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Stereoselective and Divergent Aza-Adenosine and Aza-Guanosine Syntheses from Xylofuranose, the Key Fragments of a STING Cyclic Dinucleotide Agonist

Changxia Yuan,* Adrian Ortiz, Zhongmin Xu, Jason Zhu, Michael A. Schmidt, Amanda Rogers, and Martin Eastgate

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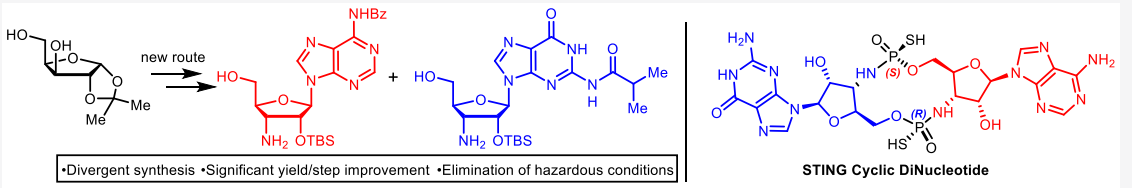

ABSTRACT: The stereoselective and divergent synthesis of two aza-nucleosides is reported. Starting from xylofuranose **9**, aza-adenosine **2** was prepared in 13 steps and 7% overall yield, and aza-guanosine **3** was prepared in 13 steps and 7.8% overall yield. Compared to the original syntheses, some advantages of these new routes are significant yield improvement, overall step-count reduction, an optimized protecting group strategy, the development of a versatile platform for nitrogenous base incorporation, and the elimination of hazardous reagents (e.g., benzyl isocyanate, $Et_3N{\cdot}HF$).

INTRODUCTION

In recent years, biopharmaceutical companies have and will continue to allocate resources in immune oncology for the treatment of cancers.[1] Among these efforts, one promising strategy is activating **STING** (**ST**imulator of **IN**terferon **G**enes), fostering an immune response to achieve a durable anticancer outcome.[2] One class of active pharmaceutical ingredients (APIs) under development in this area consists of cyclic thiophosphorous dinucleotides, such as **1**, featuring two unnatural 3′-aza-nucleosides cyclized with two stereogenic thiophosphates on both 3′-N and 5′-O (Scheme 1).[3] This challenging structure required an efficient synthesis to enable a commercial-scale API supply. In this report, we discuss our efforts to develop new routes to both key fragments, aza-nucleosides **2** and **3**, with excellent diastereoselectivity and good yield.

RESULTS AND DISCUSSION

The first-generation syntheses of aza-nucleosides **2** and **3** started from naturally occurring adenosine **4** and guanosine **5**, respectively (Scheme 2). The routes contained multiple challenges for future development: (1) Both routes were lengthy and low-yielding: 13 steps/4% overall yield for adenosine **2** and 15 steps/2% overall yield for guanosine **3**. (2) The current routes had high process mass intensities (PMI) and long lead times. (3) Some transformations suffered from low chemo- and/or regioselectivity (details in SI-1). (4) Both routes contained multiple protection−deprotection steps. (5) Some of the reagents, such as benzyl isocyanate and $Et_3N{\cdot}HF$, were highly hazardous and nonoptimal for manufacturing.

New Route Analysis and Synthesis of Intermediate 21. Embracing the challenges (Scheme 3) and recognizing that both aza-nucleosides, besides nitrogenous bases at C-1′, possessed identical atom connections and diastereochemistry, we envisioned that **7** could serve as a common intermediate to both fragments via a Vorbrüggen reaction. Further retro-synthetic analysis then led to acetonide **8**, followed by final simplification to widely commercially available protected xylofuranose **9**.

The synthesis commenced with selective benzoyl protection of xylofuranose **9** at C5′-OH, which proved scalable with an 85% in-process yield. Instead of isolating the resulting mono-Bz protected product, the stream was telescoped into the next step (Scheme 4). While the subsequent oxidation failed using IBX, Dess-Martin, and Moffatt conditions, Swern conditions worked moderately well (i.e., 60% yield at −70 °C) to afford decagram quantities of ketone **10** for early route exploration. Further screenings revealed that PIDA-TEMPO in CH_2Cl_2 delivered **10** in 71% in-process yield over the two telescoped

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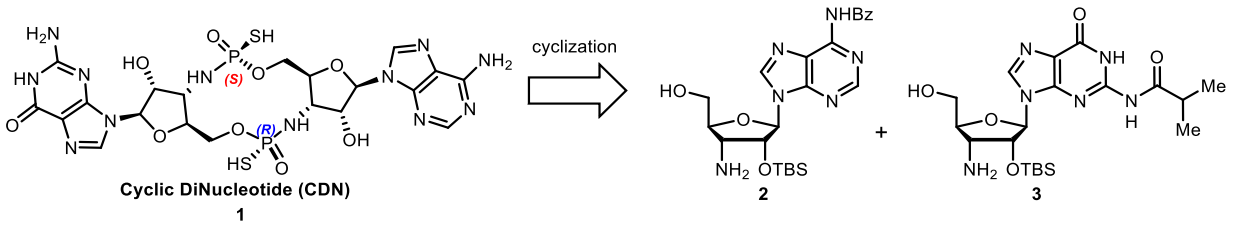
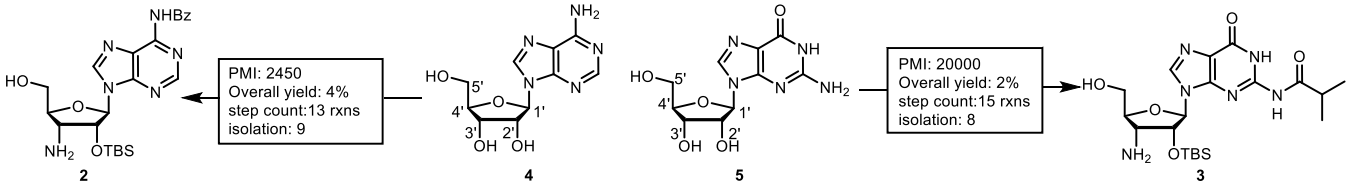
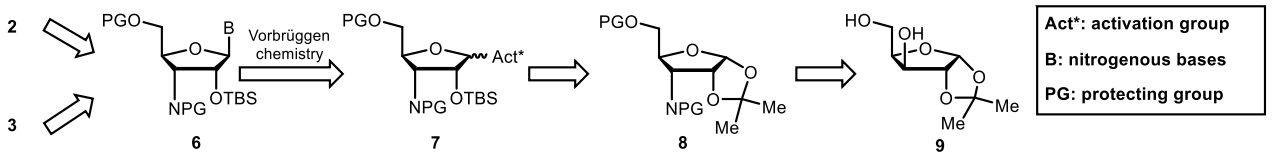
Scheme 1. Cyclic Dinucleotide and Key Aza-Nucleoside Fragment



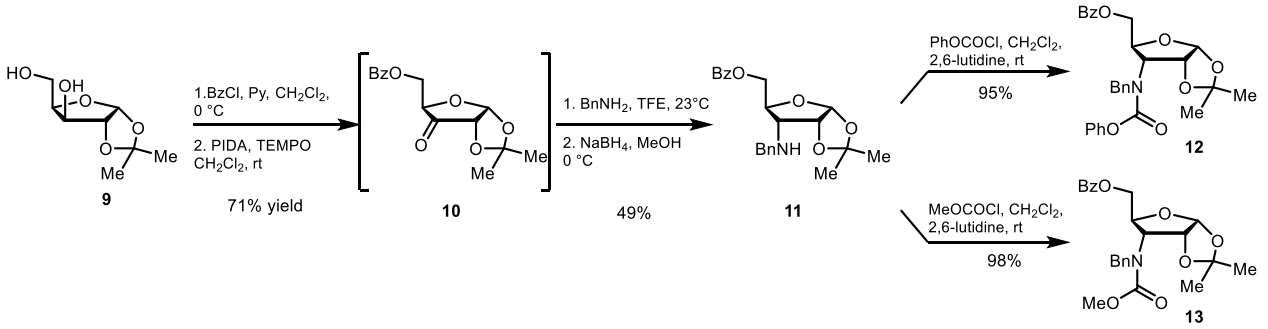
Scheme 2. Summary of First-Generation Synthesis of 2 and 3



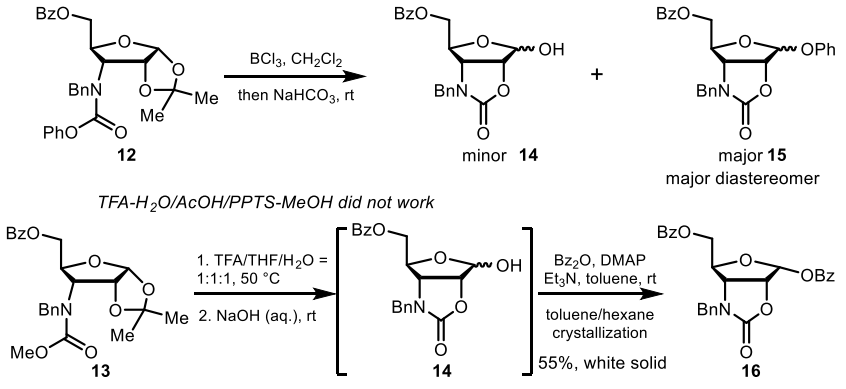
Scheme 3. Retrosynthetic Analysis of 2 and 3



Scheme 4. Initial Functionalization of Xylofuranose 9



Scheme 5. Acetonide Deprotection and Cyclization



steps. Imine formation then proceeded smoothly with benzylamine in TFE, followed by reduction with sodium borohydride in MeOH at 0 °C to give benzylamine **11** with a 49% isolated yield.[4] Poor conversion was observed during imine formation using other common solvents, with or without boron or zinc-based Lewis acids. Benzylamine **11** was then reacted with either phenyl chloroformate or methyl chloroformate to afford **12** and **13**, respectively.

To prepare precursor **7** for Vorbrüggen chemistry,[5] deprotection of the acetonide and C1′-OH activation were required. Brønsted acid-mediated deprotection conditions, such as TFA−water, AcOH, or PPTS-MeOH worked poorly on **12**, resulting in decomposition (Scheme 5). BCl_3 was

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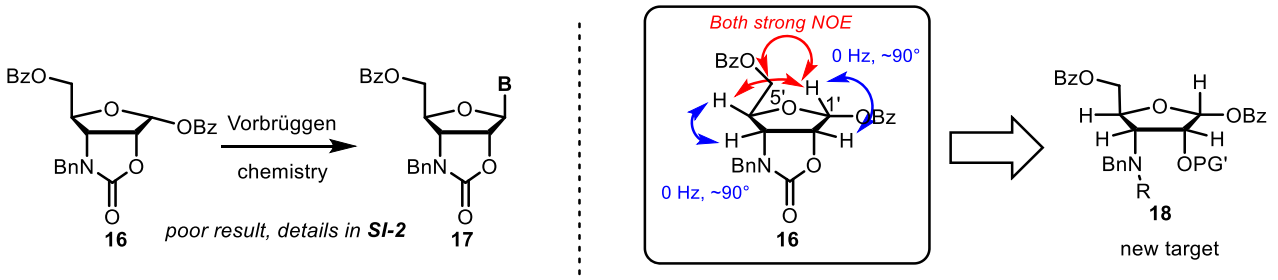
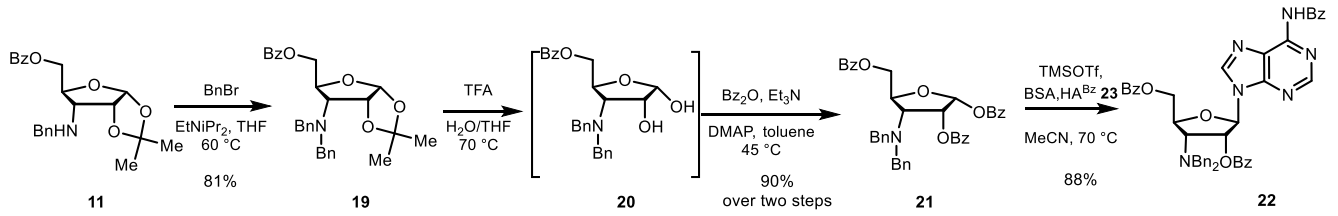
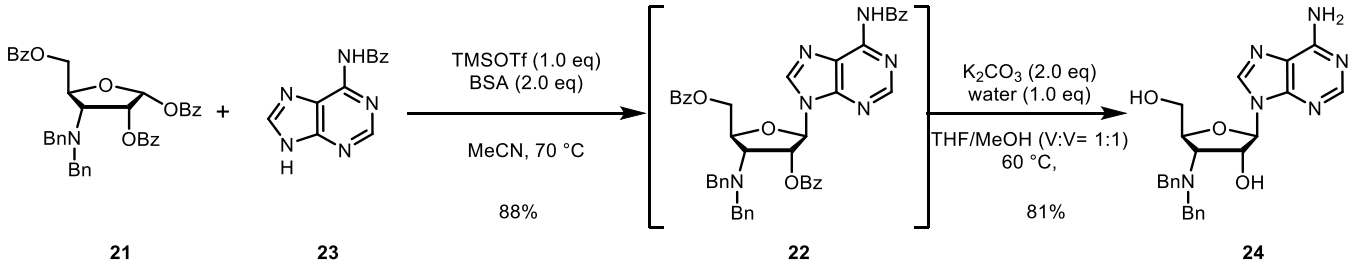
Scheme 6. Detour of Vorbrüggen Chemistry and New Proposal



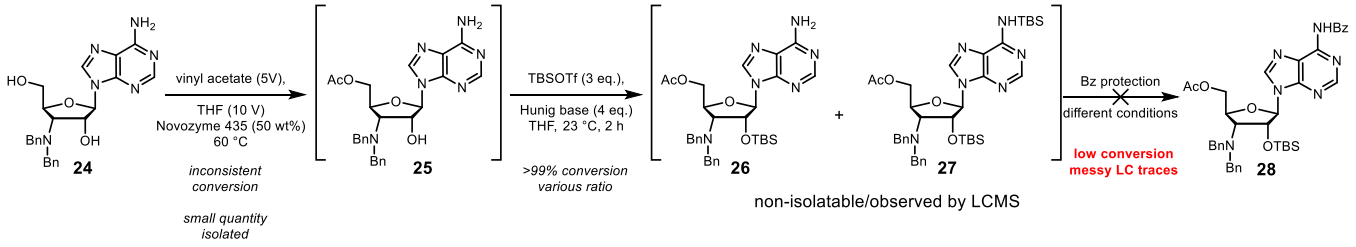
Scheme 7. Summary of Early Steps and Vorbrüggen Chemistry



Scheme 8. Optimized Vorbrüggen Chemistry and Deprotection



Scheme 9. Challenges in First-Generation Protection−Deprotection



effective, but it led to OPh adduct **15** rather than desired hemiacetal **14**. Gratifyingly, using TFA-THF-H_2O conditions, methyl carbamate **13** smoothly deprotected to give hemiacetal **14** with a minimal C1′ methoxy adduct. The reaction of **14** in solution with either benzoyl chloride in the presence of Et_3N, DMAP, levamisole, or lutidine was unsuccessful. Eventually, the protection worked efficiently using benzoic anhydride in the presence of both DMAP and Et_3N to give **16** in 55% yield over the two steps. This process was reproducible on the gram scale to produce high-quality product as a single diastereomer after workup and crystallization from toluene/hexane.

To our surprise (Scheme 6), subjecting **16** to various Vorbrüggen conditions using different nitrogenous bases (i.e., 6-chloropurine, 6-benzoylaminopurine, adenine, and 6-benzoyladenine) and activating agents (i.e., TMSOTf, $SnCl_4$) led only to trace product **17**, with most of the starting material intact (details in SI-2). Interestingly, a closer examination of 2-D NMR data supported that bicycle **16** was very rigid and a 1,3 interaction between C5′ and C1′ likely discouraged the desired Vorbrüggen chemistry. On the basis of this hypothesis, we envisioned that releasing the ring strain in the carbamate (i.e., new target **18**) would prove beneficial.

During the subsequent development, we found dibenzylamino sugar **19** to be stable and robust and thus used this compound as the handle for future development (Scheme 7). While direct reductive amination of ketone **10** with dibenzylamine to afford **19** was unsuccessful, **19** was readily prepared from **11** in 81% yield. After TFA deprotection of **19**, acetal **20** was worked up and the concentrated crude product was subjected to Bz_2O, Et_3N, and DMAP in warm toluene to deliver **21** in 90% yield, isolated as a pale-brown crystalline solid. The Vorbrüggen chemistry between **21** and 6-benzoyladenine (HA^{Bz}) **23**, activated by BSA and TMSOTf in MeCN, worked very well to give adenosine nucleoside **22** in 88% isolated yield. In summary, the synthesis of key intermediate **21** was accomplished in six chemical transformations, with only three isolations (i.e., **11**, **19**, and **21**), no chromatography, and a 25% overall yield.

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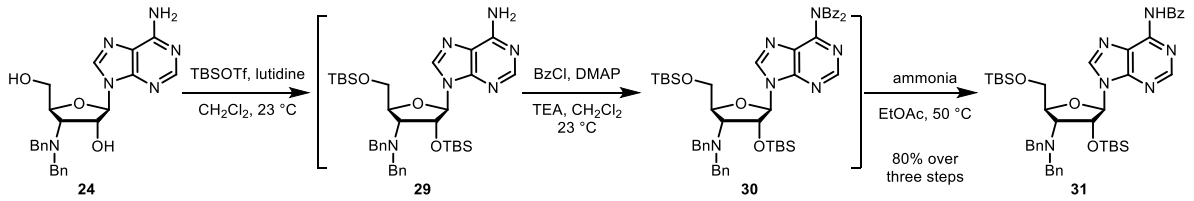
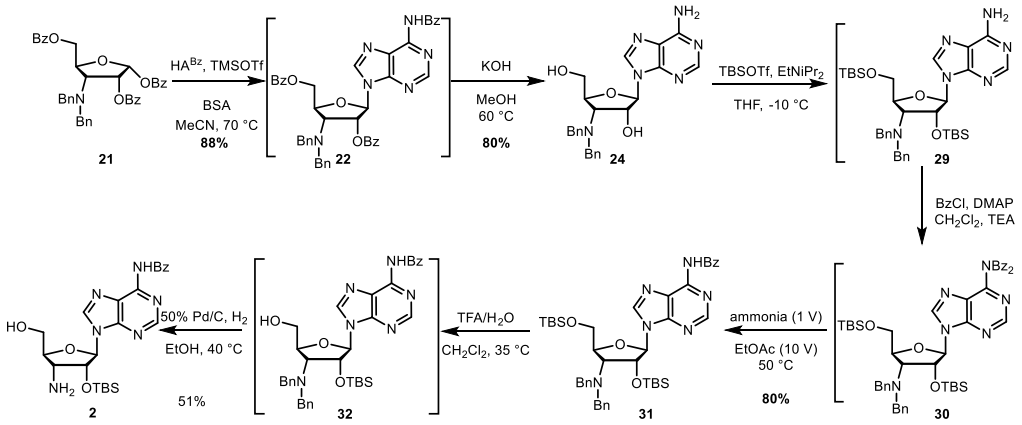
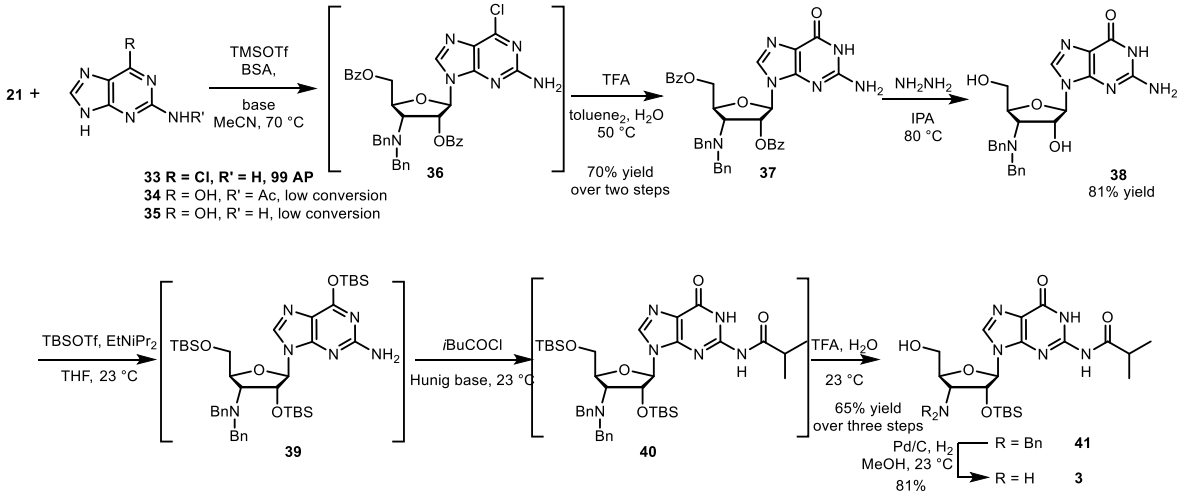
Scheme 10. Second-Generation End-Game Approach to 31



Scheme 11. Adenosine 2 End-Game Summary



Scheme 12. Guanosine 3 Synthesis Route Development



Aza-Adenosine 2 Synthesis. Having obtained a proof-of-concept for the challenging Vorbrüggen chemistry, additional development revealed a few key factors. First, 6-benzoylaminopurine (**23**) should be premixed with **21** and BSA to avoid precipitation. Second, the amount of TMSOTf was critical. At least 1.0 equiv of TMSOTf was required for consistent conversion (≥95%)[6] and low impurity formation.[7] After the workup, crude **22** was globally hydrolyzed with K_2CO_3 in the mixture of THF, MeOH, and water to deliver diol **24** on a gram scale in 81% yield (Scheme 8).

We next needed to selectively protect the most reactive primary alcohol in **24**, followed by sequential protection of the secondary alcohol and aniline nitrogen (Scheme 9). To our surprise, selective monoprotection of diol **24** proved challenging under numerous conditions (details in SI-3), resulting in complex mixtures in most cases. During the screening process, enzymatic conditions using Novozyme 435 afforded **25**, though with varying conversion.[8] Unfortunately, any scale-up efforts (>100 mg) resulted in complicated mixtures for this transformation. Furthermore, since subsequent TBS protection produced **26** and **27** as an inseparable mixture and benzoyl protection led to complex mixtures that required tedious chromatography, C5′ acetyl protection was deemed unsuitable for long-term development.

On the basis of the previous knowledge, we obtained a proof of concept for an improved endgame that started with the TBS protection of alcohol **24** (Scheme 10). The TBS protection produced **29** on a small scale (<500 mg). Because of stability challenges associated with **29**, the reaction stream was telescoped into bis-benzoyl protection using catalytic DMAP, BzCl, and TEA in CH_2Cl_2, followed by mono-Bz deprotection with ammonia in EtOAc to afford **31** in 80% yield over three steps.

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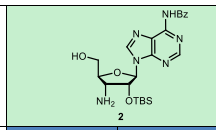
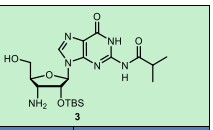
Piecing all of the knowledge together, the final optimized route to aza-nucleoside **2** is shown in Scheme 11. Starting from **21**, optimization of the temperature, solvent volume, and reagent equivalents led to consistent performance of the Vorbrüggen reaction on the decagram scale. For subsequent benzoyl deprotection, we found that a 3:1 aqueous KOH:MeOH ratio was optimal to minimize the reaction stalling during the formation of **24** and ultimately developed a two-step telescope to convert **21** to **24**, by performing a crystallization without the need for any chromatography. For the TBS protection of **24**, the optimal conditions involved the use of $EtiPr_2N$ at −10 °C in THF, followed by the telescoped benzoyl protection/deprotection to afford **31** as an amorphous solid in 80% yield over the three steps. It is worth mentioning that, for the TBS protection step, controlling the reaction temperature to −10 °C reduced the exotherm and changing the solvent from DCM to THF improved the safety robustness. Monodesilyation of **31** proceeded without issue using TFA/water/CH_2Cl_2. After a few rounds of hydrogenation screening, we chose to telescope the crude solution of **32** using 50 wt % Pd/C in EtOH to afford **2** in 51% isolated yield over the two steps. In brief summary, the synthesis of aza-nucleosides **2** proceeded in six chemical transformations from common intermediate **21**, with only three isolations (i.e., **24**, **31**, and **2**), no chromatography, and a 28% overall yield.

Guanosine Synthesis. With the success of the aza-adenosine **2** synthesis, we applied our experience to the synthesis of the aza-guanosine nucleoside **3** (Scheme 12). Built on the prior success, we explored the Vorbrüggen reaction with multiple guanosines, revealing that N2 acetylguanine **34** and guanine **35** led to sluggish reactivity and/or poor selectivity. Fortunately, the Vorbrüggen reaction using 6-chloropurine **33** afforded **36** in over 95% conversion and was isolatable by chromatography on small scale.[9] Further exploration of the next steps led to the decision to telescope crude **36** into the hydrolysis with TFA to afford **37** in 70% isolated yield over the two steps with no need for chromatography.[10] Because of the low solubility of monobenzoyl intermediates and **38**, initial attempts to prepare **38** using inorganic bases in various solvents failed. Fortunately, the addition of hydrazine in hot IPA led to bis-benzoyl hydrolysis to afford diol **38** in 81% yield. These three steps were readily conducted on a multigram scale to prepare more than 10 g of **38**. To mirror the experience in the aza-adenosine route, we initially investigated the enzymatic conditions to selectively acylate the 5′-primary alcohol in **38** but were unsuccessful. Switching to the TBSOTf conditions delivered the triTBS-protected product **39** with excellent conversion. As **39** was unstable to chromatographic purification, we successfully telescoped **39** into a reaction with iBuCOCl and Hünig base to simultaneously install the isobutyl group and deprotect the guanine TBS moiety. This observation was consistent with the prior finding[11] that the presence of the guanine TBS group assisted the acetylation. In addition, we found that isobutyryl chloride was superior to isobutyl anhydride and Hünig's base was optimal. In the last step of three-step telescope, we found that the primary TBS group in **41** was surprisingly robust and using TFA led to the optimal balance between reaction time and yield. Overall, this three-step telescope reaction from **38** afforded **41** in 65% isolated yield after crystallization from $iPrOH/H_2O$. Finally, guanosine substrate **41** readily debenzylated to **3** in 85% yield with Pd/C under H_2 in EtOH at ambient temperature.[12] In summary, starting from **21**, we prepared **3** through a seven-step synthesis, isolating intermediates **37**, **38**, **41**, and **3** by crystallization and proceeding in 31% overall yield on gram scales with no chromatography.

CONCLUSIONS

We have developed a second-generation synthesis of aza-nucleosides **2** and **3** with significantly improved efficiency. As summarized in Table 1, the new routes are highly advanta-

Table 1. Route Comparison for Step Count, Overall Yield, PMI, and Isolation Number

	 2		 3	
	Old route	New-route	Old route	New route
Total steps	13	13	15	13
Overall Yield**	4%	7%	2%	7.8%
PMI	2400[W]	1000[Z]	20000[W]	1300[Z]
Isolation number	9	6	8	7

[W] Average number based on the scale-up batches (0.5 -1.1 kg), considering the crystallizations are not fully optimized.

[Z] Estimation based on the current conditions, considering the crystallizations are not fully optimized.

	2 old route	2 new-route	3 old route	3 new route
total steps	13	13	15	13
overall yield**	4%	7%	2%	7.8%
PMI	2400[a]	1000[b]	20000[a]	1300[b]
isolation number	9	6	8	7

[a]Average number based on the scale-up batches (0.5−1.1 kg), considering that the crystallizations are not fully optimized. [b]Estimation based on the current conditions, considering that the crystallizations are not fully optimized.

geous considering that (1) the overall step count was reduced from 28 (13 + 15) to 20 (6+7+7) steps through the current divergent synthesis, (2) the overall yield was improved from less than 4% to 7% for aza adenosine **2** and from 2% to 7.8% for aza-guanosine **3**, (3) the overall PMI was reduced by >90% for **3** and by 50% for **2**,[13] and (4) the number of overall isolations were reduced from 17 (9 (**2** first gen) + 8 (**3** firstgen)) to 9 (2 (**21**) + 3 (**2** sec gen) + 4 (**3** sec gen)). Further efforts toward the kilogram-scale synthesis of **2** and **3** are currently under development and will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Information. All reactions were performed under a nitrogen atmosphere using anhydrous techniques unless otherwise noted. The xylofuranose is a known compound that is widely available from vendors, for both laboratory and non-laboratory use. The compound was received and used as is. 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 a Bruker DRX-400 or

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DRX-500 instrument and are referenced to residual undeuterated solvents. The following abbreviations are used to explain multiplicities: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. High-resolution mass spectra (HRMS) were recorded on a Thermo Orbi-trap ESI Discovery instrument.

*((3aR,5R,6aS)-2,2-Dimethyl-6-oxotetrahydrofuro[2,3-d][1,3]-dioxol-5-yl)methyl Benzoate (**10**).* CH_2Cl_2 (50 mL) was added to a N_2-flushed 250 mL flask. Xylofuranose **9** (50 g, LR) and pyridine (42 mL, 2.0 equiv) were charged into the flask. Benzoyl chloride (39.1 g, 1.08 equiv) was slowly added to the reactor at −10 °C, in a dry ice−brine bath, over 1 h and quenched the reaction until the TLC indicated the reaction to finish in 1 h. Water (100 mL) was added to the cold solution. Layers were partitioned, and the organic stream was washed with citric acid (30 mL, 10 wt %, aq), $NaHCO_3$ (30 mL, 10 wt %, aq), and brine (20 mL, 15 wt %, aq). The organic crude was dried over Na_2SO_4 and concentrated to oil in a 500 mL flask. Into the crude was charged CH_2Cl_2 (250 mL). TEMPO (2.05 g, 0.05 equiv) and PIDA (8.5 g, 2.0 equiv) were added portionwise at 23 °C and quenched the reaction until the TLC indicated the reaction to finish in 4 h. The organic crude was washed with sodium sulfite (100 mL), and the aqueous phase was back-extracted with CH_2Cl_2 (50 mL × 2). The combined organic phase was washed with brine (50 mL), and the isolated organic layer was dried over Na_2SO_4. The crude was filtered and solvent-swapped with MTBE (200 mL) and added to heptane (200 mL) at 40 °C in 1 h, and then the slurry was further cooled to rt for 2 h before filtration to give **10** as an off-white solid, after drying to give **10** (54.5 g, 71%). Data for compound **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.7 Hz, 2H), 7.55 (t, J = 7.2 Hz, 1H), 7.42 (t, J = 7.7 Hz, 2H), 6.12 (d, J = 4.4 Hz, 1H), 4.70−4.65 (m, 2H), 4.48−4.39 (m, 2H), 1.49 (s, 3H), 1.41 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 207.6, 165.7, 133.3, 129.4, 129.2, 128.4, 114.3, 103.0, 76.1, 63.3, 27.3, 26.9. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{15}H_{17}O_6Na$ 315.0839; found 315.0846.

*((3aR,5S,6R,6aR)-6-(Benzylamino)-2,2-dimethyltetrahydrofuro-[2,3-d][1,3]dioxol-5-yl)methyl Benzoate (**11**).* To the N_2 flushed 250 mL flask, **10** (30 g), TFE (150 mL), and $BnNH_2$ (13.2 g, 1.2 equiv) were charged in such a sequence at 10 °C in a cold water batch. After 6 h, HPLC confirmed that no more than 7% of compound **10** was in the solution. The solution was immediately cooled to 0 °C. In a separate reactor, MeCN (150 mL) and STAB (65 g, 3.0 equiv) were added. To the suspension at 23 °C, the imine solution was transferred in about 10 min. After transfer, the reaction was agitated for an extra hour. Then the solution was washed with citric acid (150 mL, 5 wt %, aq) and brine (90 mL). The resulting organic solution was washed with Na_2CO_3 (150 L, 15 wt %, aq) and separated while controlling the pH between 7 and 8. The organic stream was washed with $NaHCO_3$ (90 mL, 6 wt %, aq) and 20 wt % brine (90 mL). The solvent of the crude was distilled, and the resulting oil was purified by flash chromatography with hexane:EtOAc (3:1) to give a yellow oil (19.3 g, 49%). Data for compound **11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 7.3 Hz, 2H), 7.56 (t, J = 7.1 Hz, 1H), 7.46−7.36 (m, 4H), 7.34−7.19 (m, 3H), 5.84 (d, J = 3.8 Hz, 1H), 4.76 (br d, J = 12.2 Hz, 1H), 4.64 (t, J = 4.2 Hz, 1H), 4.45−4.35 (m, 1H), 4.02 (br d, J = 13.2 Hz, 2H), 3.82 (d, J = 13.2 Hz, 1H), 3.05 (dd, J = 9.9, 4.5 Hz, 1H), 1.59 (s, 3H), 1.40 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.3, 132.9, 130.0, 129.8, 128.4, 128.3, 128.1, 127.2, 112.1, 104.7, 78.0, 76.9, 63.8, 60.7, 51.9, 26.7, 26.5. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{27}NO_5$ 384.1805; found 384.1813.

*((3aR,5S,6R,6aR)-6-(Benzyl(phenoxycarbonyl)amino)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methyl Benzoate (**12**).* In a nitrogen flushed 40 mL vial, **11** (0.84 g) was dissolved with CH_2Cl_2 (8 mL). To the solution, 2,6-lutidine (0.20 mL, 1.5 equiv) and phenyl chloroformate (0.33 mL, 1.2 equiv) were added dropwise at 25 °C. After 30 min, the crude was quenched with $NaHCO_3$(aq) (5 wt %, 5 mL). The organic layer was isolated and washed with aqueous citric acid (5 wt %, 5 mL) and aqueous brine (20 wt %, 5 mL) separately. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The resulting oil was purified by flash chromatography with hexane:EtOAc (5:1) to give a colorless oil (1.05 g, 95%). Data for compound **12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07−7.95 (m, 2H), 7.61−7.49 (m, 1H), 7.46−7.32 (m, 8H), 7.32−7.19 (m, 2H), 7.18−7.08 (m, 2H), 5.86 (d, J = 3.7 Hz, 1H), 5.18 (br d, J = 16.3 Hz, 1H), 4.98−4.75 (m, 2H), 4.70−4.60 (m, 2H), 4.0−4.24 (m, 1H), 4.02−3.80 (m, 1H), 1.69 (br s, 3H), 1.41 (br s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.3, 155.7, 151.4, 139.0, 138.9, 133.3, 130.0, 129.6, 129.0, 128.7, 128.6, 128.1, 127.8, 127.3, 125.9, 121.8, 113.2, 104.1, 104.0, 80.2, 79.7, 74.4, 63.5, 62.7, 58.6, 50.0, 27.0, 26.5. HRMS (ESI) m/z: [M + Na]+ Calcd for $C_{29}H_{29}NO_7Na$ 526.1842; found 526.1840.

*((3aR,5S,6R,6aR)-6-(Benzyl(methoxycarbonyl)amino)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methyl Benzoate (**13**).* In a nitrogen-flushed 40 mL vial, **11** (0.53 g, LR) was dissolved with CH_2Cl_2 (8 mL). To the solution, 2,6-lutidine (0.24 mL, 1.5 equiv) and methyl chloroformate (0.13 mL, 1.2 equiv) were added dropwise at 25 °C. After 30 min, the crude was quenched with $NaHCO_3$(aq) (5 wt %, 5 mL). The organic layer was isolated and washed with aqueous citric acid (5 wt %, 5 mL) and aqueous brine (20 wt %, 5 mL) separately. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The resulting oil was purified by flash chromatography with hexane:EtOAc (5:1) to give a colorless oil (0.95 g, 98%). Data for compound **13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 7.7 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.7 Hz, 2H), 7.39−7.14 (m, 5H), 5.80 (d, J = 3.7 Hz, 1H), 5.18−4.91 (m, 1H), 4.81 (br s, 1H), 4.4.86−4.37 (m, 4H), 4.33−4.13 (m, 1H), 3.84−3.72 (m, 4H), 1.64 (s, 3H), 1.35 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.4, 157.8, 133.3, 130.1, 130.0, 128.9, 128.6, 127.7, 113.1, 104.1, 74.4, 60.7, 58.3, 53.6, 27.1, 26.4, 21.3, 14.5. HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{24}H_{27}NO_7Na$ 464.1680; found 464.1686.

*((3aR,4S,6R,6aR)-6-(Benzoyloxy)-3-benzyl-2-oxohexahydrofuro-[3,4-d]oxazol-4-yl)methyl Benzoate (**16**).* In the N_2-flushed 250 mL flask, **13** (4.0 g) was dissolved in THF (50 mL). To the solution at 50 °C, on a heating mantle, H_2O (50 mL) and TFA (50 mL) were charged in such a sequence dropwise. After 24 h, HPLC confirmed no more **13**, provided that the reaction was quenched with 6 M NaOH (110 mL, aq) until pH 8 while controlling the temperature to no more than 40 °C. The crude was agitated for another hour. Then the solution was extracted with EtOAc (50 mL × 2), and the combined organic solution was washed with citric acid (23 mL, 5 wt %, aq) and brine (30 mL), and the organic crude was dried over Na_2SO_4. The crude was filtered and solvent swapped with toluene (50 mL). To the solution was added Et_3N (3.8 mL, 3.0 equiv), benzoic anhydride (2.3 g, 1.1 equiv) and DMAP (55 mg, 0.05 equiv) at 35 °C on a heating mantle. After 14 h, the crude was cooled to rt and washed with citric acid (25 mL, 5 wt %, aq), $NaHCO_3$ (25 mL, 5 wt % aq), and brine (30 mL). To the crude oil was slowly added hexane (50 mL) in 1 h at 50 °C. The slurry was cooled to rt and filtered to give an off-white solid, after drying to give a solid (2.35 g, 55%). Data for compound **16**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (br d, J = 7.7 Hz, 2H), 7.82 (br d, J = 7.7 Hz, 2H), 7.71−7.59 (m, 2H), 7.54−7.40 (m, 4H), 7.38−7.25 (m, 5H), 6.48 (s, 1H), 5.44 (d, J = 7.6 Hz, 1H), 4.78 (t, J = 6.6 Hz, 1H), 4.66 (d, J = 15.7 Hz, 1H), 4.54 (d, J = 7.6 Hz, 1H), 4.46−4.27 (m, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO) δ 165.6, 164.6, 156.5, 136.2, 134.4, 134.0, 129.9, 129.7, 129.5, 129.2, 129.2, 128.3, 128.2, 102.6, 82.5, 81.4, 64.8, 61.2, 46.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{27}H_{24}NO_7$ 474.1552; found 474.1547.

*((3aR,5S,6R,6aR)-6-(Dibenzylamino)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)methyl Benzoate (**19**).* To a nitrogen-flushed 250 mL flask with **11** (5.1 g), MeCN (50 mL), DIPEA (5.2 g, 3.0 equiv), and BnBr (4.6 g, 2.0 equiv) were added to the reactor. The reactor was warmed to 70 °C on a heating mantle for 7 h. The solution was cooled to 20 °C and charged with Et_3N (1.3 g, 1.0 equiv) in 30 min. After 12 h, the solution was added to toluene (200 mL) and stirred for 30 min. The solution was washed with citric acid (50 mL, 20 wt %, aq) and 20 wt % brine (20 mL). The resulting organic solution was filtered and concentrated. The resulting oil was purified by flash chromatography with hexane:EtOAc (5:1) to give **19** as a yellow oil (5.1 g, 81%). Data for compound **19**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 7.3 Hz, 2H), 7.44 (t, J = 7.6 Hz, 1H), 7.31−7.23 (m, 6H), 7.15 (t, J = 7.5 Hz, 4H), 7.10−7.01 (m, 2H), 5.61 (d, J = 3.7 Hz, 1H), 4.74−4.66 (m, 2H), 4.52 (dt, J = 10.4, 2.2 Hz, 1H),

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4.24 (dd, J = 12.2, 4.5 Hz, 1H), 4.02 (d, J = 14.1 Hz, 2H), 3.72 (d, J = 14.1 Hz, 2H), 3.06 (dd, J = 10.4, 3.9 Hz, 1H), 1.52 (s, 3H), 1.31 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.4, 139.7, 132.9, 129.9, 129.8, 128.5, 128.4, 128.2, 127.1, 112.7, 104.3, 78.3, 73.9, 63.5, 61.3, 56.1, 26.9, 26.4. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{29}H_{31}NO_5$ 474.2275; found 474.2262.

*(2R,3R,4R,5S)-5-((Benzoyloxy)methyl)-4-(dibenzylamino)-tetrahydrofuran-2,3-diyl Dibenzoate (**21**).* To a nitrogen flushed 100 mL flask, **19** (8.0 g), THF (16 mL), and water (8.0 mL) were charged to stir to a homogeneous solution. TFA (16 mL) was added to the reactor, and the solution was aged for 8 h at 70 °C on a heating mantle. The solution was then cooled to 10 °C and diluted with toluene (50 mL). The layer was separated, and the organic crude was washed with $NaHCO_3$ (20 mL × 2, 5 wt %, aq). The organic layer was washed with 20 wt % brine (16 mL), and the solution was used in the next step without further purifications. To the solution was added DMAP (0.1 g, 0.05 equiv), Et_3N (5.1 g, 3.0 equiv), and Bz_2O (7.6 g, 2.0 equiv). The crude was aged at 45 °C on a heating mantle for 16 h. Into the crude was charged THF (50 mL). The solution was washed with brine (40 mL, 20 wt %), and the layers were separated. The organic crude was washed with citric acid + NaCl mixed solution (20 mL, citric acid 5 wt %, NaCl solution 15 wt %, aq) and separated. The crude was washed again with brine (40 mL, 20 wt %), and the layers were separated. The solvent of the crude was swapped with 2-MeTHF (20 mL). At 70 °C, heptane (30 mL) was added dropwise in 30 min. The slurry was cooled to 25 °C in 2 h. The slurry was filtered, and the solid was dried in the oven. A brown solid, **21** (9.7 g, 90%), was isolated. Data for compound **21**: ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 7.6 Hz, 2H), 7.81 (d, J = 7.7 Hz, 2H), 7.75−7.53 (m, 6H), 7.48−7.36 (m, 7H), 7.28 (t, J = 7.5 Hz, 4H), 7.23−7.10 (m, 4H), 6.50 (s, 1H), 5.92 (d, J = 4.2 Hz, 1H), 4.98 (brd, J = 9.8 Hz, 1H), 4.76 (dd, J = 12.3, 2.0 Hz, 1H), 4.49 (dd, J = 12.3, 3.7 Hz, 1H), 4.22 (d, J = 13.6 Hz, 2H), 4.05 (dd, J = 9.8, 4.1 Hz, 1H), 3.77 (d, J = 13.6 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.3, 165.7, 164.5, 138.9, 133.9, 133.4, 132.8, 130.0, 129.9, 129.5, 129.3, 129.3, 128.6 (t, J = 18.3 Hz, 1C), 128.1, 128.5 (t, J = 115.5 Hz, 1C), 98.9, 74.8, 63.4, 58.2, 55.9. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{40}H_{36}NO_7$ 642.2486; found 642.2487.

*((2S,3R,4R,5R)-5-(6-Benzamido-9H-purin-9-yl)-4-(benzoyloxy)-3-(dibenzylamino)tetrahydrofuran-2-yl)methyl Benzoate (**22**).* Into a nitrogen-flushed 100 mL flask, MeCN (20 mL) and compound **21** (2.5 g) were charged to give a solution. To the solution were added HA^{Bz} (1.86 g, 2 equiv) and BSA (1.19 g, 1.5 equiv). The suspension was heated to 65 °C for 2 h on a heating mantle, and TMSOTf (0.87 g, 1.0 equiv) was added. The solution was heated to 70 °C for 6 h, cooled to 25 °C, and quenched with $NaHCO_3$ (10 mL, 5 wt %, aq). To the mixture, EtOAc (20 mL) was charged, and the organic solution was separated. The aqueous layer was extracted with EtOAc (10 mL), and the combined organic layers were washed with $NaHCO_3$ (10 mL, 5 wt %, aq) and brine (10 mL, 20 wt %, aq). The organic solution was concentrated (the crude at this point can be used in the next step) to paste and purified by flash chromatography with hexane:EtOAc (3:1) to give **22** as a yellow oil (2.6 g, 88%). Data for compound **22**: ^1H NMR (400 MHz, DMSO-d_6) δ 11.16 (s, 1H), 8.50 (s, 1H), 8.27 (s, 1H), 8.16 (d, J = 8.1 Hz, 2H), 8.03 (d, J = 7.8 Hz, 2H), 7.73 (t, J = 7.0 Hz, 1H), 7.67−7.51 (m, 8H), 7.41−7.31 (m, 6H), 7.30−7.13 (m, 6H), 6.45−6.37 (m, 2H), 5.09 (br d, J = 9.5 Hz, 1H), 4.79 (br d, J = 11.6 Hz, 1H), 4.62 (dd, J = 9.8, 6.1 Hz, 1H), 4.50 (dd, J = 12.4, 3.5 Hz, 1H), 4.16 (br d, J = 14.1 Hz, 2H), 4.03 (d, J = 7.1 Hz, 1H), 3.88 (br d, J = 14.1 Hz, 2H), 3.33 (s, 1H), 1.99 (s, 1H), 1.17 (t, J = 7.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO) δ 166.0, 165.9, 165.8, 151.8, 151.7, 151.0, 144.7, 139.9, 134.4, 133.8, 133.7, 132.9, 130.2, 129.6, 129.6, 129.4, 129.0, 128.8, 128.8, 128.7, 127.4, 126.3, 89.2, 76.9, 75.8, 63.2,, 58.7, 55.8. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{45}H_{39}N6O_6$ 759.2926; found 759.2917.

*(2R,3R,4S,5S)-2-(6-Amino-9H-purin-9-yl)-4-(dibenzylamino)-5-(hydroxymethyl)tetrahydrofuran-3-ol (**24**).* To a nitrogen-flushed 50 mL flask, **22** (2.2 g), MeOH (9 mL), THF (11 mL), and water (1 mL) were added to give a homogeneous solution. KOH solution (2.9 mL, 1 M, 4.0 equiv) was slowly added to the solution at 25 °C in 10 min. The solution was aged at 60 °C for 10 h on a heating mantle. The solution was then cooled to 0 °C in an ice batch, and water (15.0 mL) was introduced slowly to maintain the internal temperature. Then the suspension was further agitated for 1 h. The solid was filtered and washed with water (5 mL). The solid was dried and suspended in MTBE (20 mL) and warmed to 45 °C for 1 h. The slurry was cooled to 23 °C and filtered. The solid was washed with MTBE (10 mL) and dried in the oven to afford **24** as a pale-brown solid (1.05 g, 81%). Data for compound **24**: ^1H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 1H), 8.06 (s, 1H), 7.40 (d, J = 7.5 Hz, 3H), 7.35−7.28 (m, 5H), 7.26−7.18 (m, 2H), 6.02 (d, J = 4.8 Hz, 1H), 5.88 (br s, 1H), 5.41−5.30 (m, 1H), 4.73 (br t, J = 5.6 Hz, 1H), 4.43 (br s, 1H), 4.03 (d, J = 14.1 Hz, 2H), 3.89 (br d, J = 14.1 Hz, 2H), 3.74 (br d, J = 11.6 Hz, 1H), 3.55−3.40 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO) δ 156.6, 152.7, 149.2, 140.6, 140.0, 128.8, 128.6, 127.2, 119.7, 91.0, 82.2, 75.4, 63.0, 59.5, 55.3 .HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{27}N_6O_3$ 447.2139; found 447.2145.

*N-(9-((2R,3R,4R,5S)-3-((tert-Butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-4-(dibenzylamino)tetrahydrofuran-2-yl)-9H-purin-6-yl)benzamide (**31**).* To a nitrogen-flushed 50 mL flask, diol **24** (2.8 g) was suspended in THF (14 mL). To the flask, $EtNiPr_2$ (2.42 g, 3 equiv) was added at 23 °C. To the suspension, TBSOTf (3.5 g, 2.5 equiv) was added dropwise at −10 °C in an dry ice−brine batch. The solution was aged at −10 °C for 1 h and was added to MeOH (2.5 mL) and aged for 1 h. To the reaction mixture, water (3 mL) and heptane (20 mL) were charged into the flask. Crude were extracted and separated. To the aqueous layer was added heptane (10 mL), and the crude was extracted and separated. The organic crude was washed with brine (10 mL, 15 wt %, aq) and separated. The organic was dried over Na_2SO_4 and filtered. The organic was concentrated in a 50 mL flask and used in the next step without further purification. Under nitrogen, CH_2Cl_2 (14 mL), 2,6-lutidine (2.69 g, 4.0 equiv), and BzCl (2.65 g, 3.0 equiv) were added. The solution was agitated at 23 °C for 14 h and charged with MTBE (28 mL). The organic solution was washed with $NaHCO_3$ (10 mL, 5 wt %, aq) and brine (10 mL, 20 wt %, aq). The resulting organic mixture was concentrated to paste. To the solution, EtOAc (15 mL) was added to give a solution. Ammonia in MeOH (1 mL, 7 M) was added dropwise at 0 °C in an ice bath. The solution was agitated at 0 °C for 7 h. The reaction mixture was washed with citric acid (15 mL, 10 wt %, aq) and brine (10 mL, 20 wt %, aq) and concentrated to paste (this material can be telescoped to the next step without isolation) and purified through flash chromatography with hexane:EtOAc (3:1) to give **31** as a yellow oil (3.9 g, 80%). Data for compound **31**: ^1H NMR (400 MHz, $CDCl_3$) δ 9.53 (br s, 1H), 8.84 (s, 1H), 8.44 (s, 1H), 8.12−8.05 (m, 2H), 7.66−7.46 (m, 4H), 7.39−7.24 (m, 9H), 6.29 (d, J = 4.3 Hz, 1H), 4.78 (dd, J = 5.9, 4.5 Hz, 1H), 4.60 (brd, J = 5.7 Hz, 1H), 4.12−3.95 (m, 5H), 3.78−3.61 (m, 2H), 0.97 (s, 9H), 0.90 (s, 9H), 0.15 (s, 3H), 0.01 (s, 3H), −0.19 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.0, 165.0, 152.7, 151.5, 149.6, 141.4, 139.6, 133.9, 133.2, 132.7, 130.1, 130.0, 128.8, 128.7, 128.6, 128.4, 128.3, 128.0, 127.2, 122.5, 90.2, 82.4, 78.3, 63.9, 61.2, 60.9, 59.4, 55.3, 26.0, 25.9, 18.5, 17.8, −4.5, −5.0, −5.5, −5.5. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{43}H_{59}N_6O_4Si_2$ 779.4131; found 779.4121.

*N-(9-((2R,3R,4R,5S)-4-Amino-3-((tert-butyldimethylsilyl)oxy)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-9H-purin-6-yl)benzamide (**2**).* To a nitrogen flushed 50 mL flask, **31** (3.1 g) and CH_2Cl_2 (30 mL) were charged to give a homogeneous solution at 23 °C. To the solution, TFA (3 mL) and water (1 mL) was added. The solution was warmed to 35 °C on a heating mantle for 8 h and then cooled and diluted with CH_2Cl_2 (20 mL) at 23 °C. The organic solution was washed with water (10 mL), $NaHCO_3$ (10 mL, 5 wt %, aq), and brine (10 mL, 15 wt %). The organic layer was dried over Na_2SO_4 and concentrated to a yellow oil. The crude oil was dissolved with EtOH (20 mL) and transferred to a 50 mL pressure vessel. Pd/C (0.22 g, 5 wt %, 0.5 equiv) was added to the solution, the vessel was refilled with N_2 three times and H_2 three times, and the H_2 pressure was kept at 30 psi. The reaction was agitated for 18 h at 23 °C. After the hydrogen was swapped with N_2 and air, the crude was filtered through a pad of

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Celite and the organic solution was concentrated. The paste was diluted with MTBE (6 mL), and heptane (30 mL) was added slowly to generate solid precipitate at 0 °C first and then slowly to 25 °C over 8 h. The suspension was then filtered, and **2** was isolated as an amorphous solid (0.98 g, 51%). Data for compound **2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.18 (s, 1H), 8.02 (d, J = 7.3 Hz, 2H), 7.60−7.54 (m, 1H), 7.53−7.45 (m, 2H), 5.94 (d, J = 5.3 Hz, 1H), 4.85 (t, J = 5.3 Hz, 1H), 4.10−4.06 (m, 1H), 3.99 (dd, J = 12.7, 1.6 Hz, 1H), 3.80−3.69 (m, 2H), 0.82 (s, 9H), −0.10 (s, 3H), −0.24 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.7, 152.3, 150.5, 150.1, 142.6, 133.5, 132.8, 128.8, 127.9, 123.9, 91.2, 87.6, 75.4, 62.7, 53.6, 25.5, 17.8, −5.2. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{23}H_{33}N_6O_4Si$ 485.2337; found 485.2327.

*((2S,3R,4R,5R)-5-(2-Amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-4-(benzoyloxy)-3-(dibenzylamino)tetrahydrofuran-2-yl)methyl Benzoate (**37**).* To a nitrogen-backfilled 250 mL flask with **21** (7.5 g), MeCN (60 mL) was added to give a homogeneous solution. To the solution, HG^{Cl} (3.95 g, 2.0 equiv) and BSA (3.56 g, 1.5 equiv) were added in such an order at 23 °C to generate precipitates. The suspension was then held to 65 °C for 20 min. TMSOTf (2.6 g, 1.0 equiv) was added, and the resulting homogeneous solution was held to 70 °C on a heating mantle for 7 h. The solution was cooled to 25 °C and quenched with $NaHCO_3$ (40 mL, 5 wt %, aq). Toluene (60 mL) was added to the crude, and the two layers were separated. The aqueous layer was back-extracted with toluene (15 mL) and combined with the first toluene layer. The organic layers were washed with $NaHCO_3$ (30 mL, 5 wt %, aq) and brine (30 mL, 20 wt %, aq) and separated. The organic solution of **36** was concentrated and added to toluene (15 mL). Then the H_2O (5 mL) and TFA (40 mL) were placed in the flask. The reaction crude was stirred for at least 20 h at 40 °C and then cooled to 15 °C before H_2O (75 mL) was added to the mixture at 25 °C. The organic phase and water phase were separated. The aqueous phase was extracted with toluene (30 mL) and separated. The two toluene solutions were combined and washed with water (70 mL), $NaHCO_3$ (50 mL, 5 wt %, aq), and brine (30 mL, 15 wt %, aq) separately. The final organic crude was concentrated to 15 mL under vacuum. The concentrated crude was slowly reversely added to heptane (70 mL) to afford a suspension in 2 h at 25 °C. The solid was filtered and washed with heptane (15 mL) to give **37** as a light-brown solid (5.49 g, 70%). Data for compound **37**: ^{1}H NMR (600 MHz, DMSO-d_6, 25 °C): δ 10.84 (v br s, 1H), 8.11 (br d, J = 7.8 Hz, 2H), 7.77 (br d, J = 7.8 Hz, 2H), 7.72 (br t, J = 7.4 Hz, 1H), 7.65 (s, 1H), 7.65 (t, J = 7.4 Hz, 1H), 7.59 (t, J = 7.7 Hz, 2H), 7.47 (t, J = 7.7 Hz, 2H), 7.29 (br d, J = 7.6 Hz, 4H), 7.19 (br t, J = 7.6 Hz, 4H), 7.13 (br t, J = 7.2 Hz, 2H), 6.16 (overlapped, 2H), 5.00 (m, 1H), 4.73 (dd, J = 12.2, 2.7 Hz, 1H), 4.51 (dd, J = 12.2, 4.8 Hz, 1H), 4.16 (dd, J = 8.3, 5.9 Hz, 1H), 4.05 (d, J = 14.2 Hz, 2H), 3.86 (d, J = 14.2 Hz, 2H). ^{13}C{^{1}H} NMR (153 MHz, DMSO) δ 165.5, 165.0, 156.7, 153.7, 150.6, 139.1, 135.7, 133.9, 133.4, 129.6, 129.2, 129.2, 128.9, 128.9, 128.6, 128.2, 128.2, 127.0, 117.0, 87.2, 76.3, 75.2, 63.8, 59.2, 54.8. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{38}H_{35}N_6O_6$ 671.2613; found 671.2597.

*2-Amino-9-((2R,3R,4S,5S)-4-(dibenzylamino)-3-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1,9-dihydro-6H-purin-6-one (**38**).* To a nitrogen-backfilled 100 mL flask, IPA (25 mL) and **37** (7.8 g) were added to give a suspension. N_2H_4 (0.97 g, 2.6 equiv) was charged into the reactor on a heating mantle at 35 °C. The solution was heated to 80 °C for 2 h. The reaction mixture was cooled to 25 °C, and water (25 mL) was added dropwise to the flask to give a suspension at 25 °C. The suspension was filtered and washed with MeCN/IPA (15 mL, 1/1 = v/v). The solid was dried in an oven under vacuum to give **38** as a light-brown solid (4.4 g, 81%, 90% HPLC purity).The solid is ready for the next step. For characterization, the solid was then dissolved with NMP (5 mL) and purified with reverse-HPLC using solvent pair MeCN/H_2O (0.05% TFA) to afford **38** as a white solid with more than 98% purity. **Data for Compound 38:** ^{1}H NMR (600 MHz, DMSO-d_6, 25 °C): δ 7.70 (s, 1H), 7.40 (br d, J = 7.6 Hz, 4H), 7.31 (br t, J = 7.5 Hz, 4H), 7.22 (br t, J = 7.4 Hz, 2H), 5.82 (d, J = 5.3 Hz, 1H), 4.61 (m, 1H), 4.36 (m, 1H), 4.01 (d, J = 14.1 Hz, 2H), 3.85 (d, J = 14.1 Hz, 2H), 3.66 (dd, J = 11.5, 1.7 Hz, 1H), 3.43 (dd, J = 11.6, 3.7 Hz, 1H), 3.40 (m, 1H). ^{13}C{^{1}H} NMR (153 MHz, DMSO) δ δ 158.2, 154.9, 151.0, 140.1, 134.8, 128.3, 128.1, 126.8, 116.7, 89.1, 81.3, 75.0, 62.6, 59.2, 54.7. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{24}H_{27}N_6O_4$ 463.2088; found 463.2070.

*N-(9-((2R,3R,4R,5S)-3-((tert-Butyldimethylsilyl)oxy)-4-(dibenzylamino)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide (**41**).* To a nitrogen-backfilled 100 mL flask, THF (10 mL) and **38** (2.44 g) were charged at 23 °C to give a suspension. TBSOTf (3.47 g, 2.5 equiv) and Hünig base (3.4 g, 5.0 equiv) were charged at −10 °C and aged for 2 h at 23 °C. MeOH (1 mL) was added dropwise, and the solution was aged for 30 min at 23 °C. MTBE (25 mL) was charged into the solution and extracted with citric acid (10 mL, 5 wt %, aq) and water (12 mL), and the isolated organic phase was concentrated under vacuum to 10 mL. To the crude was added THF (12 mL), and it was concentrated under vacuum to 5 mL. To the solution, pyridine (7 mL) was charged and the solution was cooled to 10 °C in a cold water batch. Isobutyryl chloride (1.69 g, 3.0 equiv) was charged dropwise into the mixture at 10 °C. After 2 h, the solution was warmed to 23 °C and THF (3.0 L) was charged into the reaction. $NH_3{\cdot}H_2O$ (3 mL, 10 wt %, aq) was charged dropwise into the reaction mixture at 10 °C, and the reaction was agitated for 6 h until no **39** was observed. The crude was diluted with MTBE (12 mL) and water (24 mL). Layers were partitioned, and the aqueous phase was extracted with MTBE (12 mL). The combined organic phases were washed with critic acid (24 mL × 2, 30 wt %, aq). The organic phase was then washed with water (24 mL, 10 V) and concentrated to 5 mL. To the concentrate, TFA (5 mL) and water (2.5 mL) were added and agitated for 3 h at 10 °C. DIPEA was added dropwise to the mixture at 10 °C to adjust the pH of the mixture to 7−8. Water (24 mL) was added, and the organic phase was separated. The organic phase was concentrated to 5 mL, and iPrOH (12 mL) was charged into the mixture. The mixture was concentrated to 7 mL, and the slurry was filtered. The solid was dried in an oven under vacuum to give **41** as a light-brown solid (2.22 g, 65%). Data for compound **41**: ^{1}H NMR (600 MHz, DMSO-d_6, 25 °C): δ 12.09 (br s, 1H), 11.56 (s, 1H), 8.25 (s, 1H), 7.42 (br d, J = 7.7 Hz, 4H), 7.33 (br t, J = 7.6 Hz, 4H), 7.25 (br t, J = 7.4 Hz, 2H), 6.02 (d, J = 6.8 Hz, 1H), 5.14 (t, J = 5.0 Hz, 1H), 4.85 (br t, J = 7.4 Hz, 1H), 4.53 (m, 1H), 4.33 (d, J = 4.2 Hz, 1H), 3.96 (d, J = 13.6 Hz, 2H), 3.75 (d, J = 13.6 Hz, 2H), 3.66 (m, 1H), 3.50 (dt, J = 11.6, 4.3 Hz, 1H), 3.44 (dd, J = 7.9, 3.1 Hz, 1H), 2.74 (sept, J = 6.9 Hz, 1H), 1.09 (br d, J = 6.9 Hz, 6H), 0.79 (s, 9H), 0.01 (s, 3H), −0.41 (s, 3H). ^{13}C{^{1}H} NMR (153 MHz, DMSO) δ 180.1, 154.7, 149.0, 148.2, 139.4, 137.4, 128.5, 128.2, 127.0, 119.8, 88.8, 81.8, 77.2, 63.0, 60.1, 54.1, 34.7, 25.5, 18.8, 18.7, 17.5, −4.8, −5.9. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{34}H_{47}N_6O_5Si$ 647.3372; found 647.3347.

*N-(9-((2R,3R,4R,5S)-4-Amino-3-((tert-butyldimethylsilyl)oxy)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-6-oxo-6,9-dihydro-1H-purin-2-yl)isobutyramide (**3**).* To a 50 mL nitrogen-backfilled pressure bomb, **41** (1.11 g) was dissolved in EtOH (11 mL) at 23 °C. Pd on carbon (0.22 g, 20 wt %) was added to the solution to afford a suspension at 23 °C, and the reactor was backfilled with H_2 three times. The reaction was agitated for 6 h at 23 °C. The reaction mixture was backfilled with N_2 three times and filtered through Celite, and the cake was washed with EtOH (5.0 mL × 2). The solution was solvent swapped with MeCN at 10 mL under vacuum at no more than 40 °C on a heating mantle. Water (10 mL) was added dropwise to the solution, and the slurry was agitated for 30 min. The slurry was filtered and the cake was washed with MeCN:H_2O = 1:3 (2 mL × 2), followed by MTBE (2.0 mL). The solid was dried in an oven under vacuum to give **3** as an off-white solid (0.65 g, 81%). Data for compound **3**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (s, 1H), 5.58 (d, J = 4.5 Hz, 1H), 4.71 (br t, J = 5.0 Hz, 1H), 4.19 (t, J = 5.0 Hz, 1H), 3.50−3.36 (m, 2H), 3.33−3.16 (m, 2H), 3.03 (br s, 1H), 2.50 (quin, J = 6.8 Hz, 1H), 0.83 (d, J = 6.8 Hz, 6H), 0.51 (s, 9H), −0.31 (s, 3H), −0.41 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 180.6, 155.3, 149.2, 148.6, 138.0, 120.5, 87.6, 86.7, 77.4, 61.9, 53.9, 35.2, 26.0, 19.4, 19.3, 18.2, −4.7, −4.7. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{20}H_{35}N4O_5Si$ 467.2440; found 467.2433.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00984.

First-generation route to access aza-adeonsine **2** and aza-guanosine **3**; Vorbrüggen chemistry screening **16** to **17**; selective protection of **25** screening; ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra for compounds **2**, **3**, **10**, **11**, **12**, **13**, **16**, **19**, **21**, **22**, **24**, **31**, **37**, **38**, and **41** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Changxia Yuan − *Chemical Process Development, Bristol Myers Squibb, New Brunswick, New Jersey 08903, United States;* orcid.org/0000-0001-8442-676X; Email: Changxia.yuan@bms.com

Authors

Adrian Ortiz − *Chemical Process Development, Bristol Myers Squibb, New Brunswick, New Jersey 08903, United States;* Present Address: Amgen, 1 Amgen Center Drive, Thousand Oaks, California 91320, United States

Zhongmin Xu − *Chemical Process Development, Bristol Myers Squibb, New Brunswick, New Jersey 08903, United States*

Jason Zhu − *Chemical Process Development, Bristol Myers Squibb, New Brunswick, New Jersey 08903, United States*

Michael A. Schmidt − *Chemical Process Development, Bristol Myers Squibb, New Brunswick, New Jersey 08903, United States;* orcid.org/0000-0002-4880-2083

Amanda Rogers − *Chemical Process Development, Bristol Myers Squibb, New Brunswick, New Jersey 08903, United States*

Martin Eastgate − *Chemical Process Development, Bristol Myers Squibb, New Brunswick, New Jersey 08903, United States;* orcid.org/0000-0002-6487-3121

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c00984

Notes

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