A New and Easy Synthesis of Silylated Furanoid Glycals in One Step from Nucleosides

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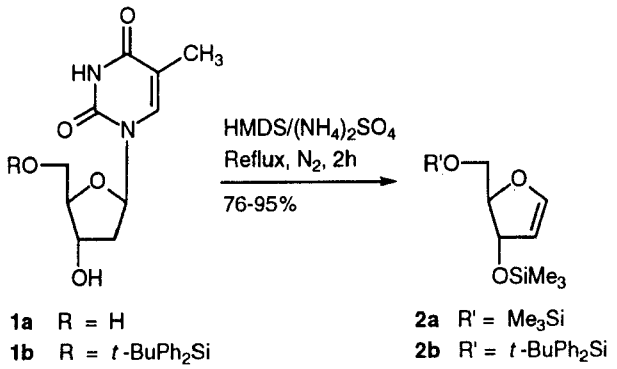
Silylated furanoid glycals are synthesized in high yields by elimination of the nucleobase in thymidine **(1a)** and 5′-*O*-(*tert*-butyldiphenylsilyl)thymidine **(1b)** on treatment with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) in the presence of ammonium sulfate at reflux temperature for 2 hours.

Furanoid glycals (cyclic enol ether derivatives of sugars) are key intermediates in a palladium-mediated coupling reaction leading to C-nucleosides.[1] Recently, these nucleosides have received considerable attention due to their remarkable antiviral and antitumor activities.[2] Furanoid glycals are also key intermediates in the synthesis of 6-*epi*-leukotrienes C and D,[3] and for the class of compounds known as ionophores (polyether antibiotics).[4] 2′-Deoxynucleosides have been stereoselectively synthesized from glycals using phenylselenenyl reagents,[5] and α-arabino nucleosides have been synthesized from a 1,2-epoxide via a glycal intermediate, using silylated thymine.[6] Electrophilic addition reactions to a furanoid glycal have been used as key steps in the synthesis of 2′,3′-dideoxyadenine (ddA) and 2′,3′-didehydro-2′,3′-dideoxythymidine (d4T).[7]

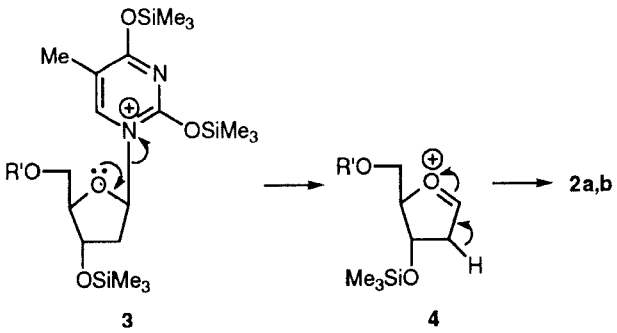
The first known glycal derivative that possessed a furanose structure 1,4-anhydro-3,5-di-*O*-benzoyl-2-deoxy-D-*erythro*-pent-1-enitol was prepared by Ness and Fletcher in 1963 and was found to be extremely labile,[8] undergoing an allylic rearrangement reaction and eliminating benzoic acid in water to give furfuryl benzoate. Ireland et al.[4,9] developed a general procedure for the synthesis of 3-hydroxylated glycals, in 5 steps, starting from ribonic-γ-lactone, involving as a key step the reductive fragmentation of 2,3-*O*-isopropylidene protected furanosyl chloride. This method gives high yields using a combination of chromatography and distillation. 3-Alkoxy-substituted furanoid glycals have been prepared in 6–25% yield using a modification of Fischer and Zach's method.[10] Recently Abramski and Chmielewski[11] developed a procedure for the transformation of D-ribose into the 3,5-di-*O*-substituted 1,4-anhydro-2-deoxy-D-*erythro*-pent-1-enitol in high yields. Brånalt et al.[12] observed trimethylsilyl triflate (TMS triflate) promoting elimination of acetate in 1-*O*-acetyl-5-*O*-benzoyl-3-*C*-[(benzoyloxy)methyl]-2,3-dideoxy-4-thio-α,β-D-*erythro*-1-enofuranose in 85% yield.

In this paper we describe the simplest way reported until now to obtain furanoid glycals from commercially available starting materials. 5′-*O*-(*tert*-Butyldiphenylsilyl)thymidine **(1b)** was synthesized with a modification of the known procedure[13] using 4-dimethylaminopyridine as a catalyst. Pure **1b** was obtained without using chromatography as a white solid by crystallization from cyclohexane in 95% yield. The glycals **2a, b** were prepared in one step from the nucleosides **1a, b** by refluxing in 1,1,1,3,3,3-hexamethyldisilazane (HMDS) in the presence of ammonium sulfate for 2 hours under a nitrogen atmosphere. Products were obtained in 76–95% yields as oils after workup. TLC analysis showed glycal ($R_f \approx 1$ in chloroform) as a spot which turned violet upon heating with H_2SO_4/MeOH as an indicator for the presence of a double bond. The glycals **2a, b** are stable for several months at 0°C under a nitrogen atmosphere.



Scheme 1

The amount of ammonium sulfate used was important because no glycal was obtained in its absence and the reaction did not go to completion with reduced amounts of ammonium sulfate. In the presence of oxygen the reaction gave rise to brownish byproducts and addition of pyridine retarded the reaction. 2′-Deoxycytidine gave a similar reaction to thymidine, whereas nucleosides with a 2′-OH group (uridine) or a purine base (2′-deoxyguanosine and 2′-deoxyadenosine) gave no reaction except trimethylsilyl protection. No glycal formation was observed when methyl 2-deoxy-α,β-D-*erythro*-pentofuranosides were treated as above. With 3′-azido-3′-deoxythymidine (AZT) the reaction gave rise to a complex mixture of products. With 2,3′-anhydrothymidine and 3′-*O*-toluoylthymidine furfuryl alcohol was obtained. If the reaction with thymidine was stopped just after the solvation of the nucleoside (approximately 15 min), the trimethylsilyl protected thymidine could be obtained without anomerization of the base. A 4,4′-dimethoxytrityl group at the 5′-*O* position was not stable under the reaction conditions.



Scheme 2

We assume that formation of the glycal **2** proceeds via **3** by silylation of the nucleobase which in turn is converted into a good leaving group. The remaining oxocarbenium ion **4** loses a proton to form the final product. The unprotected glycal, 1,4-anhydro-2-deoxy-D-*erythro*-pent-1-enitol, was produced by removal of silyl protective groups from **2a, b** using tetrabutylammonium fluoride in tetrahydrofuran.[14] The ^1H and ^{13}C NMR data were in accordance with the reported values.[14]

Optical rotations were measured with a Perkin-Elmer 141 polarimeter. NMR spectra were recorded on a Bruker AC-250 FT NMR spectrometer at 250 MHz for ^1H NMR and 62.9 MHz for ^{13}C NMR with TMS as an internal standard. FAB mass spectra were recorded on a Kratos MS-50 TS spectrometer. Analytical silica gel TLC plates 60 F_{254} were purchased from Merck.

5′-*O*-(*tert*-Butyldiphenylsilyl)thymidine (1b):
To a solution of thymidine (**1a**, 9.70 g, 40 mmol) in dry pyridine (20 mL) was added 4-dimethylaminopyridine (0.04 g, 0.40 mmol) and *tert*-butylchlorodiphenylsilane (11.55 g, 42 mmol). After the reaction had been stirred at r.t. for 6 h, the mixture was quenched with CH_3OH (1 mL) and the solvent was removed in vacuo. The mixture was diluted with $CHCl_3$ (200 mL), washed with sat. aq $NaHCO_3$ (200 mL) and dried (Na_2SO_4). The solvent was removed in vacuo. The title compound **1b** was obtained as a white solid by crystallization from cyclohexane (200 mL); yield: 20.21 g (95%); mp 163–164 °C.

^1H NMR ($CDCl_3$/TMS): δ = 1.08 (9 H, s, *tert*-butyl), 1.62 (3 H, s, CH_3), 2.19 (1 H, m, 2a′-H), 2.43 (1 H, m, 2b′-H), 3.19 (1 H, m, 4′-H), 3.85 (1 H, dd, J = 11.4, 2.6 Hz, 5a′-H), 3.97 (1 H, dd, J = 11.4, 2.7 Hz, 5b′-H), 4.04 (1 H, m, 3′-H), 4.56 (1 H, s, 3′-OH), 6.42 (1 H, dd, J = 5.7, 2.6 Hz, 1′-H), 7.38–7.67 (11 H, m, H_{arom}), 9.52 (1 H, s, NH).

^{13}C NMR ($CDCl_3$/TMS): δ = 12.03 (CH_3), 19.33 ((CH_3)$_3C$), 26.98 ((CH_3)$_3$C), 40.97 (C-3′), 64.19 (C-5′), 72.16 (C-3′), 84.78 (C-4′), 87.19 (C-1′), 111.22 (C-5), 127.91, 127.96, 130.01, 130.10, 132.43, 132.97, 135.29, 135.35 (C_{arom}, C-6), 150.65 (C-2), 163.97 (C-4).
FAB MS (3-nitrobenzyl alcohol): m/z (%) = 481 ($M + H^+$).

1,4-Anhydro-2-deoxy-3,5-bis-*O*-(trimethylsilyl)-D-*erythro*-pent-1-enitol (2a):
A mixture of thymidine (**1a**, 9.70 g, 40 mmol), $(NH_4)_2SO_4$ (1 g, 7.57 mmol) and HMDS (50 mL) was refluxed (140 °C) with stirring for 2 h under N_2. After evaporation of the HMDS in vacuo, the title compound **2a** was obtained as a colorless oil by distillation at 61–62 °C/1.1 Torr; yield: 9.34 g (76%). $[\alpha]_D$ and ^1H NMR were in accordance with reference 11.

^{13}C NMR (DMSO-d_6/TMS): δ = 0.11, 0.47 (2 × (CH_3)$_3$Si), 61.47 (C-5), 75.10 (C-3), 87.83 (C-4), 103.04 (C-2), 148.88 (C-1).

1,4-Anhydro-5-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-3-*O*-(trimethylsilyl)-D-*erythro*-pent-1-enitol (2b):
A mixture of **1b** (9.6 g, 20 mmol), $(NH_4)_2SO_4$ (0.5 g, 3.78 mmol) and HMDS (50 mL) was refluxed (140 °C) with stirring for 2 h under N_2. After evaporation of the HMDS in vacuo the mixture was diluted with cyclohexane (200 mL), washed with sat. aq $NaHCO_3$ (100 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the title compound **2b** was obtained as a light yellow oil; yield: 8.48 g (95%). $[\alpha]_D^{27}$ + 170° (c = 2.437, neat).

^1H NMR ($CDCl_3$/TMS): δ = 0.15 (9 H, s, (CH_3)$_3$Si), 1.09 (9 H, s, *tert*-butyl), 3.65 (1 H, dd, J = 10.9, 5.6 Hz, 5a-H), 3.75 (1 H, dd, J = 10.9, 5.4 Hz, 5b-H), 4.39 (1 H, td, J = 5.5, 2.9 Hz, 4 H), 4.98 (1 H, t, J = 2.6 Hz, 3-H), 5.05 (1 H, t, J = 2.5 Hz, 2-H), 6.55 (1 H, d, J = 2.5 Hz, 1-H), 7.36–7.71 (10 H, m, H_{arom}).

^{13}C NMR ($CDCl_3$/TMS): δ = 0.41 ((CH_3)$_3$Si), 19.26 ((CH_3)$_3C$), 26.80 ((CH_3)$_3$C), 63.64 (C-5), 75.71 (C-3), 88.78 (C-4), 103.28 (C-2), 127.67, 129.71, 133.34, 135.60 (C_{arom}), 149.36 (C-1).

FAB MS (3-nitrobenzyl alcohol): m/z (%) = 427 ($M + H^+$).

(1) Hacksell, U.; Daves, G.D. *J. Org. Chem.* **1983**, *148*, 2870.
(2) Hacksell, U.; Daves, G.D. *Prog. Med. Chem.* **1985**, *22*, 1.
(3) Corey, E.J.; Goto, G. *Tetrahedron Lett.* **1980**, *21*, 3463.
(4) Ireland, R.E.; Thaisrivongs, S.; Varier, N.; Wilcox, C.S. *J. Org. Chem.* **1980**, *45*, 48.
(5) El-Laghdach, A.; Diás, Y.; Castillón, S. *Tetrahedron Lett.* **1993**, *34*, 2821.
(6) Chow, K.; Danishefsky, S. *J. Org. Chem.* **1990**, *55*, 4211.
(7) Kim, C.U.; Misco, P.F. *Tetrahedron Lett.* **1992**, *33*, 5733.
(8) Ness, R.K.; Fletcher, H.G. *J. Org. Chem.* **1963**, *28*, 435.
(9) Ireland, R.E.; Wilcox, C.S.; Thaisrivongs, S. *J. Org. Chem.* **1978**, *43*, 786.
(10) Bischofberger, K.; Hall, R.H. *Carbohydr. Res.* **1976**, *52*, 223.
(11) Abramski, W.; Chmielewski, M. *J. Carbohydr. Chem.* **1994**, *13*, 125.
(12) Brånalt, J.; Kvarnström, I.; Niklasson, G.; Svensson, S.C.T. *J. Org. Chem.* **1994**, *59*, 1783.
(13) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.
(14) Chen, J.C.-Y.; Hacksell, U.; Daves, G.D. *J. Org. Chem.* **1985**, *50*, 2778.