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NMR Investigation of a Rearrangement Mechanism at Branched-chain Uloses using ^{13}C-Labeling [1])

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Dedicated to Prof. Dr. H. Dehne on the Occasion of his 60th Birthday

Push-pull substituted alkenes have often been used for the synthesis of ketene-*N,N*-acetals and substituted *N*-heterocycles. Thus, α-oxoketene dithioacetals reacted with several amines to give, by replacement of alkyl thio groups, the corresponding *N, S*- and *N,N*-acetals [1].

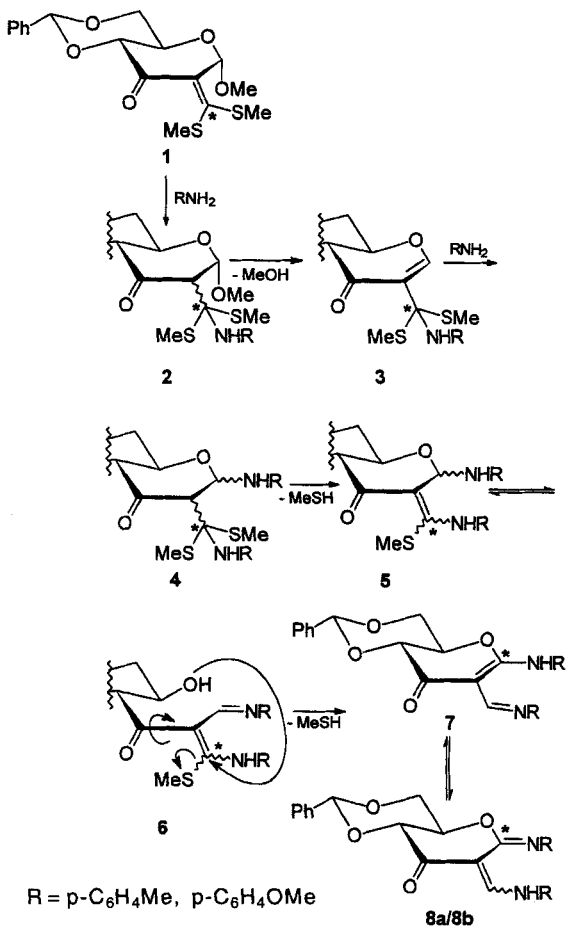
One point of our interest is to use push-pull functionalized sugar derivatives for the synthesis of amino compounds containing two stereogenic centres.

In a recent paper we reported on the unusual synthesis of branched-chain amino sugars **7** and **8a/8b**, respectively, by treatment of methyl 4,6-*O*-benzylidene-2-[bis(methylthio)-methylene]-2-deoxy-α-*D-erythro*-hexopyranosid-3-ulose **1** with *p*-toluidine and *p*-anisidine, respectively [2].

At this time it has neither been possible to distinguish between the tautomers **7** and **8a/8b**, nor to prove the postulated mechanism of their formation. Now we elucidate the structure of the uloses **7/8a/8b** in solution and verify the key step of their formation.

As shown in Scheme 1 the postulated mechanism involves several substitution and elimination reactions. The key step is the opening of the pyranose ring of the α-oxoketene *N,S*-acetal **5** to give the acyclic hydroxy intermediate **6**, which undergoes intramolecular replacement of the methylthio group by the 5-hydroxy group. Hence, there should occur a rotation around the C–2, C–3 bond so that the former exocyclic C–2' of the α-oxoketene dithioacetal **1** is the anomeric carbon of **7/8a/8b**. Likewise, the former C–1 of **1** should occupy the exocyclic position 2' of the uloses **7/8a/8b**.

In order to substantiate this mechanism the exocyclic position 2' of compound **1** was ^{13}C-labeled. This was achieved by treatment of methyl 4,6-*O*-benzylidene-2-deoxy-α-*D-erythro*-hexopyranosid-3-ulose with 20% ^{13}C-carbon disulfide and methyl iodide in the presence of NaH in DMF. The carbon



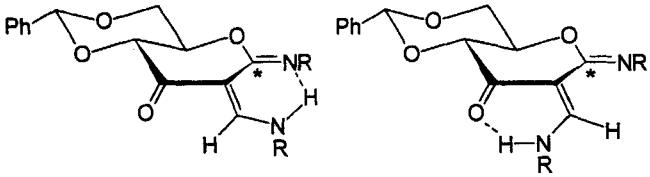
Scheme 1

1) Presented in part at the 2. Iminiumsalz-Tagung in Stimpfach–Rechenberg, Germany (September 20–22th, 1995)

NMR spectrum of **1** indicates an increased signal intensity for the donor-substituted exocyclic C-2' (δ = 160.9). The ^{13}C-labeled compound **1** was treated with *p*-anisidine in refluxing ethanol, and the product was analyzed by NMR spectroscopy. The ^{13}C NMR-spectrum shows an intensive signal at δ = 155.5, which stems from a quarternary C atom. Since the exocyclic C–2' bears a hydrogen atom, the labeled carbon has to be the C–1 of the compounds **7/8a/8b**. This outcome was further verified by the corresponding ^{13}C, ^{13}C coupling with C–2 ($^1J_{C-1,C-2}$ = 73.4 Hz) and the ^1H, ^{13}C coupling with H–2' ($^3J_{C-1,H-2'}$ = 10.4 Hz). With these facts, the reaction mechanism illustrated in Scheme 1 could be confirmed.

Both the ^{13}C and ^1H NMR spectrum exhibit doubled signals and, therefore, the existence of at least two isomers. In the proton NMR spectrum of uloses **7/8a/8b** two doublets for the nitrogen-bonded H atom at δ = 12.68 and δ = 13.53 in a ratio of 1:10 were found. These doublets show coupling constants of 12.4 Hz (major isomer) and 13.8 Hz (minor isomer), which occur again in the CH signal of the hydrogen atom at the exocyclic C–2' (δ = 8.66). The quantity of the coupling constants confirm an interaction between vicinal protons.

These results prove, that neither of the two isomers belongs to the structure of glycal **7**, because the coupling between NH and CH (H–2') in this case would reach over five bonds. For that, J-values larger than 10 Hz are excluded. Hence, the NMR signals can be assigned to the *E/Z*-isomers **8a** and **8b**.



8a **8b**

R = p-C_6H_4Me, p-C_6H_4OMe

Scheme 2

^1H NMR measurements at different temperatures revealed the existence of intramolecular hydrogen bonds [3, 4], illustrated in Scheme 2. The fixation of the NH protons in this way causes the distinct coupling with the proton at C–2', which is generally not observable when fast exchanging protons are involved [4]. Similar to the $^3J_{C-H,C-H}$ coupling the corresponding vicinal CH,NH coupling can also be interpreted with the help of the Karplus equation [5]. The $^3J_{C-H,N-H}$ values of the isomers **8a** (12.4 Hz) and **8b** (13.8 Hz) support the proposed structures, since the angle between CH and NH bond in both cases should be around 180°.

For the decision of weather the structure of major and minor isomer is *E* or *Z*, again the ^{13}C-labeling was shown to be very useful. In the ^{13}C, ^1H coupled (gated decoupling) NMR spectrum, the C–1 signal of the major isomer (δ = 155.5) occurs as a doublet due to coupling with H–2' ($^3J_{C-1,H-2'}$ = 10.4 Hz).

In consequence to the isotope enrichment also the C–1 of the minor isomer has to give an intensive observable signal. This effect is revealed by the comparison of the ^{13}C NMR spectra of labeled and unlabeled isomers **8a/8b**. The spectrum of the labeled products shows an additional resonance at δ = 151.7, caused by C–1 of the minor isomer. In the ^{13}C,^1H coupled NMR spectrum this signal appears as a doublet, caused by coupling with the corresponding H–2' and with a coupling constant $^3J_{C-1,H-2'}$ = 3.1Hz. On the basis of the different coupling constants found for the major and the minor isomers a decision with respect to the structures **8a** and **8b** is possible. According to the Karplus equation, the major isomer with the larger coupling constant $^3J_{C-1,H-2'}$ has to be assigned as *Z*-isomer (**8a**), whereas the minor isomer with the lower constant has the *E*-configuration (**8b**) (see also ref.[6], [7]).

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Experimental

The ^1H and ^{13}C NMR spectra were recorded with a BRUKER ARX-300 spectrometer. The chemical shifts are related to TMS using the solvent peaks ($CDCl_3$: $\delta(^1H)$ = 7.25, $\delta(^{13}C)$ = 77.0). The assignment of the signals of the major isomer was confirmed by recording the DEPT, $^1H/^1H$ COSY and $^{13}C/^1H$ COSY spectra.

^{13}C-Enriched methyl 4,6-O-benzylidene-2-[bis(methylthio)methylene]-2-deoxy-α-D-erythro-hexopyranosid-3-ulose (1)

0.681 g (28.38 mmol) sodium hydride (as an oil suspension) are stirred with 10 mL dry toluene. After decanting the liquid layer to the activated sodium hydride a solution of 3.0 g (11.35 mmol) methyl 4,6-*O*-benzylidene-2-deoxy-α-*D*-erythro-hexopyranosid-3-ulose (**1**), 1.73 g (22.7 mmol) ^{13}C-enriched carbon disulfide and 8.06 g (56.8 mmol) methyl iodide in 70 mL dry *N,N*-dimethyl formamide at 0 °C is added. The mixture is stirred for 5 min. at 0 °C and another 50 min. at room temperature. Afterwards it is poured into 250 mL of ice water, the precipitation is filtered off, washed with 2 × 50 mL of water and 2 × 30 mL of petrol ether and recrystallized from ethanol. Yield: 2.38 g (56.9%), m.p.: 196–198 °C.

^{13}C-Enriched (2E/Z)-2-(p-anisidinomethylene)-1-(p-anisylimino)-4,6-O-benzylidene-1,2-dideoxy-α-D-erythro-hexopyranos-3-ulose (8a, 8b) [2]

^{13}C-NMR: **8a**: δ 68.3 (C-6), 68.9 (C-5), 77.2 (C-4a), 96.7 (C-2), 147.7 (C-2'), 155.5 (C-1*), 185.6 (C-3);
8b: 151.7 (C-1*).

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