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Synthesis of *erythro* and *threo* Furanoid Glycals Using 5-*endo*-trig Selenoetherification as Key Step

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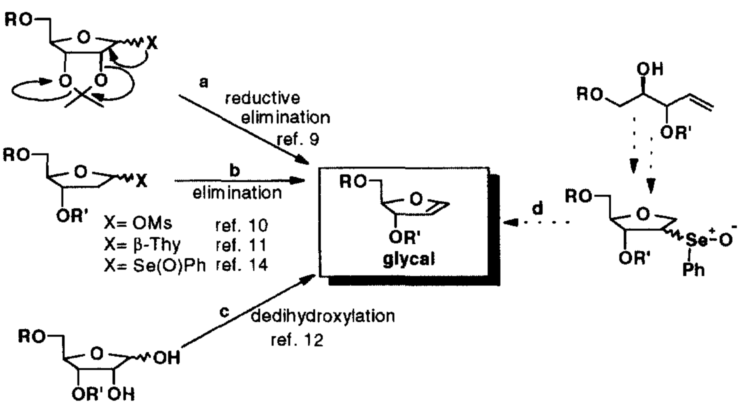
Abstract
Differently protected *erythro* and *threo* furanoid glycals were synthesised from 4-pentene-1,2,3-triol, through selenium induced 5-*endo*-trig cyclization and selenoxide elimination. © 1999 Elsevier Science Ltd. All rights reserved.

The use of glycals as important glycosyl donors has been extensively discussed in the literature.[1] Indeed, a number of recent articles describe them as important precursors of oligosaccharides,[2] *C*-glycosides[3] and *C*-nucleosides,[4] nucleosides[5] and others.[6-8] Both pyranoid and furanoid glycals are usually obtained by reductive elimination of appropriately activated compounds. Ireland's method,[9] which starts from 1-halo-2,3-*O*-isopropylidenefuranoses and Li/NH_3(l) as reducing agent, has been widely used for the synthesis of differently protected furanoid glycals of *erythro* configuration (Scheme 1, via a). Some of the drawbacks of this method are that many useful protecting groups are not stable in the strongly reducing conditions of the reaction, and that glycals of *threo* configuration require a long multistep synthesis.

In attempts to overcome these limitations, several new procedures based on elimination reactions from 1-*O*-mesyl furanoses[10] (Scheme 1, via b, X=OMs), or thymidine[11] (Scheme 1,

Scheme 1



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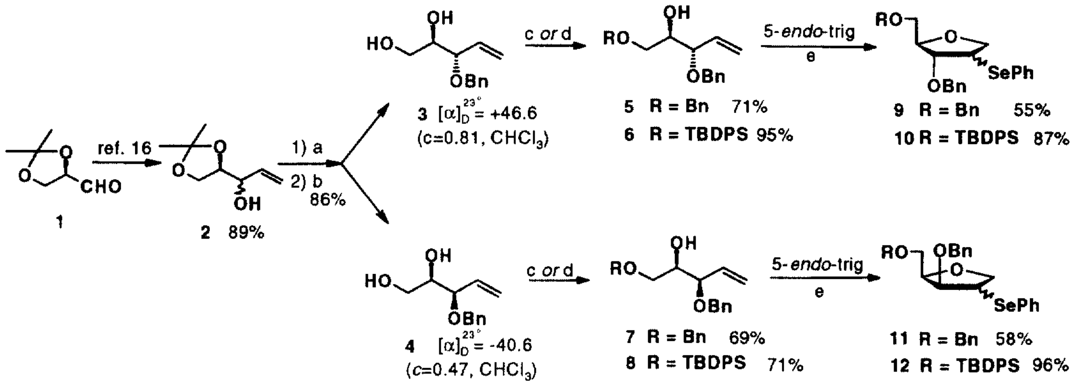
via b, X=β-Thy), dedihydroxylation of furanoses with I_2/PPh_3/imidazole[12] (Scheme 1, via c) or 5-*endo*-dig cyclization of 4-pentyne-1,2-diols catalysed by molybdenum complexes[13] have recently been described. In particular, we reported an efficient procedure for synthesising furanoid glycals from 1-phenylselenofuranoses, through oxidation and thermal elimination of the selenoxide generated at low temperature[14] (Scheme 1, via b, X=Se(O)Ph). This procedure was compatible with the presence of a wide number of protecting groups. We assumed that the synthesis of glycals could also proceed if the phenylselenenyl group were located at position 4 of the tetrahydrofuran ring (Scheme 1, via d). These seleno derivatives, in turn, could be obtained from protected 4-pentene-1,2,3-triols.

Scheme 2

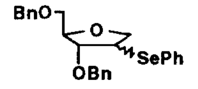
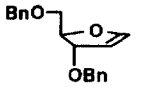
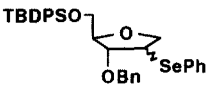
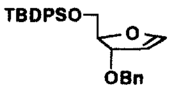
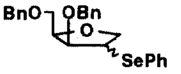
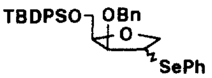
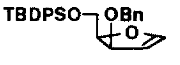


a) NaH, BnBr; separation of isomers; b) H^+, MeOH; c) To obtain **5** and **7**: 1) Bu_2SnO, Toluene, 4 Å M.S.; 2) BnBr, Bu_4NBr; d) To obtain **6** and **8**: TBDPSCl, imidazole, DMF; e) *N*-PSP, CSA, CH_2Cl_2

With this purpose, we synthesised alkenols **5-8** from *D*-glyceraldehyde **1**, which is accessible from *D*-mannitol[15] (Scheme 2). Treating **1** with vinylmagnesium chloride[16] in ether/THF gave a mixture of alcohols **2** in a ratio of nearly 1:1. It should be pointed out that the *syn* or *anti* isomer can be obtained selectively with the aid of titanium or zinc complexes.[17] Protection of the free alcohol with benzyl bromide, followed by isopropylidene cleavage, gave alcohols **3** and **4**[18] (Scheme 2). The primary hydroxyl group was selectively protected by reacting **3** and **4** with benzyl bromide via the stannylidene procedure[19] to give alcohols **5** and **7**, and with TBDPSCl to obtain alcohols **6** and **8** (Scheme 2).

Previous reports on cyclizations of related compounds with iodine electrophiles showed a greater preference for the 5-*exo*-trig cyclization, even when the hydroxyl that undergoes cyclization is protected with an ether function.[20] However, the reaction of dibenzyl derivatives **5** and **7** with *N*-phenylselenophthalimide (*N*-PSP) in the presence of camphorsulfonic acid (CSA)[21] preferentially gave products **9** (ratio of isomers 1:1) and **11** (ratio 7:4) through unusual 5-*endo*-trig cyclization.[22] Nevertheless, cyclization of the primary oxygen also took place and provided minor amounts of the 6-*endo*-trig and 5-*exo*-trig products. We assumed that the stability of the benzyl cation may be the reason for it being released when there is no good nucleophile,[23] thus allowing cyclization through oxygen 1. These side reactions were suppressed by using *tert*-butyldiphenylsilyl ether as protecting group, and the only products

Table 1. Formation of *erythro* and *threo* furanoid glycals

Entry	2-phenylselenenyl derivative	Conditions[a]	Yield	Glycal
1	 **9**	A	62%	 **13**
2	 **10**	A	82%	 **14**
3		B	95%	
4	 **11**	A	74%	 **15**
5	 **12**	A	65%	 **16**
6		B	82%	

a) Formation of selenoxide carried out by adding ^{t}BuOOH (2.5 eq), NEt^{i}Pr$_2$ (1.7 eq.) and Ti(O^{i}Pr)$_4$ (1 eq.) in CH$_2$Cl$_2$ or ClCH$_2$CH$_2$Cl. Conditions of thermal elimination: (A) Reflux in CH$_2$Cl$_2$, 48h; (B) Reflux in ClCH$_2$CH$_2$Cl, 4h.

that could be isolated after the selenoetherification of **6** and **8** were **10** (ratio 5:4) and **12** (ratio 1:1), respectively (Scheme 2).

The first attempts to generate glycals were made by oxidizing each diastereoisomer of **9** and **11** with H_2O_2.[24] The selenoxide formed slowly (6-8 hours), but no glycal formation was observed. In this case, the elimination of the formed selenoxide must proceed towards a carbon that supports an oxygen atom, which explains the stability of the selenoxide.[25] Treating the selenoxide in refluxing dichloromethane did not give the corresponding glycal, and standing in boiling dichloroethane resulted in decomposition. So we tried the conditions we used in our previous synthesis of glycals[14] (^{t}BuOOH, NEt^{i}Pr$_2$, Ti(O^{i}Pr)$_4$, CH$_2$Cl$_2$, Scheme 1, via b, X=Se(O)Ph). Under these conditions, selenoxide formed rapidly (ca. 15 minutes), but again no evolution to the glycal was observed. However, after prolonged heating in dichloromethane, glycals were isolated from the different isomers in good yields (see Table 1).

The 2,3-unsaturated products, which can be formed by *syn* elimination of the phenylselenenyl group under oxidative conditions,[26] depending on its relative stereochemistry, were not observed. Therefore, we concluded that isomer separation was not necessary. Treating mixtures **10** and **12** under these conditions gave the respective glycals (Table 1). The excessively long time required for the formation of the glycal was significantly reduced when dichloromethane was replaced by dichloroethane, and this led to excellent yields of glycals.

In conclusion, glycals of both *erythro* and *threo* configuration have been efficiently synthesised by oxidizing 4-phenylselenenyltetrahydrofurans. These products have been obtained through an unusual 5-*endo*-trig selenoetherification of 4-pentene-1,2,3-triols, which are obtained from inexpensive *D*-mannitol.

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18. ^{1}H NMR spectral data for compounds (**3**) and (**4**) taken in $CDCl_3$ at 300 MHz: (**3**) 7.35 (m, 5H, Ph), 5.82 (ddd, 1H, $J_{4,5'}$=17.3 Hz, $J_{4,5}$=10.4 Hz, $J_{3,4}$=7.7 Hz, H-4), 5.40 (dt, 1H, $J_{5,5'} \approx J_{3,5}$=0.8 Hz, H-5), 5.36 (dt, 1H, $J_{5,5'} \approx J_{3,5'}$=0.9 Hz, H-5'), 4.63 (d, 1H, J_{AB}=11.7 Hz, CH_2Ph), 4.36 (d, 1H, J_{AB}=11.7 Hz, CH_2Ph), 3.89 (dd, 1H, $J_{2,3}$=4.0 Hz, H-3), 3.8-3.6 (m, 3H, H-1, H-1', H-2), 3.1-2.5 (bs, 2H, 2xOH); (**4**) 7.4-7.2 (m, 5H, Ph), 5.77 (ddd, 1H, $J_{4,5'}$=16.8 Hz, $J_{4,5}$=11.0 Hz, $J_{3,4}$=7.7 Hz, H-4), 5.39 (ddd, 1H, $J_{5,5'}$=1.6 Hz, $J_{3,5}$=0.6 Hz, H-5), 5.37 (ddd, 1H, $J_{3,5'}$=0.8 Hz, H-5'), 4.65 (d, 1H, J_{AB}=11.5 Hz, CH_2Ph), 4.34 (d, 1H, J_{AB}=11.5 Hz, CH_2Ph), 3.84 (t, 1H, $J_{2,3} \approx J_{3,4} \approx$ 7.7 Hz, H-3), 3.8-3.5 (m, 3H, H-1, H-1', H-2), 3.0 (bs, 1H, OH), 2.8 (bs, 1H, OH).
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