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Researches on Antiviral Agents. 31. Synthesis and Transformations of Racemic and Chiral 6-Oxiranyl Pyrimidinones.

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Abstract: *The synthesis of epoxides 3, 4 and 6 has been described. The transformation of 3 into C-6 alkylated uracils 22a-e, 23a-d, 24 and 25 is also reported. The chiral epoxide (S)-(+)-3 has been prepared via a modified Solladiè procedure, while the $ZnCl_2$- DIBAH reduction step failed to give the expected enantiomer (R)-(-)-3. This result has been discussed on the ground of molecular modeling studies.*

African swine fever virus (ASFV) is responsible for an important disease of wild and domestic pigs that threatens the swine industry of many European, African, and South American countries. At present, no effective means of eradication has been found, and the control of the disease is still confined to recognition, quarantine, slaughter, and decontamination procedures.

There are not many known examples of molecules possessing anti-ASFV activity at the moment. Only recently (S)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine (HPMPA) and other broad spectrum antiviral compounds have been found to exhibit activity against ASFV in vitro.[2,3] Nevertheless, no reference structures have thus far been proposed to be used as a prototype for medicinal chemistry research in this field.

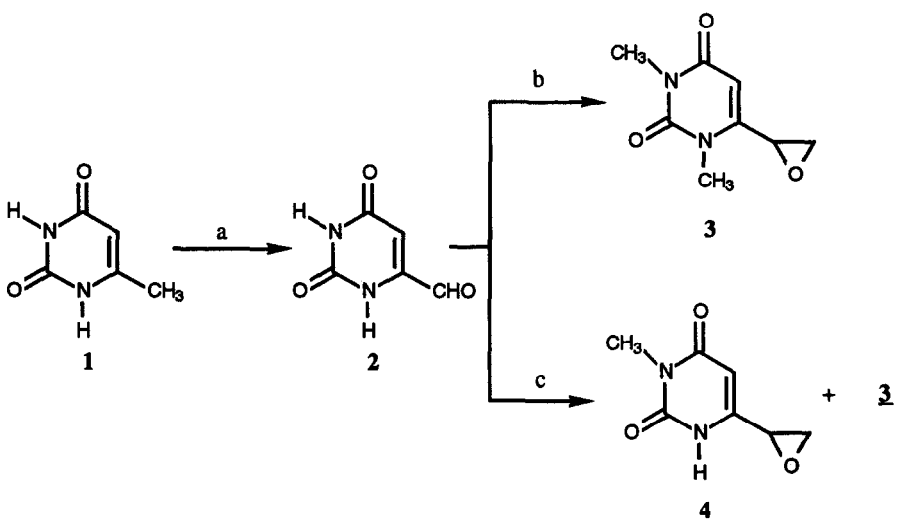
Although C-6 substituted uracils have been recently found to be active against Human Immunodeficiency virus (HIV)[4] and some C-6 substituted pyrimidines[5] are active against other viruses, to the best of our knowledge, literature reports concerning the anti-ASFV activity of C-6 substituted uracils and/or pyrimidines

are still lacking.

In the course of our studies on the synthesis and biological evaluation of potential antitumor and antiviral agents[6,7] we decided to start a research project on new pyrimidines derivatives substituted mainly at C-6 position. These can be directly prepared via cyclization of various β-ketoesters with O-methylisourea[8], with thiourea[9] or with alkylisothiourea[10]. The limitation of these syntheses is the preparation of the appropriate β-ketoester via procedures that are not necessarily straightforward. Similarly, the alternative activation of the C-6 position of the uracil ring to produce functionalized derivatives from commercially available substrates has been little studied.

A simple procedure to activate the C-6 position through the preparation of the N,N-diprotected epoxide **3**, obtained also as a chiral substrate, is reported here. The epoxide **3** was obtained, in good yield, from 6-formyluracil **2** (the latter having been prepared from 6-methyl-uracil **1** by utilizing our modification of the literature procedure[1]) using an excess of diazomethane in MeOH at room temperature . To the best of our knowledge, this compound has never been reported and we believe it could be an important synthon for the functionalization at the C-6 position of the pyrimidine nucleus (see later).

SCHEME 1



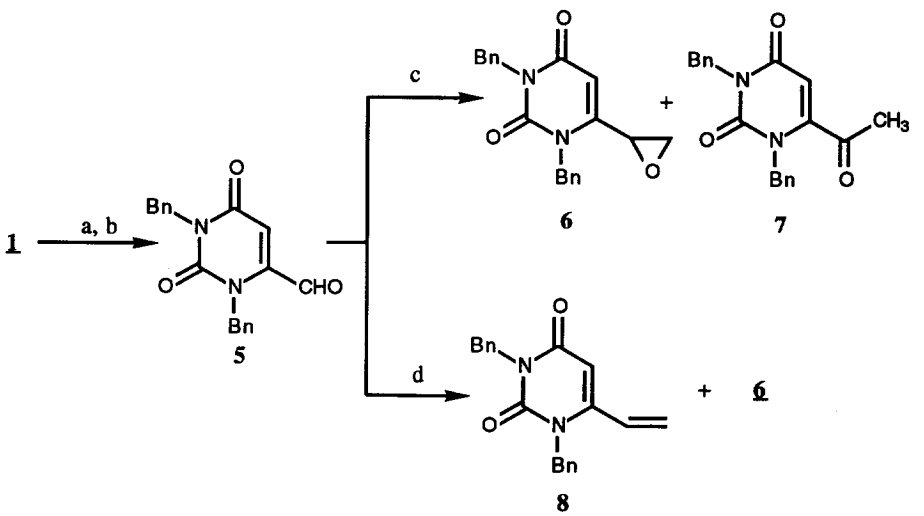
(a) SeO_2, CH_3COOH, reflux; (b) CH_2N_2, CH_3OH, T=0 °C, t=3h; (c) CH_2N_2, CH_3OH, T=0 °C, t=0.5 h.

Alternative synthetic approaches to pyrimidine epoxides are not particularly appropriate in that they usually require multistep procedures.[11] Consequently we decided to investigate the application of our methodology to substituted uracil aldehydes.

The epoxide **4** was prepared from **2** under the same experimental conditions

used for the preparation of compound **3**, but with a shorter reaction time. Methylation at N-1 requires, in fact, stronger reaction conditions due to the well known encumbering of the C-6 substituents thereby restricting the access to the N-1 position[12] (Scheme 1). On the other hand, protection of the 6-methyluracil nitrogen atoms with benzyl chloride in dry THF in the presence of tetrabutylammoniumfluoride (TBAF)[13], followed by SeO_2 oxidation in acetic acid at reflux, afforded the aldehyde **5** in a very high yield (98%). It is interesting to note that when we attempted to oxidize 1,3,6-trimethyluracil to 1,3-dimethyl-6-formyluracil under the same experimental conditions, we obtained only minor amount of the desired product. Subsequent epoxidation of the aldehyde **5** was performed with diazomethane to afford **6** in an acceptable yield (46%). The reaction mixture was purified by chromatography to remove 6-(1,3-dibenzyl-2,4-dioxopyrimidil)methyl ketone **7** also formed during the reaction (Scheme 2). This product was completely absent in the preparation of **3** and **4**.

SCHEME 2



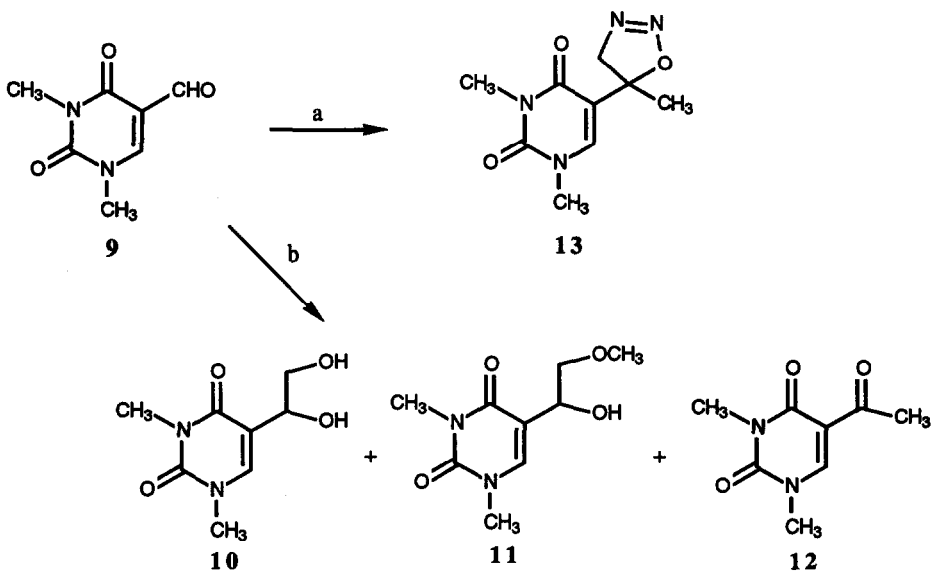
(a) benzyl chloride, TBAF, dry THF; (b) SeO_2, CH_3COOH, reflux; (c) CH_2N_2, CH_3OH, T=0 °C, t=0.5 h; (d) $(CH_3)_3SI$, CH_3SOCH_2Li, DMSO, T=- 20 °C.

Earlier attempts to prepare the epoxide **6** using Corey's procedure[14], by reacting the aldehyde **5** with dimethyloxosulfonium methylide under usual experimental conditions, furnished only a small amount of the desired product along with an appreciable amount of the unexpected compound **8** (10%).

With the aim of activating the C-5 position of the uracil ring, we attempted to prepare the C-5 epoxide starting from 1,3-dimethyl-5-formyluracil **9**[1]. Using the procedure described above, we obtained the diol **10** (72%) along with the

methoxyalcohol **11** (10%) and the methyl ketone **12** (10%) (Scheme 3).
Subsequent attempts at direct epoxidation of 1,3-dimethyl-5-formyluracil with a large excess of diazomethane afforded a single product **13**, found to be stable at room temperature. The FAB-MS spectrum showed a fragment ion at m/z 224, while ^{1}H-NMR and IR data proved the presumed structure. Compound **13** probably derives from a reaction of diazomethane with the initially formed ketone **12**.
Upon further reaction, compound **13** underwent nitrogen elimination giving a complex mixture of products in which 1,3-dimethyl-5-[(1'-hydroxy-1'-methyl)ethyl] uracil is also present.

SCHEME 3



(a) large excess of CH_2N_2, CH_3OH, T=0 °C; (b) CH_2N_2, CH_3OH, T=0 °C.

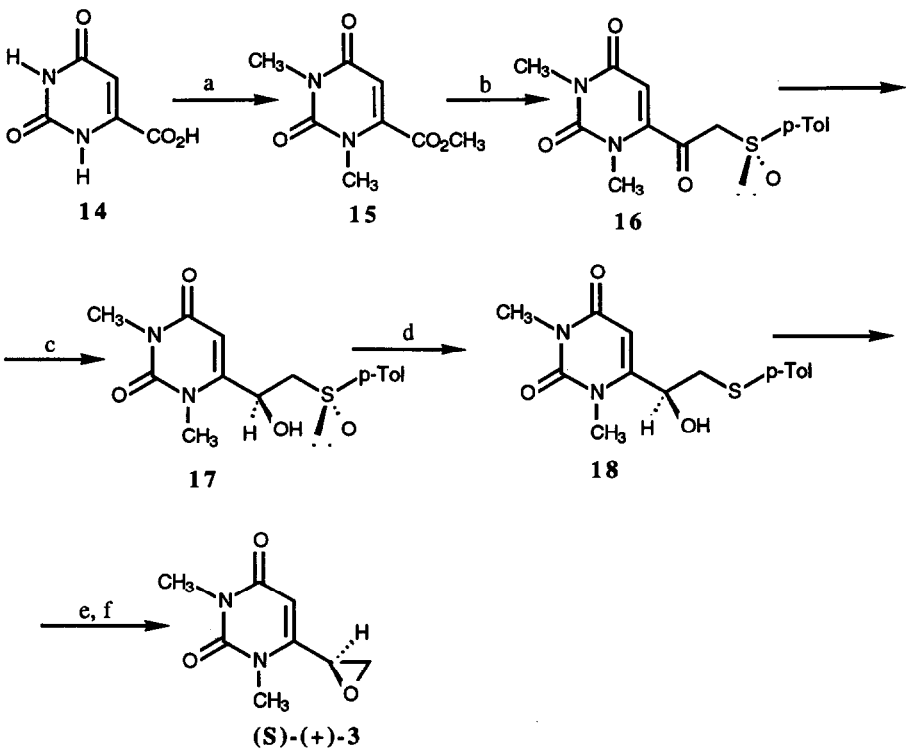
The failure of the preparation of the epoxide at the C-5 position of a pyrimidine ring has also been recently reported by Kumar[15] and by Thornburg[16], the latter in the enzyme-catalysed epoxidation of 5-vinyluracil. In both cases the formed epoxide is so reactive that it is immediately opened by the solvent giving rise to side products.

In conclusion the procedure described here represents a general and straightforward method for the conversion, in moderate to good yield, of C-6 formyluracils into the corresponding 6-oxyranyluracils, which in turn, can be regarded as valuable synthons for the preparation of potentially active C-6 substituted pyrimidines. Preliminary microbiological evaluation showed that the epoxide **3**[17] exhibits significant activity against ASFV virus. It is well known that, due to the ability to bind to cellular macromolecules, the most

electrophilically reactive epoxides can give rise to many types of effects[18] to extents that can be markedly dependent on their stereochemistry[19]. Accordingly, we deemed it of interest to evaluate the antiviral activity of a pure enantiomer of **3**.

To the best of our knowledge, no records are available in the literature prior to our communication[20], dealing with the chiral synthesis or the resolution into the enantiomers of compounds similar to **3**. We describe here, in detail, the synthesis of the chiral epoxides R-(-) and S-(+)-**3** in high yield and in very good enantiomeric excess using our modification of the Solladié procedure[21]. We started from commercially available orotic acid **14** (Scheme 4), which was permethylated in a single step, with an excess of diazomethane to afford **15** (93% yield). Condensation of **15** with (R)-methyl p-tolyl sulfoxide at -78°C, in spite of the presence of a possibly competitive reactive center[1], gave only the expected product **16** isolated in very good yield (92%).

SCHEME 4



(a) CH_2N_2, CH_3OH, 0 °C; (b) (R)-methyl p-tolylsulfoxide, LDA, THF, -78 °C; (d) PBr_3,CH_2Cl_2, 0 °C;(e) CH_3I, $AgBF_4$, THF, 25 0 °C; (f) NaOH 2N, TBAF, 25 °C. For the synthesis of epoxide (R)-(-)-3: (b) (S)-methyl p-tolyl sulfoxide.

Diisobutylaluminiumhydride (DIBAH) reduction of the β-ketosulfoxide **16** gave a single product **17** (90%), as shown by chromatography and by 300 MHz ^{1}H-NMR spectroscopy. It was possible to assign its absolute stereochemistry through a conformational analysis performed by ^{1}H-NMR spectroscopy. In fact, the relationship between vicinal coupling constants of the α-carbon to sulfoxide group of several β-hydroxysulfoxides has been used to establish the relative configuration of the chiral centers, the differences in the values of their coupling constants[22,23,24] being used as a criterion of configurational assignment[25]. In our case the (R_S, S) configuration was assigned to compound **17**.

Reduction of the β-hydroxysulfoxide **17** with $LiAlH_4$, attempted at different temperatures, gave a complex mixture of compounds, while PBr_3 reduction afforded a single sulfide **18**, which showed all the expected resonance signals in the 300 MHz ^{1}H-NMR spectrum and a fragment ion at m/z 307 in the FAB-MS spectrum.

Methylation at the sulfur atom of **18** with MeI, in the presence of silver tetrafluoroborate ($AgBF_4$), resulted to be more efficient than the trimethyloxonium tetrafluoroborate procedure usually used in these cases[22]. The resulting intermediate sulfonium ion then underwent intramolecular displacement when treated in situ with NaOH and a catalytic amount of TBAF (tetrabutylammonium fluoride) to afford cleanly the epoxide S-(+)-**3**.

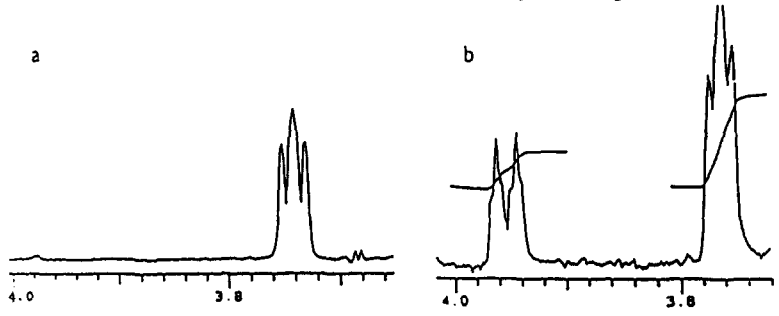


Fig. 1: (a) Part of the 300 MHz ^{1}H-NMR spectrum of (+)-3 in $CDCl_3$ after the addition of Eu(hfc)$_3$, proton on asymmetric carbon. (b) Part of 300 MHz ^{1}H-NMR spectrum of the mixture of (+)-3 and (-)-3 from DIBAH /$ZnCl_2$ reduction, proton on asymmetric carbon

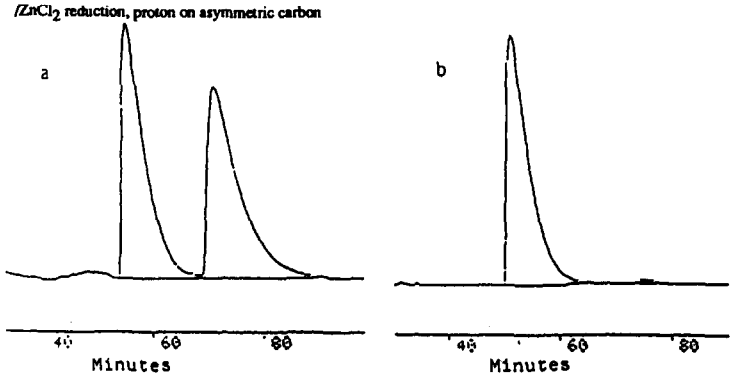


Fig. 2: (a) Chiral HPLC chromatogramme of 3 performed on a chiral column of chiralcel OD 250 x 4 mm (eluting with hexane/isopropanol =90/10). (b) Chiral HPLC chromatogramme of (+)-3.

The enantiomeric purity (98%) of this compound was checked by ^{1}H-NMR spectroscopy utilizing the chiral shift reagent tris-3-(hepta-fluoropropyl-hydroxymethylen)-d-canforate europium (III) ,Eu(hfc)$_3$ [fig 1a], and by HPLC (fig 2) performed on a chiral column.
The absolute configuration of the chiral epoxide (S)-(+)-3 was confirmed by X-ray crystallographic analysis (Figure 3)[26].

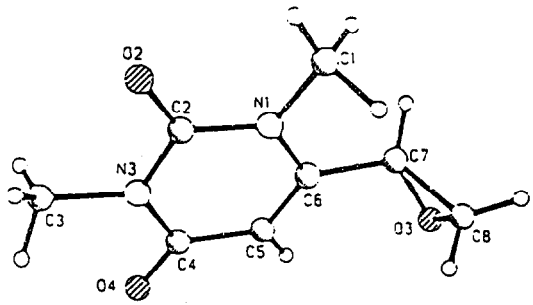
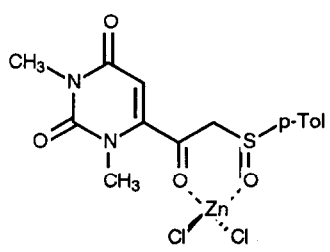


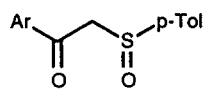
Fig. 3: X-ray structure of epoxide (S)-(+)-3 with numbering of atoms.

With the purpose to obtain the (R)-(-)-**3** isomer, we attempted the reduction of the β-ketosulfoxide **16** with DIBAH/$ZnCl_2$ as described by Solladiè in the case of simple aromatic and aliphatic β-ketosulfoxides[22] such as **19** (Scheme 5).
The stereoselectivity of this reaction that affords the alcohol in which the configuration of the OH is inverted with respect to that of the DIBAH reduction,. has been explained by involving a complexation of the $ZnCl_2$ with the carbonyl and sulfoxide oxygen atoms, as depicted in our case in structure **20**, prior to the reduction, followed by the approach of the reducing agent from the less hindered face.

SCHEME 5



20



19 Ar= 4-substituted phenyl

21 Ar= 2-pyrimidil

In this case, we obtained a diastereoisomeric mixture of alcohols which were difficult to separate by chromatography. Using a very large concentration of $ZnCl_2$ (6 mole equivalents) only part of the diastereoisomer with the OH inverted was obtained as shown by the ^{1}H-NMR spectrum of the mixture. Without further purification, we subjected the mixture to S-methylation followed by intramolecular displacement to afford the epoxide. The latter was obtained in an enantiomeric excess of 30% for the R-(-)3 enantiomer as shown by the 300 MHz ^{1}H-NMR spectrum of the mixture employing the chiral shift reagent Eu(hfc)3 (see Fig 1b).

With the aim to understand the lack of stereoselectivity in the DIBAH/$ZnCl_2$ reduction of the β-ketosulfoxide **16** , we performed a modeling study.
The failure of this general reaction in the case described here might be ascribed to two main factors: either the complex **20** is not formed, or, if it is, it does not react in the anticipated manner. A careful examination of the literature provided a precedent[27] in which a failure of the DIBAH/$ZnCl_2$ procedure was noted when applied to the compound **21**.

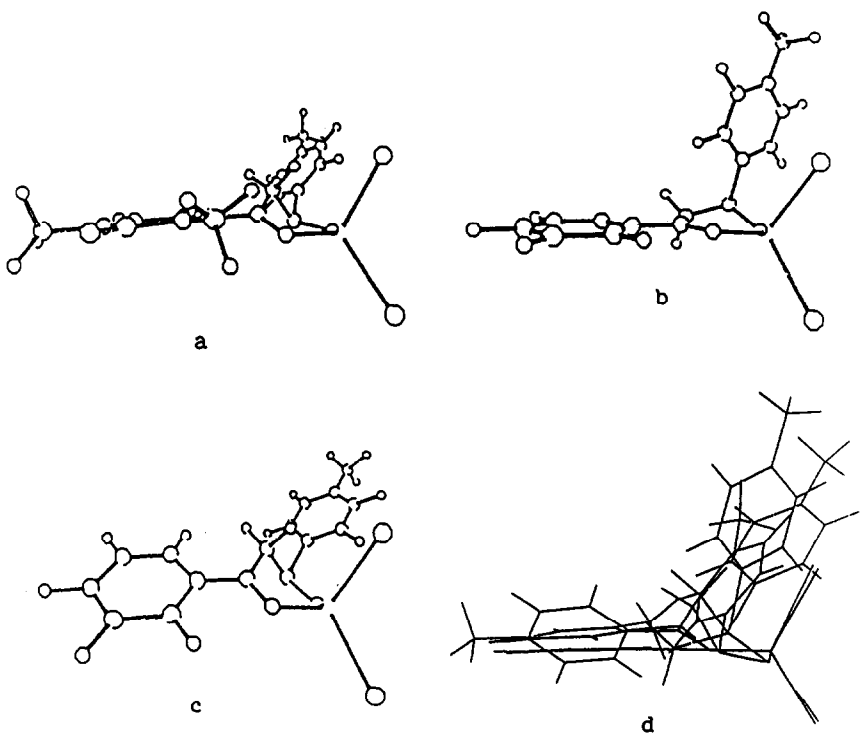


Fig. 4: Computer-drawn plots of the energy-minimized conformation of complexes: a=20; b=21; c=19; d= Superimposition of structures a, b and c.

We started our studies with an examination of the possible behaviour of the three molecules **16**, **19** and **21** when subjected to the DIBAH reduction, with the purpose to visualize the face of the attack of the reducing agent. Structures **16**, **19** and **21** have been drawn and the energy minimized with the MM2 force field as implemented in Model[R28]; a conformational analysis was done using the grid option of the programme Backmodel[R28]. The conformations so obtained were minimized to convergence with the programme MMX[29], which is particularly useful for aromatic systems. Comparison of the minima energy conformers, visualized on an Evans and Sutherland PS 390 using the Sybyl[30] programme, showed an identical preferred face of attack for the bulky reducing agent in a complete agreement with what proposed by Solladiè.[20] Indeed a very good stereofacial discrimination has also been found in our case.

We then drew the structure of the hypothetical complex **20**. The minimum energy conformation was found using the programme MMX and we compared it on the Evans and Sutherland graphic terminal with the minimum energy conformations of the complexes **19**-$ZnCl_2$ and **21**-$ZnCl_2$, drawn and minimized in the same way. The three complexes were shown (see fig 4) to be very similar in the 3D-space and to present the same preferred direction of attack by the hydride. Consequently, if the complex **20** was feasible, we would have obtained products having an inverted configuration of the OH with respect to DIBAH reduction in all the three cases. This reaction was unsuccessful in our hands, even when a very high concentration of $ZnCl_2$ was used, showing that the complex, as depicted in this study, is not feasible. Our molecule probably possesses too many other electron rich centres available for the $ZnCl_2$ complexation; hence the reaction does not proceed in a stereoselective manner.

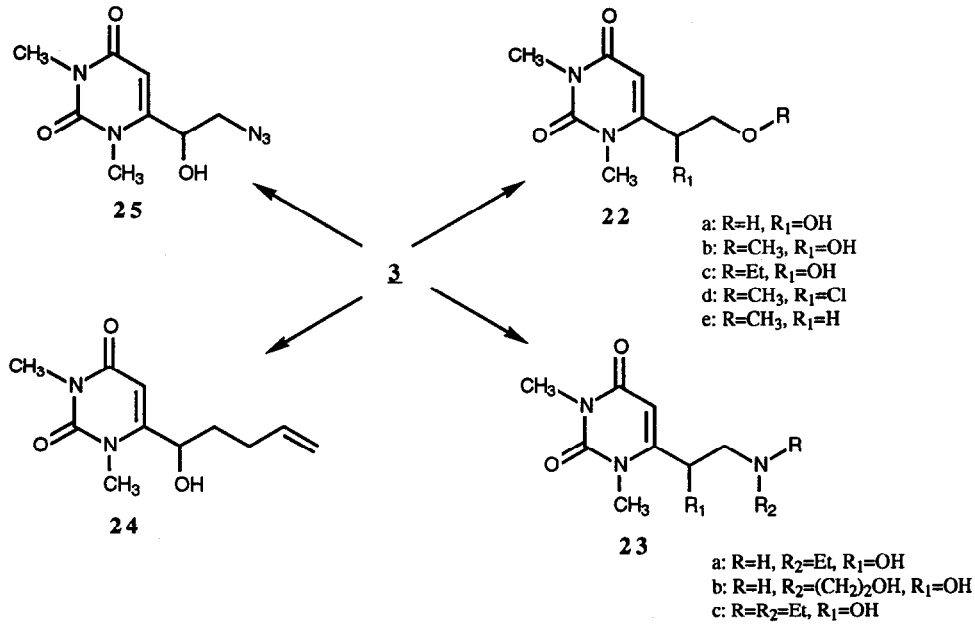
The R-(-)epoxide **3** was finally synthesized in high yield and in very good enantiomeric excess, starting from orotic acid methyl ester **15** and (S)-methyl p-tolyl sulfoxide as chiral inducing agent.

When tested for anti-ASFV activity, the pure enantiomers showed a selectivity index identical to that of the racemic mixture **3**, showing that the activity is probably due to the alkylating properties of the epoxide function.

Once the C-6 position has been activated we proceeded to study the nucleophilic opening of the oxirane ring with the purpose to prepare products **22-25** (Scheme 6) for biological assays and to test the reactivity of the C-6 epoxide. Reactions were performed by adding the nucleophiles to the epoxide **3**, the antiviral activity of the racemic and the pure enantiomers was, in fact, identical. The reactions were performed in alcohol at room temperature (in MeOH at reflux for nitrogen nucleophiles). In all the described cases we have obtained only one regioisomer, as shown by the coupling between the OH group and a C-1' proton in the ^{1}H-NMR spectrum, probably because of the already mentioned encumbering of the N-1 methyl group, that sterically inhibits the substitution at the secondary carbon atom.[12] With the purpose to investigate whether the tertiary OH present in all the products so obtained required for antiviral activity we prepared also the desoxy compound **22e** in two steps and in good yield. Compound **22b** was transformed into the chloroderivative **22d** with $SOCl_2$ in dichloromethane which was subsequently reduced with $NaBH_4$ at room temperature. The antiviral activity of compounds **22-25** was evaluated

against conventional RNA (Vescicular Stomatitis Virus) and DNA (Herpes Simplex Virus-1, Vaccinia Virus, ASFV and Adeno Virus) viruses. The compounds did not inhibit any of the viruses when tested at concentrations equal to the TD_{50} with the exception of compound **22c** which showed a modest activity against VSV virus. It is interesting to note that the nitrogen containing products resulted to be less toxic than the oxygen containing analogs.[17] The pharmacological data will be presented elsewhere.

SCHEME 6



Acknowledgements

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EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer 257 instrument and n.m.r. spectra at 300 MHz on a XL Varian 300. Mass spectra were recorded on a Kratos MS 80 spectrometer. Mycroanalyses were performed on a Carlo Erba Model 1106 analyzer. $[\alpha]_D$ was performed

on a Perkin-Elmer 241 Polamiter. Column chromatography was performed using Merck Kieselgel 60 (70-230 mesh ASTM). All chemicals and solvents were reagent grade unless otherwise specified. Unless otherwise stated, the organic solutions were dried over anhydrous sodium sulfate (Na_2SO_4).

6-Oxiranyl-1,3-dimethyl-pyrimidin-2,4-dione (**3**)- An excess of diazomethane in ethereal solution was added to a solution of *orotoaldehyde* (**2**) (882 mg, 6.3 mmol) in methanol (20 ml) at 0 °C for 2 h. The solution was evaporated to dryness. Chromatography on silica gel with chloroform:methanol (9:1) as eluant yielded (**3**) (688 mg, 60%), oil; ν_{max} ($CHCl_3$) 1710 (CO) and 1680 cm^{-1} (α,β-unsaturated ketone); δ_H (300 MHz; $CDCl_3$) 2.95 (2H, m, 2'-H), 3.30 (3H, s, NCH_3), 3.45 (3H, s, NCH_3), 3.70 (1H, m, 1'-H), and 5.75 (1H, s, 5-H); m/z 182 (M^+, 20%).

*(+)-(S)-6-Oxiranyl-1,3-dimethyl-pyrimidin-2,4-dione (+)-(**3**)* and *(-)-(R)-6-Oxiranyl-1,3-dimethyl-pyrimidin-2,4-dione (-)-(**3**)* - A solution of *methyliodide* (284 mg, 2 mmol) in tetrahydrofuran (5 ml) was added to a solution of (**18**) (367 mg, 1.2 mmol) in tetrahydrofuran (15 ml) in the presence of a catalitic amount of silver tetrafluoroboride at 25 °C . After 2 h. a 10% solution of aqueous sodium hydroxyde (10 ml) and a catalytic amount of tetrabutylammonium fluoride were added and the resulting mixture was stirred for 0.5 h. The solution was poured into water and extracted with dichloromethane. The extract was dried and evaporated to dryness. Chromatography on silica gel with chloroform:methanol (9:1) as eluant yielded (+)-(**3**) (164 mg, 75%), m.p. 75-77 °C (Found: C, 52.80, H, 5.55; N, 15.45 . $C_8H_{10}N_2O_3$ requires C, 52.74, H, 5.54; N, 15.37%); $[\alpha]_D$ +51.6° (c 1.0 in $CHCl_3$); e.e>98% determined by chiral column of chiracel OD 250x4 mm. eluting with hexane:isopropanol (9:1) in comparison with the chromatogramme of the racemic mixture (**3**) and by ^{1}H-nmr (300 MHz; $CDCl_3$) with the addition of chiral shift reagent $Eu(hfc)_3$. (-)-(**3**) (94 mg, 43%), $[\alpha]_D$-51.6° (c 1.0 in $CHCl_3$), e.e> 98%.

6-Oxiranyl-3-methyl-pyrimidin-2,4-dione (**4**)- An excess of diazomethane in ethereal solution was added to a solution of aldehyde (**2**) (882 mg, 6.3 mmol) in methanol (20 ml) at 0 °C for 0.5 h.The solution was evaporated to dryness. Chromatography on silica gel with chloroform:methanol (9:1) as eluant yielded (**3**) (344 mg, 30%) and (**4**) (296 mg, 28%), oil; ν_{max} ($CHCl_3$) 3400 (NH),1700 (CO) and 1680 cm^{-1} (α,β-unsaturated ketone); δ_H (300 MHz; $CDCl_3$) 3.30 (3H, s, NCH_3), 4.50 (2H, m, 2'-H), 5.25 (1H, m, 1'-H) and 5.80 (1H, s, 5-H); m/z 168 (M^+, 10%).

1,3-Dibenzyl-6-formyl-pyrimidin-2,4-dione (**5**) - A solution of *1,3-dibenzyl-6-methyl-pyrimidin-2,4-dione* (**1**) (1.53 g, 5 mmol) in tetrahydrofuran (15 ml) and acetic acid (15 ml) was oxidized with SeO_2 (1.66 g, 15 mmol) at reflux for 24 h. After cooling the solution was filtered on celite and the filtrate was evaporated to dryness. Chromatography on silica gel with chloroform as eluant yielded (**5**) (1.57 g, 98%), m.p. 65-67 °C (Found: C, 71.30, H, 5.00; N, 8.80. $C_{19}H_{16}N_2O_3$ requires C, 71.25, H, 5.0; N, 8.75%); ν_{max} ($CHCl_3$) 1710 (CO) and 1680 cm^{-1} (α,β-unsaturated ketone); δ_H (300 MHz; $CDCl_3$) 5.20 (2H, s, $PhCH_2$), 5.50 (2H, s, $PhCH_2$), 6.25 (1H, s, 5-H), 7.35 (10H, m, Ph) and 9.59 (1H, s, CHO); m/z 320 (M^+, 100%).

1,3-Dibenzyl-6-oxiranyl-pyrimidin-2,4-dione(**6**),*6-(1,3-Dibenzyl-2,4-dioxopyrimidil)methyl ketone* (**7**) and *6-Vinyl-1,3-dibenzyl-pyrimidin-2,4-dione* (**8**)- procedure (a): An ethereal solution of diazomethane was added to a solution of the aldehyde (**5**) (320 mg, 1 mmol) in diethyl ether (20 ml) at 0 °C for 4h. The solution was evaporated to dryness. Chromatography on silica gel with chloroform:methanol (9.9:0.1) as eluant yielded (**6**) and (**7**): (**6**) (167 mg, 50%), oil; ν_{max} ($CHCl_3$) 1710 (CO) and 1680 cm^{-1} (α,β-unsaturated ketone); δ_H (300 MHz; $CDCl_3$) 2.75 (2H, m, 2'-H), 3.50 (1H, m, 1'-H), 5.25 (4H, m, $PhCH_2$), 5.80 (1H, s, 5-H) and 7.20 (10H, m, Ph); m/z 334 (M^+, 20%). (**7**) (33.4 mg, 10 %), oil; ν_{max} ($CHCl_3$) 1720 (CO), 1690 (CO) and 1670 cm^{-1} (α,β-unsaturated ketone); δ_H (300 MHz; $CDCl_3$) 3.40 (3H, s, $COCH_3$), 5.30 (4H, m, $PhCH_2$), 5.85 (1H, s, 5-H) and 7.20 (10H, m, Ph); m/z 334 (M^+, 30%). Procedure (b): Sodium hydride (31 mg, 1.3 mmol) was added to dry dimethylsulfoxide (3 ml) and the solution was heated to 80 °C for 1 h. After cooling the mixture was diluted with dry tetrahydrofuran (5 ml) and a solution of trimethylsolfoniumiodide (265 mg, 1.3 mmol) in dry dimethylsulfoxide (5 ml) was added dropwise. After 1 h. the mixture was cooled at -20 °C and (**5**) (320 mg, 1 mmol) in dry tetrahydrofuran (5 ml) was added rapidly. The quenching of the reaction was performed after 4 h. with water and the solution was extracted with ethylacetate. The extract was washed with aqueous sodium hydrogen carbonate, dried and evaporated to dryness. Chromatography on silica gel with chloroform:methanol (9.9:0.1) as eluant yielded (**6**) (167 mg, 50%) and (**8**) (32 mg, 10%), oil; ν_{max} ($CHCl_3$) 1710 (CO), 1680 (α,β-unsaturated ketone) and 1650 (C=C) cm^{-1}; δ_H (300 MHz; $CDCl_3$) 5.0 (4H, m, $PhCH_2$), 5.10 (2H, m, 2'-H), 5.66 (1H, m, 1'-H), 5.85 (1H, s, 5-H) and 7.28 (10H, m, Ph); m/z 318 (M^+, 18%).

5-(1,3-Dimethyl-2,4-dioxopyrimidil)ethan-1',2'-diol (**10**), *5-(1,3-Dimethyl-2,4-dioxopyrimidil)ethan-2'-methoxy-1'-ol* (**11**) and *5-(1-3-Dimethyl-2,4-dioxopyrimidil)methyl ketone* (**12**) - Diazomethane in ethereal solution was added to a solution of *5-formyl-1,3-dimethyl-pyrimidin-2,4-dione* (**9**) (504 mg, 3 mmol) in methanol at 0 °C until the substrate disappeared (TLC). The solution was evaporated to dryness. Chromatography on silica gel with chloroform:methanol (9.5:0.5) as eluant yielded the products: (**10**) (432 mg, 72%), m.p. 130-132 °C (Found: C, 47.80, H, 6.01; N, 14.00 . $C_8H_{12}N_2O_4$ requires C, 47.99, H, 6.04; N, 13.99 %); ν_{max} ($CHCl_3$) 3400 (OH), 1710 (CO) and 1670 cm^{-1} (α,β-unsaturated ketone); δ_H

(300 MHz; $CDCl_3$) 3.25 (3H, s, NCH_3), 3.35 (3H, s, NCH_3), 3.65 (2H, m, 2'-H), 4.70 (1H, m, 1'-H) and 7.40 (1H, s, 6-H); m/z 200 (M^+, 10%). (**11**) (64.2 mg, 10%), m.p. 120-122 °C (Found: C, 50.50, H, 6.50; N, 13.10. $C_9H_{14}N_2O_4$ requires C,50.46, H, 6.58; N, 13.07 %); ν_{max} ($CHCl_3$) 3400 (OH), 1710 (CO) and 1670 cm^{-1} (α,β-unsaturated ketone); δ_H (300 MHz; $CDCl_3$) 3.28 (3H, s, NCH_3), 3.34 (3H, s, NCH_3), 3.40 (3H, s, OCH_3), 3.53 (2H, m, 2'-H), 4.37 (1H, m, 1'-H) and 7.10 (1H, s, 6-H); m/z 214 (M^+, 25%). (**12**) (54.6 mg, 10%), m.p. 115-117 °C (Found: C, 52.30, H, 5.48; N, 15.40.$C_8H_{10}N_2O_3$ C, 52.35, H, 5.54; N, 15.38 %); ν_{max} ($CHCl_3$) 1720 (CO), 1690 (CO) and 1670 cm^{-1} (α, β- unsaturated ketone) ; δ_H (300 mHz; $CDCl_3$) 2.59 (3H, s, $COCH_3$), 3.30 (3H, s, NCH_3), 3.40 (3H, s, NCH_3) and 8.10 (1H, s, 6-H); m/z 182 (M^+, 30%).

5-(1,3-Dimethyl-2,4-dioxopyrimidil)-5'-(5'-methyl)-1',2',3'-oxadiazolo (**13**) - A large excess of diazomethane in ethereal solution was added to a solution of (**9**) (403 mg, 2.4 mmol) in methanol (20 ml) at 0 °C until the complete disappearance of substrate. The solution was evaporated to dryness. Chromatography on silica gel with chloroform:methanol (9.2:0.8) as eluant yielded (**13**) (430 mg, 80%), oil; ν_{max} ($CHCl_3$) 1720 (CO) and 1670 cm^{-1} (α,β-unsaturated ketone); δ_H (300 MHz; $CDCl_3$) 3.10 (3H, s, 5'-H), 3.25 (3H, s, NCH_3), 3.45 (3H, s, NCH_3), 3.85 (2H, m, 4'-H) and 6.70 (1H, s, 6-H); m/z 224 (M^+, 15%).

1,3-Dimethyl-methylorotate (**15**) - Diazomethane in ethereal solution was added to *orotic acid* mono-hydrate (**14**) (452 mg, 2.6 mmol) in methanol (20 ml) at 0 °C until complete disappearance of substrate. The solution was evaporated to dryness. Chromatography on silica gel with chloroform as eluant yielded (**15**) (489 mg, 95%), m.p. 57-59 °C (Found: C, 48.40 , H, 4.59; N, 14.10. $C_8H_{10}N_2O_4$ requires C, 48.47, H, 5.09; N, 14.14 %); ν_{max} ($CHCl_3$) 1750 (CO_2Et),1710 (CO) and 1670 cm^{-1} (α,β-unsaturated ketone); δ_H (300 MHz; $CDCl_3$) 3.30 (3H, s, NCH_3), 3.45 (3H, s, NCH_3), 3.95 (3H, s, OCH_3) and 6.20 (1H, s, 5-H); m/z 198 (M^+, 100%).

(+)-(R)-β-Ketosulfoxide (**16**) and *(-)-(S)-β-ketosulfoxide* (**16'**) - A solution of *(+)-methyl p-tolylsulfoxide* (400 mg, 2.6 mmol) in dry tetrahydrofuran (4 ml) was added dropwise to a solution of lithiumdiisopropylamide (1.4 mmol) in dry tetrahydrofuran (10 ml) at -78 °C for 1 h. A solution of (**15**) (554 mg, 2.8 mmol) in dry tetrahydrofuran (10 ml) was added dropwise at -78 °C and the solution was stirred for 5 h. The solution was poured into water and extracted with ethyl acetate. The extract was dried and evaporated to dryness. Chromatography on silica gel with chloroform:methanol (9.8:0.2) as eluant yielded (**16**) (824 mg, 92%), m.p. 83-85 °C (Found: C, 56.28, H, 5.06; N, 8.70. $C_{15}H_{16}N_2O_4S$ requires C, 56.24, H, 5.03; N, 8.74 %); $[\alpha]_D$ + 66° (c 1.5 in $CHCl_3$); ν_{max} ($CHCl_3$) 1720 (CO) and 1650 cm^{-1} (α,β-unsaturated ketone); δ_H (300 MHz; $CDCl_3$) 2.40 (3H, s, $PhCH_3$), 3.30 (3H, s, NCH_3), 3.40 (3H, s, NCH_3),

4.35 (2H, m, 2'-H), 6.29 (1H, s, 6-H) and 7.55 (4H, m, Ph); m/z 320 (M^+, 8%). (**16'**) (717 mg, 80%); $[\alpha]_D$ -66° (c 1.5 in $CHCl_3$).

(+)-(RS)-β-Hydroxysulfoxide (**17**) and *(-)-(SR)-β-Hydroxysulfoxide* (**17'**) - A solution of (**16**) or (**16'**) (416 mg, 1.3 mmol) in tetrahydrofuran (5 ml) was reduced with diisobutylaluminum hydride (1.2 ml of a 1.2 N hexane solution) at -78 °C for 4 h. The solution was poured into water and extracted with dichloromethane. The extract was dried and evaporated to dryness. Chromatography on silica gel with chloroform:methanol (9.5:0.5) as eluant yielded (**17**) (377 mg, 90%), m.p. 88-90 °C (Found: C, 55.80, H, 5.69; N, 8.70. $C_{15}H_{18}N_2O_4S$ requires C, 55.89, H, 5.63; N, 8.69 %); $[\alpha]_D$ + 113.9° (c 1.0 in $CHCl_3$); ν_{max} ($CHCl_3$) 1710 (CO) and 1670 cm^{-1} (α,β-unsaturated ketone); δ_H (300 MHz; $CDCl_3$) 2.35 (3H, s, $PhCH_3$), 3.15 (2H, m, 2'-H), 3.35 (3H, s, NCH_3), 3.35 (3H, s, NCH_3), 5.20 (1H , m, 1'-H), 5.95 (1H, s, 5-H) and 7.45 (4H, m, Ph); m/z 322 (M^+, 12%). (**17'**) (347 mg, 83%), m.p. 85-87 °C; $[\alpha]_D$-113.9° (c 1.0 in $CHCl_3$).

(-)-(S)-β-Hydroxysulfide (**18**) and *(+)-(R)-β-Hydroxysulfide* (**18'**) - A solution of phosphorus tribromide (487 mg, 1.8 mmol) was added dropwise to a solution of (**17**) or (**17'**) (580 mg, 1.8 mmol) in dichloromethane (20 ml) at 0 °C for 0.5 h. The solution was poured into water and extracted with dichloromethane. The extract was dried and evaporated to dryness. Chromatography on silica gel with chloroform:methanol (9.5:0.5) as eluant yielded (**18**) (413 mg, 75%), m.p. 165-166 °C (Found: C, 58.77, H, 5.82; N, 9.10 $C_{15}H_{18}N_2O_3S$ requires C, 58.82, H, 5.92; N, 9.15 %); $[\alpha]_D$+18.3° (c 1.4 in $CHCl_3$); ν_{max} ($CHCl_3$) 1710 (CO) and 1670 cm^{-1} (α,β-unsaturated ketone); δ_H (300 MHz; $CDCl_3$) 2.31 (3H, s , $PhCH_3$), 3.02 (2H, m, 2'-H), 3.26 (6H, s, NCH_3), 5.21 (1H, m, 1'-H), 6.0 (1H, s, 5-H) and 7.40 (4H, m, Ph); m/z 307 (M++1, 30%). (**18'**) (468 mg, 85%); $[\alpha]_D$-18.3° (c 1.4 in $CHCl_3$).

6-(1,3-Dimethyl-2,4-dioxopyrimidil)ethan-1',2'-diol (**22a**) - A 10% water solution of sodium hydroxide (5 ml) was added to a solution of (**3**) (200 mg, 1.1 mmol) in tetrahydrofuran (20ml) at 50 °C for 5h. The solution was extracted with ethylacetate, and the extract was dried and evaporated to dryness. Chromatography on silica gel with chloroform:methanol (9:1) as eluant yielded (**22a**) (176 mg, 80%), oil; ν_{max} ($CHCl_3$) 3400 (OH), 1710 (CO) and 1670 cm^{-1} (α,β-unsaturated ketone); δ_H (300 MHz; $CDCl_3$) 3.30 (3H, s, NCH_3), 3.45 (3H, s, NCH_3), 3.45 (2H, m, 2'-H), 4.80 (1H, m, 1'-H) and 6.95 (1H, s, 5-H); m/z 200 (M^+, 15%).

General procedure for the synthesis of *6-(1,3-Dimethyl-2,4-dioxopyrimidil)ethan-2'-methoxy-1'-ol* (**22b**) and *6-(1,3-Dimethyl-2,4-dioxopyrimidil)ethan-2'-ethoxy-1'-ol* (**22c**) - An alcoholic solution of the alcolate (2 2 mmol in 10 ml of alcohol) was added to a solution of (**3**) (200 mg, 1.1 mmol) in dry alcohol (10 ml) at 25 °C for 6h. The solution was poured into water and

extracted with ethylacetate. The extract was dried and evaporated to dryness. Chromatography on silica gel with chloroform:methanol (9.5:0.5) as eluant yielded the products: (**22b**) (212 mg, 90%), m.p. 76-77 °C (Found: C, 50.40, H,6.60; N, 13.00. $C_9H_{14}N_2O_4$ requires C, 50.46, H, 6.59; N, 13.08 %); ν_{max} ($CHCl_3$) 1710 (CO) and 1670 cm^{-1} (α,β-unsaturated ketone); δ_H (300 MHz; $CDCl_3$) 3.30 (3H, s, NCH_3), 3.45 (3H, s, NCH_3), 3.50 (2H, m, 2'-H), 3.55 (3H, s, OCH_3), 4.70 (1H, m, 1'-H) and 5.90 (1H, s, 5-H); m/z 214 (M^+, 10%). (**22c**) (213 mg, 85%), m.p. 83-84 °C (Found: C, 52.60, H, 7.10; N, 12.30 . $C_{10}H_{16}N_2O_4$ requires C, 52.62, H, 7.06; N, 12.27%), ν_{max} ($CHCl_3$) 3400 (OH), 1710 (CO) and 1680 cm^{-1} (α,β-unsaturated ketone); δ_H (300 MHz; $CDCl_3$) 1.25 (3H, m, CH_3), 3.30 (3H, s, NCH_3), 3.45 (3H, s, NCH_3), 3.55 (4H, m, CH_2), 4.70 (1H, m, 1'-H) and 5.95 (1H, s, 5-H); m/z 228 (M^+, 30%).

6-(1,3-Dimethyl-2,4-dioxopyrimidil)ethan-1'-chloro-2'-methoxy (**22d**) - *Thionyl chloride* (228 mg, 1.92 mmol) was added to a solution of (**22b**) (257 mg, 1.2 mmol) in dry dichloromethane (8 ml) at reflux for 24 h. The solution was poured into cold water and extracted with dichloromethane. The extract was washed with aqueous sodium hydrogen carbonate, dried and evaporated to dryness. Chromatography on silica gel with chloroform:methanol (9.5:0.5) as eluant yielded (**22d**) (237 mg, 85%); m.p. 70-72 °C (Found: C, 46.50, H, 5.70; N, 12.10. $C_9H_{13}N_2O_3Cl$ requires C, 46.46, H, 5.63; N, 12.07%) ; ν_{max} ($CHCl_3$) 1710 (CO) and 1670 cm^{-1} (α,β-unsaturated ketone); δ_H (300 MHz; $CDCl_3$) 3.30 (3H, s, NCH_3), 3.40 (3H, s, NCH_3), 3.50 (3H, s, OCH_3), 3.85 (2H, m, 2'-H), 4.85 (1H, m, 1'-H) and 5.90 (1H, s, 5-H); m/z 232 (M^+, 18 %).

6-(1,3-Dimethyl-2,4-dioxopyrimidil)ethan-2'-methoxy (**22e**) - A solution of (**22d**) (348 mg, 1.5 mmol) in dry dimethylformamide (10 ml) was reduced with sodiumborohydride (114 mg, 3 mmol) at 25 °C for 3h. The solution was poured into water and extracted with ethyl acetate. The extract was dried and evaporated to dryness. Chromatography on silica gel with chloroform:methanol (9.5:0.5) as eluant yielded (**22d**) (252 mg, 85%), m.p. 80-82 °C (Found: C, 54.50, H, 7.08; N, 14.10. $C_9H_{14}N_2O_3$ C, 54.52, H, 7.12; N, 14.14 %); ν_{max} ($CHCl_3$) 1710 (CO) and 1670 cm^{-1} (α,β-unsaturated ketone); δ_H (300 MHz; $CDCl_3$) 2.78 (2H, m, 1'-H), 3.34 (3H, s, NCH_3), 3.40 (3H, s, NCH_3), 3.43 (3H, s, OCH_3), 3.65 (2H, m, 2'-H) and 5.66 (1H, s, 5-H); m/z 198 (M^+, 22%).

General procedure for the synthesis of *6-(1,3-Dimethyl-2,4-dioxopyrimidil)ethan-2'-ethylamino-1'-ol* (**23a**), *6-(1,3-Dimethyl-2,4-dioxopyrimidil)ethan-2'-ethanolamino-1'-ol* (**23b**) and *6-(1,3-Dimethyl-2,4-dioxopyrimidil)ethan-2'-diethylamino-1'-ol* (**23c**) - The amine (2.2 mmol) was added to a solution of (**3**) (200 mg, 1.1 mmol) in dry methanol (15 ml) at reflux until complete disappearance of substrate. The solution was evaporated to dryness.

Chromatography on silica gel with chloroform as eluant yielded the products: (**23a**) (187 mg, 75%), m.p. 121-122 °C (Found: C, 52.90, H, 7.50; N, 18.48. $C_{10}H_{17}N_3O_3$ requires C, 52.86, H, 7.54; N, 18.50%); ν_{max} ($CHCl_3$) 3400 (OH), 3300 (NH), 1710 (CO) and 1670 cm^{-1} (α,β-unsaturated ketone); δ_H (300 MHz; $CDCl_3$) 1.0 (3H, m, CH_3), 2.80 (4H, m, NCH_2), 3.10 (3H, s, NCH_3), 3.15 (3H, s, NCH_3), 4.30 (1H, m, 1'-H) and 5.80 (1H, s, 5-H); m/z 227 (M^+, 43%). (**23b**) (214 mg, 80%), oil; ν_{max} ($CHCl_3$) 1710 (CO) and 1670 cm^{-1} (α,β-unsaturared ketone); δ_H (300 MHz; $CDCl_3$) 2.80 (4H, m, NCH_2), 3.30 (3H, s, NCH_3), 3.45 (3H, s, NCH_3), 3.70 (2H, m, OCH_2), 4.30 (1H, m, 1'-H) and 6.0 (1H s, 5-H); m/z 243 (M^+, 10%). (**23c**) (196 mg, 70%), oil; ν_{max} ($CHCl_3$) 1720 (CO) and 1670 cm^{-1} (α,β-unsaturated ketone); δ_H (300 MHz; $CDCl_3$) 1.10 (6H, m, CH_3), 2.45 (4H, m, NCH_2), 2.50 (2H, m, NCH_2), 3.30 (3H, s, NCH_3), 3.45 (3H, s, NCH_3), 4.55 (1H, m, 1'-H) and 5.95 (1H, s, 5-H); m/z 255 (M^+, 5%).

6-(1,3-Dimethyl-2,4-dioxopyrimidil)pentan-5'-en-1'-ol (**24**) - *Allylmagnesium bromide* (1.5 ml, 1.0 N diethyl ether solution) was added dropwise to a solution of (**3**) (200 mg, 1.1 mmol) in dry tetrahydrofuran (10 ml) at -20 °C for 1h. The solution was poured into water and extracted with ethyl acetate. The extract was dried and evaporated to dryness. Chromatography on silica gel with chloroform:methanol (9.7:0.3) as eluant yielded (**24**) (172 mg, 70%), oil, ν_{max} ($CHCl_3$) 1710 (CO), 1670 (α,β-unsaturated ketone), and 1580 (C=C) cm^{-1}; δ_H (300 MHz; $CDCl_3$) 1.0 (2H, m, 2'-H), 2.72 (2H, m, 3'-H), 2.82 (3H, s, NCH_3), 3.04 (3H, s, NCH_3), 4.20 (1H, m, 1'-H), 5.20 (2H, m, 5'-H), 5.80 (1H, m, 4'-H) and 6.20 (1H, s, 5-H); m/z 224 (M^+, 22%).

6-(1,3-Dimethyl-2,4-dioxopyrimidil)ethan-2'-azido-1'-ol (**25**) - *Sodium azide* (143 mg, 2.2 mmol) was added to a solution of (**3**) (200 mg, 1.1 mmol) in dimethylformamide (20 ml) at 25 °C for 5 h. The solution was poured into water and extracted with ethylacetate. The extract was dried and evaporated to dryness. Chromatography on silica gel with chloroform:methanol (9.0:1.0) as eluant yielded (**25**) (205 mg, 83%), oil; ν_{max} ($CHCl_3$) 2210 (N_3), 1710 (CO) and 1680 cm^{-1} (α,β-unsaturated ketone); δ_H (300 MHz;$CDCl_3$) 3.25 (3H, s, NCH_3), 3.45 (3H, s, NCH_3), 3.55 (2H, m, 2'-H), 4.80 (1H, m, 1'-H) and 6.80 (1H, s, 5-H); m/z 225 (M^+, 30%).

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