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An efficient and cost-effective preparation of di-O-acetyl-D-rhamnal

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ABSTRACT

We have developed a synthetic route to the frequently utilized deoxysugar building block di-*O*-acetyl-D-rhamnal originating from the inexpensive starting material methyl α-D-glucopyranoside. Our approach proceeds in five steps with minimal column chromatography purification needed to afford the title compound in good overall yield.

Many biologically-active secondary metabolites are adorned with carbohydrate residues that have been demonstrated to be crucial in modulating the biological efficacy of the parent glycoconjugate.[1,2] As a result, numerous researchers have initiated programs aimed at investigating the effects of altering the oligosaccharide domain of various natural product families such as the aminocoumarin, aureolic acid, and glycopeptide antibiotics, to mention only a few, in attempts to discover architecturally-novel compounds with enhanced biological profiles.[3–7] A common structural motif found within members of these secondary metabolites are 2-deoxy and 2,6-dideoxysugars.

A common entry point for the synthesis of various D-configured 2-deoxy and 2,6-dideoxysugars is di-*O*-acetyl-D-rhamnal (**1**) illustrated in Figure 1. While the corresponding enantiomer for **1** is readily available from L-rhamnose, at a much lower cost, the preparation of **1** requires substantially more time and effort to access.[8–11] Moreover, the most commonly employed synthetic routes directed towards the production of **1** originate from the commercially-available, albeit highly expensive, tri-*O*-acetyl-D-glucal.[12] While these approaches have become the standard means to access **1** and its subsequent derivatives, the continuing rise in cost of tri-*O*-acetyl-D-glucal has begun to make these approaches cost-prohibitive for many researchers. Surprisingly, few synthetic approaches to this critical carbohydrate building block, di-*O*-acetyl-D-rhamnal (**1**), have been reported in the chemical literature over the past thirty years considering its near universal role as a synthetic intermediate to access suitably derivatized D-configured 2-deoxy and 2,6-dideoxysugars.[13] Moreover, an efficient and inexpensive route to **1** would add another readily accessible chiron to the pool of asymmetric building blocks for use in various synthetic applications.

During the course of our group's work aimed at investigating various aspects related to the angucycline antitumor antibiotics, we required access to significant quantities of di-*O*-acetyl-D-rhamnal (**1**). Previously, we had employed either Torri's or Tius' approach to access either **1** or its deacetylated derivative D-rhamnal, respectively, depending on our specific needs.[9,10] However, both of these routes required the use of tri-*O*-acetyl-D-glucal as

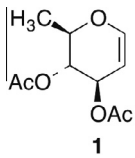

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Figure 1. Structure of di-*O*-acetyl-D-rhamnal.

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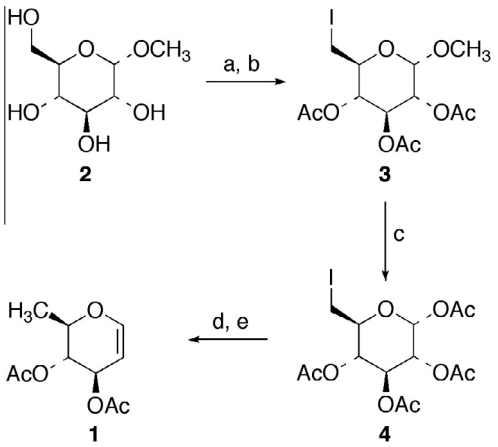

Scheme 1. Reaction Conditions (a) I_2, ImH, Ph_3P, Ph-Me; (b) Ac_2O, Pyr, DMAP (90% over two-steps); (c) Ac_2O, H_2SO_4 (88%); (d) *n*-Bu_3SnH, Et_3B, air, Ph-Me, −78 °C (78%); (e) PBr_3, CH_2Cl_2 then Zn, NaH_2PO_4, EtOAc (55%)

the starting material, which proved to be too expensive for us to continue employing, considering the quantity of material we required. Additionally, we explored the use of Nicolaou's apparent two-step route towards D-rhamnal as described in his group's pursuit of the complex deoxysugar D-callipeltose.[11] Unfortunately, our efforts to utilize Nicolaou's scheme proved capricious and resulted in dramatically lower yields upon attempting larger scale reactions.

More recently, Osman described the preparation of a protected D-rhamnal derivative beginning from methyl α-D-galactopyranoside.[13f] However, his route was lengthy and required multiple protection/deprotection steps. As such, we deemed Osman's synthetic approach too laborious and inefficient to pursue for our purposes. As a result, we elected to develop a simple, expedient, and cost-effective synthetic route towards di-*O*-acetyl-D-rhamnal (**1**) that would help to facilitate our group's research goals and is presented below in Scheme 1.

Our synthetic approach towards di-*O*-acetyl-D-rhamnal (**1**) originates from methyl α-D-glucopyranoside (**2**), a commercially-available and inexpensive starting material.[14] Regioselective conversion of the primary C(6)-OH to an iodide utilizing iodine (I_2), imidazole (ImH), and triphenylphosphine (Ph_3P) in warm toluene (Ph-Me) followed by peracetylation of the remaining alcohol functional groups under standard conditions afforded methyl α-D-2,3,4-triacetoxy-6-deoxy-6-iodoglucopyranoside (**3**) in excellent yield for the two-step process.[15] Next, exchange of the acid-labile anomeric methoxy group for an acetate was accomplished by employing sulfuric acid (H_2SO_4) in acetic anhydride (Ac_2O) to provide iodide **4** in high yield that was isolated solely as the α-anomer as determined by ^1H and ^{13}C NMR analysis.[16] From the outset, we were cognizant that the sequence of events would require careful orchestration to allow us to process large quantities of material from methyl α-D-glucopyranoside (**2**) to di-*O*-acetyl-D-rhamnal (**1**). In turn, we concluded that it would be critical to remove the C(6)-I functional group prior to glycal formation to avoid possible undesirable side reactions when performing our anticipated Fischer–Zach reaction to establish the endocyclic glycal olefin in **1**. As such, reductive removal of the C(6)-I was realized by exposure of **4** to tributyltin hydride (*n*-Bu_3SnH) in Ph-Me at subambient temperature (−78 °C) using triethylborane (Et_3B), with a trace amount of air as the radical initiator, according to the procedure of Oshima.[17] The resulting 6-deoxysugar was transformed into di-*O*-acetyl-D-rhamnal (**1**) by treatment with phosphorus tribromide (PBr_3) in cold methylene chloride (CH_2Cl_2) to yield the corresponding anomeric bromide which immediately underwent a Fischer–Zach reaction employing zinc metal (Zn) in a sodium dihydrogen phosphate (NaH_2PO_4) buffer, following the recently disclosed work of Shao, to afford di-*O*-acetyl-D-rhamnal (**1**) in good overall yield.[18]

In summary, we have developed a simple, efficient, and inexpensive route towards the ubiquitous deoxysugar building block, and chiron, di-*O*-acetyl-D-rhamnal (**1**). Our synthetic scheme progresses in five steps (thirty-five percent overall yield) and requires only a single column chromatography purification step after reductive removal of the C(6)-I group. We anticipate that our approach will help facilitate research programs requiring the synthesis of various D-configured 2-deoxy- and 2,6-dideoxysugars in both academic and industrial research laboratories.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.035.

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