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Unified strategy for the synthesis of *C*-aryl glycosides*

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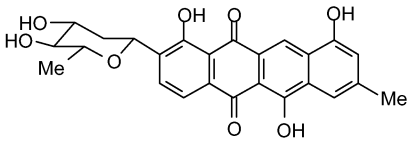
Abstract: A unified approach for the synthesis of the four major groups of *C*-aryl glycosides has been developed. The strategy incorporates two integrated approaches, the first of which features the [4+2] cycloaddition of a glycosyl furan with a substituted benzyne followed by the acid-catalyzed opening of the resultant adduct. The second route involves the sequential palladium-catalyzed opening of a benzyne-furan cycloadduct with an iodo glycal followed by oxidation of the resultant dihydronaphthol ring and reduction of the glycal moiety. The utility of this strategy has been established by a concise formal synthesis of the *C*-aryl glycoside antibiotic galtamycinone.

INTRODUCTION

The *C*-aryl glycoside antibiotics comprise a subclass of a broader family of naturally occurring *C*-glycosides that have gained considerable attention because of their range of biological activities and resistance to enzymatic hydrolysis [1]. Some representative members of this class of natural products that are of current interest in our labs include galtamycinone (**1**), vineomycinone B_2 (**2**), and kidamycin (**3**). The *C*-aryl glycosides may be classified into four different subgroups based upon the orientation of the sugar residue(s) relative to the phenolic hydroxyl group on the aromatic ring. Indeed, development of a general approach for the syntheses of the four major classes of *C*-aryl glycosides constitutes a significant challenge.



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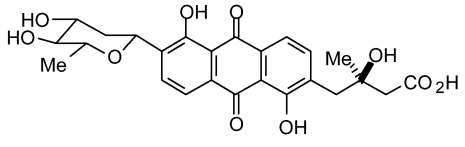

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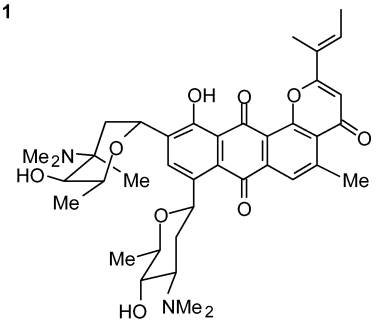

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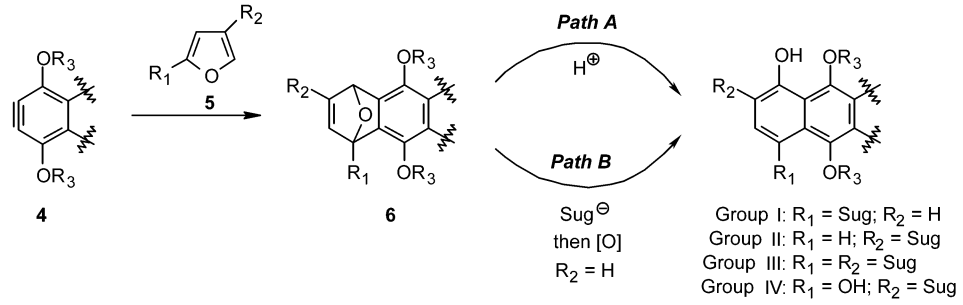
As part of an ongoing program directed toward the design and development of new strategies for the synthesis of biologically active natural products, we envisioned that the general transformations outlined in Scheme 1 might afford a facile entry to the four common structural types of *C*-aryl glycosides. The first route (***Path A***) features the [4+2] cycloaddition of a glycosyl furan **5** (R_1 and/or R_2 = Sug) with a substituted benzyne **4** followed by acid-catalyzed opening of the resultant adduct **6** to give, depending upon the substitution pattern, members of the respective Groups I–IV of *C*-aryl glycosides. The second pathway is applicable to preparing *C*-aryl glycosides of Groups II, III, and IV and involves the S_N2'-like opening of benzyne-furan cycloadducts **6** (R_1 = H, Sug; R_2 = H) with sugar nucleophiles followed by oxidation to generate the aromatic system (***Path B***). Significantly, each of these pathways features annelating new benzene rings while enabling the introduction of carbohydrate residues at a late stage of the synthesis. Such characteristics not only render the overall strategy highly convergent, but they also endow it with significant flexibility for modifying the carbohydrate groups in order to tune the biological activity of *C*-aryl glycoside derivatives in structure–activity relationship studies.



Scheme 1

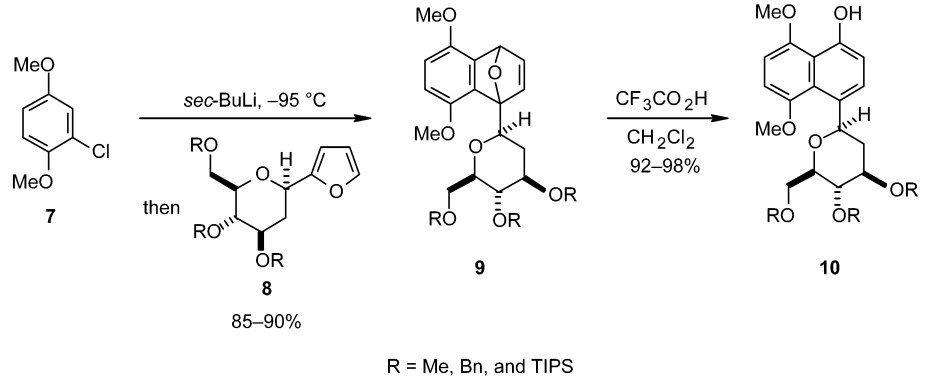
Although the acid-catalyzed rearrangement of compounds related to **6** to give naphthols was well known at the time we initiated this investigation, 2-glycosyl furans had never been employed as dienes in cycloadditions with benzynes. Moreover, the ring opening of compounds like **6** with carbanions to give dihydronaphthols was well known [2], and there were examples of the palladium-catalyzed reaction of aryl iodides with adducts related to **6** [3]. However, sugars had never been used in these transformations, and the feasibility of oxidizing the intermediate dihydronaphthols *without* accompanying dehydration was uncertain. We thus set to the task of evaluating the basic tenets of these routes to *C*-aryl glycosides and report some of these results herein.

RESULTS AND DISCUSSION

Diels–Alder approach (*Path A*)

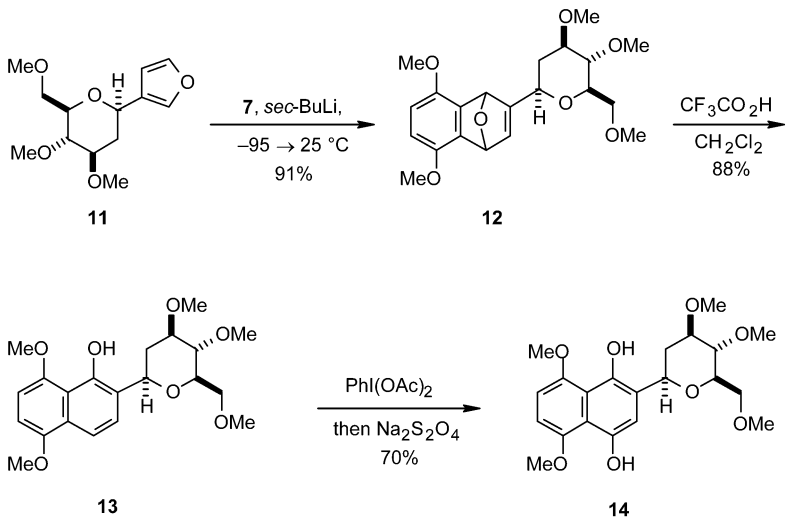
The first task before us was to ascertain whether a 2-glycosyl furan would undergo an efficient Diels–Alder reaction with a benzyne as we were cognizant of the potentially detrimental steric interactions that would occur in the transition state for the cycloaddition. In order to address this question, we examined simple models involving a series of protected 2-glycosyl furans **8** that were prepared by application of known chemistry [4]. We were delighted to discover that deprotonation of **7** with *sec*-BuLi at –95 °C followed by addition of furans **8** and slow warming of the resultant mixture gave the cycloadducts **9** in excellent yields (Scheme 2). As we had hoped, the benzyne generated from **7** was cleanly trapped in situ by the 2-glycosyl furans. The subsequent acid-catalyzed rearrangement of the adducts **9** to give the Group I models **10** also proceeded without difficulty.

In a similar fashion, the 3-glycosyl furan **11**, which was prepared by reduction of the hemiacetal produced by adding 3-lithiofuran to the corresponding sugar lactone [5], underwent [4+2] cycloaddi-



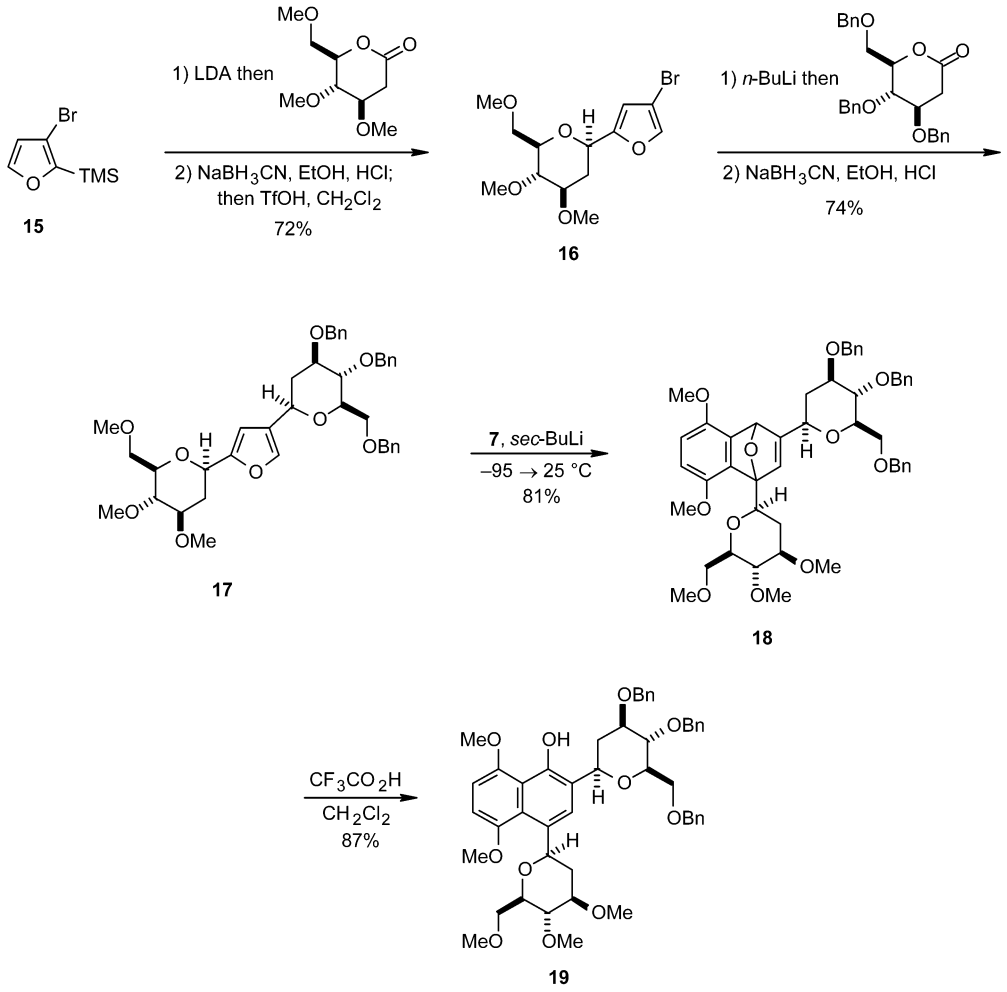
Scheme 2

tion with the benzyne generated from **7** to give **12**. When **12** was treated with trifluoroacetic acid, a separable mixture (10:1) of the Group II model **13** and the isomeric *m*-substituted product was obtained (Scheme 3). Subsequent oxidation of the phenolic ring of **13** to a quinone followed by reduction furnished the Group IV model **14**.



Scheme 3

Having established the viability of preparing *C*-aryl glycosides of Groups I, II, and IV via ***Path A*** (Scheme 1), it remained to extend this methodology to the more demanding class of the Group III *C*-aryl glycosides. The first task was to prepare the requisite 2,4-diglycosyl furan **17**. This was quickly accomplished in an unoptimized series of reactions involving sequential addition/reduction reactions of lithiated furans with readily available glucose-derived lactones (Scheme 4). When **17** was allowed to react with the benzyne generated in situ from **7** as previously described, [4+2] cycloaddition ensued to deliver **18** as a mixture of diastereomers that converged to the Group III model **19** upon exposure to trifluoroacetic acid.

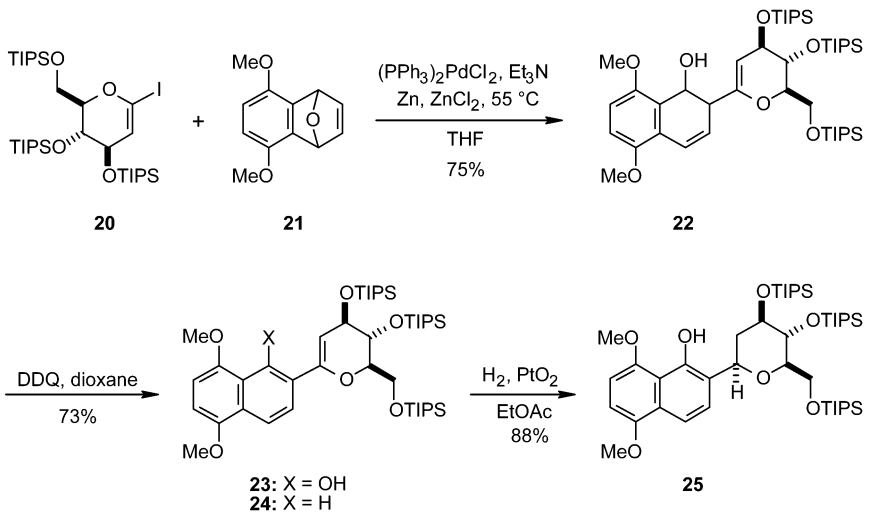


Scheme 4

S_N2' Opening-oxidation approach (*Path B*)

It is apparent from the preceding experiments that the glycosyl furan-benzyne Diels–Alder route to *C*-aryl glycosides (***Path A***) allowed facile access to all four major groups of *C*-aryl glycosides. However, we were interested in developing the alternative approach outlined in ***Path B*** as advantages might attend its use in some circumstances. For example, the ***Path B*** entry would offer the opportunity of introducing carbohydrate residues at an even later stage of the synthesis of Group III *C*-aryl glycosides. It would also eliminate altogether the need to prepare glycosyl furans in the synthesis of Group II/IV *C*-aryl glycosides.

Our initial experiments directed toward the ring opening of benzyne-furan cycloadducts **6** with sugar-derived carbanions via a S_N2' reaction were not promising, although additional studies are necessary before abandoning this approach. Concurrently, we were intrigued by the possibility that the palladium-catalyzed reaction of iodo glycals with cycloadducts like **6** might proceed to give the desired dihydronaphthols in accord with literature precedent for the related reactions of such adducts with aryl iodides [5]. In order to evaluate this hypothesis, the iodo glycal **20** [6] was allowed to react with **21** using the catalyst and reaction conditions optimized by Cheng [5c], and a mixture (ca. 1:1) of diastereomeric *cis*-dihydronaphthols **22** was obtained (Scheme 5). A preliminary screen of various oxidants to transform

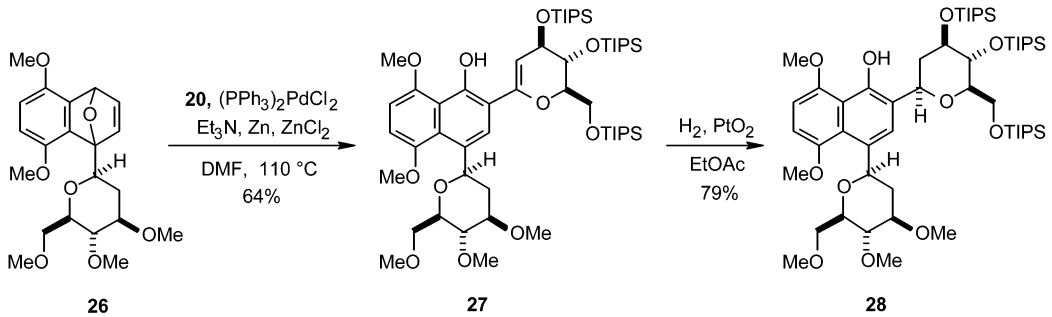


Scheme 5

22 into **23** quickly revealed the problematic nature of this conversion; the naphthalene **24** was isolated as the major product from attempted oxidations under a number of conditions. As noted previously, this result was not unexpected. Eventually, we discovered that the transformation of **22** into **23** could be cleanly induced using freshly recrystallized 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Stereoselective reduction of **23** according to the protocol of Beau then delivered the Group II model **25** [7].

The strategy depicted in ***Path B*** of Scheme 1 could also be implemented to prepare a Group III model *C*-aryl glycoside. For example, the palladium-catalyzed reaction of the sugar-substituted cycloadduct **26** with **20** gave the naphthol **27**, reduction of which furnished **28** (Scheme 6). It is noteworthy that the ring opening reaction of **26** with **20** required more forcing conditions than the reaction with the adduct **21**. At this higher temperature, the intermediate dihydronaphthols underwent spontaneous oxidation, thereby obviating the need to perform the oxidation as a separate step as was done in earlier experiments.

At this stage, we had clearly established the viability of our general entries to the four major groups of *C*-aryl glycoside antibiotics. It was now appropriate to apply these useful transformations to the syntheses of naturally occurring *C*-aryl glycosides.

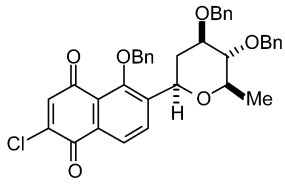


Scheme 6

Formal synthesis of galtamycinone

Galtamycinone (**1**) is a member of the angucycline family of *C*-aryl glycosides, and its only synthesis has been recorded by Suzuki [8]. Galtamycinone poses a challenge not only for *C*-aryl glycoside syn-

thesis but also for the efficient assembly of the linear tetracyclic framework that constitutes the aromatic core. Nevertheless, we focused our first efforts upon applying our methods for *C*-aryl glycoside synthesis. In this exercise, we were guided by prior art as Suzuki had converted the chlorojuglone **29** into **1** using a tactic developed by Tamura to annelate the requisite naphthalene subunit [9]. Hence, the chlorojuglone **29** and analogs thereof became our first subgoal.



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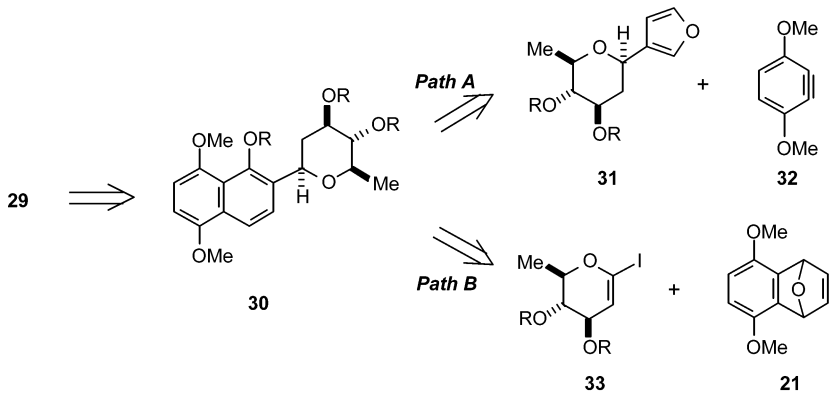
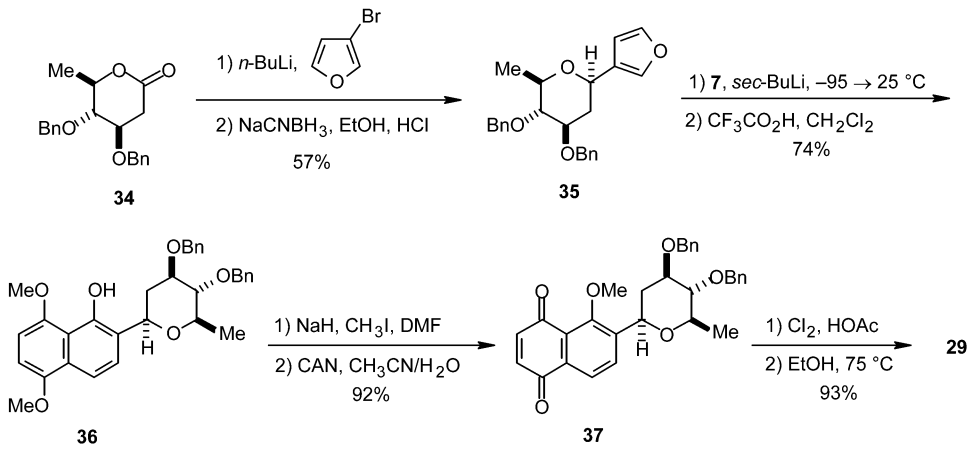
We envisioned two distinct routes to juglones generally related to **29** by implementing our strategy for *C*-aryl glycoside synthesis. In each of these approaches, a naphthalene **30** would be converted via oxidation and chlorination to the chlorojuglone **29** (Scheme 7). The *C*-aryl glycoside **30** would then in turn be accessible via a Diels–Alder reaction of a furyl glycoside **31** with benzyne **32** followed by acid-catalyzed ring opening of the intermediate adduct. Alternatively, **30** would be accessible via the palladium-catalyzed opening of **21** with an iodo glycal **33**.



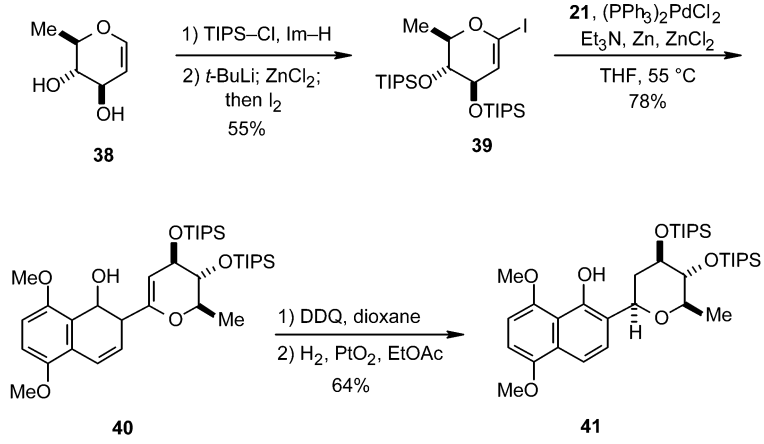
Scheme 7

In keeping with this plan, the lactone **34**, which was prepared by the same procedure reported for its enantiomer [10], was first converted into the glycosyl furan **35** (Scheme 8). Reaction of **35** with the benzyne that was generated in situ from 2-chloro-1,4-dimethoxybenzene (**7**) furnished a mixture of diastereomeric Diels–Alder adducts. The acid-catalyzed rearrangement of these adducts provided the desired *C*-aryl glycoside **36**. *O*-Methylation of **36** followed by selective oxidation of the dimethyl hydroquinone ring gave the juglone **37**. Sequential chlorination–dehydrochlorination of **37** afforded the targeted chlorojuglone **29** [11].

In order to apply the strategy embodied in ***Path B*** to the synthesis of a possible precursor of juglone **29**, D-olivose glycal (**38**) [12] was converted into the protected iodo glycal **39** according to the protocol developed by Friesen (Scheme 9) [9]. The palladium-catalyzed opening of **21** with **39** then furnished **40** [5], which was transformed into the desired *C*-aryl glycoside **41** by sequential oxidation of the dihydronaphthol moiety and stereoselective reduction of the glycal. Tactics for elaborating **41** into galtamycinone (**1**) may be readily envisioned, but these were not pursued.



Scheme 8



Scheme 9

CONCLUSIONS

In summary, we have developed several general protocols for the efficient preparation of the four major classes of *C*-aryl glycosides. The first entry features the [4+2] cycloaddition of a glycosyl furan with a substituted benzyne followed by the acid-catalyzed opening of the resultant adduct. The second pathway involves a palladium-catalyzed S_N2'-like opening of a furan-benzyne cycloadduct with an iodo glycal followed by oxidation and reduction. There are several advantages that attend the application of this methodology to the synthesis of complex *C*-aryl glycosides. For example, the ability to annelate benzene rings in concert with introducing the carbohydrate residue on the aromatic core imbues the approach with a high degree of convergency. The option of introducing the sugar moiety by opening a benzyne-furan cycloadduct permits the introduction of the carbohydrate residues at an even later stage of a synthesis, thereby increasing opportunities for diversity generation in the final targets. The utility of these methods has been established in a preliminary study by their application to a concise formal synthesis of the *C*-aryl glycoside antibiotic galtamycinone. Current efforts focus upon the development of regioselective variants of these approaches and their application to the syntheses of other naturally occurring *C*-aryl glycoside antibiotics.

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