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# Stereoselective Synthesis of 2',3'-Dideoxy-nucleosides via Intramolecular Glycosylation of Phenyl 1-Seleno-glycosides. Synthesis of 2',3'-Dideoxythymidine.

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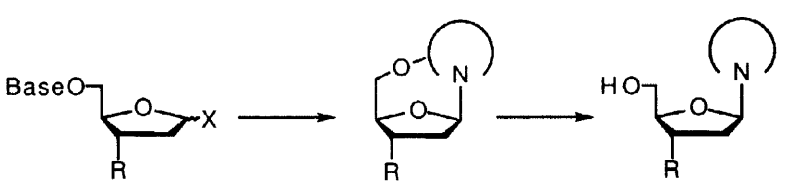
***Abstract***: 4-methoxy and 4-(2-trimethylsilylethoxy)pyrimidine bases were attached to the 5-position of the phenyl 2,3-dideoxy-1-seleno-*glycero*-pentofuranoside moiety. The presence of the silyl protecting group in the base is necessary to lead to neutral ß-anhydro nucleosides by intramolecular glycosylation. The subsequent ring opening affords 3'-deoxythymidine with complete stereocontrol. 

Since the discovery of the antiviral activity of 3'-azido-3'-deoxythymidine (AZT)[1] against the human immunodeficiency virus (HIV), there has been intense concern with synthesizing 2',3'-dideoxynucleosides and their analogs[2] as potential antiviral and antibiotic agents.

Although the standard Vorbrüggen couplings[3] between 2-deoxyribose derivatives and pyrimidine or purine bases is one of the simplest methods for obtaining such nucleoside derivatives, the main problem in this approach is the lack of stereocontrol. Moreover, only ß-nucleosides usually exhibit high biological activity.

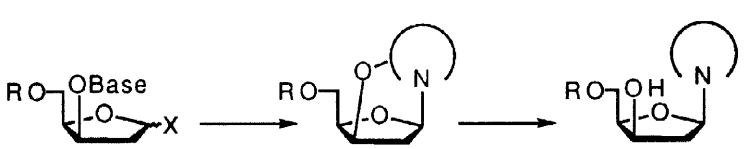
An attractive way of forming selectively ß-nucleosides is based on the intramolecular glycosylation strategy. The key step in this approach is the attachment of the base to a 2-deoxy-pentofuranoside at the 5-[4,5,6] (Scheme 1) or 3-ß-position[7] (Scheme 2), and the formation of a ß-anhydro-nucleoside intermediate by intramolecular attack on C-1. Lastly, a ß-elimination[4] at C-5/C-6 or a basic hydrolysis[5-7] leads to the desired nucleoside.

**Scheme 1**




| | | |
|---|---|---|
| X= OMe | R= OTBDPS | Ref. 4 |
| X= SPh | R=OBn, H, $N_3$, F | Ref. 5 |
| X= OAc | R= OMe | Ref. 6 |

**Scheme 2**




| | | |
|---|---|---|
| X = OBn | R = Tr, MOM | Ref. 7 |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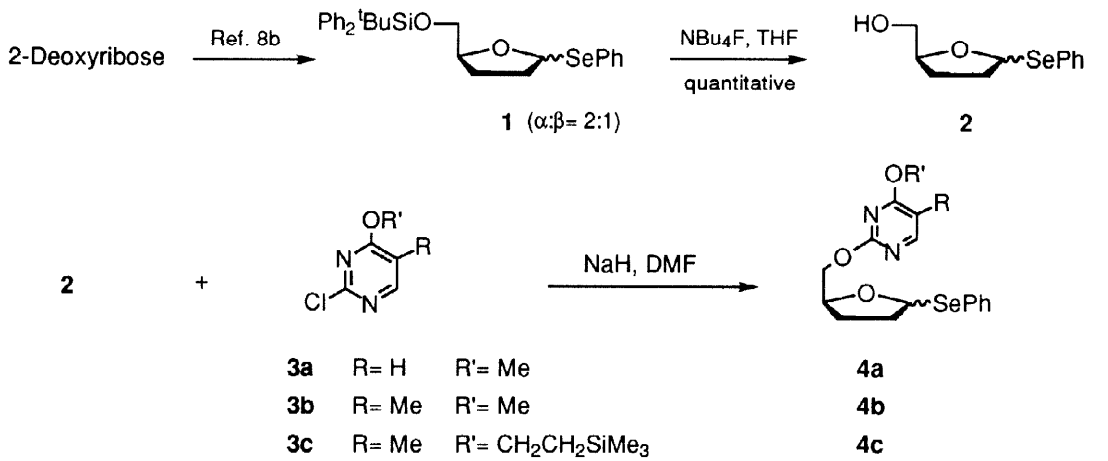
Hence, as part of a general project which aims to use selenium in the stereoselective synthesis of 2'-deoxy and 2',3'-dideoxy-nucleosides,[8] we devised an intramolecular strategy to synthesise them from selenoglycosides.

Thus, the starting selenoglycoside **2**[9] was prepared from 2-deoxyribose in five steps (Scheme 3): methyl glycoside synthesis, selective 5-OH protection, Barton deoxygenation, treatment with PhSeH in the presence of $BF_3{\cdot}OEt_2$ –to give compound **1**[8b]– and deprotection of the $^tBuPh_2Si$ group.

**Scheme 3**




On the other hand, pyrimidine derivatives (**3a**,[10a] **3b**[10b] and **3c**[11]) were prepared from 2,4-dichloro-pyrimidine and 2,4-dichloro-5-methylpyrimidine. Subsequently, **3a**, **3b** and **3c** were attached to phenyl 1-seleno-glycoside **2** following reported procedures;[5,7] using sodium hydride in DMF compounds **4a**, **4b** and **4c**[12] were obtained in 60-70% yields (Scheme 3).

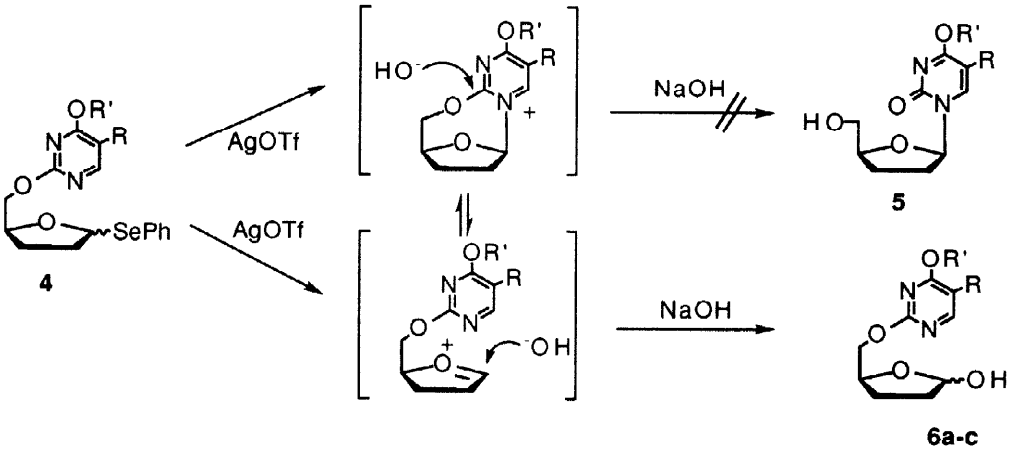
We initially explored the intramolecular glycosylation from **4a** and **4b**. The starting material generated –by activating the anomeric position with AgOTf– a charged anhydronucleoside in equilibrium with the oxonium ion (Scheme 4). The subsequent hydrolysis will lead to the formation of the desired nucleoside **5** or the furanose **6**.

However, all the attempts of glycosylation from the selenoglycosides **4a** and **4b** were negative. The reaction with AgOTf was monitored by TLC which indicated that the starting material disappeared and a different product with lower $R_f$ was formed. But the single product isolated from the subsequent hydrolysis with 1N-NaOH at 0°C[5] was the C-1 hydrolyzed products **6a** and **6b** respectively, in quantitative yield (Scheme 4). The same product was obtained when the hydrolysis was carried out with a saturated solution of $Na_2CO_3$. No glycosylation products such us **5** were observed.

In view of these results we next turned our attention to the use of the silyl-protected product **4c**. The idea was to generate a charged intermediate such as **7** which could attack at the C-1 after anomeric group had been activated by the silver salt (Scheme 5). The formation of a neutral ß-anhydronucleoside would prevent the problem of hydrolysis, since it is well known that this kind of product reacts selectively at the 2-position of the base under hydrolytic conditions.

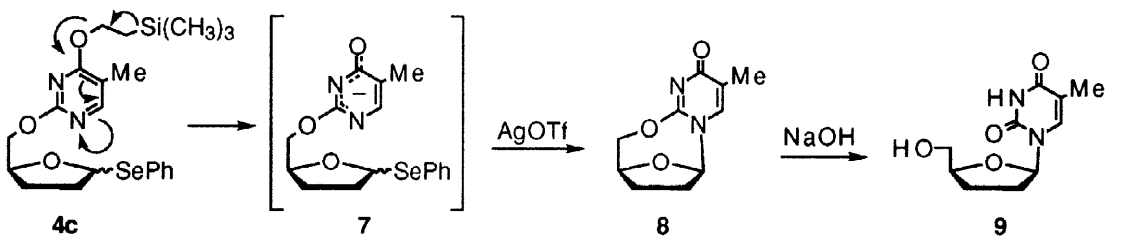
By treating **4c** with AgOTf under the usual conditions (4Å molecular sieves, anhydrous $CH_3CN$, -20°C, and then NaOH 1N, 0°C) the furanose **6c** (R=Me, R'=$CH_2CH_2SiMe_3$) was obtained. We also tried to remove the silyl protecting group at the same time activating the anomeric position with AgF. In this case, only the starting material was recovered and no reaction ocurred. We also used other reagents such as KF/crown ether or $F_2HK$ used in conjunction with AgOTf and these too gave negative results. The problem was ultimately solved

Scheme 4




by treating **4c** with $Bu_4NF$ in anhydrous $CH_3CN$ at r.t. and then adding AgOTf. Thus, the corresponding 3'-deoxy-2,5'-anhydro-thymidine **8**[13,14] was obtained in 68% yield. Minor quantities of hydrolyzed product **6** were also recovered. Finally, basic hydrolysis of **8** led to 1-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)thymine **9**[15] in quantitative yield.

Scheme 5




In conclusion, 3'-deoxythymidine was synthesized from a phenyl 1-seleno-glycoside via intramolecular glycosylation. The key step is the deprotection of the silyl group at the 4-position of the pyrimidine ring using $Bu_4NF$ prior to activation of the selenoglycoside, and the subsequent formation of a neutral ß-anhydronucleoside.

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## References and Notes

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9. (**2α**): $^1$H NMR (300 MHz, $CDCl_3$) δ 7.63-7.25 (m, 5H, Ph), 5.94 (dd, 1H, $J_{1,2a}$= 6.9 Hz, $J_{1,2b}$= 3.3 Hz, H-1), 4.33 (m, 1H, H-4), 3.75 (dd, 1H, $J_{5',5''}$= 11.9 Hz, $J_{5,4}$= 5.9 Hz, H-5), 3.54 (dd, 1H, $J_{5',4'}$= 6.7 Hz, H-5'), 2.46–1.67 (m, 4H, H-2, H-3). $^{13}$C NMR (75.4 MHz, $CDCl_3$) δ 133.9-127.3 (Ph), 84.6 (C-1), 79.2 (C-4), 63.8 (C-5), 33.8 (C-2), 25.8 (C-3). Anal. Calcd for $C_{11}H_{14}O_2Se$: C, 50.76; H, 5.49. Found: C, 51.05; H, 5.49.
(**2ß**): $^1$H NMR (300 MHz, $CDCl_3$) δ 7.60-7.20 (m, 5H, Ph), 5.90 (dd, 1H, $J_{1,2a}$= 6.7 Hz, $J_{1,2b}$= 2.8 Hz, H-1), 4.30 (m, 1H, H-4), 3.8 (m, 2H, H-5, H-5'), 2.50–1.50 (m, 4H, H-2, H-3). $^{13}$C NMR (75.4 MHz, $CDCl_3$) δ 134.0-127.4 (Ph), 84.6 (C-1), 82.6 (C-4), 64.2 (C-5), 34.6 (C-2), 26.2 (C-3).
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11. 2-Chloro-5-methyl-4-(2'-(trimethylsilyl)ethoxy)pyrimidine **3c**: A solution of 2,4-dichloro-5-methyl-pyrimidine[10] (12.3 mmol) in THF (6mL) was cooled to -20°C and a mixture of sodium 2-(trimethylsilyl)-ethoxide (1.2 mol) in THF (6.5 mL) was added dropwise. The sodium 2-(trimethylsilyl)-ethoxide was prepared from 2-(trimetylsilyl)-ethanol and NaH. After a night at -20°C, workup of the reaction afforded a crude that was chromatographed over silica gel, eluting with EtOAc/hexane= 1:6. The residue obtained was further purified by means of radial chromatography to give compound **3c** as a white solid (82%): mp: 51-52 °C. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H, H-6), 4.46 (t, 2H, $J_{CH2\text{-}O,CH2\text{-}Si}$= 8.2 Hz, $CH_2$-O), 2.07 (s, 3H, $CH_3$), 1.11 (t, 2H, $CH_2$-Si), 0.06 (s, 9H, $Si(CH_3)_3$). $^{13}$C NMR (75.4 MHz, $CDCl_3$) δ 168.9 (C-4), 157.3 (C-6), 116.7 (C-5), 65.8 ($CH_2$-O), 17.2 ($CH_2$-Si), -1.4 ($Si(CH_3)_3$). Anal. Calcd for $C_{10}H_{17}N_2OSiCl$: C, 49.38; N, 11.42; H, 7.26. Found: C, 49.16; N, 11.56; H, 7.10.
12. Spectroscopic data of compounds **4cα**, and **4cβ**:
(**4cα**): $^1$H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, 1H, J= 0.9 Hz, H-6'), 7.64-7.24 (m, 5H, SePh), 6.04 (dd, 1H, $J_{1,2A}$= 6.9 Hz, $J_{1,2B}$= 2.8 Hz, H-1), 4.66 (ddd, 1H, H-4), 4.47 (t, 2H, $J_{CH2\text{-}O,CH2\text{-}Si}$= 8.1 Hz, $CH_2$-O), 4.39 (dd, 2H, H-5A, H-5B), 2.60-1.80 (m, 4H, H-3, H-2), 1.12 (t, 2H, $CH_2$-Si), 0.07 (s, 9H, $Si(CH_3)_3$). $^{13}$C NMR (75.4 MHz, $CDCl_3$) δ 169.3 (C-4'), 163.4 (C-2'), 156.7 (C-6'),133.7-127.2 (SePh), 111.1 (C-5'), 84.70 (C-1), 76.8 (C-4), 68.1 (C-5), 64.7 ($CH_2$-O), 33.6 (C-2), 27.2 (C-3), 17.3 ($CH_2$-Si), 12.9 ($CH_3$), -1.4 ($Si(CH_3)_3$).
(**4cβ**): $^1$H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, 1H, J= 0.9 Hz, H-6'), 7.63-7.24 (m, 5H, SePh), 5.88 (dd, 1H, $J_{1,2A}$= 6.4 Hz, $J_{1,2B}$= 3.2 Hz, H-1), 4.52 (ddd, 1H, H-4), 4.47 (t, 2H, $J_{CH2\text{-}O,CH2\text{-}Si}$= 8.2 Hz, $CH_2$-O), 4.38 (dd, 2H, H-5A, H-5B), 2.50-2.10 (m, 4H, H-3, H-2), 2.04 (d, 3H, J= 0.8 Hz, $CH_3$), 1.13 (t, 2H, $CH_2$-Si), 0.08 (s, 9H, $Si(CH_3)_3$). $^{13}$C NMR (75.4 MHz, $CDCl_3$) δ 169.3 (C-4'), 163.3 (C-2'), 156.7 (C-6'),134.2-127.3 (SePh), 111.1 (C-5'), 84.00 (C-1), 79.3 (C-4), 69.3 (C-5), 64.7 ($CH_2$-O), 34.1 (C-2), 28.3 (C-3), 17.3 ($CH_2$-Si), 12.1 ($CH_3$), -1.3 ($Si(CH_3)_3$).
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14. **8**: m.p.: 199-201° (reported 202-203)[13]; UV (MeOH) $\lambda_{max}$ 248 nm; IR (ν max in $cm^{-1}$) 1639, 1529,1474, 1285, 1080; $^1$H NMR (300 MHz, $CD_3OD$) 7.35 (s, 1H, H-6), 5.62 (d, 1H, 7.1 Hz, H-1'), 4.56 (d, 1H, 7.4 Hz, H-4'), 4.22 (d, 1H, 12.0 Hz, H-5'), 4.03 (d, 1H, 12 Hz, H-5''), 2.42 (m, 1H, H-2'), 2.04 (m, 3H, H-2'', H-3', H-3''), 1.82 (s, 3H, Me). $^{13}$C NMR (75.4 MHz, $CD_3OD$) 172.95 (C-4), 157.57 (C-2), 139.01 (C-6), 118.60 (C-5), 94.39 (C-1'), 79.02 (C-4'), 76.82 (C-5'), 31.97 (C-2'), 26.10 (C-3'), 12.45 (Me). Elemental Analysis for $C_{10}H_{12}N_2O_3$: Calcd. C 57.69, H 5.77, N 13.46. Found C 57.40, H 5.71, N 13.30.
15. Spectroscopic data of compound **9** ($^1$H and $^{13}$C) agrees with a that of a commercial sample and with the previously reported, Barren Beach, J.; Kim, H.O.; Jeong, L.S.; Nampalli, S.; Islam, Q.; Ahn, S.K.; Babu, J.R.; Chu, C.K. *J. Org. Chem.* **1992**, *57*, 3887.