

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

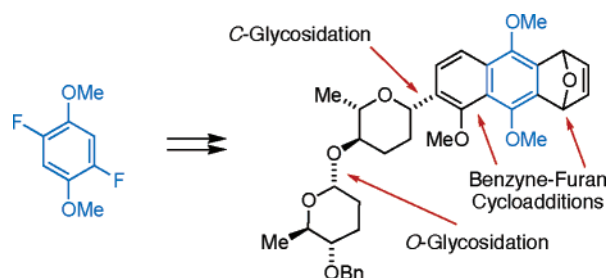
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ABSTRACT



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 oxabridged 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 antibiotics¹ 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**).

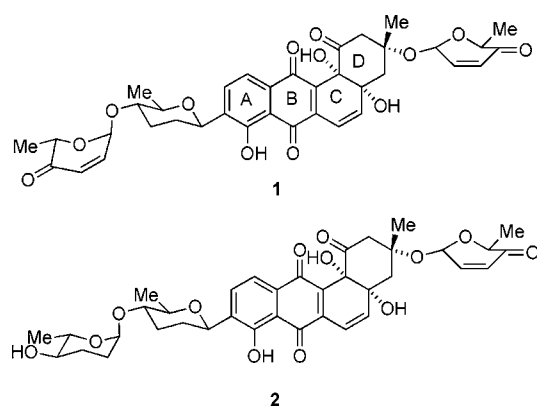


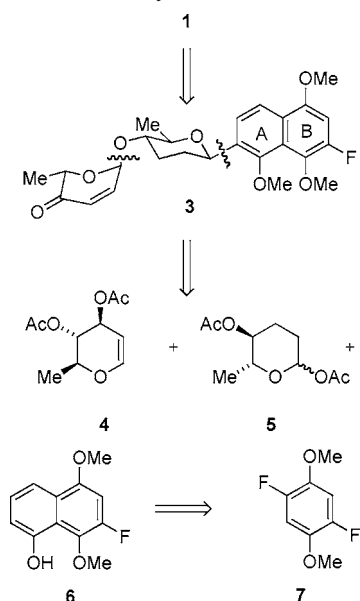
Figure 1. Sch 47554 (**1**) and Sch 47555 (**2**).

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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.

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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 rearrangement²⁵ using glycal **4**. We have previously reported the synthesis of naphthol **6** from 1,4-difluoro-2,5-dimethoxybenzene (**7**) via a benzene–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 triflate¹⁶ or excess hafnocene dichloride and silver perchlorate²¹ 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

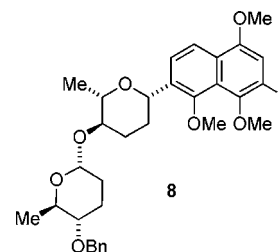


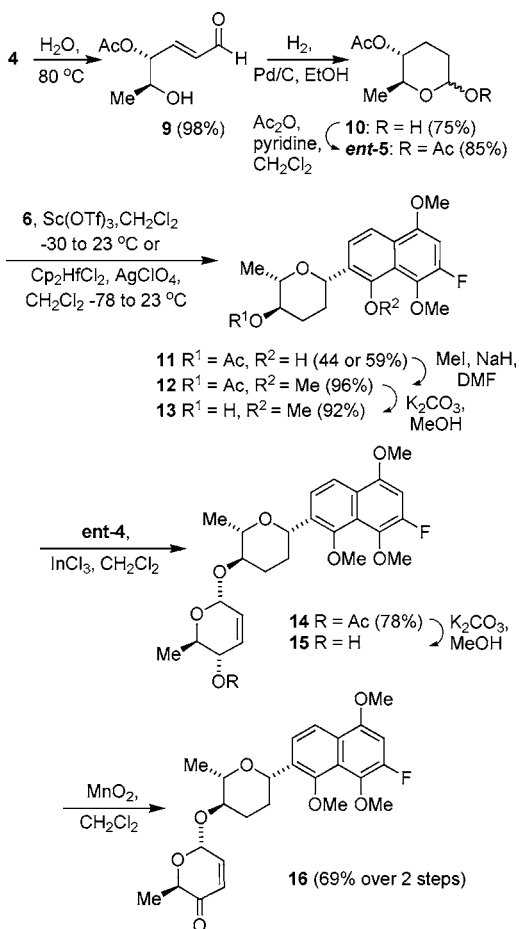
Figure 2. Target model disaccharide **8**.

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 °C¹¹ 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-rhamnal³¹ (*ent*-**4**) in the presence of alcohol **13** promoted by indium trichloride³² gave acetate

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Scheme 2. Synthesis of Disaccharide **16**

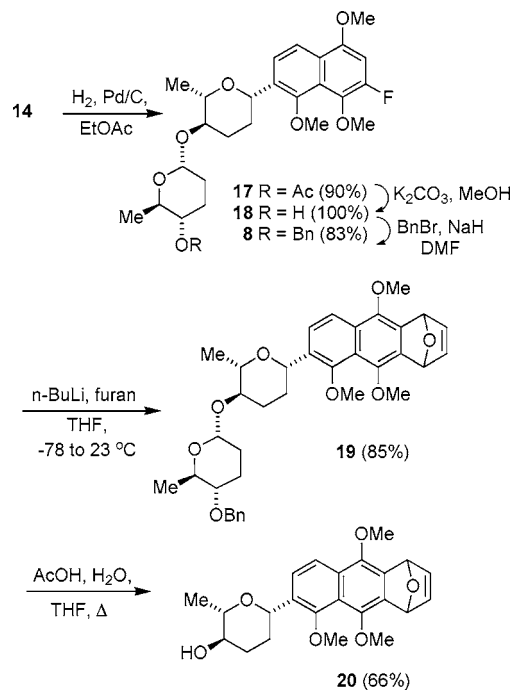


14 (78%). The full structure and relative stereochemistry of C-glycoside **14** was confirmed by X-ray crystallographic structure determination. Subsequently enone **16** was prepared in two steps (69%) by hydrolysis of acetate **14** using potassium carbonate in methanol followed by immediate oxidation 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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Scheme 3. Synthesis of the Ring A–C Unit **8** and Cycloaddition with Furan



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 ¹H NMR, ¹³C 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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