

A Nitro Sugar Route Synthesis and Calcium Ions Catalyzed Epimerization of 2-Thiosophorose and 2-Thioepisophorose*

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The development of efficient methods of synthesis of thiooligosaccharides, especially of S-glycosylthioglycoses, has become an important problem in carbohydrate chemistry. The reason is that the compounds are of increasing interest since they find multiple uses in carbohydrate enzymology as inhibitors, nonmetabolizable inducers, model substrates, as well as stable ligands for affinity chromatography [1].

A usual approach to their syntheses is based on a 1-thioaldose nucleophile displacement of a leaving group of a protected aldose under inversion of configuration at a non-anomeric carbon atom. For the preparation of 2-thiosophorose (2-S-β-D-glucopyranosyl-2-thio-D-glucose, VII) however, deprotection procedures at the anomeric carbon atom can lead to ambiguous results [2–4].

The communication reports on a new method of the synthesis of VII, namely a 1-thio-β-D-glucose nucleophile addition to a sugar nitroalkene followed by the Nef transformation of the deprotected adduct. The presented procedure involves also a newly discovered epimerization of 2-thioepisophorose (2-S-β-D-glucopyranosyl-2-thio-D-mannose, VI) and its epimer VII in neutral aqueous solutions catalyzed by calcium ions (Scheme 1).

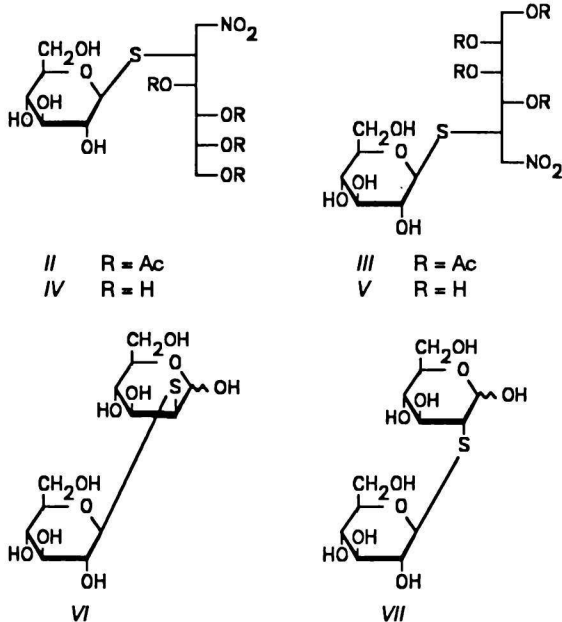
Addition of 1-thio-β-D-glucose sodium salt (I) to 3,4,5,6-tetra-O-acetyl-1,2-dideoxy-1-nitro-D-arabino-hex-1-enitol [5] in methanol followed by decationization with Dowex 50 W, H⁺ form gave 71 % of a mixture of 3,4,5,6-tetra-O-acetyl-1-deoxy-2-S-(β-D-glucopyranosyl)-1-nitro-D-mannitol (II) and -D-glucitol (III) in the ratio 2.3 : 1. Following deacetylation of the mixture in methanolic HCl afforded 97 % of a mixture of IV and V. Compound IV (m.p. = 148–150 °C (methanol), [α]_D (20 °C, ρ = 5.0 g dm⁻³, water) = -27.3°) was obtained by the crystallization of the mixture in an overall yield of 43 % based on I.

Final transformation of acyclic precursors IV and V to VI and VII was done by the Nef reaction [6]. When IV was submitted to the conversion, 85 % of VI ([α]_D (20 °C, ρ = 6.1 g dm⁻³, water) = -30.2°) were isolated as an amorphous powder.

The Nef reaction done with a directly obtainable mixture of IV and V gave however, besides corresponding thiodisaccharides VI and VII, also a significant amount of degradation products (ca. 15 %). In a most favourable case, a mixture containing 55 % of VI and 30 % of VII was obtained.

Experiments to turn the ratio of VI and VII in favour of more interesting VII using alkaline isomerization were not very successful. The treatment of pure VI, e.g. with aqueous ammonia caused mainly an extensive degradation and gave rise to only about 10 % of VII.

Chromatography on a column of Dowex 50 W X-8 in the Ca²⁺ form [7] using water as a mobile phase separated VII (eluted first) from the mixture of VI and degradation products. The separation enabled to



Scheme 1

* Full paper should appear in *Carbohydrate Research*.

purify *VII* enough to obtain it for the first time in a crystalline form. The purification procedure gave a 21 % overall yield of *VII* (m.p. = 173–175 °C (methanol–acetone, volume ratio = 1 : 1), $[\alpha]_D^{20}$ (20 °C, $\rho = 20 \text{ g dm}^{-3}$, water) = -8.0° (3 min) $\rightarrow -13.1^\circ$ (equil.)). Moreover, during the chromatographic process, a slow turn of the ratio of *VI* and *VII* in favour of *VII* was observed.

The treatment of *VI* with a half-molar amount of calcium chloride in water at ambient temperature within 3 d resulted in the formation of an equilibrium mixture of *VI* and *VII* in the ratio 1 : 4. The same mixture was achieved from the starting *VII* within 4 d. The epimerization did not proceed in a solution of *VII* and calcium chloride acidified to pH 2.

The removal of calcium chloride from the epimerization mixture of *VI* and *VII* using a mixture of Dowex 50 W in the H^+ form and Dowex 1 in the HCO_3^- form was very slow and achieved less than 10 % within 24 h. Therefore, Dowex 50 W in the Ca^{2+} form in an aqueous suspension was used for the epimerization. When this was a case, the equilibrium mixture of *VI* and *VII* in the ratio 1 : 4 was achieved after 20 d epimerization of *VI* at ambient temperature. The removal of the ion exchanger followed by passing the filtrate through a column of Dowex 50 W in the H^+ form afforded a mixture of *VI* and *VII*, from which 65 %

of *VII* crystallized (m.p. = 173–175 °C, $[\alpha]_D^{20}$ (20 °C, $\rho = 5.0 \text{ g dm}^{-3}$, water) = -13.1°).

The application of the epimerization procedure to the mixture of *VI* and *VII* obtained after the Nef transformation of *IV* and *V* enabled to obtain *VII* in the crystalline form with an overall yield of 50–56 % based on starting *I*.

The structures of compounds *II*–*VII* were supported by ^1H and ^{13}C NMR data and those of *IV*, *VI*, and *VII* also by elemental analyses.

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