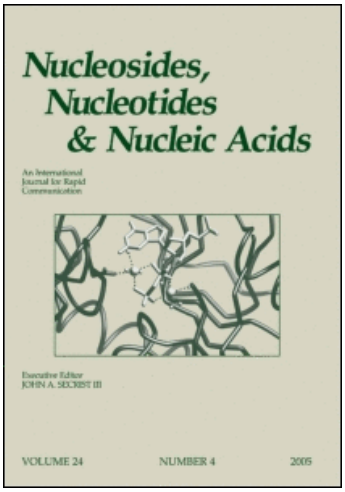

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SYNTHESIS OF A NEW N-9 RIBITYL ANALOGUE OF CYCLIC INOSINE DIPHOSPHATE RIBOSE (cIDPR) AS A MIMIC OF CYCLIC ADP RIBOSE (cADPR)

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▫ *A new analogue of cyclic inosine diphosphate ribose (cIDPR), in which the N-1 and N-9 ribosyl moieties were substituted by a carbocyclic moiety and a hydroxyl-alkyl chain, has been synthesized and characterized.*

Keywords Cyclic ADP Ribose (cADPR), cIDPR, IP3

INTRODUCTION

Many cellular functions are modulated by the concentration of intracellular calcium ions.[1] Two major mechanisms of calcium mobilization are known that utilize calcium stored in cytoplasmic compartments for signalling. The release of Ca^{2+} is triggered by the interaction of the second messenger, inositol 1,4,5-triphosphate (IP3), with its receptor, a ligand-activated calcium-selective channel. A second class of intracellular calcium-releasing channels is the ryanodine receptor.[2] Although the physiological activator of this receptor is unknown, it can be activated by Ca^{2+}, causing the so called Ca^{2+}-induced Ca^{2+} release (CICR). Recent research establishes that, in addition to inositol triphosphate, the internal calcium stores can be mobilized by new messenger molecules *via* cyclic ADP-ribose (cADPR, Figure 1). cADPR that serves as a second messenger to activate the ryanodine receptors of the sarcoplasmic reticulum and to mobilize intracellular Ca^{2+} in many cell types in different species covering protozoa, plants, animals, and human.[3] However, the mechanisms mediating the effect of cADPR remain unknown. Since Ca^{2+} ions are regulators of several cell functions, muscle contraction, secretion of neurotransmitters, hormones and enzymes, fertilization of ovocytes, and

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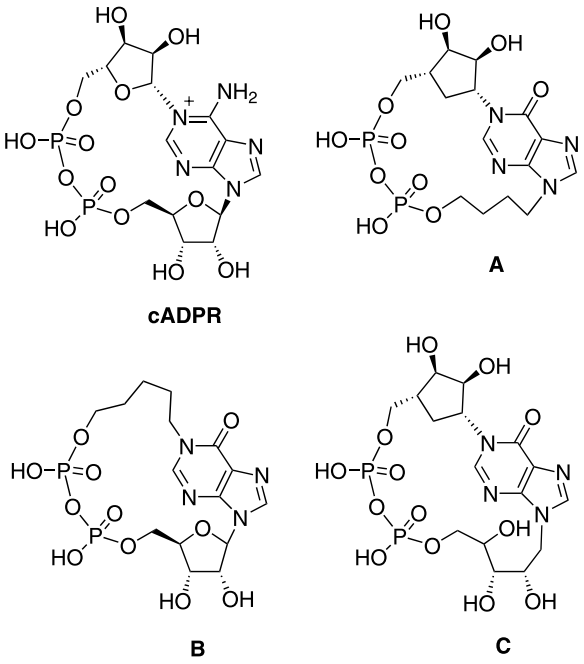


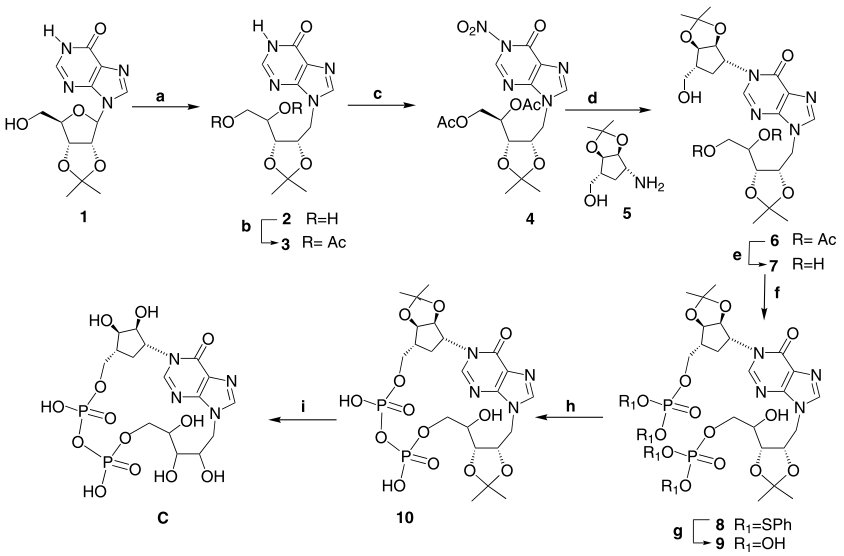
FIGURE 1

lymphocyte activation and proliferation, the cADPR signaling pathway may become a valuable target for pharmaceutical intervention.

cADPR is characterized by a very labile *N-1* glycosidic bond which is rapidly hydrolyzed both enzymatically, by cADP hydrolase, and non-enzymatically, to give ADP-ribose even in neutral aqueous solution. This biological and chemical instability deeply hinders further studies on cADPR aimed at elucidating its physiological role, particularly as far as regulation of Ca^{2+}mobilization in the cells is concerned. Hence, stable yet active cADPR analogues are of great interest in this field.[4]

In our laboratories we have previously synthesized two analogues of cADPR (**A** and **B**, Figure 1).[5,6] These compounds, which display a carboribosyl and a butyl moiety at N-1 and N-9 of a hypoxantine base, respectively, are designed to investigate the role of a ribosyl moiety in the mechanism of Ca^{2+} intracellular modulation. We wish to report here the synthesis of a new cIDPR analogue (**C**, Figure 1) having a three-hydroxylated butyl chain at the N-9 of the hypoxanthine base and a carboribosyl moiety at the N-1 position, which is expected to be resistant to both enzymatic and chemical hydrolysis as are the similar N-1 alkylated analogues.

The synthetic strategy adopted for **C** is shown in Scheme 1. The 2′,3′-O-isopropylidene-inosine **1** was allowed to react with DIBAL-H in anhydrous THF. In this way the sugar moiety was reduced to afford the corresponding 1-D-ribitylinosine derivative **2**. Acetylation of the hydroxyl functions of **2** gave derivative **3**. N-1



SCHEME 1 Reagents and conditions: a) DIBAL-H, THF; b) Ac_2O, pyridine, r.t.; c) NH_4NO_3, TFA, CH_2Cl_2, 0°C; d) **5**, DMF, r.t.; 8 h; e) K_2CO_3, CH_3OH, r.t.;15 min; f) S,S-diphenylphosphorodithioate, TPSCl, pyridine, N_2, r.t.; 8 h; g) AcAg, pyridine/H_2O; h) EDC, NMP, r.t.; 60 h; i) aq. CH_3CO_2H, r.t.; 3.5 h.

nitroinosine derivative **4** was prepared according to the procedure proposed by Vilarrasa and coworkers[7] by treatment of **3** with ammonium nitrate and trifluoroacetic anhydride (TFAA) in dichloromethane. Derivative **6** could be obtained by reaction of **4** with **5** in DMF as previously described.[5] Removal of the acetyl protecting groups of **6** by treatment with K_2CO_3 in MeOH yielded **7**. The bis(phenylthio)phosphoryl groups were introduced on the primary hydroxyl functions by treatment of **7** with S,S-diphenyl-phosphorodithioate (cyclohexylammonium salt) in the presence of 2,4,6-triisopropylbenzenesulphonylchloride (TPSCl) and tetrazole in pyridine to give the protected bisphosphate derivative **8** as the main product together with the triphosphate derivative in a 8:2 ratio. After HPLC (RP18) purification, **8** was treated with silver acetate (Ag Ac) for complete removal of protecting groups of both phosphate residues. The deprotected bisphosphate derivative **9** was further purified by HPLC (RP18) before cyclization, which was performed as previously described,[6] to obtain **10** (50% yield after purification). Finally, **10** was deprotected at phosphate residues by treatment with acetic acid, which afforded the target compound **C** (10% overall yield starting from **1**) whose structure was confirmed by ^1H and ^{31}P NMR and MS data.

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