Nucleosides and Nucleotides. 173. Synthesis of Cyclic IDP-carbocyclic-ribose, a Stable Mimic of Cyclic ADP-ribose. Significant Facilitation of the Intramolecular Condensation Reaction of *N*-1-(Carbocyclic-ribosyl)inosine 5′,6″-Diphosphate Derivatives by an 8-Bromo-Substitution at the Hypoxanthine Moiety

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Received September 24, 1997

Cyclic ADP-ribose (cADPR, **1**) is a general mediator involved in cellular Ca^{2+} signaling. However, both the biological and chemical instability of cADPR limit studies on its physiological role. We designed cyclic ADP-carbocyclic-ribose (**3**) and its inosine congener **4** as stable mimics of cADPR and successfully synthesized **4**. Starting with cyclopentadiene, the optically active carbocyclic unit **8** was constructed via enzymatic optical resolution. S_N2 reactions of **8** with inosine derivative **7** and the 8-bromoinosine derivative **25** gave the *N*-1-substituted derivatives **6** and **26**, which were converted to the corresponding diphosphate derivatives **5** and **22**. The intramolecular condensation reactions between the two phosphate groups of **5** and **22** were investigated. Although the reaction with inosine derivative **5** did not produce any of the cyclization product **20**, treatment of the corresponding 8-bromoinosine derivative **22** with EDC gave the desired intramolecular condensation product **29** in 23% yield. Thus, the significant effect of the 8-bromo group at the hypoxanthine moiety in facilitating the key intramolecular condensation reaction between the phosphate groups of the substrate **22** was recognized. This is possibly due to conformational restriction of the molecule in a syn-form around its glycosyl linkage. The 8-bromo and isopropylidene groups were removed in succession to give the target compound **4**. This is the first total synthesis of this type of cyclic nucleotide.

Introduction

Cyclic ADP-ribose (cADPR, **1**), a recently discovered cyclic nucleotide,[2] has been shown to mobilize intracellular Ca^{2+} in various cells, indicating that it is a general mediator involved in Ca^{2+} signaling.[3] It is also known that cADPR mobilizes Ca^{2+} more actively than inositol 1,4,5-triphosphates (IP_3) by a mechanism completely independent of IP_3.[3] The structure of cADPR has been investigated,[4] and the structure shown in Figure 1 was recently confirmed by X-ray crystallographic analysis.[4c] In cells, cADPR is synthesized from NAD^+ by ADP-ribosyl cyclase and acts as a transient second messenger; it is hydrolyzed promptly by cADPR hydrolase to give ADP-ribose and inactivated under physiological conditions.[3] cADPR is also known to be readily hydrolyzed nonenzymatically at the unstable *N*-1-glycosidic linkage of its adenine moiety to give ADP-ribose, even in neutral aqueous solution ($t_{1/2}$ = 40 h).[5] Although further intensive studies of cADPR is needed because of its biological importance, this biological as well as chemical instability of cADPR limits studies of its physiological role, at least to some extent. Therefore, stable analogues of cADPR that have a Ca^{2+}-mobilizing activity in cells similar to that of cADPR are urgently required.

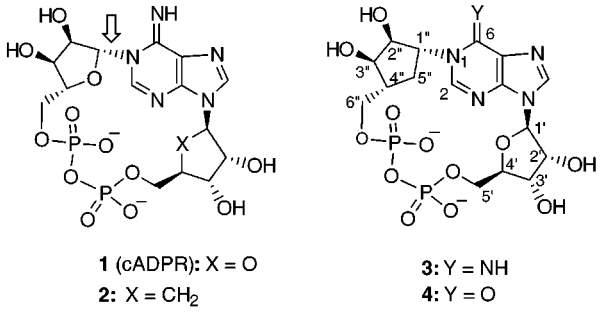


Figure 1.

Recently, the synthesis of cADPR analogues and their biological effects have been studied extensively.[6,7] One analogue, cyclic aristeromycin-diphosphate-ribose (**2**), reported by Potter and co-workers,[6i] may be a useful biological tool, since it acts as a poorly hydrolyzable Ca^{2+}-mobilizing mimic of cADPR. However, **2** is hydrolyzed

(1) Part 172: Shuto, S.; Kanazaki, M.; Ichikawa, S.; Minakawa, N.; Matsuda, A. *J. Org. Chem.*, in press.

(2) Clapper, D. L.; Walseth, T. F.; Dargie, P. J.; Lee, H. C. *J. Biol. Chem.* **1987**, *262*, 9561−9568.

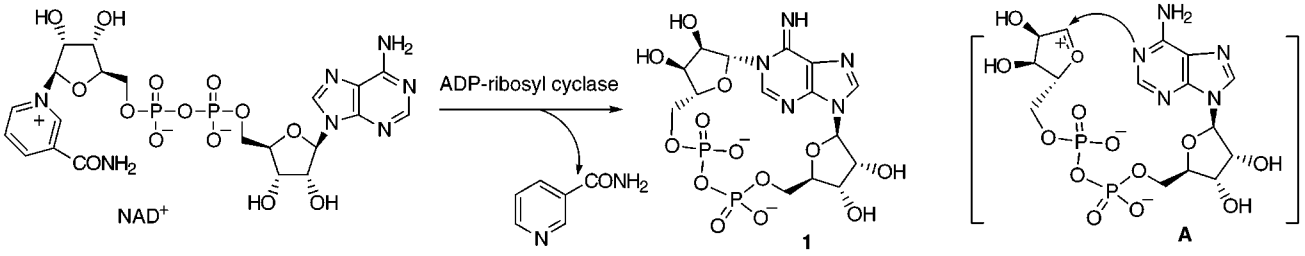
(3) (a) Galione, A. *Trends Pharmacol. Sci.* **1992**, *13*, 304−306. (b) Galione, A. *Science* **1993**, *259*, 325−326. (c) Lee, H. C.; Galione A.; Walseth, T. F. *Vitamines Hormones* **1994**, *48*, 199−257. (d) Jacobson, M. K.; Ame, J. C.; Lin, W. S.; Coyle, D. L.; Jacobson, E. L. *Receptor* **1995**, *5*, 43−49. (e) Lee, H. C. *Cell. Signalling* **1994**, *6*, 591−600.

(4) (a) Lee, C. H.; Walseth, T. F.; Bratt, G. T.; Hayes, R. N.; Clapper, D. L. *J. Biol. Chem.* **1989**, *264*, 1608−1615. (b) Kim, H.; Jacobson, E. L.; Jacobson, M. K. *Biochem. Biophys. Res. Commun.* **1993**, *194*, 1143−1147. (c) Lee, H. C.; Aarhus, R.; Levitt, D. *Nature Struct. Biol.* **1994**, *1*, 143−144. (d) Gu, Q.-M.; Sih, C. J. *J. Am. Chem. Soc.* **1994**, *116*, 7481−7486. (e) Wada, T.; Inageda, K.; Aritomo, K.; Tokita, K.; Nishina, H.; Takahashi, K.; Katada, T.; Sekine, M. *Nucleosides Nucleotides*, **1995**, *14*, 1301−1341.

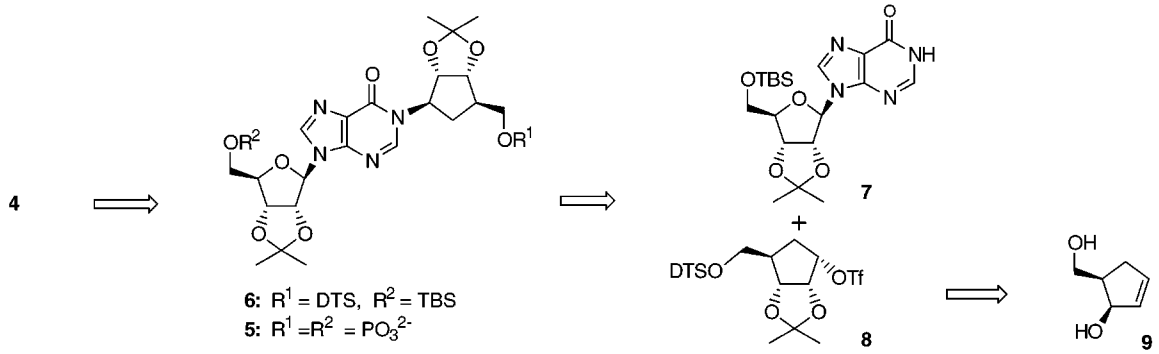
(5) Lee, H. C.; Aarhus, R. *Biochim. Biophys. Acta* **1993**, *1164*, 68−74.

S0022-3263(97)01779-9 CCC: $15.00
Published on Web 02/27/1998

Scheme 1



Scheme 2



by enzymes, although the rate is considerably slower than that of cADPR.[6i] We designed cyclic ADP-carbocyclic-ribose (**3**) and its inosine congener **4** (cIDP-carbocyclic-ribose), as stable mimics of cADPR, in which an oxygen in the ribose ring of cADPR is replaced by a methylene group. The mimics **3** and **4** should be completely resistant to both enzymatic and chemical hydrolysis, because they lack the unstable *N*-1-glycosidic linkage of cADPR. These analogues preserve all the functional groups of cADPR, except for this ring oxygen, and the conformation of these molecules is similar to that of cADPR. Therefore, we expect that these analogues would effectively mobilize intracellular Ca^{2+}, in the same way as cADPR, so that they could be used as pharmacological tools for proving the mechanism of cADPR-modulated Ca^{2+} signaling pathways.

cADPR and its analogues, including **2**, have been synthesized by enzymatic or chemoenzymatic methods.[6,7] As shown in Scheme 1, ADP-ribosyl cyclase from *Aplysia california* mediates the intramolecular ribosylation of NAD^+ and some modified NAD^+ (prepared chemically or enzymatically) at the *N*-1-position of the purine moiety, to yield cADPR or the corresponding analogues.[6] Although the specificity of ADP-ribosyl cyclase is somewhat loose, the analogues that can be obtained by this method are limited by the substrate specificity of the enzyme. A chemical intramolecular ribosylation reaction of NAD^+ mediated by metal halides, such as NaBr, which yields cADPR, has also been reported.[7] This synthesis does not offer any advantages over the enzymatic method.[6f,g] Accordingly, it is important to develop a general method for synthesizing cADPR analogues.[8] Both the enzymatic and chemical intramolecular ribosylation reactions using NAD^+ or its analogues as substrates proceed via nucleophilic substitution at the anomeric 1″-position of a nicotinamide riboside moiety via an oxocarbenium intermediate, such as **A** (Scheme 1), or an enzymatically stabilized equivalent. Our targets **3** and **4** could not be synthesized by the previous methods using enzymatic or chemical intramolecular ribosylation reaction, because they lack *N*-1-glycosidic linkage. We therefore decided to attempt a total synthesis of **3** and **4**. In this paper, we describe the synthesis of the inosine congener **4**.[9]

Results and Discussion

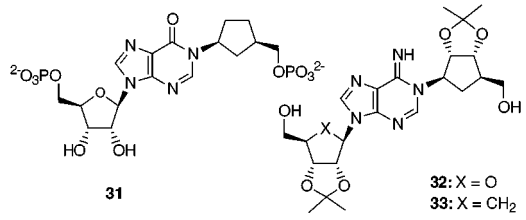
Our synthetic plan is shown in Scheme 2. Cyclization of the 18-membered ring is carried out by intramolecular condensation between the two phosphate groups of diphosphate **5**, which can be prepared from the *N*-1-(carbocyclic-ribosyl)inosine derivative **6**. Compound **6** is obtained in an S_N2 reaction between carbocyclic unit **8**

(6) (a) Walseth, T. F.; Lee, H. C. *Biochim. Biophys. Acta* **1993**, *1178*, 235−242. (b) Lee, H. C.; Aarhus, R.; Walseth, T. F. *Science* **1993**, *261*, 352−355. (c) Graeff, R. M.; Walseth, T. J.; Fryxell, K.; Branton, W. D.; Lee, H. C. *J. Biol. Chem.* **1994**, *269*, 30260−30267. (d) Zhang, F.-J.; Sih, C. J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1701−1706. (e) Zhang, F.-J.; Gu, Q.-M.; Jing, P. C.; Sih, C. J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2267−2272. (f) Zhang, F.-J.; Yamada, S.; Gu, Q.-M.; Sih, C. J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1203−1208. (g) Zhang, F.-J.; Sih, C. J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2311−2316. (h) Ashamu, G. A.; Galione, A.; Potter, B. V. L. *J. Chem. Soc., Chem. Commun.* **1995**, 1359−1356. (i) Bailey, B. C.; Fortt, S. M.; Summerhill, R. J.; Galione, A.; Potter, B. V. L. *FEBS Lett.* **1996**, *379*, 227−230. (j) Bailey, V. C.; Sethi, J. K.; Fortt, S. M.; Galione, A.; Potter, B. V. L. *Chem. Biol.* **1997**, *4*, 51−60. (k) Bailey, V. C.; Sethi, J. K.; Galione, A.; Potter, B. V. L. *J. Chem. Soc., Chem. Commun.* **1997**, 695−696.

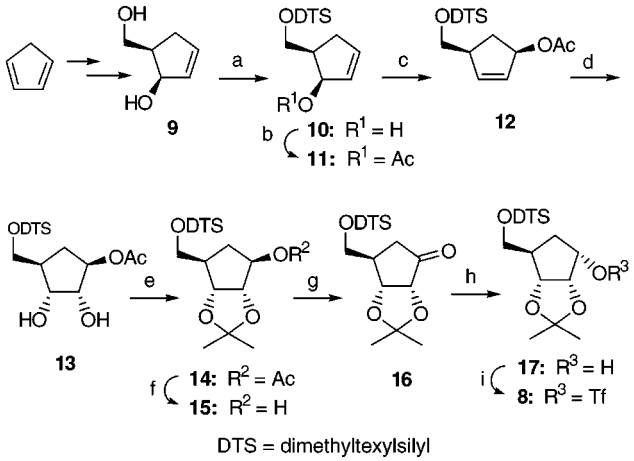
(7) Yamada, S.; Gu, Q.-M.; Sih, C. J. *J. Am. Chem. Soc.* **1994**, *116*, 10787−10788.

(8) Synthesis of cADPR via *N*-1-phosphoribosyladenosine 5′-triphosphate with the enzymes of the histidine biosynthetic pathway has been reported (see ref 4d). However, this method is not applicable to synthesizing various cADPR analogues.

(9) During preparation of this paper, two communications on approaches to carbocyclic analogues of cADP-ribose were published. (a) Synthesis of 1-[(3-hydroxymethyl)cyclopentenyl]inosine diphosphate **31** was described: Fortt, S.; Potter, B. V. L. *Tetrahedron Lett.* **1997**, *38*, 5371−5374. (b) Synthesis of N^1-carbocyclic-ribosyladenosine derivatives, **33** and **34**, was described: Hutchinson, E. J.; Taylor, B. F.; Blackburn, G. M. *J. Chem. Soc. Chem. Commun.* **1997**, 1859−1860.



Scheme 3



Reagents: a) DTSCl, Et_3N, DMAP; b) Ac_2O, Et_3N; c) $PdCl_2(MeCN)_2$, *p*-benzoquinone; d) OsO_4, NMO; e) 2,2-dimethoxypropane, TsOH; f) K_2CO_3, MeOH, g) PDC, molecular sieves 4A; h) $NaBH_4$; i) TfCl, DMAP

and the protected inosine derivative **7**. Carbocyclic unit **8**[10] can be prepared from an optically active cyclopentene derivative **9**, which can also be synthesized from cyclopentadiene.[11]

The synthesis of carbocyclic unit **8** was shown in Scheme 3. Starting with cyclopentadiene, an optically active diol **9**[12] was prepared via optical resolution with *Pseudomonas fluorescens lipase* using the method previously reported by MacKeith and co-workers.[11] The hydroxyls of **9** were successively protected with dimethylthexylsilyl (DTS) and acetyl groups to give **11** in 69% yield. Treatment of **11** with Pd^{2+} in the presence of *p*-benzoquinone in THF[13] produced the desired allylic rearrangement product **12** in a mixture with **11** (60%, **12**:**11** = 10:1). When the mixture of **12** and **11** was treated with OsO_4 in the presence of morpholine *N*-oxide (NMO) in acetone and *t*-BuOH, oxidation proceeded in a highly stereoselective manner. The desired *cis*-diol **13** was isolated in a pure form in 55% yield from **11**, following silica gel column chromatography. After protecting the *cis*-diol of **13** with an isopropylidene group, the 1-*O*-acetyl group was removed with K_2CO_3 in MeOH to give (1*R*)-alcohol **15**. The 1-hydroxyl moiety of **15** was oxidized with PDC/molecular sieves 4 A in CH_2Cl_2 to give**16** in 92% yield. When the ketone **16** was treated with $NaBH_4$ in MeOH at −20 °C, highly stereoselective reduction at the 1-position occurred to give the (1*S*)-alcohol **17** in 88% yield. The stereochemistries of **15** and **17** were confirmed from *J* values in ^1H NMR and NOE experiments.[14] The (1*S*)-alcohol **17** was converted to the corresponding 1-*O*-triflate **8**. This was unstable and used for the next reaction immediately without purification.

S_N2 reactions between the carbocyclic unit **8** and 2′,3′-*O*-isopropylidene-5′-*O*-TBS-inosine **7** in the presence of a base were investigated under various conditions.[15,16] When the reactions were performed using organic bases, such as DBU, or in polar solvents, such as DMF, the O^6-substituted derivative **18** was a major product. The use of relatively softer bases and nonpolar solvents increased the yield of the desired product **6**. The optimum result occurred when the reaction was performed with equimolar **8** and **7**, in the presence of K_2CO_3 in DME at 50 °C. The product included the *N*-1-(carbocyclic-ribosyl) derivative **6** in 48% yield and the O^6-substituted derivative **18** in 7% yield. Adding 18-crown-6 to the reaction system did not improve the yield of **6**. The IR spectrum of **6** showed a strong $\nu_{C=O}$ absorption peak at 1703 cm^{-1} caused by the C-6 carbonyl, which is typical for the 1*H*-hypoxanthine structure. Similar absorption around 1700 cm^{-1} was not observed in the spectrum of **18**. The ^{13}C NMR chemical shift pattern of the base moiety of **6** was analogous to those of inosine and *N*-1-ribosyl inosine derivatives, but the shift pattern of the base moiety of **18** was significantly different.[17] These results suggest *N*-1- and O^6-substituted structures for **6** and **18**, respectively. The regio- and stereochemistries of **6** were further confirmed by NOE experiments. When the H-2 of **6** was irradiated, 4.2% NOE at the H-2″ of the carbocyclic moiety was observed. No NOE at the H-2″ was produced by irradiation at the H-2 of **18**.

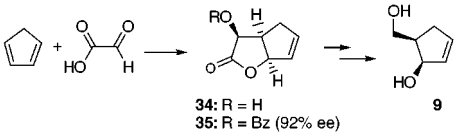
Simultaneous removal of the TBS and DTS groups by treating **6** with TBAF in THF produced **19**. The two phosphate groups were introduced by Yoshikawa's method:[18] treatment of **19** with $POCl_3$ in $PO(OEt)_3$ at 0 °C and subsequent C-18 column chromatography gave the diphosphate derivative **5** as a triethyammonium salt in 37% yield. The intramolecular condensation reaction between the two phosphate groups of **19** was investigated with 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDC) in *N*-methylpyrrolidone (MPD) under various conditions. However, the desired cyclization product **20** was not obtained.

Sih and co-workers attempted to synthesize cADPR by intramolecular condensation of *N*-1-phosphoribosyl-AMP (**21**) with EDC,[4d] but it was unsuccessful (<1%),[4d] similar to our result. It is presumed that the conformation of

(10) Although synthesis of an optically active 1-trifluoromethanesulfonyloxy cyclopentane derivative similar to **8** via resolution with (+)-*N*,*S*-dimethyl-*S*-phenylsulfoximine or electric eel acetylcholinesterase has been reported (Schmitt, L.; Caperelli, C. A. *Nucleosides Nucleotides* **1995**, *14*, 1929−1945, and references therein), the synthetic route is different from our route.

(11) MacKeith, R. A.; McCague, R.; Olivo, H. F.; Palmer, C. F.; Roberts, S. M. *J. Chem. Soc., Perkin Trans 1* **1993**, 313−314.

(12) Compound **34**, a precursor for **9**, was converted to the benzoate **35**, and its optical purity was determined as 92% ee by chiral HPLC (Chiralcel-OJ, Daicel Chemical).



(13) (a) Oehlschlager, A. C.; Mishra, P.; Dhami, S. *Can. J. Chem.* **1984**, *62*, 791−797. (b) Medich, J. R.; Kunnen, K. B.; Johnson, C. R. *Tetrahedron Lett.* **1987**, *28*, 4131−4134.

(14) **15**: $J_{1,2}$ = about 0 Hz; NOE, irradiated H-1, observed H-5$_\alpha$ (3.2%), H-2 (2.2%). **17**: $J_{1,2}$ = 5.4 Hz; NOE, irradiated H-1, observed H-5$_\beta$ (4.2%), H-2 (5.1%).

(15) Reactions of **7** with the corresponding 1-*O*-mesylate of **17** was also tried. However, **6** was not obtained at all.

(16) Sekine et al. investigated *N*-1 selective ribosylation of sugar-protected inosines under various conditions, but the yields were very low: Arimoto, K.; Urashima, C.; Wada, T.; Sekine, M. *Nucleosides Nucleotides* **1996**, *15*, 1−16.

(17) ^{13}C NMR data of base moieties: inosine (Kalinowski, H.-O.; Berger, S.; Braun, S. *Carbon-13 NMR spectroscopy*; John Miley & Sons: 1988); δ 156.9 (C6), 148.5 (C4), 146.2 (C2), 140.2 (C8), 124.6 (C5). 1-(5-*O*-Trityl-2, 3-*O*-isopropylidene-α-D-ribofuranosyl)-2′,3′,5′-*O*-tris(*tert*-butyldimethylsilyl)inosine (ref 16); δ 155.2 (C6), 146.1 (C2), 145.1 (C4), 139.5 (C8), 123.4 (C5). **6**; δ 156.5 (C6), 146.5 (C2), 146.3 (C4), 138.4 (C8), 125.2 (C5). **18**; δ 160.1 (C6), 152.5 (C2), 151.9 (C4), 141.0 (C8), 122.5 (C5).

(18) Yoshikawa, M.; Kato, T.; Takenishi. T. *Bull, Chem. Soc. Jpn.* **1969**, *42*, 3505−3508.

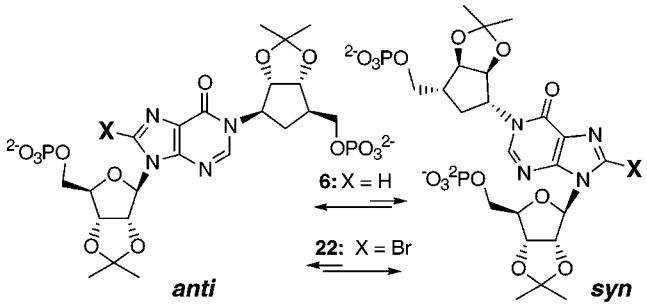


Figure 2.

the molecule determines whether the intramolecular condensation reaction between the two phosphate groups of **5** and **21** occurs. The syn-anti conformation around the glycosyl linkages of the nucleosides has been recognized as an important determinant of the three-dimensional structure of these molecules.[19] Although a syn conformation in **5** and **21**, in which the two phosphate moieties are near each other, may be preferable for occurrence of the desired condensation reaction, the predominance of anti- over syn-conformers is well-known for natural nucleosides and their analogues. This may be why the intramolecular condensation reactions of **5** and **21** were unsuccessful. Introducing a bulky substituent into the 8-position of purine nucleosides is known to restrict the conformation in a syn-form, through the steric repulsion for the ribose moiety.[19,20] We therefore designed an 8-bromo-substituted substrate **22** for the intramolecular condensation reaction. As shown in Figure 2, the 8-bromo group may restrict the conformation of **22** to the syn-form and facilitate the desired intramolecular condensation reaction between the two phosphate groups. After cyclization, it can be readily removed by catalytic hydrogenation.

The 8-bromo-substituted substrate **22** was synthesized following the steps in Scheme 6. 8-Bromo-2′,3′-*O*-isopropylideneadenosine (**23**), prepared by a previously reported method,[21] was treated with $NaNO_2$ in aqueous AcOH to give the corresponding inosine derivative **24**. The 5′-hydroxy group of **24** was protected with a TBS group to give the 8-bromoinosine unit **25**. The S_N2 reaction between **25** and the carbocyclic unit **8** was performed in a manner similar to that used for preparing **6** to gave the desired *N*-1-substituted **26** in 44% yield, along with the corresponding O^6-substituted isomer **27** (9%). The structures of **26** and **27** were confirmed by analyses similar to those described above, used to determine the structures of **6** and **18**. The silyl protecting groups of **26** were removed with TBAF to give **28**. First, the phosphorylation of the two hydroxy groups of **28** was performed with $POCl_3/PO(OEt)_3$. Although phosphorylation at the two hydroxyl groups proceeded under the conditions, the reaction was somewhat tricky and not reproducible: replacement of the 8-bromo group with a chloro atom was sometimes observed which was recognized from the mass spectrometric analysis. The desired diphosphate **22** was successfully obtained by a phosphoramidite method. Treatment of **28** with (2-cyanoethoxy)(*N*,*N*-diisopropylamino)chlorophosphine and *i*-Pr_2-NEt in MeCN afforded the corresponding 5′,6″-bis(phosphoramidite) compound which was successively treated with I_2/tetrazole in aqueous pyridine−THF and NH_3/MeOH to give diphosphate **22**, the substrate for cyclization, in a pure form after DEAE-Sephadex column chromatography. The intramolecular condensation reaction of **22** was investigated with EDC in MPD. At room temperature, the reaction barely proceeded. However, when **22** was treated with 2.0 equiv of EDC in MPD at 50 °C, the desired cyclization product **29** was obtained as a sodium salt in 23% yield after purification by ion-exchange column chromatography. The cyclic structure of **29** was confirmed by the following data: (1) The molecular-ion peaks corresponding to **29** were observed at *m*/*z* 697 and at *m*/*z* 699 in a FAB mass spectrum; (2) Its ^{31}P NMR spectrum showed two signals, observed at −10.67 and −10.95 ppm, which are typical chemical shifts for a pyrophosphate moiety, with a coupling constant (J = 15.0 Hz) similar to that of cADPR (−9.92 and −10.67 ppm, J = 14.6 Hz);[4e] (3) It was completely resistant to alkaline phosphatase which hydrolyzes phosphomonoester linkages.[22] These results suggest that, as expected, the conformation of **22** may be restricted in a syn-form to facilitate the intramolecular condensation reaction between the two phosphates. Next, the 8-bromo group of **29** was removed reductively by catalytic hydrogenation with Pd−carbon in MeOH to give **30** in 77% yield. Finally, **30** was treated with aqueous formic acid, and the target cIDP-carbocyclic-ribose (**4**) was isolated in 67% yield.

In conclusion, we designed carbocyclic analogues **3** and **4** as stable mimics of cADPR and successfully synthesized the inosine congener **4**. This is the first total synthesis of a cADPR related compound and may lead to the development of a general method for synthesizing these compounds, hopefully including **3**, our next target. In this study, we found a significant effect of the 8-bromo group in the hypoxanthine moiety. This is probably due to conformational restriction of the molecule in a syn-form around its glycosyl linkage, which facilitates the key intramolecular condensation reaction between the phosphate groups of the *N*-1-(carbocyclic-ribosyl)inosine diphosphates.

Synthesis of **3** and the biological evaluation of **4** are now under investigation.

Experimental Section

Melting points are uncorrected. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded at 270, 400, and 500 MHz (^1H), at 67.8 and 125 MHz (^{13}C), and at 125 MHz (^{31}P). Chemical shifts are reported in ppm downfield from TMS (^1H and ^{13}C) or H_3PO_4 (^{31}P), and J values are given in hertz. Mass spectra were obtained by the electron ionization (EI) or fast atom bombardment (FAB) methods. Thin-layer chromatography was done on Merck coated plate $60F_{254}$. Silica gel chromatography was done with Merck silica gel 5715. Reactions were carried out under an argon atmosphere.

(1*S*,5*R*)-1-Hydroxy-5-[[(dimethylthexylsilyl)oxy]methyl]-2-cyclopentene (10). To a stirring solution of **9**[11] (5.00 g, 43.8 mmol), DMAP (300 mg, 2.50 mmol), and Et_3N (15.0 mL, 108

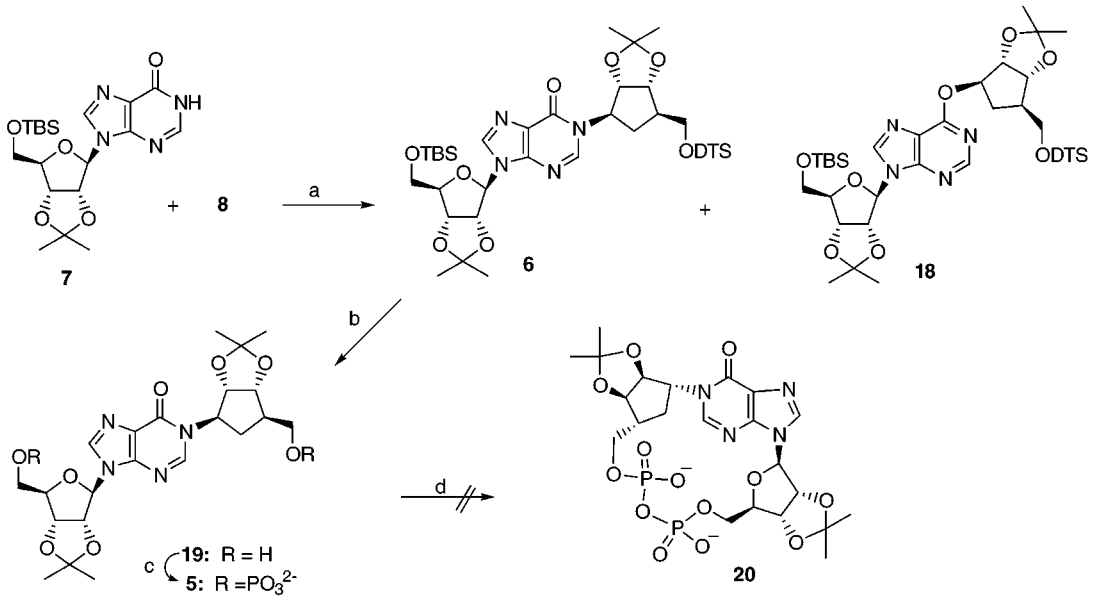
(19) Saenger, W. *Principals of nucleic acid structure*; Springer-Verlag: 1983.

(20) (a) Travale, S. S.; Sobell, M. *J. Mol. Biol.* **1970**, *48*, 109−123. (b) Ikehara, M.; Uesugi, S.; Yoshida, K. *Biochemistry* **1972**, *11*, 830−836.

(21) Ikehara, M.; Uesugi, S.; Kaneko, M. *Tetrahedron* **1970**, *26*, 4251−4259.

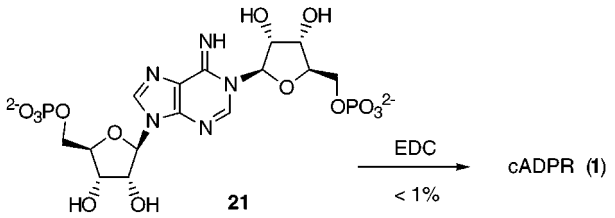
(22) Compound **29** (0.1 OD) was incubated with calf intestinal alkaline phosphatase (6 units) in Tris-HCl buffer (500 mM, pH 8.0, 100 μL) containing 10 mM of $MgCl_2$ at 37 °C for 12 h, and the reaction mixture was analyzed by HPLC.

Scheme 4



Reagents: a) K_2CO_3 ; b) TBAF; c) $POCl_3$, $(EtO)_3PO$; d) EDC

Scheme 5



mmol) in DMF (70 mL) and CH_2Cl_2 (150 mL) was added DTSCl (3.8 mL × 5, at 8 h intervals, total 96.6 mmol) at room temperature, and the mixture was stirred at room temperature for tolal 40 h. The resulting mixture was partitioned between $CHCl_3$ (500 mL) and brine (300 mL). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 5−50% of EtOAc in hexane) to give **10** (8.00 g, 71%) as an oil: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.97−5.92 (m, 1 H), 5.86−5.80 (m, 1 H), 4.90−4.83 (m, 1 H), 3.85 (dd, 1 H, J = 4.6, 10.0), 3.76 (dd, 1 H, J = 7.5, 10.1), 2.48−2.38 (m, 1 H), 2.35−2.29 (m, 1 H), 2.23−2.13 (m, 1 H), 1.62 (m, 1 H, J = 6.8), 0.88 (d, 6 H, J = 6.8), 0.86 (s, 6 H), 0.11, 0.10 (each s, each 3 H); MS (EI) m/z 256 (M^+). This oil was directly used in the next reaction.

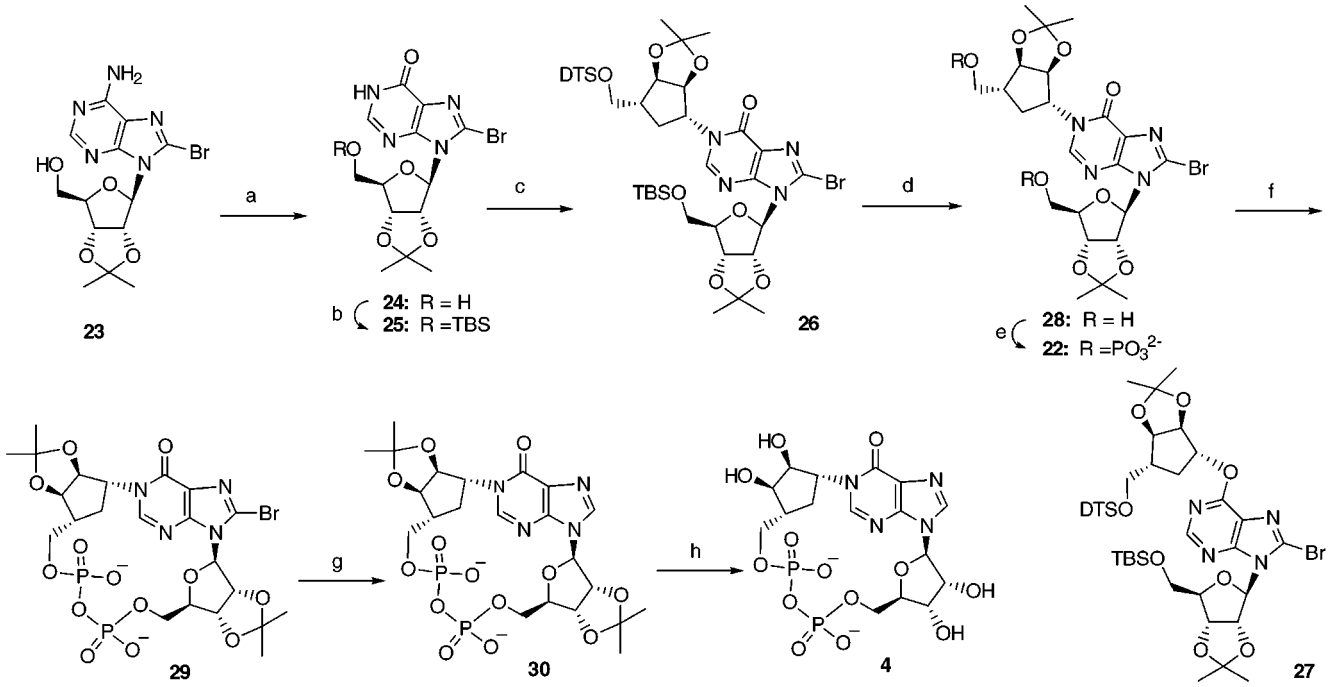
(1*S*,5*R*)-1-Acetoxy-5-[[(dimethylthexylsilyl)oxy]methyl]-2-cyclopentene (11). A mixture of **10** (4.11 g, 16.0 mmol), DMAP (100 mg, 0.82 mmol), Et_3N (7.80 mL, 56.0 mmol), and Ac_2O (4.9 mL, 52 mmol) in MeCN (300 mL) was stirred at 0 °C for 1 h. After EtOH (50 mL) was added, the resulting solution was evaporated under reduced pressure, and the residue was partitioned between EtOAc (300 mL) and water (150 mL). The organic layer was washed with brine (150 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 5% of EtOAc in hexane) to give **11** (4.60 g, 98%) as an oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.12−6.06 (m, 1 H), 5.85 (m, 1 H), 5.68 (ddd, 1 H, J = 6.9, 6.9, 2.1), 3.76 (dd, 1 H, J = 7.3, 9.9), 3.57 (dd, 1 H, J = 7.2, 9.9), 2.59−2.42 (m, 1 H), 2.40−2.35 (m, 1 H), 2.28−2.15 (m, 1 H), 2.01 (s, 3 H), 1.60 (m, 1 H), 0.86 (d, 6 H, J = 6.8), 0.83 (s, 6 H), 0.080, 0.070 (each s, each 3 H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 170.6, 137.1, 129.6, 78.6, 61.6, 43.3, 34.6, 34.2, 24.9, 21.1, 20.4, 20.2, 20.2, 18.5, −3.30, −3.50; $[\alpha]^{19}_D$ −96.7 (c 0.390, $CHCl_3$); MS (EI) m/z 213 (M^+ − thexyl). Anal. Calcd for $C_{16}H_{30}O_3Si$: C, 64.38; H, 10.13. Found: C, 64.36; H, 10.09.

(1*R*,2*R*,3*R*,4*R*)-1-Acetoxy-4-[[(dimethylthexylsilyl)oxymethyl]cyclopentane-2,3-diol (13). A mixture of **11** (7.01 g, 23.5 mmol), *p*-benzoquinone (891 mg, 7.96 mmol), and $PdCl_2(MeCN)_2$ (180 mg, 0.690 mmol) in THF (250 mL) was stirred at 50 °C for 30 min. After cooling to room temperature, the mixture was evaporated under reduced pressure, and the residue was purified by column chromatography (SiO_2, 5% of EtOAc in hexane) to give **12** as a mixture with **11** (4.20 g, 60%, **12**:**11** = 10:1, from ^{1}H NMR spectrum) as an oil, which was directly used in the next reaction: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 6.05−6.02 (m, 1 H), 5.83 (dt, 1 H, J = 2.1, 5.6), 5.67−5.62 (m, 1 H), 3.51 (d, 2 H, J = 6.8), 2.84−2.77 (m, 1 H), 2.42 (ddd, 1 H, J = 8.0, 8.0, 14), 2.00 (s, 3 H), 1.63 (m, 1 H), 1.50 (ddd, 1 H, J = 8.0, 8.0, 14), 0.88 (d, 6 H, J = 6.8), 0.82 (s, 6 H), 0.09 (s, 6 H); MS (FAB) m/z 331 (MH^+). ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 170.9, 138.5, 130.3, 79.7, 66.6, 47.4, 33.1, 20.4, 20.3, 20.1, 20.0, 18.6, 18.5, 18.4, −1.5, −3.5.

A solution of OsO_4 in *t*-BuOH (5 mg/mL, 3 mL) was added to a solution of the above oil (4.20 g) and NMO (1.98 g, 16.9 mmol) in acetone (60 mL) and *t*-BuOH (10 mL), and the resulting mixture was stirred at room temperature for 8 h. After $Na_2S_2O_4$ (1.0 g) and talc (2.0 g) were added, the resulting mixture was stirred at room temperature for 20 min, and the insoluble materials were filtered off. The filtrate was evaporated under reduced pressure, and the residue was purified by column chromatography (SiO_2, 40% of EtOAc in hexane) to give **13** (4.30 g, 55% from **11**) as an oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.96−4.92 (m, 1 H), 3.96 (dd, 1 H, J = 5.3, 9.4), 3.95 (dd, 1 H, J = 4.1, 9.4), 3.72 (dd, 1 H, J = 4.7, 9.9), 3.55 (dd, 1 H, J = 6.3, 9.9), 3.27 (br s, 1 H), 2.84 (br s, 1 H), 2.31 (ddd, 1 H, J = 8.4, 8.4, 13.7), 2.20−2.12 (m, 1 H), 2.05 (s, 3 H), 1.61 (m, 1 H), 1.39 (ddd, 1 H, J = 4.6, 8.3, 13.7), 0.87 (d, 6 H, J = 6.8), 0.83 (s, 6 H), 0.09 (s, 6 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.8, 79.9, 76.8, 74.7, 64.5, 44.3, 34.1, 29.4, 25.1, 21.0, 20.3, 20.1, 18.5, 18.5, −3.6, −3.7; $[\alpha]^{18}_D$ −0.679 (c 0.588, $CHCl_3$); MS (FAB) m/z 333 (MH^+). Anal. Calcd for $C_{16}H_{32}O_5Si$: C, 57.80; H, 9.70. Found: C, 57.70; H, 9.52.

(1*R*,2*R*,3*R*,4*R*)-1-Acetoxy-2,3-(isopropylidenedioxy)-4-[[(dimethylthexylsilyl)oxy]methyl]cyclopentane (14). A mixture of **13** (5.0 g, 15.0 mmol), dimethoxypropane (18.8 mL, 153 mmol), and $TsOH\cdot H_2O$ (290 mg, 1.53 mmol) in acetone (120 mL) was stirred at room temperature for 3 h. After being neutralized with aqueous saturated $NaHCO_3$, the mixture was evaporated under reduced pressure, and the residue was partitioned between EtOAc (300 mL) and water (150 mL). The organic layer was washed with brine (150 mL), dried (Na_2-

Scheme 6



Reagents: a) $NaNO_2$, AcOH ; b) TBSCl, imidazole; c) **8**, K_2CO_3; d) TBAF; e) 1) $CNCH_2CH_2OP(Cl)N$*i*-Pr_2, *i*-Pr_2NEt, 2) I_2, tetrazole, aq.py, 3) NH_3/MeOH; f) EDC; g) H_2, Pd-C; h) 60% HCO_2H

SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 15% of EtOAc in hexane) to give **14** (5.1 g, 91%) as an oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.05−5.00 (m, 1 H), 4.50 (d, 1 H, J = 6.1), 4.47 (d, 1 H, J = 6.1), 3.52 (dd, 1 H, J = 7.0, 10.1), 3.52 (dd, 1 H, J = 6.4, 10.1), 2.32−2.25 (m, 2 H), 2.05 (s, 3 H), 1.69 (m, 1 H), 1.61 (m, 1 H), 1.46, 1.28 (each s, each 3 H), 0.88 (d, 6 H, J = 6.8), 0.84 (s, 6 H), 0.09 (s, 6 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.0, 111.1, 84.8, 81.7, 79.8, 63.4, 47.1, 34.2, 31.6, 26.8, 25.1, 24.3, 21.1, 20.3, 20.3, 18.4, −3.51, −3.55; $[\alpha]^{18}_D$ −23.0 (*c* 0.482, $CHCl_3$); MS (FAB) *m*/*z* 373 (MH^+). Anal. Calcd for $C_{19}H_{36}O_5Si$: C, 61.25; H, 9.74. Found: C, 61.06; H, 9.77.

(1*R*,2*S*,3*R*,4*R*)-2,3-*O*-Isopropylidene-4-[[(dimethylthexylsilyl)oxy]methyl]cyclopentane-1,2,3-triol (15). A mixture of **14** (5.00 g, 13.4 mmol) and K_2CO_3 (500 mg, 3.6 mmol) in MeOH (120 mL) was stirred at room temperature for 1 h. After being neutralized with 1 M AcOH in benzene, the mixture was evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 15% of EtOAc in hexane) to give **15** (4.00 g, 90%) as an oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.55 (d, 1 H, H-3, $J_{2,3}$ = 5.7), 4.39 (d, 1 H, H-2, $J_{2,3}$ = 5.7), 4.07 (d, 1 H, H-1, $J_{1,5\alpha}$ = 5.2), 4.07 (br s, 1 H, OH), 3.83 (dd, 1 H, H-6a, $J_{4,6a}$ = 3.4, $J_{6a,6b}$ = 10.1), 3.62 (dd, 1 H, H-6b, $J_{4,6b}$ = 2.9, $J_{6a,6b}$ = 10.1), 2.45 (ddd, 1 H, H-5α, $J_{1,5\alpha}$ = 5.2, $J_{4,5\alpha}$ = 9.6, $J_{5\alpha,5\beta}$ = 14.4), 2.31 (br d, 1 H, H-4, $J_{4,5\alpha}$ = 9.6), 1.64 (m, 1 H, thexyl CH), 1.55 (br d, 1 H, H-5β, $J_{5\alpha,5\beta}$ = 14.4), 1.42, 1.28 (each s, each 3 H, isopropyl CH_3), 0.88 (d, 6 H, thexyl CH_3, J = 6.8), 0.87 (s, 6 H, thexyl CH_3), 0.16, 0.15 (each s, each 3 H, $SiCH_3$), the assignments were in agreement with COSY spectrum; NOE ($CDCl_3$, 500 MHz) irradiated H-1, observed H-2 (5.1%), H-5β (4.2%); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 109.8, 88.3, 83.9, 76.4, 65.7, 47.6, 35.8, 33.9, 26.7, 25.4, 24.1, 20.2, 20.1, 18.4, −3.5, −3.56; $[\alpha]^{18}_D$ +2.41 (*c* 0.935, $CHCl_3$); MS (FAB) *m*/*z* 331 (MH^+). Anal. Calcd for $C_{17}H_{34}O_4Si$: C, 61.77; H, 10.37. Found: C, 61.65; H, 10.32.

(2*R*,3*R*,4*R*)-2,3-(Isopropylidenedioxy)-4-[[(dimethylthexylsilyl)oxy]methyl]cyclopentanone (16). A mixture of **15** (4.00 g, 12.1 mmol), PDC (9.10 g, 24.2 mmol), and molecular sieves 4 A powder (4.0 g) in CH_2Cl_2 (300 mL) was stirred at room temperature. After 3 h, PDC (1.00 g, 2.60 mmol) was added, and the resulting mixture was further stirred at room temperature for 3 h. The reaction mixture was diluted with Et_2O (700 mL) and filtered through Celite. The filtrate was evaporated under reduced pressure, and the residue was purified by column chromatography (SiO_2, 10% of EtOAc in hexane) to give **16** (3.66 g, 92%) as an oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.61 (d, 1 H, J = 5.4), 4.22 (d, 1 H, J = 5.4), 3.81 (dd, 1 H, J = 2.6, 9.8), 3.61 (dd, 1 H, J = 2.9, 9.8), 2.71 (dd, 1 H, J = 9.1, 18.2), 2.50 (br d, 1 H, J = 9.1), 2.08 (br d, 1 H, H-5b, J = 18.2), 1.56 (m, 1 H, J = 6.8), 1.42, 1.34 (each s, each 3 H), 0.83 (d, 6 H, J = 6.8), 0.80, 0.79 (s, each 3 H), 0.07, 0.06 (each s, each 3 H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 212.9, 111.0, 81.8, 79.0, 65.1, 39.1, 37.2, 34.0, 26.8, 25.2, 24.6, 20.2, 20.0, 18.4, 18.3, −3.7, −3.8; $[\alpha]^{20}_D$ −84.7 (*c* 0.885, $CHCl_3$); MS (FAB) *m*/*z* 329 (MH^+). Anal. Calcd for $C_{17}H_{32}O_4Si$: C, 62.15; H, 9.82. Found: C, 62.13; H, 9.66.

(1*S*,2*S*,3*R*,4*R*)-2,3-*O*-Isopropylidene-4-[[(dimethylthexylsilyl)oxy]methyl]cyclopentane-1,2,3-triol (17). A mixture of **16** (3.60 g, 11.0 mmol) and $NaBH_4$ (393 mg, 10.4 mmol) in MeOH (100 mL) was stirred at −20 °C for 30 min. After being neutralized with 1 M AcOH in benzene, the mixture was evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 10% of EtOAc in hexane) to give **17** (3.17 g, 88%) as an oil; ^{1}H NMR ($CDCl_3$+D_2O, 500 MHz) δ 4.49 (dd, 1 H, H-3, $J_{2,3}$= 5.9, $J_{3,4}$ = 1.0), 4.44 (dd, 1 H, H-2, $J_{1,2}$ = 5.4, $J_{2,3}$ = 5.9), 4.20 (ddd, 1 H, H-1, $J_{1,2}$ = 5.4, $J_{1,5\beta}$ = 7.3, $J_{1,OH}$ = 8.3), 3.60 (dd, 1 H, H-6a, $J_{6a,4}$ = 4.4, $J_{6a,b}$ =10.3), 3.47 (dd, 1 H, H-6b $J_{6b,4}$ = 4.9, $J_{6a,b}$ =10.3), 2.20 (dddd, 1 H, H-4, $J_{3,4}$ = 1.0, $J_{4,5\alpha}$ = 5.4, $J_{4,6a}$ = 4.4, $J_{4,6b}$ = 4.9,), 1.853 (d, 1 H, H-5β, $J_{1,5\beta}$ = 7.3), 1.852 (d, 1 H, H-5α, $J_{4,5\alpha}$ = 5.4), 1.60 (m, 1 H, thexyl CH), 1.40, 1.35 (each s, each 3 H), 0.88 (d, 6 H, thexyl CH_3, J = 6.8), 0.87 (s, 6 H, thexyl CH_3), 0.08 (s, each 6 H, $SiCH_3$), the assignments were in agreement with COSY spectrum and the J values were determined by decouplings of H-1 and H-4; NOE ($CDCl_3$, 500 MHz) irradiated H-1, observed H-2 (2.2%), H-5a (3.2%); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 111.3, 83.0, 80.0, 71.8, 64.4, 44.0, 35.7, 34.1, 26.2, 25.1, 24.3, 20.3, 20.2, 18.5, 18.4, −3.63; $[\alpha]^{20}_D$ −11.1 (*c* 0.842, $CHCl_3$). MS (FAB) *m*/*z* 331 (MH^+). Anal. Calcd for $C_{17}H_{34}O_4Si$: C, 61.77; H, 10.37. Found:C, 61.51; H, 10.30.

1-[(1*R*,2*S*,3*R*,4*R*)-2,3-(Isopropylidenedioxy)-4-[[(dimethylthexylsilyl)oxy]methyl]cyclopentyl]-5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylideneinosine (6) and *O*^{6}-[(1*R*,2*S*,3*R*,4*R*)-2,3-(Isopropylidenedioxy)-4-[[(dimethylthexylsilyl)oxy]methyl]cyclopentyl]-5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylideneinosine (18). To a solution of **17** (500 mg. 1.52 mmol) and DMAP (555 mg, 4.52 mmol) in CH_2Cl_2 (10 mL) was added TfCl (660 μL, 6.2 mmol) at −20 °C, and the resulting mixture was stirred at room temperature for 30 min. Ice−water (20 mL) and $CHCl_3$ (25 mL) were added, and the mixture was partitioned. The organic layer was washed with aqueous HCl (0.5 N, 10 mL) and brine (15 mL), dried (Na_2SO_4), and evaporated under reduced pressure to give **8** as an oil. The oil was dissolved in DME (0.5 mL), which was directly used the next reaction without purification due to the instability of **8**.

A suspension of **7** (642 mg, 1.52 mmol) and K_2CO_3 (399 mg, 2.9 mmol) in DME (2 mL) was heated under reflux for 1 h. To the mixture, was added the above prepared solution of **8** at 60 °C, and the resulting mixture was stirred at the same temperature for 13 h. EtOAc (30 mL) and water (15 mL) were added, and the resulting mixture was partitioned. The organic layer was washed with brine (15 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 25% of EtOAc in hexane) to give **6** (534 mg, 48%) as a solid and **18** (78 mg, 7%) as an oil. **6**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.02 (s, 1 H, H-8), 7.99 (s, 1 H, H-2), 6.12 (d, 1 H, H-1′, J = 2.6), 5.08 (dd, 1 H, H-2′, J = 2.6, 6.1), 4.98 (dd, 1 H, H-2″, J = 4.9, 6.8), 4.92 (dd, 1 H, H-3′, J = 2.5, 6.1), 4.85−4.81 (m, 1 H, H-1″), 4.62 (m, 1 H, H-3″), 4.41 (m, 1 H, H-4′), 3.86 (dd, 1 H, H-5′a, J = 3.7, 11.2), 3.81−3.75 (m, 2 H, H-5′b, 6″a), 3.70 (dd, 1 H, H-6″b, J = 5.5, 9.9), 2.37−2.24 (m, 3 H, H-4″, 5″a,b), 1.62 (m, 1 H, thexyl CH), 1.64, 1.55, 1.40, 1.29 (each s, each 3 H, isopropyl CH_3), 0.89−0.85 (m, 21 H, *t*-Bu, thexyl CH_3), 0.10−0.00 (m, 12 H, $SiCH_3$), the assignments were in agreement with COSY spectrum; NOE ($CDCl_3$, 400 MHz) irradiated H-2, observed H-1″ (13.5%), H-2″ (4.2%), H-1′ (0.6%), H-2′ (0.6%); ^{13}C NMR (67.8 Mz, $CDCl_3$) δ 156.5, 146.6, 146.3, 138.4, 125.2, 114.2, 113.1, 91.1, 87.0, 85.4, 83.4, 81.2, 81.0, 63.9, 63.4, 46.6, 34.2, 33.8, 27.7, 27.2, 25.9, 25.3, 25.1, 20.3, 18.5, 18.3, −3.6; HRMS (FAB, positive) calcd for $C_{36}H_{63}N_4O_8Si_2$ 735.4181, found 735.4185; UV (MeOH) λ_{max} 248, 253 nm, sh 265 nm; IR ($CHCl_3$) 1703 cm^{-1} ($\nu_{C=O}$). Anal. Calcd for $C_{36}H_{62}N_4O_8Si_2 \cdot {}^1/_2H_2O$: C, 58.11; H, 8.53; N, 7.53. Found: C, 58.13; H, 8.37; N, 7.50. **18**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.58 (s, 1 H, H-2), 8.16 (s, 1 H, H-8), 6.22 (d, 1 H, H-1′, J = 2.5), 5.66−5.64 (m, 1 H, H-1″), 5.23 (dd, 1 H, H-2′, J = 2.5, 6.1), 4.96 (dd, 1 H, H-3′, J = 2.4, 6.1), 4.82 (d, 1 H, H-2″, J = 6.0), 4.65 (dd, 1 H, H-3″, J = 2.1, 6.0), 4.44−4.42 (m, 1 H, H-4′), 3.88 (dd, 1 H, H-5′a, J = 3.8, 11.2), 3.77 (dd, 1 H, H-5′b, J = 4.2, 11.2), 3.74 (dd, 1 H, H-6″a, J = 7.8, 10.3), 3.62 (dd, 1 H, H-6″b, J = 6.7, 10.3), 2.51−2.45 (m, 1 H, H-5″a), 2.38 (m, 1 H, H-4″), 1.94−1.90 (m, 1 H, H-5″b), 1.64, 1.51, 1.41, 1.31 (each s, each 3 H, isopropyl CH_3), 1.57 (m, 1 H, thexyl CH), 0.84 (m, 21 H, *t*-Bu, thexyl CH_3), 0.03 (m, 12 H, $SiCH_3$), the assignments were in agreement with COSY spectrum; NOE ($CDCl_3$, 400 MHz) irradiated H-2, observed H-1″ (0.8%), H-2″ (0.6%), H-2′ (0.3%); ^{13}C NMR (67.8 Mz, $CDCl_3$) δ 160.1, 152.5, 151.9, 141.0, 122.5, 114.5, 111.3, 91.8, 87.5, 85.4, 85.1, 82.3, 82.10, 81.7, 63.8, 47.8, 34.5, 32.2, 27.5, 27.1, 26.2, 25.7, 25.3, 24.6, 20.6, 18.8, 18.6, −3.2, −3.4; HRMS (FAB, positive) calcd for $C_{36}H_{63}N_4O_8Si_2$ 735.4181, found 735.4169; UV (MeOH) λ_{max} 253 nm; IR ($CHCl_3$) $\nu_{C=O}$ (around 1700 cm^{-1}) was not observed.

1-[(1*R*,2*S*,3*R*,4*R*)-2,3-(Isopropylidenedioxy)-4-(hydroxymethyl)cyclopentyl]-2′,3′-*O*-isopropylideneinosine (19). A mixture of **6** (222 mg, 0.30 mmol), and TBAF (1 M in THF, 640 μL, 0.64 mmol) in THF (3 mL) was stirred at room temperature for 5 h. The resulting mixture was evaporated under reduced pressure, and the residue was purified by column chromatography (SiO_2, 9% EtOH in $CHCl_3$) to give **19** (153 mg, quant) as a white solid; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.07 (s, 1 H), 7.91 (s, 1 H), 5.89 (d, 1 H, J = 4.1), 5.09−5.05 (m, 3 H), 5.02 (dd, 1 H J = 1.8, 10.0), 4.74 (dd, 1 H, J = 5.9, 6.0), 4.71−4.66 (m, 1 H), 4.49 (d, 1 H, J = 1.5), 3.96−3.93 (m, 1 H), 3.82−3.77 (m, 3 H), 2.46−2.31 (m, 3 H) 1.64, 1.54, 1.38, 1.29 (each s, each 3 H); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 156.34, 147.0, 146.1, 139.9, 126.3, 114.3, 113.2, 93.4, 86.1, 83.8, 83.3, 82.2, 81.3, 66.0, 63.9, 63.0, 46.5, 32.7, 27.7, 27.5, 25.2; HRMS (FAB, positive) calcd for $C_{22}H_{30}N_4O_8$ 479.2141, found 479.2168; UV (MeOH) λ_{max} 253 nm, 247 nm, sh 265 nm.

1-[(1*R*,2*S*,3*R*,4*R*)-2,3-(Isopropylidenedioxy)-4-(phosphonooxymethyl)cyclopentyl]-2′,3′-*O*-isopropylidene-5′-*O*-phosphonoinosine (5). $POCl_3$ (54 μL, 0.58 mmol) was added to a solution of **19** (56 mg, 0.12 mmol) in $PO(OEt)_3$ (3 mL) at 0 °C, and the mixture was stirred at the same temperature for 4 h. The reaction was quenched by aqueous saturated $NaHCO_3$ (5 mL), and the resulting mixture was washed with $CHCl_3$ (20 mL × 2). The aqueous layer was applied to a C-18 column (1.8 × 14 cm). After washing with water (100 mL), the column was developed using a linear gradient of 0.1 N triethylammonium acetate (TEAA) buffer (pH 7.0) to 0.5 M TEAA buffer (pH 7.5)/MeCN (1:1) (300 mL). Appropriate fractions were evaporated under reduced pressure, and excess TEAA was coevaporated with water. The residue was freeze-dried to give triethylammonium salt of **5** (43 mg, 37%) as a solid: ^{1}H NMR (D_2O, 500 MHz) δ 8.53 (s, 1 H, H-8 or H-2), 8.45 (s, 1 H, H-8 or H-2), 6.30 (d, 1 H, H-1′, J = 2.4), 5.43 (dd, 1 H, H-2′, J = 2.4, 3.0), 5.21−5.12 (m, 3 H, H-1″, 2″, 3′), 4.84 (dd, 1 H, H-3″, J = 5.9, 6.7 Hz), 4.68 (m, 1 H, H-4′), 4.07−3.98 (m, 4 H, H-5′a, 5′b, 6″a, 6″b), 3.22 (q, 12 H, $CH_3CH_2N^+$, J = 5.7), 2.59−2.55 (m, 1 H, H-4″), 2.50−2.26 (m, 2 H, H-5″), 1.68, 1.61, 1.46, 1.38 (each s, isopropyl CH_3), 1.30 (t, 18 H, $CH_3CH_2N^+$, J = 5.7), the assignments were in agreement with COSY spectrum; ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 160.7, 150.3, 117.6, 117.0, 93.5, 88.2, 88.1, 87.0, 86.4, 84.2, 84.1, 68.5, 68.4, 67.6, 67.6, 65.0, 49.4, 47.0, 46.9, 35.4, 29.2, 28.8, 27.1, 10.9; ^{31}P NMR (125 MHz, D_2O) δ 0.77 (s), 0.42 (s); HRMS (FAB, negative) calcd for $C_{22}H_{31}N_4O_{14}P_2$ 637.1310, found 637.1314; UV (MeOH) λ_{max} 253 nm, sh 270 nm.

8-Bromo-2′,3′-O-isopropylideneinosine (24). $NaNO_2$ (18 g, 240 mmol) was added to a solution of **23**[21] (8.00 g, 20.7 mmol) in AcOH (200 mL) and water (30 mL), and the resulting mixture was stirred at room temperature for 6 h. After the mixture was evaporated under reduced pressure, the residue was dissolved in EtOH (100 mL), and the solution was evaporated under reduced pressure. The residue was partitioned between $CHCl_3$ (300 mL) and water (150 mL), and the organic layer was washed with aqueous saturated $NaHCO_3$ (100 mL) and brine (150 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was treated with aqueous EtOH to give **24** (4.7 g, 59%) as crystals: mp 225 °C (dec); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 12.9 (br s, 1 H), 8.31 (s, 1 H), 6.11 (d, 1 H, J = 4.8), 5.25 (dd, 1 H, J = 4.8, 5.9), 5.07 (dd, 1 H, J = 1.7, 5.9), 5.00 (br s, 1 H), 4.49 (dd, 1 H, J = 1.7, 1.7), 3.95 (dd, 1 H, J = 1.7, 12.6), 3.79 (dd, 1 H, J = 1.7, 12.6), 1.67, 1.39 (each s, each 3 H); ^{13}C NMR (DMSO-d_6, 67.8 MHz) δ; 157, 149, 146, 126, 126, 114, 93.4, 85.7, 82.9, 81.3, 63.0, 27.5, 25.5; MS (FAB) *m*/*z* 331 (MH^+); UV (MeOH) λ_{max} 253 nm, sh 275 nm. Anal. Calcd for $C_{13}H_{15}BrN_4O_5$: C, 40.33; H, 3.90; N, 14.47. Found: C, 40.23; H, 3.93; N, 14.52.

8-Bromo-5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylideneinosine (25). To a solution of **24** (2.50 g, 7.57 mmol) and imidazole (1.35 g, 19.8 mmol) in DMF (50 mL) was added TBSCl (1.49 g, 9.9 mmol) at 0 °C, and the mixture was stirred at the same temperature for 20 min. Ice−water (50 mL) and EtOAc (250 mL) were added, and the resulting mixture was partitioned. The organic layer was washed with water (50 mL x 5) and brine (50 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 50% of EtOAc in hexane) to give **25** (2.83 g, 75%) as a solid: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.21 (s, 1 H), 6.16 (d, 1 H, J = 2.0), 5.61 (dd, 1 H, J = 2.0, 6.6), 5.05 (dd, 1 H, J = 4.0, 6.6), 4.24 (ddd, 1 H, J = 4.0, 5.9, 6.6), 3,73 (dd, 1 H, J = 6.6, 20.5), 3.70 (dd, 1 H, J = 5.9, 20.5), 1.60, 1.39 (each s, each 3 H), 0.83 (s, 9 H), −0.63 (s, 6 H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 157.9, 149.6, 145.7, 126.9, 125.4, 114.4, 91.5, 87.9, 83.1, 81.7, 76.5, 63.1, 27.2, 25.8, 25.5, 18.3; HRMS (FAB, positive) calcd for $C_{19}H_{30}BrN_4O_5Si$ 501.1169, found 501.1176;

UV (MeOH) λ_{max} 253, sh 275. Anal. Calcd for $C_{19}H_{29}BrN_4O_5Si$: C, 45.51; H, 5.83; N, 11.17. Found: C, 45.50; H, 5.92; N, 10.99.

8-Bromo-1-[(1*R*,2*S*,3*R*,4*R*)-2,3-(isopropylidenedioxy)-4-[[(dimethylthexylsilyl)oxy]methyl]cyclopentyl]-5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylideneinosine (26) and 8-Bromo-O^6-[(1*R*,2*S*,3*R*,4*R*)-2,3-(isopropylidenedioxy)-4-[[(dimethylthexylsilyl)oxy]methyl]cyclopentyl]-5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylideneinosine (27). Compound **26** (solid, 320 mg, 44%), along with the corresponding O^6-regioisomer **27** (solid, 65 mg, 9%), was obtained from **8** (412 mg, 0.90 mmol) as described for **6**, with **25** (460 mg, 0.90 mmol) instead of **7**. **26**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.91 (s, 1 H, H-2), 6.14 (d, 1 H, H-1′, J = 2.2), 5.56 (dd, 1 H, H-2′, J = 2.2, 6.3), 5.04 (dd, 1 H, H-3′, J = 3.9, 6.3), 4.96 (dd, 1 H, H-2′, J = 4.9, 6.6), 4.77−4.75 (m, 1 H, H-1″), 4.61 (dd, 1 H, H-3″, J = 4.9, 5.3), 4.23−4.20 (m, 1 H, H-4′), 3.78 (dd, 1 H, H-5′, J = 3.4, 9.8), 3.74−3.68 (m, 3 H, H-5′, 6″a, 6″b), 2.31−2.30 (m, 3 H, 4″, 5″a, 5″b), 1.63 (m, 1 H, thexyl CH), 1.61, 1.59, 1.39, 1.26 (each s, each 3 H, isopropyl CH_3), 0.89−0.85 (m, 21 H, *t*-Bu, thexyl CH_3), 0.09−0.02 (m, 12 H, $SiCH_3$), the assignments were in agreement with COSY spectrum; NOE ($CDCl_3$, 400 MHz) irradiated H-2, observed H-1″ (14.7%), H-2″ (6.0%), H-2′ (0.6%); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 155.1, 147.7, 146.2, 126.3, 125.5, 114.4, 113.1, 91.1, 87.5, 83.2, 81.6, 81.0, 64.6, 63.4, 63.0, 46.5, 34.2, 33.5, 27.7, 27.2, 25.9, 25.7, 25.6, 25.4, 25.3, 25.1, 20.3, 18.5, 18.3, −3.6, −3.7; MS (FAB) *m*/*z* 813 (MH^+); UV (MeOH) λ_{max} 253, 258 nm, sh 275 nm; IR ($CHCl_3$) 1707 cm^{-1} ($\nu_{C=O}$). Anal. Calcd for $C_{36}H_{62}BrN_4O_8Si_2$: C, 53.12; H, 7.55; N, 6.88. Found: C, 52.91; H, 7.48; N, 6.72. **27**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.48 (s, 1 H, H-2), 6.21 (d, 1 H, H-1′, J = 2.0), 5.75 (dd, 1 H, H-2′, J = 2.0, 6.3), 5.61−5.60 (m, 1 H, H-1″), 5.15 (dd,1 H, H-3′, J = 2.1, 6.2), 4.77 (d, 1 H, H-2″, J = 6.1), 4.63 (dd, 1 H, H-3″, J = 2.1, 6.2), 4.27 (m, 1 H, H-4′), 3.76−3.61 (m, 4 H, H-5′a, 5′b, 6″a, 6″b), 2.48−2.31 (m, 3 H, H-5″a, 5″b, 4″), 1.62, 1.50. 1.40, 1.31 (each s, each 3 H, isopropyl CH_3), 1.57 (m, 1 H, thexyl CH), 0.91−0.78 (m, 21 H, *t*-Bu, thexyl CH_3), 0.09−0.06 (m, 12 H, $SiCH_3$), the assignments were in agreement with COSY spectrum; NOE ($CDCl_3$, 400 MHz) irradiated H-2, observed H-1″ (0.8%), H-2′ (0.6%), H-3′ (0.4%); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.6, 158.9, 152.7, 152.2, 130.5, 122.6, 114.4, 111.5, 111.3, 91.9, 88.2, 85.0, 83.1, 82.6, 82.0, 80.4, 70.1, 63.7, 63.3, 59.6, 47.7, 47.2, 34.5, 32.1, 27.5, 27.0, 26.1, 25.7, 25.4, 25.4, 24.6, 20.6, 18.7, −3.3, −5.2; MS (FAB) *m*/*z* 813 (MH^+); UV (MeOH) λ_{max} 260, sh 265 nm; IR ($CHCl_3$), $\nu_{C=O}$ (around 1700 cm^{-1}) was not observed. Anal. Calcd for $C_{36}H_{61}BrN_4O_8Si_2$: C, 53.12; H, 7.55; N, 6.88. Found: C, 53.22; H, 7.47; N, 6.62.

8-Bromo-1-[(1*R*,2*S*,3*R*,4*R*)-2,3-(isopropylidenedioxy)-4-(hydroxymethyl)cyclopentyl]-2′,3′-*O*-isopropylideneinosine (28). Compound **28** (solid, 1.22 g, 89%) was obtained from **26** (2.00 g, 2.46 mmol) as described for **19**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.09 (s, 1 H), 6.08 (d, 1 H, J = 5.1), 5.15 (dd, 1 H, J = 5.1, 5.6), 5.04−4.99 (m, 2 H), 4.74−4.70 (m, 3 H), 3.93−3.75 (m, 4 H), 2.45−2.28 (m, 3 H), 2.01 (s, 2 H), 1.66, 1.54, 1.38, 1.29 (each s, each 3 H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 155.0, 147.2, 147.0, 126.1, 126.0, 93.2, 85.5, 83.2, 82.9, 82.1, 81.1, 65.9, 63.7, 63.0, 46.3, 32.6, 27.6, 27.6, 25.4, 25.2; HRMS (FAB, positive) calcd for $C_{22}H_{30}BrO_8N_4$ 557.1248, found 557.1257; UV (MeOH) λ_{max} 253, sh 275 nm. Anal. Calcd for $C_{22}H_{29}BrN_4O_8$: C, 47.41; H, 5.24; N, 10.05. Found: C, 47.11; H, 5.51; N, 9.75.

8-Bromo-1-[(1*R*,2*S*,3*R*,4*R*)-2,3-(isopropylidenedioxy)-4-(phosphonooxymethyl)cyclopentyl]-2′,3′-*O*-isopropylidene-5′-*O*-phosphonoinosine (22). (2-Cyanoethoxy)(*N*,*N*-diisopropylamino)chlorophosphine (161 μL, 0.72 mmol) and *i*-Pr_2NEt (188 μL, 1.1 mmol) were added to a solution of **28** (100 mg, 0.18 mmol) in CH_2Cl_2 (5 mL) at room temperature, and the mixture was stirred at the same temperature for 15 min. After the reaction was quenched by aqueous saturated $NaHCO_3$ (1 mL), $CHCl_3$ (30 mL) was added, and the resulting mixture was partitioned. The organic layer was washed with brine (5 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (neutral SiO_2, 33% of EtOAc in hexane) to give the corresponding 5′,6″-bis(phosphoramidite) of **28** (135 mg, 79%) as a foam: ^{31}P NMR (D_2O, 125 MHz) δ 149.02 (s), 148.36 (s), 148.13 (s); HRMS (FAB, positive) calcd for $C_{40}H_{64}BrN_8O_{10}P_2$ 957.3404, found 957.3422, which was immediately used in the next reaction.

To a mixture of the above form (135 mg, 0.14 mmol) and 1*H*-tetrazole (30 mg, 0.43 mmol) in aqueous MeCN (94%, 3.2 mL) was added a solution of I_2 (3% in water:pyridine:THF = 5:19:76, 2 mL), and the resulting mixture was stirred at room temperature for 15 min. After the reaction was quenched by aqueous $Na_2S_2O_3$ (1 mL), $CHCl_3$ (2 mL) was added, and the resulting mixture was partitioned. To the aqueous layer was added a saturated NH_3 in MeOH (30 mL), and the mixture was allowed to stand at room temperature for 2 days. The resulting solution was evaporated under reduced pressure. The residue was dissolved in water (150 mL) and then pH of the solution was adjusted about 6 with AcOH, and the solution was applied to a DEAE-Sephadex A-25 column (HCO_3^- form, 3.5 × 8 cm). The column was developed using a linear gradient of 0 to 0.4 M triethylammonium bicarbonate (TEAB) buffer (pH 8.1, 400 mL) and was further developed with 0.4 M TEAB buffer (pH 8.1, 600 mL). Appropriate fractions were evaporated under reduced pressure, and excess TEAB was coevaporated with water. The residue was freeze-dried to give **22** (75 mg) as triethylammonium salts: ^{31}P NMR (D_2O, 125 MHz) δ 0.85 (s), 0.68 (s); HRMS (FAB, negative) calcd for $C_{22}H_{30}BrN_4O_{14}P_2$ 715.0417, found 715.0398. The countercations were exchanged for sodium with a Diaion WK-20 resin column (Na^+ form, 1.2 × 5 cm, developed by water). The eluent was evaporated under reduced pressure, and the residue was freeze-dried to give **22** (white solid, 64 mg, 34% from **28**) as sodium salts: ^{1}H NMR (D_2O, 500 MHz) δ 8.46 (s, 1 H, H-2), 6.34 (d, 1 H, H-1′, J = 2.3), 5.69 (dd, 1 H, H-2′, J = 2.3, 6.5), 5.28 (dd, 1 H, H-3′, J = 4.5, 6.5), 5.14−5.08 (m, 2 H, H-1″, 2″), 4.82 (m, 1 H, H-3″), 4.46 (m, 1 H, H-4′), 4.03−3.82 (m, 4 H, H-5′a, 5′b, 6″a, 6″b), 2.50 (m, 1 H, H-4″), 2.41 (m, 1 H, H-5″a), 2.27 (m, 1 H, 5″b), 1.66, 1.60, 1.44, 1.37 (each s, each 3 H, isopropyl CH_3), the assignments were in agreement with COSY spectrum; ^{13}C NMR (D_2O, 125 MHz) δ 159.6, 151.1, 150.4, 130.0, 126.9, 118.3, 116.9, 92.9, 89.0, 86.2, 85.6, 84.5, 84.0, 67.5, 66.4, 65.3, 47.2, 35.6, 29.1, 28.8, 27.1, 27.0; ^{31}P NMR (D_2O, 125 MHz) δ 4.26 (s, two signals were coincident); UV (MeOH) λ_{max} 255 nm, sh 280 nm.

8-Bromo-cyclic IDP-carbocyclic-ribose Diacetonide (29). Compound **22** (sodium salts, 56 mg, 0.074 mmol) was dissolved in MPD (11 mL) by heating. EDC (21 mg, 0.11 mmol) was added to the solution of **22**, and the mixture was stirred at 50 °C for 60 h. After cooling the mixture with ice-bath, the mixture was diluted with water (90 mL). The solution was applied to a DEAE-Sephadex A-25 column (HCO_3^- form, 1.8 × 8 cm). The column was washed with 0.1 M TEAB buffer (pH 7.5, 100 mL) and developed using a linear gradient of 0.1 to 0.4 M TEAB buffer (pH 7.5, 300 mL). Appropriate fractions were evaporated under reduced pressure, and excess TEAB was coevaporated with water. Countercations were exchanged for sodium with a Diaion WK-20 resin column (Na^+ form, 1.2 × 5 cm, developed by water). The eluate was evaporated under reduced pressure, and the residue was freeze-dried to give **29** (solid, 13 mg, 23%) as sodium salts: ^{1}H NMR (D_2O, 500 MHz) δ 8.52 (s, 1 H, H-2), 6.39 (d, 1 H, H-1′ J = 1.3), 5.83 (dd, 1 H, H-2′, J = 1.3, 6.2), 5.53 (dd, 1 H, H-3′, J = 2.2, 6.2), 4.88 (d, 1 H, H-2″, J = 9.3), 4.69 (m, 2 H, H-1″, 3″), 4.63−4.57 (m, 1 H, H-4′), 4.18−4.15 (m, 1 H′, H-5′a), 4.04−3.97 (m, 2 H, H-6″a, 6″b) 3.81−3.76 (m, 1 H′, H-5′b), 2.93−2.82 (m, 2 H, H-5″a, 4″), 2.64 (d, 1 H, H-5″b, J = 16.4), 1.66, 1.60, 1.48, 1.39 (each s, each 3 H, isopropyl CH_3), the assignments were in agreement with COSY spectrum; ^{13}C NMR (D_2O, 125 MHz) δ 160.3, 150.4, 148.5, 141.5, 125.2, 117.12 113.7, 93.5, 90.5, 89.5, 86.5, 85.6, 84.8, 68.1, 66.9, 61.8, 47.4, 29.6, 28.59, 26.9, 26.3; ^{31}P NMR (D_2O, 125 MHz) δ −10.67 (d, J = 15.0), −10.95 (d, J = 15.0); MS (FAB, negative) *m*/*z* 677, 699 (M^-); UV (MeOH) λ_{max} 256 nm, sh 280 nm. Anal. Calcd for $C_{22}H_{27}BrN_4O_8P_2Na_2 \cdot {}^1/_{14}Et_3N$: C, 35.55; H, 3.66; N, 7.54. Found: C, 35.89; H, 3.76; N, 7.59.

Cyclic IDP-carbocyclic-ribose diacetonide (30). A mixture of **29** (162 OD_{254} units) and Pd−C (10%, 1.5 mg) in EtOH/aqueous $NaHCO_3$ (0.5 M) (1:2, 6 mL) was stirred under atmospheric pressure of H_2 at room temperature for 17 h. The catalyst was filtered off with Celite, and the filtrate was evaporated under reduced pressure. The residue was dissolved in water (50 mL), and pH of the mixture was adjusted to about 6 with AcOH. The solution was applied to a DEAE-Sephadex A-25 column (HCO_{3-} form, 1.8 × 4 cm), and the column was developed using a gradient of 0.1 to 0.4 M TEAB buffer (pH 7.5, 200 mL). Appropriate fractions were evaporated under reduced pressure, and excess TEAB was coevaporated with water. The residue was freeze-dried to give **30** (triethylammonium salt, 125 OD_{254} units, 77%). The countercations were exchanged for sodium with a Diaion WK-20 resin column (Na^+ form, 1.2 × 5 cm, developed by water). The eluent was evaporated under reduced pressure, and the residue was freeze-dried to give **30** as sodium salts: ^{1}H NMR (D_2O, 500 MHz) δ 8.55 (s, 1 H, H-2), 8.19 (s, 1 H, H-8), 6.36 (d, 1 H, H-1′, J = 1.6), 5.75 (dd, 1 H, H-2′, J = 1.6, 6.2), 5.32 (dd, 1 H, H-3′, J = 2.3, 6.2), 4.91 (d, 1 H, H-2″, J = 9.3), 4.73−4.69 (m, 2 H, H-1″, 3″), 4.59 (m, 1 H, H-4′), 4.18−4.03 (m, 3 H, H-5′a, 6″a, 6″b), 3.80−3.75 (m, 1 H, H-5′b), 2.93−2.83(m, 2 H, H-5″a, H-4″), 2.65 (d, 1 H, H-5″b, J = 19.6), 1.67, 1.61, 1.48, 1.40 (each s, each 3 H), the assignments were in agreement with COSY spectrum; ^{13}C NMR (D_2O, 125 MHz) δ 161.3, 149.5, 148.1, 145.0, 126.8, 117.2, 113.66, 94.2, 90.5, 89.0, 86.6, 85.6, 84.7, 71.2, 68.1, 67.9, 67.1, 47.5, 29.7, 28.6, 27.0, 26.3, 22.8; ^{31}P NMR (D_2O, 125 MHz) δ −10.42 (d, J = 15.3), −10.82 (d, J = 15.3); HRMS (FAB, positive) calcd for $C_{22}H_{29}N_4O_{13}P_2Na_2$ 665.0999, found 665.1209; UV (MeOH) λ_{max} 250, 256 nm.

Cyclic IDP-carbocyclic-ribose (4). A solution of **30** (triethylammonium salts, 122 OD_{254} units) in aqueous HCO_2H (60%, 3 mL) was stirred at room temperature for 6 h. After the solvent was evaporated under reduced pressure, the residue was dissolved in water (100 mL), and the resulting solution was applied to a DEAE-Sephadex A-25 column (HCO_3^- form, 1.8 × 4 cm). The column was developed using a linear gradient of 0.1 to 0.4 M TEAB buffer (pH 7.5, 200 mL). Appropriate fractions were evaporated under reduced pressure, and excess TEAB was coevaporated with water. The residue was freeze-dried to give **4** (triethylammonium salts, 82 OD_{254} units, 67%). The triethylammonium salts were dissolved in water (1 mL) and desalted with a C-18 column (1.8 × 16 cm, developed by water). Countercations were exchanged for sodium with a Diaion WK-20 resin column (Na^+ form, 1.0 × 9 cm, developed by water). The eluent was evaporated under reduced pressure, and the residue was freeze-dried to give **4** as sodium salts: ^{1}H NMR (D_2O, 500 MHz) δ 9.02 (s, 1 H, H-2), 8.19 (s, 1 H, H-8), 6.02 (d, 1 H, H-1′, J = 6.5), 5.20−5.17 (m, 2 H, H-2′, 1″), 4.66−4.62 (m, 2 H, H-2″, 3′), 4.43 (m, 1 H, H-4′), 4.27−4.10 (m, 5 H, H-3″, 5′a, 5′b, 6″a, 6″b), 2.95 (m, 1 H, H-5″a), 2.48 (m, 1 H, H-4″), 2.25 (m, 1 H, H-5″b); ^{13}C NMR (D_2O, 125 MHz) δ 161.3, 150.1, 145.2, 126.8, 93.1, 87.6, 87.5, 81.2, 75.9, 75.1, 73.7, 67.8, 67.6, 61.5, 49.5, 44.9, 29.9, 11.0; ^{31}P NMR (D_2O, 125 MHz) δ −9.16 (d, J = 10.7), −10.51 (d, J = 10.7); HRMS (FAB, negative) calcd for $C_{16}H_{21}N_4O_{13}P_2Na$ 561.0398, found 561.0358; UV (MeOH) λ_{max} 250 nm.

Acknowledgment. This investigation was supported in part by a Grant from the Ministry of Education, Science, Sports, and Culture of Japan. We are grateful to Prof. Kazuyoshi Ikeda (Hokkaido University) and Dr. Tamotsu Yamamoto (Asahi Chemical Industry) for their helf for mass spectra measurements.

Supporting Information Available: ^{1}H NMR spectral charts of **4**, **5**, **19**, **22**, **29**, and **30** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9717797