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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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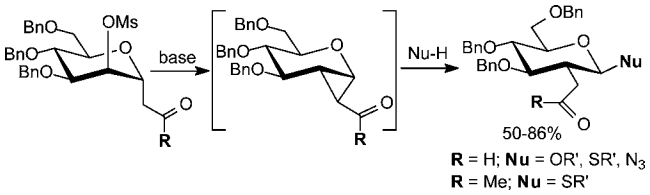
ABSTRACT



Under basic conditions, 2′-aldehydo (acetonyl) 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 engineering[2] 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 oxocarbonium-like intermediate, with α-glycosides being

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(1) (a) Chapleur, Y.; Chétien, F. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997; pp 207−262. (b) Yoshima, J. *Adv. Carbohydr. Chem. Biochem.* **1984**, *42*, 69−134. (c) Lindberg, B. *Adv. Carbohydr. Chem. Biochem.* **1987**, *48*, 279−318. (d) Celmer, W. D. *Pure Appl. Chem.* **1971**, *28*, 413−453.

(2) Hang, H. C.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2001**, *123*, 1242−1243.

(3) (a) Jackman, J. E.; Fierke, C. A.; Tumey, L. N.; Pirrung, M.; Uchiyama, T.; Tahir, S. H.; Hindsgaul, O.; Raetz, C. R. H. *J. Biol. Chem.* **2000**, *275*, 11002−11009. (b) Li, X.; Uchiyama, T.; Raetz, C. R. H.; Hindgaul, O. *Org. Lett.* **2003**, *5*, 539−541.

(4) For reviews, see: (a) Cousins, G. S.; Hoberg, J. O. *Chem. Soc. Rev.* **2000**, *29*, 165−174. (b) Lebel, H.; Marcoux, J.-F.; Malinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977−1050. (c) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151−1196. (d) Doyle, M. P.; Protopopova, M. N. *Tetrahedron* **1998**, *54*, 7919−7946. (e) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165−198.

(5) For solvolysis conditions, see: (a) Scott, R. W.; Heathcock, C. H. *Carbohydr. Res.* **1996**, *291*, 205−208. (b) Collum, D. B.; Still, W. C.; Mohamadi, F. *J. Am. Chem. Soc.* **1986**, *108*, 2094−2096. (c) Kim, C.; Hoang, R.; Theodorakis, E. A. *Org. Lett.* **1999**, *1*, 1295−1297. (d) Hoberg, J. O.; Claffey, D. J. *Tetrahedron Lett.* **1996**, *37*, 2533−2536. (e) Ramana, C. V.; Murali, R.; Nagarajan, M. *J. Org. Chem.* **1997**, *62*, 7694−7703. (f) Ramana, C. V.; Nagarajan, M. *Synlett* **1997**, 763−764. (g) Bertinato, P.; Sorensen, E. J.; Meng, D.; Danishefsky, S. J. *J. Org. Chem.* **1996**, *61*, 8000−8003. (h) Beyer, J.; Skaanderup, P. R.; Madsen, R. *J. Am. Chem. Soc.* **2000**, *122*, 9575−9583. (i) Beyer, J.; Madsen, R. *J. Am. Chem. Soc.* **1998**, *120*, 12137−12138.

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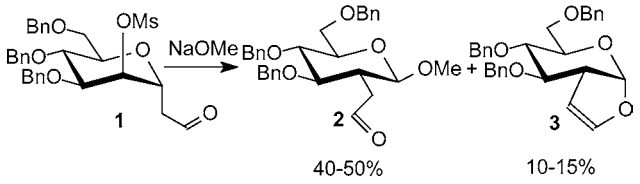
Scheme 1. Base-Mediated Rearrangements

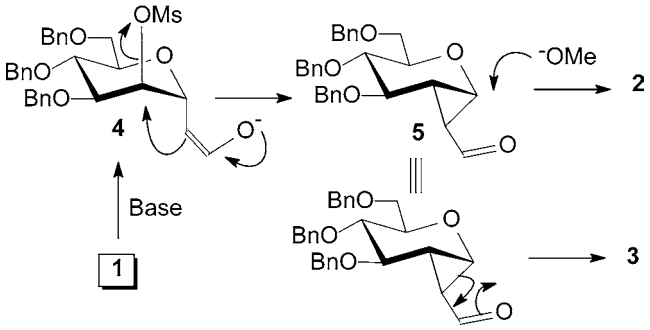


favored due to the anomeric effect. A recent ring-opening of sugar cyclopropanecarboxylates mediated by NIS provided 1,2-trans 2-C-branched glycosides.[6] We report herein a tandem S_N2-S_N2 reaction involving a base-mediated 1,2-cyclopropanation from 2′-carbonylalkyl 2-*O*-Ms(Ts)-*C*-glycosides and 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′-aldehydo 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).

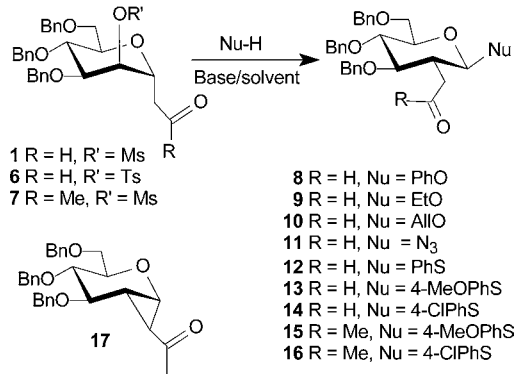
Scheme 2 Tandem S_N2-S_N2 Mechanism



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′-aldehydo 2-*O*-Ts-*C*-glycoside (**6**) and 2′-acetonyl 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

(6) Sridhar, P. R.; Ashalu, K. C.; Chandrasekaran *Org. Lett.* **2004**, *6*, 1777−1779.

(7) (a) Shao, H.; Wang, Z.; Lacroix, E.; Wu, S.-H.; Jennings, H.; Zou, W. *J. Am. Chem. Soc.* **2002**, *124*, 2130−2131. (b) Wang, Z.; Shao, H.; Lacroix, E.; Wu, S.-H.; Jennings, H.; Zou, W. *J. Org. Chem.* **2003**, *68*, 8097−8105. (c) Zou, W.; Lacroix, E.; Wang, Z.; Wu, S.-H. *Tetrahedron Lett.* **2003**, *44*, 4431−4433.

(8) (a) Sanjayan, G. J.; Stewart, A.; Hachisu, S.; Gonzalez, R.; Watterson, M. P.; Fleet, G. *Tetrahedron Lett.* **2003**, *44*, 5847−5851. (b) Watterson, M. P.; Edwards, A. A.; Leach, J. A. Smith, M. D.; Ichihara, O.; Fleet, G. *Tetrahedron Lett.* **2003**, *44*, 5853−5857.

(9) (a) Zou, W.; Wang, Z.; Lacroix, E.; Wu, S.-H.; Jennings, H. *Carbohydr. Res.* **2001**, *334*, 223−231. (b) Uchiyama, T.; Vassilev, V. P.; Kajimoto, T.; Wong, W.; Huang, H.; Lin, C.-C.; Wong, C.-H. *J. Am. Chem. Soc.* **1995**, *117*, 5395−5396. (c) Minehan, T. G.; Kishi, Y. *Tetrahedron Lett.* **1997**, *38*, 6815−6818. (d) Praly, J.-P.; Chen, G.-R.; Gola, J.; Hetzer, G.; Raphoz, C. *Tetrahedron Lett.* **1997**, *38*, 8185−8188. (e) Roe, B. A.; Boojamra, C. G.; Griggs, J. L.; Bertozzi, C. R. *J. Org. Chem.* **1996**, *61*, 6442−6445.

(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.

(11) (a) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 5811−5819. (b) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 5863−5864. (c) Danishefsky, S. J.; Koseki, K.; Griffith, D. A.; Gervay, J.; Peterson, J. M.; McDonald, F. E.; Oriyama, T. *J. Am. Chem. Soc.* **1992**, *114*, 8331−8333.

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, K_2CO_3/MeCN; C, TEA/EtOH; D, K_2CO_3/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 K_2CO_3/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 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, ^{13}C, 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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(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.

(13) Nucleophilic addition only takes place on cyclopropanes substituted with electron-withdrawing groups, see: Danishefsky, S. J. *Acc. Chem. Res.* **1979**, *12*, 66−72.