[1,2]-Wittig Rearrangement of Acetal Systems: A Highly Stereocontrolled Conversion of *O*-Glycosides to *C*-Glycosides

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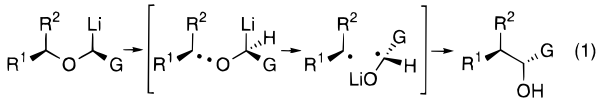
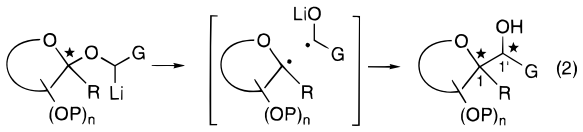
The [1,2]-Wittig rearrangement is a classic class of carbanion rearrangements which is now well recognized to proceed via the radical dissociation−recombination mechanism.[1,2] A unique feature of the rearrangement is that, despite its radical character, the stereogenicities of the two proradical centers are retained to appreciable extents, *i.e.*, retention of configuration at the migrating carbon and inversion at the Li-bearing terminus (eq 1).[2,3] However, the synthetic utilization of the [1,2]-Wittig



(1)

rearrangement remains severely limited, because of the rather low yields and restricted range of substrates,[4] whereas the [2,3]-Wittig sigmatropic version currently enjoys wide application in organic synthesis.[2b,5] Thus, we envisioned that acetal systems such as *O*-glycosides would undergo the [1,2]-Wittig shift with great facility owing to the relatively large stability of the α-oxy radical, together with retention of the anomeric configuration (eq 2). We now wish to report that the [1,2]-Wittig rearrange-

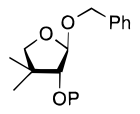
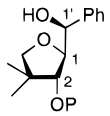
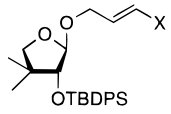
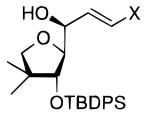
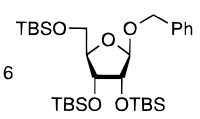
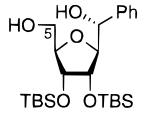
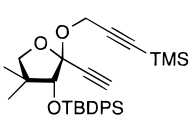
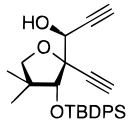
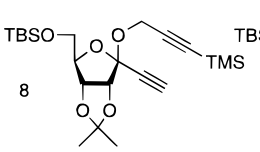
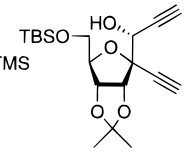


(2)

ment of *O*-glycosides proceeds with efficient stereocontrol over both the anomeric center and the new chiral center formed on the side chain to give the stereo-defined *C*-glycosides in high yields.[6]

At the outset, we examined the rearrangements of the pantolactone-derived benzyl acetals **1a-c** and allyl acetals **3a-b** (>98% β at Cl)[7] under the standard conditions [*n*-BuLi (2.0−3.0 equiv), THF, −78 → 0 °C] (Table 1). The model studies reveal that the rearrangements proceed with complete retention of the β-anomeric configuration to give the [1,2]-Wittig products

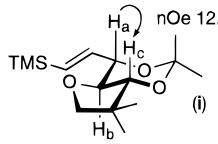
Table 1. [1,2]-Wittig Rearrangements of β-*O*-Glycosides[a]

entry	substrate[b]	major product[c]	yield[d] (%)	dr[e]
				
1	**1a** P=H	**2a**	44	40:60
2	**1b** P=TBS	**2b**	71	89:11
3	**1c** P=TBDPS	**2c**	77	>98:<2
				
4	**3a** X=H	**4a**	35	>98:<2
5[f]	**3b** X=TMS	**4b**	60	>98:<2
6	 **5**	 **6**[g]	40	>98:<2
7	 **7**	 **8**	81	96:4
8	 **9**	 **10**	90	90:10

[a]Unless otherwise noted, all reactions were conducted in THF solutions with *n*-BuLi (2.0-3.0 equiv) at -78 °C followed by warming to 0 °C for 2 h. [b]All substrates were of >98% β. [c]All products were of >98% β at C1. [d]Isolated yield. [e] Refers to the ratio of the C1'-epimers, determined by ^{1}H NMR assay. [f]Conducted in a 1:1 mixture of Et_2O and THF at 0 °C. [g]Strange enough, the product was exclusively the 5-*O*-desilylated one.

(**2**, **4**) as a mixture of the C1′-epimers,[8] both the yield and isomeric ratio depending markedly upon the steric factor of the alkoxy group (OP) used. The best results were obtained with **1c** and **3b** to provide exclusively (1β,1′*S*)-**2c** and -**4b**, respectively (entries 3 and 5), suggesting that the choice of a proper siloxy group as OP is the key to the high stereoselection and yield.[9] Significant enough, a similar rearrangement of the D-ribose-derived benzyl acetal **5**[10] was found to give *C*-glycoside

(1) Wittig, G.; Löhmann, L. *Liebigs Ann. Chem.* **1942**, *550*, 260.
(2) Reviews: (a) Schöllkopf, U. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 763. (b) Marshall, J. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: London, 1991; Vol. 3, p 975.
(3) (a) Lansbury, P. T.; Pattison, V. A.; Sidler, J. D.; Bieber, J. B. *J. Am. Chem. Soc.* **1966**, *88*, 78. (b) Schäfer, H.; Schöllkopf, U.; Walter, D. *Tetrahedron Lett.* **1968**, 2809. (c) Verner, E. J.; Cohen, T. *J. Am. Chem. Soc.* **1992**, *114*, 375. (d) Hoffmann, R.; Brückner, R. *Chem. Ber.* **1992**, *125*, 1957. (e) Tomooka, K.; Igarashi, T.; Nakai, T. *Tetrahedron Lett.* **1993**, *34*, 8139. (f) Tomooka, K.; Igarashi, T.; Nakai, T. *Tetrahedron* **1994**, *50*, 5927.
(4) (a) Schreiber, S. L.; Goulet, M. T. *Tetrahedron Lett.* **1987**, *28*, 1043. (b) Schreiber, S. L.; Goulet, M. T.; Schulte, G. *J. Am. Chem. Soc.* **1987**, *109*, 4718. (c) Grindley, T. B.; Wickramage, C. *J. Carbohydr. Chem.* **1988**, *7*, 661. (d) Yadav, J. S.; Ravishankar, R. *Tetrahedron Lett.* **1991**, *32*, 2629.
(5) Reviews: (a) Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 855. (b) Nakai, T.; Mikami, K. *Org. React.* **1994**, *46*, 105.
(6) For a recent review on *C*-glycosidation, see: Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545.
(7) The substrates were prepared exclusively as the β-anomers via reaction of the 2-siloxy pantolactol acetate with the selected alcohol in the presence of BF_3 etherate.
(8) The stereochemical assignments were made on the basis of the ^{1}H and ^{13}C NMR analyses of the products and derivatives thereof. For instance, the 1-benzoyl derivatives from **2b** and **2c** were found to consist of the single diastereomer, and acetonide **i** derived from **4b** provided the ^{1}H NMR data consistent with the assigned stereochemistry as shown below. The details are described in the supporting information.



(i) $J_{a,b}$=9.1 Hz, $J_{b,c}$=9.4 Hz

(9) It is worth noting that the absence of the 2-alkoxy substituent led to a much lower yield of the [1,2]-Wittig products due to occurrence of the "β-elimination"[3a] (ref 3f).

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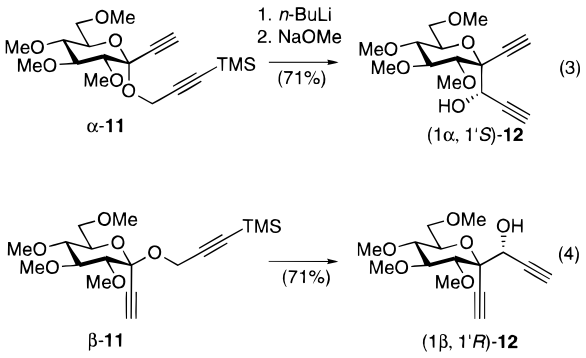
6, as the single stereoisomer, but with the opposite configuration at the C1′ chiral center (entry 6).[11,12]

With these observations in hand, we turned our attention to the rearrangement of ketal systems leading to *C*-glycosides with an additional *C*-substituent at the anomeric center. Thus, we selected the C1-ethynylated propargylic ketals as the substrates with a viewpoint that the ethynyl substituent not only enhances the [1,2]-Wittig reactivity owing to the great radical stabilizing effect[3f] but also imparts the unique multifunctionality to the products. The substrates were prepared from the corresponding lactones via reaction with lithium acetylide followed by the montmorillonite (K-10)-catalyzed *O*-glycosidation[13] with γ-(trimethylsilyl)propargyl alcohol. The rearrangements of **7** and **9** were found to proceed, again, with complete retention of the β-anomeric configuration to give 1′*S*-**8** and 1′*R*-**10**, respectively, in high stereoselectivity (entries 7 and 8).[11,12] Of more significance are the rearrangements of the anomeric pair of D-glucose-derived *O*-glycoside **11**[14] (eqs 3 and 4). The rearrangement of α-**11** was found to proceed with complete retention of the α-anomeric configuration to give (1α,1′*S*)-**12** exclusively, whereas anomer β-**11** provided (1β,1′*R*)-**12** as a major product (1′-*R*/*S* = 87:13).[15]



A key feature of the present *C*-glycosidation processes is the complete retention of either the α- or β-anomeric configuration, in stark contrast to the poor stereospecificity reported for the *intermolecular* radical *C*-glycosidation onto D-glucoses where a high α-selectivity is observed independent of the configuration at the proradical anomeric center.[16] It thus appears likely that the anomeric radical involved is coupled in a "cage" rapidly enough to avoid epimerization. A more striking feature is the remarkably efficient stereocontrol over the side-chain chiral center, suggesting that the α- or β-anomeric radical would efficiently and differently discriminate between the enantiotopic faces of the prochiral benzylic or propargylic radical during the recombination process.[12,17]

In summary, we have demonstrated that the [1,2]-Wittig rearrangement of *O*-glycosides proceeds with efficient stereocontrol over both the anomeric center and the side-chain chiral center to give a novel class of the stereo-defined *C*-glycosides which is otherwise difficult to obtain. The investigation into the scope and limitation of the present *C*-glycosidation methodology as well as its applications to natural products synthesis is in progress.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture, Japan. We thank Dr. Masako Tanaka (Tokyo Institute of Technology) for the X-ray analysis.

Supporting Information Available: Experimental procedures with spectroscopic data for compounds **1c**, **2c**, **3b**, **4b**, and **5**−**12** and crystallographic data of (1α,1′*S*)-**12** (79 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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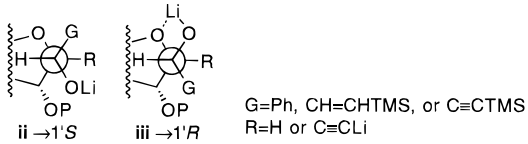
(10) This compound was obtained as pure β-form via chromatographic purification of an anomeric mixture (α/β = 17:83) of the *O*-glycoside and prepared via reaction of D-ribose with benzyl alcohol followed by protection with TBDMSCl.

(11) The 1β-configuration was confirmed by its conversion to the 3,8-dioxabicyclo[3.2.1]octane derivative. The C1′-configuration was assigned by the modified Mosher method (supporting information): Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(12) The exact origin of the stereo changeover is not clear at present; while it might be considered as the result that between the two possible transition states **ii** and **iii**, **ii** is sterically more favorable for the rearrangements of **1**, **3**, and **7**, whereas **iii** is more favorable for those of **5** and **9**.



(13) (a) Trost, B. M.; Edstrom, E. D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 520. (b) Tomooka, K.; Nakamura, Y.; Nakai, T. *Synlett* **1995**, 321. The pure β-forms were obtained by chromatographic purification of the anomeric mixture (α/β = 13:87 for **7** and 6:94 for **9**).

(14) The pure α- and β-form were obtained by chromatographic separation of a 72:28 anomeric mixture of **11**. The α-configuration of the major anomer was assigned by selective semihydrogeneation of the 1-ethynyl group to give the 1-vinyl-α-*O*-glycoside (ref 13b).

(15) The stereochemistry of (1α, 1′*S*)-**12** was established by X-ray crystallography (supporting information). The β-configuration of the *C*-glycoside obtained from β-**11** was assigned by comparison with C1′-epimeric mixture of α-**12** derived from (1α, 1′*S*)-**12** (MnO_2, $NaBH_4$−$CeCl_3$), and the 1′*R*-configuration of the major epimer was determined by the modified Mosher method (ref 11).

(16) (a) Giese, B.; Dupuis, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 622. (b) Adlington, R. M.; Baldwin, J. E.; Basak, A.; Kozyrod, R. P. *J. Chem. Soc., Chem. Commun.* **1983**, 944. (c) Giese, B.; Dupuis, J.; Leising, M.; Nix, M.; Lindner, H. J. *Carbohydr. Res.* **1987**, *171*, 329.

(17) It should be noted that the above-cited principle of "inversion of configuration at the Li-bearing terminus" proved for *configurationally stable* α-oxy alkyllithiums[2,3] does not hold for the present [1,2]-Wittig variants, since the α-oxy benzylic and propargylic lithiums involved are likely to possess an essentially planar (prochiral) structure: *cf.* Reich, H. J.; Holladay, J. E.; Mason, J. D.; Sikorski, W. H. *J. Am. Chem. Soc.* **1995**, *117*, 12137. Zarges, W.; Marsch, M.; Harms, K.; Koch, W.; Frenking, G.; Boche, G. *Chem. Ber.* **1991**, *124*, 543. In fact, D_2O quenching of the lithium species of **1c** was found to give a 1:1 epimeric mixture of the deuterated **1c**. In any events, more detailed studies are need to elucidate the mechanistic origin of the high stereoselectivity. Semiempirical calculations on the transition states concerned are under way.