Epoxidation of 1,2-O-isopropylidene-L-glycero-\(\beta\)-pent-4-enopyranose-3-ulose

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Abstract

The rapid growth in the synthetic carbohydrate chemistry research field requires specifically modified chiral building blocks with improved functional properties. One of these blocks is, 4-deoxy-1,2-O-isopropylidene-L-glycero-pent-4-enopyranose-3-ulose (4) conveniently prepared from L-arabinose.

Further functionalization of 4 into epoxide 5 and its thio analog 6 which are suitable for the synthesis of bioactive thioloigosaccharides was accomplished in our laboratory. However, new protocol that allows stereoselective functionalization of a selected pool of new precursors as functional analogs must be further elaborated. The great feasibility of this new strategy has been demonstrated in a number of new chiral intermediates which can be derived from both epoxides 5 and 6 as new functionalized thio-sugars.

In this work we present preparation of both epoxides 5 and 6 as new chiral building blocks as convenient precursors for the synthesis of new classes of bioactive thiocompounds based oligosaccharides. Those seminal studies also provide a backdrop to our current approaches to the novel (1→5)-5-C-thiodioligosaccharides (Carbohydr. Res. 342, 2007, 1929) as new potential therapeutic agents.

Introduction

Thio-sugars have attracted extremely wide attention as convenient probes for enzyme inhibition studies. Recent evidence suggests that these sulfur derivatives may have therapeutic potential in the treatment of pathological conditions characterized by inappropriate and exuberant cell proliferation, including neoplasia and vascular restenosis. The hyperproliferative activity of epithelial cancers is well known and has been the subject of intensive research over the last 50 years. Restenotic tissue is histologically comprised of neointimal formation due, in large part, to progressive proliferation and migration of smooth muscle cells after the procedure. As part of our continuous interest in thio-sugars as antiproliferative agents we turned our attention to a new method of synthesis of (1→4)-thio- and (1→5)-5-C-thio-disaccharides containing biologically important sugar moieties such as galactose, glucose, fucose and mannose. These compounds are efficiently produced by functionalization of the universal precursor levoglucoesenone and L-arabinose epoxide. The effect of functionalized sulfur containing carbohydrates, including thiobridged disaccharides on cancer or smooth muscle cell line viability/cell growth has not yet been explored in detail.

Methods

General method for the preparation of isomeric 1,2-O-isopropylidene-3-deoxy-3-enoyl-4,5-anhydro-L-arabinose 5A & 5B.

The general methodology of MCPBA epoxidation was improved and modified accordingly: To a solution of enone 4 (126 mg, 0.1 mmol) in anhydrous acetone (40 mL), a 250 mg, 0.34 mmol) of m-chloroperoxybenzoic acid (MCPBA) was added in small portions. The reaction mixture stirred at room temperature for 72 h. TLC (see below) showed quantitative conversion of 4 into 5. The reaction mixture was neutralized with saturated sodium bicarbonate. The separated有机 layer was washed with water (30 mL) and dried with anhydrous magnesium sulfate. After evaporation of the solvent, the syrupy residue was purified by crystallization from acetone/methanol to give two isomeric (1→1) epoxides 5A and 5B in 86% yield. The second crystallization from methyl alcohol gave epoxide 5A, (65 mg) m.p. 86-89°C and 5B (52 mg) m.p. 94-96C.

Isomeric epoxides 2A & 2B and their MM2 minimized molecular model

General method for the preparation of 1,2-O-isopropylidene-3-deoxy-3-enoyl-4,5-thio-\(\alpha\)-arabinose 6.

To a solution of epoxide 5A, (126 mg, 0.1 mmol) in anhydrous acetone (40 mL), a thiourea (125 mg, 0.34 mmol) was added in one portion followed by addition of 1 mL of triethylamine. The reaction mixture was stirred for 72 h. TLC 1:1 EtOAc-hexane (see below) indicated the completion of the reaction in 72 h. After evaporation of the solvent, the syrupy residue was purified by crystallization from methanol. gave pure product 6. Yield 96 mg (76%). M.p. 174-176°C.

MM2 minimized molecular models of epoxide 5A & thioepoxide 6.

Sulfur atom (yellow color) is most accessible to nucleophilic opening

Conclusion

The synthesis of universal precursors of functionalized L-arabinose epoxides and thioepoxides is presented. The conventional epoxidation of L-arabinose enone (4) with m-chloroperoxybenzoic acid (MCPBA) produces easily separable mixture of isomeric epoxides 5A and 5B of extremely high synthetic value. The subsequent conversion of epoxide into thioepoxide derivative 6 proceeds with opening oximate with thiourea to produce thioepoxide 6. These functionalized epoxides are extremely valuable precursors of new class of non-hydrolyzable thioloigosaccharides functionalized at the C-5 position (as indicated with red arrows and red C-5position ) by opening epoxide and thioepoxide with reactive thioles. All synthesized new compounds were obtained in pure forms as examined by TLC and will be analyzed by 1H NMR.

References