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Short Total Synthesis of 8,10-Di-*O*-methylbergenin

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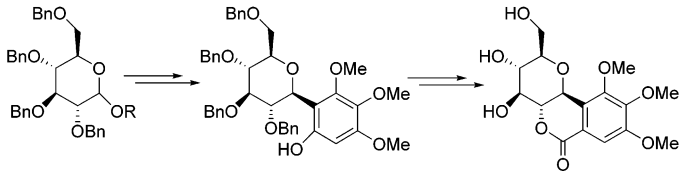
ABSTRACT



A short, high-yielding synthesis of the *C*-glucoside 8,10-di-*O*-methylbergenin is reported. Key elements of the synthesis are a stereoselective installation of a *β*-*C*-aryl linkage, a palladium(0)-catalyzed aryl carbonylation, and a regioselective lactonization reaction. This pathway should allow access to a host of bergenin analogues.

C-Glycoside natural products exhibit medicinally interesting properties and have potential as antifungal and antitumorigenic treatments.[1] In addition, *C*-glycoside analogues of biologically active carbohydrates are attractive pharmaceutical targets since they are not enzymatically degraded in vivo.[2] 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]

Bergenin **1**, norbergenin **2**, and 8,10-di-*O*-methylbergenin **3** (Figure 1) are gallic acid-derived *C*-glycosides that have been isolated from a variety of plants.[4]

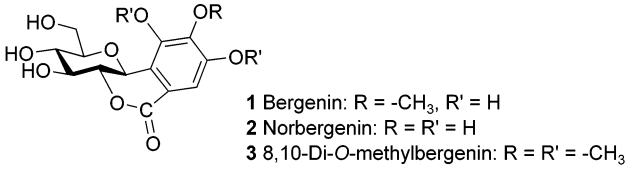


Figure 1.

Numerous reports about the biological and pharmacological properties of bergenin-type *C*-glycosides have been disclosed. Bergenin-containing extracts from *Macaranga peltata* are used in Indian folk medicine for the treatment of veneral deseases,[5] and acetylated bergenin has shown an antihepatotic effect in animal experiments.[6] Bergenin itself is antidermatic and shows activity against HIV.[7] It is the active pharmaceutical ingredient of a Chinese drug described to be effective against cough and bronchitis.

Despite the interesting biological properties of this class of natural products, current methods for the chemical synthesis of bergenin and its derivatives are unsatisfying. Schmidt and co-workers reported a 10-step synthesis of 8,10-di-*O*-methylbergenin **3** in 8.8% overall yield from perben-

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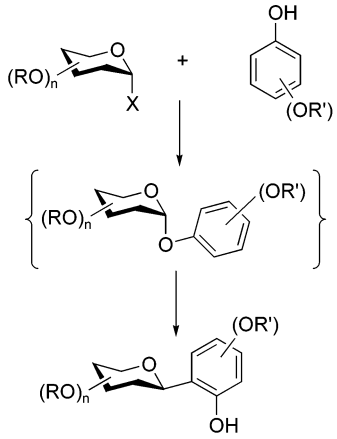
zylated trifluoroacetyl glucose.[8] Martin et al. developed a synthesis of **3** based on an intramolecular *C*-glycosylation of a 2-(3′,4′,5′-trimethoxy)benzyl *n*-pentenyl glucoside followed by oxidation of the benzylic methylene group. 8,10-Di-*O*-methylbergenin **3** was prepared in 12.1% yield over eight steps from peracetylated glucosyl bromide.[9] Apart from the modest overall yield, these syntheses require numerous protecting group manipulations, thus rendering them unsuitable for the synthesis of an extended set of bergenin derivatives.

Here we describe a short and high-yielding total synthesis of **3** based on an *O*-to-*C* rearrangement with 3,4,5-trimethoxyphenol. A common route to fashion *C*-aryl glycosidic linkages involves the initial installation of an *O*-glycosidic linkage with an electron-rich phenol, followed by a Fries-like *O*-to-*C* rearrangement (Scheme 1). A glycosyl donor is

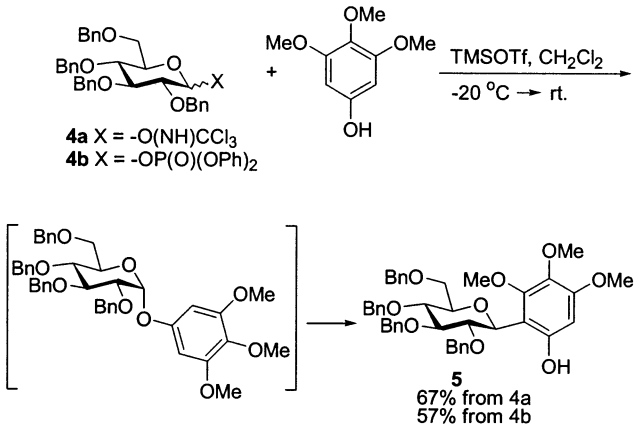
Scheme 1 *O*-to-*C* Rearrangement



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. The *O*-to-*C* conversion exclusively affords the sterically favored *β*-*C*-aryl phenolic glucoside product.[10] We envisioned that the *O*-to-*C* rearrangement product of 3,4,5-trimethoxyphenol could be further functionalized via a carbonylation and subsequent lactone formation to give the desired bergenin scaffold.

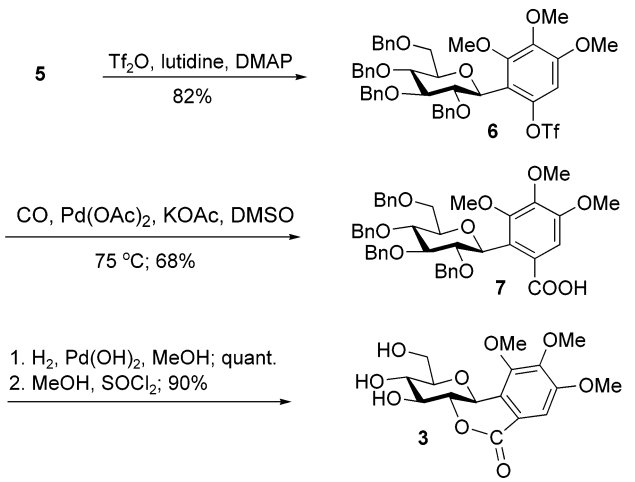
Upon activation with trimethylsilyl trifluoromethanesulfonate (TMSOTf), 2,3,4,6-tetra-*O*-benzyl glucopyranosyl trichloroacetimidate **4a**[11] and perbenzylated glucosyl diphenyl phosphate **4b**[12] reacted with 3,4,5-trimethoxyphenol to give the *β*-configured *C*-glycoside **5** in 67 and 57% yields, respectively (Scheme 2). Treatment of the phenolic hydroxyl group of **5** with triflic anhydride/lutidine resulted in the formation of triflate **6** (Scheme 3). Due to steric hindrance

Scheme 2. Installation of the *C*-Aryl Linkage



of this hydroxyl group, the addition of DMAP as an acylation catalyst proved to be essential.

Scheme 3. Completion of the Bergenin Structure



Palladium(0)-catalyzed carbonylation[13] at ambient pressure under careful exclusion of water and oxygen yielded 68% of *C*-glucosyl benzoic acid derivative **7**. Attempts to convert **6** directly into the *C*-glycosyl methyl benzoate failed,[14] as did attempts to obtain the methyl ester of **7** by direct *C*-glycosylation with methyl 3,4,5-trimethoxybenzoate.

Debenzylation of **7** by hydrogenation with Pearlman's catalyst in methanol provided the tetrahydroxyl *C*-glucoside in quantitative yield. Regioselective lactonization of the C2 hydroxyl group of the glucose scaffold was achieved by treatment with DCC/DMAP in DMF to furnish **3** in 71% yield. A more efficient procedure was the treatment of deprotected **7** with $SOCl_2$ in methanol to provide cleanly 8,10-di-*O*-methylbergenin in 90% yield.

In conclusion, we have developed a short synthesis of the bergenin scaffold that provides the target structure **3** in 33%

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overall yield in only four steps from common glycosyl donors. The application of this synthetic route to the preparation of a series of bergenin derivatives is currently under examination.

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Supporting Information Available: Experimental procedures for the preparation of compounds **3** and **5**−**7**, including spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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