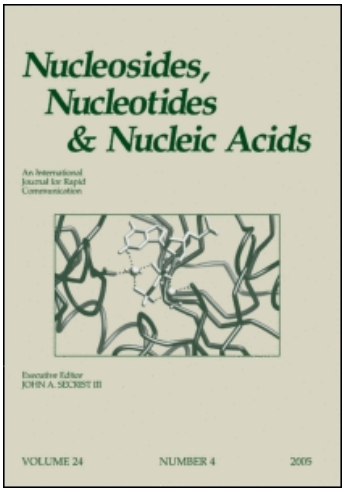

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NUCLEOSIDE ANALOGUES WITH A NOVEL GLYCONE BASED ON THE BENZO[*c*]FURAN CORE

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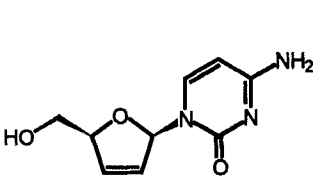
ABSTRACT: Routes to novel nucleoside analogues based on 1,3-dihydrobenzo[*c*]furan have been investigated. Thus 1-(1,3-dihydro-3-hydroxymethylbenzo[*c*]furan-1-yl)-thymine, an analogue of d4T, was obtained as two diastereoisomers. The *cis* compound (*quasi* β-D/α-L stereochemistry) was obtained pure but the *trans* compound was only 90% pure. A purine analogue with a four atom spacer group between base and glycone was also prepared. The conformation of these constrained nucleosides was studied by molecular modelling.

Introduction

Although the role of 3'-azido-3'-deoxythymidine (AZT) and the related 2',3'-dideoxynucleo-sides, ddI and ddC, as drugs for the control of HIV-1 and other viruses is well documented[1] the search for alternative agents continues because of growing concerns about resistance and long term toxicity.[2] One of the many other nucleoside structure modifications which was explored in the early work was the introduction of a double bond in the 2',3' position to give the 2',3'-didehydro-2',3'-dideoxy-ribonucleosides (d4Ns). A study of the anti-HIV activity of the d4Ns was reported by Balzarini *et al.*[3] in 1987 and there has subsequently been increasing interest in this class of compound. Of the four d4Ns tested initially, 2',3'-didehydro-2',3'-dideoxycytosine (d4C) **1** was the



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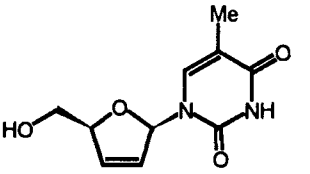

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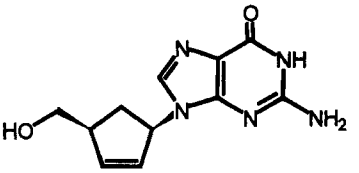

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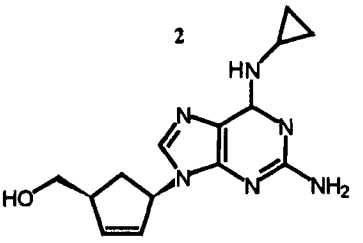

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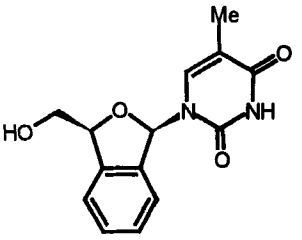

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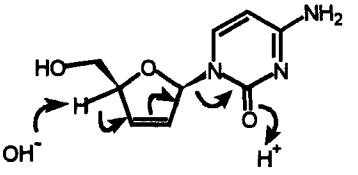


6

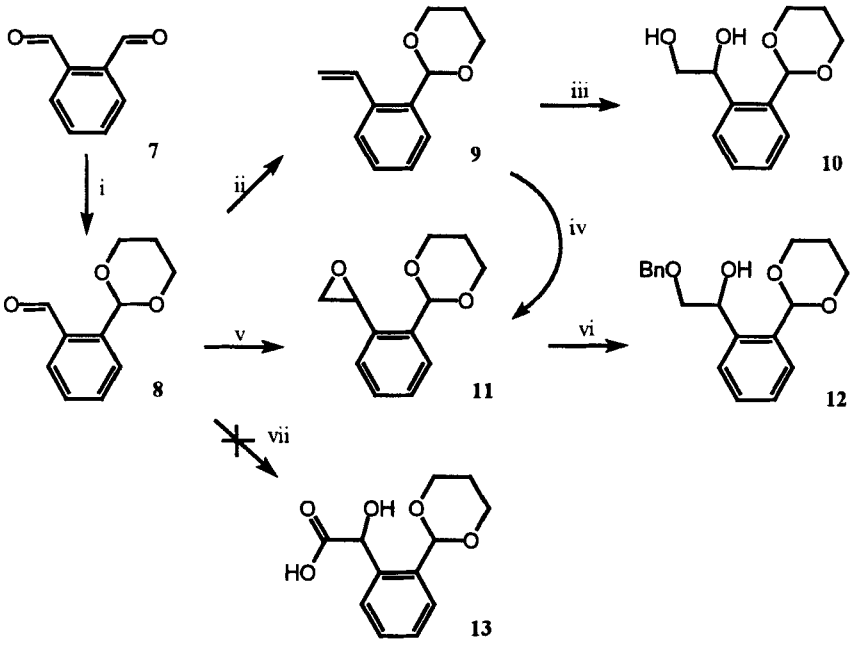
most potent agent against the ATH8 cell line although 2',3'-didehydro-3'-deoxythymidine (d4T) **2** was only slightly less effective and also less cytotoxic. Both compounds have a chemotherapeutic index close to that observed for the corresponding compounds without a double bond. The corresponding uridine and adenine compounds (d4U and d4A) were much less active as anti-viral agents when compared with their saturated analogues. Many substituted variants of d4C, d4T and d4U have been examined for antiviral activity[4] and d4T is now an approved anti-HIV drug (Stavudine).[5] It notable that the carbocyclic analogue of d4G (carbovir) **3** and the related compound **4** also have potent anti-HIV activity.[6] Although d4T is as effective as AZT in reducing the cytopathogenicity induced by HIV-1 and has less serious side effects (*e.g.* lower toxicity to bone marrow cells[7]) it is considerably less lipophilic then AZT and hence is less able to cross the blood-brain barrier.[8] 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. These include various 5'-O esters, phosphates and phosphoramidates,[8,9] and modifications to the pyrimidine moiety.[10]

We report in this work[11] a novel approach to the generation of a d4T analogue. A new glycone has been designed in which the 2',3' double bond is incorporated into a benzene ring to give a derivative of the benzo[*c*]furan system **5**. This new class of modified sugar nucleoside is attractive for several reasons. First, it retains the phosphorylation site. This is essential since the active form of d4T and the other anti-HIV agents is the corresponding 5'-triphosphate. The efficiency of 5'-O-phosphorylation of **5** a similar effect has been observed in some imidazole ribonucleosides.[12] Second, incorporation of the 2',3' double bond into an aromatic ring reduces the likelihood of the hydrolytic mechanism[4] which has been proposed for d4C (see **6**) since this mechanism would result in the loss of aromatic stability. Hydrolysis may contribute to the short half-life of d4T *in vivo*.[3] Third, the lipophilicity of **5** will be greater than that of d4T. Fourth, the rigidity of the system is enhanced. 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 locking the conformation of the furanose (or carbocyclic) ring by introducing a second ring are now of great interest. Several nucleosides with a bicyclic glycone have been synthesised in the search for conformationally restricted systems which might lead to enhanced duplex formation when incorporated into oligonucleotides.[13,14]

Results and Discussion

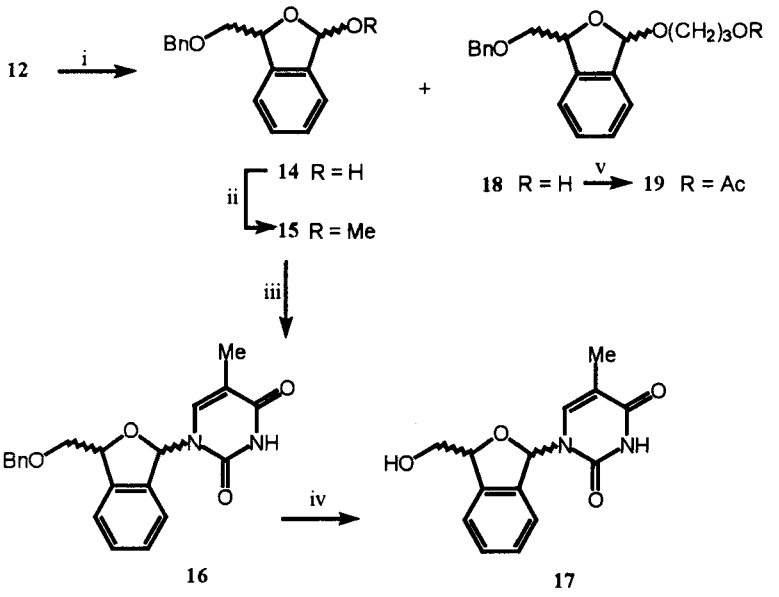
The target compound for the synthesis of nucleoside analogue **5** is 1,3-dihydro-1-hydroxy-3-hydroxymethylbenzo[*c*]furan (**14**, Bn = H) and retrosynthetic analysis suggests that *o*-phthalaldehyde **7** is the most promising starting point. This compound has the advantage of being stable, inexpensive and easily available. Phthalaldehyde was converted to the semi-protected aldehyde **8** by reaction with propane-1,3-diol in 78% yield (Scheme 1). Introduction of a one carbon fragment (which would become C-5 of the glycone) was attempted by several routes. Application of the Wittig reaction gave the alkene **9** in 80% yield Epoxidation of the double bond with *m*-chloroperbenzoic acid



Scheme 1 *Reagents and conditions:* i, propane-1,3-diol, *p*-$MeC_6H_4SO_3H$, toluene, reflux; ii, Ph_3PCH_2Br, *n*-BuLi, THF; iii, $KMnO_4$, NaOH, $PhCH_2NEt_3^+Cl^-$ *or* OsO_4 25% in *t*-BuOH, *N*-methylmorpholine-*N*-oxide, pyridine, H_2O; iv, *m*-Chloroperbenzoic acid, $CHCl_3$; v, $Me_3SO^+ I^-$, NaH, DMSO, THF, 100°; vi, BnOH, NaH, DMF; vii $CHCl_3$, NaOH, $PhCH_2NEt_3^+Cl^-$.

to give compound **11** could not be achieved with a reproducible yield. On a 2 mmol scale the yield of the oxirane was 87% but this could not be repeated when scaled up and this route was not pursued. Dihydroxylation of alkene **9** with alkaline aqueous potassium permanganate using phase transfer conditions[15] gave the diol **10** in only 23% yield. The reagents osmium tetroxide and N-methyl morpholine N-oxide reacted smoothly with the alkene on a small scale and the diol **10** was obtained in 85% yield. However, the high toxicity of the agent precluded its use on a larger scale.

The direct conversion of aldehyde **7** to the oxirane **11** was achieved by methylene insertion with trimethylsulfonium iodide, a method developed by Corey.[16] The oxirane was subjected directly to ring opening with the sodium salt of benzyl alcohol. The benzylated compound **12** was obtained after chromatography in 72% yield. Formation



Scheme 2 *Reagents and conditions:* i, Acetone, *p*-$MeC_6H_4SO_3H$; ii, MeOH, HCl; iii, Silylated thymine, TMSOTf, MeCN; iv, Pd/C, H_2, MeOH; v, AcCl, pyridine.

ofthe epoxide under heterogeneous conditions[17] gave a similar yield. An interesting direct preparation of mandelic acid has been reported involving reaction of benzaldehyde with dichlorocarbene under phase transfer conditions.[18] Unfortunately application of this procedure to aldehyde **7** to obtain the mandelic acid derivative **13** was unsuccessful due to steric inhibition by the large ortho substituent.

Removal of the acetal group from compound **12** under acidic conditions resulted in spontaneous cyclisation to afford a mixture of *cis* and *trans* isomers of 3-benzyloxymethyl-1,3-dihydro-1-hydroxybenzo[*c*]furan **14** in 45% yield (Scheme 2). The ratio of diastereoisomers was 1.5:1, the minor (*trans*) isomer showing a cross-ring coupling $J_{1,3}$ which was absent in the major (*cis*) isomer. The assignment of stereochemistry is discussed below. An interesting byproduct of this reaction (28% yield) was the hydroxypropyl derivative **18** (the result of intramolecular transacetalisation without displacement of the protecting group). This compound was also obtained as a pair of diastereoisomers (*ca.* 1:1). If the amount of acid catalyst was doubled,

compound **14** was the only product (85% yield). The 1,3-dihydrobenzo[*c*]furan derivative **14** is analogous to a dideoxysugar and was easily converted using HCl in methanol to the corresponding 1-methoxy derivative **15** (pseudo glycoside) in 92% yield with the *trans* isomer in excess (isomer ratio 1.5/1). The corresponding 1-acetoxy derivative was obtained by direct acetylation of **14** but it degraded on workup and that route was not pursued further. In contrast, the hydroxypropyl compound **18** gave a stable acetyl derivative **19**, as a pair of diastereoisomers in the ratio 2:1.

The pseudo glycoside **15** was converted to the nucleoside analogue **16** by standard Vorbruggen chemistry to give a pair of isomers in the ratio 1.5:1. This 20% diastereomeric excess is the same as that observed for the aglycone since the major isomer has the *cis* geometry (see below). This isomer crystallised and was finally obtained stereochemically pure. The *trans* isomer would not crystallise and was obtained in only 90% stereochemical purity. Removal of the benzyl group by catalytic hydrogenation gave the pure *cis* isomer of 1-(1',3'-dihydro-3'-hydroxy-methylbenzo[*c*]furan-1'-yl)thymine **17** and the 90% pure *trans* isomer.

Configuration

The assignment of stereochemistry for each isomer of the compounds **14–19** was initially based on the magnitude of the coupling between the dihydrofuran ring protons. The NMR spectra of the 1,3-dihydrobenzo[*c*]furan system have been investigated for several compounds with one or no substituent in the dihydrofuran ring.[19,20] The observed coupling between H-1 and H-3 in a *cis* arrangement is in the range 0–2 Hz and the corresponding *trans* coupling is in the range 2.0–3.4 Hz. Theoretical calculations on this system and on 2,5-dihydrofuran indicate that the magnitude of the four-bond cross ring coupling is dependent on the degree of the ring pucker. But for all small pucker angles the *trans* coupling is larger than both the *cis* couplings and hence the isomer of compounds **14–20** with the larger cross-ring coupling is assigned the *trans* configuration. The data in Table 1 indicate that there are several spectral features which taken together strongly support the assignment of a common configuration to the compounds with a measurable cross-ring coupling. Further support is found in the NOESY spectrum of the mixed isomers of **16.** This spectrum showed a strong contact between the thymine H6

Table 1. Comparative data[a] for the 1,3-dihydrobenzo[*c*]furan stereoisomers

	cis isomer			*trans* isomer			
Compd.	δ(H-1)	δ(H-3)	$J_{1,3}$	δ(H-1)	δ(H-3)	$J_{1,3}$	ratio *cis/trans*[b]
14	6.30	5.29	<0.5	6.52	5.54	2.1	1.5
15	6.12	5.33	<0.5	6.22	5.54	2.2	0.6
16	7.49	5.40	*c*	7.55	5.66	2.6	1.5
17	7.28	5.23	*c*	7.33	5.55	2.8	
18	6.19	5.32	<0.5	6.28	5.5	1.6	1.0
19	6.19	5.33	<0.5	6.27	5.5	2.1	2.0
20	6.19	5.34	<0.5	6.27	5.5	2.2	0.7

[a] The benzo[*c*]furan protons in the pseudo nucleosides are numbered with primes (see Fig 2 below) but that distinction is ignored in this Table. [b] From crude reaction products. [c] Not accessible.

proton and H-3 in the *trans* isomer (protons on the same side of the furan ring) but no analogous contact in the *cis* isomer (protons on the opposite side of the furan ring).

An attempt was made to determine the value of the cross-ring coupling in both isomers of compound **16**. In the *trans* isomer the H-8'a and H-8'b protons are easily decoupled from H-3' revealing a $J_{1',3'}$ value of 2.6 Hz. However the magnitude of the corresponding coupling in the *cis* isomer was much more difficult to establish. The chemical shift separation of the H-8' protons is such that they could not be precisely decoupled simultaneously from H-3'. Proton H-1' overlaps with some of the aromatic protons and cannot be examined directly. Decoupling H-1' together with the use of extreme line narrowing indicated at least two small couplings between H-3' and the aromatic protons (*ca.* 0.6 Hz) and a value for $J_{1',3'}$ could not be determined unequivocally.

Molecular modelling

In order to confirm the assignment of structure the relative energies of the diastereoisomers of glycone **14** and its derivatives have been examined by molecular modelling using the Nemesis programme. For the purposes of calculation the benzyl

Fig. 1 Conformational forms of 1,3-disubstituted benzo[*c*]furans.

group in **14** was replaced by methyl. This reduces the computing time without prejudicing the evaluation of the energetics of the ring. These dihyrobenzo[*c*]furan compounds exists in a puckered form with the oxygen atom of the dihydrofuran ring either above or below the plane containing the benzene ring and carbons C-1 and C-3 (envelope conformation). The substituents at the 1,3 positions adopt pseudo axial or pseudo equatorial orientations. The *cis* isomer can thus exist in *ee* or *aa* forms and the trans isomer in *ea* and *ae* forms (Fig 1). In all cases the energies are likely to be similar.

In each of these four forms there are three rotatable bonds allowing 27 possible conformations. An attempt was made to determine the energy of every rotamer but many are unstable and convert to a lower energy conformation during the minimisation procedure. (This sometimes involved inversion of the dihydrofuran ring. The energy barrier for inversion of the *trans* isomer between *ae* and *ea* conformations is less than 1 kcal mol^{-1}). A complete mapping of the conformational space revealed only 32 minima in the *trans* compound and 31 in the *cis* compound, but in nearly all cases the energies are too high for the corresponding conformers to be significantly populated. Only four conformations had a population of 5% or greater and the energies and population distribution are shown in Table 2. All other forms contribute 2% or less.

Perhaps not surprisingly, these four conformations correspond to the most stable conformer of each of the general types shown in Fig. 1.

The cis isomer of compound **14** exists mainly (population *ca.* 75%) as the *aa* form with the OH group at C1 directed over the ring to form a hydrogen bond to the oxygen atom of the CH_2OR group at C3. The only other significant conformation is the *ee* form (16%, 0.9 kcal mol^{-1} higher in energy) with the OH group directed over the ring but with

Table 2 Conformational energies and populations of the isomers of **14** and **17.**

	Isomer	Relative conformer energy[a]/kcal mol^{-1}	Relative conformer populations for each isomer[b]	Overall relative population[c]
14	*cis* (aa)	0	75%	71%
14	*cis* (ee)	0.89	16%	16%
14	*trans* (ea)	1.32	37%	7%
14	*trans* (ae)	1.46	29%	6%
17[d]	*cis*(ee)	0	29%	18%
17	*cis*(ee)	0.07	26%	16%
17	*cis*(ee)	0.24	19%	12%
17	*cis*(ee)	0.51	12%	8%
17	*cis*(ee)	0.78	8%	5%
17	*cis*(ee)	0.91	6%	4%
17	*trans*(ea)	0.04	46%	17%
17	*trans*(ea)	0.50	21%	8%
17	*trans*(ea)	0.54	20%	7%
17	*trans*(ea)	1.11	8%	3%
17	*trans*(ea)	1.35	5%	2%

[a] Expressed relative to the global minimum for each isomer pair. [b] Calculated on the basis of excluding all forms with less than 2% population for **14**, or 4% for **17**. [c] Calculated by including both *cis* and *trans* contributing forms. [d] Data are listed for the set of conformers corresponding to rotational variation about the C3'–C8' and C8'–O8' bonds.

the C3 substituent arranged all-trans with respect to the ring oxygen. No hydrogen bonding is possible between the substituents in the *trans* form of **14** but the two lowest energy forms are the *ae* and *ea* conformations each with the hydroxy group pointing over the ring to the C3 substituent which adopts an all-trans relationship to the ring oxygen. These two forms differ by only 0.14 kcal mol^{-1} and account for about 66% of the population of this diastereoisomer. If the selectivity of the ring closure step (**12** to **14**) is evidence of thermodynamic control then the expected ratio *cis:trans* should reflect the overall population distribution shown in Table 2. The *cis* isomer clearly predominates (87%) but the predicted diastereoisomeric excess (0.74) is greater than that observed (0.2).

Similar calculations were carried out for the thymine derivative **17**. In this case the threefold potentials for the C3'–C8' and C8'–O8' bonds were combined with a twofold potential for the C1'–N1 bond (*syn* and *anti*). Every conformation was investigated and it was found in all cases that the *syn* orientation of the thymine group had a higher energy than that calculated for the *anti* orientation. The energy difference was 3–4 kcal mol^{-1} in most cases and the *syn* conformation does not contribute.

For both the *trans* and *cis* isomers of **17**, the form with the thymine group in an axial position was unstable (*i.e.* only two of the four forms in Fig. 1 contribute). Thus each isomer has only one stable ring conformation, in each case with the thymine substituent in equatorial orientation. The *cis* isomer adopts an *ee* form with the ring oxygen below the ring plane (*i.e.* trans to the substituents). Depending on the conformation of the CH_2OH group the dihedral angle between the two planes of this envelope form† is in the range 10°–30°. In the minimum energy form this angle is 28° and the C8' oxygen is trans to the benzene ring. The plane of the *anti* thymine group is nearly orthogonal to the benzo[*c*]furan ring plane (notional dihedral angle between these planes is *ca.* 102°).

The *trans* isomer has very similar stereochemical features. It adopts a minimum energy (*ea)* conformation which has the ring oxygen 27° out of the plane, (angle defined as above) the thymine ring in an equatorial position with its ring plane nearly orthogonal to the benzo[*c*]furan ring plane (100°) and the C8' oxygen trans to the benzene ring. It is evident that the two substituents in a nucleoside analogue based on a benzo[*c*]furan core have negligible interaction and hence quasi α and β configurations will behave similarly. Table 2 gives the relative energies for all conformers of the isomers of **17** which have a population greater than 4% (column 4). The fact that there are eleven of these confirms that the conformation of the C3' substituent is little influenced by the thymine group. The final column of Table 2 gives the normalised populations for the pair of isomers of **17** assuming these are in thermodynamic equilibrium. These figures indicate a *cis:trans* ratio of 1.7:1, in excellent agreement with the observed isomeric ratio of 1.5:1 for the ring closure reaction.

† The two planes of the ring are those defined by (i) the atoms C1', C3' and the benzene ring and (ii) the atoms C1', O2' and C3'

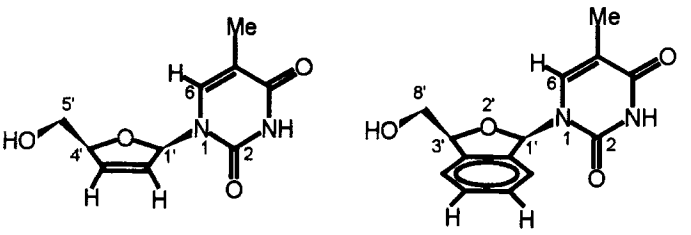


Fig 2. Numbering system for d4T and benzo[*c*]furan nucleoside analogues

The *cis* isomer of **17** is the analogue of d4T and could be expected to have similar biochemical behaviour *in vivo*. Comparison of the molecular shape of *cis*-**17** with d4T shows that these molecules have essentially the same shape. With the CH_2OH group in an all-trans arrangement with respect to the ring oxygen atom the minimum energy forms gave the following intramolecular distances (in Å, d4T first using the numbering indicated in Fig. 2): H6–O2' 2.38, H6–O4' 2.42; O2–H1' 2.44, O2–H1' 2.41; N1–C5' 4.56, N1–C8' 4.57; N1–O5' 5.75, N1–O8' 5.80. The relationship of the thymine ring plane to the CH_2OH group is indicated by the notional dihedral angle C5'–C4'–C1'–N1 in d4T which is 2.1° and angle C8'–C3'–C1'–N1 in *cis*-**17** which is 2.6°. The one crucial difference between these two molecules is the size of the lipophilic part; in d4T the olefinic hydrogen atoms are *ca.*2.3 Å out from the approximate plane containing all the polar bonds whereas the corresponding distance to the remote benzene ring protons in *cis*-**17** is *ca.* 4.8 Å. The close spatial similarity of these two compounds when taken with this crucial difference suggests that the benzo[*c*]furan system has chemotherapeutic potential.

Experimental

General procedures. NMR spectra were recorded with JEOL GX270 and Lambda 400 spectrometers using standard conditions with a data point resolution of *ca.* 0.1Hz. ^1H 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 ^1H spectra were made by detailed analysis using decoupling

or correlation techniques where appropriate. Diastereomeric 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.

2-(1,3-Dioxan-2-yl)benzaldehyde (8). A stirred mixture of *o*-phthalaldehyde (25 g, 186.4 mmol), 1,3-propanediol (14.2 g, 186.37 mmol), toluene-4-sulphonic acid (0.4 g) and toluene (50 mL) was refluxed for 5 h using a Dean-Stark condenser. Et_3N (2 mL) was added and the reaction mixture cooled and extracted with diethyl ether (100 mL). The extract was worked up and the crude product purified by column chromatography (hexanes–diethyl ether gradient). The monoprotected compound **8** was obtained as a light yellow syrup (27 g, 75%); R_f= 0.3 (1:1 hexane–diethyl ether); ^{1}H NMR ($CDCl_3$): δ 1.48, 2.26, 4.05, 4.28 (6 H, m, dioxanyl), 6.03 (1 H, s, dioxanyl), 7.45–7.95 (4 H, m, benzene ring), 10.53 (1 H, s, CHO); ^{13}C NMR ($CDCl_3$): δ 25.7, 67.7, 100.1 (dioxanyl), 127.3, 129.2, 129.7, 133.5, 133.8, 139.6 (benzene ring), 192.3 (CHO). Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29; Found: C, 69.70; H, 6.32. deg

[2-(1,3-Dioxan-2-yl)phenyl]ethene (9). *n*-BuLi (2.5 M in hexane, 28 mL, 70 mmol) was added dropwise to a solution of methyl triphenylphosphonium bromide (25g , 70 mmol) in dry THF (150 mL) under nitrogen. After the solution became red, compound **8** (9.6 g) was added at 0 °C. The mixture was stirred for 1 h at room temperature then poured into water (10 mL) and extracted twice with diethyl ether. The extract was worked up and the crude product was purified by column chromatography (hexane–ethyl acetate 9:1) to give compound **9** (7.32 g, 77%), mp 78–80 °C (from aqueous ethanol), R_f 0.6 (hexane–ethyl acetate 7:3); ^{1}H NMR ($CDCl_3$): δ 1.39, 2.18, 3.89, 4.17 (6 H, m, dioxanyl), 5.33 (1 H, dd, J_{gem}1.4, J_{cis} 11.0, ethene), 5.66 (1 H, dd, J_{trans} 17.5, ethene), 5.66 (1 H, s, dioxanyl), 7.14 (1 H. dd, H-1), 7.25–7.65 (4 H, m, benzene ring); ^{13}C NMR ($CDCl_3$): δ 25.8, 67.5, 67.5, 100.2 (dioxanyl), 116.2 (C-1), 126.0, 127.7, 128.9, 134.2 (benzene ring). Anal. Calcd. for $C_{12}H_{14}O_2$: C 75.76; H 7.42. Found C 75.60; H 7.60.

[2-(1,3-Dioxan-2-yl)phenyl]oxirane (11). (a) From alkene 9: Compound **9** (0.4 g, 2.10 mmol) in chloroform (15 mL) was added to a mixture of 3-chloroperbenzoic acid

(2.18 g, 50-60% technical, 12.6 mmol) and solid sodium carbonate (0.67 g, 6.3 mmol) in chloroform (20 mL) at 0 °C over a period of 30 min. The reaction was stirred for a further 5 h. Dichloromethane was added and the solution washed with 10% aqueous sodium bisulfite solution (20 mL) and worked up to give a crude product which was purified by column chromatography (hexane–diethyl ether, 7:3) to afford **11** as a yellow oil (0.380 g, 87%): R_f 0.3 (hexane–diethyl ether, 1:1); ^{1}H NMR ($CDCl_3$): δ 1.45, 2.22, 3.98, 4.26 (6 H, m, dioxanyl), 5.71 (1 H, s, dioxanyl), 2.7, 3.16, 4.34 (3 H, m, oxirane ring), 7.25–7.55 (4 H, m, benzene ring); ^{13}C NMR ($CDCl_3$) δ 25.7, 67.5, 100.6 (dioxanyl), 49.8, 51.0 (oxirane ring), 124.3, 126.2, 127.7, 129.2, 135.8, 136.6 (benzene ring). Anal. Calcd. for $C_{12}H_{14}O_3$: C 69.89; H 6.84; Found C 69.82; H 6.52.

(b) From aldehyde 8: A solution of ylide was prepared[15] under nitrogen from sodium hydride (0.7 g, 31.2 mmol), trimethylsulfoxonium iodide (6.9 g, 31.2 mmol) and 60 mL of dimethylsulfoxide. After 30 min. a solution of **8** (4.0 g, 20.8 mmol) in dry THF (30 mL) was added and the mixture stirred at room temperature for 1h. The reaction mixture was poured into cold water (100 mL) and the aqueous layer extracted with ether. The combined extracts were worked up and the crude product purified by column chromatography (hexane–diethyl ether 7:3) to give compound **11** (2.1 g, 49%) as a pale yellow syrup; R_f 0.3 (hexane–diethyl ether 1:1); the NMR data were identical to those given above.

2-*O*-Benzyl-1-[2-(1,3-dioxan-2-yl)phenyl]ethanediol (12). Benzyl alcohol (2.0 g, 18.2 mmol) was added to a suspension of sodium hydride (0.4 g, 18.2 mmol) in dry DMF (60 mL) and the mixture stirred at room temperature under nitrogen for 30 min. The oxirane **11** (3.0 g, 15.16 mmol) was added dropwise and the mixture stirred for further 3 h at 100°C. The solution was poured into ice–water and extracted with ether (2x60 mL). The combined extracts were worked up and the crude product purified by column chromatography (hexane–ethyl acetate gradient) to give compound **12** as an oil (3.3 g, 72%); R_f 0.25 (hexane-ethyl acetate 1:1); ^{1}H NMR ($CDCl_3$): δ 1.39, 2.18, 3.89, 4.17 (6 H, m, dioxanyl), 2.95 (1 H, d, OH), 3.54 (1 H, dd, $J_{2a,2b}$ 9.8, H-2a), 3.71 (1 H, dd, H-2b), 4.56, 4.62 (2 H, AB q, J_{AB} 12.2, benzyl), 5.34 (1 H, dt, $J_{1,2a}$ 9.0, $J_{1,2b}$ 3.2, $J_{1,OH}$ 3.2, H-1), 5.61 (1 H, s, dioxanyl), 7.25–7.55 (4 H, m, benzene ring); ^{13}C NMR: ($CDCl_3$): δ 25.7, 67.4, 67.5, 100.5 (dioxanyl), 73.1, 75.0, 76.6 (C-1, C-2, benzyl).

[2-(1,3-Dioxan-2-yl)phenyl]ethanediol (10). *N*-Methylmorpholine-*N*-oxide (2.97 g, 21.9 mmol), pyridine (1.6 mL), H_2O (2.15 mL) and OsO_4 (454 μL of a 25% solution in *tert*-BuOH, 0.036 mmol) were added to a solution of alkene **9** (0.7 g, 3.6 mmol) in *tert*-BuOH (35 mL). The mixture was stirred at 75 °C under nitrogen for 1 h then treated with 20% aq. sodium bisulfite solution (7 mL) and evaporated to dryness. Saturated aq. NaCl (7 mL) was added and the mixture was extracted twice with ethyl acetate. The combined extracts were worked up and the crude product purified by column chromatography (hexane–ethyl acetate, 1:4) to give diol **10** in 85% yield; R_f 0.1 (hexane-ethyl acetate, 3:7); ^{1}H NMR ($CDCl_3$): δ 1.46, 2.25, 3.98, 4.27 (6 H, m, dioxanyl), 2.58 (1 H, br t, OH), 3.78 (2 H, m, H-2), 3.17 (1 H, d, OH), 5.27 (1 H, m, H-1), 5.65 (1 H, s, dioxanyl), 7.25–7.55 (4 H, m, benzene ring); ^{13}C NMR ($CDCl_3$): δ 25.5, 67.5, 101.1 (dioxanyl), 67.5, 70.4, (C-1, C-2), 126.7, 126.9, 127.8, 129.3, 135.6, 138.9 (benzene ring). Anal. Calcd. for $C_{12}H_{16}O_4 \cdot 0.25H_2O$: C 62.99; H 7.27. Found C 63.03; H 7.35.

3-Benzyloxymethyl-1,3-dihydro-1-hydroxybenzo[*c*]furan (14) and 3-benzyl-oxymethyl-1,3-dihydro-1-(3-hydroxypropyloxy)benzo[*c*]furan (18). Compound **12** (10 g, 32 mmol) was dissolved in a mixture of acetone (104 mL) and water (12 mL) containing a catalytic amount of toluene-4-sulphonic acid (0.8 g) and the mixture refluxed for 3 h. Saturated Na_2CO_3 was added and the acetone was removed under reduced pressure. The residue was extracted twice with chloroform, the extract worked up and the product purified by column chromatography (gradient hexane–EtOAc). The first component to elute was a yellow syrup, identified as compound **14** (4.3 g, 45%) R_f 0.75 (hexane–diethyl ether,7:3), obtained as a pair of diastereoisomers with a *cis/trans* ratio of 1.5:1.0; *Cis* isomer:^{1}H NMR ($CDCl_3$): δ 3.65 (1 H, m, H-8a), 3.86 (1 H, m, H-8b), 4.01 (1 H, d, OH), 4.41, 4.52 (2 H, ABq, J_{AB} 10.2, benzyl), 5.29 (1 H, t, $J_{3,8}$ 2.8, H-3'), 6.30 (1 H, d, $J_{1,OH}$ 11.6, $J_{1,3}$ <0.5, H-1); ^{13}C NMR ($CDCl_3$): δ 82.0 (C-3), 73.5 (C-8), 71.5 (benzyl), 100.8 (C-1),). *Trans* isomer: ^{1}H NMR ($CDCl_3$): δ 3.68 (3 H, m, H-8a, H-8b, OH), 4.59 (2 H, m, benzyl), 5.54 (1 H, dt, $J_{3,8}$ 5.2, $J_{1,3}$ 2.1, H-3), 6.52 (1 H, m, $J_{1,OH}$ 6.0, H-1); ^{13}C NMR ($CDCl_3$): δ 71.5 (benzyl), 73.0 (C-8), 81.6 (C-3), 101.1 (C-1),. For the mixture of diastereoisomers; Anal. Calcd. for $C_{16}H_{16}O_3$: C 74.98; H 6.29. Found C 74.91; H 5.85.

The second component to elute was identified as 3-benzyloxymethyl-1,3-dihydro-1-(3-hydroxypropyloxy)benzo[*c*]furan **18** (2.6 g, 32%), R_f 0.3 (hexane–ethyl acetate 7:3). This compound was also a pair of isomers, *trans/cis* ratio of 1:1; *Cis* isomer: ^{1}H NMR ($CDCl_3$): δ 1.9, 3.8 (6 H, m, propyl), 3.67 (1 H, m, H-8a, H-8b), 4.61 (2 H, benzyl), 5.32 (1 H, t, $J_{3,8}$ 6.0, H-3), 6.19 (1 H, s, H-1); ^{13}C NMR ($CDCl_3$): δ 106.7 (C-1), 81.8 (C-3), 73.5 (C-8), 73.0 (benzyl). *Trans* isomer: ^{1}H NMR ($CDCl_3$): δ 1.9, 3.8 (6 H, m, propyl), 3.67 (2 H, m, H-8a, H-8b), 4.61 (2 H, benzyl), 5.50 (1 H, m, H-3), 6.28 (1 H, d, $J_{1,3}$ 1.6, H-1); ^{13}C NMR ($CDCl_3$): δ 73.0 (benzyl), 73.5 (C-8), 82.3 (C-3), 106.4 (C-1).

3-Benzyloxymethyl-1,3-dihydro-1-methoxybenzo[*c*]furan (15). Compound **14** (5.0 g, 19.5 mmol) was dissolved in methanolic HCl (1%, 100 ml) and the mixture stirred for 2 h at room temperature. Water (120 ml) was added and the mixture extracted with diethyl ether. The extract was worked up and chromatographed to give compound **15** as a yellow oil (92% yield, *trans:cis* ratio 1.5:1) which was used directly. *Cis* isomer: ^{1}H NMR ($CDCl_3$): δ 3.468 (3 H, s, OMe), 3.70 (1 H, m, H-8a), 3.74 (1 H, m, H-8b), 4.64 (2 H, m, benzyl), 5.33 (1 H, dd, H-3), 6.12 (1 H, s, $J_{1,3}$ <0.5, H-1); ^{13}C NMR ($CDCl_3$): δ 54.9 (OMe), 73.5, 74.6 (C-8, benzyl), 82.4 (C-3), 107.3 (C-1); *Trans* isomer: ^{1}H NMR ($CDCl_3$): δ 3.46 (3 H, s, OMe), 3.69 (1 H, m, $J_{3,8a}$ 6.1, H-8a), 3.75 (1 H, m, $J_{3,8b}$ 4.4, H-8b),), 4.61, 4.64 (2 H, ABq, J_{AB} 12.2, benzyl), 5.54 (1 H, dt, $J_{3,8}$ 5.2, H-3), 6.22 (1 H, d, $J_{1,3}$ 2.2, H-1); ^{13}C NMR ($CDCl_3$): δ 4.5 (OMe), 73.0, 73.5 (C-8, benzyl), 82.0 (C-3), 107.1 (C-1).

1-(3-Benzyloxymethyl-1,3-dihydro-benzo[*c*]furan-1-yl)thymine (16). A suspension of thymine (0.56 g, 4,44 mmol) and a small crystal of ammonium sulphate in a mixture of hexamethyldisilazane (12 ml) and trimethylchlorosilane (1 ml) was refluxed until the solution was clear. This solution was concentrated to a syrup which was co-evaporated repeatedly with toluene. The final residue was dissolved in dry MeCN (20 ml) under N_2, compound **15** (1.0 g, 3.7 mmol) added and the mixture cooled to –15 °C. Trimethsilyl trifluoromethanesulphonate (510 μl, 4.44 mmol) was added and the mixture slowly warmed to room temperature. After 2 h saturated aq. $NaHCO_3$ was added and the mixture stirred for a further 30 min then extracted with CH_2Cl_2. The extracts were

worked up and the crude product purified by flash chromatography (hexane–ethyl acetate, 1:1) to give compound **16** as a pair of diastereoisomers (0.87 g, 65%). This syrup had a *cis/trans* ratio of 1.5:1, *i.e.* a diastereomeric excess (*de*) of 20%. Anal. Calcd. for $C_{21}H_{20}N_2O_4$: C 69.21; H 5.53; N 7.68. Found C 69.20; H 5.56; N 7.64.

The major isomer crystallised preferentially from ethanol to give a fraction with a *de* of 88%. Further recrystallisation gave the pure *cis* isomer, mp. 145–147 °C; ^{1}H NMR ($CDCl_3$): δ 1.45 (3 H, d, Me), 3.90 (1 H, m, $J_{3',8'a}$ 2.8, $J_{8'a,8'b}$ 11.0, H-8'a), 4.00 (1 H, m, $J_{3',8'b}$ 2.8, H-8'b), 4.50, 4.58 (2 H, ABq, $J_{A,B}$ 12.1, benzyl), 5.40 (1 H, m, H-3'), 7.10 (1 H, q, J_{Me} 1.4, H-6), 7.49 (1 H, m, H-1'), 8.45 (1 H, br s, NH); ^{13}C NMR ($CDCl_3$): δ 11.9 (Me), 71.1 (benzyl), 73.5 (C-8'), 83.2 (C-3'), 87.2 (C-1'), 111.1, 136.9, 151.3, 163.9 (thymine).

The residues from the isomer mixture after removal of the *cis* isomer were concentrated and a second crop of *cis* isomer removed. The final residue would not crystallise. It consisted of mainly *trans* isomer (*de* of 83–92%). *Trans* isomer: ^{1}H NMR ($CDCl_3$): δ 1.8 (3 H, d, Me), 3.71 (1 H, m, $J_{3',8'a}$ 5.8, $J_{8'a,8'b}$ 10.1, H-8'a), 3.75 (1 H, m, $J_{3',8'b}$ 4.4, H-8'b), 4.62 (2 H, s, benzyl), 5.66 (1 H, m, H-3'), 6.60 (1 H, q, H-6), 7.55 (1 H, m, $J_{1',3'}$ 2.8, H-1'), 8.55 (1 H, br s, NH); ^{13}C NMR ($CDCl_3$) δ 11.9 (Me), 71.1 (benzyl), 73.5 (C-8), 83.2 (C-3), 87.2 (C-1), 111.1, 136.9, 151.3, 163.9 (thymine).

1-(1,3-Dihydro-3-hydroxymethylbenzo[*c*]furan-1-yl)thymine (17). The pure *cis* isomer of compound **16** was deprotected using hydrogen over 10% Pd on carbon in methanol by standard procedures. After chromatography the *cis* isomer of **17** had mp 202-204 °C: ^{1}H NMR ([$(CD_3)_2SO$]): δ 1.65 (3 H, Me), 3.87 (2 H, dd, $J_{3',8'}$ 3.5, $J_{8',OH}$ 5.0, H-8'a, H-8'b), 5.1 (1 H, t, OH), 5.23 (1 H, m, H-3'), 7.25 (1 H, q, J_{Me} 1.4, H-6), 7.28 (1 H, m, H-1'), 11.4 (1 H, br s, NH); ^{13}C NMR ([$(CD_3)_2SO$]): δ 12.1 (Me), 62.7 (C-8'), 86.3 (C-1'), 84.4 (C-3'), 109.5, 136.5, 151.1, 163.8 (thymine). The stereochemically impure *trans* was obtained similarly as a foam: ^{1}H NMR ([$(CD_3)_2SO$]): δ 1.62 (3 H, Me), 3.66 (1 H, m, $J_{3',8a}$ 4.8, $J_{8'a,8'b}$ 11.6, H-8'a), 3.74 (1 H, m, $J_{3',8'b}$ 3.9, H-8'b), 5.0 (1 H, br s, OH), 5.55 (1 H, m, $J_{1,3}$ 2.8, H-3'), 6.89 (1 H, q, J_{Me} 1.3, H-6), 7.33 (1 H, m, H-1'), 11.3 (1 H, br s, NH), ^{13}C NMR ([$(CD_3)_2SO$]): δ 12.1 (Me), 63.9 (C-8'),

85.1 (C-3'), 87.4 (C-1'), 110.2, 136.5, 150.9, 163.8 (thymine). Anal. Calcd. for $C_{14}H_{14}N_2O_4$: C 61.30; H 5.14; N 10.22. Found C 61.01; H 5.33; N 10.54.

1-(3-Acetoxypropyloxy)-3-benzyloxymethyl-1,3-dihydrobenzo[*c*]furan (19). The minor species **18** was acetylated by standard procedures in order to confirm the structure. It was obtained as a gum which was not purified further. *Trans/cis* ratio is 2:1 ^{1}H NMR ($CDCl_3$): δ 2.05 (3 H, s, acetyl), 1.9, 4.2 (6 H, m, propyl), 3.67 (2 H, m, H-8a, H-8b), 4.62 (2 H, benzyl), 5.33 (1 H, t, $J_{3,8}$ 6.0, *c*-H-3), 5.50 (1 H, m, *t*-H-3), 6.19 (1 H, s, *c*-H-1), 6.27 (1 H, d, $J_{1,3}$ 2.1, *t*-H-1); ^{13}C NMR ($CDCl_3$): δ 74.6 (*c*-C-8), 73.0 (*t*-C-8), 73.0 (benzyl), 82.4 (*c*-C-3), 82.0 (*t*-C-3), 106.6 (*c*-C-1), 106.3 (*t*-C-1), 21.0, 171.0 (acetyl).

REFERENCES

1. For recent reviews of antiviral research see: (a) *Design of Anti-AIDS Drugs*, E. De Clercq Ed., Vol 14, Pharmacochemistry Library, Timmerman, H. Ed., Elsevier Amsterdam (1990); (b). Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *98* 1745-1768, (c*) Modified Nucleosides as Anti-AIDS Drugs: Current Status and Perspectives*, Krayevsky, A. A.; Watanabe, K. A. Bioinform, Moscow (1993); (d) *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*, Chu, C. K.; Baker D. C. Eds, Plenum Press, New York, London (1993); (e) *Antiviral Chemotherapy*, Young, R. J.; Challand, R.; Biochemical & Medicinal Chemistry Series, J. Mann Ed., Spectrum Academic Publishers, Oxford, (1996).
2. Chui, D.T.; Duesberg, P.H. *Genetica* **1997**, *95*, 103-109.
3. Balzarini, J.; Kang, G.-J.; Dalal, M.; Herdewijn, P.; De Clercq, E.; Broder, S.; Johns, D. G. *Mol. Pharmacol.* **1987**, *32*, 162-167.
4. Lin T.-S.; Lui, M.-C.; *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*, Chu, C. K.; Baker D. C.; Eds, Plenum Press, New York, London, (1993), pp 177-201; see also Nasr M.; and Turk, S. R.; pp 203-217.
5. Lea A. P.; Faulds, D. *Drugs* **1996**, *51*, 846-864.
6. Crimmins M. T.; King, B. W.; *J. Org. Chem.* **1996**, *61*, 4192-4193.
7. Mansuri, M. M.; Hitchcock, M. J.; Burocker, R. A.; Bregman, C. L.; Ghazzouli, I.; Desiderio, J. V.; Starrett, J. E.; Sterzycki R. Z.; Martin, J. C. *Antimicrob. Agents Chemother.* **1990**, *34*, 637-641; Zhu, Z.; Hitchcock M. J. M.; Sommadossi, J.-P. *Mol. Pharmacol.* **1991**, *40*, 838-845.
8. Palomino, E.; Kessel D.; Horwitz J. P. *J. Med. Chem.* **1989**, *32*, 622-625; Gallo J. M. *Advan. Drug Delivery Rev.* **1994**, *14*, 199-209.
9. Mullah, K. B.; Rao, T. S.; Balzarini, J.; De Clercq E.; Bentrude, W. G. *J. Med. Chem.* **1992**, *35*, 2728-2735; Hasegawa, T.; Seki, T.; Juni, K.; Saneyoshi, M.; Kawaguchi, T. *J. Pharm. Sci.* **1993**, *83*, 1232-36 ; Sergheraert, C.; Pierlot, C.; Tartar, A.; Henin Y.; Lemaitre M. *J. Med. Chem.* **1993**, *36*, 826-30; McGuigan, C.; Sheeka, H. M.; Mahmood N.; Hay, A. *Biorg. Med. Chem. Lett.* **1993**, *3*,

1203-1206; Tortolani, D. R.; Russell, J. W.; Whiterock, V. J.; Hitchcock, M. J. M.; Ghazzouli, I.; Martin, J. C.; Mansuri, M. M.; Starrett, J. E. *J. Pharm. Sci.* **1994**, *83*, 339-343; Girardet, J. L.; Perigaud, C.; Aubertin, A. M.; Gosselin, G.; Kirn, A.; Imbach, J.-L. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2981-2984; McGuigan, C.; Cahard, D.; Sheeka, H. M.; De Clercq E.; Balzarini, L. *J. Med. Chem.* **1996,** *39*, 1748-1753; *ibid.*, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1183-1186.

10. Palomino, E.; Meltsner, B. R.; Kessel, D.; Horwitz, J. P. *J. Med. Chem.*, **1990**, *33*, 258-263; Kumar, R.; Wang, L.; Wiebe L. I.; Knaus, E. E. *Nucleosides Nucleotides* **1996**, *15*, 265-286.
11. For a preliminary communication see: Ewing, D. F.; Fahmi, N.; Len, C.; Mackenzie, G.; Ronco, G.; Villa P.; Shaw, G. *Collect. Czech. Chem. Commun.* **1996**, *61*, S145-S147.
12. Humble, R. W.; Mackenzie, G.; Shaw, G. *Nucleosides Nucleotides* **1984**, *3*, 363-367.
13 Okabe M.; Sun, R.-C. *Tetrahedron Lett.* **1989**, *17*, 2203-2206; Marquez, V. E.; Siddiqui, M. A.; Ezzitouni, A.; Russ. P.; Wang, J.; Wagner R. W.; Matteucci, M. D. *J. Med. Chem.* **1996**, *39*, 3739-3747; Ezzitouni, A.; Russ P.; Marquez, V. E. *J. Org. Chem.* **1997**, *62*, 4870-4873.
14. Obika, S.; Nabu, D.; Hari, Y.; Morio, K-I.; In, Y.; Ishada T.; Imanishi, T. *Tetrahedron Lett.* **1997**, *38*, 8735-8738; Nielsen, P.; Pfundheller, H. M.; Olsen, C. E. Wengel, J. *J. Chem. Soc., Perkin Trans 1* **1997**, 3423-3433.
15. Weber, W. P.; Shepherd, J. P. *Tetrahedron Lett.* **1972**, 4907-4908.
16. Corey E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353-1364.
17. Borredon, M. E.; Delmas, M.; Gaset, A. *Tetrahedron Lett.* **1982**, *23*, 5283-5286; *Tetrahedron* **1987**, *43*, 3945-3954.
18. Merz, A. *Synthesis* **1974**, 724-725.
19. Barfield, M.; Spear R. J.; Sternhell, S. *J. Am. Chem. Soc.* **1975**, *97*, 5160-5167.
20. Mirsadeghi S.; Rickborn, B. *J. Org. Chem.* **1987**, *52*, 787-792.

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