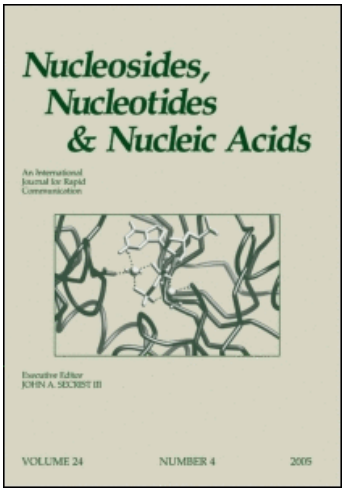

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Cyclic Uridine Diphosphate Glucose: A New Pyrimidine Analog of Cyclic ADP Ribose

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ABSTRACT

Novel compound **1**, as the first example of cyclic ADP-ribose analogs containing a pyrimidine residue, was synthesized by a chemical strategy employing a Mitsunobu reaction for the condensation of the glucosyl moiety on protected uridine, and a Matsuda procedure for the cyclization step.

Key Words: Cyclic ADP-ribose analogs; Uridine derivatives; Mitsunobu reaction; Cyclization.

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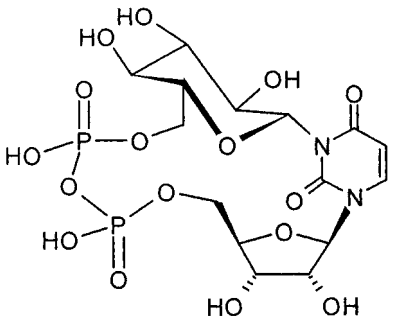
Cyclic ADP-ribose (cADPR) is a newly discovered general mediator involved in Ca^{2+} signaling.[1] The low stability of this cyclic nucleotide, even spontaneously hydrolyzing to yield ADP-ribose, stimulated extensive studies on more stable mimics of cADPR. The ready availability of the NAD^+ cyclising enzyme, ADP-ribosyl cyclase from *Aplysia californica*, rendered enzymatic and chemo-enzymatic methods particularly efficient in the synthesis of cADPR. However, due to the substrate specificity of the enzyme, the analogs that can be obtained following this strategy are limited. In principle the chemical approach is more general and versatile, compared to the enzymatic strategy. Matsuda et al.[2,3] recently proposed an efficient method for the chemical synthesis of cADPR analogs and synthesized cyclic inosine diphosphate-carbocyclic-ribose (cIDPcR) and cyclic adenosine diphosphate-carbocyclic-ribose (cADPcR) as stable mimics of cIDPR and cADPR, respectively, both having the O atom in the ribose ring at the 1-N replaced by a CH_2 group.

We accomplished the chemical synthesis of a new analog of cADPR, i.e., cyclic uridine diphosphate glucose (cUDPG, **1**) as the first example of cyclic nucleotide structurally related to cADPR containing a pyrimidine base. With respect to the natural molecule, the ribose unit is replaced by a glucose moiety, inserted, via a β-glycosidic linkage, in the 3-N position of the pyrimidine.



1, cUDPG

The key steps in the synthetic scheme to efficiently obtain cUDPG are:

i) The regio- and stereoselective insertion of the glycosidic unit on the 3-N position of the uracil base.
ii) The pyrophosphate linkage formation, thus realising the 16-membered cyclic molecule.

The first issue has been addressed by exploiting a Mitsunobu approach;[4] the condensation of 6-O-TBDMS-2,3,4-tri-O-acetylglucose (as an anomeric mixture) with 5′-O-DMT, 2′,3′-di-O-acetyluridine in the presence of tri-*n*-butylphosphine and ADDP led to the desired 3-N derivative **4** in 65% yields (see Sch. 1), which was easily

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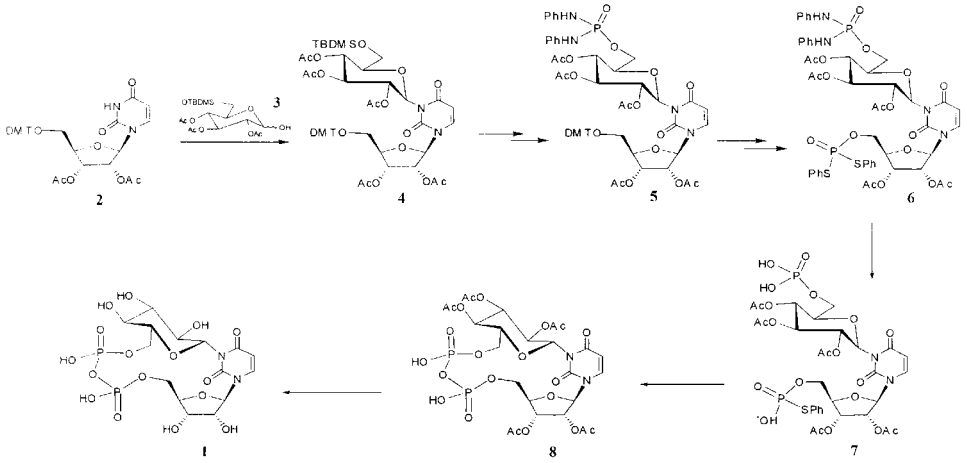

Scheme 1. Preparation of target compound **1**.

separated from the O-4 adduct, obtained in 30% yields, by silica gel chromatography. Both the adducts had only β configuration at the new generated N-glycosidic bond, as ascertained by ROESY experiments.

Compound **4** was then converted, in 6 steps, into key compound **7**, having two distinct phosphate groups: a phosphate esterified at the 6-position of the glucosyl moiety and a phenylthiophosphate esterified at the 5-position of the ribose. The desired pyrophosphate linkage in **1** was achieved essentially following the cyclization procedure described by Matsuda and coworkers.[2,3] Particularly, as the condensing agents, both $AgNO_3$ and I_2 in the presence of molecular sieves were tested, with the latter procedure always being superior, in our experience, both in terms of yields and ease of purification of the reaction mixture. A simple aq. ammonia treatment allowed then target compound **1**. Work is still in progress to optimize yields and scale-up the synthetic process for **1**, in order to test its biological activity.

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