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General Method for Synthesizing Pyranoid Glycals. A New Route to Allal and Gulal Derivatives

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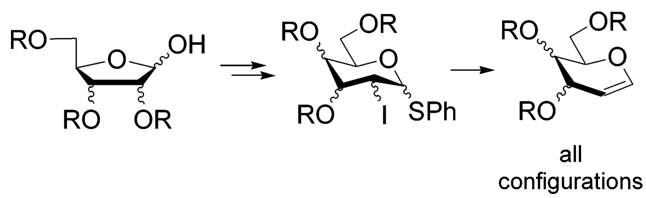
ABSTRACT



Pyranoid glycals of all configurations can be obtained from pentoses through an olefination–cyclization–elimination sequence. The elimination can be carried out with excellent yields under radical conditions or by using common reductive reagents such as Zn/Cu, $TiCl_4$/$LiAlH_4$, or lithium naphthalenide. The proposed method is appropriate for the synthesis of glycals with *allo* or *gulo* configurations because the cyclization step is more efficient for these substrates.

Access to glycals is important in the glycosylation field for the synthesis of oligosaccharide motifs,[1] *C*-glycosides,[2] *C*-nucleosides,[3] nucleosides,[4] and other biologically important molecules.[5−7] The growing appreciation that glycoconjugates play an important role in cell recognition processes has spurred the synthesis of many glycoconjugates via the glycal method. In some cases, this effort has been conducted with the aim of developing synthetic vaccines. If new structural motifs are to be built up, it will be necessary to provide a variety of glycals of different configurations. In this respect, the only pyranoid glycals that are readily accessible currently are either D-glucal and D-galactal or L-rhamnal. Other D-glycals (such as D-gulal and D-allal, etc.) are not readily available.[8]

The Fischer−Zach method for forming glycals, which uses zinc dust in acetic acid in the reductive elimination of acylated glycosyl bromides, has been one of the most popular methods for synthesizing glycals (Scheme 1).[9] Over the years, this procedure has undergone countless modifications regarding the anomeric leaving group (Cl, SPh, S(O)Ph, SO_2Ph,

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(2) (a) Thorn, S. N.; Gallagher, T. *Synlett* **1996**, 856. (b) Hosokawa, S.; Kirschbaum, B.; Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 1917−1920.

(3) (a) Erion, M. D.; Rydzewski, R. M. *Nucleosides Nucleotides* **1997**, *16*, 315−337. (b) Walker, J. A., II; Chen, J. J.; Hinkley, J. M.; Wise, D. S.; Townsend, L. B. *Nucleosides Nucleotides* **1997**, *16*, 1999−2012.

(4) (a) Robles, R.; Rodríguez, C.; Izquierdo, I.; Plaza, M. T.; Mota, A. *Tetrahedron: Asymmetry* **1997**, *8*, 2959−2965. (b) Díaz, Y.; El-Laghdach, A.; Castillón, S. *Tetrahedron* **1997**, *53*, 10921−10938. (c) Díaz, Y.; El-Laghdach, A.; Matheu, M. I.; Castillón, S. *J. Org. Chem.* **1997**, *62*, 1501−1505. (d) Chao, Q.; Zhang, J.; Pickering, L.; Jahnke, T. S.; Nair, V. *Tetrahedron* **1998**, *54*, 3113−3124. (e) Bravo, F.; Kassou, M.; Díaz, Y.; Castillón, S. *Tetrahedron Lett.* **2001**, *336*, 83−97.

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(6) For use in a novel class of glycosylation based in a [4+2] cycloaddition, see: (a) Capozzi, G.; Dios, A.; Frank, R. W.; Geer, A.; Marzabadi, C.; Menichetti, S.; Nativi, C.; Tamarez, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 777−779. (b) Franck, R. W.; Marzabadi, C. H. *J. Org. Chem.* **1998**, *63*, 2197−2208.

(7) For the synthesis of thionucleosides from thioglycals, see: Haraguchi, K.; Nishikawa, A.; Sasakura, E.; Tanaka, H.; Nakamura, K. T.; Miyasaka, T. *Tetrahedron Lett.* **1998**, *39*, 3713−3716.

(8) (a) Wittman, M. D.; Halcomb, R. L.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 1979−1981. (b) Guthrie, R. D.; Irvine, R. W. *Carbohydr. Res.* **1979**, *72*, 285−288.

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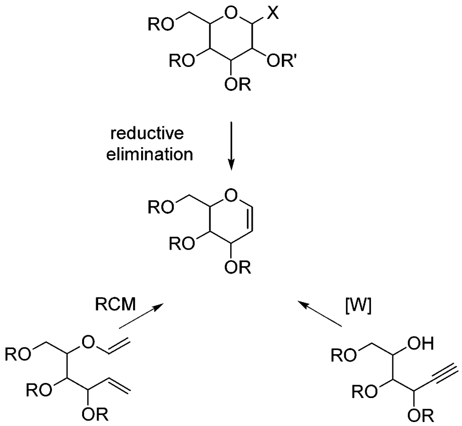
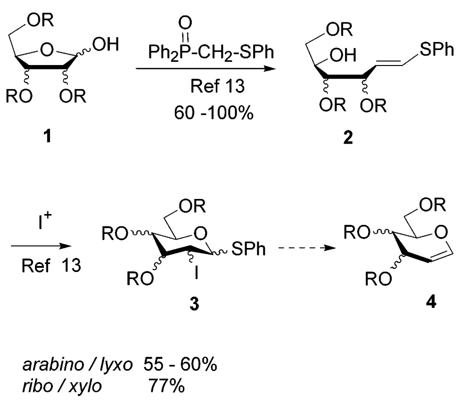
Scheme 1



SePh, TePh, etc.) and the reducing agent (modifications of the initial Zn reagents, $(Cp_2TiCl)_2$, Cr(EDTA), Al−Hg, lithium naphthalenide, potassium-graphite, SmI_2, etc.) used for glycal generation.[10] When appropriate groups are present at positions 1 and 2, the reaction can be performed under radical conditions.[10] These methods are limited to readily available pyranoses. Glycals have also been recently prepared by ring-closing metathesis[11] and via tungsten- and molybdenum-promoted alkynol endo cycloisomerization.[12]

In a previous report,[13] we described a new route to glycosides that makes use of a new kind of glycosyl donor, 2-deoxy-2-iodo-thioglycosides, which are synthesized from pentoses through a short synthetic route that involves olefination and iodonium-ion-mediated 6-endo cyclization (Scheme 2). As an extension of this work, we envisioned an

Scheme 2



easy and general route to glycals from 2-deoxy-2-iodo-thioglycosides that would allow the preparation of D-allal and D-gulal derivatives.

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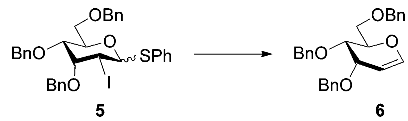
The presence of PhS and I groups at positions 1 and 2 in compound **3** makes such substrates appropriate for glycal preparation under anionic or radical conditions. Initially, we treated the 1-thioglycoside **5** with a Zn−Cu couple following the Fischer−Zach method as modified by Bredenkamp[14] and obtained a quantitative yield of the D-allal **6** (entry 1, Table 1). The use of zinc in the presence of vitamin B_{12},[15] a very

Table 1. Optimization of the Synthesis of the Glycal **6** from the 2-Deoxy-2-iodo-1-thioglycoside **5**



entry[a]	conditions	yield (%)
1[b]	Zn−Cu, THF−AcOH 20:1, NaOAc, 0 °C to rt, 6 h	100
2	Zn, B_{12}, NH_4Cl, MeOH−CH_3CN 3:1, rt, 45 min	94
3	*n*-BuLi, THF, −78 °C, 1 h	41
4	2LN[c] (1 M), THF, −78 °C, 4.5 h	94
5	$2TiCl_4$, $4LiAlH_4$, THF, reflux, 2 h	85[d]
6	2NaI, acetone, 0 °C to reflux, 40 h	*e*
7	SmI_2, THF−HMPA, rt, 15 h	15[f]
8	Bu_3SnH, AIBN, toluene, reflux, 30 min	91
9[g]	*t*-BuOK, THF, 0 °C to reflux, 10.5 h	*h*

[a] A 2:5 α/β mixture was used unless otherwise indicated. [b] A 1:9 α/β mixture was used. [c] LN = lithium naphthalenide. [d] Benzyl-deprotected glycals were detected by TLC. [e] 100% of starting material was recovered. [f] 49% of starting material was recovered. [g] A 2:5 α/β mixture was used. [h] 87% of starting material was recovered.

efficient reduction system, also afforded an excellent yield of **6** but in a shorter reaction time (entry 2). The reaction of **5** with BuLi only gave a modest yield of the glycal **6** (entry 3); however, when **5** was treated with lithium naphthalenide (LN),[16] the yield increased to 94% (entry 4). When **5** was treated with $TiCl_4/LiAlH_4$,[17] the glycal **6** was obtained in 85% yield (entry 5).

The reaction of **5** with NaI left the starting material unaltered even after 40 h of heating (entry 6). Phenyl

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(11) (a) Calimente, D.; Postema, M. H. D. *J. Org. Chem*. **1999**, *64*, 1770−1771. (b) Postema, M. H. D.; Calimente, D. *Tetrahedron Lett*. **1999**, *40*, 4755−4759. (c) Schmidt, B.; Wildemann, H. *Eur. J. Org. Chem*. **2000**, 3145−3163. (d) Postema, M. H. D.; Calimente, D.; Liu, L.; Behrmann, T. L. *J. Org. Chem*. **2000**, *65*, 6061−6068.

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(15) Forbes, C. L.; Franck, R. W. *J. Org. Chem*. **1999**, *64*, 1424−1425.

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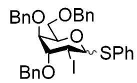
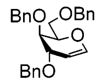
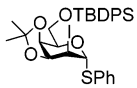
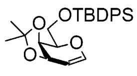
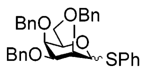
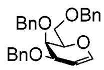
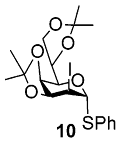
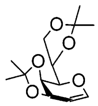
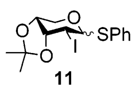
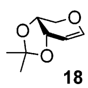
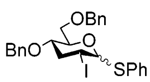
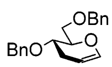
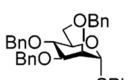
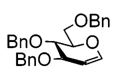
Table 2. Synthesis of Pyranoid Glycals from Various 2-Deoxy-2-iodo-1-thiohexoglycosides[a]

Entry	Starting material	Glycal	Conditions	Yield(%)
1	 **7**	 **14**	0 °C, 1 h	92
2[b]	 **8**	 **15**	0 °C, 1 h	86
3[c,d]	 **9**	 **16**	0 -10 °C, 4.5 h	89
4[b]	 **10**	 **17**	0 °C, 1 h	97
5	 **11**	 **18**	0 °C, 1.5 h	91
6[c]	 **12**	 **19**	15 °C, 4 h	71
7[b]	 **13**	 **20**	0 °C- rt, 3 h	100

[a] Standard conditions: Zn−Cu couple, 1.4 equiv of NaAcO, THF−AcOH 20:1. (α/β mixture was used unless otherwise indicated.) [b] A 1:0 α/β mixture was used. [c] A 1:1 α/β and C-2 mixture of isomers was used. [d] The β-galacto starting material isomer decomposes on standing.

1-thioglycosides have been reported to be unreactive toward SmI_2 even in the presence of HMPA, although the corresponding sulfones give glycals under these conditions.[18] When we tested the reaction of **5** with SmI_2, very low yields of **6** were obtained and a large amount of starting material was always recovered (entry 7). By contrast, when we performed the reaction under classical radical conditions, the expected glycal was obtained in very good yield (entry 8).[19]

Finally, when we treated **5** with potassium *tert*-butoxide in refluxing THF, only the starting material was recovered after 10 h.

(18) Pouilly, P.; Chénedé, A.; Mallet, J. M.; Sinaÿ, P. *Tetrahedron Lett.* **1992**, *33*, 8065−8068.

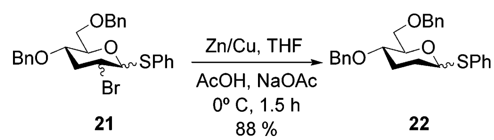
(19) (a) Boothe, T. E.; Greene, J. L.; Shevlin, P. B. *J. Org. Chem.* **1980**, *45*, 794−797. (b) Lin, T.-S.; Yang, J.-H.; Liu, M.-C.; Zhu, J. L. *Tetrahedron Lett.* **1990**, *31*, 3829−3832.

Because tri-*O*-benzyl-D-allal was most efficiently obtained from 2-deoxy-2-iodo-1-thio-D-allo-pyranosides by using a Zn−Cu couple as the reductant, we selected it to explore the synthesis of all the glycals shown in Table 2.

Thus, treatment of the 2-iodo-1-thioglycosides **7**−**13** with Zn−Cu gave the glycals **14**−**20** in excellent yield. Importantly, glycals of all configurations, including the D-allo (**6**) and D-gulo (**14**) configurations, were accessible using this method. A variety of protecting groups, including benzyl and silyl ethers and acetals, were stable under the reaction conditions. Significantly, the procedure described here can be used to obtain pyranoid glycals derived from heptoses (**17**), pentoses (**18**), and 3-deoxyhexoses (**19**).

Interestingly, the bromo derivative **21**, obtained from the corresponding thioalkenyl derivative by NBS-induced electrophilic cyclization, gave rise to **22** when subjected to the above conditions, indicating that the 2-iodo sugars are the best substrates for this reaction (Scheme 3).

Scheme 3



In conclusion, we have devised a new method for accessing pyranoid glycals of different configurations by a short route that uses readily available starting materials and conventional transformations. Our method is particularly valuable for the synthesis of nonreadily accessible glycals such as D-allal **6** and D-gulal **14** that are present in some oligosaccharide molecules with biologically interesting properties.

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Supporting Information Available: The general procedure for the synthesis of glycals and spectroscopic data of the reported compounds **6**, **14**, **15**, **17**−**19**, and **22**, plus NMR spectra of compounds **5**−**8**, **10**−**15**, and **17**−**19** are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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