Stereoselective Synthesis of Novel Isonucleoside Analogues of Purine with a Tetrahydropyran Ring

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To the memory of our colleague and friend Maykel Pérez González

Abstract: New tetrahydropyran isonucleoside derivatives of purine, with *cis* or *trans* configuration, were stereoselectively synthesized in moderate yield by a convergent strategy based on Mitsunobu coupling. The key starting material was a bicyclic lactone.

Key words: isonucleosides, heterocycles, tetrahydropyran, purine, Mitsunobu reaction

Nucleoside analogues play an important role in chemotherapy.[1] Modifications in the sugar moiety of nucleosides have led to the development of novel derivatives, including acyclic and carbocyclic nucleosides, four- or six-membered ring analogues, 2′,3′-dideoxynucleosides, and isonucleosides, that have shown interesting antiviral and anticancer properties.[2] These modifications are often associated with increased stability[2] and decreased toxicity,[3] together with target specificity.[2] In isonucleosides the heterocyclic base is linked to the non-anomeric carbon atom of the sugar moiety, in particular at C2′ or C3′ of the furanose ring. The change in the position of the sugar-base bond keeps the spatial placement between the base and the 5′-hydroxy group, while the glycosidic bond is more stable toward enzymatic hydrolysis. Several isonucleosides show interesting biological activity.[4] For example, 2′-isodideoxynucleoside analogues such as isoddA (**I**) or the isonucleoside **II** (Figure 1) have potent anti-HIV[5] and anti-HCV activity,[6] respectively. Nevertheless, the 3′-isodideoxinucleoside analogue 3′-isoddA (**III**) has a low level of activity.[7] Thus, some of the structural factors that modify the activity of nucleoside analogues are the distance between the base and the 5′-hydroxy group, the electronic effects of the oxygen in the sugar ring, and the lack of a hydroxy group at 3′.[8] The high stability together with the significant activity exhibited by some isonucleosides have led to an increase in the number of analogues reported as promising therapeutic agents.[9,10]

In the last few years we have described some modified nucleosides with the hydroxymethyl group and the heterocyclic base bound to contiguous positions of a carbocycle.[11–14] Several of these carbocyclic analogues have exhibited significant and selective anticancer[11] or antiviral activity,

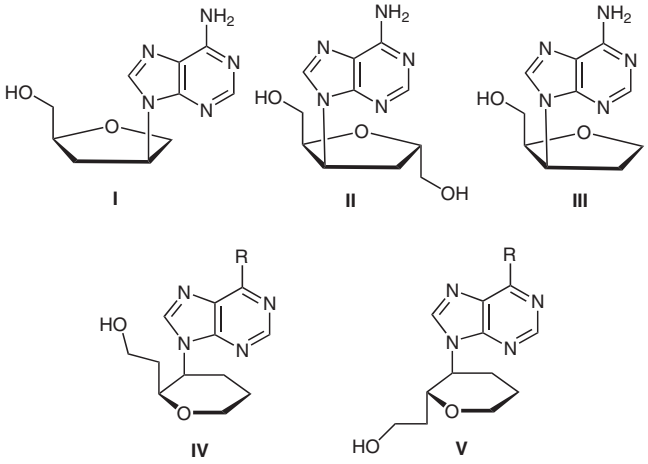

Figure 1

in particular against HIV.[14] Taking into account the therapeutic potential of nucleosides and looking for new active compounds, our attention has been drawn to the tetrahydropyran isodideoxynucleoside derivatives of structure **IV** and **V** (Figure 1). We are in particular interested in compounds **IV**, structural analogues of 3′-isoddA, where tetrahydropyran (THP) replaces tetrahydrofuran and a methylene group enlarges the side chain, transforming it into a hydroxyethyl group. This keeps the base and the hydroxy group separated by four carbon atoms, as in natural nucleosides.

On the basis of these considerations, in this paper we describe a convergent and stereoselective synthesis of target compounds **IV** as racemic mixtures. This strategy, also applied to compounds **V**, is based on Mitsunobu coupling.

In this approach, the key starting material is bicyclic lactone **1** (Scheme 1), which was obtained in good yield in a four-step sequence from commercially available ethyl 3-(2-furyl)propionate, by an approach based on the oxidation of the furan ring with singlet oxygen, followed by an intramolecular Michael addition.[15] Treatment of **1** with lithium aluminum hydride in the presence of boron trifluoride–diethyl ether complex afforded an 85% yield of a *cis–trans* mixture of diols **2** and **3** (Scheme 1). Although the two diols could be separated by column chromatography,[15] we carried out their stereoselective synthesis here. Thus, the mixture of compounds **2** and **3** was treated with *tert*-butyldiphenylsilyl chloride, imidazole, and 4-(*N*,*N*-

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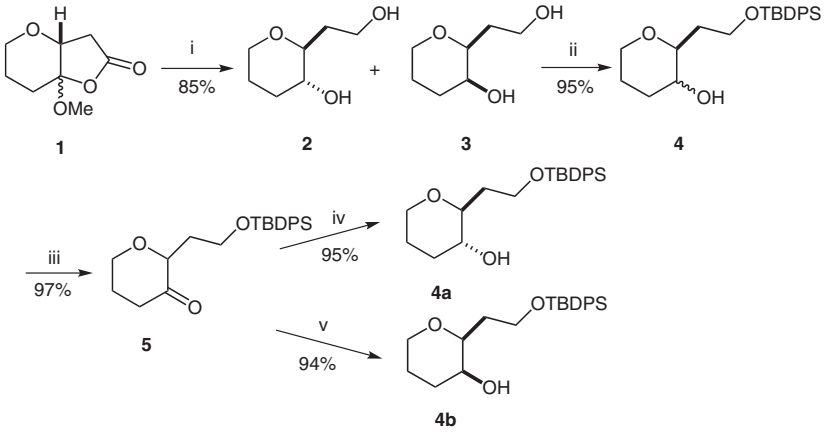
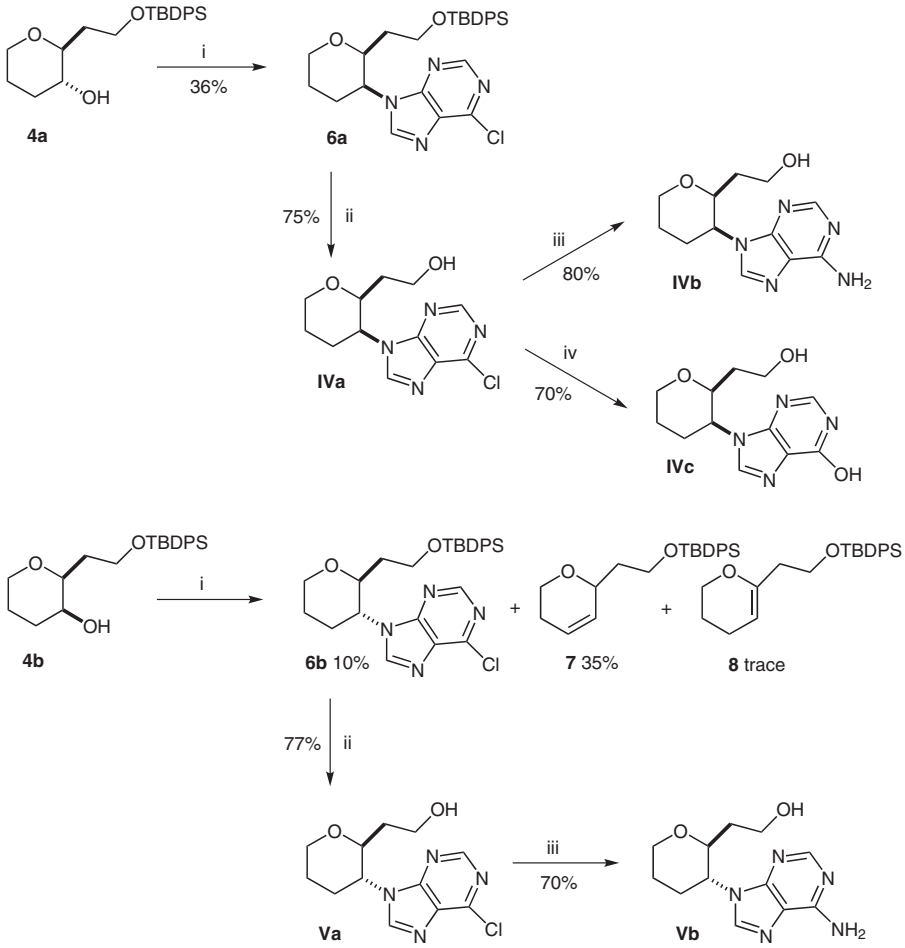


Scheme 1 *Reagents and conditions*: (i) LAH, BF_3·OEt_2, Et_2O, r.t.; (ii) TBDPSCl, imidazole, DMF, r.t.; (iii) TPAP, NMO, CH_2Cl_2, MS; (iv) $NaBH_4$, MeOH–CH_2Cl_2, –78 °C; (v) L-Selectride, THF, –78 °C to r.t.

dimethylamino)pyridine in *N*,*N*-dimethylformamide to selectively protect the primary hydroxy group. The resulting secondary alcohol **4** was then oxidized with tetrapropylammonium perruthenate (TPAP), affording ketone **5** in excellent yield (97%). Finally, the stereoselective reduction of **5** by use of different reduction agents such as sodium borohydride or L-Selectride allowed us to obtain alcohols **4a** or **4b** selectively (Scheme 1). Thus, treatment of **5** with sodium borohydride in methanol–dichloromethane at –78 °C gave the *trans*-alcohol **4a** in 95% yield. In addition, ketone **5** on reaction with L-Selectride in tetrahydrofuran at –78 °C gave monoprotected *cis*-diol **4b** in 94% yield. The relative configuration of alcohols **4a** and **4b** was unequivocally established by comparison of the spectroscopic data with those of compounds obtained from the selective monoprotection with *tert*-butyldiphenylsilyl chloride of diols **2** and **3**, previously separated.[15]



Scheme 2 *Reagents and conditions*: (i) 6-chloropurine, Ph_3P, DEAD, THF, 0 °C to r.t.; (ii) 1 M TBAF, THF, r.t.; (iii) 25% aq NH_3, reflux; (iv) 0.5 M aq NaOH, reflux.

Mitsunobu coupling of *trans*-alcohol **4a** with 6-chloropurine in the presence of triphenylphosphine and diethyl azodicarboxylate in tetrahydrofuran gave the *cis*-6-chloropurine derivative **6a**, in 36% yield (Scheme 2). However, when the *cis*-isomer **4b** was treated with 6-chloropurine under identical Mitsunobu conditions, an important portion of unchanged compound was recovered, affording the desired *trans*-chloropurine derivative **6b** in 10% yield, and giving as major product the dehydration compound **7** (35%). In addition, a new dehydration isomer (compound **8**) was detected in a trace amount. It should be mentioned that compound **7** was also obtained as a secondary product of Mitsunobu reaction of **4a** with 6-chloropurine, but in this case it was the only dehydration product. These results are a consequence of the competition between an S_N2 displacement and an E2 elimination, previously described for tetrahydropyran derivatives when Mitsunobu reaction conditions were used.[16]

Deprotection of silyl derivatives **6a** and **6b** was carried out by treatment with tetrabutylammonium fluoride in tetrahydrofuran, to afford *cis*- and *trans*-6-chloropurine derivatives **IVa** and **Va** in 75% and 77% yield, respectively (Scheme 2). The *cis* and *trans* configurations were assigned by means of NOE correlations.

Finally, compounds **IVa** and **Va** were transformed into the adenine derivatives **IVb** (80% yield) and **Vb** (82% yield), respectively, by reflux with 25% aqueous ammonia (Scheme 2). Similarly, reaction of **IVa** with 0.5 M aqueous sodium hydroxide afforded the hypoxanthine derivative **IVc** in 70% yield.

In conclusion, new tetrahydropyran isonucleosides, derivatives of purine, with *cis* (**IV**) or *trans* (**V**) stereochemistry, were stereoselectively synthesized in moderate yield, starting from bicyclic lactone **1** and using a convergent strategy based on Mitsunobu coupling. Reductive cleavage of **1** with lithium aluminum hydride gave a mixture of *trans*- and *cis*-diols (compounds **2** and **3**). Protection of the primary hydroxy group and then oxidation of the secondary hydroxy group allowed us, in a subsequent reduction, with sodium borohydride at –78 °C, to obtain stereoselectively the *trans*-alcohol **4a**, precursor of the *cis*-isonucleosides **IV**. Moreover, the same strategy allowed us, using L-Selectride as reducing agent, to obtain selectively the *cis*-alcohol **4b**, precursor of *trans*-isonucleosides **V**. Both alcohols (**4a** and **4b**) afforded via Mitsunobu coupling the desired isonucleoside analogues (**IV** and **V**, respectively). However, the *trans*-alcohol **4a** is a better synthon for the Mitsunobu coupling than the *cis*-alcohol **4b**.

Compounds **IVa–c** and **Va**,**b** were tested for their *in vitro* cytostatic activity in three cell cultures: human cervix carcinoma cells (HeLa 229), human breast adenocarcinoma cells (MCF-7), and human promyelocytic leukemia cells (HL-60). The five compounds exhibited percent cell growth inhibition values below 50% at 100 μM. We may therefore assume that no significant cytostatic activity was observed in any of the cell lines employed in these preliminary assays. Further biological studies are in progress.

Melting points of samples in capillary tubes were determined on a Gallenkamp apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-400 instrument, using TMS as internal standard. Mass spectra were recorded on Hewlett-Packard 5988A and Bruker FTMS APEX XIII spectrometers. Silica gel (Merck 60, 230–400 mesh) was used for flash chromatography. Analytical TLC was carried out on plates precoated with silica gel (Merck 60 F254, 0.25 mm).

(±)-Diols 2 and 3

To a mixture of **1** (598 mg, 3.47 mmol) and $BF_3{\cdot}OEt_2$ (1.07 mL, 10.71 mmol) in anhyd Et_2O (75 mL), previously stirred at r.t. for 40 min, and cooled at 0 °C, was added LAH (1.2 g, 34.70 mmol). The reaction mixture was stirred at r.t. for 1.5 h and carefully quenched with H_2O (2 mL), 1 M aq NaOH (2 mL), and H_2O (6 mL). After filtration of the mixture, the residue was purified by flash chromatography (silica gel, CH_2Cl_2–MeOH, 9:1); this gave a mixture of *trans*- and *cis*-alcohols **2** and **3**;[15] yield: 430 mg (85%). A 100-mg portion of this mixture was further rechromatographed (silica gel, hexane–EtOAc, 1:1); this afforded **2** (46.5 mg), a mixture of **2** and **3** (31.5 mg), and **3** (22 mg).

(±)-*trans*-2-(2-Hydroxyethyl)-2,3,5,6-tetrahydro-4*H*-pyran-3-ol (2)

Yellow oil; R_f = 0.21 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.90–3.88 (m, 1 H, 1 × H6), 3.84–3.76 (m, 2 H, H2′), 3.40–3.30 (m, 2 H, H3 and 1 × H6), 3.21–3.18 (m, 1 H, H2), 2.75 (br s, 1 H, OH), 2.49 (br s, 1 H, OH), 2.12–2.09 (m, 1 H, 1 × H4), 2.05–2.00 (m, 1 H, 1 × H1′), 1.82–1.77 (m, 1 H, 1 × H1′), 1.73–1.65 (m, 2 H, H5), 1.43–1.36 (m, 1 H, 1 × H4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 82.9 (C2), 70.2 (C3), 67.7 (C6), 61 (C2′), 35.3 (C1′), 32.5 (C4), 25.5 (C5).

(±)-*cis*-2-(2-Hydroxyethyl)-2,3,5,6-tetrahydro-4*H*-pyran-3-ol (3)

Yellow oil; R_f = 0.10 (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.03–3.99 (m, 1 H, 1 × H6), 3.86–3.75 (m, 2 H, H2′), 3.67–3.40 (m, 3 H, H3, H2, and 1 × H6), 2.32 (br s, 2 H, 2 × OH), 2.02–1.90 (m, 3 H), 1.73–1.62 (m, 2 H), 1.40–1.30 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 79.6 (C2), 68.6 (C6), 67.1 (C3), 60.6 (C2′), 34.3 (C1′), 30.5 (C4), 20.1 (C5).

(±)-*cis*/*trans*-2-[2-(*tert*-Butyldiphenylsiloxy)ethyl]-2,3,5,6-tetrahydro-4*H*-pyran-3-ol (4)

Imidazole (213 mg, 3.12 mmol), DMAP (cat.), and TBDPSCl (0.81 mL, 3.12 mmol) were added to a soln of a mixture of alcohols **2** and **3** (416 mg, 2.84 mmol) in DMF (6 mL). The reaction mixture was stirred at r.t. for 1 h, quenched with H_2O (12 mL), and extracted with *t*-BuOEt (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and filtered and the solvent was evaporated to dryness. The residue was purified by flash chromatography (hexane–EtOAc, 9:1 to 8:2); this gave **4**.

Yield: 1.04 g (95%); yellow oil.

(±)-2-[2-(*tert*-Butyldiphenylsiloxy)ethyl]-2,3,5,6-tetrahydro-4*H*-pyran-3-one (5)

A suspension of **4** (941 mg, 2.45 mmol) and 4-Å MS (1.48 g) in CH_2Cl_2 (45 mL) was stirred at r.t. for 5 min. Then NMO (573 mg, 4.90 mmol) and TPAP (27 mg, 0.12 mmol) were added and the mix-

ture was stirred for 40 min. The solvent was evaporated to dryness and the residue was purified by flash chromatography (silica gel, hexane–EtOAc, 9:1); this gave **5**.

Yield: 907 mg (97%); colorless oil; R_f = 0.41 (hexane–EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.64 (m, 4 H), 7.43–7.35 (m, 6 H), 4.07–3.98 (m, 2 H, H2), 3.84–3.75 (m, 2 H), 3.70–3.64 (m, 1 H), 2.60–2.54 (m, 1 H), 2.47–2.38 (m, 1 H), 2.22–2.10 (m, 2 H), 2.09–2.01 (m, 1 H), 1.82–1.72 (m, 1 H), 1.00 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.0, 135.5, 133.8, 129.5, 127.6, 79.8, 65.6, 59.6, 37.6, 32.5, 26.8, 26.2, 19.2.

HRMS–FAB: *m*/*z* calcd for $C_{23}H_{31}O_3Si$ [M + 1]: 383.2043; found: 383.2042.

(±)-*trans*-2-[2-(*tert*-Butyldiphenylsiloxy)ethyl]-2,3,5,6-tetrahydro-4*H*-pyran-3-ol (4a)

$NaBH_4$ (62 mg, 1.64 mmol) was added in portions to a soln of **5** (314 mg, 0.82 mmol) in MeOH–CH_2Cl_2 (1:1; 5.2 mL) at –78 °C. The mixture was stirred at –78 °C for 40 min, followed by quenching with MeOH (5 mL). The solvent was evaporated to dryness and the residue was purified by flash chromatography (silica gel, hexane–EtOAc, 8:2); this gave **4a**.

Yield: 297 mg (95%); yellow oil; R_f = 0.69 (hexane–EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.65 (m, 4 H), 7.44–7.36 (m, 6 H), 3.90–3.78 (m, 3 H), 3.43–3.37 (m, 1 H), 3.34–3.21 (m, 2 H), 3.19–3.09 (m, 1 H), 2.19–2.07 (m, 1 H), 2.02–1.90 (m, 1 H), 1.80–1.71 (m, 1 H), 1.69–1.60 (m, 2 H), 1.38–1.30 (m, 1 H), 0.98 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.6, 133.1, 129.8, 127.7, 81.0, 70.5, 67.6, 61.1, 36.7, 32.2, 26.8, 25.6, 19.1.

HRMS–FAB: *m*/*z* calcd for $C_{23}H_{33}O_3Si$ [M + 1]: 385.2199; found: 385.2198.

(±)-*cis*-2-[2-(*tert*-Butyldiphenylsiloxy)ethyl]-2,3,5,6-tetrahydro-4*H*-pyran-3-ol (4b)

A 1 M soln of L-Selectride in THF (1.98 mL) was added dropwise to a soln of **5** (300 mg, 0.79 mmol) in THF (16 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 1 h, followed by quenching with sat. aq NH_4Cl (80 mL). The product was extracted with EtOAc (3 × 50 mL), the combined organic phases were dried (Na_2SO_4), and the solvent was evaporated to dryness. The residue was purified by flash chromatography (silica gel, hexane–EtOAc, 8:2); this gave **4b**.

Yield: 286 mg (94%); yellow oil; R_f = 0.65 (hexane–EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.64 (m, 4 H), 7.44–7.34 (m, 6 H), 4.12–3.92 (m, 1 H), 3.77–3.71 (m, 2 H), 3.64–3.61 (m, 1 H), 3.58–3.51 (m, 1 H), 3.47–3.40 (m, 2 H), 1.99–1.93 (m, 1 H), 1.90–1.75 (m, 2 H), 1.74–1.60 (m, 2 H), 1.40–1.29 (m, 1 H), 1.04 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.6, 133.7, 129.6, 127.6, 76.8, 68.5, 66.8, 60.2, 34.8, 30.6, 26.8, 20.3, 19.2.

HRMS–FAB: *m*/*z* calcd for $C_{23}H_{33}O_3Si$ [M + 1]: 385.2199; found: 385.2197.

***cis*-9-{2-[2-(*tert*-Butyldiphenylsiloxy)ethyl]-2,3,5,6-tetrahydro-4*H*-pyran-3-yl}-6-chloropurine (6a)**

6-Chloropurine (327 mg, 2.12 mmol) and Ph_3P (556 mg, 2.12 mmol) were added to a soln of **4a** (408 mg, 1.06 mmol) in THF (30 mL) . The mixture was cooled at 0 °C and treated with a soln of DEAD (0.33 mL, 2.12 mmol) in THF (3 mL). The reaction mixture was stirred at 0 °C for 10 min and then for 32 h at r.t. The solvent was evaporated to dryness and the residue was purified by flash chromatography (silica gel, hexane–EtOAc, 85:15); this gave **6a**.

Yield: 198 mg (36%); white solid; mp 123–125 °C; R_f = 0.67 (hexane–EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.77 (s, 1 H), 8.70 (s, 1 H), 7.61–7.58 (m, 4 H), 7.42–7.32 (m, 6 H), 4.92–4.90 (m, 1 H), 4.24–4.20 (m, 1 H), 4.12–4.08 (m, 1 H), 3.72–3.68 (m, 1 H), 3.63–3.55 (m, 2 H), 2.17–2.08 (m, 1 H), 2.07–1.90 (m, 1 H), 1.82–1.68 (m, 1 H), 1.61–1.49 (m, 2 H), 1.45–1.38 (m, 1 H), 1.02 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.1, 151.7, 151.0, 145.9, 135.4, 133.4, 130.8, 129.7, 127.7, 75.1, 68.6, 59.5, 52.2, 35.1, 29.1, 26.8, 20.6, 19.2.

HRMS–FAB: *m*/*z* calcd for $C_{28}H_{34}ClN_4O_2Si$ [M + 1]: 521.2140; found: 521.2161.

***trans*-9-{2-[2-(*tert*-Butyldiphenylsiloxy)ethyl]-2,3,5,6-tetrahydro-4*H*-pyran-3-yl}-6-chloropurine (6b)**

Compound **6b** was prepared from **4b** (289 mg, 0.75 mmol) in the same way as **6a** from **4a**. The residue was purified by flash chromatography (silica gel, hexane–EtOAc, 95:5 to 85:15); this gave compounds **7** (36%) and **6b** (10%), both of them as colorless oils.

Compound 6b

Yield: 40 mg (10%); colorless oil; R_f = 0.61 (hexane–EtOAc, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.68 (s, 1 H), 8.08 (s, 1 H), 7.56–7.54 (m, 2 H), 7.48–7.45 (m, 2 H), 7.41–7.27 (m, 6 H), 4.33–4.29 (m, 1 H), 4.22–4.09 (m, 1 H), 4.04–3.99 (m, 1 H), 3.80–3.72 (m, 1 H), 3.62–3.51 (m, 2 H), 2.33–2.31 (m, 1 H), 2.20–2.15 (m, 1 H), 1.90–1.82 (m, 2 H), 1.34–1.30 (m, 1 H), 1.28–1.20 (m, 1 H), 0.96 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.8, 151.6, 151.3, 143.9, 135.4, 133.6, 131.8, 129.6, 127.6, 75.3, 67.6, 59.0, 57.1, 34.9, 30.2, 26.8, 25.8, 19.1.

HRMS–FAB: *m*/*z* calcd for $C_{28}H_{34}ClN_4O_2Si$ [M + 1]: 521.2140; found: 521.2131.

2-[2-(*tert*-Butyldiphenylsiloxy)ethyl]-5,6-dihydro-2*H*-pyran (7)

Yield: 95 mg (36%); colorless oil; R_f = 0.41 (hexane–EtOAc, 95:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.68 (m, 4 H), 7.44–7.37 (m, 6 H), 5.84–5.80 (m, 1 H), 5.66 (dd, *J* = 10.3, 1.8 Hz, 1 H), 4.39–4.29 (m, 1 H), 3.95–3.87 (m, 2 H), 3.77–3.68 (m, 1 H), 3.64–3.57 (m, 1 H), 2.28–2.17 (m, 1 H), 1.95–1.89 (m, 1 H), 1.79 (q, *J* = 6.4 Hz, 2 H), 1.07 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.5, 133.9, 130.6, 129.5, 127.6, 124.5, 70.7, 63.1, 60.4, 38.1, 26.9, 25.3, 19.2.

HRMS–FAB: *m*/*z* calcd for $C_{23}H_{31}O_2Si$ [M + 1]: 367.2093; found: 367.2102.

***cis*-6-Chloro-9-[2-(2-hydroxyethyl)-2,3,5,6-tetrahydro-4*H*-pyran-3-yl]purine (IVa)**

A 1 M soln of TBAF in THF (0.36 mL, 0.36 mmol) was added dropwise to a soln of **6a** (190 mg, 0.364 mmol) in anhyd THF (6 mL). The reaction mixture was stirred at r.t. for 3 h and then treated with sat. aq $NaHCO_3$ (7 mL). The product was extracted with *t*-BuOMe (3 × 7 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by flash chromatography (silica gel, CH_2Cl_2–MeOH, 7:3); this gave **IVa**.

Yield: 77 mg (75%); white solid; mp 137–139 °C; R_f = 0.5 (MeOH–CH_2Cl_2, 1:9).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.91 (s, 1 H), 8.80 (s, 1 H), 4.93–4.91 (m, 1 H), 4.41 (t, *J* = 4.3 Hz, 1 H), 4.13–4.10 (m, 1 H), 3.99–3.96 (m, 1 H), 3.64–3.58 (m, 1 H), 3.38–3.28 (m, 2 H), 2.20–2.16 (m, 1 H), 1.94–1.91 (m, 1 H), 1.85–1.81 (m, 1 H), 1.53–1.49 (m, 1 H), 1.33–1.26 (m, 1 H), 1.21–1.15 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 152.2, 151.5, 149.1, 146.6, 129.9, 74.5, 67.5, 56.7, 51.6, 34.7, 27.6, 20.2.

HRMS (EI): *m*/*z* calcd for $C_{12}H_{15}N_4O_2Cl$: 282.0884; found: 282.0873.

***cis*-9-[2-(2-Hydroxyethyl)-2,3,5,6-tetrahydro-4*H*-pyran-3-yl]adenine (IVb)**

A mixture of **IVa** (31 mg, 0.11 mmol) and 25% aq NH_3 (3 mL) was heated under reflux for 8 h. The mixture was concentrated to dryness in vacuo and the residue was purified by flash chromatography (silica gel, CH_2Cl_2–MeOH, 92:8); this gave **IVb**.

Yield: 29 mg (80%); white solid; mp 204–206 °C; R_f = 0.2 (MeOH–CH_2Cl_2, 1:9).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.37 (s, 1 H), 8.15 (s, 1 H), 7.24 (s, 2 H), 4.74–4.72 (m, 1 H), 4.35 (br s, 1 H), 4.11–4.09 (m, 1 H), 3.93–3.91 (m, 1 H), 3.61–3.56 (m, 1 H), 3.34–3.31 (m, 2 H), 2.14–2.08 (m, 1 H), 1.85–1.79 (m, 2 H), 1.51–1.48 (m, 1 H), 1.31–1.28 (m, 1 H), 1.18–1.15 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.0, 152.4, 149.8, 140.1, 117.7, 74.7, 67.5, 56.7, 50.1, 34.8, 28.0, 20.4.

HRMS (EI): *m*/*z* calcd for $C_{12}H_{17}N_5O_2$: 263.1382; found: 263.1375.

***cis*-9-[2-(2-Hydroxyethyl)-2,3,5,6-tetrahydro-4*H*-pyran-3-yl]hypoxanthine (IVc)**

A mixture of **IVa** (29 mg, 0.11 mmol) and 0.5 M aq NaOH (3 mL) was heated under reflux for 6 h. The mixture was concentrated to dryness in vacuo and the residue was purified by flash chromatography (CH_2Cl_2–MeOH, 90:10); this gave **IVc**.

Yield: 19 mg (70%); white solid; mp 219–221 °C; R_f = 0.1 (MeOH–CH_2Cl_2, 1:9).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.29 (s, 1 H), 8.04 (s, 1 H), 4.71–4.69 (m, 1 H), 4.40 (br s, 1 H), 4.09–4.07 (m, 1 H), 3.92–3.89 (m, 1 H), 3.60–3.54 (m, 1 H), 3.32–3.30 (m, 2 H), 2.14–2.09 (m, 1 H), 1.85–1.77 (m, 2 H), 1.51–1.47 (m, 1 H), 1.32–1.26 (m, 1 H), 1.19–1.13 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.8, 148.6, 145.6, 139.5, 122.9, 74.5, 67.4, 56.7, 50.7, 34.7, 28.0, 20.3.

HRMS (EI): *m*/*z* calcd for $C_{12}H_{16}N_4O_3$: 264.1222; found: 264.1226.

***trans*-6-Chloro-9-[2-(2-hydroxyethyl)-2,3,5,6-tetrahydro-4*H*-pyran-3-yl]purine (Va)**

Compound **Va** was prepared from **6b** (20 mg, 0.038 mmol) in the same way as **IVa** from **6a**. The residue was purified by flash chromatography (hexane–EtOAc, 1:5); this gave compound **Va**.

Yield: 8.4 mg (77%); R_f = 0.12 (hexane–EtOAc, 1:5).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.86 (s, 1 H), 8.80 (s, 1 H), 4.41–4.37 (m, 1 H), 4.18 (t, *J* = 5.3 Hz, 1 H), 4.07–3.93 (m, 2 H), 3.52–3.48 (m, 1 H), 3.34–3.30 (m, 2 H), 2.44–2.36 (m, 1 H), 2.12–2.08 (m, 1 H), 1.81–1.76 (m, 2 H), 1.41–1.36 (m, 1 H), 1.10–1.01 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 152.2, 152.0, 149.7, 146.9, 131.4, 76.0, 67.5, 57.0, 56.7, 35.7, 29.5, 26.1.

ESI-HRMS: *m*/*z* calcd for $C_{12}H_{16}ClN_4O_2$: 283.09563; found: 283.09556.

***trans*-9-[2-(2-Hydroxyethyl)-2,3,5,6-tetrahydro-4*H*-pyran-3-yl]adenine (Vb)**

Compound **Vb** was prepared from **Va** (24 mg, 0.085 mmol) in the same way as **IVb** from **IVa**. The residue was purified by flash chromatography (silica gel, CH_2Cl_2–MeOH, 92:8); this gave compound **Vb**.

Yield: 18 mg (82%); R_f = 0.28 (MeOH–CH_2Cl_2, 1:9).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.25 (s, 1 H), 8.14 (s, 1 H), 7.23 (s, 2 H), 4.30–4.17 (m, 2 H), 3.99–3.87 (m, 2 H), 3.52–3.42 (m, 1 H), 3.34–3.29 (m, 2 H), 2.41–2.32 (m, 1 H), 2.06–1.98 (m, 1 H), 1.82–1.70 (m, 2 H), 1.40–1.34 (m, 1 H), 1.10–0.98 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.9, 152.2, 149.3, 139.6, 118.8, 75.9, 66.9, 56.7, 55.1, 35.3, 29.3, 25.7.

ESI-HRMS: *m*/*z* calcd for $C_{12}H_{18}N_5O_2$: 264.14550; found: 264.14624.

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