General Strategies for the Synthesis of the Major Classes of *C*-Aryl Glycosides

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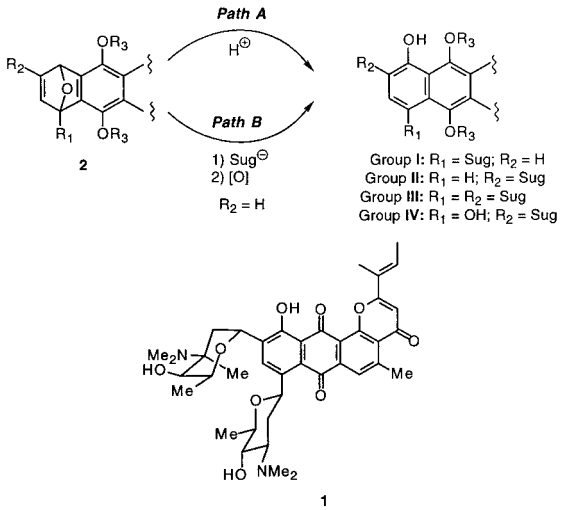
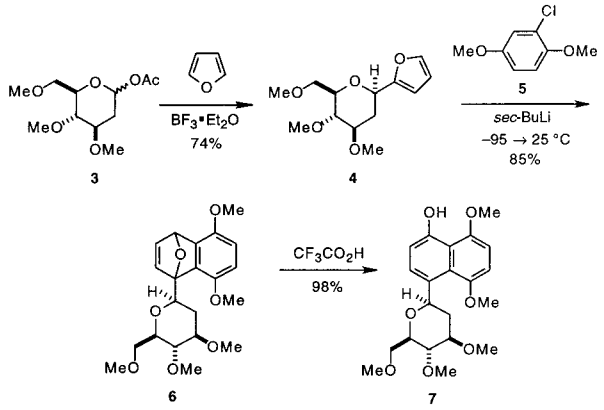
The *C*-aryl glycoside antibiotics, as exemplified by kidamycin (**1**), constitute an important class of biologically active natural products.[1] While kidamycin represents a member of one subgroup of this family, there are four common structural types of *C*-aryl glycosides (Groups **I**−**IV**), which have been classified on the basis of the substitution pattern of the sugar residue(s) and the hydroxyl group(s) on the aromatic ring.[2] Hence, one of the significant challenges presented by these complex antibiotics lies in the design and development of a unified strategy for the synthesis of the four major subgroups of this family.[3,4]

Scheme 1



After considering a number of novel approaches to *C*-aryl glycosides, we were attracted to the two pathways that are summarized in Scheme 1. The acid-catalyzed rearrangement of compounds related to **2**, which are formed by cycloadditions of furans and benzynes, was well-known to give naphthols (Path A).[5] However, *C*-furyl glycosides have never been employed as dienes in such processes. As a precedent for the introduction of a second sugar residue via Path B, it is relevant that opening of oxabicyclic compounds **2** via an S_N2' reaction with carbanions and via a palladium-catalyzed reaction with aryl iodides to give dihydronaphthols was known.[6,7] However, sugars had never been used in such constructions, and the feasibility of oxidizing the intermediate, electron-rich dihydronaphthols efficiently to the corresponding naphthols *without* accompanying dehydration was clearly uncertain. To establish the underlying viability of this new approach to *C*-aryl glycosides we embarked on a series of model studies, some of which are summarized in Schemes 2−6. Our first initiative was to determine whether a 2-glycosyl furan would undergo a Diels−Alder reaction with benzynes. To address this question, **4** was prepared (α:β 1:9) by the reaction of furan with the glycosyl acetate **3** (Scheme 2).[8] After some preliminary experimentation using various bases and temperatures, we discovered that **5** could be efficiently deprotonated *ortho* to the chloro group using *sec*-BuLi at −95 °C. After furan **4** was added, the mixture was allowed to warm slowly to room temperature during which time benzyne generation and cycloaddition ensued to give **6**.[9] Acid-catalyzed rearrangement of **6** then delivered the Group **I** *C*-aryl glycoside representative **7** as a single diastereomer in excellent overall yield.

Scheme 2



Similarly, we found that the 3-glycosyl furan **9**, which was prepared by application of known procedures,[10,11] reacted with 1,4-dimethoxybenzyne to give **10** in 91% yield (Scheme 3). The acid-catalyzed rearrangement of **10** furnished a readily separable mixture (10:1) of the Group **II** *C*-aryl glycoside model **11**, which was obtained as a single diastereomer, and the isomeric *m*-substituted product. Oxidation of **11** with $PhI(OAc)_2$ and reduction of the quinone thus produced with $Na_2S_2O_4$ gave the Group **IV** *C*-aryl glycoside **12** in 70% overall yield.

Having demonstrated that representative *C*-aryl glycosides of Groups **I** (i.e., **7**), **II** (i.e., **11**), and **IV** (i.e., **12**) were accessible via Path A of Scheme 1, it remained to prepare a model of the more challenging Group **III** *C*-aryl glycosides. The key intermediate 2,4-diglycosyl furan **16** was first prepared by sequential additions of metalated furans derived from **13**[12] to the glucose-derived lactones **8**[13] and **15**[14] followed by hydride reduction of

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(6) For reviews, see: (a) Chiu, P.; Lautens, M. *Top. Curr. Chem.* **1997**, *190*, 3. (b) Woo, S.; Keay, B, A. *Synthesis* **1996**, 669.

(7) (a) Duan, J.-P.; Cheng, C.-H. *Tetrahedron Lett.* **1993**, *34*, 4019. (b) Moinet, C.; Fiaud, J.-C. *Tetrahedron Lett.* **1995**, *36*, 2051. (c) Duan, J.-P.; Cheng, C.-H.; *Organometallics* **1995**, *14*, 1608. (d) Feng, C.-C.; Nandi, M.; Sambaiah,; Cheng, C.-H. *J. Org. Chem.* **1999**, *64*, 3538.

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(9) All new compounds were purified (>95%) by flash chromatography and were characterized by ^1H and ^{13}C NMR, IR, and HRMS. Cycloadducts **6**, **10**, and **17** were obtained as mixtures (ca 1:1) of diastereomers. Only the β-anomers of **7**, **11**, **12**, **18**, **22**, and **24** were observed (determined by ^1H NMR); the anomeric proton was a dd or a br d with one large (ax-ax, 10.9-11.4 Hz) and one small (ax-eq, 1.9−2.1 Hz) coupling constant.

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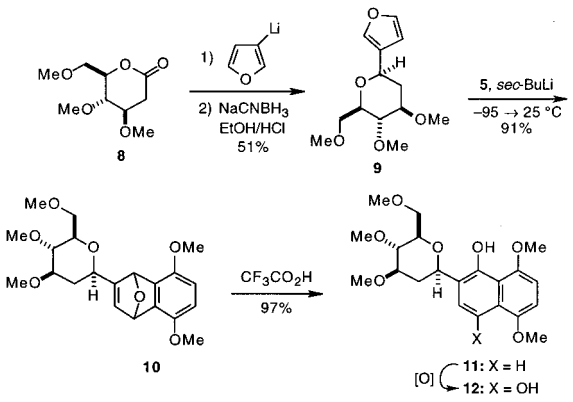
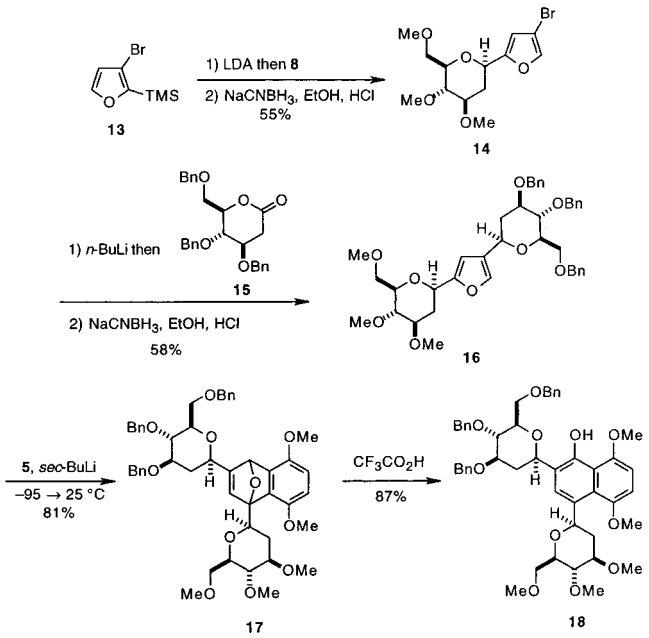
Scheme 3



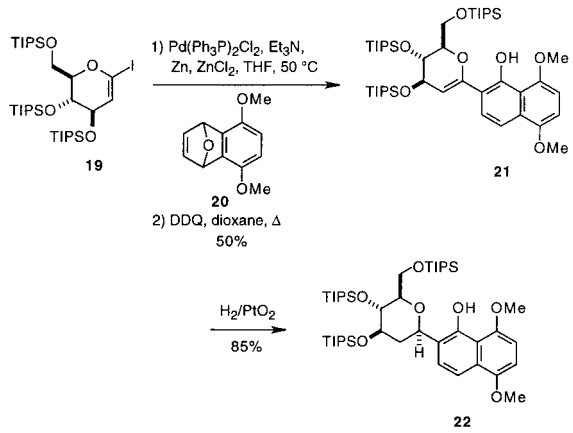
Scheme 4



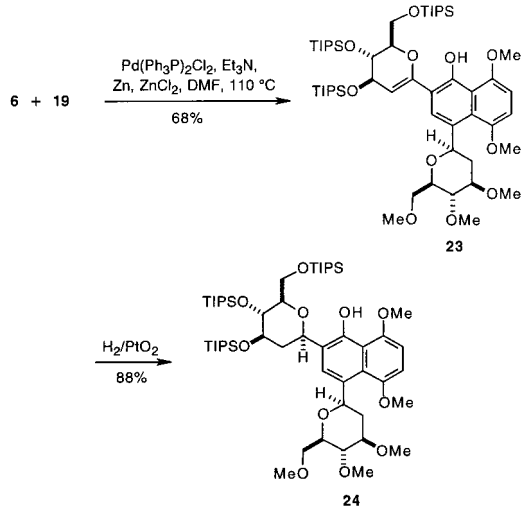
the intermediate lactols (Scheme 4). Gratifyingly, when 1,4-dimethoxybenzyne was generated in the presence of **16,** smooth cycloaddition ensued to deliver **17**, which underwent facile acid-catalyzed rearrangement to provide the Group **III** *C*-aryl glycoside model **18** as a single diastereomer.

Even though we had convincingly established the general applicability of the approach to *C*-aryl glycosides outlined in Path A of Scheme 1, we were intrigued by the alternative approach of Path B as it might possess some advantage in certain circumstances. In the event, we conducted a number of preliminary experiments to determine whether glycosyl carbanions might induce the S_N2' opening of **20**. However, significant quantities of ring-opened products could not be isolated. While the possibility remains that such reactions might prove useful, we were attracted instead to the possibilities afforded by the palladium-catalyzed reaction of iodo glycals such as **19**[15] with **20** according to the precedent of Cheng and others.[7] Indeed, we discovered that the reaction of **19** with **20** proceeded readily under the conditions optimized by Cheng to give a mixture (1:1) of the diastereomeric *cis*-dihydronaphthol precursors of **21** (Scheme 5). Although the oxidation of these dihydronaphthols to **21** under numerous conditions gave substantial quantities of the naphthalene

Scheme 5



Scheme 6



derived from dehydration, we eventually found that use of recrystallized DDQ as the oxidant gave the naphthol **21**. Reduction of **21** by catalytic hydrogenation then delivered the Group **II** *C*-aryl glycoside **22** as a single diastereomer.

Similarly, we found that the sugar-substituted cycloadduct **6** underwent ring opening, albeit under more forcing conditions, with **19** to give intermediate dihydronaphthols that underwent oxidation in situ to give **23** in 68% overall yield (Scheme 6). Reduction of the glycal by catalytic hydrogenation then provided the Group **III** *C*-aryl glycoside model **24**.

We have thus developed general protocols for *C*-aryl glycoside synthesis that may be applied to the efficient preparation of the four major classes of *C*-aryl glycoside antibiotics. The first approach showcases the cycloadditions of glycosyl furans with benzynes followed by acid-catalyzed rearrangement of the intermediate cycloadduct, whereas the second features the palladium-catalyzed, S_N2'-like opening of furan−benzyne cycloadducts with iodo glycals. The application of regioselective variants of these novel routes to the syntheses of naturally occurring *C*-aryl glycoside antibiotics is the subject of several active investigations, the results of which will be disclosed in due course.

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Supporting Information Available: Experimental procedures for compounds **7**, **21**, and **23**, complete characterization (^{1}H and ^{13}C NMR, IR, and mass spectral data) for **7**, **11**, **12**, **18**, **21**, **22**, **23**, and **24**, and copies of ^{1}H NMR spectra for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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