Synthesis and Reactions of Branched-chain Anhydrouloses with Push–Pull Functionality

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Abstract. The α-oxoketene dithioacetal **1** was demethylthiolated with sodium borohydride to give the branched chain anhydroulose **2** which yielded with amines the corresponding aminomethylene enuloses **3**, **4** and **5**. The heterocyclic anellated pyranose derivatives **6**, **7** and **8** were prepared by reaction of **2** with hydrazine hydrate, methylhydrazine and hydroxylamine, respectively. By treatment of methylthiomethylene enulose **18** with guanidine, acetamidine and benzamidine the pyrimidoanellated pyranose derivatives **12**–**14** have been obtained.

The development of new methods for the synthesis of anellated monosaccharide derivatives has attracted a current interest in the organic synthesis [1–4] because of the biological importance that some compounds of this class have shown, for example as antibiotics, cancerostatics [5–8] or as inhibitors of different glycosidases [9, 10].

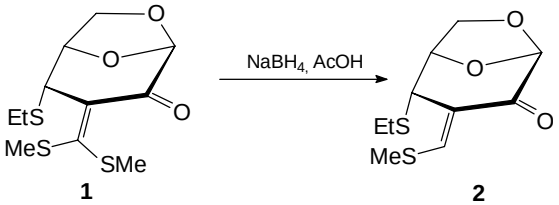
In the last few years levoglucosenone and its derivatives have been intensively used as chiral precursors for the synthesis of numerous natural products [11, 12] as well as special carbohydrate derivatives [13–17]. Some of them exhibit interesting biological properties [17, 18].

Continuing our studies on the chemistry of levoglucosenone we describe herein the stereoselective hydrodesulfurization reactions of α-oxoketene dithioacetals derived from this anhydrosugar to give uloses with push–pull functionality allowing the synthesis of several anellated pyranose derivatives.

In an earlier paper we reported that the α-oxoketene dithioacetal **1** reacted with hydrazine hydrate to provide a pyranopyrazol derivative [19]. However, the compound **1** underwent neither any reaction with simple *N*-nucleophiles (amines) nor with *C*-nucleophiles [20].

The low reactivity of **1** toward these reagents may be attributed to two factors. The first one is the relatively high stability of its push-pull system whereas the second one may be the steric hindrance towards a nucleophilic attack. According to the push-pull concept, the removal of one methylthio group may lead to a compound with higher electrophilic reactivity [21, 22].

The ulose **1** was demethylthiolated with sodium borohydride in acetic acid according to the procedure described by Junjappa and coworkers [23, 24]. This procedure has already been successfully used for the stereoselective hydrodesulfurization of uloses [25]. The conversion of **1** was completed in a few minutes. After column chromatography and recrystallization from ethanol yellowish needles could be isolated. The lack of a methylthio group and the appearance of an olefinic proton signal in the NMR spectrum showed that an hydrodesulfurization took place (Scheme 1). The NMR data also indicated that just one isomer had been isolated.



Scheme 1 Demethylthiolation of 1,6-Anhydro-3-[bis(methylthio)methylene]-3-deoxy-4-ethylthio-β-*D*-*erythro*-hexopyranos-2-ulose (**1**)

An X-ray structure analysis proved compound **2** to be the (*Z*) isomer (Figure 1).

As expected the reactions of **2** with *p*-anisidine, pyrrolidine and piperidine resulted in the straightforward substitution of the methylthio group leading to formation of the branched chain amino enuloses **3**, **4** and **5**. These structures were established by means of NMR and IR studies, mass spectra and elemental analyses. ^{1}H NMR measurements of compound **3** at higher temperature did not show any upfield shift for the NH signal at δ = 11.85 which indicates the existence of an intramolecular hydrogen bond. Therefore, the (*Z*) configuration for this compound can be assumed. Compounds

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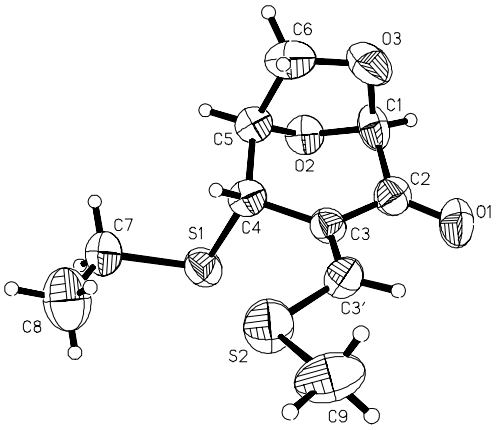
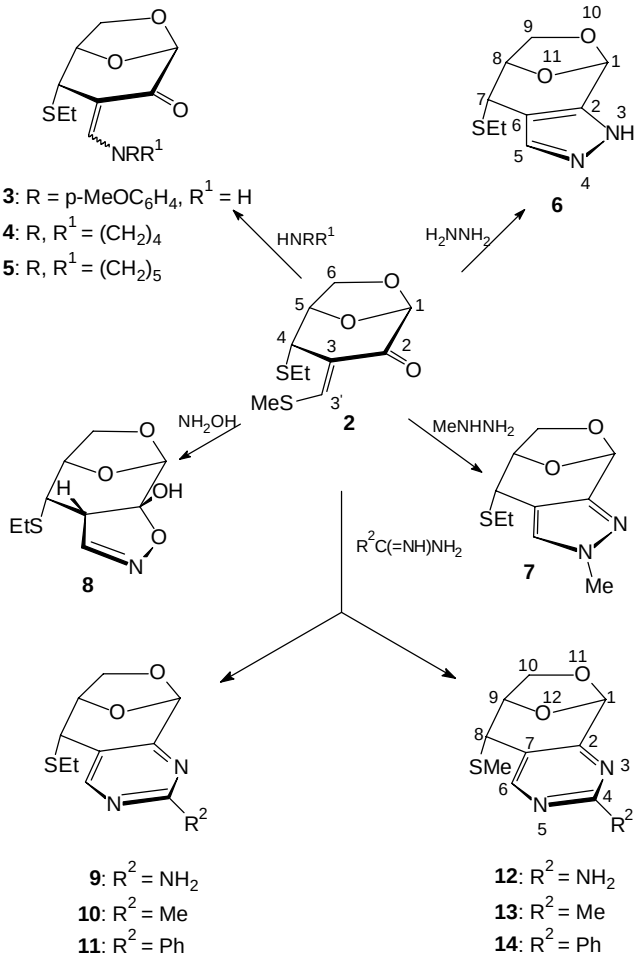


Fig. 1 ORTEP drawing of 1,6-Anhydro-3(*Z*)-[(methylthio) methylene]-3-deoxy-4-ethylthio-*β*-*D*-*erythro*-hexopyranos-2-ulose (**2**)

4 and **5** are not able to form any hydrogen bond. Hence, we tried to determine the configuration of these compounds by NOESY experiments, but we could not find any crucial correlation to make an exact statement about their configuration.



Scheme 2 Reaction of methylthiomethylene ulose **2**

In order to prepare heterocyclic anellated pyranose derivatives, the methylthiomethylene enulose **2** was treated with hydrazine hydrate, methylhydrazine and hydroxylamine, respectively. By this way, compounds **6**, **7** and **8** were obtained. The lack of a signal for the methylthio group in the NMR spectra of all these compounds and the disappearance of a carbonyl band in the IR spectra proved that a cyclization had taken place. The corresponding mass spectra showed the expected molecular peaks for these products.

The NMR spectra of the (1*R*,7*S*,8*R*)-3,4-diaza-10,11-dioxa-tricyclo [6.2.1.0^{2,6}]undeca-2(6),4-dien-7-yl-ethylthioether (**6**) permitted to assume that, in contrast to the already reported analogous compound ethyl-(1*R*,7*S*,8*R*)-5-methylthio-3,4-diaza-10,11-dioxa-tricyclo[6.2.1.0^{2,6}] undeca-2,5-dien-7-yl-thioether [19], just one of the two possible tautomers was formed. Both the NH and H-5 give rise to singlets in the ^{1}H NMR spectrum. A proton at N-4 instead of N-3 should cause a CH-NH coupling as seen for compound **3**.

The position of the methyl group in the ethyl-(1*R*,7*S*, 8*R*)-4-methyl-10,11-dioxa-3,4-diaza-tricyclo[6.2.1.0^{2,6}] undeca-2,5-dien-7-yl-thioether (**7**) was determined on the basis of an NOE experiment. Irradiating the frequency of the methyl group enhanced the intensity of the H-5 signal in the ^{1}H spectrum. Thus, it can be concluded that the methyl group has to be bound to N-4.

In contrast to these reactions, the treatment of compound **2** with hydroxylamine occurred without loss of water and yielded only one stereoisomer. The spectroscopic and analytical data of the isolated (1*R*,2*R*,6*S*,7*S*, 8*R*)-7-ethylthio-4-aza-3,10,11-trioxa-tricyclo[6.2. 1.0^{2,6}] undec-4-en-2-ol (**8**) are in agreement with this structure. The configurations at C-2 and C-6 (*R* and *S*, respectively) were determined on the basis of an X-ray crystal structure investigation (Figure 2).

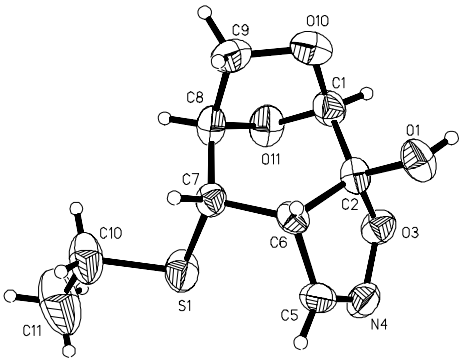
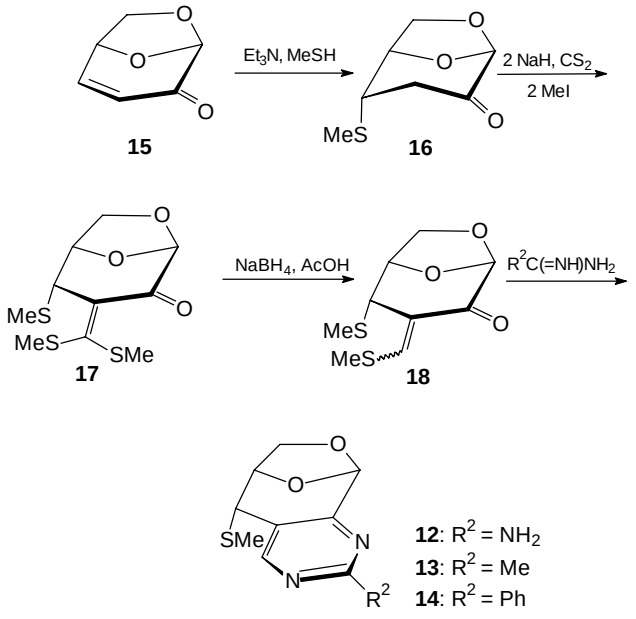


Fig. 2 ORTEP drawing of (1*R*,2*R*,6*S*,7*S*,8*R*)-7-Ethylthio-4-aza-3,10,11-trioxa-tricyclo[6.2.1.0^{2,6}]undec-4-en-2-ol (**8**)

Similarly, the ulose **2** was reacted with guanidine, acetamidine and benzamidine in order to synthesize the corresponding pyrimidoanellated pyranosides. Spectros-

copic investigations of the isolated products proved in all cases the formation of mixtures of compounds **9**–**11** and **12**–**14**, respectively. The two components of the mixtures could not be separated. In the NMR spectra almost all signals were doubled and mass spectra showed the characteristic molecular peaks of both components. The formation of these mixtures from the ulose **2** could be explained with the following reaction steps. The addition of guanidine and amidines, respectively, to the C3–C3' double bond of compound **2** was followed under the basic reaction conditions by elimination of ethanethiol to give a C3–C4 unsaturated anhydroulose. This could add ethanethiol or methanethiol to furnish the corresponding saturated 4-ethylthio- and 4-methylthiouloses, respectively. Regeneration of the C3–C3' double bond by elimination of methanethiol and cyclization involving the amino and the carbonyl group yielded then the mixtures of pyrimidoanellated pyranosides **9**–**11** and **12**–**14**, respectively.

In order to avoid the formation of these mixtures, we prepared the methylthiomethylene enulose **18** with a methylthio group in position 4 of the sugar pyran ring (Scheme 3).



Scheme 3 Preparation of pyrimidine derivatives **12**–**14**

The ulose **16** was prepared from levoglucosenone **15** by reaction with methanethiol according to the procedure described by Essig [26]. The α-oxoketene dithioacetal **17** was obtained in a similar way as described for the analogous compound **1** in 62% yield [19]. The synthesis of the methylthiomethylene enulose **18** was achieved by hydrodesulfurization of **17** analogously to the preparation of compound **2**. The structure of compound **18** was determined by NMR, IR and mass spectra. The corresponding spectral data of **18** are almost identical with those of **2**. But, it was not possible to establish the (*E*) or (*Z*) configuration for this compound. In contrast to **2**, it was not possible to obtain a suitable crystal for X-ray structure analysis. On the other hand, NOE experiments did not give a clear information about the configuration at the exocyclic double bond.

Finally, the reactions with guanidine, acetamidine and benzamidine were repeated with the anhydroulose **18** giving the pyrimidine derivatives **12**–**14** in pure form. The spectroscopic data prove the structures **12**–**14**. The mass spectra showed the expected molecular peaks. Neither in the ^{13}C NMR nor in the IR spectra a carbonyl signal was observed. The signal of just one methylthio group, the typical signals of a pyrimidine moiety and an amino, a methyl or a phenyl group appeared in the ^{1}H and ^{13}C NMR spectra.

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Experimental

Melting points were determined with a Boëtius apparatus and are corrected. IR spectra were recorded with a Nicolet 205 FT-IR spectrometer. Specific optical rotations were measured with a Gyromat HP (Dr. Kernchen). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker instruments ARX 300 and AC 250 with $CDCl_3$ or DMSO-d_6 as solvents. The calibration of spectra was carried out by means of solvent peaks (DMSO-d_6: δ ^{1}H= 2.50; δ ^{13}C= 39.7; $CDCl_3$: δ ^{1}H= 7.25; δ ^{13}C= 77.0). The assignment of signals was confirmed by DEPT and/or ^{1}H,^{13}C COSY experiments. 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 charring with sulfuric acid. Elemental analyses were performed on a Leco-CHNS-932 instrument. Table 1 provides a summary of the crystallographic data of compounds **2** and **8**. The crystals were sealed onto a glass fiber and mounted on a Siemens P4 automated four circle diffractometer ($Mo_{K\alpha}$ radiation; λ = 0.71073 Å; T = 298 K). The structures were solved by direct methods (SHELXS-86, G.M. Sheldrick, Universität Göttingen, 1986 for **2** and Siemens SHELXTL-version 4.2 for MS-DOS, Siemens Analytical Xray Inst. Inc.) and refined by the full-matrix least-squares method of SHELXL-97. Non-H atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed into theoretical positions and were refined by using the riding model.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary

Table 1 Crystal data and structure refinement data for **2** and **8**

Identification code	**2**	**8**
Empirical formula	$C_{10}H_{14}O_3S_2$	$C_9H_{13}NO_4S$
Formula weight	246.33	231.26
Temperature [K]	293(2)	293(2)
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
Unit cell dimensions	a = 5.5320(10) Å	a = 7.5110(10) Å
	b = 8.664(3) Å	b = 9.880(3) Å
	c = 24.746(11) Å	c = 14.121(2) Å
	α = 90°.	α = 90°.
	β = 90°.	β = 90°.
	γ = 90°.	γ = 90°.
Volume [Å^3]	1186.1(7)	1047.9(4)
Z	4	4
Density (calculated) [Mg/m^3]	1.380	1.466
Absorption coefficient [mm^{-1}]	0.433	0.303
F(000)	520	488
Crystal size [mm^3]	0.52 × 0.12 × 0.1	0.24 × 0.24 × 0.16
Θ range for data collection [°]	2.49 to 21.99	2.52 to 21.97
Index ranges	−5 <= h <= 5,	−7 <= h <= 7,
	−9 <= k <= 9,	−10 <= k <= 10,
	−26 <= l <= 26	−14 <= l <= 14
Reflections collected	1767	1536
Independent reflections	1450 [R(int) = 0.0624]	1276 [R(int) = 0.0362]
Completeness to Θ = 21.97°	99.9%	100%
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	1450/0/136	1276/0/136
Goodness-of-fit on F^2	1.084	1.003
Final R indices [I>2σ(I)]	R1 = 0.0573	R1 = 0.0509
	wR2 = 0.1206	wR2 = 0.1150
R indices (all data)	R1 = 0.0830	R1 = 0.0621
	wR2 = 0.1337	wR2 = 0.1215
Absolute structure parameter	−0.3(2)	0.1(2)
Largest diff. peak and hole [e.Å^{-3}]	0.304 and −0.183	0.156 and −0.172

publication no. CCDC-137931 for **2** and CCDC-137932 for **8**. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: int. code +(1223) 336-033; e-mail: deposit@ccdc.cam.ac.uk).

1,6-Anhydro-3-[bis(methylthio)methylene]-3-deoxy-4-methylthio-β-D-erythro-hexopyranos-2-ulose (**17**)

was prepared according to the literature procedure [19] Yellow syrup; yield 173 mg (62%). – $[\alpha]_D^{25.9}$ = – 253° (*c* 1.0, chloroform). – ^{1}H NMR (250.1 MHz, $CDCl_3$): δ/ppm = 2.21 (s, 3H, SCH_3), 2.46 (s, 3H, SCH_3), 2.48 (s, 3H, SCH_3), 3.77 (dd, 1H, J_{5-6b} = 1.5Hz, H-6b), 3.94 (dd, 1H, J_{6a-6b} = 7.6 Hz, J_{5-6a} = 5.8 Hz, H-6a), 4.26 (d, 1H, J_{4-5} = 0.9 Hz, H-4), 4.86 (m, 1H, H-5), 5.24 (s, 1H, H-1). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ/ppm = 186.2 (C-2), 161.3 (C-3'), 129.0 (C-3), 101.3 (C-1), 77.9 (C-5), 67.7 (C-6), 52.4 (C-4), 19.9, 18.5, 14.6 (3 SCH_3). – IR(KBr): $\tilde{\nu}_{max}$/cm^{-1} = 1669 (C=O), 1472 (C=C). – MS (CI): *m/z* (%) = 278.8 (51, $M^{+\cdot}$), 230.9 (100).

$C_{10}H_{14}O_3S_3$	Calcd.:	C 43.14	H 5.07 S 34.55
(278.40)	Found:	C 43.73	H 4.95 S 33.97.

Reduction of the α-Oxoketene Dithioacetals 1 and 17 (General Procedure)

1,6-Anhydro-3-[bis(methylthio)methylene]-3-deoxy-4-ethylthio-*β-D-erythro*-hexopyranos-2-ulose (**1**, 292 mg, 1 mmol) or 1,6-anhydro-3-[bis(methylthio)methylene]-3-deoxy-4-methylthio-*β-D-erythro*-hexopyranos-2-ulose (**17**, 278 mg, 1 mmol) were dissolved in anhydrous acetic (20 mL) and sodium tetrahydridoborate (190 mg, 5 mmol) was added. After completion of the reaction (approximately 15 min), the solution was diluted with chloroform (50 mL) and poured into a saturated aqueous $NaHCO_3$ solution (150 mL) under vigorous stirring. The organic layer was separated, the aqueous phase was extracted with chloroform (2 × 50 mL) and washed with water (2 × 50 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The compounds were purified by column chromatography (toluene/ethyl acetate 8:1) and recrystallized from ethanol.

1,6-Anhydro-3(Z)-[(methylthio)methylene]-3-deoxy-4-ethylthio-β-D-erythro-hexopyranos-2-ulose (**2**)

Yellow needles; yield 129 mg (52%). *m.p.* 53–55 °C. – $[\alpha]_D^{25.9}$ = – 909.9° (*c* 0.5, chloroform). – ^{1}H NMR (300.1 MHz, $CDCl_3$): δ/ppm = 1.27 (t, 3H, *J* = 7.5 Hz, $SCH_2C\underline{H}_3$), 2.49 (s, 3H, SCH_3), 2.69 (m, 2H, SCH_2), 3.60 (br, 1H, H-4), 3.76 (dd, 1H, J_{5-6b} = 1.6 Hz, H-6b), 3.95 (dd, 1H, J_{6a-6b} = 7.8 Hz, J_{5-6a} = 5.7 Hz, H-6a), 4.82 (m, 1H, H-5), 5.22 (s, 1H, H-1), 7.86 (d, 1H, $J_{3'-4}$ = 1.1 Hz, H-3'). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ/ppm = 184.2 (C-2), 151.6 (C-3'), 124.8 (C-3), 100.9 (C-1), 78.5 (C-5), 68.1 (C-6), 47.5 (C-4), 25.3 (SCH_2), 18.2 (SCH_3),

14.5 ($SCH_2\underline{C}H_3$). – IR(KBr): $\tilde{\nu}_{max}/cm^{-1}$ = 1688 (C=O), 1541 (C=C). – MS (70 eV, EI): *m/z* (%) = 246.0 (58, $M^{+\cdot}$), 185.1 (100).

$C_{10}H_{14}O_3S_2$ (246,34) Calcd.: C 48.76 H 5.73 S 26.03 Found: C 49.23 H 5.96 S 25.22.

1,6-Anhydro-[(methylthio)methylene]-3-deoxy-4-methylthio-β-D-erythro-hexopyranos-2-ulose (**18**)

Yellow needles; yield 119 mg (51%); *m.p.* 91–93 °C. – $[\alpha]_D^{23.7}$ = – 1093.0° (*c* 0.2, chloroform). – ^{1}H NMR (300.1 MHz, $CDCl_3$): δ/ppm = 2.19 (s, 3H, SCH_3), 2.52 (s, 3H, SCH_3), 3.54 (br, 1H, H-4), 3.79 (dd, 1H, J_{5-6b} = 1.5 Hz, H-6b), 3.97 (dd, 1H, J_{6a-6b} = 7.8 Hz, J_{5-6a} = 5.7 Hz, H-6a), 4.89 (dt, 1H, H-5), 5.25 (s, 1H, H-1), 7.94 (d, 1H, $J_{3'-4}$ = 1.3 Hz, H-3'). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ/ppm = 184.2 (C-2), 151.9 (C-3'), 124.2 (C-3), 100.8 (C-1), 78.9 (C-5), 68.1 (C-6), 47.9 (C-4), 18.3, 13.9 (2 SCH_3). – IR(KBr): $\tilde{\nu}_{max}/cm^{-1}$ = 1684 (C=O), 1541 (C=C). – MS (70 eV, EI): *m/z* (%) = 231.9 (37, $M^{+\cdot}$), 184.8 (100).

$C_9H_{12}O_3S_2$ (232.31) Calcd.: C 46.53 H 5.21 S 27.60 Found: C 46.26 H 5.20 S 25.48.

Synthesis of the Enamines 3–5 (General Procedure)

To a solution of 1,6-anhydro-3(*Z*)-[(methylthio)methylene]-3-deoxy-4-ethylthio-*β-D-erythro*-hexopyranos-2-ulose (**2**, 123 mg, 0.5 mmol) in ethanol (10 mL) the corresponding amine (0.5 mmol) was added. The solution was heated under reflux for 10 min. Afterwards the reaction solution was concentrated and the compound was recrystallized from ethanol.

1,6-Anhydro-3(Z)-(p-anisidino-methylene)-3-deoxy-4-ethylthio-β-D-erythro-hexopyranos-2-ulose (**3**)

Yellow needles; yield 110 mg (69%); *m.p.* 128–130 °C. – $[\alpha]_D^{23.7}$ = – 680.9° (*c* 0.5, chloroform). – ^{1}H NMR (250.1 MHz, $CDCl_3$): δ/ppm = 1.28 (t, 3H, *J* = 7.4 Hz, $SCH_2C\underline{H}_3$), 2.70 (m, 2H, SCH_2), 3.57 (br, 1H, H-4), 3.71 (dd, 1H, J_{5-6b} = 1.5 Hz, H-6b), 3.77 (s, 3H, OCH_3), 3.96 (dd, 1H, J_{6a-6b} = 7.6 Hz, J_{5-6a} = 6.1 Hz, H-6a), 4.86 (ddd, 1H, J_{4-5} = 1.2 Hz H-5), 5.21 (s, 1H, H-1), 6.86 (m, 2H, C_6H_4), 7.01 (m, 2H, C_6H_4), 7.57 (d, 1H, $J_{3'-NH}$ = 12.8 Hz, H-3'), 11.85 (d, 1H, NH). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ/ppm = 188.7 (C-2), 156.9 (*p*-C_6H_4(NH)), 150.2 (C-3'), 132.8 (*i*-C_6H_4(NH)), 118.4 (*o*-C_6H_4(NH)), 114.9 (*m*-C_6H_4(NH)), 100.5 (C-1), 97.0 (C-3), 77.4 (C-5), 67.8 (C-6), 55.5 (OMe), 46.2 (C-4), 24.6 (SCH_2), 14.6 ($SCH_2\underline{C}H_3$). – IR(KBr): $\tilde{\nu}_{max}/cm^{-1}$ = 3447 (NH), 1646 (C=O), 1572 (C=C). – MS (70 eV, EI): *m/z* (%) = 321.3 (4, $M^{+\cdot}$), 259.1 (100).

$C_{16}H_{19}NO_4S$ (321.39) Calcd.: C 59.80 H 5.96 N 4.36 S 9.98 Found: C 59.53 H 5.94 N 4.56 S 9.89.

1,6-Anhydro-3-deoxy-4-ethylthio-3-(pyrrolidino-methylene)-β-D-erythro-hexopyranos-2-ulose (**4**)

White needles; yield 92 mg (69%); *m.p.* 103–105 °C. – $[\alpha]_D^{25.8}$ = – 337.6° (*c* 0.5, chloroform). – ^{1}H NMR (250.1 MHz, $CDCl_3$): δ/ppm = 1.24 (t, 3H, *J* = 7.3 Hz, CH_3), 1.92 (m, 4H, N–$CH_2C\underline{H}_2$), 2.67 (m, 2H, SCH_2), 3.54 (m, 4H, NCH_2), 3.75 (dd, 1H, J_{5-6b} = 1.5 Hz, H-6b), 3.82 (br, 1H, H-4), 3.93 (dd, 1H, J_{6a-6b} = 7.5 Hz, J_{5-6a} = 5.8 Hz, H-6a), 4.77 (dt, 1H, J_{4-5} = 1.2 Hz H-5), 5.17 (s, 1H, H-1), 7.81 (s, 1H, H-3'). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ/ppm = 186.8 (C-2), 148.7 (C-3'), 101.7 (C-1), 95.0 (C-3), 77.1 (C-5), 67.3 (C-6), 52.2 (br, NCH_2), 45.2 (C-4), 25.2 (br, $NCH_2\underline{C}H_2$), 24.2 (SCH_2), 14.5 (CH_3). – IR(KBr): $\tilde{\nu}_{max}/cm^{-1}$ = 1656 (C=O), 1555, 1548 (C=C). – MS (70 eV, EI): *m/z* (%) = 268.9 (3, $M^{+\cdot}$), 177.9 (100).

$C_{13}H_{19}NO_3S$ (269.35) Calcd.: C 57.97 H 7.11 N 5.20 S 11.90 Found: C 57.76 H 7.04 N 5.33 S 11.65.

1,6-Anhydro-3-deoxy-4-ethylthio-3-(piperidino-methylene)-β-D-erythro-hexopyranos-2-ulose (**5**)

White needles; yield 110 mg (78%); *m.p.* 165–167 °C. – $[\alpha]_D^{25.3}$ = – 85.0° (*c* 1.0, chloroform). – ^{1}H NMR (250.1 MHz, $CDCl_3$): δ/ppm = 1.24 (t, 3H, *J* = 7.3 Hz, CH_3), 1.67 (m, 6H, N–$CH_2C\underline{H}_2C\underline{H}_2$), 2.64 (m, 2H, SCH_2), 3.55 (m, 4H, NCH_2), 3.63 (br, 1H, H-4), 3.75 (dd, 1H, J_{5-6b} = 1.5 Hz, H-6b), 3.93 (dd, 1H, J_{6a-6b} = 7.6 Hz, J_{5-6a} = 5.8 Hz, H-6a), 4.78 (dt, 1H, J_{4-5} = 1.2 Hz, H-5), 5.19 (s, 1H, H-1), 7.57 (s, 1H, H-3'). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ/ppm = 187.0 (C-2), 150.3 (C-3'), 101.8 (C-1), 93.5 (C-3), 77.4 (C-5), 67.3 (C-6), 53.3 (br, NCH_2), 46.4 (C-4), 26.5 ($NCH_2\underline{C}H_2$), 24.6 (SCH_2), 23.8 (br, $N(CH_2)_2\underline{C}H_2$), 14.5 ($CH_3$). – IR(KBr): $\tilde{\nu}_{max}/cm^{-1}$ = 1655 (C=O), 1550 (C=C). – MS (70 eV, EI): *m/z* (%) = 283.4 (2, $M^{+\cdot}$), 222.2 (100).

$C_{14}H_{21}NO_3S$ (283.38) Calcd.: C 59.34 H 7.47 N 4.94 S 11.31 Found: C 58.80 H 7.05 N 5.28 S 11.32.

Synthesis of the Pyrazol and Isoxazol Derivatives 6, 7 and 8 (General Procedure)

To a solution of ulose **2** (123 mg, 0.5 mmol) in ethanol (10 mL) hydrazine, methylhydrazine and hydroxylamine, respectively, (3.0 mmol) were added. The solution was stirred for 10 min at room temperature. Afterwards the reaction solution was concentrated and the compounds were purified by column chromatography (toluene/ethyl acetate 1:1). Compound **8** was recrystallized from ethanol.

(1R,7S,8R)-3,4-Diaza-10,11-dioxa-tricyclo[6.2.1.0^{2,6}]undeca-2(6),4-dien-7-yl-ethyl-thioether (**6**)

Colourless syrup; yield 51 mg (48%). – $[\alpha]_D^{23.4}$ = – 79.4° (*c* 1.0, chloroform). – ^{1}H NMR (250.1 MHz, $CDCl_3$): δ/ppm = 1.24 (t, 3H, *J* = 7.3 Hz, CH_3), 2.62 (m, 2H, SCH_2), 3.57 (dd, 1H, J_{8-9b} = 2.2 Hz, H-9b), 3.76 (br s, 1H, H-7), 4.07 (dd, 1H, J_{9a-9b} = 7.9 Hz, J_{8-9a} = 6.7 Hz, H-9a), 4.86 (ddd, 1H, J_{7-8} = 0.9 Hz, H-8), 6.22 (s, 1H, H-1), 7.48 (s, 1H, H-5). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ/ppm = 147.9 (C-2), 127.9 (C-5), 111.1 (C-6), 96.5 (C-1), 77.6 (C-8), 67.5 (C-9), 41.6 (C-7), 24.7 (SCH_2), 13.6 (CH_3). – IR(capillary): $\tilde{\nu}_{max}/cm^{-1}$ = 3207 (NH), 1571, 1473 (C=N, C=C). – MS (70 eV, EI): *m/z* (%) = 212.1 (52, $M^{+\cdot}$), 121.2 (100).

$C_9H_{12}N_2O_2S$ (212.26) Calcd.: C 50.93 H 5.70 N 13.20 S 15.10.

$C_9H_{12}N_2O_2S \cdot H_2O$ (230.28)
Calcd.: C 46.94 H 6.13 N 12.16 S 13.92
Found: C 47.62 H 5.88 N 12.38 S 14.18.

Ethyl-(1R,7S,8R)-4-methyl-3,4-diaza-10,11-dioxa-tricyclo[6.2.1.0^{2,6}]undeca-2,5-dien-7-yl-thioether (**7**)

Colourless syrup; yield 67 mg (60%). – $[\alpha]_D^{23.4}$ = – 83.1° (*c*

0.5, chloroform). – ^{1}H NMR (250.1 MHz, $CDCl_3$): δ/ppm = 1.22 (t, 3H, J = 7.4 Hz, CH_3), 2.60 (m, 2H, SCH_2), 3.55 (dd, 1H, J_{8-9b} = 2.2 Hz, H-9b), 3.69 (br s, 1H, H-7), 3.82 (s, 3H, NCH_3), 4.03 (dd, 1H, J_{9a-9b} = 7.9 Hz, J_{8-9a} = 6.5 Hz, H-9a), 4.80 (ddd, 1H, J_{7-8} = 0.9 Hz, H-8), 6.12 (s, 1H, H-1), 7.23 (s, 1H, H-5). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ/ppm = 148.3 (C-2), 128.9 (C-5), 111.3 (C-6), 96.6 (C-1), 77.4 (C-8), 67.4 (C-9), 41.6 (C-7), 38.9 (NCH_3), 24.7 (SCH_2), 14.5 (CH_3). – IR(capillary): $\tilde{\nu}_{max}$/cm^{-1} = 1564, 1475 (C=N, C=C). – MS (iso-butane, CI): *m/z* (%) = 227.0 (100, $[M+1]^{+\cdot}$).

$C_{10}H_{14}N_2O_2S$	Calcd.:	C 53.08	H 6.24	N 12.38	S 14.17
(226.29)	Found:	C 51.92	H 5.84	N 12.75	S 13.72.

(1R,2R,6S,7S,8R)-7-Ethylthio-4-aza-3,10,11-trioxa-tricyclo[6.2.1.0^{2,6}]undec-4-en-2-ol (**8**)

White crystals; yield 58 mg (50%); *m.p.* 166–168 °C. – $[\alpha]_D^{22.1}$ = + 40.6° (*c* 0.5, DMSO). – ^{1}H NMR (250.1 MHz, DMSO-d_6): δ/ppm = 1.14 (t, 3H, J = 7.4 Hz, CH_3), 2.55 (m, 2H, SCH_2), 3.35 (d, 1H, H-7), 3.50 (dd, 1H, J_{6-7} = 10.0 Hz, J_{5-6} = 2.2 Hz, H-6), 3.65–3.82 (m, 2H, H-9b, H-9a), 4.53 (dd, 1H, J_{8-9a} = 5.8 Hz, J_{8-9b} = 2.7 Hz, H-8), 5.23 (s, 1H, H-1), 6.73 (s, 1H, OH), 7.42 (d, 1H, H-5). – ^{13}C NMR (75.5 MHz, DMSO-d_6): δ/ppm = 149.1 (C-5), 99.0 (C-2), 98.1 (C-1), 75.8 (C-8), 66.7 (C-9), 49.9 (C-6), 43.4 (C-7), 25.3 (SCH_2), 14.6 (CH_3). – IR(KBr): $\tilde{\nu}_{max}$/cm^{-1} = 3236 (OH), 1599 (C=N). – MS (70 eV, EI): *m/z* (%) = 230.9 (0.5, $M^{+\cdot}$), 96.9 (100).

$C_9H_{13}NO_4S$	Calcd.:	C 46.74	H 5.67	N 6.06	S 13.86
(231.26)	Found:	C 46.40	H 5.51	N 6.22	S 13.27.

Synthesis of Pyrimidine Derivatives 12 – 14 (General Procedure)

Sodium (23 mg, 1 mmol) was dissolved in anhydrous ethanol (10 mL), 1 mmol of the guanidine carbonate, acetamidine hydrochloride and benzamidine hydrochloride, respectively, was added and the solution was stirred approximately for 30 min until the corresponding sodium salt precipitated. The solution was decanted, 0.7 mL of this solution were added to a solution of **18** (116 mg, 0.5 mmol) in ethanol (10 mL). The mixture was stirred at room temperature until completion of the reaction (monitored by thin layer chromatography). Afterwards the solvent was eliminated under reduced pressure and the raw compounds purified by column chromatography (toluene/ethyl acetate 1:2 for **12**, **13** and 15:1 for **14**). Compound **12** could be recrystallized from ethanol.

(1R,8S,9R)-8-Methylthio-3,5-diaza-11,12-dioxa-tricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-trien-4-amine (**12**)

White crystals; yield 52 mg (46%); *m.p.* 165–167 °C. – $[\alpha]_D^{23.4}$ = – 13.0° (*c* 1.0, chloroform). – ^{1}H NMR (250.1 MHz, $CDCl_3$): δ/ppm = 2.13 (s, 3H, SCH_3), 3.55 (br s, 1H, H-8), 3.60 (dd, 1H, J_{9-10b}= 1.8 Hz, H-10b), 4.05 (dd, 1H, $J_{10a-10b}$ = 7.9 Hz, J_{9-10a} = 6.1 Hz, H-10a), 4.99 (ddd, 1H, J_{8-9} = 0.8 Hz, H-9), 5.17 (br, 2H, NH_2), 5.72 (s, 1H, H-1), 8.38 (s, 1H, H-6). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ/ppm = 162.5, 162.1 (C-2, C-4), 160.7 (C-6), 113.4 (C-7), 99.9 (C-1), 78.6 (C-9), 68.0 (C-10), 43.6 (C-8), 13.5 (SCH_3). – IR(KBr): $\tilde{\nu}_{max}$/cm^{-1} = 3334, 3175 (NH_2), 1618, 1601, 1558 (C=N, C=C). – MS (isobutane, CI): *m/z* (%) = 226.0 (100, $[M+1]^+$).

$C_9H_{12}N_3O_2S$	Calcd.:	C 47.99	H 4.92	N 18.65	S 14.23
(225.26)	Found:	C 47.34	H 5.07	N 17.96	S 13.91.

Methyl-(1R,8S,9R)-4-methyl-3,5-diaza-11,12-dioxa-tricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-trien-8-yl-thioether (**13**)

Colourless syrup; yield 57 mg (51%). – $[\alpha]_D^{22.9}$ = – 253.8° (*c* 0.5, chloroform). – ^{1}H NMR (250.1 MHz, $CDCl_3$): δ/ppm = 2.12 (s, 3H, SCH_3), 2.71 (s, 3H, CH_3), 3.60 (dd, 1H, J_{9-10b} = 1.8 Hz, H-10b), 3.62 (br s, 1H, H-8), 4.08 (dd, 1H, $J_{10a-10b}$ = 7.9 Hz, J_{9-10a} = 6.1 Hz, H-10a), 5.04 (ddd, 1H, J_{8-9} = 0.8 Hz, H-9), 5.92 (s, 1H, H-1), 8.73 (s, 1H, H-6). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ/ppm = 167.3, 161.2 (C-2, C-4), 159.2 (C-6), 121.4 (C-7), 99.9 (C-1), 78.6 (C-9), 68.2 (C-10), 43.3 (C-8), 25.7 (CH_3), 13.6 (SCH_3). – IR(capillary): $\tilde{\nu}_{max}$/cm^{-1} = 1585, 1556 (C=N, C=C). – MS (70 eV, EI): *m/z* (%) = 223.8 (67, M^+), 145.9 (100).

$C_{10}H_{12}N_2O_2S$	Calcd.:	C 53.55	H 5.39	N 12.49	S 14.29.
(224.28)					
$C_{10}H_{12}N_2O_2S \cdot H_2O$ (242.29)					
Calcd.:		C 49.57	H 5.82	N 11.56	S 13.23
Found:		C 50.37	H 5.77	N 11.46	S 13.46.

Methyl-(1R,8S,9R)-4-phenyl-3,5-diaza-11,12-dioxa-tricyclo[7.2.1.0^{2,7}]dodeca-2,4,6-trien-8-yl-thioether (**14**)

Colourless syrup; yield 64 mg (45%). – $[\alpha]_D^{23.6}$ = – 214.1° (*c* 0.5, chloroform). – ^{1}H NMR (250.1 MHz, $CDCl_3$): δ/ppm = 2.14 (s, 3H, SCH_3), 3.64 (dd, 1H, J_{9-10b} = 1.8 Hz, H-10b), 3.69 (m, 1H, H-8), 4.11 (dd, 1H, $J_{10a-10b}$ = 7.9 Hz, J_{9-10a} = 6.1 Hz, H-10a), 5.07 (ddd, 1H, J_{8-9} = 0.8 Hz, H-9), 6.05 (s, 1H, H-1), 7.48 (m, 3H, *m*-Ph, *p*-Ph), 8.45 (m, 2H, *o*-Ph), 8.89 (s, 1H, H-6). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ/ppm = 163.6, 161.5 (C-2, C-4), 159.5 (C-6), 122.2 (C-7), 137.0 (*i*-Ph), 131.0 (*p*-Ph), 128.6, 128.4, (*o*-Ph, *m*-Ph), 100.1 (C-1), 78.8 (C-9), 68.2 (C-10), 43.5 (C-8), 13.5 (SCH_3). – IR(capillary): $\tilde{\nu}_{max}$/cm^{-1} = 1582, 1548, 1474 (C=N, C=C). – MS (70 eV, EI): *m/z* (%) = 286.0 (28, M^+), 209.1 (100).

$C_{15}H_{14}N_2O_2S$	Calcd.:	C 62.92	H 4.93	N 9.78	S 11.20
(286.34)	Found:	C 62.35	H 5.33	N 9.58	S 10.98.

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