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Synthesis, conformation and antiviral activity of nucleoside analogues with the (2-hydroxy-1-phenylethoxy)methyl glycone—a family of nucleoside analogues related to d4T and aciclovir

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A complete family of acyclic nucleoside analogues has been obtained by combining the (2-hydroxy-1-phenylethoxy)methyl glycone with the nucleoside bases adenine, guanine, cytosine, thymine and uracil. In each case both optical antipodes have been prepared in enantiomerically pure form from styrene *via* asymmetric dihydroxylation. The conformation of the uracil and adenine derivatives has been compared by comprehensive calculations using the PM3 method with the conformation of 2′,3′-didehydro-2′,3′-dideoxyuridine (d4U) and the analogous 3-hydroxymethyl-1,3-dihydrobenzo[*c*]furan nucleoside (bfU). Some antiviral activity has been observed.

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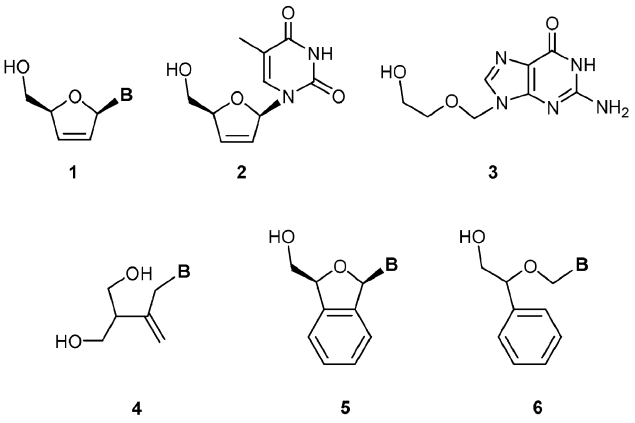
Introduction

The realisation that nucleoside analogues have chemotherapeutic potential as antiviral agents has led to prodigious chemical effort directed to the synthesis of a very large number of structural variations to both the heterocyclic base and the sugar moiety of regular nucleosides. Although the discovery of new anti-HIV chemotherapeutic agents has been of greatest interest,[1] compounds with activity against many other viral infections have also been sought and found.[2]

Of particular importance has been the discovery of antiviral activity in 2′,3′-didehydro-2′,3′-dideoxynucleosides (d4Ns, **1**) especially the thymidine derivative (d4T, **2**),[3] now a well known agent (stavudine)[4] employed in protocols for the clinical treatment of AIDS through inhibition of reverse transcriptase. This clinical advance has in turn generated intense effort to design further structural variants of the d4N template and recent examples include synthetic schemes to replace the ring oxygen with carbon,[5] to insert a 2′- or 3′-fluorine substituent,[6] to move the 4′-substituent to the 3′ position,[7] to change the position of the double bond,[8] and to change the ring size.[9] Although the full range of standard nucleoside bases has not been employed in all cases, several interesting examples of antiviral activity have been found in this way. A parallel development in the synthesis of nucleoside analogues with therapeutic potential has been the replacement of the sugar ring of the nucleoside with an acyclic group. This has followed from the highly successful application of aciclovir (**3**) (and the valine ester prodrug valaciclovir) to the treatment of herpes simplex virus (HSV) infections and related infections produced by the herpes family of viruses.[10,11] Recent work includes the synthesis of nucleoside bases with a variety of acyclic chains attached at the glycone position.[12–17] These novel acyclic nucleoside analogues may incorporate an element of unsaturation in the side chains as exemplified by the nucleoside family **4**.[13] The presence of an acyclic glycone can lead to increased diversity of function (for example as an oligonucleotide conjugate[16] or a probe of enzyme affinity[17]) and a widening of the activity range (adefovir, 9-{2-[phosphonomethoxy]ethyl}adenine, has become crucial to the management of hepatitis B associated with organ transplantation).[18]



B = nucleoside base U, T, C, A, G

As part of a continuing effort to study the structure–activity relationship of antiviral nucleoside analogues, we have reported recently[19–21] a number of routes to another variant of the d4N template in which the glycone double bond is incorporated into a benzene ring, giving a derivative of the dihydrobenzo[*c*]furan system. The presence of the benzene ring in this family of 3-hydroxymethyl-1,3-dihydrobenzo[*c*]furan nucleosides (bfNs, **5**) increases the lipophilicity relative to the d4N family but there is also a significant increase in molecular size and rigidity. A recent study[22] of the anti-HIV activity of the thymine member of the family of bfNs (**5**, B = T) has found that this compound and the analogous 5′-triphosphate were inactive as inhibitors of HIV-1 reverse transcriptase. This lack of activity is likely to be due to the steric effect of the rigid benzene ring, which reduces the ability of the molecule to access the enzyme binding site. We now report the preparation of another complete family of ten nucleosides based on the (2-hydroxy-1-phenylethoxy)methyl glycone. This family of

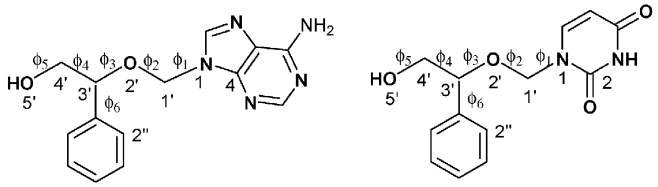
acyclic nucleosides **6** can be regarded as *seco*-derivatives of the bfNs which implies that they will show the same increased lipophilicity relative to the d4Ns but with a large increase in molecular flexibility. More importantly, the nucleoside family **6** is obviously closely related to families **1** and **5** and provides an interesting link between d4T **2** and aciclovir **3**.

Although many variants of the (2-hydroxyethoxy)methyl glycone present in **3** have been synthesised, there are few reports of nucleosides incorporating the corresponding phenyl substituted glycone. Pan *et al.*[23] obtained some racemic pyrimidine derivatives and this system was included in a German patent[24] but no chiral strategies were proposed. Some of our preliminary studies have also been reported elsewhere.[25]

Results and discussion

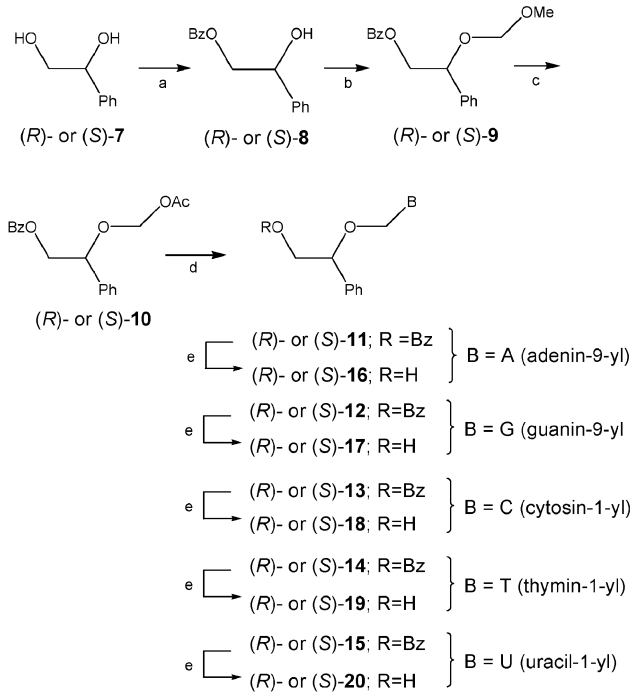
Synthesis

The family of nucleosides **6** was obtained by the five step sequence of reactions shown in Scheme 1. The starting phenylethanediols, (*R*)-**7** and (*S*)-**7**, were obtained in 99% yield and 97% ee by asymmetric dihydroxylation of styrene using the available reagents AD-mix β and AD-mix α, respectively.[26]



16 **20**

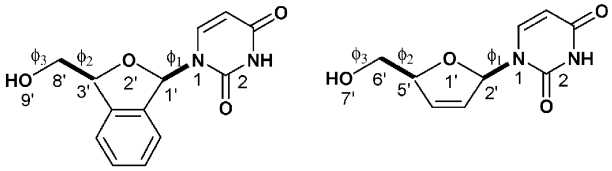
With the primary hydroxyl group protected as the benzoate (**8**), the first attempt to derivatise the secondary hydroxyl group involved conversion to a chloromethyl ether[23] with paraformaldehyde and dry hydrogen chloride in methylene chloride. This reaction proceeds in poor yield and was abandoned in favour of the high yield conversion to the methoxymethyl ether



Scheme 1 a: BzCl, pyridine; b: dimethoxymethane, P_2O_5, chloroform; c: acetic anhydride, $BF_3 \cdot Et_2O$; d: silylated base, dibenzo-18-crown-6-ether, KI, acetonitrile, toluene; e: NH_3 in MeOH.

9 by treatment with dimethoxymethane and P_2O_5 in chloroform. To promote better glycosidation the methoxy/acetyl exchange was accomplished with boron trifluoride–diethyl ether in acetic anhydride at 4 °C to give the corresponding acetate **10** in 89% yield.

The benzoylated nucleosides **11–15** were obtained in 70–98% yield by application of standard Vorbruggen chemistry (condensation with the silylated purine or pyrimidine base in anhydrous acetonitrile and toluene using dibenzo-18-crown-6-ether in the presence of KI for phase transfer catalysis). The purine bases reacted to give the *N*-9 isomers **11** and **12** with no evidence for the formation of the analogous *N*-7 isomers. Similarly the pyrimidine derivatives were obtained only as the *N*-1 isomers **13–15**. The benzoyl groups were removed and the nucleoside analogues **16–20** were isolated in satisfactory yields. The complete sequence was carried through starting from both the (*R*)- and the (*S*)-diol (**7**). The retention of chiral integrity was confirmed for the acetates (*R*)-**10** and (*S*)-**10** by NMR spectroscopy using the europium chiral shift reagent Eu(D-3-trifluoroacetylcamphorate)$_3$ and for the nucleoside analogues **11–15** by chiral chromatography on a variety of columns.[27] In most cases the enantiomeric purity was 99% or better.



21 **22**

Molecular modelling

In order to investigate the shape and flexibility of the nucleoside analogues in series **6**, especially when compared to both the bfN series **5** and the d4N series **1**, detailed calculations were made at the semi-empirical level for each system. All calculations were carried out using the PM3 semi-empirical method in the MOPAC 97 package as implemented in the Chem3D Ultra (v. 5.0 or v. 6.0) program.[28] The PM3 method has been widely used for carbohydrate and nucleoside calculations.[29] Individual conformational minima were established by repeated optimisation from at least six deviating conformations, randomly selected, using the standard MOPAC convergence criterion and convergence was finally confirmed by a calculation at 100-fold increase in SCF precision. Every combination of rotatable bonds was investigated in this way using the appropriate twofold or threefold rotational potential. The values of the heat of formation for individual conformations (ΔH_f) are reproducible within ±0.01 kJ mol^{-1}.

Although the thymine derivative d4T is the most active compound in the d4N family, the present comparative analysis was carried out on the analogous uracil, d4U (**22**) and the corresponding uracil derivatives of the other two systems **20** and **21** since the presence of a methyl group in the pyrimidin-2,4-dione ring has no effect on the relative energy (ΔH_f) of individual conformers corresponding to changes in the rest of the molecule. Unfortunately the numbering is different in the conformationally mobile part of these derivatives and, for convenience, this numbering is shown in structures **16**, **20–22** together with the labelling of the torsion angles. Where a threefold rotational potential applies the conformation is described by the conventional labels *t*, g^+ or g^- for the variable dihedral angles (although individual angles can deviate by 20° or more from the ideal value) and the overall molecular conformation is described by a suitable combination of these labels, one for each rotatable bond as defined below. For

Table 1 Relative energies, populations and selected geometrical parameters for six conformers of **21**

Conformer	ϕ_2[a] (°)	ϕ_3[b] (°)	Relative ΔH_f (kJ mol^{-1})	Relative % population[c]	Separation of N1 and C8′ (Å)	Separation of H6 and H8′ (Å)
g^+g^-	75	−61	0.0	67	4.0	1.73
$t\,g^+$	172	52	3.8	14	4.0	1.74
g^+g^+	65	54	5.3	8	4.0	1.73
$t\,g^-$	172	−63	6.2	5	3.9	1.76
g^-g^-	−75	−66	7.6	3	4.0	1.84[d]
g^-g^+	−76	54	8.1	2	4.3	1.77[e]

[a] Angle O2′C3′C8′O9. [b] Angle C3′C8′O9′H9′. [c] Based on all nine conformers. [d] Separation of N1 and O9′. [e] Separation of H6 and H5′.

compound **20** a more subtle labelling is required and that is indicated below.

Conformational analysis of (1*R*,3*S*)-1-(3-hydroxymethyl-1,3-dihydrobenzo[*c*]furan-1-yl)uracil (21)[30]

The uracil ring is expected to show a twofold rotational potential with angle C2N1C1′O2′ (ϕ_1) around +60° or −120°. The *anti* orientation, $\phi_1 \sim -120°$, was favoured by 16–17 kJ mol^{-1} for all conformations so the *syn* conformation was not considered further. Angle ϕ_1 is −119° in the lowest energy conformation (the g^+g^- in Table 1) and in the range −100° to −121° in the other populated forms. There are nine possible rotamers for **21** corresponding to rotation of the CH_2OH moiety and variations in angles O2′C3′C8′O9′ (ϕ_2) and C3′C8′O9′H9′ (ϕ_3). A full geometry optimisation was achieved in each case and details for the six significant conformers are given in Table 1. In all conformations the average deviation from a plane for the nine ring atoms of the benzo[*c*]-furan ring was in the range 0.013–0.028 Å. This is a negligible deviation, *i.e.* in every conformation the bicyclic dihydrobenzo[*c*]furan was essentially planar. The uracil ring was also planar, as expected, and these two ring planes are approximately orthogonal with the line of intersection lying between C3′ and C3′a.

Of the six conformations with a population greater than 1% (Table 1) the g^+g^- form (labels correspond to ϕ_2 then ϕ_3) clearly predominates, due in part to the weak H-bond which is formed with the ring oxygen (H9′···O2′ separation is 2.8 Å). The shape of the mobile part of the molecule varies very little between the main conformers as shown (Table 1) by the separation between N1 and C8′, the two substituent atoms attached to the dihydrofuran ring, and by the magnitude of the closest non-bonded contact (usually H6···H8′).

Conformational analysis of (2*R*,5*S*)-1-(5-hydroxymethyl-2,5-dihydrofuran-2-yl)uracil (22)[31]

Compound **22** is the member of the d4N family analogous to the bfU species **21**. The uracil ring again shows a twofold rotational potential with the *anti* orientation strongly favoured by about 18 kJ mol^{-1}. The nine possible conformations for **22** were fully optimised for variations in angles O1′C5′C6′O7′ (ϕ_2) and C5′C6′O7′H7′ (ϕ_3) and details of the five conformers with a population greater than 1% are given in Table 2. The average deviation from a plane for the ring atoms of the dihydrofuran ring is less than 0.01 Å. The uracil ring is planar, and these two ring planes are approximately orthogonal, with the line of intersection lying between C4′ and C5′. Although there is a slight reordering of the populations of the minor rotamers, the main species is again the g^+g^- form, with a virtually identical geometrical relationship between the ring substituents as that observed in the bfU analogue **21**. The very strong similarity of the dominant conformation for the d4U and bfU species is confirmed by the models in Fig. 1.

Conformational analysis of 1-[(2-hydroxy-1-phenylethoxy)methyl]uracil (20)

Although there are six rotatable bonds in compound **20**, a full analysis of the conformational space was undertaken, to investigate not only the stable minima but also the overall flexibility of this acyclic nucleoside analogue. Around two thousand individual minimisations were undertaken including some preliminary conformational calculations on model compounds. The conformation around the N1–C1′ bond linking the uracil ring to the acyclic side chain in compound **20** is described by a twofold rotational potential. The C1′O2′ bond is approximately orthogonal to the uracil ring plane in both orientations of the ring and hence the two conformations of the dihedral angle C2N1C1′O2′ are labelled as o^+ ($\phi_1 \sim +90°$) and o^- ($\phi_1 \sim -90°$). The position of the actual minimum depends on the conformation of the rest of the molecule and can deviate in some cases towards the position where one or other of the H1′ protons is eclipsed by the ring.

The conformation around the ether oxygen varied markedly but, in the main, the ether linkages could each be treated as a threefold potential with minima in the *trans* (*t*) and both orthogonal positions (o^+ and o^-). The *gauche* positions were inaccessible except for g^+ for ϕ_3. Thus, over the set of conformations, angle N1C1′O2′C3′ falls in three ranges, *trans* (*t*) ($\phi_2 = -156°$ to −167°), orthogonal (o^+) ($\phi_2 = 84°$ to 103°) and o^- ($\phi_2 = -90°$ to −110°). Angle C1′O2′C3′C4′ falls in ranges *t* ($\phi_3 = -162°$ to −174°), g^+ ($\phi_3 = 54°$ to 80°), o^-($\phi_3 = -78°$ to −105°). In a few cases ϕ_2 and ϕ_3 are in an intermediate range (123° to 135°) labelled as *anticlinal* (*a*). The remaining two dihedral angles in the side chain (ϕ_4 = O2′C3′C4′O5′ and ϕ_5 = C3′C4′O5′H5′) are labelled as g^+, g^- or *t*, although

Table 2 Relative energies, populations and selected geometrical parameters for five conformers of **22**

Conformer	ϕ_2[a] (°)	ϕ_3[b] (°)	Relative ΔH_f (kJ mol^{-1})	Relative % population[c]	Separation of N1 and C6′ (Å)	Separation of H6 and H6′ (Å)
g^+g^-	75	−60	0.0	65	4.0	1.73
$t\,g^-$	174	−67	4.2	12	3.9	1.75
$t\,g^+$	170	62	4.8	9	4.0	1.74
g^+g^+	66	54	5.3	7	4.0	1.73
g^-g^+	−77	56	6.2	5	4.2	1.77

[a] Angle O1′C5′C6′O7′. [b] Angle C5′C6′O7′H7′. [c] Based on all nine conformers.

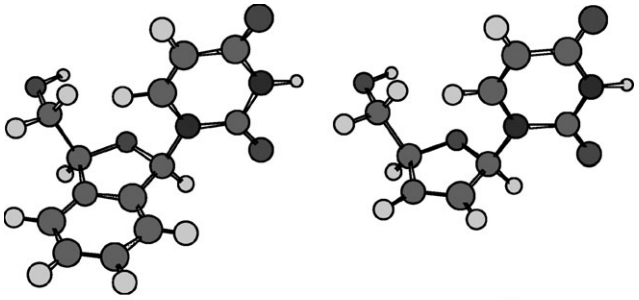


Fig. 1 The *anti*-g^+g^- (global minimum) conformations of compound **21** and compound **22**.

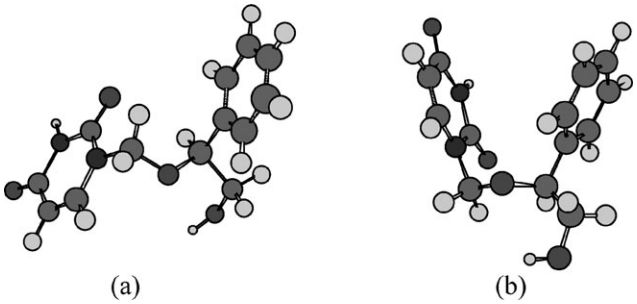


Fig. 2 The $o^-o^+t\ g^+g^-$ (global minimum) conformation (a) and the $o^+o^-a^-g^+g^-$ conformation (b) of compound (*S*)-**20**.

values can deviate by ±20° from the normal values of a staggered chain.

The conformation of the phenyl group was generally close to the position where the ring plane bisected the O2′C3′C4′ angle *i.e.* the C3′–H3′ bond was close to the benzene ring plane.[32] (The orthogonal orientation for this bond was also explored). In a few cases, for both the uracil and phenyl rings, a second minimum of similar energy was found corresponding to *ca.* 20° rotation with respect to the primary conformation. These additional forms are ignored since the overall molecular shape is little affected.

There are 162 notional conformations for the combination of dihedral angles detailed above for compound **20** but some of these are impossibly crowded and are so unstable the minimisation reverts to another form. About 140 stable minima were found and of these 18 had a relative ΔH_f of 5 kJ mol^{-1} or less, corresponding to a relative population of 1% or more. Details of the ten conformations with the lowest energy are given in Table 3. It is clear that compound **20** has great flexibility and the global minimum is not as highly populated as is the case for the rigid compounds **21** and **22**.

At the global minimum compound **20** has the $o^-o^+t\ g^+g^-$ conformation (labels in the order of the torsion angles ϕ_1 to ϕ_5) which has the shape shown in Fig. 2(a). The two aromatic rings lie in approximately parallel planes bridged by the ether oxygen. The next lowest energy conformation (Table 3) has a very similar overall shape and the third conformation is also similar but with the uracil ring reversed. However this extended linear shape is not the only available form since the fourth entry in the table is a $o^+o^-a^-g^+g^-$ conformation which has no *trans* linkages and the shape shown in Fig. 2(b). In this case the aromatic rings are facing and the reactive site is fully exposed at the bottom of the V-shaped molecule. A range of molecular shapes between these two extreme forms is found among the lower population conformers. This diversity of molecular shape over a large number of conformers confirms that compound **20** is extremely flexible and able to adopt a range of conformations of similar energy. Thus this family of nucleoside analogues is of interest for potential antiviral activity.

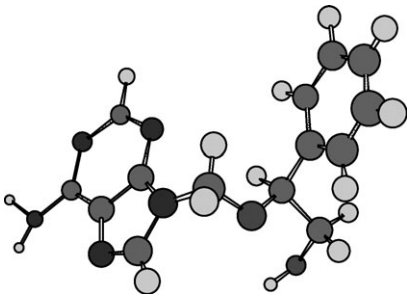


Fig. 3 The $o^-o^+t\ g^+g^-$ (global minimum) conformation of compound (*S*)-**16**.

Conformational analysis of 9-[(2-hydroxy-1-phenylethoxy)methyl]adenine (16)

The adenine analogue **16** was also investigated over the range of conformations which had a significant population in the uracil derivative. Details of the five lowest energy forms are given in Table 4. The global minimum conformation for the adenine derivative (Fig. 3) is virtually identical to that for the uracil derivative. Apart from a slight reordering of energies, the five lowest energy forms are the same in both the uracil and adenine derivatives (**20** and **16**, respectively). This suggests that the whole class of acyclic nucleoside of type **6** is likely to show the increased flexibility required for potential antiviral activity.

Table 3 Relative energies, populations and selected geometrical parameters for the ten most stable conformers of **20**

Conformer[a]	ϕ_1[b] (°)	ϕ_2[c] (°)	ϕ_3[d] (°)	ϕ_4[e] (°)	ϕ_5[f] (°)	ϕ_6[g] (°)	Relative ΔH_f (kJ mol^{-1})	Relative % population[h]
$o^-o^+t\ g^+g^-$	−96	97	−169	74	−66	−4	0	20
$o^-o^+t\ t\ g^+$	−97	95	−168	163	59	19	1.7	10
$o^+o^+t\ g^+g^-$	96	94	−168	73	−70	−11	1.8	9
$o^+o^-a^-g^+g^-$	102	−93	−134	71	−66	−11	2.7	7
$o^+t\ g^+g^+g^-$	80	−156	57	76	−72	8	2.7	6
$o^-o^+t\ g^+g^+$	−94	99	−164	77	63	1	2.9	6
$o^+o^-g^-g^+g^+$	96	−95	−89	76	62	−6	3.1	6
$o^-a^+g^-g^+g^-$	−82	142	−93	81	−66	−8	3.3	5
$a^+a^-g^+g^+g^+$	112	−109	64	56	59	1	3.8	4
$o^+o^-g^-g^-g^-$	94	−98	−78	−40	−45	−5	3.9	4

[a] The conformational labels are in the order of the dihedral angles ϕ_1 through to ϕ_5. The symbols *o* and *a* mean orthogonal and *anticlinal*, respectively. [b] Angle C2N1C1′O2′. [c] Angle N1C1′O2′C3′. [d] Angle C1′O2′C3′C4′. [e] Angle O2′C3′C4′O5′. [f] Angle C3′C4′O5′H5′. [g] Angle H3′C3′C1″C2″. [h] Based on all conformers with a population >1%.

Table 4 Relative energies, populations and selected geometrical parameters for the five most stable conformers of **16**

Conformer[a]	ϕ_1[b] (°)	ϕ_2[c] (°)	ϕ_3[d] (°)	ϕ_4[e] (°)	ϕ_5[f] (°)	ϕ_6[g] (°)	Relative ΔH_f (kJ mol^{-1})	Relative % population[h]
$o^-o^+t\ g^+g^-$	−102	82	−175	75	−66	−5	0	30
$o^+o^+t\ g^+g^-$	85	93	−169	76	−64	−6	2.1	13
$o^-o^+t\ t\ g^+$	−102	92	−167	170	58	−6	2.5	11
$a^+o^-a^-g^+g^-$	113	−93	−140	72	−66	−11	3.2	9
$a^+a^-g^+g^+g^-$	118	−114	67	72	−62	2	3.4	8

[a] The conformational labels are in the order of the dihedral angles ϕ_1 through to ϕ_5. The symbols *o* and *a* mean orthogonal and *anticlinal*, respectively. [b] Angle C4N1C1′O2′. [c] Angle N1C1′O2′C3′. [d] Angle C1′O2′C3′C4′. [e] Angle O2′C3′C4′O5′. [f] Angle C3′C4′O5′H5′. [g] Angle H3′C3′C1″C2″. [h] Based on all conformers with a population >1%.

Biological results

The set of twenty compounds **11–20**, comprising each enantiomer of the five different nucleosides with or without benzoyl protection, was tested against a wide range of viruses using three different cell lines.

Using HEL cell cultures antiviral activity was examined for herpes simplex virus type 1 (HSV-1 KOS) and type 2 (HSV-2 G), an aciclovir resistant strain (HSV-1 ACV^r), vaccinia virus (VV) and vesicular stomatitis virus (VSV). Four established antiviral compounds were used for comparison, namely 2-(2-bromovinyl)deoxyuridine (BVDU), 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (ribavirin, RB), aciclovir **3** (ACV) and 9-[2-hydroxy-1-(hydroxymethyl)ethoxymethyl]guanine (ganciclovir, GCV). Activity was determined as the minimum inhibitory concentration (mic), the concentration required to reduce virus induced cytopathogenicity by 50%.

None of compounds **11–20** had activity approaching that of ACV and GCV against HSV-1 KOS and HSV-2 G. However, weak but significant antiherpes activity was observed for the adenine derivative (*S*)-**11** (mic 16 μg ml^{-1}) against HSV-1 KOS. It is notable that there is a clear dependence on substrate stereochemistry because the activity of the other stereoisomer (*R*)-**11** is less (mic >80 μg ml^{-1}) and similar to that of most other compounds in the set. The only other compound with some activity was the cytosine derivative (*R*)-**18** (mic 48 μg ml^{-1}), where the stereochemical effect is reversed [(*S*)-**18** has mic >80 μg ml^{-1}].

Stereochemical discrimination is also evident in the activity of the benzoylated adenine derivatives against HSV-1 ACV^r, VV and VSV although exact mic values were not determined [(*S*)-**11** mic >16 μg ml^{-1} and (*R*)-**11** >80 μg ml^{-1}]. It is interesting that the weak activity of (*S*)-**11** against VSV is probably significantly higher than that of any of the reference antivirals.

Using HeLa cell cultures the antiviral activities of **11–20** were determined for VSV, Coxsackie B4 virus (CB4V), and respiratory syncytial virus (RSV). For these screens the reference antiviral compounds were BDVU, RB and (*S*)-9-(2,3-dihydroxypropyl)adenine [(*S*)-DHPA].

None of compounds **11–20** had activity approaching that of RB against VSV, CB4V and RSV but several of the benzoylated compounds were slightly more active than BVDU or (*S*)-DHPA. Furthermore this mild activity again showed a clear dependence on the stereochemistry of the tested compound. Thus the adenine derivative (*S*)-**11** and the uracil derivative (*S*)-**15** showed mild activity against VSV, CB4V and RSV, whereas the other enantiomers (*R*)-**11** and (*R*)-**15** were inactive (mic >400 μg ml^{-1}).

Using Vero cell cultures the activity was also investigated against parainfluenza-3 virus, reovirus-1, Sindbis virus, Coxsackie B4 virus and Punta Toro virus. All of compounds **11–20** showed mild activity against all of the above viruses [against which BDVU and (*S*)-DHPA were inactive] but with no evidence of stereochemical selectivity. Ribavirin also show mild activity against all of the above viruses except Coxsackie B4. A mic value of 240 μg ml^{-1} was determined for both (*S*)-**14** and (*R*)-**14** against the Punta Toro virus, about five time less active than ribavirin (48 μg ml^{-1}).

In each of the cell lines employed for the above screens, cytoxicity of the twenty nucleoside analogues was low, similar to that determined for the reference antiviral compounds.

The antiherpes activity found for the adenine derivative (*S*)-**11** is the most interesting finding from the thirteen screens reported above. The stereochemical selectivity favours the configuration opposite to that in D-ribose, a consequence of the conformational freedom conferred by the acyclic nature of these compounds and established by the modelling studies described above. Generally the compounds with a free hydroxyl group were inactive, probably indicating poor transport through the cell wall.

Conclusion

The modelling studies have shown that the conversion of the nucleoside family **5** to nucleoside family **6** introduces extensive flexibility which is likely to greatly increase the potential for antiviral activity as observed in aciclovir and prodrugs.[33] It is also notable that some nucleosides with a hydroxylated acyclic glycone have potent hepatitis B activity[34] but the potential of nucleoside family **6** extends into the wider antiviral area. This is confirmed by finding mild activity against a wide range of viruses.

Experimental

General procedures

NMR spectra were recorded with a JEOL Lambda 400 spectrometer using standard conditions with a data point resolution of *ca.* 0.1 Hz. ^{1}H chemical shifts were measured relative to Me_4Si and ^{13}C chemical shifts relative to $CDCl_3$ (77.05 ppm), $(CD_3)_2SO$ (39.5 ppm) or CD_3OD (49.0 ppm). All coupling constants are given in hertz. Assignments of the ^{1}H spectra were made by detailed analysis using decoupling or correlation techniques where appropriate. Column chromatography was performed on silica gel (230–400 mesh; Prolabo) and TLC on silica gel 60, F_{254} (Merck) with detection by UV absorbance or phosphomolybdic acid. Chiral HPLC was carried out using Chiralcel OD-H and Chiralpak AD columns [5 μm cellulose tris(3,5-dimethylphenylcarbamate)], a Chiralpak AS column [amylose tris{(*S*)-1-phenylethylcarbamate}] and a Chiralcel OJ column [10 μm cellulose tris(methylbenzoate)] (all 250 × 4.6 mm stainless steel columns from Daicel Chemical Industries). Optical rotation values are given in 10^{-1} deg cm^2 g^{-1}.

(*R*)- and (*S*)-Phenylethane-1,2-diol [(*R*)-7 and (*S*)-7]

AD-mix α or AD-mix β (50.0 g) in a mixture of *tert*-butanol (180 mL) and water (180 mL) was stirred at room temperature until both phases were clear. Styrene (3.72 g, 35.72 mmol) was added to this mixture at −10 °C and the resulting slurry was stirred vigorously at 0 °C for 1 h. Sodium sulfite (40 g) was

added and the mixture stirred at 20 °C for 30 min, then diluted with water (160 mL) and extracted with dichloromethane. This extract was worked up and the crude product purified by column chromatography (gradient of hexane–ethyl acetate, 7 : 3, then 1 : 1) to give the diol (*R*)-**7** or (*S*)-**7** as colourless crystals, 4.9 g (99%), as reported previously.[21]

(*R*)- and (*S*)-(2-Hydroxy-2-phenyl)ethyl benzoate [(*R*)-8 and (*S*)-8]

Benzoyl chloride (4.4 mL, 38.2 mmol) was added to (*R*)-**7** or (*S*)-**7** (4.8 g, 37.7 mmol) in pyridine (70 mL) at 0 °C and the mixture stirred for 24 h at room temperature. Ice–water was added, the mixture stirred for 30 min and then extracted with CH_2Cl_2. This extract was worked up and the crude product purified by column chromatography (hexane–ethyl acetate, 7 : 3) to afford the protected diol (*R*)-**8** or (*S*)-**8** as colourless crystals, 7.3 g (88%), mp 50 °C; R_f 0.3 (hexane–ethyl acetate, 7 : 3); δ_H ($CDCl_3$) 4.40 (1H, dd, *J* 6.0, 8.6, H2a), 4.50 (1H, dd, *J* 2.5, 8.6, H2b), 5.07 (1H, dd, *J* 6.0, 2.5, H1), 7.37–7.42 (8H, m, aromatic H), 8.03 (2H, m, aromatic H); δ_C ($CDCl_3$) 69.8 (C2), 72.5 (C1), 126.2, 128.2, 128.4, 128.6, 129.7, 133.2, 139.8 (aromatic C), 166.7 (CO); (*R*)-**8** had $[\alpha]_D^{22}$ −25.7 (*c* 0.58 in $CHCl_3$); (found: C, 74.06; H, 5.98; calc. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82%); (*S*)-**8** had $[\alpha]_D^{22}$ +22.8 (*c* 0.19 in $CHCl_3$); (found: C, 74.42; H, 5.83%).

(*R*)- and (*S*)-[2-(Methoxymethoxy)-2-phenyl]ethyl benzoate [(*R*)-9 and (*S*)-9]

Phosphorus pentoxide (6.15 g, 43.34 mmol) was added, portionwise with vigorous stirring, to a solution of (*R*)-**8** or (*S*)-**8** (7.0 g, 24.76 mmol) in anhydrous chloroform (100 mL) and formaldehyde dimethyl acetal (5.46 mL, 61.91 mmol), the temperature being maintained at 40–45 °C. The mixture was then stirred at room temperature for 24 h. The supernatant was diluted with CH_2Cl_2 (150 mL) and worked up and the crude product purified by column chromatography (hexane–ethyl acetate, 97 : 3) to afford (*R*)-**9** or (*S*)-**9** as an oil, 6.6 g (80%), R_f 0.4 (hexane–ethyl acetate, 9 : 1); δ_H ($CDCl_3$) 4.46 (1H, dd, *J* 2.9, 8.6, H2a), 4.53 (1H, dd, *J* 6.1, 8.6, H2b), 4.64 (1H, q, *J* 5.1, 7.8, CH_2), 5.04 (1H, dd, *J* 2.9, 6.1, H1), 7.32–7.56 (8H, m, aromatic H), 8.05 (2H, m, aromatic H); δ_C ($CDCl_3$) 55.6 (CH_3O), 68.2 (C2), 75.8 (C1), 94.4 (CH_2), 127.2, 128.5, 128.7, 129.7, 130.1, 133.1, 138.0 (aromatic C), 166.4 (CO); (*R*)-**9** had $[\alpha]_D^{22}$ −100.7 (*c* 0.71 in $CHCl_3$); (found: C, 71.16; H, 6.70; calc. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34%); (*S*)-**9** had $[\alpha]_D^{22}$ +103.9 (*c* 0.80 in $CHCl_3$); (found: C, 71.34; H, 6.74%).

(*R*)- and (*S*)-[2-(Acetoxymethoxy)-2-phenyl]ethyl benzoate [(*R*)-10 and (*S*)-10]

Acetic anhydride (2.64 mL, 27.94 mmol) and boron trifluoride –diethyl ether (1.05 mL, 8.38 mmol) were added to a solution of (*R*)-**9** or (*S*)-**9** (4.0 g, 13.97 mmol) in anhydrous diethyl ether (60 mL) at −10 °C. This mixture was stirred at 4 °C for 48 h then poured into ice–water (35 mL), neutralised with saturated $NaHCO_3$ and extracted twice with diethyl ether (35 mL). The extract was worked up and the crude product purified by column chromatography (hexane–ethyl acetate, 95 : 05) to afford (*R*)-**10** or (*S*)-**10** as an oil, 3.9 g (90%), R_f 0.5 (hexane–ethyl acetate, 9 : 1); δ_H ($CDCl_3$) 1.81 (3H, s, CH_3), 4.44 (1H, dd, *J* 5.9, 8.9, H2a), 4.48 (1H, dd, *J* 3.2, 8.9, H2b), 5.03 (1H, dd, *J* 3.2, 5.9, H1), 5.14 (1H, d, *J* 4.8, CH_2), 5.46 (1H, d, *J* 4.8, CH_2), 7.25–7.58 (8H, m, aromatic H), 8.04 (2H, m, aromatic H); δ_C ($CDCl_3$) 20.8 (CH_3), 67.8 (C2), 79.5 (C1), 87.3 (CH_2), 127.0, 128.5, 128.7, 128.8, 129.7, 130.0, 133.2, 137.6 (aromatic C), 166.3 (COPh), 170.5 ($COCH_3$); (*R*)-**10** had $[\alpha]_D^{22}$ −63.3 (*c* 0.57 in $CHCl_3$); (found: C, 69.08; H, 5.75; calc. for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77%); (*S*)-**10** had $[\alpha]_D^{22}$ +64.2 (*c* 0.30 in $CHCl_3$); (found: C, 68.90; H, 5.86%).

Preparation of nucleoside analogues 11–15

The unprotected nucleobase (A, C, G, T, U) (3.18 mmol) in hexamethyldisilazane (13 mL) containing a catalytic amount of $NH_4(SO_4)_2$ was refluxed overnight then excess reagent cautiously removed under reduced pressure. Dibenzo-18-crown-6-ether (0.24 g, 0.67 mmol) and potassium iodide (0.22 g, 1.30 mmol) were added to a solution of the silylated nucleobase and (*R*)-**10** or (*S*)-**10** (0.5 g, 1.59 mmol) in acetonitrile–toluene (1 : 1, 12 mL). The mixture was stirred overnight in the case of pyrimidines and for 3 days in the case of purines under an atmosphere of argon. The insoluble material was filtered off and the filtrate evaporated under reduced pressure. The crude product was chromatographed using CH_2Cl_2–CH_3OH as specified below.

(*R*)- and (*S*)-9-[(2-Benzoyloxy-1-phenylethoxy)methyl]adenine [(*R*)-11 and (*S*)-11]

After chromatography with CH_2Cl_2–CH_3OH (95 : 5) (*R*)-**11** or (*S*)-**11** was recrystallised (71%) from ethanol, mp 155–157 °C; R_f 0.3 (CH_2Cl_2–CH_3OH, 95 : 5); δ_H ($CDCl_3$) 4.34 (1H, dd, *J* 2.7, 8.8, H2a), 4.45 (1H, dd, *J* 6.3, 8.8, H2b), 4.97 (1H, dd, *J* 2.7, 6.3, H1), 5.55 (1H, d, *J* 8.4, CH_2), 5.68 (1H, d, *J* 8.4, CH_2), 6.22 (2H, s, NH_2), 7.31–7.54 (8H, m, aromatic H), 7.79–7.81 (2H, m, aromatic H), 7.84 (1H, s, H2), 8.33 (1H, s, H8); δ_C ($CDCl_3$) 67.5 (C2′), 71.3 (C1′), 79.2 (CH_2), 119.3 (C5), 127.0, 128.4, 128.5, 128.9, 129.5, 133.2, 136.6 (aromatic C), 140.5 (C8), 150.2 (C4), 153.5 (C2), 155.6 (C6), 165.3 (COPh); (*R*)-**11** had $[\alpha]_D^{22}$ −67.1 (*c* 0.15 in $CHCl_3$); (found: C, 62.55; H, 4.80; N, 17.71; calc. for $C_{21}H_{19}N_5O_3$: C, 64.77; H, 4.92; N, 17.98%); (*S*)-**11** had $[\alpha]_D^{22}$ +65.5 (*c* 0.14 in $CHCl_3$); (found: C, 64.51; H, 4.83; N, 17.69%).

(*R*)- and (*S*)-9-[(2-Benzoyloxy-1-phenylethoxy)methyl]guanine [(*R*)-12 and (*S*)-12]

After chromatography with CH_2Cl_2–CH_3OH (90 : 10) (*R*)-**12** or (*S*)-**12** was recrystallised (70%) from dichloromethane, mp 238–240 °C; R_f 0.4 (CH_2Cl_2–CH_3OH, 90 : 10); δ_H [$(CD_3)_2SO$] 4.27 (1H, dd, *J* 2.7, 8.8, H2a), 4.32 (1H, dd, *J* 5.9, 8.8, H2b), 5.03 (1H, q, *J* 2.7, 5.9, H1), 5.24 (1H, d, *J* 8.4, CH_2), 5.48 (1H, d, *J* 8.4, CH_2), 6.48 (2H, s, NH_2), 7.31–7.69 (5H, m, aromatic H), 7.78 (1H, s, H8), 10.60 (1H, s, H1); δ_C [$(CD_3)_2SO$] 67.1 (C2′), 70.7 (C1′), 77.5 (CH_2), 116.6 (C5), 127.0, 128.4, 128.5, 129.0, 129.3, 133.4, 137.4 (aromatic C), 137.6 (C8), 151.4 (C4), 153.8, (C2), 156.8 (C6), 165.3 (COPh); (*R*)-**12** was too insoluble for OR determination (found: C, 62.24; H, 4.56; N, 17.14; calc. for $C_{21}H_{19}N_5O_4$: C, 62.22; H, 4.72; N, 17.27%); (*S*)-**12** was too insoluble for OR determination; (found: C, 62.29; H, 4.63; N, 17.12%).

(*R*)- and (*S*)-1-[(2-Benzoyloxy-1-phenylethoxy)methyl]cytosine [(*R*)-13 and (*S*)-13]

After chromatography with CH_2Cl_2–CH_3OH (95 : 5) (*R*)-**13** or (*S*)-**13** was recrystallised (88%) from CH_3OH, mp 183–185 °C; R_f 0.5 (CH_2Cl_2–CH_3OH, 90 : 10); δ_H [$(CD_3)_2SO$] 4.36 (1H, dd, *J* 3.1, 8.8, H2a), 4.40 (1H, dd, *J* 5.7, 8.8, H2b), 5.06 (1H, dd, *J* 3.1, 5.7, H1), 5.19 (1H, dd, *J* 8.0, 12.8, CH_2), 5.76 (1H, d, *J* 5.7, H5), 7.34–7.90 (13H, m, aromatic H, H6, NH_2), 8.39 (1H, s, NH); δ_C [$(CD_3)_2SO$] 67.2 (C2′), 76.1 (C1′), 78.0 (CH_2), 94.1 (C5), 126.9, 128.3, 128.5, 128.8, 129.2, 129.3, 133.5, 137.7 (aromatic C), 147.0 (C6), 152.0 (C2), 162.7 (C4), 165.4 (COPh); (*R*)-**13** had $[\alpha]_D^{22}$ −50.7 (*c* 0.90 in $CHCl_3$); (found: C, 65.47; H, 5.61; N, 11.37; calc. for $C_{20}H_{21}N_3O_4$: C, 65.56; H, 5.78 N, 11.47%); (*S*)-**13** had $[\alpha]_D^{22}$ +49.0 (*c* 0.13 in $CHCl_3$); (found: C, 65.63; H, 5.58; N, 11.37%).

(*R*)- and (*S*)-1-[(2-Benzoyloxy-1-phenylethoxy)methyl]thymine [(*R*)-14 and (*S*)-14]

After chromatography with CH_2Cl_2–CH_3OH (99 : 1) (*R*)-**14** or (*S*)-**14** was recrystallised (98%) from CH_3OH, mp 106–108 °C; R_f 0.5 (CH_2Cl_2–CH_3OH, 97 : 3); δ_H ($CDCl_3$) 1.64 (3H, s, CH_3), 4.32 (1H, dd, *J* 2.5, 9.0, H2a), 4.57 (1H, dd, *J* 6.7, 9.0, H2b), 4.96 (1H, dd, *J* 2.5, 6.7, H1), 5.04 (1H, d, *J* 8.2, CH_2), 5.27 (1H, d, *J* 8.2, CH_2), 7.03 (1H, dd, *J* 0.84, 1.89, H6), 7.33–7.57 (8H, m, aromatic H), 7.97–7.99 (2 H, m, aromatic H), 9.59 (1H, s, NH); δ_C ($CDCl_3$) 12.1 (CH_3), 67.5 (C2′), 75.1 (C1′), 79.3 (CH_2), 111.7 (C5), 127.2, 128.6, 128.9, 129.6, 129.8, 133.3, 136.9 (aromatic C), 139.0 (C6), 151.4 (C2), 164.2 (C4), 166.2 (COPh); (*R*)-**14** had $[\alpha]_D^{22}$ −66.8 (*c* 0.14 in $CHCl_3$); (found: C, 66.33; H, 5.33; N, 7.20; calc. for $C_{21}H_{20}N_2O_5$: C, 66.21; H, 5.29; N, 7.35%); (*S*)-**14** had $[\alpha]_D^{22}$ +65.8 (*c* 0.14 in $CHCl_3$); (found: C, 66.29; H, 5.30; N, 7.16%).

(*R*)- and (*S*)-1-[(2-Benzoyloxy-1-phenylethoxy)methyl]uracil [(*R*)-15 and (*S*)-15]

After chromatography with CH_2Cl_2–CH_3OH (98 : 2) (*R*)-**15** or (*S*)-**15** was recrystallised (97%) from methanol, mp 106–108 °C; R_f 0.4 (CH_2Cl_2–CH_3OH, 97 : 3); δ_H ($CDCl_3$) 4.34 (1H, dd, *J* 2.5, 8.9, H2a), 4.55 (1H, dd, *J* 6.5, 8.9, H2b), 4.96 (1H, dd, *J* 2.5, 6.5, H1), 5.10 (1H, d, *J* 8.2, CH_2), 5.26 (1H, d, *J* 8.2, CH_2), 5.54 (1H, dd, *J* 0.9, 5.9, H5), 7.24 (1H, d, *J* 5.9, H6), 7.33–7.58 (8H, m, aromatic H), 7.97–8.00 (2H, m, aromatic H), 9.88 (1H, s, NH); δ_C ($CDCl_3$) 67.3 (C2′), 75.3 (C1′), 79.4 (CH_2), 103.0 (C5), 127.0, 128.4, 128.7, 128.8, 129.5, 129.6, 133.2, 136.6 (aromatic C), 143.1 (C6), 151.1 (C2), 163.6 (C4), 166.1 (COPh); (*R*)-**15** had $[\alpha]_D^{22}$ −69.8 (*c* 0.14 in $CHCl_3$); (found: C, 65.66; H, 5.05; N, 7.71; calc. for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.95; N, 7.65%); (*S*)-**15** had $[\alpha]_D^{22}$ +67.8 (*c* 0.18 in $CHCl_3$); (found: C, 65.72; H, 4.93; N, 7.85%).

Deprotection of nucleoside analogues 11–15

Ammonia in methanol was added to a stirred solution of the protected nucleoside in dioxane. The mixture was stirred overnight at room temperature and then neutralised with acetic acid. After evaporation under reduced pressure the crude product was chromatographed using CH_2Cl_2–CH_3OH as specified below.

(*R*)- and (*S*)-9-[(2-Hydroxy-1-phenylethoxy)methyl]adenine [(*R*)-16 and (*S*)-16]

After chromatography with CH_2Cl_2–CH_3OH (90 : 10) (*R*)-**16** or (*S*)-**16** was recrystallised (95%) from ethanol, mp 172–173 °C; R_f 0.5 (CH_2Cl_2–CH_3OH, 90 : 10); δ_H (CD_3OD) 3.52 (1H, dd, *J* 3.0, 8.8, H2a), 3.63 (1H, dd, *J* 6.1, 8.8, H2b), 4.55 (1H, s, OH), 4.69 (1H, dd, *J* 3.0, 6.1, H1), 5.70 (1H, q, *J* 8.2, 16.5, CH_2), 7.24–7.30 (5H, m, aromatic H), 8.13 (1H, s, H2), 8.23 (1H, s, H8). δ_C (CD_3OD) 68.3 (C2′), 74.1 (C1′), 84.9 (CH_2), 120.6 (C5), 128.6, 129.8, 130.1, 140.5 (aromatic C), 143.5 (C8), 151.7 (C4), 154.8 (C2), 158.0 (C6); (*R*)-**16** had $[\alpha]_D^{22}$ −87.0 [*c* 0.10 in $(CH_3)_2SO$]; (found C, 58.80; H, 5.42; N, 24.42; calc. for $C_{14}H_{15}N_5O_2$: C, 58.94; H, 5.30; N, 24.55%); (*S*)-**16** had $[\alpha]_D^{22}$ +89.1 [*c* 0.15 in $(CD_3)_2SO$]; (found: C, 58.74; H, 5.07; N, 24.25%).

(*R*)- and (*S*)-9-[(2-Hydroxy-1-phenylethoxy)methyl]guanine [(*R*)-17 and (*S*)-17]

After chromatography with CH_2Cl_2–CH_3OH (90 : 10) (*R*)-**17** or (*S*)-**17** was recrystallised (92%) from CH_3OH, mp >250 °C; R_f 0.5 (CH_2Cl_2–CH_3OH, 85 : 15); δ_H [$(CD_3)_2SO$] 3.40 (1H, m, H2a), 3.48 (1H, m, H2b), 4.58 (1H, dd, $J_{1,2a}$ 3.2, $J_{1,2b}$ 5.5, H1), 4.88 (1H, t, OH), 5.28 (1H, d, *J* 8.2, CH_2), 5.39 (1H, d, *J* 8.2, CH_2), 6.48 (2H, s, NH_2), 7.21–7.32 (5H, m, aromatic H), 7.69 (1H, s, H8), 10.60 (1H, s, H1); δ_C [$(CH_3)_2SO$] 65.6 (C2′), 71.0 (C1′), 81.5 (CH_2), 116.3 (C5), 126.8, 127.6, 128.1, 137.5 (aromatic C), 139.1, 151.3, 153.8, 156.7 (C8, C4, C2, C6); (*R*)-**18** had $[\alpha]_D^{22}$ −100.3 [*c* 0.10 in $(CH_3)_2SO$]; *m*/*z* (CI) 302.1247 (M^+ + H, calc. for $C_{14}H_{16}N_5O_3$ 302.1253); (*S*)-**18** had $[\alpha]_D^{22}$ + 100.2 [*c* 0.60 in $(CH_3)_2SO$]; *m*/*z* (CI) 302.1249.

(*R*)- and (*S*)-1-[(2-Hydroxy-1-phenylethoxy)methyl]cytosine [(*R*)-18 and (*S*)-18]

After chromatography with CH_2Cl_2–CH_3OH (85 : 15) (*R*)-**18** or (*S*)-**18** was recrystallised (94%) from CH_2Cl_2, mp 101–103 °C; R_f 0.3 (CH_2Cl_2–CH_3OH, 85 : 15); δ_H (CD_3OD) 3.51 (1H, dd, *J* 2.8, 9.1, H2a), 3.64 (1H, dd, *J* 6.1, 9.1, H2b), 4.61 (1H, dd, *J* 2.8, 6.1, H1), 5.19 (1H, q, *J* 7.9, 10.8, CH_2), 5.73 (1H, d, *J* 5.5, H5), 7.25–7.33 (5H, m, aromatic H), 7.51 (1H, d, *J* 5.5, H6); δ_C (CD_3OD) 68.5 (C2′), 79.4 (C1′), 84.7 (CH_2), 96.9 (C5), 128.9, 129.9, 130.3, 140.7 (aromatic C), 147.6 (C6), 159.4 (C4), 168.6 (C2); (*R*)-**17** had $[\alpha]_D^{22}$ −97.2 (*c* 0.70 in CH_3OH); (found: C, 59.68; H, 6.15; N, 15.91; calc. for $C_{13}H_{17}N_3O_2$: C, 59.53; H, 6.53 N, 16.02%); (*S*)-**17** had $[\alpha]_D^{22}$ +100.8 (*c* 0.90 in CH_3OH); (found: C, 59.39; H, 6.39; N, 16.13%).

(*R*)- and (*S*)-1-[(2-Hydroxy-1-phenylethoxy)methyl]thymine [(*R*)-19 and (*S*)-19]

After chromatography with CH_2Cl_2–CH_3OH (98 : 2) (*R*)-**19** or (*S*)-**19** was recrystallised (98%) from CH_3OH, mp 132–134 °C; R_f 0.2 (CH_2Cl_2–CH_3OH, 97 : 3); δ_H (CD_3OD) 1.72 (3H, d, *J* 0.9, CH_3), 3.50 (1H, dd, *J* 2.7, 9.0, H2a), 3.64 (1H, dd, *J* 6.3, 9.0, H2b), 4.58 (1H, dd, *J* 2.7, 6.3, H1), 4.84 (1H, s, OH), 5.19 (2H, q, *J* 8.0, 9.9, CH_2), 7.22–7.31 (6H, aromatic H, H6); δ_C (CD_3OD) 12.9 (CH_3), 68.4 (C2′), 78.3 (C1′), 85.3 (CH_2), 112.1 (C5), 128.8, 129.9, 130.2, 140.8 (aromatic C), 142.6 (C6), 153.7 (C2), 167.3 (C4); (*R*)-**19** had $[\alpha]_D^{22}$ −79.8 (*c* 0.18 in CH_3OH); (found: C, 60.73; H, 5.81; N, 9.89; calc. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14%); (*S*)-**19** had $[\alpha]_D^{22}$ +79.0 (*c* 0.18 in CH_3OH); (found: C, 60.76; H, 5.80; N, 9.82%).

(*R*)- and (*S*)-1-[(2-Hydroxy-1-phenylethoxy)methyl]uracil [(*R*)-20 and (*S*)-20]

After chromatography with CH_2Cl_2–CH_3OH (98 : 2) (*R*)-**20** or (*S*)-**20** was recrystallised (96%) from CH_3OH, mp 132–134 °C; R_f 0.2 (CH_2Cl_2–CH_3OH, 95 : 5); δ_H (CD_3OD) 3.51 (1H, dd, *J* 2.7, 9.0, H2a), 3.64 (1H, dd, *J* 6.3, 9.0, H2b), 4.60 (1H, dd, *J* 2.7, 6.3, H1), 4.87 (1H, s, OH), 5.20 (2H, s, CH_2), 5.51 (1H, d, *J* 6.1, H5), 7.22–7.33 (4H, m, aromatic H, H6), 7.49–7.51 (2 H, aromatic H); δ_C (CD_3OD) 68.4 (C2′), 78.4 (C1′), 85.3 (CH_2), 103.5 (C5), 128.8, 130.0, 130.3, 140.7 (aromatic C), 147.1 (C6), 153.5 (C2), 167.2 (C4); (*R*)-**20** had $[\alpha]_D^{21}$ −90.1 (*c* 0.18 in CH_3OH); *m*/*z* (CI) 280.1300 (M^+ + NH_4, calc. for $C_{13}H_{18}N_3O_4$ 280.1297); (*S*)-**20** had $[\alpha]_D^{22}$ +88.5 (*c* 0.16 in CH_3OH); *m*/*z* (CI) 280.1299.

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