

C-Glycosylation-Cycloaddition Approach to C-Glycosyl Juglones. Versatile Intermediates toward Aryl C-Glycoside Antibiotics

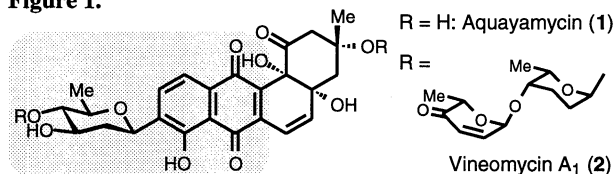
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An efficient two-step access to C-glycosyl juglones, promising synthetic intermediates toward aryl C-glycoside antibiotics, has been developed based on (1) the *O*→*C*-glycoside rearrangement and (2) the regioselective cycloaddition of α -alkoxybenzyne and α -oxyfuran.

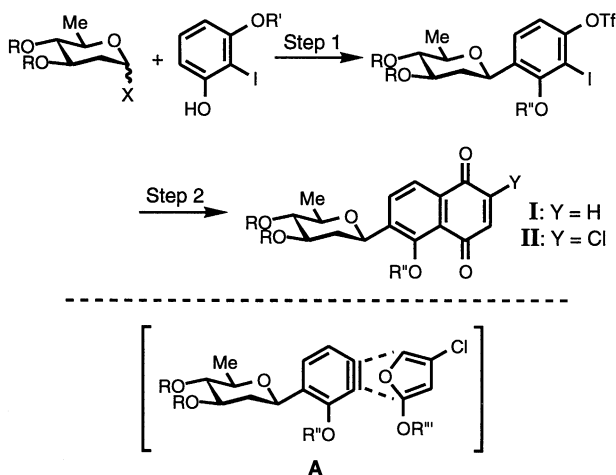
C-Glycosylated juglone (5-hydroxy-1,4-naphthoquinone) is seen as a common partial structure in certain classes of antibiotics, such as the angucyclines **1** and **2** (Figure 1).¹ Such a structural motif in turn would serve as a valuable synthetic intermediate *en route* to these natural products,² because various annulation and related transformations have been well established for *aglyco* naphthoquinones, leading to polyaromatic skeletons.³

Figure 1.

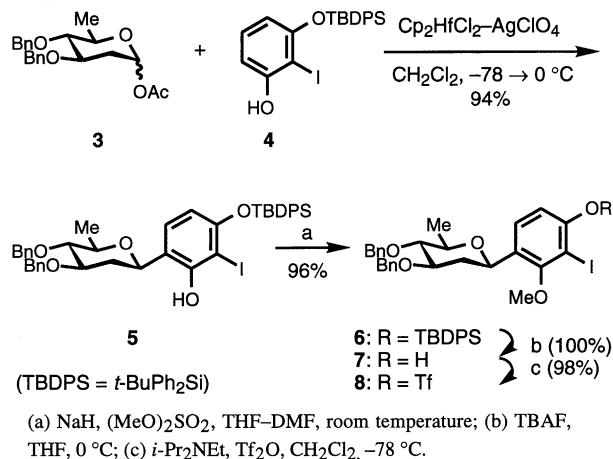


Herein, we report a regio- and stereocontrolled approach to these intermediates by way of two processes: (1) the *O*→*C*-glycoside rearrangement⁴ to form the aryl C-glycoside bond and (2) [2 + 4] cycloaddition⁵ of benzyne and α -oxyfuran to construct the juglone skeleton (see I, Scheme 1).⁶ Furthermore, the C(2)-chloro congener **II** proved to be accessible by the rigorously regioselective cycloaddition of chlorofuran as shown in A.

Scheme 1.



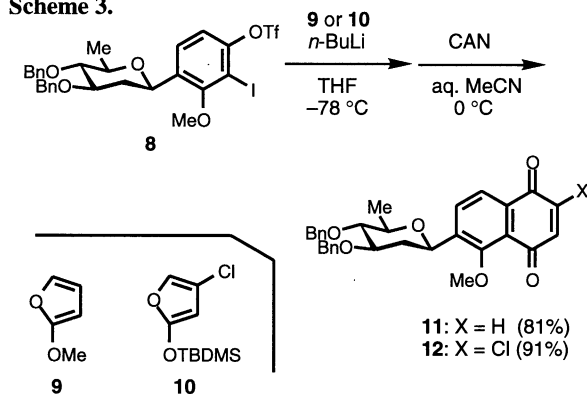
Scheme 2.



The first stage is the C-glycosylation of a mono-protected 2-iodoresorcinol (Scheme 2).⁴ D-Olivose was arbitrarily chosen as the sugar, as it is found in many aryl C-glycoside antibiotics. Thus, D-olivose acetate **3** (1.0 equiv.) and resorcinol **4**⁷ (1.4 equiv.) were treated with Cp₂HfCl₂ (1.5 equiv.) and AgClO₄ (3.0 equiv.) in CH₂Cl₂ at -78 °C.⁴ The phenol was rapidly glycosylated at the temperature to give the *O*-glycoside, which was smoothly converted in situ to the C-glycoside during subsequent warming to 0 °C to give desired β -C-glycoside **5** as a sole product in 94% yield.^{8,9} Methylation of the phenolic hydroxyl followed by removal of the TBDPS group afforded phenol **7**, which was then treated with Tf₂O in the presence of *i*-Pr₂NEt to give triflate **8** in high overall yield.

With the benzyne precursor **8** in hand, the second step, i.e., the cycloaddition, was carried out (Scheme 3).⁵ Triflate **8** was treated with *n*-BuLi (1.6 equiv.) at -78 °C in the presence of 2-methoxyfuran (**9**, 3.0 equiv.). The benzyne-furan cycloaddition and the subsequent spontaneous aromatization of

Scheme 3.



the initial adduct cleanly proceeded to furnish, after oxidative workup with CAN, quinone **11** in high yield.⁵ Thus, this cycloaddition provides an effective way to the synthesis of C-glycosylated juglone.

Our previous data^{2,5} suggested that this class of cycloaddition proceeds in regioselective manner, which could, though of no consequence in the above-stated case, be exploited for the selective synthesis of more elaborated juglones. This expectation proved indeed the case as illustrated by the reaction of chlorofuran **10**.^{10,11} Thus, chlorofuran **10** underwent the cycloaddition in rigorously regioselective manner (see **A** in Scheme 1) to give an excellent yield of 2-chlorojuglone **12** as a sole detectable product.^{12,13} None of the 3-chloro congener, if any, was detected. The chlorine atom in **12** would promise to serve as a pivot for controlling the regioselectivity in further synthetic transformations.³

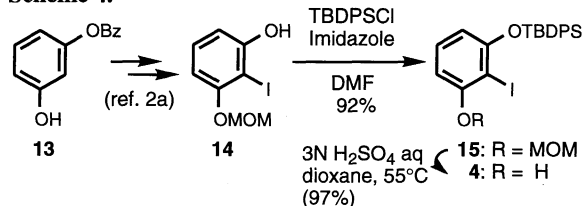
In summary, an efficient synthesis of naphthoquinones armed with a C-glycoside at C(6) has been established. These C-glycosyl juglones, represented by **11** and **12**, would serve as versatile intermediates for the synthesis of aryl C-glycoside antibiotics. Further study is in progress and the results will be reported shortly.

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References and Notes

- Reviews on the synthesis of aryl C-glycoside compounds: a) U. Hacksell and G. D. Daves, Jr., *Prog. Med. Chem.*, **22**, 1 (1985). b) M. H. D. Postema, *Tetrahedron*, **48**, 8545 (1992). c) K. Suzuki and T. Matsumoto, in "Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products," ed by G. Lukacs, Springer, Berlin (1993), Vol. 2, p 353.
- Recent articles on the total synthesis of aryl C-glycoside antibiotics: a) T. Hosoya, E. Takashiro, T. Matsumoto, and K. Suzuki, *J. Am. Chem. Soc.*, **116**, 1004 (1994). b) T. Matsumoto, T. Sohma, H. Yamaguchi, S. Kurata, and K. Suzuki, *Synlett*, **1995**, 263.
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- a) T. Matsumoto, M. Katsuki, and K. Suzuki, *Tetrahedron Lett.*, **29**, 6935 (1988). b) T. Matsumoto, T. Hosoya, and K. Suzuki, *Tetrahedron Lett.*, **31**, 4629 (1990). c) T. Matsumoto, T. Hosoya, and K. Suzuki, *Synlett*, **1991**, 709. Also see, Ref. 2.
- T. Matsumoto, T. Hosoya, M. Katsuki, and K. Suzuki, *Tetrahedron Lett.*, **32**, 6735 (1991). Also see, Ref. 2.
- The approaches via C-glycosylation of juglone derivatives are also possible. T. Hosoya, Y. Ohashi, unpublished results. Also see, F. L. Andrews and D. S. Larsen, *Tetrahedron Lett.*, **35**, 8693 (1994).
- Resorcinol **4** was easily prepared in two steps from the known MOM ether **14**^{2a} as shown below.

Scheme 4.



- All new compounds were fully characterized by ¹H and ¹³C NMR, IR, and high-resolution MS.
- The β-configuration of C-glycoside **5** was evident from the ¹H NMR (*J*_{1,2ax} = 11.7, *J*_{1,2eq} = 2.0 Hz).
- Chlorofuran **10** [bp 110–120 °C/3 mmHg (Kugelrohr)] was prepared from 4-chloro-2(5*H*)-furanone¹¹ according to the procedure described for the corresponding bromo congener. G. Jas, *Synthesis*, **1991**, 965.
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- Fortunately, lithiation of chlorofuran **10** did not compete thanks to the extremely rapid iodine–lithium exchange.
- Structure confirmation relies on the NOE experiment on acetate **16** which was obtained by acetylation of the product, the naphthol.

