Nucleic Acid Related Compounds. 93. A Solution for the Historic Problem of Regioselective Sugar−Base Coupling To Produce 9-Glycosylguanines or 7-Glycosylguanines[1]

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Per(trimethylsilyl)-2-*N*-acylguanine derivatives and tetra-*O*-acylpentofuranoses were coupled [tin(IV) chloride or titanium(IV) chloride catalysis] to give predominant formation of 7-glycosylguanines. With $TiCl_4$, a fortuitous organic/aqueous partitioning allowed isolation of 7-glycosylguanines from the 7/9 isomer mixtures. Per(trimethylsilyl)-2-*N*-acyl-6-*O*-(diphenylcarbamoyl)guanine derivatives and tetra-*O*-acylpentofuranoses underwent regioselective coupling (trimethylsilyl trifluoromethanesulfonate catalysis) to give 9-glycosylguanines. The 6-*O*-(diphenylcarbamoyl)peracyl-9-*β*-D-ribofuranosyl isomer was shown to be both the kinetic *and* thermodynamic coupling product. Deprotection of all of the peracyl coupling products was effected under mild conditions to give good to high yields of guanine nucleoside analogues. These methodologies provide solutions for the regioselective synthesis of 7- and 9-glycosylguanine nucleosides.

Introduction

The most problematic chemistry and greatest difficulties with manipulation of the five common bases found in DNA and RNA occurs with the polyfunctional guanine (pK_{a1} ~1.7, pK_{a2} ~9.2) nucleosides and nucleotides. Coupling of guanine-type bases with protected sugar derivatives produces N7/N9 isomeric mixtures of nucleosides that are frequently difficult to separate.[2,3] Coupling of "directly protected" derivatives of guanine have consistently produced 7/9 isomer mixtures, whereas constriction of the guanine system into "6-enolate" derivatives can result in enhancement of 9/7 isomer ratios.[3] The Vorbrüggen procedures overcame many difficulties with base−sugar couplings, and high regioselectivities were obtained with most bases. It was reported that coupling per(trimethylsilyl)-2-*N*-acetylguanine and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranose [trimethylsilyl trifluoromethanesulfonate (TMSOTf) catalysis] at elevated temperature, followed by deprotection and recrystallization, afforded pure guanosine (66%).[4]

However, Dudycz and Wright observed that 7-isomers were formed as kinetic products of glycosylation of per(trimethylsilyl)-2-*N*-(substituted)guanines, and mixtures rich in the more thermodynamically stable 9-isomers were obtained upon heating.[5] Garner and Ramakanth also found that coupling of glycosyl acetates with per(trimethylsilyl)-2-*N*-acetylguanine gave 7-glycosyl products (7/9, ~95:1 with a ribose derivative) under kinetic conditions ($SnCl_4/CH_3CN$/room temperature), whereas 9-isomers predominated (7/9, ~1:6) under thermodynamic conditions (TMSOTf/1,2-dichloroethane (DCE)/Δ).[6] Similar results (with variable isomer ratios) have been observed by others.[7,8] It was recently suggested that initial glycosylation of 2-*N*-acetylguanine and 2-*N*,9-diacetylguanine occurs at the unsubstituted imidazole ring nitrogen. Reversible 7/9 acetyl tautomerization and transglycosylation occur under different reaction conditions to give observed product ratios.[9] It is undisputed that Vorbrüggen's procedure[4] gives naturally occurring guanosine in good yields by fortuitous crystallization of the 9-isomer from aqueous solutions of the 7/9 mixtures.[3,10] However, this facile fractional crystallization has not been demonstrated with other analogues derived from different sugars or with biologically relevant acyclic side chains such as the (2-hydroxyethoxy)methyl moiety of acyclovir and related antiviral agents.

We now report studies on regioselective kinetic formation of 7-(D-pentofuranosyl)guanine derivatives by ambient temperature coupling of per(trimethylsilyl)-2-*N*-acetylguanine and tetra-*O*-acetyl-D-pentofuranoses [tin(IV) chloride or titanium(IV) chloride catalysis]. With $TiCl_4$, fortuitousorganic/aqueous partitioning resulted in isola-

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(10) (a) Zou, R.; Robins, M. J. *Can. J. Chem.* **1987**, *65*, 1436. (b) Zou, R. Ph.D. Dissertation, University of Alberta, 1986. (c) ^{13}C NMR correlations for 7/9 isomer structures and examples of couplings to give anomeric 2′-deoxyguanosines and arabino analogues are in ref 10b. (d) Difficulties were encountered during preliminary investigations with preparation of and/or coupling reactions with derivatives of 2-amino-6-[benzyloxy, (dimethylcarbamoyl)oxy, (2,4,6-triisopropylbenzenesulfonyl)oxy, and 2-(4-nitrophenyl)ethoxy]purine[10b] and derivatives of 2-amino-6-(alkyl and aryl)thiopurines, their sulfone oxidation products, and 2-amino-6-[(diisopropylcarbamoyl)oxy]purine (Zou, R.; Guo, Z. unpublished results).

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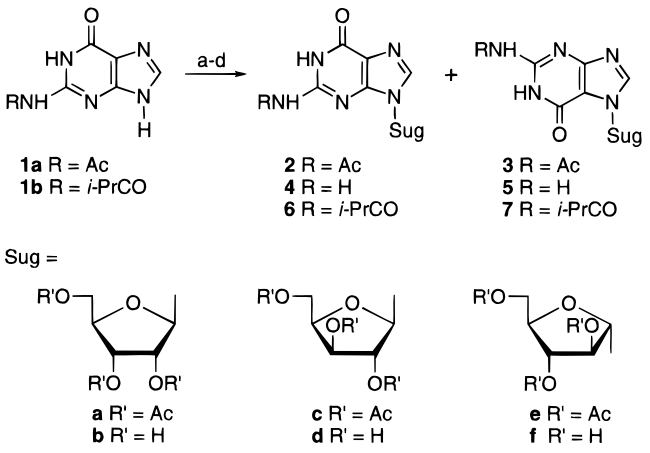
Scheme 1[a]



[a] Key: (a) BSA/DCE/Δ; (b) TMSOTf or $SnCl_4$ or $TiCl_4$; (c) 1,2,3,5-tetra-*O*-acetyl-D-pentofuranose; (d) NH_3/H_2O/MeOH/Δ.

tion of 7-isomers. We also have developed glycosyl couplings with per(trimethylsilyl)-2-*N*-acetyl-6-*O*-(diphenylcarbamoyl)guanine (TMSOTf catalysis) to give high-yield preparations of 9-(D-pentofuranosyl)guanines, without contamination by 7-isomers,[10] and a completely regioselective synthesis of guanosine with per(trimethylsilyl)-2-*N*-isobutyryl-6-*O*-(diphenylcarbamoyl)guanine and 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose.

Results and Discussion

Trimethylsilylation of 2-*N*-acetylguanine[11] (**1a**) [hexamethyldisilazane (HMDS)/$(NH_4)_2SO_4$] and coupling of the derivative [tris(trimethylsilyl)] with 1,2,3,5-tetra-*O*-acetyl- (or 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl)-β-D-ribofuranose under Vorbrüggen's conditions[4a] [TMSOTf/DCE/80 °C overnight] gave mixtures of protected guanosine **2a** and its 7-isomer **3a** (or the 2′,3′,5′-tri-*O*-benzoyl derivatives) (2-5:1, respectively)[6,10b] in high yields (Scheme 1). Analogous coupling with the 1,2,3,5-tetra-*O*-acetyl-D-xylo- and -arabinofuranose derivatives gave similar mixtures of 9/7-isomers (**2c**/**3c** and **2e**/**3e**).[10b] Workup conditions alter the relative amounts of minor isomers retained, especially when emulsions result with $SnCl_4$ catalysis. Small differences in integrated intensity measurements (^{1}H NMR) for the minor-isomer peaks cause amplified differences in normalized isomer ratios since the values for the minor isomers are in the denominator. However, the relative percentages reported for major and minor isomers are quite similar.[3a,5−8,10]

Treatment of a suspension of **1a** with bis(trimethylsilyl)acetamide (BSA)/DCE/80 °C gave a solution that was then cooled, and ≥2 equiv of $SnCl_4$ was added to give an active organometallic complex. A solution of the respective tetra-*O*-acetylpentofuranose in DCE was added to this complex, and the mixture was stirred overnight at ambient temperature. ^{1}H NMR analysis of crude coupling mixtures indicated *maximum* normalized 7/9 isomer ratios of ∼13:1 (**3a**/**2a**), ∼15:1 (**3c**/**2c**), and ∼18:1 (**3e**/**2e**). Ratios varied somewhat, but isolated yields of the 7-isomers were quite consistent when emulsions were allowed to separate adequately. Flash chromatography gave purified 7-isomers **3a** (70%), **3c** [76%; plus the isolated 9-isomer **2c** (3%)], and **3e** (72%). Deprotection (NH_3/H_2O/MeOH) and crystallization gave analytically pure hemihydrates of the 7-(D-pentofuranosyl)guanines **5b** (78%, β-ribo), **5d** (86%, β-xylo), and **5f** (85%, α-arabino).

Analogous coupling of silylated 2-*N*-isobutyrylguanine[12] (**1b**) with the tetra-*O*-acetyl ribo- and xylofuranose derivatives in CH_3CN or DCE with $TiCl_4$ as catalyst resulted in isolation of the 7-isomers **7a** and **7c** in moderate yields (43−67%, after workup and chromatography) without detected contamination by the 9-isomers **6a** and **6c**. We were surprised to discover that only the 7-isomers were isolated after the initial reaction mixtures were heated at 80 °C for 3 h. However, the aqueous layers after workup contained 7/9 isomer mixtures. Apparently, stronger complexation between the guanine base and $TiCl_4$ (and/or hydrolysis products) occurs with the 9-isomers, which results in clean partitioning of the 9-regioisomers **6a** and **6c** into the water layer. It is noteworthy, in harmony with prior results,[6] that solvent and reaction temperature changes failed to alter the 7/9 isomer compositions significantly. Therefore, acceleration of the coupling reaction rate by reflux and fortuitous enhanced partitioning of the 9-isomers into the aqueous layer provides a convenient selective procedure for preparation of the 7-isomers **7a** and **7c**. Deprotection of **7a** and **7c** and crystallization gave the hemihydrates of **5b** (78%) and **5d** (76%), respectively.

Literature precedents indicated that coupling of 2,6-disubstituted purines with protected sugars generally gave enhanced 9/7 isomer ratios, and the 9-isomer was sometimes the only product isolated.[3,13] We reasoned that nucleoside regioisomers derived from appropriate "lactim" structures (masked guanine precursors) might have sufficiently different thermodynamic stabilities to strongly favor formation of the 9-isomer. Attachment of a bulky electron-withdrawing group at O6 of **1** (peri to N7) might also favor kinetic coupling at N9 to directly produce the more thermodynamically stable regioisomer. Several 2-amino-6-(substituted)purine derivatives were prepared and subjected to coupling with glycosyl acetate derivatives.[10d] We found that 2-*N*-acetyl-6-*O*-(diphenylcarbamoyl)guanine (**8a**, Scheme 2), prepared readily from guanine in high yield, gave excellent results in coupling reactions under controlled conditions.[10] The 6-*O*-(diphenylcarbamoyl) (DPC) group was quite stable in aprotic coupling media and was removed by mild deacylation procedures. It is *crucial* to avoid cleavage of the (diphenylcarbamoyl)oxy function during coupling reactions, since the resulting 2-*N*-acetylguanine derivatives give 7/9 isomer mixtures (vide supra). Treatment of 2-*N*,9-diacetylguanine[10a] with DPC chloride/ethyldiisopropylamine/pyridine at ambient temperature[14] followed by solvolysis of the 9-acetyl group[11] gave crystalline 2-*N*-acetyl-6-*O*-(diphenylcarbamoyl)guanine (**8a**, 92%).

Per(trimethylsilyl)-**8a** (BSA/DCE) and tetra-*O*-acetylribofuranose (1.2 equiv) were coupled (TMSOTf/*anhydrous* toluene/80 °C/1 h) to give 9-isomer **9a** (91% after chromatography). No 7-isomer was detected (^{1}H NMR) in purified **9a**, or in the crude coupling mixture, but a

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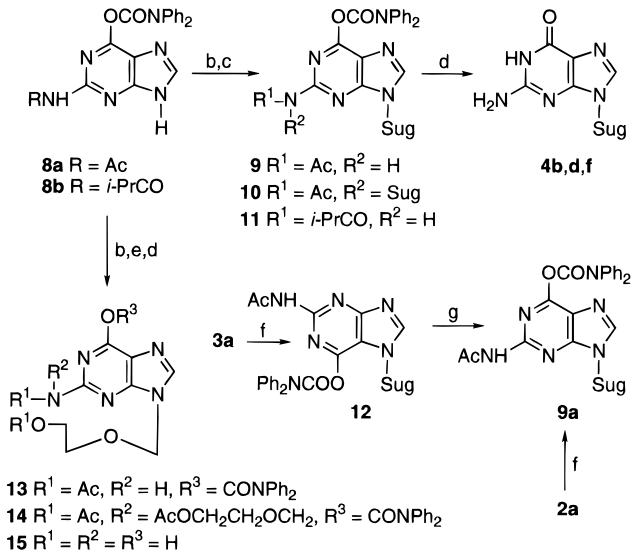
Scheme 2[a]



[a] Key: (a) the structures of "Sug" are in Scheme 1; (b) BSA/DCE/Δ; (c) 1,2,3,5-tetra-*O*-acetyl-D-pentofuranose/TMSOTf/toluene/Δ; (d) NH_3/H_2O/MeOH/D; (e) $AcOCH_2CH_2OCH_2Br$/toluene; (f) $Ph_2NCOCl/EtN(i\text{-}Pr)_2$/pyridine; (g) TMSOTf/toluene/Δ.

trace byproduct **10a** (second sugar residue at N2) was present. Excess (2.5 equiv) tetra-*O*-acetylribofuranose gave enhanced formation of the bis(ribosyl) byproduct **10a**, whose composition was analyzed by NMR and FAB MS. Coupling of the tetra-*O*-acetyl derivatives of xylose and arabinose produced **9c** (86%, 9-β) and **9e** (82%, 9-α), respectively. Trace bis(glycosyl) byproducts were detected, and **10c** was isolated (4%) in one experiment, but no 7-isomers were observed. The ^{1}H-coupled ^{13}C NMR spectrum of the bis(xylosyl) byproduct **10c** had three-bond coupling to C2 of the guanine base in harmony with attachment of the second sugar residue at N2. Deprotection (NH_3/H_2O/MeOH/60 °C) of **9a**, **9c**, and **9e** and crystallization gave analytically pure hemihydrates of guanosine (**4b**, 75%), **4d** (67%), and **4f** (84%), respectively. Analogous treatment of **10c** gave **4d**. This demonstrated that the bis(sugar) byproduct was cleaved during deprotection and did not interfere with overall regioselective production of the desired 9-isomer.

Treatment[14] of 2-*N*-acetyl-2′,3′,5′-tri-*O*-acetylguanosine (**2a**) with DPC chloride gave a compound that was identical to the coupling product **9a**. This verified the same site of attachment of the DPC group, and X-ray crystallographic analysis of **13** proved that site to be O6.[10a,b]

We considered that a more bulky acyl group on N2 might impede formation of the bis(sugar) byproduct. Guanine was readily converted into 2-*N*-isobutyryl-6-*O*-(diphenylcarbamoyl)guanine (**8b**, 87%). Coupling of per(trimethylsilyl)-**8b** and tetra-*O*-acetylribofuranose under standard conditions gave the 9-isomer **11a** (89%). No bis(sugar) byproduct, or 7-isomer, was detected in crude coupling mixtures or in a control reaction with excess sugar derivative. Deprotection (NH_3/H_2O/MeOH/60 °C) of **11a** gave **4b** (80%).

We then investigated mechanistic aspects of this synthesis. Diphenylcarbamoylation of synthetic tetraacetyl 7-isomer **3a** occurred without difficulty to give the corresponding 6-*O*-DPC derivative **12a**. Treatment of **12a** by the standard coupling conditions (TMSOTf/anhydrous toluene/80 °C) required ~2 h for its complete rearrangement to the 9-glycosyl isomer **9a**. Stirring a solution of per(trimethylsilyl)-**8a**, tetra-*O*-acetylribofuranose, and TMSOTf in anhydrous toluene at ambient temperature for 4 days resulted in progressive formation of the 9-glycosyl isomer **9a**, without observed formation of its 7-isomer **12a**. These two experiments indicate that 9-isomer **9a** is both the kinetic and thermodynamic product. Absence of detected 7-isomer **12a** in the ambient temperature coupling indicates kinetic formation of **9a**, and this also is supported indirectly by the longer time (~2 h) required for the rearrangement of **12a** → **9a** at 80 °C relative to the standard N9 glycosylation (1 h). Complete isomerization of **12a** → **9a** under the standard coupling conditions, however, demonstrated the enhanced thermodynamic stability (**9a** ≫ **12a**) of the 9-isomer of this 6-*O*-DPC pair relative to that of the 6-oxo pair (**2a** > **3a**).

The broader generality of our methodology was demonstrated by coupling per(trimethylsilyl)-**8a** and (2-acetoxyethoxy)methyl bromide[15a] at 80 °C in *anhydrous* toluene (no catalyst required). The "acyclovir"[15] derivative **13** (63%) was produced plus traces of the 2-*N*,9-bis(acetoxyethoxymethyl) byproduct **14**. Deprotection of **13** and crystallization gave the hemihydrate of acyclovir (**15**, 91%).

In summary, we have discovered a fortuitous organic/aqueous partitioning that allows isolation of 7-glycosylguanines from 7/9 isomer mixtures obtained by coupling per(trimethylsilyl)-2-*N*-acylguanine derivatives and tetra-*O*-acylpentofuranoses ($TiCl_4$ catalysis). A completely regioselective synthesis of 9-glycosylguanine isomers has been developed by coupling per(trimethylsilyl)-2-*N*-acyl-6-*O*-(diphenylcarbamoyl)guanine derivatives and tetra-*O*-acylpentofuranoses (TMSOTf catalysis). The protected 9-isomer, 2-*N*-acetyl-2′,3′,5′-tri-*O*-acetyl-6-*O*-(diphenylcarbamoyl)guanosine (**9a**), was shown to be both the kinetic and thermodynamic coupling product. Quantitative deprotection of all of the per(acyl) coupling products occurred under mild conditions to give good to high yields (recrystallization recovery) of guanine nucleoside analogues. These methodologies provide generally applicable solutions to the prior absence[2–9] of demonstrated regioselective syntheses of 7- and 9-glycosylguanine nucleosides in the cases we have investigated.

Experimental Section

Uncorrected melting points were obtained with a hot stage apparatus. UV spectra were determined with solutions in MeOH unless otherwise noted. Table 1 (^{1}H) and Table 2 (^{13}C) contain NMR spectral data (solutions in Me_4Si/Me_2SO-d_6). Mass spectra (EI MS, CI, FAB) were determined with direct probe techniques at 20 or 70 eV. Solvents were purified, dried (CaH_2 or $LiAlH_4$), and distilled before use. Pyridine was dried by refluxing with and distillation from CaH_2. Reagent-grade chemicals were used without further purification. TLC was performed with silica gel 60 F_{254} sheets, and silica gel (200–425 mesh) was used for column chromatography. General "*procedures*" are illustrated with specific examples and can be applied to other compounds with minor noted modifications.

2-*N*-Acetyl-2′,3′,5′-tri-*O*-acetylguanosine (2a). Guanosine (**4b**; 283 mg, 1 mmol) was acetylated as described[14] (Ac_2O: 1.42 mL, 1.54 g, 15 mmol) to give a residue that was chromatographed ($CHCl_3$ → 3% MeOH/$CHCl_3$) to give **2a** (255

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Table 1. ^{1}H NMR Spectral Data[a,b]

compd	H1′[c] ($J_{1'-2'}$)	H2′[d] ($J_{2'-3'}$)	H3′[d] ($J_{3'-4'}$)	H4′[e] ($J_{4'-5',5''}$)	H5′,5″[e] ($J_{5'-5''}$)	H8[f]	(N^{1}H or N^{2}H)[g]	others[f]
2c	5.97 (3.0)	5.58[h] (2.5)	5.52 (4.5)	4.56 (4.5, 7.0)	4.28−4.56 (11.5)	8.18	11.70, 12.10	2.02, 2.08, 2.10, 2.18 (Ac's)
3a	6.31 (6.0)	5.80[h] (6.0)	5.44 (5.0)	4.32 (4.0, 6.0)	4.24[d] (12.0)	8.52	11.66, 12.24	2.04, 2.11, 2.17 (Ac's)
3c	6.36 (3.0)	5.58[h] (2.5)	5.48 (4.5)	4.61 (4.5, 7.0)	4.34 (12.0)	8.40	11.63, 12.20	2.05, 2.06, 2.10 2.18 (Ac's)
3e	6.36 (5.0)	5.93 (5.0)	5.37 (6.0)	4.83 (3.5, 6.0)	4.18,[d] 4.28[d] (12.0)	8.44	11.66, 12.23	2.03, 2.04, 2.06, 2.16 (Ac's)
5b	5.98 (5.5)	4.36[e] (5.5)	4.07[e] (4.0)	3.89 (4.0, 4.0)	3.53, 3.66 (12.0)	8.30	10.96, 6.25	5.01,[h] 5.10,[c] 5.36,[c] (OH's)
5d	6.08 (1.0)	4.23[e] (1.5)	4.01[e] (3.5)	4.15 (5.0, 6.5)	3.67, 3.74 (12.0)	8.12	10.98, 6.25	4.73,[h] 5.45,[c] 5.80[c] (OH's)
5f	5.91 (5.0)	4.49[e] (5.5)	3.93 (6.5)	4.19 (3.5, 5.5)	3.47, 3.58 (12.0)	8.16	10.92, 6.24	4.84, 5.45, 5.68 (OH's)
7a	6.30 (6.0)	5.80 (6.5)	5.44 (6.0)	4.19−4.44	4.19−4.44 (11.0)	8.51	11.62, 12.24	1,11,[c] 2.74[i] (*i*-Pr), 2.03, 2.10 (Ac's)
7c	6.37 (3.0)	5.58[h] (2.5)	5.49 (5.0)	4.62[d] (5.0, 5.0)	4.34[c]	8.41	11.24, 11.63	1.13,[c] 2.76[i] (*i*-Pr), 2.05, 2.11 (Ac's)
9a	6.26 (5.0)	5.95[h] (5.5)	5.78[h] (5.5)	4.38 (3.5, 6.0)	4.33,[d] 4.43[d] (11.0)	8.61	10.77	1.99, 2.05, 2.12, 2.18 (Ac's), 7.28−7.54[e] (Ph_2)
9c	6.18 (3.5)	5.81[h] (2.5)	5.55 (4.5)	4.61 (4.0, 7.0)	4.29 (12.0)	8.59	10.74	2.01, 2.09, 2.10, 2.22 (Ac's), 7.28−7.56[e] (Ph_2)
9e	6.32 (4.0)	6.04[h] (5.0)	5.40 (6.5)	5.00 (3.5, 5.5)	4.20,[d] 4.32[d] (12.0)	8.59	10.76	2.04, 2.22 (Ac's), 7.26−7.56[e] (Ph_2)
11a	6.29 (5.0)	5.99[h] (5.5)	5.80 (6.0)	4.34−4.48 (4.0, 4.0)	4.34−4.48 (12.0)	8.66	10.78	1.11,[c] 2.81[i] (*i*-Pr), 2.01, 2.10, 2.25 (Ac's), 7.36−7.61[e] (Ph_2)
12a	6.09 (6.0)	5.68[h] (6.5)	5.44[h] (4.5)	4.47 (3.5, 6.0)	4.21,[d] 4.32[d] (12.0)	8.91	10.70	1.95, 2.00, 2.16, 2.20 (Ac's), 7.30−7.65[e] (Ph_2)

[a] Chemical shifts (δ; 400 or 200 MHz). [b] "Apparent" first-order coupling constants (Hz; in parentheses). [c] Doublet unless otherwise noted. [d] Doublet of doublets unless otherwise noted. [e] Multiplet unless otherwise noted. [f] Singlet unless otherwise noted. [g] Broad singlet. [h] Triplet. [i] Septet.

Table 2. ^{13}C NMR[a,b]

compd	C2	C4	C5	C6	C8	C1′	C2′	C3′	C4′	C5′
2c[c]	147.97	148.33	119.81	154.50	136.98	85.58	78.82	73.86	77.74	60.92
3a[c]	147.35	158.26	110.49	152.07	143.85	87.50	73.00	69.58	79.40	62.79
3c[c]	147.00	157.35	110.55	152.10	142.02	88.16	79.35	73.89	77.96	60.96
3e[c]	147.48	158.42	110.45	152.48	143.80	88.18	79.01	74.54	79.86	63.08
5b	152.87	160.63	107.67	154.31	142.36	89.10	74.39	69.69	85.17	61.12
5d	152.60	159.98	107.41	154.36	141.75	91.11	81.39	75.11	83.44	59.31
5f	152.83	160.66	107.49	154.28	142.44	90.33	80.26	75.03	84.82	61.13
7a[c,d]	148.01	158.66	110.84	152.46	144.45	87.78	73.32	69.93	79.77	63.27
7c[c,d]	147.76	157.87	111.00	152.63	142.73	89.69	79.73	74.27	78.54	61.64
9a[c,e]	152.16	153.98	120.26	155.25	144.10	86.27	72.16	70.25	79.76	63.04
9c[c,e]	152.33	154.23	119.69	155.12	143.18	86.15	78.25	73.98	77.69	61.11
9e[c,e]	152.18	153.99	120.09	155.18	143.95	86.71	78.26	74.87	80.18	62.56
11a[c−e]	152.69	154.49	120.84	155.57	144.60	86.29	72.58	70.74	80.29	63.54
12a[c,e]	149.19	164.84	110.59	152.33	147.73	87.21	72.86	69.87	80.00	62.95

[a] Chemical shifts (δ; 100 or 50 MHz). [b] Proton-decoupled singlets. [c] Also peaks at δ 19.80−24.40 and 168.50−173.50 (Ac's). [d] Also peaks at δ 19.00−19.20, 34.90−35.10, and 175.00−180.40 (*i*-PrCO). [e] Also peaks at δ 126.60−141.80 and 149.70−150.40 (Ph_2NCO).

mg, 57%; white foam): MS *m*/*z* 451.1348 (11, $M^+[C_{18}H_{21}N_5O_9]$ = 451.1339) with spectral data as reported.[16]

7-(β-D-Ribofuranosyl)guanine (5b). Method A. Procedure A. A suspension of 2-*N*-acetylguanine[11] (**1a**; 193 mg, 1 mmol) and BSA (0.5 mL, 407 mg, 2 mmol) in dried DCE (10 mL) was stirred in a stoppered flask at 80 °C until a clear solution was obtained (∼2.5 h). The solution was cooled, $SnCl_4$ (0.25 mL, 550 mg, 2.1 mmol) was added, and stirring was continued at ambient temperature for 30 min. A solution of tetra-*O*-acetyl-β-D-ribofuranose (350 mg, 1.1 mmol) in DCE (5 mL) was added, and stirring was continued for 1 day. MeOH (5 mL) was added, the reaction mixture was diluted with $CHCl_3$ (50 mL), and the solution was washed [brine (50 mL), saturated $NaHCO_3/H_2O$ (50 mL × 2), brine (50 mL)]. The organic layer was dried (Na_2SO_4) and filtered, and the filtrate was evaporated. The residue was chromatographed (Et_2O → 10% MeOH/Et_2O) to give 2-*N*-acetyl-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)guanine (**3a**; 317 mg, 70%; white foam) with data as reported:[6] UV max 263 nm; MS *m*/*z* 451.1331 (6, $M^+[C_{18}H_{21}N_5O_9]$ = 451.1339).

Method B. Procedure B. A suspension of 2-*N*-isobutyrylguanine[12] (**1b**; 221 mg, 1 mmol) and BSA (0.5 mL, 407 mg, 2 mmol) in dried CH_3CN (15 mL) was heated at 80 °C under argon until a clear solution was obtained (∼1.5 h). The solution was cooled to ambient temperature, $TiCl_4$ (0.23 mL, 398 mg, 2.1 mmol) was added, and stirring was continued for 30 min. A solution of tetra-*O*-acetyl-β-D-ribofuranose (350 mg, 1.1 mmol) in dried CH_3CN (8 mL) was added, the reaction mixture was heated at 80 °C for 3 h and cooled to ambient temperature, and MeOH (5 mL) was added. Volatiles were evaporated, and the residue was dissolved (EtOAc, 150 mL). The solution was washed [brine (50 mL), saturated $NaHCO_3/H_2O$ (2 × 50 mL), brine (50 mL)], dried (Na_2SO_4), and chromatographed (3% MeOH/EtOAc) to give 7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-2-*N*-isobutyrylguanine (**7a**; 320 mg, 67%; white foam): UV max 264 nm (ε 13 600); MS (FAB) *m*/*z* 480.1728 (100, $MH^+[C_{20}H_{26}N_5O_9]$ = 480.1731).

Analogous coupling with **1b** ($TiCl_4$/DCE) and workup gave **7a** (43%). Combined aqueous wash layers were evaporated,

(16) Reese, C. B.; Saffhill, R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2937.

and the residue was subjected to procedure C. Volatiles were evaporated, and the residue was extracted (MeOH). The combined extracts were evaporated, and the residue was crystallized (H_2O) to give **4b**/**5b** (~1.5:1, 29%). Treatment of **1b** by procedure A (with $TiCl_4$ as catalyst instead of $SnCl_4$) gave **7a**/**6a** (~16:1, 44%).

Deprotection. Procedure C. A solution of **3a** (451 mg, 1 mmol) in NH_3/MeOH (20 mL; saturated at −10 °C) in a sealed flask was stirred at ambient temperature for 24 h. Volatiles were evaporated, and the residue was washed (2 × $CHCl_3$) and then crystallized (H_2O) to give **5b** hemihydrate (228 mg, 78%): mp ~275 °C dec (lit.[17] mp 230−260 °C dec, lit.[6] mp 298 °C dec); UV (H_2O) max 286 nm (ϵ 6800); MS *m*/*z* 283.0910 (1, $M^+[C_{10}H_{13}N_5O_5]$ = 283.0917), (FAB) *m*/*z* 284 (12, MH^+).

Analogous treatment of **7a** (240 mg, 0.5 mmol) [the residue was dissolved (H_2O), the solution was washed ($CHCl_3$), the aqueous layer was evaporated, and the residue was crystallized (H_2O)] gave **5b** hemihydrate (110 mg, 78%) with identical data.

7-(β-D-Xylofuranosyl)guanine (5d). Method A. Tetra-*O*-acetyl-D-xylofuranose (350 mg, 1.1 mmol) was subjected to procedure A to give a residue that was chromatographed ($CHCl_3$ → 2% MeOH/$CHCl_3$) to give 2-*N*-acetyl-7-(2,3,5-tri-*O*-acetyl-β-D-xylofuranosyl)guanine (**3c**; 341 mg, 76%; white foam): UV max 264 nm; MS *m*/*z* 451.1338 (9, $M^+[C_{18}H_{21}N_5O_9]$ = 451.1339). Further elution gave 2-*N*-acetyl-9-(2,3,5-tri-*O*-acetyl-β-D-xylofuranosyl)guanine (**2c**; 13 mg, 3%): UV max 258 and 280 nm.

Method B. Treatment of **1b** (1 mmol) and tetra-*O*-acetyl-β-D-xylofuranose (350 mg, 1.1 mmol) by procedure B gave 7-(2,3,5-tri-*O*-acetyl-β-D-xylofuranosyl)-2-*N*-isobutyrylguanine (**7c**; 56% with CH_3CN; 59% with DCE): UV max 264 nm (ϵ 12 900); MS (FAB) *m*/*z* 480.1725 (100, $MH^+[C_{20}H_{26}N_5O_9]$ = 480.1731).

Deprotection. Procedure D. NH_3/H_2O (28−30%; 20 mL) was added to a stirred solution of **3c** (451 mg, 1 mmol) in MeOH (20 mL). The flask was sealed and heated at 60 °C for 1 day. Volatiles were evaporated, and the residue was washed (2 × $CHCl_3$) and crystallized (H_2O) to give **5d** hemihydrate (251 mg, 86%; two crops): mp ~285 °C dec (Lit.[8a] mp > 220 °C dec); UV (H_2O) max 285 (ϵ 7300); MS (FAB) *m*/*z* 284 (26, MH^+). Anal. Calcd for $C_{10}H_{13}N_5O_5 \cdot 0.5H_2O$: C, 41.10; H, 4.83; N, 23.96. Found: C, 41.01; H, 4.58; N, 23.78.

Deprotection of **7c** (479 mg, 1 mmol) by procedure C and crystallization (H_2O) gave **5d** (215 mg, 76%; white powder) with identical data.

7-(α-D-Arabinofuranosyl)guanine (5f). Tetra-*O*-acetyl-D-arabinofuranose (350 mg, 1.1 mmol) was subjected to procedure A to give a residue that was chromatographed (Et_2O → 10% MeOH/Et_2O) to give 2-*N*-acetyl-7-(2,3,5-tri-*O*-acetyl-α-D-arabinofuranosyl)guanine (**3e**; 326 mg, 72%; white foam): UV max 263 nm; MS *m*/*z* 451.1328 (4, $M^+[C_{18}H_{21}N_5O_9]$ = 451.1339). Deprotection of **3e** (451 mg, 1 mmol) by procedure C and crystallization (H_2O) gave **5f** hemihydrate (249 mg, 85%): mp 250 °C dec; UV (H_2O) max 286 nm (ϵ 7500); MS (FAB) *m*/*z* 284 (12, MH^+). Anal. Calcd for $C_{10}H_{13}N_5O_5 \cdot 0.5H_2O$: C, 41.10; H, 4.83; N, 23.96. Found: C, 41.35; H, 4.83; N, 24.18.

2-*N*-Acetyl-6-*O*-(diphenylcarbamoyl)guanine (8a). Procedure E. Diphenylcarbamoyl chloride (6.37 g, 2.75 mmol) was added portionwise to a suspension of 2-*N*,9-diacetylguanine[10a] (5.88 g, 25 mmol) in $EtN(i\text{-}Pr)_2$ (8.7 mL, 6.46 g, 50 mmol) and dried pyridine (120 mL), and stirring was continued at ambient temperature for 1 h. H_2O (10 mL) was added, stirring was continued for 10 min, and volatiles were evaporated. The residue was coevaporated (toluene, 3 × 20 mL) and then was heated (steam bath) with EtOH/H_2O (1:1, 300 mL) for 1.5 h. The cooled suspension was filtered, and the product was washed (98% EtOH) until the washings were colorless. **8a** (8.93 g, 92%; white powder): mp ~254−256 °C (dec; fast heating); UV max 278 nm; MS *m*/*z* 388.1283 (8, $M^+[C_{20}H_{16}N_6O_3]$ = 388.1284); ^1H NMR δ 2.18 (s, 3), 7.26−7.56 (m, 10), 8.46 (s, 1), 10.66 (br s, 1), 13.02 (br s, 1). Anal. Calcd for $C_{20}H_{16}N_6O_3$: C, 61.85; H, 4.15; N, 21.64. Found: C, 61.84; H, 4.24; N, 21.51.

6-*O*-(Diphenylcarbamoyl)-2-*N*-isobutyrylguanine (8b). Treatment of 9-acetyl-2-*N*-isobutyrylguanine[12] (2.63 g, 10 mmol) by procedure E gave **8b** (3.71 g, 87%; white powder): mp ~218−220 °C dec; UV max 278 (ϵ 12 600); MS (FAB) *m*/*z* 417.1693 (100, $MH^+[C_{22}H_{21}N_6O_3]$ = 417.1675); ^1H NMR δ 1.03 (d, *J* = 6 Hz, 6), 2.78 (septet, 1), 7.28−7.54 (m, 10), 8.44 (s, 1), 10.59 (br s, 1), 13.58 (br s, 1); ^{13}C NMR (10 mol % CF_3CO_2H/DMSO-d_6) δ 19.53, 34.75, 118.81* (C5), 127.49, 129.23, 129.65, 141.90, 144.87* (C8), 150.52 (6-COO), 152.34 (C2), 154.19* (C4), 157.41* (C6), 174.81 (signals followed by an asterisk were observed only after adding TFA). Anal. Calcd for $C_{22}H_{20}N_6O_3 \cdot 0.5H_2O$: C, 62.11; H, 4.98; N, 19.75. Found: C, 62.13; H, 4.86; N, 19.65.

Guanosine (4b). Method A. Procedure F. BSA (0.5 mL, 407 mg, 2 mmol) was added to a suspension of **8a** (388 mg, 1 mmol) in dried DCE (10 mL), and stirring was continued in a stoppered flask at 80 °C for 15 min. The clear solution was evaporated, the residue was dissolved in dried toluene (5 mL), and TMSOTf (0.24 mL, 289 mg, 1.3 mmol) and a solution of tetra-*O*-acetyl-β-D-ribofuranose (382 mg, 1.2 mmol) in dried toluene (5 mL) were added. The solution was stirred at 80 °C for 1 h and cooled, and EtOAc (50 mL) was added. The organic phase was washed [saturated $NaHCO_3/H_2O$ (50 mL × 2), brine (50 mL)], dried (Na_2SO_4), and evaporated. The residue was chromatographed (Et_2O → 20% Me_2CO/Et_2O) to give 2-*N*-acetyl-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-6-*O*-(diphenylcarbamoyl)guanine (**9a**; 589 mg, 91%; white foam): UV max 278 nm; MS (FAB) *m*/*z* 647 (3, MH^+).

Method B. Treatment of **2a** (177 mg, 0.39 mmol) by procedure E [chromatography ($CHCl_3$ → 1% MeOH/$CHCl_3$)] gave **9a** (194 mg, 77%) with NMR (^1H and ^{13}C) and UV spectra identical with those of **9a** from method A. The two samples comigrated in three TLC systems.

Method C. Treatment of **8a** (388 mg, 1 mmol) in DCE (15 mL) with BSA (0.5 mL, 407 mg, 2 mmol) followed by tetra-*O*-acetyl-β-D-ribofuranose (796 mg, 2.5 mmol) and TMSOTf (0.38 mL, 467 mg, 2.1 mmol) by procedure F (80 °C, 2 h) gave a residue that was chromatographed (3 → 10% $Me_2CO/CHCl_3$). Early fractions contained 2-*N*-acetyl-2-*N*,9-bis(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-6-*O*-(diphenylcarbamoyl)guanine (**10a**; 26 mg, 3%; white foam): UV max 263 (sh) nm; MS (FAB) *m*/*z* 905 (1, MH^+); ^1H NMR δ 1.60, 1.95, 2.04, 2.06, 2.12, 2.14 (6 × s, 21), 3.83, 4.18, 4.23, 4.37 (4 × m, 6), 5.28, 5.60, 5.80, 5.97 (4 × m, 4), 6.11, 6.36 (2 × d, 2), 7.30−7.60 (m, 10), 8.55 (s, 1). Intermediate fractions contained **9a** and **10a** (115 mg), and later fractions contained **9a** (160 mg, 25%).

Method D. Treatment of **8b** (416 mg, 1 mmol) by procedure F gave 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-6-*O*-(diphenylcarbamoyl)-2-*N*-isobutyrylguanine (**11a**; 619 mg, 89%; white foam): UV max 278 nm (ϵ 13 400); MS (FAB) *m*/*z* 675.2420 (100, $MH^+[C_{33}H_{35}N_6O_{10}]$ = 675.2415). Anal. Calcd for $C_{33}H_{34}N_6O_{10} \cdot 1.25H_2O$: C, 56.85; H, 5.28; N, 12.05. Found: C, 56.83; H, 5.24; N, 11.79.

Deprotection. Treatment of **9a** (647 mg, 1 mmol) (or **9a** plus **10a**) by procedure C gave **4b** hemihydrate (from H_2O) (220 mg, 75%): mp ~265 °C dec (authentic sample, mp ~250 °C dec); UV (H_2O) max 252 nm (ϵ 13 800), (0.1 M HCl) max 255 nm (ϵ 12 300), (0.1 M KOH) max 264 nm (ϵ 11 500); MS (FAB) *m*/*z* 284 (23, MH^+). Anal. Calcd for $C_{10}H_{13}N_5O_5 \cdot 0.5H_2O$: C, 41.10; H, 4.83; N, 23.96. Found: C, 41.03; H, 4.63; N, 23.99.

Analogous deprotection of **11a** gave **4b** (80%).

9-(β-D-Xylofuranosyl)guanine (4d). Treatment of tetra-*O*-acetyl-D-xylofuranose (1.2 mmol) by procedure F [chromatography ($CHCl_3$ → 1% MeOH/$CHCl_3$)] gave 2-*N*-acetyl-9-(2,3,5-tri-*O*-acetyl-β-D-xylofuranosyl)-6-*O*-(diphenylcarbamoyl)guanine (**9c**; 553 mg, 86%; white foam): UV max 278 nm; MS (FAB) *m*/*z* 647 (4, MH^+) plus 2-*N*-acetyl-2-*N*,9-bis-(2,3,5-tri-*O*-acetyl-β-D-xylofuranosyl)-6-*O*-(diphenylcarbamoyl)-guanine (**10c**; 40mg, 4%): UV max 263 nm (sh); MS (FAB) *m*/*z* 905 (6, MH^+); ^1H NMR δ 1.43, 1.90, 1.96, 2.02, 2.10 (5 × s, 21), 3.88, 4.03, 4.30, 4.62 (4 × m, 6), 5.22, 5.52, 5.75, 5.80 (4 × m, 4), 6.14, 6.29 (2 × d, 2), 7.30−7.60 (m, 10), 8.83 (s, 1);

(17) Rousseau, R. J.; Robins, R. K.; Townsend, L. B. *J. Am. Chem. Soc.* **1968**, *90*, 2661.

^{13}C NMR δ 19.27, 20.15, 20.28, 23.28, 61.02, 61.20, 74.13, 74.79, 75.54, 76.94, 78.07, 78.40, 86.83, 87.72, 122.59, 126.72, 127.21, 129.24, 141.35, 145.73, 149.62, 151.82 (C2), 154.12, 155.17, 168.83, 169.09, 169.63, 169.75, 170.13.

Deprotection. Treatment of **9c** (647 mg, 1 mmol) (or **9c** and **10c**) by procedure D gave **4d** hemihydrate (from H_2O) (197 mg, 67%; two crops): mp ~250 °C dec (lit.[8a] mp 241−243 °C dec); UV (H_2O) max 252 nm (ϵ 13 700); MS (FAB) *m*/*z* 284 (14, MH^+). Anal. Calcd for $C_{10}H_{13}N_5O_5 \cdot 0.5H_2O$: C, 41.10; H, 4.83; N, 23.96. Found: C, 40.97; H, 4.52; N, 23.83.

9-(α-D-Arabinofuranosyl)guanine (4f). Treatment of tetra-*O*-acetyl-D-arabinofuranose (382 mg, 1.2 mmol) by procedure F [chromatography (Me_2CO/Et_2O, 1:4)] gave 2-*N*-acetyl-9-(2,3,5-tri-*O*-acetyl-α-D-arabinofuranosyl)-6-*O*-(diphenylcarbamoyl)guanine (**9e**; 531 mg, 82%; white foam): UV max 278 nm; MS (FAB) *m*/*z* 647 (1, MH^+). Deprotection of **9e** (647 mg, 1 mmol) by procedure D gave **4f** hemihydrate (from H_2O) (246 mg, 84%): mp ~290 °C dec (lit.[18] mp >300 °C dec); UV (H_2O) max 252 nm (ϵ 13 000); MS (FAB) *m*/*z* 284 (16, MH^+). Anal. Calcd for $C_{10}H_{13}N_5O_5 \cdot 0.5H_2O$: C, 41.10; H, 4.83; N, 23.96. Found: C, 41.23; H, 4.57; N, 24.08.

Rearrangement of 2-*N*-Acetyl-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-6-*O*-(diphenylcarbamoyl)guanine (12a) To Give 9a. Treatment of **3a** (226 mg, 0.5 mmol) by procedure E (ambient temperature, 3 h) [chromatography ($CHCl_3$ → 2% MeOH/$CHCl_3$)] gave **12a** (264 mg, 82%): MS (FAB) *m*/*z* 647 (25, MH^+). Subjection of **12a** to the conditions of procedure F for 2 h (TMSOTf/dried toluene/80 °C/2 h) resulted in its complete conversion to **9a**.

9-[(2-Hydroxyethoxy)methyl]guanine (Acyclovir) (15). Treatment of **8a** (388 mg, 1 mmol) and (2-acetoxyethoxy)-methyl bromide[15a] (0.158 mL, 236 mg, 1.2 mmol) by procedure F (ambient temperature, 1.5 h; no TMSOTf) gave a residue that was chromatographed (Et_2O → 30% Me_2CO/Et_2O). Evaporation of later fractions gave a white foam that was recrystallized (Et_2O/CH_3CN) to give 9-[(2-acetoxyethoxy)methyl]-2-*N*-acetyl-6-*O*-(diphenylcarbamoyl)guanine (**13**; 319 mg, 63%): mp 136−138 °C; UV max 278 nm (ϵ 13 600); MS *m*/*z* 504.1770 (1, $M^+[C_{25}H_{24}N_6O_6]$ = 504.1757), (FAB) *m*/*z* 505 (25, MH^+); ^{1}H NMR δ 1.91 (s, 3), 2.22 (s, 3), 3.78 (m, 2), 4.08 (m, 2), 5.62 (s, 2), 7.30−7.56 (m, 10), 8.60 (s, 1), 10.76 (br s, 1); ^{13}C NMR δ 20.16, 24.27, 62.44, 67.20, 72.47, 119.54, 126.64, 126.97, 129.08, 141.43, 145.36, 149,81, 152.33, 154.88, 155.04, 168.62, 169.83. Evaporation of earlier fractions gave 2-*N*,9-bis[(2-acetoxyethoxy)methyl]-2-*N*-acetyl-6-*O*-(diphenylcarbamoyl)-guanine (**14**; 20 mg, 3%) [repurified on a silica plate (5 × 20 cm, developed twice with Me_2CO/Et_2O (3:7) before NMR analysis]: ^{1}H NMR δ 1.85, 1.86, 2.28 (3 × s, 9), 3.66, 3.74 (2 × m, 4), 4.03 (m, 4), 5.42, 5.68 (2 × s, 4), 7.30−7.60 (m, 10), 8.73 (s, 1).

Deprotection. Treatment of crystalline **13** (504 mg, 1 mmol) by procedure D gave **15** hemihydrate (from H_2O) (212 mg, 91%; two crops): mp 250−253 °C (lit.[15a] mp 265−266 °C, lit.[15b] mp 247−248 °C); UV (H_2O) max 251 nm (ϵ 13 200); MS *m*/*z* 225.0865 (7, $M^+[C_8H_{11}N_5O_3]$ = 225.0862), (FAB) *m*/*z* 226 (80, MH^+); ^{1}H NMR δ 3.46 (s, 4), 4.67 (br s, 1), 5.35 (s, 2), 6.51 (br s, 2), 7.81 (s, 1), 10.64 (br s, 1); ^{13}C NMR δ 59.88, 70.34, 72.01, 116.43 (C5), 137.71 (C8), 151.39 (C4), 153.78 (C2), 156.76 (C6).

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