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New Approach to C-Aryl Glycosides Starting from Phenol and Glycosyl Fluoride. Lewis Acid-Catalyzed Rearrangement of O-Glycoside to C-Glycoside#

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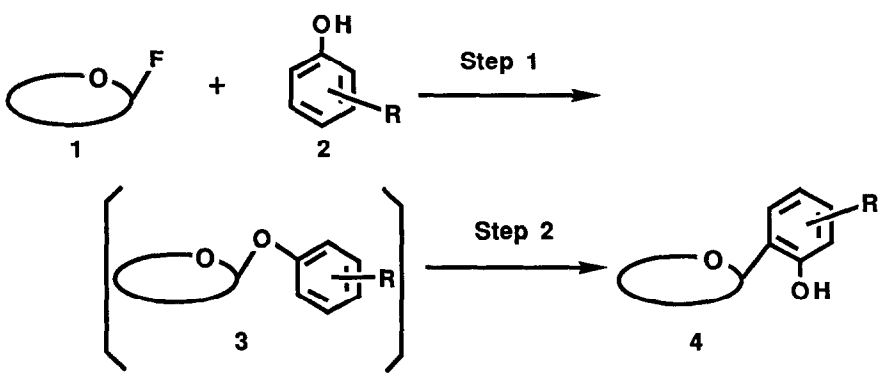
Summary: C-Glycosidation of phenols is achieved by treatment of glycosyl fluoride with phenolic compound under Lewis acidic conditions, which leads to initial O-glycoside formation followed by rearrangement to C-congener. Cp_2HfCl_2-$AgClO_4$ *is particularly effective for this conversion.*

C-Aryl glycosides are now attracting growing interests stemming not only from the well-recognized versatility in C-nucleoside area[1] but also from the recent finding of new classes of antitumor compounds possessing C-aryl glycoside linkage, such as aquayamycin[2a] and pluramycin.[2b] Thus, several synthetic approaches have been recently proposed toward these particular structures.[3]

Scheme 1



We tested an unexplored approach as shown in Scheme 1, based on the rearrangement[4] of O-aryl glycoside **3** to its C-congener **4**. This tactics proved to be promising after a series of model study described in this communication. Both of the two processes, the O-glycoside formation (step 1) and the rearrangement (step 2), are promoted by Lewis acids such as $BF_3 \cdot OEt_2$ and $SnCl_4$. Both steps were even more effectively accelerated by a new activator of glycosyl fluoride, Cp_2MCl_2-$AgClO_4$ (M=Ti, Zr, Hf), which we have found in our recent study on macrolide synthesis.[5]

Model experiments were carried out by the treatment of ribose-derived

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#*Dedicated to the memory of the late Professor Gen-ichi Tsuchihashi.*

fluoride 5[6] with phenol (**6a**) or *p*-methoxyphenol (**6b**) in the presence of Lewis acid. Table 1 clearly shows the difference of three kinds of Lewis-acidic promoters, i.e. $BF_3 \cdot OEt_2$, $SnCl_4$, and Cp_2HfCl_2-$AgClO_4$.

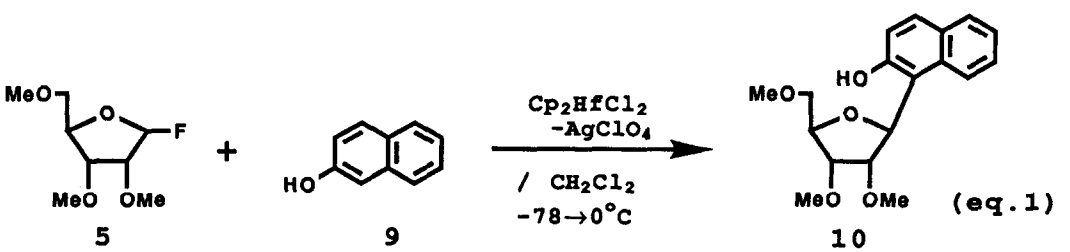
The progress of this two-step process could be outlined as follows: The initial step, O-glycosidation, proceeds rapidly at -78°C within 10 min in standard cases. After consumption of **5** (detected by TLC), gradual warming of the reaction mixture causes the rearangement of the initial O-adduct **7** into its C-congener **8**.[7,8,9] While step 1 is quite rapid by any of the Lewis acids, step 2 is highly dependent on the nature of the promoter as judged by the temperature required for completion of the reaction (cf. run 5, 7, 9).

With the weaker activator, $BF_3 \cdot OEt_2$, the latter step (rearrangement) was incomplete at -20°C (run 4), even after prolonged reaction period. Further warming, however, cleanly afforded the desired product **8** in high yield (run 5), which indicates the mildness of the reagent toward both the intermediary O-adduct **3** and the final product **8**. Thus, $BF_3 \cdot OEt_2$ proved to be synthetically useful in this context.

In contrast, many unidentified byproducts tend to be formed with $SnCl_4$ (run 2, 7), although its reactivity as a Lewis acid appears to be higher than that of $BF_3 \cdot OEt_2$. Interestingly, α-**8** predominated, though the reason is unclear.[10,11]

The equimolar mixture of Cp_2HfCl_2 and $AgClO_4$ effected the rearrangement to proceed smoothly and cleanly around -20°C. The efficiency of this metallocene-based promoter, particularly in step 2, is notable from both synthetic and mechanistic standpoints.[12] The prominence of this mixed promoter is further demonstrated when the reduced amount of the promoter is employed. A half equivalent of the promoter suffices (run 11), which is in sharp contrast to other two promoters (run 6, 8). The related promoters, Cp_2MCl_2-$AgClO_4$ (M=Zr or Ti), exhibited slightly lower reactivities compared with the Hf-system.

The glycosyl-aryl bond forms at the *ortho* position to the phenolic hydroxyl in high, if not exclusive, regioselectivity. In cases of phenol (run 1-3), small amount (ca. 5 %) of *para*-C-glycoside was obtained.[11]

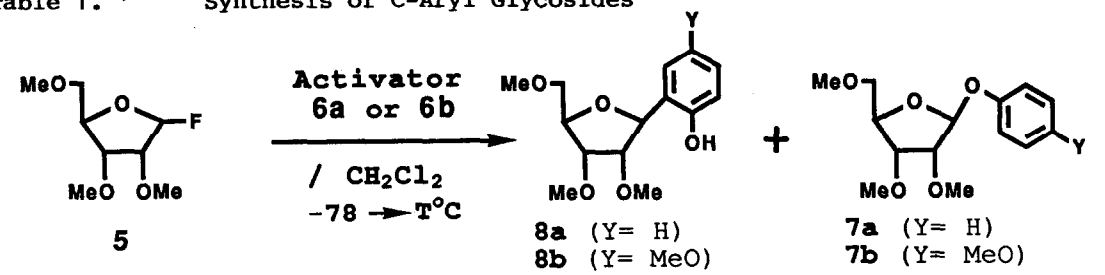


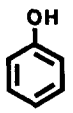
92%, α/β = 1/9

Coupling with 2-naphthol gave an excellent result (eq. 1). The anomeric composition was largely *beta*, and the aromatic substitution occurred exclusively at the C(1)-position as evidenced by the extensive NMR study.[11]

The present methodology opens an new and promising entry into C-aryl glycosidic compounds. Further investigation is now in progress.

Table 1.[9,11] Synthesis of C-Aryl Glycosides



Run	Phenol[a]	Activator (equiv.)	Temp.[b] -78→ T°C	8	(α/β)	7 (α/β)
1	 6a	$BF_3 \cdot OEt_2$ (3.0)	-5	45	(5/1)[d]	28
2		$SnCl_4$ (3.0)	-10	51	(4/1)[d]	9
3		Cp_2HfCl_2 -$AgClO_4$ (3.0)	-20	71	(1/14)[d]	—[e]
4	 6b	$BF_3 \cdot OEt_2$ (3.0)	-20	50	(1/1)	41 (1/7)
5		(3.0)	+15	85	(1/9)	—[e]
6		(0.5)	-20	14	(3/1)	71 (1/6)
7		$SnCl_4$ (3.0)	-15	73	(5/1)	6
8		(0.5)	-20	11	(14/1)	67 (1/4)
9		Cp_2HfCl_2 -$AgClO_4$ (3.0)	-20	79	(1/9)	—[e]
10		(1.5)	-20	76	(1/10)	—[e]
11		(0.5)	-20	76	(1/11)	—[e]
12		(0.25)	0	31	(1/1)	59 (1/5)

a) Two equiv. were used; b) See typical procedure; c) Yields and ratios are based on isolated pure materials; d) Besides the shown yield of 8, para-C-isomer was isolated in ca. 5 %; e) Not detected.

Typical procedure: To a stirred mixture of Cp_2HfCl_2 (81.6 mg, 215 μmol), $AgClO_4$ (44.6 mg, 215 μmol), p-methoxyphenol (35.5 mg, 287 μmol) and powdered molecular sieves 4A (ca. 200 mg) in CH_2Cl_2 (0.5 ml) was added fluoride **5** (27.8 mg, 143 μmol) in CH_2Cl_2 (1.5 ml) at -78°C, and temperature was gradually raised to -20°C during 30 min. After stirring for another 30 min, reaction was stopped by saturated $NaHCO_3$ solution. Filtration (Celite pad), extractive workup and purification by TLC (silica gel; hexane/AcOEt=3/7) gave α-**8b** (2.9 mg, 6.7 %) and β-**8b** (29.8 mg, 69.7 %).

References and Notes

1) S. Hanessian and A. G. Pernet, Adv. Carbohydr. Chem. Biochem., 33, 111 (1976).
2) a) M. Sezaki, S. Kondo, K. Maeda, H. Umezawa, and M. Ohno, Tetrahedron, 26, 5171 (1970); b) H. Nadig and U. Sequin, Helv. Chim. Acta, 70, 1217 (1987).
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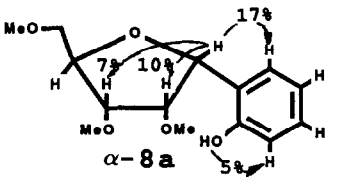
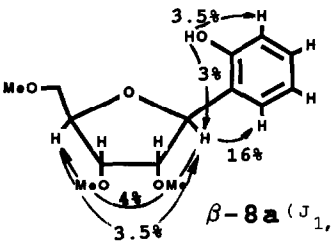
4) H. J. Shine, in "Aromatic Compounds," H. Zollinger, Ed., MTP Int. Rev. Sci., Org. Chem. Ser. 1, Vol 3, Butterworths, London (1973), pp 65-103.
5) T. Matsumoto, H. Maeta, K. Suzuki, and G. Tsuchihashi, Tetrahedron Lett., 29, 3567, 3571, 3575 (1988).
6) Fluoride 5 was prepared from the corresponding lactol by $(HF)_n$·pyr / CH_2Cl_2, 0 °C, 1 hr (77 %, α/β=1/1). ^1H NMR (δ, $CDCl_3$) α-form: 5.55 (dd, $J_{1,F}$ = 65.4, $J_{1,2}$ = 2.5 Hz); β-form: 5.46 (d, $J_{1,F}$ = 64.2 Hz, ($J_{1,2}$ = 0 Hz)); W. A. Szarek, G. Grynkiewicz, B. Doboszewski, and G. W. Hay, Chem. Lett., 1984, 1751.
7) In solvents with stronger donor property, e.g. Et_2O, CH_3CN, the reaction cleanly stops at the O-glycosidation stage, the details of which will be reported soon.
8) This procedure gave better result than the reaction carried out at a certain higher temperture from the outset.
9) All new compounds were fully characterized by ^1H NMR (400 MHz), ^{13}C NMR (100 MHz), IR and high-resolution MS.
10) Typical $J_{1,2}$ values of 8 are 2~3 Hz (for α), ca. 8 Hz (for β), respectively.
11) The anomeric stereochemistry and the regiochemistry of aromatic substitution were determined by NOE and decoupling study as typified by the case of **8a** shown below.

(In $CDCl_3$)

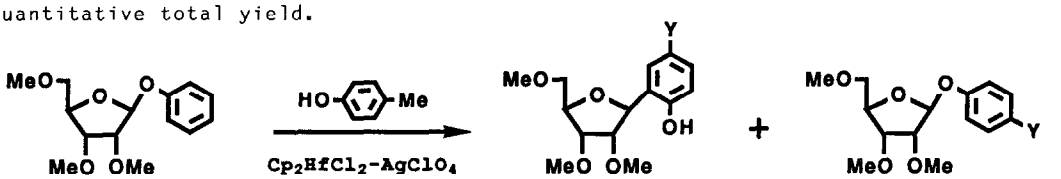


α-**8a** ($J_{1,2}$ = 2.5 Hz)



β-**8a** ($J_{1,2}$ = 7.8 Hz)

12) Preliminary mechanistic study revealed the rearrangement step is composed of the competitive intra-/inter-molecular paths, as evidenced by a crossover experiment shown below, which afforded a mixture of all the possible products (**7a**, **7c**, **8a**, **8c**) in quantitative total yield.



7a

8a: Y=H
8c: Y=Me

7a: Y=H
7c: Y=Me

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