adsorbed directly onto CdSe surfaces was monitored by following changes in the CdSe photoluminescence: A. Ivanisevic, M. F. Reynolds, J. N. Burstyn, A. B. Ellis, *J. Am. Chem. Soc.* **2000**, *122*, 3731 – 3738.
[10] M. Bruening, E. Moons, D. Yaron-Marcovich, D. Cahen, J. Libman, A. Shanzer, *J. Am. Chem. Soc.* **1994**, *116*, 2972 – 2977.
[11] R. Cohen, S. Bastide, D. Cahen, J. Libman, A. Shanzer, Y. Rosenwaks, *Adv. Mater.* **1997**, *9*, 746 – 749.
[12] R. Cohen, L. Kronik, A. Shanzer, D. Cahen, A. Liu, Y. Rosenwaks, J. K. Lorenz, A. B. Ellis, *J. Am. Chem. Soc.* **1999**, *121*, 10545 – 10553.
[13] BB values (±5 mV) as derived from the CPD measurements: bare surface −265 mV, GaAs derivatized by: **1**: −210, **2**: −255, **3**: −115, and **4**: −125 mV.
[14] J. A. Harbie, J. R. Klose, D. A. Wink, L. K. Keefer, *J. Org. Chem.* **1993**, *58*, 1472 – 1476.
[15] C. M. Maragos, D. Morley, D. A. Wink, T. M. Dunams, J. E. Saavedra, A. Hoffman, A. A. Bove, L. Isaac, J. A. Harbie, L. K. Keefer, *J. Med. Chem.* **1991**, *34*, 3242 – 3247.
[16] C. M. Maragos, J. M. Wang, J. A. Harbie, J. J. Oppenheim, L. K. Keefer, *Cancer Res.* **1993**, *53*, 564 – 568.
[17] The normalized current was calculated from $I_n(t) = I_m(t)/\Delta I$, where $I_n(t)$ is the normalized current, $I_m(t)$ is the measured current, and ΔI is the difference between the currents measured in the buffer solution and dry under N_2.
[18] Y. Rudich, I. Benjamin, R. Naaman, E. Thomas, S. Trakhtenberg, R. Ussyshkin, *J. Phys. Chem. A* **2000**, *104*, 5238 – 5245.
[19] The term "steady-state" concentration refers to NO concentrations when $t > t_{1/2}$, and the precursor decomposition is slow.
[20] M. Hoshino, L. Laverman, P. C. Ford, *Coord. Chem. Rev.* **1999**, *187*, 75 – 102.
[21] A small change in the opposite direction explains the small decrease in current seen for bare devices. The interaction of NO with the surface of the bare device, which follows a release of surface-bound water molecules, leaves the surface more negative than before.
[22] G. Ashkenasy, A. Ivanisevic, R. Cohen, C. E. Felder, D. Cahen, A. B. Ellis, A. Shanzer, *J. Am. Chem. Soc.* **2000**, *122*, 1116 – 1122.
[23] A. Vilan, M.Sc. Thesis, Weizmann Institute of Science, Rehovot **1996**.
[24] C. Rovira, K. Kunc, J. Hutter, P. Ballone, M. Parrinello, *J. Phys. Chem. A* **1997**, *101*, 8914 – 8925.
[25] A. Ivanisevic, A. B. Ellis, G. Ashkenasy, A. Shanzer, Y. Rosenwaks, *Langmuir* **2000**, *16*, 7852 – 7858.

Stereoselective Synthesis of Highly Functionalized *C*-Glycosides based on Acetal [1,2] and [1,4] Wittig Rearrangements**

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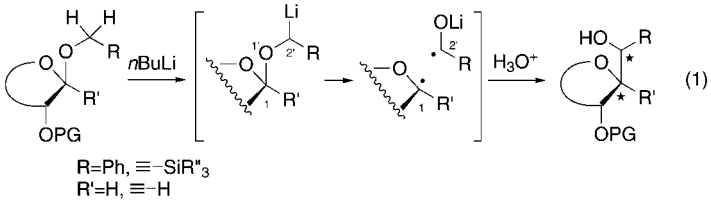
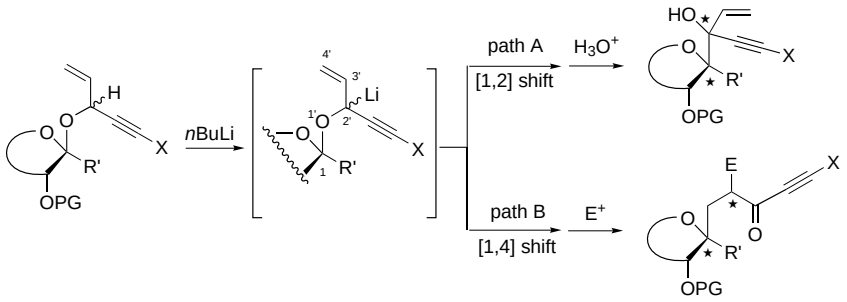
The [1,2] Wittig rearrangement is a classic class of carbanion rearrangements which is now well recognized to proceed by a radical dissociation – recombination mechanism.[1] Despite potentially useful carbon – carbon bond forming reactions, however, synthetic application of this rearrangement still remains severely limited, mainly because of the rather low yields and the restricted range of substrates. To this end, we have recently developed the acetal [1,2] Wittig rearrangement protocol which provides *C*-glycosides from primary-alcohol-derived *O*-glycosides in a highly diastereoselective manner [Eq. (1)].[2, 3]



(1)

To extend this protocol we envisioned that the rearrangement of a more functionalized *O*-glycoside system with a secondary-alcohol-derived migrating terminus might afford the *C*-glycoside with a tertiary alcohol side chain.[4] A key feature for the success of the rearrangement is a rational design of a migrating terminus. Thus, we selected the ethynylvinylmethanol system as the migrating terminus with a view that the ethynyl and vinyl substituent not only enhances the [1,2] Wittig reactivity, as a result of the large radical stabilizing effect, but also imparts unique multifunctionality to the products (Scheme 1, path A). Here we report a stereoselective entry to the highly functionalized *C*-glycosides based on an acetal [1,2] Wittig rearrangement and also a novel [1,4] Wittig rearrangement of an acetal system (Scheme 1, path B), which was discovered by chance in the [1,2] rearrangement study.



Scheme 1. [1,2] and [1,4] Wittig rearrangement approach to the multi functionalized *C*-glycosides.

At the outset we studied the rearrangement of acetal β-**3** which was prepared from (−)-dihydro-3-hydroxy-4,4-dimethyl-2(3*H*)-furanone ((−)-pantolactone) as a 1:1 epimeric mixture at the C1′ position in three steps: protection of the hydroxyl groups, addition of lithium acetylide, and a montmorillonite K 10 clay catalyzed acetalization[5] with the protected ethynylvinylmethanol **2** (racemate) [Eq. (2); TBDPS = *tert*-butyldiphenylsilyl]. Two epimers of β-**3** were separable by chromatography on silica gel and their stereochemistries were determined by X-ray crystallography and by chemical conversion.[6] The reaction of β-(*R*)-**3** with *n*BuLi (3 equiv) in THF at −78 °C afforded (< 10 min) the [1,2] re-

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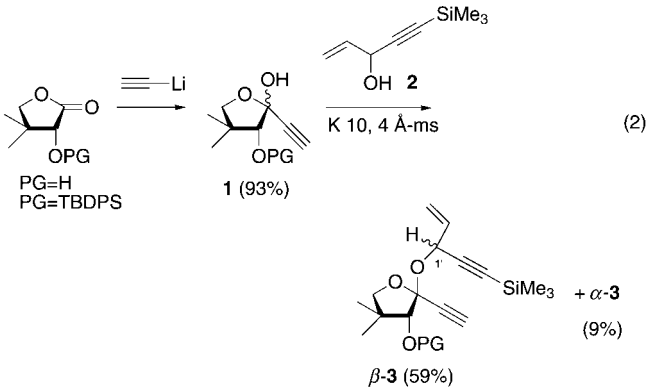
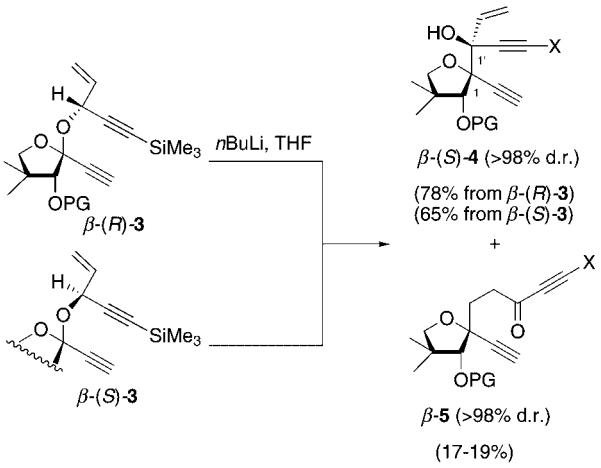


(2)

arrangement product β-(*S*)-**4** as a single diastereomer[6] in 78% yield,[7] along with a small amount of the [1,4] rearrangement product β-**5** (Scheme 2).[8] Significantly, a similar

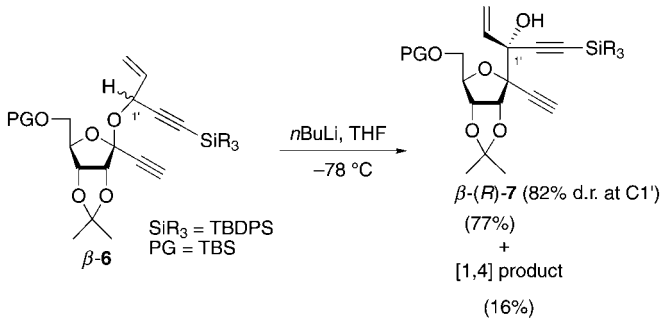


Scheme 2. Wittig rearrangement of *O*-glycosides (β-(*R*)-**3** and β-(*S*)-**3**). X = $SiMe_3$ or H.

reaction of the β-(*S*)-**3** epimer gave the same diastereomer, β-(*S*)-**4** (> 95% d.r., 65% yield) even though the reaction was slower than with the *R* epimer ($-78 \rightarrow -10\,^{\circ}C$, 50 min). These stereochemical outcomes indicate that acetal **3** undergoes the rearrangement with complete retention at the migrating anomeric center as expected, and in a highly diastereoselective manner (not a stereospecific manner) in regard to the chiral center at the tertiary alcohol in the side chain. This result means that efficient stereocontrol does occur during the rearrangement, and hence no separation of the C1′ epimers is required to obtain the single stereoisomer of the rearrangement product.

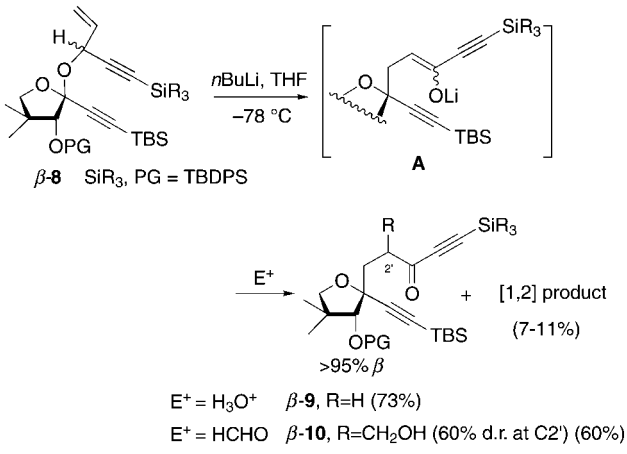
This protocol is an efficient approach to multifunctionalized *C*-glycosides. In fact, a similar rearrangement of a 1:1 epimeric mixture of *O*-glycoside **6**, prepared from the lactone derived from D-ribose, was found to give *C*-glycoside **7** in a highly diastereoselective manner (> 95% β, 82% *R* configuration)[9, 10] in 77% yield [Eq. (3); TBS = *tert*-butyldimethylsilyl].

Next, our interest turned to the previously observed side reaction—the [1,4] rearrangement—because of its potential value as a unique approach to *C*-glycosides. A key issue to



(3)

address was the switching of the periselectivity from a [1,2] to a [1,4] fashion. After several attempts, we finally found that the introduction of a *tert*-butyldimethylsilyl group to the ethynyl unit at the C1 position could solve this problem. The reaction of β-**8** (1:1 epimeric mixture at C1′) with *n*BuLi provided the [1,4] rearrangement product β-**9** as the major product [73% yield; Eq. (4)]. This protocol represents the first example of a *C*-glycoside synthesis based on a [1,4] Wittig rearrangement. Moreover, we attempted to intercept the lithium enolate **A**[11] with an external electrophile. Thus, β-**8** was treated successively with *n*BuLi and formaldehyde to afford the expected adduct **10** (60% d.r.) in good yield.



(4)

In summary, we have demonstrated that the [1,2] Wittig rearrangement of the ethynylvinylmethanol-derived *O*-glycoside proceeds in a highly diastereoselective manner to afford the 1β-*C*-glycoside that has contiguous quarternary chiral centers at the C1 and C1′ positions. In addition, we have shown a novel approach to the *C*-glycoside that is based on a [1,4] Wittig rearrangement. The scope and limitation of the present C-glycosidation methodologies as well as its applications to natural products synthesis are in progress.

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[1] Reviews: a) U. Schöllkopf, *Angew. Chem.* **1970**, *82*, 795 – 805; *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 763 – 773; b) R. W. Hoffmann, *Angew. Chem.* **1979**, *91*, 625 – 634; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 563 – 572; c) J. A. Marshall, in *Comprehensive Organic Synthesis*, *Vol. 3* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 975 – 1014; d) K. Tomooka, T. Nakai, *J. Synth. Org. Chem. Jpn.* **1996**, *54*, 1000 – 1008; e) K. Tomooka, H. Yamamoto, T. Nakai, *Liebigs Ann.* **1997**, 1275 – 1281.

[2] a) K. Tomooka, H. Yamamoto, T. Nakai, *J. Am. Chem. Soc.* **1996**, *118*, 3317 – 3318; b) K. Tomooka, M. Kikuchi, K. Igawa, P.-H. Keong, T. Nakai, *Tetrahedron Lett.* **1999**, *40*, 1917 – 1920.
[3] Pioneering work on simple systems has been reported: T. B. Grindeley, C. Wickramage, *J. Carbohydr. Chem.* **1988**, *7*, 661 – 685.
[4] For a recent review on C-glycosidation, see a) D. Levy, C. Tang, *The Chemistry of C-Glycosides*, Pergamon, Oxford **1995**; b) Y. G. Du, R. J. Linhardt, I. R. Valhov, *Tetrahedron* **1998**, *54*, 9913 – 9959.
[5] a) B. M. Trost, E. D. Edstrom, *Angew. Chem.* **1990**, *102*, 541 – 542; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 520 – 521; b) K. Tomooka, Y. Nakamura, T. Nakai, *Synlett* **1995**, 321 – 322.
[6] Crystallographic data (excluding structure factors) for the structures β-(*R*)-**3** and β-(*S*)-**4** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-144556 and -144557, respectively. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
[7] Combined yield of *C*-glycosides **4**, X = $SiMe_3$ and X = H. These are interconvertible through silylation or desilylation.
[8] For pioneering studies related to the [1,4] Wittig rearrangement, see a) H. Felkin, C. Frajerman, *Tetrahedron Lett.* **1977**, *39*, 3485 – 3488; b) M. Schlosser, S. Strunk, *Tetrahedron* **1989**, *45*, 2649 – 2664.
[9] The stereochemical assignment was made on the basis of the ^{1}H NMR analysis and NOE experiment of the product and derivative thereof (see Supporting Information).
[10] In this case the stereoselectivity at the C1′ position is opposite that observed in the pantolactone-derived system. A similar stereochangeover has been observed in the rearrangement of *O*-glycosides derived from primary alcohols; see ref. [2a].
[11] The trapping experiment of enolate **A** ($SiMe_3Cl$, −78 °C) gave an *E*:*Z* mixture (ca. 1:1) of silyl enol ether in 69 % yield.

Stereoselective Total Synthesis of Zaragozic Acid A based on an Acetal [1,2] Wittig Rearrangement**

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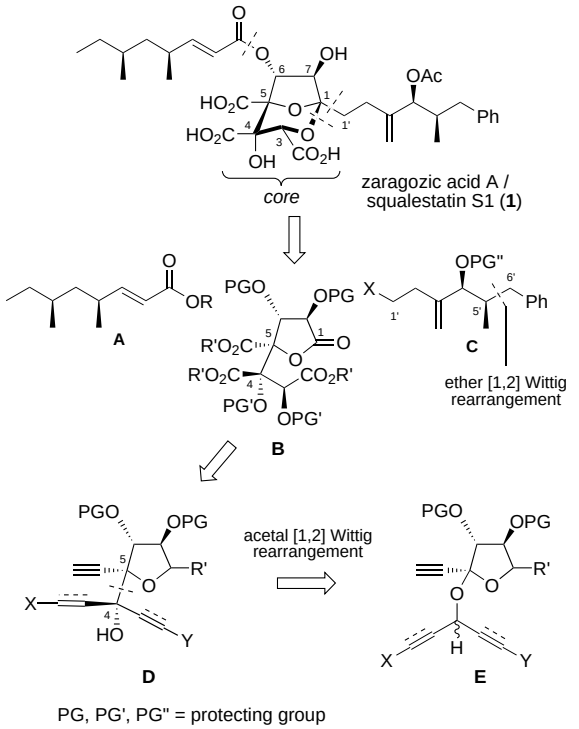
The zaragozic acids and squalestatins are a family of naturally occurring fungal metabolites independently isolated and characterized by researchers at Merck[1] and Glaxo.[2] These natural products are potent inhibitors of squalene synthase and have potential as therapeutic agents for the treatment of hypercholesterolemia.[1a, 2a] All the zaragozic acids and squalestatins have a common 2,8-dioxabicyclo[3.2.1]octane core with an array of six stereogenic centers including contiguous quarternary carbon atoms, and are different only at the alkyl and acyl side chains at C1 and C6, respectively. Therefore, it is not surprising that the these compounds have elicited considerable attention from numerous synthetic chemists.[3, 4] Zaragozic acid A (squalestatin S1; **1**) is a representative example of this novel class of compounds. Herein, we report the efficient, convergent synthesis of **1** by highlighting the acetal [1,2] Wittig rearrangement[5] for forming the C4–C5 bond together with the simultaneous creation of the contiguous quaternary carbon atoms as the key step.

Our strategy is shown in Scheme 1. Disconnection of the C6 side chain **A**, unraveling of the C1 acetal, and cleavage of the C1–C1′ bond led to lactone **B** and an alkyl anion equivalent



Scheme 1. Retrosynthetic analysis of zaragozic acid A (**1**).

C.[6] Our interest in the carbanion rearrangement of the sugar derivatives led us to consider a strategy for lactone **B** starting from the *C*-glycoside **D**, namely an acetal [1,2] Wittig rearrangement product of the *O*-glycoside **E**. The preceding paper describes the synthesis of this class of highly functionalized *C*-glycosides based on a rearrangement protocol.[7] Furthermore, we planned to construct a C5′–C6′ bond in segment **C** using the original ether [1,2] Wittig rearrangement.[8]

Our synthesis begins from the *O*-glycoside **5a** (≅**E**), which can be prepared from the hemiketal **3** derived from L-arabino-γ-lactone[9] and the protected ethynylvinylmethanol **4** (racemate; Scheme 2). Previous work suggested that the carbanion rearrangement of an *O*-glycoside such as **5a** should produce the [1,2] rearrangement product with high diastereoselectivity and in good yield.[7, 9] In contrast to this expect-

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