Synthesis of spiroacetal-nucleosides as privileged natural product-like scaffolds†

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The elaboration of a 6,6-spiroacetal scaffold to incorporate a nucleoside unit at the anomeric position is described. The novel spiroacetal-nucleoside hybrids **11** were generated *via* nucleosidation of acetoxy-spiroacetal **10** with a series of silylated nucleobases under Vorbrüggen conditions.

Introduction

Nature has always been an important source of lead compounds for the development of new therapeutic agents. Evolutionary selection pressures have resulted in chemical biodiversity that has been exploited extensively by the pharmaceutical industry. By modifying a biologically active lead compound, libraries of structurally similar, but non-natural, synthetic analogues are created such that the molecular complexity is kept to a minimum whilst improvements are made to the desired pharmacological activity.[1]

The number of biological targets available for screening has increased substantially in recent years through a better understanding of biological pathways and the successful sequencing of the human genome.[2] Hence, it has become increasingly common to subject natural products and their synthetic analogues to broad phenotypic discovery screens to identify any biological activity not found in the original natural product. By combining biologically active motifs within a natural product-inspired scaffold system, a library of compounds can be generated for screening of potential bioactivity.[3,4]

Spiroacetals, in particular 1,7-dioxaspiro[5.5]undecanes, are a common structural element in many natural products isolated from a variety of sources that display a wide range of biological activities. For example, many simple spiroacetals are insect pheromones;[5,6] routiennocin is an ionophore antibiotic;[7] okadaic acid and tautomycin are protein phosphatase inhibitors;[8] integramycin is a HIV-1 intregrase inhibitor;[9] the milbemycins and avermectins are anthelmintic and insecticidal agents[5] and the spongistatins are marine antimitotic macrolides.[10]

More importantly, many truncated synthetic spiroacetals derived from more complex spiroacetal containing natural products, such as spiroacetals **1–3**, provide the basic pharmacophore for the observed biological activity.[11,12] The 6,6-spiroacetal unit has also been used to replace the rigid galactose disaccharide core in a sialyl Lewis X mimetic **4** (Fig. 1).[13]

Several research groups have reported the generation of libraries based on a 6,6-spiroacetal scaffold. For example, Ley *et al.*[3] and

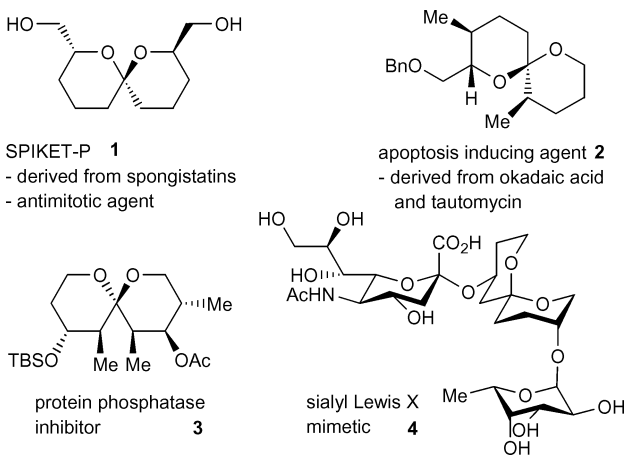

Fig. 1 Privileged 6,6-spiroacetal structures.[11–13]

Porco *et al.*[14] synthesised a series of 6,6-spiroacetal derivatives containing three sites for further synthetic elaboration to probe for biological activity. A structurally diverse 6,6-spiroacetal-based library constructed by Waldmann *et al.*[12] resulted in the discovery of the lead compound **3** as an inhibitor of several important protein phosphatases (Fig. 1).

Nucleoside analogues are an important class of antiviral agent that are designed to mimic naturally occurring nucleosides. After phosphorylation, the activated nucleoside analogue inhibits viral polymerases and terminates the elongating viral nucleic acid chain, thus selectively suppressing viral replication.[15]

A naturally occurring nucleoside consists of a hydroxymethyl group, a glycoside linker and a heterocyclic base (Fig. 2). The hydroxymethyl group is crucial for intracellular phosphorylation whereas the glycoside unit is not well recognised by the nucleic acid processing enzymes and merely acts as a spacer to present the hydroxymethyl substituent and the heterocyclic base to the

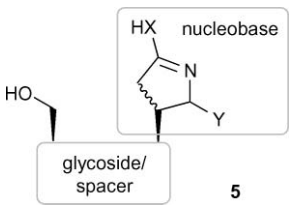

Fig. 2 General structure of naturally occurring nucleosides and nucleoside analogues.[16]

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† Electronic supplementary information (ESI) available: Characterisation data of acetoxy-spiroacetal **10**, nucleosides **15a–h** and **11a–k**. See DOI: 10.1039/b818314g

target enzymes. Based on these observations, the synthesis of nucleoside analogues that vary in the nature of spacer and nucleobase, provides a significant opportunity to develop new antiviral agents.[16]

Our research group has a long standing interest in the synthesis of spiroacetals present in a wide range of biologically significant compounds.[17] This synthetic effort has prompted the investigation of elaborating the 6,6-spiroacetal unit to provide novel and diverse functionality. In the present work, we were interested in the chemical attachment of the spiroacetal scaffold to a biologically relevant nucleobase. These spiroacetal derivatives allow diversification at the biologically relevant anomeric position, providing novel spiroacetal-based nucleosides. Further incorporation of a hydroxymethyl group on the spiroacetal ring also provides an additional site for further derivatisation as well as furnishing an essential phosphorylation site. The combination of these important bioactive motifs provides access to a unique hybrid of functionality and the collection of spiroacetal-nucleosides reported herein provides novel probes to screen for potential bioactivity in phenotypic assays.

To date, the synthesis of a 6,6-spiroacetal ring system bearing a heterobase at the anomeric position, has not been reported. Related examples of spirocyclic nucleosides include the naturally occurring herbicidal (+)-hydantocidin (**6**)[18] and synthetic anti-HIV TSAO-T (**7**).[19] Biological evaluation of the 2′-spirocyclic nucleosides **8** prepared by Wengel *et al.*[20] and the 4′-spirocyclic nucleosides **9** prepared by Paquette *et al.*[21] are also currently underway (Fig. 3).

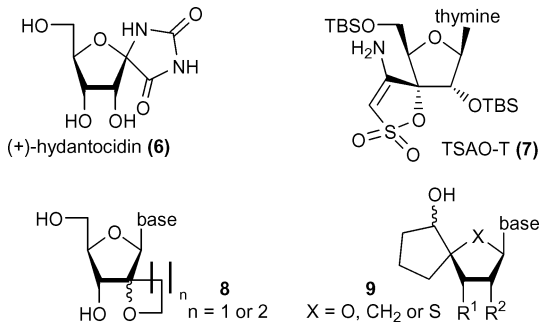
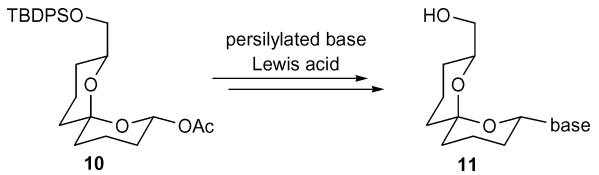


Fig. 3 (+)-Hydantocidin (**6**),[18] TSAO-T (**7**),[19] 2′-spirocyclic nucleosides **8**[20] and 4′-spirocyclic nucleosides **9**.[21]

We recently reported the synthesis of a series of spiroacetal hybrids containing a triazole unit at the anomeric position that provided an isostere to mimic the biological relevant peptide bond.[22] Using a similar rationale, we herein report the synthesis of a series of spiroacetal-nucleosides **11** generated by the nucleosidation of acetoxy-spiroacetal **10** with several persilylated bases under Vorbrüggen conditions (Scheme 1).

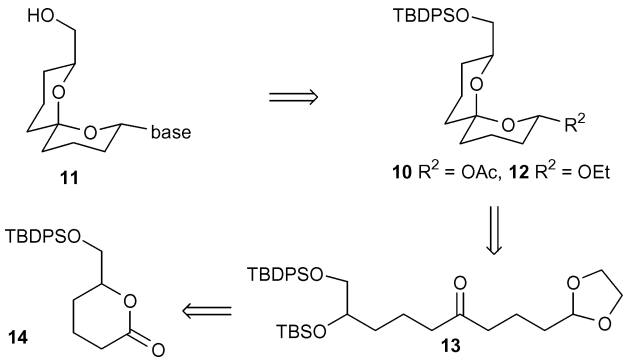
Results and discussion

The retrosynthesis adopted for the desired spiroacetal-nucleosides **11** hinged on disconnection of the anomeric C–N bond linking the spiroacetal to the nucleobase. With this idea in mind, it was proposed that previously prepared ethoxy-spiroacetal **12**[22] can be converted to acetoxy-spiroacetal **10** which is then elaborated to nucleosides **11**. Ethoxy-spiroacetal **12** is synthesised from ketone



Scheme 1 Synthesis of spiroacetal-nucleosides **11** generated by the nucleosidation of acetoxy-spiroacetal **10** with a range of persilylated bases under Vorbrüggen conditions.

13[22] which is accessible from the previously reported lactone **14** (Scheme 2).[23]



Scheme 2 Retrosynthesis of spiroacetal-nucleosides **11**.

Preparation of acetoxy-spiroacetal 10

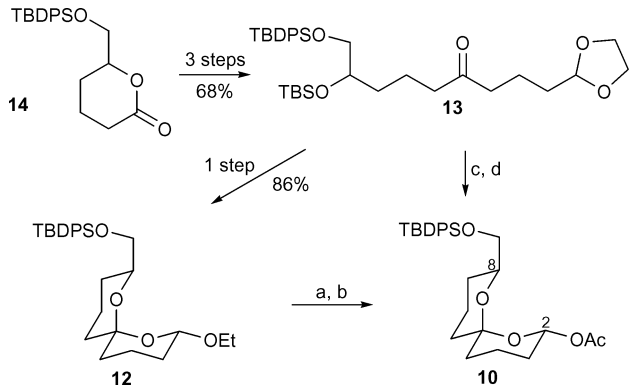
Lactone **14** was prepared from commercially available ethyl 2-oxocyclopentanecarboxylate in 87% yield over five steps using procedures adapted from the work reported by Taylor *et al.*[23] Conversion of lactone **14** to ethoxy-spiroacetal **12** was carried out in 58% yield over four steps *via* ketone **13** using procedures recently reported by our research group.[22]

With ethoxy-spiroacetal **12** in hand, attention focused on its conversion to acetoxy-spiroacetal **10** under a range of reagents and conditions. The best result was obtained when ethoxy-spiroacetal **12** was treated with camphorsulfonic acid (CSA) in aqueous THF at 40 °C to give a lactol intermediate which was immediately acetylated to afford acetoxy-spiroacetal **10** in 58–66% yield over two steps (Scheme 3). Many attempts to effect the direct conversion of ketone **13**[22] to acetoxy-spiroacetal **10** using a variety of reagents and conditions only afforded the desired acetoxy-spiroacetal **10** in 30–35% yield after acetylation.

NMR analysis of acetoxy-spiroacetal **10** revealed a characteristic anomeric 2-H resonance at δ_H 6.00 ppm (dd, $J_{2ax,3ax}$ 10.1 Hz) establishing that the acetoxy group adopted an equatorial position. A characteristic quaternary spirocarbon C-6 resonated at δ_C 99.1 ppm and a NOESY correlation between 2-H and 8-H established the bis-anomerically stabilised spiroacetal ring system (Fig. 4).

Preparation of spiroacetal-nucleosides 15

With acetoxy-spiroacetal **10** and ethoxy-spiroacetal **12** in hand, attention next turned to the subsequent nucleosidation with a range of silylated nucleobases to access the desired spiroacetal-nucleosides **15**. Under Vorbrüggen conditions, a persilylated



Scheme 3 Synthesis of acetoxy-spiroacetal **10**. *Reagents and conditions*: (a) CSA, aq. THF, 40 °C, 18 h; (b) Ac_2O, DMAP (cat.), NEt_3, CH_2Cl_2, rt, 2 h, 58–66% over 2 steps; (c) PPTS (pyridinium *para*-toluenesulfonate), aq. acetone, reflux, 6–24 h; (d) Ac_2O, DMAP (cat.), NEt_3, CH_2Cl_2, rt, 2 h, 30–35% over 2 steps.

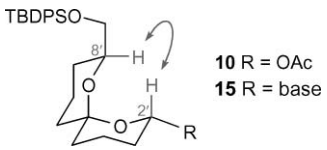
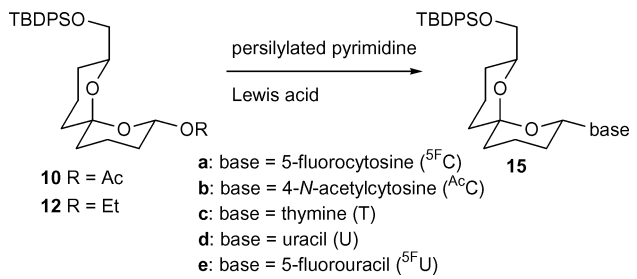


Fig. 4 Structures of acetoxy-spiroacetal **10** and nucleoside analogues **15a–h** showing the bis-anomerically stabilised spiroacetal ring system and their equatorial substituents. NOESY correlations are denoted by arrows.

heterobase is added to an oxonium ion generated from a spiroacetal bearing a leaving group at the anomeric position in the presence of a Lewis acid.[24,25] TMSOTf was the initial choice of Lewis acid due to its proven ability to effect successful oxonium ion generation in a model study,[22,26] and its use by others for structurally related spiroacetals.[27,28]

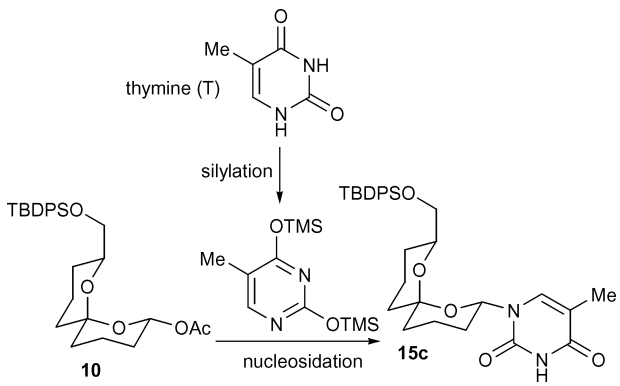
Nucleosidation of ethoxy-spiroacetal **12** was first attempted because acetal **12** was obtained in higher yield in one less synthetic step than acetoxy-spiroacetal **10**. Unfortunately, nucleosidation of ethoxy-spiroacetal **12** with persilylated 5-fluorocytosine using the two-pot Vorbrüggen conditions[24,25] only gave a trace amount (<1%) of the desired spiroacetal-5-fluorocytidine **15a** as identified by NMR spectroscopy (Scheme 4). The starting ethoxy-spiroacetal **12** was also recovered from the reaction in more than 50% yield together with a complex mixture of degraded material. Recovery of starting material indicated that ethoxy-spiroacetal **12** was a weak glycosyl donor for nucleosidation in the context of the present work.



Scheme 4 Nucleosidation of acetoxy-spiroacetal **10** with a range of persilylated pyrimidines under Vorbrüggen conditions. See Table 1 for reaction conditions.

Given the inability of ethoxy-spiroacetal **12** to effect the desired reaction, the nucleosidation of acetoxy-spiroacetal **10** using a persilylated pyrimidine was next investigated using the two-pot Vorbrüggen procedure.[24,25] The silylation was effected using hexamethyldisilazane (HMDS) with catalytic ammonium sulfate which avoided the use of *N*,*O*-bis(trimethylsilyl)acetimide (BSA) and the subsequent formation of the acetamide by-product. Gratifyingly, nucleosidation using 5-fluorocytosine (^{5F}C), 4-*N*-acetylcytosine (^{Ac}C), thymine (T), uracil (U) and 5-fluorouracil (^{5F}U) carried out in the presence of TMSOTf in CH_2Cl_2 at room temperature successfully produced spiroacetal-nucleosides **15a–e** in 20–46% yield (Scheme 4 and Table 1).

Although the nucleosidation of acetoxy-spiroacetal **10** with a range of persilylated pyrimidines was successful, the yields obtained for the reactions were moderate. Hence, an optimisation study of the nucleosidation was conducted using the synthesis of thymidine **15c** as a model reaction (Scheme 5).

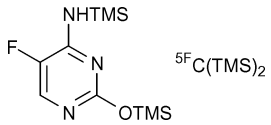
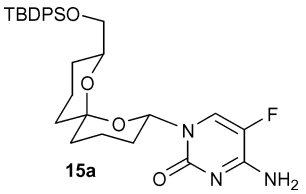
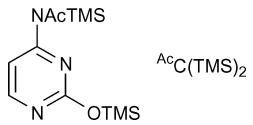
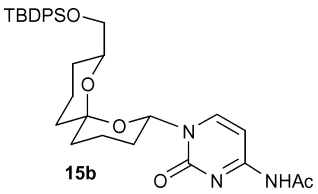
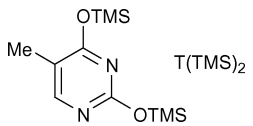
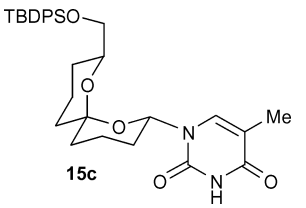
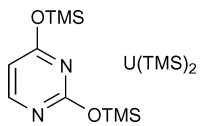
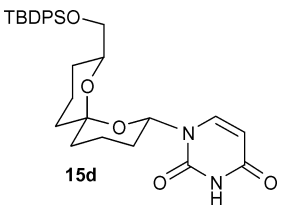
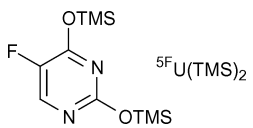
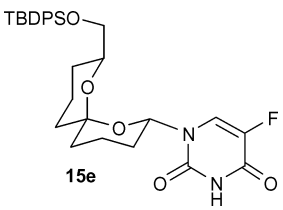


Scheme 5 Nucleosidation of acetoxy-spiroacetal **10** with persilylated thymine under a range of Vorbrüggen conditions. See Table 2 for reaction conditions.

A variety of reagents and conditions were evaluated as summarised in Table 2. Nucleosidation reactions conducted using one-pot conditions wherein acetoxy-spiroacetal **10** was treated with BSA and TMSOTf in MeCN for 3 h were disappointing. Similarly, the two pot procedure wherein acetoxy-spiroacetal **10** was treated with $SnCl_4$ or $BF_3{\cdot}OEt_2$ in MeCN or CH_2Cl_2 only proceeded in low yield. An equivalent yield of 45% was obtained using TIPSOTf[29] in CH_2Cl_2 at room temperature but the reaction took longer to proceed than the reaction using TMSOTf under similar conditions.

TIPSOTf is a stronger Lewis acid than TMSOTf but with better air and moisture stability due to its steric bulk.[29] Therefore, TIPSOTf was suggested to provide a good alternative to the use of TMSOTf.[29] This suggestion was consistent with the above results for the nucleosidation of acetoxy-spiroacetal **10** with persilylated thymine under Vorbrüggen conditions. However, attempts to extend the use of TIPSOTf to nucleosidations involving other persilylated pyrimidines, namely uracil and 5-fluorouracil, only proceeded in lower yield than the analogous reaction using TMSOTf (Scheme 6 and Table 3). It was therefore established that the use of TMSOTf in CH_2Cl_2 at room temperature was in fact the preferred method for the nucleosidation of acetoxy-spiroacetal **10** with persilylated pyrimidines.

Table 1 Summary of reagents and conditions used for the nucleosidation of acetoxy-spiroacetal **10** with a range of persilylated pyrimidines using two-pot Vorbrüggen conditions (Scheme 4)

Entry	Persilylated pyrimidine	Silylation conditions	Nucleosidation conditions	Product	Yield (%)
1		a	b	 **15a**	22
2		a	b	 **15b**	46
3		a	b	 **15c**	45
4		a	b	 **15d**	36
5		a	b	 **15e**	20

Reagents and conditions: (a) pyrimidine, HMDS, $(NH_4)_2SO_4$ (cat.), reflux, 1–4 h; (b) **10**, TMSOTf, CH_2Cl_2, rt, 2–3 h.

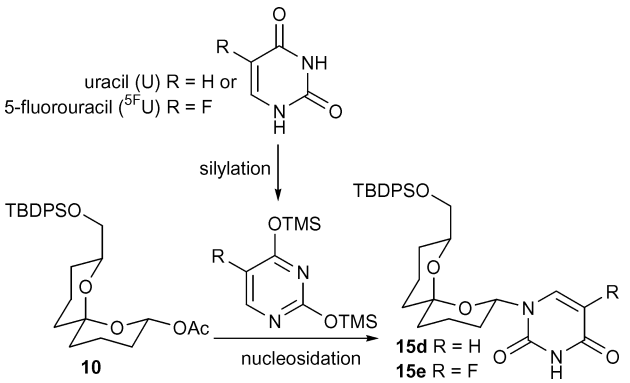
Table 2 Summary of reagents and conditions used for optimising the nucleosidation of acetoxy-spiroacetal **10** with persilylated thymine under a range of Vorbrüggen conditions (Scheme 5)

Entry	Silylation reagent	Lewis acid	Reaction conditions	Yield (%)
1	BSA (one pot)	TMSOTf	MeCN, rt, 3 h	33
2	HMDS	TMSOTf	CH_2Cl_2, rt, 3 h	45
3	HMDS	$SnCl_4$	CH_2Cl_2, rt, 3 h	24
4	HMDS	$SnCl_4$	MeCN, rt, 3 h	Complex mixture
5	HMDS	TIPSOTf	CH_2Cl_2, rt, 18 h	45
6	HMDS	$BF_3{\cdot}OEt_2$	CH_2Cl_2, rt, 3 h	Complex mixture

Having demonstrated the successful nucleosidation of acetoxy-spiroacetal **10** with pyrimidine bases, the more difficult nucleosidations using purine bases were next investigated. Purines have several nitrogens available for possible alkylation. Unlike the pyrimidines, the difference in the steric hindrance exerted by the neighbouring groups near the nitrogens is not significant enough to allow for selective alkylation. Alkylation of purines, therefore, may not be regioselective and a mixture of N7 and N9 regioisomers are commonly isolated for guanosine and some adenosine derivatives.[25,30]

Table 3 Summary of reagents and conditions used for the nucleosidation of acetoxy-spiroacetal **10** with persilylated uracil or 5-fluorouracil under two-pot Vorbrüggen conditions (Scheme 6). The percentages in parentheses represent the yield obtained when TMSOTf was used for the nucleosidation (Table 1)

Entry	Persilylated pyrimidine	Silylation conditions	Nucleosidation conditions	Product	Yield
1	$U(TMS)_2$	U, BSA, reflux, 1 h	TIPSOTf, CH_2Cl_2, rt, 18 h	**15d**	9% (*cf.* 36%)
2	$^{5F}U(TMS)_2$	^{5F}U, BSA, reflux, 1 h	TIPSOTf, CH_2Cl_2, rt, 18 h	**15e**	Complex mixture (*cf.* 20%)
3	$^{5F}U(TMS)_2$	^{5F}U, HMDS, $(NH_4)_2SO_4$ (cat.), reflux, 1 h	TIPSOTf, CH_2Cl_2, rt, 18 h	**15e**	Complex mixture (*cf.* 20%)

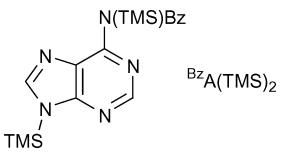
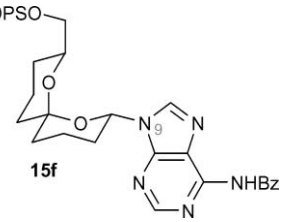
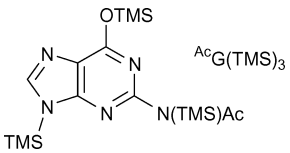
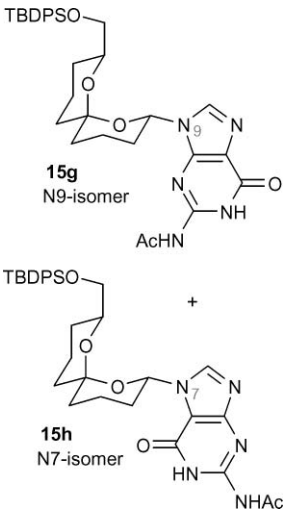


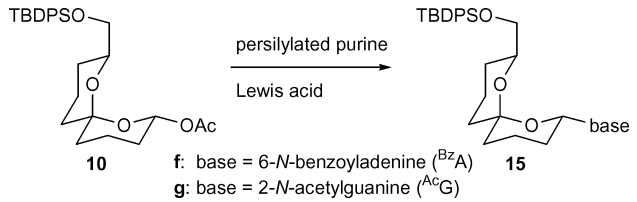
Scheme 6 Nucleosidation of acetoxy-spiroacetal **10** with persilylated uracil or 5-fluorouracil under a range of Vorbrüggen conditions. See Table 3 for reaction conditions.

Nevertheless, the nucleosidation of acetoxy-spiroacetal **10** with *N*-acylated adenine or guanine was carried out. The silylation step was carried out using BSA under reflux after discovering that the use of HMDS was very slow by comparison. Later, the silylation step was effected by heating the purine base with a mixture of BSA, HMDS and toluene under reflux, thus producing cleaner persilylated purines. In this case, TIPSOTf was used to generate the oxonium ion intermediate for the nucleosidation due to its better air and moisture stability.

Gratifyingly using these conditions, the nucleosidation of acetoxy-spiroacetal **10** with persilylated *N*-benzoyladenine gave the desired N9-substituted spiroacetal-adenosine **15f** in 35–37% yield as the only regioisomer. On the other hand, nucleosidation of persilylated *N*-acetylguanine gave a mixture of N9-guanosine **15g** and N7-guanosine **15h** in 20% and 11% yield, respectively (Scheme 7 and Table 4). Preparative thin layer chromatography (PLC) was required to separate the N7 and N9 regioisomers.

Table 4 Summary of reagents and conditions used for the nucleosidation of acetoxy-spiroacetal **10** with persilylated purines using the two-pot Vorbrüggen procedure (Scheme 7)

Entry	Persilylated purine	Silylation conditions	Nucleosidation conditions	Product	Yield (%)
1		*N*-Benzoyladenine, HMDS–BSA–toluene, reflux, 1 h	**10**, TIPSOTf, CH_2Cl_2, rt, 18 h		35–37%
5		*N*-Acetylguanine, HMDS–BSA–toluene, reflux, 1 h	**10**, TIPSOTf, CH_2Cl_2, rt, 18 h		**15g**: 20%, **15h**: 11%



Scheme 7 Nucleosidation of acetoxy-spiroacetal **10** with a range of persilylated purines under Vorbrüggen conditions. See Table 4 for reaction conditions.

For all the nucleosidations performed using acetoxy-spiroacetal **10**, only a single diastereomer of the individual nucleosidation was obtained. NMR analysis of nucleoside analogues **15a–h** revealed the characteristic anomeric H2′ protons at δ_H 5.85–6.22 ppm. These protons resonated as doublets of doublets with a characteristic large 1,2-diaxial coupling constant ($J_{2ax,3ax}$ 10.6–11.1 Hz) establishing that the nucleoside substituent in analogues **15a–h** adopted the equatorial position. Characteristic NOESY correlations between H2′ and H8′ were observed for nucleosides **15a–h**, thus confirming the adoption of the bis-anomerically stabilised spiroacetal conformation in which both the TBDPS-protected hydroxymethyl and nucleobase adopted equatorial positions on their associated tetrahydropyran rings (Fig. 4).

Recrystallisation of uridine **15d** from dichloromethane–hexane afforded pale yellow needles that allowed structural determination by X-ray crystallography.[31] The results were consistent with the above NMR analysis which established that the spiroacetal rings adopted a bis-anomerically stabilised conformation and both the uracil and TBDPS-protected hydroxymethyl substituent occupied the equatorial positions on their respective tetrahydropyran rings (Fig. 5).

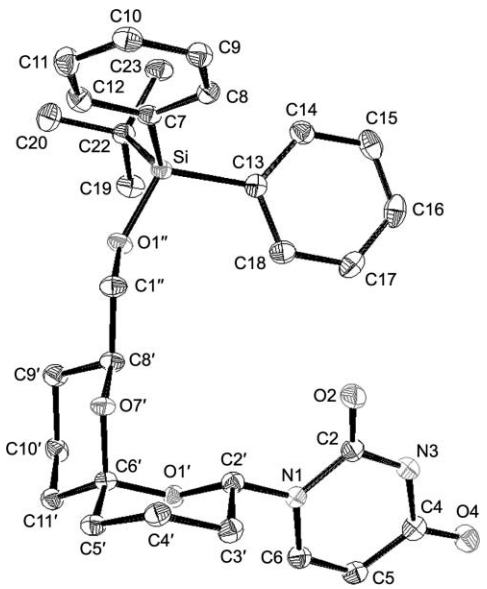
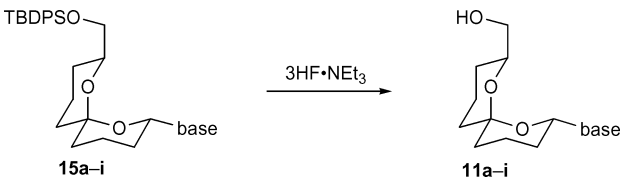


Fig. 5 X-Ray crystal structure of uridine **15d** with displacement ellipsoids drawn at the 50% probability level.[31]

Only the equatorial substituted nucleoside analogues **15a–h** were isolated from the nucleosidation step. This may be due to the destabilising steric interactions exerted by the bulky TBDPS-protected hydroxymethyl group if the nucleoside occupied an axial position. The alignment of 1,3-dipole moments between the basic substituent and the C–O bond of the neighbouring ring may also disfavour the formation of axial isomer.[32] The formation of the equatorial substituted nucleosidation was consistent with the experimental observations and *ab initio* calculations carried out by Mead and Zemribo[27] on a closely related 6,6-spiroacetal ring system. Similar exclusive production of the equatorial isomers from the nucleosidation of pyranosides or furanosides lacking a stereodirecting neighbouring group have also been reported in the literature.[33]

Desilylation and deacylation of spiroacetal-nucleosides 15

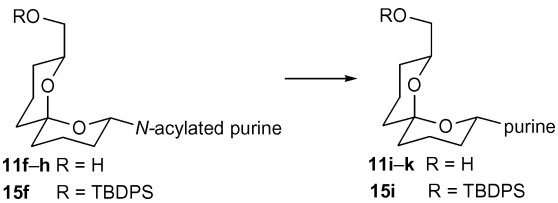
The desilylation of TBDPS-protected spiroacetal-nucleosides **15a–i** was carried out primarily using the mild reagent, HF·triethylamine[34] after the successful deprotection of structurally related spiroacetal-triazole series.[22] Removal of the silyl ether group in spiroacetal-nucleosides **15a–i** using HF·triethylamine proceeded smoothly in THF to give nucleosides **11a–i** in 65–92% yield. The reactions were very sluggish at room temperature and required use of prolonged reaction times and excess reagents. The deprotections were, therefore, carried out at an elevated temperature of 40 °C to increase the rate of reaction (Scheme 8 and Table 5).



Scheme 8 Desilylation of TBDPS-protected nucleosides **15a–i**. See Table 5 for reaction conditions.

Attempts to desilylate protected thymidine **15c** using a non-fluoride based reagent, caesium(III) chloride and sodium iodide in MeCN[35] failed to give thymidine **11c** with only a complex mixture resulting (Table 5).

Using the favoured desilylation conditions (HF·triethylamine at 40 °C), *N*-deacetylation of protected cytidine **15b** also occurred concomitantly to give the desired cytidine **11b** in 69% yield. However, deacylation was not observed for the reaction of adenosine **15f** and guanosines **15g** and **15h** with HF·triethylamine under the same conditions (Table 5). Therefore, use of a separate *N*-deacylation step under mild conditions was required to unmask the purine moiety in protected spiroacetal-nucleosides **11f–h** and **15f** without effecting cleavage of the sensitive spiroacetal ring and the pseudo *N*-glycosidic bond (Scheme 9).



Scheme 9 *N*-Deacylation of protected purines **11f–h** and **15f**. See Table 6 for reaction conditions.

Table 5 Summary of reagents and conditions used for the desilylations of TBDPS-protected nucleosides **15a–i** (Scheme 8)

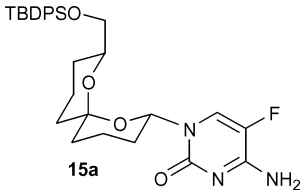
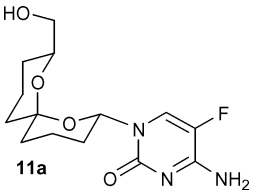
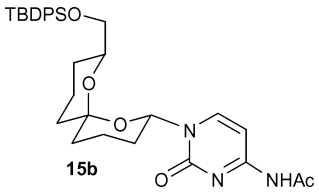
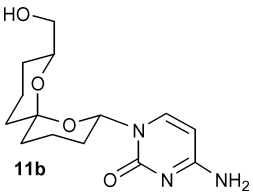
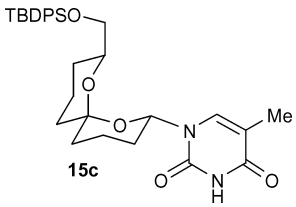
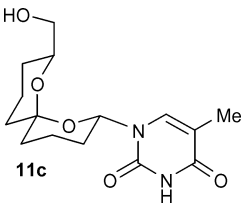
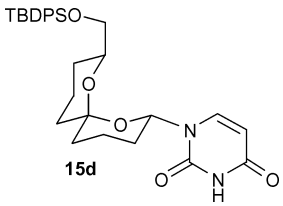
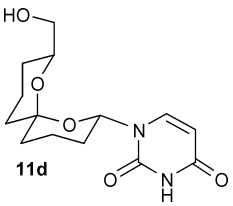
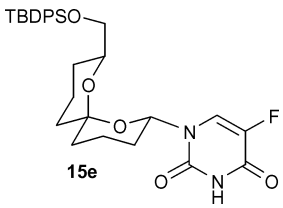
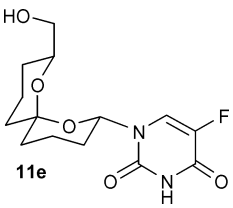
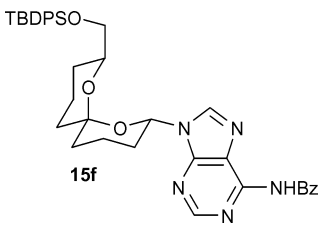
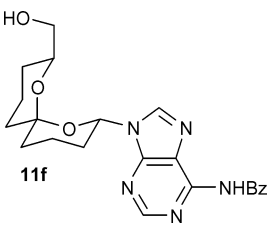
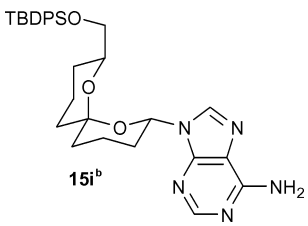
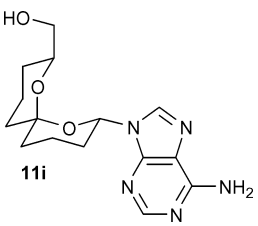
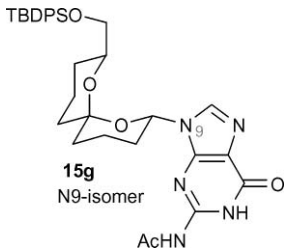
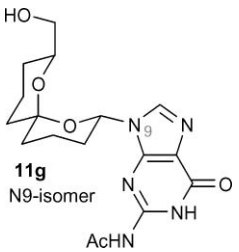
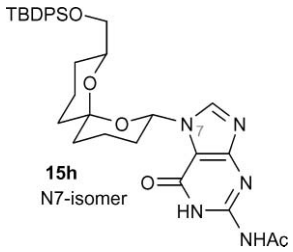
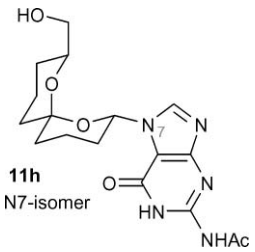
Entry	TBDPS ether	Reagents and conditions	Product	Yield (%)
1	 **15a**	a	 **11a**	77
2	 **15b**	a	 **11b**	69[a]
3	 **15c**	a	 **11c**	76–79
4		b		Complex mixture
5	 **15d**	a	 **11d**	73
6	 **15e**	a	 **11e**	65
7	 **15f**	a	 **11f**	85
8	 **15i**[b]	a	 **11i**	92

Table 5 *(Contd.)*

Entry	TBDPS ether	Reagents and conditions	Product	Yield (%)
9		a		91
10		a		82

Reagents and conditions: (a) 3HF·NEt_3, THF, 40 °C, 1–2 d; (b) $CeCl_3 \cdot H_2O$, NaI, MeCN, reflux, 3 h. [a] One-pot desilylation/*N*-deacetylation was achieved for this particular reaction. [b] Synthesised *via* *N*-debenzoylation of adenosine **15f**. See Table 6 for reaction conditions.

Use of the mild reagent, zinc(II) bromide in MeOH–$CHCl_3$[36] failed to effect *N*-deacylation of protected purine **11f** and only a complex mixture was recovered. This result was attributed to the undesired coordination of zinc(II) ion to the spiroacetal ring oxygens rather than the purine N1, thus initiating undesired ring-opening side reactions. Given the metal-coordinating ability of spiroacetals in general, metal based *N*-deacylation was deemed unsuitable (Scheme 9 and Table 6).

N-Deacylation using non-metal based reagents was next examined. Gratifyingly, protected purines **11g**, **11h** and **15f** were heated at 100–120 °C under microwave irradiation in a mixture of NEt_3, H_2O and MeOH[37] successfully affording the desired spiroacetal-nucleosides **11j**, **11k** and **15i** in 86–93% yield (Scheme 9 and Table 6).

No epimerisation of the C6′ spirocentre or the C2′/C8′ anomeric centre was observed during the desilylation and deacylation reactions. Similar to other spiroacetal analogues synthesised in this series, the structures of spiroacetal-nucleosides **11a–k** were confirmed by NMR analysis. Spiroacetal-nucleosides **11a–k** also adopted the bis-anomerically stabilised spiroacetal conformation with both the hydroxymethyl and basic substituents occupying equatorial positions on their respective tetrahydropyran rings.

Conclusion

In conclusion, the elaboration of a 6,6-spiroacetal ring system to incorporate a nucleoside unit at the anomeric position together with a synthetically useful hydroxymethyl group has been successfully accomplished. Given the importance of a nucleobase unit as a molecular handle recognised by nucleic acid processing enzymes, the assembly of a spiroacetal containing a nucleobase as reported herein, generates a novel series of spiroacetal-containing nucleosides. The knowledge gleaned in this synthetic study also provides momentum for future elaboration of 6,6-spiroacetals to incorporate other biologically active motifs.[22] In addition to the chemical diversity reflected by this series of spiroacetal hybrids, compounds prepared in this study can also be used as probes to screen for potential bioactivity in broad phenotypic assays.

Experimental

General

Experiments requiring anhydrous conditions were performed under a dry nitrogen atmosphere using flame-dried apparatus and standard techniques in handling air- and moisture-sensitive materials unless otherwise stated. Solvents used for reactions, extractions and chromatographic purifications were distilled (except for diethyl ether), unless otherwise stated. Commercial reagents were analytical grade or were purified by standard procedures prior to use.[38] Microwave reactions were conducted in sealed reaction vessels using a Discover® LabMate microwave synthesiser (CEM Corporation) at the temperature stated. Separation of mixtures was performed by flash chromatography using Kieselgel S 63–100 μm (Riedel-de-Hahn) silica gel with the indicated eluent or by PLC using Kieselgel 60 F_{254} (Merck) silica plates with the indicated eluent.

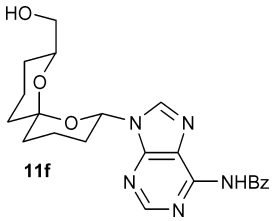
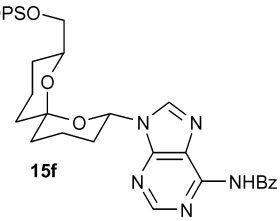
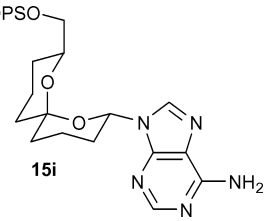
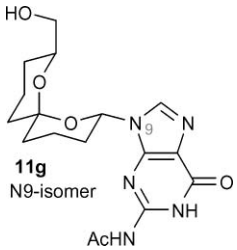
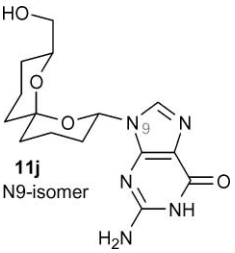
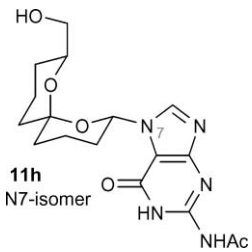
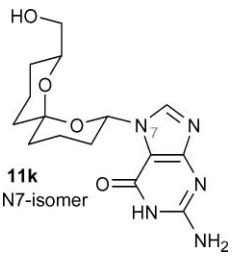
Synthesis of acetoxy-spiroacetal 10

(2*R**,6*S**,8*S**)-8-(*tert*-Butyldiphenylsilyloxymethyl)-2-acetoxy-1,7-dioxaspiro[5.5]undecane (10)

Method A: using ketone 13 as the starting material

A solution of ketone **13**[22] (100 mg, 167 μmol) and PPTS (8.39 mg, 33.4 μmol) in a 2 : 1 mixture of acetone–water (3.0 mL) was

Table 6 Summary of reagents and conditions used for the *N*-deacylation of protected purines **11f–h** and **15f** (Scheme 9)

Entry	*N*-Acylated nucleoside	Reagents and conditions	Product	Yield (%)
1	 **11f**	a	—	Complex mixture
2	 **15f**	b	 **15i**	90[a]
3	 **11g** N9-isomer	b	 **11j** N9-isomer	93
4	 **11h** N7-isomer	b	 **11k** N7-isomer	86

Reagents and conditions: (a) $ZnBr_2$, MeOH–$CHCl_3$, rt, 3 d; (b) aq. MeOH–NEt_3, microwave, 100–120 °C, 30 min. [a] Adenosine **15i** was then desilylated using HF·triethylamine. See Table 5 for reaction conditions.

heated to reflux. After 24 h, a saturated solution of $NaHCO_3$ (3 mL) and toluene (3 mL) were added and the aqueous phase was extracted with Et_2O (3 × 3 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude lactol as a pale yellow oil. This unstable lactol was used directly in the acetylation described below without further purification.

To a solution of crude lactol in anhydrous CH_2Cl_2 (1.5 mL) at room temperature was added DMAP (4.08 mg, 33.4 μmol), NEt_3 (23.3 μL, 167 μmol) and Ac_2O (13.3 μL, 134 μmmol). After 2 h, brine (2 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography using hexane–Et_2O–EtOAc (99 : 1 : 0, 99 : 0 : 1 to 97 : 0 : 3) yielded the *title compound* **10** (27.5 mg, 34% over 2 steps) as a white powder. Recrystallisation of acetoxy-spiroacetal **10** from hexane–CH_2Cl_2 afforded white prisms.

Method B: using ethoxy-spiroacetal 12 as the starting material

To a solution of ethoxy-spiroacetal **12** (485 mg, 1.04 mmol) in a 4 : 1 mixture of THF–water (18 mL) was added CSA monohydrate (104 mg, 414 μmol) and the mixture was stirred at 40 °C overnight. A saturated solution of $NaHCO_3$ (20 mL) and Et_2O (20 mL) were added and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to yield the lactol as a pale yellow oil. The unstable lactol was used directly in the acetylation described below without further purification.

To a solution of crude lactol in anhydrous CH_2Cl_2 (9.0 mL) at room temperature was added DMAP (25.3 mg, 207 μmol), NEt_3 (216 μL, 1.55 mmol) and Ac_2O (117 μL, 1.24 mmol). After 3 h, the mixture was filtered through a pad of silica and the eluent was concentrated *in vacuo*. Purification by flash chromatography using hexane–Et_2O–EtOAc (99 : 1 : 0, 99 : 0 : 1 to 97 : 0 : 3) yielded the

title compound **10** (298 mg, 58% over 2 steps) as a white powder. Recrystallisation of acetoxy-spiroacetal **10** from hexane–CH_2Cl_2 afforded white prisms.

General procedures for nucleosidation under Vorbrüggen conditions[24,25]

Method A: nucleosidation with pyrimidine bases

To a suspension of the pyrimidine base (1.2–2.0 equiv.) in HMDS (0.50–1.0 mL) under an atmosphere of argon was added ammonium sulfate (2 crystals) and the mixture was heated to reflux until the white solid dissolved. After 3–4 h, the mixture was concentrated *in vacuo* to afford a thick yellow oil. A solution of acetoxy-spiroacetal **10** in CH_2Cl_2 (1.0–1.1 mL) was transferred to the yellow oil *via* cannula. Freshly prepared TMSOTf solution (1.6–2.2 equiv., 0.70 mol L^{-1} in CH_2Cl_2) was then added dropwise. After 3 h, a solution of saturated $NaHCO_3$ (2 mL) and CH_2Cl_2 (2 mL) were added and the mixture was stirred for 15 min. The aqueous phase was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo.* Purification by flash chromatography using hexane–EtOAc as eluent yielded the spiroacetal nucleoside **15**.

Method B: nucleosidation with purine bases

A suspension of the purine base (1.3 equiv.) in a 1 : 4 : 5 mixture of *N*,*O*-bis(trimethylsilyl)acetimide–HMDS–toluene (1.0 mL) under an atmosphere of argon was heated to reflux until the white solid dissolved. After 2 h, the mixture was concentrated *in vacuo* to afford a thick yellow oil. A solution of acetoxy-spiroacetal **10** in CH_2Cl_2 (1.5 mL) was transferred to the yellow oil *via* cannula. Freshly prepared TIPSOTf solution (1.4 equiv., 0.52 mol L^{-1} in CH_2Cl_2) was then added dropwise. After 18 h, a saturated solution of $NaHCO_3$ (2 mL) and CH_2Cl_2 (2 mL) were added and the mixture stirred for 15 min. The aqueous phase was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo.* Purification by flash chromatography using hexane–EtOAc as eluent yielded the spiroacetal nucleoside **15**.

1-{(2′*S**,6′*S**,8′*S**)-8′-(*tert*-Butyldiphenylsilyloxymethyl)-1′,7′-dioxaspiro[5.5]undecan-2′-yl}-5-fluorocytidine (15a)

Method A. The *title compound* **15a** (6.10 mg, 22%) was prepared as a pale yellow oil from 5-fluorocytosine (12.4 mg, 97.0 μmol), acetoxy-spiroacetal **10** (24.0 mg, 49.7 μmol) and TMSOTf solution (159 μL, 111 μmol) using the general procedure (method A) described above. Purification was carried out by flash chromatography using hexane–EtOAc (19 : 1, 1 : 1 to 1 : 4) as eluent.

4-*N*-Acetyl-1-{(2′S*,6′S*,8′S*)-8′-(*tert*-butyldiphenylsilyloxymethyl)-1′,7′-dioxaspiro[5.5]undecan-2′-yl}cytidine (15b)

Method A. The *title compound* **15b** (14.3 mg, 46%) was prepared as a colourless oil from 4-*N*-acetylcytosine (9.86 mg, 64.4 μmol), acetoxy-spiroacetal **10** (25.9 mg, 53.7 μmmol) and TMSOTf solution (123 μL, 86.4 μmol) using the general procedure (method A) described above. Purification was carried out by flash chromatography using hexane–EtOAc (9 : 1 to 1 : 1) as eluent.

1-{(2′*S**,6′*S**,8′*S**)-8′-(*tert*-Butyldiphenylsilyloxymethyl)-1′,7′-dioxaspiro[5.5]undecan-2′-yl}thymidine (15c)

Method A. The *title compound* **15c** (10.5 mg, 45%) was prepared as a pale yellow oil from thymine (8.49 mg, 67.3 μmol), acetoxy-spiroacetal **10** (20.4 mg, 42.3 μmol) and TMSOTf solution (104 μL, 72.5 μmol) using the general procedure (method A) described above. Purification was carried out by flash chromatography using hexane–EtOAc (19 : 1, 9 : 1 to 4 : 1) as eluent.

1-{(2′*S**,6′*S**,8′*S**)-8′-(*tert*-Butyldiphenylsilyloxymethyl)-1′,7′-dioxaspiro[5.5]undecan-2′-yl}uridine (15d)

Method A. The *title compound* **15d** (7.50 mg, 36%) was prepared as a pale yellow powder from uracil (6.95 mg, 61.9 μmol), acetoxy-spiroacetal **10** (18.8 mg, 38.9 μmol) and TMSOTf solution (95.4 μL, 66.8 μmol) using the general procedure (method A) described above. Purification was carried out by flash chromatography using hexane–EtOAc (19 : 1 to 7 : 3) as eluent. Recrystallisation of uridine **15d** from hexane–CH_2Cl_2 afforded pale yellow needles.

1-{(2′*S**,6′*S**,8′*S**)-8′-(*tert*-Butyldiphenylsilyloxymethyl)-1′,7′-dioxaspiro[5.5]undecan-2′-yl}-5-fluorouridine (15e)

Method A. The *title compound* **15e** (4.00 mg, 19%) was prepared as a pale yellow oil from 5-fluorouracil (7.75 mg, 59.6 μmol), acetoxy-spiroacetal **10** (18.0 mg, 37.2 μmol) and TMSOTf solution (92.0 μL, 64.4 μmol) using the general procedure (method A) described above. Purification was carried out by flash chromatography using hexane–EtOAc (19 : 1, 4 : 1 to 7 : 3) as eluent.

6-*N*-Benzoyl-9-{(2′*S**,6′*S**,8′*S**)-8′-(*tert*-butyldiphenylsilyloxymethyl)-1′,7′-dioxaspiro[5.5]undecan-2′-yl}adenosine (15f)

Method B. The *title compound* **15f** (14.5 mg, 35%) was prepared as a pale yellow oil from 6-*N*-benzoyladenine (19.3 mg, 80.8 μmol), acetoxy-spiroacetal **10** (30.0 mg, 62.2 μmol) and TIPSOTf (167 μL, 86.9 μmol) using the general procedure (method B) described above. Purification was carried out by flash chromatography (twice) using hexane–EtOAc (19 : 1, 9 : 1 to 1 : 1) as eluent.

2-*N*-Acetyl-9-{(2′*S**,6′*S**,8′*S**)-8′-(*tert*-butyldiphenylsilyloxymethyl)-1′,7′-dioxaspiro[5.5]undecan-2′-yl}guanosine (15g) and (2*S**,6*S**,8*S**)-2-*N*-acetyl-7-{8′-(*tert*-butyldiphenylsilyloxymethyl)-1′,7′-dioxaspiro[5.5]undecan-2′-yl}guanosine (15h)

Method B. The *title N9-guanosine* **15g** (7.72 mg, 20%) and *N7-guanosine* **15h** (4.00 mg, 11%) were prepared as colourless oils from 2-*N*-acetylguanine (15.6 mg, 80.8 μmol), acetoxy-spiroacetal **10** (30.0 mg, 62.2 μmol) and TIPSOTf (167 μL, 87.1 μmol) using the general procedure (method B) described above. Purification was carried out by flash chromatography using hexane–EtOAc (19 : 1, 3 : 2, 1 : 4 to 0 : 1) as eluent followed by PLC using hexane–EtOAc (1 : 1) as eluent.

General procedures for deprotection of spiroacetal nucleosides 15

Method A: desilylation using 3HF·NEt_3[34]

A solution of TBDPS-protected nucleoside **15** and 3HF·NEt_3 (3.0–5.4 μL per 1.0 μmol) in anhydrous THF (300 μL–1.5 mL) under an atmosphere of argon was stirred at 40 °C for 24–48 h. A solution of saturated $NaHCO_3$ (2 mL) was added dropwise. The aqueous phase was extracted with EtOAc (6 × 3 mL) and the combined organic extracts were concentrated *in vacuo*. Purification by flash chromatography using the appropriate eluent yielded spiroacetal-nucleoside **11**.

Method B: deacylation using NEt_3–H_2O–MeOH and microwave irradiation[37]

A solution of acyl-protected purine nucleosides in a mixture of NEt_3–H_2O–MeOH was irradiated in a sealed tube at 100–120 °C under microwave irradiation. After 30 min, the reaction was concentrated *in vacuo* and a solution of saturated $NaHCO_3$ (0.5 mL) was added. The aqueous phase was extracted with EtOAc (5 × 3 mL) and the combined organic extracts were concentrated *in vacuo*. Purification by flash chromatography using the appropriate eluent yielded spiroacetal-nucleoside **11**.

1-{(2′*S**,6′*S**,8′*S**)-8′-(Hydroxymethyl)-1′,7′-dioxaspiro[5.5]undecan-2′-yl}-5-fluorocytidine (11a)

Method A. The *title compound* **11a** (2.40 mg, 77%) was prepared as a pale yellow oil from TBDPS-protected fluorocytidine **15a** (5.50 mg, 9.97 μmol) and 3HF·NEt_3 (30.0 μL) in THF (500 μL) using the general procedure (method A) described above. Purification was carried out by flash chromatography using hexane–EtOAc–MeOH (4 : 1 : 0, 0 : 1 : 0, 0 : 19 : 1 to 0 : 9 : 1) as eluent.

1-{(2′*S**,6′*S**,8′*S**)-8′-(Hydroxymethyl)-1′,7′-dioxaspiro[5.5]undecan-2′-yl}cytidine (11b)

Method A. The *title compound* **11b** (3.90 mg, 69%) was prepared as a pale yellow oil from TBDPS-protected cytidine **15b** (11.0 mg, 19.1 μmol) and 3HF·NEt_3 (104 μL) in THF (700 μL) using the general procedure (method A) described above. Purification was carried out by flash chromatography using hexane–EtOAc–MeOH (4 : 1 : 0, 0 : 1 : 0 to 0 : 9 : 1) as eluent.

1-{(2′*S**,6′*S**,8′*S**)-8′-(Hydroxymethyl)-1′,7′-dioxaspiro[5.5]undecan-2′-yl}thymidine (11c)

Method A. The *title compound* **11c** (3.30 mg, 79%) was prepared as a pale yellow oil from TBDPS-protected thymidine **15c** (7.40 mg, 13.5 μmol) and 3HF·NEt_3 (72.0 μL) in THF (300 μL) using the general procedure (method A) described above. Purification was carried out by flash chromatography using hexane–EtOAc (4 : 1 to 1 : 1) as eluent.

1-{(2′*S**,6′*S**,8′*S**)-8′-(Hydroxymethyl)-1′,7′-dioxaspiro[5.5]undecan-2′-yl}uridine (11d)

Method A. The *title compound* **11d** (2.90 mg, 73%) was prepared as a pale yellow oil from TBDPS-protected uridine **15d** (7.20 mg, 13.5 μmol) and 3HF·NEt_3 (40.5 μL) in THF (1.0 mL) using the general procedure (method A) described above. Purification was carried out by flash chromatography (twice) using hexane–EtOAc (4 : 1, 1 : 1 to 0 : 1) as eluent.

1-{(2′*S**,6′*S**,8′*S**)-8′-(Hydroxymethyl)-1′,7′-dioxaspiro[5.5]undecan-2′-yl}-5-fluorouridine (11e)

Method A. The *title compound* **11e** (1.00 mg, 65%) was prepared as a pale yellow oil from TBDPS-protected fluorouridine **15e** (2.70 mg, 4.89 μmmol) and 3HF·NEt_3 (25.0 μL) in THF (500 μL) using the general procedure (method A) described above. Purification was carried out by flash chromatography (twice) using hexane–EtOAc–MeOH (4 : 1 : 0, 0 : 1 : 0 to 0 : 19 : 1) as eluent.

6-*N*-Benzoyl-9-{(2′*S**,6′*S**,8′*S**)-8′-(hydroxymethyl)-1′,7′-dioxaspiro[5.5]undecan-2′-yl}adenosine (11f)

Method A. The *title compound* **11f** (6.50 mg, 85%) was prepared as a pale yellow oil from TBDPS-protected adenosine **15f** (12.0 mg, 18.1 μmol) and 3HF·NEt_3 (54.0 μL) in THF (1.5 mL) using the general procedure (method A) described above. Purification was carried out by flash chromatography (twice) using hexane–EtOAc–MeOH (4 : 1 : 0, 0 : 1 : 0 to 0 : 19 : 1) as eluent.

2-*N*-Acetyl-9-{(2′*S**,6′*S**,8′*S**)-8′-(hydroxymethyl)-1′,7′-dioxaspiro[5.5]undecan-2′-yl}guanosine (11g)

Method A. The *title compound* **11g** (2.80 mg, 91%) was prepared as a colourless oil from TBDPS-protected guanosine **15g** (5.00 mg, 8.12 μmol) and 3HF·NEt_3 (24.6 μL) in THF (750 μL) using the general procedure (method A) described above. Purification was carried out by flash chromatography using hexane–EtOAc–MeOH (4 : 1 : 0, 0 : 1 : 0 to 0 : 9 : 1) as eluent followed by PLC using EtOAc–MeOH (99 : 1) as eluent.

2-*N*-Acetyl-7-{(2′*S**,6′*S**,8′*S**)-8′-(hydroxymethyl)-1′,7′-dioxaspiro[5.5]undecan-2′-yl}guanosine (11h)

Method A. The *title compound* **11h** (2.00 mg, 82%) was prepared as a colourless oil from TBDPS-protected guanosine **15h** (4.00 mg, 6.50 μmol) and 3HF·NEt_3 (20.0 μL) in THF (750 μL) using the general procedure (method A) described above. Purification was carried out by flash chromatography using hexane–EtOAc–MeOH (1 : 1 : 0, 0 : 1 : 0 to 0 : 19 : 1) as eluent.

9-{(2′*S**,6′*S**,8′*S**)-8′-(*tert*-Butyldiphenylsilyloxymethyl)-1′,7′-dioxaspiro[5.5]undecan-2′-yl}adenosine (15i)

Method B. The *title compound* **15i** (8.50 mg, 90%) was prepared as a colourless solid from adenosine **15f** (11.2 mg, 16.9 μmol) in a 1 : 2 : 10 mixture of NEt_3–H_2O–MeOH (2.6 mL) using the general procedure (method B) described above. Purification was carried out by flash chromatography (twice) using hexane–EtOAc (4 : 1, 1 : 1 to 0 : 1) as eluent.

9-{(2′*S**,6′*S**,8′*S**)-8′-(Hydroxymethyl)-1′,7′-dioxaspiro[5.5]undecan-2′-yl}adenosine (11i)

Method A. The *title compound* **11i** (4.20 mg, 92%) was prepared as a colourless powder from TBDPS-protected adenosine **15i** (8.00 mg, 14.3 μmol) and 3HF·NEt_3 (42.9 μL) in THF

(1.5 mL) using the general procedure (method A) described above. Purification was carried out by flash chromatography using CH_2Cl_2–MeOH (99 : 1 to 9 : 1) as eluent.

9-{(2′*S**,6′*S**,8′*S**)-8′-(Hydroxymethyl)-1′,7′-dioxaspiro[5.5]undecan-2′-yl}guanosine (11j)

Method B. The *title compound* **11j** (2.90 mg, 93%) was prepared as a colourless oil from guanosine **11g** (3.50 mg, 9.27 μmol) in a 1 : 1 : 10 mixture of NEt_3–H_2O–MeOH (3.6 mL) using the general procedure (method B) described above. Purification was carried out by flash chromatography using CH_2Cl_2–MeOH (99 : 1, 19 : 1 to 9 : 1) as eluent.

7-{(2′*S**,6′*S**,8′*S**)-8′-(Hydroxymethyl)-1′,7′-dioxaspiro[5.5]undecan-2′-yl}guanosine (11k)

Method B. The *title compound* **11k** (1.30 mg, 86%) was prepared as a colourless oil from guanosine **11h** (1.70 mg, 4.50 μmol) in a 1 : 1 : 10 mixture of NEt_3–H_2O–MeOH (3.6 mL) using the general procedure (method B) described above. Purification was carried out by flash chromatography using CH_2Cl_2–MeOH (99 : 1, 19 : 1 to 9 : 1) as eluent.

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References

1 I. Paterson and E. A. Anderson, *Science*, 2005, **310**, 451–453.
2 J. C. Venter, et al., *Science*, 2001, **291**, 1304–1351.
3 G. Zinzalla, L.-G. Milroy and S. V. Ley, *Org. Biomol. Chem.*, 2006, **4**, 1977–2002.
4 R. I. Anegundi, V. G. Puranik and S. Hotha, *Org. Biomol. Chem.*, 2008, **6**, 779–786.
5 F. Perron and K. F. Albizati, *Chem. Rev.*, 1989, **89**, 1617–1661.
6 W. Francke and W. Kitching, *Curr. Org. Chem.*, 2001, **5**, 233–251.
7 *U.S. Pat.*, US 4547523, 1985; W. P. Cullen, W. D. Celmer, L. R. Chappel, L. H. Huang, M. T. Jefferson, M. Ishiguro, H. Maeda, S. Nishiyama, J. R. Oscarson, R. Shibakawa and J. Tone, *J. Ind. Microbiol.*, 1988, **2**, 349–357; N. R. Kotecha, S. V. Ley and S. Mantegani, *Synlett*, 1992, 395–399.
8 K. Tachibana, P. J. Scheuer, Y. Tsukitani, H. Kikuchi, D. Van Engen, J. Clardy, Y. Gopichand and F. J. Schmitz, *J. Am. Chem. Soc.*, 1981, **103**, 2469–2471; R. E. Honkanen and T. Golden, *Curr. Med. Chem.*, 2002, **9**, 2055–2075; A. B. Dounay and C. J. Forsyth, *Curr. Med. Chem.*, 2002, **9**, 1939–1980; X. C. Cheng, T. Kihara, H. Kusakabe, J. Magae, Y. Kobayashi, R. P. Fang, Z. F. Ni, Y. C. Shen, K. Ko, I. Yamaguchi and K. Isono, *J. Antibiot.*, 1987, **40**, 907–909; M. Ubukata, X.-C. Cheng, M. Isobe and K. Isono, *J. Chem. Soc., Perkin Trans. 1*, 1993, 617–624; H. Oikawa, *Curr. Med. Chem.*, 2002, **9**, 2033–2054.
9 S. B. Singh, D. L. Zink, B. Heimbach, O. Genilloud, A. Teran, K. C. Silverman, R. B. Lingham, P. Felock and D. J. Hazuda, *Org. Lett.*, 2002, **4**, 1123–1126.
10 G. R. Pettit, Z. A. Cichacz, F. Gao, C. L. Herald, M. R. Boyd, J. M. Schmidt and J. N. A. Hooper, *J. Org. Chem.*, 1993, **58**, 1302–1304; J. S. Guo, K. J. Duffy, K. L. Stevens, P. I. Dalko, R. M. Roth, M. M. Hayward and Y. Kishi, *Angew. Chem., Int. Ed.*, 1998, **37**, 187–192; M. M. Hayward, R. M. Roth, K. J. Duffy, P. I. Dalko, K. L. Stevens, J. S. Guo and Y. Kishi, *Angew. Chem., Int. Ed.*, 1998, **37**, 192–196.
11 F. M. Uckun, *Curr. Pharm. Des.*, 2001, **7**, 1627–1639; F. M. Uckun, C. Mao, A. O. Vassilev, H. Huang and S.-T. Jan, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 541–545; H. Huang, C. Mao, S.-T. Jan and F. M. Uckun, *Tetrahedron Lett.*, 2000, **41**, 1699–1702; S. Mitsuhashi, H. Shima, T. Kawamura, K. Kikuchi, M. Oikawa, A. Ichihara and H. Oikawa, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2007–2012.
12 O. Barun, K. Kumar, S. Sommer, A. Langerak, T. U. Mayer, O. Müller and H. Waldmann, *Eur. J. Org. Chem.*, 2005, 4773–4788.
13 A. A. Birkbeck, S. V. Ley and J. C. Prodger, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 2637–2642.
14 B. A. Kulkarni, G. P. Roth, E. Lobkovsky and J. A. Porco, Jr., *J. Comb. Chem.*, 2002, **4**, 56–72.
15 R. G. Finch, D. Greenwood, S. R. Norrby and R. J. Whitney, *Antibiotics and Chemotherapy: Anti-Infective Agents and their Use in Therapy*, Churchill Livingstone, Edinburgh, 8th edn., 2003; H. P. Rang, M. M. Dale, and J. M. Ritter, *Pharmacology*, Churchill Livingstone, Edinburgh, 4th edn., 1999.
16 R. Challand and R. J. Young, *Antiviral Chemotherapy*, Oxford University Press, Oxford, 1997.
17 J. E. Robinson and M. A. Brimble, *Chem. Commun.*, 2005, 1560–1562; K. Meilert and M. A. Brimble, *Org. Lett.*, 2005, **7**, 3497–3500; K. Meilert and M. A. Brimble, *Org. Biomol. Chem.*, 2006, **4**, 2184–2192; R. Halim, M. A. Brimble and J. Merten, *Org. Biomol. Chem.*, 2006, **4**, 1387–1399; M. A. Brimble, C. L. Flowers, M. Trzoss and K. Y. Tsang, *Tetrahedron*, 2006, **62**, 5883–5896; M. A. Brimble and C. J. Bryant, *Chem. Commun.*, 2006, 4506–4508; M. A. Brimble and C. V. Burgess, *Synthesis*, 2007, 754–760; M. A. Brimble and C. J. Bryant, *Org. Biomol. Chem.*, 2007, **5**, 2858–2866; J. E. Robinson and M. A. Brimble, *Org. Biomol. Chem.*, 2007, **5**, 2572–2582; K. Y. Tsang and M. A. Brimble, *Tetrahedron*, 2007, **63**, 6015–6034.
18 M. Nakajima, K. Itoi, Y. Takamatsu, T. Kinoshita, T. Okazaki, K. Kawakubo, M. Shindo, T. Honma, M. Tohjigamori and T. Haneishi, *J. Antibiot.*, 1991, **44**, 293–300; *Germany Pat.*, DE 4129616 A1, 1992; *Japan Pat.*, JP 04222589 A, 1992.
19 J. Balzarini, M.-J. Pérez-Pérez, A. San-Félix, D. Schols, C.-F. Perno, A.-M. Vandamme, M.-J. Camarasa and E. De Clercq, *Proc. Natl. Acad. Sci. U. S. A.*, 1992, **89**, 4392–4396.
20 B. R. Babu, L. Keinicke, M. Petersen, C. Nielsen and J. Wengel, *Org. Biomol. Chem.*, 2003, **1**, 3514–3526.
21 L. A. Paquette, *Aust. J. Chem.*, 2004, **57**, 7–17 and references cited therein; S. Dong and L. A. Paquette, *J. Org. Chem.*, 2005, **70**, 1580–1596 and references cited therein; R. Hartung and L. A. Paquette, *J. Org. Chem.*, 2005, **70**, 1597–1604; R. E. Hartung and L. A. Paquette, *Synthesis*, 2005, 3209–3218; L. A. Paquette and S. Dong, *J. Org. Chem.*, 2005, **70**, 5655–5664; R. E. Hartung and L. A. Paquette, *Heterocycles*, 2006, **67**, 75–78; S. Dong and L. A. Paquette, *J. Org. Chem.*, 2006, **71**, 1647–1652.
22 K. W. Choi and M. A. Brimble, *Org. Biomol. Chem.*, 2008, **6**, 3518–3526.
23 R. J. K. Taylor, K. Wiggins and D. H. Robinson, *Synthesis*, 1990, 589–590.
24 H. Vorbrüggen, K. Krolikiewicz and B. Bennua, *Chem. Ber.*, 1981, **114**, 1234–1255.
25 H. Vorbrüggen and C. Ruh-Pohlenz, *Org. React.*, 2000, **55**, 1–630; H. Vorbrüggen and C. Ruh-Pohlenz, *Handbook of Nucleoside Synthesis*, John Wiley & Sons, Inc., Chichester, UK, 2001.
26 M. A. Brimble, J. E. Robinson, K. W. Choi and P. D. Woodgate, *Aust. J. Chem.*, 2004, **57**, 665–668.
27 K. T. Mead and R. Zemribo, *Synlett*, 1996, 1063–1064.
28 R. Zemribo and K. T. Mead, *Tetrahedron Lett.*, 1998, **39**, 3891–3894; R. Zemribo and K. T. Mead, *Tetrahedron Lett.*, 1998, **39**, 3895–3898; M. A. Brimble, F. A. Fares and P. Turner, *J. Chem. Soc., Perkin Trans. 1*, 1998, 677–684.
29 R. Ben Othman, T. Bousquet, A. Fousse, M. Othman and V. Dalla, *Org. Lett.*, 2005, **7**, 2825–2828.
30 K. Izawa and H. Shiragami, *Pure Appl. Chem.*, 1998, **70**, 313–318.
31 K. W. Choi, M. A. Brimble and T. Groutso, *Acta Crystallogr., Sect. E: Struct. Rep. Online*, 2008, **E64**, O715.
32 P. R. Allen, M. A. Brimble and H. Prabaharan, *J. Chem. Soc., Perkin Trans. 1*, 2001, 379–389; M. A. Brimble, *Molecules*, 2004, **9**, 394–404; G. J. McGarvey and M. W. Stepanian, *Tetrahedron Lett.*, 1996, **37**, 5461–5464; G. J. McGarvey, M. W. Stepanian, A. R. Bressette and J. F. Ellena, *Tetrahedron Lett.*, 1996, **37**, 5465–5468.

33 M. Böhringer, H.-J. Roth, J. Hunziker, M. Göbel, R. Krishnan, A. Giger, B. Schweizer, J. Schreiber, C. Leumann and A. Eschenmoser, *Helv. Chim. Acta*, 1992, **75**, 1416–1477; L. A. Paquette, C. K. Seekamp, A. L. Kahane, D. G. Hilmey and J. Gallucci, *J. Org. Chem.*, 2004, **69**, 7442–7447.
34 M. C. Pirrung, S. W. Shuey, D. C. Lever and L. Fallon, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 1345–1346; D. K. Ress, S. N. Baytas, Q. Wang, E. M. Munoz, K. Tokuzoki, H. Tomiyama and R. J. Linhardt, *J. Org. Chem.*, 2005, **70**, 8197–8200.
35 G. Bartoli, M. Bosco, E. Marcantoni, L. Sambri and E. Torregiani, *Synlett*, 1998, 209–211.
36 R. Kierzek, H. Ito, R. Bhatt and K. Itakura, *Tetrahedron Lett.*, 1981, **22**, 3761–3764.
37 E. Söderberg, J. Westman and S. Oscarson, *J. Carbohydr. Chem.*, 2001, **20**, 397–410.
38 W. L. F. Armarego and D. D. Perrin, *Purification of Laboratory Chemicals*, Pergamon, Oxford, UK, 4th edn., 1997.

