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Mechanistic studies in the synthesis of a series of thieno-expanded xanthosine and guanosine nucleosides

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ABSTRACT

During the synthetic pursuit of guanosine (tri-G) and xanthosine (tri-X) tricyclic nucleosides analogues, an interesting side product was discovered. In an effort to uncover the mechanistic factors leading to this result, a series of reaction conditions were investigated. It was found that by varying the conditions, the appearance of the side product could be controlled. In addition, the yield of the desired products could be manipulated to afford either a 50:50 mix of both tri-G and tri-X, or a majority of one or the other. To demonstrate the broad utility of the method, it was also adapted to the synthesis of guanosine and xanthosine from 5-amino-1-β-D-ribofuranosyl-4-imidazolecarboxyamide (AICAR). The mechanistic details surrounding the synthetic efforts are reported herein.

1. Introduction

A number of laboratories,[1–9] including ours,[10–13] have designed and synthesized various structurally unique unnatural nucleosides to study nucleic acid structure and function. Expanding the 'letters' of the genetic alphabet beyond the five natural nucleosides would allow further investigation of the requirements for base pairing and stacking, helix stability and interactions, and recognition by enzyme systems such as polymerases or other nucleoside metabolizing enzymes involved in biological processes. A number of design approaches to realize this goal have been explored, including pairings based on size or shape complementarity.[14–18]

A more traditional strategy relies on pairing up complementary donor–acceptor patterns between unnatural bases.[9,19–21] Recently, use of expanded purine nucleosides such as Nelson Leonard's[22–24] *lin*-benzoadenosine has been explored, an approach we began to pursue some time ago beginning with the synthesis of a series of thieno-expanded tricyclic nucleosides.[11,13,25,26]

In contrast to Leonard's linear system, which has been extensively studied by Kool,[2–4,27–29] and Matteucci's extended cytidine analogues[30–33] the use of a heteroaromatic spacer ring provides a number of advantages over the benzene spacer, including offering forth a less dramatic expansion of the helix due to the curvature of the base pairing, which contracts the helix width while still retaining the hydrogen bonding elements involved in recognition and base pairing.

In addition, molecular dynamics calculations have shown that inclusion of the heteroaromatic spacer will increase the overall aromaticity and polarizability for the base, which in turn, will result in an increase in stacking effects, an important factor in stabilization of the DNA helix.[34–37]

We have previously reported the design and synthesis of the first three tricyclic thieno-expanded purine ribonucleosides[11] and their corresponding bases,[13] tricyclic adenosine (tri-A), guanosine (tri-G), and inosine (tri-I) shown in Figure 1. In parallel to the studies in DNA,[34] the tricyclic nucleosides were investigated in

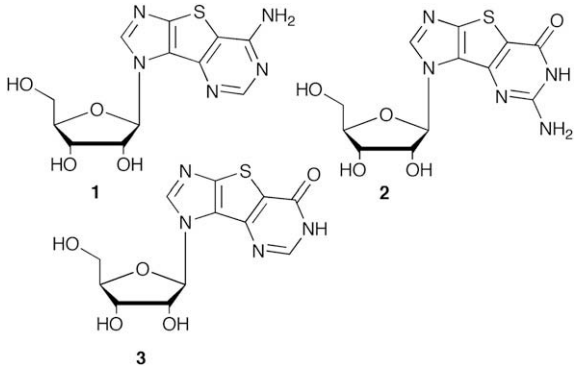

Figure 1. Thieno-expanded nucleosides.

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several enzyme systems and not surprisingly, all three were recognized by nucleoside transporters, both in their original nucleoside form as well as the corresponding nucleobases.[38] The extended aromatic system resulted in an increase in recognition and uptake over the natural nucleobases. In addition, the tricyclic nucleosides were readily recognized, and in some cases, preferentially, by nucleoside metabolizing enzymes such as guanosine fucose pyrophosphorylase[39–41] and RNA dependent RNA polymerases, thus providing impetus for expanding our drug design studies with additional analogues.

In that regard, xanthosine (Fig. 2) is a naturally occurring purine nucleoside that has attracted some interest in recent years due to the ability to act as a universal base.[42,43] Xanthosine offers forth a Watson–Crick 'acceptor–donor–acceptor' pairing pattern, thus can advantageously pair with a number of unnatural nucleosides. One notable example is Benner's diaminopyrimidine pairing with xanthosine.[44–49] This nonstandard pairing was recently shown to be utilized with satisfactory fidelity by variants of HIV reverse transcriptase for synthesis of duplex DNA.[44] This finding is highly encouraging to those pursuing expansion of the genetic alphabet, since this is the first example of DNA containing base pairs with alternative hydrogen bonding patterns that was efficiently amplified by PCR.[44] Spurred on by those findings, we employed our tricyclic scaffold to produce the corresponding expanded tricyclic xanthosine (tri-X, **4**) and the corresponding 2′-deoxyxanthosine **5**, shown in Figure 2. In the process of this synthetic effort, an unexpected side product was discovered, thus prompting a mechanistic study of the formation of these analogues.

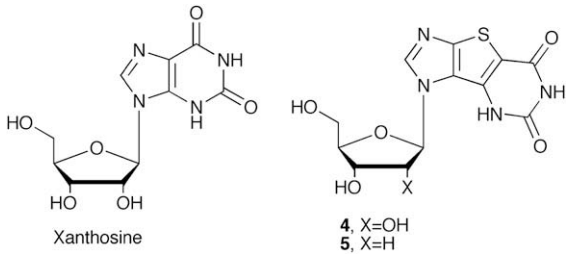


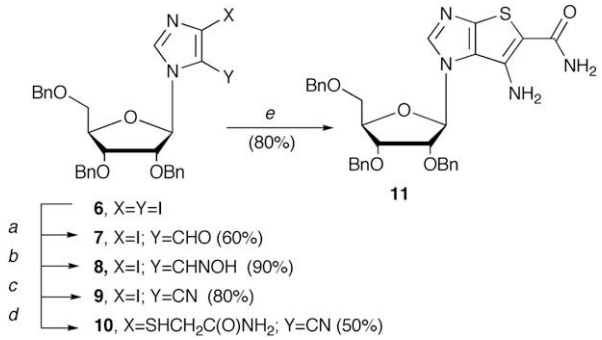
Figure 2. Xanthosine and thieno-expanded xanthosine nucleosides.

2. Results and discussion

2.1. Manipulation of the ring closure reaction

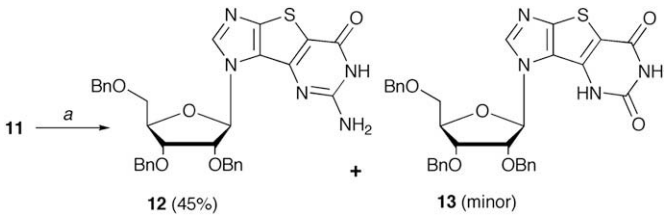
In reviewing the literature, only a few routes appeared to be available to obtain xanthosine nucleosides directly, and both were plagued with extremely poor yields, ranging from a low of 8% to a moderate yield of 47%.[50–53] Interestingly, a number of literature routes to guanosine have noted xanthosine as a minor side product, however, none of these reports evaluated the mechanistic details that would result in successfully obtaining various ratios of the products. Indeed, during the course of scaling up our synthesis of the tri-G analogue **2**, we also noted that a small amount of tricyclic xanthosine was formed. Speculating that it might be possible to obtain both **12** and **13** in more satisfactory quantities by altering the reaction conditions, or by manipulating the conditions such that either the xanthosine or the guanosine would be obtained as the major product, we began a mechanistic investigation, since either scenario would prove useful to us and the synthetic community.

Our original route[11,13,26] began with ribosylated 4,5-dibromoimidazole, however, more recently[12] a switch to the 4,5-diiodo substituted imidazole intermediate **6** shown in Scheme 1 was made, since it provided a much more facile workup for several of the steps, no longer requiring tedious column chromatography, since the products could be readily purified via recrystallization. Beginning with **6** (Scheme 1), conversion to the key bicyclic intermediate **11** was accomplished in five steps in a 16% overall yield.



Scheme 1. Reagents and conditions: (a) (i) EtMgBr, THF, 4 h; (ii) anhydrous DMF; (b) pyrimidine, hydroxylamine hydrochloride, anhydrous EtOH, reflux; (c) Ac_2O, reflux; (d) $NH_2C(O)CH_2SH$, K_2CO_3, DMF, 60 °C; (e) NaOEt, EtOH.

At this point the ring closure was undertaken using a one-pot, four-step procedure detailed in Scheme 2 to give both benzyl-protected tri-G (**12**) and a small amount of tri-X (**13**).[11,54] Next, increasing the ratio of sodium hydroxide to substrate in step 1 successfully improved the ratio of tri-G to tri-X (entry 2 in Table 1) but surprisingly, this also resulted in the formation of a new compound not previously observed. Following characterization by NMR and elemental analysis, this product proved to be a methoxy-substituted nucleoside (**14**, Fig. 3). This was quite unexpected, because to our knowledge, no similar methoxy side product had ever been reported in the literature for these reactions, thus we sought to further investigate the cause of this result.



Scheme 2. Reagents and conditions: (a) (i) NaOH, MeOH, rt; (ii) CS_2, MeOH, 145 °C, 18 h; (iii) H_2O_2, MeOH, 0 °C, 2 h; (iv) NH_3, MeOH, 125 °C, 18 h.

The most straightforward explanation could be attributed to a methoxy anion acting as a nucleophile due to the increase in base present, however, this seemed unlikely given the intermediates proposed in the literature for similar reactions. It should be noted that in contrast to the literature reports,[52,53] which utilize NaOH instead of NaOMe in the final step, this was not possible with our compounds due to lack of solubility in aqueous solution as a result of the benzyl protecting groups, which were not present in the literature examples. In an effort to more closely follow those procedures, removal of the benzyl groups at the bicyclic stage was carried out, however, the yield for the cyclization reaction for the deprotected bicyclic intermediate (step 1) was unsatisfactory, thus this route was not pursued further.

Speculating that the nucleophilic attack by the OMe could not be occurring in the first step, but most likely in the third or fourth step when the leaving groups would be more favorable, we returned to the benzyl-protected bicyclic intermediate **11**. It was rationalized that by significantly increasing the amount of MeOH used in the last step, it would effectively decrease the overall concentration of the NaOH still present in the reaction mixture, thus lowering the concentration of the OMe anion. This indeed proved to be the case;

Table 1
Ring closure conditions and product ratio[a]

Entry	Substrate/NaOH equivalents (step 1)	Temperature (°C) (step 2)	Reaction time (h) (step 2)	Volume of MeOH (mL) (step 4)	Product ratio **12**/**14**/**13**
1	1:5	145	18	80	3:0:1
2	1:6	145	18	80	3:1:1
3	1:10	145	18	80	2:4:3
4	1:40	145	18	80	2:7:3
5	1:5	180	6	80	3:2:1
6	1:5	145	18	160	2:1:2
7	**1:5**	**145**	**18**	**250**	**1:0:1**
8	1:6	145	18	250	1:Trace:1
9	1:8	145	18	250	2:1:2

[a] Based on an average of at least five separate reactions for each set of conditions.

an initial increase of MeOH from 80 mL to 160 mL improved the ratio of **12** to **13**, and significantly decreased the formation of the OMe product **14**. Further dilution with 250 mL of MeOH produced the desired affect, and resulted in a 1:1 ratio of **12** to **13** with no formation of the tri-OMe side product **14**. To test this further, the amount NaOH was increased by 1 equiv (entry 8 in Table 1), and only a trace of tri-OMe was found, while increasing it even further resulting in the reappearance of the tri-OMe product **14**, thus supporting our theory.

To substantiate this hypothesis, each step of the one pot reaction mixture was monitored closely by mass spectrometry. In the second step, following the addition of CS_2, mass spectrometry analysis showed three major components, one with a mass of 649.1 [M+Na] $C_{33}H_{29}N_4NaO_5S_2$ corresponding to intermediate **15** (Fig. 4), the other with a mass of 633.2 [M+Na] $C_{33}H_{29}N_4NaO_6S$ corresponding to the tri-X **13**, and a third corresponding to the mass of the glycosidic bond cleaved sugar moiety, coincidentally, with a methoxy group present, however, no mass corresponding to the C2-OMe side product **14**.

After addition of H_2O_2 in the next step, TLC showed a new product had formed and mass spectrometry indicated that this was the oxidized sulfonic acid product **16** (Fig. 4), however, it was not until after addition of the NH_3 in the final step that the tri-OMe side product **14** began to appear. This observation supports the premise that the side product was not forming until the last step, despite the fact that the MeOH and NaOH are introduced in the first step of the one pot procedure. The OMe anion present in the reaction mixture is obviously in competition with the ammonia as a nucleophile, however, the other intermediates formed in previous steps are not reactive enough to undergo nucleophilic substitution by the OMe anion. Once the sulfonic acid moiety has formed, however, it presents an excellent leaving group that is then attacked by both the OMe and ammonia. Indeed, increasing the amount of NaOH added in the first step leads to the formation of the OMe byproduct **14** as the major product, but only after formation of the $-SO_3Na$ adduct (**16**), thus confirming our mechanistic hypothesis for the formation of the methoxy analogue.

Mechanistic questions answered, we moved on to test the utility of the ring closure conditions for more standard nucleosides. AICAR is a key intermediate in the synthesis of a number of nucleosides

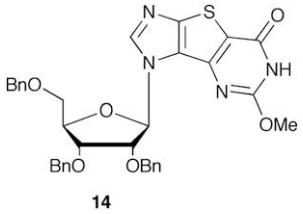


Figure 3. 2-Methoxy-substituted thieno-expanded xanthosine.

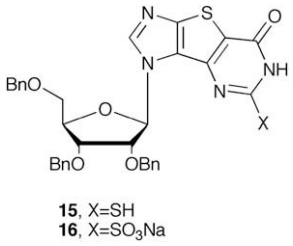
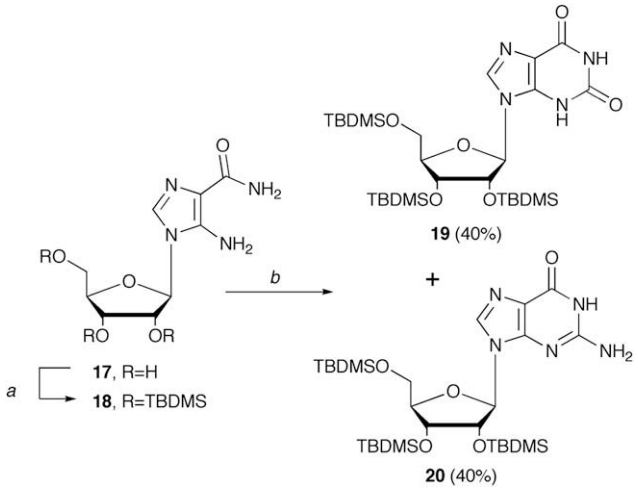


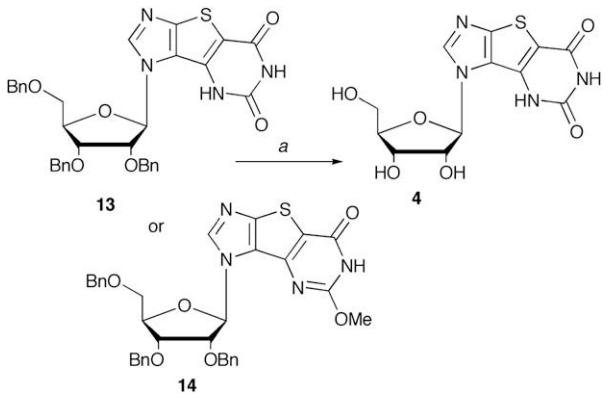
Figure 4. Ring closure reaction intermediates.

such as guanosine and xanthosine, as well as an important player in the field of universal nucleosides. Using the conditions in Table 1, entry 7, AICAR (**17**, Scheme 3) was converted to a 1:1 ratio of xanthosine (**19**) and guanosine (**20**) (40% for each), thus confirming the practicality of this method and the ability to manipulate the reaction conditions to deliver both nucleosides in good yield. It should be noted that the TBDMS group was utilized in place of the benzyl protecting group, since AICAR was obtained commercially, and use of the benzyl group would have required a protracted protection–deprotection strategy, since AICAR contains labile amino groups in addition to the ribose hydroxyls.



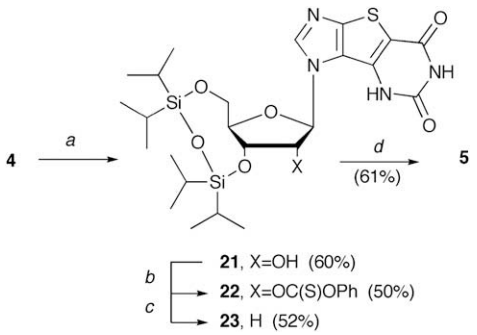
Scheme 3. Reagents and conditions: (a) TBDMSCl, imidazole, DMF; (b) (i) NaOH, MeOH, rt; (ii) CS_2, MeOH, 145 °C, 18 h; (iii) H_2O_2, MeOH, 0 °C, 2 h; (iv) NH_3, MeOH, 125 °C, 18 h.

Finally, our efforts turned to conversion of **4** to the requisite 2′-deoxy tri-X (**5**). Deprotection of the OBn groups also fortuitously deblocked the 2-OMe group resulting in an excellent yield of **4** (Scheme 4).



Scheme 4. Reagents and conditions: (a) THF·BF_3, CH_2Cl_2, rt, 24 h.

Next, using the well-known Barton deoxygenation procedures,[55,56] bis-silyl protection of the 3′- and 5′-hydroxyl groups (Scheme 5), followed by treatment with phenyl chlorothionoformate to give the thio-ester resulted in **22**. Treatment with AIBN and tributyl tin hydride removed the 2′-hydroxyl group to give **23**. Subsequent deblocking of the silyl protecting group with standard conditions then provided **5** in a 9.5% overall yield in four steps from **4**.



Scheme 5. Reagents and conditions: (a) 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane, pyridine, rt, 24 h; (b) phenyl chlorothionoformate, DMAP, rt, 24 h; (c) AIBN, Bu_3SnH, toluene, reflux, 6 h; (d) 1 M TBAF, THF, rt, 4 h.

3. Summary

In summary, reaction conditions were developed to provide a facile route to realize both guanosine and xanthosine analogues in a 1:1 ratio in excellent yield. In addition, two new tricyclic xanthosine analogues were synthesized and a mechanistic puzzle for the formation of an unexpected, but potentially interesting, side product was unraveled. Current efforts are focused on the synthesis of the triphosphate and phosphoramidite of **5**, for use in studying the unique hydrogen bonding properties of xanthosine analogues, as well as their recognition by biological significant systems. The details of those studies will be reported in due time as they become available.

4. Experimental

4.1. General

All chemicals were obtained from commercial sources and used without further purification unless otherwise noted. Anhydrous DMF, MeOH, DMSO, and toluene were purchased from Fisher Scientific. Anhydrous THF, acetone, CH_2Cl_2, CH_3CN, and ether were obtained using a solvent purification system (mBraun Labmaster 130). Melting points are uncorrected. NMR solvents were purchased from Cambridge Isotope Laboratories (Andover, MA). All ^1H and ^{13}C NMR spectra were obtained on a JEOL ECX 400 MHz NMR, operated at 400 and 100 MHz, respectively, and referenced to internal tetramethylsilane (TMS) at 0.0 ppm. The spin multiplicities are indicated by the symbols s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), and br (broad). Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm Whatman Diamond silica gel 60-F_{254} precoated plates. Column chromatography was performed using silica gel (63–200 μ) from Dynamic Adsorbtions Inc. (Norcross, GA), and eluted with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials. Mass spectra were recorded at the Johns Hopkins Mass Spectrometry Facility. Elemental analyses were recorded at Atlantic Microlabs, Inc. (Norcross, GA).

4.2. New procedures in the synthesis of bicyclic intermediate 11

*4.2.1. 2,3-Dibenzyloxy-5-benzyloxymethyl-1-[(5-iodo-4-carbaldehyde)imidazole-3-yl]-β-D-ribofuranose (**7**)*

Compound **6** (28.47 g, 39.41 mmol) was dissolved in anhydrous THF (300 mL), then EtMgBr (12.88 mL, 3 M solution) was added dropwise under N_2. The reaction mixture was stirred for 5 h at room temperature. Anhydrous DMF (20 mL) was added and the reaction mixture stirred overnight, at which point the solvent was removed under vacuum. Saturated NH_4Cl (200 mL) was added, and the reaction mixture extracted with CH_2Cl_2 (3×500 mL). The organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and the solvent removed under vacuum to give a yellow syrup. The crude syrup was purified via column chromatography eluting with hexanes/EtOAc (5:1) to give 16.1 g of **7** as a white solid (60%), mp 160–161.5 °C. ^1H NMR (400 MHz, $CDCl_3$): 9.70 (s, 1H), 8.63 (s, 1H), 7.25–7.31 (m, 15H), 6.45 (d, 1H, J=4.0 Hz), 4.36–5.01 (m, 6H), 4.27–4.30 (m, 1H), 4.20–4.22 (m, 1H), 3.90–3.99 (m, 2H), 3.63–3.66 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 181.0, 143.5, 137.5, 137.4, 137.3, 128.8, 128.5, 128.3, 128.1, 128.0, 127.8, 102.5, 89.8, 80.9, 80.1, 74.3, 73.5, 72.7, 72.3, 67.0; ESI-MS calcd for $C_{30}H_{29}IN_2NaO_5$ $[M+Na]^+$ 647.11, found 647.2; HR-FAB calcd for $C_{30}H_{30}IN_2O_5$ $[M+H]^+$ 625.11995, found 625.12032.

*4.2.2. 2,3-Dibenzyloxy-5-benzyloxymethyl-1-[(5-iodo-4-carbaldehydeoxime)imidazole-3-yl]-β-D-ribofuranose (**8**)*

Compound **7** (22.8 g, 36.5 mmol) was dissolved in anhydrous EtOH (300 mL) and hydroxyamine hydrochloride (3.10 g, 44.15 mmol) was added, followed by addition of pyridine (3 mL). The reaction mixture was refluxed for 2.5 h, the solvent removed under vacuum, H_2O (200 mL) added, and the reaction mixture extracted with CH_2Cl_2 (3×500 mL). The organic phases were combined, dried over anhydrous $MgSO_4$, then evaporated to afford 23.0 g of **8** (quantitative) as a white solid, which was used directly without further purification, mp 158 °C. ^1H NMR (400 MHz, $CDCl_3$): 8.27 (s, 1H), 8.07 (s, 1H), 7.25–7.31 (m, 15H), 6.43 (d, 1H, J=1.8 Hz), 4.47–4.70 (m, 6H), 4.31–4.33 (m, 1H), 4.18–4.23 (m, 1H), 3.99–4.03 (m, 1H), 3.83 (dd, J=2.3, 11.0 Hz, 1H), 3.56 (dd, J=2.3, 11.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 142.0, 140.6, 138.1, 137.5, 128.7, 128.6, 128.1, 128.0, 127.9, 127.7, 90.1, 81.2, 81.1, 75.3, 73.5, 73.1, 72.9, 67.6; HR-FAB calcd for $C_{30}H_{31}IN_3O_5$ $[M+H]^+$ 640.13085, found 640.13096.

*4.2.3. 2,3-Dibenzyloxy-5-benzyloxymethyl-1-[(5-iodo-4-carbonitrile)imidazole-3-yl]-β-D-ribofuranose (**9**)*

Compound **8** (22.0 g, 34.5 mmol) was suspended in anhydrous acetic anhydride (300 mL), refluxed for 3 h, at which point the acetic anhydride was removed under reduced pressure to afford a crude brown syrup. Following purification by silica gel chromatography eluting with hexanes/EtOAc (6:1), 16.6 g of **9** was obtained as a white solid (85%). ^1H NMR (400 MHz, $CDCl_3$): 7.84 (s, 1H), 7.22–7.39 (m, 15H), 5.87 (d, 1H, J=4.6 Hz), 4.47–4.70 (m, 6H), 4.38–4.40 (m, 1H), 4.14–4.20 (m, 2H), 3.78 (dd, 1H, J=3.2, 10.5 Hz), 3.60 (dd, 1H, J=3.2, 10.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 139.0, 137.3, 137.3, 136.7, 128.8, 128.7, 128.3, 128.1, 110.1, 103.9, 89.7, 82.9, 80.7, 75.5, 73.7, 72.8, 72.6, 68.6, 63.9; HR-FAB calcd for $C_{30}H_{29}IN_3O_4$ $[M+H]^+$ 622.12028, found 622.12037.

4.3. Ring closure procedures

*4.3.1. 2,3-Dibenzyloxy-5-benzyloxymethyl-1-[(2-amino-imidazo-[4′,5′:4,5]-thieno-[3,2-d]pyrimidin-3-yl-7-one)]-β-D-ribofuranose (**12**), 2,3-dibenzyloxy-5-benzyloxymethyl-1-[(5-hydroxylimidazo-[4′,5′:4,5]-thieno-[3,2-d]-pyrimidin-3-yl-7-one)]-β-D-ribofuranose (**13**), and 2,3-dibenzyloxy-5-benzyloxymethyl-1-[(5-methyl-*

*oxyimidazo-[4′,5′:4,5]-thieno-[3,2-d]-pyrimidin-3-yl-7-one)]-β-D-ribofuranose (**14**)*

In a steel reaction vessel, compound **11** (993 mg, 1.7 mmol) was dissolved in 40 mL anhydrous MeOH, NaOH (680 mg, 17 mmol) added and the mixture stirred at room temperature for 30 min until a clear solution was obtained. CS_2 (615 μL, 10.2 mmol) was added, the vessel sealed, and the reaction heated in an oil bath at 145 °C for 18 h. The vessel was cooled, and the solvent removed under reduced pressure to give an orange solid to which MeOH (80 mL) was added. The mixture was cooled to 0 °C and 7.5 mL H_2O_2 added. This mixture was stirred at 0 °C for 2 h, then transferred to a steel reaction vessel, cooled to 0 °C, and NH_3 bubbled into the solution for 20 min. The reaction vessel was sealed and heated in oil bath at 120 °C for 18 h. The vessel was cooled, the reaction mixture evaporated to dryness under vacuum to give a yellow solid. The crude mixture was purified by chromatography eluting with hexanes/EtOAc (1:1) to afford 424.4 mg of **14** as a white solid (40%), mp 182 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 8.22 (s, 1H), 7.22–7.34 (m, 10H), 7.05–7.16 (m, 5H), 6.41 (d, 1H, *J*=4.6 Hz), 4.62–4.70 (m, 3H), 4.50–4.58 (m, 3H), 4.41–4.44 (m, 1H), 4.25–4.28 (m, 1H), 4.08–4.13 (m, 1H), 3.80–3.82 (m, 1H), 3.78 (s, 3H), 3.65 (dd, 1H *J*=3.6, 10.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 161.5, 156.4, 151.6, 144.4, 143.1, 137.5, 137.2, 128.6, 128.0, 127.9, 115.6, 88.9, 82.1, 80.1, 75.6, 73.6, 72.5, 72.4, 68.9, 60.5, 55.3. ESI-MS calcd for $C_{34}H_{32}N_4O_6S$: 624.2, found 625.4 $[M+1]^+$. Anal. Calcd for $C_{34}H_{32}N_4O_6S$: C 65.37, H 5.16, N 8.97, S 5.13. Found C 65.22, H 4.86, N 9.04, S 5.19. Further elution with hexanes/EtOAc (1:2) afforded 207.5 mg of **13** as a white foam (20%). ^{1}H NMR (400 MHz, $CDCl_3$): 9.59 (s, 1H), 9.20 (s, 1H), 7.89 (s, 1H), 6.94–7.34 (m, 15H), 5.80 (d, 1H, *J*=8.2 Hz), 4.99–5.06 (m, 1H), 4.41–4.64 (m, 4H), 4.24–4.27 (m, 2H), 3.89–3.92 (m, 1H), 3.77–3.83 (m, 2H), 3.36–3.39 (dd, 1H, *J*=1.8, 11.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 159.9, 152.4, 151.0, 144.3, 137.1, 135.9, 128.8, 128.7, 128.4, 128.3, 122.0, 110.3, 100.0, 88.0, 84.4, 80.3, 75.1, 73.6, 73.1, 72.9, 67.8; HR-FAB calcd for $C_{33}H_{31}N_4O_6S$ $[M+H]^+$ 611.19643, found 611.19878. Further elution with hexanes/EtOAc (1:3) provided **12** as a white foam (310.65 mg, 30%) whose spectral data agreed with the literature values.[11]

*4.3.2. 2,3-Dibenzyloxy-5-benzyloxymethyl-1-[(2-amino-imidazo-[4′,5′:4,5]-thieno-[3,2-d]-pyrimidin-3-yl-7-one)]-β-D-ribofuranose (**12**) and 2,3-dibenzyloxy-5-benzyloxymethyl-1-[(5-hydroxyl-imidazo-[4′,5′:4,5]-thieno-[3,2-d]-pyrimidin-3-yl-7-one)]-β-D-ribofuranose (**13**)*

In a steel reaction vessel, **11** (1.35 g, 2.31 mmol) was dissolved in 40 mL anhydrous MeOH and NaOH (462 mg, 11.55 mmol) added. This mixture was stirred at room temperature for 30 min until a clear solution was obtained, then CS_2 (836 μL, 13.87 mmol) was added and the vessel sealed and heated in an oil bath at 145 °C for 18 h. The solvent was removed under reduced pressure to obtain an orange solid, and 80 mL MeOH added. The reaction mixture was cooled to 0 °C, 7.5 mL H_2O_2 added, and the mixture stirred at 0 °C for 2 h. The mixture was transferred to a steel reaction vessel, diluted with MeOH (250 mL), cooled to 0 °C, and NH_3 bubbled in for 20 min. The vessel was sealed and heated in oil bath at 120 °C for 18 h. The vessel was cooled, the solvents removed under vacuum to give a yellow solid. The crude compound was purified by chromatography eluting with hexanes/EtOAc (1:2) to afford **12** as white foam (634.67 mg, 45%). As before, further elution with hexanes/EtOAc (1:3) gave **13** (633.51 mg, 45%). Spectral data was identical to the previous entries.

*4.3.3. Synthesis of TBDMS-protected AICAR (**18**)*

To commercially obtained AICAR (**17**) (300 mg, 1.12 mmol) dissolved in 5 mL anhydrous DMF was added imidazole (613.4 mg, 8.96 mmol) and TBDMSCl (676.1 mg, 4.48 mmol). The reaction solution was stirred at room temperature for 2 days. The DMF was removed under reduced pressure to give a crude yellow syrup, which was purified via column chromatography eluting with hexane/EtOAc (2:1) to give **18** as a colorless syrup (450 mg, 66.6%). ^{1}H NMR (400 MHz, $CDCl_3$): 7.53 (s, 1H), 5.48 (d, 1H, *J*=5.96 Hz), 4.42 (s, 2H, NH_2), 4.26–4.25 (m, 1H), 4.17–4.16 (m, 1H), 4.06–4.03 (m, 1H), 3.88–3.84 (m, 1H), 3.78–3.75 (m, 1H), 0.91 (s, 9H), 0.89 (s, 9H), 0.83 (s, 9H), 0.87 (s, 3H), 0.82 (s, 3H), 0.80 (s, 3H), 0.77 (s, 3H), 0.06 (s, 3H), −0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 159.3, 137.4, 132.0, 112.9, 89.9, 85.8, 82.8, 72.1, 62.6, 26.1, 25.9, 25.8, 18.5, 18.1, 17.9, −4.6, −5.3, −5.4; ESI-MS calcd for $C_{27}H_{56}N_4O_5Si_3$+H: 601.01, found: 601.03.

*4.3.4. Synthesis of TBDMS-protected xanthosine (**19**) and guanosine (**20**)*

In a steel reaction vessel, **18** (150 mg, 0.25 mmol) was dissolved in 10 mL anhydrous MeOH, NaOH (100 mg, 2.5 mmol) added, and the mixture stirred at room temperature for 30 min until a clear solution was obtained. CS_2 (90 μL, 1.5 mmol) was then added and the steel vessel sealed and heated at 145 °C for 18 h. The vessel was cooled, and the solvent removed under reduced pressure to give an orange solid, to which MeOH (10 mL) was added. The mixture was then cooled to 0 °C, 1.1 mL H_2O_2 added, and the mixture stirred at 0 °C for 2 h. Following transfer to a steel reaction vessel, the mixture was again cooled to 0 °C and NH_3 bubbled into the solution for 20 min. After saturation with NH_3, the vessel was sealed and heated at 120 °C for 18 h. The bomb was cooled and the reaction mixture evaporated to dryness to give a crude yellow solid, which was purified by column chromatography eluting with hexanes/EtOAc (2:1) to afford **19** (62.4 mg, 40%) as a colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$): 12.45 (s, 1H), 10.25 (s, 1H), 7.45 (s, 1H), 5.67 (d, 1H, *J*=5.6 Hz), 4.31–4.33 (m, 1H), 4.20–4.22 (m, 1H), 4.04–4.11 (m, 2H), 4.01–4.03 (m, 1H), 0.96 (s, 9H), 0.94 (s, 9H), 0.92 (s, 9H), 0.90 (s, 3H), 0.87 (s, 3H), 0.85 (s, 3H), 0.79 (s, 3H), 0.09 (s, 3H), −0.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 160.1, 152.2, 142.7, 130.9, 122.5, 110.1, 91.2, 83.0, 75.6, 69.5, 60.9, 29.8, 25.8, 22.8, 17.3, 17.2, 17.0, −4.6, −5.4, −5.6; ESI-MS calcd for $C_{28}H_{54}N_4O_6Si_3$+H: 627.3, found: 627.3. Further elution with hexane/EtOAc (1:3) gave **20** (62.3 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$): 12.5 (s, 1H), 8.5 (s, 1H), 8.08 (s, 1H), 6.06 (d, 1H, *J*=4.6 Hz), 4.79–4.88 (m, 1H), 4.15–4.29 (m, 2H), 3.97–4.01 (m, 1H), 3.71–3.74 (m, 1H), 3.40–3.41 (m, 1H), 0.95 (s, 9H), 0.93 (s, 9H), 0.91 (s, 9H), 0.90 (s, 3H), (s, 3H), 0.88 (s, 3H), 0.85 (s, 3H), 0.77 (s, 3H), 0.09 (s, 3H), −0.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 157.4, 137.6, 112.8, 89.89, 85.81, 82.9, 72.1, 62.6, 29.1, 26.2, 25.9, 18.8, 18.5, 17.7, −4.6, −5.3, −5.5; ESI-MS calcd for $C_{28}H_{55}N_5O_5Si_3$+H: 626.02, found: 626.3.

4.4. Deprotection procedures

*4.4.1. 1-[(5-Hydroxylimidazo[4′,5′:4,5]thieno[3,2-d]pyrimidin-3-yl-7-one)]-β-D-ribofuranose (**4**)*

Compound **13** (200 mg, 0.328 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL), and $BF_3 \cdot OEt_2$ (586.4 μL, 2.82 mmol) and EtSH (2.82 mL, 37.53 mmol) were added, and the solution stirred at room temperature for 2 days. After evaporation of the solvent and excess reagents, the residue was dissolved in 40 mL H_2O, and washed with CH_2Cl_2 (3×75 mL). The water phase was evaporated to dryness to give a yellow syrup, which was dissolved in H_2O/MeOH (1:1), then cooled to 4 °C, and a white solid precipitated. The solid was filtered, washed with small portions of cold H_2O and MeOH, and dried under vacuum to give 98.27 mg of a hygroscopic white solid (88%) (Note: compound **14** can be deprotected in an analogous manner to afford **4** in similar yields). ^{1}H NMR (400 MHz, DMSO-d_6): 11.34 (s, 1H) 11.26 (s, 1H), 8.44 (s, 1H), 5.90 (d, 1H, *J*=7.3 Hz), 4.80–5.40 (br, 3H), 4.02–4.08 (m, 2H), 3.90–3.97 (m, 1H), 3.60–3.69 (m, 2H); ^{13}C

NMR (100 MHz, DMSO-d_6): 160.4, 151.7, 150.4, 146.0, 131.6, 122.8, 108.8, 89.5, 86.7, 76.1, 70.2, 61.2; HR-FAB calcd for $C_{12}H_{13}N_4O_6S$ $[M+H]^+$ 341.05558, found 341.05614. Anal. Calcd for $C_{12}H_{12}N_4O_6S$ $(1.2H_2O)$ C, 39.82; H, 4.01; N, 15.48; S, 8.86. Found: C, 39.91; H, 4.17; N, 15.65; S, 8.88.

4.5. Synthesis of the 2′-deoxy thieno-expanded xanthosine nucleoside

*4.5.1. 1-[(5-Hydroxylimidazo[4′,5′:4,5]thieno[3,2-d]pyrimidin-3-yl-7-one)]-1′-β-D-ribofuranoside-3′,5′-O-(tetraisobutyrylsilicoane)ether (**21**)*

To a solution of **4** (292 mg, 0.86 mmol) dissolved in 12 mL anhydrous pyridine stirring under N_2 was added 1,3-dichloro-1,1,3,3-tetraisopropylsiloxane (293 μl, 0.93 mmol). This solution was stirred at room temperature for 24 h. The solvent was then evaporated under reduced pressure, and an off-white solid obtained, which was dissolved in CH_2Cl_2 (20 mL), washed with water (10 mL), then saturated $NaHCO_3$ (10 mL). The organic phases were combined, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was purified via column chromatography eluting with hexanes/EtOAc (1:1) to give 300 mg of **21** as a white foam (60%). ^{1}H NMR (400 MHz, DMF-d_7): 11.34 (s, 1H), 8.48 (s, 1H), 7.99 (s, 1H), 6.36 (d, 1H, J=6.0 Hz), 4.76–4.78 (m, 1H), 4.41–4.45 (m, 1H), 4.27–4.30 (m, 1H), 4.18–4.22 (m, 1H), 4.04–4.07 (m, 1H), 0.93–1.06 (m, 28H); ^{13}C NMR (100 MHz, DMF-d_7): 160.2, 151.5, 150.0, 131.5, 108.8, 91.8, 90.3, 83.3, 75.7, 74.3, 70.7, 60.5, 18.7, 18.0, 17.3, 17.1, 16.3, 16.0, 15.5, 14.2, 14.1, 13.7, 13.6, 13.3, 12.9, 12.7; ESI-MS calcd for $C_{24}H_{38}N_4O_7SSi_2$ $[M+1]^+$ 583.2, found 583.1; HR-FAB calcd for $C_{24}H_{39}N_4O_7SSi_2$ $[M+H]^+$ 583.2478, found 583.2478.

*4.5.2. [(5-Hydroxylimidazo[4′,5′:4,5]thieno[3,2-d]pyrimidin-3-yl-7-one)]-1′-β-D-ribofuranoside-3′,5′-O-(tetraisobutyrylsilicoane)-2′-thiocarbonate phenyl ester (**22**)*

Stirring under N_2, **21** (274 mg, 0.47 mmol) suspended in 15 mL anhydrous CH_3CN was treated with DMAP (314.9 mg, 2.58 mmol), followed by phenyl chlorothionoformate (118.9 μl, 0.86 mmol). The yellow solution was stirred at room temperature for 24 h, the solvent was evaporated, and the crude yellow solid was purified via chromatography eluting with hexanes/EtOAc (1:1) to afford 169 mg of **22** as a colorless glass-like solid (50%). ^{1}H NMR (400 MHz, $CDCl_3$): 10.01 (s, 1H), 9.75 (s, 1H), 8.24 (s, 1H), 7.26–7.38 (m, 3H), 7.07–7.09 (m, 2H), 6.06 (d, 1H, J=4.2 Hz), 4.57–4.61 (m, 1H), 4.32–4.42 (m, 3H), 4.01–4.09 (m, 1H), 0.93–1.06 (m, 28H); ^{13}C NMR (100 MHz, $CDCl_3$): 194.4, 160.2, 153.3, 151.7, 151.3, 142.2, 130.4, 129.7, 123.2, 120.9, 112.4, 110.5, 89.5, 88.5, 84.7, 84.2, 83.5, 82.5, 17.5, 17.3, 17.1, 16.9, 16.8, 16.0, 12.9, 12.6, 12.5; HR-FAB calcd for $C_{31}H_{43}N_4O_8S_2Si_2$ $[M+H]^+$ 719.20609, found 719.20562.

*4.5.3. [(5-Hydroxylimidazo[4′,5′:4,5]thieno[3,2-d]pyrimidin-3-yl-7-one)]-1′-β-D-ribofuranoside-3′,5′-O-(tetraisobutyrylsilicoane)ether (**23**)*

Under N_2, **22** (122 mg, 0.17 mmol) was suspended in 10 mL anhydrous toluene and AIBN (11.23 mg, 0.068 mmol) added, followed by n-Bu_3SnH (499.24 μL, 1.85 mmol). The reaction mixture was refluxed for 6 h, and the solvent was evaporated under vacuum to give a yellow syrup. The crude syrup was purified via chromatography eluting with hexanes/EtOAc (1:1) to give 50 mg of **23** (52%). ^{1}H NMR (400 MHz, DMF-d_7): 11.60 (s, 1H), 8.67 (s, 1H), 8.17 (s, 1H), 6.88–6.89 (m, 1H), 4.85–4.87 (m, 1H), 4.11–4.16 (m, 3H), 3.85–3.87 (m, 2H), 1.24–1.28 (m, 4H), 0.97–1.06 (m, 24H); ^{13}C NMR (100 MHz, DMF-d_7): 160.2, 157.3, 152.0, 148.3, 138.0, 117.3, 85.6, 69.2, 61.5, 41.2, 36.7, 18.1, 16.7, 16.6, 16.5, 16.3, 16.2, 16.1, 13.3, 13.0, 12.8, 12.5; ESI-MS calcd for $C_{24}H_{39}N_4O_6SSi_2$ $[M+H]^+$ 567.2, found 567.1; HR-FAB calcd for $C_{24}H_{39}N_4O_6SSi_2$ $[M+H]^+$ 567.18771, found 567.18462.

*4.5.4. 1-[(5-Hydroxylimidazo[4′,5′:4,5]thieno[3,2-d]pyrimidin-3-yl-7-one)]-β-D-2-deoxyribofuranose 3,5-diol (**5**)*

Compound **23** (86 mg, 0.15 mmol) was dissolved in 10 mL anhydrous THF, then 1 M TBAF in THF (680 μL) was added. The solution was stirred at room temperature for 4 h, the solvent was evaporated to provide a pale-brown syrup. Purification with silica gel chromatography eluting with hexanes/EtOAc (1:2) gave 30 mg of **5** as a hygroscopic white solid (61%). ^{1}H NMR (400 MHz, DMF-d_7): 11.03 (s, 1H), 10.94 (s, 1H), 8.4 (s, 1H), 6.25–6.29 (m, 1H), 5.54 (br s, 1H), 5.25 (br s, 1H), 4.32 (br s, 1H), 3.82–3.83 (m, 1H), 3.50–3.63 (m, 2H); ^{13}C NMR (100 MHz, DMF-d_7): 160.2, 151.6, 131.7, 127.7, 113.9, 111.2, 108.7, 88.5, 86.9, 70.5, 61.3, 42.7; HR-FAB calcd for $C_{12}H_{13}N_4O_5S$ $[M+H]^+$ 325.06067, found 325.06021. Anal. Calcd for $C_{12}H_{12}N_4O_5S$ $(1.65H_2O)$ C, 40.71; H, 4.36; N, 15.83; S, 9.06. Found: C, 40.77; H, 3.99; N, 15.56; S, 8.89.

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