Stereoisomeric pyrimidine nucleoside analogues based on the 1,3-dihydrobenzo[*c*]furan core

David F. Ewing,* Nour-Eddine Fahmi, Christophe Len, Grahame Mackenzie * and Alessandra Pranzo

Department of Chemistry, University of Hull, Hull, UK HU6 7RX

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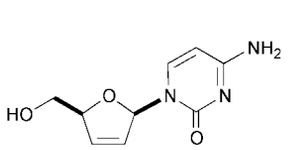
A new efficient route is described to uracil, thymidine and cytosine derivatives of 1,3-dihydrobenzo[*c*]furan which are aromatic analogues of the well known antiviral 2′,3′-dideoxy-2′,3′-didehydronucleosides. These systems contain two chiral centres (corresponding to α/β and D/L centres in a furanose sugar) and a route involving application of the Sharpless asymmetric oxidation methodology allowed access to each of the four stereoisomers of the uracil derivative in enantiomerically pure form.

Introduction

One of the many modifications which have been made to the structure of a regular nucleoside in an attempt to enhance chemotherapeutic potential is the introduction of a double bond into the 2′,3′ position to give a 2′,3′-didehydro-2′,3′-dideoxyribonucleoside (d4N).[1] A study of the anti-HIV activity of the d4Ns was reported by Balzarini *et al.*[2] over ten years ago and since then there has been increasing interest in this class of compound. Both the cytosine (d4C) **1** and thymidine (d4T) **2** analogues are potent antiviral agents against the ATH8 cell line. Many substituted variants of d4C, d4T and d4U have been examined for antiviral activity[3] and d4T is now an approved anti-HIV drug (Stavudine®).[4] It is notable that the carbocyclic analogue of d4G (carbovir) **3** also has potent anti-HIV activity.[5]



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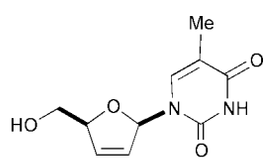

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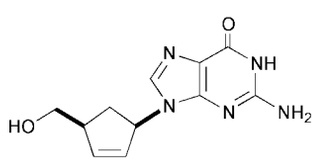

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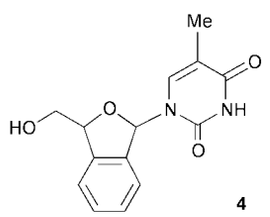

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An important aspect of anti-HIV therapy is the suppression of viral replication in the brain and many derivatives of d4T have been synthesised and tested as prodrugs, particularly targeted at producing a therapeutic brain concentration.[6] In this regard enhanced lipophilicity is likely to be advantageous. We have recently reported[7] the first synthesis of the interesting analogue of d4T in which the 2,3 double bond is incorporated into a benzene ring producing a derivative of the benzo[*c*]furan system **4**. This new class of nucleoside with a modified glycone is attractive because it retains the phosphorylation site, it is likely to be more resistant to the hydrolytic process that contributes to the short half-life of d4T *in vivo*[3] and it has enhanced lipophilicity compared to d4T. Furthermore, this system is clearly very rigid. It has been speculated[1c] that the conformational restriction imposed by the double bond in d4T is an important factor in its interaction with viral enzymes. Nucleoside analogues with conformational rigidity imposed by cyclopropanation of a furanose or carbocyclic ring have been reported recently.[8]

We now report further studies of a synthetic route which allows more efficient access to the 1,3-dihydrobenzo[*c*]furan glycone and thus to the corresponding uracil, thymine and cytosine nucleoside analogues. Since two chiral centres are generated in this system the nucleoside analogues are normally obtained as a pair of diastereoisomers although the ultimate objective was the synthesis of stereoisomerically pure nucleoside analogues. The nucleoside diastereoisomers could be separated by chromatography but resolution of the optical isomers was not considered feasible. Hence a method has been developed which allows complete stereoselectivity in the generation of the C3 chiral centre in the 1,3-dihydrobenzo-[*c*]furan system and thus provides access to each of the four uracil stereoisomers in enantiomerically pure form.

Results and discussion

The starting point is compound **5** which is *o*-phthalaldehyde with one aldehyde group protected with propane-1,3-diol[7] (Scheme 1). The remaining aldehyde group is easily converted to the cyanohydrin **6** in high yield. Treatment of crude **6** with HCl in methanol results in a sequence of reactions. The aldehyde protecting group is cleaved and the resulting aldehyde cyclises spontaneously with the cyanohydrin hydroxy group to generate the dihydrofuran ring. Subsequently the hydroxy group generated at C1 is converted to a methoxy group and the cyano group converted to the methyl ester (possibly *via* an imidate). Thus a one-pot set of reactions results in the conversion of compound **6** to methoxy ester **7** with the hydroxy ester **8** as a minor product. These two esters are readily separated by chromatography. Reduction of the ester function with $LiAlH_4$ and protection of the resulting alcohol **9** as the benzoyl derivative **10** are both high yield steps. The overall yield of 3-benzoyloxymethyl-1,3-dihydro-1-methoxybenzo[*c*]furan (**10**) from aldehyde **5** was 42% and hence the procedure shown in Scheme 1 constitutes an efficient route to the required glycone.

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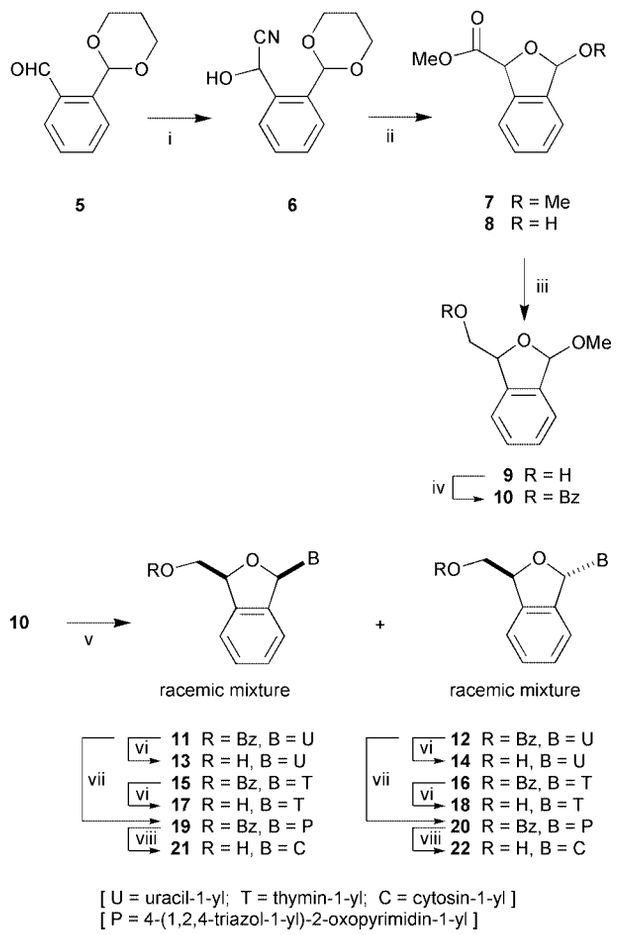
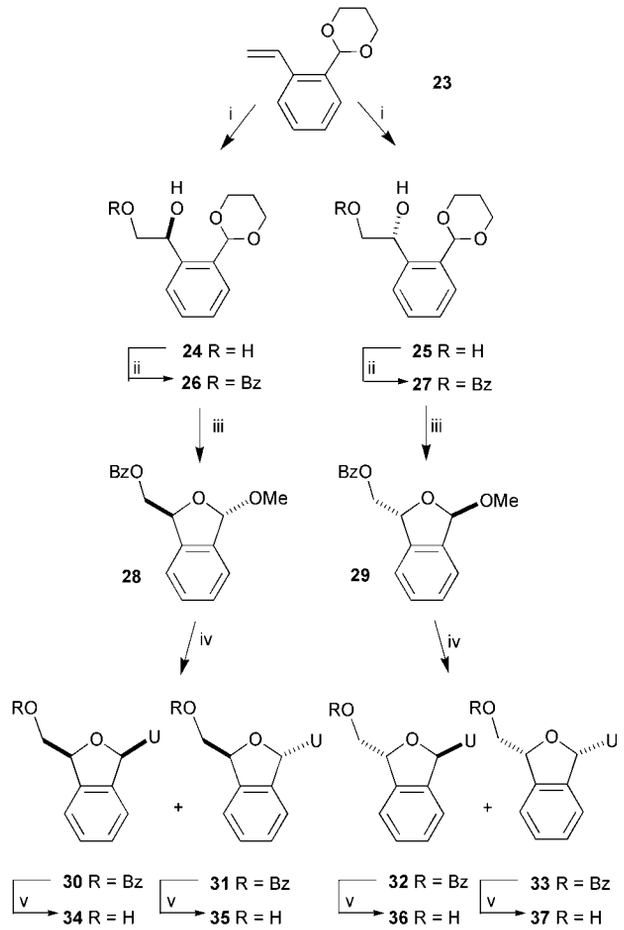


Scheme 1 *Reagents and conditions*: i, $NaHSO_3$, KCN, aq. THF at 5 °C; ii, HCl in MeOH, 0 °C; iii, $LiAlH_4$, ether at 0 °C; iv, BzCl in pyridine at 0 °C; v, silylated uracil or thymine, TMSOTf; vi, NH_3 in MeOH; vii, Et_3N, 1,2,3-triazole, $POCl_3$, 0 °C, then reacted with uracil nucleoside at 24 °C for 24 h; viii, aq. NH_3 in dioxane at 20 °C for 12 h.



Scheme 2 *Reagents and conditions*: i, AD-mix-α (or AD-mix-β), aq. *t*-BuOH, −10 °C; ii, BzCl, pyridine, $CHCl_3$; iii, PTSA, aq. acetone; MeOH–HCl; iv, silylated uracil, TMSOTf, MeCN; v, NH_3 in MeOH.

Compound **10** is obtained as a pair of diastereoisomers in the ratio 1:1.25. The major species was identified as the *trans*-isomer by the criteria established previously,[7] principally the value of the four-bond coupling $J_{1,3}$ which is large in this isomer. Separation of the isomers at this stage was difficult and only the *cis*-isomer could be isolated in pure crystalline form. Coupling of the diastereoisomeric mixture with silylated uracil in presence of trimethylsilyl triflate gave a corresponding mixture of nucleoside analogues **11** and **12** which were readily separated by chromatography. An analogous condensation of the glycone with silylated thymine gave the corresponding mixture of *cis*- and *trans*-nucleoside analogues **15** and **16**. Crystallisation of this isomeric mixture gave the pure *cis*-isomer but the *trans*-isomer was obtained as a 7:1 mixture with the *cis*-isomer. The protected cytosines **19** and **20** were obtained by standard nucleoside conversion[9] from the separated uracils and were thus obtained as pure diastereoisomers. Debenzoylation of these six compounds gave the corresponding unprotected nucleoside analogues **13**, **14**, **17**, **18**, **21** and **22**. Thus the 1,3-dihydrobenzo[*c*]furan nucleoside analogues with the range of standard pyrimidine bases are readily accessible as pure diastereoisomers.

Each of the nucleoside analogues obtained by the method shown in Scheme 1 is of course a pair of enantiomers *i.e.* the *cis* compound **13** is a mixture of the (1*R*,3*S*) and (1*S*,3*R*) species. Since enantiomerically pure nucleosides were required for screening purposes a synthetic strategy was sought which would avoid the need for tedious resolution procedures. This has been achieved by application of the Sharpless asymmetric dihydroxylation methodology[10] (Scheme 2). The ethene derivative **23**, obtained from phthalaldehyde,[7] was converted to the corresponding dihydroxy derivatives **24** and **25** using the commercial Sharpless reagents, AD-mix-α and AD-mix-β, respectively. This asymmetric dihydroxylation reaction was quantitative and completely stereoselective (ee >99% as confirmed by the use of a chiral shift reagent) and this effectively leads to a resolution of one of the chiral centres in the 1,3-dihydrobenzo[*c*]furan system. The configuration at this chiral centre, as indicated in the structures, was assigned by the asymmetric dihydroxylation mnemonic rules.[10] Selective benzoylation of the primary hydroxy group in the diols **24** and **25** gave the esters **26** and **27** and these were each cyclised and methylated to afford the corresponding 1,3-dihydrobenzo[*c*]furan derivatives **28** and **29**. Both compounds are obtained as a single stereoisomer. This means that the configuration at the chiral centre generated in the Sharpless reaction (which becomes C3 in the product) exerts complete stereocontrol over the cyclisation step and only the *trans* species is formed (*i.e.* **28** and **29** are enantiomers). This is in sharp contrast to the cyclisation of the analogous benzyl derivative of the racemic diol which gives a mixture of *cis* and *trans* racemic 1,3-dihydrobenzo[*c*]furans.[7] Formation of the uracil derivatives by standard Vorbrüggen chemistry[11] results in anomerisation and in each case a mixture of diastereoisomers is formed *i.e.* species **28** leads to a mixture of uracils **30** (1*R*,3*S*) and **31** (1*S*,3*S*) and species **29** gives uracils **32** (1*R*,3*R*) and **33** (1*S*,3*R*). Fortunately these isomer pairs (equivalent to an anomeric pair of glycosyl nucleosides) can be readily separated by silica gel chromatography. The stereochemical purity of compounds **30**–**33** was confirmed by chiral HPLC.[12] After removal of the protecting group the four stereoisomers of 1-(3-hydroxymethyl-1,3-dihydrobenzo[*c*]furan-1-yl)uracil were obtained. Thus there has been no loss in the chiral integrity of the C3 site throughout

the sequence of reactions starting from the diols **24** and **25**. These enantiomerically pure nucleoside analogues are being screened for antiviral activity and the results will be reported elsewhere.

Experimental

General

NMR spectra were recorded with a 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 $CDCl_3$ (77.0 ppm) or $(CD_3)_2SO$ (39.5 ppm). All coupling constants are given in Hz. Assignments of the ^{1}H spectra were made by detailed analysis using decoupling or correlation techniques where appropriate. Diastereoisomer ratios were determined from the integration of suitable peaks. 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. Optical rotation values are given in 10^{-1} deg cm^2 g^{-1}.

2-[2-(1,3-Dioxan-2-yl)phenyl]-2-hydroxyacetonitrile (6)

A saturated aqueous solution of sodium bisulfite (85 mL) was added dropwise to a stirred solution of 2-(1,3-dioxan-2-yl)benzaldehyde[7] **5** (24.0 g, 125 mmol) and potassium cyanide (9.7 g, 150 mmol) in aqueous THF (1:1, 100 mL). Crushed ice was added to maintain the temperature at 5 °C during the addition and the mixture was stirred for 2 h at this temperature until the aldehyde was totally consumed (TLC). The mixture was extracted with dichloromethane and the organic layer worked up to give **6** as a yellow oil (24.8 g, 91%) which was used directly; δ_H ($CDCl_3$) 1.55, 2.20, 3.89, 4.10, 4.33 (6 H, m, dioxanyl), 4.5 (1 H, br s, OH), 5.81 (1 H, s, dioxanyl), 5.99 (1 H, s, H-2), 7.4–7.65 (4 H, m, aromatic H); δ_C ($CDCl_3$) 25.5, 67.5, 67.6, 102.0 (dioxanyl), 62.5 (C-2), 118.7 (CN), 128.3, 129.6, 134.1, 135.6 (aromatic C).

1,3-Dihydro-1-methoxy-3-methoxycarbonylbenzo[*c*]furan (7)

A solution of the nitrile **6** (24 g, 0.109 mol) in dry methanol was saturated with dry HCl at 0 °C for 1 h. The solution was maintained at this temperature for a further 2 h then poured into ice and slowly neutralised with sat. $NaHCO_3$ solution (500 mL). The solution was extracted with CH_2Cl_2, the extract worked up and the residue either used directly or chromatographed using a gradient of ethyl acetate in hexane (10–50%) to afford the ester **7** as a yellow oil (14.0 g, 66%). This compound was a diastereoismeric mixture (*cis*:*trans* ratio, 1:1.4); R_f 0.69 (hexane–EtOAc, 1:1); δ_H ($CDCl_3$) 3.45, 3.50 (2 s, OMe), 3.75, 3.77 (2 s, CO_2Me), 5.59 (1 H, s, H-3, *cis*), 5.78 (1 H, d, $J_{1,3}$ 1.8, H-3, *trans*), 6.2 (1 H, s, H-1, *cis*), 6.37 (1 H, d, H-1, *trans*), 7.3–7.50 (4 H, m, aromatic H); δ_C ($CDCl_3$) 52.4, 52.5, 54.3, 55.0 (OMe), 80.6, 80.8 (C-3), 107.7, 108.2 (C-1), 121.9, 122.5, 122.9, 123.0, 128.9, 129.0, 129.5, 129.7, 137.1, 137.2 (aromatic C), 170.5, 170.6 (CO).

A second component was the hydroxy ester **8**, obtained as a yellow solid (1.36 g, 6%). The diastereomeric mixture had a *cis*:*trans* ratio of 2.7:1 (Found: C, 61.75; H, 5.14. Calc. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19%); δ_H ($CDCl_3$) 3.85, 3.86 (2 s, CO_2Me), 5.62 (1 H, s, H-3, *cis*), 5.85 (1 H, d, $J_{1,3}$ 2.2, H-3, *trans*), 6.48 (1 H, d, $J_{1,OH}$ 11, H-1, *cis*), 6.48 (1 H, dd, $J_{1,3}$ 2.2, $J_{1,OH}$ 8.5 Hz, H-1, *trans*), 3.25 (1 H, d, OH *cis*), 3.7 (1 H, d, OH *trans*), 7.3–7.50 (4 H, m, aromatic H); δ_C ($CDCl_3$) 52.7, 53.0 (OMe), 81.04, 81.08 (C-3), 102.5, 102.6 (C-1), 172.5 (CO).

3-Benzoyloxymethyl-1,3-dihydro-1-methoxybenzo[*c*]furan (10)

A solution of ester **7** (13.5 g, 64.9 mmol) in dry Et_2O (300 mL) was added dropwise at 0 °C to a suspension of $LiAlH_4$ (3.3 g, 86.5 mmol) in Et_2O (300 mL). The mixture was stirred at room temperature for 1 h, then EtOAc (100 mL) was added at 0 °C and the mixture stirred for a further 1 h. Water was added dropwise and the mixture filtered and extracted with EtOAc. The extract was worked up and the crude product purified by chromatography (hexane–EtOAc, 7:3) to afford 1,3-dihydro-3-hydroxymethyl-1-methoxybenzo[*c*]furan (**9**) (R_f 0.18, hexane–EtOAc, 7:3) as a yellow oil (10.0 g, 86%).

A solution of benzoyl chloride (7.88 g, 61.9 mmol) in $CHCl_3$ (7 mL) was added to a solution of compound **9** (9.3 g, 51.6 mmol) in pyridine (50 mL) at 0 °C. The mixture was stirred overnight at room temperature and then poured into ice–water and extracted with CH_2Cl_2. The organic layer was worked up and the crude product chromatographed (hexane–EtOAc, 9:1) to give the 1,3-dihydrobenzo[*c*]furan **10** as a pair of diastereoismers, *cis*:*trans* ratio 1:1.25, obtained as a gum (12.0 g, 82%); R_f 0.6 (hexane–EtOAc, 7:3) (Found: C, 71.93; H, 5.66. Calc. for $C_{17}H_{16}O_4$: C, 71.81; H, 5.67%). The major isomer (*trans*) was obtained in a stereochemically pure form by crystallization from hexane–EtOAc; mp 84–86 °C; δ_H ($CDCl_3$) 3.45 (3 H, s, OMe), 4.52 (1 H, m, $J_{3,8a}$ 6.0, $J_{8a,8b}$ 11.9, H-8a), 4.68 (1 H, m, $J_{3,8b}$ 3.7, H-8b), 5.69 (1 H, m, H-3), 6.28 (1 H, d, $J_{1,3}$ 2.2, H-1), 7.3–7.60 (7 H, m, aromatic H), 7.95 (2 H, m, benzoyl); δ_C ($CDCl_3$) 54.5 (OMe), 66.9 (C-8), 81.0 (C-3), 107.2 (C-1), 166.3 (CO); *cis* isomer δ_H ($CDCl_3$) 3.52 (3 H, s, OMe), 4.54 (1 H, m, $J_{3,8a}$ 6.0, $J_{8a,8b}$ 11.9, H-8a), 4.64 (1 H, m, $J_{3,8b}$ 3.7, H-8b), 5.49 (1 H, m, H-3), 6.15 (1 H, s, H-1), 7.3–7.60 (7 H, m, aromatic H), 8.06 (2 H, m, benzoyl); δ_C ($CDCl_3$) 54.5 (OMe), 67.9 (C-8), 81.1 (C-3), 107.4 (C-1), 166.4 (CO).

cis- and *trans*-1-(3-Benzoyloxymethyl-1,3-dihydrobenzo[*c*]furan-1-yl)uracil (11 and 12)

Chlorotrimethylsilane (1 mL) and a crystal of ammonium sulfate were added to a suspension of uracil (1.41 g, 12.66 mmol) in hexamethyldisilazane (25 mL) and the mixture refluxed with exclusion of moisture until a clear solution was obtained (3 h). Volatiles were removed by repeated co-evaporation with toluene to leave a syrup. This syrup and the 1,3-dihydrobenzo[*c*]furan **10** (3.0 g, 10.55 mmol) were taken up in dry MeCN (60 mL) and trimethylsilyl trifluoromethanesulfonate (2.44 mL, 12.66 mmol) added at −15 °C. After stirring for 2 h at 0 °C, sat. $NaHCO_3$ solution (20 mL) was added, the mixture stirred for 30 min and then extracted with CH_2Cl_2. This extract was worked up and the crude product chromatographed (hexane–EtOAc 1:1) to give a mixture of the uracil nucleoside analogues **11** and **12** as a white foam (2.6 g, 70%), *cis*:*trans* ratio 1:2.3 (Found: C, 65.91; H, 4.40; N, 7.78. Calc. for $C_{17}H_{16}O_4$: C, 65.92; H, 4.42; N, 7.68%).

These diastereoisomers were separated by column chromatography (hexane–EtOAc, 7:3); the compound eluting first was the *cis* isomer **11**, mp 168–170 °C (EtOH); R_f 0.22 (hexane–EtOAc, 1:1); δ_H ($CDCl_3$) 4.82 (2 H, tight AB m, $J_{3,8}$ 3.2, 3.9, H-8), 5.32, 6.98 (2 H, d, *J* 8.4, uracil), 5.60 (1 H, m, H-3), 7.20–7.60 (8 H, m, H-1 and aromatic H), 7.85 (2 H, m, benzoyl), 8.12 (1 H, br s, NH); δ_C ($CDCl_3$) 65.3 (C-8), 81.9 (C-3), 87.5 (C-1), 103.1 (uracil), 150.9, 162.8, 166.1 (CO); *trans* isomer (**12**), mp 150–152 °C (EtOH), R_f 0.17 (hexane–EtOAc, 1:1); δ_H ($CDCl_3$) 4.55 (1 H, m, $J_{3,8a}$ 5.7, $J_{8a,8b}$ 11.9, H-8a), 4.68 (1 H, m, $J_{3,8b}$ 3.7, H-8b), 5.65, 6.81 (2 H, 2 d, *J* 8.4, uracil), 5.83 (1 H, $J_{1,3}$ 2.9, H-3), 7.59 (1 H, d, H-1), 7.30–7.60 (8 H, m, aromatic H), 7.95 (2 H, m, benzoyl), 8.95 (1 H, br s, NH); δ_C ($CDCl_3$) 66.6 (C-8), 82.5 (C-3), 88.5 (C-1), 103.3 (uracil), 150.8, 162.8, 166.2 (CO).

cis- and *trans*-1-(3-Benzoyloxymethyl-1,3-dihydrobenzo[*c*]furan-1-yl)thymine (15 and 16)

Chlorotrimethylsilane (1 mL) and a crystal of ammonium sulfate were added to a suspension of thymine (0.67 g, 5.28 mmol) in hexamethyldisilazane (10 mL) and the mixture refluxed with exclusion of moisture until a clear solution was obtained

(2 h). The solvent was evaporated and the residue taken up in dry MeCN (20 mL). The 1,3-dihydrobenzo[*c*]furan **10** (1.0 g, 3.52 mmol) was added and then trimethylsilyl trifluoromethanesulfonate (0.956 g, 0.78 mL, 4.22 mmol) was added at −35 °C, under nitrogen. After stirring under nitrogen for 1 h sat. $NaHCO_3$ (20 mL) was added, the mixture stirred for 30 min and then extracted with CH_2Cl_2 (40 mL). The extract was worked up and the crude product (yellow oil) chromatographed (hexane–EtOAc 7 : 3, then 1 : 1) to give a mixture of the thymine nucleoside analogues **15** and **16** as white solid (65%), mp 175–177 °C, *cis* : *trans* ratio 1 : 1.6 (Found: C, 66.50; H, 4.97; N, 7.24. Calc. for $C_{21}H_{18}O_5N_2$: C, 66.66; H, 4.79; N, 7.40%).

Crystallisation of this mixture of diastereoisomers from EtOH gave the pure *cis* isomer **15**; δ_H ($CDCl_3$) 1.6 (3 H, d, Me), 4.75 (1 H, m, $J_{3,8}$ 4.5, $J_{8a,8b}$ 12.5, H-8a), 4.83 (1 H, m, $J_{3,8b}$ 3.2, H-8b), 5.59 (1 H, m, H-3), 6.72 (1 H, q, thymine), 7.20–7.60 (8 H, m, H-1 and aromatic H), 7.85 (2 H, m, benzoyl), 8.15 (1 H, br s, NH); δ_C ($CDCl_3$) 12.0 (Me), 65.6 (C-8), 81.5 (C-3), 87.4 (C-1), 112.4 (thymine), 151.5, 163.7, 166.8 (CO); from the crystallisation liquor the *trans* isomer **16** was obtained in 70% diastereoisomeric purity; δ_H ($CDCl_3$) 1.5 (3 H, d, Me), 4.54 (1 H, m, $J_{3,8a}$ 6.6, $J_{8a,8b}$ 11.9, H-8a), 4.66 (1 H, m, $J_{3,8b}$ 3.6, H-8b), 6.57 (1 H, q, thymine), 5.85 (1 H, $J_{1,3}$ 2.9, H-3), 7.30–7.60 (8 H, m, aromatic H and H-1), 7.95 (2 H, m, benzoyl), 8.15 (1 H, br s, NH); δ_C ($CDCl_3$) 12.8 (Me), 66.6 (C-8), 82.5 (C-3), 88.2 (C-1), 151.0, 163.8, 166.8 (CO).

cis- and *trans*-1-(1,3-Dihydro-3-hydroxymethylbenzo[*c*]furan-1-yl)uracil (13 and 14)

The protected nucleoside **11** (0.5 g, 1.37 mmol) was dissolved in methanolic ammonia (20 mL) and the mixture stirred for 24 h. Evaporation of the solvent and column chromatography ($CHCl_3$–MeOH, 9 : 1) gave the *cis* isomer **13** (0.27 g, 75%); mp 115–117 °C (EtOH) (Found: C, 59.90; H, 4.75; N, 10.44. Calc. for $C_{13}H_{12}N_2O_4$: C, 59.99; H, 4.65; N, 10.77%); δ_H (DMSO) 3.83 (2 H, dd, $J_{3,8}$ 3.2, $J_{8,OH}$ 5.0, H-8), 5.05 (1 H, t, OH), 5.24 (1 H, m, H-3), 7.29 (1 H, s, H-1), 5.52, 7.31 (2 H, 2 d, *J* 8.1, uracil), 7.30–7.50 (4 H, m, aromatic H), 11.4 (1 H, br s, NH); δ_C (DMSO) 62.8 (C-8), 84.4 (C-3), 86.6 (C-1), 102.1, 136.3 (uracil), 122.2, 122.5, 129.5, 131.2, 140.5, 141.0 (aromatic C), 151.1, 163.2 (CO).

Nucleoside **12** was deprotected in the same way as above to give the *trans* isomer **14** (88%) as a hygroscopic off-white solid; δ_H (DMSO) 3.64 (1 H, ddd, $J_{8a,8b}$ 11.9, $J_{3,8a}$ 4.8, $J_{8,OH}$ 5.5, H-8a), 3.73 (1 H, ddd, $J_{3,8b}$ 4.0, H-8b), 4.94 (1 H, t, OH), 5.49 (1 H, m, H-3), 5.51, 7.03 (2 H, 2 d, *J* 8.1, uracil), 7.32 (1 H, d, $J_{1,3}$ 2.68 [in $CDCl_3$], H-1), 7.30–7.50 (4 H, m, aromatic H), 11.4 (1 H, br s, NH); δ_C (DMSO) 63.8 (C-8), 85.1 (C-3), 87.6 (C-1), 102.4, 136.2 (uracil), 122.2, 122.4, 128.6, 129.6, 140.7, 140.8 (aromatic C), 150.9, 163.1 (CO).

cis- and *trans*-1-(1,3-Dihydro-3-hydroxymethylbenzo[*c*]furan-1-yl)thymine (17 and 18)

Protected nucleoside **15** or **16** (1.39 g, 3.67 mmol) in methanolic ammonia (70 mL) was stirred at room temperature for 24 h. The solvent was evaporated off and the residue purified by chromatography (hexane–ethyl acetate, 3 : 8) to give compound **17** or **18** identical to the products reported previously.[7]

cis- and *trans*-1-(1,3-Dihydro-3-hydroxymethylbenzo[*c*]furan-1-yl)cytosine (21 and 22)

Et_3N (1.91 mL, 13.73 mmol) was added dropwise to a stirred mixture of 1,2,4-triazole (0.99 g, 14.37 mmol), $POCl_3$ (0.47 g, 0.29 mL, 3.05 mmol) and acetonitrile (10 mL) cooled to 0 °C. A solution of the uracil nucleoside analogue **11** or **12** (1.0 g, 1.37 mmol) in acetonitrile (5 mL) was added and the mixture stirred at 24 °C for 24 h. Et_3N (1.4 mL, 9.59 mmol) and water (0.6 mL) were added, and after 10 min the solvents were removed under vacuum. The residue was partitioned between dichloromethane (30 mL) and ice-cold sat. aq. $NaHCO_3$ (30 mL). The aqueous phase was extracted with dichloromethane and the combined extracts worked up to give the 1,2,4-triazol-1-yl derivatives **19** or **20** respectively which were each used directly without further purification. *cis*-Isomer **19**, R_f 0.59 ($CHCl_3$–MeOH, 9 : 1); δ_H (DMSO) 4.80 (1 H, m, $J_{3,8a}$ 5.4, $J_{8a,8b}$ 12.0, H-8a), 4.84 (1 H, m, $J_{3,8b}$ 3.2, H-8b), 5.74 (1 H, m, H-3), 6.66 (1 H, d, *J* 7.2, cytosine), 7.45–7.65 (8 H, m, H-1 and aromatic H), 7.85 (2 H, m, benzoyl), 8.02 (1 H, d, cytosine), 8.37 (1 H, s, NH), 9.44 (1 H, s, triazolyl); δ_C (DMSO) 66.1 (C-8), 82.6 (C-3), 89.6 (C-1); *trans* isomer **20**, R_f 0.62 ($CHCl_3$–MeOH 9 : 1); δ_H (DMSO) 4.63 (1 H, m, $J_{3,8a}$ 5.1, $J_{8a,8b}$ 12.0, H-8a), 4.76 (1 H, m, $J_{3,8b}$ 3.2, H-8b), 6.10 (1 H, $J_{1,3}$ 2.9, H-3), 6.90 (1 H, 2 d, *J* 7.2, cytosine), 7.40–7.66 (8 H, m, aromatic H and H-1), 7.81 (2 H, m, benzoyl), 8.19 (1 H, d, cytosine), 8.38 (1 H, br s, NH), 9.44 (triazolyl); δ_C (DMSO) 66.3 (C-8), 83.0 (C-3), 90.6 (C-1).

30% Aq. NH_3 (3 mL) was added to a solution of the 1,2,4-triazol-1-yl derivative **19** or **20** (0.5 g, 1.05 mmol) in 1,4-dioxane (9 mL) and the mixture stirred at 20 °C for 12 h. The solvent was evaporated and the residue dissolved in methanol (10 mL) which was previously saturated with ammonia. The mixture was stirred for 24 h, the solvent evaporated and the residue purified by flash chromatography ($CHCl_3$–MeOH, 4 : 1) to give the cytosine nucleoside analogue **21** or **22** respectively; *cis* isomer **21**, 235 mg (75%); mp 164–166 °C (aq. EtOH); R_f 0.11 ($CHCl_3$–MeOH 9 : 1); δ_H (DMSO) 3.83 (2 H, m, H-8), 5.04 (1 H, t, OH), 5.22 (1 H, m, H-3), 5.62 (1 H, d, *J* 7.3, uracil), 7.2 (3 H, br m, NH_2 and cytosine), 7.2–7.45 (8 H, m, H-1 and aromatic H); δ_C (DMSO) 63.1 (C-8), 84.2 (C-3), 87.2 (C-1), 94.5, 137.7, 165.9 (cytosine), 122.1, 122.4, 128.5, 129.2, 140.3, 141.8 (aromatic C), 155.7 (CO); *trans* isomer **22**, 275 mg (88%); mp 204–206 °C (aq. EtOH); R_f 0.11 ($CHCl_3$–MeOH, 9 : 1) (Found: C, 59.70; H, 5.11; N, 16.06. Calc. for $C_{13}H_{14}N_3O_3$: C, 59.85; H, 5.41; N, 16.11%); δ_H (DMSO) 3.63 (1 H, m, $J_{3,8a}$ 5.5, $J_{8a,8b}$ 11.7, H-8a), 3.72 (1 H, m, $J_{3,8b}$ 4.5, H-8b), 4.95 (1 H, t, OH), 5.48 (1 H, m, $J_{1,3}$ 2.7, H-3), 5.63 (1 H, d, *J* 7.6, cytosine), 7.05 (1 H. d, cytosine), 7.21 (2 H, br s, NH_2), 7.39 (1 H, d, $J_{1,3}$ 2.7, H-1), 7.25–7.45 (aromatic H); δ_C (DMSO) 64.0 (C-8), 84.8 (C-3), 88.1 (C-1), 94.7, 137.8, 165.6 (cytosine), 122.1, 122.3, 128.5, 129.2, 140.4, 141.2 (aromatic C), 155.5 (CO).

(*S*)- and (*R*)-1-[2-(1,3-Dioxan-2-yl)phenyl]ethane-1,2-diol (24 and 25)

AD-mix-α or AD-mix-β (19.98 g) in a mixture of *tert*-butyl alcohol (71.35 mL) and water (71.35 mL) was stirred at room temperature until both phases were clear. The mixture was cooled to 0 °C and [2-(1,3-dioxan-2-yl)phenyl]ethene (2.71 g, 14.27 mmol) was added to the mixture at −10 °C. The resulting slurry was stirred vigorously at 0 °C for 1 h. Sodium sulfite (21.4 g) was added and the mixture stirred at 20 °C for 30 min, then diluted with water (80 mL) and extracted with dichloromethane. This extract was worked up and the crude product purified by column chromatography (gradient of hexane–EtOAc, 3 : 7; then 2 : 8, then 1 : 9, then pure EtOAc) to give the diol as an oil (Found: C, 63.03; H, 7.35. Calc. for $C_{12}H_{16}O_4 \cdot 0.25H_2O$: C, 63.00; H, 7.27%); AD-mix-α reagent gave the (*S*)-enantiomer **24**, 2.7 g (85%) (ee >99% by comparison of NMR spectra with added chiral shift reagent), $[\alpha]_D^{22}$ +32.8 (*c* 3.86 in $CHCl_3$); AD-mix-β gave the (*R*)-enantiomer **25**, 2.5 g (78%) (ee >99% by comparison of NMR spectra with added chiral shift reagent), $[\alpha]_D^{22}$ −33.6 (*c* 3.42 in $CHCl_3$); both enantiomers had R_f 0.1 (hexane–ethyl acetate, 3 : 7); δ_H ($CDCl_3$) 1.46, 2.25, 3.89, 4.25 (6 H, m, dioxanyl), 2.7, 3.2 (2 H, two br s, OH), 3.75 (2 H, m, OCH_2), 5.24 (1 H, m, OCH), 5.81 (1 H, s, dioxanyl), 7.4–7.65 (4 H, m, aromatic H); δ_C ($CDCl_3$) 25.6, 67.2, 67.6, 101.0 (dioxanyl), 67.2, 70.5 (OCH_2CHO), 126.7, 126.9, 127.8, 129.3, 135.6, 139.0 (aromatic C).

(*S*)- and (*R*)-1-*O*-Benzoyl-2-[2-(1,3-dioxan-2-yl)phenyl]ethane-1,2-diol (26 and 27)

Benzoyl chloride (12.55 g, 18.15 mmol) in chloroform (6 mL) was added to the diol **24** or **25** (3.7 g, 16.53 mmol) in pyridine (39 mL) at −20 °C and the mixture stirred for 2 h at −10 °C, then overnight at 20 °C. Ice–water was added, the mixture stirred for 30 min and then extracted with dichloromethane. This extract was worked up and the crude product purified by column chromatography (hexane–ethyl acetate, 7:3) to afford the protected diol **26** or **27** as an oil, 4.9 g (89%) (Found: C, 69.02; H, 6.08. Calc. for $C_{19}H_{14}O_4$: C, 69.49; H, 6.14%); (*S*)-enantiomer (**26**) $[a]_D^{22}$ +30.2 (*c* 4.04 in $CHCl_3$), (*R*)-enantiomer **27** $[a]_D^{22}$ −28.9 (*c* 3.97 in $CHCl_3$); both enantiomers had R_f 0.5 (hexane–ethyl acetate, 7:3); δ_H ($CDCl_3$) 1.45, 2.23, 4.00, 4.25 (6 H, m, dioxanyl), 3.1 (1 H, d, OH), 4.43, 4.67 (2 H, two dd, OCH_2), 5.55 (1 H, m, OCH), 5.74 (1 H, s, dioxanyl), 7.2–8.2 (4 H, m, aromatic H); δ_C ($CDCl_3$) 25.6, 67.47, 67.54, 100.8 (dioxanyl), 68.6, 69.1 (OCH_2CHO), 171.2 (CO).

(1*S*,3*S*)- and (1*R*,3*R*)-3-Benzoyloxymethyl-1,3-dihydro-1-methoxybenzo[*c*]furan (28 and 29)

Compound **26** or **27** (4.74 g, 14.43 mmol) and toluene-*p*-sulfonic acid (0.18 g, 0.9 mmol) in a mixture of acetone (47 mL) and water (54 mL) was refluxed for 2.5 h. The solution was neutralised (sat. aq. Na_2CO_3) and extracted with ethyl acetate, dried ($MgSO_4$) and concentrated *in vacuo* to give the 1-hydroxy-1,3-dihydrobenzo[*c*]furan derivative as a white solid, 3.5 g (90%), mp 94–96 °C, R_f 0.2 (hexane–ethyl acetate, 7:3) (Found: C, 70.92; H, 5.27. Calc. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22%). This material (3.21 g, 11.88 mmol) was methylated directly by stirring with methanolic HCl (1%, 60 mL) at 20 °C for 1 h. The solution was concentrated to about 10 mL and the precipitate collected to give the 1,3-dihydro-1-methoxybenzo[*c*]furan **28** or **29** as a white solid, 3.1 g (92%); R_f 0.5 (hexane–ethyl acetate, 7:3); mp 102–104 °C (Found: C, 72.00; H, 5.60. Calc. for $C_{17}H_{16}O_4$: C, 71.81; H, 5.67%); (1*S*,3*S*)-enantiomer $[a]_D^{22}$ +53.5 (*c* 2.5 in $CHCl_3$) (1*R*,3*R*)-enantiomer $[a]_D^{22}$ −54.2 (*c* 2.5 in $CHCl_3$); both enantiomers had NMR data identical to those for the racemic compound *trans*-**10**.

(1*R*,3*S*)-, (1*S*,3*S*)-, (1*R*,3*R*)- and (1*S*,3*R*)-1-(3-Benzoyloxymethyl-1,3-dihydrobenzo[*c*]furan-1-yl)uracils (30, 31, 32 and 33)

Compound **28** was converted to the uracil nucleoside analogue by the procedure employed above for the racemate. The mixture of stereoisomers (*cis*:*trans* ratio 1:2) was separated by chromatography as above to give the minor (1*R*,3*S*) isomer **30** $[a]_D^{27}$ −26 (*c* 2.4 in $CHCl_3$), and the major (1*S*,3*S*) isomer **31**, $[a]_D^{27}$ −97 (*c* 2.4 in $CHCl_3$). Similarly compound **29** was converted to a *cis*–*trans* mixture of uracil derivatives which was separated to give the (1*S*,3*R*) isomer **33**, $[a]_D^{27}$ +25 (*c* 2.4 in $CHCl_3$), and the (1*R*,3*R*) isomer **32** $[a]_D^{27}$ +98 (*c* 2.4 in $CHCl_3$). Each of these isomers had NMR data identical to those of the corresponding racemic compounds **11** and **12**.

(1*R*,3*S*)-, (1*S*,3*S*)-, (1*R*,3*R*)- and (1*S*,3*R*)-1-(3-Hydroxymethyl-1,3-dihydrobenzo[*c*]furan-1-yl)uracils (34, 35, 36 and 37)

Each of the protected nucleosides was treated as detailed above for the racemic compounds to give the stereochemically pure uracil derivatives; (1*R*,3*S*) isomer **34**, mp 164–166 °C, $[a]_D^{25}$ +69 (*c* 1.5, MeOH); (1*S*,3*S*) isomer **35**, mp 87 °C, $[a]_D^{25}$ −90 (*c* 1.0, MeOH); (1*R*,3*R*) isomer **36**, $[a]_D^{25}$ +89 (*c* 1.2, MeOH); (1*S*,3*R*) isomer **37**, $[a]_D^{25}$ −67 (*c* 0.9, MeOH). In all cases the NMR data were identical to those of the racemic compounds **13** and **14**.

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