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Synthesis and antiviral evaluation of α-D-2′,3′-didehydro-2′,3′-dideoxy-3′-*C*-hydroxymethyl nucleosides

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ABSTRACT

We have identified a selective S_N2' reaction triggered by iodide ion that leads to the ring-opening of 2,2′-anhydro-α-nucleosides. By applying the method, we have synthesized α-D-2′,3′-didehydro-2′,3′-dideoxy-3′-*C*-hydroxymethyl nucleosides, designed as potential antiviral agents.

For a few decades, sugar-modified nucleosides have provided important leads for the development of novel antitumor and antiviral agents.[1] Among them, branched nucleosides with a 3′-hydroxymethyl group, mimicking the oxetanose structure of the antibiotic oxetanocin A[2] (Fig. 1, Oxt-A, **1**), were proven to have potent antiviral activities: the ring-expanded oxetanocins **2** were synthesized, and showed significant biological activities.[3] It has also been reported that isonucleoside derivatives of **2**, in which the base moiety is transposed from the anomeric position to the 2′-position, displayed antiviral activities against Hepatitis B virus.[4] Jeong and co-workers, on the other hand, reported that (±)-apio-dideoxydidehydro nucleosides (**3**; apio-d4Ns) showed potent anti-human cytomegalovirus (HCMV) activity.[5] Apio-d4 nucleosides **3** are considered to be 2′,3′-dideoxy-2′-oxo analogues of antiviral neplanocin A[6] (NepA, **4**). Drug design of **3** based on the structure of neplanocin A was reasonable since both **4** and its cytosine counterpart **5** were known to have potent antiviral activity.[6,7] Thus, the α-D-2′,3′-didehydro-2′,3′-dideoxy-3′-*C*-hydroxymethyl nucleosides **6**, bearing the hydroxymethyl group at the C-4′ position of apio-d4Ns **3** with an *anti* relationship to the nucleobase, were expected to be potential antiviral agents. In this Letter, we describe the synthesis and antiviral evaluation of α-D-2′,3′-didehydro-2′,3′-dideoxy-3′-*C*-hydroxymethyl nucleosides **6**.

First, we attempted to synthesize 2′-*O*-acetyl-3′-*C*-methylene-α-arabinosyl thymine **11a** starting from D-arabinose as a key intermediate for palladium-catalyzed allylic ester rearrangements.[8] As shown in Scheme 1, after protecting the primary hydroxyl group of D-arabinose with a *t*-butyldiphenylsilyl group, introduction of an acetal group at the *O*-1,2 positions gave acetal **7** in 51% yield.[9] The secondary hydroxyl group of **7** was oxidized with DMSO/Ac_2O to give **8**, which was treated with methylenetriphenylphosphorane to give **9** in 47% yield from **7**.[1j,1k] Subsequent acetolysis of **9** gave diacetate **10** (anomer ratio ≈ 2:1) in 76% yield. Treatment of **10** with trimethylsilylated thymine in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) at 60 °C gave the thymidine derivative **11a** in 83% yield. Only the α-anomer was formed in this reaction due to participation of the 2-acetoxy group of **10**. To convert the secondary acetate **11a** into the primary **12a**, we next examined the palladium-catalyzed allylic ester rearrangement. We treated **11a** with 10 mol % of palladium catalysts (e.g., $(PPh_3)_2PdCl_2$, $(CH_3CN)_2PdCl_2$, and $Pd(PPh_3)_4$) in THF under various

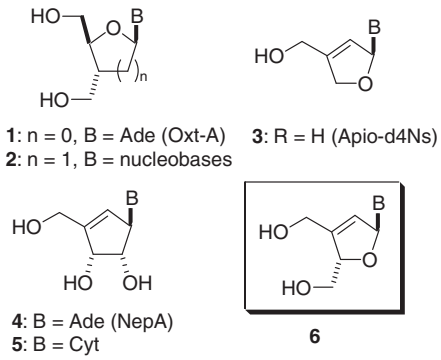

Figure 1.

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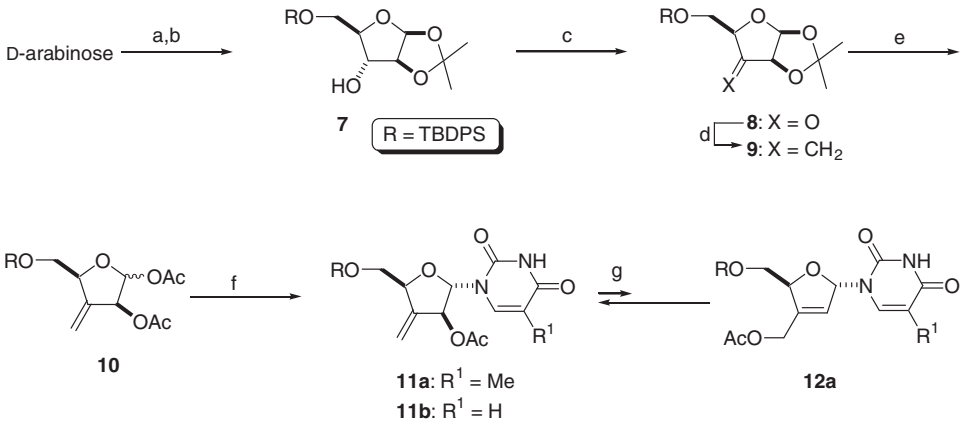


Scheme 1. Reagents and conditions: (a) TBDPSCl, imidazole, DMF; (b) 2,2-dimethoxypropane, TsOH·H_2O, acetone, 51% from D-arabinose; (c) Ac_2O, DMSO; (d) $Ph_3P^+CH_3 \cdot Br^-$, NaH, *tert*-amyl alcohol, 47% from **7**; (e) AcOH, concd H_2SO_4, Ac_2O, 76%; (f) silylated base, TMSOTf, CH_2ClCH_2Cl, 60 °C, **11a** (83%), **11b**; (g) 10 mol % $Pd(PPh_3)_4$, THF, reflux, 34% (**11a**/**12a** = 2.3:1).

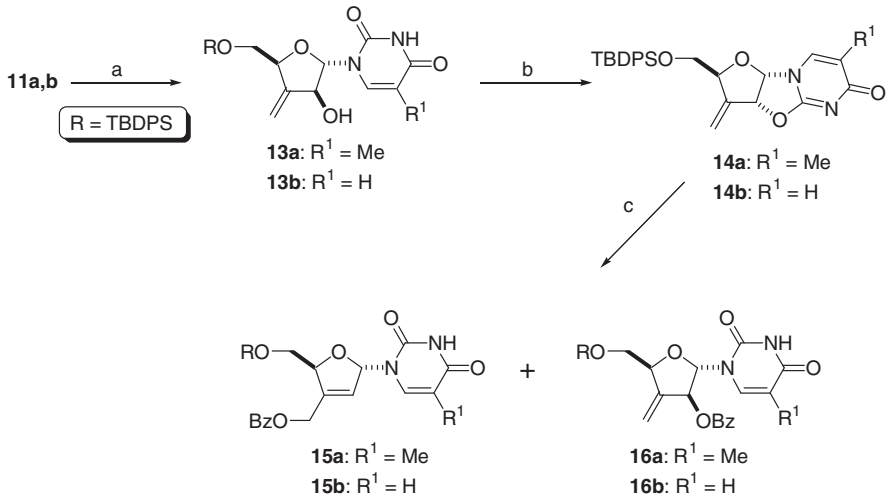
conditions from room temperature to reflux. However, the allylic rearrangement of **11a** using either Pd(II) or Pd(0) catalysts gave only a mixture of isomers, which were difficult to separate. For example, the reaction of **11a** with 10 mol % of $Pd(PPh_3)_4$ under a reflux condition produced a mixture of **11a** and **12a** in a low yield (34%, **11a**/**12a** = 2.3:1), accompanied with the formation of more polar byproducts. Due to the low reactivity of the allylic ester substituted at the C-2 position,[8] the conversion of **11a** to **12a** was considered to be difficult. Thus, we needed an alternative approach to synthesize the target nucleosides.

We next examined the S_N2' type substitution reaction by ring-opening of 2,2′-anhydro-α-nucleosides (**14a**,**b**). As shown in Scheme 2, deacetylation of **11a** by transesterification led to **13a**, which was converted into 2,2′-anhydro-α-nucleoside **14a** by mesylation of the 2′-hydroxyl group and subsequent intramolecular cyclization. In the same way, 2,2′-anhydro-α-nucleoside **14b** was prepared from diacetate **10**. Initially, 2,2′-anhydro-α-nucleoside **14a** was treated with excess benzoic acid and sodium benzoate in DMF at 130 °C (Table 1, entry 1). However, only the undesired **16a** was obtained in 64% yield. The same result was obtained when the reaction was performed using non-polar toluene as the solvent (entry 2). On the other hand, reaction in the presence of iodide ion gave a mixture of two isomers in 80–90% yield (**15a**/**16a** ≈ 1:1, entries 3 and 4). Thus, to obtain the desired S_N2' adduct, the iodide ion appeared to be important.

Czernecki[10] reported the synthesis of 3′-*C*-azidomethyl branched d4Ns using the S_N2' opening of the 2,2′-anhydro-β-nucleoside, in which azide ion selectively attacked the *exo*-methylene group at the C-3′ position. These results suggest that soft anions, for example, iodide and azide, preferentially attack at the 3′-*exo*-methylene carbon by S_N2' reaction and that hard anions, including benzoate, favor S_N2 attack at the 2′-carbon. A similar tendency was reported by Matsuda and co-workers in the synthesis of 2′-*exo*-methylene nucleoside analogues.[11] Thus, it was considered that the S_N2' reaction of iodide ion was preferable than the S_N2 reaction of benzoate ion and that the desired d_4-benzoate **15** should be formed by nucleophilic substitution of the iodomethyl derivative **19a** (Scheme 3).

In this reaction, there seemed to be equilibrium between **17a** and **19a** due to an intramolecular nucleophilic substitution by a 2-keto group of thymine to reproduce starting **14a**. This may have caused the reaction to give a mixture of **15a** and **16a**.

On the basis of this hypothesis, we anticipated that the S_N2' reaction would proceed selectively if the intramolecular reaction triggered by the 2-keto group could be suppressed. Thus, 2,2′-anhydro-α-nucleoside **14a** was treated with sodium iodide and a catalytic amount of benzoic acid (10 mol %) in the presence of benzoic anhydride, which was expected to trap the N-3 nitrogen of **19a** generated along with the ring-opening reaction by benzoylation. To our delight, the reaction proceeded selectively and the desired **15a** was obtained as the major product (72% yield, **15a**/

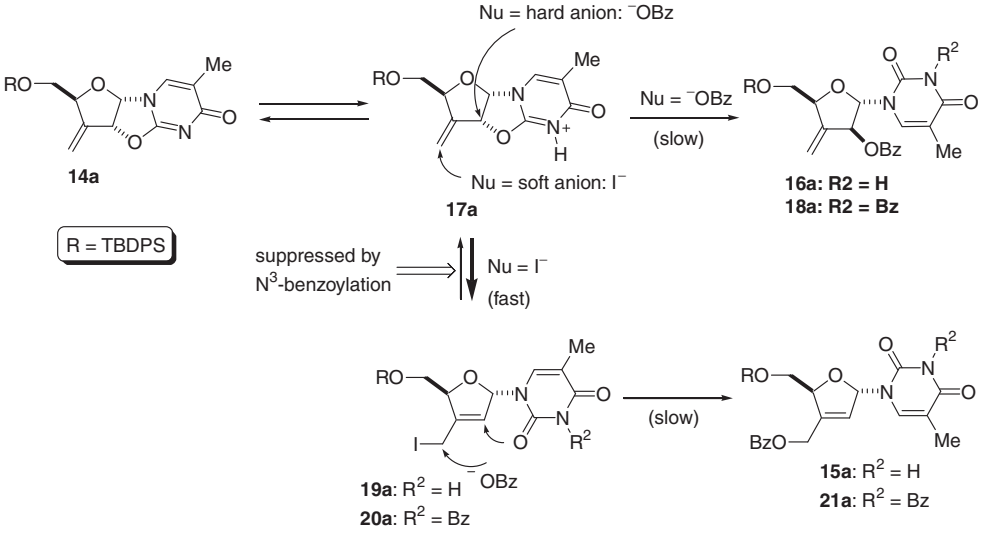


Scheme 2. Reagents and conditions: (a) K_2CO_3, MeOH, **13a** (98% from **11a**), **13b** (70% from **10**); (b) MsCl, Et_3N, CH_3CN, **14a** (76%), **14b** (79%); (c) see Table 1.

Table 1
The S_N2' type substitution reaction via a ring-opening of 2,2′-anhydro-α-nucleoside (**14a**)

Entry	Reagents	Solvent	Time (h)	Yield[a] (%)	Ratio (**15a**:**16a**)
1	BzONa, BzOH	DMF	9	64	Only **16a**
2	BzOH	Toluene	7	84	Only **16a**
3	BzONa, BzOH, NaI	DMF	3	83	1.4:1[b]
4	BzONa, TMSI	DMF	3	90	1:1[b]
5	Bz_2O, cat. BzOH, NaI	DMF	4	72	23:1[c]

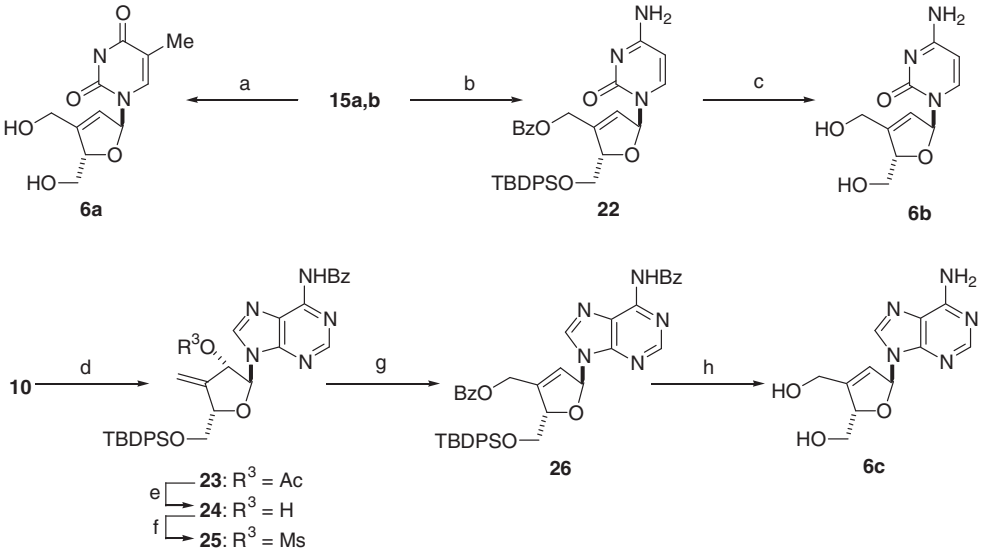
[a] Isolated yields.
[b] Ratio was determined based on integrations of ^1H NMR analysis.
[c] Ratio was determined based on isolated yields of two isomers.



Scheme 3. Proposed mechanism for the selective benzoylation.

16a = 23:1, entry 5).[12] Since only a trace amount of dibenzoate **21a** was isolated, the N^3-benzoyl group of **21a** seemed to be unstable under the reaction conditions. Similarly, uracil derivative **14b** was converted into **15b** in 84% yield. The ^1H NMR spectrum of **15** showed no signals due to geminal vinylic protons, which were present in the spectra of **14** and **16**.

The *C*-3′-methyl benzoate derivatives **15a**,**b** in hand were converted into the final pyrimidine apio-d4 nucleosides **6a**,**b**, as



Scheme 4. Reagents and conditions: (a) (i) NH_4OH, MeOH, THF, (ii) NH_4F·HF, DMF, 70%; (b) TPSCl, Et_3N, DMAP, CH_3CN, and then NH_4OH; (c) (i) NH_4F·HF, DMF, (ii) NH_4OH, MeOH, THF, 72% from **15b**; (d) N^6-BzAdenine, $SnCl_4$, CH_3CN, 0 °C; (e) K_2CO_3, MeOH, 63% from **10**; (f) MsCl, Et_3N, CH_3CN, 78%; (g) BzONa, NaI, DMF, 130 °C, 80%; (h) (i) TBAF, THF; (ii) NH_4OH, MeOH, THF, 64% from **15c**.

shown in Scheme 4. Thymine derivative **6a** was obtained in 70% yield by debenzoylation and subsequent desilylation.[13] Uracil derivative **15b** was aminated at the 4-position by treatment with 2,4,6-triisopropylbenzenesulfonyl chloride (TPSCl) in acetonitrile in the presence of triethylamine and 4-(dimethylamino)pyridine (DMAP), followed by aqueous ammonia, to give cytosine derivative **22**. As with the thymine derivative, **22** was deprotected to give apio-d4C derivative **6b** in 72% yield from **15b**.[14] Next, we tried to prepare a purine derivative using the above-mentioned reaction. Treatment of diacetate **10** with N^6-benzoyladenine and tin(IV) chloride at 0 °C gave **23**, which was subsequently deacetylated to afford **24** in 63% yield from **10**. Moreover, **24** was converted into 2′-mesylate **25** in 78% yield. As we expected, the substitution reaction of 2′-mesylate **25** proceeded selectively to give only the desired **26** in 80% yield. Attempted desilylation of **26** with ammonium hydrogen fluoride in DMF was unsuccessful because a deglycosylation reaction occurred even under the weakly acidic conditions. Instead of using ammonium hydrogen fluoride, the desilylation was successfully accomplished with TBAF, and subsequent debenzoylation gave the adenine derivative **6c** in 64% yield.[15]

In conclusion, we describe a selective S_N2' reaction triggered by iodide ion that leads to the ring-opening of 2,2′-anhydro-α-nucleosides (**14**). By applying the method, we have synthesized α-D-2′,3′-didehydro-2′,3′-dideoxy-3′-*C*-hydroxymethyl nucleosides (**6**). These nucleosides were assayed for antiviral activities against several viruses, such as HIV-1, herpes simplex virus (HSV) types-1,2, and HCMV.[16] Although the thymine derivative **6a** was found to exhibit very weak anti-HSV type-1 activity (EC_{50} = 33 μg/mL, CC_{50} >100 μg/mL), none of the other compounds that we tested showed any antiviral activity or cytotoxicity. To clarify the reason why these nucleosides except **6a** were inactive, the further study on their structure–activity relationships should be needed.

Acknowledgment

We are grateful to Dr. K. Kodama of Yamasa Corporation for his encouragement throughout this work.

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12. *Procedure of the preparation of* **15a**: To a solution of **14a** (200 mg, 0.42 mmol) in DMF (12 ml), sodium iodide (189 mg, 1.26 mmol), benzoic anhydride (285 mg, 3.75 mmol) and benzoic acid (15 mg, 0.04 mmol) were added, and the mixture was stirred at 130 °C for 4 h. Solvent was removed under reduced pressure, and the residue was extracted with AcOEt, and the organic phase was washed with saturated $NaHCO_3$, water and brine, and then dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by column chromatography over silica gel (2.2 × 13 cm, 30–50% AcOEt in *n*-hexane) to give **15a** (174 mg, 69%) and **16a** (9 mg, 3%) as an amorphous foam, respectively.
13. *Data for* **6a**: white solid. Mp 160 °C; UV (MeOH): λ_{max} 265 nm; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.27 (1H, s, NH), 7.16 (1H, d, H-6, *J* = 1.5 Hz), 6.82–6.81 (1H, m, H-1′), 5.63 (1H, t, H-2′, *J* = 1.5 Hz), 5.09 (1H, t, OH, *J* = 5.4 Hz), 4.94 (1H, br s, H-4′), 4.77 (1H, dd, OH, *J* = 5.4, 6.4 Hz), 4.17–4.13 (2H, m, H-allyl), 3.56 (1H, ddd, H-5′a, *J* = 3.9, 5.4, 12.2 Hz), 3.44 (1H, ddd, H-5′b, *J* = 3.9, 6.4, 12.2 Hz), 1.77 (1H, d, Me, *J* = 1.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): 163.8, 150.6, 149.7, 135.8, 118.7, 109.6, 88.8, 86.6, 62.0, 56.7, 12.0; FAB-MS (*m*/*z*) 255 (M^++H); HR-ESIMS (*m*/*z*). Calcd for $[C_{11}H_{14}N_2O_5Na]^+$: 277.0800; found: 277.0820. Anal. Calcd for $C_{11}H_{14}N_2O_5$: C, 51.97; H, 5.55; N, 11.02. Found: C, 51.80; H, 5.61; N, 10.94.
14. *Data for* **6b**: amorphous foam. UV (MeOH): λ_{max} 238, 272 nm; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.34 (1H, d, H-6, *J* = 7.3 Hz), 7.16 (1H, br s, NH), 7.11 (1H, br s, NH), 6.88–6.86 (1H, m, H-1′), 5.72 (1H, d, H-5, *J* = 7.3 Hz), 5.64 (1H, t, H-2′, *J* = 1.5 Hz), 5.06 (1H, t, OH, *J* = 5.4 Hz), 4.91–4.90 (1H, m, H-4′), 4.78 (1H, t, OH, *J* = 5.9 Hz), 4.18–4.08 (2H, m, H-allyl), 3.56 (1H, ddd, H-5′a, *J* = 3.9, 5.9, 11.7 Hz), 3.46 (1H, ddd, H-5′b, *J* = 4.4, 5.9, 11.7 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): 165.6, 155.3, 148.7, 141.0, 119.9, 94.3, 89.5, 86.4, 62.2, 56.7; FAB-MS (*m*/*z*) 240 (M^++H); HR-ESIMS (*m*/*z*). Calcd for $[C_{10}H_{13}N_3O_4Na]^+$: 262.0804; found: 262.0847. Anal. Calcd for $C_{10}H_{13}N_3O_4{\cdot}0.6H_2O$: C, 48.04; H, 5.72; N, 16.81. Found: C, 48.03; H, 5.86; N, 17.02.
15. *Data for* **6c**: amorphous foam. UV (MeOH): λ_{max} 261 nm; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.16 (1H, s, H-2 or H-8), 8.08 (1H, s, H-8 or H-2), 7.24 (2H, br s, NH_2), 6.94–6.93 (1H, m, H-1′), 5.90 (1H, t, H-2′, *J* = 1.5 Hz), 5.11 (1H, br s, OH), 5.00 (1H, br s, H-4′), 4.81 (1H, br s, OH), 4.25–4.15 (2H, m, H-allyl), 3.63–3.51 (2H, m, H-5′); ^{13}C NMR (125 MHz, DMSO-d_6): 155.9, 152.6, 149.4, 149.0, 138.4, 118.9, 118.6, 87.2, 86.5, 62.0, 56.8; FAB-MS (*m*/*z*) 264 (M^++H); HR-ESIMS (*m*/*z*). Calcd for $[C_{11}H_{13}N_5O_3Na]^+$: 286.0916; found: 286.0939. Anal. Calcd for $C_{11}H_{13}N_5O_3{\cdot}0.1H_2O$: C, 49.85; H, 5.02; N, 26.42. Found: C, 49.87; H, 4.93; N, 26.54.
16. Antiviral activities, except against HIV, and cytotoxicities were assayed at the Biological Laboratory of Yamasa Corp. Anti-HIV activity was tested at the Rational Drug Design Laboratories, Fukushima, Japan. We greatly appreciate the assistance of the staff there.