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

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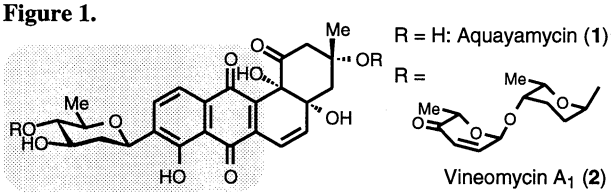
An efficient two-step access to *C*-glycosyl juglones, promising synthetic intermediates toward aryl *C*-glycoside antibiotics, has been developed based on (1) the *O*→*C*-glycoside rearrangement and (2) the regioselective cycloaddition of α-alkoxybenzyne and α-oxyfuran.

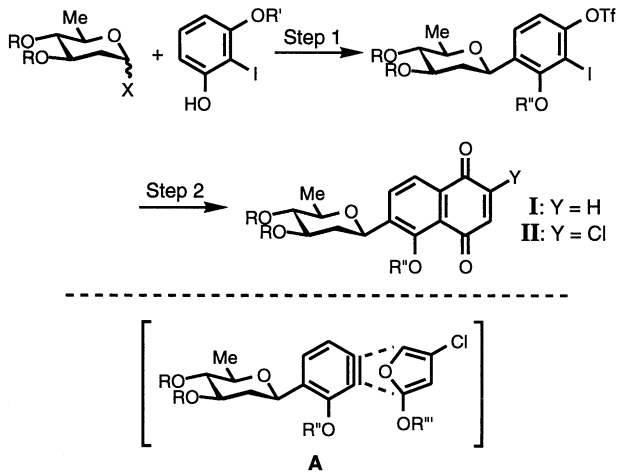
C-Glycosylated juglone (5-hydroxy-1,4-naphthoquinone) is seen as a common partial structure in certain classes of antibiotics, such as the angucyclines **1** and **2** (Figure 1).[1] Such a structural motif in turn would serve as a valuable synthetic intermediate *en route* to these natural products,[2]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

Figure 1.

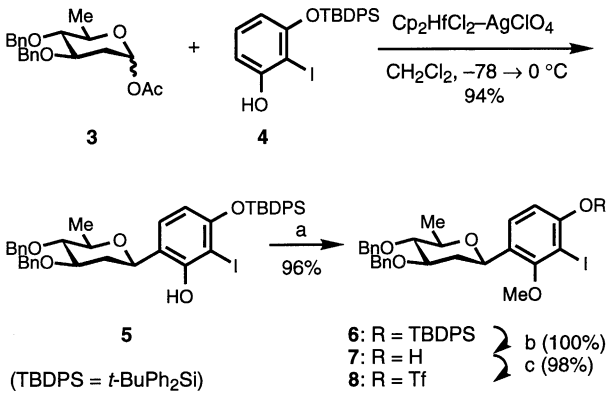


Herein, we report a regio- and stereocontrolled approach to these intermediates by way of two processes: (1) the *O*→*C*-glycoside rearrangement[4] to form the aryl *C*-glycoside bond and (2) [2 + 4] cycloaddition[5] of benzyne and α-oxyfuran to construct the juglone skeleton (see **I**, Scheme 1).[6] 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.

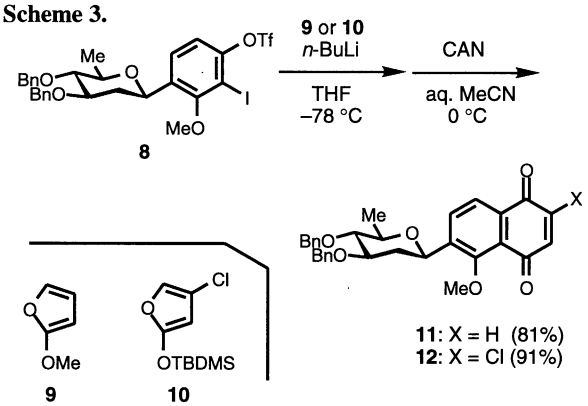


(a) NaH, $(MeO)_2SO_2$, THF–DMF, room temperature; (b) TBAF, THF, 0 °C; (c) *i*-Pr_2NEt, Tf_2O, CH_2Cl_2, –78 °C.

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-olivosyl acetate **3** (1.0 equiv.) and resorcinol **4**[7] (1.4 equiv.) were treated with Cp_2HfCl_2 (1.5 equiv.) and $AgClO_4$ (3.0 equiv.) in CH_2Cl_2 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 Tf_2O in the presence of *i*-Pr_2NEt 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.

Partial financial support from the Ciba–Geigy Foundation (Japan) for the Promotion of Science is gratefully acknowledged.

References and Notes

1 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.

2 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.

3 Y. Naruta and K. Maruyama, in "The Chemistry of Functional Group: The Chemistry of the Quinonoid Compounds," ed by S. Patai and Z. Rappoport, Wiley, New York (1988), Vol. 2, Chap. 8, p 241.

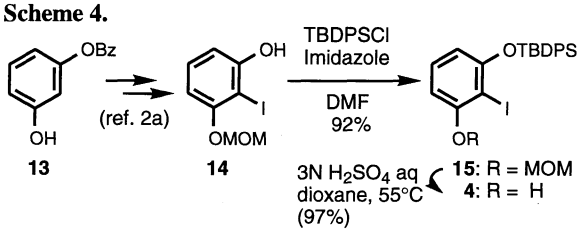
4 a) T. Matsumoto, M. Katsuki, and K. Suzuki, *Tetrahedron Lett.*, **29**, 6935 (1988). b) T. Matsumoto, T. Hosoya, and K. Suzuki, *Tetrahedron Lett.*, **31**, 4629 (1990). c) T. Matsumoto, T. Hosoya, and K. Suzuki, *Synlett*, **1991**, 709. Also see, Ref. 2.

5 T. Matsumoto, T. Hosoya, M. Katsuki, and K. Suzuki, *Tetrahedron Lett.*, **32**, 6735 (1991). Also see, Ref. 2.

6 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).

7 Resorcinol **4** was easily prepared in two steps from the known MOM ether **14**[2a] as shown below.

Scheme 4.



8 All new compounds were fully characterized by ^{1}H and ^{13}C NMR, IR, and high-resolution MS.

9 The β-configuration of *C*-glycoside **5** was evident from the ^{1}H NMR ($J_{1,2ax}$ = 11.7, $J_{1,2eq}$ = 2.0 Hz).

10 Chlorofuran **10** [bp 110–120 °C/3 mmHg (Kugelrohr)] was prepared from 4-chloro-2(5*H*)-furanone[11] according to the procedure described for the corresponding bromo congener. G. Jas, *Synthesis*, **1991**, 965.

11 R. C. Larock, B. Riefling, and C. A. Fellows, *J. Org. Chem.*, **43**, 131 (1978).

12 Fortunately, lithiation of chlorofuran **10** did not compete thanks to the extremely rapid iodine–lithium exchange.

13 Structure confirmation relies on the NOE experiment on acetate **16** which was obtained by acetylation of the product, the naphthol.