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Articles

An Efficient Amination Method for Manufacturing Cytidines

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Abstract:

A novel method for amination of uridine derivatives was developed and applied to the syntheses of cytidines. The method consists of an activation step with 1-methylpiperidine at the C^4-position of a uracil base. Large-scale preparation of 2′-deoxycytidine was performed using this method.

Introduction

Cytidine structures are frequently found in pharmaceutically useful drugs.[1] They are difficult to synthesize due to the low stereoselectivity of glycosylation with cytosine. In addition to the synthesis of 2′-deoxycytidine, aminations of the corresponding uridine derivatives also have practical applications. Among the number of amination methods reported over a few decades, reactions with $POCl_3$/triazoles,[2] 4-chlorophenyl phosphorodichloridate/1,2,4-triazole,[3] and 2,4,6-triisopropylsulfonyl chloride (TPS-Cl),[4] followed by ammonolysis, are currently the best protocols so far. In some cases, however, manufacturing cost and scalability of purification limit their applicability to large-scale production. Toluenesulfonyl chloride (TsCl) is an alternative inexpensive and industrially available reagent for activating the C^4-carbonyl group of uridines. Unlike TPS-Cl, ammonolysis at the C^4-position competes with an attack at a sulfonyl group (path B and path A in Scheme 1). Bulky isopropyl groups of TPS-Cl are indispensable for suppressing this undesirable side reaction (path A in Scheme 1). A transient substitution with 1,2,4-triazole avoids this pathway, but a large excess amount of 1,2,4-triazole and a long reaction time are required to complete the reaction. We report an efficient amination that selectively proceeds, even with TsCl, in the presence of 1-methylpiperidine and its application to the large-scale preparation of 2′-deoxycytidine-HCl (**1**).

Scheme 1

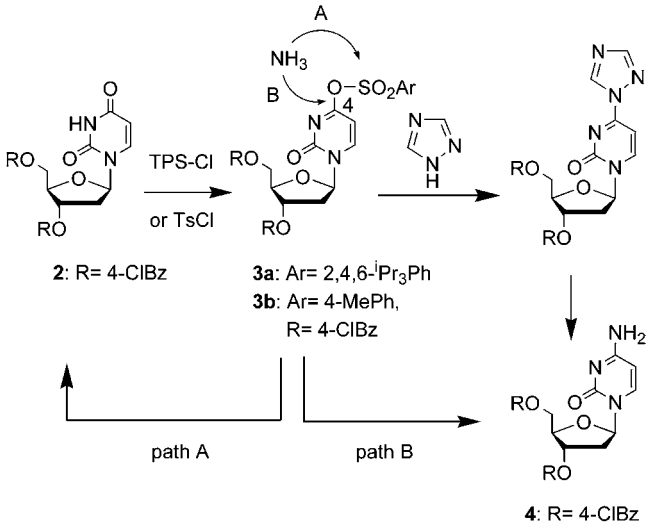

Table 1. **Results of the amination of 3′,5′-bis(4-chlorobenzoyl)-2′-deoxyuridine[a]**

entry	additives	amount (equiv)	reaction time (h)	ratio of **4**:**2**[b]	yield of **4**[c,g] (%)
1	1-methyl-piperidine	1.2	1	99.7:0.3	80
2	DABCO	1.2	0.5	99.8:0.2[f]	81
3	DABCO	2.0	4	93:6	ND
4	4-DMAP	2.1	22	99:1	60
5	4-DMAP	1.2	30	89:11	ND
6	4-DMAP	0.5	30	86:14	ND
7	4-DMAP	0.5[d]	40	92:8	ND
8	4-DMAP	0.1[d]	47	84:16[f]	ND
9	K_2CO_3	2.2[e]	22	72:28	ND
10	K_2CO_3	2.2[e]	22	91:9[f]	ND

[a] Reaction conditions: TsCl (1.2 equiv), Et_3N (2 equiv), CH_3CN, rt, then NH_4OH. [b] The ratios were monitored by HPLC. [c] Isolated yields were shown. [d] TsCl (2 equiv) was used. [e] TsCl (3.2 equiv) was used. [f] NH_3 was used instead of NH_4OH. [g] ND: not determined because of the low selectivity between **4** and **2**.

Results and Discussion

As a substrate for amination, 3′,5′-*O*-bis(4-chlorobenzoyl)-2′-deoxyuridine (**2**)[5] was used to investigate appropriate reaction conditions. Initially, **2** was reacted with TsCl in the presence of Et_3N in CH_3CN. The reaction was monitored by HPLC and completed in 1 h to give an intermediate tosylate (**3b**). Activators that could be replaced with the TsO group of **3b** were selected from nucleophilic tertiary amines

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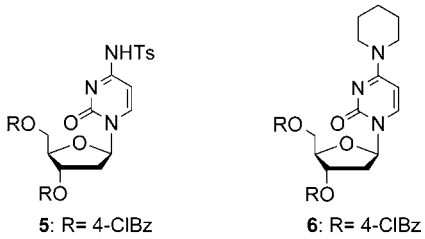
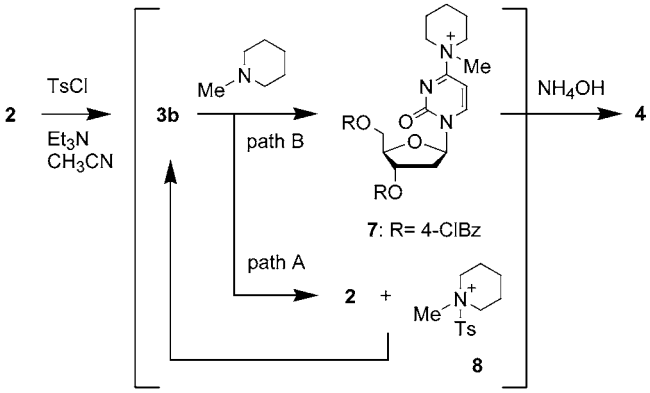


Figure 1. **Presumed structures of byproducts observed in the amination.**

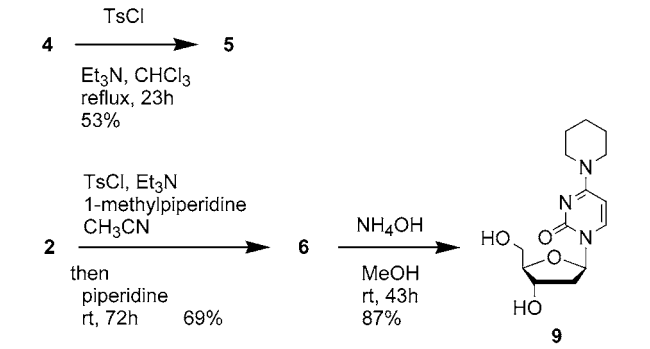
such as 4-DMAP,[4d] 1-methylpiperidine, and DABCO. The results were monitored by HPLC after ammonolysis conducted with NH_4OH (Table 1). The selectivity between path B and path A was determined as the ratio of **4** and **2**. The isolated yields were determined when the reaction proceeded selectively. 1-Methylpiperidine demonstrated rapid conversion and high selectivity, even when 1.2 equiv was used [**4**:**2** = 99.7:0.3 (entry 1)]. The resulting product (**4**) was crystallized directly from the reaction solution, thus simple filtration was sufficient to isolate **4** (80% of isolated yield). The reaction with DABCO was fast, but gaseous NH_3 was required for ammonolysis to obtain high selectivity and high isolated yield (compare entries 2 and 3; **4**:**2** = 99.8:0.2 and 93:6, respectively). When NH_4OH was used for the ammonolysis, competitive hydrolysis occurred and there was no crystallization of **4**. The reaction with 4-DMAP was rather slow, and 1.2 equiv was insufficient to complete the reaction (entries 4−8). Use of 2.1 equiv of 4-DMAP, however, resulted in moderate selectivity [**4**:**2** = 99:1 (entry 4)] and in a low isolated yield (60%). The high basicity of 4-DMAP compared with 1-methylpiperidine or DABCO contributed to these results, because 4-DMAP rather than Et_3N would favorably capture HCl and a substitution with 4-DMAP would likely be inhibited. The reaction proceeded with K_2CO_3, but with low selectivity [**4**:**2** = 72:28 (entry 9)]. Selectivity was slightly improved when ammonolysis was performed with gaseous NH_3 [**4**:**2** = 91:9 (entry 10)]. This result reflected substantial selectivity between path B and path A, because the intermediate was apparently **3b** and no other activator was involved in this reaction.

There were two major byproducts observed in the reaction solution of entry 1 in Table 1. Their molecular weights were determined by LC-MS analyses, and the chemical structures were presumed as depicted in Figure 1. The samples of **5** and **6** were alternatively synthesized and were identical to the compounds observed in the reaction solution of entry 1 by HPLC analyses. The results supported the reaction mechanism described in Scheme 2. 1-Methylpiperidine was replaced with the TsO group, and a quaternary ammonium salt (**7**) was produced as an intermediate. Demethylation of **7** gave **6**, and this side reaction was suppressed by conducting the reaction at a low reaction temperature (0 °C). Even if path B competed with path A, a presumable product (**8**) is likely to reproduce **3b** without consuming the reagents.[6] Ammonolysis by nucleophilic NH_3 rather than hydrolysis selectively occurred at the C^4-position of **7**, and **4** was

Scheme 2



Scheme 3



obtained in high yield. A small amount of byproduct (**5**) was produced by reacting with residual TsCl.

Syntheses of **5** and **6** are shown in Scheme 3. Reaction of **4** with TsCl/Et_3N was performed to afford **5** in 53% yield. The compound (**6**) was obtained by applying the newly developed amination method by using piperidine instead of NH_4OH. Reaction of **2** with TsCl/Et_3N/1-methylpiperidine was followed by the addition of piperidine to obtain **6** in 69% yield. Additionally, deprotection of **6** by NH_4OH/MeOH afforded **9** in 87% yield. This result demonstrated the applicability of this amination method to secondary amines and preparations of cytidine derivatives such as **6** or **9**.

The method was applied to a large-scale production of 2′-deoxycytidine-HCl (**1**) (Scheme 4). Uracil (**10**) was silylated by using hexamethyldisilazane (HMDS) in the presence of $(NH_4)_2SO_4$. The resulting compound (**11**) was condensed with a chloro sugar (**12**)[7] in $CHCl_3$ at 50 °C, and **2** was obtained in 95% yield. Stereoselectivity at an anomeric position was 96:4 (β:α). The α-isomer was removed by recrystallization in MeOH, and the ratio was improved to 99.3:0.7 (β:α). Amination of **2** was performed by TsCl/Et_3N/1-methylpiperidine followed by ammonolysis with NH_4OH. Selectivity, as determined by the ratio of **4**:**2**, was 99.5:0.5 for the reaction solution and 99.1:0.9 for the isolated product by HPLC analyses. The ratio of β:α increased to 99.9:0.01 after isolation. The resulting solid was further washed with MeOH, and **4** was obtained in 75% yield. The ratios of **4**:**2** and β:α were 99.4:0.6 and 99.98:0.02, respectively, on HPLC. This purification procedure was effective for remov-

(6) For sulfonylation with Me_3N^+-Ts, see: Yoshida, Y.; Sakakura, Y.; Aso, N.; Okada, S.; Tanabe, Y. *Tetrahedron* **1999**, *55*, 2183.

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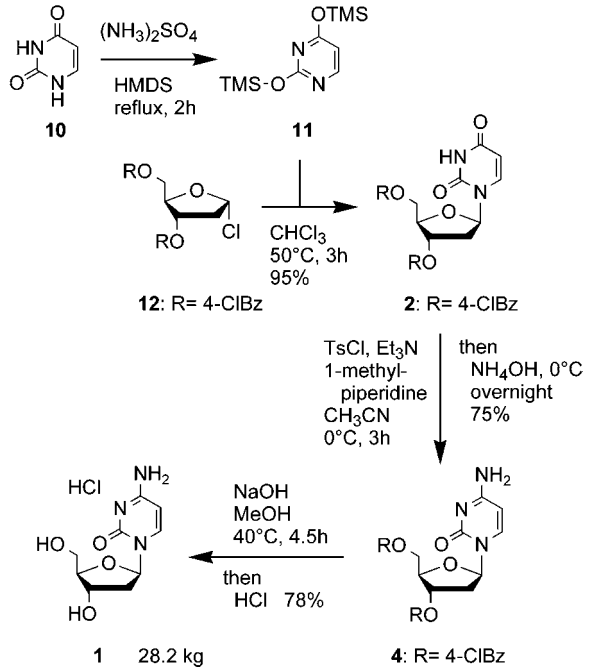
Scheme 4



ing the byproducts, **5** and **6** (4.8% of **5** and 0.25% of **6** decreased to 1.4% and 0.14%, respectively). Finally, deprotection of **4** was performed by NaOH/MeOH, and **1** was obtained as HCl salts by acidification with HCl/MeOH in 78% isolated yield. The comparatively low yield was due to the isolation loss. The ratio of β:α was 99.99:0.01, and the content of 2′-deoxyuridine was under the HPLC detection limit (<0.01%). Consequently, 28.2 kg of 2′-deoxycytidine-HCl (**1**) was synthesized from 95.0 kg (net 82.7 kg) of chloro sugar (**12**), and we demonstrated the applicability of the newly developed amination method to large-scale preparations.

Experimental Section

Melting points were measured with a Buchi 535 melting point apparatus and are uncorrected. IR spectra were obtained on a JASCO FT/IR-300 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL GSX-270 spectrometer. The ^{1}H NMR chemical shifts are described as δ values in ppm relative to TMS as an internal standard. The ^{13}C NMR chemical shifts are reported as δ values in ppm relative to the used solvents. Mass spectra were obtained with a JEOL SX-102A spectrometer. HPLC analyses were carried out using a Shimadzu SCL-10A apparatus equipped with an SPD-10AV UV detector.

3′,5′-*O*-Bis(4-chlorobenzoyl)-2′-deoxy-β-D-uridine (2). A mixture of uracil (**10**; 30 kg, 268 mol), $(NH_4)_2SO_4$ (0.35 kg, 2.65 mol), and HMDS (129.6 kg, 803 mol) was heated at reflux for 2 h. The resulting solution was concentrated, and the residual liquid, 2,4-bis(trimethylsilyloxy)pyrimidine (**11**), was dissolved in $CHCl_3$ (1331 kg). To the solution 3′,5′-*O*-bis(4-chlorobenzoyl)-2′-deoxy-α-D-ribosyl-1-chloride (**12**; 95.0 kg, 92 mol)[7] was added, and the mixture was stirred at 50 °C for 3 h. Aqueous $NaHCO_3$ solution was added to the reaction mixture. The organic phase was separated and evaporated. MeOH was added to the residue, and the mixture was stirred at rt. The resulting crystals were collected by filtration and dried in vacuo to give **2** (92.0 kg, 95%) as a white powder: mp 206−8 °C; $[\alpha]^{25}_D$ −27.2° (*c* 0.372, $CHCl_3$); IR (KBr) 3440, 2360, 2340, 1720, 1700, 1680, 1270 cm^{-1}; NMR δ_H (270 MHz, $CDCl_3$) 8.58 (1H, s), 8.1−7.9 (4H, m), 7.6−7.4 (5H, m), 6.36 (1H, dd, J = 2.7, 8.4 Hz), 5.67 (1H, d, J = 8.4 Hz), 5.59 (1H, m), 4.70 (2H, m), 4.54 (1H, m), 2.75 (1H, ddd, J = 2.7, 5.7, 14.6 Hz), 2.32 (1H, ddd, J = 7.6, 8.4, 14.6 Hz); NMR δ_C (67.8 MHz, $CDCl_3$) 165.2, 165.1, 162.8, 150.1, 140.4, 140.2, 138.8, 131.2, 130.9, 129.1, 129.0, 127.7, 127.3, 103.0, 85.8, 82.6, 74.8, 64.2, 38.0; MS (FD) *m*/*z* 504 (M − 1)$^-$. HPLC t_R 11.9 min (**2**), t_R 10.8 min (α-**2**) [column, Inertsil ODS-2 (250 mm × 4.6 mm) (from GL Sciences K. K.); mobile phase, CH_3CN−H_2O−Et_3N−AcOH (800:200:2:1); flow rate, 0.4 mL/min; UV wavelength, 254 nm; column temperature, 30 °C], β-**2**:α-**2** = 99.3:0.7.

3′,5′-*O*-Bis(4-chlorobenzoyl)-2′-deoxy-β-D-cytidine (4). TsCl (72.5 kg, 380 mol) in CH_3CN (181 kg) was added to a mixture of **2** (91.9 kg, 182 mol), Et_3N (38.5 kg, 380 mol), and 1-methylpiperidine (21.7 kg, 219 mol) in CH_3CN (361 kg) at 0 °C, and the reaction mixture was stirred for 3 h. 25% NH_4OH was added, and the reaction solution was stirred at rt overnight. The resulting precipitates were filtered, washed with CH_3CN, and stirred with MeOH at 0 °C for 2 h. The resulting crystals were collected by filtration and dried in vacuo to give **4** (68.8 kg, 70%) as a white powder: mp 237−8 °C; $[\alpha]^{25}_D$ −3.6° (*c* 0.162, $CHCl_3$); IR (KBr) 3370, 3199, 2368, 2345, 1718, 1655, 1490, 1271, 1094 cm^{-1}; NMR δ_H (400 MHz, DMSO-d_6) 8.04−7.96 (4H, m), 7.66−7.59 (5H, m), 7.21 (1H, s, D_2O exchangeable), 7.17 (1H, s, D_2O exchangeable), 6.29 (1H, dd, J = 6.95, 6.95 Hz), 5.70 (1H, d, J = 7.56 Hz), 5.61−5.59 (1H, m), 4.63−4.50 (3H, m), 2.55−2.47 (2H, m); NMR δ_H (270 MHz, $CDCl_3$) 8.1−7.85 (4H, m), 7.61 (1H, d, J = 7.3 Hz), 7.6−7.35 (4H, m), 6.8−5.2 (2H, br), 6.37 (1H, dd, J = 5.7, 7.8 Hz), 5.65 (1H, d, J = 7.3 Hz), 5.56 (1H, m), 4.67 (2H, m), 4.55 (1H, m), 2.94 (1H, ddd, J = 1.7, 5.7, 14.6 Hz), 2.23 (1H, ddd, J = 6.8, 7.8, 14.6 Hz); NMR δ_C (100 MHz, DMSO-d_6) 165.6, 164.6, 164.4, 154.8, 140.8, 138.5, 138.4, 131.2, 131.0, 128.9, 128.9, 128.1, 128.05, 94.4, 85.6, 80.9, 75.2, 64.6, 36.7; MS (FD) *m*/*z* 504 (M$^+$). HPLC 1 t_R 9.8 min (**4**); t_R 9.1 min (α-**4**), t_R 11.8 min (**2**) [column, Inertsil ODS-2 (250 mm × 4.6 mm) (from GL Sciences K. K.); mobile phase, CH_3CN−H_2O−Et_3N−AcOH (800:200:2:1); flow rate, 0.4 mL/min; UV wavelength, 254 nm; column temperature, 30 °C], **4**:**2**= 99.4:0.6, β-**4**:α-**2**= 99.98:0.02. HPLC 2 t_R 8.5 min (**7**), 10.1 min (**4**), 15.9 min (**2**), 28.0 min (**6**), t_R 41.1 min (**5**) [column, Inertsil ODS-2 (250 mm × 4.6 mm) (from GL Sciences K. K.); mobile phase, CH_3CN−10mM KH_2PO_4 (55:45); flow rate, 1.0 mL/min; UV wavelength, 254 nm; column temperature, 40 °C].

2′-Deoxy-β-D-cytidine hydrochloride (1). A mixture of **4** (68.8 kg, 136 mol) and NaOH (0.56 kg, 3.07 mol) in MeOH (392 L) was heated at 40 °C for 4.5 h. The reaction mixture was neutralized with HCl−MeOH and diluted with H_2O. The solution was washed with $CHCl_3$ and concentrated. The resulting crystals were collected by filtration and dried

in vacuo to give **1** (28.2 kg, 78%) as a white powder: mp 163 °C; $[\alpha]^{25}_{D}$ +56.5° (*c* 6, H_2O); IR (KBr) 3363, 2921, 2366, 2344, 1714, 1670, 1541, 1270 cm^{-1}; NMR δ_H (270 MHz, D_2O) 7.98 (1H, d, J = 8.1 Hz), 6.12 (1H, dd, J = 6.2, 6.2 Hz), 6.11 (1H, d, J = 8.1 Hz), 4.33 (1H, ddd, J = 3.8, 3.8, 6.8 Hz), 3.98 (1H, ddd, J = 3.8, 3.8, 4.8 Hz), 3.74 (1H, dd, J = 3.8, 12.7 Hz), 3.64 (1H, dd, J = 4.8, 12.7 Hz), 2.39 (1H, ddd, J = 4.6, 6.8, 14.6 Hz), 2.28 (1H, ddd, J = 6.8, 7.8, 14.6 Hz); NMR δ_C (67.8 MHz, D_2O) 160.0, 149.1, 145.4, 95.7, 88.1, 87.5, 71.1, 61.9, 40.0; MS (FD) *m*/*z* 228 $(M + 1)^+$. HPLC 1 t_R 6.0 min (**1**) [column, Inertsil ODS-2 (250 cm × 4.6 mm) (from GL Sciences K. K.); mobile phase, $CH_3CN-H_2O-Et_3N-AcOH$ (800:200:2:1); flow rate, 0.4 mL/min; UV wavelength, 254 nm; column temperature, 30 °C]. HPLC 2 t_R 15.0 min (**1**), t_R 13.6 min (α-**1**) [column, Inertsil ODS-2 (250 cm × 4.6 mm) (from GL Sciences K. K.); mobile phase, $CH_3CN-H_2O-Et_3N-AcOH$ (10:990:3:3); flow rate, 0.4 mL/min; UV wavelength, 254 nm; column temperature, 35 °C], β-**1**:α-**1**= 99.99:0.01.

3′,5′-*O*-Bis(4-chlorobenzoyl)-N^4-(4-toluenesulfonyl)-2′-deoxy-β-D-cytidine (5). A mixture of **4** (2.0 g, 3.67 mmol), TsCl (1.51 g, 7.93 mmol), and Et_3N (803 mg, 7.93 mmol) in $CHCl_3$ (29.6 g) was heated at reflux for 15 h, and the reaction solution was concentrated. The residual solid was washed with AcOEt and filtered. The resulting crude crystals were recrystallized from MeOH to give **5** (1.01 g, 39%) as a white powder: IR (KBr) 3424, 2365, 2347, 1719, 1655, 1626, 1509, 1491 cm^{-1}; NMR δ_H (400 MHz, DMSO-d_6) 12.2 (1H, d, J = 1.7 Hz), 8.01 (2H, d, J = 8.8 Hz), 7.96 (2H, d, J = 8.8 Hz), 7.91 (1H, d, J = 8.1 Hz), 7.69 (2H, d, J = 8.5 Hz), 7.61 (2H, d, J = 8.8 Hz), 7.57 (2H, d, J = 8.8 Hz), 7.35 (2H, d, J = 8.5 Hz), 6.51 (1H, dd, J = 1.7, 8.1 Hz), 6.18 (1H, dd, J = 6.8, 6.8 Hz), 5.59 (1H, m), 4.59−4.56 (3H, m), 2.64−2.63 (2H, m), 2.37 (3H, s); MS [ESI (+)] *m*/*z* 658 (M^+). HPLC t_R 10.4 min (**4**), t_R 46.5 min (**5**) [column, Inertsil ODS-2 (250 mm × 4.6 mm) (from GL Sciences K. K.); mobile phase, $CH_3CN-10mM\ KH_2PO_4$ (55:45); flow rate, 1.0 mL/min; UV wavelength, 254 nm; column temperature, 40 °C].

3-[3,5-*O*-Bis(4-chlorobenzoyl)-2-deoxy-β-D-ribofuranos-1-yl]-4-(1-piperidino)pyrimidin-2-one (6). A mixture of **2** (10.0 g, 19.8 mmol), TsCl (7.55 g, 39.6 mmol), and Et_3N (4.01 g, 39.6 mmol) in CH_3CN (39.0 g) was stirred at rt for 2 h. To the solution piperidine (2.87 mL, 23.7 mmol) was added, and the mixture was stirred at rt for 72 h. The reaction solution was concentrated. The residual solid was washed with CH_3CN and filtered. The resulting crude crystals were recrystallized from MeOH to give **6** (3.23 g, 69%) as a white powder: IR (KBr) 3450, 2959, 2677, 2492, 2364, 1725, 1656, 1626, 1490, 1278 cm^{-1}; NMR δ_H (400 MHz, DMSO-d_6) 8.03 (2H, d, J = 8.8 Hz), 7.96 (2H, d, J = 8.4 Hz), 7.70 (1H, d, J = 7.6 Hz), 7.63 (2H, d, J = 8.4 Hz), 7.59 (2H, d, J = 8.4 Hz), 6.29 (1H, dd, J = 6.8, 7.6 Hz), 6.16 (1H, d, J = 7.6 Hz), 5.60 (1H, dd, J = 3.2, 3.2 Hz), 4.60 (2H, m), 4.52 (1H, m), 3.70−3.50 (4H, m), 2.60 (2H, m), 1.62 (2H, m), 1.49 (4H, m); MS [ESI (+)] *m*/*z* 572 (M^+). HPLC t_R 16.5 min (**2**), t_R 29.0 min (**6**) [column, Inertsil ODS-2 (250 mm × 4.6 mm) (from GL Sciences K. K.); mobile phase, $CH_3CN-10mM\ KH_2PO_4$ (55:45); flow rate, 1.0 mL/min; UV wavelength, 254 nm; column temperature, 40 °C].

3-(2-Deoxy-β-D-ribofuranos-1-yl)-4-(1-piperidino)pyrimidin-2-one (9). A mixture of **6** (1.0 g, 1.75 mmol) and 25% NH_4OH (8.98 g, 148 mmol) in MeOH (39.6 g) was stirred at rt for 45 h, and the reaction solution was concentrated. The residual solid was washed with AcOEt−H_2O and filtered. The resulting crude crystals were washed with AcOEt to give **9** (447 mg, 87%) as a white powder: NMR δ_H (400 MHz, DMSO-d_6) 10.3 (1H, brs), 7.90 (1H, d, J = 8.0 Hz), 6.18 (1H, d, J = 8.0 Hz), 6.15 (1H, dd, J = 6.4, 7.2 Hz), 5.22 (1H, s), 5.03 (1H, s), 4.21 (1H, m), 3.78 (1H, m), 3.8−3.3 (6H, m), 2.12 (1H, ddd, J = 3.2, 6.4, 12.4 Hz), 1.98 (1H, ddd, J = 5.6, 7.2, 12.4 Hz), 1.62 (2H, m), 1.49 (4H, m); MS [ESI (+)] *m*/*z* 296 (M^+).

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