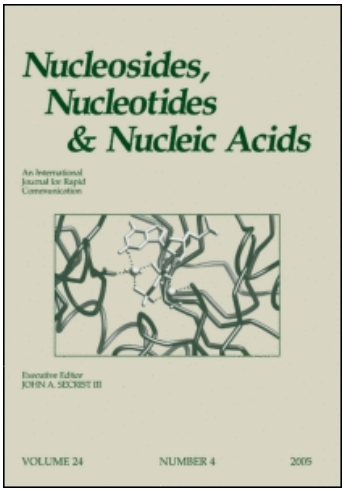

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis and Antiviral Activity of Carbocyclic 5-Substituted Uridines and Cytidines

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To cite this Article Popescu, Anne , Hörnfeldt, Anna-Britta and Gronowitz, Salo(1995) 'Synthesis and Antiviral Activity of Carbocyclic 5-Substituted Uridines and Cytidines', Nucleosides, Nucleotides and Nucleic Acids, 14: 6, 1233 — 1249
To link to this Article: DOI: 10.1080/15257779508010687
URL: http://dx.doi.org/10.1080/15257779508010687

NUCLEOSIDES & NUCLEOTIDES, 14(6), 1233-1249 (1995)

SYNTHESIS AND ANTIVIRAL ACTIVITY OF CARBOCYCLIC 5-SUBSTITUTED URIDINES AND CYTIDINES

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Abstract: Some carbocyclic uridines and cytidines have been prepared in a palladium-catalyzed reaction between 5-substituted uracils and cytosines and diacetoxymethylcyclopentene, prepared in a Prins reaction. The antiviral activity of the nucleoside analogues have been tested.

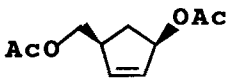
During recent years nucleoside analogues have been investigated with renewed urgency in the search for agents effective against Human Immunodeficiency virus (HIV), the causative agent for the AIDS epidemic. More effective treatment has also been sought for other viral infections, in particular herpes simplex virus (HSV types 1 and 2), Varicella Zoster virus (VZV), Cytomegalovirus (CMV) and Epstein-Barr virus (EBV), which can prove lethal to AIDS patients and other immuno-compromised individuals. This has resulted in an explosion of synthetic activity in the field of carbocyclic nucleosides and the discovery of several derivatives with potent antiviral activity. This area has been reviewed in detail.[1-3] For example carbocyclic 5-bromovinyldeoxyuridine* is a potent inhibitor *in vitro* of HSV 1 and VZV infections.[5,6] Marquez and co-workers have discovered that by replacing the tetrahydrofuran ring by 4-cyclopentene moirties they obtained compounds, which displayed very potent antiviral activity.[7-9] Carbovir, 9-(4-hydroxymethyl-2-cyclopenten-1-yl)guanine and other 2-cyclopentenyl containing nucleoside analoges have been extensively investigated for their potential as anti-HIV agents.[10-14] In our laboratory it was previously found that the triphosphate of β-5-(2"-thienyl)-2'-deoxyuridine was quite potent against HIV-1 reverse trancriptase.[15] A consequence of this was our interest to in-

* In this work carbocyclic analogues and their precursors will be identified using the same numbering system used to describe their furanose isosters with the carbon replacing the furan ring oxygen being designated as C-6'. This nomenclature has been used by Borthwich and Briggadike[1] and Marquez *et al.*[4]

vestigate some carbocyclic 5-substituted nucleoside analogues. In a previous paper[16] we described some derivatives of 1-(4'-hydroxy-2'-cyclopentenyl-5-(2"-thienyl)uracil, using the palladium-catalyzed nucleophilic opening of an epoxide, a technique introduced by Trost.[17] In this work we describe some cyclopentenylcytidines and -uridines.

Carbocyclic nucleosides can be obtained through ring-opening of epoxides or alternatively *via* Michael additions. Kitakava *et al.* have developed a novel lengthy convergent approach to chiral carbocyclic nucleosides, which involves the Michael addition of purine base to an optically pure nitrocyclopentene or nitrocyclohexene, both of which were derived from D-glucose.[18-20]

A third approach, used by us, is nucleophilic displacement of an activated hydroxyl group. The bases are coupled with an allylic acetate under palladium catalysis.[21-25]



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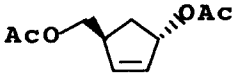

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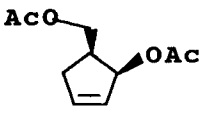

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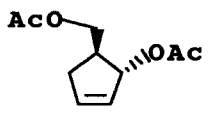


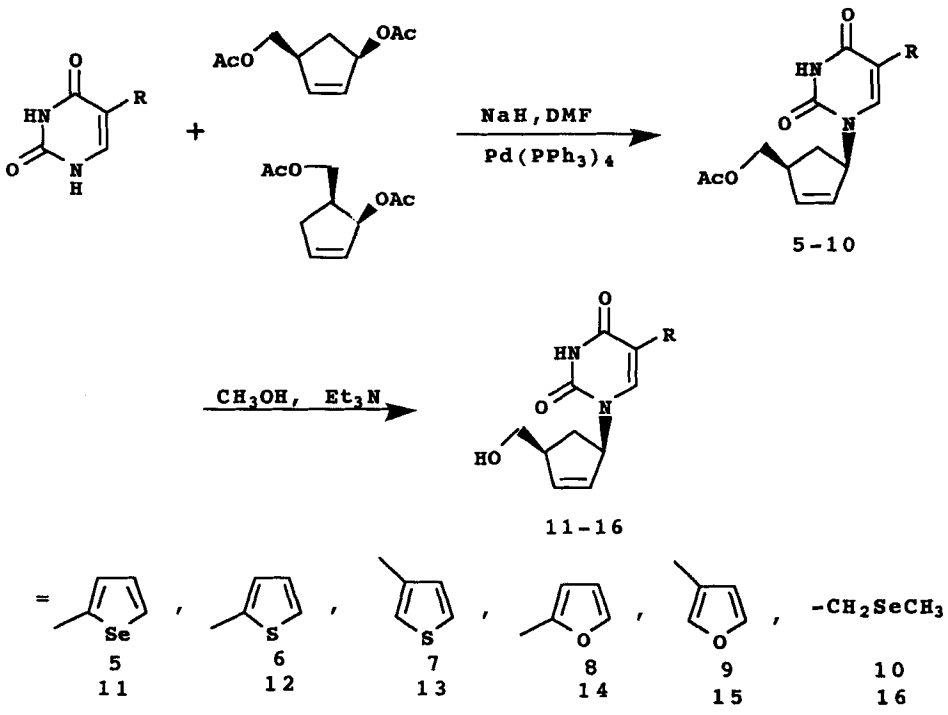
4

cis-1-Acetoxy-4-acetoxymethyl-2-cyclopentene (**1**) is available *via* a Prins reaction between cyclopentadiene and paraformaldehyde. A drawback with this reaction is that three other isomers (**2-4**) are formed. Lindell *et al.* were not able to separate the four isomeric acetates.[26] Previously, Paulsen *et al.* were able to separate the *cis*-hydroxycyclopentene methanols from the *trans* isomers through careful chromatography.[27]

In our case, the acetates were hydrolysed according to Paulsen and the resulting hydroxycyclopentene methanols were separated into *cis* and *trans* pairs, which were reacetylated. Each pair of these gives the same π-allyl complex with palladium.

The six 5-substituted uracils in Scheme 1 were prepared through Pd(0)-catalyzed coupling of tributylstannylaryls and 5-bromo-2,4-di-(trimethylsilyloxy)pyrimidine followed by dealkylation according to Peters *et al.*[28] The six 5-substituted uracils are crystalline compounds, which were recrystallized from ethanol, giving the same melting points as previously described, [28,29] and yields between 19 and 56 %.

The couplings between the 5-substituted uracils and the mixture of *cis*-1-acetoxy-4-acetoxymethyl-2-cyclopentene (**1**) and *cis*-1-acetoxy-5-acetoxymethyl-2-cyclopentene (**3**) were perfomed in *N,N*-dimethylformamide using sodium hydride as base and *tetrakis*-(triphenylphosphine)palladium(0)[30] as catalyst. The 5'-acetyl derivatives, **5-9**, were obtained in yields between 50 and 70 %, while **10** was obtained in only 2 %. It is difficult to obtain 5-methylselenomethyluracil pure[28] and consequently the yield of **10** is poor.



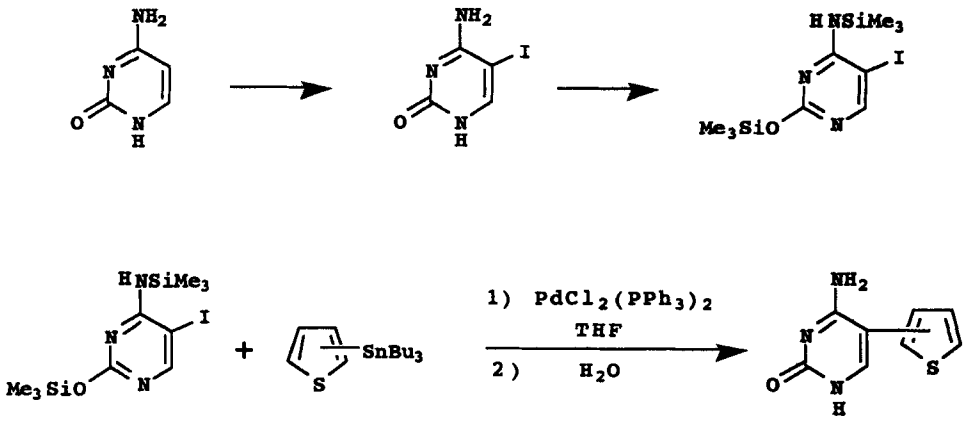
Scheme 1

Compounds **5** - **10** were deprotected in methanol containing triethylamine, to give the uridines **11-16.**

In another experiment the four acetates, **1-4**, were reacted with 5-(2'-thienyl)uracil under the same coupling conditions, giving a mixture of *cis* and *trans* coupling products. As the *cis* compound is less soluble it could be obtained in 75 % yield by triturating the mixture with ethyl acetate/diisopropyl ether (1:1) for four hours at room temperature according to Saville-Stones *et al.*[26] A competing reaction is that coupling occurs on the 3-nitrogen as well.

In the case of the 2- and 3-furyl compounds, **8** and **9**, respectively, the acetyl-protected derivative could not be separated by HPLC into enantiomers on a triacetyl cellulose column either by using methanol or ethanol as eluents. For the 2-furyl compound, **8**, even hexane/2-propanol/water (70:27:3) was used as eluent. However, the deprotected compounds, **14** and **15**, were separated into enantiomers.

5-(2'-Thienyl)- and (3'-thienyl)cytosines were prepared as shown in Scheme 2.[31] The first step, the iodination, was performed according to Watanabe *at al.*[32] The silylation can be carried out either as described by Peters *et al.*[33] or as in ref.[32]

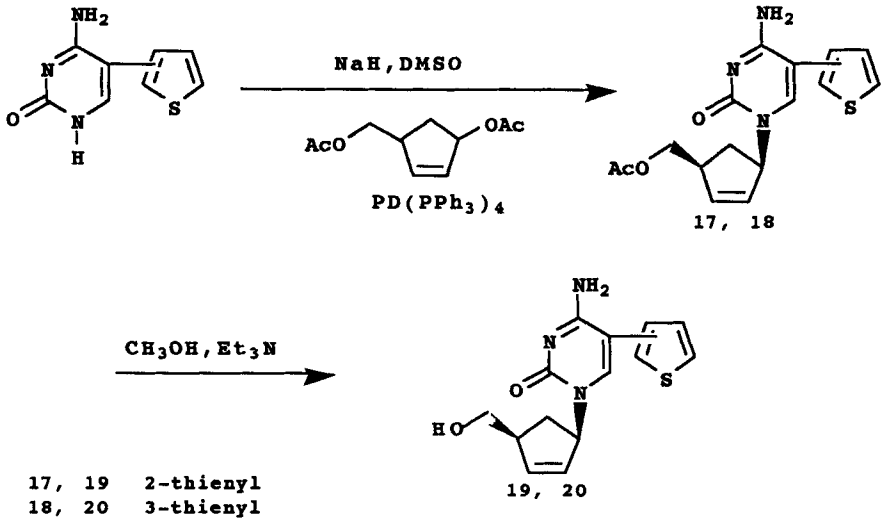


Scheme 2

When the coupling conditions for 5-(2'-aryl)uracils were used for the cytosines, the yields were very low, probably due to the low solubility of the sodium salt in *N,N*-dimethylformamide. However, the yield was improved to 18 % when the cytosines were silylated and the solvent changed to tetrahydrofuran containing triethylamine, and even more so by using dimethylsulfoxide as solvent. Normally dimethylsulfoxide is not used as solvent in couplings involving allylic alkylation of allylic acetates as it is a good coordinating solvent and decreases the activity of the catalyst.[34] This was compensated for by increasing the amount of the catalyst from 3.0 mol % to 5.0 mol %.

Compounds **17** and **18** were successfully prepared as racemates from the mixture of **1** and **3** (Scheme 3). By HPLC **17** could be separated into enantiomers on a triacetyl cellulose column. However, **18** could not be separated into enantiomers either by using methanol or ethanol as eluents. After hydrolysis in methanol containing triethylamine the cytidines **19** and **20** were obtained. Compound **20** could not be separated into enantiomers using methanol, ethanol or methanol/water (9:1) as eluents.

Structure elucidation of the carbocyclic nucleoside analogues described in this work was mainly carried out by ^{1}H NMR. The assignments of the protons were made according to those of the protons in (±)-*cis*-(4'-hydroxy-2'-cyclopentenyl)-5-(2"-thienyl)uracil,[16] assuming that a hydroxymethylene group instead of a hydroxy group in the 4'-position would not influence the chemical shifts in the rest of the molecule. This was also confirmed by the coupling pattern for the different proton absorptions.



Scheme 3

Inhibition of viral replication in cell-culture assays

Compounds **5-20** were tested in cell-culture assays for effect on multiplication of HIV-1, HSV-1, influenza virus and CMV. Most of the compounds were inactive at the highest concentration 100 μg/ml. A few compounds had weak inhibitory activities with IC_{50}-values in the range 50-100 μg/ml. This activity was exhibited by both the carbocyclic nucleoside analogue and the corresponding 5'-acetyl ester. Thus, influenza virus was marginally inhibited by the 5-(2'-thienyl)uracil compounds **6** and **12** and HSV-1 by the 5-(3'-furyl)uracil compounds **9** and **15** and by the 5-(2'-thienyl)cytosine and 5-(3'-thienyl)-cytosine compounds **17**, **19** and **18**, **20**, respectively. Approximate IC_{50} values: **6**, **12** and **19** 50 μg/ml; **9**, **15**, **17**, **18** and **20** 100 μg/ml.

The best antiviral activity was shown by the 5'-acetyl-5-methylselenomethyluracil compound, **10**, which inhibited both HIV-1 and influenza virus with an IC_{50}-value of about 10 μg/ml. Interestingly, the corresponding non-acetylated analogue, **16**, was not active. None of these two compounds had any activity against HSV-1 or CMV.

Discussion

The antiviral activity of the nucleoside analogues carbocyclic 5-bromovinyl-2'-deoxyuridine[35,36] and carbocyclic 2'-deoxyguanosine[37] against herpes virus and carbovir[38,

[39] against HIV, depend on their phosphorylation by viral or cellular kinases and ultimately formation of triphosphates of the compounds. The triphosphates are inhibitory to the viral polymerases and/or are incorporated into viral DNA. 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, but it is worth noting that several 5-heteroaryl substituted pyrimidine 2'-deoxyribose nucleoside analogues are very efficient substrates of thymidine kinase (TK) and are phosphorylated to monophosphates by human TK 2[40] and by herpes simplex virus TK.[41] However, these 2'-deoxyribose compounds are not inhibitory to HIV in cell-culture assays although the triphosphates of some of these compounds inhibit the reverse transcriptase of HIV.[42]

The activity of the 5'-acetylated 5-methylselenomethyluracil compound **10** and the lack of activity of the corresponding compound **16** with a free 5'-hydroxyl group is surprising. Since **10** is active against HIV and influenza virus but not against HSV and CMV it is not a general nonspecific mechanism of action. Also, when tested for inhibition of HIV reverse transcriptase, **10** was not inhibitory even at a concentration of 100 μg/ml.

Experimental

The reactions were carried out in dried glassware equipped with tight-fitting septa and under dry nitrogen. Reagents and solvents were handled by using standard syringe techniques. The ^{1}H NMR spectra were recorded on a Varian XL 300 spectrometer. The mass spectra were recorded on a JEOL JMS-SX 102 spectrometer with EI or FAB techniques. The racemates were resolved by HPLC using a Combrio triacetyl cellulose (TAC) column (600x10 mm). The separated enantiomers showed the same R_f values as those of the corresponding racemate. The polarimeter used was an Optical Activity, AA-1000. All melting points are uncorrected. Column chromatography was carried out using Merck silica. Anhydrous reagents and solvents were used. Tetrahydrofuran was freshly distilled from sodium dispersion. Dichloromethane, petroleum ether, pentane, *N,N*-dimethylformamide, dimethylsulfoxide and ethyl acetate were distilled over molecular sieves prior to use. The elemental analyses were carried out by Dornis and Kolbe, Mikroanalytisches Laboratorium, Mülheim a.d. Ruhr, Germany.

The assays for determining the inhibition of HIV multiplication in a cell-culture XTT assay and growth of uninfected cells were performed in M cells essentially as previously described.[43] MT4 cells (human T cell line) grown in RPMI 1640 medium supplemented with 10 % fetal calf serum, penicillin and streptomycin were seeded into 96 well microplates (20,000 cells/well) and infected with 10-20 $TCID_{50}$ of HIV-1, IIIb per well. Test compounds in different concentrations were added. The cultures were incubated at 37 °C in carbon dioxide atmosphere and the viability of cells was determined at day five or

six with XTT vital dye.[43] The anti HIV-1 activity was measured as the reduction in cytopatic effect (CPE) caused by the virus.

In the anti HSV activity assay vero cells grown in Minimum Essential Medium, Eagle (MEM) with the same supplement and seeding procedure as described above were infected with 10-50 $TCID_{50}$ of herpes simplex virus type 1 (HSV-1). After one hour of virus adsorption, test compounds in different concentrations were added. The cultures were incubated three to four days and the result determined as described above.

In the anti influenza activity assay MDCK cells (ATCC CCL 34) grown in MEM with the same supplement and seeding procedure as described above were infected with 10-50 $TCID_{50}$ of influenza A virus Victoria 3/75. After one hour of virus adsorption, test compounds diluted in MEM without fetal calf serium and without phenol red were added. The cultures were incubated as described above for four or five days and the result determined as described above.

In the anti CMV activity assay MRC-5 (human embryonic cells (ATCC CCL 171) grown in MEM with the same supplement and seeding procedure as described above were infected with 10-50 $TCID_{50}$ of cytomegalo virus (CMV) strain Towne. After one hour of virus adsorption, test compounds diluted in MEM containing 2 % fetal calf serum were added. The microplates were incubated at 37 °C in 5 % carbon dioxide atmosphere and after one week the cultures were inspected microscopically for cytopathic effect (CPE) . The anti CMV activity was measured as the reduction in CPE caused by the virus using the following score system: +++, ++, + and - representing >75 %, 50-75 %, <50 % and no reduction of CPE.

Preparation of 1-acetoxy-4-acetoxymethyl-2-cyclopentene (1) and 1-acetoxy-5-acetoxymethyl-2-cyclopentene (3)

To a solution of 6.23 g (54.7 mmol) of the *cis*-hydroxycyclopentene methanols[26,27] and 120 ml of dichloromethane, 334 mg (2.73 mmol) of 4-dimethylaminopyridine was added. After cooling the solution to -10 °C, 25.8 ml (0.27 mmol) of acetic acid anhydride was added dropwise during 10 min and the temperature was kept between -10 and -5 °C. Between -5 and 0 °C, 36 ml (0.26 mol) of triethylamine was added dropwise during 10 min. The reaction mixture was allowed to reach room temperature and stirred for an additional hour, when the starting material was consumed. The reaction was followed by thin-layer chromatography (chloroform/methanol, 9:1) using anisaldehyde solution as detector. The reaction mixture was treated with 1 M hydrochloric acid until pH 2-3, diluted with 120 ml of diethyl ether, washed with sodium hydrogen carbonate until pH 8 and water. After drying over sodium sulfate and evaporation, 9.82 g (91 %) of **1** and **3** was obtained as an oil, which was dried *in vacuo* and used in the coupling experiments without further purification.

Carbocyclic (±)-cis-5-(2"-selenienyl)-2',3'-didehydro-2',3'-dideoxy-5'-acetoxy-uridine (5)

A 250 ml two-necked flask equipped with condenser, magnetic bar and nitrogen in- and outlet was charged with 1.00 g (4.15 mmol) of 5-(2'-selenienyl)uracil[29] in 40 ml of anhydrous *N,N*-dimethylformamide. The flask was immersed in a preheated oil bath at 65 °C, and after 10 min the suspension gave a clear solution, which was cooled to room temperature. Sodium hydride (124 mg, 4.15 mmol, 80 % oil dispersion) was added to the selenienyluracil solution. The reaction mixture was heated in an oil bath at 65 °C for 30 min, cooled to room temperature, and 143 mg (0.124 mmol) of *tetrakis*(triphenylphosphine)palladium(0)[30] was added. A solution of 985 mg (4.98 mmol) of **1** and **3** in 3 ml of anhydrous *N,N*-dimethylformamide was transferred dropwise at room temperature to the reaction mixture during 10 min. The reaction flask was kept in an oil bath at 65 °C for 18h. The reaction was followed with thin-layer chromatography using ethyl acetate/petroleum ether (50:50) as eluent. The reaction mixture was cooled to room temperature and poured into 60 ml of diethyl ether. The resulting solution was filtered and the solid material washed with acetone. The filtrate was evaporated and the remaining oil taken up in 100 ml of dichloromethane. This solution was washed with 100 ml of water and the water phase extracted five times with 30 ml of dichloromethane. The combined organic phases were dried over magnesium sulfate and evaporated. The residue, 2.2 g of a thick oil, was chromatographed using ethyl acetate/petroleum ether (30:70) and (50:50), giving 1.10 g (70 %) of **5** as a tan solid mp 176-178 °C (methanol). ^{1}H NMR (CD_3OD): δ 8.05 (dd, 1H, H5", J = 5.7, 1.0 Hz), 7.88 (s, 1H, H6), 7.52 (dd, 1H, H3", J = 3.9, 1.0 Hz), 7.27 (dd, 1H, H4", J = 5.7, 3.9 Hz), 6.22 (ddd, 1H, H3', J = 5,7, 2.2, 2.2 Hz), 5.89 (ddd, 1H, H2', J = 5.7, 2.3, 2.3 Hz), 5.68 (ddddd, 1H, H1', J = 8.8, 6.3, 2.3, 2.2, 2.1 Hz), 4.20 (dd, 1H, 5'CH_2, J = 11.2, 5.3 Hz), 4.11 (dd, 1H, 5'CH_2, J = 11.2, 5.5 Hz), 3.15 (m, 1H, H4'), 2.77 (ddd, 1H, H6'$_\beta$, J = 14.1, 8.8, 8.8 Hz), 1.90 (s, 3H, CH_3), 1.55 (ddd, 1H, H6'$_\alpha$, J = 14.1, 6.3, 3.22 Hz). Anal. Calcd. for $C_{16}H_{16}N_2O_4Se$: C, 50.66; H, 4.25; N, 7.38; MWt, 379.27. Found: C, 50.50; H, 4.25; N, 7.40; MWt, 380.

(+)- and (-)-Enantiomers of 5

The racemate was resolved using methanol as eluent $[\alpha]^{25}_D$ = +98.8° (c = 113 mg/100 ml, ethanol) and -97.9° (c = 95 mg/100 ml, ethanol).

Carbocyclic (±)-cis-5-(2"-thienyl)-2',3'-didehydro-2'.3'-dideoxy-5'-acetoxy-uridine (6)

This compound was prepared as described for **5** from 0.50 g (2.58 mmol) of 5-(2'-thienyl)uracil,[28] 20 ml of anhydrous *N,N*-dimethylformamide, 77 mg (2.58 mmol) of sodium hydride (80 % oil dispersion), 89.0 mg (0.077 mmol) of *tetrakis*(triphenylphosphine)palladium(0) and 613 mg (3.10 mmol) of **1** and **3** in 1.5 ml of anhydrous *N,N*-dimethylformamide. After work up and chromatography as described for **5**, 0.55 g (64 %)

of **6** was obtained, mp 162-163 °C (ethyl acetate). ^{1}H NMR (CD_3OD): δ 7.75 (s, 1H, H6), 7.37 (m, 2H, H3", H5"), 7.04 (dd, 1H, H4", J = 4.8, 3.9 Hz), 6.20 (ddd, 1H, H3', J = 5.6, 2.1, 2.1 Hz), 5.88 (ddd, 1H, H2', J = 5.7, 2.2, 2.2 Hz), 5.68 (ddddd, 1H, H1', J = 8.9, 6.3, 2.2, 2.1, 2.1 Hz), 4.20 (dd, 1H, 5'CH_2, J = 11.1, 5.1 Hz), 4.10 (dd, 1H, 5'CH_2, J = 11.1, 5.2 Hz), 3.15 (m, 1H, H4'), 2.78 (ddd, 1H, H6'$_\beta$, J = 14.0, 8.9, 8.9 Hz), 1.88 (s, 3H, CH_3), 1.55 (ddd, 1H, H6'$_\alpha$, J = 14.0, 6.3). Anal. Calcd. for $C_{16}H_{16}N_2O_4S$: C, 57.81; H, 4.85; N, 8.43; MWt, 332.38 . Found: C, 57.88; H, 4.91; N, 8.38; MWt, 332.

(+)- and (-)-Enantiomers of ***6***

The racemate was resolved using methanol as eluent $[\alpha]^{25}_D$ = +103.8° (c = 106 mg/100 ml, ethanol) and -102.0° (c = 100 mg/100 ml, ethanol).

Carbocyclic (±)-cis-5-(3"-thienyl)-2',3'-didehydro-2'.3'-dideoxy-5'-acetoxy-uridine (7)

This compound was prepared as described for **5** from 1.00 g (5.15 mmol) of 5-(3'-thienyl)uracil[29,28] in 54 ml of anhydrous *N,N*-dimethylformamide, 155 mg (5.15 mmol) of sodium hydride (80 % oil dispersion), 178 mg (0.15 mmol) of *tetrakis*(triphenylphosphine)palladium(0) and 1.22 g (6.18 mmol) of **1** and **3** in 3.5 ml of anhydrous *N,N*-dimethylformamide. After work up and chromatography (30:70) and (50:50) as described for **5**, 1.10 g (64 %) of **7** was obtained as white crystals, mp 144-146 °C (ethyl acetate). ^{1}H NMR (CD_3OD): δ 7.79 (dd, 1H, H2", J = 3.0, 1.3 Hz), 7.68 (s, 1H, H6), 7.42 (dd, 1H, H5", J = 5.1, 3.0 Hz), 7.31 (dd, 1H, H4", J = 5.1, 1.3 Hz), 6.2 (ddd, 1H, H3', J = 5.7, 2.2, 2.2 Hz), 5.87 (ddd, 1H, H2', J = 5.7, 2.2, 2.2 Hz), 5.68 (ddddd, 1H, H1', J = 8.9, 6.4, 2.2, 2.2, 2.2 Hz), 4.18 (dd, 1H, 5'CH_2, J = 11.1, 5.2 Hz), 4.09 (dd, 1H, 5'CH_2, J = 11.1, 5.4 Hz), 3.12 (m, 1H, H4'), 2.75 (ddd, 1H, H6'$_\beta$, J = 14.1, 8.9, 8.9 Hz), 1.86 (s, 3H, CH_3), 1.52 (ddd, 1H, H6'$_\alpha$, J = 14.1, 6.4, 6.4 Hz). Anal. Calcd. for $C_{16}H_{16}N_2O_4S$: C, 57.81; H, 4.85; N, 8.43; MWt, 332.38. Found: C, 57.94; H, 4.97; N, 8.49; MWt, 332.

(+)- and (-)-Enantiomers of ***7***

The racemate was resolved using methanol as eluent $[\alpha]^{25}_D$ = +77.16° (c = 30.00 mg/100 ml, methanol) and -77.14° (c = 29.75 mg/100 ml, methanol).

Carbocyclic (±)-cis-5-(2"-furyl)-2',3'-didehydro-2'.3'-dideoxy-5'-acetoxy-uridine (8)

This compound was prepared as described for **5** from 1.00 g (5.62 mmol) of 5-(2'-furyl)uracil,[28] in 40 ml of anhydrous *N,N*-dimethylformamide, 169 mg (5.62 mmol) of sodium hydride (80 % oil dispersion) 195 mg (0.17 mmol) of *tetrakis*(triphenylphosphine)-palladium(0) and 1.33 g (6.74) of **1** and **3** in 3.5 ml of anhydrous *N,N*-dimethylformamide. After work up and chromatography (30:70 and 50:50) as described for **5**, 1.25 g (70 %) of **8** was obtained as light pink crystals, mp 164-166 °C (ethyl acetate). ^{1}H NMR (CD_3OD): δ 7.85 (s, 1H, H6), 7.45 (dd, 1H, H5", J = 1.8, 0.8 Hz), 6.93 (dd, 1H, H3", J = 3.4, 0.8 Hz), 6.47 (dd, 1H, H4", J = 3.4, 1.4 Hz), 6.21 (ddd, 1H, H3', J = 5.7, 2.2. 2.2 Hz), 5.85 (ddd,

1H, H2', J = 5.7, 2.2, 2.2 Hz), 5.71 (ddddd, 1H, H1', J = 8.8, 6.4, 2.2, 2.2, 2.2 Hz), 4.25 (dd, 1H, 5'CH_2, J = 11.2, 4.7 Hz), 4.08 (dd, 1H, 5'CH_2, J = 11.2, 4.7 Hz), 3.15 (m, 1H, H4'), 2.77 (ddd, 1H, H6'$_\beta$, J = 14.1, 8.8, 8.8 Hz), 1.98 (s, 3H, CH_3), 1.54 (ddd, 1H, H6'$_\alpha$, J = 14.1, 6.4, 6.4). Anal. calcd. for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.09; N, 8.85, MWt, 316.31. Found: C, 60.73; H, 5.20; N, 8.85; MWt, 316.

*Carbocyclic (±)-cis-5-(3"-furyl)-2',3'-didehydro-2',3'-dideoxy-5'-acetoxy-uridine (**9**)*

This compound was prepared as described for **5** from 0.85 g (4.78 mmol) of 5-(3'-furyl)uracil,[28] in 36 ml *N,N*-dimethylformamide, 143 mg (4.78 mmol) of sodium hydride (80 % oil dispersion), 165 mg (0.143 mmol) of *tetrakis*(triphenylphosphine)palladium(0) and 1.13 g (5.73 mmol) of **1** and **3** in 5.0 ml of anhydrous *N,N*-dimethylformamide. After work up and chromatography (30:70) and (60:40) as described for **5**, 0.76 g (50 %) of **9**, was obtained mp 125-127 °C (ethyl acetate). ^{1}H NMR (CD_3OD): δ 8.09 (dd, 1H, H2", J = 1.7, 0.9 Hz), 7.60 (s, 1H, H6), 7.50 (dd, 1H, H5", J = 1.9, 1.7 Hz), 6.66 (dd, 1H, H4", J = 1.9, 0.9 Hz), 6.18 (ddd, 1H, H3', J = 5.7, 2.2. 2.2 Hz), 5.87 (ddd, 1H, H2', J = 5.7, 2.2, 2.2 Hz), 5.65 (ddddd, 1H, H1', J = 8.8, 6.4, 2.2, 2.2, 2.2 Hz), 4.17 (dd, 1H, 5'CH_2, J = 11.0, 5.6 Hz), 4.12 (dd, 1H, 5'CH_2, J = 11.0, 5.4 Hz), 3.10 (m, 1H, H4'), 2.74 (ddd, 1H, H6'$_\beta$, J = 14.0, 8.7, 8.7 Hz), 1.92 (s, 3H, CH_3), 1.51 (ddd, 1H, H6'$_\alpha$, J = 14.0, 6.4, 6.4 Hz). HRMS calcd. for $C_{16}H_{16}N_2O_5$: 316.1059 . Found: 316.1065.

*Carbocyclic (±)-cis-5-(methylselenomethyl)-2',3'-didehydro-2',3'-dideoxy-5'-acetoxyuridine (**10**)*

This compound was prepared as described for **5** from 0.685 g (3.11 mmol) of 5-methylselenomethyluracil,[28] 23 ml of anhydrous *N,N*-dimethylformamide, 85 mg (2.82 mmol) of sodium hydride (80 % oil dispersion), 108 mg (0.093 mmol) of *tetrakis*(triphenylphosphine)palladium(0) and 0.743 g (3.75 mmol) of **1** and **3** in 3.5 ml of anhydrous *N,N*-dimethylformamide. Reaction time 48 h at 65 °C. After work up as described for **5** and chromatography using dichloromethane and dichloromethane/methanol (95:5) as eluents followed by HPLC using a nucleosil column (500x10 mm) and heptane/ethyl acetate/2-propanol (65:35:10) as eluent, 22.4 mg (2 %) of **10** was obtained as an oily solid, mp 90-94 °C. ^{1}H NMR (CD_3OD): δ 7.40 (s, 1H, H6), 6.15 (ddd, 1H, H3', J = 5.7, 2.2, 2.2 Hz), 5.79 (ddd, 1H, H2', J = 5.7, 2.2, 2.2 Hz), 5.65 (ddddd, 1H, H1', J = 8.7, 6.7, 2.2, 2.2, 2.2 Hz), 4.16 (dd, 1H, 5'CH_2, J = 11.0, 6.2 Hz), 4.09 (dd, 1H, 5'CH_2, J = 11.0, 5.9 Hz), 3.43 (s, 2H, SeCH_2), 3.10 (m, 1H, H4'), 2.72 (ddd, 1H, H6'$_\beta$, J = 13.7, 8.7, 8.7 Hz), 2.05 (s, 3H, $COCH_3$), 1.96 (s, 3H, $SeCH_3$), 1.42 (ddd, 1H, H6'$_\alpha$, J = 13.7, 6.7, 6.7 Hz). HRMS calcd. for $C_{14}H_{18}N_2O_4Se$: 358.0432. Found 358.0441.

*Carbocyclic (±)-cis-5-(2"-selenienyl)-2',3'-didehydro-2',3'-dideoxyuridine (**11**)*

A one-necked flask was charged with 10 ml of methanol/triethylamine (9:1),and 100 mg (0.264 mmol) of **5.** The reaction mixture was refluxed for 16 h, after which the solvent

was evaporated and the residue chromatographed using ethyl acetate/petroleum ether (80:20) as eluent. 77 mg (86 %) of a tan solid with mp 183-185 °C (ethyl acetate) was obtained. ^{1}H NMR (CD_3OD): δ 8.26 (s, 1H, H6), 8.03 (dd, 1H, H5", J = 5.7, 1.0 Hz), 7.52 (dd, 1H, H3", J = 4.00, 1.0 Hz), 7.25 (dd, 1H, H4", J = 5.7, 4.0 Hz), 6.19 (ddd, 1H, H3', J = 5.7, 2.2, 2.2 Hz), 5.75 (m, 2H, H2', H1'), 3.79 (dd, 1H, 5'CH_2, J = 11.0, 3.9 Hz), 3.58 (dd, 1H, 5'CH_2, J = 11.0, 4.1 Hz), 2.96 (m, 1H, H4'), 2.72 (ddd, 1H, H6'$_\beta$, J = 14.3 9.2, 9.2 Hz), 1.64 (ddd, 1H, H6'$_\alpha$, J = 14.3, 5.6, 5.6 Hz). HRMS calcd. for $C_{14}H_{14}N_2O_3Se$: 338.0170. Found: 338.0173.

Carbocyclic (±)-cis-5-(2"-thienyl)-2',3'-didehydro-2',3'-dideoxyuridine (12)

This compound was prepared as described for **11** from 100 mg (0.30 mmol) of **6**. Upon chromatography the proportions of eluent were 75:25 and 60 mg (69 %) of **12** was obtained, mp 185-223 °C (decomp.) (methanol). ^{1}H NMR (CD_3OD): δ 8.10 (s, 1H, H6), 7.37 (dd, 1H, H3", J = 3.7, 1.2 Hz), 7.33 (dd, 1H, H5", J = 5.2, 1.2 Hz), 7.02 (dd, 1H, H4", J = 5.2, 3.7 Hz), 6.19 (ddd, 1H, H3', J = 5.8, 2.1, 2.1 Hz), 5.77 (ddd, 1H, H2', J = 5.8, 2.2, 2.2 Hz), 5.74 (ddddd, 1H, H1', J = 9.2, 5.60, 2.2, 2.1, 2.0 Hz), 3.76 (dd, 1H, 5'CH_2, J = 11.0, 3.9 Hz), 3.58 (dd, 1H, 5'CH_2, J = 11.0, 4.3 Hz), 2.95 (m, 1H, H4'), 2.72 (ddd, 1H, H6'$_\beta$, J = 14.3, 9.2, 9.2 Hz), 1.63 (ddd, 1H, H6'$_\alpha$, J = 14.3, 5.6, 5.6 Hz). HRMS (FAB) calcd. for ($C_{14}H_{14}N_2O_3S$+1): 291.0803. Found: 291.0802.

Carbocyclic (±)-cis-5-(3"-thienyl)-2',3'-didehydro-2',3'-dideoxyuridine (13)

This compound was prepared as described for **11** from 100 mg (0.30 mmol) of **7**. The reaction time was 16 h. Upon chromatography the proportions of eluent were 70:30, and 78 mg (89 %) of **13** as white crystals was obtained mp 212-214 °C (methanol). ^{1}H NMR (CD_3OD): δ 8.04 (s, 1H, H6), 7.84 (dd, 1H, H2", J = 3.0, 1.4 Hz), 7.39 (dd, 1H, H5", J = 5.1, 3.0 Hz), 7.34 (dd, 1H, H4", J = 5.1, 1.4 Hz), 6.17 (ddd, 1H, H3', J = 3.5, 2.1, 2.1 Hz), 5.75 (m, 2H, H2', H1'), 3.75 (dd, 1H, 5'CH_2, J = 11.1, 3.8 Hz), 3.58 (dd, 1H, 5'CH_2, J = 11.1, 4.1 Hz), 2.96 (m, 1H, H4'), 2.70 (ddd, 1H, H6'$_\beta$, J = 14.2, 9.2, 9.2 Hz), 1.63 (ddd, 1H, H6'$_\alpha$, J = 14.2, 5.6, 5.6 Hz). HRMS calcd. for ($C_{14}H_{14}N_2O_3S$): 290.0725. Found: 290.0729.

Carbocyclic (±)-cis-5-(2"-furyl)-2',3'-didehydro-2',3'-dideoxyuridine (14)

This compound was prepared as described for **11** from 100 mg (0.32 mmol) of **8**. The reaction time was 16 h. Upon chromatography the proportions of eluent were 70:30, and 72 mg (82 %) of **14** was obtained as white crystals, mp 212-236 °C (decomp) (methanol). ^{1}H NMR (CD_3OD): δ 8.04 (s, 1H, H6), 7.44 (dd, 1H, H5", J = 1.9, 0.8 Hz), 6.90 (dd, 1H, H3", J = 3.3, 0.8 Hz), 6.45 (dd, 1H, H4", J = 3.3, 1.9 Hz), 6.23 (ddd, 1H, H3', J = 5.6, 2.1, 2.1 Hz), 5.80 (ddd, 1H, H2', J = 5.6, 2.2, 2.2 Hz), 5.71 (m, 1H, H1'), 3.69 (dd, 1H, 5'CH_2, J = 11.0, 4.8 Hz), 3.58 (dd, 1H, 5'CH_2, J = 11.0, 4.9 Hz), 2.95 (m, 1H, H4'), 2.71 (ddd, 1H, H6'$_\beta$, J = 14.1, 9.0, 9.0 Hz), 1.55 (ddd, 1H, H6'$_\alpha$, J = 14.1, 5.8, 5.8 Hz). HRMS calcd. for $C_{14}H_{14}N_2O_4$: 274.0954. Found: 274.0959.

*(+)- and (-)-Enantiomers of **14***

The racemate was resolved using methanol as eluent $[\alpha]^{25}_D$ = +188.2° (c = 81 mg/100 ml, ethanol) and -188.4° (c = 65 mg/100 ml, ethanol).

*Carbocyclic (±)-cis-5-(3"-furyl)-2',3'-didehydro-2',3'-dideoxyuridine (**15**)*

This compound was prepared as described for **11** from 100 mg (0.32 mmol) of **9**. Upon chromatography the proportions of eluent were 70:30, and 62 mg (71 %) of **15** was obtained as a white solid, mp 180-216 °C (decomp.) (methanol). ^{1}H NMR (CD_3OD): δ 8.09 (dd,1H, H2", J=1.7, 0.8 Hz), 7.98 (s, 1H, H6), 7.48 (dd, 1H, H5", J = 1.9, 1.7 Hz), 6.66 (dd, 1H, H4", J = 1.9, 0.8 Hz), 6.18 (ddd, 1H, H3', J = 5.6, 2.0, 2.0 Hz), 5.75 (m, 2H, H1', H2'), 3.79 (dd, 1H, 5'CH_2, J = 11.1, 3.7 Hz), 3.58 (dd, 1H, 5'CH_2, J = 11.1, 4.2 Hz), 2.97 (m, 1H, H4'), 2.69 (ddd, 1H, H6'$_\beta$, J = 14.3, 9.3, 9.3 Hz), 1.62 (ddd, 1H, H6'$_\alpha$, J = 14.3, 5.8, 5.8 Hz). HRMS calcd, for $C_{14}H_{14}N_2O_4$: 274.0954. Found: 274.0961.

*(+)- and (-)-Enantiomers of **15***

The racemate was resolved using methanol as eluent $[\alpha]^{25}_D$ = +111.8° (c = 123 mg/100 ml, ethanol) and -108.9° (c = 79 mg/100 ml, ethanol).

*Carbocyclic (±)-cis-5-(methylselenomethyl)-2',3'-didehydro-2'.3'-dideoxyuridine (**16**)*

A one-necked flask was charged with 1.0 ml of 0.01 M sodium methoxide solution and 4.30 mg (0.012 mmol) of **10**. The reaction mixture was stirred at room temperature for 4.5 h. The alcaline solution was neutralized with Dowex 50W-X8 (H), after which the sieves were filtered and washed with methanol. The filtrate was concentrated, giving 3.40 mg (90 %) of **16** as a thick oil. ^{1}H NMR (CD_3OD): δ 7.55 (s, 1H, H6), 6.16 (ddd, 1H, H3', J = 5.6, 2.2 Hz), 5.73 (ddd, 1H, H2', J = 5.6, 2.2, 2.2 Hz), 5.65 (ddddd, 1H, H1', J = 8.9, 6.2, 2.2, 2.2, 2.2 Hz), 3.68 (dd, 1H, 5'CH_2, J = 10.9, 4.9 Hz), 3.57 (dd, 1H, 5'CH_2, J = 10.9, 5.0 Hz), 3.43 (s, 2H, SeCH_2), 2.90 (m, 1H, H4'), 2.66 (ddd, 1H, H6'$_\beta$, J = 14.0, 8.9, 8.9 Hz), 1.96 (s, 3H, SeCH_3), 1.49 (ddd, 1H, H6'$_\alpha$, J = 14.0, 6.2, 6.2 Hz). HRMS calcd. for $C_{12}H_{16}N_2O_3Se$: 316.0326. Found: 316.0323.

*Carbocyclic (±)-cis-5-(2"-thienyl)-2',3'didehydro-2',3'dideoxy-5'-acetoxycytidine (**17**)*

A 250 ml two-necked flask equipped with condenser, magnetic bar and nitrogen inlet was charged with 1.50 g (7.77 mmol) of 5-(2'-thienyl)cytosine[31] in 60 ml of dimethylsulfoxide and 280 mg (9.32 mmol) of sodium hydride (80 % oil dispersion) and the flask with the suspension was immersed in a preheated oil bath at 70 °C for 30 min. The solution remained clear when the temperature was lowered to room temperature. At this temperature, 448 mg (0.39 mmol) of *tetrakis(*triphenylphosphine)palladium(0)[30] was added and 1.85 g (9.32 mmol) of **1** and **3** in 4.0 ml of anhydrous tetrahydrofuran was pressed with nitrogen into the reaction flask during 10 min. The reaction mixture was kept at 70 °C with stirring for 48 h. The reaction was followed by thin-layer chromatography using

dichloromethane/methanol (90:10) as eluent. After cooling to room temperature, the reaction mixture was diluted with 120 ml of ether and filtered with suction. The recovered thienylcytosine was washed twice with 10 ml of methanol and three times with 15 ml of dichloromethane. The filtrate was evaporated and the remaining dimethylsulfoxide was taken off with a Kugel-Rohr apparatus. The residue, a black oil, was taken up in 150 ml of dichloromethane and again the unreacted thienylcytosine was filtered off and washed four times with 15 ml of dichloromethane. To the filtrate 120 ml of water was added, the phases were separated and the water phase extracted five times with 50 ml of dichloromethane. The combined organic phases were treated with charcoal, dried over magnesium sulfate and chromatographed using dichloromethane and dichloromethane/methanol (95:5) as eluents. The residue, 1.13 g of a thick tan oil, was crystalized from methanol giving 466 mg, another 261 mg was obtained when the filtrate was chromatographed and recrystallized, yielding 28 %. After HPLC using a polygosil RPC column (250x20 mm) and dichloromethane/methanol (95:5) as eluent an oil was obtained, which gave **17** as white crystals from methanol, with mp 186-189 °C. ^{1}H NMR (CD_3OD): δ 7.52 (m, 2H, H6 and H5"), 7.15 (m, 2H, H3" and H4"), 6.17 (ddd, 1H, H3', J = 5.6. 2.1, 2.1 Hz), 5.81 (ddd, 1H, H2', J = 5.6, 2.2, 2.2 Hz), 5.72 (ddddd, 1H, H1', J = 9.0, 6.1, 2.2, 2.1, 2.0 Hz), 4.18 (dd, 1H, 5'CH_2, J = 11.2, 4.8 Hz), 4.02 (dd, 1H, 5'CH_2, J = 11.2, 4.8 Hz), 3.11 (m, 1H, H4'), 2.81 (ddd, 1H, H6'$_\beta$, J = 14.1, 9.0, 9.0 Hz), 1.78 (s, 3H, CH_3), 1.45 (ddd, 1H, H6'$_\alpha$, J = 14.1, 6.1, 6.1 Hz). HRMS calcd. for $C_{16}H_{17}O_3N_3S$: 331.0991. Found: 331.1001.

(+)- and (-)-Enantiomer of 17

The racemate was resolved by HPLC using ethanol/water (95:5) as eluent $[\alpha]^{25}_D$= +35.7° (c = 126 mg/100 ml ethanol) and -40.0° (c = 120 mg/100 ml ethanol).

Carbocyclic (±)-cis-5-(3"-thienyl)-2',3',didehydro-2'.3'-dideoxy-5'-acetoxy-cytidine (18)

This compound was prepared as described for **17** from 250 mg (1.30 mmol) of 5-(3'-thienyl)cytosine[31], 47 mg (1.55 mmol) of sodium hydride (80 % oil dispersion), 75 mg (0.065 mmol) *tetrakis*(triphenylphosphine)palladium(0) in 16 ml of anhydrous dimethylsulfoxide and 309 mg (1.56 mmol) of **1** and **3**. Gradient chromatography with dichloromethane, dichloromethane/methanol (99:1), (97:3) and (95:5) as eluents gave 203 mg (47 %) crude product, a thick tan oil, and after recrystallization from methanol 125 mg (29 %) was obtained. HPLC purification on a polygosil RPC column (250x20 mm) and dichloromethane/methanol (95:5) as eluent gave **18** as a white oil, which crysallized in methanol, mp 178-180 °C. ^{1}H NMR (CD_3OD): δ 7.57 (dd, 1H, H5", J = 5.0, 3.0 Hz), 7.48 (dd, 1H, H2", J = 3.0, 1.4 Hz), 7.46 (s, 1H, H6), 7.16 (dd, 1H, H4", J = 5.0, 1.4 Hz), 6.12 (ddd, 1H, H3', J = 5.7, 2.2, 2.2 Hz), 5.82 (ddd, 1H, H2', J = 5.7, 2.2, 2.2 Hz), 5.73 (ddddd, 1H, H1', J = 8.9, 6.1, 2.2, 2.2, 2.2 Hz), 4.17 (dd, 1H, 5'CH_2, J = 11.1, 5.0 Hz), 4.08 (dd,

1H, 5'CH_2, J = 11.1, 5.0 Hz), 3.10 (m, 1H, H4'), 2.80 (ddd, 1H, H6'$_\beta$, J = 14.1, 8.9, 8.9 Hz), 1.70 (s, 3H, CH_3), 1.45 (ddd, 1H, H6'$_\alpha$, J = 14.1, 6.1, 6.1 Hz). HRMS calcd. for $C_{16}H_{17}N_3O_3S$: 331.0991. Found: 331.0997.

Carbocyclic (±)-cis-5-(2"-thienyl)-2',3'-didehydro-2',3'-dideoxycytidine (19)

A one-necked flask equipped with condenser was charged with 10 ml of methanol/ triethylamine (9:1) and 100 mg (0.30 mmol) of **17.** The reaction mixture was refluxed for 40 h, after which the solvent was evaporated and the residue chromatographed using dichloromethane/methanol (9:1) as eluent. 70.0 mg (81 %) of a white solid was obtained, which after recrystallization from methanol had mp 195-240 °C (decomp.). ^{1}H NMR (CD_3OD): δ 7.72 (s, 1H, H6), 7.49 (dd, 1H, H5", J = 4.6, 1.8 Hz), 7.14 (m, 2H, H3", H4"), 6.15 (ddd, 1H, H3', J = 5.7, 1.9, 1.9 Hz), 5.75 (m, 2H, H1', H2'), 3.65 (dd, 1H, 5CH_2, J = 11.0, 4.4 Hz), 3.51 (dd, 1H, 5CH_2, J = 11.0, 4.5 Hz), 2.90 (m, 1H, H4'), 2.74 (ddd, 1H, H6'$_\beta$, J = 13.9, 8.7, 8.7 Hz), 1.52 (ddd, 1H, H6'$_\alpha$, J = 13.9, 5.6, 5.6 Hz). HRMS calcd. for $C_{14}H_{15}N_3O_2S$: 289.0885. Found: 289.0877.

Carbocyclic (±)-cis-5-(3"-thienyl)-2',3'-didehydro-2',3'-dideoxycytidine (20)

This compound was hydrolyzed and chromatographed as described above for **19** from 100 mg (0.30 mmol) of **18** giving 68 mg (78 %) of a white solid from methanol with mp 200-246 °C (decomp). ^{1}H NMR (CD_3OD): δ 7.67 (s, 1H, H6), 7.55 (dd, 1H, H5", J = 5.0, 3.0 Hz), 7.44 (dd, 1H, H2", J = 3.0, 1.4 Hz), 7.15 (dd, 1H, H4", J = 5.0, 1.4 Hz), 6.13 (ddd, 1H, H3', J = 5.8, 2.1, 2.1 Hz), 5.74 (m, 2H, H1', H2'), 3.67 (dd, 1H, 5'CH_2, 11.0, 4.3 Hz), 3.52 (dd, 1H, 5'CH_2, J = 11.0, 4.6 Hz), 2.94 (m, H4'), 2.73 (ddd, 1H, H6'$_\beta$, J = 14.0, 9.0, 9.0 Hz), 1.52 (ddd, 1H, H6'$_\alpha$, J = 14.0, 5.8, 5.8 Hz). HRMS calcd. for $C_{14}H_{15}N_3O_2S$: 289.0885. Found: 289.0885.

Acknowledgement

The authors are grateful to Mr Jan Glans for the HPLC separations, Mr Einar Nilsson for mass analyses, Dr Lotta Vrang and Ms Susanne Sedig for the test results. Grants from the Swedish National Board for Industrial and Technical Development (NUTEK) are gratefully acknowledged.

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Received October 17, 1994
Accepted December 27, 1994