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Synthetic Study toward Vineomycins. Synthesis of C-Aryl Glycoside Sector via Cp_2HfCl_2-$AgClO_4$-Promoted Tactics

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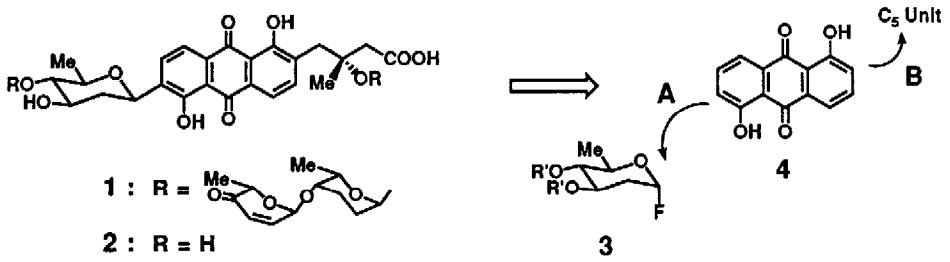
Summary: Regio- and stereo-controlled formation of C-aryl β-D-olivoside linkage is achieved by the reaction of naphthol or anthrol derivatives with D-olivosyl fluoride. The reaction is efficiently promoted by Cp_2HfCl_2-$AgClO_4$ and the bond formation occurs selectively at the ortho position of the phenolic hydroxyl. A short and stereoselective synthesis of the C-aryl glycoside sector of vineomycin B_2 is described.

C-Aryl glycosidic bonds are characteristically embedded in several novel classes of quinone antibiotics such as aquayamycin and pluramycins[1] in which the sugars are directly bound to the polyarene chromophores by C-C bond. The unique structures as well as the significant bioactivities, *e.g.*, antitumor properties, stimulated a growing synthetic interests to these compounds.

Vineomycin B_2 (1) is an antitumor antibiotic isolated from *Streptomyces matensis veneus*,[2] whose structure with such anthraquinone C-glycoside is synthetically attractive, since it condenses the essential problems in the synthesis of this class of antibiotics. There have been reported some synthetic efforts and also the total synthesis of aglycon 2 by the pioneering work by Danishefsky.[3]

We have recently exploited a new C-glycosidation of phenols based on the O→C glycoside rearrangement, which effects the regioselective formation of sugar-aryl bond at the *ortho*-position of phenolic hydroxyl (**Scheme 1**; next page).[4] To test its synthetic potential, we embarked on the synthetic study of 1 based on the retrosynthesis shown below. The initial focus was centered on the selective formation of bond **A**, where the D-olivosyl donor **3** and the synthon of anthrarufin (**4**) must be carefully designed for the coupling reaction. An additional and seemingly difficult problem is the stereocontrol in the glycosidation of *2-deoxy* sugar **3**.

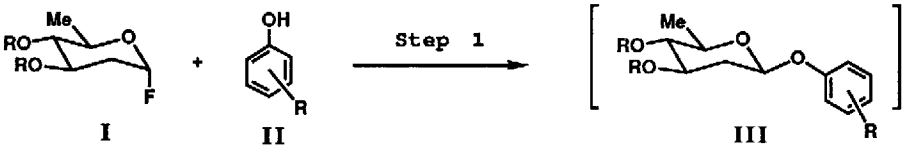
In this communication, we wish to describe the preliminary but quite promising results for the regio- and stereo-controlled formation of C-aryl glycosidic bond between **3** and **4**.



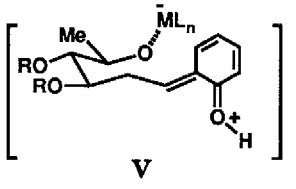
Scheme 1 summarizes the approach based on the O→C glycoside rearrangement: the initial O-glycosidation of phenol II with glycosyl fluoride I proceeds at low temperature (Step 1) and the resulting O-glycoside III rearranges to its C-congener IV by raising the temperature (Step 2). Both processes

proceed sequentially *in one pot* in the presence of Lewis acid such as $BF_3 \cdot OEt_2$ or Cp_2MCl_2-$AgClO_4$ (M = Zr, Hf), a new glycosidic activator we recently found.[4)]

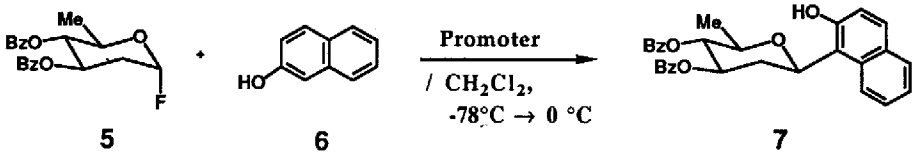
Scheme 1



Our former experiences suggested that there is an additional step in this scheme, that is, the Lewis acid-catalyzed conversion of the kinetically formed α/β-mixture of IV to the thermodynamically favored anomeric composition *via* the intermediacy of V (Step 3). In the present case, this ring opening-reclosure would give β-olivoside mainly, since the anomeric effect is no longer decisive at the stage of C-glycoside IV.[5)]



With this scenario in mind, we examined the reaction of 3,4-di-O-benzoyl-D-olivosyl fluoride (5)[6)] with some naphthol and anthrol derivatives.



Promoter	Yield	α / β
Cp_2HfCl_2 - $AgClO_4$	98 %	β only
$BF_3 \cdot OEt_2$	70 % [a)]	3.4 / 1

a) Besides, corresponding O-Glycoside was isolated in 28 % yield (α/β = 4.6/1).

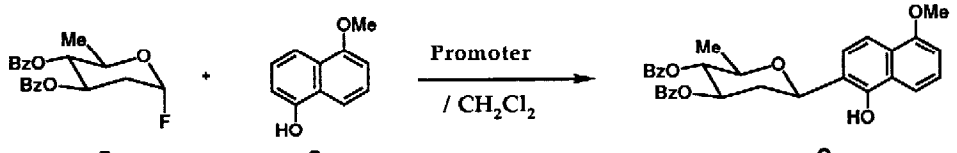
Fluoride 5 was added to a mixture of Cp_2HfCl_2, $AgClO_4$, and 2-naphthol (6) (each 3 equiv. per 5) in CH_2Cl_2 at -78 °C in the presence of molecular sieves 4A. After complete consumption of 5 (ca. 5 min at - 78 °C), the temperature was gradually raised to 0 °C during 1 h. Under these conditions, the desired C-glycoside 7 was cleanly formed in excellent yield. Moreover, the anomeric center of 7 was solely β as evidenced by ^1H NMR: δ 5.73 (H_1, dd, $J_{H1\text{-}2eq}$ = 2.0 Hz, $J_{H1\text{-}2ax}$ = 11.7 Hz) with the $^4C_1$(D) conformation inferred from $J_{H3\text{-}4} = J_{H4\text{-}5}$ = 9.8 Hz.[7)]

Markedly different result was obtained by the same reaction utilizing $BF_3 \cdot OEt_2$ (3 equiv.) as the reaction promoter. The initial O-glycosidation was similarly rapid around -70 °C, however, the subsequent O→C rearrangement was considerably slower to result in the decreased yield of 7 and the

unrearranged O-glycoside was also obtained in 28 % yield (see table). Moreover, an impressive reversal of the anomer ratio was observed to give rise to α-7 predominantly. Thus, both of the two processes, the O→C rearrangement (Step 2) as well as the anomerization (Step 3), are facilitated more efficiently by Cp_2HfCl_2-$AgClO_4$ than BF_3•OEt_2.

Reaction of **5** with 5-methoxy-1-naphthol (**8**) was next carried out, which turned out to be more problematic. Use of BF_3•OEt_2 led to intractable mixture and the only isolable product was α-O-glycoside (39 %). By using Cp_2HfCl_2-$AgClO_4$ (3 equiv. each), we were able to isolate the desired C-glycoside **9** (β), however, in moderate yield.

We recently found that use of Cp_2HfCl_2-$AgClO_4$ in 1:2 molar ratio (rather than 1:1) provides higher activation level of glycosyl fluoride.[8] Actually, the reaction of **5** and **8** by using Cp_2HfCl_2 (3 equiv.) and $AgClO_4$ (6 equiv.) cleanly afforded C-glycoside **9** in 78 % yield, and here again, β-**9** was the sole product and neither α-**9** nor O-glycosides were isolated.

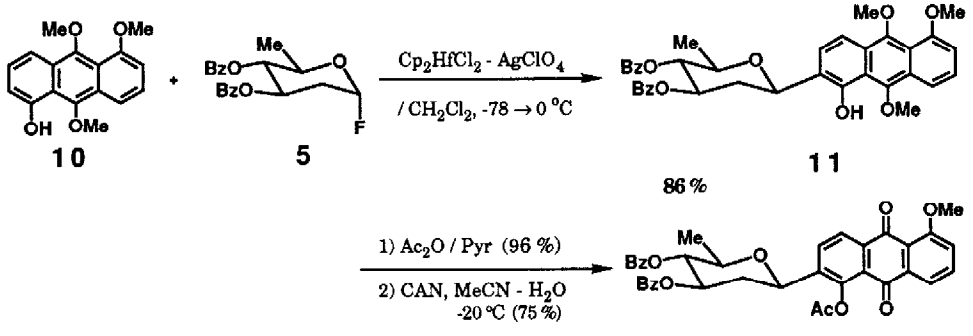


5 **8** **9**

Promoter	Conditions	Yield	α / β
BF_3•OEt_2	-78 °C → 0 °C	– a)	–
Cp_2HfCl_2 - $AgClO_4$ (1 : 1)	-78 °C → r. t.	50 %	β only
Cp_2HfCl_2 - $AgClO_4$ (1 : 2)	-78 °C → 0 °C	78 %	β only

a) α-O-Glycoside was isolated in 39 % yield.

Based on these model reactions, we finally attempted the reaction of **5** with an anthrol derivative **10**, readily derivable from commercial anthrarufin (**4**).[9] The reaction was cleanly effected by Cp_2HfCl_2-$AgClO_4$ (3 equiv. each) to give β-glycoside **11** in 86 % yield as the sole product. Further, simple acylation and oxidation converted **11** to an anthraquinone C-glycoside **12** in high yield.



10 **5** **11** **12**

The anthracene β-C-olivosides, **11** and **12**, correspond to the C-glycoside sector of vineomycin B_2, which will find versatility as synthetic intermediates in the total synthesis.

In summary, the C-aryl glycosidation based on the O→C rearrangement promoted by Cp_2HfCl_2-$AgClO_4$ provides a quite promising solution to the regio- and stereo-selective synthesis of C-aryl glycoside class of natural products. Further study directed toward the total synthesis of vineomycins is now in progress and the results will be reported shortly.

Acknowledgments: Financial support from the Ministry of Education, Science and Culture of Japan [Grant-in-aid for Scientific Research on Priority Area (No. 01649519)] is deeply acknowledged.

References and Notes

1) Aquayamycin: M. Sezaki, S. Kondo, K. Maeda, H. Umezawa, and M. Ohno, *Tetrahedron*, **26**, 5171 (1970); Pluramycins: H. Nadig and U. Séquin, *Helv. Chim. Acta*, **70**, 1217 (1987).

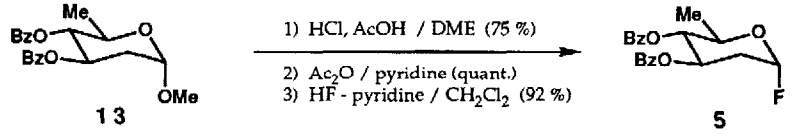
2) N. Imamura, K. Kakinuma, N. Ikekawa, H. Tanaka, and S. Ōmura, *J. Antibiot.*, **34**, 1517 (1981).

3) Total Synthesis: S. J. Danishefsky, B. J. Uang, and G. Quallich, *J. Am. Chem. Soc.*, **107**, 1285 (1985). Synthetic approaches: M. A. Tius, J. G.-Galeno, and J. H. Zaidi, *Tetrahedron Lett.*, **29**, 6909 (1989); K. Krohn and W. Baltus, *Tetrahedron*, **44**, 49 (1988).

4) T. Matsumoto, M. Katsuki, and K. Suzuki, *Tetrahedron Lett.*, **29**, 6935 (1988). Also see, T. Matsumoto, H. Maeta, K. Suzuki, and G. Tsuchihashi, *Tetrahedron Lett.*, **29**, 3567, 3571, 3575 (1988).

5) T. Matsumoto, M. Katsuki, and K. Suzuki, *Tetrahedron Lett.*, **30**, 833 (1989).

6) Glycosyl fluoride **5** was prepared as follows:



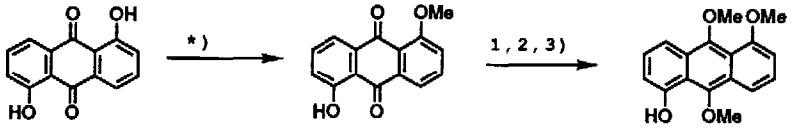
13 **5**

For the preparation of **13**, see J. Staněk, Jr., M. Marek, and J. Jarý, *Carbohydr. Res.*, **64**, 315 (1978). For fluorination: M. Hayashi, S. Hashimoto, and R. Noyori, *Chem. Lett.*, **1984**, 1747.

7) All new compounds were fully characterized by ^1H NMR (400 MHz), IR, and HRMS. Selected ^1H NMR data relevant to the determination of anomeric stereochemistry follow: α-**7**: δ 6.20 (H_1, dd, $J_{H1\text{-}2ax}$ = 12.2 Hz, $J_{H1\text{-}2eq}$ = 2.0 Hz), δ 5.56 (H_4, m, $J_{H3\text{-}4}$, $J_{H4\text{-}5} \leq$ 2Hz). β-**9**: δ 5.08 (H_1, dd, $J_{1\text{-}2ax}$ = 11.7 Hz, $J_{1\text{-}2eq}$ = 2.4 Hz). β-**11**: δ 5.40 (H_1, dd, $J_{H1\text{-}2ax}$ = 11.7 Hz, $J_{H1\text{-}2eq}$ = 2.0 Hz), δ 5.40 (H_4, dd, $J_{H3\text{-}4} = J_{H4\text{-}5}$ = 9.76 Hz) β-**12**: δ 4.91 (at 55 °C*); H_1, dd, $J_{H1\text{-}2ax}$ = 11.4Hz, $J_{H1\text{-}2eq}$ = 1.8 Hz), δ 5.31 (H_4, dd, $J_{H3\text{-}4} = J_{H4\text{-}5}$ = 9.5 Hz). *) Measurement at ambient temperature only showed a broad signal of the anomeric-proton, presumably, due to the hindered rotation of the sugar-aryl single bond.

8) K. Suzuki, H. Maeta, and T. Matsumoto, submitted for publication.

9) Anthrol **10** was prepared from commercially available anthrarufin (**4**) as follows:



4 **14** **10**

Keys: 1) MOMCl, $(i\text{-}Pr)_2NEt$ / CH_2Cl_2 (quant.); 2) H_2, Pd-C / DMF, then NaH, Me_2SO_4 (95 %); 3) EtSH, $BF_3 \cdot OEt_2$ / CH_2Cl_2 (92 %).

*) P. N. Preston, T. Winwick, and J. O. Morley, *J. Chem. Soc., Perkin I*, **1983**, 1439.

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