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# Novel Methodologies for the Synthesis of *C*-Aryl Glycosides and Progress Toward the Synthesis of the *C*-Aryl Glycoside Natural Products Galtamycinone and Kidamycin

Committee:

_____

Stephen F. Martin, Supervisor

_____

Philip D. Magnus

_____

Nathan L. Bauld

_____

Marvin L. Hackert

_____

Christian P. Whitman

# Novel Methodologies for the Synthesis of *C*-Aryl Glycosides and Progress Toward the Synthesis of the *C*-Aryl Glycoside Natural Products Galtamycinone and Kidamycin

**by**

**David Earl Kaelin Jr., B.S.**

**Dissertation**

Presented to the Faculty of the Graduate School of

The University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

**Doctor of Philosophy**

**The University of Texas at Austin**

**December, 2002**

# Novel Methodologies for the Synthesis of *C*-Aryl Glycosides and Progress Toward the Synthesis of the *C*-Aryl Glycoside Natural Products Galtamycinone and Kidamycin

Publication No. _____

David Earl Kaelin Jr., Ph.D.

The University of Texas at Austin, 2002

Supervisor: Stephen F. Martin

The development of methodologies for the synthesis of *C*-aryl glycosides has been described. Novel *C*-aryl glycosides were prepared by [4+2] cycloadditions between benzynes and glycosyl-substituted furans. A modification of the cycloaddition approach, wherein the two reactants were linked *via* a cleavable tether, allowed *C*-aryl glycosides to be prepared in a highly regioselective manner. An alternate method for the preparation of *C*-aryl glycosides *via* an $S_N2'$ ring opening reaction of benzyne/furan cycloadducts with sugar nucleophiles has been described.

Extension of the benzyne/glycosyl-substituted furan cycloaddition methodology to natural product synthesis has been described. A formal total synthesis of the antitumor antibiotic galtamycinone has been completed. Application of the cycloaddition methodology toward the total synthesis of the *bis*-*C*-aryl glycoside antitumor antibiotic kidamycin has also been described.

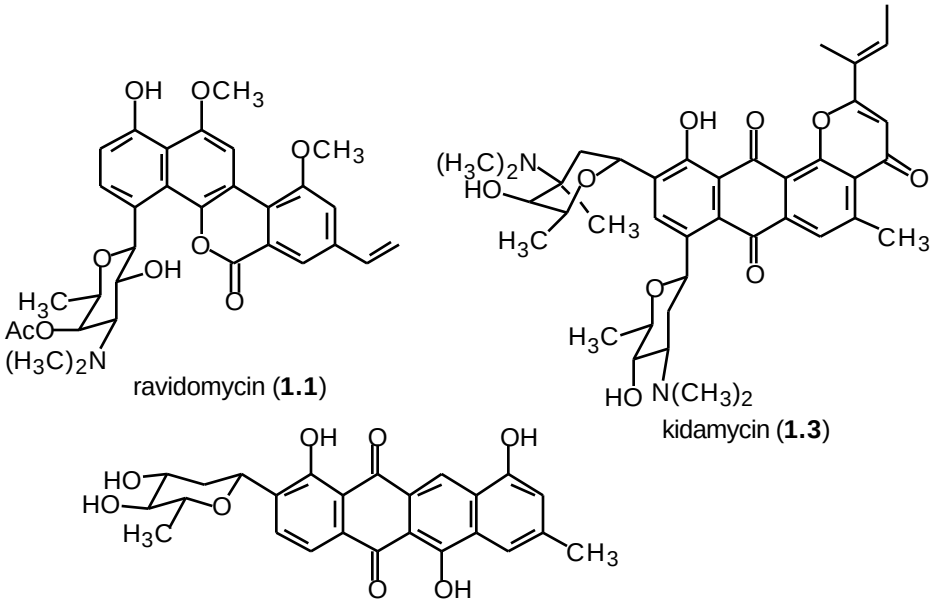
# Table of Contents

# Chapter 1. Methods for the Synthesis of *C*-Aryl Glycosides

## 1.1 INTRODUCTION

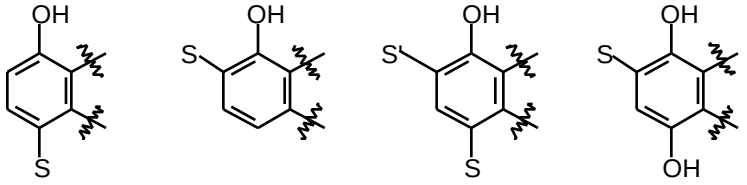
The *C*-aryl glycoside moiety is found in a number of structurally and biologically fascinating natural products. For this reason, the design and development of new methods for *C*-glycoside construction is an area of research that has received significant attention over the past two decades. A few representative examples of naturally occurring *C*-aryl glycoside antibiotics are illustrated in Figure 1.1. Ravidomycin (**1.1**), the aminosugar congener of the gilvocarcin antitumor antibiotics, shows enhanced activity over its non-amino analogues with respect to anticancer properties.[1] Galtamycinone (**1.2**), an atypical member of the angucycline family, shows both antibiotic and antitumor characteristics. Kidamycin (**1.3**) has been shown to be active against leukemia L-1210, Sarcoma-180 (solid type), NF-sarcoma, and Yoshida sarcoma.[2] Some of these molecules will be discussed in more detail in Chapter 2.

**Figure 1.1**




The *C*-aryl glycoside antibiotics can be subdivided into four classes based on the substitution pattern of the phenolic hydroxy group(s) relative to the carbohydrate moiety(ies) (Figure 1.2).[3] Many examples of methods for *C*-aryl glycoside synthesis can be found in the literature; however, very few of these would allow access to all four *C*-glycoside groups. A new methodology that would permit the preparation of Groups I-IV with good regio- and diastereoselectivity would help to address some of the deficiencies that exist in current techniques. Additionally, it is almost certain that a methodology that meets these criteria would allow for the synthesis of *C*-aryl glycoside natural products and their analogues that have yet to be prepared.

**Figure 1.2**




S = sugar

## 1.2 METHODS

Several excellent reviews detailing advancements in the arena of *C*-glycoside synthesis have been published in the past decade. Postema prepared two very thorough general reviews of methods developed up to 1995 for the synthesis of *C*-glycosides.[4] Suzuki has written a review on *C*-aryl glycoside synthesis with an emphasis on application of these methods to the total synthesis of naturally occurring *C*-aryl glycosides.[5] Knapp has reviewed *C*-aryl glycoside synthesis as well.[6] Levy and Tang published a book on *C*-glycoside synthesis that thoroughly discussed the methods used up to 1995.[7] Du and co-workers reviewed various aspects of stereoselective *C*-glycoside synthesis through 1998 but with no particular emphasis on *C*-aryl glycoside formation.[8] These reviews were used as a guide for the discussion of currently available methods for the construction of *C*-aryl glycosides reported up to 1998.

The methods available for *C*-aryl glycoside synthesis can be broadly classified into five major groups: 1) Attack of an aromatic nucleophile on a carbohydrate with an electrophilic anomeric center, such as a glycosyl halide, or after activation of the anomeric center in the presence of a suitable Lewis acidic promoter. 2) Attack of a carbohydrate nucleophile on an aromatic electrophile equivalent. 3) Transition metal-mediated reactions in which the carbohydrate and aromatic moieties may function as either the nucleophile or electrophile. 4) Cycloaddition strategies and related

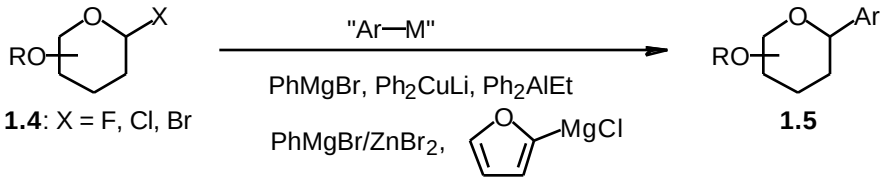
approaches that rely on the *de novo* construction of the carbohydrate on an aromatic nucleus that contains the appropriate functionality, for example an aldehyde. The electrophilic cyclization of acyclic precursors wherein the *C*-aryl bond has already been formed will also be considered in this group. 5) Benzannulation strategies wherein the aromatic nucleus is constructed from acyclic precursors after formation of the *C*-glycosidic bond.

### 1.2.1 Nucleophilic Attack on a Carbohydrate Electrophile

One of the most common methods for assembling *C*-aryl glycosides involves formation of the *C*-glycoside bond by reaction of a suitable aromatic nucleophile with a carbohydrate or carbohydrate equivalent. This approach takes advantage of the inherent electrophilicity at the anomeric carbon of glycosyl donors. The electrophilicity of this site is often enhanced by refunctionalization or reaction in the presence of an activator, for example, by conversion of the substituent at the anomer center to a better leaving group or by the addition of an appropriate Lewis acid.

Some of the earliest nucleophilic addition approaches to *C*-aryl glycosides relied on the displacement of a glycosyl halide with an organometallic reagent.[9] This basic concept is illustrated in Equation 1.1. One drawback of this methodology is that it can sometimes be difficult to obtain the glycosyl halide with high stereoselectivity at the anomeric center. Because the additions tend to occur in an $S_N2$ fashion with inversion of configuration at the anomeric center, mixtures of anomers are often observed in the products.

**Equation 1.1**

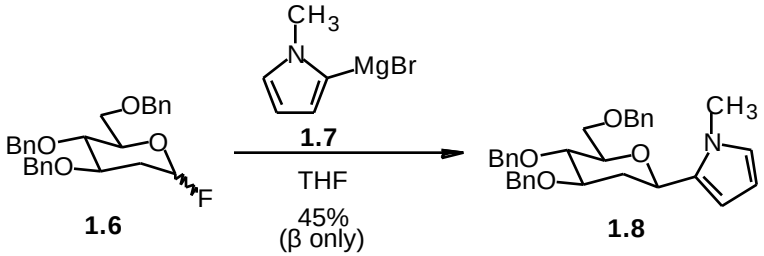



**1.4**: X = F, Cl, Br

**1.5**

Several recent examples for preparing heteroaryl-*C*-glycosides by displacement of glycosyl fluorides with aryl Grignard reagents were reported by Yokoyama,[10] and a representative example is shown in Equation 1.2. Treatment of a mixture of anomeric fluorides **1.6** with *N*-methylpyrrol-2-ylmagnesium bromide (**1.7**) provided a 44% yield of exclusively the β-anomer of **1.8**. An oxocarbenium mechanism, rather than a direct $S_N2$ displacement, was used to rationalize the formation of a single diastereomer of **1.8**. Other aromatic and heteroaromatic reagents were employed in similar transformations. The authors also examined the preparation of *C*-aryl furanoses using glycosyl fluoride donors.

**Equation 1.2**



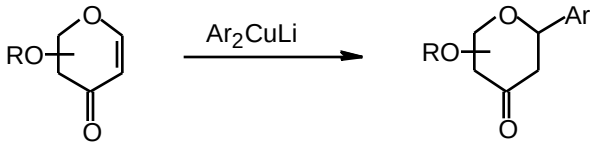

**1.6**

**1.8**

Enones derived from glycals have been shown to be useful intermediates in the synthesis of *C*-aryl glycosides. One of the earliest examples of this type of transformation involved the conjugate addition of an aryl organocuprate to a carbohydrate-derived α,β-unsaturated pyranone (Equation 1.3).[11] Subsequently, milder

approaches have been developed that allowed for the preparation of *C*-aryl glycosides using this basic disconnection.[12]

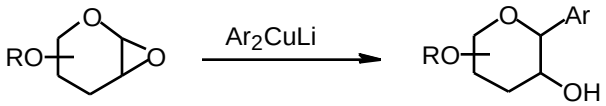
**Equation 1.3**




**1.9** **1.10**

Additions of aryl nucleophiles to 1,2-anhydrosugars represent another useful method for *C*-aryl glycoside preparation.[13] This transformation is illustrated in Equation 1.4. The requisite epoxides can be stereoselectively obtained by a variety of methods, and the subsequent ring openings often proceed with high stereoselectivity as well.

**Equation 1.4**

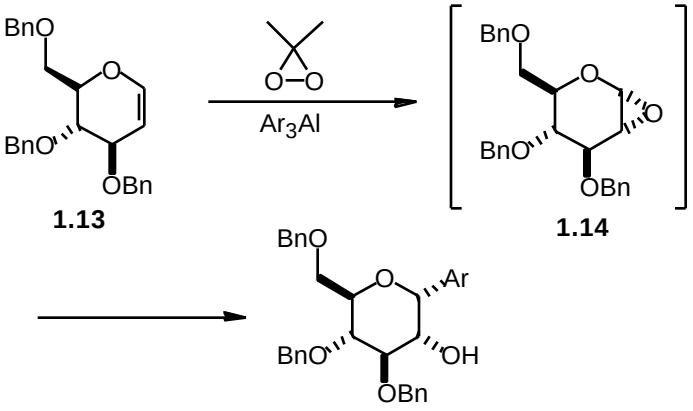



**1.11** **1.12**

A very recent application of this approach was developed by Rainier that involved the nucleophilic opening of 1,2-anhydroglycosides with triarylaluminum- and triarylboron reagents.[14] For example, treatment of tri-*O*-benzyl-D-glucal (**1.13**) with dimethyldioxirane (DMDO) generated the epoxide **1.14** that was not isolated, instead it was treated with either triphenylaluminum or trifurylaluminum to give *C*-aryl glycosides **1.15** or **1.16** (Scheme 1.1). The epoxide formation and subsequent ring opening reactions proceeded in a highly stereoselective fashion to deliver only the α-glycoside products. The authors noted that opening of the epoxide **1.14** with an aryl organocuprate would be expected to occur to give the corresponding β-glycoside

because these reactions tend to occur with inversion of stereochemistry at the anomeric center. The authors were unaware of any other methodology that would allow one to predictably access either α- or β-anomers of *C*-aryl glycosides from a single starting material.

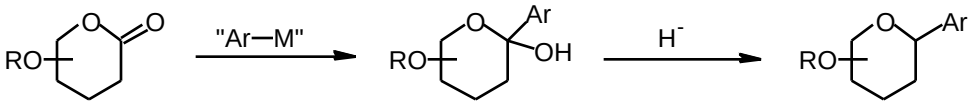
**Scheme 1.1**




**1.15**: Ar = Ph 79%
**1.16**: Ar = 2-furyl 85%

Organometallic reagents also add efficiently to carbohydrate-derived lactones of the general type **1.17** to give hemiacetals of the general type **1.18**. Several procedures have been developed for reducing these lactols to the corresponding *C*-aryl glycosides **1.19** (Scheme 1.2). Reagents that effect this generally stereoselective transformation include $NaBH_3CN/ROH/H^+$ and $BF_3{\cdot}OEt_2/Et_3SiH$.[15]

**Scheme 1.2**

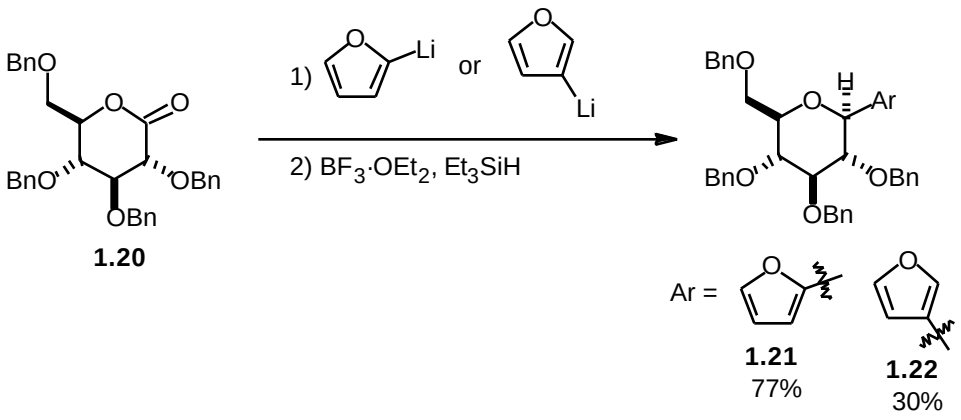



**1.17** **1.18** **1.19**

Czernecki and Ville have utilized this chemistry for the synthesis of *C*-furyl glycosides.[16] Thus, treatment of sugar lactone **1.20** with either 2- or 3-lithiofuran

followed by reduction of the intermediate lactols gave **1.21** or **1.22** with high β-selectivity (Scheme 1.3). Unfortunately, the overall yield in the reaction of 3-furyllithium with **1.22** was quite low. The authors suggested that the lability of the furan to the acidic reduction conditions may be the reason for this.

**Scheme 1.3**

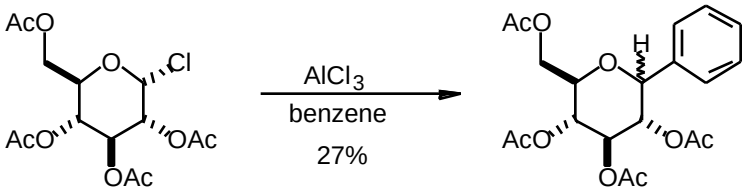



Some of the earliest examples of *C*-aryl glycoside synthesis, and some of the most current for that matter, are based on a Friedel-Crafts approach wherein a glycosyl donor is activated at the anomeric position for attack by an aromatic ring. These reactions typically proceed best when a more electron-rich aromatic partner is used. Examples of leaving groups on the carbohydrate partner that have been successfully employed include halide, acetate, trichloroacetimidate, thiopyridyl and others.[17] Among the Lewis acids that have been shown to effect this transformation are $BF_3{\cdot}OEt_2$, $AlCl_3$, $ZnX_2$ (X = Cl, Br), $SnCl_4$, and AgOTf.

The basic concept is illustrated by one of the earliest examples that involved treatment of glycosyl chloride **1.23** with the strong Lewis acid $AlCl_3$ in the presence of benzene to give *C*-aryl glycoside **1.24**, albeit in low yield and with low diastereoselectivity (Equation 1.5).[18] More recent examples have shown that

stereoselectivity tends to be better if the glycosyl donor is a 6-membered (pyranose) ring whereas lower levels of selectivity are often seen in the 5-membered (furanose) ring preparations. Typically the β-anomer predominates, presumably *via* an equilibration process.

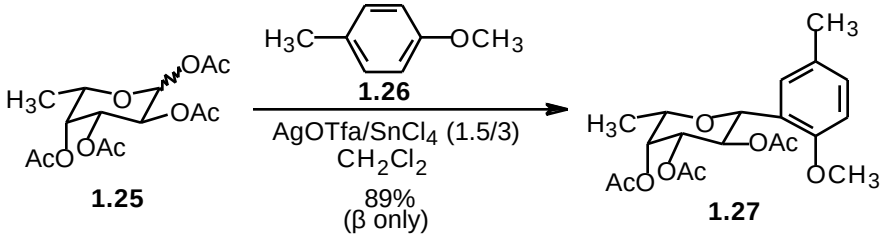
**Equation 1.5**




**1.23** **1.24**

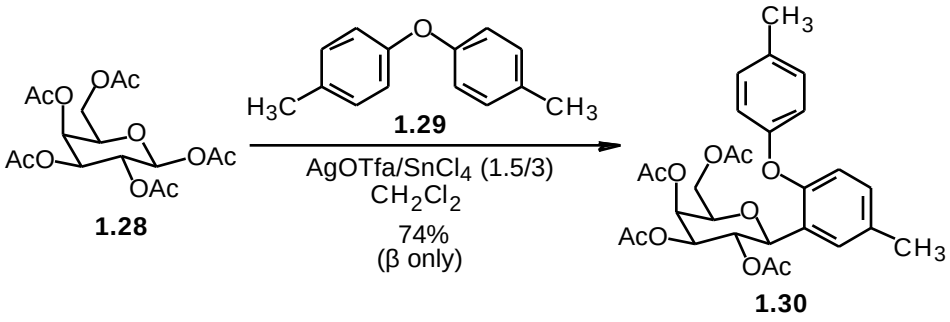
Satoh reported on a very mild Friedel-Crafts approach to *C*-aryl glycosides using glycosyl acetates as donors and AgOTfa/$SnCl_4$ as promoters.[19] Two representative examples are illustrated in Equations 1.6 and 1.7. It is obvious from the conversions of **1.25** → **1.27** and **1.28** → **1.30** that these reactions proceed with high regio- and diastereoselectivity and in quite good yields. The authors commented that this promoter system allows for facile reactions with moderately electron-rich aromatics, as opposed to other promoters that will only facilitate reactions with polyalkoxy-substituted benzenes. It was also possible to prepare *C*-aryl furanoses and *C*-aryl aminoglycosides using this methodology.

**Equation 1.6**



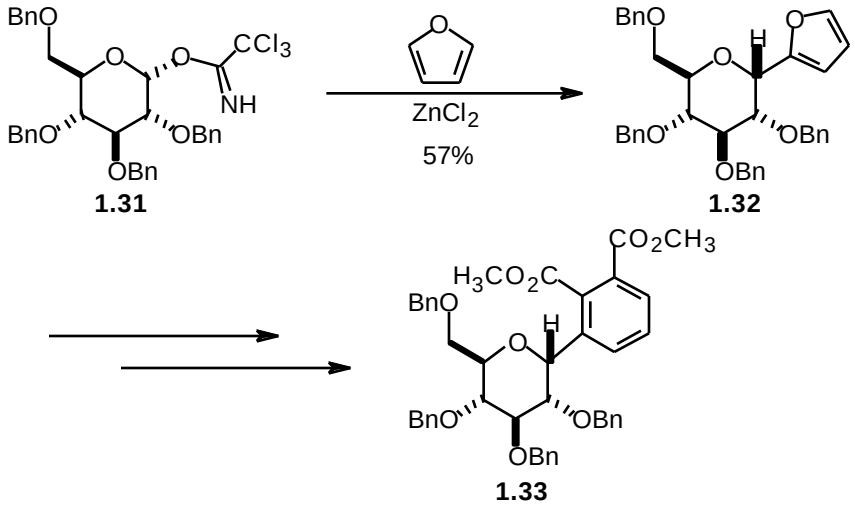

**1.25** **1.27**

**Equation 1.7**



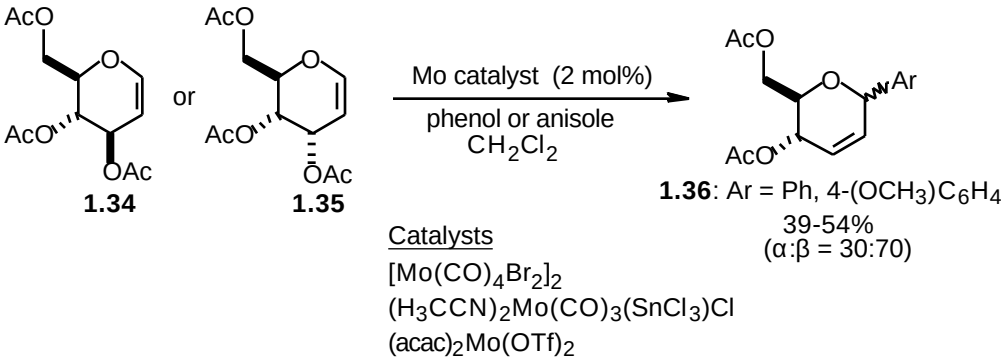

The Friedel-Crafts approach has also been used to prepare heteroaromatic *C*-aryl glycosides.[20] Treatment of the anomeric trichloroacetimidate **1.31** with $ZnCl_2$ in the presence of furan delivered α-*C*-glycoside **1.32** in 57% yield. The authors also successfully prepared thiophenyl- and indole-substituted *C*-glycosides using similar chemistry. The furyl-*C*-glycoside **1.32** was further transformed into the benzenoid glycoside **1.33** by a Diels-Alder reaction with dimethylacetylenedicarboxylate (DMAD), followed by treatment of the resulting cycloadduct with $TiCl_4$ and $Et_3N$ (Scheme 1.4). It is noteworthy that the α-glycoside was obtained from these reactions, despite the strong Lewis acid employed. Additionally, this methodology is unique in that it allows for the preparation of electron-deficient *C*-aryl glycosides like **1.33** that would not normally be accessible by a direct Friedel-Crafts approach.

**Scheme 1.4**



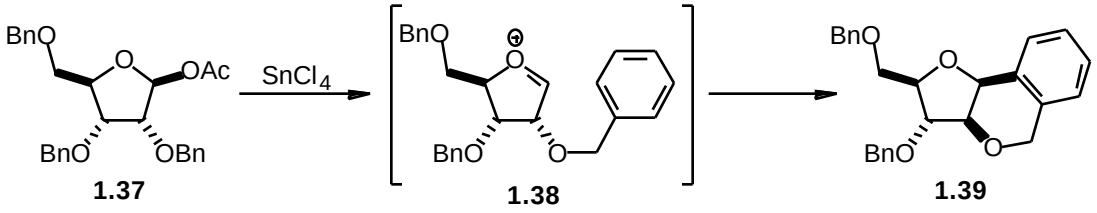

Recently it was discovered that mild, Lewis acidic complexes of molybdenum were capable of catalyzing the Ferrier-type rearrangement and subsequent *C*-glycosylation of glycal acetates and electron-rich aromatic systems.[21] Reaction of either glycal **1.34** or **1.35** with phenol or anisole in the presence of 2 mol% of one of the molybdenum complexes listed in Equation 1.8 gave the *C*-aryl glycosides **1.36** in rather low yields. The products formed were predominately of the β-configuration, a result that was explained by invoking an equilibration process.

**Equation 1.8**



Martin and others have developed intramolecular variants of the Friedel-Crafts approach.[22] For example, if a glycosyl-oxonium ion **1.38** is generated in the presence of an adjacent benzyl protected alcohol, an intramolecular cyclization may occur to give compounds like **1.39** (Equation 1.9). These transformations, which typically occur with extremely high stereoselectivity, have been utilized in both the furanoside and pyranoside series.

**Equation 1.9**

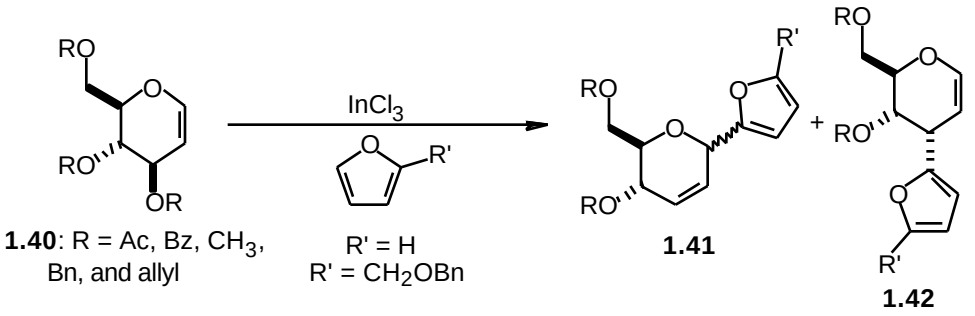



**1.37** **1.38** **1.39**

The preparation of *C*-glycosides attached to heteroaromatic cores is an active area of research. Grynkiewicz and BeMiller examined the use of glycals as donors in the Friedel-Crafts reaction of furan and thiophene.[23] Reaction of an acetylated glycal with either of these aromatic nucleophiles gave a 1:1 mixture of regioisomeric adducts arising from double bond transposition and attachment without net movement of the double bond.

Recently, Yadav and co-workers investigated a closely related $InCl_3$-mediated glycosidation of furan, thiophene, and other heteroaromatic compounds using glycals as donors.[24] These additions could occur either with or without transposition of the glycal double bond, and the course of the reaction appeared to be highly dependent on the substitution of the furan. Reaction of **1.40** with furan gave almost exclusively **1.42**, whereas the benzyloxy-substituted furan gave **1.41** as the only regioisomer (Equation 1.10).

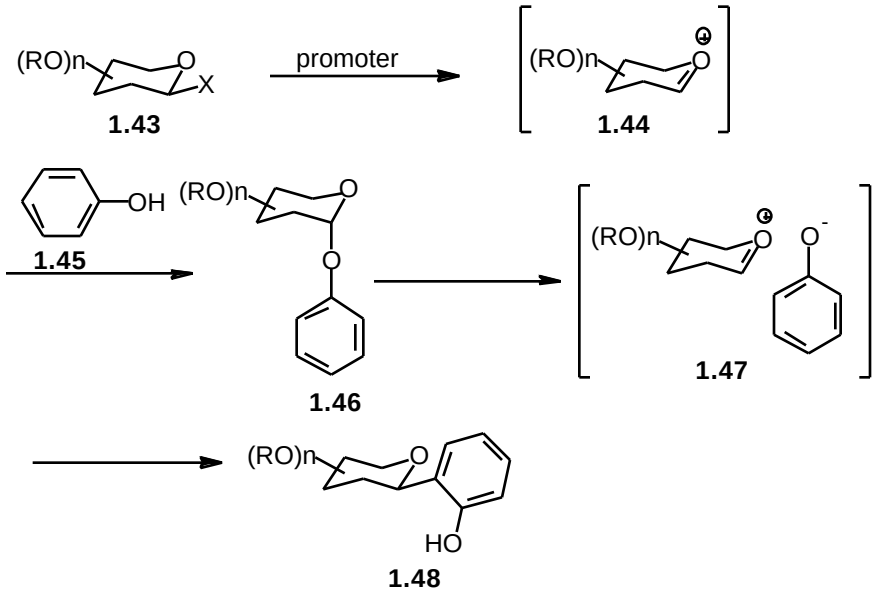
**Equation 1.10**




**1.40**: R = Ac, Bz, $CH_3$, Bn, and allyl

Suzuki has done an extensive amount of work in the area of *C*-aryl glycoside natural product synthesis using a variant of the Friedel-Crafts approach. His group has pioneered the use of $Cp_2HfCl_2$-$AgClO_4$ as a catalyst for a reaction known as the $O \rightarrow C$-glycoside rearrangement.[25] The proposed mechanism of the $O \rightarrow C$-glycoside rearrangement is depicted in Scheme 1.5. A glycosyl donor **1.43** is activated by a promoter to generate an oxocarbenium intermediate **1.44** that is subsequently intercepted by the hydroxyl group of an aromatic system such as **1.45** to give **1.46**. At low temperatures this intermediate *O*-glycoside can often be observed. At higher temperatures the *O*-glycoside dissociates to form a tight ion pair **1.47** that subsequently undergoes an irreversible Friedel-Crafts reaction to give *C*-glycoside **1.48**.

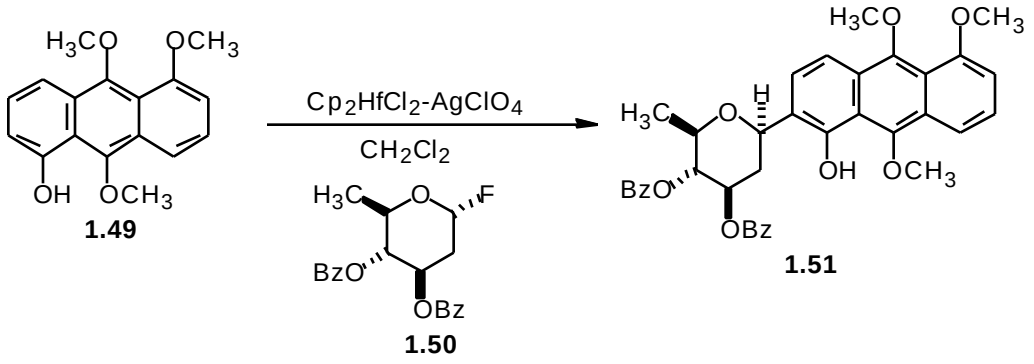
**Scheme 1.5**




Early examples of the *O*→*C*-glycoside rearrangement involved the use of rather unstable glycosyl halides, particularly fluorides, to achieve these transformations. Discovery of the aforementioned catalyst system has allowed the use of readily available and stable anomeric acetates. Various 2-deoxy-*C*-aryl glycosides have been prepared using this approach.

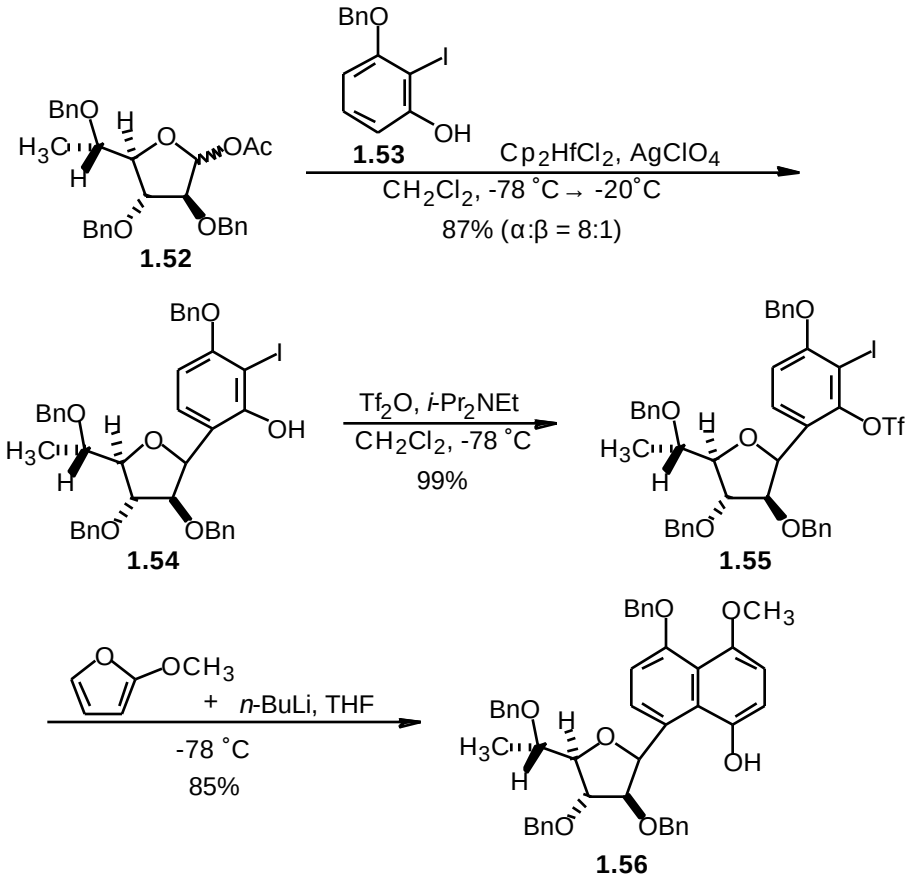
One interesting example of the *O*→*C*-glycoside rearrangement was seen in Suzuki's approach to the vineomycins. Reaction of glycosyl fluoride **1.50** with the anthraquinone derivative **1.49** in the presence of the aforementioned hafnium catalyst provided the complex *C*-aryl glycoside **1.51** in 86% yield as a single anomer (Equation 1.11).[26]

**Equation 1.11**



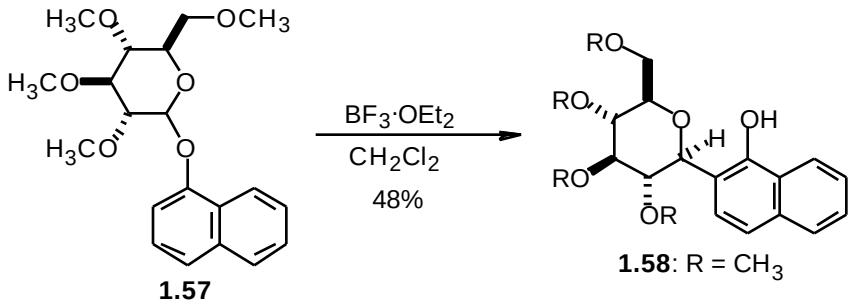

Suzuki has also developed a convergent approach to *C*-aryl glycosides that relies on cycloadditions with glycosyl-substituted benzynes and oxygenated furans. The requisite glycosyl benzynes are obtained by functionalization of benzenoid *C*-glycosides obtained using the $O \rightarrow C$-glycoside rearrangement. One impressive application of this methodology was used in the total synthesis of the *C*-glycoside antibiotic gilvocarcin M.[27] In a key step, a solution of glycosyl acetate **1.52** and iodophenol **1.53** was treated with the hafnium/silver perchlorate system to deliver **1.54** as a mixture of anomers, with the α-anomer being predominant. Reaction of **1.54** with trifluoromethanesulfonic anhydride provided the benzyne precursor **1.55**. Treatment of a solution of **1.55** and 2-methoxyfuran in THF with *n*-BuLi, followed by a work-up gave *C*-naphthyl glycoside **1.56** in excellent yield (Scheme 1.6).

**Scheme 1.6**



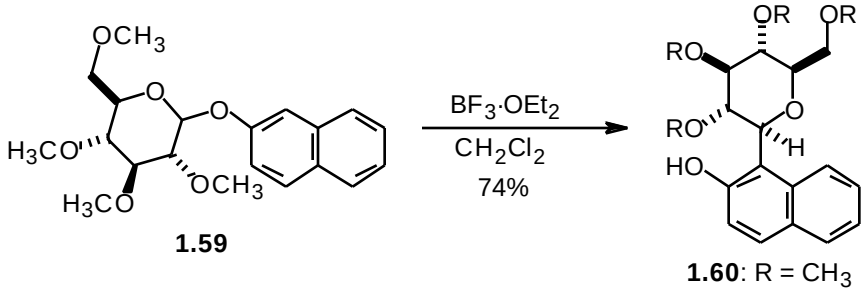

Kometani has utilized the $O \rightarrow C$-glycoside rearrangement in order to prepare several *C*-naphthyl glycosides.[28] The examples shown below help to demonstrate the regioselectivity with which these reactions typically proceed (Equations 1.12 and 1.13). The *O*-glycosides were prepared by Mitsunobo reaction of the corresponding sugar lactol with either 1- or 2-naphthol. Addition of $BF_3 \cdot OEt_2$ to a solution of either *O*-glycoside **1.57** or **1.59** in $CH_2Cl_2$ delivered the naphthyl glycosides **1.58** or **1.60** with high selectivity for the regio- and diastereomer shown. The yield improved substantially on going from the 1-naphthol system to the one derived from 2-naphthol.

**Equation 1.12**




**1.57** **1.58**: R = $CH_3$

**Equation 1.13**

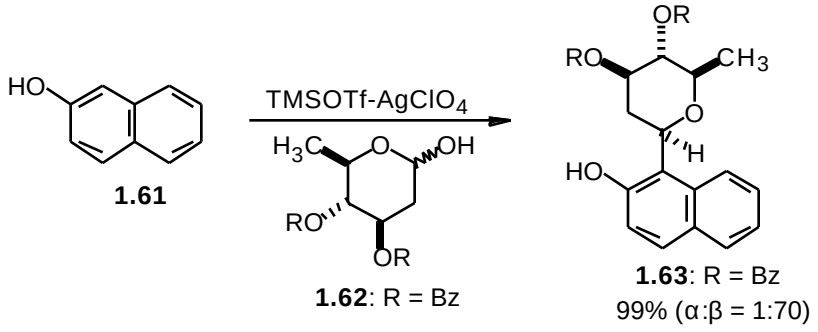



**1.59** **1.60**: R = $CH_3$

Toshima also examined the $O \rightarrow C$-glycoside rearrangement of several protected 2,6-deoxy sugars with a naphthols.[29,30] Treatment of a solution of **1.61** and protected sugar **1.62** in $CH_2Cl_2$ with TMSOTf/AgClO4 gave the desired naphthyl glycoside **1.63** in excellent yield and with very high β-selectivity (Equation 1.14). *C*-Aryl glycosides of aminosugars are found in many naturally occurring glycosidic natural products (see Fig. 1). For this reason, it is useful to develop methods that allow for the introduction of aminosugars onto aromatic systems. Toshima demonstrated that the dimethylaminosugar **1.64** could be appended to 2-naphthol (**1.61**) using the TMSOTf-$AgClO_4$ system (Equation 1.15). Here again, both the yield and the diastereoselectivity of the product were extremely high. It is notable that the $O \rightarrow C$-rearrangement proceeded well even in the presence of the unprotected highly basic dimethylamino functionality. In this series of reactions, it is interesting that it was not necessary to

preform the *O*-glycoside in a separate step; rather the *O*-glycoside was formed and underwent rearrangement in one pot. One final example (not shown) illustrated that a completely unprotected sugar **1.62** (R = H) could be used under identical conditions to those shown in Equations 1.14 and 1.15 to give the corresponding naphthyl glycoside in 92% yield and with very high stereoselectivity (β:α = >99:1). Toshima and co-workers also demonstrated that methyl glycosides could be used equally well in these naphthol rearrangements. In one example, rather labile acetate protecting groups were employed, but the yield of β-*C*-naphthyl glycoside product was still nearly quantitative.[31]

**Equation 1.14**



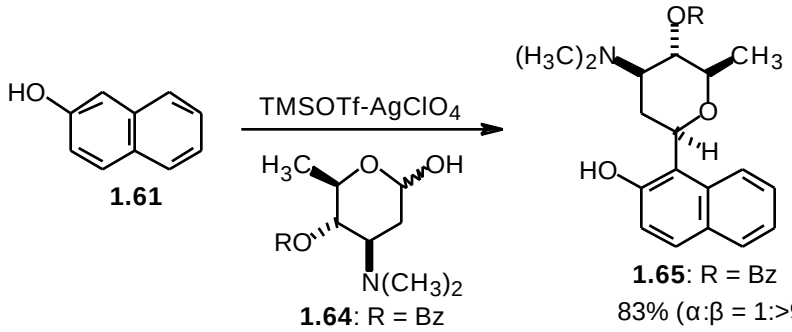

**1.61**

**1.62**: R = Bz

**1.63**: R = Bz

99% (α:β = 1:70)

**Equation 1.15**




**1.61**

**1.64**: R = Bz

**1.65**: R = Bz

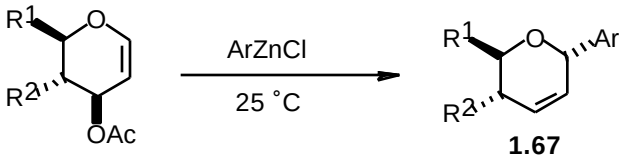
83% (α:β = 1:>99)

Toshima recently disclosed a thorough account of *O*→*C*-glycosidation methodology permitted the use of unprotected glycosyl donors.[30] A variety of reactions

were conducted using the TMSOTf-$AgClO_4$ system with carbohydrate donors that contained free dimethylamino- and hydroxyl groups. Additionally, many different naphthol and phenol coupling partners were examined with the yields and stereoselectivity for the β-anomers generally being excellent.

An approach to dihydropyran-based *C*-aryl glycosides was developed by Du Bois that relied on the addition of arylzinc chlorides to dihydropyranyl acetates.[32] The general transformation is illustrated in Equation 1.16. These reactions typically afforded the corresponding α-anomers. One of the advantages of this methodology stems from the mildness of the arylzinc reagent and hence its tolerance of a variety of functional groups, such as carbamates, esters, and silyl ethers, in either the aromatic or glycosidic partner. The dihydropyran products are potentially useful synthetic intermediates, and one can envision many possibilities for their further transformation.

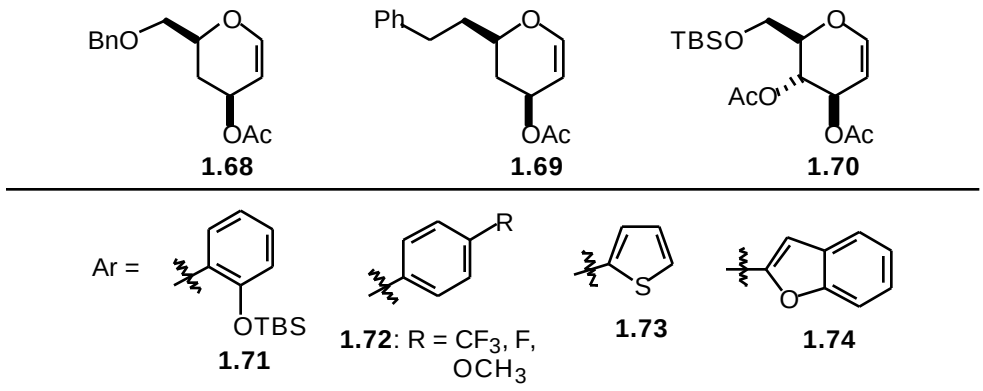
**Equation 1.16**




**1.66** **1.67**

Three glycoside substrates **1.68**-**1.70** were examined in this addition reaction. A variety of arylzinc chlorides were employed and the yields ranged from 66-88%. With respect to the aryl fragment, substitution proximal to the reacting center was tolerated, and the presence of either electron-donating and electron-withdrawing groups on the aromatic partner was not detrimental. One important aspect of this methodology was that heteroaromatic derivatives could also be prepared in yields ranging from 66-74% (Figure 1.3).

**Figure 1.3**



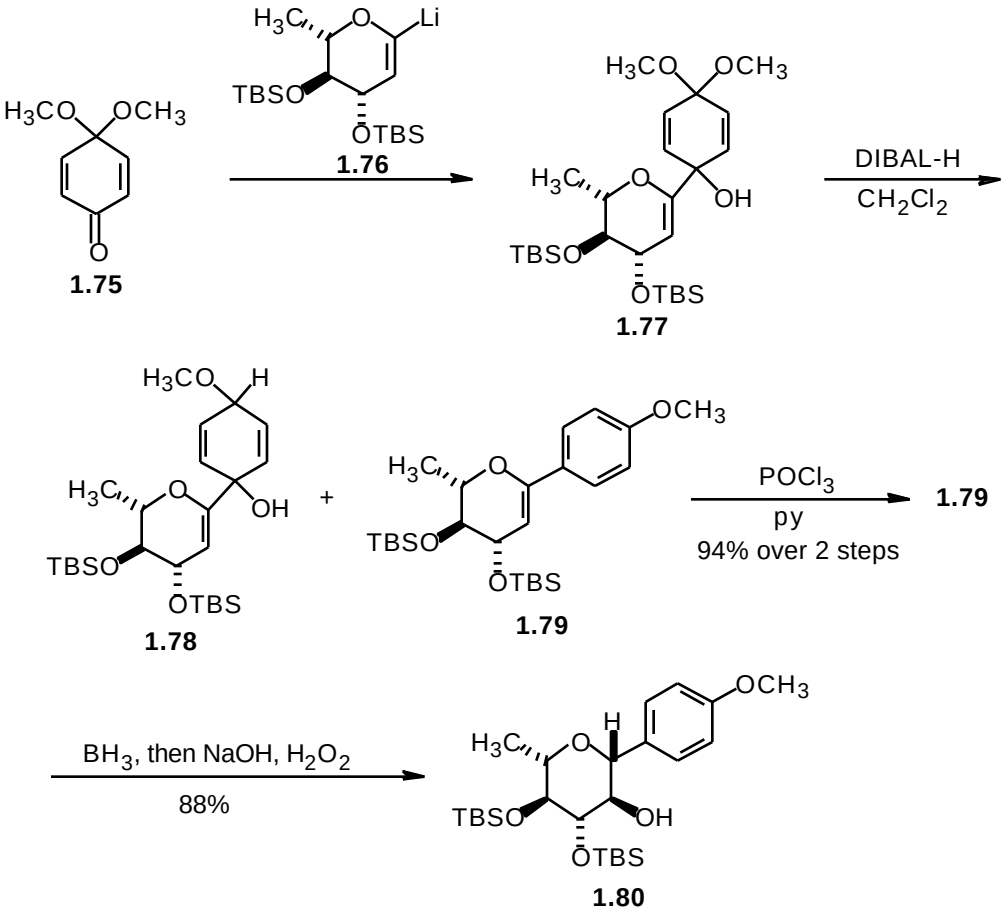

### 1.2.2 Nucleophilic Additions to "Aromatic" Electrophile Equivalents

While approaches to *C*-aryl glycosides that involve reaction of a carbohydrate nucleophile with an electrophilic "aromatic" equivalent are not nearly as prevalent as the reverse strategy, they nevertheless represent a powerful tool for their construction. There are many examples in the literature concerning the generation of carbohydrate nucleophiles.[33] With these methods at ones disposal, it is only necessary to find a suitable electrophilic acceptor that could subsequently be transformed into an aromatic system.

Parker has developed an interesting *umpolung* approach to *C*-aryl glycoside synthesis that relied on the addition of lithiated glycals to quinones and their derivatives. In early work, attempts to utilize unprotected quinones in these additions were unsuccessful however, quinone ketals worked quite well. Later, conditions were developed that allowed for the use of unprotected quinones. This method is notable in that it is one of the few that has been demonstrated to provide access to all four *C*-aryl glycoside groups (Figure 2).

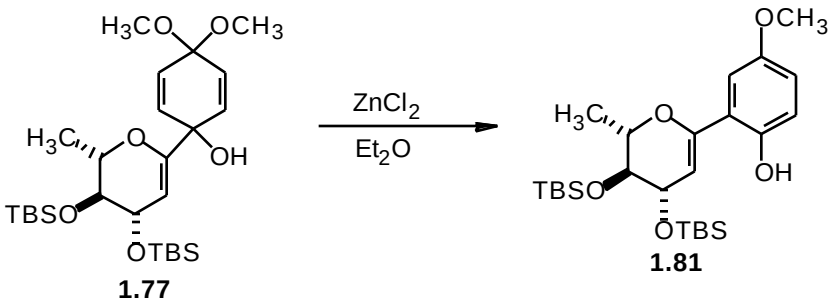
Addition of lithiated glycal **1.76** to quinone ketal **1.75** gave an adduct that was reduced with DIBAL-H.[34] This reduction gave a mixture of *C*-aryl glycoside **1.79**, derived from reductive aromatization, as well as unrearranged **1.78**. Treatment of the mixture of **1.78** and **1.79** with $POCl_3$ resulted in conversion to exclusively **1.79** (Scheme 1.7). The olefin in **1.79** was hydrated by employing a stereoselective hydroboration/oxidation protocol to provide **1.80**. In this way, the methodology provided access to both 6-deoxy and 2,6-dideoxy *C*-aryl glycosides.

**Scheme 1.7**



Alternatively, if a solution of **1.77** in $Et_2O$ was treated with $ZnCl_2$, a dienone-phenol rearrangement occurred to give **1.81** (Equation 1.17). The possibility of accessing the two substitution patterns typified by **1.79** and **1.81** from a single addition product **1.77** makes this a particularly powerful methodology.

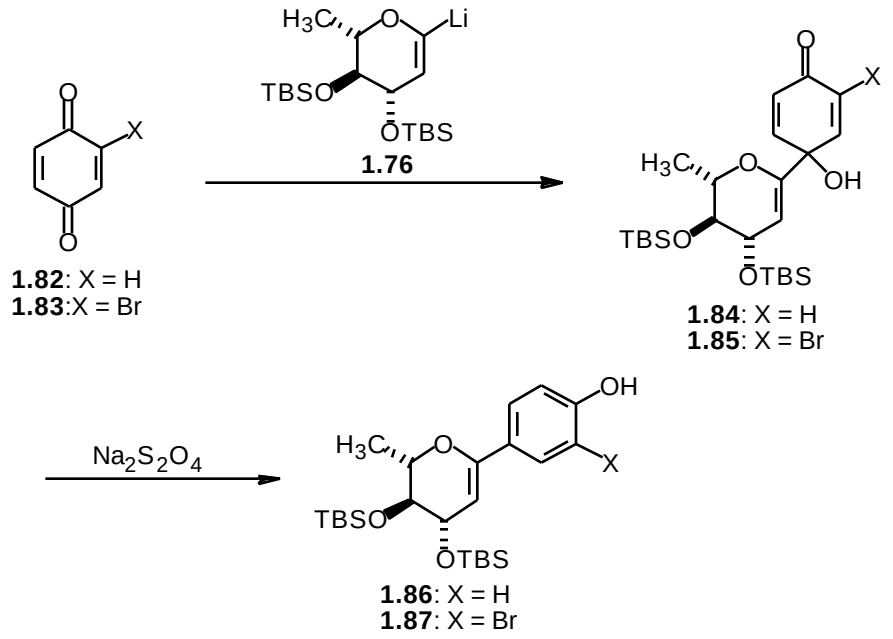
**Equation 1.17**




**1.77** **1.81**

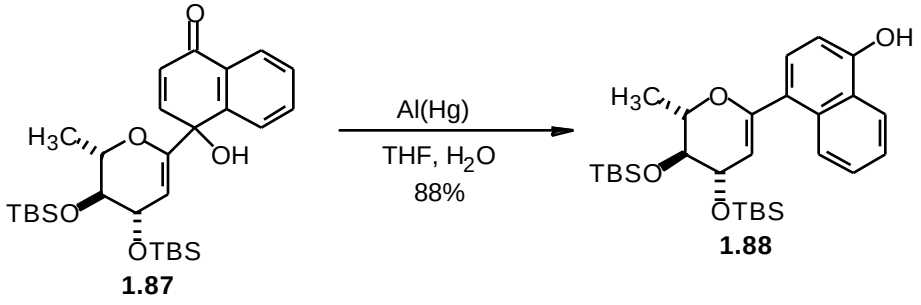
It was later discovered that treatment of either benzoquinone (**1.82**) or the bromoquinone **1.83** with the lithiated glycal **1.76** gave the addition products **1.84** or **1.85**.[35] Reaction of either of these adducts with $Na_2S_2O_4$ resulted in reductive aromatization to give *p*-*C*-aryl glycosides **1.86** or **1.87** (Scheme 1.8). A similar approach has been successfully applied to the synthesis of *C*-aryl furanosides as well.[36]

**Scheme 1.8**




Attempts to utilize the above procedure to prepare naphthol-based *C*-aryl glycosides were unsuccessful. However, it was found that treatment of a solution of **1.87** in THF/$H_2O$ with Al(Hg) under more forcing conditions (reflux, 22h) did afford the desired naphthol product **1.88** in 88% yield (Equation 1.18).

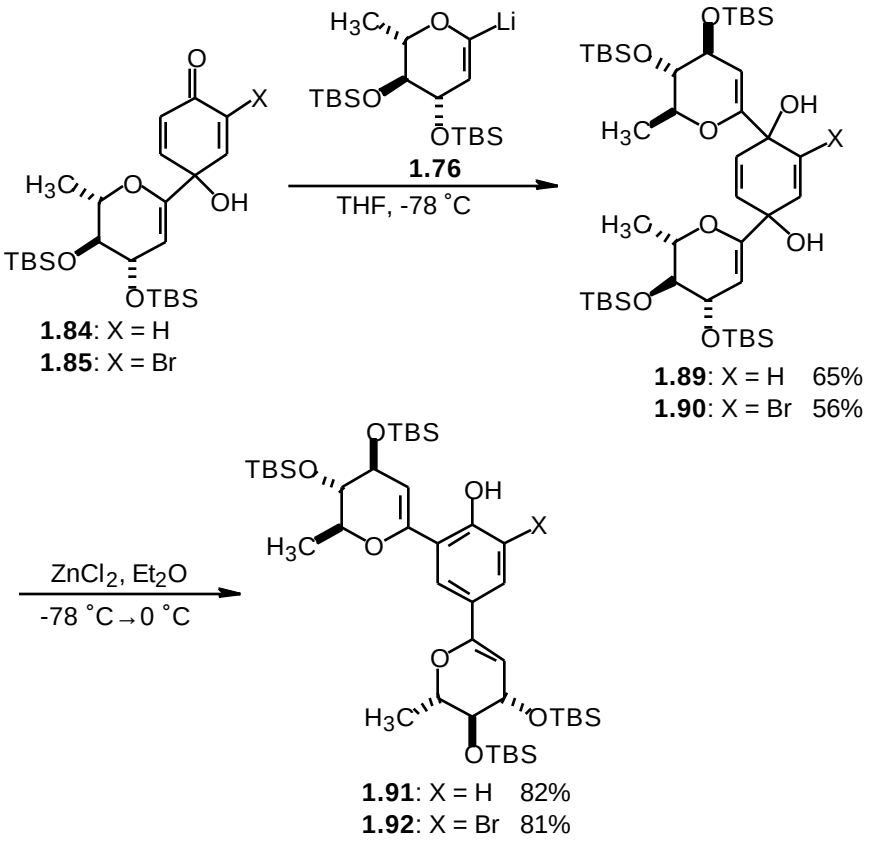
**Equation 1.18**




There are very few reports of the synthesis of *bis*-*C*-aryl glycosides, which are typified by the naturally occurring pluramycin class of antibiotics like kidamycin (**1.3**)

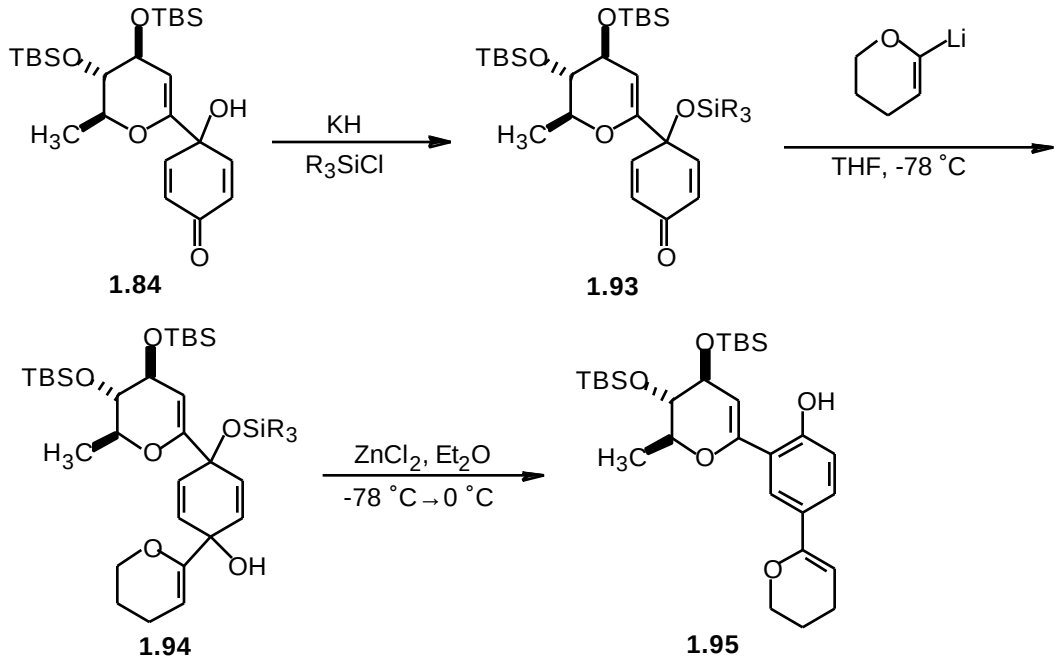
(Figure 1). To date, no total synthesis of any naturally occurring *bis*-*C*-aryl glycoside has been disclosed; however, Parker has developed an elegant route to models of the pluramcyins using the quinone/glycal anion addition approach.[37] Thus treatment of either **1.84** or **1.85** with the lithiated glycal **1.76**, which was obtained from rhamnal, afforded 1,4-diols **1.89** or **1.90** in moderate yields. Reaction of **1.89** or **1.90** with $ZnCl_2$ initiated a regioselective 1,2-shift to deliver the simple pluramycin models **1.91** or **1.92** in excellent yields (Scheme 1.9). It was necessary to chromatograph the *bis*-glycals on neutral alumina, as they were particularly sensitive to acidic hydrolysis.

**Scheme 1.9**




This methodology was also extended to naphthol- and anthrol-based *bis*-*C*-aryl glycosides. In these cases it was necessary to silylate one of the free hydroxyl groups after addition of the lithiated glycal; otherwise the glycal in the resulting adducts was particularly sensitive to hydrolysis after the rearrangement step. Thus, treatment of **1.84** with potassium hydride and a silyl chloride delivered **1.93**. 2-Lithiodihydropyran was added to a solution of **1.93** to give **1.94**, which underwent a regioselective dienone-phenol rearrangement upon treatment with $ZnCl_2$ to afford **1.95** (Scheme 1.10). Several related systems were investigated in order to show that whichever glycal was attached to the carbon bonded to the silyl-protected alcohol was the one that underwent migration.

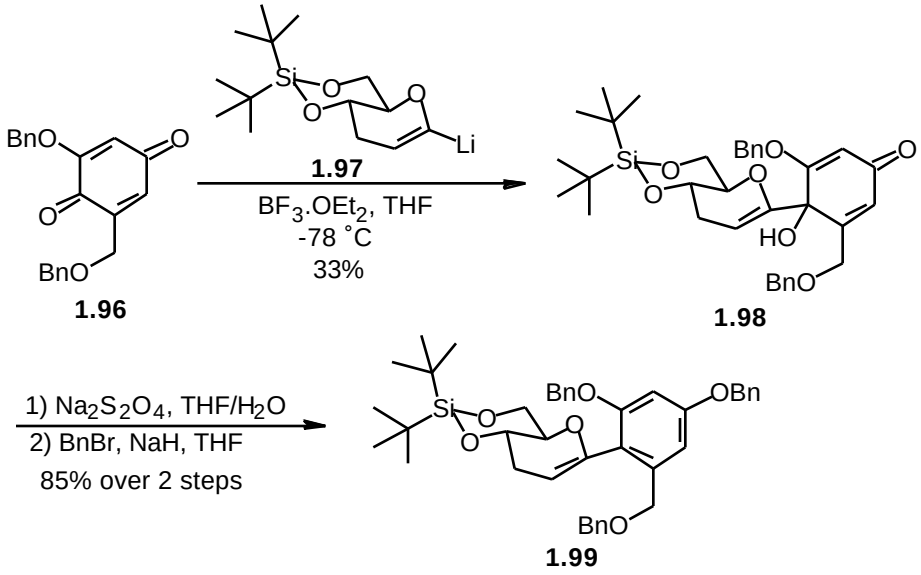
**Scheme 1.10**




**1.84** **1.93** **1.94** **1.95**

Recently, Parker applied the glycal anion addition/reductive aromatization sequence to the synthesis of core structures of the papulacandins and chaetiacandin.[38] Addition of lithiated glycal **1.97** to the quinone **1.96** proceeded in relatively low yield; however, it was possible to recover 58% of **1.96** that was pure enough to be recycled. Reductive aromatization of **1.98** followed by benzylation of the free phenolic hydroxyl group afforded **1.99**, which was an intermediate in the preparation of the cores of the aforementioned natural products (Scheme 1.11).

**Scheme 1.11**



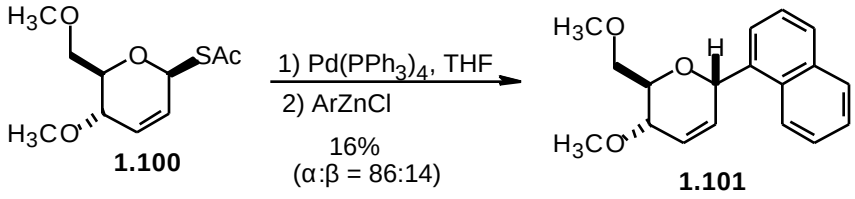

### 1.2.3 Transition Metal-mediated Approaches

Many approaches to *C*-aryl glycoside synthesis have been developed in the past decade that rely on the transition metal-catalyzed coupling of appropriately functionalized aromatic compounds with carbohydrate derivatives. Procedures exist that allow either partner to function as the nucleophile or the electrophile. In other words, couplings have been performed with aryl organometallic species and iodoglycals or alternatively with aryl halides and metalated glycals. Daves pioneered the use of Heck-type couplings to prepare *C*-aryl glycosides.[39] Many transition metal-catalyzed systems have been discovered that allow for addition of aromatic nucleophiles to carbohydrate electrophiles, such as enones, under quite mild conditions; these will be presented in the following discussion as well.

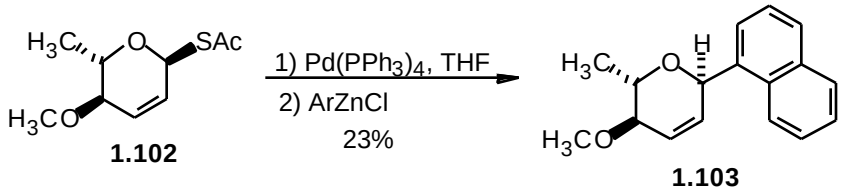
Transition metal-mediated allylic substitution reactions have been used for the preparation of *C*-aryl glycosides. Treatment of either **1.100** or **1.102** with Pd(0)

followed by reaction of the corresponding π-allyl intermediate with a naphthylzinc chloride gave a low yield of the corresponding *C*-glycosides **1.101** or **1.103** (Equations 1.19 and 1.20).[40]

**Equation 1.19**



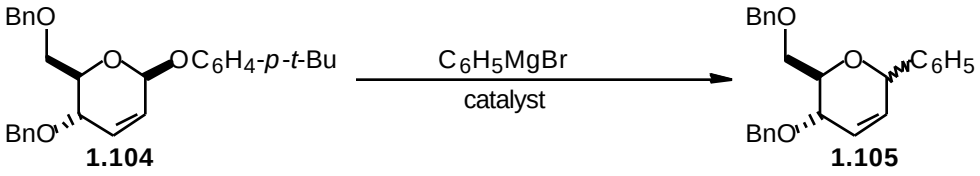

**Equation 1.20**




Sinou was able to successfully prepare *C*-aryl glycosides by palladium- or nickel-catalyzed allylic substitution reactions.[41] A representative example is presented in Equation 1.21. Treatment of enopyranoside **1.104** with phenylmagnesium bromide in the presence of $PdCl_2$(dppf) [dppf = 1,1'-*bis*-(diphenylphosphino)ferrocene] provided almost exclusively the α-*C*-aryl glycoside **1.105** in excellent yield. Alternatively, the use of $NiCl_2$(dppe) [dppe = 1,2-*bis*-(diphenylphosphino)-ethane] delivered β-*C*-aryl glycoside **1.105** as a single diastereomer (Equation 1.21). The rationale for this reversal in selectivity was base on the assumption that the π-allyl intermediate was formed with inversion of configuration at the anomeric center. When palladium was used as the catalyst, it was suggested that nucleophilic attack occurred in an *exo* fashion to provide the product with net retention of configuration. Alternatively, in the case where a nickel catalyst was employed, it was proposed that the nucleophile

was delivered in an *endo* fashion from the metal resulting in net inversion of configuration. The authors also examined the use of different enopyranosides and the effect of varying the Pd- and Ni-catalyst systems. One obvious attractive feature of this methodology is that it allows for the selective preparation of either *C*-glycoside anomer from the same starting material by simply altering the catalyst used.

**Equation 1.21**



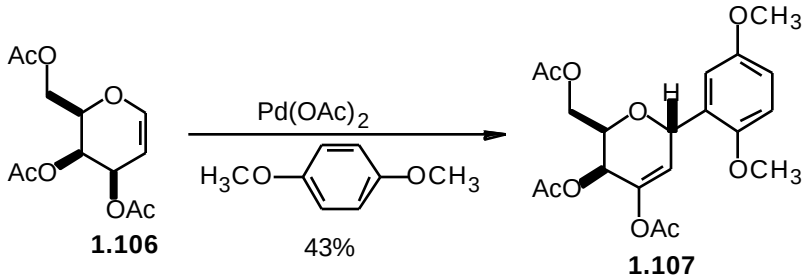

**1.104** **1.105**

cat. $PdCl_2$(dppf), 0 ˚C, 0.5 h — 87% (α:β = 95:5)

cat. $NiCl_2$(dppe), -40 ˚C, 24 h — 50% (α:β =0:100)

Czernecki examined the direct coupling of glycals and aromatic compounds in the presence of palladium.[42] Treatment of acetylated glycal **1.106** with $Pd(OAc)_2$ in the presence of *p*-dimethoxybenzene provided the enol acetate **1.107** in rather low yield (Equation 1.22). The authors showed that benzene and other benzenoid compounds could also be used in these couplings. It should be noted that it was necessary to employ a stoichiometric amount of $Pd(OAc)_2$ in order to obtain **1.107**.

**Equation 1.22**

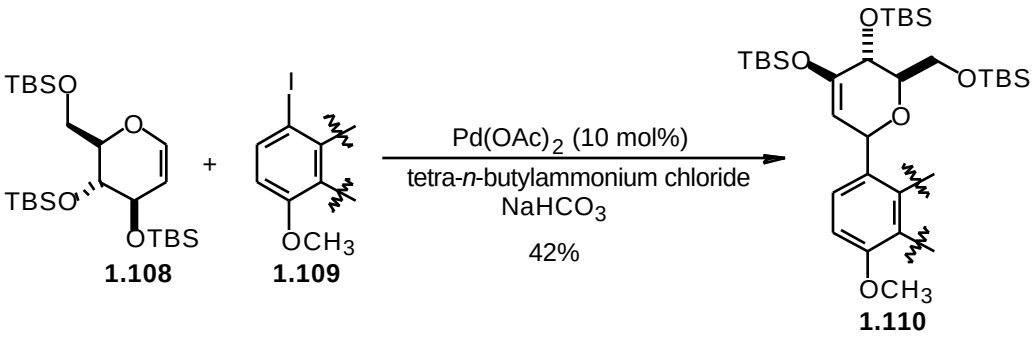



**1.106** 43% **1.107**

Daves has used aryl iodides **1.109** in similar couplings with furanose and pyranose glycals **1.108** (Equation 1.23).[43] The reaction depicted in Equation 1.23

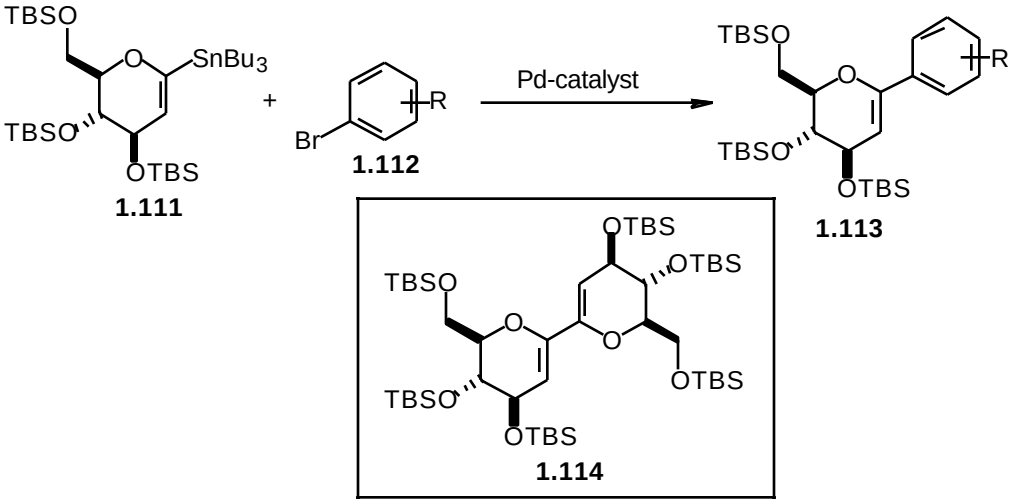
allowed the authors to prepare models of the Group I class of *C*-aryl glycoside antibiotics (Figure 2) that were related to ravidomycin (**1.1**) (Figure 1). No comments were made concerning the stereochemistry at the anomeric center of **1.110**.

**Equation 1.23**



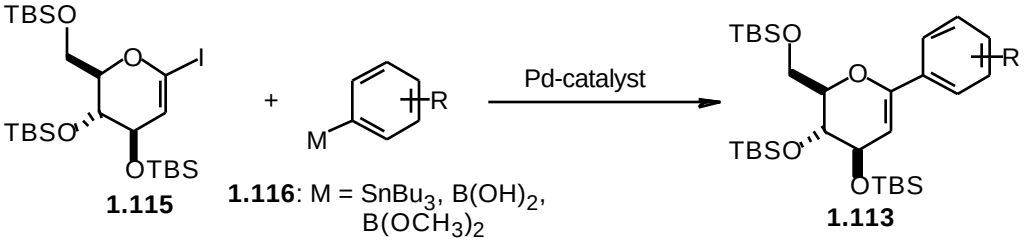

Friesen and Beau disclosed, at approximately the same time, a Stille-type coupling of tributylstannyl glycals and aryl halides as a route to *C*-aryl glycosides. They reported on the coupling of aryl halides **1.112** and tributylstannyl glycals **1.111** in the presence of a palladium catalyst (Equation 1.24).[44] Relatively simple aromatic coupling partners were used in these early communications. One drawback of the methodology, noted by Friesen, was that regardless of the reaction conditions employed, some quantity of the dimerized glycal **1.114** was always produced (up to ~30%) in addition to the desired cross-coupled product. Subsequently, Friesen reported on the stereoselective hydration of aryl glycals like **1.113** employing a hydroboration/oxidation protocol.[45]

**Equation 1.24**




Some years later, Friesen examined an alternative $(PPh_3)_2PdCl_2$-catalyzed coupling of arylmetal species **1.116** with the iodoglucal **1.115** (Equation 1.25).[46] This methodology delivered the *C*-aryl glycoside products in significantly higher yields and prevented/decreased the formation of the previously mentioned glycal dimer **1.114**. The authors were able to successfully couple the iodoglucal **1.115** with a wide range of aromatic partners, including those with electron-donating or electron-withdrawing substituents.

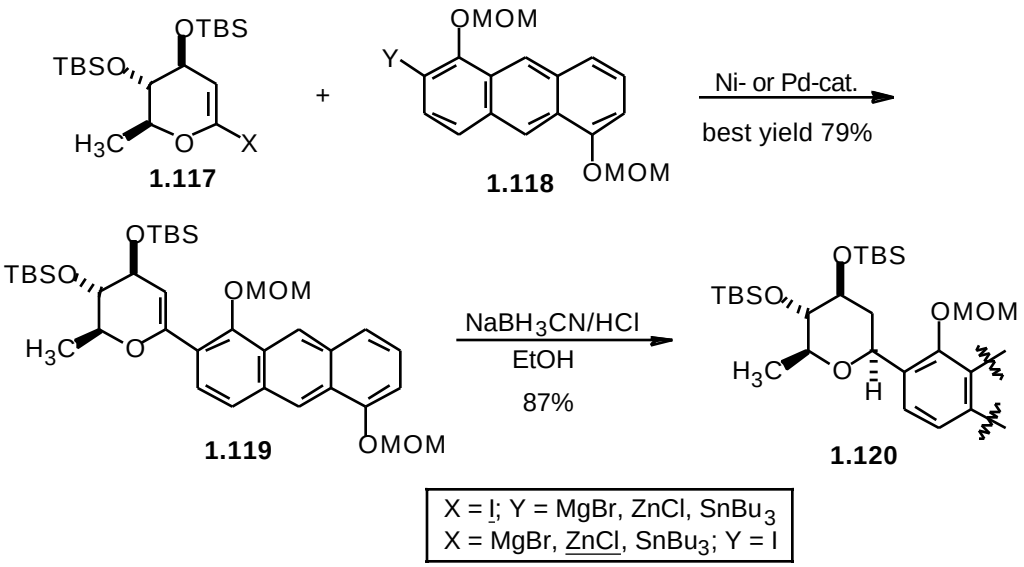
**Equation 1.25**




Tius developed a Negishi-coupling approach for the preparation of *C*-aryl glycosides that was eventually applied to a total synthesis of vineomycinone $B_2$ methyl ester.[47] In order to effect the key coupling of glycal **1.117** and the anthracene **1.118** a

number of conditions were explored. Initially a coupling strategy was investigated that used the iodoglucal **1.117** (X = I) and a metalated anthracene **1.118** (Y = MgBr, ZnCl, $SnBu_3$) in the presence of either Ni- or Pd-catalysts, but these methods failed to afford more than 32% of the desired *C*-aryl glycoside **1.119**. The authors then examined the electronically reversed situation wherein a metalated glycal **1.117** (X = MgBr, $SnBu_3$, ZnCl) was coupled with the halogenated anthracene **1.118** (Y = I) using the same Ni- or Pd-catalysts. This strategy worked substantially better than the original approach and eventually led to the formation of the coupled product **1.119** (X = ZnCl, Y = I, catalyst = $Pd(OAc)_2$/DIBAL-H) in 79% yield (Scheme 1.12). This transformation was quite interesting in its own right, but the authors also needed to reduce the glycal double bond in order to move forward with their synthetic efforts. After experimenting with several reducing systems, they found that treatment of **1.119** with $NaBH_3CN$/HCl effected the transformation quite well to give the β-*C*-aryl glycoside **1.120** in 87% yield. The reduction of aryl glycals with $NaBH_3CN$ appears to be quite general and has been used successfully by many other research groups.

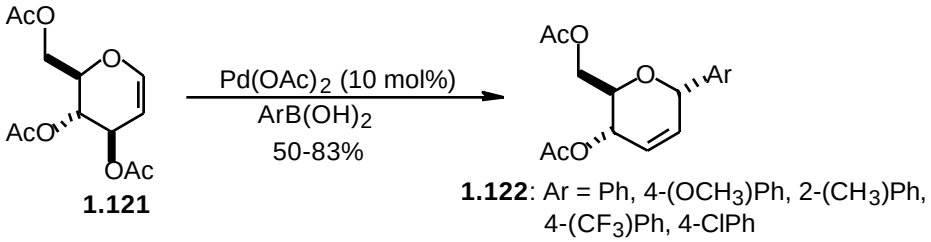
**Scheme 1.12**




Maddaford reported the reaction of arylboronic acids with peracetylated glycals in the presence of catalytic amounts of $Pd(OAc)_2$.[48] While other methods that involved the Pd(II)-mediated arylation of glycals had been developed, these typically required the use of organometallic reagents that were air- or moisture-sensitive, toxic, pyrophoric, or not easy to handle. The advantage of using arylboronic acids in these transformations was the low air and moisture sensitivity of the reagents as well as their decreased toxicity.

The substitution of a variety of arylboronic acids with **1.121** gave the corresponding "Carbon-Ferrier rearranged" products **1.122** with high selectivity for the α-anomer (Equation 1.26). This transformation was proposed to occur by transmetalation of the organic fragment from boron to palladium followed by carbopalladation of the glycal. After *anti*-elimination of Pd-OAc from the intermediate, the expected 2,3-dihydropyran would be obtained with regeneration of the catalyst occurring concomitantly.

**Equation 1.26**

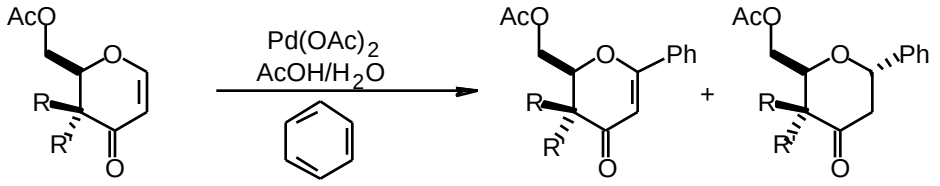



**1.121**

**1.122**: Ar = Ph, 4-($OCH_3$)Ph, 2-($CH_3$)Ph, 4-($CF_3$)Ph, 4-ClPh

Czernecki and co-workers have prepared *C*-aryl glycosides by the palladium-mediated addition of aryl groups to acetylated enones derived from glycals.[49] Treatment of **1.123** or **1.124** with $Pd(OAc)_2$ with benzene in the presence of AcOH and $H_2O$ gave a mixture of **1.125**/**1.126** or **1.127**/**1.128** in identical yields (Equation 1.27). Similarly, treatment of deoxyenone **1.129** under similar conditions delivered a mixture of **1.130** and **1.131** (Equation 1.28). Reduction of each of these mixtures by hydrogenation in the presence of Pd/C cleanly afforded the three *C*-aryl glycosides **1.132** (80%), **1.133** (95%), or **1.134** (95%) (Figure 1.4).

**Equation 1.27**

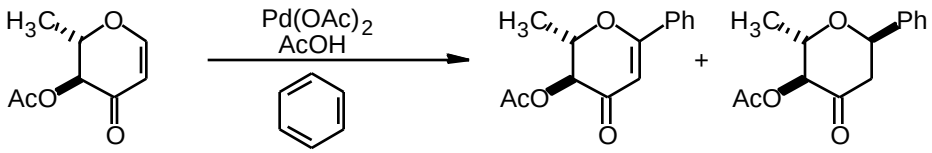



**1.123**: R = H, R' = OAc
**1.124**: R = OAc, R' = H

70 30

**1.125**/**1.126**: R = H, R' = OAc 70%
**1.127**/**1.128**: R = OAc, R' = H 70%

**Equation 1.28**



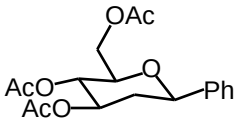

**1.129**

90%

70 30

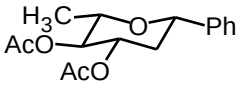
**1.130** **1.131**

**Figure 1.4**




**1.132**

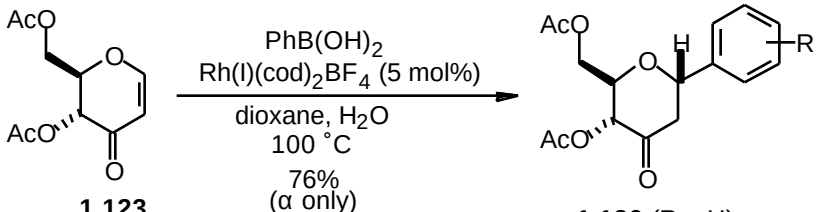

**1.133**




**1.134**

Using the chemistry of Miyaura as precedent, Maddaford and co-workers developed a strategy for appending aromatic residues to carbohydrate-derived α,β-unsaturated pyranones *via* Rh(I)-catalyzed 1,4-addition of arylboronic acids.[50] The pyranone **1.126** was prepared in good yield by simply heating a solution of enone **1.123** in the presence of phenylboronic acid and a Rh(I) source in dioxane/$H_2O$ (Equation 1.29). The *C*-glycoside was obtained as a single anomer having the α-configuration. This is a particularly useful feature of the methodology because certain naturally occurring *C*-aryl glycosides contain a carbohydrate that is not in its most thermodynamically stable configuration at the anomeric center, for example kidamycin (**1.3**) (Figure 1). It was also possible to prepare *C*-aryl glycosides that were substituted on the aromatic ring (R = *p*-$OCH_3$, *p*-Cl, and *o*-$CH_3$). An additional aspect that deserves comment is the protecting groups that were selected for the α,β-unsaturated pyranones. Very often in *C*-glycoside synthesis, one must rely on relatively robust protecting groups, such as benzyl or a bulky silane, for the carbohydrate hydroxyl functionalities. In this case, it was possible to use rather labile acetate protecting groups.

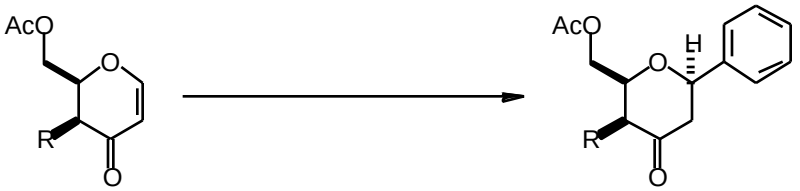
**Equation 1.29**




**1.123** **1.126** (R = H)

Similar chemistry could also be used with other enones that were obtained from the corresponding glycals. Thus, treatment of **1.124** or **1.135** under conditions identical to those above gave **1.128** or **1.136** as single anomers and in good yield (Equation 1.30). With respect to further transformations, it seems reasonable that compounds like **1.126**, **1.128**, and **1.136** could be valuable precursors to dimethylaminosugars similar to those found in the pluramycin antibiotics. Presumably, these compounds could be obtained by treatment of the aforementioned pyranones with dimethylamine followed by reduction of the resultant iminium ion or enamine.

**Equation 1.30**




**1.124**: R = OAc
**1.135**: R = H

**1.128**: R = OAc, 70%
**1.136**: R = H, 75%

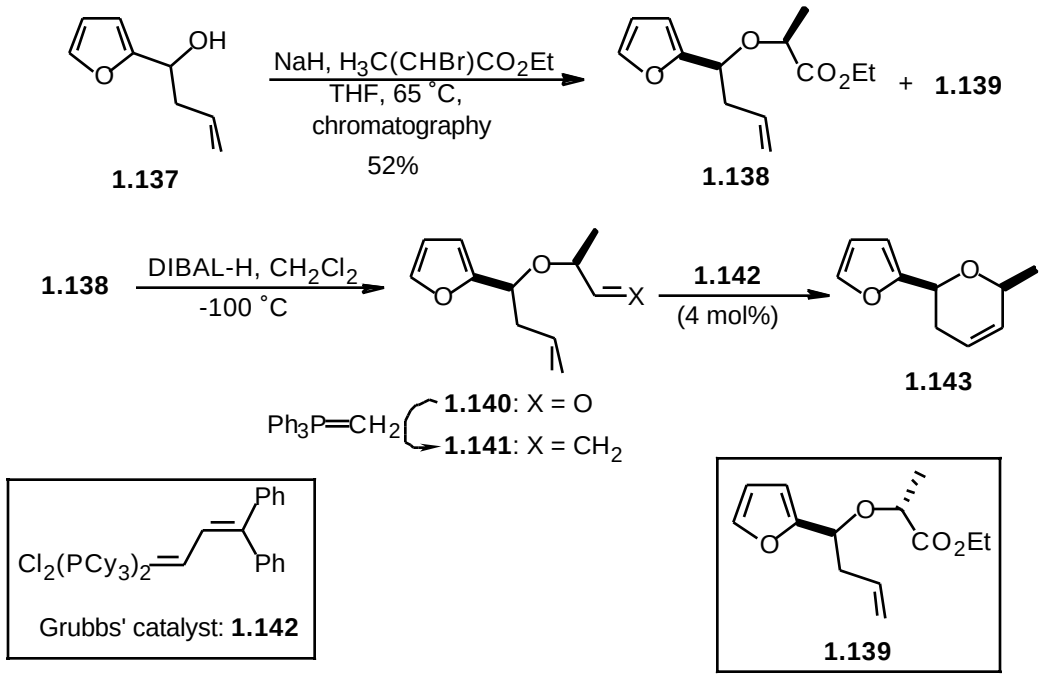
### 1.2.4 Cycloaddition Strategies and Related *de novo* Carbohydrate Syntheses

There are many routes to *C*-aryl glycosides that utilize cycloaddition approaches for the *de novo* construction of the carbohydrate *after* the *C*-aryl bond has been formed. Recently, ring closing metathesis has been implemented successfully for the synthesis of pyran-based *C*-aryl glycosides. Methods that involve the cyclization of acyclic carbohydrate precursors that have already been attached to an aromatic nucleus will also be discussed in this section.

In 1997 Schmidt reported an approach to *C*-furyl glycosides that relied on ring closing metathesis to form the pyran moiety.[51] Treatment of the racemic alcohol **1.137**, which was obtained from a Grignard addition to furfuraldehyde, with NaH and ethyl-2-

bromopropionate delivered the esters **1.138** and **1.139**. After separation of these two diastereomers by column chromatography, each one was carried through the subsequent steps separately. Partial reduction of **1.138** with DIBAL-H at -100 ˚C provided aldehyde **1.140**, which was transformed to the diene **1.141** by a Wittig reaction. Reaction of **1.141** with Grubbs' catalyst (**1.142**) gave racemic **1.143** as a single diastereomer (Scheme 1.13). The identical sequence was performed on the diastereomer **1.139** to give the corresponding *trans*-pyran in comparable yields over all steps. In this early communication there was little discussed with respect to yields for the aforementioned transformations.

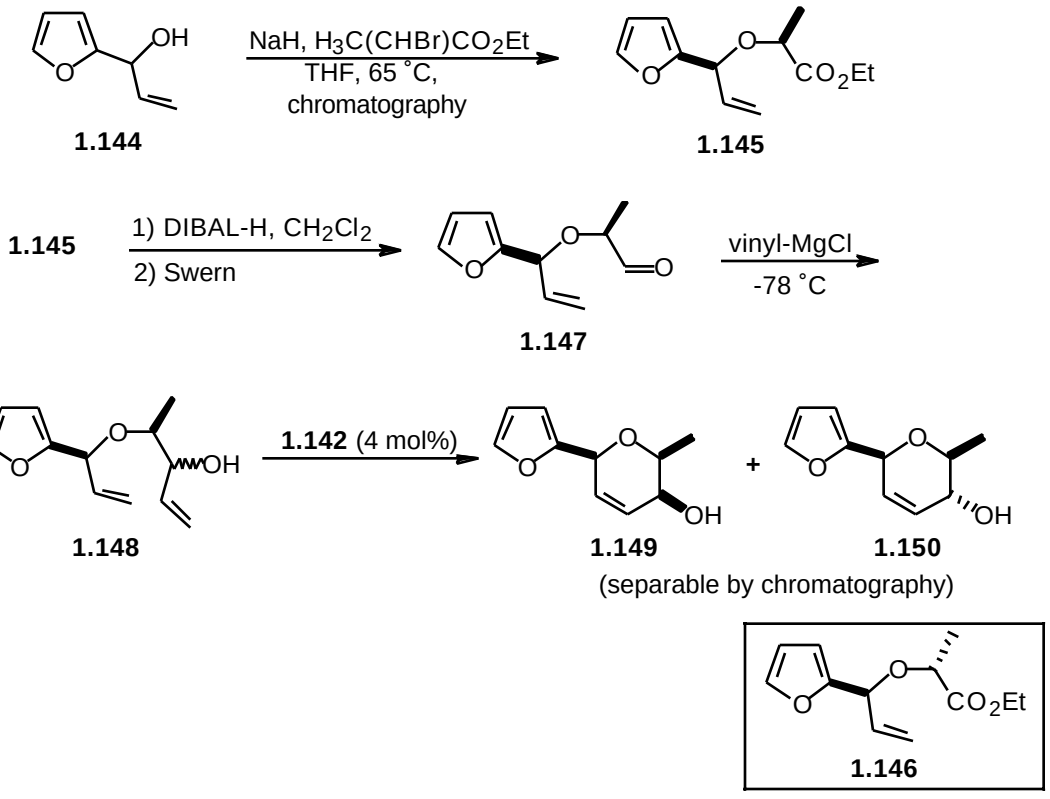
**Scheme 1.13**




More highly oxygenated pyrans were available by implementing a similar approach. Allylic alcohol **1.144** was alkylated as before with ethyl-2-bromopropionate. After separation of the diastereomers, **1.145** was converted to aldehyde **1.147** by a

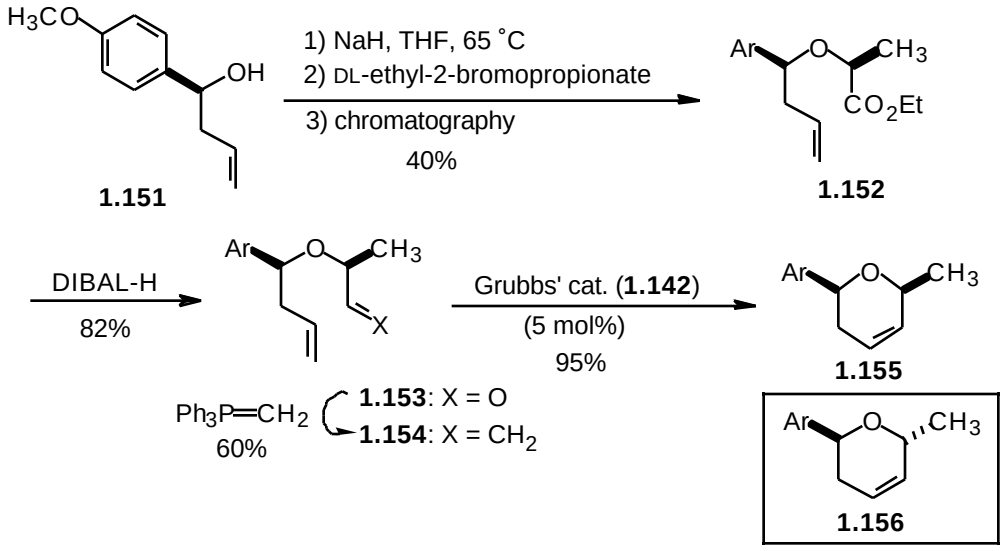
reduction/oxidation sequence. Addition of vinylmagnesium chloride to a solution of **1.147** in THF/$Et_2O$ gave the metathesis precursor **1.148**, as a mixture (not separated) of -OH epimers. Reaction of a mixture of **1.148** and **1.142** in $CH_2Cl_2$ delivered the two dihydropyrans **1.149** and **1.150** that were separated by column chromatography (Scheme 1.14). The same set of conditions was also used on **1.146** to give a total of four separable *C*-furyl glycosides. The relative configurations of each of these diastereomers was assigned based on coupling constants obtained from the $^1H$ NMR spectrum as well as NOESY experiments. It should be noted that the olefins present in compounds like **1.149** and **1.150** provide a useful handle for further functionalization.

**Scheme 1.14**



Schmidt recently disclosed a similar ring closing metathesis approach that was designed for the synthesis of enantiomerically enriched *C*-aryl glycosides.[52] This sequence commenced with enantioenriched (90% ee) homoallylic alcohol **1.151**, which was obtained by enzymatic resolution of the racemate. Reaction of the sodium alkoxide of **1.151** with racemic ethyl-2-bromopropionate delivered an easily separable mixture of diastereomeric esters **1.152** in 80% overall yield. The ester functionality in **1.152** was then transformed by sequential reduction and Wittig reaction to give metathesis precursor **1.154**. Ring closing metathesis of **1.154** in the presence of Grubbs' catalyst (**1.142**) gave the dihydropyran **1.155** (Scheme 1.15). Alternatively, the other diastereomer from the alkylation of **1.151** could be used in the aforementioned sequence to give the *trans*-dihydropyran **1.156** in comparable yields over all steps.

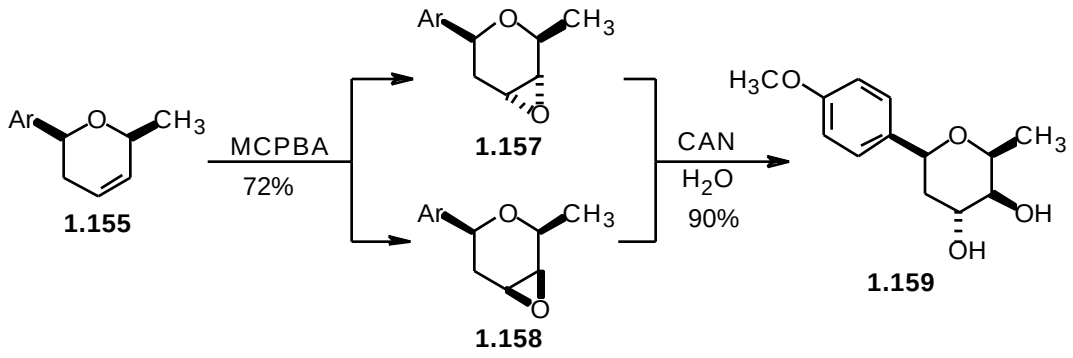
**Scheme 1.15**




Peracid induced epoxidation of **1.155** gave a 1:1 mixture of dihydropyran oxides **1.157** and **1.158**. Treatment of these epoxides, either separately or together, with $H_2O$ in the presence of CAN afforded *C*-aryl glycoside **1.159** as a single diastereomer

in excellent yield (Scheme 1.16). The rationale for the formation of only **1.159** from either dihydropyran oxide was derived from the "Fürst-Plattner rule," which states that nucleophilic opening of epoxides in rigid systems occurs to give the *trans*-diaxial cleavage products. Schmidt had previously determined that an aromatic substituent provided sufficient rigidity to dihydropyran oxides so as to ensure exclusive *trans*-diaxial cleavage of a single conformer of each diastereomeric epoxide.[53] A unique feature of this particular aspect of the methodology is that it provided access to non-natural *C*-aryl glycosides with axially disposed hydroxyl groups.

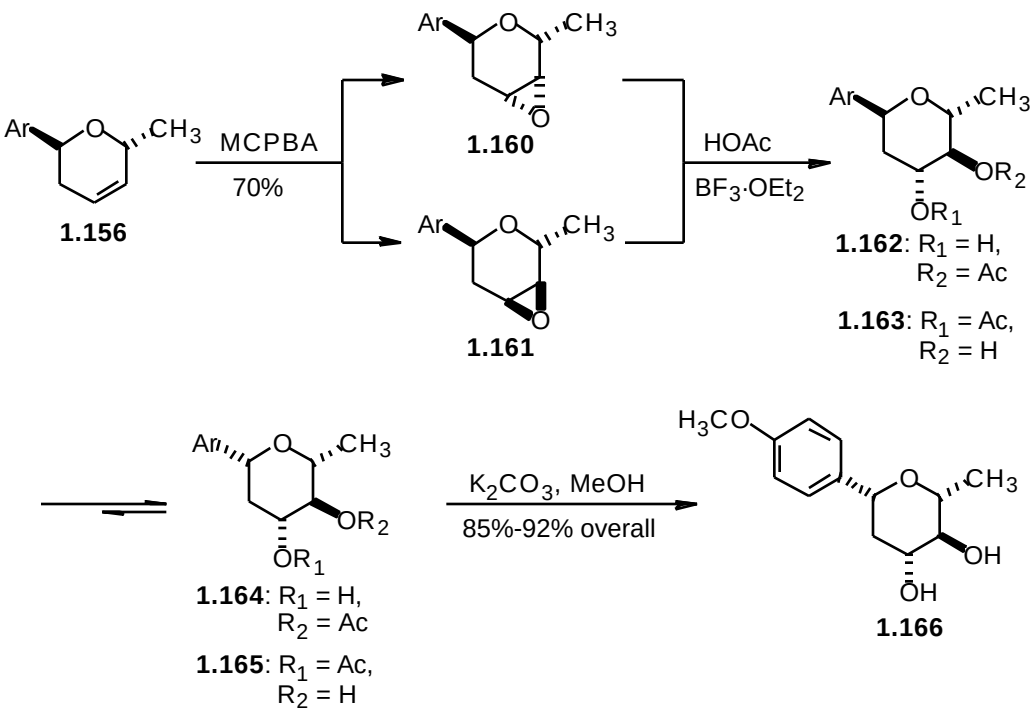
**Scheme 1.16**




*C*-aryl glycosides that possessed equatorially configured substituents were available by the application of a similar approach. Enantiomerically enriched *trans*-dihydropyran **1.156** was epoxidized with MCPBA, and the resulting epoxides were treated with acetic acid in the presence of $BF_3{\cdot}OEt_2$. The resultant mixture of regioisomeric acetates underwent an anomerization process in the presence of the Lewis acid to give the all equatorial tetrahydropyrans **1.164** and **1.165**. The first step in the proposed mechanism for this process was Lewis acid-assisted ionization of the benzylic C-O bond in **1.162** or **1.163** to give a benzylic cation, then the oxygen that was still coordinated to the Lewis acid recyclized by attack on the carbocation to give the

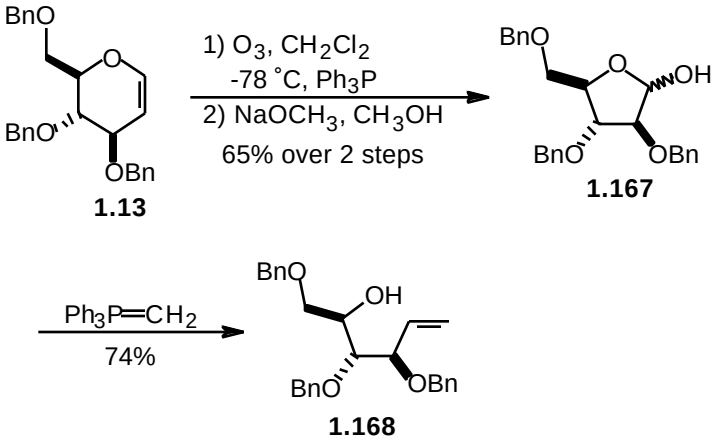
thermodynamically more stable **1.164** and **1.165**. Cleavage of the acetates by basic hydrolysis delivered *C*-aryl glycoside **1.166**, which has the same relative and absolute configuration as those found in naturally occurring systems like the vineomycins or aquayamycin (Scheme 1.17).

**Scheme 1.17**



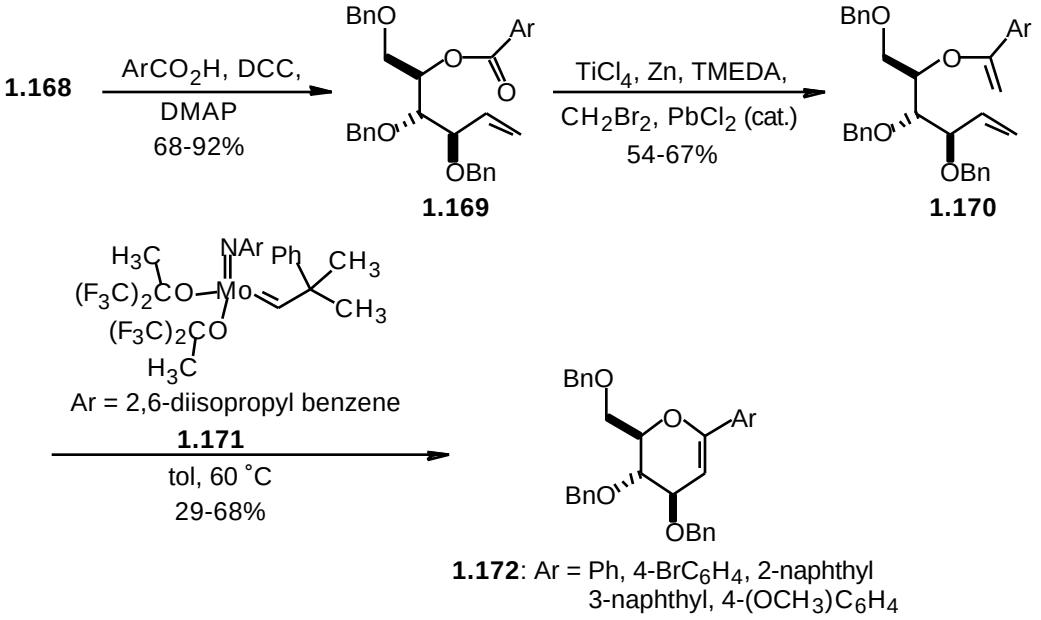

Postema has also developed a ring closing metathesis approach for the preparation of *C*-aryl glycosides.[54] The requisite dienes were obtained from a carbohydrate precursor *via* a straightforward series of steps. Commercially available glycal **1.13** was treated with ozone followed by triphenylphosphine to give an intermediate formate ester that was hydrolyzed upon treatment with sodium methoxide in methanol to give a mixture of lactols **1.167**. Wittig methyleneation afforded alcohol **1.168** in 48% yield over the three steps (Scheme 1.18).

**Scheme 1.18**



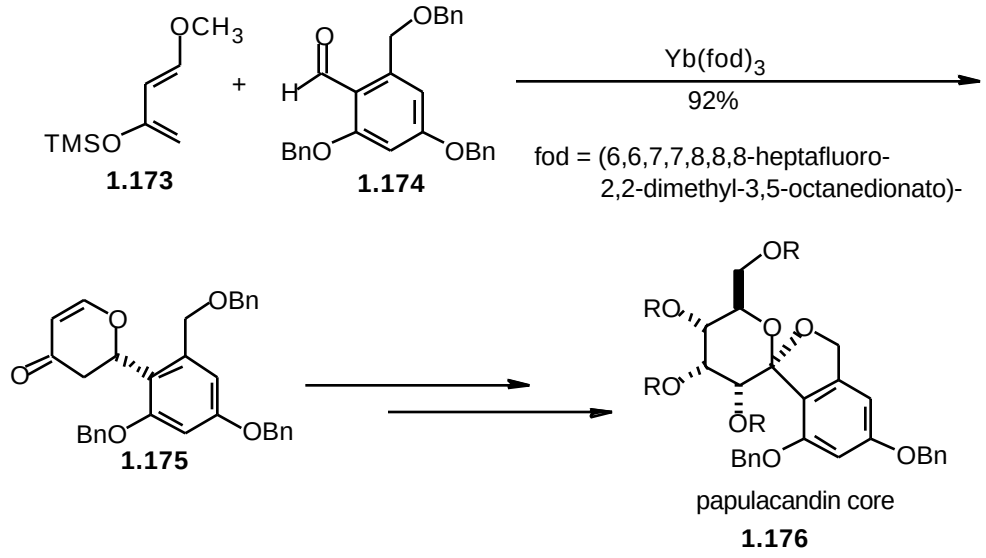

The requisite aromatic esters **1.169** were prepared by DCC-mediated coupling of **1.168** with the appropriate carboxylic acid. The metathesis precursors **1.170** were synthesized by employing a modified Takai procedure. Exposure of these dienes to the Schrock catalyst (**1.171**) provided the *C*-aryl glycals **1.172** in yields ranging from 29-68% (Scheme 1.19). It was necessary to employ up to 50 mol% of **1.171** to obtain reasonable yields in the RCM reaction. It is also noteworthy that optimum yields in the conversion of **1.170** → **1.172** were only realized if the reaction was carried out in a glove-box.

**Scheme 1.19**




The hetero-Diels-Alder (HDA) reaction has proven to be a powerful tool for the *de novo* construction of carbohydrates on aromatic systems. Early work by Danishefsky, which involved a HDA reaction between the aromatic aldehyde **1.174** and the oxygenated butadiene **1.173** provided a novel access to simple skeletons like **1.175**. The olefin and ketone present in **1.175** were refunctionalized in a diastereoselective fashion to provide a substituted carbohydrate. This intermediate was subsequently elaborated further to afford *C*-aryl glycosides related to the papulacandins **1.176** (Scheme 1.20).[55]

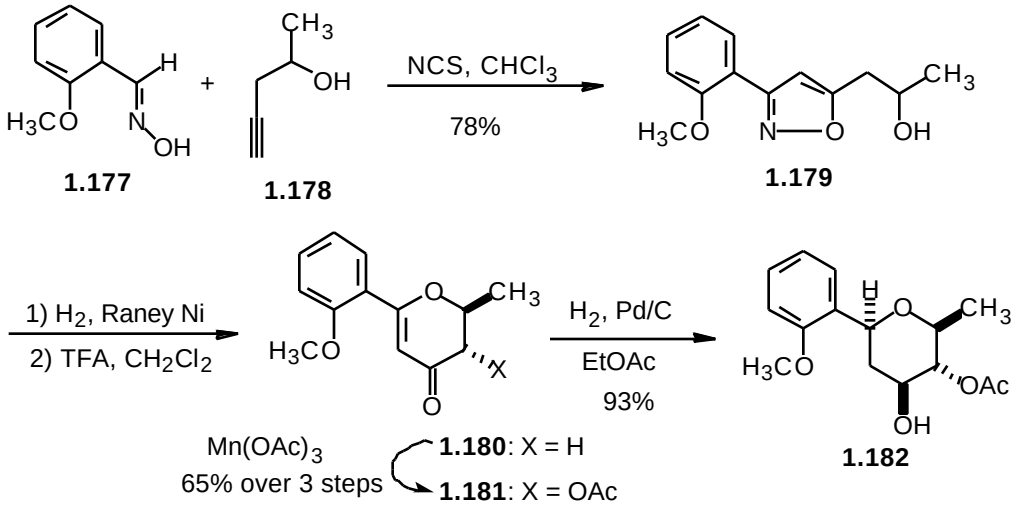
**Scheme 1.20**




Yamamoto has developed an asymmetric hetero-Diels-Alder approach to *C*-aryl glycosides.[56] Various benzaldehydes were allowed to react with highly oxygenated dienes in the presence of a chiral organoaluminum catalyst. One advantage of this methodology is that either antipode of the catalyst is accessible; this allows one to easily obtain unnatural L-sugars using this chemistry.

Hauser has recently developed a route to *C*-aryl glycosides that utilized a [3+2] cycloaddition between a nitrile oxide and a homopropargylic alcohol as a key step in the formation of a *C*-aryl glycoside portion.[57] Treatment of a solution of **1.177** and **1.178** with NCS (*N*-chlorosuccinimide) delivered the isoxazole **1.179**. The N-O bond in **1.179** was hydrogenolyzed by the action of $H_2$/Raney Ni to give a diketone that underwent cyclization/dehydration to afford pyranone **1.180**. The oxygen functionality present in **1.181** was introduced by stereoselective α-acetoxylation of **1.180**, then the major *trans*-isomer was isolated and subsequently hydrogenated to give **1.183** in excellent yield and as a single diastereomer (Scheme 1.21).

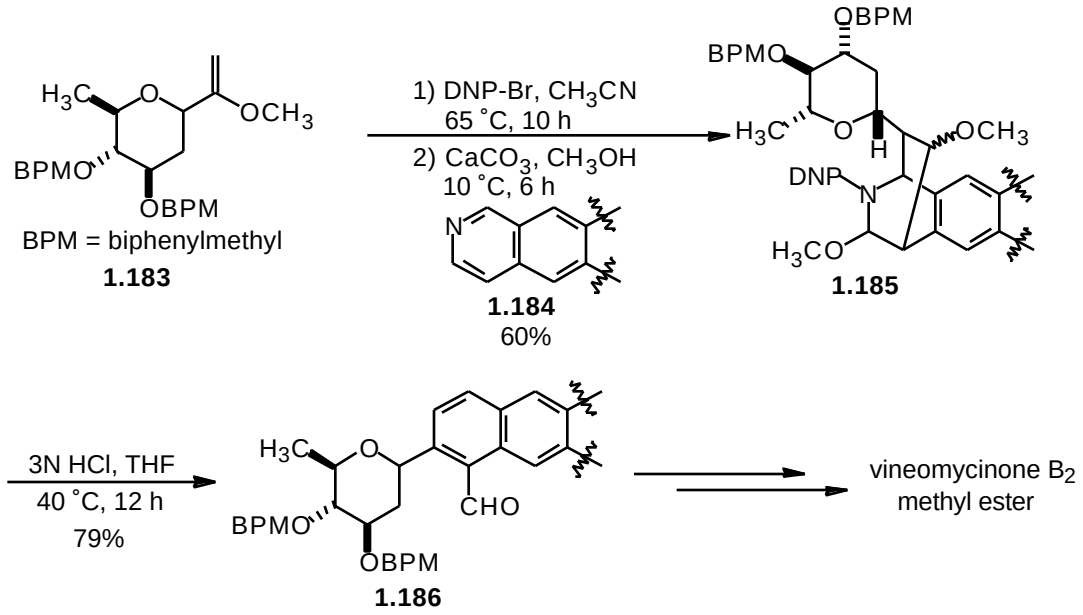
**Scheme 1.21**




The ability to prepare 2,6-deoxy *C*-aryl glycosides is a clear advantage of this method, as is the diastereoselective construction of the glycoside portion starting from non-carbohydrate precursors. Although racemic homopropargylic alcohol **1.178** was used to produce racemic **1.182**; chiral non-racemic *C*-aryl glycosides could be obtained by starting with enantioenriched materials. By using essentially the same procedure, the authors were also able to prepare an analogous anthraquinone *C*-aryl glycoside system.

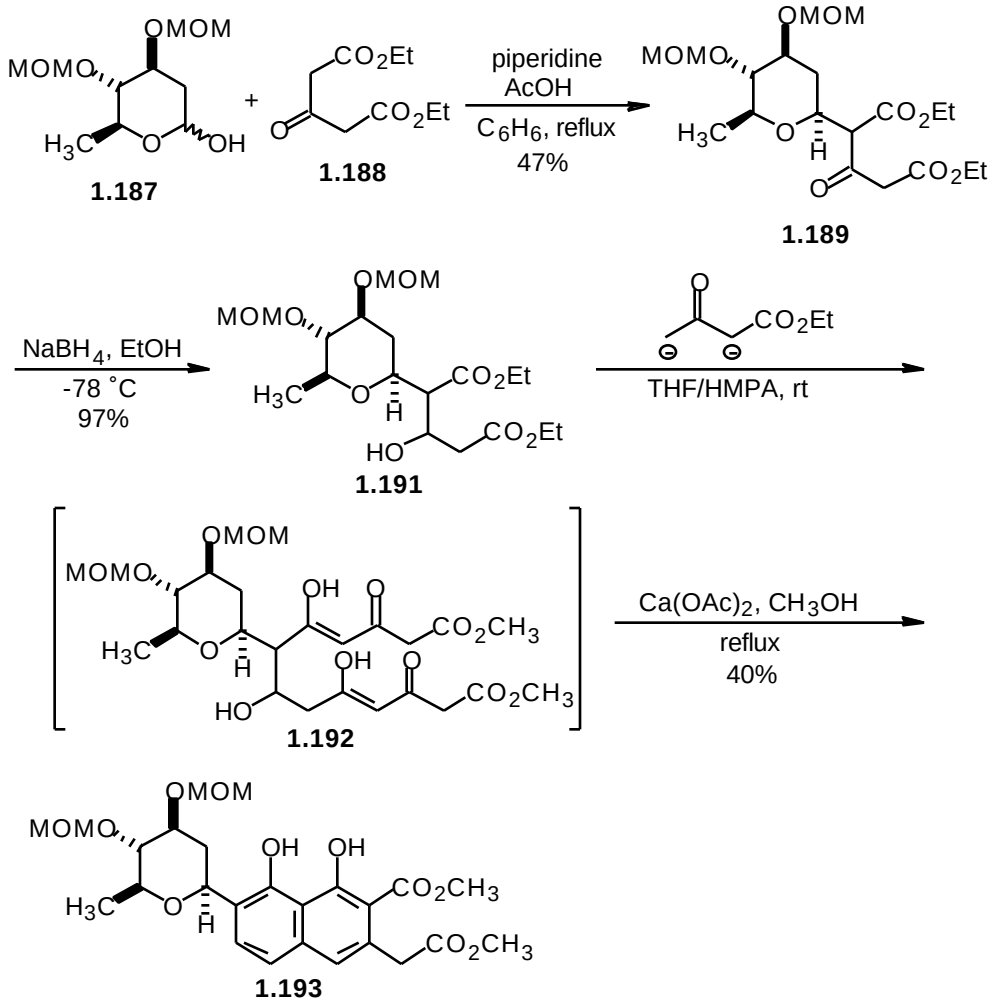
Mioskowski and Falck disclosed a highly efficient Bradsher cyclization approach for *C*-aryl glycoside construction in their total synthesis of vineomycinone $B_2$ methyl ester.[58] Thus, Bradsher cyclization of a solution of the DNP (2,4-dinitrophenyl) salt of pyridoisoquinoline **1.184** and *C*-glycoside **1.183** delivered cycloadduct **1.185** in 60% yield for the two steps. Treatment of this adduct with 3 N HCl/THF gave anthracene-derived *C*-aryl glycoside **1.186** that was further transformed to the natural product (Scheme 1.22).

**Scheme 1.22**




Yamaguchi and co-workers have used a biosynthetic approach, namely the cyclization of carbohydrate-substituted polyketides, for the synthesis of *C*-aryl glycosides.[59] The details of one of the more interesting syntheses are presented in Scheme 1.23. Thus, a solution of lactol **1.187** and β-oxoglutarate (**1.188**) in benzene was heated at reflux in the presence of piperidine and HOAc to give **1.189**. The ketone functionality in **1.189** was reduced with $NaBH_4$ to deliver **1.191** in excellent yield. Treatment of a solution of **1.191** with the dianion of methylacetoacetate in THF/HMPA presumably gave the intermediate **1.192** that was treated directly with $Ca(OAc)_2$ to give the naphthyl glycoside **1.193** (Scheme 1.23).

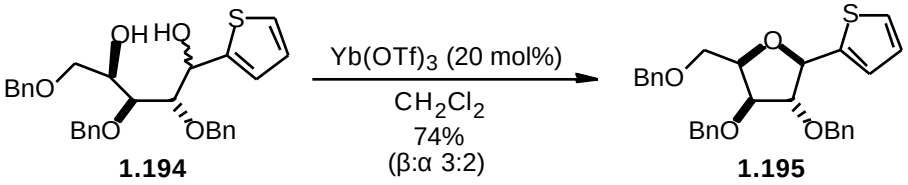
**Scheme 1.23**




One approach to the preparation of *C*-aryl furanosides is based on the cyclization of 1,4-diols. This cyclodehydration concept has been applied to tetrahydrofuran synthesis in the past, but Sharma and co-workers have reported on the extremely mild $Yb(OTf)_3$ catalyzed cyclization of 1,4-diols. Treatment of a solution of diol **1.194** in $CH_2Cl_2$ with a catalytic amount of $Yb(OTf)_3$ afforded the *C*-thiophenyl glycoside **1.195** in reasonably good yield but with rather low diastereoselectivity (Equation 1.31). Benzenoid *C*-aryl furanosides like **1.197** were also available using this

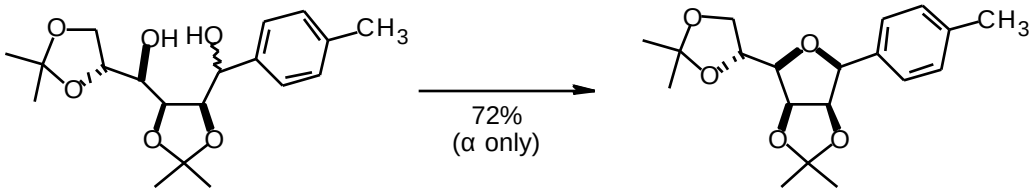
approach. In the example shown, cyclization of the diol **1.196** delivered **1.197** with high diastereoselectivity and in good yield (Equation 1.32).

**Equation 1.31**




**1.194** **1.195**

**Equation 1.32**

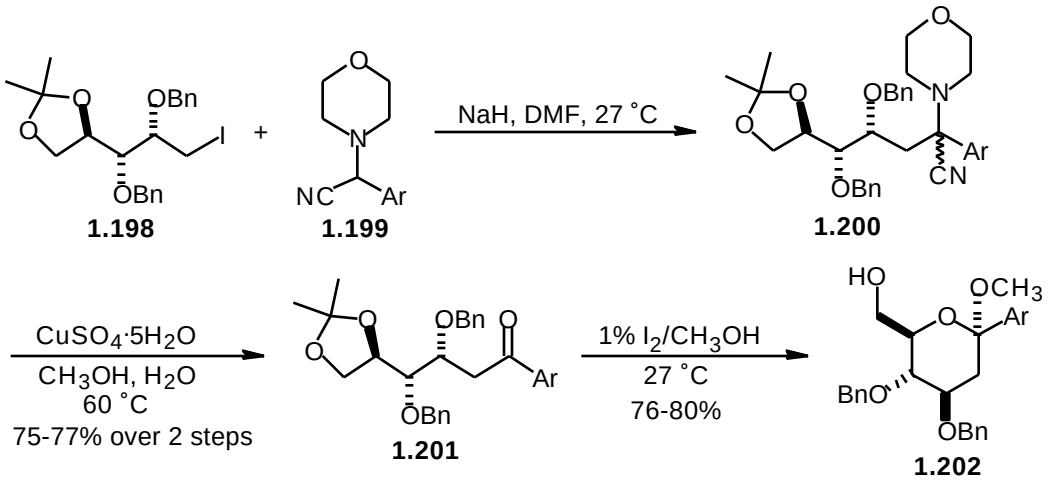



**1.196** **1.197**

Aidhen recently developed an *umpolung* strategy designed for the synthesis of *C*-aryl glycosides that commenced with the addition the α-anion of an aminonitrile, which is an acyl anion equivalent, to carbohydrate-derived alkyl iodides.[60] The choice of using the anion of an α-aminonitrile was made because of the ease with which they can be generated (NaH) as well as the fact that stringently dry conditions and low temperatures are not required for their alkylation. A solution of the iodide **1.198**, prepared from D-arabinose, was allowed to react with the sodium anion of aminonitrile **1.199** in DMF to give **1.200**. Hydrolysis of the aminonitrile functionality in **1.200** gave aryl ketone **1.201**. A variety of aryl aminonitriles of the general structure **1.200** (Ar = Ph, 4-chlorophenyl, 4-methoxyphenyl, 3,4-(methylenedioxy)phenyl) were prepared, and in all cases the yield of **1.201** consistently high. Attempts to cleave the isopropylidene group in **1.201** using dilute protic acid resulted in the formation of a furanoside product

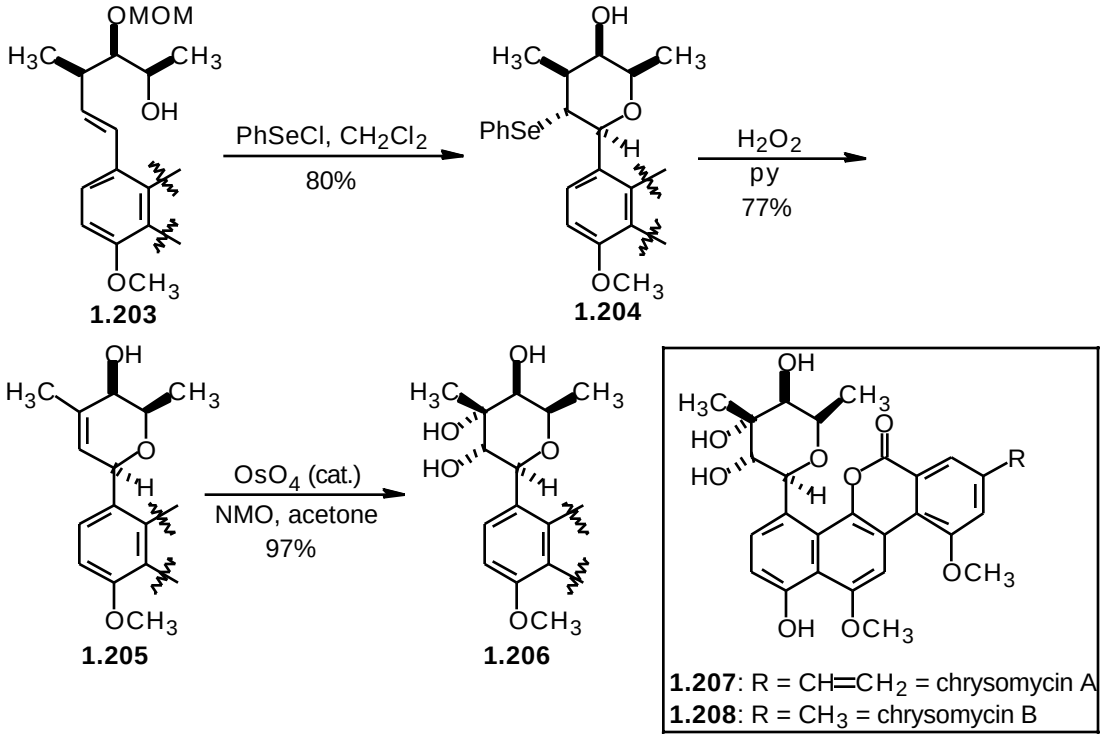
however, treatment with 1% $I_2$ in $CH_3OH$ provided the α-*C*-aryl glycoside **1.202** in good yield (Scheme 1.24). It should be straightforward to stereoselectively reduce the acetal functionality present in **1.202** with $NaBH_3CN$ in the presence of an acid to give the corresponding *C*-glycoside.

**Scheme 1.24**




Hart developed an intramolecular electrophilic selenoetherification strategy for the *de novo* synthesis of carbohydrates on aromatic scaffolds,[61,62] Application of this approach has allowed the preparation of *C*-aryl glycosides related to the chrysomycins.[62] Treatment of a solution of **1.203** with PhSeCl induced a stereoselective selenoetherification reaction to deliver **1.204**. Oxidation of the selenide moiety in **1.204** presumably gave a selenoxide intermediate that rapidly underwent a *syn*-elimination to give glycal **1.205**. The glycal was stereoselectively dihydroxylated to provide **1.206**, which was further transformed to compounds related to the chrysomycins A (**1.207**) and B (**1.208**) (Scheme 1.25).

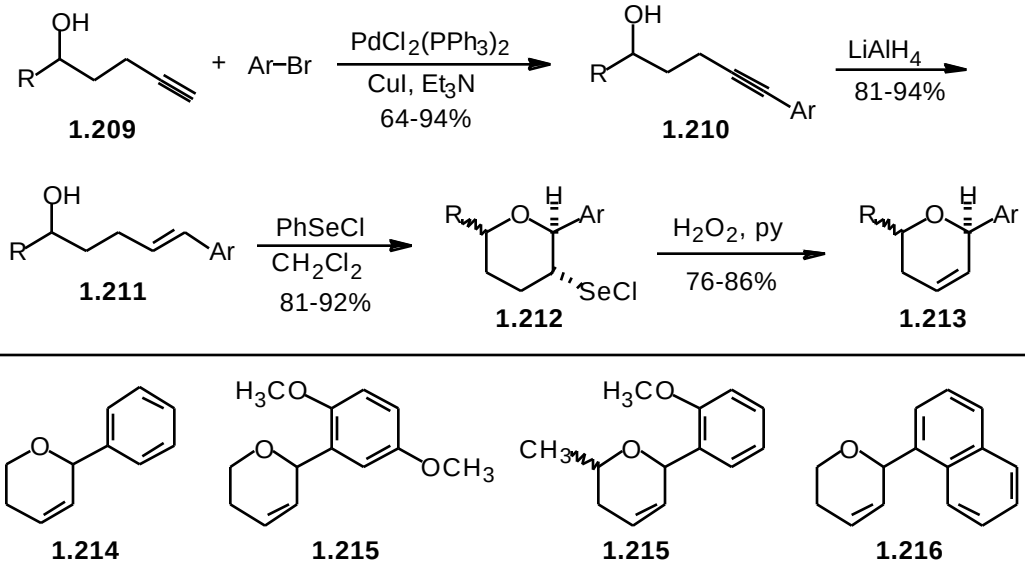
**Scheme 1.25**




Brimble recently disclosed an approach that was very similar to Hart's strategy, but it addressed one of the drawbacks of the earlier methodologies that stemmed from difficulties encountered in the preparation of the cyclization precursor. A Sonogashira coupling was used for the assembly of the cyclization precursors, and this appears to solve the aforementioned problems. Using this methodology, Brimble chose to prepare aryl dihydropyrans, rather than *C*-aryl glycosides, but presumably carbohydrate precursors could be utilized in order to allow for this.[63] Sonogashira couplings of various aryl bromides with 5-hydroxyacetylenes of the general type **1.209** gave **1.210**. Stereoselective partial reduction of the alkyne functionality in **1.210** provided the cyclization precursors **1.211** with exclusively the *E*-configuration at the olefin. Treatment of **1.211** with PhSeCl resulted in selenoetherification to provide the *trans*-

tetrahydropyrans **1.212**. Oxidation of the selenide moiety delivered the corresponding selenoxide that underwent a regioselective *syn*-elimination to give dihydropyrans **1.213** (Scheme 1.26). Application of this methodology facilitated the preparation of *C*-aryl "glycosides" **1.214-1.217** among others. The yields of aryldihydropyran products were generally good, however the diastereoselectivity in substituted cases (R ≠ H) was rather low.

**Scheme 1.26**



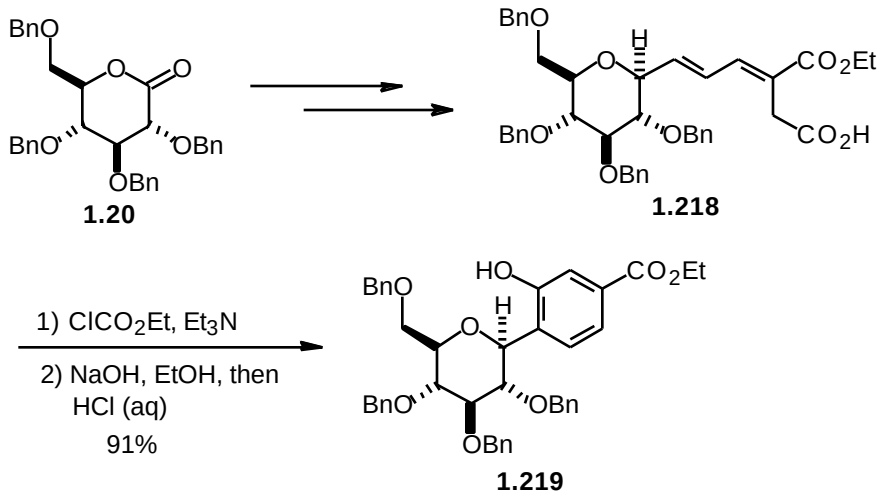

### 1.2.5 Benzannulation Strategies

In recent years, many interesting examples have appeared in the literature that detail the preparation of *C*-aryl glycosides by forming the aromatic ring after the *C*-glycosidic bond has been formed.

For example, Serra and Fuganti modified an approach they developed for preparing substituted phenols *via* cyclization of 3-alkoxycarbonyl-3,5-hexadienoic acids in order to allow for the synthesis of β-linked *C*-aryl glycosides as illustrated in the

conversion of **1.218**→**1.219**.[64] The known tetrabenzylgluconolactone **1.20** was converted to the dienoic acid **1.218** using known chemistry. This acid underwent cyclization upon treatment with $ClCO_2Et$ and $Et_3N$ to provide **1.219** and its carboxyethyl derivative. Treatment of this mixture with NaOH in EtOH for a brief period followed by acidification cleanly afforded the benzannulated *C*-glycoside **1.219** in 91% yield (Scheme 1.27). The ability to prepare *C*-glycosides attached to electron-deficient aromatic cores is a useful aspect of this methodology.

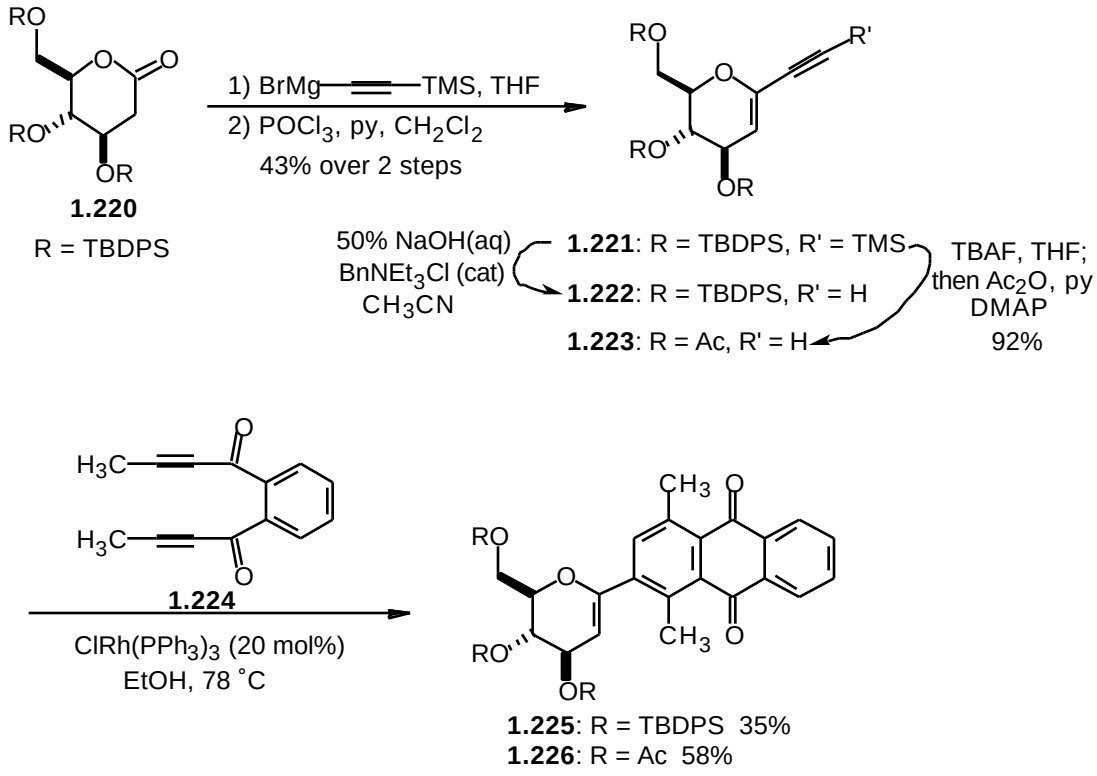
**Scheme 1.27**




McDonald developed an approach to *C*-aryl glycosides that relied on construction of the aromatic system subsequent to formation of the *C*-glycosidic bond. The strategy utilized a Rh-catalyzed alkyne cyclotrimerization in order to access simple benzenoid *C*-aryl glycosides as well as more complex anthraquinone systems.[65] For example, 2-(trimethylsilyl)ethynylmagnesium bromide was added to the protected lactone **1.230** to provide a mixture of intermediate lactols that was treated with $POCl_3$ to give enyne **1.221**. Cycloaddition precursors **1.222** and **1.223** were then prepared by employing a series of straightforward protecting group manipulations. Reaction of a

solution of either of these enynes with ketodiyne **1.224** in the presence of $ClRh(PPh_3)_3$ (Wilkinson's catalyst) (20 mol%) delivered the *C*-glycoside anthraquinones **1.225** or **1.226** in moderate yield (Scheme 1.28). The use of a protic solvent apparently renders the aforementioned reaction catalytic in rhodium. However, if the purported intermediate rhodium metallacycle was preformed stoichiometrically from diketodiyne **1.224** was then allowed to react with **1.222**, the yield of anthraquinone **1.225** could be improved to 46% as compared to the catalytic system that gave a yield of only 35%. A similar sequence was applied for the preparation of **2.226**.

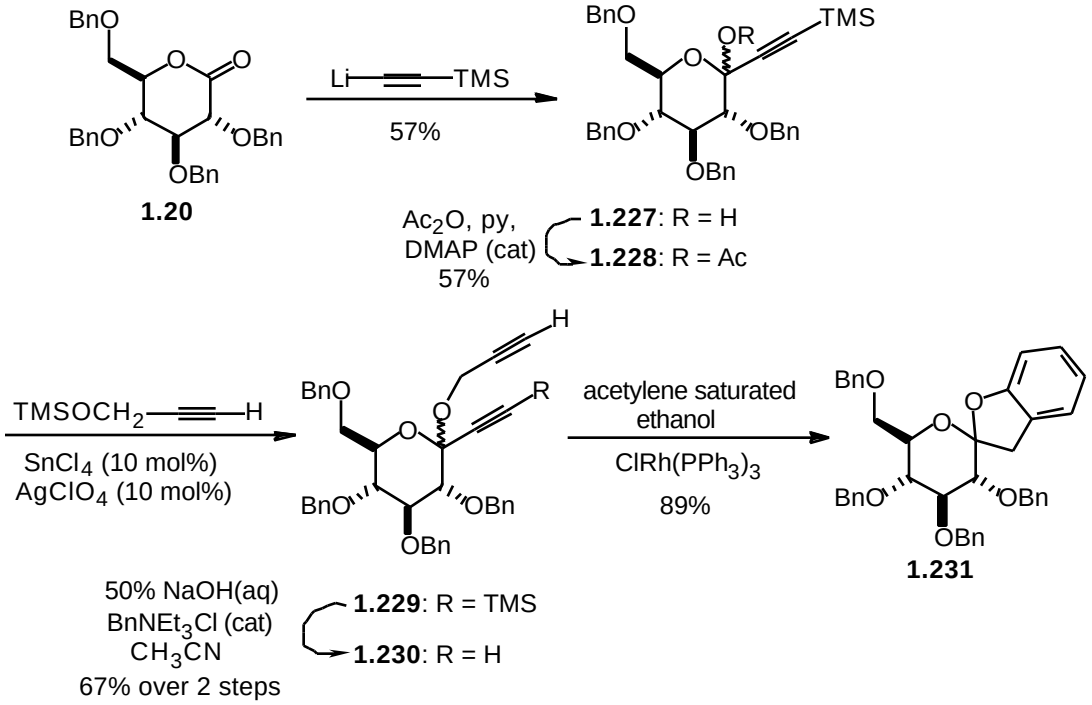
**Scheme 1.28**




A similar strategy was also utilized by McDonald to prepare the spiroglycoside **1.231**, which bears resemblance to the papulacandin class of natural products previously prepared by Friesen, Beau, and Danishefsky. Thus, addition of 2-

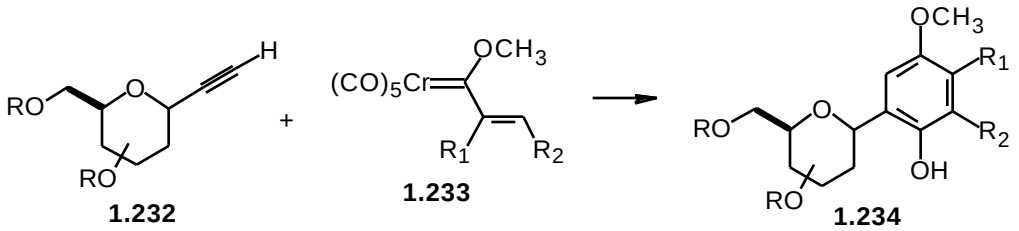
(trimethylsilyl)ethynyllithium to **1.20** gave a mixture of lactols **1.227** that was treated with $Ac_2O$ to provide the anomeric acetate **1.228**. This compound was *O*-glycosylated by the action of $SnCl_4$ and $AgClO_4$ in the presence of *O*-propargyl trimethylsilyl ether to give **1.229**. Removal of the TMS group followed by reaction with Wilkinson's catalyst (20 mol%) and acetylene saturated EtOH gave spiroacetal **1.231** in high yield (Scheme 1.29).

**Scheme 1.29**



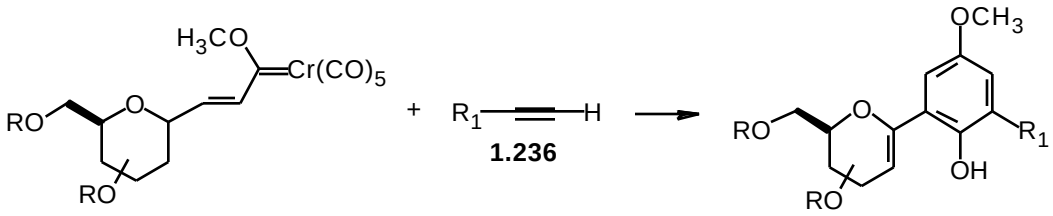

Pulley and co-workers have developed an approach to *C*-aryl glycosides based on metal vinylidene cycloadditions to assemble an aromatic scaffold.[66] The authors utilized a [3+2+1] cycloaddition (the Dötz reaction) between either a *C*-alkynyl-substituted sugar **1.232** and an alkenyl chromium carbene **1.233** or between a glycosylated chromium carbene **1.235** and a simple substituted alkyne **1.236** (Equations 1.33 and 1.34).

**Equation 1.33**




**1.232** **1.233** **1.234**

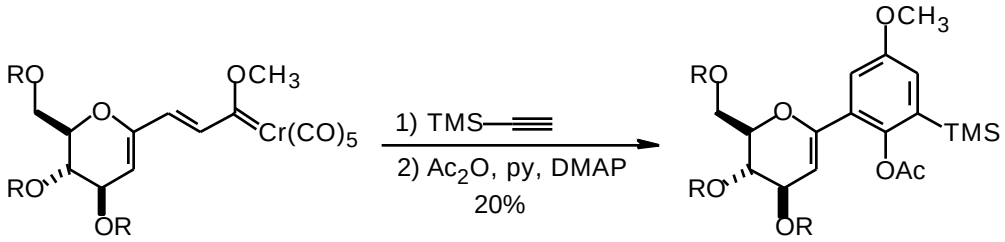
**Equation 1.34**




**1.235** **1.236** **1.237**

The first approach commenced with the glycal-derived chromium carbene **1.238**, which was obtained from the corresponding glycosyl aldehyde. Heating a solution of **1.238** in the presence of TMS-acetylene, followed by air oxidation to demetalate the resultant complex gave an intermediate phenol. This phenol was acetylated to give **1.239** as a single regioisomer in rather low yield (Equation 1.35). The TMS group, which is present in the final product, provides a potentially useful handle for subsequent transformations.

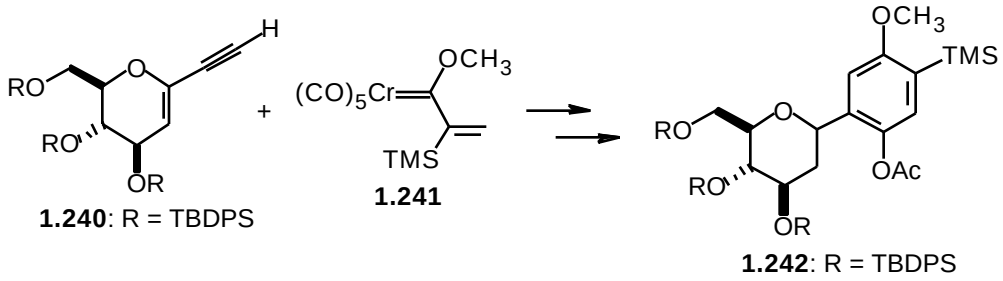
**Equation 1.35**




**1.238**: R = TBDPS **1.239**: R = TBDPS

The alternative procedure involved cycloaddition between an alkynyl sugars such as **2.240** or **2.241** with a chromium carbene complex **1.241** to give, after demetalation followed by acetylation as in Equation 1.35, the corresponding TMS-substituted *C*-aryl glycosides **1.231** and **1.233** (Equation 1.36). This protocol provided a different regioisomer of **1.239** with respect to placement of the TMS group. The aforementioned strategy was also amenable to the preparation of *C*-aryl glycosides that were oxygenated at the 2-position as well as the corresponding 2-deoxy analogues.

**Equation 1.36**

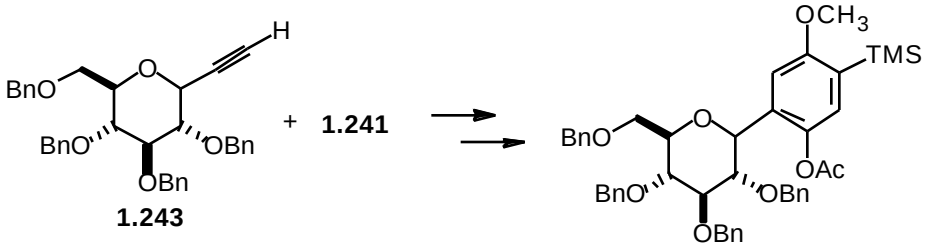



**1.240**: R = TBDPS

**1.241**

**1.242**: R = TBDPS

**Equation 1.37**

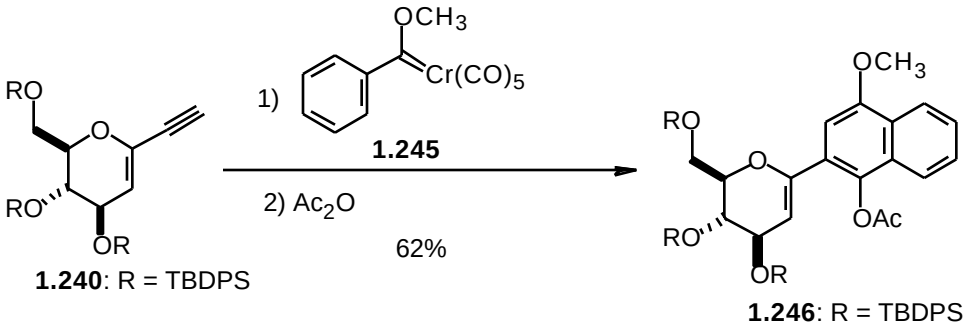



**1.243**

**1.244**

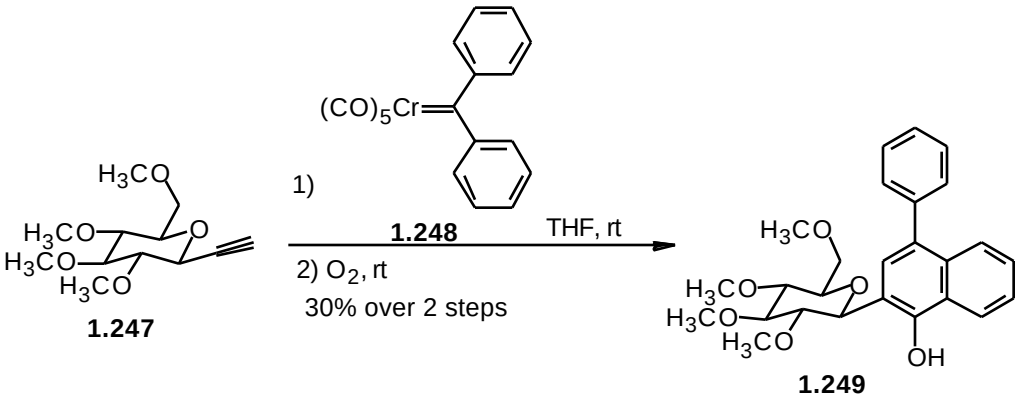
Reaction of the alkynylglycoside **1.240** with methoxy phenyl carbene complex **1.245** followed by molecular oxygen induced demetalation gave a naphthol. The free hydroxyl group in this naphthol was acetylated as before to give differentially protected naphthalene **1.246** in moderate yield (Equation 1.38). Attempts to use other alkynyl glycoside derivatives as the ring-saturated analog of **1.240** were unsuccessful.

**Equation 1.38**




At approximately the same time that the aforementioned work was completed, Dötz reported a similar approach to *C*-aryl glycosides that utilized a diphenyl chromium carbene complex instead of the alkoxy carbene complexes used by Pulley and co-workers.[67] Treatment of the alkynyl glycoside **1.247** with chromium complex **1.248** afforded a new cyclized complex that could demetalated upon exposure to molecular oxygen to give *C*-naphthyl glycoside **1.249** in 30% overall yield (Equation 1.39). One advantage of this methodology is that the use of the highly electrophilic carbene complex **1.248** allows the reaction to be conducted at room temperature. The lower reaction temperature permits isolation of the intermediate chromium naphthalene complex after column chromatography as long as $O_2$ is excluded. Presumably, this intermediate could participate in further transformations such as nucleophilic substitution.

**Equation 1.39**




## 1.3 CONCLUSION

It should be apparent from the previous discussion that there are a great number of approaches to the synthesis of *C*-aryl glycosides. Arguably the most common approach, involves addition of an aryl nucleophile to a carbohydrate electrophile for the preparation of a number of *C*-glycoside natural products. The addition of carbohydrate nucleophiles to "aromatic" electrophiles is a less prevalent technique, but nonetheless it has been shown to be a powerful methodology. The *umpolung* approach developed by Parker represents a highly useful route to *C*-aryl glycosides. In particular, it allows one to predictably access all four of the *C*-aryl glycoside groups (Figure 1.2). Transition metal-catalyzed couplings between aromatic and carbohydrate partners represent a particularly mild technique for *C*-aryl glycoside construction. Since the pioneering work of Danishefsky, many research groups have employed methods that rely on *de novo* synthesis of the carbohydrate after attachment to an aromatic nucleus. The hetero-Diels-Alder reaction between aryl aldehydes and highly oxygenated dienes is a particularly relevant example of this approach. Finally, the complementary approach

that involves construction of the aromatic portion after the *C*-aryl bond has been formed, represents a recent and powerful method for the synthesis of *C*-aryl glycosides.

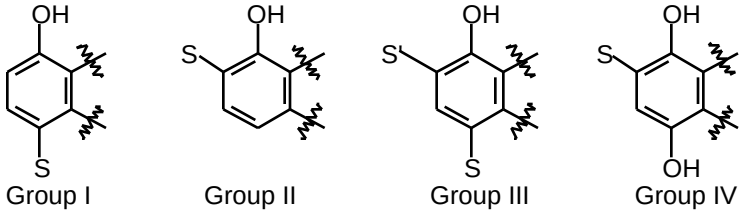
Despite the large number of methods available for *C*-aryl glycoside construction, it is noteworthy that very few can provide predictable and general access to *all* four of the classes of *C*-aryl glycoside antibiotics (Figure 1.2). The upcoming chapter will detail work in the Martin group toward the goal of developing novel methodologies for the preparation of the four classes of *C*-aryl glycosides as well as application of these new techniques to the synthesis of biologically important *C*-aryl glycoside natural products.

# Chapter 2. Novel Methodologies for the Construction of *C*-Aryl Glycosides. Progress Toward the Synthesis of *C*-Aryl Glycoside Natural Products Kidamycin and Galtamycinone

## 2.1 INTRODUCTION

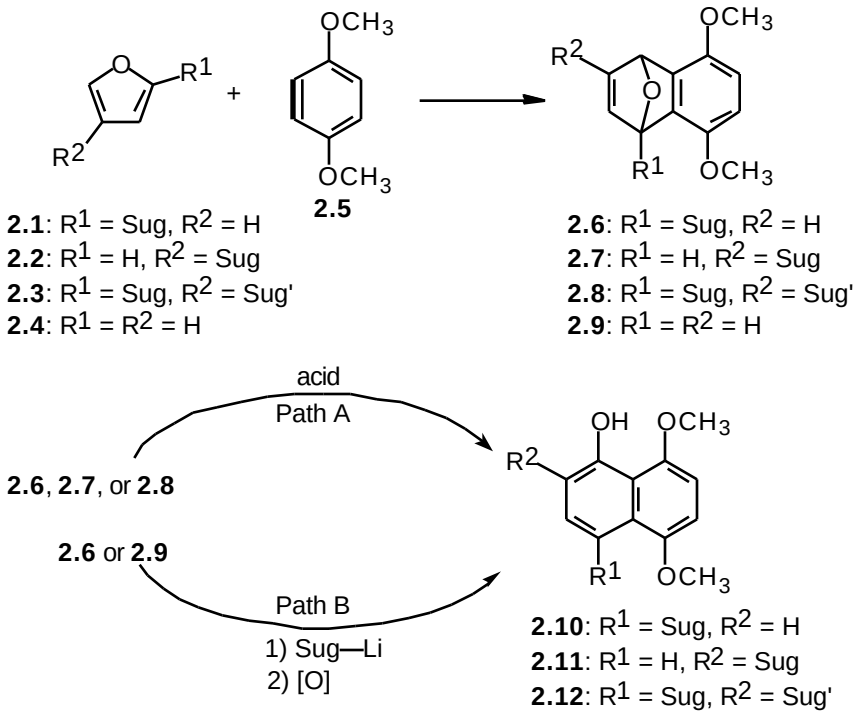
Parker has classified the naturally occurring *C*-aryl glycoside antibiotics by the relative position(s) of the carbohydrate(s) and the phenolic -OH group(s).[3] Using this system, *C*-aryl glycosides can be divided into four distinct groups (Figure 2.1).

**Figure 2.1**




We have examined two potential routes for the preparation of the four major classes of *C*-aryl glycosides The first relied on [4+2] cycloadditions between benzynes of the type **2.5** and glycosyl-substituted furans **2.1**, **2.2**, or **2.3**, followed by acid-catalyzed ring opening of the resultant adducts (Scheme 2.1, Path A). The second approach focused on the $S_N2'$ ring opening of oxabicyclic compounds **2.6** or **2.9**, which were obtained from benzyne/furan cycloadditions, with glycosyl nucleophiles, followed by oxidation of the resultant dihydronaphthol products (Scheme 2.1, Path B). We felt confident that application of either of these techniques would allow us to access naturally occurring *C*-aryl glycoside antibiotics in a rapid manner.

**Scheme 2.1**



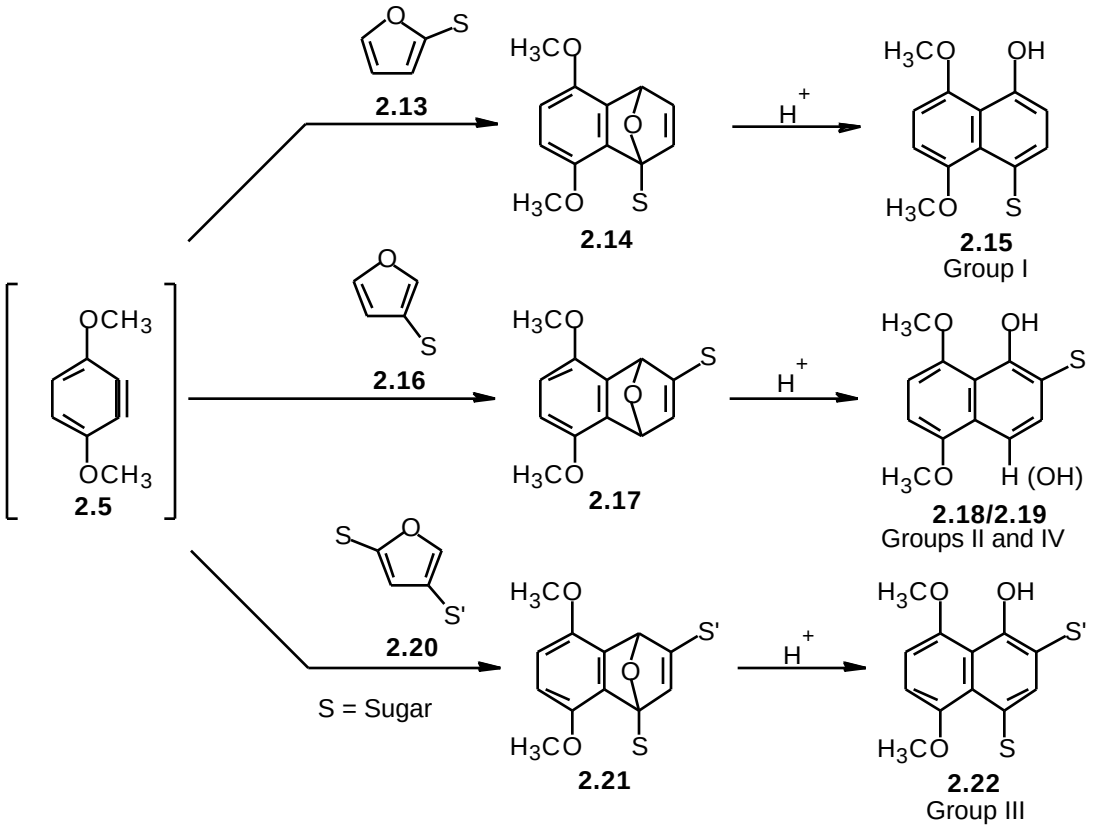

We felt that there were several advantages to using *C*-furyl glycosides as scaffolds for the construction of larger aromatic sitemaps. First, we believed that it would be fairly easy to regioselectively prepare 2- and 3-glycosyl furans **2.1** and **2.2** as well as 2,4-diglycosyl furans **2.3**. In fact there were several useful methods in the literature for the synthesis of furans of the general type **2.1** and **2.2**. Another advantage of this approach was the possibility of introducing the *C*-glycoside moiety at a late stage of a synthesis. This would be particularly useful if one were to apply this method to the synthesis of a complex *C*-aryl glycoside natural product that contained carbohydrates that were valuable or difficult to obtain . We were also interested in the possibility of being able to prepare analogs of naturally occurring *C*-aryl glycosides so that they could be used to provide better understanding of the chemistry and biological activity of these fascinating compounds. Hence, late stage introduction would be highly desirable with

respect to the ability to rapidly prepare highly diversified systems. A detailed discussion of the advantages and disadvantages of the $S_N2'$ route proposed in Scheme 2.1, Path B, will be reserved for a later section of this chapter.

## 2.2 BENZYNE APPROACH

It is well precedented that benzyne/furan cycloadditions are a powerful tool for the construction of polycylic aromatic systems.[68,69] We envisioned that *C*-glycosyl furans would participate in [4+2] cycloadditions with benzynes to give cycloadducts that would undergo an acid-catalyzed ring opening isomerization in a predictable fashion to give *C*-aryl glycosides Groups I-IV. One of the powerful aspects of this methodology was that by controlling the position of attachment of the glycoside on a furan, a relatively easy task, we could prepare a number of *C*-aryl glycosides with good control of regiochemistry in the final compounds. The basic concept is outlined below (Scheme 2.2).

**Scheme 2.2**

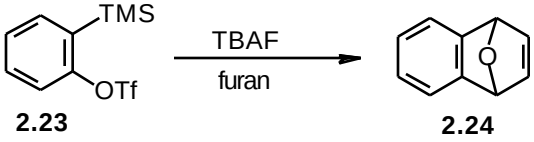



### 2.2.1 Methods for Benzyne Generation

In order for our idea to be useful, we needed to utilize a relatively mild and reliable method for benzyne generation. Over the years, many methods for benzyne generation have been disclosed,[70] but some of the more recently discovered methods have the advantage of being extremely mild and safe.[71] Benzynes can be prepared from the corresponding anthranilic acids after diazotization and slight heating of the intermediate diazonium salt.[72] This particular method is advantageous in that it allows for the generation of benzyne in an extremely clean fashion, without the use of strongly basic organometallic reagents. The method does however, suffer from the need to

isolate the explosive intermediate diazonium salt. Benzyne intermediates are also available *via* oxidative cleavage of the corresponding aminobenzotriazoles.[73] Metalation of 1,2-dihalogenated benzenes either through Grignard or aryllithium formation is an extremely useful method to generate benzynes. Metal-halogen exchange is followed by elimination of a stable MX compound (M = metal, X = halogen) with simultaneous formation of the benzyne intermediate.[74,75] One fairly recent example of a mild technique to generate involves treating an *o*-silyl triflate **2.23** with tetrabutylammonium fluoride (TBAF) or some other anhydrous fluoride source (Equation 2.1). This method allowed benzyne generation to occur at or near ambient temperature and under nearly neutral reaction conditions.[76] Suzuki, has shown that benzyne can be generated easily at -78 ˚C by treatment of *o*-halo triflates with *n*-BuLi.[77]

**Equation 2.1**



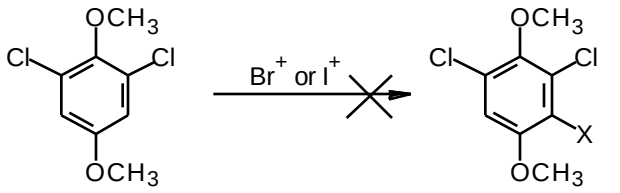

**2.23** **2.24**

### 2.2.2 Martin Group Approach to Benzyne Generation

We first decided to examine a technique for generating benzyne that would rely on the halogen-metal exchange of an *o*-dihalobenzene. Toward this end, we set out to prepare a dimethoxybenzyne precursor such as **2.26**. This trihalogenated substrate was expected to undergo selective halogen-metal exchange of X upon treatment with an organolithium reagent such as *n*-BuLi. Upon warming, elimination of LiX was expected to occur to produce the desired benzyne intermediate. Unfortunately, attempts to halogenate **2.25** to give **2.26** using a wide range of conditions met with failure.

Reagents that were investigated included *N*-iodosuccinimide, *N*-bromosuccinimide, $Br_2$, $I_2$, ICl, and IBr. Additionally we explored the effects of running the halogenation reactions in the presence of Lewis acids and other additives at various reaction temperatures and in many different solvents, but unfortunately, no significant quantities of **2.26** were obtained (Equation 2.2). In most cases, unchanged starting material was recovered, but when more forcing conditions were employed, decomposition pathways to give unidentified by-products dominated.

**Equation 2.2**

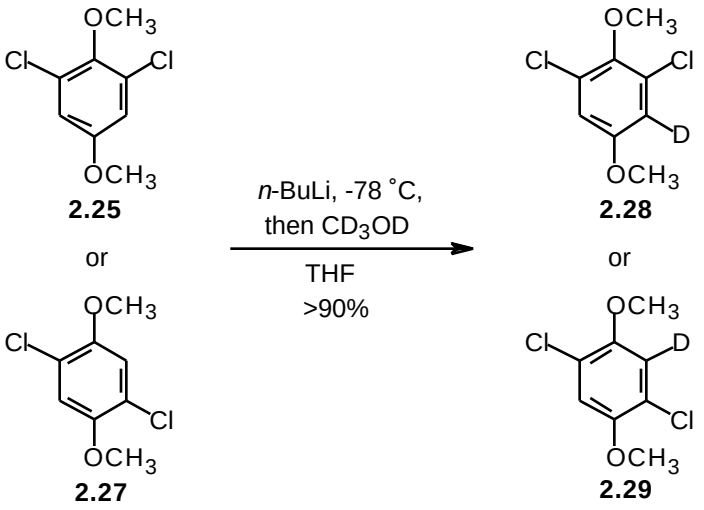



**2.25** **2.26**: X = Br, I

We eventually questioned whether it was actually necessary to halogenate a substrate like **2.25** in order to make it a suitable benzyne precursor. It was well known that aromatic systems that contain groups capable of forming a chelate with an organometallic reagent (e.g. amide, alkoxy, carbamate, and others) can be regioselectively metalated *ortho* to the chelating group under appropriate conditions.[78] We wondered if it might be possible to lithiate **2.25** directly, thereby obviating the need to halogenate. We quickly discovered that treating **2.25** or **2.27**, which were prepared by methylation of the corresponding hydroquinones,[79] with *n*-BuLi at -78 ˚C followed by quenching with $d_4$-$CH_3OH$ resulted in >90% deuterium incorporation in both substrates (Equation 2.3). We then found that adding furan or 2-methylfuran to the solution of aryllithium derived from **2.25** or **2.27** at -78 ˚C followed by removal of the cooling bath, gave a mixture of regioisomeric cycloadducts. Thus, the lithiated chloro

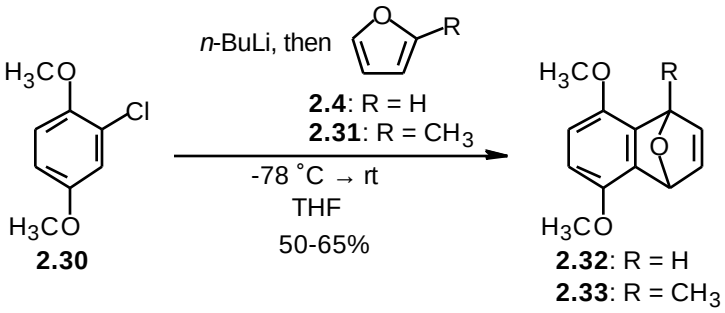
arene lost a chloride ion, and the benzyne thus generated *in situ* was captured by the furan. The dichlorobenzenes **2.25** and **2.27** were useful benzyne precursors that could be cleanly deprotonated with *n*-BuLi at -78 ˚C.

**Equation 2.3**



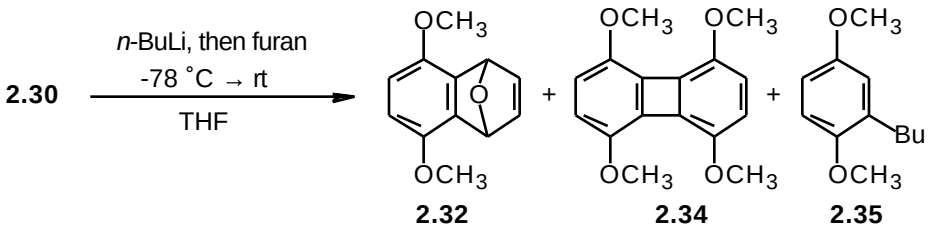

Subsequent to these experiments, cycloadditions with the benzyne intermediate derived from commercially available monochlorobenzene **2.30** were examined. A solution of *n*-BuLi in hexanes was added to a solution of **2.30** in THF at -78 ˚C. The resulting solution was stirred for 15 min at -78 ˚C, and then furan **2.4** or **2.31** was added. The mixture was then allowed to warm to room temperature whereupon, benzyne generation and cycloaddition ensued (Equation 2.4). This method typically afforded cycloadducts **2.32** or **2.33** in yields ranging from 50-65%. These reactions were characterized almost without exception, by the recovery of varying amounts of starting diene **2.4**/**2.31**. In some cases excess benzyne precursor could be employed to improve yields slightly, but the problem of incomplete consumption of diene remained.

**Equation 2.4**



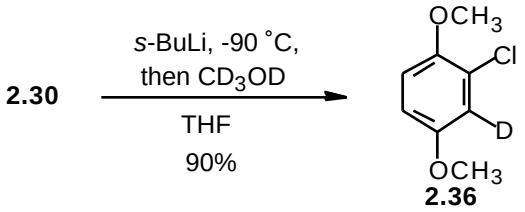

Subsequently, Dr. Susan Downing, a postdoctoral associate in the group, needed to prepare large quantities of cycloadduct **2.32** (Equation 2.4) for methodological studies.[80] Dr. Downing attempted to prepare **2.32** by employing the conditions previously developed in our group. She analyzed the $^1$H-NMR spectrum of the reaction mixture and observed not only the desired cycloadduct **2.32**, but also varying amounts of benzyne dimer **2.34** and an adduct **2.35** resulting from addition of *n*-butyllithium to the benzyne (Equation 2.5). The starting benzyne precursor **2.30** was also observed in all cases. It was surmised based on this information that deprotonation was not occurring quantitatively and that benzyne formation was occurring to a significant extent during the deprotonation step. Dr. Downing initiated a systematic study to determine how this problem could be circumvented. She experimented with various bases, number of equivalents of base, solvents, and reaction temperatures, quenching the mixtures with $d_4$-$CH_3OH$, but no significant improvements in the deprotonation reaction were seen.

**Equation 2.5**



Using the data collected by Dr. Downing as a guide, some further experimentation was initiated. It was quickly discovered that if **2.30** was treated with *s*-BuLi at a temperature of less than -90 ˚C (bath temp, $Et_2O$/liquid $N_2$) for 10 min followed by quenching with $d_4$-$CH_3OH$ at the same temperature, greater than 90% deuterium incorporation occurred (Equation 2.6). Furthermore, neither of the by-products **2.34** or **2.35** was observed (Equation 2.5). This result was not particularly surprising since it was well known that *s*-BuLi is a particularly good base for rapid, low temperature directed metalations.[78] When this technique for benzyne generation was applied to cycloadditions with a variety of substituted furans in which *n*-BuLi had been employed previously, all yields improved substantially (to >80%).

**Equation 2.6**




### 2.2.3 Preparation of Group I *C*-Aryl Glycosides

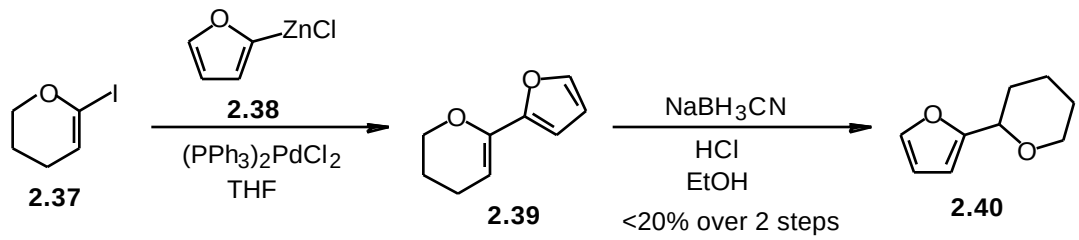
#### *2.2.3.1 Model System*

With a reliable method for benzyne generation in hand we wanted to begin to test the feasibility of the transformations in Scheme 2.2. To determine whether carbohydrate-substituted furans would undergo cycloadditions with benzynes, we sought to prepare a simple model system based on the tetrahydropyranyl-substituted furan **2.40** (Scheme 2.3). It was expected that it would be fairly easy to prepare this compound, and we believed that cycloadditions with this simple model system would

provide information that would be useful when we began to examine cycloadditions with carbohydrate-substituted furans.

We prepared the furan **2.40** by three different methods. The first relied on a Negishi-type coupling between **2.37** and **2.38** using chemistry developed by Friesen for the coupling of iodoglucals with arylzinc halides.[81] First, the highly unstable iododihydropyran **2.37** was prepared by sequential treatment of dihydropyran with *t*-BuLi, $ZnCl_2$, and $I_2$. This iodide was not fully characterized and was always used as a dilute solution in THF. With **2.37** in hand, we followed the protocol described by Friesen in order to couple it with 2-furylzinc chloride (**2.38**). Treatment of **2.39** with $NaBH_3CN$ in acidic EtOH afforded the rather volatile **2.40** in <20% overall yield (Scheme 2.3).

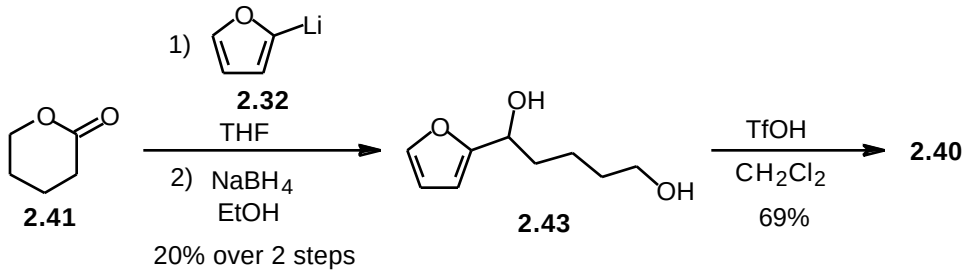
**Scheme 2.3**




Furan **2.40** could also be accessed by the method depicted in Scheme 2.4. δ-Valerolactone (**2.41**) was allowed to react with 2-furyllithium (**2.42**), and the resultant hydroxy ketone was reduced with $NaBH_4$ to give diol **2.43** in 20% yield (unoptimized). Evidence that the intermediate derived from addition of 2-furyllithium to the lactone existed as the open, hydroxy ketone was provided by both IR (strong absorbance at 1672 $cm^{-1}$) and $^1H$ NMR (δ 2.83 t, $J$ = 7.1 Hz, 2 H corresponding to the methylene α to the ketone as well as the absence of an "anomeric" proton resonance). Initial attempts to cyclize this diol using TsOH were unsuccessful, but we eventually found that TfOH

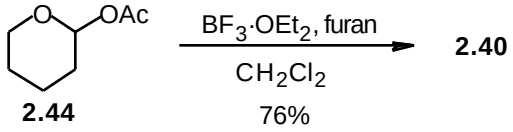
mediated the desired etherification reaction cleanly and rapidly to give **2.40** in 69% yield.

**Scheme 2.4**



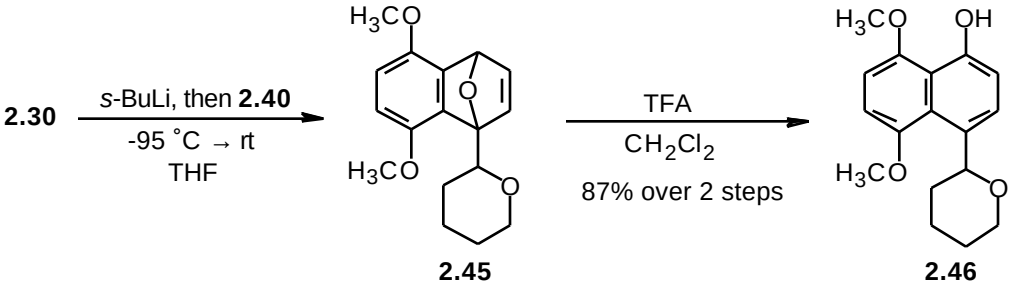

The third and simplest approach to **2.40** relied on the Friedel-Crafts reaction of tetrahydropyranyl acetate **2.44**[82] with furan in the presence of $BF_3{\cdot}OEt_2$ (Equation 2.7). This method turned out to be the highest yielding and also represented the simplest way to prepare and isolate the volatile **2.40** cleanly. With quantities of the model glycosyl furan in hand we set out to investigate the cycloadditions of interest.

**Equation 2.7**




Treatment of **2.30** with *s*-BuLi at -95 ˚C followed by addition of a solution of **2.40** in THF and then warming to room temperature afforded cycloadduct **2.45** in good yield. Treatment of **2.45** with trifluoroacetic acid induced ring opening to occur, and after proton loss, phenol **2.46** was produced in 87% overall yield from **2.40** (Scheme 2.5).

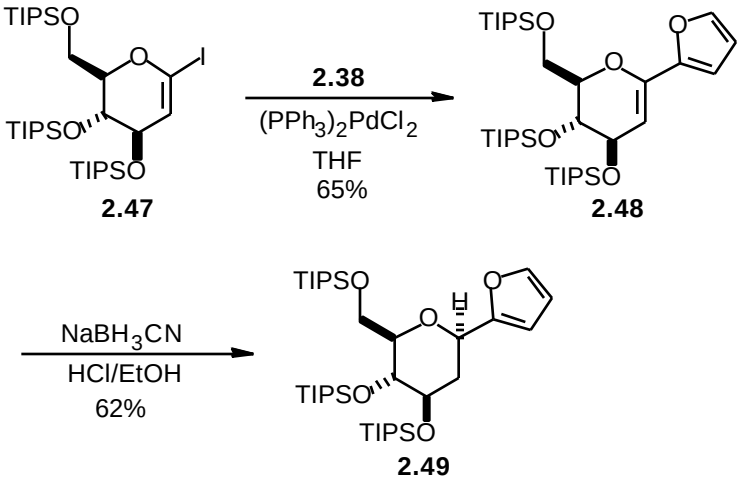
**Scheme 2.5**




### *2.2.3.2 Group I C-Aryl Glycosides*

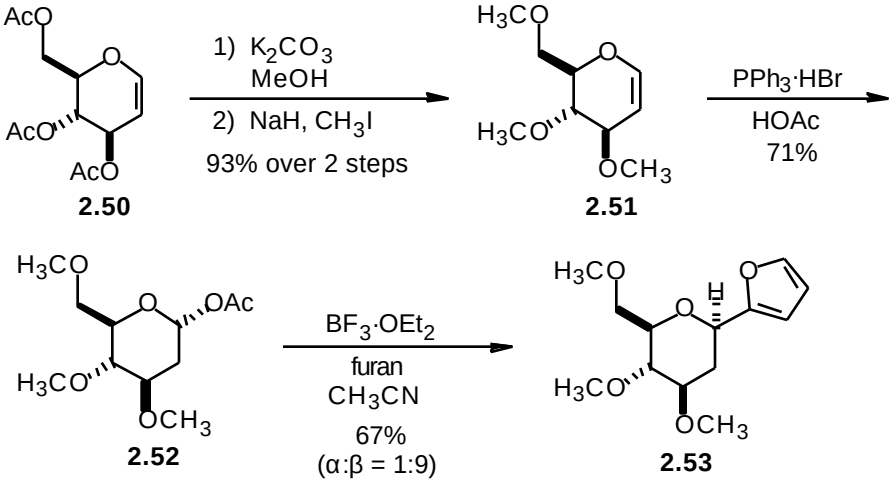
We next turned our attention to the syntheses and cycloadditions of more complex carbohydrate-substituted furans. The triisopropylsilyl-protected glycosyl furan **2.48** was prepared using the method of Friesen.[81] Thus, the known iodoglucal **2.47** was coupled with 2-furylzinc chloride (**2.38**) in the presence of *bis*-triphenylphosphinepalladium dichloride to give **2.48**. This glycal was reduced to the saturated glycosyl furan **2.49** by employing $NaBH_3CN$ in ethanolic HCl (Scheme 2.6).[47] Attempts to effect the reduction by hydrogenation using a number of different catalysts including $Rh/Al_2O_3$, Pd/C, Pt/C, $(PPh_3)_3RhCl$, and Raney Ni resulted in the formation of complex mixtures of uncharacterized products.

**Scheme 2.6**



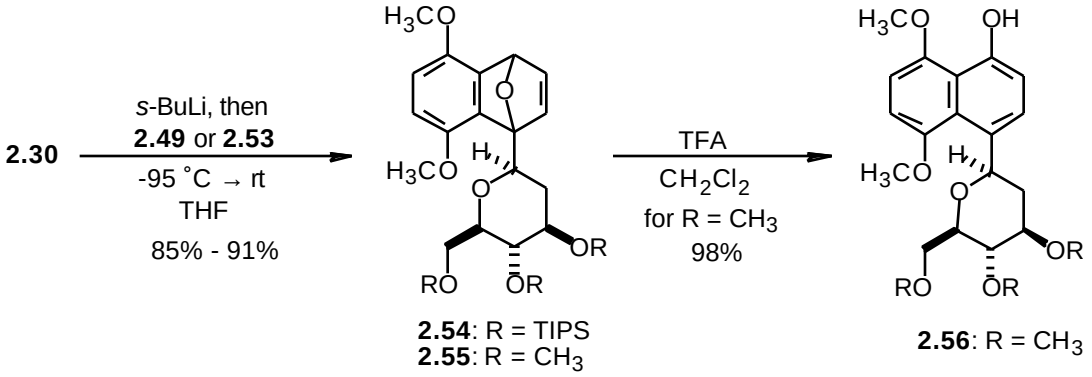

The trimethoxy glycosyl furan **2.53** was prepared using a complementary procedure. Hydrolysis of commercially available tri-*O*-acetyl-D-glucal (**2.50**) with $K_2CO_3$ in $CH_3OH$ followed by exhaustive methylation of the resultant triol afforded the known glucal **2.51**.[83] Treatment of **2.51** with catalytic triphenylphosphine hydrobromide in the presence of acetic acid gave predominately ($\alpha$:$\beta$ = 4:1) $\alpha$-glycosyl acetate **2.52**.[84] This method proved to be particularly useful for the acid-catalyzed conversion of glycals to *O*-glycosides without competing Ferrier rearrangement. Using a known procedure for the preparation of a related compound, a solution of **2.52** and furan in $CH_3CN$ was treated with $BF_3{\cdot}OEt_2$ to promote a Friedel-Crafts reaction that afforded **2.53** with high diastereoselectivity ($\beta$:$\alpha$ = >9:1) as determined by integration of the anomeric protons in the $^1$H-NMR) (Scheme 2.7).[85]

**Scheme 2.7**




We were pleased to find that both furyl sugars **2.49** or **2.53** reacted readily with the benzyne generated from **2.30** to give oxabicyclic compounds **2.54** or **2.55**, each as a mixture of diastereomers. Treatment of the trimethoxyglucal-derived cycloadduct **2.55** with trifluoroacetic acid (TFA) afforded phenol **2.56** in excellent yield (Scheme 2.8). Unfortunately, attempts to open the TIPS protected cycloadduct **2.54** by treatment with acid were plagued by formation of multiple products; presumably partial cleavage of the silyl ethers is occurring. It should be noted that Dr. Omar Lopez, a former postdoctoral researcher in the Martin group, successfully prepared the tribenzylated analog of **2.56** (R = Bn) in good overall yield using chemistry identical to that outlined in Scheme 2.8.

**Scheme 2.8**

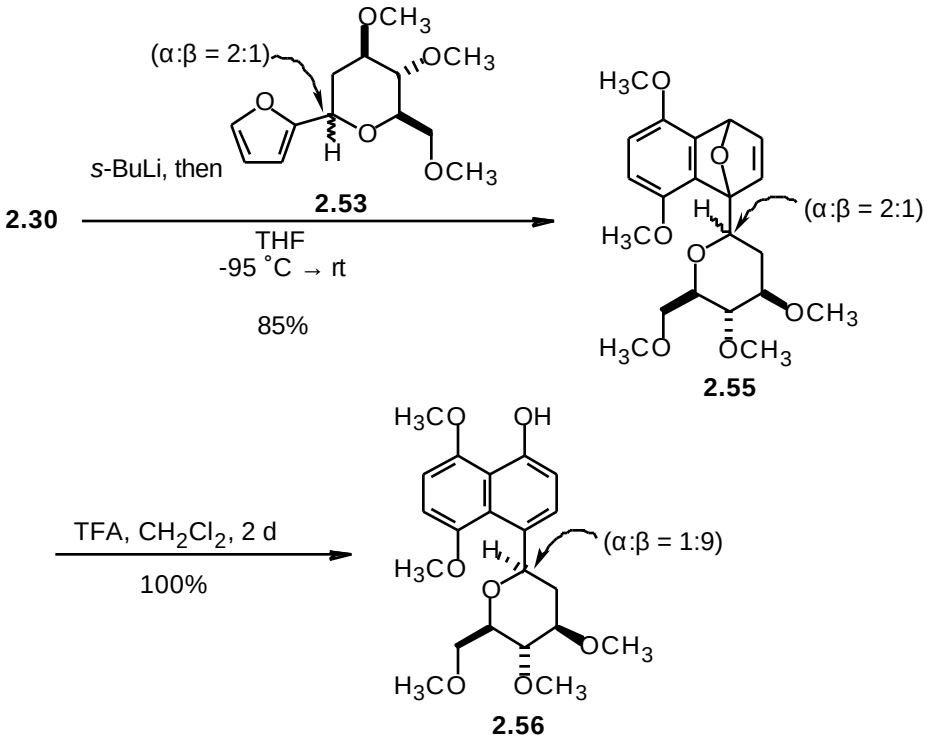



In all previous cases, benzyne cycloadditions with sugar-substituted furans had been conducted using starting materials that were predominately (>9:1) the β-anomers. Up to this point, we had been fortunate in that the methods we had used to prepare the glycosyl-furans had proven to be highly stereoselective. We were curious however, as to whether or not the stereochemistry at the anomeric center of the Group I systems could be altered after introduction onto the aromatic nucleus. This might be useful in the event that setting the stereochemistry of the anomeric carbon of glycosyl furans proceeded in a non-selective fashion.

To probe this question, 2-glycosyl furan **2.53** was prepared as a mixture (α:β = 2:1) of anomers by conducting the same Friedel-Crafts reaction that was used in the conversion of **2.52**→**2.53** (Scheme 2.7) with one minor modification. If the reaction was conducted at -20 ˚C and quenched immediately after addition of the $BF_3{\cdot}OEt_2$, the α-anomer predominated in the products. Cycloaddition of this mixture with the benzyne generated from **2.30** afforded the expected cycloadduct **2.55** as a mixture (α:β = 2:1) of diastereomers in good yield. Prolonged treatment (2 d) of the cycloadduct with trifluoroacetic acid (TFA) in dichloromethane afforded the expected Group I phenol **2.56** as a mixture (α:β = 1:9) of anomers in quantitative yield (Scheme 2.9).

This experiment demonstrated that it is in fact possible to equilibrate the anomeric center after cycloaddition.

**Scheme 2.9**

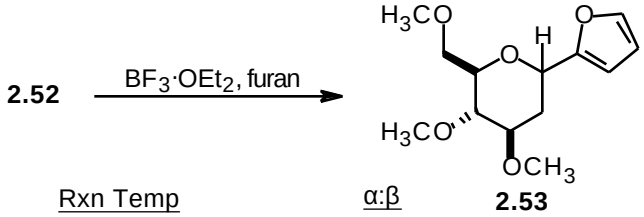



Up to this point, we had prepared glycosidic systems that possessed predominately the β configuration at the anomeric stereocenter. It is of interest that certain known *C*-aryl glycoside antibiotics actually contain sugars that are locked in a less thermodynamically favorable configuration.[86] An example of this is demonstrated in the chemical behavior of the antitumor antibiotic kidamycin (**1.3**) (Chapter 1, Figure 1). Treatment of a solution of kidamycin with TsOH in refluxing $CH_3OH$ results in the formation of a single compound, isokidamycin, wherein the carbohydrate adjacent to the phenolic hydroxyl group has undergone inversion at the anomeric center.[87] Since we were interested in the possibility of being able to prepare naturally occurring *C*-aryl

glycosides, we wondered if our methodology would permit the introduction of sugars in their less thermodynamically stable configuration onto an aromatic nucleus *without* concomitant epimerization to the more thermodynamically stable anomer.

To test this idea, we reexamined the Friedel-Crafts approach we had been using to prepare 2-glycosyl furans such as **2.53**. Based on a simple mechanistic analysis we were able to devise a way to access the kinetic product. It was assumed that the initial adduct had the α-configuration. We based this assumption on the idea that the furan would attack the intermediate oxonium ion *via* a chair-like transition state as is generally accepted for this type of transformation.[88] Presumably, the β-anomer was then being formed by an equilibration process that involved opening and then reclosure of the pyran ring. We wondered then, if we could simply stop the reaction before the aforementioned equilibration could occur. Gratifyingly, if the Friedel-Crafts reaction was performed at -20 ˚C and quenched immediately after addition of the Lewis acid, a complete reversal in selectivity was observed (Equation 2.8). The question that remains is whether we will be able to open a cycloadduct that was prepared using this α-anomer without epimerizing the stereocenter.

**Equation 2.8**

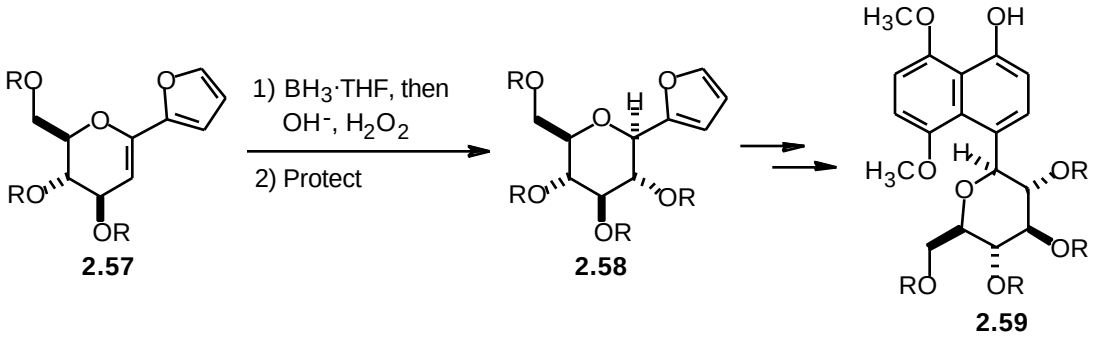



**2.53**

| Rxn Temp | α:β |
|---|---|
| -20 ˚C | >10:1 |
| 0 ˚C to rt | 1:>9 |

The previous experiments have shown that *C*-aryl glycosides of the Group I type can be obtained using the benzyne/furan cycloaddition methodology. The carbohydrate moiety can be appended to the furan in a variety of ways. To this point we have detailed the preparation of Group I systems that possess a 2-deoxy-*C*-aryl glycoside, however it should be noted that glycosides which are not deoxygenated at the 2-position (i.e. **2.59**) should be available by stereo- and regioselective (anti-Markovnikov) hydration of the double bond in systems such as **2.57** (Scheme 2.10).[45,89] After protection of the free hydroxyl group in **2.58**, we would proceed with the cycloaddition strategy previously discussed. If hydration of the glycal in the presence of the furan nucleus turns out to be problematic, it should be possible to perform the cycloaddition/ring opening sequence prior to hydroboration and oxidation. Additionally, it should be mentioned that compounds of the general structure **2.58** have been prepared by both Friedel Crafts reactions as well as by the addition of metalated furans to carbohydrate-derived lactones.

**Scheme 2.10**



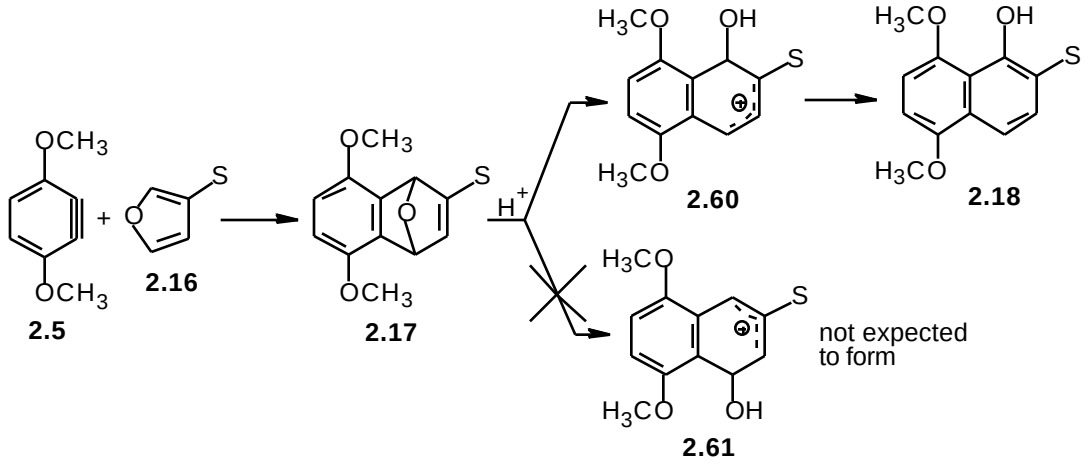

**2.57** **2.58** **2.59**

### 2.2.4 Preparation of Group II and Group IV *C*-Aryl Glycosides

#### *2.2.4.1 Model System*

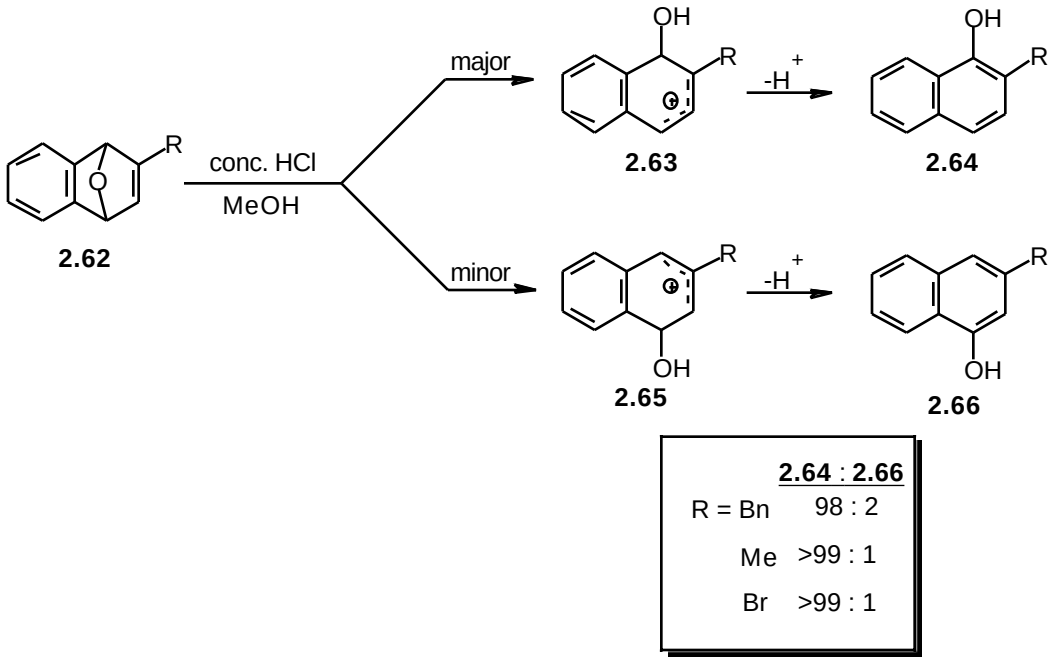
We envisioned that it might be possible to access the Group II *C*-glycosides by a similar cycloaddition between a benzyne intermediate **2.5** and a 3-glycosyl furan of the general type **2.16**. The cycloadduct **2.17** obtained from this reaction was expected to open to give an allylic carbocation upon treatment with acid. It was expected based on a rate determining heterolysis of one of the carbon-oxygen bonds of the bridging ether, that the more stable carbocation would be produced more rapidly. We expected that the doubly secondary allylic (also benzylic) cation **2.61** would be formed more slowly than the secondary/tertiary allylic (also benzylic) cation **2.60**. The latter carbocation would give after proton loss, a Group II 2-substituted *C*-aryl glycoside of general structure **2.18** (Scheme 2.11).

**Scheme 2.11**




As precedent for this type of chemistry, it was relevant that Batt and co-workers had demonstrated that acid-catalyzed ring opening of a series of oxabicyclic compounds **2.62** (R = halogen, alkyl, Bn) gave almost exclusively the corresponding 2-substituted system **2.64** rather than the 3-substituted one **2.66** (Scheme 2.12).[90] The authors argued that the selectivity observed arises from more rapid formation of the allylic carbocation **2.63** that receives stabilization from the electron donating R-group.

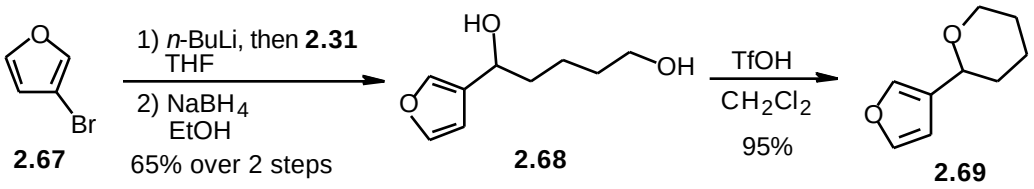
**Scheme 2.12**




| | 2.64 : 2.66 |
|---|---|
| R = Bn | 98 : 2 |
| Me | >99 : 1 |
| Br | >99 : 1 |

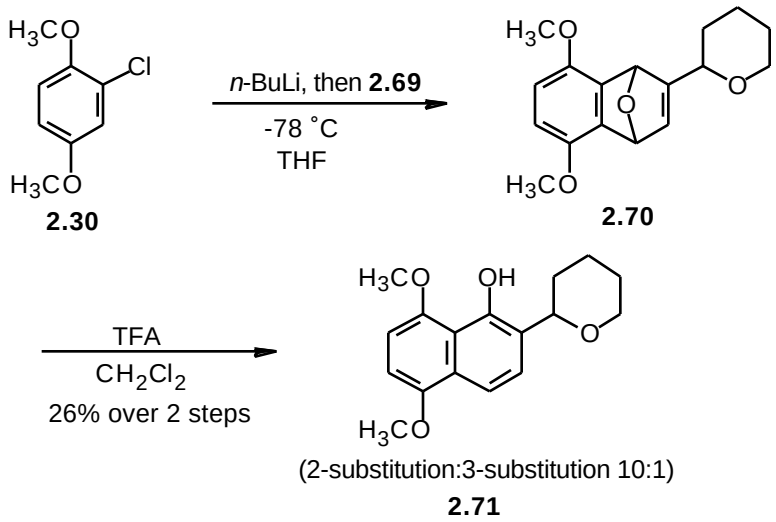
To investigate whether the aforementioned chemistry would prove useful for the synthesis of Group II *C*-aryl glycosides, we prepared 3-tetrahydropyranyl furan **2.69**[91] by the sequence shown in Scheme 2.13. 3-Lithiofuran, generated by halogen-metal exchange of commercially available 3-bromofuran (**2.67**) with *n*-BuLi, was added to δ-valerolactone (**2.41**) to provide an intermediate hydroxy ketone that was subsequently reduced with $NaBH_4$ to give diol **2.68**. Evidence that the product of the reaction of 3-furyllithium to δ-valerolactone existed as the open-chain form was obtained from the IR spectrum (strong absorption at 1665 $cm^{-1}$) as well as the 1H NMR (no "anomeric" proton resonances). Cyclization of **2.68** using TfOH afforded the desired furan **2.69** in 95% yield.

**Scheme 2.13**




We were pleased to find that cycloaddition of **2.69** and the benzyne generated from **2.30** smoothly afforded oxabicyclic compound **2.70**. Acid-catalyzed ring opening of **2.700** gave the 2-substituted naphthol **2.71** as the major product (Scheme 2.14).[92] A small amount (2-substituted:3-substituted = 10:1, as determined by integration of the phenolic -OH groups in the $^1$H-NMR) of the undesired 3-substituted regioisomer was also formed. This small impurity could be removed by careful column chromatography to deliver pure **2.71** in 26% yield (unoptimized) from **2.69**. It should be noted that we made no attempts to optimize the transformations depicted in Scheme 2.14 rather, we were simply trying to establish proof of concept.

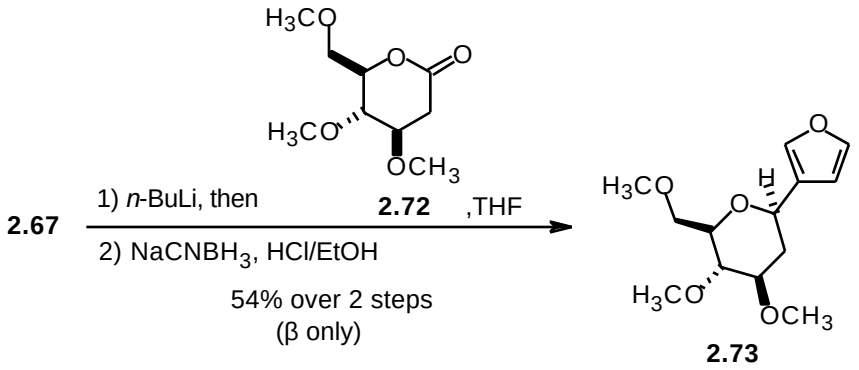
**Scheme 2.14**



### *2.2.4.2 Group II C-Aryl Glycosides*

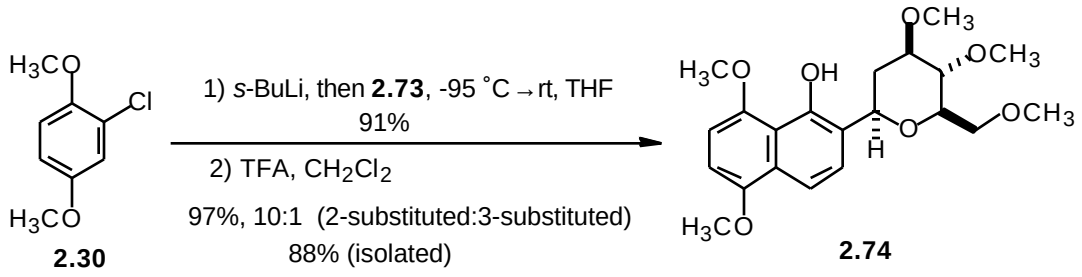
With the results of the successful model cycloaddition in hand, we moved forward with benzyne cycloadditions with carbohydrate-substituted furans. The requisite 3-glycosyl furan **2.73** was prepared by sequential addition of 3-lithiofuran to the known sugar lactone **2.72**[93] followed by reduction of the resultant anomeric mixture of lactols to give exclusively the β-anomer (Scheme 2.15).[16,94]

**Scheme 2.15**




Cycloaddition of **2.73** with the benzyne generated from **2.73** gave the desired adduct in good yield. Acid-catalyzed ring opening of this adduct with TFA gave the expected phenol **2.74** contaminated with a small amount of the undesired 3-substituted naphthol (2-substituted:3-substituted = 10:1) (Scheme 2.16). Careful column chromatography delivered the regioisomerically and diastereomerically pure **2.74**, a Group II *C*-aryl glycoside, in 87% yield.

**Scheme 2.16**

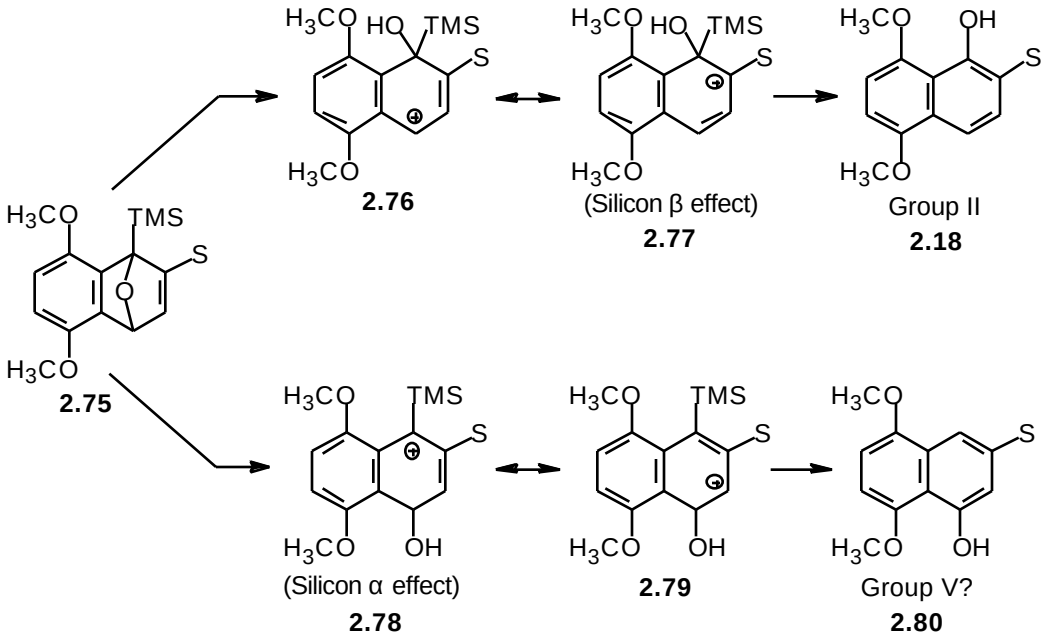



In the previous examples, acid-catalyzed ring opening of both tetrahydropyranyl- and trimethoxy glucal-derived cycloadducts gave small amounts of the undesired 3-substituted regioisomer as a by-product. We wondered if it might be possible to alter the electronics of the systems to prevent the formation of this product.

It has been questioned in the literature whether a carbocation is stabilized or destabilized by α-silyl substitution,[95] and conflicting reports have appeared regarding the stabilizing ability of silicon to α-cationic centers.[96] The most current reports seemed to indicate that indeed silicon was significantly less stabilizing to α-positive charge when compared to carbon, but that both carbon and silicon afforded more stabilization than a hydrogen. Despite these reports, we thought it would be worthwhile to investigate the ability of silicon to stabilize incipient positive charge in our systems. Our idea involved preparing an oxabicyclic compound such as **2.75** that possessed a TMS group at the bridgehead position and adjacent to the sugar. Treatment of this cycloadduct with acid could then conceivably generate two resonance stabilized carbocations **2.76**/**2.77** or **2.78**/**2.79**. Direct loss of the -TMS group, by nucleophilic attack on silicon, from **2.76/2.77** would afford the Group II system **2.18**. Alternatively, proton loss from **2.78/2.79** followed by *in situ* protiodesilylation would afford the 3-

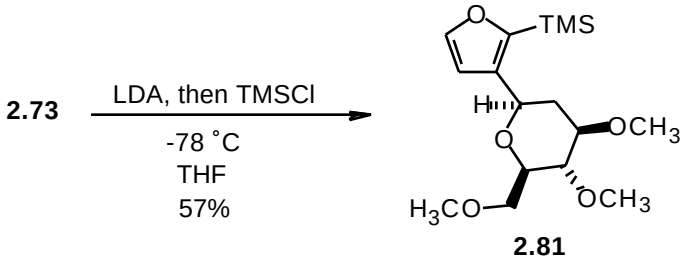
substituted naphthol **2.80** (Scheme 2.17). If the latter occurred, it would represent an opportunity to prepare non-natural *C*-aryl glycoside analogs.

**Scheme 2.17**



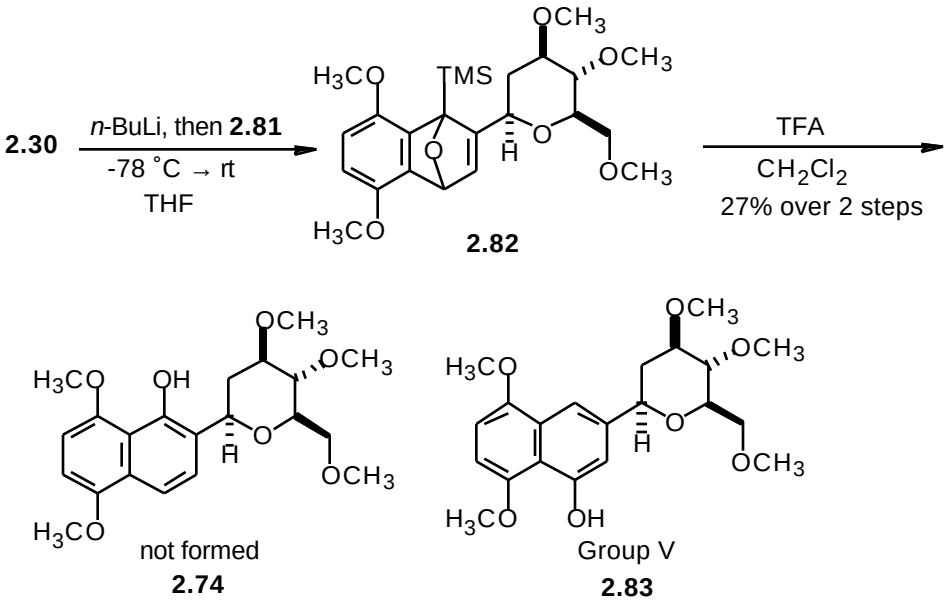

To test this theory, furan **2.73** was treated with LDA followed by TMSCl to give furan **2.81** (Equation 2.9). It is interesting to note the complete regioselectivity that is seen in the lithiation and electrophilic trapping step. The basic phenomenon of groups of even mild coordinating ability to direct deprotonations proximally in these furan systems was seen repeatedly.

**Equation 2.9**




Cycloaddition of **2.81** under our standard benzyne conditions gave the expected adduct **2.82**. When **2.82** was treated with TFA, the 3-substituted naphthol **2.83** was formed exclusively (Scheme 2.18).

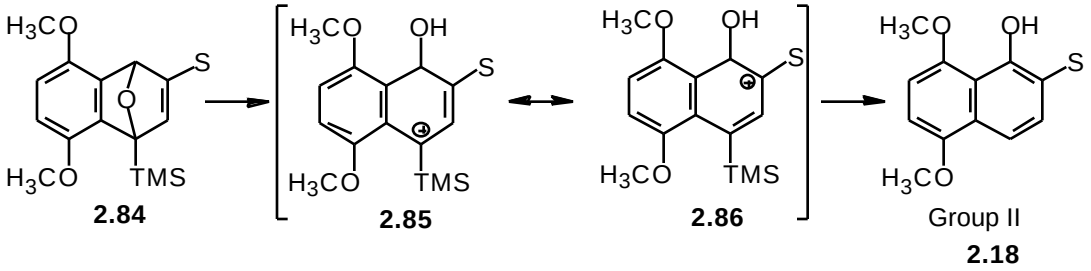
**Scheme 2.18**




Apparently in this system, a bridgehead -TMS group is stabilizing to incipient positive charge relative to hydrogen. In fact, it is interesting to note that this group's ability to stabilize positive charge seems to outweigh the allylic stabilization afforded by the sugar. Presumably if we could prepare and open a system in which the bridgehead

TMS group was distal to the sugar as in **2.84**, we would expect to see high regioselectivity for the 2-substituted isomer. In this system ring opening would be expected to generate an allylic cation **2.85**/**2.86** that is stabilized by both silicon and the sugar. After proton loss and protiodesilylation the Group II system **2.18** should be produced (Scheme 2.19).

**Scheme 2.19**



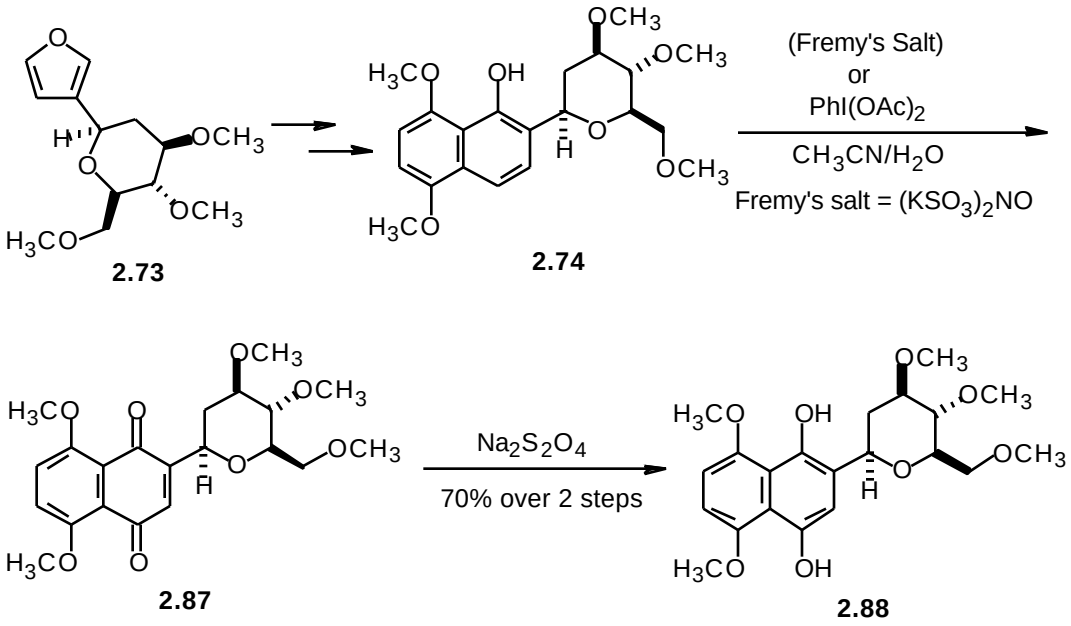

In any event, despite the fact that the results summarized in Scheme 26 were not what was expected, they still represent potentially useful chemistry. While no naturally occurring *C*-aryl glycoside antibiotics reported to date contain a 3-substituted naphthol system, it is nevertheless useful to be able to prepare analogs of this type. The ability to generate and test the activity of unnatural analogs of naturally occurring Group I or Group II *C*-aryl glycoside antibiotics could provide unique information regarding SAR's in some of these biologically important systems. Also, the ability to synthesize *C*-aryl glycosides that contain multiple carbohydrates at various positions could be useful in the context of the preparation of glycoepitopes or glycoconjugates.[97] With the anticipation that this new 3-substituted system may someday prove to be useful in *C*-aryl glycoside synthesis, we have adopted the name Group V to describe its members (Scheme 2.18).

### *2.2.4.3 Group IV C-Aryl Glycosides*

Next, we turned our attention to the preparation of the Group IV "hybrid" class of *C*-glycoside antibiotics (Figure 1). We believed that members of the Group IV system would be accessible from previously prepared Group II systems by way of a simple oxidation/reduction protocol. The oxidation of free phenols to the corresponding *p*-quinones is readily achieved using a variety of reagents such as Fremy's salt,[98] *bis*(trifluoroacetoxy)iodobenzene,[99] and $Tl(NO_3)_3 \cdot 3H_2O$.[100] The facile reduction of *p*-quinones to the corresponding hydroquinones can also be accomplished with a variety of different reagents including sodium dithionite ($Na_2S_2O_4$), $Zn/H_2SO_4$,[101] and $H_2$/Pd/C.[102]

Initially, we investigated the oxidation of **2.74** using the potassium nitrosodisulfonate radical known as Fremy's salt[103] to prepare quinone **2.87**. The yields in this reaction tended to be variable, possibly due to the low stability of Fremy's salt and the limited pH range at which it can be used.[98] Fortunately, it was found that (diacetoxyiodo)benzene in aqueous acetonitrile oxidized **2.74** to the quinone **2.87** in consistently good yield. Rather than purify this quinone, it was operationally simpler to reduce it to the desired hydroquinone **2.88** by employing a biphasic mixture of aqueous $Na_2S_2O_4$ and $CH_2Cl_2$ in the workup (Scheme 2.20).

**Scheme 2.20**



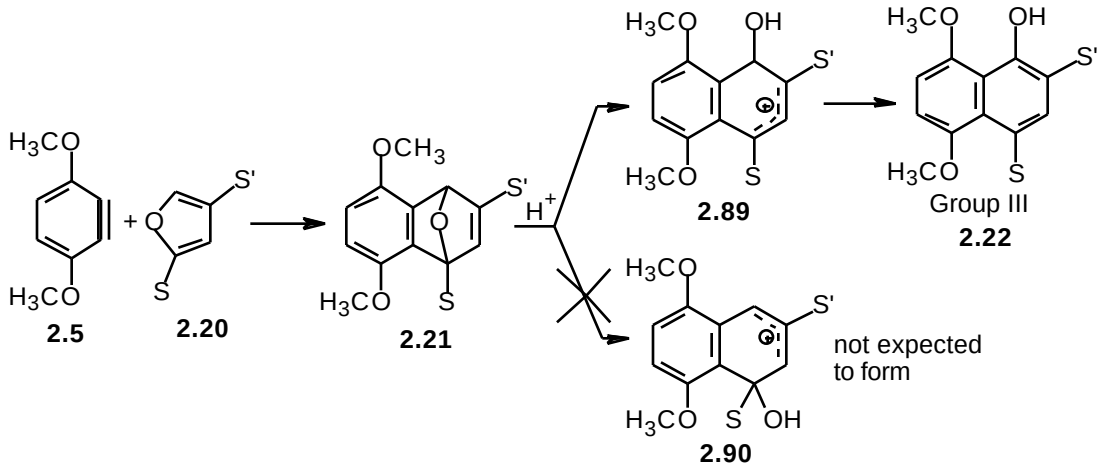

## 2.2.5 Preparation of Group III *C*-Aryl Glycosides

### *2.2.5.1 Model System*

The *bis*-*C*-aryl glycoside antibiotics known as the pluramycins are current synthetic targets in our group (Chapter 1, Figure 1).[104] Each of these belongs to the Group III class of *C*-aryl glycoside antibiotics. We envisioned several tactics for introducing two sugars onto an aromatic core. The first would involve a cycloaddition with a benzyne and a 2-glycosyl-substituted furan followed by acid-catalyzed ring opening to give the corresponding 4-substituted or Group I *C*-aryl glycoside. The second sugar could then be appended using the well known $O \rightarrow C$ glycoside rearrangement, discussed in Chapter 1, developed by Suzuki and co-workers.[105] A second possibility would involve benzyne cycloadditions with 2,4-diglycosyl-substituted furans (Scheme 2.21). In analogy to the systems we had investigated earlier, we

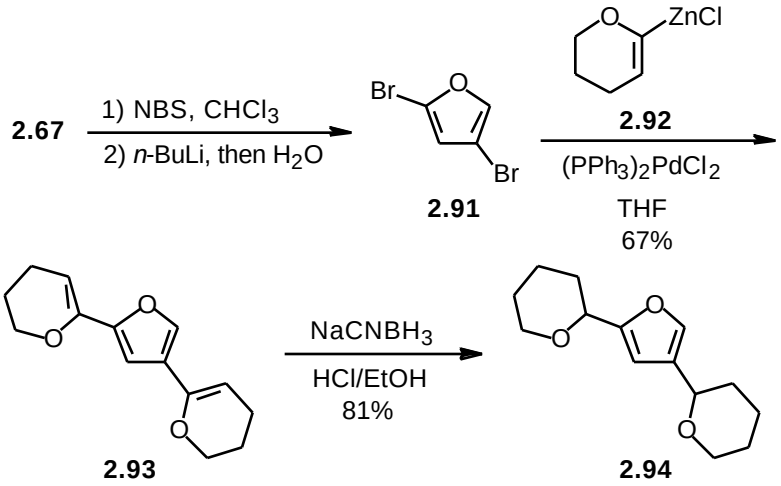
expected that a 2,4-diglycosyl furan of the general type **2.20** would undergo a cycloaddition with the benzyne **2.5**. We believed, based on favorable electronic interactions, that allylic cation **2.89** would be formed more rapidly than **2.90**. If this were the case, then after proton loss the Group III *bis*-*C*-aryl glycoside **2.22** system should be obtained.

**Scheme 2.21**



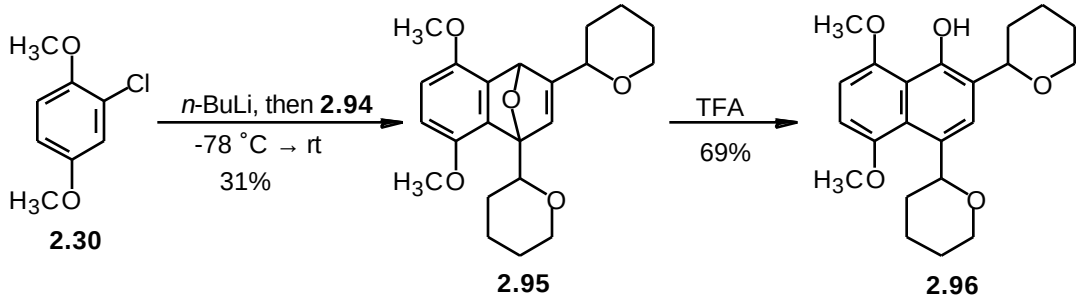

To test the viability of this strategy, we prepared a simple 2,4-*bis*-tetrahydropyranyl furan **2.94** as a model substrate. 3-Bromofuran (**2.67**) was dibrominated at the 2- and 5-positions to give the known 2,3,5-tribromofuran.[106] Selective halogen-metal exchange at the 2-position of this furan with *n*-BuLi followed by protonation gave 2,4-dibromofuran (**2.91**) contaminated with varying amounts of the 2,3-isomer.[106] Coupling of **2.91** with dihydropyranylzinc chloride **2.92**, prepared by sequential treatment of dihydropyran with *t*-BuLi and anhydrous $ZnCl_2$, in the presence of *bis*-triphenylphosphinepalladium dichloride gave furan **2.93**. This adduct was reduced to the furan **2.94** as a mixture (1:1) of inseparable diastereomers upon treatment with $NaBH_3CN$ in ethanolic HCl (Scheme 2.22).

**Scheme 2.22**




We were pleased to find that cycloaddition of **2.94** with the benzyne generated from **2.30** gave the desired cycloadduct **2.95**. Acid-catalyzed ring opening of **2.95** gave a mixture (1:1) of separable diastereomeric phenols **2.96** (Scheme 2.23).

**Scheme 2.23**




One of the diastereomers was isolated cleanly by flash chromatography, but upon standing in $CDCl_3$, this compound equilibrated to a nearly equal mixture of diastereomers. The ability to equilibrate systems like this when the carbohydrate is a conformationally biased pyranose was noted previously, and may prove synthetically useful if a mixture of anomers is obtained in the reduction step.

### *2.2.5.2 Group III C-Aryl Glycosides*

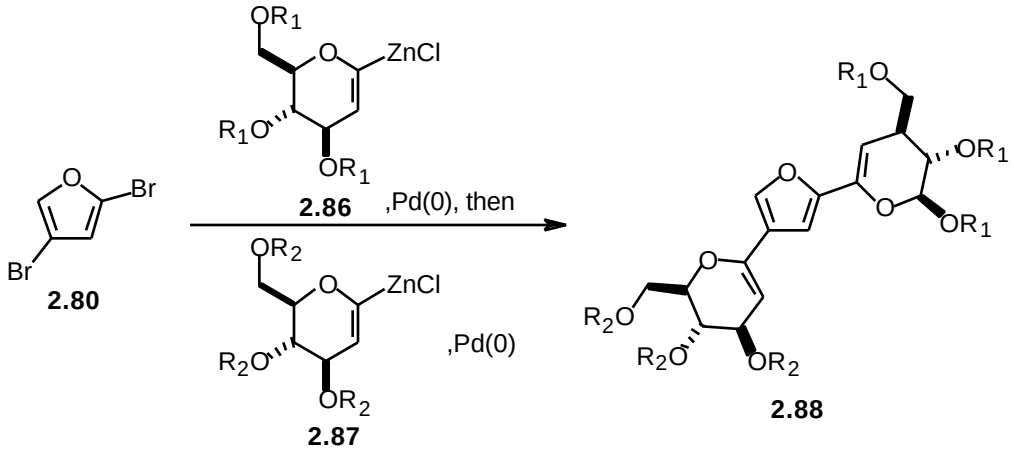
With the success of the tetrahydropyran-based model, emphasis was put on preparing a more complex Group III system containing carbohydrates. We were initially attracted to two different strategies for preparing the complex 2,4-diglycosyl furan that would be required to complete the Group III system. It is important to note that all of the known naturally occurring *bis*-*C*-aryl glycoside antibiotics contain *different* sugars at the 2- and 4-positions. For this reason, we needed to be able to prepare a 2,4-diglycosyl furan in which the sugar at each position was different.

It was known that 2,4-dihalogenated furans such as **2.91** undergo regioselective Pd-catalyzed couplings at the 2-position first. This strategy was exploited in order to prepare regioselectively a variety of 5-(bromoaryl)-substituted uracils for potential antiviral applications.[107] We believed it might be possible to sequentially regioselectively couple two different metalated glucals with a 2,4-dihalofuran in a regioselective manner (Equation 2.10). We did, however, anticipate several problems with this basic idea. First, despite the fact that 2,4-dibromofuran (**2.91**) was a known compound,[106] we had encountered some difficulties preparing it. In our hands, the aforementioned procedure always provided the desired furan contaminated with varying amounts of the undesired regioisomeric 2,3-dibromofuran. The authors made no explicit mention of 2,3-dibromofuran being formed upon protonation of the anion derived from 2,3,5-tribromofuran. It was exceedingly difficult to remove the impurity at this stage or at a later time in the route.

Additionally, we were a bit wary of the conditions that would be required to introduce the -ZnCl moiety onto the glycal. Typically the glycal would be deprotonated using *t*-BuLi, and the resulting lithio-anion would be treated with anhydrous $ZnCl_2$.

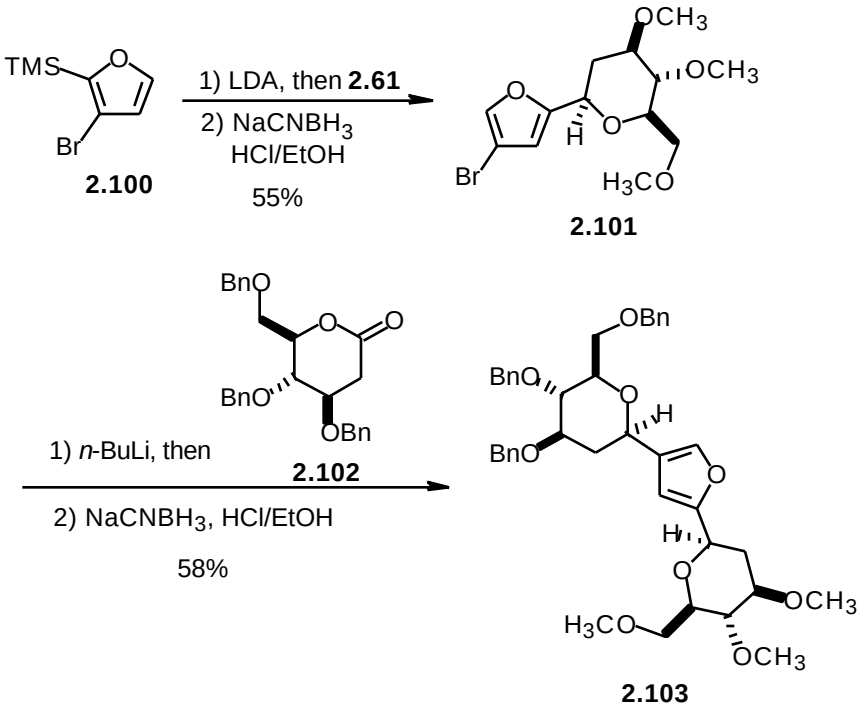
Only highly robust hydroxyl protecting group like triisopropylsilyl (TIPS) can be utilized in these deprotonations. Also, we were unsure whether this chemistry would work when we attempted to prepare metalated glycals of aminosugars, potential intermediates for the total synthesis of kidamycin and related pluramycin antibiotics. For the aforementioned reasons, we decided to investigate an alternate strategy for the preparation of 2,4-diglycosyl furans.

**Equation 2.10**




The second strategy we considered involved sequential metalation of **2.100** followed by trapping with two different sugar lactones and eventual cleavage of the -TMS blocking group. With this in mind, the known bromofuran **2.100**[108] was deprotonated using LDA, and the resultant anion was treated with sugar lactone **2.72**. The lactols thus obtained were reduced with $NaBH_3CN$ in ethanolic HCl. After reduction was complete, the reaction mixture was simply treated with excess HCl and heated to induce protiodesilylation to give **2.101**. Addition of the known lactone **2.102**[109] to a solution of the anion generated by halogen-metal exchange of **2.101** with *n*-BuLi gave a second lactol that was reduced with $NaBH_3CN$ as before to give *bis*-sugar-substituted furan **2.103** (Scheme 2.24).

**Scheme 2.24**

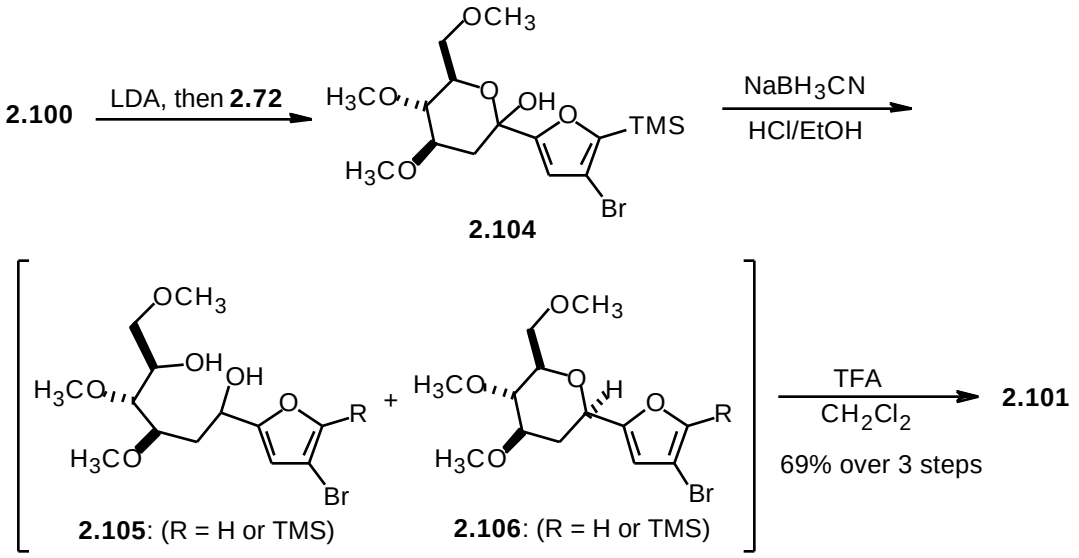



Due to the fact that the yield in the preparation of **2.103** was generally low (<60%), we decided to investigate this sequence to see if it might be improved. A careful examination of the reaction mixture after the furyllithium addition/lactol reduction sequence revealed that diol **2.105** was being formed in varying amounts depending on the reaction temperature. Presumably, this diol resulted from reduction of the hydroxyketone that was in equilibrium with the lactol. It is not surprising that some of this open form is present at equilibrium because of conjugation of the ketone with the aromatic furan. Apparently, this diol underwent cyclization to the desired furan **2.101** only very slowly, if at all under the reaction conditions. Additionally, it was found that the protiodesilylation step could be quite sluggish at times, requiring extended periods of heating at 50 ˚C and addition of a large excess of ethanolic HCl. It was suspected

that this prolonged acid treatment was at least partially responsible for the low yields observed.

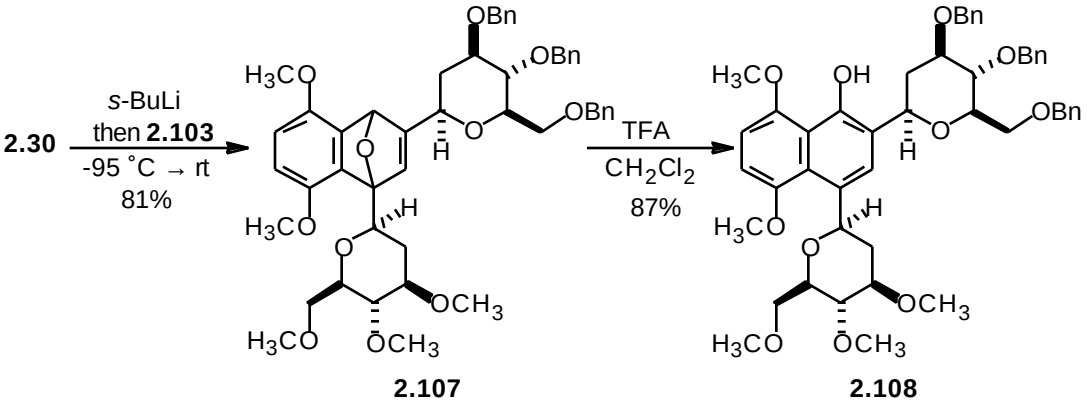
Both of these problems were overcome by stopping the reaction immediately after all **2.104** was consumed (as evidenced by TLC analysis). After a simple aqueous workup, the crude mixture was redissolved in $CH_2Cl_2$ and cooled to 0 ˚C, whereupon TFA was added. This resulted in cyclization of **2.105** and desilylation of any **2.106** present to give **2.101** 69% yield (Scheme 1.25).

**Scheme 1.25**




Cycloaddition of the benzyne generated from **2.30** with diglycosyl furan **2.103** afforded the expected oxabicyclic intermediate **2.107**. This mixture of diastereomers was treated with TFA in $CH_2Cl_2$ to give **2.108**, a Group III *C*-aryl glycoside, in good overall yield as a single regio- and diastereomer (Scheme 2.26).

**Scheme 2.26**



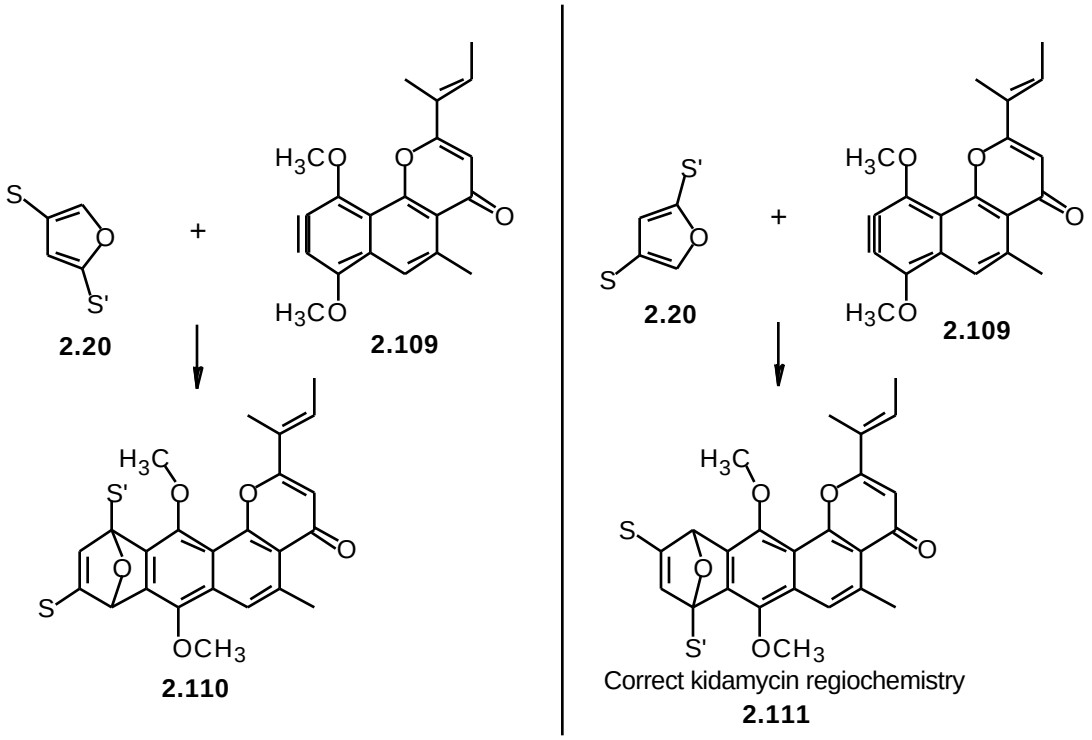

### 2.2.6 Control of Global Regioselectivity: The Problem

We have developed a general methodology that allows for the construction of all four *C*-aryl glycoside substitution patterns (Figure 2.1). The furan-benzyne cycloaddition/ring opening methodology provides the four systems in a highly regioselective fashion with respect to the sugar moiety(ies) and the phenolic -OH group(s). Until recently, we had not attempted to address the very important problem of global regioselectivity with respect to the rest of the molecule. It should be noted that all of the naturally occurring *C*-aryl glycoside antibiotics are unsymmetrically substituted.

In order to illustrate the potential problems associated with controlling global regioselectivity, a hypothetical cycloaddition approach for the preparation of the *C*-aryl glycoside kidamycin (**1.3**) is in Figure 2.3. If it were possible to generate a benzyne **2.109** and allow it to react with a diglycosyl furan, two possible products **2.110** or **2.111** could be obtained. In this example, it seems unlikely that one regioisomer would predominate over the other because there is presumably little difference between the orbital coefficients of either the benzyne or the diglycosyl furan. Additionally, it seems

unlikely that either side of the benzyne is more crowded from a steric standpoint. In order for our methodology to be viable in the context of total synthesis, we needed to control predictably the positions of the glycosidic residue(s) and the phenol relative to the *rest of the molecule*.

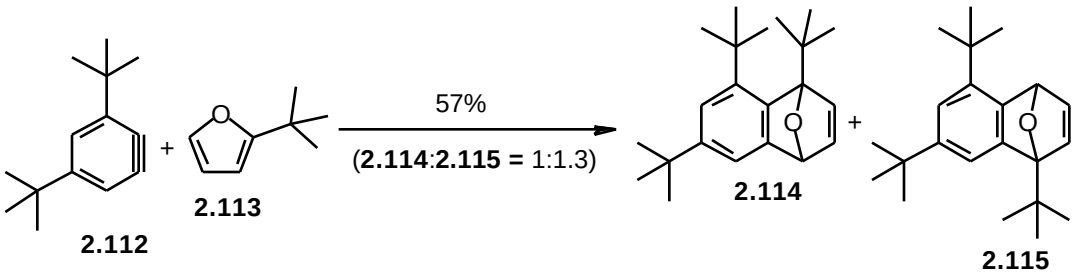
**Figure 2.3**




Several reports have appeared in the literature wherein various 3-substituted benzynes were allowed to react with different 2-substituted furans in an attempt to establish whether or not any regioselectivity would be observed. Franck and co-workers examined cycloadditions between 3,5-di-*tert*-butylbenzyne (**2.112**) and 2-*tert*-butylfuran (**2.113**), 2-benzylfuran, and 2,3-di-*tert*-butyl furan.[110,111] In the case of 2-*tert*-butylfuran (**2.113**), two regioisomeric products were obtained in 57% yield in which the less sterically congested adduct predominated only slightly (**2.115**:**2.114** = 1.3:1)

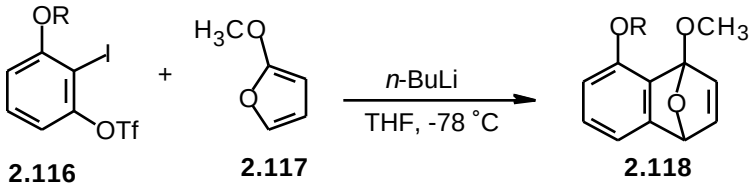
(Equation 2.11). In any event, the regioselectivity was rather unimpressive in all cases. These experiments would lead one to believe that steric effects have little influence on the regioselectivity in benzyne/furan cycloadditions.

**Equation 2.11**




It is noteworthy that significant success has been achieved with respect to regioselective benzyne cycloadditions by altering the electronics of the two components, particularly the benzyne intermediate. Suzuki has utilized highly regioselective cycloadditions between substituted 3-alkoxybenzynes and 2-alkoxyfurans.[77] A simple example of this is illustrated in Equation 2.12. Treatment of a solution of *o*-iodotriflate **2.116** and 2-methoxyfuran (**2.117**) in THF with *n*-BuLi at -78 ˚C followed by warming to 0 ˚C to induce benzyne formation, delivered the cycloadduct **2.118** as a single regioisomer. This approach has been successfully applied to the synthesis of several naturally occurring *C*-aryl glycosides.[112]

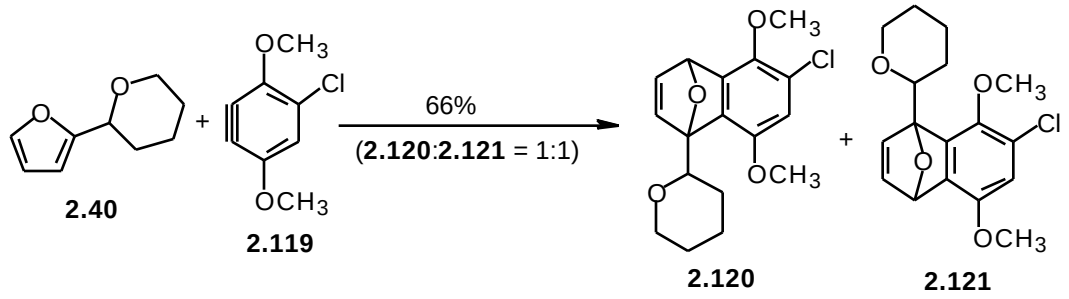
**Equation 2.12**




Based on experiments conducted in our own labs we were concerned about the possibility of obtaining regioisomers in the event that we attempted to apply our

methodology to the preparation of systems that were not symmetrically substituted. The example shown in Equation 2.13 serves to illustrate this. When we performed a cycloaddition between **2.40** and the benzyne **2.119** that was generated from 2,5- or 2,6-dichloro-*p*-dimethoxybenzene, we obtained a mixture (ca. 1:1) of regioisomeric cycloadducts **2.120** and **2.121**.

**Equation 2.13**

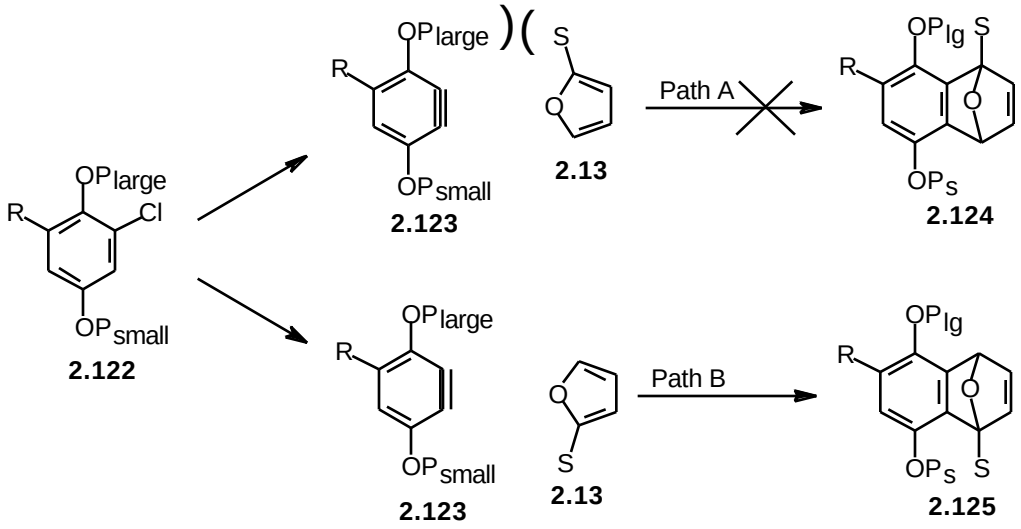



**2.40** **2.119** **2.120** **2.121**

### *2.2.6.1 Sterics to Control Regiochemistry*

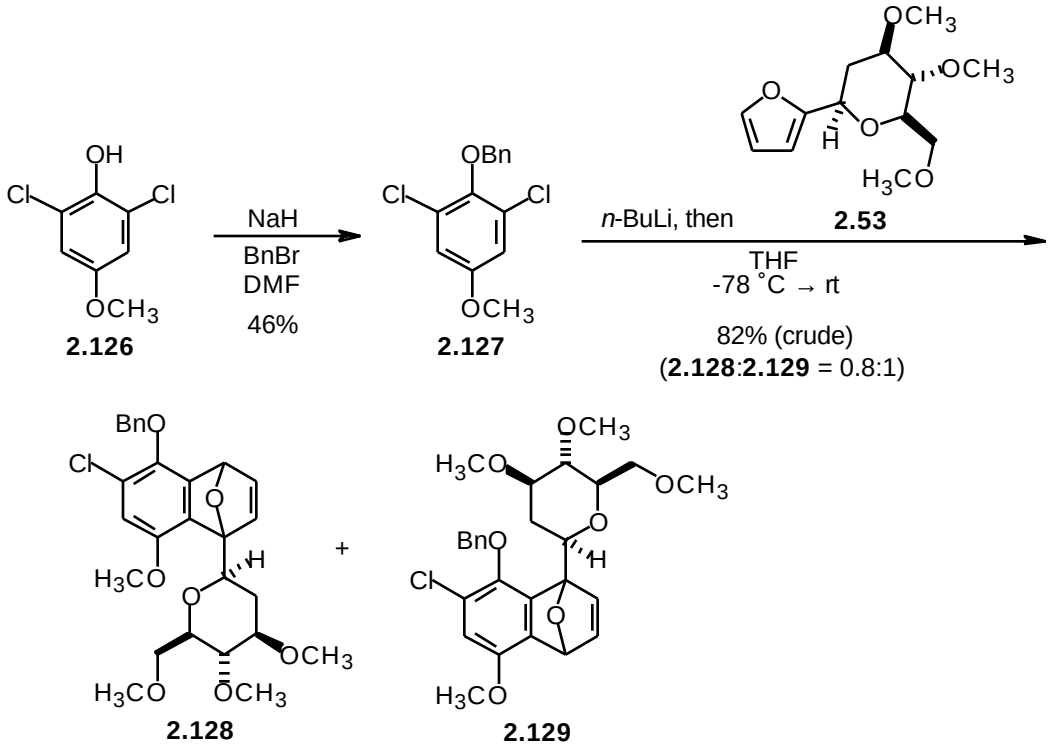
The first method we considered as a potential solution to the problem of global regioselectivity involved differentially protecting a benzyne precursor with a large group and a small one to give **2.122**. We thought it might be possible that the large group in the benzyne **2.123** would hinder the approach of **2.13**, and hence raise the transition state energy for Path A, which would be expected to provide higher levels of regioselectivity compared to cycloadditions with benzynes like **2.119** (Scheme 2.27). We were wary of this approach, however, due to the aforementioned fact that there are a few examples in the literature of poor selectivities in intermolecular benzyne cycloadditions even in congested systems.[110,111]

**Scheme 2.27**




To test the viability of using sterics to control regiochemistry in our cycloadditions, we prepared the differentially protected benzyne precursor **2.122** by reacting 2,6-dichloro-4-methoxyphenol (**2.126**) with sodium hydride and benzyl bromide in DMF. Cycloaddition of the benzyne derived from **2.127** and glycosyl furan **2.53** gave the expected cycloadducts **2.128** and **2.129** (Scheme 2.28). $^{1}$H-NMR analysis of the crude reaction after workup showed a mixture of regio- and diastereomers. It was determined by integration of the bridgehead protons in the $^{1}$H NMR, that the ratio of **2.128** to **2.129** was 0.8:1. That the minor component was the less sterically congested one **2.128** was verified by comparison of a $^{1}$H NMR of the crude reaction mixture of **2.128** and **2.129** with an authentic sample of **2.128**, prepared using chemistry that was recently discovered in our group (vide infra).

**Scheme 2.28**




### *2.2.6.2 Tether to Control Regiochemistry*

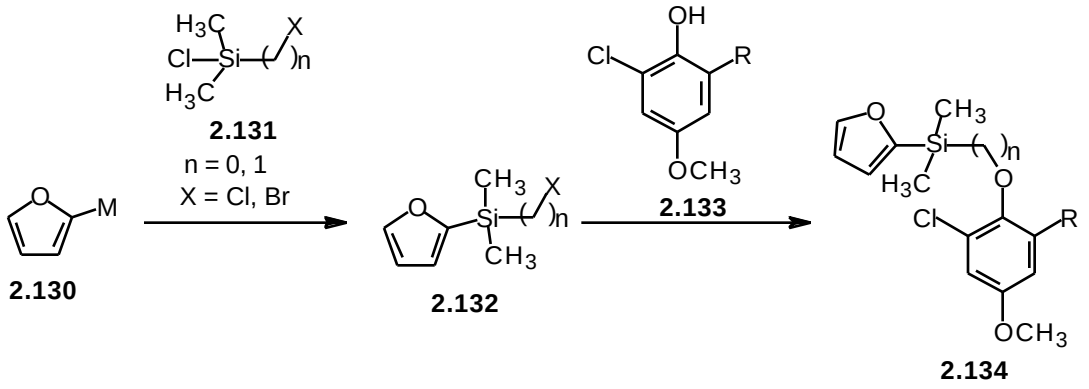
In light of the rather disappointing result obtained above, we focused on an alternative approach to control regiochemistry in benzyne-glycosyl furan cycloadditions. We noted that there were many literature examples of intermolecular Diels-Alder reactions that had been rendered intramolecular *via* the use of a temporary tether.[113] These intramolecular reactions were typically characterized by being highly regio- and stereoselective.

There existed however, only a few examples of intramolecular benzyne/furan cycloadditions.[114] Rather, in all of the intramolecular benzyne/furan cycloadditions, the tether used to hold the reactants in close proximity was present in the final molecule.

Quayle demonstrated that intramolecular benzyne cycloadditions are feasible for constructing polycyclic indole systems. In this case, an amide linkage was present in the tether and the cycloadduct, but it was not cleaved.[115] In the first report of an intramolecular benzyne cycloaddition.[114a] Wege did allude to the idea of using a cleavable tether, but to date this has not been reduced to practice as far as we know. We hoped that the use of a cleavable tether in our cycloadditions would provide a novel way to control global regiochemistry.

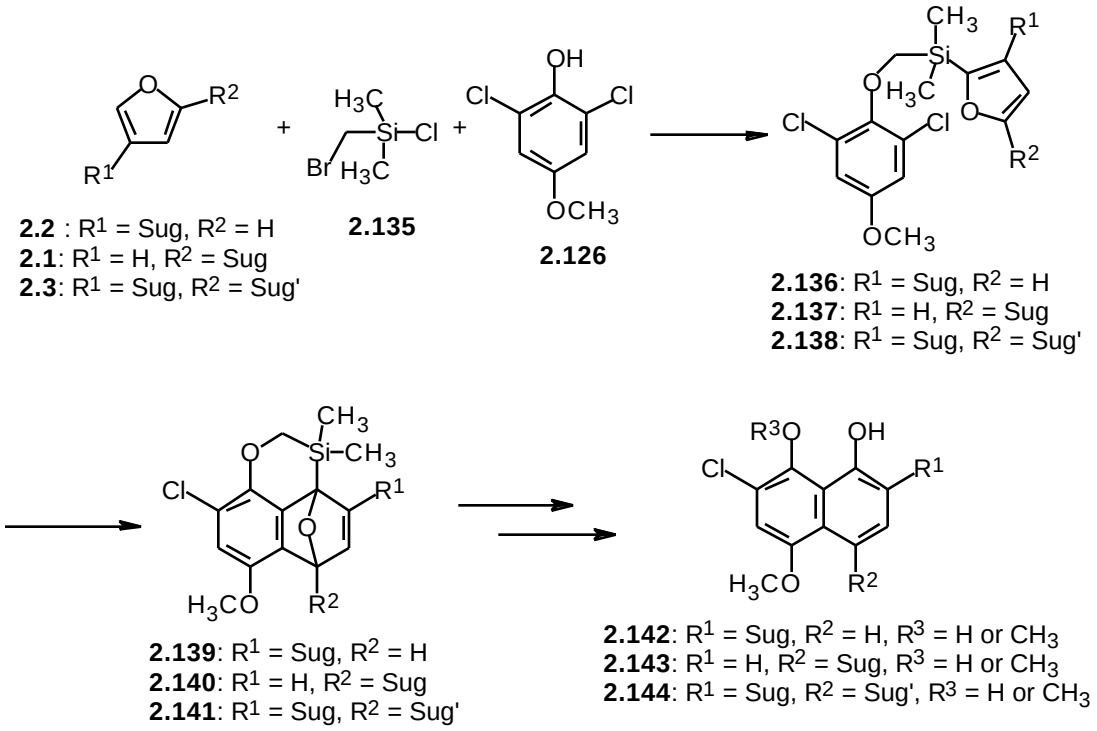
The basic idea for using a disposable tether is summarized below. First we would require a doubly electrophilic tether that could be reacted sequentially with a metalated furan such as **2.130** to give **2.132** and then with a benzyne precursor such as **2.133** to give **2.134**. For the tether **2.131**, we initially considered either a dichlorodimethyl silane (X = Cl, n = 0) or a bromomethylsilane (X = Br, n = 1). We eventually settled on the latter for several reasons. First, we anticipated that a dichlorodimethylsilane would potentially undergo over alkylation when treated with a metalated furan. Second, it was anticipated that isolation/purification of the intermediate chlorosilane would be difficult. Finally, we were unsure whether formation of a five-membered (in the tether) ring during the cycloaddition would be less favorable (because of strain) than forming the corresponding six-membered ring. As for the benzyne precursor **2.133**, we wanted to choose an R group that would function as both a marker that regioselectivity had occurred and also a useful handle for further synthetic transformations (Scheme 2.29).

**Scheme 2.29**



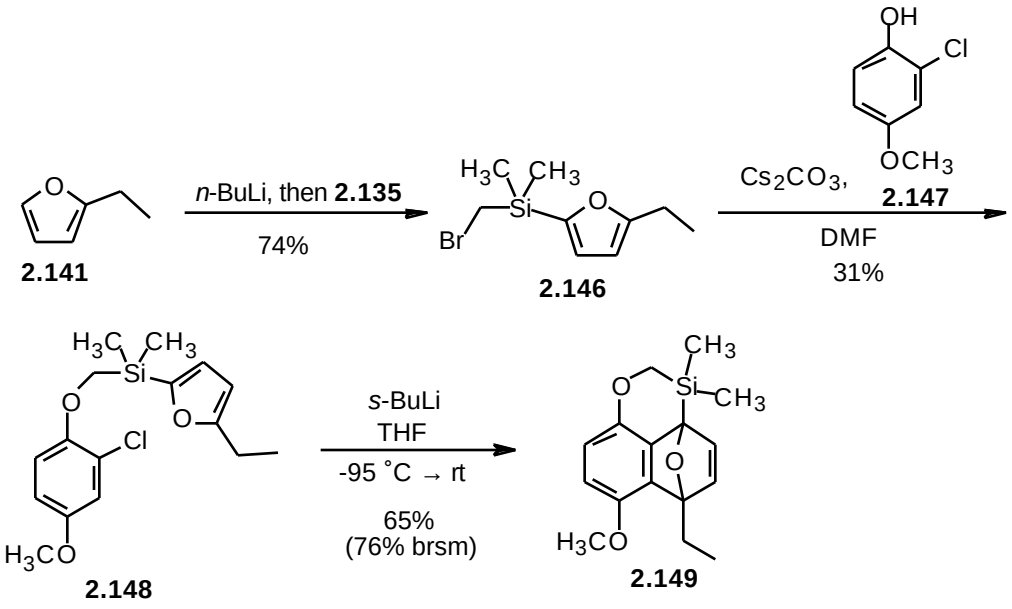

With the basic ideas listed above, we formulated the following plan: An appropriately substituted glycosyl furan **2.1**, **2.2**, or **2.3** would be selectively mono-alkylated with (bromomethyl)chlorodimethylsilane (**2.121**) to give a (bromomethylsilane) that would then be used to alkylate a dichloromethoxyphenol such as **2.126**. The resulting substrates **2.136**-**2.138** should then undergo intramolecular furan-benzyne cycloadditions under our standard conditions to afford bridged tetracycles **2.139**-**2.141**. After cleavage of the tether with a suitable fluoride reagent, like tetrabutylammonium fluoride (TBAF), the adduct would undergo acid-catalyzed ring opening to afford the desired isomerically pure naphthols **2.142**-**2.144** (Scheme 2.30).

**Scheme 2.30**



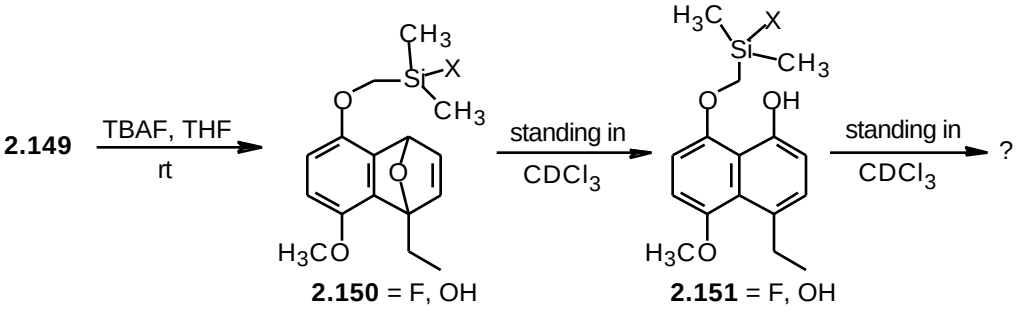

First we examined a simple model system in which commercially available 2-ethylfuran (**2.145**) and 2-chloro-4-methoxyphenol (**2.147**) were utilized. Treatment of **2.145** with *n*-BuLi followed by addition of (bromomethyl)chlorodimethylsilane (**2.135**) gave an intermediate bromomethylsilane that was used to *O*-alkylate **2.147** to give **2.144**. A solution of **2.144** in THF at -95 ˚C was treated with *s*-BuLi and then allowed to slowly warm to room temperature. Benzyne generation and intramolecular cycloaddition ensued to deliver tetracycle **2.149** in good yield (Scheme 2.31). Fortunately, we were able to obtain a crystal of **2.149** suitable for X-ray analysis, and show thereby that the intramolecular cycloaddition had in fact occurred.

**Scheme 2.31**




This initial result seemed to indicate that a tether could be implemented to solve the problem of controlling global regiochemistry in our methodology for preparing *C*-aryl glycosides. However, in order for this approach to be applied, it would be necessary to find a way to cleave the tether and unmask the naphthol system. With this in mind, cycloadduct **2.149** was treated with TBAF in THF at room temperature to give **2.150** (Scheme 2.32).[116,117]

**Scheme 2.32**

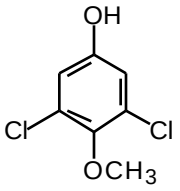


Evidence supporting the desired cleavage included the appearance of a distinctive doublet at δ 5.80 ppm in the $^{1}$H-NMR corresponding to the bridgehead proton. The group (X) on silicon was assigned as -OH based on LRMS and the fact that no fluorine resonances were present in the $^{19}$F-NMR spectrum. Interestingly, on standing in $CDCl_3$ for 24 h the product rearranged spontaneously to give phenol **2.151**. On further standing however, the phenol was converted into another as yet unidentified product (Scheme 2.32). We were a bit surprised to obtain as the product of a fluoride induced silicon-carbon bond cleavage, a compound in which it appeared as though hydroxide had replaced fluoride. Notably, in an unrelated cleavage of the silicon-oxygen bond of a siloxane using potassium fluoride, Fraser-Reid noted the formation of two products in a ratio of 9:1. The major product was actually found to be the corresponding silanol and the minor one was a silyl fluoride.[118] Presumably the hydroxide present in commercial solutions of TBAF is displacing the fluoride after the Si-C bond cleavage. In any event, it was clear that we would need to refine our tether cleavage to provide stable and useful adducts.

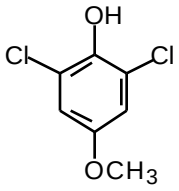
#### 2.2.6.2.1 Preparation of a Suitable Benzyne Precursor

It was decided at an early stage that a dichloro-*p*-methoxyphenol such as **2.152** or **2.126** would be a good choice for a benzyne precursor (Figure 2.4). The basis for this decision was that these molecules should, in theory, be easily accessible in large quantities. Additionally, the chloro-substituent on the non-reacting side would fulfill the previously determined role as a marker of regiocontrol and would also provide a useful handle for subsequent synthetic manipulation.

**Figure 2.4**




**2.152**



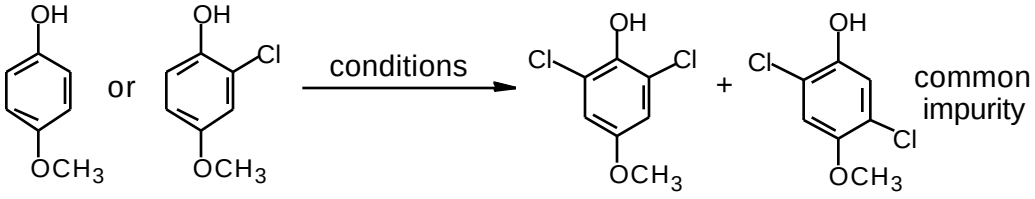

**2.126**

We settled on phenol **2.126** as the precursor of choice for two reasons. First, it seemed that this phenol might be more easily accessed from a synthetic standpoint, and the only published procedure for preparing **2.126** or **2.152** reportedly delivered an inseparable mixture of both compounds.[119] Secondly, we were unsure of the viability of deprotonating **2.152** *ortho* to one of the chlorine atoms after the tether had been attached. In other words, we questioned whether a silylmethylene group would be an effective director for *ortho* metalation. We were, however, fairly certain that *ortho* lithiation of a suitably derivatized version of **2.126** would not be problematic based on previous laboratory experience.

As mentioned previously, there were no useful literature preparations available for **2.126**. Initial attempts to access this compound by electrophilic chlorination of either **2.153** or **2.147** proved to be more difficult than expected. Chlorination of **2.153** with *N*-chlorosuccinimide (NCS) in a variety of solvents failed to provide a single regioisomer, and mixtures of chlorinated regioisomers were invariably obtained. In fact, attempted chlorination of **2.147** resulted in halogenation *para* to the chlorine atom already present. Next, **2.153** and **2.147** were each allowed to react with NCS after the phenol had been deprotonated with NaH. It was believed that this prior deprotonation would substantially increase the electron density at the position(s) *ortho* to the phenol, thus facilitating chlorination at this site. This procedure had previously afforded small

quantities of isomerically pure **2.126**, but on scale up this method also failed. Chlorinations with sulfuryl chloride ($SO_2Cl_2$) were then examined. This highly electrophilic $Cl^+$ source often chlorinates electron rich aromatic systems with high levels of regioselectivity. Unfortunately, several attempts to chlorinate either **2.153** or **2.147** in a variety of solvents gave mixtures of starting material, desired product, and undesired chloro regioisomers as well as overchlorinated by-products. Finally, a technique was found that provided **2.126** in good yield and in a highly regioselective fashion. Gnaim and Sheldon had shown that the addition of catalytic amounts of various amines to chlorination reactions that employ $SO_2Cl_2$ gave very high levels of *ortho* regioselectivity when a free phenol was present.[120] The use of a catalytic (8 mol%) amount of BnMeNH afforded the authors the highest level of regioselectivity. Reaction of **2.153** or **2.147** with $SO_2Cl_2$ in benzene in the presence of catalytic BnMeNH provided isomerically pure **2.126**. Due to its significantly lower cost, phenol **2.153** was chosen as the starting material for the preparation of larger quantities of **2.126** (Equation 2.14).

**Equation 2.14**



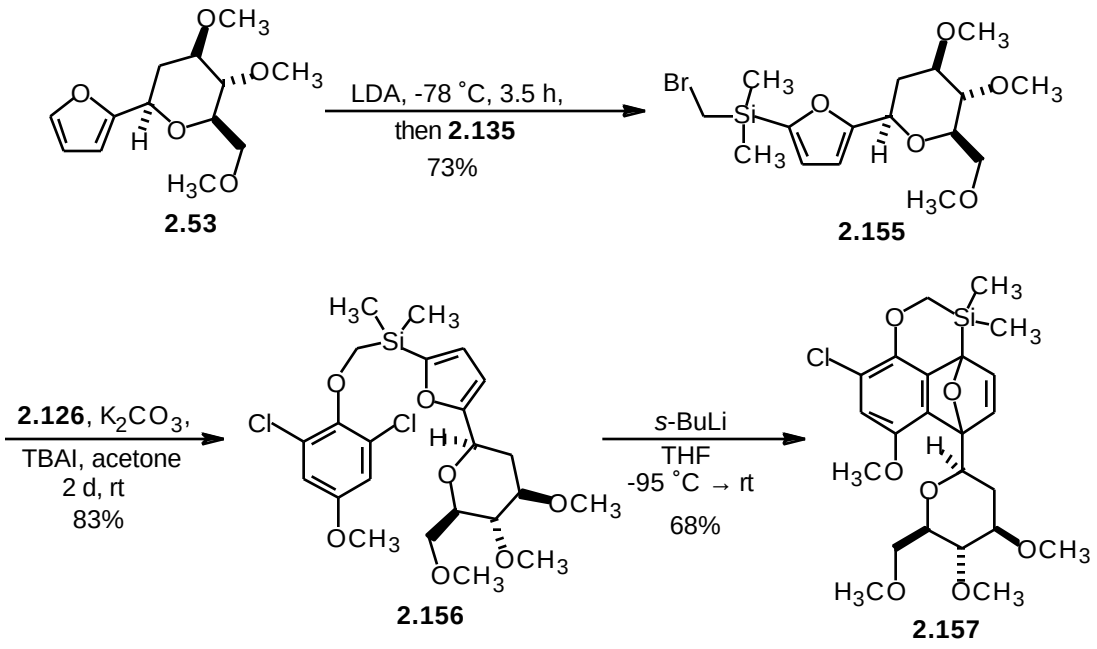

**2.153** **2.147** **2.126** **2.154**

| Conditions | Result |
|---|---|
| NCS, DMF | mixture of regioisomers |
| NaH, NCS, DMF | " |
| $SO_2Cl_2$, PhH | " |
| $SO_2Cl_2$, $CCl_4$ | " |
| $SO_2Cl_2$, $Et_2O$ | " |
| $SO_2Cl_2$, PhH, BnMeNH (cat.) | one isomer 52% |

### 2.2.6.2.2 Regiospecific Synthesis of a Group I System

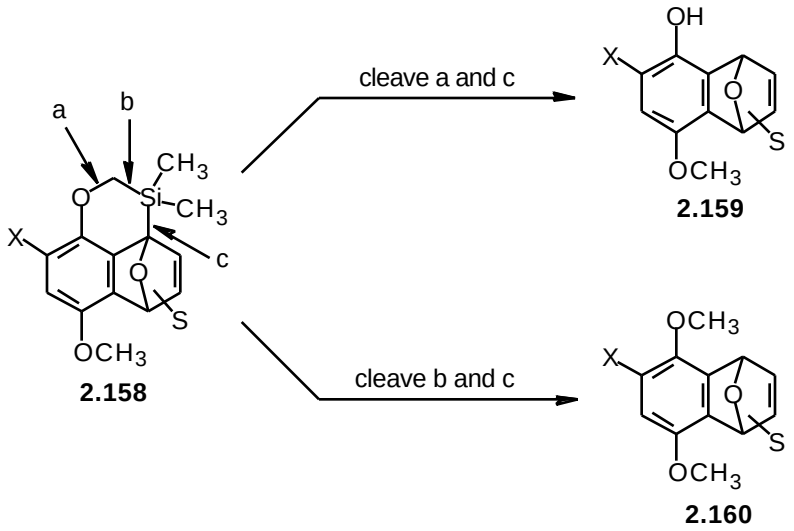
With ample quantities of the benzyne precursor **2.126** in hand, efforts were begun to prepare a Group I system. Toward this end the glycosyl furan **2.53** was treated with LDA at low temperature followed by addition of chlorosilane **2.135** gave **2.155**. Reaction of **2.155** with dichlorophenol **2.135** in the presence of $K_2CO_3$ and tetrabutylammonium iodide (TBAI) in acetone then gave **2.156**. The TBAI was not required in order for the reaction to proceed, but it did result in a more rapid alkylation. Gratifyingly, treatment of a solution of **2.156** in THF at -95 ˚C with *s*-BuLi, followed by warming to generate the benzyne afforded tetracycle **2.157** in good yield (Scheme 2.33). At this point it was necessary to determine what conditions would be required to cleave the tether.

**Scheme 2.33**



We were attracted to two possibilities with respect to cleaving the Si-C bonds in the tether of systems like **2.158**. The first involved scission of the bridgehead carbon-silicon bond (c) and bond (a) (Scheme 2.34). This would regiospecifically generate a hydroquinoid system **2.159** in which one of the -OH groups was free while the other one remained protected. Protection of the free phenol in **2.159** (P ≠ CH3), followed by acid-catalyzed ring opening of the bridging ether, would be expected to afford a naphthalene system in which all three phenolic hydroxyl groups would be differentiated. In the context of total synthesis, this differentiation could potentially be exploited in order to further elaborate the aromatic scaffold in a regioselective manner. We already knew, based on early model studies discussed previously, that nucleophilic attack on silicon would result in a reasonably facile cleavage of bond (c) with concomitant attachment of a heteroatom (-F, or -OH) to silicon. As additional precedent for this type of transformation, Rickborn had demonstrated that bridgehead TMS groups could be cleaved using KOH or KO-*t*-Bu in DMSO or TBAF in THF.[121] With this information in hand, the goal became cleavage of bond (a). We anticipated that if we could oxidize the carbon attached to bonds (a) and (b) that a simple aqueous workup would afford the desired phenol (Scheme 2.34). Fortunately, the work of Fleming and Tamao provided us with ample precedent for this type of oxidation.[122,123,124]

**Scheme 2.34**

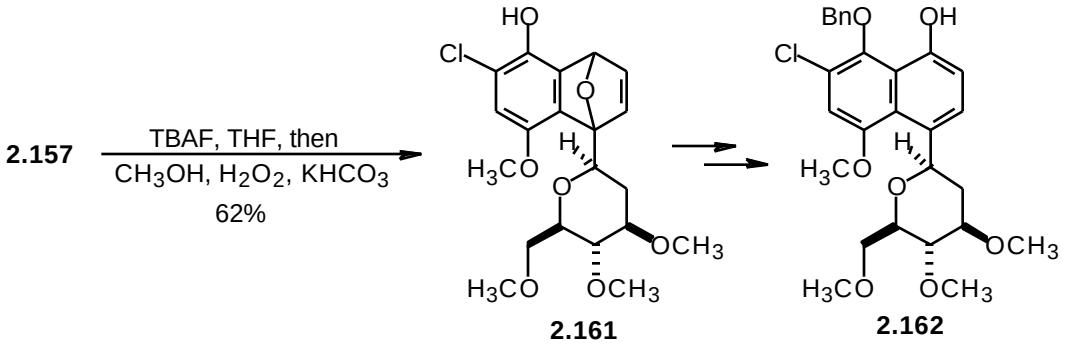



We were also intrigued by the second possibility of cleaving bonds (b) and (c) to give a dimethylhydroquinone of the general structure **2.160**. The dimethylhydroquinone moiety has been employed routinely as a protected form of a hydroquinone (or quinone) during the total synthesis of many quinonoid natural products. While cleavage of two carbon-silicon bonds in a single reaction did not seem to be precedented, Stork had shown that cleavage of a silicon-oxygen and an unactivated silicon-carbon bond could be performed in one pot as a method to install angular methyl groups in steroid skeletons.[117]

With this basic plan, we set forth to discover what reagents would allow for the preparation of compounds of the general structures **2.159** and **2.160**. Initially, we hoped to employ a one pot transformation of **2.157** to **2.161**. In an attempt to use conditions previously developed by Fraser-Reid for the one pot cleavage of a silicon-oxygen bond followed by oxidation of a carbon atom attached to the silicon, **2.157** was treated with KF, $H_2O_2$, and $KHCO_3$ in a THF/$CH_3OH$ mixture.[125] Unfortunately, this

afforded none of the desired phenol. We wondered about the viability of treating **2.157** with TBAF in THF as we had done on a similar system, but rather than isolate the partially cleaved adduct from this reaction, we would attempt to oxidize it *in situ*. With this in mind, tetracycle **2.157** was first treated with TBAF in THF; upon consumption of starting material (as evidenced by TLC analysis) $H_2O_2$, $KHCO_3$, and $CH_3OH$ were added. After 24 h at room temperature, the reaction was subjected to an aqueous workup to deliver the phenol **2.161** in which all atoms of the tether have been completely removed (Scheme 2.35). It was later demonstrated by Dr. Stephen Sparks, a postdoctoral associate in the group, that the phenolic hydroxyl group in **2.161** could be protected as its benzyl ether and that the bridging ether could then be ring-opened in the presence of TFA to give the corresponding differentially protected naphthol **2.162**.

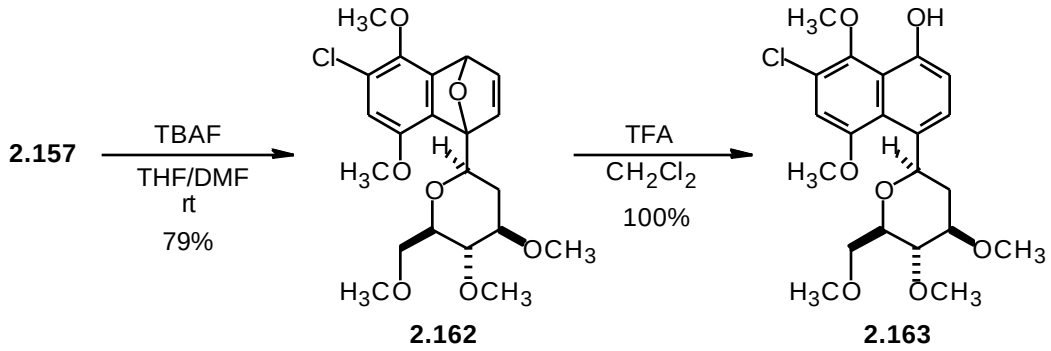
**Scheme 2.35**




In order to cleave both carbon-silicon bonds, the procedure of Stork[116] was followed. Treatment of a solution of tetracycle **2.157** with TBAF/THF in DMF resulted in the almost instantaneous formation of dimethylhydroquinone **2.162** in good yield (Scheme 2.36). It is rather amazing that this transformation occurs under such mild conditions. Treatment of cycloadduct **2.162** with TFA in $CH_2Cl_2$ at room temperature

rapidly provided the Group I *C*-aryl glycoside **2.163** in quantitative yield as a single regioisomer.

**Scheme 2.36**

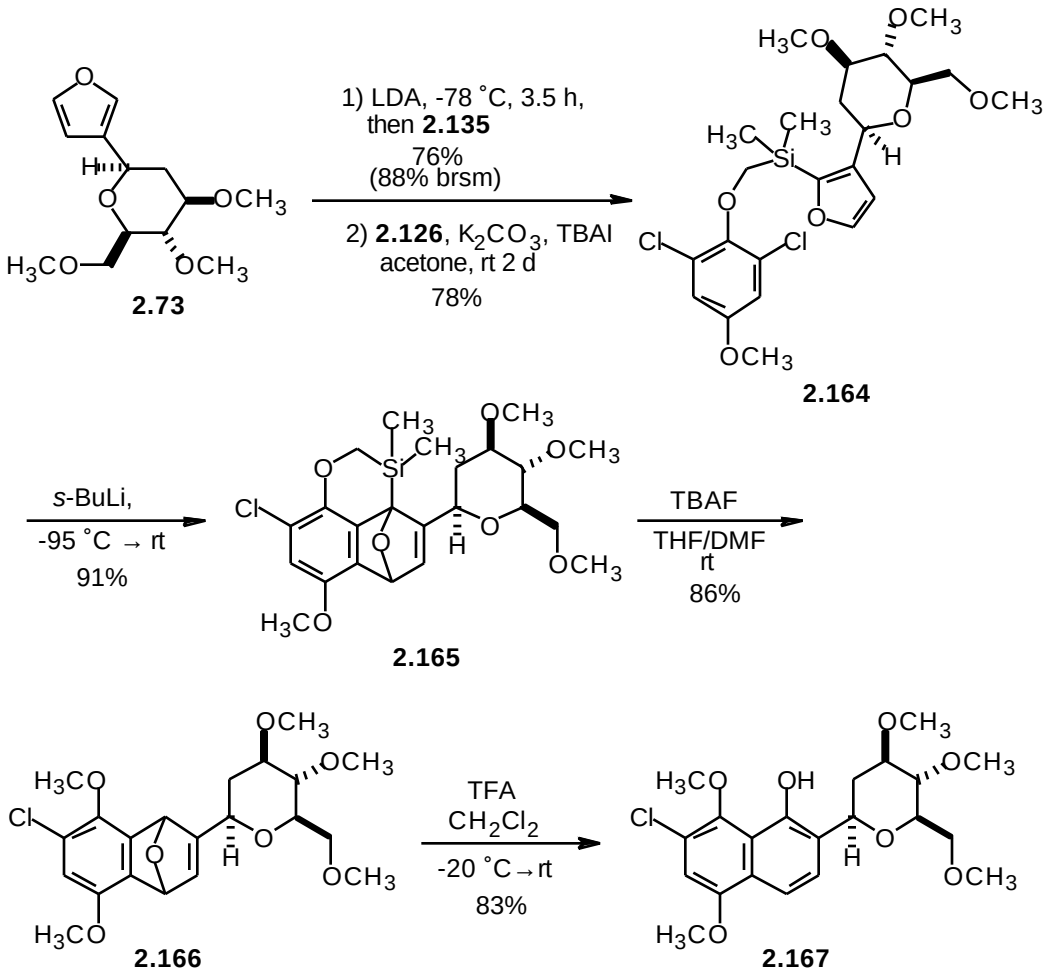



**2.162** **2.163**

**2.2.6.2.3 Regiospecific Synthesis of a Group II System**

Next, we focused our attention on the preparation of a Group II system. We were able to do this by using a tether approach in a manner that was analogous to the Group I case. Furan **2.73** was lithiated regioselectively at the 2-position using LDA, and the resulting anion was allowed to react with **2.135**. The bromomethylsilane thus obtained was used to alkylate phenol **2.126** as before to furnish **2.164**. Upon treatment of **2.164** with *s*-BuLi at -95 ˚C followed by warming to room temperature, benzyne generation and cycloaddition ensued to provide tetracycle **2.165** in 91% yield (Scheme 2.37). Initially, we were concerned about regioselectivity in the lithiation step (**2.164** → **2.165**) that leads to the intermediate benzyne. It should be noted that in addition to the two benzene protons available for abstraction, there is also a kinetically and thermodynamically acidic furan proton that could be removed. In any event, this deprotonation appears to not have been a detrimental competitive side reaction.

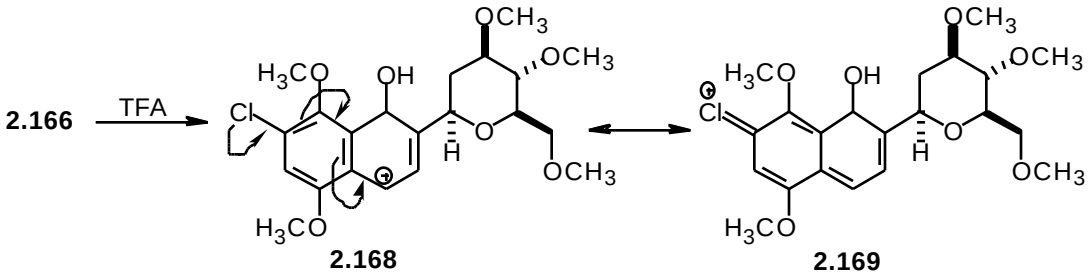
**Scheme 2.37**




Cleavage of the tether in **2.165** was accomplished by employing TBAF/THF in DMF to give **2.166**. Compound **2.166** underwent completely regioselective ring opening when exposed to TFA in $CH_2Cl_2$ at low temperature to give Group II glycoside **2.167**. It is noteworthy that a single regioisomer was obtained here because ring opening of systems similar to **2.166** with TFA had previously afforded mixtures of 2- and 3-substituted and naphthols. These openings had been performed at room temperature, and it was hoped that by conducting the acid-catalyzed opening of **2.166** at

a lower temperature that an increase in regioselectivity might be observed. While it appears that this may have been the case, it is important to note that the substitution on **2.166** is different from previous examples. Hence, it is also possible that the presence of the slightly electron donating -Cl atom on the aromatic ring is responsible for the improved level of regioselectivity. Treatment of **2.166** with TFA would be expected to form a carbocation. Two of the resonance forms **2.168** and **2.169** that are relevant to the chlorine-substituent's ability to stabilize the carbocation that leads to the 2-substituted product are shown below (Equation 2.15).

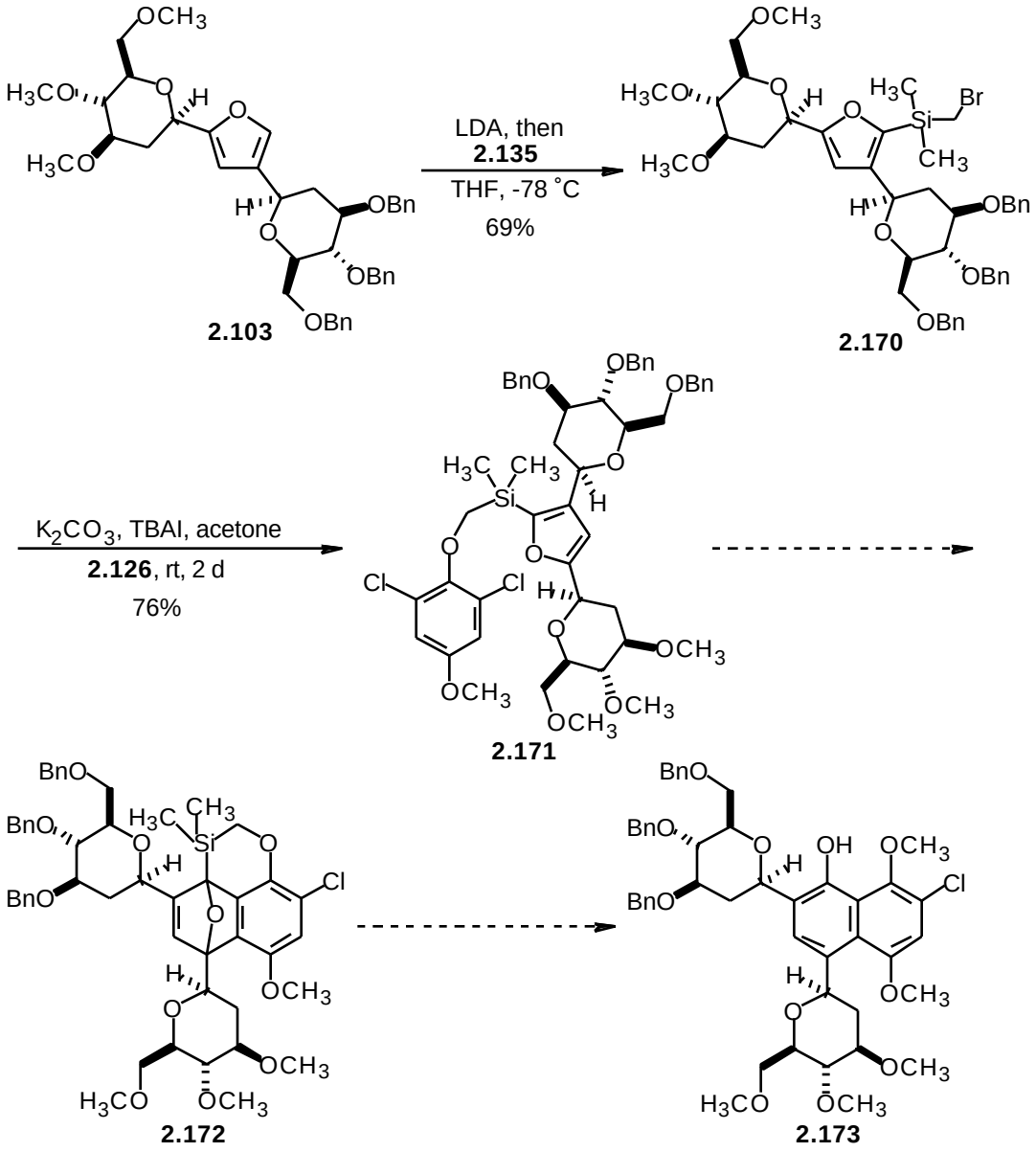
**Equation 2.15**




**2.2.6.2.4 Efforts Toward the Regiospecific Preparation of a Group III System**

In light of the success we had experienced so far applying the tether approach to the preparation of Groups I and II, we sought to extend it to the synthesis of the more challenging Group III system. In analogy to the other two systems, diglycosyl furan **2.103** was treated with LDA at -78 ˚C, and the resulting anion was allowed to react with **2.135**. *O*-alkylation of **2.126** with **2.170** gave the tethered benzyne precursor **2.171**. Currently Hilary Plake, a graduate student in the Martin group, is focusing on completing the necessary transformations to prepare **2.173** (Scheme 2.38).

**Scheme 2.38**


LDA, then
2.135
THF, -78 °C
69%
2.103
2.170
K2CO3, TBAI, acetone
2.126, rt, 2 d
76%
2.171
2.172
2.173

## 2.3 *C*-ARYL GLYCOSIDES *via* $S_N2'$ RING OPENING REACTIONS

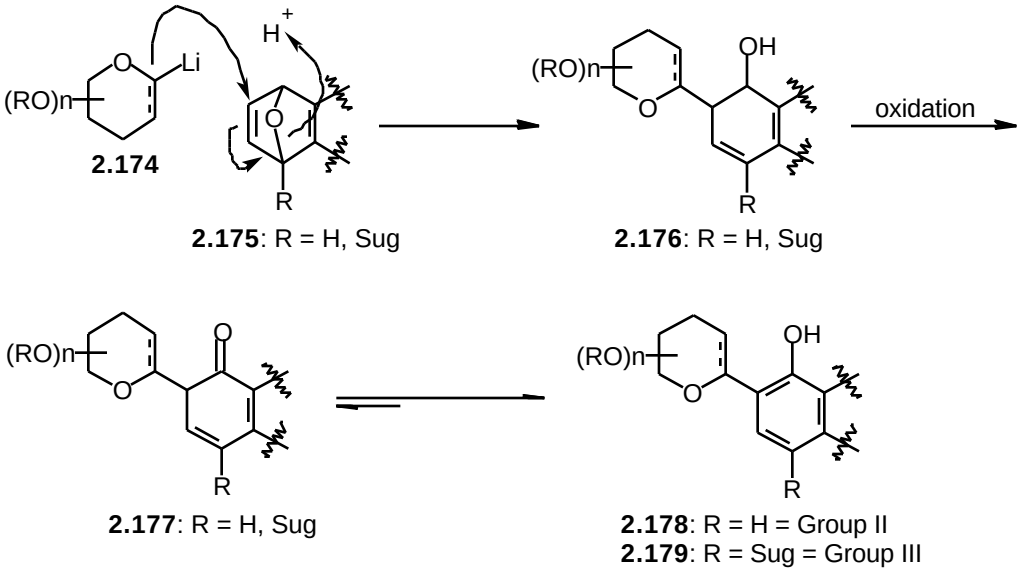
### 2.3.1 Introduction

Despite the significant success that we had with the benzyne/furan cycloaddition approach, we felt that there were some drawbacks that could be addressed by building off of the methodology we had already developed. One potential drawback of the benzyne/furan cycloaddition approach was the need to prepare the glycosyl furans. Sometimes the synthesis of these compounds could be rather cumbersome, requiring long reaction sequences. This problem could become more significant if one was attempting to prepare furyl-glycosides derived from valuable aminosugars. Another concern we had was whether it would be possible to easily access either anomer of a *C*-aryl glycoside system using the benzyne/furan cycloaddition method. We had conducted some preliminary experiments (Equation 2.8) to probe this question however, there still remained some uncertainty as to whether we would be able to prepare α-*C*-aryl glycosides and then further transform them over a number of steps without epimerizing the anomeric center. Finally, we felt that it was important that any new method should allow us to append valuable sugars onto an aromatic scaffold at a late stage of a total synthesis.

We were intrigued the possibility of preparing *C*-aryl glycosides belonging to Groups II and III (Figure 2.1) *via* an $S_N2'$ ring opening reaction of an oxabicyclic compound by a sugar nucleophile (Scheme 2.39). If a sufficiently reactive sugar nucleophile (i.e. **2.174)** could be generated and was allowed to react with an oxabicyclic compound **2.175** derived from a benzyne/furan cycloaddition, it is reasonable to expect that an $S_N2'$ ring opening reaction might occur to give a dihydronaphthol of the general type **2.176**.[126,127,128] If this dihydronaphthol could be oxidized without dehydration to

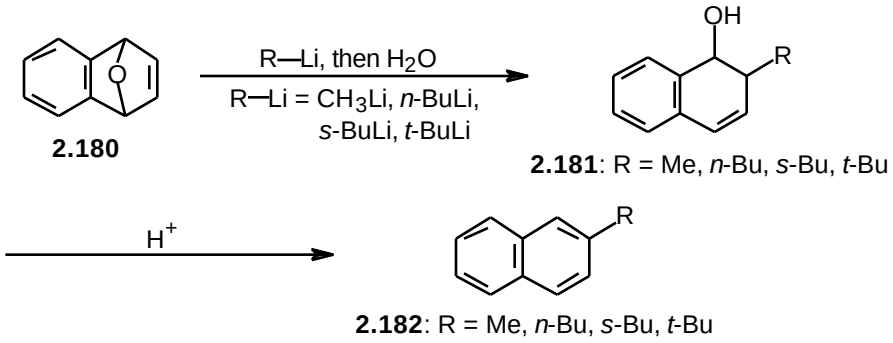
the corresponding naphthalene, then it might be possible to obtain *C*-aryl glycosides belonging to Group II **2.178** (R = H) or Group III **2.179** (R = sug) after tautomerization of **2.177** (Scheme 2.39).

**Scheme 2.39**



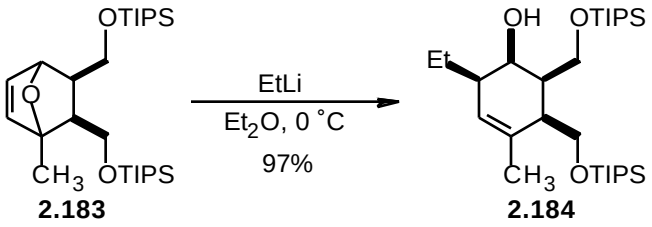

As precedent for the aforementioned transformations, Caple was the first to show that a variety of organolithium reagents opened oxabicyclic compounds like **2.167** in an $S_N2'$ fashion.[126] In this instance the authors simply dehydrated the dihydronaphthols **2.181** obtained to give the corresponding substituted naphthalenes **2.182** (Scheme 2.40). Subsequently, reactions of this general type have been shown to be a powerful tool for stereoselective organic synthesis, and this topic has been the subject of several excellent reviews.[127,128]

**Scheme 2.40**




Particularly relevant to the preparation of the Group III systems by the aforementioned $S_N2'$ approach, is the remarkably high regioselectivities with which the ring openings occur. For example, Lautens has shown that even when a small bridgehead substituent, such as a methyl group, is present and a relatively unhindered nucleophile is used, attack occurs completely (>97%) distal to the bridgehead substituent. This selectivity is clearly demonstrated in the ring opening of **2.183** with ethyllithium to give **2.184** as a single regioisomer in high yield (Equation 2.16).[129]

**Equation 2.16**

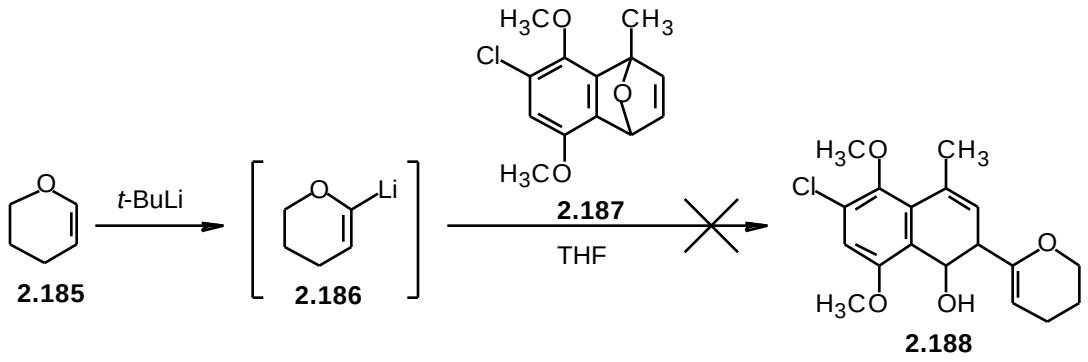



### 2.3.2 Carbohydrate Organolithium Route

In order for our proposed methodology to be successful, we first needed to be able to generate a sufficiently reactive sugar nucleophile. We initially considered a lithiated glycal to be a potentially good nucleophile for this type of chemistry, so as a simple model system, we investigated the $S_N2'$ ring opening reactions of benzyne/furan

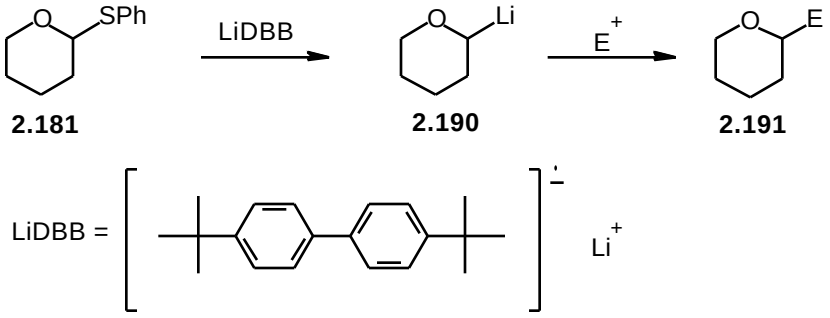
cycloadducts with 2-lithiodihydropyran (**2.186**). As per literature precedent, treatment of dihydropyran (**2.185**) with *t*-BuLi presumably generated the reactive organometallic intermediate **2.186**.[130] A solution of **2.187** in THF was then added to the solution of **2.186**, and the reaction mixture was allowed to warm to room temperature. Unfortunately, upon workup, only recovered starting materials were obtained. We investigated the use of different solvents, additives (e.g., $BF_3{\cdot}OEt_2$, HMPA, copper salts[131]), and temperatures, but none of the desired dihydronaphthol **2.188** was ever obtained (Scheme 2.41).

**Scheme 2.41**



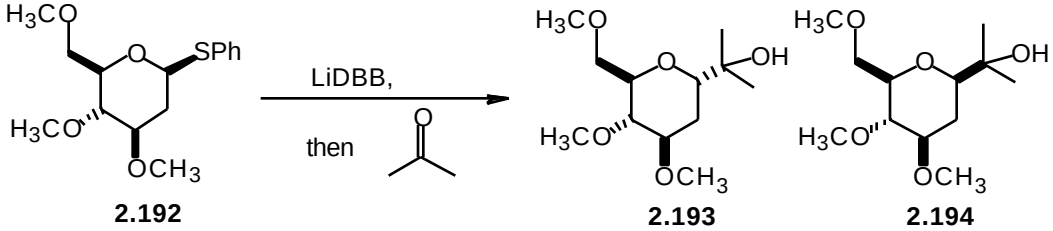

We decided that one potential problem was that the sugar nucleophile we had chosen was not sufficiently reactive. Cohen had shown that α-thiophenyl ethers could be reductively lithiated with LiDBB to generate highly reactive α-lithioethers like **2.190**[132] that could be subsequently trapped with electrophiles to give adducts **2.191** (Scheme 2.42).[133] We felt that substituting an $sp^2$ anion with a more reactive $sp^3$ anion might help to overcome the difficulties we were having.

**Scheme 2.42**




Furthermore, Rychnovsky had demonstrated that in conformationally biased rings, α-lithioethers could be generated and trapped stereoselectively. For example, reductive lithiation of **2.192** at -78 ˚C followed by trapping with acetone at the same temperature provided the alcohols **2.193** and **2.194** in good yield and with excellent stereoselectivity *via* trapping of the kinetically produced axial organolithium reagent.[134] Alternatively, if the initially formed anion was allowed to warm for a brief period and then trapped as before, a complete reversal in stereoselectivity was observed (Equation 2.17).

**Equation 2.17**

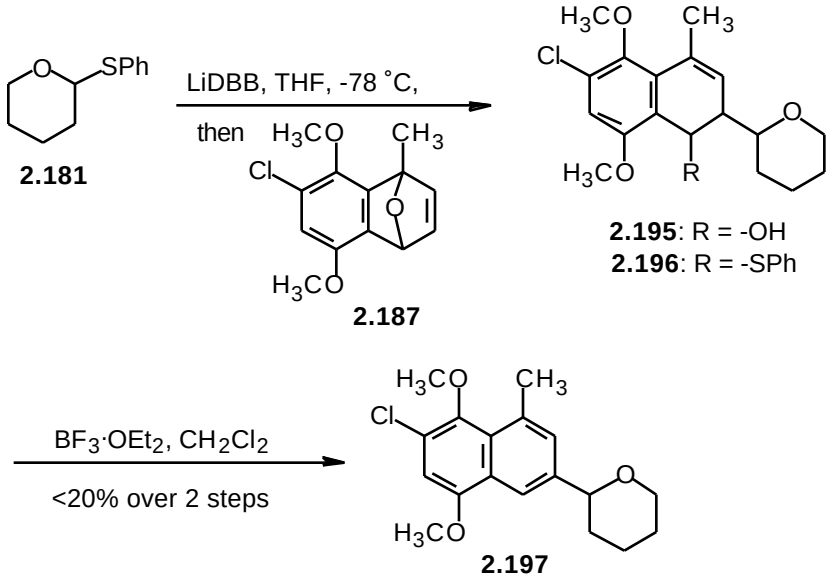



| Temperature | Ratio (ax : eq) | Yield |
|---|---|---|
| -78 ˚C | 97.7 : 2.3 | 81% |
| -20 ˚C, 45 min | 1.2 : 98.8 | 59% |

With respect to our chemistry, these highly reactive α-lithioethers appeared to offer an interesting solution. We would expect the $sp^3$ anion used by Rychnovsky to be more reactive than the $sp^2$ anions we had been examining initially. Additionally, the potential to access either anomer in a selective fashion by a simple epimerization of the sugar anion prior to $S_N2'$ opening was also quite attractive.

With this information in hand, we set out to reduce the nucleophilic $S_N2'$ ring openings to practice. Our first efforts involved an $S_N2'$ opening of **2.187** with the anion derived from model phenylthioglycoside **2.181**. Thus, treatment of **2.181** with a solution of LiDBB,[135] which was generated sonication according to the method of Yanagida,[136] followed by addition of **2.187** afforded products that appeared to incorporate structural features of both components. We tentatively assigned the structure of the adduct as dihydronaphthol **2.195**, but we noticed some additional aromatic protons in the $^1$H-NMR of the crude reaction mixture. We initially assumed these protons arose from the thiophenol by-product of the reductive lithiation. Due to the fact that dehydration to the corresponding naphthalene was so facile in this system, we decided to simplify characterization of the products obtained. Rather than attempt to purify the mixture of diastereomeric products, we simply dehydrated them by reaction with $BF_3{\cdot}OEt_2$. This reaction did in fact deliver the expected naphthalene **2.197** albeit in a rather low overall yield (Scheme 2.43).

**Scheme 2.43**




Later we came to believe that the disturbing aromatic resonances noted above were actually arising from the introduction of both a thiophenyl group and a tetrahydropyran moiety to give **2.196**. We came to this conclusion based on the fact that the proton NMR spectrum contained resonances that were consistent, based on chemical shifts and integrations, with thiophenyl incorporation. We considered the production of **2.197** upon treatment of **2.196** with $BF_3{\cdot}OEt_2$ evidence for the structural assignment. We have tentatively postulated that the benzylic alcohol was displaced by thiophenoxide after workup. Due to the low yield in the ring opening reaction, the unexpected incorporation of the thiophenyl moiety was not investigated further. Should this chemistry be revisited, it would make sense to examine the generation of the α-lithioether from a precursor that would generate a less nucleophilic leaving group such as $Cl^-$ upon reductive lithiation.[137]

Subsequent to the work performed with lithiotetrahydropyran, we also examined the $S_N2'$ ring opening of **2.187** with the anion derived from **2.192** that was used by

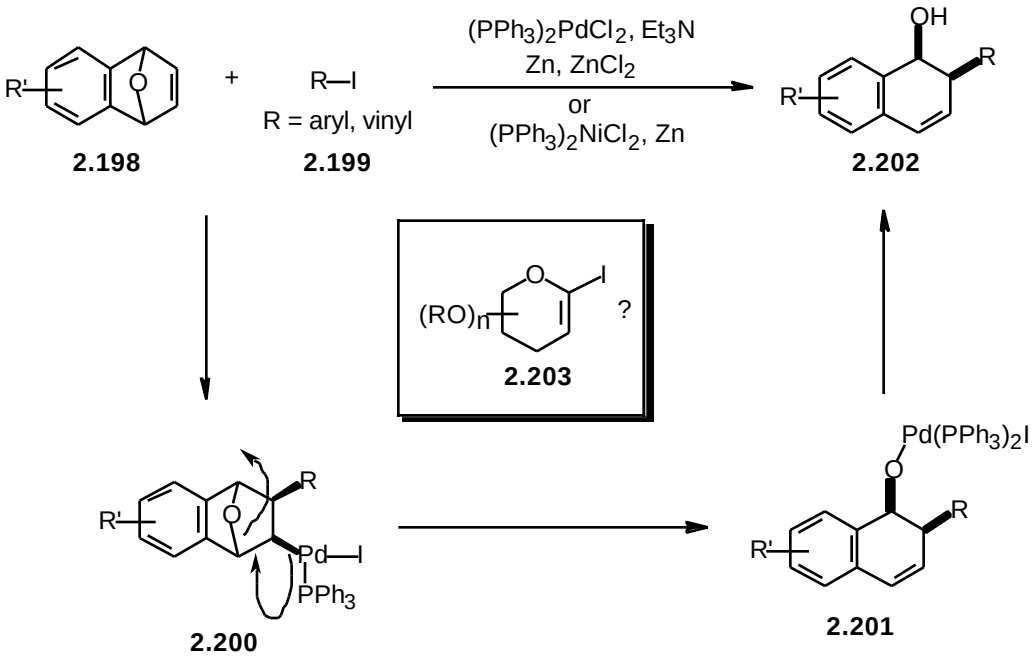
Rychnovsky (Equation 2.17).[134] Despite the use of different solvents and additives such as Cu salts, HMPA, or $BF_3 \cdot OEt_2$, only low yields of adducts that appeared to arise from $S_N2'$ ring opening were ever obtained. Again, the incorporation of a thiophenyl moiety appeared to be an additional interference. Due to the rather disappointing results obtained with attempted $S_N2'$ chemistry using α-lithio ethers, our group began an investigation of milder, transition metal-catalyzed conditions in an attempt to effect the desired transformation.

### 2.3.3 *C*-Aryl Glycosides *via* Pd-Catalyzed $S_N2'$ Ring Opening Reactions

Due to the difficulties we encountered in the work discussed in the previous section, we decided to examine an alternate approach. The plan that we devised would utilized the same disconnection as above, but instead of using carbohydrate-derived anions to open the cycloadducts, we would explore transition metal-catalyzed $S_N2'$ ring opening reactions of benzyne/furan cycloadducts with iodoglucals.

It had been demonstrated by Cheng, Fiaud, and others that oxabicyclic compounds like **2.198** could be ring opened in the presence of aryl and vinyl iodides **2.199** under Pd-catalysis.[138] The mechanism proposed by Cheng for this transformation is presented in Scheme 2.44. We were curious whether it might be possible to use an iodoglucal of the general type **2.203** in this type of transformation.

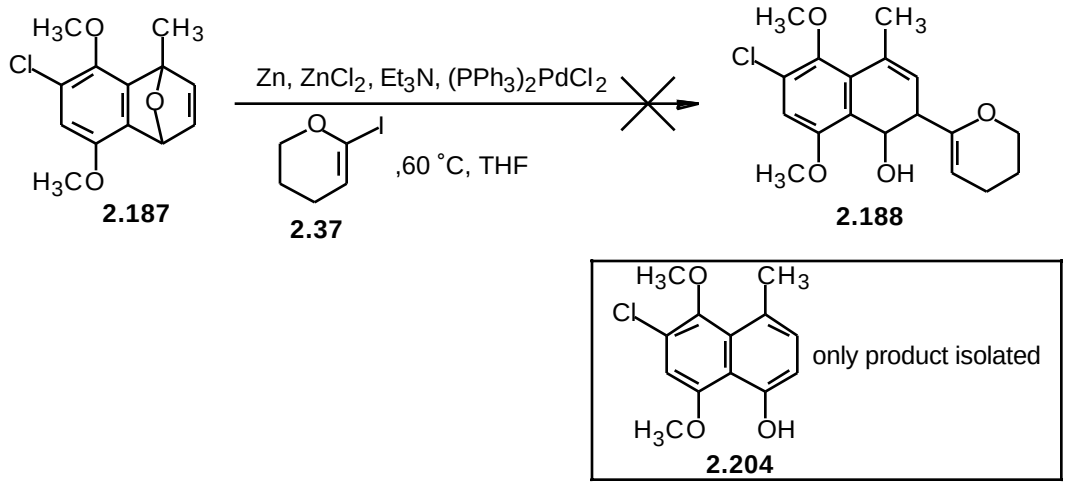
**Scheme 2.44**




To test this theory, a model study using 2-iododihydropyran (**2.37**) was investigated. We were aware that 2-iododihydropyran (**2.37**) was quite unstable, but we had some success working with it while attempting to prepare simple tetrahydropyranyl-substituted furans. Hence, we believed that if we handled the 2-iododihydropyran as a dilute solution in the dark we might be able to use it in an $S_N2'$ transformation. However, treatment of benzyne/furan cycloadduct **2.187** with 2-iododihydropyran (**2.37**) under Cheng's conditions afforded none of the desired dihydronaphthol **2.188**, and only phenol **2.204** was obtained, most likely the result of Lewis acid-catalyzed ring opening of **2.187**. Cheng had noted the formation of products that had arisen from acid-catalyzed ring opening in reactions that were sluggish with respect to the $S_N2'$ pathway. We presume that the iododihydropyran was decomposing fairly rapidly under the reaction conditions, and that in the absence of a suitable coupling partner, the

unreacted **2.187** simply underwent an acid-catalyzed ring opening reaction in the presence of $ZnCl_2$ (Equation 2.18).

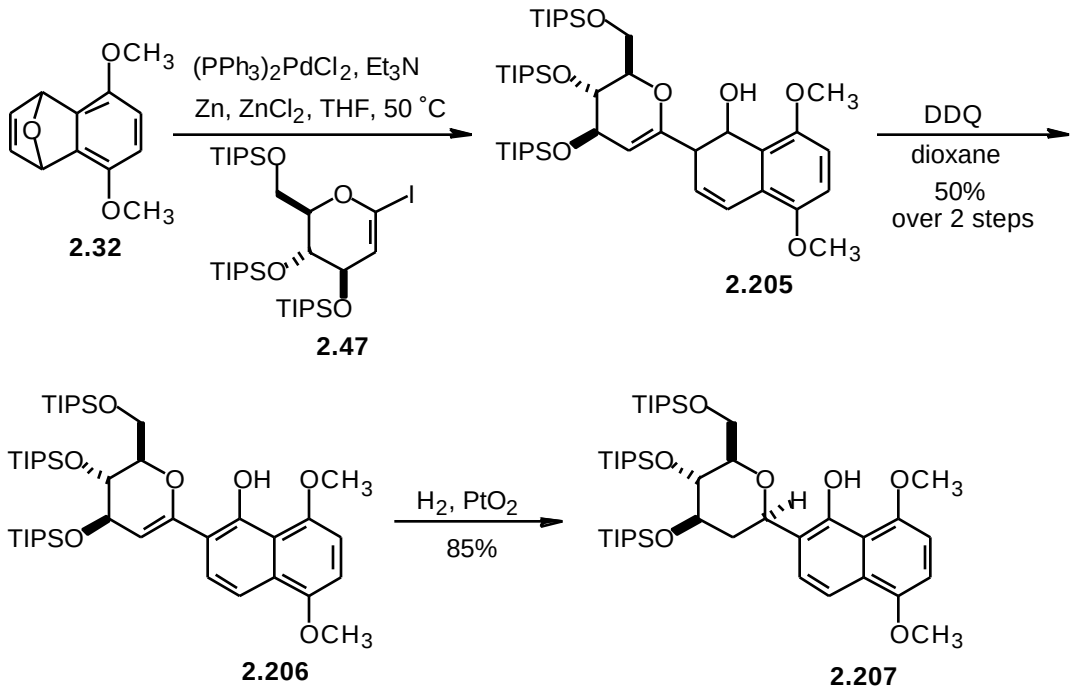
**Equation 2.18**




Subsequent to these efforts, Pd-catalyzed $S_N2'$ ring openings, Dr. Omar Lopez, a former Martin Group postdoctoral associate was able to implement successfully the idea utilizing known iodoglucals, which were significantly more stable than the 2-iododihydropyran (**2.37**).

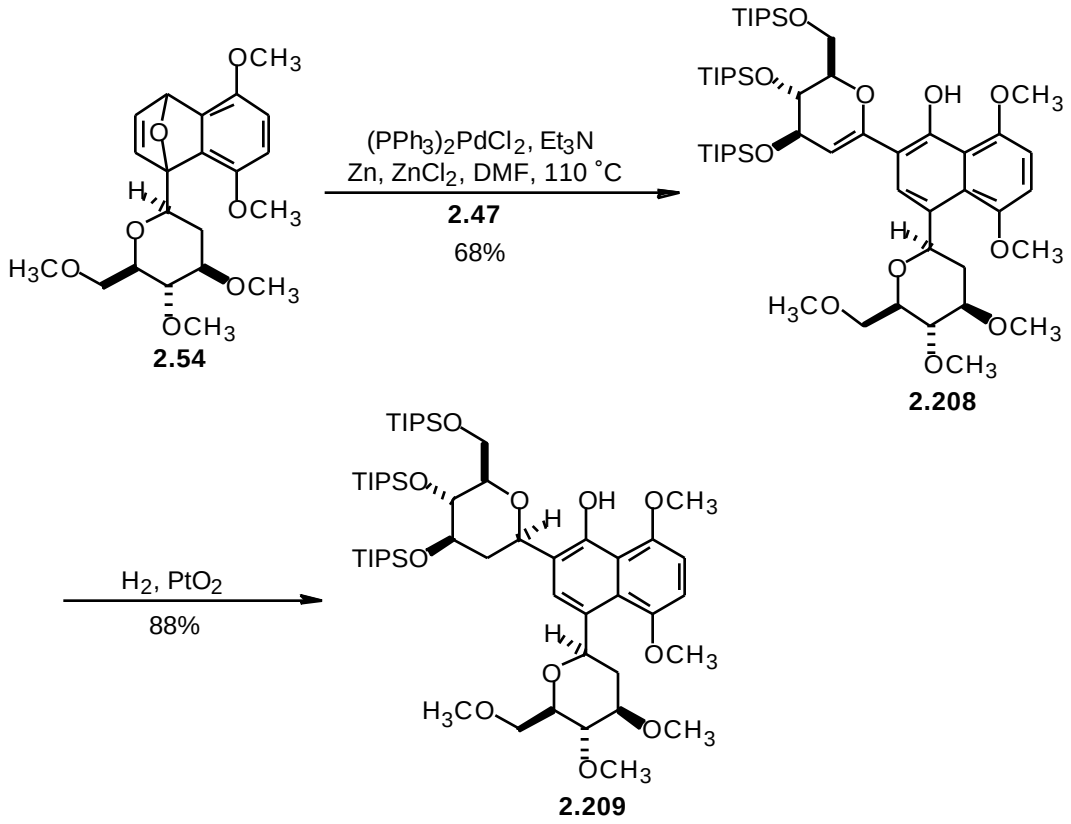
Dr. Lopez found that reaction of cycloadduct **2.32** with iodoglucal **2.47** under Cheng's conditions gave the desired dihydronaphthol **2.205**, which was then oxidized to the naphthol **2.206** using freshly recrystallized DDQ in dioxane. The use of DDQ was essential, as it was discovered that other oxidants such as pyridinium chlorochromate (PCC), Dess Martin periodinane, tetrapropylammonium perrhuthenate (TPAP), $MnO_2$, $BaMnO_4$, and Swern conditions afforded only the product derived from dehydration of **2.205** or unreacted starting material. Reduction of the glycal moiety by catalytic hydrogenation occurred stereoselectively to give the Group II system **2.207** (Scheme 2.45).[89]

**Scheme 2.45**




When Dr. Lopez applied a slightly modified protocol in which the reaction was conducted at 110 ˚C using DMF as solvent, the glycosyl-substituted cycloadduct **2.54** and iodoglucal **2.47** underwent coupling and oxidation to give naphthol **2.208** directly. It turned out that the more forcing conditions required to open the cycloadduct **2.54** also resulted in concomitant oxidation of the dihydronaphthol. Presumably the Pd(II) alkoxide formed, a proposed intermediate in the $S_N2'$ opening, undergoes a β-hydride elimination to regenerate Pd(0) and produce **2.208**.[138c] Stereoselective reduction of the glycal as before provided the Group III *C*-aryl glycoside **2.209** in good yield (Scheme 2.46).

**Scheme 2.46**




Dr. Lopez's results demonstrated that palladium-catalyzed $S_N2'$ ring openings of benzyne/furan cycloadducts with iodoglucals are a viable route to *C*-aryl glycosides of Groups II and III. It is our hope that this type of chemistry will be applicable to the synthesis of many naturally occurring *C*-aryl glycoside systems of biological importance.

We feel confident that the $S_N2'$ route for the preparation of *C*-aryl glycosides will be quite useful in the context of natural product synthesis. An important advantage of using this methodology instead of the benzyne/glycosyl-furan cycloaddition approach is that it is not necessary to prepare a 3- or 2,4-disubstituted furan in order to access Group II and Group III systems. Additionally, it seems likely that introduction

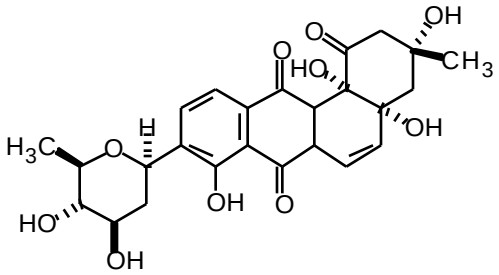
of valuable carbohydrates onto aromatic cores could be performed at a late stage in a synthesis using the $S_N2'$ methodology. There are, however, a few disadvantages of this technique. Due to the fact that the requisite iodoglucals are obtained by metalation of a glycal with *t*-BuLi, only highly robust protecting groups can be used and sensitive functional groups cannot be present. Additionally, iodoglucals are somewhat labile and nothing is known about the stability of iodoglucals derived from aminosugars. This could present a serious problem if one were attempting to prepare a compound like kidamycin (**1.3**) (see Chapter 1, Figure 1) using this approach.

## 2.4 THE FORMAL TOTAL SYNTHESIS OF GALTAMYCINONE

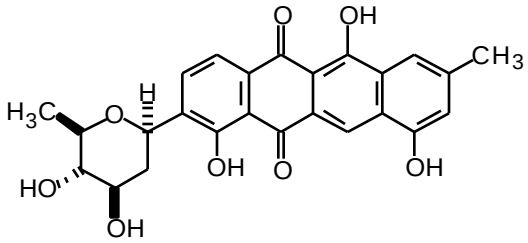
### 2.4.1 Introduction and Prior Art.

Having established several novel methods for the synthesis of *C*-aryl glycosides, we wished to demonstrate the utility of the methodology by application to total syntheses of biologically interesting natural products. The *C*-aryl glycoside angucycline antibiotics have attracted considerable interest in recent years due to their synthetically challenging structures as well as their significant biological activities.[69,139] Two representative angucycline antibiotics are aquayamycin (**2.210**) and galtamycinone (**2.211**) (Figure 2.5). Aquayamycin possesses the typical angular decaketide derived tetracyclic skeleton from which the angucyclines get their name. Galtamycinone on the other hand, possesses a linear framework, but because it is related to angular antibiotics like aquayamycin from a biogenetic standpoint, it is also classified as an angucycline.

**Figure 2.5**



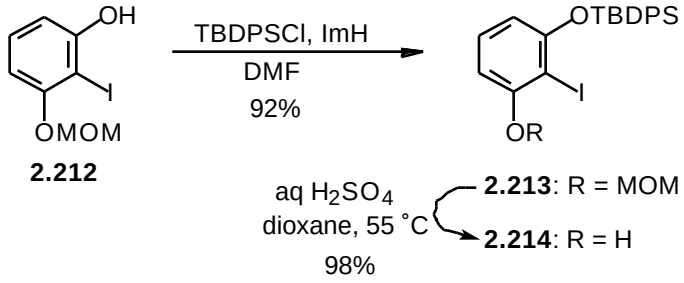
**2.210**: aquayamycin



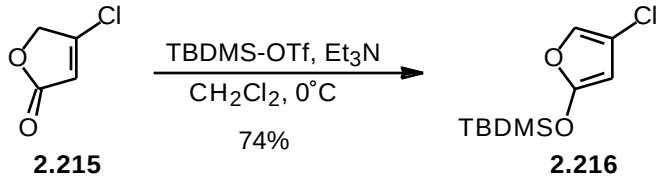
**2.211**: galtamycinone

To date, Suzuki has reported the only total synthesis of galtamycinone.[139,69] Suzuki's synthesis commenced with the known phenol **2.212**[68] which was prepared in five steps from resorcinol monobenzoate. Protection of the phenolic hydroxyl group TBDPSCl followed by cleavage of the MOM ether under acidic conditions gave **2.214** (Scheme 2.47). The requisite furanone **2.215** was prepared in two steps from propargyl alcohol. Enolization/silylation of this furanone delivered **2.216** in 74% yield (Equation 2.19).[140]

**Scheme 2.47**

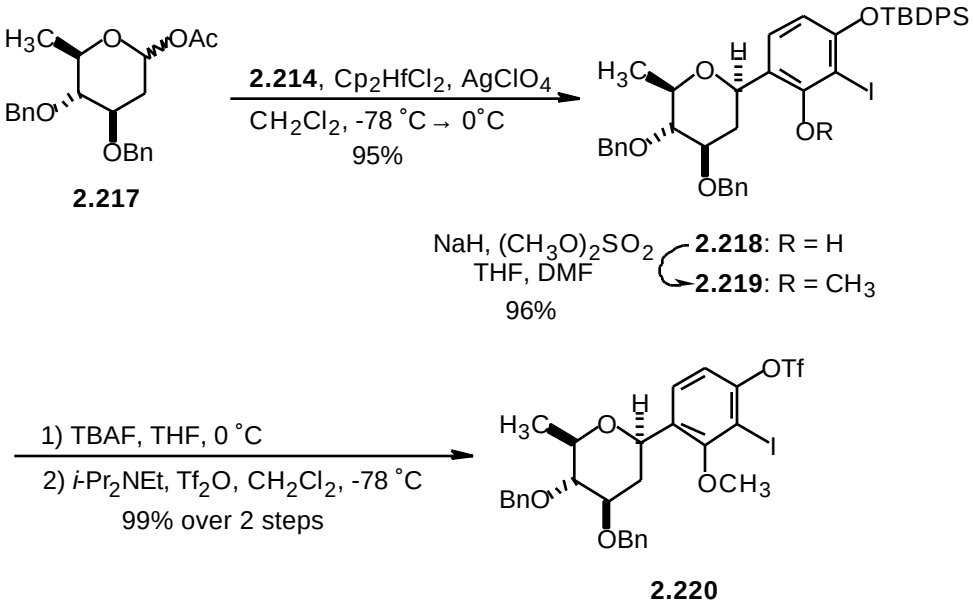



**Equation 2.19**



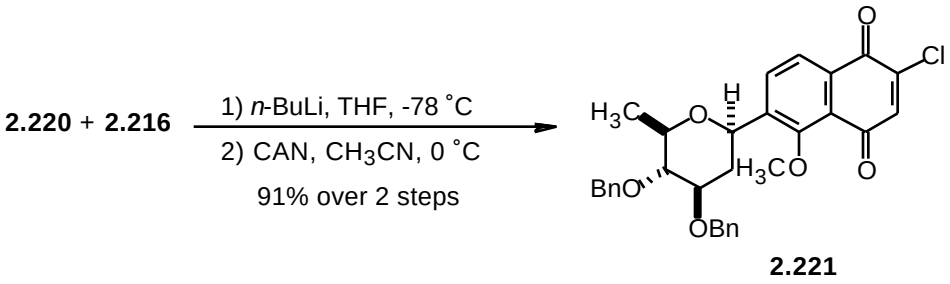
Treatment of 3,4-di-*O*-benzyl-D-olivosyl acetate (**2.217**)[84,141] and **2.214** with $Cp_2HfCl_2$ presumably gave an *O*-glycoside that underwent a facile $O \rightarrow C$-glycoside rearrangement under the conditions of the reaction to give *C*-glycoside **2.218**.[25,26,27,105,142] The phenolic hydroxyl group in **2.218** was methylated, and the silyl group was removed with TBAF. Reaction of the resultant phenol with $Tf_2O$ gave the benzyne precursor **2.220** (Scheme 2.48).

**Scheme 2.48**




Treatment of a solution of **2.220** and **2.216** in THF with *n*-BuLi at -78 °C resulted in a rapid benzyne cycloaddition. The crude product thus obtained was oxidized directly to give the chlorojuglone **2.221** as a single regioisomer in excellent yield (Equation 2.20)

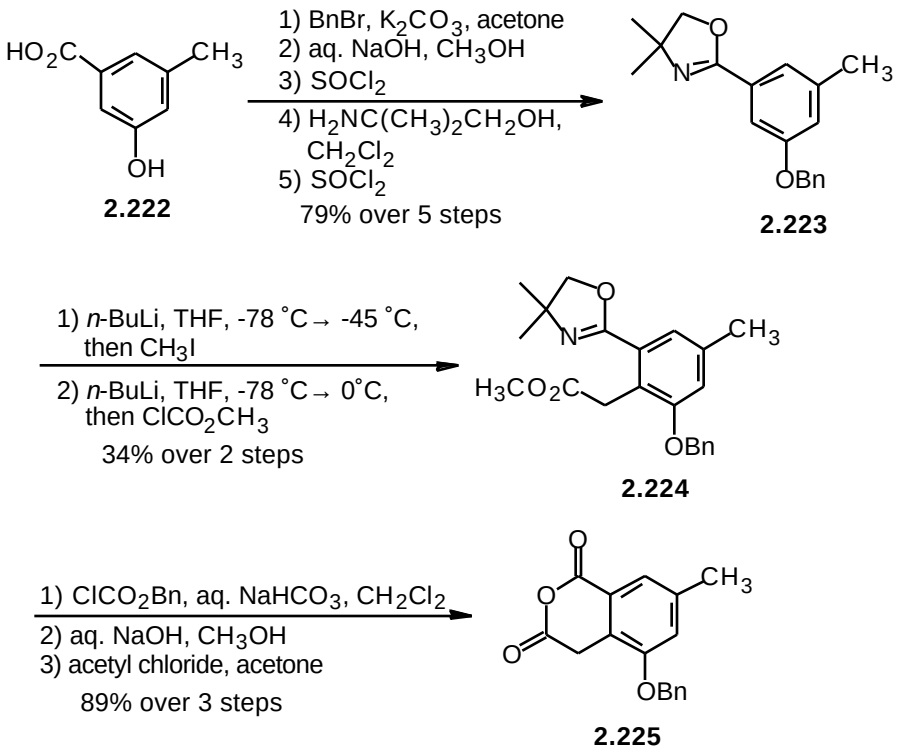
**Equation 2.20**




**2.221**

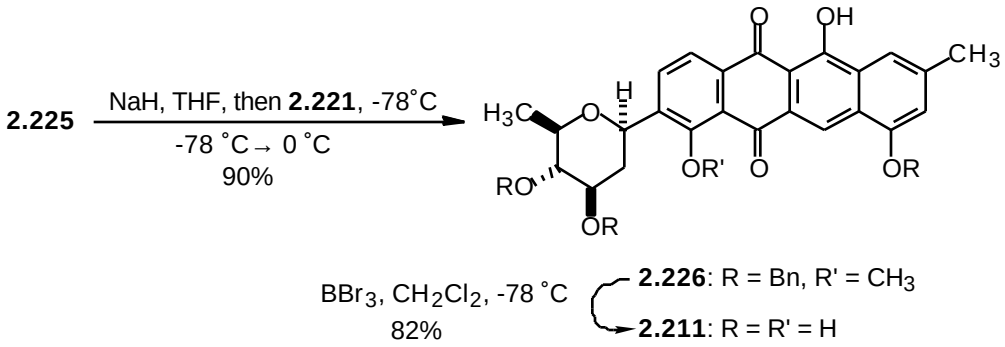
The coupling partner for **2.221** was prepared starting from the known benzoic acid **2.222**, which is available in 3 steps from diethyl oxalate.[143] The hydroxyl group in **2.222** was protected as its benzyl ether, and the product was treated with aq. NaOH and $CH_3OH$, presumably to saponify some benzyl ester by-product. The resultant benzoic acid was treated with $SOCl_2$ followed by 2-amino-1-methyl-1-propanol, and the resultant amide was treated with $SOCl_2$ to induce cyclization to the oxazoline **2.223** in 87% yield. The oxazoline **2.224** was prepared by repeated directed lithiation of **2.223**. Thus, treatment of **2.223** with *n*-BuLi followed by trapping of the resultant anion with $CH_3I$ gave an intermediate that was also treated with *n*-BuLi and then $ClCO_2CH_3$ gave oxazoline **2.224**. Treatment of **2.224** with $ClCO_2Bn$ in aq. $NaHCO_3/CH_2Cl_2$ followed by addition of aq. $NaOH/CH_3OH$ resulted in the simultaneous hydrolysis of both the ester and oxazoline moieties to deliver a diacid. This diacid was subsequently cyclized and dehydrated to the corresponding anhydride **2.225** by the action of acetyl chloride (Scheme 2.49).

**Scheme 2.49**




Using the chemistry of Kita and Tamura, a solution of anhydride **2.225** in THF was treated with NaH at 0 ˚C to generate an anion that was added to chloroquinone **2.221**.[144] Upon gradual warming, reaction ensued, and after spontaneous decarboxylation, naphthacenequinone **2.226** was obtained in 90% yield. Global deprotection of the benzyl and methyl ethers with $BBr_3$ delivered galtamycinone (**2.211**) in 82% yield (Scheme 2.50).

**Scheme 2.50**

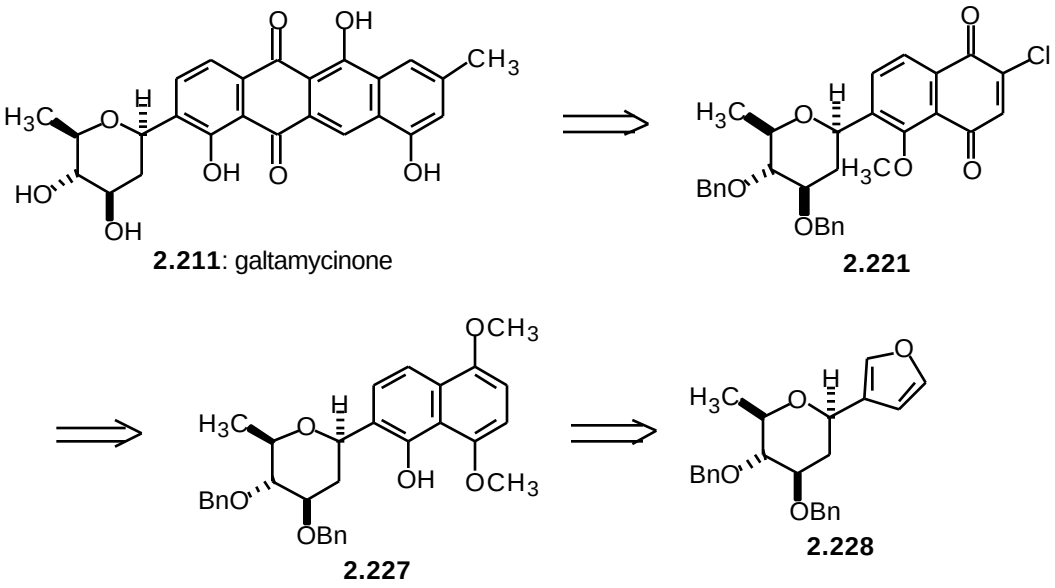



### 2.4.2 Martin Group Benzyne/Furan Approach to Galtamycinone

With several routes to *C*-aryl glycosides in various stages of development, we thought it would be useful to test our methodologies in the context of a total synthesis. We felt that galtamycinone (**2.211**) would not only be an interesting target, but we also felt that we would be able to prepare the natural product fairly rapidly. A formal total synthesis of galtamycinone (**2.211**) has been completed using our benzyne/furan cycloaddition approach. The results of this synthetic endeavor will be discussed below.

Since Suzuki was able to prepare the natural product from protected chlorojuglone **2.221**, we chose this as our initial target. We believed that it would be possible to obtain juglone **2.221** from dimethylhydroquinone **2.227** *via* a protection/oxidation sequence followed by regioselective introduction of a chlorine atom (Scheme 2.60). The *C*-aryl glycoside **2.227** would arise from a cycloaddition of dimethoxybenzyne with a glycosyl furan **2.228** followed by acid-catalyzed ring opening of the resultant cycloadduct. We felt that the requisite glycosyl furan could be obtained using chemistry similar to that utilized earlier for our *C*-aryl glycoside methodology.

**Scheme 2.60**




**2.211**: galtamycinone

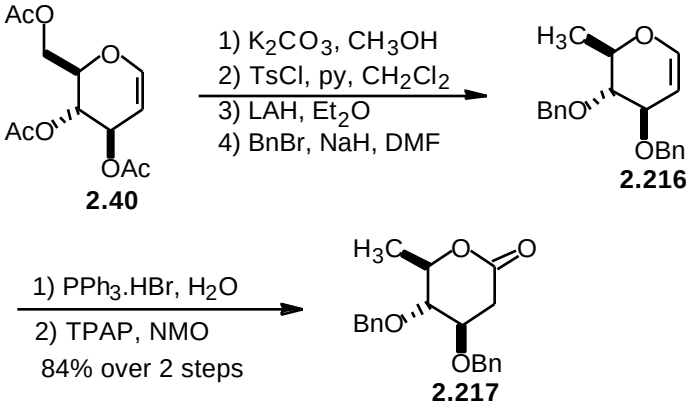
**2.221**

**2.227**

**2.228**

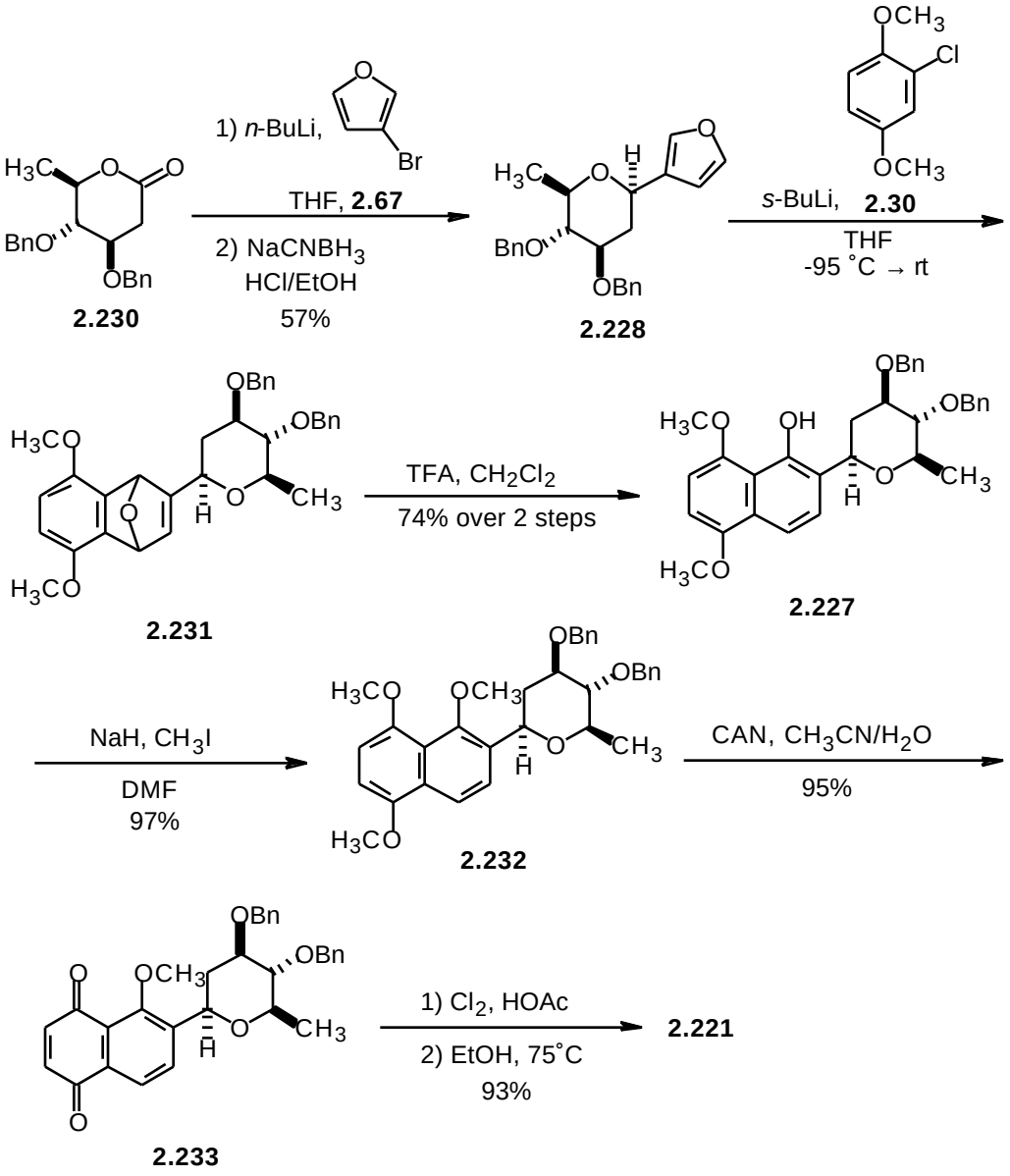
The known sugar lactone **2.230**[145] was prepared by conversion of commercially available tri-*O*-acetyl-D-glucal (**2.50**) to the dibenzylated 6-deoxyglycal **2.229** according to a literature procedure.[146] Next, the double bond in **2.229** was hydrated using a procedure similar to one recently discovered in our group and subsequently reported on by Halcomb.[147] This procedure entailed treatment of **2.229** with $H_2O$ and a catalytic amount of $PPh_3$·HBr to deliver an intermediate lactol. The lactol was then oxidized to lactone **2.230** in high yield using a protocol that was developed to oxidize sugar lactols to sugar lactones using tetrapropylammonium perrhuthenate (TPAP) (Scheme 2.51).[148] An alternative procedure was examined wherein the glycal **2.229** was directly oxidized to the corresponding lactone **2.230** using PCC in DCE,[109] however this reaction was rather capricious, often producing varying amounts of an α,β-unsaturated lactone that was difficult to remove from the desired lactone.

**Scheme 2.51**




The sugar lactone **2.230** was allowed to react with 3-furyllithium, which was prepared from 3-bromofuran, to give a mixture of lactols that was treated with $NaBH_3CN$ in acidic EtOH to provide **2.228** as a single diastereomer. Evidence for this was obtained from the $^1H$ NMR spectrum of **2.228** in which a single anomeric proton resonance was observed at $\delta$ 4.38 as a doublet of doublets with $J$ = 11.7 and 2.0 Hz. Cycloaddition with the benzyne derived from **2.30** delivered **2.231** as a mixture of diastereomers, which was treated with TFA to induce ring opening and give dimethylhydroquinone **2.227** in good overall yield. The free phenol in **2.227** was methylated, and then the hydroquinone ring was oxidized with CAN in aqueous $CH_3CN$.[149] This methylation/oxidation protocol was employed because we had discovered, during earlier attempts to oxidize related dimethylhydroquinones in the presence of a free phenolic hydroxyl group, that oxidation occurred in the wrong ring. Regioselective chlorination/dehydrochlorination of **2.233** using the methods of Rapoport and Belitskaya gave the chloroquinone **2.221**, thus constituting a formal total synthesis of galtamycinone (**2.211**) (Scheme 2.52).[150]

**Scheme 2.52**




Based on the success we had with the formal synthesis of galtamycinone, we were tempted to see if our methodologies could be applied to more challenging *C*-aryl glycoside antibiotics. We were immediately attracted to the *bis*-*C*-aryl glycoside class of antibiotics known as the pluramycins. It was our belief that attempting a total

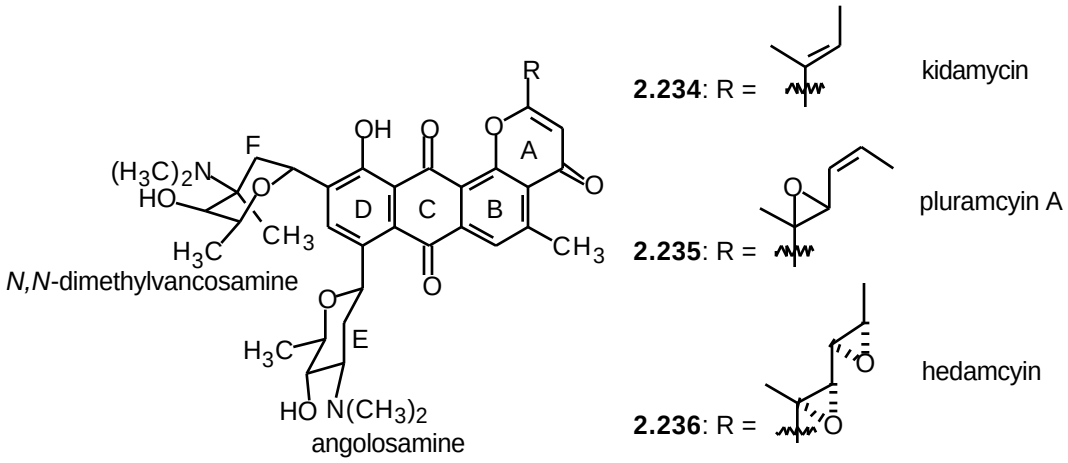
synthesis of a member of the pluramycins would allow us to test the limits of our methodology and perhaps develop it further. The known instability of this class of compounds coupled with the presence of two highly functionalized dimethylaminosugars on the aromatic nucleus would certainly make our total synthesis endeavor a challenging one.

## 2.5 PROGRESS TOWARD THE TOTAL SYNTHESIS OF KIDAMYCIN

### 2.5.1 Structure and Biological Activity

The pluramycins[151] and related antibiotics are a group of structurally evolved DNA-reactive agents that represent a range of 4*H*-anthra[1,2-*b*]pyran-4,7,12-trione structures containing carbohydrate and epoxide moieties. The rings of the anthraquinone system are labeled B through D with the pyrone being the A ring. Ring D bears two deoxyaminosugars, one is at the 2-position relative to the phenol and the other at the 4-position (Figure 2.6).

**Figure 2.6**




Kidamycin (**2.234**), a secondary metabolite of *Streptomyces phaeoveriticillatus*, is one of the most thoroughly studied pluramycin antibiotics.[152] Its structure and chemistry has been thoroughly reviewed by Séquin.[151] The structure of kidamycin has been unequivocally proven using a combination of chemical analysis, spectroscopic investigation, and X-ray analyses of several crystalline derivatives.[153]

The cytotoxic antibiotics that comprise the pluramycin family show activity against a number of tumor cell lines.[154] Hurley and co-workers have performed

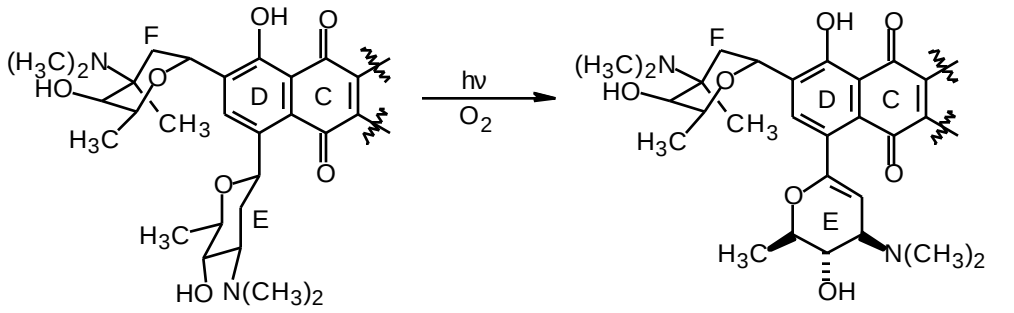
extensive studies of pluramycin A (**2.235**) in an attempt to elucidate the mechanism of action of this unique class of compounds.[104] Base upon these studies, it has been proposed that the drug intercalates the DNA helix, positioning the carbohydrate moieties into the minor groove and placing the epoxide into the major groove. The carbohydrate residues are held in place by strong hydrogen bonding interactions between the protonated dimethylamino groups and the DNA strand. The epoxide is held proximal to a guanine residue that is subsequently alkylated on *N*-7, leading to the formation of a cationic lesion on the DNA. In the presence of a base, this lesion can lead to single strand cleavage of the DNA.[104]

The pluramycins have generally been found to be cardiotoxic, and kidamycin is the only member of this family that has been derivatized in an attempt to obtain a less toxic, more therapeutically useful drug. Administration (i.p.) of single doses of kidamycin ranging from just below the $LD_{50}$ to 1/16 of the $LD_{50}$ significantly prolonged the lives of mice that were infected with Ehrlich ascites tumors. Kidamycin has also been shown to be active against leukemia L-1210, Sarcoma-180 (solid type), NF-sarcoma, and Yoshida sarcoma.[2]

The pluramycins are chemically labile, decomposing readily in solution and upon irradiation with UV- and daylight. One of the products of irradiation of kidamycin (**2.234**) in the presence of oxygen is photokidamycin A (**2.237**) (Equation 2.21).[155] The formation of this product is rationalized by an initial photoreduction of the anthraquinone moiety to the corresponding hydroquinone oxidation state. This type of photoreduction is precedented in other anthraquinone systems.[156,157] It is believed that the E-ring (angolosamine) is appropriately positioned to act as an intramolecular

hydrogen donor, losing two hydrogen atoms. The hydroquinone is eventually reoxidized to the quinone by oxygen.

**Equation 2.21**

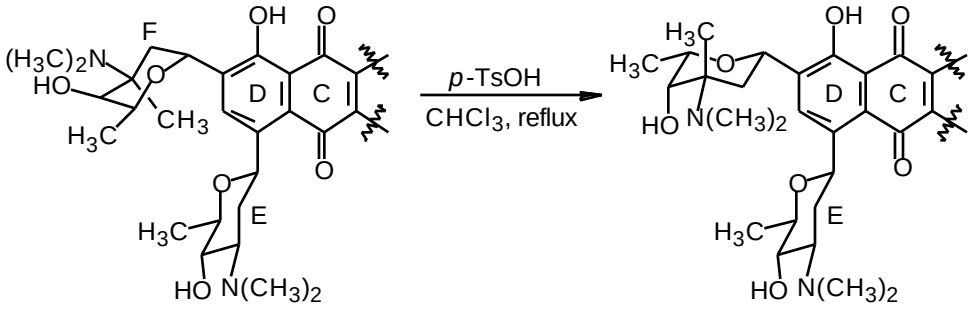



**2.234**: kidamycin

**2.237**: photokidamycin A

The pluramycin antibiotics have been found to undergo only a few degradation reactions that lead to identifiable compounds. For example, treatment of kidamycin (**2.234**) with *p*-toluenesulfonic acid in reluxing $CHCl_3$ affords isokidamycin (**2.238**) (Equation 2.22).[87] Apparently, acid-catalyzed epimerization to the more stable anomer is occurring in analogy to similar behavior we have observed in the course of working with unrelated *C*-aryl glycosides.

**Equation 2.22**




**2.234**: kidamycin

**2.237**: isokidamycin

To date, there has been no total synthesis of pluramycin A, kidamycin, or any of the related *bis*-*C*-aryl glycoside antibiotics; however, Hauser has reported the synthesis

of *O*-methylkidamycinone, an aglycone derivative of kidamycin.[158] The potent biological activity of kidamycin coupled with its instability and unique structure make it an attractive and challenging target for total synthesis. We believed that achieving a total synthesis of kidamycin would allow us to develop further our new methods for the construction of *C*-aryl glycosides with an emphasis on aminosugar incorporation.

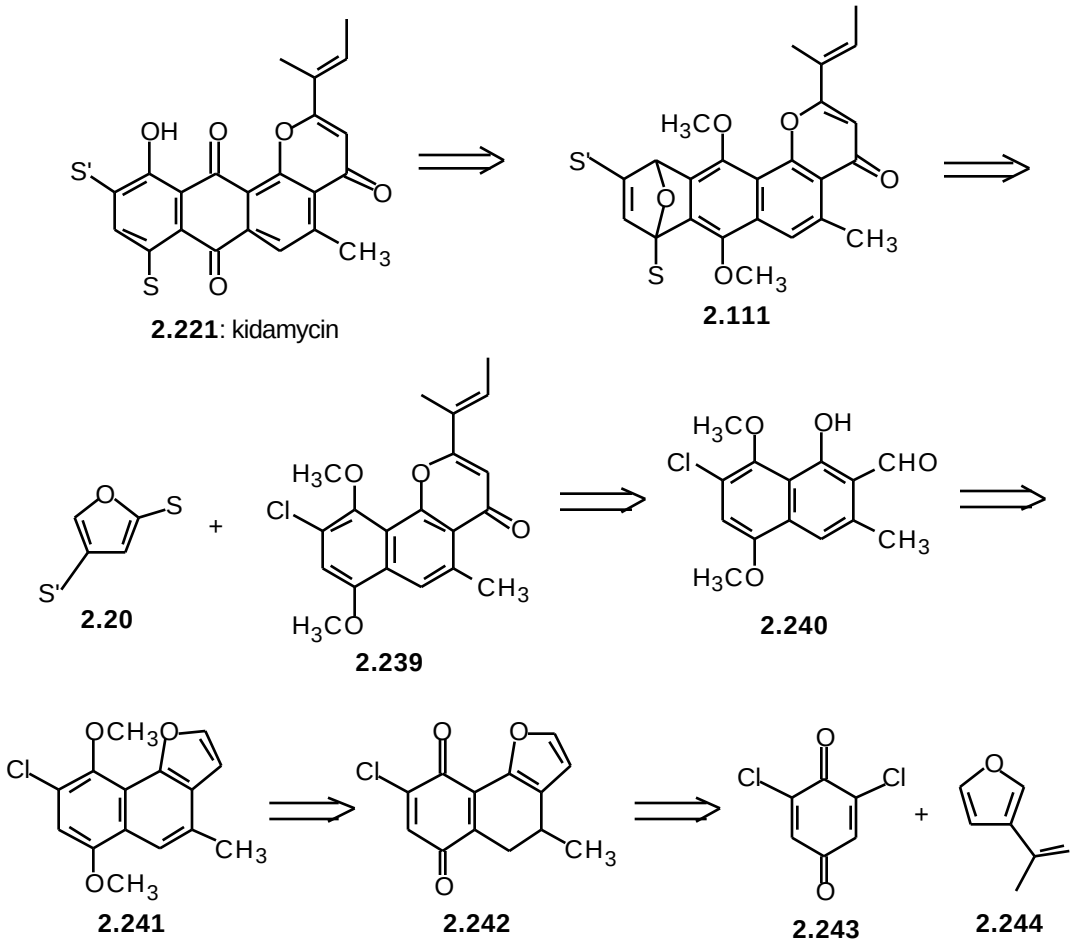
### 2.5.2 Martin Group First Generation Approach

Initially we believed that aldehyde **2.240** might be a useful intermediate in a total synthesis of kidamycin (**2.234**) (Scheme 2.53). We envisioned that kidamycin could be obtained from cycloadduct **2.111** by acid-catalyzed ring opening, oxidation of the aromatic core to the anthraquinone, and protecting group removal. Cycloadduct **2.111** would be derived from a Diels-Alder reaction between diglycosyl furan of the general structure **2.20** and the benzyne generated from **2.239**. Early in our investigations we were under the assumption that the peri C-O bond of the chromone would cause the methoxy group on the upper half of **2.239** to reside near the reacting portion of the benzyne generated from **2.239**. We believed that the resulting difference in steric environments on either side of the benzyne might produce the desired regioisomer (shown) preferentially over the undesired one.

Chromone **2.239** should be available from aldehyde **2.240** *via* incorporation of a tiglaldehyde-derived side chain and several oxidation/reduction manipulations. The aldehyde **2.240** could be obtained from oxidative cleavage of benzofuran **2.241** followed by hydrolysis of the resultant formate ester. We envisioned that the benzofuran would arise from a regioselective cycloaddition between furan **2.244** and 2,6-dichloroquinone

(**2.243**) to give an intermediate **2.242** that could be sequentially oxidized, reduced to the hydroquinone, and protected to give **2.241** (Scheme 2.53).

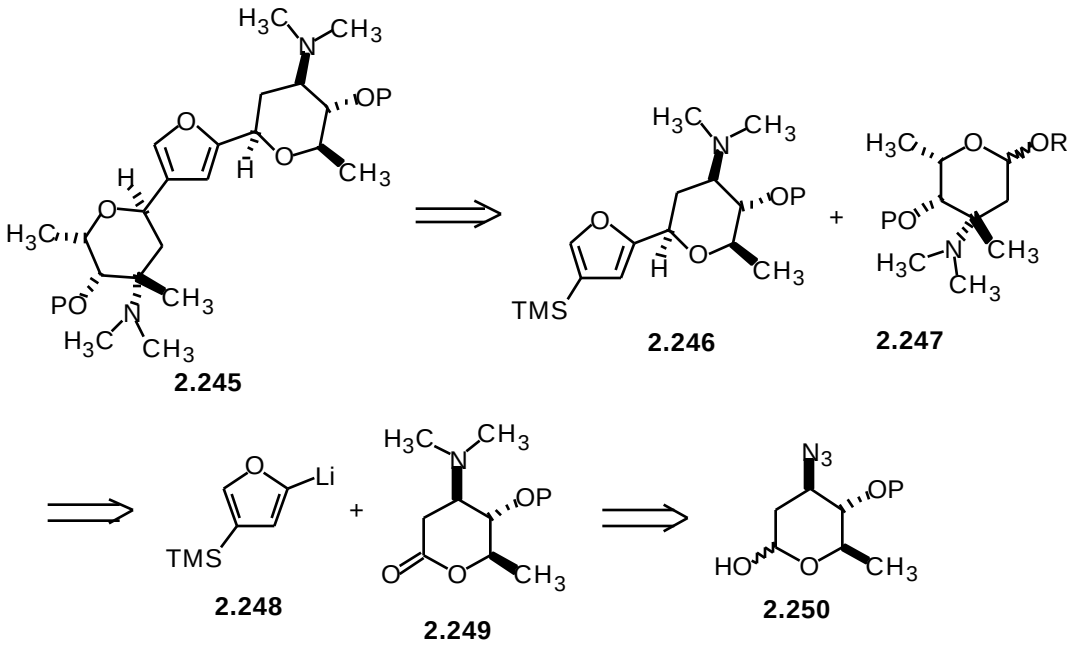
**Scheme 2.53**




We envisioned the requisite diglycosyl furan **2.245** arising from a Friedel-Crafts reaction, under kinetic control, between vancomycin-derived *O*-glycoside **2.247**[159] and TMS-furan **2.246**. While there was no specific literature precedent for *ipso*-substitution of a silyl group on a furan by a carbon electrophile, there were several examples in the literature detailing *ipso*-substitution reactions, such as electrophilic iodination, of TMS-substituted furans.[160] We hoped that by carefully controlling the reaction conditions,

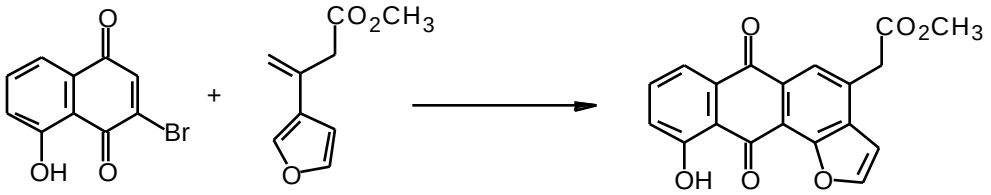
we would be able to prevent epimerization of the *N,N*-dimethylvancosamine after attachment to the furan. The furan **2.246** would be derived from reaction of the known furyllithium intermediate **2.248**[161] with the angolosamine lactone **2.249** followed by dehydration of the formed lactols and then hydrogenation of the glycal double bond. The lactone **2.249** would be obtained from the known azidolactol **2.250**[162] *via* a straightforward series of steps (Scheme 2.54).

**Scheme 2.54**




We hoped to access aldehyde **2.240** utilizing chemistry similar to that used by Kishi in the preparation of aklavinone.[163] His group had shown that 3-vinyl furan **2.252** underwent a facile Diels-Alder reaction with bromojuglone **2.251** to give, after double bond isomerization and aromatization, benzofuran **2.253**. We suspected that a similar sequence would provide benzofuran **2.241** (Equation 2.23).

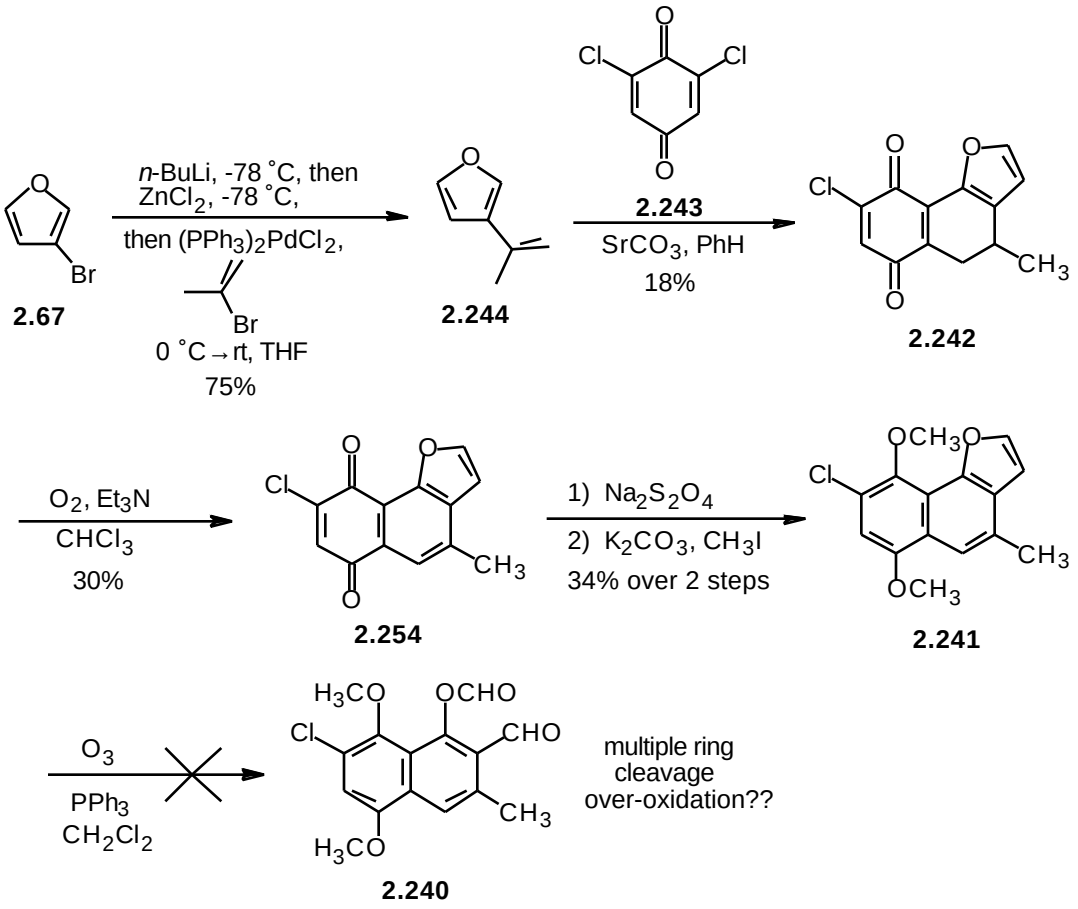
**Equation 2.23**




**2.232** **2.233** **2.234**

Using an alternative to the literature procedure, the known furan **2.244**[164] was obtained by palladium-catalyzed coupling of the organozinc halide derived from 3-bromofuran (**2.67**) with 2-bromopropene. The Diels-Alder reaction of furan **2.244** and 2,6-dichloroquinone (**2.243**) in the presence of strontium carbonate, which was added to scavenge the HCl produced, formed a cycloadduct that was not isolated, but rather underwent spontaneous isomerization to give **2.242** as a single regioisomer. Oxidation of **2.242** with molecular $O_2$ in the presence of triethylamine gave **2.254**.[163] Reduction of naphthoquinone **2.254** to the corresponding hydroquinone followed by exhaustive methylation gave the dimethylhydroquinone **2.241**. Unfortunately, attempts to cleave the furan ring with ozone, even at -78 °C, resulted in the apparent additional cleavage of the electron rich hydroquinone ring (Scheme 2.55). Due to the problems encountered in the attempted oxidation of **2.241**, as well as fact that the furan **2.244** rather labile and hence, difficult to prepare, we decided to abandon this route.

**Scheme 2.55**



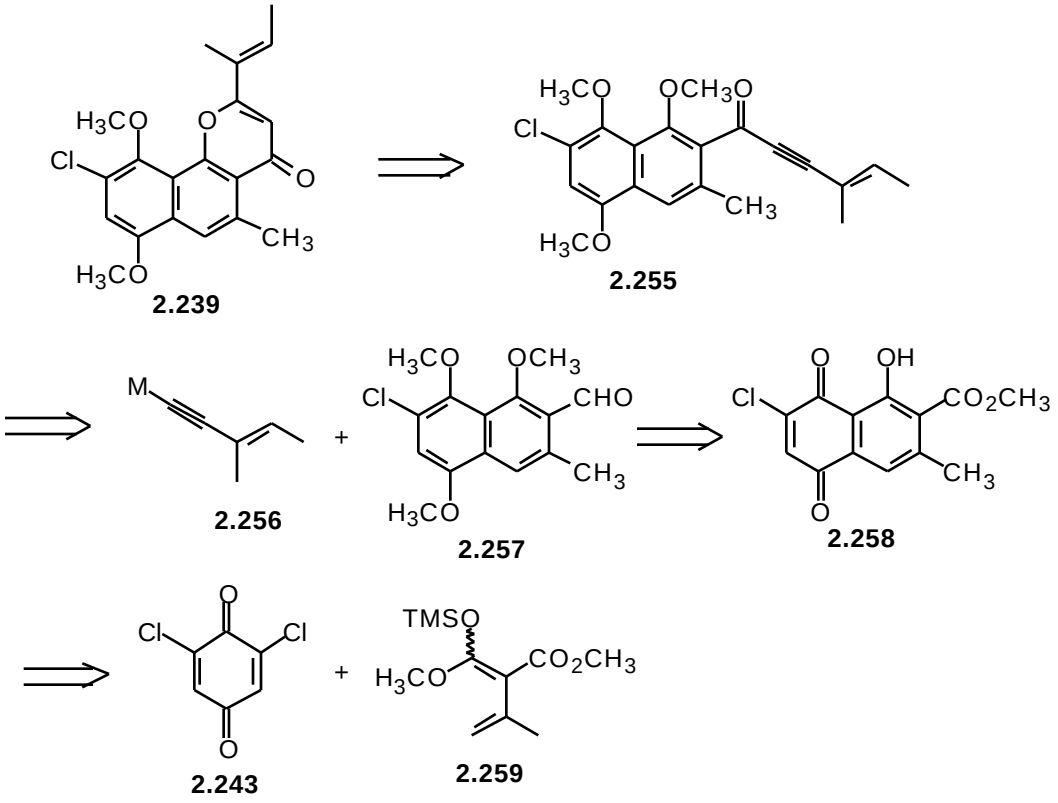

### 2.5.3 Martin Group Second Generation Approach

A substantial amount of work has been performed by Brassard and co-workers directed toward the regioselective construction of diverse arrays of oxygenated aromatic compounds *via* cycloadditions of quinones with silylketene acetals.[165] We thought that this basic approach might provide access to an oxygenated naphthalene of a similar structure to **2.240**.

We expected that the requisite benzyne precursor **2.239** could arise from selective *O*-demethylation of acetylenic ketone **2.255** followed by a 6-*endo*-dig

cyclization. Saito and others have shown that cyclization of phenols onto aromatic acetylenic ketones is a viable method for generating chromones.[166] The acetylenic ketone would be derived from aldehyde **2.257** *via* addition of an acetylide anion **2.256**, followed by oxidation of the resultant benzylic alcohol. The aldehyde **2.257** would arise from protection and functional group manipulation of chlorojuglone **2.258** that could be obtained from cycloaddition of 2,6-dichloroquinone (**2.243**) and silylketene acetal **2.259** (Scheme 2.56).

**Scheme 2.56**



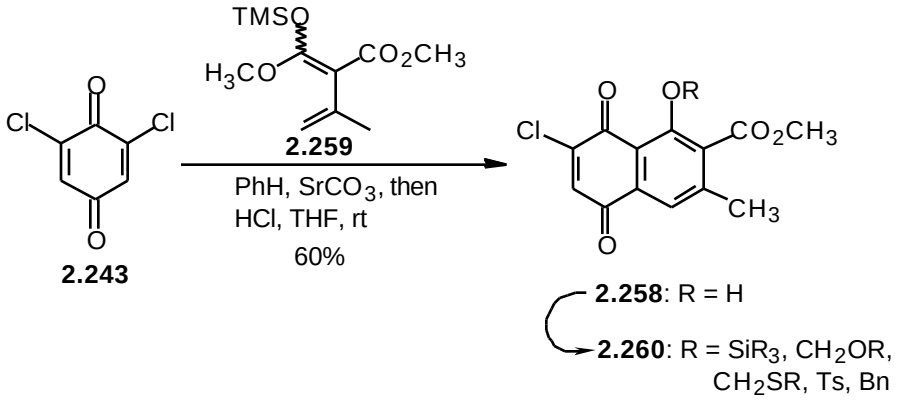

In our first experiments, a solution 2,6-dichloroquinone (**2.243**) was allowed to react with the known silylketene acetal **2.259**[167] in benzene in the presence of $SrCO_3$, which was used to scavenge the HCl produced during the reaction. This presumably

afforded a mixed silyl acetal, which was then hydrolyzed by the action of aqueous HCl/THF to provide the chlorojuglone **2.258** in 60% (Scheme 2.57). We chose to add $SrCO_3$ to the aforementioned cycloaddition reaction because we were concerned that any HCl that was liberated might hydrolyze unreacted **2.259** that was still present. A systematic study was initiated to determine if altering the reaction solvent would improve the yield. Additionally, we were curious whether it was necessary to add base to the reaction. The reaction of **2.243** with **2.259** in THF, $CHCl_3$, and PhH each in the presence and absence of base was examined. Based on these experiments it was determined that PhH was the superior solvent as use of THF and $CHCl_3$ failed to provide significant amounts of the desired cycloadduct. Moreover, the addition of base was not necessary. In fact, when no base was added to the reaction, the desired juglone **2.258** could be isolated directly from the cycloaddition reaction in approximately the same yield as seen previously without the need for a separate hydrolysis step .

With ample quantities of **2.258** in hand, attempts to protect the highly acidic phenol moiety were undertaken, but this turned out to be a much more difficult task than anticipated. For example, reaction of **2.258** with MOM-Cl resulted in partial conversion to what was believed to be, based on analysis of the crude $^1H$ NMR spectrum, the expected acetal. Unfortunately, all attempts to purify this compound or use it in subsequent transformations met with failure and delivered only deprotected **2.258** or decomposition products. Presumably the highly electron-withdrawing nature of the naphthoquinone allows for facile cleavage of protecting groups on the phenolic oxygen *via* expulsion of the highly stabilized phenoxide/phenol. Attempts were also made to prepare the analogous methylthiomethyl- and phenylthiomethyl acetals, but to no avail. Next, bulky silyl groups were examined as potential protecting groups. Efforts to

protect the phenol of **2.258** either as its triisopropylsilyl- or *t*-butyldimethylsilyl ether resulted in no reaction. Although reaction of the phenol with either TIPS-OTf or TBS-OTf did afford the desired silyl ethers, which could be carefully isolated and characterized, these compounds were exceedingly unstable and could not be further transformed. Attempted benzylation of **2.258** using both basic and Lewis acidic conditions afforded only recovered starting materials. An aryl tosylate was used by Wolfrom and co-workers as a phenol protecting group in a total synthesis of naturally occurring pigments.[168] However, the tosylate derived from **2.258** proved to be too robust; the tosyl group could not be cleaved at a later stage in the synthesis (Scheme 2.57).

**Scheme 2.57**




Another protecting group that was investigated for the free hydroxyl group in naphthol **2.258** was an acetate. Thus, treatment of **2.258** with acetyl chloride in pyridine gave the juglone acetate **2.261** in quantitative yield. When **2.261** was treated with $Na_2S_2O_4$, reduction to the hydroquinone occurred as expected but, unexpectedly, concomitant migration of the acetate to the hydroxyl group in the hydroquinone ring also occurred to give **2.262** (Scheme 2.58). A nOe experiment was used to determine

that the migration had occurred (Figure 2.7). Irradiation of the proton on the phenol showed a strong enhancement to both the acetate and ester moieties, and irradiation of the ester protons showed an enhancement to the phenol and benzyl methyl group. Treatment of a solution of **2.262** in $CH_2Cl_2$ with a solution of $CH_2N_2$ in $Et_2O$ afforded **2.263** after 24 h at room temperature. We are fairly confident that the acetate in **2.262** did not undergo further rearrangement during the methylation step, and thus we believe that the single regioisomer that was obtained from this reaction does in fact have the structure **2.263**.

**Scheme 2.58**

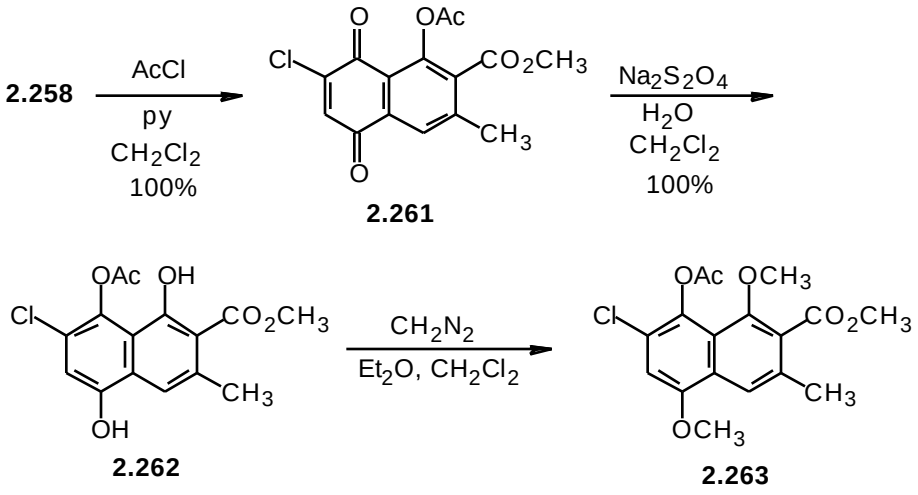
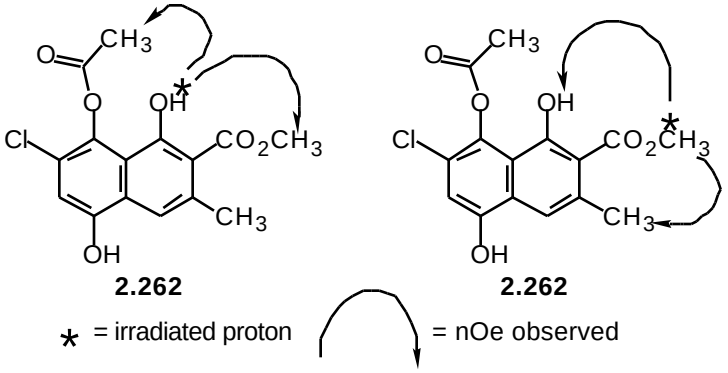
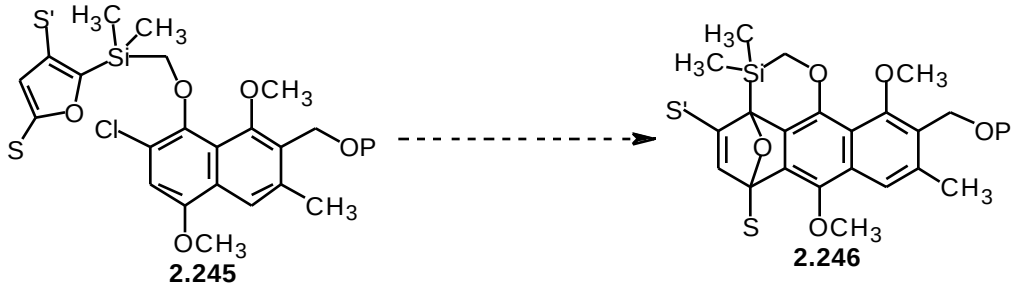



**Figure 2.7**



The aforementioned acetate migration inspired us to examine the possibility of applying our tethered intramolecular benzyne cycloaddition methodology to the regioselective preparation of members of the pluramycin class of antibiotics. Presumably, after refunctionalization and protection of the ester side chain in **2.263** and removal of the acetate, we could append a diglycosyl furan using chemistry previously developed to give an intermediate of the general type **2.264**. Benzyne generation from **2.264** should result in intramolecular cycloaddition to regiospecifically give a compound of general structure **2.265**. Cleavage of the tether and further manipulation of **2.265** could lead to kidamycin and related *bis*-*C*-glycoside antibiotics (Equation 2.24).

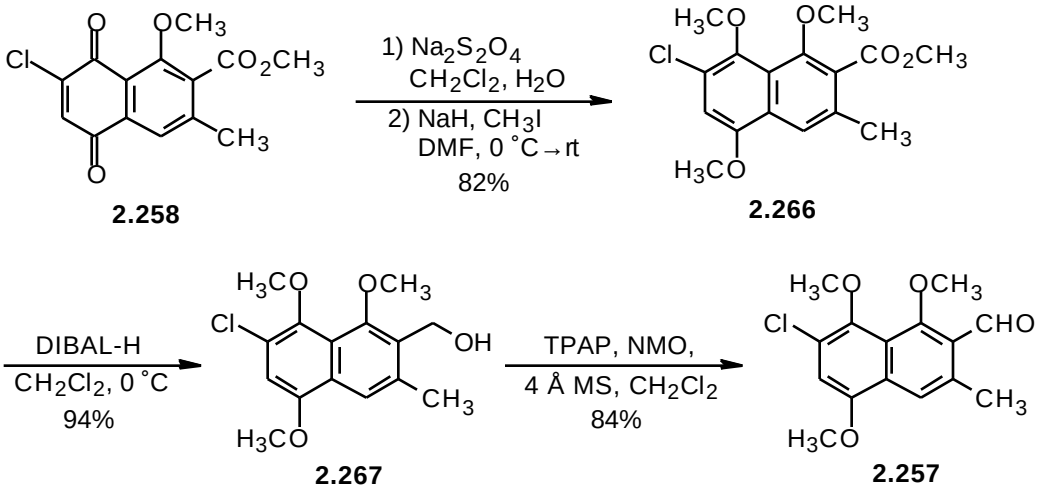
**Equation 2.24**




While we were in the process of determining whether the acetate migration depicted in Scheme 2.58 would prove to be useful to our synthetic efforts, we decided to move forward with a more robust protecting group that would be less likely to migrate. We eventually decided to protect the phenol in **2.258** as its methyl ether. We suspected that the electron withdrawing ester and quinone on either side of the phenol were rendering it an extremely weak nucleophile and hence making it difficult to protect and keep protected. Ultimately, it was decided that it might be easier to reduce the quinone functionality and then protect each of the free hydroxyl groups of the resultant triphenol with the same protecting group. It is well precedented that in molecules that contain

multiple phenolic groups protected as their methyl ethers, it is possible to demethylate selectively any of the ethers that are in close proximity to groups capable of Lewis acid chelation using reagents like $BBr_3$ and $AlCl_3$.[169] In the event, reduction of juglone **2.258** with $Na_2S_2O_4$ followed by exhaustive methylation gave the trimethoxy naphthalene **2.266**. The ester side chain was converted to an aldehyde by sequential reduction to the benzylic alcohol **2.267** and oxidation to give **2.257** (Scheme 2.59).

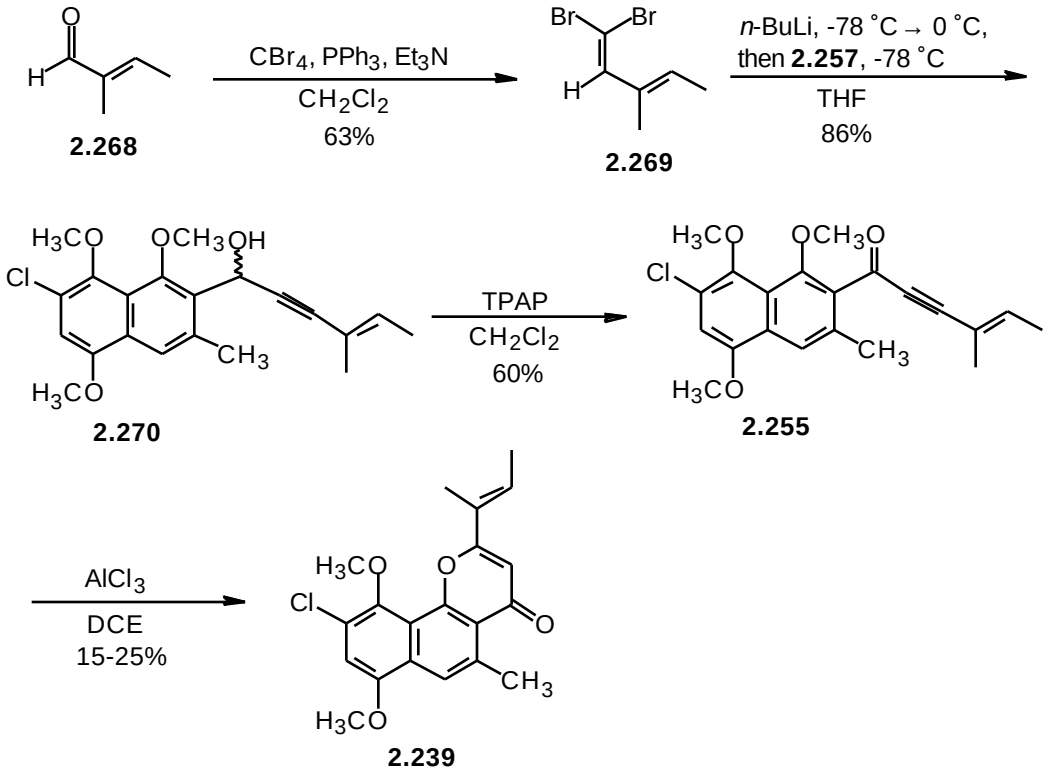
**Scheme 2.59**




The synthesis of the enyne sidechain found in kidamycin was then undertaken. Using a modified procedure for the preparation of 1,1-dibromoalkenes from the corresponding aldehydes,[170] commercially available tiglaldehyde (**2.268**) was allowed to react with $CBr_4$ and $PPh_3$ in the presence of $Et_3N$ to give the moderately unstable dibromoalkene **2.269**.[171] Following the Corey-Fuchs protocol,[172] **2.269** was treated with *n*-BuLi (2.1 equiv) at -78 °C followed by warming to 0 °C in order to generate the corresponding lithium acetylide *in situ*. Addition of a solution of **2.257** in THF to a solution of this lithium acetylide gave the benzylic alcohol **2.270**. Oxidation of the

alcohol in **2.270** to the corresponding ketone using TPAP/NMO in the presence of 4 Å molecular sieves gave **2.255**. Following a procedure for the selective demethylation and cyclization of a closely related compound,[166e] **2.255** was treated with $AlCl_3$ to give chromone **2.239** directly, albeit in low yield (Scheme 2.60). Although the concomitant cyclization to give the pyrone directly was unexpected, it was not particularly surprising. Apparently under the reaction conditions the free phenol (or its aluminate) cyclized onto the acetylenic ketone in a 6-*endo*-dig mode, presumably promoted by Lewis acid coordination with the ketone oxygen. The yield in the deprotection/cyclization sequence could likely be improved if one could find a way to protect the phenol present in **2.258** with a group that could be removed under milder conditions (e.g. MOM).

**Scheme 2.60**

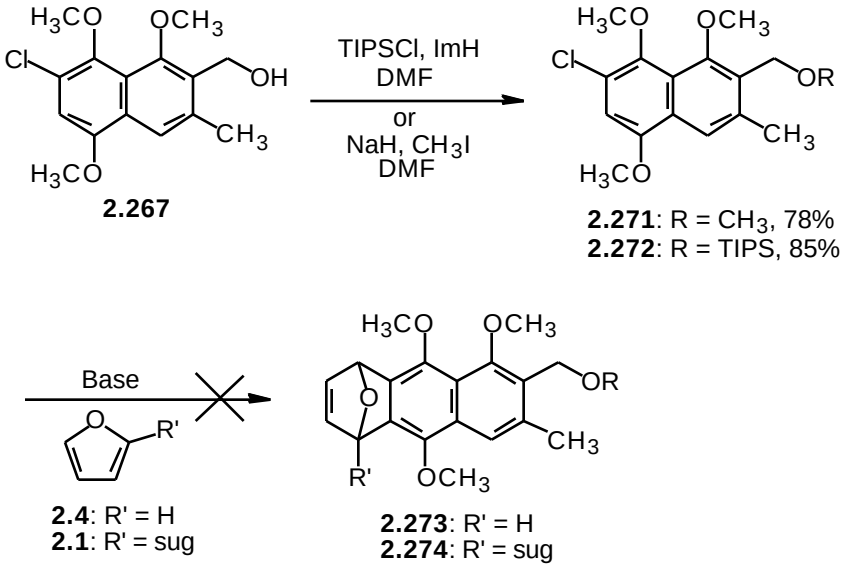


With **2.239** in hand, we quickly discovered that it was not particularly stable. Upon standing in $CDCl_3$ for 24 h, the side chain double bond in **2.239** isomerized to a mixture (ca. 1:1) of *E*- and *Z*-isomers. Evidence for this isomerization was obtained by nOe analysis of the newly formed mixture. Additionally, it was discovered that **2.239** decomposed to unidentified by-products on storage at room temperature in the light. Nevertheless, we attempted to generate a benzyne from **2.239** by treatment with *n*-BuLi. Perhaps unexpectedly, addition to the carbonyl appeared to be the major reaction pathway. Due to the fact that **2.239** was unstable and that we were unable to generate a benzyne from it, we decided to examine other strategies. We believed that construction of the core (B- to D-rings) of kidamycin first, followed by late stage introduction of the troublesome A-ring would alleviate our difficulties.

In order to probe the viability of this strategy, we decided to investigate benzyne generation and cycloaddition of some of the protected naphthalene intermediates we had used earlier in the synthesis. Thus, the alcohol group in **2.267** was protected as its methyl- and triisopropylsilyl ether **2.271** or **2.272**. Unfortunately, treatment of **2.271** or **2.272** with various bases including *n*-BuLi, *s*-BuLi, *t*-BuLi, and LDA followed by addition of unsubstituted and glycosyl-substituted furans returned only unchanged starting materials. No cycloadducts of the general structure **2.273** or **2.274** were detected in any of the reaction mixtures (Scheme 2.61). Due to the difficulties we were experiencing, it seemed logical to examine whether deprotonation of **2.271** or **2.272** was occurring to a significant extent. Treatment of a solution of **2.271** or **2.272** in THF with any of the aforementioned bases followed by quenching with $d_4$-$CH_3OH$, revealed that no significant metalation was occurring anywhere in either compound. Amazingly, treatment of **2.272** or **2.272** with up to 10 equivalents of bases such as *n*-BuLi or *s*-

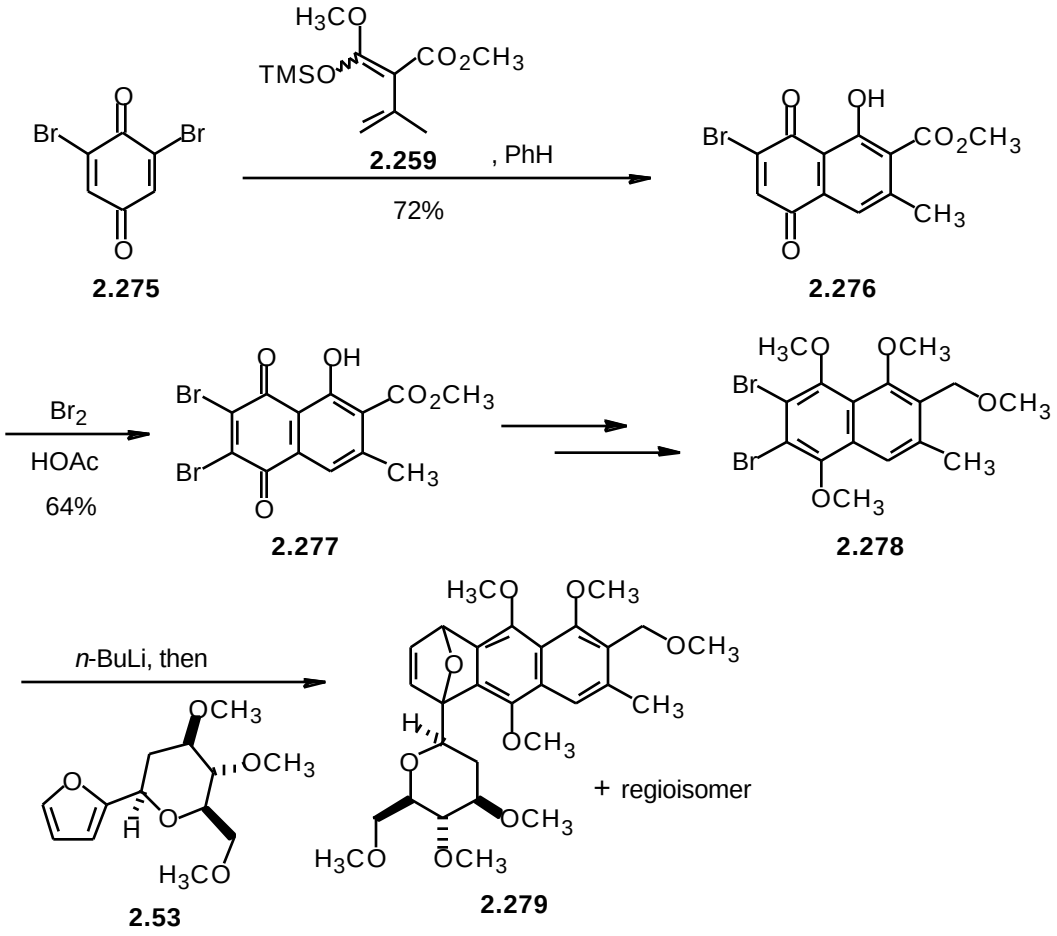
BuLi followed by warming failed to induce any significant deprotonation or other reaction.

**Scheme 2.61**




Since it now appeared that benzyne generation *via* deprotonation of **2.271/2.272** was not going to be a viable strategy, we briefly investigated an idea that relied on halogen-metal exchange to generate the requisite *o*-lithio halide precursor to benzyne. Thus, cycloaddition of dibromoquinone **2.275** with **2.259** delivered bromojuglone **2.276** 72% yield. This juglone was treated with $Br_2$ in HOAc at 100 ˚C to induce bromination/dehydrobromination to give dibromojuglone **2.277**. Manipulation of **2.277** using chemistry identical to that used in the preparation of **2.271/2.272** afforded benzyne precursor **2.278**. Treatment of a solution of **2.278** and glycosyl furan **2.53** at -78 ˚C with *n*-BuLi, followed by warming to room temperature delivered a low yield (unoptimized) of what has been tentatively assigned as **2.279** (based on the presence of signals in the $^1$H NMR corresponding to the bridgehead protons δ 5.9-5.7) as a mixture (ca 1:1:1:1) of regio- and diastereomers (Scheme 2.61).

**Scheme 2.61**

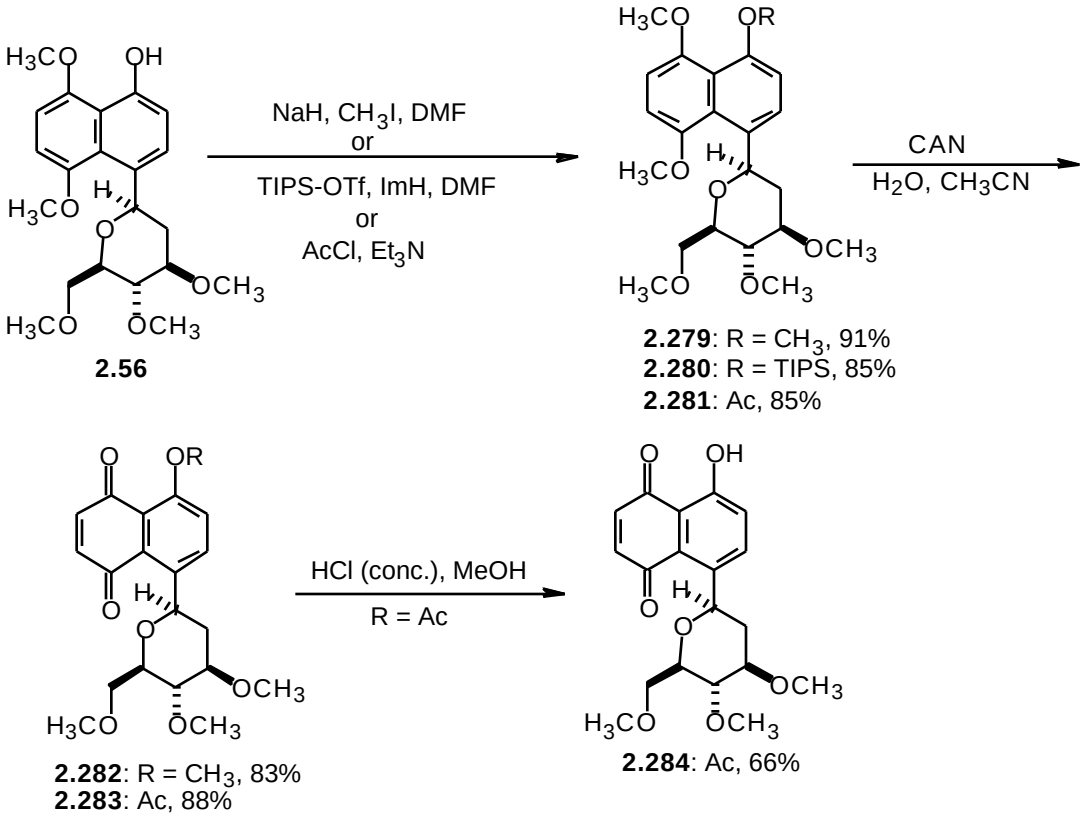



### *2.5.3.1 Kidamycin Model Chemical Behavior Studies*

To date, there has been relatively few ways to access 4-substituted *C*-aryl glycosides, so few such compounds have been synthesized. It is well precedented that members of the pluramycin class of antibiotics are fairly unstable to light as well as acidic and basic conditions. For this reason, we thought it might be useful to perform some of the projected steps toward kidamycin/pluramycin on a 4-substituted glycoside model system in order to determine at what stages the aforementioned instabilities

With quantities of **2.56** (Scheme 2.8) in hand, a series of investigations directed toward its oxidation to the requisite naphthoquinone were initiated. We first attempted to oxidize **2.56** directly to the corresponding juglone. Perhaps not unexpectedly, oxidation had occurred in the phenol ring which resulted in destruction of the carbohydrate moiety. The basis for this conclusion was the absence of pyran -$CH_2$ resonances in the $^1$H NMR. Hence, the phenol of **2.56** was protected with -$CH_3$, -TIPS, and -Ac. The dimethylhydroquinone ring was oxidatively demethylated with ceric ammonium nitrate (CAN) in aqueous $CH_3CN$ to give naphthoquinones **2.282** and **2.283** (R = -$CH_3$ and -Ac). The silyl group in **2.280** appeared to be too labile to withstand the reaction conditions, and only decomposition to many unidentified products was observed. We expected that the acetate in **2.283** would be more easily cleaved than the methyl ether in **2.282**, and its removal using basic and acidic conditions was examined. However, using $K_2CO_3$ in $CH_3OH$ gave products that appeared to arise from conjugate addition of methoxide to the quinone. The basis for this assumption was the absence of vinyl resonances and the presence of several additional -$OCH_3$ signals. Fortunately, the acetate was cleaved in excellent yield upon treatment of **2.283** with HCl in $CH_3OH$ to give **2.284** (Scheme 2.62).

**Scheme 2.62**




**2.56**

**2.279**: R = $CH_3$, 91%
**2.280**: R = TIPS, 85%
**2.281**: Ac, 85%

**2.282**: R = $CH_3$, 83%
**2.283**: Ac, 88%

**2.284**: Ac, 66%

We were surprised to discover that *C*-glycosyl juglone **2.284** was in fact quite unstable. That it was light sensitive was verified by performing a simple experiment in which **2.284** was first dissolved in $CHCl_3$. Half of the resulting solution was stored in the dark while the other half was left exposed to standard fluorescent laboratory lighting. After only 24 h, the sample stored in the light showed significant by-product formation, whereas the sample from which light had been excluded appeared unchanged as determined by TLC analysis. After several days in the light, the bright yellow solution of **2.284** had become almost completely colorless, and TLC analysis indicated that no **2.284** remained. Analysis of the $^1$H NMR spectrum of the photodegradation products revealed that several unidentifiable compounds were present. These results

were not completely surprising since the instability of kidamycin and related *C*-glycoside antibiotics in the presence of light was well documented.[155] In terms of our total synthesis, knowing that adducts like **2.284** are photosensitive will most likely prove useful as we begin to incorporate valuable aminosugars.

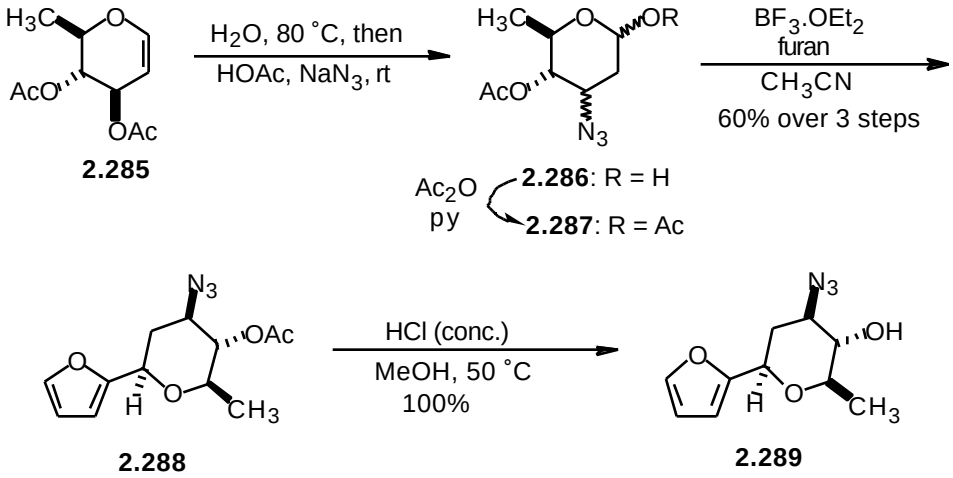
#### *2.5.3.2 Efforts Toward the Synthesis and Attachment of the E-Ring Sugar, Angolosamine*

With routes to the core of kidamycin under development we began to examine methods for preparing the deoxyaminosugars present in the natural product. Angolosamine, the *N*,*N*-dimethyl derivative of D-acosamine, is one of three glycosidic residues found in the macrolide antibiotic angolomycin.[173] Several syntheses of D-acosamine starting from carbohydrate precursors have been reported.[174] Hauser and Ellenberger have extensively reviewed the chemistry, structures, isolation, and total syntheses of 2,3,6-trideoxy-3-aminohexoses including angolosamine and *N*,*N*-dimethylvancosamine, the aminosugars found in kidamycin.[175] We decided that the most expeditious way to access a useful synthetic precursor to angolosamine would be to utilize one of the existing procedures.

Following a literature procedure, an aqueous solution of **2.285** was heated at 50 ˚C for 1 h, whereupon the reaction was cooled to room temperature and HOAc and $NaN_3$ were added to provide azidolactol **2.286** as a mixture (ratio not determined) of four diastereomers.[162] This mixture of lactols **2.286** and furan in $CH_3CN$ at room temperature was treated with $BF_3{\cdot}OEt_2$ to give **2.288** as a mixture (unknown ratio) of four diastereomers. The all equatorial β-diastereomer **2.288** was obtained in pure form (50%) by careful chromatography. It was critical that the Friedel-Crafts reaction be run

at room temperature, not lower temperatures, in order to ensure the highest selectivity for the all equatorial glycoside. A slightly modified procedure for the preparation of **2.288** that was significantly cleaner involved first acylating the lactol **2.286** to give the glycosyl acetate **2.287**, again as a mixture of four diastereomers. Friedel-Crafts reaction between the acetate **2.287** afforded the desired furan in 60% yield (Scheme 2.63). The hydroxyl group in **2.288** was unmasked by hydrolysis of the acetate under acidic conditions to give an excellent yield of the crystalline hydroxy azide **2.289**, the structure of which was established by an X-ray analysis. This clearly showed that we had in fact successfully prepared the desired all equatorial azidosugar.

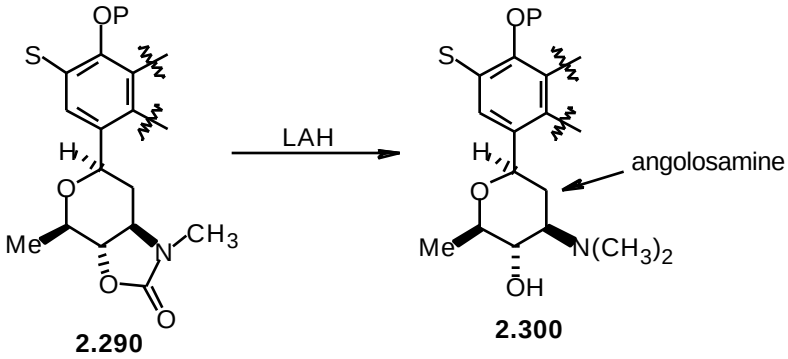
**Scheme 2.63**




We anticipated that it might be necessary to protect the hydroxyl and azido functionalities present in **2.289** before attempting any benzyne cycloadditions. Initially, we considered the possibility of reducing the azide in **2.289**, and then protecting the resultant 1,2-aminoalcohol. Later in the synthesis we would want to remove the protecting group(s) to unmask the hydroxyl and methylamino functionalities. The requisite dimethylamino group would then be prepared using an Eschweiler-Clark or

related reductive amination protocol.[176] Later we came to the assumption that a cyclic *N*-methyl carbamate would be an ideal choice for protecting the 1,2-aminoalcohol since this array would simultaneously protect both functionalities. Furthermore, if we could successfully carry the *N*-methyl carbamate through the synthesis, it should be possible to reduce with lithium aluminum hydride (LAH) to unmask the hydroxyl and dimethylamino functionalities in a single step (Equation 2.25).

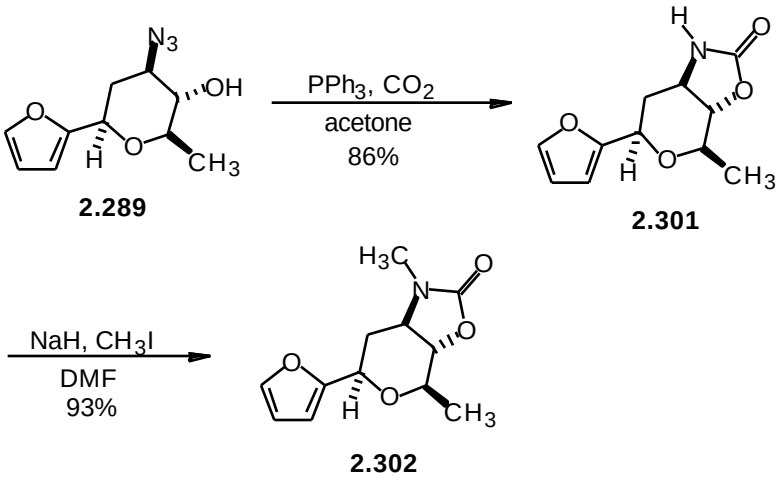
**Equation 2.25**




**2.290** **2.300**

We were further attracted to a carbamate protecting group because we believed it would be possible to introduce it in an highly efficient and facile manner. Pintér and co-workers demonstrated that it was possible to reduce β-hydroxy azides with $PPh_3$ in the presence of $CO_2$ to directly obtain carbamates.[177] The mechanism proposed for this transformation involves initial reaction of $PPh_3$ with the azide to give an aza-ylide that is intercepted by $CO_2$ to give an intermediate isocyanate. Intramolecular attack of the hydroxyl group on this isocyanate provides the carbamate. Gratifyingly, treatment of **2.289** under the conditions of Pintér delivered the highly crystalline cyclic carbamate **2.301** in excellent yield. The *N*-methyl carbamate **2.302** was easily prepared using standard alkylation conditions (Scheme 2.64).

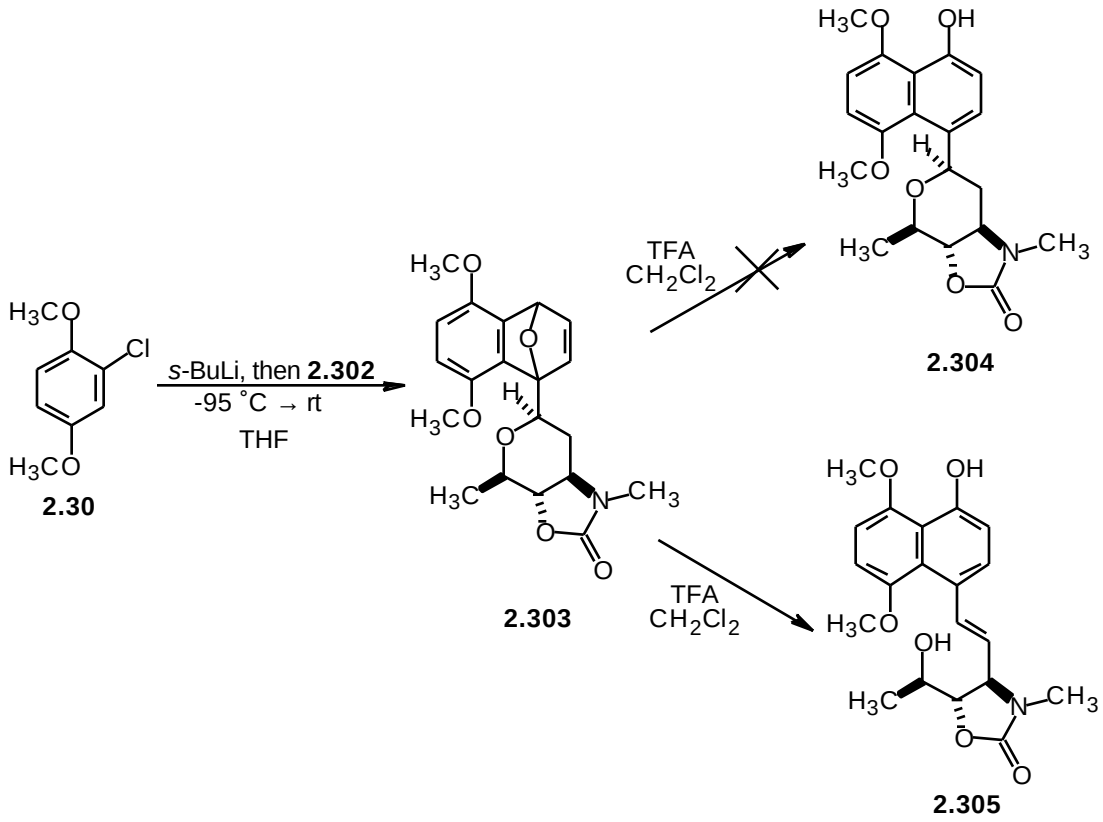
**Scheme 2.64**




**2.289** **2.301** **2.302**

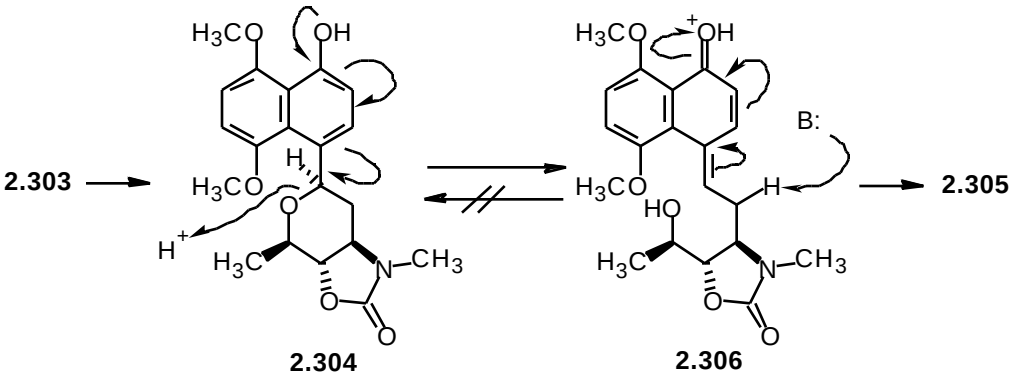
Cycloaddition of **2.302** with the benzyne generated from **2.30** did afford the expected adduct **2.303**. Unexpectedly, when this cycloadduct was treated with TFA the desired naphthol **2.304** was not produced. Instead, a naphthol was produced in which the carbohydrate moiety was no longer intact as evidenced by absence of signals corresponding to the anomeric and pyran methylene protons in the $^{1}$H-NMR. The structure of this adduct was tentatively assigned as **2.305** based on the aforementioned data as well as the fact that the compound appeared to contain a disubstituted olefin. One possible explanation for the formation of an adduct that possessed an olefin is depicted in Scheme 2.65.

**Scheme 2.65**



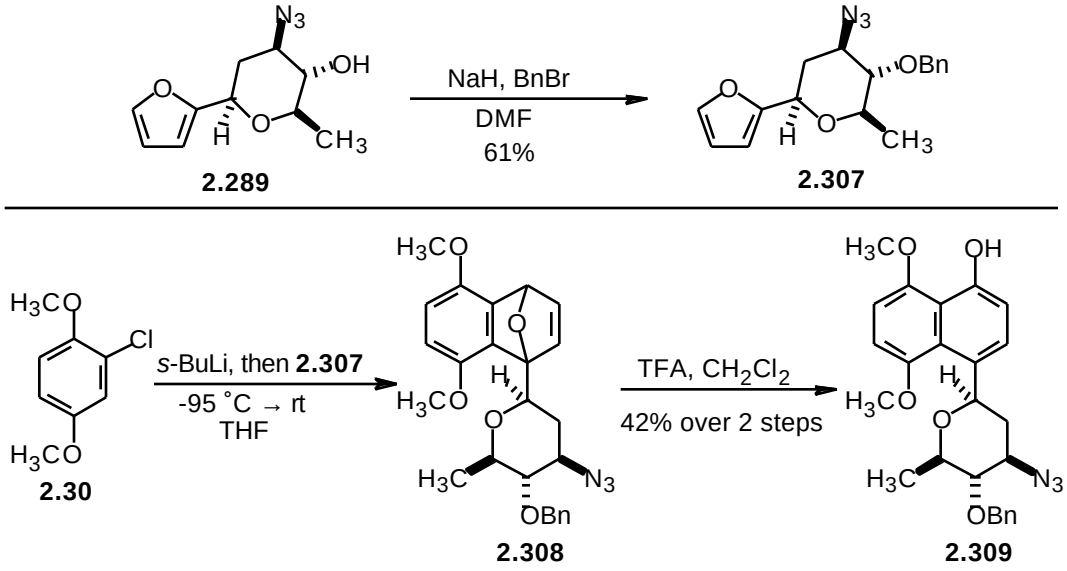

It is believed that after ring opening of the bridging ether and aromatization had occurred, the pyran ring opened to give an extended cationic system such as **2.306**. A related mechanism was proposed previously to explain the observation that α-anomers of *C*-aryl glycosides undergo equilibration in the presence of acid to give the more thermodynamically stable β-anomer. However, in the case of **2.306** reclosure of the pyran would be disfavored due to reformation of the rather strained *trans*-[4.3.0] system. Instead of reclosure, proton loss gives alkene **2.305** (Scheme 2.66).

**Scheme 2.66**




With the rather disappointing results obtained using the *N*-methyl carbamate protected sugar **2.302**, we decided to investigate benzyne cycloadditions in which the hydroxyl functionality in **2.289** was protected and the azide was not. Thus, the hydroxyl group in **2.289** was protected as a benzyl ether by the action of NaH and BnBr to give **2.307**. Treatment of a solution of **2.30** in THF with *s*-BuLi followed by addition of furan **2.307**, and then warming to room temperature resulted in benzyne formation and cycloaddition to give **2.308**. Treatment of **2.308** with TFA gave the naphthol **2.309** in 42% (unoptimized) yield from **2.307** (Scheme 2.67). Significantly, **2.309** contained all the atoms as well as the necessary stereochemistry for rapid conversion to angolosamine. This example represents the first time we have successfully prepared a precursor to an aminosugar using the benzyne/furan cycloaddition approach. We believe that the low yield in the transformation of **2.307** → **2.308** may be due in part to a competitive [3+2] cycloaddition between the benzyne generated from **2.30** and the azide moiety in **2.307**. Dipolar cycloadditions between azides and benzynes are well documented.[178]

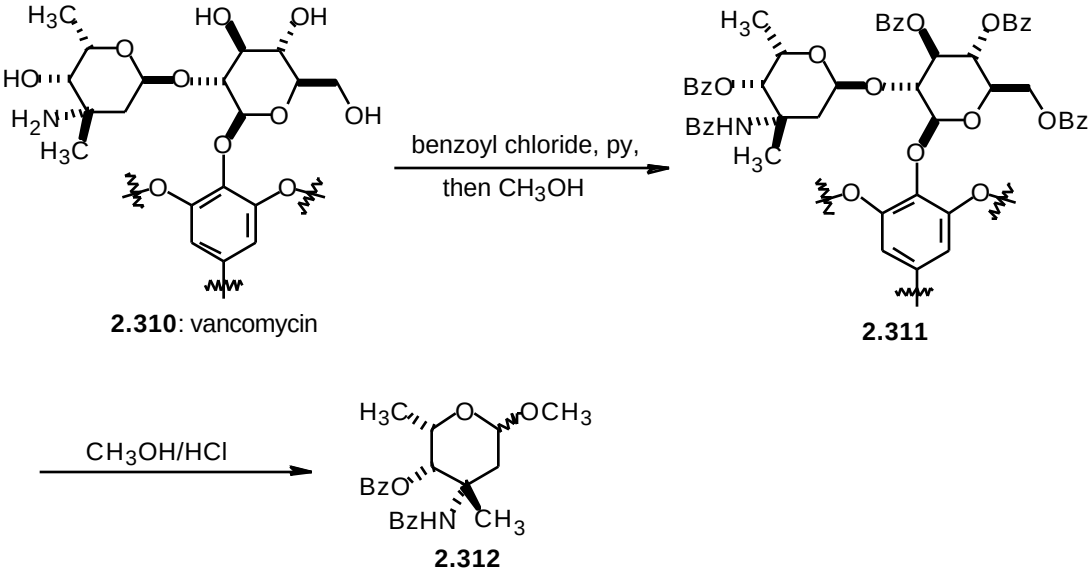
**Scheme 2.67**




### 2.5.4 The F-Ring Sugar, *N*,*N*-Dimethylvancosamine

We planned to acquire *N*,*N*-dimethylvancosamine, the F-ring sugar of kidamycin, by degradation of vancomycin. Following the protocol of Danishefsky, vancomycin hydrochloride **2.310**[179] was treated with benzoyl chloride and pyridine.[159] The fully benzoylated product **2.311** was then hydrolyzed by the action of acidic methanol to give benzoyl-protected vancosamine **2.312** as a mixture of anomers (Scheme 2.68). Future work will involve exploring the stereochemical outcome of $O \rightarrow C$-glycoside rearrangements of protected vancosamine derivatives in order to see if it is possible to selectively prepare the required axial *C*-aryl glycoside as is found in the pluramycin antibiotics.

**Scheme 2.68**




**2.310**: vancomycin

**2.311**

**2.312**

## 2.6 CONCLUSIONS

A unified strategy has been developed that allows for the preparation of all four of the structural types of *C*-aryl glycosides. The first method involves the [4+2] cycloaddition of glycosyl-substituted furans and benzynes followed by acid-catalyzed ring opening of the adducts. By controlling the position(s) of the glycoside(s) on the furan, it is possible to obtain the *C*-aryl glycosides Groups I-IV with high regioselectivity between the phenolic hydroxyl group(s) and the glycosidic moiety(ies).

It was important that we also be able to control the global regioselectivity in the aforementioned cycloadditions. With this goal in mind, a silicon tether approach was developed that rendered the benzyne/furan cycloadditions intramolecular. Thus, by simply linking the glycosyl furan and benzyne precursor together, absolute regiocontrol was realized in the cycloaddition. The tether could then be removed in one of two ways: by nucleophilic cleavage of the tether to yield a hydroquinone dimethyl ether; or by

nucleophilic cleavage with an additional oxidative step to completely excise the tether and unmask a free phenol.

A second strategy that was investigated for the synthesis of *C*-aryl glycosides was the $S_N2'$ ring opening of benzyne/furan cycloadducts with glycosyl anions. While this transformation was not particularly successful, it did lead to the discovery of a closely related approach; namely, the palladium-catalyzed $S_N2'$ ring opening of benzyne/furan cycloadducts using iodoglucals. In the hands of a former postdoctoral associate in the group, this technique allowed for the preparation of *C*-aryl glycosides of the Group II and Group III types.

In an effort to establish some of the recently discovered methods for *C*-aryl glycoside construction in the context of a total synthesis, we attempted to prepare the naturally occurring antibiotic galtamycinone. A concise formal total synthesis of the natural product was successfully completed using the benzyne/furan cycloaddition approach.

With the goal of further developing our methods in the area of total synthesis, we have also undertaken efforts toward the synthesis of the *bis*-*C*-aryl glycoside antitumor antibiotic, kidamycin. An efficient approach to the core of the antibiotic has been developed. Additionally, a viable strategy has been discovered that allows for the introduction of the E-ring sugar, angolosamine, onto a substituted aromatic nucleus.

# Chapter 3. Experimental Procedures

## 3.1 GENERAL

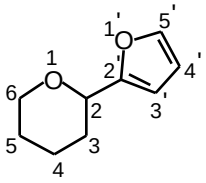
Unless otherwise noted, solvents and reagents were used without purification. Tetrahydrofuran (THF) and diethyl ether ($Et_2O$) were dried by passage through two columns of activated neutral alumina. Methanol ($CH_3OH$), acetonitrile ($CH_3CN$), and *N*,*N*-dimethylformamide (DMF) were dried by passage through two columns of activated molecular sieves. Toluene was dried by sequential passage through a column of activated neutral alumina followed by a column of Q5 reactant. All solvents were deemed to contain less than 50 ppm $H_2O$ by Karl Fischer coulometric moisture analysis. Reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of argon in glassware that had been oven or flame dried.

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded with a Perkin Elmer FT-IR 1600 series spectrometer, either neat on sodium chloride plates or as solutions in $CHCl_3$ as indicated and are reported in wavenumbers ($cm^{-1}$). $^1H$ and $^{13}C$ NMR spectra were obtained on a Bruker 250, Varian 300, Varian 400, or Varian 500 spectrometer at the indicated field strength as solutions in the appropriate deuterated solvent ($CDCl_3$ unless otherwise indicated). Chemical shifts are reported in parts per million (ppm, $\delta$) downfield from tetramethylsilane (TMS, $\delta$ 0.00 = ppm) and referenced to the residual proton signal of the solvent. Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; comp, complex multiplet; and br, broad. Low resolution chemical ionization mass spectra (CIMS) were obtained with a Finnigan TSQ-70 instrument using methane

($CH_4$) as the ionization gas. High resolution measurements were made with a VG Analytical ZAB2-E instrument.

Analytical thin layer chromatography (TLC) was performed on EM Science 60 $F_{254}$ silica gel plates (5.0 cm x 2.5 cm) eluting with solvents as indicated. The plates were visualized with short wave UV light and ceric ammonium nitrate/ammonium molybdate (AMCAN) stain. Flash chromatography was performed using ICN 32-63 60 Å silica gel and following the method of Still.[180]

## 3.2 COMPOUNDS




**2.40**

**2-Furan-2-yltetrahydropyran (2.40)**. **Procedure 1:** A mixture of TsOH (253 mg, 1.5 mmol), **2.33** (2.50 g, 14.7 mmol), and 4 Å molecular sieves (3 g) in $CH_2Cl_2$ (500 mL) was stirred at rt for 28 h. The molecular sieves were removed by vacuum filtration, and the filtrate was treated with excess $Et_3N$ and then concentrated. The residue was purified by flash chromatography eluting with 20% $CH_2Cl_2$/hexanes as eluent to give 1.33 g (60%) of **2.40** as a colorless oil. The use of trifluoromethanesulfonic acid (0.1 eq) in place of TsOH at 0 ˚C resulted in immediate conversion of **2.33** to **2.40** in (69%) yield.

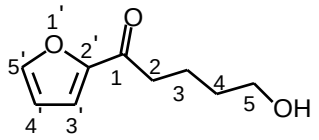
**Procedure 2:** A solution of *t*-butyllithium in pentane (1.58 M, 7.5 mL, 11.9 mmol) was added to a solution of dihydropyran (500 mg, 5.9 mmol) in THF (18 mL) at -78 ˚C, and the reaction mixture was warmed to 0 ˚C and stirred for 1.5 h. The solution was cooled to -78 ˚C, and $ZnCl_2$ in $Et_2O$ (1.0 M, 17.8 mL, 17.8 mmol) was added. The reaction mixture was warmed to rt and stirred for 50 min. $I_2$ (3.0 g, 11.8 mmol) was added in several portions, and the mixture was stirred for 12 h at rt. The reaction mixture was transferred to a separatory funnel and 5% aqueous $Na_2S_2O_3$ (30 mL) was added. The solution was shaken vigorously, and the layers were separated. The aqueous phase was extracted with $Et_2O$ (2 x 200 mL), and the combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure to a volume of ~5 mL. Anhydrous THF (10 mL) was added to give a ~0.34 M

solution of dihydropyranyl iodide 2.37 that was used without further purification. $Pd(PPh_3)_2Cl_2$ (60 mg, 0.09 mmol) was added to a solution of 2-furylzinc chloride (6.8 mmol) and dihydropyranyl iodide 2.37 (0.34 M, 5 mL, 1.7 mmol) in THF (10 mL) at rt, and the mixture was stirred for 0.5 h at rt. The solvent was removed under reduced pressure and the residue was purified directly by flash chromatography eluting with 2% EtOAc/hexanes to give crude 2.29. The crude 2.29 thus obtained was dissolved in EtOH (10 mL) containing a spatula tip of bromocresol green. Sodium cyanoborohydride (641 mg, 10.2 mmol) and methanolic HCl were added alternatively, and after 3 h at rt, the yellow color persisted, whereupon saturated aqueous $NaHCO_3$ (10 mL) was added. The aqueous mixture was extracted with $Et_2O$ (3 x 10 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 1% EtOAc/hexanes to give <20% of slightly impure 2.30.

**Procedure 3:** Boron trifluoride etherate ($BF_3{\cdot}OEt_2$) (0.97 mL, 7.6 mmol) was added to a solution of dihydropyranyl acetate 2.44 (1.0 g, 6.9 mmol) and furan (1.42 g, 20.9 mmol) in $CH_2Cl_2$ (35 mL) at 0 ˚C. Saturated aqueous $NaHCO_3$ (20 mL) was immediately added, and the layers were separated. The organic layer was washed sequentially with saturated aqueous $NaHCO_3$ (40 mL) and brine (40 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 10% EtOAc/hexanes to give 802 mg (76%) of 2.30 as a colorless oil: $^1$H NMR (250 MHz) δ 7.35 (dd, *J* = 1.8, 0.7 Hz, 1 H), 6.30 (dd, *J* = 3.3, 1.8, Hz, 1 H), 6.23 (br d, *J* = 3.3 Hz, 1 H), 4.41-4.35 (m, 1 H), 4.08-4.01 (m, 1 H), 3.64-3.53 (m, 1 H), 1.96-1.52 (comp, 6 H); $^{13}$C NMR (75 MHz) δ 155.2, 141.9, 109.9, 106.1, 72.9, 68.6, 29.5, 25.7, 23.2; IR ($CDCl_3$) 2944, 2852, 1727, 1504, 1442,

1359, 1271, 1216 $cm^{-1}$; mass spectrum (CI) *m/z* 153.0910 [$C_9H_{13}O_2$ (M + H) requires 153.0916].

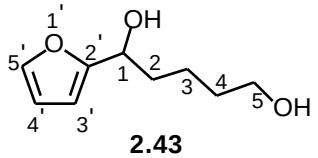
**NMR Assignments.** $^1$H NMR (250 MHz) δ 7.35 (dd, *J* = 1.8, 0.7 Hz, 1 H, C5'-H), 6.30 (dd, *J* = 3.3, 1.8, Hz, 1 H, C4'-H), 6.23 (br d, *J* = 3.3 Hz, 1 H, C3'-H), 4.41-4.35 (m, 1 H, C2-H), 4.08-4.01 (m, 1 H, C6-H), 3.64-3.53 (m, 1 H, C6-H), 1.96-1.52 (comp, 6 H, C3-H & C4-H & C5-H); $^{13}$C NMR (75 MHz) δ 155.2 (C2'), 141.9 (C5'), 109.9 (C4'), 106.1 (C3'), 72.9 (C2'), 68.6 (C6), 29.5 (C3), 25.7 (C5), 23.2 (C4).




**1-Furan-2-yl-5-hydroxypentan-1-one.** A solution of *n*-butyllithium in hexanes (2.29 M, 8.6 mL, 19.7 mmol) was added to a solution of furan (1.43 mL, 19.7 mmol) in THF (40 mL) at -78 ˚C. The reaction was warmed to 0 ˚C and stirred for 1 h. The solution was then cooled to -78 ˚C, and a solution of δ-valerolactone (**2.41**) (1.88 g, 18.8 mmol) in THF (5 mL) was added. After 15 min at -78 ˚C, saturated aqueous $NH_4Cl$ (10 mL) was added, and the mixture was warmed to rt. The mixture was stirred at rt for 12 h, and then the aqueous mixture was extracted with EtOAc (2 x 75 mL). The combined organic layers were washed with water (2 x 75 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 60% EtOAc/hexanes to give 629 mg (20%) of ketoalcohol as a colorless oil: $^1$H NMR (250 MHz) δ 7.54 (m, 1 H), 7.16-7.14 (m, 1 H), 6.49 (dd, *J* = 3.4, 1.7 Hz, 1 H), 3.62 (t, *J* = 6.3 Hz, 2 H), 2.83 (t, *J* = 7.1 Hz, 2 H), 2.04 (br s, 1 H), 1.83-1.72 (m, 1 H), 1.65-1.54 (m, 1 H); $^{13}$C NMR (75 MHz) δ 189.6, 152.6, 146.3, 117.0, 112.1, 62.2, 37.9, 32.1, 20.1; IR ($CDCl_3$) 3623, 3478, 2941, 2879, 1672, 1569,

1469, 1395, 1288, 1264, 1166 $cm^{-1}$; mass spectrum (CI) *m/z* 169.0863 [$C_9H_{13}O_3$ (M + H) requires 169.0865].

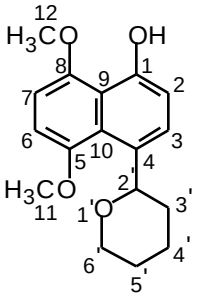
**NMR Assignments.** $^1H$ NMR (250 MHz) δ 7.54 (m, 1 H, C5-H), 7.16-7.14 (m, 1 H, C3-H), 6.49 (dd, *J* = 3.4, 1.7 Hz, 1 H, C4-H), 3.62 (t, *J* = 6.3 Hz, 2 H, C2'-H), 2.83 (t, *J* = 7.1 Hz, 2 H, C5'-H), 2.04 (br s, 1 H, -OH), 1.83-1.72 (m, 1 H, C3'-H), 1.65-1.54 (m, 1 H, C4'-H); $^{13}C$ NMR (75 MHz) δ 189.6 (C1'), 152.6 (C2), 146.3 (C5), 117.0 (C3), 112.1 (C4), 62.2 (C5), 37.9 (C2'), 32.1 (C3'), 20.1 (C4').




**2.43**

**1-Furan-2-yl-1,5-diol (2.43).** Sodium borohydride (212 mg, 5.60 mmol) was added to a solution of the ketoalcohol described above (629 mg, 3.74 mmol) in EtOH (19 mL) at 0 ˚C, and then the reaction mixture was stirred at rt for 12 h. Saturated aqueous $NH_4Cl$ (20 mL) and $H_2O$ (10 mL) were added, and the aqueous mixture was extracted with $Et_2O$ (2 x 40 mL). The combined organic layers were washed with brine (80 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 60% EtOAc/hexanes to give 522 mg (82%) of **2.43** as a colorless oil: $^1H$ NMR (250 MHz) δ 7.31-7.30 (m, 1 H), 6.27 (dd, *J* = 3.1, 1.9 Hz, 1 H), 6.16 (br d, *J* = 3.1 Hz, 1 H), 4.60 (br t, *J* = 6.6 Hz, 1 H), 3.54 (br t, *J* = 6.1 Hz, 2 H), 3.42 (br s, 1 H), 2.89 (br s, 1 H), 1.83-1.75 (comp, 2 H), 1.58-1.27 (comp, 4 H); $^{13}C$ NMR (75 MHz) δ 156.9, 141.7, 110.0, 105.6, 67.3, 62.2, 35.0, 32.0, 21.6; IR ($CDCl_3$) 3688, 3607, 3444, 2941, 2865, 1601, 1504, 1458, 1388, 1150, 1068 $cm^{-1}$; mass spectrum (CI) *m/z* 170.0940 [$C_9H_{14}O_3$ (M) requires 170.0943].

**NMR Assignments.** $^{1}$H NMR (250 MHz) δ 7.31-7.30 (m, 1 H, C5'-H), 6.27 (dd, *J* = 3.1, 1.9 Hz, 1 H, C4'-H), 6.16 (br d, *J* = 3.1 Hz, 1 H, C3'-H), 4.60 (br t, *J* = 6.6 Hz, 1 H, C1-H), 3.54 (br t, *J* = 6.1 Hz, 2 H, C5-H), 3.42 (br s, 1 H, -OH), 2.89 (br s, 1 H, -OH), 1.83-1.75 (comp, 2 H, C2-H), 1.58-1.27 (comp, 4 H, C3-H & C4-H); $^{13}$C NMR (75 MHz) δ 156.9 (C2'), 141.7 (C5'), 110.0 (C4'), 105.6 (C3'), 67.3 (C1), 62.2 (C5), 35.0 (C2), 32.0 (C4), 21.6 (C3).

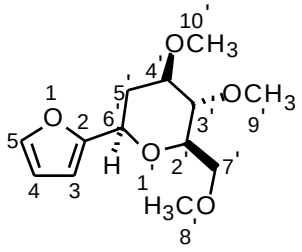



**2.46**

**5,8-Dimethoxy-4-(tetrahydropyran-2-yl)naphthalen-1-ol (2.46).** A solution of *s*-butyllithium in cyclohexane (1.26 M, 626 μL, 0.79 mmol) was added to 2-chlorodimethoxybenzene (**2.30**) (136 mg, 0.79 mmol) in THF 4 mL at -95 ˚C, and the resultant solution was stirred for 12 min at -95 ˚C. Furan **2.40** (100 mg, 0.66 mmol) in THF (1 mL) was added, and the reaction was warmed to -30 ˚C. Saturated aqueous $NH_4Cl$ (10 mL) and $H_2O$ (20 mL) were added, and the aqueous mixture was extracted with $Et_2O$ (2 x 20 mL). The combined organic layers were washed with brine (40 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude **2.45** was dissolved in $CH_2Cl_2$ (4 mL) and TFA (10 drops) was added and the resultant solution was stirred for 1 h at rt. Saturated aqueous $NaHCO_3$ (5 mL) was added, and the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (2 x 5 mL), and the

combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 20% EtOAc/hexanes to give 165 mg (87%) of **2.46** as a colorless oil: $^1$H NMR (250 MHz) δ 9.77 (s, 1 H), 7.72 (d, *J* = 8.3 Hz, 1 H), 6.91 (d, *J* = 8.3 Hz, 1 H), 6.66 (s, 1 H), 6.66 (s, 1 H), 5.50 (br d, *J* = 9.3 Hz, 1 H), 4.21-4.15 (m, 1 H), 3.97 (s, 3 H), 3.87 (s, 3 H), 3.69 (dt, *J* = 11.4, 2.7 Hz, 1 H), 2.09-2.03 (m, 1 H), 1.92-1.90 (m, 1 H), 1.75-1.55 (comp, 3 H), 1.42-1.24 (m, 1 H); $^{13}$C NMR (75 MHz) δ 153.5, 151.9, 150.6, 131.5, 125.6, 125.3, 116.4, 111.5, 104.8, 103.5, 78.8, 69.3, 56.6, 55.6, 36.1, 26.4, 24.8; IR ($CDCl_3$) 3372, 2939, 2847, 1619, 1526, 1429, 1396, 1355, 1255 $cm^{-1}$; mass spectrum (CI) *m/z* 289.1441 [$C_{17}H_{21}O_4$ (M + H) requires 289.1440].

**NMR Assignments.** $^1$H NMR (250 MHz) δ 9.77 (s, 1 H, C1-OH), 7.72 (d, *J* = 8.3 Hz, 1 H, C3-H), 6.91 (d, *J* = 8.3 Hz, 1 H, C2-H), 6.66 (s, 1 H, C6-H/C7-H), 6.66 (s, 1 H, C6-H/C7-H), 5.50 (br d, *J* = 9.3 Hz, 1 H, C2'-H), 4.21-4.15 (m, 1 H, C6'-H), 3.97 (s, 3 H, C12-H), 3.87 (s, 3 H, C11-H), 3.69 (dt, *J* = 11.4, 2.7 Hz, 1 H, C6'-H), 2.09-2.03 (m, 1 H, pyran-H), 1.92-1.90 (m, 1 H, pyran-H), 1.75-1.55 (comp, 3 H, pyran-H), 1.42-1.24 (m, 1 H, pyran-H); $^{13}$C NMR (75 MHz) δ 153.5 (C1), 151.9 (C5), 150.6 (C8), 131.5 (Ar-C), 125.6 (C3), 125.3 (Ar-C), 116.4 (Ar-C), 111.5 (C2), 104.8 (C6), 103.5 (C7), 78.8 (C2'), 69.3 (C6'), 56.6 (C12), 55.6 (C11), 36.1 (pyran-C), 26.4 (pyran-C), 24.8 (pyran-C).

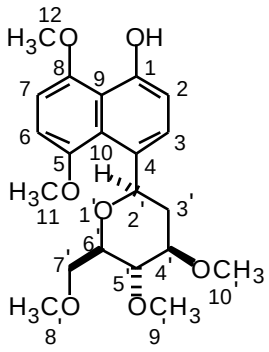


**2.53**

**6(*R*)-Furan-2-yl-3(*R*),4(*S*)-dimethoxy-2(*R*)-methoxymethyltetrahydropyran (2.53).** Boron trifluoride etherate (0.330 mL, 2.6 mmol) was added dropwise to a solution of **2.52** (647 mg, 2.6 mmol) and freshly distilled furan (0.750 mL, 7.8 mmol) in anhydrous $CH_2Cl_2$ (25 mL) at 0 °C. After 5 min at 0 ˚C, the reaction mixture was diluted with $CH_2Cl_2$ (50 mL) and transferred to a separatory funnel. The mixture was washed with saturated aqueous $NaHCO_3$ (2 x 50 mL). The combined fractions were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 30% EtOAc/hexanes to give 449 mg (67%) of **2.53** as a mixture (β:α 9:1) of diastereomers as a colorless oil: $^1$H NMR (300 MHz) δ 7.34-7.33 (m, 1 H), 6.29-6.26 (comp, 2 H), 4.42 (dd, *J* = 12.1, 1.8 Hz, 1 H), 3.66 (dd, *J* = 10.7, 2.0 Hz, 1 H), 3.59 (dd, *J* = 10.7, 4.6 Hz, 1 H), 3.54 (s, 3 H), 3.50-3.34 (comp, 2 H), 3.45 (s, 3 H), 3.37 (s, 3 H), 3.16 (app t, *J* = 9.1 Hz, 1 H), 2.34 (ddd, *J* = 12.7, 5.0, 1.8 Hz, 1 H), 1.81 (app dt, *J* = 12.1, 11.9 Hz, 1 H); $^{13}$C NMR (75 MHz) δ 153.3, 142.2, 110.1, 107.1, 82.4, 79.7, 79.1, 71.7, 70.9, 60.6, 59.3, 57.0, 34.1; IR (neat) 2929, 1451, 1379, 1307, 1112 cm$^{-1}$; mass spectrum (CI) *m/z* 256.1310 [$C_{13}H_{20}O_5$ (M + H) requires 256.1311].

**NMR Assignments.** $^1$H NMR (300 MHz) δ 7.33 (m, 1 H. C5-H), 6.29-6.26 (comp, 2 H, C3-H & C4-H), 4.42 (dd, *J* = 12.1, 1.8 Hz, 1 H, C6'-H), 3.66 (dd, *J* = 10.7, 2.0 Hz, 1 H, C7'-H), 3.59 (dd, *J* = 10.7, 4.6 Hz, 1 H, C7'-H), 3.54 (s, 3 H, Sug-$OCH_3$),

3.50-3.34 (comp, 2 H, C2'-H & C4'-H), 3.45 (s, 3 H, Sug-$OCH_3$), 3.37 (s, 3 H, Sug-$OCH_3$), 3.16 (app t, $J$ = 9.1 Hz, 1 H, C3'-H), 2.34 (ddd, $J$ = 12.7, 5.0, 1.8 Hz, 1 H, C5'-$H_{eq}$), 1.81 (app dt, $J$ = 12.1, 11.9 Hz, 1 H, C5'-$H_{ax}$); $^{13}$C NMR (75 MHz) δ 153.3 (C2), 142.2 (C5), 110.1 (C4), 107.1 (C3), 82.4 (C4'), 79.7 (C5'), 79.1 (C6'), 71.7 (C7'), 70.9 (C2'), 60.6 (C9'), 59.3 (C8'), 57.0 (C10'), 34.1 (C5').

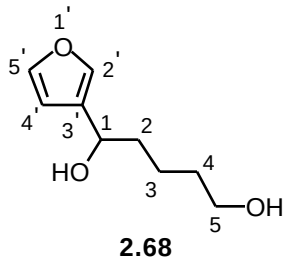


**2.56**

**4-[4(*R*),5(*S*)-Dimethoxy-6(*R*)-methoxymethyltetrahydropyran-2(*R*)-yl]-5,8-dimethoxynaphthalen-1-ol (2.56)**. A solution of *s*-butyllithium in cyclohexane (0.79 M, 1.46 mL, 1.15 mmol) was added dropwise to a stirred solution of **2.30** (210 mg, 1.22 mmol) in THF (4.1 mL) at –95 ˚C. The reaction was stirred for 15 min at –95 °C, and then a solution of **2.53** (155 mg, 0.61 mmol) in THF (1.5 mL) was added dropwise. The reaction was allowed to warm slowly to 0 ˚C, whereupon saturated $NH_4Cl$ (5 mL) and $H_2O$ (1 mL) were added sequentially. The layers were separated, and the aqueous phase was extracted with EtOAc (4 x 4 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 50% EtOAc/hexanes to afford 201 mg (85%) of **2.55** as a mixture (ca 1:1) of diastereomers as a pale yellow oil. This oil was dissolved in $CH_2Cl_2$ (4.1 mL), trifluoroacetic acid

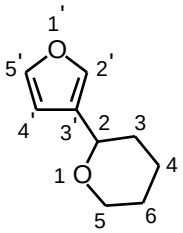
(TFA) (5 drops) was added, and the solution was stirred at rt for 4 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with 30% EtOAc/hexanes to give 197 mg (98%) of **2.56** as a pale yellow oil: $^{1}$H NMR (500 MHz) δ 9.76 (s, 1 H), 7.74 (d, *J* = 8.2 Hz, 1 H), 6.89 (d, *J* = 8.2 Hz, 1 H), 6.68 (app s, 2 H), 5.57 (br d, *J* = 11.4 Hz, 1 H), 3.99 (s, 3 H), 3.87 (s, 3 H), 3.69 (app d, *J* = 3.4 Hz, 2 H), 3.58 (s, 3 H), 3.53-3.48 (comp, 2 H), 3.45 (s, 3 H), 3.42 (s, 3 H), 3.19 (dd, *J* = 9.6, 8.8 Hz, 1 H), 2.55 (ddd, *J* = 12.8, 4.8, 1.6 Hz, 1 H), 1.32 (app dt, *J* = 12.8, 11.4, Hz, 1 H); $^{13}$C NMR (125 MHz) δ 153.8, 151.7, 150.7, 129.2, 125.8, 125.2, 116.5, 111.5, 105.0, 103.7, 83.5, 80.1, 79.4, 76.0, 72.4, 60.6, 59.5, 56.6, 56.4, 55.6, 39.7; IR (neat) 3364, 2932, 2833, 1445, 1391, 1259, 1113 cm$^{-1}$; mass spectrum (CI) *m/z* 392.1837 [$C_{21}H_{28}O_7$ (M) requires 392.1835].

**NMR Assignments:** $^{1}$H NMR (500 MHz) δ 9.76 (s, 1 H, C1-OH), 7.74 (d, *J* = 8.2 Hz, 1 H, C3-H), 6.89 (d, *J* = 8.2 Hz, 1 H, C2-H), 6.68 (app s, 2 H, C6-H & C7-H), 5.57 (br d, *J* = 11.4 Hz, 1 H, C2'-H), 3.99 (s, 3 H, Ar-$OCH_3$), 3.87 (s, 3 H, Ar-$OCH_3$), 3.69 (app d, *J* = 3.4 Hz, 2 H, C7'-H), 3.58 (s, 3 H, Sug-$OCH_3$), 3.53-3.48 (comp, 2 H, C4'-H & C6'-H), 3.45 (s, 3 H, Sug-$OCH_3$), 3.42 (s, 3 H, Sug-$OCH_3$), 3.19 (dd, *J* = 9.6, 8.8 Hz, 1 H, C5'-H), 2.55 (ddd, *J* = 12.8, 4.8, 1.6 Hz, 1 H, C3'-$H_{eq}$), 1.32 (app dt, *J* = 12.8, 11.4, Hz, 1 H, C3'-$H_{ax}$); $^{13}$C NMR (125 MHz) δ 153.8 (Ar**C**-$OCH_3$), 151.7 (C1), 150.7 (Ar**C**-$OCH_3$), 129.2 (C4), 125.8 (C3), 125.2 (Ar-C), 116.5 (Ar-C), 111.5 (C2), 105.0 (Ar-C), 103.7 (Ar-C), 83.5 (C4'/C6'), 80.1 (C5'), 79.4 (C4'/C5'), 76.0 (C2'), 72.4 (C7'), 60.6 (Sug-$OCH_3$), 59.5 (Sug-$OCH_3$), 56.6 (Sug-$OCH_3$), 56.4 Ar-$OCH_3$), 55.6 (Ar-$OCH_3$), 39.7 (C3').



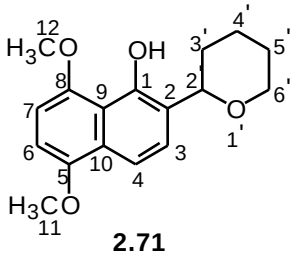

**2.68**

**1-Furan-3-ylpentane-1,5-diol (2.68).** A solution of *n*-butyllithium in hexanes (1.47 M, 3.6 mL, 5.3 mmol) was added to a solution of 3-bromofuran (**2.67**) (770 mg, 5.2 mmol) in $Et_2O$ (25 mL) at -78 ˚C, and the resultant solution was stirred for 1 h at -78 ˚C. Neat δ-valerolactone (**2.41**) (463 μL, 5.0 mmol) was added, and stirring was continued for 25 min at -78 ˚C. Saturated aqueous $NH_4Cl$ (5 mL) was added, and the mixture was warmed to rt. The mixture was poured into saturated aqueous $NH_4Cl$ (50 mL), and the layers were separated. The aqueous layer was extracted with $Et_2O$ (3 x 50 mL), and the combined organic layers were washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give 781 mg of an oil. This oil was dissolved in $CH_3OH$ (14 mL), and the solution was cooled to 0 ˚C. Sodium borohydride (194 mg, 5.1 mmol) was added portionwise over 1 min, and the reaction was heated under reflux for 2 min. The reaction was cooled to rt, and saturated aqueous $NH_4Cl$ (3 mL) was added. The mixture was poured into saturated aqueous $NH_4Cl$ (20 mL), and the mixture was extracted with $Et_2O$ (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with $Et_2O$ to give 553 mg (65%) of the diol **2.68** that was identical in all respects to the reported compound.[91]



**2.69**

**2-Furan-3-yltetrahydropyran (2.69).** Trifluoromethanesulfonic acid (TfOH) (5 drops) was added to a solution of **2.68** (650 mg, 3.8 mmol) and 4 Å molecular sieves (975 mg) in $CH_2Cl_2$ (150 mL) at 0 ˚C, and the mixture was stirred for 0.5 h at 0 ˚C. Saturated aqueous $NaHCO_3$ (50 mL) was added, and the mixture was filtered through Celite washing with $CH_2Cl_2$ (50 mL). The layers were separated, and the organic layer was washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give 552 mg (95%) of pure **2.59** as an oil that was identical in all respects to the reported compound.[91]



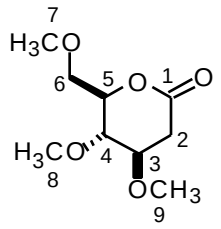
**2.71**

**5,8-Dimethoxy-2-(tetrahydropyran-2-yl)naphthalen-1-ol (2.71).** A solution of *s*-butyllithium in cyclohexane (1.16 M, 1.64 mL, 1.90 mmol) was added to a solution of 2-chloro-1,4-dimethoxybenzene (**2.30**) (329 mg, 1.90 mmol) in THF (7 mL) at -95 ˚C, and stirring was continued for 10 min at -95 ˚C. A solution of **2.69** (58 mg, 0.38 mmol) in THF (1 mL) was then added and the reaction was warmed to -25 ˚C over 30 min. Saturated aqueous $NH_4Cl$ (10 mL) and $H_2O$ (0.5 mL) were added, and the

aqueous mixture was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 25% EtOAc/hexanes to give cycloadduct **2.70** as a mixture (ca 1:1) of diastereomers. The crude mixture of cycloadducts was dissolved in $CH_2Cl_2$ (2 mL), and the solution was cooled to 0 ˚C. Trifluoroacetic acid (10 drops) was added, and the reaction was stirred for 10 min at 0 ˚C and then an additional 10 min at rt. The reaction was diluted with $CH_2Cl_2$ (2 mL), and the mixture was washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL). The organic layer was dried ($MgSO_4$), and concentrated under reduced pressure to give 29 mg (26%) of pure **2.71** as a white solid: mp 107-109 ˚C; $^1$H NMR (250 MHz) δ 9.75 (s, 1 H), 7.71 (d, *J* = 8.7 Hz, 1 H), 7.56 (d, *J* = 8.7 Hz, 1 H), 6.65 (d, *J* = 8.4 Hz, 1 H), 6.58 (d, *J* = 8.4 Hz, 1 H), 4.89 (dd, *J* = 11.1, 1.6 Hz, 1 H), 4.20-4.14 (m, 1 H), 3.98 (s, 3 H), 3.91 (s, 3 H), 3.69 (app dt, *J* = 11.5, 2.5 Hz, 1 H), 1.94-1.53 (comp, 6 H); $^{13}$C NMR (63 MHz) δ 150.3, 150.2, 149.8, 127.4, 125.4, 125.0, 115.2, 112.9, 103.5, 102.6, 74.4, 69.2, 56.4, 55.7, 32.6, 26.2, 24.2; IR ($CDCl_3$) 3374, 3008, 2940, 2848, 1614, 1518, 1464, 1391, 1252, 1215, 1097 cm$^{-1}$; mass spectrum (CI) *m*/*z* 392.1834 [$C_{21}H_{28}O_7$ (M) requires 392.1835].

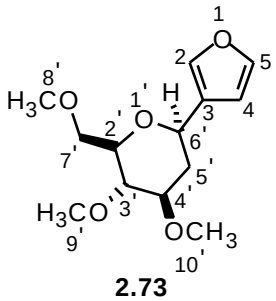
**NMR Assignments.** $^1$H NMR (250 MHz) δ 9.75 (s, 1 H, C1-OH), 7.71 (d, *J* = 8.7 Hz, 1 H, C3-H), 7.56 (d, *J* = 8.7 Hz, 1 H, C4-H), 6.65 (d, *J* = 8.4 Hz, 1 H, C7-H/C8-H), 6.58 (d, *J* = 8.4 Hz, 1 H, C7-H/C8-H), 4.89 (dd, *J* = 11.1, 1.6 Hz, 1 H, C2'-H), 4.20-4.14 (m, 1 H, C6'-H), 3.98 (s, 3 H, Ar-$OCH_3$), 3.91 (s, 3 H, Ar-$OCH_3$), 3.69 (app dt, *J* = 11.5, 2.5 Hz, 1 H, C6'-H), 1.94-1.53 (comp, 6 H, C3'-H & C4'-H & C5'-H); $^{13}$C NMR (63 MHz) δ 150.3 (C1), 150.2 (C5/C8), 149.8 (C5/C8), 127.4 (Ar-C), 125.4 (Ar-C), 125.0 (Ar-C), 115.2 (C2), 112.9 (C4), 103.5 (C6/C7), 102.6 (C6/C7), 74.4

(C2'), 69.2 (C6'), 56.4 (Ar-$OCH_3$), 55.7 (Ar-$OCH_3$), 32.6 (pyran-C), 26.2 (pyran-C), 24.2 (pyran-C).




**2.72**

**4(*R*),5(*S*)-Dimethoxy-6(*R*)-methoxymethyltetrahydropyran-2-one (2.72).** Pyridinium chlorochromate (4.7 g, 21.7 mmol) was added to known trimethoxy-D-glucal (2.0g, 10.8 mmol) in dry dichloroethane (50 mL), and the mixture was stirred for 12 h at rt. The reaction mixture was purified directly by flash chromatography eluting with 40% EtOAc/hexanes to give 536 mg (24%) of the known lactone **2.72**[93] as a colorless oil along with 590 mg of **2.72** contaminated with an enone by-product and 194 mg of starting glucal.



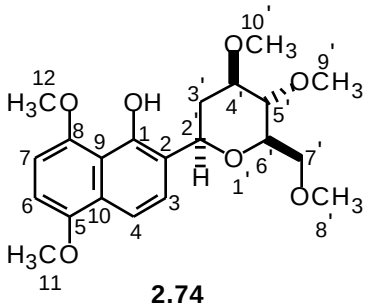

**2.73**

**6(*R*)-Furan-3-yl-3(*S*),4(*R*)-dimethoxy-2(*R*)-methoxymethyltetrahydropyran (2.73).** A solution of *n*-butyllithium in hexanes (1.54 M, 207 μL, 0.32 mmol) was added to a stirred solution of 3-bromofuran (47 mg,

0.32 mmol) in $Et_2O$ (2 mL) at -78 ˚C. After 20 min at -78 ˚C, a solution of lactone **2.72** (62 mg, 0.30 mmol) in $Et_2O$ (2 mL) was added. The solution was stirred for 20 min at -78 ˚C, whereupon saturated $NH_4Cl$ (5 mL) was added and the solution allowed to warm to rt. The resulting mixture was extracted with $Et_2O$ (3 x 15 mL), and the combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford an oil. This oil was dissolved in EtOH (1 mL), and the resulting solution was heated to 50 ˚C. Sodium cyanoborohydride ($NaCNBH_3$) (114 mg, 1.8 mmol) and a spatula tip of bromocresol green were added. Ethanolic HCl, which was prepared by mixing AcCl (100 μL) and EtOH (4 mL), was added dropwise at such a rate so as to maintain a yellow color. After 15 min, the yellow color persisted without further addition of acid. The reaction mixture was cooled to rt and poured into saturated $NaHCO_3$ (2 mL). The resulting solution was extracted with $Et_2O$ (3 x 15 mL), and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 30% EtOAc/hexanes to give 42 mg (54%) of **2.73** as a clear colorless oil: $^1$H NMR (300 MHz) δ 7.37 (br s, 1 H), 7.33 (dd, *J* = 1.7, 1.7 Hz, 1 H), 6.38 (m, 1 H), 4.35 (dd, *J* = 11.7, 1.8 Hz, 1 H), 3.66-3.56 (comp, 2 H), 3.54 (s, 3 H), 3.47-3.34 (comp, 2 H), 3.44 (s, 3 H), 3.38 (s, 3 H), 3.12 (app t, *J* = 9.2 Hz, 1 H), 2.29 (ddd, *J* = 12.8, 4.9, 1.9 Hz), 1.60 (ddd, *J* = 12.8, 11.7, 11.5 Hz, 1 H); $^{13}$C NMR (65 MHz) δ 143.0, 139.3, 125.8, 108.9, 82.4, 79.9, 79.1, 71.9, 70.5, 60.6, 59.3, 57.0, 36.7; IR (neat) 2927, 1113 cm$^{-1}$; mass spectrum (CI) *m/z* 256.1303 [$C_{13}H_{20}O_5$ (M + H) requires 256.1311].

**NMR Assignments.** $^1$H NMR (300 MHz) δ 7.37 (br s, 1 H, C2-H), 7.33 (dd, *J* = 1.7, 1.7 Hz, 1 H, C5-H), 6.38 (m, 1 H, C4-H), 4.35 (dd, *J* = 11.7, 1.8 Hz, 1 H, C6'-

H), 3.66-3.56 (comp, 2 H, C7'-H), 3.54 (s, 3 H, Sug-$OCH_3$), 3.47-3.34 (comp, 2 H, C2'-H & C4'-H), 3.44 (s, 3 H, Sug-$OCH_3$), 3.38 (s, 3 H, Sug-$OCH_3$), 3.12 (app t, $J$ = 9.2, Hz, 1 H, C3'-H), 2.29 (ddd, $J$ = 12.8, 4.9, 1.9 Hz, C5'-Heq), 1.60 (ddd, $J$ = 12.8, 11.7, 11.5 Hz, 1 H, C5'-Hax); $^{13}$C NMR (65 MHz) δ 143.0 (C5), 139.3 (C2), 125.8 (C3), 108.9 (C4), 82.4 (C4'), 79.9 (C5'), 79.1 (C6'), 71.9 (C7'), 70.5 (C2'), 60.6 (C9'), 59.3 (C8'), 57.0 (C10'), 36.7 (C5').

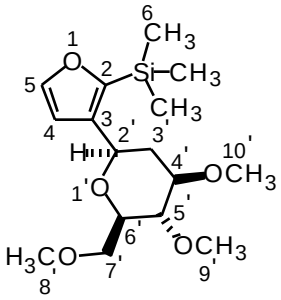



**2.74**

**2(4(*R*),5(*S*)-Dimethoxy-6(*R*)-methoxymethyltetrahydropyran-2(*R*)-yl)5,8-dimethoxynaphthalen-1-ol (2.74)**. A solution of *s*-butyllithium in cyclohexane (1.07 M, 243 μL, 0.26 mmol) was added to a stirred solution of 2-chloro-1,4-dimethoxybenzene (**2.30**) (47 mg, 0.27 mmol) in THF (1.4 mL) at -95 ˚C. The reaction was stirred at -95 ˚C for 15 min, and then a solution of furan **2.73** (35 mg, 0.14 mmol) in THF (0.4 mL) was added. The reaction was allowed to warm slowly to 0 ˚C, whereupon saturated $NH_4Cl$ (5 mL) and $H_2O$ (1 mL) were added sequentially. The layers were separated, and the aqueous phase was extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with brine (3 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 50% EtOAc/hexanes to afford 49 mg (91%) of a mixture of diastereomeric cycloadducts as a clear colorless oil. This oil was dissolved in

$CH_2Cl_2$ (1 mL), trifluoroacetic acid (TFA) (4 drops) was added, and the solution was stirred at rt for 2 d. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with 30% EtOAc/hexanes to give 4.3 mg (9%) of *meta*-isomer and 43 mg (88%) of **2.74** as a colorless oil: $^1$H NMR (500 MHz) δ 9.73 (s, 1 H), 7.69 (d, *J* = 8.7 Hz, 1 H), 7.59 (d, *J* = 8.7 Hz, 1 H), 6.65 (d, *J* = 8.4 Hz, 1 H), 6.59 (d, *J* = 8.4 Hz, 1 H), 4.95 (dd, *J* = 11.2, 2.0 Hz, 1 H), 3.99 (s, 3 H), 3.91 (s, 3 H), 3.71 (dd, *J* = 10.8, 4.0 Hz, 1 H) 3.68 (dd, *J* = 10.8, 2.0 Hz, 1 H), 3.58 (s, 3 H), 3.55-3.48 (comp, 2 H), 3.44 (s, 3 H), 3.44 (s, 3 H), 3.21 (dd, *J* = 9.4, 8.8 Hz, 1 H), 2.47 (ddd, *J* = 12.9, 5.0, 2.0 Hz, 1 H), 1.46 (app dt, *J* = 12.9, 11.2 Hz, 1 H); $^{13}$C NMR (125 MHz) δ 150.4, 150.1, 149.7, 127.5, 124.9, 123.6, 115.2, 113.1, 103.6, 102.7, 82.8, 80.1, 79.4, 72.2, 71.8, 60.5, 59.5, 56.7, 56.4, 55.7, 36.8; IR (neat) 3355, 2927, 1613, 1516, 1455, 1387, 1250, 1105 cm$^{-1}$; mass spectrum (CI) *m/z* 392.1823 [$C_{21}H_{28}O_7$ (M) requires 392.1835].

**NMR Assignments.** $^1$H NMR (500 MHz) δ 9.73 (s, 1 H, C1-OH), 7.69 (d, *J* = 8.7 Hz, 1 H, C4-H), 7.59 (d, *J* = 8.7 Hz, 1 H, C3-H), 6.65 (d, *J* = 8.4 Hz, 1 H, C7-H), 6.59 (d, *J* = 8.4 Hz, 1 H, C6-H), 4.95 (dd, *J* = 11.2, 2.0 Hz, 1 H, C2'-H), 3.99 (s, 3 H, C12-H), 3.91 (s, 3 H, C11-H), 3.71 (dd, *J* = 10.8, 4.0 Hz, 1 H, C7'-H) 3.68 (dd, *J* = 10.8, 2.0 Hz, 1 H, C7'-H), 3.58 (s, 3 H, Sug-$OCH_3$), 3.55-3.48 (comp, 2 H, C4'-H & C6'-H), 3.44 (s, 3 H, Sug-$OCH_3$), 3.44 (s, 3 H, Sug-$OCH_3$), 3.21 (dd, *J* = 9.4, 8.8 Hz, 1 H, C5'-H), 2.47 (ddd, *J* = 12.9, 5.0, 2.0 Hz, 1 H, C3'-$H_{eq}$), 1.46 (app dt, *J* = 12.9, 11.2 Hz, 1 H, C3'-$H_{ax}$); $^{13}$C NMR (125 MHz) δ 150.4 (C5/C8), 150.1 (C5/C8), 149.7 (C1), 127.5 (C2), 124.9 (C4), 123.6 (Ar-C), 115.2 (Ar-C), 113.1 (C3), 103.6 (C6/C7), 102.7 (C6/C7), 82.8 (C4'), 80.1 (C5'), 79.4 (C6'), 72.2 (C7'), 71.8 (C2'), 60.5 (Sug-$OCH_3$), 59.5 (Sug-$OCH_3$), 56.7 (Sug-$OCH_3$), 56.4 (Ar-$OCH_3$), 55.7 (Ar-$OCH_3$), 36.8 (C3').

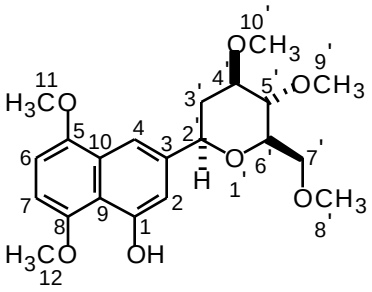


**2.81**

**[3-(4(*R*),5(*S*)-Dimethoxy-6(*R*)-methoxymethyltetrahydropyran-2(*R*)-yl)furan-2-yl]trimethylsilane (2.81).** A solution of *n*-butyllithium in hexanes (1.90 M, 47 μL, 0.09 mmol) was added to a solution of furan **2.73** (19 mg, 0.07 mmol) in THF (1 mL) at -78 ˚C, and the reaction was warmed to 0 ˚C and stirred for 35 min. The reaction was then cooled to -78 ˚C, whereupon trimethylsilyl chloride (TMSCl) (13 μL, 0.10 mmol) was added. The mixture was stirred for 25 min at -78 ˚C, saturated aqueous $NH_4Cl$ (3 mL) and $H_2O$ (0.5 mL) were added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 1 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 20% EtOAc/hexanes to give 14 mg (57%) of **2.81** as a colorless oil: $^1$H NMR (250 MHz) δ 7.50 (d, *J* = 1.6 Hz, 1 H), 6.38 (d, *J* = 1.6 Hz, 1 H), 4.42 (dd, *J* = 11.7, 1.9 Hz, 1 H), 3.61 (app d, *J* = 3.2 Hz, 2 H), 3.55 (s, 3 H), 3.45 (s, 3 H), 3.43-3.32 (comp, 2 H), 3.35 (s, 3 H), 3.16 (app t, *J* = 9.1 Hz, 1 H), 2.22 (ddd, *J* = 13.0, 4.9, 1.9 Hz, 1 H), 1.65 (ddd, *J* = 13.0, 11.7, 11.6 Hz, 1 H), 0.27 (s, 9 H); $^{13}$C NMR (63 MHz) δ 156.3, 145.9, 135.5, 108.7, 82.6, 79.7, 79.1, 71.8, 71.0, 60.5, 59.1, 57.0, 37.3, -1.1; IR ($CDCl_3$) 2953, 2930, 2897, 2834, 1602, 1449, 1379,

1307, 1251, 1190, 1143, 1106, 1081 $cm^{-1}$; mass spectrum (CI) *m*/*z* 329.1790 [$C_{16}H_{29}O_5Si$ (M + H) requires 329.1784].

**NMR Assignments.** $^1H$ NMR (250 MHz) δ 7.50 (d, *J* = 1.6 Hz, 1 H, C5-H), 6.38 (d, *J* = 1.6 Hz, 1 H, C4-H), 4.42 (dd, *J* = 11.7, 1.9 Hz, 1 H, C2'-H), 3.61 (app d, *J* = 3.2 Hz, 2 H, C7'-H), 3.55 (s, 3 H, Sug-$OCH_3$), 3.45 (s, 3 H, Sug-$OCH_3$), 3.43-3.32 (comp, 2 H, C4'-H & C6'-H), 3.35 (s, 3 H, Sug-$OCH_3$), 3.16 (app t, *J* = 9.1 Hz, 1 H, C5'-H), 2.22 (ddd, *J* = 13.0, 4.9, 1.9 Hz, 1 H, C3'-$H_{eq}$), 1.65 (ddd, *J* = 13.0, 11.7, 11.6 Hz, 1 H, C3'-$H_{ax}$), 0.27 (s, 9 H, C6-H); $^{13}C$ NMR (63 MHz) δ 156.3 (C2), 145.9 (C5), 135.5 (C3), 108.7 (C4), 82.6 (C4'/C6'), 79.7 (C5'), 79.1 (C4'/C6'), 71.8 (C2'), 71.0 (C7'), 60.5 (Sug-$OCH_3$), 59.1 (Sug-$OCH_3$), 57.0 (Sug-$OCH_3$), 37.3 (C3'), -1.1 (C6).

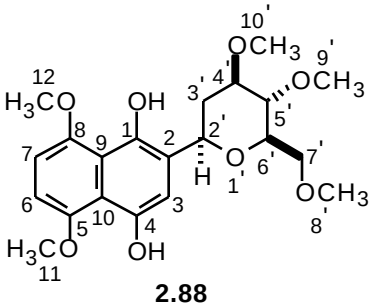



**2.83**

**3-(4(*R*),5(*S*)-Dimethoxy-6(*R*)-methoxymethyltetrahydropyran-2(*R*)-yl)-5,8-dimethoxynaphthalen-1-ol (2.83).** A solution of *n*-butyllithium in hexanes (1.90 M, 33 μL, 0.06 mmol) was added to a solution of 2-chlorodimethoxybenzene (**2.30**) (11 mg, 0.06 mmol) and **2.81** (10 mg, 0.03 mmol) in THF (0.5 mL) at -78 ˚C, and the solution was stirred for 15 min at -78 ˚C. The reaction was warmed to rt, whereupon saturated aqueous $NH_4Cl$ (3 mL) was added. The mixture was extracted with EtOAc (3 x 2 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 20%

EtOAc/hexanes to give a mixture of diastereomeric cycloadducts **2.82**. These cycloadducts were dissolved in $CH_2Cl_2$ (1 mL), and trifluoroacetic acid (TFA) (5 drops) was added. The mixture was stirred for 0.5 h at rt. The reaction mixture was purified directly by flash chromatography eluting with 20% EtOAc/hexanes to give 4 mg (27%) of **2.83** as an oil: $^1$H NMR (500 MHz) δ 9.42 (s, 1 H), 7.66 (d, *J* = 1.6 Hz, 1 H), 6.98 (d, *J* = 1.6 Hz, 1 H), 6.65 (d, *J* = 8.4 Hz, 1 H), 6.63 (d, *J* = 8.4 Hz, 1 H), 4.49 (dd, *J* = 11.6, 1.8 Hz, 1 H), 4.00 (s, 3 H), 3.93 (s, 3 H), 3.71 (app d, *J* = 3.4 Hz, 2 H), 3.59 (s, 3 H), 3.50-3.45 (comp, 2 H), 3.46 (s, 3 H), 3.45 (s, 3 H), 3.20 (dd, *J* = 9.4, 9.0 Hz, 1 H), 2.40 (ddd, *J* = 13.0, 5.0, 2.0 Hz, 1 H), 1.65 (app dt, *J* = 13.0, 11.6 Hz, 1 H); $^{13}$C NMR (125 MHz) δ 154.6, 150.4, 150.0, 140.7, 128.2, 115.1, 110.1, 109.5, 103.2, 103.2, 82.9, 80.0, 79.5, 77.7, 72.2, 60.6, 59.5, 56.8, 56.3, 55.7, 38.3; IR ($CDCl_3$) 3384, 2934, 2834, 1731, 1616, 1462, 1453, 1391, 1250, 1183, 1094 $cm^{-1}$; mass spectrum (CI) *m/z* 392.1834 [$C_{21}H_{28}O_7$ (M) requires 392.1835].

**NMR Assignments.** $^1$H NMR (500 MHz) δ 9.42 (s, 1 H, C1-OH), 7.66 (d, *J* = 1.6 Hz, 1 H, C4-H), 6.98 (d, *J* = 1.6 Hz, 1 H, C2-H), 6.65 (d, *J* = 8.4 Hz, 1 H, C6-H/C7-H), 6.63 (d, *J* = 8.4 Hz, 1 H, C6-H/C7-H), 4.49 (dd, *J* = 11.6, 1.8 Hz, 1 H, C2'-H), 4.00 (s, 3 H, Ar-$OCH_3$), 3.93 (s, 3 H, Ar-$OCH_3$), 3.71 (app d, *J* = 3.4 Hz, 2 H, C7'-H), 3.59 (s, 3 H, Sug-$OCH_3$), 3.50-3.45 (comp, 2 H, C4'-H & C6'-H), 3.46 (s, 3 H, Sug-$OCH_3$), 3.45 (s, 3 H, Sug-$OCH_3$), 3.20 (dd, *J* = 9.4, 9.0 Hz, 1 H, C5'-H), 2.40 (ddd, *J* = 13.0, 5.0, 2.0 Hz, 1 H, C3'-$H_{eq}$), 1.65 (app dt, *J* = 13.0, 11.6 Hz, 1 H, C3'-$H_{ax}$); $^{13}$C NMR (125 MHz) δ 154.6 (C1), 150.4 (C5/C8), 150.0 (C5/C8), 140.7 (Ar-C), 128.2 (Ar-C), 115.1 (Ar-C), 110.1 (C4), 109.5 (C2), 103.2 (C6/C7), 103.2 (C6/C7), 82.9 (C4'/C6'), 80.0 (C5'), 79.5 (C4'/C6'), 77.7 (C2'), 72.2 (C7'), 60.6 (Sug-$OCH_3$), 59.5 (Sug-$OCH_3$), 56.8 (Sug-$OCH_3$), 56.3 (Ar-$OCH_3$), 55.7 (Ar-$OCH_3$), 38.3 (C3').

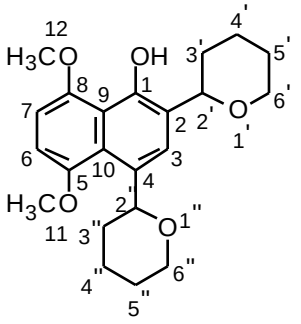


**2.88**

**2-(4(*R*),5(*S*)-Dimethoxy-6(*R*)-methoxymethyltetrahydropyran-2(*R*)-yl)-5,8-dimethoxynaphthalene-1,4-diol (2.88).** (Diacetoxyiodo)benzene ($PhI(OAc)_2$) (47 mg, 0.15 mmol) was added with stirring to a solution of **2.74** (11 mg, 0.03 mmol) in $CH_3CN/H_2O$ (1 mL/0.5 mL) at 0 ˚C. After 0.5 h at 0 ˚C, the reaction mixture was warmed to rt. After 1 h at rt, the reaction was diluted with EtOAc (5 mL) and the organic phase was washed with $H_2O$ (3 mL) and brine (3 mL), dried ($MgSO_4$), and concentrated under reduced pressure to a volume of ~1 mL. This solution was filtered through a short plug of silica eluting with EtOAc to provide quinone **2.87**. This quinone was then dissolved in $CH_2Cl_2$ (10 mL), and the resulting solution was transferred to a separatory funnel. The organic phase was shaken vigorously with saturated aqueous $Na_2S_2O_4$ (10 mL) until the orange solution became pale yellow (5 min) and TLC indicated complete consumption of the quinone. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give 8 mg (70%) of pure hydroquinone **2.88** as a pale yellow solid: mp 132 ˚C (dec.); $^1$H NMR (500 MHz) δ 9.37 (s, 1 H), 9.02 (s, 1 H), 7.08 (s, 1 H), 6.60 (d, *J* = 8.4 Hz, 1 H), 6.57 (d, *J* = 8.4 Hz, 1 H), 4.88 (dd, *J* = 11.2, 1.9 Hz, 1 H), 3.97 (s, 3 H), 3.96 (s, 3 H), 3.68-3.67 (comp, 2 H), 3.57 (s, 3 H), 3.54-3.41 (comp, 2 H), 3.44 (s, 3 H), 3.43 (s, 3 H), 3.16 (dd, *J* = 9.4, 8.8 Hz, 1 H), 2.46 (ddd, *J* = 12.8, 5.0, 1.9 Hz, 1 H), 1.41 (app dt, *J* = 12.8, 11.2, Hz, 1

H); $^{13}$C NMR (125 MHz) δ 151.1, 151.0, 146.9, 142.3, 125.3, 116.1, 115.7, 110.4, 103.6, 102.9, 82.8, 80.1, 79.4, 72.3, 71.6, 60.5, 59.5, 56.7, 56.5, 56.4, 36.5; IR ($CHCl_3$) 3406, 3032, 2933, 1398 $cm^{-1}$; mass spectrum (CI) *m/z* 408.1784 [$C_{21}H_{28}O_8$ (M) requires 408.1784].

**NMR Assignments.** $^1$H NMR (500 MHz) δ 9.37 (s, 1 H, C1-OH), 9.02 (s, 1 H, C4-OH), 7.08 (s, 1 H, C3-H), 6.60 (d, *J* = 8.4 Hz, 1 H, C6-H), 6.57 (d, *J* = 8.4 Hz, 1 H, C7-H), 4.88 (dd, *J* = 11.2, 1.9 Hz, 1 H, C2'-H), 3.97 (s, 3 H, Ar-$OCH_3$), 3.96 (s, 3 H, Ar-$OCH_3$), 3.68-3.67 (comp, 2 H, C7'-H), 3.57 (s, 3 H, Sug-$OCH_3$), 3.54-3.41 (comp, 2 H, C4'-H & C6'-H), 3.44 (s, 3 H, Sug-$OCH_3$), 3.43 (s, 3 H, Sug-$OCH_3$), 3.16 (dd, *J* = 9.4, 8.8 Hz, 1 H, C5'-H), 2.46 (ddd, *J* = 12.8, 5.0, 1.9 Hz, 1 H, C3'-$H_{eq}$), 1.41 (app dt, *J* = 12.8, 11.2, Hz, 1 H, C3'-$H_{ax}$); $^{13}$C NMR (125 MHz) δ 151.1 (C5/C8), 151.0 (C5/C8), 146.9 (C1/C4), 142.3 (C1/C4), 125.3 (Ar-C), 116.1 (Ar-C), 115.7 (Ar-C), 110.4 (C3), 103.6 (C6/C7), 102.9 (C6/C7), 82.8 (C4'), 80.1 (C5'), 79.4 (C6'), 72.3 (C7'), 71.6 (C2'), 60.5 (Sug-OCH3), 59.5 (Sug-OCH3), 56.7 (Sug-OCH3), 56.5 (Ar-OCH3), 56.4 (Ar-OCH3), 36.5 (C3').



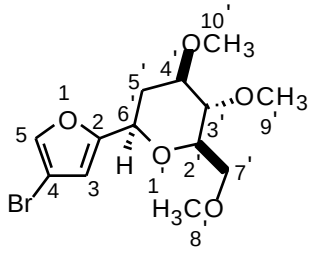

**2.96**

**5,8-Dimethoxy-2,4-*bis*(tetrahydropyran-2-yl)naphthalen-1-ol (2.96).** A solution of *t*-BuLi in pentane (1.28 M, 1.46 mL, 1.87 mmol) was added to a solution of

dihydropyran (163 μL, 1.78 mmol) in THF (2 mL) at -78 ˚C. The resultant solution was allowed to warm to 0 ˚C and stirring was continued for 1 h. The mixture was recooled to -78 ˚C whereupon a solution of $ZnCl_2$ in THF (0.99 M, 1.89 mL, 1.87 mmol) was added. The solution was allowed to warm to rt and stirring was continued for 2 h whereupon neat 2,4-dibromofuran (200 mg, 0.89 mmol) and $(PPh)_2PdCl_2$ (62 mg, 0.09 mmol) were added and stirring was continued for 2 h. Aqueous $NH_4Cl$ (5 mL) and $Et_2O$ (5 mL) were added and the layers were separated. The aqueous layer was extracted with $Et_2O$ (2 x 5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give crude **2.82** (138 mg). All of the crude residue was dissolved in $CH_3OH$ (2 mL) and then $NaBH_3CN$ (167 mg, 2.66 mmol) and a spatula tip of bromocresol green were added. Methanolic HCl (1 M) was added dropwise with stirring so as to maintain a yellow color. After 45 min, saturated aqueous $NaHCO_3$ (5 mL) and $Et_2O$ (5 mL) were added and the layers were separated. The aqueous layer was extracted with $Et_2O$ (2 x 5 mL) and the combined organic layers were washed with $H_2O$ (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$) and then concentrated under reduced pressure to give crude **2.94** (160 mg). A solution of *n*-butyllithium (1.44 M, 0.294 mL, 0.42 mmol) was added to a solution of **2.30** (73 mg, 0.42 mmol) in THF (2 mL) at -78 ˚C. After 15 min at -78 ˚C, a solution of **2.94** (100 mg, 0.42 mmol) in THF (0.2 mL) was added, and the reaction was warmed to rt. Saturated aqueous $NH_4Cl$ (10 mL) was added, and the layers were separated. The aqueous phase was extracted with $Et_2O$ (3 x 25 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure The residue was purified by flash chromatography eluting with 30% EtOAc/hexanes to give 49 mg (31%) of **2.95** as a white foam. A portion of this foam (13 mg) was dissolved in dry

$CH_2Cl_2$ (2 mL) and TFA (2 drops) was added. After 2 h at rt, the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with 20% EtOAc/hexanes to give 9 mg (69%) of **2.96** as a mixture of separated diastereomers. The less polar diastereomer was fully characterized: $^1$H NMR (300 MHz) δ 10.10 (s, 1 H), 7.89 (s, 1 H), 6.67 (d, *J* = 8.5 Hz, 1 H), 6.62 (d, *J* = 8.5 Hz, 1 H), 5.46-5.44 (m, 1 H), 4.83-4.79 (m, 1 H), 4.20-4.17 (comp, 2 H), 3.97 (s, 3 H), 3.85 (s, 3 H), 3.68-3.61 (comp, 2 H), 2.07-1.36 (comp, 12 H); $^{13}$C NMR (75 MHz), compound epimerized on standing in $CDCl_3$ (all signals doubled), δ 152.1, 152.0, 150.8, 150.8, 149.1, 149.1, 125.0, 125.0, 124.6, 124.5, 123.7, 123.3, 123.3, 116.3, 104.6, 104.5, 103.9, 103.9, 78.9, 78.9, 75.3, 74.6, 69.4, 69.3, 69.3, 69.2, 56.8, 56.7, 55.7, 55.6, 36.1, 35.9, 32.2, 32.1, 29.7, 29.7, 26.4, 26.4, 26.1, 26.1, 24.9, 24.9, 24.3, 24.3; IR ($CHCl_3$) 3694, 3346, 3019, 2937, 2851, 1618, 1452, 1397, 1358, 1249, 1225 $cm^{-1}$; mass spectrum (CI) *m/z* 373.2005 [$C_{22}H_{21}O_5$ (M + H) requires 373.2015].

**NMR Assignments.** $^1$H NMR (300 MHz) δ 10.10 (s, 1 H), 7.89 (s, 1 H), 6.67 (d, *J* = 8.5 Hz, 1 H), 6.62 (d, *J* = 8.5 Hz, 1 H), 5.46-5.44 (m, 1 H), 4.83-4.79 (m, 1 H), 4.20-4.17 (comp, 2 H), 3.97 (s, 3 H), 3.85 (s, 3 H), 3.68-3.61 (comp, 2 H), 2.07-1.36 (comp, 12 H).

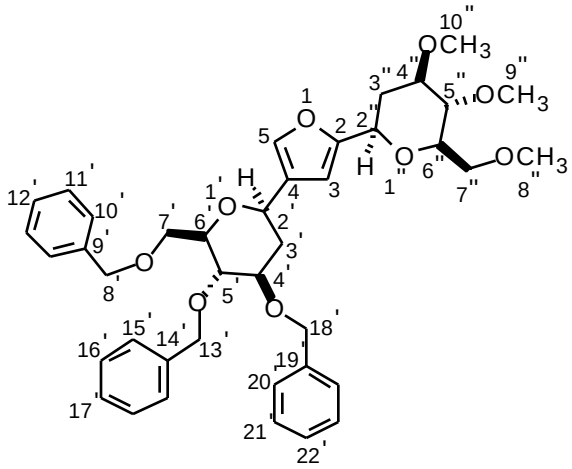



**2.101**

**6(*R*)-(4-Bromo-furan-2-yl)-3(*R*),4(*S*)-dimethoxy-2(*R*)-methoxymethyl-tetrahydropyran (2.101).** A solution of freshly prepared LDA in THF/hexanes (0.48 M, 1.04 mL, 0.50 mmol) was added to a stirred solution of bromofuran **2.100** (100 mg, 0.46 mmol) in THF (2 mL) at -78 ˚C. The solution was stirred for 20 min at -78 ˚C, and lactone **2.72** (93 mg, 0.46 mmol) was then added as a solution in THF (0.7 mL). After 15 min at -78 ˚C, saturated aqueous $NH_4Cl$ (3 mL) was added. The mixture was warmed to rt, and then extracted with EtOAc (4 x 2 mL). The combined organic layers were washed with brine (8 mL), dried ($MgSO_4$), and concentrated to afford an oil. This oil was dissolved in EtOH (2 mL), and the resulting solution was heated to 50 ˚C. Sodium cyanoborohydride ($NaCNBH_3$) (172 mg, 2.74 mmol) and a spatula tip of bromocresol green were added. Ethanolic HCl, which was prepared by mixing AcCl (100 μL) and EtOH (4 mL), was added dropwise at such a rate so as to maintain a yellow color. After 15 min, the yellow color persisted without further addition of acid. Additional ethanolic HCl (2 mL) was added, and the solution was stirred at 50 ˚C for 1 h. The reaction mixture was cooled to rt and poured into saturated $NaHCO_3$ (5 mL). The resulting solution was extracted with EtOAc (3 x 2 mL), and the combined organic layers were washed with brine (6 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 30% EtOAc/hexanes to give 84 mg (55%) of **2.101** as a colorless oil: $^1$H NMR (500 MHz) δ 7.33 (d, *J* = 1.0 Hz, 1 H), 6.33 (dd, *J* = 1.0, 0.8 Hz, 1 H), 4.38 (dd, *J* = 12.0, 1.6 Hz, 1 H), 3.64 (dd, *J* = 10.6, 2.0 Hz, 1 H), 3.58 (dd, *J* = 10.6, 4.8 Hz, 1 H), 3.54 (s, 3 H), 3.45 (s, 3 H), 3.40-3.34 (comp, 2 H), 3.37 (s, 3 H), 3.14 (dd, *J* = 9.6, 8.8 Hz, 1 H), 2.32 (ddd, *J* = 12.8, 5.0, 2.0 Hz, 1 H), 1.74 (ddd, *J* = 12.8, 11.8, 11.4 Hz, 1 H); $^{13}$C NMR (125 MHz) δ 154.3, 140.4, 110.7, 100.0, 82.2, 79.6, 79.2, 71.7, 70.7, 60.3, 59.3, 57.1, 34.0;

IR ($CHCl_3$) 3052, 2987, 2932, 1265, 1100, 909 $cm^{-1}$; mass spectrum (CI) *m*/*z* 334.0430 [$C_{13}H_{19}O_5Br$ (M + H) requires 334.0416].

**NMR Assignments.** $^1H$ NMR (500 MHz) δ 7.33 (d, *J* = 1.0 Hz, 1 H, C5-H), 6.33 (dd, *J* = 1.0, 0.8 Hz, 1 H, C3-H), 4.38 (dd, *J* = 12.0, 1.6 Hz, 1 H, C6'-H), 3.64 (dd, *J* = 10.6, 2.0 Hz, 1 H, C7'-H), 3.58 (dd, *J* = 10.6, 4.8 Hz, 1 H, C7'-H), 3.54 (s, 3 H, Sug-$OCH_3$), 3.45 (s, 3 H, Sug-$OCH_3$), 3.40-3.34 (comp, 2 H, C2'-H & C4'-H), 3.37 (s, 3 H, Sug-$OCH_3$), 3.14 (dd, *J* = 9.6, 8.8 Hz, 1 H, C3'-H), 2.32 (ddd, *J* = 12.8, 5.0, 2.0 Hz, 1 H, C5'-$H_{eq}$), 1.74 (ddd, *J* = 12.8, 11.8, 11.4 Hz, 1 H, C5'-Hax); $^{13}C$ NMR (125 MHz) δ 154.3 (C2), 140.4 (C5), 110.7 (C3), 100.0 (C4), 82.2 (C4'), 79.6 (C5'), 79.2 (C6'), 71.7 (C7'), 70.7 (C2'), 60.3 (C9'), 59.3 (C8'), 57.1 (C10'), 34.0 (C5').



**2.103**

**6-(R)-[4-(4(R),5(S)-bis-Benzyloxy-6(R)-benzyloxymethyltetrahydropyran-2(R)-yl)furan-2-yl]-3(S),4(R)-dimethoxy-2(R)-methoxymethyltetrahydropyran (2.103).**

**Procedure 1:** A solution of *n*-butyllithium in hexanes (1.58 M, 52 μL, 0.08 mmol) was added to a solution of furan **2.101** (25 mg, 0.07 mmol) in THF (1 mL) at -

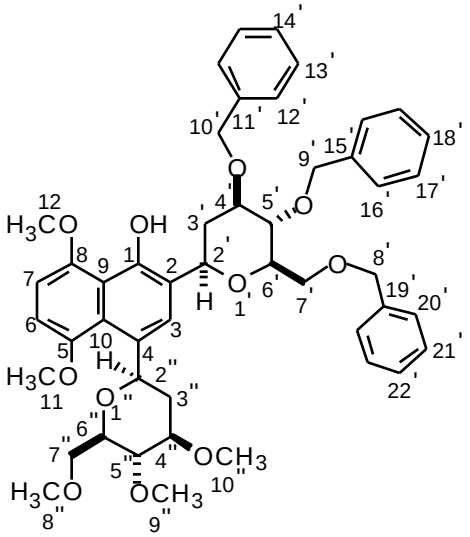
78 ˚C. After 15 min at -78 ˚C, lactone **2.102** (35 mg, 0.08 mmol) was added as a solution in THF (0.3 mL). After stirring for 20 min at -78 ˚C, saturated $NH_4Cl$ (5 mL) was added and the solution was allowed to warm to rt. The resulting mixture was extracted with $Et_2O$ (3 x 2 mL), and the combined organic layers were washed with brine (6 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford an oil. This oil was dissolved in EtOH (1 mL), and the resulting solution was heated to 50 ˚C. Sodium cyanoborohydride ($NaCNBH_3$) (28 mg, 0.45 mmol) and a spatula tip of bromocresol green were added. Ethanolic HCl [prepared by mixing AcCl (100 μL) and EtOH (4 mL)] was added dropwise at such a rate so as to maintain a yellow color. After 15 min, the yellow color persisted without further addition of acid. The reaction mixture was cooled to rt and poured into saturated $NaHCO_3$ (2 mL). The resulting solution was extracted with $Et_2O$ (3 x 2 mL), and the combined organic layers were washed with brine (6 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 30% EtOAc/hexanes to give 29 mg (58%) of **2.103** as a clear colorless oil.

**Procedure 2:** The first part of this procedure is identical to that listed above with the exception that during the reduction step as soon as all of the starting material has been consumed (as evidenced by TLC), the reaction mixture is cooled to rt and worked up as above. The residue that is obtained after concentration of the organic layer was dissolved in $CH_2Cl_2$ (concentration = 0.5 M in adduct) and trifluoroacetic acid (2 eq.) is added. After stirring at rt for 2 d, the resultant mixture was diluted with $CH_2Cl_2$ and the resulting solution was washed with saturated $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue thus obtained was purified as in Procedure 1 to give a single diastereomer of

**2.103** (69%) as a colorless oil: $^{1}$H NMR (500 MHz) δ 7.36-7.20 (comp, 16 H), 6.33 (br s, 1 H), 4.92 (d, *J* = 10.7 Hz, 1 H), 4.71 (d, *J* = 11.6 Hz, 1 H), 4.64 (d, *J* = 11.6 Hz, 1 H), 4.61 (d, *J* = 12.4 Hz, 1 H), 4.59 (d, *J* = 10.7 Hz, 1 H), 4.54 (d, *J* = 12.4 Hz, 1 H), 4.39 (dd, *J* = 11.9, 1.7 Hz, 1 H), 4.33 (dd, *J* = 11.7, 1.4 Hz, 1 H), 3.77-3.70 (comp, 3 H), 3.67 (dd, *J* = 10.6, 2.0 Hz, 1 H), 3.61 (dd, *J* = 10.6, 4.6 Hz, 1 H), 3.58-3.50 (comp, 2 H), 3.56 (s, 3 H), 3.46 (s, 3 H), 3.42-3.37 (comp, 2 H), 3.39 (s, 3 H), 3.17 (app t, *J* = 9.2 Hz, 1 H), 2.35 (ddd, *J* = 12.8, 5.0, 2.0 Hz, 1 H), 2.30 (ddd, *J* = 12.9, 5.0, 2.0 Hz, 1 H), 1.82-1.70 (comp, 2 H); $^{13}$C NMR (125 MHz) δ 153.8, 138.9, 138.5, 138.4, 128.4, 128.4, 128.3, 128.0, 127.8, 127.7, 127.7, 127.6, 127.5, 126.5, 107.5, 106.5, 82.4, 80.9, 79.7, 79.3, 79.2, 78.4, 75.1, 73.5, 71.8, 71.5, 71.0, 70.5, 69.6, 60.6, 59.3, 57.0, 37.6, 34.1; IR ($CHCl_3$) 3016, 2931, 2868, 1454, 1362, 1105, 1082 $cm^{-1}$; mass spectrum (CI) *m/z* 673.3393 [$C_{40}H_{49}O_9$ (M + H) requires 673.3377].

**NMR Assignments.** $^{1}$H NMR (500 MHz) δ 7.36-7.20 (comp, 16 H, C5-H & Ph-H's), 6.33 (br s, 1 H, C3-H), 4.92 (d, *J* = 10.7 Hz, 1 H, -$OCH_2$Ph), 4.71 (d, *J* = 11.6 Hz, 1 H, -$OCH_2$Ph), 4.64 (d, *J* = 11.6 Hz, 1 H, -$OCH_2$Ph), 4.61 (d, *J* = 12.4 Hz, 1 H, -$OCH_2$Ph), 4.59 (d, *J* = 10.7 Hz, 1 H, -$OCH_2$Ph), 4.54 (d, *J* = 12.4 Hz, 1 H, -$OCH_2$Ph), 4.39 (dd, *J* = 11.9, 1.7 Hz, 1 H, C2"-H), 4.33 (dd, *J* = 11.7, 1.4 Hz, 1 H, C2'-H), 3.77-3.70 (comp, 3 H, C4'-H & C7'-H), 3.67 (dd, *J* = 10.6, 2.0 Hz, 1 H, C7"-H), 3.61 (dd, *J* = 10.6, 4.6 Hz, 1 H, C7"-H), 3.58-3.50 (comp, 2 H, C5'-H & C6'-H), 3.56 (s, 3 H, Sug-OCH3), 3.46 (s, 3 H, Sug-OCH3), 3.42-3.37 (comp, 2 H, C4"-H & C6"-H), 3.39 (s, 3 H, Sug-OCH3), 3.17 (app t, *J* = 9.2 Hz, 1 H, C5"-H), 2.35 (ddd, *J* = 12.8, 5.0, 2.0 Hz, 1 H, C3"-Heq), 2.30 (ddd, *J* = 12.9, 5.0, 2.0 Hz, 1 H, C3'-Heq), 1.82-1.70 (comp, 2 H, C3'-Hax & C3"-Hax); $^{13}$C NMR (125 MHz) δ 153.8 (C2), 138.9 (C5), 138.5 (Ar-C), 138.4 (Ar-C), 128.4 (Ar-C), 128.4 (Ar-C), 128.3 (Ar-C), 128.0 (Ar-C), 127.8 (Ar-C),

127.7 (Ar-C), 127.7 (Ar-C), 127.6 (Ar-C), 127.5 (Ar-C), 126.5 (C4), 106.5 (C3), 82.4 (C4''/C6''), 80.9 (C4'/C7'), 79.7 (C5''), 79.3 (C5'/C6'), 79.2 (C4''/C6''), 78.4 (C5'/C6'), 75.1 (-$OCH_2Ph$), 73.5 (-$OCH_2Ph$), 71.8 (C7''), 71.5 (-$OCH_2Ph$), 71.0 (C2''), 70.5 (C2'), 69.6 (C4'/C7'), 60.6 (Sug-$OCH_3$), 59.3 (Sug-$OCH_3$), 57.0 (Sug-$OCH_3$), 37.6 (C3'), 34.1 (C3'').



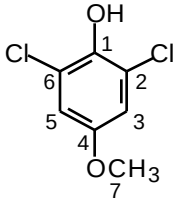
**2.108**

**2-(4(R),5(S)-Bis-benzyloxy-6(R)-benzyloxymethyltetrahydropyran-2(R)-yl)-4-(4(R),5(S)-dimethoxy-6(R)-methoxymethyltetrahydropyran-2(R)-yl)-5,8-dimethoxynaphthalen-1-ol (2.108).** A solution of *s*-butyllithium in cyclohexane (0.79 M in hexanes, 49 μL, 0.040 mmol) was added to a stirred solution of 2-chloro-1,4-dimethoxybenzene (**2.30**) (6.7 mg, 0.039 mmol) in THF (0.5 mL) at -95 ˚C. The reaction was stirred at -95 ˚C for 15 min, and then a solution of furan **2.103** (10 mg, 0.015 mmol) in THF (0.1 mL) was added. The reaction was allowed to warm slowly to 0 ˚C, whereupon saturated $NH_4Cl$ (1 mL) and $H_2O$ (1 mL) were added sequentially. The layers were separated, and the aqueous phase was extracted with

EtOAc (4 x 1 mL). The combined organic layers were washed with brine (4 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 50% EtOAc/hexanes to afford 9.6 mg (80%) of **2.107** as a mixture (ca 1:1) of diastereomers as a clear colorless oil. This oil was dissolved in $CH_2Cl_2$ (1 mL), trifluoroacetic acid (TFA) (2 drops) was added, and the solution was stirred at rt for 1 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with 40% EtOAc/hexanes to give 8.4 mg (87%) of **2.108** as a colorless oil: $^1$H NMR (500 MHz) δ 10.10 (s, 1 H), 7.97 (s, 1 H), 7.39-7.23 (comp, 15 H), 6.69 (d, *J* = 8.6 Hz, 1 H), 6.66 (d, *J* = 8.6 Hz, 1 H), 5.56 (br d, *J* = 11.0 Hz, 1 H), 4.96 (br d, *J* = 11.3 Hz, 1 H), 4.96 (d, *J* = 11.0 Hz, 1 H), 4.75 (d, *J* = 12.1 Hz, 1 H), 4.70 (d, *J* = 11.5 Hz, 1 H), 4.67 (d, *J* = 11.0 Hz, 1 H), 4.64 (d, *J* = 12.1 Hz, 1 H), 4.61 (d, *J* = 11.5 Hz, 1 H), 3.98 (s, 3 H), 3.91-3.88 (m, 1 H), 3.86 (s, 3 H), 3.82-3.80 (comp, 2 H), 3.65-3.62 (comp, 2 H), 3.60-3.59 (comp, 2 H), 3.55 (s, 3 H), 3.52-3.47 (comp, 2 H), 3.40 (s, 3 H), 3,40 (s, 3 H), 3.09 (dd, *J* = 9.6, 8.6 Hz, 1 H), 2.54-2.50 (comp, 2 H), 1.69 (ddd, *J* = 12.8, 11.3, 11.3 Hz, 1 H), 1.43 (ddd, *J* = 12.4, 11.0, 11.0 Hz, 1 H); $^{13}$C NMR (125 MHz) δ 151.8, 150.8, 149.5, 138.8, 138.8, 138.7, 129.1, 128.4, 128.4, 128.3, 128.1, 127.9, 127.7, 127.5, 127.5, 127.4, 124.8, 123.6, 123.1, 116.3, 104.9, 104.1, 83.6, 81.6, 80.3, 79.9, 79.8, 78.6, 75.8, 75.1, 73.5, 72.5, 71.9, 71.1, 69.6, 60.6, 59.7, 56.8, 56.4, 55.6, 39.3, 37.1; IR (neat) 3690, 3607, 2977, 2933, 2870, 2256, 1602 cm$^{-1}$; mass spectrum (CI) *m/z* 808.3841 [$C_{48}H_{56}O_{11}$ (M) requires 808.3823].

**NMR Assignments.** $^1$H NMR (500 MHz) δ 10.10 (s, 1 H, C1-OH), 7.97 (s, 1 H, ), 7.39-7.23 (comp, 15 H, Ph-H), 6.69 (d, *J* = 8.6 Hz, 1 H, C7-H), 6.66 (d, *J* = 8.6 Hz, 1 H, C6-H), 5.56 (br d, *J* = 11.0 Hz, 1 H, C2"-H), 4.96 (br d, *J* = 11.3 Hz, 1 H, C2'-H), 4.96 (d, *J* = 11.0 Hz, 1 H, -$OCH_2$Ph), 4.75 (d, *J* = 12.1 Hz, 1 H, -$OCH_2$Ph), 4.70 (d,

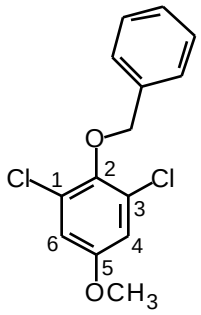
*J* = 11.5 Hz, 1 H, -$OCH_2Ph$), 4.67 (d, *J* = 11.0 Hz, 1 H, -$OCH_2Ph$), 4.64 (d, *J* = 12.1 Hz, 1 H, -$OCH_2Ph$), 4.61 (d, *J* = 11.5 Hz, 1 H, -$OCH_2Ph$), 3.98 (s, 3 H, C12-H), 3.89 (m, 1 H), 3.86 (s, 3 H, C11-H), 3.82-3.80 (comp, 2 H), 3.65-3.62 (comp, 2 H), 3.60-3.59 (comp, 2 H), 3.55 (s, 3 H, Sug-$OCH_3$), 3.52-3.47 (comp, 2 H), 3.40 (s, 3 H, Sug-$OCH_3$), 3,40 (s, 3 H, Sug-$OCH_3$), 3.09 (dd, *J* = 9.6, 8.6 Hz, 1 H, C5'-H), 2.54-2.50 (comp, 2 H, C3'-$H_{eq}$ & C3''-$H_{eq}$), 1.69 (ddd, *J* = 12.8, 11.3, 11.3 Hz, 1 H, C3''-$H_{ax}$), 1.43 (ddd, *J* = 12.4, 11.0, 11.0 Hz, 1 H, C3'-$H_{ax}$); $^{13}C$ NMR (125 MHz) δ 151.8 (C5/C8), 150.8 (C5/C8), 149.5 (C1), 138.8 (Ar-C), 138.8 (Ar-C), 138.7 (Ar-C), 129.1 (Ar-C), 128.4 (Ph-C), 128.4 (Ph-C), 128.3 (Ph-C), 128.1 (Ph-C), 127.9 (Ph-C), 127.7 (Ph-C), 127.5 (Ph-C), 127.5 (Ph-C), 127.4 (Ph-C), 124.8 (Ph-C), 123.6 (C3), 123.1 (Ar-C), 116.3 (Ar-C), 104.9 (C6), 104.1 (C7), 83.6 (C-O), 81.6 (C-O), 80.3 (C5'), 79.9 (C-O), 79.8 (C-O), 78.6 (C-O), 75.8 (C2''), 75.1 (-$OCH_2Ph$), 73.5 (-$OCH_2Ph$), 72.5 (C-O), 71.9 (C2'), 71.1 (-$OCH_2Ph$), 69.6 (C-O), 60.6 (Sug-$OCH_3$), 59.7 (Sug-$OCH_3$), 56.8 (Ar-$OCH_3$), 56.4 (Sug-$OCH_3$), 55.6 (Ar-$OCH_3$), 39.3 (C3'), 37.1 (C3'').




**2.126**

**2,6-Dichloro-4-methoxyphenol (2.126).** Sulfuryl chloride ($SO_2Cl_2$) (4.0 mL, 49.6 mmol) was added to a solution of 4-methoxyphenol (**2.153**) (5.0 g, 40.3 mmol) and BnNH($CH_3$) (416 μL, 3.2 mmol) in benzene (120 mL) at rt, and the solution was stirred for 12 h at rt. Additional portions of BnNH($CH_3$) (416 μL, 3.2 mmol) and $SO_2Cl_2$ (2.0 mL, 24.9 mmol) were then added and stirring was continued for 6 h. 10%

aqueous HCl (10 mL) was added, and the layers were separated. The organic layer was washed with $H_2O$ (2 x 100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by recrystallization from petroleum ether/$Et_2O$ (95:5) to give 4.1 g (52%) of the known phenol **2.126** as pale pink needles that were identical in all respects to the reported compound.[119]

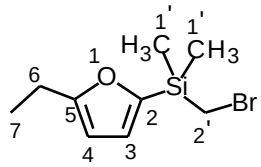



**2.127**

**2-Benzyloxy-1,3-dichloro-5-methoxybenzene (2.127).** A solution of **2.126** (300 mg, 1.45 mmol) in DMF (1 mL) was added to a slurry of sodium hydride (60% dispersion in mineral oil) (70 mg, 1.74 mmol) and benzyl bromide (207 μL, 1.74 mmol) in DMF (7 mL) and the mixture was stirred for 1.5 h at 0 ˚C. Saturated aqueous $NH_4Cl$ (1 mL) and $H_2O$ (25 mL) were added, and the aqueous mixture was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (40 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 7% EtOAc/hexanes to give 189 mg (46%) of **2.127** as a white solid: mp 73-74 ˚C; $^1$H NMR (250 MHz) δ 7.57 (dd, *J* = 7.8, 1.8 Hz, 2 H), 7.45-7.33 (comp, 3 H), 6.88 (s, 2 H), 4.99 (s, 2 H), 3.75 (s, 3 H); $^{13}$C NMR (63 MHz) δ 155.8, 144.8, 136.5, 129.8, 128.4, 128.4, 128.3, 114.5, 75.0, 55.8; IR ($CDCl_3$) 3091, 3034, 3011, 2941, 2883, 2839, 1597, 1561, 1463, 1435, 1404, 1375,

1302, 1219, 1181 $cm^{-1}$; mass spectrum (CI) *m/z* 283.0286 [$C_{14}H_{13}O_2Cl_2$ (M + H) requires 283.0293].

**NMR Assignments.** $^1$H NMR (250 MHz) δ 7.57 (dd, *J* = 7.8, 1.8 Hz, 2 H, C3'-H), 7.45-7.33 (comp, 3 H, C4'-H & C5'-H), 6.88 (s, 2 H, C4-H & C6-H), 4.99 (s, 2 H, C1'-H), 3.75 (s, 3 H, C7-H); $^{13}$C NMR (63 MHz) δ 155.8 (C5), 144.8 (C2), 136.5 (Ar-C), 129.8 (Ar-C), 128.4 (Ar-C), 128.4 (Ar-C), 128.3 (Ar-C), 114.5 (C4/C6), 75.0 (C1'), 55.8 (C7).

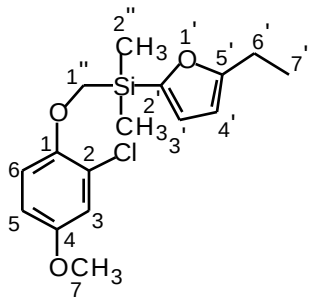



**2.146**

**Bromomethyl-(5-ethyl-furan-2-yl)dimethylsilane (2.146).** A solution of *n*-butyllithium in hexanes (1.30 M, 8.0 mL, 10.4 mmol) was added to a solution of 2-ethylfuran (freshly distilled from 4 Å molecular sieves, 1.1 mL, 10.4 mmol) in THF (35 mL) at -78 ˚C. The reaction was stirred at 0 ˚C for 1.75 h and then recooled to -78 ˚C. Neat (bromomethyl)chlorodimethylsilane (1.4 mL, 10.4 mmol) was added, and the reaction was stirred for 8 h at 0 ˚C and then at rt for 2 d. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (30 mL), and the aqueous phase was extracted with $CHCl_3$ (3 x 25 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes to give 1.91 g (74%) of **2.146** as a colorless liquid: $^1$H NMR (250 MHz) δ 6.62 (d, *J* = 3.3 Hz, 1 H), 5.97 (m, 1 H), 2.66 (app q, *J* = 7.6 Hz, 2 H), 2.60 (s, 2 H), 1.22 (t, *J* = 7.6 Hz, 3 H), 0.37 (s, 6 H); $^{13}$C NMR (75 MHz) δ 163.0, 154.2, 122.3, 104.3, 21.5, 16.2, 12.0, -4.3; IR ($CDCl_3$) 3110,

2974, 2940, 1588, 1495, 1253, 1190 $cm^{-1}$; mass spectrum (CI) *m/z* 247.0153 [$C_9H_{16}OSiBr$ (M + H) requires 247.0154].

**NMR Assignments.** $^1H$ NMR (250 MHz) δ 6.62 (d, *J* = 3.3 Hz, 1 H, C3-H), 5.97 (m, 1 H, C4-H), 2.66 (app q, *J* = 7.6 Hz, 2 H, C6-H), 2.60 (s, 2 H, C2'-H), 1.22 (t, *J* = 7.6 Hz, 3 H, C7-H), 0.37 (s, 6 H, C1'-H); $^{13}C$ NMR (75 MHz) δ 163.0 (C2), 154.2 (C5), 122.3 (C3), 104.3 (C4), 21.5 (C6), 16.2 (C2'), 12.0 (C7), -4.3 (C1').

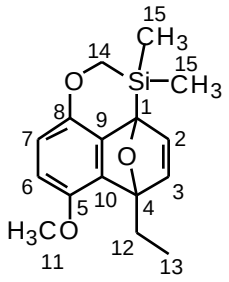



**2.148**

**(2-Chloro-4-methoxyphenoxymethyl)-(5-ethylfuran-2-yl)dimethylsilane (2.148).** A mixture of cesium carbonate ($Cs_2CO_3$) (62 mg, 0.19 mmol), **2.146** (20 mg, 0.13 mmol), and 2-chloro-4-methoxyphenol (**2.147**) (37 mg, 0.15 mmol) in DMF (0.2 mL) was stirred for 1 h at rt. The reaction mixture was poured into saturated aqueous $NH_4Cl$ (2 mL), and the aqueous mixture was extracted with $CH_2Cl_2$ (3 x 2 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 10% EtOAc/hexanes to give 13 mg (31%) of **2.148** as a colorless oil: $^1H$ NMR (250 MHz) δ 6.93 (d, *J* = 9.0 Hz, 1 H), 6.93 (d, *J* = 3.0 Hz, 1 H), 6.73 (dd, *J* = 9.0, 3.0 Hz, 1 H), 6.69 (d, *J* = 3.1 Hz, 1 H), 6.00 (d, *J* = 3.1 Hz, 1 H), 3.78 (s, 2H), 3.74 (s, 3 H), 2.69 (br q, *J* = 7.5 Hz, 2 H), 1.24 (t, *J* = 7.5 Hz, 3 H), 0.43 (s, 6 H); $^{13}C$ NMR (75 MHz) δ 162.9, 154.4, 153.6,

151.1, 123.4, 122.3, 115.8, 113.8, 112.7, 104.3, 61.8, 55.8, 21.5, 12.1, -4.8; IR ($CDCl_3$) 3003, 2971, 2901, 2834, 1586, 1498, 1428, 1283, 1255, 1211, 1182 $cm^{-1}$; mass spectrum (CI) *m/z* 324.0945 [$C_{16}H_{21}O_3SiCl$ (M) requires 324.0949].

**NMR Assignments.** $^1H$ NMR (250 MHz) δ 6.93 (d, *J* = 9.0 Hz, 1 H, C6-H), 6.93 (d, *J* = 3.0 Hz, 1 H, C3-H), 6.73 (dd, *J* = 9.0, 3.0 Hz, 1 H, C5-H), 6.69 (d, *J* = 3.1 Hz, 1 H, C4'-H), 6.00 (d, *J* = 3.1 Hz, 1 H, C3'-H), 3.78 (s, 2H, C1''-H), 3.74 (s, 3 H, C7-H), 2.69 (br q, *J* = 7.5 Hz, 2 H, C6'-H), 1.24 (t, *J* = 7.5 Hz, 3 H, C7'-H), 0.43 (s, 6 H, C2''-H); $^{13}C$ NMR (75 MHz) δ 162.9 (C4), 154.4 (C1), 153.6 (C2'), 151.1 (C5'), 123.4 (Ar-C), 122.3 (Ar-C), 115.8 (Ar-C), 113.8 (Ar-C), 112.7 (Ar-C), 104.3 (C2), 61.8 (C1''), 55.8 (C7), 21.5 (C6'), 12.1 (C7'), -4.8 (C2'').

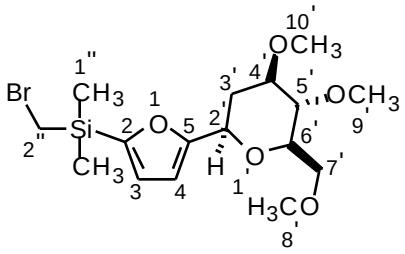



**2.149**

**Cycloadduct 2.149.** A solution of *s*-butyllithium in cyclohexane (1.07 M, 151 μL, 0.16 mmol) was added to a stirred solution of **2.148** (50 mg, 0.15 mmol) in THF (1 mL) at -95 ˚C. After 15 min at -95 ˚C, the reaction mixture was warmed to rt, whereupon saturated aqueous $NH_4Cl$ (2 mL) was added. The aqueous layer was extracted with EtOAc (3 x 2 mL), and the combined organic layers were washed with brine (6 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 30% EtOAc/hexanes to give 7 mg of recovered **2.148** and 29 mg [65% (76%brsm)] of **2.149** as a white solid: mp 108-109

˚C; $^{1}$H NMR (250 MHz) δ 7.00 (d, *J* = 5.4 Hz, 1 H), 6.85 (d, *J* = 5.4 Hz, 1 H), 6.47 (d, *J* = 8.9 Hz, 1 H), 6.40 (d, *J* = 8.9 Hz, 1 H), 3.99 (d, *J* = 15.1 Hz, 1 H), 3.72 (s, 3 H), 3.62 (d, *J* = 15.1 Hz, 1 H), 2.55-2.33 (comp, 2 H), 1.09 (app t, *J* = 7.4 Hz, 3 H), 0.33 (s, 3 H), 0.31 (s, 3 H); $^{13}$C NMR (65 MHz) δ 148.1, 147.1, 146.2, 144.4, 137.7, 136.7, 115.6, 112.5, 96.3, 78.0, 60.9, 56.3, 23.5, 9.4, -6.6, -7.6; mass spectrum (CI) *m*/*z* 289.1249 [$C_{16}H_{21}O_3Si$ (M + H) requires 289.1260].

**NMR Assignments.** $^{1}$H NMR (250 MHz) δ 7.00 (d, *J* = 5.4 Hz, 1 H, (C6-H), 6.85 (d, *J* = 5.4 Hz, 1 H, C7-H), 6.47 (d, *J* = 8.9 Hz, 1 H, C3-H), 6.40 (d, *J* = 8.9 Hz, 1 H, C2-H), 3.99 (d, *J* = 15.1 Hz, 1 H, C14-H), 3.72 (s, 3 H, C11-H), 3.62 (d, *J* = 15.1 Hz, 1 H, C14-H), 2.55-2.33 (comp, 2 H, C12-H), 1.09 (app t, *J* = 7.4 Hz, 3 H, C13-H), 0.33 (s, 3 H, C15-H), 0.31 (s, 3 H, C15-H); $^{13}$C NMR (65 MHz) δ 148.1 (Ar-C), 147.1 (Ar-C), 146.2 (C2/C3), 144.4 (C2/C3), 137.7 (Ar-C), 136.7 (Ar-C), 115.6 (C6/C7), 112.5 (C6/C7), 96.3 (C-O), 78.0 (C4), 60.9 (C-O), 56.3 (C-O), 23.5 (C12), 9.4 (C13), -6.6 (C15), -7.6 (C15).

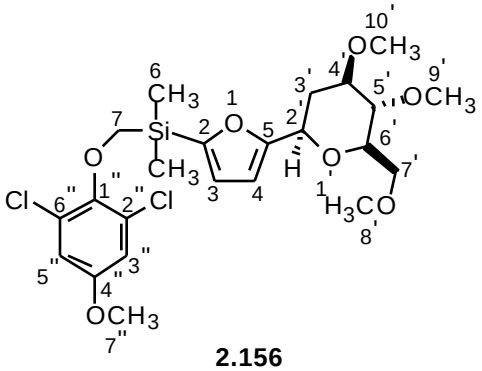



**2.155**

**Bromomethyl-[5-(4(*R*),5(*S*)-dimethoxy-6(*R*)-methoxymethyltetrahydropyran-2(*R*)-yl)furan-2-yl]dimethylsilane (2.155).** A solution of lithium diisopropylamide (LDA) in THF/hexanes (0.51 M, 2.51 mL, 1.28 mmol) was added to a solution of **2.53** (218 mg, 0.85 mmol) in THF (4 mL) at -78 ˚C.

After 3.5 h at -78 ˚C, (bromomethyl)chlorodimethylsilane (**2.121**) (freshly distilled from $CaH_2$, 128 μL, 0.94 mmol) was added, and the reaction was warmed to rt. After 12 h at rt, saturated aqueous $NaHCO_3$ (40 mL) was added, and the aqueous mixture was extracted with $CH_2Cl_2$ (3 x 30 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 20% EtOAc/hexanes to give 254 mg (73%) of **2.155** as an oil: $^1$H NMR (250 MHz) δ 6.62 (d, *J* = 3.2 Hz, 1 H), 6.28 (d, *J* = 3.2 Hz, 1 H), 4.44 (dd, *J* = 11.9, 1.9 Hz, 1 H), 3.68-3.60 (comp, 2 H), 3.54 (s, 3 H), 3.45 (s, 3 H), 3.43-3.35 (comp 2 H), 3.37 (s, 3 H), 3.15 (app t, *J* = 5.3 Hz, 1 H), 2.58 (s, 2 H), 2.34 (ddd, *J* = 12..9, 5.0, 2.0 Hz, 1 H), 1.78 (app dt, *J* = 12.9, 11.6 Hz, 1 H), 0.36 (s, 6 H); $^{13}$C NMR (65 MHz) δ 158.3, 156.0, 122.0, 107.3, 82.4, 79.8, 79.2, 71.7, 71.1, 60.6, 59.3, 57.1, 34.4, 15.9, -4.4; IR (neat) 2930, 2894, 2830, 1253, 1188, 1111, 1083 $cm^{-1}$; mass spectrum (CI) *m/z* 406.0817 [$C_{27}H_{27}O_5SiBr$ (M + H) requires 406.0811].

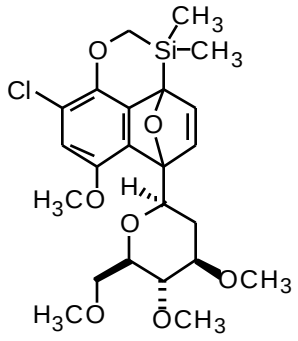
**NMR Assignments.** $^1$H NMR (250 MHz) δ 6.62 (d, *J* = 3.2 Hz, 1 H, C3-H), 6.28 (d, *J* = 3.2 Hz, 1 H, C4-H), 4.44 (dd, *J* = 11.9, 1.9 Hz, 1 H, C2'-H), 3.68-3.60 (comp, 2 H, C7'-H), 3.54 (s, 3 H, Sug-$OCH_3$), 3.45 (s, 3 H, Sug-$OCH_3$), 3.43-3.35 (comp 2 H, C4'-H & C6'-H), 3.37 (s, 3 H, Sug-$OCH_3$), 3.15 (app t, *J* = 5.3 Hz, 1 H, C5'-H), 2.58 (s, 2 H, C2"-H), 2.34 (ddd, *J* = 12..9, 5.0, 2.0 Hz, 1 H, C3'-$H_{eq}$), 1.78 (app dt, *J* = 12.9, 11.6 Hz, 1 H, C3'-$H_{ax}$), 0.36 (s, 6 H, C1"-H); $^{13}$C NMR (65 MHz) δ 158.3 (C2), 156.0 (C5), 122.0 (C3), 107.3 (C4), 82.4 (C4'), 79.8 (C5'), 79.2 (C6'), 71.7 (C7'), 71.1 (C2'), 60.6 (C9'), 59.3 (C8'), 57.1 (C10'), 34.4 (C3'), 15.9 (C2"), -4.4 (C1").



**2.156**

**(2,6-Dichloro-4-methoxyphenoxymethyl)-[5-(4(R),5(S)-dimethoxy-6(R)-methoxymethyltetrahydropyran-2(R)-yl)-furan-2-yl]dimethylsilane (2.156).** A mixture of tetrabutylammonium iodide (65 mg, 0.18 mmol), $K_2CO_3$ (100 mg, 0.80 mmol), **2.155** (65 mg, 0.16 mmol), and 2,6-dichloro-4-methoxyphenol (**2.126**) (36 mg, 0.17 mmol) in acetone (1.7 mL) was stirred for 48 h at rt. $H_2O$ (5 mL) was added, and the aqueous mixture was extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with brine (9 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 20% EtOAc/hexanes to give 75 mg (83%) of **2.156** as a colorless oil: $^1$H NMR (250 MHz, acetone-$d_6$) δ 6.96 (s, 2 H), 6.84 (d, *J* = 3.2 Hz, 1 H), 6.36 (dd, *J* = 3.2, 0.5 Hz, 1 H), 4.50 (br dd, *J* = 11.9, 2.0 Hz, 1 H), 3.90 (s, 2 H), 3.80 (s, 3 H), 3.54-3.53 (comp, 2 H), 3.49 (s, 3 H), 3.45-3.34 (comp, 2 H), 3.41 (s, 3 H), 3.29 (s, 3 H), 3.04 (app t, *J* = 9.4 Hz, 1 H), 2.36 (ddd, *J* = 12.8, 5.0, 1.9 Hz, 1 H), 1.67 (ddd, *J* = 12.8, 11.8, 11.5 Hz, 1 H), 0.44 (s, 3 H), 0.44 (s, 3 H); $^{13}$C NMR (65 MHz) δ 160.1, 156.8, 156.5, 148.4, 129.8, 123.1, 115.4, 107.7, 83.2, 80.6, 80.0, 72.7, 71.5, 67.0, 60.5, 59.1, 56.9, 56.4, 35.4, -4.7; IR (neat) 2930, 2833, 1560, 1474, 1437, 1221, 1112, 1076, 1043 cm$^{-1}$; mass spectrum (CI) *m*/*z* 518.1291 [$C_{23}H_{32}O_7SiCl_2$ (M) requires 518.1294].

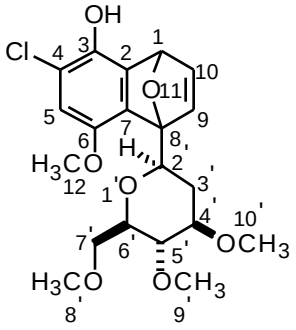
**NMR Assignments.** $^{1}$H NMR (250 MHz) δ 6.96 (s, 2 H, C3''-H & C5''-H), 6.84 (d, *J* = 3.2 Hz, 1 H, C3-H), 6.36 (dd, *J* = 3.2, 0.5 Hz, 1 H, C4-H), 4.50 (br dd, *J* = 11.9, 2.0 Hz, 1 H, C2'-H), 3.90 (s, 2 H, C7-H), 3.80 (s, 3 H, C7''-H), 3.54-3.53 (comp, 2 H, C7'-H), 3.49 (s, 3 H, Sug-$OCH_3$), 3.45-3.34 (comp, 2 H, C4'-H & C6'-H), 3.41 (s, 3 H, Sug-$OCH_3$), 3.29 (s, 3 H, Sug-$OCH_3$), 3.04 (app t, *J* = 9.4 Hz, 1 H, C5'-H), 2.36 (ddd, *J* = 12.8, 5.0, 1.9 Hz, 1 H, C3'-$H_{eq}$), 1.67 (ddd, *J* = 12.8, 11.8, 11.5 Hz, 1 H, C3'-$H_{ax}$), 0.44 (s, 3 H, C6-H), 0.44 (s, 3 H, C6-H); $^{13}$C NMR (65 MHz) δ 160.1 (C2), 156.8 (C5), 156.5 (Ar-C), 148.4 (Ar-C), 129.8 (Ar-C), 123.1 (Ar-C), 115.4 (Ar-C), 107.7 (C-O), 83.2 (C-O), 80.6 (C-O), 80.0 (C-O), 72.7 (C-O), 71.5 (C-O), 67.0 (C-O), 60.5 (C-O), 59.1 (C-O), 56.9 (C-O), 56.4 (C-O), 35.4 (C3'), -4.7 (C6).




**2.157**

**Cycloadduct 2.157.** A solution of *s*-butyllithium in cyclohexane (1.30 M, 49 μL, 0.06 mmol) was added to a solution of **2.156** (30 mg, 0.06 mmol) in THF (0.8 mL) at -95 ˚C. The solution was stirred for 10 min at -95 ˚C, and then warmed to -5 ˚C over 40 min. Saturated aqueous $NH_4Cl$ (2 mL) and $H_2O$ (1 mL) were added, and the aqueous mixture was extracted with EtOAc (3 x 2 mL). The combined organic layers were washed with brine (6 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 40%

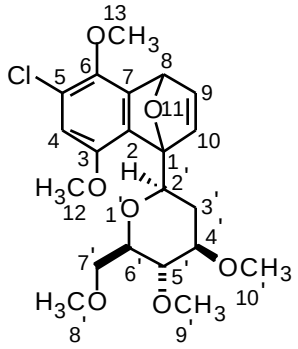
EtOAc/hexanes to give 19 mg (68%) of **2.157** as an oil: $^1$H NMR (250 MHz) δ 7.08 (d, *J* = 5.3 Hz, 0.5 H), 7.00 (d, *J* = 0.5 H), 6.97 (d, *J* = 5.3 Hz, 0.5 H), 6.95 (d, *J* = 5.3 Hz, 0.5 H), 6.59 (s, 0.5 H), 6.58 (s, 0.5 H), 4.65 (br d, *J* = 11.5 Hz, 0.5 H), 4.24 (br d, *J* = 10.0 Hz, 0.5 Hz), 4.17 (d, *J* = 15.2 Hz, 0.5 Hz), 4.16 (d, *J* = 15.0 Hz, 0.5 H), 3.75 (s, 1.5 H), 3.74 (s, 1.5 H), 3.71-3.38 (comp, 5 H), 3.57 (s, 1.5 H), 3.55 (s, 1.5 H), 3.44 (s, 1.5 H), 3.42 (s, 1.5 H), 3.41 (s, 1.5 H), 3.35 (s, 1.5 H), 3.18 (app t, *J* = 9.1 Hz, 0.5 H), 3.00 (app t, *J* = 9.1 Hz, 0.5 H), 2.27-2.15 (comp, 1 H), 1.79-1.53 (comp, 1 H), 0.36 (s, 1.5 H), 0.35 (s, 1.5 H), 0.34 (s, 1.5 H), 0.32 (s, 1.5 H); mass spectrum (CI) *m/z* 483.1597 [$C_{23}H_{32}O_7SiCl$ (M + H) requires 483.1606].




**2.161**

**4-Chloro-8-(4(*R*),5(*S*)-dimethoxy-6-(*R*)-methoxymethyltetrahydropyran-2(*R*)-yl)-6-methoxy-11-oxatricyclo[6.2.1.0$^{0,0}$]undeca-2(7),3,5,9-tetraen-3-ol (2.161).** A solution of tetrabutylammonium fluoride (TBAF) in THF (1.0 M, 25 μL, 0.03 mmol) was added to a solution of **2.157** (4.0 mg, 0.01 mmol) in THF (0.5 mL), and the solution was stirred for 15 min at rt. When the starting material was consumed (as indicated by TLC), $CH_3OH$ (0.5 mL) and 30% aqueous $H_2O_2$ (100 μL) were added, and stirring was continued for 12 h. The reaction was diluted with EtOAc (2 mL), and the resulting

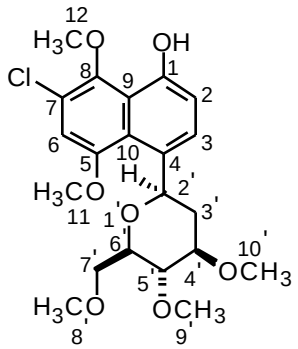
mixture was washed sequentially with 5% aqueous sodium thiosulfate (2 mL), $H_2O$ (2 mL), and brine (2 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 40% EtOAc/hexanes to give 2.1 mg (62%) of **2.161**: $^1$H NMR (250 MHz) δ 7.07 (dd, *J* = 5.5, 1.8 Hz, 0.5 H), 7.06 (d, *J* = 5.5 Hz, 0.5 H), 7.02 (dd, *J* = 5.5, 1.8 Hz, 0.5 H), 6.83 (d, *J* = 5.5 Hz, 0.5 H), 6.59 (s, 0.5 H), 6.58 (s, 0.5 H), 5.92 (d, *J* = 1.8 Hz, 0.5 H), 5.92 (d, *J* = 1.8 Hz, 0.5 H), 5.25 (br s, 0.5 H), 5.25 (br s, 0.5 H), 4.61 (dd, *J* = 11.3, 1.5 Hz, 0.5 H), 4.42 (dd, *J* = 12.0, 1.8 Hz, 0.5 H), 3.75 (s, 1.5 H), 3.74 (s, 1.5 H), 3.70-3.41 (comp, 4 H), 3.55 (s, 1.5 H), 3.55 (s, 1.5 H), 3.45 (s, 1.5 H), 3.40 (s, 1.5 H), 3.39 (s, 1.5 H), 3.28 (s, 1.5 H), 3.06 (app t, *J* = 9.0 Hz, 0.5 H), 2.99 (app t, *J* = 9.0 Hz, 0.5 H), 2.25-2.18 (comp, 1 H), 1.78-1.55 (comp, 1 H); mass spectrum (CI) *m/z* 413.1376 [$C_{20}H_{26}O_7Cl$ (M + H) requires 413.1367].



**2.162**

**5-Chloro-1-(4(*R*),5(*S*)-dimethoxy-6(*R*)-methoxymethyltetrahydropyran-2(*R*)-yl)-3,6-dimethoxy-11-oxatricyclo[6.2.1.0$^{0,0}$]undeca-2(7),3,5,9-tetraene (2.162).** A solution of tetrabutylammonium fluoride (TBAF) in THF (1.0 M, 62 μL, 0.06 mmol) was added to a solution of **2.157** (10 mg, 0.02 mmol) in DMF (0.5 mL) at rt, and the reaction was stirred for 15 min. Saturated aqueous $NaHCO_3$ (2 mL) and

$H_2O$ (0.5 mL) were added. The aqueous mixture was extracted with EtOAc (3 x 2 mL). The combined organic layers were washed with brine (6 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 50% EtOAc/hexanes to give 7 mg (79%) of **2.162** as a colorless oil: $^1$H NMR (250 MHz) δ 7.07 (d, *J* = 5.5 Hz, 0.5 Hz), 7.04 (dd, *J* = 5.5, 1.8 Hz, 0.5 H), 6.99 (dd, *J* = 5.5, 1.8 Hz, 0.5 H), 6.84 (d, *J* = 5.5 Hz, 0.5 H), 6.63 (s, 0.5 H), 6.62 (s, 0.5 H), 5.95-5.93 (comp, 1 H), 4.61 (dd, *J* = 11.5, 1.5 Hz, 0.5 H), 4.42 (dd, *J* = 12.0, 1.8 Hz, 0.5 H), 3.85 (s, 1.5 H), 3.84 (s, 1.5 H), 3.77 (s, 1.5 H), 3.75 (s, 1.5 H), 3.73-3.41 (comp, 4 H), 3.55 (s, 1.5 H), 3.55 (s, 1.5 H), 3.45 (s, 1.5 H), 3.40 (s, 1.5 H), 3.39 (s, 1.5 H), 3.28 (s, 1.5 H), 3.04 (app t, *J* = 9.0 Hz, 0.5 H), 2.99 (app t, *J* = 9.0 Hz, 0.5 H), 2.24-2.17 (comp, 1 H), 1.78-1.54 (comp, 1 H); mass spectrum (CI) *m/z* 427.1524 [$C_{21}H_{28}O_7Cl$ (M + H) requires 427.1524].

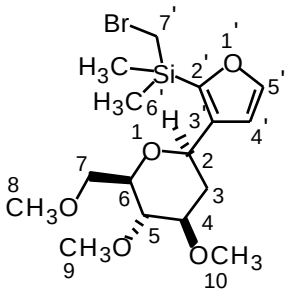



**2.163**

**7-Chloro-4-(4(*R*),5(*S*)-dimethoxy-6(*R*)-methoxymethyltetrahydropyran-2(*R*)-yl)-5,8-dimethoxynaphthalen-1-ol (2.163).** A solution containing trifluoroacetic acid (TFA) (3 drops) and **2.162** (7 mg, 0.02 mmol) in $CH_2Cl_2$ (0.5 mL) was stirred for 5 h at rt in a reaction vessel that was sealed with a glass stopper. The reaction mixture was diluted with $CH_2Cl_2$ (2 mL), and the solution was washed with

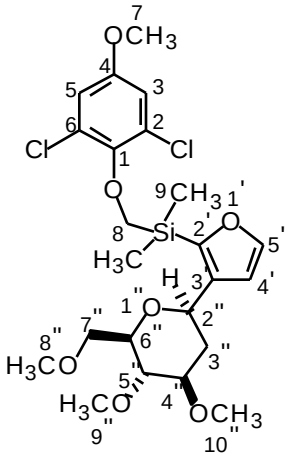
saturated aqueous $NaHCO_3$ (2 mL) and brine (2 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give 7 mg (quant.) of **2.163** as a colorless oil: $^1$H NMR (500 MHz) δ 9.72 (s, 1 H), 7.74 (br d, *J* = 8.1 Hz, 1 H), 6.94 (d, *J* = 8.1 Hz, 1 H), 6.72 (s, 1 H), 5.49 (br d, *J* = 10.2 Hz, 1 H), 3.96 (s, 3 H), 3.90 (s, 3 H), 3.68 (app d, *J* = 3.4 Hz, 2 H), 3.58 (s, 3 H), 3.51-3.46 (comp, 2 H), 3.43 (s, 3 H), 3.42 (s, 3 H), 3.18 (dd, *J* = 9.6, 8.6 Hz, 1 H), 2.51 (ddd, *J* = 12.7, 4.8, 1.4 Hz, 1 H), 1.34 (app dt, *J* = 12.7, 11.2 Hz, 1 H); $^{13}$C NMR (125 MHz) δ 154.0, 152.6, 145.4, 129.9, 125.9, 124.0, 121.0, 118.9, 112.5, 107.2, 83.5, 80.1, 79.4, 75.6, 72.4, 62.5, 60.6, 59.5, 56.5, 55.8, 39.4; IR ($CDCl_3$) 3346, 2938, 2841, 1599, 1516, 1467, 1385, 1351, 1111 $cm^{-1}$; mass spectrum (CI) *m/z* 426.1438 [$C_{21}H_{27}O_7Cl$ (M) requires 426.1445].

**NMR Assignments.** $^1$H NMR (500 MHz) δ 9.72 (s, 1 H, C1-OH), 7.74 (br d, *J* = 8.1 Hz, 1 H, C3-H), 6.94 (d, *J* = 8.1 Hz, 1 H, C2-H), 6.72 (s, 1 H, C6-H), 5.49 (br d, *J* = 10.2 Hz, 1 H, C2'-H), 3.96 (s, 3 H, C12-H), 3.90 (s, 3 H, C11-H), 3.68 (app d, *J* = 3.4 Hz, 2 H, C7'-H), 3.58 (s, 3 H, Sug-$OCH_3$), 3.51-3.46 (comp, 2 H, C4'-H & C6'-H), 3.43 (s, 3 H, Sug-$OCH_3$), 3.42 (s, 3 H, Sug-$OCH_3$), 3.18 (dd, *J* = 9.6, 8.6 Hz, 1 H, C5'-H), 2.51 (ddd, *J* = 12.7, 4.8, 1.4 Hz, 1 H, C3'-$H_{eq}$), 1.34 (app dt, *J* = 12.7, 11.2 Hz, 1 H, C3'-$H_{ax}$); $^{13}$C NMR (125 MHz) δ 154.0 (C5), 152.6 (C1), 145.4 (C8), 129.9 (C4), 125.9 (C3), 124.0 (C10), 121.0 (Ar-C), 118.9 (Ar-C), 112.5 (C2), 107.2 (C6), 83.5 (C4'/C6'), 80.1 (C5'), 79.4 (C4'/C6'), 75.6 (C2'), 72.4 (C7'), 62.5 (C12), 60.6 (Sug-$OCH_3$), 59.5 (Sug-$OCH_3$), 56.5 (Sug-$OCH_3$), 55.8 (C11), 39.4 (C3').




**Bromomethyl-[3-(4(*R*),5(*S*)-dimethoxy-6(*R*)-methoxymethyltetrahydropyran-2(*R*)-yl)furan-2-yl]dimethylsilane (Precursor to 2.164).** A solution of lithium diisopropylamide (LDA) in a THF/hexanes mixture (0.70 M, 457 μL, 0.32 mmol) was added to a solution of **2.73** (68 mg, 0.27 mmol) in THF (1.3 mL) at -78 ˚C, and the mixture was stirred for 1.5 h at -78 ˚C. (Bromomethyl)chlorodimethylsilane (**2.135**) (51 μL, 0.37 mmol) was added, and the reaction was stirred for 2 min at rt. Saturated aqueous $NaHCO_3$ (3 mL) was added, and the aqueous mixture was extracted with EtOAc (3 x 8 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 30% EtOAc/hexanes to give 9 mg recovered **2.73** and 83 mg [76% (88% brsm)] of product as a colorless oil: $^1$H NMR (250 MHz) δ 7.51 (d, *J* = 1.7 Hz, 1 H), 6.32 (d, *J* = 1.7 Hz, 1 H), 4.44 (dd, *J* = 11.7, 1.9 Hz, 1 H), 3.61-3.59 (comp, 2 H), 3.54 (s, 3 H), 3.44 (s, 3 H), 3.41-3.34 (comp, 2 H), 3.36 (s, 3 H), 3.14 (app t, *J* = 9.1 Hz, 1 H), 2.77 (d, *J* = 12.7 Hz, 1 H), 2.71 (d, *J* = 12.7 Hz, 1 H), 2.30 (ddd, *J* = 13.0, 5.0, 2.0 Hz, 1 H), 1.56 (ddd, *J* = 13.0, 11.6, 11.6 Hz, 1 H), 0.42 (s, 3 H), 0.40 (s, 3 H); $^{13}$C NMR (75 MHz) δ 152.8, 146.5, 137.2, 108.9, 82.4, 79.7, 79.1, 71.6, 71.5, 60.6, 59.0, 57.0, 37.4, 17.0, -3.9, -4.0; IR ($CDCl_3$) 2927, 2893, 2831, 1113 $cm^{-1}$; mass spectrum (CI) *m/z* 406.0798 [$C_{16}H_{27}O_5SiBr$ (M) requires 406.0811].

**NMR Assignments.** $^{1}$H NMR (250 MHz) δ 7.51 (d, *J* = 1.7 Hz, 1 H, C5'-H), 6.32 (d, *J* = 1.7 Hz, 1 H, C4'-H), 4.44 (dd, *J* = 11.7, 1.9 Hz, 1 H, C2-H), 3.61-3.59 (comp, 2 H, C7-H), 3.54 (s, 3 H, Sug-$OCH_3$), 3.44 (s, 3 H, Sug-$OCH_3$), 3.41-3.34 (comp, 2 H, C4-H & C6-H), 3.36 (s, 3 H, Sug-$OCH_3$), 3.14 (app t, *J* = 9.1 Hz, 1 H, C5-H), 2.77 (d, *J* = 12.7 Hz, 1 H, C7'-H), 2.71 (d, *J* = 12.7 Hz, 1 H, C7'-H), 2.30 (ddd, *J* = 13.0, 5.0, 2.0 Hz, 1 H, C3-$H_{eq}$), 1.56 (ddd, *J* = 13.0, 11.6, 11.6 Hz, 1 H, C3-$H_{ax}$), 0.42 (s, 3 H, C6'-H), 0.40 (s, 3 H, C6'-H); $^{13}$C NMR (75 MHz) δ 152.8 (C2'), 146.5 (C5'), 137.2 (C3'), 108.9 (C4'), 82.4 (C4), 79.7 (C5), 79.1 (C6), 71.6 (C7), 71.5 (C2), 60.6 (C9), 59.0 (C8), 57.0 (C10), 37.4 (C7'), 17.0 (C3), -3.9 (C6'), -4.0 (C6').

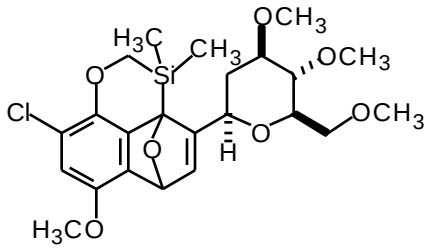


**2.164**

**(2,6-Dichloro-4-methoxyphenoxymethyl)-[3-(4(*R*),5(*S*)-dimethoxy-6(*R*)-methoxymethyltetrahydropyran-2(*R*)-yl)furan-2-yl]dimethylsilane (2.164).** A mixture of tetrabutylammonium iodide (TBAI) (62 mg, 0.17 mmol), $K_2CO_3$ (116 mg, 0.84 mmol), compound from previous experimental (38 mg, 0.18 mmol), and **2.126** (62 mg, 0.15 mmol) in acetone (0.5 mL) was stirred for 3 d at rt. $H_2O$ (3 mL) was added, and the aqueous mixture was extracted with EtOAc (3 x 2 mL). The combined organic

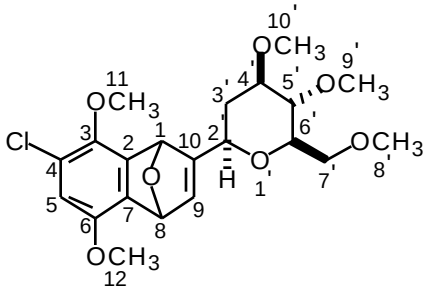
layers were washed with brine (6 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 20% EtOAc/hexanes to give 62 mg (78%) of **2.164** as a colorless oil: $^1$H NMR (250 MHz) δ 7.53 (d, *J* = 1.7 Hz, 1 H), 6.79 (s, 2 H), 6.40 (d, *J* = 1.7 Hz, 1 H), 4.53 (dd, *J* = 11.6 1.8 Hz, 1 H), 3.91 (s, 2 H), 3.73 (s, 3 H), 3.60 (app d, *J* = 3.1 Hz, 2 H), 3.54 (s, 3 H), 3.44-3.29 (comp, 2 H), 3.39 (s, 3 H), 3.32 (s, 3 H), 2.27 (ddd, *J* = 13.0, 5.0, 1.9 Hz, 1 H), 1.61 (app q, *J* = 13.0 Hz, 1 H), 0.51 (s, 3 H), 0.49 (S, 3 H); $^{13}$C NMR (75 MHz) δ 155.4, 153.1, 148.0, 146.6, 137.2, 129.2, 114.5, 108.9, 82.6, 79.7, 79.2, 71.7, 71.0, 66.8, 60.6, 59.0, 56.9, 55.9, 37.4, -4.2, -4.5; IR (neat) 2927, 2832, 1560, 1478, 1220, 1111, 1075 cm$^{-1}$; mass spectrum (CI) *m/z* 519.1353 [$C_{23}H_{33}O_7SiCl_2$ (M + H) requires 519.1373].

**NMR Assignments.** $^1$H NMR (250 MHz) δ 7.53 (d, *J* = 1.7 Hz, 1 H, C5'-H), 6.79 (s, 2 H, C3-H & C5-H), 6.40 (d, *J* = 1.7 Hz, 1 H, C4'-H), 4.53 (dd, *J* = 11.6 1.8 Hz, 1 H, C2''-H), 3.91 (s, 2 H, C8-H), 3.73 (s, 3 H, C7-H), 3.60 (app d, *J* = 3.1 Hz, 2 H, C7''-H), 3.54 (s, 3 H, Sug-$OCH_3$), 3.44-3.29 (comp, 2 H, C4''-H & C6''-H), 3.39 (s, 3 H, Sug-$OCH_3$), 3.32 (s, 3 H, Sug-$OCH_3$), 3.16 (app t, *J* = 9.1 Hz, 1 H, C5'-H), 2.27 (ddd, *J* = 13.0, 5.0, 1.9 Hz, 1 H, C-3''-$H_{eq}$), 1.61 (app q, *J* = 13.0 Hz, 1 H, C3''-$H_{ax}$), 0.51 (s, 3 H, C9-H), 0.49 (S, 3 H, C9-H); $^{13}$C NMR (75 MHz) δ 155.4 (C4), 146.6 (C5'), 137.2 (Ar-C), 129.2 (Ar-C), 114.5 (C3 & C5), 108.9 (C4'), 82.6 (C4''), 79.7 (C6''), 79.2 (C-O), 71.7 (C7''), 71.0 (C2''), 66.8 (C-O), 60.6 (C9''), 59.0 (C8''), 56.9 (C10''), 55.9 (C-O), 37.4 (C3''), -4.2 (C9), -4.5 (C9).



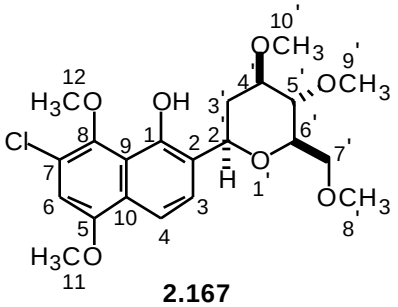

**2.165**

**Cycloadduct 2.165.** A solution of *s*-butyllithium in cyclohexane (1.26 M, 119 μL, 0.15 mmol) was added to a solution of **2.164** (65 mg, 0.13 mmol) in THF (1.3 mL) at -95 ˚C. The solution was stirred for 12 min at -95 ˚C, and then the reaction was warmed to -30 ˚C over 40 min. Saturated aqueous $NH_4Cl$ (2 mL) and $H_2O$ (2 mL) were added, and the aqueous mixture was extracted with EtOAc (3 x 2 mL). The combined organic layers were washed with brine (3 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography eluting with 40% EtOAc/hexanes to give 55 mg (91%) of a mixture (ca. 1:1) of diastereomers **2.165** as a colorless oil: $^1$H NMR (250 MHz) δ 6.78 (app t, *J* = 2.0 Hz, 0.4 H), 6.65 (app t, *J* = 1.8 Hz, 0.6 H), 6.59 (s, 0.4 H), 6.58 (s, 0.6 H), 5.82 (d, *J* = 1.8 Hz, 0.6 H), 5.75 (d, *J* = 2.0 Hz, 0.4 H), 4.42 (d, *J* = 14.9 Hz, 0.4 H), 4.23-4.18 (m, 0.4 H), 4.15-3.91 (comp, 2.2 H), 3.72 (s, 3 H), 3.58-3.07 (comp, 4.6 H), 3.51 ( s, 1.8 H), 3.48 (s, 1.2 H), 3.42 (s, 1.2 H), 3.40 (s, 1.8 H), 3.32 (s, 1.8 H), 3.31 (s, 1.2 H), 2.93 (t, *J* = 9.2 Hz, 0.4 H), 2.31 (ddd, *J* = 12.8, 4.8, 1.6 Hz, 0.4 H), 2.16 (ddd, *J* = 12.8, 1.9, 0.6 Hz, 0.6 H), 1.58 (app q, *J* = 12.8 Hz, 0.6 H), 1.40 (app q, *J* = 12.8 Hz, 1 H), 0.46 (s, 1.8 H), 0.34 (s, 1.2 H), 0.19 (s, 1.2 H), 0.14 (s, 1.8 H); mass spectrum (CI) *m/z* 482.1527 [$C_{23}H_{31}O_7SiCl$ (M) requires 482.1528].



**2.166**

**4-Chloro-10-(4(*R*),5(*S*)-dimethoxy-6(*R*)-methoxymethyltetrahydropyran-2(*R*)-yl)-3,6-dimethoxy-11-oxatricyclo[6.2.1.0$^{0,0}$]undeca-2(7),3,5,9-tetraene (2.166).** A solution of tetrabutylammonium fluoride (TBAF) in THF (1.0 M, 236 μL, 0.24 mmol) was added to a solution of **2.165** (38 mg, 0.08 mmol) in DMF (1 mL) at rt, and the solution was stirred for 5 h at rt. Saturated aqueous $NaHCO_3$ (2 mL) and $H_2O$ (0.5 mL) were added, and the aqueous mixture was extracted with EtOAc (3 x 2 mL). The combined organic layers were washed with brine (6 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 45% EtOAc/hexanes to give 29 mg (86%) of a mixture (ca. 1:1) of diastereomers **2.166** as a colorless oil: $^1$H NMR (250 MHz) δ 6.73 (app t, *J* = 1.8 Hz, 0.4 H), 6.66 (app t, *J* = 2.0 Hz, 0.6 H), 6.62 (s, 1 H), 5.99 (m, 0.6 H), 5.89 (m, 0.4 H), 5.84 (m, 0.6 H), 5.81 (m, 0.4 H), 4.15 (app dt, *J* = 11.9, 1.8 Hz, 0.4 H), 4.04 (app dt, *J* = 11.4, 1.8 Hz, 0.6 H), 3.94 (s, 1.2 H), 3.92 (s, 1.8 H), 3.74 (s, 3 H), 3.59-3.56 (comp, 2 H), 3.51 (s, 3 H), 3.41 (s, 3 H), 3.37 (s, 1.8 H), 3.34 (s, 1.2 H), 3.33-3.23 (comp, 2 H), 3.06 (app t, *J* = 9.2 Hz, 0.6 H), 3.04 (app t, *J* = 9.2 Hz, 0.4 H), 2.23 (ddd, *J* = 12.9, 5.0, 2.0 Hz, 0.6 H), 2.13 (ddd, *J* = 12.8, 4.8, 2.0 Hz, 0.4 H), 1.47-1.31 (m, 1 H) mass spectrum (CI) *m/z* 426.1434 [$C_{21}H_{27}O_7Cl$ (M) requires 426.1445].

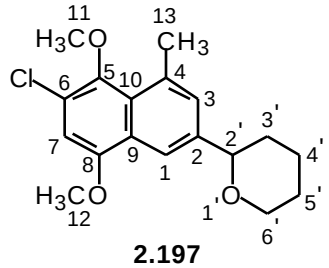


**2.167**

**7-Chloro-2-(4,5-dimethoxy-6-methoxymethyltetrahydropyran-2-yl)-5,8-dimethoxynaphthalen-1-ol (2.167).** Trifluoroacetic acid (TFA) (5 drops) was added to a solution of **2.166** (29 mg, 0.68 mmol) in $CH_2Cl_2$ (1 mL) at -5 ˚C. The reaction vessel was sealed with a glass stopper, warmed slowly to rt, and stirred for 12 h at rt. The reaction mixture was diluted with $CH_2Cl_2$ (3 mL), and the solution was washed with saturated aqueous $NaHCO_3$ (3 mL) and brine (3 mL). The organic layer was dried ($MgSO_4$), and concentrated under reduced pressure to give 24 mg (83%) of pure **2.167** as a colorless oil: $^1$H NMR (250 MHz) δ 9.70 (s, 1 H), 7.68 (d, *J* = 8.8 Hz, 1 H), 7.59 (d, *J* = 8.8 Hz, 1 H), 6.65 (s, 1 H), 4.96 (dd, *J* = 11.5, 2.0 Hz, 1 H), 3.99 (s, 3 H), 3.92 (s, 3 H), 3.70 (d, *J* = 2.1 Hz, 1 H), 3.69 (app s, 1 H), 3.58 (s, 3 H), 3.54-3.47 (comp, 2 H), 3.45 (s, 3 H), 3.44 (s, 3 H), 3.20 (dd, *J* = 9.6, 8.9 Hz, 1 H), 2.46 (ddd, *J* = 13.0, 4.9, 1.9 Hz, 1 H), 1.46 (app dt, *J* = 12.9, 11.4 Hz, 1 H); $^{13}$C NMR (75 MHz) δ 152.7, 148.5, 144.9, 126.2, 125.0, 124.8, 121.4, 117.5, 113.6, 105.5, 82.7, 80.1, 79.4, 72.2, 71.6, 62.4, 60.5, 59.5, 56.8, 55.9, 36.8; IR ($CHCl_3$) 3343, 3020, 3008, 2937, 2837, 1600, 1514, 1453, 1382, 1342, 1206, 1107, 1046 cm$^{-1}$; mass spectrum (CI) *m/z* 426.1450 [$C_{21}H_{27}O_7Cl$ (M) requires 426.1445].

**NMR Assignments.** $^1$H NMR (250 MHz) δ 9.70 (s, 1 H, C1-OH), 7.68 (d, *J* = 8.8 Hz, 1 H, C3-H), 7.59 ( d, *J* = 8.8 Hz, 1 H, C4-H), 6.65 (s, 1 H, C6-H), 4.96 (dd, *J*

= 11.5, 2.0 Hz, 1 H, C2'-H), 3.99 (s, 3 H, C12-H), 3.92 (s, 3 H, C11-H), 3.70 (d, *J* = 2.1 Hz, 1 H, C7'-H), 3.69 (app s, 1 H, C7'-H), 3.58 (s, 3 H, C9'-H), 3.54-3.47 (comp, 2 H, C4'-H & C6'-H), 3.45 (s, 3 H, C10'-H), 3.44 (s, 3 H, C8'-H), 3.20 (dd, *J* = 9.6, 8.9 Hz, 1 H, C5'-H), 2.46 (ddd, *J* = 13.0, 4.9, 1.9 Hz, 1 H, C3'-$H_{eq}$), 1.46 (app dt, *J* = 12.9, 11.4 Hz, 1 H, C3'-$H_{ax}$); $^{13}$C NMR (75 MHz) δ 152.7 (C5), 148.5 (C1), 144.9 (C8), 126.2 (C2), 125.0 (C4), 124.8 (C2), 121.4 (C7), 117.5 (C9), 113.6 (C3), 105.5 (C6), 82.7 (C4'), 80.1 (C5'), 79.4 (C6'), 72.2 (C7'), 71.6 (C2'), 62.4 (C12), 60.5 (C9'), 59.5 (C8'), 56.8 (C10'), 55.9 (C11), 36.8 (C3').

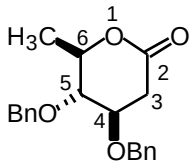



**2.197**

**2-(6-Chloro-5,8-dimethoxy-4-methylnaphthalen-2-yl)tetrahydropyran (2.197).** Lithium di-*tert*-butylbiphenylide (LiDBB) in THF (0.17 M, 5.0 mL, 0.85 mmol) was added to a solution of phenylsulfide **2.181** (92 mg, 0.47 mmol) in THF (1 mL) at -78 ˚C, and the mixture was stirred for 10 min at -78 ˚C. Borontrifluoride etherate ($BF_3{\cdot}OEt_2$) (21 μL, 0.17 mmol) was added to the reaction, and stirring was continued for 10 min at -78 ˚C. A mixture (ca 1:1) of regioisomeric cycloadducts **2.187** (40 mg, 0.16 mmol) in THF (1 mL) was added, and the resultant solution was stirred for 2 h at -78 ˚C. $CH_3OH$ (0.5 mL) and saturated aqueous $NH_4Cl$ (2 mL) were sequentially added, and the mixture was warmed to rt. Brine (3 mL) was added, and the aqueous mixture was extracted with $Et_2O$ (3 x 2 mL). The combined organic layers

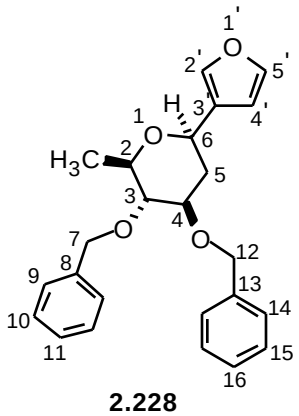
were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting first with 25% EtOAc/hexanes and then 30% EtOAc/hexanes to give 3 mg of an $S_N2'$ adduct. This adduct was dissolved in $CH_2Cl_2$ (1 mL) and the solution was cooled to -60 ˚C, whereupon $BF_3{\cdot}OEt_2$ (3 drops) was added with stirring. The reaction was warmed to rt, and the solvent was removed under reduced pressure. The residue was purified directly by flash chromatography eluting with 5% EtOAc/hexanes to give a product that was further purified by preparative thin layer chromatography eluting with 5% EtOAc/hexanes to give 2 mg (<20% overall) of **2.197** as a single regioisomer: $^1$H NMR (300 MHz) δ 8.02 (br s, 1 H), 7.32 (br s, 1 H), 6.73 (s, 1 H), 4.43-4.40 (m, 1 H), 4.18-4.14 (m, 1 H), 3.93 (s, 3 H), 3.81 (s, 3 H), 3.67-3.59 (m, 1 H), 2.86 (s, 3 H), 1.95-1.53 (comp, 6 H); $^{13}$C NMR (125 MHz) δ 152.4, 147.1, 140.3, 133.8, 129.0, 128.0, 126.6, 124.0, 117.3, 105.9, 80.1, 69.1, 61.4, 55.8, 33.8, 25.9, 24.0, 23.3; mass spectrum (CI) *m/z* 320.1185 [$C_{18}H_{21}O_3Cl$ (M) requires 320.1179].

**NMR Assignments.** $^1$H NMR (300 MHz) δ 8.02 (br s, 1 H), 7.32 (br s, 1 H), 6.73 (s, 1 H), 4.43-4.40 (m, 1 H), 4.18-4.14 (m, 1 H), 3.93 (s, 3 H), 3.81 (s, 3 H), 3.67-3.59 (m, 1 H), 2.86 (s, 3 H), 1.95-1.53 (comp, 6 H); $^{13}$C NMR (125 MHz) δ 152.4, 147.1, 140.3, 133.8, 129.0, 128.0, 126.6, 124.0, 117.3, 105.9, 80.1, 69.1, 61.4, 55.8, 33.8, 25.9, 24.0, 23.3.




**2.230**

**4(R),5(R)-Bis-benzyloxy-6(R)-methyltetrahydropyran-2-one (2.230).** Triphenylphosphine hydrobromide (166 mg, 0.48 mmol) was added to a solution of **2.229** (500 mg, 1.61 mmol) in THF/$H_2O$ (10 mL:0.5 mL) at rt, and the solution was stirred for 3 d at rt. The reaction mixture was concentrated to a volume of ~0.5 mL, and purified directly by flash chromatography eluting with 30% EtOAc/hexanes as eluent to give 477 mg of a mixture of lactols. These lactols were dissolved in $CH_2Cl_2$ (7 mL) and 4-methylmorpholine N-oxide (NMO) (255 mg, 2.18 mmol) and 4 Å molecular sieves (620 mg) were added. The mixture was stirred for 30 min at rt, and then tetrapropylammonium perrhuthenate (TPAP) (15 mg, 0.04 mmol) was added. Stirring was continued for 3.5 h at rt, and then the reaction mixture was purified directly by flash chromatography eluting with 30% EtOAc/hexanes to give 444 mg (84%) of the known lactone (enantiomer) **2.230** as a white solid that was identical in all respects to the reported compound.[145]

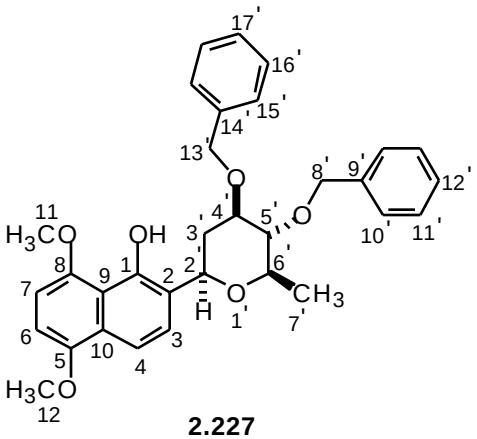


**2.228**

**3(*R*),4(*R*)-Dibenzyloxy-6(*R*)-furan-3-yl-2(*R*)-methyltetrahydropyran (2.228).** A solution of *n*-butyllithium in hexanes (2.24 M, 668 μL, 1.50 mmol) was added to a solution of 3-bromofuran (**2.67**) (147 μL, 1.63 mmol) in THF (8 mL) at -78 ˚C, and the resulting mixture was stirred for 10 min at -78 ˚C. A solution of lactone **2.230** (444 mg, 1.36 mmol) in THF (6 mL) was added, and stirring was continued for 10 min. Saturated aqueous $NH_4Cl$ (15 mL) was added, and the solution was allowed to warm to rt. The mixture was poured into $H_2O$ (15 mL), and the aqueous mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a crude mixture of lactols. These lactols were dissolved in EtOH (7 mL), and the resulting solution was heated to 60 ˚C. Sodium cyanoborohydride (554 mg, 8.82 mmol) and a spatula tip of bromocresol green were added. Ethanolic HCl [prepared by mixing AcCl (100 μL) and EtOH (4 mL)] was added dropwise at such a rate as to maintain a yellow color. After 15 min, the yellow color persisted without further addition of acid. Additional ethanolic HCl (2 mL) was added, and the reaction mixture was stirred for 30 min at 60 ˚C. The reaction was cooled to rt and poured into saturated $NaHCO_3$ (30 mL). The resulting mixture was extracted with EtOAc (3 x 20 mL), and the combined

organic layers were washed with brine (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 5% EtOAc/hexanes to give 292 mg (57%) of **2.228** as a colorless oil: $^1$H NMR (250 MHz) δ 7.41-7.25 (comp, 12 H), 6.42 (dd, *J* = 1.6, 0.7 Hz, 1 H), 5.00 (d, *J* = 10.8 Hz, 1 H), 4.74 (d, *J* = 11.6 Hz, 1 H), 4.70 (d, *J* = 10.8 Hz, 1 H), 4.66 (d, *J* = 11.6 Hz, 1 H), 4.38 (dd, *J* = 11.7, 2.0 Hz, 1 H), 3.74 (ddd, *J* = 11.4, 8.7, 5.0 Hz, 1 H), 3.49 (dq, *J* = 9.3, 6.2 Hz, 1 H), 3.20 (dd, *J* = 9.3, 8.7 Hz, 1 H), 2.37 (ddd, *J* = 12.8, 5.0, 2.0 Hz, 1 H), 1.78 (ddd, *J* = 12.8, 11.7, 11.4 Hz, 1 H), 1.36 (d, *J* = 6.2 Hz, 3 H); $^{13}$C NMR (75 MHz) δ 143.1, 139.2, 138.5, 128.4, 128.4, 128.4, 128.0, 127.7, 127.6, 127.6, 126.1, 108.8, 84.0, 80.6, 75.6, 75.3, 71.5, 70.0, 37.6, 18.5; IR (neat) 3063, 2973, 2922, 2863, 1952, 1875, 1810, 1604, 1498, 1454, 1364, 1300, 1208, 1162, 1113, 1027, 996 $cm^{-1}$; mass spectrum (CI) *m/z* 379.1916 [$C_{24}H_{27}O_4$ (M + H) requires 379.1909].

**NMR Assignments.** $^1$H NMR (250 MHz) δ 7.41-7.25 (comp, 12 H, C2'-H & C5'-H & Ph-H's), 6.42 (dd, *J* = 1.6, 0.7 Hz, 1 H, C4'-H), 5.00 (d, *J* = 10.8 Hz, 1 H, -$OCH_2$Ph), 4.74 (d, *J* = 11.6 Hz, 1 H, -$OCH_2$Ph), 4.70 (d, *J* = 10.8 Hz, 1 H, -$OCH_2$Ph), 4.66 (d, *J* = 11.6 Hz, 1 H, -$OCH_2$Ph), 4.38 (dd, *J* = 11.7, 2.0 Hz, 1 H, C6-H), 3.74 (ddd, *J* = 11.4, 8.7, 5.0 Hz, 1 H, C4-H), 3.49 (dq, *J* = 9.3, 6.2 Hz, 1 H, C2-H), 3.20 (dd, *J* = 9.3, 8.7 Hz, 1 H, C3-H), 2.37 (ddd, *J* = 12.8, 5.0, 2.0 Hz, 1 H, C5-Heq), 1.78 (ddd, *J* = 12.8, 11.7, 11.4 Hz, 1 H, C5-Hax), 1.36 (d, *J* = 6.2 Hz, 3 H, C2-$CH_3$); $^{13}$C NMR (75 MHz) δ 143.1 (C5'), 139.2 (C2'), 138.5 (Ph-C), 128.4 (Ph-C), 128.4 (Ph-C), 128.4 (Ph-C), 128.0 (Ph-C), 127.7 (Ph-C), 127.6 (Ph-C), 127.6 (Ph-C), 126.1 (C3'), 108.8 (C4'), 84.0 (C3/C4), 80.6 (C3/C4), 75.6 (C2), 75.3 -$OCH_2$Ph, 71.5 -$OCH_2$Ph, 70.0 (C6), 37.6 (C5), 18.5 (C2-$CH_3$).

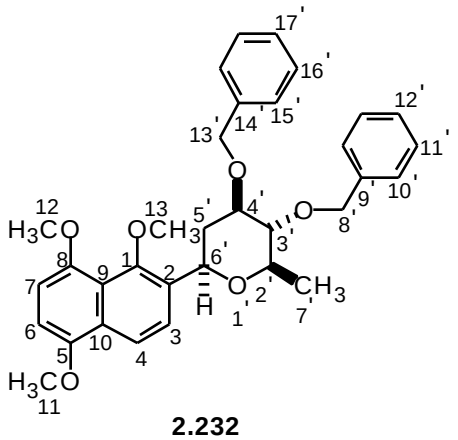


**2.227**

**2-(4(*R*),5(*R*)-*Bis*-benzyloxy-6(*R*)-methyltetrahydropyran-2(*R*)-yl)-5,8-dimethoxynaphthalen-1-ol (2.227).** A solution of *s*-butyllithium in cyclohexane (1.18 M, 255 μL, 0.30 mmol) was added to a solution of 2-chloro-1,4-dimethoxybenzene (**2.30**) (55 mg, 0.32 mmol) in THF (1.6 mL) at -95 ˚C, and the mixture was stirred for 15 min at -95 ˚C. A solution of furan **2.228** (60 mg, 0.16 mmol) in THF (0.6 mL) was then added, and the reaction was warmed to rt over 30 min. Saturated aqueous $NH_4Cl$ (7 mL) and $H_2O$ (0.5 mL) were added sequentially, and the aqueous mixture was extracted with EtOAc (3 x 7 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give an oil. This oil was dissolved in $CH_2Cl_2$ (1.6 mL), and the solution was cooled to -5 ˚C. Trifluoroacetic acid (12 μL, 0.16 mmol) was added, and the reaction was allowed to warm to 15 ˚C. The reaction was cooled to 10 ˚C, and additional trifluoroacetic acid (20 drops) was added and stirring continued for 1 h. Saturated aqueous $NaHCO_3$ (3 mL) was added, and the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (3 x 3 mL), and the combined organic layers were washed with brine (9 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 20% EtOAc/hexanes to give

63 mg (77%) of **2.227** as an oil: $^{1}$H NMR (300 MHz) δ 9.79 (s, 1 H), 7.74 (d, *J* = 8.7 Hz, 1 H), 7.62 (d, *J* = 8.7 Hz, 1 H), 7.42-7.24 (m, 10 H), 6.66 (d, *J* = 8.4 Hz, 1 H), 6.61 (d, *J* = 8.4 Hz, 1 H), 5.03 (d, *J* = 11.1 Hz, 1 H), 5.01 (br d, *J* = 11.4 Hz, 1 H), 4.73 (app d, *J* = 11.1 Hz, 2 H), 4.63 (d, *J* = 11.1 Hz, 1 H), 3.99 (s, 3 H), 3.92 (s, 3 H), 3.88 (ddd, *J* = 11.2, 9.0, 5.0 Hz, 1 H), 3.61 (dq, *J* = 9.0, 6.1 Hz, 1 H), 3.26 (app t, *J* = 9.0 Hz, 1 H), 2.58 (ddd, *J* = 12.8, 5.0, 1.6 Hz, 1 H), 1.67 (app dt, *J* = 12.8, 11.4 Hz, 1 H), 1.42 (d, *J* = 6.1 Hz, 3 H); $^{13}$C NMR (75 MHz) δ 150.2, 150.1, 149.7, 138.7, 128.3, 128.3, 128.3, 128.3, 128.1, 128.1, 127.6, 127.6, 127.5, 127.5, 124.7, 123.6, 115.1, 113.1, 103.6, 102.7, 84.3, 81.3, 75.7, 75.3, 71.3, 71.1, 56.3, 55.7, 37.5, 18.7; IR ($CHCl_3$) 3359, 3063, 3030, 2936, 2873, 1615, 1518, 1454, 1392, 1252, 1096, 1060 cm$^{-1}$; mass spectrum (CI) *m/z* 514.2355 [$C_{32}H_{34}O_6$ (M) requires 514.2357].

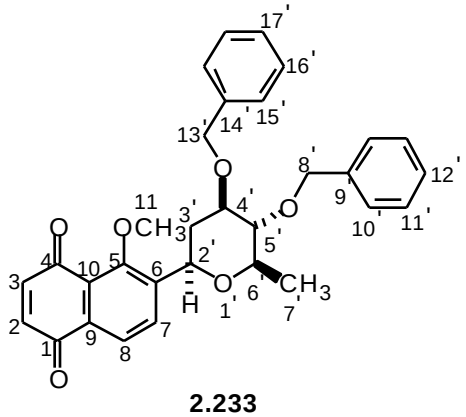
**NMR Assignments.** $^{1}$H NMR (300 MHz) δ 9.79 (s, 1 H), 7.74 (d, *J* = 8.7 Hz, 1 H), 7.62 (d, *J* = 8.7 Hz, 1 H), 7.42-7.24 (m, 10 H), 6.66 (d, *J* = 8.4 Hz, 1 H), 6.61 (d, *J* = 8.4 Hz, 1 H), 5.03 (d, *J* = 11.1 Hz, 1 H), 5.01 (br d, *J* = 11.4 Hz, 1 H), 4.73 (app d, *J* = 11.1 Hz, 2 H), 4.63 (d, *J* = 11.1 Hz, 1 H), 3.99 (s, 3 H), 3.92 (s, 3 H), 3.88 (ddd, *J* = 11.2, 9.0, 5.0 Hz, 1 H), 3.61 (dq, *J* = 9.0, 6.1 Hz, 1 H), 3.26 (app t, *J* = 9.0 Hz, 1 H), 2.58 (ddd, *J* = 12.8, 5.0, 1.6 Hz, 1 H), 1.67 (app dt, *J* = 12.8, 11.4 Hz, 1 H), 1.42 (d, *J* = 6.1 Hz, 3 H).



**2.232**

**3(*R*),4(*R*)-Bis-benzyloxy-2(*R*)-methyl-6(*R*)-(1,5,8-trimethoxynaphthalen-2-yl)tetrahydropyran (2.232).** Sodium hydride (60% dispersion in mineral oil) (19 mg, 0.51 mmol) was added to a solution of **2.227** (53 mg, 0.10 mmol) in DMF (1 mL) at 5 ˚C, and the mixture was stirred for 20 min at 5 ˚C. Methyl iodide (36 μL, 0.62 mmol) was added, and the reaction was warmed to rt and stirred for 12 h. 1% aqueous HCl (2 mL) was added, and the aqueous mixture was extracted with EtOAc (3 x 2 mL). The combined organic layers were washed with brine (6 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 20% EtOAc/hexanes to give 53 mg (97%) of **2.232**: $^1$H NMR (300 MHz) δ 8.10 (d, *J* = 8.4 Hz, 1 H), 7.66 (dd, *J* = 8.9 Hz, 1 H), 7.44-7.25 (comp, 10 H), 6.79 (d, *J* = 8.4 Hz, 1 H), 6.72 (d, *J* = 8.4 Hz, 1 H), 5.07 (d, *J* = 10.9 Hz, 1 H), 5.03 (dd, *J* = 11.2, 1.8 Hz, 1 H), 4.76 (d, *J* = 10.9 Hz, 1 H), 4.73 (d, *J* = 11.5 Hz, 1 H), 4.64 (d, *J* = 11.5 Hz, 1 H), 3.98-3.94 (m, 1 H), 3.97 (s, 3 H), 3.95 (s, 3 H), 3.86 (s, 3 H), 3.65 (dq, *J* = 9.2, 6.2 Hz, 1 H), 3.30 (dd, *J* = 9.2, 8.9 Hz, 1 H), 2.50 (ddd, *J* = 12.8, 5.0, 1.8 Hz, 1 H), 1.78 (ddd, *J* = 12.8, 11.4, 11.2 Hz, 1 H), 1.44 (d, *J* = 6.2 Hz, 3 H); $^{13}$C NMR (75 MHz) δ 152.2, 149.7, 149.7, 138.7, 138.5, 132.1, 128.3, 128.3, 128.3, 128.3, 128.0, 128.0, 127.6, 127.6, 127.6, 127.5, 127.5, 124.1, 120.4, 118.7,

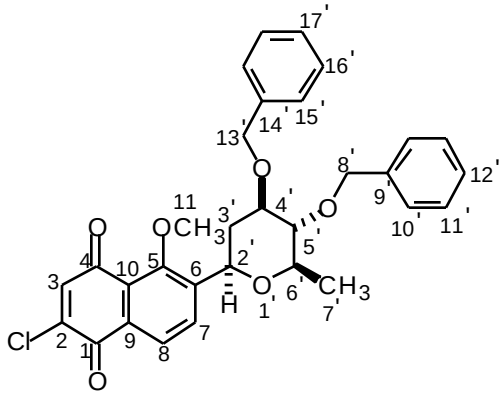
105.9, 103.7, 84.1, 81.2, 75.8, 75.2, 71.7, 71.1, 62.9, 56.6, 55.8, 38.5, 18.7; IR; mass spectrum (CI) *m/z* 528.2505 [$C_{33}H_{36}O_6$ (M) 528.2512].



**2.233**

**6-(4(*R*),5(*R*)-*Bis*-benzyloxy-6(*R*)-methyltetrahydropyran-2(*R*)-yl)-5-methoxy[1,4]naphthoquinone (2.233).** A solution of ceric ammonium nitrate (104 mg, 0.19 mmol) in $H_2O$ (1.6 mL) was added to a solution of **2.232** (50 mg, 0.09 mmol) in $CH_3CN$ (1.6 mL) at 0 ˚C, and the mixture was stirred for 20 min at 0 ˚C. The reaction mixture was then extracted with $Et_2O$ (3 x 2 mL). The combined organic layers were washed with brine (6 mL) dried ($MgSO_4$), and concentrated under reduced pressure to give 45 mg (95%) of pure **2.233**: $^1$H NMR (300 MHz) δ 7.95 (s, 2 H), 7.41-7.26 (comp, 10 H), 6.93 (d, *J* = 10.2 Hz, 1 H), 6.89 (d, *J* = 10.2 Hz, 1 H), 5.04 (d, *J* = 10.9 Hz, 1 H), 4.82 (dd, *J* = 11.4, 1.8 Hz, 1 H), 4.74 (d, *J* = 10.9 Hz, 1 H), 4.73 (d, *J* = 11.6 Hz, 1 H), 4.65 (d, *J* = 11.6 Hz, 1 H), 3.89 (s, 3 H), 3.92-3.81 (m, 1 H), 3.60 (dq, *J* = 9.1, 6.1 Hz, 1 H), 3.24 (dd, *J* = 9.1, 8.8 Hz, 1 H), 2.54 (ddd, *J* = 12.8, 5.0, 1.8 Hz, 1 H), 1.54 (app dt, *J* = 12.8, 11.4 Hz, 1 H), 1.41 (d, *J* = 6.1 Hz, 1 H); $^{13}$C NMR (75 MHz) δ 184.7, 184.4, 156.5, 143.7, 140.3, 138.5, 138.3, 136.8, 133.0, 132.4, 128.4, 128.4, 128.3, 128.3, 128.0, 128.0, 127.6, 127.6, 123.5, 123.2, 83.7, 80.7, 75.8, 75.3,

71.5, 71.3, 62.3, 38.1, 18.6; IR; mass spectrum (CI) *m/z* 500.2190 [$C_{31}H_{30}O_6$ (M + 2) requires 500.2199].



**2.221**

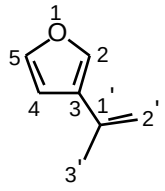
**6-(4(*R*),5(*R*)-*Bis*-benzyloxy-6(*R*)-methyltetrahydropyran-2(*R*)-yl)-2-chloro-5-methoxy[1,4]naphthoquinone (2.221).** Chlorine was vigorously bubbled (10 s) through a solution of **2.233** (10 mg, 0.02 mmol) in HOAc (1 mL) at rt. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOH (1 mL), and the solution was heated at 75 ˚C for 1 h. The reaction was cooled to rt, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with 20% EtOAc/hexanes to give 10 mg (94%) of **2.221** as a yellow oil that was identical in all respects to the chloroquinone that was prepared by Suzuki.[69]

**NMR Data**

| Suzuki | Martin |
|---|---|
| $^1$H NMR (400 MHz, $CDCl_3$) | $^1$H NMR (500 MHz, $CDCl_3$) |
| | |
| 8.02 (d, *J* = 8.1 Hz, 1 H) | 8.02 (d, *J* = 8.1 Hz, 1 H) |

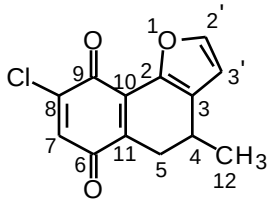
| | |
|---|---|
| 7.93 (d, *J* = 8.1 Hz, 1 H) | 7.93 (d, *J* = 8.1 Hz, 1 H) |
| 7.38-7.25 (m, 10 H) | 7.36-7.27 (m, 10 H) |
| 7.12 (s, 1 H) | 7.13 (s, 1 H) |
| 5.01 (d, *J* = 11.0 Hz, 1 H) | 5.01 (d, *J* = 11.0 Hz, 1 H) |
| 4.78 (dd, *J* = 11.2, 1.7 Hz, 1 H) | 4.78 (dd, *J* = 11.3, 1.7 Hz, 1 H) |
| 4.72 (d, *J* = 11.0 Hz, 1 H) | 4.72 (d, *J* = 10.8 Hz, 1 H) |
| 4.70 (d, *J* = 11.5 Hz, 1 H) | 4.69 (d, *J* = 10.7 Hz, 1 H) |
| 4.63 (d, *J* = 11.5 Hz, 1 H) | 4.63 (d, *J* = 11.6 Hz, 1 H) |
| 3.87 (s, 3 H) | 3.87 (s, 3 H) |
| 3.83 (ddd, *J* = 11.2, 8.5, 4.9 Hz, 1 H) | 3.82 (ddd, *J* = 11.2, 8.5, 4.9 Hz, 1 H) |
| 3.57 (dq, *J* = 9.3, 6.1 Hz, 1 H) | 3.56 (dq, *J* = 9.3, 6.1 Hz, 1 H) |
| 3.22 (dd, *J* = 9.3, 8.5 Hz, 1 H) | 3.21 (app t, *J* = 8.9 Hz, 1 H) |
| 2.51 (ddd, *J* = 12.7, 4.9, 1.7 Hz, 1 H) | 2.50 (ddd, *J* = 12.7, 5.0, 1.9 Hz, 1 H) |
| 1.49 (ddd, *J* = 12.7, 11.2, 11.2 Hz, 1 H) | 1.49 (ddd, *J* = 12.7, 11.3, 11.3 Hz, 1 H) |
| 1.39 (d, *J* = 6.1 Hz, 3 H) | 1.39 (d, *J* = 6.1 Hz, 3 H) |
| | |
| $^{13}$C NMR (100 MHz, $CDCl_3$) | $^{13}$C NMR (125 MHz, $CDCl_3$) |
| 181.9 | 181.9 |
| 177.9 | 177.9 |
| 156.9 | 157.0 |
| 144.6 | 144.6 |
| 144.5 | 144.5 |
| 138.5 | 138.6 |

| | |
|---|---|
| 138.3 | 138.4 |
| 137.4 | 137.4 |
| 132.6 | 132.6 |
| 132.4 | 132.4 |
| 128.42 | 128.44 |
| 128.39 | 128.41 |
| 128.0 | 128.0 |
| 127.71 | 127.73 |
| 127.66 | 127.69 |
| 124.4 | 124.4 |
| 123.3 | 123.3 |
| 83.7 | 83.7 |
| 80.7 | 80.8 |
| 75.9 | 75.9 |
| 75.3 | 75.3 |
| 71.6 | 71.6 |
| 71.4 | 71.4 |
| 62.5 | 62.5 |
| 38.1 | 38.2 |
| 18.6 | 18.6 |
| | |
| Rotation (*c* 1.22, $CHCl_3$) | Rotation (*c* 0.22, $CHCl_3$) |
| [α] -56.7 | [α] -54.9 |




**2.244**

**3-Isopropenylfuran (2.244).** A solution of *n*-butyllithium in hexanes (1.47 M, 2.3 mL, 3.4 mmol) was added to a solution of 3-bromofuran (**2.67**) (500 mg, 3.4 mmol) in THF (8.5 mL) at -78 ˚C, and stirring was continued for 1.5 h at -78 ˚C. A solution of anhydrous $ZnCl_2$ in THF (0.99 M, 3.4 mL, 3.4 mmol) was added, and the resultant mixture was stirred for 1.75 h at -78 ˚C. Neat 2-bromopropene (302 μL, 3.4 mmol) was then added, and the reaction was warmed to rt, whereupon $(PPh_3)_2PdCl_2$ (72 mg, 0.10 mmol) was added, and the mixture was stirred for 10 min at rt. Saturated aqueous $NH_4Cl$ (15 mL) was added, and the layers were separated. The organic layer was washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by Kügel-Rohr distillation (bp 130 ˚C @ 760 mmHg) to give 276 mg (75%) of the known furan **2.244** that was identical in all respects to the reported compound.[164]

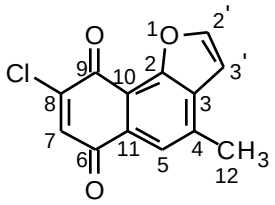



**2.242**

**8-Chloro-4-methyl-4,5-dihydronaphtho[1,2-*b*]furan-6,9-dione (2.242).** A mixture of furan **2.244** (452 mg, 2.55 mmol), 2,6-dichloroquinone (**2.243**) (276 mg, 2.55 mmol), and strontium carbonate ($SrCO_3$) (452 mg, 3.06 mmol) in benzene (15

mL) was heated at reflux. After 3 h, the reaction mixture was cooled to rt. The reaction mixture was filtered through a plug of Celite washing with $CH_2Cl_2$ (100 mL), and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 10% EtOAc/hexanes to give 112 mg (18%) of **2.242**: $^1$H NMR (300 MHz) δ 7.62 (d, *J* = 1.7 Hz, 1 H), 6.96 (s, 1 H), 6.43 (d, *J* = 1.7 Hz, 1 H), 3.08-2.94 (comp, 2 H), 2.52-2.40 (m, 1 H), 1.24 (d, *J* = 6.6 Hz, 3 H); $^{13}$C NMR (75 MHz) δ 184.1, 176.4, 147.4, 144.7, 142.2, 133.7, 133.6, 129.5, 110.0, 107.1, 29.1, 26.3, 19.4; IR ($CHCl_3$) 3008, 2936, 2856, 1586, 1513, 1464, 1435, 1364, 1312 cm$^{-1}$; mass spectrum (CI) *m*/*z* 249.0326 [$C_{13}H_{10}O_3Cl$ (M + H) requires 249.0318].

**NMR Assignments.** $^1$H NMR (300 MHz) δ 7.62 (d, *J* = 1.7 Hz, 1 H, C2'-H), 6.96 (s, 1 H, C7'-H), 6.43 (d, *J* = 1.7 Hz, 1 H, C3'-H), 3.08-2.94 (comp, 2 H, C5-H), 2.52-2.40 (m, 1 H, C4-H), 1.24 (d, *J* = 6.6 Hz, 3 H, C12-H); 13C NMR (75 MHz) δ 184.1 (C9), 176.4 (C6), 147.4 (C2'), 144.7 (C2), 142.2 (C=C), 133.7 (C=C), 133.6 (C=C), 129.5 (C=C), 110.0 (C3'), 107.1 (C3), 29.1 (C5), 26.3 (C4), 19.4 (C12).

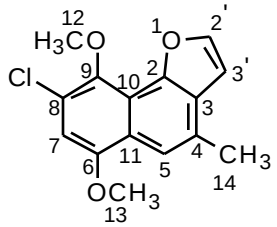



**2.254**

**8-Chloro-4-methylnaphtho[1,2-*b*]furan-6,9-dione (2.254).** A solution of quinone **2.229** (74 mg, 0.30 mmol) and triethylamine (0.083 mL, 0.60 mmol) in $CHCl_3$ (9 mL) was stirred under an $O_2$ (balloon) atmosphere at rt. After 48 h at rt, the solvent was removed under reduced pressure. The residue was dissolved in $CH_2Cl_2$ (5 mL)

and a small spatula of silica gel was added. The solvent was removed under reduced pressure, and the adsorbed material was purified by flash chromatography eluting with 15% EtOAc/hexanes to give 22 mg (30%) of **2.254**: $^{1}$H NMR (300 MHz) δ 7.94 (d, *J* = 2.3 Hz, 1 H), 7.76 (d, *J* = 0.8 Hz, 1 H), 7.13 (s, 1 H), 6.89 (d, *J* = 2.3 Hz, 1 H), 2.62 (d, *J* = 0.8 Hz, 3 H); $^{13}$C NMR (75 MHz) δ 183.0, 176.3, 151.5, 149.9, 146.0, 139.1, 135.0, 134.5, 128.6, 122.0, 114.6, 105.4, 19.3; mass spectrum (CI) *m/z* 247.0160 [$C_{13}H_7O_3Cl$ (M + H) requires 247.0162].

**NMR Assignments.** $^{1}$H NMR (300 MHz) δ 7.94 (d, *J* = 2.3 Hz, 1 H, C2'-H), 7.76 (d, *J* = 0.8 Hz, 1 H, C5-H), 7.13 (s, 1 H, C7-H), 6.89 (d, *J* = 2.3 Hz, 1 H, C3'-H), 2.62 (d, *J* = 0.8 Hz, 3 H, C12-H); $^{13}$C NMR (75 MHz) δ 183.0 (C9), 176.3 (C6), 151.5 (C2), 149.9 (C2'), 146.0 (C=C), 139.1 (C=C), 135.0 (C7), 134.5 (C=C), 128.6 (C=C), 122.0 (C5), 114.6 (C=C), 105.4 (C3'), 19.3 (C12).

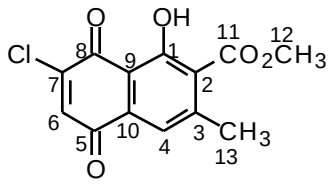



**2.241**

**8-Chloro-6,9-dimethoxy-4-methylnaphtho[1,2-*b*]furan (2.241).** A mixture of zinc dust (16 mg, 2.47 mmol) and **2.254** (61 mg, 0.25 mmol) in glacial acetic acid (5 mL) was stirred for 10 min at rt. The solvent was removed under reduced pressure, and the residue was transferred to a separatory funnel using $Et_2O$ (30 mL). The organic layer was washed with $H_2O$ (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and again with $H_2O$ (30 mL). The organic layer was dried ($MgSO_4$) and concentrated

under reduced pressure to give the crude hydroquinone. This hydroquinone was dissolved in acetone (10 mL), and $K_2CO_3$ (31 mg, 2.23 mmol) and $CH_3I$ (0.139 mL, 2.23 mmol) were added. The septum on the reaction vessel was quickly replaced with a glass stopper. The reaction mixture was heated for 4 h at 40-45 °C and then cooled to rt. After 12 h at rt, the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with 7% EtOAc/hexanes to give 23 mg (34%) of **2.241**: $^1$H NMR (300 MHz) δ 7.85 (d, *J* = 2.0 Hz, 1 H), 7.82 (d, *J* = 0.9 Hz, 1 H), 6.92 (d, *J* = 2.0 Hz, 1 H), 6.78 (s, 1 H), 4.01 (s, 3 H), 3.98 (s, 3 H), 2.62 (d, *J* = 0.9 Hz, 3 H); $^{13}$C NMR (75 MHz) δ 152.0, 148.1, 144.9, 143.6, 129.6, 126.6, 123.4, 123.3, 116.5, 116.5, 105.6, 105.6, 61.5, 56.0, 19.2; IR ($CHCl_3$) 2966, 2929, 2872, 1681, 1638, 1548, 1472, 1458, 1344, 1311 cm$^{-1}$; mass spectrum (CI) *m/z* 277.0633 [$C_{15}H_{14}O_3Cl$ (M + H) requires 277.0631].

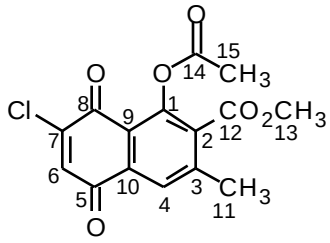
**NMR Assignments.** $^1$H NMR (300 MHz) δ 7.85 (d, *J* = 2.0 Hz, 1 H, C2'-H), 7.82 (d, *J* = 0.9 Hz, 1 H, C5-H), 6.92 (d, *J* = 2.0 Hz, 1 H, C3'-H), 6.78 (s, 1 *H*, C7-H), 4.0$^1$ (s, 3 H, C12-H), 3.98 (s, 3 H, C13-H), 2.62 (d, *J* = 0.9 Hz, 3 H, C14-H); $^{13}$C NMR (75 MHz) δ 152.0 (C6/C9), 148.1 (C6/C9), 144.9 (C2'), 143.6 (Ar-C), 129.6 (Ar-C), 126.6 (Ar-C), 123.4 (Ar-C), 123.3 (Ar-C), 116.5 (C5), 116.5 (Ar-C), 105.6 (C3'), 105.6 (C7), 61.5 (C12), 56.0 (C13), 19.2 (C14).




**2.258**

**7-Chloro-1-hydroxy-3-methyl-5,8-dioxo-5,8-dihydronaphthalene-2-carboxylic acid methyl ester (2.258).** Silylketene acetal **2.259** (7.11 g, 29.10 mmol) was added dropwise to a solution of 2,6-dichloroquinone (**2.243**) (4.29 g, 24.24 mmol) and strontium carbonate ($SrCO_3$) (4.65 g, 31.50 mmol) in dry benzene (48 mL). The mixture was stirred overnight at rt, and the reaction mixture was filtered through Celite washing with $CH_2Cl_2$ (200 mL). The filtrate was concentrated under reduced pressure, and the residue was redissolved in THF (30 mL). 10% Aqueous HCl (30 mL) was added, and the mixture was stirred for 24 h at rt. The reaction mixture was poured into $H_2O$ (60 mL), and the aqueous mixture was extracted with $CH_2Cl_2$ (3 x 100 mL). The combined organic layers were washed sequentially with $H_2O$ (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was recrystallized from boiling methanol to give 3.70 g (54%) of **2.258** as an orange solid. Concentration of the mother liquor to approximately 1/2 the starting volume yielded a second crop 0.38 g (6%) of x for a total of 4.08 g (60%): mp 157-158 ˚C; $^1$H NMR (500 MHz) δ 11.92 (s, 1 H), 7.47 (d, *J* = 0.5 Hz, 1 H), 7.17 (s, 1 H), 3.96 (s, 3 H), 2.42 (d, *J* = 0.5 Hz, 3 H); $^{13}$C NMR (75 MHz) δ 182.2, 181.5, 166.0, 159.2, 146.7, 146.0, 136.6, 131.6, 129.0, 121.3, 112.6, 52.8, 20.5; IR ($CDCl_3$) 3682, 3049, 2955, 1734, 1667, 1644, 1593, 1438, 1367, 1276, 1242, 1205, 1153 cm$^{-1}$; mass spectrum (CI) *m/z* 281.0229 [$C_{13}H_{10}O_5Cl$ (M + H) requires 256.1311].

**NMR Assignments.** $^{1}$H NMR (500 MHz) δ 11.92 (s, 1 H, C1-OH), 7.47 (d, *J* = 0.5 Hz, 1 H, C4-H), 7.17 (s, 1 H, C6-H), 3.96 (s, 3 H, C12-H), 2.42 (d, *J* = 0.5 Hz, 3 H, C13-H); $^{13}$C NMR (75 MHz) δ 182.2 (C8), 181.5 (C5), 166.0 (C11), 159.2 (C1), 146.7 (C7), 146.0 (Ar-C), 136.6 (C6), 131.6 (Ar-C), 129.0 (Ar-C), 121.3 (C4), 112.6 (Ar-C), 52.8 (C12), 20.5 (C13).

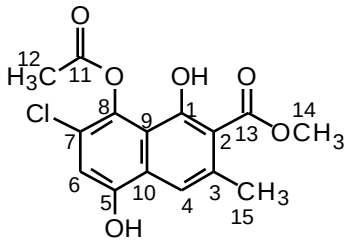



**2.261**

**1-Acetoxy-7-chloro-3-methyl-5,8-dioxo-5,8-dihydronaphthalene-2-carboxylic acid methyl ester (2.261).** Pyridine (0.018 mL, 0.23 mmol) was added dropwise to a solution of **2.258** (53 mg, 0.19 mmol) and acetyl chloride (0.015 mL, 0.21 mmol) in $CH_2Cl_2$ (1 mL) at rt. $CH_3OH$ (0.1 mL) was added, and the mixture was purified directly by flash chromatography eluting with 50% EtOAc/hexanes to give 50 mg (82%) of **2.261** as a pale yellow solid: mp 119-120 ˚C; $^{1}$H NMR (300 MHz) δ 7.88 (s, 1 H), 7.19 (s, 1 H), 3.94 (s, 3 H), 2.45 (s, 3 H), 2.40 (s, 3 H); $^{13}$C NMR (63 MHz) δ 181.4, 175.4, 168.3, 165.3, 147.8, 147.4, 145.0, 134.7, 134.2, 133.1, 126.7, 120.8, 52.8, 20.7, 20.4; IR ($CDCl_3$) 3005, 2955, 1782, 1737, 1682, 1601, 1466, 1437, 1370, 1335, 1283, 1239, 1186, 1155 cm-1; mass spectrum (CI) m/z 323.0314 [$C_{15}H_{12}O_6Cl$ (M + H) requires 323.0322].

**NMR Assignments.** $^{1}$H NMR (300 MHz) δ 7.88 (s, 1 H, C4-H), 7.19 (s, 1 H, C6-H), 3.94 (s, 3 H, C13-H), 2.45 (s, 3 H, C11-H), 2.40 (s, 3 H, C15-H); $^{13}$C NMR (63

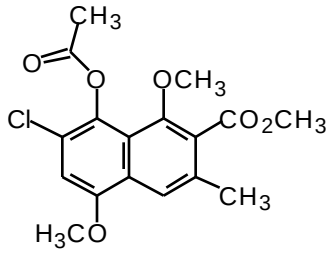
MHz) δ 181.4 (C8), 175.4 (C5), 168.3 (C14), 165.3 (C12), 147.8 (Ar-C), 147.4 (Ar-C), 145.0 (Ar-C), 134.7 (Ar-C), 134.2 (Ar-C), 133.1 (Ar-C), 126.7 (Ar-C), 120.8 (Ar-C), 52.8 (C13), 20.7 (C15), 20.4 (C11).




**2.262**

**8-Acetoxy-7-chloro-1,5-dihydroxy-3-methyl-naphthalene-2-carboxylic acid methyl ester (2.262).** Naphthoquinone **2.261** (58 mg, 0.18 mmol) in $CH_2Cl_2$ (15 mL) was shaken with saturated aqueous $Na_2S_2O_4$ (15 mL) for 5 min. The layers were separated, and the organic layer was washed with $H_2O$ (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated to afford 58 mg (quant.) or pure **2.262** as a pale yellow solid: $^1$H NMR (500 MHz) δ 12.98 (s, 1 H), 6.89 (d, *J* = 0.9 Hz, 1 H), 6.55 (s, 1 H), 6.48 (br s, 1 H), 3.99 (s, 3 H), 2.51 (d, *J* = 0.9 Hz, 3 H), 2.45 (s, 3 H).

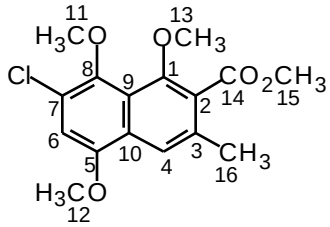
**NMR Assignments.** $^1$H NMR (500 MHz) δ 12.98 (s, 1 H, C1-OH), 6.89 (d, *J* = 0.9 Hz, 1 H, C4-H), 6.55 (s, 1 H, C6-H), 6.48 (br s, 1 H, C5-OH), 3.99 (s, 3 H, C14-H), 2.51 (d, *J* = 0.9 Hz, 3 H, C15-H), 2.45 (s, 3 H, C12-H).



**2.263**

**8-Acetoxy-7-chloro-1,5-dimethoxy-3-methylnaphthalene-2-carboxylic acid methyl ester (2.263).** A biphasic mixture of **2.261** (80 mg, 0.25 mmol) in $CH_2Cl_2$ (20 mL) and saturated aqueous $Na_2S_2O_4$ (20 mL) was shaken vigorously for 5 min. The layers were separated, and the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to a volume of ~1 mL. $CH_2Cl_2$ (1 mL) and a solution of $CH_2N_2$ in $Et_2O$ (4 mL, large excess) were added sequentially. The reaction was sealed with a rubber septum (no vent) and stirred at rt for 12 h. HOAc (5 drops) was added, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography eluting with 20% EtOAc/hexanes to give 63 mg (82%) of **2.263** as a white foam: $^1$H NMR (500 MHz) δ 7.84 (d, *J* = 1.0 Hz, 1 H), 6.82 (s, 1 H), 3.95 (s, 3 H), 3.94 (s, 3 H), 3.86 (s, 3 H), 2.38 (d, *J* = 1.0 Hz, 3 H), 2.37 (s, 3 H), $^{13}$C NMR (125 MHz) δ 168.6, 168.4, 153.2, 151.9, 135.1, 133.0, 129.2, 127.2, 124.6, 120.7, 119.3, 106.6, 64.1, 56.0, 52.3, 20.4, 19.6; IR ($CDCl_3$) 2999, 2953, 2841, 1760, 1729, 1596, 1492, 1453, 1430, 1343, 1271, 1208, 1194, 1159, 1092, 1076 $cm^{-1}$; mass spectrum (CI) *m/z* 352.0719 [$C_{17}H_{17}O_6Cl$ (M) requires 352.0714].

**NMR Assignments.** $^1$H NMR (500 MHz) δ 7.84 (d, *J* = 1.0 Hz, 1 H), 6.82 (s, 1 H), 3.95 (s, 3 H), 3.94 (s, 3 H), 3.86 (s, 3 H), 2.38 (d, *J* = 1.0 Hz, 3 H), 2.37 (s, 3 H).

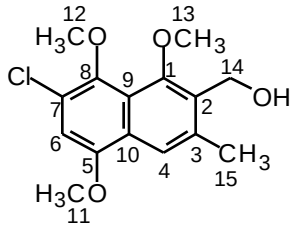


**2.266**

**7-Chloro-1,5,8-trimethoxy-3-methylnaphthalene-2-carboxylic acid methyl ester (2.266).** A mixture of quinone **2.258** (200 mg, 0.71 mmol) in $CH_2Cl_2$ (25 mL) and saturated aqueous $Na_2S_2O_4$ (15 mL) was shaken vigorously until the orange color changed to pale yellow (5 min). The layers were separated, and the organic phase was washed with $H_2O$ (15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was dissolved in DMF (4 mL), and the solution was cooled to 0 ˚C. Sodium hydride (NaH) (60% dispersion in mineral oil) (171 mg, 4.28 mmol) was added in one portion and the reaction mixture was stirred for 15 min at 0 ˚C. Dimethyl sulfate (405 μL, 4.28 mmol) was added in small portions over 15 min, and the reaction was stirred for 3 d at rt. Saturated aqueous $Na_2CO_3$ (15 mL) was added, and the aqueous mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 10% EtOAc/hexanes to give 200 mg (87%) of **2.266** as an off-white solid: mp 72-74 ˚C; $^1$H NMR (250 MHz) δ 7.82 (s, 1 H), 6.78 (s, 1 H), 3.97 (s, 3 H), 3.93 (s, 3 H), 3.84 (s, 3 H), 3.82 (s, 3 H), 2.39 (s, 3 H); $^{13}$C NMR (63 MHz) δ 168.7, 152.3, 151.5, 144.6, 132.5, 129.0, 127.7, 124.6, 121.5, 119.1, 107.0, 64.3, 61.9, 55.9, 52.4, 19.5; IR ($CDCl_3$) 3004, 2938, 2839, 1729, 1591, 1492, 1456, 1440, 1337,

1268, 1209, 1157, 1097, 1078 $cm^{-1}$; mass spectrum (CI) *m/z* 325.0840 [$C_{16}H_{18}O_5Cl$ (M + H) requires 325.0843].

**NMR Assignments.** $^1H$ NMR (250 MHz) δ 7.82 (s, 1 H, C4-H), 6.78 (s, 1 H, C6-H), 3.97 (s, 3 H, $-OCH_3$), 3.93 (s, 3 H, $-OCH_3$), 3.84 (s, 3 H, $-OCH_3$), 3.82 (s, 3 H, $-OCH_3$), 2.39 (s, 3 H, C16-H); $^{13}C$ NMR (63 MHz) δ 168.7 (C14), 152.3 (C8), 151.5 (C5), 144.6 (C1), 132.5 (Ar-C), 129.0 (Ar-C), 127.7 (Ar-C), 124.6 (Ar-C), 121.5 (Ar-C), 119.1 (Ar-C), 107.0 (C7), 64.3 (C12), 61.9 (C11), 55.9 (C15), 52.4 (C13), 19.5 (C16).

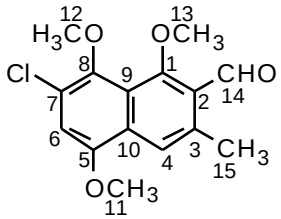



**2.267**

**(7-Chloro-1,5,8-trimethoxy-3-methylnaphthalen-2-yl)methanol (2.267).** A solution of diisobutylaluminum hydride (DIBAL-H) in $CH_2Cl_2$ (1.0 M, 0.98 mL, 0.98 mmol) was added to a stirred solution of **2.266** (79 mg, 0.24 mmol) in $CH_2Cl_2$ (1.2 mL) at 0 °C. Aqueous 1 N NaOH (3 drops) was added, and then $CH_2Cl_2$ and 1N NaOH were added alternately in small portions to the rapidly stirred solution until no further precipitation of aluminum salts occurred. The organic layer was separated, and washed with saturated aqueous Rochelle salt (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford 68 mg (94%) of pure **2.267** as an off-white foam: $^1H$ NMR (300 MHz) δ 7.82 (s, 1 H), 6.75 (s, 1 H), 4.89 (s, 2 H), 3.93 (s, 3 H), 3.87 (s, 3 H), 3.83 (s, 3 H), 2.53 (s, 3 H); $^{13}C$ NMR (75 MHz) δ 153.8, 151.5, 144.4, 135.8,

131.9, 127.1, 124.1, 121.8, 119.3, 106.3, 63.6, 61.8, 57.5, 55.9, 19.9; IR ($CDCl_3$) 3611, 2964, 2936, 2839, 1591, 1453, 1424, 1331, 1207 $cm^{-1}$; mass spectrum (CI) *m*/*z* 296.0819 [$C_{15}H_{17}O_4Cl$ (M) requires 296.0815].

**NMR Assignments.** $^1H$ NMR (300 MHz) δ 7.82 (s, 1 H, C4-H), 6.75 (s, 1 H, C6-H), 4.89 (s, 2 H, C14-H), 3.93 (s, 3 H, Ar-$OCH_3$), 3.87 (s, 3 H, Ar-$OCH_3$), 3.83 (s, 3 H, Ar-$OCH_3$), 2.53 (s, 3 H, C15-H); $^{13}C$ NMR (75 MHz) δ 153.8 (C1), 151.5 (C8), 144.4 (C5), 135.8 (C4), 131.9 (Ar-C), 127.1 (Ar-C), 124.1 (Ar-C), 121.8 (Ar-C), 119.3 (C6), 106.3 (C7), 63.6 (C14), 61.8 (C12), 57.5 (C13), 55.9 (C4), 19.9 (C15).

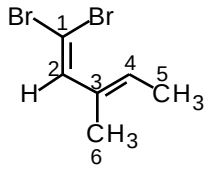



**2.257**

**7-Chloro-1,5,8-trimethoxy-3-methylnaphthalene-2-carbaldehyde (2.257).** Tetrapropylammonium perrhuthenate (TPAP) (4 mg, 0.01 mmol) was added to a solution of **2.267** (68 mg, 0.23 mmol), 4-methylmorpholine *N*-oxide (NMO) (81 mg, 0.34 mmol), and 4 Å molecular sieves (102 mg) in $CH_2Cl_2$ (1.2 mL) at rt. After 15 min at rt, the reaction mixture was purified directly by flash chromatography eluting with 20% EtOAc/hexanes to afford 57 mg (84%) of **2.257** as a pale yellow solid: mp 164-166 ˚C; $^1H$ NMR (300 MHz) δ 10.74 (d, *J* = 0.7 Hz, 1 H), 7.81 (dd, *J* = 0.9, 0.7 Hz, 1 H), 6.88 (s, 1 H), 3.95 (s, 3 H), 3.95 (s, 3 H), 3.87 (s, 3 H), 2.65 (d, *J* = 0.9 Hz, 3 H); $^{13}C$ NMR (75 MHz) δ 193.1, 160.1, 151.4, 136.1, 136.1, 129.5, 127.3, 124.9, 120.6, 108.9, 106.3, 65.5, 62.0, 56.0, 21.6; IR ($CDCl_3$) 3690, 2968, 2936, 2842, 1684, 1590,

1491, 1337, 1209, 1081, 1058 $cm^{-1}$; mass spectrum (CI) *m/z* 295.0742 [$C_{15}H_{16}O_4Cl$ (M + H) requires 295.0737].

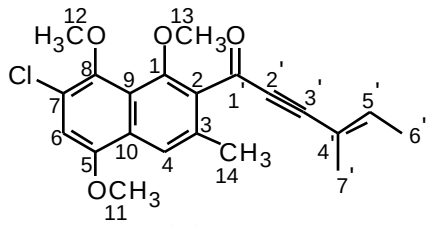
**NMR Assignments.** $^1H$ NMR (300 MHz) δ 10.74 (d, *J* = 0.7 Hz, 1 H, C14-H), 7.81 (dd, *J* = 0.9, 0.7 Hz, 1 H, C4-H), 6.88 (s, 1 H, C6-H), 3.95 (s, 3 H, Ar-$OCH_3$), 3.95 (s, 3 H, Ar-$OCH_3$), 3.87 (s, 3 H, Ar-$OCH_3$), 2.65 (d, *J* = 0.9 Hz, 3 H, C15-H); $^{13}C$ NMR (75 MHz) δ 193.1 (C14), 160.1 (C1), 151.4 (C5), 136.1 (C8), 136.1 (Ar-C), 129.5 (Ar-C), 127.3 (Ar-C), 124.9 (Ar-C), 120.6 (Ar-C), 108.9 (C6), 106.3 (C7), 65.5 (C12), 62.0 (C13), 56.0 (C11), 21.6 (C15).




**2.269**

**1,1-Dibromo-3-methylpenta-1,3(*E*)-diene (2.269).** A solution of $PPh_3$ (1.87 g, 7.1 mmol) in $CH_2Cl_2$ (143 mL) was added to a solution of carbon tetrabromide (2.37 g, 7.1 mmol) in $CH_2Cl_2$ (71 mL) at -20 ˚C, and the solution was stirred for 15 min at -20 ˚C. The mixture was then cooled to -78 ˚C, and a solution of tiglaldehyde (**2.268**) (344 μL, 3.6 mmol) and $Et_3N$ (497 μL, 3.6 mmol) in $CH_2Cl_2$ (20 mL) was added. The reaction was warmed to rt over 40 min, whereupon pentane (250 mL) was added. The mixture was poured into pentane (250 mL), and the suspension was filtered through a plug of Celite washing with additional pentane. The filtrate was concentrated to ~20 mL, and the precipitated solids were removed by vacuum filtration through a plug of Celite washing with additional pentane. The filtrate was again concentrated to ~20 mL, and the solution was purified by passage through a plug of silica gel eluting with

pentane to give 535 mg (63%) of the known **2.269** as a colorless oil that was identical in all respects to the reported compound.[171]

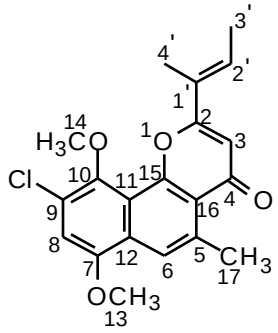



**2.255**

**1-(7-Chloro-1,5,8-trimethoxy-3-methyl-naphthalen-2-yl)-4-methylhex-4(*E*)-en-2-yn-1-one (2.255).** A solution of *n*-butyllithium in hexanes (1.46 M, 2.8 mL, 4.0 mmol) was added to a solution of dibromide **2.269** (532 mg, 2.2 mmol) in THF (10 mL) at -78 ˚C, and the solution was stirred for 1 h at -78 ˚C. The reaction was warmed to 0 ˚C and stirred for 1 h at 0 ˚C. The reaction mixture was then cooled to -78 ˚C, and a solution of aldehyde **2.257** (198 mg, 0.67 mmol) in THF (5 mL) was added. Stirring was continued for 15 min at -78 ˚C, whereupon saturated aqueous $NH_4Cl$ (3 mL) was added. The mixture was warmed to rt and poured into saturated aqueous $NH_4Cl$ (20 mL). The mixture was extracted with $Et_2O$ (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 10% EtOAc/hexanes to give 217 mg (86%) of **2.270** as a colorless oil. A mixture of tetrapropylammonium perrhuthenate (TPAP) (1 crystal) and **2.270** (5 mg, 0.01 mmol) in $CH_2Cl_2$ was stirred at rt for 1 h. A second portion of TPAP (1 crystal) was added and the mixture was stirred at rt for 1 h. The reaction mixture was passed through a short plug of silica gel (pipette column) eluting with $CH_2Cl_2$ to give 3 mg (60%) of **2.255**: $^1$H NMR (300 MHz) δ 7.82 (s, 1 H), 6.80 (s, 1 H), 6.31-6.25 (m, 1 H), 3.94 (s,

3 H), 3.90 (s, 3 H), 3.84 (s, 3 H), 2.43 (s, 3 H), 1.81 (m, 3 H), 1.74 (dd, *J* = 7.3, 1.1 Hz, 3 H); $^{13}$C NMR (125 MHz) δ 181.9, 152.8, 151.6, 144.8, 141.4, 135.0, 132.6, 127.8, 124.6, 121.8, 119.5, 117.1, 107.2, 97.5, 87.1, 64.4, 62.0, 56.0, 19.4, 16.1, 14.8; IR ($CDCl_3$) 2937, 2360, 2254, 2179, 1648, 1619, 1590, 1488, 1455, 1335 $cm^{-1}$; mass spectrum (CI) *m/z* 373.1195 [$C_{21}H_{22}O_4Cl$ (M + H) requires 373.1207].

**NMR Assignments.** $^1$H NMR (300 MHz) δ 7.82 (s, 1 H, C4-H), 6.80 (s, 1 H, C6-H), 6.31-6.25 (m, 1 H, C5'-H), 3.94 (s, 3 H, Ar-$OCH_3$), 3.90 (s, 3 H, Ar-$OCH_3$), 3.84 (s, 3 H, Ar-$OCH_3$), 2.43 (s, 3 H, C14-H), 1.81 (m, 3 H, C6'-H), 1.74 (dd, *J* = 7.3, 1.1 Hz, 3 H, C7'-H). $^{13}$C NMR (125 MHz) δ 181.9, 152.8, 151.6, 144.8, 141.4, 135.0, 132.6, 127.8, 124.6, 121.8, 119.5, 117.1, 107.2, 97.5, 87.1, 64.4, 62.0, 56.0, 19.4, 16.1, 14.8.

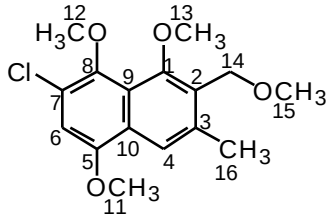



**2.239**

**9-Chloro-7,10-dimethoxy-5-methyl-2-(1-methyl-1(*E*)-propenyl)-benzo[*h*]chromen-4-one (2.239).** Ketone **2.255** (7 mg, 0.02 mmol) in dichloroethane (DCE) (1 mL) was added to a slurry of $AlCl_3$ (25 mg, 0.19 mmol) in DCE (1 mL) at -25 ˚C. After 1.5 h at -25 ˚C, the reaction mixture was stirred at 0 ˚C for 3 h. The reaction mixture was recooled to -20 ˚C, and saturated aqueous $NaHCO_3$ (2 mL) was added. The solution was warmed to rt and partitioned between $CHCl_3$ (2 mL) and $H_2O$

(2 mL), and the layers were separated. The aqueous layer was extracted with $CHCl_3$ (2 mL), and the combined organic layers were washed with $H_2O$ (3 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by radial chromatography eluting with 20% EtOAc/hexanes to give 1 mg (15%) of **2.239** as an oil: $^1$H NMR (500 MHz) δ 7.85 (d, *J* = 1.2 Hz, 1 H), 7.30 (m, 1 H), 6.96 (s, 1 H), 6.40 (s, 1 H), 3.98 (s, 3 H), 3.82 (s, 3 H), 2.92 (d, *J* = 1.2 Hz, 3 H), 1.99 (m 3 H), 1.94 (d, *J* = 6.2 Hz, 3 H); $^{13}$C NMR (125 MHz) δ 120.1, 109.6, 109.3, 60.9, 23.5, 14.2, 12.9 mass spectrum (CI) *m/z* 359.1054 [$C_{20}H_{20}O_4Cl$ (M + H) requires 359.1050].

**NMR Assignments.** $^1$H NMR (500 MHz) δ 7.85 (d, *J* = 1.2 Hz, 1 H, C6-H), 7.30 (m, 1 H, C2'-H), 6.96 (s, 1 H, C8-H), 6.40 (s, 1 H, C3-H), 3.98 (s, 3 H, Ar-$OCH_3$), 3.82 (s, 3 H, Ar-$OCH_3$), 2.92 (d, *J* = 1.2 Hz, 3 H, C17-H), 1.99 (m 3 H, C3'-H), 1.94 (d, *J* = 6.2 Hz, 3 H, C4'-H).

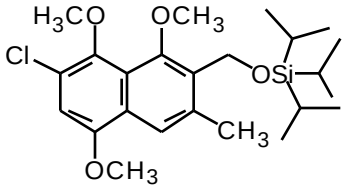



**2.271**

**7-Chloro-1,5,8-trimethoxy-2-methoxymethyl-3-methylnaphthalene (2.271).** Sodium hydride (60% dispersion in mineral oil) (13 mg, 0.33 mmol) and methyl iodide (20 μL, 0.32 mmol) were added sequentially to a solution of **2.267** (32 mg, 0.11 mmol) in DMF (1 mL) at 0 ˚C. The reaction mixture was then stirred for 12 h at rt. Saturated aqueous $NH_4Cl$ (1 mL) and $H_2O$ (0.5 mL) were added, and the aqueous mixture was extracted with EtOAc (3 x 2 mL). The combined organic layers were

washed with brine (6 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 10% EtOAc/hexanes to give 26 mg (78%) of **2.271** as a colorless oil: $^1$H NMR (250 MHz) δ 7.82 (br s, 1 H), 6.75 (s, 1 H), 4.66 (s, 2 H), 3.93 (s, 3 H), 3.84 (s, 3 H), 3.84 (s, 3 H), 3.45 (s, 3 H), 2.52 (d, *J* = 0.5 Hz, 3 H); $^{13}$C NMR (63 MHz) δ 154.2, 151.5, 144.7, 137.0, 129.2, 127.3, 124.0, 121.8, 119.0, 106.4, 66.2, 64.0, 61.8, 58.4, 55.9, 19.7; IR ($CDCl_3$) 2962, 2934, 2838, 1592, 1454, 1424, 1330, 1207, 1190, 1091, 1056 cm$^{-1}$; mass spectrum (CI) *m*/*z* 310.0971 [$C_{16}H_{19}O_4Cl$ (M) requires 310.0972].

**NMR Assignments.** $^1$H NMR (250 MHz) δ 7.82 (br s, 1 H, C4-H), 6.75 (s, 1 H, C6-H), 4.66 (s, 2 H, C14-H), 3.93 (s, 3 H, Ar-$OCH_3$), 3.84 (s, 3 H, Ar-$OCH_3$), 3.84 (s, 3 H, Ar-$OCH_3$), 3.45 (s, 3 H, C15-H), 2.52 (d, *J* = 0.5 Hz, 3 H, C16-H); $^{13}$C NMR (63 MHz) δ 154.2 (C5), 151.5 (C1), 144.7 (C8), 137.0 (Ar-C), 129.2 (Ar-C), 127.3 (Ar-C), 124.0 (Ar-C), 121.8 (Ar-C), 119.0 (C7), 106.4 (C6), 66.2 (C14), 64.0 (Ar-$OCH_3$), 61.8 (Ar-$OCH_3$), 58.4 (Ar-$OCH_3$), 55.9 (C15), 19.7 (C16).

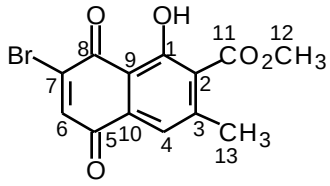



**2.272**

**7-Chloro-1,5,8-trimethoxy-3-methylnaphthalen-2-ylmethoxy)triisopropylsilane (2.272).** Imidazole (43 mg, 0.63 mmol) and triisopropylsilyl chloride (TIPSCl) (136 μL, 0.63 mmol) were added sequentially to a solution of **2.267** (63 mg, 0.21 mmol) in DMF (1 mL) at rt, and the mixture was then heated at 50 ˚C for 12 h. The reaction was cooled to rt and diluted with EtOAc (3 mL).

The organic layer was washed with saturated aqueous $NaHCO_3$ (4 mL) and brine (4 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 5% EtOAc/hexanes to give 82 mg (85%) of **2.272** as a colorless oil: $^1$H NMR (250 MHz) δ 7.81 (br s, 1 H), 6.74 (s, 1 H), 5.02 (s, 2 H), 3.93 (s, 3 H), 3.83 (s, 3 H), 3.81 (s, 3 H), 2.59 (br s, 3 H), 1.24-0.95 (comp, 24 H); $^{13}$C NMR (63 MHz) δ 153.0, 151.5, 137.5, 132.1, 126.9, 123.8, 121.7, 119.6, 118.9, 106.1, 64.0, 61.8, 57.4, 55.9, 20.1, 18.1, 12.2; IR ($CDCl_3$) 2943, 2892, 2866, 1592, 1456, 1424, 1329, 1206, 1087, 1061 cm$^{-1}$; mass spectrum (CI) *m/z* 452.2137 [$C_{24}H_{37}O_4ClSi$ (M) requires 452.2150].

**NMR Assignments.** $^1$H NMR (300 MHz) δ 8.02 (br s, 1 H, C1-H), 7.32 (br s, 1 H, C3-H), 6.73 (s, 1 H, C7-H), 4.43-4.40 (m, 1 H, C2'-H), 4.18-4.14 (m, 1 H, C6'-H), 3.93 (s, 3 H, Ar-$OCH_3$), 3.81 (s, 3 H, Ar-$OCH_3$), 3.67-3.59 (m, 1 H, C6'-H), 2.86 (s, 3 H, C13-H), 1.95-1.53 (comp, 6 H, C3'-H & C4'-H & C5'-H); $^{13}$C NMR (125 MHz) δ 152.4 (C8), 147.1 (C5), 140.3 (Ar-C), 133.8 (Ar-C), 129.0 (Ar-C), 128.0 (Ar-C), 126.6 (Ar-C), 124.0 (C1), 117.3 (C6), 105.9 (C7), 80.1 (C2'), 69.1 (C6'), 61.4 (C11/C12), 55.8 (C11/C12), 33.8 (pyran-C), 25.9 (pyran-C), 24.0 (pyran-C), 23.3 (C13).

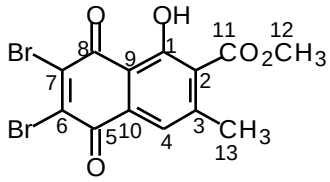



**2.276**

**7-Bromo-1-hydroxy-3-methyl-5,8-dioxo-5,8-dihydronaphthalene-2-carboxylic acid methyl ester (2.276).** A solution of the silylketene acetal **2.259**

(1.155g, 4.34 mmol) in PhH (30 mL) was added to a solution of **2.275** (1.59 g, 6.52 mmol) in PhH (30 mL) and the resulting mixture was stirred at rt for 1 d. The solvent was removed under reduced pressure and the resultant residue was purified by flash chromatography eluting with 15% EtOAc/hexanes. The material thus obtained was recrystallized from boiling $CH_3OH$ (200 mL), in order to remove minor impurities, to deliver 1.02 g of **2.276** (72%) as a reddish-orange solid: mp 132-133 ˚C; $^1$H NMR (250 MHz) δ 11.39 (s, 1 H), 7.44 (s, 1 H), 7.43 (s, 1 H), 3.95 (s, 3 H), 2.40 (s, 3 H); $^{13}$C NMR δ 182.2, 181.2, 166.0, 159.1, 146.5, 140.9, 139.5, 131.4, 128.9, 121.3, 112.2, 52.8, 20.4; IR ($CDCl_3$) 3690, 3064, 3005, 2955, 2847, 1735, 1668, 1641, 1587, 1493, 1438, 1367, 1273, 1241, 1204, 1151, 1092, 1064 cm$^{-1}$; mass spectrum (CI) *m/z* 324.9707 [$C_{13}H_{10}BrO_5$ (M + H) requires 324.9712].

**NMR Assignments.** $^1$H NMR (250 MHz) δ 11.39 (s, 1 H, C1-OH), 7.44 (s, 1 H, C4-H), 7.43 (s, 1 H, C3-H), 3.95 (s, 3 H, C12-H), 2.40 (s, 3 H, C13-H); $^{13}$C NMR δ 182.2 (C5/C6), 181.2 (C5/C6), 166.0 (C11), 159.1 (C1), 146.5 (C6/C7), 140.9 (C6/C7), 139.5 (Ar-C), 131.4 (Ar-C), 128.9 (Ar-C), 121.3 (Ar-C), 112.2 (C2), 52.8 (C12), 20.4 (C13).

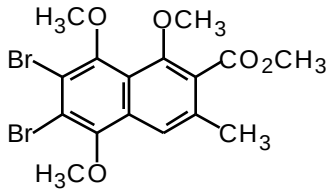



**2.277**

**6,7-Dibromo-1-hydroxy-3-methyl-5,8-dioxo-5,8-dihydronaphthalene-2-carboxylic acid methyl ester (2.277).** A solution of bromine in HOAc (2 M, 891 μL, 1.78 mmol) was added to a solution of bromoquinone **2.276** (500 mg, 1.54 mmol) in

HOAc (10 mL) at rt, and the reaction was heated for 3 d at 50 ˚C. The reaction mixture was cooled to rt and poured into $H_2O$ (20 mL). The aqueous mixture was extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic layers were washed sequentially with $H_2O$ (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give 461 mg (64%) of **2.277** as an orange solid: mp 210-211 ˚C (sublimed); $^1$H NMR (250 MHz) δ 11.92 (s, 1 H), 7.58 (s, 1 H), 3.97 (s, 3 H), 2.42 (s, 3 H); $^{13}$C NMR (75 MHz) δ 183.1, 180.1, 165.7, 159.4, 146.3, 143.2, 142.0, 133.7, 130.5, 129.4, 123.1, 112.0, 52.9, 20.4; IR ($CDCl_3$) 3690, 3038, 2955, 1734, 1679, 1638, 1549, 1438, 1363, 1342, 1285, 1244, 1204, 1149 cm$^{-1}$; mass spectrum (CI) *m/z* 402.8819 ($C_{13}H_9Br_2O_5$ (M + H) requires 402.8817).

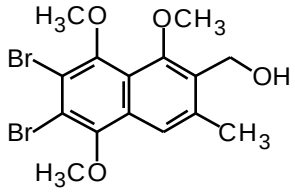
**NMR Assignments.** $^1$H NMR (250 MHz) δ 11.92 (s, 1 H, C1-OH), 7.58 (s, 1 H, C4-H), 3.97 (s, 3 H, C12-H), 2.42 (s, 3 H, C13-H); $^{13}$C NMR (75 MHz) δ 183.1 (C8), 180.1 (C5), 165.7 (C11), 159.4 (C1), 146.3 (Ar-C), 143.2 (Ar-C), 142.0 (Ar-C), 133.7 (Ar-C), 130.5 (Ar-C), 129.4 (Ar-C), 123.1 (C7), 112.0 (C6), 52.9 (C12), 20.4 (C13).




**6,7-Dibromo-1,5,8-trimethoxy-3-methylnaphthalene-2-carboxylic acid methyl ester (Precursor to 2.278).** A biphasic mixture of **2.277** (50 mg, 0.12 mmol) in $CHCl_3$ (20 mL) and saturated aqueous $Na_2S_2O_4$ (20 mL) was shaken vigorously for 5 min. The layers were separated, and the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in DMF (1.5 mL), and

the solution was added to a slurry of NaH (60% dispersion in mineral oil) (50 mg, 1.20 mmol) and methyl iodide (77 μL, 1.20 mmol) in DMF (1 mL) at 0 ˚C. The reaction was warmed to rt over 2 h, and stirred for 12 h at rt. Saturated aqueous $NH_4Cl$ (4 mL) and $H_2O$ (0.5 mL) were added sequentially, and the aqueous mixture was extracted with EtOAc (3 x 4 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 10% EtOAc/hexanes to give 35 mg (63%) of the ester: $^1$H NMR (250 MHz) δ 7.69 (d, *J* = 0.8 Hz, 1 H), 3.98 (s, 3 H), 3.92 (s, 3 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 2.42 (d, *J* = 0.8 Hz, 1 H); IR ($CDCl_3$) 3005, 2940, 2856, 1729, 1615, 1551, 1453, 1392, 1380, 1336, 1276, 1245 cm-1; mass spectrum (CI) m/z 446.9428 [$C_{16}H_{17}O_5Br_2$ (M + H) requires 446.9443].

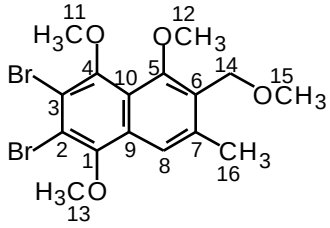
**NMR Assignments.** $^1$H NMR (250 MHz) δ 7.69 (d, *J* = 0.8 Hz, 1 H), 3.98 (s, 3 H), 3.92 (s, 3 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 2.42 (d, *J* = 0.8 Hz, 1 H).




**6,7-Dibromo-1,5,8-trimethoxy-3-methylnaphthalen-2-yl)methanol.** A solution of DIBAL-H in $CH_2Cl_2$ (1.0 M, 201 μL, 0.20 mmol) was added to a solution of the compound from the previous experimental (30 mg, 0.07 mmol) in $CH_2Cl_2$ (1 mL) at 0 ˚C. Saturated aqueous Rochelle salt (0.5 mL) was added dropwise, and $CH_2Cl_2$ (4 mL) was added. The layers were separated, and the organic layer was washed sequentially with saturated aqueous Rochelle salt (2 mL) and brine (5 mL). The organic layer was dried ($MgSO_4$), and concentrated under reduced pressure to give 24

mg (85%) of benzylic alcohol: $^1$H NMR (400 MHz) δ 7.70 (d, *J* = 0.9 Hz, 1 H), 4.91 (s, 2 H), 3.93 (s, 3 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 2.58 (d, *J* = 0.9 Hz, 3 H); IR ($CDCl_3$) 3692, 3611, 3002, 2965, 2937, 2854, 1615, 1551, 1450, 1392, 1328 cm$^{-1}$.

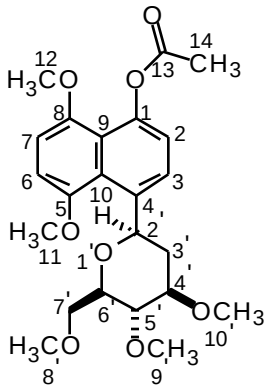
**NMR Assignments.** $^1$H NMR (400 MHz) δ 7.70 (d, *J* = 0.9 Hz, 1 H), 4.91 (s, 2 H), 3.93 (s, 3 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 2.58 (d, *J* = 0.9 Hz, 3 H).




**2.278**

**2,3-Dibromo-1,4,5-trimethoxy-6-methoxymethyl-7-methylnaphthalene (2.278).** Sodium hydride (60% dispersion in mineral oil) (5 mg, 0.12 mmol) was added to a solution of the compound from the previous experimental (24 mg, 0.06 mmol) and methyl iodide (7 μL, 0.12 mmol) in DMF (1 mL) at 0 ˚C, and the mixture was stirred for 2h at 0 ˚C. Saturated aqueous $NH_4Cl$ (1 mL) and $H_2O$ (0.5 mL) were added, and the aqueous mixture was extracted with EtOAc (3 x 2 mL). The combined organic layers were washed with brine (6 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 25% EtOAc/hexanes to give 20 mg (81%) of **2.278** as a white solid: mp 104-105 ˚C; $^1$H NMR (250 MHz) δ 7.69 (br s, 1 H), 4.65 (s, 2 H), 3.91 (s, 3 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.46 (s, 3 H), 2.55 (br s, 3 H); $^{13}$C NMR (100 MHz) δ 153.9, 149.9, 149.7, 138.5, 129.7, 128.9, 120.7, 118.9, 117.4, 116.6, 66.2, 64.2, 62.0, 61.4, 58.7, 20.3; IR ($CDCl_3$) 2960, 2933, 2873, 2855, 1731, 1616, 1551, 1450 ,1392, 1378, 1328 cm$^{-1}$; mass spectrum (CI) *m/z* 431.9570 [$C_{16}H_{18}O_4Br_2$ (M) requires 431.9572].

**NMR Assignments.** $^{1}$H NMR (250 MHz) δ 7.69 (br s, 1 H, C8-H), 4.65 (s, 2 H, C14-H), 3.91 (s, 3 H, Sug-$OCH_3$), 3.85 (s, 3 H, Sug-$OCH_3$), 3.83 (s, 3 H, Sug-$OCH_3$), 3.46 (s, 3 H, C15-H), 2.55 (br s, 3 H, C16-H); $^{13}$C NMR (100 MHz) δ 153.9 (C1), 149.9 (C4), 149.7 (C5), 138.5 (Ar-C), 129.7 (Ar-C), 128.9 (Ar-C), 120.7 (Ar-C), 118.9 (C8), 117.4 (C2/C3), 116.6 (C2/C3), 66.2 (C14), 64.2 (C15), 62.0 (Ar-$OCH_3$), 61.4 (Ar-$OCH_3$), 58.7 (Ar-$OCH_3$), 20.3 (C16).

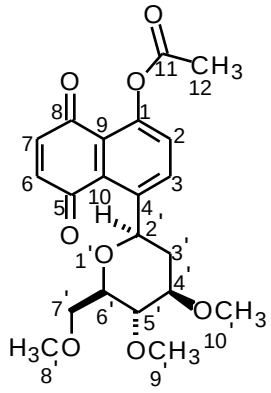


**2.281**

**Acetic acid 4-(4(*R*),5(*S*)-dimethoxy-6(*R*)-methoxymethyltetrahydropyran-2(*R*)-yl)-5,8-dimethoxynaphthalen-1-yl ester (2.281).** A solution containing acetyl chloride (16 μL, 0.23 mmol), **2.56** (18 mg, 0.05 mmol), and pyridine (22 μL, 0.23 mmol) in $CH_2Cl_2$ (0.5 mL) was stirred for 36 h at rt in a stoppered flask. $H_2O$ (3 mL) was added, and the mixture was extracted with EtOAc (3 x 2 mL). The combined organic layers were washed with brine (6 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 50% EtOAc/hexanes to give 17 mg (85%) of **2.281** as an off-white foam: $^{1}$H NMR (250 MHz) δ 7.84 (d, *J* = 8.1 Hz, 1 H), 7.06 (d, *J* = 8.1 Hz, 1 H), 6.75 (app s, 2 H), 5.62 (br d, *J* = 10.3 Hz, 1 H), 3.88 (s, 3 H), 3.84 (s, 3 H), 3.70

(app d, *J* = 3.3 Hz, 2 H), 3.59 (s, 3 H), 3.55-3.47 (comp, 2 H), 3.45 (s, 3 H), 3.42 (s, 3 H), 3.19 (app t, *J* = 9.07 Hz, 1 H), 2.62 (ddd, *J* = 12.8, 4.8, 1.2 Hz, 1 H), 2.34 (s, 3 H), 1.31 (app dt, *J* = 12.8, 11.1 Hz, 1 H); $^{13}$C NMR (100 MHz) δ 169.4, 150.1, 149.1, 144.9, 136.5, 125.0, 123.6, 120.0, 119.7, 105.8, 105.8, 83.3, 79.9, 79.2, 76.1, 72.4, 60.7, 59.6, 56.8, 56.5, 55.7, 39.8, 21.3; IR ($CDCl_3$) 2988, 2937, 2837, 1759, 1606, 1524, 1460, 1383 $cm^{-1}$; mass spectrum (CI) *m/z* 434.1945 [$C_{23}H_{30}O_8$ (M) requires 434.1941].

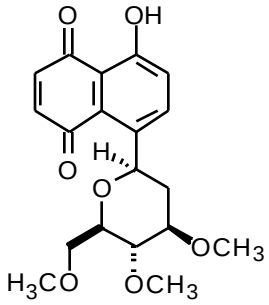
**NMR Assignments.** $^1$H NMR (250 MHz) δ 7.84 (d, *J* = 8.1 Hz, 1 H, C3-H), 7.06 (d, *J* = 8.1 Hz, 1 H, C2-H), 6.75 (app s, 2 H, C6-H & C7-H), 5.62 (br d, *J* = 10.3 Hz, 1 H, C2'-H), 3.88 (s, 3 H, Ar-$OCH_3$), 3.84 (s, 3 H, Ar-$OCH_3$), 3.70 (app d, *J* = 3.3 Hz, 2 H, C7'-H), 3.59 (s, 3 H, Sug-$OCH_3$), 3.55-3.47 (comp, 2 H, C4'-H & C6'-H), 3.45 (s, 3 H, Sug-$OCH_3$), 3.42 (s, 3 H, Sug-$OCH_3$), 3.19 (app t, *J* = 9.07 Hz, 1 H, C5'-H), 2.62 (ddd, *J* = 12.8, 4.8, 1.2 Hz, 1 H, C3'-$H_{eq}$), 2.34 (s, 3 H, C14-H), 1.31 (app dt, *J* = 12.8, 11.1 Hz, 1 H, C3'-$H_{ax}$); $^{13}$C NMR (100 MHz) δ 169.4 (C13), 150.1 (Ar**C**-$OCH_3$), 149.1 (Ar**C**-$OCH_3$), 144.9 (C1), 136.5 (Ar-C), 125.0 (C3), 123.6 (Ar-C), 120.0 (Ar-C), 119.7 (C2), 105.8 (C6/C7), 105.8 (C6/C7), 83.3 (C4'/C6'), 79.9 (C5'), 79.2 (C4'/C6'), 76.1 (C2'), 72.4 (C7'), 60.7 (Sug-$OCH_3$), 59.6 (Sug-$OCH_3$), 56.8 (Sug-$OCH_3$), 56.5 (Ar-$OCH_3$), 55.7 (Ar-$OCH_3$), 39.8 (C3'), 21.3 (C14).



**2.283**

**Acetic acid 4-(4(*R*),5(*S*)-dimethoxy-6(*R*)-methoxymethyltetrahydropyran-2(*R*)-yl)-5,8-dioxo-5,8-dihydronaphthalen-1-yl ester (2.283).** A solution of ceric ammonium nitrate (CAN) (44 mg, 0.08 mmol) in $H_2O$ (0.5 mL) was added to a solution of **2.281** (17 mg, 0.04 mmol) in $CH_3CN$ (0.5 mL), and the solution was stirred for 15 min at rt. $H_2O$ (2 mL) was added, and the aqueous mixture was extracted with $Et_2O$ (3 x 2 mL). The combined organic layers were washed with $H_2O$ (6 mL) and brine (6 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give 14 mg (88%) of pure **2.283** as a yellow solid: mp 111 ˚C (dec.); $^1$H NMR (250 MHz) δ 8.17 (d, *J* = 8.8 Hz, 1 H), 7.36 (d, *J* = 8.8 Hz, 1 H), 6.83 (d, *J* = 10.2 Hz, 1 H), 6.77 (d, *J* = 10.2 Hz, 1 H), 5.34 (br d, *J* = 9.3 Hz, 1 H), 3.68-3.60 (comp, 2 H), 3.57 (s, 3 H), 3.52-3.44 (comp, 2 H), 3.45 (s, 3 H), 3.41 (s, 3 H), 3.12 (app t, *J* = 9.0 Hz, 1 H), 2.52 (ddd, *J* = 12.8, 4.9, 1.6 Hz, 1 H), 2.41 (s, 3 H), 1.22 (app dt, *J* = 12.8, 11.0 Hz, 1 H); $^{13}$C NMR (100 MHz) δ 186.7, 183.0, 168.8, 148.4, 142.7, 138.2, 137.9, 133.7, 129.6, 128.6, 123.2, 82.4, 79.9, 78.9, 73.9, 72.3, 60.7, 59.5, 57.0, 37.8, 21.5; IR ($CDCl_3$) 2984, 2932, 2834, 1764, 1663, 1621, 1573, 1467, 1409, 1370, 1327, 1272, 1252, 1197, 1096 cm$^{-1}$; mass spectrum (CI) *m/z* 405.1541 [$C_{21}H_{25}O_8$ requires 405.1549].

**NMR Assignments.** $^{1}$H NMR (250 MHz) δ 8.17 (d, *J* = 8.8 Hz, 1 H, C3-H), 7.36 (d, *J* = 8.8 Hz, 1 H, C2-H), 6.83 (d, *J* = 10.2 Hz, 1 H, C7-H), 6.77 (d, *J* = 10.2 Hz, 1 H, C6-H), 5.34 (br d, *J* = 9.3 Hz, 1 H, C2'-H), 3.68-3.60 (comp, 2 H, C7'-H), 3.57 (s, 3 H, Sug-$OCH_3$), 3.52-3.44 (comp, 2 H, C4'-H & C6'-H), 3.45 (s, 3 H, Sug-$OCH_3$), 3.41 (s, 3 H, Sug-$OCH_3$), 3.12 (app t, *J* = 9.0 Hz, 1 H, C5'-H), 2.52 (ddd, *J* = 12.8, 4.9, 1.6 Hz, 1 H, C3'-$H_{eq}$), 2.41 (s, 3 H, C12-H), 1.22 (app dt, *J* = 12.8, 11.0 Hz, 1 H, C3'-$H_{ax}$); $^{13}$C NMR (100 MHz) δ 186.7 (C5), 183.0 (C8), 168.8 (C11), 148.4 (C1), 142.7 (C6/C7), 138.2 (C6/C7), 137.9 (Ar-C), 133.7 (Ar-C), 129.6 (Ar-C), 128.6 (Ar-C), 123.2 (Ar-C), 82.4 (C4'/C6'), 79.9 (C5'), 78.9 (C4'/C6'), 73.9 (C2'), 72.3 (C7'), 60.7 (Sug-$OCH_3$), 59.5 (Sug-$OCH_3$), 57.0 (Sug-$OCH_3$), 37.8 (C3'), 21.5 (C12).

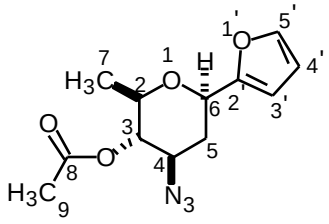



**2.284**

**5-(4(*R*),5(*S*)-Dimethoxy-6(*R*)-methoxymethyltetrahydropyran-2(*R*)-yl)-8-hydroxy-[1,4]naphthoquinone (2.284).** Note: All procedures performed on this compound were done in the dark. Concentrated aqueous HCl (10 drops) was added to a solution of **2.262** (68 mg, 0.17 mmol) in $CH_3OH$ (3 mL), and the reaction vessel was sealed with a glass stopper. The reaction was stirred for 12 h at rt, and then $CH_2Cl_2$ (15 mL) was added. The layers were separated and the organic layer was washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was

purified by flash chromatography eluting with 40% EtOAc/hexanes that contained HOAc (20 drops/100 mL) to give 40 mg (66%) of **2.284** as an orange oil: $^1$H NMR (400 MHz) δ 12.54 (s, 1 H), 8.05 (d, *J* = 9.0 Hz, 1 H), 7.28 (d, *J* = 9.0 Hz, 1 H), 6.90 (d, *J* = 10.1 Hz, 1 H), 6.84 (d, *J* = 10.1 Hz, 1 H), 5.31 (dd, *J* = 10.7, 1.7 Hz, 1 H), 3.66 (app d, *J* = 3.5 Hz, 2 H), 3.64-3.59 (m 1 H), 3.58 (s, 3 H), 3.50-3.46 (m, 1 H), 3.46 (s, 3 H), 3.42 (s, 3 H), 3.14 (dd, *J* = 9.6, 8.8 Hz, 1 H), 2.45 (ddd, *J* = 12.5, 4.9, 1.8 Hz, 1 H), 1.25 (app dt, *J* = 12.5, 11.0 Hz, 1 H); $^{13}$C NMR (100 MHz) δ 189.6, 185.4, 161.0, 140.1, 137.4, 136.9, 135.6, 126.1, 125.0, 114.2, 82.4, 80.0, 78.9, 73.6, 72.3, 60.7, 59.5, 57.1, 37.4; IR ($CDCl_3$) 2987, 2932, 2834, 1643, 1607, 1581, 1466, 1429, 1376, 1334, 1308, 1271, 1237, 1190, 1152, 1097, 1073 cm$^{-1}$; mass spectrum (CI) *m/z* 363.1436 [$C_{19}H_{23}O_7$ (M + H) requires 363.1444].

**NMR Assignments.** $^1$H NMR (400 MHz) δ 12.54 (s, 1 H), 8.05 (d, *J* = 9.0 Hz, 1 H), 7.28 (d, *J* = 9.0 Hz, 1 H), 6.90 (d, *J* = 10.1 Hz, 1 H), 6.84 (d, *J* = 10.1 Hz, 1 H), 5.31 (dd, *J* = 10.7, 1.7 Hz, 1 H), 3.66 (app d, *J* = 3.5 Hz, 2 H), 3.64-3.59 (m 1 H), 3.58 (s, 3 H), 3.50-3.46 (m, 1 H), 3.46 (s, 3 H), 3.42 (s, 3 H), 3.14 (dd, *J* = 9.6, 8.8 Hz, 1 H), 2.45 (ddd, *J* = 12.5, 4.9, 1.8 Hz, 1 H), 1.25 (app dt, *J* = 12.5, 11.0 Hz, 1 H).

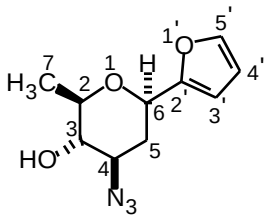



**2.288**

**Acetic acid 4(*R*)-azido-6(*R*)-furan-2-yl-2(*R*)-methyltetrahydropyran-3(*S*)-yl ester (2.288).** Borontrifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) (740 μL, 5.83 mmol) was added to a solution of **2.287** (1.43 g, 5.56 mmol) and furan (2.02 mL, 27.76

mmol) in $CH_3CN$ (111 mL) at rt and the solution was stirred for 35 min at rt Saturated aqueous $NaHCO_3$ (50 mL) and $H_2O$ (50 mL) were added, and the aqueous mixture was extracted with EtOAc (3 x 75 mL), The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography eluting with 10% EtOAc/hexanes to give 885 mg (60%) of **2.288** as a colorless oil: $^1$H NMR (250 MHz) δ 7.38 (dd, *J* = 1.8, 0.8 Hz, 1 H), 6.33 (dd, *J* = 3.2, 1.8 Hz, 1 H), 6.30 (d, *J* = 3.2 Hz, 1 H), 4.73 (app t, *J* = 9.6 Hz, 1 H), 4.53 (dd, *J* = 11.7, 2.1 Hz, 1 H), 3.62 (ddd, *J* = 12.0, 9.6, 4.9 Hz, 1 H), 3.57 (dq, *J* = 9.2, 6.1 Hz, 1 H), 2.29 (ddd, *J* = 13.2, 4.9, 2.1 Hz, 1 H), 2.13 (s, 3 H), 2.04 (ddd, *J* = 13.2, 12.0, 11.7 Hz, 1 H), 1.22 (d, *J* = 6.1 Hz, 3 H); $^{13}$C NMR (75 MHz) δ 170.0, 152.4, 142.6, 110.2, 107.4, 75.1, 74.7, 70.8, 61.2, 34.5, 20.8, 17.8; IR ($CDCl_3$) 2988, 2938, 2866, 2103, 1745, 1505, 1444, 1374, 1231, 1154, 1063, 1047 $cm^{-1}$; mass spectrum (CI) *m/z* 266.1140 [$C_{12}H_{16}N_3O_4$ (M + H) requires 266.1141].

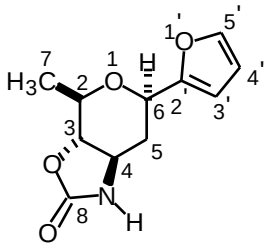
**NMR Assignments.** $^1$H NMR (250 MHz) δ 7.38 (dd, *J* = 1.8, 0.8 Hz, 1 H, C5'-H), 6.33 (dd, *J* = 3.2, 1.8 Hz, 1 H, C4'-H), 6.30 (d, *J* = 3.2 Hz, 1 H, C3'-H), 4.73 (app t, *J* = 9.6 Hz, 1 H, C3-H), 4.53 (dd, *J* = 11.7, 2.1 Hz, 1 H, C6-H), 3.62 (ddd, *J* = 12.0, 9.6, 4.9 Hz, 1 H, C4-H), 3.57 (dq, *J* = 9.2, 6.1 Hz, 1 H, C2-H), 2.29 (ddd, *J* = 13.2, 4.9, 2.1 Hz, 1 H, C5-$H_{eq}$), 2.13 (s, 3 H, C9-H), 2.04 (ddd, *J* = 13.2, 12.0, 11.7 Hz, 1 H, C5-$H_{ax}$), 1.22 (d, *J* = 6.1 Hz, 3 H, C7-H); $^{13}$C NMR (75 MHz) δ 170.0 (C8), 152.4 (C2'), 142.6 (C5'), 110.2 (C4'), 107.4 (C3'), 75.1 (C2), 74.7 (C3), 70.8 (C6), 61.2 (C4), 34.5 (C5), 20.8 (C9), 17.8 (C7).



**2.289**

**4(*R*)-Azido-6(*R*)-furan-2-yl-2(*R*)-methyltetrahydropyran-3(*S*)-ol (2.289).** A solution of **2.288** (34 mg, 0.13 mmol) in $CH_3OH$ (2 mL) containing HCl (conc.) (5 drops) was heated to 50 ˚C for 15 h. The reaction was cooled to rt, and diluted with EtOAc (4 mL). The layers were separated, and the organic layer was washed with saturated aqueous $NaHCO_3$ (4 mL) and brine (4 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give 28 mg (quant.) of pure **2.289** as a white solid: mp 85 ˚C; $^1$H NMR (250 MHz) δ 7.38 (dd, *J* = 1.9, 0.8 Hz, 1 H), 6.32 (dd, *J* = 3.3, 1.9 Hz, 1 H), 6.29 (br d, *J* = 3.3 Hz, 1 H), 4.53 (dd, *J* = 11.7, 2.1 Hz, 1 H), 3.59-3.41 (comp, 2 H), 3.22 (app t, *J* = 9.1 Hz, 1 H), 2.28 (ddd, *J* = 13.1, 4.9, 2.1 Hz, 1 H), 2.03 (app dt, *J* = 13.1, 11.9 Hz, 1 H), 1.35 (d, *J* = 6.2 Hz, 3 H); $^{13}$C NMR (75 MHz) δ 152.7, 142.6, 110.2, 107.3, 76.3, 75.6, 70.8, 63.9, 34.2, 18.0; IR ($CDCl_3$) 3615, 3480, 2981, 2935, 2879, 2104, 1603, 1505, 1444, 1354, 1252, 1152, 1075 $cm^{-1}$; mass spectrum (CI) *m/z* 224.1034 [$C_{10}H_{14}N_3O_3$ (M + H) requires 224.1035].

**NMR Assignments.** $^1$H NMR (250 MHz) δ 7.38 (dd, *J* = 1.9, 0.8 Hz, 1 H, C5'-H), 6.32 (dd, *J* = 3.3, 1.9 Hz, 1 H, C4'-H), 6.29 (br d, *J* = 3.3 Hz, 1 H, C3'-H), 4.53 (dd, *J* = 11.7, 2.1 Hz, 1 H, C6-H), 3.59-3.41 (comp, 2 H, C2-H & C4-H), 3.22 (app t, *J* = 9.1 Hz, 1 H, C3-H), 2.28 (ddd, *J* = 13.1, 4.9, 2.1 Hz, 1 H, C5-$H_{eq}$), 2.03 (app dt, *J* = 13.1, 11.9 Hz, 1 H, C5-$H_{ax}$), 1.35 (d, *J* = 6.2 Hz, 3 H, C7-H); $^{13}$C NMR (75 MHz) δ 152.7 (C2'), 142.6 (C5'), 110.2 (C4'), 107.3 (C3'), 76.3 (C2), 75.6 (C3), 70.8 (C6), 63.9 (C4), 34.2 (C5), 18.0 (C7).

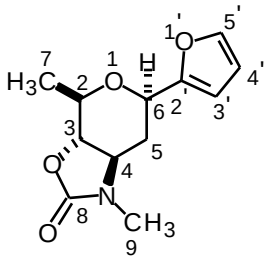


**2.301**

**6(*R*)-Furan-2-yl-4(*R*)-methylhexahydropyrano[4(*S*),3(*R*)-*d*]oxazolo-2-one (2.301).** $CO_2$ was bubbled through a solution of **2.89** (44 mg, 0.20 mmol) in anhydrous acetone (8 mL). After 5 min, $PPh_3$ (517 mg, 1.97 mmol) was added in one portion, and $CO_2$ was bubbled through the reaction mixture for 1 h. The reaction vessel was sealed with a glass stopper, and the mixture was stirred for 12 h at rt. The solution was concentrated under reduced pressure to a volume of 1 mL, and the residue was purified directly by flash chromatography eluting with 40% EtOAc/hexanes to afford 38 mg (86%) of **2.301** as a white solid: mp 173-175 ˚C; $^1$H NMR (250 MHz) δ 7.38 (dd, *J* = 1.7, 0.8 Hz, 1 H), 6.33 (dd, *J* = 3.3, 1.7 Hz, 1 H), 6.30 (br d, *J* = 3.3 Hz, 1 H), 5.76 (br s, 1 H), 4.62 (dd, *J* = 11.0, 2.5 Hz, 1 H), 3.93 (dq, *J* = 9.2, 6.0 Hz, 1 H), 3.80-3.66 (comp, 2 H), 2.36-2.29 (m, 1 H), 2.23-2.09 (m, 1 H), 1.36 (d, *J* = 6.0 Hz, 3 H); $^{13}$C NMR (75 MHz) δ 160.1, 152.2, 142.7, 110.3, 107.6, 83.8, 74.3, 71.3, 58.4, 34.5, 18.1; IR ($CHCl_3$) 3380, 3266, 3116, 2979, 2887, 1763, 1722, 1358, 1230, 1086, 1013 cm$^{-1}$; mass spectrum (CI) *m/z* 224.0916 [$C_{11}H_{14}NO_4$ (M + H) requires 224.0923].

**NMR Assignments.** $^1$H NMR (250 MHz) δ 7.38 (dd, *J* = 1.7, 0.8 Hz, 1 H, C5'-H), 6.33 (dd, *J* = 3.3, 1.7 Hz, 1 H, C4'-H), 6.30 (br d, *J* = 3.3 Hz, 1 H, C3'-H), 5.76 (br s, 1 H, N-H), 4.62 (dd, *J* = 11.0, 2.5 Hz, 1 H, C6-H), 3.93 (dq, *J* = 9.2, 6.0 Hz, 1 H, C2-H), 3.80-3.66 (comp, 2 H, C3-H & C4-H), 2.36-2.29 (m, 1 H, C5-$H_{eq}$), 2.23-2.09

(m, 1 H, C5-$H_{ax}$), 1.36 (d, *J* = 6.0 Hz, 3 H, C7-H); $^{13}$C NMR (75 MHz) δ 160.1 (C8), 152.2 (C2'), 142.7 (C5'), 110.3 (C4'), 107.6 (C3'), 83.8 (C3), 74.3 (C2), 71.3 (C6??, 58.4 (C4), 34.5 (C5), 18.1 (C7).

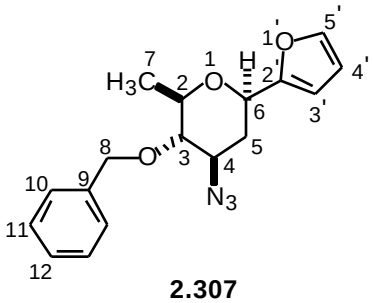


**2.302**

**6(R)-Furan-2-yl-1,4(R)-dimethylhexahydropyrano[4(S),3(R)-d]oxazolo-2-one (2.302).** Methyl iodide (4 μL, 0.06 mmol) and sodium hydride (60% dispersion in mineral oil) (3 mg, 0.08 mmol) were added sequentially to a solution of **2.301** in DMF (0.2 mL) at rt, and the mixture was stirred for 36 h at rt. Saturated aqueous $NH_4Cl$ (2 mL) and $H_2O$ (0.5 mL) were added, and the aqueous mixture was extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 30% EtOAc/hexanes to give 3 mg (93%) of **2.302** as a colorless oil: $^1$H NMR (250 MHz) δ 7.39 (dd, *J* = 1.9, 0.8 Hz, 1 H), 6.34 (dd, *J* = 3.1, 1.9 Hz, 1 H), 6.32 (br d, *J* = 3.1 Hz, 1 H), 4.64 (dd, *J* = 11.0, 2.5 Hz, 1 H), 3.90 (dq, *J* = 9.3, 6.2 Hz, 1 H), 3.66 (dd, *J* = 11.0, 9.3 Hz, 1 H), 3.38 (app dt, *J* = 11.0, 3.8 Hz, 1 H), 2.82 (s, 3 H), 2.31 (ddd, *J* = 11.2, 3.8, 2.5 Hz, 1 H), 2.09 (app dt, *J* = 12.2, 11.0 Hz, 1 H), 1.37 (d, *J* = 6.2 Hz, 3 H); $^{13}$C NMR (75 MHz) δ 159.7, 152.2, 142.6, 110.3, 107.6, 81.4, 74.5, 71.4, 62.7, 33.6, 29.9, 18.1; IR ($CDCl_3$) 3692, 2983, 2938,

1760, 1732, 1375, 1248, 1118, 1026 $cm^{-1}$; mass spectrum (CI) *m/z* 238.1087 [$C_{12}H_{16}NO_4$ (M + H) requires 238.1079].

**NMR Assignments.** $^1$H NMR (250 MHz) δ 7.39 (dd, *J* = 1.9, 0.8 Hz, 1 H, C5'-H), 6.34 (dd, *J* = 3.1, 1.9 Hz, 1 H, C4'-H), 6.32 (br d, *J* = 3.1 Hz, 1 H, C3'-H), 4.64 (dd, *J* = 11.0, 2.5 Hz, 1 H, C6-H), 3.90 (dq, *J* = 9.3, 6.2 Hz, 1 H, C2-H), 3.66 (dd, *J* = 11.0, 9.3 Hz, 1 H, C3-H), 3.38 (app dt, *J* = 11.0, 3.8 Hz, 1 H, C4-H), 2.82 (s, 3 H, C9-H), 2.31 (ddd, *J* = 11.2, 3.8, 2.5 Hz, 1 H, C5-$H_{eq}$), 2.09 (app dt, *J* = 12.2, 11.0 Hz, 1 H, C5-$H_{ax}$), 1.37 (d, *J* = 6.2 Hz, 3 H, C7-H); $^{13}$C NMR (75 MHz) δ 159.7 (C8), 152.2 (C2'), 142.6 (C5'), 110.3 (C4'), 107.6 (C3'), 81.4 (C3), 74.5 (C2), 71.4 (C6), 62.7 (C4), 33.6 (C5), 29.9 (C9), 18.1 (C7).

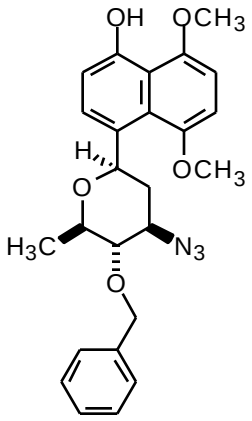



**2.307**

**4(*R*)-Azido-3(*S*)-benzyloxy-6(*R*)-furan-2-yl-2(*R*)-methyltetrahydropyran (2.307).** Sodium hydride (60% suspension in mineral oil) (10 mg, 0.25 mmol) was added to a solution of **2.289** (7 mg, 0.03 mmol) and benzyl bromide (30 μL, 0.25 mmol) in DMF (0.2 mL) at rt. Saturated aqueous $NH_4Cl$ (1 mL) and $H_2O$ (1 mL) were added immediately, and the aqueous mixture was extracted with EtOAc (3 x 1 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 10% EtOAc/hexanes to give 6 mg (61%) of **2.307** as a

white solid: mp 87-88 ˚C; $^{1}$H NMR (250 MHz) δ 7.40-7.29 (comp, 6 H), 6.32 (dd, *J* = 3.3, 1.9 Hz, 1 H), 6.28 (br d, *J* = 3.3 Hz, 1 H), 4.88 (d, *J* = 10.6 Hz, 1 H), 4.65 (d, *J* = 10.6 Hz, 1 H), 4.49 (dd, *J* = 11.8, 2.0 Hz, 1 H), 3.65 (ddd, *J* = 12.1, 9.2, 5.1 Hz, 1 H), 3.52 (dq, *J* = 9.2, 6.3 Hz, 1 H), 3.08 (app t, *J* = 9.2 Hz, 1 H), 2.26 (ddd, *J* = 13.1, 5.1, 2.0 Hz, 1 H), 1.99 (app dt, *J* = 13.1, 11.8 Hz, 1 H), 1.36 (d, *J* = 6.1 Hz, 3 H); $^{13}$C NMR (75 MHz) δ 152.7, 142.5, 137.5, 128.5, 128.3, 128.1, 110.2, 107.2, 83.4, 76.1, 75.3, 70.7, 63.6, 35.0, 18.4; IR ($CDCl_3$) 2980, 2935, 2865, 2101, 1602, 1498, 1454, 1367, 1258, 1152, 1106, 1077 $cm^{-1}$; mass spectrum (CI) *m/z* 314.1497 [$C_{17}H_{20}N_3O_3$ (M + H) requires 314.1505].

**NMR Assignments.** $^{1}$H NMR (250 MHz) δ 7.40-7.29 (comp, 6 H, C5'-H & Ph-H's), 6.32 (dd, *J* = 3.3, 1.9 Hz, 1 H, C4'-H), 6.28 (br d, *J* = 3.3 Hz, 1 H, C3'-H), 4.88 (d, *J* = 10.6 Hz, 1 H, C8-H), 4.65 (d, *J* = 10.6 Hz, 1 H, C8-H), 4.49 (dd, *J* = 11.8, 2.0 Hz, 1 H, C6-H), 3.65 (ddd, *J* = 12.1, 9.2, 5.1 Hz, 1 H, C4-H), 3.52 (dq, *J* = 9.2, 6.3 Hz, 1 H, C2-H), 3.08 (app t, *J* = 9.2 Hz, 1 H, C3-H), 2.26 (ddd, *J* = 13.1, 5.1, 2.0 Hz, 1 H, C5-$H_{eq}$), 1.99 (app dt, *J* = 13.1, 11.8 Hz, 1 H, C5-$H_{ax}$), 1.36 (d, *J* = 6.1 Hz, 3 H, C7-H); $^{13}$C NMR (75 MHz) δ 152.7 (C2'), 142.5 (C5'), 137.5 (Ph-C), 128.5 (Ph-C), 128.3 (Ph-C), 128.1 (Ph-C), 110.2 (C4'), 107.2 (C3'), 83.4 (C8), 76.1 (C2), 75.3 (C3), 70.7 (C6), 63.6 (C4), 35.0 (C5), 18.4 (C7).




**2.309**

**4-(4(*R*)-Azido-5(*S*)-benzyloxy-6(*R*)-methyltetrahydropyran-2(*R*)-yl)-5,8-dimethoxynaphthalen-1-ol (2.309).** A solution of *s*-butyllithium in cyclohexane (1.16 M, 26 μL, 0.03 mmol) was added to a solution of 2-chloro-1,4-dimethoxybenzene (**2.30**) (6 mg, 0.03 mmol) in THF (0.4 mL) at -95 ˚C, and the resulting mixture was stirred for 10 min at -95 ˚C A solution of **2.307** (5 mg, 0.02 mmol) in THF (0.2 mL) was added, and the reaction was warmed to -25 ˚C over 30 min. Saturated aqueous $NH_4Cl$ (1 mL) and $H_2O$ (0.5 mL) were added, and the aqueous mixture was extracted with EtOAc (3 x 1 mL). The combined organic layers were washed with brine (3 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with 25% EtOAc/hexanes to give cycloadduct **2.308** as a mixture (ca 1:1) of diastereomers. The cycloadducts were dissolved in $CH_2Cl_2$ (0.2 mL), and the solution was cooled to 0 ˚C. Trifluoroacetic acid (3 drops) was added, and the reaction was stirred for 10 min at 0 ˚C and then an additional 10 min at rt. The reaction was diluted with $CH_2Cl_2$ (2 mL), and the mixture was washed with saturated aqueous $NaHCO_3$ (1 mL) and brine (2 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give 3 mg (42%) of pure **2.309** as a colorless oil: $^1$H NMR (500

MHz) δ 9.81 (s, 1 H), 7.73 (d, *J* = 8.4 Hz, 1 H), 7.44-7.30 (comp, 5 H), 6.92 (d, *J* = 8.4 Hz, 1 H), 6.71 (app s, 2 H), 5.67 (br d, *J* = 9.4 Hz, 1 H), 4.93 (d, *J* = 10.5 Hz, 1 H), 4.71 (d, *J* = 10.5 Hz, 1 H), 4.01 (s, 3 H), 3.88 (s, 3 H), 3.75 (ddd, *J* = 12.2, 9.2, 4.8 Hz, 1 H), 3.63 (dq, *J* = 9.0, 6.1 Hz, 1 H), 3.13 (app t, *J* = 9.2 Hz, 1 H), 2.50 (ddd, *J* = 12.9, 4.4, 1.4 Hz, 1 H), 1.53 (ddd, *J* = 12.9, 12.2, 10.6 Hz, 1 H); $^{13}$C NMR (125 MHz) δ 154.1, 151.6, 150.8, 137.9, 128.7, 128.5, 128.3, 128.0, 125.7, 125.3, 116.5, 111.5, 105.2, 103.8, 84.1, 76.2, 75.8, 75.2, 64.7, 56.7, 55.7, 40.5, 18.8; IR ($CDCl_3$) 3686, 3363, 3018, 2958, 2929, 2856, 2097, 1729, 1619, 1524, 1497, 1466, 1445, 1429, 1401, 1362, 1263, 1216 $cm^{-1}$; mass spectrum (CI) *m/z* 449.1956 [$C_{25}H_{27}N_3O_5$ (M) requires 449.1951].

**NMR Assignments.** $^1$H NMR (500 MHz) δ 9.81 (s, 1 H), 7.73 (d, *J* = 8.4 Hz, 1 H), 7.44-7.30 (comp, 5 H), 6.92 (d, *J* = 8.4 Hz, 1 H), 6.71 (app s, 2 H), 5.67 (br d, *J* = 9.4 Hz, 1 H), 4.93 (d, *J* = 10.5 Hz, 1 H), 4.71 (d, *J* = 10.5 Hz, 1 H), 4.01 (s, 3 H), 3.88 (s, 3 H), 3.75 (ddd, *J* = 12.2, 9.2, 4.8 Hz, 1 H), 3.63 (dq, *J* = 9.0, 6.1 Hz, 1 H), 3.13 (app t, *J* = 9.2 Hz, 1 H), 2.50 (ddd, *J* = 12.9, 4.4, 1.4 Hz, 1 H), 1.53 (ddd, *J* = 12.9, 12.2, 10.6 Hz, 1 H); $^{13}$C NMR (125 MHz) δ 154.1, 151.6, 150.8, 137.9, 128.7, 128.5, 128.3, 128.0, 125.7, 125.3, 116.5, 111.5, 105.2, 103.8, 84.1, 76.2, 75.8, 75.2, 64.7, 56.7, 55.7, 40.5, 18.8.

# Appendix A: X-Ray Crystallography Experiments

**X-ray Experimental for $C_{16}H_{20}O_3Si$ (2.135):** Crystals grew as large colorless plates by slow evaporation from dichloromethane. The data crystal was cut from a large plate and had approximate dimensions; 0.40 x 0.33 x 0.31 mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoKα radiation (λ = 0.71073Å). A total of 182 frames of data were collected using ω-scans with a scan range of 1.1° and a counting time of 92 seconds per frame. The data were collected at –120 °C using a Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data reduction were performed using DENZO-SMN.[181] The structure was solved by direct methods using SIR92[182] and refined by full-matrix least-squares on $F^2$ with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[183] The hydrogen atom positions were observed in a ΔF map and refined with isotropic displacement parameters. The function, $\Sigma w(|F_O|^2 - |F_C|^2)^2$, was minimized, where $w = 1/[(\sigma(F_O))^2 + (0.0351*P)^2 + (0.7061*P)]$ and $P = (|F_O|^2 + 2|F_C|^2)/3$. $R_W(F^2)$ refined to 0.0882, with R(F) equal to 0.0341 and a goodness of fit, S, = 1.028. Definitions used for calculating R(F), $R_W(F^2)$ and the goodness of fit, S, are given below.[184] Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[185] All figures were generated using SHELXTL/PC.[186] Tables of positional and thermal parameters, bond lengths and angles, figures and lists of observed and calculated structure factors are located in tables 1 through 5.

Table 1. Crystal data and structure refinement for $C_{16}H_{20}O_3Si$ (**2.135**).

| | | |
|---|---|---|
| Empirical formula | $C_{16}H_{20}O_3Si$ | |
| Formula weight | 288.41 | |
| Temperature | 153(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P21/c | |
| Unit cell dimensions | a = 8.0737(1) Å | α= 90°. |
| | b = 26.3286(5) Å | β= 101.824(1)° |
| | c = 7.2435(2) Å | γ = 90°. |
| Volume | 1507.07(5) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.271 $Mg/m^3$ | |
| Absorption coefficient | 0.160 $mm^{-1}$ | |
| F(000) | 616 | |
| Crystal size | 0.40 x 0.33 x 0.31 mm | |
| Theta range for data collection | | 3.01 to 27.47°. |
| Index ranges | -10<=h<=10, -33<=k<=24, -9<=l<=9 | |
| Reflections collected | 5150 | |
| Independent reflections | 3353 [R(int) = 0.0126] | |
| Completeness to theta = 27.47° | | 96.7 % |
| Absorption correction | None | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3353 / 0 / 261 | |
| Goodness-of-fit on $F^2$ | 1.028 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0341, wR2 = 0.0841 | |
| R indices (all data) | R1 = 0.0393, wR2 = 0.0882 | |
| Largest diff. peak and hole | 0.311 and -0.221 $e.Å^{-3}$ | |

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for $C_{16}H_{20}O_3Si$ (**2.135**). U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| Si1 | 3427(1) | 821(1) | 4253(1) | 21(1) |
| C2 | 2344(2) | 1466(1) | 4028(2) | 27(1) |
| O3 | 2251(1) | 1718(1) | 5801(1) | 28(1) |
| C4 | 3736(2) | 1738(1) | 7137(2) | 22(1) |
| C5 | 3833(2) | 2075(1) | 8657(2) | 25(1) |
| C6 | 5313(2) | 2121(1) | 10011(2) | 25(1) |
| C7 | 6756(2) | 1829(1) | 9926(2) | 21(1) |
| C8 | 6617(2) | 1475(1) | 8490(2) | 18(1) |
| C9 | 7821(2) | 1083(1) | 7865(2) | 19(1) |
| C10 | 8263(2) | 1304(1) | 6058(2) | 22(1) |
| C11 | 6858(2) | 1282(1) | 4745(2) | 21(1) |
| C12 | 5504(2) | 1042(1) | 5697(2) | 19(1) |
| O13 | 6567(1) | 703(1) | 7030(1) | 19(1) |
| C14 | 5143(2) | 1445(1) | 7101(2) | 19(1) |
| C15 | 3623(2) | 595(1) | 1875(2) | 31(1) |
| C16 | 2389(2) | 370(1) | 5626(2) | 32(1) |
| O17 | 8292(1) | 1872(1) | 11162(1) | 25(1) |
| C18 | 8503(2) | 2291(1) | 12443(2) | 29(1) |
| C19 | 9231(2) | 848(1) | 9294(2) | 24(1) |
| C20 | 8639(2) | 594(1) | 10931(2) | 29(1) |

Table 3. Bond lengths [Å] and angles [°] for $C_{16}H_{20}O_3Si$ (**2.135**).

| | | | |
|---|---|---|---|
| Si1-C16 | 1.8547(15) | C10-H10 | 0.960(16) |
| Si1-C15 | 1.8586(15) | C11-C12 | 1.5423(16) |
| Si1-C12 | 1.8778(13) | C11-H11 | 0.943(16) |
| Si1-C2 | 1.9034(14) | C12-O13 | 1.4584(14) |
| C2-O3 | 1.4607(17) | C12-C14 | 1.5387(16) |
| C2-H2A | 0.980(18) | C15-H15A | 1.00(2) |
| C2-H2B | 0.962(17) | C15-H15B | 0.97(2) |
| O3-C4 | 1.3786(16) | C15-H15C | 0.94(2) |
| C4-C14 | 1.3792(17) | C16-H16A | 0.93(2) |
| C4-C5 | 1.4024(18) | C16-H16B | 0.98(2) |
| C5-C6 | 1.388(2) | C16-H16C | 0.96(3) |
| C5-H5 | 0.974(17) | O17-C18 | 1.4298(15) |
| C6-C7 | 1.4084(18) | C18-H18A | 0.965(19) |
| C6-H6 | 0.977(18) | C18-H18B | 0.999(19) |
| C7-O17 | 1.3774(15) | C18-H18C | 0.973(19) |
| C7-C8 | 1.3829(17) | C19-C20 | 1.5208(19) |
| C8-C14 | 1.3941(17) | C19-H19A | 1.021(18) |
| C8-C9 | 1.5490(16) | C19-H19B | 0.982(18) |
| C9-O13 | 1.4633(14) | C20-H20A | 0.961(18) |
| C9-C19 | 1.5055(17) | C20-H20B | 0.96(2) |
| C9-C10 | 1.5404(17) | C20-H20C | 1.000(19) |
| C10-C11 | 1.3243(18) | | |

| | | | |
|---|---|---|---|
| C16-Si1-C15 | 115.24(7) | C16-Si1-C2 | 111.55(7) |
| C16-Si1-C12 | 110.48(6) | C15-Si1-C2 | 109.30(7) |
| C15-Si1-C12 | 112.26(6) | C12-Si1-C2 | 96.48(6) |

| | | | |
|---|---|---|---|
| O3-C2-Si1 | 115.82(9) | C11-C10-C9 | 106.24(10) |
| O3-C2-H2A | 108.1(10) | C11-C10-H10 | 129.8(9) |
| Si1-C2-H2A | 109.1(10) | C9-C10-H10 | 123.8(9) |
| O3-C2-H2B | 104.4(10) | C10-C11-C12 | 106.20(11) |
| Si1-C2-H2B | 112.6(10) | C10-C11-H11 | 129.9(10) |
| H2A-C2-H2B | 106.3(14) | C12-C11-H11 | 123.9(10) |
| C4-O3-C2 | 116.17(10) | O13-C12-C14 | 98.60(9) |
| O3-C4-C14 | 124.49(11) | O13-C12-C11 | 99.90(9) |
| O3-C4-C5 | 118.44(11) | C14-C12-C11 | 105.09(9) |
| C14-C4-C5 | 117.06(12) | O13-C12-Si1 | 121.10(8) |
| C6-C5-C4 | 120.83(12) | C14-C12-Si1 | 108.27(8) |
| C6-C5-H5 | 119.9(10) | C11-C12-Si1 | 120.81(9) |
| C4-C5-H5 | 119.3(10) | C12-O13-C9 | 96.83(8) |
| C5-C6-C7 | 121.38(12) | C4-C14-C8 | 122.59(11) |
| C5-C6-H6 | 119.9(10) | C4-C14-C12 | 131.86(12) |
| C7-C6-H6 | 118.8(11) | C8-C14-C12 | 105.54(10) |
| O17-C7-C8 | 117.90(11) | Si1-C15-H15A | 110.8(11) |
| O17-C7-C6 | 124.66(11) | Si1-C15-H15B | 111.8(13) |
| C8-C7-C6 | 117.44(12) | H15A-C15-H15B | 106.0(17) |
| C7-C8-C14 | 120.49(11) | Si1-C15-H15C | 108.8(14) |
| C7-C8-C9 | 135.21(11) | H15A-C15-H15C | 111.9(18) |
| C14-C8-C9 | 104.16(10) | H15B-C15-H15C | 107.5(18) |
| O13-C9-C19 | 111.39(10) | Si1-C16-H16A | 111.4(14) |
| O13-C9-C10 | 99.73(9) | Si1-C16-H16B | 110.1(13) |
| C19-C9-C10 | 117.76(10) | H16A-C16-H16B | 107.1(18) |
| O13-C9-C8 | 98.90(9) | Si1-C16-H16C | 111.7(14) |
| C19-C9-C8 | 120.33(10) | H16A-C16-H16C | 108.7(19) |
| C10-C9-C8 | 105.28(10) | H16B-C16-H16C | 107.6(18) |

| | |
|---|---|
| C7-O17-C18 | 117.23(10) |
| O17-C18-H18A | 111.8(10) |
| O17-C18-H18B | 110.7(11) |
| H18A-C18-H18B | 109.4(14) |
| O17-C18-H18C | 104.7(11) |
| H18A-C18-H18C | 111.5(15) |
| H18B-C18-H18C | 108.6(14) |
| C9-C19-C20 | 113.73(11) |
| C9-C19-H19A | 106.7(10) |
| C20-C19-H19A | 110.6(10) |
| C9-C19-H19B | 107.8(10) |
| C20-C19-H19B | 110.0(10) |
| H19A-C19-H19B | 107.8(14) |
| C19-C20-H20A | 111.5(10) |
| C19-C20-H20B | 111.4(12) |
| H20A-C20-H20B | 105.9(15) |
| C19-C20-H20C | 113.6(10) |
| H20A-C20-H20C | 108.9(15) |
| H20B-C20-H20C | 105.1(15) |

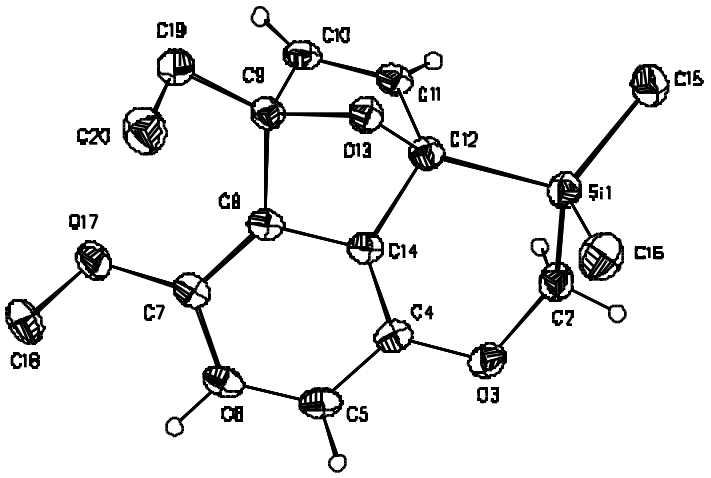
Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for $C_{16}H_{20}O_3Si$ (**2.135**). The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$.

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| Si1 | 20(1) | 20(1) | 23(1) | -1(1) | 2(1) | -1(1) |
| C2 | 24(1) | 27(1) | 28(1) | -1(1) | 1(1) | 2(1) |
| O3 | 20(1) | 28(1) | 34(1) | -4(1) | 4(1) | 5(1) |
| C4 | 20(1) | 19(1) | 27(1) | 2(1) | 7(1) | 1(1) |
| C5 | 26(1) | 20(1) | 32(1) | 1(1) | 13(1) | 6(1) |
| C6 | 33(1) | 19(1) | 25(1) | -3(1) | 13(1) | 2(1) |
| C7 | 26(1) | 17(1) | 20(1) | 0(1) | 8(1) | -2(1) |
| C8 | 21(1) | 15(1) | 21(1) | 0(1) | 8(1) | 0(1) |
| C9 | 19(1) | 16(1) | 22(1) | -4(1) | 5(1) | -1(1) |
| C10 | 22(1) | 21(1) | 26(1) | -3(1) | 11(1) | -1(1) |
| C11 | 25(1) | 20(1) | 21(1) | -1(1) | 9(1) | -1(1) |
| C12 | 20(1) | 16(1) | 21(1) | 0(1) | 5(1) | 1(1) |
| O13 | 20(1) | 16(1) | 21(1) | -1(1) | 2(1) | 0(1) |
| C14 | 21(1) | 16(1) | 23(1) | 0(1) | 8(1) | -1(1) |
| C15 | 30(1) | 34(1) | 26(1) | -5(1) | 0(1) | 0(1) |
| C16 | 30(1) | 29(1) | 37(1) | 1(1) | 8(1) | -6(1) |
| O17 | 29(1) | 22(1) | 24(1) | -8(1) | 3(1) | 0(1) |
| C18 | 42(1) | 19(1) | 24(1) | -6(1) | 3(1) | -2(1) |
| C19 | 22(1) | 24(1) | 25(1) | -4(1) | 3(1) | 3(1) |
| C20 | 34(1) | 26(1) | 25(1) | 1(1) | 2(1) | 3(1) |

Table 5. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for $C_{16}H_{20}O_3Si$ (**2.135**)

| x | y | z | U(eq) | |
|---|---|---|---|---|
| H2A | 2930(20) | 1694(7) | 3300(20) | 34(4) |
| H2B | 1190(20) | 1450(6) | 3350(20) | 31(4) |
| H5 | 2850(20) | 2280(7) | 8750(20) | 32(4) |
| H6 | 5370(20) | 2367(7) | 11030(20) | 39(5) |
| H10 | 9340(20) | 1449(6) | 6000(20) | 24(4) |
| H11 | 6650(20) | 1392(6) | 3480(20) | 26(4) |
| H15A | 4310(30) | 276(9) | 1970(30) | 55(6) |
| H15B | 2530(30) | 512(9) | 1100(30) | 60(6) |
| H15C | 4100(30) | 855(9) | 1270(30) | 63(6) |
| H16A | 1220(30) | 375(9) | 5220(30) | 64(6) |
| H16B | 2640(30) | 464(8) | 6960(30) | 62(6) |
| H16C | 2780(30) | 29(10) | 5530(30) | 72(7) |
| H18A | 8310(20) | 2612(7) | 11790(20) | 36(4) |
| H18B | 7730(20) | 2259(7) | 13350(30) | 38(5) |
| H18C | 9660(20) | 2263(7) | 13140(30) | 39(5) |
| H19A | 10070(20) | 1132(7) | 9770(20) | 35(4) |
| H19B | 9810(20) | 599(7) | 8640(20) | 36(4) |
| H20A | 7720(20) | 362(7) | 10500(20) | 35(4) |
| H20B | 8210(20) | 839(8) | 11700(30) | 48(5) |
| H20C | 9560(20) | 410(7) | 11810(30) | 42(5) |

Figure 1. View of $C_{16}H_{20}O_3Si$ (**2.135**) showing the atom labeling scheme. Thermal ellipsoids are scaled to the 50% probability level. Some hydrogen atoms have been removed for clarity.



**X-ray Experimental for $C_{10}H_{13}N_3O_3$ (2.289):** Crystals grew as clusters of colorless plates by slow evaporation from $Et_2O$/pentane. The data crystal was cut from a large cluster into an irregular shaped fragment with approximate dimensions; 0.23 x 0.22 x 0.20 mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoKα radiation (λ = 0.71073Å). A total of 521 frames of data were collected using ω-scans with a scan range of 0.8° and a counting time of 111 seconds per frame. The data were collected at –120 °C using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 1. Data reduction were performed using DENZO-SMN.[1] The structure was solved by direct methods using SIR92[2] and refined by full-matrix least-squares on $F^2$ with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[3] The hydrogen atoms were observed in a ΔF map and refined with isotropic displacement parameters. The function, $\Sigma w(|F_O|^2 - |F_C|^2)^2$, was minimized, where $w = 1/[(\sigma(F_O))^2 + (0.0337*P)^2 + (0.0622*P)]$ and $P = (|F_O|^2 + 2|F_C|^2)/3$. $R_W(F^2)$ refined to 0.0705, with R(F) equal to 0.0267 and a goodness of fit, S, = 1.047. Definitions used for calculating R(F), $R_W(F^2)$ and the goodness of fit, S, are given below.[4] The data were checked for secondary extinction effects but no correction was necessary. The absolute configuration was assigned by internal comparison. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992).[5] All figures were generated using SHELXTL/PC.[6] Tables of positional and thermal parameters, bond lengths and angles, torsion angles, figures and lists of observed and calculated structure factors are located in tables 1 through 7.

Table 1. Crystal data and structure refinement for $C_{10}H_{13}N_3O_3$ (**2.289**).

| | | |
|---|---|---|
| Empirical formula | $C_{10}H_{13}N_3O_3$ | |
| Formula weight | 223.23 | |
| Temperature | 153(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P21 | |
| Unit cell dimensions | a = 4.9400(1) Å | α= 90°. |
| | b = 8.6875(2) Å | β= 90.377(1)°. |
| | c = 12.5988(2) Å | γ = 90°. |
| Volume | 540.682(19) $Å^3$ | |
| Z | 2 | |
| Density (calculated) | 1.371 $Mg/m^3$ | |
| Absorption coefficient | 0.103 $mm^{-1}$ | |
| F(000) | 236 | |
| Crystal size | 0.23 x 0.22 x 0.20 mm | |
| Theta range for data collection | 3.23 to 29.99°. | |
| Index ranges | -6<=h<=6, -8<=k<=12, -17<=l<=17 | |
| Reflections collected | 2545 | |
| Independent reflections | 2545 [R(int) = 0.0000] | |
| Completeness to theta = 29.99° | 98.2 % | |
| Absorption correction | None | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2545 / 1 / 197 | |
| Goodness-of-fit on $F^2$ | 1.047 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0267, wR2 = 0.0693 | |
| R indices (all data) | R1 = 0.0279, wR2 = 0.0705 | |
| Absolute structure parameter | -0.2(7) | |

Largest diff. peak and hole 0.26 and -0.13 e.Å$^{-3}$

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for $C_{10}H_{13}N_3O_3$ (**2.239**). U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O1 | 2944(1) | 7350(1) | 2991(1) | 26(1) |
| C2 | 4555(2) | 8575(1) | 2565(1) | 24(1) |
| C3 | 5199(2) | 8236(1) | 1400(1) | 21(1) |
| C4 | 6603(2) | 6683(1) | 1307(1) | 21(1) |
| C5 | 4964(2) | 5424(1) | 1841(1) | 23(1) |
| C6 | 4378(2) | 5905(1) | 2983(1) | 23(1) |
| C7 | 2962(3) | 10050(2) | 2702(1) | 32(1) |
| O8 | 6967(2) | 9374(1) | 985(1) | 27(1) |
| N9 | 6927(2) | 6255(1) | 168(1) | 25(1) |
| N10 | 8753(2) | 6968(1) | -300(1) | 24(1) |
| N11 | 10369(2) | 7515(1) | -801(1) | 33(1) |
| C12 | 2732(2) | 4774(1) | 3582(1) | 25(1) |
| O13 | 637(2) | 4072(1) | 3062(1) | 34(1) |
| C14 | -602(2) | 3137(2) | 3789(1) | 37(1) |
| C15 | 626(3) | 3228(2) | 4731(1) | 41(1) |
| C16 | 2808(3) | 4288(2) | 4600(1) | 41(1) |

Table 3. Bond lengths [Å] and angles [°] for $C_{10}H_{13}N_3O_3$ (**2.239**).

| | | | |
|---|---|---|---|
| O1-C2 | 1.4351(12) | C6-H6 | 0.974(12) |
| O1-C6 | 1.4417(12) | C7-H7A | 0.922(18) |
| C2-C7 | 1.5138(15) | C7-H7B | 0.970(16) |
| C2-C3 | 1.5320(13) | C7-H7C | 0.995(16) |
| C2-H2 | 0.982(14) | O8-H8 | 0.83(2) |
| C3-O8 | 1.4215(12) | N9-N10 | 1.2460(12) |
| C3-C4 | 1.5216(14) | N10-N11 | 1.1261(13) |
| C3-H3 | 1.002(12) | C12-C16 | 1.3501(15) |
| C4-N9 | 1.4929(12) | C12-O13 | 1.3650(14) |
| C4-C5 | 1.5203(14) | O13-C14 | 1.3708(15) |
| C4-H4 | 0.987(12) | C14-C15 | 1.332(2) |
| C5-C6 | 1.5282(13) | C14-H14 | 0.997(19) |
| C5-H5A | 0.920(16) | C15-C16 | 1.4281(19) |
| C5-H5B | 0.984(13) | C15-H15 | 0.979(18) |
| C6-C12 | 1.4849(14) | C16-H16 | 0.90(2) |
| | | | |
| C2-O1-C6 | 111.71(7) | O8-C3-H3 | 110.3(7) |
| O1-C2-C7 | 107.16(8) | C4-C3-H3 | 110.0(8) |
| O1-C2-C3 | 109.55(8) | C2-C3-H3 | 108.2(7) |
| C7-C2-C3 | 112.55(9) | N9-C4-C5 | 107.83(8) |
| O1-C2-H2 | 109.7(8) | N9-C4-C3 | 110.31(8) |
| C7-C2-H2 | 110.5(9) | C5-C4-C3 | 111.08(7) |
| C3-C2-H2 | 107.4(8) | N9-C4-H4 | 106.5(8) |
| O8-C3-C4 | 107.87(7) | C5-C4-H4 | 111.6(8) |
| O8-C3-C2 | 110.55(8) | C3-C4-H4 | 109.4(8) |
| C4-C3-C2 | 109.99(8) | C4-C5-C6 | 108.93(8) |

| | | | |
|---|---|---|---|
| C4-C5-H5A | 110.9(8) | C3-O8-H8 | 104.6(13) |
| C6-C5-H5A | 109.5(8) | N10-N9-C4 | 114.42(8) |
| C4-C5-H5B | 109.3(8) | N11-N10-N9 | 173.32(11) |
| C6-C5-H5B | 111.8(8) | C16-C12-O13 | 109.46(10) |
| H5A-C5-H5B | 106.4(12) | C16-C12-C6 | 132.67(10) |
| O1-C6-C12 | 107.58(8) | O13-C12-C6 | 117.85(9) |
| O1-C6-C5 | 109.90(8) | C12-O13-C14 | 106.50(9) |
| C12-C6-C5 | 113.95(9) | C15-C14-O13 | 110.94(11) |
| O1-C6-H6 | 108.7(9) | C15-C14-H14 | 133.7(11) |
| C12-C6-H6 | 106.7(8) | O13-C14-H14 | 115.4(11) |
| C5-C6-H6 | 109.8(7) | C14-C15-C16 | 105.95(11) |
| C2-C7-H7A | 110.2(10) | C14-C15-H15 | 126.8(10) |
| C2-C7-H7B | 109.4(11) | C16-C15-H15 | 127.2(10) |
| H7A-C7-H7B | 108.2(14) | C12-C16-C15 | 107.15(12) |
| C2-C7-H7C | 111.6(10) | C12-C16-H16 | 127.4(13) |
| H7A-C7-H7C | 107.6(14) | C15-C16-H16 | 125.2(13) |
| H7B-C7-H7C | 109.7(13) | | |

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for $C_{10}H_{13}N_3O_3$ (**2.239**). The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| O1 | 28(1) | 25(1) | 24(1) | 0(1) | 6(1) | 5(1) |
| C2 | 27(1) | 23(1) | 21(1) | -3(1) | -1(1) | 1(1) |
| C3 | 22(1) | 22(1) | 20(1) | -1(1) | -1(1) | 0(1) |
| C4 | 23(1) | 24(1) | 16(1) | -2(1) | 1(1) | 1(1) |
| C5 | 26(1) | 21(1) | 21(1) | 0(1) | 3(1) | 2(1) |
| C6 | 25(1) | 25(1) | 20(1) | 1(1) | 2(1) | 4(1) |
| C7 | 39(1) | 26(1) | 31(1) | -6(1) | 1(1) | 7(1) |
| O8 | 27(1) | 23(1) | 31(1) | 5(1) | 1(1) | -1(1) |
| N9 | 29(1) | 27(1) | 20(1) | -4(1) | 5(1) | -5(1) |
| N10 | 28(1) | 24(1) | 21(1) | -2(1) | 1(1) | 1(1) |
| N11 | 37(1) | 33(1) | 29(1) | 0(1) | 8(1) | -6(1) |
| C12 | 26(1) | 28(1) | 22(1) | 0(1) | 3(1) | 3(1) |
| O13 | 34(1) | 38(1) | 31(1) | 5(1) | -1(1) | -6(1) |
| C14 | 33(1) | 32(1) | 47(1) | 6(1) | 9(1) | -2(1) |
| C15 | 42(1) | 44(1) | 36(1) | 11(1) | 14(1) | 4(1) |
| C16 | 42(1) | 57(1) | 23(1) | 7(1) | 3(1) | -7(1) |

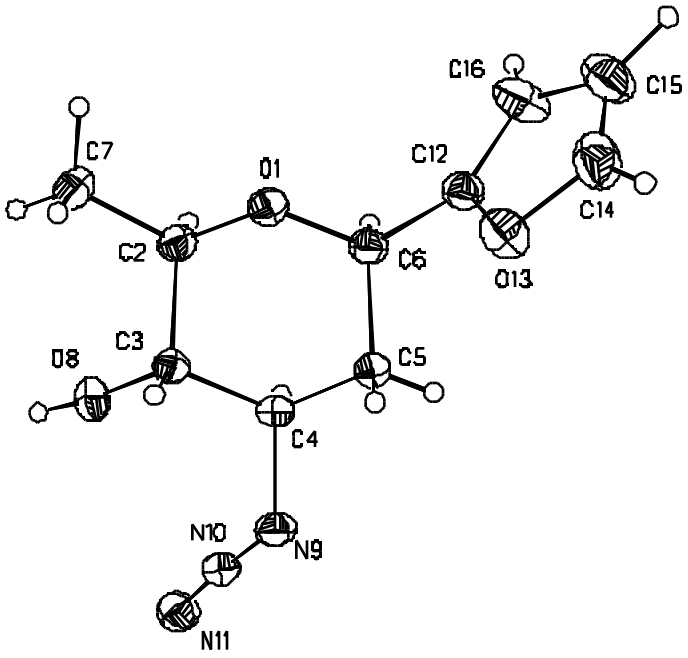
Table 5. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for $C_{10}H_{13}N_3O_3$ (**2.239**).

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H2 | 6280(30) | 8635(17) | 2951(11) | 29(3) |
| H3 | 3460(20) | 8223(15) | 990(10) | 20(3) |
| H4 | 8450(20) | 6757(17) | 1611(10) | 23(3) |
| H5A | 5890(30) | 4506(19) | 1841(11) | 27(3) |
| H5B | 3290(30) | 5246(17) | 1433(11) | 25(3) |
| H6 | 6070(20) | 6028(17) | 3374(10) | 19(3) |
| H7A | 3940(30) | 10880(20) | 2452(13) | 38(4) |
| H7B | 1290(30) | 9980(20) | 2297(12) | 41(4) |
| H7C | 2550(30) | 10250(20) | 3462(13) | 38(4) |
| H8 | 5950(40) | 9990(30) | 670(15) | 55(5) |
| H14 | -2170(40) | 2530(20) | 3512(15) | 52(5) |
| H15 | 160(30) | 2660(20) | 5374(14) | 48(5) |
| H16 | 4060(40) | 4520(30) | 5101(16) | 62(5) |

Table 6. Torsion angles [°] for $C_{10}H_{13}N_3O_3$ (**2.239**).

| | | | |
|---|---|---|---|
| C6-O1-C2-C7 | -175.01(8) | C4-C5-C6-C12 | 178.84(8) |
| C6-O1-C2-C3 | 62.61(10) | C5-C4-N9-N10 | -163.23(9) |
| O1-C2-C3-O8 | -175.50(7) | C3-C4-N9-N10 | 75.31(11) |
| C7-C2-C3-O8 | 65.39(11) | C4-N9-N10-N11 | 169.4(9) |
| O1-C2-C3-C4 | -56.48(10) | O1-C6-C12-C16 | -95.85(15) |
| C7-C2-C3-C4 | -175.59(9) | C5-C6-C12-C16 | 142.04(13) |
| O8-C3-C4-N9 | -66.41(9) | O1-C6-C12-O13 | 81.83(11) |
| C2-C3-C4-N9 | 172.94(7) | C5-C6-C12-O13 | -40.28(12) |
| O8-C3-C4-C5 | 174.08(7) | C16-C12-O13-C14 | 0.26(13) |
| C2-C3-C4-C5 | 53.43(10) | C6-C12-O13-C14 | -177.93(9) |
| N9-C4-C5-C6 | -174.84(8) | C12-O13-C14-C15 | 0.00(14) |
| C3-C4-C5-C6 | -53.85(10) | O13-C14-C15-C16 | -0.24(15) |
| C2-O1-C6-C12 | 171.51(8) | O13-C12-C16-C15 | -0.41(14) |
| C2-O1-C6-C5 | -63.90(10) | C6-C12-C16-C15 | 177.42(12) |
| C4-C5-C6-O1 | 58.02(10) | C14-C15-C16-C12 | 0.40(15) |

Figure 1. View of $C_{10}H_{13}N_3O_3$ (**2.289**) showing the atom labeling scheme. Displacement ellipsoids are scaled to the 50% probability level. Hydrogen atoms are drawn to an arbitrary size.



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# Vita

David Earl Kaelin Jr. was born in State College, Pennsylvania on February 22, 1973, the only son of David Earl Kaelin Sr. and Beverly Anne Kaelin. After graduating from Randallstown High School, Randallstown, Maryland, in 1991, he attended the Pennsylvania State University at University Park. During his education at the Pennsylvania State University, he was fortunate to serve as an undergraduate research assistant in the labs of Professor Raymond L. Funk. He graduated with a degree of Bachelor of Science in Chemistry in 1996. In June of 1997, he entered the Graduate School of the University of Texas at Austin, under the direction of Professor Stephen F. Martin. In May of 2000, he was awarded the Roche Award for Excellence in Organic Chemistry. In September of 2001, he was awarded the Hemphill-Gilmore fellowship. He is currently working as a research scientist in the medicinal chemistry group at Merck in Rahway, NJ.

Permanent address: 57 Essex Place, Newtown PA 18940

This dissertation was typed by the author.