

Novel methods for the synthesis of C-aryl glycoside natural products

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Abstract: A unified strategy for the synthesis of C-aryl glycosides with different substitution patterns has been developed.

The C-aryl glycoside natural products¹ have attracted attention because of their antibiotic, antimicrobial, and antitumor activity. The defining structural feature of these compounds is the carbon-carbon bond which connects C-1 of a carbohydrate moiety directly to an aromatic ring (Figure 1). Control of the stereochemistry of the anomeric center is one of the fundamental problems in the synthesis of any of the C-aryl glycosides.

In thinking about the C-aryl glycosides as targets for synthesis, we chose to classify them, as Suzuki has done,² on the basis of the substitution pattern of the glycosylated aromatic ring. In so doing, we divided them into the groups shown in Figure 2.

Figure 1.
The C-Aryl
Glycoside
Bond

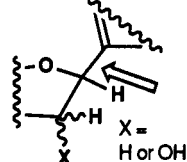
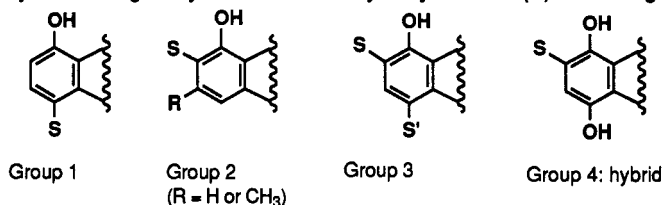


Figure 2.
The Naturally Occurring Polyketide C-1 C-Aryl Glycosides (S, S' = sugars)



This classification emphasizes the second fundamental problem in the synthesis of the C-aryl glycosides - i.e. control of the position of attachment of the sugar to the aromatic ring. The group 1

compounds have a C-glycoside linkage para to a phenolic hydroxyl group. In group 2, the sugar is attached ortho to the phenolic hydroxyl group. The group 3 compounds actually have two sugars attached to the same ring, one ortho and the other para to the hydroxyl group. In group 4, the sugar is ortho to one hydroxyl of a hydroquinone ring and meta to the other. In this paper, we are pleased to present a unified synthetic approach to compounds with the substitution patterns of groups 1 - 4. This approach has been applied to representatives of groups 1 and 4 and it holds promise for the synthesis of compounds in groups 2 and 3 as well.

Representatives of the four classes of C-aryl glycosides are shown in Figures 3-6. The gilvocarcins exhibit antitumor activity and have been shown to be intercalators. Gilvocarcins M and V have recently been synthesized by Suzuki, whose papers² contain a comprehensive listing of related literature. Vineomycin B₂ is also an antitumor compound. Several syntheses of vineomycinone B₂ methyl ester have been reported.³ Members of the kidamycin class are ortho, para bis C-glycosides. They have a variety of biological activities including antitumor activity.⁴ Synthetic approaches to these compounds have been limited. The mederrhodins are "hybrid antibiotics," i.e. they are the products of a recombinant organism.⁵

Figure 3.
Examples of Group 1:
Gilvocarcin Antitumor
Antibiotics

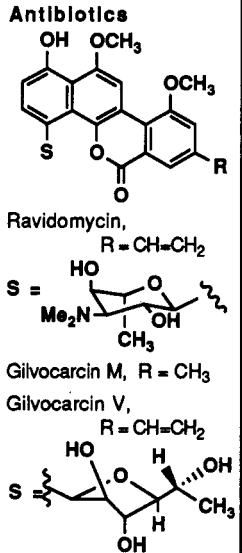


Figure 4.
Example of Group 2:
Vineomycin B₂

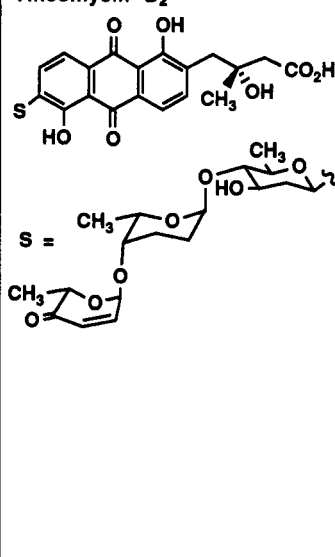


Figure 5.
Example of Group 3:
Kidamycin

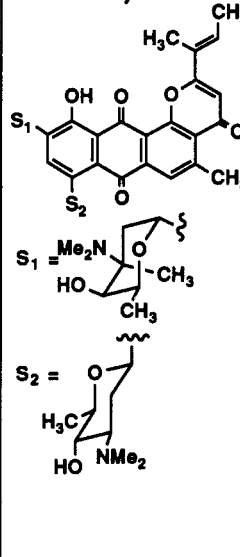
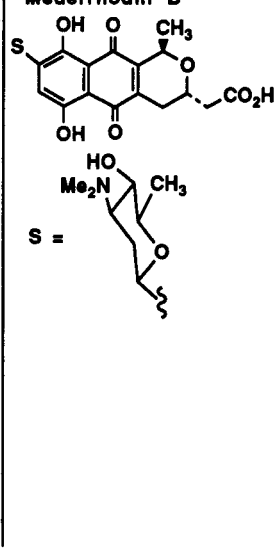


Figure 6.
Example of Group 4:
Mederrhodin B



We have recently reported the development of an umpolung strategy⁶ to C-aryl glycosides of the group 1 substitution pattern. In conversions illustrating this approach, the adduct of a lithiated glycol

and a quinone ketal (Figure 7) or a quinone (Figure 8) is reduced to a para alkoxy- or para hydroxyphenyl glycal.

Figure 7. Quinol Ketal Reduction Affords the Group 1 (Ravidomycin) Substitution Pattern

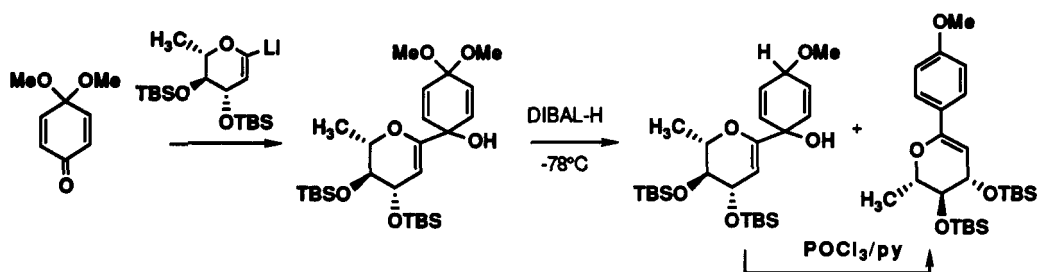
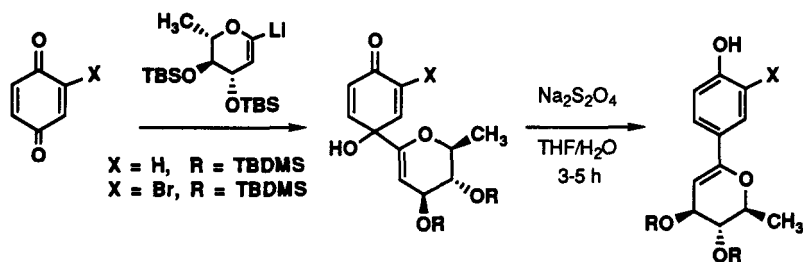
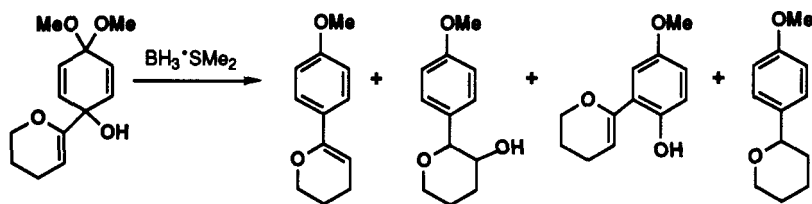


Figure 8. Quinol Reduction Also Affords the Group 1 Substitution Pattern



In model studies related to the transformation shown in Figure 7, we had examined the fate of quinol glycal ketals with borane. The distribution of products (Figure 9) was dependent on the ratio of reagent to substrate.

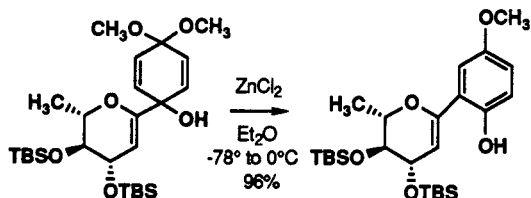
Figure 9. Glycal Model for Quinol Ketal Reduction by Diborane



Although the appearance of several products in these experiments was disappointing in terms of the preparation of group 1 structures, the identification of by-products from this reaction provided the key to expanding the umpolung strategy to compounds in groups 2-4. The third product above has the substitution pattern contained in the group 4 antibiotics. It is the product of rearrangement of the carbonium ion generated by the Lewis acidity of the reducing agent.

If we want to optimize production of the rearrangement product, we should use a reagent which is a Lewis acid but not a hydride donor. Indeed, the very mild Lewis acid, zinc chloride, effects this rearrangement in quantitative yield at low temperature (Figure 10). This rearrangement is related to cyclohexadienediol rearrangements reported by Chamberlin.⁷

Figure 10. Rearrangement Affords the Group 4 Substitution Pattern



At this point then, the umpolung approach to C-aryl glycosides has given access to compounds with both type 1 and type 4 substitution patterns. The further development of this quinol glycal chemistry for the preparation of compounds with patterns of types 2 and 3 is underway and we are currently exploring its application in total synthesis.

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