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# Substitution and Remote Protecting Group Influence on the Oxidation/ Addition of α-Substituted 1,2-Anhydroglycosides: A Novel Entry into *C*-Ketosides

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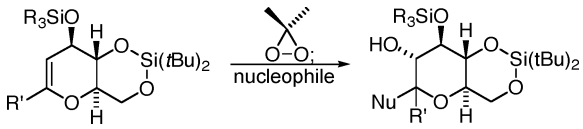
## ABSTRACT




***C*-Ketosides are valuable intermediates in chemical synthesis and as glycoside mimics. This manuscript describes the efficient generation of these substrates from α-alkyl-substituted glycals and an oxidative, C–C bond-forming sequence where the choice of C(3) protecting group was critical.**

Carbon (*C*)-glycosides that contain two exocyclic C−C bonds at C(1) (*C*-ketosides) and the analogous agents having one exocyclic C−C bond (*C*-glycosides) have attracted the interest of the synthetic community for a number of reasons. For some, these agents have served as valuable precursors to other targets.[1] For a number of others, their intrinsic stability and resulting utility as glycoside mimics has made *C*-glycosides and *C*-ketosides attractive targets.[2,3] Regardless of the reasons for being interested in these compounds, to the best of our knowledge, they can only be accessed through chemical synthesis. Along these lines, while arrays of synthetic methods are available for *C*-glycosides, the list of procedures to generate the corresponding *C*-ketosides is much shorter. To date, these have included the following: (1) the coupling of carbon nucleophiles with pyranose hemiketals in the presence of Lewis acids;[4] (2) acid-catalyzed ring expansion reactions of glycal-derived carbinols;[5] (3) [1,2]-Wittig rearrangements of anomeric ketals;[6] (4) electrophilic alkylations of exocyclic enol ethers;[7] (5) free-radical coupling reactions;[8] (6) the generation of spiro-fused cyclopropyl sugars from glycosidic carbenes;[9] (7) [4 + 3] cycloadditions

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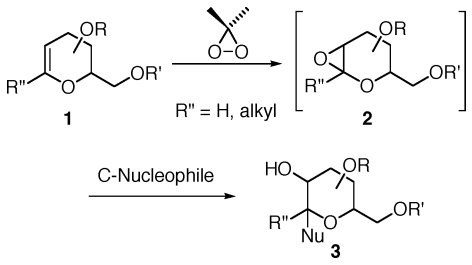
and subsequent fragmentations;[10] (8) samarium enolate-aldehyde condensations;[11] (9) electrophilic cyclizations of hydroxy-alkenes;[12] and (10) acid-catalyzed cyclizations of styrenyl alcohols.[13]

As part of our program targeting the synthesis of the polycyclic ether-containing natural products hemibrevetoxin B,[14] gambierol,[15] and gambieric acid,[16] *C*-ketosides emerged as necessary targets. From the various possibilities, we opted to pursue the same approach that had proven successful for us in the generation of the corresponding *C*-glycosides,[1,17,18] one involving a single flask enol ether oxidation/carbon−carbon bond-forming sequence (Scheme 1).

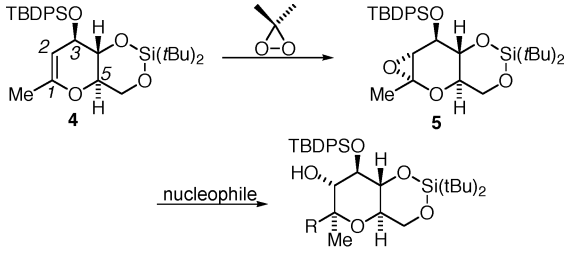
**Scheme 1**




Unfortunately, our early attempts to generate *C*-ketosides from anhydrides were mostly unsuccessful. We were unable to stereoselectively add any nucleophiles other than trimethyl aluminum to α-substituted glycals.[19] This changed for the better during our gambierol work when we found that anhydride **5** underwent a stereoselective coupling reaction with 2-methylpropenylmagnesium bromide, propenylmagnesium chloride, and propargylmagnesium chloride to give *β-C*-ketosides **6**, **7**, and **8**, respectively.[20] Hopeful that **5** and related substrates might enable us to finally solve the anhydride to *C*-ketoside problem, we elected to examine the scope of these transformations. Of interest to us was the influence of the nucleophile and substitution about the anhydride on the reaction. The results of these efforts are described here.

We initially studied the influence of C(3) silyl ether substitution on the addition of *C*-nucleophiles to α-methyl anhydrides. Surprisingly, the choice of silyl ether proved to be critical; while C(3) TBDPS ether **5** gave **6** in 92% yield with >95:5 diastereoselectivity when exposed to 2-methylpropenylmagnesium bromide (Table 1, entry 1), the use of

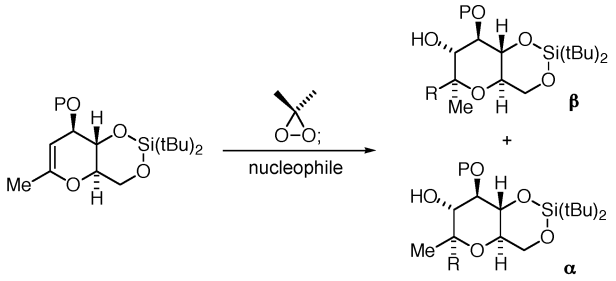
**Table 1.**




| entry | nucleophile | R | *C*-ketoside | Yield |
|---|---|---|---|---|
| 1 | MgBr | $CH_2C(CH_3)CH_2$ | **6** | 92% |
| 2 | MgCl | $CH_2CHCH_2$ | **7** | 97% |
| 3 | MgBr | $CH_2CCH$ | **8** | 94% |

the anhydride from the corresponding TBDMS ether **9** gave *C*-ketoside **12** in 80% yield as a 2:1 mixture of isomers (Table 2, entry 1). Similarly, the anhydride from **9** coupled

**Table 2.**




| entry | glycal | P | nucleophile | ketoside | R | β:α | yield |
|---|---|---|---|---|---|---|---|
| 1 | **9** | TBDMS | MgBr | **12** | $CH_2C(Me)CH_2$ | 2:1 | 80% |
| 2 | **9** | TBDMS | MgCl | **13** | $CH_2CHCH_2$ | 4:1 | 56% |
| 3 | **10** | TES | MgCl | **14** | $CH_2CHCH_2$ | ----- | <24% |
| 4 | **11** | TIPS | MgCl | **15** | $CH_2CHCH_2$ | >95:5 | 91% |

with propenylmagnesium chloride to give **13** as a 4:1 mixture of diastereomers in 56% yield (entry 2), while TBDPS ether

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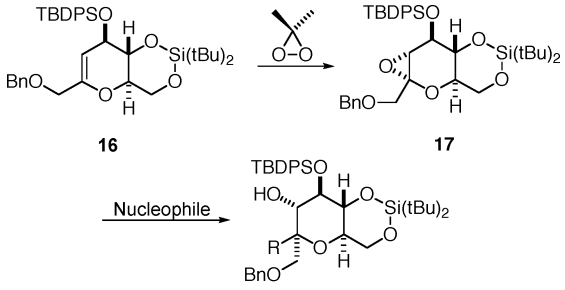
**5** gave **7** in a 97% yield with >95:5 stereoselectivity (Table 1, entry 2). Substrates containing smaller silyl ethers (TES; Table 2, entry 3) were even less successful, and substrates containing silyl ethers of comparable size to TBDPS (TIPS; Table 2, entry 4) gave the corresponding ketoside in high yield and selectivity.

Having demonstrated that α-methylglycals having the appropriate C(3) substituent can be used to stereoselectively synthesize *C*-ketosides, we became interested in determining whether glycals of higher synthetic utility might also undergo these transformations and settled upon α-benzyloxyglycal **16**. We were pleased to find that the anhydride **17** from the oxidation of **16** with DMDO was efficiently converted into *β*-*C*-ketosides **18** and **19** when subjected to propenyl and propynylmagnesium chloride, respectively (Table 3). In

**Table 3.**




| entry | nucleophile | ketoside | R | yield | β:α |
|---|---|---|---|---|---|
| 1 | MgCl | **18** | $CH_2CHCH_2$ | 91% | >95:5 |
| 2 | MgBr | **19** | $CH_2CCH$ | 99% | >95:5 |

contrast to related substrates, anhydride **17** was surprisingly robust, as exemplified by its recovery following aqueous workup and its stability to silica gel chromatography.[21]

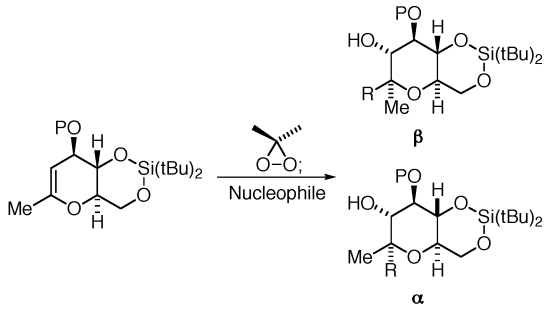
Next, we examined the efficiency with which nonallylic and propargylic Grignard nucleophiles coupled with **5** (Table 4). Interestingly, ethenylmagnesium bromide and phenylmagnesium chloride both coupled with **5** to give the α-anomers **20** and **21**, respectively. As in the propenylmagnesium chloride additions, **4** and **11** gave identical results (entries 2 and 3).

Anhydride **5** was also employed in Mukaiyama-type addition reactions with ketene acetal **23** (eq 1).[22] The addition of **23** to **5** in the presence of TBSOTf gave *β*-C-ketoside **24** in 77% yield as a single diastereomer. To the best of our knowledge, the generation of **24** is novel in that it represents the first example of the addition of any ketene acetal to a glycosyl anhydride. As evidenced by its C(3) and C(4) $^1$H

(21) Isolated **17** from silica gel chromatography was coupled with propenylmagnesium chloride to give ketoside **18**.

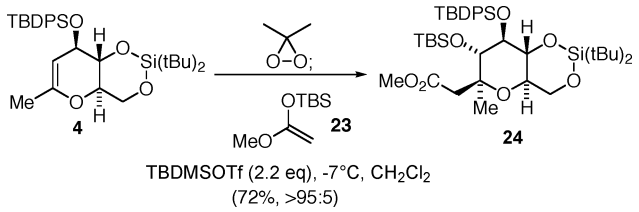
(22) For the addition of silyl ketene acetals to epoxides, see: Maslak, V.; Matovic, R.; Saicic, R. N. *Tetrahedron* **2004**, *60*, 5987.

**Table 4.**




| entry | glycal | P | nucleophile | *C*-ketoside | R | yield | β:α |
|---|---|---|---|---|---|---|---|
| 1 | **4** | TBDPS | MgBr | **20** | $CHCH_2$ | 45% | 1:13.5 |
| 2 | **4** | TBDPS | PhMgBr | **21** | Ph | 75% | <5:95 |
| 3 | **11** | TIPS | PhMgBr | **22** | Ph | 72% | <5:95 |

NMR coupling constants,[23] the pyranyl ring in **24** exists in a boat conformation.[24] Presumably, this conformation minimizes relatively severe gauche interactions between the C(2) TBDMS and C(3) TBDPS ethers and, as outlined below, may explain the stereochemical outcome of the subsequent addition reaction.




The disparate stereochemical outcomes described above can be rationalized (Figures 1−3). For propargyl and allyl

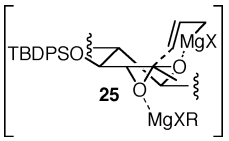



**Figure 1.**

nucleophiles, coordination of the Mg counterion to the axial lone pair of the pyranyl oxygen and ligand transfer via six-membered transition structure **25** would lead to the observed *β*-addition products. The importance of C(3) substitution on

(23) $J_{1,3}$ values for H(2),H(3) and H(3),H(4) were much smaller than one would expect for equatorially substituted pyranosides (i.e., $J_{H(2),H(3)} = 1.0$ Hz, $J_{H(3),H(4)} = 4.2$ Hz).

(24) Calculated low-energy conformer of **24** is also a boat conformation. See ref 26.

these reactions is presumably tied to the ability of the substituent to sterically protect the epoxide and inhibit the competitive formation of oxocarbenium ion intermediates.

Nucleophiles (phenyl, vinyl, and silyl ketene acetals) incapable of forming a six-membered transition structure presumably react through oxocarbenium ion intermediates. Curiously, while ketene acetal **23** adds to the *si*-face of the oxocarbenium ion intermediate, Grignard nucleophiles add to the *re*-face. The Grignard additions can be rationalized either by invoking the conformation having all groups equatorial and a chair transition state as depicted in **26** or through a directed addition and a boat conformer as illustrated for **27**.[25]

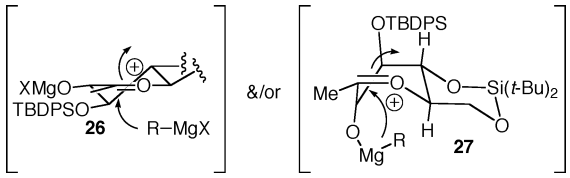



**Figure 2.**

In an effort to explain *si*-face addition for **23**, we calculated the low-energy conformer for the oxocarbenium resulting from the interaction of anhydride **5** with TBSOTf and found it to exist in a boat conformation as depicted by **28**.[26]

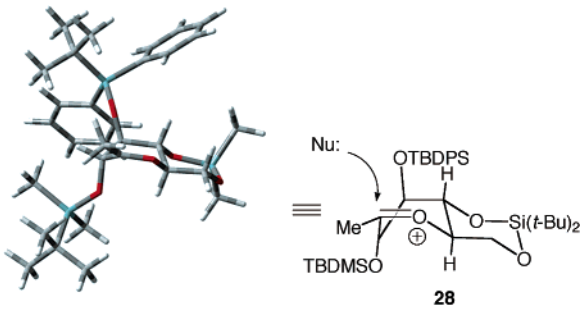



**Figure 3.**

Assuming **28** to also be the reactive conformer, approach of the nucleophile to the oxocarbenium from the face opposite the adjacent pseudoaxial TBDMS ether would give the observed product.

To conclude, we have investigated the role of C(1) substitution, C(3) protecting group, and nucleophile on the generation of *C*-ketosides from from α-substituted glycal anhydrides. Successful coupling is highly dependent upon the size of the C(3) silyl ether and the nucleophile used with allyl, propargyl, and ketene acetal nucleophiles giving *β*-substituted products and Grignards giving α-products. We are continuing to explore these reactions, including their application to total synthesis problems.

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**Supporting Information Available:** Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) For an excellent discussion of the influence of substituents on the conformations of oxocarbenium ions, see: Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521.

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