SYNTHESIS OF ANOMALOUSLY COUPLED NUCLEOSIDES BY ADDITION OF PURINES TO UNSATURATED SUGAR ALDEHYDES

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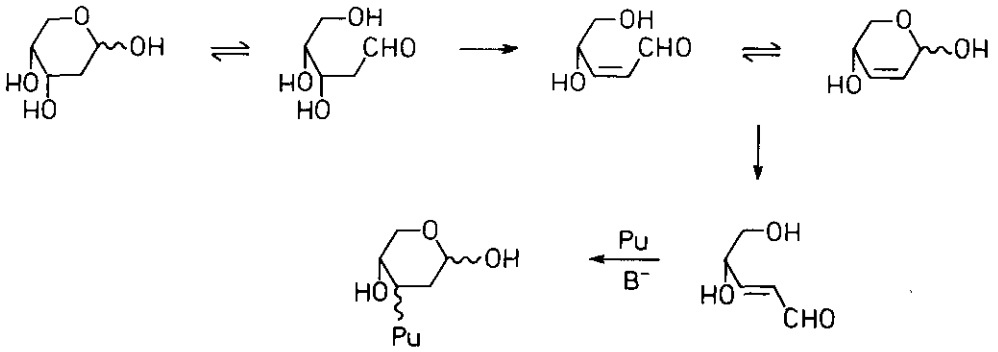
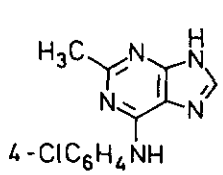
Abstract - α,β-Unsaturated sugar aldehydes were reacted in a Michael type of reaction with purines in the presence of an organic base to give isonucleosides.

Recently, we have shown that unprotected 2-deoxy-D-ribose is anomalously coupled with nucleobases when reacted with a tributylammonium polyphosphate mixture in chloroform[1]. The reaction of the 2-deoxysugar at C-3 with purines was assumed to take place *via* a dehydration/addition process as follows:



To prove this assumption the attention was turned to the addition of bases **1** and **2** to unsaturated sugar aldehydes **3** and **4** as well as hemiacetal **5**.



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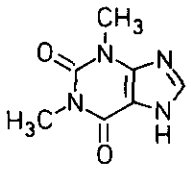

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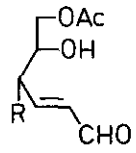
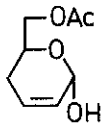
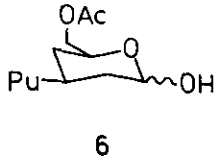


3 R=H
4 R=OAc

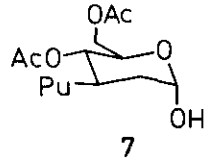


5

Compound **3** reacted with **1** in the presence of triethylamine (TEA) in DMF at 40°C for 7 days to produce the threo adduct **6** in 20% yield. The hemiacetal **5** reacted similarly, but not in a clean reaction according to silica TLC. The aldehyde **4** easily available from tri-O-acetyl-D-glucal[2], was treated with **1** and TEA in DMF at 40°C for 8 days and the α-D-glucopyranose anomer **7** could be isolated in 21% yield by flash chromatography on silica with methanol/dichloromethane (1:25). In an addition reaction of theophylline (**2**) with the aldehyde **4** in DMF a large increase was observed in reaction rate when 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used instead of TEA. After 3 h at room temperature an adduct was isolated by adding water to the reaction mixture, neutralizing to pH 7, extraction with dichloromethane, and silica chromatography with methanol/ether (1:20). The primary adduct was deacetylated by treatment with 2% HCl in methanol at 60°C for 15 h to give a mixture of the methyl glycosides **8** in 31% overall yield form **4**.



6



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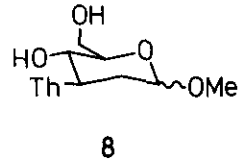

8

Pu = 6-(4-Chlorophenylamino)-2-methyl-9-purinyl

Th = 7-Theophyllyl

The structures and their corresponding conformations were assigned on the basis of their ^{1}H, ^{13}C-NMR and mass spectra. 500 MHz ^{1}H-NMR spectra were recorded for **6** and **8**[3]. The assignment of the shift values in the ^{1}H-NMR spectra was based on the use of ^{1}H-^{1}H homonuclear shift correlated 2-D NMR. With this technique it was possible to assign the axial 4a-H in the β-anomer of **6** as a quartet with J = 12 Hz. This can be explained by assuming couplings to one geminal proton and two vicinal axial protons which prove threo

configuration of **6** in the C1 conformation. This is confirmed by large couplings of the axial 3a-H to vicinal and axial orientated 2a-H and 4a-H for both α and β-anomers. In the same manner the coupling constants of 3-H in **7** and **8** prove the arabino configuration in the C1 conformation with the bulky purin-yl group at C-3 always in an equatorial position.

Characterization of **6**, **7** and **8** as follows:

6: mp 200-201°C; m/z (EI): 431 (M^+, 11); NMR (DMSO-d_6) from the mixture of α and β-anomers (3:2).

α-anomer: ^{1}H-NMR (500 MHz) δ = 1.94-2.04 (m, 4e-H, 4a-H, 2e-H), 2.03 (s, OAc), 2.29 (t, $J_{2e,2a} = J_{2a,3}$ = 12Hz, 2a-H), 2.50 (s, CH_3) 4.03-4.10 (m,6,6'-H), 4.33 (m, Σ [J] = 24Hz, 5-H), 5.02 (tt, $J_{2a,3} = J_{3,4a}$ = 12Hz, $J_{2e,3} = J_{3,4e}$ = 4Hz, 3-H) 5.39 (unresolved s, 1-H), 6.01 (d,J = 4Hz, OH) 7.35 (d, J = 9Hz, ArH), 8.01 (d, J = 9Hz, ArH), 8.38 (s, 8'-H), 9.87 (s, NH). ^{13}C-NMR (63 MHz) δ = 20.62 (Ac), 25.87 (CH_3), 33.66 (C-4), 36.38(C-2), 46.22 (C-3), 65.24 (C-6), 66.10 (C-5), 90.42 (C-1), 118.06 (C-5'), 121.7 (C-2"), 125.67 (C-4"), 128.10 (C-3"), 138.97 (C-1"), 139.57 (C-8"), 150.03 (C-4'), 151.29 (C-6'), 160.37 (C-2'), 170.21 (C=O).

β-anomer: ^{1}H-NMR (500 MHz) δ = 1.89 (q, $J_{4a,4e} = J_{3,4a} = J_{4a,5}$ = 12Hz, 4a-H), 1.92-2.04 (m, 4e-H, 2a-H), 2.03 (s, OAc, 2.14 (m, $J_{2e,2a}$ = 12Hz, 2e), 2.50 (s, CH_3), 3.89 (m, Σ [J] = 24Hz, 5-H), 4.03-4.10 (m,6,6'-H), 4.79 (tt, $J_{2a,3} = J_{3,4a}$ = 12Hz, $J_{2e,3} = J_{3,4e}$ = 4Hz, 3H) 4.87 (ddd, $J_{1,OH}$ = 6Hz, $J_{1,2e}$ = 2Hz, $J_{1,2a}$ = 10Hz, 1-H), 6.91 (d, J = 6Hz, OH), 7.35 (d, J = 9Hz, ArH), 8.01 (d, J = 9Hz, ArH), 8.35 (s, 8'-H), 9.88 (s,NH). ^{13}C- NMR (63 MHz) δ = 20.62 (Ac), 25.87 (CH_3), 32.87 (C-4), 38.36 (C-2), 49.51 (C-3), 65.86 (C-6), 70.01 (C-5), 94.01 (C-1), 118.06 (C-5'), 181.73 (C-2"), 125.67 (C-4"), 128.10 (C-3"), 138.97 (C-1"), 139.66 (C-8'), 150.05 (C-4'), 151.29 (C-6'), 160.37 (C-2"), 170.21 (C=O).

7: mp 200-201°C, m/z (EI): 489 (M^+, 1.4); ^{1}H-NMR (DMSO-d_6, 250 MHz) δ = 1.67 (s, 4-OAc), 2.03 (s, 6-OAc), 2.08 (m, 2e-H), 2.57 (s, CH_3), 2.82 (t, $J_{2a,3} = J_{2a,2e}$ = 13.1 Hz, 2a-H), 4.04 (dd, $J_{5,6}$ = 1.6, $J_{6,6'}$= 12 Hz, 6-H), 4.21 (dd, $J_{5,6'}$= 5.1 Hz, 6'-H), 4.30 (m, $J_{4,5}$ = 9.9 Hz, 5-H), 5.05 (m, $J_{3,4}$ = 9.9 Hz

$J_{2a,3}$ = 13.1 Hz, $J_{2e,3}$ = 4.4 Hz, 3-H), 5.25 (t, 4-H), 5.42 (m, 1-H), 6.99 (d, $J_{1,OH}$ = 3.7 Hz, OH) 7.37 (d, $J_{2",3"}$ = 8.9 Hz, 3"-H), 8.05 (d 2"-H), 8.45 (s, 8'-H), 9.89 (s, NH). ^{13}C-NMR (DMSO-d_6, 63 MHz) δ = 19.88, 20.55 (2Ac), 25.86 (CH_3), 35.20 (C-2), 50.71 (C-3), 62.67 (C-6), 67.36, 69.68 (C-4,C-5), 89.81 (C-1), 117.8 (C-5'), 121.67 (C-2"), 125.67 (C-4"), 128.12 (C-3"), 138.94 (C-1"), 140.38 (C-8'), 150.70 (C-4'), 151.17 (C-6'), 160.44 (C-2'), 168.80, 170.05 (2 C=O).

8: mp 269-271°C; m/z (EI): 340 (M^+, 21); NMR (DMSO-d_6) from the mixture of α and β-anomers (2:1).

α-anomer: ^{1}H-NMR (500 MHz) δ = 2.04 (dd, $J_{2a,2e}$ = 12 Hz, $J_{2e,3}$ = 4 Hz, 2e-H), 2.50 (hidden by DMSO, 2a-H), 3.25 (s,NCH_3), 3.31 (s,NCH_3), 3.42 (s, CH_3), 3.49 (m, 5-H), 3.54 (m, 6-H), 3.70 (m, $J_{6,6}$ = 11 Hz, 6-H), 3.93 (dt,$J_{3,4}$ = $J_{4,5}$ = 10 Hz, $J_{4,OH}$ = 7 Hz, 4-H), 4.60 (t, $J_{6,OH}$ =$J_{6',OH}$≈ 6 Hz, 6-OH), 4.77 (m, 3-H), 4.83 (d, $J_{1,2a}$ = 3 Hz, 1-H). ^{13}C-NMR (63 MHz) δ = 27.61, 29.27 (2 CH_3), 35.66 (C-2), 53.66 (OCH_3), 57.27 (C-3), 60.79 (C-6), 67.26 (C-4), 73.84 (C-5), 96.65 (C-1), 106.12 (C-5'), 142.44 (C-8'), 148.78 (C-4'), 150.66 (C-2'), 154.04 (C-6').

β-anomer: ^{1}H-NMR (500 MHz) δ = 2.12 (ddd, $J_{1,2e}$ = 2 Hz, $J_{2a,2e}$ = 11Hz, $J_{2e,3}$ = 4 Hz, 2e-H), 2.26 (q, $J_{1,2a}$ = $J_{2a,3}$ = 10 Hz, 2a-H), 3.25 (s, CH_3), 3.27 (m, 5-H), 3.31 (CH_3), 3.42 (s, CH_3), 3.54 (m, 6'-H), 3.74 (m, 6-H), 3.88 (dt, $J_{3,4}$ = $J_{4,5}$ = 10 Hz, $J_{4,OH}$ = 7Hz, 4-H), 4.55 (dd, 1-H), 4.59 (hidden by 6-OH, 3-H), 4.63 (t, $J_{6,OH}$ =$J_{6',OH}$ = 7 Hz, 6-OH), 5.18 (d, 4-OH). ^{13}C-NMR (63 MHz) δ = 27.61, 29.27 (2 CH_3), 37.03 (C-2), 55.58 (CH_3), 59.47 (C-3), 60.98 (C-6), 67.25 (C-4), 78.23 (C-5), 100.32 (C-1), 106.04 (C-5'), 142.11 (C-8'), 148.78 (C-4'), 150.66 (C-2'), 154.04 (C-6').

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3. K. Bock, The Technical University of Denmark is greatly acknowledged for recording 500 MHz ^{1}H-NMR and ^{1}H-^{1}H homonuclear shift correlated 2-D NMR.

Received, 18th January, 1988