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Synthesis of derivatives of *C*-nucleoside analogues using 'push–pull' functionalized monosaccharides

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Dedicated to Professor Dr. István Farkas on the occasion of his 75th birthday

Abstract

7-Deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-heptopyranos-6-ulose (**1**) reacted with carbon disulphide and methyl iodide in the presence of a base to furnish 7,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-8,8-[bis(methylthio)]-α-D-*galacto*-oct-7-enopyranos-6-ulose (**2**). This 'push–pull' activated unsaturated monosaccharide underwent a ring closure reaction with hydrazine hydrate to give the 'inversed' *C*-nucleoside analogue **3**. Compound **1** and malononitrile yielded the 7-cyano-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-6-methyl-α-D-*galacto*-oct-6-enopyranurononitrile (**4**). Treatment of **4** with carbon disulphide and methyl iodide in the presence of a base afforded the sugar 'push–pull' butadiene **5** which was transformed into the pyridine nucleoside analogue **6**.

Keywords: Heptopyranos-6-ulose; Oct-6-enopyranurononitrile; *C*-Nucleoside analogues; α-Oxoketene-*S*,*S*-acetals; 'Push–pull' butadienes

1. Introduction

Numerous modifications of natural nucleosides have been performed to optimize their pharmacological behavior. Variations of the heterocyclic unit and/or the replacement of D-ribose and 2-deoxy-D-ribose through other naturally occurring sugar moieties are well known. In recent years a great number of *C*-nucleosides with cyclopentyl,[1,2] cyclobutyl[3] and cyclopropyl[4,5] moieties have been synthesized especially because representatives have antiviral, anti-HIV and antitumor properties. Pyrrolidine,[6,7] dioxolane,[8,9] oxathiolane[10] and isoxazolidine[11] nucleoside analogues have also been intensively investigated which have been tested as glycosidase inhibitors for anti-HIV activity. The subclass of *C*-nucleosides represents important biologically active natural products with an increased hydrolytic and enzymatic stability and the synthesis of them and their analogues is of growing interest.[12–14] In 'inversed' *C*-nucleosides the nucleobase is linked by a carbon–carbon bond to the sugar unit through a carbon other than C-1. Examples of such 'inversed' *C*-nucleosides are relatively rare in the literature but recently, intensified efforts could be observed in this field.[15–17]

In this paper we describe the synthesis of *C*-nucleoside analogues with a pyrazole and a pyridine ring starting from the pyranos-5-yl substituted α-oxoketene-*S*,*S*-acetal (**2**) and the 'push–pull' butadiene **5**, respectively.

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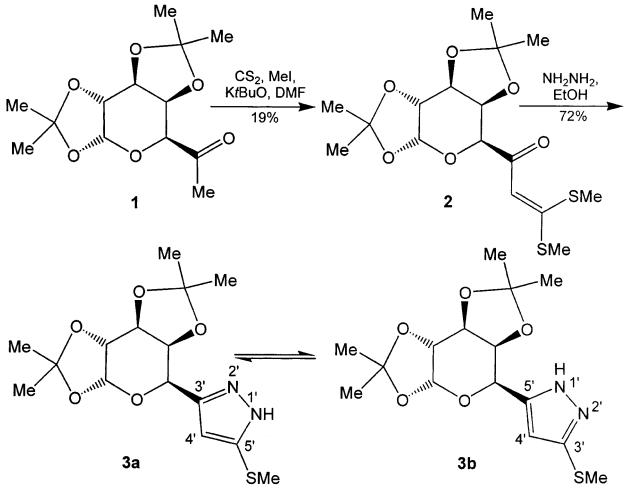
2. Results and discussion

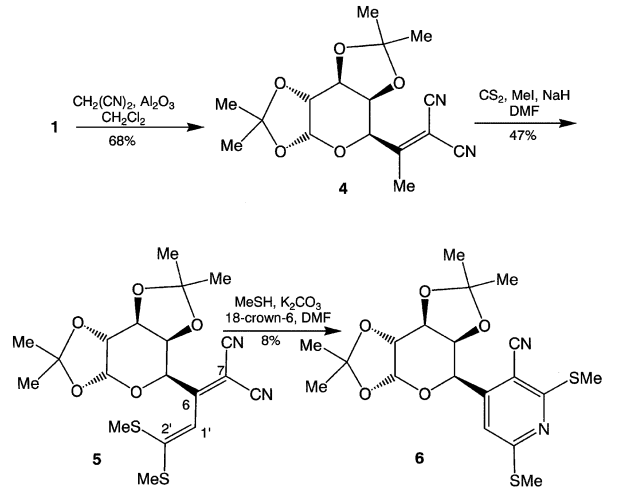
The 'push–pull' functionalized monosaccharides **2** and **5** were synthesized by chain elongation via the deoxyheptopyranosulose **1** which was synthesized from D-galactose via 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose following the procedure by Kraus and Shi.[18] Chain elongation[19] to give the α-oxoketene-*S*,*S*-acetal **2** was achieved by the reaction of the heptopyranosulose **1** with an excess of carbon disulphide, methyl iodide and potassium *tert*-butoxide as base in *N*,*N*-dimethylformamide (Scheme 1) without isolation of the dithiolate that is formed as an intermediate. The pyranos-5-yl substituted 'push–pull' alkene **2** could be isolated as a pale yellow syrup in 19% yield. This compound is unstable since it readily loses methanethiol. Therefore, we could not obtain correct elemental analyses.



Scheme 1.

In general, such α-oxoketen-*S*,*S*-acetals react easily with hydrazines to form pyrazoles.[20] The reaction of compound **2** with hydrazine hydrate was carried out in ethanol at room temperature to form the desired 'inversed' *C*-nucleoside **3** in 72% yield. The spectroscopic data clearly verify the formation of compound **3**. The mass spectrum contained a signal for M^+ at m/z 342. Only one methylthio group at 2.46 and 18.6 ppm, respectively, was found in the ^{1}H NMR and ^{13}C NMR spectra. On the other hand, in the ^{13}C NMR spectrum the carbonyl signal at 191 ppm disappeared. In this structure the carbohydrate moiety is linked through the 5-position to the heterocycle via a C–C single bond. For compound **3**, an equilibrium of the tautomeric forms **3a** and **3b** can be formulated. Due to the fast NH-proton exchange the atoms C-3′ and C-5′ appear as broad signals in the ^{13}C NMR spectrum.

Cyano-substituted 'push–pull' butadienes with their characteristic unsymmetrical arrangement of donor and acceptor substituents form pyridines in the presence of methanethiol under basic conditions.[21] In order to prepare a convenient pyranosyl substituted 'push–pull' butadiene for this electrocyclization reaction, compound **1** was treated first with malononitrile to obtain the Knoevenagel product **4**. The reaction was carried out in the presence of basic aluminium oxide in dichloromethane at room temperature[22,23] (Scheme 2). In the second step, compound **4** was treated with carbon disulphide and methyl iodide in *N*,*N*'-dimethylformamide using sodium hydride as a base. The desired functionalized pyranose derivative **5** was isolated as an orange crystalline compound in 47% yield. The orange colour results from the 'push–pull' property of the butadiene moiety which causes characteristic alternating chemical shifts of the sp^2 carbon atoms [168.1 (C-2′), 156.2 (C-6), 117.6 (C-1′), 81.5 ppm (C-7)].[24]



Scheme 2.

Normally, the intended heterocyclization requires drastic conditions. For instance potassium carbonate has been used as the catalyst in boiling *N*,*N*-dimethylformamide. We found

that this type of reaction can also be performed at room temperature by adding crown ether to the reaction mixture. Under these conditions we obtained the nicotinonitrile *C*-nucleoside analogue **6** as a colourless syrup, but only in a very low yield of 8%.

3. Experimental

General methods.—Melting points were determined with a Boëtius melting point apparatus and are corrected. Optical rotations were measured with a Polar LμP (IBZ Meßtechnik) polarimeter. IR spectra were recorded with a Nicolet 205 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were obtained with a Bruker AC 250 (250.13 and 62.90 MHz, respectively) and a Bruker ARX 300 (75.47 MHz). All NMR spectra were recorded in $CDCl_3$ with $CHCl_3$ at $\delta_H = 7.26$ and $\delta_C = 77.0$ as internal standard. The ^{13}C NMR signals were assigned by DEPT and/or ^{1}H,^{13}C COSY spectra. Mass spectra were obtained with an AMD 402/3 spectrometer (AMD Intectra GmbH). Elemental analyses were performed with a Leco CHNS-932. Column chromatography was carried out on Silica gel 60 (230–400 μm, E. Merck). Thin-layer chromatography (TLC) was performed on Silica gel 60 GF_{254} foils (E. Merck) with detection by UV-light and by charring with H_2SO_4. Solvents and liquid reagents were purified and dried according to recommended procedures.

*7,8-Dideoxy-1,2:3,4-di-*O*-isopropylidene-8,8-[bis(methylthio)]-α-*D*-galacto-oct-7-enopyranos-6-ulose* (**2**).—A solution of 7-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-heptopyranos-6-ulose[18] (**1**, 0.54 g, 2.0 mmol), carbon disulphide (0.25 mL, 4.0 mmol) and MeI (0.35 mL, 5.5 mmol) in DMF (10 mL) was cooled to 0 °C. Then potassium *tert*-butoxide (0.8 g, 7.13 mmol) was added. The mixture was stirred for 10 min at 0 °C and 30 min at rt, then poured onto ice water and extracted with $CHCl_3$. The combined organic layers were washed with water, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (7:1 toluene–EtOAc) to yield 0.14 g (19%) of **2** as a yellow syrup; TLC: 2:1 toluene–EtOAc R_f: 0.54; IR (capillary): 1640.1 cm^{-1} (CO); ^{1}H NMR (250.1 MHz, $CDCl_3$): δ 6.54 (s, 1 H, H-7), 5.63 (d, 1 H, $J_{1,2}$ 4.9 Hz, H-1), 4.70–4.60 (m, 2 H, H-3, H-4), 4.32 (dd, 1 H, $J_{2,3}$ 2.0 Hz, H-2), 4.23 (d, 1 H, $J_{4,5}$ 1.5 Hz, H-5), 2.47 (2s, 6 H, 2 SCH_3), 1.49, 1.41, 1.32, 1.29 (4s, 12 H, 2 $C(CH_3)_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 191.0 (CO), 166.4 ($C(SCH_3)_2$), 109.6 (C-7), 109.4, 108.9 ($2C(CH_3)_2$), 96.6 (C-1), 72.8 (C-5), 72.4 (C-4), 70.8, 70.8 (C-2, C-3), 26.0, 26.0, 24.8, 24.8 ($2C(CH_3)_2$), 17.2, 14.9 (2 SCH_3); HRMS: Anal. Calcd for $C_{16}H_{24}O_6S_2$ 376.10143; Found: $[M]^+$ m/z 376.10192.

*(5*R*)-1,2:3,4-Di-*O*-isopropylidene-5-*C*-[5(3)-methylthio-pyrazol-3(5)-yl]-β-*L*-arabino-pentopyranose* (**3**).—A solution of **2** (82 mg, 0.22 mmol) and hydrazine hydrate (0.6 mL, 12 mmol) in EtOH (15 mL) was stirred for 24 h at rt and then evaporated. The residue was purified by column chromatography (4:1 toluene:EtOAc) to yield 54 mg (72%) of **3** as colourless crystals; TLC: 2:1 toluene–EtOAc, R_f: 0.27; mp 150–151 °C; $[\alpha]_D^{21}$: −134.4° (*c* 1.0, $CHCl_3$); IR (KBr): 3334.6 cm^{-1} (NH); ^{1}H NMR (250.1 MHz, $CDCl_3$): δ 6.25 (s, 1 H, H-4′), 5.60 (d, 1 H, $J_{1,2}$ 4.9 Hz, H-1), 4.94 (d, 1 H, $J_{4,5}$ 1.8 Hz, H-5), 4.68 (dd, 1 H, $J_{2,3}$ 2.2, $J_{3,4}$ 7.9 Hz, H-3), 4.42 (dd, 1 H, H-4), 4.36 (dd, 1 H, H-2), 2.46 (s, 3 H, SCH_3), 1.56, 1.48, 1.35, 1.34 (4s, 12 H, 2 $C(CH_3)_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 144.8, 143.0 (brs, C-3′, C-5′), 109.6, 108.9 (2 $C(CH_3)_2$), 105.7 (C-4′), 96.6 (C-1), 72.8 (C-4), 70.8 (C-3), 70.6 (C-2), 63.3 (C-5), 26.2, 25.9, 24.8, 24.1 (2 $C(CH_3)_2$), 16.8 (SCH_3); MS, EI (m/z): 342 $[M]^+$; Anal. Calcd for $C_{15}H_{22}N_2O_5S$: C, 52.62; H, 6.48; S, 9.36. Found: C, 52.65; H, 6.59; S, 9.57.

*7-Cyano-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-6-methyl-α-*D*-galacto-oct-6-enopyranurononitrile* (**4**).—Aluminium oxide (0.9 g, type T, E. Merck) was added to a mixture of **1** (0.2 g, 0.7 mmol) and malononitrile (0.1 g, 1.5 mmol) in CH_2Cl_2 (12 mL). The suspension was stirred for 1 h at rt and then filtered through Celite. The filtrate was concentrated and the residue was purified by column chromatography (7:1 toluene–EtOAc) to yield 0.16 g (68%) of **4** as a colourless syrup; TLC: 7:1 toluene–EtOAc R_f: 0.40; $[\alpha]_D^{21}$: −98.9° (*c* 1.0, $CHCl_3$); IR (capillary): 2234.7 cm^{-1} (CN); ^{1}H NMR (250.1 MHz, $CDCl_3$): δ 5.59

(d, 1 H, $J_{1,2}$ 4.9 Hz, H-1), 4.92 (d, 1 H, $J_{4,5}$ 2.1 Hz, H-5), 4.69 (dd, 1 H, $J_{2,3}$ 2.8, $J_{3,4}$ 7.6 Hz, H-3), 4.67–4.37 (m, 2 H, H-2, H-4), 2.37 (s, 3 H, CH_3), 1.57, 1.46, 1.34, 1.32 (4s, 12 H, 2 $C(CH_3)_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 179.9 (C-6), 111.3, 111.0 (2 CN), 110.3 109.6 (2$C(CH_3)_2$), 96.4 (C-1), 85.3 (C-7), 72.9 (C-4), 71.1 (C-3), 70.1 (C-2), 69.6 (C-5), 26.0, 25.7, 24.8, 24.1 (2 $C(CH_3)_2$), 20.6 (CH_3); MS, CI (m/z): 321 $[M+H]^+$; Anal. Calcd for $C_{16}H_{20}N_2O_5$: C, 60.00; H, 6.29; N, 8.74. Found: C, 60.63; H, 6.30; N, 8.89.

7-Cyano-6,7-dideoxy-1,2:3,4-di-O-*isopropylidene-6-[2,2-(bismethylthio)vinyl]-α*-D-galacto-*oct-6-enopyranurononitrile* (**5**).—Sodium hydride (0.27 g, 6.15 mmol, 60%) was stirred for 10 min in heptane (3 mL). The solvent was decanted after the sodium hydride had settled. Then toluene (2 mL) was added and the mixture was stirred for another 5 min. Then a solution of **4** (0.98 g 3.07 mmol), carbon disulphide (0.37 mL, 6.15 mmol) and MeI (1.15 mL, 18.5 mmol) in DMF (45 mL) was added. The mixture was stirred for 30 min, then poured onto ice water and extracted with $CHCl_3$. The combined organic layers were washed with water, dried (Na_2SO_4) and concentrated. Recrystallization from EtOH–water yielded 0.62 g (47%) of **5** as orange crystals; TLC: 7:1 toluene–EtOAc R_f: 0.37; mp 160–163 °C; $[\alpha]_D^{21}$ +243.0° (*c* 1.0, $CHCl_3$); IR (KBr): 2220.3 cm^{-1} (CN); ^1H NMR (250.1 MHz, $CDCl_3$): δ 6.24 (s, 1 H, H-1′), 5.60 (d, 1 H, $J_{1,2}$ 4.9 Hz, H-1), 5.24 (d, 1 H, $J_{4,5}$ 2.1 Hz, H-5), 4.69 (dd, 1 H, $J_{2,3}$ 2.4, $J_{3,4}$ 7.6 Hz, H-3), 4.42 (dd, 1 H, H-4), 4.37 (dd, 1 H, H-2), 2.52, 2.45 (2s, 6 H, 2 SCH_3), 1.58, 1.48, 1.34, 1.32 [4s, 12 H, 2 $C(CH_3)_2$]; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 168.1(C-2′), 156.2 (C-6), 117.6 (C-1′), 113.6, 112.9 (2 CN), 110.1, 109.4 (2 $C(CH_3)_2$), 96.4 (C-1), 81.5 (C-7), 72.7 (C-4), 71.2 (C-3), 70.1 (C-2), 69.1 (C-5), 26.1, 25.7, 24.8, 24.1 (2 $C(CH_3)_2$), 17.6, 17.1 (2 SCH_3); MS, EI (m/z): 424 $[M]^+$; Anal. Calcd for $C_{19}H_{24}N_2O_5S_2$: C, 53.75; H, 5.70; N, 6.60; S, 15.12. Found: C, 53.69; H, 5.63; N, 6.64; S, 15.01.

(5R)-5-C-[3-Cyano-2,6-(bismethylthio)-pyridin-4-yl]-1,2:3,4-di-O-*isopropylidene-β*-L-arabino-*pentopyranose* (**6**).—A mixture of **5** (0.3 g, 0.71 mmol), 18-crown-6 (1.0 g, 3.8 mmol), K_2CO_3 (1.5 g, 10.8 mmol) and methanethiol (2 mL) was stirred for 7 h at rt, then poured onto ice water and extracted with $CHCl_3$. The combined organic layers were washed with water, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (15:1 toluene–EtOAc) to yield 24 mg (8%) of **6** as a colourless syrup; TLC: 7:1 toluene–EtOAc R_f: 0.60; ^1H NMR (250.1 MHz, $CDCl_3$): δ 7.12 (s, 1 H, H-5′), 5.66 (d, 1 H, $J_{1,2}$ 5.2 Hz, H-1), 5.07 (d, 1 H, $J_{4,5}$ 2.1 Hz, H-5), 4.73 (dd, 1 H, $J_{2,3}$ 2.6, $J_{3,4}$ 7.8 Hz, H-3), 4.54 (dd, 1 H, H-4), 4.41 (dd, 1 H, H-2), 2.63, 2.58 (2s, 6 H, 2 SCH_3), 1.59, 1.42, 1.35, 1.27 (4s, 12 H, 2 $C(CH_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 164.4, 162.9 (C-2′, C-6′), 149.6 (C-4′), 115.8 (C-5′), 115.0 (CN), 109.8, 109.5 (2 $C(CH_3)_2$), 98.9 (C-3′), 96.8 (C-1), 71.8 (C-4), 71.1 (C-3), 70.4 (C-2), 67.3 (C-5), 26.0, 25.8, 24.9, 24.3 (2 $C(CH_3)_2$), 13.3, 13.3 (2SCH_3); HRMS: Anal. Calcd for $C_{19}H_{24}N_2O_5S_2$ 424.11266; Found: $[M]^+$ m/z 424.11267.

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