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Highly Facialselective Synthesis of Pyranose 1,3-Oxazines and Their Ring Opening with Nucleophiles: A Novel Entry to 2-*C*-Branched Glycosides

Biao-Lin Yin,*,† Ze-Ren Zhang,† Li-Wen Xu,‡ and Huanfeng Jiang†

School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou, Guangdong, 510640, China, and Key Laboratory of Organosilicon Chemistry and Material Technology of Ministry of Education, Hangzhou Normal University, Hangzhou, P. R. China

blyin@scut.edu.cn

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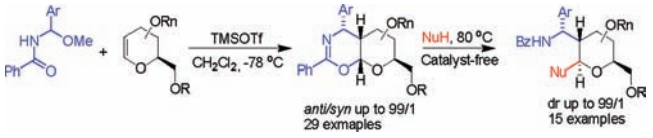
ABSTRACT



A TMSOTf-promoted cycloaddition of *N*-benzoyl-*N*,*O*-acetals with various glycals and 3-deoxy glycals affords pyranose 1,3-oxazines with high facial selectivity. In addition, a highly diastereoselective ring opening of the resulting pyranose 1,3-oxazines is reported. With diverse nucleophiles, these reactions take place upon heating at 80 °C. This novel ring-opening reaction affords structurally diversified 2-*C*-branched glycosides with three newly formed contiguous stereocenters.

C-Branched sugars of either natural or synthetic origin have been the focus of intense studies in carbohydrate chemistry. Many *C*-branched sugars in natural antibiotics, bacterial polysaccharides, and macrolides are often associated with specific biological function.[1] *C*-Branched sugars have also frequently been used as building blocks for the total synthesis of natural products and carbohydrate mimics.[2,3] Recently much attention has been paid to unnatural 2-*C*-branched sugars, since they have been found to be mimics of 2-*N*-acetylsugars for cell surface engineering and inhibitors of the biosynthesis of lipid.[4] However, the synthesis of 2-*C*-branched sugars is not a trivial task and problems are frequently encountered with stereochemical control at the *C*-branching point and at the anomeric center.[1,5] In addition, multiple-step manipulations and the use of toxic tin, mercury, or strongly basic organolithium and Grignard reagents are often required for their synthesis.[6] Therefore, an efficient and selective

† South China University of Technology.
‡ Hangzhou Normal University.

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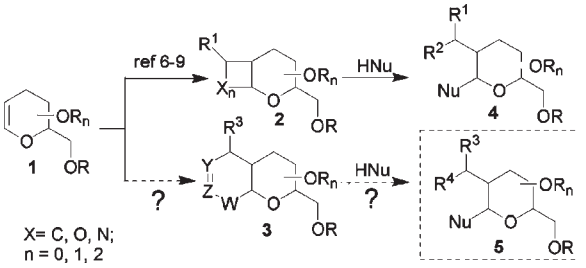
access to 2-*C*-branched sugars with structural diversity, under mild conditions, is highly desirable in organic and medicinal chemistry.

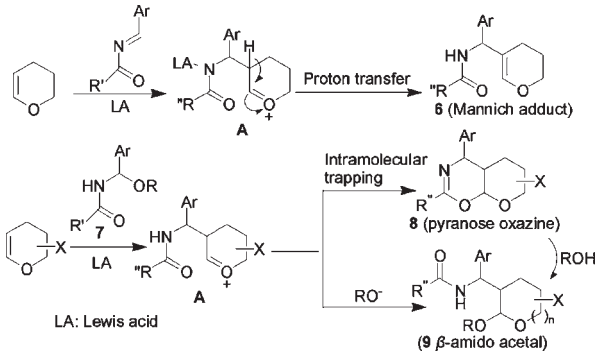
Presently, most 2-*C*-branched sugars of structure **4** have been synthesized from glycal **1**, *via* cycloadditions with carbenes, ketene, and 1,3-dipoles, and yielded three-,[6,7] four-,[8] or five-membered[9] rings fused to the tetrahydropyran ring, respectively. Nucleophilic ring-opening reactions then occurred at the anomeric center to relieve strains in the newly formed ring system. Nevertheless, such ring-opening reactions have never been effected on six-membered oxazines such as **3** (Scheme 1).[10]

Scheme 1. Accesses to 2-*C*-Branched Glycosides



The reaction of *N*-acyl imines with cyclic enol ethers such as 3,4-dihydro-2*H*-pyran under acidic conditions usually leads to oxocarbenium **A** (Scheme 2) which is then converted into **6** (Mannich product).[11] *N*-Acyl-*O*-alkylacetals **7** are frequently used as precursors of *N*-acyl imines in organic synthesis.[12] Upon exposure to suitable acids, **7** can be converted into the corresponding *N*-acyliminium ions. It was our hope that the reaction of **7** with enol ethers under acidic conditions would also furnish **A** and that it would be transformed into **8** or **9** by an intramolecular trapping of the oxocarbenium ion with the carbonyl oxygen atom or with the alkyloxide generated *in situ*. If the enol ether was a glycal, two classes of novel 2-*C*-branched glycosides might be produced. Moreover, an unprecedented ring opening of pyranose oxazine (**9**) into *β*-amido acetal (**8**) might also be anticipated.[13] To the best of our knowledge, the addition of *N*-acyl-*O*-alkylacetals to glycals has never been reported. Herein, we now present the detailed results of exploring this novel reaction of *N*-acyl-*O*-alkylacetals, which has resulted in structurally diversified 2-*C*-branched glycosides.

Scheme 2. Possible Pathways of the Reaction of **7** with Enol Ethers



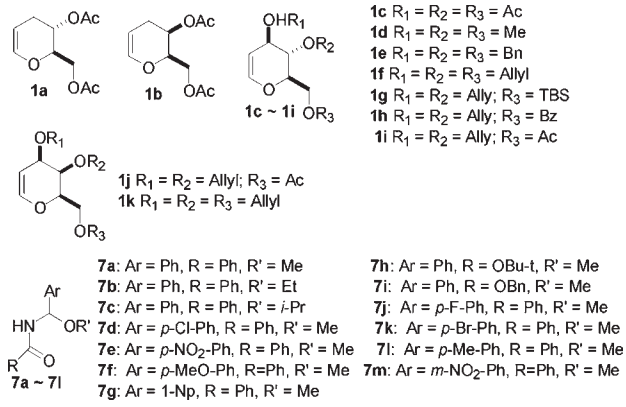


Figure 1. *N*-Acyl-*O*-alkylacetals **7** and enol ethers **1** used in this study.

Initially, 3-deoxy glycal **1a** was employed as the substrate to react with **7a** (Figure 1). With the aid of TMSOTf (trimethylsilyl trifluoromethane-sulfonate) (1 equiv) in CH_2Cl_2 at −78 °C, cycloadducts **8aa** were formed in 82% yield and with high facial selectivity favoring the *anti*-adduct (Table1, entry 1).[14] The stereochemistry of the major isomer was determined by single-crystal X-ray data analysis (*anti*-**8am**, see Supporting Information (SI)). The minor isomer was assumed to be *syn*-**8am**.[15] Other Lewis acids such as $SnCl_4$, $BF_3 \cdot Et_2O$, Bu_2BOTf, and $Yb(OTf)_3$ as promoters led to complicated reaction mixtures and lower yields of **8aa**. Varying the alkoxy groups of **7** slightly

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(13) For similar ring opening, see: Cai, Y.; Ling, C.-C.; Bundle, D. R. *Org. Lett.* **2005**, *7*, 4021.

(14) The *anti*-**8** isomer refers to the configuation of the substituents at the 2 and 6 positions of the pyran ring.

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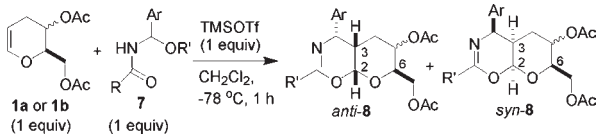
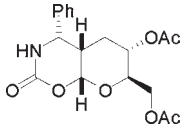
Table 1. Reactions of 3-Deoxyl Glycals with **7**[a]



entry	enol ether	*N*,*O*-acetal	product (yield (%)[b], *anti*/*syn*[c])
1	**1a**	**7a**	**8aa** (82, 85/15)
2	**1a**	**7b**	**8aa** (79, 86/14)
3	**1a**	**7c**	**8aa** (78, 86/14)
4	**1a**	**7d**	**8ad** (85, 89/11)
5	**1a**	**7e**	**8ae** (52, 91/9)
6	**1a**	**7f**	**8af** (trace)
7	**1a**	**7g**	**8ag** (83, >99/1)
8	**1a**	**7h**	**8ah**[d] (79, 99/1)
9	**1a**	**7i**	**8ai** (ND)
10	**1a**	**7m**	**8am** (49, 87/11)
11	**1b**	**7a**	**8ba** (80, >99/1)
12	**1b**	**7g**	**8bg** (88, >99/1)
13	**1b**	**7l**	**8bl** (89, >99/1)

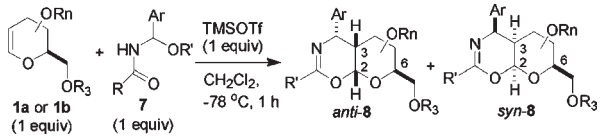
[a] All reactions were carried out on a 0.5 mmol scale. [b] Isolated yield. [c] Based on ^{1}H NMR. [d] The structure of **8ah**:



influenced the yields and facial selectivities (entries 2 and 3). The nature of the Ar group of **7** had a remarkable influence on the reaction. Electron-withdrawing nitro groups on the phenyl ring gave rise to a lower yield (entries 5 and 10). Compound **7f**, carrying a 4-MeO group, led to decomposition with trace amounts of the desired product (entry 6). When a sterically demanding 1-naphthyl was present, higher facial selectivity was obtained (entry 7). Interestingly, when N-Boc protected acetal **7h** (R = OBu-t) was used as a substrate (entry 8), tetrahydrooxazine **8ah** (Figure 2) was produced exclusively. However, when the *N*-Cbz protected acetal was used, the reaction with **7i** was very complicated and none of the desired product was isolated (entry 9). The reaction of 3-deoxy galactal **1b** with **7a**, **7g**, and **7l** provided the corresponding adducts in good yields and with excellent facial selectivities (entries 11−13).

Based on the above results, the reactions of *N*-benzoyl-*N*,*O*-acetals with glycals under the same reaction conditions were then investigated. When tri-*O*-acetyl-D-glucal (**1c**) was employed as the substrate, only Ferrier-type transformation of **1c** was observed (Table 2, entry 1). To circumvent this problem, 3-*O*-alkylation of glycals was required. Tri-*O*-methyl-D-glucal **1d** reacted with **7a** giving adducts **8da** in good yield but with moderate facial selectivity (*anti*/*syn* = 63/37, entry 2). Owing to the great steric hindrance of the 3-*O*-benzyl protective group, **1e** did not produce the desired adduct but led to degradation of **7a** and recovery of **1e** (entry 3). Therefore, D-glucals **1f**−**1h** with a smaller *O*-allyl group at the 3-position and variable *O*-protective groups, such as allyl, TBS, Bz, Ac at the 6-position, were investigated (entries 4−7). Among them, **1i** was found to be the best in terms of the yield and facial selectivity, and the reaction gave the desired adduct **8ia** in 79% yield and in 70:30 ratio of *anti* to *syn* (entry 7). The nature of the Ar group in **7** also remarkably influenced the reactions. An electron-withdrawing nitro group on the phenyl ring produced the ring-opened product **9ie** in a lower yield but with good facial selectivity (entry 8). Substrate **7f** gave no desired product but decomposition (entry 9). The 1-naphthyl group in **7** gave excellent facial selectivity in this reaction (entry 10). When two galactals **1j** and **1k** were used as substrates, the respective addition reactions proceeded well, providing the corresponding adducts in higher yields and with higher facial selectivities than those of glucals (entries 12−17).

Table 2. Reactions of Glycals with **7**[a]



entry	enol ether	*N*,*O*-acetal	product (yield (%)[b], *anti*/*syn*[c])
1	**1c**	**7a**	**8ca** (ND)
2	**1d**	**7a**	**8da** (75, 63/37)
3	**1e**	**7a**	**8ea** (ND)
4	**1f**	**7a**	**8fa** (63, 60/40)
5	**1g**	**7a**	**8ga** (trace)[d]
6	**1h**	**7a**	**8ha** (trace)[d]
7	**1i**	**7a**	**8ia** (79, 70/30)
8	**1i**	**7e**	**9ie** (60, 90/10)
9	**1i**	**7f**	**8if** (ND)
10	**1i**	**7g**	**8ig** (69, 88/12)
11	**1i**	**7l**	**8il** (73, 70/30)
12	**1j**	**7a**	**8ja** (79, >99:1)
13	**1j**	**7d**	**8jd** (85, >99:1)
14	**1k**	**7e**	**8ke** (69, 97:3)
15	**1k**	**7j**	**8kj** (73, >99:1)
16	**1k**	**7k**	**8kk** (84, >99:1)
17	**1k**	**7l**	**8kl** (88, >99:1)

[a] All reaction were carried out on a 0.5 mmol scale. [b] Isolated yield. [c] Based on ^{1}H NMR. [d] Detected by MS (ESI).

To rationalize the stereoselectivities obtained, we proposed stereochemical models **A** and **B**. In these, we postulate that electron pairs of the *O*-acetate or the π-electrons of the allyl group at the O(6)-position are donated to the oxo carbonium ion to stabilize the transition state (Figure 2). The reaction of glycal with **7** presumably proceeds through transition state model **A** instead of model **B**. Model **A** is preferred because of the absence of the developing nonbonding interactions between the benzoyl group and the group at 6-position of glycals, forming *anti*-adducts. For galactals, their three substituted groups oriented at the same face made the opposite side less

hindered than that of the glucals. Therefore, better facial selelctivities for the galactals were obtained.

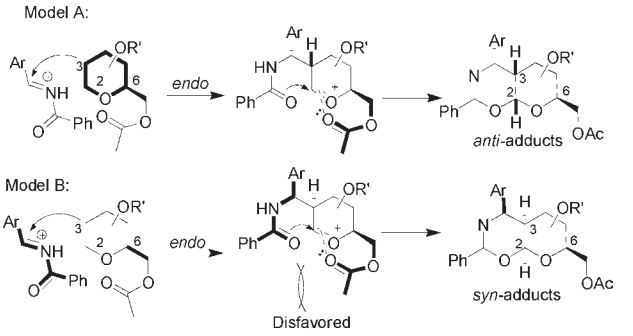


Figure 2. Stereochemical models.

The formation of **9ie** (Table 2, entry 10) gave us the hint that **8** would possibly undergo ring opening at the anomeric center with alcohols to form **9**. This conversion would be useful because it could produce a wide range of 2-*C*-branched glycosides with diverse donor groups at the anomeric position. After careful chromatography, **8aa**, **8ig**, **8ja**, and **8kl** were obtained in the enantiopure form and submitted to the ring-opening reaction. Initially, **8aa** was treated with MeOH in DCM in the presence of a series of acids such as PTSA, CSA, and $BF_3 \cdot Et_2O$ at different temperatures. We found that the ring-opening reaction was reversibile and that the amide and ester groups underwent partial alcoholysis under acidic conditions. Much to our delight, the dihydroxazine ring **8aa** was opened diastereoselectively (dr $>$99:1) by simple heating with excessive MeOH for 24 h, providing **9aaa** in 89% yield (Figure 3). The stereochemistry of **9aaa** was assigned by 400 MHz NOESY experiments in $CDCl_3$. The coupling constant of the acetal proton (dd, J = 7.6 Hz, 2.4 Hz) indicated that MeOH attacked preferentially with inversion. The ring opening proved to be generally effective for a range of primary alcohols with variable functionalities. A series of structurally diversified 2-*C*-branched glycosides **9** were obtained in high yield and with good to excellent diastereoselectivity (Figure 3). Amide and secondary mercaptans can also act as nucleophiles for the ring opening (**9kli**, **9klj**). Due to steric hindrance, secondary alcohols failed to ring open (**9kll**) under these conditions.

In summary, a TMSOTf-promoted cycloaddition of *N*-acyl-*N*,*O*-acetals with glycals and its use for the synthesis of 5*H*-pyrano[3,2-*d*] oxazines were studied. The nature of the Ar, the *O*- and *N*-protective groups of the mixed acetal, and cyclic enol ethers influenced the formation of the product structure and the facial selectvity. In addition, for the first time, the ring opening of the resulting 5*H*-pyrano[3,2-*d*] oxazines with diverse nucleophiles under catalyst-free conditions was achieved. By using this protocol, a highly diastereoselective synthesis of 2-*C*-branched glycosides with three newly formed contiguous stereocenters was developed. Further studies on the synthesis of some bioactive natural or unnatural products including disaccharides and glycoconjugates employing this protocol are ongoing in our laboratory.

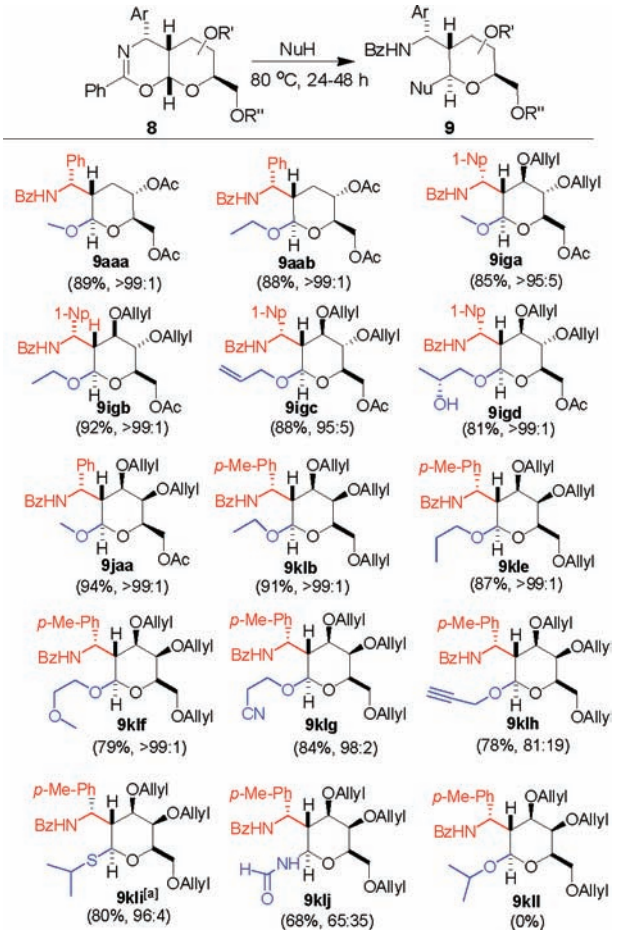


Figure 3. 9 obtained by the ring opening of **8** with variable nucleophiles. Reaction conditions: **8** (0.5 mmol), HNu (1 mL). Yields of isolated products are given. Ratio was determined by ^{1}H NMR of the crude product. [a] Reaction conditions for **9kli**: **8kl** (0.5 mmol), isopropyl mercaptan (2 mmol), 2-propanol (1 mL).

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Supporting Information Available. Details on general experimental methods, X-ray data for **8am**, copies of ^{1}H and ^{13}C NMR spectra of all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.