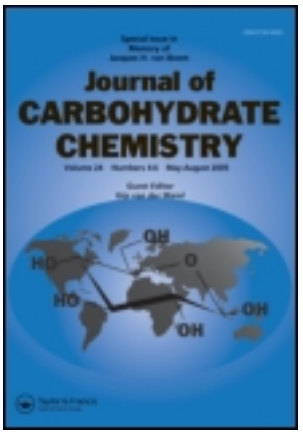

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SYNTHESES OF PYRAZOLE *ISO*-C-NUCLEOSIDES ☆

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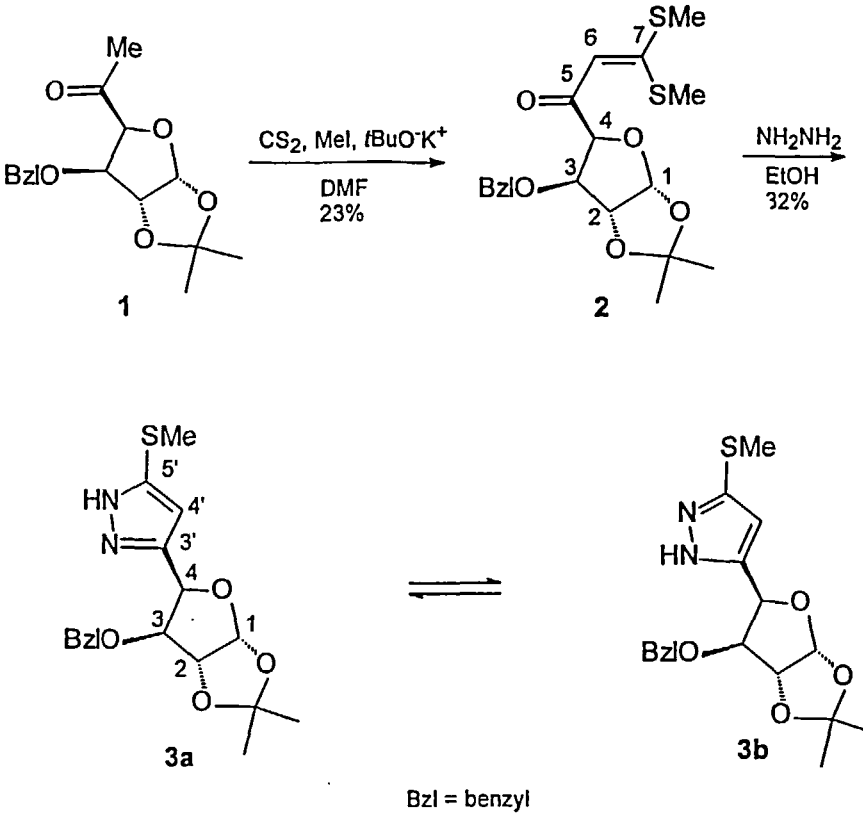
ABSTRACT

3-*O*-Benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose **(1)** and 3,6-dideoxy-1,2-*O*-isopropylidene-α-D-*glycero*-hex-3-enofuranos-5-ulose **(6)** reacted with carbon disulfide and methyl iodide under basic conditions to give the α-oxoketene-*S,S*-acetals **2** and **7**, respectively. Treatment of **2** and **7** with hydrazine hydrate yielded the pyrazole derivatives **3** and **8**, respectively.

INTRODUCTION

Naturally occurring C-nucleosides such as pyrazofurin, showdomycin, oxazinomycin, and formycin B are important, in part, due to their antibacterial, antiviral, and antitumor properties.[1-3] The development of strategies for the formation of C-nucleoside analogues is a topic of current interest in organic synthesis.[4] In recent years we have reported the preparation of 4,6-*O*-benzylidene-3(2)-[bis(methylthio)methylene]-3(2)-deoxy-α-D-*erythro*-hexopyranosid-2(3)-uloses by reaction of carbanions generated from corresponding deoxyuloses with carbon disulfide.[5,6] These C-branched monosaccharides with push-pull functionality could be used as

☆ Dedicated to Professor Dr. *Ralf Miethchen* on the occasion of his 60th birthday.



Scheme 1

precursors for the syntheses of "inversed" C-nucleoside analogues (cf. 7,8). We describe herein the synthesis of such compounds with a pyrazole moiety based on tetrofuranos-4-yl and tetrenofuranos-4-yl substituted α-oxoketene-*S*,*S*-acetals from a deoxyhexofuranosulose and the corresponding α,β-unsaturated ulose derivative.

RESULTS AND DISCUSSION

The 3-*O*-benzylated ulose **1** was synthesized starting from D-glucose.[9-13] The preparation of the tetrofuranosyl substituted α-oxoketene-*S*,*S*-acetal **2** was performed using carbon disulfide, an excess of methyl iodide and potassium *tert*-butoxide as base in *N*,*N*-dimethylformamide and was carried out in a one-pot reaction without isolation

Table 1. ^{13}C chemical shifts of the sp^2-carbon atoms of compounds **2** and **7** (in ppm).

	C=O	–HC=	=C(SMe)$_2$
2	190.3	109.9	166.6
7	176.7	108.6	170.0

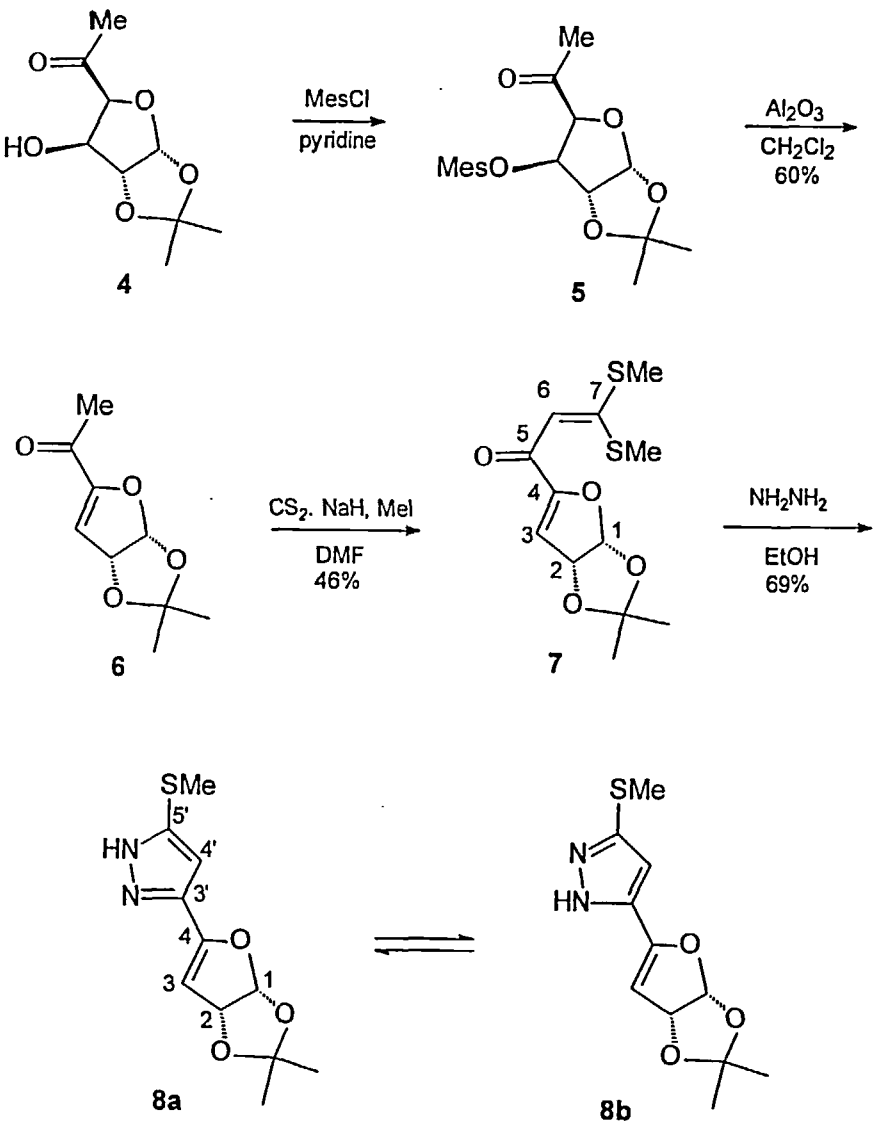
of the intermediate dithiolate (Scheme 1). Compound **2** could be isolated in 23% yield as a pale yellow syrup. The push-pull character of the α-oxoketene-*S*,*S*-acetal was confirmed by this yellow color and the characteristic alternating chemical shifts of the sp^2-carbon atoms [14] (Table 1).

Formation of different unisolated side products was the reason for a low yield. The main side reaction was the β-elimination to form the corresponding α,β-unsaturated ulose **6** (Scheme 2). Another side reaction was caused by utilization of an excess of methyl iodide resulting in an additional methylation at C-4 and C-6. However, the yield of the desired tetrofuranosyl substituted α-oxoketene-*S*,*S*-acetal **2** is much lower if only a quantitative amount of methyl iodide was used.

α-Oxoketen-*S*,*S*-acetals react easily with hydrazines to form pyrazoles.[15] One thiomethyl group is displaced by a substitution reaction and ring closure occurs through attack of the hydrazino group on the carbonyl C-atom with elimination of water. The reaction of tetrofuranosyl substituted α-oxoketene-*S*,*S*-acetal **2** was performed in ethanol at room temperature using hydrazine hydrate. After 48 h the TLC indicated the absence of starting material. The *iso*-C-nuleoside **3** could be isolated in a yield of 32%.

The tetrofuranos-4-yl substituted pyrazole **3** can exist in tautomeric forms **3a** and **3b** but a decision between them was not possible. Due to the fast NH-proton exchange, the atoms C-3' and C-5' appear as broad signals in the ^{13}C NMR spectrum. In compound **3** which can be seen as a C-nucleoside analogue, the furanose is linked to the heterocycle *via* a C-C single bond not at the anomeric position but at C-4.

Taking advantage of the easily occuring β-elimination of the ulose **1** to give the α,β-unsaturated ulose **6**, we carried out the preparation of the corresponding α-oxo-ketene-*S*,*S*-acetal **7**. In order to obtain the unsaturated ulose **6** in high yield we started from 6-deoxy-1,2-*O*-isopropylidene-3-*O*-mesyl-α-D-*xylo*-hexofuranos-5-ulose (**5**) pre-



Ms = mesyl

Scheme 2

pared by mesylation of the 6-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (4). Compound 4 was obtained by a procedure described by Ohle et al.[16-18] starting from D-glucose. Treatment of 5 with basic aluminium oxide in dichloromethane afforded the expected unsaturated sugar 6 in a yield of 60% (Scheme 2).

The reaction of the α,β-unsaturated ulose 6 with carbon disulfide and an excess of methyl iodide was performed in *N,N*-dimethylformamide using sodium hydride. The α-oxoketene-*S,S*-acetal 7 could be isolated in 46% yield as a pale yellow crystalline compound. The yield was much higher compared to the formation of 2 because no elimination reaction could occur.

The treatment of α-oxoketene-*S,S*-acetal 7 with hydrazine hydrate in ethanol at room temperature for 24 h yielded the moderately stable pyrazole 8 in 69% yield. Again, the assignment between the tautomeric forms 8a and 8b was impossible.

EXPERIMENTAL

General procedures. Melting points were measured with a Boëtius apparatus and are corrected. Specific rotations were determined with a Polar LμP polarimeter. IR spectra were recorded with a Nicolet 205 FT-IR spectrometer. ^{1}H NMR (300.13 and 250.13 MHz, respectively) and ^{13}C NMR (62.90 MHz) spectra were recorded on Bruker instruments ARX 300 and AC 250, respectively, with $CDCl_3$ as solvent. The calibration of spectra was carried out by means of solvent peaks ($CDCl_3$: δ ^{1}H= 7.25; δ ^{13}C= 77.0). The ^{13}C NMR signals were assigned by DEPT and/or ^{13}C ,^{1}H correlations. The mass spectra were recorded on an AMD 402/3 spectrometer (AMD Intectra GmbH). For chromatography Merck silica gel 60 (230-400 mesh) was used. TLC was performed on silica gel 60 GF_{254} (Merck) with detection by using UV-light and charring with sulfuric acid. Elemental analysis were performed on a Leco CHNS-932 instrument.

3-*O*- Benzyl- 6-deoxy- 1,2-*O*-isopropylidene- 7-*S*-methyl- 7-*C*-methylthio-7-thio-α-D-*xylo*-hept-6-enofuranos-5-ulose (2). A solution of 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (**1**,[9-13] 0.8 g, 2.7 mmol), carbon disulfide (0.3 mL, 5.0 mmol) and methyl iodide (0.6 mL, 9.6 mmol) in *N,N*-dimethylformamide (15 mL) was cooled to 0 °C. Then potassium *tert*-butoxide (1.2 g, 11.1 mmol) was added. The mixture was stirred for 20 min at 0 °C and 40 min at

room temperature, then poured into ice water and extracted with chloroform. The combined organic layers were washed with water, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (toluene/ethyl acetate 15:1) to give **2** as a yellow syrup (0.25 g, 23%); R_f = 0.33 (toluene/ethyl acetate 7:1); $[\alpha]_D^{24}$ -92.7 (*c* 1.0, chloroform); IR (capillar) 1639 (CO) cm^{-1}; ^1H NMR (250.13 MHz, $CDCl_3$): δ 7.40-7.10 (m, 5H, Ph); 6.54 (s, 1H, H-6); 6.05 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1); 4.70 (d, 1H, $J_{3,4}$ = 3.4 Hz, H-4); 4.55 (d, 1H, $J_{2,3}$ = 0 Hz, H-2); 4.50 (s, 2H, CH_2Ph); 4.31 (d, 1H, H-3); 2.49, 2.41 (2s, 6H, 2 SCH_3); 1.47, 1.31 (2s, 6H, $C(CH_3)_2$); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 190.3 (CO); 166.6 ($C(SCH_3)_2$); 137.4 (i-Ph); 128.3, 127.8 (*o*-, *m*-Ph); 127.8 (*p*-Ph); 112.2 ($C(CH_3)_2$); 109.9 (C-6); 105.7 (C-1); 84.8 (C-4); 83.6 (C-3); 82.6 (C-2); 73.0 (CH_2); 26.9, 26.4 ($C(CH_3)_2$); 17.1, 14.9 (2 SCH_3). MS, e.i. (*m/z*): 397 $[M+H]^+$. HRMS: Calcd for $C_{19}H_{24}O_5S_2$: 396.10651. Found: 396.10764.

3-*O*-Benzyl- 1,2-*O*-isopropylidene- 4*C*- (5-methylthiopyrazol-3-yl)- α-D-*xylo*-tetrofuranose (3). A solution of **2** (96 mg, 0.24 mmol) and hydrazine hydrate (0.3 mL, 6 mmol) in ethanol (15 mL) was stirred for 2 days at room temperature and then concentrated. The residue was purified by column chromatography (toluene/ethyl acetate 4:1) to yield **3** as a colourless syrup (28 mg, 32%); R_f = 0.26 (toluene/ethyl acetate 2:1); $[\alpha]_D^{24}$ -52.5 (*c* 1.0, chloroform); ^1H NMR (250.13 MHz, $CDCl_3$): δ 7.30-7.10 (m, 5H, Ph); 6.25 (s, 1H, H-4'); 6.01 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1); 5.26 (d, 1H, $J_{3,4}$ = 2.9 Hz, H-4); 4.69 (d, 1H, $J_{2,3}$ = 0 Hz, H-2); 4.47 (d, 1H, $J_{CH(a),CH(b)}$ = 11.6 Hz, CH_2Ph(a)); 4.30 (d, 1H, CH_2Ph(br)); 4.01 (d, 1H, H-3); 2.47 (1s, 3H, SCH_3); 1.52, 1.34 (2s, 6H, $C(CH_3)_2$); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 145.2, 140.8 (2 x br, C-3', C-5'); 136.7 (i-Ph); 128.5, 127.8 (o-, m-Ph); 128.1 (p-Ph); 112.0 ($C(CH_3)_2$); 106.1 (C-4'); 104.6 (C-1); 83.1 (C-3); 82.8 (C-2); 75.0 (C-4); 72.5 (CH_2); 26.8, 26.2 ($C(CH_3)_2$); 16.9 (SCH_3). MS, e.i. (*m/z*): 362 $[M]^+$. HRMS: Calcd for $C_{18}H_{22}N_2O_4S$: 362.13004. Found: 362.12882.

6-Deoxy-1,2-*O*-isopropylidene-3-*O*-mesyl-α-D-*xylo*-hexofuranos-5-ulose (5). A solution of 6-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranosid-5-ulose (**4**,[16-18] 1.14 g, 5.76 mmol) in pyridine (20 mL) was cooled to 0 °C. Then methanesulfonyl chloride (0.52 mL, 6.72 mmol) was added. The mixture was stirred for 30 min at 0 °C and afterwards for an additional 24 h at room temperature, then poured into ice water

and extracted with chloroform. The combined organic layers were washed with water, 10% hydrochloric acid, $NaHCO_3$ solution and water, dried (Na_2SO_4) and concentrated. The residue was crystallized from ethanol and yielded **5** as colourless needles (1.23 g, 76%): mp 83-85 °C; R_f = 0.61 (toluene/ethyl acetate 1:1); $[\alpha]_D^{23}$ -100.8 (*c* 1.0, $CHCl_3$), IR (KBr) 1737 (CO) cm^{-1}; ^1H NMR (250.13 MHz, $CDCl_3$): δ6.08 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1); 5.14 (d, 1H, $J_{3,4}$ = 3.4 Hz, H-4); 4.81 (d, 1H, $J_{2,3}$ = 0 Hz, H-2); 4.71 (d, 1H, H-3); 2.96 (s, 3H, SO_2CH_3); 2.29 (s, 3H, CH_3); 1.48, 1.32 (2s, 6H, $C(CH_3)_2$); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ205.2 (CO); 113.1 ($C(CH_3)_2$); 105.5 (C-1); 83.8 (C-3); 83.1 (C-2); 83.0 (C-4); 37.9 (SO_2CH_3); 28.1 (CH_3); 26.7, 26.2 ($C(CH_3)_2$). MS, e.i. (*m/z*): 265 $[M\text{-}CH_3]^+$.

Anal. Calcd for $C_{10}H_{16}O_7S$ (280.3): C, 42.85; H, 5.75; S, 11.44. Found: C, 42.80; H, 5.74; N; 7.47; S; 11.50.

3,6-Dideoxy-1,2-*O*-isopropylidene-α-D-*glycero*-hex-3-enofuranos-5-ulose (6). A mixture of **5** (0.4 g, 1.43 mmol) and aluminium oxide (11 g, activity AI) in dichloromethane (30 mL) was stirred vigorously for 30 min, then filtered through Celite, concentrated to yield **5** as a colourless syrup (0.16 g, 60%); R_f = 0.32 (toluene/ethyl acetate 7:1); $[\alpha]_D^{23}$ +24.9 (*c* 1.0, $CHCl_3$); ^1H NMR (300.13 MHz, $CDCl_3$): δ6.15 (d, 1H, $J_{1,2}$ = 5.3 Hz, H-1); 5.99 (d, 1H, $J_{2,3}$ = 2.7 Hz, H-3); 5.36 (dd, 1H, H-2); 2.33 (s, 3H, CH_3); 1.44, 1.42 (2s, 6H, $C(CH_3)_2$); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 190.9 (C-5); 156.0 (C-4); 113.4 ($C(CH_3)_2$); 109.1 (C-3); 106.6 (C-1); 83.2 (C-2); 28.2 (CH_3); 27.9, 27.6 ($C(CH_3)_2$). MS, e.i. (*m/z*): 184 $[M]^+$. HRMS: Calcd for $C_9H_{12}O_4$: 184.07356. Found: 184.06958.

3,6-Dideoxy- 1,2-*O*-isopropylidene- 7-*S*-methyl- 7-*C*-methylthio- 7-thio-α-D-*glycero*-hepto-3,6-dienofuranos-5-ulose (7) A suspension of sodium hydride (80%, 37 mg, 1.1 mmol) in heptane (2 mL) was stirred for 10 min. The solvent was decanted after the sodium hydride had settled. Then toluene (1 mL) was added and stirred for another 5 min. Afterwards a solution of **6** (100 mg, 0.54 mmol), carbon disulfide (0.065 mL, 1.09 mmol) and methyl iodide (2.17 mL, 3.47 mmol) in *N,N*-dimethylformamide (5 mL) was added. The mixture was stirred for 1 h, then poured into ice water and extracted with chloroform. The combined organic layers were washed with water, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (toluene/ethyl acetate 7:1). Recrystallization from

ethanol/water yielded **7** as pale yellow crystals (72 mg, 46%): mp 96 °C; R_f = 0.37 (toluene/ethyl acetate 7:1); $[\alpha]_D^{23}$ +25.1 (*c* 0.5, $CHCl_3$), IR (KBr) 1602 (CO) cm^{-1}; ^1H NMR (250.13 MHz, $CDCl_3$): δ 6.25 (s, 1H, H-6); 6.15 (d, 1H, $J_{1,2}$ = 5.2 Hz, H-1); 5.97 (d, 1H, $J_{2,3}$ = 2.5 Hz, H-3); 5.35 (dd, 1H, H-2); 2.51, 2.50 (2s, 6H, 2 SCH_3); 1.44, 1.43 (2s, 6H, $C(CH_3)_2$); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 176.7 (C-5); 170.0 ($C(SCH_3)_2$); 157.5 (C-4); 112.7 ($C(CH_3)_2$); 108.6 (C-6); 106.8 (C-1); 106.4 (C-3); 82.2 (C-2); 28.0, 27.7 $C(CH_3)_2$); 17.3, 15.1 (2 SCH_3). MS, e.i. (*m/z*): 288 $[M]^+$. HRMS: Calcd for $C_{12}H_{16}O_4S_2$: 288.04901. Found: 288.04762.

3-Deoxy-1,2-*O*-isopropylidene-4-*C*-(5-methylthiopyrazol-3-yl)-α-D-*glycero*-tetr-3-enofuranose (8). A solution of **7** (15 mg, 0.052 mmol) and hydrazine hydrate (3 mL, 0.061 mmol) in ethanol (3 mL) was stirred for 24 h at room temperature and then concentrated. The residue was purified by column chromatography (toluene/ethyl acetate 2:1) to give **8** as a colourless syrup (9 mg, 69%); R_f = 0.32 (toluene/ethyl acetate 2:1); ^1H NMR (250.13 MHz, $CDCl_3$): δ 6.47 (s, 1H, H-4'); 6.18 (d, 1H, $J_{1,2}$ = 5.2 Hz, H-1); 5.56 (d, 1H, $J_{2,3}$ = 2.6 Hz, H-3); 5.43 (dd, 1H, H-2); 2.49 (s, 3H, SCH_3); 1.46, 1.45 (2s, 6H, $C(CH_3)_2$); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 150.4, 149.9 (2br, C-3', C-5'); 112.8 ($C(CH_3)_2$); 106.2, 105.6 (C-1, C-4'); 98.4 (C-3); 83.8 (C-2); 28.0, 27.8 ($C(CH_3)_2$); 17.1(SCH_3). HRMS: Calcd for $C_{11}H_{14}O_3N_2S$: 254.07251. Found: 254.07118.

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