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**Functionalization of *C*-Aryl Glycols and  
Studies Toward the Total Synthesis of 5-Hydroxyaloïn A**

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**FUNCTIONALIZATION OF C-ARYL GLYCALS AND STUDIES  
TOWARD THE TOTAL SYNTHESIS OF 5-HYDROXYALOIN A**

**by**

**Kristen Jean Procko, B.S.**

**Dissertation**

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for the Degree of

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**The University of Texas at Austin**

**August, 2009**

## **Dedication**

To Mom and Dad, for their boundless support and encouragement.

To Michael Wainwright, for showing me what is important in life.

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# Functionalization of C-Aryl Glycals and Studies Toward the Total Synthesis of 5-Hydroxyaloin A

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Supervisor: Stephen F. Martin

In the context of ongoing efforts toward *C*-aryl glycoside synthesis, a recently developed approach to form *C*-aryl glycals from 2-deoxysugar lactones was expanded to form novel substrates. This approach has been applied to the synthesis of various furyl glycals, allowing access to *C*-aryl glycals via a benzyne furan [4+2] cycloaddition methodology. The hydroboration-oxidation of said *C*-aryl glycals has allowed access to C(2)-oxygenated *C*-aryl glycosides via the benzyne cycloaddition approach.

An approach to the total synthesis of 5-hydroxyaloin A is detailed, in which regioselective benzyne furan [4+2] cycloadditions were achieved via the use of a silicon tether. Two approaches to the anthrone core have been applied; one in which an unsymmetrically-substituted aryl ring is first constructed by means of a silicon tether, and one in which the unsymmetrically-substituted ring is formed last, also utilizing a silicon tether. The latter approach has allowed access to the anthrone core of 5-hydroxyaloin A, and only a final desulfurization remains in order to access the natural product.

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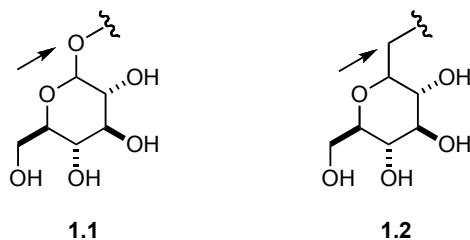
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## CHAPTER 1: C-Aryl glycoside synthesis

### 1.1. C-GLYCOSIDE NATURAL PRODUCTS

The synthetic community has seen marked development in methods to synthesize *C*-aryl glycosides over the past three decades. The increased interest is owed to their range of biological activity, in particular, the anti-cancer properties of many of these compounds. Carbohydrates in general are significant biologically; the glycoside moiety of cell surface glycoproteins plays a role in inflammation, metastasis, and immune response.<sup>1</sup> In biological systems, the *O*-glycosidic linkage is subject to hydrolysis by glycosidases (Figure 1.1). Replacement of the *O*-glycosidic **1.1** bond with a *C*-glycosidic linkage **1.2** results in analogs that retain the biological activity of the natural *O*-glycoside, but are more resistant to both enzymatic- and acid-hydrolysis.<sup>2</sup>

Figure 1.1: The *O*- vs. *C*-glycosidic linkage

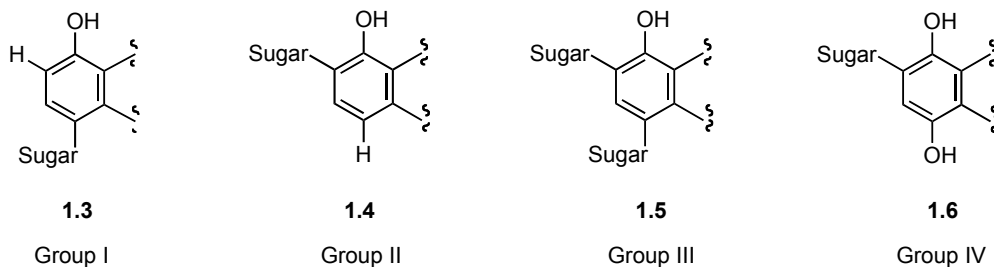


*C*-Aryl glycosides have been classified by Parker using a system that relates the substitution pattern of sugar and hydroxyl groups about the aromatic ring (Figure 1.2).<sup>3</sup> Group I examples of *C*-aryl glycosides **1.3** possess a sugar moiety para to a hydroxyl group, while in Group II members **1.4** the phenol and sugar moieties are ortho. Members of the Group III family **1.5** contain two sugar moieties, which are arranged ortho and para



to a phenolic hydroxyl group. Finally, Group IV examples of *C*-aryl glycosides **1.6** contain a single glycoside on a hydroquinone ring.

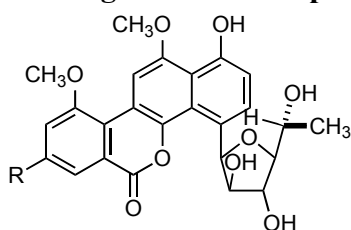
**Figure 1.2: Major classes of *C*-aryl glycosides**



There are members of each class that exhibit biological activity, so the development of approaches to all four groups is a worthwhile synthetic task. Gilvocarcin M (**1.7a**), V (**1.7b**), and E (**1.7c**) are examples of *C*-aryl glycosides belonging to the Group I family (Figure 1.3). Isolated from a streptomyces culture broth, these compounds exhibit antimicrobial activity.<sup>4</sup> A representative example of a Group II *C*-aryl glycoside is vineomycinone B<sub>2</sub> methyl ester (**1.8**), which was also isolated from a streptomyces culture broth. There has been much interest in the synthesis of this natural product, owing to its activity against gram-positive bacteria and sarcoma-180 tumors in mice.<sup>5</sup> Five syntheses of this molecule have been reported,<sup>6-9</sup> with the most recent approach coming from the Martin research group.<sup>10,11</sup> Kidamycin (**1.9**), which belongs to the Group III family of *C*-aryl glycosides, is also a member of the pluramycin family, all members of which exhibit potent antitumor activity.<sup>12</sup> Although a number of groups have reported efforts toward the total synthesis of this molecule,<sup>13-15</sup> to date a successful total synthesis has not been described. Mederrhodin A (**1.10**) belongs to the Group IV subclass of *C*-aryl glycosides.<sup>5</sup> This family of antimicrobial compounds comes from a genetically

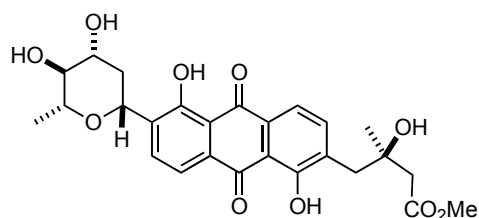
engineered strain of streptomyces. The strain is recombinant and the natural products that are produced by this organism are referred to as “hybrid antibiotics.”

**Figure 1.3: Examples of C-aryl glycoside natural products**



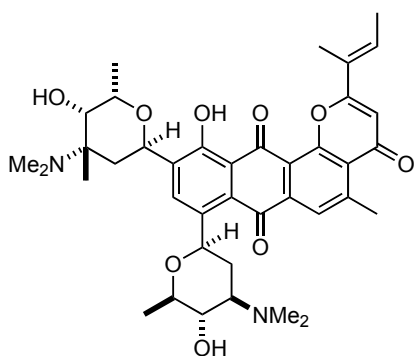
The gilvocarcins

- 1.7a: R = Me
- 1.7b: R = vinyl
- 1.7c: R = Et



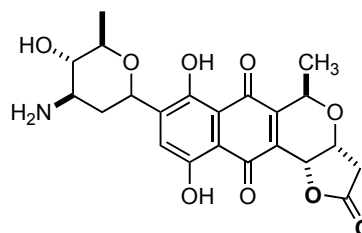
Vineomycinone B2 methyl ester

1.8



Kidamycin

1.9



Mederrhodin A

1.10

## 1.2. MAJOR APPROACHES TO C-ARYL GLYCOSIDES

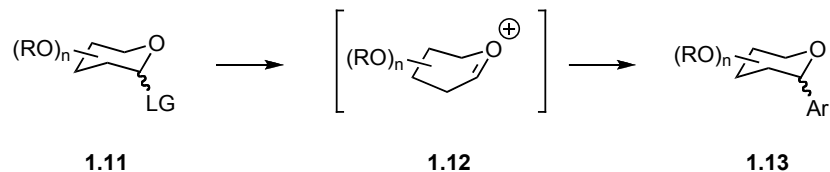
There are several reviews on the varied approaches to C-aryl glycosides.<sup>16-21</sup> Key approaches will be discussed here with emphasis placed on those methods that have been utilized in natural product synthesis. In the majority of these processes, the inherent electrophilicity of the sugar moiety has been used to create the C-glycosidic bond; however, carbohydrate glycals have allowed for the development of methods in which the sugar is the nucleophile. Cross coupling of substituted arenes and sugars has allowed

direct access to *C*-aryl glycosides and there are now several examples of these types of reactions in the total syntheses of *C*-aryl glycoside natural products. Other approaches involve the *de novo* synthesis of a sugar moiety onto a preformed aromatic core, although this method has yet to find utility in total synthesis. Finally, methods exist in which an appropriately substituted *C*-glycoside is elaborated to form a *C*-aryl glycoside.

### 1.2.1. Electrophilic sugars

Sugars are naturally pro-electrophiles, thus many methods to form *C*-aryl glycosides have relied on the formation of an oxonium ion by displacement of a leaving group at the anomeric position of the sugar moiety (Scheme 1.1); the earliest examples of this type of transformation date back to the 1950s.<sup>22-24</sup> In these types of *C*-glycoside forming reactions, a glycoside bearing an anomeric leaving group **1.11** forms an oxonium ion **1.12** when treated with Lewis acid. Friedel–Crafts reaction of an aryl group onto the anomeric carbon would furnish *C*-aryl glycosides **1.13**. There have been reports of lactols, thioglycosides, anomeric acetates, and glycosyl halides being utilized in the transformation shown in Scheme 1.

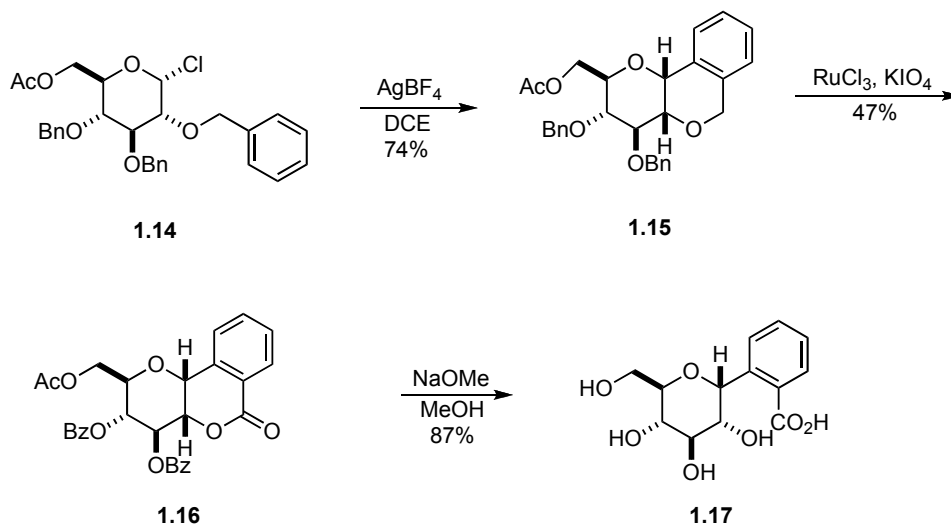
**Scheme 1.1: *C*-Aryl glycoside formation via addition to oxonium ion**



An intramolecular variant of this transformation allowed for the synthesis of an ortho acid **1.17** (Scheme 1.2).<sup>25</sup> Veyrieres and coworkers reported that the treatment of

glycosyl chloride **1.14** with silver tetrafluoroborate ( $\text{AgBF}_4$ ) resulted in the formation of an intermediate oxonium ion, which underwent intramolecular Friedel–Crafts reaction with the benzyl protecting group at the C(2) position of the sugar. The resultant tricyclic **1.15** was oxidized to lactone **1.16**, which resulted in oxidation of the benzylic carbon atom of the protecting groups as well. Methanolysis of **1.16** resulted in the global deprotection and lactone cleavage, providing *C*-aryl glycoside **1.17**. This intramolecular approach allowed for the facile introduction of a sugar ortho to an electron-withdrawing group, the formation of which would not have been trivial via an intermolecular Friedel–Crafts reaction.

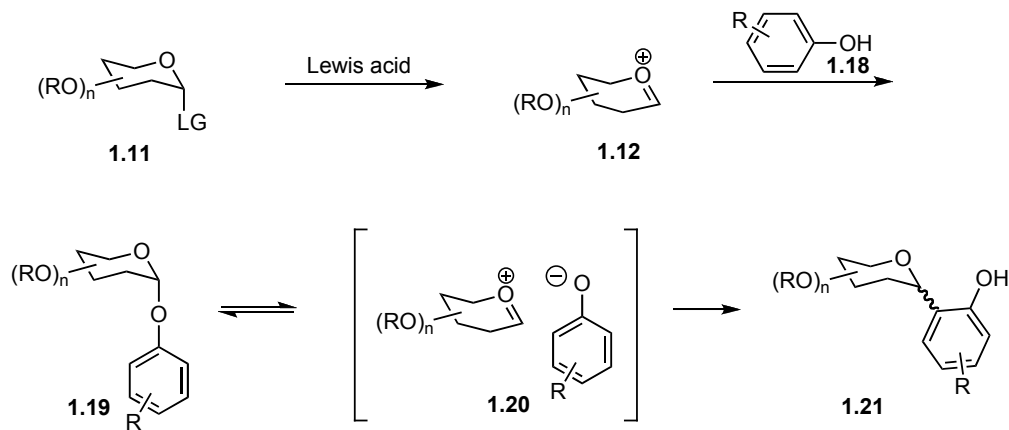
**Scheme 1.2: Intramolecular Friedel–Crafts reaction via oxonium ion**



The *O*→*C* glycoside rearrangement has been a widely employed method in *C*-glycoside synthesis and has allowed access to various *C*-aryl glycoside natural products (Scheme 1.3). In general, this rearrangement involves the nucleophilic addition of a phenol **1.18** to an oxonium ion **1.12** to give adduct **1.19**. Direct evidence for the initial

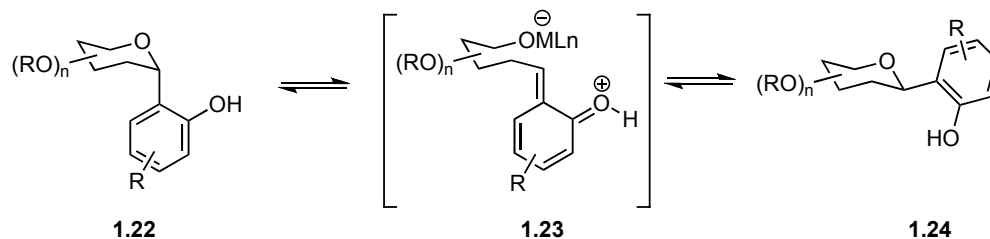
formation of *O*-glycosylated products such as **1.19** was first shown by Ramesh and Balasubramanian.<sup>26</sup> Dissociation of **1.19** to form the tight ion pair **1.20** often results in preferential, if not exclusive, formation of the ortho *C*-aryl glycoside **1.21**, which is a member of the Group II subclass. This reaction has been thoroughly investigated by Suzuki, who has demonstrated that the choice of Lewis acid is critical to the stereochemical outcome of the resultant glycoside in both furanose<sup>27</sup> and pyranose<sup>27-38</sup> sugar systems.

**Scheme 1.3: The *O*→*C* rearrangement**



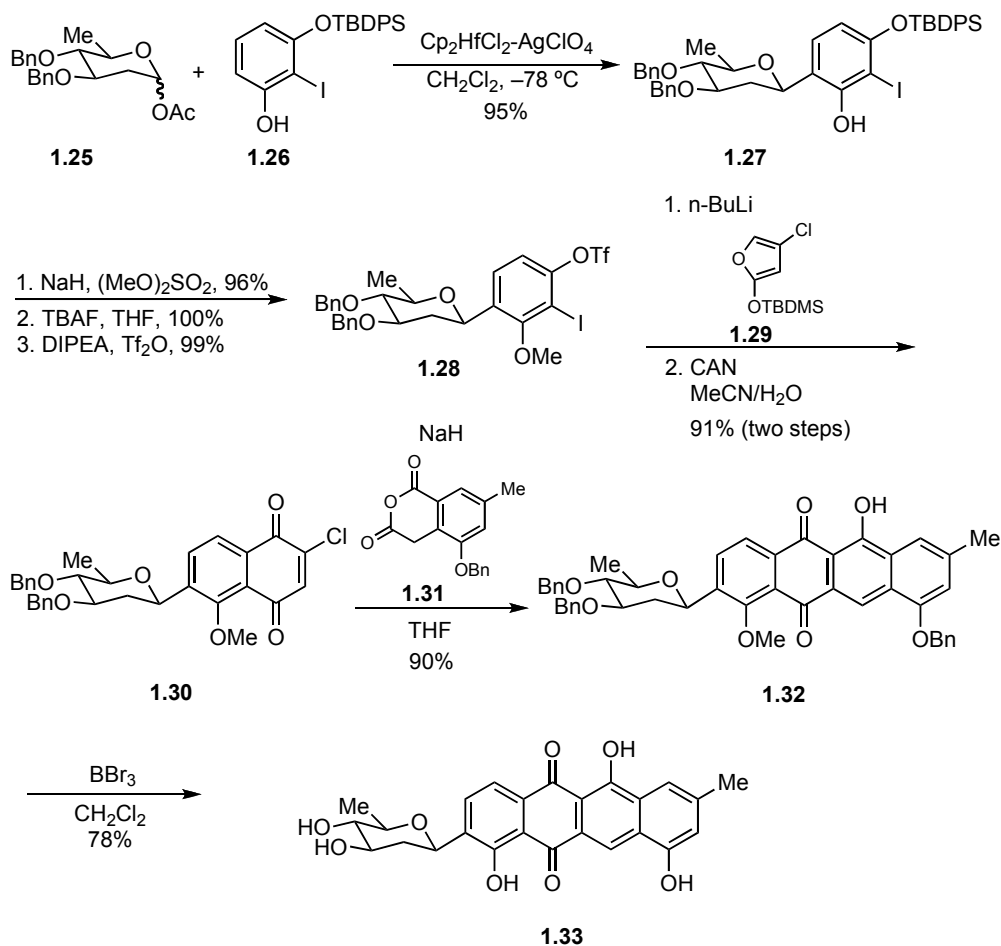
The reaction conditions can dictate the stereochemical outcome of the Friedel–Crafts reaction, and reaction temperature can also play a role. The formation of the kinetic product should be favored with the correct choice of Lewis acid at low temperature. In many pyranose systems this is the  $\alpha$ -anomer, due to axial attack of the nucleophilic arene. It is proposed that the  $\alpha$ - and  $\beta$ -anomer **1.22** and **1.24**, respectively, can equilibrate by interconversion via the intermediate quinone methide **1.23**, thus equilibrating conditions will favor the thermodynamic product (Scheme 1.4).<sup>39</sup>

#### Scheme 1.4: C-Glycoside epimerization via a quinone methide



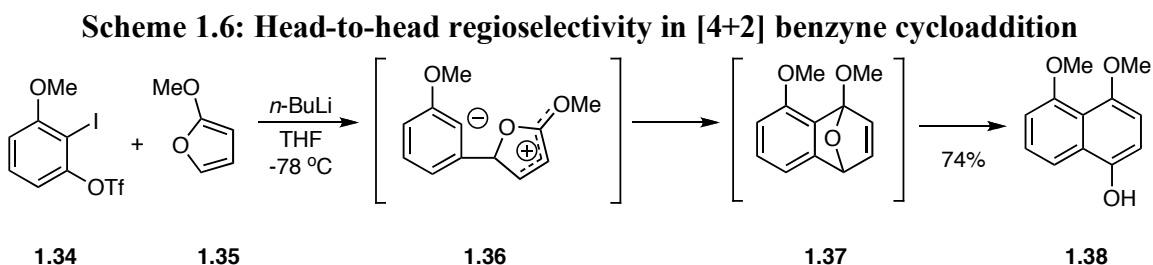
In Suzuki's total synthesis of galtamycinone,<sup>40,41</sup> the  $O \rightarrow C$  rearrangement allowed for the regioselective coupling of glycoside **1.25** with phenol **1.26** (Scheme 1.5). Treatment of **1.25** and **1.26** with  $\text{Cp}_2\text{HfCl}_2\text{-AgCl}_2$  as the Lewis acid, which had been shown to give excellent  $\beta$  selectivity, provided  $C$ -aryl glycoside **1.27** in 95% yield.  $O$ -Methylation of **1.27**, followed by cleavage of the silyl ether provided an intermediate phenol, which was converted to triflate **1.28** by treatment with diisopropylethylamine (DIPEA) and triflic anhydride ( $\text{Tf}_2\text{O}$ ). Triflate **1.28** underwent a regioselective benzyne cycloaddition with furan **1.29**. Acidification of the intermediate provided chlorojuglone **1.30** following oxidation. A dipolar cycloaddition of **1.30** with the anion generated from **1.31** followed by decarboxylation furnished angucycline **1.32**, which was deprotected by treatment with boron tribromide ( $\text{BBr}_3$ ) to provide galtamycinone (**1.33**).

### Scheme 1.5: Suzuki's total synthesis of galtamycinone



The regioselective cycloaddition of the benzyne generated from **1.28** and furan **1.29** is another key feature of Suzuki's galtamycinone synthesis. Suzuki has shown remarkable selectivity in benzyne cycloaddition reactions that involve substrates containing electron-donating groups. Suzuki demonstrated that the [4+2] cycloaddition of the benzyne generated from triflate **1.34** with 2-methoxyfuran (**1.35**) proceeded with complete regioselectivity to give cycloadduct **1.37**,<sup>42</sup> which spontaneously underwent ring opening to provide phenol **1.38** (Scheme 1.6). The methoxy groups are aligned on the

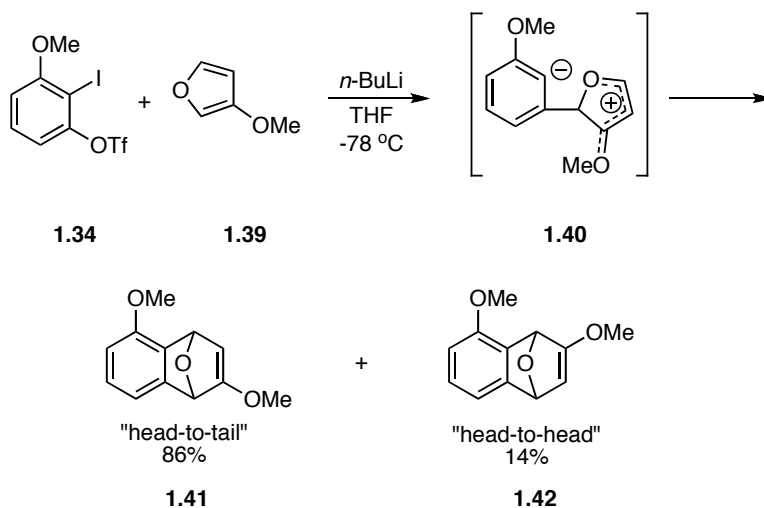
same side of the molecule, thus this has been termed a “head-to-head” cycloaddition.<sup>41</sup> The formation of the single regioisomer can be rationalized by depicting a stepwise mechanism for the cycloaddition involving the formation of a zwitterionic intermediate, as shown by **1.36**. If indeed the bonds form at different rates, the formation of **1.36** would produce an anion that is inductively stabilized by the electron withdrawing methoxy group, while the positive charge developing in the furan moiety could be resonance stabilized as shown.



Sargent and coworkers have demonstrated “head-to-tail” regioselectivity in the cycloaddition of the benzyne generated from **1.34** with 3-methoxyfuran (**1.39**) (Scheme 1.7).<sup>43, 44</sup> Invoking the stepwise mechanism for the cycloaddition would result in the formation of adduct **1.40**. The methoxy group could participate in resonance stabilization of the positive charge developing in the furan. Indeed, **1.41** was the major product, although this reaction did not proceed with complete regioselectivity, as the head-to-head product **1.42** was also formed in 14% yield.



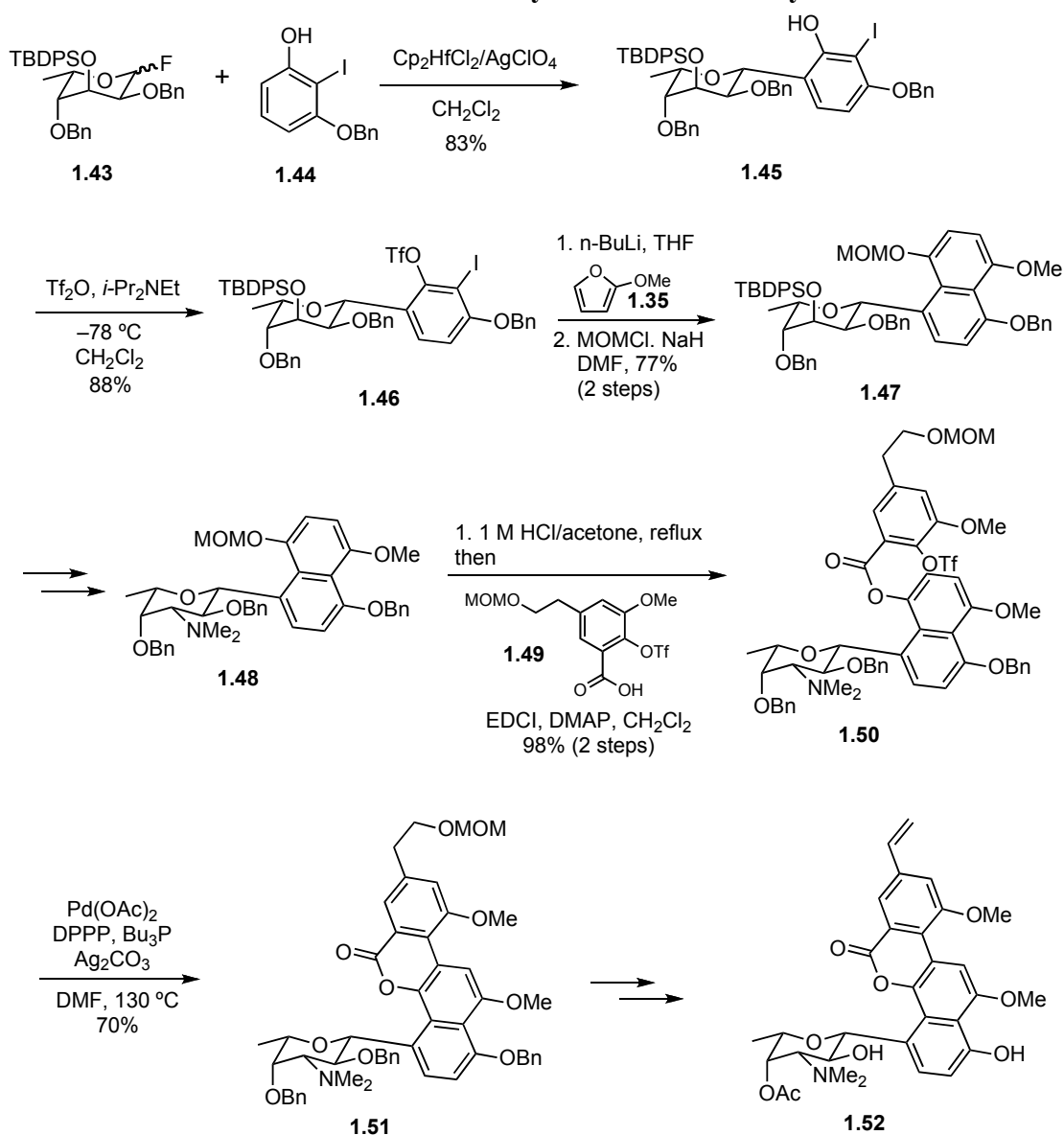
**Scheme 1.7: Head-to-tail regioselectivity in [4+2] benzyne cycloaddition**



Suzuki has had much success in natural product synthesis by employing both the  $O \rightarrow C$  rearrangement and regioselective benzyne cycloadditions. However, at first glance it seems that the  $O \rightarrow C$  is not amenable to the synthesis of Group I examples of  $C$ -aryl glycosides, as the sugar moiety is almost always introduced ortho to the phenol. Suzuki has developed a method to work around this limitation, which he applied to the total synthesis of ravidomycin,<sup>45, 46</sup> a member of the Group I class of  $C$ -aryl glycosides (Scheme 1.8). Treatment of a mixture of fluoride **1.43** and phenol **1.44** with Lewis acid resulted in the formation of ortho phenol **1.45** in 83% yield with exclusive  $\beta$ -selectivity. The phenol **1.45** was converted to triflate **1.46**. Upon treatment of **1.46** with  $n$ -BuLi, a benzyne was generated that underwent a head-to-head cycloaddition with 2-methoxyfuran (**1.35**) to provide an intermediate cycloadduct and effectively eliminate the ortho hydroxyl group. Ring opening and protection of the resultant phenol as its MOM ether gave **1.47**. The C(3)-amino group was introduced in a four step process to provide **1.48**. Cleavage of the MOM ether of **1.48** by treatment with HCl followed by coupling with acid **1.49** provided ester **1.50**. The next step of the synthesis required oxidative

insertion of palladium into the triflate–arene bond, followed by cyclization via C–H insertion. The insertion reaction was complicated by deactivation of various palladium catalysts, which the author attributed to the poisoning of the catalyst by the amine. Although an obvious disadvantage to this synthesis, treatment of **1.50** with stoichiometric palladium acetate in the presence of silver carbonate furnished tetracycle **1.51**, which was converted to ravidomycin (**1.52**) in three steps.

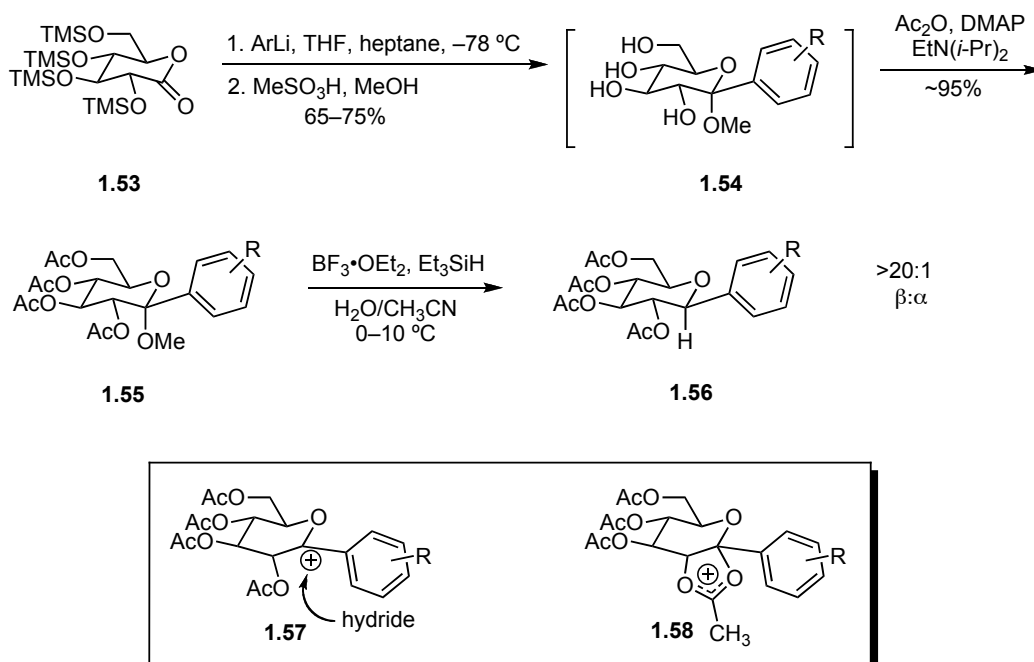
### Scheme 1.8: The total synthesis of ravidomycin



Another method to form *C*-aryl glycosides that has been widely utilized in *C*-aryl glycoside synthesis involves the addition of aryl nucleophiles to sugar lactones.<sup>47, 48</sup> The process group at Bristol-Meyers Squibb wanted to prepare the *C*-aryl glycosides **1.56** on a multikilogram scale (Scheme 1.9).<sup>49</sup> Protecting groups that had to be removed by

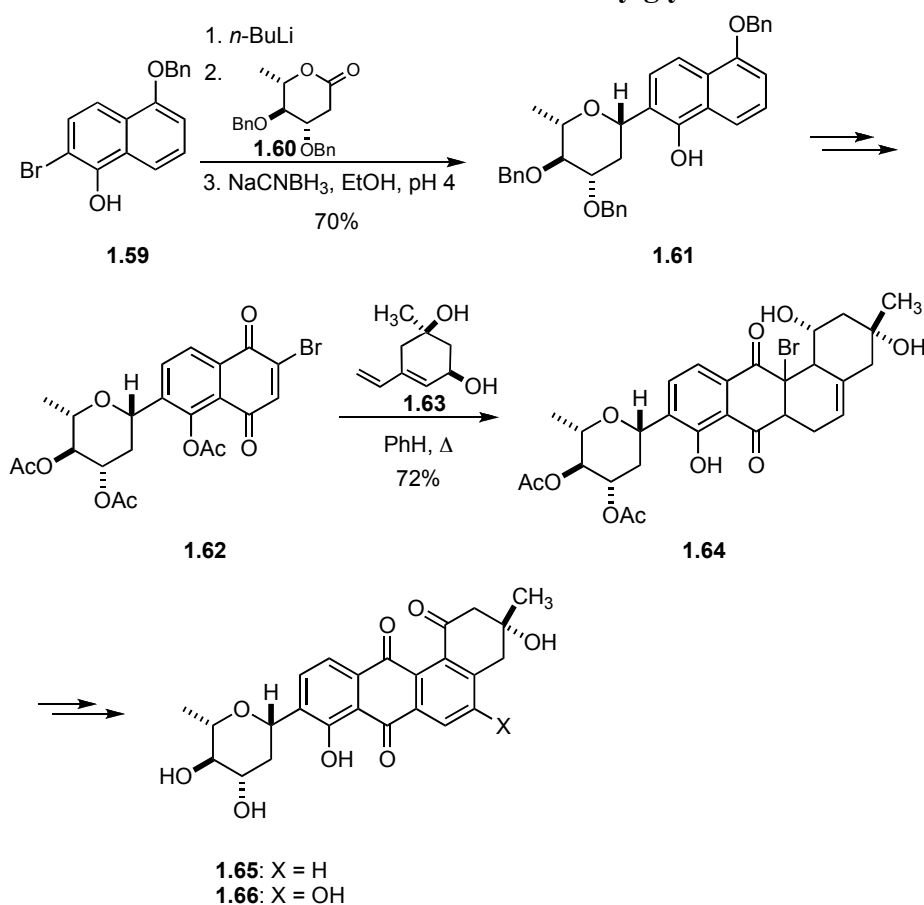
hydrogenolysis were avoided because of the size of the reaction. Thus, silyl ether protecting groups were introduced onto the sugar, and then various aryllithium reagents were added to lactone **1.53**. The resultant lactols were converted to methyl acetals **1.54**. A protecting group swap furnished peracylated sugars **1.55**, which were reduced by treatment with boron trifluoride diethyl etherate ( $\text{BF}_3 \cdot \text{OEt}_2$ ) and triethylsilane ( $\text{Et}_3\text{SiH}$ ) to provide *C*-aryl glycosides **1.56** with high  $\beta$ -selectivity. The authors state that *C*-aryl glycosides **1.56** were formed in “good yield,” although they do not specify yields in the article or supporting information. Hydride delivery occurred from the bottom face, as shown by **1.57**. It is well precedented that acetate protecting groups can engage in neighboring group participation,<sup>50, 51</sup> as shown by intermediate **1.58**, which would result in the formation of the  $\alpha$ -anomer; however, in this study this was not the case. Another interesting finding of this investigation was that water was necessary for the reduction of **1.55** to occur. On large scale, the reduction did not reach completion without the addition of water, a result believed to be due to the formation of the Brønsted acid,  $\text{BF}_3 \cdot \text{OH}_2^+$ . The authors hypothesized that this acid was required to facilitate formation of the required oxonium ion in the presence of the electron withdrawing protecting groups.

**Scheme 1.9: Formation of  $\beta$ -C-arylglycosides via the reduction of acetate-protected sugars**

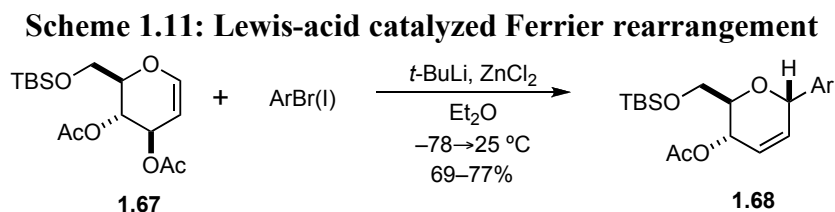


Boyd and Sulikowski utilized a similar approach for the synthesis of urdamycinone B (**1.65**) and antibiotic 104-2 (**1.66**), angucycline antibiotics isolated from *Streptomyces fradiae* (Scheme 1.10).<sup>52</sup> Lithiation of phenol **1.59**, followed by addition of the lactone **1.60** provided an intermediate lactol that was reduced using NaCNBH<sub>4</sub> to give the C-aryl glycoside **1.61**. Bromojuglone **1.62**, which was accessed in several steps from **1.61**, underwent a regioselective Diels-Alder cycloaddition with diene **1.63** to give the tetracycle **1.64**. This approach allowed for the synthesis of urdamycinone (**1.65**) and antibiotic 104-2 (**1.66**).

**Scheme 1.10: Lactone addition to form C-arylglycoside antibiotics**



The electrophilicity of glycol enol ethers allows for aromatic substitution in the Ferrier rearrangement. In an example reported by DuBois, S<sub>N</sub>2' addition of the zincates of various arenes to glycol **1.67** provided **1.68** (Scheme 1.11).<sup>53</sup> This method resulted in the loss of a stereocenter at C(3), which may be disadvantageous in some cases. Notably, no β-hydride elimination was observed in this case, which is surprising, as Daves and others have reported such elimination products when similar substrates were employed.<sup>54</sup>

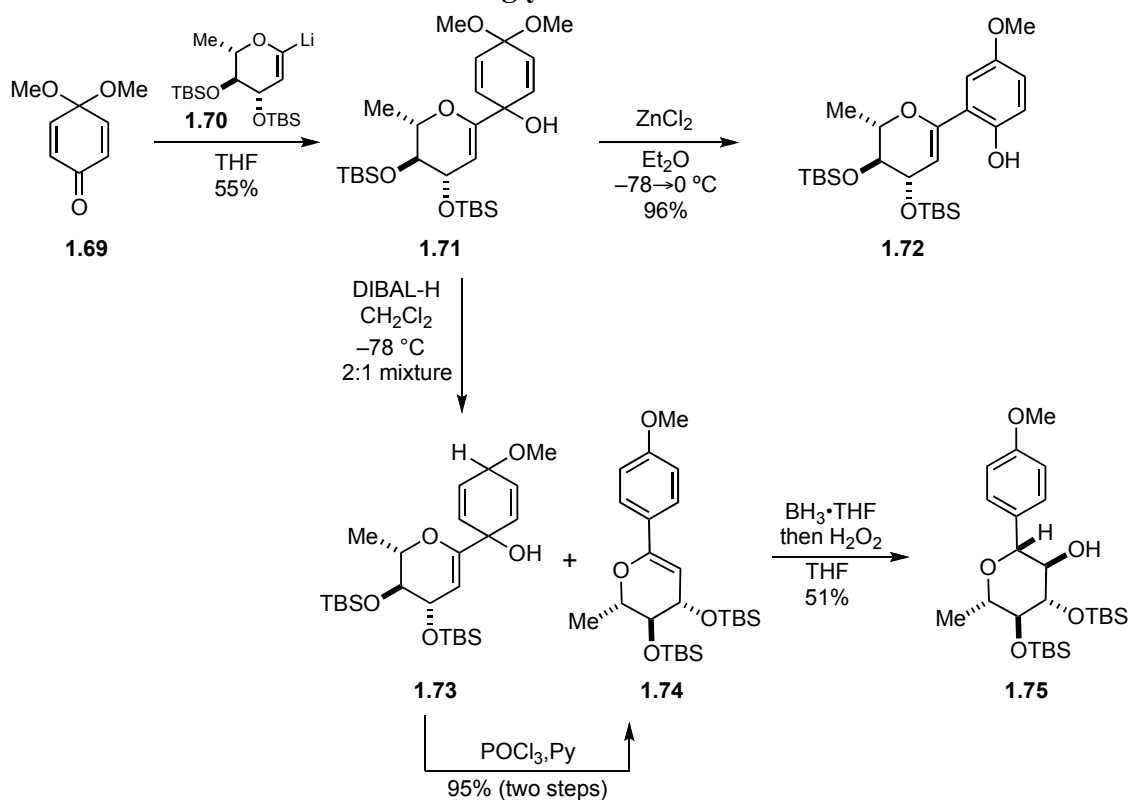


### 1.2.2. The nucleophilic sugar approach

Parker has developed a method in which nucleophilic sugar derivatives are used to form *C*-aryl glycosides (Schemes 1.12–1.14). In this “reverse polarity” approach, lithiated glycols were added to quinones,<sup>3, 13, 56-62</sup> which allowed access to *C*-aryl glycosides that are models for members of Groups I, III, and IV.

The divergent approach to Groups I and IV involved the addition of lithiated rhamnal **1.70** to quinone ketal **1.69** to provide alcohol **1.71** (Scheme 1.12). When treated with ZnCl<sub>2</sub>, **1.71** underwent rearrangement, furnishing *C*-aryl glycol **1.72**, which has the Group IV substitution pattern. Alternatively, **1.71** could be reduced by treatment with DIBAL-H to form a mixture (2:1) of **1.73** and *C*-aryl glycol **1.74**; quinol **1.73** could be converted to **1.74** in 95% overall yield. Hydroboration-oxidation of **1.74** furnished the C(2)-oxygenated *C*-aryl glycoside **1.75**. It should be noted that hydroboration occurred selectively from the face opposite the C(3) substituent, as is well preceded for this reaction.<sup>63-65</sup>

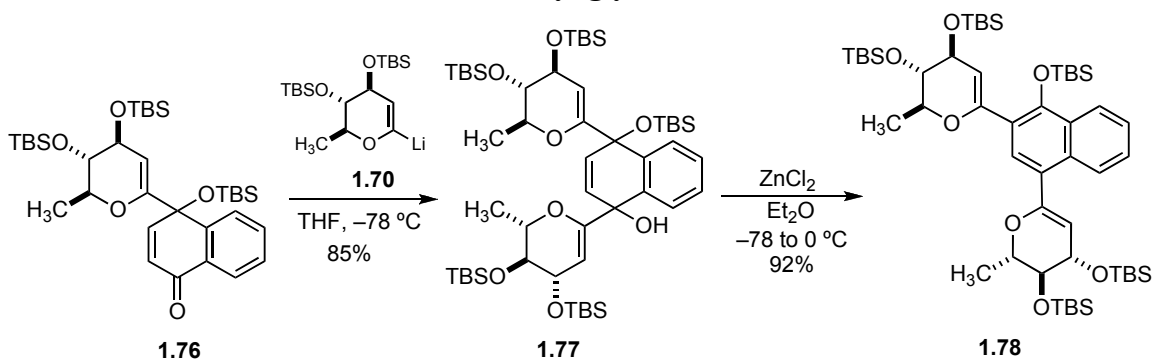
**Scheme 1.12: Parker's "reverse polarity" approach in the synthesis of C-aryl glycosides**



Parker applied this strategy to the synthesis of a Group III C-aryl glycoside model compound for the pluramycin family (Scheme 1.13).<sup>13</sup> Quinol **1.76** was treated with lithiated glycol **1.70**, furnishing alcohol **1.77** in 85% yield. The alcohol **1.77** was converted to bis C-aryl glycol **1.78** by treatment with  $\text{ZnCl}_2$ .

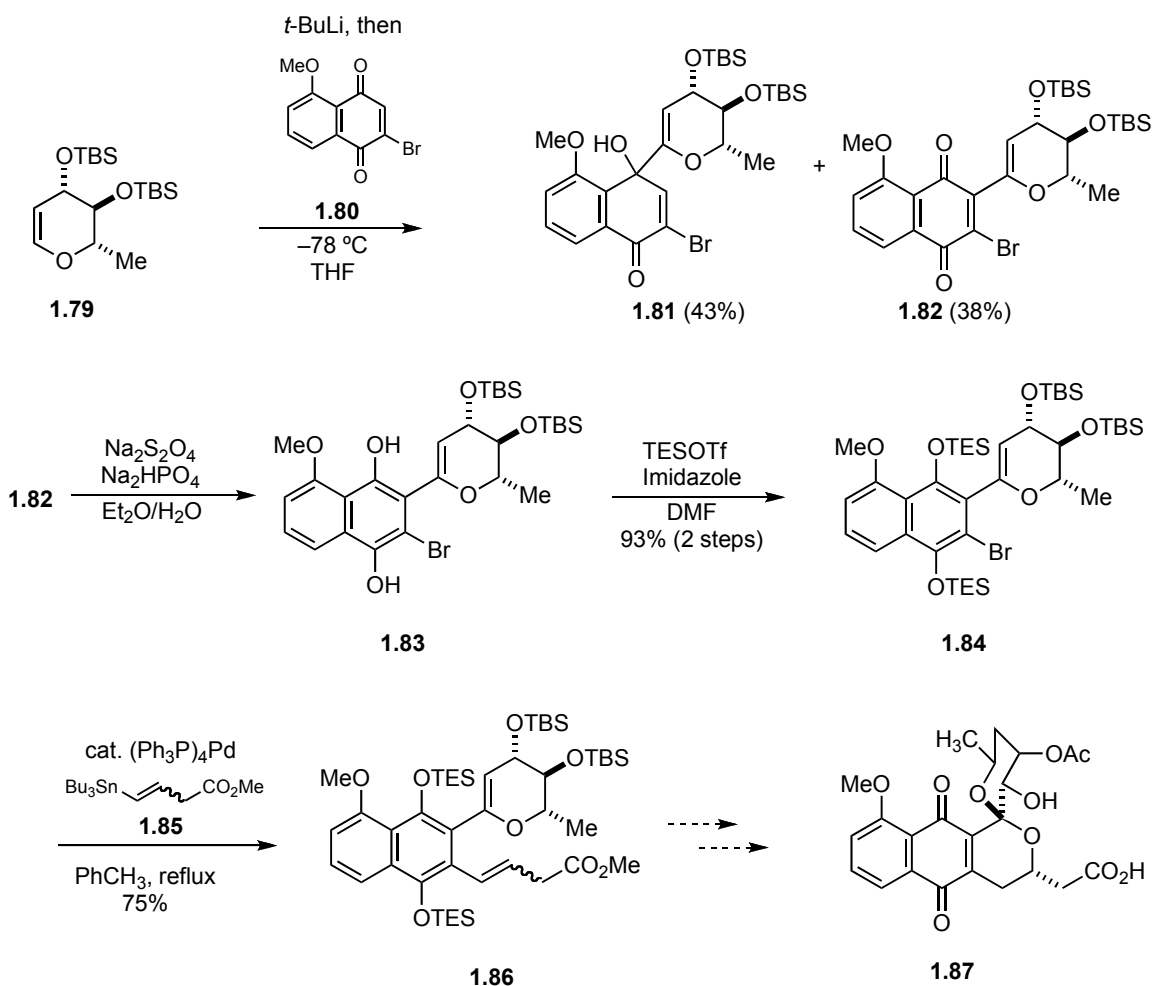


**Scheme 1.13: The reverse polarity approach in the synthesis of a model of a Group III C-aryl glycoside**



Parker has attempted to apply the reverse polarity approach to the synthesis of the griseusin family of natural products (Scheme 1.14).<sup>62</sup> In this approach, glycal **1.79** was lithiated and added to the quinone **1.80** to give quinol **1.81** and the conjugate addition product **1.82**. Unfortunately, all attempts to convert quinol **1.81** to quinone **1.82** failed. Reduction of **1.82** provided **1.83**, which was protected as its bis TES ether to provide **1.84**. Because direct cross coupling reaction of **1.82** with stannane **1.85** was unsuccessful, **1.84** was used in the coupling reaction. Palladium-catalyzed cross coupling of **1.84** and **1.85** provided **1.86**, which was not elaborated to griseusin A (**1.87**), but served as a model system for this family of natural products.

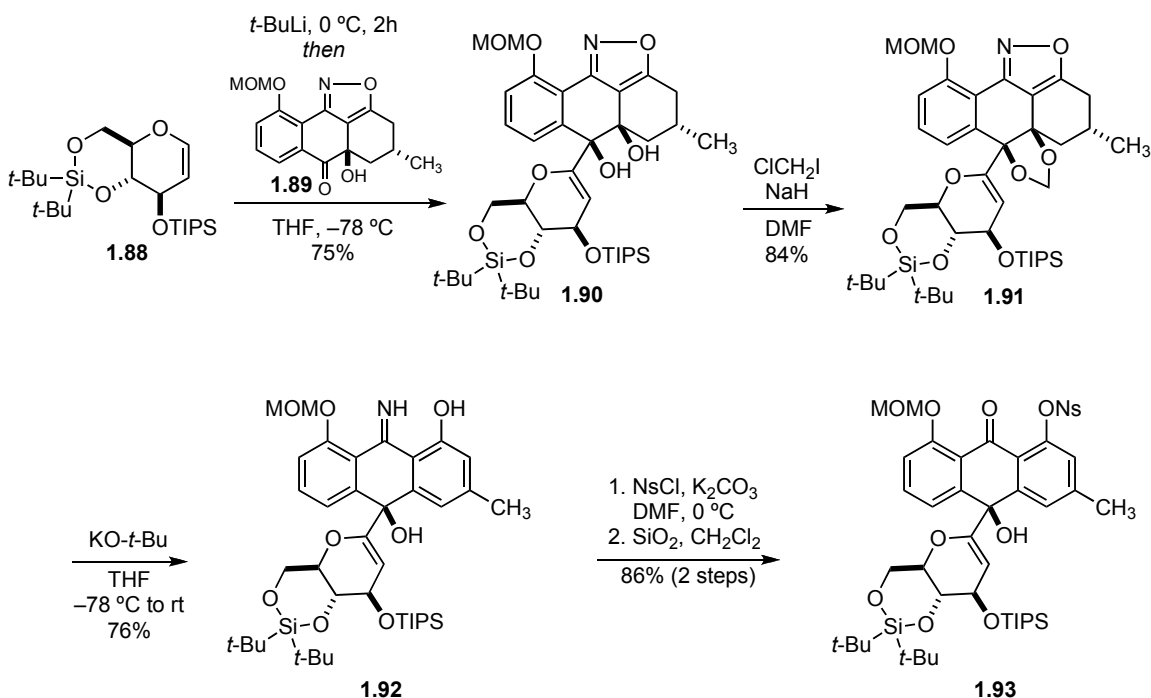
### Scheme 1.14: Attempted synthesis of the griseusins



Although not *C-aryl*-glycosides, anthrone *C*-glycosides are of interest to the Martin group as well. The only anthrone *C*-glycoside to be successfully synthesized and reported in the literature is cassialoin (**1.95**) (Scheme 1.15).<sup>66</sup> Recently, Suzuki reported the total synthesis of this molecule, involving the regioselective addition of lithiated glycal **1.88** to nitrile oxide **1.89**, which served as a masked anthrone. Methylenation of the resultant adduct **1.90** gave bis ether **1.91**, which underwent aromatization when

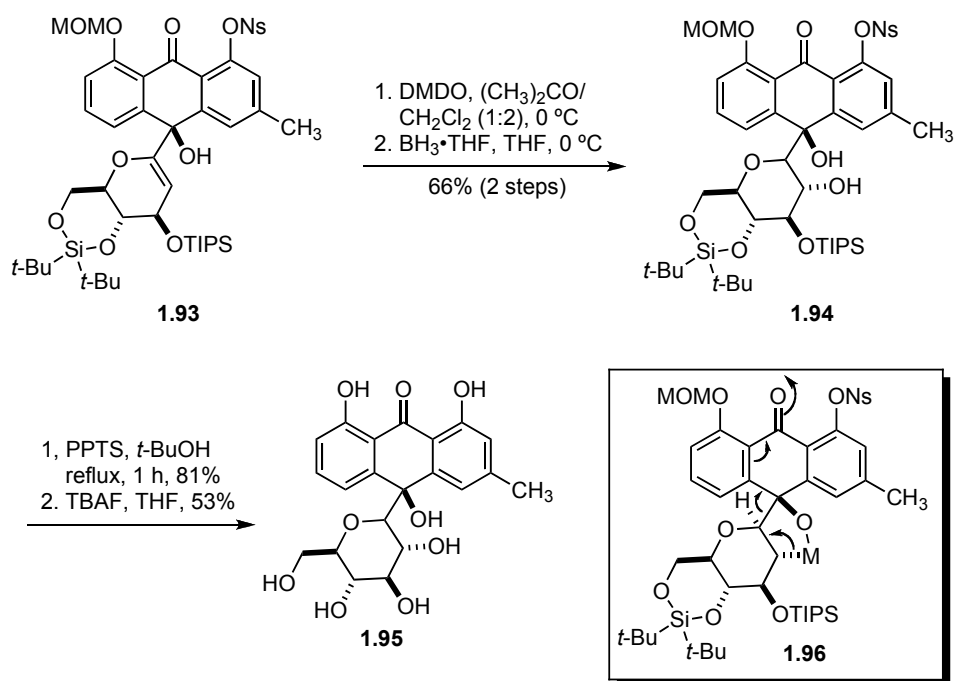
treated with strong base furnishing phenol **1.92**. Protection of **1.92** and hydrolysis of the imine unmasked the anthrone to give **1.93**.

**Scheme 1.15: Joining of a glycal with the cassialoin aglycone**



The stage was now set for a C(2)-functionalization of the glycal, which would provide all of the necessary oxygen atoms of the sugar moiety (Scheme 1.16). Direct hydroboration of **1.93** failed; product mixtures contained cleaved sugar and aglycone, which Suzuki hypothesized was the result of the decomposition pathway depicted by **1.96**. This problem was remedied by epoxidizing the glycal **1.93** followed by reductive opening to provide the C(2)-oxygenated glycoside **1.94**. Global deprotection then furnished the natural product **1.95**.

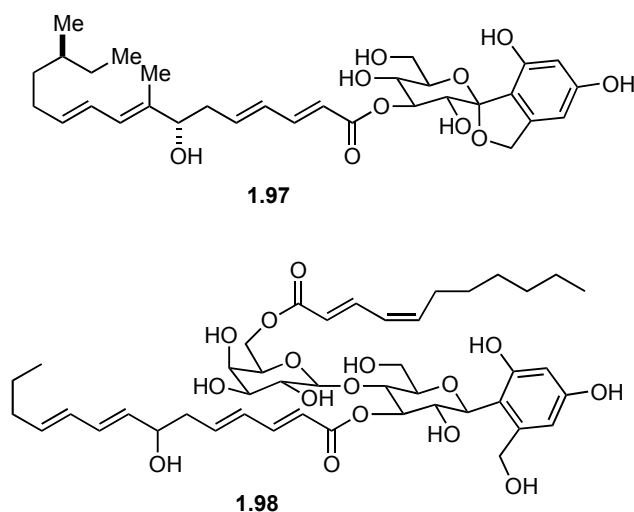
### Scheme 1.16: Cassialoin endgame via epoxide opening



### 1.2.3: Metal-Mediated approaches to *C*-aryl glycosides

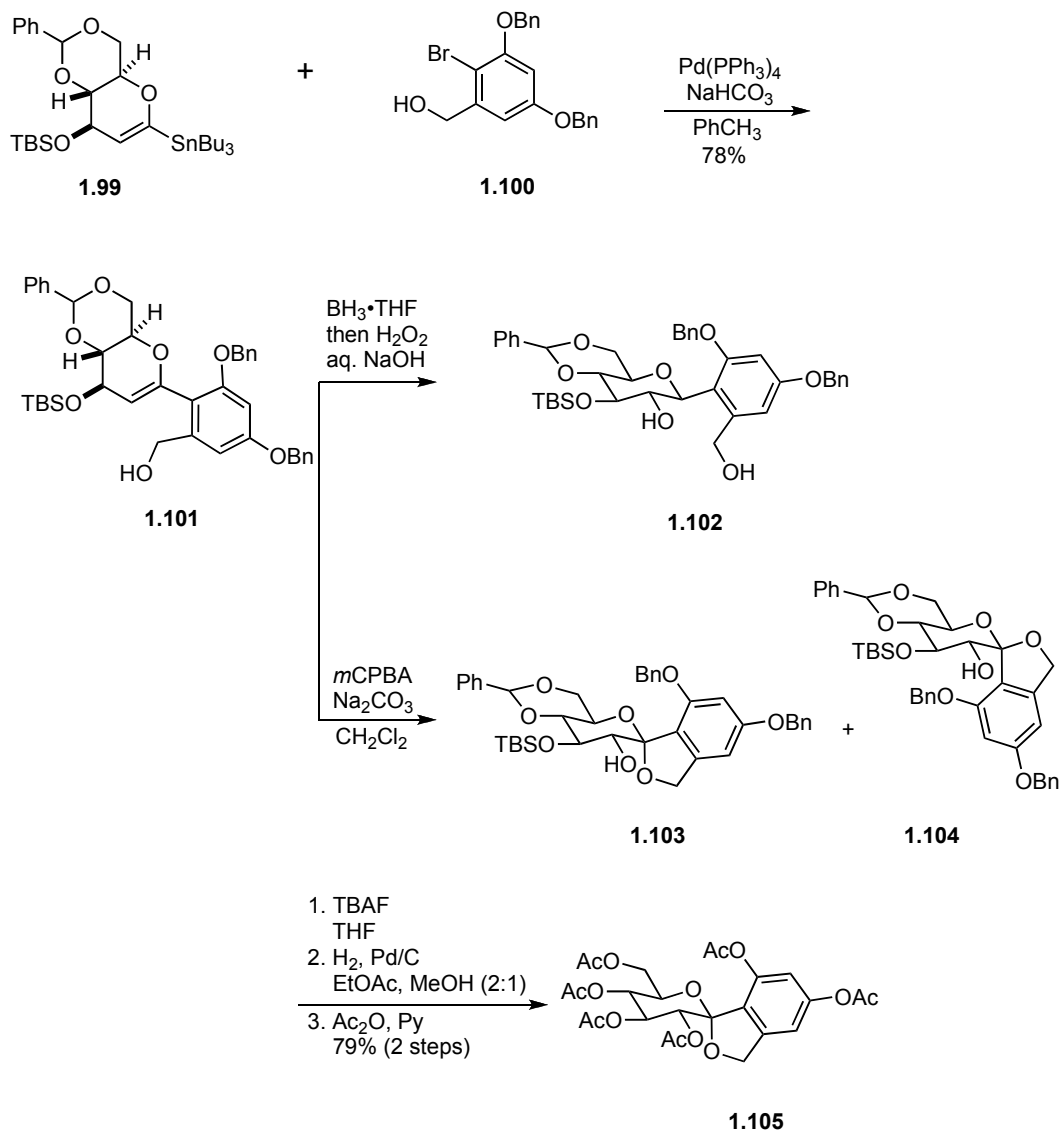
Metal-mediated approaches, such as cross couplings, have proved valuable synthetic tools to access *C*-aryl glycosides. Dubois and Beau reported an early approach to both the chaetiacandin **1.102** and papulacandin skeletons **1.105** (Scheme 1.17).<sup>53,67</sup> The natural product chaetiacandin (**1.97**) is a simple *C*-aryl glycoside, while papulacandins are spirocyclic *C*-aryl glycosides (Figure 1.4). Papulacandin A (**1.98**) is an illustrative example of this class of natural products.

**Figure 1.4: Papulacandin D and chaeticandin**



A common approach to these classes of natural products was applied, as they are structurally similar (Scheme 1.17). To accomplish this, glycol stannane **1.99** was coupled with bromide **1.100** in the presence of palladium tetrakis ( $\text{Pd}(\text{PPh}_3)_4$ ) and base to provide glycol **1.101**. It is noteworthy that in the absence of sodium bicarbonate ( $\text{NaHCO}_3$ ) a spirocycle was obtained. Because these natural products contain a C(2)-substituent, the concomitant spirocyclization was a disadvantage. Hydroboration-oxidation provided **1.102**, which is a model for the chaeticandins. A model for the papulacandin skeleton was obtained via epoxidation of glycol **1.101** by treatment with meta chloroperbenzoic acid (*m*CPBA) in the presence of base. Epoxidation occurred from the face opposite the C(3) substituent. Subsequent cyclization of the benzyl alcohol provided a mixture of spirocycles **1.103** and **1.104**. This mixture could be converted to a single isomer following deprotection. *O*-Acetylation of **1.103** and **1.104** provided heptaacetate **1.105**, which is identical to a heptaacetate isolated from degradation of the natural product **1.97**.

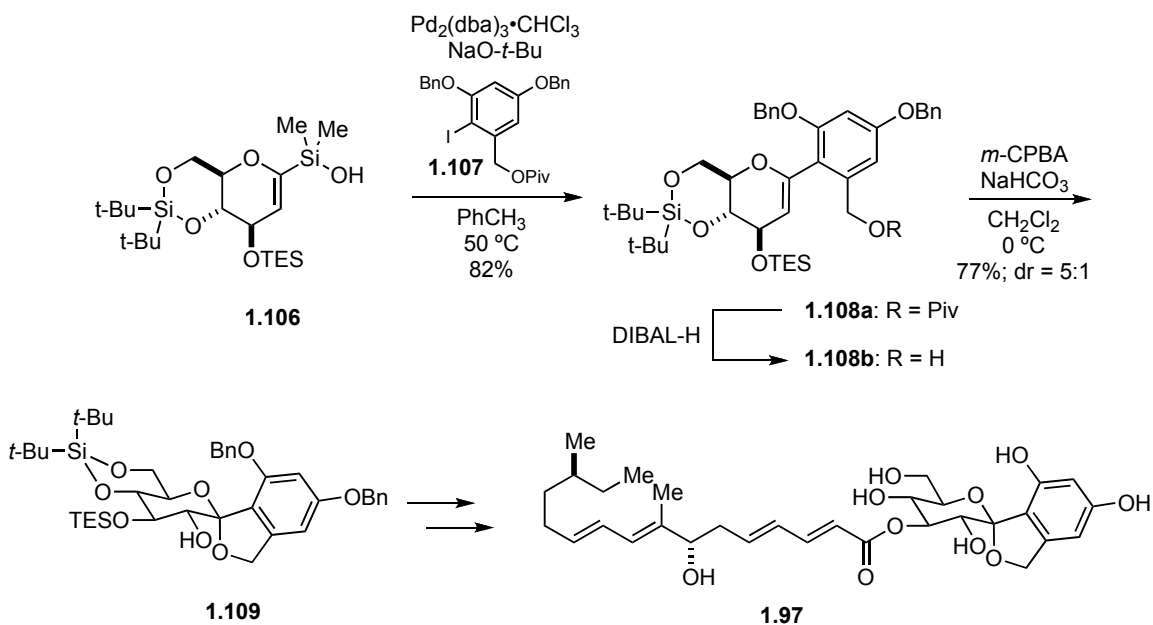
**Scheme 1.17: Cross-coupling approach to the papulacandin skeleton**



Recently, Denmark and coworkers reported the successful synthesis of papulacandin D (**1.97**) using a similar cross coupling approach (Scheme 1.18).<sup>68</sup> Treatment of a mixture of silanol **1.106** and iodide **1.107** with Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> in the presence of sodium *t*-butoxide furnished *C*-aryl glycal **1.108a** in 82% yield. The addition of DIBAL-H to **1.108a** effected the removal of the Piv group and furnished benzyl

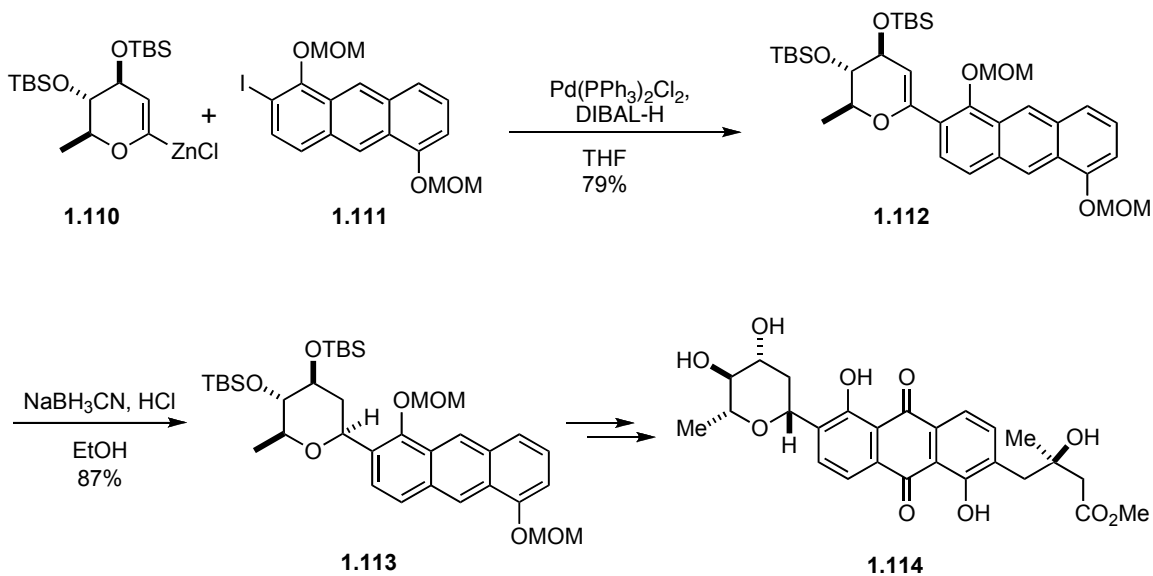
alcohol **1.108b**, which underwent epoxidation and cyclization to provide **1.109**. Spirocycle **1.109** was converted to the natural product **1.97** in six steps.

**Scheme 1.18: Successful papulacandin D synthesis via cross coupling**



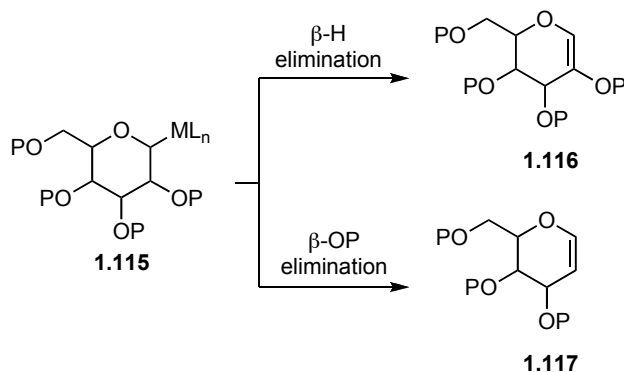
Tius reported the total synthesis of vineomycinone B<sub>2</sub> methyl ester using a palladium-catalyzed cross coupling approach (Scheme 1.19).<sup>7, 69</sup> The coupling was achieved by treating ZnCl<sub>2</sub> **1.110** and aryl iodide **1.111** with Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> in the presence of (diisobutylaluminum hydride) DIBAL-H. Reduction of the resultant C-aryl glycol **1.112** by treatment with NaCNBH<sub>4</sub> furnished the desired β-C-aryl glycoside **1.113**, which was elaborated to vineomycinone B<sub>2</sub> methyl ester (**1.114**) in six steps.

**Scheme 1.19: The total synthesis of vineomycinone B<sub>2</sub> methyl ester via palladium catalyzed cross coupling**



Cross coupling approaches have historically been limited to  $sp^2$  hybridized anomeric centers. When  $sp^3$  substrates are employed in these reactions,  $\beta$ -hydride elimination of **1.115** to produce glycal **1.116** or elimination of the C(2)-substituent to form glycal **1.117** is a competing reaction (Scheme 1.20).<sup>54</sup>

**Scheme 1.20: Difficulties cross-coupling C(2)-oxygenated substrates**





Fu and others have demonstrated that  $\beta$ -elimination can be suppressed when “pincer” ligands, tridentate ligands that bind a metal in a coplanar arrangement, are employed in cross coupling reactions.<sup>70</sup> Mechanistically, it is believed that the ligand blocks the coordination site on the metal that is aligned with the C-H bond in the transition state, preventing  $\beta$ -hydride elimination from occurring. Gagné and coworkers utilized a modification of Fu’s conditions to access *C*-alkyl and *C*-aryl glycosides; examples of the latter are shown (Table 1.1).<sup>71</sup>

**Table 1.1: Negishi approach with  $sp^3$  hybridized sugars**

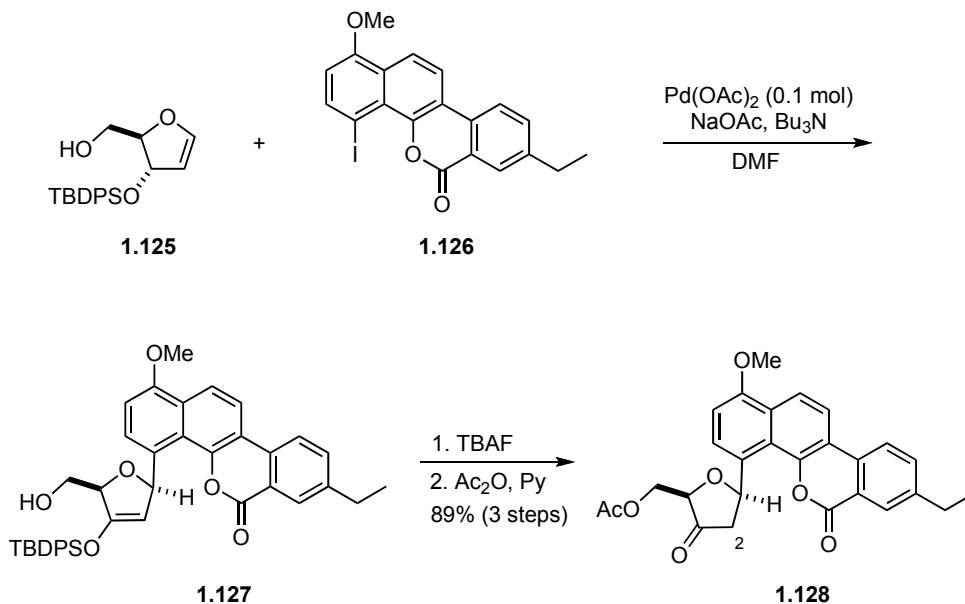
entry	halide	product	Results/Yield ( $\alpha:\beta$ )
1	Br	 <b>1.120</b>	76% (2.9:1) Glycal 19%
2	Br	 <b>1.121</b>	75% (1:10) Glycal: trace
3	Cl	 <b>1.122</b>	20% (1:20)
4	Cl	 <b>1.123</b>	28% (>20:1) Glycal: trace Hydrolysis: ~40%
5	Br	 <b>1.124</b>	80% (1:15) Glycal: trace

Reaction conditions: glycosyl bromide (0.24 mmol, 0.19 M in DMF), Ni(COD)<sub>2</sub> (0.024 mmol), *t*-Bu-Terpy (0.036 mmol), and ArZnI·LiCl (~0.5 M in DMF at room temperature for 12 h.

Peracetylated *C*-aryl glycosides **1.120** and **1.121** were obtained in over 70% yield (entries 1 and 2). The method was extended to the formation of furanosyl *C*-aryl glycoside **1.122** with less efficiency. In cases in which the reaction was slow, hydrolysis of the sugar halide to a lactol was observed (entry 4), which accounted for lower yields of perbenzylated **1.123**.

Daves was among the first to apply a Heck-type coupling to the synthesis of *C*-aryl glycosides.<sup>54, 72</sup> Early work with mercuric arenes required the use of stoichiometric palladium,<sup>72</sup> however by employing aryl iodides the reaction could be rendered catalytic (Scheme 1.21).<sup>54</sup> Coupling of glycal **1.125** with aryl iodide **1.126** in the presence of catalytic palladium acetate provided silyl enol ether **1.127**. Treatment of **1.127** with TBAF furnished a ketone, and acylation of the primary alcohol by treatment with Ac<sub>2</sub>O in pyridine furnished **1.128**. This model for the gilvocarcins lacks the C(2)-substituent of the sugar, and some functionality on the aromatic ring.

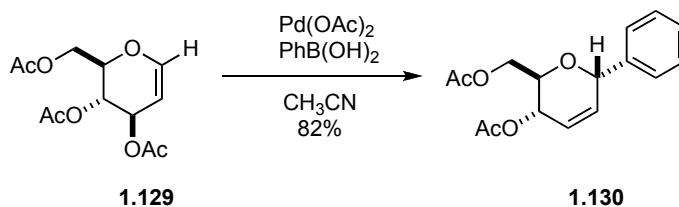
**Scheme 1.21: Heck reaction approach to a gilvocarcin model system**



Maddaford utilized a palladium catalyzed Ferrier rearrangement to access *C*-aryl glycosides (Scheme 1.22).<sup>73</sup> A mixture of glycal **1.129** and phenylboronic acid was treated with palladium acetate. The intermediate  $\pi$ -allyl underwent addition of the boronic acid to give **1.130**. Notably, none of the  $\beta$ -hydride elimination product was

formed under these reaction conditions, which had been reported in palladium catalyzed reactions by Daves with similar glycals.<sup>54</sup>

**Scheme 1.22: Palladium catalyzed Ferrier rearrangement**



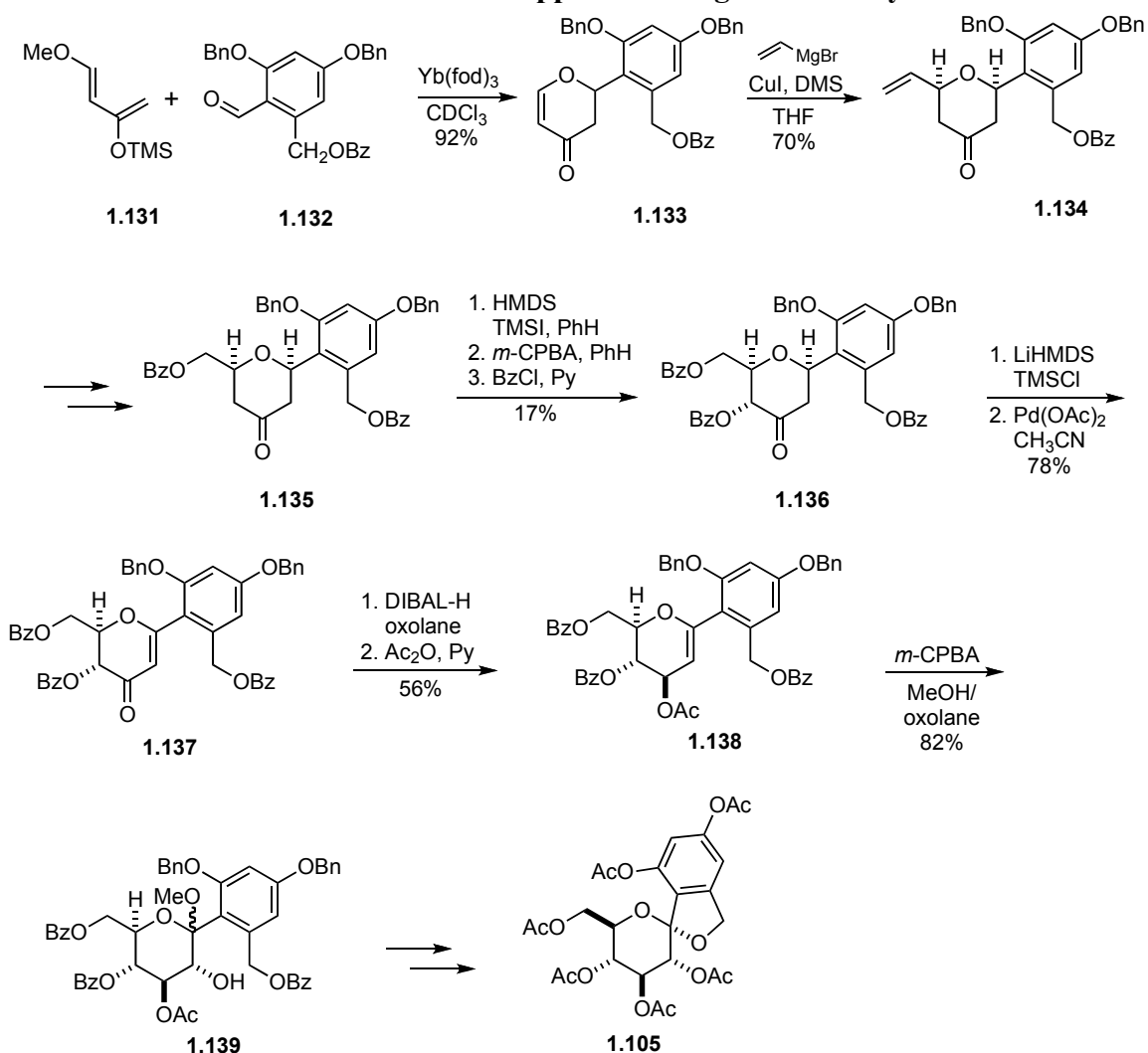
**1.2.4: Approaches involving sugar cyclization**

Some methods to form *C*-aryl glycosides rely on the *de novo* formation of the sugar onto a preformed aromatic ring. A major drawback to many of these approaches is the fact that all of the stereocenters of the sugar must be introduced at a later time. Approaches that involve cleavage and subsequent reformation of the sugar moiety are included in this section as well.

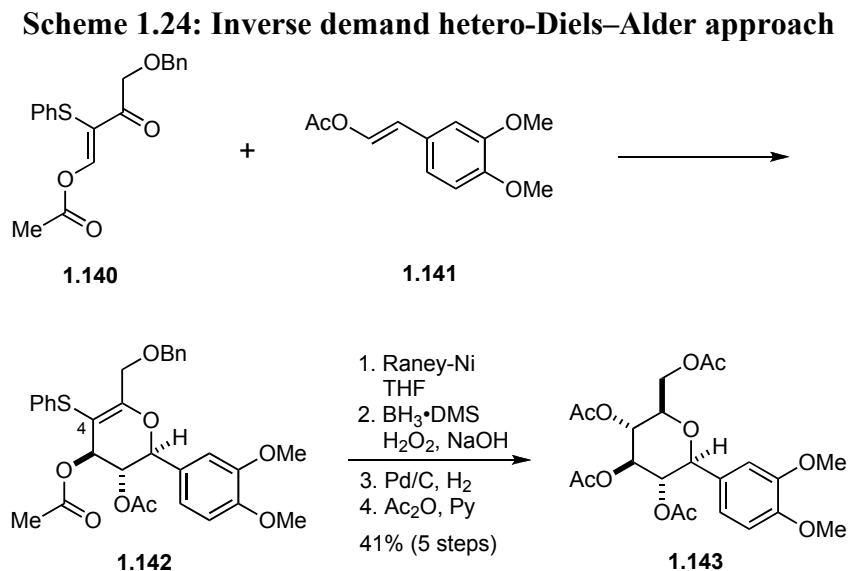
In an approach to the papulacandin skeleton, Danishefsky employed his namesake diene **1.131** in a ytterbium-mediated hetero Diels–Alder reaction with aldehyde **1.132** to form the vinylogous lactone **1.133** (Scheme 1.23).<sup>74</sup> Upon treatment of **1.133** with vinylmagnesium bromide in the presence of CuI and DMS, **1.133** underwent conjugate addition to provide the tetrahydropyrone **1.134**. The alkene moiety was converted to benzoyl ester **1.135** using a multistep sequence that was not well outlined in the publication. Treatment of **1.135** with HMDS and TMSI formed an intermediate silyl enol ether, which underwent stereoselective epoxidation, followed by desilylation and concomitant epoxide opening. Protection of the intermediate alcohol as its benzoyl ester provided **1.136**. Treatment of ketone **1.136** with LiHMDS and TMSCl, followed by

stirring with Pd(OAc)<sub>2</sub> gave enone **1.137**. Treatment of **1.137** with DIBAL-H effected the stereoselective reduction of the ketone to give an alcohol that was subsequently protected as the acetate to give **1.138**. Epoxidation of **1.138** by treatment with *m*-CPBA in methanol resulted in the formation of **1.139**. Methyl acetal **1.139** could be converted to **1.105**, a compound obtained from degradation studies of papulacandin A, in three steps.

**Scheme 1.23: Diels-Alder approach using Danishefsky diene**

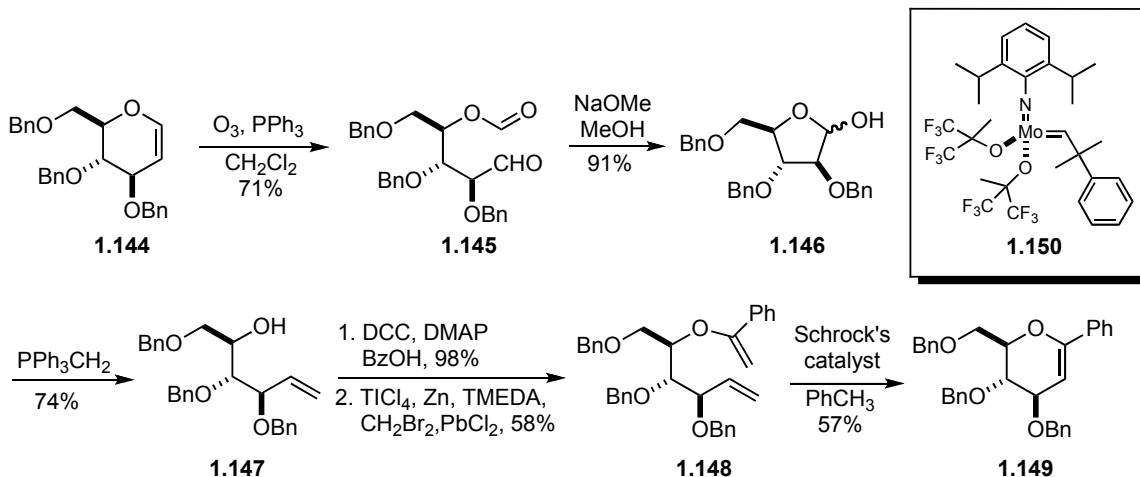


Danishefsky's approach was quite lengthy, highlighting the difficulty of installing many stereocenters onto an unsubstituted pyran ring. In another *de novo* sugar approach, Schmidt used inverse electron demand hetero-Diels–Alder reaction to furnish *C*-aryl glycosides (Scheme 1.24).<sup>75</sup> The elegant feature of this synthesis was the early establishment of the stereocenters on the dihydropyran ring, which set the stage for elaboration of the glycoside to a glucose moiety. Also, the olefin would allow for introduction of the C(4)-substituent. Toward this end, substituted vinyl sulfide **1.140** underwent cycloaddition with styrene **1.141** to provide **1.142**. This reaction set the stereocenters at the anomeric carbon, C(2), and C(3). Desulfurization of **1.142** by treatment with Raney-Ni allowed for regio- and stereoselective hydroboration/oxidation to install the C(4)-hydroxyl group. Debenzylation of the intermediate benzyl ether using palladium on activated carbon, followed by treatment with acetic anhydride in pyridine furnished the *C*-aryl glycoside **1.143**.



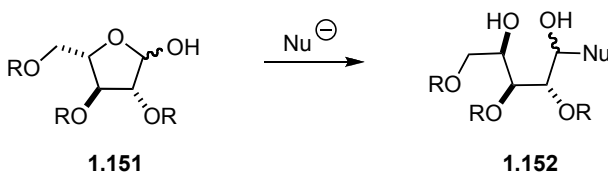
In a ring-closing metathesis approach to *C*-aryl glycosides, Postema utilized glycal **1.144** as a starting material, to benefit from the existing stereochemistry on the sugar moiety (Scheme 1.25).<sup>76</sup> In this approach, the perbenzylated glycal **1.144** was subjected to ozonolysis, and deprotection of the formyl group followed by cyclization provided lactol **1.146**. Wittig reaction on the open form of hemiacetal **1.146** provided alcohol **1.147**. Subsequent oxidation of **1.147**, followed by a modified Takeda olefination gave **1.148**, which underwent ring-closing metathesis when treated with Schrock's catalyst (**1.150**) to provide *C*-aryl glycal **1.149**. Although this approach was much shorter than Danishefsky's, this route suffered from its own setbacks as well. Disadvantages of this sequence were high catalyst loading, which was up to 23%, and the fact that in order to achieve high yields the reaction had to be performed in the glove box. Another major drawback is the length of the synthesis; it takes *six steps* to introduce a phenyl ring onto **1.144**. From this example, it is clear that efficient methods to form *C*-aryl glycols were lacking at this point in time.

**Scheme 1.25: Ring-closing metathesis approach to sugar**

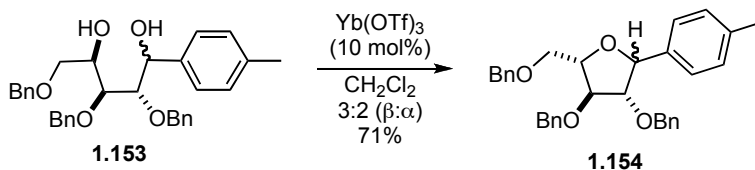


An approach by Sharma and coworkers involved nucleophilic additions to lactols **1.151**, which provided diols **1.152** (Scheme 1.26).<sup>77-79</sup> Nucleophiles utilized in the transformation shown in Scheme 26 ranged from thiophene<sup>78</sup> to substituted phenyl rings.<sup>79</sup> Treatment of diols such as **1.153** with lanthanide Lewis acids, such as ytterbium triflate ( $\text{Yb}(\text{OTf})_3$ ), or iron trichloride ( $\text{FeCl}_3$ ) effected cyclization providing tetrahydrofuran **1.154** (Scheme 1.27).

**Scheme 1.26: Nucleophilic addition to lactols**



**Scheme 1.27: Cyclization of diols to form C-aryl glycosides**

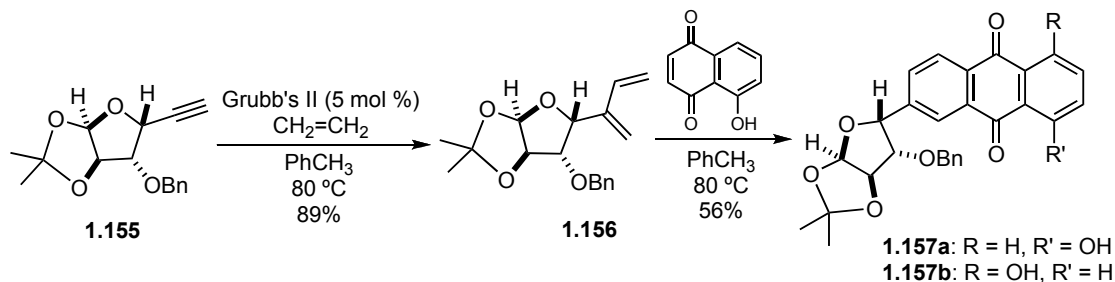


### 1.2.5. C-aryl glycosides via C-glycosides

There have been approaches to C-aryl glycosides that involve the use of an appropriately substituted C-glycoside to construct the aryl moiety. A popular application of this approach involves the use of alkynyl-substituted C-glycosides. For example, Kaliappan used alkynyl substituted pyranose **1.155** in a metathesis approach to C-aryl glycosides (Scheme 1.28).<sup>80</sup> Enyne metathesis of **1.155** under an ethylene atmosphere yielded diene **1.156**. When diene **1.156** was heated with juglone, the Diels–Alder reaction was followed by elimination to provide a mixture of C-aryl glycoside **1.157a** and **1.157b**.

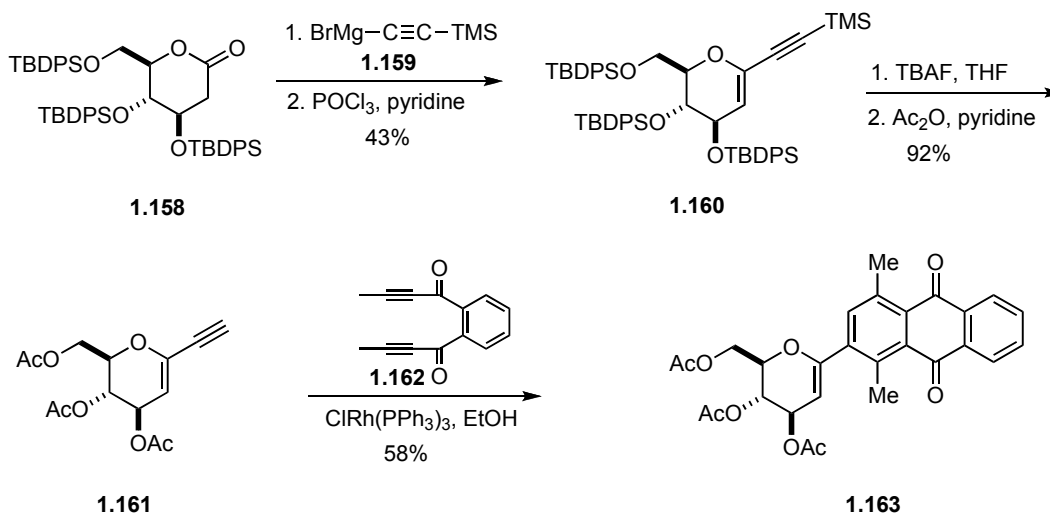


### Scheme 1.28: Cycloaddition of a diene with juglone



McDonald was able to utilize an alkyne to directly access a C-aryl glycoside in a cyclotrimerization reaction (Scheme 1.29).<sup>81</sup> Alkynyl glycal **1.160** was formed by treatment of lactone **1.158** with alkynyl Grignard reagent **1.159**. Alkynyl glycal **1.161** and diyne **1.162** were then treated with  $\text{ClRh}(\text{PPh}_3)_3$  to afford the C-aryl glycal **1.163**.

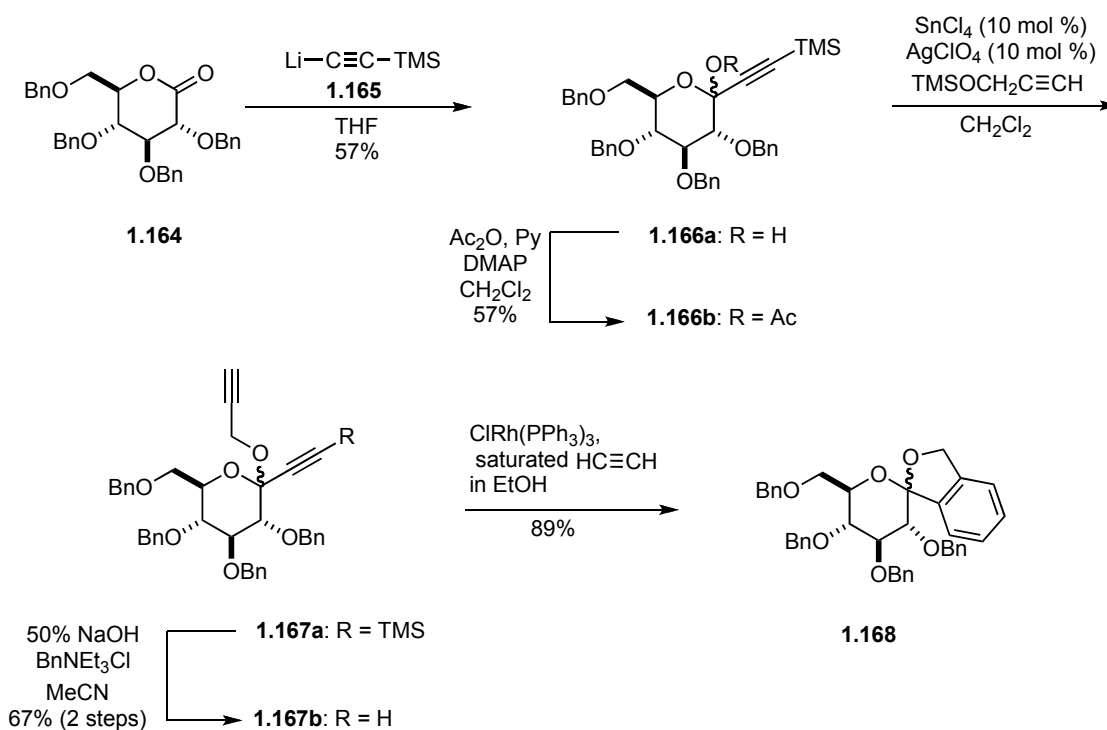
### Scheme 1.29: Cyclotrimerization approach



The cyclotrimerization approach was also used by McDonald to form a spirocyclic C-aryl glycoside (Scheme 1.30).<sup>81</sup> Addition of the lithiated alkyne **1.165** to

lactone **1.164** gave a lactol **1.166a**, which was acylated to provide the anomeric acetates **1.166b**. Lewis acid catalyzed *C*-glycosylation of **1.166b** with silylated propargyl alcohol provided **167a**, which was deprotected to furnish the bis terminal alkyne **1.167b**. Cyclotrimerization provided a mixture of *C*-aryl glycosides **1.168**.

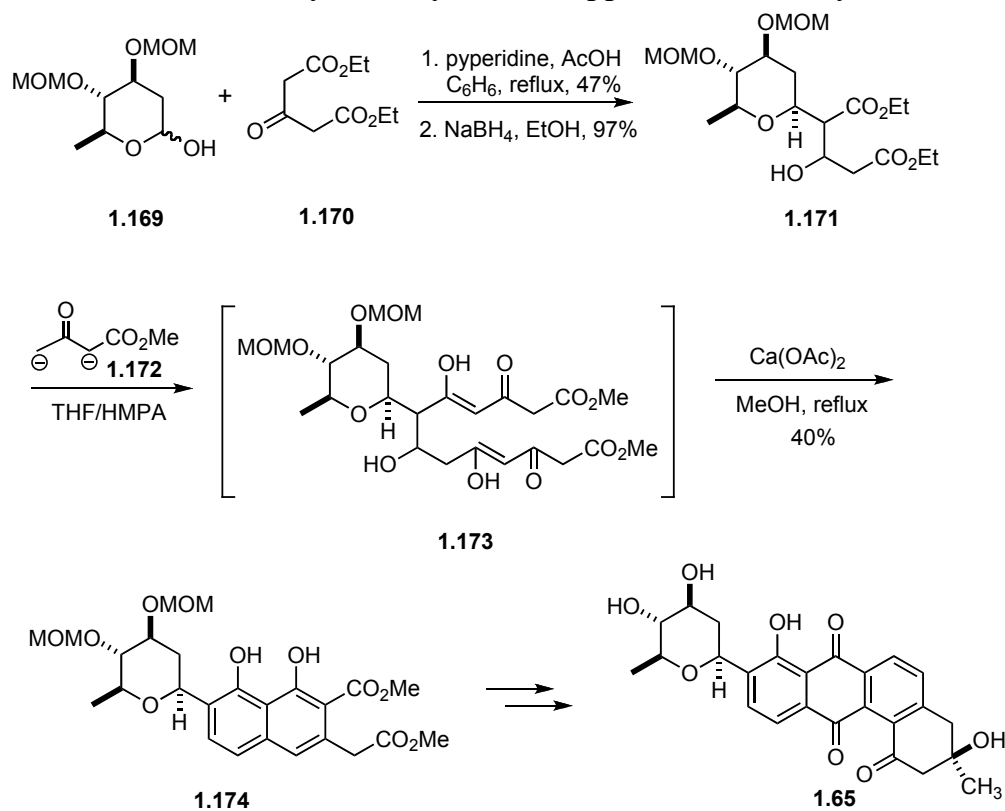
**Scheme 1.30: Spirocyclic *C*-aryl glycosides via cyclotrimerization**



An elegant example of *C*-aryl glycoside formation from a *C*-glycoside was reported by Yamaguchi and coworkers in the total synthesis of urdamycinone (**1.65**) (Scheme 1.31).<sup>82</sup> To set the stage for a polyketide cyclization, the enolate of **1.170** was added into lactone **1.169**, and reduction provided diester **1.171**. Double Claisen condensation of dianion **1.172** with **1.173** provided **1.174**, which underwent

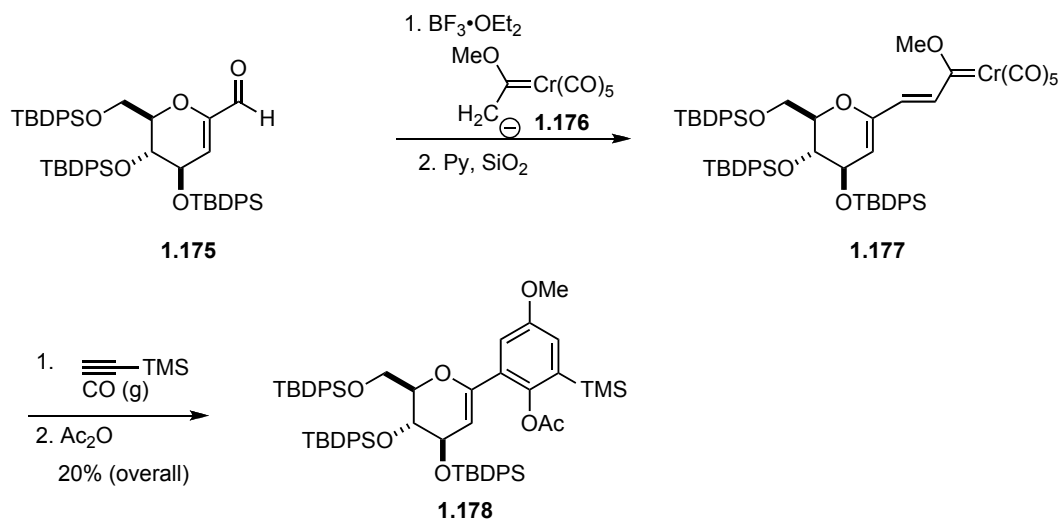
cycloaddition when treated with  $\text{Ca}(\text{OAc})_2$  in refluxing MeOH. Intermediate **1.174** was converted to urdamycinone (**1.65**).

**Scheme 1.31: Polyketide cyclization approach to urdamycinone**



The Dötz reaction has been utilized to access *C*-aryl glycosides as well.<sup>83</sup> Although this is a metal-mediated approach, it also involves the elaboration of a *C*-glycoside to a *C*-aryl glycoside via two complementary approaches (Scheme 1.32). In the first, the anion of the chromium carbene complex **1.176** was added to lactone **1.175**, forming an alcohol, which underwent elimination to provide **1.177**. Treatment of the glycosidic carbene with TMS-acetylene under a carbon monoxide atmosphere formed a phenol, which was acylated to provide *C*-aryl glycoside **1.178**.

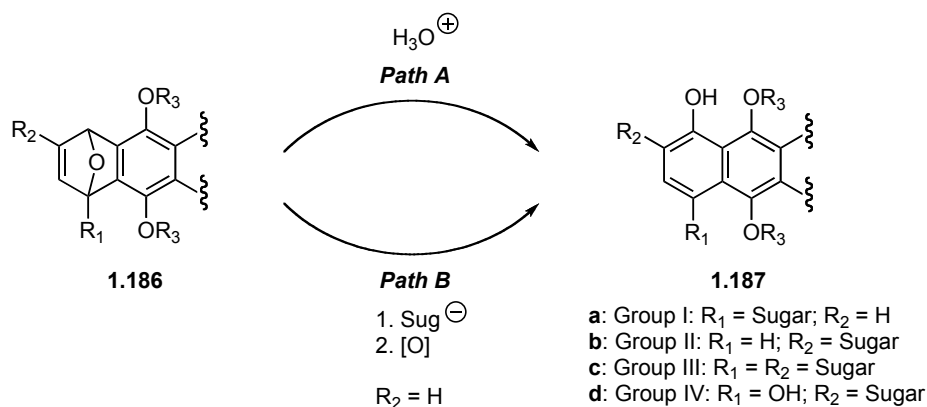
**Scheme 1.32: The Dötz reaction via a C-alkyl carbene**



The complementary approach involved the addition of the Grignard reagent **1.180** to lactone **1.179**, followed by reduction to furnish the glycoside **1.181** or dehydration to provide glycal **1.184** (Scheme 1.33). When **1.181** or **1.184** was treated with carbene **1.182**, both sugars underwent Dötz reaction to provide C-aryl glycoside **1.183** or C-aryl glycal **1.185**, respectively.

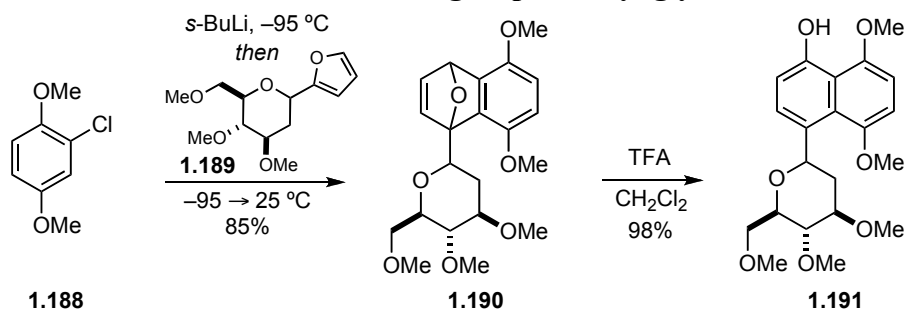


### Scheme 1.34: The unified approach to C-aryl glycosides



The synthesis of a model for Group I C-aryl glycosides was achieved via the cycloaddition of the benzyne generated from 2-chloro-1,4-dimethoxybenzene (**1.188**) with furan **1.189** (Scheme 1.35). Acid-catalyzed ring opening of the resultant cycloadduct **1.190** using TFA provided C-aryl glycoside **1.191** in excellent yield.

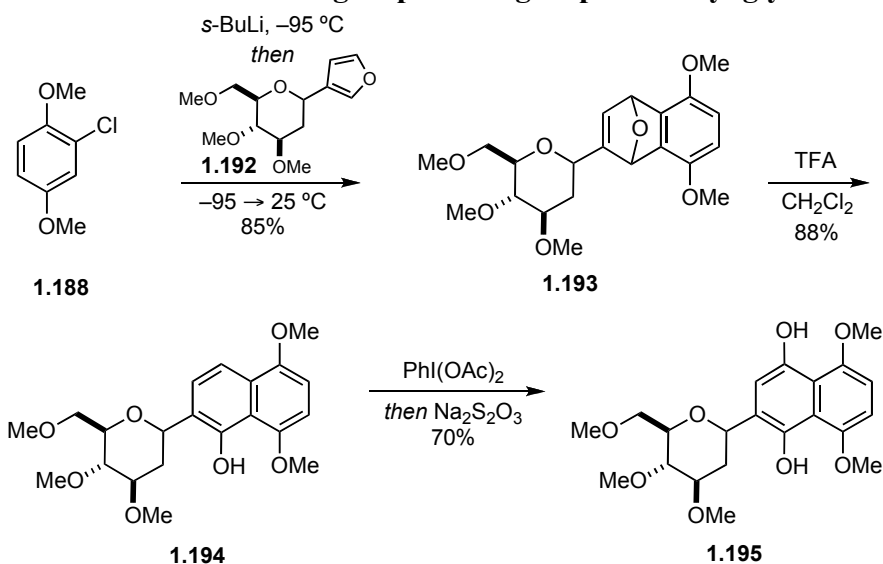
### Scheme 1.35: Access to group I C-aryl glycosides



Compounds representing Group II and IV C-aryl glycosides were accessed in a similar fashion (Scheme 1.36). Cycloaddition of the benzyne generated from 2-chloro-1,4-dimethoxybenzene with the C(3)-substituted furan **1.192** provided oxabicyclo **1.193**, which underwent ring opening when treated with acid to give **1.194**, which is a Group II

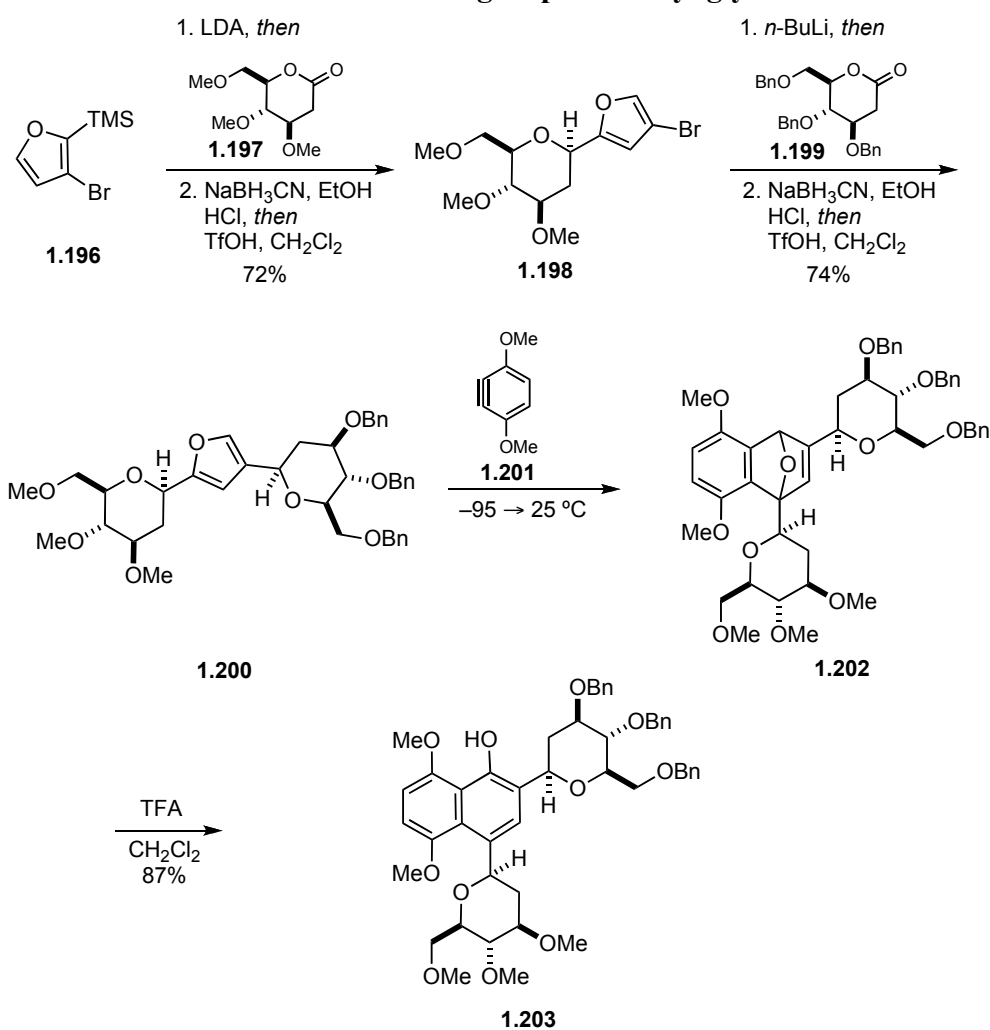
C-aryl glycoside. Oxidation of **1.194** to the quinone using iodosobenzene diacetate, followed by reduction to the hydroquinone furnished **1.195**, a Group IV C-aryl glycoside.

**Scheme 1.36: Access to group II and group IV C-aryl glycosides**



Glycosides that serve as models for Group III C-aryl glycosides were then accessed via the acid-catalyzed ring-opening of oxabicycles (Scheme 1.37). Successive additions of furyl anions to sugar lactones **1.197** and **1.199** gave disubstituted furan **1.200**. The furan **1.200** underwent cycloaddition with benzyne **1.201**, which was generated from 2-chloro-1,4-dimethoxybenzene. The resultant bis-glycoside **1.202** was subjected to acid-catalyzed ring opening to give C-aryl glycoside **1.203**.

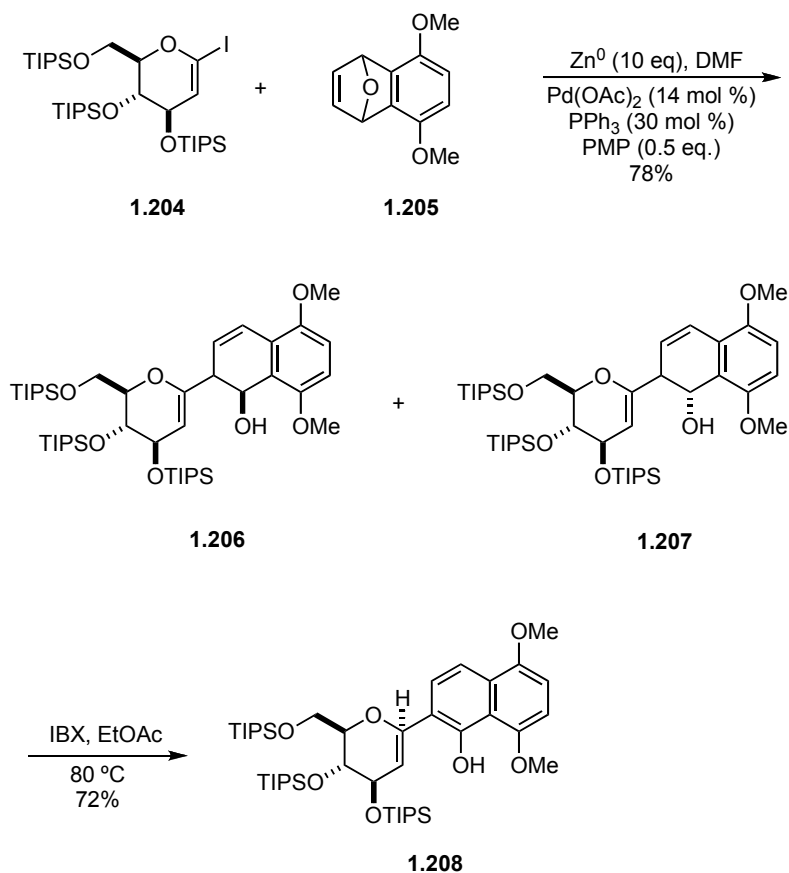
### Scheme 1.37: Access to group III C-aryl glycosides



An alternative approach to access Group II and III was developed as well. In this method, the S<sub>N</sub>2' ring opening of oxabicyclic **1.205** via a sugar nucleophile was employed (Schemes 1.38 and 1.39). Palladium-catalyzed coupling of iodide **1.204** and oxabicyclic **1.205** to give a mixture (4:1) of alcohols **1.206** and **1.207**, oxidation of which provided C-aryl glycol **1.208**.<sup>86</sup>

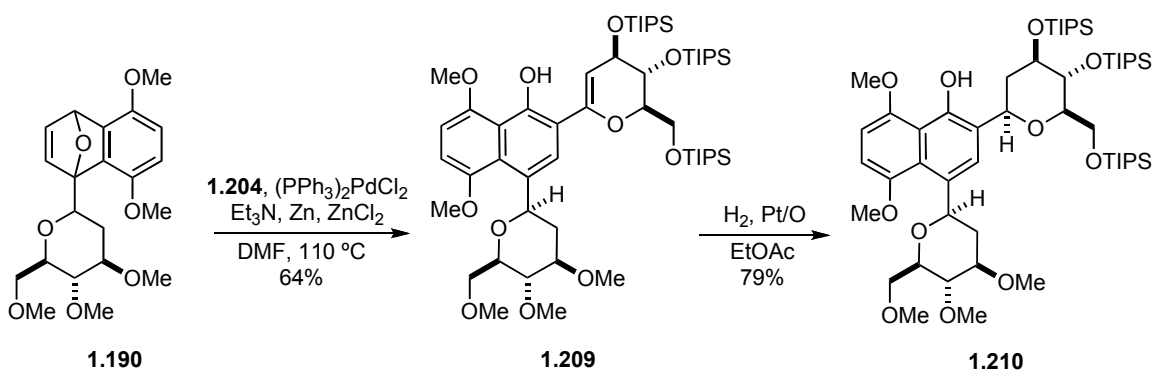


**Scheme 1.38: Access to group II C-aryl glycosides ( $S_N2'$  approach)**



An efficient synthesis of Group III C-aryl glycosides was developed via a similar approach.<sup>84</sup> In this process, sugar nucleophile **1.204** was used to open oxabicyclic **1.190** in an  $S_N2'$  fashion (Scheme 1.39). Simple reduction of glycal **1.209** allowed access to glycoside **1.210**.

### Scheme 1.39: Access to group III C-aryl glycosides ( $S_N2'$ approach)



#### 1.3.2. Regioselective benzyne cycloadditions using a silicon tether

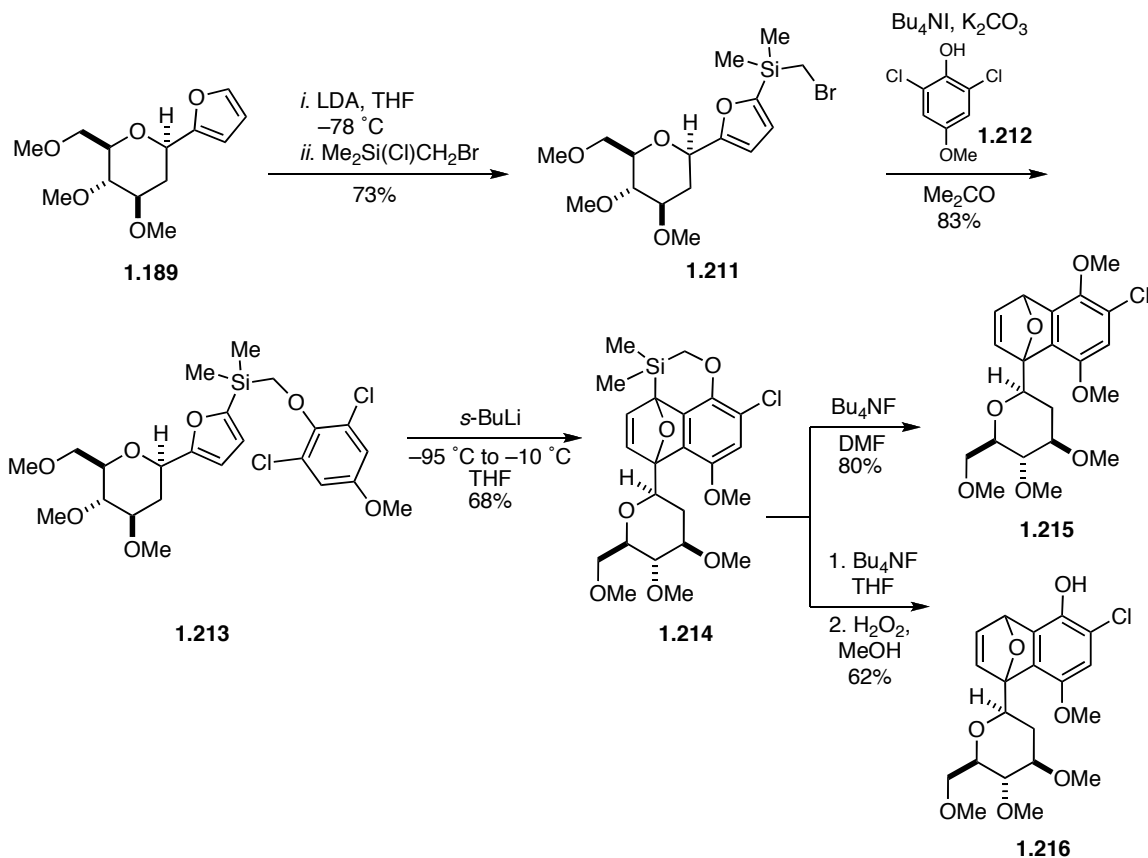
In order to synthesize simple C-aryl glycosides, 2-chloro-1,4-dimethoxybenzene (**3**) was invariably used as the benzyne precursor. Because a symmetrical benzyne was generated, the regiochemistry of the [4+2] cycloaddition was therefore not an issue with these systems. However, in the context of natural product synthesis, C-aryl glycosides often contain unsymmetrically-substituted ring systems. Suzuki has addressed the regioselectivity problem by using systems that are electronically tuned to undergo regioselective cycloadditions based on substrate control alone (Section 1.2.1). *How is regioselectivity to be invoked in a system that is not electronically modified to undergo a regioselective cycloaddition?* The Martin group elegantly addressed this question by developing a method that utilizes silicon tethers<sup>87</sup> to control the regioselectivity of the cycloaddition, but then can be readily cleaved.

Two approaches were established,<sup>88, 89</sup> which utilized tethers of varying length. To create the system with a silicon linker that contained one carbon atom, which will be referred to as the “one-carbon tether,” furan **1.189** was treated with LDA, and the resultant anion was trapped with bromomethyl chlorodimethylsilane to provide silane

**1.211** (Scheme 1.40). Williamson etherification<sup>90</sup> of **1.211** with phenol **1.212** provided ether **1.213** in 83% yield. When performing the Williamson etherification with the one-carbon tether, attack at the silicon atom can be problematic *vide infra*.<sup>91,92</sup>

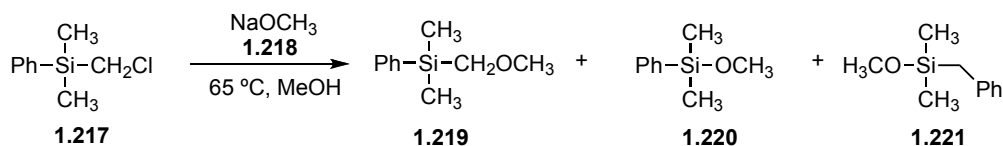
When ether **1.213** was treated with *s*-BuLi, adduct **1.214** was formed in 68% yield. The tether could now be cleaved to provide one of two products. If TBAF in DMF was used, both carbon–silicon bonds were cleaved to provide methyl ether **1.215**. If a free phenol was the target, a two-step sequence was employed where adduct **1.214** was treated with TBAF in THF to give a silanol that was subsequently oxidized to provide phenol **1.216**.

#### Scheme 1.40: The one-carbon tether approach



The major side reaction that occurred during the etherification reaction of **1.217** was attack at the silicon atom (Scheme 1.41).<sup>91, 92</sup> When silane **1.217** was treated with sodium methoxide (**1.218**), **1.219** was obtained, along with a small amount **1.220**, which arose from the attack at the silicon atom. In dioxane, attack at the silicon atom increased, and the rearranged product **1.221** was the major product. Formation of **1.221** involved initial attack at the silicon atom followed by migration of a methyl group. The authors hypothesized this was a solvation effect; the more “naked” nucleophile attacked at the silicon atom more readily. In a separate study, they discovered that using KOMe or CsOMe as nucleophiles also resulted in increased attack at the silicon atom, supporting their “naked” anion hypothesis. In some cases with the one-carbon tether, attack at the silicon atom was problematic, and careful selection of bases and solvent was required for optimization. With this initial one-carbon tether model system (Scheme 1.40), it was found that K<sub>2</sub>CO<sub>3</sub> in acetone was sufficient for minimal attack at silicon.<sup>88</sup>

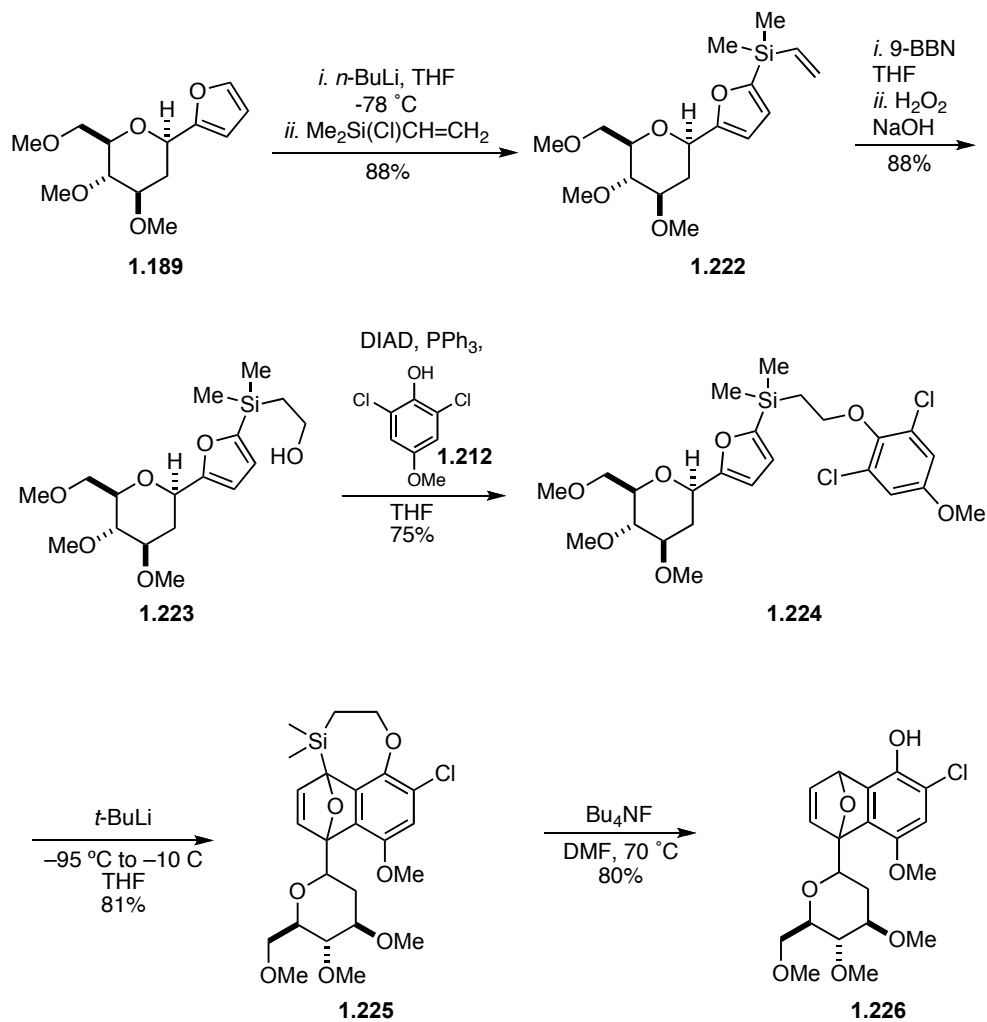
**Scheme 1.41: Nucleophilic attack at either C or Si**



solvent	time (h)	yields		
		<b>1.219</b>	<b>1.220</b>	<b>1.221</b>
MeOH	19	98	0.5	0
Dioxane	7	1	6	>80

In addition to the one-carbon tether, a two-carbon silicon linker was also developed, which will be referred to as the “two-carbon tether.” Treatment of the anion generated by the lithiation of furan **1.189** with chlorodimethylvinylsilane gave **1.222**, which was converted into alcohol **1.223** by hydroboration-oxidation (Scheme 1.42). The issues associated with the Williamson etherification could be avoided with the two-carbon tether. Because an alcohol was formed, a Mitsunobu etherification<sup>93</sup> could be used to link **1.223** with phenol **1.212**, affording **1.224** in 75% yield. Using these “more neutral” conditions there was no attack at the silicon atom observed. When ether **1.224** was treated with *t*-BuLi, adduct **1.225** was obtained in 81% yield. Cleavage of the tether using TBAF in DMF afforded oxabicyclic **1.226**. Perhaps noteworthy is that this cycloaddition was slightly more efficient than that leading to **1.214**.

### Scheme 1.42: The two-carbon tether

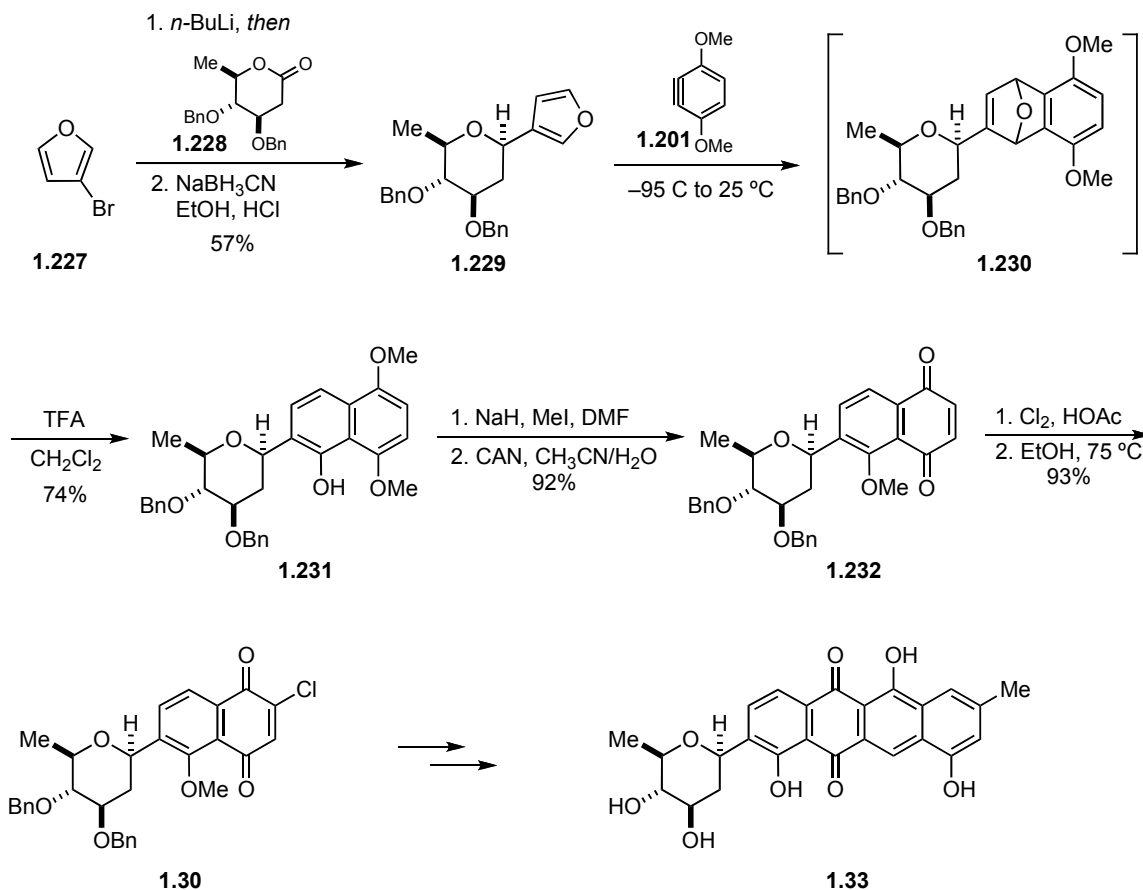


### 1.3.3. The unified approach in synthesis

In order to demonstrate the utility of the methodology, a formal synthesis of galtamycinone, which belongs to the Group II family of *C*-aryl glycosides, was achieved (Scheme 1.43).<sup>94</sup> Thus, 3-bromofuran (**1.227**) was lithiated, and the resultant anion was added to lactone **1.228** to provide glycosyl furan **1.229**. Cycloaddition of **1.229** with benzyne **1.201**, which was generated by lithiation of 2-chloro-1,4-dimethoxybenzene,

provided oxabicyclic **1.230**. Adduct **1.230** was not purified, but rather the crude mixture was subjected to ring opening to give phenol **1.231** in 74% yield over two steps. Protection of phenol **1.231** and oxidation of the aromatic ring to the quinone furnished **1.232**, which was converted to chloroquinone **1.30** by sequential chlorination and elimination. This constituted a formal synthesis of galtamycinone, as Suzuki had formerly converted chloride **1.30** into galtamycinone (**1.33**) as previously discussed (Section 1.2.1, Scheme 1.5).<sup>40,41</sup>

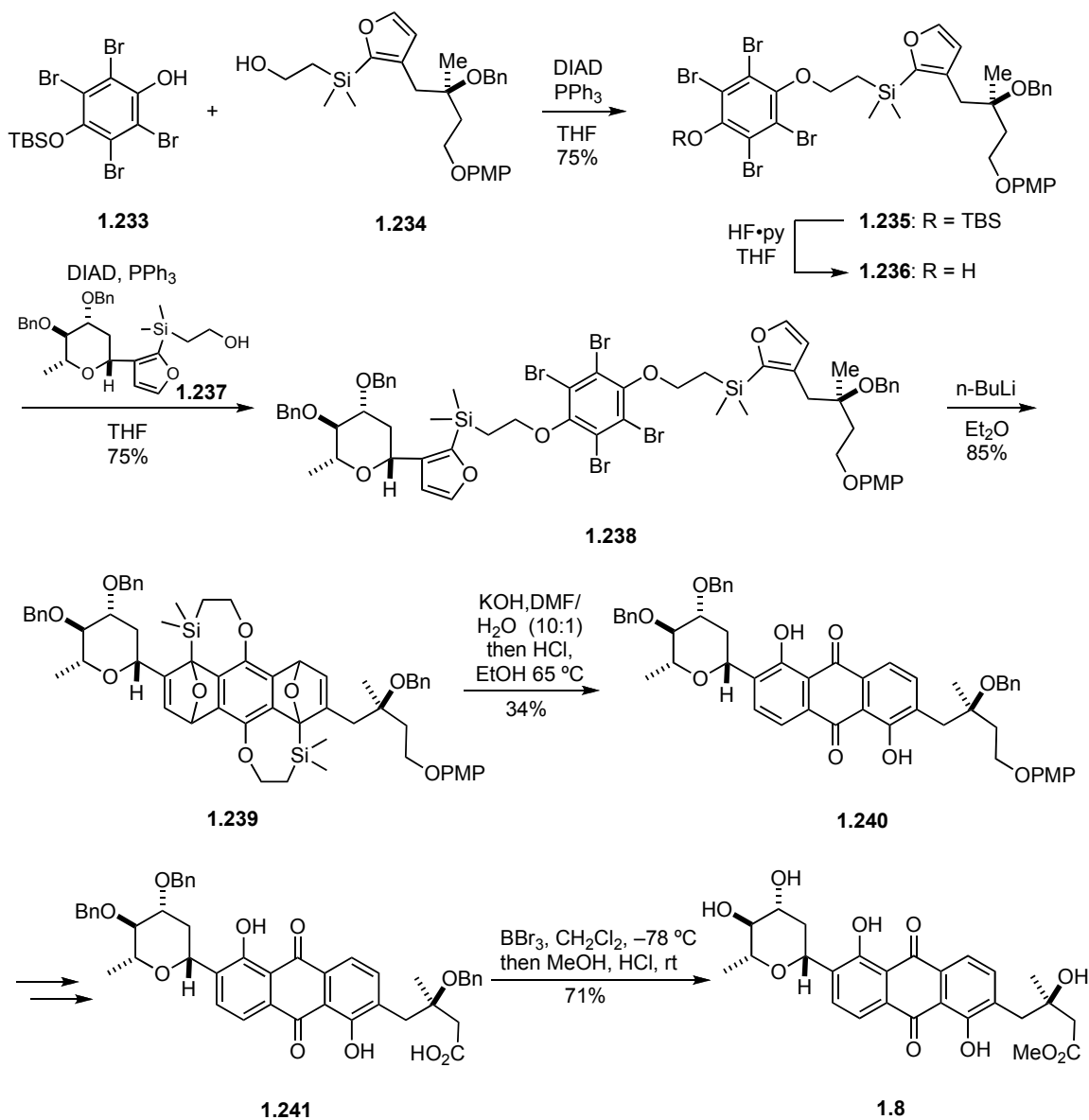
**Scheme 1.43: The formal synthesis of galtamycinone**



The total synthesis of vineomycinone B<sub>2</sub> methyl ester (**1.8**) was achieved using a two-carbon tether,<sup>10, 11</sup> representing the first total syntheses of a C-aryl glycoside natural product using the Martin group's tether approach (Scheme 1.44). The first furan unit **1.234** was installed onto **1.233** via Mitsunobu etherification, and then selective removal of the TBS group of ether **1.235** provided phenol **1.236**. A second Mitsunobu etherification was used to install the glycosyl furan moiety **1.237** to provide the bis ether **1.238**. A double benzyne-furan cycloaddition of **1.238** provided adduct **1.239**. In this synthesis, the tether was not cleaved with a fluoride source, but rather treatment with base to afford an intermediate silanol, which was treated with acid to provide the quinone **1.240**. Removal of the PMP group, followed by oxidation of the resultant alcohol to the acid provided **1.241**. Global debenylation was effected by treatment with BBr<sub>3</sub>, and subsequent methanolysis provided vineomycinone B<sub>2</sub> methyl ester (**1.8**).



### Scheme 1.44: The synthesis of vineomycinone B<sub>2</sub> methyl ester



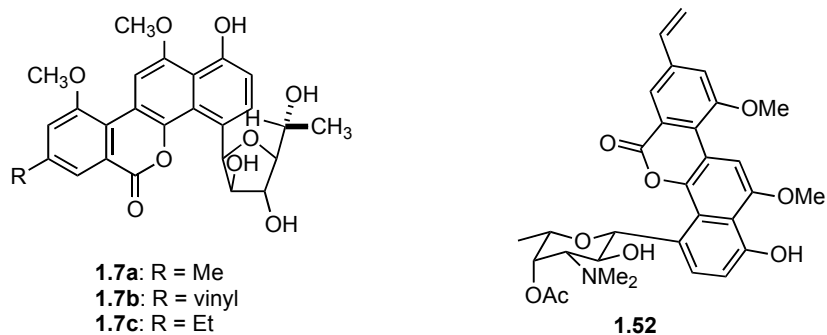
## 1.4. C(2)-OXYGENATED C-ARYL GLYCOSIDES

### 1.4.1. Biologically important 2-oxygenated C-aryl glycosides

Although less abundant, C-aryl glycosides containing (C)2-oxygenated sugar moieties are also important. (C)2-Oxygenated C-aryl glycosides exhibit antiproliferic

activity against human promyelocytic leukemia cell line (HL60).<sup>1</sup> The previously discussed examples of C(2)-oxygenated C-aryl glycosides also exhibit biological activity. Recall that the gilvocarcins **1.7a–c**, which contain 2-oxygenated fucose sugar moieties, exhibit antimicrobial and antitumor activity (Figure 1.5). A C-aryl glycoside related to the gilvocarcins, ravidomycin (**1.52**) also exhibits biological activity (Figure). Isolated from *Streptomyces ravidus* culture broth, ravidomycin exhibits antibacterial activity against gram-positive organisms in addition to potent antitumor activity. The ravidomycin aglycone is identical to that of the gilvocarcin V, and the synthesis of ravidomycin was also achieved by Suzuki, via another application of his regioselective benzyne cycloaddition methodology (Section 1.2.1, Scheme 1.8).<sup>45,46</sup>

**Figure 1.5: C-Aryl glycosides containing a C(2)-hydroxyl group**



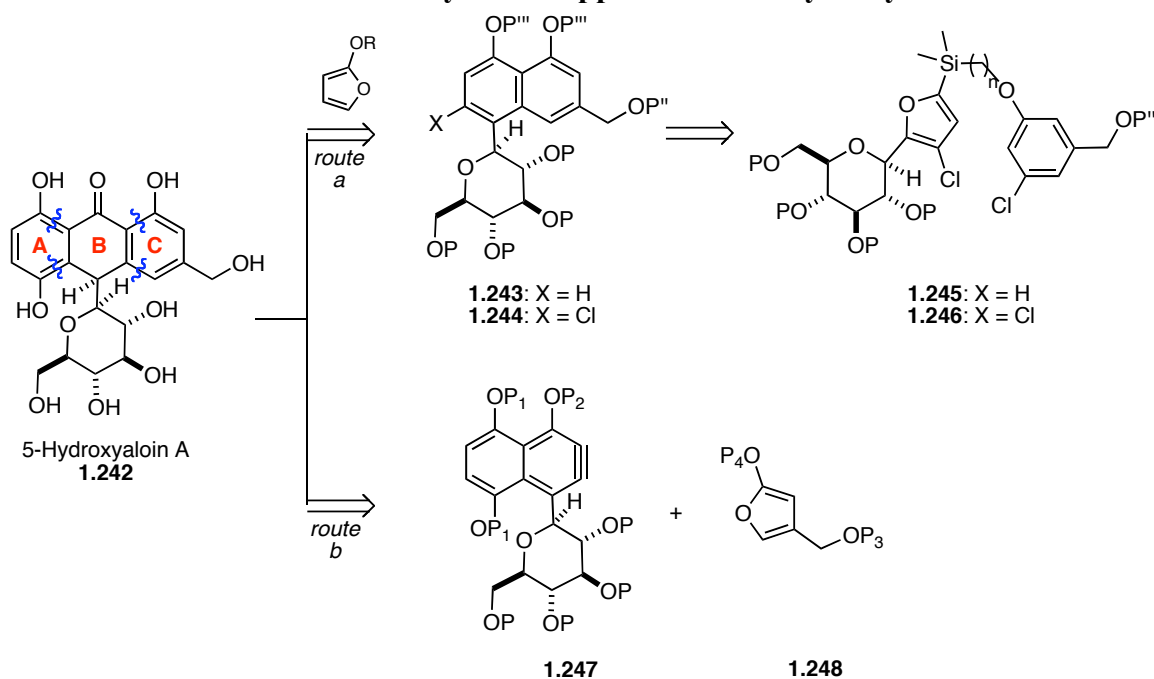
5-Hydroxyaloin A (**1.243**) is a C(2)-oxygenated anthrone C-glycoside that can be envisioned as synthetically coming from a group I C-aryl glycoside (Scheme 1.45). The biological activity of aloins will be discussed in Section 3.1.

### 1.4.2. Previous studies toward the total synthesis of 5-hydroxyaloin A

5-Hydroxyaloin A was selected as a synthetic target for several reasons. Until this point, all target molecules pursued in the Martin group had been C(2)-deoxygenated sugars, and we wished to explore the application of our method to C(2)-oxygenated sugars, and 5-hydroxyaloin A was a suitable target. In addition, the unsymmetrically substituted C ring of 5-hydroxyaloin A would allow us to again apply our silicon tether methodology.

When Dr. Li began his analysis of 5-hydroxyaloin A (**1.242**), he envisioned two approaches to the molecule (Scheme 1.45).<sup>95</sup> The first of these is via *route a*, in which the hydroquinone, ring A, is formed last. This approach would involve a benzyne–furan cycloaddition of the naphthyne generated from either glycoside **1.243** or **1.244** and a substituted furan. The C ring in this route would be constructed by an intramolecular cycloaddition of silane **1.245** or **1.246** using a one- or two-carbon tether. The alternative *route b* would involve formation of the C ring last, where a substrate-controlled head-to-head naphthyne cycloaddition would be implemented in the endgame (Section 1.2.1, Scheme 1.6), between naphthyne **1.247** and furan **1.248**. The resultant cycloadduct would contain an additional oxygen atom relative to the natural product, thus this approach would involve a late stage deoxygenation.

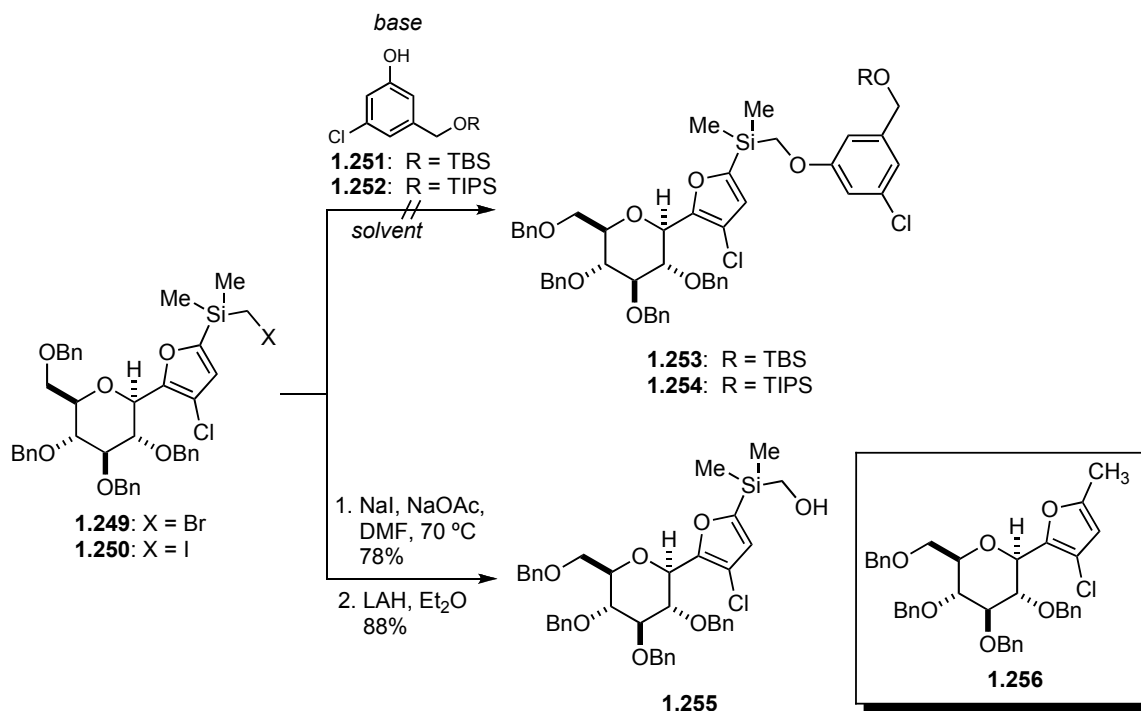
### Scheme 1.45: Retrosynthetic approaches to 5-hydroxyaloin A



#### 1.4.2.1. Tether to control regioselectivity

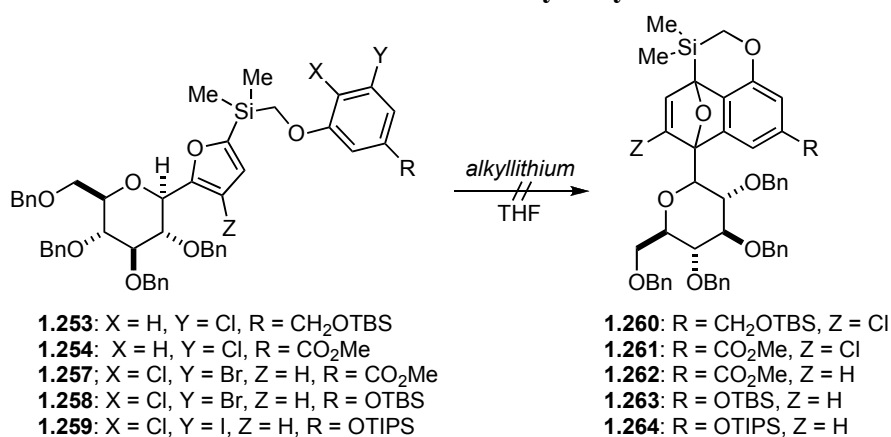
Li first attempted to use a one carbon tether as a means to control the regiochemistry of the first cycloaddition, according to *route a* (Scheme 1.46). Li had considerable difficulty implementing the Williamson etherification. An assortment of bases and solvents were explored for the etherification reaction of iodide **1.250**. However, ethers **1.253** or **1.254** were never isolated from the reaction mixture, and only the rearrangement product **1.256**, which resulted from attack at the silicon atom, was observed.

### Scheme 1.46: Difficulties with the Williamson etherification



Because of these difficulties, Li investigated the Mitsunobu etherification as well. To explore this route, bromide **1.249** was converted to alcohol **1.255**. Alcohol **1.255** did allow access to ethers **1.253** and **1.254**. However, when these ethers were treated with *s*-BuLi, cycloadducts **1.260** and **1.261** were not obtained (Scheme 1.47). Instead, significant cleavage of the tether was observed, presumably from direct attack of *s*-butyllithium at the silicon atom. Also complicating this reaction was the loss of chloride from the furan, presumably due to metal-halogen exchange and protonation upon workup. Although metal-halogen exchange with chlorine is usually a slow process, it was clearly competing with deprotonation under these reaction conditions.

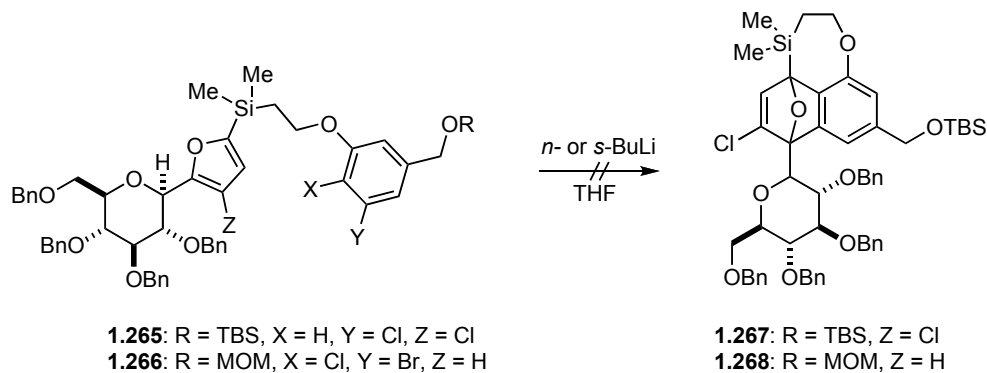
### Scheme 1.47: Unsuccessful benzyne cycloadditions



Dr. Li thus switched to a substrate lacking a chlorine substituent on the furan. Although he was able to form **1.257–1.259** via Mitsunobu etherifications, he was unable to effect the cycloadditions to access cycloadducts **1.262–1.263** upon treatment of **1.257–1.259** with *n*-BuLi. Again, products resulting from alkyllithium attack at the silicon atom were observed.

Dr. Li also investigated the use of a two-carbon tether. Namely, the intramolecular cycloaddition of the benzyne generated from **1.265** was attempted, but cycloadduct **1.267** was not obtained (Scheme 1.48). Cleavage of the silicon tether was again observed based upon the <sup>1</sup>H NMR spectrum of the crude mixture, and the reaction was further complicated by loss of the chlorine atom from the furan ring. A dihaloarene benzyne precursor **1.266** was also synthesized using the two-carbon tether. Unfortunately, treating ether **1.266** with *n*-BuLi only resulted in an intractable mixture, and cycloadduct **1.268** was not isolated. Problematic side reactions, including tether cleavage, caused Li to reexamine the route, and he chose to investigate systems that could potentially undergo regioselective benzyne cycloadditions based on electronic effects.

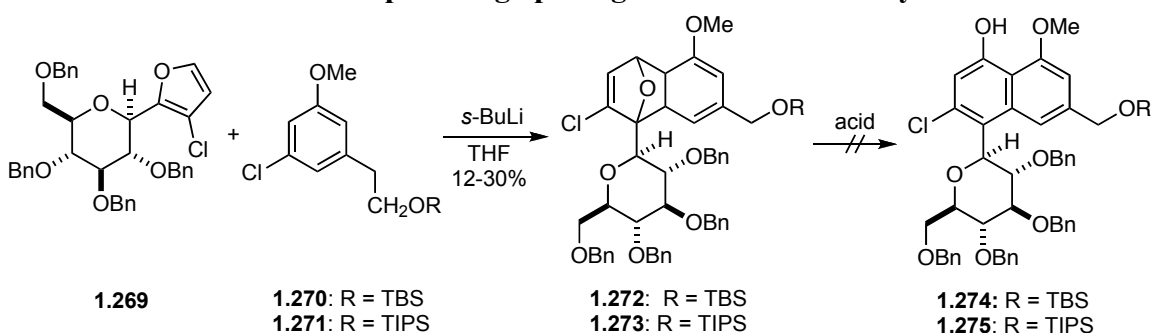
### Scheme 1.48: Attempted cycloaddition of a monohalide using the two-carbon tether



#### 1.4.2.2. Bimolecular cycloadditions

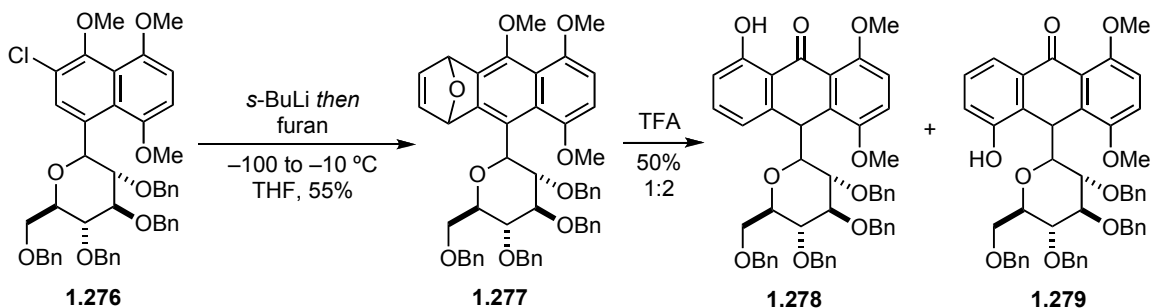
Li began to investigate bimolecular cycloadditions as a method to form the C ring of 5-hydroxyaloin A. Given the precedent for electronically-driven, regioselective benzyne cycloadditions of Suzuki, Li attempted the cycloaddition of chlorofuran **1.269** with benzyne generated from **1.270** and **1.271** (Scheme 1.49). From these reactions, Li reported the isolation of only one regioisomeric cycloadduct, although due to the low yield it is not certain that this was the only regioisomer formed. Regardless, attempts to achieve the ring opening of **1.272** and **1.273** with various Lewis and Brønsted acids failed; the cycloadducts were extremely resistant to ring opening. When stronger Lewis acids such as TMSOTf were employed, cleavage of the sugar from the aglycone was observed, and phenols **1.274** and **1.275** were not formed.

### Scheme 1.49: Attempted ring opening of the chlorinated cycloadduct



As 2-chloro-1,4-dimethoxybenzene (**1.188**) readily underwent benzyne generation when deprotonated, Dr. Li sought to develop a route to the tricyclic core of hydroxyaloin A building the hydroquinone ring first (Cf. Scheme 1.44, *route b*). Li was able to synthesize chloronaphthalene **1.276**. Generation of a naphthyne from chloride **1.276** with *s*-BuLi was successful, and Dr. Li was able to obtain a 55% yield of diastereomeric cycloadducts **1.277** (Scheme 1.50). When cycloadducts **1.277** were treated with TFA, a mixture of anthrones **1.278** and **1.279** was obtained. This experiment provided critical precedent that these chloronaphthalenes could be directly deprotonated to generate naphthynes.

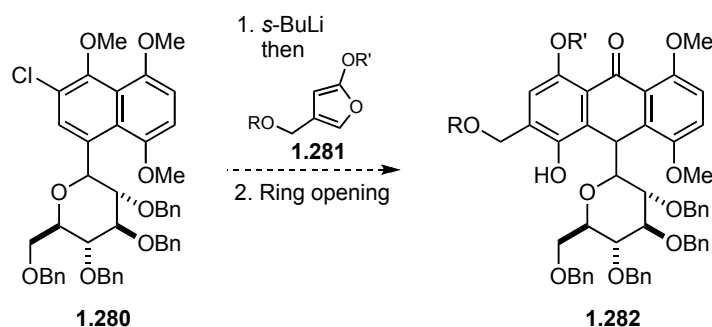
### Scheme 1.50: Formation of an anthrone





Having successfully formed the anthrone core, Dr. Li performed some model studies to see if a late stage dehydration or deoxygenation would be possible, since construction of the unsymmetrical ring via a cycloaddition of **1.280** with a substituted furan **1.281** would yield a product with an additional oxygen atom (Scheme 1.51). He tried to effect such transformations with a variety of model substrates, however all attempts to deoxygenate were ultimately unsuccessful.

**Scheme 1.51: Proposed formation of a substrate requiring deoxygenation**

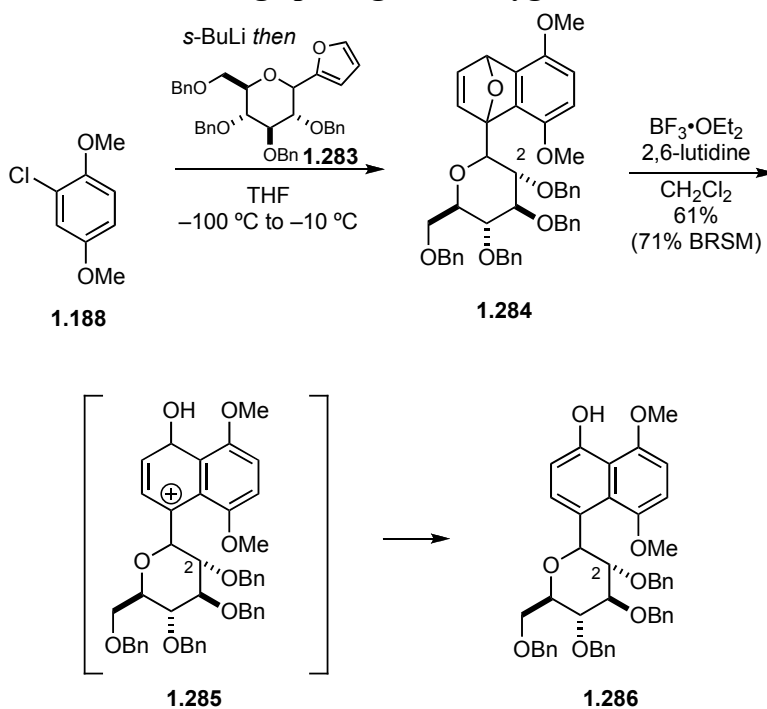


### 1.4.3. 2-Oxygenated glycosides vs. 2-deoxygenated glycosides

The acid-catalyzed ring opening of oxabicycles to provide C-aryl glycosides had proceeded smoothly in prior work in the group (Section 1.3.1). The C(2)-deoxygenated cycloadduct **1.190** underwent ring-opening upon treatment with TFA at room temperature for several days (Scheme 1.34).<sup>84</sup> Li's 2-oxygenated cycloadducts such as **1.284** rearranged under these conditions to form naphthol **1.286** in only moderate yield (Scheme 1.52).<sup>95</sup> Dr. Li hypothesized that a glycol might allow for a smoother entry into naphthols, reasoning that it may be the electron-withdrawing C(2)-substituent of cycloadducts **1.284** that was destabilizing the formation of the requisite carbocation in

intermediate **1.285** when these adducts were treated with acid, which in turn resulted in low yields of **1.286**.

**Scheme 1.52: Ring opening of a 2-oxygenated substrate**

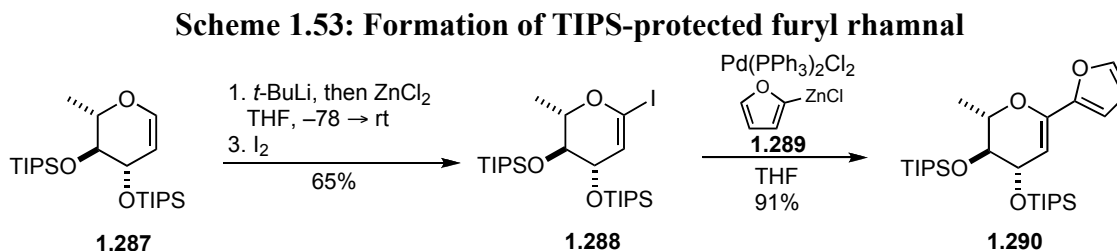


Such a destabilizing effect might have contributed not only to lower yields of naphthol **1.286** relative to those for forming naphthol **1.191**, but also the more forcing conditions required for the opening of C(2)-oxygenated substrates. An additional pitfall was that the cycloadditions that formed oxabicycles such as **1.284** proceeded in slightly lower yield in substrates with a C(2)-substituent. Li's hypothesis prompted him to consider an approach that utilized glycals. Glycals lack an electron withdrawing C(2)-substituent but the double bond could provide a functional handle for introducing various

functionality at C(2). For example, a C(2)-oxygenated glycoside could potentially be accessed from a glycal via hydroboration-oxidation.

#### 1.4.4. Attempted hydroboration of TIPS-protected glycals

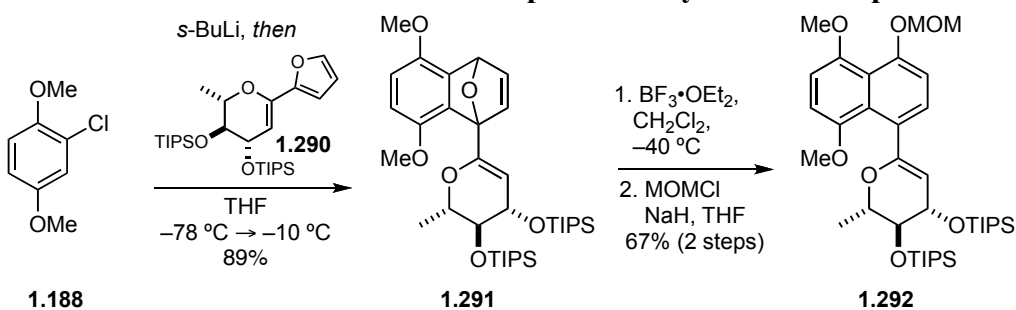
Preliminary investigations into the hydroboration and oxidation of C-aryl glycals were initiated by J. Gabrielle Kolakowski.<sup>96</sup> TIPS-protected glucal **1.287** was lithiated and transmetalated to its zincate, which was treated with I<sub>2</sub> to give unstable iodoglycal **1.288** (Scheme 1.53). Compound **1.288** underwent Negishi coupling with 2-furylzinc chloride (**1.289**), to provide furyl glycal **1.290** in 91% yield. A major complication to this approach is the instability of iodoglycal **1.288**, which was extremely difficult to work with as this glycal had to be stored under vacuum and used immediately in the coupling reaction.



The [4+2] cycloaddition reaction of furan **1.290** with the benzyne generated from **1.188** gave cycloadduct **1.291** in good yield (Scheme 1.54). As Dr. Li had expected, the ring opening did proceed more efficiently with this substrate. While many of the glycosides previously investigated opened with protic acid at room temperature over the course of days, these glycals opened readily at low temperature with Lewis acid. The intermediate naphthol was isolated and protected to provide naphthalene **1.292** in 67%

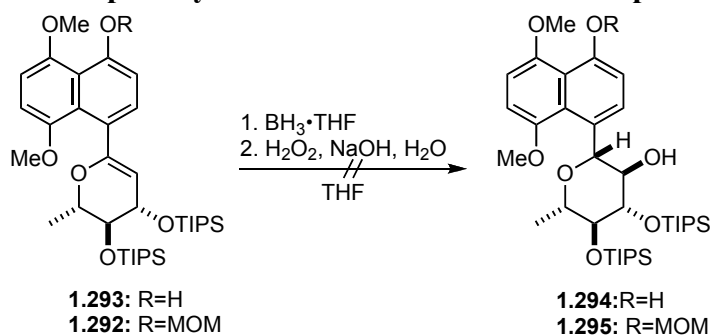
yield over two steps, thereby setting the stage for the investigation of the hydroboration step.

**Scheme 1.54: Formation of the TIPS-protected hydroboration precursor**



Kolakowski attempted to hydroborate both the free phenol **1.293** and naphthalene **1.292** (Scheme 1.55). Unfortunately, these rhamnals did not undergo hydroboration-oxidation, and prolonged reaction times only resulted in substrate decomposition. Because she hypothesized that the bulky TIPS group was hindering the hydroboration step, she decided to introduce a smaller protecting group onto the sugar.

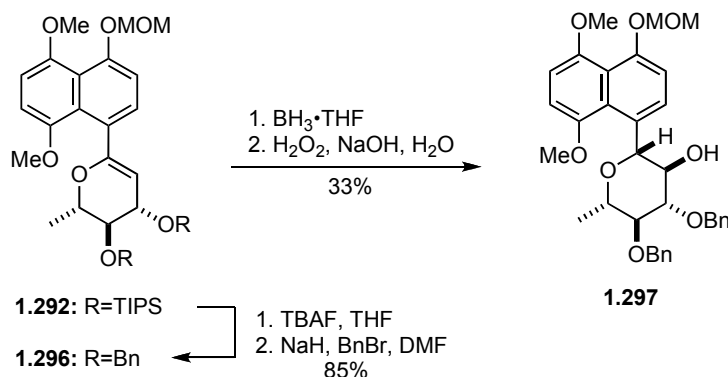
**Scheme 1.55: Attempted hydroboration oxidation of TIPS protected rhamnol**



Toward this end, the TIPS protecting group was removed and benzyl groups were introduced onto rhamnol **1.292**, providing glycal **1.296** (Scheme 1.56). Hydroboration-oxidation of **1.296** was successful, and alcohol **1.297** was formed in 33% unoptimized yield. Hydroboration occurred from the face opposite the C(3) substituent, as evidenced by the two large coupling constants for the proton at C(2) (dd,  $J = 9.2, 8.6$  Hz). As mentioned previously, hydroboration from this face is well precedented in the literature.<sup>57</sup>

64, 65, 97

### Scheme 1.56: Protecting group swap and the first successful hydroboration

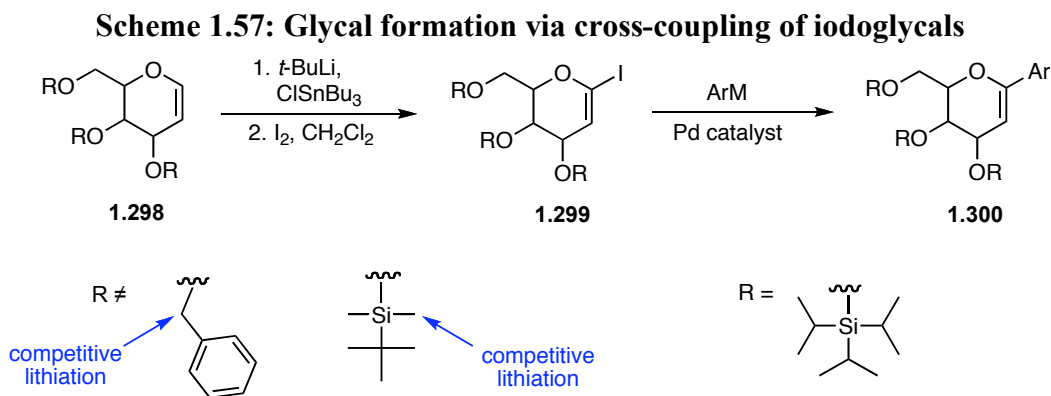


In order to streamline the synthesis of **1.297**, a route was required that did not involve this late stage protecting group swap. This necessitated the development of an improved method to synthesize benzyl-protected furyl glycols.

#### 1.4.5. Furyl Glycols via Sugar-Derived Lactones

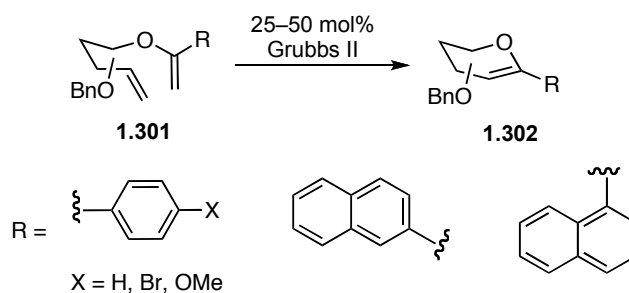
There was a need to develop a versatile, expedient synthesis of *C*-aryl glycols. Use of the Negishi coupling illustrated by the conversion of **1.287** to **1.289** would not be feasible with benzylated glycols (Scheme 1.56) because Friesen had previously reported

that *t*-BuLi is necessary to lithiate glycols **1.298** at the C(1) position.<sup>98</sup> Although TIPS-protected glycols were compatible with this process, benzylated glycols suffered from lithiation of the benzylic methylene group when treated with *t*-BuLi (Scheme 1.57). We required a method to form glycols **1.300** containing benzyl protecting groups, thus this method would not be compatible.



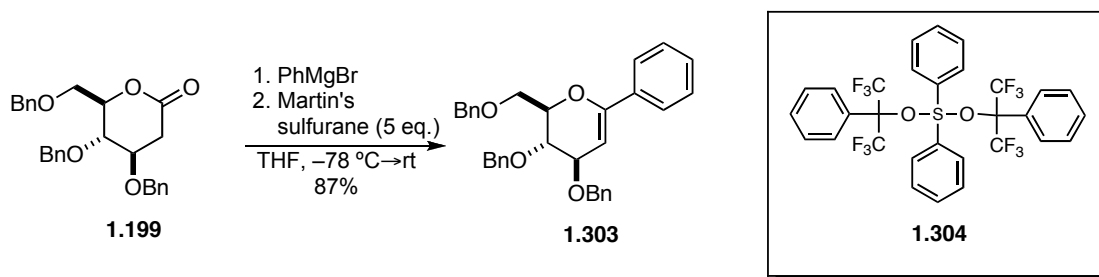
The method described by Postema using a ring closing metathesis approach would also not be viable (Scheme 1.58). Although they were able to employ a perbenzylated glycol **1.301** as a starting material, this approach required the use of 25–50 mol% of Grubbs catalyst, making this approach not amenable to scale up. In addition, the sequence was lengthy, requiring eight steps to glycols **1.302** from commercially available tri-*O*-acetyl-D-glucal.

### Scheme 1.58: Ring closing metathesis approach to C-aryl glycols



Sulikowski had also described an approach to C-aryl glycols, which utilized readily available 2-deoxy glycosyl lactones as the starting material (Scheme 1.59). Unfortunately, this two step approach involved the use of excess Martin sulfurane (**1.304**) in order to achieve good yields of glycol **1.303**.<sup>99</sup>

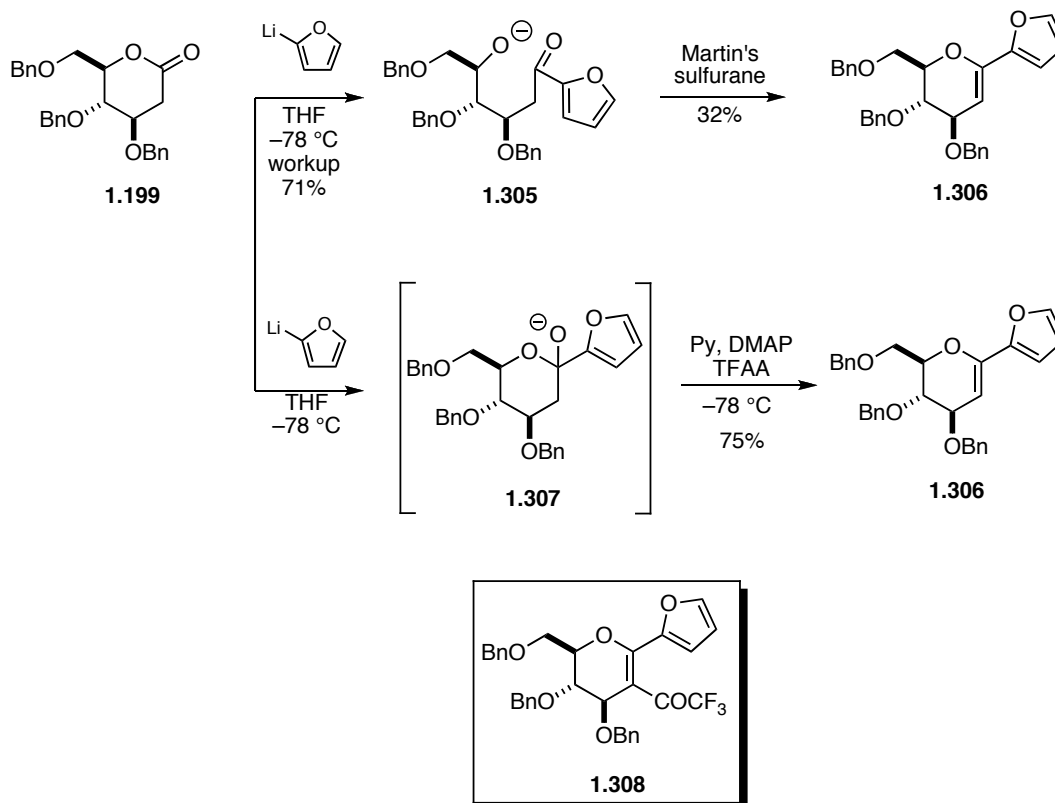
### Scheme 1.59: Access to C-aryl glycols using Martin's sulfurane



The procedure of Sulikowski served as the starting point for Dr. Li's investigations. For example, the addition of 2-furyllithium to sugar lactone **1.199** proceeded smoothly, but Dr. Li found that the hemiacetal addition product **1.307** existed primarily in the open form **1.305** at room temperature in CDCl<sub>3</sub> (Scheme 1.60). Although this equilibrium is well known, it did not appear to interfere with previously reported reductive processes to form C-aryl glycosides. However, when this mixture of hemiacetal

**1.307** and hydroxy ketone **1.305** was treated with Martin's sulfurane according to the two-pot procedure of Sulikowski, the desired glycal **1.306** was obtained in only 32% yield; Li was unable to optimize the procedure.

**Scheme 1.60: Unfavorable equilibrium in the addition of 2-furyllithium to sugar lactones**



Li reasoned that the difficulties with the ring-chain tautomerism might be avoided if the intermediate lithium alkoxide of the hemiketal **1.307** could be trapped *in situ* to give a derivative that would undergo elimination to provide the desired glycal **1.306**. Thus, following addition of 2-furyllithium to lactone **1.199**, the resultant alkoxide **1.307** was treated at  $-78\text{ }^{\circ}\text{C}$  with a mixture of pyridine, 4-*N,N*-dimethylaminopyridine



(DMAP), and trifluoroacetic anhydride (TFAA) to furnish furylglucal **1.306** in very good yield (Scheme 1.59). If an excess of TFAA was present, acylation of the glycal enol ether ensued, affording the  $\alpha$ -furyl- $\beta$ -trifluoroacetoxyglucal **1.308** as a significant by-product (22% yield). Indeed, when **1.307** was treated with a large excess of TFAA in the presence of pyridine and DMAP, trifluoroacetate **1.308** was isolated in 63% yield.

Dr. Li extended this method to the formation of various aryl glycals, examples of which are shown (Table 1.2).<sup>100</sup> Aryl glycals **1.303** and **1.310** were typically formed in about 75% yield (entries 1 and 2), whereas *C*-aryl rhamnals **1.312–1.314** were invariably formed in high yield, regardless of the aryl substituent (entries 3–5).

**Table 1.2: Formation of aryl glycols derived from glucal and rhamnal**

Entry	Lactone	Ar-Li	Product <sup>a</sup>	Yield <sup>b</sup>
1	<b>1.199</b>	Ph-Li	 <b>1.303</b>	76%
2	 <b>1.309</b>	Furyl-Li	 <b>1.310</b>	75%
3	 <b>1.311</b>	Ph-Li	 <b>1.312</b>	91%
4	<b>1.311</b>	4-methoxyphenyl-Li	 <b>1.313</b>	86%
5	<b>1.311</b>	1-naphtyl-Li	 <b>1.314</b>	95%

<sup>a</sup> Products obtained were >95% pure by <sup>1</sup>H NMR.

<sup>b</sup> Reported yield for 0.2 mmol scale reaction.

<sup>c</sup> Reaction also performed on 8.3 mmol scale in 71% yield

## 1.5. SUMMARY AND CONCLUSION

The methods to synthesize *C*-aryl glycosides were summarized, with emphasis placed on those that have found utility in natural product synthesis. Of the many methods

to synthesize this class of antibiotics, only two allow access to all four groups of *C*-aryl glycosides: the umpolung method of Parker, and the acid-catalyzed opening of oxabicycles developed in the Martin group.

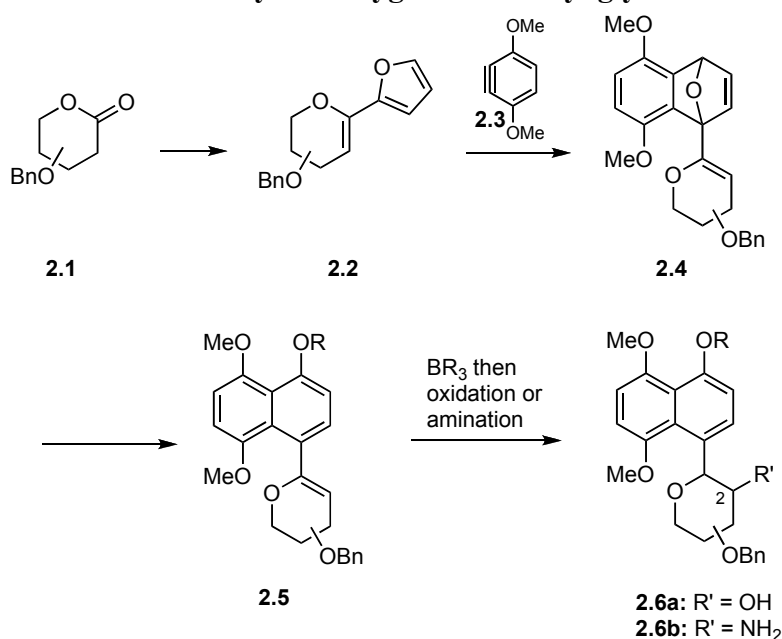
The Martin group method had yet to be applied to an efficient synthesis of C(2)-oxygenated *C*-aryl glycosides via glycols, due to limited protecting group choices for the existing methods to make glycols. Thus, a novel approach to benzylated aryl glycols was developed within the group. This method allowed for the formation of 1-aryl glycols in a *one pot process* from 2-deoxysugar lactones. However, there remained a need explore the substrate scope of this reaction and to extend the method to sugars with varying substitution on the sugar moiety. In addition, the streamlined route to the C(2)-oxygenated sugars by employing perbenzylated glycols required investigation.

## Chapter 2: The synthesis and functionalization of C-aryl glycols

A novel, one pot method to form aryl glycols, including furyl glycols **2.2**, from sugar lactones **1.1** had been developed to circumvent difficulties with the hydroboration-oxidation of TIPS-protected C-aryl glycols (Scheme 2.1). *Because Li had established the generality of the method, my first task was to synthesize furyl glycols 2.2 and convert them to C-aryl glycols 2.5.* Cycloadducts **2.4** would come from the cycloaddition of furyl glycols **2.2** with benzyne **2.3**, which would be generated *in situ* from 2-chloro-1,4-dimethoxybenzene. Ring opening of oxabicyclic **2.4** would provide naphthols, which could be protected as ethers if necessary. The resultant glycols **2.5** could be functionalized stereoselectively to provide C(2)-oxygenated C-aryl glycosides **2.6a**, R' = OH via hydroboration-oxidation.

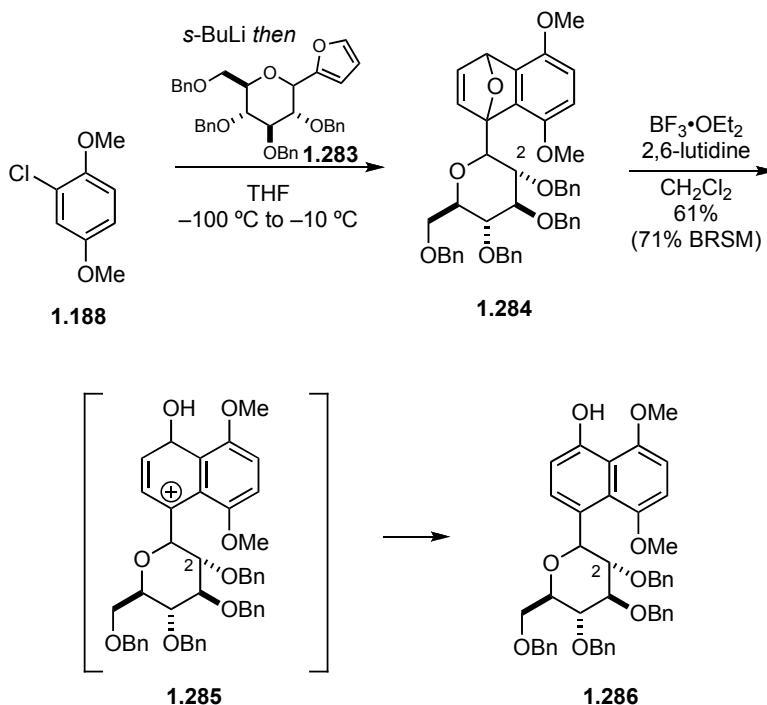
In addition to forming the aforementioned C(2)-oxygenated substrates, we foresaw an opportunity to introduce other R' groups via the functionalization of **2.5**. The antibiotic properties of aminoglycosides inspired us to also target C(2)-aminated C-aryl glycosides via the hydroboration-amination of glycols **2.5**, allowing access to **2.6b**.

### Scheme 2.1: General entry to 2-oxygenated C-aryl glycosides via glycols

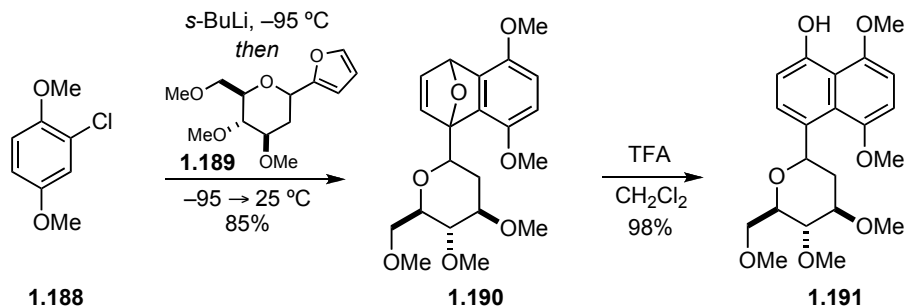


We anticipated that this approach may also help to circumvent difficulties that had been observed when C(2)-oxygenated examples were engaged in the Martin group methodology. Namely, glucose-derived glycosides synthesized by Li underwent cycloaddition and ring opening with less efficiency as compared to the C(2)-deoxygenated substrates typically employed by Kaelin and others (Schemes 2.2 and 2.3). Li could obtain phenol **1.286** in only 61% yield over two steps from furan **1.283** (Scheme 2.2). He reported the formation of many “phenolic” products when other acids were used. By contrast, the C(2)-deoxygenated phenol **1.191** was obtained in 83% yield over two steps (Scheme 2.3).

**Scheme 2.2: Difficulties with the ring opening of C(2) oxygenated glycosides**



**Scheme 2.3: Facile ring opening of C(2) deoxygenated substrates**

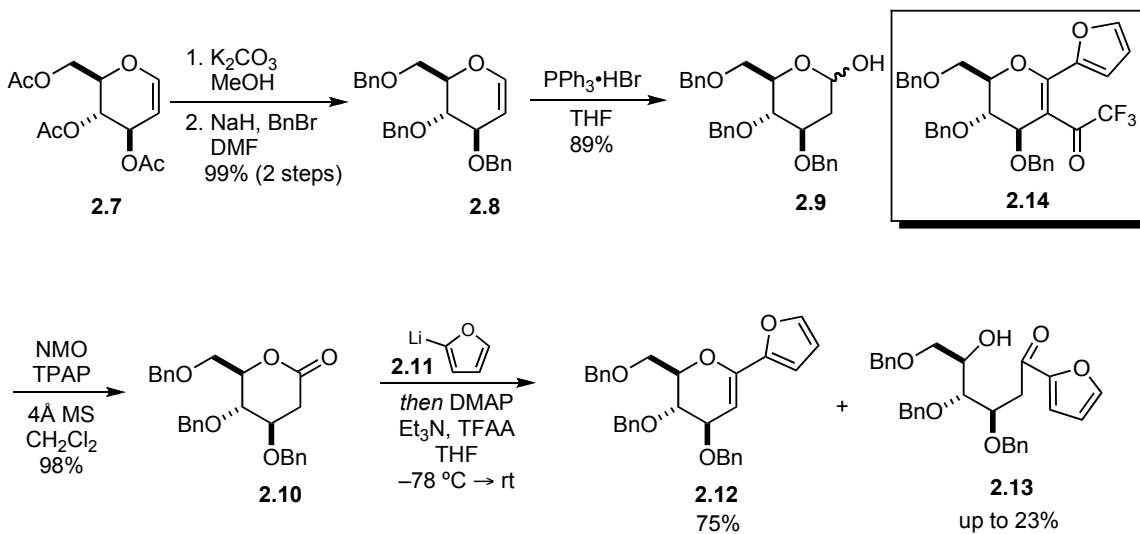


Li hypothesized that the electron withdrawing C(2) substituent was destabilizing the cationic intermediate formed in the ring opening step as illustrated by **1.285**. If it was indeed this substituent that was the cause of the inefficiency in these reactions, the approach detailed in this chapter could potentially be employed to improve the route to 5-hydroxyaloin A.

## 2.1 GLUCAL

Tri-*O*-acetyl-D-glucal (**2.7**) was chosen as the starting point for the investigation shown in Scheme 2.1, as this sugar is relatively inexpensive and readily available. Multigram quantities of lactone **2.10** were prepared using a previously developed sequence (Scheme 2.4).<sup>88</sup> The acetoxy groups of peracylated glucal **2.7** were first removed by saponification, and the hydroxyl groups were then globally protected as benzyl ethers, providing glycal **2.8** in high yield. Although pyridinium chlorochromate (PCC) has been used to oxidize glycals to lactones,<sup>101</sup> this process had been shown to be somewhat unpredictable in prior work in the group,<sup>88</sup> and we had found a two-step procedure that was more efficient. Thus, hydration of glucal **2.8** in the presence of  $\text{PPh}_3 \cdot \text{HBr}$ <sup>102</sup> gave lactol **2.9** that was subsequently oxidized with TPAP,<sup>103</sup> providing sugar lactone **2.10** in 87% yield over two steps. Conversion of lactone **2.10** to the furyl glycal **2.12** proceeded smoothly on a mmol scale when lactone **2.10** was treated with 2-furyllithium (**2.11**) at low temperature, followed by the addition of DMAP, pyridine, and TFAA and warming to room temperature.

### Scheme 2.4: Formation of furyl glucal



Although the formation of **2.12** was efficient on mmol scale, the yields were generally about 10% lower when the reaction was performed on a smaller scale. This is perhaps due to adventitious water, which could quench the anion resulting from the addition of **2.11** to lactone **2.10**. The hydroxy ketone side product **2.13** was consistently isolated from these small-scale reactions in yields up to 23%.

In order to improve this reaction to give **2.12**, a number of variables were screened (Table 2.1). In this study, the molar equivalents of 2-furyllithium, DMAP and Et<sub>3</sub>N remained a constant at 1.2, 1.2, and 3.0 equivalents, respectively. The amount of TFAA was varied, with an upper limit set at 3.0 equivalents because the trifluoride **2.14** was formed in the presence of a large excess of TFAA. It was determined that a minimum of 2.0 equivalents of TFAA was required in order to obtain the glycal **2.12** as the major product, rather than hydroxy ketone **2.13** (entry 1). There was, however, no significant difference in yield when 2.0 or 3.0 equivalents of TFAA were used (entries 2

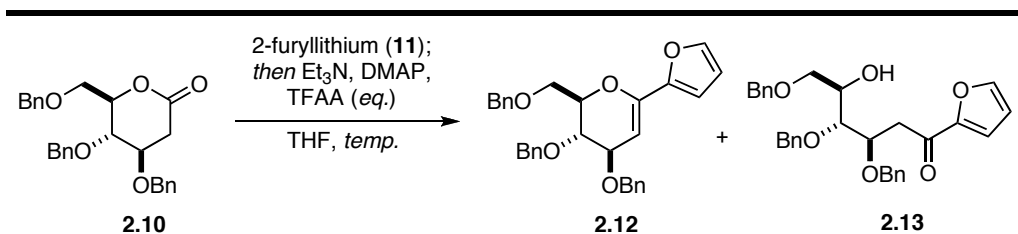


and 3). Of the solvents investigated, THF was the optimal choice, as the reaction was less efficient when other solvents were used (entries 4 and 5).

When the two stages of the reaction were performed at  $-78\text{ }^{\circ}\text{C}$ , only hydroxy ketone **2.13** was isolated, indicating that the dehydration step occurred at warmer temperature (entry 8). Accordingly, the reaction was warmed to  $-20\text{ }^{\circ}\text{C}$  after the addition of 2-furyllithium, and then  $\text{Et}_3\text{N}$ , DMAP, and TFAA were added at this temperature (entry 9); however, no improvement was observed.

The use of HMPA as an additive was also explored, with the intention of making the tertiary alkoxide ion more nucleophilic, thereby facilitating acylation (entries 10 and 11), but hydroxy ketone **2.13** was again the major product. One possible explanation of these results is that HMPA destabilized the addition adduct by sequestering the lithium counterion, thus making the undesired ring opening more favorable. If the amine bases could sequester the lithium counterion similarly, this could be the reason for the formation of hydroxy ketone **2.13**. This hypothesis prompted an experiment in which the TFAA was added to the reaction mixture first at  $-78\text{ }^{\circ}\text{C}$  to trap the alkoxide. The amine bases were then added to the reaction. This change in the order of addition furnished furan **2.12** in only 56% yield.

**Table 2.1: Attempts to optimize furyl glucal formation**



entry	eq. TFAA	solvent	temp (°C) <sup>a</sup>	result
1	1.0	THF	-78 → rt	mainly <b>2.13</b> <sup>b</sup>
2	2.0	THF	-78 → rt	63% <sup>c</sup>
3	3.0	THF	-78 → rt	67% <sup>c</sup>
4	2.5	DME	-78 → rt	complex mixture
5	2.5	Et <sub>2</sub> O	-78 → rt	mainly <b>2.13</b> <sup>b</sup>
6	2.5	THF	-78 → 0	57% <sup>c</sup>
7	2.5	THF	-78 → rt	66% <sup>c</sup>
8	2.5	THF	-78	mainly <b>2.13</b> <sup>b</sup>
9	2.5	THF	-20	complex mixture
10 <sup>c</sup>	2.5	THF	-78 → rt	mainly <b>2.13</b>
11 <sup>d</sup>	2.5	THF	-78 → rt	mainly <b>2.13</b>

<sup>a</sup> Following the addition of 2-furyllithium, the reaction was stirred at the initial temperature for 2 h. Following the addition of the other reagents, the mixture was allowed to warm to the second temperature.

<sup>b</sup> reaction analyzed by TLC. <sup>c</sup> isolated yield of product after chromatography.

<sup>d</sup> HMPA added prior to the addition of Et<sub>3</sub>N, DMAP, and TFAA. <sup>d</sup> HMPA added after the addition of Et<sub>3</sub>N, DMAP, and TFAA.

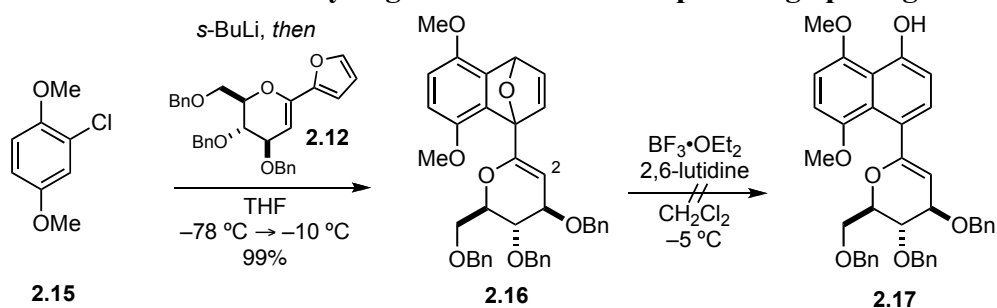
We explored other reagents to acylate the alkoxide. Namely methanesulfonyl chloride (MsCl), acetyl chloride (AcCl), and methyl chloroformate were used in lieu of TFAA. MsCl was the best of these three reagents, but comparing the ratios of the desired glycal **2.12** and hydroxy ketone **2.13** in the <sup>1</sup>H NMR spectrum of the crude material

revealed a mixture (~1:1) of products, and a more thorough investigation of alternative acylating reagents was not undertaken.

All attempts to improve Li's results for the formation of furyl glycal **2.12** did not meet with success; however, these investigations were needed to determine if it was a matter of reaction conditions or substrate specificity that was determining the yield of furyl glycal in this reaction (see Section 2.3.2). Although the original conditions employed by Li proved to be the best, we had gained valuable information regarding substrate specificity that will be discussed further (Section 2.3.2).

With furyl glycal **2.12** in hand, its reaction with the benzyne generated from 2-chloro-1,4-dimethoxybenzene was examined. In the event, **2.15** was lithiated with *s*-BuLi at  $-95\text{ }^{\circ}\text{C}$ , and furyl glycal **2.12** was added after 10 min to the mixture at  $-95\text{ }^{\circ}\text{C}$  (Scheme 2.5). The mixture was warmed quickly to  $-10\text{ }^{\circ}\text{C}$  to effect benzyne generation and subsequent [4+2] cycloaddition, and the cycloadduct **2.16** was isolated in 99% yield. This was a clear benefit to using glycols in this reaction, as yields in the range of 50–75% are observed when C(2)-substituted glycosides are employed in the benzyne cycloaddition with the benzyne generated from 2-chloro-1,4-dimethoxybenzene (Sections 1.4.3 and 3.6).

### Scheme 2.5: Benzyne generation and attempted ring opening



We then attempted to apply the conditions developed by Kolakowski and Li for the ring opening of TIPS-protected rhamnall **1.291** to the benzyl protected glucal **2.16**. However, treatment of **2.16** with  $\text{BF}_3 \cdot \text{OEt}_2$  and 2,6-lutidine gave a complex mixture of phenols as evidenced by the appearance of many singlets between 9.8 and 10.0 ppm in the  $^1\text{H}$  NMR spectrum of the crude material (Scheme 2.5).

Various oxaphilic Lewis acids were employed in an effort to improve this reaction (Table 2.2, entries 1-7),<sup>104</sup> but these reactions also failed to provide **2.17**. The first promising result was achieved when cycloadduct **2.16** was treated with scandium triflate ( $\text{Sc}(\text{OTf})_3$ ) at room temperature for 1 h (entry 8). Although a significant amount of starting material remained, one singlet was observed in the  $^1\text{H}$  NMR spectrum of the crude material at 9.86 ppm. When this reaction was allowed to run for extended periods of time, many phenolic products were formed (entries 6 and 7). When trimethylsilyl trifluoromethanesulfonate (TMSOTf) was employed as the Lewis acid, the desired phenol **2.17** was formed, albeit in low isolated yield (entry 9).

The Lewis acid of choice for this reaction was  $\text{ZnCl}_2$  (entries 10 and 11). Complex mixtures of phenolic products were observed when the reaction was run at  $0\text{ }^{\circ}\text{C}$ , and the reaction did not proceed at  $-78\text{ }^{\circ}\text{C}$ . However, when  $\text{ZnCl}_2$  was added to **2.16** at  $-78\text{ }^{\circ}\text{C}$  and the reaction mixture was warmed to  $0\text{ }^{\circ}\text{C}$ , the reaction went to completion

within minutes. Only one singlet at 9.86 ppm was observed in the  $^1\text{H}$  NMR spectrum of the crude material. It was critical to the success of this reaction to add  $\text{ZnCl}_2$  at low temperature, or more complex product mixtures were obtained.

**Table 2.2: Optimization of the ring-opening of glucal**

COC1=CC=C2C(OC1)C=C(C2)OC(COC1=CC=CC=C1)OC(COC1=CC=CC=C1)C
 $\xrightarrow[\text{CH}_2\text{Cl}_2]{\text{Lewis acid}}$ 
COC1=CC=C2C(O)C=C(C2)OC(COC1=CC=CC=C1)OC(COC1=CC=CC=C1)C

**2.16** **2.17**

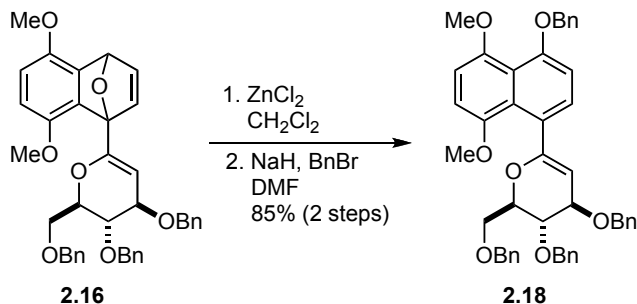
entry	Lewis acid	temp (°C)	time	result
1	TMSCl	rt	12 h	many phenolic products <sup>a</sup>
2	$\text{SnCl}_2$	rt	3 h	
3	$\text{SnCl}_4$	-78	5 min	
4	$\text{Sn}(\text{OTf})_3$	0	1 h	
5	$\text{Yb}(\text{OTf})_3$	rt	16 h	
6	$\text{Sc}(\text{OTf})_3$	0	1 d <sup>b</sup>	
7	$\text{Sc}(\text{OTf})_3$	rt	2 d <sup>b</sup>	
8	$\text{Sc}(\text{OTf})_3$	rt	1 h	SM, 1 phenol
9	TMSOTf	-78	10 min	25–50% <sup>c</sup>
10	$\text{ZnCl}_2$	0	10 min	many phenolic products <sup>a</sup>
11	$\text{ZnCl}_2$	-78 to 0	10 min	53–85% <sup>c</sup>

<sup>a</sup> Analysis of the  $^1\text{H}$  NMR spectrum of the crude material; many singlets between 9.8–10.0 ppm.  
<sup>b</sup> Both  $\text{CH}_2\text{Cl}_2$  and  $\text{THF}/\text{H}_2\text{O}$  used as solvent. <sup>c</sup> Isolated yield after flash chromatography.

Although the  $^1\text{H}$  NMR spectra of the crude reaction mixtures from reactions using the conditions described in entry 11 appeared to be nearly identical, the yields of **2.17** following flash chromatography on silica gel ranged from 53–85%. When a sample of naphthol **2.17** containing a minor impurity was resubjected to flash chromatography, the “purified” material contained more side products than the original sample. In addition, when a sample of **2.17** was stored in the freezer, the formation of side products was apparent after as little as 12 h.

Because naphthol **2.17** could not be stored without significant decomposition, immediate protection of **2.17** was necessary. Accordingly, naphthol **2.17** was converted to its benzyl ether **2.18** (Scheme 2.6). This tandem procedure provided naphthalene **2.18** in very good yield.

**Scheme 2.6:  $\text{ZnCl}_2$ -mediated ring opening and protection of glucal**



Although a hydroboration/oxidation of a substrate similar to **2.18** had already been successfully performed, the reaction had proceeded in only 33% yield (Section 1.4.4, Scheme 1.56). It was necessary to optimize this step (Table 2.3).

**Table 2.3: Representative hydroboration conditions for glucal**

entry	borane	eq. borane	temp (°C) <sup>a</sup>	time	yield
1	BH <sub>3</sub> •DMS	3	rt/rt	4 h	19% <sup>b</sup>
2	BH <sub>3</sub> •DMS	3	50/rt	1.5 h	44%
3	BH <sub>3</sub> •THF	3	50/rt	0.5 h	50%
4	BH <sub>3</sub> •THF	3	50/rt	0.5 h	56% <sup>c</sup>
5	BH <sub>3</sub> •THF	10	25/50	5.5 h	N/A <sup>d</sup>
6	BH <sub>3</sub> •THF	10	25/rt	2 h	64%

<sup>a</sup> Hydroboration temp/oxidation temp <sup>b</sup> Isolated yield after flash chromatography.  
<sup>c</sup> Sodium perborate was used as the oxidant, instead of H<sub>2</sub>O<sub>2</sub>. <sup>d</sup> Complex mixture obtained following oxidation.

Hydroboration of **2.18** using borane-methylsulfide (BH<sub>3</sub>•DMS) complex was sluggish at room temperature (entry 1), and even reaction times of several days resulted in low conversion. Raising the temperature increased the yield, and the optimal conditions involved heating glycal **2.18** with BH<sub>3</sub>•DMS at 50 °C for 1.5 h, which provided alcohol **2.19** in 44% yield (entry 2). Longer reaction times resulted in decreased yields of alcohol **2.19**. Hydroboration of glycal **2.18** using BH<sub>3</sub>•THF was also slow at room temperature, although conversion in the hydroboration stage appeared superior to the BH<sub>3</sub>•DMS reaction by TLC. When this reaction was conducted at 50 °C, the yields

were better, though still moderate (entry 3). Concerned that the oxidation step might be problematic, sodium perborate was used in lieu of peroxide (entry 4).<sup>105</sup> However, there was no dramatic improvement in yield, and the reaction mixture has to be heated to 50 °C to effect oxidation.

With extended hydroboration times, many new spots were observed by TLC during the first stage of the reaction, which led us to think that the intermediate borane may not be stable under the reaction conditions. Indeed, longer reaction times resulted in the formation of complex mixtures following oxidation (entry 5). Optimized conditions for this reaction required the use of a large excess of borane, and the oxidation was performed after 2 h (entry 6) to give **2.19** in 64% yield. As expected, hydroboration occurred from the face opposite the C(3)-substituent, as evidenced by the two large coupling constants for the proton at C(2) (app td,  $J = 9.0, 5.2$  Hz), which is indicative of the axial orientation of the proton at C(2) that is coupled to axial protons of C(1) and C(3). The coupling constant of 5.2 Hz derives from coupling of the C(2)-H with the -OH proton of alcohol **2.19**.

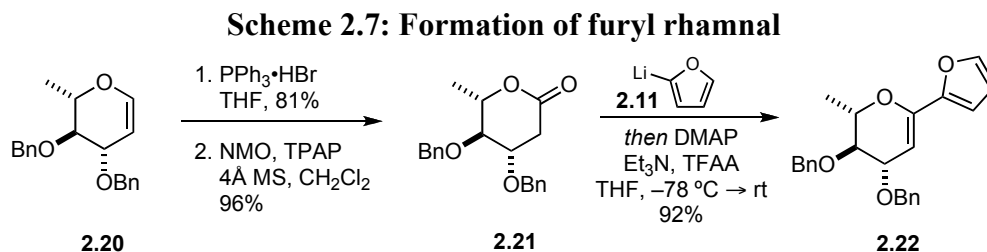
Having optimized conditions for the ring opening transformation of **2.16** to **2.17** and the hydroboration of glycal **2.18** to form **2.19**, efforts were made to apply these conditions to other substrates in order to evaluate the scope of our method. Our initial targets were 2-oxygenated *C*-aryl glycosides derived from commercially available substrates tri-*O*-acetyl-L-rhamnol and tri-*O*-acetyl-D-galactal.



## 2.2. RHAMNAL

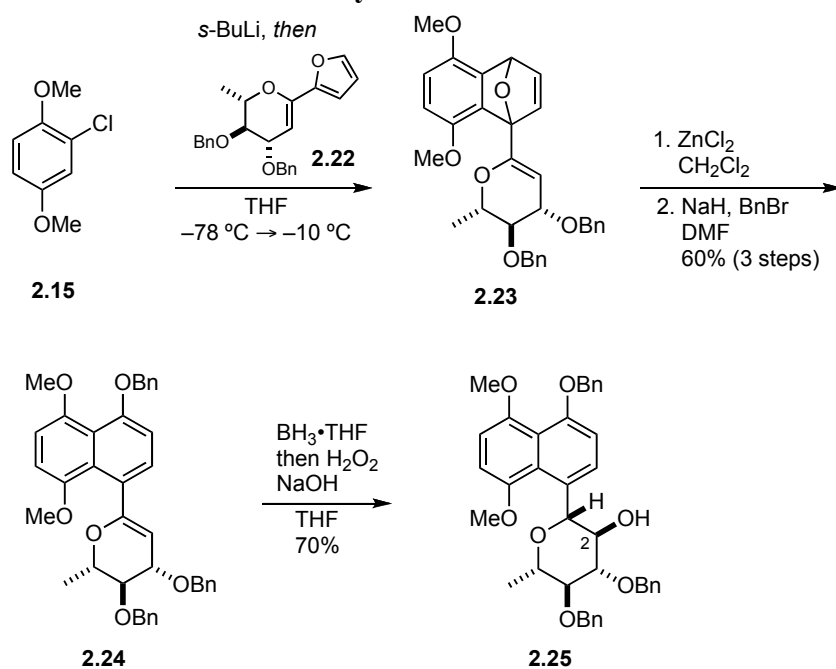
### 2.2.1. Hydroboration studies

The optimized conditions for the glucal were readily applied to form a C(2)-oxygenated C-aryl rhamnose. Hydration of enol ether **2.20** and subsequent oxidation of the intermediate hemiacetal furnished lactone **2.21** in 96% overall yield (Scheme 2.7). Treating lactone **2.21** with 2-furyllithium (**2.11**), followed by acylation and elimination furnished furyl rhamnal **2.22** in 92% yield. This result was consistent with Dr. Li's results, in which C-aryl rhamnals were invariably formed in high yield, regardless of the aryl substituent (Section 1.4.5).



Furyl rhamnal **2.22** then underwent cycloaddition with the benzyne generated from 2-chloro-1,4-dimethoxybenzene to give cycloadduct **2.23**, and sequential ring opening of **2.23**, followed by protection of the intermediate naphthol gave **2.24** in 60% yield over three steps (Scheme 2.8). Subsequent hydroboration of the enol ether **2.24** occurred from the face opposite the C(3)-substituent to give **2.25**. The stereochemical assignment was based upon the appearance of the proton at C(2) in the <sup>1</sup>H NMR spectrum (app td, *J* = 9.0, 5.6 Hz) of alcohol **2.25**.

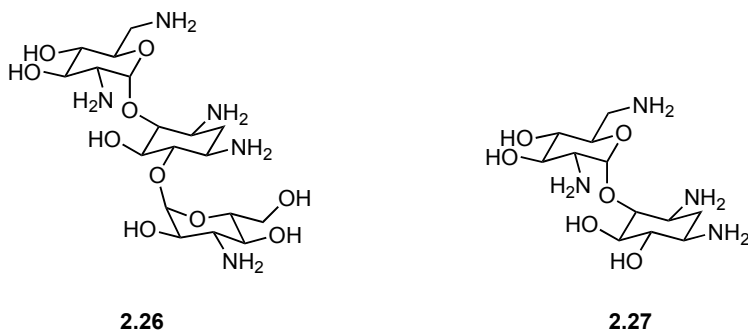
### Scheme 2.8: Hydroboration of rhamnal



#### 2.2.2. Hydroboration-amination studies and attempted aziridination

We became interested in the hydroboration-amination of glycals due to the diverse array of biological activities exhibited by aminoglycoside antibiotics, examples of which include kanamycin (**2.26**) and neamine (**2.27**) (Figure 2.1). These aminoglycosides are active against both gram positive and gram negative bacteria.<sup>106</sup> The mode of antibiotic activity involves binding the bacterial ribosome and preventing protein biosynthesis, thus resulting in cell death. Aminoglycoside antibiotics are also active against some viral strains, including herpes simplex 1 and influenza virus.<sup>107</sup>

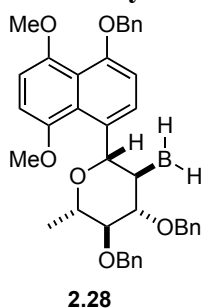
**Figure 2.1: Aminoglycoside antibiotics**



As with all microbes, the development of antibiotic resistant genes has rendered some aminoglycoside antibiotics useless in the treatment of certain diseases. For example, various aminoglycosides have become ineffective against methicillin-resistant streptococcus aureus (MRSA).<sup>106</sup> This resistance occurs due to the production of aminoglycoside modifying enzymes (AMEs) that alter the structure of the antibiotics.<sup>108</sup> The development of antibiotic resistance has necessitated the production of novel aminoglycoside antibiotics. By targeting C-aryl aminoglycosides, we aimed to synthesize new antibiotics that might be engendered with interesting biological properties.

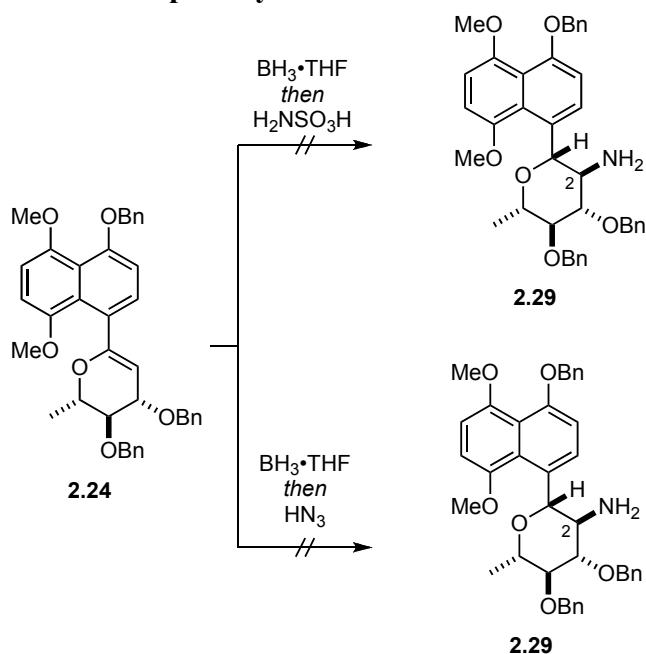
Of the commercially available substrates investigated (Sections 2.1–2.3) tri-*O*-acetyl-L-rhamnal **2.24** underwent hydroboration-oxidation in the best yield. Hence attempts were been made to effect the hydroboration-*amination* of this glycal. Hydroxylamine-*O*-sulfonic acid is often the reagent of choice for hydroboration-amination of simple substrates, but it is often ineffective with monoalkylboranes.<sup>109</sup> As rhamnal **2.24** is large, it is likely that under these hydroboration conditions there is only one sugar moiety associated with the boron atom as shown by **2.28** (Figure 2.2).

**Figure 2.2: Proposed formation of a monoalkylborane via hydroboration of 2.28**



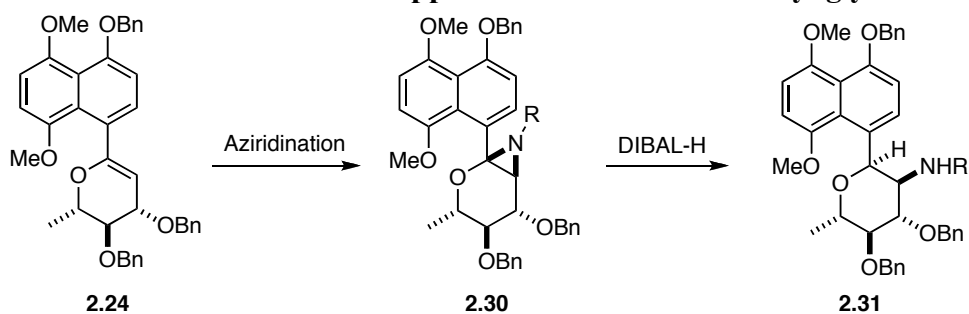
Even though the formation of a monoalkylborane such as **2.28** might make the amination difficult, we attempted the hydroboration/amination of **2.24** (Scheme 2.9). When the alkyl borane generated by hydroboration of **2.24** was treated with hydroxylamine-*O*-sulfonic acid, a complex mixture was obtained. The presence of an anomeric proton at the typical shift of 6.0 ppm in the  $^1\text{H}$  NMR spectrum of the crude material was not observed. In another attempt, hydrazoic acid was generated in situ from hydroxylamine and sulfuric acid.<sup>110</sup> This reaction resulted in the formation of a complex mixture.

### Scheme 2.9: Attempted hydroboration-amination of rhamnal



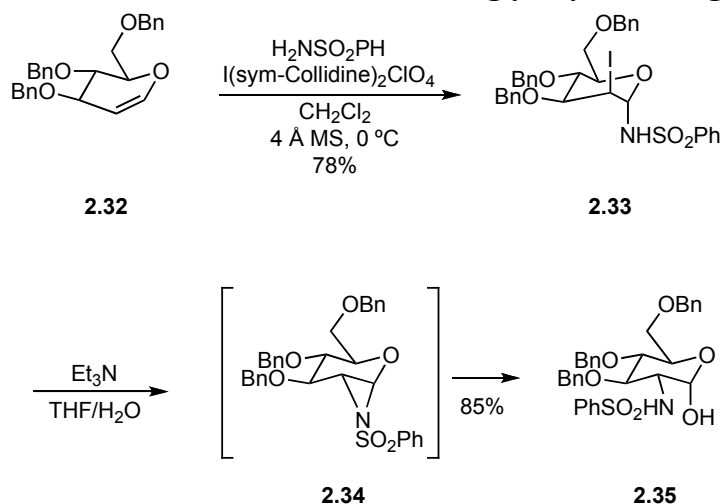
We had already optimized the hydroboration of glycols, so hydroboration-amination would be a convenient one-pot extension of the method we were developing. However, this is not the only way to form C(2)-aminated C-aryl glycosides. Namely, the aziridination of glycols has been previously reported to give 2-amino lactols (Schemes 2.11 and 2.13),<sup>111, 112</sup> and it was thought that aziridination of **2.24**, followed by opening of the aziridine with diisobutylaluminum hydride (DIBAL-H) might provide the desired 2-amino glycoside **2.31** (Scheme 2.10).

**Scheme 2.10: Aziridination approach to 2-aminated C-aryl glycosides**



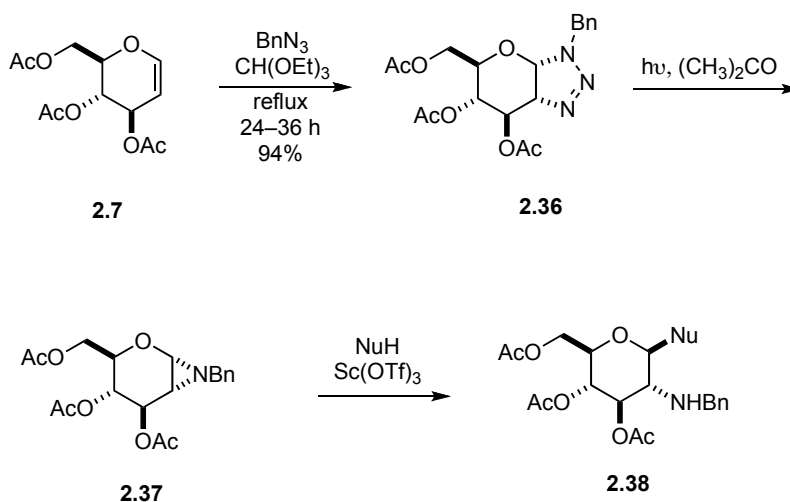
Generally, the aziridination of glycals is a multistep procedure. In the two step protocol described by Griffith and Danishefsky, glycal **2.32** was converted into iodosulfamide **2.33** (Scheme 2.11).<sup>111</sup> Upon treatment of **2.33** with Et<sub>3</sub>N in THF/H<sub>2</sub>O, the amino alcohol **2.35** was formed in good yield; however, the yields were low to moderate when other nucleophiles were employed.

**Scheme 2.11: Aziridines via sulfonamidoglycosylation of glycals**



An efficient dipolar cycloaddition approach to 2-aminosugars has been reported (Scheme 2.12).<sup>113</sup> Treatment of tri-*O*-acetyl-D-glucal (**2.7**) with benzyl azide and triethylorthoformate provided the triazine **2.36** in excellent yield, and irradiation of **2.36** in acetone yielded the aziridine **2.37**. The intermediate aziridine could be treated with various nucleophiles, affording 2-aminosugars **2.38** in 88–98% yield. Unfortunately this method only works well with strongly electron-withdrawing substituents on the sugar moiety. Acetate *O*-protecting groups worked best for the example shown in Scheme 2.10. Few readily removable electron withdrawing groups would be compatible with the strong base chemistry required to form glycols such as **2.24**, thus excluding this method for aziridination.

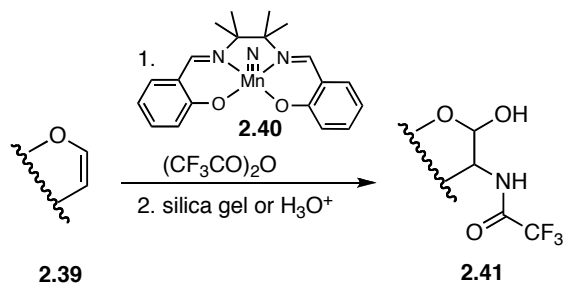
**Scheme 2.12: Aziridines via triazolines**



A method developed by Du Bois and Carriera,<sup>112, 114, 115</sup> which utilizes the manganese nitrido complex (saltmen)Mn(N) (**2.40**) as the nitrogen transfer agent, seemed most appealing as they have demonstrated the compatibility of this one-pot method with a variety of sugar protecting groups (Scheme 2.13). A range of furanose and pyranose

glycals **2.39** were aziridinated using (saltmen)Mn(N) activated with trifluoroacetic anhydride (TFAA); these aziridines were then hydrated to form amino alcohols **2.41**. This method was shown to be compatible with various *O*-protecting groups on the sugar, including PMB, benzyl, acetal, and silyl groups.

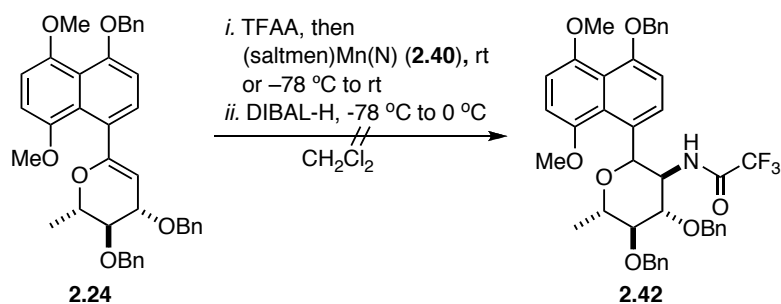
**Scheme 2.13: Literature precedent for the aziridination of glycals**



Based upon the work of Du Bois and Carreira, we intended to open the aziridine in a tandem process using DIBAL-H. The (saltmen)Mn(N) nitrido complex (**2.40**) was prepared, and we attempted the aziridination of rhamnol-derived glycal **2.24** using the procedure reported for the aziridation of 6-membered glycals (Scheme 2.14). In this protocol, TFAA was added to the glycal first, and then (saltmen)Mn(N) (**2.40**) was added as a solution in  $\text{CH}_2\text{Cl}_2$ . DIBAL-H was then added to the mixture at  $-78\text{ }^\circ\text{C}$ . Unfortunately, a complex mixture of intractable products resulted, and the doublet typical of the anomeric C-H ( $J \sim 6.0\text{ ppm}$ ) of glycosides such as **2.25** was not observed in the  $^1\text{H}$  NMR spectrum of the crude material. We also tried to apply Carreira's exact conditions for the formation of *five*-membered glycals in which 2,6-di-*tert*-butylpyridine and (saltmen)Mn(N) (**2.40**) were added prior to TFAA. Unfortunately, a complex mixture resulted from this reaction as well.

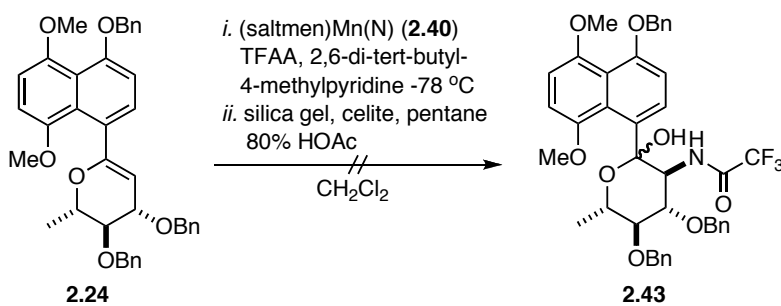


### Scheme 2.14: Attempted aziridination-opening of rhamnal glycol **2.24**



Attempts were then made to repeat Du Bois and Carreira's aziridination/hydration procedure on glycol **2.24** to determine if we could access rhamnose-derived amino lactol **2.43** (Scheme 2.15). The absence of the -OH stretch in the infrared spectrum (IR) of the crude material and the formation of many products by analysis of the crude <sup>1</sup>H NMR spectrum finally caused us to abandon this method.

### Scheme 2.15: Attempts to form a 2-aminated lactol



## 2.3 GALACTAL

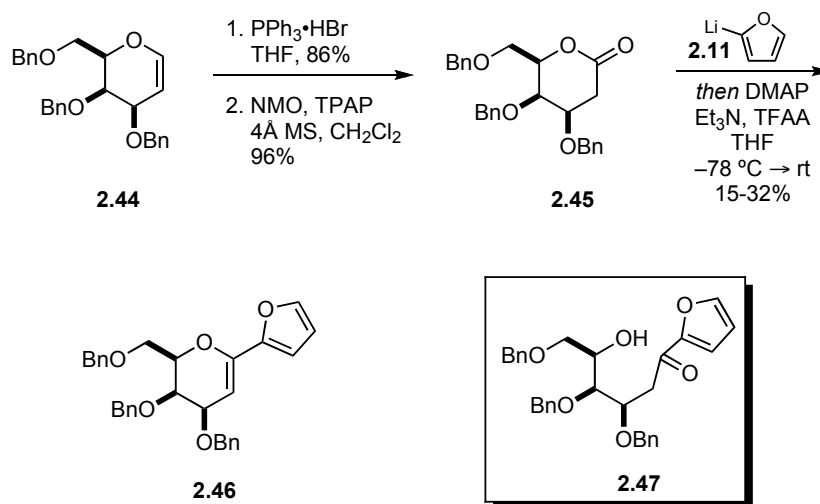
### 2.3.1. The hydroboration-oxidation of galactal

There have been no reported hydroboration-oxidation reactions using galactals to give 2-oxygenated C-aryl galactoses. Introducing this sugar moiety onto aromatic rings

might also produce *C*-aryl glycosides with interesting biological properties, as galactose motifs are present in various naturally occurring sugars. The role of galactose moieties on cell surface sugars in processes such as inflammation and infection makes aryl galactals interesting targets for the study of biological properties.<sup>1</sup> Furthermore, *C*-glycoside analogs of *O*-glycosides that contain galactose moieties have been found to retain the biological activity of the corresponding *O*-linked analog, while being less susceptible to hydrolysis.<sup>116</sup>

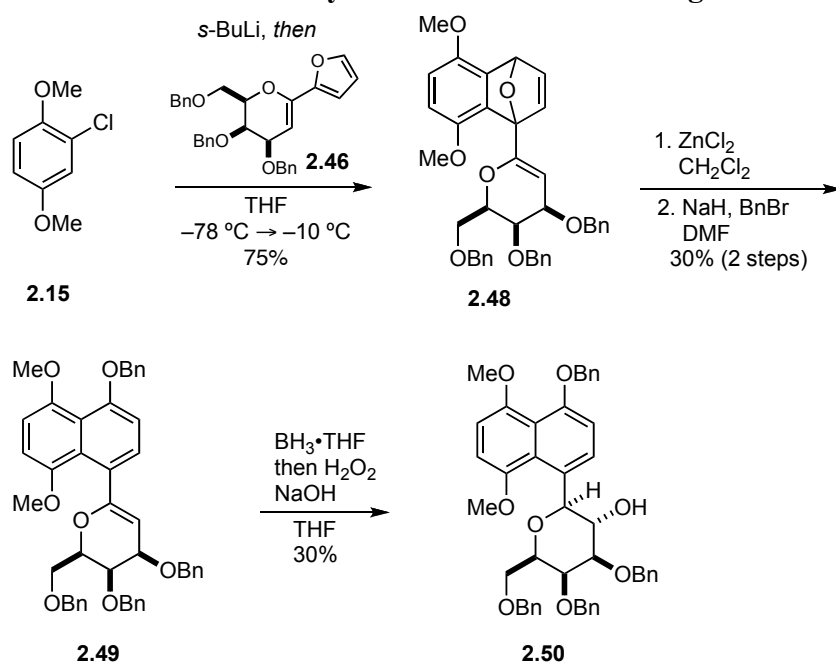
Hydration and oxidation of perbenzylated galactal **2.44** furnished lactone **2.45** in 96% overall yield (Scheme 2.16). Formation of the furyl galactal **2.46** was highly problematic, however. When optimized conditions for forming glucal **2.12** were employed, only low yields of **2.46** were obtained. Even on a 5.0 mmol scale, the best yield was 36%. Hydroxy ketone **2.47** was isolated from all reactions, in yields up to 53%.<sup>100</sup>

### Scheme 2.16: Formation of furyl galactal



Although further optimization of the transformation from **2.45** to **2.46** was not achieved, we were able to access the 2-oxygenated *C*-aryl glycoside **2.50** (Scheme 2.17). The cycloaddition of **2.46** with the benzyne generated from 2-chloro-1,4-dimethoxybenzene provided cycloadduct **2.48** in 75% yield. Ring opening and protection of **2.48** gave naphthalene **2.49** in moderate yield over two steps. Hydroboration-oxidation of **2.49** gave a single alcohol **2.50**. The stereochemistry of **2.50** was assigned based on prior precedent because the C(2)-proton was obscured in the  $^1\text{H}$  NMR spectrum in various solvents and the coupling constants could not be measured. Due to the oily nature of this alcohol, a crystal structure could not be obtained. Although this route did not provide 2-oxygenated *C*-aryl galactal **2.50** with high efficiency, this example was significant, as it represented the first reported hydroboration-oxidation of a galactal.

### Scheme 2.17: The hydroboration/oxidation of galactal



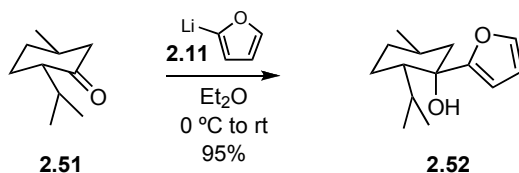
#### 2.3.2. Rationale for the difficulty with furyl glycol formation

Attempts to optimize the addition/elimination reaction to form galactal, illustrated by the transformation of **2.45** to **2.46**, led us to conclude that it is the nature of the sugar substituents that dictates the efficiency of this reaction. In addition, the glucal-derived lactone **2.10** underwent the addition/elimination sequence less efficiently than rhamnol-derived lactone **2.21**. Aside from relative stereochemistry, the C(6)-benzyloxy substituent is the only difference between glucal and rhamnol, therefore this group must be contributing in some way to the formation of hydroxy ketone **2.10**.

The first step of the sequence is addition to the lactone by 2-furyllithium, which can occur in an axial or equatorial fashion. Because 2-furyllithium is a large nucleophile, equatorial attack is expected to predominate. This prediction is based on precedent involving a substituted cyclohexanone, which allows for accurate analysis of the attack

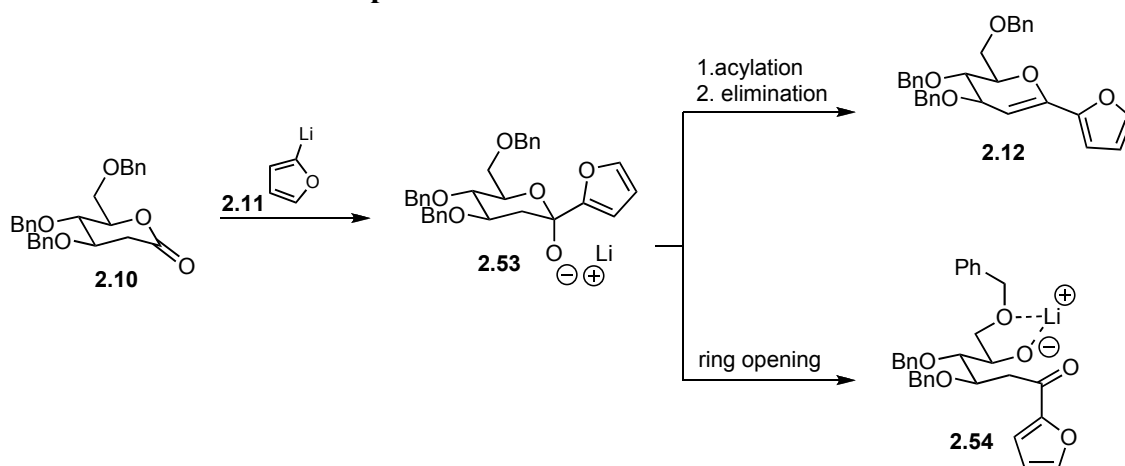
(Scheme 2.14).<sup>117</sup> Cyclohexanone **2.51** should sit in the chair-like conformation, with the methyl and isopropyl groups equatorial as drawn. In this example, furan addition occurs selectively, providing axial alcohol **2.52** as a single regioisomer due to favorable equatorial attack.

**Scheme 2.18: 2-Furyllithium addition into a substituted cyclohexanone**

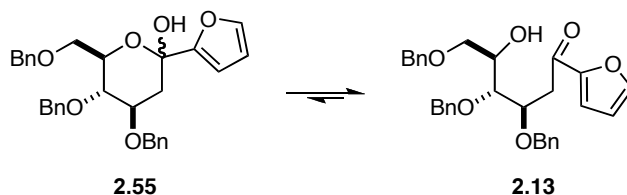


Thus, we can expect equatorial attack to predominate in the addition to our sugars and, although we cannot rule out that some axial attack will also occur with this pyranose system, the products resulting from equatorial attack are shown (Schemes 2.19 and 2.21). Treatment of **2.10** with 2-furyllithium (**2.11**) would yield intermediate alkoxide **2.53**, which can be acylated and undergo elimination leading to the formation of **2.12**. There is an equilibrium favoring the open-chain form **2.13** of hemiacetal **2.55** in CDCl<sub>3</sub> (Scheme 2.20). It is possible that there is a similar equilibration with this system as well. If ring-opened, glucal **2.53** could produce a favorable 5-membered chelate **2.54**. Ring closure to reform **2.53** would be less favorable, and hydroxy ketone **2.13** would be formed. The rhamnol-derived lactone **2.20** lacks a C(6)-substituent to participate in chelation, which may allow the equilibrium to favor the closed chain form.

**Scheme 2.19: Proposed chelate formation in the lactone addition**

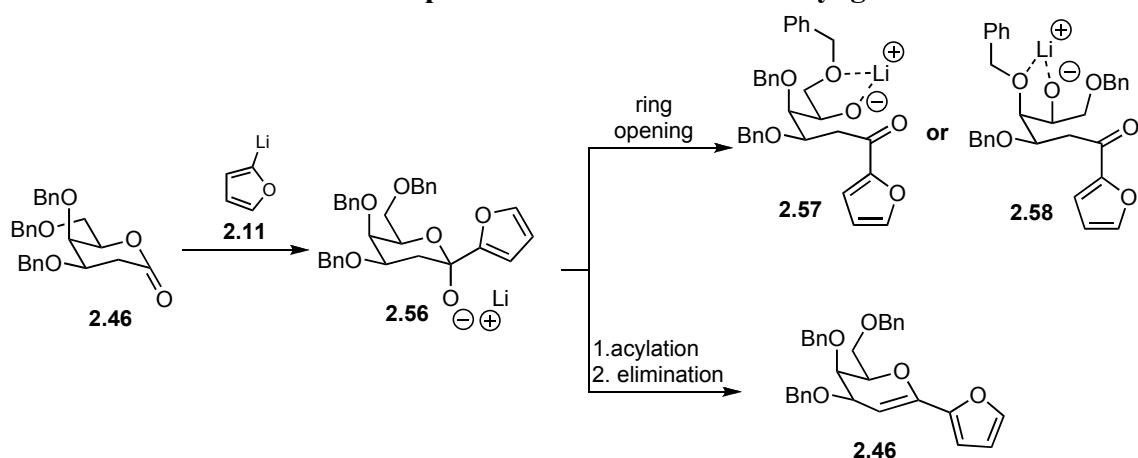


**Scheme 2.20: Equilibration of the hemiacetal form of 2.53**



The differences in glucal and galactal must also be addressed, due to the marked difference in efficiency between these substrates. The lower yields in forming furyl galactal **2.46** may be due to equilibration to the ring opened form being more favorable (Scheme 2.21). Indeed, galactose is present in open chain form to a greater extent as compared to glucose in aqueous solution, 0.002 and 0.02 percent acyclic form, respectively.<sup>118</sup> If alkoxide **2.56** equilibrates with the open chain form, there are two favorable 5-membered chelates **2.57** and **2.58** that may form readily, which could prevent reclosure.

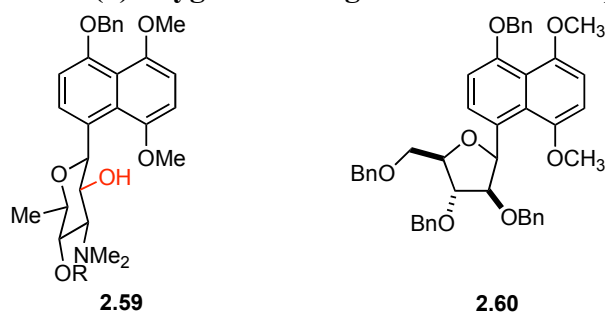
### Scheme 2.21: Rationale for potential difficulties with furyl galactal formation



## 2.4. AMINOGLYCALS

With the hydroboration sequence successfully applied to commercially available substrates (Scheme 2.1), the next goal became targeting other structures that could serve as models for naturally occurring C-aryl glycosides. Model systems for ravidomycin and the gilvocarcins were chosen (Figure 2.3). The ravidomycin analog **2.59**, a C(3)-aminoglycoside, was targeted first. Ravidomycin contains a C(6)-deoxysugar, and these are most compatible with our method to produce furyl glycals, as exemplified by the excellent yield obtained in the transformation of **2.21** to furyl rhamnal **2.22** (Scheme 2.7).

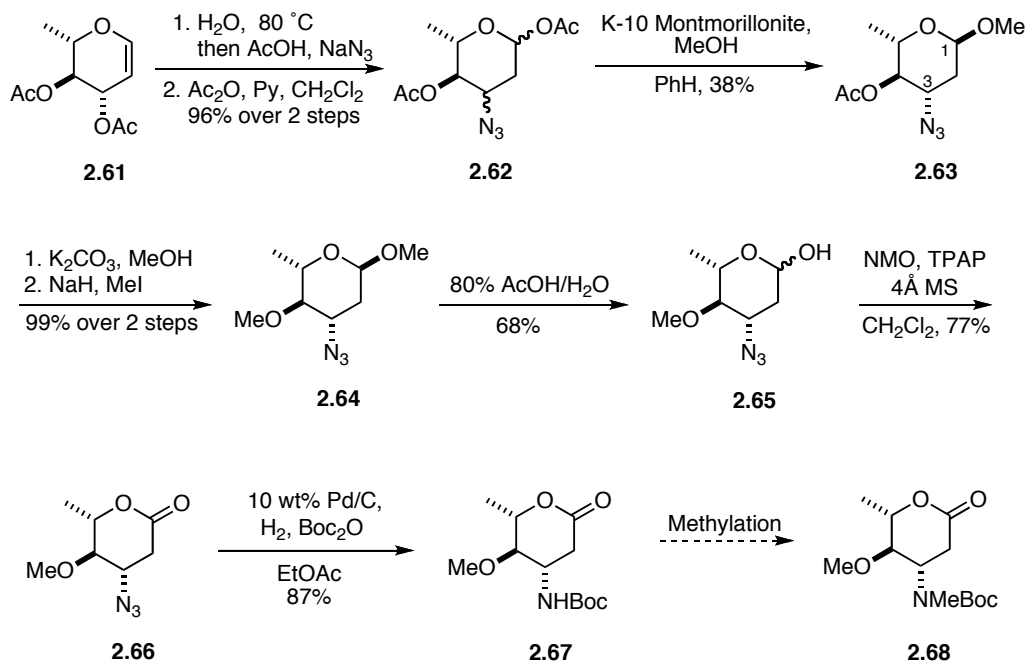
**Figure 2.3: C(2)-oxygenated targets for model compounds**



To access an aminosugar, di-*O*-acetyl-L-rhamninal (**2.61**) was converted to azide **2.62** in two steps (Scheme 2.22).<sup>119</sup> Lewis acid-catalyzed methanolysis of **2.62** gave a mixture of acetals, which could be separated by chromatography, to provide the  $\alpha$ -methyl acetal **2.63** as the major diastereomer. The stereochemistry at C(1) was assigned to be  $\alpha$  based on the small coupling constant for this proton in the <sup>1</sup>H NMR spectrum (d,  $J = 3.4$  Hz). The C(3) proton was determined to be equatorial (ddd,  $J = 12.3, 9.6, 4.8$  Hz) based on the two large coupling constants. Removal of the acetyl group from **2.63** using K<sub>2</sub>CO<sub>3</sub> in MeOH, followed by *O*-methylation provided dimethoxy azide **2.64** in 99% yield over two steps. Hydrolysis of the acetal moiety of **2.64**, followed by oxidation of the resultant lactol **2.65** using NMO/TPAP furnished lactone **2.66**. Reduction of the azide group of **2.66** and protection of the amino group gave carbamate **2.67** in 87% yield. Unfortunately, all attempts to *N*-methylate the amine of **2.67** were unsuccessful. No reaction was observed upon treatment of **2.67** with NaH and MeI, and stronger bases caused the formation of many products, possibly due to competitive enolization of the lactone.



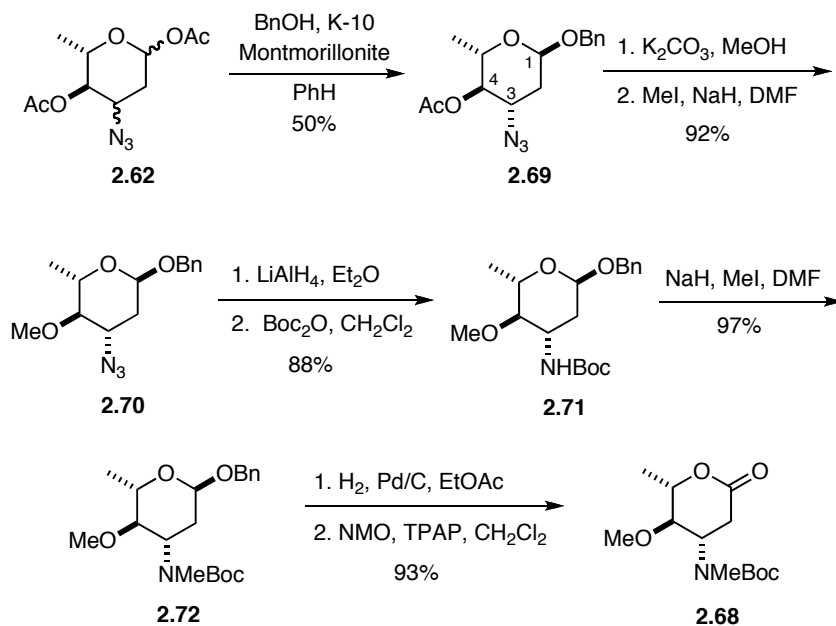
**Scheme 2.22: Formation of an aminolactone**



The aminolactone synthesis was modified such that a selective deprotonation was not required. The acetate **2.62** was treated with K-10 Montmorillonite and benzyl alcohol to provide benzyl acetal **2.69** in 50% yield (Scheme 2.23). The  $\alpha$ -anomer was separated by chromatography, and the stereochemistry at the anomeric carbon of **2.69** was assigned based on the small coupling constant for the proton at C(1) (d,  $J = 3.5$  Hz), which suggests the C(1) hydrogen is equatorial. The stereochemistry of the C(3) azide was assigned based on the two large coupling constants for the hydrogen atom at C(3) (ddd,  $J = 12.3, 9.8, 4.9$  Hz), which is expected for an axial hydrogen. Removal of the acetate at C(4) of **2.69** followed by *O*-methylation gave **2.70**. Reduction of the azide and protection of the resultant amine as a Boc carbamate gave **2.71**. The amino group of carbamate **2.71** was then *N*-methylated to give **2.72**, and hydrogenolysis of the anomeric benzyl group

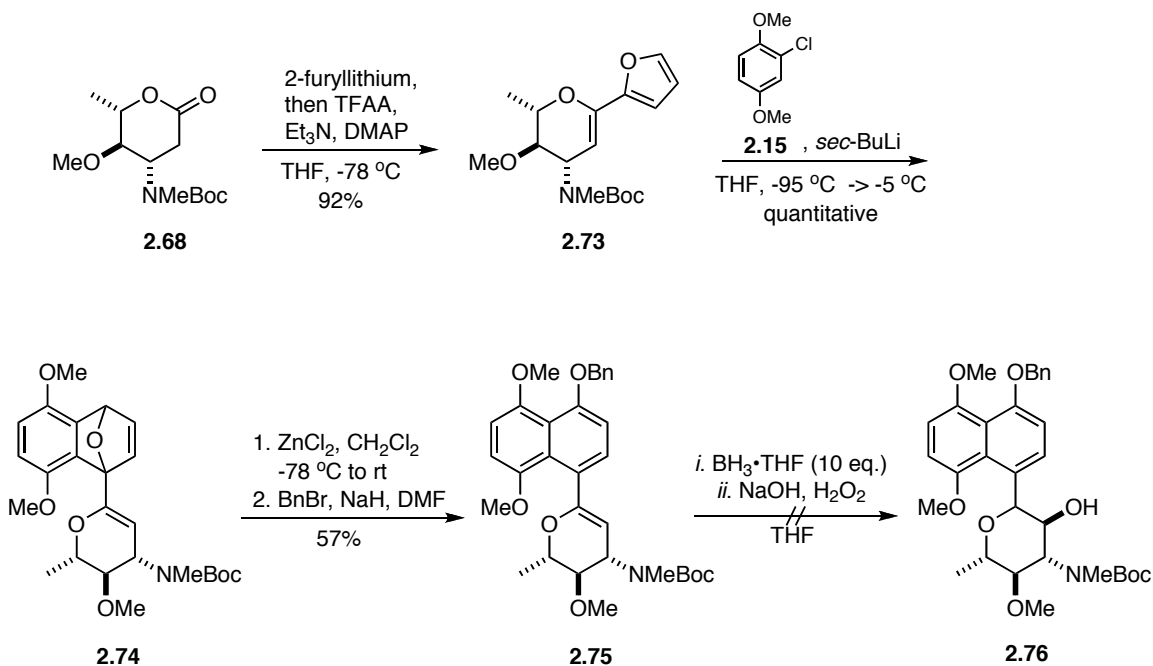
followed by NMO/TPAP oxidation of the intermediate lactol furnished the desired lactone **2.69** in 93% yield over two steps.

**Scheme 2.23: Access to the desired aminolactone**



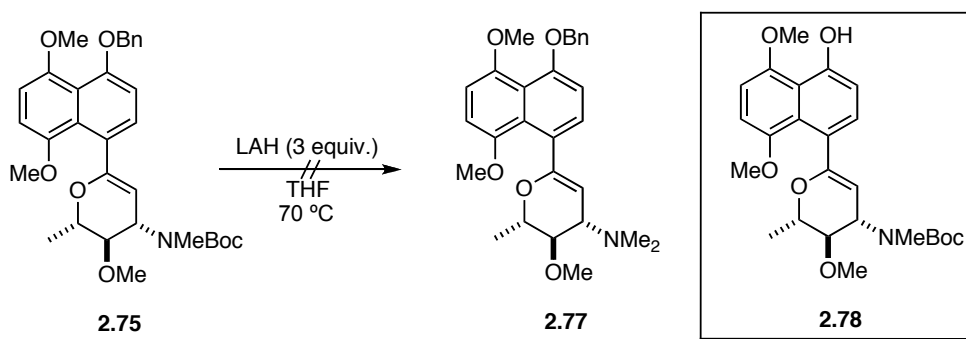
Conversion of lactone **2.68** to furyl glycol **2.73** was accomplished by treating **2.68** with 2-furyllithium followed by dehydration (Scheme 2.24).<sup>100</sup> Cycloaddition of **2.73** with the benzyne generated from 2-chloro-1,4-dimethoxybenzene proceeded smoothly to give **2.74**, which underwent ring opening when treated with  $\text{ZnCl}_2$ . However, the mixture had to be warmed from  $-78\text{ }^\circ\text{C}$  to room temperature in order for the reaction to go to completion. The resultant phenol was protected as its benzyl ether to give naphthalene **2.75** in 57% yield over two steps. Unfortunately, glycol **2.75** did not undergo hydroboration using the previously developed conditions, and only starting material was recovered from the reaction, in nearly quantitative yield.

### Scheme 2.24: Formation of a benzyne precursor



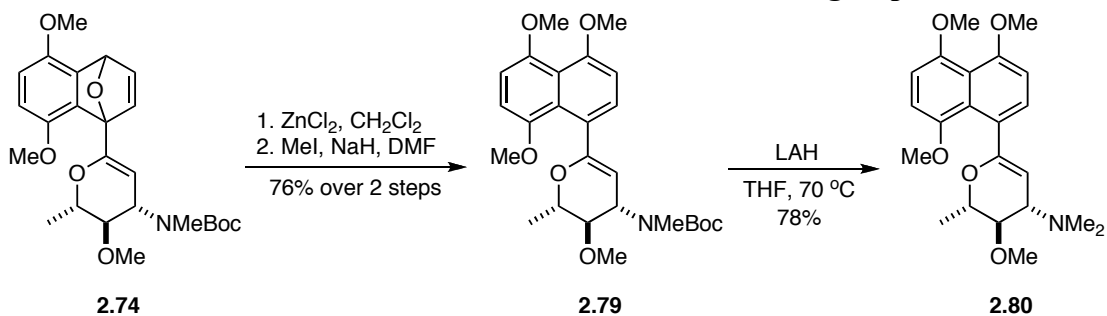
In prior studies in the group, it had been observed that TIPS-protected glycals such as **1.292** did not undergo hydroboration, and this failure was attributed to a steric interaction between the bulky protecting groups and the approaching borane (Section 1.4.4). Hypothesizing that a similar steric interaction between the *N*-Boc group of **2.75** and  $\text{BH}_3\cdot\text{THF}$  prevented hydroboration from occurring, attempts were made to convert the Boc group of carbamate **2.75** to a methyl group using LAH (Scheme 2.25). This reaction was slow at room temperature, and when the mixture was stirred for extended periods of time, starting material and free phenol **2.78** were observed in the  $^1\text{H}$  NMR spectrum.<sup>120,121</sup> None of the desired tertiary amine **2.77** was obtained.

### Scheme 2.25: Attempted Boc reduction



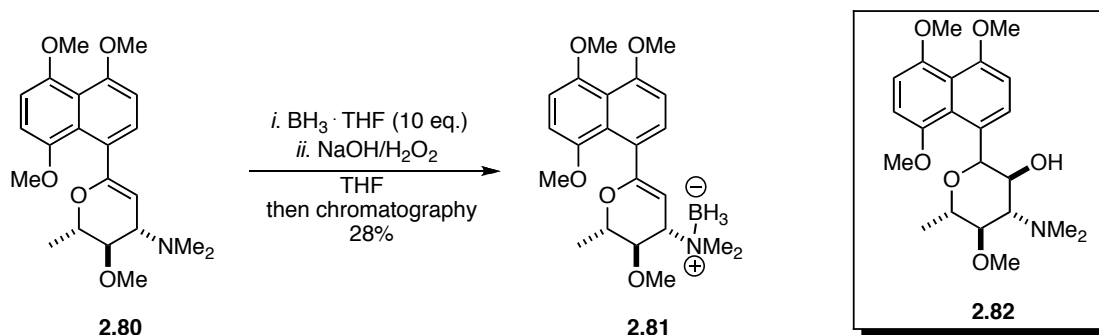
Because the benzyl protecting group of naphthalene **2.75** was labile under these reductive conditions, the phenol was protected as its methyl ether (Scheme 2.26). In the event, ring-opening of **2.74** gave naphthalene **2.79** in 76% yield. Reduction of the Boc group with LAH proceeded smoothly when the reaction mixture was heated to 70 °C, providing tertiary amine **2.80** in 78% yield.

### Scheme 2.26: Successful reduction of the Boc group



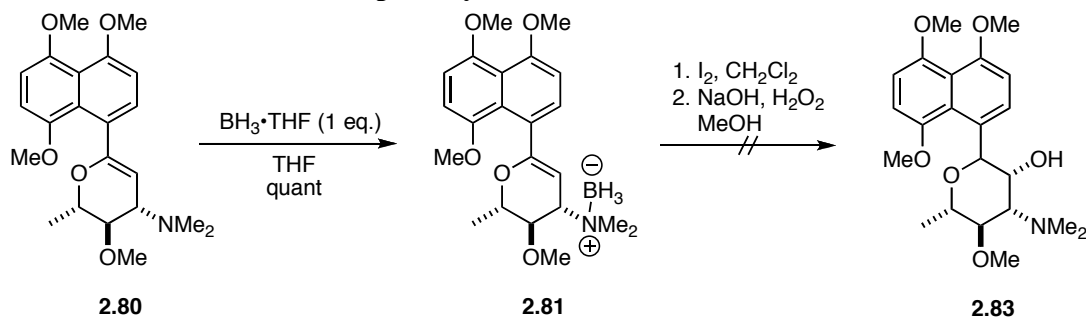
With **2.80** in hand, efforts were turned to its hydroboration-oxidation (Scheme 2.27). Treatment of **2.80** with a large excess of BH<sub>3</sub>•THF did not result in the formation of alcohol **2.82**, but rather amine borate salt **2.81**.

### Scheme 2.27: Attempted hydroboration of the aminosugar



At this point, Vedejs' method for the intramolecular hydroboration of homoallylic amines seemed a viable approach, as the amine borate salt is utilized to direct hydroboration to the same face as the amine.<sup>122</sup> If this procedure were successful, we would extend this method to *allylic* examples, and we would obtain a regiochemistry opposite that observed in the direct hydroboration-oxidation of glycols. Toward that end, we found that simple concentration of the reaction mixture from the hydroboration reaction provided salt **2.81** in quantitative yield (Scheme 2.28).

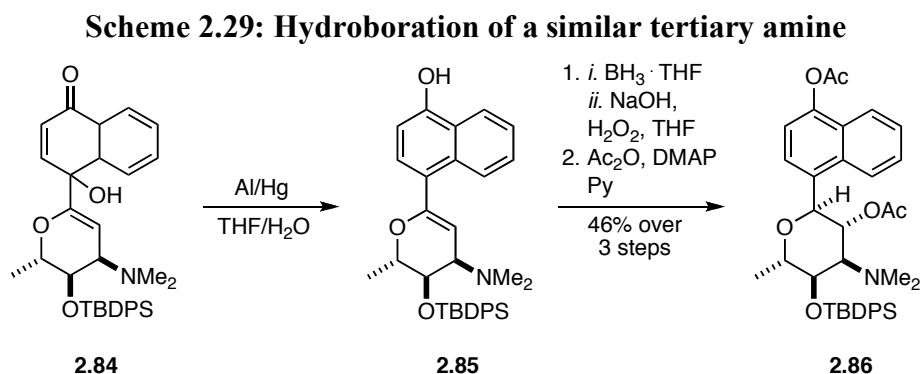
### Scheme 2.28: Attempted hydroboration via the amine borane salt



Unfortunately, when **2.81** was treated sequentially with iodine and then basic H<sub>2</sub>O<sub>2</sub>, a complex mixture was obtained (Scheme 2.28). The presence of a doublet (*J* = 9.0 Hz) in the crude <sup>1</sup>H NMR spectrum at 5.7 ppm may indicate the presence of the

desired alcohol **2.83**, as this signal is near the typical shift for anomeric protons in  $\text{CDCl}_3$  for similar molecules. However, the desired product could not be isolated cleanly from the complex mixture. Attempts to optimize the sequence by varying the temperature of the iodination reaction failed, and a complex mixture of many products was again obtained.

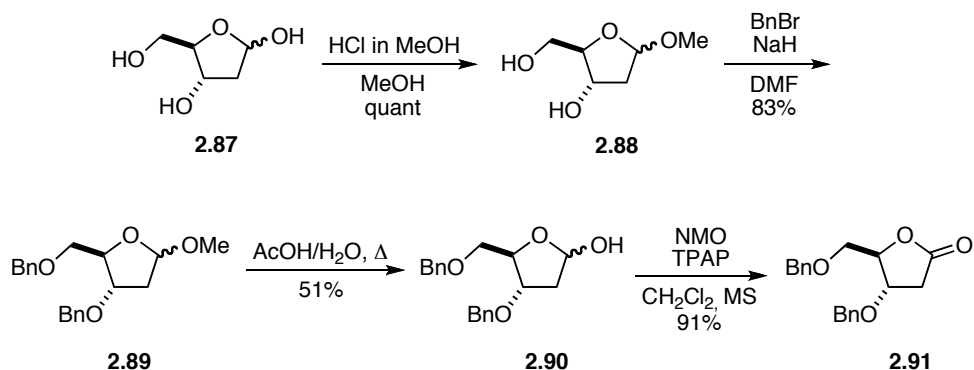
Parker has reported the hydroboration-oxidation of a similar amine (Scheme 2.29).<sup>61</sup> Specifically, the phenol **2.85** was subjected to hydroboration-oxidation, and the intermediate was acylated to give the diacetate **2.86** in good overall yield from quinol **2.84**. When **2.80** was subjected to the Parker conditions, salt **2.81** was again obtained. The reason for this difference in reactivity of the substrates could be due to a steric interaction between the OTBDPS and  $\text{NMe}_2$  groups. This interaction could cause the methyl groups of the amine could orient themselves away from the large silyl group, rendering the lone pair of amine **2.85** less available for attack at the boron atom. We chose not to further explore this system, because the protecting group changes would necessitate a reworking of the entire synthesis.



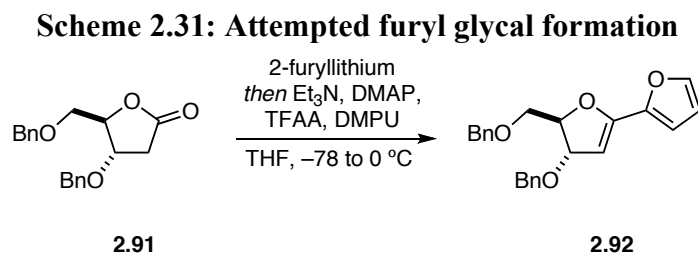
## 2.5. RIBOSE-DERIVED GLYCAL

To investigate gilvocarin-like substrates, a five-membered sugar lactone **2.91** was synthesized (Scheme 2.30). 2-Deoxy-D-ribose (**2.87**) was converted to its methyl acetal by treatment with HCl in MeOH.<sup>123</sup> The resultant acetal **2.88** was protected to give benzyl ether **2.89** in 83% yield.<sup>124</sup> Hydrolysis of the acetal in aqueous acetic acid afforded lactol **2.90**, which was oxidized using TPAP to give benzylated lactone **2.91**.

**Scheme 2.30: Formation of the deoxyribose-derived lactone**



Lactone **2.91** was then treated with 2-furyllithium, followed by the addition of Et<sub>3</sub>N, DMAP, and TFAA (Scheme 2.31). However, this reaction yielded a complex mixture of multiple products. When DMPU was added to the reaction, a compound tentatively assigned as the desired product **2.92** was obtained, albeit in low yield. The instability of the isolated compound precluded full characterization.



We attempted to optimize the first step, addition of 2-furyllithium into the lactone, however starting material was consistently observed in the  $^1\text{H}$  NMR spectrum of the crude material. This gave important information regarding the scope of this reaction; the application to five-membered sugars was not straightforward. We chose not to further explore this model system.

## 2.6. EXPLORING NAPHTHYNE CYCLOADDITIONS WITH GLYCAL

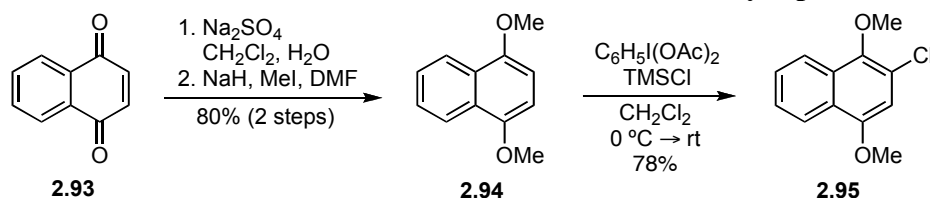
The naphthylene cycloaddition is an area central to the total syntheses in our group. Several of our projects, including the total synthesis of 5-hydroxyaloin A, involve a naphthylene cycloaddition, so we took advantage of this opportunity to explore naphthylene reactivity. Li's example of *naphthylene* generation via *direct deprotonation* of a chloronaphthalene is not well preceded in the literature, thus we wanted to explore this approach further (Section 1.4.2.2).

To this end, 2-chloro-1,4-dimethoxynaphthalene (**2.95**) was synthesized as a potential precursor of a naphthylene. Utilizing a procedure developed in the group,<sup>125</sup> sodium hydrosulfite ( $\text{Na}_2\text{S}_2\text{O}_4$ ) reduction of 1,4-naphthoquinone (**2.93**), followed by methylation delivered 1,4-dimethoxynaphthalene (**2.94**) in 80% yield over two steps (Scheme 2.30). Reacting **2.94** with a mixture of iodosobenzene diacetate and



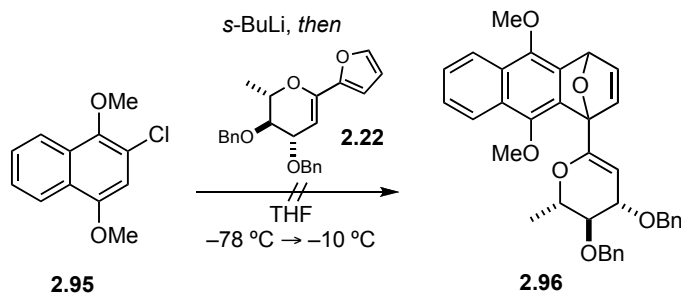
chlorotrimethylsilane (TMS-Cl) according to a procedure described by Evans gave 2-chloro-1,4-dimethoxynaphthalene (**2.95**) in 78% yield.<sup>126</sup>

**Scheme 2.32: The formation of 2-chloro-1,4-dimethoxynaphthalene**



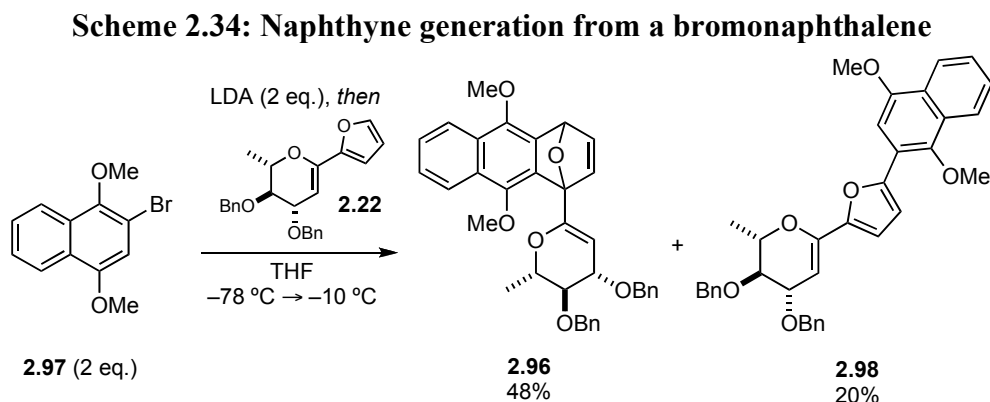
Treatment of naphthalene **2.95** with *s*-BuLi or *t*-BuLi did not provide oxabicyclic **2.96**, but rather resulted in recovered starting material exclusively (Scheme 2.33). This result was unexpected, as Dr. Li had been able to deprotonate chloronaphthalene with *s*-BuLi (Section 1.4.2.2). Deuterium-labeling studies were performed in order to assess if the problem was with the deprotonation or elimination step. There was *no detectible deuterium incorporation* with this substrate.

**Scheme 2.33: Attempted naphthyne generation and cycloaddition using 2-chloro-1,4-dimethoxynaphthalene**



Investigation of the deprotonation of an aryl bromide was also undertaken. 2-Bromo-1,4-dimethoxynaphthalene (**2.97**) was synthesized according to Evans'

procedure.<sup>126</sup> Deprotonation of **2.97** was attempted using lithium diisopropylamide (LDA) (Scheme 2.34). Because cycloadduct **2.96** was not isolated when the reaction was performed at  $-78\text{ }^{\circ}\text{C}$ , the reagents were combined at  $-78\text{ }^{\circ}\text{C}$ , and then the reaction was allowed to warm to  $-10\text{ }^{\circ}\text{C}$ . This procedure gave the desired oxabicyclic **2.96** in 48% yield, along with 20% yield of **2.98**, which arose from the competitive deprotonation of furan **2.22**.

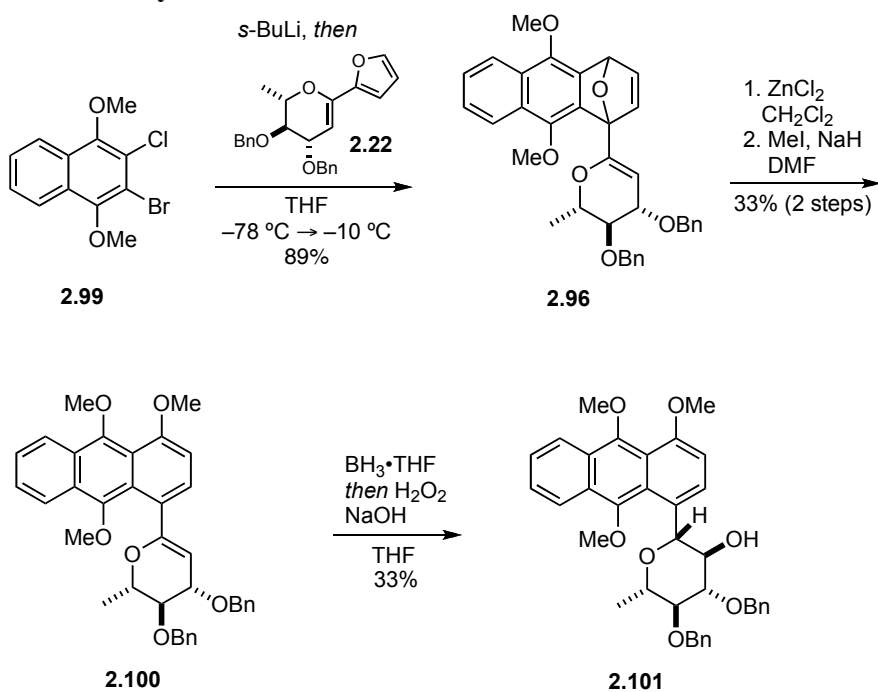


As direct deprotonation of **2.97** to effect naphthyne formation met with limited success, naphthyne generation from a dihalonaphthalene was explored. Metal-halogen exchange, followed by elimination is an alternate method to generate naphthyne. To explore this, 2-chloro-3-bromo-1,4-dimethoxynaphthalene (**2.99**) was prepared according to Evans' procedure.<sup>126</sup> When **2.99** was allowed to react with *n*-BuLi and furan **2.22**, **2.96** was obtained in 89% yield (Scheme 2.35).

Previously, oxabicyclic glycals were shown to undergo ring opening smoothly when treated with  $\text{ZnCl}_2$  at  $-78\text{ }^{\circ}\text{C}$ , followed by warming to  $0\text{ }^{\circ}\text{C}$  (Sections 2.1–2.3). However, when  $\text{ZnCl}_2$  was added to oxabicyclic **2.96** at  $-78\text{ }^{\circ}\text{C}$ , starting material was not consumed, even when the reaction was warmed to room temperature. When **2.96** was

treated with  $\text{ZnCl}_2$  at  $-25\text{ }^\circ\text{C}$  and the reaction mixture was warmed to room temperature, starting material was consumed; however, **2.100** was obtained in only 33% yield (Scheme 2.35). The hydroboration-oxidation of **2.100** was performed to provide the 2-hydroxy *C*-aryl glycoside **2.101** in an unoptimized 33% yield.

**Scheme 2.35: Efficient benzyne generation from a dihalonaphthalenes and the hydroboration/oxidation of anthracene 2.100**



**2.7. SUMMARY AND CONCLUSION**

In the context of expanding methods to form *C*-aryl glycals, a one-pot two-stage synthesis of glycals from sugar lactones was applied to novel substrates. Namely, a furyl galactal and 3-aminoglycal were synthesized using this procedure. The difficulty in applying the dehydration method to the formation of a furanosyl glycal represents an

ongoing challenge for the synthetic community. Although furanosyl glycols are known,<sup>112, 127, 128</sup> methods to synthesize C(1)-substituted furanoid glycols remain rare.<sup>129</sup>

A two-stage benzyne furan cycloaddition methodology was successfully applied to form 2-oxygenated C-aryl glycosides. Cycloadditions using glycols proceed more efficiently as compared with 2-oxygenated substrates, demonstrating an important advantage to the use of 1,2-anhydrosugars. The hydroboration-oxidation of these substrates provided target C(2)-oxygenated substrates derived from glucose, rhamnose, and galactose. Careful considerations must be made when performing hydroboration-oxidation on aminoglycosides, as amine borate salt formation can interfere with hydroboration.

Benzyne generation via the direct deprotonation of arenes is not always general. Dihalonaphthalenes can serve as a reliable alternative, and can undergo metal-halogen exchange followed by elimination to form naphthyne. We have demonstrated the effectiveness of dihalonaphthalenes for benzyne generation in a situation in which deprotonation of a monohalonaphthalene was unsuccessful.

## CHAPTER 3: 5-Hydroxyaloin A

### 3.1. THE BIOLOGY AND CHEMISTRY OF ALOE

Since Roman times, and perhaps even earlier, aloe has been recognized as an important therapeutic agent.<sup>130</sup> The aloe plant has persevered as a remedy throughout history and remains a constituent of burn creams and cosmetics today.<sup>131, 132</sup> The prevalent interest in the aloe plant is evidenced by its widespread cultivation. Although naturally found in eastern and southern Africa predominantly, large farms in the United States, Mexico, Columbia, Venezuela, China, and Thailand exist for the farming of the plant for commercial aloe products.<sup>133</sup>

**Figure 3.1: *Aloe vera* (photograph is copyright by the author)**



The medicinal extracts are derived from two sections of the aloe plant, and different therapeutic properties have been attributed to the mucilage from each segment. The thick substance from the inside of the leaves is referred to as gel and is the component found in cosmetics and skin care creams. Some of the drug-like effects of the

gel include enhanced immunity, improved liver function, prevention of asthma, and anti-inflammatory, anti-ulcer, anti-diabetes and anti-hypertension properties.<sup>133</sup> The liquid derived from the cells adjacent to the vascular bundle is referred to as the exudate,<sup>131</sup> which is known to exhibit purgative properties, owing to its use in laxatives.<sup>133</sup> The exudate is sometimes used as a bittering agent in beverages as well.<sup>133</sup>

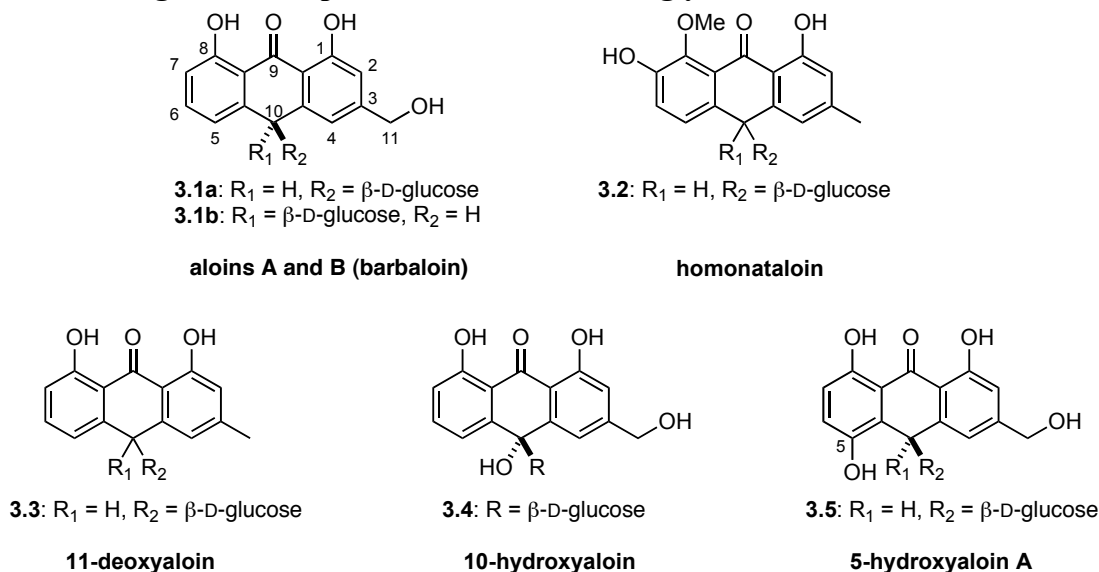
The longstanding interest in aloe and its diverse applications have prompted the study of its constituents in order to gain a better understanding of the therapeutic properties associated with the plant extracts. In a 2000 review, Dagne and coworkers compiled a list of all compounds known to exist in the gel and exudate.<sup>133</sup> The gel, or leaf pulp, is more than 98% water, and its alcohol-insoluble portion comprises polysaccharides, monosaccharides, uronic acid, and several enzymes. The exudate contains a diverse array of compounds; the major groups include alkaloids, anthraquinones, anthrones, chromones, coumarins, pyrans, pyrones, flavanoids, steroid-derived compounds, phenols, and other small aromatic compounds. Although many compounds have been isolated from aloe, a systematic study of each individual component has not been reported, and it is still believed the synergistic action of many of these compounds produces the ultimate therapeutic effect.<sup>131</sup> In some cases, the processing of aloe may destroy many of the believed active components, and in these instances, it may simply be the moisturizing effect of the gel that lends to its curative properties in the context of dry skin and burn relief.<sup>132</sup>

Of the classes of natural products produced by aloe plants, the anthrones are of greatest interest to the Martin group (Figure 3.2). Many of the anthrones contain a sugar moiety at C(10). Although not technically *C*-aryl glycosides, the fact that the sugar moiety is connected directly to the anthrone could lend to an application of our unified approach to form *C*-aryl glycosides.<sup>84, 85</sup> Some representative members of this group are

shown; the most abundant and well-studied are aloins A (**3.1a**) and B (**3.1b**) (Figure 3.2).

The numbering for the anthrone aglycone is shown on structure 3.1.

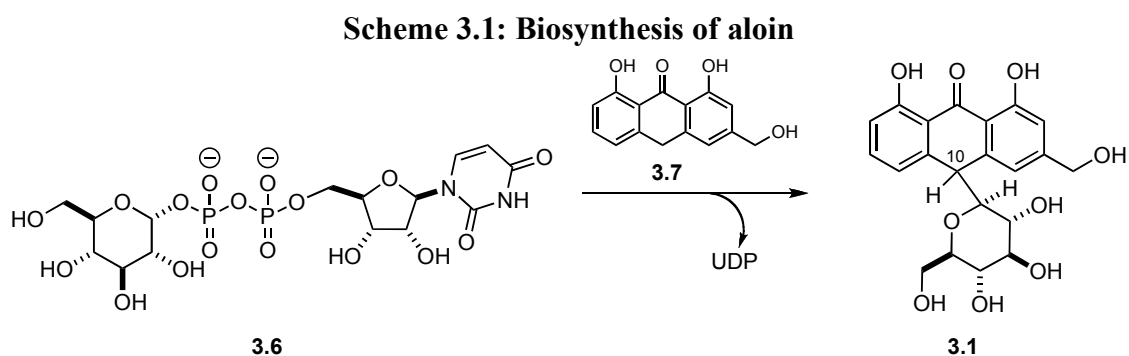
**Figure 3.2: Representative anthrone C-glycosides found in aloe**



Aloins A (**3.1a**) and B (**3.1b**) are collectively known as barbaloin, as they were first isolated from *aloe vera*, which was formerly called barbados aloe. Barbaloin is present in about 85% of the aloe species and comprises between 10–30% of the exudate. Structurally, the aloins differ in configuration only at C(10) of the anthrone. Aloin B (**3.1a**) (10R, 1'S) is the natural product synthesized by the plant, which epimerizes to the more stable aloin A (**3.1b**) (10S, 1'S) upon standing.<sup>133</sup>

The aloe-emodin anthrone (**3.7**) has been detected thus far in the flowers of the aloe plant, but not in the leaves.<sup>133</sup> It is believed that the aloe-emodin anthrone and glucose moiety are attached as a final step in the biosynthesis of aloin B. In a study by Grün and Franz, a crude enzyme extract from the leaves of *A. arborescens* was prepared

in order to investigate the attachment of the sugar to aloin-emodin anthrone in a cell-free environment.<sup>134</sup> They studied various labeled glucose-containing moieties, including free glucose, glucose-1-phosphate, ADP-glucose, GDP-glucose, and UDP-glucose (**3.6**), and they discovered that the species that transfers the glucose molecule to the aloin-emodin anthrone (**3.7**) is UDP-glucose (Scheme 3.1). The mechanism of the transfer has not been elucidated to this date, and the authors do not comment on the stereochemistry at C(10) in the aloin product **3.1**.



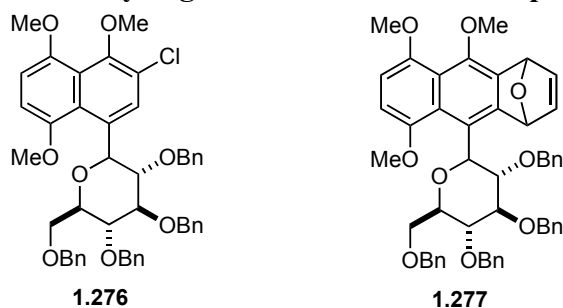
5-Hydroxyaloin A (**3.5**) is a scarcer anthrone, isolated from only a few aloe species, including *Aloe marlothii*<sup>135</sup> and *Aloe broomi*.<sup>136</sup> Its name derives from the fact that it differs from aloins A and B by an additional hydroxyl group at C(5) of the anthrone. The absolute configuration is the more stable A-configuration (10R, 1'S), and it is the only anthrone C-glycoside that has not been found to exist as a diastereomeric pair in plants. The biological activity of this specific anthrone has not been studied; however it may have biological effects similar to other aloe-derived anthrones. The fact that 5-hydroxyaloin A is less abundant also makes it an apt synthetic target, and efforts toward its total synthesis have been undertaken by our research group.



### 3.2. THE INTRAMOLECULAR CYCLOADDITION APPROACH TO 5-HYDROXYALOIN A

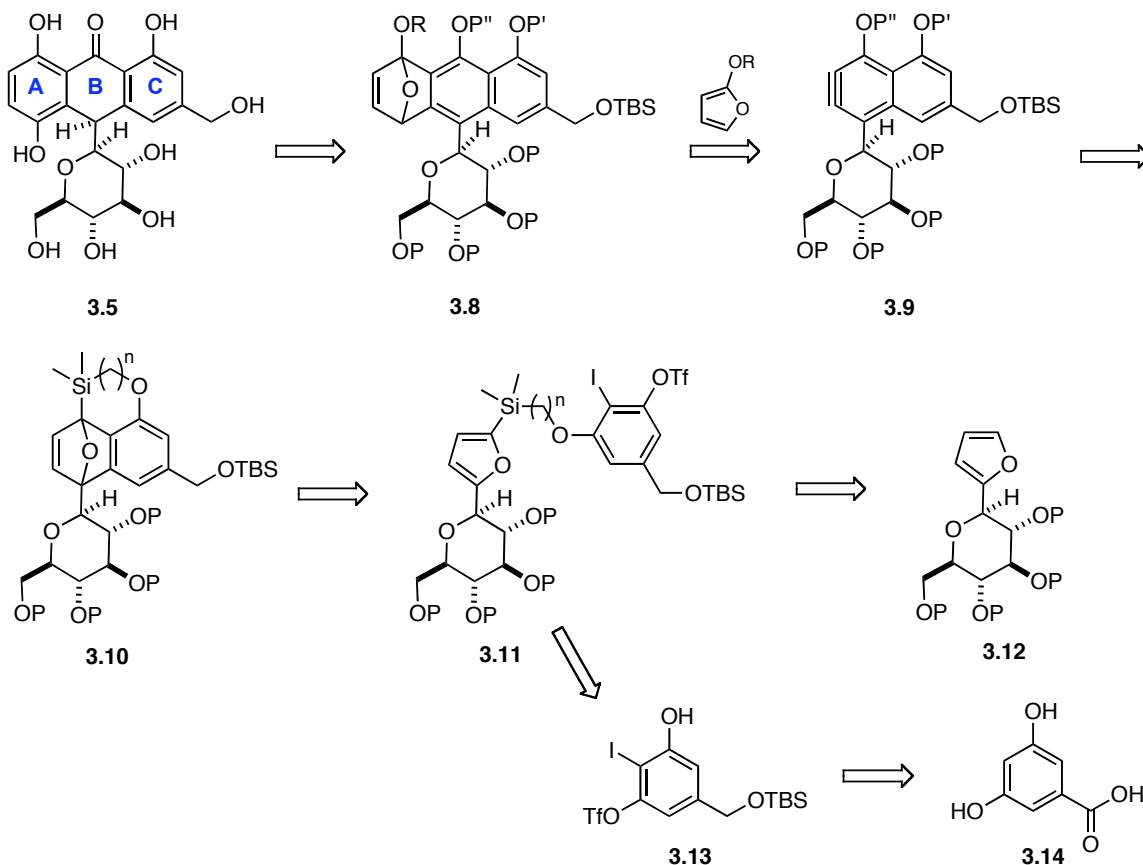
Li's investigations provided valuable insight into the synthetic approach to 5-hydroxyaloin A (Section 1.4.2). Li had generated a naphthyne via chloronaphthalene **1.276**, and was able to access **1.277**, demonstrating that the tricyclic aryl moiety of 5-hydroxyaloin A could be formed by benzyne generation via the direct deprotonation of a chloronaphthalene (Figure 3.3). The ring system Li had generated could not be elaborated to the natural product, however.

**Figure 3.3: Benzyne generation from chloronaphthalenes**



Given this precedent, we expected to be able to generate naphthyne **3.9** from a chloronaphthalene, providing access to 5-hydroxyaloin A (**3.7**) (Scheme 3.2). Our retrosynthetic analysis involves the use of *path a* to access the natural product (Section 1.4.2, Scheme 1.45). Thus, 5-hydroxyaloin A (**3.5**) would come from cycloadduct **3.8**, which would be synthesized via the cycloaddition of naphthyne **3.9** with a substituted furan (Scheme 3.2). Naphthyne **3.9** would derive from silane **3.10**, which is formed via an intramolecular benzyne cycloaddition of ether **3.11**. The ether would come from the linkage of furan **3.12** with triflate **3.13**, via a one-carbon or two-carbon tether. Triflate **3.13** would be accessed from the commercially available  $\alpha$ -resorcylic acid (**3.14**).

### Scheme 3.2: Retrosynthetic approach to 5-hydroxyaloin A



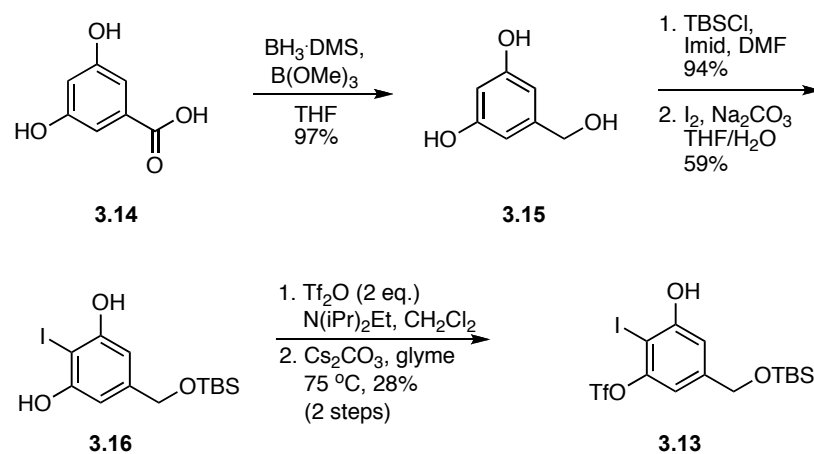
#### 3.2.1. The one-carbon tether approach

Recall that Li had often experienced difficulties generating benzyne via the direct deprotonation of benzenes (Section 1.4.2, Schemes 1.47 and 1.48). This issue, coupled with the fact that his benzyne precursors such as **1.251** and **1.252** required many steps to synthesize, made the first task the development of an expedient synthesis of a suitable aryne. We sought an aromatic substrate that would undergo metal-halogen exchange followed by elimination to produce the reactive species, as prior experiments had revealed that this to be an efficient method to form benzyne without problematic side

reactions (Section 2.6). A resorcinol derivative seemed suitable, as it could be converted to an iodo-triflate species readily, which Suzuki had shown to undergo benzyne generation successfully in various publications.<sup>37,137</sup>

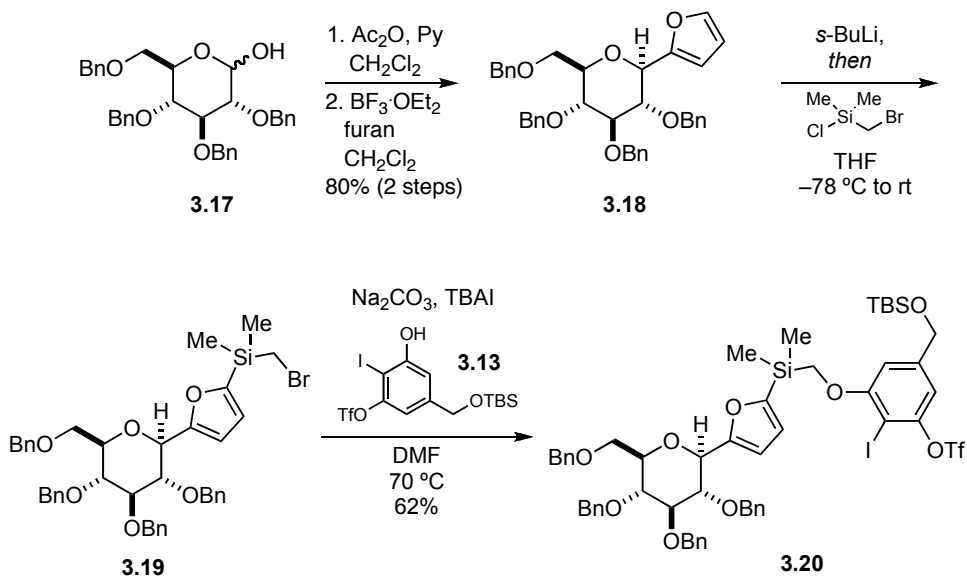
To form the triflate, alcohol **3.15** was prepared from acid **3.14** according to a known literature procedure.<sup>138</sup> Alcohol **3.15** was protected to give an intermediate that underwent regioselective iodination as is well preceded for resorcinol systems,<sup>139</sup> and the desired iodide **3.16** was isolated in 59% yield after recrystallization. The introduction of a single triflate group onto bis-phenol **3.16** was unsuccessful. In fact, starting phenol **3.16** and a bis triflate were the only products isolated from such reactions. Suzuki has addressed this unselective process by developing a procedure for *removal* of one triflate group from a bis triflate using Cs<sub>2</sub>CO<sub>3</sub> in glyme,<sup>139</sup> and we adapted this procedure to arrive at the desired target, iodotriflate **3.13**. Unfortunately, this two-step process was not as efficient as when performed on 2-iodoresorcinol; we were only able to obtain a 28% yield of the phenol **3.13** from bis phenol **3.16**.

### Scheme 3.3: Generation of a resorcinol-derived iodo-triflate



With the synthesis of the requisite phenol **3.13** in place, we then formed a sugar containing the one-carbon tether (Scheme 3.4). Lactol **3.17**, which was available in two steps from commercially available methyl  $\alpha$ -D-glucopyranoside, was converted to the corresponding acetate, which underwent Friedel-Crafts alkylation to afford furan **3.18**. The furan that is initially formed is the  $\alpha$ -anomer, so the mixture must be equilibrated overnight to yield exclusively the  $\beta$ -furyl glycoside **3.18** in 80% yield.<sup>48</sup> Lithiation of **3.18**  $\alpha$  to the furan oxygen atom, followed by treatment with bromomethyl chlorodimethylsilane provided silane **3.19**. The Williamson etherification of bromide **3.19** and phenol **3.13** proceeded in 62% yield,<sup>89</sup> furnishing ether **3.20** and setting the stage for a benzyne cycloaddition.

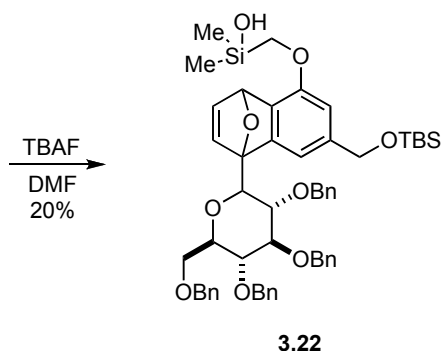
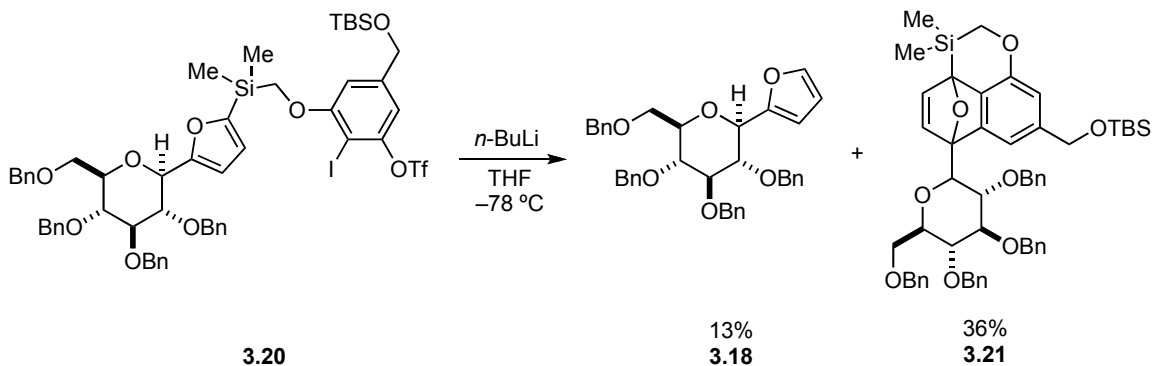
### Scheme 3.4: Synthesis of a sugar containing a one-carbon silicon linker



Although Dr. Li had experienced difficulty with tether cleavage when using the one-carbon tether, we thought that our new aryl piece might render our system a superior benzyne precursor. Instead of direct deprotonation of the aromatic ring to form benzyne as is required by many of Li's precursors, iodide **3.20** could undergo metal-halogen exchange followed by elimination to generate a benzyne. Hopefully, metal-halogen exchange would occur faster than attack at the silicon atom, and tether cleavage would be minimized with our system.

Treatment of iodo-triflate **3.20** with *n*-BuLi did indeed furnish cycloadduct **3.21**, in better yield than most of Dr. Li's precursors, but furan **3.18** was also formed in 13% isolated yield (Scheme 3.5). The remaining material was an intractable mixture of products that was not identified. Cleavage of the tether with TBAF in DMF furnished silanol **3.22** in an unoptimized 20% yield.

### Scheme 3.5: Cycloaddition using the one-carbon tether

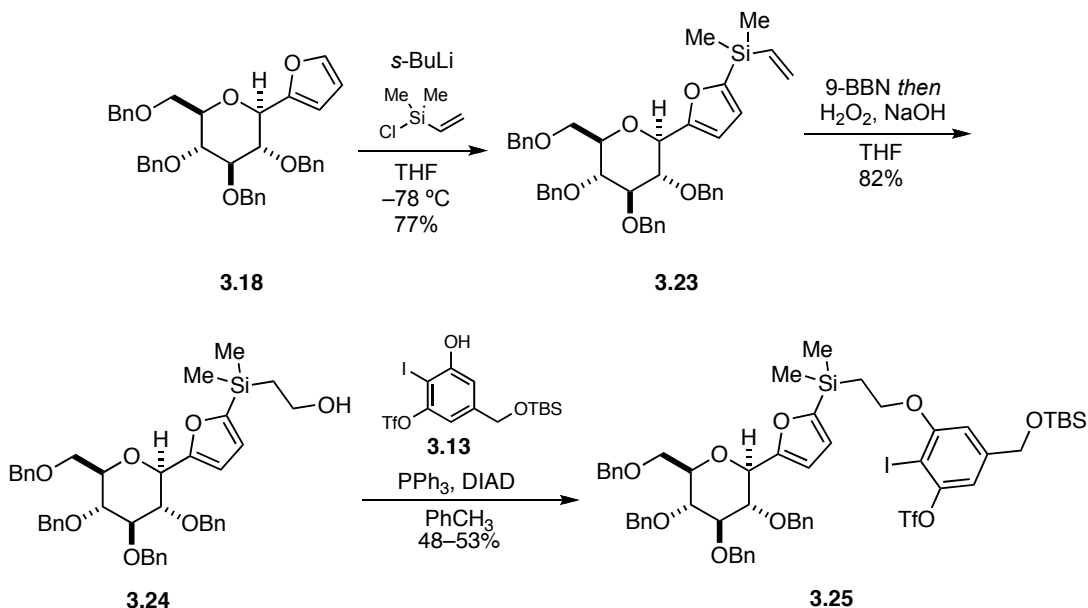


#### 4.1.2. The two-carbon tether approach

Because of the problems associated with attack at the silicon atom during Williamson etherifications when using the one-carbon tether, intermediates containing the two-carbon tether was being formed concurrently.<sup>89</sup> Installation of the vinylsilane proceeded smoothly when furan **3.18** was lithiated and treated with chlorodimethylvinylsilane, which provided **3.23** in 77% yield. Hydroboration/oxidation of **3.23** furnished alcohol **3.24**, a suitable partner for a Mitsunobu etherification. With the requisite alcohol in hand, efforts were turned to the coupling of sugar **3.24** with phenol **3.13**. The etherification of **3.13** proceeded in an average 50% yield, and although various parameters were changed, including solvent, coupling reagent, and order of addition, the

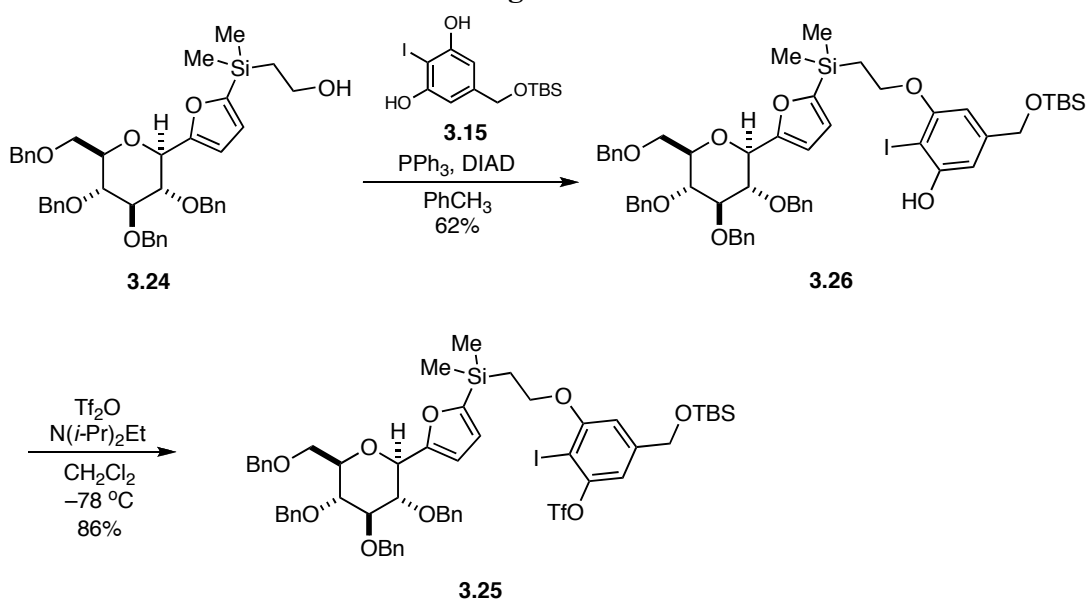
yield could not be improved. We began preliminary investigations into the intramolecular cycloaddition of **3.25** (Table 3.1).

**Scheme 3.6: Introduction of a two-carbon silicon tether**



Although we were able to begin investigating the intramolecular cycloaddition of **3.25**, low yields in the synthesis of triflate **3.13** left little material to work with, thus an alternative approach to benzyne precursor **3.25** was developed. The Mitsunobu etherification was attempted with phenol **3.15**, a precursor in the synthesis of **3.13** (Scheme 3.7). The optimized conditions for the etherification of alcohol **3.24** with bisphenol **3.15** provided ether **3.26** in 62% yield. Phenol **3.26** was converted to triflate **3.25** in 86% yield. In addition to circumventing the inefficient two-step procedure to form monotriflate **3.13**, the etherification was slightly more efficient when phenol **3.15** was used.

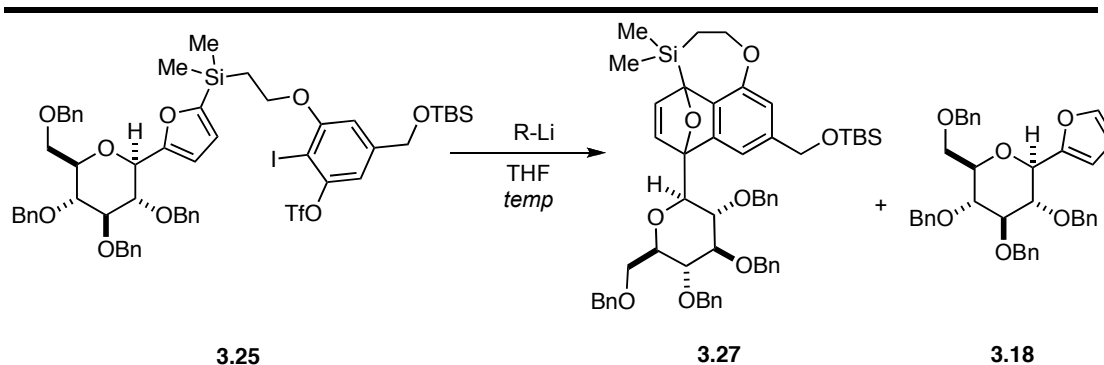
### Scheme 3.7: Streamlining the Mitsunobu etherification



With an improved synthesis of the triflate in place, efforts were focused on the intramolecular cycloaddition (Table 3.1). In order to assess if tether cleavage could be minimized using **3.25**, we attempted metal-halogen exchange with various alkyllithiums at a range of temperatures. When *n*-BuLi was added at  $-78^\circ\text{C}$  and this temperature was maintained for 3 h, cycloadduct **3.27** was not formed (entry 1). At  $-45^\circ\text{C}$  (entry 2), traces of both the desired product **3.27** and furan **3.18** were present; however, the reaction was still very slow. Adding *n*-BuLi at  $-20^\circ\text{C}$  resulted in the formation of both cycloadduct **3.27** and furan **3.18** (entry 3). When **3.25** was treated with *s*-BuLi at  $-20^\circ\text{C}$ , we observed the desired cycloadduct **3.27** in the  $^1\text{H}$  NMR spectrum of the crude material (entry 4); however, starting material remained and furan **3.18** was also observed.



**Table 3.1: Attempted cycloadditions with triflate **3.25****



entry	R-Li	temp	time	result <sup>a</sup>
1	<i>n</i> -BuLi	-78 °C	3 h	slow reaction
2	<i>n</i> -BuLi	-45 °C	1 h	slow reaction
3	<i>n</i> -BuLi	-20 °C	45 min	both <b>3.27</b> and <b>3.18</b> formed
4	<i>s</i> -BuLi	-20 °C	45 min	both <b>3.27</b> and <b>3.18</b> formed
5	<i>t</i> -BuLi	-78 °C	45 min	<b>3.27</b> observed, many TBS signals
6	<i>t</i> -BuLi	-20 °C	45 min	<b>3.27</b> observed, many TBS signals

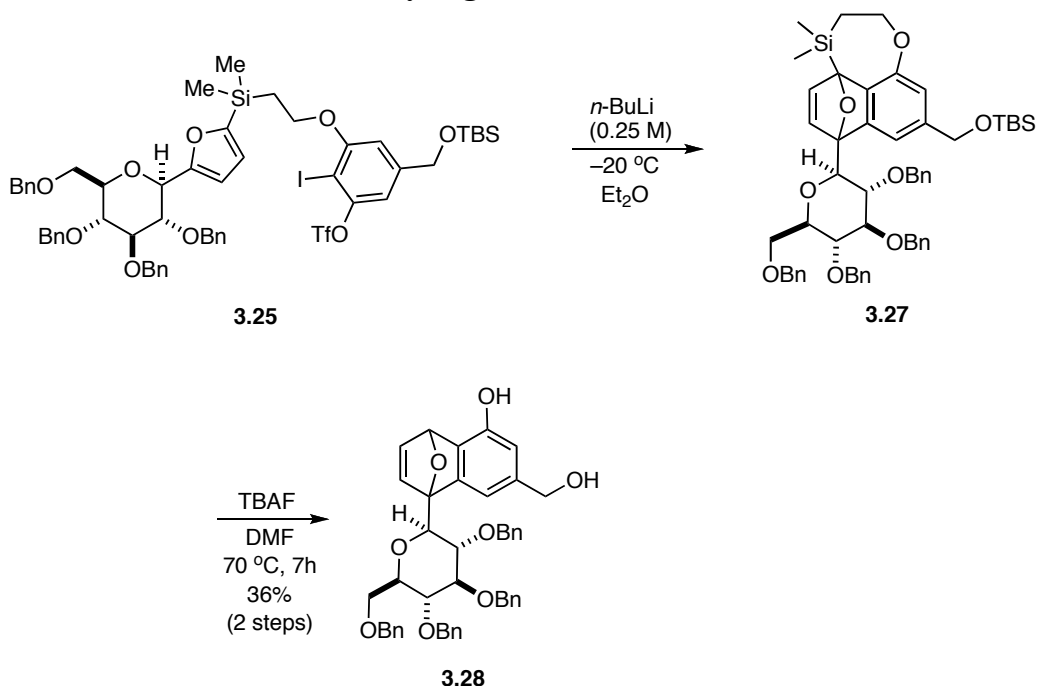
<sup>a</sup> The reactions were analyzed by the <sup>1</sup>H NMR spectrum of the crude reaction mixture.

We thought that use of a bulkier base might minimize tether cleavage, thus *t*-BuLi was tried (entries 5 and 6). Cycloadduct **3.27** was observed by <sup>1</sup>H NMR spectroscopy; however, the appearance of many peaks in the crude <sup>1</sup>H NMR from 0.00–0.10 ppm caused us to abandon this method. This result was not observed in any of the other trials and those peaks were known to not correspond with the diastereomeric cycloadducts **3.27**.

The best conditions for generating a benzyne from triflate **3.25** involved the slow addition, via syringe pump, of a dilute solution of *n*-BuLi (Scheme 3.8). Following workup, the crude mixture of cycloadduct **3.27**, which contained furan **3.18**, was treated

with TBAF in DMF. Using this procedure we could access alcohol **3.28** in 36% yield over two steps.

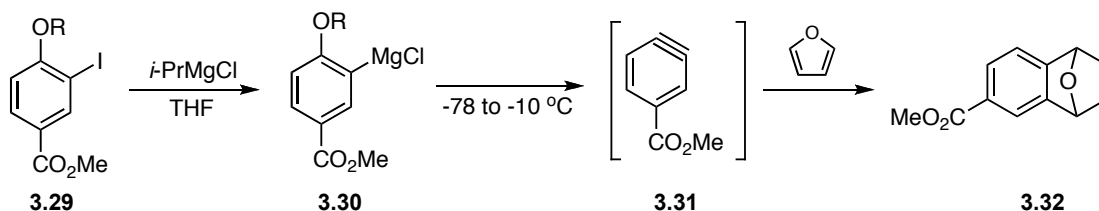
**Scheme 3.8: Benzyne generation via the iodo-triflate**



The unavoidable attack at the silicon atom of the tether prompted us to investigate other reagents to form benzyne. Knochel used Grignard reagents to induce benzyne formation from iodosulfonates, so this seemed an appealing method to try.<sup>140</sup> Knochel found that benzyne could be generated from aryl sulfonates using *i*-PrMgCl; however, the reactions were leaving group dependant. To investigate the effect of the departing group, he reacted sulfonates **3.29a–d** with *i*-PrMgCl at  $-78$  °C, and the mixture was stirred at  $-78$  °C for 15 min (Scheme 3.9). At this point, furan was cannulated into the flask, and the mixture was allowed to warm from  $-78$  °C to  $-10$  °C. The reaction mixture

was then stirred for the amount of time indicated to allow for the generation of benzyne **3.31**, and subsequent [4+2] cycloaddition to form the desired cycloadduct **3.32**.

**Scheme 3.9: Knochel's approach to benzyne generation via Grignard reagents**



a: R = CF <sub>3</sub> SO <sub>2</sub>	0 % yield of oxabicyclic
b: R = CH <sub>3</sub> SO <sub>2</sub>	72 % (30 h)
c: R = 2,5-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub> SO <sub>2</sub>	87% (1 h)
d: R = 4-ClC <sub>6</sub> H <sub>4</sub> SO <sub>2</sub>	93% (4 h)

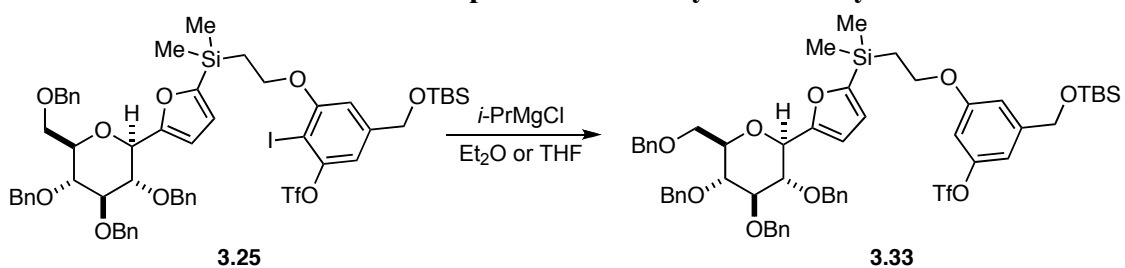
Knochel was unable to isolate **3.32** when triflate **3.29a** was used; a result he hypothesized had to do with the “rapid decomposition” of aryl triflates to form benzyne. If benzyne was generated quickly, by the time furan was added, there would be no benzyne left to trap, and benzyne dimerization products would predominate. However, Knochel did not report the isolation of dimers. The optimal leaving group was the *p*-chlorophenylsulfonate group, which allowed for the formation of cycloadduct **3.32** in 93% yield after 4 h.

We were eager to try these conditions using triflate **3.25**, as our cycloaddition partner was tethered to the molecule. We felt that this “rapid decomposition” of aryl triflates proposed by Knochel would engender our molecule with the reactivity we needed to form cycloadduct **3.27** efficiently. We also hoped that the *i*-PrMgCl would not attack the silicon tether as readily as alkyl lithium reagents.

When we treated **3.25** with *i*-PrMgCl, we did not observe attack on the silicon tether, however reduced triflate **3.33** was the only product from the reaction (Scheme 3.10). We hypothesized that the triflate group did not eliminate at cold temperature and that the arylmagnesium species was quenched with water upon workup to give **3.33**, hence the reaction was warmed from  $-78\text{ }^{\circ}\text{C}$  to room temperature, but reduced material was again obtained.

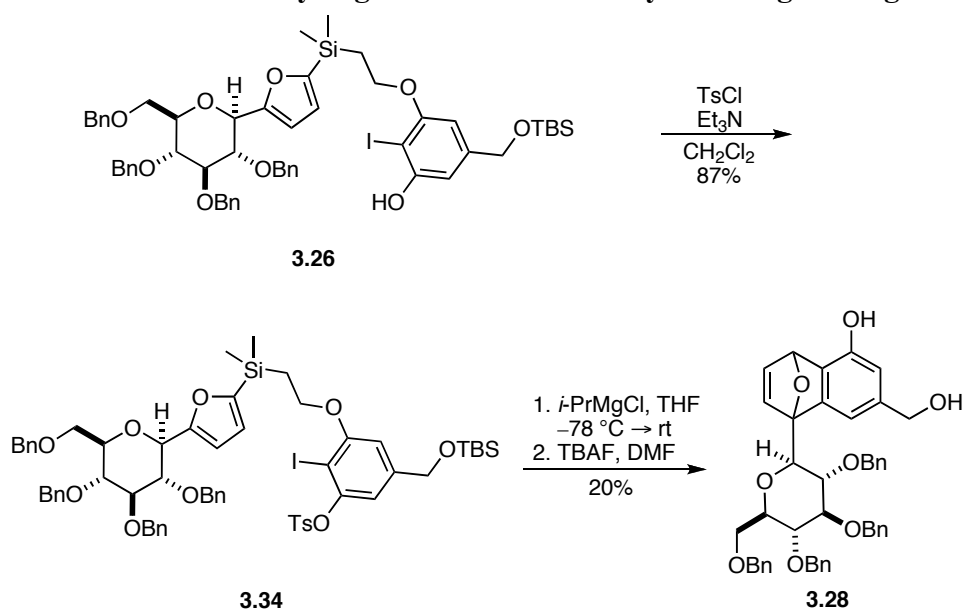
Glycosides like **3.25** often exist as viscous oils, which can trap solvents and water, Consequently, the starting material was rigorously dried by azeotroping it with benzene and heating the oils at  $90\text{ }^{\circ}\text{C}$  under vacuum in an oil bath. Regardless of all efforts to dry the material, **3.33** was the only product isolated from the reaction of triflate **3.25** with *i*-PrMgCl. It seems likely that the reducing agent in this case was the Grignard reagent itself, perhaps resulting from a single electron transfer mechanism being operative.<sup>141, 142</sup>

### Scheme 3.10: Failed attempts to form benzyne from aryl triflate 25



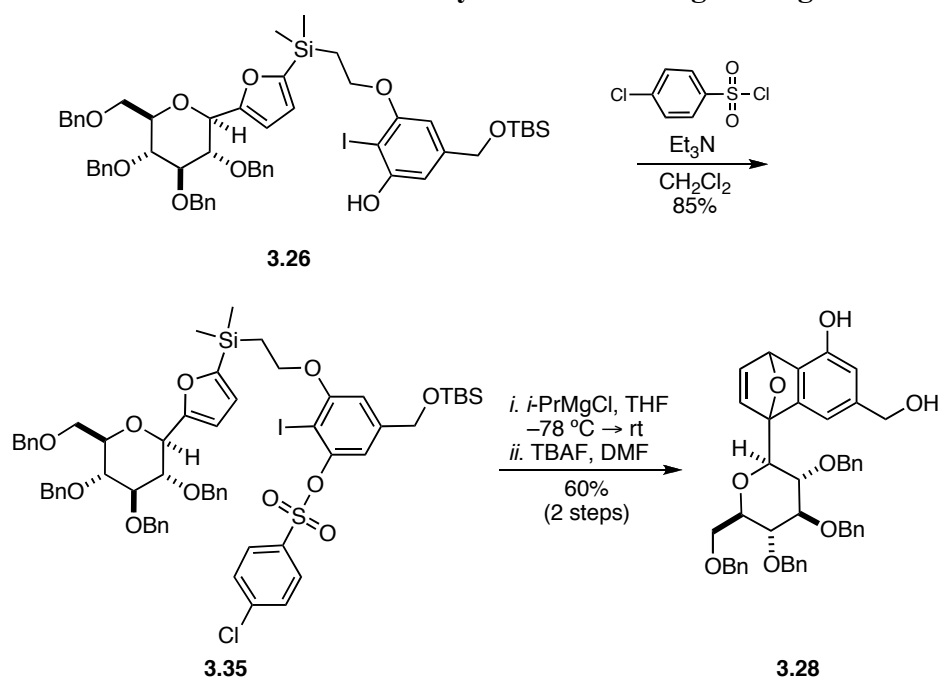
Difficulties using triflate as a leaving group for this reaction prompted us to look at other sulfonate leaving groups that Knochel had used, although we expected these to be less reactive. Toward this goal, the tosyl analog **3.34** and *p*-chlorophenylsulfonyl **3.35** analogs were both synthesized (Scheme 3.11 and 3.12). Benzyne generation from tosylate **3.34** was inefficient (Scheme 3.11), and even with extended reaction times as Knochel had described, **3.28** was isolated in only 20% yield following cleavage of the tether.

**Scheme 3.11: Benzyne generation from a tosylate using *i*-PrMgCl**



Use of the *p*-chlorobenzene sulfonyl group as the leaving group was also explored (Scheme 3.12). When phenol **3.26** was treated with the *p*-chlorosulfonyl chloride and  $\text{Et}_3\text{N}$ , sulfonate **3.35** was obtained in excellent yield. Treatment of **3.35** with *i*-PrMgCl, according to Knochel's protocol, followed by cleavage of the tether and concomitant TBS removal, gave alcohol **3.28** in 60% yield over two steps. This procedure provided the most efficient synthesis of the C ring of 5-hydroxyaloin A.

**Scheme 3.12: Successful cycloaddition using *i*-PrMgCl**



The ability to generate benzyne from **3.35** and not **3.25** raised questions about the effectiveness of the triflate leaving group. In theory, triflate should be a superior leaving group to the *p*-chlorobenzene sulfonate group that finally provided us with acceptable yield of **3.28**. Knochel had assumed that the failure of triflate with his method was due to the high reactivity of the group; however it is not certain that this was the case. When they treated triflate **3.29a** with *i*-PrMgCl then added furan, they did not isolate any of cycloadduct **3.32** from the mixture. However, they do not specify what the products of the reaction were, i. e. dimers or reduced material. It is possible that benzyne was not at all formed in this case. Perhaps the triflate group is so inductively electron withdrawing that it promotes reduction by the Grignard reagent via nucleophilic aromatic substitution, as shown by **3.25a** and **3.25b**, rather than functioning as a leaving group.

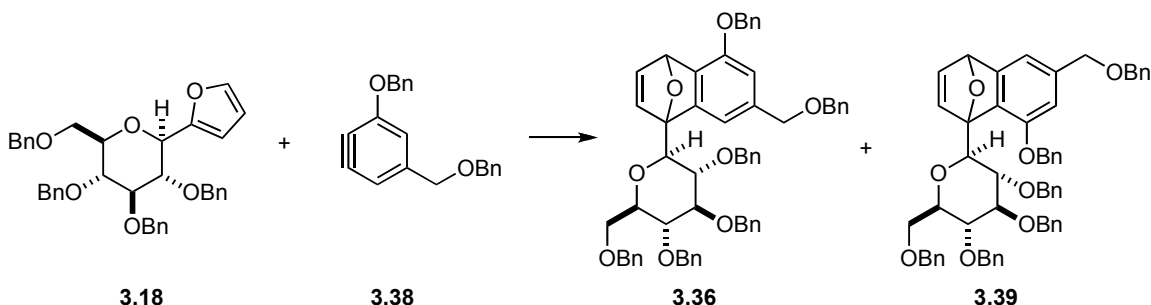




enough material to investigate the halogenation of phenol **3.37**. Thus, a *bimolecular* approach to **3.36** was also explored.

The aim of the bimolecular cycloaddition was to form a benzyne precursor that could undergo a non-regioselective cycloaddition. A mixture of four cycloadducts, **3.36** and **3.39**, would be formed (Scheme 3.14). We could then separate the desired regioisomers **3.36** at this stage. Thus, half of the material would be discarded, but if this route proceeded more efficiently than the intramolecular cycloaddition, we could still perhaps achieve a more efficient, though less elegant, synthesis of phenol **3.37**.

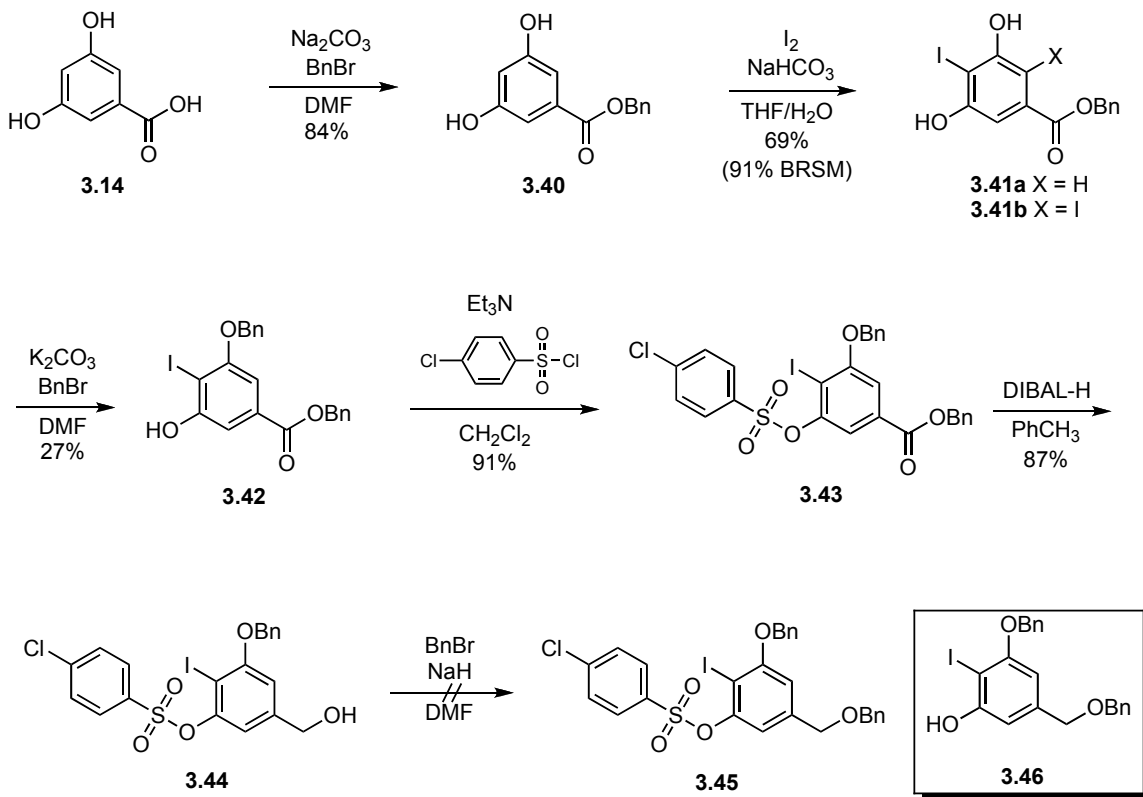
**Scheme 3.14: Rationale for the bimolecular benzyne**



With the synthesis of furan **3.18** already in place, all that was required was a route to a suitable precursor of benzyne **3.38**. Sulfonate **3.45** was chosen to generate **3.38** (Scheme 3.15). Toward this end, acid **3.16** was converted into benzyl ether **3.40** using a known procedure.<sup>143</sup> Iodination of **3.40** proceeded regioselectively, but slowly to give **3.41a**. When 1.2 equivalents of iodine were used, the reaction did not reach completion; however, starting material could be recovered. If a large excess of iodine was used, the bis-iodinated compound **3.41b** would form before the first iodination went to completion. Although **3.41a** could not be monobenzylated selectively, **3.42** could be separated from the mixture of starting material and a bisbenzyloxy compound and was obtained in 27%

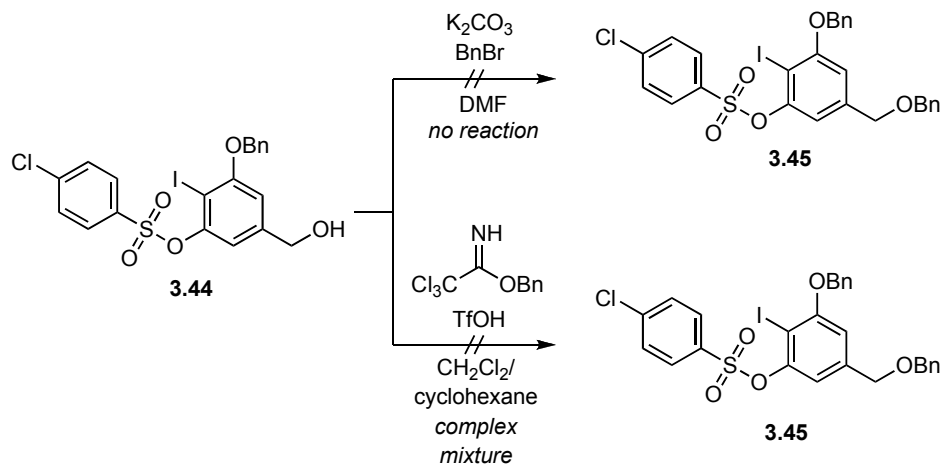
yield. Phenol **3.42** was converted to sulfonate **3.43** in excellent yield. Reduction of the ester efficiently provided alcohol **3.44**, but reaction of **3.44** with NaH and BnBr did not afford **3.45**; rather phenol **3.46** was obtained.

**Scheme 3.15: Attempted formation of the benzyne precursor**



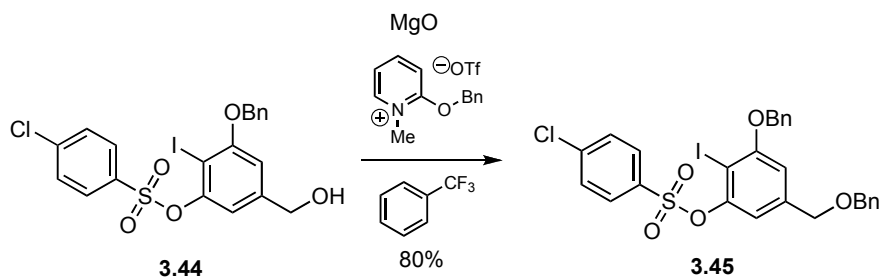
Benzylation of alcohol **3.44** was then attempted using  $\text{K}_2\text{CO}_3$  and BnBr, but even with overnight heating, only starting material was recovered (Scheme 3.16). Treatment of alcohol **3.44** with benzyl-2,2,2-trichloroacetimidate<sup>144</sup> in the presence of a catalytic amount of TfOH afforded a complex mixture of products, from which the desired benzyl ether **3.45** was not isolated.

### Scheme 3.16: Failed *O*-benzylation attempts



Dudley has reported the benzylation of acid- and base-sensitive substrates under mild, neutral conditions using 2-benzyloxy-1-methylpyridinium triflate (Scheme 3.17).<sup>145</sup> <sup>146</sup> These conditions proved ideal for protecting alcohol **3.44** as its benzyl ether. Heating alcohol **3.44** with the pyridinium salt and MgO in  $\alpha,\alpha,\alpha$ -trifluorotoluene provided **3.45** in 80% yield.

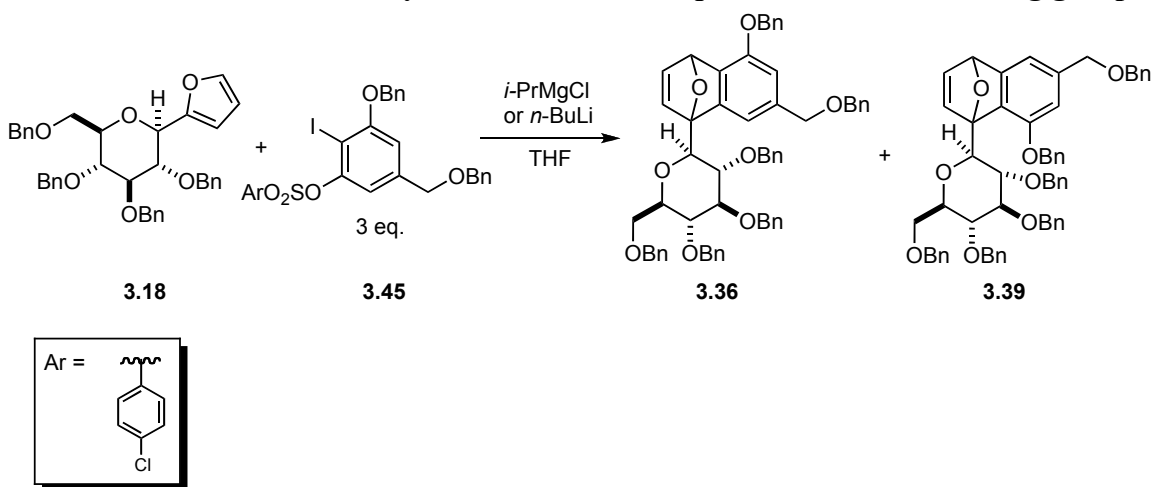
### Scheme 3.17: Successful benzylation using Dudley's reagent



When a mixture of **3.18** and **3.45** was treated with *i*-PrMgCl, the desired cycloadduct was formed in low yield, as evidenced by the <sup>1</sup>H NMR spectrum of the crude reaction mixture (Scheme 3.18). Because we did not need to worry about attack at the Si

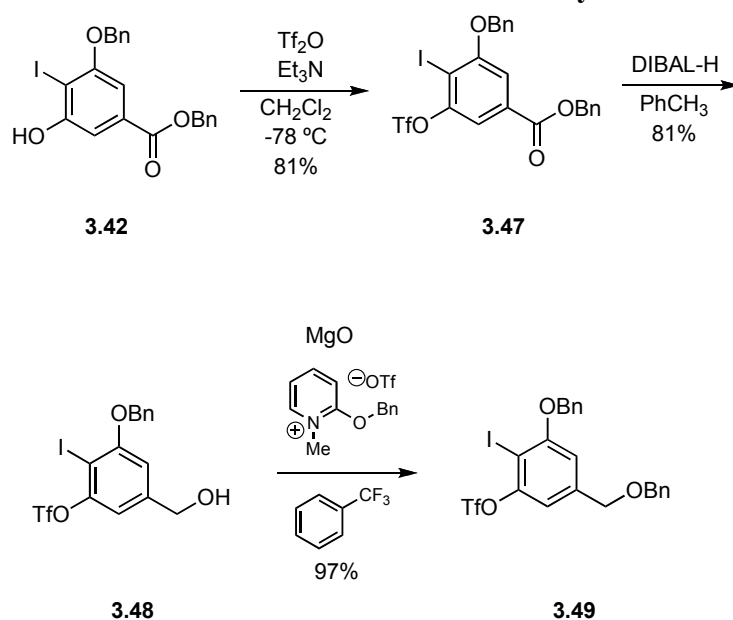
atom with this system, *n*-BuLi was also tried; however, only a trace of the cycloadducts was again observed.

**Scheme 3.18: Bimolecular cycloaddition with the *p*-chlorosulfonate leaving group**



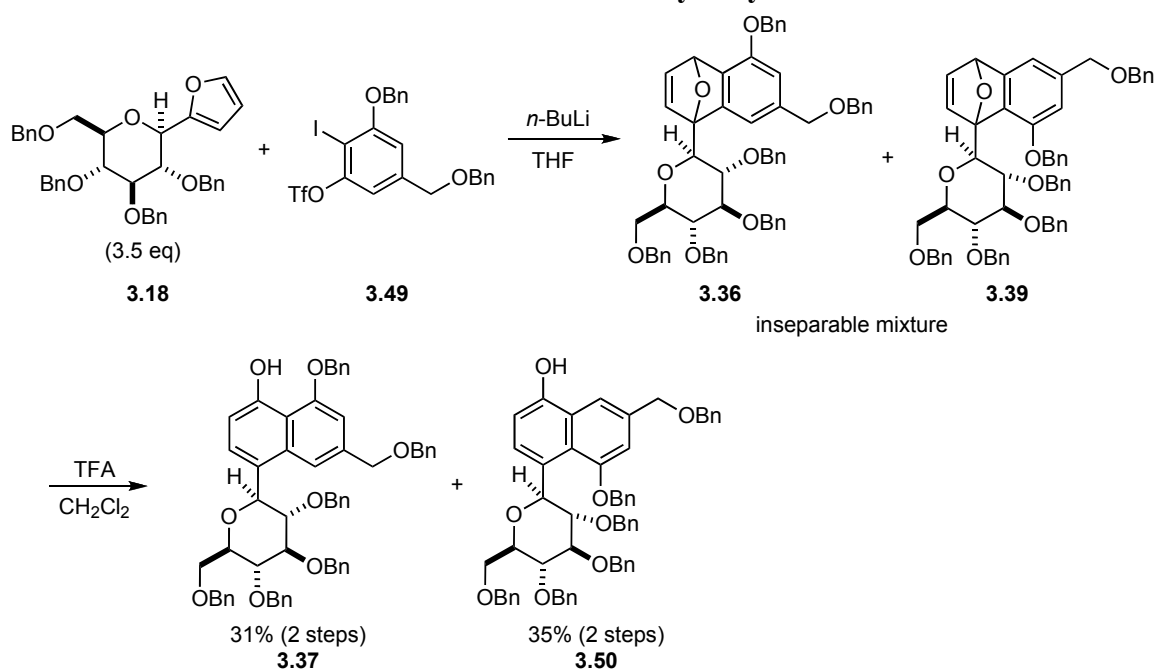
In this situation the silicon tether is not an issue; therefore, we decided to again try a triflate leaving group and use *n*-BuLi for the metal-halogen exchange. Phenol **3.42** was converted to triflate **3.47** (Scheme 3.19). Reduction of the benzyl ester provided **3.48**. *O*-Benzoylation of the alcohol using Dudley's reagent gave triflate **3.49**.

### Scheme 3.19: Triflate for the untethered cycloaddition



The cycloaddition using triflate **3.49** was much more successful, but in order to achieve moderate yields, 3.5 equivalents of **3.18** had to be used (Scheme 3.20). Although unreacted furan could be recovered, its isolation required a difficult separation. Despite challenging chromatographic separations, we were able to obtain phenol **3.37** in appreciable quantities, so we could explore the next steps of the sequence.

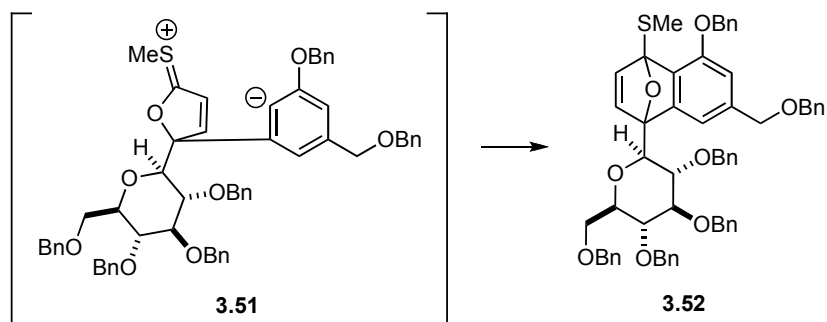
### Scheme 3.20: Bimolecular benzyne cycloaddition



### 3.3.2. Attempted bimolecular, regioselective benzyne cycloaddition

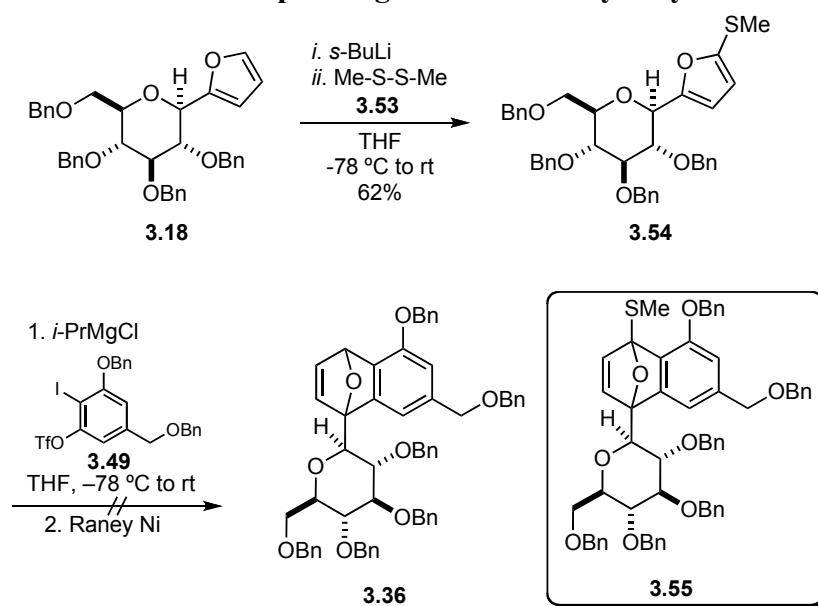
While exploring the bimolecular reaction with sulfonate **3.46**, it occurred to us that perhaps we could design a substrate that would undergo a regioselective cycloaddition based on electronics. Because the  $\alpha$ -position of furan **3.18** is readily deprotonated, we sought to introduce an electron donating group that would direct the cycloaddition in a head-to-head fashion, providing the correct regiochemistry of the unsymmetrical ring of 5-hydroxyaloin A (Scheme 3.21). We required a group that could be readily removed, so we thought a sulfide might prove effective for our purposes.

### Scheme 3.21: Proposed regioselectivity with a furyl sulfide



Introduction of the sulfide moiety proceeded smoothly when furan **3.18** was lithiated and treated with dimethyl disulfide (**3.53**) (Scheme 3.22). Again, 3.5 equivalents of triflate **3.49** were used in the cycloaddition, and an inseparable mixture of products was obtained from the reaction. In order to determine if the desired regioisomer predominated, or was present at all, cleavage of the carbon-sulfur bond was attempted. Cleavage would provide **3.36**, a compound that had been fully characterized previously. Because of the extremely reactive double bond in the molecule, we attempted to use deactivated Raney-Ni for this process; however, we were unable to cleave the C-S bond.

### Scheme 3.22: Attempted regioselective benzyne cycloaddition

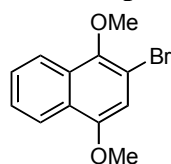


### 3.4. THE ORTHO HALOGENATION OF NAPHTHOLS

At this stage, it was necessary to introduce a halogen ortho to the phenol of **3.37** (Scheme 3.24). Because of our past success generating naphthene from monobromonaphthalene **2.97** using LDA (Figure 3.4 and Section 2.9), we first targeted bromonaphthalene **3.57** (Scheme 3.23). Ortho brominations of phenols have been reported using molecular bromine as the halogenating reagent,<sup>147</sup> however, good results for ortho brominations have also been reported using pyridium bromide perbromide (PyHBr•Br<sub>2</sub>).<sup>148</sup> Treatment of phenol **3.37** with PyHBr•Br<sub>2</sub> furnished the ortho-bromophenol **3.56** in quantitative yield, and protection of **3.56** as its benzyl ether gave bromonaphthalene **3.57**, from which we aimed to form a naphthene.

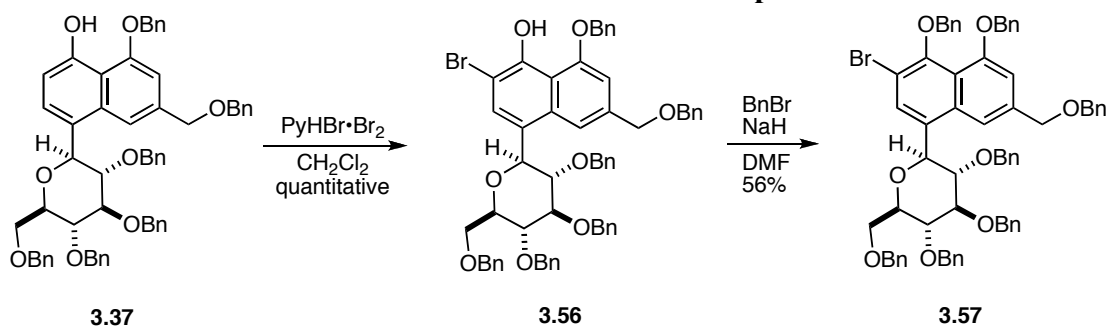


**Figure 3.4: Bromide naphthylene precursor**



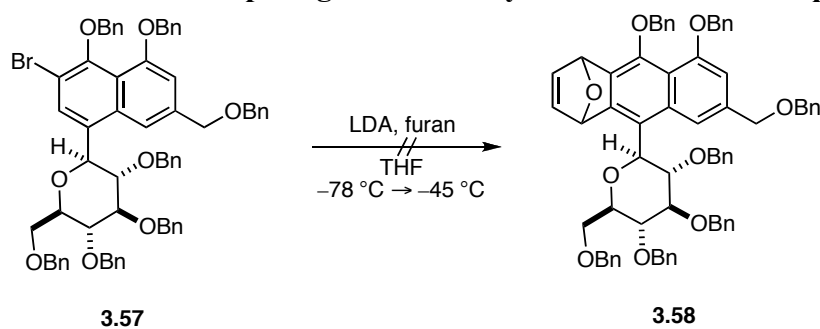
**2.97**

**Scheme 3.23: Formation of a bromonaphthalene**



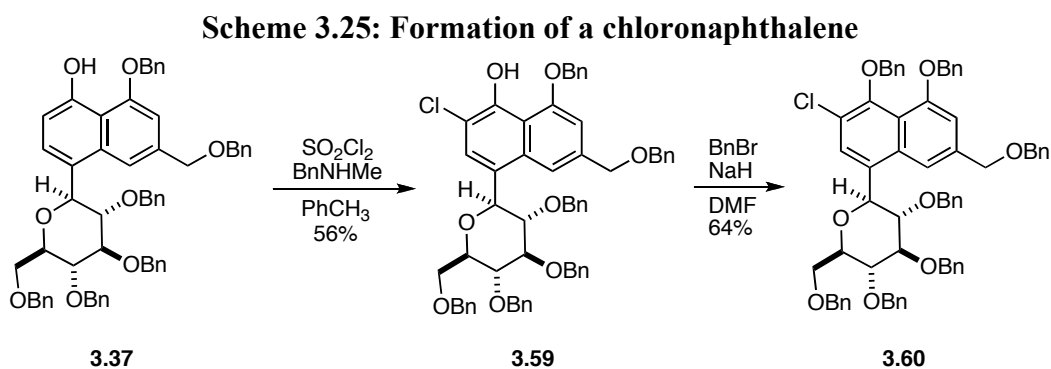
At this point, a model reaction was performed to assess whether a naphthylene could be formed from bromide **3.57** (Scheme 3.24). Treatment of bromide **3.57** with LDA and furan unfortunately did not provide cycloadduct **3.58**, and starting bromide **3.57** was recovered in 90% yield.

**Scheme 3.24: Failed attempt to generate benzyne from the bromonaphthalene**



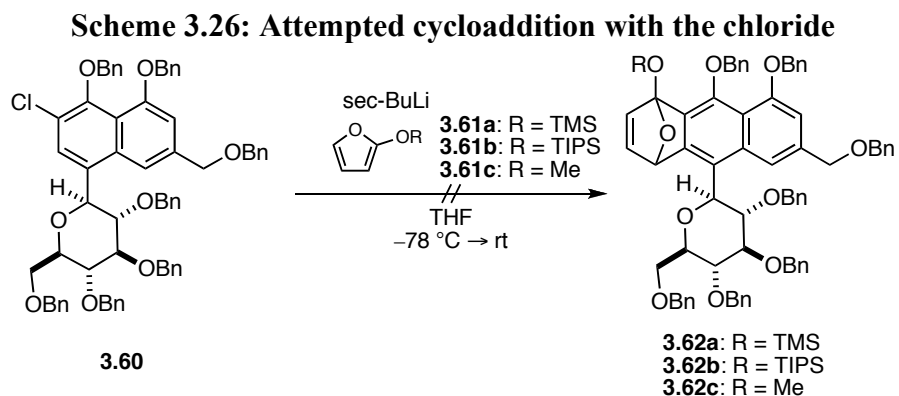
The reaction shown in Scheme 3.24 could be complicated by side reactions, as LDA can also deprotonate furan  $\alpha$  to the oxygen atom at  $-45\text{ }^{\circ}\text{C}$  (Section 2.6). Given this possibility, and the fact that **3.58** was not formed, we targeted the chloro and fluoro analogs of **3.58**.

The chlorination of phenol **3.37** with sulfuryl chloride in the presence of benzylmethylamine provided **3.59** in acceptable yield (Scheme 3.25).<sup>149, 150</sup> Chlorinations using NCS were much less efficient. The phenol was then protected as its benzyl ether to give naphthalene **3.60**.



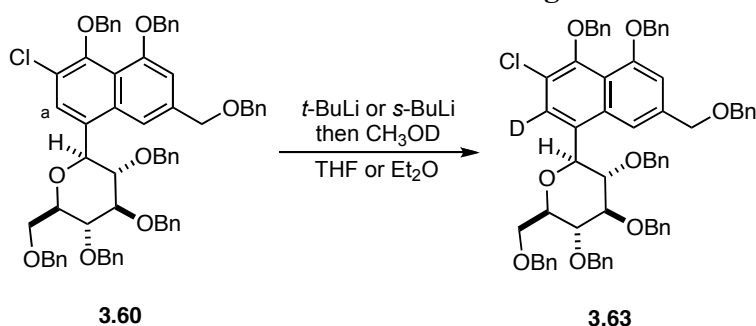
Furans **3.61a** and **3.61b** were first explored as cycloaddition partners for the naphthylene generated from **3.60**. These furans should react to provide cycloadducts **3.62a** or **3.62b** that could be desilylated (Scheme 3.26). *s*-BuLi was added at  $-78\text{ }^{\circ}\text{C}$  to a solution of **3.60**, furan **3.61b** was added, and the solution was warmed to room temperature. Unfortunately, only chloride **3.60** was observed in the  $^1\text{H}$  NMR spectrum. We attempted to use 2-(trimethylsilyloxy)furan (**3.61a**) in the reaction, and then the more robust 2-methoxyfuran (**3.61c**) in the event that the furan was labile under the reaction

conditions. None of these reagents resulted in the formation of cycloadduct **3.62**, however.



In view of these failures, investigations were undertaken in order to determine whether or not deprotonation of **3.60** was occurring (Scheme 3.27). Toward this end, chloride **3.60** was treated with *t*-BuLi or *s*-BuLi at  $-45$ ,  $-78$ , and  $-100$  °C in THF or Et<sub>2</sub>O, and then the reaction mixture was treated with CH<sub>3</sub>OD. These results were inconclusive, unfortunately, as the singlet corresponding to proton “a” is obscured in the <sup>1</sup>H NMR spectrum by the numerous signals from the phenyl rings of the benzyl protecting groups. HRMS was also inconclusive for determining if deuterium incorporation had indeed occurred.

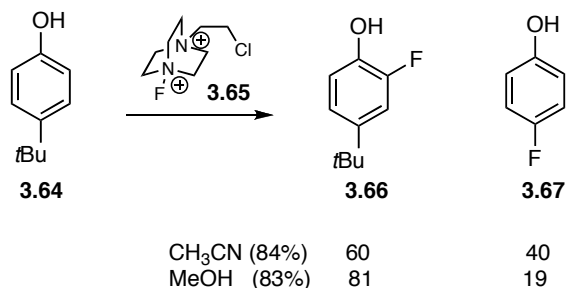
### Scheme 3.27: Deuterium-labeling studies



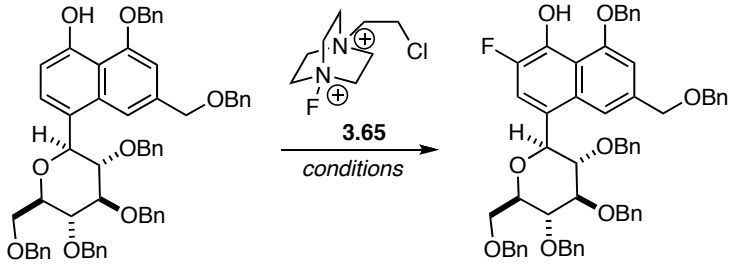
We thought that we might have better results if we could render the proton  $\alpha$  to the halogen more acidic by introducing a more electronegative halogen. Because very good results have been reported for the generation of benzyne via deprotonation  $\alpha$  to a fluorine atom,<sup>151-155</sup> routes to the fluoro analog of **3.60** were investigated. We searched the literature for procedures for the ortho fluorination of phenols using electrophilic fluorinating reagents, which led us to examine the DABCO-derived Selectfluor (**3.65**).<sup>156-161</sup> This reagent is a commercially available electrophilic source of fluorine and is soluble in a limited number of polar solvents, including water, CH<sub>3</sub>CN, MeOH, and DMF. An advantage to this reagent is that the consumption of Selectfluor can be monitored via starch-iodide paper; a positive test indicates that the reagent has not been fully consumed.

The fluorination of phenols using Selectfluor is most often carried out at elevated temperature in CH<sub>3</sub>CN,<sup>162</sup> although in one case, the selectivity of ortho fluorination was improved using MeOH as solvent (Scheme 3.28).<sup>157</sup> The ipso substitution product **3.67** was observed in the fluorinations of phenol **3.64** in CH<sub>3</sub>CN; however, in MeOH, improved yields of the desired ortho-fluorinated phenol **3.66** were reported. In this study, the alkyl group was varied, with smaller alkyl groups showing greater amounts of the ipso-substitution product being formed in CH<sub>3</sub>CN.

### Scheme 3.28: Solvent selectivity with Selectfluor



Despite the fact that ipso substitution could be problematic, we attempted to form ortho-fluorophenol **3.68**. We initially tried the reaction in DMF because we found that phenol **3.37** was insoluble in both MeOH and CH<sub>3</sub>CN (Table 3.2, entry 1). After 10 min the reaction was worked up, based on a negative starch-iodide paper test. On this 20 mg scale however, the test was deceptive and the reaction was not complete. Stopping the reaction early was fortunate, as multiple products had formed, and we were able to recover some of our starting phenol from this trial. Two singlets, interpreted as phenolic signals were observed downfield from 10 ppm in the <sup>1</sup>H NMR spectrum of the crude material, which were presumably phenolic products from unselective fluorination.

**Table 3.2: Attempted fluorination with Selectfluor**

**3.37** **3.65** **3.68**

entry	solvent	temp	time	result <sup>a</sup>
1	DMF	rt	10 min	2 singlets > 10 ppm, 71% RSM
2	CH <sub>3</sub> CN	0 °C	2 h	6 singlets > 10 ppm
3	CH <sub>3</sub> CN	rt	0.5 h	2 singlets > 10 ppm, 63% RSM
4	CH <sub>3</sub> CN	70 °C	0.5 h	Many singlets >10 ppm
5	MeOH	rt	0.5 h	Many singlets > 10 ppm
6	CH <sub>3</sub> CN <sup>b</sup>	rt to 90 °C	5 h	No reaction

<sup>a</sup> The reactions were analyzed by the <sup>1</sup>H NMR spectrum of the crude reaction mixture. <sup>b</sup> 1 eq. DABCO was added to the reaction

We found **3.37** was soluble in hot CH<sub>3</sub>CN, although fluorination of phenol **3.37** under reflux in CH<sub>3</sub>CN proved too harsh (entry 2), and many singlets were observed in the <sup>1</sup>H NMR spectrum around 10 ppm. When **3.37** in CH<sub>3</sub>CN was cooled from 70 °C to room temperature, phenol **3.37** remained in solution, and we were thus able to attempt this reaction at room temperature. Unfortunately, many phenolic products were again observed. Running the reaction in MeOH (entry 5), warming first to solubilize the phenol, gave similar results. Finally, one equivalent of DABCO was added to the reaction, as we hypothesized that the presence of a phenoxide ion might help direct the ortho fluorination; unfortunately, no reaction occurred (entry 6).

Other commercially available fluorinating reagents that have been utilized for the ortho-fluorination of phenols are *N*-fluoropyridinium triflate (NFPT) (**3.69**)<sup>163</sup> and *N*-fluorosulfonimide (NFS) (**3.70**) (Table 3.3),<sup>158</sup> so phenol **3.37** was treated with these fluorinating reagents under a variety of conditions. The reactions were sluggish as compared to those using Selectfluor. Over long periods of time, phenolic peaks were observed in the <sup>1</sup>H NMR spectrum of the crude reaction mixture when phenol **3.37** was treated with NFS. NFPT in CH<sub>2</sub>Cl<sub>2</sub> provided none of the desired product at room temperature (entry 2), and when this reagent was heated with **3.37**, many phenolic signals were again observed (entries 3 and 4), perhaps resulting from non-selective fluorination on various positions of the aromatic ring.

**Table 3.3: Other attempted fluorinations of phenol 3.37**

Reaction scheme: Phenol **3.37** (with OH and OBn groups) reacts under *conditions* to form product **3.68** (with F and OH groups). Reagents **3.69** (N-fluoropyridinium salt) and **3.70** (N-fluorophenylsulfonamide) are shown in boxes.

entry	"F <sup>+</sup> "	solvent	temp	time	result <sup>a</sup>
1	NFS	CH <sub>3</sub> CN	rt	24 h	mainly <b>3.37</b> , 3 new phenolic signals
2	NFPT	CH <sub>2</sub> Cl <sub>2</sub>	rt	24 h	no reaction
3	NFPT	CH <sub>2</sub> Cl <sub>2</sub>	50 °C	6 h	mainly <b>3.37</b> , 3 new phenolic signals
4	NFPT	CH <sub>3</sub> CN/CH <sub>2</sub> Cl <sub>2</sub> <sup>b</sup>	50 °C	6 h	mainly <b>3.37</b> , 3 new phenolic signals
5	NFPT	CH <sub>2</sub> Cl <sub>2</sub>	rt to 70 °C <sup>c</sup>	4 h/24 h	no reaction
6	NFPT	CH <sub>3</sub> CN	rt to 70 °C <sup>c</sup>	4 h/24 h	no reaction
7	NFS	CH <sub>3</sub> CN	rt to 70 °C <sup>c</sup>	4 h/24 h	no reaction

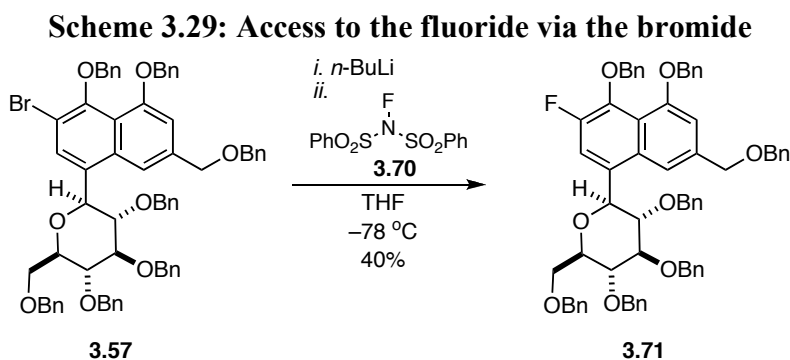
<sup>a</sup> The reactions were analyzed by the <sup>1</sup>H NMR spectrum of the crude reaction mixture. <sup>b</sup> (1:10) ratio <sup>c</sup> 1 eq. of 2,6-lutidine was added to the reaction prior to the fluorinating reagent.

In an attempt to improve the reaction, 2,6-lutidine was added to the reaction. We hoped that this non-nucleophilic base would furnish the phenoxide ion of **3.37** and potentially improve the reaction by directing the ortho fluorination. Unfortunately, the addition of base completely shut down the reactions (entries 5–7), and even with prolonged heating, only starting material was recovered.

As the direct ortho fluorination of phenol **3.37** was not providing the desired fluoride **3.68** cleanly, a new approach to **3.68** was needed. Based on literature example,



bromides can be converted into fluorides via metal-halogen exchange followed by treatment of the intermediate anion with NFS (**3.70**) (Scheme 3.29).<sup>158</sup> Accordingly, bromide **3.57** was lithiated, and NFS (**3.70**) was then added to provide fluoride **3.71** in moderate yield.



We attempted to lithiate **3.71**, and to introduce a deuterium atom ortho to fluorine by adding deuterated methanol to the mixture. Although these reactions were inconclusive, we attempted the cycloaddition reaction nevertheless. Fluoride **3.71** was treated with *t*-BuLi at  $-78\text{ }^{\circ}\text{C}$  for 3 h (Table 3.4), siloxyfuran **3.61a** was added, and the reaction was warmed to rt. Unfortunately, only starting material was observed. We were concerned that adventitious water might be quenching the alkyllithium reagent, so another reaction was attempted, in which NaH was added to the reaction in order to dry fluoride **3.71** (entry 2). Lithiation and cycloaddition were attempted as described in the previous reaction; however, starting fluoride **3.71** was again recovered, along with 2-furanone.

2-Methoxyfuran **3.61c** was also examined as a reaction partner (Table 3.4). Lithiation of **3.71** was attempted at various temperatures using various alkyllithiums, furan **3.61c** was added, and the reaction was warmed to room temperature and stirred

overnight. Unfortunately, we did not isolate **3.62a** or **3.62c** from the reaction, and only starting fluoride **3.71** and butenolide were observed in the  $^1\text{H}$  NMR spectrum of the crude material.

**Table 3.4: Attempted benzyne generation with the fluoride**

$\text{R-Li, } -78\text{ }^\circ\text{C}$   
then 
  
**3.61a:** R = TMS  
**3.61c:** R = Me

THF  
 $-78\text{ }^\circ\text{C}$  to rt

**3.71**

**3.62a:** R = TMS  
**3.62b:** R = Me

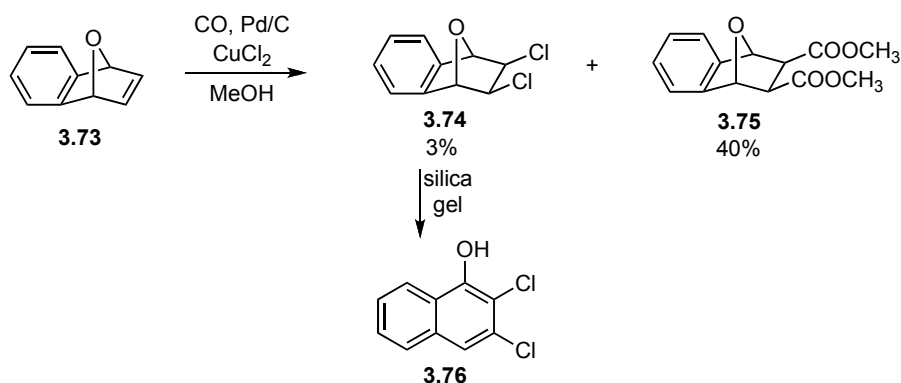
entry	furan	R <sup>a</sup>	temp	time <sup>b</sup>	result <sup>d</sup>
1	<b>3.61a</b>	<i>t</i> -Bu	$-78\text{ }^\circ\text{C}$ to rt	3 h	<p>Major result:</p> <p>Starting fluoride <b>3.71</b> was detected.</p> <p>Decomposition of furan to the butenolide was often observed.</p>
2	<b>3.61a</b>	<i>t</i> -Bu	$-78\text{ }^\circ\text{C}$ to rt	3 h <sup>c</sup>	
3	<b>3.61c</b>	<i>t</i> -Bu	$-78\text{ }^\circ\text{C}$ to rt	3 h <sup>c</sup>	
4	<b>3.61c</b>	<i>t</i> -Bu	$-50\text{ }^\circ\text{C}$ to rt	3 h <sup>c</sup>	
5	<b>3.61c</b>	<i>s</i> -Bu	$-50\text{ }^\circ\text{C}$ to rt	3 h <sup>c</sup>	
6	<b>3.61c</b>	<i>s</i> -Bu	$-78\text{ }^\circ\text{C}$ to rt	6 h <sup>c</sup>	
7	<b>3.61c</b>	<i>s</i> -Bu	$-30\text{ }^\circ\text{C}$ to rt	5 h <sup>c</sup>	

<sup>a</sup> 1.5–2 eq. of the alkyllithium was used. <sup>b</sup> Time at the initial temperature prior to warming to rt. <sup>c</sup> NaH was added to the mixture for drying. <sup>d</sup> The reactions were analyzed by the  $^1\text{H}$  NMR spectrum of the crude reaction mixture.

Repeated difficulties accessing naphthylene from a monohalonaphthalene prompted us to revise our approach. In the synthesis of vineomycinone B12 and in prior glycol work (Sections 1.3.3 and 2.6), we had found that dihalonaphthalenes were excellent precursors of benzyne, and we moved to a tactic to access these dihaloarenes.

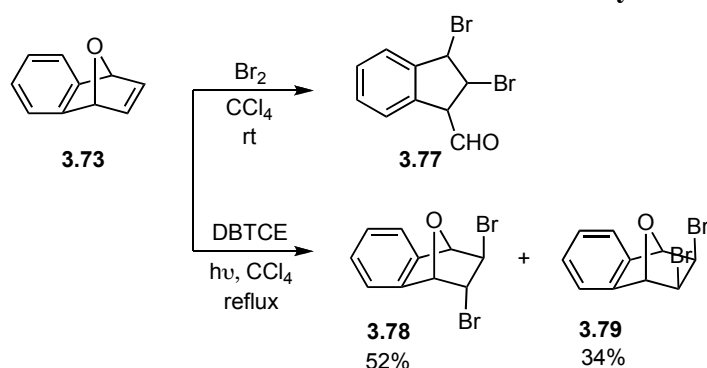


**Scheme 3.30: The formation of a dichloronaphthalene from an oxabicyclic**



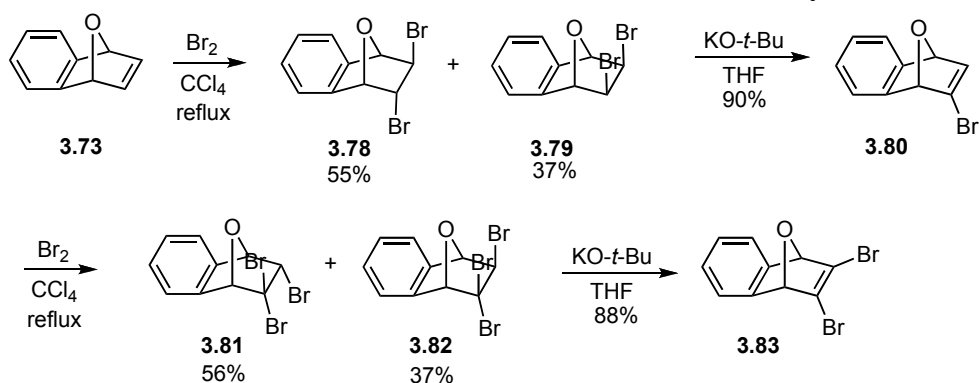
For our synthesis, we would need to introduce a halogen atom that would undergo metal-halogen exchange readily, so we examined the dibromination of oxabicycles with the aim of converting them to dibromonaphthols. Indeed, the dibromination of oxabicycles is also known. However, rearrangement products are observed under certain conditions (Scheme 3.31).<sup>165</sup> Dastan reported that the treatment of oxabicyclic **3.73** with Br<sub>2</sub> at room temperature resulted in the exclusive formation of rearranged aldehyde **3.77**. When oxabicyclic **3.73** was treated with dibromotetrachloroethane (DBTCE) at elevated temperature and irradiated with a sunlamp, a regioisomeric mixture of the dibrominated oxabicycles **3.78** and **3.79** was formed in very good yield. It appears that it is the cationic species that undergoes the rearrangement readily, whereas the radical species does not rearrange.

### Scheme 3.31: The dibromination of oxabicycles

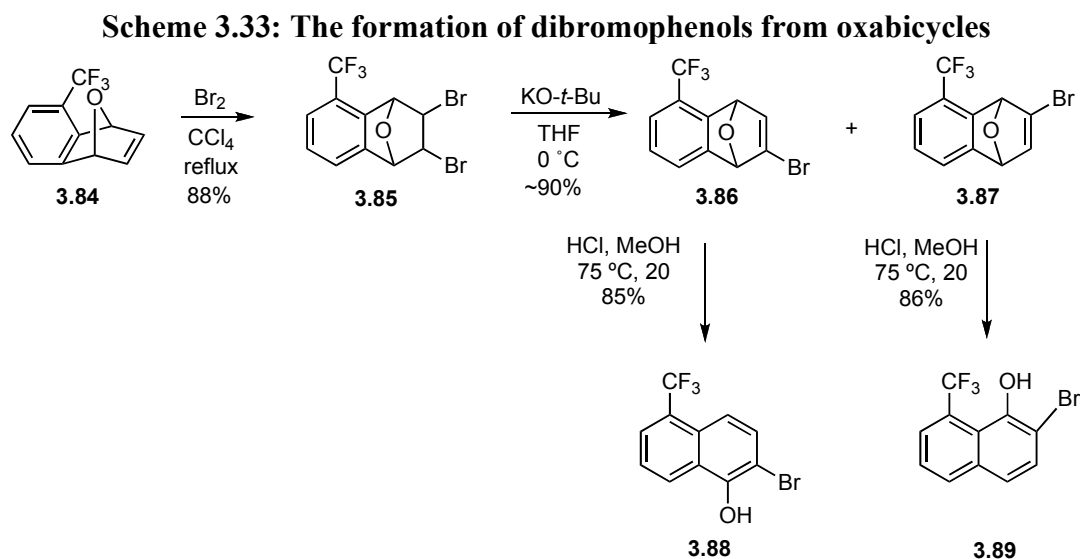


Balci and Dastan also used molecular bromine at elevated temperature to attain a mixture of dibromides **3.78** and **3.79** (Scheme 3.32). These oxabicyclic dibromides can undergo elimination to furnish alkenes when treated with potassium *tert*-butoxide.<sup>166</sup> Bromoalkene **3.80** can undergo bromination again at elevated temperature to furnish tribromides **3.81** and **3.82**, and when this mixture was subjected to the same conditions for elimination, dibromoalkene **3.83** was obtained.

### Scheme 3.32: Formation of a dibrominated oxabicyclic



The conversion of brominated alkenes to phenols has been reported by Schlosser (Scheme 3.33).<sup>167</sup> Schlosser used the same conditions as Balci to access bromoalkenes **3.86** and **3.87**. Both alkenes **3.86** and **3.87** underwent ring opening in good yield by treatment with HCl in MeOH, affording phenols **3.88** and **3.89**, respectively.



Given this promising precedent, our aim was to perform successive bromination-elimination reactions and then to effect ring opening of the dibromide **3.90**, forming dibromonaphthalene **3.91** (Table 3.5). Bromination of alkene **3.36** using molecular bromine at elevated temperature provided a complex mixture of products (entry 1). Analysis of the mixture by IR spectroscopy revealed the presence of an OH stretch and carbonyl stretch, presumably from a rearranged product and a ring-opened product. After several attempts to brominate **3.36** using molecular bromine, Dastan's conditions were tried (entries 2-4). No reaction occurred when **3.36** was treated with AIBN and DBTCE (entry 2), and attempts to brominate alkene **3.36** at elevated temperature for extended

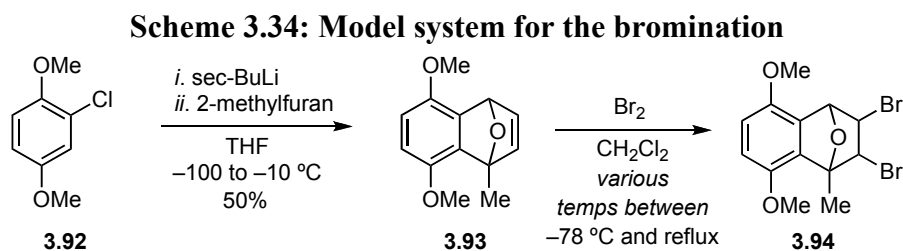
periods of time resulted in a mixture of unidentified products (entries 3 and 4). Bromination of the olefin using  $\text{PyHBr}_3$  was examined (entry 5); however, this reaction also gave a complex mixture, and dibromide **3.90** was not isolated.

**Table 3.5: Attempted dibromination of our oxabicyclic**

entry	conditions	temp	time	result
1	$\text{Br}_2$ , $\text{CCl}_4$	77 °C	5 min	OH and C=O stretch <sup>a</sup>
2	AIBN, DBTCE, $\text{CCl}_4$ hv	70 °C	1 h	NR <sup>b</sup>
3	AIBN, DBTCE, $\text{CCl}_4$ hv	77 °C	20 h	singlets at 9.8, 10.0 ppm <sup>b</sup> OH stretch <sup>a</sup>
4	AIBN, DBTCE, $\text{CCl}_4$ hv	77 °C	1.5 h	mainly SM, s at 10.0 ppm <sup>b</sup>
5	$\text{PyHBr}_3$ , $\text{CH}_2\text{Cl}_2$	rt	15 min	complex mixture

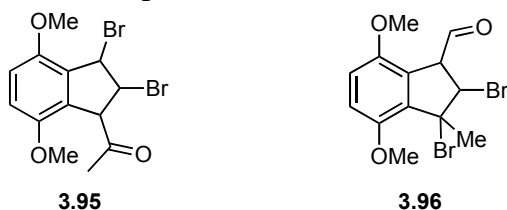
<sup>a</sup> IR analysis <sup>b</sup> NMR analysis

Our attention was turned to a model system at this point, as the supply of oxabicyclic **3.36** was limited (Scheme 3.34). To synthesize the model, the cycloaddition of 2-chloro-1,4-dimethoxybenzene (**3.92**) and 2-methylfuran was conducted to provide alkene **3.93** in 50% unoptimized yield. The bromination of **3.93** was tried both under reflux and at colder temperatures, but it did not appear that dibromide **3.94** was being formed by LRMS.



In addition to the desired brominated oxabicyclic **3.94**, the rearranged compounds, ketone **3.95** and aldehyde **3.96** are potential products of the bromination (Figure 3.4). When **3.93** was treated with  $\text{Br}_2$  at elevated temperature, singlets that may correspond to aldehyde protons were observed in the  $^1\text{H}$  NMR spectrum of the crude mixture. The major spot by TLC was found to be a mixture of products, and analysis of this mixture by IR spectroscopy revealed an OH stretch. It was obvious at this point that this method would be difficult to apply to our system, and this approach to dibromonaphthalenes was abandoned.

**Figure 3.6: Potential products from the bromination of 3.93**



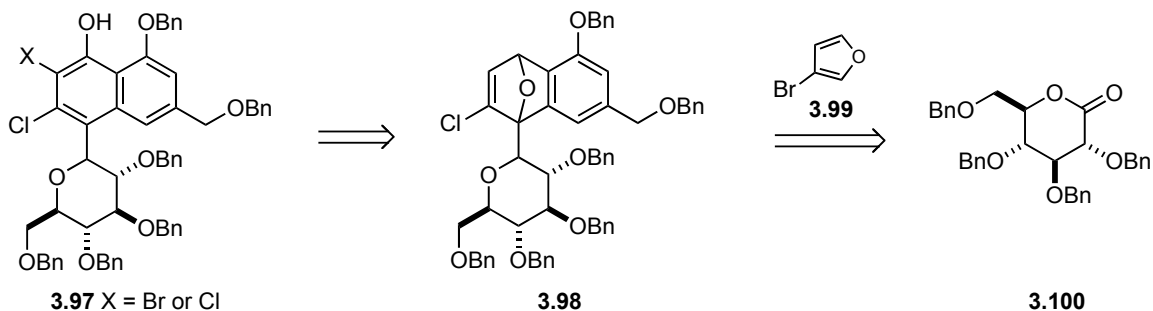
### 3.5.2. 3-Halofurans to access dihalonaphthalenes

We were still interested in accessing dihalonaphthalenes, so we reinvestigated an approach that was briefly attempted by Dr. Li. Dihalonaphthalenes **3.97** could come



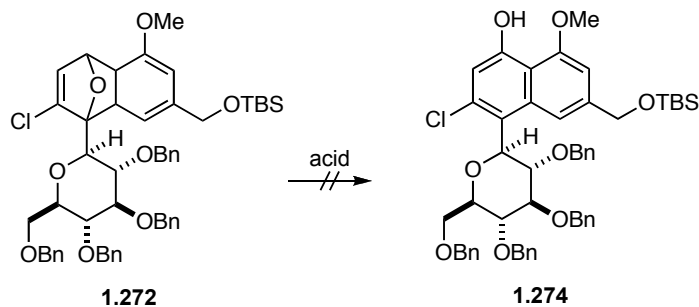
from halogenated oxabicyclic **3.98** via ring-opening and halogenation (Scheme 3.35). The oxabicyclic would be accessed via the addition of a 3-halofuran **3.99** to a sugar lactone **3.100**.

**Scheme 3.35: Approach to dihalonaphthalenes via lactones**



Dr. Li had attempted the ring opening with chlorinated oxabicyclic **1.272**, but when **1.272** was treated with TFA, there was no reaction (Scheme 3.36). Treatment of **1.272** with TMSOTf did not furnish **1.274**; rather a phenolic product that had lost the sugar portion of the molecule was isolated, although this phenol was not fully characterized.

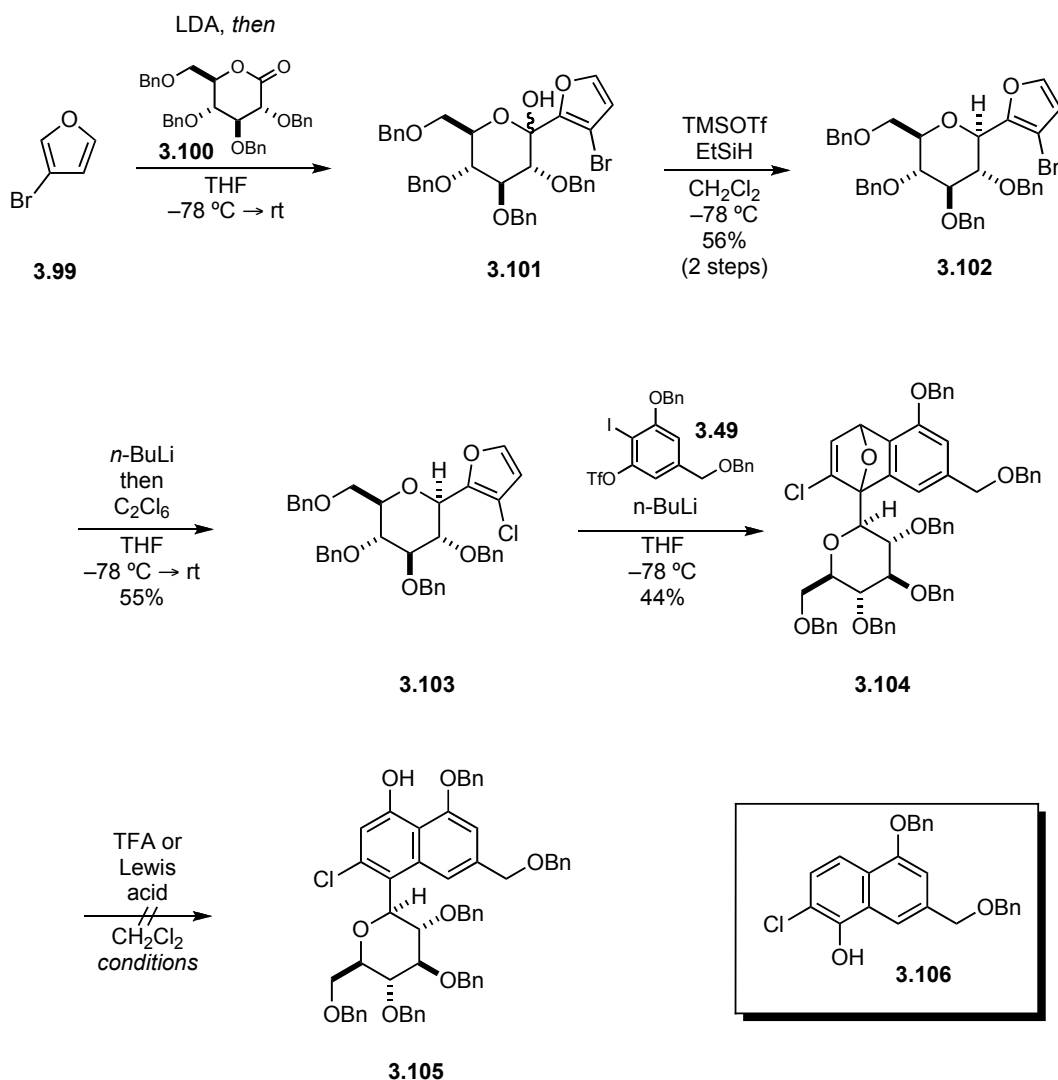
**Scheme 3.36: Failed ring opening of halogenated oxabicyclic**



We felt that this approach warranted reinvestigation because we had discovered that ring-opening conditions are very substrate-specific, and perhaps a chlorinated oxabicyclic could be opened with a different Lewis acid.  $\text{ZnCl}_2$  would serve as our starting point, given our success using this Lewis acid for the ring opening of glycols.

Our studies began with chlorofuran **3.103** that Li had used, although we developed a modified synthesis (Scheme 3.37). Due to the inefficiency and difficult distillations when generating 3-chlorofuran from 3-bromofuran,<sup>168</sup> lactone **3.100** was reacted with lithiated 3-bromofuran to provide lactol **3.101**. Reduction of **3.101** furnished furyl glycoside **3.102**, which was efficiently converted to the chloride **3.103**. The stage was set to investigate the benzyne cycloaddition with this substrate. We again used triflate **3.49** as we had the most success using this substrate in other bimolecular cycloadditions. The reaction proceeded in 44% yield, and required a threefold excess of furan **3.103**. The cycloaddition was not regioselective as we had hoped, but we were able to separate the desired regioisomer **3.104** and test the ring opening step. If we could access naphthol **3.105**, this would allow for two possible methods of benzyne generation. Naphthol **3.105** could either be protected and deprotonated to form benzyne directly, or an additional halogen could be introduced to produce a dihalonaphthalene, followed by benzyne generation. Unfortunately, chloride **3.104** proved as robust as chloride **1.272**, and was unreactive when mild Lewis or Brønsted acids were used. When **3.104** was subjected to stronger Lewis acidic conditions, such as TMSOTf, the naphthol **3.106** was formed.

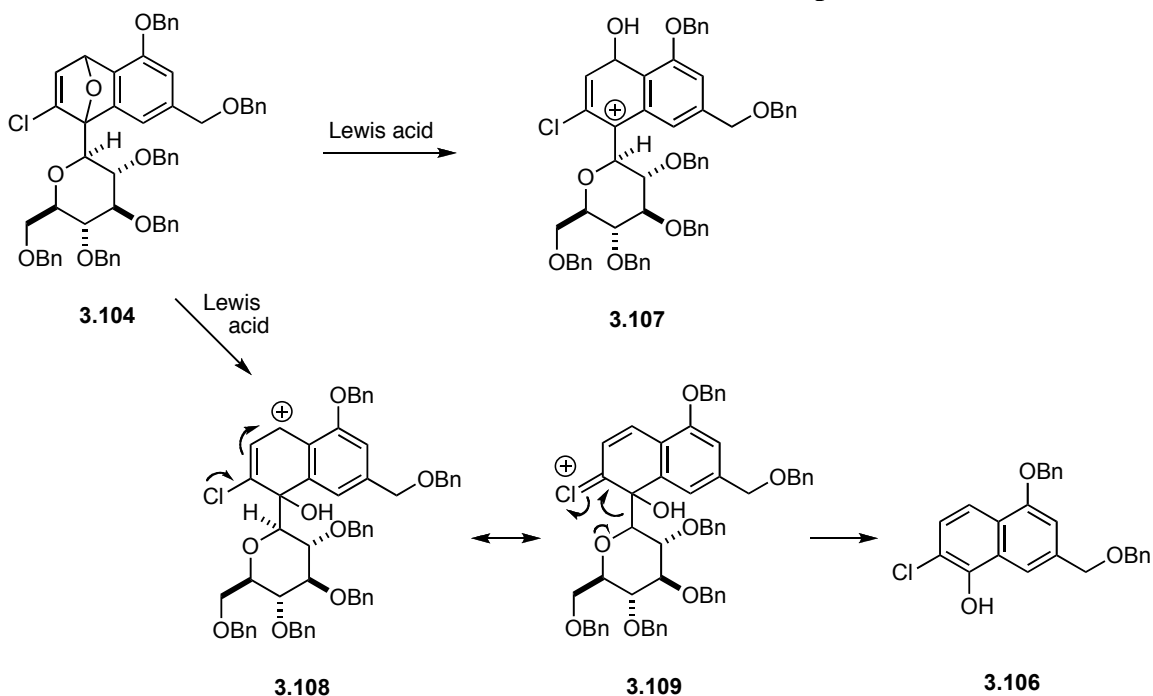
### Scheme 3.37: Formation and cycloaddition of a halofuran



The difficulty encountered in effecting ring opening of **3.104** and the formation of naphthol **3.106** can both be attributed to carbocation stability (Scheme 3.38). Ring opening in the desired orientation would give intermediate **3.107**, with a carbocation that is *destabilized* by the inductive electron withdrawing effect of the chlorine atom. Opening of the oxabicyclic in the undesired orientation would give intermediate **3.108**, where the carbocation can be stabilized, as shown by canonical form **3.109**.

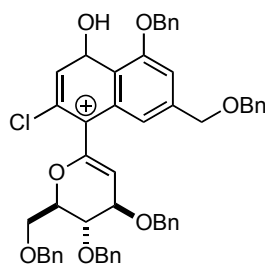
Unfortunately, this system cannot rearomatize without expulsion of the glycoside to produce naphthol **3.106**.

**Scheme 3.38: Rationale for the formation of naphthol 3.106**



This setback prompted us to reexamine this approach. We needed a substrate that had electronic factors that would outweigh the destabilization of **3.107**. We decided to investigate a glycal for the sequence (Scheme 3.39). Glycals have been found to ring open more readily in prior work (Chapter 2), and the stabilizing effect of the enol ether was hoped to outweigh the destabilizing effect of the chlorine atom in the ring opening step (Figure 3.7).

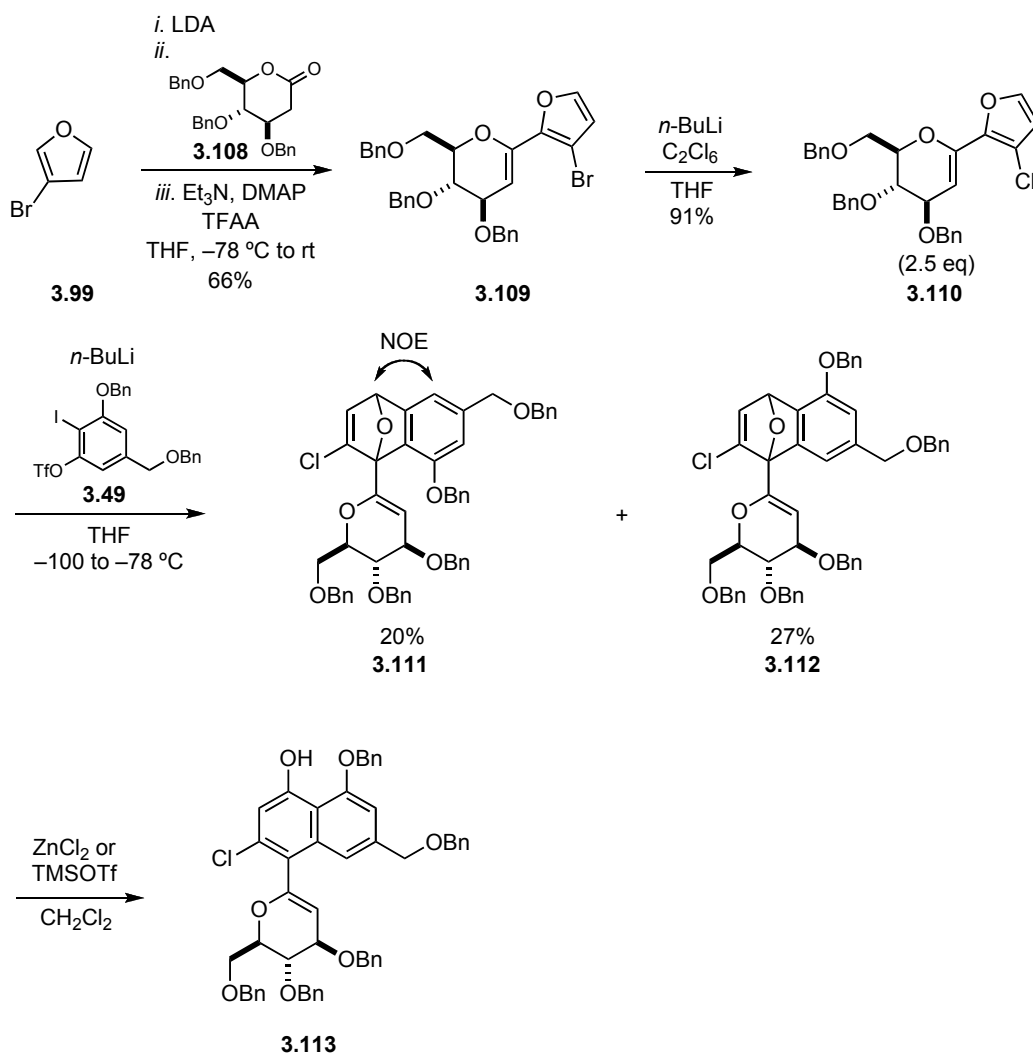
**Figure 3.7: Stabilized carbocation formed from ring opening of glycal**



**3.107**

In a novel application of our methodology to form furyl glycols, lithiated 2-bromofuran was reacted with 2-deoxysugar lactone **3.108**, and the intermediate adduct underwent elimination to provide furyl glycal **3.109** (Scheme 3.39). Reaction of **3.109** with *n*-BuLi effected metal-halogen exchange, and trapping the intermediate anion with  $C_2Cl_6$  gave **3.110**. The benzyne that was generated from triflate **3.49** reacted with **3.110** to give a separable mixture of cycloadducts. Cycloadduct **3.112** was found to open to form a hydrogen-bonded phenol that was tentatively assigned **3.113**; however, other “phenolic” signals were observed as singlets around 9–10 ppm in the  $^1H$  NMR spectrum of the crude material. As noted in Chapter 2, these glycols are prone to decomposition on silica gel. We were unable to optimize this ring-opening reaction.

### Scheme 3.39: Attempts to utilize a glycol to facilitate ring-opening

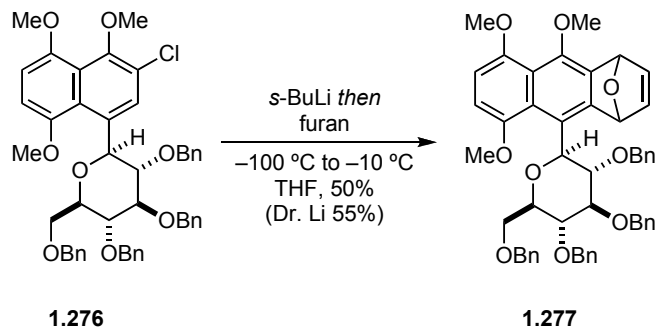


### 3.6. REVISION OF THE SYNTHESIS: A NEW TETHER STRATEGY

The continual difficulties with the generation of benzyne from monohalonaphthalenes prompted us to repeat Dr. Li's successful reaction for generating benzyne from a chloronaphthalene. Thus, benzyne generation from chloride **1.276** was investigated to ensure that the prior art could be reproduced (Scheme 3.40).

Treatment of chloronaphthalene **1.276** with *s*-BuLi at  $-100\text{ }^{\circ}\text{C}$ , followed by treatment with furan effectively produced adduct **1.277** in 50% yield. Having reproduced Dr. Li's result, a question was raised: Why could we deprotonate chloride **1.276** and not chloride **3.53**, which had the C ring installed and could be readily elaborated to the natural product? One possible reason is the acidity of the additional benzylic positions on the aromatic ring in chloride **3.53**. It is well precedented that benzylic positions can be deprotonated using strong base.<sup>169</sup> We reexamined the  $^1\text{H}$  NMR spectra obtained from the attempted deuteration reactions of compounds such as **3.53** to determine if there was any deuterium incorporated in the benzylic region of the spectrum. Unfortunately, due to the numerous benzyl protecting groups on the glycoside, it could not be determined definitively if deuterium had indeed been incorporated.

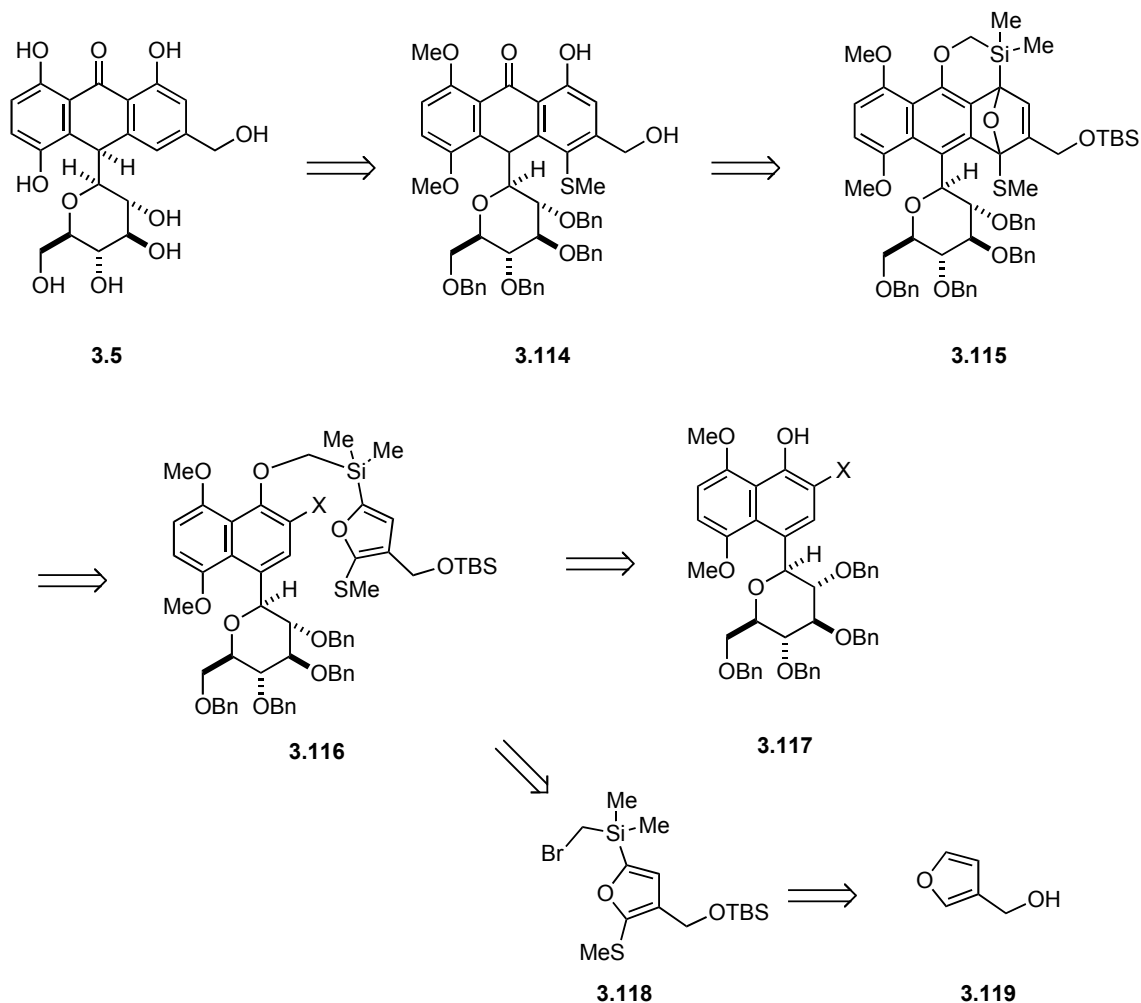
**Scheme 3.40: Successful cycloaddition with monochloronaphthalene 1.276**



We sought to form a molecule similar to chloride **1.276**, which was known to form naphthyne, and we revised our retrosynthesis accordingly. In this new approach, 5-hydroxyaloin A (**3.5**) would come from the global deprotection and desulfurization of **3.114** (Scheme 3.41). Phenol **3.114** would arise from cleavage of the one-carbon silicon tether and ring opening of silane **3.115**, which is the product of the intramolecular

cycloaddition of halide **3.116**. Introduction of the sulfide moiety is key, as it is necessary to control the regioselectivity of the ring opening. Compound **3.116** would come from the etherification of halophenol **3.117** and silyl bromide **3.118**. 3-Furanmethanol (**3.119**) would be used to access **3.118**. The use of the one-carbon tether is preferred since hydroboration-oxidation conditions used to install the two-carbon tether could potentially oxidize the sulfur atom. We sought to avoid an oxidation step completely, as a sulfoxide or sulfone would destabilize the desired carbocation in ring opening step.

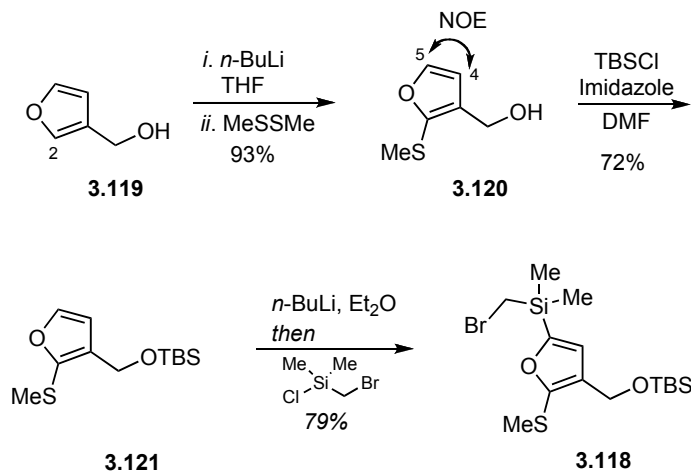
**Scheme 3.41: A new tethered approach to 5-hydroxyaloin A**





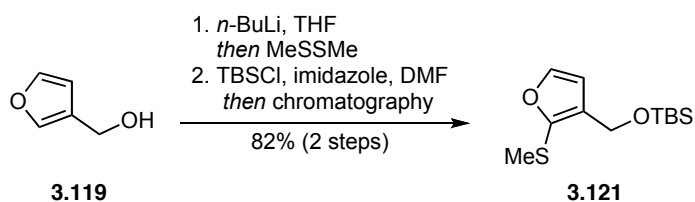
In order to evaluate this new plan, 3-furanmethanol (**3.119**) was treated with *n*-BuLi, followed by treatment with dimethyl disulfide (Scheme 3.42). According to literature precedent, lithiation of **3.119** occurs at C(2) due to chelation, thus we were able to form sulfide **3.120** regioselectively.<sup>170</sup> The regiochemistry was assigned based on the <sup>1</sup>H NMR spectrum (C4: d, *J* = 2.1 Hz; C5: d, *J* = 2.1 Hz) and was confirmed by NOE experiments. Protection of **3.120** provided silyl ether **3.121**, which was lithiated and treated with bromomethyl chlorodimethylsilane to provide **3.118**.

#### Scheme 3.42: Synthesis of the furan



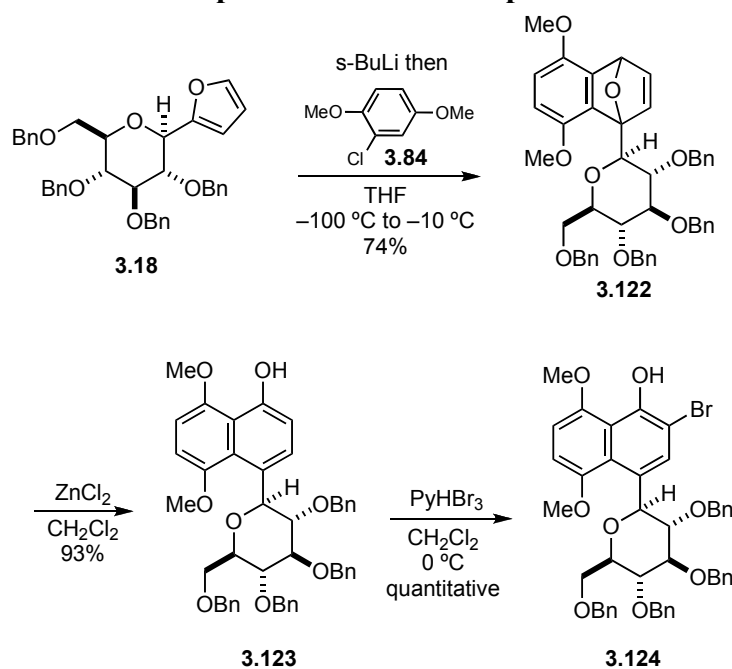
During scale up, we found that the yield of silyl ether **3.121** could be improved by carrying on the crude mixture from the sulfide-forming step (Scheme 3.43). In the event, unpurified **3.120** was treated with TBSCl and imidazole to give **3.121** in 82% yield.

### Scheme 3.43: Improvement of the furan synthesis



With the synthesis of the furan for the C ring of 5-hydroxyaloin A (**3.5**) in place, efforts were turned toward optimizing the synthesis of bromophenol **3.124**, which had been previously synthesized using a different route. Cycloaddition of furan **3.18** with the benzyne generated from **3.84** gave **3.122** in 74% yield (Scheme 3.44). Dr. Li had reported the ring-opening of adduct **3.122** to be low yielding when  $\text{BF}_3 \cdot \text{OEt}_2$  was used. *We discovered that this reaction could be optimized by treating cycloadduct **3.122** with  $\text{ZnCl}_2$ .* Although the mixture of **3.122** and  $\text{ZnCl}_2$  had to be stirred at least 24 h for starting material to be consumed, this modification provided phenol **3.123** in 93% yield. This was a significant result, as Dr. Li had hypothesized that the C(2)-substituent of sugars was responsible for decreased yields in the ring opening step, which had prompted us to investigate glycals as a 2-deoxygenated substrate for this reaction (Chapter 2). The result for the conversion of **3.122** to **3.123** was significant; we had shown that it is the choice of Lewis acid, rather than the C(2)-substituent that is responsible for low yields in the ring opening step. Finally, treatment of **3.123** with  $\text{PyHBr}_3$  furnished bromide **3.124** in quantitative yield.

### Scheme 3.44: Optimization of bromophenol formation



With an efficient synthesis of furan **3.118** and phenol **3.124** in place, efforts were made to link these compounds via an etherification reaction (Table 3.6). Keeping in mind studies by Schecter and Kreeger (Section 1.3.2, Scheme 1.41),<sup>91,92</sup> which indicated that sodium alkoxides were less likely to attack at the silicon atom, we began with  $\text{Na}_2\text{CO}_3$  and  $\text{NaH}$  (entries 1-3). Even with heating, starting phenol **3.124** was recovered in nearly quantitative yield (entries 1 and 2). Using  $\text{K}_2\text{CO}_3$  gave a complex mixture, and an additional phenolic signal in the  $^1\text{H}$  NMR spectrum of the crude material prompted us to investigate other conditions. The best results for this reaction were obtained when  $\text{Cs}_2\text{CO}_3$  was used (entries 6-10). This transformation was very slow, and stirring at room temperature for 2 days furnished the desired ether in only 27% yield. Increasing the molar equivalencies of silane **3.118** did not improve the yield (entry 8), and omission of

TBAI resulted in no reaction (entry 9). Switching the solvent to DMF led to no significant improvement.

**Table 3.6: Williamson etherification with bromophenol 3.125**

Reaction scheme: **3.118** (2-bromo-4-(tert-butyldimethylsilyloxy)phenyl methyl sulfide) reacts with **3.124** (a complex polyhydroxylated aromatic compound) in the presence of TBAI and a base, in a solvent, for a certain time and temperature, to yield **3.125** (the corresponding ether product).

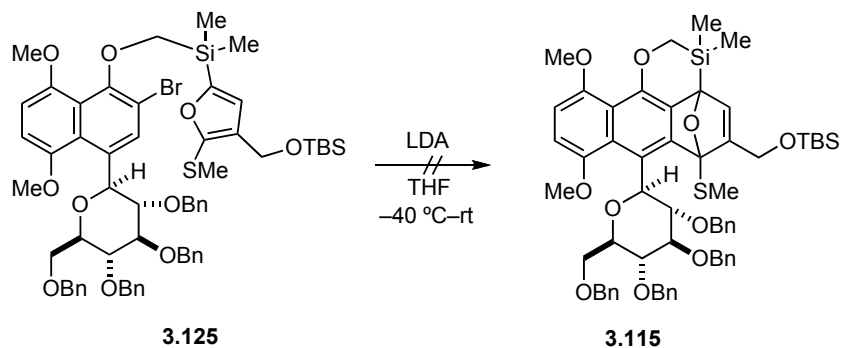
entry	base	solvent	temp	time (h)	result
1	Na <sub>2</sub> CO <sub>3</sub>	DMF	70 °C	2	recovered phenol <b>3.124</b>
2	Na <sub>2</sub> CO <sub>3</sub>	DMF	70 °C	24	complex mixture
3	NaH	DMF	rt	24	recovered phenol <b>3.124</b>
4	K <sub>2</sub> CO <sub>3</sub>	(CH <sub>3</sub> ) <sub>2</sub> CO	rt	44	complex mixture
5	K <sub>2</sub> CO <sub>3</sub>	(CH <sub>3</sub> ) <sub>2</sub> CO	70 °C	44	complex mixture
6	Cs <sub>2</sub> CO <sub>3</sub>	(CH <sub>3</sub> ) <sub>2</sub> CO	rt	44	27% <sup>a</sup>
7	Cs <sub>2</sub> CO <sub>3</sub>	(CH <sub>3</sub> ) <sub>2</sub> CO	70 °C	24	23% <sup>a</sup>
8 <sup>b</sup>	Cs <sub>2</sub> CO <sub>3</sub>	(CH <sub>3</sub> ) <sub>2</sub> CO	rt	48	23% <sup>a</sup>
9 <sup>c</sup>	Cs <sub>2</sub> CO <sub>3</sub>	(CH <sub>3</sub> ) <sub>2</sub> CO	70 °C	48	recovered phenol <b>3.124</b>
10	Cs <sub>2</sub> CO <sub>3</sub>	DMF	rt	48	6% <sup>a</sup>

<sup>a</sup> Isolated yield after column chromatography. <sup>b</sup> 2 eq. of silane **3.118** were used.  
<sup>c</sup> Reaction run without TBAI

Although the yield of the etherification was low, enough of ether **3.125** was prepared to determine if the cycloaddition could be achieved with this substrate (Scheme

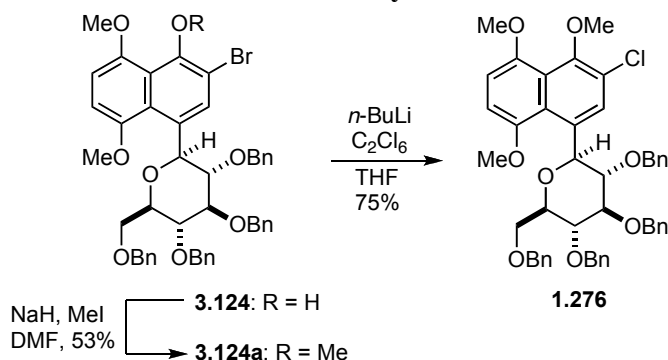
3.45). Unfortunately, we were not able to effect the intramolecular cycloaddition when bromide **3.125** was treated with LDA.

**Scheme 3.45: Attempted cycloaddition with bromide 3.125**



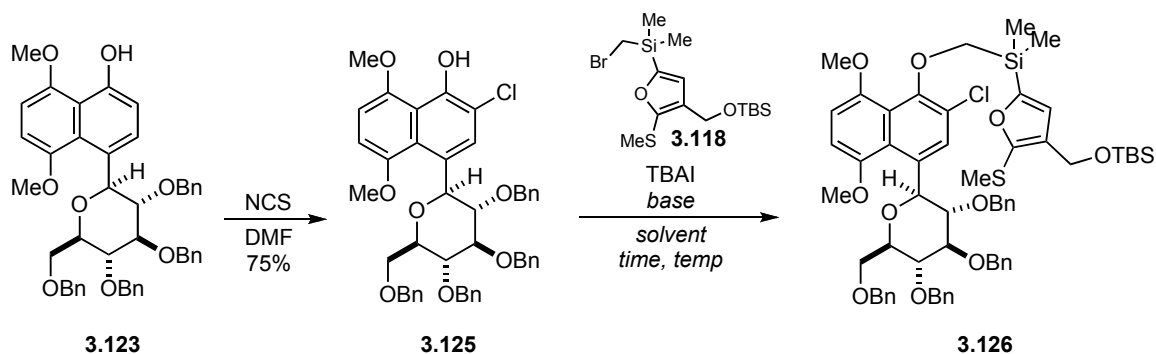
The reason that the cycloaddition reaction was first tried with bromide **3.125** was simply accessibility. A direct synthesis of chlorophenol **125** had not yet been achieved; we had formed chloride **1.276** via bromide **3.124a** in past work (Scheme 3.46). Since we wanted to maintain a free phenol, we could not readily convert bromide **3.124** to a chloride using this method.

**Scheme 3.46: Previous synthesis of 1.276**



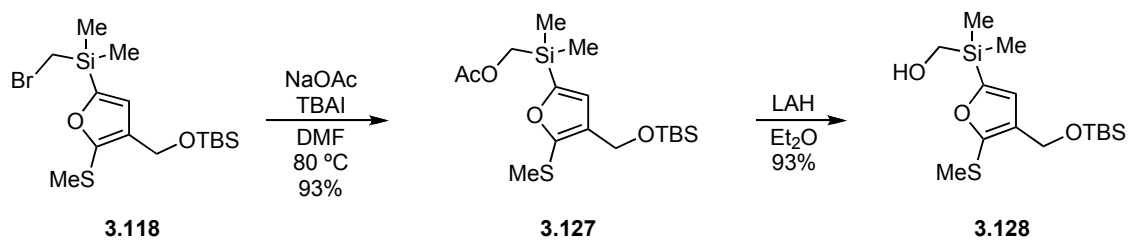
While working on the etherification of bromide **3.124**, the direct chlorination of naphthol **122** finally proved fruitful, and NCS in DMF gave chloronaphthol **125** cleanly and in good yield (Scheme 3.47). The etherification reaction was not straightforward, however. The reaction was very slow when  $K_2CO_3$  was used, even with prolonged heating. Many reaction conditions were tried using  $Cs_2CO_3$ , and by comparison of the  $^1H$  NMR spectra of bromide **124** and the “purified” mixture of chloride **126**, it appeared that the desired ether was present; however, it could not be separated from the mixture.

**Scheme 3.47: Williamson etherification with the chlorophenol**



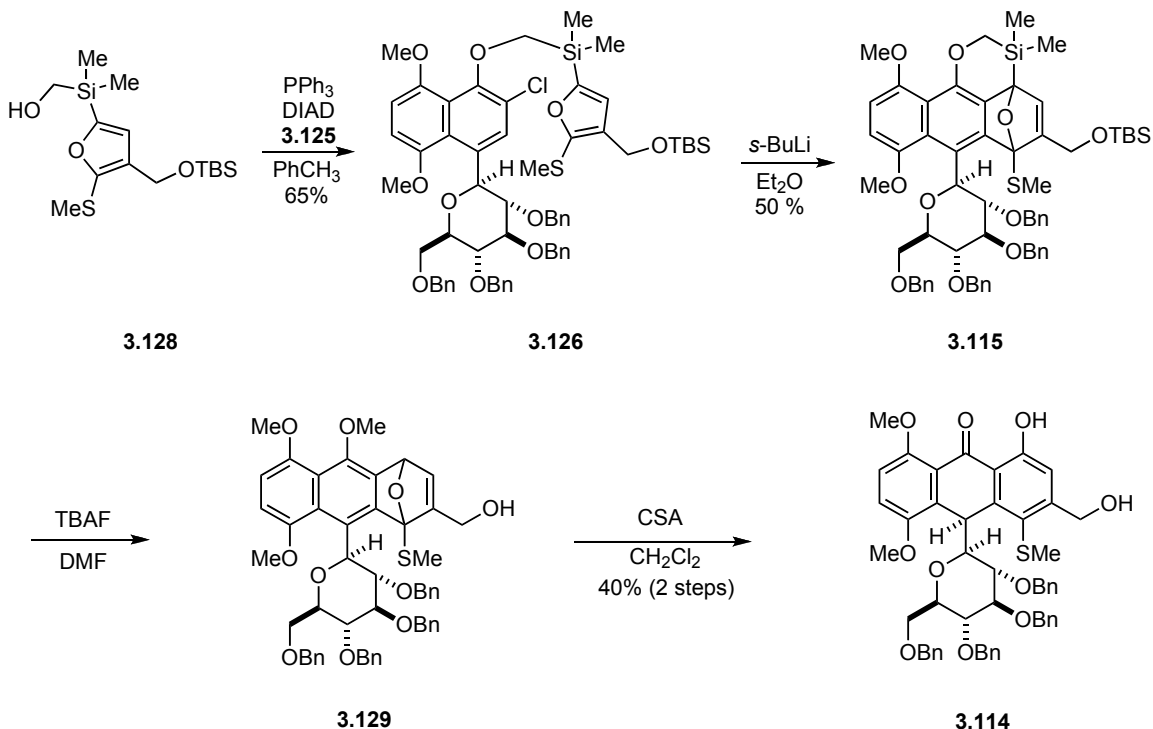
We have consistently found the Mitsunobu etherification to be the most efficient method to link furans to phenols. Consequently, we converted bromide **3.118** to acetate **3.127** in 93% yield, and reduction of **3.127** provided alcohol **3.128**, also in 93% yield (Scheme 3.48).

### Scheme 3.48: Conversion of the furan from a bromide to an alcohol



Alcohol **3.128** underwent the Mitsunobu etherification smoothly with **3.125**, and the desired ether **3.126** was produced in 65% yield (Scheme 3.49). Treatment of ether **3.126** with *s*-BuLi at  $-45\text{ }^{\circ}\text{C}$ , followed by warming to  $-10\text{ }^{\circ}\text{C}$  provided cycloadduct **3.114** in 50% yield. Desilylation by treatment with TBAF afforded methyl ether **3.129**. When TFA or  $\text{ZnCl}_2$  was added to **3.129**, this resulted in intractable mixtures. However treatment with CSA furnished anthrone **3.114**. Only a desulfurization and global deprotection was needed to convert **3.114** to the natural product. We had finally achieved a synthesis of a tricyclic structure that could potentially be elaborated to 5-hydroxyaloin A.

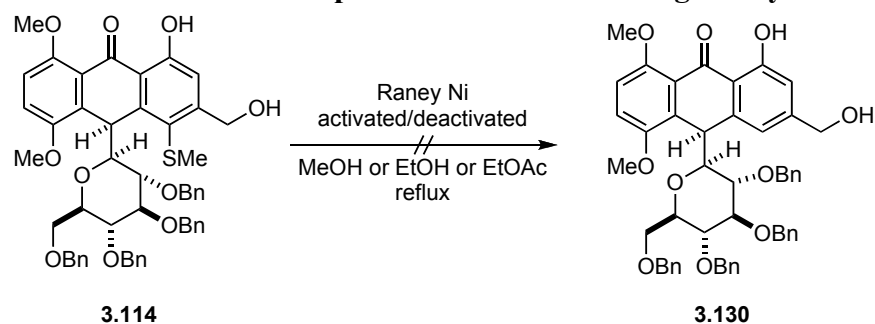
**Scheme 3.49: Access to the aromatic core of 5-hydroxyaloin A**



The desulfurization of **3.114** was then attempted using excess Raney-Ni (Scheme 3.50). Deactivated Raney Ni was first tried, using both MeOH and EtOH as solvent. Unfortunately, at room temperature there was no reaction. Activated Raney Ni gave mixtures, most likely due to various debenzylation products, some of which were isolated. Incomplete debenzylation was a continual problem with this reaction. We could not achieve complete debenzylation using Raney Ni, and heating and prolonged reaction times led to intractable mixtures of many products.

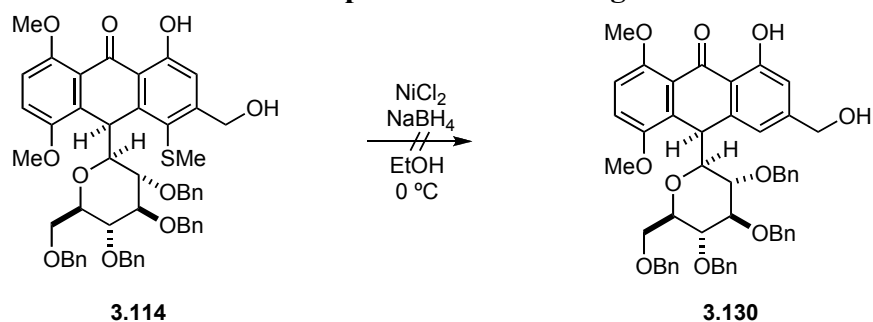


### Scheme 3.50: Attempted desulfurization using Raney-Ni



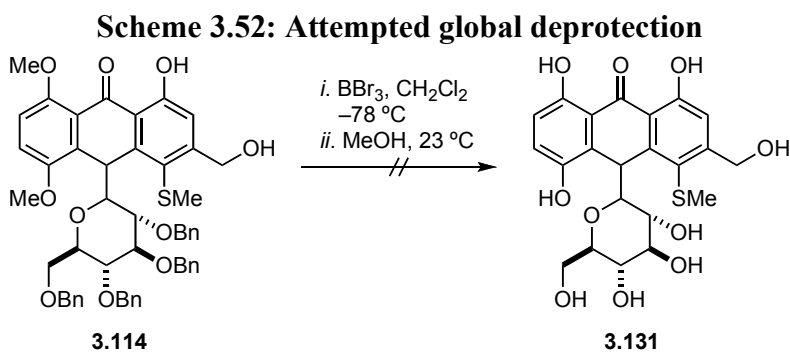
The desulfurization of **3.114** was also attempted using nickel boride, generated *in situ* from the reaction of  $\text{NiCl}_2$  and sodium borohydride (Scheme 3.51).<sup>171, 172</sup> The product of this reaction was a reduced anthrone, as evidenced by the disappearance of the carbonyl stretch in the IR spectrum. Surprisingly, the carbon-sulfur bond remained intact. We began to wonder about the accessibility of the thiomethyl group and whether our system might be too hindered for the desulfurization to take place.

### Scheme 3.51: Attempted reduction using nickel boride



In order to determine if the benzyloxy protecting groups on the sugar might be preventing the desulfurization, we reversed the order of the final steps and performed the global deprotection step first. Compound **3.114** was thus treated with  $\text{BBr}_3$  to remove the benzyl groups from the sugar and the methyl groups protecting the hydroquinone

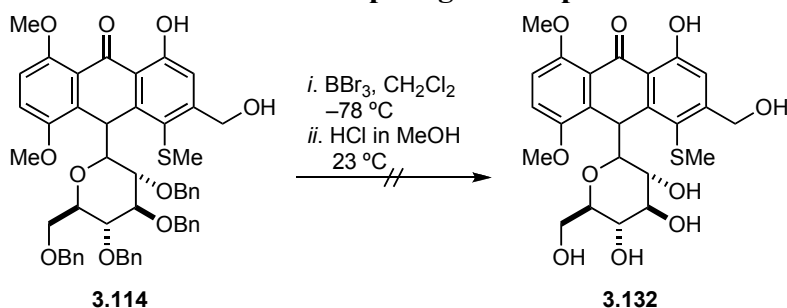
(Scheme 3.52). The product that we obtained had not undergone demethylation, although the benzyl groups were effectively removed. An unexpected observation in the  $^1\text{H}$  NMR spectrum of the major product was the disappearance of the singlet corresponding to the hydrogen-bonded phenol.



Although the product of the reaction in Scheme 3.52 was not fully characterized, we hypothesized that a boron chelate was formed, and the reaction was run again, this time adding acidic methanol and stirring overnight in an attempt to break up any such chelates (Scheme 3.53). The reappearance of the singlet corresponding to the hydrogen-bonded phenol at 12.2 ppm in the  $^1\text{H}$  NMR spectrum supported our hypothesis.

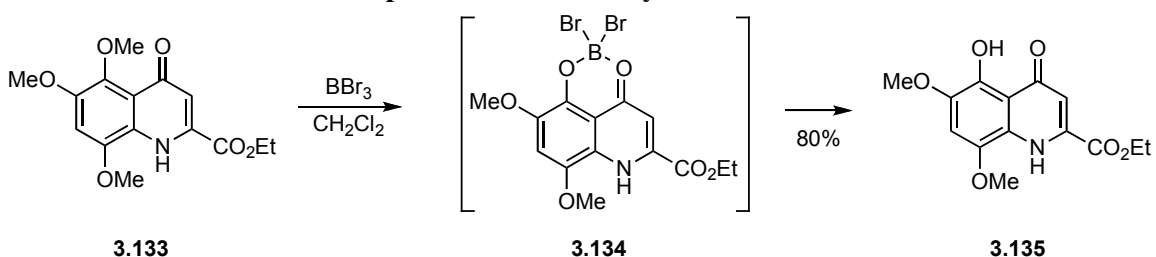
We made many attempts to demethylate **3.114** using BBr<sub>3</sub>. We increased reaction time and temperature in an effort to remove the methyl protecting groups from **3.114**; however, none of these trials met with success. Increasing the temperature at which BBr<sub>3</sub> was added resulted in reduced isolated yield of **3.132**.

### Scheme 3.53: Attempted global deprotection



Our difficulties effecting the demethylation of this system are not particularly surprising, as there are many examples in the literature where methyl ether cleavage using  $\text{BBr}_3$  is problematic, especially in situations where stable chelates can form. For example, it is often difficult to cleave a second methyl ether in examples where removal of the first results in the formation of a chelate (Scheme 3.54).<sup>173</sup> The formation of **3.134** would build up negative charge up on the aromatic ring, making other methoxy groups on that ring harder to remove. One methoxy group was removed from **3.133**, furnishing exclusively phenol **3.135**.

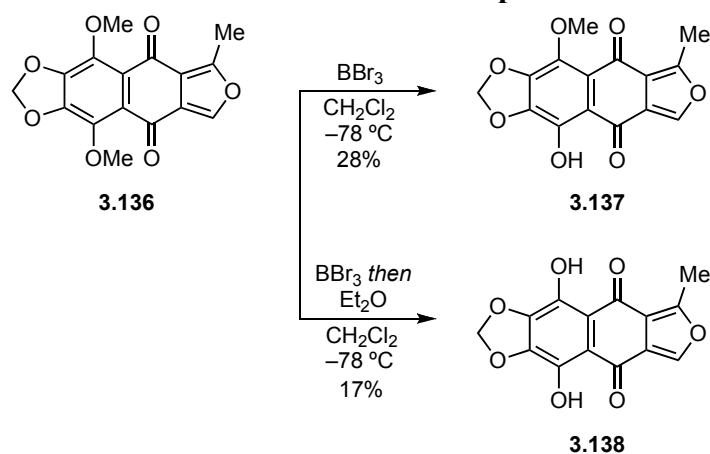
### Scheme 3.54: Deprotection difficulty due to chelate formation



In the synthesis of ventilone, Piggot and Wege report difficulty removing the second methoxy group from quinone **3.136** (Scheme 3.55).<sup>174</sup> When **3.136** was treated

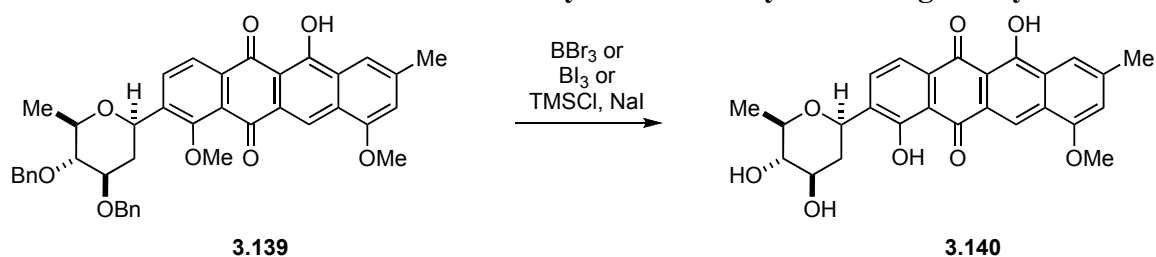
with  $\text{BBr}_3$ , they were only able to isolate **3.137**, the product of a single demethylation. In order to access the desired hydroquinone **3.138**,  $\text{Et}_2\text{O}$  was added to the reaction, and the mixture was stirred for an extended period of time at  $-78\text{ }^\circ\text{C}$ . They proposed that the ether broke up the chelate that had formed, allowing the second methyl ether to be cleaved.

**Scheme 3.55: Use of  $\text{Et}_2\text{O}$  to break up boron chelates**



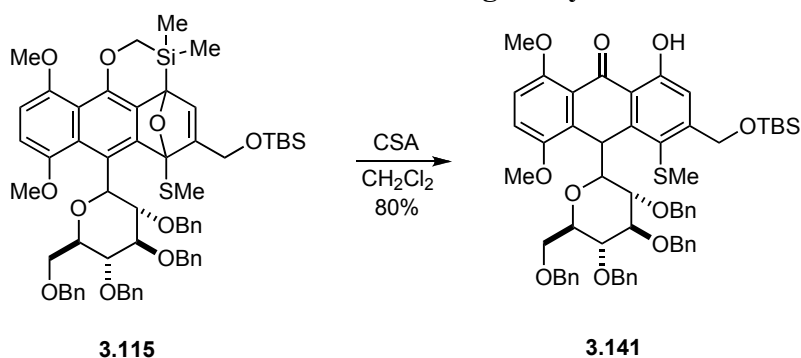
Deprotecting methyl groups had presented problems in the Martin group synthesis of galtamycinone (Scheme 3.56).<sup>94</sup> Various conditions were tried in an attempt to demethylate, however, the methyl group was extremely robust. The inability to cleave methyl ether **3.139** caused the group to publish a formal synthesis, in which the route to an earlier intermediate was reported. The compound that constituted the formal synthesis was a key intermediate of Suzuki's total synthesis of the natural product.

### Scheme 3.56: Difficulties with demethylation in the synthesis of galtamycinone



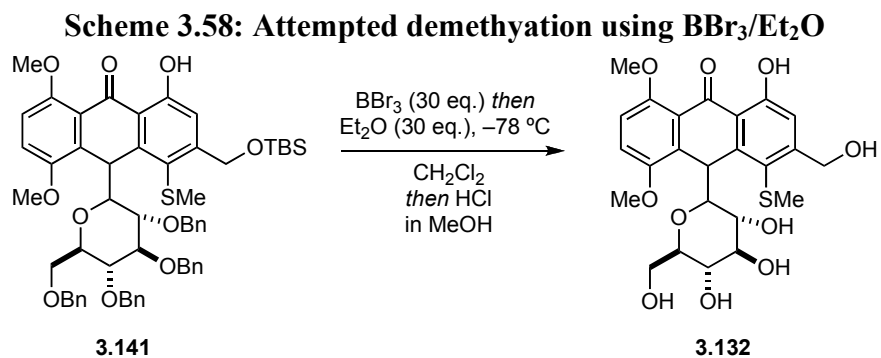
Given this precedent, we knew that our system would be difficult to demethylate, however we hoped that we could employ non-chelating conditions to accomplish this. We had found that we could streamline the synthesis by treating cycloadduct **3.115** with CSA (Scheme 3.57), providing **3.141** 80% yield. Recall that the two-step tether cleavage/ring opening procedure provided **3.114** in only 40% yield over two steps. Compound **3.141** was thus used from this point on in the deprotection reactions, as the TBS ether should be also be cleaved under the strong Lewis acidic conditions.

### Scheme 3.57: Streamlining the synthesis



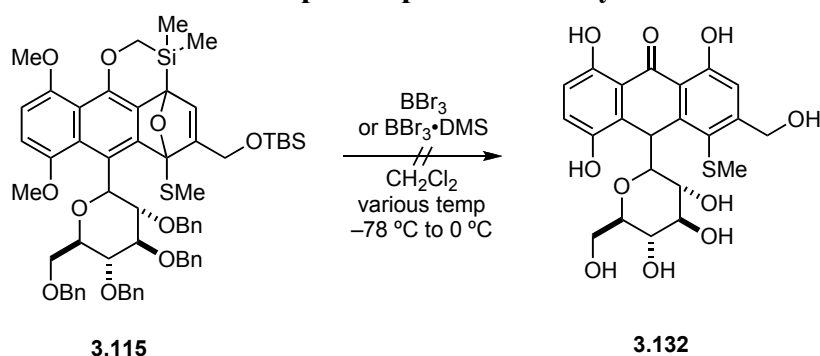
We first attempted to utilize the procedure from the synthesis of ventilonone A to deprotect anthrone **3.141** (Scheme 3.58).<sup>174</sup> Following the addition of  $\text{BBr}_3$  at  $-78\text{ }^\circ\text{C}$ ,  $\text{Et}_2\text{O}$  was added, and then the mixture was allowed to warm to room temperature. Even

with overnight stirring following the addition of Et<sub>2</sub>O, **3.132** was the major product of the reaction.



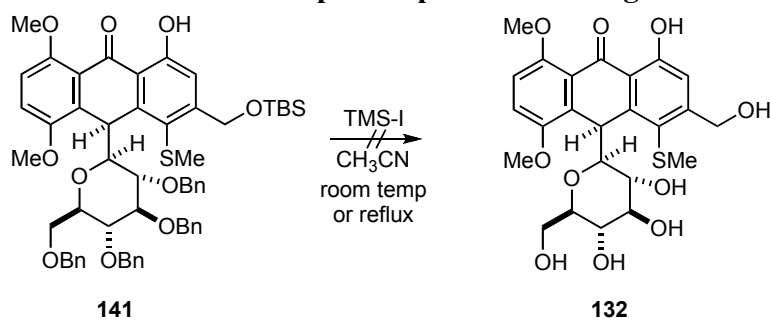
Because the free phenol group of **3.141** could facilitate chelate formation, we attempted the deprotection on **3.115**. Given our precedent for tandem desilylation/ring opening (Scheme 3.57), we treated **3.115** with BBr<sub>3</sub> and BBr<sub>3</sub>•DMS (Scheme 3.59). The chelate would not be able to form as readily with this molecule, and we thought that we might be able to streamline the synthesis even further. Unfortunately, complex mixtures of products were obtained from these reactions.

### Scheme 3.55: Attempted deprotection of cycloadduct 115



TMS-I was also examined as a reagent for the demethylation of **3.141** (Scheme 3.60). Demethylation of **3.141** did not occur at cold temperature, and when **3.141** was treated with TMSI at room temperature or elevated temperature an intractable mixture was obtained, and the desired anthrone **3.132** was not isolated.

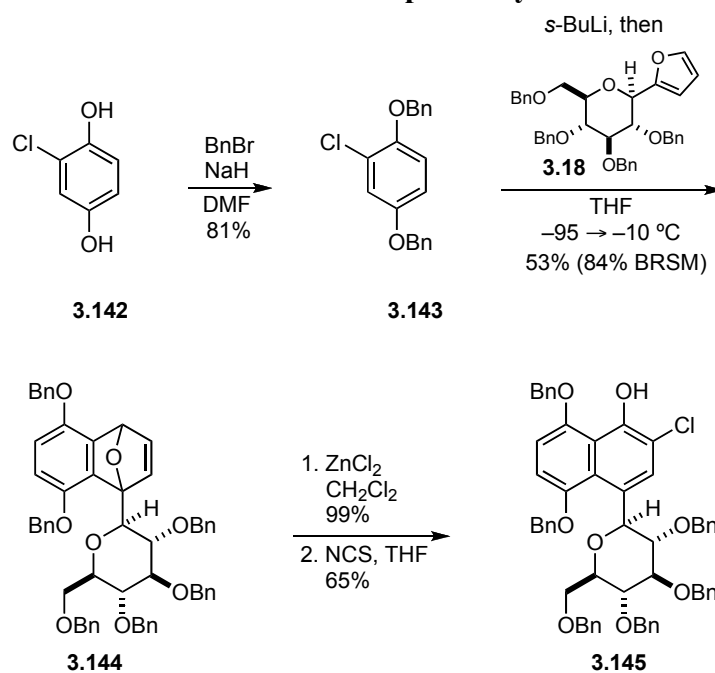
### Scheme 3.60: Attempted deprotection using TMS-I



Given our difficulties in the present synthesis of hydroxyaloin A, coupled with literature and group precedent for difficulties associated with the demethylation of similar systems, we investigated an approach that did not rely on such a difficult deprotection late in the game. With benzyl groups already present on the sugar, it was logical to pursue a benzyne that would introduce the same protecting groups onto the aryl portion

of the molecule. Toward this end, the phenols of chlorohydroquinone (**3.142**) were protected as benzyl ethers, giving **3.143** in 81% yield (Scheme 3.61). The cycloaddition of the benzyne generated from **3.143** with glycosyl furan **3.18** provided cycloadduct **3.144** in only 53% yield. Although the conditions were identical to those used to form methyl analog **3.122**, we could not achieve the same yields. We attribute the decreased yield in this reaction with a steric interaction. We had seen in the past a decrease in efficiency when C(2)-substituted sugars were employed as opposed to 2-deoxysugars.<sup>95</sup> The large protecting groups on the benzyne are probably the cause for the diminished yields.

**Scheme 3.61: Formation of a perbenzylated substrate**



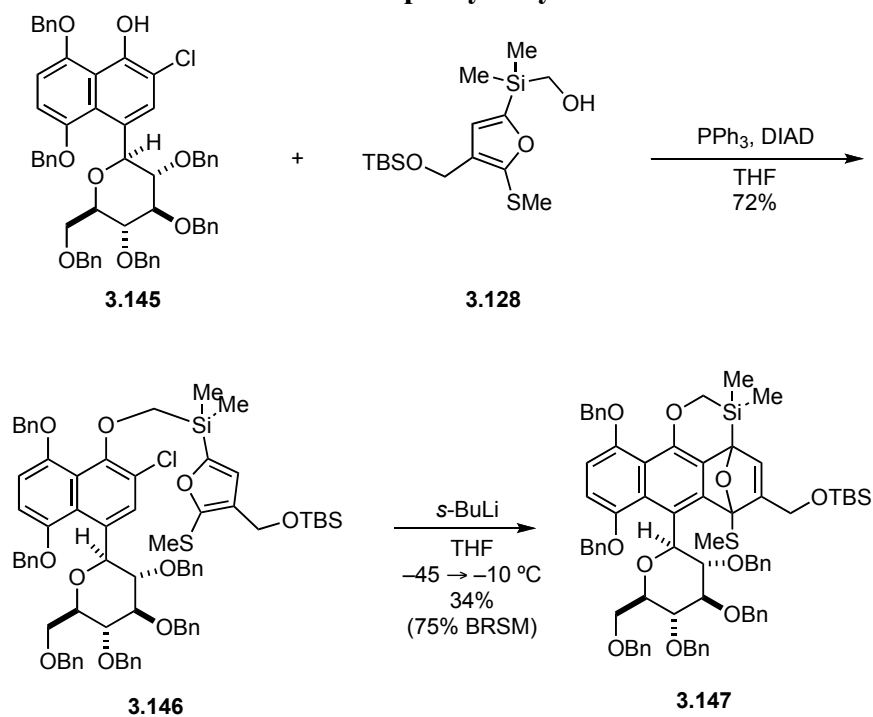
Nevertheless, we were able to obtain cycloadduct **3.144** in 53% yield, and we were able to recover furan **3.18**. Fortunately, ring opening of **3.144** proceeded in



excellent yield, and ortho chlorination of the resultant phenol was achieved, providing **3.145** in 64% overall yield from **3.144**.

We were poised to perform the etherification of chloride **3.145** with silyl alcohol **3.128**. This reaction had previously been optimized for the methyl analog in PhCH<sub>3</sub>, with a high yield of 65%. Optimal conditions for this etherification using THF allowed us to achieve a 72% yield of ether **3.146** (Scheme 3.62). The intramolecular naphthyne cycloaddition of **3.146** was achieved in 33% yield. Despite many attempts, this reaction could not be further optimized.

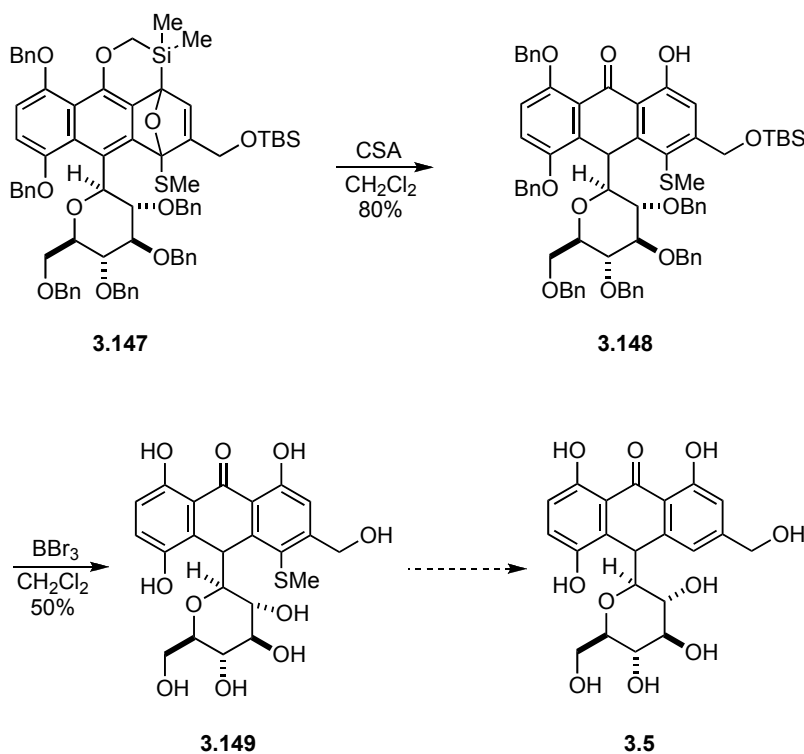
### Scheme 3.62: Naphthyne cycloaddition



We accessed an anthrone using our newly developed tandem process; treatment of **3.147** with CSA produced anthrone **3.148** in 80% yield (Scheme 3.63). Deprotection of

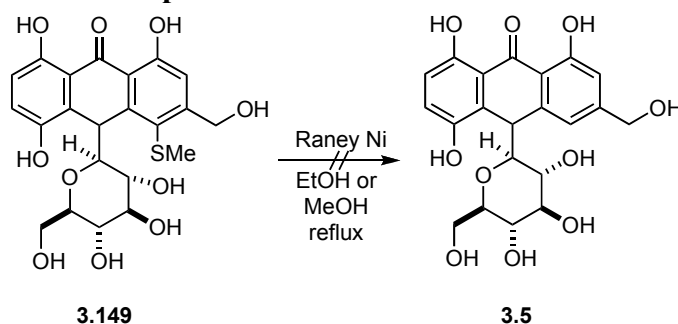
**3.148** using  $\text{BBr}_3$  resulted in the formation of a thiomethyl analog of 5-hydroxyaloin A **3.149**, leaving only a final desulfurization to access the natural product.

### Scheme 3.63: Access to the anthrone



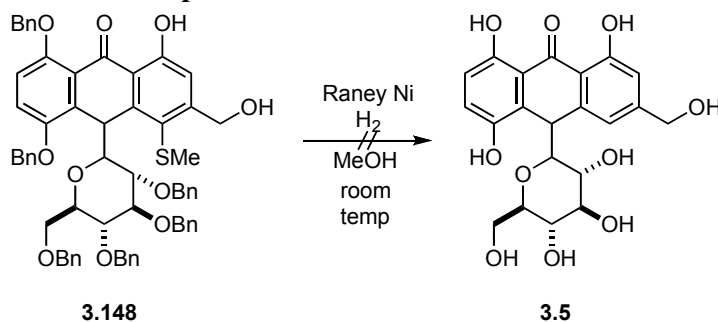
Desulfurizations were then attempted on both the perbenzylated anthrone **3.148** and thiomethyl analog **3.149**. Because desulfurizations of aryl thiomethyl compounds using Raney nickel are well preceded, <sup>175-178</sup> we again attempted to apply these conditions (Scheme 3.64). Unfortunately, the sulfide was extremely robust, and we were unable to desulfurize **3.149**.

**Scheme 3.64: Attempted desulfurization of 3.149 with Raney nickel**



The debenzoylation and desulfurization of **3.148** was also attempted, with an added balloon of hydrogen gas in an attempt to speed up the reaction (Scheme 3.65). The major product was fully debenzoylated, however the sulfide was still present, and the benzylic methylene of the aglycone was not present in the  $^1\text{H}$  NMR spectrum. It is preceded that activated Raney nickel can cleave the hydroxy group of benzylic alcohols.<sup>179</sup>

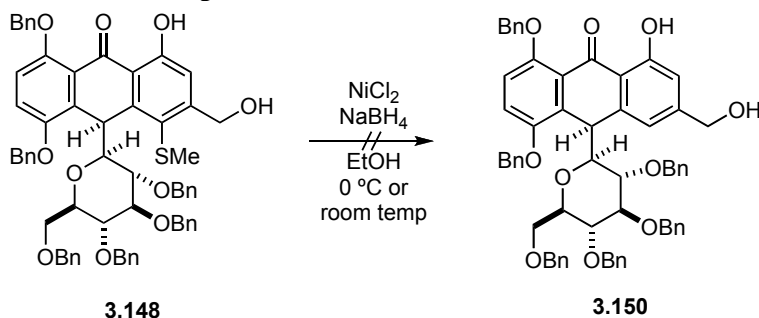
**Scheme 3.65: Attempted desulfurization of 3.148 with Raney nickel**



Desulfurization of **3.148** using nickel boride was also attempted (Scheme 3.66).<sup>172</sup> Again, the anthrone was reduced, and the sulfide was still present. It should be noted that when 2–3 equivalents of nickel boride was employed, the reduced anthrone was the only

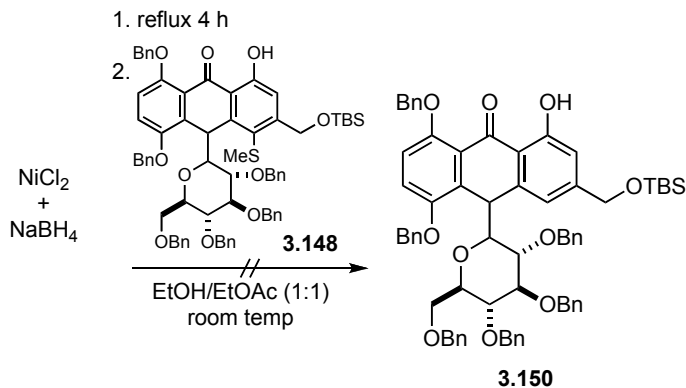
product. Use of a large excess of nickel boride (10–20 equivalents) resulted in the formation of an intractable mixture of products.

**Scheme 3.66: Attempted desulfurization of 3.148 with nickel boride**

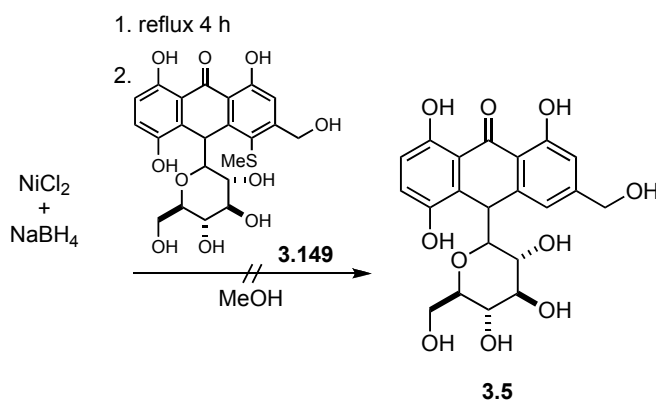


We then attempted to “deactivate” the nickel boride to prevent the reduction of the anthrone. The mixture of  $\text{NiCl}_2$  and  $\text{NaBH}_4$  was first heated under reflux, and then **3.148** was added to the mixture as a solution in EtOAc (Scheme 3.66) or **3.149** as a solution in MeOH (Scheme 3.67). These reactions were completely ineffective, and starting material was recovered from the reaction.

**Scheme 3.66: Attempted desulfurization of 3.148 using “deactivated” nickel boride**



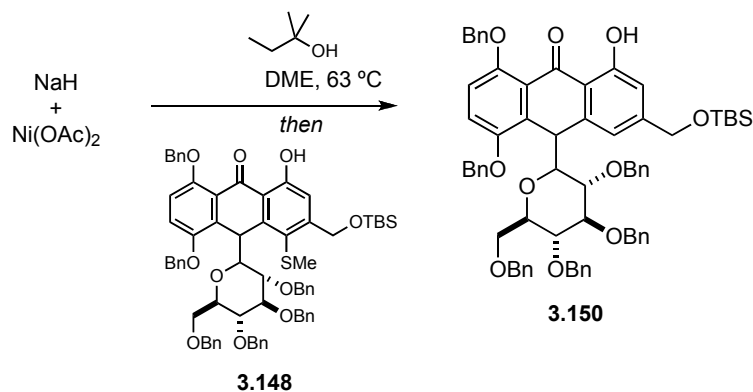
**Scheme 3.67: Attempted desulfurization of 3.148 using “deactivated” nickel boride**



Further investigation into the proposed mechanism for desulfurization using nickel boride may give insight into the lack of success with these reactions. Mechanistically, it is believed that hydrogen gas, formed from sodium borohydride and the protic alcohol, is adsorbed to the metal surface, forming  $\text{Ni}_2\text{B}_2\cdot\text{H}_3$ .<sup>172</sup> However, nickel boride loses its activity upon aging much faster than Raney nickel. It has been speculated that the active reducing agent is a transient nickel hydride complex is formed, and this is critical to the activity of the complex, and that it is not simply preadsorbed hydrogen on the surface that contributes to the activity.<sup>172</sup> This is the reason these desulfurizations are generally carried out in a manner such that the nickel boride is generated in the presence of the sulfide and, even after five minutes, nickel boride has been shown to lose activity. In retrospect, the reactions shown in Schemes 3.66 and 3.67 may have failed because the active reducing species was not present in the mixture.

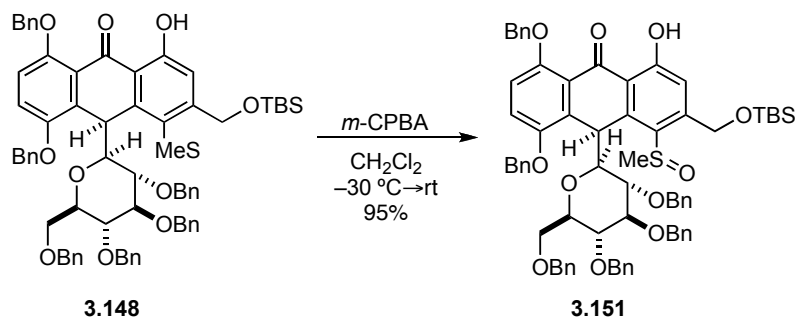
NiCRAs are non-pyrophoric nickel complex reducing agents that are known to cleave sulfides<sup>180</sup> as well as sulfoxides and sulfones.<sup>181</sup> We thus attempted to use NiCRA to desulfurize **3.148** (Scheme 3.68). This approach was also ineffective, as complex mixtures of products were obtained.

### Scheme 3.68: Attempted desulfurization of 3.148 using NiCRA



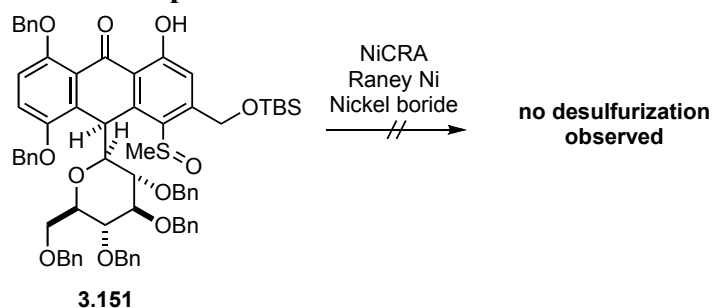
Given the lack of success in the desulfurization of sulfides, sulfoxide **3.151** was formed by from **3.148** by treatment with *m*CPBA at  $-30\text{ }^{\circ}\text{C}$  (Scheme 3.69). Because sulfoxides and sulfones are more easily reduced, this approach might be superior, although sulfoxide formation added steps to our synthesis. We also anticipated that this would allow for more options for conditions to desulfurize **3.151** as sulfoxides are more amenable to reduction via single electron transfer reagents.

### Scheme 3.69: Sulfoxide formation



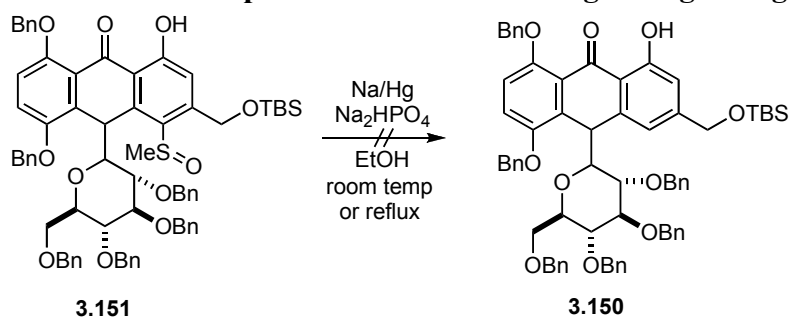
We initially tried the previously mentioned methods to desulfurize sulfone **3.151**. Namely, activated and deactivated Raney nickel, sodium boride, and NiCRAs were employed in an attempt to cleave sulfoxide **3.151** (Scheme 3.70). Sulfoxide **3.151** proved as resistant as sulfides **3.148** and **3.149** to desulfurization under these reductive conditions, and we were unable to effect C–S bond scission.

**Scheme 3.70: Attempted reductive desulfurization of sulfoxide 3.151**

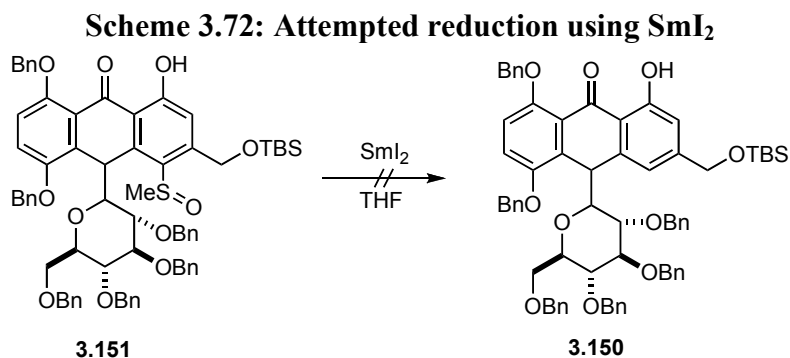


Single electron transfer reagents were then explored for the desulfurization of sulfoxide **3.151**. Sodium/mercury amalgam in the presence of dibasic sodium phosphate is known to cleave sulfoxides, however starting material was recovered quantitatively from this reaction (Scheme 3.71). Increasing the reaction time to several days or heating only resulted in lower recovery of **3.151**.

### Scheme 3.71: Attempted desulfurization using Na/Hg amalgam

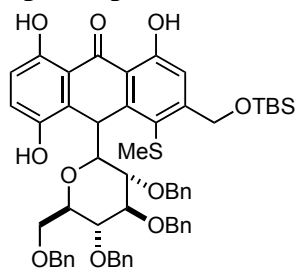


Desulfurization of **3.151** was then attempted using samarium iodide, generated by sonication of a mixture of samarium metal and iodine in THF (Scheme 3.72).<sup>182</sup> When **3.151** was treated with the samarium iodide solution, a new spot formed, however the product was not desulfurized **3.150** as was expected, rather a *sulfide* peak was detected in the <sup>1</sup>H NMR spectrum. Partial debenylation had also occurred, and the isolated compound was tentatively assigned **3.153** based on the <sup>1</sup>H NMR spectrum.





**Figure 3.8: Proposed product from  $\text{SmI}_2$  reaction**



**3.153**

## SUMMARY AND CONCLUSIONS

Two approaches to 5-hydroxyaloin A have been explored. In our first approach, the symmetrically substituted C ring of 5-hydroxyaloin A was formed first, using both an intramolecular and bimolecular approach. We demonstrated reduced cleavage of the silicon tether by implementing Grignard reagents for benzyne generation. Silicon tethers are extremely useful when performing aryne cycloadditions that are not electronically poised to undergo regioselective cycloadditions. However, this work has also shown that, in some situations, it is more convenient to perform the cycloaddition without regiocontrol and to separate the regioisomers that are formed.

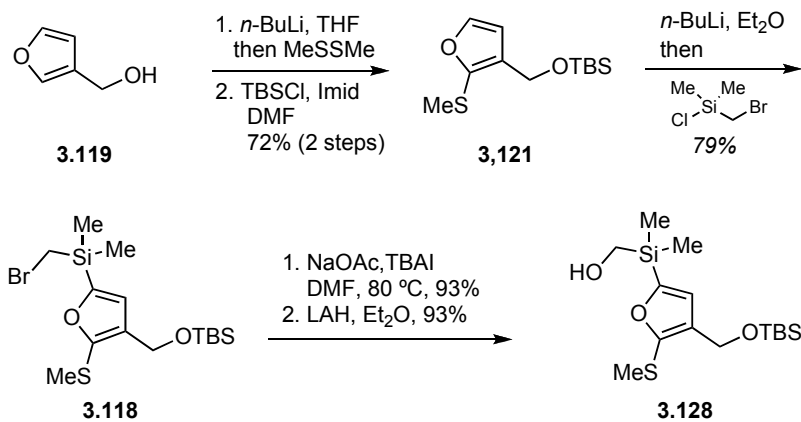
Naphthyne generation via direct deprotonation of monohalonaphthalenes is an extremely substrate-dependent process, and seems to work better when more inductively electron-withdrawing groups are directly attached to the naphthalene ring. This is illustrated by the difficulty in generating naphthyne from substrates such as **3.57**, **3.60**, and **3.71** and our successes generating naphthyne from substrates such as **1.276**, **3.126**, and **3.146**.

The demethylation of aryl methyl ethers is not always a straightforward task, and can be extremely problematic with chelating substrates. Our difficulties with

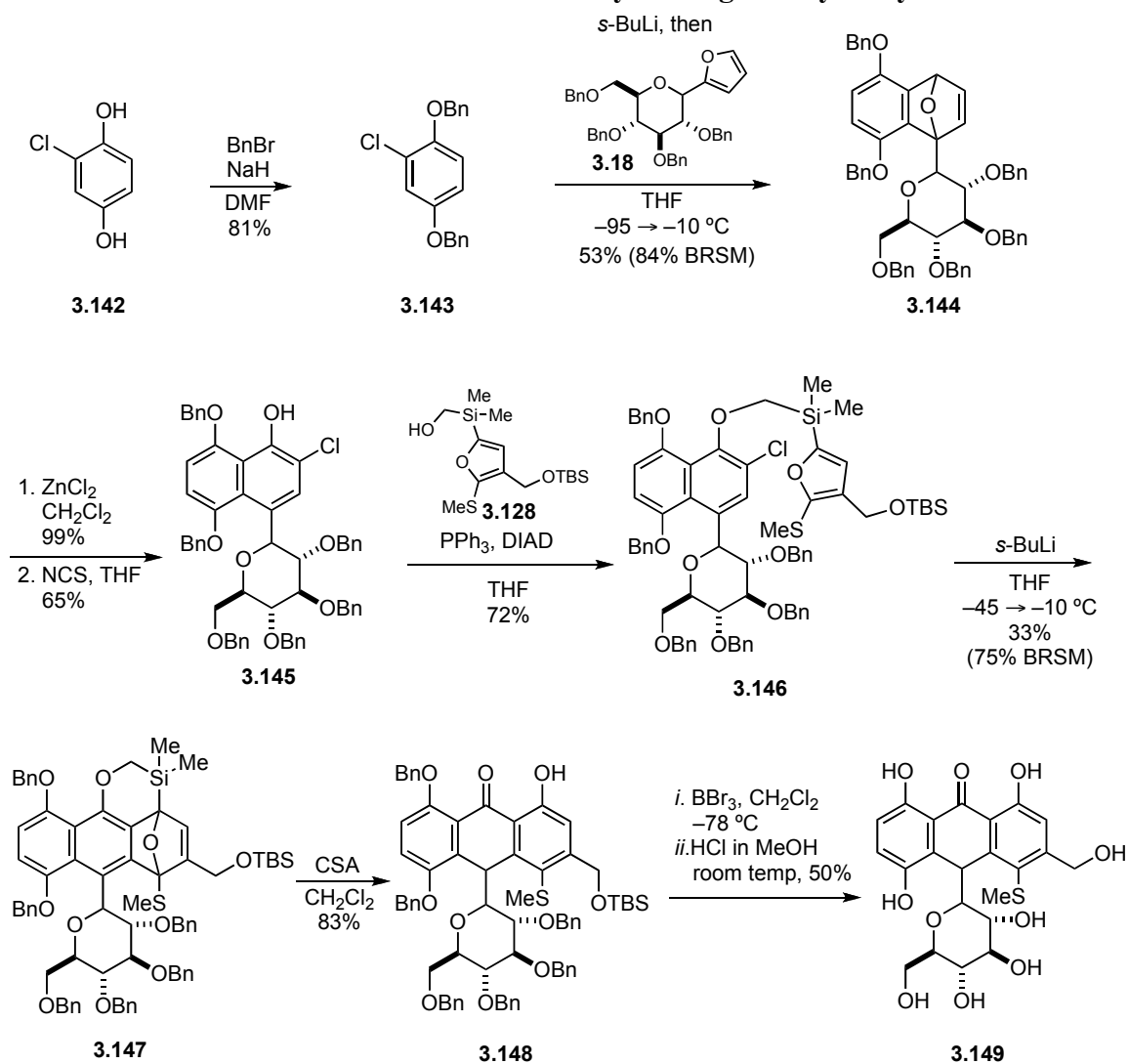
demethylation necessitated a reworking of our synthesis, which involved employing a novel, perbenzylated aryne.

A synthesis of the thiomethyl analog of hydroxyaloin A **3.159** has been accomplished using a one carbon silicon tether to control the regiochemistry of a naphthyne cycloaddition (Schemes 3.73 and 3.74). Although the desulfurization of this molecule has yet to be achieved, current efforts are focused on finding conditions to effect this transformation, and the details of this work will be disclosed in due course.

### Scheme 3.73: Synthesis of the furan



**Scheme 3.74: Access to the thiomethyl analog of 5-hydroxyaloin A**



## Chapter 4: Experimental Methods

### 4.1. GENERAL

Unless otherwise noted, solvents and reagents were used without purification. Tetrahydrofuran (THF) and diethyl ether (Et<sub>2</sub>O) were dried by passage through two columns of activated neutral alumina. Methanol (CH<sub>3</sub>OH), acetonitrile (CH<sub>3</sub>CN), 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. Methylene chloride, triethylamine, *N,N*-diisopropylamine, and *N,N*-diisopropylethylamine were distilled from calcium hydride prior to use. Benzene was distilled from sodium/benzophenone. Acetone was prepared by drying over 4Å MS overnight. All solvents were determined to contain less than 50 ppm H<sub>2</sub>O by Karl Fischer coulometric moisture analysis. All reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of nitrogen or argon in glassware that was flame dried. Volatile solvents were removed under reduced pressure using a Büchi rotary evaporator. Thin layer chromatography was run on pre-coated silica gel plates with a 0.25 mm thickness containing 60F-254 indicator (Merck). The plates were visualized by staining with AMCAN (ammonium molybdate/cerium ammonium nitrate), potassium permagnate, or *p*-anisaldehyde. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on 230–400 mesh silica gel (E. Merck reagent silica gel 60). Flash chromatography was performed with ICN Silica gel 60 according to Still's protocol.<sup>183</sup>

Proton nuclear magnetic resonance (<sup>1</sup>H NMR) were obtained as solutions in the indicated deuterated solvent. Chemical shifts are reported in parts per million (ppm) and

are referenced to the indicated deuterated solvent. Coupling constants ( $J$ ) are reported in Hz and the splitting abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, complex multiplet; br, broad; app, apparent. Carbon nuclear magnetic resonance spectra ( $^{13}\text{C}$  NMR) were obtained using the solvent indicated as the internal reference. Infrared (IR) spectra were obtained either neat on sodium chloride or as solutions in the solvent indicated.

Reaction temperatures refer to the bath temperature, and baths between  $-10\text{ }^{\circ}\text{C}$  and  $-20\text{ }^{\circ}\text{C}$  were maintained using a brine/ice/dry ice. Bath temperatures between  $-40\text{ }^{\circ}\text{C}$  and  $-50\text{ }^{\circ}\text{C}$  were prepared with dry ice/ $\text{CH}_3\text{CN}$ .  $-78\text{ }^{\circ}\text{C}$  baths were made using  $(\text{CH}_3)_2\text{O}$ /dry ice. Baths between  $-95\text{ }^{\circ}\text{C}$  and  $-100\text{ }^{\circ}\text{C}$  were prepared by adding  $\text{N}_2(\text{l})$  to  $\text{Et}_2\text{O}$ .

#### 4.2. REAGENT PREPARATION

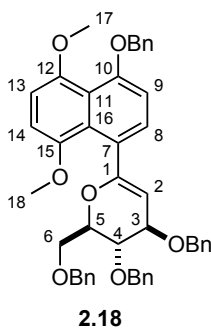
Triflic anhydride ( $\text{Tf}_2\text{O}$ ), acetic anhydride ( $\text{Ac}_2\text{O}$ ), and trifluoroacetic anhydride (TFAA) were distilled from  $\text{P}_2\text{O}_5$  immediately prior to use. Benzyl bromide (BnBr) and methyl iodide (MeI) were passed through a column of neutral alumina just before use.  $\text{ZnCl}_2$  was prepared by heating under vacuum three times, and then dissolving in the indicated solvent. Triethylsilane ( $\text{Et}_3\text{SiH}$ ) and trimethylsilyl trifluoromethanesulfonate (TMSOTf) were distilled from calcium hydride prior to use.

**2-Furyllithium:** *t*-Butyllithium (1.6 M, 0.94 mL, 1.5 mmol) was added dropwise to a stirred solution of freshly distilled furan (102 mg, 109  $\mu\text{L}$ , 1.5 mmol) in THF (2.7 mL) at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was stirred for 10 min at  $-78\text{ }^{\circ}\text{C}$  whereupon it was transferred to a  $-10\text{ }^{\circ}\text{C}$  bath and stirring was continued for 40 min.

**Isopropyl magnesium chloride (i-PrMgCl):** *i*-PrCl (3.9 mL, 43 mmol) was added dropwise to acid-washed Mg<sup>0</sup> (1.13 g, 47 mmol) in THF (40 mL). The mixture was heated gently with a heat gun until the reaction initiated, and then the solution was stirred for 20 h at rt. Stirring was discontinued and the solids were allowed to settle, at which point the clear liquid was cannulated into a Schlenk flask.

**Lithium diisopropylamine (LDA):** *n*-BuLi (0.25 mL, 2.03 M, 0.50 mmol) was added dropwise to a solution of (*i*-Pr)<sub>2</sub>NH (70 μL, 50.6 mg, 0.5 mmol) in THF (0.5 mL) at 0 °C. The solution was stirred at 0 °C for 30 min.

### 4.3. COMPOUNDS



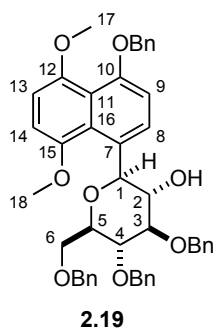
**3,4-Bis-benzyloxy-6-(4-benzyloxy-5,8-dimethoxy-naphthalen-1-yl)-2-benzyloxymethyl-3,4-dihydro-2H-pyran (2.18). (KP1-226).** A solution of ZnCl<sub>2</sub> in Et<sub>2</sub>O (540 μL, 0.54 mmol, 1 M) was added to **2.16** (319 mg, 0.45 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4.5 mL) at -78 °C. The reaction was stirred at -78 °C for 5 min. The reaction flask was transferred to a 0 °C bath, and stirring was continued for 20 min. A solution of saturated NaHCO<sub>3</sub> (5 mL) was added, the layers were separated, and the aqueous layer was

extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 1 mL). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), filtered through a pad of Celite, and concentrated under reduced pressure. The residue was dried under vacuum, and used directly in the next step without further purification.

BnBr (165  $\mu\text{L}$ , 1.40 mmol) and NaH (54 mg, 1.40 mmol, 60% dispersion in mineral oil) were added to the crude naphthol in DMF (4.5 mL). The reaction mixture was stirred at 25 °C for 0.5 h, whereupon 50%  $\text{NaHCO}_3$  (15 mL) and ether (10 mL) were added. The layers were separated, and the aqueous layer was extracted with ether (3 x 5 mL). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated under reduced pressure. The crude product was purified by flash chromatography, eluting with EtOAc/hexanes (1:5) to afford 271 mg (85%) of **2.18** as a viscous yellow oil:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.51 (comp, 2 H), 7.35-7.15 (comp, 19 H), 6.81 (d,  $J = 8.0$  Hz, 1 H), 6.78 (d,  $J = 8.6$  Hz, 1 H), 6.73 (d,  $x = 8.4$  Hz, 1 H), 5.12 (s, 2 H), 4.92 (br s, 1 H), 4.88 (d,  $J = 11.0$  Hz, 1 H), 4.68–4.87 (comp, 2 H), 4.59 (d,  $J = 11.6$  Hz, 1 H), 4.49 (d,  $J = 12.0$  Hz, 1 H), 4.46 (br d,  $J = 6.8$ , 1 H), 4.41 (d,  $J = 12.0$ , 1 H), 4.21 (br d,  $J = 9.8$ , 1 H), 4.00 (dd,  $J = 6.8, 9.8$  Hz, 1 H), 3.81 (d,  $J = 3.2$ , 2 H), 3.79 (s, 3 H), 3.73 (s, 3 H);  $^{13}\text{C}$  NMR  $\delta$  156.8, 151.5, 150.5, 138.8, 138.5, 138.4, 137.4, 130.6, 128.6, 128.4, 128.3, 128.2, 128.0, 127.8, 127.64, 127.59, 127.5, 127.4, 127.3, 127.1, 127.0, 119.7, 108.1, 107.9, 107.3, 78.7, 78.1, 75.2, 74.1, 73.4, 71.5, 70.1, 69.0, 57.7, 56.9; IR (neat) 3062, 3029, 1272, 1086, 1054  $\text{cm}^{-1}$ ; mass spectrum (CI)  $m/z$  708.3091 [ $\text{C}_{46}\text{H}_{44}\text{O}_7$  ( $\text{M}^+$ ) requires 708.3087] 709 (base), 601.

**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.51 (comp, 2 H, Ph C-H and C9-H), 7.35-7.15 (comp, 19 H, Ph C-H and C8-H), 6.81 (d,  $J = 8.0$  Hz, 1 H, Ph C-H), 6.78 (d,  $J = 8.6$  Hz, 1 H, C15-H), 6.73 (d,  $J = 8.4$  Hz, 1 H, C14-H), 5.12 (s, 2 H, Bn C-H), 4.92 (br s, 1 H, C2-H), 4.88 (d,  $J = 11.0$  Hz, 1 H, Bn C-H), 4.68–4.87 (comp, 2 H, Bn C-H), 4.59 (d,  $J = 11.6$  Hz, 1 H, Bn C-H), 4.41 (d,  $J = 12.0$  Hz, 1 H, Bn C-H), 4.21 (br d,  $J$

= 9.8, 1 H, C5-H), 4.00 (dd,  $J = 6.8, 9.8$  Hz, 1 H, C4-H), 3.81 (d,  $J = 3.2$ , 2 H, C6-H), 3.79 (s, 3 H, C17-H), 3.73 (s, 3 H, C18-H);  $^{13}\text{C}$  NMR  $\delta$  156.8, 151.5, 150.5, 138.8, 138.5, 138.4, 137.4, 130.6, 128.6, 128.4, 128.3, 128.2, 128.0, 127.8, 127.64, 127.59, 127.5, 127.4, 127.3, 127.1, 127.0, 119.7, 108.1, 107.9, 107.3, 96.8 (C2) 78.7 (C3), 78.1 (C5), 75.2 (C4), 74.1 (Bn C), 73.4 (Bn C), 71.5 (Bn C), 70.1 (Bn C), 69.0 (C4), 57.7 (C17), 56.9 (C18).

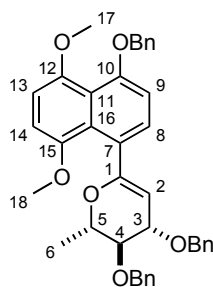


**4,5-Bis-benzyloxy-2-(4-benzyloxy-5,8-dimethoxy-naphthalen-1-yl)-6-benzyloxymethyl-tetrahydro-pyran-3-ol (2.19). (KP1-270).**  $\text{BH}_3 \cdot \text{THF}$  in THF (380  $\mu\text{L}$ , 0.382 mmol, 1 M) was added to naphthalene **2.18** (27 mg, 0.038 mmol) in THF (0.4 mL). The mixture was stirred at room temperature for 2 h, and then was cooled to 0  $^\circ\text{C}$ , whereupon NaOH (0.6 mL, 1.78 mmol, 3 M) was added, dropwise over 5 min.  $\text{H}_2\text{O}_2$  (0.24 mL, 1.78 mmol, 30 wt % aqueous solution) was added, the ice bath was removed, and stirring was continued for 1 h. Water (1 mL) and  $\text{Et}_2\text{O}$  (1.5 mL) were added, the layers were separated, and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 x 2 mL). The organic layers were combined, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated. The residue was purified by flash chromatography, eluting with  $\text{EtOAc/Hexanes}$  (1:5), to give 18 mg (64%) of glycoside **2.19** as a yellow oil:  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.92 (d,  $J = 8.4$  Hz, 1 H), 7.52–7.46 (comp, 4 H), 7.36–7.03 (comp, 16 H), 6.75 (d,  $J = 8.4$  Hz, 1 H), 6.56 (d,



$J = 8.6$  Hz, 1 H), 6.47 (d,  $J = 8.6$  Hz, 1 H), 6.00 (d,  $J = 9.4$  Hz, 1 H), 5.21 (d,  $J = 11.6$  Hz, 1 H), 5.09 (d,  $J = 11.6$  Hz, 1 H), 5.01 (d,  $J = 11.6$  Hz, 1 H), 4.84 (s, 2 H), 4.75 (d,  $J = 11.2$  Hz, 1 H), 4.53 (d,  $J = 12.2$  Hz, 1 H), 4.43 (d,  $J = 12.2$  Hz, 1 H), 4.06 (dt,  $J = 5.2, 9.0$  Hz, 1 H), 4.02 (app t,  $J = 8.3$  Hz, 1 H) 8.86–3.83 (comp, 2 H), 3.55 (s, 3 H), 3.33 (s, 3 H), 2.47 (d,  $J = 5.4$  Hz, 1 H);  $^{13}\text{C}$  NMR (125 MHz)  $\delta$  156.6, 153.0, 151.0, 140.0, 139.6, 139.2, 138.3, 128.51, 128.48, 128.3, 127.9, 127.6, 127.5, 127.4, 127.2, 120.7, 109.5, 107.8, 107.5, 88.4, 80.5, 78.9, 78.7, 78.6, 75.2, 75.1, 73.6, 71.4, 70.1, 57.3, 55.6; IR (neat) 3474, 3062, 3029, 1595, 1280, 1057  $\text{cm}^{-1}$ ; mass spectrum (CI)  $m/z$  727.3285 [ $\text{C}_{39}\text{H}_{41}\text{O}_7$  (M+1) requires 727.3271], 709 (base), 621, 601.

**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.92 (d,  $J = 8.4$  Hz, 1 H, C9-H), 7.52–7.46 (comp, 4 H, Ar-H), 7.36–7.03 (comp, 16 H, Ar-H), 6.75 (d,  $J = 8.4$  Hz, 1 H, C8-H), 6.56 (d,  $J = 8.6$  Hz, 1 H, C14-H), 6.47 (d,  $J = 8.6$  Hz, 1 H, C13-H), 6.00 (d,  $J = 9.4$  Hz, 1 H, C1-H), 5.21 (d,  $J = 11.6$  Hz, 1 H, Bn C-H), 5.09 (d,  $J = 11.6$  Hz, 1 H, Bn C-H), 5.01 (d,  $J = 11.6$  Hz, 1 H, Bn C-H), 4.84 (s, 2 H, Bn C-H), 4.75 (d,  $J = 11.2$  Hz, 1 H, Bn C-H), 4.53 (d,  $J = 12.2$  Hz, 1 H, Bn C-H), 4.43 (d,  $J = 12.2$  Hz, 1 H, Bn C-H), 4.06 (dt,  $J = 5.2, 9.0$  Hz, 1 H, C2-H), 4.02 (app t,  $J = 8.3$  Hz, 1 H, C4-H) 8.86–3.83 (comp, 3 H, C5-H and C6-H), 3.55 (s, 3 H, C17-H), 3.33 (s, 3H, C18-H), 2.47 (d,  $J = 5.4$  Hz, 1 H, OH);  $^{13}\text{C}$  NMR (125 MHz)  $\delta$  156.6, 153.0, 151.0, 140.0, 139.6, 139.2, 138.3, 128.51, 128.48, 128.3, 127.9, 127.6, 127.5, 127.4, 127.2, 120.7, 109.5 (C8), 107.8 (C13), 107.5 (C14), 88.4 (C4), 80.5 (C5), 78.9 (C1 or C2), 78.7 (C1 or C2), 78.6 (C4), 75.2 (Bn C), 75.1 (Bn C), 73.6 (Bn C), 71.4 (Bn C), 70.1 (C6), 57.3 (C17), 55.6 (C18).



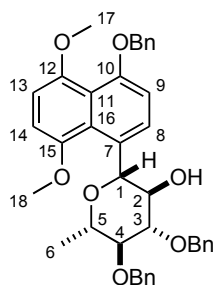
**2.24**

**3,4-Bis-benzyloxy-6-(4-benzyloxy-5,8-dimethoxy-naphthalen-1-yl)-2-methyl-3,4-dihydro-2H-pyran (2.24). (KP1-203).** A solution of  $\text{ZnCl}_2$  in  $\text{Et}_2\text{O}$  (110  $\mu\text{L}$ , 0.11 mmol, 1 M) was added to **2.23** (49 mg, 0.096 mmol) in  $\text{CH}_2\text{Cl}_2$  (1.0 mL) at  $-78^\circ\text{C}$  and the mixture was stirred at  $-78^\circ\text{C}$  for 5 min. The reaction flask was transferred to a  $0^\circ\text{C}$  bath, and stirring was continued for 20 min. A solution of saturated  $\text{NaHCO}_3$  (1 mL) was added, the layers were separated, and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 1 mL). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), filtered through a pad of Celite, and concentrated under reduced pressure. The residue was dried under vacuum, and used directly in the next step without further purification.

$\text{BnBr}$  (35  $\mu\text{L}$ , 0.29 mmol) and  $\text{NaH}$  (12 mg, 0.29 mmol, 60% dispersion in mineral oil) were added to the crude naphthol in  $\text{DMF}$  (1.0 mL). The reaction mixture was stirred at  $25^\circ\text{C}$  for 0.5 h, whereupon 50%  $\text{NaHCO}_3$  (2 mL) and ether (2 mL) were added. The layers were separated, and the aqueous layer was extracted with ether (3 x 2 mL). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with  $\text{EtOAc}$ /hexanes (1:5) to afford 32 mg (55%) of **2.24** as a yellow oil:  $^1\text{H NMR}$  (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.50–7.46 (comp, 2 H), 7.41–7.38 (comp, 3 H), 7.26–7.10 (comp, 12 H), 6.60 (d,  $J = 8.5$  Hz, 1 H), 6.57 (d,  $J = 8.5$  Hz, 1 H), 5.17 (m, 1 H), 5.06 (d,  $J = 11.5$  Hz, 1 H), 4.79 (s, 2 H), 4.76 (d,  $J = 11.5$  Hz, 1 H), 4.69–4.66 (comp, 2 H), 4.54 (d,  $J = 12.0$  Hz, 1 H),

4.41 (m, 1 H), 3.87 (dd,  $J = 9.9, 6.8$  Hz, 1 H), 3.54 (s, 3 H), 3.50 (br s, 3 H), 1.50 (d,  $J = 6.8$  Hz, 3 H);  $^{13}\text{C}$  NMR (125 MHz)  $\delta$  160.0, 157.3, 152.4, 151.1, 139.7, 139.5, 138.2, 130.7, 128.53, 128.48, 128.47, 128.3, 128.2, 128.1, 127.92, 127.91, 127.64, 127.58, 127.56, 127.2, 120.5, 108.4, 108.19, 108.2, 80.7, 79.4, 75.0, 74.2, 71.2, 70.2, 57.4, 56.7, 55.0, 18.2; IR (neat) 3060, 3025, 1655, 1273, 1056  $\text{cm}^{-1}$ ; mass spectrum (CI)  $m/z$  603.2747 [ $\text{C}_{39}\text{H}_{39}\text{O}_6$  (M+1) requires 603.2747] 495 (base), 325, 309.

**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.50–7.46 (comp, 2 H, Ph-H or C8-H or C9-H), 7.41–7.38 (comp, 3 H, Ph-H or C8-H or C9-H), 7.26–7.10 (comp, 12 H, Ph-H or C8-H or C9-H), 6.60 (d,  $J = 8.5$  Hz, 1 H, C14-H), 6.57 (d,  $J = 8.5$  Hz, 1 H, C13-H), 5.17 (m, 1 H, C2-H), 5.06 (d,  $J = 11.5$  Hz, 1 H, Bn C-H), 4.79 (s, 2 H, Bn C-H), 4.76 (d, 11.5 Hz, 1 H, Bn C-H), 4.69–4.66 (comp, 2 H, Bn C-H and C3-H), 4.54 (d,  $J = 12.0$  Hz, 1 H, Bn C-H), 4.41 (m, 1 H, C5-H), 3.87 (dd,  $J = 9.9, 6.8$  Hz, 1 H, C4-H), 3.54 (s, 3 H, C17-H), 3.50 (br s, 3 H, C18-H), 1.50 (d,  $J = 6.8$  Hz, 3 H, C6-H);  $^{13}\text{C}$  NMR (125 MHz)  $\delta$  160.0, 157.3, 152.4, 151.1, 139.7, 139.5, 138.2, 130.7, 128.53, 128.48, 128.47, 128.3, 128.2, 128.1, 127.92, 127.91, 127.64, 127.58, 127.56, 127.2, 120.5, 108.4 (C14), 108.1 (C13), 97.2 (C2), 80.7 (C4), 79.4 (C3), 75.0 (C5), 74.2 (C2), 71.2 (Bn C), 70.2 (Bn C), 57.4 (Bn C), 56.7 (C17), 55.0 (C18), 18.2 (C6).

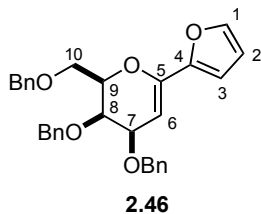


**2.25**

**4,5-Bis-benzyloxy-2-(4-benzyloxy-5,8-dimethoxy-naphthalen-1-yl)-6-methyl-tetrahydro-pyran-3-ol (2.26) (KP1-278).**  $\text{BH}_3 \cdot \text{THF}$  in THF (790  $\mu\text{L}$ , 0.79 mmol, 1 M) was added to naphthalene **2.24** (47 mg, 0.079 mmol) in THF (1.0 mL). The mixture was stirred at room temperature for 2 h, and then was cooled to 0 °C, whereupon NaOH (0.9 mL, 2.6 mmol, 3 M) was added, dropwise over 5 min.  $\text{H}_2\text{O}_2$  (0.24 mL, 2.6 mmol, 30 wt % aqueous solution) was added, the ice bath was removed, and stirring was continued for 1 h. Water (7 mL) and  $\text{Et}_2\text{O}$  (7 mL) were added, the layers separated, and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 x 7 mL). The organic layers were combined, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated. The residue was purified by flash chromatography, eluting with  $\text{EtOAc/Hexanes}$  (1:5) to give 34 mg (70%) of **2.26** as a white solid: mp 131–133 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.91 (d,  $J = 8.4$  Hz, 1 H), 7.52–7.47 (comp, 4 H), 7.39–7.37 (comp, 2 H), 7.27–7.09 (comp, 9 H), 6.80 (d,  $J = 8.4$  Hz, 1 H), 6.55 (d,  $J = 8.6$  Hz, 1 H), 6.46 (d,  $J = 8.6$  Hz, 1 H), 5.98 (d,  $J = 9.0$  Hz, 1 H), 5.23 (d,  $J = 11.2$  Hz, 1 H), 5.06 (d,  $J = 11.2$  Hz, 1 H), 5.00 (d,  $J = 11.2$  Hz, 1 H), 4.85 (s, 2 H), 4.66 (d,  $J = 11.2$  Hz, 1 H), 4.03 (td,  $J = 9.0, 5.6$  Hz, 1 H), 3.8 (app t,  $J = 9.0$  Hz, 1 H), 3.77–3.72 (m, 1 H), 3.55 (s, 3 H), 3.43 (app t,  $J = 9.0$  Hz, 1 H), 3.32 (s, 3 H), 2.52 (d,  $J = 5.6$  Hz, 1 H), 1.42 (d,  $J = 6.2$  Hz, 3 H);  $^{13}\text{C}$  NMR (125 MHz)  $\delta$  156.5, 153.0, 151.0, 140.0, 139.6, 138.4, 128.6, 128.51, 128.49, 128.48, 128.40, 128.29, 128.26, 128.19, 128.1, 127.9, 127.64, 127.59, 127.58, 127.3, 127.2, 120.6, 109.6, 108.0, 107.4, 88.3, 84.7, 78.9, 78.4, 76.4, 75.3, 75.2, 71.5,

57.3, 55.6, 18.9; IR (neat) 3572, 3060, 3025, 1602, 1290  $\text{cm}^{-1}$ ; mass spectrum (CI)  $m/z$  622.2845 [ $\text{C}_{39}\text{H}_{41}\text{O}_7$  (M+1) requires 622.2852], 603, 530, 515 (base).

**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  7.91 (d,  $J = 8.4$  Hz, 1 H, C9-H), 7.52–7.47 (comp, 4 H, Ph-H), 7.39–7.37 (comp, 2 H, Ph-H), 7.27–7.09 (comp, 9 H, Ph-H), 6.80 (d,  $J = 8.4$  Hz, 1 H, C8-H), 6.55 (d,  $J = 8.6$  Hz, 1 H, C14-H), 6.46 (d,  $J = 8.6$  Hz, 1 H, C13-H), 5.98 (d,  $J = 9.0$  Hz, 1 H, C1-H), 5.23 (d,  $J = 11.2$  Hz, 1 H, Bn C-H), 5.06 (d,  $J = 11.2$  Hz, 1 H, Bn C-H), 5.00 (d,  $J = 11.2$  Hz, 1 H, Bn C-H), 4.85 (s, 2 H, Bn C-H), 4.66 (d,  $J = 11.2$  Hz, 1 H, Bn C-H), 4.03 (td,  $J = 9.0, 5.6$  Hz, 1 H, C2-H), 3.8 (app t,  $J = 9.0$  Hz, 1 H, C3-H), 3.77–3.72 (m, 1 H, C5-H), 3.55 (s, 3 H, C17-H), 3.43 (app t,  $J = 9.0$  Hz, 1 H, C4-H), 3.32 (s, 3 H, C18-H), 2.52 (d,  $J = 5.6$  Hz, 1 H, O-H), 1.42 (d,  $J = 6.2$  Hz, 3 H, C6-H);  $^{13}\text{C}$  NMR (125 MHz)  $\delta$  156.5, 153.0, 151.0, 140.0, 139.6, 138.4, 128.6, 128.51, 128.49, 128.48, 128.40, 128.29, 128.26, 128.19, 128.1, 127.9, 127.64, 127.59, 127.58, 127.3, 127.2, 120.6, 109.6 (C8), 108.0 (C13), 107.4 (C14), 88.3 (C3), 84.7 (C4), 78.9 (C2), 78.4 (C1), 76.4 (Bn C), 75.3 (Bn C), 75.2 (Bn C), 71.5 (Bn C), 57.3 (C17), 55.6 (C18), 18.9 (C6).

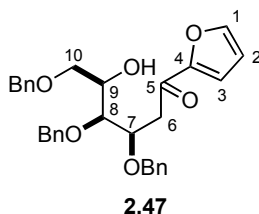


**(2R, 3R, 4R)-3,4-Bis(benzyloxy)-2-(benzyloxy)methyl-6-(furan-2-yl)-3,4-dihydro-2H-pyran (2.46). (KP1-117).** 2-Furyllithium (1.2 mL, 0.29 mmol, 2.5 M) was added dropwise via syringe to **2.45** (115 mg, 0.27 mmol) in THF (2.7 mL) at  $-78$   $^{\circ}\text{C}$ . The mixture was stirred at  $-78$   $^{\circ}\text{C}$  for 1.5 h, whereupon triethylamine (82 mg, 112  $\mu\text{L}$ ,

0.81 mmol), DMAP (36 mg, 0.32 mmol) in THF (300  $\mu$ L), and TFAA (142 mg, 95  $\mu$ L, 0.66 mmol) were added sequentially. The reaction was allowed to warm slowly with stirring to room temperature over a period of 4 h, and then stirring was continued at room temperature for 14 h. A 50% solution of aqueous NaHCO<sub>3</sub> (4 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with Et<sub>2</sub>O/Hexanes (1:5) to afford 19 mg (15%) of **2.46** as a yellow solid: mp = 41–44 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.37–7.25 (comp, 16 H), 6.43 (d, *J* = 3.4 Hz, 1 H), 6.37 (dd, *J* = 3.4, 1.8 Hz, 1 H), 5.47 (dd, *J* = 3.4, 0.9 Hz, 1 H), 4.87 (d, *J* = 12.0 Hz, 1 H), 4.72 (d, *J* = 12.1 Hz, 1 H), 4.67 (d, *J* = 12.0 Hz, 1 H), 4.66 (d, *J* = 12.1 Hz, 1 H), 4.53 (d, *J* = 12.0 Hz, 1 H), 4.45 (d, *J* = 12.0 Hz, 1 H), 4.37–4.34 (m, 1 H), 4.32 (dd, *J* = 0.9, 3.4 Hz, 1 H), 4.02 (ddd, *J* = 3.4, 2.5, 0.9 Hz, 1 H), 3.86 (dd, *J* = 10.3, 6.9 Hz, 1 H), 3.80 (dd, *J* = 10.3, 5.2 Hz, 1 H); <sup>13</sup>C NMR (125 MHz)  $\delta$  149.0, 144.6, 142.4, 138.6, 138.4, 138.2, 128.4, 128.3, 128.1, 127.8, 127.7, 127.6, 127.5, 127.5, 111.4, 107.4, 95.0, 76.3, 73.4, 73.1, 71.4, 71.0, 70.9, 68.2; IR (neat) 3013, 2849, 1661, 1091 cm<sup>-1</sup>; mass spectrum (CI) *m/z* 483.2158 [C<sub>31</sub>H<sub>30</sub>O<sub>5</sub> (M+1) requires 483.2171], 471, 465 (base).

**NMR Assignments:** <sup>1</sup>H NMR (500 MHz)  $\delta$  7.37–7.25 (comp, 16 H, Ph C-H), 6.43 (d, *J* = 3.4 Hz, 1 H, C3-H), 6.37 (dd, *J* = 3.4, 1.8 Hz, 1 H, C2-H), 5.47 (dd, *J* = 3.4, 0.9 Hz, 1 H, C6-H), 4.87 (d, *J* = 12.0 Hz, 1 H, BnC-H), 4.72 (d, *J* = 12.1 Hz, 1 H, Bn C-H), 4.67 (d, *J* = 12.0, 1 H, Bn C-H), 4.66 (d, *J* = 12.1 Hz, 1 H, BnC-H), 4.53 (d, *J* = 12.0 Hz, 1 H, Bn C-H), 4.45 (d, *J* = 12.0 Hz, 1 H, Bn C-H), 4.37–4.34 (m, 1 H, C9-H), 4.32 (dd, *J* = 3.4, 0.9, Hz 1 H, C7-H), 4.02 (ddd, *J* = 3.4, 2.5, 0.9 Hz, 1 H, C8-H), 3.86 (d, *J* = 10.3, 6.9 Hz, 1 H, C10-H), 3.80 (d, *J* = 10.3, 5.2 Hz, 1 H, C10-H); <sup>13</sup>C NMR (125 MHz)  $\delta$  149.0, 144.6, 142.4, 138.6, 138.4, 138.2, 128.4, 128.3, 128.1, 127.8, 127.7, 127.6, 127.5,

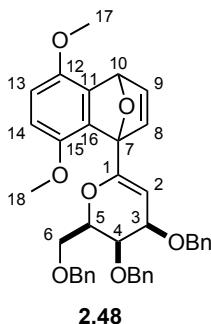
127.5 (Ar-C), 111.4 (C2), 107.4 (C3), 95.0 (C6), 76.3 (C9), 73.4 (C11, C12, or C13), 73.1 (C11, C12, or C13), 71.4 (C8), 71.0 (C7), 70.9 (C11, C12, or C13), 68.2 (C10).



**(2R, 3R, 4R)-Trisbenzyloxy-1-furan-2-yl-5-hydroxyhexan-1-one.** The above reaction also yielded 72 mg (62%) of hydroxy ketone **2.47** as a yellow oil:  $^1\text{H}$  NMR (400 MHz)  $\delta$  7.55 (dd,  $J = 1.4$  Hz, 0.7, 1 H), 7.35–7.20 (comp, 15 H), 7.15 (dd,  $J = 3.8$ , 0.7 Hz, 1 H), 6.50 (dd,  $J = 3.8$ , 1.7 Hz, 1 H), 4.79 (d,  $J = 11.3$  Hz, 1 H), 4.63 (d,  $J = 11.3$  Hz, 1 H), 4.60–4.57 (comp, 3 H), 4.51 (d,  $J = 12.0$  Hz, 1 H), 4.48–4.42 (comp, 2 H), 4.00–3.94 (m, 1 H), 3.77 (dd,  $J = 4.1$ , 3.4 Hz, 1 H), 3.58–3.48 (comp, 2 H), 3.11 (dd,  $J = 16.4$ , 4.1 Hz, 1 H), 2.86 (d,  $J = 5.5$  Hz, 1 H);  $^{13}\text{C}$  NMR (100 MHz)  $\delta$  187.2, 152.8, 146.5, 137.9, 128.4, 128.3, 128.1, 127.91, 127.88, 127.83, 127.72, 127.67, 117.5, 112.3, 79.1, 73.8, 73.4, 73.1, 71.0, 70.0, 40.5; IR (neat) 3481, 3020, 2867, 1672, 1085  $\text{cm}^{-1}$ ; mass spectrum (CI)  $m/z$  501.2260 [ $\text{C}_{31}\text{H}_{33}\text{O}_6$  (M+1) requires 501.2277], 483 (base), 393, 375, 285.

**NMR assignments:**  $^1\text{H}$  NMR (400 MHz)  $\delta$  7.55 (dd,  $J = 1.4$ , 0.7 Hz, 1 H, C1-H), 7.35–7.20 (comp, 15 H, Ph C-H), 7.15 (dd,  $J = 3.8$ , 0.68 Hz, 1 H, C3-H), 6.50 (dd,  $J = 1.7$ , 3.8 Hz, 1 H, C2-H), 4.79 (d,  $J = 11.3$  Hz, 1 H, Bn C-H), 4.63 (d,  $J = 11.3$  Hz, 1 H, Bn C-H), 4.60–4.57 (comp, 3 H), 4.51 (d,  $J = 12.0$  Hz, 1 H, Bn C-H), 4.48–4.42 (comp, 2 H, Bn C-H), 4.00–3.94 (m, 1 H), 3.77 (dd,  $J = 4.1$ , 3.4 Hz, 1 H), 3.58–3.48 (comp, 2 H), 3.11 (dd,  $J = 16.4$ , 4.1 Hz, 1 H), 2.86 (d,  $J = 5.5$  Hz, 1 H);  $^{13}\text{C}$  NMR (100 MHz)  $\delta$  187.2

(C5), 152.8, 146.5, 137.9, 128.4, 128.3, 128.1, 127.91, 127.88, 127.83, 127.72, 127.67  
(C1), 117.5 (C3), 112.3 (C2), 79.1, 73.8, 73.4, 73.1, 71.0, 70.0, 40.5.

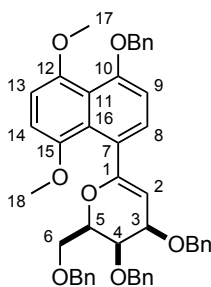


**1-(4,5-Bisbenzyloxy-6-benzyloxymethyl-5,6-dihydro-4H-pyran-2-yl)-3,6-dimethoxy-11-oxatricyclo[6.2.1.0<sup>2,7</sup>]undeca-2(7)3,5,9-tetraene (KP1-283).** (**2.48**) A solution of *s*-BuLi (1.21 M, 0.41 mL, 0.57 mmol) was added to 2-chloro-1,4-dimethoxybenzene (**2.15**) (81  $\mu$ L, 0.57 mmol) in THF at  $-95$   $^{\circ}$ C, dropwise over a 5 min period. The reaction mixture was stirred at  $-95$   $^{\circ}$ C for 10 min, whereupon a solution of **2.46** (91.4 mg, 149  $\mu$ mol) in THF (0.4 mL) was added dropwise over a 5 min period. The reaction mixture was warmed to  $-10$   $^{\circ}$ C over 45 min, whereupon a 30% aqueous solution of  $\text{NH}_4\text{Cl}$  (2 mL) was added. The layers were separated, and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 x 4 mL). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with  $\text{Et}_2\text{O}$ /Hexanes (1:7 then 1:5) to afford 89 mg (75%) of cycloadduct **2.48** as a 1:1 mixture of diastereomers:  $^1\text{H}$  NMR  $\delta$  7.37–7.22 (comp, 15 H), 7.08 (d,  $J = 5.6$  Hz, 1 H), 6.89 (dd,  $J = 5.6, 1.81$  Hz, 1 H), 6.52 (d,  $J = 8.8$  Hz, 1 H), 6.46 (d,  $J = 9.0$  Hz, 1 H), 5.88 (d,  $J = 1.8$  Hz, 1 H), 4.97 (d,  $J = 11.2$  Hz, 1 H), 4.67–4.57 (comp, 3 H), 4.55 (d,  $J = 11.7$  Hz, 1 H), 4.52 (d,  $J = 11.7$  Hz, 1 H), 4.16–4.12 (m, 1 H), 4.00 (s, 1 H), 4.95–4.92 (m, 1 H), 3.85 (m, 1 H), 3.74, (s, 3 H), 3.59–3.52 (m, 2 H), 3.42



(br s, 3 H);  $^{13}\text{C}$  NMR  $\delta$  148.5, 147.2, 144.0, 141.9, 139.6, 139.5, 138.9, 138.3, 137.0, 128.4, 128.3, 128.0, 127.8, 127.64, 127.57, 127.33, 127.30, 127.25, 112.3, 111.6, 99.6, 98.2, 79.2, 75.7, 74.8, 73.6, 73.5, 71.9, 70.3, 69.3, 56.3, 56.2; IR (neat) 3062, 3029, 1602, 1494, 1257, 1056  $\text{cm}^{-1}$ ; mass spectrum (CI)  $m/z$  603.2747 [ $\text{C}_{39}\text{H}_{39}\text{O}_7$  (M+1) requires 603.2747] 495 (base), 325, 309.

**NMR Assignments:**  $^1\text{H}$  NMR  $\delta$  7.37–7.22 (comp, 15 H, Ph-H), 7.08 (d,  $J = 5.6$  Hz, 1 H, C8-H), 6.89 (dd,  $J = 5.6, 1.8$  Hz, 1 H, C9-H), 6.52 (d,  $J = 9.0$  Hz, 1 H, C13-H or C14-H), 6.46 (d,  $J = 9.0$  Hz, 1 H, C13-H or C14-H), 5.88 (d,  $J = 1.8$  Hz, 1 H, C10-H), 4.97 (d,  $J = 11.2$  Hz, 1 H, Bn C-H), 4.67–4.57 (comp, 3 H, Bn C-H), 4.55 (d,  $J = 11.7$  Hz, 1 H, Bn C-H), 4.52 (d,  $J = 11.7$  Hz, 1 H, Bn C-H), 4.16–4.12 (m, 1 H), 4.00 (s, 1 H), 4.95–4.92 (m, 1 H), 3.85 (m, 1 H), 3.74 (s, 3 H, C15-H), 3.59–3.52 (comp, 2 H), 3.42 (br s, 3 H, C16-H);  $^{13}\text{C}$  NMR  $\delta$  148.5, 147.2, 144.0, 141.9, 139.6, 139.5, 138.9, 138.3, 137.0, 128.4, 128.3, 128.0, 127.8, 127.64, 127.57, 127.33, 127.30, 127.25, 112.3, 111.6, 99.6, 98.2, 79.2, 75.7, 74.8, 73.6, 73.5, 71.9, 70.3, 69.3, 56.3, 56.2



**2.49**

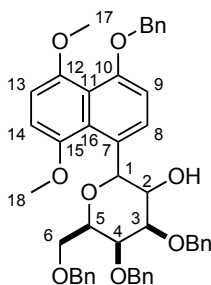
**3,4-Bis-benzyloxy-6-(4-benzyloxy-5,8-dimethoxy-naphthalen-1-yl)-2-benzyloxymethyl-3,4-dihydro-2H-pyran (KP1-286). (2.49).** A solution of  $\text{ZnCl}_2$  in  $\text{Et}_2\text{O}$  (1 M, 0.44  $\mu\text{L}$ , 0.44 mmol) was added to **2.48** (186 mg, 0.360 mmol) in  $\text{CH}_2\text{Cl}_2$  (3.6 mL) at  $-78$   $^\circ\text{C}$ . The reaction was stirred at  $-78$   $^\circ\text{C}$  for 5 min. The reaction flask was

transferred to a 0 °C bath, and stirring was continued for 20 min. A solution of saturated NaHCO<sub>3</sub> (4 mL) was added, the layers were separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 4 mL). The combined organic layers were combined, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered through a pad of Celite, and concentrated under reduced pressure. The crude naphthol was dried under vacuum, and used in the next step without further purification.

BnBr (27 µL, 0.23 mmol) and NaH (9.2 mg, 0.23 mmol, 60% dispersion in mineral oil) were added to the crude naphthol in DMF (3.5 mL) and the reaction mixture was stirred at 25 °C for 0.5 h, whereupon a 25% solution of NaHCO<sub>3</sub> (4 mL) and ether (4 mL) were added. The layers were separated and the aqueous layer was extracted with ether (3 x 5 mL). The organic layers were combined, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with EtOAc/hexanes (1:5) to afford 75 mg (30%) of naphthalene **2.49**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.57–7.56 (comp, 2H), 7.40–7.22 (comp, 19 H), 6.86 (d, *J* = 8.0 Hz, 1 H), 6.81 (d, *J* = 8.6 Hz, 1 H), 6.78 (d, *J* = 8.6 Hz, 1 H), 5.17 (s, 2 H), 4.98 (d, *J* = 12 Hz, 1 H), 4.90 (d, *J* = 1.4 Hz, 1 H), 4.71 (d, *J* = 12.0 Hz, 1 H), 4.73 (d, *J* = 12.2 Hz, 1 H), 4.68 (d, *J* = 12.2 Hz, 1H), 4.43–4.39 (comp, 4 H), 4.08–4.07 (m, 1 H), 3.83 (s, 3 H), 3.79–3.77 (comp, 2 H), 3.72 (br s, 3 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 158.0, 156.6, 151.6, 150.5, 138.9, 138.3, 137.4, 130.6, 128.4, 128.3, 128.2, 128.1, 127.8, 127.6, 127.5, 127.4, 127.1, 119.8, 108.2, 108.1, 107.9, 107.7, 96.5, 76.6, 73.3, 72.4, 71.5, 70.7, 70.0, 68.7, 57.6, 57.1; IR (neat) 3060, 3025, 1258, 1063 cm<sup>-1</sup>; mass spectrum (CI) *m/z* 727.3193 [C<sub>39</sub>H<sub>39</sub>O<sub>8</sub> (M+1) requires 727.3193] 727 (base), 710, 602.

**NMR Assignments:** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.57–7.56 (comp, 2 H, Ph C-H, C9-H), 7.40-7.22 (comp, 19 H, Ph C-H), 6.86 (d, *J* = 8.0z, 1 H, C8-H), 6.81 (d, *J* = 8.6 Hz, 1 H, C13-H), 6.78 (d, *J* = 8.6 Hz, 1 H, C14-H), 5.17 (s, 2 H, Bn C-H), 4.98 (d, *J* = 12

Hz, 1 H, Bn C-H), 4.90 (d,  $J = 1.4$  Hz, 1 H, C2-H), 4.71 (d,  $J = 12.0$  Hz, 1 H, Bn C-H), 4.73 (d,  $J = 12.2$  Hz, 1 H, Bn C-H), 4.68 (d,  $J = 12.2$  Hz, 1 H, Bn C-H), 4.43–4.39 (comp, 4H, Bn C-H and C5-H and C3-H), 4.08–4.07 (m, 1 H, C4-H), 3.83 (s, 3 H, C17-H), 3.79–3.77 (comp, 2 H, C6-H), 3.72 (br s, 3 H, C18-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  158.0, 156.6, 151.6, 150.5, 138.9, 138.3, 137.4, 130.6, 128.4, 128.3, 128.2, 128.1, 127.8, 127.6, 127.5, 127.4, 127.1, 119.8, 108.2, 108.1, 107.9, 107.7, 96.5 (C2), 76.6 (C3), 73.3 (Bn C), 72.471.5 (C5), 70.7 (Bn C), 70.0 (C4), 68.7 (C6), 57.6 (C17), 57.1 (C18).

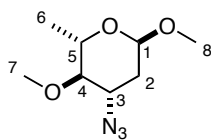


**2.50**

**4,5-Bis-benzyloxy-2-(4-benzyloxy-5,8-dimethoxy-naphthalen-1-yl)-6-benzyloxymethyl-tetrahydro-pyran-3-ol (2.50). (KP1-282).** A solution of  $\text{BH}_3 \cdot \text{THF}$  in THF (0.31 mL, 0.31 mmol, 1 M) was added to **2.49** (22 mg, 0.31 mmol) in THF (0.5 mL) at rt. The mixture was stirred at room temperature for 2 h, and then was cooled to 0 °C, whereupon NaOH (3 M, 0.30 mL, 0.92 mmol) was added, dropwise over 5 min.  $\text{H}_2\text{O}_2$  (80  $\mu\text{L}$ , 0.92 mmol, 30 wt % aqueous solution) was added at 0 °C, and the reaction mixture was warmed to room temperature and stirring was continued for 1 h. Water was added (2 mL), and the reaction mixture was diluted with  $\text{Et}_2\text{O}$  (3 mL). The layers were separated, and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 x 3 mL). The organic layers were combined, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated. The residue was purified by flash chromatography, eluting with  $\text{EtOAc}/\text{Hexanes}$  (1:5), to give 12 mg (55%) of **2.50** as a

viscous yellow oil:  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  8.00 (d,  $J = 8.2$  Hz, 1 H), 7.51–7.47 (comp, 4 H), 7.42–7.40 (comp, 2 H), 7.26–7.07 (comp, 14 H), 6.63 (d,  $J = 8.5$  Hz, 1 H), 6.57 (d,  $J = 8.5$  Hz, 1 H), 6.51 (d,  $J = 8.5$  Hz, 1 H), 6.06 (d,  $J = 9.2$  Hz, 1 H), 5.18 (d,  $J = 11.6$  Hz, 1 H), 4.77–4.68 (comp, 6 H), 4.33 (d,  $J = 12.0$  Hz, 1 H), 4.28 (d,  $J = 12.0$  Hz, 1 H), 4.15 (d,  $J = 3.0$  Hz, 1 H), 3.77–3.73 (comp, 2 H), 3.76 (dd,  $J = 13.4, 9.7$  Hz, 1 H), 3.63 (dd,  $J = 9.6, 3.0$  Hz, 1 H), 3.55 (s, 3 H), 3.42 (s, 3 H), 2.31 (d,  $J = 4.5$  Hz, 1 H);  $^{13}\text{C}$  NMR (125 MHz)  $\delta$  156.5, 153.0, 151.4, 140.0, 139.7, 139.0, 138.4, 128.62, 128.59, 128.5, 128.4, 127.7, 127.63, 127.60, 127.5, 127.4, 120.7, 109.6, 108.1, 107.6, 85.6, 79.4, 78.4, 75.8, 75.3, 74.5, 73.6, 72.8, 71.4, 69.7, 57.4, 55.8; IR (neat) 3478, 3062, 3029, 1595, 1281, 1109, 1064  $\text{cm}^{-1}$ ; mass spectrum (CI)  $m/z$  726.3193 [ $\text{C}_{46}\text{H}_{46}\text{O}_8$  ( $\text{M}^+$ ) requires 726.3193], 710, 602 (base).

**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  8.00 (d,  $J = 8.2$  Hz, 1 H, C9-H), 7.51–7.47 (comp, 4 H, Ph-H), 7.42–7.40 (comp, 2 H, Ph-H), 7.26–7.07 (comp, 14 H, Ph-H), 6.63 (d,  $J = 8.5$  Hz, 1 H, C8-H), 6.57 (d,  $J = 8.5$  Hz, 1 H, C13-H or C14-H), 6.51 (d,  $J = 8.5$  Hz, 1 H, C13-H or C14-H), 6.06 (d,  $J = 9.2$  Hz, 1 H, C1-H), 5.18 (d,  $J = 11.6$  Hz, 1 H, Bn C-H), 4.77–4.68 (comp, 6 H, Bn C-H and C2-H), 4.33 (d,  $J = 12.0$  Hz, 1 H, Bn C-H), 4.28 (d,  $J = 12.0$  Hz, 1 H, Bn C-H), 4.15 (d,  $J = 3.0$  Hz, 1 H, C4-H), 3.77–3.73 (comp, 2 H, C5-H and C6-H), 3.76 (dd,  $J = 13.4, 9.7$  Hz, 1 H, C6-H), 3.63 (dd,  $J = 9.6, 3.0$  Hz, 1 H, C3-H), 3.55 (s, 3 H, C17-H or C18-H), 3.42 (s, 3 H, C17-H or C18-H), 2.31 (d,  $J = 4.5$  Hz, 1 H, OH);  $^{13}\text{C}$  NMR (125 MHz)  $\delta$  156.5, 153.0, 151.4, 140.0, 139.7, 139.0, 138.4, 128.62, 128.59, 128.5, 128.4, 127.7, 127.63, 127.60, 127.5, 127.4, 120.7, 109.6 (C9), 108.1 (C13 or C14), 107.6 (C13 or C14), 85.6 (C3), 79.4 (C1), 78.4 (C5), 75.8 (Bn C), 75.3 (C2), 74.5 (Bn C), 73.6 (Bn C), 72.8 (Bn C), 71.4 (Bn C), 69.7 (C6), 57.4 (C17 or C18), 55.8 (C17 or C18).

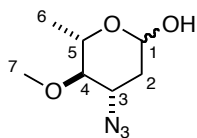


**2.64**

**4-Azido-3,6-dimethoxy-2-methyltetrahydropyran (2.64).** (KP2-124). MeI (106  $\mu$ L, 1.70 mmol) and NaH (85 mg, 2.13 mmol, 60 wt % dispersion) were added to a solution of **2.63** (266 mg, 1.42 mmol) in DMF (14 mL). The reaction was stirred for 1 h at ambient temperature, whereupon MeI (100  $\mu$ L, 228 mg, 1.61 mmol) and NaH (40 mg, 1.0 mmol, 60 wt % dispersion) were added. The reaction mixture was stirred at room temperature for 25 h, whereupon water (20 mL) and Et<sub>2</sub>O (40 mL) were added. The layers were separated, and the aqueous layer was extracted with Et<sub>2</sub>O (3 x 40 mL). The organic layers were combined, and then washed with water (2 x 150 mL) and brine (1 x 150 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with Et<sub>2</sub>O/hexanes (1:9) to afford 285 mg (quantitative) of **2.64** as a clear oil: <sup>1</sup>H NMR (500 MHz)  $\delta$  4.66 (d,  $J$  = 3.6 Hz, 1 H), 3.73 (ddd,  $J$  = 12.4, 9.4, 5.0 Hz, 1 H), 3.62 (dq,  $J$  = 9.4, 6.2 Hz, 1 H), 3.57 (s, 3 H), 3.29 (s, 3 H), 2.70 (app t,  $J$  = 9.4 Hz, 1 H), 2.06 (ddd,  $J$  = 13.2, 5.0, 1.2 Hz, 1 H), 1.59 (ddd,  $J$  = 13.2, 12.4, 3.6, 1 H), 1.27 (d,  $J$  = 6.2 Hz, 3 H); <sup>13</sup>C NMR (125 MHz)  $\delta$  97.3, 86.0, 67.2, 60.6, 59.6, 54.6, 35.5, 17.9; IR (neat) 2012, 1128, 1099, 1050 cm<sup>-1</sup>; mass spectrum (LRCI)  $m/z$  202 [C<sub>8</sub>H<sub>15</sub>N<sub>3</sub>O<sub>3</sub> (M+1) requires 202.1113] 170 (base), 127, 115.

**NMR Assignments.** <sup>1</sup>H NMR (500 MHz)  $\delta$  4.66 (d,  $J$  = 3.6 Hz, 1 H, C1-H), 3.73 (ddd,  $J$  = 12.4, 9.4, 5.0 Hz, 1 H, C3-H), 3.62 (dq,  $J$  = 9.4, 6.2 Hz, 1 H, C5-H), 3.57 (s, 3 H, C7-H or C8-H), 3.29 (s, 3 H, C7-H or C8-H), 2.70 (app t,  $J$  = 9.4 Hz, 1 H, C4-H), 2.06 (ddd,  $J$  = 13.2, 5.0, 1.2 Hz, 1 H, C2-H), 1.59 (ddd,  $J$  = 13.2, 12.4, 3.6 Hz, 1 H, C2-H),

1.27 (d,  $J = 6.2$  Hz, 3 H, C6-H);  $^{13}\text{C}$  NMR (125 MHz)  $\delta$  97.3 (C1), 86.0 (C4), 67.2 (C5), 60.6 (C7 or C8), 59.6 (C2), 54.6 (C7 or C8), 35.5 (C2), 17.9 (C6).

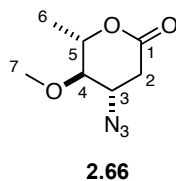


**2.65**

**4-Azido-5-methoxy-6-methyltetrahydropyran-2-ol (2.65). (KP2-126).** Methyl acetate **2.64** (109 mg, 0.542 mmol) in AcOH/H<sub>2</sub>O (4:1, 3 mL) was heated at 110 °C for 1.5 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure to give the crude product as a solid that was purified by flash chromatography eluting with Et<sub>2</sub>O/hexanes (1:5) to give 69 mg (68%) of **2.65** (white solid) as an inseparable mixture of diastereomers (85:15); mp = 99–101 °C;  $^1\text{H}$  NMR (500 MHz)  $\delta$  5.27–5.26 (m, 0.85 H), 4.80 (ddd,  $J = 9.4, 6.2, 2.0$  Hz, 0.15 H), 3.90 (dq,  $J = 9.4, 6.2, 0.4$  Hz, 0.85 H), 3.82 (ddd,  $J = 12.4, 9.4, 5.0$  Hz, 0.85 H), 3.58 (s, 2.55 H), 3.57 (s, 0.45 H), 3.44 (ddd,  $J = 12.4, 9.2, 5.0$  Hz, 0.15 H), 3.34 (dq,  $J = 9.0, 6.2$  Hz, 0.15 H), 2.96–2.90 (m, 0.15 H), 2.73 (app t,  $J = 9.2$  Hz, 0.15 H), 2.70 (app t,  $J = 9.4$  Hz, 0.85 H), 2.44–2.41 (m, 0.85 H), 2.24 (ddd,  $J = 12.9, 5.0, 2.0$  Hz, 0.15 H), 2.10 (ddd,  $J = 6.4, 5.0, 1.4$  Hz, 0.85 H), 1.62–1.55 (m, 0.85 H), 1.54–1.53 (m, 0.15), 1.47 (td,  $J = 12.9, 9.2$  Hz, 0.15 H), 1.32 (d,  $J = 6.2$  Hz, 0.45 H), 1.26 (d,  $J = 6.2$  Hz, 2.55 H);  $^{13}\text{C}$  NMR (125 MHz)  $\delta$  93.7, 91.1, 86.2, 85.6, 72.4, 67.5, 61.6, 60.7, 60.6, 59.1, 38.0, 35.5, 18.0; IR (neat) 3367, 2109, 1264, 1146, 1103 cm<sup>-1</sup>; mass spectrum (CI)  $m/z$  186.0886 [C<sub>7</sub>H<sub>12</sub>N<sub>3</sub>O<sub>3</sub> (M+1) requires 186.0879] 170 (base), 101.

**NMR Assignments.**  $^1\text{H}$  NMR (500 MHz)  $\delta$  5.27–5.26 (m, 0.85 H, C1-H), 4.80 (ddd,  $J = 9.4, 6.2, 2.0$  Hz, 0.15 H, C1-H), 3.90 (dq,  $J = 9.4, 6.2, 0.4$  Hz, 0.85 H, C5-H),

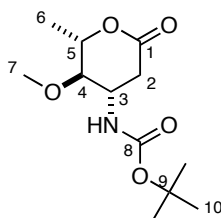
3.82 (ddd,  $J = 12.4, 9.4, 5.0$  Hz, 0.85 H, C3-H), 3.58 (s, 2.55 H, C7-H), 3.57 (s, 0.45 H, C7-H), 3.44 (ddd,  $J = 12.4, 9.2, 5.0$  Hz, 0.15 H, C3-H), 3.34 (dq,  $J = 9.0, 6.2$  Hz, 0.15 H, C5-H), 2.96–2.90 (m, 0.15 H, OH), 2.73 (app t,  $J = 9.2$  Hz, 0.15 H, C4-H), 2.70 (app t,  $J = 9.4$  Hz, 0.85 H, C4-H), 2.44–2.41 (m, 0.85 H, OH), 2.24 (ddd,  $J = 12.9, 5.0, 2.0$  Hz, 0.15 H, C2-H), 2.10 (ddd,  $J = 6.4, 5.0, 1.4$  Hz, 0.85 H, C2-H), 1.62–1.55 (m, 0.85 H, C2-H), 1.54–1.53 (m, 0.15, C1-H), 1.47 (td,  $J = 12.9, 9.2$  Hz, 0.15 H, C2-H), 1.32 (d,  $J = 6.2$  Hz, 0.45 H, C6-H), 1.26 (d,  $J = 6.2$  Hz, 2.55 H, C6-H);  $^{13}\text{C}$  NMR (125 MHz)  $\delta$  93.7 (C1 minor), 91.1 (C1 major), 86.2 (C4 major), 85.6 (C4 minor), 72.4 (C5 minor), 67.5 (C5 major), 61.6 (C5 minor), 60.7 (C7 minor), 60.6 (C7 minor), 59.1 (C3 major), 38.0 (C2 minor), 35.5 (C2 major), 18.0 (C6 major and minor).



**4-Azido-5-methoxy-6-methyl-tetrahydro-pyran-2-one (2.66). (KP2-127).** 4 Å Molecular sieves (127 mg) were added to **2.65** (68 mg, 0.36 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 mL). The solution was stirred for 10 min, and NMO (64 mg, 0.55 mmol) and TPAP (10 mg, 0.028 mmol) were added. The reaction was stirred for 20 min then the solvents were removed under reduced pressure. The residue was passed through a plug of silica, eluting with EtOAc to yield 52 mg (77%) of **2.66** as a clear oil.  $^1\text{H}$  NMR (500 MHz)  $\delta$  4.15 (dq,  $J = 8.8, 6.4$  Hz, 1 H), 3.88 (dt,  $J = 7.4, 6.4$  Hz, 1 H), 3.57 (s, 3 H), 3.08 (dd,  $J = 8.8, 6.4$  Hz, 1 H), 2.95 (dd,  $J = 17.3, 6.4$  Hz, 1 H), 2.92 (dd,  $J = 17.3, 7.4$  Hz, 1 H), 1.46 (d,  $J = 6.4$  Hz, 3 H);  $^{13}\text{C}$  NMR (125 MHz)  $\delta$  168.0, 88.4, 76.1, 59.8, 58.8, 34.1, 18.7; IR (neat)

3437, 2104, 1745, 1238, 1109, 1066  $\text{cm}^{-1}$ ; MASS SPECTRUM (CI)  $m/z$  186.0884 [ $\text{C}_7\text{H}_{12}\text{N}_3\text{O}_3$  (M+1) requires 186.0879] 186 (base), 170, 143, 127.

**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz)  $\delta$  4.15 (dq,  $J = 8.8, 6.4$  Hz, 1 H, C5-H), 3.88 (dt,  $J = 7.4, 6.4$  Hz, 1 H, C3-H), 3.57 (s, 3 H, C7-H), 3.08 (dd,  $J = 8.8, 6.4$  Hz, 1 H, C4-H), 2.95 (dd,  $J = 17.3, 6.4$  Hz, 1 H, C2-H), 2.92 (dd,  $J = 17.3, 7.4$  Hz, 1 H, C2-H), 1.46 (d,  $J = 6.4$  Hz, 3 H, C6-H);  $^{13}\text{C}$  NMR (125 MHz)  $\delta$  168.0 (C1), 88.4 (C4), 76.1 (C5), 59.8 (C7), 58.8 (C3), 34.1 (C2), 18.7 (C6).



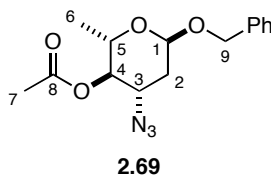
**2.67**

**(3-Methoxy-2-methyl-6-oxo-tetrahydro-pyran-4-yl)-carbamic acid *tert*-butyl ester (2.67).** (**KP2-141**). Palladium on activated carbon (7 mg, 10 wt % palladium) was added to azide **2.66** (70 mg, 0.38 mmol) in optima grade EtOAc (4 mL). The reaction vessel was purged with Ar, and a solution of Boc anhydride (124 mg, 0.57 mmol) in optima grade EtOAc (1 mL) was added. The reaction vessel was purged with  $\text{H}_2$ , and the reaction was stirred at room temperature under a  $\text{H}_2$  atmosphere for 8 h. The reaction was filtered through a plug of Celite eluting with EtOAc. The filtrate was concentrated under reduced pressure and the crude residue was purified by flash chromatography, eluting with EtOAc/hexanes (1:2) to give 85 mg (87%) of **2.67** as a white solid: mp = 131–132  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (500 MHz)  $\delta$  4.68 (br d,  $J = 5.8$  Hz, 1 H), 4.10 (ddd,  $J = 8.2, 6.2$  Hz, 1 H), 4.02 (br s, 1 H), 3.49 (s, 3 H), 3.14 (dd,  $J = 8.2, 4.2$  Hz, 1 H), 2.89 (dd,  $J =$



16.3, 5.8 Hz, 1 H), 2.61 (dd,  $J = 16.3, 4.2$  Hz, 1H), 1.44 (d,  $J = 6.2$  Hz, 3 H), 1.42 (s, 9 H);  $^{13}\text{C}$  NMR (125 MHz)  $\delta$  170.4, 154.7, 83.6, 76.4, 58.5, 48.7, 34.4, 28.3, 19.0; IR (neat) 3354, 1754, 1678, 1526, 1245, 1168, 1118  $\text{cm}^{-1}$ ; mass spectrum (CI)  $m/z$  260.1501 [ $\text{C}_{12}\text{H}_{22}\text{NO}_5$  (M+1) requires 260.1498] 244, 232, 204 (base).

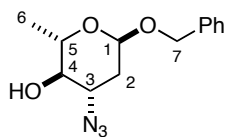
**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz)  $\delta$  4.68 (br d,  $J = 5.8$  Hz, 1 H, N-H), 4.10 (ddd,  $J = 8.2, 6.2$  Hz, 1 H, C5-H), 4.02 (br s, 1 H, C3-H), 3.49 (s, 3 H, C7-H), 3.14 (dd,  $J = 8.2, 4.2$  Hz, 1 H, C4-H), 2.89 (dd,  $J = 16.3, 5.8$  Hz, 1 H, C2-H), 2.61 (dd,  $J = 16.3, 4.2$  Hz, 1H, C2-H), 1.44 (d,  $J = 6.2$  Hz, 3 H, C6-H), 1.42 (s, 9 H, C12-H);  $^{13}\text{C}$  NMR (125 MHz)  $\delta$  170.4 (C10), 154.7 (C1), 83.6 (C11), 76.4 (C5), 58.5 (C7), 48.7 (C3), 34.4 (C2), 28.3 (C12), 19.0 (C6).



**(2*S*,3*R*,4*S*,6*R*)-Acetic acid 4-azido-6-benzyloxy-2-methyltetrahydropyran-3-yl ester (2.69).** (KP2-201). A mixture of acetic acid 5-acetoxy-4-azido-6-methyltetrahydropyran-2-yl ester **2.62** (171 mg, 0.67 mmol), benzyl alcohol (172  $\mu\text{L}$ , 180 mg, 1.66 mmol), and K-10 Montmorillonite (340 mg) in anhydrous benzene (2 mL) was heated at 90  $^{\circ}\text{C}$  for 24 h. The mixture was allowed to cool to room temperature and filtered through Celite, eluting with EtOAc. The combined filtrate and washings were concentrated and the residue was purified by flash chromatography, eluting with  $\text{Et}_2\text{O}$ /hexanes (1:15) to give 102 mg (50%) of **2.69** as a colorless oil:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37–7.24 (comp, 5 H), 7.94 (d,  $J = 3.5$  Hz, 1 H), 4.67 (app t,  $J = 9.8$  Hz, 1 H), 4.66 (d,  $J = 11.9$  Hz, 1 H), 4.46 (d,  $J = 11.9$  Hz, 1 H), 3.90 (ddd,  $J = 12.3, 9.8, 4.9$  Hz, 1

H), 3.82 (dq,  $J = 9.8, 6.3$  Hz, 1 H), 2.17–2.02 (m, 1 H), 2.11 (s, 3 H), 1.74 (ddd,  $J = 13.1, 12.3, 3.5$  Hz, 1 H), 1.15 (d,  $J = 6.3$  Hz, 3 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  170.0, 137.3, 128.5, 127.91, 127.89, 95.5, 75.5, 69.1, 66.1, 57.7, 35.2, 20.8, 17.4; IR (neat) 2101, 1764, 1225, 1043  $\text{cm}^{-1}$ ; mass spectrum (CI)  $m/z$  306.1457 [ $\text{C}_{15}\text{H}_{20}\text{N}_3\text{O}_4$  (M+1) requires 306.1454], 198 (base), 156.

**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37–7.24 (comp, 5 H, Ph C-H), 7.94 (d,  $J = 3.5$  Hz, 1 H, C1-H), 4.67 (app t,  $J = 9.8$  Hz, 1 H, C4-H), 4.66 (d,  $J = 11.9$  Hz, 1 H, C9-H), 4.46 (d,  $J = 11.9$  Hz, 1 H, C9-H), 3.90 (ddd,  $J = 12.3, 9.8, 4.9$  Hz, 1 H, C3-H), 3.82 (dq,  $J = 9.8, 6.3$  Hz, 1 H, C5-H), 2.17–2.02 (m, 1 H, C2-H), 2.11 (s, 3 H, C7-H), 1.74 (ddd,  $J = 13.1, 12.3, 3.5$  Hz, 1 H, C2-H), 1.15 (d,  $J = 6.3$  Hz, 3 H, C6-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  170.0 (C8), 137.3 (Ph C), 128.5 (Ph C), 127.91 (Ph C), 127.89 (Ph C), 95.5 (C1), 75.5 (C4), 69.1 (C9), 66.1 (C5), 57.7 (C3), 35.2 (C2), 20.8 (C7), 17.4 (C6).

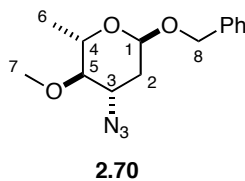


**2.69a**

**(2*S*,3*R*,4*S*,6*R*)-4-Azido-6-benzyloxy-2-methyltetrahydropyran-3-ol (2.69a)**  
**(KP2-202).** A mixture of acetate **2.69** (313 mg, 1.03 mmol) and  $\text{K}_2\text{CO}_3$  (7 mg, 0.05 mmol) in MeOH (10 mL) was stirred at room temperature for 24 h. The solvent was removed under reduced pressure, and the residue was dried under vacuum to give an alcohol:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36–7.27 (comp, 5 H), 4.93 (d,  $J = 3.5$  Hz, 1 H), 4.66 (d,  $J = 12.5$  Hz, 1 H), 4.45 (d,  $J = 12.5$  Hz, 1 H), 3.80 (ddd,  $J = 12.0, 9.6, 4.9$  Hz, 1 H), 3.73 (dq,  $J = 9.6, 6.2$  Hz, 1 H), 3.14 (td,  $J = 9.6, 3.9$  Hz, 1 H), 2.19 (ddd,  $J = 12.9,$

4.9, 1.1 Hz, 1 H), 2.11 (d,  $J = 3.9$  Hz, 1 H), 1.73 (ddd,  $J = 12.9, 12.0, 3.5$  Hz, 1 H), 2.56 (d,  $J = 6.2$  Hz, 3 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  137.4, 128.5, 127.92, 127.86, 95.7, 76.0, 70.0, 67.9, 60.5, 34.9, 17.7; IR (neat) 3438, 2103, 1255, 1123, 1049, 1023  $\text{cm}^{-1}$ ; mass spectrum (CI)  $m/z$  278.1505 [ $\text{C}_{14}\text{H}_{20}\text{N}_3\text{O}_3$  (M+1) requires 278.1426], 191, 170, 159, 127 (base).

**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36–7.27 (comp, 5 H, Ph C-H), 4.93 (d,  $J = 3.5$  Hz, 1 H, C1-H), 4.66 (d,  $J = 12.5$  Hz, 1 H, C7-H), 4.45 (d,  $J = 12.5$  Hz, 1 H, C7-H), 3.80 (ddd,  $J = 12.0, 9.6, 4.9$  Hz, 1 H, C3-H), 3.73 (dq,  $J = 9.6, 6.2$  Hz, 1 H, C5-H), 3.14 (td,  $J = 9.6, 3.9$  Hz, 1 H, C4-H), 2.19 (ddd,  $J = 12.9, 4.9, 1.1$  Hz, 1 H, C2-H), 2.11 (d,  $J = 3.9$  Hz, 1 H, OH), 1.73 (ddd,  $J = 12.9, 12.0, 3.5$  Hz, 1 H, C2-H), 2.56 (d,  $J = 6.2$  Hz, 3 H, C6-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  137.4 (Ph C), 128.5 (Ph C), 127.92 (Ph C), 127.86 (Ph C), 95.7 (C1), 76.0 (C4), 70.0 (C7), 67.9 (C5), 60.5 (C3), 34.9 (C2), 17.7 (C6).

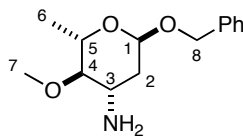


**(2*S*,3*R*,4*S*,6*R*)-4-Azido-6-benzyloxy-3-methoxy-2-methyltetrahydropyran**

**(2.70).** (**KP2-204**). MeI (77  $\mu\text{L}$ , 176 mg, 1.24 mmol) and NaH (62 mg, 1.55 mmol, 60% dispersion) were added to alcohol **2.69a** in DMF (10 mL) and the mixture was stirred for 20 h at room temperature.  $\text{H}_2\text{O}$  (10 mL) and EtOAc (25 mL) were added, and the layers were separated. The organic layer was washed with  $\text{H}_2\text{O}$  (2 x 15 mL) and brine (15 mL), dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with  $\text{Et}_2\text{O}$ /hexanes (1:10) to give 262 mg (92%) of **2.70** as

a colorless oil:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35–7.26 (comp, 5 H), 4.88 (d,  $J = 3.6$  Hz, 1 H), 4.64 (d,  $J = 11.8$  Hz, 1 H), 4.42 (d,  $J = 11.8$  Hz, 1 H), 3.81 (ddd,  $J = 12.5, 9.4, 5.0$  Hz, 1 H), 3.71 (dq,  $J = 9.4, 6.4$  Hz, 1 H), 3.57 (s, 3 H), 2.72 (app t,  $J = 9.4$  Hz, 1 H), 2.11 (ddd,  $J = 13.2, 5.0, 1.2$  Hz, 1 H), 1.62 (ddd,  $J = 13.2, 12.5, 3.6$  Hz, 1 H), 1.27 (d,  $J = 6.4$  Hz, 3 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  137.5, 128.5, 127.9, 127.8, 95.5, 86.1, 68.9, 67.6, 60.6, 59.8, 35.5, 17.9; IR (neat) 2102, 1255, 1124, 1099, 1024  $\text{cm}^{-1}$ ; mass spectrum (CI)  $m/z$  278.1505 [ $\text{C}_{14}\text{H}_{20}\text{N}_3\text{O}_3$  (M+1) requires 278.1426], 191, 170, 159, 127 (base).

**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35–7.26 (comp, 5 H, Ph C-H), 4.88 (d,  $J = 3.6$  Hz, 1 H, C1-H), 4.64 (d,  $J = 11.8$  Hz, 1 H, C8-H), 4.42 (d,  $J = 11.8$  Hz, 1 H, C8-H), 3.81 (ddd,  $J = 12.5, 9.4, 5.0$  Hz, 1 H, C3-H), 3.71 (dq,  $J = 9.4, 6.4$  Hz, 1 H, C5-H), 3.57 (s, 3 H, C7-H), 2.72 (app t,  $J = 9.4$  Hz, 1 H, C4-H), 2.11 (ddd,  $J = 13.2, 5.0, 1.2$  Hz, 1 H, C2-H), 1.62 (ddd,  $J = 13.2, 12.5, 3.6$  Hz, 1 H, C2-H), 1.27 (d,  $J = 6.4$  Hz, 3 H, C6-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  137.5 (Ph C), 128.5 (Ph C), 127.9 (Ph C), 127.8 (Ph C), 95.5 (C1), 86.1 (C4), 68.9 (C8), 67.6 (C5), 60.6 (C7), 59.8 (C3), 35.5 (C2), 17.9 (C6).



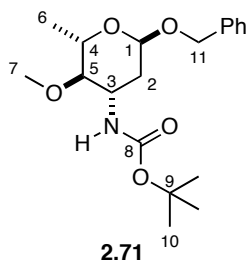
**2.70a**

**(2*S*,3*R*,4*S*,6*R*)-6-Benzyloxy-3-methoxy-2-methyltetrahydropyran-4-amine**

**(2.70a). (KP2-157).** A solution of azide **2.70** (127 mg, 0.46 mmol) in  $\text{Et}_2\text{O}$  (2.3 mL) was cooled to 0  $^\circ\text{C}$  and  $\text{LiAlH}_4$  (480  $\mu\text{L}$ , 18 mg, 1 M in THF) was added dropwise. The reaction was warmed to room temperature, and stirring was continued for 10 min. The mixture was cooled to 0  $^\circ\text{C}$ , and  $\text{H}_2\text{O}$  (18  $\mu\text{L}$ ), 15% aqueous  $\text{NaOH}$  (18  $\mu\text{L}$ ), and  $\text{H}_2\text{O}$  (55

$\mu\text{L}$ ) were then added sequentially. The mixture was filtered through Celite, and the filtrate was removed under reduced pressure to give 115 mg of an amine:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32–7.26 (comp, 5 H), 4.86 (d,  $J = 3.8$  Hz, 1 H), 4.65 (d,  $J = 11.9$  Hz, 1 H), 4.42 (d,  $J = 11.9$  Hz, 1 H), 3.69 (dq,  $J = 9.3, 6.4$  Hz, 1 H), 3.54 (s, 3 H), 3.22 (ddd,  $J = 12.2, 9.3, 4.8$  Hz, 1 H), 2.55 (app t,  $J = 9.3$  Hz, 1 H), 2.01 (ddd,  $J = 13.3, 4.8, 1.1$  Hz, 1 H), 1.56 (ddd,  $J = 13.3, 12.2, 3.8$  Hz, 1 H), 1.26 (d,  $J = 6.4$  Hz, 3 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  137.9, 128.4, 127.7, 127.6, 96.1, 89.2, 68.7, 67.5, 60.7, 48.9, 38.4, 18.3; IR (neat) 3553, 3283, 1123, 1097, 1024  $\text{cm}^{-1}$ ; mass spectrum (CI)  $m/z$  252.1599 [ $\text{C}_{14}\text{H}_{20}\text{N}_3\text{O}_3$  (M+1) requires 252.1521], 144 (base), 127, 118.

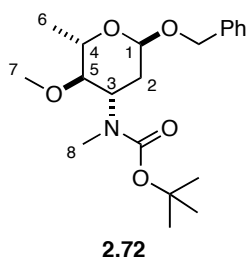
**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32–7.26 (comp, 5 H, Ph C-H), 4.86 (d,  $J = 3.8$  Hz, 1 H, C1-H), 4.65 (d,  $J = 11.9$  Hz, 1 H, C8-H), 4.42 (d,  $J = 11.9$  Hz, 1 H, C8-H), 3.69 (dq,  $J = 9.3, 6.4$  Hz, 1 H, C5-H), 3.54 (s, 3 H, C7-H), 3.22 (ddd,  $J = 12.2, 9.3, 4.8$  Hz, 1 H, C3-H), 2.55 (app t,  $J = 9.3$  Hz, 1 H, C4-H), 2.01 (ddd,  $J = 13.3, 4.8, 1.1$  Hz, 1 H, C2-H), 1.56 (ddd,  $J = 13.3, 12.2, 3.8$  Hz, 1 H, C2-H), 1.26 (d,  $J = 6.4$  Hz, 3 H, C6-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  137.9 (Ph C), 128.4 (Ph C), 127.7 (Ph C), 127.6 (Ph C), 96.1 (C1), 89.2 (C4), 68.7 (C8), 67.5 (C5), 60.7 (C7), 48.9 (C3), 38.4 (C2), 18.3 (C6).



**(2*S*,3*R*,4*S*,6*R*)-(6-Benzyloxy-3-methoxy-2-methyltetrahydropyran-4-yl)-carbamic acid *tert*-butyl ester (2.71). (KP2-158).** A solution of the amine **2.70a**

experiment (115 mg, 0.458 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was cooled to 0 °C, and Boc<sub>2</sub>O (150 mg, 0.678 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was added. The mixture was stirred at 0 °C for 5 min, and then at room temperature for 24 h. The mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography, eluting with Et<sub>2</sub>O/hexanes (1:1) to give 141 mg (88%) of **2.71** as a white solid: mp 113–115 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.31–7.23 (comp, 5 H), 4.85 (dd, *J* = 3.7, 1.4 Hz, 1 H), 4.65 (d, *J* = 12.0 Hz, 1 H), 4.46 (br s, 1 H), 4.43 (d, *J* = 12.0 Hz, 1 H), 3.96–3.89 (m, 1 H), 3.76 (dq, *J* = 9.3, 6.2 Hz, 1 H), 3.46 (s, 3 H), 2.83–2.79 (m, 1 H), 2.13 (dd, *J* = 4.7, 1.6 Hz, 1 H), 1.79–1.74 (m, 1 H), 1.43 (s, 9 H), 1.25 (d, *J* = 6.2 Hz, 3 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 155.4, 137.9, 128.3, 127.7, 127.5, 95.5, 85.0, 79.4, 68.6, 57.6, 59.4, 48.8, 36.3, 28.4, 18.2; IR (neat) 3344, 1686, 1534, 1176, 1127, 1104 cm<sup>-1</sup>; mass spectrum (CI) *m/z* 352.2125 [C<sub>19</sub>H<sub>29</sub>NO<sub>5</sub> (M+1) requires 352.2046], 244, 188 (base), 127.

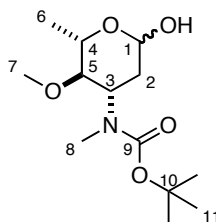
**NMR Assignments:** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.31–7.23 (comp, 5 H, Ph C-H), 4.85 (dd, *J* = 3.7, 1.4 Hz, 1 H, C1-H), 4.65 (d, *J* = 12.0 Hz, 1 H, C11-H), 4.46 (br s, 1 H, NH), 4.43 (d, *J* = 12.0 Hz, 1 H, C11-H), 3.96–3.89 (m, 1 H, C3-H), 3.76 (dq, *J* = 9.3, 6.2 Hz, 1 H, C5-H), 3.46 (s, 3 H, C7-H), 2.83–2.79 (m, 1 H, C4-H), 2.13 (dd, *J* = 4.7, 1.6 Hz, 1 H, C2-H), 1.79–1.74 (m, 1 H, C2-H), 1.43 (s, 9 H, C10-H), 1.25 (d, *J* = 6.2 Hz, 3 H, C6-H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 155.4 (C8), 137.9 (Ph C), 128.3 (Ph C), 127.7 (Ph C), 127.5 (Ph C), 95.5 (C1), 85.0 (C4), 79.4 (C9), 68.6 (C11), 67.6 (C5), 59.4 (C7), 48.8 (C3), 36.3 (C2), 28.4 (C10), 18.2 (C6).



**(2*S*,3*R*,4*S*,6*R*)-(6-Benzyloxy-3-methoxy-2-methyltetrahydropyran-4-yl)-methylcarbamic acid *tert*-butyl ester (2.72). (KP2-167).** A mixture of carbamate **2.71** (398 mg, 1.13 mmol), MeI (84  $\mu$ L, 1.36 mmol) and NaH (68 mg, 1.70 mmol, 60% dispersion in mineral oil) in anhydrous DMF (15 mL) was stirred at room temperature for 30 min, whereupon MeOH (5 mL), H<sub>2</sub>O (30 mL), and Et<sub>2</sub>O (50 mL) were added. The layers were separated, and the organic layer was washed with H<sub>2</sub>O (2 x 30 mL) and brine (1 x 30 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with Et<sub>2</sub>O/hexanes (1:1) to afford 400 mg (97%) of **2.72** as a clear oil: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.36–7.26 (comp, 5 H), 4.91 (d, *J* = 3.5 Hz, 1 H), 4.61 (d, *J* = 12.1 Hz, 1 H), 4.46 (d, *J* = 12.1 Hz, 1 H), 4.25–4.20 (m, 1 H), 3.64 (dq, *J* = 9.3, 6.3 Hz, 1 H), 3.33 (s, 3 H), 3.08 (app t, *J* = 9.3 Hz, 1 H), 2.74 (s, 3 H), 1.97 (td, *J* = 12.9, 3.5 Hz, 1 H), 1.73 (dd, *J* = 12.9, 4.7 Hz, 1 H), 1.41 (s, 9H), 1.19 (d, *J* = 6.3 Hz, 3 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  154.5, 137.7, 127.6, 126.9, 126.8, 95.3, 80.2, 78.1, 67.6, 67.1, 57.4, 52.8, 32.8, 27.6, 17.5; IR (neat) 1693, 1365, 1151, 1127 cm<sup>-1</sup>; mass spectrum (CI) *m/z* 366.2284 [C<sub>20</sub>H<sub>32</sub>NO<sub>5</sub> (M+1) requires 366.2202], 258, 202 (base).

**NMR Assignments:** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.36–7.26 (comp, 5 H, PhC-H), 4.91 (d, *J* = 3.5 Hz, 1 H, C1-H), 4.61 (d, *J* = 12.1 Hz, 1 H, C12-H), 4.46 (d, *J* = 12.1 Hz, 1 H, C12-H), 4.25–4.20 (m, 1 H, C3-H), 3.64 (dq, *J* = 9.3, 6.3 Hz, 1 H, C5-H), 3.33 (s, 3 H, C7-H), 3.08 (app t, *J* = 9.3 Hz, 1 H, C4-H), 2.74 (s, 3 H, C8-H), 1.97 (td, *J* =

12.9, 3.5 Hz, 1 H, C2-H), 1.73 (dd,  $J = 12.9, 4.7$  Hz, 1 H, C2-H), 1.41 (s, 9H, C11-H) 1.19 (d,  $J = 6.3$  Hz, 3 H, C6-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  154.5 (C9), 137.7 (PhC), 127.6 (PhC), 126.9 (PhC), 126.8 (PhC), 95.3 (C1), 80.2 (C4), 78.1 (C10), 67.6 (C12), 67.1 (C5), 57.4 (C7), 52.8 (C3), 32.8 (C2), 27.6 (C11), 17.5 (C6).



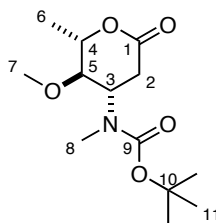
**2.72a**

**(2*S*,3*R*,4*S*)-(3-Methoxy-2-methyl-6-hydroxytetrahydropyran-4-yl)-methylcarbamic acid *tert*-butyl ester (2.72a). (KP2-160).** A mixture of benzyl acetal **2.72** (100 mg, 0.27 mmol) and 10% Pd/C (10 mg) in EtOAc (7 mL) was stirred under  $\text{H}_2$  (1 atm) for 38 h. An additional portion of 10% Pd/C was added (15 mg), and stirring was continued under  $\text{H}_2$  for 10 h. The reaction was filtered through celite, and the filtrate was concentrated to afford 70 mg of an anomeric mixture of lactols as a white solid. The lactols were isolated as a mixture (1:5) of  $\alpha$ - and  $\beta$ -anomers: mp 138–140 °C. Upon heating at 100 °C in  $\text{DMSO-d}_6$ , the lactols equilibrated to a 1:1 mixture of anomers:  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-d}_6$ , 100 °C)  $\delta$  6.16–6.15 (m, 1 H), 5.82 (s, 1 H), 5.10–5.09 (m, 1 H), 4.66 (dd,  $J = 11.6, 6.2$  Hz, 1 H), 4.25–4.20 (m, 1 H), 3.87–3.80 (comp, 2 H), 3.32 (s, 6 H), 3.28 (dq,  $J = 8.8, 6.1$  Hz, 1 H), 3.03–2.96 (comp, 2 H), 2.75 (s, 3 H), 2.73 (s, 3 H), 1.88 (td,  $J = 12.9, 3.5$  Hz, 1 H), 1.72–1.70 (comp, 2 H), 1.60 (dd,  $J = 12.6, 4.4$  Hz, 1 H), 1.420 (s, 9 H), 1.417 (s, 9 H), 1.21 (d,  $J = 6.1$  Hz, 3 H), 1.11 (d,  $J = 6.2$  Hz, 3 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO-d}_6$ , 100 °C)  $\delta$  154.5, 154.4, 93.4, 89.5, 80.8, 80.1, 78.2, 78.0, 70.9, 66.0, 57.5, 57.2, 56.0, 52.6, 36.1, 34.1, 29.7, 27.67, 27.66, 17.73, 17.70; IR (neat)



3388, 1692, 1673, 1364, 1155, 1112  $\text{cm}^{-1}$ ; mass spectrum (CI)  $m/z$  276.1817 [ $\text{C}_{13}\text{H}_{25}\text{NO}_5$  (M+1) requires 276.1733], 258 (base), 220, 202.

**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-d}_6$ , 100  $^\circ\text{C}$ )  $\delta$  6.16–6.15 (m, 1 H, OH), 5.82 (s, 1 H, OH), 5.10–5.09 (m, 1 H, C1-H), 4.66 (dd,  $J = 11.6, 6.2$  Hz, 1 H, C1-H), 4.25–4.20 (m, 1 H, C3-H), 3.87–3.80 (comp, 2 H, C5-H and C3-H), 3.32 (s, 6 H, C7-H), 3.28 (dq,  $J = 8.8, 6.1$  Hz, 1 H, C5-H), 3.03–2.96 (comp, 2 H, C4-H and C4-H), 2.75 (s, 3 H, C8-H), 2.73 (s, 3 H, C8-H), 1.88 (td,  $J = 12.9, 3.5$  Hz, 1 H, C2-H), 1.72–1.70 (comp, 2 H, C2-H and C2-H), 1.60 (dd,  $J = 12.6, 4.4$  Hz, 1 H, C2-H), 1.420 (s, 9 H, C11-H), 1.417 (s, 9 H, C11-H), 1.21 (d,  $J = 6.1$  Hz, 3 H, C6-H), 1.11 (d,  $J = 6.2$  Hz, 3 H, C6-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO-d}_6$ , 100  $^\circ\text{C}$ )  $\delta$  154.5 (C9), 154.4 (C9), 93.4 (C1), 89.5 (C1), 80.8 (C4), 80.1 (C4), 78.2 (C10), 78.0 (C10), 70.9 (C5), 66.0 (C5), 57.5 (C7), 57.2 (C7), 56.0 (C3), 52.6 (C3), 36.1 (C2), 34.1 (C2), 29.7, 27.67 (C8), 27.66 (C8), 17.73 (C6), 17.70 (C6).

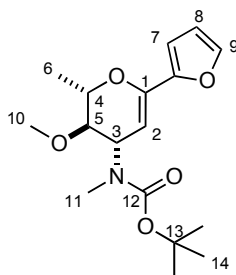


**2.68**

**(2*S*,3*R*,4*S*)-(3-Methoxy-2-methyl-6-oxotetrahydropyran-4-yl)-methylcarbamic acid *tert*-butyl ester (2.68). (KP2-162).** Lactol **2.72a** from the preceding experiment (74 mg) in  $\text{CH}_2\text{Cl}_2$  (7 mL), NMO (47 mg, 0.41 mmol), and TPAP (5 mg, 0.014 mmol) containing 4  $\text{\AA}$  powdered molecular sieves (95 mg) was stirred for 0.5 h. The solvent was removed under reduced pressure, and the residue was purified by

flash chromatography eluting with EtOAc/hexanes (2:3) to give 69 mg (93%) of lactone **2.68** as a white solid: mp 73–74 °C;  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ , 100 °C)  $\delta$  4.23 (dq,  $J = 8.7, 6.4$  Hz, 1 H), 4.16 (td,  $J = 8.7, 6.4$  Hz, 1 H), 3.48 (app t,  $J = 8.7$  Hz, 1 H), 3.39 (s, 3 H), 2.98 (dd,  $J = 17.2, 8.7$  Hz, 1 H), 2.79 (s, 3 H), 2.52 (dd,  $J = 17.2, 6.4$  Hz, 1 H), 1.43 (s, 9 H), 1.35 (d,  $J = 6.4$  Hz, 3 H);  $^{13}\text{C}$  NMR (125 MHz, DMSO- $d_6$ , 100 °C)  $\delta$  169.1, 154.1, 79.2, 79.0, 74.4, 57.5, 54.6, 33.2, 31.3, 27.6, 17.6; IR (neat) 1750, 1690, 1366, 1148, 1109  $\text{cm}^{-1}$ ; mass spectrum (CI)  $m/z$  274.1649 [ $\text{C}_{13}\text{H}_{24}\text{NO}_5$  (M+1) requires 274.1576], 246, 218 (base).

**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ , 100 °C)  $\delta$  4.23 (dq,  $J = 8.7, 6.4$  Hz, 1 H, C5-H), 4.16 (td,  $J = 8.7, 6.4$  Hz, 1 H, C3-H), 3.48 (app t,  $J = 8.7$  Hz, 1 H, C4-H), 3.39 (s, 3 H, C3-H), 2.98 (dd,  $J = 17.2, 8.7$  Hz, 1 H, C2-H), 2.79 (s, 3 H, C8-H), 2.52 (dd,  $J = 17.2, 6.4$  Hz, 1 H, C2-H), 1.43 (s, 9 H, C11-H), 1.35 (d,  $J = 6.4$  Hz, 3 H, C6-H);  $^{13}\text{C}$  NMR (125 MHz, DMSO- $d_6$ , 100 °C)  $\delta$  169.1 (C9), 154.1 (C1), 79.2 (C4 or C10), 79.0 (C4 or C10), 74.4 (C5), 57.5 (C4), 54.6 (C3), 33.2 (C2), 31.3 (C8), 27.6 (C11), 17.6 (C6)

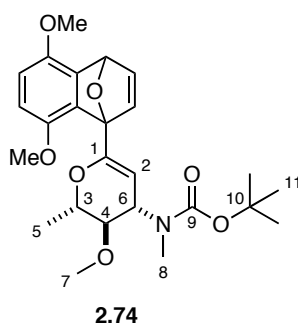


**2.73**

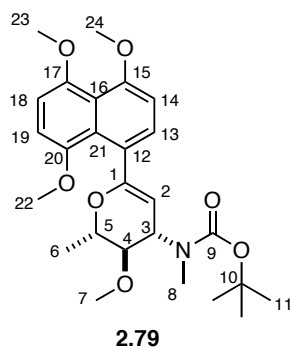
**(2S,3S,4S)-(6-Furan-2-yl-3-methoxy-2-methyl-3,4-dihydro-2H-pyran-4-yl)-methylcarbamic acid *tert*-butyl ester (2.73). (KP2-188).** 2-Furyllithium (0.910 mmol, 0.27 M, 3.4 mL) was added to a solution of lactone **2.68** (0.758 mmol) in THF (8.0 mL)

at  $-78\text{ }^{\circ}\text{C}$ . The mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 2 h, whereupon  $\text{Et}_3\text{N}$  (230 mg, 2.27 mmol, 316  $\mu\text{L}$ ), DMAP (102 mg, 0.910 mmol) in THF (0.30 mL) and TFAA (398 mg, 1.90 mmol, 267  $\mu\text{L}$ ) were added sequentially. The cold bath was allowed to warm to room temperature over 4.5 h. A 50% aqueous solution of  $\text{NaHCO}_3$  (15 mL) and  $\text{Et}_2\text{O}$  (15 mL) were added, the layers were separated, and the mixture was extracted with  $\text{EtOAc}$  (3 x 15 mL). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with  $\text{Et}_2\text{O}$ /hexanes (1:3) to give 226 mg (92%) of furyl glycal **2.73**:  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-d}_6$ ,  $100\text{ }^{\circ}\text{C}$ )  $\delta$  7.58–7.57 (m, 1 H), 6.48–6.46 (comp, 2 H), 4.97 (d,  $J = 2.8\text{ Hz}$ , 1 H), 3.97 (dq,  $J = 9.5, 6.2\text{ Hz}$ , 1 H), 3.42 (s, 3 H), 3.33 (app t,  $J = 8.6\text{ Hz}$ , 1 H), 2.73 (s, 3 H), 1.43 (s, 9 H), 1.40 (d,  $J = 6.2\text{ Hz}$ , 3 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO-d}_6$ ,  $100\text{ }^{\circ}\text{C}$ )  $\delta$  154.6, 147.8, 145.6, 142.5, 110.7, 106.4, 96.8, 78.4, 77.2, 74.5, 57.7, 55.4, 29.2, 27.6, 17.0; IR (neat) 3119, 1693, 1392, 1366, 1327, 1139, 1115  $\text{cm}^{-1}$ ; mass spectrum (CI)  $m/z$  324.1803 [ $\text{C}_{17}\text{H}_{26}\text{NO}_5$  (M+1) requires 324.1811] 268 (base), 194.

**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-d}_6$ ,  $100\text{ }^{\circ}\text{C}$ )  $\delta$  7.58–7.57 (m, 1 H, C9-H), 6.48–6.46 (comp, 2 H, C7-H and C8-H), 4.97 (d,  $J = 2.8\text{ Hz}$ , 1 H, C2-H), 3.97 (dq,  $J = 9.5, 6.2\text{ Hz}$ , 1 H, C5-H), 3.42 (s, 3 H, C10-H), 3.33 (app t,  $J = 8.6\text{ Hz}$ , 1 H, C4-H), 2.73 (s, 3 H, C11-H), 1.43 (s, 9 H, C14-H), 1.40 (d,  $J = 6.2\text{ Hz}$ , 3 H, C6-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO-d}_6$ ,  $100\text{ }^{\circ}\text{C}$ )  $\delta$  154.6, 147.8, 145.6, 142.5, 110.7 (C8 or C7), 106.4 (C8 or C7), 96.8 (C2), 78.4 (C4), 77.2, 74.5 (C5), 57.7, 55.4 (C3), 29.2, 27.6 (C14), 17.0 (C6).



**(2*S*,3*S*,4*S*)-[6-(3,6-Dimethoxy-11-oxatricyclo[6.2.1.0<sup>0,0</sup>]undeca-2,4,6,9-tetraen-1-yl)-3-methoxy-2-methyl-3,4-dihydro-2*H*-pyran-4-yl]-methylcarbamic acid *tert*-butyl ester (2.74).** (KP2-166). *s*-BuLi (220  $\mu$ L, 0.30 mmol, 1.21 M) was added dropwise to a solution of 2-chloro-1,4-dimethoxybenzene (51 mg, 0.30 mmol) in THF (1.5 mL) at  $-95$   $^{\circ}$ C. The solution was stirred at  $-95$   $^{\circ}$ C for 15 min, whereupon **2.73** (48 mg, 0.15 mmol) in THF (0.3 mL) was added dropwise. The resultant mixture was warmed to  $-5$   $^{\circ}$ C over a 1 h period, at which time a 50% aqueous  $\text{NH}_4\text{Cl}$  (2 mL) was added and the solution warmed to rt. The layers were separated, and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 x 2 mL). The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The residue was purified by flash chromatography, eluting with  $\text{EtOAc}$ /hexanes (1:2) to give 68 mg (quantitative) of **2.74**: mass spectrum (CI)  $m/z$  460.2336 [ $\text{C}_{25}\text{H}_{34}\text{NO}_7$  ( $M+1$ ) requires 460.2335] 404, 386 (base) 329; IR (neat) 1692, 1496, 1256, 1140  $\text{cm}^{-1}$ .

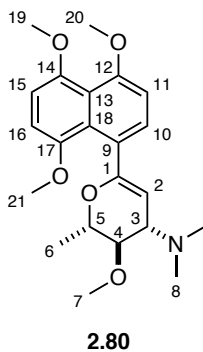


**(2*S*,3*S*,4*S*)-[3-Methoxy-2-methyl-6-(4,5,8-trimethoxynaphthalen-1-yl)-3,4-dihydro-2*H*-pyran-4-yl]-methylcarbamic acid *tert*-butyl ester (2.79). (KP2-195).** A solution of ZnCl<sub>2</sub> in Et<sub>2</sub>O (380 μL, 0.38 mmol, 1 M) was added to **2.74** (146 mg, 0.32 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6 mL) at -25 °C. The cold bath was immediately removed, and stirring was continued at rt for 45 min, whereupon a saturated aqueous solution of NaHCO<sub>3</sub> (6 mL) and Et<sub>2</sub>O (6 mL) were added. The layers were separated, and the aqueous layer was extracted with Et<sub>2</sub>O (3 x 6 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated, and dried under vacuum.

A mixture of the crude naphthol, MeI (71 mg, 0.50 mmol, 31 μL), and NaH (25 mg, 0.626 mmol, 60% dispersion in mineral oil) in DMF (4.2 mL) was stirred for 1.5 h at rt, whereupon H<sub>2</sub>O (8 mL) and Et<sub>2</sub>O (15 mL) were added. The layers were separated, and the organic layer was washed with H<sub>2</sub>O (2 x 10 mL) and brine (1 x 10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue was purified by flash chromatography, eluting with EtOAc/hexanes (1:4) to give 108 mg (72%) of **2.79** as a yellow oil: <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>, 100 °C) δ 7.28 (d, *J* = 7.9 Hz, 1 H), 6.96 (d, *J* = 8.6 Hz, 1 H), 6.93–6.89 (comp, 2 H), 4.89–4.87 (m, 1 H), 4.37 (d, *J* = 2.4 Hz, 1 H), 4.06 (dq, *J* = 9.6, 6.4 Hz, 1 H) 3.87 (s, 3 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.45 (s, 3 H), 3.33 (app t, *J* = 9.6 Hz, 1 H), 2.83 (s, 3 H), 1.45 (s, 9 H), 1.31 (d, *J* = 6.4 Hz, 3 H); <sup>13</sup>C NMR (125 MHz, DMSO-d<sub>6</sub>, 100 °C)

$\delta$  159.2, 157.0, 154.8, 150.8, 149.8, 129.5, 126.0, 123.7, 118.8, 109.1, 107.8, 106.3, 97.0, 78.2, 77.4, 74.1, 57.5, 57.4, 56.4, 56.1, 55.7, 27.7, 17.0; mass spectrum (CI)  $m/z$  474.2491 [ $C_{26}H_{36}NO_7$  (M+1) requires 474.2492] (base), 418, 343; IR (neat) 1691, 1590, 1391, 1271, 1137  $cm^{-1}$ .

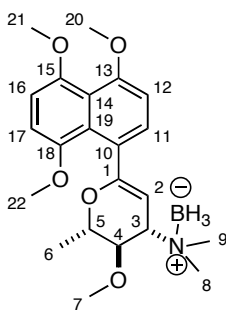
**NMR Assignments:**  $^1H$  NMR (500 MHz, DMSO- $d_6$ , 100 °C)  $\delta$  7.28 (d,  $J = 7.9$  Hz, 1 H, C13-H), 6.96 (d,  $J = 8.6$  Hz, 1 H, Ar-H), 6.93–6.89 (comp, 2 H, Ar-H), 4.89–4.87 (m, 1 H, C3-H), 4.37 (d,  $J = 2.4$  Hz, 1 H, C2-H), 4.06 (dq,  $J = 9.6, 6.4$  Hz, 1 H, C5-H), 3.87 (s, 3 H), 3.84 (s, 3 H), 3.80 (s, 3 H), 3.45 (s, 3 H, C7-H), 3.33 (app t,  $J = 9.6$  Hz, 1 H, C4-H), 2.83 (s, 3 H, C8-H), 1.45 (s, 9 H, C11-H), 1.31 (d,  $J = 6.4$  Hz, 3 H, C6-H);  $^{13}C$  NMR (125 MHz, DMSO- $d_6$ , 100 °C)  $\delta$  159.2, 157.0, 154.8, 150.8, 149.8, 129.5 (C13), 126.0, 123.7, 118.8, 109.1 (Ar C), 107.8 (Ar C), 106.3 (Ar C), 97.0 (C2), 78.2 (C4), 77.4 (C1), 74.1 (C5), 57.5, 57.4, 56.4, 56.1, 55.7 (C3), 27.7 (C11), 17.0 (C6).



**(2*S*,3*S*,4*S*)-[3-Methoxy-2-methyl-6-(4,5,8-trimethoxynaphthalen-1-yl)-3,4-dihydro-2*H*-pyran-4-yl]-dimethylamine (2.80). (KP2-207).** LAH in THF (1.0 mL, 1.0 mmol, 1 M) was added to a solution of **2.79** in THF (3 mL), and the solution was warmed to 70 °C in a sealed vial for 12 h. The mixture was cooled to 0 °C, whereupon H<sub>2</sub>O (40  $\mu$ L), 15% NaOH (40  $\mu$ L), and H<sub>2</sub>O (120  $\mu$ L) were added sequentially. The mixture was

filtered through Celite, and the filtrate was concentrated to give 51 mg (78%) of **2.80** as a yellow oil:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33 (d,  $J = 8.0$  Hz, 1 H), 6.82 (s, 2 H), 6.78 (d,  $J = 8.0$  Hz, 1 H), 4.77 (br s, 1 H), 4.07 (dq,  $J = 8.4, 6.4$  Hz, 1 H), 3.93 (s, 3 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.61 (s, 3 H), 3.51 (dd,  $J = 8.4, 2.4$  Hz, 1 H), 3.24 (app t,  $J = 8.4$  Hz, 1 H), 2.41 (s, 6 H), 1.40 (d,  $J = 6.4$  Hz, 3 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  159.7, 157.7, 151.4, 150.5, 130.6, 126.9, 124.7, 119.5, 108.4, 107.4, 105.8, 95.4, 78.9, 75.5, 64.9, 59.8, 57.9, 56.9, 56.5, 40.9, 17.9; mass spectrum (CI)  $m/z$  388.2125 [ $\text{C}_{22}\text{H}_{30}\text{NO}_5$  (M+1) requires 388.2124], 343 (base), 315, 284; IR (neat) 1589, 1462, 1391, 1271, 1252, 1097, 1076, 1056  $\text{cm}^{-1}$ .

**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33 (d,  $J = 8.0$  Hz, 1 H, C10-H), 6.82 (s, 2 H, C15-H and C16-H), 6.78 (d,  $J = 8.0$  Hz, 1 H, C11-H), 4.77 (br s, 1 H, C2-H), 4.07 (dq,  $J = 8.4, 6.4$  Hz, 1 H, C5-H), 3.93 (s, 3 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.61 (s, 3 H, C7-H), 3.51 (dd,  $J = 8.4, 2.4$  Hz, 1 H, C3-H), 3.24 (app t,  $J = 8.4$  Hz, 1 H, C4-H), 2.41 (s, 6 H, C8-H), 1.40 (d,  $J = 6.4$  Hz, 3 H, C6-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  159.7, 157.7, 151.4, 150.5, 130.6 (C10), 126.9, 124.7, 119.5, 108.4 (C15 or C16), 107.4 (C15 or C16), 105.8 (C11), 95.4 (C2), 78.9 (C4), 75.5 (C5), 64.9 (C3), 59.8 (C7), 57.9, 56.9, 56.5, 40.9 (C8), 17.9 (C6).

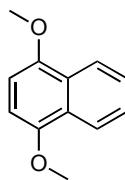


**2.81**

**(2*S*,3*S*,4*S*)-[3-Methoxy-2-methyl-6-(4,5,8-trimethoxynaphthalen-1-yl)-3,4-dihydro-2*H*-pyran-4-yl]-dimethylammonium borate (2.81). (KP2-255).** BH<sub>3</sub>•THF in THF (97 μL, 0.097 mmol, 1 M) was added to a solution of **2.80** (34 mg, 0.088 mmol) in THF (1 mL) at 0 °C. The mixture was stirred for 45 min, warmed to rt, and concentrated to give 35 mg of **2.81** (quantitative): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.42 (d, *J* = 8.0 Hz, 1 H), 6.83 (s, 2 H), 6.79 (d, *J* = 8.0 Hz), 5.26 (d, *J* = 2.8 Hz, 1 H), 4.10 (dq, *J* = 10.2, 6.6 Hz, 1 H), 3.94 (s, 3 H), 3.88 (s, 3 H), 3.84 (s, 3 H), 3.77 (dd, *J* = 7.4, 2.8 Hz, 1 H), 3.62–3.58 (m, 1 H), 3.54 (s, 3 H), 2.76 (s, 3 H), 2.68 (s, 3 H), 2.68 (s, 3 H), 1.45 (d, *J* = 6.4 Hz, 3 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 161.8, 158.1, 151.6, 150.3, 130.9, 128.0, 127.8, 127.6, 126.7, 123.6, 119.5, 108.5, 107.7, 105.7, 95.0, 78.7, 75.7, 70.3, 58.1, 57.9, 57.1, 56.5, 52.0, 48.1, 18.3; mass spectrum (CI) *m/z* 402.2446 [C<sub>22</sub>H<sub>33</sub>BNO<sub>5</sub> (M+1) requires 402.2452], 388, 345, 344 (base), 343; IR (neat) 2379, 2320, 2276, 1588, 1463, 1392, 1274, 1248, 1168, 1091, 1057 cm<sup>-1</sup>.

**NMR Assignments:** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.42 (d, *J* = 8.0 Hz, 1 H, C11-H), 6.83 (s, 2 H, C16-H and C17-H), 6.79 (d, *J* = 8.0 Hz, C12-H), 5.26 (d, *J* = 2.8 Hz, 1 H, C2-H), 4.10 (dq, *J* = 10.2, 6.6 Hz, 1 H, C5-H), 3.94 (s, 3 H, C20-H), 3.88 (s, 3 H, C21-H or C22-H), 3.84 (s, 3 H, C21-H or C22-H), 3.77 (dd, *J* = 7.4, 2.8 Hz, 1 H, C3-H), 3.62–3.58 (m, 1 H, C4-H), 3.54 (s, 3 H, C7-H), 2.76 (s, 3 H, C8-H or C9-H), 2.68 (s, 3 H, C8-H or C9-H) 1.45 (d, *J* = 6.4 Hz, 3 H, C6-H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 161.8, 158.1, 151.6, 150.3, 130.9 (C11), 128.0, 127.8, 127.6, 126.7, 123.6, 119.5, 108.5 (C16 or C17), 107.7 (C16 or C17), 105.7 (C12), 95.0 (C2), 78.7 (C4), 75.7 (C5), 70.3 (C3), 58.1 (C7), 57.9 (C20), 57.1 (C21 or C22), 56.5 (C21 or C22), 52.0 (C8 or C9), 48.1 (C8 or C9), 18.3 (C6).

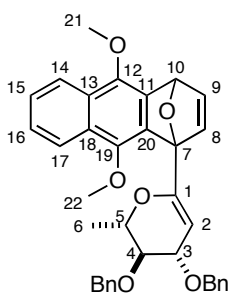




**2.95**

**1,4-Dimethoxynaphthalene (2.95). (KP1-300).** Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> (11 g, 61 mmol) was dissolved in 100 mL of H<sub>2</sub>O, and the resulting solution was added to a solution of 1,4-naphthoquinone (1.20 g, 7.6 mmol) in CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O (1:3, 130 mL). The biphasic mixture was shaken in a separatory funnel for 10 min. The layers were separated, and the organic layer was washed with brine (80 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. The residue was then dried under vacuum for 0.5 h and used directly in the next step.

NaH (0.76 g, 19.0 mmol, 60 wt % dispersion) was added in three portions over a 20 min period to a mixture of the residue and MeI (2.4 g, 1.1 mL, 17 mmol) in DMF (16 mL). The reaction mixture was stirred at ambient temperature for 3 h, at which point MeOH (7 mL) was added. The mixture was partitioned between EtOAc (15 mL) and H<sub>2</sub>O (15 mL), and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with water (3 x 100 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with Et<sub>2</sub>O/hexanes (1:30) to give (1.15 g, 80%) of **2.95** as a white solid. Spectra were in accordance with literature data.<sup>126</sup>

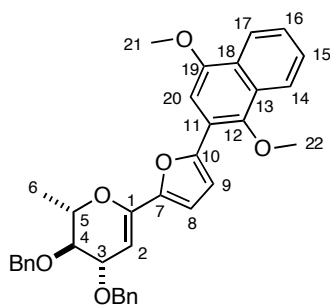


**2.96**

**1-(4,5-Bis-benzyloxy-6-methyldihydro-4*H*-pyran-2-yl)-1,4-dihydro-5,10-dimethoxy-1,4-epoxyanthracene (2.96).** (KP2-38). *n*-BuLi (85  $\mu$ L, 0.20 mmol, 2.37 M) was added dropwise to a solution of furan **2.99** (51 mg, 0.13 mmol) and 2-bromo-3-chloro-1,4-dimethoxynaphthalene **2.95** (61 mg, 0.20 mmol) in Et<sub>2</sub>O (1.3 mL) at  $-78$  °C. The reaction was warmed from  $-78$  °C to  $0$  °C over a 1 h period, whereupon 50% NH<sub>4</sub>Cl (2 mL) and Et<sub>2</sub>O (1 mL) were added and the layers were separated. The aqueous layer was extracted with Et<sub>2</sub>O (3 x 2 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc/hexanes (1:5) to give 67 mg (89%) of 1,4-epoxyanthracene **2.96** as a yellow foam (60:40 inseparable mixture of diastereomers): <sup>1</sup>H NMR (500 MHz)  $\delta$  8.10–8.00 (comp, 1 H), 7.98–7.93 (comp, 1 H), 7.49–7.43 (comp, 2 H), 7.36–7.25 (comp, 10 H), 7.03 (d, *J* = 6.6 Hz, 0.6 H), 7.00 (dd, *J* = 5.6, 1.8 Hz, 0.4 H), 6.99–6.97 (comp, 1 H), 6.18–6.17 (comp, 1 H), 5.49 (d, *J* = 2.6 Hz, 0.4 H), 5.38 (d, *J* = 2.4 Hz, 0.6 H), 4.69 (d, *J* = 11.0 Hz, 0.6 H), 4.93 (d, *J* = 11.0 Hz, 0.4 H), 4.77–4.71 (comp, 3 H), 4.62–4.58 (comp, 1 H), 4.44–4.10 (comp, 1 H), 4.29–4.22 (comp, 1 H), 4.04 (s, 1.8 H), 4.03 (s, 1.2 H), 3.82 (s, 1.8 H), 3.80 (s, 1.2 H), 3.71–3.65 (comp, 1 H), 1.51 (d, *J* = 6.4 Hz, 1.8 H), 1.48 (d, *J* = 6.4 Hz, 1.2 H); <sup>13</sup>C NMR (125 MHz)  $\delta$  150.7, 150.3, 144.9, 144.73, 144.68, 144.6, 142.1, 141.6, 140.4, 140.2, 138.53, 138.48, 138.4, 138.3, 134.1, 133.4, 129.0, 128.9, 128.8, 128.5, 128.39,

128.37, 128.3, 128.23, 128.21, 128.03, 128.00, 127.8, 127.74, 127.70, 127.57, 127.5, 126.5, 126.4, 122.8, 122.7, 122.4, 122.3, 100.0, 98.4, 90.3, 89.8, 80.8, 80.7, 79.8, 79.5, 77.5, 77.1, 75.4, 74.8, 74.3, 74.2, 70.44, 70.38, 63.4, 63.3, 61.01, 60.99, 17.78, 17.76; IR (neat) 3069, 3035, 1343, 1285, 1092  $\text{cm}^{-1}$ .

**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz)  $\delta$  8.10–8.00 (comp, 1 H, Ar-H), 7.98–7.93 (comp, 1 H, Ar-H), 7.49–7.43 (comp, 2 H, Ar-H), 7.36–7.25 (comp, 10 H, Ph-H), 7.03 (d,  $J = 6.6$  Hz, 0.6 H, C8-H or C9-H), 7.00 (dd,  $J = 5.6, 1.8$  Hz, 0.4 H, C8-H or C9-H), 6.99–6.97 (comp, 1 H, C8-H or C9-H), 6.18–6.17 (comp, 1 H, C10-H), 5.49 (d,  $J = 2.6$  Hz, 0.4 H, C2-H), 5.38 (d,  $J = 2.4$  Hz, 0.6 H, C2-H), 4.69 (d,  $J = 11.0$  Hz, 0.6 H, Bn C-H), 4.93 (d,  $J = 11.0$  Hz, 0.4 H, Bn C-H), 4.77–4.71 (comp, 2 H, Bn C-H), 4.62–4.58 (comp, 1 H, Bn C-H), 4.44–4.10 (comp, 1 H, C3-H), 4.29–4.22 (comp, 1 H, C5-H), 4.04 (s, 1.8 H, C21-H or C22-H), 4.03 (s, 1.2 H, C21-H or C22-H), 3.82 (s, 1.8 H, C21-H or C22-H), 3.80 (s, 1.2 H, C21-H or C22-H), 3.71–3.65 (comp, 1 H, C4-H), 1.51 (d,  $J = 6.4$  Hz, 1.8 H, C6-H), 1.48 (d,  $J = 6.4$  Hz, 1.2 H, C6-H);  $^{13}\text{C}$  NMR (125 MHz)  $\delta$  150.7, 150.3, 144.9, 144.73, 144.68, 144.6, 142.1 (C8 or C9), 141.6 (C8 or C9), 140.4 (C8 or C9), 140.2 (C8 or C9), 138.53, 138.48, 138.4, 138.3, 134.1, 133.4, 129.0, 128.9, 128.8, 128.5, 128.39, 128.37, 128.3, 128.23, 128.21, 128.03, 128.00, 127.8, 127.74, 127.70, 127.57, 127.5, 126.5 (Ar C), 126.4 (Ar C), 122.8 (Ar C), 122.7 (Ar C), 122.4 (Ar C), 122.3 (Ar C), 100.0 (C2 minor), 98.4 (C2 major), 90.3, 89.8, 80.8 (C10), 80.7 (C10), 79.8 (C4), 79.5 (C4), 77.5 (C3), 77.1 (C3), 75.4 (C5), 74.8 (C5), 74.3 (Bn C), 74.2 (Bn C), 70.44 (Bn C), 70.38 (Bn C), 63.4 (C21 or C22 minor), 63.3 (C21 or C22 major), 61.01 (C21 or C22), 60.99 (C21 or C22), 17.78 (C6), 17.76 (C6).

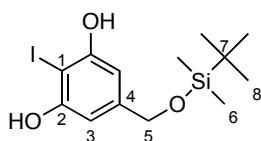


**2.98**

**3,4-Bis-benzyloxy-6-[5-(1,4-dimethoxy-naphthalen-2-yl)furan-2-yl]-2-methyl-3,4-dihydro-2H-pyran (2.98).** (KP2-78). LDA (0.29 mL, 0.179 mmol, 0.61 M) was added to a solution of 2-bromo-1,4-dimethoxynaphthalene **2.97** in THF at  $-78\text{ }^{\circ}\text{C}$ . Furan **2.22** (48 mg, 0.179 mmol) was added, and the reaction mixture was transferred to a  $-45\text{ }^{\circ}\text{C}$  bath, where stirring was continued for 2.5 h. A 50% solution of  $\text{NH}_4\text{Cl}$  was added (1 mL), and the layers were separated. The aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 x 1 mL). The organic layers were combined, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with  $\text{EtOAc/Hexanes}$  (1:5) to afford 24 mg (48%) of cycloadduct **2.96**, along with 10 mg (20%) of disubstituted furan **2.98**:  $^1\text{H NMR}$  (500 MHz)  $\delta$  8.21 (d,  $J = 8.2\text{ Hz}$ , 1 H), 8.08 (d,  $J = 8.2\text{ Hz}$ , 1 H), 7.54 (ddd,  $J = 8.2, 6.8, 1.2\text{ Hz}$ , 1 H), 7.47 (ddd,  $J = 8.2, 6.8, 1.2\text{ Hz}$ , 1 H), 7.41–7.39 (comp, 2 H), 7.36–7.27 (comp, 8 H), 7.22 (s, 1 H), 7.08 (d,  $J = 3.4\text{ Hz}$ , 1 H), 6.67 (d,  $J = 3.4\text{ Hz}$ , 1 H), 5.58 (d,  $J = 3.0\text{ Hz}$ , 1 H), 4.90 (d,  $J = 11.4\text{ Hz}$ , 1 H), 4.75 (d,  $J = 11.4\text{ Hz}$ , 1 H), 4.74 (d,  $J = 11.4\text{ Hz}$ , 1 H), 4.68 (d,  $J = 11.6\text{ Hz}$ , 1 H), 4.43 (dd,  $J = 6.2, 3.0\text{ Hz}$ , 1 H), 4.17 (dq,  $J = 8.6, 6.4\text{ Hz}$ , 1 H), 4.04 (s, 3 H), 3.83 (s, 3 H), 3.61 (dd,  $J = 8.6, 6.2\text{ Hz}$ , 1 H), 1.49 (d,  $J = 6.4\text{ Hz}$ , 3 H);  $^{13}\text{C NMR}$  (125 MHz)  $\delta$  152.0, 150.6, 147.7, 146.1, 145.6, 138.5, 138.2, 129.1, 128.4, 128.0, 127.80, 127.77, 127.7, 126.9, 126.2, 125.7, 122.4, 122.2, 111.7, 110.4, 101.0, 95.5, 79.4, 76.9, 74.5, 73.9, 70.6, 60.6, 55.8,

17.5; mass spectrum (CI)  $m/z$  563.3435 [ $C_{36}H_{34}O_6$  (M+1) requires 563.2433] 563 (base), 457, 455, 316.

**NMR Assignments:**  $^1H$  NMR (500 MHz)  $\delta$  8.21 (d,  $J = 8.2$  Hz, 1 H, C14-H or C17-H), 8.08 (d,  $J = 8.2$  Hz, 1 H, C14-H or C17-H), 7.54 (ddd,  $J = 8.2, 6.8, 1.2$  Hz, 1 H, C15-H or C16-H), 7.47 (ddd,  $J = 8.2, 6.8, 1.2$  Hz, 1 H, C15-H or C16-H), 7.41–7.39 (comp, 2 H, Ph-H), 7.36–7.27 (comp, 8 H, Ph-H), 7.22 (s, 1 H, C20-H), 7.08 (d,  $J = 3.4$  Hz, 1 H, C8-H or C9-H), 6.67 (d,  $J = 3.4$  Hz, 1 H, C8-H or C9-H), 5.58 (d,  $J = 3.0$  Hz, 1 H, C2-H), 4.90 (d,  $J = 11.4$  Hz, 1 H, Bn C-H), 4.75 (d,  $J = 11.4$  Hz, 1 H, Bn C-H), 4.74 (d,  $J = 11.4$  Hz, 1 H, Bn C-H), 4.68 (d,  $J = 11.6$  Hz, 1 H, Bn C-H), 4.43 (dd,  $J = 6.2, 3.0$  Hz, 1 H, C3-H), 4.17 (dq,  $J = 8.6, 6.4$  Hz, 1 H, C5-H), 4.04 (s, 3 H, C21-H or C22-H), 3.83 (s, 3 H, C21-H or C22-H), 3.61 (dd,  $J = 8.6, 6.2$  Hz, 1 H, C4-H), 1.49 (d,  $J = 6.4$  Hz, 3 H, C6-H);  $^{13}C$  NMR (125 MHz)  $\delta$  152.0, 150.6, 147.7, 146.1, 145.6, 138.5, 138.2, 129.1, 128.4, 128.0, 127.80, 127.77, 127.7, 126.9 (C15 or C16), 126.2, 125.7 (C15 or C16), 122.4 (C14 or C17), 122.2 (C14 or C17), 111.7 (C8 or C9), 110.4 (C8 or C9), 101.0 (C20), 95.5 (C2), 79.4 (C4), 76.9 (C3), 74.5 (C5), 73.9 (Bn C), 70.6 (Bn C), 60.6 (C21 or C22), 55.8 (C21 or C22), 17.5 (C6).



**3.16**

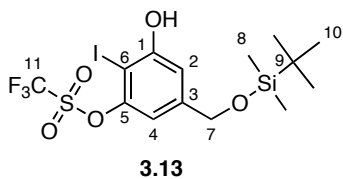
**5-(*tert*-Butyldimethylsilyloxymethyl)-benzene-1,3-diol (3.16). (KP2-212).**

Imidazole (133 mg, 1.95 mmol) and TBSCl (249 mg, 1.50 mmol) were added to a solution of 3,5-dihydroxybenzyl alcohol<sup>138</sup> (**3.15**) (210 mg, 1.50 mmol) in DMF (7 mL). The mixture was stirred at rt for 2 h, whereupon H<sub>2</sub>O (15 mL) and EtOAc (15 mL) were

added. The layers were separated, and the organic layer was washed with brine (1 x 15 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo. The residue was purified by flash chromatography, eluting with EtOAc/hexanes (1:2) to give 359 mg (94%) of a silyl ether.

I<sub>2</sub> (789 mg, 3.12 mmol) and NaHCO<sub>3</sub> (285 mg, 3.40 mmol) were added sequentially to a solution of the ether from the preceding reaction (720 mg, 2.83 mmol) in THF/H<sub>2</sub>O (1:1, 36 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min, then warmed at rt for 15 min. EtOAc (50 mL) and H<sub>2</sub>O (40 mL) were added, and the layers were separated. The organic layer was washed with brine (1 x 50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated, and dried under vacuum to give **3.16** (white needles): mp = 151–152 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.53 (s, 2 H), 5.23 (s, 2 H), 4.62 (s, 2 H), 0.92 (s, 9 H), 0.079 (s, 6 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 155.42, 144.7, 104.8, 75.0, 64.1, 25.9, 18.4, -5.3; mass spectrum (CI) *m/z* 380.0307 [C<sub>13</sub>H<sub>21</sub>IO<sub>3</sub>Si (M<sup>+</sup>) requires 380.0305] 271, 127 (base); IR (neat) 3458, 1035, 836.

**NMR Assignments:** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.53 (s, 2 H, C3-H), 5.23 (s, 2 H, OH), 4.62 (s, 2 H, C5-H), 0.92 (s, 9 H, C8-H), 0.079 (s, 6 H, C6-H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 155.42, 144.7, 104.8, 75.0, 64.1 (C5), 25.9 (C8), 18.4 (C7), -5.3 (C6).

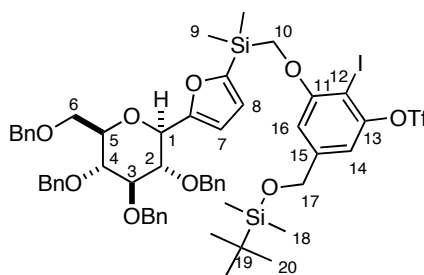


**Trifluoromethanesulfonic acid 5-(tert-butyl(dimethyl)silyloxy)methyl-3-hydroxy-2-iodo-phenyl ester (3.13). (KP2-304).** Tf<sub>2</sub>O (1.84 g, 6.51 mmol, 1.1 mL) was added to a solution of aryl **3.16** iodide containing N(*i*Pr)<sub>2</sub>Et (1.2 mL, 6.79 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) at -78 °C. The mixture was stirred at -78 °C for 10 min, at which time a

saturated solution of  $\text{NH}_4\text{Cl}$  (30 mL) was added and the reaction mixture warmed to rt. The layers were separated, and the organic layer was washed with brine (1 x 30 mL), dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated. The residue was purified by flash chromatography eluting with  $\text{Et}_2\text{O}$ /hexanes (1:20) to give 1.44 g (79%) of a bis triflate.

$\text{Cs}_2\text{CO}_3$  (5.20 g, 16.0 mmol) was added to a solution of the bis triflate from the previous reaction in glyme (100 mL), and the mixture was warmed at 75 °C for 16 h. The reaction mixture was then cooled to rt, and a 50% aqueous solution of  $\text{NH}_4\text{Cl}$  (100 mL) and  $\text{Et}_2\text{O}$  (70 mL) were added. The layers were separated, and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 x 100 mL). The organic layers were combined, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated. The residue was purified by flash chromatography, eluting with  $\text{EtOAc}$ /hexanes (1:9) to give 1.50 g, 28% of **3.13** as a yellow oil:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.93–6.92 (comp, 2H), 5.66 (s, 1 H), 4.68 (s, 2 H), 0.92 (s, 9 H), 0.086 (s, 6 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  156.8, 150.3, 145.9, 120.3, 117.1, 111.5, 111.4, 63.4, 25.8, 18.3, -5.4; mass spectrum (CI)  $m/z$  512.9864 [ $\text{C}_{14}\text{H}_{21}\text{O}_5\text{F}_3\text{SiI}$  (M+1) requires 512.9876], 381 (base); IR (neat) 3490, 1426, 1215, 1139, 839  $\text{cm}^{-1}$ .

**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.93–6.92 (comp, 2H, C4-H and C2-H), 5.66 (s, 1 H, OH), 4.68 (s, 2 H, C7-H), 0.92 (s, 9 H, C10-H), 0.086 (s, 6 H, C8-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  156.8 (C5), 150.3, 145.9, 120.3, 117.1, 111.5, 111.4, 63.4 (C7), 25.8 (C10), 18.3 (C9), -5.4 (C8).



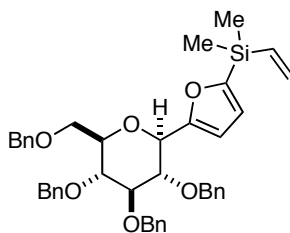
**3.20**

**Trifluoromethanesulfonic acid 5-(*tert*-butyldimethylsilyloxyethyl)-3-((dimethyl[5-(2,4,5-tris-benzyloxy-6-benzyloxymethyltetrahydropyran-2-yl)-furan-2-yl]-silyl)-methoxy)-2-iodophenyl ester (3.20). (KP2-295).** A solution of furyl glycoside **3.18** (178 mg, 0.24 mmol), phenol **3.13** (123 mg, 0.24 mmol), TBAI (106 mg, 0.29 mmol), and Na<sub>2</sub>CO<sub>3</sub> (107 mg, 1.0 mmol) in DMF (3 mL) was heated at 70 °C for 16 h, at which time the mixture was cooled to room temperature, and EtOAc (15 mL) and H<sub>2</sub>O (10 mL) were added. The mixture was shaken vigorously, and the layers were separated. The organic layer was washed with H<sub>2</sub>O (2 x 15 mL) and brine (2 x 15 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue was purified by flash chromatography, eluting with Et<sub>2</sub>O/hexanes (1:10) and Et<sub>2</sub>O/hexanes (1:4) to give 174 mg (62%) of **3.20** as a clear oil: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.33–7.22 (comp, 13 H), 7.16–7.13 (comp, 5 H), 6.91 (s, 1 H), 6.90–6.88 (comp, 2 H), 6.82 (d, *J* = 3.2 Hz, 1 H), 6.70 (s, 1 H), 6.48 (d, *J* = 3.2 Hz, 1 H), 4.90 (d, *J* = 11.0 Hz, 1 H), 4.85 (d, *J* = 11.0 Hz, 1 H), 4.83 (d, *J* = 10.7 Hz, 1 H), 4.62 (s, 2 H), 4.59 (d, *J* = 12.1 Hz, 1 H), 4.57 (d, *J* = 10.7 Hz, 1 H), 4.52 (d, *J* = 12.1 Hz, 1 H), 4.45 (d, *J* = 10.3 Hz, 1 H), 4.37 (d, *J* = 9.7 Hz, 1 H), 4.00 (td, *J* = 9.3, 4.5 Hz, 1 H), 3.76–3.70 (comp, 6 H), 3.58–3.55 (m, 1 H), 0.92 (s, 9 H), 0.48 (s, 3 H), 0.47 (s, 3 H), 0.07 (s, 6 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 161.5, 156.8, 156.3, 151.4, 145.5, 138.9, 138.4, 138.3, 138.1, 128.7, 128.6, 128.5, 128.3, 128.1, 128.03, 127.96, 127.94,



127.85, 123.1, 120.3, 117.7, 111.5, 110.6, 107.7, 86.8, 82.0, 80.5, 79.7, 78.4, 75.9, 75.4, 75.1, 75.0, 73.7, 69.2, 64.0, 61.9, 26.0, 18.5, -4.41, -4.40, -5.1; mass spectrum (CI)  $m/z$  1171.2618 [ $C_{55}H_{63}O_{11}F_3Si_2SI$  (M+1) requires 1171.2627] (base); IR (neat) 1424, 1213, 1140, 1096, 1062, 838  $cm^{-1}$ .

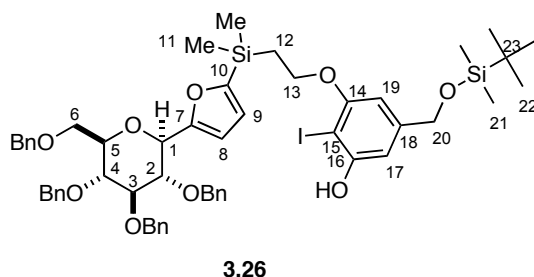
**NMR Assignments:**  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.33–7.22 (comp, 13 H, PhC-H), 7.16–7.13 (comp, 5 H, PhC-H), 6.91 (s, 1 H, C14-H), 6.90–6.88 (comp, 2 H, PhC-H), 6.82 (d,  $J = 3.2$  Hz, 1 H, C8-H), 6.70 (s, 1 H, C16-H), 6.48 (d,  $J = 3.2$  Hz, 1 H, C7-H), 4.90 (d,  $J = 11.0$  Hz, 1 H), 4.85 (d,  $J = 11.0$  Hz, 1 H), 4.83 (d,  $J = 10.7$  Hz, 1 H), 4.62 (s, 2 H, C17-H), 4.59 (d,  $J = 12.1$  Hz, 1 H), 4.57 (d,  $J = 10.7$  Hz, 1 H), 4.52 (d,  $J = 12.1$  Hz, 1 H), 4.45 (d,  $J = 10.3$  Hz, 1 H), 4.37 (d,  $J = 9.7$  Hz, 1 H), 4.00 (td,  $J = 9.3, 4.5$  Hz, 1 H), 3.76–3.70 (comp, 6 H), 3.58–3.55 (m, 1 H), 0.92 (s, 9 H, C20-H), 0.48 (s, 3 H, C10-H), 0.47 (s, 3 H, C10-H), 0.07 (s, 6 H, C18-H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  161.5, 156.8, 156.3, 151.4, 145.5, 138.9, 138.4, 138.3, 138.1, 128.7, 128.6, 128.5, 128.3, 128.1, 128.03, 127.96, 127.94, 127.85, 123.1, 120.3, 117.7, 111.5 (C14), 110.6 (C7), 107.7 (C16), 86.8, 82.0, 80.5, 79.7, 78.4, 75.9, 75.4, 75.1, 75.0, 73.7, 69.2, 64.0 (C17), 61.9, 26.0, 18.5 (C20), -4.41 (C19), -4.40 (C9), -5.1 (C18).



**3.23**

**(5-((2*R*,3*R*,4*S*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-tetrahydro-2*H*-pyran-2-yl)furan-2-yl)dimethyl(vinyl)silane (3.23). (KP3-115). A**

solution of *s*-BuLi (1.53 mL, 2.14 mmol, 1.4 M) in hexanes was added dropwise to a solution of furan **3.18** (973 mg, 1.65 mmol) in THF (20 mL) at  $-78\text{ }^{\circ}\text{C}$ . The resultant black mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 3 h, whereupon chlorodimethylvinylsilane was added dropwise. The cold bath was allowed to warm to rt over a 4 h period, and stirring was continued at rt for 12 h. A 60% aqueous NaCl solution (30 mL) and EtOAc (30 mL) were added, and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with  $\text{Et}_2\text{O}$ /hexanes (1:5) to give 858 mg (77%) of **3.23** as a light yellow oil. Spectra were identical to those previously reported for this compound.<sup>95</sup>

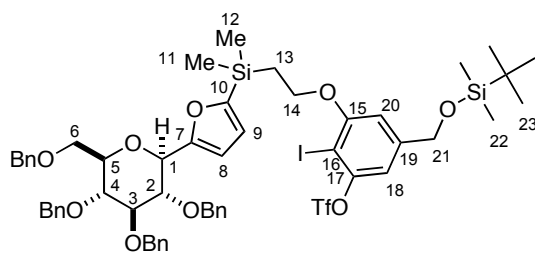


**5-(*tert*-Butyldimethylsilyloxy)methyl)-3-({dimethyl-[5-(2,4,5-tris-benzyloxy-6-benzyloxymethyltetrahydropyran-2-yl)-furan-2-yl]-silyl}-methoxy)-2-iodophenyl alcohol (3.26). (KP3-151).** DIAD (9 mg, 0.043 mmol, 8  $\mu\text{L}$ ) was added dropwise to a solution of **3.24** (23 mg, 0.033 mmol), phenol **3.15** (38 mg, 0.099 mmol), and  $\text{PPh}_3$  (17 mg, 0.043 mmol) in  $\text{Et}_2\text{O}$  (400  $\mu\text{L}$ ) and the mixture was stirred at rt for 17 h, whereupon it was concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with EtOAc/toluene (1:99 then 1:49) to give 31 mg (89%) of **3.26** as a clear oil:  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32–7.23 (comp, 13 H), 7.18–7.14

(comp, 5 H), 6.94–6.92 (comp, 2 H), 6.68 (d,  $J = 3.2$  Hz, 1 H), 6.59–6.58 (m, 1 H), 6.45 (d,  $J = 3.2$  Hz, 1 H), 6.30–6.29 (m, 1 H), 5.39 (s, 1 H), 4.91 (d,  $J = 11.0$  Hz, 1 H), 4.86 (d,  $J = 11.0$  Hz, 1 H), 4.83 (d,  $J = 10.0$  Hz, 1 H), 4.61 (s, 2 H), 4.59 (d,  $J = 12.1$  Hz, 1 H), 4.58 (d,  $J = 10.0$  Hz, 1 H), 4.52 (d,  $J = 12.1$  Hz, 1 H), 4.46 (d,  $J = 10.3$  Hz, 1 H), 4.35 (d,  $J = 9.7$  Hz, 1 H), 4.14–4.06 (comp, 2 H), 3.99 (d,  $J = 10.3$  Hz, 1 H), 3.91–3.87 (m, 1 H), 3.76–3.70 (comp, 4 H), 3.57–3.54 (dt,  $J = 7.1, 3.1$  Hz, 1 H), 1.42 (app t,  $J = 8.0$  Hz, 2 H), 0.92 (s, 9 H), 0.34 (s, 6 H), 0.07 (s, 6 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  158.4, 157.9, 156.1, 155.9, 144.5, 138.7, 138.2, 138.1, 137.8, 128.4, 128.33, 128.28, 128.0, 127.91, 127.86, 127.76, 127.73, 127.70, 127.59, 127.57, 121.6, 110.1, 105.0, 101.7, 86.5, 81.8, 79.4, 78.1, 76.2, 75.6, 75.1, 74.8, 74.7, 73.5, 69.0, 66.4, 64.3, 25.9, 18.3, 16.2, -2.8, -2.9, -5.3; IR (neat) 3354, 1430, 1252, 1078  $\text{cm}^{-1}$ ; mass spectrum (CI)  $m/z$  1054.3361 [ $\text{C}_{55}\text{H}_{67}\text{NiO}_9\text{Si}_2$  (M<sup>+</sup>) requires 1054.3368], 949, 929, 839 (base).

**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32–7.23 (comp, 13 H, Ph C-H), 7.18–7.14 (comp, 5 H, Ph C-H), 6.94–6.92 (comp, 2 H, Ph C-H), 6.68 (d,  $J = 3.2$  Hz, 1 H, C8-H), 6.59–6.58 (m, 1 H, C19-H), 6.45 (d,  $J = 3.2$  Hz, 1 H, C9-H), 6.30–6.29 (m, 1 H, C17-H), 5.39 (s, 1 H, OH), 4.91 (d,  $J = 11.0$  Hz, 1 H, Bn C-H), 4.86 (d,  $J = 11.0$  Hz, 1 H, Bn C-H), 4.83 (d,  $J = 10.0$  Hz, 1 H, Bn C-H), 4.61 (s, 2 H, C20-H), 4.59 (d,  $J = 12.1$  Hz, 1 H, Bn C-H), 4.58 (d,  $J = 10.0$  Hz, 1 H, Bn C-H), 4.52 (d,  $J = 12.1$  Hz, 1 H, Bn C-H), 4.46 (d,  $J = 10.3$  Hz, 1 H, Bn C-H), 4.35 (d,  $J = 9.7$  Hz, 1 H, C6-H), 4.14–4.06 (comp, 2 H, C13-H), 3.99 (d,  $J = 10.3$  Hz, 1 H, Bn C-H), 3.91–3.87 (m, 1 H, C5-H), 3.76–3.70 (comp, 4 H), 3.57–3.54 (dt,  $J = 7.1, 3.1$  Hz, 1 H), 1.42 (app t,  $J = 8.0$  Hz, 2 H, C12-H), 0.92 (s, 9 H, C22-H), 0.34 (s, 6 H, C11-H), 0.07 (s, 6 H, C21-H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  158.4, 157.9, 156.1, 155.9, 144.5, 138.7, 138.2, 138.1, 137.8, 128.4 (Ph C), 128.33 (Ph C), 128.28 (Ph C), 128.0 (Ph C), 127.91 (Ph C), 127.86 (Ph C), 127.76 (Ph C), 127.73 (Ph C), 127.70 (Ph C), 127.59 (Ph C), 127.57 (Ph C), 121.6 (C8), 110.1

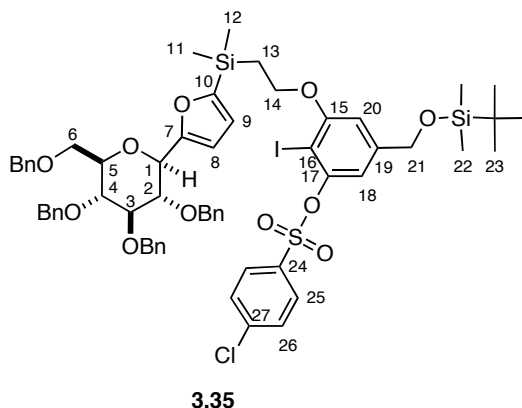
(C9), 105.0 (C19), 101.7 (C17), 86.5, 81.8 (C13), 79.4 (C5), 78.1, 76.2 (Bn C), 75.6 (Bn C), 75.1 (Bn C or C6), 74.8 (Bn C or C6), 74.7, 73.5 (Bn C), 69.0, 66.4 (C13), 64.3 (C20), 25.9 (C22), 16.2 (C12), -2.8 (C11), -2.9 (C11), -5.3 (C21).



**3.25**

**Trifluoromethanesulfonic acid 5-(*tert*-butyldimethylsilyloxymethyl)-3-({dimethyl-[5-(2,4,5-trisbenzyloxy-6-benzyloxymethyltetrahydropyran-2-yl)-furan-2-yl]-silyl}methoxy)-2-iodophenyl ester (3.25). (KP3-147).** Tf<sub>2</sub>O (42 mg, 0.15 mmol, 25  $\mu$ L), which was freshly distilled from P<sub>2</sub>O<sub>5</sub>, was added dropwise to a solution of **3.26** (143 mg, 0.14 mmol) and N(*i*Pr)<sub>2</sub>Et (21 mg, 0.163 mmol, 28  $\mu$ L) in CH<sub>2</sub>Cl<sub>2</sub> at -78 °C. Stirring was continued at -78 °C for 20 min, whereupon 50% aqueous NH<sub>4</sub>Cl (2 mL) was added, and the mixture was warmed to rt. The layers were separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 4 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The crude residue was purified by column chromatography, eluting with Et<sub>2</sub>O/hexanes (1:5) to afford 138 mg (86%) of **3.25** as a clear oil: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.34–7.26 (comp, 13 H), 7.19–7.16 (comp, 5 H), 6.95–6.94 (comp, 2 H), 6.92 (s, 1 H), 6.72 (d, *J* = 3.1 Hz, 1 H), 6.63 (s, 1 H), 6.48 (d, *J* = 3.1 Hz, 1 H), 4.92 (d, *J* = 10.9 Hz, 1 H), 4.88 (d, *J* = 10.9 Hz, 1 H), 4.86 (d, *J* = 10.5 Hz, 1 H), 4.66 (s, 2 H), 4.62–4.59 (comp, 2 H), 4.53 (d, *J* = 12.0 Hz, 1 H), 4.50 (d, *J* = 10.3 Hz, 1 H), 4.17–4.07 (comp 2 H), 4.00 (d, *J* = 10.3 Hz, 1 H), 3.92 (td, *J* = 9.2, 4.4 Hz, 1 H), 3.79–3.72 (comp,

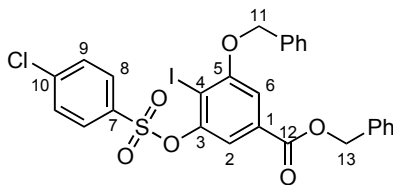
4 H), 3.60–3.57 (m, 1 H), 1.47 (t,  $J = 8.2$  Hz, 1 H), 0.94 (s, 9 H), 0.37 (s, 3 H), 0.36 (s, 3 H), 0.096 (s, 3 H).



**4-Chlorophenylsulfonic acid 5-(tert-butyl dimethylsilanyloxymethyl)-3-({dimethyl-[5-(2,4,5-trisbenzyloxy-6-benzyloxymethyltetrahydropyran-2-yl)-furan-2-yl]-silanyl}methoxy)-2-iodophenyl ester (3.35).** (KP3-278). *p*-Chlorobenzenesulfonyl chloride (108 mg, 0.51 mmol) was added to a solution of 3.26 (490 mg, 0.47 mmol) and Et<sub>3</sub>N (56 mg, 0.56 mmol, 77  $\mu$ L) in CH<sub>2</sub>Cl<sub>2</sub>, (5 mL) and the mixture was stirred at room temperature for 16 h, whereupon H<sub>2</sub>O (5 mL) was added. The layers were separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue was purified by flash chromatography eluting with Et<sub>2</sub>O/hexanes (1:5) to give 505 mg (88%) of **3.35** as a viscous oil: <sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  7.86 (dt,  $J = 11.3, 2.4$  Hz, 2 H), 7.45 (dt,  $J = 11.3, 2.4$  Hz, 2 H), 7.32–7.23 (comp, 13 H), 7.17–7.14 (comp, 5 H), 6.93–6.91 (comp, 3 H), 6.67 (d,  $J = 3.2$  Hz, 1 H), 6.60 (s, 1 H), 6.44 (d,  $J = 3.2$  Hz, 1 H), 4.90 (d,  $J = 11.0$  Hz, 1 H), 4.85 (d,  $J = 11.0$  Hz, 1 H), 4.83 (d,  $J = 10.7$  Hz, 1 H), 4.62–4.57 (comp, 4 H), 4.51 (d,  $J = 12.1$  Hz, 1 H), 4.47 (d,  $J = 10.3$  Hz, 1 H), 4.35 (d,  $J = 9.7$  Hz, 1 H), 4.11–4.03 (m,

1 H), 3.96 (d,  $J = 10.3$  Hz, 1 H), 3.89–3.86 (m, 1 H), 3.75–3.70 (comp, 4 H), 3.55 (dt,  $J = 9.3, 3.1$  Hz, 1 H), 1.40 (dd,  $J = 8.5, 6.9$  Hz, 2 H), 0.91 (s, 9 H), 0.310 (s, 3 H), 0.0308 (s, 3 H), 0.068 (s, 3 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  159.1, 158.2, 156.3, 150.8, 144.6, 141.1, 138.6, 138.2, 138.1, 137.8, 134.6, 130.2, 129.4, 128.4, 128.34, 128.28, 128.0, 127.9, 127.84, 127.77, 127.73, 127.61, 127.58, 121.7, 112.2, 110.0, 107.6, 86.5, 81.8, 80.9, 79.5, 78.1, 76.3, 75.6, 75.1, 74.8, 74.7, 73.5, 69.0, 66.8, 63.9, 25.9, 16.1, -2.89, -2.93, -5.3; IR (neat) 3060, 3025, 1384, 1363, 1190, 1095, 1065, 838, 781  $\text{cm}^{-1}$ ; mass spectrum (ESI)  $m/z$  1246.398 [ $\text{C}_{61}\text{H}_{70}\text{ClIO}_{11}\text{SSi}_2\text{H}_2\text{O}^+$  requires 1246.302] 635, 335, 301 (base), 149.

**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.86 (dt,  $J = 11.3, 2.4$  Hz, 2 H, C25-H), 7.45 (dt,  $J = 11.3, 2.4$  Hz, 2 H, C26-H), 7.32–7.23 (comp, 13 H, Ph C-H), 7.17–7.14 (comp, 5 H, Ph C-H), 6.93–6.91 (comp, 3 H, Ph C-H and C18-H), 6.67 (d,  $J = 3.2$  Hz, 1 H, C8-H), 6.60 (s, 1 H, C20-H), 6.44 (d,  $J = 3.2$  Hz, 1 H, C9-H), 4.90 (d,  $J = 11.0$  Hz, 1 H, Bn C-H), 4.85 (d,  $J = 11.0$  Hz, 1 H, Bn C-H), 4.83 (d,  $J = 10.7$  Hz, 1 H, Bn C-H), 4.62–4.57 (comp, 4 H, Bn C-H and C21-H), 4.51 (d,  $J = 12.1$  Hz, 1 H, Bn C-H), 4.47 (d,  $J = 10.3$  Hz, 1 H, C6-H), 4.35 (d,  $J = 9.7$  Hz, 1 H, Bn C-H), 4.11–4.03 (m, 1 H, C14-H), 3.96 (d,  $J = 10.3$  Hz, 1 H, C6-H), 3.89–3.86 (m, 1 H, C5-H), 3.75–3.70 (comp, 4 H, Bn C-H), 3.55 (dt,  $J = 9.3, 3.1$  Hz, 1 H), 1.40 (dd,  $J = 8.5, 6.9$  Hz, 2 H, C13-H), 0.91 (s, 9 H, C23-H), 0.310 (s, 3 H, C11-H or C12-H), 0.0308 (s, 3 H, C11-H or C12-H), 0.068 (s, 3 H, C22-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  159.1, 158.2, 156.3, 150.8, 144.6, 141.1, 138.6, 138.2, 138.1, 137.8, 134.6, 130.2 (C25), 129.4 (C26), 128.4 (Ph C), 128.34 (Ph C), 128.28 (Ph C), 128.0 (Ph C), 127.9 (Ph C), 127.84 (Ph C), 127.77 (Ph C), 127.73 (Ph C), 127.61 (Ph C), 127.58 (Ph C), 121.7 (C8), 112.2 (C18), 110.0 (C9), 107.6 (C20), 86.5, 81.8 (C5), 80.9, 79.5, 78.1, 76.3, 75.6, 75.1, 74.8, 74.7, 73.5, 69.0, 66.8 (C14), 63.9, 25.9, 16.1 (C13), -2.89 (C11 or C12), -2.93 (C11 or C12), -5.3 (C22).

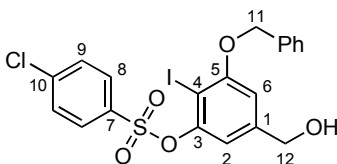


**3.43**

**Benzyl-3-(benzyloxy)-5-(4-chlorophenylsulfonyloxy)-4-iodobenzoate (3.43).** (KP4-267). 4-Chlorobenzene sulfonyl chloride (1.51 g, 7.15 mmol) was added to a solution of **3.42** (2.99 g, 6.50 mmol) and Et<sub>3</sub>N (790 mg, 7.80 mmol, 1.1 mL) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and the mixture was stirred for 18 h. H<sub>2</sub>O (50 mL) was added and the layers were separated. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 50 mL). The combined organic layers were dried (MgSO<sub>4</sub>), concentrated, and the residue was recrystallized from EtOH to give 3.75 g of **3.43** (91%) (white needles): mp = 108–110 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.87 (dt, *J* = 9.2, 2.4 Hz, 2 H), 7.58 (d, *J* = 1.7 Hz, 1 H), 7.47 (dt, *J* = 9.2, 2.4 Hz, 2 H), 7.45–7.30 (comp, 11 H), 5.34 (s, 2 H), 5.17 (s, 2 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 164.7, 159.0, 151.1, 141.5, 135.4, 134.3, 132.2, 130.2, 129.6, 128.7, 128.6, 128.5, 128.3, 128.2, 127.1, 116.1, 111.1, 90.8, 71.6, 67.4; IR (neat) 1720, 1444, 1383, 1187, 1055 785 cm<sup>-1</sup>; mass spectrum (CI) *m/z* 634.9789 [C<sub>27</sub>H<sub>21</sub>O<sub>6</sub>SCl (M+1) requires 634.9792].

**NMR Assignments:** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.87 (dt, *J* = 9.2, 2.4 Hz, 2 H, C8-H) 7.58 Hz (d, *J* = 1.7 Hz, 1 H, C2-H), 7.47 (dt, *J* = 9.2, 2.4 Hz, 2 H, C9-H), 7.45–7.30 (comp, 11 H, Ph C-H, C6-H), 5.34 (s, 2 H, C13-H), 5.17 (s, 2 H, C11-H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 164.7, 159.0, 151.1, 141.5, 135.4, 134.3, 132.2, 130.2 (C8), 129.6

(C9), 128.7, 128.6, 128.5, 128.3, 128.2, 127.1, 116.1 (C6), 111.1 (C2), 90.8, 71.6 (C11), 67.4 (C13).



**3.44**

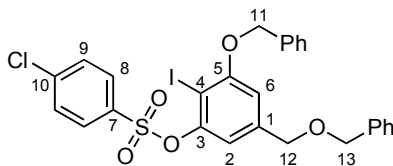
**3-(Benzyloxy)-5-(hydroxymethyl)-2-iodophenyl-4-chlorobenzenesulfonate**

**(3.44). (KP4-240).** A solution of DIBAL-H in PhCH<sub>3</sub> (3.82 mmol, 3.8 mL, 1 M) was added to **3.43** (971 mg, 1.53 mmol) in PhCH<sub>3</sub> (15 mL) at -78 °C, and the mixture was stirred at for 5 min. The cold bath was removed, and stirring was continued for 1.5 h. 2 N HCl was added and the layers were separated. The aqueous layer was extracted with Et<sub>2</sub>O (2 x 15 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by flash chromatography, eluting with CH<sub>2</sub>Cl<sub>2</sub> to afford 706 mg (87%) of **3.44** as a cottony solid: mp = 99–100 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.89 (dt, *J* = 9.3, 2.4 Hz, 2 H), 7.50 (dt, *J* = 9.3, 2.4 Hz, 2 H), 7.45–7.43 (comp, 2 H), 7.38–7.34 (comp, 2 H), 7.32–7.29 (m, 1 H), 7.02–7.01 (m, 1 H), 6.828–6.825 (m, 1 H), 5.12 (s, 2 H), 4.65 (d, *J* = 3.4 Hz, 2 H), 1.86 (t, *J* = 3.4 Hz, 1 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 159.0, 150.9, 143.9, 141.3, 135.9, 134.4, 130.3, 129.5, 128.6, 128.1, 127.0, 113.5, 108.9, 82.0, 71.3, 64.2; IR (neat) 3377, 1574, 1421, 1380, 1188, 1085, 783 cm<sup>-1</sup>; mass spectrum (CI) *m/z* 530.9534 [C<sub>20</sub>H<sub>17</sub>O<sub>5</sub>SCl (M+1) requires 530.9530], 513 (base).

**NMR Assignments:** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.89 (dt, *J* = 9.3, 2.4 Hz, 2 H, C8-H), 7.50 (dt, *J* = 9.3, 2.4 Hz, 2 H, C9-H), 7.45–7.43 (comp, 2 H, Ph C-H), 7.38–7.34 (comp, 2 H, Ph C-H), 7.32–7.29 (m, 1 H, Ph C-H), 7.02–7.01 (m, 1 H, C2-H), 6.828–



6.825 (m, 1 H, C6-H), 5.12 (s, 2 H, C11-H), 4.65 (d,  $J = 3.4$  Hz, 2 H, C12-H), 1.86 (t,  $J = 3.4$  Hz, 1 H, OH);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  159.0, 150.9, 143.9, 141.3, 135.9, 134.4, 130.3 (C8), 129.5 (C9), 128.6 (Ph C), 128.1(Ph C), 127.0 (Ph C), 113.5 (C2), 108.9 (C6), 82.0, 71.3 (C11), 64.2 (C12).



**3.45**

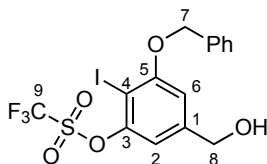
**3-(Benzyloxy)-5-(benzyloxymethyl)-2-iodophenyl-4-chlorobenzenesulfonate**

**(3.45). (KP4-241):** A mixture of **3.44** (35 mg, 0.066 mmol), MgO (5 mg, 0.13 mmol), and 2-benzyloxy-1-methylpyridinium triflate (46 mg, 0.13 mmol) in  $\text{PhCF}_3$  (1 mL) was heated at 80 °C for 22 h. The mixture was cooled to rt and filtered through celite, eluting with  $\text{PhCH}_3$ . The filtrate was concentrated, and the resulting residue was purified by flash chromatography, eluting with  $\text{Et}_2\text{O}$ /hexanes (1:7) to give 33 mg (80%) of **3.45** as a white cottony solid: mp = 123–124 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.88 (dt,  $J = 9.3$ , 2.4 Hz, 2 H), 7.47 (dt,  $J = 9.3$ , 2.4 Hz, 2 H), 7.44–7.43 (comp, 2 H), 7.38–7.29 (comp, 8 H), 7.00–6.99 (m, 1 H), 6.813–6.810 (m, 1 H), 5.11 (s, 2 H), 4.52 (s, 2 H), 4.49 (s, 2 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  159.0, 150.9, 141.4, 141.3, 137.7, 135.9, 134.4, 130.3, 129.5, 128.6, 128.5, 128.1, 127.9, 127.8, 127.0, 114.3, 109.6, 82.2, 72.4, 71.3, 70.9; IR (neat) 1421, 1382, 1189, 1085, 1083, 783; mass spectrum (CI)  $m/z$  621.0004 [ $\text{C}_{27}\text{H}_{23}\text{O}_5\text{S}$  (M+1) requires 621.0000], 621 (base), 513.

**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.88 (dt,  $J = 9.3$ , 2.4 Hz, 2 H, C8-H), 7.47 (dt,  $J = 9.3$ , 2.4 Hz, 2 H, C9-H), 7.44–7.43 (comp, 2 H, PhC-H), 7.38–7.29



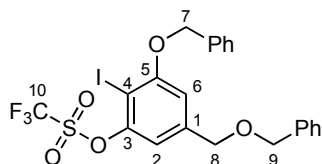
**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ );  $\delta$  7.61 (s, 1 H, C2-H), 7.51 (s, 1 H, C6-H), 7.48–7.34 (comp, 10 H, PhC-H), 5.36 (s, 2 H, C9-H), 5.22 (s, 2 H, C7-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  164.3, 159.5, 151.3, 135.3, 132.7, 128.74 (Ph C), 128.71 (Ph C), 128.6 (Ph C), 128.4 (Ph C), 128.2 (Ph C), 127.2 (Ph C), 115.3 (C6), 111.9 (C2), 90.1, 71.8 (C7), 67.6 (C9).



**3.48**

**3-(Benzyloxy)-5-(hydroxymethyl)-2-iodophenyl trifluoromethanesulfonate (3.48). (KP4-294).** DIBAL-H (3.80 mmol, 3.8 mL, 1 M solution in  $\text{PhCH}_3$ ) was added to a solution of **3.47** (900 mg, 1.52 mmol) in  $\text{PhCH}_3$  (10 mL) at  $-78\text{ }^\circ\text{C}$ , and the mixture was stirred at for 5 min. The cold bath was removed, and stirring was continued at for 0.5 h. 2 N HCl was added, and the layers were separated. The aqueous layer was extracted with  $\text{Et}_2\text{O}$  (2 x 10 mL), and the combined organic layers were dried and concentrated. The residue was heated under reflux in hexanes while EtOH was added dropwise until the solid went into solution. Recrystallization from this solution gave 702 mg (93%) of **3.48** as a cottony solid: mp =  $120\text{--}121\text{ }^\circ\text{C}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.49–7.47 (comp, 2 H), 7.41–7.38 (comp, 2 H), 7.35–7.34 (m, 1 H), 6.95 (s, 1 H), 6.89 (s, 1 H), 5.17 (s, 2 H), 4.68 (d,  $J = 5.9\text{ Hz}$ , 2 H), 1.83 (t,  $J = 5.9\text{ Hz}$ , 1 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  159.5, 151.3, 144.5, 135.6, 128.7, 128.2, 127.1, 112.3, 109.5, 81.5, 71.5, 63.9; IR (neat) 3160, 1426, 1215, 1196, 820  $\text{cm}^{-1}$ ; mass spectrum (CI)  $m/z$  488.9479 [ $\text{C}_{15}\text{H}_{13}\text{O}_5\text{F}_3\text{S}$  (M+1) requires 488.9481], 471 (base).

**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.49–7.47 (comp, 2 H, Ph C-H), 7.41–7.38 (comp, 2 H, Ph C-H), 7.35–7.34 (m, 1 H, Ph C-H), 6.95 (s, 1 H, C2-H), 6.89 (s, 1 H, C6-H), 5.17 (s, 2 H, C7-H), 4.68 (d,  $J = 5.9$  Hz, 2 H, C8-H), 1.83 (t,  $J = 5.9$  Hz, 1 H, OH);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  159.5, 151.3, 144.5, 135.6, 128.7 (Ph C), 128.2 (Ph C), 127.1 (Ph C), 112.3 (C2), 109.5 (C6), 81.5, 71.5 (C7), 63.9 (C8).

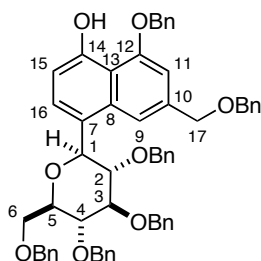


**3.49**

**3-(Benzyloxy)-5-(benzyloxymethyl)-2-iodophenyl trifluoromethanesulfonate (3.49).** (KP4-273). A mixture of **3.48** (105 mg, 0.215 mmol), MgO (15 mg, 0.363 mmol), and 2-benzyloxy-1-methylpyridinium triflate (127 mg, 0.363 mmol) in  $\text{PhCF}_3$  (1 mL) was heated at 80 °C for 20 h. The mixture was cooled to rt and filtered through celite, eluting with  $\text{PhCH}_3$ . The filtrate was concentrated, and the residue was purified by flash chromatography, eluting with  $\text{Et}_2\text{O}$ /hexanes (1:10) to give 120 mg (97%) of **3.49** as a yellow oil:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.48–7.46 (comp, 2H), 7.40–7.30 (comp, 8 H), 6.94 (s, 1 H), 6.88 (s, 1 H), 5.16 (s, 2 H), 4.53 (s, 2 H), 4.51 (s, 2 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  159.4, 151.2, 142.1, 137.5, 135.7, 128.7, 128.5, 128.2, 128.0, 127.1, 113.1, 110.3, 81.6, 72.6, 71.5, 70.6; IR (neat) 1422, 1217, 1138, 1066, 741; mass spectrum (CI)  $m/z$  578.9943 [ $\text{C}_{22}\text{H}_{19}\text{O}_5\text{F}_3\text{S}$  (M+1) requires 578.9950].

**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.48–7.46 (comp, 2H, Ph C-H), 7.40–7.30 (comp, 8 H, Ph C-H), 6.94 (s, 1 H, C2-H), 6.88 (s, 1 H, C6-H), 5.16 (s, 2 H, C8-H), 4.53 (s, 2 H, C9-H or C11-H), 4.51 (s, 2 H, C9-H or C11-H);  $^{13}\text{C}$  NMR (125

MHz, CDCl<sub>3</sub>)  $\delta$  159.4, 151.2, 142.1, 137.5, 135.7, 128.7 (Ph C), 128.5 (Ph C), 128.2 (Ph C), 128.0 (Ph C), 127.1 (Ph C), 113.1 (C2), 110.3 (C6), 81.6, 72.6 (C8), 71.5 (C9 or C11), 70.6 (C9 or C11).



**3.37**

**4-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2*H*-pyran-2-yl)-8-(benzyloxy)-6-((benzyloxy)methyl)naphthalen-1-ol (3.37). (KP3-285). **Method A (via tether)** *i*-PrMgCl (0.089 mmol, 100  $\mu$ L, 0.90 M) was added dropwise to a solution of sulfonate **3.35** (91 mg, 0.074 mmol) in THF at  $-78$   $^{\circ}$ C. The mixture was stirred at  $-78$   $^{\circ}$ C for 5 min, the cold bath was removed, and the mixture was stirred at ambient temperature for 12 h, whereupon a 50% solution of NH<sub>4</sub>Cl (2 mL) and Et<sub>2</sub>O (2 mL) were added. The layers were separated and the aqueous layer was extracted with Et<sub>2</sub>O (3 x 2 mL). The combined organic layers were washed with brine (1 x 5 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue was dissolved in DMF (1.5 mL) and solid TBAF (90 mg, 0.34 mmol) was added. The mixture was then heated at 70  $^{\circ}$ C for 7 h, whereupon H<sub>2</sub>O (3 mL) and EtOAc (3 mL) were added. The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 3 mL). The combined organic layers were washed with brine (2 x 10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated, and the residue was purified by flash chromatography eluting with EtOAc/hexanes (1:2) to give 34 mg (64%) of a diol. BnBr (17 mg, 0.098 mmol, 12  $\mu$ L) and NaH (7 mg, 0.10 mmol, 60%**

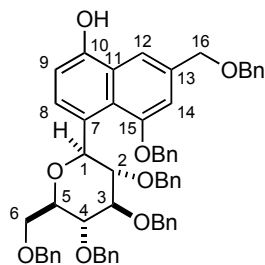
dispersion) were added to the diol in DMF, and the mixture was stirred for 3 h at rt, whereupon H<sub>2</sub>O (3 mL) and EtOAc (3 mL) were added. The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 3 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residue was purified by flash chromatography eluting with Et<sub>2</sub>O/hexanes (1:2) to give 24 mg (56%) of **3.37**. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) and TFA (5 drops) was added. The mixture was stirred for 18 h, whereupon a saturated solution of NaHCO<sub>3</sub> (2 mL) and CH<sub>2</sub>Cl<sub>2</sub> (1 mL) were added. The layers were separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 2 mL). The combined organic layers were combined, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo. The residue was purified by flash chromatography eluting with Et<sub>2</sub>O/hexanes (1:4) to give 20 mg (87%) of **3.37** as a yellow oil.

**Method B (untethered approach) (KP5-51):** *n*-BuLi (770 μL, 2.5 M, 1.93 mmol) was added dropwise over 30 min to a mixture of triflate **3.49** (1.01 g, 1.75 mmol) and furan **3.18** (3.60 g, 6.10 mmol) in THF (20 mL) at -78 °C. The mixture was stirred for 20 min at -78 °C, whereupon a saturated solution of NH<sub>4</sub>Cl was added (20 mL). The mixture was warmed to rt and the layers were separated. The aqueous layer was extracted with Et<sub>2</sub>O (3 x 20 mL), dried (MgSO<sub>4</sub>), and concentrated. The residue was purified by flash chromatography eluting with Et<sub>2</sub>O/hexanes (1:5 then 1:4) to give 863 mg (55%) of a mixture of 4 isomers, **3.36** and **3.39**.

TFA (6 drops) was added to the mixture of isomers **3.36** and **3.39** (109 mg, 0.122 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) and the mixture was stirred for 14 h, whereupon NaHCO<sub>3</sub> (3 mL) and Et<sub>2</sub>O (5 mL) were added. The layers were separated, and the aqueous layer was extracted with Et<sub>2</sub>O (2 x 3 mL), dried (MgSO<sub>4</sub>), and concentrated. The residue was purified by flash chromatography, eluting with Et<sub>2</sub>O/hexanes (1:3 then 1:1) to give 31 mg (28%) of phenol **3.37**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.64 (s, 1 H), 7.89 (s, 1 H), 7.53-

7.48 (comp, 3H), 7.44–7.23 (comp, 22 H), 7.10–6.97 (comp, 4 H), 6.86 (d, 8.2 Hz, 1 H), 6.64 (m, 2 H), 5.29 (s, 2 H), 4.95 (d,  $J = 10.9$ , 1 H), 4.92 (d,  $J = 9.9$  Hz, 1 H), 4.89 (d,  $J = 10$  Hz, 1 H), 4.76 (s, 1 H), 4.67 (d,  $J = 9.9$  Hz, 1 H), 4.62 (d,  $J = 12.0$  Hz, 1 H), 4.52 (s, 2 H), 4.51 (d,  $J = 12.0$  Hz, 1 H), 4.41 (s, 2 H), 4.17 (d,  $J = 10.3$  Hz, 1 H), 3.94–3.76 (comp, 5 H), 3.67–3.62 (m, 1 H), 3.52 (d,  $J = 10.3$  Hz, 1 H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  156.0, 155.1, 138.7, 138.5, 138.4, 138.3, 137.5, 136.0, 135.1, 134.5, 129.0, 128.9, 128.4, 128.3, 128.2, 128.1, 127.95, 127.82, 127.73, 127.65, 127.61, 127.5, 127.45, 127.43, 117.5, 114.9, 110.3, 104.7, 87.0, 79.5, 78.3, 75.8, 75.2, 74.6, 73.3, 72.4, 72.0, 71.7, 69.1; IR (neat) 3388, 1453, 1097, 1068  $\text{cm}^{-1}$ ; mass spectrum (ESI)  $m/z$  893.4048 [ $\text{C}_{59}\text{H}_{57}\text{O}_8^+$  (M+1) requires 893.4012].

**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.64 (s, 1 H, OH), 7.89 (br s, 1 H), 7.53–7.48 (comp, 3H, Ph C-H and C15-H), 7.44–7.23 (comp, 22 H, Ph C-H), 7.10–6.97 (comp, 4 H, Ph C-H), 6.86 (d, 8.2 Hz, 1 H, Ph C-H), 6.64 (m, 2 H, Ph C-H), 5.29 (s, 2 H, Bn C-H), 4.95 (d,  $J = 10.9$ , 1 H, Bn C-H), 4.92 (d,  $J = 9.9$  Hz, 1 H, Bn C-H), 4.89 (d,  $J = 10$  Hz, 1 H, Bn C-H), 4.76 (s, 1 H), 4.67 (d,  $J = 9.9$  Hz, 1 H, Bn C-H), 4.62 (d,  $J = 12.0$  Hz, 1 H, Bn C-H), 4.52 (s, 2 H), 4.51 (d,  $J = 12.0$  Hz, 1 H, Bn C-H), 4.41 (s, 2 H, Bn C-H), 4.17 (d,  $J = 10.3$  Hz, 1 H, C6-H), 3.94–3.76 (comp, 5 H), 3.67–3.62 (m, 1 H), 3.52 (d,  $J = 10.3$  Hz, 1 H, C6-H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  156.0 (C14), 155.1, 138.7 (Ph C), 138.5 (Ph C), 138.4 (Ph C), 138.3 (Ph C), 137.5 (Ph C), 136.0 (Ph C), 135.1 (Ph C), 134.5 (Ph C), 129.0, 128.9, 128.4, 128.3, 128.2, 128.1, 127.95, 127.82, 127.73, 127.65, 127.61, 127.5, 127.45, 127.43, 117.5, 114.9, 110.3 (C15), 104.7, 87.0, 79.5, 78.3, 75.8, 75.2, 74.6, 73.3, 72.4, 72.0, 71.7, 69.1.



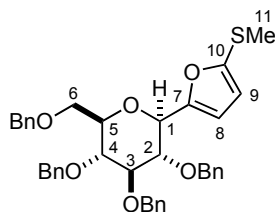
**3.50**

**5-(Benzyloxy)-7-(benzyloxymethyl)-4-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2*H*-pyran-2-yl)naphthalen-1-ol**

**(3.50).** From the above reaction (Method B) 33 mg (31%) of **3.50** was also isolated:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36 (s, 1 H), 7.52 (d,  $J = 8.1$  Hz, 1 H), 7.48–7.46 (comp, 2 H), 7.36–7.20 (comp, 25 H), 7.02–6.90 (comp, 4 H), 6.68 (d,  $J = 8.1$  Hz, 1 H), 6.50–6.48 (comp, 2 H), 6.13 (d,  $J = 9.5$  Hz, 1 H), 5.90 (s, 1 H), 5.11 (d,  $J = 10.7$  Hz, 1 H), 4.86 (d,  $J = 10.7$  Hz, 1 H) 4.82 (d,  $J = 11.2$  Hz, 1 H), 4.78 (d,  $J = 11.0$  Hz, 1 H), 4.66–4.61 (comp, 4 H), 4.57–4.51 (comp, 4 H), 4.20 (d,  $J = 10.5$  Hz, 1 H), 3.70 (dd,  $J = 11.0, 1.9$  Hz, 1 H), 3.68–3.66 (m, 1 H), 3.63 (app t,  $J = 9.5$  Hz, 1 H), 3.48 (d,  $J = 10.3$  Hz, 1 H), 3.39 (app t,  $J = 9.3$  Hz, 1 H), 3.31 (ddd,  $J = 9.8, 4.4, 1.9$  Hz, 1 H), 3.27 (app t,  $J = 8.8$  Hz, 1 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  156.8, 151.2, 138.9, 138.8, 138.3, 138.22, 138.20, 136.9, 134.4, 128.66, 128.56, 128.54, 128.4, 128.32, 128.29, 128.25, 128.1, 127.91, 127.89, 127.86, 127.77, 127.72, 127.6, 127.53, 127.45, 127.42, 127.0, 125.9, 125.8, 124.8, 113.8, 109.5, 107.5, 86.5, 86.4, 78.7, 78.6, 78.7, 78.6, 75.4, 74.4, 74.3, 73.4, 72.4, 71.9, 71.1, 69.6; IR (neat) 3321, 1453, 1361, 1091, 1028  $\text{cm}^{-1}$ ; mass spectrum (CI)  $m/z$  893.4049 [ $\text{C}_{59}\text{H}_{57}\text{O}_8^+$  (M+1) requires 893.4012]



**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36 (s, 1 H, C12-H), 7.52 (d,  $J = 8.1$  Hz, 1 H, C8-H), 7.48–7.46 (comp, 2 H, Ph C-H), 7.36–7.20 (comp, 24 H, Ph C-H), 7.02–6.90 (comp, 4 H, Ph C-H), 6.68 (d,  $J = 8.1$  Hz, 1 H, C9-H), 6.50–6.48 (comp, 2 H), 6.13 (d,  $J = 9.5$  Hz, 1 H, C1-H), 5.90 (s, 1 H, OH), 5.11 (d,  $J = 10.7$  Hz, 1 H Bn C-H), 4.86 (d,  $J = 10.7$  Hz, 1 H Bn C-H) 4.82 (d,  $J = 11.2$  Hz, 1 H Bn C-H), 4.78 (d,  $J = 11.0$  Hz, 1 H, Bn C-H), 4.66–4.61 (comp, 4 H Bn C-H), 4.57–4.51 (comp, 4 H), 4.20 (d,  $J = 10.5$  Hz, 1 H), 3.70 (dd,  $J = 11.0, 1.9$  Hz, 1 H, C6-H), 3.68–3.66 (m, 1 H, C6-H), 3.63 (app t,  $J = 9.5$  Hz, 1 H, C4-H), 3.48 (d,  $J = 10.3$  Hz, 1 H, Bn -H), 3.39 (app t,  $J = 9.5$  Hz, 1 H, C3-H), 3.31 (ddd,  $J = 9.5, 4.4, 1.9$  Hz, 1 H, C5-H), 3.27 (app t,  $J = 9.5$  Hz, 1 H, C2-H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  156.8, 151.2, 138.9, 138.8, 138.3, 138.22, 138.20, 136.9, 134.4, 128.66, 128.56, 128.54, 128.4, 128.32, 128.29, 128.25, 128.1, 127.91, 127.89, 127.86, 127.77, 127.72, 127.6, 127.53, 127.45, 127.42, 127.0, 125.9, 125.8, 124.8, 113.8 (C12), 109.5, 107.5, 86.5 (C5 or C2), 86.4 (C5 or C2), 78.7, 78.6, 78.7, 78.6, 75.4 (Bn C), 74.4 (Bn C), 74.3 (Bn C), 73.4 (Bn C), 72.4 (Bn C), 71.9 (Bn C), 71.1 (Bn C), 69.6 (C6).



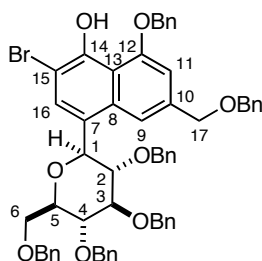
**3.54**

**(2*R*,3*R*,4*S*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-2-(benzyloxymethyl)-6-(5-(methylthio)furan-2-yl)tetrahydro-2*H*-pyran (3.54). (KP4-251).** A solution of *s*-BuLi in cyclohexane (1.47 M, 2.3 mL, 3.42 mmol) was added dropwise to furan **3.18** (1.55 g, 2.63 mmol) in THF (25 mL) at  $-78$  °C and the mixture was stirred for 3.5 h. Dimethyl

disulfide (330  $\mu$ L, 3.68 mmol) was then added dropwise. The cold bath was allowed to warm to rt over a 9 h period, and stirring was continued at rt for 8 h. Brine (20 mL) was added, and the layers were separated. The aqueous layer was extracted with Et<sub>2</sub>O (3 x 20 mL), and the combined organic layers were dried (MgSO<sub>4</sub>) and concentrated. The residue was recrystallized from EtOH to give 1.04 g (62%) of **3.54** as pale yellow needles: mp = 80–82 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.34–7.21 (comp, 16 H), 7.20–7.14 (comp, 2 H), 7.03–7.01 (comp, 2 H), 6.43 (d,  $J$  = 3.2 Hz, 1 H), 6.41 (d,  $J$  = 3.2 Hz, 1 H), 4.93 (d,  $J$  = 11.2 Hz, 1 H), 6.41 (d,  $J$  = 3.2 Hz, 1 H), 4.93 (d,  $J$  = 11.2 Hz, 1 H), 4.84 (d,  $J$  = 10.7 Hz, 1 H), 4.59 (d,  $J$  = 12.2 Hz, 1 H), 4.58 (d,  $J$  = 10.7 Hz, 1 H), 4.54 (d,  $J$  = 10.5 Hz, 1 H), 4.53 (d,  $J$  = 12.2 Hz, 1 H), 4.28 (d,  $J$  = 9.8 Hz, 1 H), 4.11 (d,  $J$  = 10.5 Hz, 1 H), 3.88 (app t,  $J$  = 8.8 Hz, 1 H), 3.76–3.68 (comp, 4 H), 3.56 (ddd,  $J$  = 6.3, 4.2, 2.2 Hz, 1 H), 2.37 (s, 3 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  153.7, 147.6, 138.7, 138.15, 138.06, 137.8, 128.4, 128.33, 128.31, 128.10, 128.07, 128.0, 127.9, 127.8, 127.7, 127.65, 127.58, 115.2, 111.7, 86.6, 81.2, 79.4, 78.0, 75.6, 75.1, 74.83, 74.77, 73.5, 69.0, 18.9; IR (neat) 1496, 1453, 1096, 1068; mass spectrum (CI)  $m/z$  637.2620 [C<sub>36</sub>H<sub>41</sub>O<sub>6</sub>S (M+1) requires 637.2624], 488, 487 (base).

**NMR Assignments:** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.34–7.21 (comp, 16 H, Ph C-H), 7.20–7.14 (comp, 2 H, Ph C-H), 7.03–7.01 (comp, 2 H, Ph C-H), 6.43 (d,  $J$  = 3.2 Hz, 1 H, C8-H or C9-H), 6.41 (d,  $J$  = 3.2 Hz, 1 H, C8-H or C9-H), 4.93 (d,  $J$  = 11.2 Hz, 1 H, Bn C-H), 6.41 (d,  $J$  = 3.2 Hz, 1 H, Bn C-H), 4.93 (d,  $J$  = 11.2 Hz, 1 H, Bn C-H), 4.84 (d,  $J$  = 10.7 Hz, 1 H, Bn C-H), 4.59 (d,  $J$  = 12.2 Hz, 1 H, Bn C-H), 4.58 (d,  $J$  = 10.7 Hz, 1 H, Bn C-H), 4.54 (d,  $J$  = 10.5 Hz, 1 H, Bn C-H), 4.53 (d,  $J$  = 12.2 Hz, 1 H, Bn C-H), 4.28 (d,  $J$  = 9.8 Hz, 1 H), 4.11 (d,  $J$  = 10.5 Hz, 1 H, Bn C-H), 3.88 (app t,  $J$  = 8.8 Hz, 1 H), 3.76–3.68 (comp, 4 H), 3.56 (ddd,  $J$  = 6.3, 4.2, 2.2 Hz, 1 H), 2.37 (s, 3 H, C11-H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  153.7, 147.6, 138.7, 138.15, 138.06, 137.8, 128.4, 128.33,

128.31, 128.10, 128.07, 128.0, 127.9, 127.8, 127.7, 127.65, 127.58, 115.2, 111.7, 86.6, 81.2, 79.4, 78.0, 75.6, 75.1, 74.83, 74.77, 73.5, 69.0, 18.9.

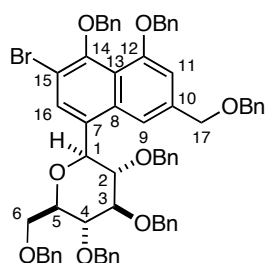


3.56

**4-((2*S*,3*S*,4*R*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-6-((benzyloxy)methyl)-tetrahydro-2*H*-pyran-2-yl)-8-(benzyloxy)-6-((benzyloxy)methyl)-2-bromonaphthalen-1-ol (3.56).** (KP4-112). Pyridinium bromide perbromide (26 mg, 0.081 mmol) was added to a solution of **3.37** in CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL) at 0 °C, and the mixture was stirred for 15 min. The ice bath was removed and stirring was continued for 15 min. A saturated solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (3 mL) and Et<sub>2</sub>O (5 mL) were added, and the layers were separated. The organic layer was washed with Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (2 x 3 mL) and H<sub>2</sub>O (2 x 3 mL), dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with Et<sub>2</sub>O/hexanes (1:3) to give 68 mg (95%) of bromophenol **3.56**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 10.30 (s, 1 H), 7.84 (s, 1 H), 7.74 (s, 1 H), 7.51-7.48 (comp, 2 H), 7.45-7.21 (comp, 23 H), 7.10-7.00 (comp, 4 H), 6.63-6.61 (comp, 2 H), 5.28 (comp, 3 H), 4.72 (s, 1 H), 4.66 (d, *J* = 10.9 Hz, 1 H), 4.61 (d, *J* = 12.0 Hz, 1 H), 4.53 (d, *J* = 12.0 Hz, 1 H), 4.50 (s, 2 H), 4.42 (s, 2 H), 4.25 (d, *J* = 10.2 Hz, 1 H), 4.25 (d, *J* = 10.2 Hz, 1 H), 3.87-3.74 (comp, 5 H), 3.64-3.63 (m, 1 H), 3.59 (d, *J* = 10.3 Hz, 1 H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 155.2, 151.1, 140.6, 138.7, 138.4, 138.3, 138.1, 137.3, 136.6, 134.6,

134.6, 133.6, 138.7, 138.4, 138.3, 138.1, 137.3, 136.6, 134.6, 133.6, 129.2, 129.1, 128.5, 128.44, 128.37, 128.3, 128.0, 127.98, 127.8, 127.7, 127.6, 127.5, 129.17, 129.15, 128.47, 128.44, 128.37, 128.3, 127.99, 127.98, 127.8, 127.75, 127.74, 127.6, 127.53, 127.51; 105.49, 86.99, 79.5, 78.2, 75.8, 75.2, 74.8, 73.3, 72.2, 72.13, 72.06, 69.0; IR (neat) 3336, 1609, 1454, 1360, 1136, 1095, 1068, 1028  $\text{cm}^{-1}$ ; mass spectrum (ESI)  $m/z$  993.2973 [ $\text{C}_{59}\text{H}_{55}\text{O}_8\text{NaBr}^+$  requires 993.3003].

**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  10.30 (s, 1 H, OH), 7.84 (s, 1 H), 7.74 (s, 1 H), 7.51-7.48 (comp, 2 H), 7.45-7.21 (comp, 23 H, Ph C-H and C11-H), 7.10-7.00 (comp, 4 H), 6.63-6.61 (comp, 2 H, C9-H), 5.28 (comp, 3 H, Bn C-H), 4.72 (s, 1 H), 4.66 (d,  $J = 10.9$  Hz, 1 H, Bn C-H), 4.61 (d,  $J = 12.0$  Hz, 1 H, Bn C-H), 4.53 (d,  $J = 12.0$  Hz, 1 H, Bn C-H), 4.50 (s, 2 H, Bn C-H), 4.42 (s, 2 H, Bn C-H), 4.25 (d,  $J = 10.2$  Hz, 1 H, Bn C-H), 4.25 (d,  $J = 10.2$  Hz, 1 H, Bn C-H), 3.87-3.74 (comp, 5 H), 3.64-3.63 (m, 1 H), 3.59 (d,  $J = 10.3$  Hz, 1 H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  155.2, 151.1, 140.6, 138.7, 138.4, 138.3, 138.1, 137.3, 136.6, 134.6, 134.6, 133.6, 138.7, 138.4, 138.3, 138.1, 137.3, 136.6, 134.6, 133.6, 129.2, 129.1, 128.5, 128.44, 128.37, 128.3, 128.0, 127.98, 127.8, 127.7, 127.6, 127.5, 129.17, 129.15, 128.47, 128.44, 128.37, 128.3, 127.99, 127.98, 127.8, 127.75, 127.74, 127.6, 127.53, 127.51, 105.49, 86.99, 79.5, 78.2, 75.8, 75.2, 74.8, 73.3, 72.2, 72.13, 72.06, 69.0.

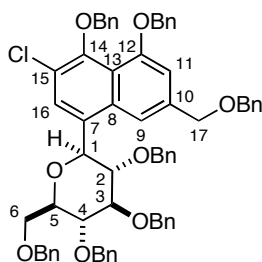


**3.57**

**(2*S*,3*S*,4*R*,5*R*,6*R*)-2-(1,8-Bis(benzyloxy)-6-((benzyloxy)methyl)-2-bromonaphthalen-4-yl)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-tetrahydro-2*H*-pyran (3.57). (KP4-106).** NaH (10 mg, 0.25 mmol, 60% dispersion) was added to a solution of phenol **3.56** (120 mg, 0.12 mmol) and BnBr (31 mg, 0.19 mmol, 23  $\mu$ L) in DMF (1 mL), and the solution was stirred for 1 h, at which point EtOAc (5 mL) and H<sub>2</sub>O (4 mL) were added. The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with Et<sub>2</sub>O/hexanes (1:5) to give 80 mg (62%) of naphthalene **3.57**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.88 (comp, 2 H), 7.39–7.16 (comp, 25 H), 7.08–6.99 (comp, 4 H), 6.56 (br s, 2 H), 5.19 (s, 2 H), 5.03–5.00 (comp, 1 or 2 H), 4.96 (d, *J* = 10.9 Hz, 1 H), 4.90 (d, *J* = 10.9 Hz, 1 H), 4.89 (s, 1 H), 4.65 (d, *J* = 10.6 Hz, 1 H), 4.62 (d, *J* = 12.3 Hz, 1 H), 4.54 (d, *J* = 12.3 Hz, 1 H), 4.48 (s, 2 H), 4.37 (s, 2 H), 4.25 (d, *J* = 10.3 Hz, 1 H), 3.87–3.74 (comp, 4 H), 3.68–3.64 (m, 1 H), 3.54 (3.54, d, *J* = 10.3 Hz, 1 H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  155.3, 138.7, 138.3, 138.2, 137.4, 137.2, 136.8, 136.5, 134.5, 138.7, 138.3, 138.2, 137.4, 137.2, 136.8, 136.5, 134.5, 128.5, 128.44, 128.40, 128.37, 128.3, 128.1, 128.0, 127.9, 127.85, 127.82, 127.77, 127.7, 127.63, 127.56, 127.53, 127.49, 121.8, 115.3, 108.4, 96.1, 86.9, 79.5, 78.2, 76.1, 75.8, 75.2, 74.8, 73.3, 72.1, 71.9, 71.7, 69.0; IR

(neat) 1570, 1453, 1094, 1067; mass spectrum (ESI)  $m/z$  1083.3442 [ $C_{66}H_{61}O_8BrNa^+$  requires 1083.346].

**NMR Assignments:**  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.88 (comp, 2 H), 7.39–7.16 (comp, 25 H), 7.08–6.99 (comp, 4 H), 6.56 (br s, 2 H), 5.19 (s, 2 H, Bn C-H), 5.03–5.00 (comp, 2 H, Bn C-H), 4.96 (d,  $J = 10.9$  Hz, 1 H, Bn C-H), 4.90 (d,  $J = 10.9$  Hz, 1 H, Bn C-H), 4.89 (s, 1 H), 4.65 (d,  $J = 10.6$  Hz, 1 H, Bn C-H), 4.62 (d,  $J = 12.3$  Hz, 1 H, Bn C-H), 4.54 (d,  $J = 12.3$  Hz, 1 H, Bn C-H), 4.48 (s, 2 H, Bn C-H), 4.37 (s, 2 H, Bn C-H), 4.25 (d,  $J = 10.3$  Hz, 1 H), 3.87–3.74 (comp, 4 H), 3.68–3.64 (m, 1 H), 3.54 (3.54, d,  $J = 10.3$  Hz, 1 H) ppm;  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  155.3 (C14), 138.7, 138.3, 138.2, 137.4, 137.2, 136.8, 136.5, 134.5, 138.7, 138.3, 138.2, 137.4, 137.2, 136.8, 136.5, 134.5, 128.5, 128.44, 128.40, 128.37, 128.3, 128.1, 128.0, 127.9, 127.85, 127.82, 127.77, 127.7, 127.63, 127.56, 127.53, 127.49, 121.8, 115.3 (C11), 108.4, 96.1, 86.9, 79.5, 78.2, 76.1, 75.8, 75.2, 74.8, 73.3, 72.1, 71.9, 71.7, 69.0.



**3.60**

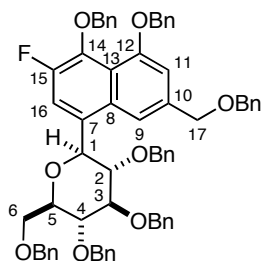
**(2*S*,3*S*,4*R*,5*R*,6*R*)-2-(1,8-Bis(benzyloxy)-6-((benzyloxy)methyl)-2-chloronaphthalen-4-yl)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-tetrahydro-2*H*-pyran (3.60). (KP3-291).**  $SO_2Cl_2$  was added to a solution of **3.37** (15 mg, 0.017 mmol) and benzylmethylamine (0.8 mg, 0.065 mmol, 1  $\mu$ L) in  $PhCH_3$  at 70  $^\circ C$ . The mixture was stirred for 1 h and cooled to rt. A saturated solution of  $NaHCO_3$  (1 mL) and EtOAc

(1 mL) were added. The layers were separated, and the organic layer was washed with 2 N HCl (1 mL) and brine (1 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue was purified by flash chromatography, eluting with Et<sub>2</sub>O/hexanes (1:4) to give 9 mg (56%) of **3.59**.

NaH (1 mg, 0.022 mmol, 60% dispersion) was added to a solution of phenol **3.59** (10 mg, 0.011 mmol) and BnBr (4 mg, 0.022 mmol, 3  $\mu$ L) in DMF (0.5 mL), and the mixture was stirred for 3 h, whereupon H<sub>2</sub>O (3 mL) and EtOAc (3 mL) were added. The layers were separated, and the organic layer was washed with H<sub>2</sub>O (2 x 3 mL) and brine (2 x 3 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue was purified by flash chromatography, eluting with Et<sub>2</sub>O/hexanes (1:4) to give 7 mg (64%) of **3.60**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.82 (s, 1 H), 7.72 (s, 1 H), 7.42-6.97 (comp, 33 H), 6.55-6.54 (comp, 3 H), 5.20 (s, 2 H), 5.01 (d,  $J$  = 12.3 Hz, 1 H), 5.00 (d,  $J$  = 12.3 Hz, 1 H), 4.95 (d,  $J$  = 10.9 Hz, 1 H), 4.89 (d,  $J$  = 10.9 Hz, 1 H), 4.88 (d,  $J$  = 10.6 Hz, 1 H), 4.65 (d,  $J$  = 10.6 Hz, 1 H), 4.62 (d,  $J$  = 12.3 Hz, 1 H), 4.54 (d,  $J$  = 12.3 Hz, 1 H), 4.49 (s, 2 H), 4.38 (s, 2 H), 4.24 (d,  $J$  = 10.3 Hz, 1 H), 3.86-3.74 (comp, 5 H), 3.69-3.64 (m, 1 H), 3.54 (d,  $J$  = 10.3 Hz, 1 H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  140.1, 138.7, 138.34, 138.26, 137.4, 137.2, 136.7, 136.6, 128.5, 128.44, 128.43, 128.41, 128.37, 128.21, 128.15, 127.97, 127.96, 127.86, 127.80, 127.78, 127.7, 127.64, 127.57, 127.54, 108.3, 86.9, 79.6, 78.2, 77.3, 77.2, 77.0, 76.9, 76.8, 76.2, 75.7, 75.1, 74.8, 73.3, 72.1, 71.9, 71.7, 69.0, 86.9, 79.6, 78.2, 77.3, 76.2, 75.7, 75.1, 74.8, 73.3, 72.1, 71.9, 71.7, 69.0; mass spectrum (ESI)  $m/z$  1039.3947 [C<sub>66</sub>H<sub>61</sub>ClNaO<sub>8</sub><sup>+</sup> requires 1039.3947].

**NMR Assignments:** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.82 (s, 1 H), 7.72 (s, 1 H), 7.42-6.97 (comp, 33 H, Ph C-H), 6.55-6.54 (comp, 3 H, Ph C-H), 5.20 (s, 2 H), 5.01 (d,  $J$  = 12.3 Hz, 1 H, Bn C-H), 5.00 (d,  $J$  = 12.3 Hz, 1 H, Bn C-H), 4.95 (d,  $J$  = 10.9 Hz, 1 H, Bn C-H), 4.89 (d,  $J$  = 10.9 Hz, 1 H, Bn C-H), 4.88 (d,  $J$  = 10.6 Hz, 1 H, Bn C-H), 4.65 (d,

$J = 10.6$  Hz, 1 H, Bn C-H), 4.62 (d,  $J = 12.3$  Hz, 1 H, Bn C-H), 4.54 (d,  $J = 12.3$  Hz, 1 H, Bn C-H), 4.49 (s, 2 H, Bn C-H), 4.38 (s, 2 H, Bn C-H), 4.24 (d,  $J = 10.3$  Hz, 1 H), 3.86–3.74 (comp, 5 H), 3.69–3.64 (m, 1 H), 3.54 (d,  $J = 10.3$  Hz, 1 H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  140.1, 138.7, 138.34, 138.26, 137.4, 137.2, 136.7, 136.6, 128.5, 128.44, 128.43, 128.41, 128.37, 128.21, 128.15, 127.97, 127.96, 127.86, 127.80, 127.78, 127.7, 127.64, 127.57, 127.54, 108.3, 86.9, 79.6, 78.2, 77.3, 77.2, 77.0, 76.9, 76.8, 76.2, 75.7, 75.1, 74.8, 73.3, 72.1, 71.9, 71.7, 69.0, 86.9, 79.6, 78.2, 77.3, 76.2, 75.7, 75.1, 74.8, 73.3, 72.1, 71.9, 71.7, 69.0.



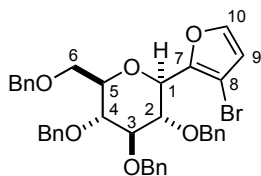
**3.71**

**(2*S*,3*S*,4*R*,5*R*,6*R*)-2-(1,8-Bis(benzyloxy)-6-((benzyloxy)methyl)-2-fluoronaphthalen-4-yl)-3,4,5-tris(benzyloxy)-6-((benzyloxy)methyl)-tetrahydro-2*H*-pyran (3.71). (KP4-106).** *n*-BuLi (0.096, 385  $\mu\text{L}$ , 0.25 M) was added dropwise to bromide **3.57** (93 mg, 0.088 mmol) in THF (1.5 mL) at  $-78$   $^\circ\text{C}$ . The mixture was stirred for 0.5 h, whereupon NFS **3.70** in THF (0.5 mL) was added dropwise, and stirring was continued at  $-78$   $^\circ\text{C}$  for 2 h. The mixture was warmed to rt and  $\text{H}_2\text{O}$  (4 mL) and  $\text{Et}_2\text{O}$  (2 mL) were added. The layers were separated, and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 x 2 mL), and the combined organic layers were dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with  $\text{Et}_2\text{O}$ /hexanes (1:6). The crude product was recrystallized from  $\text{EtOH}$  (2 x) to give



fluoride **45**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.79 (br s, 1 H), 7.48–7.46 (comp, 2 H), 7.36–7.21 (comp, 24 H), 7.05–6.93 (comp, 4 H), 6.52 (br d,  $J = 5.0$  Hz, 1 H), 5.20 (s, 2 H), 5.04 (d,  $J = 4.4$  Hz, 1 H), 5.00 (d,  $J = 4.4$  Hz, 1 H), 4.96–4.88 (comp, 3 H), 4.68–4.60 comp, 4 H), 4.56–4.51 (comp, 3 H), 4.40 (d,  $J = 12.0$  Hz, 1 H), 4.38 (d,  $J = 12.0$  Hz, 1 H), 4.21 (d,  $J = 10.4$  Hz, 1 H), 3.86–5.75 (comp, 6 H), 3.68–3.66 (m, 1 H), 3.51 (d,  $J = 10.4$  Hz, 1 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  156.0, 155.9, 152.5, 141.9, 140.9, 138.72, 138.66, 138.5, 138.42, 138.35, 137.4, 137.3, 137.2, 136.8, 135.4, 134.4, 131.5, 128.6, 128.5, 128.43, 128.42, 128.41, 128.40, 128.36, 128.3, 128.17, 128.16, 128.14, 127.95, 127.93, 127.91, 127.89, 127.86, 127.81, 127.76, 127.72, 127.70, 127.62, 127.60, 127.56, 127.0, 121.9, 107.9, 86.9, 79.5, 78.3, 77.4, 75.7, 75.1, 75.0, 74.8, 73.4, 72.2, 72.1, 71.9, 71.8, 71.5, 69.1, 65.4; mass spectrum (ESI)  $m/z$  1023.4243 [ $\text{C}_{66}\text{H}_{61}\text{O}_8\text{FNa}^+$  requires 1023.429].

**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.79 (br s, 1 H), 7.48–7.46 (comp, 2 H), 7.36–7.21 (comp, 24 H, Ph C-H), 7.05–6.93 (comp, 4 H, Ph C-H), 6.52 (br d,  $J = 5.0$  Hz, 1 H), 5.20 (s, 2 H, Bn C-H), 5.04 (d,  $J = 4.4$  Hz, 1 H), 5.00 (d,  $J = 4.4$  Hz, 1 H), 4.96–4.88 (comp, 3 H), 4.68–4.60 comp, 4 H), 4.56–4.51 (comp, 3 H), 4.40 (d,  $J = 12.0$  Hz, 1 H, Bn C-H), 4.38 (d,  $J = 12.0$  Hz, 1 H, Bn C-H), 4.21 (d,  $J = 10.4$  Hz, 1 H), 3.86–5.75 (comp, 6 H), 3.68–3.66 (m, 1 H), 3.51 (d,  $J = 10.4$  Hz, 1 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  156.0, 155.9, 152.5, 141.9, 140.9, 138.72, 138.66, 138.5, 138.42, 138.35, 137.4, 137.3, 137.2, 136.8, 135.4, 134.4, 131.5, 128.6, 128.5, 128.43, 128.42, 128.41, 128.40, 128.36, 128.3, 128.17, 128.16, 128.14, 127.95, 127.93, 127.91, 127.89, 127.86, 127.81, 127.76, 127.72, 127.70, 127.62, 127.60, 127.56, 127.0, 121.9, 107.9, 86.9, 79.5, 78.3, 77.4, 75.7, 75.1, 75.0, 74.8, 73.4, 72.2, 72.1, 71.9, 71.8, 71.5, 69.1, 65.4



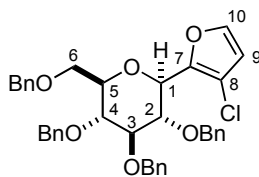
**3.102**

**(2*R*,3*R*,4*S*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-2-(benzyloxymethyl)-6-(3-bromofuran-2-yl)tetrahydro-2*H*-pyran (3.102).** (KP5-71). 3-Bromofuran (159 mg, 1.08 mmol, 97  $\mu$ L) was added dropwise to a solution of LDA (1.18 mmol, 2.7 mL, 0.44 M) at  $-78$   $^{\circ}$ C and the solution was stirred for 2.5 h, whereupon a solution of lactone **3.100** (530 mg, 0.98 mmol) in THF (2 mL) was added dropwise. The mixture was stirred for 10 min at  $-78$   $^{\circ}$ C, the cold bath was removed, and stirring was continued for 1 h, at which point H<sub>2</sub>O (5 mL) and Et<sub>2</sub>O (7 mL) were added and the layers were separated. The aqueous layer was extracted with Et<sub>2</sub>O (3 x 5 mL). The combined organics were washed with brine (15 mL), dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue was dried under vacuum and used directly in the next step.

TMSOTf (239 mg, 1.08 mmol, 195  $\mu$ L) was added, dropwise over 20 min, to the crude product and Et<sub>3</sub>SiH (375 mg, 3.23 mmol, 520  $\mu$ L) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) at  $-40$   $^{\circ}$ C and the reaction was stirred for 5 min, whereupon NaHCO<sub>3</sub> (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL), dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. Recrystallization from EtOH afforded 369 mg (56%) of glycosyl furan **3.102**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.37 (d,  $J$  = 1.9 Hz, 1 H), 7.33–7.21 (comp, 16 H), 7.17–7.15 (comp, 2 H), 7.04–7.03 (comp, 2 H), 6.45 (d,  $J$  = 1.9 Hz, 1 H), 4.91 (d,  $J$  = 11.0 Hz, 1 H), 4.86 (d,  $J$  = 10.9 Hz, 1 H), 4.84 (d,  $J$  = 10.3 Hz, 1 H), 4.60 (d,  $J$  = 12.5 Hz, 1 H), 4.58 (d,  $J$  = 11.0 Hz, 1 H), 4.53–4.46 (comp, 3 H), 4.06 (d,  $J$  = 10.6 Hz, 1 H), 3.94 (dd,  $J$  = 9.7, 9.0 Hz, 1 H), 3.78–3.70

(comp, 4 H), 3.58 (ddd,  $J = 9.7, 3.8, 2.5$  Hz, 1 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  148.0, 142.7, 138.6, 138.2, 138.1, 137.7, 128.39, 128.38, 128.1, 128.0, 127.8, 127.74, 127.70, 127.6, 127.5, 114.3, 100.9, 86.6, 80.4, 79.6, 77.9, 75.7, 75.1, 74.6, 73.5, 72.6; mass spectrum (CI)  $m/z$  669.1813 [ $\text{C}_{38}\text{H}_{37}\text{BrO}_6$  (M+1) requires 669.1812]; IR (neat) 1143, 1095, 1058.

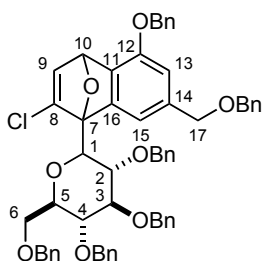
**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37 (d,  $J = 1.9$  Hz, 1 H, C 10-H), 7.33–7.21 (comp, 16 H, Ph C-H), 7.17–7.15 (comp, 2 H, Ph C-H), 7.04–7.03 (comp, 2 H, Ph C-H), 6.45 (d,  $J = 1.9$  Hz, 1 H, C9- H), 4.91 (d,  $J = 11.0$  Hz, 1 H, Bn C-H), 4.86 (d,  $J = 10.9$  Hz, 1 H, Bn C-H), 4.84 (d,  $J = 10.3$  Hz, 1 H, Bn C-H), 4.60 (d,  $J = 12.5$  Hz, 1 H, Bn C-H), 4.58 (d,  $J = 11.0$  Hz, 1 H, Bn C-H), 4.53–4.46 (comp, 3 H, Bn C-H), 4.06 (d,  $J = 10.6$  Hz, 1 H), 3.94 (dd,  $J = 9.7, 9.0$  Hz, 1 H), 3.78–3.70 (comp, 4 H), 3.58 (ddd,  $J = 9.7, 3.8, 2.5$  Hz, 1 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  148.0, 142.7 (C10), 138.6, 138.2, 138.1, 137.7, 128.39, 128.38, 128.1, 128.0, 127.8, 127.74, 127.70, 127.6, 127.5, 114.3 (C9), 100.9, 86.6, 80.4, 79.6, 77.9, 75.7, 75.1, 74.6, 73.5, 72.6.



**3.103**

**(2R,3R,4S,5R,6R)-3,4,5-Tris(benzyloxy)-2-(benzyloxymethyl)-6-(3-chlorofuran-2-yl)tetrahydro-2H-pyran (3.103).** (KP5-73). *n*-BuLi was added dropwise to bromide **3.102** (369 mg, 0.551 mmol) in THF (3 mL) at  $-78$  °C and the mixture was stirred for 20 min, whereupon  $\text{C}_2\text{Cl}_6$  (261 mg, 1.10 mmol) in THF (1.5 mL) was added and stirring was continued at  $-78$  °C for 20 min. The cold bath was

removed, and stirring was continued for 1.5 h, at which time NaHCO<sub>3</sub> (5 mL) was added and the layers were separated. The aqueous layer was extracted with Et<sub>2</sub>O (3 x 3 mL) then the combined organic layers were washed with brine (10 mL) dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 1:5 Et<sub>2</sub>O/hexanes to give 190 mg (55%) of chloride **3.103**. Spectra were in agreement with those previously reported for this compound.<sup>95</sup>

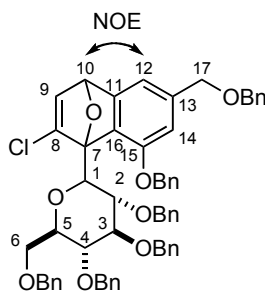


**3.104**

**Cycloadduct (3.104).** (**KP5-81**). *n*-BuLi (130  $\mu$ L, 0.30 mmol, 2.33 M) was added, dropwise over 10 min, to a mixture of furan **3.103** (125 mg, 0.200 mmol) and triflate **3.49** (39 mg, 0.067 mmol) in THF (1 mL) at  $-78$   $^{\circ}$ C and the mixture was stirred for 20 min, whereupon NH<sub>4</sub>Cl (2 mL) and Et<sub>2</sub>O (2 mL) were added and the layers were separated. The aqueous layer was extracted with Et<sub>2</sub>O (3 x 2 mL), and the organic layers were combined, washed with brine (10 mL), dried (MgSO<sub>4</sub>), and concentrated under reduced pressure. Flash chromatography, eluting with Et<sub>2</sub>O/hexanes (1:10 then 1:5) gave 13 mg (21%) of **3.104**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.38–7.16 (comp, 37 H), 7.10 (s, 1 H), 6.74 (s, 1 H), 6.61 (d, *J* = 2.0 Hz, 1 H), 6.00 (d, *J* = 2.0 Hz, 1 H), 5.07 (s, 2 H), 4.93 (d, *J* = 11.0 Hz, 1 H), 4.88 (d, *J* = 11.0 Hz, 1 H), 4.84–4.80 (comp, 2 H), 4.72 (d, *J* = 10.5 Hz, 1 H), 4.55 (d, *J* = 11.0 Hz, 1 H), 4.41–4.38 (comp, 5 H), 4.27 (s, 2 H), 3.90–3.83 (comp, 2 H), 3.68–3.65 (comp, 2 H), 3.53–3.47 (comp, 2 H); <sup>13</sup>C NMR (125 MHz,

CDCl<sub>3</sub>)  $\delta$  151.7, 150.1, 149.4, 138.6, 138.44, 138.37, 138.3, 138.0, 137.9, 137.0, 135.6, 135.4, 128.6, 128.4, 128.39, 128.35, 128.27, 128.13, 128.05, 128.01, 127.82, 127.79, 127.68, 127.62, 127.56, 127.49, 127.44, 127.41, 127.37, 116.7, 111.5, 93.9, 87.6, 79.9, 79.6, 78.8, 78.5, 75.8, 75.0, 74.6, 73.1, 72.1, 72.0, 70.7, 69.4; IR (neat) 1453, 1148, 1095, 1028 cm<sup>-1</sup>; mass spectrum (CI)  $m/z$  926.3584 [C<sub>59</sub>H<sub>55</sub>ClO<sub>8</sub> (M<sup>+</sup>) requires 926.3585].

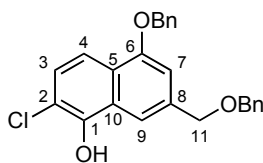
**NMR Assignments:** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.38–7.16 (comp, 37 H, Ph C-H), 7.10 (s, 1 H, C13-H), 6.74 (s, 1 H, C15-H), 6.61 (d,  $J$  = 2.0 Hz, 1 H, C9-H), 6.00 (d,  $J$  = 2.0 Hz, 1 H, C10-H), 5.07 (s, 2 H), 4.93 (d,  $J$  = 11.0 Hz, 1 H, Bn C-H), 4.88 (d,  $J$  = 11.0 Hz, 1 H, Bn C-H), 4.84–4.80 (comp, 2 H, Bn C-H), 4.72 (d,  $J$  = 10.5 Hz, 1 H, Bn C-H), 4.55 (d,  $J$  = 11.0 Hz, 1 H, Bn C-H), 4.41–4.38 (comp, 5 H, Bn C-H), 4.27 (s, 2 H, Bn C-H), 3.90–3.83 (comp, 2 H), 3.68–3.65 (comp, 2 H), 3.53–3.47 (comp, 2 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  151.7, 150.1, 149.4, 138.6, 138.44, 138.37, 138.3, 138.0, 137.9, 137.0, 135.6, 135.4, 128.6, 128.4, 128.39, 128.35, 128.27, 128.13, 128.05, 128.01, 127.82, 127.79, 127.68, 127.62, 127.56, 127.49, 127.44, 127.41, 127.37, 116.7 (C13), 111.5 (C15), 93.9, 87.6, 79.9, 79.6 (C10), 78.8, 78.5, 75.8 (Bn C), 75.0 (Bn C), 74.6, 73.1 (Bn C), 72.1 (Bn C), 72.0, 70.7, 69.4.



From the above procedure, 14 mg (23%) of the undesired regioisomer was isolated: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.35–7.22 (comp, 28 H), 7.18–7.15 (comp, 5 H),

7.11-7.10 (comp, 2 H), 6.92 (s, 1 H), 6.61 (d,  $J = 1.9$  Hz, 1 H), 6.59 (s, 1 H), 5.79 (d,  $J = 1.9$  Hz, 1 H), 4.92 (d,  $J = 11.0$  Hz, 1 H), 4.87 (d,  $J = 9.7$  Hz, 1 H), 4.86 (d,  $J = 9.1$  Hz, 1 H), 4.89 (d,  $J = 10.3$  Hz, 1 H), 4.76-4.73 (comp, 2 H), 4.56-4.54 (comp, 3 H), 4.57-4.47 (m, 1 H), 4.38 (d,  $J = 9.6$  Hz, 1 H), 4.36 (s, 2 H), 3.85 (t,  $J = 9.4$  Hz, 1 H), 3.78 (t,  $J = 11.3$  Hz, 1 H), 3.55-3.51 (comp, 2 H), 3.40 (dd,  $J = 11.3, 5.2$  Hz, 1 H), 3.24 (ddd,  $J = 10.0, 5.3, 2.1$  Hz, 1 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  153.3, 152.1, 150.6, 138.8, 138.5, 138.32, 138.31, 138.2, 137.2, 135.6, 133.5, 128.5, 128.4, 128.34, 128.32, 128.12, 128.11, 127.9, 127.82, 127.81, 127.7, 127.6, 127.5, 127.42, 127.40, 127.22, 127.21, 113.2, 110.9, 94.3, 87.4, 82.0, 79.8, 79.0, 78.9, 75.6, 75.2, 74.9, 74.7, 72.9, 72.3, 72.1, 69.8, 69.0; IR (neat) 1454, 1151, 1094, 1057  $\text{cm}^{-1}$ ; mass spectrum (CI)  $m/z$  927.3665 [ $\text{C}_{59}\text{H}_{55}\text{ClO}_8$  (M+1) requires 927.3664] (base), 892, 819.

**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35-7.22 (comp, 28 H, Ph C-H), 7.18-7.15 (comp, 5 H, Ph C-H), 7.11-7.10 (comp, 2 H, Ph C-H), 6.92 (s, 1 H, C12-H), 6.61 (d,  $J = 1.9$  Hz, 1 H, C14-H), 6.59 (s, 1 H, C14-H), 5.79 (d,  $J = 1.9$  Hz, 1 H, C10-H), 4.92 (d,  $J = 11.0$  Hz, 1 H, Bn C-H), 4.87 (d,  $J = 9.7$  Hz, 1 H, Bn C-H), 4.86 (d,  $J = 9.1$  Hz, 1 H, Bn C-H), 4.89 (d,  $J = 10.3$  Hz, 1 H, Bn C-H), 4.76-4.73 (comp, 2 H, Bn C-H), 4.56-4.54 (comp, 3 H, Bn C-H), 4.57-4.47 (m, 1 H), 4.38 (d,  $J = 9.6$  Hz, 1 H), 4.36 (s, 2 H), 3.85 (t,  $J = 9.4$  Hz, 1 H), 3.78 (t,  $J = 11.3$  Hz, 1 H), 3.55-3.51 (comp, 2 H), 3.40 (dd,  $J = 11.3, 5.2$  Hz, 1 H), 3.24 (ddd,  $J = 10.0, 5.3, 2.1$  Hz, 1 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  153.3, 152.1, 150.6, 138.8, 138.5, 138.32, 138.31, 138.2, 137.2, 135.6 (C9), 133.5, 128.5, 128.4, 128.34, 128.32, 128.12, 128.11, 127.9, 127.82, 127.81, 127.7, 127.6, 127.5, 127.42, 127.40, 127.22, 127.21, 113.2 (C12), 110.9 (C14), 94.3, 87.4, 82.0 (C10), 79.8, 79.0, 78.9, 75.6, 75.2, 74.9, 74.7, 72.9, 72.3, 72.1, 69.8, 69.0.

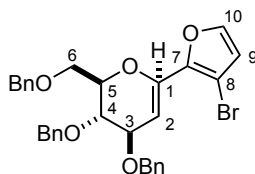


**3.106**

**5-(Benzyloxy)-7-(benzyloxymethyl)-2-chloronaphthalen-1-ol (3.106).** (KP5-79). ZnCl<sub>2</sub> (180 μL, 0.18 mmol, 1 M in Et<sub>2</sub>O) was added to **1.304** (17 mg, 0.018 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) and the mixture was heated at 85 °C for 1 h. The mixture was cooled to rt, whereupon NaHCO<sub>3</sub> (2 mL) and Et<sub>2</sub>O (2 mL) were added and the layers were separated. The aqueous layer was extracted with Et<sub>2</sub>O (3 x 2 mL), dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by flash chromatography, eluting with Et<sub>2</sub>O/hexanes (1:7) to afford 3 mg (43%) of **3.106**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.82 (dd, *J* = 9.0, 0.8 Hz, 1 H), 7.73 (s, 1 H), 7.50–7.49 (comp, 2 H), 7.41–7.38 (comp, 2 H), 7.35–7.34 (comp, 4 H), 7.31 (d, *J* = 9.0 Hz, 1 H), 7.31–7.27 (comp, 2 H), 6.99 (s, 1 H), 5.93 (br s, 1 H), 5.22 (s, 2 H), 4.69 (s, 2 H), 4.55 (s, 2 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 206.9, 154.8, 146.8, 138.2, 136.8, 128.6, 128.4, 128.0, 127.9, 127.7, 127.5, 125.3, 125.2, 125.1, 115.5, 115.0, 113.3, 105.8, 72.6, 72.1, 70.3; IR (neat) 3516, 3351, 1594, 1454, 1410, 1374, 1272, 1052; mass spectrum (CI) *m/z* 405.1256 [C<sub>25</sub>H<sub>22</sub>ClO<sub>3</sub> (M+1) requires 405.1257].

**NMR Assignments:** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.82 (d, *J* = 9.0 Hz, 1 H, C3-H), 7.73 (s, 1 H, C7-H), 7.50–7.49 (comp, 2 H), 7.41–7.38 (comp, 2 H), 7.35–7.34 (comp, 4 H), 7.31 (d, *J* = 9.0 Hz, 1 H, C4-H), 7.31–7.27 (comp, 2 H), 6.99 (s, 1 H, C9-H), 5.93 (br s, 1 H, OH), 5.22 (s, 2 H, C11-H), 4.69 (s, 2 H, Bn C-H), 4.55 (s, 2 H, Bn C-H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 154.8, 146.8, 138.2, 136.8, 128.6, 128.4, 128.0, 127.9,

127.7, 127.5, 125.3, 125.2, 125.1 (C4), 115.5 (C3), 115.0, 113.3 (C7), 105.8 (C9), 72.6 (C11), 72.1 (Bn C), 70.3 (Bn C).



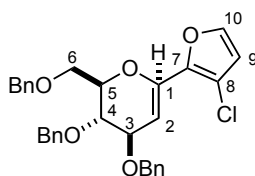
**3.109**

**(2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-6-(3-bromofuran-2-yl)-3,4-dihydro-2*H*-pyran (3.109). (KP5-114).** 3-Bromofuran (2.13 g, 14.5 mmol) was added dropwise over 3 min to a solution of LDA (0.66 M, 15.8 mmol, 24 mL) at  $-78\text{ }^{\circ}\text{C}$  and the mixture was stirred for 2.5 h, whereupon lactone **3.108** (5.70g, 13.2 mmol) in THF (15 mL) was added dropwise over 15 min. Stirring was continued for 2 h at  $-78\text{ }^{\circ}\text{C}$ , whereupon  $\text{Et}_3\text{N}$  (4.00 g, 39.6 mmol, 5.5 mL), a solution of DMAP (1.77 g, 15.8 mmol) in THF (12 mL), and TFAA (6.93, 33.0 mmol, 2.4 mL) were added sequentially and stirring was continued for 20 min. The cold bath was removed, and the mixture was stirred an additional 40 min.  $\text{NaHCO}_3$  (40 mL) was added, the layers were separated, and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 x 40 mL). The combined organic layers were washed with brine (100 mL), dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated. The residue was purified by flash chromatography, eluting with  $\text{Et}_2\text{O}$ /hexanes (1:15), affording 4.87 g (66%) of furyl glycol **3.109**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41–7.36 (comp, 16 H), 6.44 (d,  $J = 1.9$  Hz, 1 H), 5.63 (d,  $J = 3.8$  Hz, 1 H), 4.85 (d,  $J = 11.3$  Hz, 1 H), 4.70 (d,  $J = 11.3$  Hz, 1 H), 4.68 (d,  $J = 11.7$  Hz, 1 H), 4.65 (d,  $J = 12.2$  Hz, 1 H), 4.61 (d,  $J = 12.2$  Hz, 1 H), 4.60 (d,  $J = 11.7$  Hz, 1 H), 4.37 (dd,  $J = 6.2, 3.8$  Hz, 1 H), 4.00 (dd,  $J = 7.4, 6.2$  Hz, 1 H), 3.91 (dd,  $J = 11.0, 4.3$  Hz), 3.87 (dd,  $J = 11.0, 2.9$  Hz, 1 H);  $^{13}\text{C}$  NMR (125 MHz,



CDCl<sub>3</sub>)  $\delta$  144.8, 144.4, 142.2, 138.33, 138.26, 138.22, 128.41, 128.38, 128.3, 127.9, 127.8, 127.72, 127.70, 127.6, 127.5, 116.0, 98.8, 98.1, 77.7, 76.2, 74.0, 73.7, 73.6, 70.4, 68.3; IR (neat) 1496, 1454, 1099, 1027, 697 cm<sup>-1</sup>; mass spectrum (ESI)  $m/z$  561. 1276 [C<sub>31</sub>H<sub>29</sub>BrO<sub>5</sub>(M+1) requires 561.1277], 455, 454, 453 (base).

**NMR Assignments:** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.41–7.36 (comp, 16 H, Ph C-H, C10-H), 6.44 (d,  $J$  = 1.9 Hz, 1 H, C9-H), 5.63 (d,  $J$  = 3.8 Hz, 1 H, C2-H), 4.85 (d,  $J$  = 11.3 Hz, 1 H, Bn C-H), 4.70 (d,  $J$  = 11.3 Hz, 1 H, Bn C-H), 4.68 (d,  $J$  = 11.7 Hz, 1 H, Bn C-H), 4.65 (d,  $J$  = 12.2 Hz, 1 H, Bn C-H), 4.61 (d,  $J$  = 12.2 Hz, 1 H, Bn C-H), 4.60 (d,  $J$  = 11.7 Hz, 1 H, Bn C-H), 4.37 (dd,  $J$  = 6.2, 3.8 Hz, 1 H, C3-H), 4.00 (dd,  $J$  = 7.4, 6.2 Hz, 1 H, C4-H), 3.91 (dd,  $J$  = 11.0, 4.3 Hz, C6-H), 3.87 (dd,  $J$  = 11.0, 2.9 Hz, 1 H, C6-H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  144.8, 144.4, 142.2, 138.33, 138.26, 138.22, 128.41 (PhC), 128.38 (Ph C), 128.3 (Ph C), 127.9 (Ph C), 127.8 (Ph C), 127.72 (Ph C), 127.70 (Ph C), 127.6 (Ph C), 127.5 (Ph C), 116.0 (C9), 98.8 (C2), 98.1, 77.7 (C5), 76.2 (C3), 74.0 (C4), 73.7 (Bn C), 73.6 (Bn C), 70.4 (Bn C), 68.3 (C6).

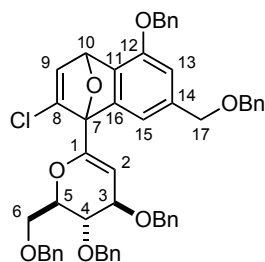


**3.110**

**(2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-6-(3-chlorofuran-2-yl)-3,4-dihydro-2*H*-pyran (3.110). (KP5-85).** *n*-BuLi (2.37 M, 1.52 mmol, 640  $\mu$ L) was added dropwise to bromide **3.109** (712 mg, 1.27 mmol) in THF (10 mL) at  $-78$  °C and the mixture was stirred for 10 min, at which point the cold bath was removed and stirring was continued for 1 h. A saturated solution of NaHCO<sub>3</sub> was added (10 mL) and the

layers were separated. The aqueous layer was extracted with Et<sub>2</sub>O (3 x 15 mL), and the organic layers were combined, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with Et<sub>2</sub>O/hexanes (1:19) to provide 598 mg (91%) of chloride **3.110**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.41–7.34 (comp, 16 H), 6.39 (d, *J* = 1.9 Hz, 1 H), 5.58 (d, *J* = 3.2 Hz, 1 H), 4.84 (d, *J* = 11.3 Hz, 1 H), 4.70–5.94 (comp, 5 H), 4.36 (dd, *J* = 6.2, 3.2 Hz, 1 H), 4.22 (ddd, *J* = 4.6, 3.2, 2.8 Hz, 1 H), 3.98 (dd, *J* = 8.5, 6.0 Hz, 1 H), 3.90 (dd, *J* = 11.0, 4.6 Hz, 1 H), 3.87 (dd, *J* = 11.0, 3.0 Hz, 1 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 144.5, 142.8, 141.5, 138.33, 138.27, 138.21, 128.41, 128.38, 128.32, 127.9, 127.8, 127.72, 127.67, 127.65, 127.5, 113.8, 113.7, 98.5, 77.6, 76.1, 74.0, 73.7, 73.5, 70.4, 68.2; mass spectrum (ESI) *m/z* 517.1783 [requires 517.1782], 409 (base); IR (neat) 1453, 1101, 1027 cm<sup>-1</sup>.

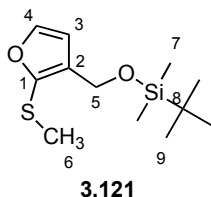
**NMR Assignments:** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.41–7.34 (comp, 16 H, Ph C,-H, C10-H), 6.39 (d, *J* = 1.9 Hz, 1 H, C9- H), 5.58 (d, *J* = 3.2 Hz, 1 H, C2-H), 4.84 (d, *J* = 11.3 Hz, 1 H, Bn C-H), 4.70-5.94 (comp, 5 H, Bn C-H), 4.36 (dd, *J* = 6.2, 3.2 Hz, 1 H, C3-H), 4.22 (ddd, *J* = 4.6, 3.2, 2.8 Hz, 1 H, C5-H), 3.98 (dd, *J* = 8.5, 6.0 Hz, 1 H, C4-H), 3.90 (dd, *J* = 11.0, 4.6 Hz, 1 H, C6-H), 3.87 (dd, *J* = 11.0, 3.0 Hz, 1 H, C6-H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 144.5, 142.8, 141.5, 138.33, 138.27, 138.21, 128.41 (Ph C), 128.38 (Ph C), 128.32 (Ph C), 127.9 (Ph C), 127.8 (Ph C), 127.72 (Ph C), 127.67 (Ph C), 127.65 (Ph C), 127.5 (Ph C), 113.8 (C9), 113.7 (C2), 98.5 (C5), 77.6 (C3), 76.1 (Bn C), 74.0, 73.7 (Bn C), 73.5 (Bn C), 70.4 (Bn C), 68.2 (C6).



**3.112**

**Cycloadduct (3.112). (KP5-99).** A solution of *n*-BuLi in hexanes (2.5 M, 24  $\mu$ L, 0.060 mmol, 2.5 M) was added dropwise to a solution of glycal **3.110** (52 mg, 0.10 mmol) and triflate **3.49** (29 mg, 0.050 mmol) in THF (1.0 mL) at  $-100$   $^{\circ}$ C and the mixture was transferred to a  $-78$   $^{\circ}$ C bath, which was allowed to warm to  $-55$   $^{\circ}$ C over a 20 min period, whereupon a saturated solution of  $\text{NH}_4\text{Cl}$  (3 mL) was added and the mixture warmed to rt.  $\text{Et}_2\text{O}$  (3 mL) was added and the layers were separated. The aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 x 2 mL), and the combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with  $\text{Et}_2\text{O}$ /hexanes (gradient column 1:20 / 1:15 / 1:10 / 1:3) to provide 11 mg (27%) of **3.112**: (major diastereomer)  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37-7.36 (comp, 4 H), 7.33-7.21 (comp, 21 H), 6.76 (s, 1 H), 6.71 (d,  $J = 2.1$  Hz, 1 H), 5.91 (d,  $J = 2.1$  Hz, 1 H), 5.41 (d,  $J = 2.9$  Hz, 1 H), 5.06 (s, 2 H), 4.83 (d,  $J = 11.4$  Hz, 1 H), 4.69 (d,  $J = 11.4$  Hz, 1 H), 4.66 (d,  $J = 11.7$  Hz, 1 H), 4.60 (d,  $J = 12.0$  Hz, 1 H), 4.57-5.52 (comp, 3 H), 4.34 (ddd,  $J = 8.2, 5.0, 3.5$  Hz, 1 H), 4.28 (dd,  $J = 6.0, 2.9$  Hz, 1 H), 4.00 (dd,  $J = 8.5, 7.0$  Hz, 1 H), 4.93-3.88 (comp, 3 H); (minor diastereomer)  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37-7.36 (comp, 4 H), 7.33-7.23 (comp, 17 H), 6.77 (s, 1 H), 6.70 (d,  $J = 2.0$  Hz, 1 H), 5.92 (d,  $J = 1.8$  Hz, 1 H), 5.38 (d,  $J = 2.6$  Hz, 1 H), 5.05 (s, 2 H), 4.86 (d,  $J = 11.2$  Hz, 1 H), 4.71 (d,  $J = 11.5$  Hz, 1 H), 4.66 (d,  $J = 11.5$  Hz, 1 H), 4.61 (d,  $J = 12.3$  Hz, 1 H), 4.57 (d,  $J = 12.3$  Hz, 1 H), 4.53 (d,  $J = 11.7$  Hz, 1 H), 4.39 (s, 1 H),

4.35 (dd,  $J = 6.5, 2.6$  Hz, 1 H), 4.32 (comp, 2 H), 4.27 (ddd,  $J = 8.8, , 4.1, 2.3$  Hz, 4.05 (d,  $J = 9.1, 6.5$  Hz, 1 H), 3.97 (d,  $J = 10.9, 4.1$  Hz, 1 H), 3.88 (d,  $J = 10.9, 2.3$  Hz, 1 H); mass spectrum (CI)  $m/z$  819.3086 [ $C_{52}H_{47}ClO_7$  (M+1) requires 819.3089], 713, 711, 611 (base).

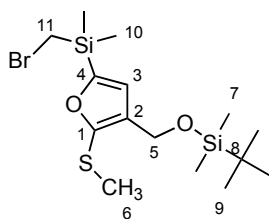


***tert*-Butyldimethyl((2-(methylthio)furan-3-yl)methoxy)silane (3.121) (KP5-279)**. A solution of *n*-BuLi in hexanes (2.5 M, 38 mL, 94 mmol) was added to 3-furanmethanol (4.5 g, 46 mmol, 4.2  $\mu$ L) in THF (250 mL) at  $-78$   $^{\circ}$ C, and the mixture was stirred for 1 h, whereupon the mixture was placed in a  $0$   $^{\circ}$ C bath and stirring was continued for 1 h. Dimethyl disulfide (923  $\mu$ L, 10.2 mmol) was added and the mixture was stirred at  $0$   $^{\circ}$ C for 4 h. The ice bath was removed, and the mixture was stirred for 16 h, at which point  $H_2O$  (800 mL) and  $Et_2O$  (800 mL) were added. The layers were separated, and organic layer was washed with brine (800 mL), dried ( $MgSO_4$ ), and concentrated under reduced pressure.

TBSCl (7.6 g, 51 mmol) was added to a solution of the residue from the previous reaction and imidazole (7.8 g, 115 mmol) in DMF (250 mL) and the mixture was stirred for 16 h, whereupon  $H_2O$  (1 L) and  $Et_2O$  (1 L mL) were added. The layers were mixed well, separated, and the organic layer was washed with brine (700 mL), dried ( $MgSO_4$ ), and concentrated. The residue was purified by flash chromatography, eluting with  $PhCH_2$ /hexanes (1:5) to afford 9.70 g (82%) of silane **3.121**:  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.41 (d,  $J = 2.1$  Hz, 1 H), 6.45 (d,  $J = 2.1$  Hz, 1 H), 4.59 (s, 2 H), 2.32 (s, 3 H), 0.90 (s,

9 H), 0.069 (s, 6 H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  144.5, 142.8, 129.3, 111.8, 57.4, 25.9, 23.9, 18.8, 18.3, -5.15. IR (neat) 1256, 1090, 1058, 837, 776  $\text{cm}^{-1}$ ; mass spectrum (ESI)  $m/z$  258.1180 [ $\text{C}_{12}\text{H}_{22}\text{O}_2\text{SSi}$  ( $\text{M}^+$ ) requires 258.1110].

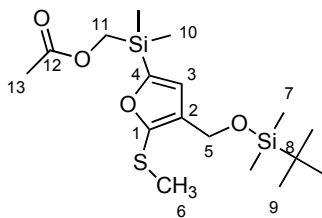
**NMR Assignments:**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41 (d,  $J = 2.1$  Hz, 1 H), 6.45 (d,  $J = 2.1$  Hz, 1 H), 4.59 (s, 2 H), 2.32 (s, 3 H), 0.90 (s, 9 H), 0.069 (s, 6 H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  144.5, 142.8, 129.3, 111.8, 57.4, 25.9, 23.9, 18.8, 18.3, -5.15.



**3.118**

**(Bromomethyl)(4-((*tert*-butyldimethylsilyloxy)methyl)-5-(methylthio)furan-2-yl)dimethylsilane (3.118). (KP5-186).** A solution of *n*-BuLi in hexanes (2.23 M, 150  $\mu\text{L}$ , 0.34 mmol) was added to furan **3.121** (80 mg, 0.31 mmol) in  $\text{Et}_2\text{O}$  (3 mL) at rt and the mixture was stirred for 2 h. Bromomethylchlorodimethylsilane (51  $\mu\text{L}$ , 0.37 mmol) was added dropwise, and the mixture was stirred for 12 h, whereupon a saturated solution of  $\text{NH}_4\text{Cl}$  (3 mL) was added. The layers were separated, and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 x 2 mL), dried ( $\text{MgSO}_4$ ), and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with  $\text{PhCH}_3$ /hexanes (1:5) to afford 101 mg (79%) of bromide **3.118** as a light oil:  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  6.76 (s, 1 H), 4.56 (s, 2 H), 2.60 (s, 2 H), 2.35 (s, 3 H), 0.90 (s, 9 H), 0.39 (s, 6 H), 0.075 (s, 6 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  159.3, 147.8, 128.4, 123.3, 57.4, 26.0, 18.4, 18.3, 15.6, -4.4, -5.2; IR (neat) 1253, 1082, 1054  $\text{cm}^{-1}$ ; mass spectrum (CI)  $m/z$  409.0686 [ $\text{C}_{15}\text{H}_{29}\text{BrO}_2\text{SSi}_2$  ( $\text{M}+1$ ) requires 409.0688], 395, 329 (base).

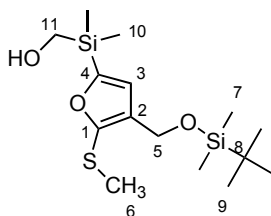
**NMR Assignments:**  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  6.76 (s, 1 H, C3-H), 4.56 (s, 2 H, C5-H), 2.60 (s, 2 H, C11-H), 2.35 (s, 3 H, C6-H), 0.90 (s, 9 H, C9-H), 0.39 (s, 6 H, C10-H), 0.075 (s, 6 H, C7-H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  159.3 (C1), 147.8 (C2), 128.4 (C4), 123.3 (C3), 57.4 (C5), 26.0 (C9), 18.4 (C8 or C6), 18.3 (C8 or C6), 15.6 (C11), -4.4 (C10), -5.2 (C7).



**3.127**

**((4-((*tert*-Butyldimethylsilyloxy)methyl)-5-(methylthio)furan-2-yl)dimethylsilyl)methyl acetate (3.127). (KP5-190).** A mixture of TBAI (227 mg, 0.615 mmol), NaOAc (126 mg, 1.54 mmol), and bromide **3.118** (126 mg, 0.307 mmol) in DMF (3 mL) was stirred at rt for 18 h, at whereupon the mixture was heated at 80 °C for 6 h. The mixture was cooled to rt,  $\text{H}_2\text{O}$  (6 mL) and  $\text{Et}_2\text{O}$  (6 mL) were added, and the layers were separated. The aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 x 4 mL), and then the combined  $\text{Et}_2\text{O}$  layers were washed with  $\text{H}_2\text{O}$  (10 mL) and brine (10 mL), dried ( $\text{MgSO}_4$ ), and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with  $\text{Et}_2\text{O}$ /hexanes (1:15) to yield 94 mg (79%) of acetate **3.127** as a light oil:  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  6.73 (s, 1 H), 4.56 (s, 2 H), 3.92 (s, 2 H), 2.35 (s, 3 H), 2.02 (s, 3 H), 0.90 (s, 9 H), 0.32 (s, 6 H), 0.073 (s, 6 H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  171.7, 159.3, 147.7, 128.3, 123.2, 57.5, 56.0, 20.7, 18.4, 18.3, -4.8, -5.2; IR (neat) 1744, 1253, 1222, 1082, 1053  $\text{cm}^{-1}$ ; mass spectrum (CI)  $m/z$  388.1562 [ $\text{C}_{17}\text{H}_{32}\text{O}_4\text{SSi}_2$  ( $\text{M}^+$ ) requires 388.1560].

**NMR Assignments:**  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  6.73 (s, 1 H, C3-H), 4.56 (s, 2 H, C5-H), 3.92 (s, 2 H, C11-H), 2.35 (s, 3 H, C6-H), 2.02 (s, 3 H, C13-H), 0.90 (s, 9 H, C9-H), 0.32 (s, 6 H, C10-H), 0.073 (s, 6 H, C7-H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  171.7 (C12), 159.3 (C1), 147.7 (C2), 128.3 (C4), 123.2 (C3), 57.5 (C5), 56.0 (C5), 20.7 (C13), 18.4 (C8 or C6), 18.3 (C8 or C6), -4.8 (C10), -5.2 (C7).



**3.128**

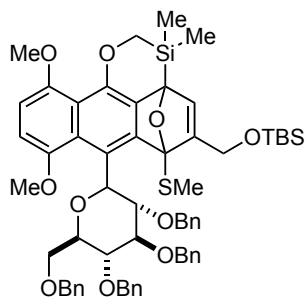
**((4-((*tert*-Butyldimethylsilyloxy)methyl)-5-(methylthio)furan-2-yl)dimethylsilyl)methanol (3.128). (KP5-235).** A solution of acetate **3.127** (59 mg, 0.152 mmol) in  $\text{Et}_2\text{O}$  (1 mL) was added dropwise to mixture of LAH (14 mg, 0.379 mmol) in  $\text{Et}_2\text{O}$  (0.5 mL) at 0 °C and the mixture was stirred for 15 min, whereupon  $\text{EtOAc}$  (1 mL) was added dropwise. The mixture was stirred an additional 10 min at 0 °C, and then  $\text{NH}_4\text{Cl}$  was added (2 mL) and stirring was continued at 0 °C for 10 min. The mixture was warmed to rt, and extracted with  $\text{Et}_2\text{O}$  (3 x 3 mL). The combined organic layers were washed with  $\text{H}_2\text{O}$  (2 mL) and brine (2 mL), dried ( $\text{MgSO}_4$ ), and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with  $\text{Et}_2\text{O}$ /hexanes (1:7), affording 49 mg (93%) of alcohol **3.128**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.76 (s, 1 H), 4.56 (s, 2 H), 3.55 (s, 2 H), 2.34 (s, 3 H), 0.90 (s, 9 H), 0.31 (s, 6 H), 0.076 (s, 6 H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  160.1, 147.7, 128.4, 123.2, 57.4, 54.6,





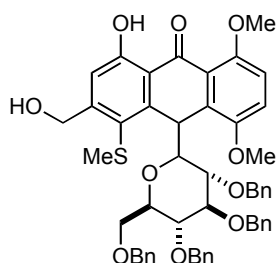
7.86 (s, 1 H), 7.37–7.24 (comp, 13 H), 7.20–7.19 (comp, 2 H), 7.06–7.04 (m, 1 H), 7.98–6.95 (comp, 2 H), 6.83 (s, 1 H), 6.78 (d,  $J = 8.7$  Hz, 1 H), 6.70 (d,  $J = 8.7$  Hz, 1 H), 6.46–6.45 (comp, 2 H), 6.15 (d,  $J = 9.2$  Hz, 1 H), 4.94 (d,  $J = 11.2$  Hz, 1 H), 4.87 (dd,  $J = 10.6, 2.8$  Hz, 1 H), 4.67–4.56 (comp, 4 H), 4.57 (s, 2 H), 4.24 (d,  $J = 10.2$  Hz, 1 H), 3.91 (d,  $J = 12.3$  Hz, 1 H), 3.84–3.76 (comp, 9 H), 3.72–3.69 (comp, 4 H), 3.53 (d,  $J = 10.2$  Hz, 1 H), 3.44 (app t,  $J = 9.2$  Hz, 1 H), 2.34 (s, 3 H), 0.89 (s, 9 H), 0.531 (s, 3 H), 0.526 (s, 3 H), 0.075 (s, 6 H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  160.3, 153.8, 152.2, 150.3, 147.5, 138.9, 138.4, 138.3, 137.8, 133.5, 128.5, 128.41, 128.36, 128.35, 128.1, 128.0, 127.8, 127.75, 127.73, 127.70, 127.6, 127.50, 127.45, 127.2, 126.4, 125.5, 123.2, 122.8, 107.8, 107.5, 87.1, 86.3, 79.5, 78.8, 75.4, 75.1, 74.8, 73.3, 69.3, 67.3, 57.49, 57.46, 56.3, 26.0, 18.4, –4.6, –5.2; IR (neat) 1357, 1258, 1102, 1079, 1053.

**NMR Assignments:**  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.86 (s, 1 H, C14-H), 7.37–7.24 (comp, 13 H, Ph C-H), 7.20–7.19 (comp, 2 H, Ph C-H), 7.06–7.04 (m, 1 H, Ph C-H), 7.98–6.95 (comp, 2 H, Ph C-H), 6.83 (s, 1 H, C3-H), 6.78 (d,  $J = 8.7$  Hz, 1 H, C18-H or C19-H), 6.70 (d,  $J = 8.7$  Hz, 1 H, C18-H or C19-H), 6.46–6.45 (comp, 2 H, Ph C-H), 6.15 (d,  $J = 9.2$  Hz, 1 H, C23-H), 4.94 (d,  $J = 11.2$  Hz, 1 H, Bn C-H), 4.87 (dd,  $J = 10.6, 2.8$  Hz, 1 H), 4.67–4.56 (comp, 4 H, Bn C-H), 4.57 (s, 2 H, C5-H), 4.24 (d,  $J = 10.2$  Hz, 1 H), 3.91 (d,  $J = 12.3$  Hz, 1 H, Bn C-H), 3.84–3.76 (comp, 9 H), 3.72–3.69 (comp, 4 H), 3.53 (d,  $J = 10.2$  Hz, 1 H), 3.44 (app t,  $J = 9.2$  Hz, 1 H, C24-H), 2.34 (s, 3 H, C6-H), 0.89 (s, 9 H, C9-H), 0.531 (s, 3 H, C10-H), 0.526 (s, 3 H, C10-H), 0.075 (s, 6 H, C7-H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  160.3, 153.8, 152.2, 150.3, 147.5, 138.9, 138.4, 138.3, 137.8, 133.5, 128.5, 128.41, 128.36, 128.35, 128.1, 128.0, 127.8, 127.75, 127.73, 127.70, 127.6, 127.50, 127.45, 127.2, 126.4, 125.5, 123.2, 122.8, 107.8 (C18 or C19), 107.5 (C18 or C19), 87.1, 86.3, 79.5, 78.8, 75.4, 75.1, 74.8, 73.3, 69.3, 67.3, 57.49, 57.46, 56.3, 26.0 (C9), 18.4 (C6), –4.6 (C10), –5.2 (C7).



**3.115**

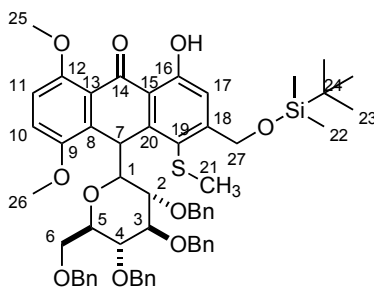
**Cycloadduct (3.115). (KP5-252).** *s*-BuLi (1.3 M, 83  $\mu$ L, 0.107 mmol) was added dropwise to ether **3.126** in THF (1 mL) at  $-78$   $^{\circ}$ C and stirring was continued for 1.5 h. The dry ice was removed from the cold bath, and the bath was allowed to warm to  $-10$   $^{\circ}$ C over a 40 min period, whereupon a saturated solution of  $\text{NH}_4\text{Cl}$  (3 mL) and  $\text{Et}_2\text{O}$  (2 mL) were added and the layers separated. The aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 x 2 mL), and the combined organics were dried ( $\text{MgSO}_4$ ) and concentrated. The residue was purified by flash chromatography, eluting with  $\text{Et}_2\text{O}$ /hexanes (1:3), providing 27 mg (36%) of cycloadduct **3.115**.



**1-Hydroxy-3-(hydroxymethyl)-5,8-dimethoxy-4-(methylthio)-10-((3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2*H*-pyran-2-yl)anthracen-9(10*H*)-one (3.114). (KP5-268).** TBAF (22 mg, 0.084 mmol) in DMF (200  $\mu$ L) was added to **3.129** in DMF (500  $\mu$ L) and the mixture was stirred for 30 min, whereupon H<sub>2</sub>O (2 mL) and Et<sub>2</sub>O (2 mL) were added. The layers were separated and the aqueous layer was extracted with Et<sub>2</sub>O (4 x 1 mL). The combined organic layers were washed with H<sub>2</sub>O (5 mL) and brine (5 mL), dried (MgSO<sub>4</sub>), and concentrated. The residue was dried under vacuum, and used crude in the next step.

Camphorsulfonic acid (CSA) (2 mg, 8  $\mu$ mol) was added to the residue in CH<sub>2</sub>Cl<sub>2</sub> (500  $\mu$ L) and the mixture was stirred at ambient temperature for 24 h, whereupon NaHCO<sub>3</sub> (1.5 mL) and Et<sub>2</sub>O (1 mL) were added and the layers were separated. The aqueous layer was extracted with Et<sub>2</sub>O (4 x 1 mL), and the organic layers were combined, dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with Et<sub>2</sub>O/hexanes (1:5 then 1:4) to provide 7 mg (39%) of anthrone **3.114**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  12.23 (s, 1 H), 7.58 (d, *J* = 7.4 Hz, 1 H), 7.41–7.10 (comp, 18 H), 6.95–6.92 (comp, 2 H), 6.13 (s, 1 H), 5.19 (d, *J* = 12.2 Hz, 1 H), 5.15 (d, *J* = 12.2 Hz, 1 H), 4.98 (d, *J* = 11.0, 1 H), 4.91 (d, *J* = 14.3 Hz, 1 H), 4.78–4.75 (comp, 2 H), 4.61 (s, 2 H), 4.41 (d, *J* = 11.3 Hz, 1 H), 4.37 (d, *J* = 11.3 Hz, 1 H) 3.93 (s, 3 H), 3.91 (s, 3 H), 3.80–3.75 (comp, 2 H), 3.67–3.62 (comp, 2 H), 3.53–3.31 (comp, 4 H),

3.11–3.09 (m, 1 H), 1.99 (s, 3 H); mass spectrum (CI)  $m/z$  869.3359 [ $C_{52}H_{52}O_{10}S$  (M+1) requires 869.3359].

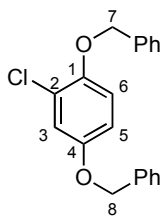


**3.141**

**3-((*tert*-Butyldimethylsilyloxy)methyl)-1-hydroxy-5,8-dimethoxy-4-(methylthio)-10-((3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2*H*-pyran-2-yl)anthracen-9(10*H*)-one (3.141). (KP6-55).** Camphorsulfonic acid (2 mg, 0.01 mmol) was added to **3.115** (9 mg, 0.009 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and the mixture was stirred for 16 h, whereupon NaHCO<sub>3</sub> (2 mL) and Et<sub>2</sub>O (2 mL) were added. The layers were separated, and the aqueous layer was extracted with Et<sub>2</sub>O (3 x 2 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by flash chromatography, eluting with EtOAc/hexanes (1:5) to afford 6 mg (75%) of **3.141**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 12.22 (s, 1 H), 7.57–7.56 (d,  $J = 7.3$  Hz, 1 H), 7.38–7.18 (comp, 18 H), 7.13–7.10 (comp, 4 H), 6.91 (d,  $J = 9.2$  Hz, 1 H), 6.12 (d,  $J = 0.9$  Hz, 1 H), 5.16 (s, 2 H), 5.05–4.96 (comp, 2 H), 4.81–4.74 (comp, 2 H), 4.61–4.58 (comp, 2 H), 4.37 (s, 2 H), 3.91 (s, 3 H), 3.89 (s, 3 H), 3.78 (dd,  $J = 11.5, 2.9$  Hz, 1 H), 3.63 (app t,  $J = 9.3$  Hz, 1 H), 3.52 (d,  $J = 11.5$  Hz, 2.9 Hz, 1 H), 3.45–3.36 (comp, 3 H), 3.09–3.06 (m, 1 H), 1.92 (s, 3 H), 0.95 (s, 9 H), 0.12 (s, 3 H), 0.10 (s, 3 H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 190.7, 160.9, 159.8, 157.4, 153.8,

151.9, 149.0, 144.1, 140.6, 138.9, 138.5, 138.2, 135.1, 128.5, 128.4, 128.1, 128.0, 127.97, 127.95, 127.7, 127.6, 127.5, 127.4, 127.3, 127.0, 126.9, 126.5, 123.1, 121.9, 121.3, 116.2, 114.7, 111.1, 88.2, 82.1, 79.1, 78.4, 78.1, 74.9, 74.7, 73.5, 73.4, 69.2, 63.9, 56.6, 56.3, 35.6, 30.3, 26.0, 25.6, 20.6, 18.4, -5.2, -5.3; mass spectrum (ESI)  $m/z$  1005.4031 [ $C_{64}H_{61}O_9S$  (M+1) requires 982.4146].

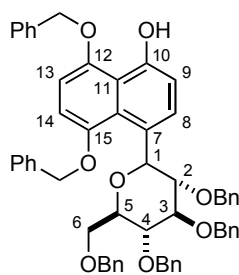
**NMR Assignments:**  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  12.22 (s, 1 H, OH), 7.57–7.56 (d,  $J = 7.3$  Hz, 1 H, Ph C-H), 7.38–7.18 (comp, 18 H, Ph C-H and C17-H), 7.13–7.10 (comp, 4 H, Ph C-H and C10-H or C11-H), 6.91 (d,  $J = 9.2$  Hz, 1 H C10-H or C11-H), 6.12 (d,  $J = 0.9$  Hz, 1 H, C7-H), 5.16 (s, 2 H, Bn C-H), 5.05–4.96 (comp, 2 H, Bn C-H), 4.81–4.74 (comp, 2 H, Bn C-H), 4.61–4.58 (comp, 2 H, Bn C-H), 4.37 (s, 2 H, Bn C-H), 3.91 (s, 3 H, C25-H or C26-H), 3.89 (s, 3 H, C25-H or C26-H), 3.78 (dd,  $J = 11.5, 2.9$  Hz, 1 H, C6-H), 3.63 (app t,  $J = 9.3$  Hz, 1 H, C3-H), 3.52 (d,  $J = 11.5$  Hz, 2.9 Hz, 1 H, C6-H), 3.45–3.36 (comp, 3 H, C4-H and C2-H and C1-H), 3.09–3.06 (m, 1 H, C5-H), 1.92 (s, 3 H, C21-H), 0.95 (s, 9 H, C23-H), 0.12 (s, 3 H, C22-H), 0.10 (s, 3 H, C22-H);  $^{13}C$  NMR (150 MHz,  $CDCl_3$ )  $\delta$  190.7 (C14), 160.9, 159.8, 157.4, 153.8, 151.9, 149.0, 144.1, 140.6, 138.9, 138.5, 138.2, 135.1, 128.5 (Ph C), 128.4 (Ph C), 128.1 (Ph C), 128.0 (Ph C), 127.97 (Ph C), 127.95 (Ph C), 127.7 (Ph C), 127.6 (Ph C), 127.5 (Ph C), 127.4 (Ph C), 127.3 (Ph C), 127.0 (Ph C), 126.9 (Ph C), 126.5 (Ph C), 123.1, 121.9, 121.3, 116.2, 114.7 (C10 or C11), 111.1, 88.2 (C3), 82.1 (C1), 79.1 (C5), 78.4 (C2), 78.1 (C4), 74.9 (Bn C), 74.7 (Bn C), 73.5 (Bn C), 73.4 (Bn C), 69.2 (C6), 63.9 (C24), 56.6 (C25 or C26), 56.3 (C25 or C26), 35.6 (C7), 30.3, 26.0, 25.6, 20.6 (C21), 18.4 (C27), -5.2 (C22), -5.3 (C22).



**(2-Chloro-1,4-phenylene)bis(oxy)bis(methylene)dibenzene (3.143). (KP6-65).**

NaH (1.23 g, 31.5 mmol, 60 % dispersion) was added in two portions to a solution of chlorohydroquinone (**3.142**) (2.08 g, 12.9 mmol, 90%) and BnBr (3.7 mL, 30.1 mmol) in DMF (100 mL). The mixture was stirred for 24 h, whereupon H<sub>2</sub>O (100 mL) and Et<sub>2</sub>O (300 mL) were added. The layers were separated, and the organic layer was washed with H<sub>2</sub>O (3 x 100 mL) and brine (2 x 100 mL), dried (MgSO<sub>4</sub>), and concentrated. The residue was recrystallized from EtOH to provide 3.37 g (81%) of **3.143**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.45–7.29 (comp, 10 H), 7.04 (d, *J* = 2.9 Hz, 1 H), 6.87 (d, *J* = 9.0 Hz, 1 H), 6.77 (dd, *J* = 9.0, 2.9 Hz, 1 H), 5.07 (s, 2 H), 4.98 (s, 2 H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 153.4, 148.7, 136.8, 136.7, 128.6, 128.5, 128.1, 127.9, 124.2, 117.2, 115.9, 113.9, 71.9, 70.8; IR (neat) 1454, 1225, 1052, 1018, 736 cm<sup>-1</sup>; mass spectrum (CI) *m/z* 324.0917 [C<sub>20</sub>H<sub>17</sub>O<sub>2</sub> (M+1) requires 324.0917] (base), 289, 181.

**NMR Assignments:** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.45–7.29 (comp, 10 H, PhC-H), 7.04 (d, *J* = 2.9 Hz, 1 H, C6-H), 6.87 (d, *J* = 9.0 Hz, 1 H, C3-H), 6.77 (dd, *J* = 9.0, 2.9 Hz, 1 H, C5-H), 5.07 (s, 2 H, C7-H), 4.98 (s, 2 H, C8-H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 153.4 (Ph C), 148.7 (Ph C), 136.8 (Ph C), 136.7 (Ph C), 128.6 (Ph C), 128.5 (Ph C), 128.1 (Ph C), 127.9 (Ph C), 124.2 (Ph C), 117.2 (C5) 115.9 (C3), 113.9 (C6), 71.9 (C7), 70.8 (C8).



**3.144a**

**5,8-Bis(benzyloxy)-4-((3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2*H*-pyran-2-yl)naphthalen-1-ol. (KP6-104).** *s*-BuLi (1.3 M, 1.7 mL, 2.2 mmol) was added dropwise to a solution of chloride **3.143** (722 mg, 2.22 mmol) in THF (20 mL) at  $-100\text{ }^{\circ}\text{C}$ . The solution was stirred for 15 min, whereupon a solution of furan **3.18** (524 mg, 0.89 mmol) in THF (5 mL) was added. The solution was allowed to warm to  $-20\text{ }^{\circ}\text{C}$  over a 45 min period, whereupon  $\text{NH}_4\text{Cl}$  (25 mL) and  $\text{Et}_2\text{O}$  (25 mL) were added. The layers were separated and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 x 25 mL). The combined organic layers were washed with brine (50 mL), dried ( $\text{MgSO}_4$ ), and concentrated. The residue was purified by flash chromatography, eluting with  $\text{Et}_2\text{O}$ /hexanes (1:7 then 1:5) to provide 414 mg (53%) of a mixture of cycloadducts **3.144** as a viscous oil.

Solid  $\text{ZnCl}_2^\dagger$  (128 mg, 0.942 mmol) was added to a solution of **3.144** (414 mg, 1.98 mmol) in  $\text{CH}_2\text{Cl}_2$  (7 mL), and the mixture was stirred for 14 h, whereupon  $\text{NaHCO}_3$  (10 mL) and  $\text{Et}_2\text{O}$  (15 mL) were added and the layers were separated. The organic layer was washed with  $\text{NaHCO}_3$  (3 x 10 mL) and brine (10 mL), dried ( $\text{MgSO}_4$ ), and concentrated to provide 411 mg (99%) of phenol **3.144a**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  10.02 (s, 1 H), 7.77 (d,  $J = 8.4$  Hz, 1 H), 7.50–7.20 (comp, 25 H), 7.11–7.08 (m, 1 H),

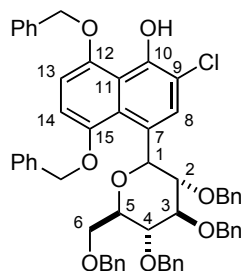
$^\dagger$   $\text{ZnCl}_2$  was used without any pretreatment.

7.03–7.00 (comp, 2 H), 6.94 (d,  $J = 8.4$  Hz, 1 H), 6.77 (d,  $J = 8.4$  Hz, 1 H), 6.71 (d,  $J = 8.7$  Hz, 1 H), 6.57–6.55 (comp, 2 H), 6.19 (d,  $J = 9.1$  Hz, 1 H), 5.25 (s, 2 H), 5.07 (d,  $J = 11.0$  Hz, 1 H), 4.87 (d,  $J = 11.2$  Hz, 1 H), 4.82 (d,  $J = 11.2$  Hz, 1 H), 4.79 (d,  $J = 10.8$  Hz, 1 H), 4.66 (d,  $J = 11.0$  Hz, 1 H), 4.65 (d,  $J = 12.3$  Hz, 1 H), 4.58 (d,  $J = 11.2$  Hz, 1 H), 4.53 (d,  $J = 12.3$  Hz, 1 H), 4.23 (d,  $J = 10.3$  Hz, 1 H), 4.70–3.69 (comp, 3 H), 3.52 (d,  $J = 10.3$  Hz, 1 H), 3.38 (app t,  $J = 9.1$  Hz, 1 H), 3.31 (comp, 2 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  154.5, 152.0, 149.7, 139.0, 138.3, 137.0, 135.4, 129.0, 128.8, 128.6, 128.32, 128.29, 128.26, 128.22, 128.1, 128.0, 127.74, 127.66, 127.57, 127.53, 127.44, 127.41, 127.08, 127.05, 116.6, 111.8, 107.0, 105.2, 86.7, 86.5, 79.0, 78.6, 76.7, 75.4, 74.6, 74.4, 73.4, 72.4, 71.5, 69.4; IR (neat) 3360, 1453, 1259, 1141, 1099, 1060, 1026, 736, 697; mass spectrum (ESI)  $m/z$  901.3711 [ $\text{C}_{58}\text{H}_{54}\text{O}_8\text{Na}$  (M<sup>+</sup>) requires 901.3711] 879, 771, 679 (base).

**NMR Assignments:**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  10.02 (s, 1 H, OH), 7.77 (d,  $J = 8.4$  Hz, 1 H, C8-H), 7.50–7.20 (comp, 25 H, Ph C-H), 7.11–7.08 (m, 1 H, Ph C-H), 7.03–7.00 (comp, 2 H, Ph C-H), 6.94 (d,  $J = 8.4$  Hz, 1 H, C9-H), 6.77 (d,  $J = 8.7$  Hz, 1 H, C13-H or C14-H), 6.71 (d,  $J = 8.7$  Hz, 1 H, C13-H or C14-H), 6.57–6.55 (comp, 2 H, Ph C-H), 6.19 (d,  $J = 9.1$  Hz, 1 H, C1-H), 5.25 (s, 2 H, Bn C-H), 5.07 (d,  $J = 11.0$  Hz, 1 H, Bn C-H), 4.87 (d,  $J = 11.2$  Hz, 1 H, Bn C-H), 4.82 (d,  $J = 11.2$  Hz, 1 H, Bn C-H), 4.79 (d,  $J = 10.8$  Hz, 1 H, Bn C-H), 4.66 (d,  $J = 11.0$  Hz, 1 H, Bn C-H), 4.65 (d,  $J = 12.3$  Hz, 1 H, Bn C-H), 4.58 (d,  $J = 11.2$  Hz, 1 H, Bn C-H), 4.53 (d,  $J = 12.3$  Hz, 1 H, Bn C-H), 4.23 (d,  $J = 10.3$  Hz, 1 H, C6-H), 4.70–3.69 (comp, 3 H), 3.52 (d,  $J = 10.3$  Hz, 1 H, C6-H), 3.38 (app t,  $J = 9.1$  Hz, 1 H, C2-H), 3.31 (comp, 2 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  154.5, 152.0, 149.7, 139.0, 138.3, 137.0, 135.4, 129.0, 128.8, 128.6, 128.32, 128.29, 128.26, 128.22, 128.1, 128.0, 127.74, 127.66, 127.57, 127.53, 127.44, 127.41, 127.08, 127.05, 116.6, 111.8 (C9), 107.0 (C14 or C15), 105.2 (C14 or C15), 86.7, 86.5, 79.0, 78.6, 76.7



(C1), 75.4 (Bn C), 74.6 (Bn C) (C6), 74.4 (Bn C), 73.4 (Bn C), 72.4 (Bn C), 71.5 (Bn C), 69.4.



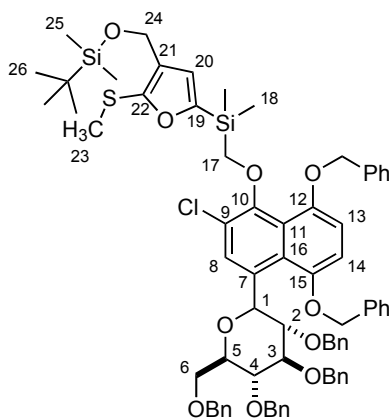
**3.145**

**5,8-Bis(benzyloxy)-2-chloro-4-((3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2*H*-pyran-2-yl)naphthalen-1-ol (3.145). (KP6-70).**

Solid NCS (21 mg, 0.16 mmol) was added to a solution of phenol **3.144a** (131 mg, 0.15 mmol) in DMF (1.5 mL). The mixture was stirred for 16 h, whereupon H<sub>2</sub>O (3 mL) and Et<sub>2</sub>O (3 mL) were added. The layers were separated, and the aqueous layer was extracted with Et<sub>2</sub>O (3 x 3 mL). The combined Et<sub>2</sub>O layers were washed with H<sub>2</sub>O (2 x 3 mL) and brine (3 mL), dried (MgSO<sub>4</sub>), and concentrated. The residue was purified by flash chromatography, eluting with Et<sub>2</sub>O/hexanes (1:7 then 1:5) to provide 88 mg (65%) of **3.145** as an oil: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 10.60 (s, 1 H), 7.82 (s, 1 H), 7.51–7.26 (comp, 25 H), 7.21–7.09 (comp, 3 H), 7.12–7.09 (m, 1 H), 7.02–6.99 (comp, 2 H), 6.83 (d, *J* = 8.4 Hz, 1 H), 6.71 (d, *J* = 8.4 Hz, 1 H), 6.55 (d, *J* = 7.5 Hz, 2 H), 6.13 (d, *J* = 9.1 Hz, 1 H), 5.24 (s, 2 H), 5.07 (d, *J* = 11.2 Hz, 1 H), 4.84 (d, *J* = 10.8 Hz, 1 H), 4.80 (d, *J* = 11.3 Hz, 1 H), 4.78 (d, *J* = 12.7 Hz, 1 H), 4.66 (d, *J* = 11.0 Hz, 1 H), 4.64 (d, *J* = 12.7 Hz, 1 H), 4.54 (d, *J* = 12.4 Hz, 1 H), 4.29 (d, *J* = 10.3 Hz, 1 H), 3.67–3.58 (comp, 4 H), 3.33–3.29 (comp, 2 H), 3.24 (app t, *J* = 8.9 Hz, 1 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 152.0,

149.5, 149.0, 138.8, 138.7, 138.4, 138.1, 136.7, 134.9, 129.1, 129.0, 128.8, 128.7, 128.6, 128.35, 128.33, 128.27, 128.26, 128.2, 128.0, 127.7, 127.64, 127.60, 127.59, 127.5, 127.4, 127.1, 125.6, 117.1, 116.5, 107.2, 106.2, 86.6, 86.5, 79.0, 78.6, 76.3, 75.3, 74.8, 74.4, 73.2, 72.6, 71.6, 69.3; IR (neat) 3306, 1453, 1042, 1255, 1105, 1098, 1060, 1026; mass spectrum (ESI)  $m/z$  935.3321 [ $C_{58}H_{54}O_8ClNa$  (M<sup>+</sup>) requires 935.3321] 914 (base), 913 (base), 901.

**NMR Assignments:**  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  10.60 (s, 1 H, OH), 7.82 (s, 1 H, C8-H), 7.51–7.26 (comp, 25 H, Ph C-H), 7.21–7.09 (comp, 3 H), 7.12–7.09 (m, 1 H), 7.02–6.99 (comp, 2 H), 6.83 (d,  $J = 8.4$  Hz, 1 H, C13-H or C14-H), 6.71 (d,  $J = 8.4$  Hz, 1 H C13-H or C14-H), 6.55 (d,  $J = 7.5$  Hz, 2 H), 6.13 (d,  $J = 9.1$  Hz, 1 H), 5.24 (s, 2 H, Bn C-H), 5.07 (d,  $J = 11.2$  Hz, 1 H, Bn C-H), 4.84 (d,  $J = 10.8$  Hz, 1 H, Bn C-H), 4.80 (d,  $J = 11.3$  Hz, 1 H, Bn C-H), 4.78 (d,  $J = 12.7$  Hz, 1 H, Bn C-H), 4.66 (d,  $J = 11.0$  Hz, 1 H, Bn C-H), 4.64 (d,  $J = 12.7$  Hz, 1 H, Bn C-H), 4.54 (d,  $J = 12.4$  Hz, 1 H, Bn C-H), 4.29 (d,  $J = 10.3$  Hz, 1 H, C6-H), 3.67–3.58 (comp, 4 H), 3.33–3.29 (comp, 2 H), 3.24 (app t,  $J = 8.9$  Hz, 1 H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  152.0, 149.5, 149.0, 138.8, 138.7, 138.4, 138.1, 136.7, 134.9, 129.1, 129.0, 128.8, 128.7, 128.6, 128.35, 128.33, 128.27, 128.26, 128.2, 128.0, 127.7, 127.64, 127.60, 127.59, 127.5, 127.4, 127.1, 125.6, 117.1, 116.5, 107.2 (C13 or C14), 106.2 (C13 or C14), 86.6, 86.5, 79.0, 78.6, 76.3 (C1), 75.3, 74.8 (C6), 74.4 (Bn C), 73.2 (Bn C), 72.6 (Bn C), 71.6 (Bn C), 69.3.



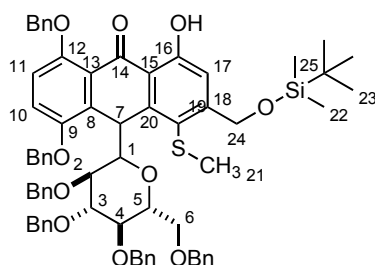
**3.146**

**((5,8-Bis(benzyloxy)-2-chloro-4-((3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2*H*-pyran-2-yl)naphthalen-1-yloxy)methyl)(4-((*tert*-butyldimethylsilyloxy)methyl)-5-(methylthio)furan-2-yl)dimethylsilane (3.146).**

**(KP6-79).** DIAD (31  $\mu$ L, 0.157 mmol) was added to a solution of phenol **3.145** (69 mg, 0.078 mmol), alcohol **3.128** (54 mg, 0.157 mmol), and PPh<sub>3</sub> (41 mg, 0.157 mmol) in THF (2 mL) and the mixture was stirred for 20 h, at which point it was concentrated. The residue was purified by flash chromatography, eluting with Et<sub>2</sub>O/hexanes to give 70 mg (72%) of ether **3.146** as a light oil: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.87 (s, 1 H), 7.39–7.18 (comp, 25 H), 7.06–7.04 (m, 1 H), 6.93–6.90 (comp, 2 H), 6.77 (s, 1 H), 6.69 (d, *J* = 8.7 Hz, 1 H), 6.62 (d, *J* = 8.7 Hz, 1 H), 6.42–6.41 (comp, 2 H), 6.19 (d, *J* = 9.1 Hz, 1 H), 5.16 (d, *J* = 13.2 Hz, 1 H), 5.11 (d, *J* = 13.2 Hz, 1 H), 4.99 (d, *J* = 11.2 Hz, 1 H), 4.78 (d, *J* = 11.2 Hz, 1 H), 4.75 (d, *J* = 11.2 Hz, 1 H), 4.71 (d, *J* = 11.2 Hz, 1 H), 4.65–4.61 (comp, 2 H), 4.55–4.52 (comp, 4 H), 4.23 (d, *J* = 10.3 Hz, 1 H), 4.05 (d, *J* = 12.4 Hz, 1 H), 3.91 (d, *J* = 12.4 Hz, 1 H), 3.663 (s, 1 H), 3.657 (s, 1 H), 3.61 (app t, *J* = 9.6 Hz, 1 H), 3.42 (d, *J* = 10.1 Hz, 1 H), 3.31–3.27 (comp, 2 H), 3.20 (app t, *J* = 8.9 Hz, 1 H), 2.30 (s, 3 H), 0.89 (s, 9 H), 0.42 (s, 3 H), 0.39 (s, 3 H), 0.066 (s, 6 H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  160.3,

153.7, 151.6, 148.8, 147.4, 138.9, 138.7, 138.4, 137.9, 137.8, 136.9, 134.2, 128.6, 128.4, 128.34, 128.31, 128.2, 128.1, 128.0, 127.9, 127.7, 127.63, 127.59, 127.56, 127.55, 127.45, 127.44, 127.41, 127.3, 127.2, 126.3, 125.7, 123.3, 123.1, 110.9, 108.1, 86.7, 86.3, 79.0, 78.5, 76.4, 75.3, 74.9, 74.4, 73.2, 72.5, 71.6, 69.3, 67.5, 57.4, 30.0, 18.5, 18.4, -4.62, -4.27, -5.2; mass spectrum (ESI)  $m/z$  1263.4670 [ $C_{73}H_{81}O_{10}SSi_2ClNa$  (M<sup>+</sup>) requires 1263.4670] 1241 (base), 1226; IR (neat) 1355, 1142, 1099, 1058, 1028  $cm^{-1}$ .

**NMR Assignments:**  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.87 (s, 1 H, C8-H), 7.39–7.18 (comp, 25 H, Ph C-H), 7.06–7.04 (m, 1 H, Ph C-H), 6.93–6.90 (comp, 2 H, Ph C-H), 6.77 (s, 1 H, C20-H), 6.69 (d,  $J = 8.7$  Hz, 1 H, C13-H or C14-H), 6.62 (d,  $J = 8.7$  Hz, 1 H, C13-H or C14-H), 6.42–6.41 (comp, 2 H, C24-H), 6.19 (d,  $J = 9.1$  Hz, 1 H, C1-H), 5.16 (d,  $J = 13.2$  Hz, 1 H, Bn C-H), 5.11 (d,  $J = 13.2$  Hz, 1 H, Bn C-H), 4.99 (d,  $J = 11.2$  Hz, 1 H, Bn C-H), 4.78 (d,  $J = 11.2$  Hz, 1 H, Bn C-H), 4.75 (d,  $J = 11.2$  Hz, 1 H, Bn C-H), 4.71 (d,  $J = 11.2$  Hz, 1 H, Bn C-H), 4.65–4.61 (comp, 2 H), 4.55–4.52 (comp, 4 H), 4.23 (d,  $J = 10.3$  Hz, 1 H), 4.05 (d,  $J = 12.4$  Hz, 1 H), 3.91 (d,  $J = 12.4$  Hz, 1 H), 3.663 (s, 1 H, C17-H), 3.657 (s, 1 H, C17-H), 3.61 (app t,  $J = 9.6$  Hz, 1 H), 3.42 (d,  $J = 10.1$  Hz, 1 H, C6-H), 3.31–3.27 (comp, 2 H), 3.20 (app t,  $J = 8.9$  Hz, 1 H), 2.30 (s, 3 H, C23-H), 0.89 (s, 9 H, C27-H), 0.42 (s, 3 H, C18-H), 0.39 (s, 3 H, C18-H), 0.066 (s, 6 H, C25-H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  160.3, 153.7, 151.6, 148.8, 147.4, 138.9, 138.7, 138.4, 137.9, 137.8, 136.9, 134.2, 128.6, 128.4, 128.34, 128.31, 128.2, 128.1, 128.0, 127.9, 127.7, 127.63, 127.59, 127.56, 127.55, 127.45, 127.44, 127.41, 127.3, 127.2, 126.3, 125.7, 123.3, 123.1, 110.9 (C13 or C14), 108.1 (C13 or C14), 86.7, 86.3, 79.0, 78.5, 76.4 (C1), 75.3, 74.9, 74.4, 73.2, 72.5, 71.6, 69.3, 67.5, 57.4, 30.0, 18.5, 18.4, -4.67 (C18), -4.72 (C18), -5.2 (C25).



**3.148**

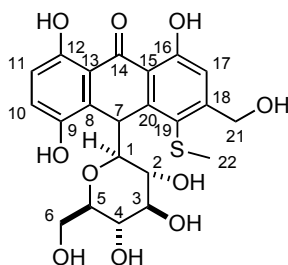
**5,8-Bis(benzyloxy)-3-((*tert*-butyldimethylsilyloxy)methyl)-1-hydroxy-4-(methylthio)-10-((3*S*,4*R*,5*R*,6*R*)-3,4,5-tris(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2*H*-pyran-2-yl)anthracen-9(10*H*)-one (3.148). (KP6-199). *s*-BuLi (205  $\mu$ L, 0.266 mmol, 1.3 M) was added dropwise to ether **3.146** (254 mg, 0.204 mmol) in THF (4 mL) at  $-50$   $^{\circ}$ C and stirring was continued for 1.5 h. The dry ice was removed from the cold bath, and the bath was allowed to warm to  $-10$   $^{\circ}$ C over a 25 min period, whereupon a saturated solution of  $\text{NH}_4\text{Cl}$  (4 mL) was added and the layers separated. The aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 x 4 mL), and the combined organics were dried ( $\text{MgSO}_4$ ) and concentrated. The residue was purified by flash chromatography, eluting with  $\text{Et}_2\text{O}$ /hexanes (1:3), providing 83 mg (34%) of a cycloadduct and 106 mg (42%) of starting ether **3.146**.**

CSA (6 mg, 0.02 mmol) was added to the cycloadduct (83 mg, 0.069 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) and the mixture was stirred for 16 h, whereupon  $\text{NaHCO}_3$  (5 mL) and  $\text{Et}_2\text{O}$  (7 mL) were added and the layers were separated. The aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 x 5 mL), dried ( $\text{MgSO}_4$ ), and concentrated. The residue was purified by flash chromatography, eluting with  $\text{EtOAc}$ /hexanes (1:8) to provide 65 mg (83%) of anthrone **3.148** as an oil:  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  12.37 (s, 1 H), 7.52–7.47 (comp, 4 H), 7.40–7.18 (comp, 27 H), 7.15–7.12 (comp, 4 H), 6.93 (d,  $J = 9.1$  Hz, 1 H), 6.78 (d,

$J = 9.1$  Hz, 1 H), 6.26 (s, 1 H), 5.26 (d,  $J = 13.8$  Hz, 1 H), 5.20 (d,  $J = 12.5$  Hz, 1 H), 5.19 (d,  $J = 13.6$  Hz, 1 H), 5.15 (d,  $J = 10.6$  Hz, 1 H), 5.08–5.05 (comp, 2 H), 4.96 (d,  $J = 11.0$  Hz, 1 H), 4.83 (dd,  $J = 15.5, 1.0$  Hz, 1 H), 4.72 (d,  $J = 11.0$  Hz, 1 H), 4.61 (s, 2 H), 4.39 (s, 2 H), 3.75 (dd,  $J = 11.7, 3.3$  Hz, 1 H), 3.65 (ddd,  $J = 10.7, 6.8, 1.4$  Hz, 1 H), 3.52 (dd,  $J = 11.6, 1.2$  Hz, 1 H), 3.43 (app t,  $J = 9.5$  Hz, 1 H), 3.41–3.37 (comp, 3 H), 3.08 (ddd,  $J = 9.7, 3.2, 1.3$  Hz, 1 H), 1.98 (s, 3 H), 0.97 (s, 9 H), 0.14 (s, 3 H), 0.13 (s, 3 H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  190.4, 152.7, 151.9, 147.8, 144.2, 140.5, 138.9, 138.5, 138.2, 137.21, 137.18, 135.2, 128.6, 128.48, 128.46, 128.38, 128.1, 128.0, 127.86, 127.85, 127.67, 127.62, 127.61, 127.5, 127.3, 127.0, 126.9, 126.7, 126.4, 124.3, 121.8, 121.4, 117.7, 114.8, 114.0, 88.3, 82.1, 79.2, 78.4, 78.2, 74.9, 74.7, 73.41, 73.38, 71.8, 70.1, 69.2, 63.9, 35.9, 29.7, 26.0, 20.7, 18.4, -5.2, -5.3; IR (neat) 1452, 1259, 1106, 1088  $\text{cm}^{-1}$ ; mass spectrum (ESI)  $m/z$  1157.4664 [ $\text{C}_{70}\text{H}_{74}\text{NaO}_{10}\text{SSi}^+$  (M<sup>+</sup>) requires 1157.4664], 703.

**NMR Assignments:**  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  12.37 (s, 1 H, OH), 7.52–7.47 (comp, 4 H, Ph C-H), 7.40–7.18 (comp, 27 H, Ph C-H), 7.15–7.12 (comp, 4 H, Ph C-H), 6.93 (d,  $J = 9.1$  Hz, 1 H, C10-H or C11-H), 6.78 (d,  $J = 9.1$  Hz, 1 H, C10-H or C11-H), 6.26 (s, 1 H, C7-H), 5.26 (d,  $J = 13.8$  Hz, 1 H, Bn C-H), 5.20 (d,  $J = 12.5$  Hz, 1 H, Bn C-H), 5.19 (d,  $J = 13.6$  Hz, 1 H, Bn C-H), 5.15 (d,  $J = 10.6$  Hz, 1 H, Bn C-H), 5.08–5.05 (comp, 2 H, Bn C-H), 4.96 (d,  $J = 11.0$  Hz, 1 H, Bn C-H), 4.83 (dd,  $J = 15.5, 1.0$  Hz, 1 H, Bn C-H), 4.72 (d,  $J = 11.0$  Hz, 1 H, Bn C-H), 4.61 (s, 2 H, Bn C-H), 4.39 (s, 2 H, Bn C-H), 3.75 (dd,  $J = 11.7, 3.3$  Hz, 1 H, C6-H), 3.65 (ddd,  $J = 10.7, 6.8, 1.4$  Hz, 1 H, C3-H), 3.52 (dd,  $J = 11.6, 1.2$  Hz, 1 H, C6-H), 3.43 (app t,  $J = 9.5$  Hz, 1 H, C4-H), 3.41–3.37 (comp, 3 H, C2-H and C1-H), 3.08 (ddd,  $J = 9.7, 3.2, 1.3$  Hz, 1 H, C5-H), 1.98 (s, 3 H, C21-H), 0.97 (s, 9 H, C23-H), 0.14 (s, 3 H, C22-H), 0.13 (s, 3 H, C22-H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  190.4 (C14), 152.7 (C16), 151.9, 147.8, 144.2, 140.5, 138.9, 138.5, 138.2, 137.21, 137.18, 135.2, 128.6 (Ph C), 128.48 (Ph C), 128.46 (Ph C), 128.38 (Ph C),

128.1 (Ph C), 128.0 (Ph C), 127.86 (Ph C), 127.85 (Ph C), 127.67 (Ph C), 127.62 (Ph C), 127.61 (Ph C), 127.5 (Ph C), 127.3 (Ph C), 127.0 (Ph C), 126.9 (Ph C), 126.7 (Ph C), 126.4 (Ph C), 124.3, 121.8, 121.4, 117.7, 114.8 (C10 or C11), 114.0 (C10 or C11), 88.3 (C3), 82.1 (C1), 79.2 (C5), 78.4 (C2), 78.2 (C4), 74.9 (Bn C), 74.7 (Bn C), 73.41 (Bn C), 73.38 (Bn C), 71.8 (Bn C), 70.1 (Bn C), 69.2 (C6), 63.9 (C25), 35.9 (C7), 26.0 (C23), 20.7 (C21), 18.4 (C24), -5.2 (C22), -5.3 (C22).



**3.149**

**1,5,8-Trihydroxy-3-(hydroxymethyl)-4-(methylthio)-10-((2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)anthracen-9(10*H*)-one (3.149).** (KP6-117).  $\text{BBr}_3$  (870  $\mu\text{L}$ , 0.87 mmol, 1 M in  $\text{CH}_2\text{Cl}_2$ ) was added dropwise to a solution of **3.148** (23 mg, 0.029 mmol) in  $\text{CH}_2\text{Cl}_2$  at  $-78\text{ }^\circ\text{C}$ . After 30 min, a solution of HCl in MeOH (0.28 M, 2 mL, 0.56 mmol) was added and stirring was continued for 1 h, whereupon the cold bath was removed and the mixture was stirred at room temperature for 16 h. The mixture was concentrated and the residue was purified twice by flash chromatography, eluting with EtOAc/MeOH (99:1) to furnish 7 mg (50%) of **3.149**:  $^1\text{H}$  NMR (600 MHz, acetone  $\text{D}_6$ )  $\delta$  12.29 (s, 1 H), 11.49 (s, 1 H), 8.15 (s, 1 H), 7.22 (s, 1 H), 7.21 (d,  $J = 8.9$  Hz, 1 H), 6.83 (d,  $J = 8.9$  Hz, 1 H), 5.59 (s, 1 H), 5.06 (d,  $J = 15.6$ , 1 H), 4.54 (br s, 1 H), 4.22 (br s, 1 H), 4.15 (br s, 1 H) 3.84–3.82 (comp, 2 H), 3.73–3.69 (comp, 3 H), 3.30–3.15 (comp, 4 H), 2.33 (s, 3 H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  126.1,

110.4, 80.5, 81.0, 78.9, 70.2, 69.0, 62.3, 61.2 40.5, 20.5; IR (neat) 3386 (br), 1458, 1419, 1196, 1078; mass spectrum (ESI)  $m/z$  481.1164 [ $C_{22}H_{24}O_{10}S^+$  (M+) requires 481.1090].

**NMR Assignments:**  $^1H$  NMR (600 MHz,  $C_6D_6$ )  $\delta$  12.29 (s, 1 H, OH), 11.49 (s, 1 H, OH), 8.15 (s, 1 H, OH), 7.22 (s, 1 H, C17-H), 7.21 (d,  $J = 8.9$  Hz, 1 H, C10-H or C11-H), 6.83 (d,  $J = 8.9$  Hz, 1 H, C10-H or C11-H), 5.59 (s, 1 H, C1-H), 5.06 (d,  $J = 15.6$ , 1 H), 4.54 (br s, 1 H), 4.22 (br s, 1 H), 4.15 (br s, 1 H) 3.84–3.82 (comp, 2 H), 3.73–3.69 (comp, 3 H), 3.30–3.15 (comp, 4 H), 2.33 (s, 3 H, C22-H);  $^{13}C$  NMR (150 MHz,  $CDCl_3$ )  $\delta$  126.1, 110.4, 80.5, 81.0, 78.9, 70.2, 69.0, 62.3, 61.2, 40.5, 20.5



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## Vita

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