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Bioorganic & Medicinal Chemistry
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Bioorganic & Medicinal Chemistry 12 (2004) 1101–1109

Synthesis of D- and L-apio nucleoside analogues with 2′-hydroxyl group as potential anti-HIV agents

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Received 13 October 2003; accepted 4 December 2003

Abstract—The present work describes the asymmetric synthesis of D- and L-apio-2′,3′-dideoxynucleoside analogues, **4** and **5** with 2′-hydroxyl group via a common intermediate **9**, starting from D-galactose. Stereoselective dihydroxylation and deoxygenation through radical inversion were successfully employed to synthesize the key intermediate **12** with D-apio structure, while stereoselecetive hydroboration-oxidation was used for the synthesis of another key intermediate **18** with L-apio structure.

1. Introduction

A number of nucleoside derivatives have been designed, synthesized and evaluated for the development of antiviral and antitumor agents. Particularly, 2′,3′-unsubstituted-2′,3′-dideoxynucleosides (ddNs) have exhibited potent antiviral activity against human immunodeficiency virus (HIV), among which 2′,3′-dideoxycytidine (**1**, ddC, zalcitabine)[1] is one of the most potent anti-HIV agent and is being clinically used for the treatment of AIDS patients (Fig. 1).

However, ddC (**1**) has side effects such as peripheral neuropathy resulting from the inhibition of mitochondrial DNA[2] and appearance of the resistant strains.

Thus, as a part of worldwide efforts to look for antiviral agents with more potent anti-HIV activity and less side effects than ddC, iso- and apio-dideoxynucleosides (iso-ddNs **2** and apio-ddNs **3**) in which base and 4′-hydroxyl group are moved to 2′ and 3′ position, respectively have been designed and synthesized by several groups including our laboratory.[3,4a,4d–4g] However, these nucleosides were less potent than ddC (**1**), although they were not reported to show peripheral neuropathy.[4a,5]

Therefore, in order to increase anti-HIV activity of apio-ddNs **3**, we designed and synthesized D- and L-apio cytidines, **4** and **5** with 2′-hydroxyl group in the hope that the 2′-hydroxyl group might play an important role in binding affinity to their target enzyme, reverse transcriptase and kinases required for their activation into triphosphates as 3′-hydroxyl group of normal substrate, 2′-deoxycytidine does. For the synthesis of the desired D- and L-apio nucleosides **4** and **5**, we employed highly stereoselective dihydroxylation, deoxygenation of *tert*-hydroxyl group, and hydroboration-oxidation as key steps, starting from carbohydrate template, D-galactose and evaluated them for anti-HIV activity. Here, we wish to report the asymmetric synth-

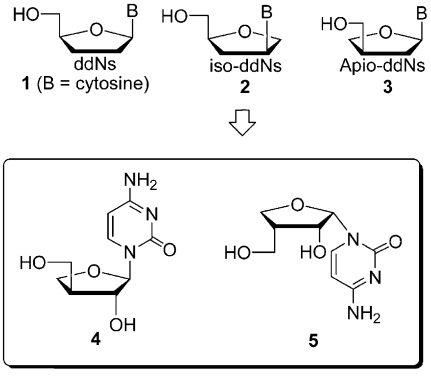

Figure 1. The rationale for the design of the target nucleosides.

Keywords: Apio nucleotides; Antiviral; Stereoselective.
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doi:10.1016/j.bmc.2003.12.002

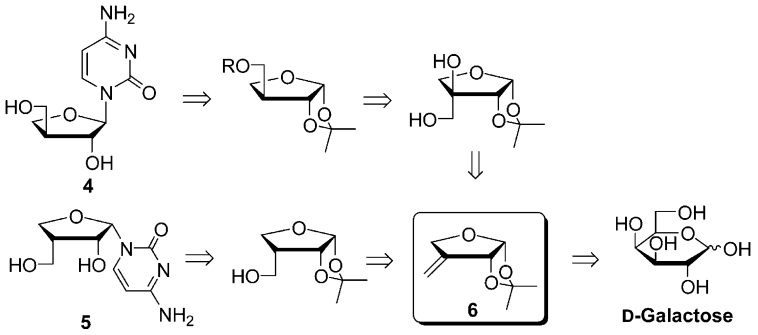
esis of D- and L-apio ddC analogues **4** and **5** and their anti-HIV activity.

2. Results and discussion

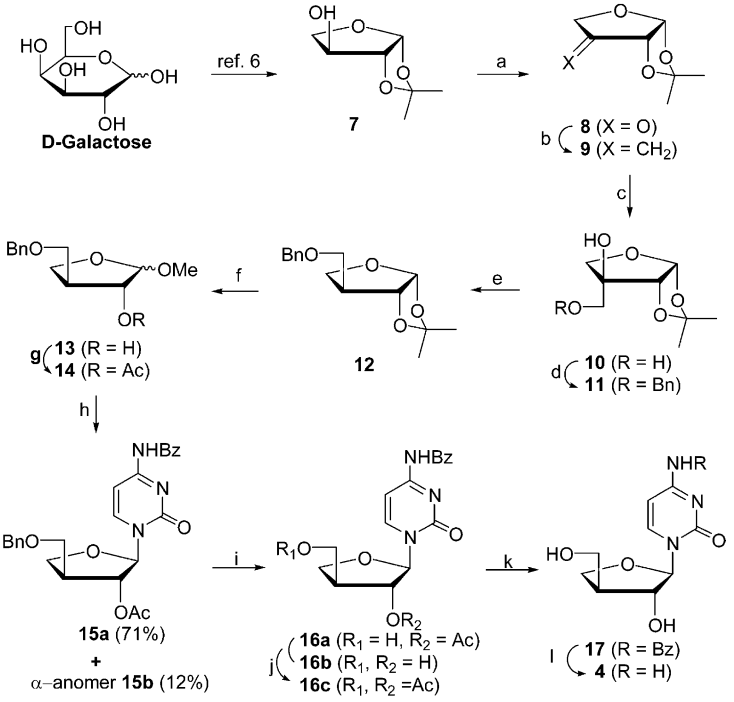
A strategy for the synthesis of D- and L-apio ddC analogues **4** and **5** is illustrated in Scheme 1.

It was envisioned that the olefin **6** could be an appropriate common key intermediate to give access to the target nucleosides **4** and **5**. Starting from the olefin **6** which can be prepared from D-galactose, stereoselective dihydroxylation followed by stereoselective deoxygenation would produce D-apio sugar intermediate, while regio- and stereoselective hydroboration-oxidation would afford L-apio sugar intermediate.

D-Apio ddC analogue **4** was synthesized starting from D-galactose, as shown in Scheme 2. The apio sugar **7** was prepared from D-galactose according to the known method.[6] Oxidation of **7** with PCC followed by treatment of the resulting ketone **8** with methyl triphenylphosphonium bromide in the presence of NaH and *t*-amyl alcohol gave the olefin **9**, which can be utilized for the synthesis of both D- and L-apio ddNs. Stereoselective *cis*-dihydroxylation of **9** with catalytic amount of OsO_4 and NMO was occurred due to the steric effect of 1,2-isopropylidene group to yield diol **10**. Primary hydroxyl group of compound **10** was regioselectively benzylated using organotin chemistry to afford monobenzyl ether **11**. Treatment of **11** with NaH, CS_2 and MeI gave the xanthate, which was subjected to the deoxygenation (Et_3B and Bu_3SnH)[7] to give **12** with D-apio skeleton through inversion of stereochemistry at



Scheme 1. Retrosynthetic analysis of the target nucleosides **4** and **5**.

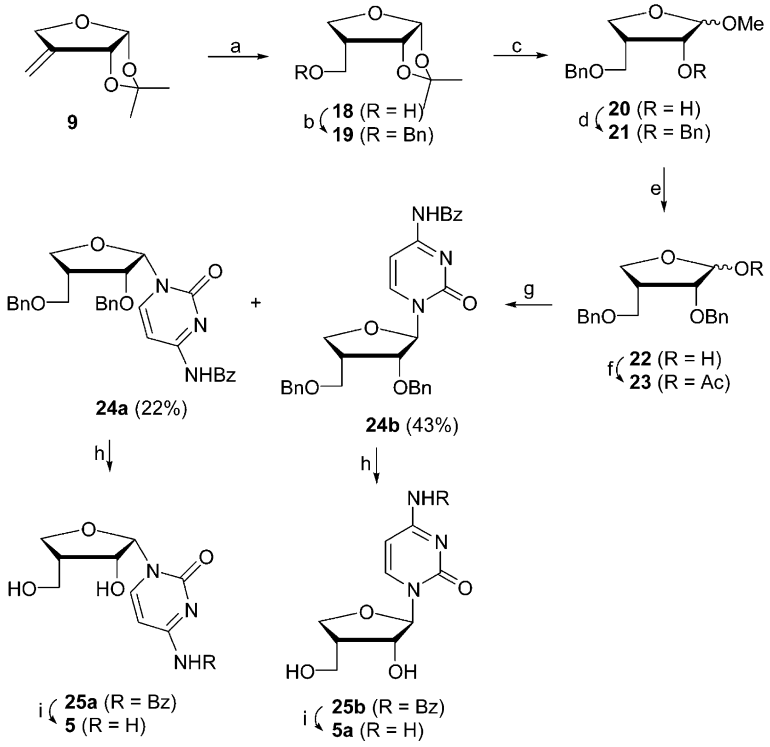


Scheme 2. Reagents: (a) PCC, 4A MS, CH_2Cl_2, rt, overnight, 68%; (b) CH_3PPh_3Br, NaH, *t*-amyl alcohol, THF, rt, 2 h, 80%; (c) OsO_4, NMO, acetone: H_2O (4:1), rt, 4 h, 98%; (d) *n*-Bu_2SnO, toluene, 140 °C, 2 h and then, *n*-Bu_4NBr, BnBr, 90–100 °C, overnight, 73%; (e) (i) NaH, THF, rt, 1 h and then, CS2, MeI, rt, 1 h; (ii) *n*-Bu_3SnH, Et3B, benzene, rt, 3 h, 70% from **11**; (f) *p*-TsOH, MeOH, rt, overnight, 75%; (g) Ac_2O, DMAP, pyridine, rt, 1 h, 86%; (h) silylated N4-benzoylcytosine, TMSOTf, CH_3CN, rt, overnight; (i) BCl_3, CH_2Cl_2, −78 °C, 2 h; (j) Ac_2O, pyridine, rt, overnight, 52% from **15a**; (k) K_2CO_3, MeOH, CH_2Cl_2, −5 °C, 40 min, 70%; (l) NaOMe, MeOH, rt, overnight, 92%.

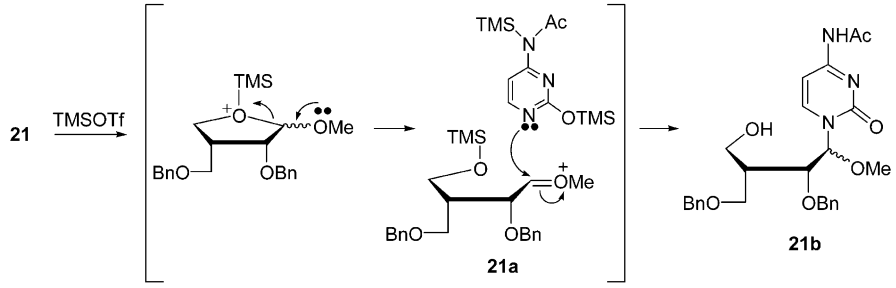
C3-position. Acid-catalyzed methanolysis of **12** using *p*-TsOH in methanol produced methyl glycosides **13**, which were acetylated to give the glycosyl donor **14**. Condensation of **14** with silylated N^4-benzoylcytosine in the presence of TMSOTf afforded β-anomer **15a** (71%) and α-anomer **15b** (12%) after silica gel column chromatography. As in our previous report,[8] the neighboring group effect by 2-acetoxy group in compound **14** was not large, when compared to that in 3-deoxy-2-ribosyl acetate, because of the repulsive effect between exomethylene group and incoming silylated N^4-benzoylcytosine nucleophile. Anomeric configurations were assigned on the basis of ^{1}H NOE experiments between 1′-H and exomethylene's H on the protected nucleosides, **15a** and **15b**. A NOE (0.65%) of β-anomer **15a** was smaller than that (2.25%) of α-anomer **15b**. Treatment of **15a** with BCl_3 at −78 °C produced the mixture of monoacetate **16a** and diol **16b**, which without further purification was acetylated with acetic anhydride in pyridine to give diacetate **16c**. The diacetate **16c** was chemoselectively deblocked in the presence of benzamide, using K_2CO_3 in a solution of methanol and methylene chloride at −5 °C to give the diol **17** (70%). D-β-Apio ddC analogue **4**[9] was finally obtained after the removal of benzoyl group of **17** with NaOMe.

The synthesis of L-apio ddC analogues **5** and its α-anomer **5a** is depicted in Scheme 3. The same intermediate **9** used for the synthesis of D-apio ddC analogue **4** was treated with 9-BBN. Hydroboration was regio- and stereoselectively occurred at the opposite side to the 1,2-isopropylidene group of **9** to afford borate, which was successively oxidized with $NaBO_3$ to give **18** with L-apio skeleton. Benzyl protection of **18** as benzyl ether **19** followed by methanolysis under acid conditions gave **20**. The secondary hydroxyl group of **20** was protected with benzyl chloride to give methyl glycosides **21**, which were ready for the condensation with N^4-benzoylcytosine. Unfortunately, coupling of **21** with N^4-benzoylcytosine in the presence of TMSOTf produced very small amounts of the desired nucleoside and two other major UV absorbing spots on TLC. ^{1}H NMR spectra of the two major spots showed the presence of methoxy group and cytosine, indicating that condensation was occurred with ring-opened intermediate **21a** generated from the binding of Lewis acid (TMSOTf) to the ring oxygen of **21**, giving a diastereomeric mixture of ring-opened product **21b** (Scheme 4).

It is worthy to note that condensation of methyl glycosides **14** afforded the desired cyclic nucleoside **15a** without giving a ring-opened nucleoside, probably due to electron withdrawing effect by 2-acetoxy group. Thus, to remove the formation of **21b**, electron-donating methoxy group of **21** was converted to the electron-withdrawing acetoxy group in two steps to give the acetate **23**. As expected, coupling of **23** with N^4-benzoylcytosine afforded a mixture of the desired nucleosides, **24a** (22%) and **24b** (43%). Higher yield of α-anomer over β-anomer appears to be due to the steric hindrance by 2-*O*-benzyl group. Anomeric configurations were assigned based on the ^{1}H NOE experiments between 1′-H and 3′-H on the protected nucleosides, **24a** and **24b**. A NOE (2.05%) of β-anomer **24a** was larger



Scheme 3. Reagents: (a) 9-BBN, THF, 0 °C, 3 h and then, $NaBO_3$, H_2O, rt, overnight, 70%; (b) BnBr, NaH, *n*-Bu4NI, THF, rt, overnight, 90%; (c) *p*-TsOH, MeOH, rt, 2 d, 97%; (d) BnBr, NaH, *n*-Bu*4*NI, THF, rt, overnight, 98%; (e) 8 N HCl, H_2O:1,4-dioxane (1:2), rt, 2 d, 95%; (f) Ac_2O, pyridine, rt, overnight, 93%; (g) silylated N^4-benzoylcytosine, TMSOTf, $ClCH_2CH_2Cl$, −35 °C, 1 h; (h) BCl_3, CH_2Cl_2, −78 °C, 30 min, 68% for **25a**, 70% for **25b**; (i) NaOMe, MeOH, rt, overnight, 97% for **5**, 81% for **5a**.



Scheme 4. Ring-opened product **21b** formed during condensation of **21** with cytosine.

than that (0.36%) of α-anomer **24b**. Removal of benzyl group of **24a** and **24b** with BCl_3 at −78 °C followed by debenzoylation with NaOMe produced L-β-apio ddC analogue **5** and its α-anomer **5a**,[9a] respectively.

The antiviral activity of D- and L-apio ddC analogues **4**, **5** and **5a** was evaluated against HIV-1 in MT-4 cells. However, all compounds showed neither significant anti-HIV activity nor cytotoxicity up to 100 μM. Lack of antiviral activity of the synthesized nucleosides may be attributed to the poor affinity to cellular kinases, not being converted into their triphosphates.

In summary, asymmetric synthesis of D- and L-apio ddC analogues **4** and **5** was achieved, using three stereoselective dihydroxylation, deoxygenation, and hydroboration-oxidation as key steps from the common intermediate **9**. These stereoselective reactions may be widely applied in the nucleoside chemistry. Chemoselective deprotection of acetyl group in the presence of the benzoyl group, poor neighboring group effect by 2-acetoxy group of apio-sugar and generation of ring-opened nucleosides may also provide nucleoside chemists with useful information.

3. Experimental

3.1. (3a*R*,6a*S*)-2,2-Dimethyl-dihydro-furo[2,3-*d*][1,3]dioxol-6-one (8)

To a suspension of PCC (21.6 g, 100.2 mmol) and 4 Å molecular sieves (16.7 g, 0.5 g/1.0 mmol) in CH_2Cl_2 (330 mL) was added a solution of **7** (5.35 g, 33.4 mmol) in CH_2Cl_2 (40 mL) at 0 °C and the mixture was stirred at room temperature overnight. Diethyl ether and Celite were added to the mixture and stirred for 1 h. The whole mixture was filtered through a short pad of silica gel and Celite and evaporated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 2:1) to give **8** (3.6 g, 68%) as a hygroscopic white solid: ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 4.06 (d, 1H, J = 17.2 Hz, 5-H_a), 4.31 (dd, 1H, J = 0.8, 4.4 Hz, 6a-H), 4.34 (dd, 1H, J = 0.8, 17.2 Hz, 5-H_b), 6.05 (d, 1H, J = 4.4 Hz, 3a-H); ^{13}C NMR ($CDCl_3$) δ 27.2, 27.5, 69.1, 75.9, 104.2, 114.4, 209.1. Anal. calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 52.84; H, 6.39.

3.2. (3a*R*,6a*R*)-2,2-Dimethyl-6-methylene-tetrahydro-furo[2,3-*d*][1,3]dioxole (9)

To a suspension of methyltriphenylphosphonium bromide (24.4 g, 68.28 mmol) and *t*-amyl alcohol (8.2 mL, 75.10 mmol) in dry THF (200 mL) was added NaH (3.1 g, 77.38 mmol, 60% in mineral oil) at 0 °C and the reaction mixture was stirred at room temperature for 2 h. To this yellow ylide was added a solution of **8** (3.6 g, 22.76 mmol) in dry THF (20 mL) dropwise at 0 °C and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 7:1) to give **9** (2.84 g, 80%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 4.31 (m, 1H, 5-H_a), 4.64 (m, 1H, 5-H_b), 4.84 (m, 1H, 6a-H), 5.19 (m, 1H, vinylic H_a), 5.38 (m, 1H, vinylic H_b), 5.86 (d, 1H, J = 10 Hz, 3a-H). Anal. calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.66; H, 7.59.

3.3. (−)-(3a*R*,6*S*,6a*R*)-6-Hydroxymethyl-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxol-6-ol (10)

To a solution of **9** (2.5g, 16.04 mmol) in acetone (86 mL) and water (21 mL) were added osmium tetroxide (2 mL, 0.16 mmol, 2.5 wt%) and *N*-methyl morpholine-*N*-oxide (19 mL, 97.31 mmol, 60 w/v%) at 0 °C and the reaction mixture was stirred at room temperature for 4 h and then quenched with saturated aqueous $Na_2S_2O_3$ solution. The reaction mixture was extracted with EtOAc and the organic layer was washed with water, dried over ahnhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (methylene chloride:methanol = 10:1) to give **10** (2.99 g, 98%) as a white solid: mp 125 °C; $[\alpha]_D^{25} = -37.4°$ (c 0.91, MeOH); ^{1}H NMR (CD_3OD) δ 1.30 (s, 3H, CH_3), 1.46(s, 3H, CH_3), 3.63 (d, 1H, J = 11.2 Hz, HOC*H*H), 3.73 (d, 1H, J = 9.6 Hz, 5-H_a), 3.78 (d, 1H, J = 11.2 Hz, HOCH*H*), 3.88 (d, 1H, J = 9.6 Hz, 5-H_b), 4.32 (d, 1H, J = 3.6 Hz, 3-H), 5.90 (d, 1H, J = 3.6 Hz, 2-H); ^{13}C NMR (CD_3OD) δ 26.6, 27.4, 63.4, 74.9, 83.5, 85.6, 107.9, 113.7. Anal. calcd for $C_8H_{14}O_5$: C, 50.52; H, 7.42. Found: C, 50.79; H, 7.71.

3.4. (−)-(3a*R*,6*S*,6a*R*)-6-Benzyloxymethyl-2,2-dimethyltetrahydro-furo[2,3-*d*][1,3]dioxol-6-ol (11)

To a solution of **10** (2.58 g, 13.56 mmol) in toluene (100 mL) was added *n*-Bu_2SnO (5.5 g, 22.09 mmol) and the reaction mixture was heated at 140–150 °C for 2 h. After the oil bath was cooled to 90–100 °C, *n*-Bu_4NBr (2.2 g, 6.82 mmol) and benzyl bromide (2.5 mL, 21.01 mmol) were added to the reaction mixture. The reaction mixture was heated at 90–100 °C overnight and evaporated to give the residue, which was purified by silica gel column chromatography (hexane:ethyl acetate = 2:1) to give **11** (2.77 g, 73%) as a white solid: mp 62 °C; $[\alpha]_D^{25} = -29.4°$ (*c* 1.26, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.29 (s, 3H, CH_3),1.45 (s, 3H, CH_3), 2.74 (br s, 1H, OH), 3.51 (d, 1H, *J* = 9.6 Hz, BnOC*H*H), 3.77 (d, 1H, *J* = 9.6 Hz, BnOCH*H*), 3.80 (d, 1H, *J* = 9.6 Hz, 5-H_a), 3.85 (d, 1H, *J* = 9.6 Hz, 5-H_b), 4.32 (d, 1H, *J* = 3.6 Hz, 3-H), 4.55 (d, 1H, *J* = 12.0 Hz, benzylic H_a), 4.61 (d, 1H, *J* = 12.0 Hz, benzylic H_b), 5.95 (d, 1H, *J* = 3.6 Hz, 2-H), 7.28–7.34 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 26.6, 27.2, 69.5, 73.9, 74.0, 81.5, 84.5, 106.4, 112.7, 127.9, 128.1, 128.7, 137.7. Anal. calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.10; H, 7.15.

3.5. (−)-(3a*R*,6*S*,6a*R*)-6-Benzyloxymethyl-2,2-dimethyltetrahydro-furo[2,3-*d*][1,3]dioxole (12)

To a solution of **11** (2.77 g, 9.88 mmol) in dry THF (60 mL) was added 60% NaH (1.18 g, 29.64 mmol) at −5 °C and the reaction mixture was stirred at room temperature for 1 h. To this mixture were added CS_2 (8.8 mL, 148.2 mmol) and MeI (19 mL, 296.4 mmol) and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was evaporated to give crude xanthate, which was used for the next step without further purification. To a solution of the xanthate in dry benzene (60 mL) were added triethylborane (14.8 mL, 14.80 mmol, 1.0 M solution in hexane) and *n*-Bu_3SnH (4 mL, 14.8 mmol) at room temperature and the mixture was stirred at the same temperature for 3 h. The reaction mixture was quenched with water, extracted with EtOAc, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 7.5:1) to give **12** (1.82 g, 70%) as a colorless oil: $[\alpha]_D^{25} = -4.2°$ (*c* 1.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.29 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.39–2.46 (m, 1H, 4-H), 3.50 (dd, 1H, *J* = 7.6, 9.2 Hz, BnOC*H*H), 3.67 (dd, 1H, *J* = 8.4, 10.8 Hz, 5-H_a), 3.76 (dd, 1H, *J* = 6.8, 9.2 Hz, BnOCH*H*), 3.99 (dd, 1H, *J* = 7.2, 8.4 Hz, 5-H_b), 4.48 (d, 1H, *J* = 12.0 Hz, benzylic H_a), 4.53 (d, 1H, *J* = 12.0 Hz, benzylic H_b), 4.63 (t, 1H, *J* = 4.0 Hz, 3-H), 5.81 (d, 1H, *J* = 4.0 Hz, 2-H), 7.26–7.32 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 26.4, 26.6, 44.8, 66.6, 69.3, 73.4, 80.2, 106.4, 111.9, 127.7, 127.8, 128.5, 138.3. Anal. calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.97; H, 7.67.

3.6. (2*RS*,3*R*,4*S*)-4-Benzyloxymethyl-2-methoxy-tetrahydro-furan-3-ol (13)

A solution of **12** (1.8 g, 6.80 mmol) and *p*-TsOH (647 mg, 3.40 mmol) in methanol (40 mL) was stirred at room temperature overnight, neutralized with triethylamine and evaporated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 1.5:1) to give **13** (1.22 g, 75%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 2.67–2.75 (m, 1H, 4-H), 3.32 (s, 3H, OCH_3), 3.71 (d, 2H, *J* = 5.6 Hz, BnOCH_2), 3.87 (t, 1H, *J* = 8.4 Hz, 5-H_a), 4.00 (t, 1H, *J* = 8.4 Hz, 5-H_b), 4.21 (d, 1H, *J* = 4.8 Hz, 3-H), 4.49 (d, 1H, *J* = 12.0 Hz, benzylic H_a), 4.54 (d, 1H, *J* = 12.0 Hz, benzylic H_b), 4.81 (s, 1H, 2-H), 7.28–7.34 (m, 5H, Ph). Anal. calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.52; H, 7.91.

3.7. Acetic acid (2*RS*,3*R*,4*S*)-4-benzyloxymethyl-2-methoxy-tetrahydro-furan-3-yl ester (14)

To a solution of **13** (1.36 g, 5.39 mmol) in pyridine (10 mL) were added acetic anhydride (1.53 g, 16.17 mmol) and 4-(dimethylamino)pyridine (100 mg) at 0 °C and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was evaporated, and partitioned between ethyl acetate and dilute HCl. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 5:1) to give **14** (1.38 g, 86%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.99 (s, 3H, $OCOCH_3$), 2.91–2.98 (m, 1H, 4-H), 3.33 (s, 3H, OCH_3), 3.44 (dd, 1H, *J* = 7.6, 9.6 Hz, BnOC*H*H), 3.60 (dd, 1H, *J* = 7.6, 9.6 Hz, BnOCH*H*), 3.77 (t, 1H, *J* = 8.4 Hz, 5-H_a), 4.13 (t, 1H, *J* = 8.4 Hz, 5-H_b), 4.45 (d, 1H, *J* = 12.0 Hz, benzylic H_a), 4.50 (d, 1H, *J* = 12.0 Hz, benzylic H_b), 4.82 (s, 1H, 2-H), 5.14 (d, 1H, *J* = 3.2 Hz, 3-H), 7.27–7.35 (m, 5H, Ph). Anal. calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.41; H, 7.27.

3.8. Acetic acid (2*R*,3*R*,4*S*)- and (2*S*,3*R*,4*S*)-2-(4-benzoylamino-2-oxo-2*H*-pyrimidin-1-yl)-4-benzyloxymethyl-tetrahydro-furan-3-yl ester (15a and 15b)

A suspension of N^4-benzoylcytosine (1.18 g, 5.50 mmol) and ammonium sulfate (catalytic amount) in hexamethyldisilazane (HMDS, 15 mL) was heated at 150–160 °C overnight to give a clear solution. The reaction mixture was cooled to room temperature and HMDS was removed under anhydrous condition in vacuo. To a solution of the residue in dry acetonitrile (15 mL) were added a solution of **15** (1.03 g, 3.67 mmol) in dry acetonitrile (5 mL) and TMSOTf (1 mL, 5.5 mmol) at 0 °C and the reaction mixture was stirred at room temperature overnight. After quenched with saturated aqueous $NaHCO_3$ solution, the reaction mixture was filtered through a Celite and the filtrate was partitioned between methylene chloride and water. The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was purified by silica gel column chromatography (methylene chloride:methanol = 40:1) to give β-isomer **15a** (1.2 g, 71%) as a white solid and α-isomer **15b** (0.2 g, 12%) as a white solid.

β-isomer **15a**: UV (CH_2Cl_2) λ_{max} 259 nm; ^1H NMR ($CDCl_3$) δ 2.08 (s, 3H, $OCOCH_3$), 2.69–2.75 (m, 1H, 4-H), 3.45 (dd, 1H, *J* = 8.0, 8.8 Hz, BnOC*H*H), 3.66 (dd, 1H, *J* = 5.6, 8.8 Hz, BnOCH*H*), 4.08 (t, 1H, *J* = 9.2 Hz, 5-H_a), 4.47 (s, 2H, benzylic CH_2), 4.52 (t, 1H, *J* = 9.2

Hz, 5-H_b), 5.60 (d, 1H, J = 5.6 Hz, 3-H), 5.93 (dd, 1H, J = 1.6, 5.6 Hz, 2-H), 7.28–8.02 (m, 12H, 2*Ph, H-5, H-6). Anal. calcd for $C_{25}H_{25}N_3O_6$: C, 64.79; H, 5.44; N, 9.07. Found: C, 64.65; H, 5.60; N, 9.02.

α-isomer **15b**: ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 3H, $OCOCH_3$), 2.69–2.75 (m, 1H, 4-H), 3.45 (dd, 1H, J = 7.2, 9.2 Hz, BnOC*H*H), 3.64 (dd, 1H, J = 6.0, 9.2 Hz, BnOCH*H*), 4.05 (t, 1H, J = 9.2 Hz, 5-H_a), 4.47 (s, 2H, benzylic CH_2), 4.53 (t, 1H, J = 9.2 Hz, 5-H_b), 5.64 (dd, 1H, J = 0.8, 5.2 Hz, 3-H), 5.83 (d, 1H, J = 0.8 Hz, 2-H), 7.26–8.12 (m, 12H, 2*Ph, H-5, H-6). Anal. calcd for $C_{25}H_{25}N_3O_6$: C, 64.79; H, 5.44; N, 9.07. Found: C, 64.52; H, 5.73; N, 8.86.

3.9. Acetic acid (2*R*,3*R*,4*S*)-4-acetoxymethyl-2-(4-benzoylamino-2-oxo-2*H*-pyrimidin-1-yl)-tetrahydro-furan-3-yl ester (16c)

To a solution of **15a** (0.96 g, 2.08 mmol) in anhydrous methylene chloride (15 mL) was added boron trichloride (20 mL, 20.0 mmol, 1.0 M solution in methylene chloride) at −78 °C and the mixture was stirred at the same temperature for 2 h. The reaction mixture was quenched with methanol, neutralized with pyridine and evaporated. Without further purification, the residue was dissolved in pyridine (15 mL) and acetic anhydride (4 mL, 41.6 mmol) at 0 °C and the reaction mixture was stirred at room temperature overnight and evaporated. The residue was partitioned between methylene chloride and water, and the organic layer was washed with dilute HCl, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (methylene chloride:methanol = 40:1) to give **16c** (0.45 g, 52%) as a white solid: UV (CH_2Cl_2) λ_{max} 259 nm; ^{1}H NMR ($CDCl_3$) δ 1.99 (s, 3H, $OCOCH_3$), 2.09 (s, 3H, $OCOCH_3$), 2.77–2.84 (m, 1H, 4-H), 3.96 (t, 1H, J = 9.2 Hz, 5-H_a), 4.01 (dd, 1H, J = 7.2, 11.2 Hz, AcOC*H*H), 4.21 (dd, 1H, J = 7.2, 11.2 Hz, AcOCH*H*), 4.45 (t, 1H, J = 8.4 Hz, 5-H_b), 5.66 (dd, 1H, J = 1.6, 5.6 Hz, 3-H), 5.82 (d, 1H, J = 1.6 Hz, 2-H), 7.45 (br t, 2H, J = 7.2, *meta*'s H), 7.54–7.56 (m, 2H, *para*'s H, H-5), 7.74 (d, 1H, J = 7.6 Hz, H-6), 7.90 (br d, 2H, J = 8.0 Hz, *ortho*'s H). Anal. calcd for $C_{20}H_{21}N_3O_7$: C, 57.83; H, 5.10; N, 10.12. Found: C, 58.00; H, 5.12; N, 9.99.

3.10. (−)-4-Amino-1-((2*R*,3*R*,4*S*)-3-hydroxy-4-hydroxymethyl-tetrahydro-furan-2-yl)-1*H*-pyrimidin-2-one (4)

To a solution of **16c** (450 mg, 1.08 mmol) in methanol (20 mL) and methylene chloride (5 mL) was added potassium carbonate (600 mg, 4.33 mmol) at −5 °C and the reaction mixture was stirred at the same temperature for 40 min. After neutralized with acetic acid, the reaction mixture was filtered through a short pad of silica gel and Celite, and evaporated. The residue was purified by silica gel column chromatography (methylene chloride:methanol = 30:1) to give **17** (250 mg, 70%) as a white solid: UV (MeOH) λ_{max} 258 nm; ^{1}H NMR (CD_3OD) δ 2.32–2.38 (m, 1H, 4-H), 3.70 (dd, 1H, J = 6.8, 10.8 Hz, HOC*H*H), 3.88 (dd, 1H, J = 6.8, 10.8 Hz, HOCH*H*), 4.03 (dd, 1H, J = 8.4, 10.8 Hz, 5-H_a), 4.38 (d, 1H, J = 4.4 Hz, 3-H), 4.49 (t, 1H, J = 8.4 Hz, 5-H_b), 5.79 (s, 1H, 2-H), 7.53–7.99 (m, 6H, Ph, H-5), 8.10 (d, 1H, J = 7.6 Hz, H-6). To a solution of **17** (27 mg, 0.08 mmol) in methanol (3 mL) was added 0.1 M NaOMe solution (0.08 mL, 0.008 mmol) and the reaction mixture was stirred at room temperature overnight. After neutralized with acetic acid, the reaction mixture was evaporated and the residue was purified by silica gel column chromatography (methylene chloride:methanol = 4:1) to give **4** (17 mg, 92%) as a white solid after crystallizaton from diethyl ether and methanol. The spectroscopic data was identical with those of authentic sample.[9c] Anal. calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.48; H, 5.89; N, 18.46

3.11. (−)-((3a*R*,6*R*,6a*R*)-2,2-Dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxol-6-yl)-methanol (18)

To a solution of **9** (10.0 g, 64.02 mmol) in dry THF (400 mL) was added 9-BBN (512 mL, 256 mmol, 0.5 M solution in THF) dropwise at 0 °C and the reaction mixture was stirred at the same temperature for 3 h. A solution of sodium perborate (59.0 g, 384.12 mmol) in water (170 mL) were added to the mixture and this mixture was stirred at room temperature overnight, extracted with EtOAc, dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 2:1) to give **18** (7.8 g, 70%) as a white solid: $[\alpha]_D^{25} = -34.2°$ (*c* 1.11, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 2.09 (t, 1H, J = 5.6 Hz, OH), 2.30–2.36 (m, 1H, 6-H), 3.85–3.90 (m, 3H, 5-H_a, $HOCH_2$), 4.96 (t, 1H, J = 8.0 Hz, 5-H_b), 4.73 (t, 1H, J = 4.0 Hz, 6a-H), 5.87 (d, 1H, J = 3.6 Hz, 3a-H); ^{13}C NMR ($CDCl_3$) δ 26.4, 26.7, 46.1, 59.1, 68.0, 81.2, 106.5, 122.2. Anal. calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.20; H, 8.23.

3.12. (−)-(3a*R*,6*R*,6a*R*)-6-Benzyloxymethyl-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3] dioxole (19)

To a suspension of 60% NaH (273 mg, 6.82 mmol) and *n*-Bu_4NI (140 mg, 0.37 mmol) in anhydrous THF (20 mL) was added a solution of **18** (645 mg, 3.79 mmol) in anhydrous THF (5 mL) slowly at 0 °C and the reaction mixture was stirred 0 °C for 20 min and then at room temperature for 30 min. After cooled to 0 °C, the reaction mixture was treated with benzyl bromide (0.49 mL, 4.16 mmol). The reaction mixture was stirred at room temperature overnight and partitioned between EtOAc and water. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 4:1) to give **19** (880 mg, 90%) as a yellowish oil: $[\alpha]_D^{25} = -27.9°$ (*c* 2.26, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 2.41–2.46 (m, 1H, 6-H), 3.51 (dd, 1H, J = 7.6, 9.2 Hz, BnOC*H*H), 3.69 (dd, 1H, J = 8.0, 11.2 Hz, 5-H_a), 3.78 (dd, 1H, J = 7.2, 9.2 Hz, BnOCH*H*), 4.01 (dd, 1H, J = 7.2, 8.4 Hz, 5-H_b), 4.50 (d, 1H, J = 12.0 Hz, benzylic H_a), 4.54 (d, 1H, J = 12.0 Hz, benzylic H_b), 4.64 (t, 1H, J = 3.6 Hz, 6a-H), 5.83 (d, 1H, J = 3.6 Hz, 3a-H), 7.28–7.34 (m, 5H, Ph). Anal. calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.40; H, 7.74.

3.13. (2*RS*,3*R*,4*R*)-4-Benzyloxymethyl-2-methoxy-tetrahydro-furan-3-ol (20)

A solution of **19** (880 mg, 3.33 mmol) and *p*-TsOH (317 mg, 1.66 mmol) in methanol (30 mL) was stirred at room temperature for 2 d. The reaction mixture was neutralized with triethylamine and evaporated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 3:1) to give **20** (770 mg, 97%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.68–2.75 (m, 1H, 3-H), 3.32 (s, 3H, OCH_3), 3.68–3.71 (m, 2H, BnOCH_2), 3.86 (t, 1H, J = 8.4 Hz, 5-H_a), 4.01 (t, 1H, J = 8.8 Hz, 5-H_b), 4.21 (t, 1H, J = 4.8 Hz, 3-H), 4.50 (d, 1H, J = 12.0 Hz, benzylic H_a), 4.55 (d, 1H, J = 12.0 Hz, benzylic H_b), 4.81 (s, 1H, 2-H), 7.28–7.34 (m, 5H, Ph). Anal. calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.85; H, 7.71.

3.14. (2*RS*,3*R*,4*R*)-3-Benzyloxy-4-benzyloxymethyl-2-methoxy-tetrahydro-furan (21)

To a suspension of 60% NaH (1.36 g, 34.0 mmol) and *n*-Bu_4NI (0.7 g, 1.89 mmol) in anhydrous THF (35 mL) was added a solution of **20** (4.5 g, 18.89 mmol) in anhydrous THF (15 mL) slowly at 0 °C and the reaction mixture was stirred 0 °C for 20 min and then at room temperature for 30 min. After cooled to 0 °C, the reaction mixture was treated with benzyl bromide (0.49 mL, 4.16 mmol). The reaction mixture was stirred at room temperature overnight and partitioned between EtOAc and water. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 6:1) to give **21** (6.1 g, 98%) as a colorless oil.

3.15. Major isomer

^{1}H NMR ($CDCl_3$) δ 2.79–2.86 (m, 1H, 4-H), 3.32 (s, 3H, OCH_3), 3.55 (dd, 1H, J = 7.6, 9.2 Hz, BnOC*H*H), 3.77 (dd, 1H, J = 6.8, 9.2 Hz, BnOCH*H*), 3.82 (t, 1H, J = 8.4 Hz, 5-H_a), 3.96 (d, 1H, J = 5.2 Hz, 3-H), 4.08 (t, 1H, J = 8.4 Hz, 5-H_b), 4.51 (s, 2H, benzylic CH_2), 4.53 (d, 1H, J = 12.0 Hz, benzylic H_a), 4.63 (d, 1H, J = 12.0 Hz, benzylic H_b), 4.92 (s, 1H, 2-H), 7.28–7.34 (m, 10H, 2*Ph). Anal. calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.10; H, 7.73.

3.16. Minor isomer

^{1}H NMR ($CDCl_3$) δ 2.58–2.67 (m, 1H, 4-H), 3.36 (s, 3H, OCH_3), 3.63 (dd, 1H, J = 9.2, 9.6 Hz, BnOC*H*H), 3.78 (dd, 1H, J = 4.8, 9.2 Hz, BnOCH*H*), 3.90 (dd, 1H, J = 4.8, 9.2 Hz, 5-H_a), 3.95 (dd, 1H, J = 4.8, 8.8 Hz, 3-H), 4.00 (t, 1H, J = 8.8 Hz, 5-H_b), 4.47 (s, 2H, benzylic CH_2), 4.55 (d, 1H, J = 12.4 Hz, benzylic H_a), 4.60 (d, 1H, J = 12.4 Hz, benzylic H_b), 4.76 (d, 1H, J = 4.4 Hz, 2-H), 7.25–7.31 (m, 10H, 2*Ph). Anal. calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.29; H, 7.11.

3.17. (2*RS*,3*R*,4*R*)-3-Benzyloxy-4-benzyloxymethyl-tetrahydro-furan-2-ol (22)

A solution of **21** (6.4 g, 19.48 mmol) in aqueous 8 N HCl (22mL) and 1,4-dioxane (44 mL) was stirred at room temperature for 2 d. After the reaction mixture was partitioned between water and EtOAc, the organic layer was washed with saturated aqueous $NaHCO_3$ solution, dried, filtered, and evaporated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 2:1) to give **22** (5.3 g, recovery yield: 95%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.55–2.62 (m, 1H, major's 4-H), 2.83–2.91 (m, 1H, minor's 4-H), 3.45 (dd, 1H, J = 4.4, 9.2 Hz, major's BnOC*H*H), 3.53 (dd, 1H, J = 7.6, 9.2 Hz, minor's BnOC*H*H), 3.65 (dd, 1H, J = 4.0, 9.2 Hz, major BnOCH*H*), 3.74–3.80 (m, 2H, minor's BnOCH*H*, 5-H_a), 3.89 (dd, 1H, J = 6.4, 8.8 Hz, major's 5-H_a), 3.93–3.98 (m, 2H, major's 5-H_b, minor's 5-H_b), 4.04 (dd, 1H, J = 4.0, 8.4 Hz, major's 3-H), 4.17 (t, 1H, J = 8.0 Hz, minor's 3-H), 4.50–4.56 (m, 6H, major's benzylic H_a, H_b, H_c, minor's H_a, H_b, H_c), 4.62 (d, 1H, J = 12.0 Hz, minor's benzylic H_d), 4.69 (d, 1H, J = 12.0 Hz, major's benzylic H_d), 5.28 (br d, 1H, J = 3.2 Hz, major's 2-H), 5.38 (s, 1H, minor's 2-H), 7.24–7.34 (m, 20H, major's 2*Ph, minor's 2*Ph). Anal. calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.44; H, 7.23.

3.18. (2*RS*,3*R*,4*R*)-3-Benzyloxy-4-benzyloxymethyl-tetrahydro-furan-2-yl ester (23)

To a solution of **22** (5.3 g, 16.86 mmol) in pyridine (25 mL) was added acetic anhydride (5.2 mL, 50.58 mmol) at 0°C and the reaction mixture was stirred at room temperature overnight, and evaporated. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 4:1) to give **23** (5.6 g, 93%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.01 (s, 3H, $OCOCH_3$), 2.55–2.65 (m, 1H, 4-H), 3.54 (dd, 1H, J = 7.2, 8.8 Hz, BnOC*H*H), 3.75 (dd, 1H, J = 7.2, 8.8 Hz, BnOCH*H*), 3.82 (dd, 1H, J = 8.0, 9.6 Hz, 5-H_a), 4.01 (d, 1H, J = 5.2 Hz, 3-H), 4.20 (t, 1H, J = 8.0 Hz, 5-H_b), 4.49 (d, 2H, J = 1.6 Hz, benzylic CH_2), 4.53 (d, 1H, J = 12.4 Hz, benzylic H_a), 4.71 (d, 1H, J = 12.4 Hz, benzylic H_b), 6.22 (s, 1H, 2-H), 7.27–7.32 (m, 10H, 2*Ph). Anal. calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.47; H, 6.81.

3.19. (+)-*N*-[1-((2*S*,3*R*,4*R*)-3-Benzyloxy-4-benzyloxymethyl-tetrahydro-furan-2-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-benzamide (24a) and (−)-*N*-[1-((2*R*,3*R*,4*R*)-3-Benzyloxy-4-benzyloxymethyl-tetrahydro-furan-2-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-benzamide (24b)

A suspension of N^4-benzoylcytosine (6.0 g, 27.88 mmol) and ammonium sulfate (catalytic amount) in hexamethyldisilazane (HMDS, 40 mL) was heated at 150–160 °C overnight to give a clear solution. The reaction mixture was cooled to room temperature and HMDS was removed under anhydrous condition in vacuo. To a solution of the residue in dry dichloroethane (40 mL) was added a solution of 23 (5.6 g, 15.71 mmol) in dry dichloroethane (10 mL) and TMSOTf (5.7 mL, 31.42 mmol) at −30 °C and the reaction mixture was stirred at the same temperature for 1 h. After quenched with saturated aqueous $NaHCO_3$ solution, the reaction mixture was filtered through a pad of Celite and the filtrate was partitioned between methylene chloride and water. The organic layer was dried over anhydrous $MgSO_4$,

filtered, and evaporated. The residue was purified by silica gel column chromatography (methylene chloride:methanol = 20:1) to give β-isomer **24a** (1.8 g, 22%) as a white solid and α-isomer **24b** (3.4 g, 43%) as a white solid.

β-isomer **24a**: mp 127 °C; UV (CH_2Cl_2) λ_{max} 258 nm; $[\alpha]_D^{25} = +89.1°$ (*c* 0.92, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.78–2.87 (m, 1H, 4-H), 3.49 (dd, 1H, *J* = 6.8, 9.2 Hz, BnOC*H*H), 3.66 (dd, 1H, *J* = 8.0, 9.2 Hz, BnOCH*H*), 3.88 (dd, 1H, *J* = 8.0, 11.2 Hz, 5-H_a), 4.16 (t, 1H, *J* = 8.0 Hz, 5-H_b), 4.22 (d, 1H, *J* = 11.6 Hz, benzylic H_a), 4.34 (d, 1H, *J* = 11.6 Hz, benzylic H_b), 4.46 (s, 2H, benzylic CH_2), 4.47 (t, 1H, *J* = 4.0 Hz, 3-H), 6.15 (d, 1H, *J* = 3.2 Hz, 2-H), 7.01–7.53 (m, 15H, 3*Ph), 7.60 (d, 1H, *J* = 7.2 Hz, H-5), 7.88 (d, 1H, *J* = 7.2 Hz, H-6). Anal. calcd for $C_{30}H_{29}N_3O_5$: C, 70.43; H, 5.71; N, 8.21. Found: C, 70.26; H, 5.99; N, 8.04.

α-isomer **24b**: UV (CH_2Cl_2) λ_{max} 258 nm; $[\alpha]_D^{25} = -62.8°$ (*c* 0.35, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.35–2.42 (m, 1H, 4-H), 3.56 (dd, 1H, *J* = 7.2, 8.8 Hz, BnOC*H*H), 3.68 (dd, 1H, *J* = 6.8, 8.8 Hz, BnOCH*H*), 4.05 (dd, 1H, *J* = 4.4, 11.6 Hz, 5-H_a), 4.17 (d, 1H, *J* = 4.8 Hz, 3-H), 4.42 (s, 2H, benzylic CH_2), 4.44 (t, 1H, *J* = 8.8 Hz, 5-H_b), 4.79 (d, 1H, *J* = 12.0 Hz, benzylic H_a), 4.97 (d, 1H, *J* = 12.0 Hz, benzylic H_b), 6.05 (s, 1H, 2-H), 7.22–7.92 (m, 17H, 3*Ph, H-5, H-6). Anal. calcd for $C_{30}H_{29}N_3O_5$: C, 70.43; H, 5.71; N, 8.21. Found: C, 70.38; H, 5.60; N, 8.34.

3.20. (+)-*N*-[1-((2*S*,3*R*,4*R*)-3-Hydroxy-4-hydroxymethyl-tetrahydro-furan-2-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-benzamide (25a)

To a solution of **24a** (82 mg, 0.15 mmol) in anhydrous methylene chloride (5 mL) was added boron trichloride (1.6 mL, 1.6 mmol, 1.0 M solution in methylene chloride) at −78 °C and the reaction mixture was stirred at the same temperature for 30 min. After quenched with methanol and neutralized with pyridine, the volatile materials were evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride:MeOH = 15:1) to give **25a** (36 mg, 68%) as a white solid: mp 202 °C; UV (MeOH) λ_{max} 257 nm; $[\alpha]_D^{25} = +91.9°$ (*c* 0.37, $CHCl_3$); ^1H NMR (CD_3OD) δ 2.61–2.68 (m, 1H, 4-H), 3.64 (dd, 1H, *J* = 6.8, 10.8 Hz, BnOC*H*H), 3.85 (dd, 1H, *J* = 6.8, 10.8 Hz, BnOCH*H*), 3.96 (dd, 1H, *J* = 8.0, 11.2 Hz, 5-H_a), 4.14 (t, 1H, *J* = 8.0 Hz, 5-H_b), 4.47 (t, 1H, *J* = 4.0 Hz, 3-H), 6.03 (d, 1H, *J* = 2.8 Hz, 2-H), 7.47–7.93 (m, 5H, Ph), 7.54 (d, 1H, *J* = 7.2 Hz, H-5), 8.04 (d, 1H, *J* = 7.2 Hz, H-6). Anal. calcd for $C_{16}H_{17}N_3O_5$: C, 58.00; H, 5.17; N, 12.68. Found: C, 57.78; H, 5.53; N, 12.64.

3.21. (−)-*N*-[1-((2*R*,3*R*,4*R*)-3-Hydroxy-4-hydroxymethyl-tetrahydro-furan-2-yl)-2-oxo-1,2-dihydro-pyrimidin-4-yl]-benzamide (25b)

Compound **24b** (42 mg, 0.08 mmol) was converted to compound **25b** (19 mg, 70%) as a white solid according to the same procedure used in the preparation of **25a**: UV (MeOH) λ_{max} 259 nm; $[\alpha]_D^{25} = -45.5°$ (*c* 0.22, MeOH); ^1H NMR (CD_3OD) δ 2.23–2.29 (m, 1H, 4-H), 3.60 (dd, 1H, *J* = 7.2, 10.8 Hz, BnOC*H*H), 3.78 (dd, 1H, *J* = 7.2, 10.8 Hz, BnOCH*H*), 3.94 (dd, 1H, *J* = 8.0, 10.4 Hz, 5-H_a), 4.28 (d, 1H, *J* = 4.8 Hz, 3-H), 4.39 (t, 1H, *J* = 8.0 Hz, 5-H_b), 5.69 (s, 1H, 2-H), 7.43–7.89 (m, 6H, Ph, H-5). 8.00 (d, 1H, *J* = 7.6 Hz, H-6). Anal. calcd for $C_{16}H_{17}N_3O_5$: C, 58.00; H, 5.17; N, 12.68. Found: C, 57.82; H, 5.46; N, 12.81.

3.22. (+)-4-Amino-1-((2*S*,3*R*,4*R*)-3-hydroxy-4-hydroxymethyl-tetrahydro-furan-2-yl)-1*H*-pyrimidin-2-one (5)

To a solution of **25a** (36 mg, 0.10 mmol) in methanol (2 mL) was added 0.1 M NaOMe solution (0.2 mL, 0.02 mmol) and the reaction mixture was stirred at room temperature overnight. After neutralized with acetic acid, the reaction mixture was evaporated and the residue was purified by silica gel column chromatography (methylene chloride:MeOH = 3:1) to give **5** (24 mg, 97%) as a white solid followed after crystallization from diethyl ether and methanol: mp 228 °C; MS *m*/*z* 228 ($M^+ + 1$); UV (MeOH) λ_{max} 273 nm; $[\alpha]_D^{25} = +120.0°$ (*c* 0.2, MeOH); ^1H NMR (CD_3OD) δ 2.61–2.68 (m, 1H, 4-H), 3.66 (dd, 1H, *J* = 6.8, 10.8 Hz, HOC*H*H), 3.87 (dd 1H, *J* = 6.8, 10.8 Hz, HOCH*H*), 3.93 (dd, 1H, *J* = 7.6, 11.2 Hz, 5-H_a), 4.12 (t, 1H, *J* = 7.6 Hz, 5-H_b), 4.40 (dd, 1H, *J* = 2.8, 4.8 Hz, 3-H), 5.86 (d, 1H, *J* = 7.2 Hz, H-5), 6.00 (d, 1H, *J* = 2.8 Hz, 2-H), 7.63 (d, 1H, *J* = 7.2 Hz, H-6); ^{13}C NMR (CD_3OD) δ 47.7, 59.9, 71.0, 71.3, 91.0, 94.6, 144.5, 158.4, 167.8. Anal. calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.56; H, 5.90; N, 18.31.

3.23. (−)-4-Amino-1-((2*R*,3*R*,4*R*)-3-hydroxy-4-hydroxymethyl-tetrahydro-furan-2-yl)-1*H*-pyrimidin-2-one (5a)[9a]

Compound **25b** (19 mg, 0.05 mmol) was converted to compound **5a** (11 mg, 81%) as a white solid according to the same procedure used in the preparation of **5**: MS *m*/*z* 228 ($M^+ + 1$); UV (MeOH) λ_{max} 273 nm; $[\alpha]_D^{25} = -87.5°$ (*c* 0.08, MeOH); ^1H NMR (CD_3OD) δ 2.25–2.33 (m, 1H, 4-H), 3.65 (dd, 1H, *J* = 7.2, 10.8 Hz, HOC*H*H), 3.83 (dd, 1H, *J* = 7.2, 10.8 Hz, HOCH*H*), 3.93 (dd, 1H, *J* = 8.0, 10.8 Hz, 5-H_a), 4.25 (d, 1H, *J* = 4.8 Hz, 3-H), 4.35 (t, 1H, *J* = 2.8, 8.0 Hz, 5-H_b), 5.66 (s, 1H, 2-H), 5.87 (d, 1H, *J* = 7.6 Hz, H-5), 8.00 (d, 1H, *J* = 7.6 Hz, H-6); ^{13}C NMR (CD_3OD) δ 44.6, 59.4, 73.0, 76.8, 95.7, 96.1, 141.7, 158.4, 168.0. Anal. calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.35; H, 5.92; N, 18.27.

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