Stereospecific, Stereoselective Rearrangement of Hexahydro-1,3-diazepin-2-ones to Tetrahydropyrimidin-2-ones and Imidazolidin-2-ones, a Useful Route for the Synthesis of HIV Protease Inhibitors

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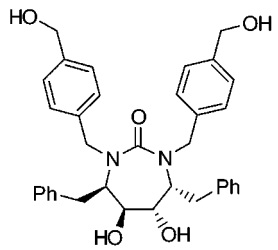
We have discovered that hexahydro-5,6-dihydroxy-1,3-diazepin-2-ones can undergo a stereospecific, stereoselective-rearrangement, ring-contraction reaction to give the corresponding tetrahydro-5-hydroxypyrimidin-2-ones. This reaction is very general and proceeds in excellent yields. The rearrangement proceeds through the formation of the aziridinium cationic intermediate **I**, which is subsequently opened by nucleophilic attack (S_N2) at the less hindered carbon to give the rearranged product. The X-ray structure determination of the rearranged product (**17a**; Figure 1) confirmed the structure and the stereochemical assignments and is consistent with the proposed mechanism. When the urea nitrogens are not substituted, the aziridine product can be isolated, and its structure (**24**; Figure 2) was also confirmed by X-ray analysis. The aziridine product can be used as a mono N-protecting group to synthesize differentially disubstituted N,N′-dialkylated tetrahydropyrimidin-2-one analogues. The tetrahydro-5-hydroxypyrimidin-2-ones can further undergo a second stereospecific, stereoselective-rearrangement, ring-contraction reaction to give the corresponding imidazolidinones. This second rearrangement is also very general and proceeds in good yields. These tetrahydro-5-hydroxypyrimidin-2-ones and imidazolidinones have previously been shown to be potent HIVPR inhibitors.

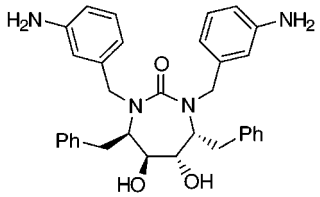
Introduction

The human immunodeficiency virus (HIV) encodes an aspartyl protease that is responsible for the processing of the gag and gag-pol gene products. This processing is required for the production of mature, infectious virions and has been a prime target for therapeutic intervention.[1] Inhibition of this essential protease (PR) has been shown to be an effective clinical treatment for AIDS.[2] There are currently four HIVPR inhibitors (saquinavir, ritonavir, indinavir, and nelfinavir) that have been approved by the FDA and are being used in AIDS therapy in combination with reverse transcriptase (RT) inhibitors.

Lam and co-workers have previously described the design and discovery of a novel class of cyclic urea based HIVPR inhibitors.[3] These C_2-symmetric hexahydro-1,3-diazepin-2-ones are complementary to the C_2-symmetric aspartic protease of HIV and are potent inhibitors of the enzyme. This work resulted in the identification of two clinical candidates in this series, **DMP 323**[4] and **DMP 450**.[5]



DMP 323



DMP 450

During our efforts to define the structure−activity relationships (SAR) of these hexahydro-1,3-diazepin-2-ones, we discovered that the seven-membered ring cyclic urea has a tendency to undergo a series of rearrange-

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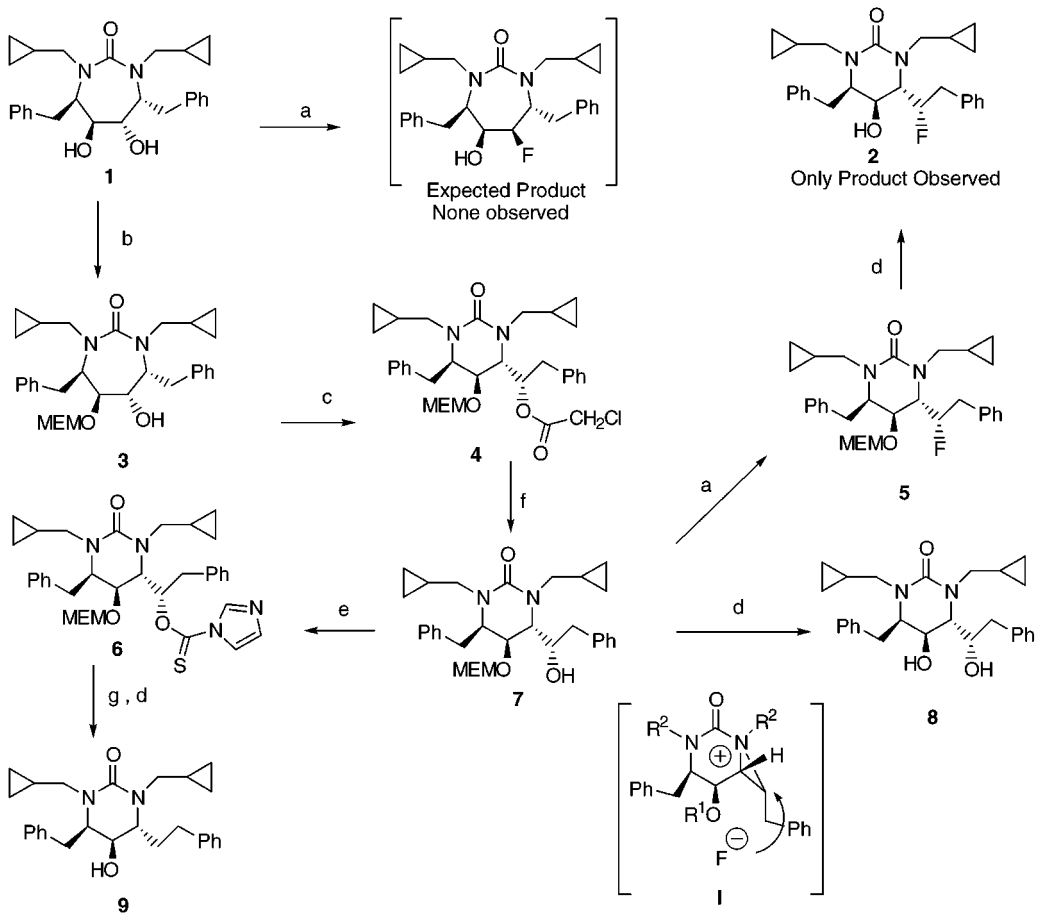
Scheme 1[a]



[a] Key: (a) 1 equiv of DAST/CH_2Cl_2; (b) MEM-Cl/Et_3N; (c) DEAD/Ph_3P/chloroacetic acid; (d) HCl/MeOH; (e) thiocarbonyldiimidazole; (f) NaOH/MeOH; (g) Bu_3SnH/AIBN.

ment, ring-contraction reactions to give sequentially, first the tetrahydropyrimidinone[6] and then the imidazolidinone.[7] In this paper we wish to describe our findings in detail.

Results and Discussion

While the seven-membered ring cyclic ureas, like **DMP 323**, are extremely potent inhibitors of HIV protease, the symmetry of these molecules contributes to their high crystallinity and low solubility. To improve solubility and to determine the SAR of the diol functionality, we became interested in substituting one of the hydroxyl groups with a fluorine. In many cases, fluorine can be a good isostere for hydroxyl groups and can have a significant impact on pharmacological properties.[8]

When diol **1**[4] was treated with 1 equiv of the fluorinating agent (diethylamino)sulfur trifluoride (DAST), we obtained a fluoro alcohol as the major product. The structure of the product was initially incorrectly assigned as the expected corresponding (hexahydro-1,3-diazepin-2-one) fluoro analogue with inversion of configuration of the carbon fluorine bond (Scheme 1). The assignment was based on the 1-D proton NMR, which seemed consistent with this structure.

When the fluoro alcohol product was tested for HIVPR activity, it was found to be more than 50-fold weaker than the diol **1**. The loss in activity was attributed to the stereochemistry of the fluoro substituent, since, from other SAR studies in our laboratory, it was known that only one hydroxyl group was needed for full potency. To obtain the fluoro analogue with the opposite configuration, we used a double inversion procedure in which the stereochemistry of one of the hydroxyls was first inverted using Mitsunobu conditions and then treated with DAST to give the fluoro alcohol with (it was expected) overall retention of configuration. However, after implemention of this tedious procedure, the fluoro alcohol that was isolated was identical to the original product obtained directly from the reaction of DAST with diol **1**.

To confirm the structure and the stereochemistry of the fluoro alcohol, a series of 2-D NMR experiments were carried out. Using a 2-D ^1H COSY experiment, it was obvious that the fluoro alcohol could not be a hexahydro-1,3-diazepin-2-one. The COSY showed that one set of benzyl protons were coupled to the proton α to the fluoro and not α to the nitrogen, consistent with the rearranged tetrahydropyrimidinone **2** (Scheme 1).

This implied that a rearrangement had also occurred under the Mitsunobu conditions as outlined in Scheme 1. The diol **1** was first monoprotected as the mono-MEM

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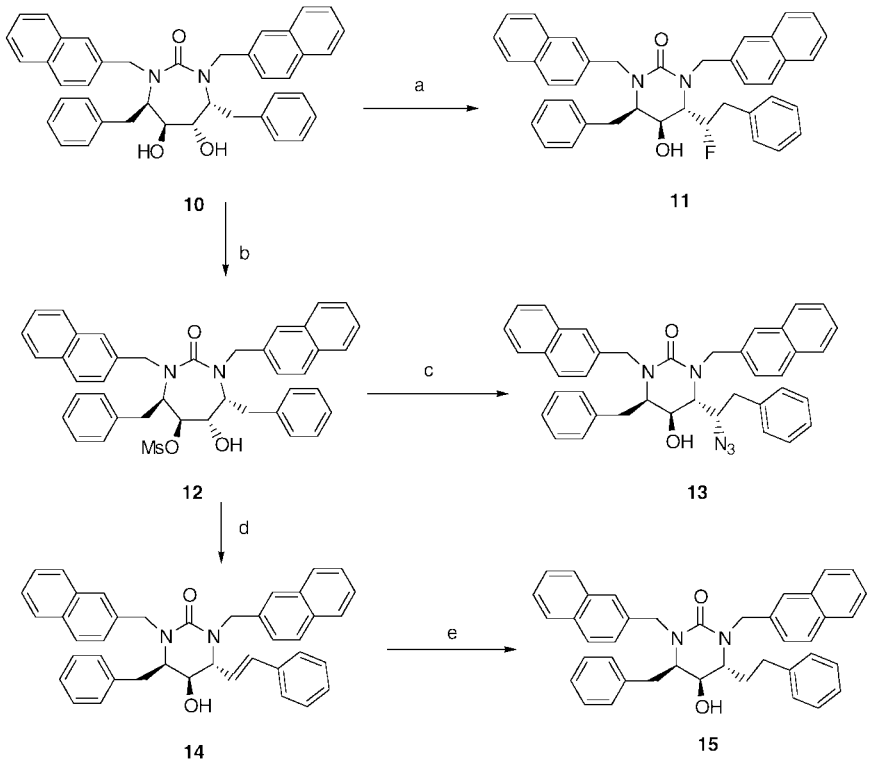
Scheme 2[a]



[a] Key: (a) 1 equiv of DAST/CH_2Cl_2; (b) Ms-Cl/Et_3N; (c) NaN_3/DMF; (d) NaI/DMF; (e) 50 psi H_2/10%Pd/C.

ether **3** by treatment with MEM-Cl. The free hydroxyl of **3** was then treated under Mitsunobu conditions (Ph_3P, DEAD, chloroacetic acid) to give, not the expected inversion product, but rather, the rearranged chloroacetate **4**. The structure of chloroacetate **4** was assigned by 2-D NMR and by converting it into the known alcohol **9** as outlined in Scheme 1. Ester **4** was hydrolyzed to the alcohol **7**, which was further converted to the thiocarbamate **6**. Reduction of **6** (Bu_3SnH, AIBN) followed by removal of the MEM group (HCl/MeOH) gave **9**, which we previously obtained by total synthesis starting from D-phenylalanine.[6]

The alcohol **7** was treated with DAST to give **5**. The MEM protecting group was removed (HCl/MeOH) to give the fluoro alcohol **2**, identical to that obtained directly from the reaction of diol **1** with 1 equiv of DAST. Alternatively, **7** was deprotected to give the non-C_2-symmetric diol **8**. A 2-D COSY NMR showed it was the rearranged tetrahydropyrimidinone analogue.

This rearrangement can be envisioned as proceeding through the aziridinium cationic intermediate **I** (Scheme 1). In the case of the diol **1** and alcohol **7**, the reaction with DAST first converts the hydroxyl group into a good leaving group. The urea nitrogen participates and displaces the leaving group (in S_N2 fashion) to give the same intermediate **I**. The fluoride ion then opens up the aziridine intermediate (S_N2) to give the observed fluoro alcohol **2**. The stereochemical assignment of the fluoro phenethyl side chain of **2** is based on this S_N2 mechanism. This assumption was subsequently supported by the X-ray structure of the bromo analogue **17a** (discussed below).

To explore the generality of this rearrangement, we examined a variety of N-substituted seven-membered ring cyclic urea analogues and found the ring contraction was equally facile. For example, the reaction of the large 2-naphthyl substituted analogue **10**[4] with 1 equiv of DAST gave the corresponding tetrahydropyrimidinone analogue **11** in good yield (Scheme 2).

The diol **10** was converted to the monomesylate **12**. Reaction of the mesylate with nucleophiles lead to rearranged products. For example, the reaction of **12** with NaN_3 gave the azido analogue **13**. Treatment of **12** with NaI gave the trans olefin **14**, presumably via the phenethyl iodide. The structure of the olefin was further confirmed by hydrogenation to give the phenethyl analogue **15**, which was also prepared independently.

We recently disclosed the design, synthesis, and evaluation of tetrahydropyrimidinones, such as **9**, and showed these to be nearly equipotent inhibitors of HIVPR as the seven-membered ring cyclic ureas.[6] Thus, the discovery of this rearrangement reaction offered an attractive alternative synthesis of tetrahydropyrimidinones employing the seven-membered ring cyclic ureas[4] as the starting material. While the unsubstituted-phenethyl tetrahydropyrimidinone analogues, such as **9**, were nearly equipotent to the diols (**1**), the substituted-phenethyl compounds (such as **2**, **8**, **11**, **13**, and **14**) were much weaker inhibitors of HIVPR.

Taking advantage of this rearrangement, we developed an efficient synthesis of the unsubstituted-phenethyl tetrahydropyrimidinone analogues using 2-acetoxyisobutyryl bromide, which has been used to convert diols to bromo acetates via a cyclic oxonium ion intermediate.[9] It was expected that, in our case, as the oxonium ion intermediate **II** is formed, the urea nitrogen would participate to give the aziridinium cationic intermediate

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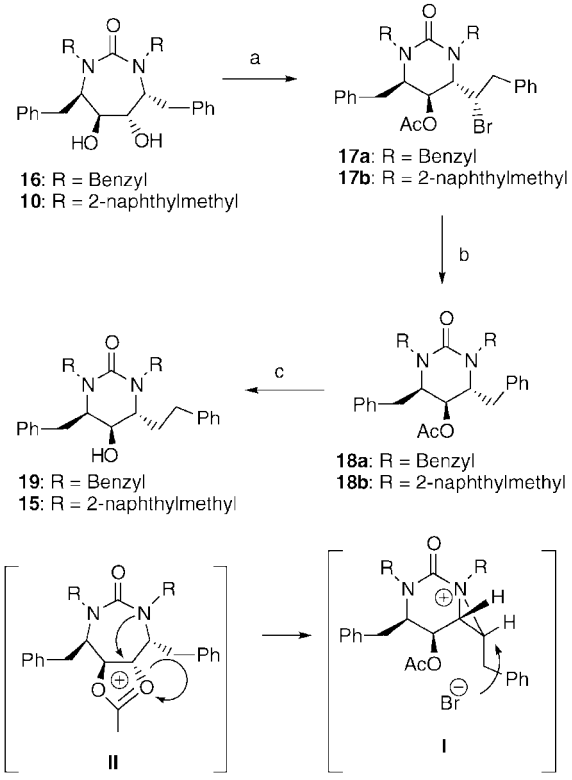
Scheme 3[a]



[a] Key: (a) acetoxyisobutyryl bromide;CH_2Cl_2; (b) Zn(dust)/acetic acid; (c) NaOH/MeOH.

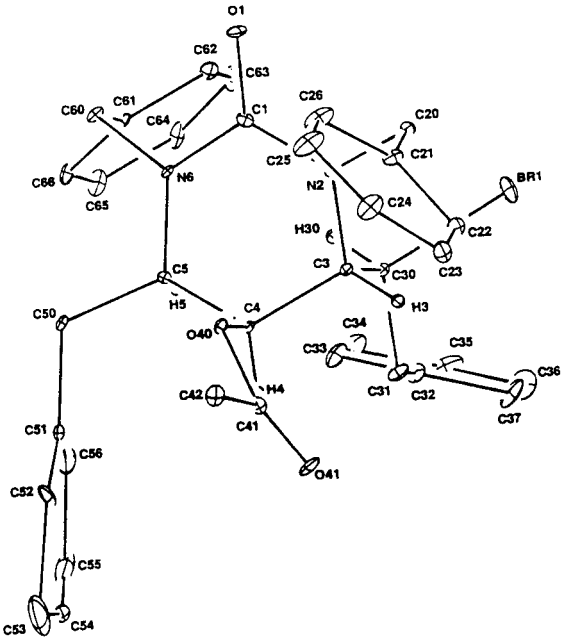
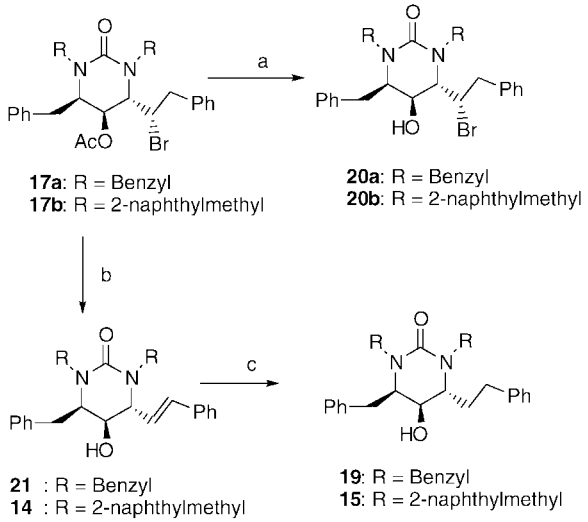


Figure 1.

I (Scheme 3). Bromide ion would then open the aziridine to give the phenethyl bromide. We were gratified to find that this was indeed the case. When diol **16**[4] was treated with 2-acetoxyisobutyryl bromide, a nearly quantitative yield of the tetrahydropyrimidinone bromo acetate **17a** was obtained. Recrystallization of the bromo acetate **17a** gave crystals of sufficient quality for analysis by X-ray crystallography (Figure 1). This analysis confirmed not only the assigned structure but also the absolute configuration of the phenethyl bromide substituent.[6] This

Scheme 4[a]



[a] Key: (a) 1 N NaOH/MeOH; (b) $KOH_{(s)}$/MeOH; (c) H_2/10% Pd/C.

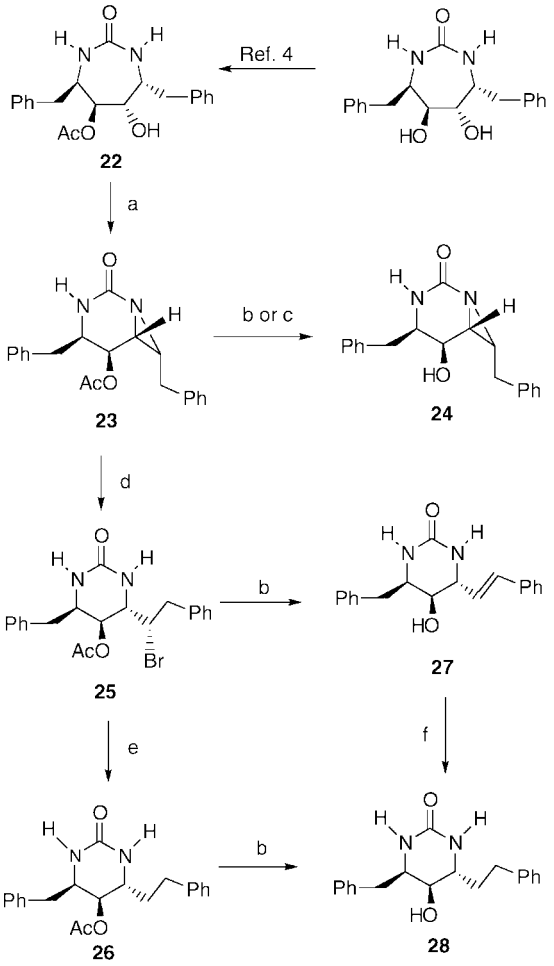
stereochemistry was consistent with (S_N2) bromide attack on the aziridinium cationic intermediate **I** as shown in Scheme 3. By analogy, the stereochemistry of the other substituted phenethyl compounds, such as **2**, **8**, **11**, **13**, and **14**, were then assigned.

The phenethyl bromide side chain of **17a** was most conveniently reduced using Zn (dust) in acetic acid to give the phenethyl analogue **18a** in nearly quantitative yield. Finally, the hydrolysis of the acetate **18a** gave the desired alcohol **19** in excellent yield. Thus, the overall transformation of the diol **16** to the tetrahydropyrimidinone **19** was achieved efficiently with an overall yield of about 90%. This reaction sequence was quite general and was used to synthesize many tetrahydropyrimidinone analogues.[6] For example, the naphthyl analogue **10** was converted to the bromo acetate **17b** and subsequently reduced and hydrolyzed to give the tetrahydropyrimidinone analogue **15**, identical to that obtained as shown in Scheme 2.

The bromo acetates **17a**,**b** were hydrolyzed to give the bromo alcohols **20a**,**b** using mildly basic conditions (0.01 M NaOH/MeOH) as shown in Scheme 4. Under more concentrated conditions (2 M NaOH or KOH in MeOH), the olefinic alcohols **21** and **14** were obtained in excellent yields. The olefin **14** was identical to that obtained from the mesylate **12** in Scheme 2. Hydrogenation of **21** or **14** gave the corresponding tetrahydropyrimidinone analogues **19** or **15** previously described above.

While the use of this three-step procedure (Scheme 3) was a very efficient method to synthesize tetrahydropyrimidinones from the corresponding hexahydro-1,3-diazepin-2-ones, it had some practical limitations. When the two N,N′ substituents of the diazepin-2-one were not the same, a mixture of the two possible regioisomeric tetrahydropyrimidinone products were obtained and their separation sometimes required tedious chromatography. In addition, the N,N′ substituents of the diazepin-2-one had to be stable to the reaction conditions, namely stable toward the following: acid bromides, reduction, and basic hydrolysis. Thus, it was desirable to find a procedure that used the parent N,N′-unsubstituted diazepin-2-one as the starting material. This became possible when we

Scheme 5[a]



[a] Key: (a) DAST/CH_2Cl_2; (b) NaOH/MeOH; (c) LAH/THF; (d) $HBr_{(gas)}$/dioxane; (e) Zn(dust)/acetic acid; (f) H_2, 10%Pd/C.

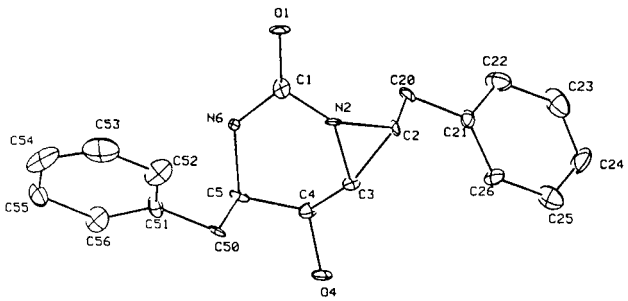
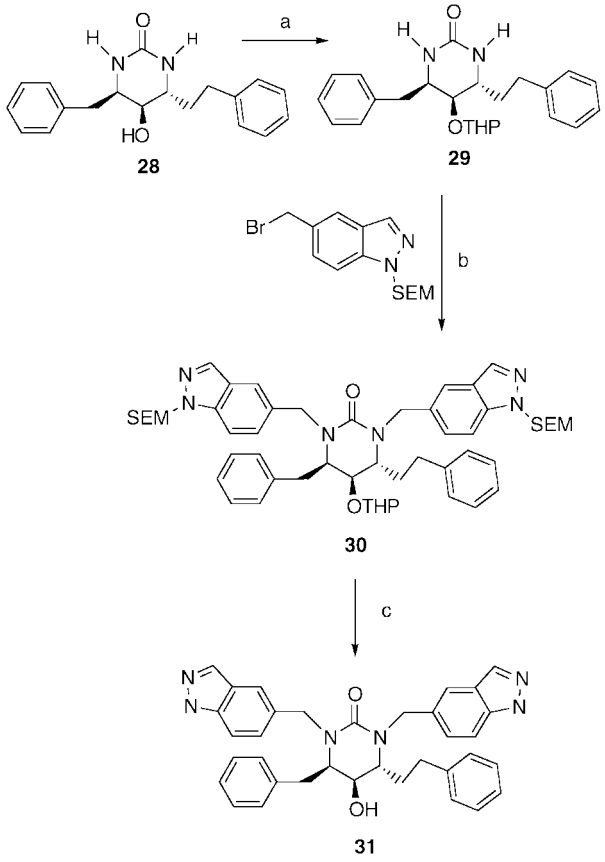


Figure 2.

discovered another unusual reaction of these hexahydro-1,3-diazepin-2-ones with DAST.

Treatment of the N,N′-unsubstituted mono acetate **22** with DAST did not give a fluoro analogue and instead provided the aziridine **23** in good yield (Scheme 5). The aziridine **23** was not acid (silica gel) stable, but was thermally stable and was purified by recrystallization from ethyl acetate. It was also stable to basic conditions and was hydrolyzed with NaOH/MeOH to give the alcohol **24**. Alternatively, the acetate **23** was treated with LAH to give the alcohol **24** in excellent yield. The structure of alcohol **24** was confirmed by X-ray crystallography (Figure 2). The crystal structure of **24** provides further support for the intermediary aziridinium ion **I** in the rearrangement reactions.

Scheme 6[a]



[a] Key: (a) DHP/$CHCl_3$/TsOH; (b) KO-*t*-Bu/THF; (c) HCl/MeOH reflux.

Treatment of the aziridine **23** with $HBr_{(gas)}$ gave a nearly quantitative yield of the phenethyl bromide **25**. The bromide was reduced with zinc in acetic acid to give the phenethyl analogue **26** in excellent yield. Hydrolysis of **26** gave the unsubstituted tetrahydropyrimidinone **28** in excellent overall yield from the monoacetate **22**. Alternatively, the bromo acetate **25** was treated with excess NaOH or KOH to give the olefinic alcohol **27** in nearly quantitative yield. Hydrogenation of **27** gave the tetrahydropyrimidinone **28**, again in excellent yield.

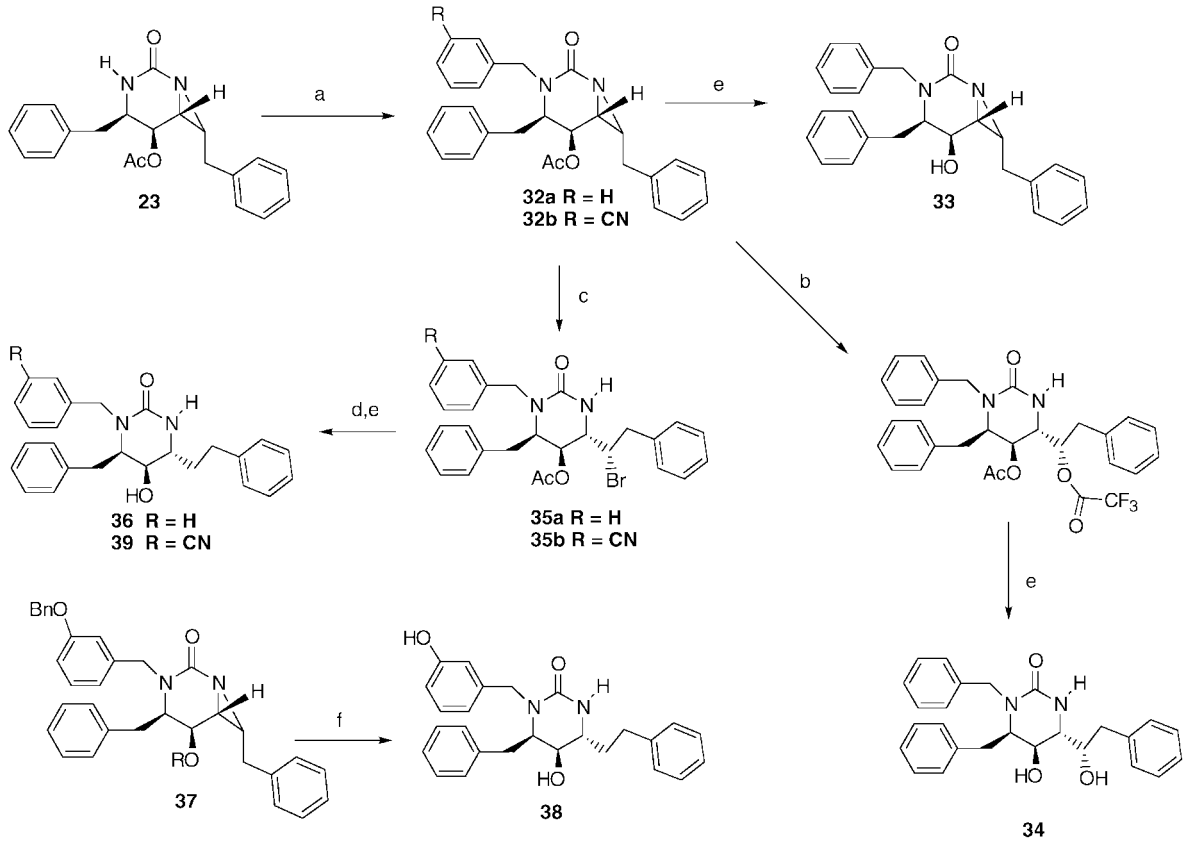
The hydroxyl group of the N,N′-unsubstituted tetrahydropyrimidinone **28** was most conveniently protected as the THP ether to give **29** in quantitative yield (Scheme 6). The urea nitrogens were substituted using a variety of alkylating agents under our standard conditions. For example, treatment of **29** with 5-(bromomethyl)-1-SEM-indazole[12] and 1 M solution of KO-t-Bu (in THF) gave the dialkylated tetrahydropyrimidinone **30**. The protecting groups were removed using acidic conditions (HCl/MeOH) to give the indazole-substituted tetrahydropyrimidinone **31** in good yield.

(10) Lam, P. Y.; Jadhav, P. K.; Eyermann, C. J.; Hodge, C. N.; De Lucca, G. V.; Rodgers, J. D. US 5,610,294, March 11, 1997.

(11) A literature search produced one example of a similar rearrangement of a tetrahydropyrimidinone to imidazolidinone via an aziridine intermediate: Berges, D. A.; Schmidt, S. J. *J. Org. Chem.* **1984**, *49*, 4555−4557.

(12) (a) Rodgers, J. D.; Johnson, B. L.; Wang, H.; Greenburg, R. A.; Erickson-Viitanen, S.; Klabe, R. M.; Cordova, B. C.; Rayner, M. M.; Lam, G. N.; Chang, C.-H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2919−2924. (b) Sun, J.-H.; Teleha, C. A.; Yan, J.-S.; Rodgers, J. D.; Nugiel, D. A. *J. Org. Chem.* **1997**, *62*, 5627−5629.

Scheme 7[a]



[a] Key: (a) NaH/DMF/Bn-Br; (b) CF_3COOH; (c) $HBr_{(gas)}$/dioxane; (d) Zn(dust)/acetic acid; (e) NaOH/MeOH; (f) H_2, 10%Pd/C.

The X-ray structural data of the aziridine **24** offers a possible explanation of why only rearranged tetrahydropyrimidinone products are obtained and none of the possible hexahydro-1,3-diazepin-2-one products are observed. When the aziridine cationic intermediate is formed, the attacking nucleophile has a choice of the two carbons of the aziridine ring. Examination of the X-ray structure of **24** (Figure 2) suggests that attack at the carbon that leads to diazepin-2-one products is sterically congested by the presence of the vicinal hydroxyl (or acetyl) group, whereas attack of the carbon leading to the tetrahydropyrimidinone products is more accessible. Thus, in every hexahydro-1,3-diazepin-2-one we have examined, only rearrangement products are observed.

The aziridine **23** can also be considered a latent or protected form of the desired tetrahydropyrimidinone final product and was used to synthesize unsymmetrically disubstituted N,N′ analogues as summarized in Scheme 7. Alkylation of aziridine **23** with benzyl bromide gave the *N*-benzylaziridine **32**. The acetate of **32** was removed under basic conditions to give alcohol **33**, whose structure was also confirmed by X-ray crystallography (Figure 3). The aziridine **32** was sequentially treated with HBr, zinc dust in acetic acid, and NaOH to give the mono-N-alkylated tetrahydropyrimidinone **36**.

The aziridine was also opened with other acids besides HBr. For example, treatment of **32** with trifluoroacetic acid gave the corresponding trifluoroacetate (Scheme 7). Treatment with NaOH then gave the diol **34**. The aziridine **37**, containing the *N*-3-(benzyloxy)benzyl group, was hydrogenated, for a prolong period of time, to remove not only the *O*-benzyl protecting groups but also reduce the aziridine ring and gave the phenol **38**.

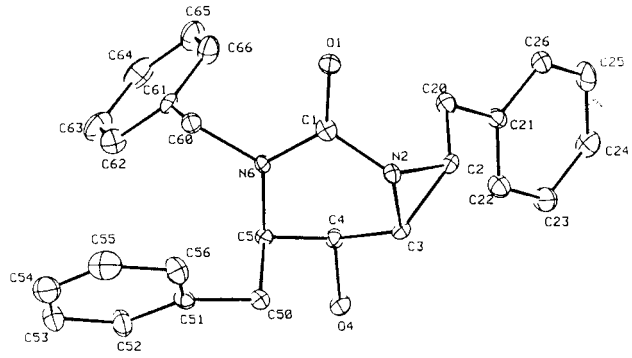
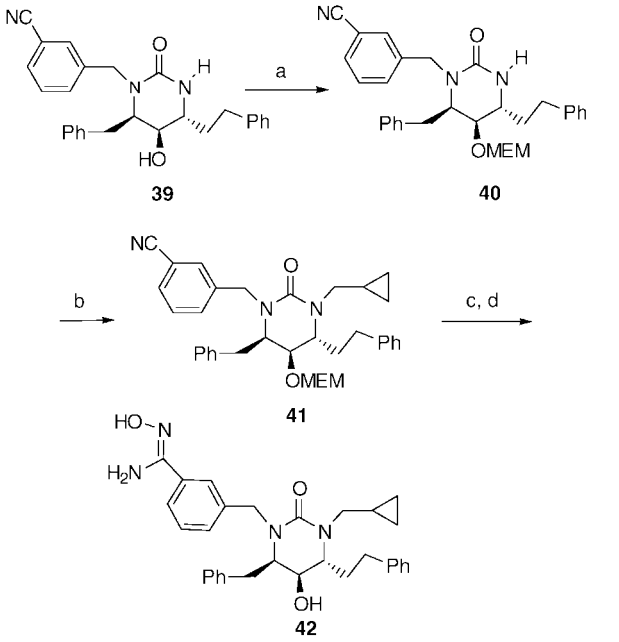


Figure 3.

Suitably protected alcohols (such as **36** or **38**) were N-alkylated a second time to obtain unsymmetrical N,N′-dialkylated tetrahydropyrimidinones with defined regiochemistry as shown in Scheme 8. For example, the alcohol of **39** was protected as the MEM ether **40**. Alkylation of the urea nitrogen with cyclopropylmethyl bromide under the usual conditions[4] gave the dialkylated product **41**. The MEM group is removed under acidic (HCl/dioxane) conditions, and the cyano group was converted to the amidoxime with hydroxylamine to give the desired unsymmetrical N,N′-dialkylated tetrahydropyrimidinone **42**.

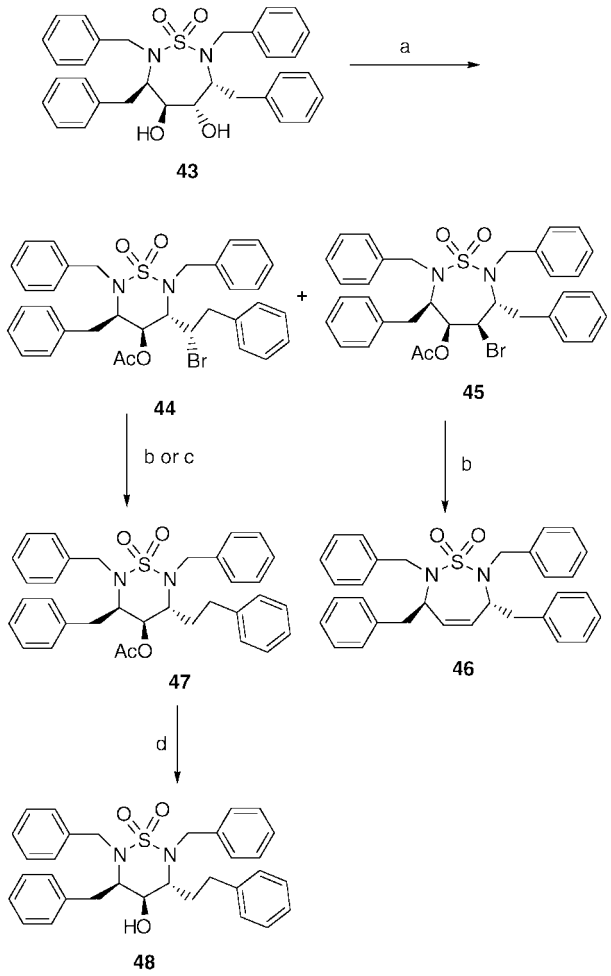
The seven-membered ring cyclic sulfamides such as **43** are also potent inhibitors of HIVPR.[10] To determine if the same kind of rearrangement reaction occurs with these compounds, we treated **43** with 2-acetoxybutyryl bromide under our usual conditions (Scheme 9). The reaction with sulfamides was not as efficient and pro-

Scheme 8[a]



[a] Key: (a) MEM-Cl/Et_3N/CH_2Cl_2; (b) NaH/DMF/cyclopropylmethyl bromide; (c) HCl/dioxane; (d) NH_2OH·HCl/Et_3N/EtOH/reflux.

Scheme 9[a]



[a] Key: (a) acetoxyisobutyryl bromide/CH_2Cl_2; (b) Zn(dust)/acetic acid; (c) Bu_3SnH/AIBN; (d) NaOH/MeOH.

duces a mixture of products. However, the major products obtained were the six- and seven-membered ring bromo acetates **44** and **45** in about equal amounts.

The structure of the seven-membered ring cyclic sulfamide **45** was deduced from its reaction with zinc dust in acetic acid which cleanly gave the C_2-symmetric olefin **46**. The structure of the six-membered-ring compound **44** was deduced by 2-D COSY NMR and by the comparison of its NMR spectra to that of the analogous tetrahydropyrimidinones **17a** and **17b**.

The reduction of the bromide **44** with Zn gave the phenethyl analogue **47** as the major product. This reduction was not as clean as the urea analogues, and a structurally undetermined olefin contamination was also obtained under a variety of reduction conditions that were explored. The product was purified by HPLC chromatography, and NMR analysis (2-D COSY) showed the familiar phenethyl group in the six-membered ring analogues **47** and **48**. The difference in behavior of the cyclic sulfamide compared to the cyclic urea clearly points to the importance of stereoelectronic effects in this rearrangement reaction.

The tetrahydropyrimidinones can undergo a second rearrangement as shown in Scheme 10, to give the corresponding imidazolidinones.[11] For example, when the fluoro alcohol **2** (or **11**) was treated with DAST, a second rearrangement occurs to give the C_2-symmetric difluoroimidazolidin-2-one **49** in nearly quantitative yield. Alternatively, the diol **1** (or **10**) was treated with excess DAST to give the same difluoro imidazolidin-2-one **49** directly.

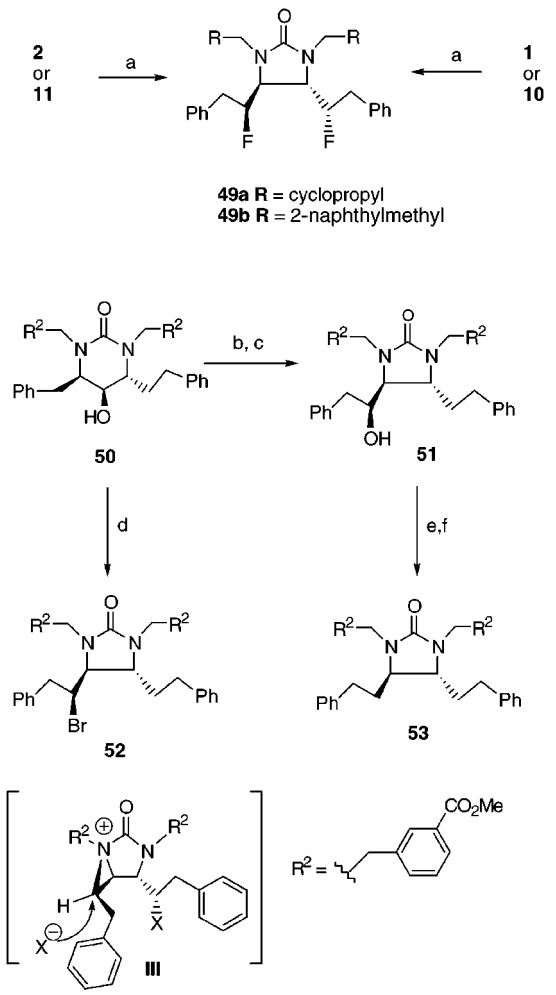
The fact that only one product was produced again shows the importance of stereoelectronic effects and the stereospecific, stereoselective nature of this rearrangement reaction. Clearly, only one of the two urea nitrogens is properly aligned to participate and produce the aziridinium cationic intermediate **III** (Scheme 10), which can then be opened by fluoride ion to give only the C_2-symmetric difluoro imidazolidin-2-one product. None of the possible 1,2-difluoro-3-phenylpropyl analogue was observed.

The rearrangement of tetrahydropyrimidin-2-ones to imidazolidin-2-one seems to be just as general as the rearrangement of hexahydro-1,3-diazepin-2-ones to tetrahydropyrimidin-2-ones. For example, when the alcohol **50** was treated under Mitsunobu conditions (Ph_3P, DEAD, chloroacetic acid), the rearranged alcohol **51** was obtained (Scheme 10). The structure of **51** was determined by NMR and confirmed by reductive removal of the alcohol (TCDI; Bu_3SnH, AIBN) to give the C_2-symmetrical phenethyl imidazolidin-2-one **53**. The alcohol **50** was also treated with Ph_3P/CBr_4 to give the rearranged phenethyl bromide **52**. We have recently shown that these imidazolidin-2-ones are also HIVPR inhibitors.[7] They are, however, much weaker inhibitors since they lack the important transition-state isostere needed for interaction with the catalytic aspartic acid residues of HIVPR.

Experimental Section

General Methods. All reactions were carried out under an atmosphere of dry nitrogen. Commercial reagents were used without further purification. A general workup consisted of diluting the reaction mixture with water and extracting into an organic solvent (ethyl acetate, CH_2Cl_2, etc.). The organic phase was washed sequentially with water (dilute acid or base

Scheme 10[a]



[a] Key: (a) DAST/CH_2Cl_2; (b) DEAD/Ph_3P/chloroacetic acid; (c) NaOH/MeOH; (d) $Ph_3P/CBr_4/CH_2Cl_2$; (e) thiocarbonyldiimidazole/THP; (f) Bu_3SnH/AIBN.

as appropriate) and brine and then dried over $MgSO_4$. The drying agent was filtered, and the organic solvent was removed under vacuum on a rotary evaporator. TLC was performed on E. Merck 15710 silica gel plates. Medium-pressure liquid chromatography (MPLC) was carried out using EM Science silica gel 60 (230−400 mesh). HPLC chromatography was carried out using Dupont Zorbax Sil or Zorbax NH_2 1-in. preparative columns. All final targets were obtained as noncrystalline amorphous solids unless specified otherwise. ^{1}H NMR (300 MHz) spectra were recorded using tetramethylsilane as an internal standard. Elemental analysis was performed by Quantitative Technologies, Inc., Bound Brook, NJ. For compounds where analysis was not obtained, HPLC analysis was used, and purity was determined to be >98% unless specified otherwise.

(4*S*,5*S*,6*R*)-Tetrahydro-1,3-bis(cyclopropylmethyl)-5-hydroxy-4-(1(*S*)-fluoro-2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (2). Method 1 from 1. A solution of (4*R*,5*S*,6*S*,7*R*)-hexahydro-5,6-dihydroxy-1,3-bis(cyclopropylmethyl)-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (**1**)[4] (0.112 g, 0.26 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C in an ice bath and treated with DAST (0.034 mL, 0.26 mmol) via syringe. The solution was stirred at 0 °C for 30 min, at which time TLC showed complete conversion. After a general workup, the residue was chromatographed (HPLC, Zorbax Sil, 65% EtOAc/hexane) to give 45 mg of **2** as a foam: ^{1}H NMR ($CDCl_3$) δ 7.36−7.21 (m, 8 H), 7.08−7.06 (m, 2 H), 4.83 (m, 0.5 H), 4.73 (m, 0.5 H), 4.05 (dd, J = 7, 15 Hz, 1 H), 3.86 (dd, J = 7, 15 Hz, 1 H), 3.81 (m, 1 H), 3.70 (m, 1 H), 3.61 (m, 1 H), 3.30 (abx m, 2 H), 2.91−2.61 (m, 4 H), 2.49 (d, J = 7 Hz, 1 H), 1.06 (m, 1 H), 0.96 (m, 1 H), 0.60−0.06 (m, 8 H); CIMS (NH_3) m/z 437.2 (M + H$^+$, 100); HRMS calcd for $C_{27}H_{34}N_2O_2F$ (M + H$^+$) 437.2604, found 437.2593.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5-[(2-methoxyethoxy)-methoxy]-6-hydroxy-1,3-bis(cyclopropylmethyl)-4,7-bis-(phenylmethyl)-2*H*-1,3-diazepin-2-one (3). A solution of diol **1** (2.06 g, 4.7 mmol) in CH_2Cl_2 (20 mL) was treated with MEM-Cl (0.71 g, 5.69 mmol) and diisopropylethylamine (1.53 g, 11.8 mmol), and the mixture was heated at reflux for 8 h. After a general workup, the residue was chromatographed (HPLC, Zorbax Sil, 5% MeOH/$CHCl_3$) to give 1.3 g of **3** as an oil; ^{1}H NMR ($CDCl_3$) δ 7.30−7.11 (m, 10 H), 4.95 (s, 2 H), 4.10 (m, 1 H), 3.89 (m, 3 H), 3.75−3.46 (m, 6 H), 3.41 (s, 3 H), 3.39−2.97 (m, 5 H), 1.98 (m, 2 H), 0.90 (m, 2 H), 0.40 (m, 4 H), 0.03 (m, 4 H); CIMS (NH_3) m/z 523 (M + H$^+$, 100).

(4*R*,5*S*,6*R*)-Tetrahydro-1,3-bis(cyclopropylmethyl)-5-(2-methoxyethoxy)methoxy)-4-(1(*S*)-hydroxy-2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (7). To a solution of **3** (1.0 g, 1.9 mmol) in THF were added triphenylphosphine (1.0 g, 3.8 mmol), DEAD (0.7 g, 4.0 mmol), and chloroacetic acid (0.40 g, 4.2 mmol) and the mixture stirred for 20 h at room temperature. The mixture was evaporated, and the residue was chromatographed (MPLC, silica gel, 50% EtOAc/hexane) to give 0.9 g of chloroacetate **4** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.27−7.21 (m, 10 H), 5.39 (m, 1 H), 4.95 (d, J = 13 Hz, 1 H), 4.80 (d, J = 13 Hz, 1 H), 4.70 (s, 1 H), 4.27 (m, 1 H), 4.19 (m, 2 H), 4.00−3.70 (m, 5 H), 3.93 (s, 2 H), 3.48 (dd, J = 7 Hz, J = 15 Hz, 1 H), 3.37, (s, 3 H), 3.02−2.90 (m, 5 H), 1.90 (dd, J = 7 Hz, J = 15 Hz, 1 H), 1.22 (m, 2 H), 0.76 (m, 1 H), 0.57 (m, 2 H), 0.40−0.20 (m, 4 H), 0.0 (m, 1 H); CIMS (NH_3) m/z 599 (M + H$^+$, 100).

A solution of the chloroacetate **4** (0.9 g, 1.5 mmol) in methanol (15 mL) was treated with 4 mL of a 1 N NaOH solution and stirred at room temperature for 1 h. After a general workup, the residue was chromatographed (HPLC, Zorbax Sil, 85% EtOAc/hexane) to give 0.4 g of alcohol **7** as a viscous oil that slowly solidified over a few days: ^{1}H NMR ($CDCl_3$) δ 7.33−7.13 (m, 10 H), 4.92 (d, J = 7 Hz, 1 H), 4.84 (d, J = 7 Hz, 1 H), 4.28 (m, 1H), 4.20 (m, 1 H), 3.91−3.79 (m, 5 H), 3.60 (m, 2 H), 3.50 (dd, J = 7, 15 Hz, 1 H), 3.38 (s, 3 H), 3.06 (d, J = 7 Hz, 2 H), 2.94 (dd, J = 7, 15 Hz, 1 H), 2.82−2.62 (m, 2 H), 2.44 (d, J = 7 Hz, 1 H), 1.91 (dd, J = 7, 15 Hz, 1 H), 1.21 (m, 1 H), 0.81 (m, 1 H), 0.58 (m, 2 H), 0.45−0.25 (m, 4 H), 0.02 (m, 2 H); CIMS (NH_3) m/z 523 (M + H$^+$, 100).

(4*S*,5*S*,6*R*)-Tetrahydro-1,3-bis(cyclopropylmethyl)-5-[(2-methoxyethoxy)methoxy]-4-(1(*S*)-fluoro-2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (5). A solution of **7** (160 mg, 0.3 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C in an ice bath and treated with DAST (0.04 mL, 0.3 mmol) via syringe. The solution was stirred at 0 °C for 30 min (TLC showed complete conversion). After a general workup, the residue was chromatographed (HPLC, Zorbax Sil, 50% EtOAc/hexane) to give 100 mg of **5** as a thick oil: ^{1}H NMR ($CDCl_3$) δ 7.34−7.19 (m, 10 H), 5.00 (m, 0.5 H), 4.87 (d, J = 7 Hz, 1 H), 4.81 (m, 0.5 H), 4.79 (d, J = 7 Hz, 1 H), 4.23 (m, 1H), 3.94−3.75 (m, 5 H), 3.59 (m, 2 H), 3.49 (dd, J = 7, 15 Hz, 1 H), 3.39 (s, 3 H), 3.09 (d, J = 7 Hz, 2 H), 3.08−2.78 (m, 3 H), 1.96 (dd, J = 7, 15 Hz, 1 H), 1.21 (m, 1 H), 0.79 (m, 1 H), 0.58 (m, 2 H), 0.50−0.25 (m, 4 H), 0.05 (m, 2 H); CIMS (NH_3) m/z 525 (M + H$^+$, 100).

(4*S*,5*S*,6*R*)-Tetrahydro-1,3-bis(cyclopropylmethyl)-5-hydroxy-4-(1(*S*)-fluoro-2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (2). Method 2 from 5. A solution of **5** (70 mg, 0.13 mmol) in methanol was cooled in an ice bath while HCl gas was bubbled in for 20 min. The solution was allowed to warm to room temperature and then stirred for 1 h. The solvent was removed under vacuum, and the residue was chromatographed (HPLC, Zorbax Sil, 80% EtOAc/hexane) to give 40 mg of **2** as a foam identical in every respect to the product of diol **1** with DAST detailed above.

(4*R*,5*S*,6*R*)-Tetrahydro-1,3-bis(cyclopropylmethyl)-5-hydroxy-4-(1(*S*)-hydroxy-2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (8). A solution of **7** (70 mg, 0.13 mmol) in methanol was cooled in an ice bath while HCl gas was

bubbled in for 20 min. The solution was allowed to warm to room temperature and stirred for 1 h. The solvent was removed under vacuum, and the residue was chromatographed (HPLC, Zorbax Sil, 80% EtOAc/hexane) to give 48 mg of **8** as a white foam: ^{1}H NMR ($CDCl_3$) δ 7.36−7.17 (m, 10 H), 4.24 (m, 2 H), 3.98 (dd, J = 8 Hz, J = 15 Hz, 1 H), 3.80 (m, 1 H), 3.72 (m, 1 H), 3.68 (dd, J = 8, 15 Hz, 1 H), 3.41 (d, J = 3 Hz, 1 H), 3.15−2.96 (m, 2 H, abx), 2. 85 (dd, J = 7, 15 Hz, 1 H), 2.79−2.51 (m, 2 H, abx), 2.19 (m, 1 H), 2.10 (dd, J = 7, 16 Hz, 1 H), 1.09 (m, 1 H), 0.82 (m, 1 H), 0.58−0.25 (m, 6 H), 0.05 (m, 2 H); CIMS (NH_3) m/z 435 (M + H$^+$, 100).

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis(cyclopropylmethyl)-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (9). A solution of **7** (160 mg, 0.3 mmol) in THF was treated with thiocarbonyldiimidazole (TCDI) (55 mg, 0.3 mmol) and the solution heated to reflux for 4 h. The solvent was removed under vacuum, and the residue was chromatographed (MPLC, silica gel, 50% EtOAc/hexane) to give 34 mg of **6**: ^{1}H NMR ($CDCl_3$) δ 8.23 (s, 1 H), 7.51 (bs, 1 H), 7.27−7.21 (m, 10 H), 7.01 (bs, 1 H), 6.10 (m, 1 H), 4.83 (d, J = 7 Hz, 1 H), 4.58 (d, J = 6 Hz, 1 H), 4.28 (m, 1 H), 3.97−3.81 (m, 3 H), 3.65−3.40 (m, 5 H), 3.38 (s, 3 H), 3.22−2.91 (m, 5 H), 1.90 (dd, J = 7, 15 Hz, 1 H), 1.20 (m, 1 H), 0.87 (m, 1 H), 0.65−0.25 (m, 6 H), 0.03 (m, 2 H).

A solution of **6** (34 mg, 0.05 mmol) in toluene was heated to reflux and treated with Bu_3SnH (0.03 mL, 0.1 mmol) and AIBN (4 mg). The mixture was heated at reflux for 1 h, the solvent was removed under vacuum, and the residue was chromatographed (HPLC, Zorbax Sil, 60% EtOAc/hexane) to give 20 mg of the reduced product as a film. The film was dissolved in methanol and cooled in an ice bath, and HCl gas was bubbled in for 20 min and then warmed to room temperature over 1 h. The solvent was removed under vacuum, and the residue was chromatographed (HPLC, Zorbax Sil, 10% MeOH/$CHCl_3$) to give 10 mg of alcohol **9** identical to the product previously reported:[6] ^{1}H NMR ($CDCl_3$) δ 7.38−7.12 (m, 8 H), 7.05 (d, J = 7 Hz, 2 H), 3.87 (dd, J = 7, 14 Hz 2 H), 3.72 (m, 1 H), 3.62 (m, 1 H), 3.40 (m, 1 H), 3.11 (dd, J = 6, 13 Hz, 1 H, abx), 2.95 (dd, J = 10, 12 Hz, 1 H, abx), 2.85 (dd, J = 7, 14 Hz, 1 H) 2.67 (dd, J = 7, 14 Hz, 1 H), 2.51 (m, 2 H), 2.30 (d, J = 10 Hz, 1 H), 1.96 (m, 1 H), 1.70 (m, 1 H), 1.03 (m, 2 H), 0.60−0.15 (m, 8 H); CIMS (NH_3) m/z 419 (M + H$^+$, 100); HRMS calcd for $C_{27}H_{34}N_2O_2$ (M + H$^+$) 419.2699, found 419.2704.

(4*S*,5*S*,6*R*)-Tetrahydro-1,3-bis(2-naphthylmethyl)-5-hydroxy-4-(1(*S*)-fluoro-2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (11). A solution of (4*R*,5*S*,6*S*,7*R*)-hexahydro-5,6-dihydroxy-1,3-bis(2-naphthylmethyl)-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (**10**)[4] (0.10 g, 0.16 mmol) in CH_2Cl_2 (20 mL) was treated with DAST (0.026 mL, 0.16 mmol) as described above and chromatographed (HPLC, Zorbax Sil, 50% EtOAc/hexane) to give 35 mg of **11** as a foam: ^{1}H NMR ($CDCl_3$) δ 8.00−7.80 (m, 8 H), 7.68−7.54 (m, 6 H), 7.34−7.19 (m, 6 H), 7.06 (m, 2 H), 6.88 (d, J = 7 Hz, 2 H), 5.83 (d, J = 15 Hz, 1 H), 5.81 (d, J = 15 Hz, 1 H), 4.80 (m, 0.5 H), 4.63 (m, 0.5 H), 4.24 (d, J = 15 Hz, 1 H), 4.18 (d, J = 15 Hz, 1 H), 3.57 (m, 2 H), 3.31 (m, 1 H), 3.20 (m, 1 H, abx), 2.98 (m, 1 H, abx), 2.80−2.55 (m, 2 H), 1.95 (d, J = 8 Hz, 1 H); CIMS (NH_3) m/z 609 (M + H$^+$, 100); HRMS calcd for $C_{41}H_{38}N_2O_2F$ (M + H$^+$) 609.2917, found 609.2911. Anal. Calcd for $C_{41}H_{37}N_2O_2F\cdot0.2H_2O$: C, 80.42; H, 6.16; N, 4.57. Found: C, 80.41; H, 6.16; N, 4.43.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5-(mesyloxy)-6-hydroxy-1,3-bis(2-naphthylmethyl)-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (12). A solution of (4*R*,5*S*,6*S*,7*R*)-hexahydro-5,6-dihydroxy-1,3-bis(2-naphthylmethyl)-4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (**10**)[4] (0.60 g, 1.0 mmol) in pyridine was treated with methanesulfonyl chloride (0.17 g, 1.5 mmol) and stirred at room temperature for 3 h. After a general workup, the solid residue was chromatographed (MPLC, silica gel, 40% EtOAc/hexane) to give 420 mg of **12** as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.84−7.76 (m, 6 H), 7.58−7.40 (m, 6 H), 7.40−7.21 (m, 8 H), 7.09 (m, 4 H), 5.05 (d, J = 14 Hz, 1 H), 5.03 (d, J = 14 Hz, 1 H), 4.45 (dd, J = 4.5, 10 Hz, 1 H), 3.91 (m, 1 H), 3.78 (m, 1 H), 3.66 (m, 1 H), 3.44 (d, J = 14 Hz, 1 H), 3.22−2.85 (m, 5 H), 2.50 (s, 3 H), 2.26 (d, J = 4 Hz, 1 H); CIMS (NH_3) m/z 685 (M + H$^+$, 100).

(4*R*,5*S*,6*R*)-Tetrahydro-1,3-bis(2-naphthylmethyl)-5-hydroxy-4-(1(*S*)-azido-2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (13). A solution of **12** (100 mg, 0.15 mmol) in DMF was treated with NaN_3 (100 mg, 1.5 mmol) and heated at 80 °C for 2 h and then at 40 °C overnight. After a general workup, the solid residue was chromatographed (HPLC, Zorbax Sil, 50% EtOAc/hexane) to give 80 mg of **13** as a white solid: IR 2114; ^{1}H NMR ($CDCl_3$) δ 7.93−7.78 (m, 7 H), 7.63−7.39 (m, 8 H), 7.25−7.05 (m, 7 H), 6.73 (d, J = 7 Hz, 2 H), 5.76 (d, J = 7 Hz, 1 H), 5.68 (d, J = 7 Hz, 1 H), 4.10 (d, J = 7 Hz, 1 H), 3.78 (d, J = 7 Hz, 1 H), 3.62 (m, 1 H), 3.52 (m, 1 H), 3.29 (m, 2 H), 3.07−2.85 (abx m, 2 H), 2.56−2.31 (abx m, 2 H), 1.97 (d, J = 7 Hz, 1 H); DCI MS (NH_3) m/z 632 (M + H$^+$, 100); HRMS calcd for $C_{41}H_{38}N_5O_2$ (M + H$^+$) 632.3025, found 632.3023. Anal. Calcd for $C_{41}H_{37}N_5O_2\cdot0.4$(EtOAc)$\cdot$0.4(hexane): C, 77.05; H, 6.58; N, 9.98. Found: C, 77.17; H, 6.27; N, 9.81.

(4*R*,5*S*,6*R*)-Tetrahydro-1,3-bis(2-naphthalenylmethyl)-5-hydroxy-4-(*β*-styrene)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (14). Method 1. A solution of **12** (100 mg, 0.15 mmol) in DMF was treated with NaI (100 mg, 1.5 mmol) and heated at 80 °C for 2 h and then at 40 °C overnight. After a general workup, the solid residue was chromatographed (HPLC, Zorbax Sil, 50% EtOAc/hexane) to give 50 mg of **14** as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.93−7.65 (m, 6 H), 7.59 (m, 1 H), 7.55−7.40 (m, 6 H), 7.40−7.20 (m, 9 H), 7.12 (d, J = 8 Hz, 2 H), 6.55 (d, J = 16 Hz, 1 H), 5.91 (dd, J = 8, 16 Hz, 1 H), 5.70 (d, J = 15 Hz, 1 H), 5.55 (d, J = 15 Hz, 1 H), 4.14 (d, J = 15 Hz, 1 H), 3.80 (m, 1 H), 3.53 (d, J = 15 Hz, 1 H), 3.53 (m, 2 H), 2.98−2.70 (abx m, 2 H), 1.85 (d, J = 5 Hz, 1 H); DCI MS (NH_3) m/z 589 (M + H$^+$, 100). Anal. Calcd for $C_{41}H_{36}N_2O_2\cdot0.5H_2O$: C, 82.38; H, 6.24; N, 4.69. Found: C, 82.52; H, 6.33; N, 4.56.

(4*R*,5*S*,6*R*)-Tetrahydro-1,3-bis(2-naphthalenylmethyl)-5-hydroxy-4-(*β*-styrene)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (14). Method 2. 1-bromo-2-phenylethyl acetate **17b** (100 mg, 0.14 mmol) was dissolved in MeOH (10 mL) and treated with solid KOH (1.0 g, 17.8 mmol) at room temperature for 1 h. After a general workup, 50 mg of **14** was obtained as a white solid identical to that obtained using method 1 above.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis(2- naphthalenylmethyl)-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (15). Method 1. A solution of **14** (30 mg) in dioxane was treated with 10% Pd/C (30 mg) and hydrogenated at 50 psi for 3 h. The solution was filtered, the solvent removed under vacuum, and the residue chromatographed (HPLC, Zorbax Sil, 70% EtOAc/hexane) to give 10 mg of **15** as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.87−7.77 (m, 6 H), 7.67 (s, 1 H), 7.61 (s, 1 H), 7.54−7.40 (m, 6 H), 7.26−7.16 (m, 6 H), 7.03−6.93 (m, 4 H), 5.66 (d, J = 15 Hz, 1 H), 5.63 (d, J = 15 Hz, 1 H), 4.06 (d, J = 15 Hz, 1 H), 4.01 (d, J = 15 Hz, 1 H), 3.41−3.34 (m, 2 H), 3.20 (m, 1 H), 3.08−2.81 (abx m, 2 H), 2.42 (m, 2 H), 1.90 (m, 1 H), 1.65 (m, 1 H), 1.60 (bs, 1 H); DCI MS (NH_3) m/z 591.5 (M + H$^+$, 100). Anal. Calcd for $C_{41}H_{38}N_2O_2$: C, 83.36; H, 6.48; N, 4.74. Found: C, 83.06; H, 6.48; N, 4.50.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis(2-naphthylmethyl)-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (15). Method 2. To a solution of (4*R*,5*S*,6*S*,7*R*)-hexahydro-5,6-dihydroxy-1,3-bis(2-naphthyl-methyl)-4,7-bis-(phenylmethyl)-2*H*-1,3-diazepin-2-one (**10**)[4] (2.0 g, 3.3 mmol) in CH_2Cl_2 (40 mL) at room temperature was added 2-acetoxyisobutyryl bromide (2.0 g, 10 mmol), and the solution was stirred at room temperature for 10 min. The solution was quenched with saturated $NaHCO_3$, and after a general workup the residue was chromatographed (MPLC silica gel 30% EtOAc/hexane) to give 1.3 g of the 1-bromo-2-phenylethyl acetate tetrahydropyrimidinone **17b**: ^{1}H NMR ($CDCl_3$) δ 7.89−7.78 (m, 6 H), 7.74 (m, 2 H), 7.60 (m, 1 H), 7.56−7.46 (m, 5 H), 7.19−7.13 (m, 4 H), 7.04 (m, 2 H), 6.47−6.74 (m, 2 H), 6.67 (d, J = 8 Hz, 2 H), 5.72 (d, J = 15 Hz, 1 H), 5.66 (d, J = 15 Hz, 1 H), 4.67 (m, 1 H), 4.28 (d, J = 15 Hz, 1 H), 4.13 (d, J = 15 Hz, 1 H), 4.06 (m, 1 H), 3.77 (dd, J = 4, 8 Hz,

1 H), 3.59 (m, 1 H), 3.20 (dd, J = 5, 13 Hz, 1 H), 2.85 (abx m, 2 H), 2.68 (dd, J = 5, 13 Hz, 1 H), 1.26 (s, 3 H); CIMS (NH_3) m/z 713 (M + H^+, 100) 711 (M + H^+, 95). Anal. Calcd for $C_{43}H_{39}N_2O_3Br$: C,72.57; H, 5.52; N, 3.95. Found: C, 72.24; H, 5.55; N, 3.72.

The 1-bromo-2-phenylethyl acetate **17b** (0.4 g, 0.6 mmol)) was dissolved in 50 mL of acetic acid, treated with Zn(dust) (1 g), and vigorously stirred at room temperature until TLC analysis showed complete conversion. The mixture was filtered and the solid washed thoroughly with EtOAc. The filtrate was washed with water, saturated $NaHCO_3$, and brine. The solvent was removed under vacuum to give the phenethyl acetate **18b**. The crude phenethyl acetate was dissolved in MeOH, treated with 1 N NaOH (5 mL), and stirred at room temperature. After a general workup, the resulting residue was chromatographed (MPLC silica gel 50% EtOAc/hexane) to give 170 mg of **15** identical to that obtained using method 1 above.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis(phenylmethyl)-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (19). Following the proceedure for **17b**, (4*R*,5*S*,6*S*,7*R*)-hexahydro-5,6-dihydroxy-1.3-bis(phenylmethyl) -4,7-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (**16**)[4] (1.3 g, 2.6 mmol) was treated with 2-acetoxyisobutyryl bromide (1.7 g, 8.1 mmol) to give after chromatography (MPLC silica gel 30% EtOAc/hexane) 1.4 g of **17a**. A fraction of the eluent from this chromatography was allowed to evaporate slowly to give crystals of the bromo acetate **17a** that were of sufficient quality for single-crystal X-ray analysis. For **17a**: mp 178−180 °C; ^{1}H NMR ($CDCl_3$) δ 7.42−7.16 (m, 16 H), 6.89−6.79 (m, 4 H), 5.50 (d, J = 15 Hz, 1 H), 5.43 (d, J = 15 Hz, 1 H), 4.71 (t, J = 4 Hz, 1 H), 4.10 (d, J = 15 Hz, 1 H), 4.02 (m, 1 H), 3.87 (d, J = 15 Hz, 1 H), 3.71 (dd, J = 4, 7 Hz, 1 H), 3.58 (m, 1 H), 3.10 (dd, J = 6, 13 Hz, 1 H), 2.95 (dd, J = 3, 15 Hz, 1 H), 2.77 (dd, J = 10, 15 Hz), 2.65 (dd, J = 10, 13 Hz, 1 H), 1.61 (s, 3 H). Anal. Calcd for $C_{35}H_{35}N_2O_3Br\cdot 0.2C_6H_{14}$: C, 69.15; H, 6.06; N, 4.45. Found: C, 69.26; H, 5.79; N, 4.31.

The bromo acetate **17a** (1.0 g) was treated with Zn(dust) (7 g) as described above for **15** to give after chromatography (MPLC silica gel 65% EtOAc/hexane) 820 mg of the acetate **18a** as a white foam. The acetate **18a** (400 mg, 0.68 mol) was dissolved in MeOH, treated with 1 N NaOH (5 mL), and stirred at room temperature. After a general workup, the residue was chromatographed (MPLC silica gel 65% EtOAc/hexane) to give 300 mg of **19** as a foam: ^{1}H NMR ($CDCl_3$) δ 7.37−7.15 (m, 16 H), 6.97 (m, 4 H), 5.46 (d, J = 15 Hz, 1 H), 5.42 (d, J = 14 Hz, 1 H), 3.89 (d, J = 14 Hz, 1 H), 3.82 (d, J = 15 Hz, 1 H), 3.41 (m, 1 H), 3.33 (m, 1 H), 3.17 (m, 1 H), 2.95 (m, 2 H), 2.85 (m, 2 H), 2.40 (t, J = 8 Hz, 2 H), 1.9 (m, 1 H), 1.61 (m, 2 H); CIMS (NH_3) m/z 491 (M + H^+, 100). Anal. Calcd for $C_{33}H_{34}N_2O_2$: C, 80.78; H, 6.98; N, 5.71. Found: C, 80.46; H, 6.97; N, 5.66.

(4*S*,5*S*,6*R*)-Tetrahydro-1,3-bis(2-naphthylmethyl)-5-hydroxy-4-(1(*S*)-bromo-2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (20b). 1-Bromo-2-phenylethyl acetate **17b** (100 mg, 0.14 mmol) was dissolved in MeOH (5 mL) and treated with 1 N NaOH (1 mL, 1.0 mmol) at room temperature for 1 h. After a general workup, 80 mg of **20b** was obtained as a white solid: mp 85 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.89−7.78 (m, 7 H), 7.64 (m, 2 H), 7.50 (m, 4 H), 7.40−7.00 (m, 9 H), 6.67 (d, J = 8 Hz, 2 H), 5.60 (d, J = 15 Hz, 1 H), 5.56 (d, J = 15 Hz, 1 H), 4.21 (d, J = 15 Hz, 1 H), 3.76 (m, 1 H), 3.62 (d, J = 15 Hz, 1 H), 3.36 (m, 1 H), 3.01−2.90 (m, 3 H), 2.68 (dd, J = 5, 13 Hz, 1 H), 2.00 (d, J = 7 Hz, 1 H); CIMS (NH_3) m/z 669.2 (M + H^+, 67), 671.2 (M + H^+, 72), 589.2 ((M − HBr + H^+, 100). Anal. Calcd for $C_{41}H_{37}N_2O_2Br\cdot 0.2H_2O$: C, 73.14; H, 5.60; N, 4.16. Found: C, 73.09; H, 5.63; N,3.99.

(4*R*,5*S*,6*R*,7*R*)-1,3-Diaza-4,7-bis(phenylmethyl)-5-(acetyloxy)[4.1.0]bicycloheptan-2-one (23). A solution of monoacetate **22**[4] (2.0 g, 5.0 mmol) in CH_2Cl_2 (30 mL) was cooled to 0 °C in an ice bath and treated with DAST (0.8 mL, 6.0 mmol) via syringe. The solution was stirred at 0 °C for 30 min. After a general workup, 1.9 g of **23** was obtained as a white solid. The solid was recrystallized from ethyl acetate: mp 222 °C; ^{1}H NMR ($CDCl_3$) δ 7.38−7.00 (m, 10 H), 5.54 (d, J = 6 Hz, 1 H), 4.97 (dd, J = 5, 7 Hz, 1 H), 3.81 (m, 1 H), 3.26 (dd, J = 4, 15 Hz, 1 H), 3.16 (dd, J = 4, 14 Hz, 1 H), 3.00−2.84 (m, 3 H), 2.65 (dd, J = 8, 15 Hz, 1 H), 2.10 (s, 3 H); DCI MS (NH_3) m/z 351 (M + H^+, 100). Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.34; N, 7.99; Found: C, 72.06; H, 6.34; N, 7.84.

(4*R*,5*S*,6*R*,7*R*)-1,3-Diaza-4,7-bis(phenylmethyl)-5-(hydroxy)[4.1.0]bicycloheptan-2-one (24). Method 1. A solution of acetate **23** (100 mg, 0.29 mmol) in methanol (5 mL) was treated with 1 N NaOH (10 drops from 2 mL disposable pipet) and stirred at room temperature for 30 min. After a general workup, 30 mg of **24** was obtained as a white solid. Anal. Calcd for $C_{21}H_{22}N_2O_3\cdot 0.25CH_3OH$: C, 73.08; H, 6.69; N, 8.85. Found: C, 73.23; H, 6.63; N, 8.49.

Method 2. A solution of acetate **23** (350 mg, 1.0 mmol) in THF was cooled in an ice bath, treated with LAH (76 mg, 2.0 mmol), and stirred while allowing the solution to warm to room temperature for 3 h. After a general workup, 300 mg of **24** was obtained as a white solid recrystallized from EtOAc/hexane: mp 170−176 °C dec; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 7.38−7.16 (m, 10 H), 3.97 (dd, J = 5 Hz, J = 7 Hz, 1 H), 3.52 (m, 1 H), 3.40−3.20 (m, 2 H), 3.00−2.74 (m, 3 H), 2.51 (dd, J = 10 Hz, J = 15 Hz, 1 H); DCI MS (NH_3) m/z 309 (M + H^+, 100). Anal. Calcd for $C_{21}H_{22}N_2O_3\cdot 0.2$(EtOAc)$\cdot 0.2$(hexane): C, 73.49; H, 7.17; N, 8.16. Found: C, 73.62; H, 6.93; N, 8.16.

(4*R*,5*S*,6*R*)-Tetrahydro-5-(acetyloxy)-4-(1(*S*)-bromo-2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (25). A solution of aziridine **23** (1.0 g, 2.9 mmol) in dioxane was cooled in an ice bath while $HBr_{(gas)}$ was bubbled into the solution for 10 min. The ice bath was removed and the solution stirred at room temperature for 20 min. The solvent was removed under vacuum, and the residue was chromatographed (MPLC, silica gel, EtOAc) to give 900 mg of **25** as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.36−7.11 (m, 10 H), 5.85 (bs, 1 H), 5.07 (bs, 1 H), 5.05 (m, 1 H), 4.23 (m, 1 H), 3.95 (m, 1 H), 3.61 (m, 1 H), 3.23 (d, J = 7 Hz, 2 H), 2.70 (abx m, 2 H), 2.12 (s, 3 H); CIMS (NH_3) m/z 433, 431 (M + H^+, 35).

(4*R*,5*R*,6*R*)-Tetrahydro-5-(acetyloxy)-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (26). A solution of bromo acetate **25** (900 mg, 2.1 mmol) in acetic acid was treated with 10 g of Zn dust as described above to give after chromatography (MPLC, silica gel, EtOAc−10% MeOH/EtOAc) 600 mg of **26** as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.35−7.10 (m, 10 H), 6.08 (bs, 1 H), 5.28 (bs, 1 H), 4.80 (m, 1 H), 3.80 (m, 1 H), 3.42 (m, 1 H), 2.83 (abx m, 2 H), 2.77 (m, 1 H), 2,62 (m, 1 H), 2.12 (s, 3 H), 1.74 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 170.2, 156.3, 140.26, 135.40, 129.0, 128.9, 128.5, 128.3, 127.3, 126.2, 67.1, 53.5, 51.2, 36.9, 31.4, 20.9; CIMS (NH_3) m/z 353 (M + H^+, 100).

(4*S*,5*R*,6*R*)-Tetrahydro-5-hydroxy-4-(*β*-styrene)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (27). Crude bromoacetate **25** (10.7 g, 25 mmol) was dissolved in MeOH, treated with 10 g of KOH, and stirred at room temperature overnight. After a general workup, 7.0 g of **27** was obtained as a white solid: mp 231−233 °C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 7.36−7.21 (m, 10 H), 6.56 (d, J = 16 Hz, 1 H), 6.06 (dd, J = 5, 16 Hz, 1 H), 5.74 (bs, 1 H, exchanges), 4.95 (bs, 1 H, exchanges), 4.18 (m, 1 H), 3.75 (m, 1 H), 3.58 (m, 1 H), 3.01 (abx dd, J = 6, 14 Hz, 1 H), 2.81 (abx dd, J = 6, 14 Hz, 1 H); CIMS (NH_3) m/z 309 (M + H^+, 100). Anal. Calcd for $C_{19}H_{20}N_2O_2\cdot 0.2H_2O$: C, 71.90; H, 6.67; N, 8.83. Found: C, 71.63; H, 6.41; N, 8.71.

(4*R*,5*R*,6*R*)-Tetrahydro-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (28). Method 1. A solution of **27** (7.0 g, 23 mmol) in THF/MeOH was treated with 3 g of 10% Pd/C and hydrogenated at 50 psi for 3 h at room temperature. The solution was filtered through Celite and the solvent removed under vacuum to give 6.3 g of **28**. Product was identical to that previously described.[6]

Method 2. A solution of **26** (0.5 g, 1.4 mmol) in methanol was treated with 5 mL of 1 N NaOH solution and stirred at room temperature for 8 h. After a general workup, 0.3 g of **28** was obtained identical to that previously described:[6] mp 162−163 °C; ^{1}H NMR ($CDCl_3$) δ 7.38−7.19 (m, 10 H), 6.69 (bs, 1 H), 5.00 (bs, 1 H), 4.61 (d, J = 8 Hz, 1 H), 3.60 (t, J = 7 Hz, 1 H), 3.49 (bm, 1 H), 3.38 (bm, 1 H), 3.30 (dd, J = 7, 14 Hz, 1 H, abx), 2.82 (dd, J = 7, 14 Hz, 1 H, abx), 2.78 (m, 1 H, abx) 2.57 (m, 1 H, abx), 1.62 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 157.1, 141.7, 137.2, 129.7, 129.2, 128.8, 128.8, 127.3, 126.4, 65.9, 57.1,

53.5, 38.4, 37.7, 32.4; CIMS (NH_3) *m/z* 311 (M + H^+, 100). Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.04. Found: C, 73.49; H, 7.03; N, 8.92.

(4*R*,5*R*,6*R*)-Tetrahydro-5-(tetrahydropyran-2-yloxy)-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (29). A solution of alcohol **28** (6.2 g, 20 mmol) in chloroform was treated with dihydropyran (12.0 g, 140 mmol) and TsOH·H_2O (0.4 g, 2 mmol) and stirred overnight at room temperature. After a general workup, 7.8 g of **29** was obtained as white solid: mp 182−184 °C; ^{1}H NMR ($CDCl_3$) δ 7.38−7.19 (m, 10 H), 4.83 (bs, 0.5 H), 4.78 (bs, 0.5 H), 4.69 (bs, 1 H), 4.45 (bs, 1 H), 3.97−3.42 (m, 5 H), 3.09−2.57 (m, 4 H), 1.92−1.51 (m, 8 H); CIMS (NH_3) *m/z* 395.3 (M + H^+, 100). Anal. Calcd for $C_{24}H_{30}N_2O_3$: C, 73.09; H, 7.68; N, 7.10. Found: C, 72.76; H, 7.51; N, 6.91.

(4*R*,5*R*,6*R*)-Tetrahydro-5-hydroxy-1,3-bis(1*H*-indazol-5-ylmethyl)-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (31). A solution of **29** (2.47 g, 6.3 mmol) and 5-(bromomethyl)-1-SEM-indazole[12] (4.70 g, 13.8 mmol) in THF was treated dropwise with a 1 M solution of KO-*t*-Bu (in THF) via syringe. The resulting solution was stirred at room temperature for 30 min. The solvent was removed and the residue chromatographed (MPLC, silica gel, 25% EtOAc/hexane) to give 4.3 g of **30** (75% yield). A solution of **30** (4.3 g, 4.6 mmol) in MeOH (150 mL) was treated with 50 mL of concentrated HCl and heated at reflux for 2 h. The solution was concentrated to half its volume on a rotary evaporator and made basic with 1 N NaOH. After a general workup, the residue was chromatographed (MPLC, silica gel, 1.5% MeOH/EtOAc) to give 2.3 g (88% yield) of **31**: mp 130−134 °C; ^{1}H NMR ($CDCl_3$) δ 10.95 (bs, 1H), 10.87 (bs, 1 H), 7.84 (s, 1 H), 7.72 (s, 1 H), 7.50 (s, 1 H), 7.47 (s, 1 H), 7.35−7.15 (m, 10 H), 7.07 (2 overlapping d, *J* = 7 Hz, 2 H), 6.95 (2 overlapping d, *J* = 7 Hz, 2 H), 5.51 (d, *J* = 15 Hz, 1 H), 5.48 (d, *J* = 15 Hz, 1 H), 4.10 (d, *J* = 16 Hz, 1 H), 3.94 (d, *J* = 15 Hz, 1 H), 3.53 (m, 1 H), 3.42 (m, 1 H), 3.32 (m, 1 H), 2.94 (m, 2 H), 2.42 (m, 2 H), 1.90 (m, 1 H), 1.76 (m, 1 H), 1.62 (bs, H); CIMS (NH_3) *m/z* 571 (M + H^+, 100). Anal. Calcd for $C_{35}H_{34}N_6O_2$: C, 73.66; H, 6.00; N, 14.73. Found: C, 73.38; H, 5.95; N, 14.50.

(4*R*,5*S*,6*R*,7*R*)-1,3-Diaza-1,4,7-tris(phenylmethyl)-5-(acetyloxy)[4.1.0]bicycloheptan-2-one (32a). A solution of **23** (0.20 g, 0.57 mmol) in DMF was cooled in an ice bath, treated with NaH (30 mg, 0.7 mmol, 60% oil dispersion), and stirred for 30 min. Then benzyl bromide (0.12 g, 0.69 mmol) was added, and the solution was allowed to warm to room temperature for 1 h. After a general workup, the residue was chromatographed (HPLC, Zorbax Sil, 50% EtOAc/hexane) to give 80 mg of **32a** as a white solid. An additional 30 mg of the 5-benzyl ether compound was also obtained. For **32a**: ^{1}H NMR ($CDCl_3$) δ 7.40−7.20 (m, 13 H), 7.08 (m, 2 H), 5.05 (d, *J* = 15 Hz, 1 H), 4.53 (dd, *J* = 5, 7 Hz, 1 H), 3.77 (m, 1 H), 3.28 (dd, *J* = 4, 15 Hz, 1 H), 3.22 (abx m, 1 H), 3.05 (abx m, 1 H), 2.94 (m, 1 H), 2.83 (m, 1 H), 2.83 (d *J* = 15 Hz, 1 H), 2.55 (dd, *J* = 8, 15 Hz, 1 H), 1.95 (s, 3 H); DCI MS (NH_3) *m/z* 441 (M + H^+, 100).

(4*R*,5*S*,6*R*,7*R*)-1,3-Diaza-1,4,7-tris(phenylmethyl)-5-hydroxy[4.1.0]bicycloheptan-2-one (33). A solution of **32a** (20 mg) in methanol was treated with 5 mL of 1 N NaOH and stirred at room temperature for 1 h. After a general workup, the residue was chromatographed (HPLC, Zorbax Sil, 70% EtOAc/hexane) to give 15 mg of **33** as a white solid. The solid was recrystallized from ethyl acetate to give crystals suitable for X-ray analysis: ^{1}H NMR ($CDCl_3$) δ 7.41−7.21 (m, 13 H), 6.96 (m, 2 H), 5.08 (d, *J* = 15 Hz, 1 H), 3.63 (m, 1 H), 3.58−3.34 (m, 3 H), 3.04 (m, 1 H), 2.95 (m, 1 H), 2.81 (m, 1 H), 2.56 (d, *J* = 15 Hz, 1 H), 2.38 (dd, *J* = 10, 15 Hz, 1 H), 2.25 (bs, 1 H); DCI MS (NH_3) *m/z* 399 (M + H^+, 100).

(4*R*,5*R*,6*R*)-Tetrahydro-1,6-bis(phenylmethyl)-5-hydroxy-4-(2-phenylethyl)-2(1*H*)-pyrimidinone (36). By using the same procedure detailed above for the sequence **25**/**26**/**28**, the aziridine **32a** was converted to **36**: mp 180 °C; ^{1}H NMR ($CDCl_3$) δ 7.36−7.15 (m, 13 H), 7.03 (m, 2 H), 5.16 (d, *J* = 15 Hz, 1 H), 4.98 (s, 1 H), 3.49 (m, 1 H), 3.36 (m, 2 H), 3.17 (d, *J* = 15 Hz, 1 H), 3.08 (dd, *J* = 5, 13 Hz, 1 H), 2.83 (dd, *J* = 9, 13 Hz, 1 H), 2.77 (m, 1 H), 2.62 (m, 1 H), 2.09 (d, *J* = 7 Hz, 1 H), 1.96 (m, 1 H), 1.73 (m, 1 H); DCI MS (NH_3) *m/z* 401 (M + H^+, 100). Anal. Calcd for $C_{26}H_{28}N_2O_2$: C, 77.97; H, 7.06; N, 6.99. Found: C, 78.06; H, 7.19; N, 6.97.

(4*R*,5*R*,6*R*)-Tetrahydro-1-[(3-cyanophenyl)methyl]-6-(phenylmethyl)-5-hydroxy-4-(2-phenylethyl)-2(1*H*)-pyrimidinone (39). By using the same procedure detailed above for the synthesis of **36**, the aziridine **23** was converted to **39**: ^{1}H NMR ($CDCl_3$) δ 7.48 (d, *J* = 7 Hz, 1 H), 7.35−7.10 (m, 13 H), 5.35 (s, 1 H), 5.00 (d, *J* = 15 Hz, 1 H), 3.53 (m, 1 H), 3.38 (m, 2 H), 3.20 (d, *J* = 15 Hz, 1 H), 3.12 (dd, *J* = 5, 13 Hz, 1 H), 2.87−2.58 (m, 3 H), 2.29 (bs, 1 H), 2.05 (m, 1 H), 1.77 (m, 1 H); DCI MS (NH_3) *m/z* 426 (M + H^+, 100); HRMS calcd for $C_{27}H_{28}N_3O_2$ (M + H^+) 426.2181, found 426.2159.

(4*R*,5*R*,6*R*)-Tetrahydro-1,6-bis(phenylmethyl)-5-hydroxy-4-(1-hydroxy-2-phenylethyl)-2(1*H*)-pyrimidinone (34). The aziridine **32** (30 mg, 0.07 mmol) was dissolved in 1 mL of trifluoroacetic acid for 1 h. After a general workup, the trifluoroacetate obtained was redissolved in methanol (5 mL), treated with 1 N NaOH (1 mL), and stirred at room temperature for 2 h. The solution was acidified with 1 N HCl and extracted into methylene chloride. After a general workup, 15 mg of **34** was obtained as a white solid: mp 193−194 °C; ^{1}H NMR ($CDCl_3$) δ 7.41−7.15 (m, 13 H), 6.95 (m, 2 H), 5.89 (bs, 1 H), 5.05 (d, *J* = 15 Hz, 1 H), 4.90 (m, 2 H), 3.41 (m, 2 H), 3.18−2.65 (m, 7 H); DCI MS (NH_3) *m/z* 417 (M + H^+, 100). Anal. Calcd for $C_{26}H_{28}N_2O_3$·0.66(CH_3OH): C, 73.16; H, 7.06; N, 6.40. Found: C, 73.33; H, 6.88; N, 6.07.

(4*R*,5*R*,6*R*)-Tetrahydro-1-[(3-hydroxyphenyl)methyl]-5-hydroxy-4-(2-phenylethyl)- 6-(phenylmethyl)-2(1*H*)-pyrimidinone (38). A solution of **23** (1.4 g, 4.1 mmol) in DMF was alkylated with 3-benzyloxybenzyl bromide (1.4 g, 6.2 mmol) as described above to give after chromatography (MPLC, silica gel, 50% EtOAc/hexane) 1 g of **37** (mixture of R = OAc and R = 3-benzyloxybenzyl) as a white solid. An additional 0.5 g of pure **37** (R = OH) was also obtained. For **37** (R = OH): mp 184−185 °C. Anal. Calcd for $C_{33}H_{32}N_2O_3$: C, 78.55 H, 6.39 N, 5.55 Found: C, 78.34 H, 6.34 N, 5.35.

A solution of **37** (mixture of R = OAc and R = 3-benzyloxybenzyl) (1 g) in methanol was treated with 1 N NaOH and stirred at room temperature for 1 h. After a general workup, the residue was chromatographed (MPLC, silica gel, 50% EtOAc/hexane) to give 800 mg of **37** (mixture of R = OH and R = 3-benzyloxybenzyl) as a white solid. A solution of **37** (mixture of R = OH and R = 3-benzyloxybenzyl) (800 mg) in ethanol was treated with 10% Pd/C (800 mg) and hydrogenated at 50 psi for 2 days. The solution was filtered through Celite and the filtrate concentrated. The residue was chromatographed (HPLC, Zorbax Sil, 3% MeOH/$CHCl_3$) to give 230 mg of **38** as a white solid. The 2-D COSY was consistent with assigned structure: ^{1}H NMR ($CDCl_3$) δ 9.13 (s, 1H), 7.35−7.12 (m, 9 H), 6.83−6.80 (m, 4 H), 6.39 (d, *J* = 7 Hz, 1 H), 5.19 (bs, 1 H), 5.00 (d, *J* = 15 Hz, 1 H), 3.36 (m, 1 H), 3.16 (m, 2 H), 3.02 (abx m, 1 H), 2.98 (d, *J* = 15 Hz, 1 H), 2.70 (abx m, 1 H), 2.45 (m, 2 H), 1.86 (m, 1 H), 1.74 (d, *J* = 5 Hz, 1 H), 1.30 (m, 1 H); DCI MS (NH_3) *m/z* 417 (M + H^+, 100); HRMS calcd for $C_{26}H_{29}N_2O_3$ (M + H^+) 417.2178, found 417.2163.

(4*R*,5*R*,6*R*)-Tetrahydro-1-[3-(*N*-hydroxycarboximidamido)-phenylmethyl]-3-(cyclopropylmethyl)-6-(phenylmethyl)-5-hydroxy-4-(2-phenylethyl)-2(1*H*)-pyrimidinone (42). The alcohol **39** (0.5 g, 1.2 mmol) in methylene chloride was treated with MEM-Cl (0.29 g, 2.4 mmol), and DIEA (0.3 g, 2.4 mmol), and the solution was heated at reflux overnight. The solvent was removed under vacuum and the residue chromatographed (MPLC, silica gel, EtOAc) to give 400 mg of the MEM ether **40** as an oil: DCI MS (NH_3) *m/z* 514.2 (M + H^+, 100).

The MEM ether **40** (0.25 g, 0.5 mmol) was alkylated with cyclopropylmethyl bromide (0.39 g, 3.0 mmol; DMF, NaH (0.11 g, 3.0 mmol, 60% dispersion, 70 °C for 1 h) as described above to give after chromatography (HPLC, Zorbax Sil, EtOAc) **41**: ^{1}H NMR ($CDCl_3$) δ 7.50 (m, 1 H), 7.37−7.10 (m, 13 H), 4.84 (d, *J* = 15 Hz, 1 H), 4.69 (dd, *J* = 7, 22 Hz, 2 H), 3.90 (dd, *J* = 7, 15 Hz, 1 H), 3.80−3.60 (m, 5 H), 3.52 (m, 2 H), 3.36 (s, 3 H), 3.20 (d, *J* = 15 Hz, 1 H), 3.20 (d, *J* = 15 Hz, 1 H), 3.06−2.88

(m, 3 H), 2.52 (m, 2 H), 2.05 (m, 2 H), 1.07 (m, 1 H), 0.54 (m, 2 H), 0.32 (m, 2 H).

The MEM group was removed (4 N HCl/dioxane, room temperature, 3 h), and **41** (40 mg) was converted to the amidoxime (NH_2OH·HCl (60 mg), Et_3N (80 mg), EtOH, reflux, 2 h). After a general workup, the residue was chromatographed (HPLC, Zorbax NH_2, 15% MeOH/CH_2Cl_2) to give **42** as a foam: mp 130−134 °C; ^{1}H NMR ($CDCl_3$) δ 7.50−6. 95 (m, 14 H), 5.15 (d, J = 15 Hz, 1 H), 4.84 (bs, 2 H), 3.90 (dd, J = 7, 15 Hz, 1 H), 3.90 (bs, 1 H), 3.76 (d, J = 15 Hz, 1 H), 3.57 (m, 1H), 3.43 (m, 1 H), 3.38 (m, 1 H), 3.52 (m, 2 H), 2.96 (m, 3 H), 2.78 (dd, J = 7, 15 Hz, 1 H), 2.42 (m, 2 H), 1.87 (m, 1 H), 1.64 (m, 1 H), 1.07 (m, 1 H), 0.54 (m, 2 H), 0.32 (m, 2 H); ESI MS (NH_3) m/z 513.3 (M + H$^+$, 100). Anal. Calcd for $C_{31}H_{36}N_4O_3$: C, 72.63; H,7.09; N, 10.93. Found: C, 73.01; H, 6.97; N, 10.16.

Reaction of Sulfamide 43 with 2-Acetoxybutyryl Bromide. Synthesis of 44 and 45. To a solution of sulfamide **43**[9] (5.3 g, 10 mmol) in CH_2Cl_2 (40 mL) at room temperature was added 2-acetoxyisobutyryl bromide (4.2 g, 20 mmol), and the solution was stirred at room temperature for 10 min. After a general workup, the residue was chromatographed (MPLC silica gel 30% EtOAc/hexane) to give 1.0 g of the seven-membered ring analogue **45** and 2.5 g of a mixture of **45** and 1-bromo-2-phenylethyl six-membered-ring analogue **44**. The mixture was further purified by HPLC (Zorbax Sil, 30% EtOAc/hexane) to obtain a pure sample of **44**.

For **44**: ^{1}H NMR ($CDCl_3$) δ 7.49−7.15 (m, 16 H), 7.02 (d, J = 7 Hz, 2 H), 6.89 (m, 2 H), 4.89 (d, J = 15 Hz, 1 H), 4.83 (m, 1 H), 4.66 (d, J = 15 Hz, 1 H), 4.61 (m, 1 H), 4.53 (d, J = 15 Hz, 1 H), 4.41 (m, 1 H), 4.23 (d, J = 15 Hz, 1 H), 3.94 (dd, J = 4, 9 Hz, 1 H), 3.06 (dd, J = 3, 15 Hz, 1 H), 2.94 (dd, J = 5, 14 Hz, 1 H), 2.90 (dd, J = 10, 15 Hz), 2.68 (dd, J = 10, 14 Hz, 1 H), 1.75 (s, 3 H); CIMS (NH_3) m/z 649 (M + H$^+$, 100) 647 (M + H$^+$, 92). Anal. Calcd for $C_{34}H_{35}N_2O_4SBr$: C,63.06; H, 5.46; N, 3.34. Found: C, 63.05; H, 5.42; N, 4.20.

For **45**: mp 103−105 °C; ^{1}H NMR ($CDCl_3$) δ 7.49−7.15 (m, 18 H), 7.00 (m, 2 H), 5.20 (m, 1 H), 5.00−4.20 (m, 6 H), 4.05 (m,1 H), 3.25−2.98 (m, 3 H), 2.75 (m, 1 H), 1.91 (s, 3 H); CIMS (NH_3) m/z 649 (M + H$^+$, 100) 647 (M + H$^+$, 95). Anal. Calcd for $C_{34}H_{35}N_2O_4SBr$: C,63.06; H, 5.46; N, 3.34. Found: C, 63.07; H, 5.45; N, 4.23.

Synthesis of Compound 46. Reduction of **45** (200 mg, 0.31 mmol) with Zn/AcOH as described above gave (MPLC silica gel 50% EtOAc/hexane) 70 mg of **46** as a white solid: mp 149−151 °C; ^{1}H NMR ($CDCl_3$) δ 7.41−7.15 (m, 18 H), 7.00 (m, 2 H), 5.55 (s, 2 H), 4.81 (d, J = 15 Hz, 2 H), 4.42 (m, 2 H), 4.38 (d, J = 15 Hz, 2 H), 2.98 (dd, J = 5, 14 Hz, 2 H), 2.75 (dd, J = 10, 14 Hz, 2 H); CIMS (NH_3) m/z 509 (M + H$^+$, 100); HRMS calcd for $C_{32}H_{33}N_2O_2S$ (M + H$^+$) 509.2262, found 509.2238. Anal. Calcd for $C_{32}H_{32}N_2O_2S$·0.033$CDCl_3$: C, 75.05; H, 6.29; N, 5.46. Found: C, 75.09; H, 6.31; N, 5.29.

Synthesis of Compound 48. The same procedure as outlined for the synthesis of **19** above was used to convert **44** to **48**: mp 170−172 °C; ^{1}H NMR ($CDCl_3$) δ 7.37−7.15 (m, 18 H), 6.82 (m, 2 H),4.8−4.6 (m, 3 H), 4.23 (s, J = 15 Hz, 1 H), 3.54−3.21 (m, 3 H), 2.98 (m, 2 H), 2.39−2.00 (m, 3 H), 1.92 (bs, 1 H), 1.70 (m, 1 H); CIMS (NH_3) m/z 527 (M + H$^+$, 100). Anal. Calcd for $C_{32}H_{34}N_2O_3S$: C, 72.97; H, 6.52; N, 5.33. Found: C, 72.94; H, 6.42; N, 5.28.

(3*S*,4*S*)-1,3-Bis(cyclopropylmethyl)-4,5-bis(1(*S*)-fluoro-2-phenylmethyl)-2-imidazolidinone (49a). The tetrahydropyrimidinone **2** (or the diazepin-2-one **1**) was treated with excess DAST as described above to give the C_2-symmetric imidazolidinone **49a**: ^{1}H NMR ($CDCl_3$) δ 7.37−7.11 (m, 20 H), 4.93−4.71 (dm, J = 48 Hz, 2 H), 4.04 (m, 2 H), 3.49 (dd, J = 7, 15 Hz, 2 H), 3.03 (m, 4 H), 2.96 (dd, J = 7, 15 Hz, 2 H), 0.95 (m, 2 H), 0.59 (m, 2 H), 0.48 (m, 2 H), 0.29 (m, 2 H), 0.21 (m, 2 H); CIMS (NH_3) m/z 439 (M + H$^+$, 100). Anal. Calcd for $C_{27}H_{32}N_2OF_2$·0.2H_2O: C, 73.34; H, 7.39; N, 6.34. Found: C, 73.44; H, 7.43; N, 6.18.

(3*S*,4*S*)-1,3-Bis(naphthalenylmethyl)-4,5-bis(1(*S*)-fluoro-2-phenylmethyl)-2-imidazolidinone (49b). The tetrahydropyrimidinone **11** (or the diazepin-2-one **10**) was treated with excess DAST as described above to give the C_2-symmetric imidazolidinone **49b**: ^{1}H NMR ($CDCl_3$) δ 7.83 (m, 3 H), 7.33 (s, 1 H0, 7.49 (m, 3 H), 7.10 (m, 3 H), 6.62 (m, 2 H), 5.15 (d, J = 15 Hz, 2 H), 4.36 (d, J = 15 Hz, 2 H), 4.57−4.42 (dm, J = 46 Hz, 2 H), 3.50 (m, 2 H), 2.66−2.25 (m, 4 H); CIMS (NH_3) m/z 611 (M + H$^+$, 100). Anal. Calcd for $C_{41}H_{36}N_2OF_2$·0.25H_2O: C, 80.04; H, 5.98; N, 4.55. Found: C, 79.98; H, 6.02; N, 4.46.

(4*S*,5*R*)-Dimethyl-3,3′-[[4-(1(*S*)-bromo-2-phenylethyl)-2-oxo-5-(2-phenylethyl)-1,3-imidazolidinyl]bis(methylene)]-bis(benzoate) (52). The tetrahydropyrimidinone **50**[6] (45 mg) was treated with triphenylphosphine (135 mg) and CBr_4 (145 mg) in methylene chloride at room temperature for 48 h. The solvent was removed under vacuum and the residue chromatographed (MPLC silica gel 50% EtOAc/hexane) to give 20 mg of **52**: ^{1}H NMR ($CDCl_3$) δ 7.98 (m, 4 H), 7.59 (d, J = 8 Hz, 1 H), 7.41 (m, 3 H), 7.21 (m, 6H), 7.01 (m, 2 H), 6.80 (m, 2 H), 5.08 (d, J = 15 Hz, 1 H), 4.86 (d, J = 15 Hz, 1 H), 4.36 (d, J = 15 Hz, 1 H), 4.07 (d, J = 15 Hz, 1 H), 4.07 (m, 1 H), 3.85 (s, 3 H), 3.75 (s, 3 H), 3.67 (m, 1 H), 3.58 (m, 1 H), 3.07 (dd, J = 2, 15 Hz, 1 H), 2.50 (m, 1 H), 2.32 (m, 2 H), 1.88 (m, 2 H); CIMS (NH_3) m/z 688 (M + NH_4^+, 100) 686 (M + NH_4^+, 92) 671 (M + H$^+$, 82) 669 (M + H$^+$, 75).

(4*S*,5*R*)-Dimethyl-3,3′-[[4-(1(*S*)-hydroxy-2-phenylethyl)-2-oxo-5-(2-phenylethyl)-1,3-imidazolidinyl]bis(methylene)]-bis(benzoate) (51). The tetrahydropyrimidinone **50**[6] (500 mg) was treated under the Mitsunobu and hydrolysis conditions described for the synthesis of **8** to give 400 mg of **51**: ^{1}H NMR ($CDCl_3$) δ 7.98 (m, 4 H), 7.59 (d, J = 8 Hz, 1 H), 7.41 (m, 3 H), 7.21 (m, 6H), 6.96 (m, 2 H), 6.89 (m, 2 H), 5.00 (d, J = 15 Hz, 1 H), 4.93 (d, J = 15 Hz, 1 H), 4.34 (d, J = 15 Hz, 1 H), 4.05 (d, J = 15 Hz, 1 H), 3.84 (s, 3 H), 3.80 (m, 1 H), 3.78 (s, 3 H), 3.48 (m, 1 H), 3.38 (m, 1 H), 2.66 (dd, J = 2, 15 Hz, 1 H), 2.43 (m, 1 H), 2.30 (m, 1 H), 2.17 (dd, J = 10, 14 Hz, 1 H), 1.92 (bs, 1 H), 1.78 (m, 2 H); CIMS (NH_3) m/z 607 (M + H$^+$, 100).

(4*R*,5*R*)-Dimethyl-3,3′-[[2-oxo-4,5-bis(2-phenylethyl)-1,3-imidazolidinediyl]bis(methylene)]bis(benzoate) (53). Compound **51** (300 mg) was treated with TCDI and reduced with Bu_3SnH as described for the synthesis of **9** to give 50 mg of the C_2-symmetric imidazolidinone **53**: ^{1}H NMR ($CDCl_3$) δ 7.95 (m, 4 H), 7.52 (d, J = 8 Hz, 2 H), 7.43 (m, 2 H), 7.21 (m, 6H), 6.93 (m, 4 H), 5.01 (d, J = 15 Hz, 2 H), 4.11 (d, J = 15 Hz, 2 H), 3.85 (s, 6 H), 3.23 (m, 2 H), 2.42 (m, 2 H), 2.30 (m, 2 H), 1.78 (m, 4 H); CIMS (NH_3) m/z 591 (M + H$^+$, 100). Anal. Calcd for $C_{34}H_{38}N_2O_5$·0.33H_2O: C, 74.48; H, 6.53; N, 4.70. Found: C, 74.66; H, 6.39; N, 4.35.

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Supporting Information Available: Summary of crystal data and structure refinement, atomic coordinates, bond lengths and angles, anisotropic thermal parameters, and intramolecular nonbonding distances for compounds **24** and **33** (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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