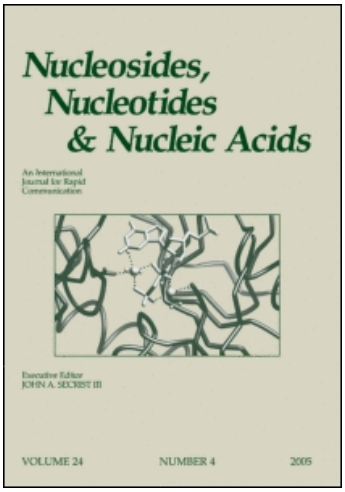

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CATALYTIC OSMYLATION AND ANTIVIRAL ACTIVITY OF SOME CARBOCYCLIC 5-SUBSTITUTED URIDINE AND CYTIDINE ANALOGUES

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Abstract: Some carbocyclic uridines and cytidines have been dihydroxylated in an osmium catalyzed reaction. Besides the nucleoside analogues, the *anti* forms, the diastereomeric *syn* forms were formed. These could be separated and tested with regard to antiviral activity.

For some time our interest has been focused on compounds with antiviral activity.[1-3] In connection with this work we have also studied some carbocyclic nucleoside analogues, as even these are known to have antiviral activity[4-7] and furthermore they are not susceptible to degradation *in vivo* by nucleosidases and phosphorylases.[8] In our previous work a palladium-mediated reaction between 5-(2'-thienyl)uracil and cyclopentadiene monoepoxide gave (±)-*cis*-1-(4'-hydroxy-2'-cyclopentenyl)-5-(2"-thienyl)-uracil, which was oxidized to (±)-*cis*-1-(2',3'-*trans*-dihydroxycyclopentyl)-5-(2"-thienyl)uracil.[9] Some carboxylic uridines and cytidines have been prepared in a palladium-catalyzed reaction between 5-substituted uracils and cytosines and diacetoxymethylcyclopentene, prepared in a Prins reaction.[10] In the present work the compounds obtained in this manner, carbocyclic (±)-5-(heteroaryl)-2',3'-didehydro-2',3'-dideoxy uridines and -cytidines have been studied with regard to their catalytic osmylation.

Results

The use of *N*-methylmorpholine *N*-oxide as a secondary oxidant for the catalytic *cis*-dihydroxylation of alkenes has previously been reported by VanRheenen *et al.*[11] In their case a mixture of water, acetone and *tert*-butanol was used as solvent for the reaction and in the work-up procedure ethyl acetate was used for extraction. As carbocyclic

nucleosides can not be extracted with organic solvents, this work-up procedure has been modified by Deardorff *et al.* in their effort to prepare *Neplanocin A*.[12]

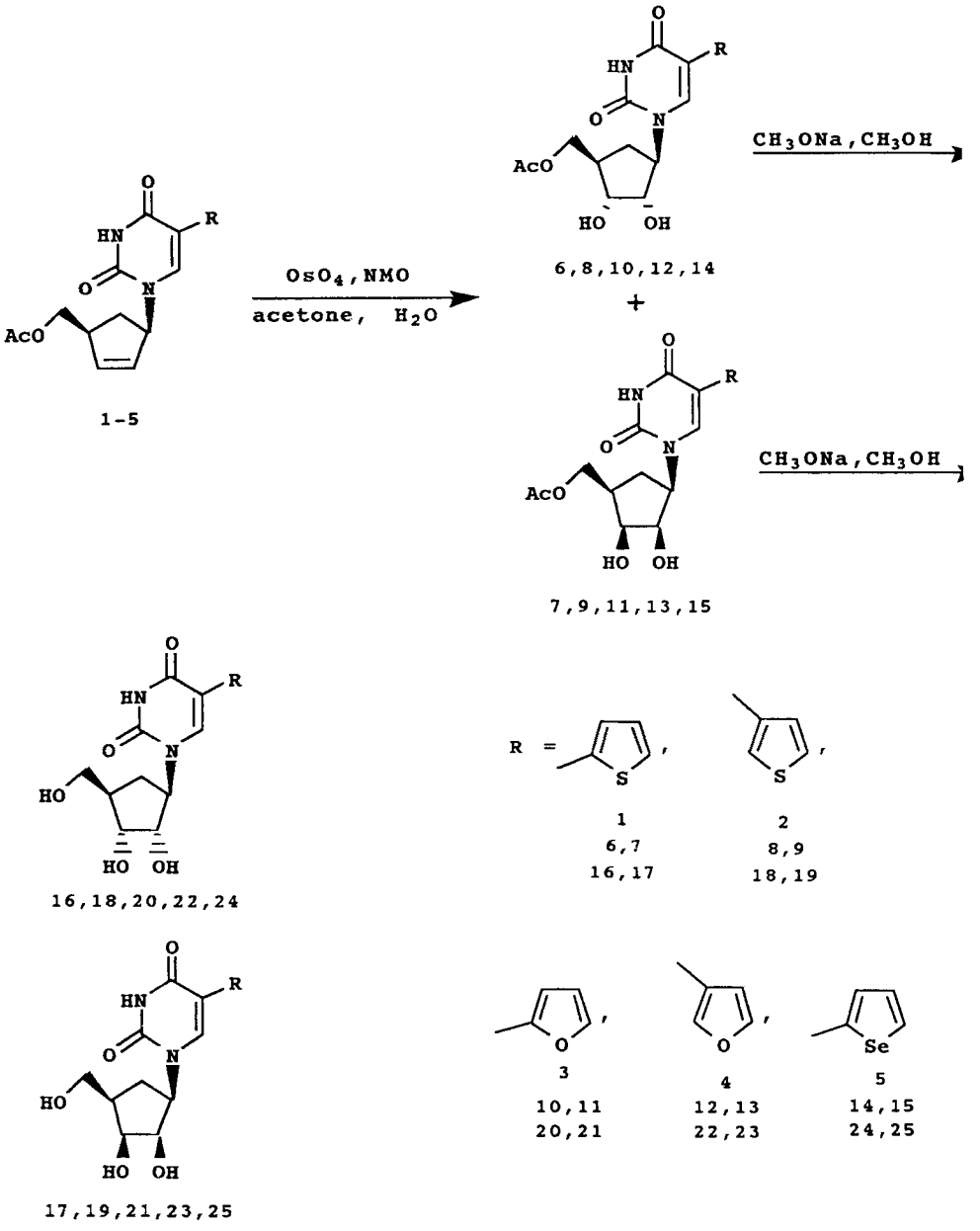
As solvent for the reactions we used a mixture of water and acetone (1:10), also used by Roberts *et al.*[13] Concerning the proportions for substrate, *N*-methylmorpholine *N*-oxide (NMO) and osmium tetroxide, those used by Lindell *et al.*[14] gave reasonable reaction times at room temperature, about 24 hours for the acetoxy derivatives of carbocyclic uridines (Scheme 1). A common feature for the dihydroxylated compounds is that the major diastereomer is less polar and the minor diastereomer is more polar. The proportions were determined by ^{1}H NMR by integration of the signals due to the protons in the 6-position prior to chromatography. The structure of the major and minor diastereomers was determined by NOE difference spectroscopy and the major form was identified as *syn* and the minor as *anti* form.

By optimizing the reaction conditions we found that the acetyl protecting group in the 5'-position did not influence the proportions between the two diastereomers. Similar results were found in the catalytic osmylation of carbocyclic *cis*- 2',3'-didehydro-2',3'-dideoxyadenosine[13] and its 5'-acetyl derivative.[14] In both cases *syn/anti* mixtures (1:1) were obtained, which were not separated.

In the dihydroxylation of **1-5** the less polar form could be separated by repeated careful chromatography, while the isolation of the other form demanded further purification by HPLC, as there are impurities formed with Rf values very close to those of the more polar form. These impurities can be due to hydroxylation of the 5-6 double bond in the pyrimidinone ring, a reaction previously observed.[15] The reaction was quenched by addition of solid sodium bisulphite and neutralized by acetic acid according to Norin *et al.*[16] The proportions between the two forms are given in Table I. By deprotection with sodium metoxide in methanol,[17] compounds **16-25** were obtained (Scheme 1).

When the substrate was carbocyclic 5-(2"-thienyl)-2',3'-didehydro-2',3'-dideoxy-5'-acetoxycytidine (**26**) (Scheme 2), the reaction time could be reduced to seven hours as only half of the solvent volume was needed due to the higher solubility of **26** compared to compounds **1-5**. It is known that the reaction time is dependent upon the concentration of osmium tetroxide.[12,18] Also in this case two diastere§omers, **27** and **28**, were formed in a *anti/syn* ratio of 37:63.

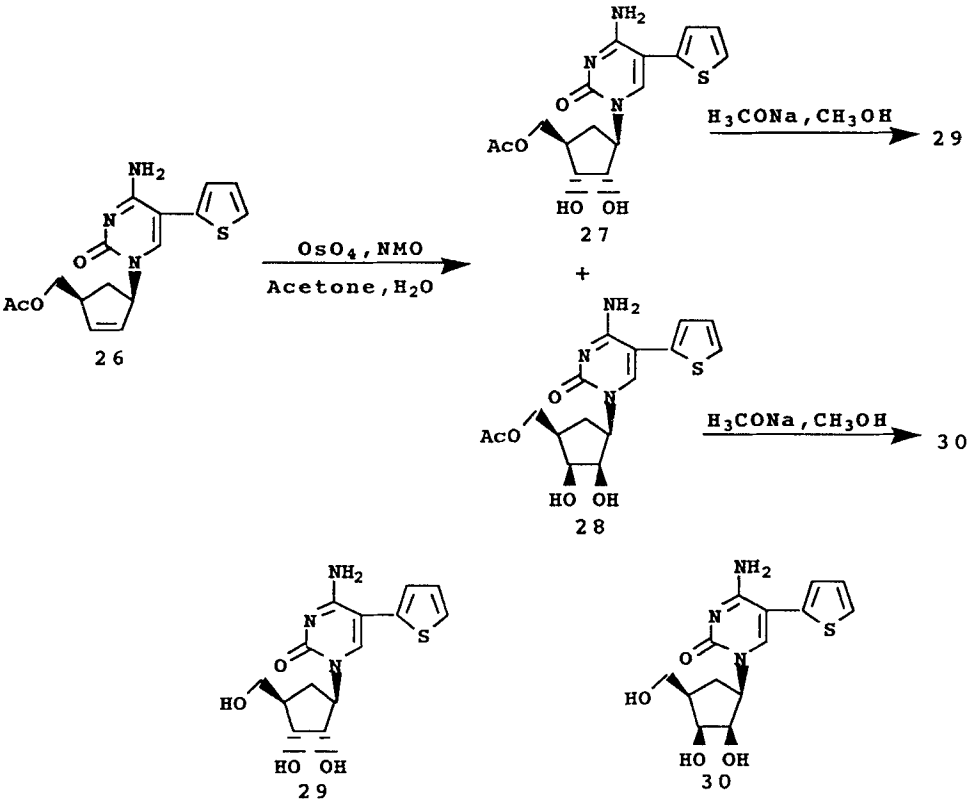
The unprotected compound **31** was hydroxylated under the conditions used by VanRheenen *et al.*, with addition of *tert*-butanol,[11] and the proportions used by Norin *et al* .[16] (scheme 3). However, a large amount of solvent and heating was needed to overcome the solubility problems. Furthermore, **18** and **19** could not be separated by column chromatography, only by HPLC.



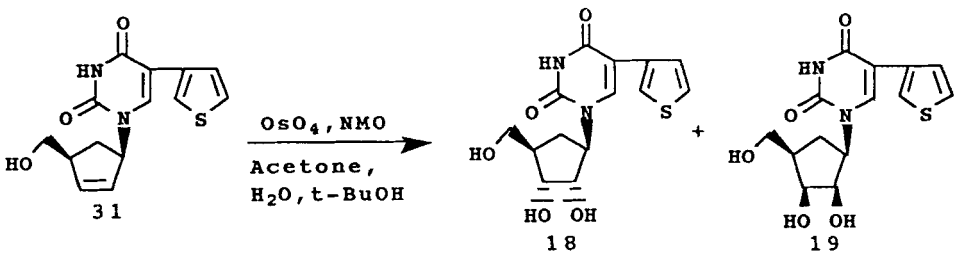
Scheme 1

Table I. Diastereoselectivity of dihydroxylation of carbocyclic (±)-*cis*-5-(2"-heteroaryl)-2′,3′didehydro-2',3'-dideoxy-5′-acetoxyuridines (**1-5**).

Compound	*Anti*	%	*Syn*	%
1	**6**	28	**7**	72
2	**8**	34	**9**	66
3	**10**	37	**11**	63
4	**12**	31	**13**	69
5	**14**	36	**15**	64



Scheme 2



Scheme 3

NMR structure elucidation

In this work the carbocyclic analogues will be named as previously, with the carbon replacing the furan ring oxygen being designated as C6'.[9] However, there are some changes regarding the nomenclature for the geminal protons at C6'. In our previous work, in which the starting materials **1** - **5** are described, we used the convention applied for cyclopentene derivatives, where these protons were arbitrarily designated as H6'α and H6'β as a function of their shift difference.[19,20] In the nucleoside analogues, α and β are used for the two sides of the cyclopentane ring, consequently the downfield absorption in the ^{1}H NMR spectra will be due to H6'α and the upfield signal due to H6'β. This convention has been used by Biggadike *et al.* [21-23] and Shealy *et al.*[24]

As described above, the hydroxylation of compounds **1** - **5** and **26** gave two forms. The protons in the ^{1}H-NMR spectra were assigned by ^{1}H-^{1}H homonuclear shift correlation 2D-NMR (COSY). It is interesting to note that two protons in the 6'-position have an internal shift of 0.48 ppm and 0.52 ppm for the less and more polar form, respectively, while in **1** this shift is 1.23 ppm. The reason for this is that in **1**, the anisotropic effect of the double bond and the shielding effect of the substituents in the 1'- and 4'-positions influence the shift for H6'β. After dihydroxylation the shift difference is only due to the effects of the α-substituents, the *syn* upfield rule.[25,26]

A COSY experiment of the less polar component in the hydroxylation of **4** showed that the shifts of the two methylene protons in the 5'-position are identical. Similar observations are made in the ^{1}H NMR spectrum of aristeromycin, the carbocyclic analogue of adenosine, in deuteriated dimethylsulfoxide.[27] By comparing the carbocyclic cytidine derivative, carbodine,[24] with the more polar diastereomer formed in the dihydroxylation of **26** the δ-values for H1 fall in the same region.

In order to determine the configuration of the carbocyclic ring, a ^{1}H-Nuclear Overhauser effect (NOE) study of the products obtained in the hydroxylations of **1** and **26** was undertaken. For **1-5** and **26** there are a *cis* relationship between H1' and H4',[10] which did not change by the hydroxylation of the double bond.

The signals from H1´, H2´ and H3´ in the ^{1}H NMR spectra of these four compounds do not overlap each other, while the H4´ signals have the same shift as those of H6´α . This multiplet signal was only irradiated for the more polar diastereomer in the hydroxylation of **1**. The irradiation of the H6´β signal, at higher field than the H6´α signal was only done for the two less polar derivatives, as these signals were rather narrow. For three of the four derivatives the internal shift due to H2´and H3´ is so small, that the NOE experiment had to be performed at 500 MHz.

Irradiation of the band due to H1´ for the less polar uridine compound gave enhancement of both the H2´ and the H6´α signal, 14 % and 11 %, respectively, consequently these protons are *cis* related. Even a small enhancement of the H6 signal was observed, 3 %. When the H2´ band was irradiated, the bands due to both H1´ and H3´ were enhanced, 13 % and 12 % respectively, showing their *cis* relationship. Irradiation of the H3´ signal enhanced both the band due to H2´ (10 %) and that due to H4´ (9 %) indicating that these protons also are *cis* related. Thus the less polar component in the dihydroxylation of **1** is the *syn* isomer, **7** (Fig. I). Irradiation of H6´β signal gave further information about the geometry of **7**, a strong enhancement of the H6 peak was observed (18 %), which means that the orientation of the uracil ring at the glycosidic bond is such that H6 is in a close proximity to H6´β. This is probably due to a hydrogen bond between the hydroxy group in the 2'-position and the 2-carbonyl group in the uracil ring.

Analogously the NOE studies for the other three compounds could be analysed. The unambiguous assignment of *anti* configuration for the more polar component in the dihydroxylation of **1** (**6** in Fig. I) was established by irradiation of the H1´ signal, which did not give any effect on the H2´ band, in accordance with their *trans* relationship. Irradiation of the H2´ band enhanced the signals due to H6 (7 %) and H3´(14 %), showing the *cis* orientation between H2' and H3'. Irradiation of the H3´ signal did not effect the H4' band in agreement with a *trans* relationship between these protons.

Once the configurations are established for compounds, **6**, **7**, **27** and **28** the structure assignment for the other hydroxylated derivatives could be established due to the similarity of their ^{1}H NMR spectra. Furthermore, the configuration does not change by deprotection. The interpretion of the ^{1}H NMR spectra of compounds **8-25**, **29** and **30** are given in the experimental part. In all protected compounds of the less polar forms, the shifts for H6 are at lower field, 8.3-8.6 ppm, compared with those of the more polar

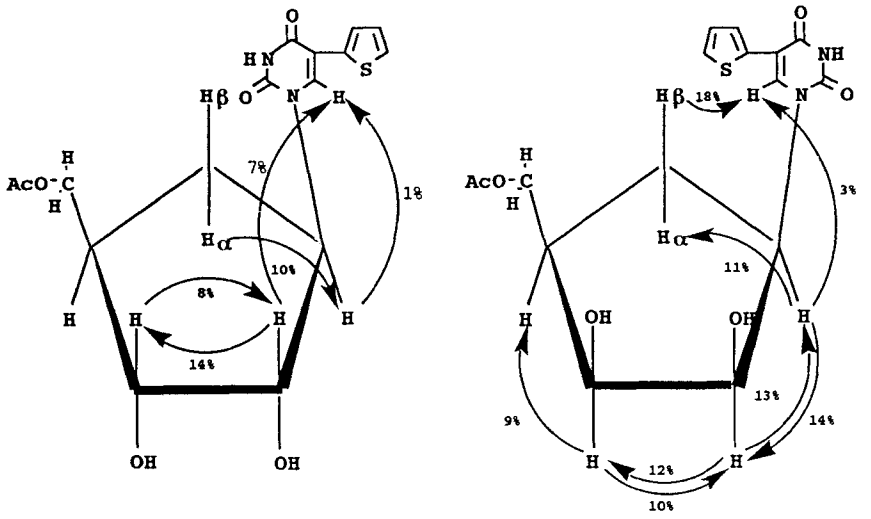


Figure I. Results from ^{1}H-Nuclear Overhauser effect experiments of carbocyclic (±)-5-(2''-thienyl)-5'-acetoxyuridine (300 Hz) and its *syn* isomer (500 MHz).

forms, 7.8-8.0 ppm. For each pair the internal shift is about 0.5 ppm. The pattern for the H1' signals in the less polar forms are quartets, as the three coupling constants are about 8.8 Hz. The corresponding absorptions in the other diastereomers appear as multiplets. The signal for H2´ is in all protected compounds downfield compared with that for H3´, in contrast to compounds **1-5** and **26**, where the relation is opposite.[10] The signals for H4´and H6´α overlap each other in all protected forms. In the deprotected derivatives the shifts for H6 and H1´ change very little compared with the protected ones, while the shift difference between H2´and H3´ diminishes and is less than 0.5 ppm. In all unprotected *syn* forms the shifts of H2' and H3' are very close when deuteriated methanol was used as solvent. However, when the solvent was changed to deuteriated dimethylsulfoxide for **21** the signals due to the two protons were shifted apart allowing measurement of the coupling constants. The shifts for H6´α are shifted upfield and apart from those of H4´ with about 0.1-0.2 ppm. Moreover, by deprotection all more polar forms show one band for the two protons in the 5'-position. The signals due to H1´ are well defined in narrow intervals for the two diasteromers at about 5.1 ppm for the *syn*, forms and about 4.8 ppm for the *anti* forms. However, these bands could not be used for integration in order to determine the proportions between the two forms, as the signal due to water formed in the exchange between the hydroxy groups and deuteriated methanol sometimes also appeared in the region of 4.8 ppm.

Influence of coordination on the syn/anti ratio

Generally, the *cis* catalytic osmium tetroxide dihydroxylation takes place from the less hindered side of the double bond in agreement with the empirical rule formulated by Kishi *et al.*[28] That was also the case in our previous work, concerning carbocyclic nor nucleosides, the dihydroxylation took place exclusively from the less hindered side giving only the *anti* diastereomers.[9] However, in the present work the major component in this reaction is the *syn* isomer. A similar stereochemical result was reported by Kon and Isoe in their study of bicyclo[3.3.0]octenol.[29] They suggested that a complex between the hydroxyl and the osmium tetroxide directed the dihydroxylation to the more hindered side, giving a ratio between the *syn* and *anti* forms equal to 86:14. This result was also suported by a steric factor; the presence of the methyl substituents on the convex face hindered the approach of osmium tetroxide to that face, forcing the dihydroxylation to occur on the concave face of the bicyclic system. This compound may be compared with the cytosine derivative, **26**, since both systems contain the assumed directing oxygen located β to the double bond. The reversible association of the olefinic substrate with osmium tetroxide, through complexation prior to the osmate ester formation, would provide an explanation favouring the formation of the *syn*-diastereomer.

Osmium tetroxide reacts with an alkene to give an osmium(IV) ester intermediate which can be hydrolyzed to give the corresponding *cis*-diol.[30] Two mechanistic proposals have been advanced for the osmylation, a classical concerted [3+2] cycloaddition[31-33] and a more recent alternative process involving a stepwise [2+2] like insertion followed by rearrangement.[34-36]

The model proposed by us for the directed osmate ester formation follows a [2+2] cycloaddition mechanism, in which the osmium is brought in close proximity to the double bond, favouring the direct attack of the alkene on the osmium atom. The approach of the osmium tetroxide on the congested concave face is possible due to the directing groups present in the molecule, both the oxygen in the 5'-position and the sulfur atom of the thiophene ring may coordinate to the osmium atom. Hence in this model, **26** acts as a bidentate ligand. The osmate ester complex coordinated to the bidante substrate **26** is octahedral.[34]

Inhibition of viral replication in cell-culture assays

Compounds **6-25**, **27-30** were tested in cell-culture assays for the effect on multiplication of influenza A virus, human immunodeficiency virus 1 (HIV-1), herpes simplex

virus-1 (HSV-1) and cytomegalus virus (CMV). All compounds were inactive against influenza A, HIV-1 and CMV at the highest concentration 100 μg/ml. In the HSV-1 assay, a few compounds exhibited weak inhibitory activities with IC_{50} values in the range 5-75 μg/ml. Best was the unprotected *syn* 2-selenienyluridine derivative (**25**), but also the corresponding *anti* 2-selenienyl (**24**) and *anti* 2-thienyl (**16**) compounds showed some activity.

Some carbocyclic nucleoside analogue have previously been described as inhibitors of herpes simplex virus. Carbocyclic 2'-deoxy-2'-β-fluoroguanosine[37,38] inhibits both HSV-1 and HVS-2, being about 100 times more active than acyclovir (ACV), both *in vitro* and *in vivo*. Also the carbocyclic 2'-deoxy-6'-α-fluoroguanosine analogue exihibited comparable activity to that of ACV *in vitro*, and was more active *in vivo*.[23] The corresponding 2'-α-and 6'-β- fluoro analogs were much less active.[38] The 2'-β-fluoro compound has been shown to be a substrate for thymidine kinase.[37] Carbocyclic 2'-deoxyguanosine inhibits HSV-1 and is phosphorylated to a triphosphate in HSV-1 infected cells.[39] In addition this compound is also a potent inhibitor of hepatitis B virus.[40]

For pyrimidine carbocyclic nucleoside analogs only activities against type 1 of HSV have been reported. This holds for carbocyclic 5-(2-bromovinyl)-2'-deoxyuridine[41-43] and 5-iodo-2'-deoxyuridine.[41,42] Both of them have been shown to be substrates for HSV thymidine kinase.[41] Also the carbocyclic analogue of 5-(2-bromovinyl)-2'-deoxycytidine[43] and 5-iodo-2'-deoxy-2'-β-fluorouridine[44] are modest inhibitors of HSV-1.

Carbocyclic 9-β-D-arabinofuranosyladenine is active against HSV *in vitro* and *in vivo*.[45] The activity is not dependent on phosphorylation by a viral thymidine kinase.[45]

The present 5-heteroaryl substituted pyrimidine carbocyclic compounds have not been studied with respect to their interaction with viral or cellular kinases or the biological properties of the triphosphates, yet it is worth noting that several 5-heteroaryl substituted pyrimidine 2'-deoxyribose nucleoside analogues are very efficient substrates of thymidine kinase 2 and are phosphorylated to monophosphates.[46]

Experimental

The ^1H NMR spectra were recorded on a Varian XL-300 spectrometer. NOE experiments were recorded on a Bruker ARX-500 spectrometer. Deuteriated methanol was used as solvent for all substances. High resolution mass spectra were recorded on a JEOL JMS-SX 102 spectrometer using EI technique.

All glassware was oven dried, quickly assembled, flushed with dry nitrogen and equipped with tight-fitting septa. The reactions were carried out under nitrogen.

The reaction assembly consisted of a 25 ml two-necked round-bottomed flask containing a magnetic bar and equipped with a reflux condenser. All reactions were monitored by thin layer chromatography (TLC) on aluminum silica gel plates, and visualization was accomplished with UV light.

N-methylmorpholine *N*-oxide monohydrate (97 %) and osmium tetroxide were purchased from Aldrich. Acetone, methanol and 2-propanol were purchased in analytical grade and used without other purification. Dichlorometane and chloroform, used in chromatography, were distilled over 4Å molecular sieves prior to use. The column used for HPLC was Polygosil RP C18 (500x50 mm) and acetonitrile/water was used as eluent.

Inhibition of influenza A, HIV-1 and HSV-1 multiplication were performed as XTT assays in MDCK cells (Victoria 3/75 strain), MT4 cells (human T cell line) and vero cells respectively. In the CMV assay reduction in cytopathic effect caused by the virus was determined in MRC-5 cells (human embryonic cells). The assays were performed as previously described.[10]

General procedure for preparation of carbocyclic (±)-5-(heteroaryl)-5'-acetoxyuridines.

A flask was charged with the carbocyclic (±)-*cis*-5-(heteroaryl)-2',3'-didehydro-2',3'-dideoxy-5'-acetoxyuridines (**1-5**),[10] aqueous acetone (1:10, v/v) and *N*-methylmorpholine *N*-oxide hydrate. Under stirring osmium tetroxide was added. Osmium tetroxide was used as stock water solution (10 mg/ml) and kept at -20 °C. The colour of the reaction mixture changed during the reaction from light yellow to light purple and finally to burgundy red. The reaction mixture was stirred at room temperature. When the starting material was almost consumed the reaction was quenched by the addition of 50 mg of solid sodium hydrosulphite. After 15-20 min of stirring, the suspension became discoloured and was neutralized with 1 % acetic acid in methanol. After dilution with 4 ml chloroform/methanol (9:1) and drying over magnesium sulphate, the resulting suspension was *vacuo* filtered through a pad of 2.0 g silica gel. The pad was washed three times with 20 ml of chloroform/methanol (9:1). The combined filtrates were concentrated under reduced presure and the residue separated into *anti* and *syn* form by repeated column chromatography on Merk silica gel and dichloromethane/2-propanol (9:1) as eluent. The separation was followed by TLC using dichloromethane/methanol (9:1) as eluent. The less polar *syn* form was obtained pure and the *anti* form was further purified by HPLC.

*Carbocyclic (±)-5-(2"-thienyl)-5'-acetoxyuridine (**6**)*

From 100 mg (0.30 mmol) of **1**, 54 mg (0.39 mmol) of NMO-hydrat, 4.5 ml of aqueous acetone (1:10, v/v) and 382 µl (0.015 mmol) of osmium tetroxide, 13 mg (12 %) of **6** was obtained. The reaction time was 21 h. ^{1}H NMR: δ 7.98 (s, 1H, H6), 7.45 (dd, 1H, H3", J = 3.7, 1.2 Hz), 7.38 (dd, 1H, H5", J = 5.2, 1.2 Hz), 7.04 (dd, 1H, H4", J = 5.2, 3.7 Hz), 4.60 (m, 1H, H1'), 4.40 (dd, 1H, H2', J = 8.3, 5.8 Hz), 4.22 (dd, 1H, 5'CH, J = 11.1, 6.4 Hz), 4.14 (dd, 1H, 5'CH, J = 11.1, 6.4 Hz), 3.97 (dd, 1H, H3', J = 5.8, 3.8 Hz), 2.27 (m, 2H, H4', H6'α), 2.05 (s, 3H, CH_3), 1.75 (s, 1H, H6'β). HRMS calcd. for $C_{16}H_{18}O_6N_2S$: 366.0886. Found: 366.0887.

*Syn isomer of **6** (**7**)*

This compound was obtained as a white solid in a yield of 42 mg (38 %). ^{1}H NMR (500 MHz): δ 8.52 (s, 1H, H6), 7.39 (dd, 1H, H3", J = 3.7, 1.2 Hz), 7.32 (dd, 1H, H5", J = 5.2, 1.2 Hz), 7.03 (dd, 1H, H4", J = 5.2, 3.7 Hz), 5.24 (ddd, 1H, H1', J = 8.8, 8.8, 8.8 Hz), 4.34 (dd, 1H, 5'CH, J = 10.8, 7.6 Hz), 4.25 (dd,1H, H2' J = 8.7, 4.0 Hz), 4.21 (dd, 1H, 5'CH, J = 10.8, 6.5 Hz), 4.13 (dd, 1H, H3', J = 4.0, 4.0 Hz), 2.26 (m, 2H, H4', H6'α), 2.04 (s, 3H, CH_3), 1.78 (m, 1H, H6'β). HRMS calcd. for $C_{16}H_{18}O_6N_2S$: 366.0886. Found: 366.0884.

*Carbocyclic (±)-5-(3"-thienyl)-5'-acetoxyuridine (**8**)*

This compound was obtained from **2** in the same scale as described for **6**. The amount of aqueous acetone was reduced to 3.0 ml and the reaction time 15 h. The yield was 17 mg (15 %). ^{1}H NMR: δ 7.91 (s, 1H, H6), 7.87 (dd, 1H, H3", J = 1.7, 2.6 Hz), 7.43 (m, 2H, H4", H5"), 4.60 (m, 1H, H1'), 4.39 (dd, 1H, H2', J = 5.7, 8.3 Hz), 4.21 (dd, 1H, 5'CH, J = 11.0, 6.4 Hz), 4.13 (dd, 1H, 5'CH, J = 11.0, 6.1 Hz), 3.95 (dd, 1H, H3', J = 5.7, 4.0 Hz), 2.28 (m, 2H, H4', H6'α), 2.05 (s, 3H, CH_3), 1.75 (m, 1H, H6'β). HRMS calcd. for $C_{16}H_{18}O_6N_2S$: 366.0886. Found: 366.0895.

*Syn isomer of **8** (**9**)*

This compound was isolated in a yield of 52 mg (47 %). ^{1}H NMR: δ 8.44 (s, 1H, H6), 7.86 (dd, 1H, H2", J = 2.5, 1.8 Hz), 7.39 ((m, 2H, H4", H5"), 5.24 (ddd, 1H, H1', J = 8.8, 8.8, 8.8), 4.33 (dd, 1H, 5'CH, J = 10.9, 7.7 Hz), 4.27 (dd, 1H, H2', J = 8.9, 4.1 Hz), 4.21 (dd, 1H, 5'CH, J = 10.9, 6.5 Hz), 4.14 (dd, 1H, H3', J = 3.9, 3.9 Hz), 2.25 (m, 2H, H4', H6'α), 2.05 (s, 3H, CH_3), 1.77 (m, 1H, H6'β). HRMS calcd. for $C_{16}H_{18}O_6N_2S$: 366.0886. Found: 366.0879.

*Carbocyclic (±) 5-(2"-furyl)-5'-acetoxyuridine (**10**)*

From 100 mg (0.32 mmol) of **3**, 59 mg (0.42 mmol) of NMO-hydrat and 407 µl (0.016 mmol) of osmium tetroxide in 3.0 ml aqueous acetone, 13 mg (12 %) of **10** was obtained after 23 h. ^{1}H NMR: δ 7.97 (s, 1H, H6), 7.48 (dd, 1H, H5", J = 1.9, 0.7 Hz),

6.93 (dd, 1H, H3", J = 3.4, 1.9 Hz), 6.48 (dd, 1H, H4", J = 3.4, 1.9 Hz), 4.69 (m, 1H, H1'),4.36 (dd, 1H, H2',J = 8.4 5.7), 4.21 (dd, 1H, 5'CH, J = 11.1, 6.0), 4.14 (dd, 1H, 5'CH, J = 11.1, 5.7), 3.96 (dd, 1H, H3', J = 5.7, 3.5), 2.30 (m, 2H, H6'α, H4'), 2.03 (s, 3H, CH_3), 1.71 (m, 1H, H6'β). HRMS calcd for $C_{16}H_{18}O_7N_2$: 350.1114. Found: 350.1114.

*Syn isomer of **10** (**11**)*

This compound was isolated in a yield of 43 mg (38 %). ^{1}H NMR: δ 8.46 (s, 1H, H6), 7.46 (dd, 1H, H5", J = 1.9, 0.7 Hz), 6.88 (dd, 1H, H3", J = 3.3, 0.7 Hz), 6.46 (dd, 1H, H4", J = 3.3, 1.9 Hz), 5.22 (ddd, 1H, H1', J = 8.7, 8.7, 8.7 Hz), 4.36 (dd, 1H, 5'CH, J = 11.0, 3.4 Hz), 4.24 (dd, 1H, H2', J = 8.7, 4.3 Hz), 4.14 (dd, 1H, H3', J = 4.3, 4.3 Hz), 2.25 (m, 2H, H4', H6'α), 2.05 (s, 3H, CH_3), 1.83 (m, 1H, H6'β). HRMS calcd for $C_{16}H_{18}O_7N_2$: 350.1114. Found: 350.1110.

*Carbocyclic (±) 5-(3"-furyl)-5'-acetoxyuridine (**12**)*

From 100 mg (0.32 mmol) of **4** 14 mg (12 %) of the title compound was obtained under de same conditions as described for **10**. ^{1}H NMR: δ 7.91 (s, 1H, H6), 7.87 (dd, 1H, H3", J = 2.6, 1.7 Hz), 7.43 (m, 2H, H4", H5"), 4.60 (m, 1H, H1'), 4.39 (dd, 1H, H2', J = 6.4, 11.0 Hz), 4.13 (dd, 1H, 5'CH, J = 6.1, 11.0 Hz), 3.95 (dd, 1H, H3', J = 4.0, 5.7 Hz), 2.28 (m, 2H, H6'α, H4'), 2.05 (s, 3H, CH_3),1.75 (m, 1H, H6'β). HRMS calcd for $C_{16}H_{18}O_7N_2$: 350.1114. Found: 350.1114.

*Syn isomer of **12** (**13**)*

This compound was isolated in a yield of 50 mg (45 %). ^{1}H NMR: δ 8.43 (s, 1H, H6), 8.08 (dd, 1H, H2", J = 1.7, 0.8 Hz), 7.49 (dd, 1H, H5", J = 1.9, 1.7 Hz), 6.69 (dd, 1H, H4", J = 1.9, 0.8 Hz), 5.23 (ddd, 1H, H1', J = 8.8, 8.8, 8.8 Hz), 4.34 (dd, 1H, 5'CH, J =10.9, 7.6 Hz), 4.26 (dd, 1H, H2', J = 8.8, 3.9 Hz), 4.21 (dd, 1H, 5'CH, J = 10.9, 6.5 Hz), 4.14 (dd, 1H, H3', J = 3.9, 3.9 Hz), 2.25 (m, 2H, H4',H6'α), 2.05 (s, 3H, CH_3), 1.77 (m, 1H, H6'β). HRMS calcd for $C_{16}H_{18}O_7N_2$: 350.1114. Found: 350.1111.

*Carbocyclic (±) 5-(2"-selenienyl)-5'-acetoxyuridine (**14**)*

From 100 mg (0.26 mmol) of **5**, 47 mg (0.34 mmol) of NMO-hydrat and 330 µl (0.013 mmol) of osmium tetroxide in 4.0 ml of aqueous acetone and a reaction time of 18 h, 6.0 mg (6 %) of **14** was obtained. ^{1}H NMR: δ 8.12 (s, 1H, H6), 8.05 (dd, 1H, H5", J = 5.7, 1.0 Hz), 7.64 (dd, 1H, H3", 5.7, 4.0 Hz), 7.28 (dd, 1H, H4", J = 5.7, 4.0 Hz), 4.62 (m, 1H, H1'), 4.42 (dd, 1H, H2', J = 8.3, 5.8 Hz), 4.22 (dd, 1H, 5'CH, J = 11.0, 6.4 Hz), 4.15 (dd, 1H, 5'CH, J = 11.0, 6.2 Hz), 3.97 (dd, 1H,J = 5.8, 3.9 Hz) ,2.30 (m, 2H, H4', H6'α), 2.06 (s, 3H, CH_3), 1.77 (m, 1H, H6'β). HRMS calcd for $C_{16}H_{18}O_6N_2Se$: 414.0330. Found: 414.0333.

*Syn isomer of **14** (**15**)*

This compound was obtained in a yield of 33 mg (31 %). ^{1}H NMR): δ 8.65 (s, 1H, H6), 8.01 (dd, 1H, H5", J = 5.7, 1.0 Hz), 7.56 (dd, 1H, H3", J = 3.9, 1.0 Hz), 7.27 (dd, 1H, H4", J = 5.7, 3.9 Hz), 5.26 (ddd, 1H, H1´, J = 8.7, 8.7, 8.7 Hz), 4.35 (dd, 1H, 5´CH, J = 10.9, 8.8), 4.27 (dd, 1H, H2´, J = 8.8, 3.9 Hz), 4.22 (dd, 1H, 5´CH, J = 10.9, 6.3 Hz), 4.15 (dd, 1H, H3´, J = 3.9, 3.9 Hz), 2.30 (m, 2H, H4´, H6´α), 2.06 (s, 3H, CH_3), 1.80 (m, 1H, H6´β). HRMS calcd for $C_{16}H_{18}O_6N_2Se$: 414.0330. Found: 414.0333.

*Carbocyclic (±) 5-(2"-thienyl)-5'-acetoxycytidine (**27**)*

From 200 mg (0.60 mmol) of **26**, 109 mg (0.78 mmol) of NMO-hydrate and 763 µl (0.030 mmol) of osmium tetroxide in 3.0 ml of aqueous acetone **27** was prepared according to the general procedure with some modifications. The reaction time was 7 h and the eluent used for TLC and separation of the two isomers (formed in a ratio of 63:37) was chloroform/methanol (9:1). After further purification by HPLC, 43 mg (20 %) of **27** was obtained as a white solid. ^{1}H NMR (500 MHz): δ 7.75 (s ,1H, H6), 7.55 (dd, 1H, H5", J = 4.1, 2.2 Hz), 7.18 (m, 2H, H3", H4"), 4.60 (m, 1H, H1´), 4.39 (dd, 1H, H2´, J = 7.7, 5.7 Hz), 4.01 (dd, 1H, H3´, J = 5.7, 4.4 Hz), 4.24 (dd, 1H, H5´, J = 11.2, 6.1 Hz), 4.17 (dd, 1H, H5´, J = 11.2, 5.9 Hz), 2.30 (m, 2H, H4´, H6´α), 2.07 (s, 3H, CH_3), 1.76 (m, 1H, H6´β). HRMS calcd. for $C_{16}H_{18}O_6N_2S$: 365.1045. Found: 365.1049.

*Syn isomer of **17** (**28**)*

This compound was obtained as a white solid after recrystallization from methanol in a yield of 112 mg (51 %). Alternatively both isomers can be isolated by HPLC using acetonitrile/water (20:80) as eluent. ^{1}H NMR (500 MHz): δ 8.06 (s, 1H, H6), 7.49 (dd, 1H, H5", J = 4.7, 1.7 Hz), 7.15 (m, 2H, H4", H3"), 5.22 (m, 1H, H1´), 4.31 (dd, 1H, 5´CH, J = 11.0, 7.6 Hz), 4.25 (dd, 1H, H2´, J = 8.1, 4.3 Hz), 4.16 (dd, 1H, 5´CH, J = 11.0, J = 6.4 Hz), 4.12 (dd, 1H, H3´, J = 4.3, 4.3 Hz), 2.25 (m, 2H', H4´, H6´α), 2.03 (s, 3H, CH_3), 1.78 (m, 1H, H6´β). HRMS calcd. for $C_{16}H_{18}O_6N_2S$: 365.1045. Found: 365.1042.

*General procedure for deprotection of the acetoxy derivatives **6 - 15**, **27** and **28**.*

The acetoxy derivatives were solved in 4.0 ml of 0.01M sodium methoxide solution, which was stirred at room temperature for 2 h. The reaction was followed by TLC and chloroform/methanol (8:2) was used as eluent. The reaction mixture was neutralized with DOWEX 50W (H^+ form) and the resin was removed by filtration and washed with methanol. The filtrate was evaporated and the residue purified by column chromatography using 2.0 g of silica 60 and chloroform/methanol (8:2) as eluent. The

product obtained was further purified by HPLC on a Polygosil RPC18 (500x10) column by using acetonitrile/water as eluent.

Carbocyclic (±) 5-(2"-thienyl)uridine (16)

From 10.0 mg (0.027 mmol) of **6**, 8.0 mg (91 %) of **16** was obtained. The proportions of the eluent for HPLC were (20:80). ^{1}H NMR: δ 8.12 (s, 1H, H6), 7.45 (dd, 1H, H3", J = 3.7, 1.2 Hz), 7.38 (dd, 1H, H5", J = 5.2, 1.2 Hz), 7.04 (dd, 1H, H4", J = 5.2, 3.7 Hz), 4.82 (m, 1H, H1'), 4.34 (dd, 1H, H2', J = 8.5, 5.5 Hz), 3.99 (dd, 1H, H3', J = 5.5, 3.3 Hz), 3.67 (d, 2H ,5'CH , 5.4 Hz), 2.29 (ddd, 1H, H6'α, J = 12.7, 12,7, 8.7 Hz), 2.16 (m, 1H, H4'), 1.72 (ddd, 1H, H6'β, J = 12.7, 10.2, 7.5 Hz). HRMS calcd. for $C_{14}H_{16}O_5N_2S$: 324.0780. Found: 324.0782.

*Syn isomer of **16** (17)*

From 10.0 mg (0.027 mmol) of **7**, 7.0 mg (80 %) of **17** was obtained. The proportions of the eluent for HPLC were (20:80). ^{1}H NMR: δ 8.52 (s, 1H, H6), 7.39 (dd, 1H, H3", J = 3.7, 1.2 Hz), 7.32 (dd, 1H, H5", J = 5.2, 1.2 Hz), 7.03 (dd, 1H, H4", J = 5.2, 3.7, H4"), 5.20 (ddd, 1H, H1', J = 8.8, 8.8, 8.8 Hz), 3.85 (dd, 1H, 5'CH, J = 10.8, 7.0 Hz) 3.70 (dd, 1H, 5'CH, J = 10.8, 6.0 Hz), 4.21 (m, 2H, H2', H3'), 2.26 (ddd, 1H, H6'α, 12.4, 8.8, 7.2 Hz), 2.21 (m, 1H, H4'), 1.78 (ddd, 1H, H6'β, J = 12.4, 12.4, 8.8 Hz). HRMS calcd. for $C_{14}H_{16}O_5N_2S$: 324.0780. Found: 324.0781.

Carbocyclic (±) 5-(3"-thienyl)uridine (18)

From 10.0 mg (0.027 mmol) of **8**, 7.0 mg (80 %) of **18** was obtained. The proportions of the eluent for HPLC were (30:70). ^{1}H NMR: δ 8.03 (s, 1H, H6), 7.88 (dd, 1H, H2", J = 2.6, 1.6 Hz), 7.43 (m, 2H, H3", H5"), 4.79 (m, 1H, H1'), 4.33 (dd, 1H, H2', J = 5.5, 8.8 Hz), 3.96 (dd, 1H, H3', J = 3.2, 5.5.Hz), 3.65 (d, 2H, 5'CH_2, J = 5.2 Hz), 2.27 (ddd, 1H, H6'α, J = 12.8, 8.7, 8.7 Hz), 2.14 (m, 1H, H4'), 1.69 (ddd, 1H, H6'β , J = 12.8, 10.4, 7.6 Hz). HRMS calcd. for $C_{14}H_{16}O_5N_2S$: 324.0780. Found: 324.0777.

*Syn isomer of **18** (19)*

From 10.0 mg (0.027 mmol) of **9**, 8.0 mg (91 %) of **19** was obtained. The proportions of the eluent for HPLC were (30:70). ^{1}H NMR: δ 8.43 (s, 1H, H6), 7.85 (dd, 1H, H2", J = 2.8, 1.4 Hz), 7.39 (m, 2H, H4", H5"), 5.20 (ddd, 1H, H1', J = 8.6, 8.6, 8.6 Hz), 4.22 (m, 2H, H2', H3'), 3.85 (dd, 1H, H5', J = 10.9, 6.9 Hz), 3.70 (dd, 1H, 5'H, J = 10.9, 5.9 Hz), 2.25 (ddd, 1H, H6'α, J = 12.8, 9.0, 7.3 Hz), 2.10 (m, 1H, H4'), 1.8 (m, 1H, H6'β). HRMS calcd. for $C_{14}H_{16}O_5N_2S$: 324.0780. Found: 324.0786.

*Alternative method for preparation of **18** and **19***

These compounds were also prepared from 50 mg (0.172 mmol) of unprotected **1** (**31**)[10] and 31 mg (0.224 mmol) of NMO in 4.0 ml of *tert*-butanol/acetone/water

(8:2:5).[16] When the suspension was warmed to 60 °C it become a clear solution, which remained clear even when it was cooled to room temperature and 438 µl (0.0172 mmol) of osmium tetroxide was added. The reaction mixture was stirred at room temperature for 19 h, after which solid hydrosulfite was added. After stirring for 20 min the reaction mixture was neutralized with 1 % acetic acid in methanol. The suspension was filtrated in *vacuo* through a pad of 2 g silica gel and the pad was washed three times with 20 ml chloroform/methanol (80:20). The combined filtrates were concentrated and column chromatographed using chloroform/methanol (80:20) as eluent. The mixture of the two diastereomers was separated by HPLC using acetonitrile/water (20:80) as eluent. The yield of **18** was 5.0 g (9 %) and of **19** 16.0 mg (29 %) and the retention times were 57 and 67 min, respectively.

Carbocyclic (±) 5-(2"-furyl)uridine (20)

From 10.0 mg (0.029 mmol) of **10**, 7.0 mg (78 %) of **20** was obtained. The proportions of the eluent for HPLC were 25:75. ^{1}H NMR: δ 8.07 (s, 1H, H6), 7.48 (dd, 1H, H5", J = 1.9, 0.7 Hz), 6.93 (dd, 1H, H3", J = 3.4, 0.7 Hz), 6.48 (dd, 1H, H4", J = 3.4, 1.9 Hz), 4.80 (m, 1H, H1´), 4.30, (dd, 1H, H2´, J = 9.0, 5.6 Hz), 3.96 (dd, 1H, H3´, J = 5.6, 3.2 Hz), 3.65 (d, 2H, 5´CH_2, J = 5.4 Hz), 2.27 (ddd, 1H, H6´α, J = 12.7, 8.7, 8.7 Hz), 2.15 (m, 1H, H4´), 1.66 (ddd, 1H, H6´β J = 12.7, 10.8, 7.8 Hz). HRMS calcd. for $C_{14}H_{16}O_6N_2$: 308.1008. Found: 308.1008.

Syn isomer of 20 (21)

From 10.0 mg (0.029 mmol) of **11**, 7.0 mg (78 %) of **21** was obtained. The proportions of the eluent for HPLC were 30:70. ^{1}H NMR: δ 8.45 (s, 1H, H6), 7,46 (dd, 1H, H5", J = 1.9, 0.7 Hz), 6.88 (dd, 1H, H3", J = 3.3, 1.9 Hz), 6.46 (dd, 1H, H4", J = 3.3, 1.9 Hz), 5.17 (m, 1H, H1´), 4.20 (d, 2H, H2´, H3´, J = 6.1 Hz), 3.86 (dd, 1H, 5´H, J = 10.8, 6.6 Hz), 3.72 (dd, 1H, 5´H, J = 10.8, 5.9 Hz), 2.22 (m, 1H, H6´α), 2.13 (m, 1H, H4´), 1.88 (m, 1H, H6´β). $(CD_3)_2SO$): δ 4.03 (dd, 1H, H2', J = 6.1, 4.0 Hz), 3.96 (dd, 1H, H3', J = 4.0, 4.0 Hz). HRMS calcd. for $C_{14}H_{16}O_6N_2$: 308.1008. Found: 308.1009.

Carbocyclic (±) 5-(3"-furyl)uridine (22)

From 10.0 mg (0.029 mmol) of **12**, 6.0 mg (67 %) of **22** was obtained. The proportions of the eluent for HPLC were (25:75). ^{1}H NMR: δ 8.12 (dd, 1H, H2", J =1.6, 0.8 Hz), 7.96 (s, 1H, H6), 7.51 (dd, 1H, H5", J = 1.9, 1.6, Hz), 6.79 (dd, 1H, H4", J = 1.9, 0.8 Hz), 4.76 (m, 1H, H1´), 4.33 (dd, 1H, H2´, J = 8.7, 5.5 Hz), 3.97 (dd, 1H, H3´, J = 5.5, 3.4 Hz), 3.67 (d, 2H, 5´CH_2, J = 5.2 Hz), 2.27 (ddd, 1H, H6´α, J = 12.6, 8.8 Hz), 2.15 (m, 1H, H4´), 1.69 (ddd, 1H, H6´β, J = 12.6, 10.0, 7.4 Hz). HRMS calcd. for $C_{14}H_{16}O_6N_2$: 308.1008. Found: 308.1008.

Syn isomer of ***22*** *(****23****)*

From 10.0 mg (0.029 mmol) of **13**, 7.0 mg (78 %) of **23** was obtained. The proportions of the eluent for HPLC were 25:75. ^{1}H NMR: δ 8.34 (s, 1H, H6), 8.08 (dd, 1H, H2", J = 1.7, 0.8 Hz), 7.49 (dd, 1H, H5", J = 1.9 1.7 Hz), 6.68 (dd, 1H, H4", J = 1.9, 0.8 Hz), 5.19 (ddd, 1H, H1´, J = 8.7, 8.7, 8.7 Hz), 4.20 (m, 2H, H2´, H3´), 3.85 (dd, 1H, 5´H, J = 10.8, 7.1 Hz), 3.7 (dd, 1H, H5´, J = 10.8, 6.0 Hz), 2.24 (ddd, 1H, H6´α, J = 12.3, 8.7, 7.3 Hz), 2.10 (m, 1H, H4´), 1.79 (ddd, 1H, H6´β, J = 12.3, 12.3, 8.7 Hz). HRMS calcd. for $C_{14}H_{16}O_6N_2$: 308.1008. Found: 308.1007.

*Carbocyclic (±) 5-(2"-selenienyl)uridine (****24****)*

From 5.0 mg (0.012 mmol) of **14** in 2.0 ml of 0.01M sodium methoxide solution, 3.3 mg (74 %) of **24** was obtained. The proportions of the eluent were15:85. ^{1}H NMR: δ 8.25 (s, 1H, H6), 8.05 (dd, 1H, H5", J = 5.7, 1.0 Hz), 7.64 (dd, 1H, H3", J = 4.0, 1.0 Hz), 7.28 (dd, 1H, H4", J = 5.7, 4.0 Hz), 4.85 (m, 1H, H1´), 4.35 (dd, 1H, H2´,J = 8.9, 5.5 Hz), 3.98 (dd, 1H, H3´, J = 5.5 3.2 Hz), 3.67 (d, 2H, 5´CH_2, J = 5.4 Hz), 2.3 (ddd, 1H, H6´α, J = 12.8, 8.8, 8.8 Hz), 2.16 (m, 1H, H4´), 1.72 (ddd, 1H, H6´β, J = 12.8, 10.1, 7.4 Hz). HRMS calcd. for $C_{14}H_{16}O_5N_2Se$: 372.0224. Found: 372.0228.

Syn isomer of ***24*** *(****25****)*

From 10.0 mg (0.024 mmol) of **15**, 7.0 mg (79 %) of **25** was obtained. The proportions of the eluent for HPLC were 25:75. ^{1}H NMR: δ 8.63 (s, 1H, H6), 8.01 (dd, 1H, H5", J = 5.7, 1.0, Hz), 7.55 (dd, 1H, H3", J = 3.9, 1.0 Hz), 7.77 (dd, 1H, H4", J = 3.9, 5.7 Hz), 5.24 (ddd, 1H, H1´, J = 8.8, Hz), 4.28 (m, 2H, H2´, H3´), 3.87 (dd, 1H, H5´, J = 10.8, 7.0 Hz), 3.72 (dd, 1H, H5´, J = 10.8, 5.9 Hz), 2.28 (ddd, 1H, H6´α, J = 12.4, 8.8, 7.3 Hz), 2.12 (m, 1H, H4´), 1.82 (ddd, 1H, H6´β, J = 12.4, 12.4, 8.8 Hz). HRMS calcd. for $C_{14}H_{16}O_5N_2Se$: 372.0224. Found: 372.0226.

*Carbocyclic (±) 5-(2"-thienyl)cytidine (****29****)*

This compound was prepared according to the general procedure for deprotection with some modifications. A suspension of 10.0 mg (0.027 mmol) of **19** in 4.0 ml of methanol was warmed to 60 °C. After cooling the clear solution at room temperature, 20 ml of 2.0 M sodium methoxide were added. The proportions of the eluent for HPLC was (30:70). The yield of **29** was 7.0 mg (80 %). ^{1}H NMR: δ 7.83 (s, 1H, H6), 7.56 (dd, 1H, H5", J = 4.2, 2.2 Hz), 7.20 (m, 2H, H3", H4"), 7.79 (m, 1H, H1´), 4.33 (dd, 1H, H2´, J = 8.6, 5.6 Hz), 4.0 (dd, 1H, H3´, J = 5.6, 3.5 Hz), 3.67 (d, 2H, 5´CH_2, J = 5.4 Hz), 2.32 (ddd, 1H, H6'α, J = 12.4, 8.6 Hz), 2.20 (m, 1H, H4´), 1.68 (ddd, 1H, H6´β, J = 12.4, 10.5, 8.0 Hz). HRMS calcd. for $C_{14}H_{17}O_4N_3S$: 323.0940. Found: 323.0945.

Syn isomer of 29 (30)

From 10.0 mg (0.027 mmol) of **20**, 6.0 mg (69 %) of **30** as a white solid was obtained in the same manner as described for **29**. The proportions of the eluent for HPLC were 25:75. ^{1}H NMR: δ 8.08 (s, 1H, H6), 7.53 (dd, 1H, H5", J = 4.4, 2.0 Hz), 7.18 (m, 2H, H4", H3"), 5.22 (m, 1H, H1'), 4.23 (m, 2H, H2', H3'), 3.83 (dd, 1H, H5', J = 10.8, 6.4 Hz), 3.72 (dd, 1H, H5', J =10.8, 5.6 Hz), 2.22 (m, 2H, H4' H6'α), 1.85 (m, 1H, H6'β). HRMS calcd. for $C_{14}H_{17}O_4N_3S$: 323.0940. Found: 323.0942.

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