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Facile Approaches to 2-Deoxy-D-glucose and 2-Deoxy-α-D-glucopyranonucleosides from D-Glucal

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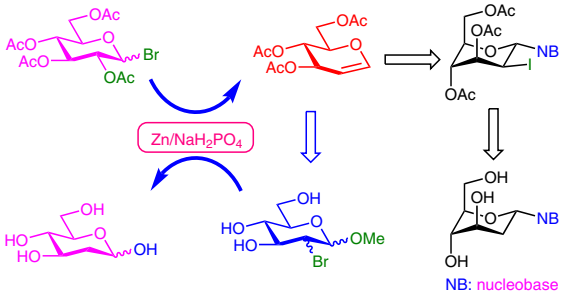

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Abstract Convenient and stereoselective methods for the preparation of 2-deoxy-D-glucose and purine 2-deoxy-α-D-glucopyranonucleosides were developed. Halogen-mediated O-glycosidation of D-glucal by bromine in MeOH followed by reductive removal of the halo group and hydrolysis of methoxy group by zinc in saturated aqueous sodium dihydrogen phosphate gave 2-deoxy-D-glucose. Treatment of 3,4,6-tri-*O*-acetyl-D-glucal with IBr and 2,6-dichloropurine based on haloetherification and subsequent reductive removal of iodine and deprotection allowed the isolation of purin-9-yl 2-deoxy-α-D-glucopyranonucleoside. Preparation of several purin-9-yl 2-deoxy-α-D-glucopyranoside derivatives is also reported. Their configuration was confirmed by single crystal X-ray analysis of the key intermediate 2,6-dichloro-9-(2-iodo-2-deoxy-α-D-glucopyranosyl)purine.

Key words glucal, 2-deoxy-D-glucose, 2-deoxy-α-D-glucopyranonucleoside, halogen-mediated O-glycosidation, stereoselective synthesis

The 2-deoxy-D-glucose scaffold is widely found in many biologically active compounds, such as aureolic acids, anthracyclines, cardiac glycosides, avermectins, erythromycins, and many others.[1] In particular, it was shown that 2-deoxy-D-glucose inhibits the growth of many tumor cells.[2] The compound has a long history of use as a building block in carbohydrate chemistry for its effectiveness as glycosyl donor.[3–5] As a result, numerous researchers have initiated programs aimed at the development of methods for the preparation of 2-deoxyglucose and 2-deoxyglucosides.[6] In many documented methods, 3,4,6-tri-*O*-acetyl-D-glucal (**4**) is the most widely used intermediate.

The acid-catalyzed addition of water or alcohol to the glucal **4** appears to be the most direct method for the synthesis of 2-deoxyhexopyranoses or pyranosides. However, the generality of these methods to prepare 2-deoxy sugars has remained unattractive, as the protected glucals often give rearranged by-products under acidic conditions.[7,8] To avoid the rearrangement reaction, various methods have been developed such as catalytic addition of alcohol by TMSI-PPh_3,[9] $CeCl_3 \cdot 7H_2O$-NaI,[1b] and halogen-mediated O-glycosidation by NIS[10] or I_2-$Cu(OAc)_2$.[11] There are several limitations to these methods including high cost of catalysts and tedious procedures hampering their wider use. Hence, the development of simple, convenient, and cheap method to produce the 2-deoxy-D-glucose and 2-deoxyglucosides is desirable. As a continuation of our work on carbohydrate chemistry, we have now developed a concise and efficient method for the preparation of the 2-deoxy-D-glucose from D-glucal based on the halogen-mediated O-glycosidation. It is noteworthy that in this method, reductive removal of a halo group and hydrolysis of an alkoxy group to give 2-deoxy-D-glucose were conducted at the same step in one-pot. Inspired by the previous introduction of diethoxyphosphorylmethoxy group to furanoid glycal by IBr via haloetherification,[12] we attempted to introduce nucleobases to 3,4,6-tri-*O*-acetyl-D-glucal to synthesize 2-deoxynucleoside analogues. As a result, a stereoselective approach to purin-9-yl 2-deoxy-α-D-glycosides from 3,4,6-tri-*O*-acetyl-D-glucal (**4**) via halo-mediated nucleophilic addition of purine was developed.

Our investigations for the envisaged protocol commenced with the preparation of the essential intermediate, 3,4,6-tri-*O*-acetyl-D-glucal (**4**). On survey of the literature, 3,4,6-tri-*O*-acetyl-D-glucal (**4**) was most often prepared by the classical Fisher–Zach reductive elimination of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl bromide using zinc dust in acetic acid.[13] Over the years, numerous reductive reagents have been used for the preparation of glycals from peracetylated glycopyranosyl bromide, such as vitamin B-

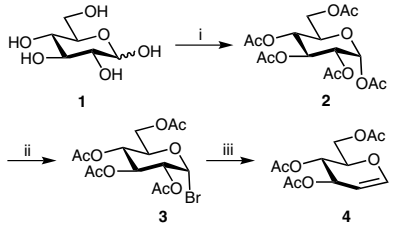
12/Zn/NH_4Cl,[14] Cr(II) complexes,[15] Zn/NaH_2PO_4/EtOAc,[6a] and titanium(III) reagents.[16]

Based on the literature,[6a,b,17] 3,4,6-tri-*O*-acetyl-D-glucal (**4**) was prepared from commercially available D-glucose by following the procedures as shown in Scheme 1.

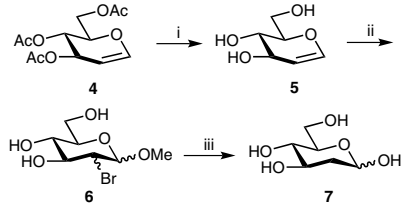
Subsequently, transformation of fully acetylated glucal **4** into 2-deoxy-D-glucose (**7**) was investigated. Initially, direct synthesis of methyl 2-deoxy-D-glucopyranoside and then hydrolysis to remove the methyl of 1-methoxy group were investigated. In view of previous studies, $CeCl_3{\cdot}7H_2O$-NaI[1b] and TMSI-PPh_3[9] systems are effective catalysts in different substrates to synthesize 2-deoxyglucopyranosides. Both systems were utilized in the conversion of 3,4,6-tri-*O*-acetyl-D-glucal (**4**) to methyl 3,4,6-tri-*O*-acetyl-2-deoxy-D-glucopyranoside. In spite of tremendous efforts to optimize reaction conditions, the yield of target product using $CeCl_3{\cdot}7H_2O$-NaI was lower than 40%, which was too low to continue the synthesis. Synthesis with TMSI-PPh_3[9] was even worse as no product was obtained. From here, we investigated utilizing a 2-halo-2-deoxyglycoside intermediate by halogen-mediated O-glycosidation of glucal. In order to avoid the prevalent Ferrier rearrangement reaction of acetylated glucal under acidic conditions, we decided to use free glucal **5** as the key intermediate. Compound **4** was first deprotected with sodium hydroxide in methanol. Then bromine was added to the resulting reaction mixture. The mixture was stirred under detection by TLC until free glucal disappeared. After workup, methyl 2-bromo-2-deoxyhexopyranoside (**6**) was obtained in 91% yield from **4**. Finally, reductive elimination of the bromide on C-2 of compound **6** was investigated. When a variety of reducing agents were screened for the reaction, we unexpectedly found that the same conditions for the preparation of fully protected glucal **4** from 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl bromide (**3**) gave a more polar product than methyl 2-deoxyhexopyranoside as observed by TLC. The resulting product was purified by silica gel chromatography and structurally confirmed as 2-deoxy-D-glucose **7** (62% yield) by ^1H and ^{13}C NMR spectral analysis. That is, removal of the 2-bromo group and hydrolysis of the 1-methoxy had been achieved by using the Zn/NaH_2PO_4/acetone system at the same step in a one-pot procedure (Scheme 2). This is the first report of this efficient method.

Furthermore, based on the experience of introducing the diethoxyphosphorylmethoxy group to furanoid glycal via haloetherification in our previous work,[12] and synthesis of 2-deoxy-N-glycosides from glucal in the presence of NIS by the De Castro group,[18] we speculated that the nucleobase could also be introduced to the glucal under suitable conditions. Thus, 2,6-dichloropurine was selected as the nucleobase to be used in the introduction reaction for its good solubility. To a solution of fully protected glucal **4** in dichloromethane was added a suspension of 2,6-dichloropurine sodium salt in THF, followed by iodine monobromide under stirring at –40 °C. The mixture was stirred for an hour under nitrogen and then worked up to furnish product **8** as a white foam. Compound **8** was elucidated as 2,6-dichloropurin-9-yl 3,4,6-tri-*O*-acetyl-2-iodo-2-deoxyhexopyranoside by NMR and HRMS spectral analysis. Subsequently, we tried to further confirm the absolute configuration of C-1′ by analysis of the ^1H NMR spectral data. In the ^1H NMR spectrum, the coupling constant between H-1′ and H-2′ is 10.4 Hz, a large constant, which indicated two axial-H's in *trans* position. Further analysis of the coupling between H-2′ and H-3′, revealed that the $J_{2,3}$ value is 3.1 Hz, a small constant, which showed that both H-2′ and H-3′ atoms should be in *cis* direction. Based on the mechanism of haloetherification, the stereochemistry of glycosylation is governed by *trans*-diaxial addition.[4] Therefore, we can deduce that the 2-iodo-2-deoxypynanonucleoside is an α-anomer.

The absolute configuration of the nucleoside was also confirmed as α-anomer by X-ray crystallographic analysis of a suitable crystal of **8** after recrystallization from ethanol (Figure 1). The pyranose ring adopts a chair $^1C_4$ conformation. The large 1-purinyl and 2-iodo groups located at opposite sides of pyranose ring were in equatorial position due to their large steric hindrance, which forced the generally stable $^4C_1$ pyranose ring to change into the unfavored $^1C_4$ conformation and the smaller 3,4-di-*O*-acetyl and 5-acetoxymethyl to be in axial positions. Furthermore, the two-dimensional NOESY spectrum of compound **8** in deuterated chloroform was recorded (Figure 2). The NOE correlations from H-1′ to H-6′ and H-2′ to H-8, respectively, indicated



Scheme 1 Synthesis of 3,4,6-tri-*O*-acetyl-D-glucal (**4**). *Reagents and conditions*: i. Ac_2O, $HClO_4$, 3 h; ii. PBr_3, H_2O, 94% from **1**; iii. Zn, sat. aq NaH_2PO_4, acetone, 86%.



Scheme 2 Conversion of glucal **4** to 2-deoxy-D-glucose (**7**). *Reagents and conditions*: i. NaOH, MeOH, 0 °C, 2 h; ii. Br_2, MeOH, 10 min, 91% from **4**; iii. Zn, sat. aq NaH_2PO_4, acetone, 5 h, 62%.

that the H-1′ and $AcOCH_2$ group are located on one side, H-2′ and purinyl group are on another side of the pyranose ring. This result is consistent with the α-configuration of C-1′ by X-ray crystallographic analysis.

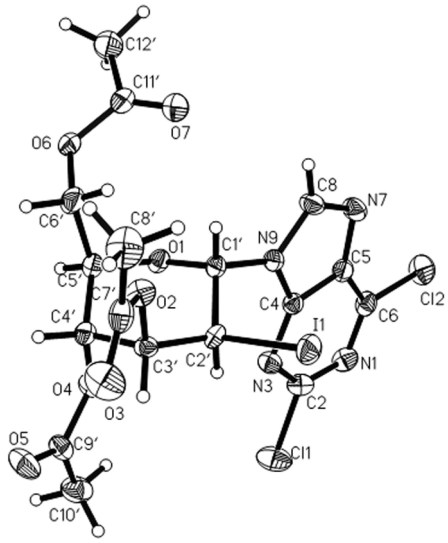


Figure 1 ORTEP of compound **8**

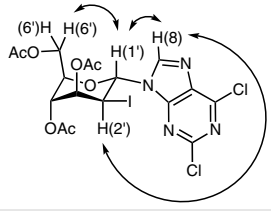


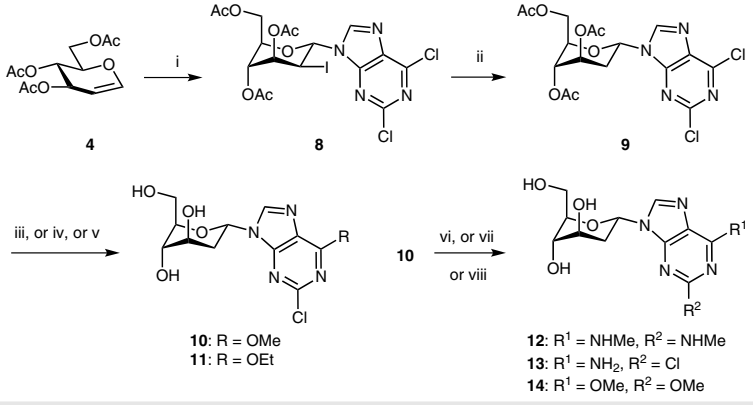
Figure 2 NOE effects of compound **8** in $CDCl_3$

Then, removal of the 2-iodo group of intermediate **8** with hypophosphorous acid (H_3PO_2) and 2,2-azobisisobutyronitrile (AIBN) gave compound **9**, and deprotection of the acetyl group in methanol and ethanol gave 2-deoxy-α-D-glucopyranoside **10** and **11**, respectively. Finally, other 2,6-disubstituted purin-9-yl 2-deoxy-D-glucopyranosides **12**–**14** were obtained by treatment of **10** with various nucleophiles (Scheme 3).

In summary, we have developed a facile and efficient method for the synthesis of 2-deoxy-D-glucose via halogen-mediated O-glycosidation of the intermediate glucal, in which reductive removal of a bromine at C-2 and hydrolysis of a methoxy group at C-1 were accomplished in one step. Furthermore, 2-deoxy-α-D-glucopyranosides were stereoselectively synthesized by haloetherification of fully acetylated glucal. Unusual $^1C_4$ conformation of pyranose ring of intermediate **9** was found in the study by X-ray single crystallographic analysis. This work provides pharmaceutical researchers and chemists alternative methods for the synthesis of 2-deoxy-D-glucose and 2-deoxynucleosides.

Reagents and solvents were purchased from commercial sources. 1,4-Dioxane, CH_2Cl_2, MeCN, and THF were distilled over CaH_2. Melting points were determined on a XT5B melting-point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were acquired on a Bruker Avance III-400 spectrometer at 300 K with chemical shifts (δ) given in parts per million relative to TMS as the internal standard (δ = 0.00). High-resolution mass spectra (HRMS) were taken with a Q-Tof Micromass spectrometer. TLC was performed on silica gel GF_{254} plates and detected by placing under the UV lamp (254 nm), or visualized by spraying the plates with 5% ethanolic ammonium phosphomolybdate and charring them with a heating gun. Column chromatography was conducted using a column of silica gel (200–300 mesh).

X-ray diffraction analysis was carried out on an Agilent Xcalibur Gemini, Eos CCD diffractometer with graphite-monochromated Cu-Kα (λ = 1.54178 Å) radiation. An orthorhombic crystal was selected and mounted on a glass fiber. All data were collected at a temperature of



Scheme 3 Synthesis of 2-deoxyglucopynanoside derivatives. *Reagents and conditions*: i. 2,6-dichloropurine, NaH, IBr, 55%; ii. H_3PO_2, Et_3N, AIBN, 86%; iii. NaOH in MeOH, for **10**, 91%; iv. K_2CO_3 in EtOH, for **11**, 75%; v. 40% aq $MeNH_2$, 100 °C, 2 h, for **12**, 93%; vi. Aq 28% NH_4OH, 100 °C, 1 h, for **13**, 90%; vii. NaOMe in MeOH, 95 °C, 2 h, for **14**, 95%.

291 K. X-ray diffraction intensities were collected, integrated, and scaled with the CrysAlisPro suite of programs. The structure was solved via direct methods and expanded using the Fourier technique. The non-hydrogen atoms were refined with anisotropic thermal parameters. Hydroxyl hydrogen atoms were refined with isotropic thermal parameters. Other hydrogen atoms were included but not refined. All calculations were performed using the SHELX-97 crystallographic software package.

3,4,6-Tri-*O*-acetyl-D-glucal (4)

Treatment of D-glucose (**1**) with Ac_2O in the presence of $HClO_4$ afforded 1,2,3,4,6-penta-*O*-acetyl-α-D-glucose (**2**). Bromination of **2** by PBr_3 in H_2O gave 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**3**). The fully protected glucosyl bromide **3** was treated with Zn in sat. aq NaH_2PO_4 containing acetone (22% volume) at r.t. to furnish 3,4,6-tri-*O*-acetyl-D-glucal (**4**) in 86% yield.

For full experimental details, see the Supporting Information.

D-Glucal 5

NaOH (8.6 g, 0.22 mol) was added to a solution of the glucal **4** (60 g, 0.22 mol) in anhyd MeOH (170 mL) with stirring at 0 °C. The solution was stirred at r.t. for 2 h to give **5**. The solution was directly used in the next step without any further purification.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.29 (dd, *J* = 6.0, 1.2 Hz, 1 H, H-1), 5.11 (d, *J* = 5.5 Hz, 1 H, H-2), 4.89 (d, *J* = 5.5 Hz, 1 H, H-3), 4.65–4.53 (m, 2 H, H-4, H-5), 3.99–3.90 (m, 1 H, H-6a), 3.77–3.65 (m, 1 H, H-6b), 3.64–3.54 (m, 2 H, OH), 3.37 (dd, *J* = 8.8, 6.4 Hz, 1 H, OH).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 143.3, 104.8, 79.8, 69. 6, 68.9, 60.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_6H_{10}O_4$ + H: 147.0652; found: 147.0652.

Methyl 2-Bromo-2-deoxy-D-glucoside (6)

Bromine (14 mL, 0.27 mol) was added to a solution of **5** obtained as above from glucal **4** (60 g, 0.22 mol) and the reaction mixture was stirred at 0 °C for 10 min. The reaction mixture became colorless. The resulting mixture was filtered, and the filter cake was washed with MeOH (50 mL). The combined MeOH solution was concentrated under vacuum. The residue was dissolved in anhyd EtOH and filtered again. The filtrate was concentrated under vacuum to afford the crude **6** (72 g, 91%) as a syrup. The crude product was used in the next step without any further purification.

2-Deoxy-D-glucose (7)

Sat. aq NaH_2PO_4 (500 mL) was added to the solution of the above-obtained crude product **6** (72 g, 0.28 mol) in acetone (150 mL) followed by Zn powder (170 g, 2.6 mol). After stirring the reaction mixture for 5 h at r.t., the mixture was filtered. The filtrate was adjusted to pH 7 with 20% aq NaOH, and the solid was filtered off. The filtrate was mixed with anhyd EtOH (5.2 L) and cooled to –20 °C for 5 h. Solids were filtered off again. The filtrate was concentrated under vacuum and purified by silica gel column chromatography to give the title product **7** as a white solid [62%, a mixture of β- and α-anomer, β/α is about 1:0.22 (mol/mol) based on the ^{1}H NMR analysis]; mp 145–146 °C; R_f = 0.3 (12% MeOH in EtOAc).

^{1}H NMR for (400 MHz, D_2O): δ (β-anomer) = 4.83 (dd, *J* = 9.8, 2.0 Hz, 1 H, H-1), 3.80 (dd, *J* = 12.2, 2.3 Hz, 1 H, H-3), 3.67–3.54 (m, 2 H, H-4, H-5), 3.28 (ddd, *J* = 9.7, 6.0, 2.3 Hz, 1 H, H-6a), 3.22–3.02 (m, 1 H, H-6b), 2.16 (ddd, *J* = 12.4, 5.0, 2.0 Hz, 1 H, H-2a), 1.41 (td, *J* = 12.1, 9.8 Hz, 1 H, H-2b).

^{13}C NMR for (101 MHz, D_2O): δ (β-anomer) = 93.4, 76.0, 70.8, 70.4, 60.9, 39.5.

^{1}H NMR and ^{13}C NMR values for α-anomer were omitted.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_6H_{12}O_5$ + H: 165.0757; found: 165.0759.

2,6-Dichloro-9-(3,4,6-tri-*O*-acetyl-2-iodo-2-deoxy-α-D-glucopyranosyl)-9*H*-purine (8)

To a solution of 2,6-dichloropurine (700 mg, 3.7 mmol) in anhyd THF (10 mL) was added NaH (60% in oil, 163 mg, 4.07 mmol), and the mixture was stirred for 30 min at r.t. Then, the mixture was added to a solution of **4** (500 mg) in anhyd CH_2Cl_2 (8 mL) at –40 °C under N_2, followed by the addition of IBr (180 μL). After stirring at –40 °C for 1 h, the solution was concentrated under vacuum to dryness. Sat. aq $NaHCO_3$ (10 mL) and CH_2Cl_2 (30 mL) were added to the residue. The organic layer was separated and washed with sat. aq $Na_2S_2O_3$ (3 × 10 mL), and dried (anhyd Na_2SO_4) overnight. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (2.5% EtOAc in CH_2Cl_2) to give the product as a white foam (594 mg, 55%); mp 143–145 °C; R_f = 0.3 (2.5% EtOAc in CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25 (s, 1 H, H-8), 6.30 (d, *J* = 10.4 Hz, 1 H, H-1′), 5.85 (dd, *J* = 10.4, 3.1 Hz, 1 H, H-2′), 5.48 (t, *J* = 3.0 Hz, 1 H, H-3′), 5.17 (dd, *J* = 12.3, 10.1 Hz, 1 H, H-6′a), 4.85 (dd, *J* = 3.4, 1.7 Hz, 1 H, H-4′), 4.45 (d, *J* = 9.5 Hz, 1 H, H-5′), 3.93 (dd, *J* = 12.4, 3.4 Hz, 1 H, H-6′b), 2.30 (s, 3 H, CH_3), 2.26 (s, 3 H, CH_3), 2.06 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.2, 169.3, 168.4, 153.3, 152.6, 152.2, 145.9, 131.5, 80.2, 76.7, 70.9, 66.8, 59.2, 22.5, 20.9, 20.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{17}Cl_2IN_4O_7Na$: 608.9411; found: 608.9421.

2,6-Dichloro-9-(3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl)-9*H*-purine (9)

To solution of **8** (300 mg, 0.51 mmol) in anhyd 1,4-dioxane (8 mL) were added H_3PO_2 (117 μL, 2.55 mmol) and Et_3N (390 μL, 2.80 mmol). The mixture was stirred and heated to reflux. A solution of 2,2′-azobis(2-methylpropionitrile) (102 mg, 0.68 mmol) in anhyd 1,4-dioxane (5 mL) was added in portions over 30 min and the mixture was stirred for 5 h. After concentration under vacuum, EtOAc (20 mL) and H_2O (10 mL) were added to the residue. The organic layer was dried (anhyd Na_2SO_4) overnight and concentrated under vacuum to dryness. The residue was purified by silica gel column chromatography (R_f = 0.3, 33% EtOAc in hexane) to give the product **9** as a white foam (230 mg, 86%); mp 117–118 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (s, 1 H, H-8), 6.28 (dd, *J* = 5.9, 4.7 Hz, 1 H, H-1′), 5.49–5.24 (m, 1 H, H-3′), 5.04 (t, *J* = 6.4 Hz, 1 H, H-6′a), 4.59 (dd, *J* = 12.3, 7.2 Hz, 1 H, H-4′), 4.21–3.94 (m, 2 H, H-5′, H-6′b), 3.24 (ddd, *J* = 14.5, 6.1, 4.3 Hz, 1 H, H-2′a), 2.53–2.32 (m, 1 H, H-2′b), 2.18 (s, 3 H, CH_3), 2.13 (s, 3 H, CH_3), 2.10 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.6, 169.6, 169.5, 153.4, 152.7, 152.2, 144.6, 131.3, 78.3, 73.2, 68.2, 67.1, 61.0, 30.8, 20.9, 20.74, 20.69.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{18}Cl_2N_4O_7Na$: 483.0445; found: 483.0455.

2-Chloro-6-methoxy-9-(2-deoxy-α-D-glucopyranosyl)-9*H*-purine (10)

NaOH (40 mg, 1 mmol) was added to a solution of **9** (460 mg, 1 mmol) in anhyd MeOH (8 mL), and the reaction mixture was stirred at r.t. for 0.5 h. The resultant mixture was concentrated under vacuum and the

residue purified by silica gel column chromatography (R_f = 0.3, 10% MeOH in EtOAc) to give the product **10** as a white foam (300 mg, 91%); mp 104–105 °C.

^{1}H NMR (400 MHz, (400 MHz, DMSO-d_6): δ = 8.53 (s, 1 H, H-8), 6.20 (t, J = 4.2 Hz, 1 H, H-1′), 5.15 (d, J = 4.5 Hz, 1 H, OH), 5.05 (d, J = 4.7 Hz, 1 H, OH), 4.62 (t, J = 5.8 Hz, 1 H, OH), 4.12 (s, 3 H, OCH_3), 3.81 (d, J = 3.3 Hz, 1 H, H-5′), 3.64 (dd, J = 10.4, 5.9 Hz, 1 H, H-6′a), 3.61–3.52 (m, 1 H, H-6′b), 3.30 (m, 2 H, H-3′, H-4′), 2.91 (m,, 1 H, H-2′a), 2.06–1.93 (m, 1 H, H-2′b).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 161.3, 153.3, 151.9, 143.6, 120.7, 79.5, 77.6, 70.5, 68.7, 60.8, 55.4, 34.3.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{11}H_{12}Cl_2N_4O_4Na$: 357.0128; found: 357.0130.

2-Chloro-6-ethoxy-9-(2-deoxy-α-D-glucopyranosyl)-9*H*-purine (11)

K_2CO_3 (230 mg, 1.67 mmol) was added to a solution of **9** (460 mg, 1 mmol) in anhyd EtOH (8 mL) and anhyd CH_2Cl_2 (8 mL), and the mixture was stirred at r.t. for 0.5 h. The solvent was removed under vacuum, and the residue was purified by silica gel column chromatography (R_f = 0.3, 10% MeOH in CH_2Cl_2) to give the product **11** as a white foam (258 mg, 75%); mp 90–92 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.52 (s, 1 H, H-8), 6.20 (dd, J = 10.2, 5.9 Hz, 1 H, H-1′), 5.16 (t, J = 5.8 Hz, 1 H, OH), 5.06 (t, J = 6.1 Hz, 1 H, OH), 4.64 (m, 1 H, OH), 4.60 (q, J = 8.0 Hz, 2 H, CH_2), 3.81 (d, J = 4.7 Hz, 1 H, H-5′), 3.71–3.47 (m, 2 H, H-6′), 3.28 (m, 2 H, H-3′, H-4′), 2.90 (dt, J = 14.1, 4.2 Hz, 1 H, H-2′a), 2.05–1.93 (m, 1 H, H-2′b), 1.45–1.36 (t, J = 8.0 Hz, 3 H, CH_3).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 161.0, 153.4, 151.9, 143.5, 120.6, 79.4, 77.6, 70.5, 68.7, 64.3, 60.9, 34.3, 14.7.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{12}H_{15}ClN_4O_5Na$: 353.0623; found: 353.0625.

2,6-Dimethylamino-9-(2-deoxy-α-D-glucopyranosyl)-9*H*-purine (12)

A 40% solution of $MeNH_2$ in H_2O (2 mL) was added to a solution of **10** (100 mg, 0.3 mmol) in 1,4-dioxane (10 mL) and the mixture was stirred at 100 °C in a teflon-sealed bomb for 2 h. The reaction mixture was concentrated under vacuum to dryness and the residue was purified by silica gel column chromatography (R_f = 0.3, 10% MeOH in EtOAc) to give the product **12** as a white foam (91 mg, 93%); mp 130–131 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.81 (s, 1 H, H-8), 7.20 (s, 1 H, NH), 6.30 (s, 1 H, NH), 6.00 (t, J = 4.1 Hz, 1 H, H-1′), 5.04 (d, J = 14.8 Hz, 1 H, OH), 4.99 (s, 1 H), 4.59 (s, 1 H, OH), 3.95–3.79 (m, 1 H, H-5′), 3.66–3.58 (m, 2 H, H-6′), 3.24 (m, 2 H, H-3′, H-4′), 2.91 (m, 4 H, H-2′a, CH_3), 2.79 (d, J = 4.7 Hz, 3 H, CH_3), 1.96–1.84 (m, 1 H, H-2′b).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 160.5, 155.7, 138.5, 135.9, 114.0, 78.0, 77.1, 70.9, 69.0, 61.1, 34.7, 28.7, 21.2.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{13}H_{20}N_6O_4Na$: 347.1438; found: 347.1446.

6-Amino-2-chloro-9-(2-deoxy-α-D-glucopyranosyl)-9*H*-purine (13)

Aq 28% NH_4OH (1.5 mL) was added to a solution of **10** (100 mg, 0.3 mmol) in 1,4-dioxane (10 mL), and the mixture was stirred at 100 °C in a teflon-sealed bomb for 1 h. The mixture was concentrated under vacuum to dryness and the residue was purified by silica gel column chromatography (R_f = 0.3, 20% MeOH in EtOAc) to give the product **13** as a white solid (86 mg, 90%); mp 169–171 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.28 (s, 1 H, H-8), 7.81 (s, 2 H, NH_2), 6.10 (t, J = 4.3 Hz, 1 H, H-1′), 5.13 (d, J = 4.5 Hz, 1 H, OH), 5.04 (d, J = 5.4 Hz, 1 H, OH), 4.62 (t, J = 5.8 Hz, 1 H, OH), 3.90–3.74 (m, 1 H, H-5′), 3.65 (ddd, J = 11.5, 5.6, 2.4 Hz, 1 H, H-6′a), 3.58 (dt, J = 11.5, 5.7 Hz, 1 H, H-6′b), 3.37–3.31 (m, 1 H, H-3′), 3.30–3.22 (m, 1 H, H-4′), 2.86 (dt, J = 13.9, 4.2 Hz, 1 H, H-2′a), 1.96 (ddd, J = 14.3, 9.5, 5.2 Hz, 1 H, H-2′b).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 157.3, 153.5, 150.7, 140.5, 118.5, 78.8, 77.5, 70.6, 68.8, 60.9, 34.5.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{11}H_{14}ClN_5O_4Na$: 338.0627; found: 338.0633.

2,6-Dimethoxy-9-(2-deoxy-α-D-glucopyranosyl)-9*H*-purine (14)

Na (100 mg, 1.2 mmol) was added to a solution of **10** (100 mg, 0.3 mmol) in anhyd MeOH (6 mL) and the mixture stirred at 95 °C in teflon-sealed bomb for 2 h. The solvent was removed under vacuum, and the residue was purified by silica gel column chromatography (R_f = 0.3, 10% MeOH in CH_2Cl_2) to give the product **14** as a white solid (94 mg, 95%); mp 82–83 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.25 (s, 1 H, H-8), 6.14 (t, J = 4.2 Hz, 1 H, H-1′), 5.11 (d, J = 4.6 Hz, 1 H, OH), 4.99 (d, J = 5.4 Hz, 1 H, OH), 4.59 (t, J = 5.9 Hz, 1 H, OH), 4.05 (s, 3 H, CH_3), 3.94 (s, 3 H, CH_3), 3.84 (m, 1 H, H-6′a), 3.67 (ddd, J = 11.7, 6.1, 2.3 Hz, 1 H, H-5′), 3.56 (m, 1 H, H-6′b), 3.32–3.21 (m, 2 H, H-3′, H-4′), 3.05 (m, J = 13.9, 4.0 Hz, 1 H, H-2′a), 2.04–1.81 (m, 1 H, H-2′b).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 161.9, 161.4, 153.4, 141.6, 117.3, 79.5, 77.4, 70.8, 68.9, 61.1, 55.2, 54.4, 34.4.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{13}H_{18}N_4O_6Na$: 349.1119; found: 349.1121.

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Supporting Information

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References

(1) (a) Sabesan, S.; Neira, S. *J. Org. Chem.* **1991**, *56*, 5468. (b) Yadav, J. S.; Reddy, B. V. S.; Bhaskar Reddy, K.; Satyanarayana, M. *Tetrahedron Lett.* **2002**, *43*, 7009.
(2) (a) Aft, R. L.; Zhang, F. W.; Gius, D. *Brit. J. Cancer* **2002**, *87*, 805. (b) Kang, H. T.; Hwang, E. S. *Life Sci.* **2006**, *78*, 1392.
(3) Christopher, L. F.; Richard, W. F. *J. Org. Chem.* **1999**, *64*, 1424.
(4) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380.
(5) Marzabadi, C. H.; Dios, A.; Geer, A.; Franck, R. W. *J. Org. Chem.* **1998**, *63*, 6673.
(6) For example: (a) Miller, J. N.; Pongdee, R. *Tetrahedron Lett.* **2013**, *54*, 3185. (b) Zhao, J.; Wei, S.; Ma, X.; Shao, H. *Carbohydr. Res.* **2010**, *345*, 168. (c) Nord, L. D.; Dalley, N. K.; McKernan, P. A.;

Robins, R. K. *J. Med. Chem.* **1987**, *30*, 1044. (d) Gervay, J.; Danishefsky, S. *J. Org. Chem.* **1991**, *56*, 5448. (e) Marzabadi, C. H.; Franck, R. W. *Tetrahedron* **2000**, *56*, 8385.
(7) Ciment, D. M.; Ferrier, R. J. *J. Chem. Soc. C* **1966**, 441.
(8) Bolitt, V.; Mioskowski, C.; Lee, S.-G.; Falck, J. R. *J. Org. Chem.* **1990**, *55*, 5812.
(9) Cui, X.-K.; Zhong, M.; Meng, X.-B.; Li, Z.-J. *Carbohydr. Res.* **2012**, *358*, 19.
(10) Durham, T. B.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1875.
(11) Sirion, U.; Purintawarrakun, S.; Sahakitpichan, P.; Saeeng, R. *Carbohydr. Res.* **2010**, *345*, 2401.
(12) Liu, F.; Liu, Y.; Xu, R.-G.; Dai, G.; Zhao, L.-X.; Wang, Y.; Liu, H.-M.; Liu, F.-W.; Pannecouque, C.; Herdewijn, P. *Chemistry & Biodiversity* **2015**, *12*, 813.
(13) Fischer, E.; Zach, K. *Sitzungsber. Kl. Preuss. Akad. Wiss.* **1913**, *27*, 311.
(14) Forbes, C. L.; Frank, R. W. *J. Org. Chem.* **1999**, *64*, 1424.
(15) Kovacs, G.; Toth, K.; Dinya, Z.; Somsak, L.; Micskei, K. *Tetrahedron* **1999**, *55*, 5253.
(16) Spencer, R. P.; Schwartz, J. *Tetrahedron* **2000**, *56*, 2103.
(17) Binch, H.; Stangier, K.; Thiem, J. *Carbohydr. Res.* **1998**, *306*, 409.
(18) Meyerhoefer, T. J.; Kershaw, S.; Caliendo, N.; Eltayeb, S.; Hanawa-Romero, E.; Bykovskaya, P.; Huang, V.; Marzabadi, C. H.; De Castro, M. *Eur. J. Org. Chem.* **2015**, 2457.