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

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

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### ABSTRACT

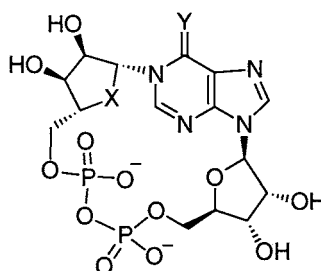
An efficient synthesis of cyclic ADP-carbocyclic-ribose (**2**), as a stable mimic for cyclic ADP-ribose, was achieved. Treatment of *N*<sup>1</sup>-carbocyclic-ribosyladenosine bisphosphate derivative **10** with AgNO<sub>3</sub> in the presence of molecular sieves 3A in pyridine gave the desired cyclic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

Cyclic ADP-ribose (cADPR, **1**)<sup>†</sup> is a newly discovered general mediator involved in Ca<sup>2+</sup> signaling (2). In cells, although cADPR is synthesized from NAD<sup>+</sup> 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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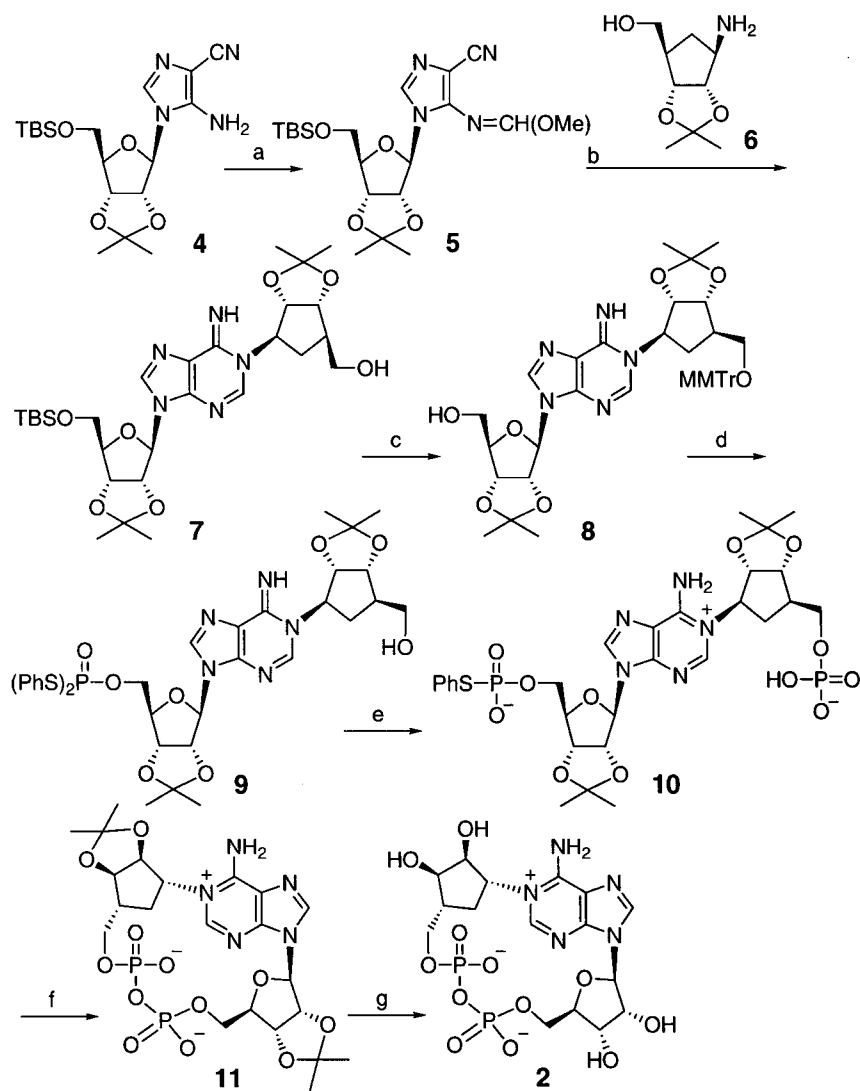
- 1** (cADPR): X = O, Y = NH  
**2**: X = CH<sub>2</sub>, Y = NH  
**3**: X = CH<sub>2</sub>, Y = O

*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 I<sub>2</sub> or AgNO<sub>3</sub> 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*<sup>1</sup>-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 CF<sub>3</sub>CO<sub>2</sub>H. 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<sub>2</sub>CO<sub>3</sub> in MeOH gave *N*<sup>1</sup>-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<sub>3</sub> in PO(OEt)<sub>3</sub> at 0°C, it was treated with H<sub>3</sub>PO<sub>2</sub> in pyridine (8) to give *N*<sup>1</sup>-carbocyclic-ribosyladenosine bisphosphate derivative **10**. The intramolecular condensation reaction was achieved by treating **10** with AgNO<sub>3</sub> and MS 3A in pyridine to give the desired **11** in 93% yield. The two isopropylidene groups of





Conditions: a)  $\text{HC(OMe)}_3$ , cat.  $\text{CF}_3\text{CO}_2\text{H}$ , reflux, quant; b)  $\text{K}_2\text{CO}_3$ , MeOH, rt, 83%; c) 1)  $\text{MMTrCl}$ , pyridine, rt, 2)  $\text{TBAF}$ , THF, AcOH, rt, 71%; d) 1)  $\text{PSS}$ ,  $\text{TPSCl}$ , py, rt, 2) aq. 80%  $\text{AcOH}$ , rt, 51%; e) 1)  $\text{POCl}_3$ ,  $(\text{EtO})_3\text{PO}$ , rt, 2)  $\text{H}_3\text{PO}_2$ ,  $\text{Et}_3\text{N}$ , pyridine, rt, 42%; f)  $\text{AgNO}_3$ , MS 3A,  $\text{Et}_3\text{N}$ , py, rt, 93%; g)  $\text{HCO}_2\text{H}$ , rt, 88%

Scheme 1.

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

## ACKNOWLEDGMENT

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