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A one-pot septanoside formation and glycosylation of acyclic dithioacetals derived from 1,2-cyclopropanated sugars†

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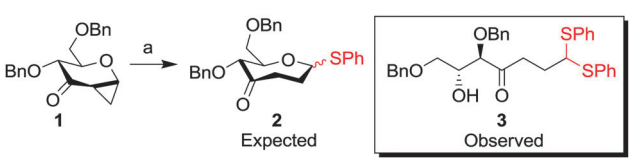
Ring opening of 3-oxo-1,2-cyclopropanated sugars with thiols leads to the serendipitous discovery of the synthesis of sugar based homologated acyclic dithioacetals. These acyclic dithioacetals were found to undergo one-pot septanoside formation followed by stereoselective glycosylation in the presence of glycosyl acceptors under glycosylation reaction conditions.

Ring expanded versions of hexoses, commonly known as septanoses or carbohydrate based oxepanes, drew special interest in recent years due to their significant application as mimics of the natural glycans, like furanoses and pyranoses.[1] Kuszmann *et al.* revealed that septanose mimics of thio-pyranose exhibited a 10 fold increase in activity with reference to beciparcil, an oral anti-thrombotic drug.[2] Similarly, the methyl β-septanoside mimic of α-mannopyranoside was found to be a competitive ligand for concanavalin A, a natural lectin for α-mannosides.[3] Damha *et al.* synthesized septanose mimics of DNA and RNA by replacing the pentofuranose ring in natural nucleic acids with cyclic seven-membered sugar units. These oxepane nucleic acids are found to be highly resistant to nuclease degradation while displaying several common features with the naturally occurring DNA.[4] Septanose mimics of nucleosides were also found to possess excellent anti-viral properties.[5] As a result, several protocols for the preparation of septanoses were developed in the last decade.[6] The majority of septanosides synthesized to date lack the substituent at the C-6 position. Furthermore, stereoselective synthesis of septanoses containing di- and oligosaccharides is still in the course of investigation. Recently several methods for the synthesis of septanoses have been reported.[7] However, very few protocols were revealed for the synthesis of septano-oligosaccharides.[8] Out of these, glycosylation of 1,2-anhydroseptanosides,[8b] *S*-phenyl septanosides[8d] and 1,2-cyclopropanated sugars[8f] as glycosyl donors with sugar derived glycosyl acceptors was found to be the promising technology.

In continuation of our efforts in developing general protocols for the preparation of septanoses and septano-oligosaccharides,[8f] we attempted to prepare the septanoside derived thio-glycoside donors[8d] from 3-oxo-1,2-cyclopropanated pyranose derivatives.[8f] However, this effort led us to the serendipitous discovery of a novel method to synthesize heptanose derived dithioacetals from 1,2-cyclopropanated sugars. Previously, the dithioacetal derivative of glucose has been converted to D-glucoseptanose in low yield.[9] Later, Hindsgaul *et al.* used appropriately protected *O*,*S*-acetal as a precursor for the synthesis of septanoside derivatives.[8c] These observations prompted us to use the obtained dithioacetals as glycosyl donors in septanoside synthesis. Thus, herein we report the synthesis of carbohydrate based dithioacetal donors from 3-oxo-1,2-cyclopropanated pyranoses as well as a one-pot intramolecular acetal exchange, followed by glycosylation to afford the septanoside containing disaccharides.

Towards the synthesis of thio-septanoside donors, 3-oxo-1,2-cyclopropanated sugar **1** was reacted with thiophenol (1.2 equiv.) in the presence of TMSOTf (0.2 equiv.) to obtain the 4-oxo-septanose donor **2**. However, the reaction provided the dithioacetal derivative **3** as the only product in 52% yield and no trace amount of **2** was observed. Increasing the equivalents of thiophenol (2.2 equiv.) provided **3** in 98% yield (Scheme 1).

Performing the reaction in the presence of EtSH or TolSH provided the corresponding dithioacetals **4** and **5**, respectively, in excellent yield. To investigate the generality of the reaction, 3-oxo-1,2-cyclopropanated galactose derivative **6** was reacted with PhSH or EtSH or TolSH. In all cases the reaction provided the corresponding dithioacetals **7**, **8** and **9** in excellent



Scheme 1 Formation of acyclic dithioacetal derivatives from 3-oxo-1,2-cyclopropanated sugar. Reagents and conditions: (a) PhSH, TMSOTf, CH_2Cl_2, −10 °C, 30 min, 98%.

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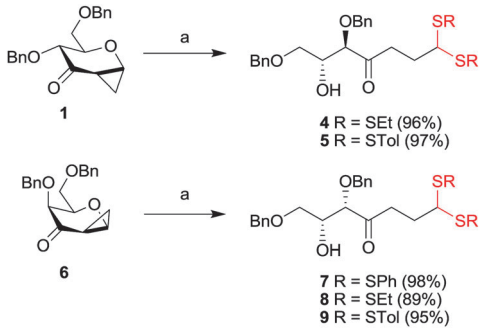
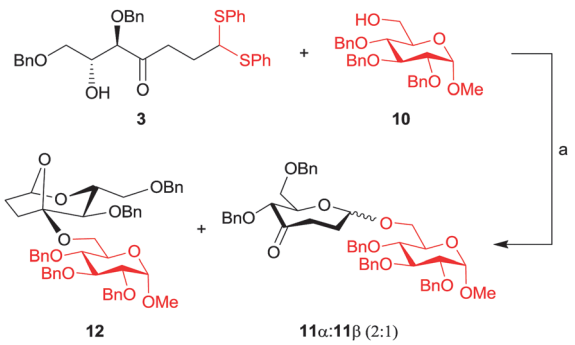


Scheme 2 Formation of acyclic dithioacetal derivatives from 3-oxo-1,2-cyclopropanated sugars. Reagents and conditions: (a) RSH, TMSOTf, CH_2Cl_2, −10 °C, 30 min.

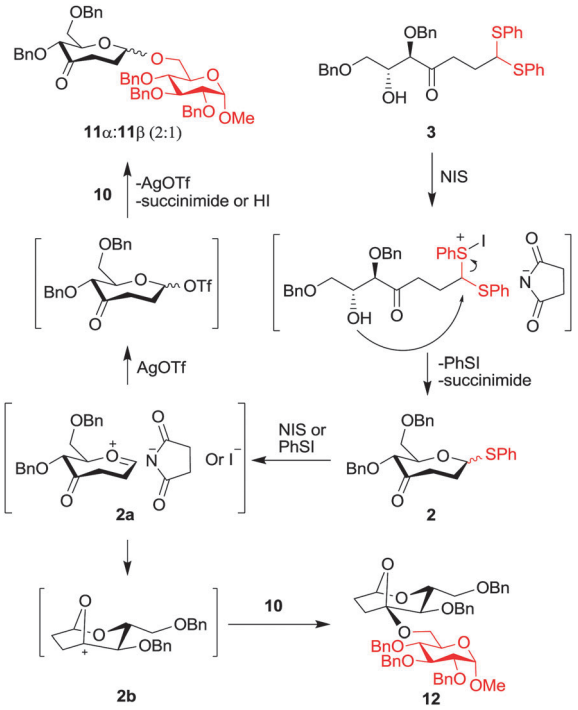
yield (Scheme 2). Although the formation of thioglycosides from 1,2-cyclopropanated hexoses is known,[10] to the best of our knowledge, this is the first report on the formation of heptanosyl dithioacetals from 1,2-cyclopropanated donor–acceptor cyclopropanes.

We further investigated whether the obtained dithioacetal **3** can be converted to the expected thioglycoside **2** in the presence of an electrophile. Thus, dithioacetal **3** was treated with *N*-iodosuccinimide (NIS)[11] and catalytic AgOTf in CH_2Cl_2 in the presence of 4 Å molecular sieves at −10 °C. However, this reaction also did not provide the expected thioseptanoside **2**. Interestingly, when the reaction was performed in the presence of a glycosyl acceptor **10**, it produced the disaccharide **11** along with the bridged bicyclic glycoside **12** in a 2 : 3 ratio,[12] respectively (Scheme 3).[13]

The formation of **12** can be speculated by the interesting intramolecular septanoside formation followed by the glycosylation reaction. As shown in Scheme 4, activation of the dithioacetal **3** with NIS would provide the septanosyl donor **2** by an intramolecular 7-*exo*-tet cyclisation reaction. Further activation of the thioglycosyl donor **2** in the presence of NIS or phenylsulfenyl iodide would lead to the formation of an oxonium ion intermediate **2a** that would be trapped by triflate (in the presence of silver triflate) and undergo glycosylation in the presence of the acceptor **10** to give the septano-hexoses **11α** and **11β**. On the other hand, trapping of the oxonium ion **2a** by carbonyl oxygen in an intramolecular fashion would lead to the formation of a tertiary carbocation intermediate **2b** which upon reaction with

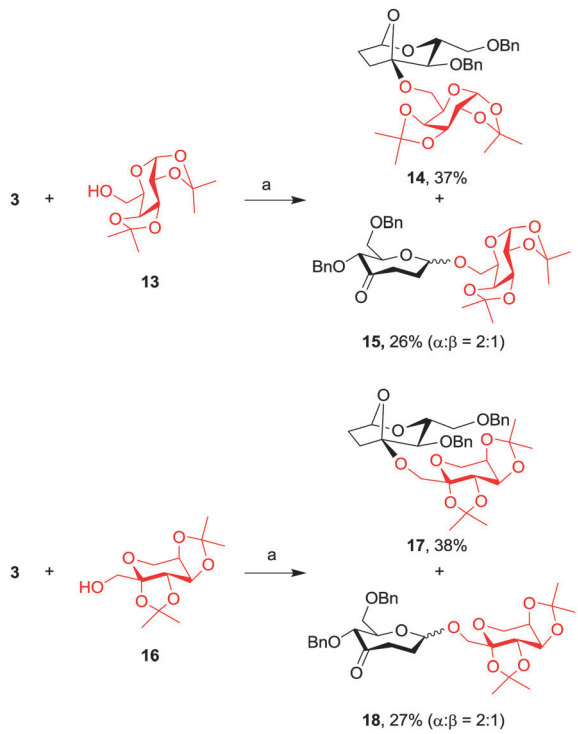


Scheme 3 One-pot septanoside formation and glycosylation reaction of sugar derived acyclic dithioacetal donors. Reagents and conditions: (a) NIS, AgOTf, CH_2Cl_2, 4 Å MS, −45 °C to −25 °C, 1 h, 71% (11 : 12 (2 : 3)).



Scheme 4 Proposed mechanism for the formation of septano-hexose disaccharide derivatives **11** and **12** from dithioacetal **3**.

glycosyl acceptor **10** would give the unexpected disaccharide derivative **12** as a single diastereomer. Carrying out the reaction in the absence of AgOTf also provided disaccharide derivatives



Scheme 5 One-pot synthesis of septano-hexoses. Reagents and conditions: (a) NIS, AgOTf, CH_2Cl_2, 4 Å MS, −45 °C to −25 °C, 1 h.

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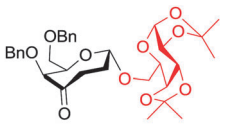
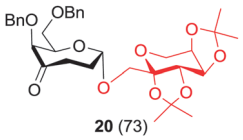
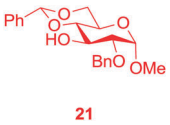
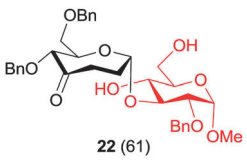
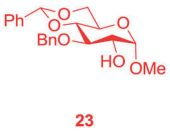
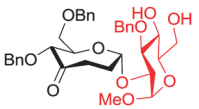
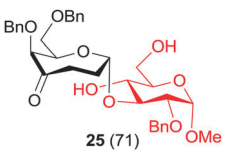
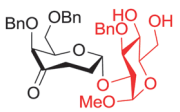
Table 1 One-pot synthesis of septano-hexoses from sugar derived acyclic dithioacetal donors

Entry	Dithioacetal donor	Glycosyl acceptor	Septano-hexose derivatives[a] (%)
1	7	13	 **19** (70)
2	7	16	 **20** (73)
3	3	 **21**	 **22** (61)
4	3	 **23**	 **24** (69)
5	7	21	 **25** (71)
6	7	23	 **26** (73)

[a] Yield refers to pure and isolated products.

11 and **12** in a prolonged period of time, 48 h, in low yield (Scheme 4).

Encouraged by this result the glycosylation reaction was performed by using dithioacetal donor **3** and sugar acceptors **13** and **16** possessing a primary hydroxyl group as a nucleophile. In both cases the reaction proceeded smoothly and provided the septano-hexoses **15** and **18** as a mixture of anomers, respectively, in low yield. However, the formation of bridged bicyclic glycosides **14** and **17** was also observed under these glycosylation reaction conditions (Scheme 5).

Interestingly, performing the glycosylation reaction between galactose based dithioacetal donor **7** and acceptors **13** and **16** provided the disaccharides **19** and **20** as the only products in good yield (Table 1, entries 1 and 2) with an α-configuration. Similarly, glycosylation of donors **3** and **7** with acceptors possessing free hydroxyl groups at C-3, acceptor **21**, and at C-2, acceptor **23**, provided the septano-hexoses **22**, **24**, **25** and **26** (Table 1, entries 3–6) respectively as single anomers with α-configuration.[14] The stereochemistry at the newly formed glycosidic center for all the septano-hexoses was assigned based on the ^{13}C chemical shift value of C1′ (for α-septanosides $\delta_{C1'}$ ranges from 99–104 ppm while for β-septanosides $\delta_{C1'}$ ranges from 104–111 ppm).[15] The stereoselectivity of the glycosylation reaction as well as the vanishing of bridged bicyclic compounds (Table 1) may be due to the combination of stereoelectronic effects of the seven membered oxocarbenium ion intermediate (similar to **2a**) and non-bonding steric interactions of glycosyl acceptors.[16] To the best of our knowledge, this is the first report on use of the acyclic dithioacetals as glycosyl donors in glycosylation reactions.

In conclusion, preparation of heptanose derived dithioacetals from 1,2-cyclopropanated sugars was discovered. Furthermore, an interesting one-pot intramolecular cyclization of acyclic dithioacetals to give septanosides followed by glycosylation, in the presence of a glycosyl acceptor, to provide septano-hexoses, is revealed. A possible mechanism for the one-pot reaction is proposed and the generality and stereoselectivity of the glycosylation reaction have been investigated. The application of these dithioacetals in oligosaccharide synthesis and preparation of carbohydrate mimics is in progress.

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11 Reaction of **3** with NIS alone at various concentrations also did not provide the expected thioseptanoside **2**.
12 The ratios were calculated based on crude ^{1}H NMR spectra.
13 Column chromatography of the crude provided only **11α** as a pure diastereomer and **11β**, **12** as a mixture. Reduction of this mixture gave the corresponding alcohol of ketone **11β** and **12** which were able to be separated by silica gel column chromatography. For the detailed procedure please see the ESI†.
14 In all cases the benzylidiene group was deprotected under the reaction conditions. This may be due to the mild acidic conditions of the reaction mixture.
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