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Efficient Procedure for the Synthesis of *Erythro* and *Threo* Furanoid Glycals from 2-Deoxyribose

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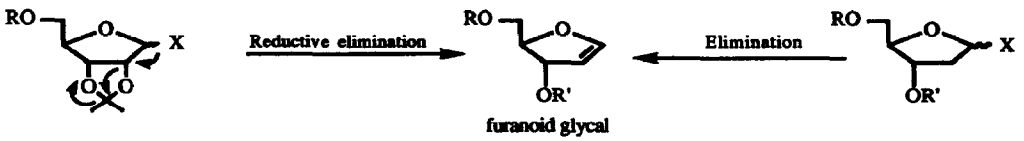
Abstract: Differently protected *erythro* and *threo* furanoid glycals have been synthesised starting from 2-deoxyribose, via selenoxide elimination as the key step.

Glycals are useful starting materials for the synthesis of enantiomerically pure compounds.[1] Recently, pyranoid glycals have been efficiently used as glycosyl donors in the stereoselective synthesis of ß-glycosides via the 1α,2α-ahydro derivatives[2] and 2-deoxyglycosides,[3] and furanoid glycals in the preparation of 2',3'-dideoxy-,[4] 2'-deoxy-,[5] and C-nucleosides.[6] Both pyranoid[7] and furanoid glycals are usually obtained by reductive elimination of appropriately activated compounds. Thus, the method of Ireland,[8] which starts from D-ribonolactone and uses Li/NH_3(l) as the reductive agent of 1-halo-2,3-O-isopropylidenefuranoses, is the method of choice for the synthesis of differently protected[9] furanoid glycals[10] of *erythro* configuration with silyl ether or acetal protecting groups. However, acyl protecting groups must be avoided and, furthermore, glycals of *threo* configuration need long multistep syntheses to be obtained.[11]

Scheme 1



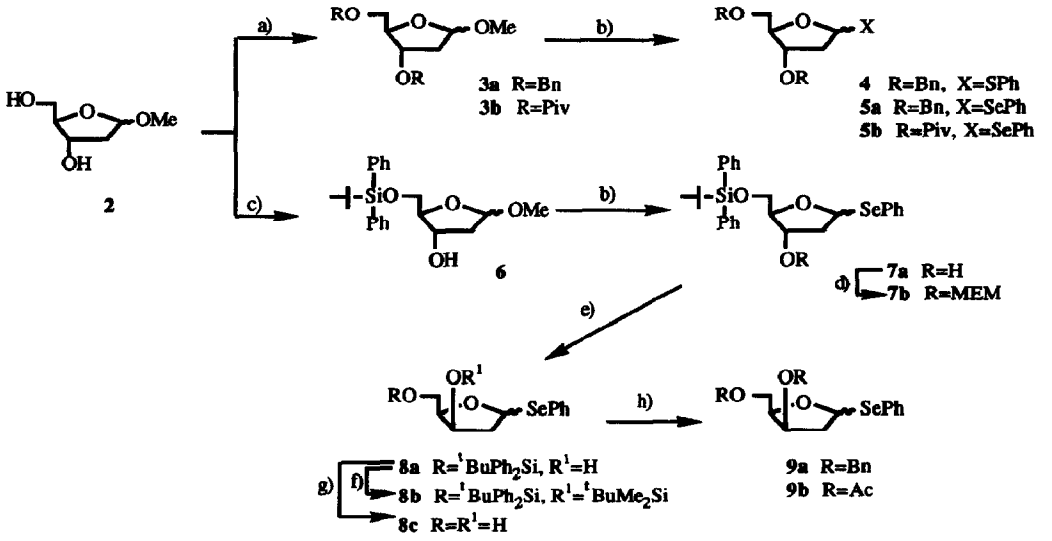
furanoid glycal

The elimination-mediated synthesis of furanoid glycals from 2-deoxycarbohydrates has scarcely been investigated (Scheme 1),[4] probably because of the strong acid and basic media required for the elimination, which are not compatible with the glycal, and the price of the starting material, 2-deoxyribose, with regard to ribonolactone. However, the later is no longer a problem. In this paper we show that both *erythro* and *threo* furanoid glycals can be easily obtained from 2-deoxyribose (**1**) in few steps using a key selenoxide elimination, and that this method has allowed us to obtain furanoid glycals with acyl protecting groups.

Taking advantage of the recently described method of the formation of enol ethers by the reaction of acetals with TMSOTf[12], we prepared the methyl furanoside (**3a**) from 2-deoxyribose (**1**) by reaction with HCl/MeOH (0.05%)[13] and BnBr/NaH. When **3a** was treated with TMSOTf only the 2-benzyloxymethyl-furan could be isolated even when the reaction was started at -20°C. The presence of other protecting groups such as ^{t}BuPh$_2$Si led to the total degradation of the starting material. Trying to avoid strong acid or basic media we turned our attention to the pyrolytic elimination of sulphoxide derivatives. Treatment of **3a** with PhSH/BF_3·Et_2O[14] gave rise to the phenylthio derivative **4**. Oxidation of **4** with 1 equiv. of MCPBA gave the

corresponding sulphoxide and its subsequent pyrolytic elimination by heating in dioxane or toluene, in the presence or in the absence of base, afforded only the furan. Heating the sulphoxide at reflux in CCl_4 in the presence of $P(OMe)_3$[15] did not allow the glycal to be obtained either.

Scheme 2



a) 1. BnBr, NaH, THF (**3a**). 2. PivCl, Py (**3b**). b) 1. $PhSH/BF_3.Et_2O/CH_2Cl_2$, -0° (**4**). 2. $PhSeH/BF_3.Et_2O/CH_2Cl_2$, -5°C (**5-7a**). c) $^tBuPh_2SiCl$/imidazol/DMF. d) MEMCl, Py. e) 1) Tf_2O, Py, 0°C. 2) KNO_2, 18-crown-6, DMF. f) $^tBuMe_2SiCl$, DBU, benzene. g) Bu_4NF,THF. h) 1. a.1 (**9a**) 2. Ac_2O, Py (**9b**).

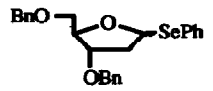
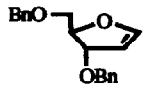
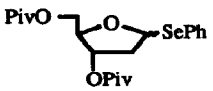
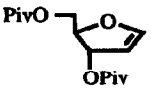
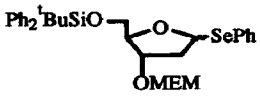
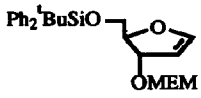
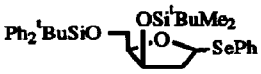
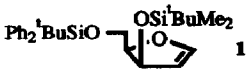
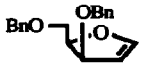
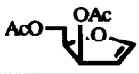
Synthesis of phenyl 2-deoxy-1-seleno-D-*erythro* and *threo*-furanosides. The drastic conditions needed for the elimination of sulphoxides led to the aromatisation of the glycal. Recently, phenyl 1-selenopyranosides have been synthesised by treating peracetylated sugars with PhSeH.[16] As the selonoxide derivatives undergo elimination at low temperature, we synthesised differently protected phenyl 2-deoxy-1-seleno-*erythro*-and *threo*-furanosides (Scheme 2). Thus, methyl 2-deoxyfuranosides **3a**, **3b** and **6**, easily prepared from **2**, were converted into phenyl 2-deoxy-1-selenofuranosides **5a**, **5b** and **7a** (α/ß mixture) in 85%, 71% and 75% yields respectively, by reaction with PhSeH and $BF_3{\cdot}Et_2O$. The $^tBuPh_2Si$ group appeared to be stable enough under the conditions of PhSeH introduction when the temperature was maintained at -5°C. From compound **7a** differently protected derivatives can be obtained; for instance, **7b** was prepared by treatment with MEMCl.

Interestingly, the configuration of the secondary alcohol in compound **7a** was inverted by reaction with Tf_2O/Py and KNO_2/18-crown-6/DMF[17] affording *threo* derivative **8a** in 75% yield for the two steps (Scheme 2). Protection of the secondary alcohol with $^tBuMe_2SiCl$ led to compound **8b**.

In the same way, the treatment of **8a** with Bu_4NF gave quantitatively the unprotected compound **8c**, from which the phenylseleno derivatives **9a** and **9b** were easily obtained by usual protection methods.

An alternative way of synthesizing *threo* derivatives could be the inversion of configuration in **6** followed by protection, but PhSe introduction fails in this case.

Table 1. Synthesis of furanoid glycals from phenyl 2-deoxy-1-seleno-furanosides[a]

Entry	Phenyl 1-seleno derivative		Glycal[18]		Yield(%)
1		**5a**		**10a**	85
2		**5b**		**10b**	71
3		**7b**		**10c**	73
4		**8b**		**11a**	74
5		**9a**		**11b**	82
6		**9b**		**11c**	70[b]

[a] Reactions were performed at a 0.2 mmol scale, in CH_2Cl_2, at 0 °C, with a 1:1:1.1:1 sugar/^{i}Pr$_2$EtN/^{t}BuOOH/Ti(O^{i}Pr)$_4$ ratio.
[b] Sample of pure material by ^{1}H NMR. It partially decompose on chromatographic purification.

Synthesis of furanoid glycals. Preliminary oxidation experiments of phenyl 1-selenofuranoside **5a** with H_2O_2 in THF led directly to glycal **10a** in 30% yield as the best result (Table 1). Use of MCPBA gave rise to decomposed products where no glycals could be detected. Oxidation of **5a** with ^{t}BuOOH[19] in CH_2Cl_2 did not produce the selenoxide but only starting material was recovered even after heating in refluxing CH_2Cl_2 for two hours.

Addition of Ti(O^{i}Pr)$_4$[20] to a mixture of **5a** and ^{t}BuOOH cooled to 0°C caused the fast oxidation of the selenium leading cleanly to glycal **10a** with a 85% yield (Table 1, Entry 1). Similarly, compounds **7b, 8b** and **9a** (Entries 3, 4 and 5) were converted into glycals **10c, 11a** and **11b** with yields above 70%. It is noteworthy that ester[21] containing phenylseleno derivatives **5b** and **9b** (Entries 2 and 6) also gave glycals **10b** and **11c**, respectively, under the same reaction conditions, and that **10b** ($[\alpha]_D$ =+188, c 2, $CHCl_3$) was isolated and characterised.

In conclusion, the oxidation of phenyl 2-deoxy-1-seleno-furanosides with the ^{t}BuOOH/Ti(O^{i}Pr)$_4$ system is an efficient and versatile procedure for the synthesis of furanoid glycals, allowing one to obtain *erythro* and *threo* furanoid glycals from 2-deoxyribose. The method is compatible with different protecting groups such as methyl, benzyl or silyl ethers, acetals and even ester. Compounds **10a** and **10c** were made in a 1-2 g scale.

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18. All glycals (except compound **11c** which was not isolated) gave correct Elemental Analysis and spectroscopical data. Selected NMR ($CDCl_3$, δ in ppm) data for glycals: (**11a**) (^1H) 6.58 (d, $J_{1,2}$=2.7 Hz, H-1), 5.15 (dd, H-2); (^{13}C) 150.4 (C-1), 100.6 (C-2). (**11b**) (^1H) 6.62 (d, $J_{1,2}$=2.6 Hz, H-1), 5.15 (dd, H-2); (^{13}C) 151.6 (C-1), 199.5 (C-2). (**11c**) (^1H) 6.53 (d, $J_{1,2}$=2.4 Hz, H-1), 5.15 (dd, H-2); (^{13}C) 150.3 (C-1), 101.0 (C-2). (**12a**) (^1H) 6.63 (d, $J_{1,2}$=2.1 Hz, H-1), 5.08 (dd, H-2); (^{13}C) 149.6 (C-1), 103.9 (C-2). (**12b**) (^1H) 6.64 (d, $J_{1,2}$=2.6 Hz, H-1), 5.26 (dd, H-2); (^{13}C) 150.6 (C-1), 101.4 (C-2). (**12c**) (^1H) 6.68 (d, $J_{1,2}$=2.4 Hz, H-1), 5.23 (dd, H-2); (^{13}C) 151.7 (C-1), 100.9 (C-2)
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