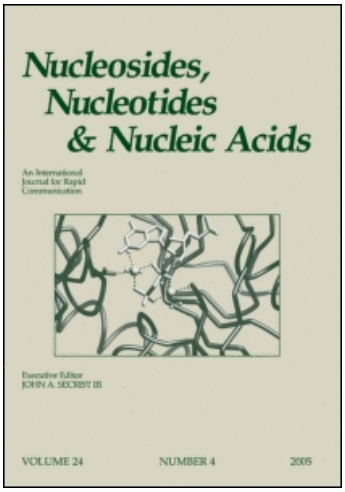


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

A Convenient Synthesis of *N,N'*-dibenzyl-2,4-diaminopyrimidine-2'-deoxyribonucleoside and 1-Methyl-2'-Deoxypseudoisocytidine

Kevin W. Wellington[a]; Hua Chee Ooi[b]; Steven A. Benner[c]
[a] CSIR Biosciences, Pinelands, Modderfontein, South Africa [b] Seattle Genetics, Bothell, Washington, USA [c] Foundation for Applied Molecular Evolution and The Westheimer Institute for Science and Technology, Gainesville, Florida, USA

To cite this Article Wellington, Kevin W. , Ooi, Hua Chee and Benner, Steven A.(2009) 'A Convenient Synthesis of *N,N'*-dibenzyl-2,4-diaminopyrimidine-2'-deoxyribonucleoside and 1-Methyl-2'-Deoxypseudoisocytidine', Nucleosides, Nucleotides and Nucleic Acids, 28: 4, 275 — 291
To link to this Article: DOI: 10.1080/15257770902946090
URL: http://dx.doi.org/10.1080/15257770902946090

Nucleosides, Nucleotides and Nucleic Acids, 28:275–291, 2009

ISSN: 1525-7770 print / 1532-2335 online
DOI: 10.1080/15257770902946090

Taylor & Francis
Taylor & Francis Group

A CONVENIENT SYNTHESIS OF *N,N′*-DIBENZYL-2,4-DIAMINOPYRIMIDINE-2′-DEOXYRIBONUCLEOSIDE AND 1-METHYL-2′-DEOXYPSEUDOISOCYTIDINE

Kevin W. Wellington,[1] Hua Chee Ooi,[2] and Steven A. Benner[3]

[1]*CSIR Biosciences, Pinelands, Modderfontein, South Africa*
[2]*Seattle Genetics, Bothell, Washington, USA*
[3]*Foundation for Applied Molecular Evolution and The Westheimer Institute for Science and Technology, Gainesville, Florida, USA*

□ *The syntheses of* N,N′*-dibenzyl-2,4-diaminopyrimidine-2′-deoxyribonucleoside and 1-methyl-2′-deoxypseudoisocytidine via Heck coupling are described. A survey of the attempts to use the Heck coupling to synthesize* N,N′*-dibenzyl-2,4-diaminopyrimidine-2′-deoxyribonucleoside is provided, indicating a remarkable diversity in outcome depending on the specific heterocyclic partner used.*

Keywords Synthesis; Heck coupling; hydrogen bonding patterns; synthetic biology; artificial genetic systems

INTRODUCTION

Some time ago, we showed that it was possible to create mutually exclusive nucleobase pairs that maintained the same geometry as the Watson-Crick base pairs, but which possessed different hydrogen bonding patterns. This not only allowed for the introduction of extra letters into the genetic alphabet,[1] but also initiated the emerging field of synthetic biology, where investigators in many laboratories are attempting to create artificial genetic systems.[2–5] In this regard, *C*-glycosides have been of particular interest to our work since they are robust with respect to chemical degradation and analogs of natural nucleotides (e.g., formycin A for adenosine,

Received 30 September 2008; accepted 20 March 2009.
We are grateful for financial support from the National Institutes of Health. This work was partly supported by R01GM08152 and R01HG004647.
Address correspondence to Steven A. Benner, Foundation for Applied Molecular Evolution and The Westheimer Institute for Science and Technology, 1115 NW 4th Street, Gainesville, FL, 32601, USA. E-mail: sbenner@ffame.org

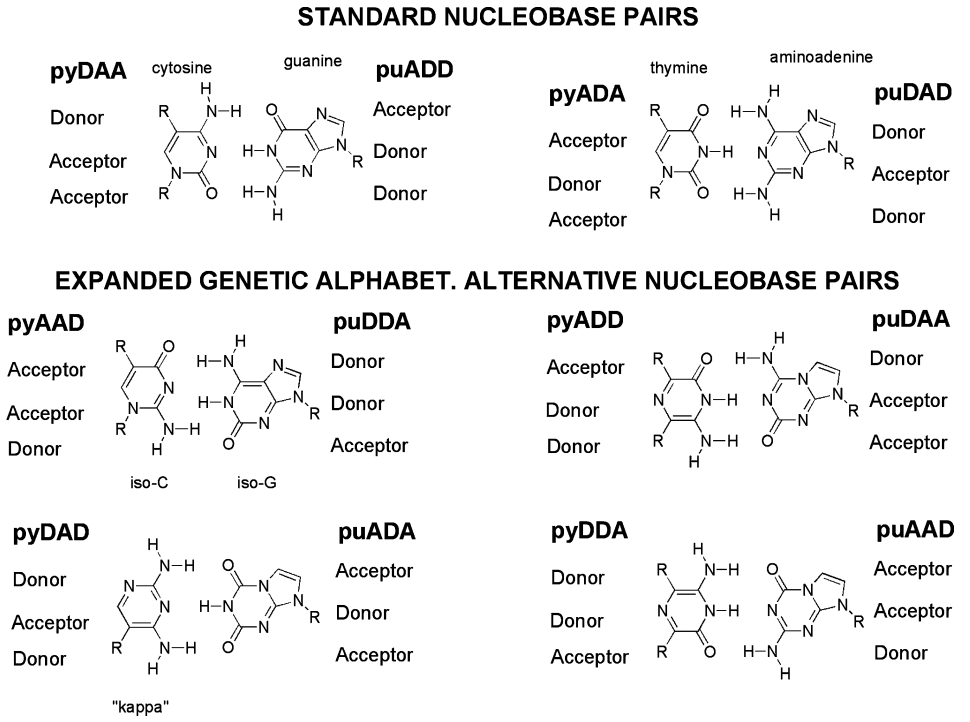


FIGURE 1 *C*-Glycosides are used to implement three nonstandard hydrogen bonding patterns in an artificially expanded genetic information system (AEGIS).[13–15]

pseudothymidine for thymidine) could be utilized to create more stable DNA structures. *C*-glycosides have also been successfully implemented in strategies that do not maintain a Watson-Crick geometry to expand the genetic alphabet.[6–8] In addition, *C*-glycosides are potentially useful in architectures to detect, amplify, quantitate, and sequence DNA and RNA.[9] They can not only be used in binding studies, but also in dynamic assay architectures where oligonucleotides incorporating multiple *C*-glycosides are both copied and synthesized by polymerases.

In *N*-glycosides, the heterocycle is joined to the sugar through a carbon-nitrogen bond. Isocytidine (Figure 1) is an example of a six-membered heterocyclic *N*-glycoside with a nonstandard acceptor-acceptor-donor hydrogen bonding pattern. It is currently being used in the 'branched DNA' diagnostic assay developed at Chiron and Bayer. Having now obtained FDA approval, this diagnostic helps manage the care of some 400,000 patients annually infected with the HIV, hepatitis B and hepatitis C viruses.[10–12] Other nonstandard hydrogen bonding patterns, however, require their six-membered heterocycle to be attached to their sugar by a carbon-carbon bond. This has led to many nonstandard hydrogen-bonding patterns being implemented on *C*-glycosides (Figure 1).

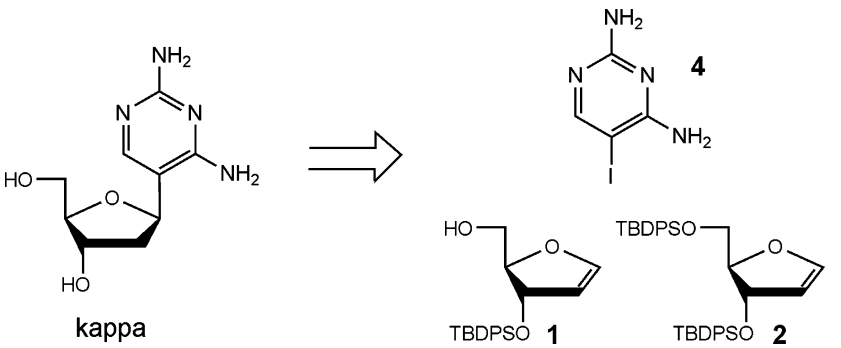
As part of our work, we required protected forms of a nonstandard nucleoside that bears a heterocycle that presents a "donor-acceptor-donor" (pyDAD) hydrogen bonding pattern on a pyrimidine skeleton such as kappa (Figure 1, bottom left). This should form a nucleobase pair having normal Watson-Crick geometry with purines and purine analogs that present an "acceptor-donor-acceptor" pattern, including xanthosine 7-deazaxanthosine, and 5-aza-7-deazaxanthosine[15] (Figure 1, bottom left). While these and other purine analogs are readily available, the 2,4-diaminopyrimidine-2′-deoxyribonucleoside that presents a "donor-acceptor-donor" hydrogen bonding pattern was available only by a long procedure that began with D-ribose.[16] This has always limited the access to protected 2,4-diaminopyrimidine-2′-deoxyribonucleoside derivatives.

The synthesis of the nonstandard 1-methyl-2′-deoxypseudoisocytidine having a "donor-acceptor-acceptor" (pyDAA) hydrogen bonding pattern on a pyrimidine skeleton has also been of interest to us since this would be the *C*-glycoside equivalent of cytidine (Figure 1, top left). This nucleoside should form a normal Watson-Crick nucleobase pair with purine or purine analogs having an "acceptor-donor-donor" hydrogen bonding pattern.

The Heck coupling is, in principle, an elegant way to synthesize such molecules by making use of a protected derivative of 5-iodo-2,4-diaminopyrimidine or 5-iodo-1-methyl-isocytosine. We report here an experimental procedure that yields the 2,4-diaminopyrimidine-2′-deoxyribonucleoside in the *N,N'*-dibenzylated form and also another that yields unprotected 1-methyl-2′-deoxypseudoisocytidine.

RESULTS AND DISCUSSION

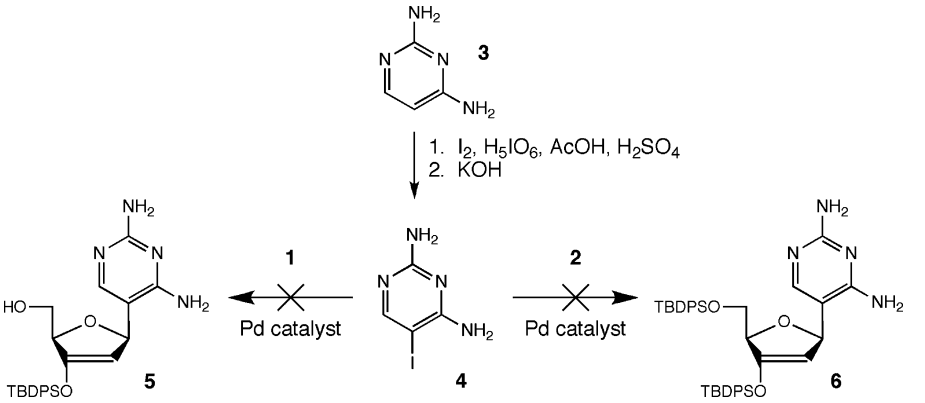
A retrosynthesis of 2,4-diaminopyrimidine-2′-deoxyribonucleoside, kappa, is shown in Scheme 1. The resulting components, the aglycon **4** and protected glycals **1** and **2** are substrates for the Heck coupling reaction.



SCHEME 1

Procedures for the synthesis of these glycals have been reported in the literature.[17–19] Glycal **1** was synthesized in five steps while **2** was synthesized in two steps from thymidine following procedures reported by Cameron et al.[19] There are several reports in the literature of Heck coupling reactions that were successful without protection of the exocyclic primary amines of the aglycon.[20–24] The reports inspired the investigation of the Heck coupling of the aglycon **4** with each of the glycals **1** and **2** to produce **5** and **6**, respectively.

The aglycon **4** was prepared from commercially available 2,4-diaminopyrimidine **3** by reacting it with iodine under acidic conditions. The Heck coupling reaction was then attempted with the unprotected aglycon **4** and glycals **1** and **2** (Scheme 2). The coupling conditions that were attempted are shown in Table 1.



SCHEME 2

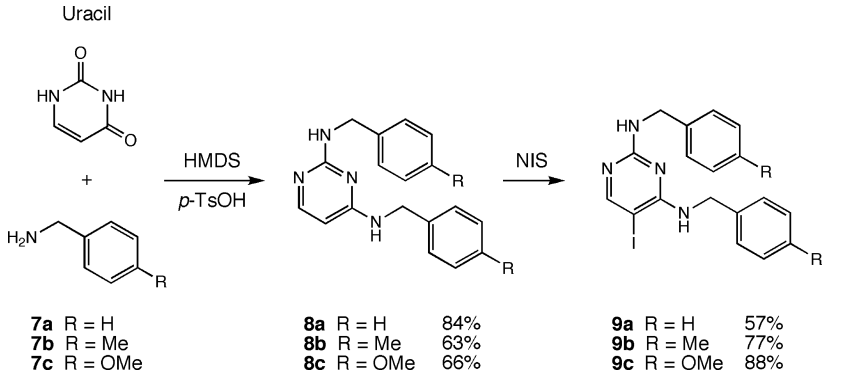
The coupling reactions were conducted at two different temperature ranges (60–65°C and 85–90°C) using two different bases [triethylamine (Et_3N) and diisopropylethylamine (DIEA)], two different palladium sources [palladium (II) acetate ($Pd(OAc)_2$) and bis(dibenzylideneacetone)palladium ($Pd(dba)_2$)], two different ligands [triphenylarsine ($AsPh_3$) and 1,3-(diphenylphosphino)propane (dppp)] and two different solvents [dimethylformamide (DMF) and acetonitrile (MeCN)]. In entry 6 silver carbonate was added to the reaction mixture because it increases conversion rates in analogous processes. Despite the variations in reaction conditions the desired coupled products **5** and **6** were not obtained. These unsuccessful attempts may be attributed to coordination of the palladium with the nitrogen atoms of the aglycon. In the light of these results, it was decided to protect the primary amines of the aglycon. For this purpose, the benzyl group was chosen as a protecting group. The synthesis of the benzylated pyrimidine **8a** was reported by Vorbrüggen and Krolikiewicz when they investigated silylation-amination

TABLE 1 Reactions conditions used for attempted coupling of glycals **1** and **2** with aglycon **4**

Entry	Aglycon	Glycal	Base and salt	Pd source	Ligand	Solvent and temperature	Reaction time	Result
1	4	2	Et_3N	$Pd(OAc)_2$	$AsPh_3$	DMF, 85–90°C	1h	—
2	4	2	DIEA	$Pd(OAc)_2$	$AsPh_3$	MeCN, 85–90°C	1h	—
3	4	1	DIEA	$Pd(OAc)_2$	$AsPh_3$	DMF, 85–90°C	1.5h	—
4	4	1	DIEA	$Pd(OAc)_2$	$AsPh_3$	DMF, 60–65°C	23.5h	—
5	4	1	DIEA	$Pd(dba)_2$	$AsPh_3$	DMF, 60–65°C	72h	—
6	4	1	Et_3N, Ag_2CO_3	$Pd(dba)_2$	dppp	MeCN, 60–65°C	72h	—

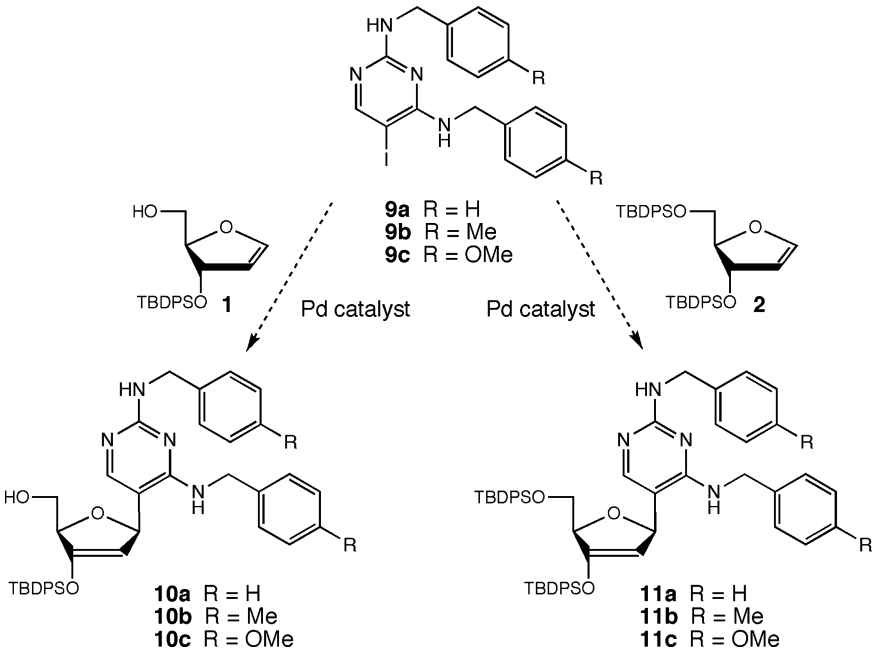
of hydroxy *N*-heterocycles.[25] This procedure was successfully employed to synthesize **8a** as well as **8b** and **8c**.

Treatment of **8a–c** with *N*-iodosuccinnimide (NIS) afforded the iodinated heterocycles **9a–c** as depicted in Scheme 3. It was envisaged that the Heck products **10a–c** and **11a–c** could be obtained by coupling each of the aglycons **9a–c** with glycals **1** and **2**, respectively (Scheme 4).



SCHEME 3

The conditions used for each of the Heck coupling reactions are listed in Table 2. For entries 1–9 in Table 2, 10 mol% of the palladium source was used. For entry 7 a yield of 22% was obtained for **10a** at 65–70°C when 10 mol% of the $Pd(dba)_2$ was used. The Heck reaction for **10a** was then optimized by using 20 mol% of $Pd(dba)_2$ and afforded a 60% yield (entry 10). For these reactions, the bulky TBDPS group at the 3-position directs addition of the aglycon to the β-face and results in the formation of the β-anomer as the only isomer. Triethylamine was used as the base for these reactions since it was easier to remove during purification and 1.5 equivalents of glycal was found to be sufficient. Desilylation of **10a** was achieved by reacting with TBAF at 0°C and afforded the ketone **12**. The free 5′-hydroxyl leads to stereospecific reduction of ketone **12** by complexation with $NaBH(OAc)_3$ and affords the benzylated nucleoside **13**



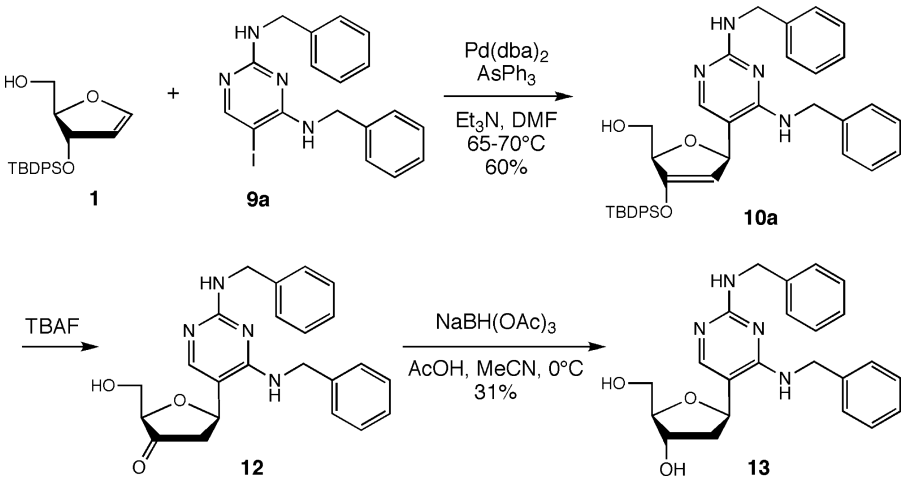
SCHEME 4

in 31% yield (Scheme 5). Attempted debenzylation of **13** by catalytic transfer hydrogenation using 10% Pd-C and ammonium formate in methanol was unsuccessful.[26] The debenzylation of **13** using Pd black and 1,4-cyclohexadiene in glacial acetic acid was also attempted.[27] Pd black is supposedly a more efficient catalyst than 10% Pd-C and glacial acetic acid has been reported to be a better solvent for performing debenzylations under

TABLE 2 Reagents and conditions employed in the Heck coupling reaction

Entry	Aglycon	Glycal	Base	Pd source	Ligand	Solvent and temperature	Reaction time	Result
1	9a	1	Et_3N	$Pd(OAc)_2$	$AsPh_3$	DMF, 85–90°C	1 h	—
2	9b	1	Et_3N	$Pd(OAc)_2$	$AsPh_3$	DMF, 85–90°C	1 h	—
3	9c	1	Et_3N	$Pd(OAc)_2$	$AsPh_3$	DMF, 85–90°C	1.5 h	—
4	9a	2	Bu_3N	$Pd(OAc)_2$	$AsPh_3$	DMF, 60–65°C	23.5 h	—
5	9a	2	Bu_3N	$Pd(dba)_2$	$AsPh_3$	MeCN, 60–65°C	72 h	—
6	9b	2	Bu_3N	$Pd(dba)_2$	$AsPh_3$	MeCN, 60–65°C	72 h	—
7	9a	1	DIEA	$Pd(dba)_2$	$AsPh_3$	DMF, 65–70°C	7.5 h	**10a** (22%)
8	9b	1	DIEA	$Pd(dba)_2$	$AsPh_3$	DMF, 65–70°C	8 h	
9	9c	1	DIEA	$Pd(dba)_2$	$AsPh_3$	DMF, 65–70°C	11 h	
10	9a	1	Et_3N	*$Pd(dba)_2$	$AsPh_3$	DMF, 65–70°C	4 h	*__10a__ (60%)

*20 mol% $Pd(dba)_2$.



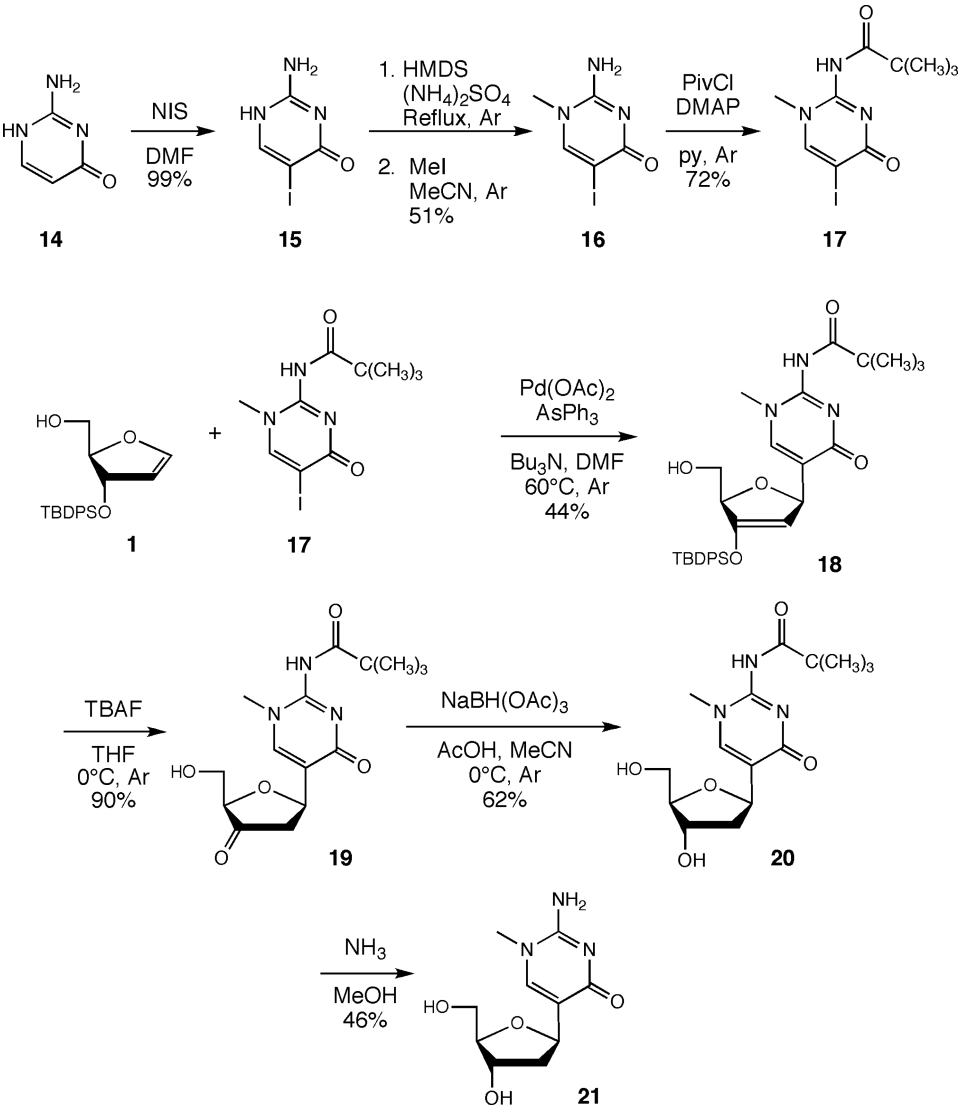
SCHEME 5

catalytic transfer hydrogenation conditions. This attempt was, however, also unsuccessful.

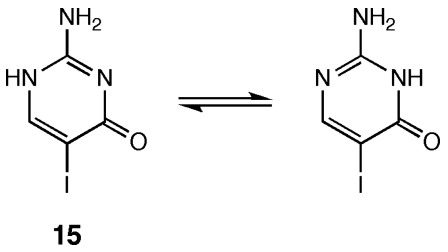
The synthesis of nucleoside **21**, which possesses a donor-acceptor-acceptor hydrogen bonding pattern, was achieved from isocytosine **14**, as outlined in Scheme 6. The heterocycle **15** was obtained in quantitative yield (99%) after reaction with NIS in DMF. Reaction of **15** with HMDS in the presence of ammonium sulfate, followed by treatment with a large excess of methyl iodide gave the methylated heterocycle **16** as the sole product in 51% yield. Methylation of *N*-1 was performed to avoid unwanted tautomerization (Figure 2) that would result in an unwanted "donor-donor-acceptor" hydrogen bonding pattern in the desired nucleoside. The structure of **16** was confirmed by an HMBC experiment that showed a long range correlation between the aromatic proton and the methyl carbon on *N*-1. If methylation had occurred on *N*-3, no correlation would have been observed.

Due to the difficulties associated with coupling the unprotected aglycon **4** with glycal **1**, it was decided to protect the exocyclic amine of **16** with a pivaloyl group prior to Heck coupling. This was achieved by reacting **16** with pivaloyl chloride in the presence of DMAP in pyridine and afforded aglycon **17** in high yield (72%).

The Heck coupling reaction was successfully conducted using palladium acetate and triphenylarsine in the presence of tri-*n*-butylamine and afforded the desired Heck product **18** in moderate yield (44%) after 3 days. Subsequent deprotection of **18** was achieved using TBAF at 0°C and stereoselective reduction of the resulting ketone **19** was achieved by using $NaBH(OAc)_3$ to afford **20** in good yield (62%). Removal of the pivaloyl group of **20** was achieved by treatment with methanolic ammonia and afforded the desired nucleoside **21** in moderate yield (46%).



SCHEME 6



15

FIGURE 2 Tautomeric forms of the iodinated heterocycle **15**.

CONCLUSION

The Heck coupling is an extremely useful reaction for the coupling of a variety of iodopyrimidinones to glycals, including those that generate 2′-deoxypseudouridine.[7] Our work here has uncovered a peculiar set of limitations on the Heck glycal coupling strategy. From a purely practical perspective, we have found the coupling quite useful to prepare large amounts of pseudothymidine[28] for conversion to triphosphates and phosphoramidites. A variety of explanations can be suggested to explain why some coupling reactions are successful, while others are not. We have not been able to generate a single explanatory set of rules that account for all of the data that we have collected. Perhaps the most curious pair of coupling experiments are those that successfully couple 2,4-*N,N′*-dibenzylamino-5-iodopyrimidine **9a** to the glycal **1**, but fail to couple 2,4-diamino-5-iodopyrimidine **4** to the same glycal **1**. Regardless of the explanation, this manuscript offers a convenient route to the dibenzyl protected derivative of the 2,4-diaminopyrimidine-2′-deoxyribonucleoside **13** as well as to 1-methyl-2′-deoxypseudoisocytidine **21**.

EXPERIMENTAL

Anhydrous solvents were used for water sensitive reactions. NMR: ^{1}H at 300 MHz and ^{13}C at 75 MHz; δ in ppm; calibration to $SiMe_4$ (^{1}H) or residual solvent peak (^{13}C). Melting points were determined by using an Electrotherm Mel-Temp apparatus and are uncorrected.

2,4-Diamino-5-iodopyrimidine 4

2,4-Diaminopyrimidine (3.00 g, 27.2 mmol) was dissolved with stirring in a mixture of 15 mL of H_2O and 100 mL of glacial acetic acid, followed by iodine (8.63 g, 68 mmol) and H_5IO_6 (8.07 g, 35.4 mmol). The mixture was treated dropwise with concentated H_2SO_4 (1.0 mL), stirred for 5.5 hours and then allowed to cool to room temperature. The solution, which was placed on ice, was treated with solid KOH until a suspension formed. The mixture solidified. The solids were recovered by filtration and washed with water (450 mL). The filtrate was treated with KOH to create solids which were recovered by filtration, dried in air, and then dried under high vacuum to afford a light brown powder (1.65 g, 26%). The remaining solid material was added to water (400 mL), stirred overnight and the suspension filtered off and dried on the high vacuum pump to afford a brown powder (4.55 g, 71%). The combined yields afforded the product in a total yield of 6.20 g (97%) m.p. 222–225°C $R_f = 0.45$ (DCM-MeOH, 10:1). ^{1}H NMR (DMSO-d_6, 300 MHz): δ6.10 (NH_2, s, 2H), 6.40 (NH_2, br s, 2H) and 7.92 (ArH, s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ162.0 and 2 × 162.8. HRMS-ESI: [MH^+] MS calcd for $C_4H_5IN_4$ 236.9632, found 236.9630.

N^2,N^4-Dibenzyl-pyrimidine-2,4-diamine 8a

Benzylamine **7a** (13.12 mL, 100 mmol) was added to a hot, stirred mixture of *p*-toluene sulfonic acid monohydrate (0.96 g, 5.2 mmol) and uracil (4.48 g, 40 mmol) in HMDS under Ar. The resulting reaction mixture was heated at 118°C for 29 hours and then the solvent was removed on the rotary evaporator at 50°C. MeOH (50 mL) was added to the residue and the mixture was allowed to stand overnight. The solvent was then removed on the rotary evaporator and the crude material purified by flash chromatography (silica: EtOAc-hexane, 1:1) to afford the product as a brown oil (9.73 g, 84%) that solidified upon standing. m.p. 62–64°C (lit.[25] 68–70°C) $R_f = 0.42$ (DCM-MeOH, 10:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ4.45 (CH_2, d, 2H, $J = 5.7$ Hz), 4.55 (CH_2, d, 2H, $J = 6$ Hz), 5.20 (NH, br s, 1H), 5.53 (NH, br s, 1H), 5.67 (ArH, d, 1H, $J = 5.7$ Hz), 7.18–7.38 (ArH, m, 10H) and 7.75 (ArH, d, 1H, $J = 6$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ45.3 ($2 \times CH_2$), 126.9, 127.3, 127.4, 128.4, 128.6, 139.8, 156.4, 162.2 and 162.9. HRMS-ESI: [MH^+] MS calcd for $C_{18}H_{18}N_4$ 291.1604, found 291.1600.

N^2,N^4-Bis-(4-methyl-benzyl)-pyrimidine-2,4-diamine 8b

Following the procedure described for the synthesis of **8a,** 4-methylbenzylamine **7b** (15.16 mL, 120 mmol), *p*-toluenesulfonic acid monohydrate (0.96 g, 5.2 mmol) and uracil (4.48 g, 40 mmol) were heated at 118°C in HMDS for 38.5 hours while stirring under Ar. The solvent was removed on the rotary evaporator at 50°C and the residue purified by flash chromatography (silica: EtOAc-hexanes, 1:2) to afford a light-brown powder (8.08 g, 63%). m.p. 78–80°C $R_f = 0.44$ (DCM-MeOH, 10:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ2.33 ($2 \times CH_3$, m, 6H), 4.42 (CH_2, d, 2H, $J = 6$ Hz), 4.53 (CH_2, d, 2H, $J = 6$ Hz), 5.08 (NH, br s, 1H), 5.33 (NH, br s, 1H), 5.67 (ArH, d, 1H, $J = 3$ Hz), 7.05–7.30 (ArH, m, 8H) and 7.75 (ArH, 1H, d, $J = 6$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ21.1 ($2 \times CH_3$), 45.0 ($2 \times CH_2$), 127.4, 129.1, 129.3, 136.5, 136.6, 137.0, 147.2, 156.3, 162.1 and 162.9. HRMS-ESI: [MH^+] MS calcd for $C_{20}H_{22}N_4$ 319.1917, found 319.1912.

N^2,N^4-Bis-(4-methoxy-benzyl)-pyrimidine-2,4-diamine 8c

4-Methoxybenzylamine **7c** (15.64 mL, 120 mmol), *p*-toluene sulfonic acid monohydrate (0.96 g, 5.2 mmol), and uracil (4.48 g, 40 mmol) were heated at 118°C in HMDS for 24 hours while stirring under Ar following the procedure described for **8a**. The solvent was removed on the rotary evaporator at 50°C and the residue purified by flash chromatography (silica: EtOAc-hexanes, 1:3; EtOAc) to afford a light-brown powder (9.32 g, 66%). m.p. 115–117°C $R_f = 0.44$ (DCM-MeOH, 10:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ3.72–3.88 ($2 \times OCH_3$, m, 6H), 4.40 (CH_2, d, 2H, $J = 5.1$ Hz), 4.49 (CH_2, d, 2H, $J = 6$ Hz), 5.11 (NH, br s, 1H), 5.37 (NH, br s, 1H), 5.68 (ArH, d, 1H,

$J = 5.7$ Hz), 6.7–6.91 (ArH, m, 4H), 7.16–7.32 (ArH, m, 4H) and 7.77 (ArH, 1H, d, $J = 5.4$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ44.7 (2 × OCH_3), 55.1 (CH_2), 55.2 (CH_2), 113.8, 114.0, 128.6, 128.7, 131.8, 156.2, 158.6, 158.8, 162.0 and 162.9. HRMS-ESI: [MH^+] MS calcd for $C_{20}H_{22}N_4O_2$ 351.1816, found 351.1809.

N^2,N^4-Dibenzyl-5-iodo-pyrimidine-2,4-diamine 9a

N-Iodosuccinimide (5.74 g, 26 mmol) was added to a stirred solution of the heterocycle **8a** (5.00 g, 17 mmol) in MeOH (50 mL) and the resulting reaction mixture was stirred at room temperature for 3 hours. The reaction was monitored by TLC (silica: EtOAc-hexanes, 1:1) and upon completion the solvent was removed on the rotary evaporator. The crude material was purified by flash chromatography (silica: EtOAc-hexanes, 1:1; 2:1) to afford a cream-yellow powder (4.00 g, 57%). m.p. 123–124°C $R_f = 0.36$ (DCM-MeOH, 20:1) ^{1}H NMR ($CDCl_3$, 300 MHz): δ4.54 (CH_2, d, 2H, $J =$ 5.7 Hz), 4.61 (CH_2, d, 2H, $J = 6$ Hz), 5.40 (NH, br s, 1H), 7.20–7.40 (ArH, m, 10H) and 7.98 (ArH, 1H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ45.1 (CH_2), 45.6 (CH_2), 127.1, 127.5, 128.5, 128.6, 138.6, 161.5 and 161.9. HRMS-ESI: [MH^+] MS calcd for $C_{18}H_{17}IN_4$ 417.0571, found 417.0563.

5-Iodo-N^2,N^4-Bis-(4-methyl-benzyl)-pyrimidine-2,4-diamine 9b

Following the procedure described for the synthesis of **9a**, *N*-iodosuccinimide (2.47 g, 11 mmol) was added to a stirred solution of the heterocycle **8b** (3.50 g, 11 mmol) in MeOH (50 mL) and the resulting reaction mixture was stirred at room temperature. Upon completion the solvent was removed on the rotary evaporator. The crude material was purified by flash chromatography (silica: EtOAc-hexanes, 1:3; 1:2) to afford a yellow powder (3.74 g, 77%). m.p. 130–132°C $R_f = 0.44$ (DCM-MeOH, 20:1) ^{1}H NMR ($CDCl_3$, 300 MHz): δ2.33 (2 × CH_3, m, 6H), 4.50 (CH_2, d, $J = 6$ Hz, 2H), 4.56 (2H, d, $J = 5.7$ Hz, CH_2), 5.34 (2H, br s, NH), 7.06–7.24 (8H, m, ArH) and 7.95 (ArH, s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ21.1 (2 × CH_3) 44.9 (CH_2), 45.3 (CH_2), 127.5, 127.6, 129.2, 129.3, 135.6, 136.7, 137.0, 159.7, 161.5, 161.9 and 174.2. HRMS-ESI: [MH^+] MS calcd for $C_{20}H_{21}IN_4$ 445.0884, found 445.0877.

5-Iodo-N^2,N^4-Bis-(4-methoxy-benzyl)-pyrimidine-2,4-diamine 9c

N-Iodosuccinimide (2.25 g, 10 mmol) was added to a stirred solution of the heterocycle **8c** (3.50 g, 10 mmol) in DMF (10 mL) and the resulting reaction mixture was stirred at room temperature. The reaction was monitored by TLC (silica: DCM-MeOH, 9:1) and upon completion the reaction mixture was added to H_2O (300 mL) and stirred overnight. The resulting precipitate was filtered off and dried on the high vacuum pump to afford a

light-brown powder (4.17 g, 88%). m.p. 114–115°C $R_f = 0.42$ (DCM-MeOH, 20:1) ^{1}H NMR ($CDCl_3$, 300 MHz): δ3.79 (2 × OCH_3, m, 6H), 4.48 (CH_2, d, 2H, $J = 5.7$ Hz), 4.54 (CH_2, d, 2H, $J = 5.7$ Hz), 5.33 (NH, br s, 1H), 6.78–6.94 (ArH, m, 4H), 7.16–7.32 (ArH, m, 4H) and 7.97 (ArH, m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ44.6 (OCH_3), 45.0 (OCH_3), 55.2 (2 × CH_2), 113.8, 114.0, 128.7, 128.8, 130.6, 131.5, 158.6, 158.9, 159.6, 161.4 and 161.8. HRMS-ESI: [MH^+] MS calcd for $C_{20}H_{21}IN_4O_2$ 477.0782, found 445.0777.

General Heck Coupling Procedure for Entries 1–6 in Table 1 and Entries 1–9 in Table 2

A mixture of the palladium source (0.05 mmol) and triphenylarsine (0.10 mmol) in dry DMF (2.0 mL) was stirred under argon at room temperature for 20–40 minutes. This mixture was then transferred by syringe to a solution of the aglycon (0.5 mmol), glycal **1** or **2** (0.8 mmol) and base (0.22 mL, 1.6 mmol) in dry DMF (1.5 mL). The resulting orange-brown solution was stirred under argon at 65–70°C. The reaction mixture was then filtered through celite and the volatiles were removed on the rotary evaporator. The residue was purified by flash chromatography.

[5-(2,4-Bis-benzylamino-pyrimidin-5-yl)-3-(*tert*-butyl-diphenyl-silanyloxy)-2,5-dihydro-furan-2-yl]-methanol 10a

A mixture of bis(dibenzylideneacetone)-palladium(0) (0.80 g, 1 mmol) and triphenylarsine (0.80 g, 2 mmol) in dry DMF (1.5 mL) was stirred under argon at room temperature for 40 minutes. This mixture was then transferred by syringe to a solution of the iodinated heterocycle **9a** (2.10 g, 5 mmol), Daves' sugar (1,4-anhydro-2-deoxy-3-*O*-[(1,1-dimethylethyl)diphenylsilyl]-D-*erythro*-pent-1-enitol) **1** (2.80 g, 8 mmol) and triethylamine (2.09 mL, 15 mmol) in dry DMF (3.00 mL) also under argon. The resulting orange-brown solution was heated under argon at 65–70°C. After 2 hours of heating more triethylamine (2.09 mL, 15 mmol) was added and the reaction monitored by TLC (silica: MeOH-DCM, 1:20). After 5 hours the reaction was complete and the reaction mixture was then filtered through celite and the volatiles removed on a rotary evaporator. The resulting crude material was purified by flash chromatography (silica: DCM-MeOH, 280:1, 140:1, 100:1, 50:1) and afforded a brown powder (1.91 g, 60%). $R_f = 0.31$ (silica: MeOH-DCM, 1:20). ^{1}H NMR ($CDCl_3$, 300 MHz): δ3.78–4.02 (CH_2OH, m, 2H), 4.22 (s,1H), 4.47 (CH_2, d, $J = 5.7$ Hz, 2H), 4.52–4.70 (m, 3H), 5.27 (m, 1H), 7.18–7.31 (10H, m, ArH), 7.32–7.54 (7H, m, ArH) and 7.63–7.76 (4H, m, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ19.2, 19.3, 26.4, 26.6, 44.36, 2 × 45.1, 61.7, 62.7, 81.4, 82.8, 83.6, 101.3, 127.0, 127.4, 127.7, 128.0, 2 × 128.4, 128.5, 130.4, 130.6, 130.7, 134.8, 135.3 and 135.4. HRMS-ESI: [MH^+] MS calcd for $C_{39}H_{43}N_40_3Si$ 643.3099, found 643.3067.

[5-(2,4-Bis-benzylamino-pyrimidin-5-yl)-2-hydroxymethyl-tetrahydro-furan-3-ol 13

The ketone **12** (0.60 g, 1.5 mmoL) was added to a mixture of acetonitrile (8 mL) and glacial acetic acid (3 mL) and the resulting mixture cooled to 0°C. Sodium triacetoxyborohydride (0.44 g, 2.1 mmol) was then added and the reaction monitored by TLC (silica: DCM-MeOH, 10:1). After 35 minutes stirring was stopped and the solvent removed on the rotary evaporator to afford a brown crude material. This was purified by flash chromatography (silica: DCM-MeOH, 40:1, 20:1, 10:1, 10:3) to afford a light brown material (0.19 g, 31%). $R_f = 0.15$ (DCM-MeOH, 10:1). ^{1}H NMR (CD_3OD, 300 MHz): δ1.81–1.86 (m, 1H), 2.23–2.40 (m, 1H), 3.71 (t, J = 2.4 and 2.1 Hz, 2H), 3.92 (m, 1H), 4.38 (d, J = 6.6 Hz, 1H), 4.42–4.63 (m, 4H), 4.88 (m, 1H), 7.12–7.26 (ArH, m, 10H) and 7.55 (ArH, s, 1H). ^{13}C NMR (CD_3OD, 75 MHz): δ40.9, 44.6, 45.8, 48.7, 63.1, 74.7, 80.1, 80.2, 89.3, 106.6, 2 × 127.6, 128.2, 129.2, 129.3, 141.5141.8, 153.6, 161.9 and 162.7. HRMS-ESI: [MH^+] MS calcd for $C_{23}H_{27}N_40_3$ 407.2078, found 407.2073.

5-Iodo-isocytosine 15

DMF (50 mL) was added to a mixture of isocytosine **14** (8.33 g, 75 mmol) and *N*-iodosuccinimide (18.56 g, 82.5 mmol) under an Ar atmosphere. The reaction vessel was covered in foil and ultrasonicated for 30 minutes to break up the solid mass at the bottom of the reaction vessel (the reaction mixture was, however, still heterogeneous). The heterogeneous mixture was then stirred for an additional 12 hours before adding it to water (150 mL). The insoluble material was collected by filtration, washed with additional water and dried over P_2O_5 to give the desired material as a pale tan solid (17.70 g, 99%). The material was used without further purification. ^{1}H NMR (DMSO-d_6, 300 MHz): δ6.70 (NH_2, br s, 2H), 7.94 (ArH, s, 1H), 11.26 (NH, br s, 1H).

5-Iodo-1-methyl-isocytosine 16

HMDS (20 mL) was added to a mixture of 5-iodo-isocytosine **15** (3.56 g, 15 mmol) and powdered ammonium sulfate (0.08 g) under an Ar atmosphere. The reaction mixture was stirred and heated to reflux for 6.5 hours. After this time it was removed from the heat, allowed to cool, and the solvent removed under reduced pressure (high vacuum pump) to afford a brown oil. The oil was dissolved in acetonitrile (20 mL) and methyl iodide (9.34 mL, 150 mmol) added under an Ar atmosphere. The reaction mixture was stirred for 1 day and the crude product was collected by filtration. Recrystallization from water, decolorizing with charcoal gave the desired material as a pale yellow crystalline solid (1.91 g, 51%). The filtrate was concentrated, which on cooling, gave an additional batch of material, also

as a pale yellow solid (0.26 g, 7%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ3.37 (3H, s, N-Me), 7.75 (1H, br s, NH), 8.15 (1H, s, ArH). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 38.3, 75.7, 149.7, 154.2, 162.7. HRMS (EI +ve) calcd for $C_5H_6N_3OI$ 250.9560 (M+), found 250.9560.

5-Iodo-1-methyl-2-pivaloylamino-4-pyrimidinone 17

Pivaloyl chloride (15.8 mL, 128.3 mmol) was added in one lot to a stirred mixture of 5-iodo-1-methyl-isocytosine **16** (2.01 g, 8 mmol) and DMAP (1.96 g, 16 mmol) in anhydrous pyridine (32 mL) under an Ar atmosphere. The reaction was stirred for 18 hours, and triethylamine (16 mL) was added. The reaction vessel was cooled in an ice/water bath, and ethanol (32 mL) was cautiously added to the reaction mixture. The reaction mixture was concentrated under reduced pressure and the resulting solid was partitioned between dichloromethane (50 mL) and water (50 mL). After removing the aqueous phase, the organic solution was washed with additional water (2 × 50 mL), dried ($MgSO_4$), filtered, and the filtrate concentrated under reduced pressure to give the crude material as a pink solid. Purification by flash chromatography (1:3 ethyl acetate:hexane) gave the desired material as a pale yellow solid (1.94 g, 72%). ^{1}H NMR (DMSO-d_6, 300 MHz,) δ 1.15 (*t*-Bu, s, 9H), 3.43 (N-Me, s, 3H), 8.44 (ArH, s, 1H), 13.10 (NH, br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ27.7, 38.2, 42.5, 71.0, 149.7, 153.2, 157.8, 193.6. MS (EI +ve) 335 (5%, M+), 279 (15), 278 (100), 152 (13), 123 (13), 83 (29). HRMS (EI +ve) calcd for C_{10} $H_{14}N_3O_2I$ 335.0130 (M+), found 335.0120.

N-{5-[4-(tert-Butyl-dimethyl-silanyloxy)-5-hydroxymethyl-2,5-dihydro-furan-2-yl]-1-methyl-4-oxo-1,2,3,4-tetrahydro-pyrimidin-2-yl}-2,2-dimethyl-propionamide 18

DMF (20 mL) was added to a mixture of palladium acetate (0.10 g, 0.44 mmol) and triphenyl arsine (0.34 g, 1.11 mmol) under an Ar atmosphere. The reaction mixture was stirred, and the initially clear yellow solution became cloudy within approximately one minute. After 20 minutes a solution of the iodoheterocycle **17** (1.85 g, 5.53 mmol), the glycal **1** (2.35 g, 6.64 mmol) and tri-*n*-butylamine (2.04 mL, 8.58 mmol) in DMF (10 mL) (prepared in a different flask under an Ar atmosphere) was added by syringe in one lot. This flask was washed with additional DMF (2 × 5 mL), and the washings also added to the reaction mixture, which was now a clear orange solution. The reaction mixture was heated to 60°C. After 3 days, TLC (silica: ethyl acetate:hexane, 1:3) showed that there was no starting material remaining. The reaction mixture was removed from the heat, allowed to cool, and the solvent removed under reduced pressure (high

vacuum pump) without the use of a heat source. The resulting dark brown oil was dissolved in methanol, adsorbed onto silica, and purified by flash chromatography (silica: ethyl acetate:hexane, 2:5) to give an impure sample of the desired product (1.64 g), as well as some dehalogenated heterocycle (0.23 g, 20%). The impure material was dissolved in a small volume of 1:3 ethyl acetate:hexane, and within approximately one minute, some of the desired material crystallized from solution as a white solid (0.62 g). The filtrate was concentrated under reduced pressure to dryness, and this was repeated to give an additional crop of material (0.15 g). The filtrate was again concentrated under reduced pressure to dryness and the solid dissolved in a small amount of 1:5 ethyl acetate:hexane, which gave more material (0.30 g). This filtrate was concentrated to dryness, and purified by flash chromatography (silica: ethyl acetate:hexane, 1:3) to give more of the desired product (0.28 g). Total yield: 1.35 g, (44%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ1.06 (s, 9H, $C(CH_3)_3$,), 1.18 (s, 9H, $C(CH_3)_3$), 2.20 (dd, J = 7.7, 5.1 Hz, 1H, 5′-OH), 3.33 (s, 3H, N-CH_3), 3.85 (ddd, J = 12.0, 5.1, 2.6, 1H, H5′a), 3.89 (ddd, J = 12.0, 7.0, 2.6 Hz, 1H, H5′b), 4.30 (s br, 1H, H2′), 4.71 (dq, J = 3.7, 2.6 Hz, 1H, H4′), 5.52 (dd, J = 3.7, 1.2 Hz, 1H, H1′), 7.02 (s, 1H, H6), 7.38–7.49 (m, 6H, ArH), 7.72 (dd, J = 7.9, 1.4 Hz, 2H, ArH) and 12.93 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ19.4, 26.5, 27.8, 38.1, 42.3, 62.3, 78.2, 83.6, 101.3, 117.7, 128.0, 128.2, 130.4, 130.5, 2 × 131.4, 135.5, 136.0, 143.4, 150.9, 153.0, 160.0 and 193.1. HRMS (FAB) calcd for $C_{31}H_{40}N_3O_5Si$ 562.2731 (MH+), found 562.2737.

N-{5-[5-hydroxymethyl-4-oxo-tetrahydro-furan-2-yl]-1-methyl-4-oxo-1,4-dihydro-pyrimidin-2-yl}-2,2-dimethyl-propionamide 19

A solution of TBAF in THF (3.00 mL, 1.0 M, 3.00 mmol) was added to a solution of the coupled product **18** (1.124 g, 2.00 mmol) in THF (4 mL) which was cooled in an ice/water bath under an Ar atmosphere. The reaction mixture immediately became yellow, and after 1 minute TLC (silica: ethyl acetate:hexane, 1:1) showed that there was no starting material remaining. The reaction was quenched by addition of methanol (2 mL) and the reaction mixture was concentrated under reduced pressure. The resulting yellow oil was purified twice by flash chromatography (silica: ethyl acetate:hexanes, 3:1) to give the desired product as a pale yellow foam (0.58 g, 90%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ1.22 (s, 9H, $C(CH_3)_3$,), 2.70 (dd, J = 18.2, 10.8 Hz, 1H, H2′a), 2.85 (dd, J = 18.2, 6.8 Hz, 1H, H2′b), 2.97 (br t, J = 6.2 Hz, 1H, 5′OH), 3.54 (s, 3H, NCH_3), 3.90–3.94 (m, 2H, H5′a, H5′b), 4.03 (t, J = 2.8 Hz, 1H, H4′), 5.00 (d, J = 10.8, 6.8 Hz, 1H, H1′), 7.49 (s, 1H, ArH) and 13.18 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ27.8, 38.4, 42.4, 42.6, 62.1, 73.1, 82.2, 115.3, 143.2, 153.0, 160.0, 193.6 and 213.3. HRMS (FAB) calcd for $C_{15}H_{22}N_3O_5$ 324.1559 (MH+), found 324.1549.

Pivaloylated 1-Methyl-2′-deoxypseudoisocytidine 20

Sodium triacetoxyborohydride (0.55 g, 2.48 mmol) was added in one lot to a solution of the hydroxyketone **19** (0.53 g, 1.65 mmol) in acetonitrile (8.00 mL) and acetic acid (4.00 mL) under an Ar atmosphere. TLC (silica: ethyl acetate) indicated that there was no starting material after 12 minutes. The reaction was quenched by the addition of acetone, and the reaction mixture concentrated under reduced pressure. The resulting pale yellow gum was dissolved in methanol, adsorbed onto silica, and purified by flash chromatography (silica: ethyl acetate) to give the desired material as a white solid (0.40 g, 62%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ1.21 (s, 9H, $C(CH_3)_3$,), 1.95 (d, J = 3.5 Hz, 1H, 3′-OH), 2.10 (ddd, J = 13.2, 5.6, 1.4 Hz, 1H, H2′a), 2.41 (ddd, J = 13.2 10.5, 5.6 Hz, 1H, H2′b), 3.51 (s, 3H, NCH_3), 3.57 (dd, J = 9.5, 2.9 Hz, 1H, 5′-OH), 3.69 (ddd, J = 11.9, 9.5, 2.7 Hz, 1H, H5′a), 3.82 (ddd, J = 11.9, 2.9, 2.7 Hz, 1H, H5′b), 4.03 (dt, J = 4.7, 2.7 Hz, 1H, H4′), 4.52–4.57 (m, 1H, H3′), 4.89 (dd, J = 10.5, 5.6 Hz, 1H, H1′), 7.69 (d, J = 0.5 Hz, 1H, ArH) and 13.12 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ27.8, 38.3, 40.9, 42.3, 63.5, 74.0, 88.0, 116.2, 143.2, 153.0, 160.4 and 193.6. HRMS (FAB) calcd for $C_{15}H_{22}N_3O_5$ 324.1559 (MH+), found 324.1549.

1-Methyl-2′-deoxypseudoisocytidine 21

The protected nucleoside **20** (0.03 g, 0.1 mmol) was dissolved in a solution of saturated methanolic ammonia (25 mL), stoppered and the reaction mixture stirred for 5 days. The reaction mixture was then concentrated under reduced pressure and the resulting film was dissolved in water (5 mL) and washed with dichloromethane (6 × 10 mL). The aqueous solution was filtered to remove particulate matter and the filtrate freeze dried to give the desired product as a white solid (0.01 g, 46%). ^{1}H NMR (D_2O, 500 MHz) δ1.95 (ddd, J = 13.5, 10.1, 6.0 Hz, 1H, H2′a), 2.15 (ddd, J = 13.5, 5.9, 2.1 Hz, 1H, H2′b), 3.39 (s, 3H, NCH_3), 3.55 (dd, J = 12.2, 5.1 Hz, 1H, H5′a), 3.63 (dd, J = 12.2, 4.1 Hz, 1H, H5′b), 3.90 (ddd, J = 5.1, 4.1, 2.8 Hz, 1H, H4′), 4.27 (dddd, J = 6.0, 2.8, 2.1, 0.6 Hz, 1H, H3′), 4.92 (dddd, J = 10.1, 5.9, 0.9, 0.6 Hz, 1H, H1′) and 7.47 (d, J = 0.9 Hz, 1H, ArH). ^{13}C NMR (D_2O, 75 MHz) δ38.7, 39.8, 62.3, 72.9, 74.9, 86.6, 117.3, 142.8, 155.9 and 171.3. HRMS (EI) calcd for $C_{10}H_{15}N_3O_4$ 241.1063, found 241.1055.

REFERENCES

1. Piccirilli, J.A.; Krauch, T.; Moroney, S.E.; Benner, S.A. Enzymatic incorporation of a new base pair into DNA and RNA extends the genetic alphabet. *Nature* **1990**, 343, 33–37.
2. Kool, E.T. Hydrogen bonding, base stacking and steric effects in DNA replication. *Annu. Rev. Biophys. Biomol. Struct.* **2001**, 30, 1–22.
3. Wu, Y.Q.; Ogawa, A.K.; Berger, M.; McMinn, D.L.; Schultz, P.G.; Romesberg, F.E. Efforts toward expansion of the genetic alphabet: optimization of interbase hydrophobic interactions. *J. Am. Chem. Soc.* **2000**, 122, 7621–7632.

4. Ohtsuki, T.; Kimoto, M.; Ishikawa, M.; Mitsui, T.; Hirao, I.; Yokoyama, S. Unnatural base pairs for specific transcription. *Proc. Natl Acad. Sc. USA* **2001**, 98, 4922–4925.
5. Rappaport, H.P. Replication of the base pair 6-thioguanine: 5-methyl-2-pyrimidinone with the large Klenow fragment of Escherichia coli DNA polymerase-I. *Biochemistry* **1995**, 32, 3047–3057.
6. Hirao, I. Unnatural base pair systems for DNA/RNA-based biotechnology. *Curr. Opin. Chem. Biol.* **2006**, 10, 622–627.
7. Wellington, K.W.; Benner, S.A. A review: Synthesis of aryl C-glycosides via the Heck coupling reaction. *Nucleosides, Nucleotides Nucleic Acids* **2006**, 25, 1309–1333.
8. Lee, A.H.F.; Kool, E.T. Novel benzopyrimidines as widened analogues of DNA bases. *J. Org. Chem.* **2005**, 70, 132–140.
9. Sismour, A.M.; Benner, S.A. Synthetic biology. *Exp. Opin. Biol. Ther.* **2005**, 5, 1409–1414.
10. Gleaves, C.A.; Welle, J.; Campbell, M.; Elbeik, T.; Ng, V.; Taylor, P.E.; Kuramoto, K.; Aceituno, S.; Lewalski, E.; et al. Multicenter evaluation of the Bayer VERSANT (TM) HIV-1 RNA 3.0 assay: Analytical and clinical performance. *J. Clin. Virol.* **2002**, 25, 205–216.
11. Elbeik, T.; Surtihadi, J.; Destree, M.; Gorlin, J.; Holodniy, M.; Jortani, S.A.; Kuramoto, K.; Ng, V.; Valdes, R.; et al. Multicenter evaluation of the performance characteristics of the Bayer VERSANT HCV RNA 3.0 assay (bDNA). *J. Clin. Microbiol.* **2004**, 42, 563–569.
12. Johnson, S.C.; Marshall, D.J.; Harms, G.; Miller, C.M.; Sherrill, C.B.; Beaty, E.L.; Lederer, S.A.; Roesch, E.B.; Madsen, G.; et al. Multiplexed genetic analysis using an expanded genetic alphabet. *Clin. Chem.* **2004**, 50, 2019–2027.
13. Benner, S.A. Understanding nucleic acids using synthetic chemistry. *Acc. Chem. Res.* **2004**, 37, 784–797.
14. Geyer, C.R.; Battersby, T.R.; Benner, S.A. Nucleobase pairing in Watson-Crick-like genetic expanded information systems. *Structure* **2003**, 11, 1485–1498.
15. Rao, P.; Benner, S.A. Fluorescent charge-neutral analogue of xanthosine: Synthesis of a 2′-deoxyribonucleoside bearing a 5-aza-7-deaza-xanthine base. *J. Org. Chem.* **2001**, 66, 5012–5015.
16. Chu, C.K.; Reichman, U.; Watanabe, K.A.; Fox, J.J. Synthesis of 4-amino-5-(D-ribofuranosyl) pyrimidine C-nucleosides from 2-(2,3-0-Isopropylidene-5-0- trityl-D-ribofuranosyl)acetonitrile. *J. Org. Chem.* **1977**, 42, 711–714.
17. Larsen, E.; Jorgensen, P.T.; Sofan, M.A.; Pedersen, E.B. A new and easy synthesis of silylated furanoid glycals in one step from nucleosides. *Synthesis* **1994**, 1037.
18. Walker, J.A.; Chen, J.J.; Wise, D.S.; Townsend, L.B. A facile, multigram synthesis of ribofuranoid glycals. *J. Org. Chem.* **1996**, 61, 2219–2221.
19. Cameron, M.A.; Cush, S.B.; Hammer, R.P. Facile preparation of protected furanoid glycals from thymidine. *J. Org. Chem.* **1997**, 62, 9065–9069.
20. Chen, D.L.; McLaughlin, L.W. Use of pKa differences To enhance the formation of base triplets involving C-G and G-C base pairs. *J. Org. Chem.* **2000**, 65, 7468–7474.
21. Chen, J.J.; Walker, J.A., II; Liu, W.; Wise, D.S.; Townsend, L.B. An efficient and stereospecific synthesis of novel pyrazine *C*-nucleosides. *Tetrahedron Lett.* **1995**, 36, 8363–8366.
22. Hsieh, H-P.; McLaughlin, L.W. Syntheses of two pyridine *C*-nucleosides as "deletion-modified" analogs of dT and dC. *J. Org. Chem.* **1995**, 60, 5356–5359.
23. Fraley, A.W.; Chen, D.; Johnson, K.; McLaughlin, L.W. An HIV reverse transcriptase-selective nucleoside chain terminator. *J. Am. Chem., Soc.* **2003**, 125, 616–617.
24. Hutter, D.; Benner, S.A. Expanding the genetic alphabet: non-epimerizing nucleoside with the *py*DDA hydrogen-bonding pattern. *J. Org. Chem.* **2003**, 68, 9839–9842.
25. Vorbrüggen, H.; Krolikiewicz, K. Amination, III. Trimethylsilanol as leaving group, V. Silylation-amination of hydroxy *N*-heterocycles. *Chem. Ber.* **1984**, 117, 1523–1541.
26. Ram, S.; Spicer, L.D. Debenzylation of *N*-benzylamino derivatives by catalytic transfer hydrogenation with ammonium formate. *Synth. Commun.* **1987**, 17, 415–418.
27. Felix, A.M.; Heimer, E.P.; Lambros, T.J.; Tzougraki, C.; Meienhofer, J. Rapid removal of protecting groups from peptides by catalytic transfer hydrogenation with 1,4-cyclohexadiene. *J. Org. Chem.* **1978**, 43, 4194–4196.
28. Lan, T.; McLaughlin, L.W. Minor groove hydration is critical to the stability of DNA duplexes. *J. Am. Chem. Soc.* **2000**, 122, 6512–6513.