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Iterative Benzyne–Furan Cycloaddition Reactions: Studies toward the Total Synthesis of *ent*-Sch 47554 and *ent*-Sch 47555

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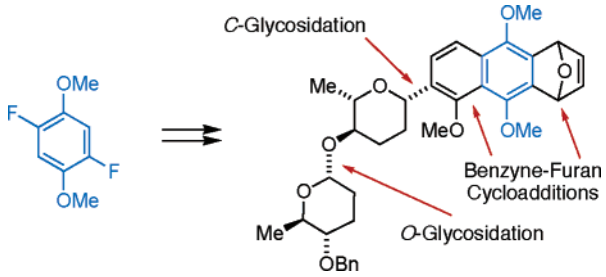
ABSTRACT



7-Fluoro-5,8-dimethoxy-1-naphthol, prepared from the lithiation and benzyne formation from 1,4-difluoro-2,5-dimethoxybenzene and Diels–Alder cycloaddition with furan, was sequentially *C*-glycosidated under Suzuki conditions and *O*-glycosidated using di-*O*-acetyl-L-rhamnal to provide the corresponding *β*-naphthyl *C*,*O*-disaccharide. Further lithiation, benzyne formation, and cycloaddition with furan gave an oxa-bridged 1,4-dihydroanthracenyl *C*,*O*-disaccharide, a model compound relevant to the total synthesis of Sch 47555.

Sch 47554 (**1**) and Sch 47555 (**2**) (Figure 1) are two angucycline antibiotics[1] that were isolated at Schering-Plough from the fermentation broths of a strain of *Streptomyces* sp. (SCC-2136), originally isolated from a Canadian soil sample.[2] Both compounds showed antifungal activities against a variety of yeasts and dermatophytes including *Candida albicans*, *Candida tropicalis*, *Candida stellatoidea*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Trichophyton tonsurans*, and *Microsporum canis* with the greater activity shown by Sch 47554 (**1**).[2] As part of our ongoing interest in diverse biologically active benz[*a*]anthracene antibiotics,[3] we wished to explore the use of 1,4-difluoro-2,5-dimethoxybenzene (**7**), an equivalent of the double benzyne 1,4-dimethoxycyclohexa-1,2,3-trien-5-yne,[4] in the synthesis of model anthraquinones structurally related to the ring ABC unit of Sch 47554 (**1**).

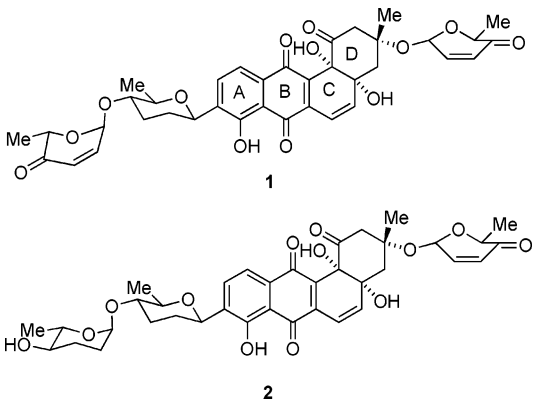


Figure 1. Sch 47554 (**1**) and Sch 47555 (**2**).

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(3) Thomson, R. H. *Naturally Occurring Quinones III*; Chapman and Hall: New York, 1987.

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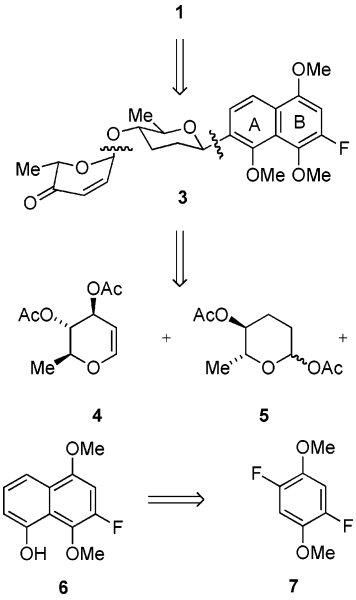
Scheme 1. Retrosynthesis of Sch 47554 (**1**)



The synthesis of *C*-aryl glycosides from the Lewis acid catalyzed rearrangement of the corresponding *O*-glycosides is well documented as a powerful method for their construction from simple precursors in a regio- and stereocontrolled manner when the glycoside is ortho to a phenol or naphthol unit.[5−8] Lewis acids including boron trifluoride etherate,[9−14] tin tetrachloride,[15] scandium triflate,[16] trimethylsilyl triflate,[17,18] and $Cp_2MCl_2-AgClO_4$ (M = Zr, Hf)[19−24] have been used to catalyze the reaction. In this rearrangement, the choice of Lewis acid is critical to the yield and the stereoselectivity of the transformation.

To construct the A−C ring unit of Sch 47554 (**1**), we sought to utilize *O*-glycosidation of naphthol **6**, *O* to *C trans*-glycosidation, and subsequent further glycosidation via a Ferrier-type rearrangement[25] using glycal **4**. We have previously reported the synthesis of naphthol **6** from 1,4-difluoro-2,5-dimethoxybenzene (**7**) via a benzyne−furan Diels−Alder reaction (Scheme 1).[4] However, the *O* to *C trans*-glycosidation does pose several potential problems. It is known that the rearrangement of a naphthol with a halide substituent at C-3 is inefficient and only provides *C*-glycosides in very poor yields (<5%).[11,26,27] These results likely arise through perturbation by the halide substituent reducing electron density at the position ortho to the naphthol. Nonetheless, Suzuki has described the use of a catalytic quantity of scandium triflate[16] or excess hafnocene dichloride and silver perchlorate[21] to mediate the rearrangement of halo-substituted *O*-glycosides to provide *C*-glycosides in good to excellent yields. As convenient model studies, we sought to prepare the naphthyl disaccharide **8** (Figure 8) and related compounds

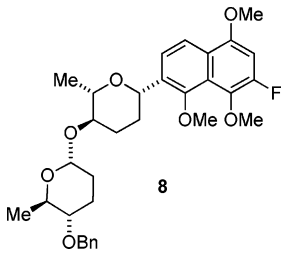


Figure 2. Target model disaccharide **8**.

corresponding to the enantiomers of the A−C ring units of the natural products **1** and **2**.

The glycosyl donor ***ent*-5** was synthesized from di-*O*-acetyl-L-rhamnal (**4**)[28] following reaction with water at 80 °C[11] to provide the *trans*-alkene **9**,[29] which was directly hydrogenated at ambient pressure to provide the lactol **10**[30] (Scheme 2). Subsequent acetylation gave the diacetate ***ent*-5**. Scandium triflate or hafnocene dichloride and silver perchlorate promoted condensation of the aryl fluoride **6** and acetate ***ent*-5** gave the desired equatorial *C*-aryl glycoside **11** (44% or 59% respectively) as a single diastereoisomer (Scheme 2). *O*-Methylation proceeded smoothly to provide naphthalene **12**, which was saponified using methanolic potassium carbonate to give alcohol **13**. Ferrier-type rearrangement of di-*O*-acetyl-D-rhamnal[31] (***ent*-4**) in the presence of alcohol **13** promoted by indium trichloride[32] gave acetate

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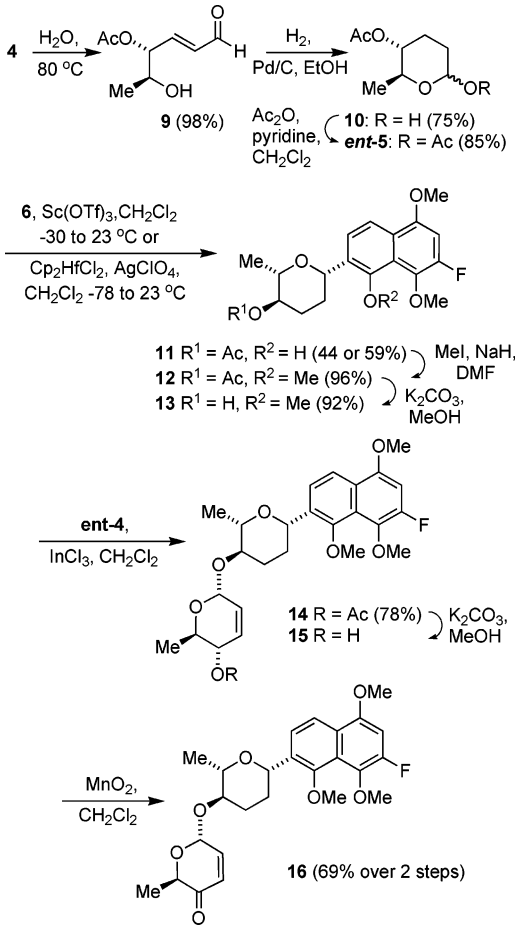
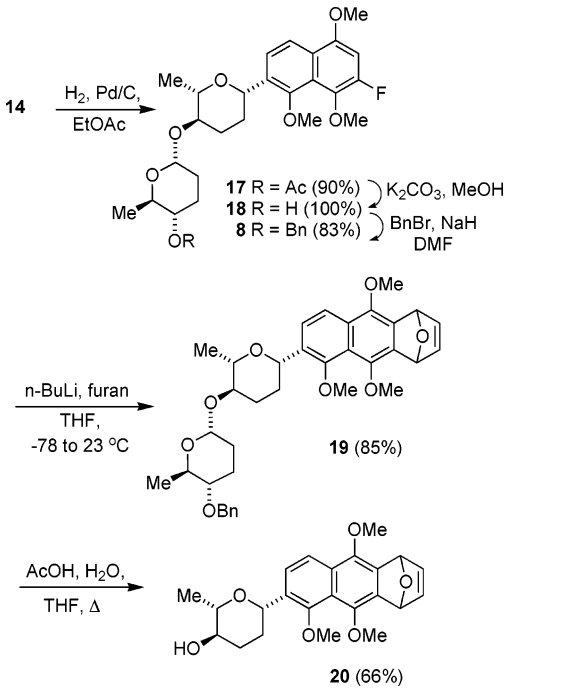
Scheme 2. Synthesis of Disaccharide **16**



Scheme 3. Synthesis of the Ring A−C Unit **8** and Cycloaddition with Furan



14 (78%). The full structure and relative stereochemistry of *C*-glycoside **14** was confirmed by X-ray crystallographic structure determination. Subsequently enone **16** was prepared in two steps (69%) by hydrolysis of acetate **14** using potassium carbonate in methanol followed by immediate oxidation of the unstable alcohol **15** using manganese dioxide.

Hydrogenation of alkene **14** and subsequent saponification gave the ring A−C unit of *ent*-Sch 47555 **18** (90%). In contrast saponification of **14** followed by hydrogenation resulted in extensive decomposition. To examine benzyne formation, alcohol **18** was protected as the benzyl ether **8** (83%) and allowed to react with *n*-butyllithium and furan. This gave the cycloadduct **19** (85%) as a 1:1 mixture of diastereoisomers (Scheme 3). Cycloadduct **19** was allowed to react with acetic acid in tetrahydrofuran at reflux to give the *C*-aryl glycoside **20** (66%). Clearly, the disaccharide unit proved to be more prone to cleavage than the oxa-bridged 1,4-dihydroanthracenyl unit under acidic conditions.

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In summary, we have successfully prepared enantiomeric model ring A−C disaccharide units **16** and **8** for Sch 47554 (**1**) and Sch 47555 (**2**) from difluoride **7** using *O* to *C trans*-glycosidation and a Ferrier-type *O*-glycosidation. In addition, the fluoride **8** was converted into the corresponding benzyne, which was trapped with furan in a Diels−Alder reaction. Further investigations into the total synthesis of Sch 47554 (**1**) and Sch 47555 (**2**) will be reported in due course.

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Supporting Information Available: Experimental procedures and structural data for all new compounds; X-ray crystallographic structure for **14** (CIF); copies of ^{1}H NMR, ^{13}C NMR, and NOESY NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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