Synthesis of *meso*-2',3'-Dideoxy-3'β-hydroxymethyl Carbocyclic Nucleosides as Potential Antiviral Drugs. Unusual Competitive 2-O- *versus* N¹-Alkylation of 3-Substituted Pyrimidines under Mitsunobu Conditions

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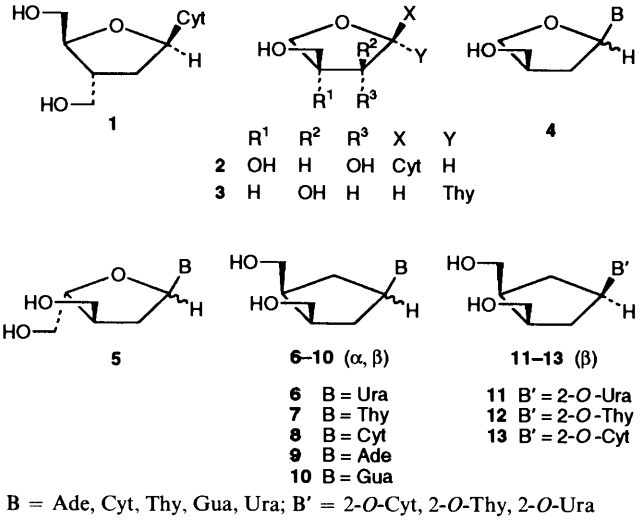
The synthesis of *meso*-2',3'-dideoxy-3'β-hydroxymethyl carbocyclic nucleosides as potential antiviral drugs *via* the alkylation of protected purines and pyrimidines with *meso*-β,β'-disubstituted cyclopentanols under Mitsunobu conditions is described. Chemical evidence for an unusual competitive 2-O-*vs.* N¹-alkylation of 3-substituted pyrimidines is presented.

To date, nucleoside analogues[1] are the most potent agents against HIV. The emergence of 3'-azido-3'-deoxythymidine[2] (AZT) as an anti-HIV agent has emphasized the biological significance of nucleosides lacking a 3'-hydroxy function. As a consequence, the proliferation of novel 2',3'-dideoxynucleoside structures[3] has led to some potent drugs, *e.g.* 2',3'-dideoxycytidine[4] (ddC) and 2',3'-dideoxyinosine[5] (ddI). Conformational modifications of the sugar moiety have been studied by introducing heteroatoms (O, N, S) to generate new biologically active molecules such as 2',3'-dideoxy-3'-thia-cytidine[6] and 3'-deoxy-3'-oxathymidine.[7] More recently, the 3'-branched nucleosides[8] and carbocyclic analogues[9] have begun to be explored, one of the most active of these series being 2',3'-dideoxy-3'α-hydroxymethyl-cytidine[8b] **1**.



B = Ade, Cyt, Thy, Gua, Ura; B' = 2-*O*-Cyt, 2-*O*-Thy, 2-*O*-Ura

Among the plethora of inactive new nucleoside analogues, it is generally not known whether their lack of antiviral activity is due to failure of phosphorylation by kinases or inactivity of the triphosphates against viral DNA polymerases. The lack of accurate structure–anti-HIV activity relationships and our *quasi* ignorance of the chemical nature of active sites of target macromolecules have led us to seek novel structures with enhanced activity and diminished toxicity. Accordingly, we have undertaken an investigation of the 3'β-hydroxymethyl group in order to define the structural requirements needed to optimize antiretroviral activity.

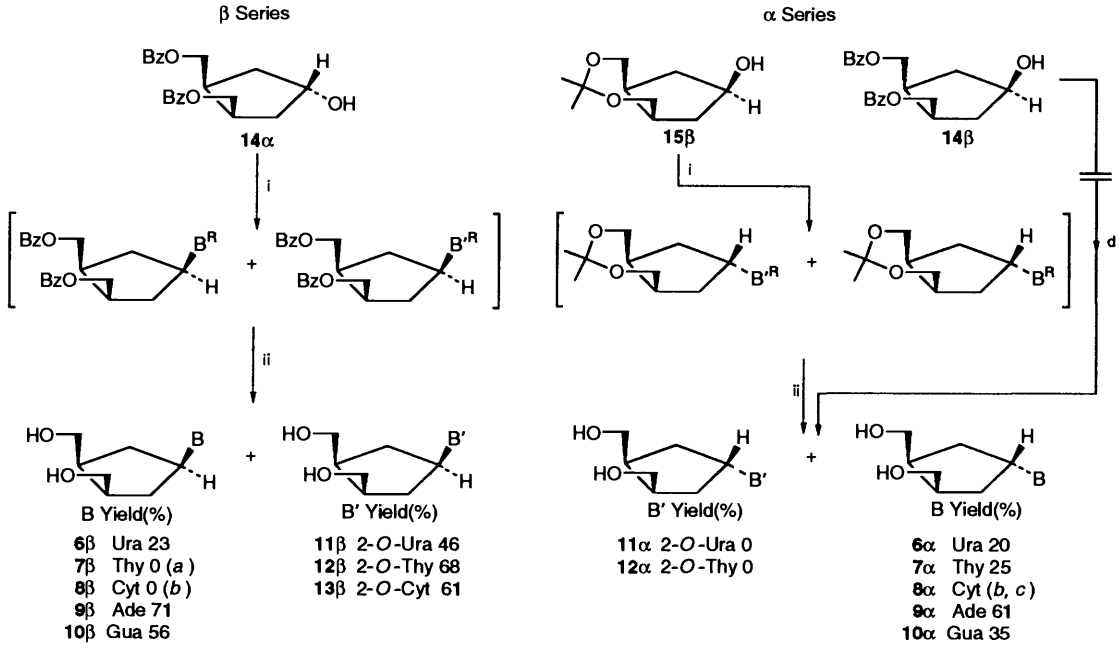
Certain nucleosides belonging to the D-*apio* series (**2**[10] and **3**[11]) or the 2',3'-dideoxy-D-*apio* series[12] **4** have been reported as inactive against HIV. One can assume that the absence of the 4'-hydroxymethyl group in these cases is partly responsible for their inactivity. Furthermore, with inactive 3'β,4'α-dihydroxymethyl derivatives **5** derived from the L-*ribo* series,[8b] it appears that the 4'α-hydroxymethyl functionality does not enhance activity.

In connection with an ongoing program, we have investigated the contribution of two β-oriented hydroxymethyl groups (C-3', C-4') to antiretroviral activity. The target molecules were the *meso*-2',3'-dideoxy-3'β-hydroxymethyl carbocyclic nucleosides (C–N¹ and C–N⁹ links) (**6α,β–10α,β**) with the five usual heterocyclic bases (B = Ade, Cyt, Thy, Gua, Ura) in the α and β configurations at the pseudo-anomeric position. Additionally, regioisomers (**11β–13β**) with an unusual 2-O–C link in the pyrimidine series (B' = 2-*O*-Thy, 2-*O*-Ura, 2-*O*-Cyt) were examined. The chemical synthesis of these molecules was performed by alkylation of the protected purines and pyrimidines with various substituted cyclopentanols under Mitsunobu reaction conditions, except for cytosine derivatives **8α** and **8β** which were directly obtained *via* a known transformation of the corresponding monosubstituted uracils **6α** and **6β**.

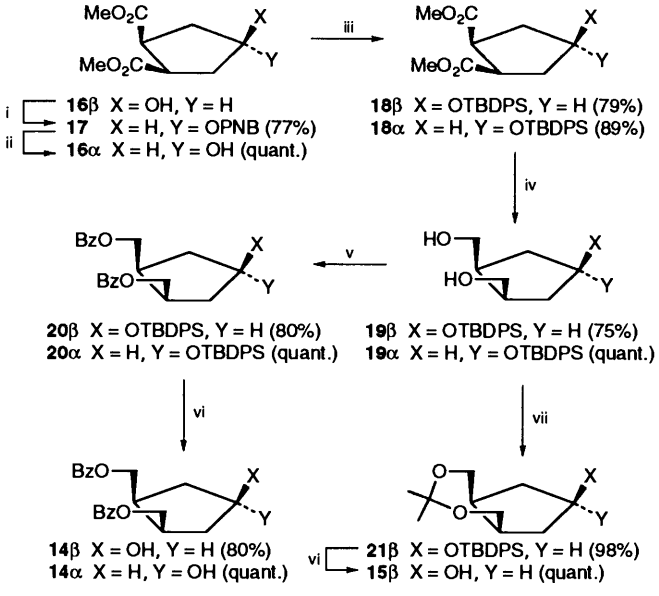
Results and Discussion

Our chemical strategy is summarized in Scheme 1. The protected pyrimidines (3-benzoyluracil,[13] 3-benzoylthymine[13] and 4-*N*-benzoylcytosine) and purine precursors (6-chloropurine, 2-*N*-acetyl-6-*O*-diphenylcarbamoylguanine[14]) were alkylated by a Mitsunobu-type reaction with suitable *meso* disubstituted cyclopentanols to afford, after deprotection, the N⁹-alkylated purines (**9α,β–10α,β**) and, depending on the experimental conditions of the Mitsunobu reaction, a mixture of N¹-alkylated pyrimidines (**6α,β–7α,β**) and 2-O-alkylated pyrimidines (**11β–13β**). Originally, benzoate protecting groups on cyclopentanetriol cores (**14α** and **14β**) were utilized to facilitate UV monitoring of the Mitsunobu reactions. Nevertheless, the steric hindrance developed by the two benzoyloxymethyl groups, especially in the case of the alcohol **14β**, made it necessary to block the diol functionality by isopropylidene protection (protected cyclopentanol **15β**) in order to perform the alkylation successfully. The letters α and β in this paper refer to the relative stereochemistry of the secondary hydroxy function or the nucleobase and the two substituents of the cyclopentane ring which are always written in the 'up' configuration.

Preparation of the Cyclopentanol Precursors **14α**, **14β** *and* **15β** (*Scheme* 2).—The *meso*-cyclopentanol diester **16β**, the common intermediate for the synthesis of compounds **14α,β**, was obtained by a four-step sequence from *cis*-1,2,3,6-tetrahy-



Scheme 1 B^R = disubstituted purine or pyrimidine with a C–N^9 or C–N^1 link; B'^R = disubstituted pyrimidine with a C–O^2 link; i: Protected nucleobase (HB^R or HB'^R) (2 mol equiv.), alcohol (1 mol equiv.), triphenylphosphine (3 mol equiv.), diethyl azodicarboxylate (DEAD) (3 mol equiv.), THF–benzene (2:1 v/v), 0 °C, 12 h; ii: methanolic ammonia for adenine derivative in β series followed by HCl (10%) in α series; HCl (10%) in water–1,4-dioxane (1:1 v/v) for guanine derivative in α series followed by NaOH (0.1 mol dm^{-3}) (4.4 mol equiv.) in water–1,4-dioxane (1:1 v/v) in both α and β series; MeONa–methanol for pyrimidine derivatives in both α and β series preceded by HCl (10%) in α series. [a] Compound obtained at lower temperature (see Table 1). [b] The cytosine-containing carbocyclic nucleosides (C–N^1 link) were synthesized according to Scheme 3 from uracil precursors. [c] Reaction not performed. [d] No isolation of condensation products from purines and very low yields from thymine and uracil derivatives after deprotection step (see Table 1).



Scheme 2 *Reagents and conditions:* i, Triphenylphosphine (2 mol equiv.), DEAD (2 mol equiv.), *p*-nitrobenzoic acid (1.5 mol equiv.), benzene, 0 °C to room temp., 12 h; ii; K_2CO_3 (0.2 mol equiv.), methanol, room temp., 30 min; iii; TBDPSCl (2.2 mol equiv.), imidazole (3 mol equiv.), DMF, 80 °C, 12 h; iv, $LiAlH_4$ (1 mol dm^{-3} in diethyl ether), THF, 0 °C to room temp., 12 h; v, benzoyl chloride (2.5 mol equiv.), pyridine (5 mol equiv.), dichloromethane, 0 °C to room temp., 12 h; vi, TBAF (1.1 mol dm^{-3} in THF) (3 mol equiv.), room temp., 24 h; vii; 2,2-dimethoxypropane, PTSA, room temp., 3 h

drophthalic anhydride by known procedures.[15] The secondary alcoholic configuration of compound **16β** was inverted *via* the *p*-nitrobenzoate intermediate **17** by a Mitsunobu reaction [triphenylphosphine, diethyl azodicarboxylate (DEAD), *p*-nitrobenzoic acid,[16] benzene, 0 °C to room temp., 77%; then K_2CO_3–methanol, 30 min, quant.] to afford the known[15] alcohol diester epimer **16α**. Both alcohols **16α** and **16β** were silylated with *tert*-butylchlorodiphenylsilane (TBDPSCl)–imidazole [dimethylformamide (DMF), 80° C, 12 h] to afford the expected silylated ethers **18α** (89%) and **18β** (79%), which were reduced [$LiAlH_4$–diethyl ether–tetrahydrofuran (THF), 0 °C to room temp., 12 h] to give the diols **19α** (quant.) and **19β** (75%), which were then protected (benzoyl chloride, pyridine, dichloromethane) as the dibenzoates **20α** (quant.) and **20β** (80%). The final desilylation step was achieved by use of tetrabutylammonium fluoride (TBAF) in THF (room temp., 24 h) to give the two epimeric alcohols **14α** (quant.) and **14β** (80%). The isopropylidene ether **21β** was obtained [2,2-dimethoxypropane, toluene-*p*-sulfonic acid (PTSA), room temp., 3 h, 98%] from diol **19β** and gave, after desilylation, the isopropylidene alcohol **15β** (quant.). The three substituted cyclopentanols **14α**, **14β** and **15β** served as starting materials for the subsequent alkylation reactions. The *meso* configuration of products **19α** and **19β** was confirmed by ^{13}C NMR spectroscopy which showed only one signal for both C-1 and C-2, whereas two signals would appear for the chiral C_2-isomer.

Alkylation of Heterocyclic Bases by the Alcohols **14α**, **14β** *and* **15β**.—In the past few years, the Mitsunobu reaction[17] has become an important regiospecific method (N^1 for pyrimidines; N^9 for purines) for the coupling of alcohols with heterocyclic bases under mild conditions. We[18] and others[19] who have employed this type of condensation have found that nucleophilic substitution of a secondary alcohol function generally occurs with satisfactory yields. Therefore, alcohols **14α** and **14β** (1 mol equiv.) were initially treated with the appropriate protected heterocyclic base (2 mol equiv.) under Mitsunobu reaction conditions [triphenylphosphine (3 mol equiv.), DEAD (3 mol equiv.), THF–benzene (2:1 v/v), 0 °C for 2 h and room

Table 1

Entry	Alcohol	Temp. (°C)	Protected base	Ratio[a] 2-O/N^1 or N^9	Deprotected base	Product	Overall yield (%)
1	**14α**	0	6Cl-purine	100	Ade	**9β**	71 (92[b] 77[c])
2	**14α**	0	Gua(dpc)(Ac)	100	Gua	**10β**	56 (62,[b] 90[c])
3	**14β**	0	6Cl-purine		Ade	**9α**	0
4	**14β**	0	Gua(dpc)(Ac)		Gua	**10α**	0
5	**15β**	0	6Cl-purine	100	Ade	**9α**	61
6	**15β**	0	Gua(dpc)(Ac)	100	Gua	**10α**	35
7	**14α**	0	3BzThy	100/0	Thy	**12β**	68 (85[b], 80[c])
8	**14α**	−40	3BzThy	50/50	Thy	**12β + 7β**	n.d.
9	**14α**	−78	3BzThy	33/67	Thy	**12β + 7β**	45
10	**14α**	0	3BzUra	67/33	Ura	**11β + 6β**	69
11	**14α**	0	4-*N*BzCyt	100/0	Cyt	**13β**	61 (80[b], 77[c])
12	**14α**	−78	4-*N*BzCyt	100/0	Cyt	**13β**	n.d.
13	**14β**	0	3BzThy	0/100	Thy	**7α**	5
14	**14β**	0	3BzUra	0/100	Ura	**6α**	1
15	**15β**	0	3BzThy	0/100	Thy	**7α**	25
16	**15β**	0	3BzUra	0/100	Ura	**6α**	20
17	**16α**	0	3BzThy	0/100	3BzThy	**23β**	67
18	**16α**	0	3BzUra	0/100	3BzUra	**22β**	62
19	**24α**	−50	3BzThy	0/100	Thy	**26β**	52 (ref. 19[c])
20	**24α**	−50	3BzUra	0/100	Ura	**25β**	47 (ref 19[c])
21	**27**	0	3BzUra	25/75	Ura	**29 + 28**	75
22	**27**	0	3EtUra	31/69	3EtUra	**31 + 30**	94
23	**27**	0	4EtOUra	96/4	4EtOUra	**32**	96 (ref. 23)
24	**33α**	0	4EtOUra	86/14	4EtOUra	**35β + 34β**	95 (ref. 23)

[a] The 2-O/N^1 ratio was determined by ^{1}H NMR spectroscopy either on the partially purified mixture obtained after the alkylation and/or on the pure mixture of fully deprotected regioisomers isolated after the deprotection steps. [b] % Yield of Mitsunobu reaction. [c] % Yield of deprotection steps.

temp. for 12 h]. The use of benzene instead of the usual THF solvent has been reported to give fair to good chemical yields with sterically crowded alcohols.[20]

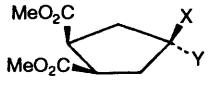
Purines (*Scheme* 1, *Table* 1). With 6-chloropurine and protected guanine, good yields (92 and 62% respectively) of the N^9-products were obtained (entries 1 and 2) from alcohol **14α** with no trace of the N^7 regioisomer. However, the alcohol epimer **14β** did not lead to the corresponding N^9-alkylated purines (entries 3 and 4), probably due to the greater steric interaction of the two benzoyloxymethyl groups which deter formation of the transient oxyphosphonium salt.[17] This problem has been solved by using the more rigid and less encumbered isopropylidene alcohol **15β** which affords the expected carbocyclic nucleosides of adenine and guanine (entries 5 and 6) in 61 and 35% yield respectively after deprotection. The observed regiospecificity of the coupling (N^9 *versus* N^7) is in accord with earlier observations[19] and was confirmed by comparison of UV literature data[21] with spectra obtained in different media. The stereochemical relationships of the three chiral centres of compounds **9α,β** and **10α,β** were supported by NOE experiments which further confirmed the assumed inversion[17] of configuration of the carbinol centre during the Mitsunobu reaction. Full deprotection of the intermediate carbocyclic nucleosides containing adenine was achieved with methanolic ammonia followed, in the α series, by acidic (HCl 10%) removal of the isopropylidene group to give the two carbocyclic nucleoside epimers **9α** and **9β**. For the guanine derivatives, prior acidic hydrolysis (HCl 10%) in the α series followed in both series (α and β) by alkaline treatment [0.1 mol dm^{-3} NaOH in water–1,4-dioxane (1:1 v/v)] gave the nucleoside analogues **10α** and **10β**.

Pyrimidines (*Scheme* 1, *Table* 1). It has been recently demonstrated[19b,c] that 3-benzoyluracil and 3-benzoylthymine undergo Mitsunobu-type alkylation with a β-substituted cyclopentanol to afford regiospecifically N^1-alkylated pyrimidines. Since our previous Mitsunobu alkylations of purine bases (above) gave satisfactory yields at 0 °C, we treated the three protected pyrimidines (3-benzoylthymine, 3-benzoyluracil and 4-*N*-benzoylcytosine) with the three alcohols **14α**, **14β** and **15β** using the same experimental procedure.

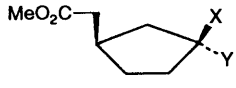
When 3-benzoylthymine, 3-benzoyluracil and 4-N-benzoylcytosine were alkylated at 0 °C with alcohol **14α**, a regiospecific 2-O-alkylation was observed for thymine (entry 7, 68% yield) and cytosine (entry 11, 61% yield) whereas uracil afforded (entry 10, 69% yield) a mixture of the 2-O and N^1-alkylated derivatives (2-O/N^1: 67/33), with predominant O-alkylation.

It is worth noting that, to our knowledge, this is the first example of a regiospecific 2-O-alkylation involving thymine and cytosine derivatives 3- and 4-substituted, respectively, in a Mitsunobu-type reaction, as well as a cytosine derivative acting as an ambident nucleophile in a Mitsunobu alkylation.

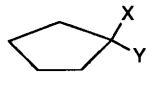
These results do not agree with those of Benner and coworkers[19c] who have reported a regiospecific alkylation of 3-benzoylthymine and 3-benzoyluracil at their N^1 positions (100% of N-alkylation at −50 °C) with the monosubstituted alcohol **24α** (entries 19 and 20, 47–52% yield).



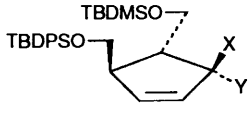
	X	Y
16α	H	OH
22β	3BzUra	H
23β	3BzThy	H



	X	Y
24α	H	OH
25β	Ura	H
26β	Thy	H



	X	Y
27	H	OH
28	Ura	H
29	2-*O*-Ura	H
30	3EtUra	H
31	2-*O*-(3EtUra)	H
32	2-*O*-(4EtOUra)	H



	X	Y
33α	H	OH
34β	4EtOUra	H
35β	2-*O*-(4EtOUra)	H

TBDMS = Bu^tMe_2Si–

Alkylation of the two aforementioned nucleobases by the alcohol **14β** afforded exclusively the N^1-alkylated products (entries 13 and 14) in very low yields (1–5%). As described for

the purines, the use of the less crowded alcohol **15β** led to the formation of products resulting from regiospecific N^1-alkylation (entries 15 and 16) in increased yields (20–25%).

According to the postulated mechanism[17b] of the Mitsunobu reaction, two possible rate-determining steps must be considered: formation of the intermediate oxyphosphonium salt, and nucleophilic substitution of this key intermediate by the deprotonated nucleobase. On steric grounds, the rates of oxyphosphonium-ion formation should follow the order **14α** ≫ **15β** > **14β**. Once formed, however, the rates of nucleophilic displacement would occur in an inverted order: **14β** ≈ **15β** ≫ **14α**. As a consequence, the observed chemical yields may reflect a combination of these opposing effects.

The results described above can be tentatively rationalized by taking account for the following facts: for a given heterocyclic base (3-benzoylthymine or 3-benzoyluracil), two structurally related cyclopentanols (**14α** and **24α**) gave opposite results, suggesting the importance of the alcohol structure on the competitive 2-O- *vs.* N^1-alkylation pathways. This result has led us to consider some of the operative factors determining the regioselectivity or regiospecificity of the Mitsunobu alkylation. The methoxycarbonylmethyl group of compound **24α** is sterically less demanding than the two benzoyloxymethyl groups of compound **14α**. It therefore appears reasonable that the liberation of triphenylphosphine oxide from the intermediate oxyphosphonium salt by the incoming deprotonated pyrimidine base will be easier in the case of the less crowded alcohol **24α**. However, this does not explain why the alkylation proceeds regiospecifically at the N^1 position of 3-benzoylthymine in the case of alcohol **24α** but at the 2-O site with the more crowded alcohol **14α**.

One can postulate that, in the absence of steric factors, the regioselectivity (2-O *vs.* N^1) is governed by the relative nucleophilicities of the deprotonated NH and OH functions. In general, the NH is more nucleophilic and favours N^1-alkylation. In the case of a more hindered alcohol, the steric interactions developed in the transition state compete to favour the O-alkylated products. The putative transition state models proposed in Fig. 1 qualitatively account for this assumption. Moreover, the 5-methyl group of thymine increases the steric constraints leading to more O-alkylation for thymine (entry 7, 100%) than for uracil (entry 10, 67%).

The observed regiospecific N^1-alkylation of 3-benzoylthymine and 3-benzoyluracil by the two alcohols **14β** (entries 13 and 14) and **15β** (entries 15 and 16) support the hypothesis formulated above. Our findings are thus consistent but apparently opposite to those of Benner and co-workers.[19c] These authors performed alkylations with alcohol **24α** (entry 20) at −50 °C (THF) which might result in a relatively frozen rotational conformation of the methoxycarbonylmethyl chain leading to an apparent decrease in steric hindrance on the side facing the incoming deprotonated base. If conformational mobility of the two benzoyloxymethyl groups were similarly restricted by lowering of the temperature, an increase in the N^1-alkylation process *versus* the 2-O-alkylation may be anticipated.

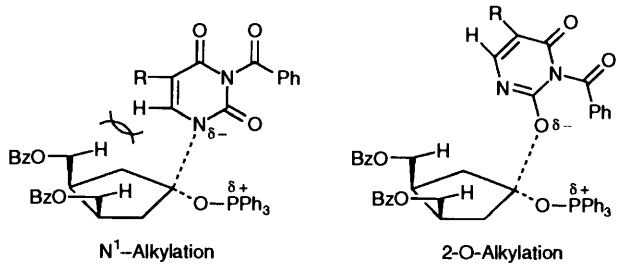


Fig. 1

This proved to be the case with 3-benzoylthymine, which afforded with alcohol **14α** an increasing proportion of N^1-alkylation from 0 °C (entry 7, 0%) to −40 °C (entry 8, 50%) and finally −78 °C (entry 9, 67%). These results accord with those of Benner; the difference in regioselectivity at −40 °C for thymine with alcohol **14α** (entry 8, 50% of N-alkylation) compared with 100% of N-alkylation from alcohol **24α** at −50 °C (entry 19) may be attributed to the relative bulkiness of the two benzoyloxymethyl substituents *versus* the one methoxycarbonylmethyl group. We verified that the replacement of the mixture THF–benzene by THF, the solvent used by Benner and co-workers, was without influence on the regioselectivity at −40 °C.

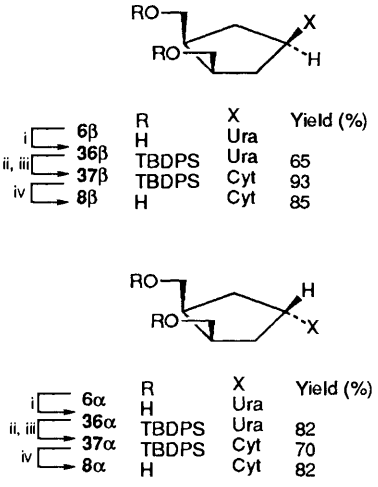
Indeed, the alcohol diester **16α** possessing two methoxycarbonyl substituents further corroborated the hypothesis by affording exclusively the N^1-alkylated products with 3-benzoylthymine (entry 17) and 3-benzoyluracil (entry 18). These results prompted us to investigate unsubstituted cyclopentanol **27** in which no problem of steric hindrance can arise. Reaction with 3-benzoyluracil gave predominantly N^1-alkylation (entry 21, 2-O/N^1: 25/75), qualitatively confirming our prediction. However, the unexpected substantial formation of the 2-O-alkylated product in this case raises certain questions.

In principle, rearrangement[22] of the N^3-substituted bases to their 4-O-substituted isomers *prior* to alkylation could play an important role in regioselectivity. For example, Mitsunobu alkylation of 4-*O*-ethyluracil with cyclopentanol gave almost exclusive 2-O-alkylation (entry 23).[23] We have observed precisely similar behaviour in the alkylation of 4-*N*-benzoylcytosine with compound **14α**: regardless of temperature (0 °C, −78 °C) or steric constraints, only 2-O-alkylation occurred (entries 11 and 12). In accord with electronic effects, it thus appears that both 4-O-substituents (uracil) and 4-N-substituents (cytosine) enhance the nucleophilicity of the 2-O atom, leading to preferential 2-O-alkylation.

With 3-benzoylthymine and 3-benzoyluracil, however, it is unlikely that $N^3 \longrightarrow$ 4-O rearrangement occurs *prior* to alkylation; these bases are stable during the course of the alkylation. The 3-ethyluracil,[24] less susceptible to rearrangement, showed (entry 22, 2-O/N^1: 31/69) regioselectivity similar to 3-benzoyluracil, thus confirming the formation of a non-negligible amount of 2-O-alkylated product when using 3-substituted pyrimidines.

Nevertheless, steric hindrance developed by the incoming deprotonated base is insufficient to account for the formation of 25–30% of O-alkylation with cyclopentanol **27** (entries 21 and 22). In our opinion, the relative steric congestion in the oxyphosphonium salt (Ph_3P^+–OR B^-) must be considered with the aforementioned steric effect. Indeed, if the unsubstituted cyclopentanol **27** is chosen as the reference substrate, no steric interactions are developed either in the key intermediate or with the incoming base. The regioselectivity will therefore reflect the usual relative nucleophilic character of N^- *versus* O^-, leading to a mixture of N- and O-alkylated compounds, where the former is both the predominant and the kinetic product, as demonstrated in the preceding low-temperature experiments. The intermediate salt derived from the cyclopentanol **15β**, which exhibits a strong steric congestion enhancing its reactivity towards the more reactive N site of the base, will afford exclusively the kinetic product. For the alcohols **16α** and **24α**, which are characterized by a lack of steric hindrance in the key intermediate and by weak steric interactions of the approaching base, will also give exclusive N-alkylation. Finally, the oxyphosphonium salt derived from alcohol **14α** is not crowded but the strong interactions developed with the incoming base, will preferentially favour O-alkylation (thermodynamic product) which minimizes the interactions with the two benzoyloxymethyl groups (Fig. 1).

Since the preparation of the cytosine-containing carbocyclic nucleosides **8α** and **8β** (C–N^1 link) was not feasible by a direct Mitsunobu alkylation of 4-*N*-benzoylcytosine with the disubstituted cyclopentanol **14α** (entries 11 and 12), we have synthesized (Scheme 3) these compounds by converting the N^1-alkylated uracils into the corresponding cytosine derivatives.[25] The unprotected uracil derivatives **6β** and **6α** were silylated (TBDPSCl, pyridine, room temp., 12 h) to afford the disilylated ethers **36β** (65%) and **36α** (82%). Treatment with Lawesson's reagent (1,2-dichloroethane, reflux, 2 h) gave the intermediate crude 4-thio derivatives, which were directly allowed to react with methanolic ammonia (100 °C, 18 h) to produce the corresponding 4-amino compounds **37β** (93%) and **37α** (70%). Desilylation was achieved with TBAF in THF (room temp., 12 h) to afford the carbocyclic nucleosides **8β** (85%) and **8α** (82%).



Scheme 3 *Reagents and conditions*: i, TBDPSCl (2.5 mol equiv.), pyridine, room temp., 12 h; ii, Lawesson's reagent (1.2 mol equiv.), 1,2-dichloroethane, reflux, 2 h; iii, methanolic ammonia, 100 °C, 18 h; iv, TBAF (1.1 mol dm^{-3} in THF) (4 mol equiv.), room temp., 12 h

The carbocyclic nucleosides **6α,β–10α,β** and **11β–13β** were all found to be inactive against both HIV and a broad range of DNA and RNA viruses. It is worth noting that recently published structurally related pyrimidine nucleosides[26] were also devoid of any antiviral activity.

In conclusion, the synthesis of a new series of *meso*-2',3'-dideoxy-3'β-hydroxymethyl carbocyclic nucleosides containing purine and pyrimidine bases by the Mitsunobu alkylation has been described. In the case of ambident 3-substituted pyrimidines, the competitive 2-O *vs.* N^1-alkylation pathways have been investigated. We have shown that both steric interactions of the substituents located on the cyclopentane core with the incoming base and steric hindrance in the intermediate oxyphosphonium salt are determining factors which together affect the observed regioisomerism in the alkylation step.

The results obtained indicate the importance of the structure of both the alcohol and base components in directing the Mitsunobu reaction toward O- or N-alkylated products. Our findings should be of value in further synthetic work in this area.

Experimental

M.p.s were obtained with a Büchi (capillary) apparatus and were uncorrected. UV spectra were obtained on an Uvikon-810 spectrophotometer. Elemental analyses were performed by the 'Service de Microanalyse du CNRS, Division de Vernaison'. ^1H NMR and ^{13}C NMR spectra were determined on a Brüker AC250 spectrometer working at 250.134 and 62.896 MHz respectively. *J*-Values are given in Hz. Mass spectra were obtained with a JEOL JMS-DX300 by the FAB ionization method. Petroleum spirit refers to the fraction boiling in the range 40–65 °C.

Dimethyl (1β,2β,4β)-4-*hydroxycyclopentane*-1,2-*dicarboxylate* **16β**.[18]—The title compound was obtained as an oil by sodium borohydride reduction of the corresponding keto diester, by a reported procedure,[18] in 91% yield; R_f 0.20 [(98:2) CH_2Cl_2–MeOH]; δ_H(250 MHz; $CDCl_3$) 2.11 (2 H, m, 3- and 5-H), 2.26 (2 H, m, 3- and 5-H), 3.10 (2 H, m, 1- and 2-H), 3.2 (1 H, br s, OH), 3.73 (6 H, s, 2 × OMe) and 4.35 (1 H, s, 4-H).

Dimethyl (1β,2β,4α)-4-(p-*Nitrobenzoyloxy*)*cyclopentane*-1,2-*dicarboxylate* **17**.—To a stirred solution of alcohol **16β** (7.79 g, 3.85 mmol), triphenylphosphine (20.22 g, 7.71 mmol) and *p*-nitrobenzoic acid (9.67 g, 5.78 mmol) in anhydrous benzene (200 cm^3) was added dropwise, under argon, at 0 °C DEAD (12.6 cm^3, 7.71 mmol). After 12 h at room temp. the solution was evaporated to dryness and the residue was chromatographed on silica gel with dichloromethane–hexane (7:3) as eluent to afford the pure *title compound* **17** (10.42 g, 77%) as a solid, m.p. 109–110 °C (from EtOH); R_f 0.61 [(98:2) CH_2Cl_2–MeOH]; δ_H 250 MHz; $CDCl_3$) 2.15 (2 H, m, 3- and 5-H), 2.5 (2 H, m, 3- and 5-H), 3.35 (2 H, m, 1- and 2-H), 3.64 (6 H, s, 2 × OMe), 5.54 (1 H, m, 4-H) and 8.05–8.26 (4 H, m, ArH) (Found: C, 54.8; H, 4.8; N, 3.9. $C_{16}H_{17}NO_8$ requires C, 54.7; H, 4.9; N, 4%).

Dimethyl (1β,2β,4α)-4-*Hydroxycyclopentane*-1,2-*dicarboxylate* **16α**.[18]—To a solution of the triester **17** (5.2 g, 14.8 mmol) in absolute methanol (200 cm^3) was added potassium carbonate (0.42 g, 3.06 mmol). The heterogeneous solution was stirred at room temp. for 30 min and evaporated under reduced pressure to give a crude solid, which was chromatographed on silica gel and eluted with dichloromethane to afford the pure title compound **16α** (2.95 g, 98%) as an oil; R_f 0.15 [(98:2) CH_2Cl_2–MeOH]; δ_H(250 MHz; $CDCl_3$) 1.95 (2 H, m, 3- and 5-H), 2.27 (2 H, m, 3- and 5-H), 3.35 (3 H, m, 1- and 2-H and OH), 3.7 (6 H, s, 2 × OMe) and 4.55 (1 H, tt, *J* 5.6 and 2.3, 4-H).

Dimethyl (1β,2β,4α)-4-(tert-*Butyldiphenylsiloxy*)*cyclopentane*-1,2-*dicarboxylate* **18α**.—To a solution of alcohol **16α** (2.1 g, 10.4 mmol) and imidazole (1.06 g, 15.6 mmol) in DMF (10 cm^3) was added dropwise at room temp. TBDPSCl (2.97 cm^3, 11.4 mmol). The solution was heated at 80 °C for 12 h, and the solvent was evaporated off under reduced pressure. The residue was extracted twice with dichloromethane, the extracts were washed once with 10% aq. $NaHCO_3$ and twice with water, and dried (Na_2SO_4), and the solvent was removed under reduced pressure. Column chromatography of the residue on silica gel with dichloromethane as eluent afforded the *title compound* **18α** (4.07 g, 89%) as an oil; R_f 0.42 [(3:2) hexane–diethyl ether]; δ_H(250 MHz; $CDCl_3$) 1.05 (9 H, s, 3 × Me), 2.05 (4 H, m, 3- and 5-H), 3.45 (2 H, m, 1- and 2-H), 3.7 (6 H, s, 2 × OMe), 4.5 (1 H, m, 4-H) and 7.4–7.7 (10 H, m, ArH); δ_C(250 MHz; $CDCl_3$) 18.96, 26.8, 38.86, 44.76, 51.66, 73.62, 127.56, 129.59, 133.83, 135.54 and 174.31; *m/z* 441 $(M + H)^+$ (Found: C, 68.5; H, 7.1. $C_{25}H_{32}O_5Si$ requires C, 68.1; H, 7.3%).

Dimethyl (1β,2β,4β)-4-(tert-*Butyldiphenylsiloxy*)*cyclopentane*-1,2-*dicarboxylate* **18β**.—The *title compound* was obtained as an oil from the diester **16β** following the aforementioned procedure. After chromatography with diethyl ether (0–30%) in petroleum spirit, the pure compound **18β** was obtained in 79% yield; R_f 0.39 (3:2 hexane–diethyl ether); δ_H(250 MHz; $CDCl_3$) 0.93 (9 H, s, 3 × Me), 2.08 (4 H, m, 3- and 5-H), 2.82 (2 H, m, 1- and 2-H), 3.6 (6 H, s, 2 × OMe), 4.13 (1 H, m, 4-H) and 7.2–7.6

(10 H, m, ArH); δ_C(250 MHz; $CDCl_3$) 18.91, 26.67, 37.80, 43.88, 51.66, 72.75, 127.49, 129.53, 133.84, 135.58 and 173.61; *m/z* 441 $(M + H)^+$ (Found: C, 68.3; H, 7.5%).

(1β,2β,4α)-4-(tert-*Butyldiphenylsiloxy*)-1,2-*bis*(*hydroxymethyl*)*cyclopentane* **19α**.—To a solution of the diester **18α** (1.73 g, 3.93 mmol) in THF (60 cm^3) was added dropwise at 0 °C under argon a solution (5.9 cm^3, 5.9 mmol) of $LiAlH_4$ (1 mol dm^{-3} in diethyl ether). The solution was then refluxed for 4 h, cooled, and hydrolysed with THF–water (1:1; 10 cm^3), acidified with HCl (2 mol dm^{-3}; 13 cm^3) and extracted twice with diethyl ether. The ethereal extracts were washed successively with saturated aq. $NaHCO_3$ and water, and dried (Na_2SO_4). The solvents were removed under reduced pressure and the residual oil was chromatographed on silica gel with dichloromethane as eluent to afford the *title compound* **19α** (1.48 g, 98%) as an oil; R_f 0.60 [(95:5) CH_2Cl_2–MeOH]; δ_H(250 MHz; $CDCl_3$) 1.05 (9 H, s, 3 × Me), 1.35 (2 H, m, 3- and 5-H), 1.8 (2 H, m, 3- and 5-H), 2.7 (2 H, m, 1- and 2-H), 3.15 (2 H, br s, 2 × OH), 3.7 (4 H, d, *J* 6.1, 2 × CH_2O), 4.3 (1 H, m, 4-H) and 7.3–7.7 (10 H, m, ArH); δ_C(250 MHz; $CDCl_3$) 18.63, 26.67, 38.91, 41.04, 61.19, 73.51, 127.66, 129.59, 133.86 and 135.03; *m/z* 385 $(M + H)^+$ (Found: C, 71.8; H, 8.3. $C_{23}H_{32}O_3Si$ requires C, 71.8; H, 8.4%).

(1β,2β,4β)-4-(tert-*Butyldiphenylsiloxy*)-1,2-*bis*(*hydroxymethyl*)*cyclopentane* **19β**.—From the diester **18β**, the *title compound* was obtained as a solid following the aforementioned procedure in 75% yield; m.p. 82–83 °C; R_f 0.35 [(95:5) CH_2Cl_2–MeOH]; δ_H(250 MHz; $CDCl_3$) 0.85 (9 H, s, 3 × Me), 1.31 (2 H, m, 3- and 5-H), 1.72 (2 H, m, 3- and 5-H), 2.0 (2 H, m, 1- and 2-H), 3.19 (2 H, br s, 2 × OH), 3.6 (4 H, m, 2 × CH_2O), 4.06 (1 H, m, 4-H) and 7.05–7.5 (10 H, m, ArH); δ_C(250 MHz; $CDCl_3$) 18.80, 26.68, 38.55, 41.85, 63.30, 73.42, 127.42, 129.47, 133.71 and 135.52; *m/z* 385 $(M + H)^+$ (Found: C, 72.2; H, 8.2%).

(1β,2β,4α)-1,2-*Bis*(*benzoyloxymethyl*)-4-(tert-*butyldiphenylsiloxy*)*cyclopentane* **20α**.—To a solution of the diol **19α** (0.76 g, 1.98 mmol) in dry dichloromethane (4 cm^3)–pyridine (0.78 cm^3) was added dropwise at 0 °C a solution of benzoyl chloride (0.57 cm^3, 4.95 mmol) in dichloromethane (5 cm^3). The reaction mixture was stirred for 12 h at room temp. and the resulting solution was poured into water, extracted with dichloromethane, and the extract was then washed successively with saturated aq. $NaHCO_3$ and water, and dried (Na_2SO_4). The solvents were removed under reduced pressure and the oily residue was chromatographed on silica gel with dichloromethane as eluent to afford the *title compound* **20α** (1.17 g, 99%) as an oil; R_f 0.57 [(3:2) hexane–diethyl ether]; δ_H(250 MHz; $CDCl_3$) 1.1 (9 H, s, 3 × Me), 1.71 (2 H, m, 3- and 5-H), 2.0 (2 H, m, 3- and 5-H), 2.9 (2 H, m, 1- and 2-H), 4.4 (4 H, d, *J* 5.7, 2 × CH_2O), 4.55 (1 H, m, 4-H) and 7.3–8.2 (20 H, m, ArH); δ_C(250 MHz; $CDCl_3$) 19.19, 27.04, 38.34, 39.33, 65.56, 73.46, 127.7, 128.44, 128.97, 129.61, 129.69, 130.21, 130.67, 132.98, 134.34, 134.62, 135.79 and 166.57; *m/z* 593 $(M + H)^+$ (Found: C, 74.6; H, 7.1. $C_{37}H_{40}O_5Si$ requires C, 74.9; H, 6.8%).

(1β,2β,4β)-1,2-*Bis*(*benzoyloxymethyl*)-4-(tert-*butyldiphenylsiloxy*)*cyclopentane* **20β**.—From the diol **19β** the *title compound* was obtained, according to the aforementioned procedure, as an oil (80% yield); R_f 0.5 [(3:2) hexane–diethyl ether]; δ_H(250 MHz; $CDCl_3$) 0.98 (9 H, s, 3 × Me), 1.69 (2 H, m, 3- and 5-H), 1.98 (2 H, m, 3- and 5-H), 2.39 (2 H, m, 1- and 2-H), 4.28 (1 H, m, 4-H), 4.43 (4 H, d, *J* 6.58, 2 × CH_2O) and 7.2–8.0 (20 H, m, ArH); δ_C(250 MHz; $CDCl_3$) 18.95, 26.85, 38.63, 38.97, 65.48, 73.35, 127.56, 127.76, 128.25, 129.33, 129.52, 129.56, 130.25, 132.76, 133.96, 134.10, 135.68 and 166.42; *m/z* 593 $(M + H)^+$ (Found: C, 75.3; H, 7.0%).

(1α,3β,4β)-3,4-*Bis*(*benzoyloxymethyl*)*cyclopentanol* **14α**.—To a stirred solution of the silylated ether **20α** (1.17 g, 1.98 mmol) in THF (40 cm^3) was added a solution (1.72 cm^3, 5.94 mmol) of TBAF (1.1 mol dm^{-3} in THF) at room temp. After 12 h the solution was evaporated to dryness under reduced pressure and the residue was chromatographed on silica gel and eluted with methanol (0–2%) in dichloromethane to afford the *title compound* **14α** (0.70 g, quantitative yield) as an oil; R_f 0.27 [(98:2) CH_2Cl_2–MeOH]; δ_H(250 MHz; $CDCl_3$) 1.7 (1 H, br s, OH), 2 (4 H, m, 2- and 5-H), 2.9 (2 H, m, 3- and 4-H), 4.45 (4 H, m, 2 × CH_2O), 4.55 (1 H, m, 1-H) and 7.3–8.1 (10 H, m, ArH); δ_C(250 MHz; $CDCl_3$) 38.26, 38.94, 65.3, 71.7, 128.35, 129.47, 129.98, 132.96 and 166.49; *m/z* 355 $(M + H)^+$ (Found: C, 70.9; H, 6.4. $C_{21}H_{22}O_5$ requires C, 71.1; H, 6.2%).

(1β,3β,4β)-3,4-*Bis*(*benzoyloxymethyl*)*cyclopentanol* **14β**.—From the ether **20β** the *title compound* was obtained as an oil in 80% yield following the aforementioned procedure; R_f 0.25 [(98:2) CH_2Cl_2–MeOH]; δ_H(250 MHz; $CDCl_3$) 1.76 (2 H, m, 2- and 5-H), 2.18 (1 H, br s, OH), 2.37 (2 H, m, 2- and 5-H), 2.68 (2 H, m, 3- and 4-H), 4.52 (1 H, m, 1-H), 4.60 (4 H, m, 2 × CH_2O) and 7.3–8.15 (10 H, m, ArH); δ_C(250 MHz; $CDCl_3$) 38.51, 39.14, 65.42, 72.03, 128.3, 129.5, 130.12, 132.92 and 166.50; *m/z* 355 $(M + H)^+$ (Found: C, 70.9; H, 6.2%).

(1β,2β,4β)-4-(tert-*Butyldiphenylsiloxy*)-1,2-[*isopropylidenebis*(*oxymethylene*)]*cyclopentane* **21β**.—The diol **19β** (2 g, 5.2 mmol) was treated with acetone dimethyl acetal (40 cm^3) and a catalytic amount of PTSA (50 mg) at room temp. for 3 h. The solution was neutralized (K_2CO_3) and the solvent was evaporated off. After addition of water and extraction with dichloromethane, the organic phase was dried (Na_2SO_4) and evaporated to afford the pure *title compound* (2.2 g, quantitative yield) as an oil; R_f 0.83 [(98:2) CH_2Cl_2–MeOH]; δ_H(250 MHz; $CDCl_3$) 0.99 (9 H, s, 3 × Me), 1.29 (3 H, s, Me), 1.33 (3 H, s, Me), 1.6 (2 H, m, 3- and 5-H), 1.78 (4 H, m, 1-, 2-, 3- and 5-H), 3.62 (4 H, m, 2 × CH_2O), 4.17 (1 H, m, 4-H) and 7.1–8.15 (10 H, m, ArH); δ_C(250 MHz; $CDCl_3$) 19.21, 24.84, 25.09, 27.08, 37.10, 41.91, 62.59, 73.95, 101.47, 127.70, 129.67, 134.62 and 135.92 (Found: C, 73.3; H, 8.7. $C_{26}H_{36}O_3Si$ requires C, 73.5; H, 8.5%).

(1β,3β,4β)-3,4-[*Isopropylidenebis*(*oxymethylene*)]*cyclopentanol* **15β**.—To a stirred solution of the silylated ether **21β** (2.36 g, 5.55 mmol) in THF (10 cm^3) was added a solution (7.56 cm^3, 8.32 mmol) of TBAF (1.1 mol dm^{-3} in THF) at room temp. After 12 h the solution was evaporated to dryness under reduced pressure and the residue was chromatographed on silica gel with dichloromethane as eluent to afford the *title compound* **15β** (1.03 g, quantitative yield) as an oil; R_f 0.21 [(98:2) CH_2Cl_2–MeOH]; δ_H(250 MHz; $CDCl_3$) 1.32 (6 H, s, 2 × Me), 1.47 (2 H, m, 2- and 5-H), 2.0 (5 H, m, 2-, 3-, 4- and 5-H and OH), 3.63 (4 H, m, 2 × CH_2O) and 4.29 (1 H, m, 1-H); δ_C(250 MHz; $CDCl_3$) 24.66, 25.0, 36.58, 41.88, 62.52, 72.32 and 101.47; *m/z* 187 $(M + H)^+$ (Found: C, 64.1; H, 9.9. $C_{10}H_{18}O_3$ requires C, 64.5; H, 9.7%).

Procedure A. General Procedure for the Alkylation of Protected Heterocyclic Bases under Mitsunobu Conditions.—To a stirred solution of the secondary alcohol (1 mmol), heterocyclic base (2 mmol) and triphenylphosphine (3 mmol) in anhydrous THF–benzene (2:1; 12 cm^3 $mmol^{-1}$ of alcohol) cooled to 0 °C (or lower temp., see Table 1), was added dropwise, under argon, DEAD (3 mmol). After 2 h at 0 °C (or lower temp.) and 12 h at room temp. the mixture was evaporated to dryness under reduced pressure. The crude residue was chromatographed on silica gel to remove both the triphenylphosphine oxide and the unchanged nucleobase, and the required product was directly deprotected to give, after chromatography, the fully deprotected carbocyclic nucleoside.

General Procedures for the Deprotection of Protected Carbocyclic Nucleosides.—Procedure B. Preparation of adenine derivatives **9α,β**. The 6-chloropurinyl derivative (1 mmol) obtained after Mitsunobu alkylation was treated with methanolic ammonia (30 cm^3 $mmol^{-1}$ of alcohol) at room temp. for 24 h. In the case of compound **9α** (α series), an acidic treatment was then performed [HCl (10%), room temp., 20 min] to remove the isopropylidene group. After removal of the solvent the residue was chromatographed on silica gel (reversed-phase C2) with water as eluent.

Procedure C. Preparation of guanine derivatives **10α,β**. The crude mixture (1 mmol) obtained after Mitsunobu alkylation was treated with HCl (10%) (room temp., 20 min) in water–1,4-dioxane (1 : 1 v/v) in the case of the α series (**10α**), and for both α and β series (**10α**) and (**10β**) were treated at 0 °C for 2 h with NaOH (0.1 mol dm^{-3}; 4.4 mmol) in water–1,4-dioxane (1 : 1 v/v; 100 cm^3 $mmol^{-1}$ of alcohol); the reaction mixture was maintained at room temp. for 12 h, the solvents were evaporated off, and the residue was chromatographed on silica gel (reversed phase C2) with water as eluent.

Procedure D. Preparation of pyrimidine derivatives **6α,β–7α,β** *and* **11β–13β**. The crude mixture (1 mmol) isolated after alkylation under Mitsunobu conditions was treated with HCl (10%) (room temp., 20 min) for the α series and was then treated in both α and β series with a solution of MeONa (3 mmol) in absolute methanol (22 cm^3) at 0 °C for 3 h: after neutralization (HCl 2 mol dm^{-3}) the solvent was removed under reduced pressure. The residue was then chromatographed on silica gel (reversed phase C2) with water as eluent.

Alkylation of 3-*Benzoyluracil by the Cyclopentanol* **14α**.—The compounds **6β** and **11β** were obtained from the alcohol **14α** and 3-benzoyluracil according to procedures A (0 °C) and D in 69% overall yield in the ratio 1 : 2, after chromatography on silica gel (reversed-phase C2) and elution with water.

1-[1′β,3′β,4′β)-3′,4′-*Bis*(*hydroxymethyl*)*cyclopentyl*]*uracil* **6β**. M.p. 134–136 °C; R_f 0.4 [(88 : 12) CH_2Cl_2–MeOH]; λ_{max}(EtOH, 95%)/nm 267 (ε 11 550), λ_{max}(0.1 mol dm^{-3} KOH)/nm 267; λ_{max}(0.1 mol dm^{-3} HCl)/nm 267; δ_H[250 MHz; $(CD_3)_2SO$] 1.55 (2 H, m, 2′- and 5′-H), 2.02 (2 H, m, 2′- and 5′-H), 2.16 (2 H, m, 3′- and 4′-H), 3.55 (4 H, m, 2 × CH_2O), 4.66 (2 H, t, *J* 4.8, 2 × OH), 4.75 (1 H, m, 1′-H), 5.6 (1 H, d, *J* 8, 5-H), 7.74 (1 H, d, *J* 8, 6-H) and 11.2 (1 H, br s, NH); δ_C[250 MHz; $(CD_3)_2SO$] 34.42, 40.34, 54.28, 61.30, 101.4, 142.08, 151.05 and 163.28; *m*/*z* 241 $(M + H)^+$ (Found: C, 54.9; H, 6.9; N, 11.5. $C_{11}H_{16}N_2O_4$ requires C, 55.0; H, 6.7; N, 11.6%).

2-O-(1′β,3′β,4′β)-3′,4′-*Bis*(*hydroxymethyl*)*cyclopentyl*]*uracil* **11β**. Oil, R_f 0.36 [(88:12) CH_2Cl_2–MeOH]; λ_{max}(EtOH, 95%)/nm 257; λ_{max}(0.1 mol dm^{-3} KOH)/nm 264; λ_{max}(0.1 mol dm^{-3} HCl)/nm 255; δ_H(250 MHz; $(CD_3)_2SO$] 1.55 (2 H, m, 2′- and 5′-H), 2.15 (4 H, m, 2′-, 3′-, 4′- and 5′-H), 3.54 (4 H, m, 2 × CH_2O), 5.2 (1 H, m, 1′-H), 5.7 (2 H, br s, 2 × OH), 5.85 (1 H, d, *J* 6.6, 5-H), 7.66 (1 H, d, *J* 6.6, 6-H) and 11.2 (1 H, br s, NH); δ_C(250 MHz; $(CD_3)_2SO$] 34.0, 41.30, 61.06, 78.07, 107.71, 152.95, 158.48 and 165.62; *m*/*z* 241 $(M + H)^+$ (Found: C, 54.9; H, 6.9; N, 11.5%).

Alkylation of 3-*Benzoyluracil by the Cyclopentanol* **15β**.—1-[(1′α,3′β,4′β)-3′,4′-*Bis*(*hydroxymethyl*)*cyclopentyl*]*uracil* **6α**. From the alcohol **15β** and 3-benzoyluracil following procedures A (0 °C) and D the *title compound* was obtained as a solid after chromatography on silica gel (reversed-phase C2), with water as eluent, in 20% yield; m.p. 106–109 °C; R_f 0.29 [(88 : 12)CH_2Cl_2–MeOH]; λ_{max}(EtOH, 95%)/nm 265 (ε 8938); λ_{max}(0.1 mol dm^{-3} KOH)/nm 263; λ_{max}(0.1 mol dm^{-3} HCl)/nm 265; δ_H[250 MHz; $(CD_3)_2SO$] 1.71 (2 H, m, 2′- and 5′-H), 1.89 (2 H, m, 2′- and 5′-H), 2.37 (2 H, m, 3′- and 4′-H), 3.45 (4 H, m, 2 × CH_2O), 4.47 (2 H, br s, 2 × OH), 4.94 (1 H, m, 1′-H), 5.58 (1 H, d, *J* 7.95, 5-H), 7.68 (1 H, d, *J* 7.95, 6-H) and 11.20 (1 H, br s, NH); δ_C[250 MHz; $(CD_3)_2SO$] 34.03, 42.27, 54.41, 60.58, 101.31, 142.56, 150.74 and 163.07; *m*/*z* 241 $(M + H)^+$ (Found: C, 54.6; H, 7.0; N, 11.3%).

Alkylation of 3-*Benzoylthymine by the Cyclopentanol* **14α**.—The compounds **7β** and **12β** were obtained in the ratio 2 : 1 from the alcohol **14α** as solids according to procedures A (−78 °C) and D in 45% overall yield.

1-[(1′β,3′β,4′β)-3′,4′-*Bis*(*hydroxymethyl*)*cyclopentyl*]*thymine* **7β**. The *title compound* was obtained after chromatography of the crude mixture on silica gel and elution with dichloromethane–methanol (95 : 5); m.p. 188–189 °C; R_f 0.34 [(90 : 10) CH_2Cl_2–MeOH]; λ_{max}(EtOH, 95%)/nm 272 (ε 8234); λ_{max}(0.1 mol dm^{-3} KOH)/nm 272; λ_{max}(0.1 mol dm^{-3} HCl)/nm 272; δ_H[250 MHz; $(CD_3)_2SO$] 1.58 (2 H, m, 2′- and 5′-H), 1.82 (3 H, d, *J* 1, 5-Me), 2.0 (2 H, m, 2′- and 5′-H), 2.22 (2 H, m, 3′- and 4′-H), 3.55 (4 H, m, 2 × CH_2O), 4.7 (2 H, t, *J* 4.9, 2 × OH), 4.7 (1 H, m, 1′-H), 7.6 (1 H, d, *J* 1, 6-H) and 11.2 (1 H, br s, NH); δ_C[250 MHz; $(CD_3)_2SO$] 11.98, 33.28, 40.33, 53.73, 61.32, 108.9, 137.29, 150.89 and 163.54; *m*/*z* 255 $(M + H)^+$ (Found: C, 56.6; H, 7.2; N, 10.7. $C_{12}H_{18}N_2O_4$ requires C, 56.7; H, 7.1; N, 11.0%).

2-O-[(1′β,3′β,4′β)-3′,4′-*Bis*(*hydroxymethyl*)*cyclopentyl*]*thymine* **12β**]. The *title compound* was obtained after chromatography on silica gel and elution with dichloromethane–methanol (95 : 5); m.p. 149–150 °C; R_f 0.32 [(90 : 10) CH_2Cl_2–MeOH]; λ_{max}(EtOH, 95%)/nm 270 (ε 10 300); λ_{max}(0.1 mol dm^{-3} KOH)/nm 268; λ_{max}(0.1 mol dm^{-3} HCl)/nm 258; δ_H[250 MHz; $(CD_3)_2SO$] 1.54 (2 H, m, 2′- and 5′-H), 1.8 (3 H, d, *J* 1, 5-Me), 2.15 (4 H, m, 2′-, 3′-, 4′- and 5′-H), 3.53 (4 H, m, 2 × CH_2O), 4.6 (2 H, br s, 2 × OH), 5.2 (1 H, m, 1′-H), 7.53 (1 H, d, *J* 1, 6-H), and 11.2 (1 H, br s, NH); δ_C[250 MHz; $(CD_3)_2SO$] 12.24, 34.61, 41.23, 61.09, 77.7, 115.9, 146.03, 156.29 and 164.47; *m*/*z* 255 $(M + H)^+$ and 127 $(B + H)^+$ (Found: C, 56.4; H, 7.3; N, 11.0%).

Alkylation of 3-*Benzoylthymine by the Cyclopentanol* **15β**.—1-[(1′α,3′β,4′β)-3′,4′-*Bis*(*hydroxymethyl*)*cyclopentyl*]*thymine* **7α**. From the alcohol **15β** and 3-benzoylthymine following procedures A (0 °C) and C the *title compound* was obtained as a solid after chromatography on silica gel (reversed-phase C2), with water as eluent, in 25% yield; m.p. 201–202 °C; R_f 0.2 [(90 : 10) CH_2Cl_2–MeOH]; λ_{max}(EtOH, 95%)/nm 272 (ε 8432); λ_{max}(0.1 mol dm^{-3} KOH)/nm 268; λ_{max}(0.1 mol dm^{-3} HCl)/nm 268; δ_H [250 MHz; $(CD_3)_2SO$] 1.73 (2 H, m, 2′- and 5′-H), 1.78 (3 H, s, 5-Me), 1.92 (2 H, m, 2′- and 5′-H), 2.39 (2 H, m, 3′- and 4′-H), 3.40 (4 H, m, 2 × CH_2O), 4.54 (2 H, t, *J* 4.53, 2 × OH), 4.95 (1 H, m, 1′-H), 7.49 (1 H, s, 6-H), and 11.50 (1 H, br s, NH); δ_C[250 MHz; $(CD_3)_2SO$] 11.79, 33.87, 42.26, 53.66, 60.51, 109.09, 137.84, 150.61 and 163.52; *m*/*z* 255 $(M + H)^+$ (Found: C, 56.6; H, 7.2; N, 10.8%).

Alkylation of 3-*Benzoyluracil and* 3-*Benzoylthymine by the Cyclopentanol* **16α**.—*Dimethyl* (1′β,2′β,4′β)-4′-(3-*benzoyl*-2,4-*dioxo*-1,2,3,4-*tetrahydropyrimidin*-1-*yl*)*cyclopentane*-1′,2′-*dicarboxylate* **22β**. The *title compound* was obtained in 62% yield as an oil from alcohol **16α** according to procedure A (0 °C) after chromatography on silica gel with dichloromethane (50–80%) in pentane as eluent; R_f 0.43 [(98 : 2) CH_2Cl_2–MeOH]; λ_{max}(EtOH, 95%)/nm 266; λ_{max}(0.1 mol dm^{-3} KOH)/nm 266; λ_{max}(0.1 mol dm^{-3} HCl)/nm 266; δ_H(250 MHz; $CDCl_3$) 2.15 (2 H, m, 3′- and 5′-H), 2.46 (2 H, m, 3′- and 5′-H), 3.32 (2 H, m, 1′- and 2′-H), 3.7 (6 H, s, 2 × MeO), 5.03 (1 H, m, 4′-H), 5.91 (1 H, d, *J* 8, 5-H), 7.4–8.2 (5 H, m, ArH) and 7.52 (1 H, d, *J* 8, 6-H); δ_C(250 MHz; $CDCl_3$) 33.76, 44.87, 52.34, 57.7, 102.78, 128.95, 131.33, 140.55, 149.65, 161.6, 168.49, 173.26 and 174.03; *m*/*z* 401 $(M + H)^+$ (Found: C, 60.2; H, 5.0; N, 6.9. $C_{20}H_{20}N_2O_7$ requires C, 60.0; H, 5.03; N, 7.0%).

Dimethyl (1′β,2′β,4′β)-4-(3-*benzoyl*-5-*methyl*-2,4-*dioxo*-1,2,3,4-*tetrahydropyrimidin*-1-*yl*)*cyclopentane*-1′,2′-*dicarboxylate* **23β**. The *title compound* was obtained in 67% yield as a solid from alcohol **16α** according to procedure A (0 °C) after chromatography on silica gel and elution with dichloromethane (50–80%) in pentane; m.p. 154–155 °C (from MeOH); R_f 0.39 [(98:2) CH_2Cl_2–MeOH]; λ_{max}(EtOH, 95%)/nm 272; λ_{max}(0.1 mol dm^{-3} KOH)/nm 272; λ_{max}(0.1 mol dm^{-3} HCl)/nm 272; δ_H(250MHz; $CDCl_3$) 2.0 (3 H, d, *J* 1, 5-Me), 2.15 (2 H, m, 3′- and 5′-H), 2.4 (2 H, m, 3′- and 5′-H), 3.15 (2 H, m, 1′- and 2′-H), 3.7 (6 H, s, 2 × MeO), 5.15 (1 H, m, 4′-H), 7.5–7.9 (5 H, m, ArH) and 7.6 (1 H, d, *J* 1, 6-H); δ_C(250 MHz; $CDCl_3$) 12.89, 33.37, 44.92, 52.45, 53.23, 112.04, 129.26, 130.61, 131.9, 135.07, 136.66, 150.37, 162.77, 169.26 and 173.65; *m/z* 415 $(M + H)^+$ (Found: C, 60.7; H, 5.6; N, 6.5. $C_{21}H_{22}N_2O_7$ requires C, 60.9; H, 5.3; N, 6.7%).

Alkylation of 4-N-*Benzoylcytosine by the Alcohol* **14α**.—2-O-[(1′β,3′β,4′β)-3′,4′-*Bis*(*hydroxymethyl*)*cyclopentyl*]*cytosine* **13β**.—The *title compound* was isolated from the alcohol **14α** and 4-*N*-benzoylcytosine following procedures A (0 °C) and D and chromatography on silica gel (reversed-phase C2) with water (100–99.5%) in methanol, in 61% overall yield; m.p. 129–131 °C, R_f 0.26 [(88:12) CH_2Cl_2–MeOH]; λ_{max}(EtOH, 95%)/nm 270; λ_{max}(0.1 mol dm^{-3} KOH)/nm 270; λ_{max}(0.1 mol dm^{-3} HCl)/nm 258; δ_H[250 MHz; $(CD_3)_2SO$] 1 (2 H, m, 2′- and 5′-H), 2.0 (4 H, m, 2′-, 3′-, 4′- and 5′-H), 3.5 (4 H, m, 2 × CH_2O), 4.65 (2 H, br s, 2 × OH), 5.18 (1 H, m, 1′-H), 6.03 (1 H, d, *J* 5.7, 5-H), 6.8 (2 H, br s, NH_2) and 7.85 (1 H, d, *J* 5.7, 6-H); δ_C[250 MHz; $(CD_3)_2SO$] 34.81, 41.09, 61.03, 75.56, 98.77, 155.92, 164.26 and 164.91; *m/z* 240 $(M + H)^+$ and 112 $(B + H)^+$ (Found: C, 54.9; H, 7.0; N, 17.3. $C_{11}H_{17}N_3O_3$ requires C, 55.2; H, 7.2; N, 17.6%).

Preparation of Cytosine-containing Carbocyclic Nucleosides from Uracil Precursors (*Scheme* 3).—1-[(1′β,3′β,4′β)-3′,4′-*Bis*-(tert-*butyldiphenylsiloxymethyl*)*cyclopentyl*]*uracil* **36β**. To a solution of the diol **6β** (90 mg, 0.374 mmol) in dry pyridine (7 cm^3) was added TBDPSCl (226 mg, 0.824 mmol) at room temp.; the reaction mixture was stirred for 12 h and the solvent then evaporated off under reduced pressure. The crude mixture was chromatographed with dichloromethane as eluent to afford the *title compound* as an oil (158 mg, 65%); R_f 0.5 [(96:4) CH_2Cl_2–MeOH]; δ_H[250 MHz; $(CD_3)_2SO$] 1.02 (18 H, s, 6 × Me), 1.58 (2 H, m, 2′- and 5′-H), 2.25 (2 H, m, 2′- and 5′-H), 2.34 (2 H, m, 3′- and 4′-H), 3.83 (4 H, m, 2 × CH_2O), 4.92 (1 H, m, 1′-H), 5.41 (1 H, d, *J* 8.1, 5-H), 7.13 (1 H, d, *J* 8.1, 6-H), 7.2–7.65 (20 H, m, ArH) and 8.2 (1 H, br s, NH) (Found: C, 72.5; H, 7.2; N, 4.2. $C_{43}H_{52}N_2O_4Si_2$ requires C, 72.3; H, 7.3; N, 3.9%).

1-[(1′α,3′β,4′β)-3′,4′-*Bis*(tert-*butyldiphenylsiloxymethyl*)*cyclopentyl*]*uracil* **36α**. From the diol **6α** the *title compound* was obtained as an oil according to the aforementioned procedure, in 82% yield; R_f 0.5 [(96:4) CH_2Cl_2–MeOH]; δ_H[250 MHz; $(CD_3)_2SO$] 0.93 (18 H, s, 6 × Me), 1.81 (2 H, m, 2′- and 5′-H), 2.08 (2 H, m, 2′- and 5′-H), 2.56 (2 H, m, 3′- and 4′-H), 3.69 (4 H, m, 2 × CH_2O), 5.09 (1 H, m, 1′-H), 5.61 (1 H, d, *J* 8, 5-H), 7.3–7.65 (20 H, m, ArH), 7.7 (1 H, d, *J* 8, 6-H) and 11.2 (1 H, br s, NH) (Found: C, 71.9; H, 7.2; N, 4.1%).

1-[(1′β,3′β,4′β)-3′,4′-*Bis*(tert-*butyldiphenylsiloxymethyl*)*cyclopentyl*]*cytosine* **37β**.—To a solution of compound **36β** (96 mg, 0.133 mmol) in dry 1,2-dichloroethane (4 cm^3) was added, under argon, Lawesson's reagent (66 mg, 0.16 mmol). The solution was then refluxed for 6 h and evaporated to dryness under reduced pressure. The crude 4-thio derivative was then treated with methanolic ammonia (4 cm^3) and heated at 100 °C for 18 h. After removal of the solvent the residue was chromatographed with dichloromethane–methanol (95:5) to give the *title compound* (88 mg, 93%) as an oil; R_f 0.19 [(92:8) CH_2Cl_2–MeOH]; δ_H[250 MHz; $(CD_3)_2SO$] 1.05 (18 H, s, 6 × Me), 1.55 (2 H, m, 2′- and 5′-H), 1.9 (2 H, m, 2′- and 5′-H), 2.2 (2 H, m, 3′- and 4′-H), 3.8 (4 H, m, 2 × CH_2O), 5.1 (1 H, m, 1′-H), 5.45 (1 H, d, *J* 7.3, 5-H) and 7.1–7.7 (23 H, m, 6-H, NH_2, and ArH) (Found: C, 71.8; H, 7.2; N, 5.7. $C_{43}H_{53}N_3O_3Si_2$ requires C, 72.1; H, 7.5; N, 5.9%).

1-[(1′α,3′β,4′β)-3′,4′-*Bis*(tert-*butyldiphenylsiloxymethyl*)-*cyclopentyl*]*cytosine* **37α**. From compound **36α**, and according to the aforementioned procedure, the *title compound* was obtained as an oil in 70% yield; R_f 0.65 [(94:6) CH_2Cl_2–MeOH]; δ_H[250 MHz; $(CD_3)_2SO$] 0.95 (18 H, s, 6 × Me), 1.79 (2 H, m, 2′- and 5′-H), 2.04 (2 H, m, 2′- and 5′-H), 2.58 (2 H, m, 3′- and 4′-H), 3.65 (4 H, m, 2 × CH_2O), 5.05 (1 H, m, 1′-H), 5.7 (1 H, d, *J* 7.3, 5-H), 6.99 (2 H, br s, NH_2) and 7.3–7.65 (21 H, m, 6-H and ArH) (Found: C, 72.4; H, 7.2; N, 6.1%).

1-[(1′β,3′β,4′β)-3′,4′-*Bis*(*hydroxymethyl*)*cyclopentyl*]*cytosine* **8β**.—The disilylated ether **37β** (255 mg, 0.357 mmol), dissolved in THF (12 cm^3), was allowed to react with a solution (1.17 cm^3, 1.29 mmol) of TBAF (1.1 mol dm^{-3} in THF) at room temp. for 12 h to afford, after chromatography on silica gel (reversed-phase C2) with water as eluent, the *title compound* (57 mg, 85%) as a solid; m.p. 75–77 °C; R_f 0.72 [(7:2:1) propan-2-ol–ammonia–water]; λ_{max}(EtOH, 95%)/nm 276 (ε 11 150); λ_{max}(0.1 mol dm^{-3} KOH)/nm 274; λ_{max}(0.1 mol dm^{-3} HCl)/nm 278; δ_H[250 MHz; $(CD_3)_2SO$] 1.3 (2 H, m, 2′- and 5′-H), 1.8 (2 H, m, 2′- and 5′-H), 2.0 (2 H, m, 3′- and 4′-H), 3.41 (4 H, m, 2 × CH_2O), 4.53 (2 H, br s, 2 × OH), 4.63 (1 H, m, 1′-H), 5.54 (1 H, d, *J* 7.3, 5-H), 6.85 (2 H, br s, NH_2) and 7.5 (1 H, d, *J* 7.3, 6-H); δ_C[250 MHz; $(CD_3)_2SO$] 33.93, 40.66, 54.73, 61.52, 93.69, 142.23, 155.96 and 165.12; *m/z* 240 $(M + H)^+$ (Found: C, 54.9; H, 7.2; N, 17.7. $C_{11}H_{17}N_3O_3$ requires C, 55.2; H, 7.1; N, 17.5%).

1-[(1′α,3′β,4′β)-3′,4′-*Bis*(*hydroxymethyl*)*cyclopentyl*]*cytosine* **8α**. From the disilylated ether **37α** and according to the aforementioned procedure, the *title compound* was obtained as a solid in 82% yield; m.p. 225–227 °C; R_f 0.68 [(7:2:1) propan-2-ol–ammonia–water]; λ_{max}(EtOH, 95%)/nm 276 (ε 10 060); λ_{max}(0.1 mol dm^{-3} KOH)/nm 274; λ_{max}(0.1 mol dm^{-3} HCl)/nm 278; δ_H[250 MHz; $(CD_3)_2SO$] 1.71 (2 H, m, 2′- and 5′-H), 1.89 (2 H, m, 2′- and 5′-H), 2.35 (2 H, m, 3′- and 4′-H), 3.42 (4 H, m, 2 × CH_2O), 4.52 (2 H, br s, 2 × OH), 4.97 (1 H, m, 1′-H), 5.67 (1 H, d, *J* 7.3, 5-H), 6.93 (2 H, br s, NH_2) and 7.58 (1 H, d, *J* 7.3, 6-H); δ_C[250 MHz; $(CD_3)_2SO$] 34.41, 42.37, 54.74, 60.69, 93.56, 142.73, 155.59 and 164.98; *m/z* 240 $(M + H)^+$ (Found: C, 55.2; H, 7.2; N, 17.2%).

Alkylation of 6-*Chloropurine by the Cyclopentanol* **14α**.—9-[(1′β,3′β,4′β)-3′,4′-*Bis*(*hydroxymethyl*)*cyclopentyl*]*adenine* **9β**. From the alcohol **14α** and 6-chloropurine the *title compound* was obtained as a solid, according to the procedures A (0 °C) and B, in 71% yield; m.p. 195–197 °C; R_f 0.29 [(88:12) CH_2Cl_2–MeOH]; λ_{max}(EtOH, 95%)/nm 260 (ε 16 150); λ_{max}(0.1 mol dm^{-3} KOH)/nm 260; λ_{max}(0.1 mol dm^{-3} HCl)/nm 258; δ_H[250 MHz; $(CD_3)_2SO$] 1.71 (2 H, m, 2′- and 5′-H), 2.08 (4 H, m, 2′-, 3′-, 4′- and 5′-H), 3.38 (4 H, m, 2 × CH_2O), 4.53 (2 H, t, *J* 5, 2 × OH), 4.6 (1 H, m, 1′-H), 7.01 (2 H, br s, NH_2), 7.93 (1 H, s, 8-H) and 8.02 (1 H, s, 2-H); δ_C[250 MHz; $(CD_3)_2SO$] 34.90, 40.91, 53.61, 61.34, 118.99, 139.01, 149.33, 152.02 and 155.85; *m/z* 264 $(M + H)^+$ and 136 $(B + H)^+$ (Found: C, 54.7; H, 6.6; N, 26.7. $C_{12}H_{17}N_5O_2$ requires C, 54.7; H, 6.5; N, 26.6%).

Alkylation of 6-*Chloropurine by the Cyclopentanol* **15β**.—9-[(1′α,3′β,4′β)-3′,4′-*Bis*(*hydroxymethyl*)*cyclopentyl*]*adenine* **9α**. The *title compound* was obtained as a solid, according to the aforementioned procedure, in 61% yield; m.p. 178–179 °C; R_f 0.10 [(88:12) CH_2Cl_2–MeOH]; λ_{max}(EtOH, 95%)/nm 259 (ε

15 900); λ_{max}(0.1 mol dm^{-3} KOH)/nm 259; λ_{max}(0.1 mol dm^{-3} HCl)/nm 258; δ_H[250 MHz; $(CD_3)_2SO$] 2.11 (4 H, m, 2'- and 5'-H_2), 2.52 (2 H, m, 3'- and 4'-H), 3.52 (4 H, m, 2 × CH_2O), 4.6 (2 H, m, 2 × OH), 5.07 (1 H, m, 1'-H), 7.15 (2 H, br s, NH_2), 8.12 (1 H, s, 8-H) and 8.22 (1 H, s, 2-H); δ_C[250 MHz; $(CD_3)_2SO$] 35.39, 42.19, 53.48, 60.78, 119.18, 139.34, 149.21, 152.03 and 155.90; *m/z* 264 $(M + H)^+$ and 136 $(B + H)^+$ (Found: C, 54.9; H, 6.7; N, 26.4%).

Alkylation of Protected Guanine by the Alcohol **14α**.—9-[(1'β,3'β,4'β)-3',4'-*Bis(hydroxymethyl)cyclopentyl*]*guanine* **10β**. From the alcohol **14α** and 2-*N*-acetyl-6-*O*-(diphenylcarbamoyl)guanine following procedures A (0 °C) and C and after purification by chromatography on silica gel (reversed-phase C2) with water as eluent the *title compound* was isolated as a solid in 56% overall yield; m.p. > 250 °C; R_f 0.5 [(7:2:1) propan-2-ol–ammonia–water]; λ_{max}(EtOH, 95%)/nm 256 (ε 14 960); λ_{max}(0.1 mol dm^{-3} KOH)/nm 256 and 267; λ_{max}(0.1 mol dm^{-3} HCl)/nm 252 and 276; δ_H[250 MHz; $(CD_3)_2SO$] 1.8 (2 H, m, 2'- and 5'-H), 2.22 (4 H, m, 2'-, 3'-, 4'- and 5'-H), 3.60 (4 H, m, 2 × CH_2O), 4.58 (1 H, m, 1'-H), 4.7 (2 H, t, *J* 4.4, 2 × OH), 6.4 (2 H, br s, NH_2), 7.79 (1 H, s, 8-H) and 10.3 (1 H, br s, NH); δ_C[250 MHz; $(CD_3)_2SO$] 35.08, 40.89, 52.92, 61.29, 116.68, 135.02, 151.06, 153.20 and 156.74; *m/z* 280 $(M + H)^+$ (Found: C, 51.2; H, 6.1; N, 24.8. $C_{12}H_{17}N_5O_3$ requires C, 51.6; H, 6.1; N, 25.0%).

Alkylation of Protected Guanine by the Alcohol **15β**.—9-[(1'α,3'β,4'β)-3',4'-*Bis(hydroxymethyl)cyclopentyl*]*guanine* **10α**. From the alcohol **15β**, and according to the aforementioned procedure, the *title compound* was isolated as a solid in 35% overall yield; m.p. > 250 °C; R_f 0.57 [(7:2:1) propan-2-ol–ammonia–water]; λ_{max}(EtOH, 95%)/nm 250 (ε 12 250) and 270; λ_{max}(0.1 mol dm^{-3} KOH)/nm 256 and 268; λ_{max}(0.1 mol dm^{-3} HCl)/nm 252 and 274; δ_H[250 MHz; $(CD_3)_2SO$] 2.0 (4 H, m, 2'- and 5'-H), 2.43 (2 H, m, 3'- and 4'-H), 3.49 (4 H, m, 2 × CH_2O), 4.6 (2 H, br s, 2 × OH), 4.84 (1 H, m, 1'-H), 6.55 (2 H, br s, NH_2), 7.88 (1 H, s, 8-H) and 10.75 (1 H, br s, NH); δ_C[250 MHz; $(CD_3)_2SO$] 35.58, 42.02, 52.92, 60.78, 116.75, 135.3, 150.89, 153.45 and 157.09; *m/z* 280 $(M + H)^+$ (Found: C, 51.4; H, 5.9; N, 25.3%).

Alkylation of 3-*Benzoyluracil by the Cyclopentanol* **27**.—Compounds **28** and **29** were obtained as oils in the ratio 3:1 from the cyclopentanol **27** according to procedures A (0 °C) and D, in 75% overall yield.

1-*Cyclopentyluracil* **28**. R_f 0.46 [(92:8) CH_2Cl_2–MeOH]; λ_{max}(EtOH, 95%)/nm 267; λ_{max}(0.1 mol dm^{-3} KOH)/nm 267; λ_{max}(0.1 mol dm^{-3} HCl)/nm 267; δ_H[250 MHz; $(CD_3)_2SO$] 1.75 (8 H, m, 4 × CH_2), 4.75 (1 H, m, 1'-H), 5.58 (1 H, d, *J* 8, 5-H), 7.68 (1 H, d, *J* 8, 6-H) and 11.2 (1 H, br s, NH); δ_C[250 MHz; $(CD_3)_2SO$] 23.48, 30.35, 56.1, 101.21, 142.35, 150.95 and 163.08 (Found: C, 59.8; H, 6.4; N, 15.9. $C_9H_{12}N_2O_2$ requires C, 60.0; H, 6.7; N, 15.6%).

2-O-*Cyclopentyluracil* **29**. R_f 0.43 [(92:8) CH_2Cl_2–MeOH]; λ_{max}(EtOH, 95%)/nm 258; λ_{max}(0.1 mol dm^{-3} KOH)/nm 264; λ_{max} (0.1 mol dm^{-3} HCl)/nm 257; δ_H[250 MHz; $(CD_3)_2SO$] 1.75 (8 H, m, 4 × CH_2), 5.38 (1 H, m, 1'-H), 5.92 (1 H, d, *J* 6.6, 5-H), 7.7 (1 H, d, *J* 6.6, 6-H) and 12.15 (1 H, br s, NH); δ_C[250 MHz; $(CD_3)_2SO$] 23.2, 32.07, 80.05, 108.09, 150.97, 157.67 and 163.1 (Found: C, 60.1; H, 6.5; N, 15.7%).

Alkylation of 3-*Ethyluracil*[24] *by the Cyclopentanol* **27**.—Compounds **30** and **31** were obtained as oils in the ratio 69:31 from the cyclopentanol **27** according to procedures A (0 °C) and D, in 94% overall yield. The two regioisomers were separated on preparative TLC.

1-*Cyclopentyl*-3-*ethyluracil* **30**. R_f 0.59 [(96:4) CH_2Cl_2–MeOH]; λ_{max}(EtOH, 95%)/nm 266; λ_{max}(0.1 mol dm^{-3} KOH)/nm 264; λ_{max}(0.1 mol dm^{-3} HCl)/nm 268; δ_H[250 MHz; $(CD_3)_2SO$] 1.09 (3 H, t, *J* 7, CH_2*Me*), 1.75 (8 H, m, 4 × CH_2), 3.84 (2 H, q, *J* 7, CH_2Me), 4.8 (1 H, m, 1'-H), 5.68 (1 H, d, *J* 8, 5-H) and 7.7 (1 H, d, *J* 8, 6-H); δ_C[250 MHz; $(CD_3)_2SO$] 12.59, 23.55, 30.4, 35.38, 57.35, 100.51, 140.8, 150.82 and 161.64 (Found: C, 63.1; H, 7.5; N, 13.6. $C_{11}H_{16}N_2O_2$ requires C, 63.4; H, 7.7; N, 13.4%).

1-*Cyclopentyl*-2-O-*ethyluracil* **31**. R_f 0.51 [(96:4) CH_2Cl_2–MeOH]; λ_{max}(EtOH, 95%)/nm 258; λ_{max}(0.1 mol dm^{-3} KOH)/nm 270; λ_{max}(0.1 mol dm^{-3} HCl)/nm 271; δ_H[250 MHz; $(CD_3)_2SO$] 1.1 (3 H, t, *J* 7.1, CH_2*Me*), 1.75 (8 H, m, 4 × CH_2), 3.9 (2 H, q, *J* 7.1, CH_2Me), 5.44 (1 H, m, 1'-H), 6.2 (1 H, d, *J* 6.5, 5-H) and 7.7 (1 H, d, *J* 6.5, 6-H); δ_C[250 MHz; $(CD_3)_2SO$] 12.86, 23.16, 32.13, 35.55, 81.38, 107.5, 152.04, 156.07 and 161.47 (Found: C, 63.5; H, 7.4; N, 13.2%).

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