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THE THIAZOLINE RING AS A PROTECTIVE GROUP OF 2-AMINO-2-DEOXY-3-THIO-MANNOSE

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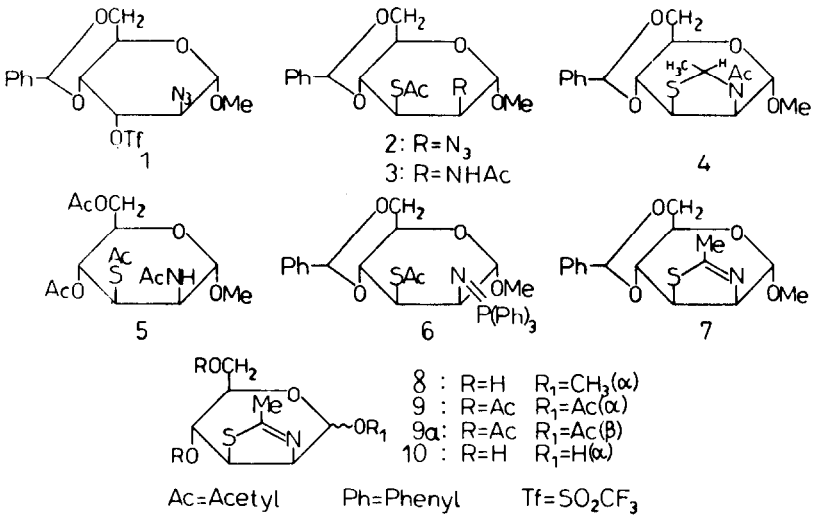
Summary: A new synthesis of 2-amino-2-deoxy-3-thio-mannose is described, in which both the amino and the thio functions are protected in form of a thiazoline ring.

We were interested in the synthesis of 2-acetamido-2-deoxy-3-thio-mannose primarily with respect to its application as a key substance for sulfur-containing sugars with an extended chain possibly revealing interesting biological properties.

According to Baker and Hullar[1] such compounds, i.g. acetamido compound 3, can be obtained on a lengthy way by neighbouring group participation of a thioureido group. However, as pointed out by Herczegh and Bognar[2], this method is not recommendable. The latter authors obtained thiazoline 7 by neighbouring group participation of a thioacetamido group[2]. Nevertheless, this procedure is also complicated by the disagreeable properties of the dithioacetic acid necessary for thioacetylation of the amino group.

The present work is to report on a synthesis, which furnishs in only a few steps both thiazoline 7 and the free thiazolino sugar 10 in partly good to excellent yield.

Treatment of methyl 2-azido-4,6-O-benzylidene-2-deoxy-α-D-altropyranoside[3] with trifluoromethanesulfonic acid anhydride produced triflate 1. The favourable properties, as generally known, of the trifluoromethanesulfonyloxy group as a "leaving group"[4] and the non-appearance of secondary reactions for lack of neighbouring group participation of the azido group[5] allow for a reaction with potassium thioacetate in DMF already at -15°C; 2 is obtained in a yield of 97% (methyl 3-S-acetyl-2-azido-4,6-O-benzylidene-2-deoxy-3-thio-α-D-mannopyranoside). In contrast, according to Herczegh and Bognar[2] the tosylate corresponding to compound 1 did not yield a defined reaction product, when being reacted in the same way. Reduction of 2 by $LiALH_4$ and subsequent acetylation revealed a complex behaviour and yielded the N,S-diacetyl compound 3 as well as the N,S-ethylidene compound 4. As far as compound 3 is concerned, the ^{1}H-NMR data (300 MHz, see table 2) are in accordance with a



manno configuration. Reduction of azido compound 2 with Na in liquid ammonia and subsequent acetylation produced tetraacetate 5 in only moderate yield.

For some time the application of triphenylphosphine for the reduction of sugar azides has been known[6], whereby after N_2 elimination a phosphinimine is usually produced. Azide 2 also reacted in this way giving phosphinimine 6 (not isolated) which was stable in ethereal solution. However, using less polar solvents like $CHCl_3$, 6 was converted by a Wittig-type reaction to thiazoline 7 (4',6'-O-benzylidene-1'-O-methyl-α-D-mannopyrano-[2',3':4,5]-2-thiazoline, MS:m/e 321,M), triphenylphosphinoxide being concomitantly formed.

Table 1

No.	Yield %	m.p.[°C]	$[\alpha]_D^{20}$	c solvent	IR(cm^{-1})
1	72	113	+34,2°	1,419 $CHCl_3$	2115(N_3)
2	97	syrup.	-48,7°	1,0495 $CHCl_3$	2120(N_3)/1700(SAc)
3	5	syrup.	-16,7°	1,0245 $CHCl_3$	1700(SAc)/1650,1530(NHAcI/II)
4	12	151	-178,0°	1,2015 $CHCl_3$	1650(NAc)
5	41	155	+47,0°	1,41 $CHCl_3$	1740(OAc)/1700(SAc)/1650,1530(NHAcI/II)
7	96	syrup.	-146,0°	0,7535 $CHCl_3$	1630(C=N)
8	82	139	-36,0°	0,5125 MeOH	1625(C=N)
9	41	135	-60,0°	2,287 $CHCl_3$	1750(C=O)/1630(C=N)
9a	12	syrup.	-15,0°	1,032 $CHCl_3$	1750(C=O)/1630(C=N)
10	67	192-195	-63,6°	0,228 H_2O	3300(OH)/1630(C=N)

Table 2: ^{1}H-NMR Spectra of Products 1-10 (90 MHz, bei 3,9 u. 10:300 MHz)

No.	Solvent	Chemical Shifts δ [ppm] J[Hz]						other protons
		H-1α(1H) ($J_{1,2}$)	H-2(1H) ($J_{2,3}$)	H-3(1H) ($J_{3,4}$)	H-4(1H) ($J_{4,5}$)	OCH_3(s)	N=C-CH_3(d) ($J_{CH_3,2}$)	
1	$CDCl_3$	4,75 (s)	(3,0)	5,06(dd) (3,0)		3,41		5,59(s,PhCH)
2	$CDCl_3$	4,72 (d) (1,3)				3,42		2,31(s,SAc)/5,49(s,PhCH)
3	$CDCl_3$	4,58 (s)	4,60(dd) (4,0) $J_{NH,2}$=10,0	4,24(dd) (10,2)	3,75(dd) (10,0)	3,39		2,05(s,NHAc)/2,30(s,SAc)/5,52(s,PhCH)/4,01(m,H-5, $J_{5,6}$=9,6;$J_{5,6'}$=4,5)/3,68(dd,H-6)/4,29(dd,H-6', $J_{6,6'}$=12)/6,29(d,NH)
4	$CDCl_3$	5,00 (d) (1,2)				3,40		1,76(d,C-CH_3,J=6,6)/2,19(s,NAc)/5,24(q,SCHN)/ 5,59(s,PhCH)
5	$CDCl_3$	4,58 (d) (1,2)		(10,0)	4,95(dd) (10,0)	3,42		2,04/2,06(s,2xOAc)/2,12(s,NHAc)/2,31(s,SAc)/ 5,88(d,NH,J=9,0)
7	$CDCl_3$	5,40 (s)				3,43	2,28 (2,4)	5,53(s,PhCH)
8	d_6-DMSO	5,25 (s)				3,30	2,18 (2,4)	
9	$CDCl_3$	6,80 (s)	4,09(qd) (6,3)	3,79(dd) (10,2)	4,84(dd) (9,9)		2,29 (2,0)	2,05/2,08/2,14(s,3xOAc)/3,95(ddd,H-5,$J_{5,6'}$=3,0; $J_{5,6}$=5,1)/4,14(dd,H-6)/4,04(dd,H-6',$J_{6,6'}$=12,3)
9a	$CDCl_3$	6,16 (d) (3,0) (H-1β)	4,50 (m)	(9,0)	5,06(dd) (9,0)		2,30 (2,0)	2,03/2,08/2,22(s,3xOAc)
10	d_6-DMSO	5,14 (s)	4,88(qd) (8,4)	4,53(dd) (5,4)	4,19(dd) (9,3)		2,10 (0,89)	6,51(s,OH-1)/3,50(m,H-5,$J_{5,6}$=1,8;$J_{5,6'}$-5,7)/ 3,61(dd,H-6,$J_{6,6'}$=11,1)/3,38(dd,H-6')

The yield was almost quantitative. The thiazoline ring in 7 showed a remarkable resistance to strong acids: By concentrated HCl at -15°C compound 8 was obtained due to cleavage of the benzylidene group. Acetolysis of 7 by Ac_2O/H_2SO_4 yielded a mixture of the α/ß-anomeric triacetates 9 and 9a, which were easy to separate by column chromatography. In contrast, acetolysis of acetamido compound 3 resulted in a complicated mixture of non-polar products. In the ^{1}H-NMR spectrum compounds 9 (9a) (1',4',6'-tri-O-acetyl-2-methyl-α(ß)-D-mannopyrano-[2',3':4,5]-2-thiazoline) equally showed two large transdiaxial couplings for $J_{3,4}$ and $J_{4,5}$, respectively (approximately 9-10 Hz, see table 2) as well as a smaller coupling of 6,3 Hz for $J_{2,3}$. These data are in agreement with a manno configuration. Due to the H-1 signal of 9a ($J_{1,2}$ = 3 Hz), which compared to that of 9 ($J_{1,2}$ = 0) is shifted to a higher field, the two compounds prove to be α/ß-isomers.

Deacetylation of 9 by $NaOCH_3$ in methanol yielded the free thiazolino sugar 10 (2-methyl-α-D-mannopyrano-[2',3':4,5]-2-thiazoline). From the NMR data it can be concluded that 10 is the α-anomer. Moreover, a change in the ring conformation directed to a partly more planar chair conformation enforced by the thiazoline ring has to be considered, as the coupling constants show significantly smaller values for $J_{3,4}$ in comparison with α-acetate 9. When heating up the aqueous solution from 10 to 40°C an anomerisation (α/ß-isomeric mixture) can be observed. $[\alpha]_D^{20}$ = -0,3° (c 0,981, DMSO), -44,9° (c 0,43, MeOH), -63,6° (c 0,228, H_2O). By aqueous trifluoroacetic acid at room temperature the thiazoline ring is cleaved resulting in the acetamido compound with a free SH group.

Mannoses 9, 9a and 10 are protected as thiazoline in an appropriate way in order to extend the sugar chain by condensation under basic conditions. First experiments in this direction provided promising results. They will be reported in a subsequent paper.

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