of 3 h and then at room temperature for an additional 20 h. The reaction was quenched with 50 mL of saturated sodium bicarbonate and extracted with 2 × 50 mL of methylene chloride. The combined organic solutions were washed with 100 mL of water, dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo to a gold oil. This was purified by flash chromatography (10% ethyl acetate in Skellysolve-F as eluant) to afford 0.362 g (59%) of the desired deoxybenzoin **37** as white prisms: mp (recrystallized from petroleum ether) 87–89 °C (lit.[40c] mp 146–148 °C).[43] A small quantity (0.040 g; 7%) of aryl ester **38** was also isolated: mp (recrystallized from petroleum ether) 73–74 °C.

Deoxybenzoin 37: R_f = 0.55 (3:2 hexanes:ethyl acetate); NMR ($CDCl_3$, 60 MHz) δ 3.69 (s, 2 H), 5.88 (s, 2 H), 6.74 (m, 6 H), 12.68 (s, 1 H, exchangeable with D_2O); IR ($CHCl_3$) 3600, 3300 (br), 1750, 1605, 1505, 1490, 1445, 1250, 1140 cm^{-1}. Anal. Calcd for $C_{15}H_{12}O_5$: C, 66.17; H, 4.44. Found: C, 65.93; H, 4.28.

Aryl Ester 38: R_f = 0.60 (3:2 hexanes:ethyl acetate); NMR ($CDCl_3$, 60 MHz) δ 3.69 (s, 2 H), 5.91 (s, 2 H), 6.65–7.45 (m, 8 H); IR ($CHCl_3$) 3550–3400 (br), 3010, 2900, 1720, 1605, 1490, 1250, 1130 cm^{-1}.

7-Hydroxy-3-(3,4-methylenedioxyphenyl)benzopyran-4-one: Pseudobaptigenin (31). A solution of 0.171 g (0.626 mmol) of pure deoxybenzoin **37** dissolved in 2 mL of bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent[39]) was heated at 90 °C under a nitrogen atmosphere for 1.5 h. The volatiles were completely removed in vacuo, and the residue was purified by flash chromatography (50% ethyl acetate in Skellysolve-F as eluant) to afford 0.050 g (28%) of pseudobaptigenin (**31**) as beige-colored microcrystals: mp (recrystallized from methanol) 299–301 °C (lit.[41i], mp 295–297 °C). This product is highly insoluble, and it was felt that a considerable amount was lost by crystallization while it was being purified by chromatography. In order to demonstrate this, the crude formylation product was used to synthesize maxima substance-B (**30**) (vide infra): NMR (CD_3COCD_3, 200 MHz) δ 6.07 (s, 2 H), 6.93 (m, 3 H), 7.03 (d, 1 H, J = 9 Hz), 7.11 (d, 1 H, J = 9 Hz), 7.20 (s, 1 H), 8.09 (d, 1 H, J = 9 Hz), 8.23 (s, 1 H); IR (KBr) 3400–2950 (br), 1620 (with shoulder at 1645), 1440, 1385, 1355, 1300 cm^{-1}; HRMS calcd for $C_{16}H_{10}O_5$ 282.0528, found 282.0562.

7-(3-Methyl-2-butenyloxy)-3-(3,4-methylenedioxyphenyl)-benzopyran-4-one: Maxima Substance-B (30). A mixture of crude pseudobaptigenin (**3**) (prepared by formylation from 0.170 g (0.625 mmol) of deoxybenzoin **37** and subsequent evaporation of the volatiles (vide supra)) and 0.200 g (1.45 mmol) of anhydrous potassium carbonate was suspended in 30 mL of acetone and treated with 0.951 g (6.38 mmol, 0.75 mL) of 1-bromo-3-methyl-2-butene (prenyl bromide). The mixture was heated at reflux for 5 h, then cooled and filtered, and the volatiles were evaporated in vacuo. The residue was purified by flash chromatography (5% ethyl acetate in Skellysolve-F as eluant) to give 0.112 g (51% overall from deoxybenzoin **32**) of maxima substance-B (**30**) as pale yellow needles: mp (recrystallized from petroleum ether:ether) 133–135 °C (lit.[40g] mp 134–135 °C); NMR ($CDCl_3$, 200 MHz) δ 1.79 (s, 3 H), 1.82 (s, 3 H), 4.61 (br d, 2 H, J = 5 Hz), 5.50 (br t, 1 H, J = 5 Hz), 5.99 (s, 2 H), 6.96 (m, 5 H), 7.90 (s, 1 H), 8.19 (d, 1 H, J = 9 Hz); IR ($CHCl_3$) 3010, 2940, 1650, 1625, 1605, 1440, 1250 cm^{-1}; HRMS calcd for $C_{21}H_{18}O_5$ 350.1154, found 350.1155.

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Synthesis of Ring-Expanded Cytidine: Homocytidine

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The syntheses of ring-expanded cytidine (**7**, homocytidine) and its corresponding dihydro analogue (**9**) were accomplished in five and four steps, respectively, starting from the very simple and easily accessible tetramethyleneurea nucleoside **10** [1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)hexahydro-2*H*-1,3-diazepin-2-one]. The key reaction was the selective oxidation at C-4 accomplished with benzeneseleninic anhydride to give both the 4-oxo-1,3-diazepinone **14** and the 4-oxo-5-(phenylseleno)-1,3-diazepinone **17**. Transformation of **14** into the ring-expanded dihydrocytidine analogue **9** was easily accomplished by using a sequence involving thiation followed by reaction with methyl iodide and treatment of the resulting compound with methanolic ammonia. A similar approach starting with **17**, but preceded by the oxidative elimination of benzeneseleninic acid, afforded the corresponding target homocytidine (**7**). The ^1H NMR properties of **7** indicate that the C-7 protons are exchangeable by deuterium in D_2O solution through the intermediacy of a tautomeric form **27**. The corresponding ring-expanded uridine analogues could not be obtained as free nucleosides, since they underwent cleavage of the diazepine ring at C-4 under the conditions used to deblock the benzoyl protective groups. Both ring-expaned cytidine and its dihydro analogue behaved as moderate substrates for cytidine deaminase.

For several years we have developed methods of syntheses for the construction of ring-expanded pyrimidine nucleosides containing the 1,3-diazepin-2-one aglycon.[1-6] These compounds had been screened for their enzymatic inhibitory properties against enzymes involved in the metabolism of uridine and cytidine. In particular, cytidine deaminase (CDA), the catabolic enzyme that converts cytidine to uridine, is an example of an enzyme that has shown significant sensitivity toward inhibition by these 1,3-diazepin-2-one nucleosides, which incorporate a variety of functional groups (e.g., compounds **1–5**).[1,3,7] Inhibition of CDA by these compounds and their relative potency as

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(2) Liu, P. S.; Marquez, V. E.; Driscoll, J. S. *J. Org. Chem.* **1980**, *45*, 5225.
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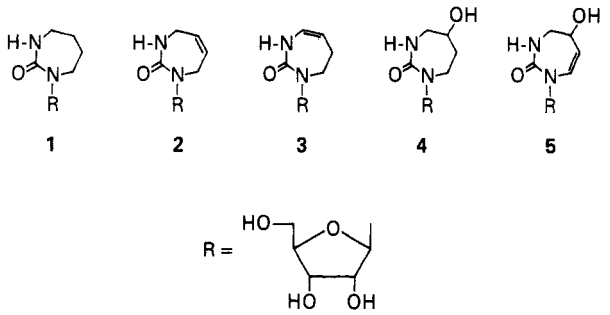
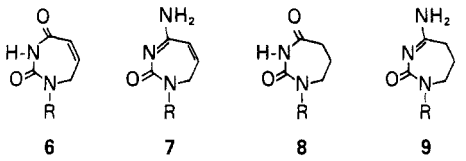
(7) For a review on this subject, see: Marquez, V. E. In *Developments in Cancer Chemotherapy*; Glazer, R. I., Ed.; CRC: Boca Raton, FL, 1984; pp 91–114.

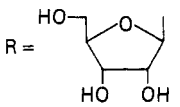


1 2 3 4 5

inhibitors can be explained in terms of the transition-state theory.[7] While these compounds resemble the distorted transition state of cytidine during the enzyme-catalyzed deamination, none of them can be considered close analogues of either the substrate cytidine or the product uridine. For this reason, we considered preparing the ring-expanded versions of uridine and cytidine which appeared as attractive synthetic targets as well as potential antimetabolites against enzymes involved in pyrimidine metabolism. The structures of these target molecules are represented by **6** and **7**, although alternative tautomeric forms could be written. Compounds **8** and **9** were also selected as targets, and they correspond to the ring-expanded dihydrouridine and dihydrocytidine analogues, respectively.



6 7 8 9



Results and Discussion

In the elegant work of Back,[8] which describes the different mechanisms of reaction of benzeneseleninic anhydride [PhSe(O)O(O)SePh] with aza steroid lactams, he was able to show that oxidation of the methylene carbon adjacent to the lactam nitrogen proceeded more readily with the seven-membered ϵ-lactams than with the more rigid six-membered δ-lactams. The key step in this reaction is the formation of a benzeneseleninamide intermediate capable of adopting the required coplanar transition state necessary for the 1,2 elimination of benzeneselenenic acid (PhSeOH). A second step, involving the ensuing reaction of the transiently generated cyclic *N*-acylimine with benzeneseleninic acid [PhSe(O)OH], resulted in the formation of a seleninic ester derivative that rapidly underwent loss of PhSeOH to form the cyclic imide. This series of addition–elimination reactions accomplished the selective introduction of a carbonyl function on the nitrogen side of the lactam ring.[8] We anticipated that a similar reaction with the seven-membered cyclic urea nucleoside 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)hexahydro-2*H*-1,3-diazepin-2-one (**10**) offered the possibility of generating the corresponding 4-oxo-1,3-diazepin-2-one nucleoside **14**. When **10** was reacted with benzeneseleninic anhydride in refluxing toluene, this repeated addition–elimination sequence, similar to that described by Back for the ϵ-lactams, resulted in the formation of the desired product **14**, albeit in low yield (13%) (Scheme I). The major product obtained was also a 4-oxodiazepinone nucleoside (**17**), which incorporated an extra phenylseleno group α to the newly introduced 4-oxo functionality. This new compound most likely arose from the conversion of **12** to the more resonance-stabilized tautomer **15**, which then underwent a similar sequence of addition–elimination reactions to give **17** (Scheme I). A similar type of product was also observed by Back with the aza steroid ϵ-lactams.[8] In our sequence, formation of **17** was advantageous, since it provided an excellent intermediate for generating a double bond conjugated to the newly introduced carbonyl function (vide infra). Typically, this reaction was conducted in refluxing toluene in the absence of triethylamine to give a 46% combined yield of **14** and **17** and a 14% recovery of unreacted starting material. The presence of triethylamine favored the formation of **14** at the expense of **17**, but without an increase in the overall yield.

Compound **14**, along with the N-3 isomer **20**, also was obtained from the reaction between persilylated tetrahydro-2*H*-1,3-diazepine-2,4(3*H*)-dione (**19**)[9] and the halogeno sugar (**18**) via a mercury-catalyzed condensation reaction (Scheme II). The X-ray crystal structure analysis of **14** confirmed, as expected, the location of the newly incorporated carbonyl function.[10] Oxidation of **17** with *m*-chloroperbenzoic acid (Scheme III), followed by a base-catalyzed elimination of selenoxide, afforded the 5,6-unsaturated 1,3-diazepine-2,4-dione nucleoside **21**. Compounds **14** and **21** represent ring-expanded forms of dihydrouridine and uridine, respectively. Unfortunately, attempts to remove the protecting benzoyl groups in these compounds under the usual conditions (viz. methanolic ammonia, sodium methoxide/methanol, KCN/methanol, etc.) invariably resulted in the simultaneous cleavage of the seven-membered ring due to methanolysis or ammonolysis at C-4.

Using a different approach, Kunieda and Witkop reported the synthesis of the isomeric 6,7-unsaturated isomer of **21** generated from the photochemical ring-expansion reaction of 1-β-D-ribofuranosyl-5,6-cyclothymine.[11] Catalytic hydrogenation of this photoproduct afforded the dihydrouridine analogue corresponding to our protected dihydrouridine **14**.[11]

Conversion of both ring-expanded uridine analogues **14** and **21** to the corresponding 4-thioxo-1,3-diazepin-2-ones (**25**, **22**) was easily accomplished after thiation with Lawesson's reagent.[12] The saturated 4-thioxo-1,3-diazepin-2-one **25** was then methylated with methyl iodide in the presence of triethylamine to give the expected methylthio intermediate **26**. This compound, after treatment with methanolic ammonia, produced the deblocked target ring-expanded dihydrocytidine analogue **9**.

Thiomethylation of the unsaturated 4-thioxo-1,3-diazepin-2-one **22** afforded a mixture of two tautomers **23** and **24**. When the reaction was followed by TLC, formation of **23** appeared to be kinetically favored, but after some time the mixture reached a nearly 50% equilibrium with the alternative tautomer **24**. This transformation occurred spontaneously, but it was greatly accelerated by traces of base. Complete separation of **24** was possible by preparative TLC, and as expected its NMR spectrum showed that there were no 1,3-diazepine aliphatic protons

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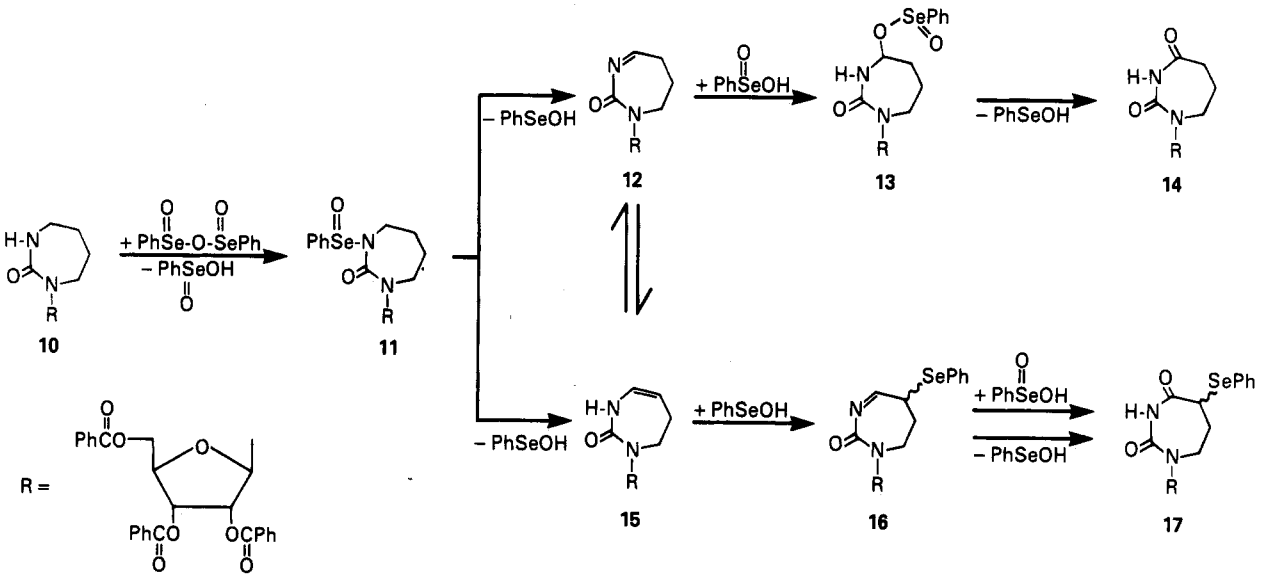
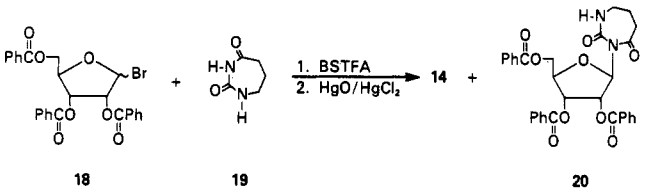
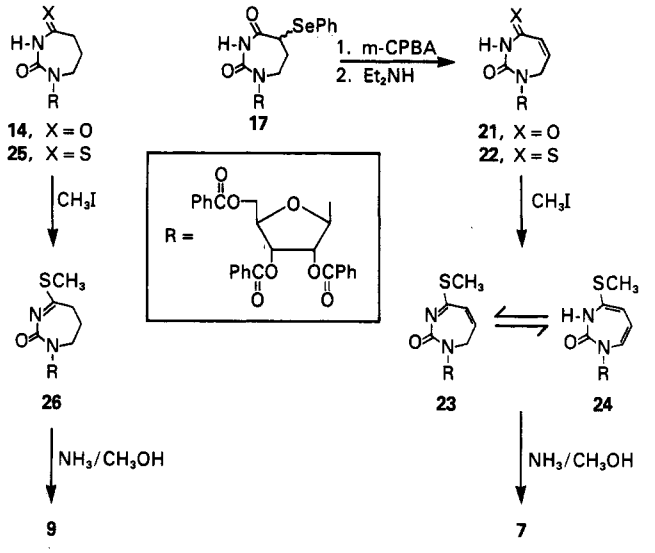
Scheme I



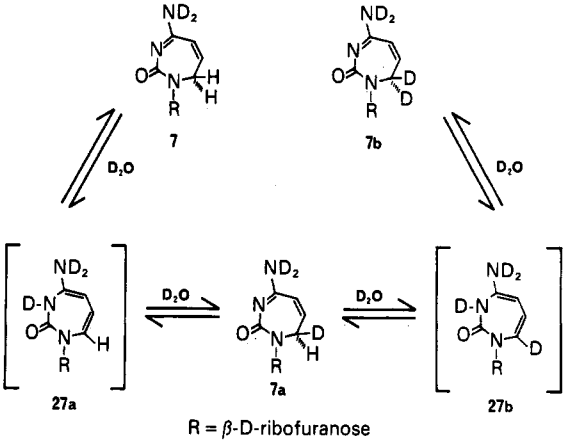
Scheme II



Scheme III



Scheme IV



present. Compound **23** was not isolated in pure form and was always contaminated with **24**. In the NMR spectrum of the mixture, however, there were two distinct CH_3S signals corresponding to **23** and **24**, and the aliphatic C-7 protons from **23** were observable as a complex multiplet at δ 3.00. This mixture of **23** and **24** was treated with methanolic ammonia at room temperature, after which it was smoothly converted to a single tautomer (compound **7**) with a regenerated methylene carbon at C-7. This may indicate that during ammonolysis only the reactive N=CSMe moiety of tautomer **23** was capable of undergoing displacement with ammonia and, as the reaction progressed, reequilibration of **24** back to **23** provided more of the reactive species to complete the transformation. In addition, this reaction simultaneously removed the protective benzoyl groups to give the desired homocytidine (**7**), whose structure was firmly established on the basis of NMR spectroscopy and FABMS analyses.

Ring-expanded cytidine (**7**) showed some interesting proton NMR properties that indicate that in D_2O solution it exists in a dynamic equilibrium with its tautomer **27**. However, contrary to the case of the protected thiomethyl precursors (**23**, **24**), where both tautomers were clearly observable, structure **7** appears to be the more favorable tautomer. Tautomer **27** was not initially detected in the NMR spectrum of **7**, but changes in the spectrum after a long period of time demonstrated that the methylene protons at C-7 were being exchanged by deuterium. This process can be explained through the intermediacy of **27** (Scheme IV). Integration of the signals for H-5, H-6, H-1′, and the two H-7 protons were initially in the expected ratio of 1:1:1:2 (Figure 1a). The assignment of these signals was made through decoupling experiments. Irradiation of the multiplet at δ 2.85 (methylene protons at C-7) caused the quartet at δ 5.50 to coalesce into a doublet, and irradiation at δ 5.50 caused the doublet at δ 6.30 to change to a singlet. The integration of the anomeric proton signal serves as an internal control, since it does not participate in the equilibrium. After 15 h, the ratio had changed to 1:1:1:1, indicating that one of the protons at C-7 had undergone exchange (compound **7a**). In addition to the decrease in intensity, the aliphatic proton signal changed from a complex multiplet to a doublet. The integration of this signal continued to decrease with time, but at a much slower rate: 1:1:1:0.6 (24 h) and 1:1:1:0.58 (48 h) (Figure

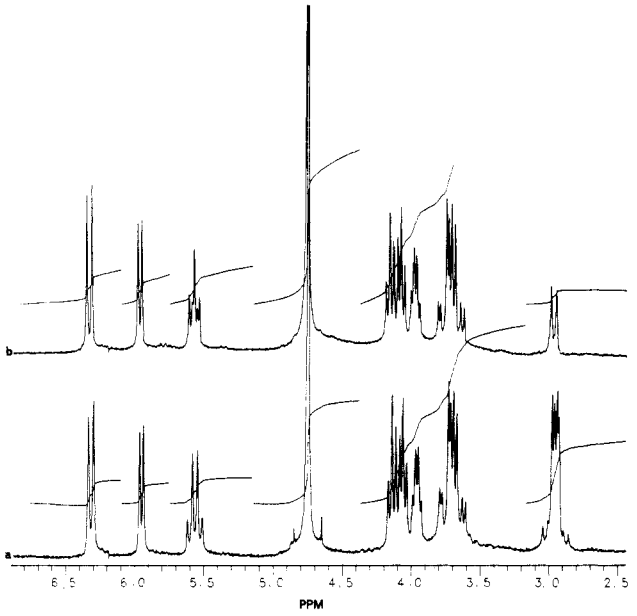


Figure 1. 200-MHz NMR spectrum of homocytidine (7) in D_2O. Key: a, recorded immediately after dissolving the sample; b, recorded after 49 h.

1b). This leveling effect suggests that one of the hydrogens at C-7 is preferentially exchanged over the other. Such an anomaly could result from the existence of a preferred spatial disposition between sugar and aglycon moieties that makes the hydrogens at C-7 prochiral and thus favors the 1,5 hydrogen shift to occur preferentially on one face of the diazepinone ring. Once the exchange of the preferred hydrogen takes place, the exchange of the remaining enantiomerically unfavorable hydrogen proceeds very sluggishly. When the 48-h sample of 7 in D_2O was lyophilized and stirred in pure water for another 48 h, the integration at C-7 recovered slightly, giving a 1:1:1:1 ratio. After 1 week of stirring in water, the ratio increased to 1:1:1:1.4, and although the integration for C-7 continued to increase with time, we were unable to observe a complete reversal to a 1:1:1:2 ratio. Unfortunately, after this long observation time, the quality of the spectrum begins to deteriorate due to decomposition of the sample. However, if, after the initial exchange of one proton (15 h), the sample is lyophilized and treated with water for 1 h in the presence of trace amounts of triethylamine, the integration recovers completely to the original 1:1:1:2 ratio.

Evaluation of 7 for cytotoxicity against L1210 cells in vitro revealed that this compound was very innocuous, displaying only a 25% inhibition of cell growth at 1 mM. In addition, the compound was a very poor inhibitor of uridine–cytidine kinase and consequently had no effect on the inhibition of uptake of uridine by L1210 cells. When both 7 and the dihydro analogue 9 were assayed as inhibitors of cytidine deaminase, the estimated K_i's were $>2 \times 10^{-4}$ M, indicating poor inhibition of the enzyme. Both compounds, however, behaved as substrates for cytidine deaminase as judged by the slow spectroscopic changes produced by the enzyme. These changes were inhibited by tetrahydrouridine as in the case of the deamination of cytidine.[13]

In conclusion, this works demonstrates that highly functionalized 1,3-diazepinone nucleosides, with structures that correspond to the ring-expanded or homoanalogues of uridine and cytidine, can be conveniently prepared from the accessible nucleoside of tetramethyleneurea (compound 10). The homocytidine analogue prepared by this procedure did not display enough biological activity to merit further investigation at this time.

(13) Tetrahydrouridine is the standard inhibitor used against cytidine deaminase. Cytidine deaminase inhibition was measured according to the procedure described by: McCormack, J. J.; Marquez, V. E.; Liu, P. S.; Victica, D. T.; Driscoll, J. S. *Biochem. Pharmacol.* **1980**, *29*, 830.

Experimental Section

All chemical reagents are commercially available and were purchased from Aldrich Chemical Co. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were measured with a Perkin-Elmer 727B spectrometer as Nujol mulls. Proton NMR spectra were recorded on a Varian XL-200 instrument. Chemical shifts are given as δ values with reference to Me_4Si. Specific rotations were measured in a 1-dm cell with a Perkin-Elmer Model 241 polarimeter. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, and by Atlantic Microlab, Inc., Atlanta, GA. Positive-ion fast atom bombardment (FAB) mass spectra were obtained on a VG 7070E mass spectrometer that was equipped with a FAB ion source. The sample was dissolved in a glycerol matrix, and ionization was effected by a beam of xenon atoms derived by neutralizing xenon ions accelerated through 8.6 kV.

Benzeneseleninic Anhydride Oxidation of 1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)hexahydro-2*H*-1,3-diazepin-2-one (10). A solution of 10 (2.34 g, 4.2 mmol) in toluene (80 mL) was treated with benzeneseleninic anhydride (1.56 g, 4.3 mmol), and the resulting solution was refluxed for 1 h. The reaction mixture was cooled and passed through a short neutral alumina column (Bio-Rad 100–200 mesh) that retained the desired compounds and permitted the elimination of much of the colored byproducts. The column was subsequently eluted with ethyl acetate, and the eluant was concentrated and purified further by silica gel chromatography (Merck, silica gel 70–230 mesh; ethyl acetate/hexanes, 2:3) to give 0.29 g (13%) of 14 and 0.95 g (33%) of 17, along with 0.22 g (14%) of 10. Compound 14 was identical with the N-1 isomer obtained via the mercury-catalyzed condensation of tetrahydro-2*H*-1,3-diazepine-2,4(3*H*)-dione (19) and 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (18) (vide infra). Compound 17, which was a mixture of diastereoisomers, was characterized by ^1H NMR spectroscopy and used without further purification: ^1H NMR ($CDCl_3$) δ 2.10 (m, 2 H), 3.50 (m, 2 H), 4.05 (m, 1 H, C*H*SePh), 4.60 (m, 2 H, H-5′$_{a,b}$), 4.80 (m, 1 H, H-4′), 5.60 (m, 1 H, H-2′), 5.80 (m, 1 H, H-3′), 6.25 (d, J = 7 Hz, 1 H, H-1′), 7.00–8.20 (m, 20 H).

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)tetrahydro-2*H*-1,3-diazepine-2,4(3*H*)-dione (14). Tetrahydro-2*H*-1,3-diazepine-2,4(3*H*)-dione (19; 0.38 g, 3 mmol) was dissolved in 12 mL of acetonitrile and treated with an excess of bis(trimethylsilyl)-trifluoroacetamide (BSTFA; 5 g) at room temperature for 0.5 h. After removal of the solvent and excess reagent under vacuum, the residue was dissolved in anhydrous benzene (15 mL). This solution was slowly added to a mixture of HgO (1.12 g) and $HgBr_2$ (1.12 g) in refluxing benzene (50 mL). Immediately, a benzene solution containing ribofuranosyl bromide 18, prepared from 1.89 g (3.75 mmol) of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl-*O*-acetate, was added dropwise to the refluxing mixture, and heating and stirring were continued for 18 h. After cooling, the reaction mixture was filtered through Celite. The organic filtrate was washed twice with a saturated $NaHCO_3$ solution and once with water. The organic layer was dried ($MgSO_4$), concentrated to ca. 5 mL, and purified by flash chromatography on a silica gel column (Biosil 200–400 mesh) by elution with ethyl acetate/hexane (1:1). The N-1 isomer (14; R_f 0.3) eluted first to afford 0.56 g (33%) of a white foamy solid, which was recrystallized from ethanol to give white needles: mp 182–183 °C; IR (Nujol) 3300, 1720, 1710, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.00 (m, 2 H), 2.60 (m, 2 H), 3.50 (m, 2 H), 4.60 (m, 2 H, H-5′$_{a,b}$), 4.80 (m, 1 H, H-4′), 5.75 (m, 2 H, H-2′, H-3′), 6.30 (d, J = 7.5 Hz, H-1′), 7.30–8.20 (m, 16 H). Anal. Calcd for $C_{31}H_{28}N_2O_9$: C, 65.03; H, 4.93; N, 4.89. Found: C, 65.15; H, 4.94; N, 4.76.

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)tetrahydro-2*H*-1,3-diazepine-2,4(3*H*)-dione (20). From the previous experiment, the second component that is obtained by flash chromatography (R_f 0.15) is the N-3 isomer 20 (0.20 g, 21%) isolated as

a white amorphous solid: mp 75–80 °C; IR (Nujol) 3300, 1720, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.00 (m, 2 H), 2.65 (m, 2 H), 3.40 (m, 2 H), 4.60 (m, 3 H, H-4′, H-5′$_{a,b}$), 6.05 (m, 3 H, H-1′, H-2′, H-3′), 6.80 (br t, 1 H, D_2O exchanged, NH), 7.20–8.20 (m, 15 H). Anal. Calcd for $C_{31}H_{28}N_2O_9$: C, 65.03; H, 4.93; N, 4.89. Found: C, 65.05; H, 5.00; N, 4.80.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-1,7-dihydro-2*H*-1,3-diazepine-2,4(3*H*)-dione (21). A solution of **17** (1.47 g, 2 mmol) in chloroform (50 mL) was treated with *m*-chloroperbenzoic acid (0.84 g, 4.87 mmol) and stirred at room temperature for 15 min. Diethylamine (2 mL) was then added, and the reaction mixture was refluxed for 15 min. Five additional portions of diethylamine were required in order to complete the reaction. After cooling, the reaction mixture was reduced to dryness and purified by flash chromatography over silica gel (Biosil 200–400 mesh; ethyl acetate/hexanes, 3:2) to give 0.73 g (63%) of **21** as a clear syrup: ^1H NMR ($CDCl_3$) δ 3.20 (m, 2 H, CH_2 at C-7), 4.90 (m, 3 H, H-4′, H-5′$_{a,b}$), 5.70 (dd, J = 16 Hz, J' = 7.5 Hz, 1 H, COCH=C*H*), 5.90 (m, 2 H, H-2′, H-3′), 6.60 (d, J = 6 Hz, 1 H, H-1′), 6.64 (d, J = 7.5 Hz, 1 H, COC*H*=CH), 7.20–8.40 (m, 16 H). Anal. Calcd for $C_{31}H_{26}N_2O_9$: C, 65.26; H, 4.59; N, 4.91. Found: C, 65.39; H, 4.72; N, 4.81.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-4-thioxo-1,3,4,7-tetrahydro-2*H*-1,3-diazepin-2-one (22). A solution of compound **21** (0.62 g, 1.09 mmol) in anhydrous benezene (40 mL) was refluxed under nitrogen in the presence of 0.88 g (2.17 mmol) of 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (Lawesson's reagent). After 4 h, the reaction mixture was cooled and reduced to dryness. The residue was purified by flash chromatography over silica gel (Biosil 200–400 mesh) using ethyl acetate/hexanes (2:3) to give 0.54 g (85%) of **22** plus 0.05 g of recovered starting material. Compound **22** was obtained as a yellowish syrup and used directly without further purification in the following step: ^1H NMR ($CDCl_3$) δ 3.60 (m, 2 H, CH_2 at C-7), 4.70 (m, 3 H, H-4′, H-5′$_{a,b}$), 5.70 (m, 3 H, H-2′, H-3′, COCH=C*H*), 6.35 (br d, 2 H, H-1′, COC*H*=CH), 7.30–8.20 (m, 15 H), 8.95 (s, 1 H, N*H*).

Methylation of 22 with Methyl Iodide. A solution of **22** (1.38 g, 2.35 mmol) in 75 mL of chloroform was treated with triethylamine (1.1 mL) and methyl iodide (0.26 mL) at room temperature under stirring. After 1 h, extra amounts of triethylamine (1.1 mL) and methyl iodide (0.26 mL) were added, and stirring was continued for another 1 h. TLC analysis (silica gel; hexanes/ethyl acetate, 3:2) revealed the disappearance of starting material and the presence of two new spots with lower R_f values of 0.65 (minor component) and 0.54 (major componet), respectively. After standing, the ratio of these products changed to almost 1:1. Elution chromatography over silica gel (70–230 mesh) with ethyl acetate/hexanes (2:3) afforded 1.1 g (78%) of the mixture. Preparative TLC (Analtech, 2000 μm) using 50 mg of this mixture allowed the separation of the high-R_f isomer **24**: ^1H NMR ($CDCl_3$) δ 2.30 (s, 3 H, SC*H*$_3$), 4.60 (m, 2 H, H-5′$_{a,b}$), 4.80 (m, 1 H, H-4′), 5.30 (m, 2 H, H-5, H-6), 5.70 (m, 3 H, H-2′, H-3′, N*H*), 6.00 (d, J = 6 Hz, 1 H, H-1′), 6.20 (d, J = 7 Hz, 1 H, H-7), 7.30–8.20 (m, 15 H). ^1H NMR of the mixture revealed additional peaks from the other isomer at δ 2.35 (s, SC*H*$_3$), 3.00 (m, methylene protons at C-7), 6.35 (d, J = 8 Hz, H-5), and 6.55 (d, J = 6 Hz, H-1′) that correspond to a compound with structure **23**. This mixture was used in the next and final step without further manipulation.

1-β-D-Ribofuranosyl-4-amino-1,7-dihydro-2*H*-1,3-diazepin-2-one (7). The mixture of compounds **23** and **24** (0.8 g) was dissolved in 50 mL of saturated methanolic ammonia and stirred at room temperature for 65 h. The solvent was removed under diminished pressure, and the residue was partitioned between water and methylene chloride. The aqueous layer was lyophilized, and the solid residue was chromatographed on a C-18 reversed-phase column (Baker, bonded phase octadecyl C-18) using water as eluant at 2 mL/min. Fractions were monitored at 254 nm, and the fractions containing a single peak combined to give 0.19 g (54%) of a slightly tan foam after lyophilization: $[\alpha]^{27}_D$ −6.6° (*c* 0.12, H_2O); ^1H NMR (D_2O) δ 2.85 (m, 2 H, CH_2 at C-7), 3.65 (m, 3 H, H-4′, H-5′$_{a,b}$), 4.00 (m, 3 H, H-2′, H-3′, H-4′), 5.50 (dd, J = 15 Hz, J' = 7.5 Hz, 1 H, H-6), 5.95 (d, J = 6 Hz, 1 H, H-1′), 6.30 (d, J = 7.5 Hz, 1 H, H-5); FABMS m/z (rel intens) 258 (MH^+, 87), 126 (b + 2 H, 100), 109 (b + 2 H − NH_3, 14). Anal. Calcd for $C_{10}H_{15}N_3O_5 \cdot 1.35H_2O$: C, 42.66; H, 6.33; N, 14.92. Found: C, 43.05; H, 6.09; N, 14.52.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-4-thioxohexahydro-2*H*-1,3-diazepin-2-one (25). In a similar fashion as performed for compound **22**, a solution of **14** (0.29 g, 0.5 mmol) in anhydrous benzene was refluxed under nitrogen for 1 h in the presence of Lawesson's reagent (0.44 g, 1.08 mmol). The reaction mixture was allowed to cool to room temperature, filtered, and concentrated. The residue was purified by preparative TLC (Analtech silica gel taper plate) using ethyl acetate/hexanes (2:3). Compound **25** was isolated as a yellowish foam (0.19 g, 65%) that was used directly in the following step.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-4-(methylthio)tetrahydro-2*H*-1,3-diazepin-2-one (26). A solution of **25** (0.19 g, 0.32 mmol) in a chloroform (7 mL) was treated with triethylamine (0.13 mL) and methyl iodide (0.04 mL) and stirred at room temperature for 1 h. The addition of these reagents was repeated thrice over the course of 5 h, when TLC analysis indicated that the starting material had disappeared. The reaction mixture was treated and extracted twice with water. The chloroform layer was dried ($MgSO_4$). The crude product was purified by preparative TLC (Analtech silica gel taper plate) using ethyl acetate/hexanes (2:3). Compound **26** (0.042 g, 23%) and 0.012 g of **25** were separated. Compound **26** was isolated as a yellowish foam: ^1H NMR ($CDCl_3$) δ 1.88 (br t, 2 H, CH_2 at C-6), 2.37 (s, 3 H, SCH_3), 2.50 (m, 2 H, CH_2 at C-5), 3.15 (m, 2 H, CH_2 at C-7), 4.50 (m, 2 H, H-5′$_{a,b}$), 4.84 (dd, J = 12 Hz, J' = 4 Hz, 1 H, H-4′), 5.54 (dd, J = 8 Hz, J' = 6 Hz, 1 H, H-2′), 5.76 (dd, J = 6 Hz, J' = 4 Hz, 1 H, H-3′), 6.53 (d, J = 8 Hz, 1 H, H-1′), 7.25–7.62 (m, 9 H), 7.87–8.12 (m, 6 H). This material was used in the next reaction without further purification.

1-β-D-Ribofuranosyl-4-aminotetrahydro-2*H*-1,3-diazepin-2-one (9). A chloroform solution (3 mL) of **26** (0.15 g, 0.25 mmol) was treated with 30 mL of saturated methanolic ammonia at room temperature for 24 h. The solvents were removed under reduced pressure, and the residue was partitioned between water (10 mL) and ethyl acetate (10 mL). The aqueous layer was lyophilized to give 0.074 g of a white powder, which was purified by reversed-phase chromatography in the same manner as compound **7**. The combined fractions containing the desired product were lyophilized to give 0.061 g of **9** (94%) as a white foamy powder: $[\alpha]^{25}_D$ −38.43° (*c* 0.14, H_2O); ^1H NMR (D_2O) δ 1.65 (m, 2 H, CH_2 at C-6), 2.15 (m, 2 H, CH_2 at C-5), 3.10 (m, 2 H, CH_2 at C-7), 3.50 (m, 2 H, H-5′$_{a,b}$), 3.80 (m, 1 H, H-4′), 4.00 (m, 2 H, H-2′, H-3′), 5.95 (d, J = 6.3 Hz, 1 H, H-1′); FABMS m/z (rel intens) 260 (MH^+, 10), 128 (b + 2 H, 7). Anal. Calcd for $C_{10}H_{17}N_3O_5 \cdot 1.65H_2O$: C, 41.57; H, 7.03; N, 14.54. Found: C, 41.97; H, 6.66; N, 14.10.

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