predominant) may correspond to the result that 4 converts to the products faster than the intermediate from 1 does.

Applying Kurz's theory of transition-state acidities,[17a] one can consider the dissociation of TS^- to TS^{2-} as shown in eq 3, from which eq 4 is derived (Scheme II). K_w is the

$$TS^- \overset{K_a^*}{\rightleftharpoons} TS^{2-} + H^+ \quad (3)$$

$$K_a^* = (k_3/k_2)K_w \quad (4)$$

ionic product of water. The pK_a^* values (30 °C) calculated for **2** and **1** are 13.0 and 11.8,[18] respectively, which are close to those of 2-chloro (pK_a 14.31)[19] and 2,2-dichloroethanols (pK_a 12.89)[20] and larger than those of phenols[21] and carboxylic acids.[22] The ratio of $[TS^-]$ to $[TS^{2-}]$ for **2** can be obtained by use of the pK_a^* value. Those values at 30 °C are calculated as 3.98, 0.63, and 0.32 at $[^-OH]$ = 0.030, 0.220, and 0.400 M, respectively. That is to say, at low $[^-OH]$ **4** mainly decomposes to the products via the k_2 step, and at high $[^-OH]$ it decomposes mainly via the k_3 step.

Transition States. The k_3/k_{-1} and k_2/k_{-1} values (Table II) show that both pathways are important for the breakdown of **4**, and a large and negative $\Delta S^{\ddagger}_{303}$ strongly suggests that some water molecules are involved in TS^- and TS^{2-}.[23]

On the other hand, it has been proved that the k_2 step is generally assisted by the general-acid catalysis, and the k_3 step involves proton transfer (for a "poor" leaving group) or solvation to a cleaving bond (for a "good" leaving group).[24]

Solvent Isotope Effects. The inverse isotope effect seems to be caused mainly by $k_1^{H_2O}/k_1^{D_2O}$ (ca. 0.74 was reported by Kershner and Schowen[17b]), because the addition step (k_1) is rate-determining.[2,4,6] Reactions of this type have been suggested to involve inverse isotope effects.[25] An example is the reacton of 2-chloroethanol with base, giving ethylene oxide.[25-27] Furthermore, it has been discussed in detail that this effect is expected in the alkaline hydrolyses of amides.[28-30]

Negative Salt Effect. The observed salt effects are consistent with the existence of a partial positive charge on either the carbonyl carbon or the amide nitrogen. That is, the former charge would disappear from the reactant to the transition state. Furthermore, **2** exists in two isomers ([*Z*] and [*E*]) in polar solvents (see the NMR spectra of **2** in Experimental).[31] The two isomers have the >C=N⁺< resonance form. Therefore, a positive charge on the amide nitrogen would decrease from the reactant to the transition state. Such a decrease in positive charge would correspond to the negative salt effect.

Experimental Section

Materials. *N*-Ethyl-2,4-dinitroacetanilide (**2**) was prepared from *N*-ethyl-2,4-dinitroaniline in acetic anhydride containing a very small amount of H_2SO_4.[32] Three subsequent recrystallizations from ethanol gave a pure product: mp 111.5-112 °C (uncor); IR ($CHCl_3$) $\nu_{C=O}$ 1675 cm^{-1}; NMR (Me_2SO-d_6, 40 °C) δ 1.10 (3 H, br, m, CH_2CH_3), 1.75, 2.16 (3 H, 2 br s, $COCH_3$) [corresponding to the forms *E* and *Z*, respectively ([*Z*]/[*E*] = 1.35)], 3.8 (2 H, br m, CH_2CH_3), 7.89, 8.58, 8.68 (3 × 1 H, d, q, d, AMX aromatic system, J_{AM} = 8.5 Hz, J_{MX} = 2 Hz, J_{AX} = 0); NMR (Me_2SO-d_6, 72 °C) δ 1.10 (3 H, *t*, CH_2CH_3, J = 7 Hz), 1.97 (3 H, s, $COCH_3$), 3.76 (2 H, q, CH_2CH_3, J = 7 Hz), 7.84, 8.52, 8.72 (3 × 1 H, d, q, d, J_{AM} = 8 Hz, J_{MX} = 2 Hz, J_{AX} = 0). Anal. Calcd for $C_{10}H_{11}N_3O_5$: C, 47.44; H, 4.38; N, 16.60. Found: C, 47.56; H, 4.37; N, 16.48.

Acetonitrile was dried with calcium hydride, distilled, and stored over molecular sieves. Sodium hydroxide used was 0.1 N standard solution (Wako). Sodium chloride used was a Wako guaranteed reagent. Deuterium oxide (99.175% D) and sodium deuterium oxide (40% solution) from Merck were used. These materials were handled with syringes and serum-capped volumetric flasks.

Kinetics. The reaction rates were measured spectrophotometrically at 360 nm with a Hitachi 139 spectrophotometer equipped with a thermostated cell compartment with temperature control to within ±0.05 °C. Prepared sodium hydroxide solutions were standardized with 0.01 N HCl and the 3-mL portions were thermostated in a stoppered cell. After 1.5 μL of 0.1 M stock solution of **2** in acetonitrile had been added, the reaction was calculated with the Guggenheim method. All rate constants listed are averages of two or more runs, their agreement usually being within ±1.5%. The activation energies and entropies were calculated as described by Bunnett.[33]

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Hydride Shifts in Cyclohexyl Tosylate Solvolysis in Fluorinated Alcohols[1]

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Hydride shifts from positions beyond Cβ to a carbonium ion center are usually considered to be a unique feature of medium-ring solvolysis reactions, where transannular proximity can lead to such rearrangements.[2] Acyclic as well as cyclohexyl derivatives show a very small hydride shift contribution besides 1,2-migration.[3] No tertiary

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Table I. Yields[a] of Solvolysis Products from Tosylates of *cis*-3-Methylcyclohexanol (1), Cyclohexanol-*1*-*d* (2), and (5α)-3β-Cholestanol (3)

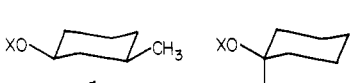
		elimination				substitution				
									at C_3	
compd	solvent	total	Δ^1	Δ^2	Δ^3	total	at C1	at C2[b]	cis	trans
1	CH_3OH[4]	36		38	62	69			8	92
	HCOOH	79.5	2	69	29	20.5[c]	3	1	7	89
	CF_3CH_2OH	90	3	61	36	10	13.5	0.5	9	78
	$(CF_3)_2CHOH$	96.5	3	67.5	29.5	3.5	44	0.5	20.5	35.6
2	CF_3CH_2OH	96	93	7	<0.5	4	92	8	<0.5[b]	
	$(CF_3)_2CHOH$[d]	98	95	5	<0.5	2	73.2	26.5	<0.5[b]	
3	CF_3CH_2OH	76.5	90:10 Δ^2/Δ^3		1[e]	24.5	>90 (3α)			
	$(CF_3)_3CHOH$	87	90	10	1[e]	13	f			

[a] In percent; solvolysis reactions in 2 M ROTs solutions with 2.5 M pyridine at 90 °C in sealed ampules for 0.5 h (HCOOH), 9 h (CF_3CH_2OH), or 1 h ($(CF_3)_2CHOH$). For CH_3OH see ref 4. Olefins Δ^1, Δ^2, and Δ^3 from **1** are 1-, 2-, and 3-methylcyclohexene and from **2** are 1-, 2-, and 3-deuteriocyclohexene. [b] Stereochemistry unidentified. [c] Identified after $LiAlH_4$ reduction to the alcohol. [d] Deuterium NMR shifts in parts per million from internal 1% cyclosilan (Merck) in $CFCl_3/CCl_4$ solutions: Δ^1, 5.60; Δ^2, 1.95 (1.5 from natural-abundance spectra); substitution at C1, 3.35; substitution at C2, 1.82 (axial), 1.32 (equatorial); substitution at C3, 1.55 (from natural-abundance spectra); stereochemistry undefined. [e] Δ^4 or Δ^5. [f] See text.

substitution products were observed in the methanolysis of *cis*-3-methylcyclohexyl tosylate (**1**, X = Ts),[4] although a 1,3-shift would generate a stable tertiary cationic intermediate and the migrating hydrogen would seem to be in a geometric position similar to the corresponding transannular pseudoaxial hydrogen at Cε in cyclooctanes, where complete rearrangements are found.[2,5]

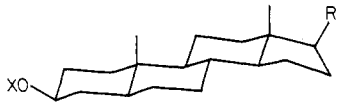
Until now it has not been clear to which degree the absence of distant hydrogen migrations is due to the lack of sufficient proximity of the cationic center Cα to the remote hydrogen or due to different solvolysis mechanisms in normal ring compounds. In fact, Schleyer et al. have shown that cyclohexyl tosylate reacts even in formic acid largely by the solvent-assisted pathway (k_s/k_c = 5.0),[6] whereas, e.g., cyclooctyl tosylate shows little solvent assistance even in ethanol.[7] In agreement, Lambert et al.[8a] have reported a strong increase of 1,2 hydride shifts for the reaction of deuterated cyclohexyl tosylate in formic acid. In contrast, complete 1,5 hydride shift is observed, e.g., with cyclooctyl tosylates even in aqueous solvents[2] and in the presence of hydroxyl anions.[1]

We therefore have investigated the solvolysis products of the cyclohexane derivatives **1**–**3** (X = Ts) in the weakly



1

2



3, R = C_8H_{17}

nucleophilic solvents formic acid, trifluoroethanol[9] (TFE), and hexafluoroisopropyl alcohol[9] (HFIP). Although very little substitution is observed in TFE and HFIP, due to their low nucleophilicity, these products could be separated and identified by GLC, ^{13}C NMR (for **1** and **3**), and ^2H NMR (for **2**) (Table I). For structural assignments attempts were undertaken to independently prepare ethers of the fluoro alcohols and to achieve ether cleavage by several methods (see Experimental Section).

The solvolysis of **1** (X = Ts) shows a dramatic increase of 1,3 hydrogen migration with decreasing solvent nucleophilicity; as observed with medium rings,[2] elimination is accompanied to a much smaller degree by rearrangements. The absence of detectable 1,3-shift products in cyclohexane **2**, where no tertiary carbonium ion can provide a driving force, clearly corrects earlier literature[3c] reports. That a direct 1,3-shift and not consecutive 1,2 hydride shifts are responsible for the large amount of rearrangement from **1** is in accordance with earlier findings with acyclic compounds[3a] and is indicated by the much smaller amount of 1,2-shift product obtained from **2**. Even, if the 1,2-shift intermediate were formed in **1** and **2** to the same degree (although no 2-methylcyclohexyl derivative was found), there should at least not be formed more 1,3-shift product from **1** than 1,2-shift product from **2**. The absence of 1,2-shift product from **1** and the comparison to products from **2** suggest that hydride shifts start from different carbonium ion intermediates than those for substitution. Shiner[10] has provided strong evidence for the formation of solvent-separated ion pairs in fluorinated alcohols, which would be responsible for the subsequent rearrangements. The increasing rearrangement in going from HCOOH to TFE to HFIP indicates that, even in these solvents, preceding species such as intimate ion pairs are present and give rise to substitution products without rearrangement.[8,11] The observed increase of equatorial attack at Cα in **1** in the sequence HCOOH, TFE, HFIP can be ascribed to the increasing bulkiness of these nucleophiles.

Force field calculated structures obtained by using Allingers MM2 program[11,12] and cycloalkanones as models

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Table II. ^{13}C NMR Shifts of Cyclohexyl TFE and HFIP Ethers

ether	shift[a] C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9(Me)
cyclohexyl TFE	80.1	32.4	24.2	26.1	24.2	32.4	67.8 (q, ^2J = 33.8)	125.1 (q, ^1J = 280)	
1-methylcyclohexyl TFE	75.6	36.5	22.3	26.0	22.3	36.5	60.5 (q, ^2J = 33.8)	125.1 (q, ^1J = 280)	24.6
cis-3-methylcyclohexyl TFE	80.6	32.0	24.2	32.9	31.7	41.1			22.4
trans-3-methylcyclohexyl TFE	76.6	29.8	20.3	34.6	26.8	38.7			22.2
cyclohexyl HFIP	83.0	32.3	23.9	25.7	23.9	32.3	74.6 (s, ^2J = 29.4)	121.3 (q, ^1J = 288)	
1-methylcyclohexyl HFIP	81.4	38.0	23.2	26.0	23.2	38.0	70.2 (s, ^2J = 32.4)		23.9

[a] In parts per million from internal Me_4Si; ^{13}C–^{19}F coupling constants are given in hertz.

for the cationic intermediates support the observation that remote hydride shifts in cyclohexane with a Cα···H3 distance of r = 2.82 Å are indeed less favorable than those in the medium rings such as cyclooctane ($r_{C\alpha-H5}$ = 2.6 Å). A twist-boat cyclohexane form with a calculated r of 3.06 Å in the relative minimum conformation will not enhance the 1,3-shift but is reported to be the relevant intermediate for E1-type eliminations from equatorial tosyloxy cyclohexanes.[13] Thus the <3% olefin formation from 1,3-shift (Table I) confirms an independent pathway for elimination, as only the chairlike substitution intermediate possesses a sufficient proximity of Cα to H3.

Different results could be expected for the solvolysis of the steroid **3** (X = Ts). Twist-boat elimination intermediates require more strain energy;[13c] the MM2-calculated distance (r_{C3-H5} = 2.67 Å) in the chair form (3.07 Å in the twist form) is shorter than that in cyclohexane. Indeed, there is less elimination observed with the steroid; the usual predominance of Δ^2 olefins is supported by strain energy calculations.[13c] However, although no quantitative analysis was possible due to insufficient GLC, TLC, or HPLC separations, the available ^1H NMR data indicate that substitution again proceeds only partially with a 1,3 hydride shift.

It is concluded that S_N1-like substitution and rearrangement reactions in cyclohexanes can be completely masked in solvents of normal nucleophilicity and/or by eliminations proceeding via nonchair intermediates which are geometrically less apt to undergo hydride shifts. The calculated longer distances between the eventually migrating hydrogen and the carbon atom bearing the leaving group in cyclohexanes in comparison to medium rings can be compensated only by formation of a tertiary carbonium ion during the rearrangement.

Experimental Section

NMR spectra were recorded by the PFT technique on Bruker HX90 and WH90 instruments under the following conditions: ^1H, 90 MHz, in $CDCl_3$ with internal Me_4Si as a reference; ^{13}C, 22.64 MHz, in $CDCl_3$ or $CFCl_3$ with Me_4Si; ^2H, 13.8 MHz, in $CFCl_3/CCl_4$ with cyclosilan (Merck, Darmstadt) as a reference. ^1H noise decoupling was used for ^{13}C and ^2H observations.

Alcohols 1 (X = H) were obtained by spinning-band distillation from a commercially available epimeric mixture in 98–99% purity (GLC). Compound **2** (X = H) was prepared by $LiAlD_4$ reduction of cyclohexanone by using standard procedures. **3** (X = H) was obtained by hydrogenation of 30 g of cholesterol[14] in 300 mL of cyclohexane/100 mL acetic acid over 0.8 g of platinum dioxide; recrystallization from 95% ethanol yielded 82.5% alcohol (purity >98% by NMR).

Tosylates were prepared by reaction of 1 mol of alcohol with 1.1 mol of tosyl chloride in pyridine and recrystallized from pentane. **1** (X = Ts): 80.5% yield; mp 34.3 °C.[15] **2** (X = Ts): 95% yield; mp 41 °C. **3** (X = Ts): 83% yield; mp 132 °C.[16]

Solvolysis reactions were carried out under conditions as described in Table I for ~20 half-lifes [by the use of 0.02 mol of **1–3** (X = Ts)]. The solutions were worked up with chloroform (trichlorofluoromethane and ice with **1** and **2**), water, dilute hydrochloric acid, and sodium hydrogen carbonate solution. After being dried over sodium sulfate, the samples were analyzed by GLC and NMR before and after removal of the solvent. Elimination and substitution products were separated for **1** and **2** by fractional distillation with a 10-cm Vigreux column and for **3** by preparative GLC with a 1 m × 0.25 in., UCCW 982, Chromosorb 60/80 AW column at 290 °C. Attempts to separate products from **3** in TFE and HFIP by HPLC on reversed-phase columns or on silver nitrate impregnated silica gel columns were unsuccessful.

Spectral Identification of Solvolysis Products. For **1** this was done by ^{13}C NMR shift comparison to authentically prepared material (Table II). For **2** identification was made by ^2H NMR (data see Table I); ^1H NMR shifts agreed within ±0.02 ppm with the ^2H shifts.

For the mixtures from **3**, NMR data indicated the presence of 3α and 3β ethers. **3** (X = α-CH_2CF_3): ^1H NMR 3.67 (C3 H), 3.76 ppm (CH_2); ^{13}C NMR 76.4 ppm (C3; calcd 76.7). **3** (X = β-$CH(CF_3)_2$: ^1H NMR 4.14 ppm ($CF_3)_2$ CH); ^{13}C NMR 83.2 ppm (calcd 84.5). The C3 signals and also a weak C5 signal at 81.8 ppm (calcd 83.3) are tentatively assigned by comparison to shifts calculated from suitable increments taken from Table II; other steroid ^{13}C NMR shifts are from ref 17.

Fluoro alcohol ethers are generally obtained in poor yields by the Williamson method,[18] as follows.

1-Methylcyclohexyl Trifluoroethyl Ether[19] **(4a, $C_6H_{10}(CH_3)OCH_2CF_3$).** 1-Methylcyclohexyl bromide (5 g, 28.2 mmol) was added to a mixture of 0.9 g (39.1 mmol) of sodium in 15 mL of TFE. After the mixture was stirred 2 h under reflux, workup with water and ether, drying, and distillation gave the product: 1.45 g (26.2%); ^{13}C NMR, Table II; ^1H NMR[19] ($CDCl_3$) δ 3.70 (q, J = 8.5 Hz, 2), 1.14 (s, 3).

Hexafluoroisopropyl ether 4b ($C_6H_{10}(CH_3)OCH(CF_3)_2$) was prepared by the same procedure: 10.6% yield; ^{13}C NMR, Table II; ^1H NMR ($CDCl_3$) δ 4.32 (septet, J = 5.9 Hz, 1), 1.25 (s, 3). Better ether yields are obtained by electrophilic addition of TFE or HFIP to olefins.

Cyclohexyl Trifluoroethyl Ether[20] **(5, $C_6H_{11}OCH_2CF_3$).** Chlorosulfonic acid (200 mg, 1.7 mmol) is added slowly to a

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mixture of 15 g (0.18 mol) of cyclohexene and 40 g (0.4 mol) of TFE with stirring. After 15 min the solution is poured into water, neutralized with sodium hydrogen carbonate, and extracted with trichlorofluoromethane (3 × 10 mL). After drying of the mixture over sodium sulfate and distillation of the solvent and residue, 22 g (64%) of ether was obtained; bp 41–42 °C (13 mmHg). The volatile product, which still contained 6% olefin, was purified by distillation over a 1-m spinning-band column. Anal. Calcd for $C_8H_{13}OF_3$: C, 52.74; H, 7.19. Found: C, 52.80; H, 7.31.

Whereas reaction of TFE and acid with cholest-5-ene only led to rearranged olefins (^{13}C NMR), the same method was successful in the preparation of the following.

1-Methylcyclohexyl Trifluoroethyl Ether (4a), bp 44 °C (14 mmHg; after spinning-band distillation). Anal. Calcd for $C_9H_{15}OF_3$: C, 55.09; H, 7.71. Found: C, 55.10; H, 7.64.

Hexafluoroisopropyl ethers of cyclohexanol (53%) and 1-methylcyclohexanol (35%) were prepared only in small quantities for spectroscopic comparison.

Ether Cleavage Experiments. Treatment of cycloalkyl methyl and steroid methyl ethers with boron trifluoride and lithium iodide in acetic anhydride is known to yield acetates with retention of configuration.[20] This method was successfully tested with several primary ethers as well as with secondary and tertiary fluoroalkyl ethers: **5** gave 91% conversion, 89% acetate, and 6% olefin; **4a** gave 94% conversion, 90% acetate, and 10% olefin; **4b** gave 85% conversion, 95% acetate, and 5% olefin (GLC). No acetate, however, could be obtained from the steroid (**3**) solvolysis products.

Alternatively, a recently published reductive cleavage method[21] was modified as follows: 1 mmol of the ether was stirred under reflux with 1 mmol of lithium aluminium hydride and 10 mmol of boron trifluoride in diethyl ether. After cautious addition of water, GLC analysis of the ether solution showed only 10% conversion with **4a**, yielding 37% 1-methylcyclohexanol and 62% 1-methylcyclohexene.

Registry No. 1 (X = H), 5454-79-5; 1 (X = Ts), 37690-41-8; 2 (X = H), 21273-02-9; 2 (X = Ts), 957-27-7; 3 (X = H), 80-97-7; 3 (X = Ts), 3381-52-0; 3 (X = α-CH_2CF_3), 80764-76-7; 3 (X = β-$CH(CF_3)_2$), 80764-77-8; **4a**, 80764-78-9; **4b**, 80764-79-0; **5**, 80764-80-3; *cis*-3-methylcyclohexyl trifluoroethyl ether, 80764-81-4; *trans*-3-methylcyclohexyl trifluoroethyl ether, 80764-82-5; cyclohexyl hexafluoroisopropyl ether, 15233-00-8.

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Simplified Synthesis of 5-Mercaptouracil Riboside Derivatives

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The conventional preparation of nucleosides involves a rather lengthy synthetic procedure. In the case of one of the most preferred general methods the base to be used must generally be converted into a moisture-sensitive trimethylsilyl derivative. In some cases the catalyst used to effect formation of the nucleoside bond also requires trimethylsilylation. Condensation of the base with the sugar to be used normally takes place in yet another synthetic step. The need to distill, transfer, and otherwise handle these delicate materials introduces an element of difficulty into conventional nucleoside synthesis.

Generally, syntheses of this type utilize a blocked halo sugar. Because of the lack of long-term stability which characterizes them, sugars of this type are best freshly prepared shortly before the synthesis is undertaken.

A further area of difficulty which characterizes conventional nucleoside syntheses is the need to separate mixtures of the α and β anomers of the nucleoside which are normally formed in these reactions. Generally, separation of these isomers is effected by either fractional crystallization or chromatography. In either case, the separation procedure frequently proves costly in terms of both time and materials.

Recently, a simplified method for the preparation of pyrimidine and purine ribosides which either eliminates or greatly attenuates the difficulties which characterize the conventional synthetic procedures utilized in nucleoside syntheses has been reported.[1] This procedure involves the in situ formation of the silylated base and catalyst and their reaction with a stable, commercially available blocked ribose sugar to afford the product nucleoside in a single synthetic step. Furthermore, this method also results in formation of the desired β form of the synthetic riboside in a high state of purity, thereby eliminating the need for separation of the α isomer of the nucleoside.

Results and Discussion

The present study was undertaken to investigate the application of this method to the synthesis of a variety of ribosides which incorporate derivatives of 5-mercaptouracil as the base. This procedure has been found to be effective with a wide variety of substituents attached to the 5-sulfur atom.

Generally, the 5-S-alkylated derivatives of 5-mercaptouracil used in this study were prepared by treatment of the pyrimidine base with the desired alkylating agent under conditions which enhance sulfur alkylation while minimizing reaction at any of the several alternate sites at which alkylation could occur. The substantial difference in acidity between the sulfhydryl and hydroxyl groups of 5-mercaptouracil[2] allows for highly selective alkylation of the 5-sulfur atom.

The tendency for 5-mercaptouracil to undergo facile autoxidation to form the corresponding disulfide in basic solution has been reported.[3] Occurrence of this dimerization would prevent effective alkylation of the 5-sulfur atom of **1** and therefore must be prevented or minimized. The use of anhydrous methanol as the solvent for the alkylation reactions proved to be effective in both reducing the tendency of **1** to undergo dimerization and in allowing effective alkylation of the sulfur atom to occur. The only substituent which could not be introduced successfully via this general procedure was the vinyl group.

Pyrimidines having vinyl or vinylic groups in the 5-position often display substantial biological activity.[4] For this reason synthesis of an 5-*S*-vinyl derivative of **1** was deemed desirable. However, attempts to prepare this product via direct alkylation, dehydration of 5-[(2-hydroxyethyl)thio]uracil (**2**), and dehydrohalogenation of 5-(2-chloroethyl)thio]uracil (**3**) proved unsuccessful. A vinylic derivative of **1**, however, was prepared from the 5-*S*-allyl derivative **4** by isomerization of the allylic double

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