Pergamon

Tetrahedron, Vol. 52, No. 26, pp. 8907-8924, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00439-5

5-Fluorouracil Derivatives. 1. Acyclonucleosides through a Tin (IV) Chloride-Mediated Regiospecific Ring Opening of Alkoxy-1,4-Diheteroepanes

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Abstract: The reaction of 5-fluorouracil with the seven-membered acetals **1a-g** in the presence of tin (IV) chloride, trimethylchlorosilane and hexamethyldisilazane at room temperature gives 1-{[3-(2-hydroxyethylhetero)-1-alkoxy]alkyl}-5-fluorouracils **2a-f** and 1-{[2-(3-hydroxypropoxy)-1-*iso*propoxy]ethyl}-5-fluorouracil **2g** in 31-86 % yields. The presence of an heteroatom on the 1-position of the cycloacetal and the use of tin (IV) chloride, capable of a 1,4-chelation, seem to impose their influence in the regiospecific ring opening of **1a-g**. The conformational analyses carried out on **2b** and (1*R*,3*R*)-**2e** and (1*R*,3*S*)-**2e** clearly indicate that the $N_1(sp^2)$-C_1-C_2-C_3 moiety tends to fold in a *gauche* conformation. The antitumour activities of compounds **2b-g** were assessed against HEp human cells showing that **2c** is 4-fold more active than 5-FU. The drugs studied do not show any clear toxicity in comparison with the toxic effect of 5-FU.

Key words: Antitumour agents/ Acyclonucleosides/ 5-Fluorouracil/ 1,4-diheteroepanes/ regiospecificity

Introduction

Novel prodrug derivatives of 5-fluorouracil (5-FU) possessing a broader spectrum of antitumour activity and fewer toxic side effects than 5-FU have been sought diligently in a number of laboratories. The emergence of acyclovir, 9-[(2-hydroxyethoxy)methyl]guanine[1] as an excellent antiviral agent has stimulated the synthesis of a wide variety of acyclic nucleosides modified either in the base moiety or the acyclic part.[2] The antiviral action of these substances or their metabolites is generally due to an inhibition of DNA polymerases. In contrast, pyrimidine-derived acyclonucleosides have not yet been found to show a significant activity against virus diseases.[2a, 3] Kelley[4] explained this fact by the lower substrate affinity and inhibition properties of these compounds. However, a structure-activity relationship has not been given so far for new antiviral agents. Therefore, new pyrimidine acyclonucleosides are still of great interest, also with regard to their anticancer activity, since it has been shown that various 5-FU derivatives are active against some malignant cell lines due to an inhibition of thymidylate synthetase by the formation of 5-fluorodeoxyuridine monophosphate or by the incorporation of 5-fluorouridine monophosphate into RNA. In some malignant tumours the activity of uridine phosphates is enhanced;[5] therefore, 5-FU acyclonucleosides may even exhibit a higher antitumour activity with simultaneously lower toxicity than 5-FU.[5]

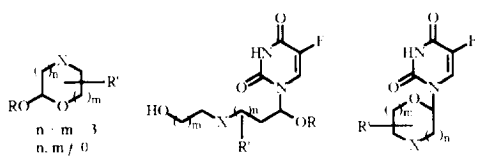
Acyclonucleosides are commonly synthesized by reaction of nucleic bases with α-chloromethyl ethers in the presence of strong bases,[6] by reaction of persilylated purines or pyrimidines with α-halo or α-acetoxymethyl ethers catalyzed by various Lewis acids or bases[1, 7] or by heating bis(trimethylsilyl)pyrimidine bases with 1,3-dioxolane (or 2-methyl-1,3-dioxolane), chlorotrimethylsilane and a metal iodide in acetonitrile at room

temperature.[8] 1-(1'-alkoxyalkyl)pyrimidines cannot be prepared by these methods. A great deal of examples for the synthesis of these compounds have been reported, e. g. by the oxidative cleavage of the pentose moiety of cyclic nucleosides,[9] a Michael-type reaction of α,β-unsaturated carbonyl compounds with uracil,[10] the $SnCl_4$-catalyzed reaction of acetals and acylals with persilylated purines and pyrimidines,[11] and the trimethylsilyl trifluoromethanesulfonate-catalyzed reactions of acetals with persilylated pyrimidines at -30°C.[12]

To our knowledge, up to now no attempt has been made to use seven-membered cycloacetals to synthesize acyclonucleosides. Our aim was to fill this gap and in this paper we report the synthesis and antitumour activity of the acyclonucleoside 5-FU derivatives **2** through the $SnCl_4$-catalyzed opening of alkoxy-1,4-diheteroepanes by 2,4-bis-*O*-trimethylsilyl-5-fluorouracil **3** generated *in situ* in acetonitrile. Acyclonucleosides of type **2** are especially interesting due to the following two reasons: (a) the presence of the hydroxyl group in the side chain that could therefore be phosphorylated; and (b) they constitute a new class of antitumour agents, since 5-FU is bound to a cytostatic aldehyde such as acrolein[13] or some of its homologues and, accordingly, two active substances are combined in one drug.

Results and Discussion

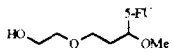
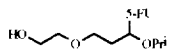
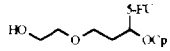
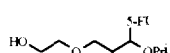
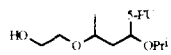
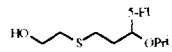
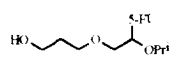
The reaction of 2,4-bis-*O*-trimethylsilyl-5-fluorouracil generated *in situ* with the seven-membered cycloacetals **1** in acetonitrile affords the desired products **2** after the addition of 1.25 equivalents of tin (IV) chloride. The reaction is complete within 0.5-1.25 h and then quenched by a concentrated aqueous solution of sodium bicarbonate. The products are purified by flash chromatography using chloroform/methanol mixtures and are isolated as thick oils.[14]



1 **2** **4**

Table 1 lists reaction times and yields obtained for compounds **2**. The 5-*iso*propoxy-6-methyl-1,4-dioxepane **1d** and the 5-*iso*propoxy-7-methyl-1,4-dioxepane **1e** have been used as the *trans* and *cis* isomers, respectively, and they give rise to the racemic mixture of diastereoisomers **2d** and **2e**, both being pairs of diastereoisomers formed in equal quantities. Thus, the title reaction is regiospecific but not diastereoselective. We were unable to separate both diastereoisomers of **2d**. Nevertheless, (1*R**,3*R**)-**2e** and (1*R**,3*S**)-**2e** were separated by flash chromatography although they were tested against HEp human cells as the racemic mixture of both diastereoisomers (Table 1). The present synthetic method is rapid and economical, does not seem to present serious scaling-up problems and is clearly adaptable to the synthesis of other pyrimidine acyclonucleosides[15] for the biological evaluation of their antitumour and/or antiviral properties. It is essential to maintain anhydrous conditions during the transformations; to obtain good yields, it is also advisable to work under argon or nitrogen.

Table 1. Reactions of alcoxy-1,4-diheteroepanes **1** with 5-FU and biological activities of compounds **2**.

Comp. No.	Alkoxy-1,4-diheteropanes **1**	time (h)	yield (%)	Product **2**	IC_{50}[a] (μM)
a		0.75	31		-
b		0.50	72		45
c		0.50	62[b]		18
d		0.50	68[c]		45
e		1.25	57[d]		25
f		0.75	86		362
g		0.50	70		4300

a) The antitumour activity of compound 2 was tested against Hep-2 human cells (IC_{50}= 90 mM, 5-FU). IC_{50} is the fifty percent inhibitory concentration, *i. e.*, the concentration required to inhibit the growth of treated cells to 50% of untreated controls.

b) Cp= Cyclopentyl.

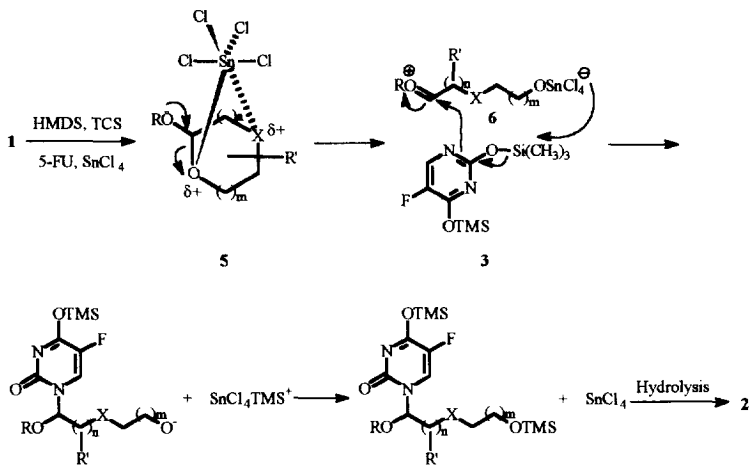
c) (Racemic) diastereomer mixture was not separated.

d) (Racemic) diastereomer mixture was separated, but was tested as such mixture.

We have carried out the reactions under several different concentrations of $SnCl_4$ and different temperatures, even as low as -35 °C, and we have not detected the presence of the cyclic seven-membered structures **4**.

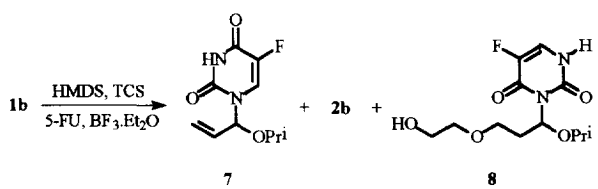
The regiospecificity outcome observed in our reactions could be accounted for by the fact that $SnCl_4$ readily forms octahedral complexes with two donor molecules (e. g., ether, THF) or with bidentate ligand systems.[16] The results are consistent with an intermediate of type **5** in which the alkoxy-1,4-diheteropane **1** is tied up by $SnCl_4$ (Scheme 1). This hypothesis provides the driving force for the cleavage of the endocyclic acetalic C-O to take place giving the oxocarbenium **6** as the only electrophilic acetalic moiety with concomitant formation of $SnCl_4OR^-$. The mild nucleophilic silylated base **3**, which does not destroy chelation is then able to attack the stable cation **6** to afford the opened *N,O*-acetal **2**, in a S_Ni-like reaction. The existence of the oxocarbenium **6** is supported by the increased yield on going from 5-methoxy-1,4-dioxepane **1a** (31%) to 5-*iso*propoxy-1,4-dioxepane **1b** (72%) as starting materials, with an increasing α-branching in relation to the oxonium ion of **6**. The approximate obtained

1:1 ratio of the diastereomers of **2d** and **2e** also supports the S_NI character of the title reaction. As a background to the complexation hypothesis, it has been recently reported that the reaction of silylated bases with oxathiolanyl and dioxolanyl ring systems and cytosine produced only the β isomer.[17,18]



Scheme 1

The following two factors prove the mechanism proposed: 1) the dependence of chelation on the identity of the non-acetalic heteroatom of the seven-membered ring.[15a] For instance, when X = NMe (Scheme 1, formulae **1**, **5** and **2**), the reaction proceeds with a very low yield (14%),[15a] probably because the great basicity of the electronic pair of the N atom leads to a strong N-Sn bond. At the same time, its strength causes the weakening of the other anchorage point, *i. e.*, the Sn-acetalic oxygen atom. It therefore seemed that "activation" by the introduction of a strong electron-withdrawing group on the nitrogen atom was desired. As the basicity lessens due to the *p*-tosyl group (**5**, X = NTs), the chelate is more balanced and an adequate charge deficiency is produced on the acetalic carbon leading to the oxocarbenium **6** which, accordingly, is susceptible to being attacked by **3** (30%);[15a] and 2) using and acid incapable of chelation, such as $BF_3.Et_2O$[19] maintaining the same experimental conditions, including the acid concentration, the experimental results proved to be different, yielding the hemiaminal acrolein derivative **7**, **2b** and its isomer **8**, in which the acyclic chain is linked through C-1 to the *N*-3 of the 5-fluorouracil moiety (Scheme 2).

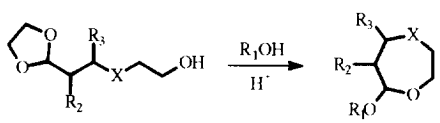


Scheme 2

The global sum of the yields of **7** (14%), **2b** (22.7%) and **8** (28.8%) is roughly the same yield as **2b** (72%, Table 1) obtained by the $SnCl_4$-mediated regiospecific opening of **1b**. The formation of **2b** may be explained by

the electrophilic attack of the BF_3 in its etherate form on the endocyclic acetalic oxygen atom of **1b** whereas the more likely explanation for the formation of **7** would involve the BF_3 complex on O-1of **1b** and the one-step proton β-elimination (on the three-carbon moiety) and subsequent leaving of the ethylene glycol moiety. The "rare" *N*-3 5-FU acyclonucleoside **8** could be rationalized on the basis of Vorbrüggen's σ-complex[20] presumably due to prior complexation between the Lewis acid and the *N*-1atom of the silylated base **3**, assuming the greatest acidity strength of BF_3 against $SnCl_4$.[21] Thus, BF_3 shows no advantage over the corresponding reaction with $SnCl_4$. In short, the products obtained using $BF_3.Et_2O$ are explained through complexation on O-1 and O-4 of the cycloacetal **1b**, proving that they are more basic than the exocyclic acetalic oxygen whose complexation and subsequent attack of the nucleophile **3** should have yielded the non-detected 1-(1,4-dioxepane-5-yl)-5-fluorouracil.

The starting cycloacetals[22] **1a-f** are obtained by acid-catalyzed alcoholysis at room temperature of the dioxolane hydroxyacetals **9-11** (Scheme 3). 5-methoxy- and 5-*iso*propoxy-1,4-dioxepanes **1a** and **1b**, respectively, have been previously reported by us[23,24] and also **9**.[25] **10** and **11** have been prepared in a one-pot reaction between the corresponding α,β-unsaturated aldehydes and ethylene glycol in dichloromethane/hydrochloric acid.

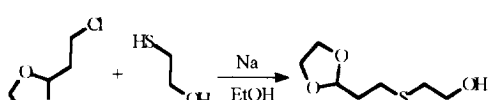


9 R_2= R_3= H; X= O
10 R_2= Me; R_3= H; X= O
11 R_2= H; R_3= Me; X= O
12 R_2= R_3= H; X= S

1c R_1= Cp; R_2= R_3= H; X= O
1d R_1= Pr^i; R_2= Me; R_3= H; X= O
1e R_1= Pr^i; R_2= H; R_3= Me; X= O
1f R_1= Pr^i; R_2= R_3= H; X= S

Scheme 3

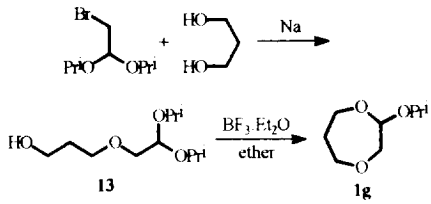
The reaction between **10** and *iso*propanol under sulfuric acid catalysis yields the *trans*-**1d** isomer (with 7 % of the *cis* isomer) whereas the same reaction carried out on **11** gives rise to the *cis*-**1e** isomer (with 4% of the *trans* isomer). In the former case, besides *trans*-**1d**, 2-(3-*iso*propoxy-2-propyl)-1,3-dioxolane is obtained as a result of a ring contraction of the seven-membered ring. A similar contraction was previously documented in our previous paper.[26] **12** is prepared by the treatment of 3-chloropropanal ethylene acetal with the sodium mercaptide of 2-mercaptoethanol in dry ethanol (Scheme 4).



12

Scheme 4

2-*iso*propoxy-1,4-dioxepane **1g** has not been described previously and we herein describe its synthesis following a similar procedure used for the preparation of 2-methoxy-1,4-dioxepane.[27] (Scheme 5)



Scheme 5

Conformational analysis

Conformational studies were performed using Sybyl[28] 6.1 program from Tripos[29] on **2a** (data not shown) and *(1R,3R)*-**2e** and *(1R,3S)*-**2e**. Energies were calculated using Tripos force field and Gasteiger-Marsili[30] charges. The geometries were optimized by the Powell[31] method. Current minimizations were performed using gradient termination of 0.05 kcal/mol. Conformational randomsearch studies were performed using 1000 cycles. Conformational populations were calculated from the Boltzman distribution law according to their relatives energies of 750 conformations in each case. A summary of the results obtained for the ten lowest energy conformations for *(1R,3R)*-**2e** and *(1R,3S)*-**2e** is shown in Tables 2 and 3, respectively. In the case of *(1R,3R)*-**2e** and *(1R,3S)*-**2e** the populations for the ten most significative conformations constitute the 83.2% and 86.8%, respectively.

Atom numbering scheme for **2e**

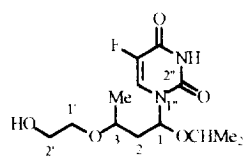


Table 2. Torsional angles (in deg), relative energies (kcal/mol) and conformational population (%) calculated for the ten most significative conformations of (*1R,3R*)-**2e**.

Conformer	$\omega_{1"123}$	ω_{123O}	$\omega_{23O1'}$	$\omega_{3O1'2'}$	$\omega_{O1'2'O}$	$\omega_{1'2'OH}$	$\omega_{21OC'H}$	$\omega_{2"1"12}$	Rel. E.	Pop.
1	-54.4	-53.6	178.0	-169.1	72.2	-58.3	179.7	113.0	0.00	38.6
2	56.3	-70.1	179.2	-178.8	-176.2	-179.6	-155.1	84.6	0.84	9.3
3	-53.3	55.4	165.6	-179.1	58.6	-176.3	179.0	114.8	1.01	7.0
4	58.4	-63.2	-66.0	-174.0	-179.6	179.5	-171.2	86.4	1.08	6.3
5	55.5	-70.6	174.1	175.4	-62.7	59.0	-170.9	85.4	1.10	6.1
6	-54.4	57.7	172.4	-178.1	-76.4	176.7	-164.2	110.3	1.22	5.0
7	-62.1	-57.1	169.6	-172.4	179.6	62.9	-160.9	103.5	1.63	4.9
8	58.7	-63.2	-65.8	-171.9	64.1	-59.4	-171.3	86.3	1.72	2.4
9	56.4	-70.2	179.2	-178.9	-176.2	-179.6	-156.3	85.2	1.97	2.1
10	-59.7	-56.4	169.7	-172.7	-178.8	-179.5	-163.9	105.8	2.09	1.4

The calculations were carried out on the enantiomer of configuration 1*R*. In all cases the relative orientation of the pyrimidine ring in relation to the rest of the molecule is a conformational constant. The torsional angle $\omega_{2''1''12}$ can change slightly on passing from an acyclonucleoside to another, but in general the heterocyclic ring bisects the angle C_2-C_1-O. In order to represent each conformation we started with the torsional angle $\omega_{2''1''12}$, then $\omega_{1''123}$, ω_{123O} and so on, up to ω_{21OCH_2} using the descriptors g^+, a or g^- according to the values of the respective torsional angles. We can assert the following: a) To start with, it is surprising that the fragment O_4-C_1-C_2-O_3 adopts the antiperiplanar arrangement (177.4 °) for the most stable conformation and not the *gauche* one, in the case of *(*1*R*, 3*S)*-**2e**, as could be expected due to the attractive *gauche* effect;[32] and b) the most important angle in the definition of the final conformation of an acyclonucleoside is N_1-C_1-C_2-C_3 and, of lesser importance, C_1-C_2-C_3-O_4 and C_2-C_3-O_4-C_1. So, the most stable conformers of *(*1*R*,3 S)-**2e** belong to the conformational series g^-g^+a and that of *(*1*R*, 3*R)*-**2e** to the series g^-g^-a, g^+g^-a and g^-g^+a (Figure). Thus, the N_1-C_1-C_2-C_3 moiety of these compounds adopts a *gauche* conformation in which the spatial arrangement of the acyclic chain is *restricted*. Hager and Liotta[33] recently reported the use of cyclization protocols for the control of the glycosidic stereochemistry in the synthesis of 3'-azido-3'-deoxythymidine (AZT), explaining the selectivity in the cyclization step through a *gauche* effect of the acyclic chain. The same conclusions can be drawn in relation to **2a**.[15b]

Table 3. Torsional angles (in deg), relative energies (kcal/mol) and conformational population (%) calculated for the ten most significative conformations of (1*R*,3*S*)-**2e**

Conformer	$\omega_{1''123}$	ω_{123O}	$\omega_{23O1'}$	$\omega_{3O1'2'}$	$\omega_{O1'2'O}$	$\omega_{1'2'OH}$	ω_{21OCH}	$\omega_{2''1''12}$	Rel. E.	Pop.
1	-55.1	65.0	-179.9	172.0	177.4	-64.5	179.3	110.6	0.00	34.2
2	-55.3	69.1	-168.7	-175.0	62.9	-59.2	180.0	107.2	0.20	24.3
3	-51.8	63.5	-178.7	58.4	-78.4	179.3	178.6	109.6	0.74	9.8
4	-55.0	70.6	-168.1	-173.9	63.4	-59.3	-165.3	104.5	1.30	3.8
5	60.1	-59.0	-172.1	173.2	-176.5	-179.7	-153.9	80.5	1.35	3.5
6	-61.4	59.6	179.8	164.2	-73.8	-59.0	-167.1	105.9	1.52	2.6
7	-52.3	65.0	179.3	57.8	168.0	61.9	-167.9	105.2	1.53	2.6
8	177.0	57.1	-171.9	173.9	178.7	63.0	-174.3	98.2	1.57	2.4
9	177.2	57.3	-172.3	172.3	-63.0	59.4	-158.4	95.1	1.72	1.9
10	-56.0	65.3	72.9	174.2	179.0	-65.6	-179.5	106.0	1.83	1.5

Structural characteristics

The structures of the acyclonucleosides **2** have been determined by ^{1}H- and ^{13}C-NMR, DEPT, HETCOR, IR spectroscopies, MS, and elemental analyses.

The resonance lines for H-1 in **2a-g** are observed at δ = 5.52-5.93. For instance, in the case of **1b** H-1 is observed as a double triplet (δ = 5.88 ppm) with the coupling constants 6.3 and 1.6 Hz, the latter being due to the long range coupling with the fluoro atom. Noteworthy are the signals for H-6" in the 5-fluoroacyclonucleosides **1a-g** appearing as a sharp doublet with J = 1.6-1.8 Hz, due to coupling with the fluoro atom, which, along with the elemental analyses shows unambiguously that the 5-FU moiety in **2a-g** is linked through *N*-1 and not through *N*-1 and *N*-3 to the acyclic chain.[34]

The most outstanding aspects of the ^{13}C spectra are the following: a) the C-4", C-5" and C-6" signals (of the pyrimidine ring) show couplings with the 5-F atom, ranging from 26.28-28.10 Hz for C-4", 232.45-239.77 Hz for C-5" and, finally, 32.96-33.55 Hz for C-6" for **2a-f**; b) The hemiaminal C-1 chemical shift undergoes a slight shielding on branching the substituent of the alkoxy group [δ = 85.17 for **2a** (Me) and 81.35 and 80.49 for **2b** (Pr^i) and **2c** (cyclopentyl), respectively]; and c) the configurational assignment of both racemic diastereomer mixture of **2e** was based on the well-known *steric compression model*. As a rule, it is found that the ^{13}C NMR chemical shifts of carbon atoms in spatially crowded alkyl groups are more upfield than similar carbon atoms in unperturbed systems. In the case of *(1R,3S)*-**2e** the conformations having a g^- arrangement for the N_1-C_1-C_2-C_3 moiety represents 79.01 % of the total population (*1, 2, 3, 4, 6, 7* and *10*) whereas for *(1R,3R)*-**2e** is only 57% (*1, 3, 6, 7* and *10*). Thus, on this basis we could assert that the acyclic chain in *(1R*,3S*)*-**2e** is more constrained than in *(1R*,3R*)*-**2e**, having assigned the structure with the more shielded acyclic carbon chain to the *(1R*,3S*)*-**2e** (80.56, C-1; 69.98, C-1'; 61.65, C-2' and 42.34, C-2) as opposed to *(1R*,3R*)*-**2e** (81.57, C-1; 69.65, C-1'; 61.88, C-2' and 43.07, C-2).

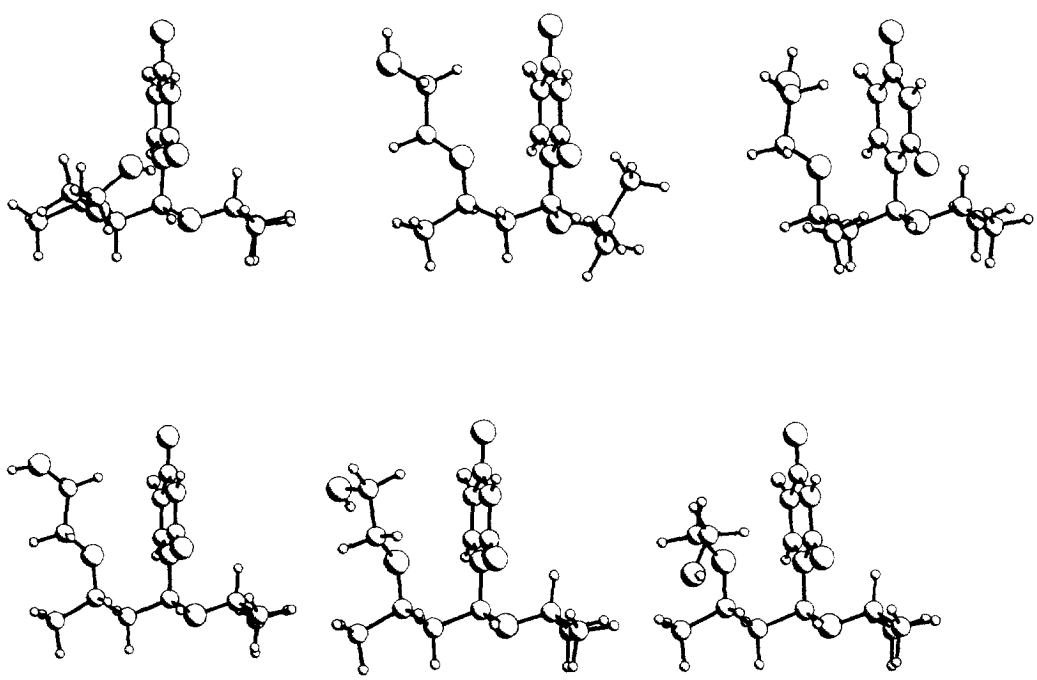


Figure.- The three most stable conformers of (1*R*,3*R*)-**2e** (up, from left to right, Rel. E.: 0.00, 0.84 and 1.01 kcal/mol) and (1*R*,3*S*)-**2e** (down, from left to right, Rel. E.: 0.00, 0.20 and 0.74 kcal/mol).

Biological activity

In vitro antitumour activity. The antitumour activity of **2b-g** was tested against HEp human cells *in vitro* and the results are shown in Table 1. Generally speaking, it can be said a) that the most active compound (IC_{50} = 18 μM) is **2c**, the most lipophilic structure being due to the cyclopentoxy moiety, and b) the less active compound (IC_{50} = 4300 μM) is **2g**, which cannot give rise to acrolein[35] by enzymic cleavage of the hemiaminal fragment, under non oxidative conditions.

Toxicity. In vivo trials. Method A. The toxicity test (**2f**) was carried out on mice of Mus Musculus species, Swiss albino race, healthy, of 10-12 cm of length (excluding tail), which reach a weight of 30-35 g when adult. Each mouse was administered single dosages of 50, 100, 200, 500 and 1000 mg/kg of weight to statistically representative animal lots. Mice of an average weight of 26 g were used for the 25-200 dosages. Animal lots of 27 g of average weight were used for the highest dosages of 500 and 1000 mg/kg. The growth of the mice were followed through weight control. Neither signs of short-term nor long-term acute toxicity were assessed since the animals died when their biological cycle finished.

Method B. We have carried out a control study with commercial 5-FU. We started with a group of 10 female OF1 mice, some six weeks old. After weighing them and calculating the average weight in grams (24 g), we established the daily dose that each of them was to receive: 4.8 mg/mouse equivalent of 200 mg/kg, a concentration similar to the LD_{50} of 5-FU (180 mg/kg). We inoculated each mouse with 0.5 mL of it in accumulative doses, *i. e.*, from day 0 to day 6. With **2b**, **2c**, **2d** (diastereomeric mixture) and **2e** (diastereomeric mixture) we proceeded in exactly the same way, keeping in mind both the percentage of 5-FU contained in our molecules and the quantity of 5-FU present in the pattern of LD_{50} that we established and that corresponds to the 200 mg/kg aforementioned. The mice treated with 5-FU clearly show a daily loss of weight compared with the controls. This loss is accompanied by changes in the aspect of the animals, such as changes in the hair and its loss and irritation of the anal zone. In the same way, a reduction in the vital activity of the individuals treated is observed. On the seventh day and after the last injection of 5-FU, eight of the ten mice treated died and the remaining two died a day later. Comparison of these results with those of our drugs, shows obvious differences. As in the controls, the change in weight follows no definite tendency, there was no variation in the aspect of the mice and no signs of apparent toxicity were observed. More conclusively, death has been produced neither during nor after each treatment, and the animals died when their biological cycle finished.

Conclusion

The compounds described here represent a novel class of 5-fluorouracil-containing acyclonucleosides that were synthesized in a one-step/one-pot reaction in acceptable yields from readily available starting materials. The reactions as well the workup procedures and the purifications for all products were readily achievable. To the best of our knowledge this acyclonucleoside formation is the first example of $SnCl_4$-mediated regiospecific ring opening of cycloacetals by silylated-5-FU generated *in situ*. The present approach relates to new chemical compounds having interesting antitumour properties and low acute toxicity.

Experimental

General. All solvents were used dried and freshly distilled. All evaporations were carried out *in vacuo* with a rotary evaporator. Solutions were dried over $MgSO_4$ before concentration under reduced pressure. Analytical samples were normally dried *in vacuo* over P_2O_5 at 40-50 °C for 16 h. Analytical thin-layer chromatography (TLC) was done on Merck silicagel F-254 plates with detection with iodine, an UV lamp or by charring with dilute sulfuric acid, using mixtures of ether-hexane as developing solvent. All analytical samples were TLC homogenous. For normal column chromatography Merck silica gel 60 was used with a particle size 0.063-0.200 mm (70-230 mesh ASTM). For flash chromatography Merck silica gel 60 was used with a particle size 0.040-0.063 mm (230-400 mesh ASTM). Melting points (mp) were obtained on an Electrothermal melting point apparatus and are uncorrected. NMR spectra were recorded on a 400.1 MHz ^1H and 100.03 MHz ^{13}C NMR Bruker ARX 400, a 300.13 MHz ^1H and 75.78 MHz ^{13}C NMR Bruker AM-300 and a 80 MHz Bruker WP-80CW spectrometers and chemical shifts are reported relative to the solvent peak ($CHCl_3$ in $CDCl_3$ at 7.24 and 77.1 ppm) Chemical shifts (δ) quoted in the case of multiplets were measured from the approximate centre. Signals are designated as follows: s, singlet, s_{br}, broad singlet; d, doublet; dd, doublet of doublets; ddd, double doublet of doublet; dddd, double double doublet of doublet; dt, double triplet; ddt, double double triplet; pt, pseudotriplet; t, triplet; q, quadruplet; h, heptuplet; m, multiplet. Coupling constants are expressed in hertz. The assignment of resonances for **2b**, (1*R**,3*R**)-**2e** and **2f** was assisted by ^{13}C-^1H COSY spectra. The infrared spectra (IR) were recorded on a Perkin-Elmer 782 instrument connected to a 3600 Data Station, as a neat film over KBr or as KBr disks. The mass spectra (MS) were obtained using a VG-Platform II spectrometer (Fisons Instruments) at 70 eV, carrying out injection through a Carlo Erba GC 8000 chromatograph. High resolution mass spectroscopy (HRMS) was carried out on a VG AutoSpec Q high resolution mass spectrometer (Fisons Instruments). Glc was performed at 125 °C on a Perkin-Elmer 8410 gas chromatograph equipped with a flame-ionisation detector and a steel column (2 x 0.125 in. i.d.) packed with 5% of OV-17 Chromosorb W (100-120 mesh). The N_2 flow rate was 30 mL/min, the injection port temperature was 250 °C, and the zone-detector temperature was 250 °C. Elemental combustion analyses were within ± 0.4 % of the theoretical values.

CAUTION: 5-fluorouracil and all α,β-unsaturated aldehydes should be treated as highly toxic and handled accordingly.

Synthesis of 5-fluorouracil acyclonucleosides 2a-g. General procedure: To a suspension of alkoxy-1,4-diheteropane **1** (1 mmol), 5-fluorouracil (1 mmol), which contains trimethylchlorosilane (TMCS, 0.8 mmol) and hexamethyldisilazane (HMDS, 0.8 mmol) in dry acetonitrile (10 ml/mmol of **1**) was added a solution of anhydrous tin (IV) chloride (1.25 mmol) in dry acetonitrile (10 ml/mmol of the Lewis acid) dropwise with stirring under argon at rt. After 0.50-1.25 h of stirring the reaction was quenched by the addition of a concentrated aqueous solution of sodium bicarbonate. The solution was concentrated and the residue extracted with chloroform. After filtration and concentration the residue was purified by flash chromatography using mixtures of chloroform/methanol (100/4) to give **2a-g**. For an analytical sample the product was purified by gravity chromatography.

(*RS*)-1-{[3-(2-hydroxyethoxy)-1-methoxy]propyl}-5-fluorouracil 2a: Reaction of 5-methoxy-1,4-dioxepane **1a** (1 g, 7.57 mmol) with 5-fluorouracil (0.984 g, 7.56 mmol) for 0.75 h according to the general

procedure yielded **2a** (0.610 g, 31%) as an amorphous white powder. R_f (95/5, $CHCl_3$/MeOH): 0.22. Mp 104-106 °C. ^{13}C NMR (75.78, $CDCl_3$) δ 157.3 (d, J = 26.30, C-4"), 150.1 (C-2"), 141.1 (d, J = 238.86, C-5"), 123.0 (d, J = 33.04, C-6"), 85.17 (C-1), 72.12 (C-2'), 65.77 (C-3), 60.99 (C-1'), 56.45 (O*Me*), 34.47 (C-2). ^1H NMR (300.13, $CDCl_3$) δ 10.68 (s, 1H, N*H*), 7.37 (d, J = 5.8, 1H, H-6"), 5.65 (dt, J = 6.3 and 1.6, 1H, H-1), 3.6-3.25 (m, 8H, O*H*, H-1', H-2' and O*Me*), 2.1-1.85 (m, 2H, H-2). MS (EI): *m z* (%) 262 (1, M^+), 230 (8), 200 (4), 131 (11), 101 (78), 71 (84), 45 (100). IR (film, cm^{-1}): 3457 (s, NH), 3071 (s, aromatics), 2970 (s), (aliphatic C-H groups), 1721 (s, C=O), 1665 (s, aromatic ring multiple bond), 1395, 1374 (s, methoxy group), 1109 (s), 1089 (s) and 1071 (s, C-O-C). Anal. for $C_{10}H_{15}O_5N_2F$: Calcd.: C, 45.80; H, 5.76; N, 10.68. Found: C, 45.90; H, 5.75; N, 10.72.

(*RS*)-1-{[3-(2-hydroxyethoxy)-1-*iso*propoxy]propyl}-5-fluorouracil 2b: Reaction of 5-*iso*propoxy-1,4-dioxepane **1b** (2 g, 12.4 mmol) with 5-fluorouracil (1.62 g, 12.5 mmol) for 0.30 h according to the general procedure yielded **2b** (2.6 g, 72%) as colourless crystals. R_f (100/3, $CHCl_3$/MeOH): 0.16. Mp 101-103 °C. ^{13}C NMR (75.78 MHz, $CDCl_3$) δ 157.32 (d, J = 26.51, C-4"), 149.92 (C-2"), 140.94 (d, J = 239.34, C-5"), 123.31 (d, J = 33.33, C-6"), 81.31 (C-1), 72.25 (C-2'), 70.88 (*C*HMe$_2$), 65.93 (C-3), 61.12 (C-1'), 35.07 (C-2), 22.64 and 21.07 (CH*Me*$_2$). ^1H NMR (300.13 MHz, $CDCl_3$) δ 10.68 (s, 1H, N*H*), 7.37 (d, J = 5.8, 1H, H-6"), 5.88 (dt, J = 6.3 and 1.6, 1H, H-1), 3.50-3.36 (m, 8H, O*H*, C*H*Me$_2$, H-3, H-1' and H-2'), 1.88 (dt, J = 6.3, 2H, H-2), 1.10 (d, J = 6.1, *Me*) and 1.03 (d, J = 6.1, *Me*). MS (EI): *m z* (%) 290(1, M^+), 230 (2), 200 (5), 161 (9), 131 (18), 101 (100), 75 (35), 45 (38). IR (cm^{-1}, film): 3467 (s, NH), 3070 (s, aromatics), 2978 (s), 2936 (s) and 2882 (s) (aliphatic C-H groups), 1727 (s, C=O), 1666 (s, aromatic ring multiple bond), 1387, 1372 (s, *iso*propoxy group), 1245 (s), 1128 (s) and 1071 (s, C-O-C). Anal. for $C_{12}H_{19}O_5N_2F$: Calcd.: C, 49.65; H, 6.60; N, 9.65. Found: C, 49.46; H, 6.60; N, 9.94.

(*RS*)-1-{[3-(2-hydroxyethoxy)-1-cyclopentoxy]propyl}-5-fluorouracil 2c: Reaction of 5-cyclopentoxy-1,4-dioxepane **1c** (0.233 g, 1.25 mmol) with 5-fluorouracil (0.22 g, 1.69 mmol) for 0.30 h according to the general procedure yielded **2c** (0.245 g, 62%) as a colourless syrup. R_f (100/4, $CHCl_3$/MeOH): 0.16. ^{13}C NMR (75.78 MHz, $CDCl_3$) δ 157.07(d, J = 26.41, C-4"), 150.03 (C-2"), 141.24 (d, J = 238.86, C-5"), 123.37 (d, J = 32.9, C-6"), 82.25 (C-1), 80.49 (Cp O-C), 72.55 (C-1'), 66.12 (C-3), 61.52 (C-2'), 35.32 (C-2), 32.47, 31.84, 23.44 and 23.16 (Cp C). ^1H NMR (300.13 MHz, $CDCl_3$) δ 9.9 (s, 1H, N*H*), 7.38 (d, J = 5.8, 1H, H-6"), 5.93 (dt, J = 6.5 and 1.8, 1H, H-1), 3.97-3.38 (m, 7H, H-3, H-1', H-2' and C*H*$_{cyclopentyl}$), 2.65 (s, 1H, O*H*), 1.96 (m, 2H, H-2), 1.73-1.47 (m, 8H, Cp). MS (EI): *m z* (%) 230 ((1, M^+ - CpOH), 187 (5, M^+-5FU), 131 (11), 101 (100), 75 (25), 45 (44). IR (cm^{-1}, film): 3474 (s, NH), 3090 (s, aromatics), 2977 (s), 1722 (s, C=O), 1662 (s, aromatic ring multiple bond), 1386, 1372 (s, *iso*propoxy group), 1244 (s), 1123 (s) (s, C-O-C). Anal. for $C_{14}H_{21}O_5N_2F$ 1/4H_2O:Calcd.: C, 52.41; H, 6.75; N, 8.73. Found: C, 52.43; H, 6.68; N, 8.98.

1-{[3-(2-hydroxyethoxy)-2-methyl-1-*iso*propoxy]propyl}-5-fluorouracil 2d (mixture of diastereomers): Reaction of *trans*-5-*iso*propoxy-6-methyl-1,4-dioxepane **1d** (1 g, 5.74 mmol) with 5-fluorouracil (0.821 g, 5.74 mmol) for 0.30 h according to the general procedure yielded a 1/1 mixture of both diastereomers of **2d** (1.188 g, 68%) as a colourless syrup. R_f (100/4, $CHCl_3$/MeOH): 0.18. ^{13}C NMR (75.78 MHz, $CDCl_3$) δ 157.12 (d, J = 26.34, C-4" of one diastereoisomer), 157.03 (d, J = 26.49, C-4" of the other one), 150.09 (C-2" of one diastereoisomer, 150.34 (C-2" of the other one), 140.86 (d, J = 238.21, C-5" of one diastereoisomer),

140.96 (d, J = 238.21, C-5" of the other one), 123.96 (d, J = 30.41, C-6" of one diastereoisomer), 123.97 (d, J = 32.98, C-6" of the other one), 84.77 (C-1 of one diastereoisomer), 85.48 (C-1 of the other one), 72.74 (C-1' of one diastereoisomer), 72.59 (C-1' of the other one), 72.09 (C-3 of both diastereoisomers), 71.66 (C-2' of both diastereoisomers), 71.35 (C*H*Me$_2$ of one diastereoisomer), 71.41 (C*H*Me$_2$ of the other one), 38.61 (C-2 of one diastereoisomer), 39.06 (C-2 of the other one), 22.88 and 21.28 (CH*Me*$_2$ of one diastereoisomer), 22.91 and 21.32 (CH*Me*$_2$ of the other one), 12.52 (C-4 of one diastereoisomer) and 13.01 (C-4 of the other one). IR (cm^{-1}, film): 3474 (s, NH), 3195, 3071 (s, aromatics), 2977 (s), (aliphatic C-H groups), 1722 (s, C=O), 1662 (s, aromatic ring multiple bond), 1386 (s, *iso*propoxy group), 1244, 1123, 1070 (s, C-O-C). MS (EI): *m/z* (%) 304 ((1, M$^+$), 246 (1), 159 (4), 131 (11), 130 (10), 115 (100), 75 (29), 45 (18). Anal. for $C_{13}H_{21}O_5N_2F.1/5H_2O$: Calcd.: C, 50.71; H, 7.00; N, 9.10. Found: C, 50.86; H, 6.73; N, 9.34.

(1'*R,3'*R**) and (1'*R**,3'*S**)-1-{[3-(2-hydroxyethoxy)-1-*iso*propoxy]butyl}-5-fluorouracil 2e**: Reaction of *cis*-5-*iso*propoxy-7-methyl-1,4-dioxepane **1e** (1 g, 5.74 mmol) with 5-fluorouracil (0.821 g, 5.74 mmol) for 1.25 h according to the general procedure yielded **2e** (0.996 g, 57%) of a thick oil which was purified by flash chromatography using a mixture of $CHCl_3$/MeOH (100/2) as eluant. The first fraction weighed 0.498 g (28.5%) as an amorphous white powder and was identified as (1'*R**,3'*R**)-**2e**. R_f (100/4, $CHCl_3$/MeOH): 0.24. Mp 120-121 °C. ^{13}C NMR (75.78 MHz, $CDCl_3$) δ 157.07 (d, J = 26.11, C-4"), 150.41 (C-2"), 141.48 (d, J = 239.52, C-5"), 123.00 (d, J = 32.68, C-6"), 80.56 (C-1), 71.16 (C-3), 70.73 (C*H*Me$_2$), 69.98 (C-1'), 61.65 (C-2'), 42.34 (C-2), 22.93 and 21.42 (CH*Me*$_2$), 19.21 (C-4). ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 10.7 (s, 1H, N*H*), 7.35 (d, J = 5.7, 1H, H-6"), 6.08 (ddd, J = 9.1, 4.4 and 1.9, 1H, H-1), 3.65 (h, J = 6.2, 1H, C*H*Me$_2$), 3.79-3.62 (m, 3H, H-1' and H-2'), 3.32 (ddd, J = 9.7, 6.3 and 3.4, 1H, H-3), 3.30 (m, 1H, H-1'), 3.21 (s, 1H, O*H*), 2.00 (ddd, J = 14.6, 9.80 and 4.4, 1H, H-2), 1.75 (ddd, J = 14.6, 9.1 and 3.4, 1H, H-2) 1.19 (d, J = 6.1, 3H, CH*Me*$_2$), 1.17 (d, J = 6.1, 3H, CH*Me*$_2$), 1.09 (d, J = 6.2, 3H, H-4). IR (cm^{-1}, film): 3458 (s, NH), 3199, 3074 (s, aromatics), 2977 (s), (aliphatic C-H groups), 1702 (s, C=O), 1667 (s, aromatic ring multiple bond), 1266, 1240, 1104 (s) and 1057 (s, C-O-C). Anal. for $C_{13}H_{21}O_5N_2F$: Calcd.: C, 51.31; H, 6.96; N, 9.21. Found: C, 51.30; H, 6.73; N, 8.92.

The second fraction weighed 0.498 g (28%) as a syrup and was identified as (1'*R**,3'*S**)-**2e**. R_f (100/4, $CHCl_3$/MeOH): 0.18. ^{13}C NMR (75.78 MHz, $CDCl_3$,) δ 157.26 (d, J = 26.34, C-4"), 149.79 (C-2"), 141.09 (d, J = 238.33, C-5"), 123.47 (d, J = 32.9, C-6"), 81.57 (C-1), 71.88 (C-3), 71.02 (C*H*Me$_2$), 69.65 (C-1'), 61.88 (C-2'), 43.07 (C-2), 22.88 and 21.33 (CH*Me*$_2$), 19.42 (C-4). ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 10.2 (s, 1H, N*H*), 7.40 (d, J = 5.8, 1H, H-6"), 5.98 (ddd, J = 7.8, 4.5 and 1.9, 1H, H-1), 3.7-3.6 (m, 4H, H-3, H-1', H-2' and C*H*Me$_2$), 3.35 (m, 1H, H-1'), 3.15 (s, 1H, O*H*), 2.00 (ddd, J = 14.6, 9.80 and 4.4, 1H, H-2), 1.81 (ddd, J = 14.1, 9.6 and 4.6, 1H, H-2), 1.72 (ddd, J = 14.1, 3.3 and 1.8, 1H, H-2), 1.19 (d, J = 6.1, 3H, CH*Me*$_2$), 1.15 (d, J = 6.2, 3H, CH*Me*$_2$), 1.10 (d, J = 6.2, 3H, H-4). IR (cm^{-1}, film): 3459 (s, NH), 3193, 3072 (s, aromatics), 2976 (s), (aliphatic C-H groups), 1716 (s, C=O), 1692, 1670 (s, aromatic ring multiple bond), 1469, 1372, 1244, 1144, 1106 and 1061 (s, C-O-C). Anal. for $C_{13}H_{21}O_5N_2F.1/4H_2O$: Calcd.: C, 50.56; H, 7.02; N, 9.07. Found: C, 50.45; H, 6.72; N, 9.28.

(*RS*)-1-{[3-(2-hydroxyethylthio)-1-*iso*propoxy]propyl}-5-fluorouracil 2f: Reaction of 7-*iso*propoxy-1,4-oxathiepane **1f** (1 g, 5.67 mmol) with 5-fluorouracil (0.794 g, 6.10 mmol) for 0.75 h according to the general procedure yielded **2f** (1.48 g, 86%) as an amorphous white powder. R_f (100/3, $CHCl_3$/MeOH): 0.11. Mp 83-85 °C. ^{13}C NMR (75.78 MHz, $CDCl_3$) δ 157.21 (d, J = 26.27, C-4"), 149.84 (C-2"), 141.03 (d, J = 239.31, C-5"),

123.2 (d, J = 33.34, C-6"), 82.70 (C-1), 71.60 (CHMe$_2$), 60.92 (C-2'), 35.12 (C-3), 34.92 (C-1'), 26.96 (C-3), 22.80 and 21.45 (CH*Me$_2$*). ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 10.31 (s, 1H, N*H*), 7.43 (d, J = 5.4, 1H, H-6"), 5.91 (dt, J = 6.3 and 1.7, 1H, H-1), 3.73 (t, J = 6.2, 2H, H-2'), 3.68 (h, J = 6.2, 1H, C*H*Me$_2$), 2.88 (s, 1H, OH), 2.79-2.51 (m, 4H, H-3, H-1'), 1.93 (dt, J = 6.3, 2H, H-2), 1.20 (d, J = 6.1, 3H, *Me*) and 1.12 (d, J = 6.1, 3H, *Me*). MS (EI): *m*/*z* (%) 286 (3, M$^+$ -18), 246 (1), 177 (3), 159 (3), 117 (100), 89 (23), 61 (21). IR (cm^{-1}, film): 3452 (s, OH), 3172 (s, NH) 3042 (s, aromatics), 2978 (s), 2837 (s) (aliphatic C-H groups), 1711 (s, C=O), 1390 and 1373 (s, *gem*-dimethyl group), 1240 (s) and 1180 (s) (C-O-C). Anal. for $C_{12}H_{19}O_4SN_2F$: Calcd.: C, 47.05; H, 6.25; N, 9.14. Found: C, 46.68; H, 6.05; N, 9.52.

(*RS*)-1-{[3-(2-hydroxypropoxy)-1-*iso*propoxy]ethyl}-5-fluorouracil 2g. Reaction of 2-*iso*propoxy-1,4-dioxepane **1g** (1 g, 6.24 mmol) with 5-fluorouracil (0.812 g, 6.24 mmol) for 0.50 h according to the general procedure yielded **2g** (1.268 g, 70%) as a colourless syrup R_f (100/3, $CHCl_3$/MeOH): 0.14. ^{13}C NMR (75.78 MHz, $CDCl_3$) δ 157.1 (d, J = 41.98, C-4"), 150.1 (C-2"), 140.90 (d, J = 238.40, C-5"), 123.9 (d, J = 27.36, C-6"), 80.99 (C-1), 71.90 (CHMe$_2$), 71.24 (C-3'), 69.98 (C-2), 60.41 (C-1'), 32.06 (C-2'), 22.77 and 21.33 (CH*Me$_2$*). ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 10.68 (s, 1H, N*H*), 7.47 (d, J = 5.8, 1H, H-6"), 5.91 (ddd, J = 6.0, 4.6 and 1.8 Hz, 1H, H-1), 3.58-3.53 (m, 2H, H-2), 3.68-3.61 (m, 4H, H-1', H-3'), 1.77 (dt, J = 5.6, 2H, H-2'), 3.73 (m, 1H, C*H*Me$_2$), 1.20 (d, J = 6.1, 3H, *Me*) and 1.14 (d, J = 6.1, 3H, *Me*). MS (EI): *m*/*z* (%) 290((1, M$^+$), 230 (2), 200 (5), 161 (9), 131 (18), 101 (100), 75 (35), 45 (38). IR (cm^{-1}, film): 3467 (s, NH), 3070 (s, aromatics), 2978 (s), 2936 (s) and 2882 (s) (aliphatic C-H groups), 1727 (s, C=O), 1666 (s, aromatic ring multiple bond), 1387, 1372 (s, *iso*propoxy group), 1245 (s), 1128 (s) and 1071 (s, C-O-C). HRMS (FAB, glycerol) calcd. for $C_{12}H_{20}O_5N_2F$ (M$^+$ + 1) 291.1356, found: 291.1351. Anal. for $C_{12}H_{19}O_5N_2F.3/10CHCl_3$: Calcd.: C, 46.41; H, 5.97; N, 8.59. Found: C, 46.20; H, 6.25, N, 9.03.

The reaction of 5-*iso*propoxy-1,4-dioxepane 1b and 5-fluorouracil using boron trifluoride etherate as acid catalyst: Obtention of (*RS*)-1-[(2-propenyl)-1-*iso*propoxy]-5-fluorouracil 7, (*RS*)-1-{[3-(2-hydroxyetoxy)-1-*iso*propoxy]propyl}-5-fluorouracil 2b and (*RS*)-3-{[3-(2-hydroxyetoxy)-1-*iso*propoxy]propyl}-5-fluorouracil 8. Reaction of 5-*iso*propoxy-1,4-dioxepane **1b** (1 g, 6.24 mmol) with 5-fluorouracil (0.812 g, 6.24 mmol) for 0.75 h according to the general procedure but using $BF_3.Et_2O$ (1.11 g, 7.8 mmol). The residue was purified by flash chromatography on silica gel using $CHCl_3$/MeOH (10/0.2) to afford three compounds. The first fraction gave **7** (0.279 g, 14%); mp 99-101°C. R_f (100/3, $CHCl_3$/MeOH): 0.36. ^{13}C NMR (100.03 MHz, $CDCl_3$) δ 157.06 (d, J = 26.51, C-4'), 149.69 (C-2'), 140.90 (d, J = 237.38, C-5'), 133.32 (C-2), 124.18 (d, J = 32.71, C-6'), 119.88 (C-3), 81.74 (C-1), 71.29 (C*H*Me$_2$), 22.85 and 21.49 (CH*Me$_2$*). ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 9.53 (s, 1H, N*H*), 7.34 (d, J = 5.7, 1H, H-6'), 6.26 (dd, J = 3.5 and 1.7, 1H, H-1), 5.75 (ddd, J = 17.11, 10.5 and 3.7, 1H, H-2), 5.54 (d, J = 17.1, 1H, H-3$_t$), 5.40 (d, J = 10.5, 1H, H-3$_c$), 3.77 (h, J = 6.1, 1H, C*H*Me$_2$), 1.23 (d, J = 6, 3H, *Me*) and 1.16 (d, J = 6.2, 3H, *Me*). IR (cm^{-1}, film): 3082 (s, aromatics), 2979 (s) and 2936 (s) (aliphatic C-H groups), 1724 (s, C=O), 1667 (s, aromatic ring multiple bond), 1466 (m, double bond), 1376, 1337 (s, *iso*propoxy group), 1245 (s), 1184 (m) and 1082 (s, C-O-C). HRMS (CI) calcd for $C_{10}H_{14}O_3N_2F$ (M$^+$ + 1) 229.0988, found: 229.0980. Anal. for $C_{10}H_{13}O_3N_2F$: Calcd.: C, 52.63; H, 5.74; N, 12.27. Found: C, 52.48; H, 5.89; N, 12.24.

Eluted second was **2b** (0.576 g, 22%). This compound was identical to that obtained from 5-*iso*propoxy-1,4-dioxepane **1b** and 5-FU but using anhydrous $SnCl_4$.

Eluted third was **8** (0.730 g, 28.8%) ^{13}C NMR (100.03 MHz, $CDCl_3$) δ (selected data) 80.49 (C-1), 72.10 (C-1'), 71.47 ($CHMe_2$), 67.13 (C-3), 61.73 (C-2'), 32.86 (C-2), 22.99 and 21.62 ($CHMe_2$). ^1H NMR (400.13 MHz, CD_3COCD_3) δ 9.67 (s, 1H, N*H*), 7.64 (pt, *J* = 5.5 Hz,1H, H-6"), 6.24 (s_b, 1H, H-1), 3.74-3.52 (m, 7H, O*H*, H-3, H-1' and H-2'), 3.44 (h, *J* = 6.2, 1H, C*H*Me$_2$), 2.50-2.27 (m, 2H, H-2), 1.15 (d, *J* = 5.9, 3H, *Me*) and 1.03 (d, *J* = 6.2, 3H, *Me*). MS (CI): *m z* (%) 131 (85, 5FU$^+$), 101 (81), 99 (51), 73 (12), 43 (100). IR (cm^{-1}, film): 3465 (s, NH), 3260 (s, OH), 3099 (s, aromatics), 2977 (s), 2936 (s) and 2881 (s) (aliphatic C-H groups), 1727 (s, C=O), 1666 (s, aromatic ring multiple bond), 1385, 1372 (m, *iso*propoxy group), 1255 (s), 1123 (s) and 1068 (s, C-O-C). HRMS (CI) calcd. for $C_{12}H_{20}O_5N_2F$ (M^+ + 1) 291.1356, found 291.1355. Anal. for $C_{12}H_{19}O_5N_2F$.1/2H_2O:Calcd.: C, 48.16, H, 6.74, N, 9.36. Found: C, 47.97, H, 6.66, N, 9.60.

5-cyclopentoxy-1,4-dioxepane 1c: 2-[2-(2-hydroxyethoxy)ethyl]-1,3-dioxolane **9**[25] (2.9 g, 17.9 mmol) were dissolved in cyclopentanol (58 mL, 640 mmol) which contained concentrated sulfuric acid (0.32 mL) to give a final 1% concentration of the acid. The solution was kept for 18 h at rt, basified (NaOH/MeOH) and concentrated. The residue was dissolved in chloroform (100 mL) and washed with water (2 x 20 mL). The organic layer was separated, dried, filtered and concentrated and the residue was purified by flash chromatography using an ether/hexane (1/2) mixture as eluant, yielding 0.515 g (15.5%) of **1c** as a colourless mobile liquid. R_f (1/1, ether/hexane) 0.41. ^{13}C NMR (100.03 MHz, $CDCl_3$) δ 99.48 (C-5), 78.4 (C-1'), 71.49 (C-3), 65.82 (C-2), 64.3 (C-7), 38.7 (C-6), 33.45 and 31.9 (C-2'), 23.53 and 23.27 (C-3'). ^1H NMR (400.1 MHz, $CDCl_3$) δ 4.84 (dd, *J* = 7.9 and 5.7, 1H, H-5), 4.14 (m, 1H, H-1'), 3.98 (ddd, J = 13.6, 9.3 and 1.5 Hz, 1H, H-3), 3.75 (ddd, *J* 12.5, 6.3 and 2.2, 1H, H-7), 3.71 (ddd, *J* = 12.7, 3.4 and 1.4, 1H, H-2), 3.55 (ddd, *J* 12.6, 9.3 and 1.7, H-2), 3.43 (ddd, *J* = 13.6, 3.4 and 1.7, 1H, H-3), 2.10 (ddt, *J* = 15.8, 6.0 and 1.7, 1H, H-6), 1.97 (dddd, *J* = 15.8, 9.3 and 8.0, 1H, H-6), 1.77-1.42 (m, 8H, H-2' and H-3'). MS (CI): *m z* (%) 187 (15, M^+ + 1), 159 (2), 145 (2), 131 (2), 119 (21), 101 (100), 73 (38). IR (cm^{-1}, film): 2956 (s) and 2873 (s) (aliphatic C-H groups), 1149, 1101, 1055, 1014 and 965 (s, C-O-C). HRMS (CI) calcd. for $C_{10}H_{19}O_3$ (M^+ + 1) 187.1334, found 187.1338.

Synthesis of 2-[2-(2-hydroxyethoxy)alkyl]-1,3-dioxolane. General procedure: A two-phase mixture of the α,β-unsaturated aldehyde (0.734 mol), ethylene glycol (210 mL, 3.67 mol), concentrated HCl (2 mL) and CH_2Cl_2 (143 mL) was distilled through a Vigreux column which was fitted with a Clevenger adapter until no more aqueous phase separated in the distillate. Then, the homogeneous mixture was made alkaline (KOH/MeOH) and the solvent was rotaevaporated off. The residue was subjected to fractional distillation giving the excess of glycol used and the 2-[2-(2-hydroxyethoxy)alkyl]-1,3-dioxolane.

2-[2-(2-hydroxyethoxy)-1-methylethyl]-1,3-dioxolane 10. It was obtained (40%) from methacrolein; bp 137-138 °C/20 torr, lit[36] 133 °C/14 torr.

2-[2-(2-hydroxyethoxy)propyl]-1,3-dioxolane 11. It was obtained (61%) from crotonaldehyde; bp 132-134 °C/19 torr, lit[37] 139 °C/17 torr (as a mixture with other compounds).

Reaction between 10 and anhydrous *iso*propanol under sulfuric acid catalysis:[38] obtention of 2-(3-*iso*propoxy-2-propyl)-1,3-dioxolane and *trans*-5-*iso*propoxy-6-methyl-1,4-dioxepane 1d: The procedure is similar to that detailed for the preparation of **1c**, but using the following amounts: **10** (10.48 g, 59.5 mmol), anhydrous *iso*propanol (150 mL, 190 mmol), concentrated sulfuric acid (0.82 mL). Reaction time: 160 h at rt. After the workup the crude was distilled under diminished pressure (bp 76-78 °C/16 torr) in a Kugelrohr

distillation system to yield a mixture of 2-(3-*iso*propoxy-2-propyl)-1,3-dioxolane and *trans*-**1d** which were purified by column chromatography using an 1/1 ether/hexane mixture as eluant. The first fraction (0.60 g, 5.8%) was identified as 2-(3-*iso*propoxy-2-propyl)-1,3-dioxolane. ^{13}C NMR (75.78 MHz, $CDCl_3$) δ 105.35 (C-5), 71.78 ($CHMe_2$), 69.58 (C-3), 65.04 (C-1'), 65.08 (C-2'), 37.93 (C-2), 22.15 and 22.06 ($CHMe_2$) and 11.37 (*Me*). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30 (d, *J* = 4.2, 1H, H-2), 3.94-3.79 (m, 4H, H-4 and H-5), 3.50 (h, *J* = 6.1, 1H, $CHMe_2$), 3.47 (dd, *J* 9.2 and 5.7, 1H, H-3'), 3.27 (dd, *J* = 9.2 and 7.1, 1H, H-3'), 1.97 (m, 1H, H-2'), 1.11 (d, *J* = 6.1, 6H, $CHMe_2$) and 0.93 (d, *J* = 6.9, 3H, *Me*). MS (EI): *m z* (%) 174(2, M$^+$), 87 (31), 73 (66), 59 (23), 43 (100). HRMS (CI) calcd. for $C_9H_{19}O_3$ (M$^+$ + 1) 175.1334, found: 175.1338.

Second eluted was *trans*-**1d** (1.97 g, 19%). Retention time (glc): 2.51 min. R_f (1/7, ether/hexane): 0.32. ^{13}C NMR (75.78 MHz, $CDCl_3$) δ 105.09 (C-5), 72.58 (C-7), 71.34 (C-2), 68.84 ($CHMe_2$), 64.50 (C-3), 43.32 (C-6), 23.70 and 21.59 ($CHMe_2$) and 15.29 (*Me*). ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 4.37 (d, *J* = 7.5, 1H, H-5), 4.06 (ddd, *J* = 13.5, 9.5 and 1.7, 1H, H-3), 3.85 (h, *J* = 6.2, 1H, $CHMe_2$), 3.71 (ddd, *J* 12.5, 3 and 1.8, 1H, H-2), 3.58 (ddd, *J* = 12.6, 9.5 and 1.8, 1H, H-2), 3.50 (m, *J* = 7.3 and 3, 2H, H-7), 3.42 (ddd, *J* 13.5, 3 and 1.9, 1H, H-3), 2.08 (ddt, *J* = 7.3, 3.2 and 1.3, 1H, H-6), 1.17 (d, *J* = 6.3, 3H, $CHMe_2$), 1.09 (d, *J* = 6.1, 3H, $CHMe_2$) and 0.90 (d, *J* = 7.2, 3H, *Me*). MS (CI): *m z* (%) 175 (2, M$^+$ + 1), 131 (4), 115 (100), 71 (16). IR (cm^{-1}, film): 2974 (s) 2943 (s) and 2903 (s) (aliphatic C-H groups), 1463, 1380 (*iso*propyl groups), 1168, 1154, 1139, 1016 and 999 (s, C-O-C). HRMS (CI) calcd. for $C_9H_{19}O_3$ (M$^+$ + 1) 175.1334, found 175.1331.

Trans-**1d** contained 7% of the *cis*-**1d** compound (retention time, glc 2.88 min), whose ^{13}C NMR data are the following: ^{13}C NMR (75.78 MHz, $CDCl_3$) δ 101.98 (C-5), 71.24 (C-2), 70.97 (C-7), 69.02 ($CHMe_2$), 66.00 (C-3), 40.37 (C-6), 23.43 and 21.46 ($CHMe_2$) and 12.96 (*Me*).

***Cis*-5-*iso*propoxy-7-methyl-1,4-dioxepane 1e:** The procedure is similar to that detailed for the preparation of **1c**, but using the following amounts: **11** (10 g, 57 mmol), anhydrous *iso*propanol (150 mL, 190 mmol), concentrated sulfuric acid (0.82 mL). Reaction time 164 h at rt. After the workup the crude was distilled under diminished pressure (bp 84-86 °C/16 torr) and purified by flash chromatography (1/1, ether/hexane) giving *cis*-**1e** (3.71 g, 34.1%). Retention time (glc): 2.29 min. R_f (1/6, ether/hexane): 0.23. ^{13}C NMR (75.78 MHz, $CDCl_3$) δ 97.54 (C-5), 71.60 (C-7), 70.44 (C-2), 68.34 ($CHMe_2$), 63.52 (C-3), 45.45 (C-6), 23.70 and 21.69 ($CHMe_2$) and 23.04 (*Me*). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.90 (dd, *J* = 8.5 and 6.2, 1H, H-5), 4.07 (dd, *J* = 13.5 and 10.4, 1H, H-2), 3.88 (h, *J* = 6.2, 1H, $CHMe_2$), 3.72 (m, 1H, H-3), 3.58 (ddd, *J* = 10.3 and 0.8, 1H, H-3), 3.42 (dt, *J* = 13.58, 1H, H-2), 1.98 (m, 2H, H-6), 1.16 (d, *J* = 6.3, 3H, $CHMe_2$), 1.16 (d, *J* = 6.4, 3H, $CHMe_2$) and 1.09 (d, *J* = 6.1, 3H, *Me*). MS (CI): *m z* (%) 175 (3, M$^+$ + 1), 159 (5), 145 (3), 131 (3), 115 (100), 73 (75), 45 (64). HRMS (CI) calcd. for $C_9H_{19}O_3$ (M$^+$ + 1) 175.1334, found: 175.1330.

Cis-**1d** contained 4% of the *trans*-**1d** compound (retention time, glc: 2.46 min), whose ^{13}C NMR data are the following: ^{13}C NMR (75.78 MHz, $CDCl_3$) δ 99.86 (C-5), 71.08 (C-2), 67.97 (C-3), 68.75 ($CHMe_2$), 67.97 (C-3), 44.86 (C-6), 23.57 and 21.43 ($CHMe_2$) and 22.03 (*Me*).

2-[2-(2-hydroxyethylthio)ethyl]-1,3-dioxolane 12: 2-mercaptoethanol (21 mL, 299 mmol) were added to a solution of sodium (6.90 g, 300 mmol) dissolved in absolute ethanol (150 mL) under continuous stirring for 1.5 h. Then, 2-(2-chloroethyl)-1,3-dioxolane[39] (40.95 g, 300 mmol) were added slowly and the reaction mixture was left for 24 h under stirring and at rt. After neutralizing with glacial acetic acid the solid was filtered and the filtrate was rotaevaporated off to dryness. The residue was dissolved in chloroform (100 mL), washed with water

(3 x 30 mL), the organic layer decanted, dried, filtered and concentrated in the rotaevaporator yielding a liquid which was distilled under diminished pressure (bp 110-112 °C/0.4 torr). A redistillation (bp 102-104 °C/0.2 torr) yielded pure **12** (42.5 g, 60%). R_f(ether): 0.29. ^{1}H NMR (80 MHz, $CDCl_3$) δ 4.98 (t, *J* = 4.5, 1H, H-2), 3.92 (m, 4H, H-4 and H-5), 3.74 (t, *J* = 6, 2H, H-2"), 2.74 (t, *J* = 6, 2H, H-1"), 2.66 (t, *J* = 7.5, 2H, H-2'), 2.55 (t, *J* = 6, 1H, O*H*), 1.95 (dt, *J* = 7.5 and 4.5, 2H, H-1'). MS (CI): *m/z* (%) 178 (5, M^+), 160 (2), 100 (85), 73 (100). IR (cm^{-1}, film): 3440 (s), 2958 (s), 2926 (s) and 2885 (s) (aliphatic C-H groups), 1475 (m), 1409 (s), 1132 (s), 1045 (s) (C-O-C). HRMS (CI) calcd. for $C_7H_{15}O_3S$ (M^+ + 1) 179.0742, found: 179.0743. Anal. for $C_7H_{14}O_3S$: Calcd.: C, 47.17; H, 7.92. Found: C, 46.94; H, 7.63.

7-*iso*propoxy-1,4-oxathiepane 1f: The procedure is similar to that detailed for the preparation of **1c**, but using the following amounts: **11** (10 g, 56 mmol), anhydrous *iso*propanol (150 mL, 190 mmol), concentrated sulfuric acid (0.7 mL). Reaction time: 14 h at rt. After the workup the crude was distilled under diminished pressure (bp 46-50 °C/16 torr) in a Kugelrohr distillation system to yield a liquid which was purified by column chromatography (1/3, ether/hexane) to give pure **1f** (2.49 g, 25.2%) as a colourless mobile liquid. R_f (1/1, ether/hexane): 0.51. ^{13}C NMR (75.78 MHz, $CDCl_3$) δ 101.66 (C-7), 68.53 (C-2), 68.11 (*C*HMe$_2$), 38.88 (C-3), 35.10 (C-5), 27.39 (C-6), 23.51 and 21.46 (CH*Me*$_2$). ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 4.95 (dd, *J* = 8.6 and 4.8, 1H, H-7), 4.24 (ddd, *J* = 12.6, 6.1 and 3, 1H, H-2), 3.86 (h, J = 6.2, 1H, C*H*Me$_2$), 3.74 (ddd, *J* = 12.6, 7.3 and 3, 1H, H-2), 2.77 (ddd, *J* = 14.7, 9.4 and 4, 1H, H-5), 2.68 (ddd, *J* = 14.7, 7.3 and 3, H-3), 2.59 (ddd, *J* = 14.7, 6.3 and 4.8, 1H, H-5), 2.67-2.6 (m, 1H, H-3), 2.32 (dddd, *J* = 14.4, 9.4 and 4.8, 1H, H-6), 2.09 (dddd, *J* = 14.4, 8.6, 6.3 and 4, 1H, H-6), 1.18 (d, *J* = 6.2, 3H, CH*Me*$_2$) and 1.11 (d, *J* = 6.2, 3H, CH*Me*$_2$). MS (CI): *m/z* (%) 176 (2, M^+), 148 (2), 116 (29), 60 (95), 43 (100). IR (cm^{-1}, film): 2973(s) and 2925 (s) (aliphatic C-H groups), 1127 (s), 1070 (s), 1050 (s), 1021 (s), 911 and 892 (m, C-O-C). HRMS (CI) calcd. for $C_8H_{17}O_2S$ (M^+ + 1) 177.0949, found: 177.0942.

1,1-di*iso*propoxy-2-(3-hydroxypropoxy)ethane 13: In a two-necked round-bottomed flask fitted with a reflux condenser and a dropping funnel were placed dry toluene (150 mL) and metallic Na (2.98 g, 0.13 mol), and the mixture was heated and stirred until the Na melts. Toluene was separated, and dry dioxane (150 mL) and 1,3-propanediol (9.89 g, 0.13 mol) were added. The mixture were refluxed for 24 h, and then, bromoacetaldehyde di*iso*propyl acetal[40] (51.72 g, 0.23 mol) was added dropwise. After 27 h under reflux, the mixture was cooled, filtered, and concentrated, and the residue was dissolved in $CHCl_3$ (100 mL) and washed with water (2 x 20 mL). The organic layer was separated, dried, filtered and concentrated. Distillation of the residue *in vacuo* (110 °C/ 16 torr) in a Kugelrohr distillation system yielded 3.80 g (13.4%) of **13** as a colourless liquid. R_f (ether): 0.40. ^{13}C NMR (75.78 MHz, $CDCl_3$) δ 98.28 (C-1), 72.84 (C-2), 71.04 (C-1'), 68.91 (*C*HMe$_2$), 62.13 (C-3'), 31.91 (C-*C*H$_2$-C), 23.33 and 22.50 (CH*Me*$_2$). ^{1}H NMR (300.13 MHz, $CDCl_3$) δ 4.68 (t, *J* = 5.2, 1H, H-1), 3.86 (h, *J* = 6.2, 2H, C*H*Me$_2$), 3.75 (q, J = 5.6, 2H, HO-C*H*$_2$-), 3.67 (t, *J* = 5.7, 2H, O-C*H*$_2$-C), 3.41 (d, *J* = 5.2, 2H, O-C*H*$_2$-CH), 2.63 (t, *J* = 5.7, 1H, O*H*), 1.80 (pseudoquintet, *J* = 5.6, 2H, C-C*H*$_2$-C), 1.19 (d, *J* = 6.2, 6H, CH*Me*$_2$) and 1.14 (d, *J* = 6.1, 6H, CH*Me*$_2$). IR (cm^{-1}, film): 3451 (m, OH), 2975 (s), 2932 (s) and 2877 (s) (aliphatic C-H groups), 1383 (m) and 1371 (m, *iso*propoxy groups), 1125 (s), 1046 (s, C-O-C). HRMS (CI) calcd. for $C_{11}H_{25}O_4$ (M^+ + 1) 221.1753, found: 221.1749. Anal. for $C_{11}H_{24}O_4.0.9H_2O$: Calcd.: C, 55.86; H, 11.00. Found: C, 55.90; H, 11.20.

2-*iso*propoxy-1,4-dioxepane 1g: 13 (3.49 g) was dissolved in dry ether (50 mL), and a few drops of $BF_3.Et_2O$ were added. The mixture was kept at rt for 24 h and washed with an aqueous solution of K_2CO_3 (10%), and the organic layer was dried, filtered, and concentrated. The residue was purified by flash chromatography with ether/hexane (1:3), yielding 0.47 g (18.6%) of **1g** as a colourless mobile liquid. R_f (1/3, ether/hexane): 0.18. ^{13}C NMR (75.78 MHz, $CDCl_3$) δ 98.87 (C-2), 74.01 (C-3), 72.67 (C-7), 69.12 (*C*HMe$_2$), 60.97 (C-5), 32.72 (C-6), 23.62 and 21.72 (CH*Me*$_2$). ^1H NMR (300.13 MHz, $CDCl_3$) δ 4.86 (dd, J = 7.8 and 4.1, 1H, H-2), 4.04 (dt, J = 12.8, and 2.5, 2H, H-5 and H-7), 3.91 (dd, J = 13.2 and 4.2, 2H, H-7 and C*H*Me$_2$), 3.64 (dt, J = 12.7 and 4.2, 1H, H-5), 3.54 (dt, J = 11.8 and 3.9, 1H, H-5), 3.37 (dd, J = 13.4 and 7.8, 1H, H-3), 2.02 (m, J = 5.6, and 3.9, 1H, H-6), 1.71 (m, 1H, H-6), 1.19 (d, J = 6.2, 3H, *Me*) and 1.10 (d, J = 6.1, 3H, *Me*). IR (cm^{-1}, film): 2973(s) and 2953(s) (aliphatic C-H groups), 1382 (m), 1372 (m, isopropoxy group), 1130 (s), 1116 (s), 1083 (s), 891(w) and 851 (w, C-O-C). HRMS (CI) calcd. for $C_8H_{17}O_3$ (M^+ + 1) 161.1178, found 161.1182.

Acknowledgement

We thank the Comisión Asesora de Investigación Científica y Técnica for their support of this work (QFN95-4710).

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(*Received in UK* 3 *April* 1996; *revised* 1 *May* 1996; *accepted* 9 *May* 1996)