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Stereochemical Features of the [1,2]-Wittig Rearrangement of *O*-Glycosides Derived from *D*-Galactono- and *D*-Xylono-γ-Lactones: A New Approach to the Core Part of Zaragozic Acids

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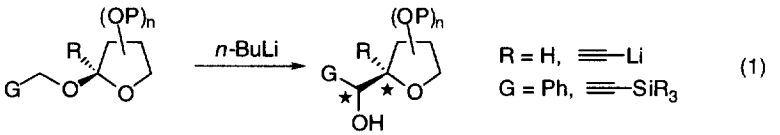
Abstract: The Wittig rearrangement of *D*-galactono-γ-lactone derived β-*O*-glycoside is shown to afford β-*C*-glycoside (retention product), a potentially useful intermediate for zaragozic acid synthesis. By contrast, the rearrangement of the *D*-xylonolactone-derived counterpart was found to violate the retention principle to yield an inversion product as the major product.

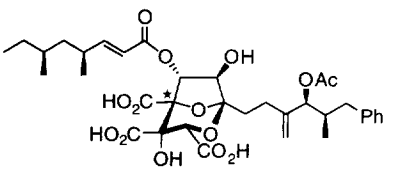
Keyword: asymmetric synthesis; rearrangement; glycosides; zaragozic acids

In an effort to enhance the synthetic utility of the classic [1,2]-Wittig rearrangement,[1] we have recently reported that the Wittig rearrangement of *O*-glycosides provides a general, efficient method for *C*-glycosidation as depicted in eq 1.[2,3] The key feature of this protocol is that the rearrangement proceeds with complete retention of configuration at the migrating anomeric center, along with highly selective formation of the hydroxy chiral center on the side chain.



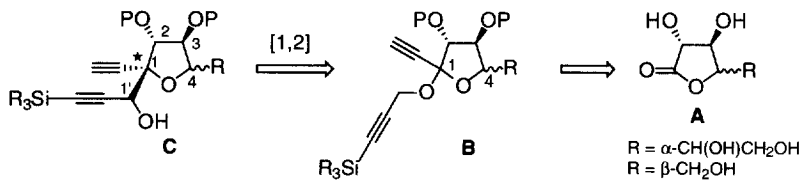
(1)

With this Wittig-based *C*-glycosidation method in hand, our attention was directed toward the total synthesis of zaragozic acid A (**1**), a potent inhibitor of enzyme squalene.[4] To this end, our interest was focused, as a preliminary study, on the [1,2]-Wittig rearrangement of *O*-glycosides **B**, easily prepared from the commercially available dihydroxy γ-lactone **A**, which might afford *C*-glycosides **C**, potential precursors of the core part of **1** (Scheme 1). A key issue is whether the rearrangement proceeds with retention of configuration at the anomeric center even under the influence of the C4 stereogenic center. Reported herein are the stereochemical outcomes of the special Wittig variant that reveal new aspects of the [1,2]-Wittig stereochemistry.



Zaragozic acid A (**1**)

Scheme 1



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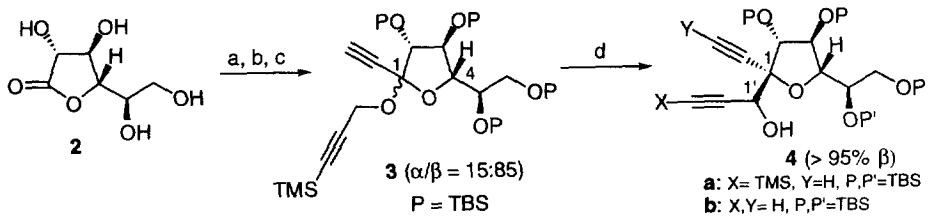
First, we studied the rearrangement of *O*-glycoside **3**[5] which was prepared as an anomeric mixture (α/β = 15:85)[6] from *D*-galactono-γ-lactone (**2**) in three steps: protection of the hydroxy groups, lithium acetylide addition, and the montmorillonite K-10 catalyzed *O*-glycosidation[7] with γ-(trimethylsilyl)propargyl alcohol (Scheme 2). The [1,2]-Wittig rearrangement of **3** was carried out with *n*-BuLi (5 equiv.) in THF at –78 °C → –20 °C to afford the (1β)-*C*-glycoside **4** (>95% β)[5,8] in 62% yield[9] as a 1:1 mixture of the C1'-epimers,[10] along with 14% recovery of the α-anomer of **3**. This outcome indicates that the β-anomer of **3** undergoes the rearrangement with complete retention at the migrating anomeric center as expected (albeit in much lower stereoselectivity at the C1'-chiral center than expected), whereas the α-anomer does not rearrange. This means that an efficient kinetic resolution does occur during the rearrangement, thereby requiring no separation of α- and β-**3** to obtain the desired isomer (1β)-**4**.

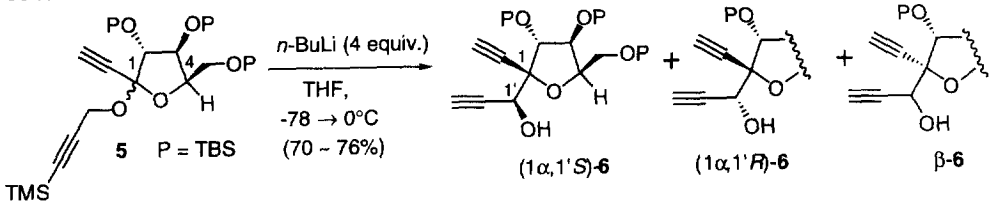
Scheme 2



(a) TBSCl, Imid., DMF, rt (95%). (b) ≡—Li, THF, -78 °C → -20 °C (59% with recovered substrate 11%). (c) TMSC≡CCH$_2$OH, K10, MS4A, CH$_2$Cl$_2$, rt (98%). (d) *n*-BuLi (5 equiv.), THF, -78 °C → -20 °C (62%: combined yield of **4a-d**).

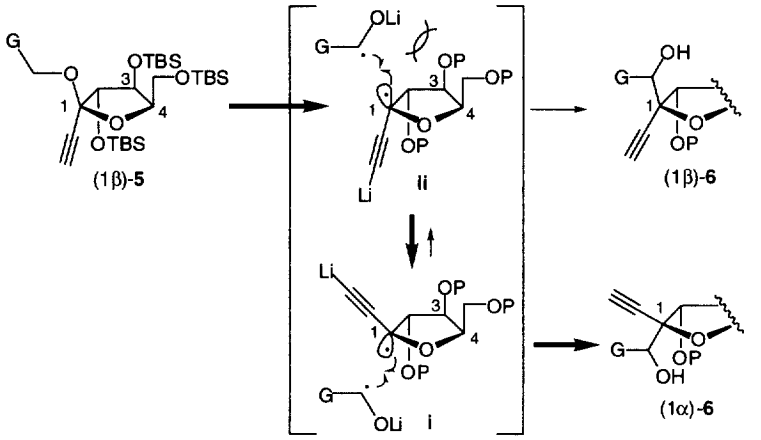
Next, we examined the rearrangement of an anomeric mixture (α/β = 50 : 50) of *O*-glycoside **5**,[5] prepared similarly from the *D*-xylonic lactone (a C4-epimeric analog of **2**). Surprisingly enough, this rearrangement was found to give (1α)-*C*-glycoside **6** as the major product (C-α/β=87 : 13) in 76% yield (Scheme 3). In order to gain insight into the steric course of this rearrangement, we separated (1α)- and (1β)-**5**,[11] and each one was subjected to the rearrangement. While the rearrangement of (1α)-**5**[12] afforded exclusively the retention product (1α)-**6** in extremely high (1'*S*)- selectivity,[13,14] (1β)-**5** provided an *inversion* product (1α)-**6** (1'-*R*/*S* = 11 : 89) as the major product (1-α/β = 75 : 25). The rearrangement of (1β)-**5** offers the first [1,2]-Wittig example that violates the general principle of "retention of configuration at the migrating carbon".[2]

Scheme 3



α / β = 1 : 1	⟶	79	:	8	:	13
>95% α	⟶	> 95	:	< 5	:	< 5
>95% β	⟶	67	:	8	:	25

The unusual stereochemistry of the rearrangement of (1β)-**5** can be visualized by the transition state **i** which should be sterically more favorable than **ii** for the radical coupling[15] because in the latter the incoming carbon radical suffers large 1,3-repulsion with the (4β)-CH_2OP group. As a result, the radical coupling occurs predominantly from the less hindered α-side after the initially formed β-anomeric radical is epimerized to the α-anomer, thus yielding (1α)-**6** as the major product. It is worth noting that the rearrangement of β-**3** does not suffer such 1,3-repulsion, thus maintaining the retention principle.



In summary, we have demonstrated that the [1,2]-Wittig rearrangement of the galactonolactone-derived *O*-glycoside proceeds with complete retention of configuration at the anomeric center to afford the (1β)-*C*-glycoside that is potentially useful as a key intermediate for synthesis of zaragozic acids. In addition, we have shown that the rearrangement of the xylonolactone-derived (1β)-*O*-glycosides violates the "retention principle" of the [1,2]-Wittig stereochemistry and hence cannot be utilized for the zaragozic acid synthesis. With these results in hand, work on the total synthesis of zaragozic acid A is underway in our laboratory

Acknowledgment: This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan and the Research for the Future Program, administered by the Japan Society for the Promotion of Science

References and Notes

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5. All the compounds were characterized by ^1H ($CDCl_3$, 300 MHz) and ^{13}C NMR ($CDCl_3$, 75 MHz). Data for selected products are as follows. β-**3**: ^1H NMR δ 4.36 (d, *J*=15.2 Hz, 1H), 4.29 (d, *J*=15.2 Hz, 1H), 4.06 (d, *J*=1.9 Hz, 1H), 4.03 (dd, *J*=3.9, 1.9 Hz, 1H), 3.85 (dd, *J*=6.1, 3.9 Hz, 1H), 3.77 (ddd, *J*=6.1, 5.8, 5.0 Hz, 1H), 3.68 (dd, *J*=10.2, 5.0 Hz, 1H), 3.56 (dd, *J*=10.2, 5.8 Hz, 1H), 2.50 (s, 1H), 0.91 (s, 9H), 0.89 (s, 9H), 0.887 (s, 9H), 0.87 (s, 9H), 0.15 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H),

0.104 (s, 3H), 0.095 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.045 (s, 3H). **4b** epimer A: ^{1}H NMR δ 4.67 (dd, *J*=10.2, 2.1 Hz, 1H), 4.35 (s, 1H), 4.21 (t, *J*=1.1 Hz, 1H), 3.99 (dd, *J*=8.1, 1.1 Hz, 1H), 3.93 (ddd, *J*=8.1, 5.0, 3.5 Hz, 1H), 3.72 (dd, *J*=10.8, 3.5 Hz, 1H), 3.58 (dd, *J*=10.8, 5.0 Hz, 1H), 3.26 (d, *J*=10.2 Hz, -OH, 1H), 2.54 (s, 1H), 2.49 (d, *J*=2.1 Hz, 1H), 0.93 (s, 9H), 0.89 (s, 27H), 0.17 (s, 3H), 0.15 (s, 6H), 0.14 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.06 (s, 6H). ^{13}C NMR δ 111.6, 91.2, 87.9, 81.6, 80.0, 77.3, 74.3 (2C), 66.6, 66.5, 29.8, 26.3, 26.3, 26.1, 25.8, 18.7, 18.5, 18.3, 17.9, -3.9, -4.2, -4.40 (2C), -4.45, -4.5, -5.0, -5.1. **4b** epimer B: ^{1}H NMR δ 4.84 (dd, *J*=6.0, 2.1 Hz, 1H), 4.21 (s, 1H), 4.17 (s, 1H), 3.90 (m, 2H), 3.71 (br d, *J*=10.8 Hz, 1H), 3.59 (br d, *J*=10.8 Hz, 1H), 2.69 (d, *J*=6.0 Hz, 1H), 2.53 (s, 1H), 4.49 (d, *J*=2.1 Hz, 1H), 0.94 (s, 9H), 0.89 (s, 18H), 0.87 (s, 9H), 0.18 (s, 3H), 0.15 (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.06 (s, 6H). ^{13}C NMR δ 90.9, 89.2, 81.9, 81.5, 79.7, 79.5, 74.7, 74.3, 77.1, 66.5, 65.4, 26.3, 26.2, 26.0, 25.7, 18.7, 18.4, 18.3, 17.8, -4.0, -4.2, -4.4, -4.59 (2C), -4.64, -5.0, -5.2. α-**5**: ^{1}H NMR δ 4.48 (d, *J*=15.5 Hz, 1H), 4.32 (d, *J*=15.5 Hz, 1H), 4.32 (d, *J*=4.8 Hz, 1H), 4.23 (dd, *J*=5.4, 4.8 Hz, 1H), 4.09 (ddd, *J*=5.4, 4.7, 4.6 Hz, 1H), 3.76 (dd, *J*=11.0, 4.6 Hz, 1H), 3.72 (dd, *J*=11.0, 4.7 Hz, 1H), 2.56 (s, 1H), 0.91 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.17 (s, 3H), 0.15 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.06 (s, 9H). ^{13}C NMR δ 102.4, 98.9, 90.1, 83.9, 80.4, 80.1, 77.1, 74.2, 61.5, 52.9, 25.9, 25.8, 25.7, 18.2, 18.1, 17.8, 0.1, -4.0 (2C), -4.7, -5.0 (2C), -5.4. β-**5**: ^{1}H NMR δ 4.39 (d, *J*=15.0 Hz, 1H), 4.32 (d, *J*=15.0 Hz, 1H), 4.24-4.27 (m, 1H), 4.12 (d, *J*=2.9 Hz, 1H), 4.09 (dd, *J*=4.8, 2.9 Hz, 1H), 3.81 (dd, *J*=10.7, 5.6 Hz, 1H), 3.74 (dd, *J*=6.3, 10.7 Hz, 1H), 2.56 (s, 1H), 0.90 (s, 18H), 0.89 (s, 9H), 0.15 (s, 3H), 0.14 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.06 (s, 3H). ^{13}C NMR δ 104.2, 101.9, 89.9, 83.7, 83.6, 78.6, 75.4, 77.2, 61.8, 52.3, 25.9 (2C), 25.7, 18.2, 17.9 (2C), 0.1, -4.2, -4.39, -4.45, -5.0, -5.19, -5.2. (α,*S*)-**6**: ^{1}H NMR δ 4.59 (br s, 1H), 4.38 (d, *J*=0.9 Hz, 1H), 4.18-4.13 (m, 2H), 3.85 (t, *J*=9.6 Hz, 1H), 3.79 (dd, *J*=9.6, 4.2 Hz, 1H), 2.63 (br s, 1H), 2.55 (s, 1H), 2.48 (d, *J*=2.1 Hz, 1H), 0.92 (s, 9H), 0.90 (s, 9H), 0.88 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H), 0.15 (s, 3H), 0.13 (s, 3H), 0.10 (s, 3H), 0.05 (s, 3H). ^{13}C NMR δ 84.8, 83.2, 83.1, 81.8, 81.7, 78.1, 77.2, 75.3, 74.6, 65.9, 60.5, 26.0, 25.8 (2C), 18.3, 18.2, 18.0, -4.0, -4.3, -4.9, -5.0, -5.15, -5.21. **7**: ^{1}H NMR δ 5.69 (d, *J*=2.2 Hz, 1H), 4.47 (d, *J*=3.0 Hz, 1H), 4.35 (ddd, *J*=5.4, 3.4, 2.2 Hz, 1H), 4.26 (ddd, *J*=8.3, 5.4, 3.0 Hz, 1H), 4.01 (ddd, *J*=12.5, 4.2, 3.4 Hz, 1H), 3.92 (ddd, *J*=12.5, 9.1, 2.2 Hz, 1H), 3.69 (d, *J*=8.3 Hz, OH), 2.72 (s, 1H), 2.52 (d, *J*=2.2 Hz, 1H), 2.41 (dd, *J*=9.1, 4.2 Hz, OH), 2.15 (s, 1H), 0.90 (s, 9H), 0.18 (s, 3H), 0.15 (s, 3H).

6. The anomeric configuration of **3** has not been determined yet. However, the β-configuration as the major epimer is strongly suggested by consideration of the thermodynamic stability of anomers. The α/β ratio was determined by ^{1}H NMR assay.
7. (a) Trost, B. M.; Edstrom, E. D. *Angew. Chem., Int. Ed Engl.* **1990**, *29*, 520-521. (b) Tomooka, K.; Nakamura, Y.; Nakai, T. *Synlett* **1995**, 321-322.
8. The 1β-configuration of **4b** was assigned by nOe experiments (Fig. 1).
9. Combined yield of *C*-glycosides **4a-d**. These are interconvertible via silylation or desilylation.
10. The oxidation of the diastereomer mixture of **4b** (TPAP, NMO) was found to produce the single diastereomer of ketone, indicating that the diastereomers are the C1' epimers of β-*C*-glycoside.
11. The pure α- and β-forms were obtained by chromatographic separation of the anomeric mixture.
12. The α-configuration of α-**5** was assigned by nOe experiments (Fig. 2).

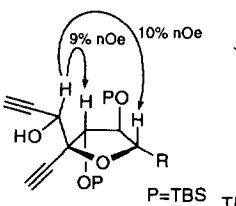


Fig. 1

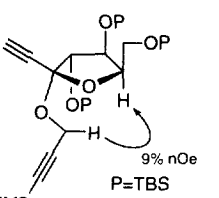
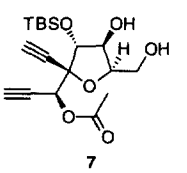
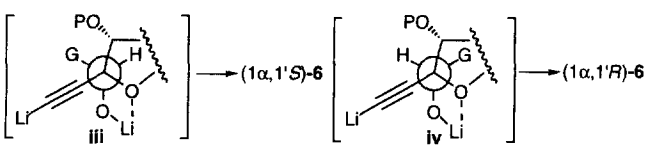


Fig. 2

13. The stereochemistry of (1α,1'*S*)-**6** was determined by X-ray crystallography of its derivative **7** (Fig. 3). Crystal data for **7** ($C_{18}H_{28}O_6Si$): orthorhombic, $P2_12_12_1$ (#19), a=10.863(2) Å, b=30.099(3) Å, c=6.363(4) Å, V= 2080(1) Å^3, Z=4. A total of 2161 reflections (*h,k,±l*) were collected in the range $2\theta_{max}$ 50.0° being used in the structural refinement by full-matrix least-squares techniques (226 variables) using the TEXSAN crystallographic package from Molecular Structures Corporation. Final R=0.042, R_w=0.025.
14. The C1'*S*-selectivity is explicable as a result that the rearrangement proceeds exclusively via the transition state **iii** which is more favorable than **iv**.



7



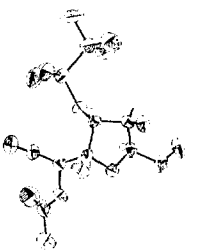


Fig. 3 ORTEP representation of **7**

15. The [1,2]-Wittig rearrangement is well recognized to proceed via the radical dissociation–recombination mechanism: see Schöllkopf, U. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 763-773 and ref. 2.