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

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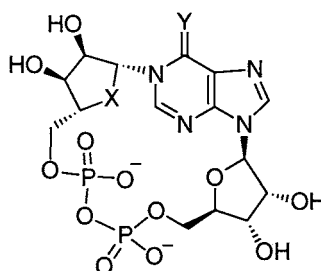
ABSTRACT

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 AgNO₃ 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**)[†] is a newly discovered general mediator involved in Ca²⁺ 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*

*Corresponding author.



1 (cADPR): X = O, Y = NH

2: X = CH₂, Y = NH

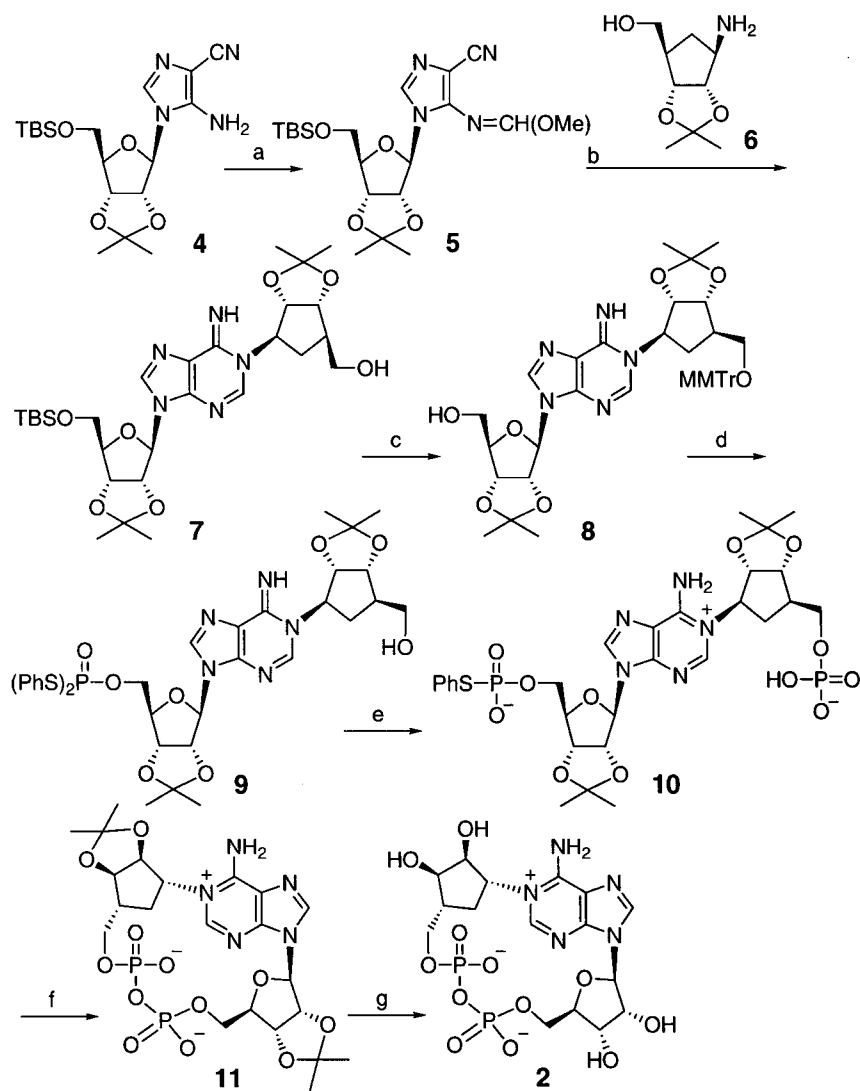
3: X = CH₂, Y = O

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-carbocyclic-ribose (**3**) using intramolecular condensation forming a pyrophosphate linkage by the activation of the phenylthiophosphate group with I₂ or AgNO₃ 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 planned to construct the *N*¹-carbocyclic-ribosyladenosine structure by modified Blackburn's procedure (6). 4-Methoxyimide derivative **5** was prepared by heating 5-cyano derivative **4** with methyl orthoformate and the catalytic amount of CF₃CO₂H. 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 K₂CO₃ 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 POCl₃ in PO(OEt)₃ at 0°C, it was treated with H₃PO₂ in pyridine (8) to give *N*¹-carbocyclic-ribosyladenosine bisphosphate derivative **10**. The intramolecular condensation reaction was achieved by treating **10** with AgNO₃ and MS 3A in pyridine to give the desired **11** in 93% yield. The two isopropylidene groups of





Conditions: a) HC(OMe)_3 , cat. $\text{CF}_3\text{CO}_2\text{H}$, 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 , $(\text{EtO})_3\text{PO}$, 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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