Short Communication

A Simple Synthetic Route to Silylated Methyl 3-Azido-2,3-dideoxy-α,β-D-*erythro*-pentofuranoside

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Hansen, P. and Pedersen, E. B., 1990. A Simple Synthetic Route to Silylated Methyl 3-Azido-2,3-dideoxy-α,β-D-*erythro*-pentofuranoside. – Acta Chem. Scand. 44: 522–523.

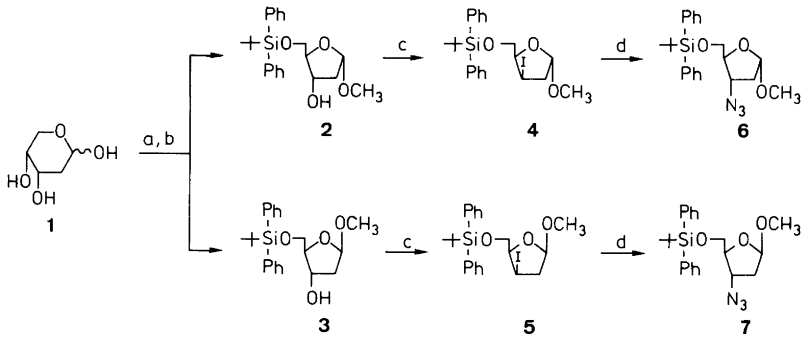
The best method for synthesizing a large number of nucleosides for the purpose of biological testing seems to be a convergent strategy in which a protected furanoside derivative is coupled with a silylated base in the presence of trimethylsilyl triflate. Because of our interest in synthesizing 3′-azido-2′,3′-dideoxyribonucleosides we have searched for a simple synthetic route to a suitable 3-substituted 2,3-dideoxy-D-*threo*-pentofuranoside as a synthon for 3-substituted 2,3-dideoxy-D-*erythro*-pentofuranosides. Several methods have been reported, but they all have in common that they use no less than 7 steps, starting from either D-xylose[1–4] or D-mannitol.[5] We report here a very simple four-step synthesis of methyl 3-azido-2,3-dideoxy-α,β-D-*erythro*-pentofuranosides (**6**) and (**7**), starting from commercially available 2-deoxy-D-ribose (**1**).

Treatment of **1** with hydrochloric acid in methanol,[6] followed by selective 5-*O* protection using *tert*-butyl(diphenyl)chlorosilane in *N,N*-dimethylformamide (DMF) and imidazole, afforded **2** and **3** as an α/β mixture in the ratio **2**:**3** = 3:2 and a total yield of 70 % for the two steps. The anomers were easily separated on a column and each of them was treated with triphenylphosphine, diethyl azodicarboxylate (DEAD) and methyl iodide in toluene at 110 °C to give **4** and **5**, respectively. These were then heated in DMF with an excess of sodium azide at 80 °C to give the corresponding azido compounds **6** and **7**. When the reactions a–d of Scheme 1 were carried out without separation of the anomeric mixture of **2** and **3**, the overall yield of the azido compounds **6** and **7** was more than 26 % for the four steps starting from 2-deoxy-D-ribose (**1**). The structures of **6** and **7** were confirmed by ^{1}H and ^{13}C NMR spectroscopy. The spectra were identical[7] with those previously reported for methyl 3-azido-2,3-dideoxy-D-*erythro*-pentofuranosides (**6**) and (**7**) which have been used as precursors of 3′-azido-3′-deoxythymidine (AZT).

In conclusion, we have developed an easy synthesis of azido sugars **6** and **7** which are useful synthons for the preparation of AZT analogues.

Experimental

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 250 spectrometer. The microanalyses were carried out by NOVO Microanalytical lab. A/S, Novo Allé, DK-Bagsvaerd.



Scheme 1. Reagents: (a) HCl/MeOH; (b) *tert*-butyl(diphenyl)chlorosilane, imidazole, DMF; (c) Ph_3P, DEAD, CH_3I, toluene; (d) NaN_3, DMF.

Methyl 5-O-tert-*butyldiphenylsilyl*-2-*deoxy*-α,β-D-erythro-*pentofuranosides* (**2** *and* **3**). To a solution of methyl 2-deoxy-α,β-D-*erythro*-pentofuranoside[6] (14.0 g, 94.5 mmol) in dry DMF was added imidazole (18.0 g, 26.4 mmol). The mixture was cooled to 0 °C and *tert*-butyl(diphenyl)chlorosilane (25.8 g, 94.0 mmol) was added dropwise with stirring. After the reaction had been stirred at 0 °C for 40 min the solvent was removed and the crude product was purified on a silica column, eluting with petroleum ether–Et_2O (4:1) to afford the α-(**2**) and β-(**3**) anomers in a total yield of 25.6 g (70 %).

Methyl 5-O-tert-*butyldiphenylsilyl*-2-*deoxy*-α-D-erythro-*pentofuranoside* (**2**). Yield 15.1 g (41 %). ^{1}H NMR ($CDCl_3$): δ 1.04 (9 H, s, *tert*-butyl), 2.01 (1 H, d, H-2, $J_{2,2}$ 13.6 Hz), 2.14–2.24 (1 H, m, H-2′), 2.88 (1 H, d, OH, *J* 10.6 Hz), 3.37 (3 H, s, OCH_3), 3.61 (1 H, dd, H-5, $J_{5,5'}$ 10.9 Hz, $J_{4,5}$ 4.8 Hz), 3.75 (1 H, dd, H-5′, $J_{4,5'}$ 3.5 Hz), 4.15–4.17 (1 H, m, H-4), 4.27–4.34 (1 H, m, H-3), 5.10 (1 H, d, H-1, *J* 6.5 Hz), 7.34–7.68 (10 H, m, aryl). ^{13}C NMR ($CDCl_3$): δ 19.26 (Me_3C), 26.85 (Me_3C), 41.16 (C-2), 54.76 (OCH_3), 64.48 (CH_2O), 73.25 (C-3), 87.84 (C-4), 105.65 (C-1) 127.73, 127.76, 129.74, 129.79, 133.24, 135.59, 135.64 (aryl). Anal. $C_{22}H_{30}O_4Si$: C, H.

Methyl 5-O-tert-*butyldiphenylsilyl*-2-*deoxy*-β-D-erythro-*pentofuranoside* (**3**). Yield 10.5 g (29 %). ^{1}H NMR ($CDCl_3$): δ 1.08 (9 H, s, *tert*-butyl), 2.00–2.23 (2 H, m, H-2 and H-2′), 3.26 (3 H, s, OCH_3), 3.66 (1 H, dd, H-5, $J_{5,5'}$ 10.2 Hz, $J_{4,5}$ 7.5 Hz), 3.80 (1 H, dd, H-5′, $J_{4,5'}$ 5.2 Hz), 3.92–3.98 (1 H, m, H-3), 4.44–4.53 (1 H, m, H-4), 5.04 (1 H, dd, H-1, $J_{1,2}$ 5.2 Hz, $J_{1,2'}$ 2.2 Hz), 7.35–7.70 (10 H, m, aryl). ^{13}C NMR ($CDCl_3$): δ 19.26 (Me_3C), 26.90 (Me_3C), 41.13 (C-2), 54.99 (OCH_3), 65.41 (CH_2O), 73.20 (C-3), 85.88 (C-4), 105.04 (C-1), 127.78, 129.81, 133.37, 135.58 (aryl). Anal. $C_{22}H_{30}O_4Si$: C, H.

Methyl 5-O-tert-*butyldiphenylsilyl*-3-*iodo*-2,3-*dideoxy*-α-D-threo-*pentofuranoside* (**4**). A solution of methyl 5-*O*-*tert*-butyldiphenylsilyl-2-deoxy-α-D-*erythro*-pentofuranoside (**2**) (11.0 g, 28.5 mmol) in dry toluene (100 ml) was treated with triphenylphosphine (7.90 g, 10.1 mmol) and DEAD (5.24 g, 30.1 mmol) at room temperature. When the reaction had been stirred for 30 min, MeI (13.0 ml, 0.210 mol) was added slowly and the reaction mixture was heated at 110 °C for 1 h; the solvent was then removed *in vacuo* and the residue was purified on a silica column, eluting with petroleum ether–Et_2O (4:1) to give **4** as a colorless oil. Yield 5.22 g (40 %). ^{1}H NMR ($CDCl_3$): δ 1.07 (9 H, s, *tert*-butyl), 2.53–2.63 (1 H, ddd, H-2, *J* 14.7, 6.5 and 3.8 Hz), 2.75–2.85 (1 H, ddd, H-2′, *J* 5.5 Hz and *J* 3.3 Hz), 3.37 (3 H, s, OCH_3), 3.43 (1 H, q, H-3, *J* 5.0 Hz), 3.71 (1 H, dd, H-5, $J_{5,5'}$ 10.5 Hz, $J_{4,5}$ 5.9 Hz), 3.96 (1 H, dd, H-5′, $J_{4,5'}$ 5.0 Hz), 4.53 (1 H, m, H-4), 5.20 (1 H, dd, H-1, $J_{1,2'}$ 5.4 Hz, $J_{1,2}$ 3.9 Hz), 7.30–7.80 (10 H, m, aryl). ^{13}C NMR ($CDCl_3$): δ 19.20 (Me_3C), 26.80 (Me_3C), 26.98 (C-3), 46.10 (C-2), 55.60 (OCH_3), 68.64 (C-5), 79.87 (C-4), 104.88 (C-1), 127.67, 129.70, 133.26, 133.32, 135.59, 135.68 (aryl). Anal. $C_{22}H_{29}IO_3Si$: C, H.

Methyl 5-O-tert-*butyldiphenylsilyl*-3-*iodo*-β-D-threo-*pentofuranoside* (**5**). The same procedure as for **4** starting with methyl 5-*O*-*tert*-butyldiphenylsilyl-2-deoxy-β-D-*erythro*-pentofuranoside (**3**) (8.70 g, 22.5 mmol) afforded **5** in a yield of 6.27 g (56 %). ^{1}H NMR ($CDCl_3$): δ 1.07 (9 H, s, *tert*-butyl), 2.50–2.59 (1 H, m, H-2), 2.75–2.86 (1 H, m, H-2′), 3.36 (3 H, s, OCH_3), 3.52–3.60 (1 H, m, H-3), 3.82–3.97 (2 H, m, H-5), 4.33–4.40 (1 H, m, H-4), 5.08–5.12 (1 H, dd, H-1, $J_{1,2}$ 2.2 Hz, $J_{1,2}$ 2.2 Hz, $J_{1,2'}$ 5.9 Hz), 7.20–7.70 (10 H, m, aryl). ^{13}C NMR ($CDCl_3$): δ 19.22 (Me_3C) 20.83 (C-3), 26.84 (Me_3C), 44.35 (C-2), 55.55 (OCH_3), 69.19 (C-5), 81.65 (C-4), 105.19 (C-1), 127.66, 129.67, 133.42, 133.51, 135.61, 135.70 (aryl). Anal. Found: C 53.74; H 5.95. Calc. for $C_{22}H_{29}IO_3Si$: C 53.23; H 5.89.

Methyl 3-azido-5-O-tert-*butyldiphenylsilyl*-2,3-*dideoxy*-α-D-erythro-*pentofuranoside* (**6**). Methyl 5-O-*tert*-butyldiphenylsilyl-3-iodo-2,3-dideoxy-α-D-*threo*-pentofuranoside (**4**) (5.00 g, 10.1 mmol) was heated in DMF (45 ml) with an excess of NaN_3 (2.00 g, 31 mmol) at 80 °C for 3½ h. The solvent was removed *in vacuo*, and the crude product was dissolved in dry Et_2O from which the insoluble salts were filtered off. After evaporation of the Et_2O, the yellow oil was purified on a silica column, eluting with petroleum ether–Et_2O (4:1) to afford (**6**) as a colorless oil in a yield of 2.45 g (59 %). ^{1}H NMR and ^{13}C NMR spectra were identical with those previously reported.[7]

Methyl 3-azido-5-O-tert-butyldiphenylsilyl-2,3-*dideoxy*-β-D-erythro-*pentofuranoside* (**7**). The same procedure as for **6**, starting with methyl 5-*O*-*tert*-butyldiphenylsilyl-3-iodo-2,3-dideoxy-β-D-*threo*-pentofuranoside (**5**) (6.00 g, 12.1 mmol) gave methyl 3-azido-5-*O*-*tert*-butyldiphenylsilyl-2,3-dideoxy-β-D-*erythro*-pentofuranoside (**7**) in a yield of 2.46 g (49 %). ^{1}H NMR and ^{13}C NMR spectra were identical with those previously reported.[7]

Acknowledgements. The Danish Medical Research Council is gratefully acknowledged for its support.

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Received November 22, 1989.