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Synthesis of L-2-Spirocyclopropyl-2-deoxyarabinose

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***Summary**: The synthesis of L-2-spirocyclopropyl-2-deoxyarabinose from L-arabinose is described. Unusual reactions of a dichlorocyclopropane intermediate are observed. The target compounds may serve as mechanism-based inactivators of β-galactosidase.*

Cell surface carbohydrates mediate cell-to-cell communication and the "social behavior" of cells. The glycosidases and glycosyltransferases,[1] responsible for the metabolism and biosynthesis of these complex carbohydrates are presumed to operate through a mechanism involving enzyme-bound glycosyl oxocarbonium intermediates, a mechanism typified by β-galactosidase (see Figure 1).[2] In an effort to prepare potential suicide inhibitors of these enzymes, we require 2-spirocyclopropyl-substituted glycosides.[3] D-Galactopyranosides with aromatic aglycones (e.g., 1 with R=2-nitrophenyl) are commonly used substrates for β-galactosidase as well as L-arabinopyranosides.[4] A synthesis of the corresponding L-2-spirocyclopropyl-2-deoxyarabino-pyranose (2, R=H) is described below.

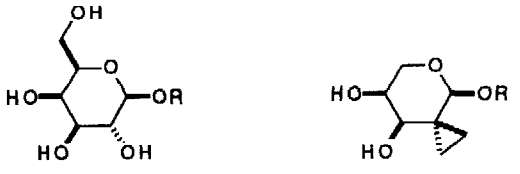
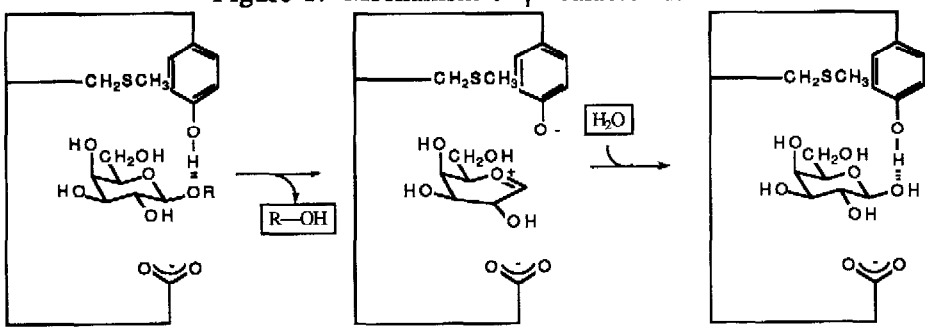


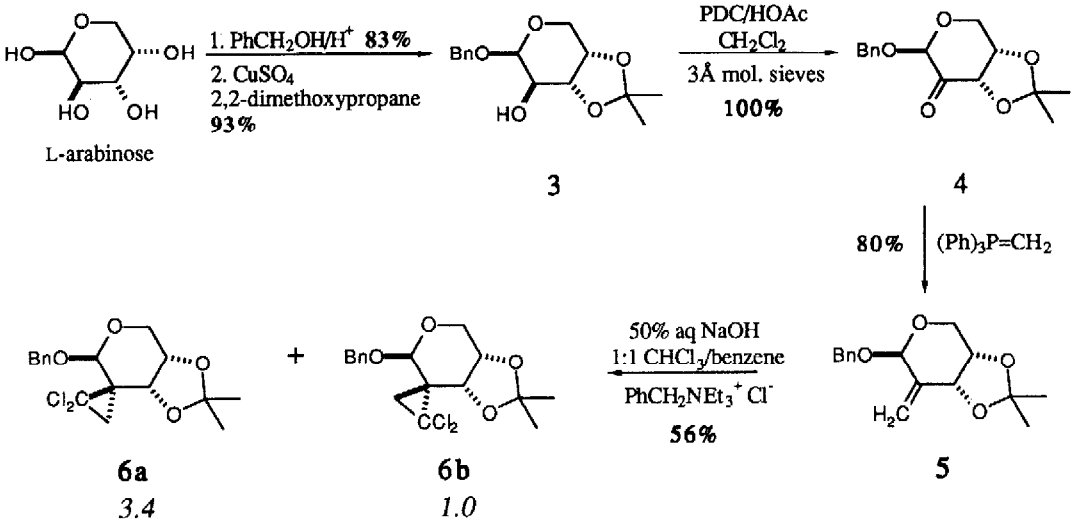
Figure 1. Mechanism of β-Galactosidase



L-Arabinose was protected according to well documented methods[5] to give **3**. Oxidation by the Swern procedure[5b] or a modification of PDC/CH_2Cl_2[6] gave ketone **4**, which hydrates readily upon exposure to ambient moisture (see Scheme I). Wittig methylenation yielded olefin **5**, which proved impervious to several variations on the Simmons-Smith cyclopropanation procedure. We

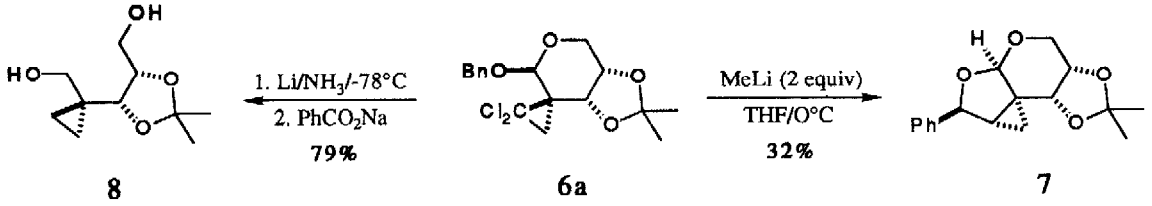
attribute this recalcitrance to good overlap of the π-orbital with the σ*-orbital of the exocyclic C—O bond,[7] rendering the olefin electron deficient.[8] Cyclopropanation of **5** was effected with :CCl_2 under phase transfer conditions, leading to a 3.8/1 mixture of **6a** (β addition) and **6b** (α addition). Considerable unreacted olefin remains and is inseparable by HPLC from **6b**; we have been unable to drive this reaction to completion.

Scheme I



Our initial attempts at dechlorination produced some unexpected results. Treatment of **6a** with methyllithium in THF at 0°C led to insertion into the adjacent benzylic C—H bond (**7**, Scheme II), presumably via a LiCl-carbenoid intermediate.[9] This cyclization may open an new avenue to a ring system encountered in microline[10] and mycorhizzin[11] antibiotics. Reduction of **6a** with Li or Na in NH_3 removed the benzyl group, but also opened and reduced the acetal giving diol **8**, without observed rearrangement of the cyclopropylcarbinyl radical intermediate, even though such rearrangements are well precedented.[12]

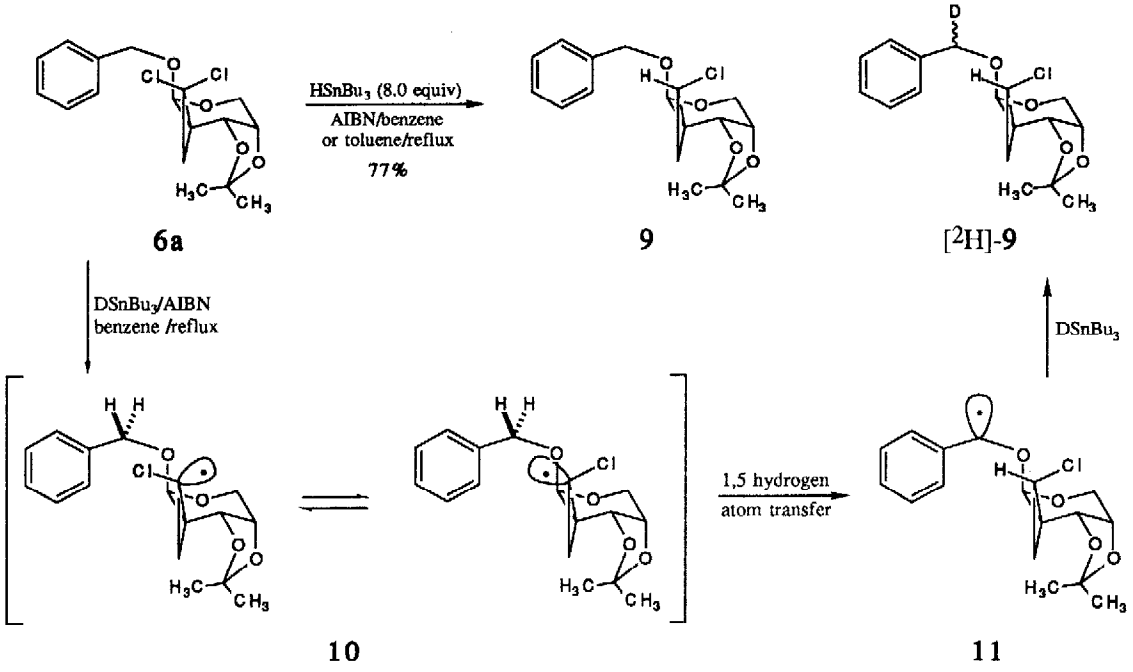
Scheme II



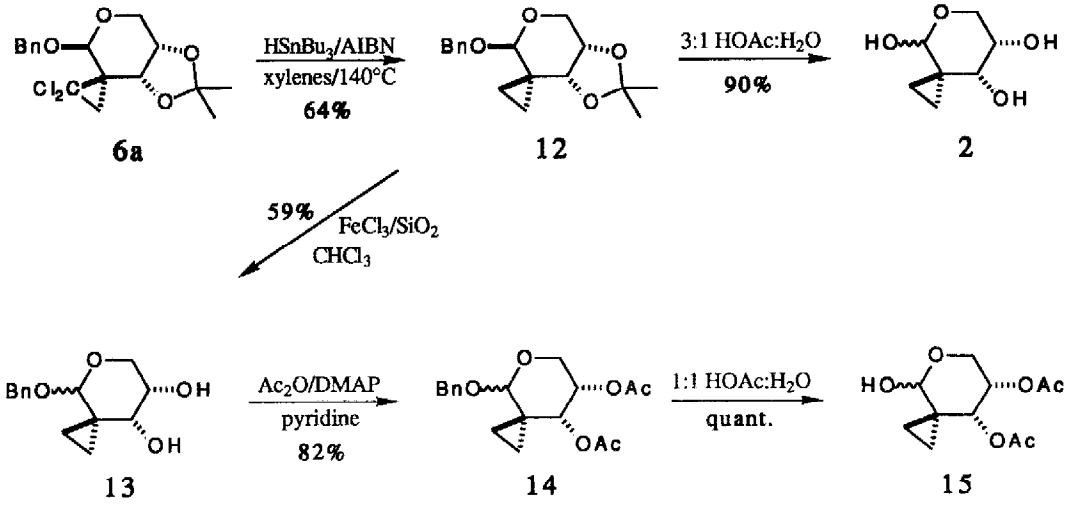
Exposure of **6a** to excess $HSnBu_3$/AIBN in refluxing benzene afforded mono-dechlorinated **9** (one isomer) in good yield. This stereoselectivity was initially puzzling, but reduction in the presence of $DSnBu_3$ yielded [^{2}H]-**9** and a likely mechanism (Scheme III): a) initial formation of α-chlorocyclopropyl radical **10** (which chlorine atom is removed is unclear), which epimerizes rapidly;[13] b) intramolecular hydrogen atom transfer from the nearby benzylic position; and c) reduction of the ensuing benzylic radical **11**. This may provide a route to stereospecifically radiolabeled substrates which would probe the topography of the β-galactosidase active site. Similar

reduction of **6b** also gave partial reduction but without intramolecular hydrogen atom transfer. Intramolecular hydrogen atom transfer competing with chain transfer has considerable precedent.[14]

Scheme III



Scheme IV



Reduction of **6a** with $HSnBu_3$ in refluxing xylenes with slow addition of AIBN/xylenes via syringe pump yielded the totally reduced cyclopropane **12** in 64% yield. Selective removal of the acetonide was considered problematic because solvolysis at the anomeric position should be enhanced by the adjacent cyclopropane.[15] However, $FeCl_3/SiO_2$[16] removed the acetonide and gave **13** as a mixture of anomers. The observation of benzyl alcohol as a by-product suggests that the anomerization proceeds via exocyclic cleavage. Acetylation and further hydrolysis gave **15**, which

can be converted to the desired glycoside substrate analogs by established protocols. Alternatively, hydrolytic deprotection of **12** (aq HOAc) led to **2** (R=H; 10.6/2.9/1.0 pyranose:furanose:open chain by ^{13}C NMR integration). Thus, we have 1) prepared the title compound, 2) discovered reactions which might lead to stereospecifically labeled substrate analogs, and 3) prepared intermediates which may be converted to the required aryl glycosides.

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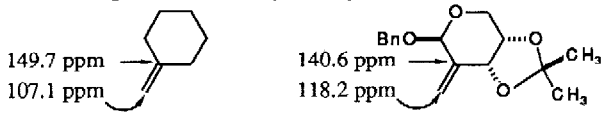

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