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Synthesis of Tri-*O*-acetyl-D-allal from Levoglucosenone

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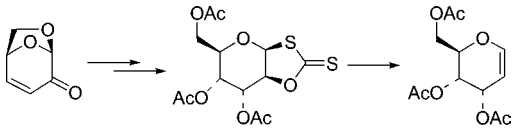
ABSTRACT



Tri-*O*-acetyl-D-allal has been enantiospecifically synthesized in six steps from levoglucosenone in 55% overall yield. A key step in the synthesis is the anhydro bridge ring-opening with concomitant formation of a 1,3-oxathiolane-2-thione ring.

Glycals are unsaturated derivatives of pentoses and hexoses with a double bond between the anomeric carbon and the adjacent one. They are very useful building blocks in organic synthesis,[1,2] as well as in carbohydrate chemistry[3] due to their enol ether functionality. Glycals were discovered by Emil Fisher and Karl Zach[4] at the beginning of the twentieth century but, despite their long existence, they remain a type of carbohydrate of great interest because of the substitution,[5] rearrangement,[6] and addition[7] reactions they undergo and, more recently, they have found uses in combinatorial chemistry.[8] The glycals most usually found in the literature are glucal and galactal, while gulal and allal are not readily available, since they are derived from rare sugars. It is noteworthy to mention that rare sugars, in particular D-allose, have received much attention because of their biological activity. In some cases they can act as inhibitors of various glycosidases and cell proliferation,[9] to induce programmed cell death in hormone refractory prostate cancer cells,[10] or protective antioxidative effects on ischemia-reperfusion damage in retina,[11] brain[12] and liver.[13] However, regardless of their potential importance in medicine and pharmacy, studies of their biological effects are still limited because of their low natural abundance.

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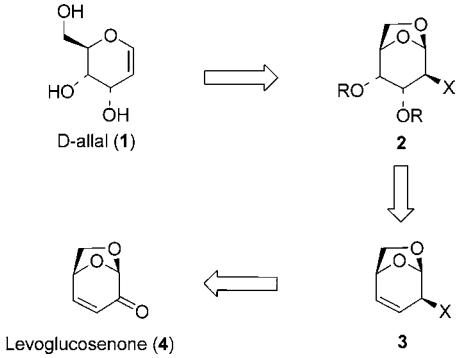
Several methods have been reported for the synthesis of D-allal[14] (1,5-anhydro-2-deoxy-D-*ribo*-hex-1-enitol, **1**), a glycal derivative of D-allose, although only a few of these are efficient, and to the best of our knowledge, none of the reported methodologies have allowed this building block to become commercially available. Therefore, the development of a simple and efficient synthetic route toward this deceptively simple, rare sugar is still a challenge for those devoted to carbohydrate synthesis.

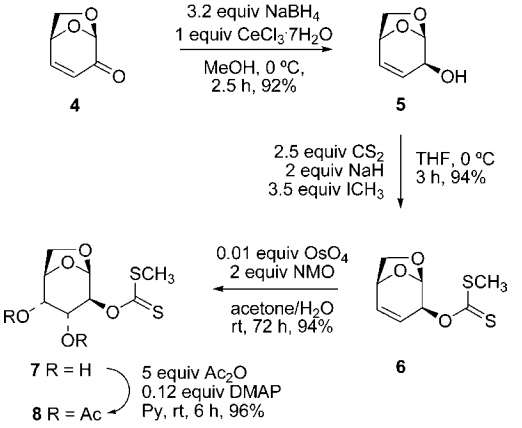
Scheme 1. Retrosynthetic Strategy



Herein we describe a new and efficient synthesis of tri-*O*-acetyl-D-allal (3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*ribo*-hex-1-enitol, **11**), from levoglucosenone (**4**), a biomass-derived starting material. Levoglucosenone (1,6-anhydro-3,4-dideoxy-β-D-*glycero*-hex-3-enopyranos-2-ulose) is a versatile and readily available chiral synthon of the carbohydrate-derived chiral pool.[15] Conventional pyrolysis of cellulose-containing materials such as waste paper is typically used to generate **4**,[16] but microwave irradiation of microcrystalline cellulose was recently found to be an effective alternative.[17]

Our initial retrosynthetic strategy (Scheme 1) suggested construction of the cyclic enol ether system through reductive ring-opening of the anhydro bridge, induced by elimination of an appropiate group at the C-2. Dihydroxylation of the double bond in **3** would precede this event. The conformational constraint characteristic of levoglucosenone is due to the 1,6-anhydro bridge, which imposes a skeletal rigidity that allows control in the generation of desired stereogenic centers. The steric hindrance produced by the anhydro bridge on the β face of the molecule directs the approach of any reagent from its opposite face. Therefore, reduction of the carbonyl moiety of the anhydropyranose can be easily obtained employing the Luche conditions[18] (Scheme 2). Treatment of **4** with the $NaBH_4$–$CeCl_3 \cdot 7H_2O$ in methanol at room temperature afforded the allylic alcohol **5** in a chemo- and stereoselective manner in 92% isolated material. Though the sp^3-hybridized C-2 carbon will be converted into an sp^2 carbon in the final compound, the configuration of this carbon is important to achieve a complete diastereoselection during the dihydroxylation process on the olefin. We observed that when the allylic substituent at C-2 has the opposite configuration; this selectivity is strongly affected.

Scheme 2. Synthesis of the Xanthate Intermediate **6**



Transformation of the allylic alcohol **5** into the corresponding allylic xanthate **6** was envisioned as a possible route toward a suitable intermediate which could form the 1,2-double bond through a radical elimination pathway. For this reason, a THF solution of **5** was reacted with carbon disulfide, methyl iodide, and sodium hydride at room temperature to afford the protected allylic xanthate **6** in 94% yield. *cis*-Dihydroxylation of **6** with catalytic amounts of osmium tetroxide in *tert*-butyl alcohol, and *N*-methylmorpholine *N*-oxide as stoichiometric oxidant, afforded **7** as the sole product in 94% yield. A stereochemical assigment of this compound was possible by the use of ^{1}H NMR spin decoupling and NOE data.

As previously mentioned, complete control of the diastereoselectivity in the dihydroxylation pathway was due to the presence of both a 1,6-anhydro bridge and the xanthate group on the β-face of the pyranoside fragment. These structural features allowed us to generate two new stereogenic centers (C-3 and C-4) with the absolute configuration present in the D-allal. Further treatment of **7** with acetic anhydride, pyridine, and 4-(dimethylamino)-pyridine produced the diacetate **8** in 96% yield.

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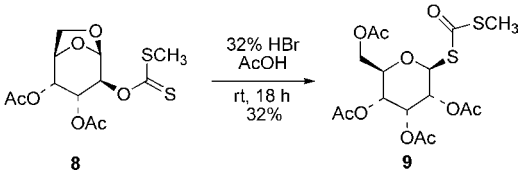
Cleavage of the 1,6-anhydro bridge of **8** was a crucial event in this synthetic strategy. The difficulties of opening the anhydro bridge system are well documented.[19] After several unsuccessful attempts employing different reaction conditions to pursue the opening of the anhydro bridge through a radical fragmentation, we focused our efforts on a two-step alternative to achieve our goal. First, an acid-mediated ring-opening of the acetal would be performed followed by glycal formation.

Reaction of xanthate **8** with hydrobromic acid in acetic acid cleaved the anhydro bridge with a migration/rearrangement transformation of the xanthate group into a dithiocarbonate at the anomeric carbon and the concomitant attack of an acetate at C-2 to afford the thioglycoside **9** in 32% yield (Scheme 3).

Scheme 3. Migration/Rearrangement of the Xanthate Group

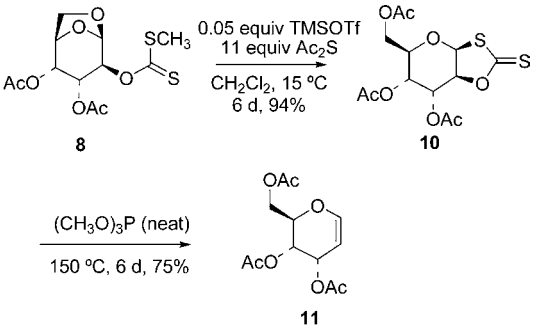


The 300 MHz ^{1}H NMR spectrum in $CDCl_3$ showed five methyl singlets. Four of these were due to acetate groups, plus there was methyl attached to a sulfur atom which suffered an upfield shift compared to the starting material. The H-1 signal also showed a downfield shift to 5.69 ppm with a strong coupling (J = 10.7 Hz) that suggested the antiperiplanar relationship between the substituents attached at C-1 and C-2. HMBC experiments allowed assigment of each of the signals in the spectrum, and irradiation of H-5 showed a NOE enhancement of H-1, confirming the β configuration of the anomeric carbon in a D-allopyranoside derivative. The 75 MHz ^{13}C NMR spectrum in $CDCl_3$ showed no signal at 215 ppm characteristic of the xanthate group. Instead, we observed an extra signal corresponding to the primary acetate group and a new carbonyl signal at 187.2 ppm, which was consistent with rearrangement of the xanthate group into a dithiocarbonate. The IR spectrum was also in agreement with the proposed structure, since it showed an absorption band at 1748 cm^{-1} assignable to the acetate groups and another band at 1651 cm^{-1} attributable to the dithiocarbonate group.

Unfortunately, even though it was an interesting transformation, neither the structure nor the yield were satisfactory. Other attemps to obtain a thioglycoside by treating the diacetate with thiophenol or thioanisole and different Lewis acid were also disappointing.

Based on these results, we decided to try a thioacetolysis procedure in order to obtain the anomeric thioacetate without affecting the xanthate group for further manipulation. Hence, we treated **8** with trimethylsilyl triflate and acetyl sulfide[20] at 15 °C, and formation of a single product was observed by TLC (Scheme 4).

Scheme 4. Synthesis of Tri-*O*-acetyl-D-allal



To our surprise, the 300 MHz NMR analysis in $CDCl_3$ revealed that we had achieved the ring-opening of the 1,6-anhydro bridge with concomitant formation of a five-membered ring 1,3-oxathiolane-2-thione, and acetylation of the primary alcohol to afford **10** in 94% yield. The 300 MHz ^{1}H NMR spectrum in $CDCl_3$ showed the presence of three methyl singlets attributed to the acetate groups but the xanthate's methyl group signal was not detected. The 75 MHz ^{13}C NMR spectrum in $CDCl_3$ showed an upfield shift (14 ppm) for the C-1 and a downfield shift for C-2 (10 ppm) compared to its precursor, as well as the presence of a signal for a thiocarbonyl group at 207.2 ppm. Also, in this case, the ring junction of the bicyclic system was clearly established by ^{1}H NMR spin decoupling and NOE data.

We assumed that compound **10** could be a feasible precursor for our target molecule if submitted to the Corey–Winter reaction.[18] Treatment of **10** with trimethyl phosphite at 150 °C afforded cleanly the tri-*O*-acetyl-D-allal (**11**) in 75% isolated yield.

This *trans*-cycloacetalization reaction involved once again the participation of the xanthate group in the ring opening (Scheme 5), but in this case probably a further attack by the thioacetate generated from the acetyl sulfide on the methyl group of the xanthate affords the cyclic system.

The result of this ring-opening process differs considerably from the outcome of the acetolysis reaction performed by treating **8** with acetic anhydride and trimethylsilyl triflate, which afforded an unseparable mixture of anomeric acetate isomers in modest yields.

A possible explanation for the different behavior can be found by taking into account the characteristics of the sulfur atom, which is an element of the third period with a wider atomic radius, higher polarizability and nucleophilicity which could permit transition states that are not feasible for smaller elements of the second period like oxygen.

In conclusion, we have synthesized tri-*O*-acetyl-D-allal in six steps and 55% overall yield from levoglucosenone, a biomass derived starting material. The key step in the synthesis was the novel *trans*-cycloacetalization pathway

(19) See ref 15a, Chapter 12, p 173 and references cited therein.
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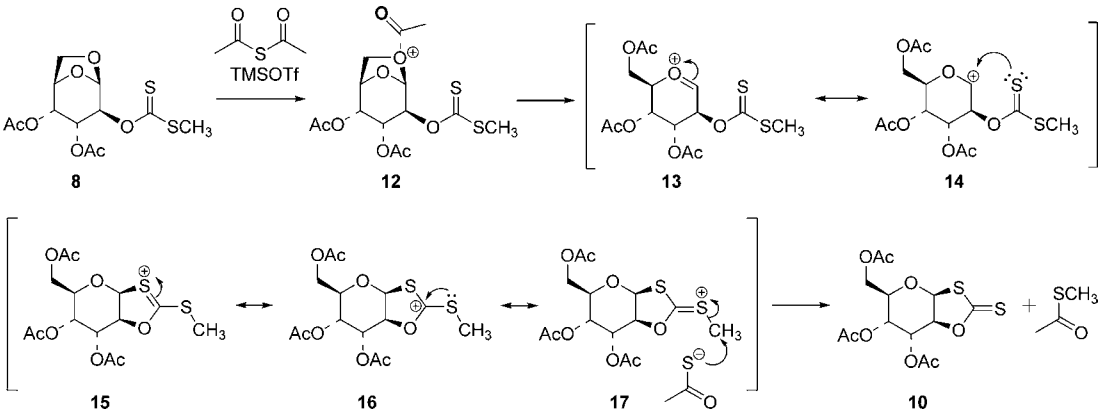
Scheme 5. Proposed Mechanism for Generation of the 1,3-Oxathiolane-2-thione Ring



from the xanthate intermediate into the 1,3-oxathiolane-2-thione ring. This new procedure for the preparation of substituted D-allal is simple and efficient with an overall yield that is significantly higher than the methodologies previously reported. We also found a new application for acetyl sulfide, which could have a more general use in the future.

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Supporting Information Available. Experimental procedures for the synthesis of all compounds, characterization data, and copies of ^{1}H and ^{13}C NMR spectra of new products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.