ORGANIC LETTERS

2010
Vol. 12, No. 3
540−543

Stereoselective Synthesis of 2-*C*-Acetonyl-2-Deoxy-D-Galactosides using 1,2-Cyclopropaneacetylated Sugar as Novel Glycosyl Donor

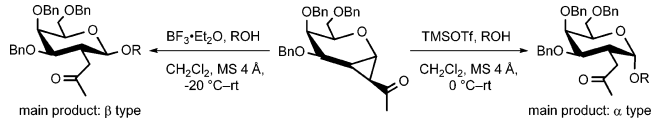
Qiang Tian,[†] Liyan Xu,[†] Xiaofeng Ma,[†] Wei Zou,[‡] and Huawu Shao*,[†]

Natural Products Research Center, Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, China, Institute for Biological Sciences, National Research Council of Canada, 100 Sussex Drive, Ottawa, Ontario K1A 0R6, Canada and Graduate School of Chinese Academy of Sciences, China

shaohw@cib.ac.cn

Received November 26, 2009

ABSTRACT



1,2-Cyclopropaneacetylated sugar is an effective glycosyl donor, which reacted with various glycosyl acceptors including monosaccharides, amino acids and other alcohols in the presence of BF_3•OEt_2 or TMSOTf. The glycosylation is stereoselective in favor of β-anomeric products with BF_3•OEt_2 as catalyst, whereas TMSOTf-catalyzed glycosylation prefers the α-anomeric products. 2-*C*-Acetonyl-2-deoxy-D-galactosides were obtained in good yields.

2-Acetamido-2-deoxy-D-glycopyranosides are widely distributed in living organisms as oligosaccharides and glycoconjugates, and play essential roles in a wide range of biological processes.[1] Hence, there is a considerable interest in glycan and glycoconjugate mimics with modified 2-*N*-acetamidosugar residues for further understanding and modulating the targets of these glycosides.[2] Among the various analogs, 2-acetonyl-2-deoxy-D-galactose (2-keto-Gal) has gained much attention.[3] This substrate can serve as ketone isostere of GalNAc for cell surface engineering,[4] conjugation of nonglycoprotein with biomolecules,[5] and labeling of a single-chain antibody.[6] Moreover, 2-keto-Gal has been taken as a substrate for mutant GalT to detect *O*-GlcNAc-glycosylated proteins,[7] and the LacNAc moiety of glycoproteins and glycolipids.[8] Notably, it may function as a linker substrate to assemble glycoconjugates with therapeutic and diagnostic applications.[6,9]

[†] Chengdu Institute of Biology.
[‡] National Research Council of Canada.

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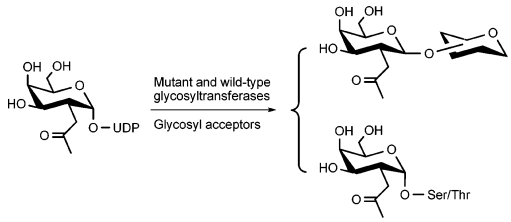
10.1021/ol902732w
Published on Web 12/30/2009

Scheme 1. Synthesis of Glycosyl Conjugates with 2-keto-Gal Residue[3,4]

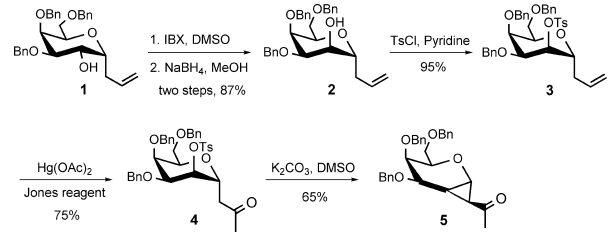


Given the complex nature of the chemoenzymatic or biological synthesis of glycans and glycoconjugates with 2-keto-Gal residue—relying on the availability of different wild-type and mutant glycosyltransferases, and UDP-2-keto-Gal—it is not surprising that access to diverse and chemically defined glycoform mimics through the above the pathways is difficult (Scheme 1). In this context, we presumed that it could be a preferred strategy to assemble these modified glycoforms through chemical glycosylation method. In addition, as the UDP-2-keto-Gal precursor, peracetylated 2-acetonyl-2-deoxy-galactose,[4,10] is not suitable for large-scale glycosylation reactions as glycosyl donor due to the synthetic route suffering from poor yield (3 steps, < 10%), we were therefore attracted to the use of cyclopropanated sugars as glycosyl donors.

1,2-Cyclopropanated glycosyl donors have been investigated and employed in the preparation of 2-*C*-branched glycosides[11] and ring expanded heptanosides[12] as a result of the versatile reactivity of cyclopropyl ring strain. Most of these unsubstituted, and ester or halo substituted sugar cyclopropanes are synthesized from glycals through 1,2-cyclopropanation, and they undergo ring-opening via solvolysis, providing anomeric mixtures of 2-*C*-branched monosaccharides,[13] or Lewis acid-assisted pyran ring expansion to oxepanes.[14] Unfortunately, only Zeise's dimer ($[Pt(C_2H_4)Cl_2]_2$)[15] and NIS/TMSOTf,[16] have been found to be effective for promoting the glycosylation of 1,2-cyclopropanated sugar donors with sugar alcohols. Herein, we report the Lewis acid-catalyzed ring-opening of a 1,2-cyclopropaneacetylated sugar and subsequent glycosylation with various glycosyl acceptors for stereoselective synthesis of 2-acetonyl-2-deoxy-D-galactopyranosyl conjugates.

The straightforward synthesis of galactose-derivative cyclopropane donor **5** commenced with the known allyl *C*-galactoside **1**.[17] Mild oxidation of **1** with IBX followed by $NaBH_4$-mediated highly diastereoselective reduction provided the epimeric allyl *C*-taloside **2** in excellent yield. Tosylation of 2′−OH gave **3**, and subsequent terminal olefin oxidation with $Hg(OAc)_2$/Jones reagent afforded 1-*C*-D-talosyl acetone **4**. Intramolecular S_N2 reaction of compound **4** under K_2CO_3/DMSO conditions produced the desired 1,2-cyclopropaneacetylated sugar **5** as the main product (Scheme 2). Extensive NMR studies and other analytical methods confirmed that compound **5** was a pure diastereoisomer with a trans configuration at bridged C1′ as indicated by the NOEs between H1′, H3 and H5, which were supported by the coupling constants ($J_{H1,\ H1'} = 2.1$ Hz).[18,19]

Scheme 2. Synthesis of 1,2-Cyclopropaneacetylated Sugar **5**



Unexpectedly, the galactose-derivative cyclopropane **5**, in $CDCl_3$, rapidly generated the hemiacetal **6** as a 2:1 mixture of α- and β-isomers (Scheme 3), whereas the structurally similar glucose cyclopropane existed stably in the same deuterated solvent.[19] This indicated that cyclopropane ring of **5** was highly reactive and it might be usable as an effective glycosyl donor.

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(10) 2-Acetonyl-2-deoxy-galactose (2-keto-Gal) was primarily prepared from D-galactal as starting material to undergo iodination, Keck radical coupling, and ozonolysis. See ref 4.

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(18) Proton−proton coupling constants in a cyclopropane system: J = 0−6 Hz for a trans stereochemistry and J = 8−10 Hz for a cis stereochemistry. See: (a) Kawabata, N.; Nakagawa, T.; Nakao, T.; Yamashita, S. *J. Org. Chem.* **1977**, *42*, 3031–3035. (b) Wiberg, K. B.; Barth, D. E.; Schertler, P. H. *J. Org. Chem.* **1973**, *38*, 378–381.

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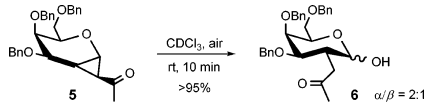
With 1,2-cyclopropaneacetylated sugar donor **5** in hand, we focused our attention on exploring its Lewis acid-catalyzed glycosylation with the primary alcohol of **7** as a model reaction (Table 1). Upon treatment of **5** and **7** with

Scheme 3. Hydrolysis of 1,2-Cyclopropaneacetylated Sugar **5**



10 mol % of BF_3•OEt_2 under an inert atmosphere, the reaction proceeded sluggishly at −78−0 °C and gave the desired disaccharide **8** in 58% yield with $\alpha/\beta = 1{:}4$ (Table 1, entry 1). Increasing the amount of BF_3•OEt_2 to 20 mol % and warming the reaction to −20 °C-rt successfully improved the yield to 84%, obtaining slightly higher β-selectivity (Table 1, entry 2). A variety of other Lewis acids were then screened (Table 1, entries 3−10). $AlCl_3$, $BiCl_3$, and $ZnCl_2$ were found to be less effective for *O*-glycosylation than BF_3•OEt_2 (Table 1, entries 3−5). The use of $InCl_3$ and $PdCl_2$

Table 1. Lewis Acid Catalyzed Glycosylation of Glycosyl Donor **5** and Acceptor **7**[a]

entry	catalyst	condition	yield[c] (%)	α/β[d]
1[b]	BF_3•Et_2O	−78−0 °C, 3 h	58	1:4
2	BF_3•Et_2O	−20 °C-rt, 2 h	84	1:5
3	$AlCl_3$	−20 °C-rt, 2 h	76	1:3
4	$BiCl_3$	−20 °C-rt, 2 h	80	1:4
5	$ZnCl_2$	−20 °C-rt, 2 h	73	1:2
6	$InCl_3$	−20 °C-rt, 16 h	trace	/
7	$PdCl_2$	−20 °C-rt, 16 h	trace	/
8	AgOTf	−20 °C-rt, 16 h	0	/
9	TMSOTf	−20 °C-rt, 2 h	87	2:1
10	TMSOTf	0 °C-rt, 1.5 h	86	7:1

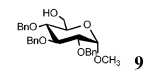
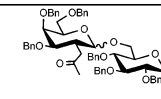
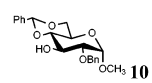
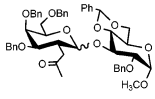
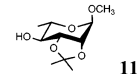
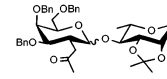
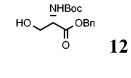
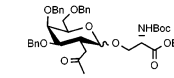
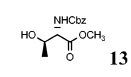
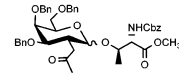
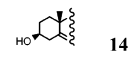
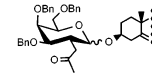
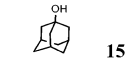
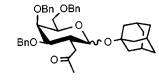
[a] Reactions were performed with 1.1 equiv of acceptor in CH_2Cl_2 (0.1 M). [b] Ten mol % catalyst was employed. [c] Isolated yield. [d] Values were determined by ^1H NMR.

resulted in only a trace amount of the desired disaccharide **8** and the reaction did not even occur in the presence of AgOTf as a promoter (Table 1, entries 6−8).

Interestingly, we found that by replacing BF_3•OEt_2 with the more reactive Lewis acid, TMSOTf, the glycosylation, under otherwise similar conditions, exhibited modest α-selectivity (Table 1, entry 9). Warming the reaction to near room temperature resulted in the diastereoselectivity improving to $\alpha/\beta = 7{:}1$ and the same yield (Table 1, entry 10). It is notable that during the course of monitoring the above Lewis acid-catalyzed glycosylation reactions by TLC, the anomerization of β- to α-*O*-glycoside was not detected through prolonging reaction time. These results clearly demonstrated the similar efficiency of both BF_3•OEt_2 and TMSOTf in promoting the ring-opening of 1,2-cyclopropaneacetylated sugar donor and the contrast in diastereoselective glycosylation.

Considering the potential application of α- and β-2-keto-galactosides in assembling special glycans and glycoconjugates, the scope of both Lewis acids-catalyzed coupling methods was further examined with a number of monosaccharides, amino acids and other alcohols **9**−**15** (Table 2).

Table 2. Glycosylation of 1,2-Cyclopropaneacetylated Sugar Donor **5**

entry	acceptor (ROH)	product	yield[d] (α:β)[e]
1[a]	 **9**	 **16**	82% (1:4)
2[b]			89% (10:1)
3[a]	 **10**	 **17**	71% (1:8)
4[b]			76% (20:1)
5[a]	 **11**	 **18**	85% (1:3)
6[b]			87% (6:1)
7[a]	 **12**	 **19**	71% (1:4)
8[b]			75% (4:1)
9[a]	 **13**	 **20**	77% (1:5)
10[b]			78% (8:1)
11[a]	 **14**	 **21**	87% (1:20)
12[c]			83% (15:1)
13[a]	 **15**	 **22**	74% (1:6)
14[c]			80% (12:1)

[a] Reactions were carried out using 20 mol % BF_3•OEt_2 at −20 °C to rt. [b] Reactions were carried out using 20 mol % TMSOTf at 0 °C to rt. [c] Reactions were carried out using 40 mol % TMSOTf at rt. [d] Isolated yield. [e] Values were determined by ^1H NMR.

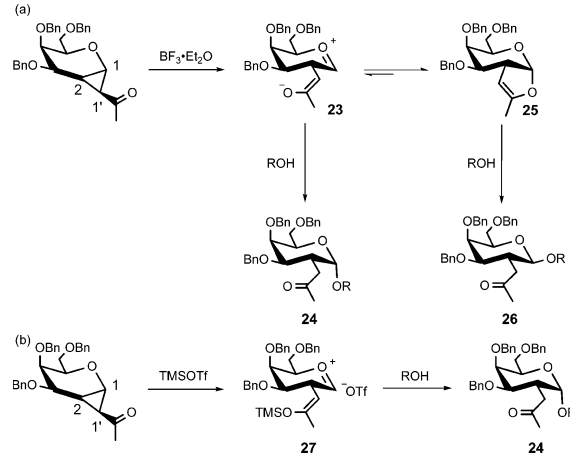
To our delight, using monosaccharides **9**−**11** as nucleophiles, the desired 2-keto-galactosyl disaccharides **16** **α/β**, **17** **α/β**, and **18** **α/β** were formed in 71−89% yield with moderate to good β-selectivity under BF_3•OEt_2-catalyzed conditions, in contrast to TMSOTf-catalyzed glycosylation which gave good to high α-selectivity (Table 2, entries 1−6). When serine and threonine derivatives **12** and **13** were employed as glycosyl acceptors, 2-keto-galactosides **19** **α/β**, and **20** **α/β** were afforded in 71−78% yield (Table 2, entries 7−10). In addition, coupling of the hindered secondary 3-OH of cholesterol **14** with **5** under both conditions gave good to excellent α- or β-selectivity respectively (Table 2, entries

11 and 12), while similar results were also obtained using adamantanol **15** as an acceptor (Table 2, entries 13 and 14). Overall, the above examples clearly demonstrate the effectiveness of BF_3•OEt_2-catalyzed β-selective glycosylation and TMSOTf-catalyzed α-selective glycosylation.

On the basis of the above result, a plausible mechanism for the BF_3•OEt_2-catalyzed β-selective glycosylation is outlined in Scheme 4 (path a). Coordination of the oxygen atom of acetyl with BF_3•OEt_2 followed by the C1−C1′ bond cleavage produces the highly reactive ion pair **23**, which then reacts with nucleophile and mainly gives 1,2-*cis* α-glycoside **24**, due to the anomeric effect. Alternatively, **23** might be equilibrating to a more stable enol ether **25** thanks to intramolecular neighboring group participation.[20] Then Lewis acid-induced nucleophilic attack by the glycosyl acceptor from β face, similar to the glycosylation of enol ether-type glycosides,[21] would form the 1,2-*trans* β-glycoside **26**.

For the TMSOTf-catalyzed α-selective glycosylation, we presumed that the tight coordination of the oxygen atom of carbonyl with TMSOTf, followed by breaking of the C1−C1′ bond, could produce oxocarbenium triflate intermediate **27**[22] with a 2-*C*-branched trimethylsilyl enol ether, which has no neighboring group participation.[23] Thus, nucleophilic attack by an acceptor alcohol at the anomeric carbon atom would afford α-glycoside **24** as the main product, favored by the anomeric effect (Scheme 4, path b). The opposite stereoselectivity of the glycosylation under BF_3•OEt_2 and TMSOTf results mainly from the nature of promoters. To the best of our knowledge, these are the first examples of catalyst-controlled stereoselective glycosylation of 1,2-cyclopropanated sugar.

Scheme 4. Proposed Mechanism for the BF_3•OEt_2 and TMSOTf Catalyzed Ring Opeing of 1,2-Cyclopropaneacetylated Sugar



In conclusion, we have demonstrated that 1,2-cyclopropanated galactosugar is a useful glycosyl donor, which undergo BF_3•OEt_2 and TMSOTf-catalyzed glycosylation reaction stereoselectively. The glycosylation favors β-anomeric products under BF_3•OEt_2 while TMSOTf-catalyzed glycosylation prefers α-anomers. These novel glycoconjugates may serve as building blocks for more complex glycomimics, and be useful substrates for enzymes.

Acknowledgment. We are grateful for the financial support from the Chinese Academy of Sciences (Hundreds of Talents Program) and the National Science Foundation of China (20972151).

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

OL902732W

(20) We considered that this kind of neighboring group participation could also be defined as intramolecular rearragement.

(21) (a) Vankar, Y. D.; Vankar, P. S.; Behrendt, M.; Schmidt, R. R. *Tetrahedron* **1991**, *47*, 9985–9992. (b) Marra, A.; Esnault, J.; Veyrieres, A.; Sinay, P. *J. Am. Chem. Soc.* **1992**, *114*, 6354–6360. (c) Boons, G. J.; Isles, S. *Tetrahedron Lett.* **1994**, *35*, 3593–3596. (d) Boons, G. J.; Isles, S. *J. Org. Chem.* **1996**, *61*, 4262–4271.

(22) Glycosyl triflates or the corresponding oxocarbenium triflates were used as glycosyl donors. See: (a) Leroux, J.; Perlin, A. S. *Carbohydr. Res.* **1978**, *67*, 163–178. (b) Lacombe, J. M.; Pavia, A. A. *J. Org. Chem.* **1983**, *48*, 2557–2563. (c) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321–8348.

(23) We hypothesized that trimethylsilyl enol ether **27** could form temporarily due to the fast coordination between oxygen atom of acetyl and trimethylsilyl cation, and decompose after nucleophilic attack because of the free proton. During this process, the trimethylsilyl enol ether **27** can hardly contribute to the stabilization of the oxocarbenium triflate.