An Efficient Approach for the Synthesis of 1′-*O*-α-Methyl Pyrrolo[2,3-*d*]pyrimidine Isonucleosides

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Abstract: A series of novel 1′-*O*-α-methyl isonucleosides were efficiently and stereoselectively synthesized with 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose as the starting material. The key steps include regioselective and stereoselective deprotection of the 2,4-dichlorobenzyl group at C2, triflation, and substitution with appropriate nucleobases using cesium carbonate as the base. Removal of the residual 2,4-dichlorobenzyl groups and subsequent transformation afforded the title compounds in 30–37% overall yield. The products represent a new type of isonucleosides with 1′-*O*-substitution.

Key words: pyrrolo[2,3-*d*]pyrimidine, isonucleoside, regioselective deprotection, triflate, cesium carbonate

Modified nucleosides represent an important class of antiviral, antibiotic, and anticancer agents, and are widely used in research in medicine and molecular biology. Among the numerous nucleoside analogues that have been obtained from either natural or synthetic sources, pyrrolo[2,3-*d*]pyrimidine nucleosides, also called 7-deazapurine nucleosides, have received much attention due to their excellent biological activity. As shown in Figure 1, tubercidin (**I**) from *Streptomyces tubercidicus*,[1] as well as its 5-substituted derivatives toyocamycin (**II**) and sangivamycin (**III**) from *Streptomyces toyocaensis*[2] and *Streptomyces*[3] are known antibiotics. Other synthetic pyrrolo[2,3-*d*]pyrimidine derivatives also exhibit attractive biological activity, such as antitumor, antiviral, antibacterial, antifungal,[4] antitrypanosomal,[5] immunosuppressive,[6] antiasthma, antioxidant, and neuroprotective[7] activities.

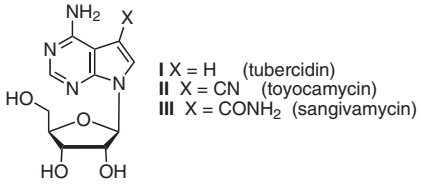
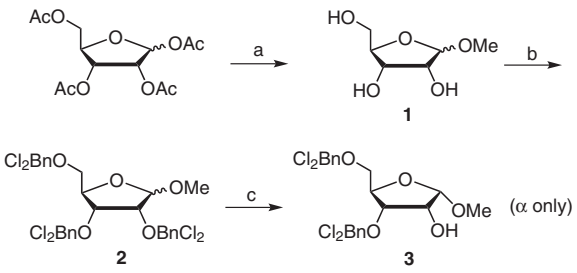


Figure 1

Other than variations on nucleobases, another approach to the development of nucleoside analogues focuses on the modification of the D-ribose. Among this type of molecules, isonucleosides, which attach nucleobases at C2 position instead of C1 of D-ribose,[8] exhibit significant antiviral and anticancer activity with improved chemical and enzymatic stability.[9] Therefore, pyrrolo[2,3-*d*]pyrimidine isonucleosides, which combine the strength of the above two approaches, appear to be an interesting type of nucleoside analogue. In our effort to investigate the biological significance of pyrrolo[2,3-*d*]pyrimidine isonucleosides, especially 1′-*O*-α-methyl isonucleosides, an efficient approach was highly required. Up to now, however, the synthesis of pyrrolo[2,3-*d*]pyrimidine isonucleosides[10] and 1′-*O*-substituted isonucleosides has been rarely reported. Their preparation has always suffered from long synthetic routes, expensive reagents, complex reactions, and poor overall yields.[11] Herein, we report a short and practical route for the synthesis of a series of novel 1′-*O*-α-methyl pyrrolo[2,3-*d*]pyrimidine isonucleosides.



Scheme 1 *Reagents and conditions:* (a) (i) NaOMe, MeOH, r.t.; (ii) Dowex-50w H^+ (87%), b/a 3:1; (b) 2,4-dichlorobenzyl chloride, NaH, DMF, 0 °C to r.t. (91%), b/a 3:1; (c) $SnCl_4$, CH_2Cl_2, 0 °C, 28 h (85%).

The key intermediate **3** for our route was prepared by the method reported by Brown et al. with slight modification.[12] Treatment of 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose with sodium methoxide in methanol, followed by direct addition of Dowex-50 H^+ resin gave **1** in excellent yield. 2,4-Dichlorobenzyl chloride (Cl_2Bn–Cl) was used as protecting reagent due to the fact that it is less irritant than benzyl bromide and the resulting product could be easily purified for large-scale production.[13] Reaction of compound **1** with sodium hydride and 2,4-dichlorobenzyl chloride afforded **2,** which could be precipitated with water and recrystallized from acetonitrile, as a pale yellow powder in 91% yield. Selective deprotection of **2** with tin(IV) chloride in dichloromethane resulted in the forma-

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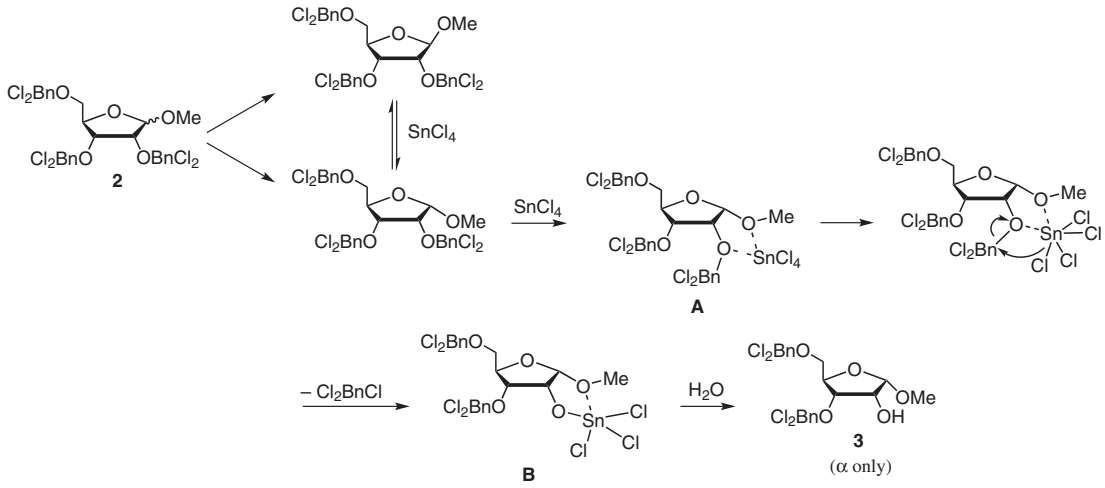
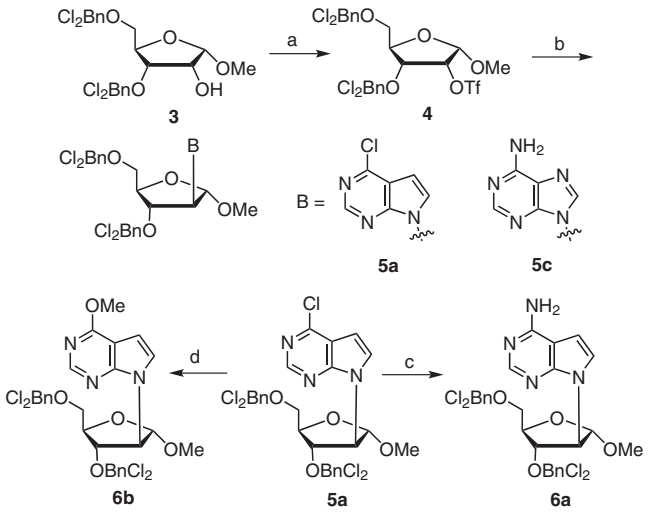


Scheme 2 Proposed mechanism for tin(IV) chloride mediated regioselective deprotection of **2**

tion of methyl 3,5-bis-*O*-(2,4-dichlorobenzyl)-α-D-ribofuranose (**3**) in high yield (Scheme 1).

Regioselective deprotection of benzyl groups on furanosides with Lewis acids, such as tin(IV) chloride and titanium(IV) chloride, has been reported in particular cases.[14] Combining Sinäy and Meguro's[10,14c,15] speculation, we presumed that an intermediate **A** could form between tin(IV) chloride and the two alkoxy oxygen atoms from C1 and C2 of the α-anomer, but not the β anomer. After the benzyl group was attacked by intramolecular chloride, the metal alkoxide **B** is hydrolyzed by water to give the regioselective deprotected riboside **3** with the α-configuration only (Scheme 2). The anomeric hydrogen atom shows a characteristic double peak with coupling constant $J = 4.4$ Hz. The structure of **3** was further determined by ^{1}H and ^{13}C NMR, HSQC, and NOESY.

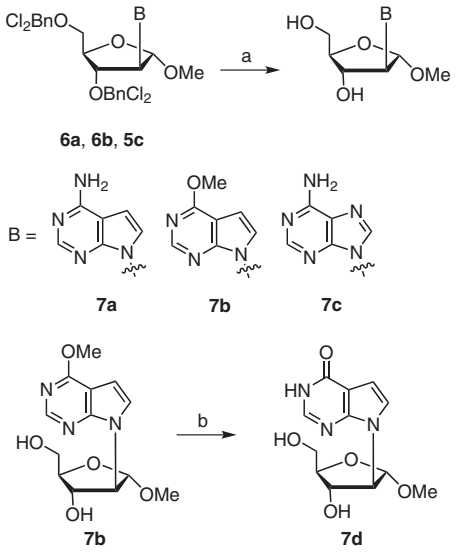
Activation of the hydroxy group at C2 with methanesulfonate and benzenesulfonate failed to result in coupling with nucleobases under normal conditions [e.g., K_2CO_3/18-crown-6/DMF,[9b–d,11c,e] KOH/TDA-1/MeCN,[16] DBU/DMF(MeCN),[11d,17] NaH/DMF(MeCN),[18] and Cs_2CO_3/DMF[19]]. Microwave irradiation, which has been reported to facilitate coupling reactions, showed no effect in this reaction. Meanwhile, even the elimination product could not be detected, which indicated a more reactive leaving group was needed. To solve this problem, trifluoromethanesulfonate (triflate) was used as a more efficient leaving group.[20] Compound **3** was converted into **4** with trifluoromethanesulfonic anhydride in 74% yield. Coupling of **4** with pyrrolo[2,3-*d*]pyrimidine nucleobases was tested with a series of bases as above. It was found that the reaction using cesium carbonate as the base proceeded most smoothly to afford **5a**, which was possibly due to the cesium effect.[21] The same conditions were also efficient for the synthesis of adenine isonucleosides **5c**. The transformation of **5a** to **6a** and **6b** was conducted using reported methods[22] in 77% and 91% yields, respectively (Scheme 3).



Scheme 3 *Reagents and conditions:* (a) Tf_2O, py, –40 °C to 0 °C (74%); (b) Cs_2CO_3, DMF, **5a** (87%), **5c** (79%); (c)NH_3/MeOH, 120 °C, 12 h (77%); (d) NaOMe, r.t. 12 h (91%).

Deprotection of **6a**, **6b**, and **5c** in the presence of triethylamine and 10% palladium hydroxide on carbon under a hydrogen atmosphere gave the corresponding products **7a–c** in excellent yields. As the 1′-*O*-α-methyl group is unstable under acidic condition, adding triethylamine is necessary to obviate the anomerization. Compound **7b** was refluxed in 2 M aqueous sodium hydroxide for 1.5 hours to afford **7d** in 84% yield (Scheme 4).[22]

In conclusion, we report a short and efficient approach for the synthesis of four new isonucleosides characterized by the 1′-*O*-α-methyl group in 30–37% overall yield. It has the merits of being cost effective, using mild reaction protocols, and giving easy access to diverse derivatives. The preliminary biological tests showed their potential as CGRP (Calcitonin Gene-Related Peptide) receptor antagonists. Further efforts to incorporate these isonucleosides to DNA are in progress and will be reported in due course.



Scheme 4 *Reagents and conditions:* (a) 20% $Pd(OH)_2$, H_2, Et_3N, EtOAc, MeOH, **7a** (92%), **7b** (94%), **7c** (88%); (b) aq NaOH, reflux, 1.5 h (84%).

$Pd(OH)_2$/C, $SnCl_4$, and Cs_2CO_3 were purchased from Sigma Aldrich. MeOH, Pyridine and CH_2Cl_2 were dried and distilled prior to use. TLC was performed using silica gel GF-254 plates (Qing-Dao Chemical Company, China) with detection by UV, or charting with 10% H_2SO_4 in EtOH. Column chromatography was performed on silica gel (200–300 mesh, purchased from Qing-Dao Chemical Company, China). NMR spectra were recorded on Bruker AV400 spectrometer. ^1H and ^{13}C NMR spectra were calibrated with TMS as internal standard. The ESI-HRMS were obtained on a Bruker Dalton microTOFQ II spectrometer in positive ion mode.

Methyl D-Ribofuranoside (1)

To a stirred soln of 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose (720.0 g, 2.26 mol) in anhyd MeOH was added Na (1.0 g, 43.5 mmol) and the mixture was stirred at r.t. overnight until no reactant was detected (TLC). Dowex-50 H^+ resin was added and the mixture was adjusted to pH 3. After stirring at r.t. for 15 h and filtration, the solvent was removed and the residual was purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 10:1) to afford **1** as a mixture of β- and α-anomers as a brown oil; yield: 323.0 g (87%, β/α 3:1); R_f = 0.49 (β-anomer), 0.37 (α-anomer) (CH_2Cl_2–MeOH, 10:1).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 109.1, 103.2, 85.1, 84.6, 75.8, 72.1, 71.7, 71.0, 63.6, 63.0, 56.0, 56.0.

MS (ESI): *m*/*z* = 165 [M + H^+]

Methyl 2,3,5-Tris-*O*-(2,4-dichlorobenzyl)-D-ribofuranoside (2)

To a stirred soln of **1** (13.84 g, 84 mmol) and 2,4-dichlorobenzyl chloride (70.1 mL, 504 mmol) in anhyd DMF (138 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 20.16 g, 504 mmol) in 4 portions. The mixture was allowed to warm up to r.t. over 1 h and stirred at r.t. for 12 h. H_2O (300 mL) was added to quench the reaction. The precipitate was filtered, washed with H_2O (2 × 100 mL), and recrystallized (MeCN, 50 mL). The solid was collected by filtration and washed with MeCN (2 × 100 mL) to afford **2** as a mixture of β- and α-anomers as a pale-yellow powder that was used directly without further separation; yield: 49.68 g (91%, β/α 3:1); R_f = 0.49 (β-anomer), 0.15 (α-anomer) (PE–EtOAc, 5:1).

A small amount of the mixture was purified over a column (silica gel, PE–EtOAc, 5:1) to afford the β- and α-anomers, respectively, for analysis.

β-Anomer

^1H NMR (400 MHz, $CDCl_3$): δ = 3.37 (s, 3 H), 3.66 (dd, *J* = 10.8, 5.2 Hz, 1 H), 3.75 (dd, *J* = 10.4, 3.6 Hz, 1 H), 3.98 (d, *J* = 4.4 Hz, 1 H), 4.18 (t, 1 H), 4.37 (m, 1 H), 4.61–4.75 (m, 6 H, 2 OCH_2Ar), 5.00 (s, 1 H), 7.16–7.46 (m, 9 H, H_{Ar}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.0, 134.6, 134.4, 134.4, 134.3, 134.0, 133.7, 133.6, 133.5, 130.4, 129.9, 129.4, 129.4, 129.3, 127.5, 127.4, 127.4, 106.5, 81.1, 80.6, 79.5, 72.1, 70.2, 69.4, 69.3, 55.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{24}Cl_6NaO_5$: 660.9647; found: 660.9645.

α-Anomer

^1H NMR (400 MHz, $CDCl_3$): δ = 3.51 (s, 3 H), 3.64 (m, 2 H), 3.94 (t, 1 H), 4.00 (dd, *J* = 6.0, 3.6 Hz, 1 H), 4.34 (d, *J* = 3.2 Hz, 1 H), 4.53 (d, *J* = 12.8 Hz, 1 H), 4.58 (d, *J* = 12.8 Hz, 1 H), 4.67 (dd, *J* = 13.2, 4.0 Hz, 2 H), 4.76 (dd, *J* = 13.6, 1.2 Hz, 1 H), 5.05 (d, *J* = 4.0 Hz, 2 H), 7.16–7.50 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.7, 134.1, 134.0, 133.7, 133.6, 133.3, 133.2, 130.2, 130.2, 129.9, 129.2, 129.0, 128.9, 127.2, 127.1, 102.2, 81.6, 78.9, 76.8, 70.7, 70.1, 69.1, 69.1, 55.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{24}Cl_6NaO_5$: 660.9647; found: 660.9644.

Methyl 3,5-Bis-*O*-(2,4-dichlorobenzyl)-α-D-ribofuranoside (3)

To a stirred soln of **2** (34.74 g, 53.7 mmol) in anhyd CH_2Cl_2 (347 mL) was added 1 M $SnCl_4$ in CH_2Cl_2 soln (54 mL, 54.0 mmol) dropwise at 0 °C under argon. The mixture was stirred for 28 h until the starting material had disappeared (TLC). H_2O (50 mL) and CH_2Cl_2 (200 mL) were added to quench the reaction. The organic layer was separated, washed with H_2O (3 × 300 mL), 0.2 M HCl (1 × 150 mL), sat. $NaHCO_3$ (1 × 150 mL), and brine (2 × 150 mL), dried (anhyd Na_2SO_4), and evaporated under reduced pressure. The residual was purified by column chromatography (silica gel, PE–EtOAc, 3:1) to afford **3** as a pale-yellow oil; yield: 22.3 g (85%); R_f = 0.42 (PE–EtOAc, 2:1).

^1H NMR (400 MHz, $CDCl_3$): δ = 2.93 (d, *J* = 11.2 Hz, 1 H, 2-OH), 3.48 (s, 3 H, 1-OCH_3), 3.59 (d, *J* = 4.0 Hz, 2 H, H5), 3.85 (m, 1 H, H3), 4.17 (m, 1 H, H2), 4.23 (d, *J* = 3.2 Hz, 1 H, H4), 4.55 (dd, *J* = 18.0, 12.8 Hz, 2 H, 5-OCH_2Ar), 4.66 (d, *J* = 13.6 Hz, 1 H, 3-OCH_2Ar), 4.75 (d, *J* = 13.2 Hz, 1 H, 3-OCH_2Ar), 4.91 (d, *J* = 4.4 Hz, 1 H), 7.20–7.42 (m, 6 H, H_{Ar}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.7, 134.6, 134.4, 133.9, 133.9, 130.3, 130.1, 129.5, 129.4, 127.4, 127.4, 103.1, 81.9, 77.8, 72.3, 71.2, 70.4, 69.8, 55.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{20}Cl_4NaO_5$: 502.9957; found: 502.9959.

Methyl 3,5-Bis-*O*-(2,4-dichlorobenzyl)-2-*O*-(trifluoromethylsulfonyl)-α-D-ribofuranoside (4)

To a stirred soln of **3** (3.73 g, 7.67 mmol) in anhyd pyridine (40 mL) was added Tf_2O (2.60 g, 11.5 mmol) dropwise at –40 °C under argon. The mixture was allowed to warm up to 0 °C over 1 h. Then, ice was added to quench the reaction. After concentration under reduced pressure, the residual was purified by column chromatography (silica gel, PE–EtOAc, 5:1) to afford **4** as a colorless oil; yield: 3.51 g (74%); R_f = 0.64 (PE–EtOAc, 3:1).

^1H NMR (400 MHz, $CDCl_3$): δ = 3.52 (s, 3 H, OCH_3), 3.60 (dd, *J* = 10.8, 2.8 Hz, 1 H, H5a), 3.71 (dd, *J* = 10.8, 2.0 Hz, 1 H, H5b), 4.16 (t, *J* = 5.6 Hz, 1 H, H3), 4.28 (d, *J* = 2.0 Hz, 1 H, H4), 4.50–

4.75 (m, 4 H, 2 OCH_2Ar), 5.07 (m, 1 H, H2), 5.13 (d, J = 4.0 Hz, 1 H, H1), 7.22–7.43 (m, 6 H, H_{Ar}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.7, 134.6, 134.2, 134.1, 133.9, 133.8, 130.7, 130.3, 129.6, 129.4, 127.7, 127.5, 120.5, 117.3, 101.4, 81.6, 80.8, 76.1, 70.5, 70.1, 69.6, 56.6.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{21}H_{19}Cl_4F_3NaO_7S$: 634.9450; found: 634.9455.

4-Chloro-7-[methyl 3,5-bis-*O*-(2,4-dichlorobenzyl)-α-D-arabinofuranosid-2-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (5a)

To a soln of **4** (1.01 g, 1.64 mmol) and 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (224 mg, 1.67 mmol) in anhyd DMF (33 mL) was added Cs_2CO_3 (540 mg, 1.67 mmol) and the mixture was stirred at r.t. for 5 h under argon. The solvent was removed under vacuum and the residual was purified by column chromatography (silica gel, PE–EtOAc, 5:1) to afford **5a** as a colorless oil; yield: 877 mg (87%); R_f = 0.39 (PE–EtOAc, 4:1).

^1H NMR (400 MHz, $CDCl_3$): δ = 3.44 (s, 3 H, 1′-OCH_3), 3.81 (dd, J = 10.8, 3.2 Hz, 1 H, H5′a), 3.97 (dd, J = 10.8, 2.0 Hz, 1 H, H5′b), 4.31 (m, 1 H, H3′), 4.39 (m, 1 H, H4′), 4.49 (d, J = 12.4 Hz, 1 H, OCH_2Ar), 4.60 (d, J = 12.4 Hz, 1 H, OCH_2Ar), 2.72 (dd, J = 12.8, 3.2 Hz, 2 H, OCH_2Ar), 5.13 (s, 1 H, H1′), 5.42 (d, J = 2.4 Hz, 1 H, H2′), 6.53 (d, J = 3.6 Hz, 1 H, H5), 7.17–7.40 (m, 7 H, H_{Ar}, H6), 8.67 (s, 1 H, H2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.7, 151.2, 151.0, 134.7, 134.5, 134.4, 134.3, 134.1, 133.8, 130.7, 130.4, 129.6, 129.5, 127.5, 127.4, 127.3, 117.9, 107.6, 100.8, 84.8, 81.7, 70.5, 69.7, 69.4, 65.9, 55.4.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{26}H_{22}Cl_5N_3NaO_4$: 637.9945; found: 637.9946.

9-[Methyl 3,5-bis-*O*-(2,4-dichlorobenzyl)-α--D-arabinofuranosid-2-yl]adenine (5c)

To a soln of **4** (306 mg, 0.49 mmol) and adenine (100 mg, 0.74 mmol) in anhyd DMF (15 ml) was added Cs_2CO_3 (242 mg, 0.74 mmol) and the mixture was stirred at 60 °C for 5 h under argon followed by concentration in vacuo. The residual was purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 40:1) to afford **5c** as a colorless oil; yield: 236 mg (79%); R_f = 0.18 (CH_2Cl_2–MeOH, 50:1).

^1H NMR (400 MHz, $CDCl_3$): δ = 3.42 (s, 3 H, 1′-OCH_3), 3.76 (dd, J = 11.2, 3.2 Hz, 1 H, H5′a), 3.93 (dd, J = 11.2, 2.4 Hz, 1 H, H5′b), 4.36 (m, 1 H, H4′), 4.41 (dd, J = 6.4, 3.2 Hz, 1 H, H3′), 4.52–4.71 (m, 4 H, 2 OCH_2Ar), 5.11 (t, J = 1.6 Hz, 1 H, H2′), 5.20 (s, 1 H, H1′), 6.18 (br s, 2 H, 6-NH_2), 7.03–7.34 (m, 6 H, H_{Ar}), 7.91 (s, 1 H, H8), 8.35 (s, 1 H, H2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0 (C6), 153.5 (C2), 149.9 (C4), 139.3 (C8), 134.7, 134.4, 134.4, 134.3, 134.0, 133.7, 130.8, 130.4, 129.6, 127.5, 127.3, 119.8 (C5), 107.0 (C1′), 84.0 (C3′), 81.7 (C4′), 70.5 (5′-OCH_2Ar), 69.8 (3′-OCH_2Ar), 69.3 (C5′), 66.5 (C2′), 55.6 (1′-OCH_3).

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{25}H_{23}Cl_4N_5NaO_4$: 620.0396; found: 620.0392.

4-Amino-7-[methyl 3,5-bis-*O*-(2,4-dichlorobenzyl)-α-D-arabinofuranosid-2-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (6a)

A soln of **5a** (428 mg, 0.69 mmol) in methanolic NH_3 (saturated with NH_3 at 0 °C, 20 mL) was introduced into an autoclave and stirred at 120 °C for 12 h. After cooling, the mixture was concentrated to dryness and the residual was purified by column chromatography (silica gel, PE–EtOAc, 1:1) to afford **6a** as a colorless oil; yield: 319 mg (77%); R_f = 0.29 (PE–EtOAc, 1:1).

^1H NMR (400 MHz, $CDCl_3$): δ = 3.41 (s, 3 H, 1′-OCH_3), 3.78 (dd, J = 10.8, 3.6 Hz, 1 H, H5′a), 3.92 (dd, J = 10.8, 2.0 Hz, 1 H, H5′b), 4.25 (m, 1 H, H3′), 4.36 (m, 1 H, H4′), 4.44–4.72 (m, 4 H, 2 OCH_2Ar), 5.11 (s, 1 H, H1′), 5.35 (d, J = 2.8 Hz, 1 H, H2′), 6.33 (br s, 2 H, 4-NH_2), 6.34 (d, J = 3.6 Hz, 1 H, H5), 7.17–7.40 (m, 7 H, H_{Ar}, H6), 8.22 (s, 1 H, H2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.9, 150.5, 150.1, 134.6, 134.5, 134.3, 134.0, 133.9, 130.8, 130.3, 129.5, 129.5, 127.4, 127.3, 123.2, 117.9, 107.9, 103.3, 99.4, 84.9, 81.5, 70.4, 69.7, 69.6, 65.6, 55.4.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{26}H_{25}Cl_4N_4O_4$: 597.0624; found: 597.0628.

7-[Methyl 3,5-Bis-*O*-(2,4-dichlorobenzyl)-α-D-arabinofuranosid-2-yl]-4-methoxy-7*H*-pyrrolo[2,3-*d*]pyrimidine (6b)

A soln of **5a** (570 mg, 0.92 mmol) in 0.5 M NaOMe (20 mL) was stirred at r.t. for 12 h until no reactant was detected (TLC). The mixture was concentrated to dryness and the residual was purified by column chromatography (silica gel, PE–EtOAc, 5:1) to afford **6b** as a colorless oil; yield: 515 mg (91%); R_f = 0.40 (PE–EtOAc, 4:1).

^1H NMR (400 MHz, $CDCl_3$): δ = 3.42 (s, 3 H, 1′-OCH_3), 3.80 (dd, J = 11.2, 3.6 Hz, 1 H, H5′a), 3.94 (dd, J = 11.2, 2.4 Hz, 1 H, H5′b), 4.14 (s, 3 H, 6-OCH_3), 4.31 (dd, J = 6.4, 3.2 Hz, 1 H, H3′), 4.37 (m, 1 H, H4′), 4.43–4.72 (m, 4 H, 2 OCH_2Ar), 5.14 (s, 1 H, H1′), 5.38 (d, J = 2.4 Hz, 1 H, H2′), 6.49 (d, J = 3.2 Hz, 1 H, H5), 7.02–7.37 (m, 7 H, H_{Ar}, H6), 8.48 (s, 1 H, H2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.4, 151.8, 151.3, 134.6, 134.4, 134.2, 133.9, 133.7, 130.7, 130.2, 129.4, 127.4, 127.1, 123.9, 107.8, 105.8, 99.8, 84.6, 81.4, 70.4, 69.7, 69.5, 65.9, 55.4, 54.0.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{27}H_{25}Cl_4N_3NaO_5$: 634.0441; found: 634.0443.

4-Amino-7-[methyl α-D-arabinofuranosid-2-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (7a); Typical Procedure for the Preparation of 7a–c

To a soln of **6a** (250 mg, 0.42 mmol) in EtOAc (5 mL) and MeOH (5 mL) was added 20% $Pd(OH)_2$/C (100 mg, 0.14 mmol) and Et_3N (176 mg, 1.74 mmol). After stirring at r.t. for 1 h under a H_2 atmosphere, another 20% $Pd(OH)_2$/C (100 mg, 0.14 mmol) was introduced. The mixture was allowed to stir overnight until only a single spot was detected (TLC), and filtered and concentrated to dryness. The residual was purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 10:1) to afford **7a** as a colorless oil; yield: 107 mg (92%); R_f = 0.42 (CH_2Cl_2–MeOH, 8:1).

^1H NMR (400 MHz, DMSO-d_6): δ = 3.26 (s, 3 H, 1′-OCH_3), 3.59 (dd, J = 12.0, 4.4 Hz, 1 H, H5′a), 3.75 (dd, J = 12.0. 1.2 Hz, 1 H, H5′b), 3.90 (m, 1 H, H4′), 4.30 (t, J = 6.8 Hz, 1 H, H3′), 4.94–4.98 (m, 2 H, H2′, 1′), 5.68 (br s, 1 H, 3′-OH), 6.80 (d, J = 3.2 Hz, 1 H, H5), 7.35 (d, J = 3.2 Hz, 1 H, H6), 7.80 (br s, 2 H, 4-NH_2), 8.19 (s, 1 H, H2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.0 (C4), 149.8 (C7a), 149.1 (C2), 124.0 (C6), 106.9 (C1′), 103.0 (C4a), 101.8 (C5), 84.2 (C4′), 75.7 (C3′), 68.2 (C2′), 61.3 (C5′), 55.4 (1′-OCH_3).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{17}O_4N_4$: 281.1244; found: 281.1246.

4-Methoxy-7-[methyl α-D-arabinofuranosid-2-yl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (7b)

Compound **7b** was prepared as described for **7a** using **6b** (571 mg, 0.92 mmol) as a colorless oil; yield: 257 mg (94%); R_f = 0.18 (CH_2Cl_2–MeOH, 30:1).

^1H NMR (400 MHz, DMSO-d_6): δ = 3.27 (s, 3 H, 1′-OCH_3), 3.61 (m, 1 H, H5′a), 3.77 (m, 1 H, H5′b), 3.93 (m, 1 H, H4′), 4.04 (s, 3 H, 6-OMe), 4.36 (q, J = 13.2, 6.4 Hz, 1 H, H3′), 4.96 (t, J = 4.2 Hz, 1 H, 5′-OH), 5.02 (d, J = 3.2 Hz, 1 H, H1′), 5.05 (m, 1 H, H2′), 5.66 (d, J = 6.0 Hz, 1 H, 3′-OH), 6.60 (d, J = 3.6 Hz, 1 H, H5), 7.53 (d, J = 3.6 Hz, 1 H, H6), 8.43 (s, 1 H, H2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.3 (C4), 152.6 (C7a), 151.4 (C2), 126.0 (C6), 106.9 (C1′), 105.6 (C4a), 99.5 (C5), 84.2 (C4′), 75.7 (C3′), 68.5 (C2′), 61.3 (C5′), 55.4 (1′-OCH_3), 54.4 (4-OCH_3).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{17}N_3NaO_5$: 318.1060; found: 318.1056.

3-[Methyl α-D-arabinofuranosid-2-yl]adenine (7c)

Compound **7c** was prepared as described for **7a** using **5c** (290 mg, 0.48 mmol) as a colorless oil; yield: 119 mg (88%); R_f = 0.18 (CH_2Cl_2–MeOH, 15:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.28 (s, 3 H, 1′-OCH_3), 3.59 (d, *J* = 10.8 Hz, 1 H, H5′a), 3.75 (d, *J* = 12.0 Hz, 1 H, H5′b), 3.92 (m, 1 H, H4′), 4.45 (q, *J* = 13.2, 6.8 Hz, 1 H, H3′), 4.74 (m, 1 H, H2′), 4.96 (br s, 1 H, 5′-OH), 5.18 (d, *J* = 3.2 Hz, 1 H, H1′), 5.73 (d, *J* = 5.2 Hz, 1 H, 3′-OH), 7.28 (br s, 2 H, 6-NH_2), 8.16 (s, 1 H, H2), 8.24 (s, 1 H, H8).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.9 (C6), 153.3 (C2), 150.3 (C4), 140.7 (C8), 119.8 (C5), 106.0 (C1′), 84.0 (C4′), 74.8 (C3′), 68.2 (C2′), 61.3 (C5′), 55.5 (1′-OCH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{16}O_4N_5$: 282.1197; found: 282.1189.

7-[Methyl α-D-arabinofuranosid-2-yl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one (7d)

Compound **7b** (202 mg, 0.68 mmol) was dissolved in 2 M NaOH (20 mL) and the soln was refluxed for 1.5 h. After cooling, the mixture was neutralized with 1 M HCl and concentrated to dryness. The residual was purified by column chromatography (silica gel, CH_2Cl_2–MeOH, 10:1) to afford **7d** as a colorless oil; yield: 162 mg (84%); R_f = 0.32 (CH_2Cl_2–MeOH, 10:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.26 (s, 3 H, 1′-OCH_3), 3.59 (dd, *J* = 12.4, 4.8 Hz, 1 H, H5′a), 3.75 (d, *J* = 12.0 Hz, 1 H, H5′b), 3.90 (m, 1 H, H4′), 4.28 (t, *J* = 6.8 Hz, 1 H, H3′), 4.38 (br s, 1 H, 5′-OH), 4.93 (d, *J* = 6.4 Hz, 1 H, H2′), 4.96 (s, 1 H, H1′), 5.66 (br s, 1 H, 3′-OH), 6.55 (d, *J* = 3.6 Hz, 1 H, H5), 7.22 (d, *J* = 3.6 Hz, 1 H, H6), 7.92 (s, 1 H, H2), 11.94 (br s, 1 H, 3-NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.2 (C4), 148.5 (C7a), 144.5 (C2), 122.0 (C6), 108.8 (C4a), 107.2 (C1′), 103.5 (C5), 84.1 (C4′), 76.0 (C3′), 68.5 (C2′), 61.2 (C5′), 55.4 (1′-OCH_3).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{15}N_3NaO_5$: 304.0904; found: 304.0912.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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References

(1) Nakamura, G. *J. Antibiot.* **1961**, *14A*, 90.
(2) Nishimura, H.; Katagiri, K.; Sato, K.; Mayama, M.; Shimaoka, N. T. *J. Antibiot.* **1956**, *9A*, 60.
(3) Ohkuma, K. *J. Antibiot., Ser. A* **1961**, *14*, 343.
(4) (a) Seela, F.; Peng, X. H. *Curr. Top. Med. Chem.* **2006**, *6*, 867. (b) Seela, F.; Peng, X. H.; Budow, S. *Curr. Org. Chem.* **2007**, *11*, 427.
(5) Kim, Y. A.; Sharon, A.; Chu, C. K. *J. Med. Chem.* **2008**, *51*, 3934.
(6) Changelian, P. S.; Flanagan, M. E.; Ball, D.; Kent, C. R.; Borie, D. C. *Science* **2003**, *302*, 875.
(7) Bundy, G. L.; Ayer, D. E.; Banitt, L. S.; Belonga, K. L.; Mizsak, S. A.; Palmer, J. R.; Tustin, J. M.; Chin, J. E.; Hall, E. D.; Linseman, K. L.; Richards, I. M.; Scherch, H. M.; Sun, F. F.; Yonkers, P. A.; Larson, P. G.; Lin, J. M.; Padbury, G. E.; Aaron, C. S.; Mayo, J. K. *J. Med. Chem.* **1995**, *38*, 4161.
(8) (a) Montgomery, J. A.; Clayton, S. D.; Thomas, H. J. *J. Org. Chem.* **1975**, *40*, 1923. (b) Montgomery, J. A.; Thomas, H. J. *J. Org. Chem.* **1978**, *43*, 541.
(9) (a) Bobek, M.; An, S.-H.; Skrincosky, D.; De Clercq, E.; Bernacki, R. J. *J. Med. Chem.* **1989**, *32*, 799. (b) Huryn, D. M.; Sluboski, B. C.; Tam, S. Y.; Weigele, M.; Sim, I.; Anderson, B. D.; Mitsuya, H.; Brodert, S. *J. Med. Chem.* **1992**, *35*, 2347. (c) Tino, J. A.; Clark, J. M.; Field, A. K.; Jacobs, G. A.; Lis, K. A.; Michalik, T. L.; McGeever-Rubin, B.; Slusarchyk, W. A.; Spergel, S. H.; Sundeen, J. E.; Tuomari, A. V.; Weaver, E. R.; Young, M. G.; Zahler, R. *J. Med. Chem.* **1993**, *36*, 1221. (d) Franchetti, P.; Cappellacci, L.; Grifantini, M.; Memini, L.; Sheikha, G. A.; Loi, A. G.; Tramontano, E.; De Mantis, A.; Spiga, M. G.; La Colla, P. *J. Med. Chem.* **1994**, *37*, 3534. (e) Alexander, P.; Krishnamurthy, V. V.; Prisbe, E. J. *J. Med. Chem.* **1996**, *39*, 1321. (f) Yu, H. W.; Zhang, L. R.; Zhou, J. C.; Ma, L. T.; Zhang, L. H. *Bioorg. Med. Chem.* **1996**, *4*, 609. (g) Jin, D. Z.; Kwon, S. H.; Moon, H. R.; Gunaga, P.; Kim, H. O.; Kim, D.-K.; Chun, M. W.; Jeong, L. S. *Bioorg. Med. Chem.* **2004**, *12*, 1101. (h) Guenther, S.; Balzarini, J.; De Clercq, E.; Nair, V. *J. Med. Chem.* **2002**, *45*, 5426.
(10) Talekar, R. R.; Wightman, R. H. *Tetrahedron* **1997**, *53*, 3831.
(11) (a) Jung, M. E.; Toyota, A. *Tetrahedron Lett.* **2000**, *41*, 3577. (b) Tian, X. B.; Min, J. M.; Zhang, L. H. *Tetrahedron: Asymmetry* **2000**, *11*, 1877. (c) Jung, M. E.; Nichols, C. J. *J. Org. Chem.* **1998**, *63*, 347. (d) Lei, Z.; Min, J. M.; Zhang, L. H. *Tetrahedron: Asymmetry* **2000**, *11*, 2899. (e) Bera, S.; Mickle, T.; Nair, V. *Nucleosides Nucleotides* **1999**, *18*, 2379.
(12) Lou, C. G.; Xiao, Q.; Brennan, L.; Light, M. E.; Vergara-Irigaray, N.; Atkinson, E. M.; Holden-Dye, L. M.; Fox, K. R.; Brown, T. *Bioorg. Med. Chem.* **2010**, *18*, 6389.
(13) Martin, P. *Helv. Chim. Acta* **1995**, *78*, 486.
(14) (a) Martin, O. R.; Kurz, K. G.; Rao, S. P. *J. Org. Chem.* **1987**, *52*, 2922. (b) Li, N. S.; Lu, J.; Piccirilli, J. A. *Org. Lett.* **2007**, *9*, 3009. (c) Hori, H.; Nishida, Y.; Ohrui, H.; Meguro, H. *J. Org. Chem.* **1989**, *54*, 1346.
(15) (a) Lecourt, T.; Hérault, A.; Pearce, A. J.; Sollogoub, M.; Sinäy, P. *Chem. Eur. J.* **2004**, *12*, 2960. (b) Jia, C.; Zhang, Y. M.; Zhang, L. H.; Sinäy, P.; Sollogoub, M. *Carbohydr. Res.* **2006**, *341*, 2135.
(16) (a) Seela, F.; Kretschmer, U. *J. Heterocycl. Chem.* **1990**, *27*, 479. (b) Seela, F.; Westermann, B.; Bindig, U. *J. Chem. Soc., Perkin Trans. 1* **1988**, 697. (c) Ugarkar, B. G.; Castellino, A. J.; DaRe, J. M.; Kopcho, J. J.; Wiesner, J. B.; Schanzer, J. M.; Erion, M. D. *J. Med. Chem.* **2000**, *43*, 2894. (d) Ugarkar, B. G.; Castellino, A. J.; DaRe, J. S.; Ramirez-Weinhouse, M.; Kopcho, J. J.; Rosengren, S.; Erion, M. D. *J. Med. Chem.* **2003**, *46*, 4750.
(17) (a) Tian, X. B.; Min, J. M.; Zhang, L. H. *Tetrahedron: Asymmetry* **2000**, *11*, 1877. (b) Bera, S.; Nair, V. *Tetrahedron* **2001**, *42*, 5813.

(18) (a) Rosemeyer, H.; Seela, F. *Helv. Chim. Acta* **1988**, *71*, 1573. (b) Bhattacharya, B. K.; Rao, T. S.; Revankar, G. R. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1543. (c) Nair, V.; Piotrowska, D. G.; Okello, M.; Vadakkan, J. *Nucleosides Nucleotides* **2007**, *26*, 687. (d) Bouisset, T.; Gosselin, G.; Griffe, L.; Meillon, J. C.; Storer, R. *Tetrahedron* **2008**, *64*, 6657.

(19) (a) Galli, C. *Org. Prep. Proced. Int.* **1992**, *24*, 287. (b) Flessner, T.; Doye, S. *J. Prak. Chem./Chem. Ztg.* **1999**, *341*, 186.

(20) Su, T. L.; Klein, R. S.; Fox, J. J. *J. Org. Chem.* **1981**, *46*, 1790.

(21) Salvatore, R. N.; Nagele, A. S.; Jung, K. W. *J. Org. Chem.* **2002**, *67*, 674.

(22) (a) Seela, F.; Peng, X. H. *J. Org. Chem.* **2006**, *71*, 81. (b) Seela, F.; Ming, X. *Tetrahedron* **2007**, *63*, 9850.