Tetrahedron Letters, Vol. 34, No. 17, pp. 2821-2822, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

SELENIUM-CONTROLLED STEREOSELECTIVE SYNTHESIS OF 2'-DEOXYNUCLEOSIDES FROM GLYCALS. A FORMAL SYNTHESIS OF AZT

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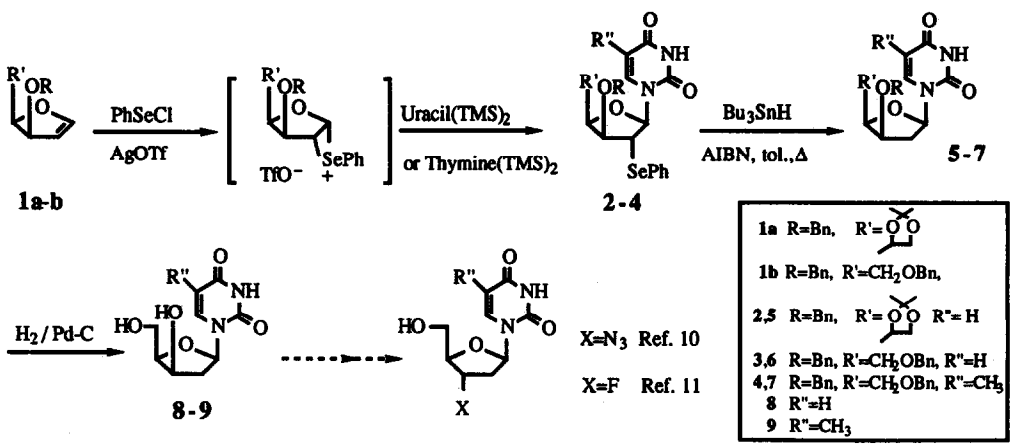
Key Words: 2'-Deoxynucleosides, stereoselective glycosylation, glycals,

***Abstract:** 2'-Deoxynucleosides have been stereoselectively synthesized starting from glycals, using phenylselenenyl reagents.*

Deoxynucleosides such as 3'-azido-3'-deoxythymidine (AZT), 2',3'-dideoxyinosine (ddI), and 2',3'-didehydro-2',3'-deoxycytidine (d4C) are among the most powerful agents against human immunodeficiency virus (HIV).[1] One of the most important problems in the convergent synthesis of 2'-deoxynucleosides is the control of the stereoselectivity at the glycosylation step. Recently, good stereoselectivity control has been achieved by using sulfur and selenium mediated reactions. In this regard, with the aim of obtaining 2',3'-dideoxynucleosides, 2-SPh[2] and 2-SePh[3] derivatives have been prepared from 5-substituted γ-lactones via their enolates. The main problem of this approach is the stereoselectivity control at the SPh or SePh introduction step.[4] Better selectivities were obtained starting from 3-deoxyfuranoid glycals and NIS.[5] In the present report we show that the addition of commercial selenium reagents to glycals, followed by glycosylation and hydrogenolysis is a good strategy for obtaining 3'-substituted 2'-deoxynucleosides.



Glycals **1a** and **1b** were prepared according to Ireland's method[6] from 2,3;5,6-di-*O*-isopropyliden-*manno*-furanose and 2,3-*O*-isopropylidene-*lyxo*-furanose, and were then appropriately protected. Different selenium reagents were checked (PhSeCl, PhSeBr, PhSeI) by addition to glycal **1a**; in all cases the addition was complete within a few minutes. Nevertheless, no glycosylation took place by reaction of the 1-halo-2-phenylselenenyl-furanoses with bis(trimethylsilyl)uracil, and therefore an activator was needed to obtain the corresponding 2-phenylselenenyl-nucleoside **2**.[7] We chose PhSeCl, since no stereoselectivity difference was observed with other haloselenenyl reagents, and we found that AgOTf was the most efficient chlorine activator, although other reagents were also active in this purpose ($AgClO_4$, $SbCl_5$, $SnCl_4$, Me_3SiOTf). As far as the solvent influence is concerned, the solvent has a strong influence on the stereoselectivity of the PhSeCl addition, since the best

Table 1. Stereoselective glycosylation of furanoid glycals with pyrimidine bases induced by PhSeCl[a]

Glycal	Pyrimidine Base	Solvent	Time(min.)	Product	Yield[b] %	α/ß[c] %
1a	Uracil(TMS)$_2$	Ether	40	**2**	87	10/90
1b	Uracil(TMS)$_2$	Benzene	25	**3**	90	9/91
1b	Thymine(TMS)$_2$	Ether	15	**4**	88	10/90

[a] Reactions were performed in a 0.2 mmole scale, at rt with a 1/1.5/1.7/2 glycal/PhSeCl/AgOTf/Pyrimidine base ratio. [b] Isolated yields after preparative TLC or flash chromatography, not optimized. [c] Ratios were determined by integration of the H-1' in the ^{1}H NMR spectra.

glycosylation results were achieved when non-polar solvents were used.

Glycal **1b** was treated with bis(trimethylsilyl)uracil and bis(trimethylsilyl)thymine to afford to compounds **3** and **4** in yields and with selectivities shown in Table 1.[8]

The observed stereoselectivity is the result of the attack of the phenylselenenyl reagent by the face opposite to the substituent at position 3. Furthermore, the nucleic base is principally *cis* with respect to this substituent owing to the anchimeric assistance provided by the selenenyl group at the glycosylation step, the ß isomer being thus predominant.

In all cases, removal of the phenylselenenyl group of the ß-isomers was carried out by reaction with Bu3SnH in refluxing toluene, to afford 2'-deoxynucleosides **5-7** in 80-90% overall yields from the glycal. Hydrogenolysis of compounds **6** and **7** using Pd/C as the catalyst gave quantitatively the unprotected nucleosides **8** and **9**, which showed identical physical constants and NMR spectra to those previously described.[9] Synthesis of AZT[10] and 3'-fluoro-3'-deoxythymidine (FDT)[11] from compound **9** have been described.

In conclusion, phenylselenenylnucleosides can be obtained from glycals in "one-pot" reactions in good yields and with high stereoselectivities, and easily converted into 2'-deoxynucleosides.

Acknowledgement: This research was supported by a grant from DGICYT (Ministerio de Educación y Ciencia, Spain), Project PB89-0277. One of us Y.D. thanks to DGU (Generalitat de Catalunya) for a doctoral fellowship. Thanks are due to Prof. Jaume Vilarrasa for helpful suggestions.

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8 Selected NMR ($CDCl_3$, δ in ppm) data for compounds **2** and **4**. (**2**): (^{1}H) 7.55 (d, H_6), 6.12 (d, $J_{1',2'}$=2.5 Hz, $H_{1'}$), 5.54 (dd, H_5), 4.36 (dt, $H_{5'}$), 4.08 (dd, $H_{4'}$), 4.04 (dd, $H_{6'}$), 3.97 (d, $H_{3'}$), 3.90 (dd, $H_{6''}$), 3.56 (d, $H_{2'}$). (^{13}C) 140.3 (C_6), 102.4 (C_5), 89.5 ($C_{1'}$), 82.9 ($C_{4'}$), 82.8 ($C_{3'}$), 71.8 ($C_{6'}$), 67.2 ($C_{5'}$), 49.5 ($C_{2'}$). (**4**): (^{1}H) 7.36 (m, H_6), 6.13 (d, $J_{1',2'}$=3.8 Hz, $H_{1'}$), 4.35 (m, $H_{4'}$), 3.95 (dd, $J_{3',4'}$=4.2 Hz, $J_{3',2'}$=2.3 Hz, $H_{3'}$), 3.73 (m, 2H, $H_{5'}$, $H_{5''}$), 3.64 (dd, $H_{2'}$), 1.57 (d, 3H, CH_3). (^{13}C) 168.4 (C_4), 149.9 (C_2).136.0 (C_6), 110.4 (C_5), 88.7 ($C_{1'}$), 82.5 ($C_{4'}$) 80.5 ($C_{3'}$), 68.0 ($C_{5'}$), 49.1 ($C_{2'}$), 12.3 (CH_3).

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(Received in UK 12 February 1993)