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Carbohydrate Research 342 (2007) 1934–1942
Carbohydrate RESEARCH

Note

Synthesis of phosphate derivatives related to the glycosidase inhibitor salacinol

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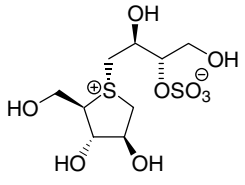
Received 8 May 2007; received in revised form 23 May 2007; accepted 25 May 2007
Available online 2 June 2007

Abstract—The syntheses of polyhydroxylated imino- and anhydro thio-alditol compounds related to the naturally occurring glycosidase inhibitor, salacinol, containing a phosphate group in the side chain are described. The compounds lack hydroxyl groups on the acyclic side chain and are prototypes of the exact salacinol analogue. The synthetic strategy relies on the Mitsunobu reaction of *N*- and *S*-hydroxyalkyl derivatives of 2,3,5-tri-*O*-benzyl-1,4-dideoxy-1,4-imino-D-arabinitol and 1,4-anhydro-2,3,5-tri-*O*-benzyl-1-thio-D-arabinitol with dibenzyl phosphate to yield the corresponding protected heteroalditol phosphates. Screening of these compounds against recombinant human maltase glucoamylase (MGA), a critical intestinal glucosidase involved in the processing of oligosaccharides of glucose into glucose itself, shows that they are not effective inhibitors of MGA and demonstrates the importance of the hydroxyl and/or sulfate substituents present on the side chain for effective inhibition. The attempted synthesis of the exact analogue of salacinol by opening of cyclic phosphates is also described.

Keywords: Glycosidase inhibitors; Salacinol-related compounds; Synthesis; Phosphate derivatives; Maltase glucoamylase

Glycosidases play an important role in the metabolism of carbohydrates and in the processing of specific oligosaccharide structures on glycoproteins; the latter play important roles in intercellular recognition processes and their modification has been implicated in disease states such as cancer.[1–7] Inhibitors of glycosidases[8] have been attractive target compounds for synthetic chemists and biochemists, not only because they serve as useful biological tools for studying the biological functions of oligosaccharides,[9] but also because they have great potential as drugs to treat a variety of carbohydrate-mediated diseases.[10]

Alkaloids mimicking the structures of monosaccharides are now believed to be widespread in plants and microorganisms, and these sugar mimics inhibit glycosidases because of their structural resemblance to the sugar moiety. It has been hypothesized that this strong binding is the outcome of electrostatic interactions of the positively charged, protonated nitrogen atom with carboxylate residues in the enzyme active-site.[11] The lead glycosidase inhibitors bearing a permanent positive charge in the form of cyclic sulfonium ions, and presumably also interacting with active-site carboxylate residues, are perhaps the naturally occurring compounds salacinol (**1**) and kotalanol (**2**).[12,13]



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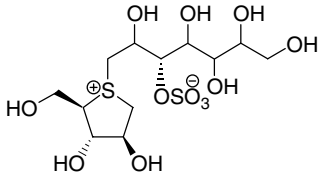

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The replacement of the carboxylic acid functional group in biologically important molecules by phosphoric acid continues to attract much interest in bioorganic and medicinal chemistry.[14] Much of the progress in this field has been associated with the phosphorus analogues of amino acids. The tetrahedral configuration, owing to

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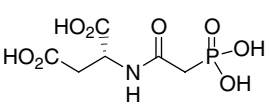
doi:10.1016/j.carres.2007.05.030

the presence of the phosphorus atom, allows these compounds to serve as stable analogues of the unstable tetrahedral intermediates formed in enzymatic processes.



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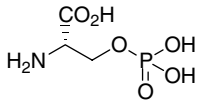

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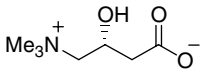

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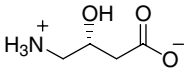

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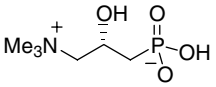

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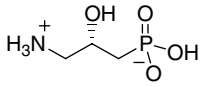

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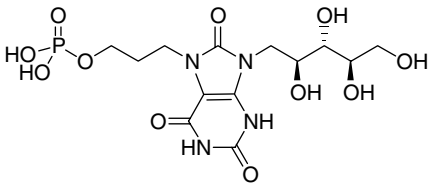

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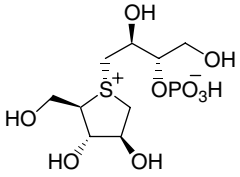

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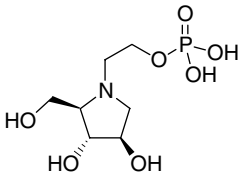

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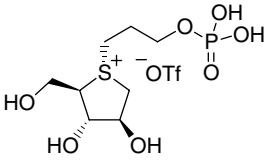

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Many of these compounds act as enzyme inhibitors. Others are very interesting because they can help elucidate the functions of biologically active compounds in living organisms. For example, *N*-(phosphonoacetyl)-L-aspartate (**3**) and *O*-phosphate serine (**4**) were shown to be inhibitors of the carbonic anhydrase enzyme.[15] The involvement of carnitine (**5**) and γ-amino-β-hydroxybutyric acid (**6**) in the biology of mammalian cells and some important aspects of medicinal treatment has led to the development of their pharmacologically potent phosphate analogues (**7**, **8**).[16] The purinetrione bearing an alkyl phosphate (**9**) was tested and found to be an inhibitor of lumazine synthase.[17]

The structural modification of known inhibitors represents a promising approach in the search for new glycosidase inhibitors. It is of interest to synthesize phosphate derivatives of known glycosidase inhibitors containing other internal anions such as sulfates and carboxylates and study their inhibitory activities. Hence, we designed the phosphate analogues (**10**–**12**) of salacinol (**1**) as potential glycosidase inhibitors. These compounds will also serve to test the significance of sulfate and/or hydroxyl groups on inhibition of glycosidases.

Compounds **10**–**12** could be synthesized by alkylating the anhydro-alditol derivatives at the ring heteroatom. The alkylation of a protected 1,4-anhydro-1-thio-D-arabinitol with the cyclic phosphate (**13**) derived from L-erythritol would afford compound **10** (Scheme 1). This potential reaction is patterned after our earlier syntheses of salacinol (**1**) and its analogues by opening of cyclic sulfates.[18–30]

In order to check the general reactivity of cyclic phosphates, the cyclic phosphates (**14**, **15**) derived from D-erythritol were synthesized, in turn, from the less expensive D-glucose using a similar protocol as for the synthesis of the corresponding cyclic sulfate (Scheme 2).[20] The diol (**16**) was prepared in three steps from D-glucose.[20] Subsequent treatment of the diol (**16**) with either *p*-nitrophenyl phosphorodichloridate or phenyl dichlorophosphate gave the D-cyclic phosphates **14** and **15**, respectively.

1,4-Anhydro-2,3,5-tri-*O*-benzyl-1-thio-D-arabinitol (**17**) was prepared from commercially available L-xylose in