Synthesis and Anti-HIV-1 Activities of 6-Arylthio and 6-Arylselenoacyclonucleosides

Bai-Chuan Pan, Zhi-Hao Chen, Giovanna Piras, Ginger E. Dutschman.
Elizabeth C. Rowe, Yung-Chi Cheng and Shih-Hsi Chu*

Division of Biology and Medicine, Brown University, Providence, RI 02912
School of Medicine, Yale University, New Haven, CT 06510
Received August 16, 1993

6-Arylthio and 6-arylselenoacyclonucleosides was synthesized and tested for the ability to inhibit replication of HIV-1. Lithiation of acyclonucleosides with LDA followed by reaction with the electrophiles phenyl disulfide, diphenyl diselenide, 2,2'-dipyrdyl disulfide or 2,2'-dipyridyl diselenide afforded 6-(arylthio or arylseleno)acyclonucleosides **5a-c, 6, 7, 9, 15a-c, 17a-c.** Compounds **19a-c** and **20a-c** were obtained by deprotection of corresponding TBDMS derivatives. Dehydrated products **16a,** and **18a-c** were also formed during the reactions. 5-Ethyl-6-(α-pyridylthio or α-pyridylseleno) disubstituted acyclouracils **6** and **7** were more active against HIV-1 in both MT-2 and CEM-IW cell lines than AZT, DDC, DDI or D4T. The EC_{50} of **6** against HIV-1 in CEM-IW cell was in the nanomolar range with a therapeutic index of 1100.

J. Heterocyclic Chem., **31**, 177 (1994).

For several years there has been an intensive search for drugs effective in the chemotherapy of AIDS. So far no compounds have been discovered that are completely satisfactory for the treatment of AIDS, or even as effective as AZT (3'-deoxy-3'-azidothymidine). Only a few compounds such as DDC (2',3'-dideoxycytidine), DDI (2',3'-dideoxyinosine), and D4T (2',3'-didehydro-3'-deoxythymidine) have been developed to the point of clinical trials and these are likely to have toxic side effects. In view of the epidemic spread of AIDS and the fact that it is ultimately fatal, there is a pressing need to find compounds more suitable for clinical use, more effective against HIV, less likely to induce drug resistance and less toxic in use for long term therapy in individuals with AIDS.

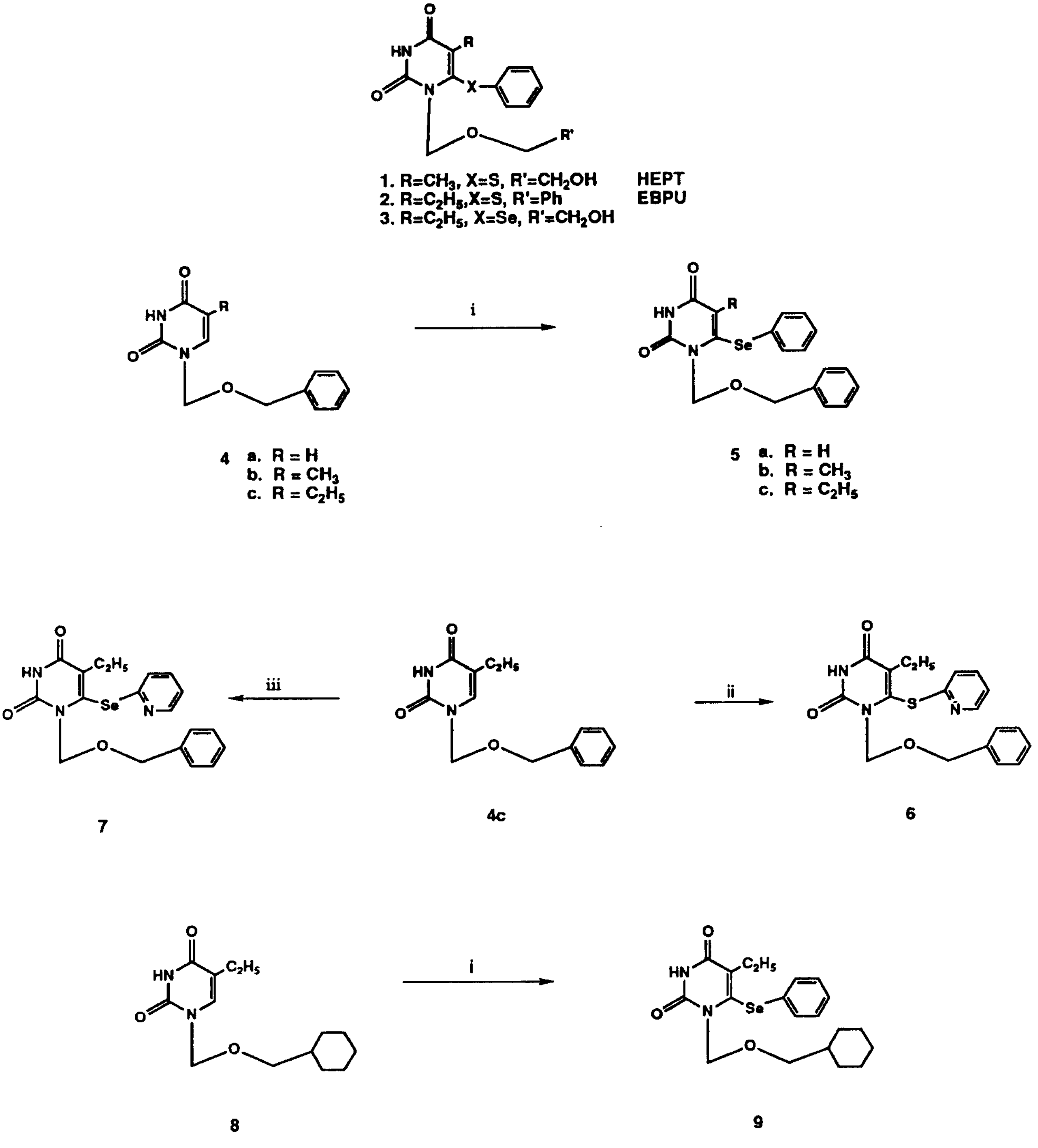
Drugs now known to inhibit the replication of HIV fall into two categories: (i) The chain terminators like AZT, DDI, DDC and D4T, which lack 3'-OH group on the deoxyribose moiety to be phosphorylated, built into nucleic acid chains of normal nucleotide units but without 3'-OH group the chain cannot be continued. (ii) Inhibitors without any OH or group that can be phosphorylated inhibit by distorting the conformation of the reverse transcriptase to the point where it cannot function as an enzyme. Examples of drugs which act by the latter mechanism are TIBO (tetrahydroimidazobenzodiazepinone) [1,2], nevirapine (11-cyclopropyl-5,11-dihydro-4-methyl-6*H*-dipyrido[3,2-*b*:2',3'-*e*][1,4]diazepin-6-one) [3,4], HEPT (**1**, 1-hydroxyethoxymethyl-6-phenyl-thiothymine) [5], EBPU (**2**, 5-ethyl-1-(benzyloxymethyl)-6-phenylthiouracil) [6,7] and BHAPs (bis(heteroaryl)piperazines) [8].

A few selenium containing nucleoside analogs have been made and tested as HIV inhibitors. 2-Seleno-4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-(1*H*)-one [1,2], a TIBO derivative, was found to be 5 times as active against HIV-1 in MT-4 cells as the corresponding sulfur compound. Benzisoselenazolone [9] and its diselenides inhibited HIV-1 at micromolar concentrations, whereas the corresponding sulfur compounds were less active and more toxic. Goudgaon and Schinazi [10] prepared a series of phenylseleno analogs of HEPT and found that 1-[(2-hydroxyethoxy)methyl]-6-(phenylselenyl)thymine (**3**) was more active than HEPT against both HIV-1 and HIV-2 in EC_{50} at the μM and 10 μM level, respectively.

In this paper we report the synthesis and evaluation of a series of arylseleno and arylthio acyclonucleosides related to HEPT and EBPU which are highly active against HIV-1.

Our first type of modification was the replacement of the phenylthio group at 6-position of EBPU **2** by a phenylseleno group, according to the synthesis shown in Scheme 1. In each case we synthesized three 5-substituted-1-benzyloxymethyl-6-(phenylseleno)uracils **5a-c**. Of these three the 5-ethyl substituted compound **5c** was found to be the most active. For comparison purposes the phenyl group of the acyclo moiety of **5c** was replaced by a cyclohexyl group for the synthesis of compound **9**. This yielded a less active compound and was not investigated further. A second modification was the replacement of the phenylthio group at 6-position of **2** by an α-pyridylthio or an α-pyridylseleno group in order to increase both water and lipid solubilities. 5-Ethyl-1-(benzyloxymethyl)-6-(α-pyridylthio)uracil (**6**) and 5-ethyl-1-benzyloxy-methyl-6-(α-pyridylseleno)uracil (**7**) were synthesized and evaluated.

The last variation was made by combining features of the two side chains on the 1-position of HEPT **1** and EBPU **2** to make a series of 5-substituted-1-benzyloxymethyl-6-phenylthio (or phenylseleno)uracils **19a-c, 20a-c**. 5-Substituted-1-[(1'-phenylvinyloxy)methyl]-6-[phenylthio-(or phenylseleno)]uracils **16a, 18a-c** were also obtained as

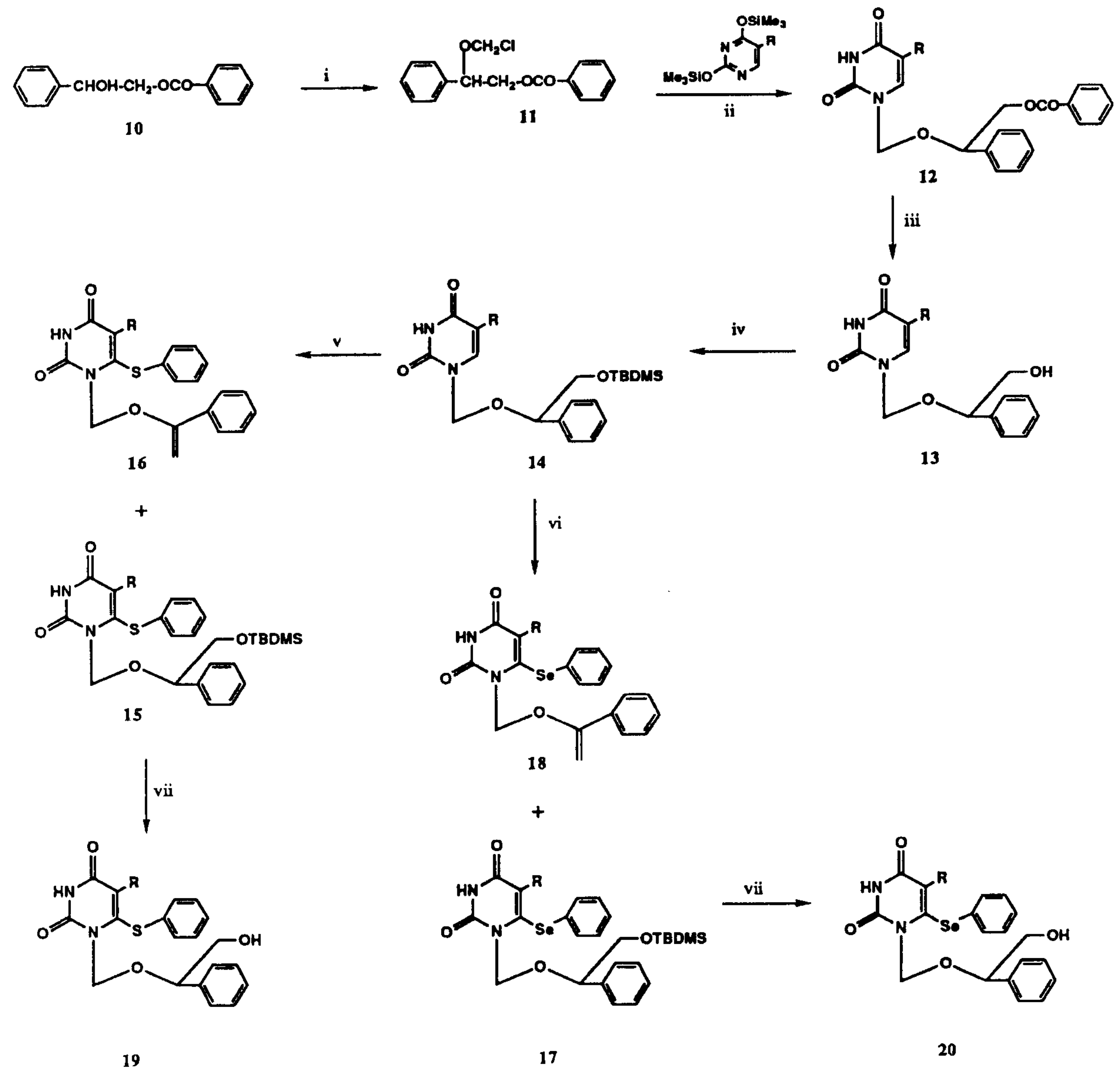


i. LDA / diphenyl diselenide; ii. LDA / a,a'-dipyridyl disulfide;
iii. LDA / a.a'-dipyridyl diselenide.

Scheme 1

byproducts during the above preparations as shown in Scheme 2.

5-Substituted-1-(benzyloxymethyl)uracil **4a-c** was lithiated with LDA, reacted with diphenyl diselenide to give 5-substituted-1-(benzyloxymethyl)-6-(phenylseleno)-uracils **5a-c**. Reaction of the lithiated 5-ethyl-1-(benzyloxymethyl)uracil (**4c**) with 2,2'-dipyridyl disulfide or 2-2'-dipyridyl diselenide [11] gave 5-ethyl-1-(benzyl-



a. R = H
b. R = CH_3
c. R = C_2H_5

i. (HCHO)n / HCl; ii. 5-substituted- 2-4-bis(trimetylsilyloxy)pyrimidine / K_2CO_3 / CH_2Cl_2; iii. K_2CO_3 / CH_3OH; iv. TBDMSCl / imidazole; v. LDA / Ph_2S_2; vi. LDA / α,α'-dipyridyl disulfide; vii. n-Bu_4NF

Scheme 2

oxymethyl)-6-(α-pyridylthio)uracil (**6**) and 5-ethyl-1-(benzyloxymethyl)-6-(α-pyridylseleno)uracil (**7**), respectively. 5-Ethyl-1-(cyclohexylmethyoxy)methyl-6-(phenylseleno)uracil (**9**) was prepared by the same method from 5-ethyl-1-[(cyclohexylmethoxy)methyl]uracil (**8**). (2-Phenyl-2-hydroxy)ethyl benzoate (**10**) was converted into the chloromethylated ether (**11**) by reacting with paraformaldehyde and dry hydrogen chloride in methylene chloride. Condensation of chloromethylated ether with the corresponding 5-substituted-2,4-bis(trimethylsilyloxy)pyrimidines was accomplished by stirring with anhydrous potassium carbonate in methylene chloride to give the corresponding 5-substituted-1-{[(1'-phenyl-2'-benzoyloxy)ethoxy]methyl}uracils **12a-c**. Hydrolysis of the benzoates **12a-c** with methanolic potassium carbonate gave the deprotected 5-substituted-1-{[(1'-phenyl-2'-hydroxy)-

ethoxy]methyl}uracils **13a-c**.

From the latter **13a-c** the corresponding 5-substituted-1-{[1'-phenyl-2'-(*t*-butyldimethylsilyloxy)ethoxy]methyl}-uracils **14a-c** were prepared by reacting with *t*-butyldimethylsilyl chloride and imidazole in DMF. Compounds **14a-c** in THF were lithiated with LDA and then reacted with phenyl disulfide. After quenching with acetic acid, the corresponding 5-substituted-1-{[1'-phenyl-2'-(*t*-butyldimethylsilyloxy)ethoxy]methyl}-6-(phenylthio)uracils **15a-c** were obtained. From the reaction mixture the more polar byproducts, 1-[(1'-phenylvinyloxy)methyl]-6-(phenylthio)uracil (**16a**) was also isolated. Decreasing the LDA used for lithiation to 2.5 equivalents and the reaction time to 2 hours reduced the quantities of **16a** that could be isolated from the reaction mixtures. Reaction of lithiated **14a-c** with diphenyl diselenide gave the corresponding 5-substituted-1-{[1'-phenyl-2'-(*t*-butyldimethylsilyloxy)-ethoxy] methyl}-6-(phenylseleno)uracils **17a-c** and 5-substituted-1-[(1'-phenylvinyloxy)methyl]-6-(phenylseleno)-uracils **18a-c**. Deprotection of *t*-butyldimethylsilyl group with tetra-*n*-butylammonium fluoride gave the corresponding 5-substituted-1-{[(1'-phenyl-2'-hydroxy)ethoxy]methyl}-6-(phenylthio)uracils **19a-c** and 5-substituted-1-{[(1'-phenyl-2'-hydroxy)ethoxy]methyl}-6-(phenylseleno)uracils **20a-c**.

Biological Activities

Evaluation by the Developmental Therapeutics Program of the National Cancer Institute against HIV-1 in CEM-IW cell line demonstrated that compounds **2** and **5c** were active at a 50% effective concentration lever (EC$_{50}$) of 10^{-2} μM. Against HIV-1 in this cell line compounds **2** and **5c** were approximately equally active and equally toxic. However the 6-α–pyridylthio substituted compound **6** was active (EC$_{50}$) at a concentration level of 9.0 x 10^{-4} μM, with a therapeutic index of 1100. Thus compound **6** is more potent in this model system than compound **2** and more potent than drugs now in clinical use (*i.e.* AZT, DDC, DDI and D4T).

Compounds **5c, 6, 7** were also evaluated for the anti-HIV-1 (HTLV-III) activity and cytotoxicity in the MT-2 cell line and compared to the activity of HEPT(**1**) and EBPU (**2**). As shown in Table 2, these compounds were 466-1400 fold more potent than HEPT, equipotent to EBPU, and more active than AZT and the other clinically used anti-HIV drugs, with EC$_{50}$s in the nanomolar range. The introduction of a pyridylthio or pyridylseleno group reduced toxicity for the host cells even though these modifications did not increase the anti-HIV-1 activity. Unlike results obtained by NCI [15], compound **6** did not have the strongest inhibitory effect; this is probably due to the different cell system employed. Since non-nucleoside compounds target the reverse transcriptase enzyme, we evaluated the ability of these compounds to inhibit an inhibition of RNA-dependent DNA polymerase. The results indicated no significant difference in inhibition of HIV- 1 RT among all compounds; indeed, the presence of the pyridyl group did not improve the inhibitory effect (Table 2 column 3). Moreover, both viral growth and enzyme activity inhibition studies revealed no quantitative potency differences between thio and seleno compounds. HIV-2 reverse transcriptase was totally unaffected by these compounds at concentrations < 10 μM (data not shown).

Table 1

Inhibition of HIV Replication in CEM-IW Cells (NCI) [15]

Compound	EC$_{50}$ [a] (μM)	IC$_{50}$ [b] (μM)	TI$_{50}$ [c]
2	0.012	>0.71	>58.0
5a	inactive	-	-
5b	0.410	53.0	130.
5c	0.012	>0.63	>50.0
6	0.00090	>0.98	>1100.
7	0.039	3.10	>80.0
9	9.30	17.0	>1.80
AZT	0.00765	>1.0	130.
DDC	0.297	>10.0	33.7
DDI	4.60	>20.0	4.30

[a] Concentration that inhibiting replication of HIV-1 by 50%. [b] Concentration that inhibiting replication of CEM-IW cells by 50%. [c] Therapeutic index, TI = IC$_{50}$/ EC$_{50}$.

Table 2

Cytotoxicity and Inhibition of HIV-1 in MT-2 Cells

Compound	MT-2 IC$_{50}$ [a] (μM)	HIV- 1 (HTLV-III) EC$_{50}$ [b] (μM)	HIV- 1 RT ED$_{50}$ [c] (μM)
5c	5 ±0.5	0.02 ± 0.005	0.07 ± 0.012
6	24 ± 0.1	0.04 ± 0.1	0.03 + 0.03
7	10 ± 1	0.06 ± 0.02	0.05 ± 0.001
2 (EBPU)	19.3	0.02 ± 0.006	0.07 ± 0.013
1 (HEPT)	182	28	23
AZT	—	0.11 ± 0.02	—
DDI	—	13 ± 5.7	—
DDC	—	1.45 ± 0.72	—
D4T	—	4.7 ± 3.2	—

[a] Cytotoxic concentration of compound required to reduce 50% of viability of MT-2 cells. [b] Effective concentration of compound required to achieve 50% protection of MT-2 cell against the cytopathic effect of HIV-1. [c] Dose of compound required to achieve the 50% inhibition of enzyme activity; poly(rC)-oligo(dG) 12-18 was used as template-primer.

In MT-2 cells, compound **7** is, if anything, more active than **6**. Compounds **6** and **7** both are more active than AZT and the other clinically-used drugs. Evaluation of **16a, 18a-c, 19a-c** and **20a-c** are presently in progress.

EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus and are uncorrected. The uv absorption maxima and extinction coefficients were obtained using a Perkin-Elmer Model Lambda 3A recording spectrophotometer. The nmr spectra were run on a Brucker WM-400. Analyses were performed by the Baron Consulting Co., of Orange, CT and the Galbraith Laboratories, of Knoxville, TN.

5-Ethyl-1-benzyloxymethyl-6-(phenylseleno)uracil (**5a**).

1-(Benzyloxymethyl)uracil (**4a**, 464 mg, 2 mmoles) was dissolved in dry THF (10 ml) and cooled to -78° in an argon atmosphere. To the solution there was added 36 ml of an LDA solution (1.4 *M* in heptane-THF-ethyl benzene, 5 mmoles) dropwise with stirring at -78°. After addition it was stirred for 1 hour at the same temperature and a solution of diphenyl diselenide (1.24 g, 4 mmoles) in dry THF (4 ml) was added at -78°. The reaction mixture was stirred for two more hours and then quenched by adding acetic acid (0.5 ml). The solvent was removed under reduced pressure and the residue extracted with methylene chloride and washed with water. After removal of solvent under reduced pressure the residue was purified by chromatography on silica gel and eluted with 10% ether in methylene chloride to give desired product **5a** (426 mg, 55%), mp 175-176°; uv (ethanol): λ max 265 nm (9519); ^{1}H nmr (deuteriochloroform): δ 4.70 (s, 2H, CH_2 of Bzl), 5.23 (d, 1 H, C5-H, J = 2.0 Hz), 5.61 (s, 2 H, NCH_2O), 7.30-7.54 (m, 8 H, ArH), 7.64-7.68 (m, 2 H, ArH).

Anal. Calcd. for $C_{18}H_{16}N_2O_3Se$: C, 55.85; H, 4.17; N, 7.24. Found: C, 56.14; H, 3.89; N, 7.29.

1-Benzyloxymethyl-6-(phenylseleno)thymine (**5b**).

This compound was prepared from 1-(benzyloxymethyl)-thymine (**4b**) in 53% yield by the method used for the preparation of compound **5c**, mp 165-167°; uv (ethanol): λ max 265 nm (9067); ^{1}H nmr (deuteriochloroform): δ 1.97 (s, 3 H, CH_3), 4.64 (s, 2 H, CH_2 of Bzl), 5.77 (s, 2 H, NCH_2O), 7.27-7.36 (m, 10 H, ArH).

Anal. Calcd. for $C_{19}H_{18}N_2O_3Se$: C, 56.90; H, 4.52; N, 6.99. Found: C, 56.88; H, 4.13; N, 6.79.

1-Benzyloxymethyl-6-(phenylseleno)uracil (**5c**).

This compound was prepared from 5-ethyl-1-(benzyloxymethyl)uracil (**4c**) in 56% yield by the method of the preparation of compound **5a**, mp 138-139°; uv (ethanol): λ max 267 nm (9345); ^{1}H nmr (deuteriochloroform): δ 0.90 (t, 3 H, CH_3, J = 7.4 Hz), 2.63 (q, 2 H, CH_2, J = 7.4 Hz), 4.62 (s, 2 H, CH_2 of Bzl), 5.55 (s, 2 H, NCH_2O), 7.25-7.34 (m, 10 H, ArH).

Anal. Calcd. for $C_{20}H_{20}N_2O_3Se$: C, 57.83; H, 4.85; N, 6.75. Found: C, 57.97; H, 4.91; N, 6.73.

5-Ethyl-1-benzyloxymethyl-6-(α-pyridylthio)uracil (**6**).

To a solution of 5-ethyl-1-(benzyloxymethyl)uracil (**4c**, 260.3 mg, 1 mmole) in dry THF (5 ml) there was added 1.8 ml of an LDA solution (1.4 *M* in heptane-THF-ethyl benzene, 2.4 mmoles) dropwise with stirring at -78° under dry nitrogen. After the mixture was stirred for 1 hour at -78°, α, α'-dipyridyl disulfide (550 mg, 2.5 mmoles) in dry THF (2 ml) was added. The reaction mixture was stirred for two more hours while maintaining the temperature at -78° and then quenched by adding acetic acid (0.5 ml). The whole was evaporated to dryness. The residue was chromatographed on silica gel and eluted with 10% ether in methylene chloride to give **6** (318 mg, 43%), mp 123-125°; uv (ethanol): λ max 279 nm (9982); ^{1}H nmr (deuteriochloroform): δ 0.96 (t, 3 H, CH_3, J = 7.4 Hz), 2.61 (q, 2 H, CH_2, J = 7.4 Hz), 4.63 (s, 2 H, CH_2 of Bzl), 5.55 (s, 2 H, NCH_2O), 7.03-7.07 (m, 1 H, ArH of pyr), 7.15-7.18 (m, 1 H, ArH of pyr), 7.22-7.31 (m, 5 H, ArH of Ph), 7.51-7.57 (m, 1 H, ArH of pyr), 8.34-8.37 (m, 1 H, ArH of pyr), 9.15 (s, 1H, NH).

Anal. Calcd. for $C_{19}H_{19}N_3O_3S$: C, 61.77; H, 5.18; N, 11.37. Found: C, 61.96; H, 5.42; N, 11.49.

5-Ethyl-1-benzyloxymethyl-6-(α-pyridylseleno)uracil (**7**).

5-Ethyl-1-(benzyloxymethyl)uracil (**4c**) was lithiated with LDA and then treated with α,α'-dipyridyl diselenide [11] by the method described for the preparation of **6**. Compound **7** was obtained in 40% yield, mp 135-136°; uv (ethanol): λ max 275 nm (9500), ^{1}H nmr (deuteriochloroform): δ, 0.95 (t, 3 H, CH_3, J = 7.4 Hz), 2.65 (q, 2 H, CH_2, J = 7.4 Hz), 4.60 (s, 2 H, CH_2 of Bzl), 5.68 (s, 2 H, NCH_2O), 7.06-7.11 (m, 1 H, ArH of pyr), 7.20-7.31 (m, 6 H, ArH of Ph and pyr), 7.45-7.52 (m, 1 H, ArH of pyr), 8.37-8.42 (m, 1 H, ArH of pyr), 9.15 (s, 1H, NH).

Anal. Calcd. for $C_{19}H_{19}N_3O_3Se$): C, 54.81; H, 4.60; N, 10.17. Found: C, 54.90; H, 4.93; N, 9.91.

5-Ethyl-1-cyclohexylmethoxymethyl-6-(phenylseleno)uracil (**9**).

This compound was prepared from 5-ethyl-1-(cyclohexylmethoxymethyl)uracil (**8**) by the method described for the preparation of compound **5c**, mp 116-118°; uv (ethanol): λ max 274 nm (8859); ^{1}H nmr (deuteriochloroform): δ 0.82-0.92 (m, 2 H, cyclohexyl H), 0.90 (t, 3 H, CH_3, J = 7.4 Hz), 1.07-1.28 (m, 4 H, cyclohexyl H), 1.41-1.52 (m, 1 H, cyclohexyl H), 1.62-1.73 (m, 4 H, cyclohexyl H), 2.64 (q, 2 H, CH_2, J = 7.4 Hz), 3.32 (d, 2 H, OCH_2, J = 6.5 Hz), 5.57 (s, 2H, NCH_2O), 7.27-7.38 (m, 5 H, ArH), 8.48 (br s, 1 H, NH).

Anal. Calcd. for $C_{20}H_{26}N_2O_3Se$: C, 57.00; H, 6.22; N, 6.65. Found: C, 57.06; H, 6.34; N, 6.56.

1-{[(1'-Phenyl-2'-benzoyloxy)ethoxy]methyl}uracil (**12a**).

Dry uracil (1.12 g, 10 mmoles) and ammonium sulfate (50 mg) were suspended in hexamethyldisilazane (5 ml) and heated under reflux for approximately 2 hours with the exclusion of moisture, until all of the uracil was dissolved. Excess hexamethyldisilazane was distilled off under reduced pressure, leaving 2,4-bis(trimethylsilyloxy)pyrimidine as a residue. A suspension of (2-phenyl-2-hydroxy)ethyl benzoate (**10**, 3.15 g, 13 mmoles) and paraformaldehyde (780 mg) in methylene chloride (45 ml) was cooled to 0° and dry hydrogen chloride bubbled through the suspension until it was saturated. The reaction mixture was allowed to stand at 0° overnight, then washed with water and dried over anhydrous magnesium sulfate. The filtered solution of chloromethylated product was added to a suspension of 2,4-bis(trimethylsilyloxy)pyrimidine and finely powdered anhydrous potassium carbonate (1.38 g, 10 mmoles) in methylene chloride (15 ml) and stirred at room temperature for 24 hours. The reaction mixture was cooled to 0° then treated with water. The water layer was separated and the solvent was evaporated to dryness under reduced pressure. The residue was chromatographed on silica gel and eluted with 5% ether in methylene chloride to give 0.7 g of **12a** (53%), mp 156-157°; uv (ethanol): λ max 257 nm (8705); ^{1}H nmr (deuteriochloroform): δ 4.35 (dd, 1 H, CH_2O, J = 3.4, 11.9 Hz), 4.55 (dd, 1 H, CH_2O, J = 8.7, 11.9 Hz), 4.94 (dd, 1 H, CH, J = 3.4, 8.7 Hz), 5.19 (dd, 2 H, NCH_2O, J = 10.8, 46.5 Hz), 5.52 (dd, 1 H, C5-H, J = 2.3, 8.0 Hz), 7.21

(d, 1 H, C6-H, J = 8.0 Hz), 7.34-7.48 (m, 7 H, ArH), 7.56-7.61 (m, 1 H, ArH), 7.98-8.03 (m, 2 H, ArH), 8.40 (br s, 1 H, NH).

Anal. Calcd. for $C_{20}H_{18}N_2O_5$: C, 65.56; H, 4.95; N, 7.65. Found: C, 65.27; H, 4.95; N, 7.43.

1-{[(1'-Phenyl-2'-benzoyloxy)ethoxy]methyl}thymine (**12b**).

This compound was synthesized from thymine in 53% yield by the method indicated above, mp 162-163°; uv (ethanol): λ max 263 nm (9012); ^{1}H nmr (deuteriochloroform): δ 1.70 (s, 3 H, CH_3), 4.33 (dd, 1 H, CH_2O, J = 3.3, 11.9 Hz), 4.56 (dd, 1 H, CH_2O, J = 8.9, 11.9 Hz), 4.94 (dd, 1 H, CH, J = 3.3, 8.9 Hz), 5.07 (d, 1 H, NCH_2O, J = 10.8 Hz), 5.25 (d, 1 H, NCH_2O, J = 10.8 Hz), 5.52 (dd, 1 H, C5-H, J = 2.3, 8.0 Hz), 7.01 (dd, 1 H, C6-H, J = 1.2, 2.5 Hz), 7.34-7.47 (m, 7 H, ArH), 7.56-7.60 (m, 1 H, ArH), 7.98-8.03 (m, 2 H, ArH), 8.40 (br s, 1 H, NH).

Anal. Calcd. for $C_{21}H_{20}N_2O_5$: C, 66.30; H, 5.30; N, 7.37. Found: C, 66.30; H, 5.20; N, 7.26.

5-Ethyl-1-{[(1'-phenyl-2'-benzoyloxy)ethoxy]methyl}uracil (**12c**).

This compound was synthesized from 5-ethyluracil in 51 % yield by the method used for preparation of **12a**. Compound **12c** had mp 157-158°; uv (ethanol): λ max 263 nm (8705); ^{1}H nmr (deuteriochloroform): δ 0.99 (t, 3H, CH_3, J = 7.5 Hz), 2.14 (m, 2 H, CH_2), 4.32 (dd, 1 H, CH_2O, J = 3.4, 11.9 Hz), 4.56 (dd, 1 H, CH_2O, J = 8.8, 11.9 Hz), 4.94 (dd, 1 H, CH, J = 3.4, 8.8 Hz), 5.13 (d, 1 H, NCH_2O, J = 10.8 Hz), 5.24 (d, 1 H, NCH_2O, J = 10.8 Hz), 6.95 (t, 1 H, C6-H, J = 1.2 Hz), 7.34-7.60 (m, 8 H, ArH), 7.98-8.02 (m, 2 H, ArH), 8.40 (br s, 1 H, NH).

Anal. Calcd. for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 66.82; H, 5.62; N, 7.28.

1-{[(1'-Phenyl-2'-hydroxy)ethoxy]methyl}uracil (**13a**).

Potassium carbonate (207 mg, 1.5 mmoles) and 1-{[(1'-phenyl-2'-benzoyloxy)ethoxy]methyl}uracil (**12a**, 366 mg, 1 mmole) was suspended in methanol (5 ml) and stirred at room temperature overnight. Methanol was evaporated under reduced pressure. The residue was partitioned between methylene chloride and water and the *p*H adjusted to about 7. After evaporation of the methylene chloride layer the residue was purified by chromatography on silica gel. Elution with 2% methanol in methylene chloride yielded the pure compound **13a** (242 mg, 92%), mp 177-178°; uv (ethanol): λ max 257 nm (8425); ^{1}H nmr (DMSO-d_6): δ 3.37-3.54 (m, 2 H, CH_2O), 4.55 (dd, 1 H, CH, J = 4.1, 7.7 Hz), 4.92 (t, 1 H, OH, J = 5.7 Hz), 5.11 (s, 2 H, NCH_2O), 5.47 (d, 1 H, C5-H, J = 7.9 Hz), 7.24-7.34 (m, 5 H, ArH), 7.61 (d, 1 H, C6-H, J = 7.9 Hz).

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38 N, 10.68. Found: C, 59.29; H, 5.49; N, 10.68.

1-{[(1'-Phenyl-2'-hydroxy)ethoxy]methyl}thymine (**13b**).

This compound was synthesized from 1-{[(1'-phenyl-2'-benzoyloxy)ethoxy]methyl}thymine (**12b**) in 94% yield by the method indicated above, mp 133-135°; uv (ethanol): λ max 263 nm (10466); ^{1}H nmr (DMSO-d_6): δ 1.70 (d, 3 H, CH3, J = 1.1 Hz), 3.36-3.43 (m, 1 H, CH_2O), 3.46-3.54 (m, 1 H, CH_2O), 4.53 (dd, 1 H, CH, J = 4.2, 7.6 Hz), 4.92 (t, 1H, OH, J = 5.7 Hz), 5.08 (dd, 2 H, NCH2O, J = 10.8, 19.1 Hz), 7.27-7.33 (m, 5 H, ArH), 7.44 (d, 1 H, C6-H, J = 1.1 Hz).

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 61.26; H, 5.84; N, 9.89.

5-Ethyl-1-{[(1'-phenyl-2'-hydroxy)ethoxy]methyl}uracil (**13c**).

This compound was synthesized from 5-ethyl-1-{[(1'-phenyl-2,-benzoyloxy)ethoxy]methyl)uracil (**12c**) in 90% yield by the method for preparation of **13a**, mp 125-127°; uv (ethanol): λ max 263 nm (8213); ^{1}H nmr (DMSO-d_6): δ 1.09 (t, 3 H, CH_3, J = 7.5 Hz), 2.28 (q, 2 H, CH_2, J = 7.5 Hz), 3.64 (dd, 1 H, CH_2O, J = 3.6, 12.1 Hz), 3.75 (dd, 1 H, CH_2O, J = 8.5, 12.1 Hz), 4.68 (dd, 1 H, CH, J = 3.6, 8.5 Hz), 5.20 (dd, 2 H, NCH_2O, J = 10.6, 23.3 Hz), 6.94 (t, 1 H, C_6-H, J = 1.2 Hz), 7.28-7.36 (m, 5 H, ArH).

Anal. Calcd. for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.25; N, 9.65. Found: C, 61.94; H, 6.29; N, 9.63.

1-{[1'-Phenyl-2'-(*t*-butyldimethylsilyloxy)ethoxy]methyl}uracil (**14a**).

A solution of 1-{[(1'-phenyl-2'-hydroxy)ethoxy]methyl}-uracil (**13a**, 552.5 mg, 2 mmoles) and imidazole (204 mg, 3 mmoles) in DMF (5 ml) was cooled to 10°, and then treated with *t*-butyldimethylsilyl chloride (332 mg, 2.2 mmoles). The reaction mixture was stirred overnight at room temperature. It was then poured into water and extracted with methylene chloride. After evaporation of the solvent, the residue was purified by chromatography on silica gel. Elution with 5% ether in methylene chloride gave pure **14a** (542 mg, 72%): mp 158-159°; uv (ethanol): λ max 257 nm (8142); ^{1}H nmr (deuteriochloroform): δ 0.02 (s, 3 H, CH_3Si), 0.04 (s, 3 H, CH_3Si), 0.87 (s, 9 H, *t*-Bu), 3.64 (dd, 1 H, CH_2O, J = 3.8, 11.2 Hz), 3.78 (dd, 1 H, CH_2O, J = 8.0, 11.2 Hz), 4.57 (dd, 1 H, CH, J = 3.8, 8.0 Hz), 5.19 (dd, 2 H, NCH_2O, J = 10.6, 12.1 Hz), 5.65 (dd, 1 H, C5-H, J = 1.2, 8.0 Hz), 7.31 (d, 1 H, C_6-H, J = 8.0 Hz), 7.27-7.36 (m, 5 H, ArH), 8.40 (br s, 1 H NH).

Anal. Calcd. for $C_{19}H_{28}N_2O_4Si$: C, 60.61; H, 7.49; N, 7.44. Found: C, 60.54; H, 7.79; N, 7.43.

1-{[1'-Phenyl-2'-(*t*-butyldimethylsilyloxy)ethoxy]methyl}thymine (**14b**).

This compound was synthesized from 1-{[(1'-phenyl-2'-hydroxy)ethoxy]methyl}thymine (**13b**) in 70% yield by the method indicated above, mp 157-158°; uv (ethanol): λ max 263 nm (8529); ^{1}H nmr (deuteriochloroform): δ 0.02 (s, 3 H, CH_3Si), 0.04 (s, 3 H, CH_3Si), 0.88 (s, 9 H, *t*-Bu), 1.86 (d, 3 H, CH_3, J = 1.2 Hz), 3.64 (dd, 1 H, CH_2O, J = 3.9, 11.1 Hz), 3.78 (dd, 1 H, CH_2O, J = 8.0, 11.1 Hz), 4.57 (dd, 1 H, CH, J = 3.9, 8.0 Hz), 5.16 (dd, 2 H, NCH_2O, J = 10.7, 13.0 Hz), 7.07 (dd, 1 H, C_6-H, J = 1.2, 2.4 Hz), 7.27-7.35 (m, 5 H, ArH), 8.40 (br s, 1 H NH).

Anal. Calcd. for $C_{20}H_{30}N_2O_4Si$: C, 61.50; H, 7.74; N, 7.17. Found: C, 61.50; H, 7.84; N, 7.06.

5-Ethyl-1-{[1'-Phenyl-2'-(*t*-butyldimethylsilyloxy)ethoxy]methyl}uracil (**14c**).

This compound was synthesized from 5-ethyl-1-{[(1'-phenyl-2'-hydroxy)ethoxy]methyl)uracil (**13c**) in 73% yield by the method for the preparation of **14a**, mp 138-140°; uv (ethanol): λ max 263 nm (8579); ^{1}H nmr (deuteriochloroform): δ 0.02 (s, 3 H, CH_3Si), 0.04 (s, 3 H, CH_3Si), 0.88 (s, 9 H, *t*-Bu), 1.10 (t, 3 H, CH_3, J = 7.5 Hz), 2.29 (m, 2 H, CH_2), 3.65 (dd, 1 H, CH_2O, J = 3.9, 11.1 Hz), 3.79 (dd, 1 H, CH_2O, J = 7.9, 11.1 Hz), 4.58 (dd, 1 H, CH, J = 3.9, 7.9 Hz), 5.19 (dd, 2 H, NCH_2O, J = 10.6, 22.9 Hz), 7.01 (t, 1 H, C_6-H, J = 1.2 Hz), 7.27-7.35 (m, 5 H, ArH), 8.40 (br s, 1 H NH).

Anal. Calcd. for $C_{21}H_{32}N_2O_4Si$: C, 62.34; H, 7.97; N, 6.93. Found: C, 62.08; H, 7.61; N, 6.70.

1-{[1'-phenyl-2'-(*t*-butyldimethylsilyloxy)ethoxy]methyl}-6-(phenylthio)uracil (**15a**).

A solution of 1-{[1'-phenyl-2'-(*t*-butyldimethylsilyloxy)-ethoxy]methyl}uracil (**14a**, 376.5 mg, 1 mmole) in dry THF (10 ml) was cooled to -78 ° in a nitrogen atmosphere and 1.5 ml 2 *M* solution of LDA in heptane-THF-ethyl benzene (3 mmoles) was added dropwise with stirring at -78°. After addition was complete the stirring was continued for 1 hour at -78° then a solution of phenyl disulfide (436 mg, 2 mmoles) in THF (2 ml) was added. The reaction mixture was stirred for two hours more at -78°, then at -50° overnight and then quenched with acetic acid (0.2 ml). After removal of solvent under reduced pressure the residue was partitioned between methylene chloride and water, and the methylene chloride solution was washed with water and evaporated to dryness under reduced pressure. The residue was chromatographed on silica gel and eluted with 2% ether in methylene chloride to give two products. The more polar product was compound **16a** and the less polar one was identified as compound **15a** (170 mg, 35%), mp 146-147°; uv (ethanol): λ max 281 nm (9364); ^{1}H nmr (deuteriochloroform): δ 0.01 (s, 3 H, CH_3Si), 0.03 (s, 3 H, CH_3Si), 0.88 (s, 9 H, *t*-Bu), 3.67 (dd, 1 H, CH_2O, J = 4.1, 11.1 Hz), 3.85 (dd, 1 H, CH_2O, J = 7.8, 11.1 Hz), 4.73 (dd, 1 H, CH, J = 4.1, 7.8 Hz), 4.89 (d, 1 H, C5-H, J = 2.2 Hz), 5.54 (d, 2 H, NCH_2O, J = 11.5 Hz), 5.68 (d, 2 H, NCH_2O, J = 11.5 Hz), 7.28-7.41 (m, 5 H, ArH), 7.47-7.58 (m, 5 H, ArH).

Anal. Calcd. for $C_{25}H_{32}N_2O_4SSi$: C, 61.95; H, 6.66; N, 5.78. Found: C, 61.87; H, 6.54; N, 5.94.

1-[(1'-Phenylvinyloxy)methyl]-6-(phenylthio)uracil (**16a**).

The more polar portion isolated from the above reaction mixture was identified as compound **16a** (58 mg, 16%), mp 143-145°; uv (ethanol): λ max 254 nm (9483), 278 (8824); ^{1}H nmr (deuteriochloroform): δ, 4.49 (d, 1 H, vinyl H, J = 3.5 Hz), 4.88 (d, 1 H, vinyl H, J = 3.5 Hz), 5.09 (d, 1 H, C5-H, J = 2.1 Hz), 5.91 (s, 2 H, NCH_2O), 7.33-7.68 (m, 10 H, ArH), 8.55 (br s, 1 H, NH).

Anal. Calcd. for $C_{19}H_{16}N_2O_3S$: C, 64.75; H, 4.58; N, 7.95. Found: C, 64.49; H, 4.42; N, 7.72.

1-{[1'-Phenyl-2'-(*t*-butyldimethylsilyloxy)ethoxy]methyl}-6-(phenylthio)thymine (**15b**).

This compound was prepared from 1-{[1'-phenyl-2'-(*t*-butyldimethylsilyloxy)ethoxy]methyl}thymine (**14b**) in 29% yield by the method used for the preparation of compound **15a**. Compound **15b** had mp 114-116°; uv (ethanol): λ max 244 nm (9776), 275 nm (7249); ^{1}H nmr (deuteriochloroform): δ 0.02 (s, 3 H, CH_3Si), 0.03 (s, 3 H, CH_3Si), 0.86 (s, 9 H, *t*-Bu), 1.93 (s, 3 H, CH_3), 3.60 (dd, 1 H, CH_2O, J = 4.3, 11.0 Hz), 3.76 (dd, 1 H, CH_2O, J = 7.7, 11.0 Hz), 4.65 (dd, 1 H, CH, J = 4.3, 7.7 Hz), 5.55 (d, 1 H, NCH_2O, J = 10.6 Hz), 5.69 (br s, 1 H, NCH_2O), 7.15-7.33 (m, 10 H, ArH), 8.25 (br s, 1 H, NH).

Anal. Calcd. for $C_{26}H_{34}N_2O_4SSi$: C, 62.61; H, 6.87; N, 5.62. Found: C, 62.51; H, 6.71; N, 5.67.

5-Ethyl-1-{[1'-phenyl-2'-(*t*-butyldimethylsilyloxy)ethoxy]-methyl}-6-(phenylthio)uracil (**15c**).

This compound was prepared from 5-ethyl-1-{[1'-phenyl-2'-(*t*-butyldimethylsilyloxy)ethoxy]methyl}uracil (**14c**) in 30% yield by the method used for the preparation of compound **15a**. It melted at 121-123 °; uv (ethanol): λ max 242 nm (9883), 275 (7836); ^{1}H nmr (deuteriochloroform): δ 0.01 (s, 3 H, CH_3Si), 0.03 (s, 3 H, CH_3Si), 0.88 (s, 9 H, *t*-Bu), 0.94 (t, 3 H, CH_3, J = 7.4 Hz), 2.58 (m, 2 H, CH_2), 3.56 (dd, 1 H, CH_2O, J = 4.4, 10.9 Hz), 3.72 (dd, 1 H, CH_2O, J = 7.7, 10.9 Hz), 4.65 (dd, 1 H, CH, J = 4.4, 7.7 Hz), 5.42 (d, 1 H, NCH_2O, J = 10.7 Hz), 5.58 (br s, 1 H, NCH_2O), 7.11-7.16 (m, 2 H, ArH), 7.20-7.32 (m, 8 H, ArH) 8.25 (br s, 1 H, NH).

Anal. Calcd. for $C_{27}H_{36}N_2O_4SSi$: C, 63.24; H, 7.08; N, 5.46. Found: C, 63.57; H, 7.31; N, 5.57.

1-{[1'-Phenyl-2'-(*t*-butyldimethylsilyloxy)ethoxy]methyl}-6-(phenylseleno)uracil (**17a**).

To a solution of 1-{[1'-phenyl-2'-(*t*-butyl-dimethylsilyloxy)-ethoxy]methyl}uracil (**14a**, 753 mg, 2 mmoles) in dry THF (20 ml) there was gradually added 3.4 ml of an LDA solution (1.5 *M* solution in cyclohexane-THF, 5 mmoles) at -78° in an argon atmosphere with stirring. After the addition was complete the reaction mixture was stirred at -78° for 1 hour and followed by the addition of diphenyl diselenide (1.24 g, 4 mmoles) in THF (4 ml) at -78°. Stirring was continued for 4 hours followed by quenching with acetic acid (0.5 ml). The solvent was removed under reduced pressure and the residue was extracted with methylene chloride and washed with water. After evaporation of solvent it was chromatographed on silica gel and eluted with 5% ether in methylene chloride to give the more polar compound **18a** and the less polar compound **17a** (361 mg, 34%), mp 150-152°; uv (ethanol): λ max 288 nm (9202); ^{1}H nmr (deuteriochloroform): δ 0.02 (s,3 H, CH_3Si), 0.04 (s, 3 H, CH_3Si), 0.86(s, 9 H, *t*-Bu), 3.67 (dd, 1 H, CH_2O, J = 4.1, 11.1 Hz), 3.84 (dd, 1 H, CH_2O, J = 7.8, 11.1 Hz), 4.67 (dd, 1 H, CH, J = 4.1, 7.8 Hz), 5.14 (d, 1 H, C5-H, J = 2.3 Hz), 5.57 (dd, 2 H, NCH_2O, J = 11.5, 24.9 Hz), 7.28-7.66 (m, 10 H, ArH), 8.05 (br s, 1 H, NH).

Anal. Calcd. for $C_{25}H_{32}N_2O_4SeSi$: C, 56.48; H, 6.07; N, 5.27. Found: C, 56.68; H, 5.77; N, 5.43.

1-[(1'-Phenyl-vinyloxy)methyl]-6-(phenylseleno)uracil (**18a**).

The more polar portion isolated from the above reaction mixture was identified as compound **18a** (122 mg, 15%), mp 183-184°; uv (ethanol): λ max 285 nm (9624); ^{1}H nmr (deuteriochloroform): δ 4.56 (d, 1 H, vinyl H, J = 3.5 Hz), 4.91 (d, 1 H, vinyl H, J = 3.5 Hz), 5.32 (d, 1 H, C5-H, J = 2.1 Hz), 5.92 (s, 2 H, NCH_2O), 7.35-7.78 (m, 10 H, ArH), 8.65 (br s, 1 H, NH).

Anal. Calcd. for $C_{19}H_{16}N_2O_3Se$: C, 57.15; H, 4.04; N, 7.02. Found: C, 57.41; H, 4.27; N, 7.31.

1-{[1'-phenyl-2'-(*t*-butyldimethylsilyloxy)ethoxy]methyl}-6-(phenylthio)thymine (**17b**).

This compound was prepared from 1-{[1'-phenyl-2'-(t-butyldimethylsilyloxy)ethoxy]methyl}thymine (**14b**) in 28% yield by the method used for the preparation of compound **17a**. Compound **17b** had mp 143-145°; uv (ethanol): λ max 260 nm (9006); ^{1}H nmr (deuteriochloroform): δ 0.01 (s, 3 H, CH_3Si), 0.03 (s, 3 H, CH_3Si), 0.84 (s, 9 H, *t*-Bu), 1.90 (s, 3 H, CH_3), 3.61 (dd, 1 H, CH_2O, J = 4.2, 11.0 Hz), 3.78 (dd, 1 H, CH_2O, J = 7.8, 11.0 Hz), 4.61 (dd, 1 H, CH, J = 4.2, 7.8 Hz), 5.67 (d, 1 H, NCH_2O, J = 10.3 Hz), 5.80 (br s, 1 H, NCH_2O), 7.27-7.34 (m, 10 H, ArH),

Anal. Calcd. for $C_{26}H_{34}N_2O_4SeSi$: C, 57.23; H, 6.23; N, 5.14. Found: C, 57.56; H, 6.08; N, 5.31.

1-[(1'-phenylvinyloxy)methyl]-6-(phenylseleno)thymine (**18b**).

The more polar portion isolated from the reaction mixture for the preparation of **17b** was identified as compound **18b** in 14% yield, mp 164-166°; uv (ethanol): λ max 254 nm (8541); ^{1}H nmr (deuteriochloroform): δ 2.06 (s, 3 H, CH_3), 4.37 (d, 1 H, vinyl H, J = 3.4 Hz), 4.82 (d, 1 H, vinyl H, J = 3.4 Hz), 5.59 (s, 2 H, NCH_2O), 7.24-7.54 (m, 10 H, ArH).

Anal. Calcd. for $C_{20}H_{18}N_2O_3Se$: C, 58.13; H, 4.39; N, 6.78. Found: C, 57.91; H, 3.98; N, 6.62.

5-Ethyl-1-{[1'-phenyl-2'-(*t*-butyldimethylsilyloxy)ethoxy] methyl}-6-(phenylseleno)uracil (**17c**).

This compound was prepared from 5-ethyl-1-{[1'-phenyl-2'-(*t*-butyldimethylsilyloxy)ethoxy]methyl}thymine (**14c**) in 26% yield by the method used for the preparation of compound **17a**, mp 168-170°; uv (ethanol): λ max 256 nm (8359); ^{1}H nmr (deuteriochloroform): δ 0.02 (s, 3 H, CH_3Si), 0.04 (s, 3 H, CH_3Si), 0.86 (s, 9 H, *t*-Bu), 0.87 (t, 3 H, CH_3, J = 7.4 Hz), 2.28 (m, 2 H, CH_2), 3.59 (dd, 1 H, CH_2O, J = 4.4, 11.0 Hz), 3.75 (dd, 1 H, CH_2O, J = 7.7, 11.0 Hz), 4.65 (dd, 1 H, CH, J = 4.4, 7.7 Hz), 5.58 (d, 1 H, NCH_2O, J = 10.6 Hz), 5.78 (br s, 1 H, NCH_2O), 7.23-7.33 (m, 10 H, ArH).

Anal. Calcd. for $C_{27}H_{36}N_2O_4SeSi$: C, 57.94; H, 6.48; N, 5.01. Found: C, 57.63; H, 6.24; N, 5.19.

5-Ethyl-1-[(1'-phenyl-vinyloxy)methyl]-6-(phenylseleno)-thymine (**18c**).

The more polar portion isolated from the reaction mixture for the preparation of **17c** in 13% yield, mp 141-143°; uv (ethanol): λ max 254 nm (8404); ^{1}H nmr (deuteriochloroform): δ 0.97 (t, 3 H, CH_3, J = 7.4 Hz), 2.73 (q, 2 H, CH_2, J = 7.4 Hz), 4.28 (d, 1 H, vinyl H, J = 3.3 Hz), 4.77 (d, 1 H, vinyl H, J = 3.3 Hz), 5.59 (s, 2 H, NCH_2O), 7.22-7.38 (m, 10 H, ArH), 8.38 (br s, 1 H, NH).

Anal. Calcd. for $C_{21}H_{20}N_2O_3Se$: C, 59.02; H, 4.71; N, 6.56. Found: C, 58.92; H, 4.13; N, 6.35.

1-{[(1'-Phenyl-2'-hydroxy)ethoxy]methyl}-6-(phenylthio)-uracil (**19a**).

A solution of 1-{[(1'-phenyl-2'-*t*-butyldimethylsilyloxy)-ethoxy]methyl}-6-(phenylthio)uracil (**15a**, 121 mg, 0.25 mmole) in THF (2 ml) was cooled to 0°, and treated with tetra-*n*-butylammonium fluoride solution (1 *M* solution in THF, 0.3 ml, 0.3 mmole). The reaction mixture was stirred at room temperature for 3 hours. The THF was removed under reduced pressure and the residue extracted with methylene chloride, washed with water and purified by chromatography on silica gel. Elution was with 3% ethanol in methylene chloride to give **19a** (80 mg, 86%), mp 178-180°; uv (ethanol): λ max 273 nm (9364); ^{1}H nmr (deuteriochloroform): δ 3.60-3.82 (m, 2 H, CH_2O), 4.45 (br s, 1 H, OH), 4.76 (dd, 1 H, CH, J = 3.4, 8.8 Hz), 4.92 (d, 1 H, C5-H J = 2.2 Hz), 5.57 (dd, 2 H, NCH_2O, J = 11.3, 26.9 Hz), 7.30-7.41 (m, 5 H, ArH), 7.45-7.59 (m, 5 H, ArH), 8.30 (br s, 1 H, NH).

Anal. Calcd. for $C_{19}H_{18}N_2O_4S$: C, 61.59; H, 4.90; N, 7.56. Found: C, 61.26; H, 4.98; N, 7.57.

1-{[(1'-Phenyl-2'-hydroxy)ethoxy]methyl}-6-(phenylthio)-thymine (**19b**).

This compound was obtained by the deprotection of 1-{[1'-phenyl-2'-(*t*-butyldimethylsilyloxy)ethoxy]methyl}-6-(phenylthio)thymine (**15b**) with tetra-*n*-butylammonium fluoride in 84% yield by the method indicated above, mp 166-168°; uv (ethanol): λ max 244 nm (10018), 275 nm (8073); ^{1}H nmr (deuteriochloroform): δ 2.00 (s, 3 H, CH_3), 2.15 (br s, 1 H, OH), 3.52-3.68 (m, 2 H, CH_2O), 4.69 (dd, 1 H, CH, J = 3.6, 7.6 Hz), 5.48 (d, 1 H, NCH_2O, J = 10.5 Hz), 5.69 (d, 1 H, NCH_2O, J = 10.5 Hz), 7.14-7.34 (m, 10 H, ArH), 8.28 (br s, 1 H, NH).

Anal. Calcd. for $C_{20}H_{20}N_2O_4S$: C, 62.48; H, 5.24; N, 7.29. Found: C, 62.16; H, 5.31; N, 7.41.

5-Ethyl-1-{[(1'-phenyl-2'-hydroxy)ethoxy]methyl}-6-(phenylthio)uracil (**19c**).

This compound was obtained by the deprotection of 5-ethyl-1-{[(1,phenyl-2'-*t*-butyldimethylsilyloxy)ethoxy]methyl}-6-(phenylthio)uracil (**15c**) with tetra-*n*-butylammonium fluoride by the method used for the preparation of **19a**. Compound **19c** was obtained in 81% yield, mp 155-156°; uv (ethanol): λ max 242 nm (10363), 275 nm (8204); ^{1}H nmr (DMSO-d_6): δ 0.76 (t, 3 H, CH_3, J = 7.4 Hz), 2.36 (m, 2 H, CH_2), 3.32-3.48 (m, 2 H, CH_2O), 4.57 (dd, 1 H, CH, J = 4.2, 7.4 Hz), 4.87 (t, 1 H, OH, J = 5.6 Hz), 5.29 (d, 1 H, NCH_2O, J = 10.4 Hz), 5.54 (br s, 1 H, NCH_2O), 7.18-7.37 (m, 10 H, ArH).

Anal. Calcd. for $C_{21}H_{22}N_2O_4S$: C, 63.29; H, 5.57; N, 7.03. Found: C, 63.45; H, 5.73; N, 7.18.

1-{[(1'-Phenyl-2'-hydroxy)ethoxy]methyl}-6-(phenylseleno)-uracil (**20a**).

This compound was obtained in 84% yield by the deprotection of 1{[(1'-phenyl-2'-*t*-butyldimethylsilyloxy)ethoxy]-methyl}-6-(phenylthio)uracil (**17a**) with tetra-*n*-butylammonium fluoride by the method indicated above, mp 172-173°; uv (ethanol): λ max 289 nm (9367); 269 nm (sh), ^{1}H nmr (deuteriochloroform): δ 3.65 (m, 1 H, CH_2O), 3.80 (m, 1 H, CH_2O), 4.71 (dd, 1 H, CH, J = 3.4, 8.8 Hz), 5.15 (s, 1 H, C5-H), 5.54 (dd, 2 H, NCH_2O, J = 11.3, 20.2 Hz), 7.30-7.68 (m, 10 H, ArH), 8.28 (br s, 1 H, NH).

Anal. Calcd. for $C_{19}H_{18}N_2O_4Se$: C, 54.57; H, 4.34; N, 6.70. Found: C, 54.31; H, 4.04; N, 6.85.

1-[(1'-Phenyl-2'-hydroxyethoxy)methyl]-6-(phenylseleno)-thymine (**20b**).

This compound was obtained by the deprotection of 1-{[(1'-phenyl-2'-*t*-butyldimethylsilyloxy)ethoxy]methyl}-6-(phenylseleno)thymine (**17b**) with tetra-*n*-butylammonium fluoride in 82% yield by the method described for the preparation of **19a**. Compound **20b** was obtained in 82% yield, mp 193-194°; uv (ethanol): λ max 262 nm (9019); 275 nm (8073); ^{1}H nmr (DMSO-d_6): δ 1.67 (s, 3 H, CH_3), 3.34-3.54 (m, 2 H, CH_2O), 4.53 (dd, 1 H, CH, J = 5.3, 7.5 Hz), 4.87 (t, 1 H, OH J = 5.9 Hz), 5.50 (d, 1 H, NCH_2O, J = 10.4 Hz), 5.65 (br s, 1 H, NCH_2O), 7.20-7.46 (m, 10 H, ArH).

Anal. Calcd. for $C_{20}H_{20}N_2O_4Se$: C, 55.71; H, 4.68; N, 6.50. Found: C, 55.44; H, 4.71; N, 6.32.

5-Ethyl-1-[(1'-phenyl-2'-hydroxyethoxy)methyl]-6-(phenylseleno)uracil (**20c**).

This compound was obtained by the deprotection of 5-ethyl-1-{[1'-phenyl-2'-(*t*-butyldimethylsilyloxy)ethoxy]methyl}-6-(phenylseleno)uracil (**17c**) with tetra-*n*-butylammonium fluoride in 81% yield by the method used for the preparation of **19a**. Compound **20c** was obtained in 81% yield, mp 168-170°; uv (ethanol): λ max 262 nm (8359); ^{1}H nmr (DMSO-d$_6$): δ 0.68 (t, 3 H, CH$_3$, J = 7.3 Hz), 2.36 (m, 2 H, CH$_2$,), 3.31-3.51 (m, 2 H, CH$_2$O), 4.55 (dd, 1 H, CH, J = 4.3, 7.6 Hz), 4.88 (t, 1 H, OH, J = 5.7 Hz), 5.44 (d, 1 H, NCH$_2$O, J = 10.5 Hz), 5.60 (br s, 1 H, NCH$_2$O), 7.19-7.37 (m, 8 H, ArH), 7.40-7.45 (m, 2 H, ArH).

Anal. Calcd. for $C_{21}H_{22}N_2O_4Se$: C, 56.63; H, 4.98; N, 6.28. Found: C, 56.29; H, 5.29; N, 6.62.

Biological Methods (Inhibition of Replication of HIV in MT-2 Cells).

In vitro Anti-drug Screening.

Inhibition of virus-induced cytotoxicity in MT-2 cells was determined according the method of Larder *et al.* [12], with slight modification [14]. Triplicate wells of 96-well plates containing 1 x 10^4 MT-2 cells were infected with HIV-1 at a multiplicity of 0.5 TCID$_{50}$ per cell. The indicated concentrations of drug were added immediately after infection. Cell viability was assessed 7 days after infection by the MTT dye reduction method (OD$_{570}$). The % protection is calculated by the formula [(a-b/c-b) x 100] in which a = OD$_{570}$ of drug-treated, virus infected wells, b = OD$_{570}$ of no-drug, infected wells and c = OD$_{570}$ of the no-drug, uninfected wells.

Reverse Transcriptase (RT) Assays:

The recombinant RT p66/p51 was prepared according to D'Aquila and Summer [12]. The standard reaction mixture contained in a 50 µl volume: 50 m*M* Tris-HCl, *p*H 7.8, 50 m*M* KCl. 6 m*M* MgCl$_2$, 0.1 mg/ml heat-inactivate bovine serum albumin (BSA), 1 m*M* dithiothreitol (DTT), 0.5 OD$_{260}$ units/ml template-primer Poly(rC)-oligo(dG)$_{12\text{-}18}$, 10 µ*M* [^{3}H]dGTP (1 Ci/mmole)and 3.3 x 10^{-3} unit of enzyme. A unit was defined as the amount of enzyme necessary to incorporate 1 nmole of [^{3}H]dTMP into the Poly(rA)-oligo(dT)$_{10}$ template in 1.0 min at 37°. The samples were incubated for 20 minutes at 37°, and all reactions were carried out in the linear range. Aliquots of 40 ml were spotted on glass fiber filters (Whatman GF/A) and processed for the determination of trichloroacetic acid-insoluble radioactivity as described [14].

Acknowledgement.

This work was supported by USPHS grant CA 39427 (to S. C.) and CA 44358 (to Y. C.). We should like to thank Dr. V. L. Narayanan and Dr. R. K. Varma, Drug Synthesis and Chemistry Branch, and Dr. J. P. Bader, Antiviral Evaluation Branch of the National Cancer Institute, for evaluation of the anti-HIV activities of our compounds and Dr. James Van Epp of the Department of Chemistry at Brown University for his assistance with the nmr spectra.

REFERENCES AND NOTES

[1] E. L. White, R. W. Buckheit, Jr., L. J. Ross, J. M. Germany, K. Andries, R. Pauwels, P. A. J. Janssen, W. M. Shannon and M. A. Chirigos, *Antiviral Res.*, **16**, 257 (1991).

[2] M. J. Kukla, H. J. Breslin, C. J. Diamond, P. P. Grous, C. Y. Ho, M. Miranda, J. D. Rodger, R. G. Sherrill, E. de Clercq, R. Pauwels, K. Andries, L. J. Moens, M. A. C. Janssen and P. A. J. Janssen, *J. Med. Chem.*, **34**, 3187 (1991).

[3] P. W. Mui, S. P. Jacober, K. D. Hargrave and J. Adams, *J. Med. Chem.*, **35**, 201 (1992).

[4] V. J. Merluzzi, K. D. Hargrave, M. Labadia, K. Grozinger, M. Skoog, J. C. Wu, K. Eckner, S. Hattox, J. Adams, A. S. Rosehthal, R. Faanes, R. J. Eckner, R. A. Koup and J. L. Sullivan, *Science*, **250**, 1411 (1990).

[5] T. Miyasaka, H. Tanaka, M. Baba, H. Hayakawa, R. T. Walker, J. Balzarini and E. De Clercq, *J. Med. Chem.*, **32**, 2507 (1989).

[6] H. Tanaka, M. Baba, H. Hayakawa, T. Sakamaki, T. Miyasaka, M. Ubasawa, H. Takashima, K. Sekiya, I. Nitta, S. Shigeta, R. T. Walker, J. Balzarini and E. De Clercq, *J. Med. Chem.*, **34**, 349 (1991).

[7] H. Tanaka, M. Baba, S. Saito, T. Miyasaka, H. Takashima, K. Sekiya, M. Ubasawa, I. Nitta, R. T. Walker, H. Nakashima and E. De Clercq, *J. Med. Chem.*, **34**, 1508 (1991).

[8] D. L. Romero, M. Busso, C. K. Tan, F. Reusser, J. R. Palmer, S. M. Poppe, P. A. Aristoff, K. M. Downey, A. G. So, L. Resnick and W. G. Tarpley, *Proc. Natl. Acad. Sci. USA*, **88**, 8806 (1991).

[9] M. Lemaitre, Y. Lelievre, M. Evers and N. Dereu, Vth International Conference on Antiviral Res., March 8-13 (1990), Abstr. # 32, pp 60.

[10] N. M. Goudgaon and R. F. Schinazi, *J. Med. Chem.*, **34**, 3305 (1991).

[11] H. G. Mautner, S. H. Chu, and C. M. Lee, J. *Org. Chem.*, **27**, 3671 (1962).

[12] B. A. Larder, B. Chesebro and D. D. Richman, *Antimicrob. Agent. Chemother.*, **34**, 436 (1990).

[13] R. T. D'Aquila and W. C. Summers, *J.of Aquired Immune Deficiency Syndromes*, **2**, 579 (1989).

[14] Y. C. Cheng, G. E. Dutschman, K. F. Bastow, M. G. Sarngadharan and R. Y. C. Ting, *J. Biol. Chem.*, **262**, 2187 (1987).

[15] Reports from the Developmental Therapeutics Program of the National Cancer Institute, Drug Synthesis and Chemistry Branch.