JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b02194 • Publication Date (Web): 25 Sep 2018

ACS Publications

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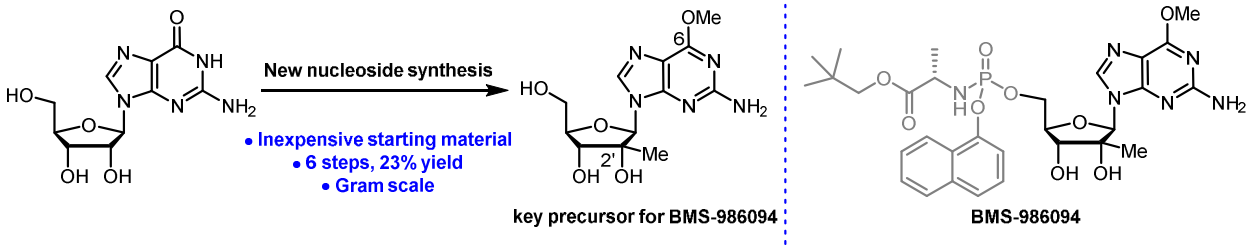
The synthesis of 2'-Me, 6-methoxyl guanosine from the parent ribonucleoside Guanosine

Changxia Yuan†,*, Ke Chen‡, Martin Eastgate†,*

†Chemical and Synthetic Development, Bristol-Myers Squibb, 1 Squibb Drive, New Brunswick, New Jersey 08903, United States

‡STA Pharmaceutical, WuXi AppTec Company, 288 Fute Zhong Road, Shanghai, 200131, China



Abstract:

A short and efficient synthesis of the nucleoside fragment contained in the NS5B nucleoside inhibitor BMS-986094 was achieved in 23% overall yield on gram scale. The synthesis uses the widely available starting material guanosine, via a short sequence ending in a Mukaiyama hydration reaction to establish the key tertiary alcohol moiety and set the C-2' methyl stereogenic center. This work resulted in a robust and scalable approach to this complex nucleoside.

Introduction:

Hepatitis C virus (HCV) is a blood-borne pathogen which, until recently, chronically infected an estimated 71-180 million people. Clinical care for patients with HCV-related liver disease has advanced considerably thanks to an enhanced understanding of the disease, significant improvements in treatment options and the commercialization of curative regimens[1a]. Traditional small molecule therapeutics have led the way in curing HCV, but other options such vaccines also under development[1].

Nucleotide analogues were first line treatments for over 40 years[2], and early drugs, such as ribavirin (**1**) (Figure 1), proved to be essential for treatment of HCV infection,[3] despite significant negative side-effects. More recently, the approval of sofosbuvir (Solvaldi) (**2**), a nucleoside featuring 2-*C*-methylcytidine with a 5'-*O*-phosphorylamidate diester, marked a milestone in the treatment of HCV with

curative regimens for geno-type one and geno-type two of HCV diseases being launched (figure 1a)[1b, 4]. Since its regulatory acceptance, multiple pan-genotypic therapies have been approved, moving this once incurable disease to one which can be treated by a simple course of tablets.

As part of BMS' efforts against this disease, we also explored the area of nucleotide based NS5B inhibitors[5], specifically on the development of **BMS-986094-01 (3)**, which showed pan-genotypic antiviral activity in *vitro*. Typical of this class, the phosphoramidate **3** is a monophosphorylated prodrug of the active guanosine nucleotide triphosphate; in this case the nucleoside component featured an unnatural sugar backbone with a tertiary alcohol at the C-2' position. We have previously reported on a highly efficient asymmetric phosphorylation of this nucleoside, to install the phosphoramidate, leading to the diastereoselective formation of ***S*-(3)**[6]. In that work, we synthesized a single diastereomer of nucleoside phosphoramidate ***S*-(3)** by coupling the nucleoside with the phosphoric acid derivative **4** (where the phosphorous atom does not contain stereochemical information until activated) through a dynamic kinetic resolution using quinine. This robust and innovative process enabled us to produce API (active pharmaceutical ingredient) as a crystalline compound in high purity and as a single stereoisomer (Figure 1b), avoiding an unselective phosphorylation and separation of the resulting diastereoisomers through extensive chromatography[5a].

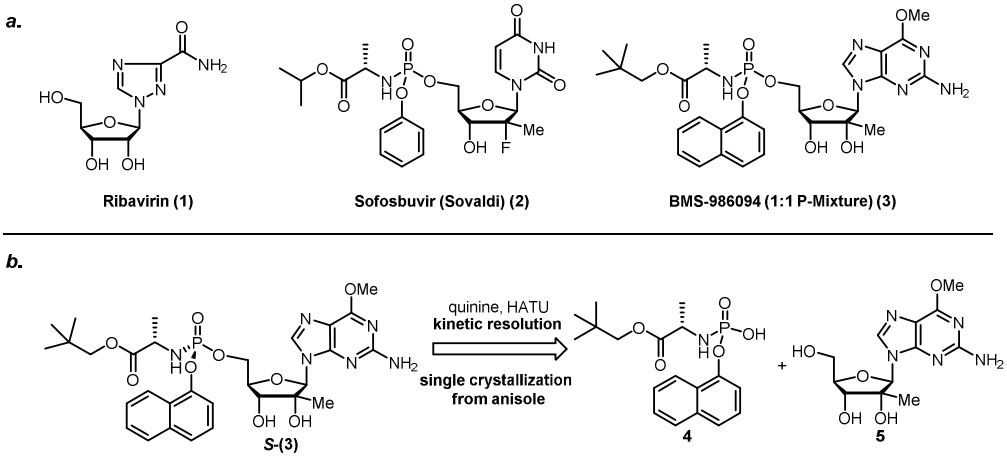
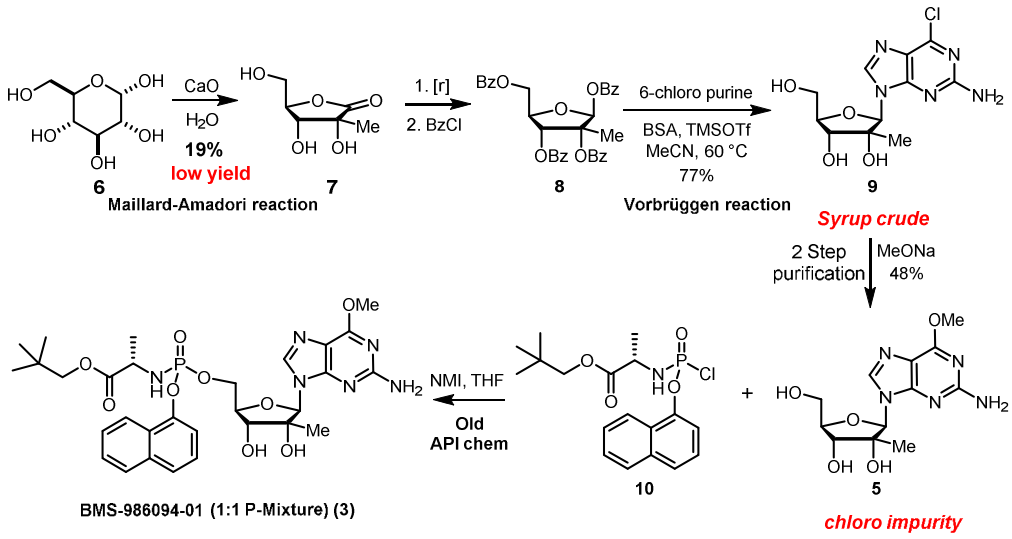


Figure 1: *a*. Representative APIs for the treatment of HCV. *b*. Final step (API step) in synthesis of ***S*-(3)**.

Results and Discussion:

While the API coupling chemistry was effective, an improved method to prepare the nucleotide **5** was required. The chemistry used to prepare nucleotide 5 had several liabilities (scheme 1): (1) the synthesis begins with conversion of D-fructose **6** to **7** through a Mailard-Amadori reaction in only 19% yield[7], and there were several isolation patents for **7**[8], (2) Chloro nucleoside **9**, derived from **8**[9] by Vorbruggen

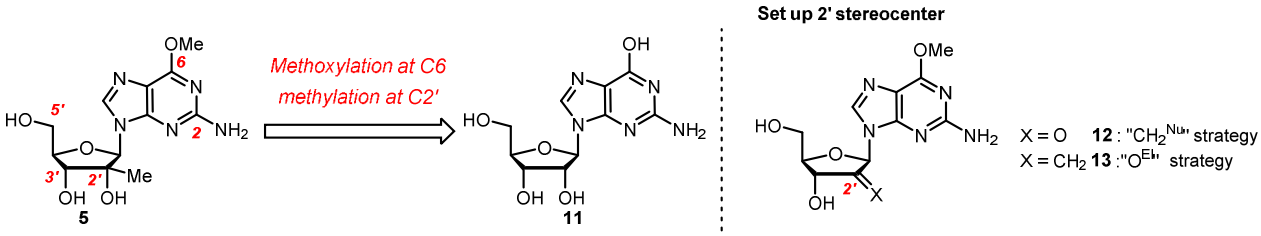
reaction**,** could not be induced to crystallize, which hampered our ability to control the several key impurities, and (3) It was very challenging to affect 100% conversion of **9** to **5**, and even residual traces of **9** failed to purge during isolation, leading to a daughter impurity which persisted through to the API. With all of these factors being taken into consideration, it was clear that an alternative synthetic route was required for the nucleoside **5** to address the above issues. Herein, we detail our work to develop an improved synthesis of **5** from widely available guanosine **(11)**.



Scheme 1: Original synthesis of nucleoside **3**.

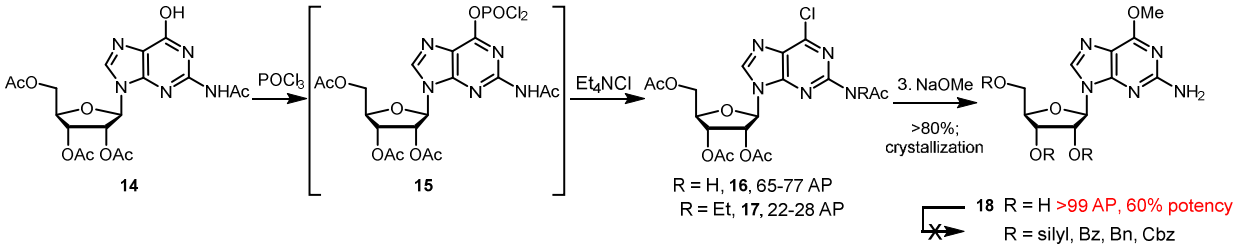
Early synthetic development:

The goals of this new route were to avoid the problematic 6-chloro impurities, along with the complexities of the existing chemical processes. Our retrosynthetic analysis is depicted in scheme 2, the desired molecule only needed the addition of two methyl groups onto the inexpensive, commercial and natural occurring guanosine **11**, with the only differences being the methoxy group on purine and methyl group at the C-2' position on the sugar. The challenges posed by this strategy were the efficiency of guanine methoxylation and the ability to establish the C-2' methyl group diastereoselectively. We pursued two approaches for establishing the C-2' stereocenter on **5**. The highest risk approach was to synthesize ketone **12**, where addition carbon nucleophile can add to the carbonyl center to give correct diastereomer at the C-2' position, if addition occurs from the side containing the base potentially through chelation. In the second option, we could utilize olefin **13**, and oxidize the tertiary carbon with the correct stereochemistry.



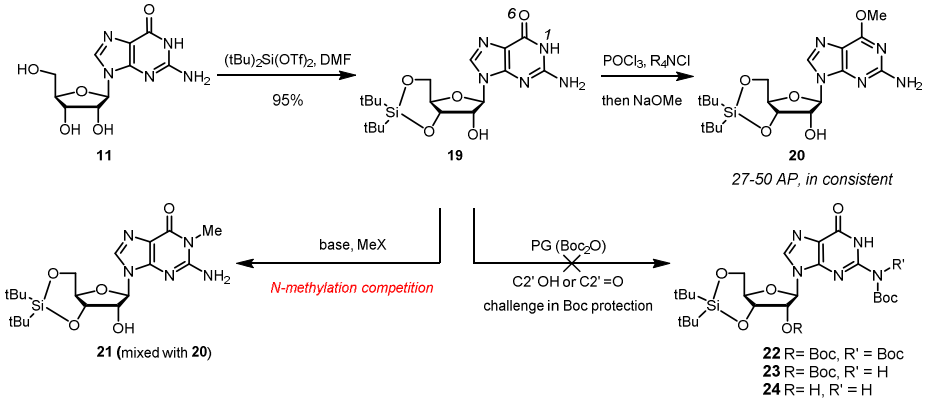
Scheme 2: Retrosynthetic analysis for nucleoside **5**.

Our exploration commenced from guanosine tetra-acetate **14**, in order to understand the C6 methylation leveraging existing known chemistry (scheme 3)[10]. We attempted the chlorination with $POCl_3$ at 100 °C, receiving, as expected, consistently low yields (~10%). We expected that the lack of an additional chloride source led to the observed poor performance. We followed Uznański's procedural modification where Et_4NCl is added and we could obtain 70% yield of the desired product at 70 °C. Unfortunately, the reaction always contained mixtures of the desired product **16** and **17** in 2:1 to 4:1 ratio, the product of ethylation by the tetraethylammonium cation. Since the crystallization at this step was unable to purge the in-process impurities, we carried out the nucleophilic displacement of sodium methoxide, to afford **18** in 80% yield (based on **14**), obtaining high purity (HPLC) after isolation. However, we found that after potency correction, the yield of **18** dropped significantly because of the presence of various salts in the solid. We faced the challenge that, while water could readily dissolve these salts, **18** was also extremely water soluble, making an aqueous wash impractical. We hypothesized that by installing multiple protecting groups, we could decrease the aqueous solubility of the substrate and use a typical wash to remove salts. However, guanosine **18** gave inconsistent conversion under standard silylation conditions, even after purification, and resulted in formation of multiple species. Further attempts off selective 3' and 5' protection over a series of common protecting groups (Bn, Bz, Cbz) failed, leading us to discontinue development of this route.



Scheme 3: Attempt on 6-purine methoxylation optimization and derivatization.

Alternatively, we tried to test a protection-deprotection approach starting from guanosine **11** (scheme 4). Following Urata's report[11], Guanosine **19** was smoothly prepared by slow addition of tBu$_2$Si(OTf)$_2$ into a solution of **11** in DMF at 0 °C. With isolated **19** in hand, we had tried different methoxylation methods resulting in mixed results. Under the previous $POCl_3$ activation condition, we could observe the formation of **20**, after addition of a sodium methoxide solution, but the reaction afforded variable purities, and low yields. We tried to deprotonate **19** with different bases, in hope of direct methylating the desired C-6 oxygen, but we observed competitive methylation of N-1, rather than O-6, resulting in a messy reaction profile containing **21**. Lastly, we considered that protecting substrate **19** with a Boc group on purine could help the purine activation. However, neither **22**, **23** nor **24** were produced under various protecting conditions.



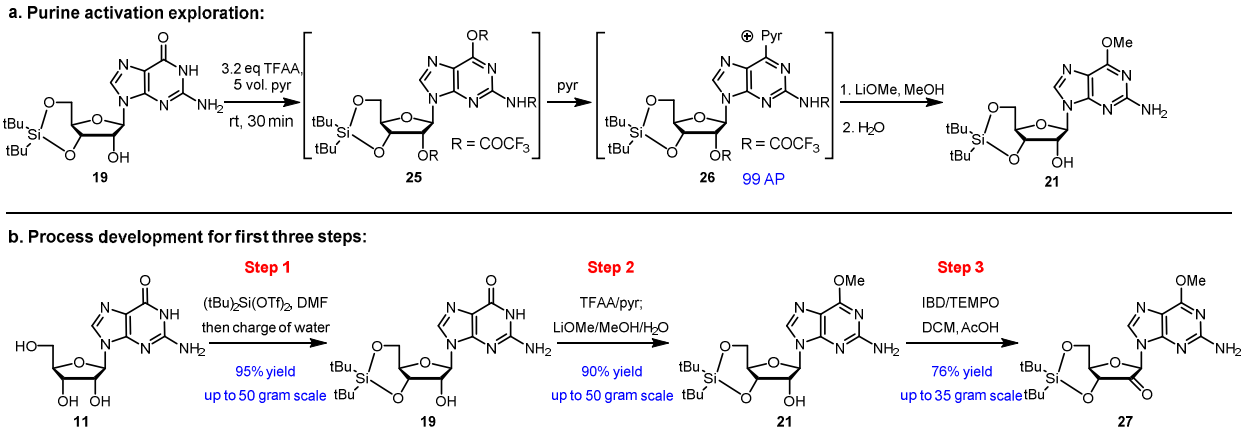
Scheme 4: Unsuccessful derivatization of **19** and **20** under different conditions.

New synthetic route:

With these observations in hand, we revised our strategy moving forward. Early results indicated the phosphoryl chloride activated intermediate **19** in the desired way and was suitable to undergo selective methoxy displacement. We also observed that a free amino group on guanosine interfered in various ways during the reaction. From previous studies, we learned that **19** was a stable crystalline compound which can serve as an intermediate for derivatization. Based on this understanding, we focused on changing the conditions for activating the purine on intermediate **19** rather than direct protection. Inspired by the work of Fathi et al, we found that treatment of **19** with 3 equivalent of TFAA in the presence of 5 volume of pyridine cleanly afforded the pyridinium adduct **26** (scheme 5a)[12]. This intermediate was subsequently quenched with LiOMe in methanol to give product **21** after methoxyl displacement and cleavage of the trifluoro acyl groups. It is worth noting that KOMe or NaOMe provided

greater levels of impurities. The ensuing water quench served as both reagent for trifluoroacetamide hydrolysis and anti-solvent for crystallization of **21**. Finally with a method for the direct functionalization of C-6 in place, we focused on oxidation of alcohol **21** proceeded smoothly with IBD (diacetoxyiodo)benzene) and TEMPO to give ketone **27**[13].

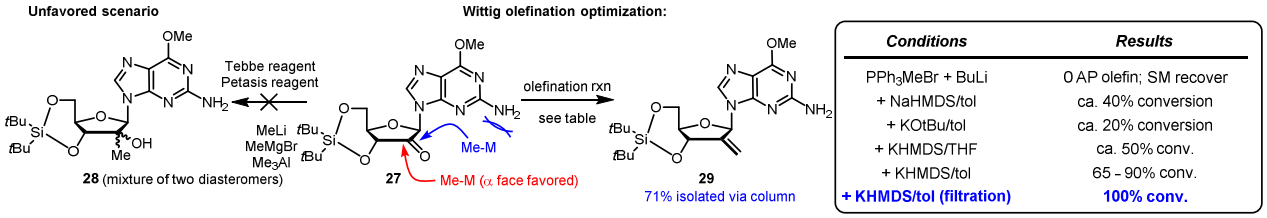
Next we developed a robust process on deca-gram scale for the first three-step (scheme 5b). On step 1, after slow addition of 0.95 equivalent TBS_2SiOTf_2 into the suspension of guanosine **11** in DMF below 2 °C, the crude was aged for 1 h at 20 °C and quenched with water to directly crystallize the silyl ether **19** with excellent yield and purity. Based on the optimized conditions, **21** was also isolated in 90% yield where we developed the crystallization after workup. In step 3, a robust IBD/TEMPO oxidation in a mixed solvent of DCM/AcOH delivered the ketone **27** at ambient temperature in 4 h. The product **27** can be consistently isolated in 78% yield by crystallization with EtOAc and water (V:V ratio 50:1) on 7 gram scale.



Scheme 5: Reaction defining and progress development for silylether ketone **27**.

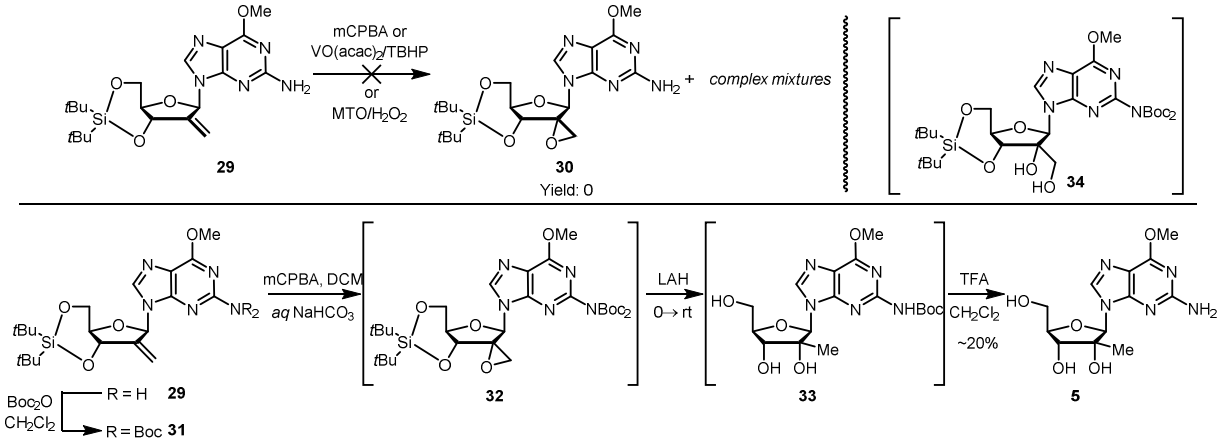
With ketone **27** in hand, we turned our attention to identifying a functionalization strategy (scheme 6). Well aligned with Piccirilli's observation[14], direct methyl addition to on ketone **27** afforded poor site and facial selectivity with methyl Grignard, methyl lithium reagent or Me_3Al under various conditions. The Tebbe or Petasis reagents also decomposed **27**. An olefination-oxidation strategy was the next option. Even though our early attempts at the olefination of **27** afforded poor conversion and no more than 50% yield with butyl lithium and PPh_3MeBr, we wondered if salt effects might interfere with the reaction conversion – given the allylic nature of the anomeric base being created, increasing the probability of

base elimination[15]. To our delight, after filtration of the solution of Ph_3PMeBr and KHMDS in toluene, a salt-free Wittig reagent was effective in the methyenylation of ketone **27**, affording for 100% conversion and 71% yield of **29** after isolation.



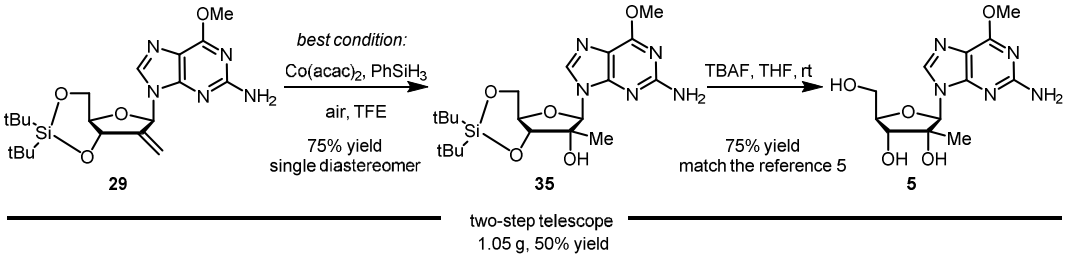
Scheme 6: Olefination of ketone **27** to olefin **29**.

To complete the synthesis of nucleoside **5**, we needed to perform a diastereoselective oxidation on olefin **29**. Oxidation failed when we utilized **29** with conditions such as mCPBA, $VO(acac)_2$/TBHP or MTO/H_2O_2, giving partially decomposed mixtures (scheme 7). We assumed that a new substrate, with the amine on the nuclear base masked, would reduce the impact of oxidation on the heterocyclic moiety enabling a clean and selective oxidation. To test this assumption, Bis-Boc protection of **29** was performed to afford **31**. Exploring a broad range of oxidation conditions and solvent options, we found that *m*CPBA oxidation in the presence of sodium bicarbonate and dichloromethane, yielded epoxidation product **32** with high diastereoselectivity[16]. Due to the lack of stability of **32**, the crude was subsequently reduced by $LiAlH_4$ in THF at 0 °C to form **33**. Upon treating **33** with TFA, we can obtain desired product **5** after chromatography. Unfortunately, scale-up efforts on this approach met with a significant issue, primarily due to the stability of **32** and **33**. We found epoxide **32** was partially hydrolyzed to form diol **34** during workup, causing various ratio between **33** and **34**. Isolation of **33** and **34** by chromatography also failed due to their instability on silica gel. Triol **33** was also unstable under our scale up conditions resulting in low and variable yields (~20%) for the three step-telescope reaction. Thus, although this approach represented a formal proof of concept for an alternate route, the instability of the intermediates forced us to explore better options.



Scheme 7: First effort towards end game to achieve the penultimate intermediate **5**.

Revisiting substrate **29**, we considered a Mukaiyama hydration since it would deliver the desired oxidation product in a single step without protecting group manipulation[17]. Moreover, based on our assumption that the alpha face of the sugar is less hindered (scheme 6), we believed that oxidation would occur from the desired face. To our delight, under air in the presence of $Co(acac)_2$ and $PhSiH_3$ in THF, **29** was smoothly converted to the desired tertiary alcohol **35** (Scheme 8). However, the reaction yield was inconsistent and low-yielding when run on more than 100 mg scale. To further optimize the condition, we revisited more catalysts, such as $Mn(dpm)_3$, and more solvents, including MeOH, iPrOH, 2-MeTHF and TFE. We found that TFE delivered highly consistent result, potentially due to the high oxygen solubility in fluorinated solvents and dielectric constant of TFE[15b], tertiary alcohol **35** was consistently obtained in 75% yield by combination of $Co(acac)_2$ and $PhSiH_3$ under air[18]. In the subsequent step, TBAF smoothly deprotected the silyl group to give final product **5** in 75% yield. After further optimization of the reaction conditions, crude **35** can be carried through the TBAF deprotection after solvent swap from TFE to THF, without isolation. The isolated yield is 50% for the two-step procedure on gram scale.



Scheme 8: End game to achieve the penultimate intermediate **5**.

Conclusion:

In summary, we have developed a short and efficient synthesis of the nucleoside **5** from widely available guanosine (**11**). This route avoided a low-yielding Mailand-Amadori reaction and an expensive, proprietary isolation technology, multiple impurities and complex reactions, which all complicated the use of the existing synthesis on scale. This new approach offers robust procedures for preparing the 2',6 dimethyl guanosine in six steps, with three crystallizations and three telescope-steps in an overall 23% yield. We believe that this approach may be amenable to SAR activities, enabling a systematic modification of alkyl groups at C-6 and C-2' positions facilitating further exploration of this chemotype.

Experimental Section

General Experimental Information: All reactions were performed under a nitrogen atmosphere using anhydrous techniques unless otherwise noted. Reagents were used as received from the vendors, unless otherwise noted. Quoted yields are for isolated material, and have not been corrected for moisture content. Reactions were monitored by silica TLC or reverse phase HPLC on a Shimadzu system using CH_3CN/H_2O/MeOH as the mobile phase (containing either 0.05% TFA, or 0.1% NH_4OAc). NMR-spectra were recorded on Bruker DRX-400 or DRX-500 instruments, and are referenced to residual undeuterated solvents. The following abbreviates are used to explain multiplicities: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra (HRMS) were recorded on a Thermo Orbi-trap Discovery instrument. Melting points were recorded using a Thomas Hoover melting point apparatus and are uncorrected. The quantitative analysis of residual palladium catalyst was performed with a Perkin-Elmer Optima 4300 DV ICP-AES instrument. UPLC (ultra pressure liquid chromatography) was recorded on Shimazu UPLC work station, with the following condition: Gradient: Complex; Start % B: 0; 2 Min. 100%; 2.5 Min. 100%; Stop Time: 4 min; Flow Rate: 1 ml/min; PDA wl1: 220 nm; Solvent Pair: TFA/MeCN/Water; Solvent A: A3 = 0.05% TFA in MeCN:Water (5:95) S194; Solvent B: B3 = 0.05% TFA in MeCN:water (95:5) S195; column ascentis express C18 2.7 um 2.1 x 50mm; Oven Temperature: 40.

2-Amino-9-((4a*R*,6*R*,7*R*,7a*S*)-2,2-di-*tert*-butyl-7-hydroxytetrahydro-4*H*-furo[3,2-*d*][1,3,2]dioxasilin-6-yl)-1,9-dihydro-6*H*-purin-6-one **19:**

To a 500 mL round bottom flask was charged with guanosine **11** (20.0 g, 1.0 eq., 70.6 mmol), DMF (100 mL) and 2, 6-lutidine (17.3 mL, 2.1 eq, 148 mmol). The crude was cooled to 0 °C under nitrogen atmosphere, and di-tert-butylsilylbis(trifluoromethanesulfonate) (30.0 g, 0.96 eq., 67.1 mmol) was added slowly while maintaining the internal temperature below 5 °C. (Note: The addition was exothermic.) Upon completion of the addition, the reaction crude was warmed up to 20 °C and stirred until the reaction finished (monitored by HPLC). After completion of the reaction (1 h), water (100 mL) was charged over a course of 5 minutes. The resulting white slurry was stirred at 20 °C for additional 30 minutes, filtered, rinsed with 50% DMF/water (2 X 30 mL) then water (30 mL). The wet cake was dried in vacuum oven (50 °C) till no weight loss was observed (24 h). Compound **19** was obtained as a white crystalline solid with desired quality (28.4 g, yield 95%). **Data for Compound 19: ^{1}H-NMR** (400 MHz, DMSO-D6, 23 °C) δ = 1.01 (s, 9H), 1.07 (s, 9H), 3.93-4.01 (m, 1H), 4.21-4.31 (m, 1H), 4.28-4.43 (m, 2H), 5.69-5.86 (m, 2H), 6.49 (brs, 2H), 7.93 (s, 1H), 10.67 (s, 1H); **^{13}C-NMR** (101 MHz, DMSO-D6, 23 °C)

δ = 156.6, 153.8, 150.6, 136.5, 116.3, 89.2, 76.3, 73.7, 73.0, 66.9, 27.3, 27.0, 22.2, 20.1; **HRMS (ESI-TOF) m/z:** [M+H]+ calcd for $C_{18}H_{29}N_5O_5Si$ 424.2016; Found 424.2007; **M.P.** 200-205 °C.

(4a*R*,6*R*,7*R*,7a*S*)-6-(2-Amino-6-methoxy-9*H*-purin-9-yl)-2,2-di-*tert*-butyltetrahydro-4*H*-furo[3,2-*d*][1,3,2]dioxasilin-7-ol **21:**

Compound **19** (5.0 g, 1.0 eq., 11.8 mol) was charged into a 250 mL round bottom flask that had previously been flushed with nitrogen. To the flask was added pyridine (25 mL) followed by trifluoroacetic anhydride (5.3 mL, 3.2 eq., 37.8 mmol). After the reaction mixture was stirred at 20 °C for 30 minutes, lithium methoxide (as 10 wt% solution in methanol; 22 mL, 4 eq., 47.2 mmol) and methanol (50 mL) were added. The resulting reaction mixture was stirred at 20 °C for 6 h. Water (50 mL) was charged and the reaction resumed for another 4 h. The white slurry was then filtered, washed with 50% MeOH/water (2 x 15 mL), and dried in vacuum oven (50 °C) till no weight loss was observed (12 h). Compound **21** was obtained as a white crystalline solid with desired quality (4.7 g, yield 90%). **Data for Compound 21: ^{1}H-NMR** (500 MHz, $CDCl_3$, 23 °C) δ = 1.04 (s, 9 H), 1.08 (s, 9 H), 4.03 (s, 3 H), 4.10 (dd, *J* = 4.9, 9.3 Hz, 1 H), 4.25 (broad, 1 H), 4.47 – 4.53 (m, 3 H), 5.29 (broad, 3 H), 6.06 (s, 1 H), 7.64 (s, 1 H); **^{13}C-NMR** (101 MHz, $CDCl_3$, 23 °C) δ = 161.8, 159.2, 152.7, 137.9, 116.4, 90.5, 75.8, 74.8, 73.7, 67.6, 54.0, 27.4, 27.2, 22.8, 20.4; **HRMS (ESI-TOF) m/z:**[M+H]+ calcd for $C_{19}H_{31}N_5O_5Si$ 438.2173; Found 438.2163; **M.P.** 240-245 °C.

(4a*R*,6*R*,7a*R*)-6-(2-Amino-6-methoxy-9*H*-purin-9-yl)-2,2-di-*tert*-butyldihydro-4*H*-furo[3,2-*d*][1,3,2]dioxasilin-7(6*H*)-one **27:**

To a 250 mL round bottom flask was charged compound **27** (6.5 g, 1.0 eq. 14.8 mmol), dichloromethane (130 mL) and acetic acid (0.85 mL, 1.0 eq., 14.8 mmol). The mixture was stirred at 20 °C for 5 minutes to form a slightly cloudy solution. Iodosobenzene diacetate (5.7 g. 1.2 eq.; 17.8 mmol) was then added, followed by 2,2,6,6-tetramethylpiperidine N-oxide (0.46 g; 0.2 eq.; 3 mmol). The resulting reaction mixture was stirred at 20 °C while the reaction progress was monitored by HPLC. After completion of the reaction (4 h), the crude was concentrated to remove dichloromethane. The crude oil was dissolved in ethyl acetate (50 mL) to form a homogeneous solution. To this solution was charged with water (1 mL) over a course of 5 minutes. The resulting white slurry was stirred at 20 °C for additional 30 minutes, filtered and rinsed with EtOAc (2 x 10 mL). After drying in vacuum oven (50 °C) till no weight loss was observed (24 h), compound **27** was obtained as a white crystalline solid with desired quality (5.0 g, yield 77%). **Data for Compound 27: ^{1}H-NMR** (500 MHz, $CDCl_3$, 23 °C) δ = 1.08 (s, 9 H), 1.14 (s, 9 H), 4.08 (s, 3 H), 4.47 – 4.53 (m, 3 H), 4.58 – 4.61 (m, 1 H), 4.90 (broad, 1 H), 6.18 (s, 1 H), 7.07 (s, 1 H), 7.79 (s,

1 H); **^{13}C-NMR** (125 MHz, $CDCl_3$, 23 °C) δ = 162.3, 156.2, 152.6, 136.5, 117.6, 87.5, 87.2, 78.1, 75.5, 67.6, 54.0, 27.3, 22.8, 22.6 (**Note: this intermediate exists as a gem-diol in standard NMR solvents). HRMS (ESI-TOF) m/z:**[2M+H]+ calcd for $C_{38}H_{59}N_{10}O_{10}Si_2$ 871.3954; Found 871.3950; **M.P.** 185-192 °C.

9-((4a*R*,6*R*,7a*S*)-2,2-Di-*tert*-butyl-7-methylenetetrahydro-4H-furo[3,2-*d*][1,3,2]dioxasilin-6-yl)-6-methoxy-9*H*-purin-2-amine **29 and** Boc protected 9-((4a*R*,6*R*,7a*S*)-2,2-di-*tert*-butyl-7-methylenetetrahydro-4H-furo[3,2-*d*][1,3,2]dioxasilin-6-yl)-6-methoxy-9*H*-purin-2-amine **32:**

To a 25 mL round bottom flask was charged methyltriphenylphosphonium bromide (2.0 g, 2.5 eq., 5.7 mmol) and toluene (10 mL). The flask was flushed with nitrogen and the white slurry was cooled to 0°C. Potassium hexamethyldisilazide (1.1 g, 2.4 eq., 5.5 mmol) was charged portion wise over a course of 5 minutes. After addition, the resulting crude was stirred at 0 °C for 1 hour, filtered, and rinsed with toluene (5 mL). The filtrate was transferred to a 50 mL round bottom flask, flushed with nitrogen, and cooled to 0 °C. To this solution was charged with compound **27** (1.0 g, 1.0 eq., 2.3 mmol) as solid. The resulting suspension was held at 0 °C for 20 minutes before warming up to 20 °C, while the reaction progress was monitored by HPLC. After completion of the olefination (6 h), di-tert-butydicarbonate (1.3 g, 2.5 eq., 5.7 mmol) was added in one portion, followed by 4-dimethylaminopyridine (10 mg, 2 mol%, 0.05 mmol). The reaction crude was warmed up to 45°C and held at 45 °C. After completion of the boc-protection (14 h), the crude was concentrated to remove most of toluene to afford a dark brown solid. Purification by column chromatography (silica gel, eluting with 10 – 25% EtOAc in hexanes) afforded compound **32** as off-white foam (1.12 g, 71% isolated yield).

Boc protected 9-((4a*R*,6*R*,7a*S*)-2,2-di-*tert*-butyl-7-methylenetetrahydro-4H-furo[3,2-*d*][1,3,2]dioxasilin-6-yl)-6-methoxy-9*H*-purin-2-amine **32: ^{1}H-NMR** (400 MHz, CD_3OD, 23 °C) δ = 1.04 (s, 9H), 1.15 (s, 9H), 1.39 (s, 18H), 3.79 (dd, *J* = 4.0 and 12.0 Hz, 1H), 4.10 (dd, *J* = 0.8 and 12.0 Hz, 1H), 4.16 (s, 3H), 4.39 (dd, *J* = 4.0 and 8.0 Hz, 1H), 5.42 (dd, *J* = 0.8 and 4.0 Hz, 1H), 5.47 (dd, *J* = 0.8 and 4.0 Hz, 1H), 5.68 (ddd, *J* = 4.0, 8.0 and 12.0 Hz, 1H), 6.67 (dd, *J* = 0.8 and 4.0 Hz, 1H), 8.49 (s, 1H); **^{13}C-NMR** (125 MHz, $CDCl_3$, 23 °C) δ = 161.5, 152.3, 152.2, 150.7, 145.3, 140.9, 120.3, 111.0, 83.2, 82.9, 77.3, 76.4, 67.6, 54.6, 27.8, 27.4, 27.0, 22.7, 20.1; **HRMS (ESI-TOF) m/z:** [M+H] calcd for $C_{30}H_{47}N_5O_8Si$ 634.3272; Found 634.3268; **M.P.** 150-158 °C.

9-((4a*R*,6*R*,7a*S*)-2,2-di-*tert*-butyl-7-methylenetetrahydro-4H-furo[3,2-*d*][1,3,2]dioxasilin-6-yl)-6-methoxy-9*H*-purin-2-amine **29:** After formation of the olefin confirmed by HPLC, the crude was added hexanes and stirred for 30 min. The crude was filtered, concentrated to give brown paste. Purification by

column chromatography (silica gel, eluting with 10 – 25% EtOAc in hexanes) afforded compound **29** as white solid (2.51 g; 79% isolated yield on 3.20 gram scale). **Data for Compound 29: ^{1}H-NMR** (400 MHz, $CDCl_3$, 23 °C) δ = 1.02 (s, 9H), 1.12 (s, 9H), 3.77 - 3.71 (m, 1H), 4.09 - 4.01 (m, 4H), 4.41 (dd, *J*=9.3, 5.1 Hz, 1H), 4.90 - 4.84 (m, 3H), 5.37 (dd, *J*=2.9, 1.6 Hz, 1H), 5.56 (t, *J*=2.3 Hz, 1H), 6.52 (q, *J*=1.8 Hz, 1H), 7.63 (s, 1H); **^{13}C-NMR** (101 MHz, $CDCl_3$, 23 °C) δ = 160.7, 160.0, 146.1, 138.1, 113.6, 109.7, 81.6, 76.3, 76.2, 66.9, 53.2, 27.3, 27.0, 22.2, 19.8; **HRMS (ESI-TOF) m/z:** [M+H]+ calcd for $C_{20}H_{32}N_5O_4Si$ 434.2218; Found 434.2213; **M.P.** 199-205 °C.

(2*R*,3*S*,4*R*,5*R*)-2-(2-Amino-6-methoxy-9*H*-purin-9-yl)-5-(hydroxymethyl)-3-methyltetrahydrofuran-3,4-diol **5 and** (4a*R*,6*R*,7*S*,7a*R*)-6-(2-amino-6-methoxy-9*H*-purin-9-yl)-2,2-di-*tert*-butyl-7-methyltetrahydro-4*H*-furo[3,2-*d*][1,3,2]dioxasilin-7-ol **35:**

In a 100 mL flask, compound **29** (1.05 g, 1.0 eq., 2.42 mmol) was dissolved in TFE (16 mL). To the solution, $PhSiH_3$ (1.25 mL, 4.0 eq., 10.1 mmol,) and $Co(acac)_2$ (1.0 g, 0.16 eq., 3.9 mmol) was added to give a grey suspension which was stirred vigorously. After 2.5 h, TLC and HPLC showed the reaction finished. The crude was filtered through celite and concentrated under vacuum. To the crude, THF (20.0 mL) was added to give dark blue solution, TBAF (4.8 mL, 2.0 eq., 4.8 mmol, 1 mol/L) was added to give a dark brown solution in 1 min. TLC showed the reaction finished in 1.5 h. The crude was concentrated and purification by column chromatography (silica gel, eluting with 0 – 10% MeOH in CH_2Cl_2) to give white solid **5** (0.378 g, 50% Yield). **Data for Compound 5: ^{1}H-NMR** (400 MHz, MeOH-D4, 23 °C): δ = 8.25 (s, 1H, H8), 5.98 (s, 1H), 4.22 (d, *J* = 9.1, 1H), 4.05 (s, 3H), 4.02 (ddd, *J* = 2.1, 5.7 and 8.5, 2H), 3.84 (dd, *J* = 3.0 and 12.1, 1H), 0.94 (s, 3H); **^{13}C-NMR** (101 MHz, $CDCl_3$, 23 °C) δ = 162.9, 162.0, 154.6, 139.5, 115.4, 93.1, 84.3, 80.5, 73.6, 61.3, 54.4, 20.5; **HRMS (ESI-TOF) m/z:** [M+H]+ calcd for $C_{12}H_{18}N_5O_5$ 312.1308; Found 312.1305.

(4a*R*,6*R*,7*S*,7a*R*)-6-(2-amino-6-methoxy-9*H*-purin-9-yl)-2,2-di-*tert*-butyl-7-methyltetrahydro-4*H*-furo[3,2-*d*][1,3,2]dioxasilin-7-ol **35:** After formation of the tertiary alcohol **35** confirmed by HPLC, the crude was filtered through celite and concentrated to give dark blue paste. Purification by column chromatography (silica gel, eluting with 20 – 35% EtOAc in hexanes) afforded compound **35** as white crystalline solid (101 mg; 75% isolated yield on 0.13 gram scale). **Data for Compound 35: ^{1}H-NMR** (400 MHz, CD_3OD, 23 °C): δ = 1.22 (s, 3H), 1.07 (s, 9H), 1.12 (s, 9H), 4.08 (s, 3H), 4.14-4.30 (m, 3H), 4.43 (dd, *J*= 8.6 and 4.5 Hz, 1H), 5.94 (s, 1H), 7.87 (s,1H); **^{13}C-NMR** (101 MHz, $CDCl_3$, 23 °C) δ = 162.9, 162.1, 154.7, 139.2, 115.7, 94.3, 81.5, 79.3, 76.1, 68.7, 54.4, 28.2, 27.8, 23.8, 21.5, 20.2; **HRMS (ESI-TOF) m/z:**[M+H]+ calcd for $C_{20}H_{34}N_5O_5Si$ 452.2329; Found 452.2315, **M.P.** 210-215 °C.

Associated Content

Supporting Information:

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxx.

1D NMR (^{1}H, ^{13}C) (PDF), and UPLC (ultra pressure liquid chromatography) data

Author Information

Corresponding Author

*E-mail: Changxia.yuan@bms.com, martin.eastgate@bms.com

ORCID

Changxia Yuan: 0000-0001-8442-676X

Martin Eastgate: 0000-0002-6487-3121

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Neil Strotman for insightful comments and editorial advice on manuscript preparation. We thank Yande Huang, Sloan Ayers, and Shasha Zhang for their help with the experiments, including NMR analysis, HRMS assistant and M. P. analysis.

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