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SEQUENTIAL SmI_2-PROMOTED ONE- AND TWO-ELECTRON REACTIONS OF CARBOHYDRATES

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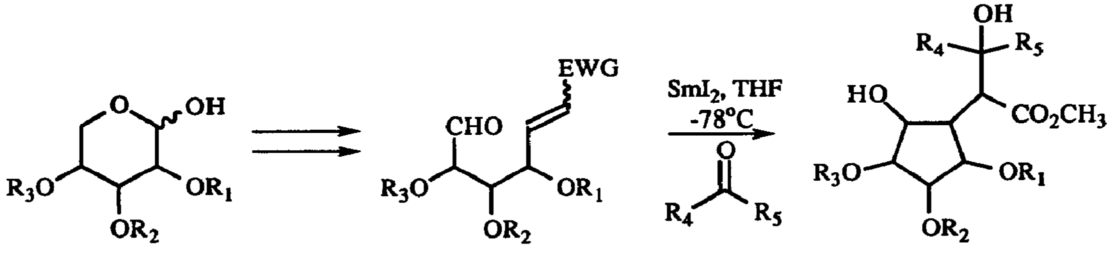
Abstract: Highly functionalized and densely oxygenated bicyclic compounds were obtained by treating a modified carbohydrate template with SmI_2 and a ketone or aldehyde which effected a tandem radical cyclization and carbonyl addition reaction.

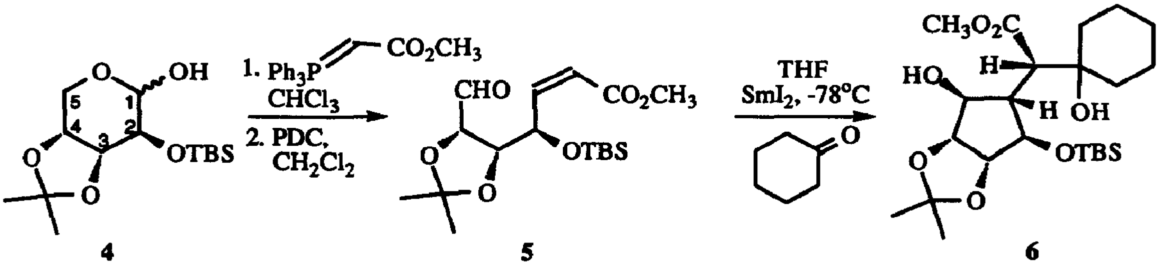
The synthetic exploitation of the reagent samarium diiodide (SmI_2) has rapidly become one of the most significant developments in organic chemistry.[1] A great number of important synthetic transformations with SmI_2 involve the one-electron reduction of ketones and aldehydes to a samarium ketyl radical anion which can promote cyclizations, deoxygenations, and reductions.[1,2] Far fewer studies have had a strong focus on synthetic reactions of carbohydrates with SmI_2, which can lead to optically active and highly oxygenated intermediates and ring-coupled compounds not accessible by other methodologies.[2] Herein we report a new reaction sequence in which the tetrahydropyran ring of carbohydrate **1** is deoxygenated and cyclized to afford an elaborated cyclopentane ring **3** with dense oxygenation and a functionalized carbon appendage. Thus, a highly modified carbocycle **3** was prepared from carbohydrate template **2** in which two carbon-carbon bonds were formed in a very stereoselective manner. In the tandem key step, SmI_2 promoted a sequential one-electron (radical) cyclization of an aldehyde carbonyl and an alkene, followed by a two-electron intermolecular carbonyl addition reaction.[3]



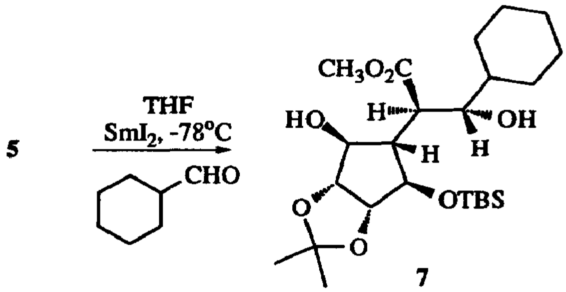
1 **2** **3**

The sugar lactol **4**, prepared in 4 steps from inexpensive D-arabinose by simple carbohydrate manipulations,[4] was ring-opened with an ester stabilized ylide. The C_5-hydroxyl was next oxidized with pyridinium dichromate to prepare the cyclization precursor **5** with cis olefin geometry in 54% overall yield.[5] Compound **5** and cyclohexanone (2 equiv.) were subsequently added slowly via syringe to a dark blue-green solution of SmI_2 (3 equiv.) in THF at -78°C, which prepared **6** in 76% yield as the sole observable stereoisomer. In addition, we found that if the ketone was added after the onset of the reaction, presumably after the ketyl cyclization had taken place, substantial decomposition resulted. The stereochemistry of **6** was confirmed by single crystal X-ray analysis.[6(a)] It is worth noting in this reaction that two new carbon-carbon bonds are formed and three new stereocenters are produced with 8 stereoisomeric products possible.

Carbohydrate template **5** was reacted with an aldehyde to determine if yet more stereocenters can be obtained. Thus, aldehyde **5** and cyclohexanecarboxaldehyde (2 equiv.) were stirred with SmI_2 (3 equiv.) in



THF at -78°C which produced a 3:1 mixture of products in 78% isolated yield. After careful flash chromatographic separation, the major product, 7, crystallized as colorless needles and the stereochemistry was determined by single crystal X-ray analysis.[6(b)] This reaction has the potential for to up to sixteen possible stereochemical permutations in the four new stereocenters produced.



In summary, a new reaction sequence which relies on a key sequential SmI_2 transformation has been examined. In a single reaction, the samarium ketyl of a carbohydrate template promoted a one-electron cyclization which was followed by a two-electron intermolecular carbonyl addition reaction with both a ketone and an aldehyde. Stereochemically complex bicyclic products with dense oxygenation were produced from potentially many possible stereoisomeric products.

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