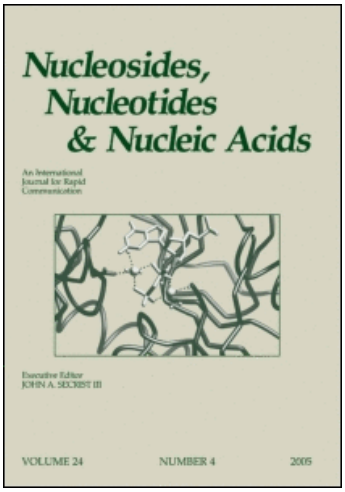

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SYNTHESIS AND BIOLOGICAL ACTIVITIES OF CYCLIC ADP-CARBOCYCLIC-RIBOSE AND ITS ANALOGS

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ABSTRACT

An efficient synthesis of cyclic ADP-carbocyclic-ribose (**2**), as a stable mimic for cyclic ADP-ribose, was achieved. Treatment of N^1-carbocyclic-ribosyladenosine bisphosphate derivative **10** with $AgNO_3$ in the presence of molecular sieves 3A in pyridine gave the desired cyclic product in 93% yield, which was deprotected to give the target cyclic ADP-carbocyclic-ribose (**2**).

Cyclic ADP-ribose (cADPR, **1**)[t] is a newly discovered general mediator involved in Ca^{2+} signaling (2). In cells, although cADPR is synthesized from NAD^+ by ADP-ribosylcyclase and acts as a potent second messenger, it is hydrolyzed promptly by cADPR hydrolase to give inactive ADP-ribose under physiological conditions (2). cADPR is also known to be readily hydrolyzed non-enzymatically at the unstable N-1 glycosidic linkage of its adenine moiety to give ADP-ribose, even in neutral aqueous solution (3). Based on these findings, we designed cyclic ADP-carbocyclic-ribose (**2**) and its inosine congener (**3**) (cyclic IDP-carbocyclic-ribose), in which an oxygen atom in the ribose ring of cADPR is replaced by a methylene group, as stable mimics of cADPR.

The synthesis of cADPR analogs has been extensively studied by enzymatic and chemo-enzymatic methods using ADP-ribosylcyclase from *Aplysia*

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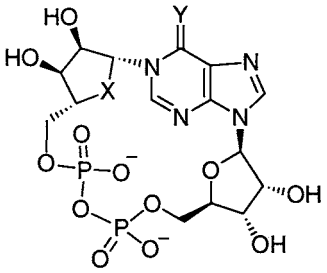

1 (cADPR): X = O, Y = NH
2: X = CH_2, Y = NH
3: X = CH_2, Y = O

Californica, due to their biological importance (4). However the analogs that can be obtained by this method are limited due to the substrate-specificity of the enzyme (4). Accordingly, the development of flexible methods for synthesizing cADPR and a variety of its analogs are needed.

We previously developed an efficient chemical method for the synthesis of cyclic IDP-cabocyclic-ribose **(3)** using intramolecular condensation forming a pyrophosphate linkage by the activation of the phenylthiophosphate group with I_2 or $AgNO_3$ as the key step (5). In this paper, we report the efficient synthesis of cyclic ADP-carbocyclic-ribose (**2)** using this method.

The synthesis of **2** is shown in Scheme 1. We planed to construct the N^1-carbocyclic-ribosyladenosine structure by modified Blackburn's procedure (6). 4-Methoxyimidate derivetive **5** was prepared by heating 5-cyano derivative **4** with methyl orthoformate and the catalytic amount of CF_3CO_2H. The optically active carbocyclic amine **6** was readily prepared from commercially available (1*R*)-(-)-azabicyclo[2.2.1]hept-5-en-3-one (7). Treating a mixture of **5** and **6** with catalytic amount of K_2CO_3 in MeOH gave N^1-carbocyclic-ribosyladenosine derivative **7** in 83% yield. After the 5″-hydroxyl of **7** was protected with a MMTr group, it was treated with TBAF in THF to give 5″-*O*-MMTr derivative **8**. A bis(phenylthio)phosphoryl group was introduced at the primary hydroxyl of the ribose moiety with cyclohexylammonium *S,S*-diphenylphosphorodithioate(PSS)/pyridine system (8), and then the 5″-*O*-MMTr group was removed with aqueous AcOH to give **9**. After the phosphorylation of 5″-primary hydroxyl of **9** with $POCl_3$ in $PO(OEt)_3$ at 0°C, it was treated with H_3PO_2 in pyridine (8) to give N^1-carbocyclic-ribosyladenosine bisphosphate derivative **10**. The intramolecular condensation reaction was achived by treating **10** with $AgNO_3$ and MS 3A in pyridine to give the desired **11** in 93% yield. The two isopropylidene groups of

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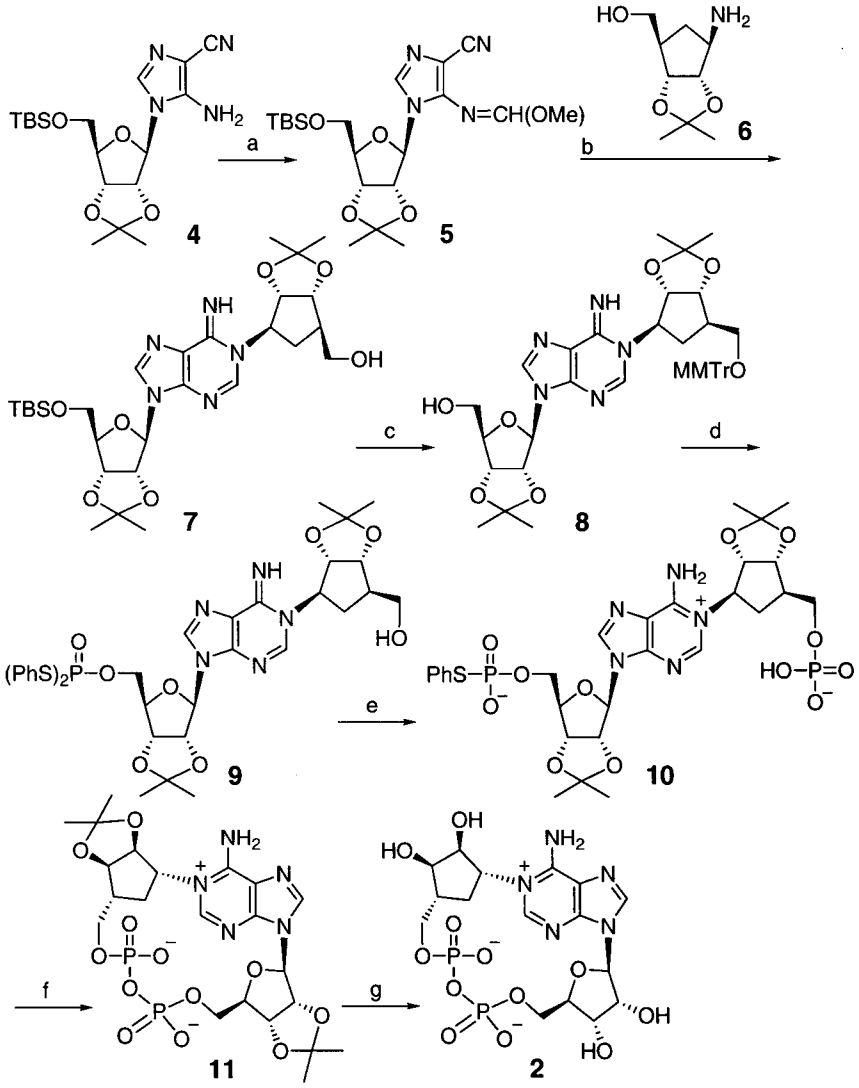

Conditions: a) $HC(OMe)_3$, cat. CF_3CO_2H, reflux, quant; b) K_2CO_3, MeOH, rt, 83%; c) 1) MMTrCl, pyridine, rt, 2) TBAF, THF, AcOH, rt, 71%; d) 1) PSS, TPSCl, py, rt, 2) aq. 80% AcOH, rt, 51%; e) 1) $POCl_3$, $(EtO)_3PO$, rt, 2) H_3PO_2, Et_3N, pyridine, rt, 42%; f) $AgNO_3$, MS 3A, Et_3N, py, rt, 93%; g) HCO_2H, rt, 88%

Scheme 1.

compound **11** was readily deprotected with formic acid, and target compound **2** was obtained in 88% yield.

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