Synthesis of Enantiomers of 2′-Aminomethyl-5-benzylacyclouridine (AM-BAU) and 2′-Aminomethyl-5-benzyloxybenzylacyclouridine (AM-BBAU). Potent Inhibitors of Uridine Phosphorylase

Bai-Chuan Pan† and Shih-Hsi Chu*

Division of Biology and Medicine, Brown University,
Providence, Rhode Island 02912, U.S.A

Received February 15, 1988

Racemic 2′-aminomethyl-5-benzyl-acyclouridine (AM-BAU, **5**) and 2′-aminomethyl-5-benzyloxybenzylacyclouridine (AM-BBAU, **6**) have been found to be very active inhibitors of uridine phosphorylase [1]. Their enantiomers were synthesized from chiral 2,2-dimethyl-1,3-dioxolane-4-methanol (**7a,b**). *S*-(−)-AM-BAU (**5a**) and *S*-(−)-AM-BBAU (**6a**) were prepared from the *R*-(−) isomer **7a**, and *R*-(+)-AM-BAU (**5b**) and *R*-(+)-AM-BBAU (**6b**) from the *S*-(+) isomer **7b**. A different route from the *S*-(+) isomer **7b** to *S*-(−)-AM-BBAU (**6a**) was also determined to be feasible.

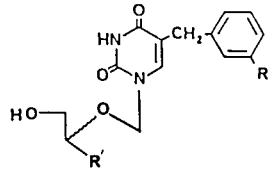
J. Heterocyclic Chem., **25**, 1587 (1988).

Uridine phosphorylase is an important enzyme in the pyrimidine salvage pathway of natural nucleotide synthesis. Inhibition of uridine phosphorylase should affect cell replication. Since by the phosphorolytic cleavage action of this enzyme the currently useful drug 5-fluoro-2′-deoxyuridine (FdUrd) would be converted into the more toxic and less effective 5-fluorouracil, it would be expected that inhibitors of uridine phosphorylase would potentiate the action of FdUrd.

5-Benzylacyclouridine (BAU, **1**) and 5-benzyloxybenzylacyclouridine (BBAU, **2**), first synthesized in this laboratory, were found to be potent inhibitors of this enzyme [2]. Their structures are shown in Scheme I. M. Chu has found that the benzylacyclouridines BAU and BBAU substantially potentiate the effect of FdUrd upon the growth of the pancreatic carcinoma DAN and human lung carcinoma LX-1 cell lines *in vitro* and *in vivo* [3]. By adding a hydroxymethyl group to the acyclo moiety, the compounds 2′-hydroxymethyl-5-benzylacyclouridine, (HM-BAU, **3**) and 2′-hydroxymethyl-5-benzyloxybenzylacyclouridine, (HM-BBAU, **4**) were obtained which showed increased inhibitory activity towards uridine phosphorylase [4]. The corresponding aminomethyl analogs, 2′-aminomethyl-5-benzylacyclouridine (AM-BAU, **5**) and 2′-aminomethyl-5-benzyloxybenzylacyclouridine (AM-BBAU, **6**) were also found to be more active inhibitors than the BAU and BBAU parent compounds [1].

In this paper we wish to report the synthesis of the enantiomers of AM-BAU and AM-BBAU from chiral starting materials. The chiral starting compounds were commercially available enantiomers of 2,2′-dimethyl-1,3-dioxolane-4-methanol. The *R*-(−) isomer **7a** was benzylated and then hydrolyzed with dilute acetic acid to give chiral benzyl 2,3-dihydroxy propyl ether (Scheme II). On selective esterification with 1 equivalent of *p*-toluenesulfonyl chloride in pyridine, the 3-mono-*p*-toluenesulfonate **8a** can be obtained [5,6]. Replacement of the sulfonyloxy group by a phthalimido group was then effected by treatment with potassium phthalimide in dry DMF. The resulting *S*-(−)-1-benzyloxy-3-phthalimidopropanol (**9a**) was treated with paraformaldehyde and dry hydrogen chloride to give the optically active chloromethyl ether, acyclo reagent **10a**.

Scheme I



1 R = H, R′ = H, BAU

2 R = OBzl, R′ = H, BBAU

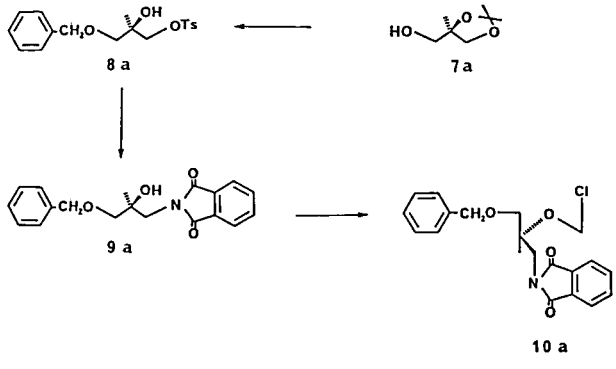
3 R = H, R′ = CH_2OH HM-BAU

4 R = OBzl, R′ = CH_2OH, HM-BBAU

5 R = H, R′ = CH_2NH_2, AM-BAU

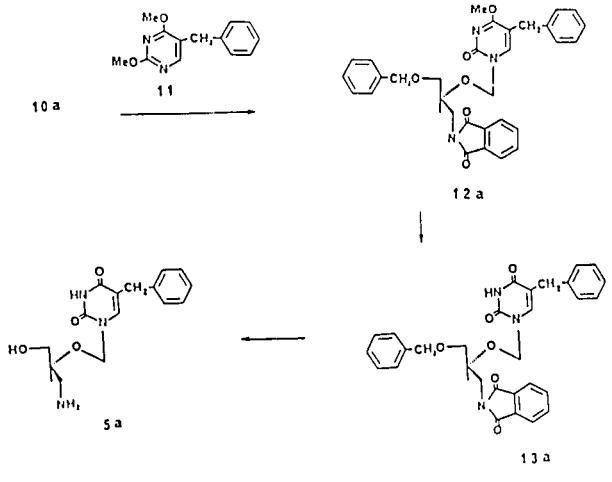
6 R = OBzl, R′ = CH_2NH_2, AM-BBAU

Scheme II



As shown in Scheme III, **10a** was condensed with 2,4-dimethoxy-5-benzylpyrimidine (**11**) in dry methylene chloride in the presence of potassium carbonate; to afford *S*-(−)-5-benzyl-1-[(1′-phthalimidomethyl-2′-benzyloxyethoxy)methyl]-2-oxo-4-methoxypyrimidine (**12a**). The methoxy compound **12a** was hydrolyzed with dilute hydrochloric acid to yield *S*-(−)-5-benzyl-1-[(1′-phthalimidomethyl-2′-benzyloxyethoxy)methyl]uracil (**13a**). The latter was then deprotected with hydrazine to yield *S*-(−)-5-benzyl-1-[(1′-aminomethyl-2′-benzyloxyethoxy)methyl]uracil and subjected without isolation to catalytic hydrogenation to yield the desired *S*-(−)-AM-BAU (**5a**).

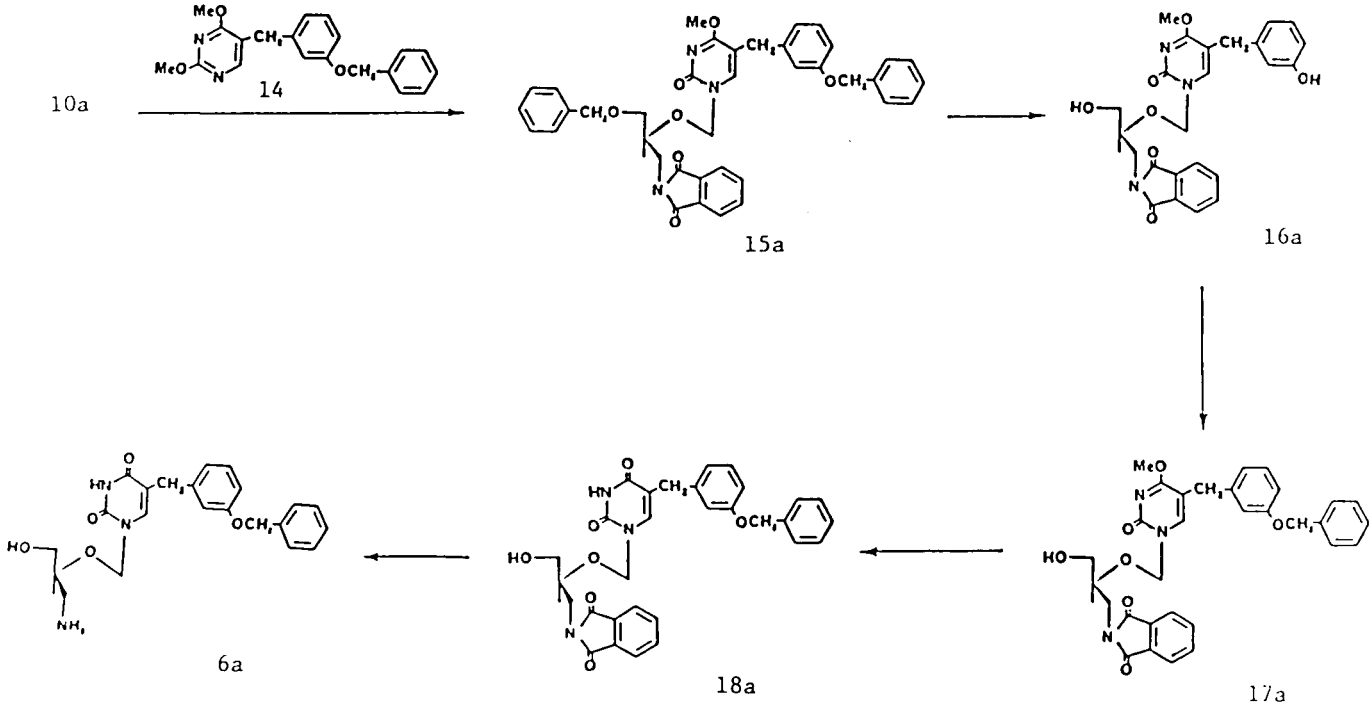
Scheme III



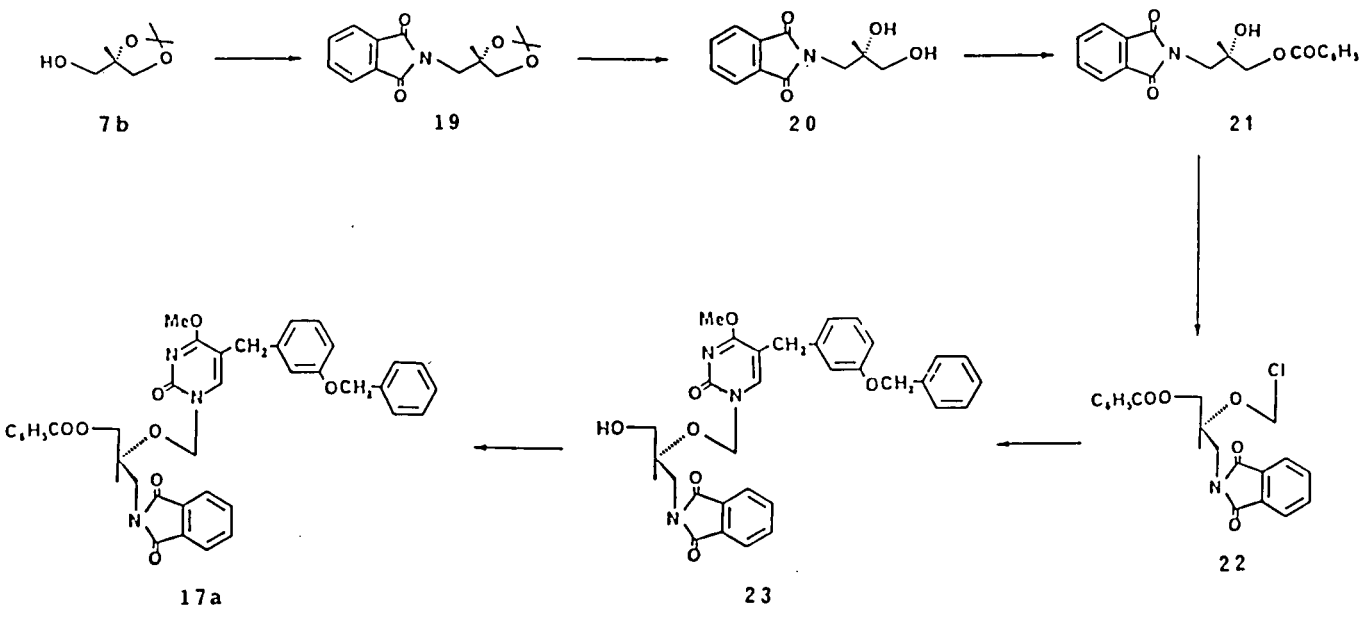
Scheme IV shows the condensation of the chiral chloromethyl ether **10a** with 2,4-dimethoxy-5-(3′-benzyloxybenzyl)pyrimidine (**14**) to give *S*-(−)-5-(3′-benzyloxybenzyl)-1-[(1′-phthalimidomethyl-2′-benzyloxyethoxy)methyl]-2-oxo-4-methoxypyrimidine (**15a**). The latter was converted into *S*-(−)-5-(3′-hydroxybenzyl)-1-[(1′-phthalimidomethyl-2′-hydroxyethoxy)methyl]-2-oxo-4-methoxypyrimidine (**16a**) by catalytic hydrogenolysis using 10% palladium-carbon as a catalyst under 4 atmospheres pressure. The chiral phenolic compound **16a** was realkylated with benzyl bromide and potassium carbonate in dry acetone to give 5-(3′-benzyloxybenzyl)-1-[1′-phthalimidomethyl-2′-hydroxyethoxy)methyl]-2-oxo-4-methoxypyrimidine (**17a**). This was hydrolyzed with dilute hydrochloric acid to give 5-(3′-benzyloxybenzyl)-1-[(1′-phthalimidomethyl-2′-hydroxyethoxy)methyl]uracil (**18a**). Deprotection of **18a** with hydrazine then yielded *S*-(−)-AM-BBAU (**6a**). *R*-(+)-AM-BAU and *R*-(+)-AM-BBAU could be prepared similarly from *S*-(+)-2,2′-dimethyl-1,3-dioxolane-4-methanol (**7b**).

A different route from *S*-(+)-2,4-dimethyl-1,3-dioxolane-4-methanol (**7b**) to *S*-(−)-AM-BBAU was also investigated, as shown in Scheme V. The *S*-(+) isomer **7b** was reacted with *p*-toluenesulfonyl chloride in pyridine [7] to give a tosylate, and the tosyl group displaced by reaction with potassium phthalimide. The phthalimido compound, **19**, was hydrolysed to the diol (**20**) with dilute acetic acid. Selective benzoylation of diol **20** with benzoyl cyanide in dry acetonitrile at −20° [8] gave the primary monobenzoate **21**.

Scheme IV



Scheme V



The latter was reacted with paraformaldehyde and anhydrous hydrogen chloride to yield its 2-chloromethyl ether **22**. Condensation of this acyclo reagent with 2,4-dimethoxy-5-(3′-benzyloxybenzyl)pyrimidine (**14**) gave *S*-(−)-5-(3′-benzyloxybenzyl)-1-[1′-phthalimidomethyl-2′-benzoyloxyethoxy)methyl]-2-oxo-4-methoxypyrimidine (**23**). This was treated with sodium methoxide in methanol to give *S*-(−)-5-(3′-benzyloxybenzyl)-1-[1′-phthalimidomethyl-2′-hydroxyethoxy)methyl]-2-oxo-4-methoxypyrimidine, identical with the compound **17a** prepared from the *R*-(−)-2,3-dimethyl-1,3-dioxolane-4-methanol described above.

Preliminary biological data showed that *R*-(+)-AM-BAU and *R*-(+)-AM-BBAU were approximately twice as active as inhibitors as the *S*-(−)-AM-BAU and *S*-(−)-AM-BBAU enantiomers [9]. The conformation of the ethoxy portion of the acyclo moiety appears to be significant but not critical in the binding of inhibitor to the active site of uridine phosphorylase.

EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus in open capillary tubes and were not corrected. The ^{1}H nmr spectra were obtained with a Bruker Model WM-400 instrument, using tetramethylsilane as an internal standard. All samples were run in deuteriochloroform except for compounds 5a and 5b, which were run in DMSO-d_6. The uv spectra were obtained on a Perkin-Elmer model 402 spectrophotometer, and optical rotation on a Perkin-Elmer Model #241 automated polarimeter.

S-(−)-1-Benzyloxy-3-phthalimidopropanol (**9a**).

R-1-benzyloxy-3-*p*-toluenesulfonyloxypropanol (**8a**, 336 mg, 1 mmole), prepared from *R*-(−)-2,2-dimethyl-1,3-dioxolane-4-methanol (Aldrich Chemical Co.; $[\alpha]_D^{25}$ −13.7°) by the procedure of Hirt [5] and Holý [6], was dissolved in 2 ml of dry DMF to which 274.5 mg (1.5 mmoles) of potassium phthalimide was added. The reaction mixture was stirred at 120° under nitrogen for 30 minutes. DMF was removed under reduced pressure and the residue chromatographed on a silica gel column with elution by methylene chloride:ether (10:1) to give 218 mg of **9a** (70%), mp 74-75°; $[\alpha]_D^{25}$ −18.31° (methylene chloride, 0.3); ^{1}H nmr (deuteriochloroform): δ 2.72 (d, 1H, OH), 3.50-3.61 (dd, 2H, C*H*$_2$NPhth), 3.80-3.95 (dd, 2H, C*H*$_2$-OBzl), 4.08-4.14 (m, 1H, *tert*-H), 4.53-4.59 (dd, 2H, OCH$_2$Ph), 7.32 (m, 5H, ArH of Bzl), 7.70-7.72 (dd, 2H, ArH of Phth), 7.82-7.85 (dd, 2H, ArH of Phth).

Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.51; N, 4.50. Found: C, 69.54; H, 5.51; N, 4.32.

R-(+)-1-Benzyloxy-3-phthalimidopropanol-2 (**9b**).

This compound was prepared from *S*-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol (Aldrich Chemical Co.; $[\alpha]_D^{25}$ +15.2°) in 72% yield by the method indicated above, mp 74-75°; $[\alpha]_D^{25}$ = +19.14° (methylene chloride, 0.3).

Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.51; N, 4.50. Found: C, 69.80; H, 5.66; N, 4.19.

S-(−)-5-Benzyl-1-[(1′-phthalimidomethyl-2′-benzyloxy)ethoxy]methyl-2-oxo-4-methoxypyrimidine (**12a**).

A suspension of 1.8 g (5.8 mmoles) of **9a** and 350 mg of paraformaldehyde in 18 ml of dry methylene chloride was cooled to 0°. Dry hydrogen chloride was bubbled through the stirred suspension for 3 hours until saturated. The mixture was allowed to stand in the refrigerator overnight and then dried over anhydrous calcium chloride. It was filtered and the solvent evaporated under reduced pressure. As in the preparation of the racemic compound [1], the oily residue **10a** was used directly to alkylate the base. To a solution of 1.5 g of 2,4-dimethoxy-5-benzylpyrimidine **11** [2] and the chloromethylated product **10a** prepared from 1.8 g of **9a** in 18 ml of dry methylene chloride there was added 2.4 g of finely ground anhydrous potassium carbonate. The mixture was stirred at room temperature for 48 hours and filtered, washing the solid well with methylene chloride. The combined filtrate and washings were evaporated to dryness, and the residue subjected to chromatography on silica gel. Elution was with methylene chloride:ether (5:1) to give 2.43 g (78%) of **12a**,

mp 132:134°; $[\alpha]_D^{20} = -14.42°$ (methylene chloride, 0.3); ^{1}H nmr (deuteriochloroform): δ 3.43 (dd, 2H, CH_2 at C_5, J = 15.6, 22.2 Hz), 3.53 (dd, 1H, CH_2-N, J = 10.5, 6.2 Hz), 3.62 (dd, 1H, CH_2-N, J = 10.5, 4.0 Hz), 3.79 (dd, 1H, OC*H*$_2$-CH, J = 4.2, 14.3 Hz), 3.83 (s, 3H, OCH_3), 3.86 (dd, 1H, OC*H*$_2$-CH, J = 7.0, 14.3 Hz), 4.29 (m, 1H, *tert*-CH), 4.51 (dd, 2H, OCH_2Ph), 5.20 (d, 1H, O-CH_2-N, J = 10.5 Hz), 5.34 (d, 1H, O-CH_2-N, J = 10.5 Hz), 7.03-7.09 (m, 3H, *o* and *p*-H of C_5-Bzl), 7.10 (s, 1H, C_6-H), 7.20-7.32 (m, 7H, ArH of Bzl and *m*-H of C_5-Bzl), 7.72 (dd, 2H, *m*-H of Phth, J = 3.1, 5.5 Hz), 7.78 (dd, 2H, *o*-H of Phth, J = 3.1, 5.5 Hz).

Anal. Calcd. for $C_{31}H_{29}N_3O_6$: C, 69.00; H, 5.42; N, 7.79. Found: C, 69.24; H, 5.60; N, 7.61.

R-(+)-5-Benzyl-1-[(1′-phthalimidomethyl-2′-benzyloxyethoxy)methyl]-2-oxo-4-methoxypyrimidine (**12b**).

Chloromethylation of **9b** to the enantiomeric acyclo reagent **10b** and alkylation of **11** with **10b** gave compound **12b** in 75% yield by the method indicated above for **12a**; mp 131-132°; $[\alpha]_D^{24} = +15.26°$ (methylene chloride, 0.4); ^{1}H nmr was identical to the spectrum of **12a**.

Anal. Cacld. for $C_{31}H_{29}N_3O_6$: C, 69.00; H, 5.42; N, 7.79. Found: C, 69.14; H, 5.28; N, 7.94.

S-(−)-5-Benzyl-1-[(1′-phthalimidomethyl-2′-benzyloxyethoxy)methyl]-uracil (**13a**).

Hydrochloric acid (6*N*, 5 ml) was added to a solution of 0.5 g of **12a** in 75 ml of methanol. The reaction mixture was stirred at 40° for 8 hours. Methanol and hydrochloric acid were removed under reduced pressure and the residue recrystallized from methanol, to yield 0.4 g of **13a** (82%), mp 125-127°; ^{1}H nmr (deuteriochloroform): δ 3.27 (d, 1H, CH_2 at C_5, J = 15.7 Hz), 3.43 (d, 1H, CH_2 at C_5, J = 15.7 Hz), 3.52 (dd, 1H, CH_2NPhth, J = 6.5, 10.5 Hz), 3.60 (dd, 1H, CH_2NPhth, J = 3.7, 10.5 Hz), 3.70 (dd, 1H, CH_4-OBzl, J = 4.1, 14.3 Hz), 3.85 (dd, 1H, CH_2-OBzl, J = 8.0, 14.3 Hz), 4.26 (m, 1H, *tert*-CH), 4.50 (d, 1H, OCH_2Ph, J = 4.0 Hz), 4.55 (d, 1H, OCH_2-Ph, J = 4.0 Hz), 4.99 (d, 1H, OCH_2-N, J = 10.8 Hz), 5.25 (d, 1H, OCH_2-N, J = 10.8 Hz), 6.79 (t, 1H, C_6-H, J = 1.0 Hz), 7.10-7.45 (m, 10H, ArH of Bzl), 7.73 (m, 2H, ArH of Phth), 7.80 (m, 2H, ArH of Phth), 8.07 (br s, 1H, N_3-H).

Anal. Calcd. for $C_{30}H_{27}N_3O_6$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.28; H, 5.29; N, 8.19.

R-(+)-Benzyl-1-[(1′-phthalimidomethyl-2′-benzyloxyethoxy)methyl]uracil (**13b**).

Compound **13b** was prepared in a similar manner by the hydrolysis of **12b**, in 80% yield, mp 125-127°. The ^{1}H nmr spectrum was identical to that of **13a**.

Anal. Calcd. for $C_{30}H_{27}N_3O_6$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.63; H, 5.38; N, 8.18.

S-(−)-5-Benzyl-1-[(1′-aminomethyl-2′-hydroxyethoxy)methyl]uracil Hydrochloride (**5a**).

Deprotection of the amino-hydroxy enantiomer was as follows. To 1 g of **13a**, dissolved in 10 ml of methylene chloride, there was added 0.5 ml of 98% hydrazine. The reaction mixture was stirred at room temperature overnight and then filtered. The filtrate was evaporated to dryness. The residue was redissolved in methylene chloride, re-evaporated to dryness and further dried under vacuum to remove traces of hydrazine. The partly deblocked, dried residue was then dissolved in 50 ml of methanol containing 2 ml of concentrated hydrochloric acid, and hydrogenated under 3 atmospheres of hydrogen, using 10% palladium-carbon as the catalyst. After hydrogenation was completed the reaction mixture was filtered and evaporated to dryness under reduced pressure to give the desired product, **5a**. It was recrystallized from methanol to yield 0.31 g (48%), mp 215-217°; $[\alpha]_D^{22} = -5.46°$ (methanol, 0.3); ^{1}H nmr (DMSO-d_6): δ 2.83 (dd, 1H, C*H*$_2$$NH_3^+$, J = 13.4, 6.5 Hz), 3.01 (dd, 1H, C*H*$_2$$NH_3^+$, J = 13.4, 3.5 Hz), 3.53 (s, 2H, CH_2 at C_5), 3.82 (m, 1H, *tert*-H), 5.08 (br s, 1H, OH, deuterium oxide-exchangeable), 5.18 (dd, 2H, OCH_2-N, J = 17.2, 10.4 Hz), 7.16-7.30 (m, 6H, C_6-H and ArH of Bzl), 7.91 (br s, 3H, NH_3^+, deuterium oxide-exchangeable), 11.40 (br s, 1H, N_3-H, deuterium oxide-exchange).

Anal. Calcd. for $C_{15}H_{19}N_3O_4 \cdot HCl$: C, 52.71; H, 5.86; N, 12.30. Found: C, 52.46; H, 5.90; N, 12.20.

R-(+)-5-Benzyl-1-[(1′-aminomethyl-2′-hydroxyethoxy)methyl]uracil Hydrochloride (**5b**).

This compound was prepared in 43% yield by the deprotection of **13b** in the same manner, mp 216-217°; $[\alpha]_D^{20} = +6.03°$ (methanol, 0.2). The ^{1}H nmr spectrum was identical to the spectrum of **5a**, including the deuterium oxide-labile peaks.

Anal. Calcd. for $C_{15}H_{19}O_4N_3 \cdot HCl$: C, 52.71; H, 5.86; N, 12.30. Found: C, 52.84; H, 5.93; N, 12.10.

S-(−)-5-(3′-benzyloxybenzyl)-1-[(1′-phthalimidomethyl-2′-benzyloxyethoxy)methyl]-2-oxo-4-methoxypyrimidine (**15a**).

A mixture of 1.85 g (5.5 mmoles) of 2,4-dimethoxy-5-(3′-benzyloxybenzyl)pyrimidine **14** [2], with the chloromethylated product **10a** (prepared from 1.56 g (5 mmoles) of *S*-(−)-1-benzyloxy-3-phthalimido-2-propanol, **9a**), and 2.07 g (15 mmoles) of finely ground anhydrous potassium carbonate in 15.6 ml of dry methylene chloride was stirred at room temperature for 48 hours. After filtering, the solution was evaporated to dryness under reduced pressure. The residue was subjected to chromatography on silica gel and eluted with methylene chloride to give 2.48 g of **15a** (75%), mp 129-130°; tlc, R_f = 0.51 (silica gel, methylene chloride:ether:-methanol, 75:25:5); $[\alpha]_D^{22} = -15.5°$ (methylene chloride, 0.1); ^{1}H nmr (deuteriochloroform): δ 3.39 (dd, 2H, CH_2 at C_5, J = 23.2, 15.7 Hz), 3.53 (dd, 1H, CH_2NPhth, J = 10.5, 6.1 Hz), 3.61 (dd, 1H, CH_2NPhth, J = 10.5, J = 3.9 Hz), 3.78 (dd, 1H, C*H*$_2$-OBzl, J = 14.3, 4.3 Hz), 3.81 (s, 3H, OCH_3), 3.85 (dd, 1H, C*H*$_2$8-OBzl, J = 14.3, 6.9 Hz), 4.29 (m, 1H, *tert*-H), 4.50 (dd, 2H, OCH_2Ph), 5.05 (s, 2H, CH_2 of terminal Bzl), 5.19 (d, 1H, O-CH_2-N, J = 10.5 Hz), 5.34 (d, 1H, O-CH_2-N, J = 10.5 Hz), 6.61-6.75 (m, 2H, *o*-H of inner Bzl), 6.82-6.86 (dd, 1H, *p*-H of inner Bzl), 7.09 (s, 1H, C_6-H), 7.20 (t, 1H, *m*-H of inner Bzl), 7.28-7.43 (m, 10H, ArH), 7.67 (dd, 2H, ArH of Phth, J = 5.5, 3.1 Hz), 7.77 (dd, 2H, ArH of Phth, J = 5.5, 3.1 Hz).

Anal. Calcd. for $C_{38}H_{35}N_3O_7$: C, 70.68; H, 5.47; N, 6.51. Found: C, 70.44; H, 5.55; N, 6.80.

R-(+)-5-(3′-Benzyloxybenzyl)-1-[(1′-phthalimidomethyl-2′-benzyloxyethoxy)methyl]-2-oxo-4-methoxypyrimidine (**15b**).

This compound was prepared by the condensation of **10b** with 5-benzyloxybenzyl-2,4-dimethoxypyrimidine (**14**) in 72% yield, by the method indicated above; F_f = 0.51 (silica gel, methylene chloride:ether:-methanol, 70:25:5), mp 128-129°; $[\alpha]_D^{22} = +16.4°$ (methylene chloride, 0.4). The ^{1}H nmr spectrum was identical to that of **15a**.

Anal. Calcd. for $C_{38}H_{35}N_3O_7$: C, 70.68; H, 5.47; N, 6.51. Found: C, 70.81; H, 5.75; N, 6.67.

S-(−)-5-(3′-Hydroxybenzyl)-1-[1′-phthalimidomethyl-2′-hydroxyethoxy)-methyl]-2-oxo-4-methoxypyrimidine (**16a**).

To a solution of 2.4 g of **15a** in a mixture of 40 ml of methanol and 30 ml of methylene chloride there was added 2 g of 10% palladium on carbon and 0.2 ml of 6*N* hydrochloric acid, and the mixture hydrogenated at 3 atmospheres pressure. The reaction was complete in 30 minutes. The reaction mixture was neutralized with aqueous sodium bicarbonate and filtered. The filtrate was evaporated to dryness under reduced pressure, to give white crystals, mp 118-120° after recrystallization from methanol; tlc, R_f = 0.06 (silica gel; methylene chloride:ether:methanol = 75:25:5); $[\alpha]_D^{27} = -15.0°$ (methanol, 0.1); ^{1}H nmr (deuteriochloroform): δ 3.44 (br s, 1H, aliph OH), 3.52 (d, 2H, CH_2 at C_5, J = 24.5 Hz), 3.61 (dd, 1H, CH_2NPhth, J = 12.2, 5.4 Hz), 3.75 (dd, 1H, CH_2NPhth, J = 12.2, 4.3 Hz), 3.81 (s, 3H, OCH_3), 3.88 (m, 2H, C*H*$_2$-OH), 4.09 (m, 1H, *tert*-H), 5..34 (dd, 2H, O-CH_2-N, J = 13.0, 10.1 Hz), 6.64-6.78 (m, 3H, *o* and *p*-H of HO-Bzl), 7.02 (br s, 1H, Ar-OH), 7.17 (t, 1H, *m*-H of HO-Bzl), 7.25 (s, 1H, C_6-H), 7.71 (dd, 2H, ArH of Phth, J = 5.5, 3.1 Hz), 7.82 (dd, 2H, ArH of Phth, J = 5.5, 3.1 Hz).

Anal. Calcd. for $C_{24}H_{23}N_3O_7 \cdot CH_3OH \cdot 0.5H_2O$: C, 59.28; H, 5.53; N, 8.30. Found: C, 59.29; H, 5.43; N, 8.16.

R-(+)-5-(3'-Hydroxybenzyl)-1-[(1'-phthalimidomethyl-2'-hydroxyethoxy)-methyl]-2-oxo-4-methoxypyrimidine (**16b**).

Compound **16b** was prepared by the hydrogenolysis of **15b** using the same method as for **16a**. The yield was 82%, mp 118-120°; $[\alpha]_D^{17}$ = +16.9° (methanol, 0.1). The ^{1}H nmr spectrum was identical with that of **16a** except for the two OH peaks at 7.02 and 3.42 ppm which were shifted to 6.80 and 3.29 ppm respectively. This enantiomer also crystallized with a molecule of methanol.

Anal. Calcd. for $C_{24}H_{23}N_3O_7 \cdot CH_3OH \cdot 0.5H_2O$: C, 59.28; H, 5.53; N, 8.30. Found: C, 59.46; H, 5.53; N, 8.00.

S-(−)-5-(3'-Benzyloxybenzyl)-1-[(1'-phthalimidomethyl-2'-hydroxyethoxy)-methyl]-2-oxo-4-methoxypyrimidine (**17a**), by Method A, Scheme IV.

A suspension of 1.5 g of *S*-(−)-5-(3'-hydroxybenzyl)-1-[(1'-phthalimidomethyl-2'-hydroxyethoxy)methyl]-2-oxo-4-methoxypyrimidine (**16a**) in 15 ml of dry acetone, to which was added 0.33 ml of benzyl bromide, 150 mg of sodium iodide and 0.8 g of potassium carbonate. The mixture was stirred and heated to reflux for 3 hours. After the reaction was complete, as shown by tlc, the reaction mixture was filtered and evaporated to dryness to yield 1.60 g of a crystalline product. After recrystallizing from methanol it melted at 143-145°; tlc, R_f = 0.33 (silica gel, methylene chloride:ether:methanol, 70:25:5); $[\alpha]_D^{17}$ = −10.9° (methylene chloride, 0.2); ^{1}H nmr (deuteriochloroform): δ 3.42 (dd, 2H, CH_2 at C_5), 3.54-3.63 (m, 2H, CH_2NPhth), 3.81-3.95 (m, 2H, C*H*$_2$-OH), 3.92 (s, 3H, OCH_3), 4.07 (m, 1*H*, *tert*-H), 5.08 (s, 2H, CH_2 of terminal Bzl), 5.20 (d, 1H, O-CH_2-N, J = 10 Hz), 5.39 (d, 1H, O-CH_2-N, J = 10 Hz), 6.74-6.88 (m, 3H, *o* and *p*-H of inner Bzl), 7.11 (s, 1H, C_6-H), 7.22 (t, 1H, *m*-H of inner Bzl), 7.29-7.43 (m, 5H, ArH of terminal Bzl), 7.71 (dd, 2H, ArH of Phth, J = 5.5, 3.1 Hz), 7.82 (dd, 2H, ArH of Phth, J = 5.5, 3.1 Hz).

Anal. Calcd. for $C_{31}H_{29}N_3O_7$: C, 67.02; H, 5.26; N, 7.56. Found: C, 66.87; H, 5.11; N, 7.84.

R-(+)-5-(3'-Benzyloxybenzyl)-1-[1'-phthalimidomethyl-2'-hydroxyethoxy)-methyl]-2-oxo-4-methoxypyrimidine (**17b**).

This compound was prepared by the benzylation of **16b** with benzyl bromide and potassium carbonate in acetone as in the preparation of **17a**, mp 142-145°; $[\alpha]_D$ = +11.48° (methylene chloride, 0.2); tlc, R_f = 0.33 (silica gel, methylene chloride:ether:methanol, 75:25:5). The ^{1}H nmr spectrum was identical with that of **17a** except for a broad single-proton peak at 3.10 ppm which could be assigned to the aliphatic hydroxyl.

Anal. Calcd. for $C_{31}H_{29}N_3O_7$: C, 67.02; H, 5.26; N, 7.56. Found: C, 66.90; H, 5.23; N, 7.33.

S-(−)-5-(3'-Benzyloxybenzyl)-1-[1'-phthalimidomethyl-2'-hydroxyethoxy)-methyl]uracil (**18a**).

Compound **17a** (0.7 g, 1.26 mmoles) was dissolved in 100 ml of methanol to which 7 ml of 6*N* hydrochloric acid had been added. The reaction mixture was stirred at 40° for 8 hours. Methanol and hydrochloride acid were evaporated under reduced pressure. The residue was recrystallized from methanol to give 0.57 g (84%) of **18a**, mp 160-162°; [α] = −11.31° (methylene chloride, 0.5); ^{1}H nmr (deuteriochloroform): δ 2.82 (t, 1H, OH, J = 6 Hz), 3.37 (d, 1H, CH_2 at C_5, J = 16 Hz), 3.52 (d, 1H, CH_2 at C_5, J = 16 Hz), 3.61 (m, 2H, CH_2NPhth), 3.86 (dd, 2H, C*H*$_2$-OH, J = 4.9, 1.0 Hz), 4.04 (m, 1H, *tert*-H), 5.05 (s, 2H, CH_2 of terminal Bzl), 5.18 (s, 2H, O-CH_2-N), 6.76-6.86 (m, 3H, *o* and *p*-H of inner Bzl), 6.87 (s, 1H, C_6-H), 7.21 (t, 1H, *m*-H of inner Bzl), 7.29-7.44 (m, 5H, ArH of terminal Bzl), 7.71 (dd, 2H, ArH of Phth, J = 5.5, 3.1 Hz), 7.82 (dd, 2H, ArH of Phth, J = 5.5, 3.1 Hz), 8.54 (s, 1H, N_3-H).

Anal. Calcd. for $C_{30}H_{27}N_3O_7$: C, 66.53; H, 5.03; N, 7.76. Found: C, 66.28; H, 5.23; N, 8.05.

R-(+)-5-(3'-Benzyloxybenzyl)-1-[(1'-phthalimidomethyl-2'-hydroxyethoxy)-methyl]uracil (**18b**).

Compound **18b** was prepared by the hydrolysis of **17b** with dilute hydrochloric acid by the same procedure as **18a**, yield 80%, mp 160-162°; $[\alpha]_D^{25}$ = +10.98° (methylene chloride, 0.5). The ^{1}H nmr spectrum was identical with that of **18a** except for N_3-H and OH which were displaced upfield to 8.30 and 2.73 respectively (2.73 (t, 1H, OH, J = 7.0 Hz)).

Anal. Calcd. for $C_{30}H_{27}N_3O_7$: C, 66.53; H, 5.03; N, 7.76. Found: C, 66.38; H, 5.13; N, 7.89.

S-(−)-5-(3'-Benzyloxybenzyl)-1-[(1'-aminomethyl-2'-hydroxyethoxy)-methyl]uracil (**6a**).

The phthalimido intermediate **18a** (950 mg, 1.8 mmoles) was dissolved in 19.5 ml of methylene chloride, to which was added 170 mg (5.3 mmoles) of anhydrous hydrazine. The mixture was stirred at room temperature for 20 hours and then filtered. The filtrate was evaporated to dryness and further dried under vacuum to remove traces of hydrazine. It was then applied to a column containing 11 g of silica gel. After removal of impurities by washing with methylene chloride:ethanol (9:1), the product was eluted with methylene chloride:ethanol (8:2), to yield 470 mg (61%) of **6a**; $[\alpha]_D^{25}$ = −6.31° (methanol, 0.5); ^{1}H nmr (deuteriochloroform): δ 2.81-2.98 (m, 2H, C*H*$_2$-NH_2, deuterium oxide-stable), 3.04 (v br s, 4H, deuterium oxide-exchangeable, OH, NH_2, and N_3-H), 3.59 (s, 2H, CH_2 at C_5), 3.61-3.73 (m, 3H, CH_2-OH, *tert*-H), 5.01 (s, 2H, CH_2 of terminal Bzl), 5.09 (d, 1H, O-CH_2-N, J = 10.3 Hz), 5.21 (d, 1H, O-CH_2-N, J = 10.3 Hz), 6.80-6.87 (m, 3H, *o* and *p*-H of inner Bzl), 6.94 (s, 1H, C_6-H), 7.20 (t, 1H, *m*-H of inner Bzl), 7.28-7.44 (m, 5H, ArH of terminal Bzl).

Anal. Calcd. for $C_{22}H_{25}N_3O_5 \cdot 0.75H_2O$: C, 62.15; H, 6.28; N, 9.93. Found: C, 61.94; H, 6.33; N, 9.67.

R-(+)-5-(3'-Benzyloxybenzyl)-1-[(1'-aminomethyl-2'-hydroxyethoxy)-methyl]uracil (**6b**).

This compound was prepared from **18b** by treatment with hydrazine as indicated above, yield, 57%; $[\alpha]_D^{25}$ = +7.10° (methanol, 0.2). The ^{1}H nmr spectrum was identical to the spectrum of **6a** except for the deuterium oxide-exchangeable protons.

Anal. Calcd. for $C_{22}H_{25}N_3O_5 \cdot 0.5H_2O$: C, 62.86; H, 6.19; N, 10.00. Found: C, 62.97; H, 6.26; N, 10.32.

S-(−)-4-Phthalimidomethyl-2,2-dimethyl-1,3-dioxolane (**19**).

R-4-*p*-Toluenesulfonyloxymethyl-2,2-dimethyl-1,3-dioxolane (0.6 g, 2.4 mmoles), prepared from *S*-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol (**7b**) by the method of Baldwin *et al.* [6], was mixed with 550 mg (3 mmoles) of potassium phthalimide in 4 ml of dry DMF. The mixture was heated to 120-130° and stirred for 30 minutes. Water (10 ml) was added and the mixture extracted with ether. The ether layer was evaporated and the residue recrystallized from methylene chloride-hexane, mp 103-104°; $[\alpha]_D^{25}$ = −47.15° (methylene chloride, 0.1); ^{1}H nmr (deuteriochloroform): δ 1.32 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 3.73 (dd, 1H, CH_2NPhth, J = 5.1, 13.8 Hz), 3.85 (dd, 1H, CH_2O, J = 5.1, 8.7 Hz), 3.94 (dd, 1H, CH_2NPhth, J = 6.5, 13.8 Hz), 4.08 (dd, 1H, CH_2O, J = 6.5, 8.7 Hz), 4.45 (m, 1H, *tert*-H), 7.73 (dd, 2H, Phth, J = 3.1, 5.4 Hz), 7.86 (dd, 2H, Phth, J = 3.1, 5.4 Hz).

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.79; N, 5.36. Found: C, 64.15; H, 5.68; N, 5.56.

S-(−)-3-Phthalimido-1,2-propanediol (**20**).

S-(−)-4-Phthalimidomethyl-2,2-dimethyl-1,3-dioxolane (**19**, 2.61 g, 10 mmoles) was suspended in 20 ml of 75% acetic acid, stirred and heated at 45° for 2 hours. After evaporation of acetic acid and water, the product can be isolated and recrystallized if a pure sample is desired, but is ordinarily carried through to the next step directly; ^{1}H nmr (deuteriochloroform): δ 2.73, 3.02 (2 br s, 1H each, CH-O*H* and CH_2-O*H*), 3.58-3.71 (octet, 2H, CH_2-NPHth), 3.81-3.95 (m, 2H, CH_2-OH), 4.00 (m, 1H, *tert*-H), 7.74 (dd, 2H, ArH of Phth), 7.87 (dd, 2H, ArH of Phth).

Anal. Calcd. for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.90; H, 4.96; N, 6.62.

S-(−)-(3-Phthalimido-1-benzoyloxy)-2-propanol (**21**).

The crude residue containing **20** was dissolved in 30 ml of dry acetonitrile containing 2 ml of triethylamine and cooled to −20°. To this mixture a solution of benzoyl cyanide (1.44 g, 11 mmoles) in 15 ml of dry ace-

tonitrile was added dropwise with stirring. Stirring was continued at −20° for 5 minutes, when tlc showed that the reaction was complete. After the addition of 2 ml of methanol the mixture was evaporated to dryness and the residue placed on a silica gel column. A small quantity of an unidentified impurity was removed ahead of the product by washing with methylene chloride:ether (10:1), and the desired benzoate subsequently eluted using the same solvent, mp 107-108°; $[\alpha]_D^{25}$ = −28.91° (methylene chloride, 0.1); ^{1}H nmr (deuteriochloroform): δ 3.01 (d, 1H, OH, J = 5.6 Hz), 3.98 (d, 2H, CH_2NPhth, J = 7.2 Hz), 4.33 (m, 1H, *tert*-H), 4.42 (dd, 2H, CH_2-OBzt, J = 1.3, 4.8 Hz), 7.44 (tt, 2H, *m*-H of OBzt, J = 1.3, 7.3 Hz), 7.57 (tt, 1H, *p*-H of OBzt, J = 1.3, 7.3 Hz), 7.74 (dd, 2H, Phth, J = 3.1, 5.5 Hz), 7.86 (dd, 2H, Phth, J = 3.1, 5.5 Hz), 8.05 (dm, 2H, *o*-H of OBzt).

Anal. Calcd. for $C_{18}H_{15}NO_5$: C, 66.45; H, 4.65; N, 4.37. Found: C, 66.24; H, 4.80; N, 4.59.

S-(−)-5-(3′-Benzyloxybenzyl)-1-[(1′-phthalimidomethyl-2′-benzoyloxyethoxy)methyl]-2-oxo-4-methoxypyrimidine (**23**).

A mixture of 2 g of *S*-(−)-(3-phthalimido-2-hydroxy)propyl benzoate (**21**), and excess paraformaldehyde in 20 ml of dry methylene chloride was cooled to 0°. Dry hydrogen chloride was bubbled through the stirred suspension until there was no further uptake of hydrogen chloride (3 hours). The solution was set in the refrigerator overnight, and then dried over anhydrous calcium chloride. After removal of solvent under reduced pressure, the chloromethylated product was used without further purification for the alkylation of **14**.

A suspension of 1.48 g (4.4 mmoles) of 2,4-dimethoxy-5-(3′-benzyloxybenzyl)pyrimidine (**14**), 2.07 g (15 mmoles) of finely powdered anhydrous potassium carbonate, and the chloromethylated intermediate **22** prepared from 1.3 g of **21**, in 15 ml of dry methylene chloride was stirred at room temperature for 48 hours, filtered and evaporated to dryness. The residue was directly applied to a column containing 40 g of silica gel. Some excess starting material and a small amount of impurity were removed by washing the column with methylene chloride. Subsequent elution with methylene chloride:ether (10:1) gave 1.90 g (70%) of the desired product, **23**; $[\alpha]_D^{25}$ = −8.32° (methylene chloride, 0.1); ^{1}H nmr (deuteriochloroform): δ 3.38 (s, 2H, CH_2 at C_5), 3.83 (s, 3H, OCH_3), 3.90 (dd, 1H, CH_2NPhth, J = 5.7, 14.2 Hz), 3.96 (dd, 1H, CH_2NPhth, J = 4.2, 14.2 Hz), 4.35 (dd, 1H, CH_2-OBzt, J = 6.1, 11.5 Hz), 4.46 (dd, 1H, CH_2-OBzt, J = 3.4, 11.5 Hz), 4.54 (m, 1H, *tert*-H), 5.03 (s, 2H, CH_2 of terminal Bzl), 5.30 (dd, 2H, O-CH_2-N, J = 10.4, 17.2 Hz), 6.68 (m, 2H, *o*-H of inner Bzl), 6.83 (dd, 1H, *p*-H of inner Bzl, J = 2.4, 8.3 Hz), 7.01 (s, 1H, C_6-H), 7.18 (t, 1H, *m*-H of inner Bzl, J = 7.6 Hz), 7.30-7.42 (m, 7H, ArH of terminal Bzl and *m*-H of Bzt), 7.55 (t, 1H, *p*-H of Bzt, J = 7.7 Hz), 7.69 (dd,, 2H, ArH of Phth, J = 2.8, 5.5 Hz), 7.78 (dd, 2H, ArH of Phth, J = 2.8, 5.5 Hz), 7.99 (dd, 2H, *o*-H of Bzt, J = 1.0, 8.0 Hz).

Anal. Calcd. for $C_{38}H_{33}N_3O_8$: C, 69.18; H, 5.04; N, 6.37. Found: C, 68.89; H, 4.80; N, 6.65.

S-(−)-5-(3′-Benzyloxybenzyl)-1-[(1′-phthalimidomethyl-2′-hydroxyethoxy)methyl]-2-oxo-4-methoxypyrimidine (**17a**) by Method B, Scheme V.

S-(−)-5-(3′-Benzyloxybenzyl)-1-[(1′-phthalimidomethyl-2′-benzoyloxyethoxy)methyl]-2-oxo-4-methoxypyrimidine (**23**, 1.32 g, 2 mmoles) was dissolved in 100 ml of absolute methanol, to which was added a solution of sodium methoxide prepared from 92 mg of sodium dissolved in 20 ml of methanol. The solution was stirred at room temperature for 1 hour and neutralized with dilute hydrochloric acid. After methanol was evaporated under reduced pressure, recrystallization of the residue from methanol yielded **17a**, mp 142-145°; $[\alpha]_D$ = −10.3° (methylene chloride, 0.2). The ^{1}H nmr spectrum was identical with that of *S*-(−)-5-(3′-benzyloxybenzyl)-1-[(1′-phthalimidomethyl-2′-hydroxyethoxy)methyl]-2-oxo-4-methoxypyrimidine (**17**) prepared from from *R*-(−)-2,2-dimethyl-1,3-dioxolane-4-methanol.

Acknowledgement.

This work was supported by USPHS grants CA 13943, CA 20892, and CA 39427. We should like to thank Dr. James Van Epp of the Department of Chemistry for his assistance with ^{1}H nmr spectra.

REFERENCES AND NOTES

† Visiting Professor from Shanghai Institute of Materia Medica, Chinese Academy of Sciences.

* To whom correspondence should be addressed.

[1] S. H. Chu, Z. H. Chen, Z. Y. Weng, E. C. Rowe, E. Chu and M. Y. Chu, *J. Heterocyclic Chem.*, **24**, 989 (1987).

[2] J. G. Niedzwicki, S. H. Chu, Z. H. Chen, E. C. Rowe and S. Cha, *Biochem. Pharmacol.*, **31**, 1857 (1982).

[3] M. Y. W. Chu, F. N. M. Naguib, M. H. el Kouni, S. H. Chu, S. Cha and P. Calabresi, *Cancer Res.*, **44**, 1862 (1984).

[4] S. H. Chu, Z. H. Chen, E. C. Rowe, F. N. M. Naguib, M. H. el Kouni and M. Y. Chu, *Nucleosides Nucleotides*, **3**, 303 (1984).

[5] G. Hirt and R. Barnes, *Helv. Chim. Acta*, **65**, 1059 (1982).

[6] A. Holý, *Collect. Czech. Chem. Commun.*, **43**, 3102 (1978).

[7] J. J. Baldwin, A. W. Raab, K. Mensler, R. H. Arison and D. E. McClure, *J. Org. Chem.*, **43**, 4876 (1978).

[8] F. A. Carey and K. O. Hodgson, *Carbohydr. Res.*, **12**, 463 (1970).

[9] M. H. Kouni, F. N. M. Naguib and S. Cha, personal communication.