



# Synthesis of $O^6$ -alkylated preQ<sub>1</sub> derivatives

Laurin Flemmich, Sarah Moreno and Ronald Micura\*

## Full Research Paper

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Address:  
Institute of Organic Chemistry, Center for molecular Biosciences  
Innsbruck (CMBI), Innrain 80–82, 6020 Innsbruck, Austria

Email:  
Ronald Micura\* - ronald.micura@uibk.ac.at

\* Corresponding author

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## Abstract

A naturally occurring riboswitch can utilize 7-aminomethyl- $O^6$ -methyl-7-deazaguanine ( $m^6$ preQ<sub>1</sub>) as cofactor for methyl group transfer resulting in cytosine methylation. This recently discovered riboswitch-ribozyme activity opens new avenues for the development of RNA labeling tools based on tailored  $O^6$ -alkylated preQ<sub>1</sub> derivatives. Here, we report a robust synthesis for this class of pyrrolo[2,3-*d*]pyrimidines starting from readily accessible  $N^2$ -pivaloyl-protected 6-chloro-7-cyano-7-deazaguanine. Substitution of the 6-chloro atom with the alcoholate of interest proceeds straightforward. The transformation of the 7-cyano substituent into the required aminomethyl group turned out to be challenging and was solved by a hydration reaction sequence on a well-soluble dimethoxytritylated precursor via in situ oxime formation. The synthetic path now provides a solid foundation to access  $O^6$ -alkylated 7-aminomethyl-7-deazaguanines for the development of RNA labeling tools based on the preQ<sub>1</sub> class-I riboswitch scaffold.

## Introduction

Methylated preQ<sub>1</sub> has attracted much attention recently because this compound has been found to function as cofactor for the conserved fold of a non-coding RNA, namely the preQ<sub>1</sub> class-I riboswitch [1]. This riboswitch acts as a ribozyme by using 7-aminomethyl- $O^6$ -methyl-7-deazaguanine ( $m^6$ preQ<sub>1</sub>) as methyl group donor; it catalyzes self-methylation of a specific cytidine in the aptamer binding pocket, yielding  $N^3$ -methyl cytidine ( $m^3C$ ) under release of 7-aminomethyl-7-deazaguanine (preQ<sub>1</sub>) [1]. Thus far, present-day riboswitches have only been known to bind – but not to be able to react – with their ligands [2,3]. This new finding now opens exciting avenues for the development of RNA labeling tools [4], in particular, for

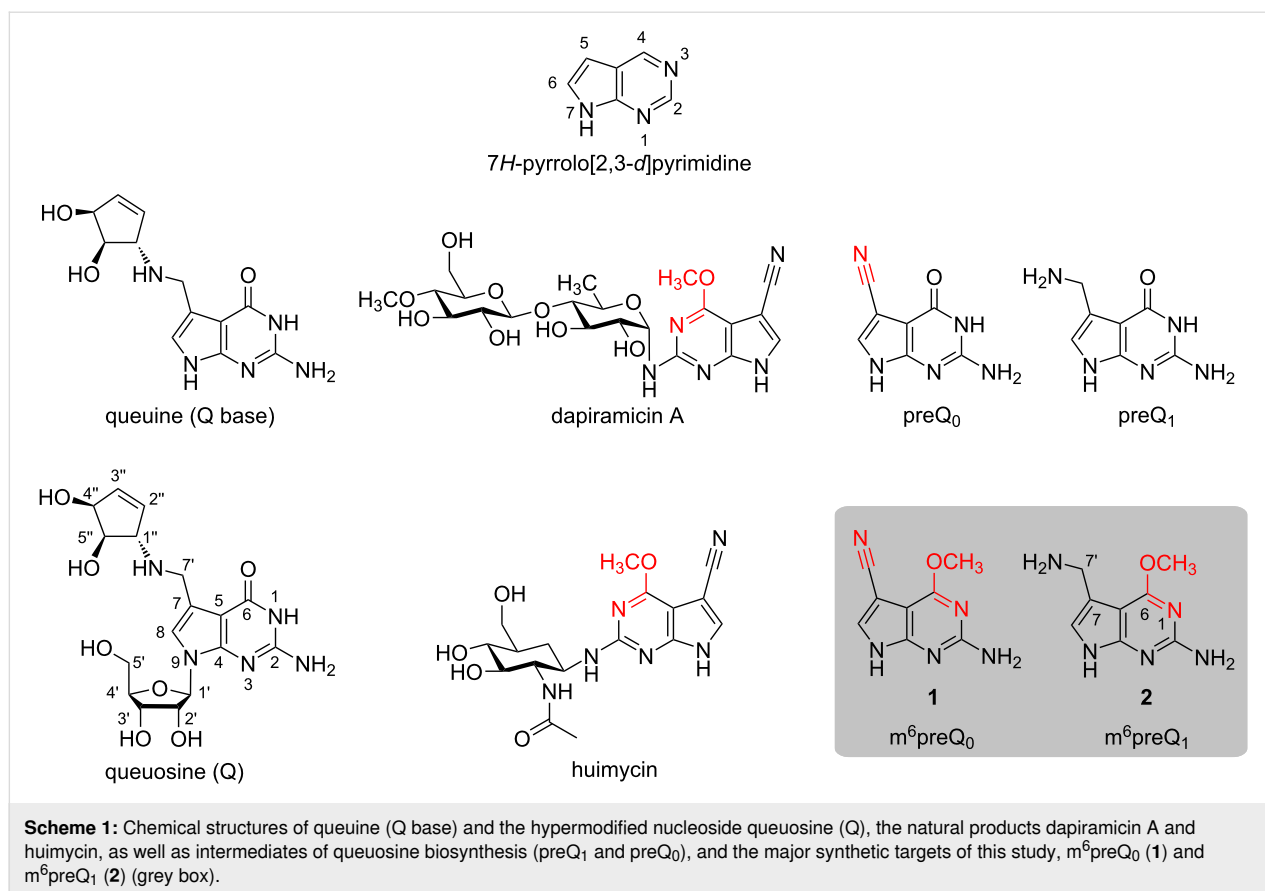
RNA methylation, and more generally, for RNA alkylation. To this end, robust synthetic routes towards  $O^6$ -alkylated 7-aminomethyl-7-deazaguanines are urgently needed and reported here.

## Results and Discussion

### Biological and synthetic background

#### Role of preQ<sub>1</sub> in queuosine biosynthesis and gene regulation

Queuine (Q base) is a derivative of guanine that is involved in the biosynthetic pathway of the hypermodified tRNA nucleoside queuosine (Q) (Scheme 1) [5]. The core structure of the nucleobase is 7-aminomethyl-7-deazaguanine, a pyrrolo[2,3-



*d*]pyrimidine also termed prequeuosine base (preQ<sub>1</sub>) [6,7]. In many bacteria, preQ<sub>1</sub> binds to specific mRNA domains and thereby regulates genes that are required for queuosine biosynthesis [8–16]. The molecular mechanism behind is called riboswitching. For most riboswitches, ligand binding induces a structural change in the untranslated leader sequence of mRNA by formation (or disruption) of a terminator stem (transcriptional control) or repressor stem (translational control). This conformational event signals on or off to gene expression and represents a feedback-type mechanism that is dependent on cellular ligand concentration [13].

#### Natural occurrence of alkylated prequeosines

Evidence for the natural occurrence of methylated prequeuosine bases stems from a recent study that demonstrated that m<sup>6</sup>preQ<sub>0</sub> is produced by *Streptomyces* [17]. Moreover, the natural products huimycin [18] and dapiramicin contain m<sup>6</sup>preQ<sub>0</sub> as core with their 2-NH<sub>2</sub> group linked to a 2'-acetamido-2'-deoxy-β-D-glucopyranosyl residue in huimycin and to a 2-[4'-(4''-O-methyl-β-D-glucopyranosyl)-6'-deoxy-α-D-glucopyranosyl] moiety in dapiramicin A [19,20]. In the biosynthetic pathway, the conversion of preQ<sub>0</sub> into huimycin requires methylation of preQ<sub>0</sub> and attachment of the *N*-acetylglucosamine moiety as final steps [18]. The methylation reaction is

likely to be catalyzed by the product of the gene *huiC*, which encodes a SAM-dependent methyltransferase [18].

To the best of our knowledge, in contrast to m<sup>6</sup>preQ<sub>0</sub> [17] the reduced counterpart 7-aminomethyl-*O*<sup>6</sup>-methyl-7-deazaguanine m<sup>6</sup>preQ<sub>1</sub> has not yet been reported to be isolated from natural sources.

#### Earlier syntheses of preQ<sub>1</sub>, preQ<sub>0</sub> and m<sup>6</sup>preQ<sub>0</sub>

The synthesis of preQ<sub>1</sub> has been first described by Goto starting from 2-methylthio-6-methoxy-7-methyl-7-deazapurine and requiring more than ten steps [21]. More efficient was a procedure reported by Nishimura applying a Mannich reaction with dibenzylamine–formaldehyde and 2-acylaminopyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one as key step, thereby selectively installing a dibenzylaminomethyl moiety [22]. Exchange of the dibenzylamine group in the Mannich base with NH<sub>3</sub> provided preQ<sub>1</sub> [22]. Alternatively, Klebe demonstrated a Michael addition of 2,6-diaminopyrimidin-4-one to the nitroolefin 2-[(2*E*)-3-nitroprop-2-en-1-yl]-1*H*-isoindole-1,3(2*H*)-dione [23]. Finally, Carell reported a cycloaddition route relying on α-brominated 3-phthalimidopropanal and diaminopyrimidin-4-one [24,25]. We further optimized this path for the synthesis of <sup>15</sup>N-labeled prequeuosine nucleobase derivatives [26] required for ad-

vanced NMR spectroscopic applications [27], and for the syntheses of azido- or amino-functionalized preQ<sub>1</sub> derivatives needed for cellular applications with engineered riboswitches [28]. Finally, we point out that only a single synthetic route has been published to a potential O<sup>6</sup>-methylated precursor of m<sup>6</sup>preQ<sub>1</sub>, namely N<sup>9</sup>-trimethylsilylethyl protected m<sup>6</sup>preQ<sub>0</sub> [20]. This synthesis, however, is based on methylation using diazomethane resulting in a mixture of N1 and O<sup>6</sup> methylated products, and we therefore did not further consider this path. Finally, one route was described for m<sup>6</sup>preQ<sub>0</sub> **1** [29] which is similar to the first step we developed for the synthesis of m<sup>6</sup>preQ<sub>1</sub> **2** as outlined below.

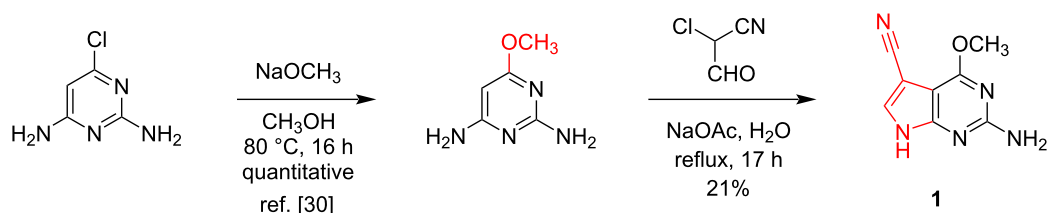
### Synthesis of m<sup>6</sup>preQ<sub>1</sub>, e<sup>6</sup>preQ<sub>1</sub>, and bn<sup>6</sup>preQ<sub>1</sub>

Our initial attempts to site-specifically methylate trimethylsilylated preQ<sub>1</sub> (which was generated in situ with *N,O*-bis[trimethylsilyl]acetamide) by trimethyloxonium tetrafluoroborate in apolar solvents resulted in the recovery of starting material only. Next, we tested a cyclocondensation reaction between 2-chloro-3-cyanopropan-1-al and 2,6-diamino-4-methoxypyrimidine [30], however, target compound **1** (m<sup>6</sup>preQ<sub>0</sub>) was

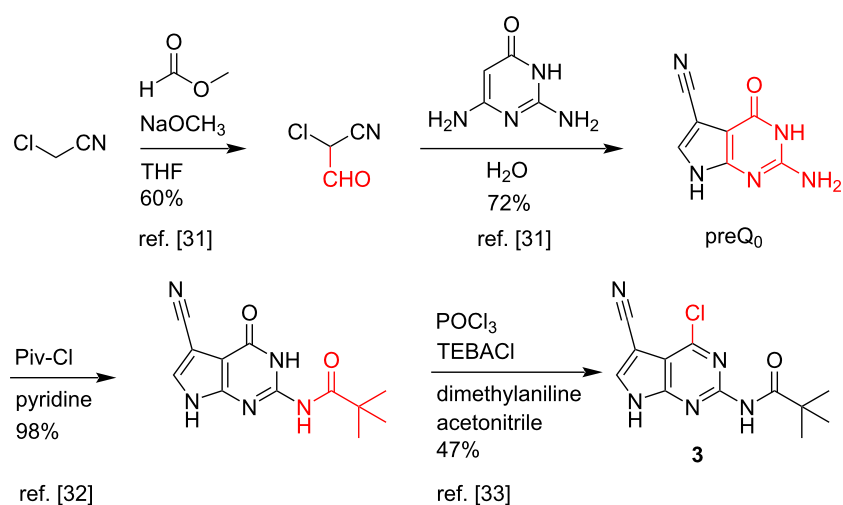
obtained in yields of 21% (Scheme 2) which is significantly lower compared to the cyclocondensations with 2,6-diamino-4-pyrimidin-4-one mentioned above [23-27].

We therefore envisaged a path involving 6-chloro-7-deazapurine derivative **3** (Scheme 3) as this compound is readily available from cheap starting materials following published procedures. Chloroacetonitrile and methyl formate gave 2-chloro-2-cyanoacetaldehyde which was then reacted with 2,6-diaminopyrimidin-4-one to provide preQ<sub>0</sub> in good yields [31]. Protection of the exocyclic amino group using pivaloyl chloride was optimized from a published procedure [32] and gave nearly quantitative yields of *N*<sup>2</sup>-pivaloyl preQ<sub>0</sub> in our hands. Finally, transformation of the 6-carbonyl group by using phosphorus oxychloride gave 6-chloro-7-deazapurine derivative **3** [33]. Notably, attempts to directly transform preQ<sub>0</sub> (without *N*<sup>2</sup> protection) into 6-chloro-7-cyano-7-deazaguanine failed in our hands.

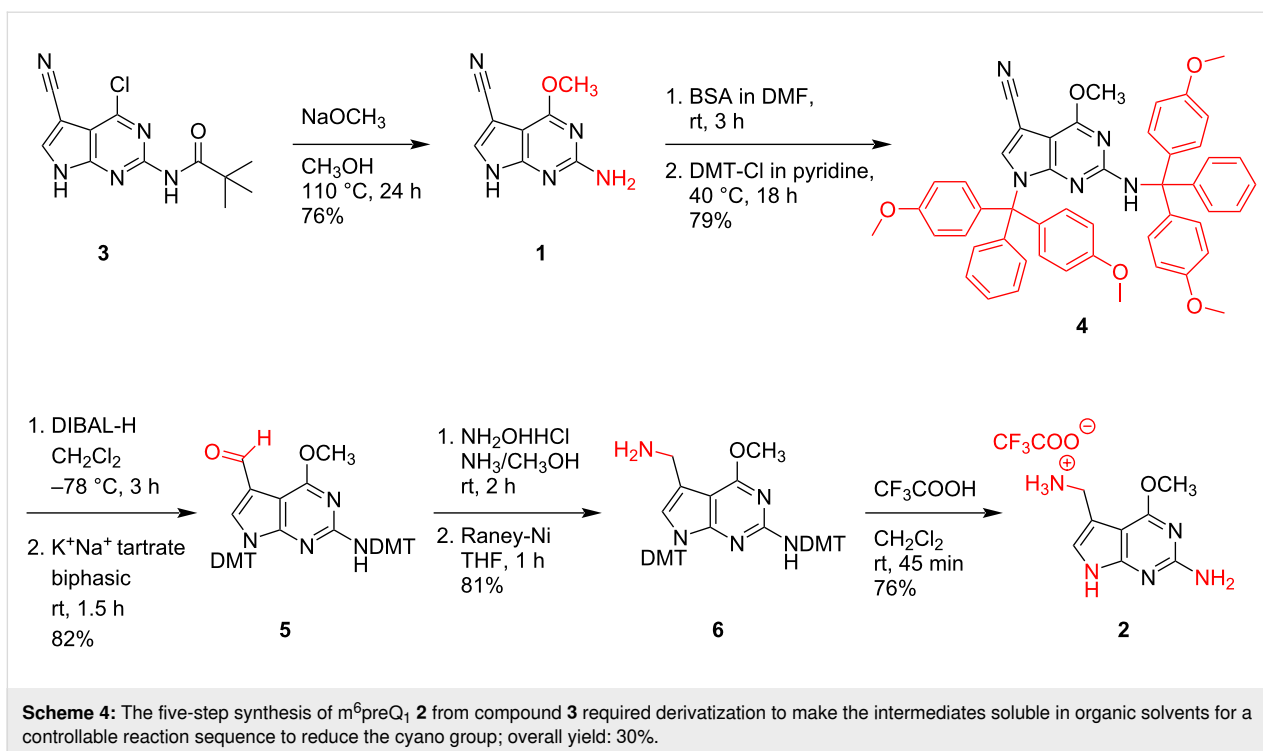
The 6-chloro atom of compound **3** was substituted using sodium methoxide under concomitant cleavage of the pivaloyl group to yield the desired O<sup>6</sup>-methylated compound **1**, m<sup>6</sup>preQ<sub>0</sub>



**Scheme 2:** Synthesis of compound **1** (m<sup>6</sup>preQ<sub>0</sub>) by cyclocondensation using a 4-methoxypyrimidine derivative resulted in unsatisfying yields.



**Scheme 3:** Synthesis of compound **3** following known procedures [31-33].

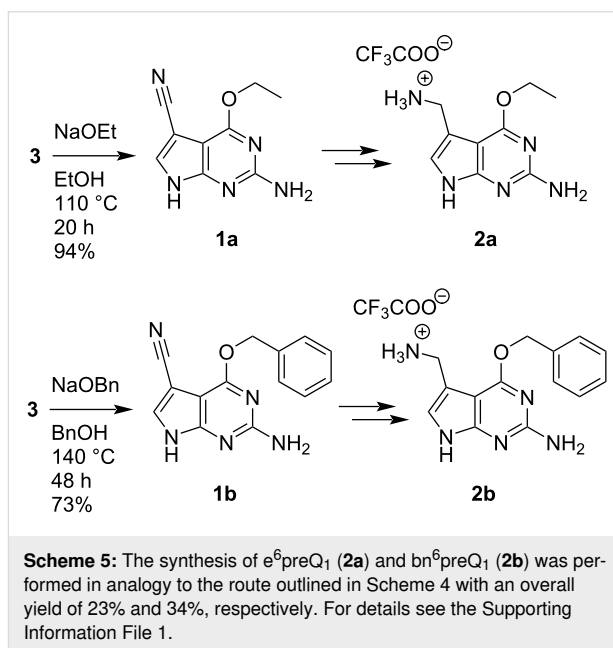


(Scheme 4). After dissolving this compound under strong silylating conditions in the presence of *N,O*-bis(trimethylsilyl)acetamide [34], simultaneous tritylation of N9 and the N<sup>2</sup> atoms was achieved using 4,4'-dimethoxytrityl chloride in pyridine. The obtained derivative **4** was amenable to nitrile reduction using diisobutylaluminium hydride (DIBAL-H) in dichloromethane at  $-78$  °C, followed by workup with potassium sodium tartrate solution (Rochelle salt) to furnish the aldehyde **5**. Then, transformation of the 7-formyl into the 7-aminomethyl group proceeded via oxime formation, applying hydroxylamine hydrochloride in methanolic ammonia, followed by reduction with Raney nickel to yield the tritylated precursor **6**. Finally, the auxiliary functions were cleaved using trifluoroacetic acid (TFA) in dichloromethane and the target compound **2**,  $m^6\text{preQ}_1$ , was isolated as TFA salt.

The here established path to synthesize  $m^6\text{preQ}_1$  offers high flexibility with respect to the  $O^6$  substituent. We demonstrate this by complementing the set of  $\text{preQ}_1$ -derived alkylating cofactors with  $e^6\text{preQ}_1$  (**2a**) and  $bn^6\text{preQ}_1$  (**2b**) that were synthesized following the same path with overall yields of 23% and 34%, respectively (Scheme 5 and Supporting Information File 1).

## Conclusion

We developed a robust synthesis for  $O^6$ -alkylated 7-aminomethyl-7-deazaguanines that starts from a readily accessible 6-chloro-7-cyano-7-deazaguanine derivative. The chloro atom



is smoothly substituted by the alcoholate of interest, followed by N9 and N<sup>2</sup> dimethoxytritylation to obtain a well-soluble intermediate. The reduction of the 7-cyano substituent into the target aminomethyl group is accomplished by a hydration reaction sequence via in situ oxime formation. The route now provides a solid basis to generate  $O^6$ -alkylated  $\text{preQ}_1$  derivatives for the development of RNA labeling tools utilizing the RNA scaffold of the  $\text{preQ}_1$  class-I riboswitch.

## Experimental

**General.** Chemical reagents and solvents were purchased from commercial suppliers (Sigma-Aldrich) and used without further purification. Organic solvents for reactions were dried overnight over freshly activated molecular sieves (4 Å). The reactions were carried out under argon atmosphere. Analytical thin-layer chromatography (TLC) was performed on Marchery-Nagel Polygram SIL G/UV254 plates. Column chromatography was done on silica gel 60 (70–230 mesh).  $^1\text{H}$ , and  $^{13}\text{C}$  NMR spectra were recorded on Bruker DRX 300 MHz, Bruker Avance 4 Neo 400 MHz, and Bruker Avance 4 Neo 700 MHz instruments. Chemical shifts ( $\delta$ ) are reported relative to tetramethylsilane (TMS) and referenced to the residual proton or carbon signal of the deuterated solvent:  $\text{CDCl}_3$  (7.26 ppm) or  $\text{DMSO-}d_6$  (2.49 ppm) for  $^1\text{H}$  NMR;  $\text{CDCl}_3$  (77.0 ppm) or  $\text{DMSO-}d_6$  (39.5 ppm) for  $^{13}\text{C}$  NMR spectra.  $^1\text{H}$  and  $^{13}\text{C}$  assignments are based on COSY, HSQC, and HMBC experiments. MS experiments were performed on a Thermo Fisher QExactive Classic. Samples were analyzed in the positive-ion mode.

**$O^6$ -Methyl preQ<sub>0</sub> (1)** ( $m^6\text{preQ}_0$ ). Procedure A: 2-Chloro-3-oxopropanenitrile [29] (6.80 g, 65.6 mmol) was added to a solution of sodium acetate (10.77 g, 131.3 mmol) and 6-methoxypyrimidine-2,4-diamine [33] (9.20 g, 65.6 mmol) in water (270 mL) at 50 °C. After 16 hours, the solution was refluxed for an additional hour and allowed to cool to room temperature. Filtration gave 2.61 g of compound **1** (21%) as grey solid. Procedure B: Sodium (42 mg, 1.8 mmol) was dissolved in 0.8 mL methanol at 0 °C. Compound **3** [29–31] (200 mg, 0.720 mmol) was added and the mixture was heated to 110 °C in a pressure tube for 24 h. After neutralization with glacial acetic acid the volatiles were removed in vacuo. The crude product was dry-loaded onto silica gel and purified via flash column chromatography (5–20% methanol in dichloromethane) to give 104 mg of compound **1** (76%) as a beige solid. TLC: 10% methanol in dichloromethane,  $R_f$  0.37;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-}d_6$ )  $\delta$  12.08 (bs, 1H, HN(9)), 7.81 (s, 1H, HC(8)), 6.45 (s, 2H,  $\text{H}_2\text{N}(2)$ ), 3.96 (s, 3H,  $\text{H}_3\text{CO}(6)$ ) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO-}d_6$ )  $\delta$  162.7 (C(6)), 160.7 (C(2)), 154.9 (C(4)), 130.3 (C(8)), 116.1 & 95.4 & 82.4 (C(5) & C(7) & CN), 53.26 ( $\text{H}_3\text{CO}(6)$ ); ESIMS ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd, 190.0723; found, 190.0721.

**$N^2,9$ -Bis(4,4'-dimethoxytrityl)- $O^6$ -methyl preQ<sub>0</sub> (4)**. Compound **1** (300 mg, 1.59 mmol) was suspended in *N,N*-dimethylformamide (12 mL). *N,O*-Bis(trimethylsilyl)acetamide (820  $\mu\text{L}$ , 3.33 mmol) was added dropwise and the reaction mixture was stirred for three hours at room temperature upon which a solution was obtained. Afterwards, the volatile components were removed under reduced pressure and the residue was coevaporated three times with toluene and twice with pyridine. The

residue was dissolved in pyridine (3.8 mL) and 4,4'-dimethoxytrityl chloride (1.18 g, 3.50 mmol) was added in portions. The solution was stirred for 18 h at 40 °C, subsequently poured into 5% aqueous sodium bicarbonate solution and the suspension was extracted three times with dichloromethane. The combined organic layers were washed with brine and dried over magnesium sulfate. The solvents were removed and the remaining crude product was purified by flash column chromatography on silica gel (10–30% ethyl acetate in cyclohexane) to give 1.00 g of compound **4** (79%) as a white foam. TLC: 40% ethyl acetate in cyclohexane,  $R_f$  = 0.68;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32–6.94 (m, 19H, HC(aromatic, DMTr) & HC(8)), 6.83–6.65 (m, 8H, HC(arom, DMTr)), 5.54 (s, 1H, HN(2)), 3.80 & 3.77 (s, 12H,  $\text{H}_3\text{CO}(\text{DMTr})$ ), 3.37 (s, 1H,  $\text{H}_3\text{CO}(\text{O}6)$ ) ppm;  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  162.4 (C(6)), 158.7 & 158.4 & 158.0 (C(aromatic, DMTr)), 154.8 (C(4)), 146.3 (C(2)), 142.15 & 138.4 & 134.3 (C(aromatic, DMTr)), 133.1 (C(8)), 131.4 & 130.4 & 130.3 & 130.2 & 129.80 & 129.1 & 127.8 & 127.5 & 127.4 & 126.4 (C(aromatic, DMTr)), 115.8 (C(5)/C(7)), 113.3 & 113.1 & 112.7 (C(aromatic, DMTr)), 99.2 (C(5)/C(7)), 83.1 (CN(nitrile)), 76.1 & 70.5 ( $\text{C}_{\text{Ar}_3}(\text{DMTr})$ ), 55.4 & 55.3 ( $\text{H}_3\text{CO}(\text{DMTr})$ ), 53.88 ( $\text{H}_3\text{CO}(6)$ ) ppm; ESIMS ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd, 794.3337; found, 794.3321.

**7-Formyl- $N^2,9$ -bis(4,4'-dimethoxytrityl)- $O^6$ -methyl-7-deaza-guanine (5)**. To a cooled solution (–78 °C) of compound **4** (1.00 g, 1.26 mmol) in dichloromethane (8 mL) diisobutylaluminum hydride (1 M in dichloromethane, 1.6 mL, 2.57 mmol) was added dropwise. The reaction was continued for three hours, quenched by the addition of ethyl acetate (4 mL) and allowed to come to room temperature. Half-saturated potassium sodium tartrate solution was added (4 mL) and the biphasic mixture was stirred vigorously for one and a half hour until satisfactory phase separation was achieved. The aqueous layer was separated and subsequently extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate and evaporated. The residue was purified by flash column chromatography on silica gel (10–25 % ethyl acetate in cyclohexane) to give 823 mg of compound **5** (82%) as a white foam. TLC: 30% ethyl acetate in cyclohexane  $R_f$  0.51;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  9.91 (s, 1H, CHO), 7.49 (s, 1H, HC(8)), 7.29–7.23 (m, 2H, HC(aromatic, DMTr)), 7.20–7.11 (m, 6H, HC(aromatic, DMTr)), 7.10–7.06 (m, 2H, HC(aromatic, DMTr)), 7.05–6.92 (m, 8H, HC(aromatic, DMTr)), 6.81–6.76 (m, 4H, HC(aromatic, DMTr)), 6.72–6.68 (m, 4H, HC(aromatic, DMTr)), 5.51 (s, 1H, HN(2)), 3.80 (s, 6H,  $\text{H}_3\text{CO}(\text{DMTr})$ ), 3.77 (s, 6H,  $\text{H}_3\text{CO}(\text{DMTr})$ ), 3.38 (s, 3H,  $\text{H}_3\text{CO}(6)$ ) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 101 MHz)  $\delta$  185.7 (CHO), 163.2 (C(6)), 158.7 & 158.0 & 156.5 (C(aromatic, DMTr)), 156.5 (C(4)), 146.4 (C(2)), 142.3 & 138.6 & 134.5 (C(aromatic, DMTr)), 131.9 (C(8)), 131.5 & 130.3 & 129.9 &

129.1 & 127.7 & 127.4 & 127.3 & 126.4 (C(aromatic, DMTr)), 115.7 (C(5)/C(7)), 113.1 & 112.7 (C(aromatic, DMTr)), 98.0 (C(5))/C(7)), 76.0 (CAr<sub>3</sub> (DMTr)), 70.5 (DMTr), 55.4 & 33.3 (H<sub>3</sub>CO(DMTr)), 54.0 (H<sub>3</sub>CO(6)) ppm; ESIMS (*m/z*): [M + H]<sup>+</sup> calcd, 797.3334; found, 797.3315.

**7-Aminomethyl-N<sup>2</sup>,9-bis(4,4'-dimethoxytrityl)-O<sup>6</sup>-methyl-7-deazaguanine (6).** To a suspension of compound **5** (200 mg, 0.251 mmol) in 7 M methanolic ammonia (6 mL) hydroxylamine hydrochloride (21 mg, 0.300 mmol) was added. A clear solution was obtained shortly thereafter. The reaction was stirred for two hours at room temperature. Tetrahydrofuran (4 mL) and damp Raney-Nickel (approximately 200 mg) were introduced and the reaction was continued for one hour. The reaction mixture was filtered over a Celite pad and the filtrate was evaporated. The residue was taken up in 3% methanol in dichloromethane and passed over a short, deactivated silica pad and evaporated once more to give 163 mg of compound **6** (81%) as a white foam. TLC: 6% MeOH, 1% NEt<sub>3</sub> in dichloromethane, *R<sub>f</sub>* 0.26; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 7.24–7.20 (m, 3H, HC(aromatic, DMTr)), 7.18–7.08 (m, 7H, HC(aromatic, DMTr)), 7.06–7.00 (m, 8H, HC(aromatic, DMTr)), 6.77–6.67 (m, 7H, HC(aromatic, DMTr)), 6.44 (s, 1H, HC(8)), 5.46 (s, 1H, HN(2)), 3.79 (s, 6H, H<sub>3</sub>CO(DMTr)), 3.77 (s, 6H, H<sub>3</sub>CO(DMTr)), 3.67 (s, 2H, H<sub>2</sub>CC(7)), 3.33 (s, 3H, H<sub>3</sub>CO(6)), 1.81 (bs, 2H, H<sub>2</sub>N) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 101 MHz) δ 162.3 (C(6)), 158.3 & 157.8 & 157.2 & (C(arom, DMTr)), 155.9 (C(4)), 146.8 (C(2)), 143.6 & 139.0 & 135.9 & 131.4 130.4 & 130.0 & 129.2 & 127.4 & 127.3 & 126.8 & 126.2 (C(arom, DMTr)), 121.4 (C(8)), 115.9 (C(5) or (C(7))), 112.71 & 112.6 (C(arom, DMTr)), 74.5 (CAr<sub>3</sub>(DMTr)), 70.3 (CAr<sub>3</sub>(DMTr)), 55.3 (H<sub>3</sub>CO(DMTr)), 53.4 (H<sub>3</sub>CO(6)), 38.9 (H<sub>2</sub>CC(7)) ppm; ESIMS (*m/z*): [M + H]<sup>+</sup> calcd, 798.3650; found, 798.3629.

**O<sup>6</sup>-Methyl preQ<sub>1</sub> (trifluoroacetate salt) (2).** Compound **6** (120 mg, 150 μmol) was dissolved in 500 μL dichloromethane. Trifluoroacetic acid (60 μL, 0.75 mmol) and 10 μL water were added. After 45 minutes the reaction was quenched by the addition of 100 μL methanol. Afterwards the solvents were removed in vacuo. The residue was triturated five times with dichloromethane and dried on high vacuum to give 35 mg of compound **2** (76%) as a white solid. TLC: 15% MeOH, 1% NEt<sub>3</sub> in dichloromethane, *R<sub>f</sub>* 0.56; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 11.64 (bs, 1H, HN(9)), 8.07 (bs, 3H, H<sub>3</sub>N<sup>+</sup>), 6.99 (d, 1H, *J<sub>HH</sub>* = 2.0 Hz, HC(8)), 4.06 (q, 2H, H<sub>2</sub>CC(7)), 3.98 (s, 3H, H<sub>3</sub>CO) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 101 MHz) δ 164.1 (C(6)), 158.4 (q, *J<sub>CF</sub>* = 34.0 Hz, CF<sub>3</sub>COO<sup>-</sup>), 158.1 (C(2)), 150.7 (C(4)), 120.0 (C(8)), 116.3 (q, *J<sub>CF</sub>* = 295.0 Hz, CF<sub>3</sub>COO<sup>-</sup>), 107.5 & 96.2 ((C(5) & C(7)), 53.7 (H<sub>3</sub>CO), 34.8 (CH<sub>2</sub>CC(7)) ppm; ESIMS (*m/z*): [M + H – NH<sub>3</sub>]<sup>+</sup> calcd, 177.0771; found, 177.0767; [M + H]<sup>+</sup> calcd, 194.1036; found, 194.1032.

## Supporting Information

### Supporting Information File 1

Synthetic procedures for compounds **1a–6a**, and **1b–6b**, and <sup>1</sup>H and <sup>13</sup>C NMR spectra of all compounds. <sup>1</sup>H, <sup>13</sup>C HSQC and <sup>1</sup>H, <sup>13</sup>C HMBC spectra of all final products **1**, **1a**, **1b**, **2**, **2a**, and **2b**.

[<https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-17-147-S1.pdf>]

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## ORCID® iDs

Ronald Micura - <https://orcid.org/0000-0003-2661-6105>

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