

2-C-Branched Glycosides from 2'-Carbonylalkyl 2-O-Ms(Ts)-C-Glycosides. A Tandem S_N2-S_N2 Reaction via 1,2-Cyclopropanated Sugars

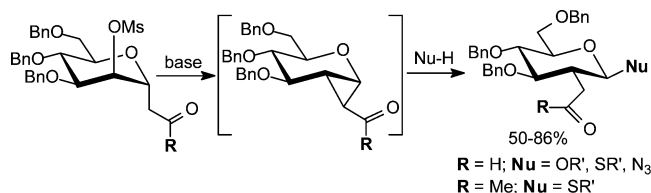
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ABSTRACT



Under basic conditions, 2'-aldehyde (acetyl) 2-O-Ms(Ts)- α -C-glycosides undergo an intramolecular S_N2 reaction to form 1,2-cyclopropanated sugars, which react with nucleophiles (alcohols, thiols, and azide) at the anomeric carbon to give 2-C-branched glycosides. By way of contrast, the 1,2-cyclopropanes derived from 2'-ketones only react with thiols to give 2-C-branched thioglycosides.

C-Branched sugars in natural antibiotics, bacterial polysaccharides, and macrolides are often associated with specific biological functions.¹ Unnatural 2-C-branched sugars also serve as metabolic substrates, e.g., Bertozzi et al. tested 2-C-acetonylsugars, derived from 2-iodosugars, as mimics of 2-N-acetylsugars for cell surface engineering² and Hindsgaul et al. prepared a 2-C-acetamide sugar from a 2,3-epoxide as an inhibitor of the biosynthesis of lipid A.³

Most 2-C-branched sugars are synthesized from glycals through 1,2-cyclopropanation followed by selective ring-opening via solvolysis,^{4,5} which often provides an anomeric mixture of glycosides because of the involvement of an oxocarbenium-like intermediate, with α -glycosides being

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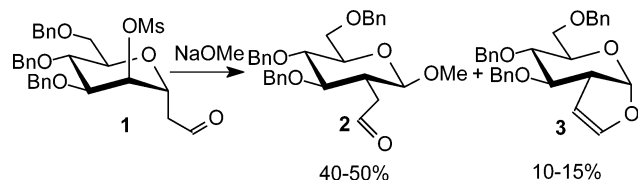
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Scheme 1. Base-Mediated Rearrangements

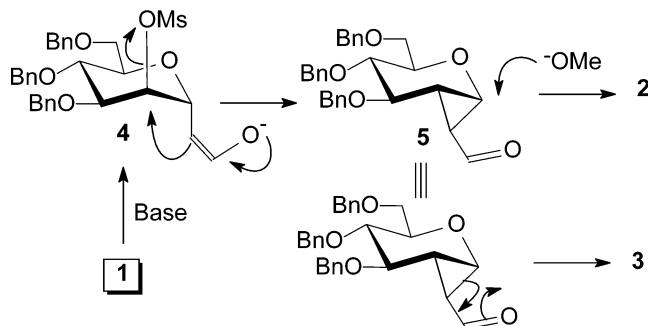


avored due to the anomeric effect. A recent ring-opening of sugar cyclopropanecarboxylates mediated by NIS provided 1,2-trans 2-C-branched glycosides.⁶ We report herein a tandem S_N2-S_N2 reaction involving a base-mediated 1,2-cyclopropanation from 2'-carbonylalkyl 2-O-Ms(Ts)-C-glycosides and subsequent nucleophilic substitution at the anomeric carbon leading to 1,2-trans 2-C-branched β -O- and β -S-glycosides and β -glycosyl azides.

It is known that 2'-carbonylalkyl α -C-glycosides epimerize to their β -anomers under basic conditions through β -elimination to an acyclic α,β -conjugated aldehyde (ketone) intermediate followed by an intramolecular hetero-Michael addition.⁷ However, this cyclization is poorly stereoselective in C-furanosides. Fleet et al. have developed an intramolecular S_N2 reaction to form furan esters via base treatment of 2-O-Tf (Ms) sugar lactones.⁸ Following the same rationale, we decided to place a leaving group at the O(2)-position of 2'-carbonylalkyl C-glycopyranosides to see if the C-furanoside would be formed stereoselectively after β -elimination and subsequent intramolecular S_N2 substitution at C(2) by C(5)-OH.

Thus, 2'-aldehyde 2-O-Ms-C-glycoside (**1**) was prepared from the respective allyl C-glycoside by ozonolysis.⁹ Upon treatment of **1** with 4% NaOMe, two major products were obtained, namely, the 2-C-branched methyl β -glucopyranoside **2** (40–50%) and the bicyclic product **3** (10–15%), but no C-furanoside was isolated (Scheme 1). Both structures were unambiguously characterized by NMR analysis.¹⁰ On the basis of the products obtained, we believe that the enolate **4** reacted to give the 1,2-cyclopropanated sugar **5**, which in turn underwent ring-opening with methoxide at the anomeric carbon to afford **2**; presumably an intramolecular rearrangement afforded **3** (Scheme 2).

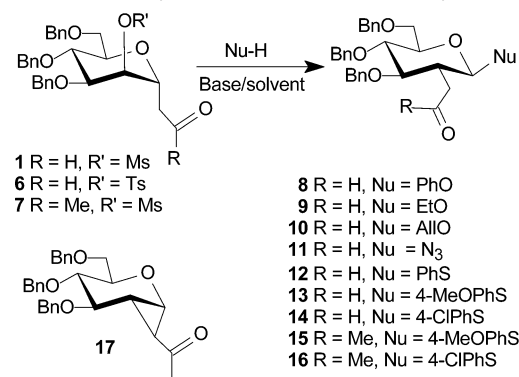
Scheme 2. Tandem S_N2-S_N2 Mechanism



The results indicate that the cyclopropanation (1,2-substitution) was favored over the β -elimination due to the 1,2-trans configurations of α -C-mannoside. This mechanism resembles one observed by Danishefsky et al. involving 1,2-migration of the *N*-sulfonamide from 2-iodo-1-*N*-sulfonamide to 2-*N*-sulfonamide glycosyl compounds.¹¹

Although highly β -selective, the reaction will not be practically useful unless better chemical selectivity is achieved and other substrates and nucleophiles can be incorporated. Thus, 2'-aldehyde 2-O-Ts-C-glycoside (**6**) and 2'-acetylonyl 2-O-Ms-C-glycoside (**7**) were included as substrates, and alcohols, thiols, and sodium azide were used as nucleophiles. After examining various base/solvent combinations, we were able to obtain 2-C-branched glycosides (**2**, **9**, and **10**) from 2-O-Ms **1** in good yields with triethylamine as base, and no byproduct **3** was isolated (see Scheme 3 and entries 1, 4,

Scheme 3. Synthesis of 2-C-Branched Glycosides



and **6** in Table 1). The same selectivity but lower yields were obtained from 2-O-Ts **6** with K_2CO_3/CH_3CN as the base and solvent (entries 2, 3, and 5). Under both sets of conditions, the 2-C-branched glycosyl azide **11** was also produced in moderate yield (entry 7). The best results, however, were obtained when **1**, **6**, and **7** were treated with thiols; this

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(10) β -Configuration of **2** was determined on the basis of the observation of NOE between H1 and H3 and the large coupling constant $J_{1,2} = 8.8$ Hz.

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Table 1. Synthesis of 2-C-Branched Glycosides^a

entry	substrate	nucleophile	base/solvent ^b	product (yield %)
1	1	MeOH	A	2 (72%)
2	6	MeOH	B	2 (52%)
3	6	PhOH	B	8 (62%)
4	1	EtOH	C	9 (71%)
5	6	EtOH	B	9 (51%)
6	6	AllylOH	A	10 (76%)
7	1 and 6	NaN ₃	A and B	11 (50–52%)
8	1 and 6	PhSH	B and D	12 (67–86%)
9	1 and 6	4-MeOPhSH	B and D	13 (70–85%)
10	1 and 6	4-ClPhSH	B and D	14 (72–83%)
11	7	4-MeOPhSH	D	15 (83%)
12	7	4-ClPhSH	D	16 (85%)
13	7	MeOH	D	17 (81%)

^a Reaction was conducted at room temperature overnight. ^b Base/solvent combinations: A, TEA/MeOH; B, K₂CO₃/MeCN; C, TEA/EtOH; D, K₂CO₃/MeOH.

produced 2-C-branched β -thioglycosides (**12–16**) in excellent yields (entries 8–12). Surprisingly, when **7** was treated with base in methanol, rather than the 2-C-branched methyl β -glycoside being isolated, we obtained the stable 1,2-cyclopropanated sugar **17**, an intermediate predicted by the mechanism illustrated in Scheme 2, as the major product (entry 13).¹² Treatment of **17** with thiols in K₂CO₃/MeOH produced the expected 2-C-branched thioglycosides, but its reaction with alcohols (MeOH and PhOH) was very sluggish and yielded multiple byproducts. The diminished reactivity

(12) An attempt to isolate 1,2-cyclopropanated **5** was unsuccessful. For **17**: δ_{H} 1.98 ppm (H-2, $J_{1,2}$ = 7.2 Hz), 2.34 (H-1', $J_{1,1'}$ = 1.6), and 3.86 (H-1, $J_{2,1'}$ = 5.6 Hz). For complete assignment, see Supporting Information.

of **17** in comparison to **5** is probably due to the acetyl group being less electron-withdrawing than the aldehyde.^{4e,13} Consequently, cyclopropane **17** only reacted with strong nucleophiles. To the best of our knowledge, these are the first examples of an S_N2 reaction at the anomeric carbon of 1,2-cyclopropanated sugars.

In summary, we have developed an alternative method for the synthesis of 2-C-branched glucosides with exclusive β -anomeric selection. 2'-Aldehydo (acetonyl) 2-*O*-Ms(Ts)- α -C-mannosides undergo an intramolecular S_N2 reaction to form 1,2-cyclopropanated sugars. The cyclopropane intermediates from the 2'-aldehydes then react with nucleophiles (alcohols, thiols, and azide) by an S_N2 reaction at the anomeric carbon leading to 2-C-branched glycosides, while 1,2-cyclopropanes derived from 2'-ketones only react with thiols to give 2-C-branched thioglycosides. Further studies on the application of this reaction and the utilities of the intermediates are currently in progress.

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Supporting Information Available: Experimental procedures and NMR spectra (¹H, ¹³C, COSY, NOESY, TOCSY, and HSQC) for products (**2**, **3**, **6–17**). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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