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Stereoselective Synthesis of N^1-Lyxitol Inosine Derivative

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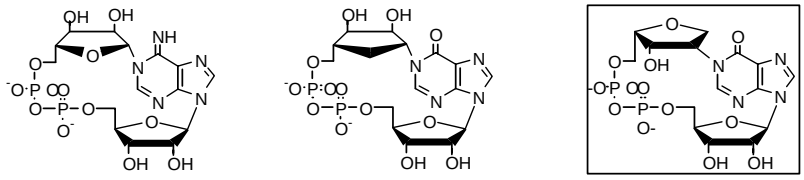
Abstract: 1,4-anhydro-2-triflyl-3,5-O-benzenylidene-L-xylitol (5) was constructed in six steps from protected D-xylose. Substitution of 5 with protected 8-bromoinosine 6 gave the key intermediate 5'-O-TBS-2',3'-di-O-acetyl-N^1-(2"-deoxy-1",4"-anhydro-3",5"-O-benzenylidene-L-lyxitol-2"-yl)-8-bromoinosine (14). Selective removal of 5'-O-TBS-group gave the corresponding 5'-O-phosphorodianilidate 4 though phosphorylation, which was characterized by X-ray crystallographic analysis.

Keywords: Cyclic ADP-ribose analogues, synthesis, X-ray crystallographic analysis.

Cyclic ADP-ribose (cADPR) **1** (**Figure 1**), a intracellular Ca^{2+}-mobilizing messenger, is of great interest because of its significant importance in the signal transduction[1]. However, the biological as well as chemical instability of cADPR limits the studies of its physiological role, at least in some aspect[2]. Recently, Shuto *et.al.*[3] constructed a mimic of cADPR, cyclic IDP-carbocyclic-ribose **2**, in which the 4'-oxo in furanose is substituted by a methylene group and the stability of **2** is improved.

Figure 1



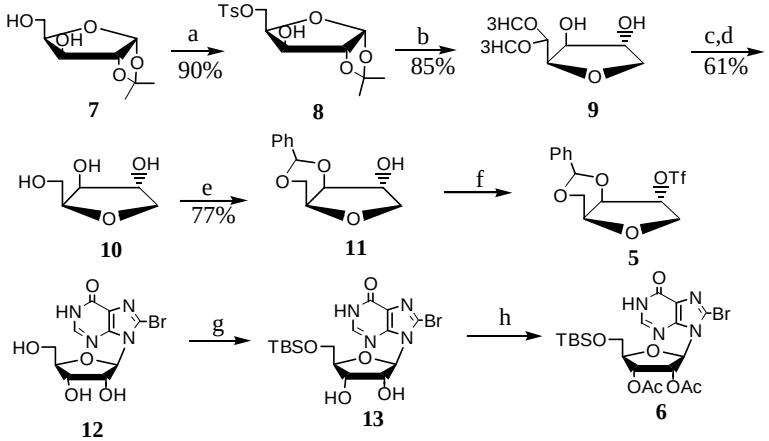
1 **2** **3**

Isonucleosides represent another class of nucleoside analogues in which the nucleobase is linked at various positions of ribose other than C-1', and have attracted great interest because of their chemical and enzymatic stability[4]. In order to study the relationship between the structure and biological activities, we designed a stable cADPR mimic with glycosyl instead of ribosyl in the N-1 position.

The key steps for the synthesis of cADPR analogue **3** involve glycosidation at N-1 position of inosine and intramolecular cyclophosphorylation. We reported here the synthesis of N^1-lyxitol inosine derivative **4**.

It was reported that N-1 substitution of hypoxanthine can be carried out *via* a rearrangment of purine[5], but we failed to construct the key intermediate by this method. The synthesis of N^1-lyxitol inosine derivative was completed by the nucleophilic substitution with compound **5** and **6**.

Scheme 1

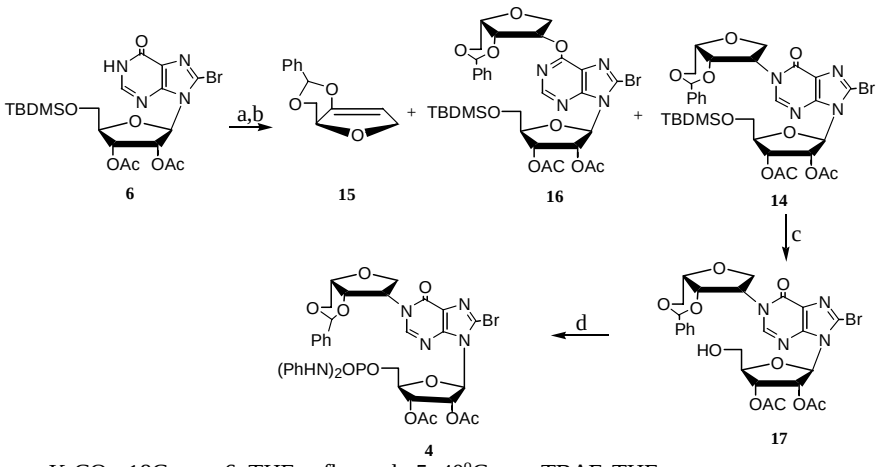


a. TsCl,;Py, rt; b. 1%HCl, MeOH, 80°C; c. 1% HCl, H_2O, 90°C; d. $NaBH_4$, rt; e. $ZnCl_2$, PhCHO, rt; f. $(CF_3SO_2)_2O$, Py, DCM, -20°C; g. TBSCl, imidazole, DMF; h. $(AcO)_2O$, Py, rt

The preparation of protected xylitol **5** and inosine was shown in **Scheme 1**. Because of the low acidity of the N^1-H in compound **6**, triflyl was selected as leaving group at 2'-position of compound **5** for the nucleophillic substitution. Compound **11**, 3,5-O-benzenylidene-1,4-anhydro-L-xylitol, was obtained from **7** using the method previously reported in five steps[6]. Addition of trifluoromethanesulphonic anhydride to the mixture of **11** and anhydrous pyridine in DCM at -20°C under argon and stirring for one hour at the same temperature afforded triflate **5** which was unstable and used for the next reaction immediately without purification. 8-bromoinosine（**12**）was synthesized from adenosine according to a publication procedure[7]. A selective protection of 5-primary hydroxyl was accomplished by the treatment of **12** with t-butyldimethylsilyl chloride (TBS) under optimized condition. The desired inosine derivative **6** was obtained in over 90% yield from **12**.

As depicted in **Scheme 2**, a suspension of **6**, K_2CO_3 and 18crown-6 was heated under reflux for one hour, and then cooled to room temperature. Equimolar **5** in THF was added to the mixture. Upon further stirring at 40°C for 36 hours, the expected product **14**[8] was isolated by column chromatography with the yield of 24%, accompanied by O^6-substituted derivative 16 in 6.8% and eliminated byproduct **15**. The 5'-O-TBS group of **14** was removed with TBAF in neutral THF solution to give the 5'-hydroxyl derivative **17** and **17** was treated with $(PhNH)_2POCl$ and tetrazole in pyridine to give **4**[9] in high yield (**Scheme 2**).

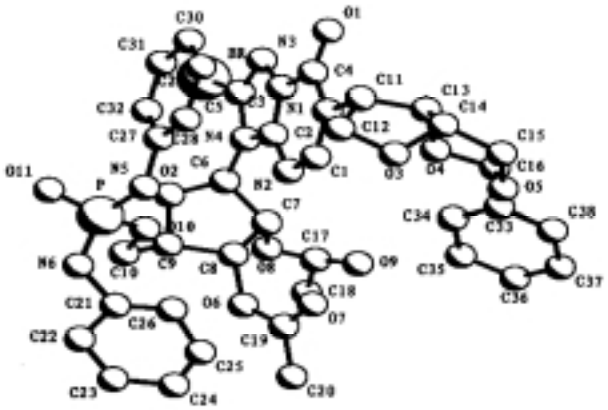
Scheme 2



a. K_2CO_3, 18Crown-6, THF, reflux; b. 5, 40°C; c. TBAF, THF.
d. $(PhNH)_2POCl$, tetrazole, Py, rt.

The N1-glycosidic linkage of inosine was confirmed by IR, UV and NMR. The IR spectrum of **14** showed a strong ν c=o absorption peak at 1706 cm^{-1}. Similar absorption around 1700 cm^{-1} was not found in the IR spectrum of **16**. Correspondingly, UV spectrum of **14** has a lower value of A260/A290 than its O^6-substitued counterpart owing to the absence of conjugation.

Figure 2



In order to determine the stereochemistry of **14**, the single crystalline of **4** was obtained from ethanol solution. The crystal belongs to tetragonal system and space group is $P4_3$ (**Figure 2**). The detail of unit-cell parameters was a=16.666(1), c=16.987(1) Å. X-ray crystallographic analysis demonstrated that inosine moiety was on the same

side as the benzenylidene group. It was deduced that the absolute configuration of C-2" is S configuration as same as C-3" and C-5" in compound **14**. The result supported an S_N2 substitution mechanism in the substitution that the nitrogen anion attacked the C-2" from the back and gave the configurational reversal product.

Acknowledgments

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References and Notes

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8. Compound **14** mp:106-108°C. FAB-MS: *m/z*=749.2 [M^+]; 300 MHz ^{1}HNMR ($CDCl_3$): δ 8.37 (s, 1H, H-2), 7.37 (m, 5H, C_6H_5), 6.27 (t, 1H, J=5.7Hz, H-2'), 5.97-6.05 (m, 2H, H-1', H-2"), 5,70 (t, 1H, J=5.4Hz, H-3'), 5.50 (s, 1H, PhCH), 4.60 (m, 1H, H-3"), 4.42-4.47 (m, 1H, H-1"), 4.27-4.34 (m, 2H, 2H-5"), 4.06-4.22 (m, 2H, H-4', H-1"), 3.97 (m, 1H, H-4"), 3.90 (dd, 1H, $J_{5'a,5'b}$=11.1Hz, $J_{5'a,4'}$=4.5Hz, H-5'a), 3.80 (dd, 1H, $J_{5'b,5'a}$=11.1Hz, $J_{5'b,4'}$=4.8Hz, H-5'b), 2.02, 2.13, (each s, each 3H, $2CH_3CO$), 0.82, -0.00, (each s, each 3H, $(CH_3)_3C$-); ^{13}C NMR ($CDCl_3$): δ 169.4, 169.1, 155.5, 148.1, 146.8, 136.9, 129.1, 128.5, 126.2, 125.7, 124.6, 99.1,88.0, 83.1, 74.2, 73.8, 71.6, 70.3, 69.8, 67.4, 62.3, 54.3, 25.7, 20.6, 20.3, 18.3, -5.5, -5.4. Anal.Calcd. for $C_{32}H_{41}BrN_4O_{10}Si$: C 51.27, H 5.51, N 7.47; Found: C 51.60, H 5.60, N 7.67.
9. Compound **4** mp:146-148°C. 500 MHz ^{1}HNMR (DMSO-d_6): 8.22 (s, 1H, H-2), 8.04 (d, 1H, $J_{P,H}$=3.5Hz, NH), 8.06 (d, 1H, $J_{P,H}$=3.0Hz, NH), 7.33-6.71, (m, 15H, Arom-H), 6.03, (dd, 1H, $J_{1',2'}$=4.0Hz, H-1'), 5.80 (t, 1H, H-3'), 5.58 (s, 1H, PhCH), 4.63 (dd, 1H, $J_{3",4"}$=5Hz, $J_{3",2"}$=2.0Hz, 3"-H), 4.44 (dt, 1H, $J_{4',5'a}$=6.5Hz, J=6.5Hz, z, $J_{4',5'b}$=3.5Hz, $J_{4',3'}$=6.5Hz, H-4'), 4.33 (m, 1H, 5'-H), 4.17-4.26 (m, 4H, H-1", H-5', 2H-5"), 4.09 (t, J=10.5Hz, 1H, H-1"), 3.88 (m, 1H, H-4"), 2.08, 2.09 (each s, each 3H, $2CH_3CO$); Anal.Calcd. for $C_{38}H_{38}BrN_6O_{11}P$: C 52.73, H 4.42, N 9.71; Found: C 52.40, H 4.36, N 9.39.

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