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Efficient one-step synthesis of 2-hydroxy and 2-aminoglycals from selenoglycosides

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Abstract—2-Hydroxy and 2-aminoglycals are readily synthesised in one step from selenoglycosides by a Sharpless-type oxidation, which is then followed by spontaneous selenoxide elimination.

Glycals are extremely useful carbohydrate derivates, which are not only versatile as glycosyl donors,[1] or as substrates for Ferrier type rearrangements,[2,3] but find extensive application for many other synthetic purposes, particularly as chiral building blocks for the synthesis of natural products.[4] As part of ongoing studies into the use of tandem Tebbe/Claisen methodology for the synthesis of *C*-glycosides[5] we sought easy access to a wide variety of differentially protected glycals, including 2-hydroxy and 2-amino substituted materials. However, existing synthetic routes to 2-hydroxy glycals typically rely on the elimination of anomeric halides by treatment with base at high temperature, and are not high yielding.

The synthesis of α,β-unsaturated carbonyl derivatives by the introduction of selenium α- to the carbonyl group, and subsequent oxidation to produce a selenoxide which then undergoes facile elimination, is well documented.[6] Since selenoglycosides, which themselves find extensive use as glycosyl donors, are accessible in one step from either the corresponding glycosyl acetates[7] or halides,[8] it was considered that selenoglycosides would prove to be excellent substrates for the introduction of 1,2-unsaturation into carbohydrate derivatives via a similar reaction sequence.[9] Thus, it was envisaged that oxidation of a selenoglycoside would produce an anomeric selenoxide which could then undergo spontaneous in situ *syn* elimination to yield the corresponding 2-hydroxy glycal (Fig. 1).

Moreover, mindful that although thioglycosides have very recently been used for such a reaction sequence,[10] an alternative oxidative/elimination sequence via selenoxides would seem more appealing, since selenoxides undergo thermal elimination at considerably lower temperature than sulfoxides.[11] Indeed spontaneous elimination of selenoxides under the reaction conditions used for the oxidation step would obviate the need for isolation of any intermediates and also eliminate the possibility of over-oxidation, which can be problematic in the case of sulfoxides.

To this end, suitable oxidation conditions were sought in order to achieve the desired transformation in a single step. Selenoglycoside **1**[7] was studied as a model compound and subjected to a variety of reaction conditions. Unfortunately attempted oxidation by treatment of **1** with either *meta*-chloroperbenzoic acid (MCPBA) or periodate was not successful, and resulted either in decomposition of the substrate, or in the formation of multiple products (Scheme 1).

However, subjection of **1** to Sharpless-type oxidation conditions,[4,12] namely *tert*-butyl hydroperoxide and titanium(IV) tetra-isopropoxide, in the presence of di-*iso*propylethylamine as a base,[13] resulted in the formation of the desired 2-hydroxy glycal product **2**[14] in

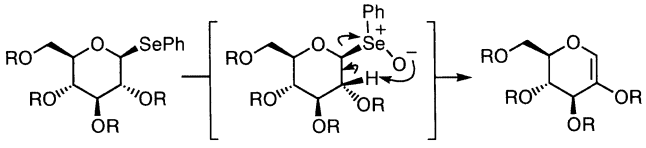

Figure 1.

Keywords: carbohydrates; glycals; selenoglycosides; oxidation; elimination; selenoxides.

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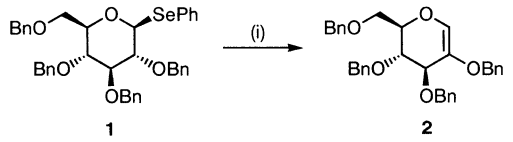
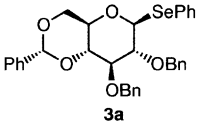
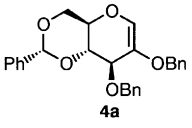
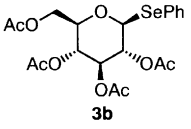
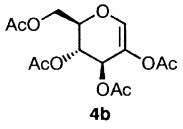
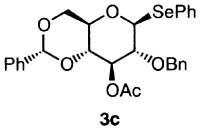
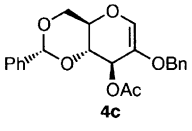
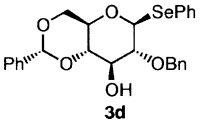
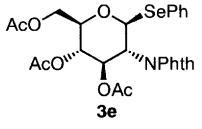
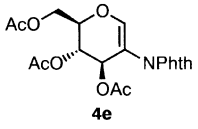
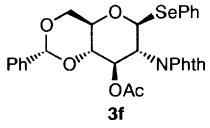
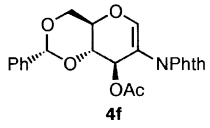


Scheme 1. *Reagents and conditions*: (i) ^{t}BuOOH, EtN*i*Pr$_2$, Ti(O*i*Pr)$_4$, CH_2Cl_2, 0°C to rt, quantitative.

quantitative yield. Clearly under these reaction conditions the intermediate selenoxide, which was not observed by NMR or TLC, underwent spontaneous elimination to produce the desired glycal product. To test the generality of this process a selection of selenoglycosides **3a**–**g** were synthesised and subjected to these reaction conditions (Table 1). In the majority of cases the desired glycal products **4a**–**c**,**e**,**f**[15] were produced in extremely high yield.[16] The exception was the attempted reaction of the alcohol **3d** which resulted in product decomposition and the formation of many minor products indicating a potential limitation in that this methodology does not currently seem to be compatible with selenoglycosides that possess a free hydroxyl group. However, the generality of the approach for use with other fully protected selenoglycosides is clearly demonstrated by successful reaction of the phthalamido protected 2-amino sugars **3e** and **3f**.

In summary, we have developed suitable methodology for the high yielding synthesis of a variety of protected 2-hydroxy and 2-amino glycals directly from selenoglycosides. Such methodology could be considered advantageous to the alternative sulfoxide approach in that neither isolation of intermediate oxidation products or elevated temperatures are required, since formation of the desired glycal occurs spontaneously subsequent to oxidation. The use of these differentially protected glycals for the synthesis of a variety of *C*-glycosides, *C*-glycosyl amino acids and *C*- and *O*-oligosaccharides is currently under investigation and the results will be published in due course.

Table 1.

Entry	Selenoglycoside	Glycal	Yield
(a)	 **3a**	 **4a**	91%
(b)	 **3b**	 **4b**	99%
(c)	 **3c**	 **4c**	quantitative
(d)	 **3d**	–	decomposition
(e)	 **3e**	 **4e**	quantitative
(f)	 **3f**	 **4f**	96%

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References

1. For a review, see: Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380–1419.
2. Ferrier, R. J.; Prasad, N. J. *J. Chem. Soc. C* **1969**, 570–575.
3. For some recent references, see: (a) Swamy, N. R.; Venkateswarlu, Y. *Synthesis* **2002**, 598–600; (b) Takhi, M.; Abdel-Rahman, A. A.-H.; Schmidt, R. R. *Synlett* **2001**, 427–429; (c) Masson, C.; Soto, J.; Bessodes, M. *Synlett* **2000**, 1281–1282.
4. For examples, see: (a) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon Press: Oxford, 1995; (b) Danishefsky, S. J.; DeNinno, S.; Lartey, P. *J. Am. Chem. Soc.* **1987**, *109*, 2082–2089; (c) Ichikawa, Y.; Isobe, M.; Konobe, M.; Goto, T. *Carbohydr. Res.* **1987**, *171*, 193–199; (d) Hannessian, S. *Total Synthesis of Natural Products: The 'Chiron' Approach*; Pergamon Press: Oxford, 1993.
5. (a) Godage, H. Y.; Fairbanks, A. J. *Tetrahedron Lett.* **2000**, *41*, 7589–7593; (b) Godage, H. Y.; Fairbanks, A. J. *Tetrahedron Lett.* **2003**, *44*, 3631–3635.
6. Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22–30.
7. Mehta, S.; Pinto, B. M. *J. Org. Chem.* **1993**, *58*, 3269–3276.
8. (a) Benhaddou, R.; Czernecki, S.; Randriamandimby, D. *Synlett* **1992**, 967–968; (b) Stick, R. V.; Tilbrook, M. G.; Williams, S. J. *Aust. J. Chem.* **1997**, *50*, 233–235.
9. For a synthetic route to furanoid glycals via selenoxide elimination, see: Bravo, F.; Kassou, M.; Díaz, Y.; Castillón, S. *Carbohydr. Res.* **2001**, *336*, 83–97.
10. For a recent paper on the use of thioglycosides for the synthesis of 2-hydroxy and 2-amino glycals that was published during the course of this work, see: Liu, J.; Huang, C.-H.; Wong, C.-H. *Tetrahedron Lett.* **2002**, *43*, 3447–3448.
11. (a) Jones, N.; Mundy, D.; Whitehouse, R. D. *J. Chem. Soc., Chem. Commun.* **1970**, 86–87; (b) Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *43*, 1697–1705.
12. (a) Hori, T.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 1689–1697; (b) Brunetière, A. P.; Lallemand, J. Y. *Tetrahedron Lett.* **1988**, *29*, 2179–2182; (c) Aggarwal, V. K.; Evans, G. R.; Moya, E.; Dowden, J. *J. Org. Chem.* **1992**, *57*, 6390–6391.
13. Required to prevent side reactions caused by selenenic acids and their disproportionation products.
14. Gent, P. A.; Gigg, R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1446–1455.
15. All new compounds possess spectroscopic data consistent with their structures, together with satisfactory microanalytical and/or high-resolution mass spectral data. Selected data: **4c**, a white crystalline solid, mp 125–127°C (methanol); $[\alpha]_D^{22}$ −12 (*c*, 0.94 in $CHCl_3$); **4f**, a white crystalline solid, mp 199–202°C (ethyl acetate/petrol); $[\alpha]_D^{25}$ +1.9 (*c*, 1.0 in $CHCl_3$); compounds **2**,[14] **4a**,[17] **4b**,[18] and **4e**[19] all possess spectroscopic data consistent with those found in the literature.
16. Typical experimental procedure: The selenoglycoside (**3a–f**, 1 equiv.) and *N*,*N*-diisopropylethylamine (1.7 equiv.) were dissolved in anhydrous dichloromethane and the solution cooled to 0°C. *tert*-Butyl hydroperoxide (5.5 M solution in decane, 2.3 equiv.) was added drop-wise over a period of 5 min, and then titanium(IV) isopropoxide (1.0 equiv.) was added. The reaction mixture was stirred under an atmosphere of argon for 2 h, after which time TLC (petrol:ethyl acetate, 4:1) indicated complete consumption of starting material. The yellow solution was concentrated in vacuo, and purified by flash column chromatography.
17. Crich, D.; Cai, W. *J. Org. Chem.* **1999**, *64*, 4926–4930.
18. Chretien, F. *Synth. Commun.* **1989**, *19*, 1015–1024.
19. Ogawa, T.; Nakabayashi, S.; Sasajima, K. *Carbohydr. Res.* **1981**, *95*, 308–312.