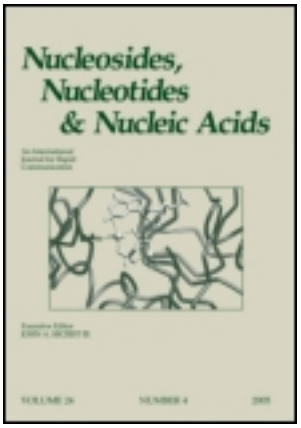


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# Synthesis of 2′-Substituted Inosine Analogs via Unusual Masking of the 6-Hydroxyl Group

Fabio Casu [a], Rebecca K. Harston [a], Maria A. Chiacchio [b] & Giuseppe Gumina [c]

[a] Department of Pharmaceutical Sciences, Medical University of South Carolina, Charleston, South Carolina, USA

[b] Dipartimento di Scienze Chimiche, Università di Catania, viale A. Doria 6, Catania, Italy

[c] Department of Pharmaceutical Sciences, South University School of Pharmacy, Savannah, Georgia, USA

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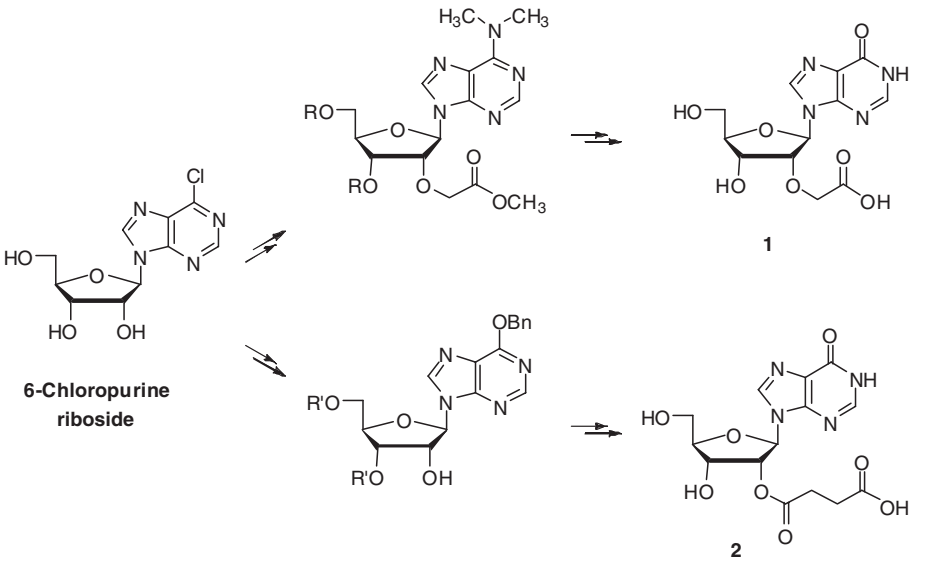
# SYNTHESIS OF 2′-SUBSTITUTED INOSINE ANALOGS VIA UNUSUAL MASKING OF THE 6-HYDROXYL GROUP

**Fabio Casu,[1] Rebecca K. Harston,[1] Maria A. Chiacchio,[2] and Giuseppe Gumina[3]**

[1]*Department of Pharmaceutical Sciences, Medical University of South Carolina, Charleston, South Carolina, USA*
[2]*Dipartimento di Scienze Chimiche, Università di Catania, viale A. Doria 6, Catania, Italy*
[3]*Department of Pharmaceutical Sciences, South University School of Pharmacy, Savannah, Georgia, USA*

**Graphical Abstract:**

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Address correspondence to Giuseppe Gumina, Department of Pharmaceutical Sciences, South University School of Pharmacy, 709 Mall Boulevard, Savannah, GA 31406. E-mail: ggumina@southuniversity.edu

□ *2′-Modified inosine analogs have been synthesized from 6-chloropurine riboside via 6-dimethylaminopurine or 6-benzyloxypurine intermediates. The dimethylaminopurine intermediate was obtained via an unusually facile dimethylamine transfer from dimethylformamide.*

**Keywords** Modified nucleosides; base modification; anticancer nucleosides



## INTRODUCTION

The continued success of nucleoside analogs as therapeutic agents in the past 40 years has driven the development of novel synthetic methodologies to access highly modified structures.[1] Research in the field of nucleoside-based compounds has focused for several years on 2′-deoxy, 2′,3′-dideoxy, *arabino* analogs and their carbocyclic or heterosubstituted analogs.[2] This focus was due to the nature of the biological targets, i.e., human or viral DNA polymerases.[2] However, more recent research has shifted its focus toward ribonucleosides due to the need to treat new or re-emerging infectious diseases caused by RNA viruses, among which hepatitis C[3] is today the most clinically relevant.

The synthesis of modified ribonucleosides is usually achieved via a convergent approach, in which a suitably activated ribose analog is coupled to a silylated base in Vorbrüggen fashion.[4] Derivatives where the ribose moiety is modified are often prepared from carbohydrates like xylose or arabinose rather than ribose.[1c] As part of our studies toward the synthesis of 2′-modified inosines as potential inhibitors of purine nucleoside phosphorylase, we explored the synthesis of 2′-inosine ether **1** and ester **2**[5] (Figure 1) via a linear approach, in which functionalization of the ribose moiety is achieved on the nucleoside. When such an approach is attainable, it has the advantage of providing target molecule in a relatively small number of steps. 2′-functionalization of nucleosides is also of great interest due to the activity of 2′-modified derivatives against hepatitis C.[6]

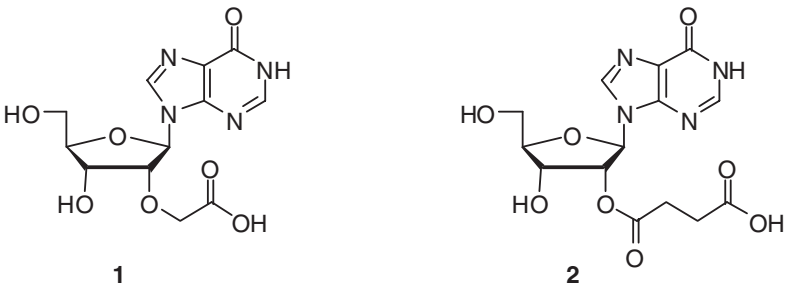


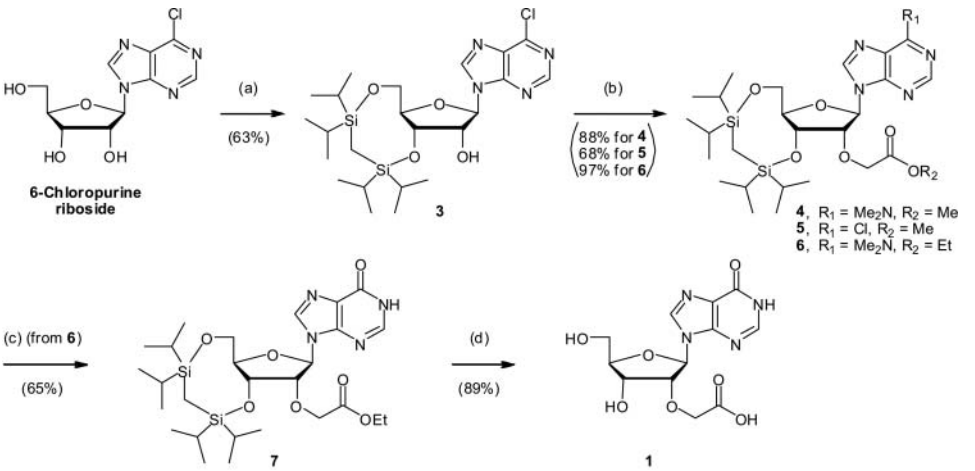

**FIGURE 1** 2′-Inosine ether **1**, and ester **2**.

## RESULTS AND DISCUSSION

### Synthesis

Bis-protection of the 3′,5-diol functionality of ribonucleosides has been the subject of extensive literature.[7] The methylene-1,3-bis-diisopropylsilanyl protecting group in **3** (Scheme 1) has been reported to be stable under the strongly basic conditions necessary for the alkylation of the 2′-hydroxyl group.[8] The protected 6-chloropurine **3** was subjected to alkylating conditions via conversion to the sodium salt using sodium bis(trimethylsilyl)amide at −20°C, and then at room temperature. Surprisingly, the alkylated product was the dimethylaminopurine analog **4**, evidently resulting from the transfer of a dimethylamino group from the solvent *N*,*N*-dimethylformamide. When commonly used 3′,5′-protecting groups, such as tetraisopropyldisiloxanyl,[1c,9] *tert*-butyldimethylsilyl,[10] or acetyl[11] were tried, the reactions did not yield the desired products. Instead, complex mixtures of products of partial desilylation or acetyl migration were detected by TLC analysis and characterized only partially.

Both the alkylation of the 2′-OH and the substitution of the 6-chlorine proceeded very smoothly at room temperature. However, the substitution at the 2′-position was very rapid, and quenching the reaction after one hour at −20°C resulted in the isolation of the 6-chloropurine derivative **5** in good yield. No product **4** was formed at this temperature. Monitoring the reaction by TLC was complicated by the fact that the intermediate chloride **5** had the same $R_f$ as the starting material **3**. However, the use of ethyl bromoacetate



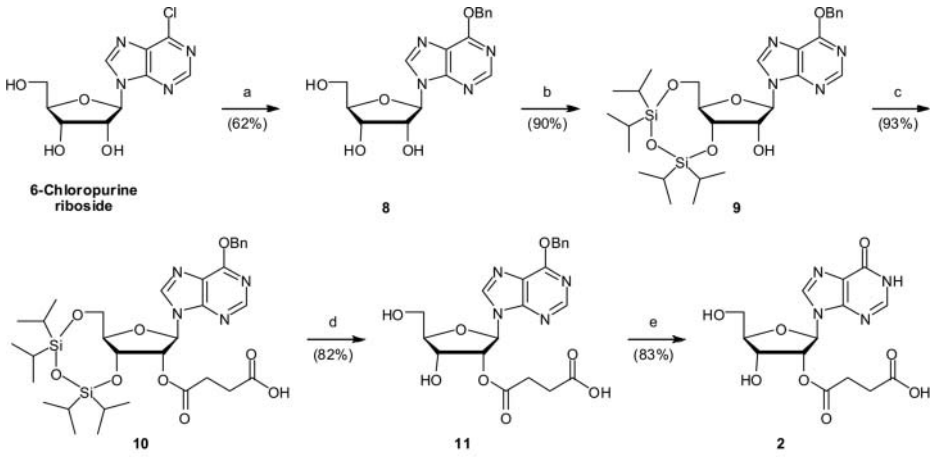

Reagents and conditions: (a) $(i\text{-Pr}_2\text{SiCl})_2\text{CH}_2$, imidazole, DMF, −20°C to rt, overnight; (b) NaHMDS, $BrCH_2CO_2Me$ or $BrCH_2CO_2Et$, TBAI, DMF, −20°C to rt, 72 h; (c) MCPBA, $CHCl_3$, 50°C, 24 h; (d) TBAF, THF, rt, 1 h.

**SCHEME 1** Synthesis of 2′-*O*-carboxymethylinosine **1**.

in place of methyl ester allowed the detection of starting material, intermediate, and product **6**, which was isolated in almost quantitative yield. When the reaction was started at −20°C, then warmed up to 0°C instead of room temperature, partial conversion to **4** or **6** was observed. The dimethylamine functionality in **6** was oxidized to give the protected inosine **7**. Deprotection of the silyl diether with tetrabutylammonium fluoride occurred with concomitant hydrolysis of the ester functionality to give the final product **1**, which was isolated as the tetrabutylammonium salt.

The amination of **3** at low temperature is interesting, because the dimethylamine transfer from dimethylformamide to a chlorinated heterocycle had been observed before, but only at high temperatures (80–150°C) and in the presence of weaker bases, such as triethylamine and potassium carbonate.[12] One possible mechanism could be the formation of dimethylamine from dimethylformamide via $\alpha$-elimination catalyzed by very strong base, although the low temperatures observed in our case would be unusual. The possibility that dimethylformamide contained significant amounts of dimethylamine as normal storage decomposition products was ruled out, because the same solvent was used in the synthesis of **3** and no amination of the starting material was observed. The use of tetrabutylammonium iodide may very well facilitate the reaction by in situ conversion of the 6-chloropurine to 6-iodopurine reactive intermediate. Indeed, nucleophilic aromatic substitution of 6-chloropurine with iodide at low temperatures has been described, although in different conditions.[13] All these possibilities deserve more thorough investigations, which are beyond the scope of the work presented herein.

For the synthesis of **2**, the masked hypoxanthine heterocyclic moiety was obtained by benzylation of 6-chloropurine to benzyl aryl ether **8** (Scheme 2).




Reagents and conditions: (a) BnONa, BnOH, DMF, rt, 5 h; (b) $TIBDSCl_2$, Py, rt, 5 h; (c) Succinic anhydride, DMAP, Py, rt, 6 h; (d) $Et_3N{\cdot}HF$, THF, rt, 4 h; (e) 20% Pd/C, $H_2$, EtOH, rt, atmospheric pressure, 7 h.

**SCHEME 2** Synthesis of 2′-*O*-succinylinosine **2**.

Benzyl protection allows circumventing the basic hydrolytic step necessary to convert 6-chloropurine to hypoxanthine. Because in this case no strong bases are required for the acylation of the 2′-oxygen, the tetraisopropyldisiloxane-1,3-diyl protecting group could be used for the protection of the 3′,5′-diol, employing the commercially available dichloride. Acylation of alcohol **9** was accomplished by treatment with succinic anhydride. Deprotection of the resulting 3′,5′-bis silyl ether **10** was effectively accomplished in mild conditions using triethylamine trihydrofluoride, whereas the classic reagent tetrabutylammonium fluoride proved to be too basic for the ester function in **10**, which was cleaved to give fully deprotected **8**. Hydrogenation of the benzyl group in **10** afforded the desired product **2**.

Although the 6-chloropurine/6-benzyloxypurine/hypoxanthine conversion seems a logical procedure, we could not find this sequence in the literature.

Neither **1** nor **2** inhibited *E. coli* or human purine nucleoside phosphorylase in concentrations of up to 200 $\mu$M.



## SUMMARY AND CONCLUSION

We have described two novel routes toward the synthesis of 2′-functionalized inosine ethers or esters. These routes feature alternative protection, deprotection, and reactivity compared to the known literature methods and allow the synthesis of inosine analogs bypassing aqueous basic hydrolytic conditions. Therefore, the described methods are compatible with the presence of the ester functionality. During the functionalization of the 2′-position, we observed an unusually mild dimethylamine transfer from dimethylformamide to 6-chloropurine. This reaction may represent a novel mild amination and its general applicability will be tested in future studies.

## EXPERIMENTAL

### General

All reactions were carried out under a positive pressure of argon and monitored by TLC on uniplates (silica gel) purchased from Analtech Co. All the reagents, purine nucleoside phosphorylase, and anhydrous solvents were purchased from commercial sources and used without further purification except where noted. Chromatographic purifications were performed on flash silica gel (particle size 40–63 $\mu$m) purchased from Silicycle or TLC-grade silica gel (particle size 5–15 $\mu$m) purchased from Sorbent Technologies. All solvents for chromatographic purifications were of HPLC grade. Melting points were determined on a Barnstead Mel-Temp and are uncorrected. $^1$H NMR spectra were recorded on Varian 500 with $Me_4Si$ as an internal standard. Signals are represented as s (singlet), d (doublet), t (triplet), m (multiplet), or combinations of the all. UV spectra were obtained on

a BECKMAN DU-650 spectrophotometer. Optical rotations were measured on a Rudolph Research Analytical Autopol IV digital polarimeter. Elemental analyses were performed by Atlantic Microlabs Inc. (Norcross, GA, USA).

## Experimental Procedures

**3′,5′-*O*-(Methylene-bis-diisopropylsilane-1,3-diyl)-6-chloropurine riboside (3).** 6-Chloropurine riboside (1.0 g, 3.49 mmol) and imidazole (1.17 g, 17.1 mmol) were dried by co-evaporation with anhydrous pyridine (3 × 30 mL) and then dissolved in anhydrous dimethylformamide (30 mL). The mixture was cooled in ice bath and 1,3 dichloro-bis(diisopropylsilyl)methane (1.27 mL, 4.19 mmol) was added dropwise. The temperature was gradually increased to rt and the mixture was stirred for 6 h. The reaction mixture was poured into water (100 mL) and the resulting suspension was extracted with dichloromethane (3 × 40 mL). The combined organic extracts were washed with brine (1 × 20 mL), dried over magnesium sulfate, and concentrated under reduced pressure. The resulting crude was purified by TLC-grade silica gel flash chromatography (1:6 ethyl acetate/hexanes) to give **3** as colorless crystals (1.15 g, yield: 63%). $R_f$ 0.5 (1:9 methanol/dichloromethane); mp 83–85°C; $[\alpha]_D^{25}$ −22.29 (*c* 0.48, $CHCl_3$); UV ($\lambda_{max}$ = 264 nm, $CH_3OH$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.73 (s, 1H), 8.32 (s, 1H), 6.08 (s, 1H, anomeric), 4.82 (dd, $J$ = 7.9, 5.4 Hz, 1H), 4.54 (d, $J$ = 5.3 Hz, 1H) 4.14–4.06 (m, 2H), 3.95 (dd, $J$ = 12.1, 2.7 Hz), 3.15 (s, 1H, $D_2O$ exchangeable), 1.11–1.03 (m, 28H), 0.05 (dd, $J$ = 21.4, 14.2 Hz, 2H); $^{13}$C NMR (400 MHz, $CDCl_3$) $\delta$ 151.7, 151.0, 150.5, 144.0, 132.3, 90.0, 81.7, 74.7, 70.3, 61.1, 17.7, 17.6, 17.6, 17.5, 17.5, 17.4, 17.4, 17.3, 17.3, 14.2, 13.9, 13.6, −9.46; Mass $[MH]^+$ 527; Anal. Calcd for $C_{23}H_{39}ClN_4O_4Si_2$: C, 52.40; H, 7.46; N, 10.63. Found: C, 52.54; H, 7.55; N, 10.39.

**3′,5′-*O*-(Methylene-bis-diisopropylsilane-1,3-diyl)-2′-*O*-(methoxycarbonyl methyl)-*N*,*N*-dimethyladenosine (4).** Sodium bis(trimethylsilyl)amide (1 M solution in tetrahydrofuran, 1.14 mL, 1.14 mmol) was added to a solution of **3** (0.20 g, 0.38 mmol), methyl bromoacetate (0.11 mL, 1.22 mmol), and tetrabutylammonium iodide (0.04 g, 0.11 mmol) in anhydrous dimethylformamide (8 mL) at −20°C, and the resulting mixture was stirred for 4 h at the same temperature. The temperature was then allowed to warm up gradually to rt and the mixture was stirred at rt for 72 h. The reaction was quenched with methanol and evaporated under reduced pressure and the residue poured into 150 mL of water, extracted with dichloromethane (3 × 20 mL) and washed with brine (2 × 10 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting crude was purified by TLC-grade silica gel flash chromatography (1:4 to 2:7 ethyl acetate/hexanes) to give **4** as a yellow solid (0.200 g, yield: 88%). $R_f$ 0.38 (1:9 methanol/dichloromethane); mp 75–77°C; $[\alpha]_D^{23}$ −57.58 (*c* 0.37, $CHCl_3$); UV ($\lambda_{max}$ = 272.5 nm, $CH_3OH$);

$^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.28 (s, 1H), 8.00 (s, 1H), 6.09 (s, 1H, anomeric), 4.75 (dd, $J = 9.4$, 4.5 Hz, 1H), 4.63 (d, $J = 16.8$ Hz, 1H), 4.44 (d, $J = 16.6$ Hz, 1H), 4.39 (d, $J = 4.5$ Hz, 1H), 4.21–4.11 (m, 2H), 3.85 (dd, $J = 13.0$, 2.5 Hz, 1H), 3.72 (s, 3H), 3.52 (br s, 6H), 1.11–1.00 (m, 28H), 0.01 (d, $J = 14.0$ Hz, 1H), −0.08 (d, $J = 14.2$ Hz, 1H); $^{13}$C NMR (400 MHz, $CDCl_3$) $\delta$ 170.7, 155.0, 152.4, 149.7, 137.2, 120.9, 88.7, 82.5, 81.1, 70.6, 68.3, 60.6, 52.0, 38.5, 18.1, 17.9, 17.9, 17.8, 17.8, 17.8, 17.7, 14.5, 14.4, 14.2, −9.59; Mass $[MH]^+$ 608; Anal. Calcd for $C_{28}H_{49}N_5O_6Si_2 \cdot 0.1$ EtOAc: C, 55.31; H, 8.14; N, 11.36. Found: C, 55.64; H, 8.16; N, 11.06.

**3′,5′-*O*-(methylene-bis-diisopropylsilane-1,3-diyl)-2′-*O*-(methoxycarbonyl methyl)-6-chloropurine riboside (5).** Sodium bis(trimethylsilyl)amide (1 M solution in tetrahydrofuran, 1.88 mL, 1.88 mmol) was added to a solution of **3** (0.300 g, 0.569 mmol), methyl bromoacetate (0.17 mL, 1.82 mmol) and tetrabutylammonium iodide (0.06 g, 0.17 mmol) in anhydrous dimethylformamide (30 mL) at −20°C, and the resulting mixture was stirred for 1 h at the same temperature. The reaction was quenched with methanol, gradually warmed up to rt and concentrated in vacuo to a residue to which 200 mL of water were added and the resulting suspension was extracted with dichloromethane (4 × 50 mL). The combined organic extracts were washed with water (1 × 50 mL) and brine (1 × 50 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting crude was purified by TLC-grade silica gel flash chromatography (13 to 15% ethyl acetate/hexanes) to give **5** as a colorless syrup (0.230 g, yield: 68%). $R_f$ 0.35 (3:7 ethyl acetate/hexanes); $[\alpha]_D^{25}$ −38.11 (*c* 1.00, $CHCl_3$); UV ($\lambda_{max}$ = 264.0 nm, $CH_3OH$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.73 (s, 1H), 8.46 (s, 1H), 6.22 (s, 1H, anomeric), 4.68 (dd, $J = 9.5$, 4.5 Hz, 1H), 4.62 (d, $J = 16.6$ Hz, 1H), 4.46 (d, $J = 16.8$ Hz, 1H), 4.39 (d, $J = 4.5$ Hz, 1H), 4.26–4.15 (m, 2H), 3.87 (dd, $J = 13.2$, 2.5 Hz, 1H), 3.74 (s, 3H), 1.11–1.00 (m, 28H), 0.03 (d, $J = 14.0$ Hz, 1H), −0.07 (d, $J = 14.2$ Hz, 1H); $^{13}$C NMR (400 MHz, $CDCl_3$): $\delta$ 170.3, 151.8, 150.9, 150.5, 144.0, 132.4, 88.9, 82.1, 81.2, 70.1, 68.1, 60.0, 51.8, 17.8, 17.6, 17.6, 17.5, 17.5, 17.4, 14.2, 14.1, 14.0, -9.85; Mass $[MH]^+$ 599; Anal. Calcd for $C_{26}H_{43}ClN_4O_6Si_2$: C, 52.11; H, 7.23; N, 9.35. Found: C, 52.32; H, 7.28; N, 9.16.

**3′,5′-O-(Methylene-bis-diisopropylsilane-1,3-diyl)-2′-*O*-(ethoxycarbonyl methyl)-*N*,*N*-dimethyladenosine (6).** Sodium bis(trimethylsilyl)amide (1 M solution in tetrahydrofuran, 4.50 mL, 4.50 mmol) was added to a solution of **3** (0.790 g, 1.50 mmol), ethyl bromoacetate (0.53 mL, 4.79 mmol), and tetrabutylammonium iodide (0.170 g, 0.449 mmol) in anhydrous dimethylformamide (40 mL) at −20°C. The mixture was stirred for 1 h at the same temperature, then allowed to warm up gradually to rt and stirred for 72 h. The reaction was quenched with methanol and evaporated under reduced pressure and the residue was poured into 200 mL of water, extracted with dichloromethane (3 × 70 mL), and washed with brine (1 × 50 mL). The combined organic extracts were dried over magnesium sulfate,

filtered, and concentrated under reduced pressure. The resulting crude was purified by TLC-grade silica gel flash chromatography (14 to 20% ethyl acetate/hexanes) to give **6** as a yellow syrup (0.90 g, yield: 97%). $R_f$ 0.6 (1:9 methanol/dichloromethane); $[\alpha]_D^{25}$ −42.60 (*c* 0.46, $CHCl_3$); UV ($\lambda_{max}$ = 277.5 nm, $CH_3OH$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 8.27 (s, 1H), 7.99 (s, 1H), 6.09 (s, 1H, anomeric), 4.77 (dd, $J$ = 9.4, 4.5 Hz, 1H), 4.60 (d, $J$ = 16.6 Hz, 1H), 4.43 (d, $J$ = 16.8 Hz, 1H), 4.41 (d, $J$ = 4.5 Hz, 1H), 4.21–4.10 (m, 4H), 3.84 (dd, $J$ = 13.1, 2.5 Hz, 1H), 3.52 (br s, 6H), 1.23 (t, $J$ = 7.0 Hz, 3H), 1.11–1.00 (m, 28H), 0.02 (d, $J$ = 14.0 Hz, 1H), −0.08 (d, $J$ = 14.2 Hz, 1H); $^{13}C$ NMR (400MHz, $CDCl_3$) $\delta$ 170.1, 154.7, 152.2, 149.4, 137.0, 120.7, 88.5, 82.0, 80.8, 70.3, 68.1, 60.8, 60.3, 38.4, 17.9, 17.7, 17.7, 17.6, 17.6, 17.6, 17.5, 14.2, 14.1, 14.1, 13.9, −9.90; Mass $[MH]^+$ 622; Anal. Calcd for $C_{29}H_{51}N_5O_6Si_2 \cdot 0.05$ Hex: C, 56.20; H, 8.32; N, 11.18. Found: C, 56.55; H, 8.30; N, 10.95.

**3′,5′-O-(Methylene-bis-diisopropylsilane-1,3-diyl)-2′-*O*-(ethoxycarbonyl methyl)inosine (7)**. A mixture of **6** (0.160 g, 0.257 mmol) and MCPBA (0.288 g, 1.29 mmol) in chloroform (10 mL) was stirred at 50°C for 24 h. The mixture was concentrated under reduced pressure to a crude that was purified by TLC-grade silica gel flash chromatography (dichloromethane to 1:19 methanol/dichloromethane), then recrystallized from ethanol to afford pure **7** as a white solid (0.100 g, 65%): $R_f$ 0.17 (1:19 methanol/dichloromethane); mp 136–138°C; $[\alpha]_D^{27}$ −37.95 (*c* 0.50, $CHCl_3$); UV ($\lambda_{max}$ = 245 nm, 269.5 nm (sh), $CH_3OH$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 13.13 (br s, 1H, $D_2O$ exchangeable), 8.18 (s, 1H), 8.08 (s, 1H), 6.15 (s, 1H, anomeric), 4.62 (dd, $J$ = 9.4, 4.4 Hz, 1H), 4.57 (d, $J$ = 16.8 Hz, 1H), 4.45 (d, $J$ = 16.6 Hz, 1H), 4.29 (d, $J$ = 4.3 Hz, 1H), 4.25–4.14 (m, 4H), 3.85 (dd $J$ = 13.2, 2.3 Hz), 1.25 (t, $J$ = 7.1 Hz, 3H), 1.11–1.00 (m, 28H), 0.03 (d, $J$ = 14.2 Hz, 1H), −0.09 (d, $J$ = 14.2 Hz, 1H); $^{13}C$ NMR (400 MHz, $CDCl_3$) $\delta$ 170.0, 159.4, 147.9, 145.0, 138.8, 125.3, 88.5, 82.3, 81.1, 70.0, 68.0, 60.9, 60.1, 17.9, 17.7, 17.6, 17.6, 17.6, 17.5, 17.5, 14.3, 14.2, 14.1, 14.1, 13.9, −9.91; Mass $[MH]^+$ 595; Anal. Calcd for $C_{27}H_{46}N_4O_7Si_2$: C, 54.52; H, 7.79; N, 9.42. Found: C, 54.29; H, 7.51; N, 9.73.

**2′-*O*-Carboxymethylinosine (1)**. To a solution of **4** (100 mg, 0.17 mmol) in anhydrous tetrahydrofuran (10 mL) was added TBAF (1 M solution in tetrahydrofuran, 0.25 mL, 0.25 mmol) and the resulting mixture was stirred at rt for 27 h, then concentrated under reduced pressure. The resulting crude was purified by preparative TLC, eluting with 3:17 methanol/dichloromethane and extracting the silica gel with 1:19 to 1:13 methanol/dichloromethane, to give **1** as a yellow syrup (49 mg, 89%): $R_f$ 0.30 (3:17 methanol/dichloromethane); $[\alpha]_D^{24}$ −56.50 (*c* 0.31, $CH_3OH$); UV ($\lambda_{max}$ = 244.0 nm, 275.0 nm (sh), $CH_3OH$); $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 12.44 (br s, 1H, $D_2O$ exchangeable), 8.34 (s, 1H), 8.08 (s, 1H), 6.03 (d, $J$ = 6.0 Hz, 1H, anomeric), 5.34 (d, $J$ = 4.9 Hz, 1H, $D_2O$ exchangeable), 5.12 (br t, $J$ = 5.4 Hz, 1H, $D_2O$ exchangeable), 4.56 (dd, $J$ = 6.0, 5.0 Hz,

1H), 4.33 (dd, $J = 8.2$, 4.9 Hz, 1H), 4.27 (d, $J = 16.8$ Hz, 1H), 4.18 (d, $J = 16.8$ Hz, 1H), 3.99–3.96 (m, 1H), 3.62 (ddd, $J = 12.1$, 5.1, 4.2 Hz, 1H), 3.50 (dd $J = 12.1$, 5.7, 4.1 Hz, 1H); $^{13}$C NMR (400 MHz, $CDCl_3$) $\delta$ 169.9, 156.6, 148.3, 146.0, 138.8, 124.4, 86.2, 85.4, 81.6, 68.7, 66.8, 60.6; Mass $[MH]^+$ 327; Anal. Calcd for $C_{28}H_{49}N_5O_7$: C, 44.18; H, 4.33; N, 17.17. Found: C, 44.46; H, 4.59; N, 17.33.

***O*$^6$-Benzylinosine (8)**. A solution of 6-chloropurine riboside (2.0 g, 6.98 mmol) in anhydrous dimethylformamide (50 mL) was treated with sodium benzyloxide (1 M solution in benzyl alcohol) at rt. After 5 h, the reaction was diluted with water (300 mL) and the resulting mixture was extracted with dichloromethane (3 × 100 mL). The combined organic phases were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting crude was purified by TLC-grade silica gel flash chromatography (dichloromethane to 1:32 methanol/dichloromethane) to give **8** as an off-white solid (1.56 g, yield: 62%): $R_f$ 0.33 (1:9 methanol/dichloromethane); mp 170–171°C; $[\alpha]_D^{25}$ −45.54 (*c* 0.36, $CH_3OH$); UV ($\lambda_{max}$ = 253.5 nm, 277 nm (sh), $CH_3OH$); $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.65 (s, 1H), 8.58 (s, 1H), 7.52–7.50 (m, 2H), 7.44–7.32 (m, 3H), 6.00 (d, $J = 5.8$ Hz, 1H, anomeric), 5.64 (s, 2H), 5.54 (d, $J = 6.0$ Hz, 1H, $D_2O$ exchangeable), 5.27 (d, $J = 4.9$ Hz, 1H, $D_2O$ exchangeable), 5.17 (t, $J = 5.6$ Hz, 1H, $D_2O$ exchangeable), 4.60 (dd, $J = 11.0$, 5.7 Hz, 1H), 4.17 (dd, $J = 8.6$, 4.9 Hz, 1H), 3.97 (dd, $J = 7.5$, 3.8 Hz, 1H), 3.72–3.60 (m, 1H), 3.60–3.53 (m, 1H); $^{13}$C NMR (400 MHz, DMSO-$d_6$) $\delta$ 159.9, 152.0, 151.7, 142.6, 136.3, 128.6, 128.4, 128.3, 121.2, 87.8, 85.8, 73.8, 70.4, 67.9, 61.4; Mass $[M + Na]^+$ 381; Anal. Calcd for $C_{17}H_{18}N_4O_5$: C, 56.98; H, 5.06; N, 15.63. Found: C, 57.04; H, 5.16; N, 15.42.

**3′,5′-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-*O*$^6$-benzylinosine (9).** 1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane (1.06 mL, 3.32 mmol) was added to a solution of **8** (1.08 g, 3.01 mmol) in anhydrous pyridine (40 mL), and the resulting solution was stirred at rt for 4 h. The solution was then concentrated in vacuo and the residue purified by TLC-grade silica gel flash chromatography (1:3 ethyl acetate/hexanes) to give **9** as a white solid (1.62 g, yield: 90%): $R_f$ 0.40 (1:19 methanol/dichloromethane); mp 48–50°C; $[\alpha]_D^{26}$ −27.38 (*c* 0.38, $CHCl_3$); UV ($\lambda_{max}$ = 248.5 nm, $CH_3OH$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.49 (s, 1H), 8.08 (s, 1H), 7.54–7.52 (m, 2H), 7.37–7.30 (m, 3H), 6.02 (s, 1H, anomeric), 5.67 (s, 2H), 5.08 (dd $J = 7.7$, 5.7 Hz, 1H), 4.55 (d, $J = 5.3$ Hz, 1H), 4.18–4.00 (m, 3H), 3.22 (s, 1H, $D_2O$ exchangeable), 1.20–1.00 (m, 28H); $^{13}$C NMR (400 MHz, $CDCl_3$) $\delta$ 160.5, 152.0, 151.2, 141.1, 136.0, 128.4, 128.3, 128.1, 122.4, 89.7, 82.1, 75.1, 70.6, 68.4, 61.5, 17.4, 17.3, 17.3, 17.2, 17.1, 17.0, 16.9, 16.9, 13.2, 13.0, 12.7, 12.5; Mass $[MH]^+$ 601; Anal. Calcd for $C_{29}H_{44}N_4O_6Si_2$: C, 57.97; H, 7.38; N, 9.32. Found: C, 58.07; H, 7.38; N, 9.15.

**3′,5′-*O*-(1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl)-2′-*O*-succinyl-*O*$^6$-benzylinosine (10)**. 4-(Dimethylamino)pyridine and succinic anhydride

were sequentially added to a stirred solution of **9** (0.31 g, 0.516 mmol) in anhydrous pyridine (4 mL). The solution was stirred at rt for 6 h, then quenched with water (20 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting crude was purified by TLC-grade silica gel flash chromatography (0 to 4% methanol/dichloromethane) to give **10** as an off-white solid (0.32 g, yield: 93%): mp 68–70°C; $[\alpha]_D^{24}$ −27.81 (*c* 0.44, $CHCl_3$); UV ($\lambda_{max}$ = 247.5 nm, $CH_3OH$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.75 (br s, 1H, $D_2O$ exchangeable), $\delta$ 8.48 (s, 1H), 8.18 (s, 1H), 7.53–7.50 (m, 2H), 7.38–7.30 (m, 3H), 6.06 (s, 1H, anomeric), 5.79 (d, $J$ = 5.3 Hz, 1H), 5.66 (s, 2H), 5.12 (dd, $J$ = 8.9, 5.4, Hz, 1H), 4.18–3.90 (m, 3H), 2.80–2.60 (m, 4H), 1.11–0.90 (m, 28H); $^{13}$C NMR (400 MHz, $CDCl_3$) $\delta$ 176.3, 171.2, 160.7, 152.5, 151.1, 141.8, 136.1, 128.6, 128.3, 122.0, 88.0, 82.2, 75.9, 69.0, 68.7, 60.5, 29.9, 29.2, 17.6, 17.6, 17.5, 17.2, 17.1, 13.5, 13.1, 13.0, 12.8; Mass $[MH]^+$ 701; Anal. Calcd for $C_{33}H_{48}N_4O_9Si_2$: C, 56.55; H, 6.90; N, 7.99. Found: C, 56.55; H, 6.96; N, 7.68.

**2′-*O*-Succinyl-*O*$^6$-benzylinosine (11)**. To a stirred solution of **10** (0.17 g, 0.24 mmol) in anhydrous tetrahydrofuran (10 mL), triethylamine trihydrofluoride 0.20 mL, 1.24 mmol) was added and the resulting solution was stirred at rt for 4 h. The solution was concentrated in vacuo and the residue was dissolved in dichloromethane, loaded onto a TLC-grade column and eluted with 2–4% methanol/dichloromethaneto give **11** as a white solid (90 mg, yield: 82%): mp 83–85°C; $[\alpha]_D^{23}$ −88.28 (*c* 0.48 $CHCl_3$); UV ($\lambda_{max}$ = 249.5 nm, $CH_3OH$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.48 (s, 1H), 8.23 (s, 1H), 7.53–7.49 (m, 2H), 7.38–7.29 (m, 3H), 5.95 (d, $J$ = 7.0 Hz, 1H, anomeric), 5.68–5.57 (m, 5H), 5.09 (t, $J$ = 5.9 Hz, 1H), 4.30 (s, 1H), 3.95 (d, $J$ = 12.7 Hz, 1H), 3.81 (d, $J$ = 12.7 Hz, 1H), 3.07 (t, $J$ = 7.0 Hz, 6H), 2.76–2.65 (m, 4H), 1.27 (t, $J$ = 7.0 Hz, 9H); $^{13}$C NMR (400MHz, $CDCl_3$) $\delta$ 177.0, 171.9, 160.3, 151.2, 150.4, 143.1, 135.5, 128.2, 128.1, 128.0, 122.4, 90.6, 85.1, 74.2, 72.9, 68.4, 62.5, 30.1, 29.4; Mass $[MH]^+$ 459; Anal. Calcd for $C_{21}H_{22}N_4O_8$: C, 55.02; H, 4.84; N, 12.22. Found: C, 54.66; H, 5.22; N, 12.51.

**2′-*O*-Succinylinosine (2)**. To a stirred solution of **11** (1.10 g, 2.40 mmol) in ethanol (40 mL), 20% $Pd(OH)_2$ (170 mg, 0.24 mmol) was added and the resulting suspension was stirred under hydrogen at rt for 7 h. The mixture was then filtered through a pad of Celite washing with ethanol and concentrated under reduced pressure to give **2** as a white solid (790 mg, yield: 88%): mp 109–111°C (dec); $[\alpha]_D^{23}$ −41.29 (*c* 0.50 $CH_3OH$); UV ($\lambda_{max}$ = 244.5 nm, 270.0 nm (sh), $CH_3OH$). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 12.44 (br s, 1H, $D_2O$ exchangeable), 8.36 (s, 1H), 8.10 (s, 1H), 5.88 (d, $J$ = 7.0 Hz, 1H, anomeric), 5.25 (dd, $J$ = 5.3, 2.3 Hz, 1H), 4.78 (dd, $J$ = 6.8, 5.5 Hz, 1H), 4.10 (dd, $J$ = 6.1, 3.5 Hz, 1H), 3.66 (dd, $J$ = 12.2, 3.7 Hz, 1H), 3.59 (dd, $J$ = 12.0, 3.7 Hz, 1H), 2.65–2.60 (m, 2H), 2.55–2.49 (m, 2H); $^{13}$C NMR (400 MHz, $D_2O$) $\delta$ 178.4, 174.3, 158.1, 148.2, 146.2, 140.4, 124.1, 88.3,

83.9, 73.4, 72.8, 61.4, 30.0, 29.6; Mass $[MH]^+$369; $[M\text{-}H]^-$ 367; Anal. Calcd for $C_{14}H_{16}N_4O_8{\cdot}H_2O$: C, 43.53; H, 4.70; N, 14.50. Found: C, 43.73; H, 5.06; N, 14.18.

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