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# Thiomonosaccharide Derivatives from D-Mannose †

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**Abstract:** Sulfur-containing monosaccharide derivatives can be highly valuable for obtaining compounds with biological activities. In this work, a synthetic route starting from D-mannose has been designed. After a convenient hydroxyl protection and anomeric carbon functionalization in a cyano group, a new carbohydrate analogous has been obtained with sulfur in the ring. The heteroatoms have been introduced by an $S_N2$ mechanism, with subsequent cyclization. Structural identification has been performed by different spectroscopic techniques.

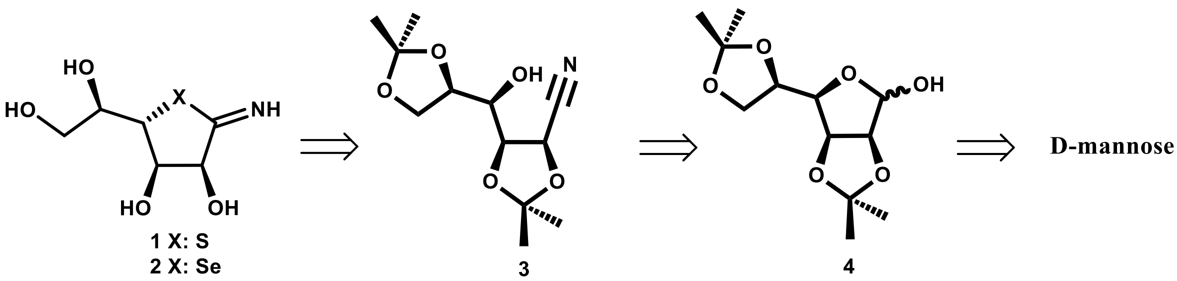
**Keywords:** thiosugar; D-mannose; nitriles

## 1. Introduction

Glycosidase inhibitors and other enzyme inhibitors play important roles in the biochemical processing of biopolymers containing carbohydrates. The biological relevance of sulfur containing carbohydrates is gaining substantial attention, especially in the medicinal and synthetic chemistry [1]. On the other hand, selenium chemistry is gaining prominence in organic synthesis. A number of selenium compounds obtained from monosaccharides have shown biological activity [2]. In our research group, we have synthesized imine sugar derivatives [3,4]. Now, our objective is to obtain thio and selenium monosaccharide analogous derivatives, such as **1** and **2** (Scheme 1).

To our knowledgement, no compounds of this type have been previously synthesized. The incorporation of both heteroatoms S or Se and N could improve the possible biological activity.

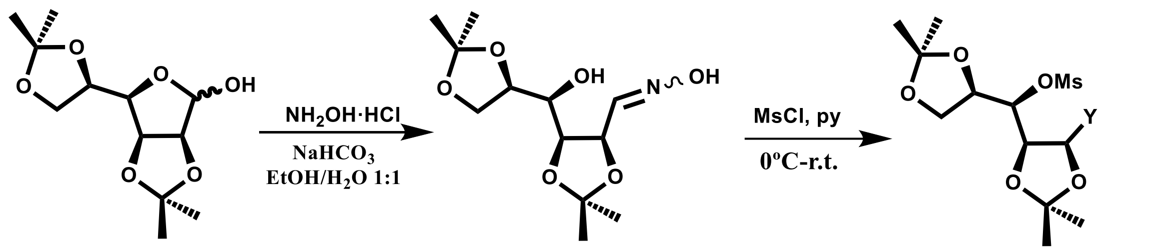
In scheme **1** is showed the retrosynthetic route. The target compounds **1** or **2** can be obtained from nitrile **3**, being OP a good leaving group. This intermediate **3** can be formed starting from D-mannose derivative **4**. The choice of isopropylidene mannose **4** was based on its stability under the reaction conditions in the following steps and the feasible acid deprotection to the final product.




**Scheme 1.** Retrosynthetic analysis of Compound **1**.

## 2. Results and Discussion

Compound **4** was obtained following the procedure described in the literature [5]. In order to transform the aldehyde directly in a nitrile group, we tested several procedures. The best choice was the conversion in the oxime **5**, which could lead to the nitrile. The oxime **5**, prepared following the described procedure [6] showed to be a mixture of isomers *Z*:*E* (83:17). The product could be used in the next reaction without purification. To convert the hydroxyl groups in a good leaving group, we tried to introduce the tosyl group, but without good results. Therefore, we decided to test the reaction with MsCl in pyridine. Following the described procedure at room temperature [6], the principal fraction consisted of a mixture of nitrile **6a** and the related amide **6b**, as showed NMR spectra (Figure 1). With the aim to increase the yield of the nitrile, we performed the reaction at a higher temperature, 60 °C, but the obtained yield was lower. The crude reaction was purified by column chromatography.




**4** **5** **6a** : Y= C≡N
**6b** : Y= $CONH_2$

**Scheme 2.** Synthesis of cyano compound **6a** and amide **6b**.

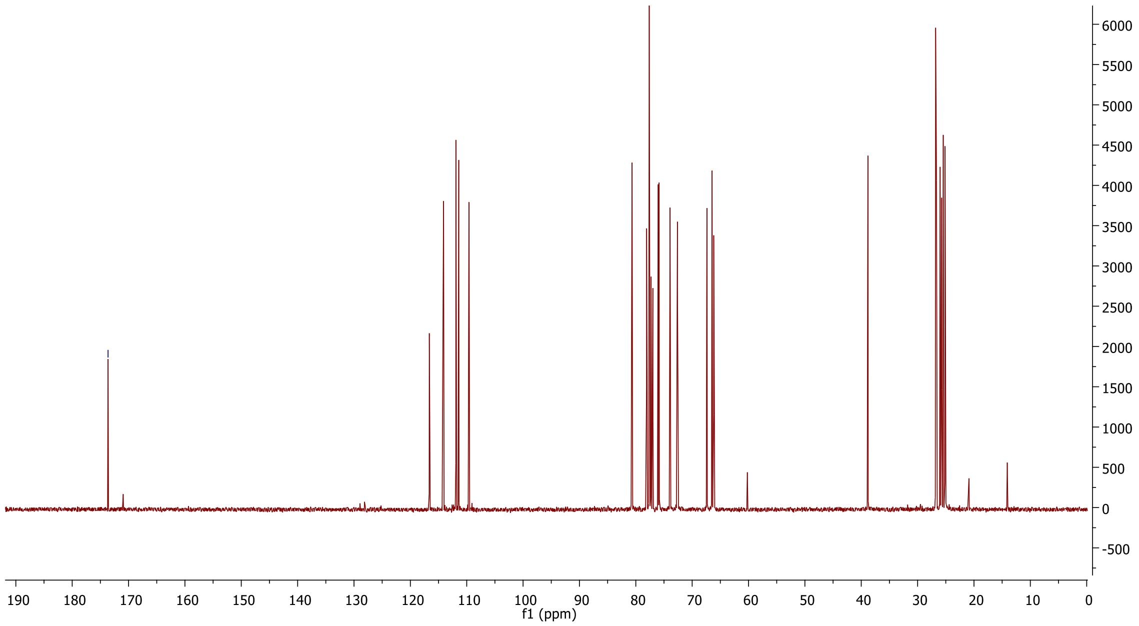
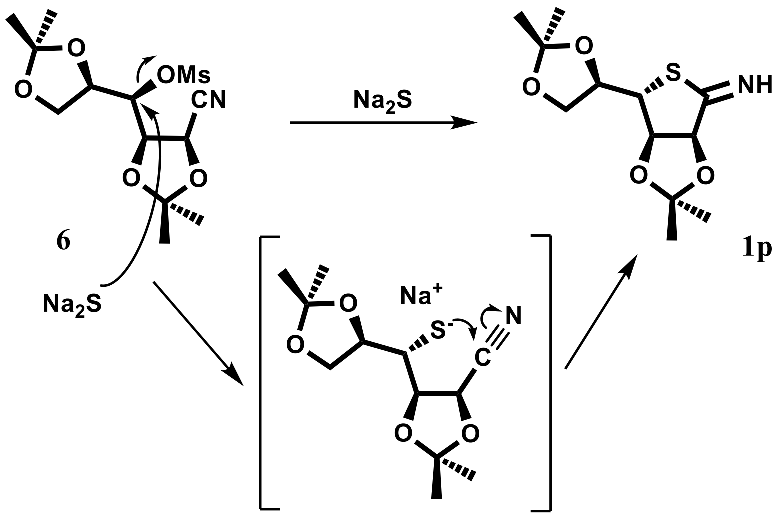



**Figure 1.** $^{13}C$-NMR ($CDCl_3$, 100MHz) of the mixture "nitrile/amide" **6a**/**6b**.

In $^{13}C$-NMR spectrum can be observed the peaks 173.9 ppm and 116.5 ppm belonging to amide and to nitrile groups, respectively. This mixture is used in the following reaction. The amide is transformed in nitrile in the reaction media.

In order to obtain the protected **1p**, compound **6** was dissolved in DMF with $Na_2S·9H_2O$ (Scheme 3). Reaction was heated at 95ºC, giving the desired product. In the proposed mechanism, sulfur anion produces the displacement of mesylate group with subsequent attack to nitrile group with cyclization, leading to the compound **1p**. Deprotection of **1p** in the target compound **1** is in progress.

116.5 ppm




**Scheme 3.** Synthesis of thiosugar **1p**.

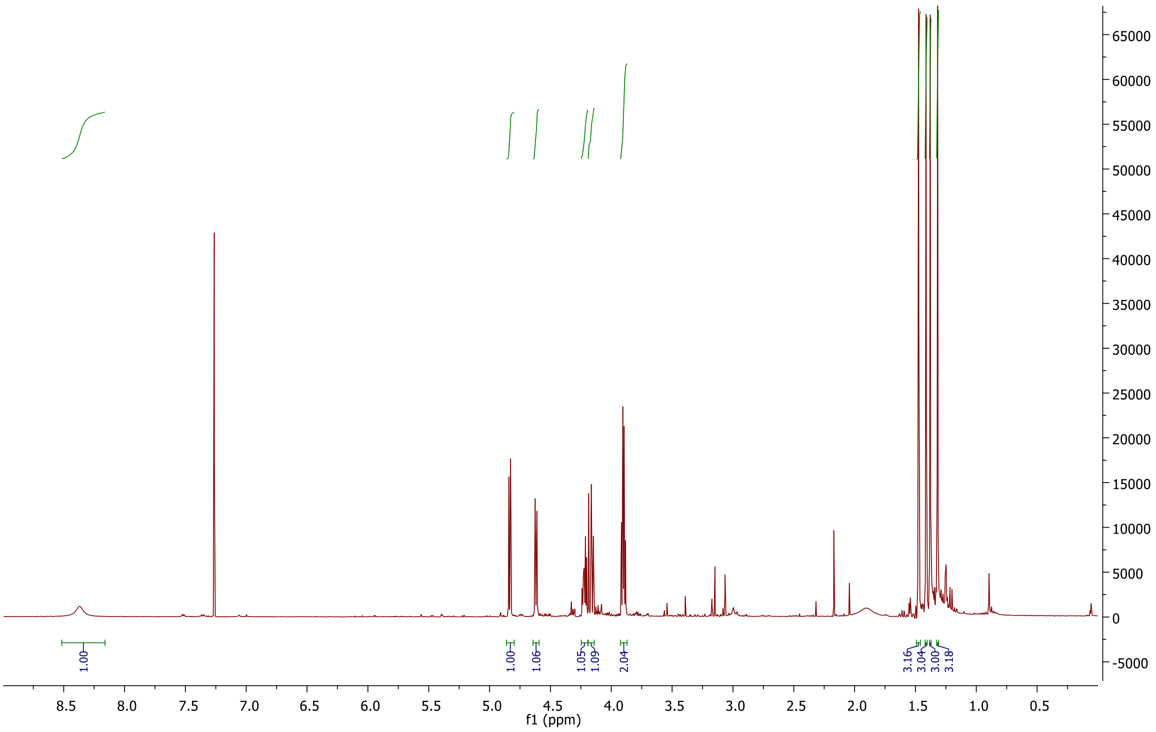



**Figure 2.** $^{1}$H-NMR of thiosugar **1p**.

In $^{1}$H-NMR spectrum, we can observe the disappearance of signal 3.04 ppm corresponding to mesyl group of **6**. At 4.83 y 4.62 ppm, two "d" are showed with $J$ = 5.5 Hz, (H-2 and H-3 respectively). The inversion of configuration at C-4 can be corroborated with $J_{3,4}$ = 0 Hz. At 8.37 ppm a broad singlet is correlated with C=NH proton.

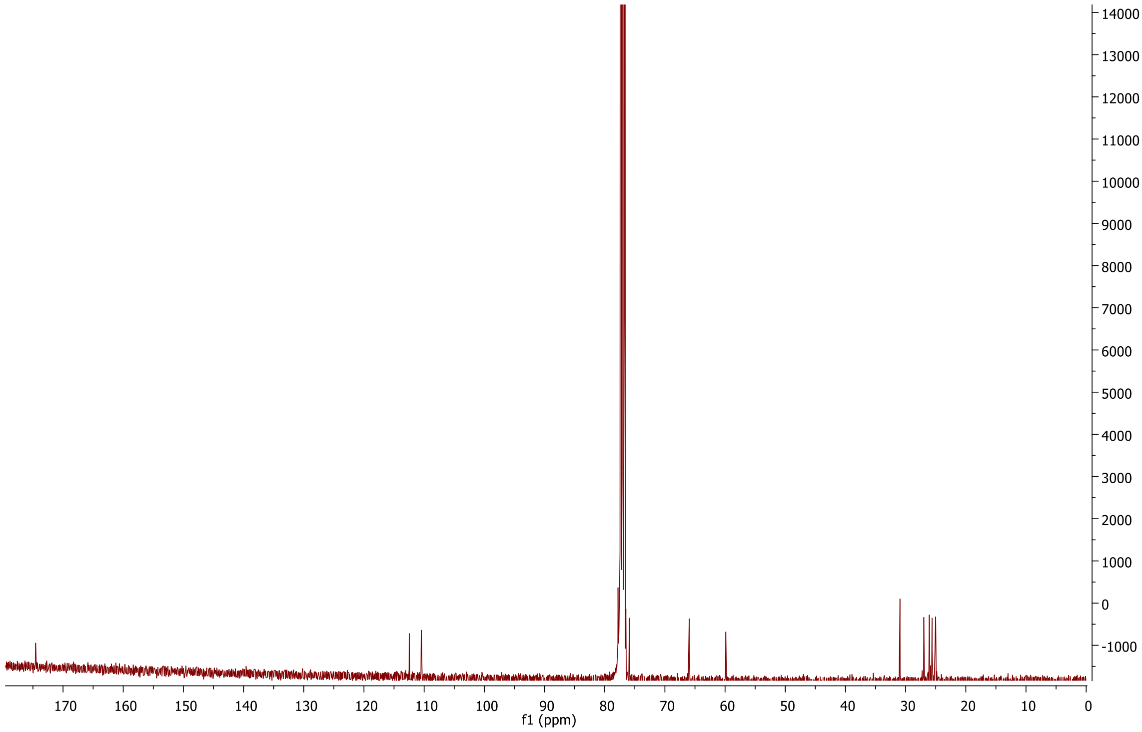



**Figure 3.** $^{13}$C-NMR of thiosugar **1p**.

Comparing $^{13}$C-NMR spectra of compound **1p** and the mesylated **6**, we can observe the disappearance of the peaks corresponding to nitrile *sp* carbon (116.5 ppm) and methyl of mesyl group (38.8 ppm). This is an evidence of the mesylate displacement by the sulfur anion and further attack to the nitrile carbon. The new structure can be confirmed by a new signal at 174.5 ppm which is in accordance with imine *sp*$^2$ carbon.

High resolution mass spectra (ESI) showed the molecular ion (M + H)$^+$: 274.11041.

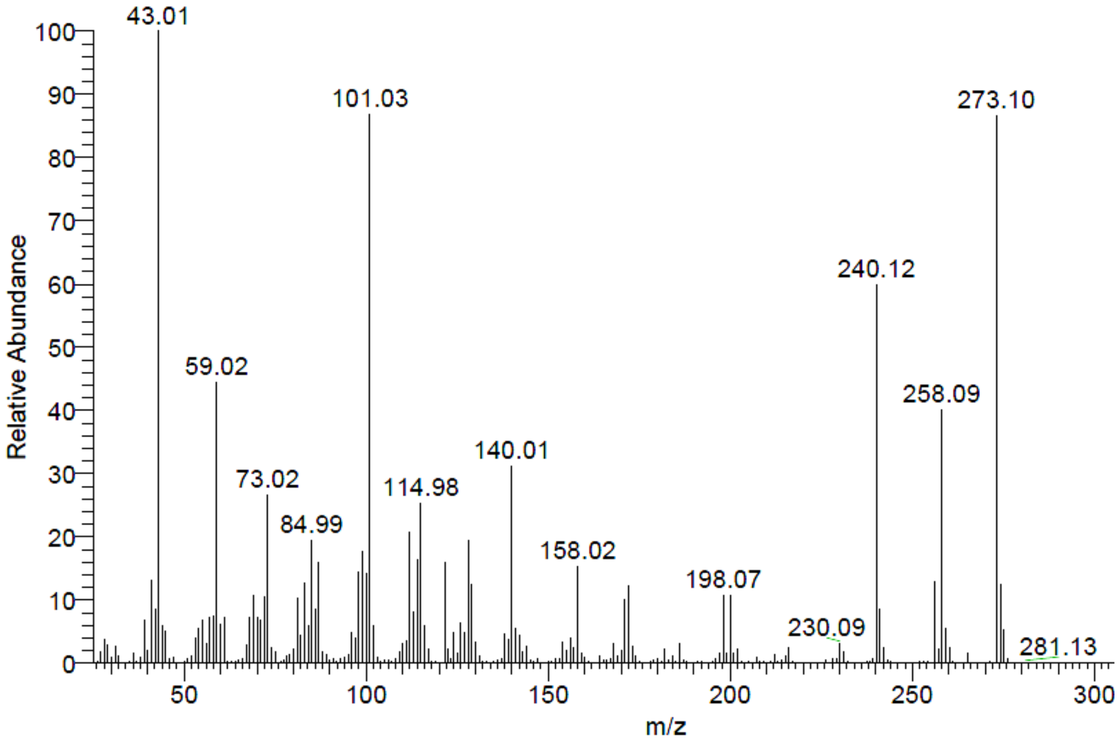



**Figure 4.** (ESI) mass spectrum of thiosugar **1p**.

In the infrared spectrum (IR) we can observe the band corresponding to C=N tension, which uses to appear at $\nu_{C=N}$ = 1700–1615 $cm^{-1}$.

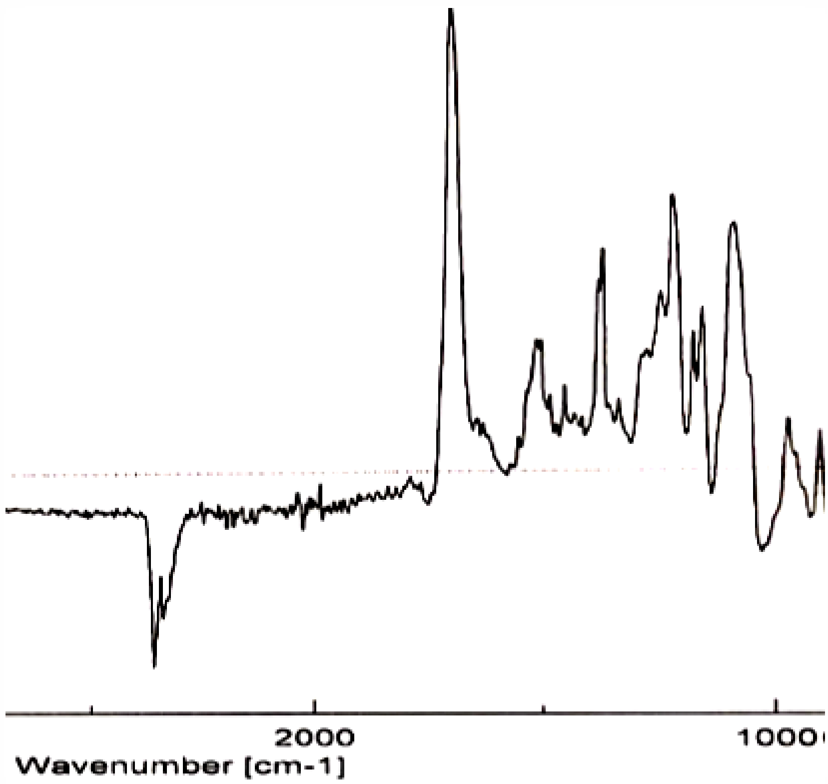



**Figure 5.** IR spectrum of thiosugar **1p.**

## 3. Conclusions

In summary, we have synthesized a new compound of a new family of heterosugars containing sulfur and nitrogen. The structural elucidation is based in NMR analyses, IR and Mass spectra data. The synthetic method is suitable for the insertion of selenium. The corresponding selenium derivatives are under study and will be reported as soon as possible.

## 4. Experimental

### *4.1. Synthesis of 2,3:5,6-di-O-isopropilidene-4-O-metilsulfonil-D-manononitrile* (**6**)

To a solution of oxime 5 (2.74 g, 9.96 mmol) in pyridine (9.37 mL), in an ice bath with stirring, was slowly added a cold solution of MsCl (3.22 mL) in pyridine (9.37 mL). Reaction was monitored by TLC and after 12 h, reaction was quenched with a cold saturated solution of $NH_4Cl$ (~30 mL). Reaction product was extracted (3x30 mL AcOEt) and organic phase was washed with saturated aq. $CuSO_4{\cdot}5H_2O$, dried (anh. $MgSO_4$) and evaporated. The crude product was purified (flash chromatography), obtaining nitrile **5** with amide (1.43 g, 43%). Compound **5** had: $R_F$, 0.5 (Hex/AcOEt 2:1). $^1$H-NMR ($CDCl_3$, 400 MHz, δ ppm): 4.8 (d, *J* = 4.8 Hz, 1 H, H-2), 4.76 (t, *J* = 4.75 Hz, 1 H, H-4), 4.28–4.34 (m, 2 H, H-3 y H-6a), 4.13–4.22 (m, 2 H, H-5 y H-6b), 3.04 (s, 3 H, $SO_2C\underline{H_3}$), 1.5, 1.36, 1.26, 1.24 [4s, 4 × 3 H, $C(C\underline{H_3})_2$]. $^{13}$C-NMR ($CDCl_3$, 100 MHz, δ ppm): 116.5 (C-1), 111.9, 111.4 [2 × $\underline{C}(CH_3)_2$], 80.7 (C-2), 77.6 (C-3), 73.9 (C-4), 67.4 (C-6), 66.1 (C-5), 38.8 ($SO_2\underline{C}H_3$), 26.8, 26.0, 25.5, 25.1 [2 × $C(\underline{C}H_3)_2$].

### *4.2. Synthesis of Thiosugar* **1p**

To a solution of compound **5** (663 mg) in DMF (16 mL) is added $Na_2S{\cdot}9H_2O$ (473 mg) and the mixture is heated at 95 °C. Reaction was monitored by TLC and after 48h, water is added (25 mL). Reaction product was extracted (4 × 25 mL AcOEt) and organic phase was washed with saturated aq.

solution of LiCl and dried (anh. MgSO) Product **1p** was purified by column chromatography (150 mg, 30%). Compound **1p** had: $R_F$, 0.2 (Hex/AcOEt 3:1). $^1$H-NMR ($CDCl_3$, 400 MHz, δ ppm): 8.37 (s, 1H, N<u>H</u>), 4.83 (d, *J* = 5.5 Hz, 1H, H-2), 4.62 (d, *J* = 5.5 Hz, 1H, H-3), 4.25–4.13 (m, 2H, H-6a y H-6b), 3.90 (dd, *J* = 8.8, 4.6 Hz, 2H, H-4 y H-5), 1.47, 1.41, 1.38, 1.32 [4s, 4 × 3H, $C(C\underline{H}_3)_2$]. $^{13}$C-NMR ($CDCl_3$, 100 MHz, δ ppm): 174.5 (C-1), 112.5, 110.5 [2 × $\underline{C}(CH_3)_2$], 77.3, 77.0, 76.3 (C-2, C-3, C-5), 65.9 (C-6), 59.9 (C-4), 26.9, 26.1, 25.6, 24.9 [2 × $C(\underline{C}H_3)_2$].

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