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On the Stereochemistry of Aryl *C*-Glycosides: Unusual Behavior of Bis-TBDPS Protected Aryl *C*-Olivosides

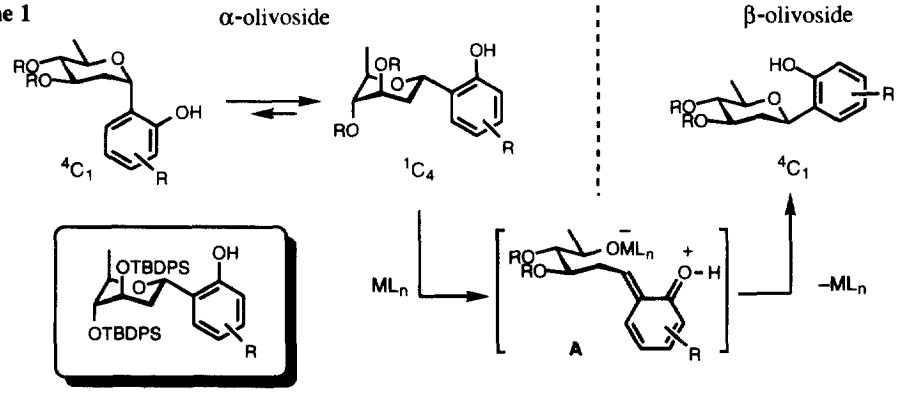
Takamitsu Hosoya, Yoriko Ohashi, Takashi Matsumoto, and Keisuke Suzuki*

Department of Chemistry, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223, Japan

Abstract: *A D-olivosyl donor in which the C(3) and C(4) hydroxyls are both protected by an extremely bulky group, t-BuPh$_2$Si, undergoes aryl C-glycosidation in an α-selective manner, and the product configuration remains unchanged under various Lewis acid conditions. The features are rationalized by the ring flipping of the pyranoside ring ($^1C_4$) in the glycosyl donor and the C-glycoside product, due to the severe repulsion of the siloxy groups.*

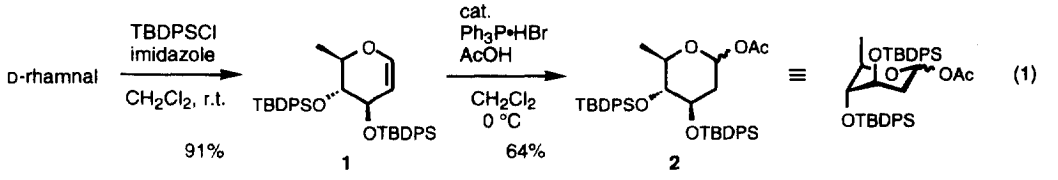
During the course of our synthetic study on aryl *C*-glycoside antibiotics,[1] we have prepared several aryl *C*-glycosides that possess D-olivose, a sugar typical of this class of natural products.[2] Although these aryl *C*-olivosides differ in their aromatic portion as well as the carbohydrate protecting groups, they show a general stereochemical behavior as summarized in Scheme 1. The conformation is dictated primarily by the strong preference of the C(1)-aryl group to orient equatorially, and the anomeric effect is generally negligible. Thus, of the two optional conformers of the α-olivoside, *i. e.*, $^4C_1$ and $^1C_4$, the latter prevails even by sacrificing three axial substituents. By contrast, the β-olivoside can adopt an ideal conformer, $^4C_1$ with all four substituents equatorial, which, therefore, is generally thermodynamically more stable than the α-anomer. Indeed, the Lewis acid-mediated equilibration of these anomers, via a quinone methide species as **A**,[2,3] gives the β-anomer, often as the exclusive product.

Scheme 1



However, we recently encountered a striking exception to this tendency, which is the subject of the present communication: *The α-anomer is favored when the C(3) and C(4) hydroxyls are protected by an extremely bulky group, t-butyldiphenylsilyl (TBDPS);* we believe this finding would add a novel insight into the stereochemistry of aryl *C*-glycosides.

Treatment of D-rhamnal with *t*-butyldiphenylsilyl chloride and imidazole gave the corresponding bis-TBDPS glycal **1** in 91% yield,[4] which was carefully subjected to the catalyzed addition of acetic acid[5] to give glycosyl acetate **2** in 64% yield as a mixture of anomers (α/β = 4/1; eq 1).[6] The ^{1}H NMR showed that both anomers of **2** adopt the flipped $^1C_4$ conformation, respectively (see below).



Acetate **2** was subjected to the aryl *C*-glycoside formation by the *O*→*C*-glycoside rearrangement.[2,3] Upon treatment with 2-naphthol in the presence of Cp_2HfCl_2 and $AgClO_4$, acetate **2** underwent a clean *C*-glycoside formation (CH_2Cl_2, –78 °C, 0.5 h) to give *C*-glycoside **3** as the sole detectable product in 91% yield (eq 2). Careful analysis of ^{1}H NMR revealed that **3** is the *α-anomer with the $^1C_4$ conformation.* This analysis was substantiated by the X-ray data of the methyl ether **4** (Fig. 1),[7] derived from **3** [$(MeO)_2SO_2$, K_2CO_3, acetone; 98% yield].[8,9] It should be noted that both of the bulky siloxy groups are axially oriented, and, hence, the pyranoside ring adopts the $^1C_4$ conformation.

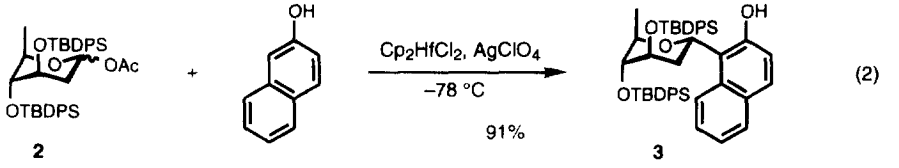
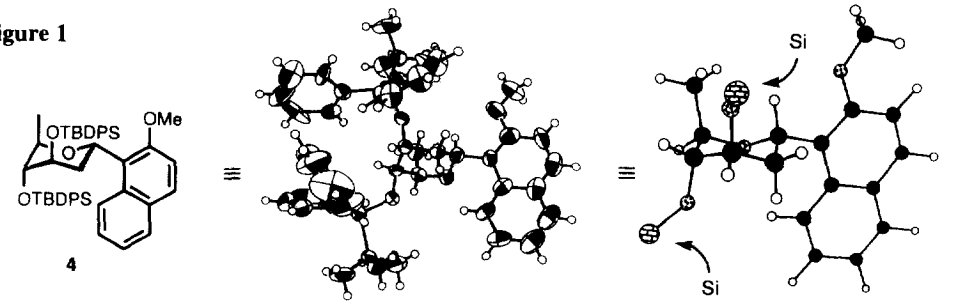


Figure 1

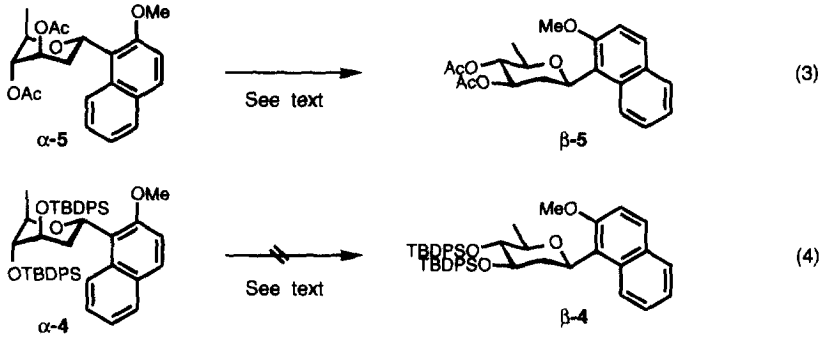


ORTEP drawing of X-ray structure

Chem3D from X-ray coordinates (Ligands on the silicons are omitted for clarity)

Moreover, in this particular *C*-glycoside **4** with bis-TBDPS protection, the α-anomer is not only selectively produced, but also is configurationally stable under various Lewis acid conditions as illustrated by the comparison experiments (eqs 3, 4). Diacetate **5** was prepared from **4** (CsF, DMF, 140 °C, 1 h; Ac_2O, 4-DMAP, pyr., 0.5 h; 87% yield), which proved to have the α-stereochemistry with the $^1C_4$ conformation. Toward the Lewis acid treatment, the behavior of the α-anomers of *C*-glycosides **4** and **5** was completely different. Upon exposure to Cp_2HfCl_2 and $AgClO_4$ (CH_2Cl_2, –78 °C → room temperature, 1 h),[2,3] α-**5** cleanly anomerized to give β-**5** (eq 3; 92% yield). No remaining α-**5** was detectable, and, needless to say, β-**5** was found to adopt the $^4C_1$ conformation. In sharp contrast, the bis-TBDPS counterpart α-**4** did not

undergo any anomerization under the same conditions (eq 4; 99% recovery). Attempts to obtain the β-anomer of **4** under the variety of Lewis acid conditions were unsuccessful.[10]



A possible rationale for these observations is the following. To avoid the severe *gauche* interaction (equatorial–equatorial), the siloxy groups become antiperiplanar to each other to cause a ring flipping (Fig. 2). This seemingly unfavorable $^1C_4$ conformation is justified by the unusually small A-value of a *t*-$BuPh_2SiO$ group.[11,12] Thus, the glycosyl donor **2**, with the $^1C_4$ conformation, undergoes an α-selective aryl *C*-glycosidation to give α-**3** (see eq 2), since the attack of an arene from the β-side is obviously discouraged by two 1,3-diaxial repulsions. In addition to this kinetic preference, even if an equilibration path is subsequently offered, the α→β transition would not be favorable because the β-anomer can not find any reasonable conformations (Fig. 3): the $^1C_4$ conformer is obviously unfavorable (all axial), while the $^4C_1$ counterpart would suffer from the *gauche* interaction as stated above.[13]

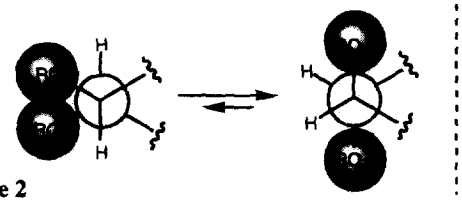


Figure 2

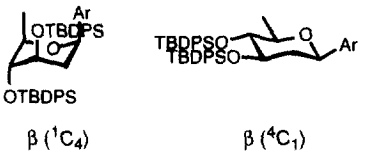
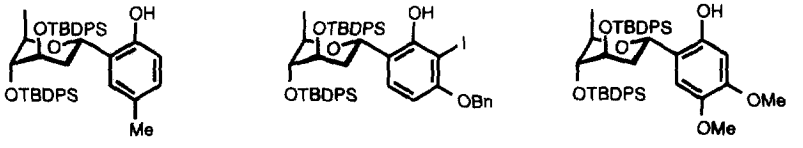


Figure 3

This finding is also of synthetic importance, offering a stereoselective access to α-aryl *C*-olivosides, which have been hitherto almost inaccessible.[1,2] Reactions of some other phenols with **2** gave the corresponding α-olivosides **6**–**8** as the sole product, respectively, and each proved to adopt the $^1C_4$ conformation.[9]

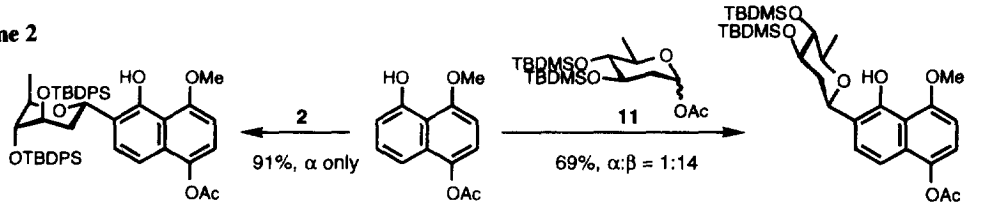


6 85% **7** 84% **8** 98%

Furthermore, a divergent approach to the α and β anomers of aryl *C*-olivosides is possible via the "fine tuning" of the protecting group (Scheme 2). A bis-silylated congener **11** with a reduced steric demand [n.b.: The silyl groups in **11** are **TBDMS** (*t*-butyldimethylsilyl) rather than **TBDPS**] showed a "normal" behavior. Glycosyl donor **11** adopts the $^4C_1$ conformation, and the aryl *C*-glycosidation occurred in a β-selective manner. Aside from the stereochemical context, it should be noted that the anomeric *C*-glycosides, **10** and

12, with trioxygenated naphthalene moiety, would serve as versatile intermediates toward various elaborate aryl *C*-glycoside antibiotics.[14]

Scheme 2



Reagents and conditions: Cp_2HfCl_2, $AgClO_4$, CH_2Cl_2, −78 °C

Acknowledgments: This work was supported by the Ministry of Education, Science and Culture of Japan [Grant-in-Aid for Scientific Research on a Priority Area (#05234105)].

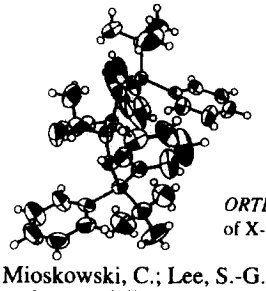
References and Notes

1 For reviews on aryl *C*-glycosides, see: (a) Hacksell, U.; Daves, G. D., Jr. *Prog. Med. Chem.* **1985**, *22*, 1. (b) Suzuki, K.; Matsumoto, T. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*; Lukacs, G., Ed.; Springer: Berlin, 1993; Vol. 2, p 353.

2 For example, see: (a) Matsumoto, T.; Katsuki, M.; Jona, H.; Suzuki, K. *J. Am. Chem. Soc.* **1991**, *113*, 6982. (b) Matsumoto, T.; Sohma, T.; Yamaguchi, H.; Kurata, S.; Suzuki, K. *Tetrahedron* **1995**, *51*, 7347, and the references cited therein. Note that our *C*-glycoside samples always have a hydroxyl group to the aryl *C*-glycoside linkage, as they were prepared via the *O*→*C*-glycoside rearrangement (ref 3).

3 For the *O*→*C*-glycoside rearrangement, see: Matsumoto, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1988**, *29*, 6935. Suzuki, K. *Pure Appl. Chem.* **1994**, *66*, 2175.

4 It is interesting to see the X-ray structure of glycal **1** (below),[7] in which two siloxy substituents are disposed to pseudo-axial orientation, and the ring is of a considerably flat half-chair conformation.



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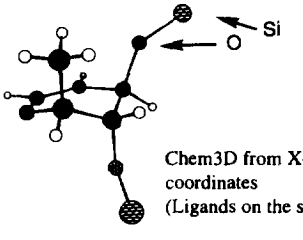

Chem3D from X-ray coordinates (Ligands on the silicons are omitted)

5 Bolitt, V.; Mioskowski, C.; Lee, S.-G.; Falck, J. R. *J. Org. Chem.* **1990**, *55*, 5812.

6 All compounds were fully characterized by ^{1}H-, ^{13}C-NMR, IR, HRMS and/or combustion analysis.

7 The X-ray crystallographic analyses were kindly performed by Drs. T. Tsuji and K. Ishikawa, Ajinomoto Co., to whom we express deep appreciation.

8 The close similarity of the coupling patterns of the ^{1}H NMR spectra of **3** and **4** supports the analysis.

9 Each of α-*C*-glycosides, **3**, **4**, **6**–**8** and **10**, shows similar coupling patterns of the ^{1}H NMR spectra: $J_{1,2ax}$ = 11.7–12.5 Hz, $J_{1,2eq}$ = 1.5–2.4 Hz, $J_{2ax,3}$ = 2.4–2.9 Hz.

10 To examine the behavior of **β-4**, we attempted to prepare it by bis-silylation of the diol, derived from **β-5**, which failed under a variety of conditions.

11 (a) Eliel, E. L.; Satici, H. *J. Org. Chem.* **1994**, *59*, 688. (b) Saito, S.; Hirohara, Y.; Narahara, O.; Moriwake, T. *J. Am. Chem. Soc.* **1989**, *111*, 4533.

12 For general discussion on the configuration and conformation of cyclic compounds, see: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: N.Y., 1994; Chapt. 11.4.

13 One of the referees suggested that we examine the behavior of the corresponding triisopropylsilyl derivative, as the silyl group is known as another extremely large group. The result turned out to be essentially the same as in the TBDPS case described herein. We thank the referee for the suggestion.

14 For an alternative approach to such structures, see: Matsumoto, T.; Sohma, T.; Yamaguchi, H.; Suzuki, K. *Chem. Lett.* **1995**, 677.

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