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Synthesis of 2′-Deoxy-9-deaza Nucleosides Using Heck Methodology

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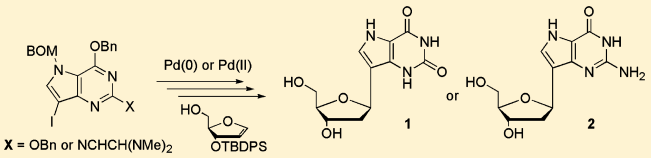
Supporting Information

ABSTRACT: During the synthesis of a series of 2′-deoxy-9-deaza nucleosides using Heck methodology, the necessity for a pyrrole protecting group was discovered. The results of this brief study revealed that the benzyloxymethyl (BOM) group proved optimal, and Heck coupling using Jeffery conditions increased the coupling yield significantly. The results are reported herein.



In the course of our efforts to introduce base modifications to nucleosides[1−4] for use in studies of modified DNA, a series of 2′-deoxy-9-deaza nucleosides were envisioned wherein the nucleobase is connected to the 2′-deoxyribofuranosyl moiety via a carbon−carbon bond, rendering them C-nucleosides.[5−9] In addition to imparting resistance to hydrolytic and enzymatic cleavage resulting from the more stable carbon−carbon glycosidic bond,[7,8,9,10] this change also results in altering H-bond accepting N7 to NH, an H-bond donor, for 2′-deoxy-9-deaza nucleosides such as **1** and **2** (Figure 1). This allows these compounds to engage in alternative hydrogen-bonding patterns such as Hoogsteen base pairing, which may find use in complex oligonucleotide structures or in the investigation of polymerases.[11−15] Similarly, Hamm et al. have evaluated alternate hydrogen-bonding patterns for 2′-deoxy-9-deazaguanosine to study the promutagenic characteristics of 8-oxo-2′-deoxyguanosine.[15]

Klein et al. first reported the synthesis of 9-deaza nucleosides by constructing the base at the anomeric carbon, resulting in the formation of epimers (2:1 β/α) and thereby lowering the yield of the desired β-product.[16−18] Subsequently, Pankiewicz and Sartorelli reported an approach using Friedel−Crafts conditions.[5,6] This route, however, also suffered similar issues and only provided the desired β-anomer in 21−25% yields as well as the α-anomer (9%).[6] As a result, an alternative was sought that would be stereospecific and higher yielding.

In that regard, cross-coupling methodology appeared to be an attractive route, and the synthesis of 2′-deoxy-9-deaza nucleosides **1** and **2** was undertaken using Heck coupling methodology described by Daves et al. In their report, Daves optimized the Heck conditions for synthesizing 2′-deoxyformycin B and found that the protecting group on the sugar moiety affected the regio- and stereoselectivity of the coupling reaction, thereby enabling synthesis of a single stereoisomer.[8] Similarly, during our attempts to realize **1** and **2** we observed that protection of the pyrrole NH was essential and that the choice of the specific protecting group affected the outcome of the coupling reaction. Herein, we report a new route for the synthesis of 2′-deoxy-9-deazaxanthosine **1** and 2′-deoxy-9-deazaguanosine **2** with greatly improved yields for the coupling reaction.

The synthesis of **1** was approached by the preparation of bis-*O*-benzylated pyrrolo[3,2-*d*]pyrimidine **3** (Scheme 1) as previously reported.[19] Because iodine is generally considered a better leaving group as compared to chlorine and bromine,[20,21] 7-iodinated pyrrolo[3,2-*d*]pyrimidine was prepared by stirring **3** with *N*-iodosuccinimide (NIS) in anhydrous methylene chloride (CH_2Cl_2)[22] to afford **4** in 90% yield (Scheme 1). Iodinated **4** was then subjected to Heck coupling; however, it resulted in a complex reaction mixture (Table 1) and nothing could be isolated. Speculation that the catalyst was being inactivated by the unprotected nitrogen was supported by a report uncovered in the literature.[8] Consequently, protection of the pyrrole nitrogen was pursued in an effort to limit the side reactions.

Toward this end, protection of the pyrrole nitrogen with *tert*-butyl dimethyl silyl (TBDMS) appeared to be an attractive option; however, the use of NaH and TBDMSCl failed to proceed at either room (22−25 °C) or lower (0−4 °C) temperatures.[23] Raising the temperature to 50 °C resulted in the complete consumption of the starting material in 1.5 to 2 h, as indicated by TLC. However, upon quenching the reaction with water only the starting material was recovered. As a result, it appeared that cleavage was occurring during the workup because of the basic nature of the reaction mixture. Alternatively, the triisopropyl silyl (TIPS) group was tried, but no formation of the product was observed by TLC. It is also worth mentioning that the acyl group was not pursued because it had previously been reported to be unstable.[8]

Subsequently, more stable protecting groups were sought, and the benzyl (Bn),[2] benzyloxymethyl (BOM),[22] tosyl (Ts),[23] and *tert*-butoxycarbonyl (Boc)[24] groups were explored, as shown in Scheme 1 and Table 1.

Benzyl protection of the pyrrole NH was achieved by treatment with NaH followed by the in situ generation of BnI from BnBr and tetrabutylammonium iodide (TBAI) to give **6**.[2]

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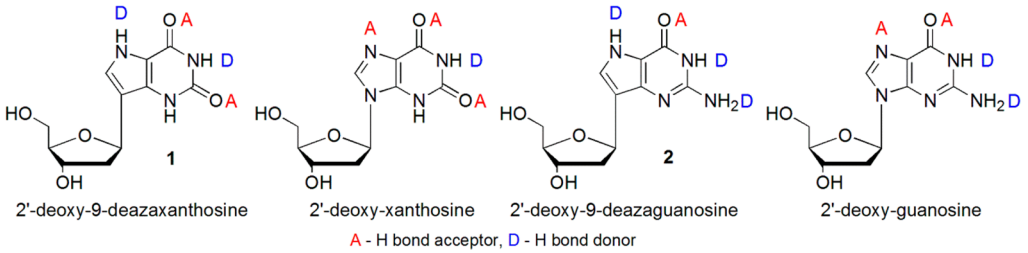
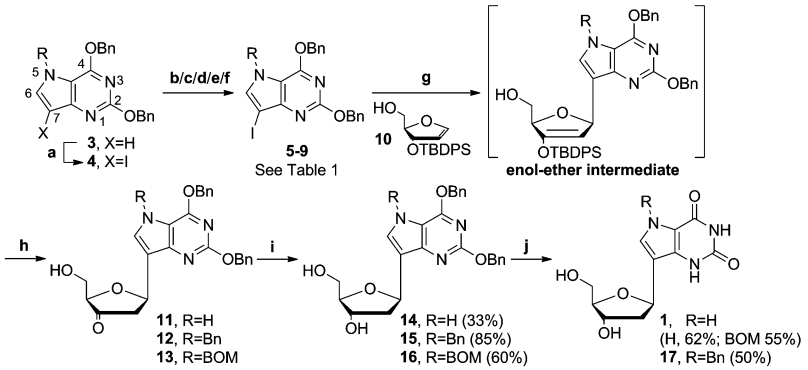


Figure 1. 2′-Deoxy-9-deazanucleosides and altered hydrogen-bonding patterns.

Scheme 1. Pyrrole Protection and Synthesis of 2′-Deoxy-9-deazaxanthosine



a. NIS, CH_2Cl_2; b. NaH, TBDMSCl; c. THF, NaH, TBAI, BnBr, THF; d. NaH, BOMCl, THF; e. NaH, TsCl, DMF; f. DMAP, Boc_2O, THF; g. $Pd_2dba_3{\cdot}CHCl_3$, $AsPh_3$, nBu_3N, DMF, 50 °C; h. nBu_4NF, THF; i. $NaB(OAc)_3H$, CH_3CN, AcOH; j. Pd/C, $NH_4^+HCOO^-$, 60-63 °C.

Table 1. Protection of Pyrrolo[3,2-*d*]pyrimidine and Heck Coupling

	pyrrole protection		Heck coupling	
R	product	yield (%)	product	yield (%)
H	**4**		complex mixture	
TBDMS	**5**	in situ	**11** (R = H)	15
Bn	**6**	56	**12**	13
BOM	**7**	90	**13**	10
Ts	**8**	47		0
Boc	**9**	53		0

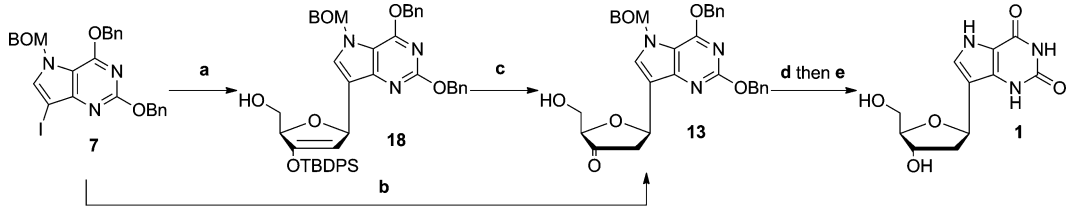
Protection with BOM was accomplished in a similar manner using NaH followed by the addition of BOMCl at room temperature (rt) to obtain **7**.[22] Tosylation was accomplished using NaH and *p*-toluenesulfonyl chloride (TsCl) at 0−4 °C to afford **8**.[23] Protection with Boc was achieved by stirring **4** with 4-dimethylaminopyridine (DMAP) and di-*tert*-butyloxycarbonyl anhydride (Boc_2O) in CH_2Cl_2 at rt to provide **9** in 53% yield.[24]

Next, coupling the protected pyrrolo[3,2-*d*]pyrimidines **4**−**9** with glycal **10** was attempted using the Heck conditions reported by Daves (Scheme 1).[8] The glycal was prepared by a method previously described by our group.[25] Upon Heck coupling, the enol-ether intermediate[8] (Scheme 1) was cleaved in situ using tetra-*n*-butylammonium fluoride (TBAF) to give ketones **11**−**13** (Scheme 1).[8,23] The yields are shown in Table 1. These results indicated a trend wherein a benzyl, BOM, or silyl group on the pyrrole NH resulted in product, whereas the presence of sulfonyl and carbonyl groups had the opposite effect and no reaction occurred.

Upon obtaining the coupled products (**11**−**13**), the ketone of the sugar was stereoselectively reduced using triacetoxy borohydride[8,26] (Scheme 1) followed by hydrogenolysis using ammonium formate ($NH_4^+HCOO^-$) and Pd/C to cleave the base-protecting groups.[2,4] All attempts to deprotect the pyrrole Bn of **17** failed; thus, the BOM group appeared to be the better choice.

Although the need for a pyrrole protecting group had now been established, the low yield (17%) on the coupling reaction was still problematic. As a result, a series of ligands were explored as shown in Scheme 2 and summarized in Table 2.[8] These included bidentate 1,2-bis(diphenylphosphino)ethane (dppe) and 1,1′-bis(diphenylphosphino) ferrocene (dppf). It

Scheme 2. Optimization of Heck Coupling Conditions



a. **10**, $Pd_2dba_3{\cdot}CHCl_3$, Ligand, Solvent, nBu_3N; b. **10**, $Pd(OAc)_2$, nBu_4NCl, $NaHCO_3$, DMF; c. nBu_4NF, THF; d. $NaB(OAc)_3H$, CH_3CN, AcOH; e. Pd/C, $NH_4^+HCOO^-$.

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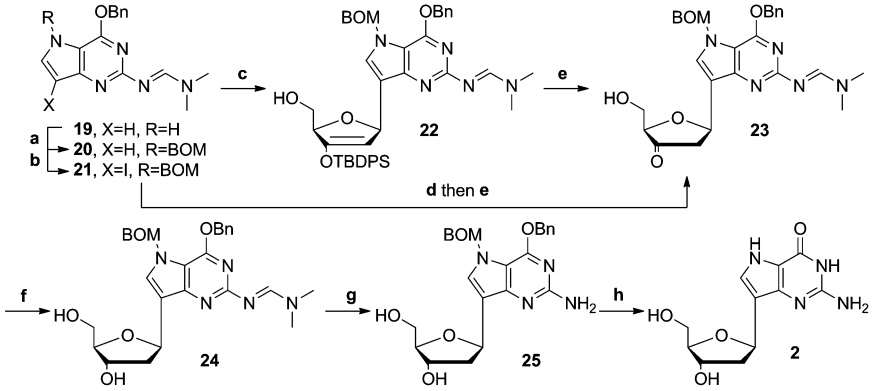
Table 2. Comparison of Heck Coupling Conditions

catalyst	additive	base	solvent	temp (°C)	product	yield(%)
$Pd_2dba_3{\cdot}CHCl_3$	$AsPh_3$	n-Bu_3N	DMF	50	**18**	17
$Pd_2dba_3{\cdot}CHCl_3$	dppe	n-Bu_3N	DMF	50	**18**	17
$Pd_2dba_3{\cdot}CHCl_3$	dppf	n-Bu_3N	DMF	50	**18**	10
$Pd_2dba_3{\cdot}CHCl_3$	$AsPh_3$	n-Bu_3N	CH_3CN	50	**18**	16
$Pd(OAc)_2$	n-$Bu_4N^+Cl^-$	$NaHCO_3$	DMF	40	**13**	76

Scheme 3. Synthesis of 2′-Deoxy-9-deazaguanosine



a.NIS, CH_2Cl_2; b. NaH, BOMCl, THF; c. Pd_2dba_3, $CHCl_3$, $AsPh_3$, nBu_3N, **10**, DMF; d. $Pd(OA)_2$, nBu_4NCl, $NaHCO_3$, **10**, DMF; e. nBu_4NF, THF; f. $NaB(OAc)_3H$, CH_3CN, AcOH; g. NH_4OH, MeOH, 50 °C; h. Pd/C, $NH_4{}^+HCOO^-$, MeOH.

should be noted that triphenylarsine ($AsPh_3$) was utilized instead of the more standard triphenylphospine (PPh_3) because of its intrinsically higher nucleophilicity.[8,9,21] Although the reactions using $Pd_2dba_3{\cdot}CHCl_3$ turned black, which is typical of palladium-catalyzed reactions,[8] and **7** and **10** were successfully coupled to give a stable and isolatable enol-ether intermediate **18**, the yields remained consistently low at only 10−17% even with the addition of more portions of catalyst. Although we considered that the nitrogens might be interfering, because products were forming, albeit in low yields, a more effective catalyst was sought.

In that regard, because $Pd(OAc)_2$ has also been used in the Heck coupling of C-nucleosides with benzene, pyrimidine, and pyridine bases as reported by Leumann,[27] Hocek,[28] and Benner,[29] we thought it might be a viable alternative.[7,9,27−29] To our delight, the use of $Pd(OAc)_2$ increased the yield to 76%, which is a dramatic improvement. It should be noted that the combination of $Pd(OAc)_2$ and tetrabutylammonium chloride (TBAC) for use in Heck coupling is also known as Jeffery conditions.[21,30] Under these phosphine-free conditions, the reduction of Pd(II) is accomplished by tetralkyl ammonium salts.[20,21] An additional benefit to coupling under Jeffery conditions is that it resulted in extremely clean reaction mixtures, thus allowing for more facile purification of the coupled product. In contrast, the use of $Pd_2dba_3{\cdot}CHCl_3$ routinely afforded complicated reaction mixtures that made their purifications tedious and unattractive.

Interestingly, Jeffery conditions also resulted in cleavage of the 3′-OTBDPS group during the coupling, resulting in ketone **13**. In contrast, when $Pd_2dba_3{\cdot}CHCl_3$ was used, the intermediate silyl enol-ether **18** was obtained which then had to be deblocked using TBAF to obtain **13** (Scheme 2). We speculated that the chloride of tetra-*n*-butylammonium chloride (TBAC) is serving as the base that cleaves the O-silyl group in a manner that is analogous to the fluoride of TBAF.[23] Thus, the use of Jeffery conditions with the BOM-protected pyrrole appeared to be optimal for Heck coupling. Upon obtaining the coupled product **13** in enhanced yields, the 3′-keto was subjected to stereoselective reduction followed by hydrogenolysis to obtain desired 2′-deoxy-9-deazaxanthosine **1** in 25% over 3 steps.

The optimized conditions for the synthesis of **1** were then applied to the preparation of 2′-deoxy-9-deazaguanosine **2** starting from the protected pyrrolo[3,2-*d*]pyrimidine **19** (Scheme 3).[19] The introduction of iodine on **19** with the pyrrole NH unprotected proved unsuccessful; consequently, the pyrrole NH was protected with BOM to give **20** in 70% yield.[22] Attempts to iodinate **20** in methylene chloride (CH_2Cl_2) or tetrahydrofuran (THF) at rt resulted in the formation of **21** in only 30% and 24% yields, respectively. However, when NIS was added to a solution of **20** in CH_2Cl_2 at 0−4 °C, **21** was obtained in 65−70% yields.

Next, to see if the trend with the catalysts continued, iodinated **21** was subjected to Heck coupling conditions using either $Pd_2dba_3{\cdot}CHCl_3$ or $Pd(OAc)_2$ (Scheme 3). Heck coupling of **21** with **10** in the presence of $Pd_2dba_3{\cdot}CHCl_3$ gave enol-ether intermediate **22** in a 17% yield, thereby matching the previously observed low yields. Under Jeffery conditions, however, a mixture of **22** and **23** was obtained that upon treatment with TBAF afforded ketone **23** following the cleavage of the 3′-OTBDPS group in situ. Interestingly, 0.4 equiv of $Pd(OAc)_2$ were required for coupling **21** with **10** instead of the 0.2 equiv that were used with bis-benzyloxy compound **7**. The initial 0.2 equiv of $Pd(OAc)_2$ were insufficient to completely couple **21** to **10**; however, upon the addition of a second portion **23** was obtained in 55% yield. As reported in the literature,[20,21,30] under phosphine-free conditions amines can affect the reduction of Pd(II) to Pd(0), and the coordination of the $NCHNMe_2$ of **21** with $Pd(OAc)_2$ was likely occurring as Pd(II)-nitrogen chelation is not uncommon;[20,21] hence, the need for the additional portion of $Pd(OAc)_2$.

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As hoped, Jeffery conditions once again proved superior, and coupled product **23** was realized in 55−60% yields as compared to only 10−12% (over 2 steps) when $Pd_2dba_3{\cdot}CHCl_3$ was used. Compared to the coupling yield of **7** and **10** (76%), the yields for coupling **21** were somewhat lower (55%); however, when one considers that the earlier reports using Friedel−Crafts conditions only gave 21−25% it still rendered this route far superior.[5]

Moving forward, the 3′-keto on **23** was stereoselectively reduced[26] as before to afford **24** in 60% yield (Scheme 3). Deprotection of the benzyl, BOM, and dimethylamino vinyl groups on **24** posed a choice for the order of sequential deprotection steps to obtain desired 2′-deoxy-9-deazaguanosine **2**. Subjecting **24** to hydrogenation to remove the benzyl and BOM groups first led to differentially protected nucleosides that could not be readily separated, so removal of the dimethylamino vinyl group was tried. The use of NaOH resulted in a tedious purification; however, ammonium hydroxide[23] in MeOH was facile and provided **25** in a 93% yield. Finally, removal of the OBn and *N*-BOM groups by hydrogenolysis[22] afforded **2** in a 66% yield from **25** and an overall yield for **2** of 21% over 4 steps.

The synthesis of 2′-deoxy-9-deazaxanthosine **1** and 2′-deoxy-9-deazaguanosine **2** using Heck/Jeffery methodology has been reported for the first time. During the course of their syntheses, the necessity for protecting the pyrrole nitrogen to achieve successful coupling was uncovered. In addition, the coupling yields were found to be optimal when using Jeffery conditions (75% for **1** and 55% for **2**) rather than the more standard Heck methodology. Significantly, this represents a dramatic increase as compared to previously reported coupling reactions using Friedel−Crafts conditions (21−25%) and will likely find use in improving the yields for other related C-nucleosides.

EXPERIMENTAL SECTION

General Information. All ^1H and ^{13}C NMR spectra were recorded on a 400 MHz NMR. The spin multiplicities are indicated by the symbols s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), and br (broad), and coupling constants (*J*) are reported in hertz. TLC was performed on 0.25 mm 60-F254 precoated silica glass plates. Column chromatography was performed on silica gel (32−63 μ). Anhydrous solvents were obtained from a solvent purification system. Melting points are uncorrected. FAB mass spectra were measured with a double-focusing magnetic sector mass spectrometer equipped with a Cs ion gun and Fourier transform ion cyclotron resonance equipped with an ESI source.

General Procedure for Iodination. To a stirring solution of 2,4-bis-*O*-benzyl-5*H*-pyrrolo[3,2-*d*]pyrimidine **3** (1.43 g, 4.3 mmol) in anhydrous CH_2Cl_2 (15 mL) under N_2 was added NIS (1.069 g, 4.7 mmol), at which point the reaction mixture turned from pink to orange. The mixture was stirred overnight until TLC indicated the absence of starting material. The reaction mixture was washed with aqueous $Na_2S_2O_3$ (15 mL) followed by brine (15 mL). The organic layer was dried over $MgSO_4$, loaded onto silica, and purified using column chromatography, eluting with 4:1 followed by 1:1 hexanes/EtOAc to obtain **4** as a pale-yellow solid (1.77 g, 3.88 mmol, 90%). R_f 0.4 in 1:3 hexanes/EtOAc. mp 157.8−158.4 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 5.53 (s, 4H), 7.32−7.41 (m, 9H), 7.55−7.57 (m, 2H), 8.71 (br s, 1H, *NH*). ^{13}C NMR: 57.3, 68.7, 69.3, 111.9, 127.9, 128.3, 128.6, 128.66, 128.7, 128.9, 132.4, 135.8, 137.2, 152.0, 156.9, 160.1. FAB-MS *m*/*z* for $C_{20}H_{16}IN_3O_2$ calculated $[M + H]^+$ 458.0360, found 458.0357.

2,4-Bis-benzyloxy-5-*N*-(*tert*-butyldimethylsilyl)-7-iodo-pyrrolo[3,2-*d*]pyrimidine (5). A 60% suspension of NaH in oil (106 mg, 4.2 mmol) was added to anhydrous THF (5 mL) under N_2. To this mixture was added 7-iodo-2,4-bis-benzyloxy-5*H*-pyrrolo[3,2-*d*]-pyrimidine **4** (1.6 g, 3.5 mmol), and the reaction mixture was stirred at rt for 15 min. The stirring mixture was then heated to 50 °C, at which point a white precipitate formed. The mixture was cooled to rt, and TBDMSCl (687 mg, 4.55 mmol) was added under N_2. The reaction mixture was then heated to 50 °C for 1.5 h until TLC indicated the absence of starting material. The reaction mixture was cooled, the THF was evaporated, and the crude product (**5**) was used in Heck coupling without further purification.

2,4-Bis-benzyloxy-5-*N*-benzyl-7-iodo-pyrrolo[3,2-*d*]-pyrimidine (6). A solution of **4** (200 mg, 0.43 mmol) in anhydrous THF (5 mL) was cooled (0−4 °C), a 60% suspension of NaH in oil (26 mg, 0.65 mmol) was added, and the mixture was stirred for 15 min. The ice bath was removed, and the reaction mixture was allowed to warm to rt. After stirring the reaction mixture at rt for 2 h, tetrabutyl ammonium iodide (79.5 mg, 0.215 mmol) was added, and the mixture was cooled on ice. Benzyl bromide (77.3 μL, 0.65 mmol) was added, the ice bath was removed after 5 min, and the mixture was warmed to rt and stirred for 1 h. The mixture was then refluxed (80−82 °C) for 2 h, at which point TLC indicated the absence of starting material. The mixture was cooled to rt and quenched with water (10 mL), the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The organic layers were combined, washed with brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was loaded onto silica and purified by column chromatography, eluting with 9:1 hexanes/EtOAc to obtain **6** a white solid (134 mg, 0.24 mmol, 56%). R_f 0.5 in 9:1 hexanes/EtOAc. mp 113.8−116.2 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 5.38 (s, 2H), 5.47 (s, 2H), 5.49 (s, 2H), 6.93−6.96 (m, 2H), 7.23−7.25 (m, 6H), 7.29−7.35 (m, 6H), 7.57−7.59 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 53.1, 55.9, 68.7, 69.3, 112.7, 126.9, 127.9, 128.3, 128.6, 128.9, 129.0, 135.9, 136.6, 137.2, 152.8, 157.4, 159.8. FAB-MS for $C_{27}H_{22}IN_3O_2$ calculated $[M + H]^+$ 548.0829, found 548.0837.

General Procedure for N7-BOM Protection. To a solution of 7-iodo-2,4-bis-benzyloxy-5*H*-pyrrolo[3,2-*d*]pyrimidine **4** (1.25 g, 2.73 mmol) in anhydrous THF (5 mL) under N_2 was added NaH (60% suspension in oil, 132 mg, 3.28 mmol), and the mixture was stirred at rt for 1 h. Benzyloxymethyl chloride (620 μL, 3.28 mmol) was added dropwise at which point the reaction mixture turned from yellow to off-white. The mixture was stirred for 1 h, at which point TLC indicated the absence of starting material. The reaction mixture was quenched with water (10 mL), the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The organic layers were combined, washed with brine (20 mL), and dried over $MgSO_4$. The organic phase was concentrated in vacuo, loaded onto silica, and purified via column chromatography, eluting with 4:1 hexanes/EtOAc to obtain **7** as a pale-yellow solid (1.42 g, 2.45 mmol, 90%). R_f 0.6 in 3:1 hexanes/EtOAc. mp 80.6−85.4 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 4.36 (s, 2H), 5.51 (s, 2H), 5.56 (s, 2H), 5.60 (s, 2H), 7.11−7.15 (m, 2H), 7.24 (s, 1H), 7.31−7.36 (m, 11H), 7.58−7.59 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 58.1, 68.6, 69.2, 70.3, 93.9, 112.4, 127.5, 127.91, 127.97, 128.1, 128.3, 128.4, 128.6, 128.9, 135.9, 136.6, 136.7, 137.1, 153.2, 157.2, 159.9. FAB-MS for $C_{28}H_{24}IN_3O_3$ calculated $[M + H]^+$ 578.0935, found 578.0915.

2,4-Bis-benzyloxy-5-*N*-(toluene-4-sulfonyl)-7-iodopyrrolo-[3,2-*d*]pyrimidine (8). A solution of 7-iodo-2,4-bis-benzyloxy-5*H*-pyrrolo[3,2-*d*]pyrimidine **4** (210 mg, 0.459 mmol) in anhydrous THF (5 mL) under N_2 was cooled (0−4 °C), NaH (60% suspension in oil, 27.57 mg, 0.689 mmol) was added, and the mixture was stirred for 15 min. The ice bath was removed, and the mixture was warmed to rt and stirred for 1 h. The mixture was then cooled over ice, and tosyl chloride (131 mg, 0.689 mmol) was added. The mixture was warmed to rt and stirred for 30 min until TLC indicated the absence of starting material. The mixture was quenched with aqueous $NaHCO_3$ (10 mL), the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The organic layers were combined, washed with brine (20 mL), dried over $MgSO_4$, concentrated in vacuo, loaded onto silica, and purified by column chromatography, eluting with 9:1 hexanes/EtOAc to obtain **8** as an off-white solid (131 mg, 0.21 mmol, 46.6%). mp 174.7−176.9 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3H), 5.47 (s, 4H), 6.99 (d, 2H, *J* = 8.12 Hz), 7.30−7.39 (m, 3H), 7.44−7.47 (m, 7H), 7.54 (d, 2H, *J* = 6.84 Hz), 8.08 (s, 1H). ^{13}C NMR

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(400 MHz, $CDCl_3$): δ 21.7, 64.4, 69.5, 69.6, 110.6, 128.1, 128.4, 128.7, 128.9, 129.1, 129.7, 134.7, 135.3, 136.1, 136.7, 145.4, 156.8, 157.2, 161.2. FAB-MS for $C_{27}H_{22}IN_3O_4S$ calculated $[M + H]^+$ 612.0448, found 612.0453.

2,4-Bis-benzyloxy-5-*N*-boc-7-iodopyrrolo[3,2-*d*]pyrimidine (9). To a solution of 7-iodo-2,4-bis-benzyloxy-5*H*-pyrrolo[3,2-*d*]-pyrimidine **4** (100 mg, 0.218 mmol) in dry THF (5 mL) were added Boc_2O (96 mg, 0.437 mmol) and DMAP (145.33 mg, 0.0437 mmol), and the mixture was stirred for 1 h until TLC indicated the absence of starting material. The solvent was removed in vacuo, and the residue was purified by column chromatography, eluting with 49:1 hexanes/EtOAc to obtain **9** as a white solid (65.1 mg, 116 mmol, 53.4%). R_f 0.5 in 19:1 hexanes/EtOAc. mp 118.5−122.5 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 1.51 (d, 9H), 5.59 (s, 2H), 5.50 (s, 2H), 7.38−7.30 (m, 6H), 7.47 (d, 2H), 7.56 (d, 2H), 7.91 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 27.8, 64.3, 68.9, 69.5, 85.3, 110.9, 127.9, 128.4, 128.5, 128.8, 136.2, 136.5, 136.9, 147.2, 156.6, 157.9, 161.1. FAB-MS *m*/*z* for $C_{25}H_{24}IN_3O_4$ calculated $[M + H]^+$ 558.0884, found 558.0885.

General Procedure for Heck Coupling Using Pd_2dba_3·$CHCl_3$. In a dry flask under N_2 containing $AsPh_3$ (39.7 mg, 0.13 mmol) and Pd_2dba_3·$CHCl_3$ (71.6 mg, 0.065 mmol) was added anhydrous DMF (3 mL), and the mixture was stirred for 30 min. In a separate flask, to a solution of 2,4-bis-benzyloxy-5-*N*-(benzyloxymethyl)-7-iodopyrrolo-[3,2-*d*]pyrimidine **7** (150 mg, 0.26 mmol) and glycal **10** (184 mg, 0.52 mmol) in DMF (3 mL) was added tri-*n*-butylamine (185 μL, 0.78 mmol). This mixture was then added to the Pd solution under N_2 and stirred at rt for 30 min followed by stirring for 18 h at 50−55 °C, at which point TLC indicated the consumption of **7**. The DMF was evaporated, and the residue was dissolved in CH_2Cl_2 (50 mL). The mixture was filtered, the filtrate was transferred to a dry flask, and the CH_2Cl_2 was evaporated. The residue was dissolved in THF (5 mL), a 1 M solution of TBAF in THF (2 mL, 2 mmol) was added, and the mixture was stirred for 1 h at rt. The mixture was evaporated, and the residue was loaded onto silica and purified via column chromatography, eluting with 9:1 followed by 3:1 hexanes/EtOAc to give **13** as an off-white syrup (14.6 mg, 0.026 mmol, 10%). R_f 0.2 in 1:1 hexanes/EtOAc. ^1H NMR (400 MHz, $CDCl_3$): δ 2.69 (dd, 1H, *J* = 6.16 Hz, *J*=17.64 Hz), 3.19 (dd, 1H, *J* = 11 Hz, *J* = 17.88 Hz), 3.91−3.99 (br m, 2H), 4.08 (t, 1H, *J* = 2.06 Hz), 4.3 (s, 2H), 5.34−5.37 (m, 1H), 5.40−5.48 (m, 2H), 5.54 (s, 2H), 5.60 (d, 2H, *J* = 2.76 Hz), 7.11−7.13 (m 2H), 7.23−7.27 (m, 4H), 7.30−7.39 (m, 6H), 7.37−7.39 (m, 2H), 7.45−7.46 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 43.8, 62.9, 68.5, 69.2, 70.5, 71.9, 82.3, 113.6, 115.0, 127.5, 127.7, 127.8, 128.0, 128.2, 128.43, 128.47, 128.5, 128.7, 132.1, 135.9, 136.8, 137.4, 150.5, 157.2, 157.5, 214.9. ESI-MS *m*/ for $C_{33}H_{31}N_3O_6$ *z* calculated $[M + H]^+$ 566.2276, found 566.2285.

2,4-Bis-benzyloxy-5*H*-7-(β-D-glycero-pentofuran-3′-ulos-1′-yl)pyrrolo[3,2-*d*]pyrimidine (11). From **4** (540 mg, 1.18 mmol), **11** was obtained as a yellow syrup (80 mg, 0.18 mmol, 15%). R_f 0.5 in 19:1 CH_2Cl_2/MeOH. ^1H NMR (400 MHz, $CDCl_3$): δ 2.69 (dd, 1H, *J* = 6.4 Hz, *J* = 17.86 Hz), 3.18−3.26 (m, 1H), 3.94−3.96 (m, 2H), 4.10−4.12 (m, 1H), 5.35−5.41 (m, 3H, $-CH_2$, H1′), 5.50 (s, 2H), 7.25−7.44 (m, 11H), 8.7 (br s, 1H, *NH*). ^{13}C NMR (400 MHz, $CDCl_3$): δ 44.0, 62.9, 68.5, 69.2, 72.0, 82.3, 113.2, 114.7, 127.7, 127.8, 128.3, 128.5, 128.7, 135.8, 137.4, 149.2, 156.8, 159.6, 215.0. FAB-MS for $C_{25}H_{23}N_3O_5$ calculated $[M + H]^+$ 446.1710, found 446.1709.

2,4-Bis-benzyloxy-5-*N*-benzyl-7-(β-D-glycero-pentofuran-3′-ulos-1′-yl)pyrrolo[3,2-*d*]pyrimidine (12). From **6** (570 mg, 1.04 mmol), **12** was obtained as a yellow syrup (73 mg, 0.136 mmol, 13%). R_f 0.5 in 1:1 hexanes/EtOAc. ^1H NMR (400 MHz, $CDCl_3$): δ 2.69 (dd, 1H, *J* = 6.2 Hz, *J* = 17.64 Hz), 3.26 (dd, 1H, *J* = 11 Hz, *J* = 17.88 Hz), 3.91−3.99 (br m, 2H), 4.08−4.10 (m, 1H), 4.11−4.13 (m, 1H), 5.32−5.49 (m, 7H, $-CH_2$, H1′), 6.97−6.99 (m, 2H), 7.20−7.21 (m, 1H), 7.23−7.26 (m, 5H), 7.28−7.32 (m, 5H), 7.43−7.46 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 43.9, 52.6, 62.9, 68.5, 69.2, 72.0, 82.4, 113.73, 113.78, 127.0, 127.7, 127.8, 128.0, 128.2, 128.4, 128.6, 128.9, 132.1, 135.8, 137.2, 137.5, 149.8, 157.3, 159.3, 215.1. $C_{32}H_{29}N_3O_5$ calculated $[M + H]^+$ 536.2180, found 536.2181.

General Procedure for Heck Coupling Using Jeffery Conditions. In a dry flask, 2,4-bis-benzyloxy-5-*N*-(benzyloxymethyl)-7-iodopyrrolo[3,2-*d*]pyrimidine **7** (1.5 g, 2.59 mmol) and TBAC (1.44 g, 5.18 mmol) were coevaporated with CH_3CN under high vacuum for 1 h. To the flask, 47.5% $Pd(OAc)_2$ (245 mg, 0.52 mmol) and $NaHCO_3$ (435 mg, 5.18 mmol) were added under N_2 followed by DMF (15 mL), and the mixture was stirred to dissolve the organic components. In a separate flask, glycal **10** (1.9 g, 5.38 mmol) was coevaporated with CH_3CN, and the residue was dissolved in DMF (7 mL). The solution of **10** in DMF was added to the previous solution, and the mixture was stirred at 40 °C for 48 h, at which point TLC indicated the absence of starting materials. The DMF was evaporated, and the residue was dissolved in CH_2Cl_2 and filtered over Celite. The filtrate was loaded onto silica, and the product was purified using column chromatography, eluting with 9:1 followed by 3:1 hexanes/EtOAc to give **13** as an off-white syrup (1.11 g, 1.96 mmol, 76%). R_f 0.2 in 1:1 hexanes/EtOAc. Spectral data of **13** matched that as reported in the previous procedure.

General Procedure for the Reduction of the 3′-Ketone. A solution of 2,4-bis-benzyloxy-5-*N*-benzyloxymethy-7-(β-D-glycero-pentofuran-3′-ulos-1′-yl)pyrrolo[3,2-*d*]pyrimidine **13** (1.15 g, 1.97 mmol) in anhydrous acetonitrile (10 mL) and glacial AcOH (10 mL) was cooled to between −10 and −5 °C under N_2. $NaB(OAc)_3H$ (500 mg, 2.36 mmol) was added in (2) 250 mg portions 15 min apart, and the mixture was stirred at −10 to −5 °C for 30 min and warmed to rt, at which point TLC indicated the absence of starting material. The solvents were evaporated, and the residue was purified by column chromatography, eluting with 99:1 CH_2Cl_2/MeOH to give **16** as an off-white foam (670 mg, 1.18 mmol, 60%). R_f 0.5 in 19:1 CH_2Cl_2/MeOH. ^1H NMR (400 MHz, $CDCl_3$): δ 2.05 (dd, 1H, *J* = 5.5, *J* = 13.3 Hz), 2.77−2.84 (m, 1H), 3.74−3.79 (m, 1H), 3.95 (dd, 1H, *J* = 2.3 Hz, *J* = 12.38 Hz), 4.13 (br s, 1H), 4.36 (s, 2H), 4.69 (d, 1H, *J* = 5.04 Hz), 5.35 (dd, 1H, *J* = 5.26 Hz, 11.22 Hz), 5.43 (s, 2H), 5.52 (s, 2H), 5.59 (s, 2H), 5.84−5.87 (br d, 1H), 7.12−7.15 (m, 2H), 7.22−7.36 (m, 12H), 7.45−7.47 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 42.6, 53.6, 62.8, 64.2, 68.4, 69.2, 70.2, 74.9, 75.4, 88.7, 113.6, 115.9, 127.6, 127.7, 127.7, 127.9, 128.1, 128.2, 128.41, 128.46, 128.5, 128.7, 132.4, 136.1, 137.0, 137.6, 150.9, 157.0, 159.2. ESI-MS *m*/*z* for $C_{33}H_{33}N_3O_6$ calculated $[M + H]^+$ 568.2442, found 568.2438.

1′-β-[7-(2,4-Bis-benzyloxy-5*H*-pyrrolo[3,2-*d*]pyrimidine)]-2′-deoxyribofuranose (14). From **11** (24 mg, 53.9 μmol), **14** was obtained as a yellow syrup (8 mg, 17.8 μmol, 33%). R_f 0.5 in 19:1 CH_2Cl_2/MeOH. ^1H NMR (400 MHz, $CDCl_3$): δ 2.04−2.07 (m, 1H), 2.79−2.86 (m, 1H), 3.77 (m br, 1H), 3.95 (dd, 1H, *J* = 1.84 Hz, *J* = 12.36 Hz), 4.12 (s, 1H), 4.69 (d, 1H, *J* = 4.6 Hz), 5.38 (dd, 1H, *J* = 5.26 Hz, *J* = 11.22 Hz), 5.44 (s, 2H), 5.51 (s, 2H), 5.97 (br s, 1H, *OH*), 7.26−7.41 (m, 9H), 7.46−7.48 (m, 2H), 8.44 (br, 1H, *NH*). ^{13}C NMR (400 MHz, $CDCl_3$): δ 29.7, 42.8, 64.2, 68.4, 69.2, 75.0, 75.9, 88.8, 113.2, 115.5, 127.6, 127.8, 128.3, 128.5, 128.7, 135.9, 137.5, 149.4, 156.6, 159.3. FAB-MS for $C_{25}H_{25}N_3O_5$ calculated $[M + H]^+$ 448.1867, found 448.1872.

1′-β-[7-(2,4-Bis-benzyloxy-5-*N*-benzylpyrrolo[3,2-*d*]-pyrimidine)]-2′-deoxyribofuranose (15). From **12** (70 mg, 0.13 mmol), **15** was obtained as a yellow syrup (60 mg, 0.11 mmol, 85%). R_f 0.05 in 1:1 hexanes/EtOAc, 0.7 in 19:1 CH_2Cl_2/MeOH. ^1H NMR (400 MHz, $CDCl_3$): δ 2.07 (dd, 1H, *J*=5.28, *J* = 13.08 Hz), 2.80−2.87 (m,1H), 3.80 (dd, 1H, *J* = 1.4 Hz, *J* = 12.38 Hz), 3.96 (dd, 1H, *J* = 1.84 Hz, *J* = 12.36 Hz), 4.14 (br s, 1H), 4.70 (d, 1H, *J* = 4.6 Hz), 5.33−5.38 (m, 3H, $-CH_2$, H1′), 5.42 (s, 2H), 5.46 (s, 2H), 6.97−7.00 (m, 2H), 7.18−7.20 (m, 1H), 7.24−7.33 (m, 11H), 7.46−7.49 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 42.7, 52.5, 64.1, 68.3, 69.2, 75.0, 75.7, 88.7, 113.7, 114.4, 126.9, 127.6, 127.81, 127.85, 128.20, 128.28, 128.39, 128.6, 128.8, 132.4, 136.0, 137.53, 137.59, 150.0, 157.0, 159.0. FAB-MS for $C_{32}H_{31}N_3O_5$ calculated $[M + H]^+$ 538.2336, found 538.2343.

General Procedure for Hydrogenolysis. To a solution of 1′-β-[7-(2,4-bis-benzyloxy-5-benzyloxymethypyrrolo[3,2-*d*]pyrimidine)]-2′-deoxyribofuranose **16** (660 mg, 1.16 mmol) in MeOH (10 mL) was added 10% Pd/C (600 mg), and the suspension was heated to reflux. Ammonium formate (1800 mg, 281 mmol) was added in 3 portions of 600 mg each over a period of 8 h, at which point TLC indicated the absence of starting material. The solvent was evaporated, and the

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residue was purified by column chromatography, eluting with 99:1 CH_2Cl_2/MeOH followed by 98:2 CH_2Cl_2/MeOH to obtain **1** as a white solid (170 mg, 0.64 mmol, 55%). mp 185.3−186.8 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.89 (ddd, 2H, J = 5.16, J = 10.93, J = 26.68), 3.54 (dd, 2H, J = 11.24, J = 19.92), 3.75 (br s, 1H), 4.19 (br s, 1H), 4.96 (d, 1H, J = 3.24 Hz), 5.05 (dd, 1H, J = 5.92 Hz, J = 10.08 Hz), 5.62 (br s, 1H), 10.56 (br s, 1H, *NH*), 10.58 (br s, 1H, *NH*), 11.67 (br s, 1H, *NH*). ^{13}C NMR (400 MHz, DMSO-d_6): δ 43.0, 62.7, 73.6, 73.7, 87.7, 111.2, 111.5, 125.2, 132.7, 151.8, 156.3. FAB-MS for $C_{11}H_{13}N_3O_5$ calculated M^+ 267.0855, found 267.0853; calculated $[M + H]^+$ 268.0928, found 268.0930.

1′-β-[7-(5-Benzylpyrrolo[3,2-*d*]pyrimidin-2,4-dione)]-2′-deoxyribofuranose (17). From **15** (44 mg, 82 μmol), **17** was obtained as an off-white foam (15 mg, 42 μmol, 50%). R_f 0.5 in 19:1 CH_2Cl_2/MeOH. ^{1}H NMR (400 MHz, MeOH-d_3): δ 2.52−2.57 (m, 1H), 2.61−2.67 (m, 1H), 4.29 (d, 2H, J = 2.28 Hz), 4.47 (d, 1H, J = 1.36 Hz), 4.91 (d, 1H, J = 5.04 Hz), 5.69 (dd, 1H, J = 5.50, J = 10.98 Hz), 5.97 (s, 2H), 7.71−7.82 (m, 6H). ^{13}C NMR (400 MHz, MeOH-d_3): 43.2, 51.5, 63.0, 74.8, 75.0, 88.3, 111.0, 111.4, 127.8, 128.1, 129.0, 129.7, 134.2, 138.7, 152.9, 157.3. FAB-MS for $C_{18}H_{19}N_3O_5$ calculated M^+ 357.1324, found 357.1321; calculated $[M + H]^+$ 358.1397, found 358.1395.

Synthesis of 18. Using the general procedure for Heck coupling with Pd_2dba_3·$CHCl_3$ but without TBAF, compound **7** (150 mg, 0.26 mmol) was reacted to give **18** as yellow syrup (33 mg, 0.042 mmol, 16.1%), which was purified by column chromatography, eluting with 19:1 followed by 9:1 hexanes/EtOAc. R_f 0.1 in 3:1 hexanes/EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (s, 9H), 3.95−4.02 (m, 2H), 4.28 (s, 2H), 4.31 (br s, 1H), 4.62 (br d, 1H, J = 8.24 Hz), 4.81−4.82 (m, 1H), 5.44−5.5 (m, 6H), 5.82 (dd, 1H, J = 1.36 Hz, J = 3.58 Hz), 6.90 (s, 1H), 7.07−7.09 (m, 2H), 7.28−7.52 (m, 19H), 7.76−7.78 (m, 2H), 7.88−7.90 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 14.3, 19.3, 21.6, 26.4, 60.4, 62.6, 68.2, 69.2, 70.2, 83.9, 102.9, 113.1, 117.8, 127.5, 127.7, 127.9, 128.11, 128.18, 128.30, 128.39, 128.44, 128.6, 129.9, 130.1, 131.4, 132.0, 135.5, 136.0, 136.1, 137.0, 137.7, 150.3, 151.1, 156.8, 159.4. FAB-MS for $C_{49}H_{49}N_3O_6Si$ calculated $[M + H]^+$ 804.3463, found 804.3441.

2-[(Dimethylamino)methyleneimino]-4-benzyloxy-5-*N*-benzyloxymethyl-pyrrolo[3,2-*d*]pyrimidine (20). From **19** (300 mg, 1.02 mmol), **20** was obtained as a syrup (278 mg, 0.67 mmol, 65%). R_f 0.5 in 1:1 hexanes/EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.03 (s, 3H), 3.09 (s, 3H), 4.55 (s, 2H), 5.54 (s, 2H), 5.88 (s, 2H), 6.28 (d, 1H, J = 3.24 Hz), 7.17 (d, 1H, J = 2.76 Hz), 7.22−7.27 (m, 7H), 7.35−7.38 (m, 3H), 8.45 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 35.1, 40.9, 45.3, 70.3, 76.4, 103.1, 114.4, 126.8, 127.7, 127.92, 127.99, 128.2, 128.4, 131.0, 137.7, 138.9, 145.3, 154.8, 155.8, 156.4. ESI-MS m/z for $C_{24}H_{25}N_5O_2$ calculated $[M + H]^+$ 416.2081, found 416.2077.

7-Iodo-2-[(Dimethylamino)methyleneimino]-4-benzyloxy-5-benzyloxymethyl-pyrrolo[3,2-*d*]pyrimidine (21). From **20** (1.7 g, 4.09 mmol), **21** was obtained as an off-white solid (1.42 g, 2.6 mmol, 64%). R_f 0.5 in 3:1 hexanes/EtOAc. mp 168−172 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.04 (s, 3H), 3.14 (s, 3H), 4.57 (s, 2H), 5.54 (s, 2H), 5.86 (s, 2H), 7.21−7.28 (m, 9H), 7.34−7.37 (m, 2H), 8.60 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 35.2, 41.1, 45.4, 58.6, 70.6, 76.6, 114.4, 126.9, 127.8, 127.9, 128.2, 128.4, 134.4, 137.4, 138.7, 145.8, 155.2, 155.4, 157.1. FAB-MS m/z for $C_{24}H_{24}IN_5O_2$ calculated $[M + H]^+$ 542.1047, found 542.1052.

Coupling of 21 and 10 Using Jeffery Conditions. The general procedure for Heck coupling under Jeffery conditions was used. TLC did not indicate the consumption of **21** by 24 h. A second portion of $Pd(OAc)_2$ (0.2 equiv) was added, and the mixture was stirred at 40 °C for another 24 h, at which point the TLC indicated the absence of **21**. The DMF was evaporated, and the residue was dissolved in CH_2Cl_2 (50 mL) and filtered over Celite. The filtrate was loaded onto silica, and the mixture (**22** and **23**) was separated via column chromatography, eluting with 9:1 followed by 3:1 hexanes/EtOAc to give **22** as a light-brown syrup (66 mg, 86 μmol, 31%). R_f 0.4 in 3:1 hexanes/EtOAc. Further elution with 2:1 hexanes/EtOAc afforded **23** as dark-yellow syrup (40 mg, 75.6 μmol, 27%). R_f 0.1 in 3:2 hexanes/EtOAc. Spectral data for **22**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (s, 9H), 3.06 (s, 6H), 4.03 (dd, 2H, J = 11.44 Hz, J = 25.2 Hz), 4.15 (dd, 1H, J = 6.88 Hz, J = 14.42 Hz), 4.38 (br s, 1H), 4.56 (d, 2H, J = 3.2 Hz), 4.82 (d, 1H, J = 2.28 Hz), 5.56 (dd, 2H, J = 14.2 Hz, J = 35.72 Hz), 5.72 (d, 1H, J = 4.6 Hz), 5.83 (s, 2H), 6.95 (s, 1H), 7.22−7.33 (m, 10H), 7.39−7.48 (m, 6H), 7.76 (d, 2H, J = 6.88 Hz), 7.86 (d, 2H, J = 6.88 Hz), 8.71 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 14.39, 19.4, 21.2, 26.5, 29.7, 34.9, 40.7, 45.4, 60.5, 62.7, 70.5, 76.9, 78.4, 83.6, 104.1, 115.9, 117.2, 126.8, 127.6, 127.7, 127.90, 127.98, 128.0, 128.2, 128.4, 129.8, 130.1, 130.3, 131.8, 132.1, 135.5, 135.8, 137.7, 139.0, 143.1, 149.7, 155.0, 155.9, 157.8. ESI-MS m/z for $C_{45}H_{49}N_5O_5Si$ calculated $[M + H]^+$ 768.3575, found 768.3584. Spectral data for **23**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.67 (dd, 1H, J = 6.4 Hz, J = 17.88 Hz), 3.01 (s, 3H), 3.08 (s, 3H), 3.16 (dd, 1H, J = 6.4 Hz, J = 17.88 Hz), 3.82−3.89 (m, 2H), 4.06−4.07 (m, 1H), 4.58 (s, 2H), 5.31 (dd, 1H, J = 6.4 Hz, J = 11 Hz), 5.84 (dd, 4H, J = 10.56 Hz, J = 23.82 Hz), 7.18 (s, 1H), 7.22−7.28 (m, 8H), 7.35−7.37 (m, 2H), 8.29 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 35.0, 40.9, 44.3, 45.5, 62.8, 70.6, 72.4, 76.4, 82.1, 115.1, 116.1, 126.9, 127.8, 128.0, 128.2, 128.4, 129.3, 137.5, 138.5, 142.5, 155.5, 155.7, 157.3, 215.5. ESI-MS m/z for $C_{29}H_{31}N_5O_5$ calculated $[M + H]^+$ 530.2398, found 530.2399.

2-[(Dimethylamino)methyleneimino]-4-benzyloxy-5-benzyloxymethyl-7-(β-D-glycero-pentofuran-3′-ulos-1′-yl)pyrrolo-[3,2-*d*]pyrimidine (23). Using the previous procedure, **21** (1.4 g, 2.58 mmol) was subjected to Heck coupling to provide a mixture of **22** and **23**. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2 (100 mL), filtered, and the filtrate was transferred to a dry flask. To this a 1 M solution of TBAF in THF (2 mL, 2 mmol) was added, and the mixture was stirred for 1 h, at which point TLC indicated the absence of **22**. The mixture was evaporated to dryness, and the residue was loaded onto silica and purified using column chromatography, eluting with 3:1 then 2:1 hexanes/EtOAc to give **23** as dark-yellow syrup (732 mg, 1.38 mmol, 54%). Spectral data of **23** matched that reported in the previous procedure.

1′-β-[7-(2-[(Dimethylamino)methyleneimino]-4-benzyloxy-5-benzyloxymethyl) pyrrolo[3,2-*d*]pyrimidine)]-2′-deoxyribofuranose (24). From **23** (732 mg, 1.38 mmol), **24** was obtained as a pink syrup (420 mg, 0.79 mmol, 57%). R_f 0.5 in 19:1 CH_2Cl_2/MeOH. ^{1}H NMR (400 MHz, CD_3OH): δ 2.01 (dd, 1H, J = 5.52 Hz, J = 13.28 Hz), 2.68 (td, 1H, J = 5.04 Hz, J = 12.18 Hz), 3.02 (s, 3H), 3.10 (s, 3H), 3.67 (d, 1H, J = 12.36 Hz), 3.87 (d, 1H, J = 11.88 Hz), 4.12 (s, 1H), 4.56 (d, 2H, d, J = 2.32 Hz), 4.60 (br d, 1H, J = 4.56 Hz), 5.32 (dd, 1H, J = 5.04 Hz, J = 10.98 Hz), 5.50 (dd, 2H, J = 14.2 Hz, J = 20.64 Hz), 5.86 (s, 2H), 7.14 (s, 1H), 7.16−7.30 (m, 8H), 7.34−7.36 (m, 2H), 8.25 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 34.9, 40.7, 43.4, 45.5, 64.0, 70.4, 75.5, 75.9, 76.3, 88.5, 115.7, 116.1, 126.9, 127.7, 127.90, 127.94, 128.2, 128.4, 129.5, 137.6, 138.6, 142.5, 155.3, 157.0. ESI-MS m/z for $C_{29}H_{33}N_5O_5$ calculated $[M + H]^+$ 532.2554, found 532.2558.

1′-β-[7-(2-Amino-4-benzyloxy-5-benzyloxymethyl)pyrrolo-[3,2-*d*]pyrimidine)]-2′-deoxy-ribofuranose (25). To a solution of **24** (420 mg, 0.79 mmol) in MeOH (5 mL) in a heavy walled glass tube (w/screw cap) were added portions of NH_4OH (1 mL) each day for 7 days at 50 °C, at which piont TLC indicated the absence of starting materials. The solvents were removed, the residue was extracted with CH_2Cl_2 (30 mL), and the organic phase was dried over $MgSO_4$, concentrated, loaded onto silica, and purified via column chromatography, eluting with 99:1 CH_2Cl_2/MeOH to obtain **25** as a white foam (350 mg, 0.735 mmol, 93%). R_f 0.45 in 19:1 CH_2Cl_2/MeOH. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.93 (dd, 1H, J = 5.26, J = 12.58 Hz), 2.04−2.11 (m, 1H), 3.40−3.42 (m, 2H), 3.67−3.69 (m, 2H), 4.15 (br s, 1H), 4.47 (s, 2H), 4.90 (d, 1H, J = 3.68 Hz), 4.98 (t, 1H, J = 5.52 Hz), 5.05 (dd, 1H, J = 5.52 Hz, J = 10.54 Hz), 5.22 (s, 2H), 5.67 (s, 2H), 6.33 (s, 2H, NH_2), 7.16−7.30 (m, 10H), 7.41 (s, 1H). ^{13}C NMR (400 MHz, DMSO-d_6): δ 42.0, 43.4, 63.3, 70.0, 72.4, 73.2, 76.6, 87.9, 112.0, 116.3, 127.2, 127.5, 127.92, 127.97, 128.7, 128.8, 130.7, 137.3, 138.4, 144.8, 151.7, 154.6. ESI-MS m/z for $C_{26}H_{28}N_4O_5$ calculated $[M + H]^+$ 477.2132, found 477.2135.

1′-β-[7-(2-Amino-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one)]-2′-deoxyribofuranose or 9-Deaza-2′-deoxyguanosine (2). The general procedure for hydrogenolysis was used. From **25** (350 mg,

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0.73 mmol), **2** was obtained as a white solid (128 mg, 0.48 mmol, 66%). mp >300 °C. R_f 0.5 in 4:1 CH_2Cl_2/MeOH. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.86 (dd, 1H, J = 5.26 Hz, J = 12.62 Hz), 2.13 (td, 1H, J = 5.04 Hz, J = 11.69 Hz), 3.37 (ddd, 2H, J = 4.12 Hz, J = 11.66 Hz, J = 11.44 Hz), 3.69 (t, 1H, J = 4.12 Hz), 4.15 (br s, 1H), 4.85 (d, 1H, J = 3.64 Hz), 5.05 (dd, 1H, J = 5.28 Hz, J = 10.76 Hz), 5.66 (br s, 2H, NH_2), 5.81 (br s, 1H), 7.09 (d, 1H, J = 3.2 Hz), 10.41 (br s, 1H, NH), 11.33 (br s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6): δ 42.6, 63.8, 73.6, 73.9, 88.3, 113.8, 115.7, 126.1, 151.3, 155.4, 164.0. ESI-MS m/z for $C_{11}H_{14}N_4O_4$ calculated $[M + H]^+$ 267.1087, found 267.1089.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra and high-resolution mass spectrometry (HRMS) for compounds **1**−**25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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