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INHIBITION OF PLANT GLYCOSIDASES BY A D-GALACTURONIC ACID ANALOG

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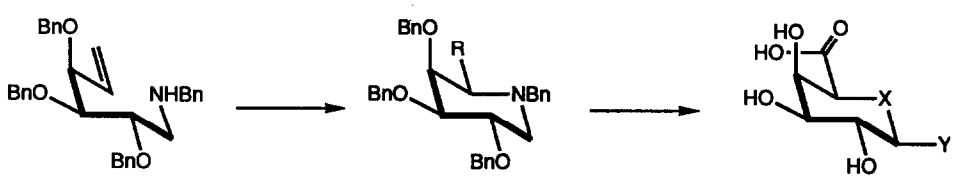
Abstract -- A simple synthesis of the aza-analog **7** of D-galacturonic acid **8** from D-galactose is reported.

The regulation of growth, development, reproduction and defense against disease in plants is largely mediated by low-molecular weight hormones and other chemical messengers. Recently oligosaccharide fragments of the semi-rigid plant cell wall have been discovered which serve as important regulatory molecules in chemical defense, morphogenesis and reproduction.[1] These so-called "oligosaccharins" are released from the cell wall by specific exo- or endoglycosidases in a complex hormonal cascade. One of the most active oligosaccharins is a polymer of D-galacturonic acid **8**, likely released from plant pectic polysaccharide by the appropriate polygalacturonase.[2] Inhibitors of such enzymes could be of significant value in probing the detailed molecular roles of oligosaccharins in the life cycles of higher plants. Recently oligosaccharides incorporating piperidine analogs of sugars have been shown to inhibit endoglycosidases.[3] We now report the enantioselective synthesis of **7** and the effect of this amino acid on various plant galactosidases and galacturonidases. Structure **7** should prove useful as a key building block for the assembly of new, low molecular weight oligosaccharin antagonists.



1

2 R= CH_2HgBr
3 R= CH_2OH
4 R= =O
5 R= CHO
6 R= CO_2H

7 X= NH, Y= H
8 X= O, Y= OH

Aminoalkene (+)-**1**, prepared in 55% yield from D-galactose,[4] was cyclized to **2** under kinetically controlled conditions [$Hg(OCOCF_3)_2$-KBr, 80%]. While ozone has been reported to oxidize primary mercurials to acids,[5] ozonolysis of **2** afforded only traces of **6**. Reductive oxygenation of **2** gave alcohol **3** ($NaBH_4$-O_2-DMF, 78%), but when the oxidation of **3** directly to **6** was attempted using a variety of chromium or manganese reagents, only lactam **4** was obtained (60-75% yield), apparently by enolization and cleavage of intermediate aldehyde **5**. Swern oxidation (DMSO-oxalyl chloride, -78°C) of **3** did afford **5** as a thermally unstable, acid and base-sensitive compound which could not be chromatographed. Brief exposure to Jones reagent (acetone, -40°C, 5 min) followed by workup with aqueous EDTA to remove trace chromium contaminants afforded the desired acid **6** in 15% overall yield[6] from **3**. Hydrogenolysis of **6** (Pd/C) gave **7** quantitatively.[6]

Preliminary assays established azasugar **7** as a potent competitive inhibitor of both plant and *Escherichia coli* α-galactosidases [$K_I = 7.5 \times 10^{-7}$ M for the green coffee bean enzyme at pH 6.6, where $K_M = 1.1$ mM for *p*-nitrophenyl α-D-galactopyranoside]. Of several pectin-degrading enzymes tested, **7** proved to be most active against exopolygalacturonase from *Zea mays* (73% inhibition at 2 mM) and endopolygalacturonase from *A. niger* (50% inhibition at 2 mM). The latter findings are particularly encouraging in view of the fact that most plant wall degrading enzymes usually bind monosaccharides only weakly. The synthesis of oligogalacturonides containing **7** is currently in progress.

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6. Satisfactory spectral and analytical data were obtained for this compound.

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