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A New Route to *C*-Aryl Glycosides

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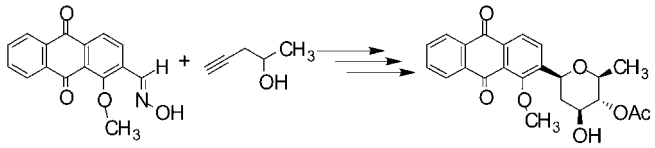
ABSTRACT



A six-step route for de novo synthesis of *C*-aryl glycosides based on cycloaddition of an aryl nitrile oxide with 4-pentyn-2-ol has been developed.

There are a large number of naturally occurring *C*-aryl glycosides, of which vineomycinone B_2[1] (Figure 1) is an example. Since many of these substances have significant anticancer activity, there has been strong interest in the development of routes for synthesis of *C*-aryl glycosides.[2] While most of these approaches have employed coupling of an aryl group with a sugar derivative, a few have involved construction of the sugar fragment from nonsaccharide precursors.[3]

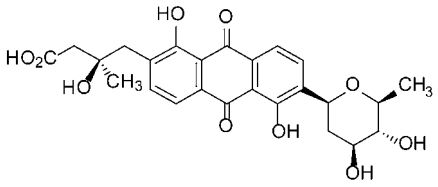
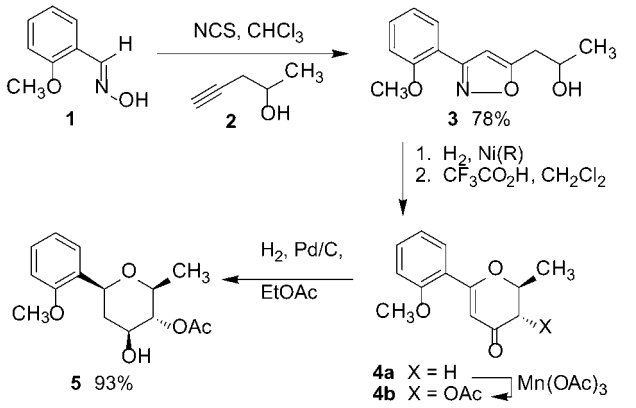


Figure 1. Vineomycinone B_2.

Our interest in total synthesis of naturally occurring *C*-aryl glycosides has led us to develop a new and brief route for de novo construction of *C*-aryl glycosides. In establishing the potential of the plan, racemic syntheses were performed.

As shown in Scheme 1, the nitrile oxide derived from reaction of the oxime **1** with NCS[4] underwent cycloaddition with the racemic acetylene **2** to afford the isoxazole (±)-**3** in 78% yield. Hydrogenolysis of **3** (H_2, Raney Ni) followed by acid treatment to effect cyclization of the diketone intermediate afforded the arylpyranone **4a**. Reaction of **4a** with $Mn(OAc)_3$[5] gave a 4.4:1 ratio of diastereoisomeric acetoxy pyranones from which the *trans*-isomer **4b** was isolated in 65% yield. Hydrogenation of **4b** furnished the pure *C*-arylpyranose (±)-**5** as the sole product in 93% yield. Although the stereochemistry of **5** could be obtained directly from the coupling constants in the ^{1}H NMR spectrum, 2D-NMR, NOE, and NOSEY were performed to confirm the assignment.

Scheme 1



Having established the viability of the plan with a simple aromatic group, we next tested the potential of the route using a more complex aromatic system; this is shown in Scheme 2. Cycloaddition of the nitrile oxide derived from the

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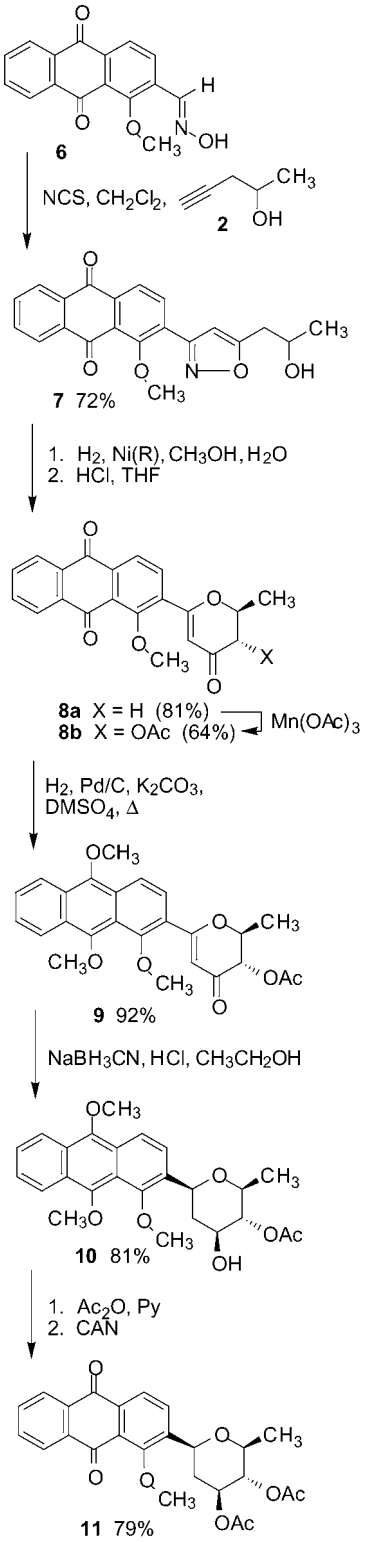
Scheme 2



anthraquinone oxime **6** with the acetylene **2** gave the isoxazole (±)-**7**, which was straightforwardly converted to the pyranone **8a** through sequential hydrogenolysis of the N−O bond of the isoxazole followed by acid-catalyzed intramolecular cyclization. Manganic acetate oxidation of **8a** afforded a 64% yield of the *trans*-acetoxy compound **8b** along with 21% of the *cis*-diastereoisomer, which were readily separated through silica chromatography. Surprisingly, catalytic hydrogenation of **8b** did not result in the expected regio- and stereoselective reduction of the enone moiety in the pyranose ring but instead proceeded with concurrent reduction of both the pyranone and the terminal aromatic ring!

Ultimately we were able to effect selective reduction of the enone moiety in **9** through use of a procedure reported by Tius et al.[6] in a similar system. A high yield (92%) one-pot procedure involving catalytic reduction of **8b** with in situ methylation afforded **9**.[7] Treatment of **9** with $NaBH_3$-CN at pH 4 in methanol gave **10** as the sole product. Here again, determination of the stereochemistry was straightforwardly achieved through $^1H-^1H$ decoupling. Protection of the alcohol group in **10** as the acetate and oxidation with CAN provided the quinone (±)-**11**.

There are a number of inherent advantages to use of this route for *C*-aryl glycoside synthesis. Principal among these is that minimal protection steps are required, and neither low temperature nor anhydrous conditions are required for any of the steps. Furthermore, since hydroxyl functionality is introduced in protected form, manipulation of individual hydroxyl groups should be possible.

In future work we will explore use of the plan for optically active total synthesis of *C*-aryl glycosides and application of the methodology to total synthesis of naturally occurring *C*-aryl glycosides.

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Supporting Information Available: Experimental details for **3**, **4a**, **4b**, **5**, **7**, **8a**, **8b**, and **9**−**11** are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Catalytic hydrogenation of **9** also resulted in concurrent reduction of both the pyranone and terminal aromatic ring.