good yields with a slight preference for α-selectivity (2.6:1 α:*β*). Gratifyingly, further lowering of the reaction temperature increased the selectivity; however, the yield diminished. The product was obtained in 63% yield with good α-selectivity (5.3:1 α:*β*) at −40 °C. Interestingly, we found that a reversed sequence of reagent addition (premixed excess potassium organotrifluoroborate and BF_3•OEt_2 in MeCN prior to addition of the fluoride) slightly increased the yield (67%) and selectivity (6.9:1) (**7ba**). The reaction between **6b** and **5b** also gave the corresponding glucoside in good selectivity under the current conditions (**7bb**). Interestingly, only the α-product was observed while **5d** was employed as the coupling partner (**7bd**).

We further examined the applicability of this methodology to natural product synthesis. (+)-Varitriol (**1**) exhibits significant cytotoxic activity toward renal, central nervous system, and breast cancer cell lines. It was first isolated from a marine-derived strain of the fungus *Emericella variecolor* in 2002.[3] Several total syntheses of (+)- and (−)-varitriol have been reported recently.[16] Based on our methodology, we envisaged that the coupling reaction of glycosyl fluoride **6h** with organotrifluoroborate **9** would be implemented as the key step in the synthesis of (+)-varitriol (**1**) (Scheme 1). Our synthesis commenced with a fluorination reaction of known compound **8**[17] to afford

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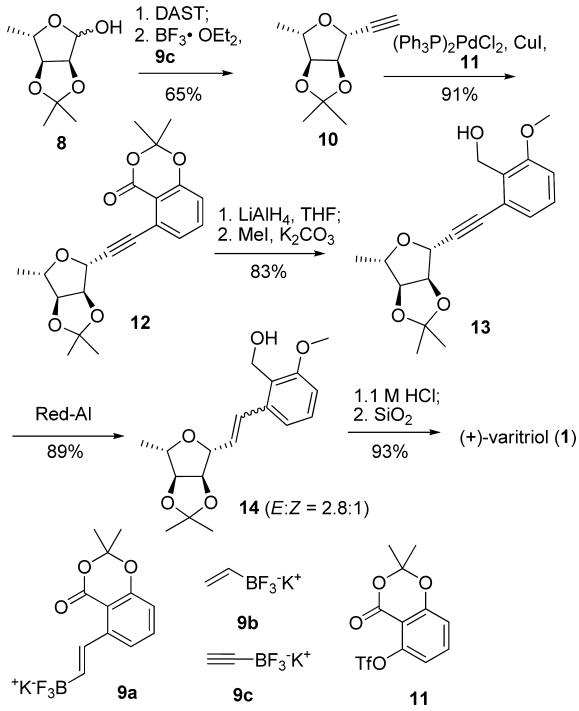
Scheme 1. Total Synthesis of (+)-Varitriol **1**



fluoride **7h**. Unfortunately, the coupling reaction of **7h** with alkenyl trifluoroborate **9a**[18] or **9b** could not give the desired products. While replacing **9a** or **9b** with ethynyltrifluoriborate **9c**, the reaction proceeded smoothly which gave **10** in 65% yield for two steps from **8**. A subsequent Sonogashira cross-coupling reaction provided internal alkyne **12** in 91% yield. Reduction of the ester group of **12** and selective protection of the generated phenol group with iodomethane and K_2CO_3 furnished **13** in 83% yield. The chemoselective reduction of the triple bond was conducted by Red-Al which produced alkene **14** in 89% yield with an *E*:*Z* ratio of 2.8:1. Interestingly, after removal of the protecting group of **14** with 1 M HCl followed by flash chromatography on silica gel, all of the *Z*-isomer was exclusively transformed to the *E*-isomer which furnished the target molecule **1** in 93% yield. Thus, we succeeded in the synthesis of (+)-varitiol (**1**) from known compound **8** in only seven steps and 41% overall yield, including the *C*-glycosylation reaction as a key step.

In conclusion, we have identified a versatile and facile method for the synthesis of *C*-glycosides *via* cross-coupling of potassium organotrifluoroborates and glycosyl fluorides. This approach furnishes *C*-glycosides in a relatively short time with good to excellent yields and high diastereoselectivity. Furthermore, this strategy enabled the concise and efficient synthesis of naturally occurring *C*-glycoside (+)-varitriol (**1**) in the shortest route and highest overall yield so far as we know.

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Supporting Information Available: Experimental procedures and compound characterization data of glycosyl fluorides and *C*-glycosylation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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