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EFFICIENT SYNTHESIS OF 6-SUBSTITUTED PURINE DERIVATIVES USING Pd-CATALYZED CROSS-COUPLING REACTIONS WITH 2'-DEOXYGUANOSINE O^6-TOSYLATE

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Abstract 6-Substituted purine analogs function in a variety of biological activities including antiviral pathways. A number of studies have reported on the development of the efficient synthesis of these nucleoside analogs. We previously demonstrated that oligonucleotides containing 2-amino-6-vinylpurine derivatives react with the cytosine at the target site with extreme selectivity. This was the first finding that O^6-tosylate derivative of guanosine worked as an efficient substrate for Pd(0)-catalyzed cross-coupling reaction with vinyltributylstannane to produce 2-amino-6-vinylpurine. In order to demonstrate usefulness of the tosylate precursor, in this study we investigated transition metal catalysts and ligands in achieving the cross-coupling reaction using boronic acids or Grignard reagents as a coupling partner.

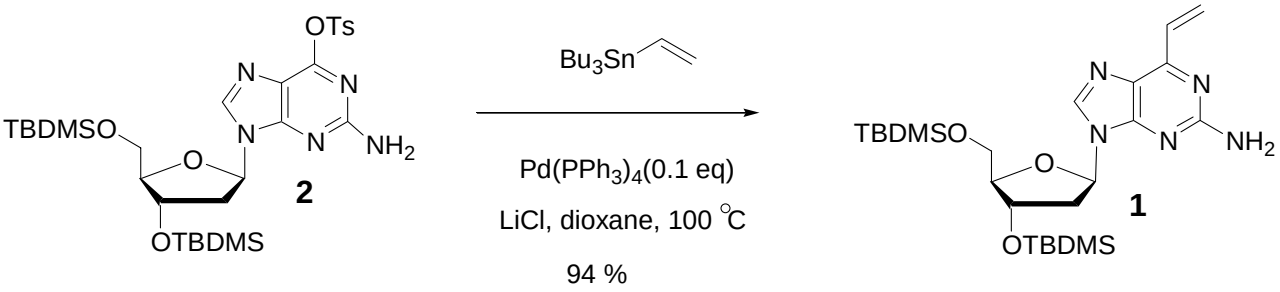
INTRODUCTION

The involvement of modified purine analogues in multiple biological pathways has garnered considerable interest in the synthesis of these compounds. For instance, several modified adenosine derivatives are

modulators of adenosine receptors[1], and a number of 6-substituted purine derivatives show potent cytokinin activity and stimulate plant cell growth and cell division.[2] Recently, C-6 arylpurine ribonucleosides have been shown to have cytostatic activity against selected transformed cell lines.[3] We previously reported that 2-amino-6-vinylpurine (**1**) exhibited efficient cross-linking reactivity to cytosine[4], and oligonucleotides containing **1** exhibited efficient antisense activity in the cell[5].

Cross-coupling reactions are a powerful tool for the synthesis of these 6-substituted purine derivatives. In many cases, 6-halopurines were used as cross-coupling substrates.[6] We developed an efficient method for the synthesis of **1**, in which the O^6-tosylate of guanosine derivative (**2**) acts as a good substrate for cross-coupling reaction with vinylstannanes under catalysis by Pd(0).[7]

Scheme 1 Synthesis of 2-Amino-6-Vinylpurine (1) by Cross-Coupling Reaction with Vinylstannanes



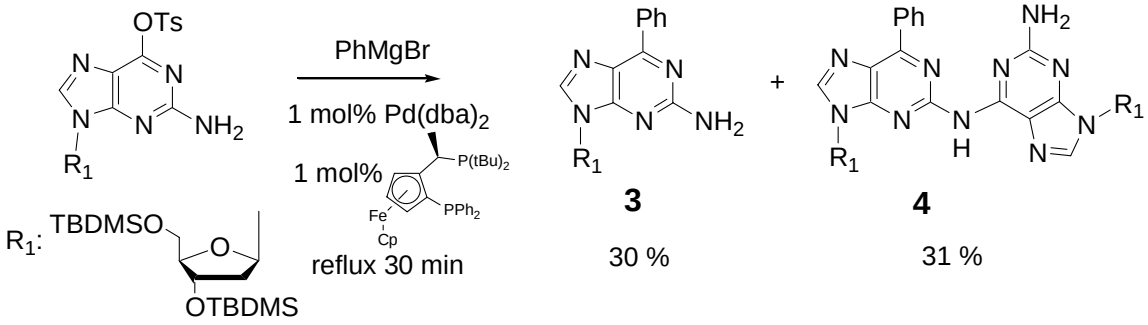
Although cross-coupling reactions of aryl tosylates are more attractive because they are generated from less expensive reagents and more stable than triflates, few studies have been reported on the cross-coupling reaction using aryl sulfonates prior to our report. Recently, Lakshman and co-workers demonstrated that 2'-deoxyguanosine O^6-arylsulfonates can be utilized for Pd-catalyzed amination and C-C coupling reactions with arylboronic acids.[8] Aryl tosylates have been utilized for many types of cross-coupling reactions as substrates in simpler aromatic systems.[9] Interestingly, Hartwig and his group have demonstrated that aryl and alkenyl tosylates can be efficiently coupled with aryl, alkenyl, and alkyl Grignard reagents under catalysis by a combination of palladium and bulky ligand.[10] These reactions to 2'-deoxyguanosine O^6-tosylates are potentially applicable for the generation of more highly functionalized 6-substituted purines. In this paper, we describe our investigation in synthesizing of 2-amino-6-aryl, alkenyl and alkyl derivatives using palladium catalyzed cross-coupling reactions between 2'-deoxyguanosine O^6-tosylate and Grignard reagents. Furthermore, we report the efficient synthesis of 2-amino-6-vinylpurine using vinylboronate ester by Suzuki-type cross-coupling.

RESULTS AND DISCUSSION

The cross-coupling reactions of 2'-deoxyguanosine O^6-tosylate **(2)** with phenylmagnesium bromide (PhMgBr) were initially investigated using hindered alkyl phosphine as ligands and palladium as catalysts.

We found that the cross-coupling between **2** and PhMgBr proceeded smoothly under reflux conditions to produce the desired coupling product (**3**) at a 30 % yield, along with dimer (**4**) at 31 % (Scheme 2). The previous studies showed that Pd-catalyzed C-N bond formations were observed between C-6 halopurine and amino group of C-6 aminopurine.[11] Under reflux conditions, **3** reacted with O^6-tosylate **(2)** to generate the cross-coupling product (**4**). The N^2-acetyl protected derivative as substrates did not produce cross-coupling product under the same conditions, although the O^6-tosylate derivative was consumed.

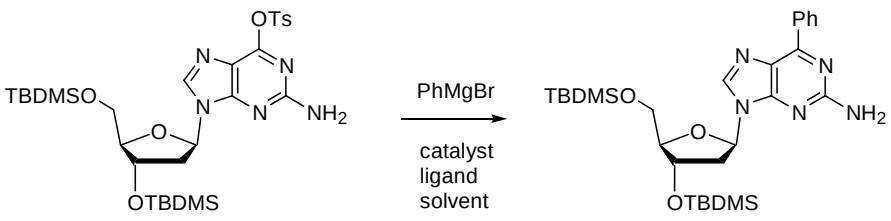
Scheme 2 Coupling of 2'-deoxyguanosine-O^6-tosylate (2) with Phenylmagnesium Bromide



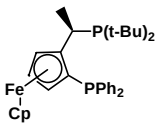
In attempting to improve the yield of **3**, it was found that 2 mol% each of the catalyst and the ligand, 3 equivalents of PhMgBr, improved the product yield of **3** at room temperature significantly. The ratio of the catalyst, the ligand and PhMgBr is very critical for the reaction yield, and lower yields were obtained with PhMgBr of more or less than 3 equivalence (Table 1, entries 1-4). Using the same ratio, effects of the combination of three catalysts, $Pd(dba)_2$, $(C_6H_5CN)_2PdCl_2$, $(dppf)NiCl_2$, and the four phosphine ligands (L1-L4) on the yields were examined (Table 1).

Interestingly, the best results were obtained with a different combination of the catalyst and the ligand, *i.e.* $Pd(dba)_2$/L1 (entry 3), $(C_6H_5CN)_2PdCl_2$/ L2 (entry 9), and $(dppf)NiCl_2$/L4 (entry 16).

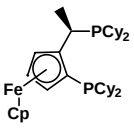
Table 1 Coupling of 2'-deoxyguanosine-O^6-tosylate (2) with Phenylmagnesium Bromide using various combinations of catalysts and ligands[a]



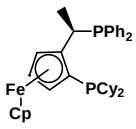
Entry	Catalyst	Ligand	PhMgBr (equiv.)	Yield (%)
1	$Pd(dba)_2$	L1	1	trace
2	$Pd(dba)_2$	L1	3	72
3	$Pd(dba)_2$	L1	3	**76**[b]
4	$Pd(dba)_2$	L1	5	52
5	$Pd(dba)_2$	L2	3	20
6	$Pd(dba)_2$	L3	3	21
7	$Pd(dba)_2$	L4	3	26
8	$(C_6H_5CN)_2PdCl_2$	L1	3	14
9	$(C_6H_5CN)_2PdCl_2$	L2	3	**56**
10	$(C_6H_5CN)_2PdCl_2$	L3	3	17
11	$(C_6H_5CN)_2PdCl_2$	L4	3	38
12	$(dppf)NiCl_2$	L1	3	16
13	$(dppf)NiCl_2$	L2	3	16
14	$(dppf)NiCl_2$	L3	3	26
15	$(dppf)NiCl_2$	L4	3	30
16	$(dppf)NiCl_2$	L4	3	**52**[b]



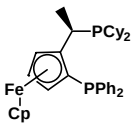
L1



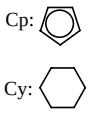
L2



L3



L4

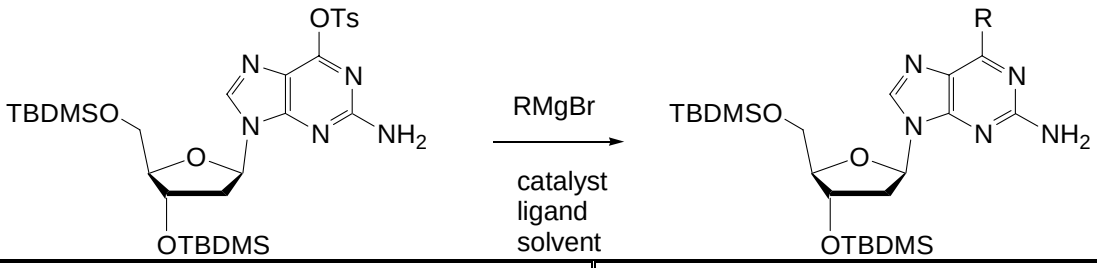


[a]Reaction conditions: Under argon, catalyst (2 mol %) and ligand (2 mol %) were added to a solution of **2** in toluene and the mixture was degassed with argon for 30 min. PhMgBr (1.0 M THF) was added to the mixture and stirred for 24 h at r.t.
[b]Toluene-THF (2:1) was used as solvent.

We next examined the cross-coupling reactions of the *O*[6]-tosylate (**2**) with several Grignard reagents (Table 2). The reactions between the tosylate (**2**) and vinylmagnesium bromide to produce 2-amino-6-vinylpurine were investigated, but, unfortunately, the desired compound was obtained in low yields (Table 2, entries 1-8). In contrast, 1-propenylmagnesium bromide generated a moderate product yield (entry 9). This differs from our previous results in that the tributylstannane substrates of the vinyl and the propenyl derivative produced the corresponding coupling product with $Pd(PPh_3)_4$ catalyst in a similar yield.[7] Reactions of allylmagnesium bromide with the tosylate (**2**) did not give the desired product under any conditions (entries 10-13). The cross-coupling products were obtained in moderate yields with the $Pd(dba)_2$/L1 catalyst system for homoallylmagnesium bromide (entry 14), and with the $(dppe)PdCl_2$/L2 or $(C_6H_5CN)_2PdCl_2$/L2 system for alkylmagnesium bromide (entries 20, 25).

Notably it may be a useful finding that 6-alkyl substituted derivatives of 2-aminopurine are prepared by the coupling reaction between O^6-tosylate (**2**) and the alkyl Grignard reagents with suitable combination of the palladium catalysts and the phosphine ligands.

Table 2 Pd-Catalyzed Cross-coupling between Grignard Reagents and 2'-deoxyguanosine-O^6-tosylate (2)[a]

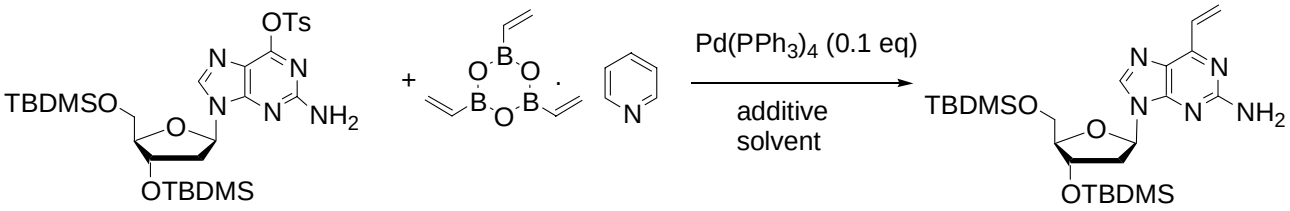


Entry	Grignard Reagents	Product (R=)	Catalyst/ligand	Yield (%)	Entry	Grignard Reagents	Product (R=)	Catalyst/Ligand	Yield (%)
1	BrMg	**1**	$Pd(dba)_2$/L1	-	14		**7**	$Pd(dba)_2$/L1	**54**
2		(vinyl)	$Pd(dba)_2$/L2	**36**	15	BrMg	(3-butenyl)	$Pd(dba)_2$/L2	31
3			$Pd(dba)_2$/L3	16	16			(dppe)$PdCl_2$/L2	36
4			$Pd(dba)_2$/L4	10	17			$(C_6H_5CN)_2PdCl_2$/L2	26
5			(dppe)$PdCl_2$/L1	-	18		**8**	$Pd(dba)_2$/L1	46
6			(dppe)$PdCl_2$/L2	14	19	BrMg	(ethyl)	$Pd(dba)_2$/L2	58
7			(dppe)$PdCl_2$/L3	20	20			(dppe)$PdCl_2$/L2	**61**[b]
8			(dppe)$PdCl_2$/L4	11	21			$(C_6H_5CN)_2PdCl_2$/L2	52
9	BrMg	**5**	$Pd(dba)_2$/L1	**71**	22		**9**	$Pd(dba)_2$/L1	39
		(1-propenyl)					(octyl)		
10	BrMg	**6**	$Pd(dba)_2$/L1	-	23	BrMg$(CH_2)_6$		$Pd(dba)_2$/L2	34
11		(3-propenyl)	$Pd(dba)_2$/L2	-	24			(dppe)$PdCl_2$/L2	50
12			(dppe)$PdCl_2$/L2	-	25			$(C_6H_5CN)_2PdCl_2$/L2	**47**
13			$(C_6H_5CN)_2PdCl_2$/L2	-					

[a] Reaction conditions: Under argon, catalyst (2 mol %) and ligand (2 mol %) were added to a solution of **2** in toluene-THF (2:1) and the mixture was degassed with argon for 30 min. Grignard reagents (3 equiv.) was added to the mixture and stirred for 24 h at r.t. The structure of the ligands (L1-L4) are shown in the footnote of Table 1. [b] Reaction time was 2 h.

After several attempts for vinylation reactions with various organometallic reagents, including magnesium, zinc, and indium derivatives, we found that vinylboronate ester by Suzuki-type cross-coupling reaction with O^6-tosylate (**2**) afforded the 6-vinylated compound (**1**) in good yield (Table 3). The use of the vinylboronate ester is superior to the previous method with the vinylstannane reagent, as this method can be applied to a large scale synthesis and the vinylboronate ester is less toxic than the vinylstannane reagent.

Table 3 Pd-Catalyzed Cross-coupling between 2,4,6-Trivinylcyclotriboroxane Pyridine and 2'-Deoxyguanosine-*O*^{6}-tosylate (2)



Entry	Additive	Solvent	Temperature	Time	Yield (%)
1	LiBr, LiOH	dioxane /H_2O	110 °C	2 h	**84**
2	LiCl, LiOH	THF/H_2O	60 °C to 80 °C	8 h	68
3	LiBr, LiOH	THF/H_2O	60 °C to 80 °C	8 h	54
4	LiCl, LiOH	dioxane/H_2O	110 °C	3.5 h	75
5	LiBr, K_2CO_3	dioxane /H_2O	110 °C	2 h	75
6	LiI, LiOH	dioxane /H_2O	110 °C	30 min	46

CONCLUSION

In conclusion, we developed the palladium catalyzed cross-coupling reactions with Grignard reagents and *O*^{6}-tosylated 2-aminopurine (**2**) using sterically hindered bisphosphine ligands to generate the corresponding 6-aryl- and 6-alkyl-substituted 2-aminopurine products. We further show that 2-amino-6-vinylpurine is obtained in good yield by palladium catalyzed cross-coupling reaction from **2** with vinylboronate ester. As *O*^{6}-tosylated 2-aminopurine nucleoside derivative is easily prepared compared to the corresponding 6-halogen derivatives, this may be a useful precursor for the cross-coupling reaction to produce a variety of 6-alkyl or aryl-2-aminopurine derivatives.

EXPERIMENTAL

General

^{1}H-NMR (400, or 500 MHz) spectra were recorded on a Varian UNITY-400, INOVA-500. ^{13}C-NMR (125 MHz) spectra were recorded on a Varian UNITY-400. IR spectra were obtained using a SHIMADZU FTIR-8400 spectrophotometer. HRMS analyses were recorded on Applied Biosystems Mariner System 5299 spectrometer using bradykinin, neurotensin and angiotensin as internal standards.

Representative Procedure for Palladium Catalyzed Cross-Coupling Reactions with Grignard Reagents. Synthesis of 2-Amino-9-(3,5-di-*O*-*tert*-butyldimethylsilyl-2-deoxy-β-D-ribofuranosyl)

-6-phenylpurine (3) A solution of catalyst (2 μmol), ligand (2 μmol) and **2** (0.1 mmol) in toluene and THF (5:1, 1.2 mL) was degassed with argon, followed by the addition of 1.0 M phenylmagnesium bromide (THF solution, 0.3 mmol), then the mixture was stirred under argon at rt. After 24 h, the reaction mixture was diluted with 20 % NH_4Cl, extracted with EtOAc and the organic layer was washed with saturated aqueous $NaHCO_3$, brine. The organic layer was dried over Na_2SO_4 and evaporated to give the crude product, which was chromatographed on a silica gel column (hexane:AcOEt=5:1 to 4.5:1) to give **3** as a yellow syrup. FTIR (cm^{-1}, neat): 2929, 1561, 1114; ^{1}H-NMR ($CDCl_3$) 8.63-8.61 (2H, m), 8.04 (1H, s), 7.52-7.43 (3H, m), 6.38 (1H, t, *J*=6.6 Hz), 5.13 (2H, s), 4.62-4.59 (1H, m), 4.01-3.98 (1H, m), 3.82-3.73 (2H, m), 2.66-2.60 (1H, m), 2.40-2.34 (1H, m), 0.91 (9H, s), 0.89 (9H, s), 0.10 (6H, s), 0.06 (6H, s)**;** ^{13}C-NMR (125 MHz, $CDCl_3$) -5.3, -5.1, -4.5, –4.4, 18.6, 26.2, 40.9, 63.1,72.4, 83.8, 88.0, 126.3, 128.7, 130.0, 130.8, 136.1, 140.0, 154.2, 156.1, 160.0; ESI-HRMS calcd for $C_{28}H_{46}N_5O_3Si_2$ $(M+H)^+$ 556.3134, found 556.3144.

4: as a yelow syrup, FTIR (cm^{-1}, neat): 2929, 1586; ^{1}H-NMR ($CDCl_3$) 8.84-8.81 (2H, m), 8.57 (1H, bs), 8.24 (1H, s), 7.92 (1H, s), 7.57-7.51 (3H, m), 6.54 (1H, dd, *J*=7.24, 6.6 Hz), 6.36 (1H, *J*=6.3 Hz), 5.01 (2H, s), 4.66-4.64 (1H, m), 4.63-4.60 (1H, m), 4.05-4.03 (1H, m), 4.02-3.99 (1H, m), 3.93 (1H, dd, *J*=5.1, 11.2 Hz), 3.85 (1H, dd, *J*=4.4, 11.2 Hz), 3.78 (1H, dd, *J*=3.2, 7.3 Hz), 3.76 (1H, dd, *J*=3.2, 7.3 Hz), 2.96 (1H, ddd, *J*=5.4, 7.6, 13.0. Hz), 2.64 (1H, ddd, *J*=5.8, 7.3, 13.0. Hz), 2.48 (1H, ddd, *J*=3.0, 5.9, 13.2. Hz), 2.39 (1H, ddd, *J*=3.2, 5.8, 13.1. Hz), 0.94 (9H, s), 0.93 (9H, s), 0.92 (9H, s), 0.90 (9H, s), 0.13 (6H, s), 0.12 (6H, s), 0.09 (6H, s), 0.07 (3H, s)**,** 0.06 (3H, s), ESI-HRMS calcd for $C_{50}H_{85}N_{10}O_6Si_4$ $(M+H)^+$ 1033.5725, found 1033.5695.

2-Amino-9-(3,5-di-*O*-*tert*-butyldimethylsilyl-2-deoxy-β-D-ribofuranosyl)-6-(1-propenyl)purine (5)

FTIR (cm^{-1}, neat): 2928, 1591, 1100; ^{1}H-NMR ($CDCl_3$) 7.99 (1H, s), 7.44 (0.6 H, dq, *J*=15.5, 6.9 Hz), 6.90 (0.4 H, dq, *J*=11.9, 2.0 Hz), 6.85 (0.6 H, dq, *J*=15.2, 1.7 Hz), 6.29 (0.4 H, dq, *J*=11.6, 7.3 Hz), 6.36 (1H, dd, *J*=5.6, 1.9 Hz), 4.89 (2H, bd), 4.60 (1H, q, *J*=3.0 Hz), 3.99 (1H, q, *J*=3.3 Hz), 3.82 (1H, dd, *J*=11.1, 4.3 Hz), 3.75 (1H, dd, *J*=11.2, 3.6 Hz), 2.64-2.59 (1H, m), 2.40-2.31 (1H, m), 2.26 (1.2 H, dd, *J*=7.3, 2.0 Hz), 2.02 (1.8 H, dd, *J*=6.9, 1.7 Hz), 0.92 (9H, s), 0.91 (9H, s), 0.11 (6H, s), 0.08 (3H, s), 0.07 (3H, s); ESI-HRMS calcd for $C_{25}H_{46}N_5O_3Si_2$ $(M+H)^+$ 520.3134, found 520.3114.

2-Amino-9-(3,5-di-*O*-*tert*-butyldimethylsilyl-2-deoxy-β-D-ribofuranosyl)-6-(3-butenyl)purine (7)

FTIR (cm^{-1}, neat): 2929, 1592; ^{1}H-NMR ($CDCl_3$) 7.93 (1H, s), 6.32 (1H, t, *J*=6.9 Hz), 5.88 (1H, ddt, *J*=8.6, 10.6, 16.9 Hz), 5.06 (1H, dd, *J*=1.4, 16.9 Hz), 5.05 (2H, bs), 4.95 (1H, dd, *J*=10.6, 1.4 Hz), 4.59-4.56 (1H, m), 3.98-3.95 (1H, m), 3.80-3.71 (2H, m), 3.07 (2H, t, *J*=7.8 Hz), 2.65-2.54 (3H, m), 2.36-2.30 (1H, m), 0.90 (9H, s), 0.88 (9H, s), 0.09 (6H, s), 0.05 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$)

-5.5, -5.4 -4.8, -4.7, 18.0, 18.3, 25.7, 25.9, 32.2, 32.4, 40.6, 62.9, 72.1, 83.5, 87.7, 115.1, 127.1, 137.5, 139.2, 152.3, 159.5, 162.9; ESI-HRMS calcd for $C_{26}H_{48}N_5O_3Si_2$ $(M+H)^+$ 534.3290, found 534.3300.

2-Amino-9-(3,5-di-*O*-*tert*-butyldimethylsilyl-2-deoxy-β-D-ribofuranosyl)-6-ethylpurine (8)

Yellow caramel; FTIR (cm^{-1}, neat): 2929, 1592; ^{1}H-NMR ($CDCl_3$) 7.93 (1H, s), 6.31 (1H, t, *J*=6.9 Hz), 4.94 (2H, s), 4.59-4.56 (1H, m), 3.98-3.95 (1H, m), 3.81-3.71 (2H, m), 3.00 (2H, q, *J*=7.8 Hz), 2.64-2.58 (1H, m), 2.36-2.30 (1H, m), 1.35 (3H, t, *J*=7.8 Hz), 0.90 (9H, s), 0.88 (9H, s), 0.09 (6H, s), 0.05 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$) -5.5, -5.4 -4.8, -4.7, 12.6, 18.0, 18.4, 25.8, 25.9, 26.5, 40.6, 62.9, 72.2, 83.6, 87.7, 126.9, 139.1, 152.2, 160.0, 164.9; ESI-HRMS calcd for $C_{24}H_{46}N_5O_3Si_2$ $(M+H)^+$ 508.3134, found 508.3112.

2-Amino-9-(3,5-di-*O*-*tert*-butyldimethylsilyl-2-deoxy-β-D-ribofuranosyl)-6-octylpurine (9)

Orange oil; FTIR (cm^{-1}, neat): 2928, 1591; ^{1}H-NMR ($CDCl_3$) 7.94 (1H, s), 6.34 (1H, t, *J*=6.7 Hz), 4.90 (2H, s), 4.62-4.57 (1H, m), 4.01-3.98 (1H, m), 3.80 (1H, dd, *J*=4.1, 11.2 Hz), 3.75 (1H, dd, *J*=3.1, 11.0 Hz), 2.98 (2H, t, *J*=7.9 Hz), 2.64 (1H, ddd, *J*=5.8, 7.3, 13.0 Hz), 2.35 (1H, ddd, *J*=3.4, 6.1, 13.0 Hz), 1.84-1.78 (2H, m), 0.93-0.91 (10H, m), 0.87 (3H, t, *J*=.7.1 Hz), 0.90 (9H, s), 0.88 (9H, s), 0.09 (6H, s), 0.05 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$) -5.5, -5.4, -4.8, -4.7, 14.1, 18.0, 18.4, 25.8, 25.9, 28.7, 29.2, 29.4, 29.7, 30.2, 31.8, 33.4, 40.5, 62.9, 72.2, 83.9, 87.7, 126.9, 140.2, 152.2, 159.4, 164.1; ESI-HRMS calcd for $C_{30}H_{58}N_5O_3Si_2$ $(M+H)^+$ 592.4073, found 592.4086.

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