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SELENIUM-MEDIATED GLYCOSIDATIONS: A SELECTIVE SYNTHESIS OF β-2-DEOXYGLYCOSIDES

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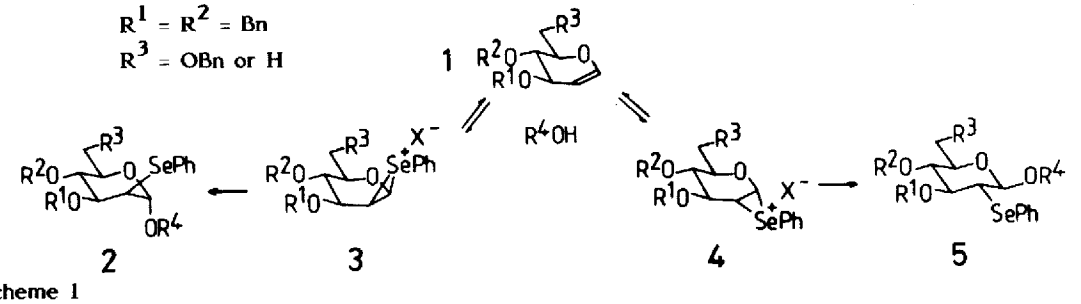
Summary: 1,2-Trans diequatorial acetoxy-selenides are selectively prepared from glycals. Their activation by trimethylsilyl trifluoromethanesulfonate in the presence of sugar alcohols followed by reductive deselenation leads to an efficient access to β-2-deoxyglycosides.

α or β-2-Deoxy glycosides appear frequently as structural units in a wide variety of biologically important natural products such as aureolic acids[1], antracycline antibiotics[2], cardiac glycosides[3], avermectins[4] or orthosomycins[5]. Efficient α-selective glycosidation reactions have been proposed[6,7,8] which are now able to solve most of the practical problems associated with 2-deoxy- (D, L) glycoside syntheses. Within this context, we have put forward[6] a selenium-based α-glycosidation reaction of benzylated glycals. Under the conditions used [a) PhSeCl, CH_3CN; b) ROH, sym-collidine, room temperature], the regio- and stereoselectivity observed was rationalized by a favored trans diaxial opening of a transitory 1,2-episelenonium ion **3** (Scheme 1) leading selectivity to the 2-deoxy-2-



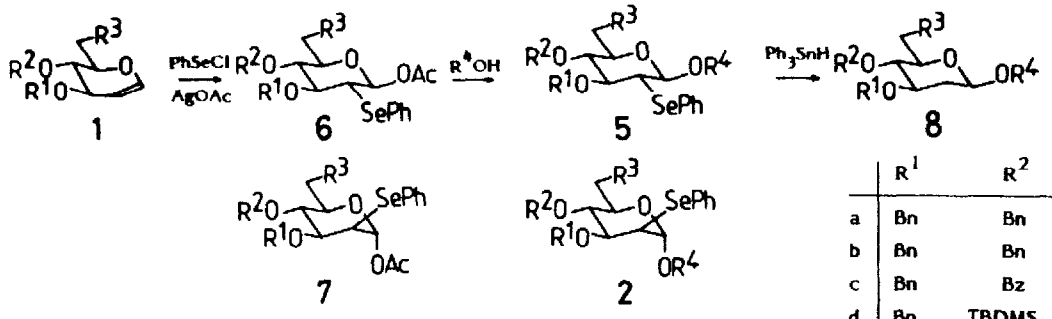
Scheme 1

phenylselenopyranosides of α-D-manno type **2**. Subsequent reductive deselenation[6a] led to the 2-deoxy glycosides in excellent yields. The directing ability of the phenylselenyl group at C-2 in the glycosidation reaction is also revealed by the formation of the minor 2-deoxy-2-phenylseleno pyranosides of β-D-gluco type **5**.

In an overall reaction, appropriate conditions that would give a trans diequatorial addition to glycals may offer, after reductive or oxidative deselenation, a selective synthetic route to β-2-deoxy-glycosides. Several recently developed procedures[9] including closely related sulfur-[9f,h] or selenium-based[9g] methods prompt us to disclose our own results in this area.

Preliminary attempts to produce β-linked glycosides from glycals in a one-step procedure by changing reaction conditions (solvents and catalysts) as previously devised in the synthesis of α-linked glycosides[10] gave uncontrollable α,β-anomeric mixtures most often with low efficiency.

The trans diequatorial 2-deoxy-2-phenylseleno glycopyranosides **5** (β-D-gluco type) may however be prepared with high selectivity by a two-step procedure as shown in Scheme 2. The protocole takes advantage of the selective preparation of the trans diequatorial acetoxy-selenides **6**, used as glycosyl donors in a trimethylsilyl trifluoromethanesulfonate (TMSOTf)-catalyzed glycosidation[11].



	R^1	R^2	R^3
a	Bn	Bn	OBn
b	Bn	Bn	H
c	Bn	Bz	H
d	Bn	TBDMS	H
e	TBDMS	H	H
f	TBDMS	Bz	H

Bn = benzyl; Bz = benzoyl; TBDMS = t-butyldimethylsilyl

Scheme 2

Entry	Glycal	MOAc	Solvent	Temp/Time (°C) (h)	Product Yield(%)	6:7(β:α)
1	1a	LiOAc/AcOH	$PhCH_3$	25/12	38	19:1
2	1a	$Hg(OAc)_2$	$PhCH_3$	25/2.5	50	3:1[a]
3	1a	AgOAc	CH_2Cl_2	0/0.5	52	2:1
4	1a	AgOAc	$PhCH_3$	25/1	81	9:1[b]
5	1b	AgOAc	CH_2Cl_2	0/0.5	80	1:3
6	1b	AgOAc	$PhCH_3$	25/1.5	80	6:1
7	1b	AgOAc	$PhCH_3$-hex[c]	25/12	60	9:1
8	1c	AgOAc	$PhCH_3$	25/6	60	1:3
9	1d	AgOAc	$PhCH_3$	0/1.5	56	1:5
10	1e	AgOAc	$PhCH_3$	0/1	80	10:1
11	1f	AgOAc	$PhCH_3$	0/2	80	1:9

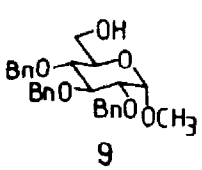
Table I. Synthesis of acetoxy-selenides 6, 7

a) determined by 300 MHz ^{1}H-nmr. b) determined after isomer separation.
c) as a 1:1 (v:v) mixture.

Treatment of a toluene solution of tri-O-benzyl-D-glucal **1a** with PhSeCl (1.3 equiv) followed by AgOAc (1.5 equiv) gave the 1,2-trans acetoxy-selenides **6a**[12,13] $[\alpha]_D$ +20° and **7a**[13] $[\alpha]_D$ +29° in a ratio of 9:1[14,15] (81% yield). Other conditions and results obtained with various glycals are listed in Table I.

All cases indicate an almost[14] exclusive trans addition. The optimal conditions for a synthetically useful β-selective reaction were found by using AgOAc (compare entries 1,2,4, Table I) in a toluene solution (compare entries 3,4 and 5,6) or, as in the case of 6-deoxy glycal **1b**, a 1:1 mixture of $PhCH_3$-hexanes (entry 7), in that a further decrease of the solvent polarity proved to be beneficial. Moreover, the stereochemistry of this addition was strongly influenced by the nature of the glycal protecting groups, benzoylation at position 4 for example (glycals **1c** and **1f**) favoring an α-selective reaction (entries 8 and 11). This change in the stereochemical course of the reaction (see also entry 9) has not yet been rationalized[17]. Further, a close inspection of the ^{1}H-nmr data of glycals **1** did not reveal any conformational effect of the protecting groups on their conformational equilibrium[18].

The ability of the acetoxy-selenides **6a,b,e** to function as glycosyl donors was tested with saccharide alcohols **9, 10, 11.** For instance, in a diethylether solution, the reaction of **6a** with methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside **9** (0.8 equiv) in the presence of molecular sieves 4 Å and a catalytic amount of *trimethylsilyl trifluoromethanesulfonate (TMSOTf, 0.1 equiv)* gave, in a fast reaction (0°C, 15 min), the expected β-linked disaccharide **5** (92%, $[\alpha]_D$ -4°) and the α-linked disaccharide **2** (6%, $[\alpha]_D$ +44°) in a β/α ratio of 16/1. A few examples are given in Table II.



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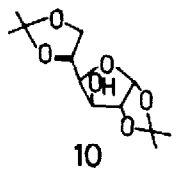

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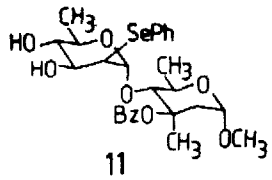

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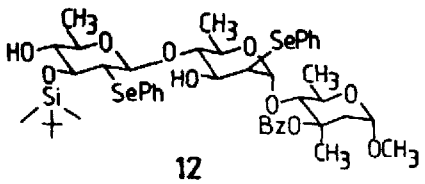

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Entry	Acetoxy-selenide	Alcohol R^4OH	Solvent	Temp/Time (°C) (min)	Product Yield(%)	5:2 (β:α)
1	6a	9	CH_2Cl_2	0°/10	82	1:1
2	6a	9	Et_2O	0°/15	98	16:1
3	6a	10	Et_2O	0°/15	97	10:1
4	6b	9	Et_2O	0°/30	81	~ 10:1[a]
5	6e	9	Et_2O	0°/15	77	1:0
6	6e	11	Et_2O	0°/15	48	1:0 (compound 12)

Table II. Synthesis of 2-deoxy-2-phenylselenoglycosides

a) **6b** was not precisely determined because of contamination by **7b.**

The formation of 1,2-trans-glycosides confirms the efficient directing effect of the phenylselenyl group at C-2 in every case. The minor formation of the α-glycoside may be derived from **3** through the equilibrium shown in Scheme 1 promoted by the Lewis acid. Indeed the phenylselenyl group is very sensitive to "isomerization" and the use of diethylether as the solvent for the glycosidation reaction is essential in order to obtain the required β-selectivity. Thus, in dichloromethane, the same reaction conditions between **6a** and **9** gave a 1:1 mixture of the disaccharides (entry 1, Table II). The reaction of acetoxy-selenide **6e** with disaccharide diol **11** (entry 6, Table II) gave regiospecifically the (1'' → 4') β-linked trisaccharide, (48%, $[\alpha]_D$ +37°) immediate precursor of the B-C-D fragment of orthosomycins[6c].

Reductive removal of the phenylselenyl group (Ph_3SnH, $PhCH_3$, reflux) on the 2'-deoxy-2'-phenylseleno disaccharides **5** led quantitatively to the 2'-deoxy-β-D-disaccharides.

In summary, provided that a judicious choice of protecting groups in the glycal substrate is made, the method presented offers a useful procedure for the selective preparation of β-linked 2-deoxy-glycosides.

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12. All new compounds gave satisfactory microanalytical and spectral data. Optical rotations were measured for solutions in $CHCl_3$ at 20°C, ^{1}H-nmr spectroscopy was performed for $CDCl_3$ solutions at 300 MHz with a Bruker AM-300WB spectrometer.
13. Selected ^{1}H-nmr data: **6a** δ 3.36 (dd, $J_{1,2}$ 9.2, $J_{2,3}$ 11.1 Hz, H-2); 5.74 (d, $J_{1,2}$ 9.2 Hz, H-1). **7a** δ 3.78 (dd, $J_{1,2}$ 2.2, $J_{2,3}$ 4.5 Hz, H-2); 6.33 (d, $J_{1,2}$ 2.2 Hz, H-1). Disaccharide **5** (from **6a** and **9**) δ 3.30 (dd, $J_{1',2'}$ 9.1, $J_{2',3'}$ 11 Hz, H-2'); 4.40 (d, $J_{1',2'}$ 9.1 Hz, H-1'). Disaccharide **5** (from **6a** and **10**) δ 3.17 (dd, $J_{1',2'}$ 9.1, $J_{2',3'}$ 11.0 Hz, H-2'); 4.57 (d, $J_{1',2'}$ 9.1 Hz, H-1'). Disaccharide **5** (from **6e** and **9**) δ 3.18 (dd, $J_{1',2'}$ 9.1, $J_{2',3'}$ 11.0 Hz, H-2'); 4.37 (d, $J_{1',2'}$ 9.1 Hz, H-1'). Trisaccharide **12** (from **6e** and **11**) δ 3.17 (dd, $J_{1'',2''}$ 9.2, $J_{2'',3''}$ 11.0 Hz, H-2''); 4.03 (m, $J_{3',OH}$ 1, $J_{2',3'}$ 5.0, $J_{3',4'}$ 9.0 Hz, H-3'); 4.56 (d, $J_{3',OH}$ 1 Hz, OH-3'); 4.56 (d, $J_{1'',2''}$ 9.2 Hz, H-1'').
14. In the case of glycal **1a**, the 1,2-cis product, 2-deoxy-2-phenylseleno-α-D-glucopyranoside could also be isolated in a 3% yield.
15. No reaction was observed using preformed phenylselenyl acetate[16] in toluene.
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17. Subtle influences of the protecting groups on the relative stability of the two possible 1,2-selenonium ions in the transition state are obviously responsible for the selectivity observed. For similar effects see P. Boullanger and G. Descotes, Carbohydr. Res., 51 (1976) 55-63; D. Horton, W. Priebe and O. Varela, J. Org. Chem., 51 (1986) 3479-3485.
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