# Improvement in O→C-Glycoside Rearrangement Approach to C-Aryl Glycosides:

Use of 1-O-Acetyl Sugar as Stable but Efficient Glycosyl Donor

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Summary: 1-O-Acetyl sugars serve as efficient glycosyl donor in the O→C-glycoside rearrangement approach to C-aryl glycosides. Model study was carried out on three types of 2-deoxy-glycosyl acetates including amino sugar derivative. Comparison of the promoters, Cp_2HfCl_2-$AgClO_4$, $SnCl_4$, $BF_3 \cdot OEt_2$ is described.

Aryl C-glycosides constitute an emerging class of synthetic targets in light of their bioactivities as well as the unique structual features.[1] For an access to such C-aryl glycoside structures, we recently reported a promising approach, *i.e.*, *the O→C-glycoside rearrangement approach* (Scheme 1).[2] The two-stage reaction proceeds in one pot in the presence of Lewis acid. Step 1 is the low-temperature O-glycosidation of 1-fluoro sugar 1 with phenol derivative 3 to give O-glycoside 4, which is further converted *in situ* to *ortho*-C-glycoside 5 simply by raising the temperature.

Scheme 1
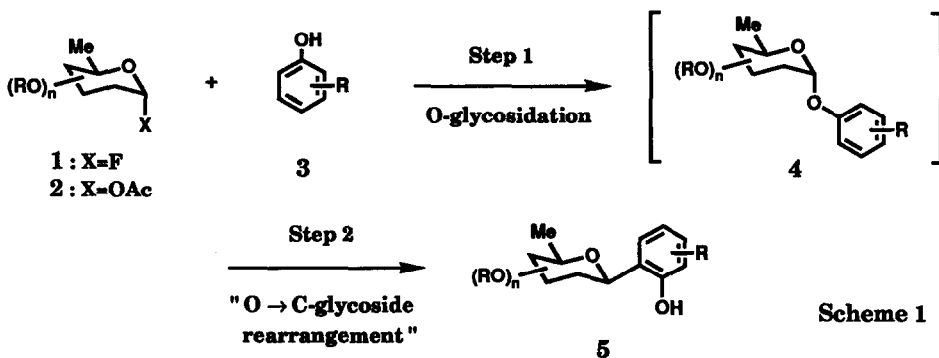
This method provides a new and efficient approach toward the *ortho*-C-aryl glycosides starting from phenol and glycosyl fluoride. We experienced in some cases, however, the experimental problem arising from the instability of glycosyl donor 1. Despite the pronounced shelf stability of 1-fluoro sugars in comparison with the 1-chloro or 1-bromo counterparts, we found nonetheless some 1-fluoro derivatives of 2-deoxy sugars are unstable for storage or even hard to be prepared in pure form.

We turned our attention to 1-O-acetyl sugar 2 as an alternative glycosyl donor with superior shelf stability. Even though acetyl sugar 2 is generally a less reactive glycosyl donor than fluoro sugar 1, we reasoned the first step (O-glycosidation) would go fast enough by virtue of the particular glycosyl acceptor, that is, phenol 3 possessing higher reactivity in comparison with the usual alcohols. Given the O-glycoside 4 was once formed, the process thereafter should be, *in principle*, the same as the original case using glycosyl fluoride 1.

Such a scenario is answered affirmatively by the model reactions described in the following.

Table 1[3)]
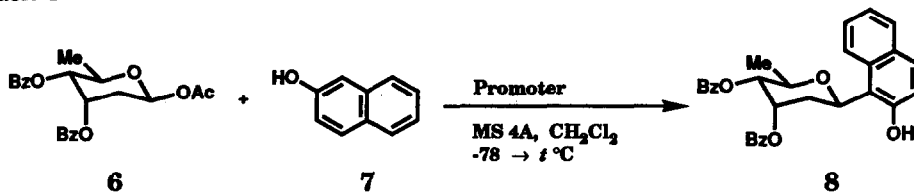
Run	Promoter	t (°C)	Yield (%)	α / β
1	BF$_3$•OEt$_2$[b)]	r. t.	75[a)]	1 / 4
2	SnCl$_4$[b)]	-25	99	1 / 14
3	Cp$_2$HfCl$_2$ - AgClO$_4$[c)]	-15	99	1 / 10

a) O-Glycoside was isolated in 16 % yield (α / β = 1.6 / 1).
b) Molar ratio: 6 : 7 : promoter = 1.0 : 2.0 : 3.0.
c) Molar ratio: 6 : 7 : Cp$_2$HfCl$_2$: AgClO$_4$ = 1.0 : 2.0 : 3.0 : 3.0.

Initial experiments were carried out on the 1-O-acetyl derivative of D-digitoxose 6,[4)] a sugar component seen in naturally occurring compounds.[5)] 2-Naphthol (7) was employed as the model phenol and three Lewis acidic reaction promoters, BF$_3$•OEt$_2$,[6)] SnCl$_4$,[7)] Cp$_2$HfCl$_2$-AgClO$_4$[8)] were employed for comparison.
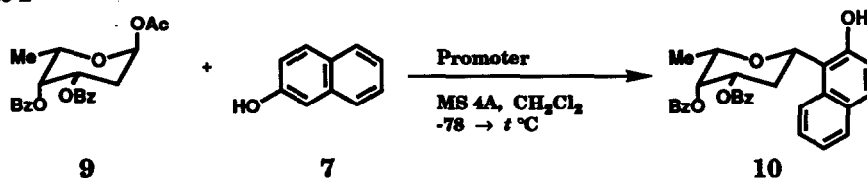
Representative procedure is described by the reaction of 6 and 7 promoted by Cp$_2$HfCl$_2$-AgClO$_4$ (run 3 in Table 1): To a stirred mixture of Cp$_2$HfCl$_2$ (126 mg, 0.34 mmol), AgClO$_4$ (70 mg, 0.34 mmol), 2-naphthol (7) (32 mg, 0.22 mmol) and powdered molecular sieves 4A (ca. 200 mg) in CH$_2$Cl$_2$ (1 ml) was added 1-O-acetyl sugar 6 (44 mg, 111 μmol) in CH$_2$Cl$_2$ (3 ml) at -78 °C. After confirming the completion of initial O-glycosidation (within 5 min by tlc assay), the temperature was gradually raised to -15 °C during 30 min to convert O-glycoside smoothly to C-glycoside 8.[3)] Usual workup and purification with TLC (silica gel; CCl$_4$ / ether = 85 /15) gave C-glycoside 8 (α-8: 5.0 mg, 9 % and β-8: 48 mg, 90 %).[3)]

Thus, a combined promotor, Cp$_2$HfCl$_2$-AgClO$_4$ is efficient even in the case when 1-O-acetyl sugar is employed. Moreover, SnCl$_4$, a poor promoter in the original protocol by using 1-fluoro sugar,[9)] is also effective in the present protocol. In contrast, BF$_3$•OEt$_2$ is less effective: the O-glycosidation required higher temperature (-20~0 °C) and yet the O-glycoside remained even after stirring at room temperature.

The anomeric composition was largely β, although a little amount of the α-anomer was detected. This stereochemical aspect is explained by the thermodynamic equilibration to the more stable β-anomer from the initially formed anomeric mixture.[2, 10)] Actually in the very early stage of the reaction, the C-glycoside was rich in the α-anomer as shown by a low-temperature quenching of the reaction of run 3 (-35 °C; α / β = 2.8 / 1; 8 % yield in 8).

Table 2 shows the application to the 1-O-acetyl derivative of 2-deoxy-L-fucose 9.[4)] Again, SnCl$_4$ and Cp$_2$HfCl$_2$-AgClO$_4$ worked quite well as the promoter, while BF$_3$•OEt$_2$ was substantially less effective. In this case, the resultant C-glycoside was exclusively β in each case. The α-anomer was not detected even when the reaction was stopped at -50 °C (in case Cp$_2$HfCl$_2$-AgClO$_4$ was employed).

Glycosidation of amino sugars is often a challenging problem in carbohydrate synthesis. Such amino sugars are embedded also in many naturally occurring C-aryl glycosides. For example, angolosamine is an amino sugar found as C-glycoside in medermycin- as well as benzanthrin-class antibiotics.[11)] Therefore, we next examined the C-aryl glycosidation of 1-O-acetyl derivative of D-angolosamine 11 (Table 3).[4)]

Table 2[3)]

9   7   10

Run	Promoter	t (°C)	Yield (%)	α / β
1	BF₃•OEt₂[b)]	r. t.	94[a)]	β
2	SnCl₄[b)]	-40	88	β
3	Cp₂HfCl₂ - AgClO₄[c)]	-15	98	β

a) O-Glycoside was isolated in 5 % yield (α-anomer only).
b) Molar ratio: 9 : 7 : promoter = 1.0 : 2.0 : 3.0.
c) Molar ratio: 9 : 7 : Cp₂HfCl₂ : AgClO₄ = 1.0 : 2.0 : 3.0 : 3.0.

BF₃•OEt₂ was totally ineffective, where the reaction stopped at the O-glycosidation stage even after prolonged refluxing.   With SnCl₄ also, the rearrangement step was slow and incomplete.   The combinational activator (Cp₂HfCl₂-AgClO₄) worked efficiently under specified conditions.   That is the employment of Cp₂HfCl₂ and AgClO₄ in 1 : 2 ratio rather than 1 : 1.[12)]   Although the slightly higher reaction temperature is required than the cases of neutral sugars, the high activation ability of this mixed reagent system is clearly documented, not only in the rearrangement step but also in the O-glycosidation step (at -20~0 °C).

Table 3[3)]

11   7   12
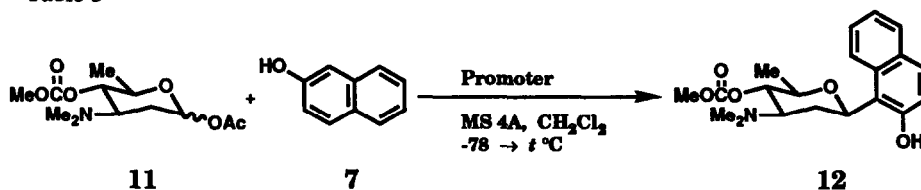
Run	Promoter	t (°C)	Yield (%)	α / β
1	BF₃•OEt₂[c)]	40	17[a)]	β
2	SnCl₄[c)]	40	47[b)]	β
3	Cp₂HfCl₂ - AgClO₄[d)]	40	94	β

a) O-Glycoside was isolated in 60 % yield (α / β = 7 / 1).
b) O-Glycoside was isolated in 43 % yield (α / β = 26 / 1).
c) Molar ratio: 11 : 7 : promoter = 1.0 : 3.0 : 3.0.
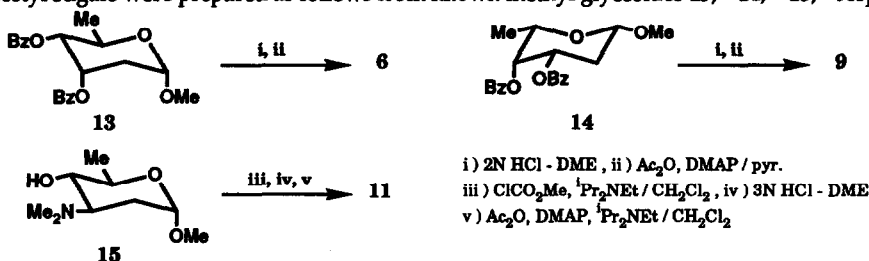d) Molar ratio: 11 : 7 : Cp₂HfCl₂ : AgClO₄ = 1.0 : 3.0 : 3.0 : 6.0.

In summary, 1-O-acetyl sugars nicely serve as an efficient glycosyl donor in the O→C-glycoside rearrangement approach to C-aryl glycoside compounds. Ready availability and high shelf stability of 1-O-acetyl sugars provides a particular advantage in this context. A promising protocol for the incorporation of amino sugar into aromatics is also described. Further study to expand the scope of the reaction and application to the total synthesis of natural products is under way in our laboratory.

References and Notes

1) For example, 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) T. Matsumoto, M. Katsuki, and K. Suzuki, *Tetrahedron Lett.*, **29**, 6935 (1988); T. Matsumoto, M. Katsuki, H. Jona, and K. Suzuki, *ibid.*, **30**, 6185 (1989).

3) All new compounds are fully characterized by 400 MHz ^{1}H-NMR, IR, and HRMS. Selected ^{1}H-NMR data (δ, CDCl$_3$) relevant to the determination of anomeric stereochemistry follow: β-8: $^4C_1$(D), δ 6.08 (H$_1$, t, J_{H1-2} = 7.3 Hz), δ 5.24 (H$_4$, dd, J_{H4-3} = 2.9 Hz, J_{H4-5} = 10.3 Hz), δ 2.48 (H$_2$, dd, J_{H2-3} = 2.9 Hz, J_{H2-1} = 7.3 Hz); α-8: $^1C_4$(D), δ 6.01 (H$_1$, dd, J_{H1-2ax} = 12.7 Hz, J_{H1-2eq} = 2.9 Hz); β-10: δ 5.74 (H$_1$, dd, J_{H1-2ax} = 11.7 Hz, J_{H1-2eq} = 2.4 Hz); β-12: δ 5.47 (H$_1$, dd, J_{H1-2ax} = 11.7 Hz, J_{H1-2eq} = 2.4 Hz).

4) 1-O-Acetyl sugars were prepared as follows from known methyl glycosides 13,[a] 14,[b] 15,[c] respectively.

i) 2N HCl - DME , ii) Ac$_2$O, DMAP / pyr.
iii) ClCO$_2$Me, ^{i}Pr$_2$NEt / CH$_2$Cl$_2$, iv) 3N HCl - DME
v) Ac$_2$O, DMAP, ^{i}Pr$_2$NEt / CH$_2$Cl$_2$

a) D. Horton, T. M. Cheng, and W. Weckerle, *Methods in Carbohyd. Chem.*, **8**, 201 (1980); b) D. Horton, T. M. Cheng, and W. Weckerle, *ibid.*, **8**, 195 (1980); c) P. Bartner, D. L. Boxer, R. Brambilla, A. K. Mallams, J. B. Morton, P. Reichert, F. D. Sancilio, H. Surprenant, G. Lukacs, A. Olesker, T. T. Thang, L. Valente, and S. Ōmura, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1600.

5) For example, Fridamycin B: P. Kricke and A. Zeeck, unpublished results; P. Kricke, Ph. D. Thesis, University Göttingen, 1984. We thank Prof. Zeeck for private communication.

6) T. Kometani, H. Kondo, and Y. Fujimori, *Synthesis*, **1988**, 1005.

7) S. Hanessian and J. Banoub, *Methods in Carbohyd. Chem.*, **8**, 243 (1980).

8) T. Matsumoto, H. Maeta, K. Suzuki, and G. Tsuchihashi, *Tetrahedron Lett.*, **29**, 3567, 3571, 3575 (1988).

9) In the case of 1-fluoro sugar, use of SnCl$_4$ tends to give multiple products as raising the temperature.

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

11) Medermycin: S. Takano, K. Hasuda, A. Ito, Y. Koide, F. Ishii, I. Haneda, S. Chihara, and Y. Koyama, *J. Antibiot.*, **29**, 765 (1976); Benzanthrin: R. J. Theriault, R. R. Rasmussen, W. L. Kohl, J. F. Prokop, T. B. Hutch, and G. J. Barlow, *ibid.*, **39**, 1509, 1515 (1986).

12) The excellent activation ability of the molar ratio of Cp$_2$HfCl$_2$-AgClO$_4$ = 1 : 2 was already described, which was tentatively ascribed to the incorporation of dicationic species: K. Suzuki, H. Maeta, and T. Matsumoto, *Tetrahedron Lett.*, **30**, 4853 (1989). In the present case, the use of 1 : 1 ratio led to considerable retardation in O→C-glycoside rearrangement stage.