Selective biocatalytic deacylation studies on furanose triesters: a novel and efficient approach towards bicyclonucleosides†‡

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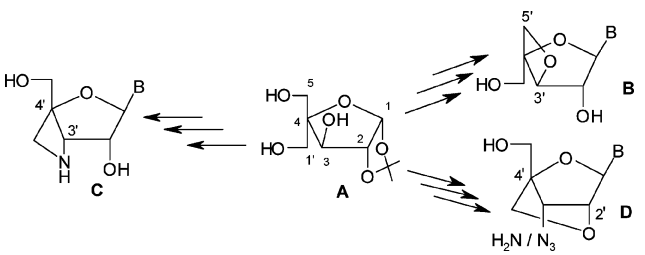
Lipozyme® TL IM catalyses the deacylation of 4-*C*-acyloxymethyl-3,5-di-*O*-acyl-1,2-*O*-(1-methylethylidene)-β-L-*threo*-pentofuranose to form 3,5-di-*O*-acyl-4-*C*-hydroxymethyl-1,2-*O*-(1-methylethylidene)-α-D-*xylo*-pentofuranose in a highly selective and efficient manner. The rate of lipase-catalyzed deacylation of tributanoyl furanose is 2.3 times faster than the rate of deacylation of the triacetyl furanose derivative. In order to confirm the structure of the lipase-catalyzed deacylated product, it was converted to a bicyclic sugar derivative, which can be used for the synthesis of bicyclic nucleosides of importance in the development of novel antisense and antigene oligonucleotides. Further, it has been established that the monohydroxy product of the lipase-catalyzed reaction is the result of selective deacylation of the 4-*C*-acyloxymethyl function in the substrate and not of any acyl migration process.

Introduction

The synthesis of novel nucleoside analogues is gaining importance because of their applications as key intermediates in the development of antisense and/or antigene oligonucleotides to regulate targeted gene expression,[2–12] and for their direct utilization as anti-tumor or antiviral compounds.[13–17] In recent studies for development of ideal and practical antisense molecules, oligonucleotide analogues containing non-genetic 2′,5′-phosphodiester linkages have been found to be good candidates due to their RNA-selective hybridization properties and resistance towards enzymatic degradation.[18–25] A novel class of 2′,5′-linked oligonucleotide analogs containing 3′-*O*,4′-*C*-methylene bridged ribonucleosides—*i.e.* an oxetane-fused ribofuranoside ring system along with normal 3′,5′-linked oligonucleotide analogs containing 2′-*O*,4′-*C*-methylene bridged ribonucleosides—commonly known as locked nucleic acids (LNAs), have been known to possess favorable features towards development of antisense and/or antigene candidates.[26–31]

One of the major problems emphasized in the synthesis of modified nucleosides is the presence of multiple functionalities of nearly identical reactivity which are difficult to protect and deprotect selectively.[32,33] Further, synthetic routes involving various protection and/or deprotection steps reduce the overall yields of the desired products and make the whole process tedious, time-consuming and inefficient.[33,34] It is at this juncture that nature's catalysts, enzymes, come into the picture. Recent advances in enzyme-assisted organic synthesis have allowed the preparation of structurally well-defined molecules in high yields and greater selectivity. The added advantages of the application of enzymes in organic synthesis are that they work under mild reaction conditions and are often environmentally benign. Among the different biocatalytic processes, lipase-catalyzed selective acylation/deacylation reactions represent an important class of enzymatic transformations in organic synthesis, which is mainly attributed to the low cost of lipases and their wide tolerance towards a variety of reaction conditions and substrates.[35,36] Enzymes are being recognized as efficient catalysts for many of the stereospecific and regioselective reactions necessary for carbohydrate modifications and nucleoside synthesis.[37–47]

4-*C*-Hydroxymethyl-1,2-*O*-(1-methylethylidene)-β-L-*threo*-pentofuranose (**A**) is an important precursor for the synthesis of different types of bicyclonucleosides, *i.e.* 3′-*O*,5′-*C*-methylene bridged nucleoside **B**, 3′-*N*,4′-*C*-methylene bridged nucleoside **C** and 2′-*O*,4′-*C*-methylene bridged 3′-azido-/3′-aminonucleoside **D** (Scheme 1). For the synthesis of these bicyclonucleosides, discrimination between the two primary hydroxyl groups of the trihydroxyfuranose precursor sugar **A** is highly desired. Chemical



Scheme 1 Compound **A**—a key precursor for the synthesis of various bicyclonucleosides.

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