Design, Synthesis, and Evaluation of Tetrahydropyrimidinones as an Example of a General Approach to Nonpeptide HIV Protease Inhibitors

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Re-examination of the design of the cyclic urea class of HIV protease (HIVPR) inhibitors suggests a general approach to designing novel nonpeptide cyclic HIVPR inhibitors. This process involves the inversion of the stereochemical centers of the core transition-state isostere of the linear HIVPR inhibitors and cyclization of the resulting core using an appropriate cyclizing reagent. As an example, this process is applied to the diamino alcohol class of HIVPR inhibitors[11] to give tetrahydropyrimidinones. Conformational analysis of the tetrahydropyrimidinones and modeling of its interaction with the active site of HIVPR suggested modifications which led to very potent inhibitors of HIVPR (**24** with a $K_i = 0.018$ nM). The X-ray crystallographic structure of the complex of **24** with HIVPR confirms the analysis and modeling predictions. The example reported in this study and other examples that are cited indicate that this process may be generally applicable to other linear inhibitors.

Introduction

Since the identification of the human immunodeficiency virus (HIV) as the causative agent of acquired immune deficiency syndrome (AIDS), there has been an intense worldwide search to find useful chemotherapeutic agents. One of the prime targets of this research has been the essential aspartic protease (PR)[2] that processes the viral gag and gag-pol polyproteins into structural and functional proteins. Inhibition of HIVPR *in vitro* results in the production of progeny virions which are immature and noninfectious.[3] With a wealth of structural information available, HIVPR has been an attractive target for computer-aided drug design strategies,[4] and this effort has produced a variety of potent inhibitors.[5]

In recent clinical studies, several HIVPR inhibitors have been shown to reduce the viral load and increase the number of $CD4^+$ lymphocytes in HIV-infected patients.[6] Saquinavir (Roche), Ritonavir (Abbott), and Indinavir (Merck) have recently been approved by the FDA and are being used in AIDS therapy in combination with reverse transcriptase inhibitors. However, the ability of the virus to rapidly generate resistant mutants[7] suggests that there is an ongoing need for new, structurally diverse HIVPR inhibitors with superior potency, pharmacokinetics, and efficacy.

The DuPont Merck group recently described the rational design of a class of novel and highly potent cyclic urea inhibitors.[8] The 7-membered ring cyclic ureas were designed[8a] by first using the structure−activity relationship (SAR) of the linear diamine diol series of HIVPR inhibitors to define a 3-D pharmacophore model. Using this model a 3-D database was searched for possible lead structures. The hits from this search were modified using computer-aided drug design tools to arrive at the 7-membered ring cyclic ureas. The urea oxygen was designed to displace the unique structural water molecule usually found in the linear HIVPR inhibitor complexes (Figure 1). The 7-membered ring cyclic urea is also an excellent nonpeptidic, low molecular weight scaffold which is highly preorganized and complementary to the HIVPR active site and optimally directs substituents into the corresponding enzyme subsites. This work resulted in the identification of two clinical candidates from this series: DMP323[8,9] and DMP450.[10]

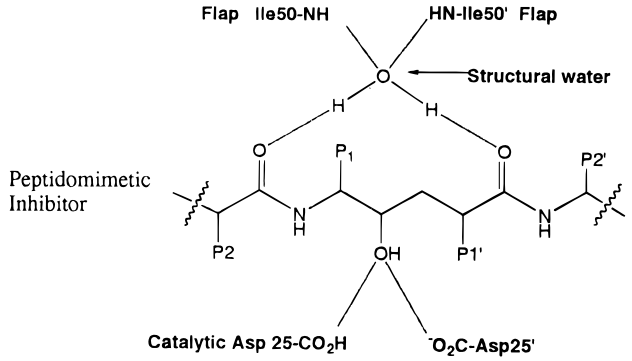
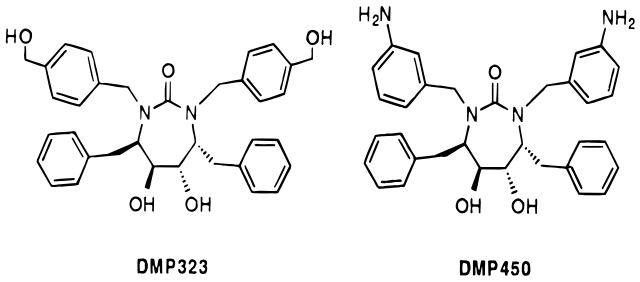


Figure 1. General hydrogen-bonding scheme found with a typical peptidomimetic inhibitor binding at the HIVPR active site via a bridging structural water.



Discovery of the 7-membered ring cyclic ureas prompted our interest in designing other heterocyclic cores that might also make good scaffolds for HIVPR inhibitors. Thus, it is important to understand the structural features that make the cyclic ureas such potent inhibitors so that these features can be incorporated into the design of any new heterocyclic core. These features can be best exemplified by analyzing the X-ray structure of

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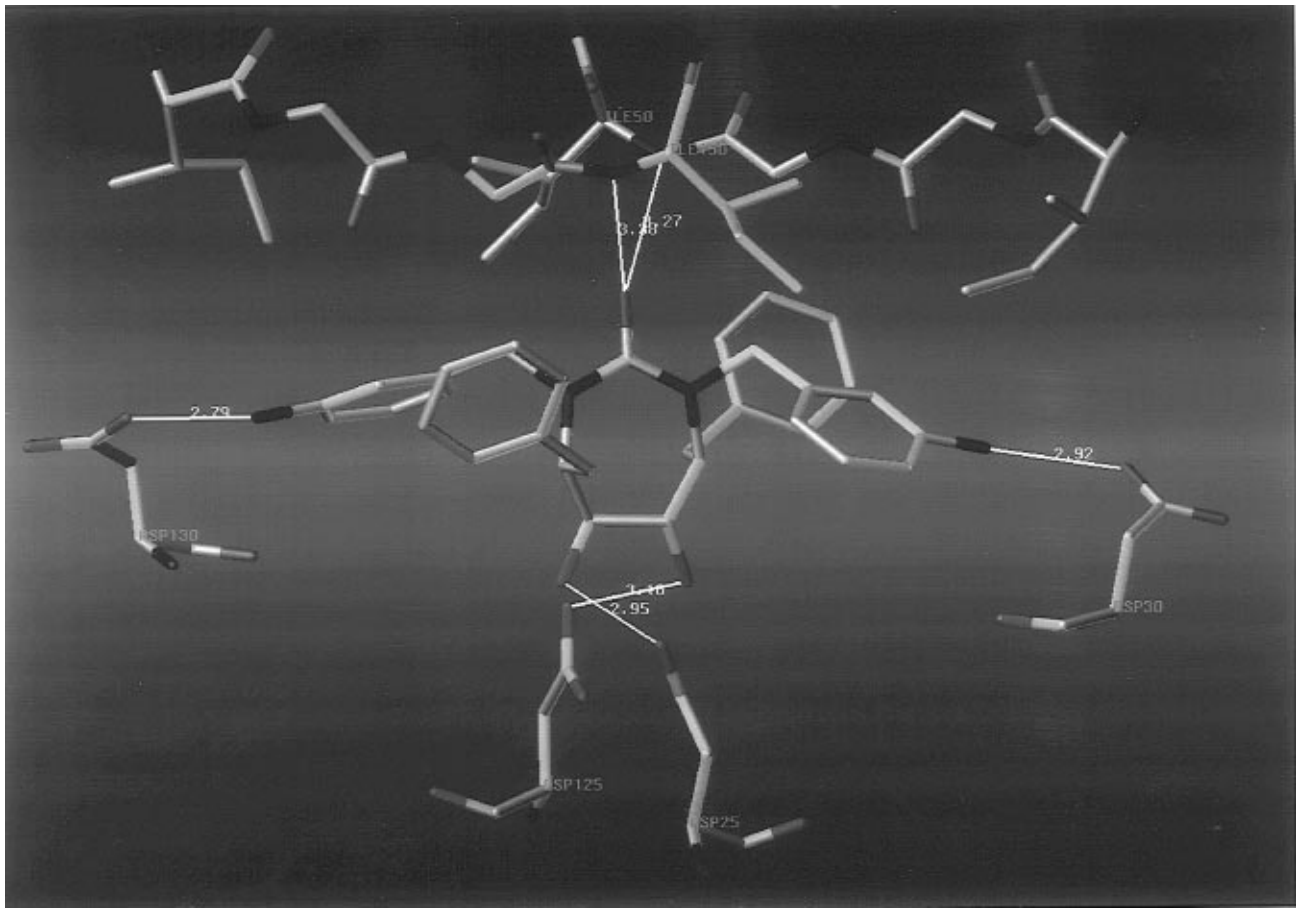


Figure 2. X-ray structure of the complex of DMP450 with HIV-1PR showing the hydrogen-bonding interactions. The urea oxygen accepts hydrogen bonds from the protease flaps Ile50/50′ with the exclusion of the intervening structural water commonly found in linear peptidomimetic inhibitors.

DMP450 bound to HIVPR as shown in Figure 2. Most of the enzyme residues have been removed to clarify and simplify the analysis. The most obvious feature is the network of hydrogen bonds between the flap and the urea carbonyl and between the diol and the catalytic aspartic acids. In the view looking down from the flaps through the urea carbonyl (Figure 3), one can see that another important feature is the conformation of the 7-membered ring that places the trans diaxial P1 benzyl groups in good contact with the lipophilic S1 pocket. The *N*-benzyl group serves two important functions. First, it contributes an important hydrophobic interaction with the lipophilic S2 enzyme pocket. Second, it provides a rigid framework for directing groups from the meta and para positions toward the S2/S3 subsites in the enzyme where there are several polar residues which are a rich source of hydrogen-bonding possibilities, in particular Asp29, Asp30, and Gly48. Thus the 7-membered ring cyclic urea provides a conformationally constrained scaffolding which properly places all the important binding elements of the inhibitor in the corresponding recognition domains of the enzyme.

Results and Discussion

Design of Tetrahydropyrimidinones. After the 7-membered ring cyclic ureas were found to be potent inhibitors of HIV-1PR, we became interested in finding a systematic approach to discovering other nonpeptide scaffoldings which might also produce potent inhibitors. As shown in Figure 4, a backward analysis of the hypothetical design steps necessary to give the cyclic ureas ("retro-design analysis") revealed that the 7-membered ring cyclic ureas were "simply" a cyclic version of the potent linear diamine diol[11] class of HIVPR inhibitors. In practice the sequence of events needed to get to the cyclic ureas starting from the linear diamine diol inhibitors is (1) invert all the stereocenters of the transition-state isostere core and (2) cyclize to give the cyclic ureas (Figure 4). In order to explore the generality and the scope and limitations of this process, we explored the possibility of cyclizing other known linear HIVPR inhibitors. We have found that this process is generally applicable. However, it is important, in this process of cyclizing linear inhibitors as outlined in Figure 4, not only to get the correct stereochemistry but also to understand the conformation of the resulting ring system and its interaction with the enzyme.

The first example that we wish to report in detail in this paper is the application of this process to the closely related linear diamino alcohol class of HIVPR inhibitors that were first developed by Abbott.[11] Inversion of the stereocenters and cyclization give the corresponding tetrahydropyrimidinone, as shown in Figure 5. Understanding the conformation of the ring is very important in order to properly analyze its interaction with the enzyme in the active site. In the 6-membered ring, with *trans*-1,3-benzyl/benzyl P1/P1′ substituents, both benzyl groups can not be axial—if one is axial then the other has to be equatorial. Thus, the equatorial benzyl group in the 6-membered ring heterocycle can not interact with the enzyme in the same way that a benzyl group on the 7-membered ring cyclic urea can interact with the enzyme, since in the 7-membered ring cyclic ureas both P1 benzyl groups are axial (see Figure 3).

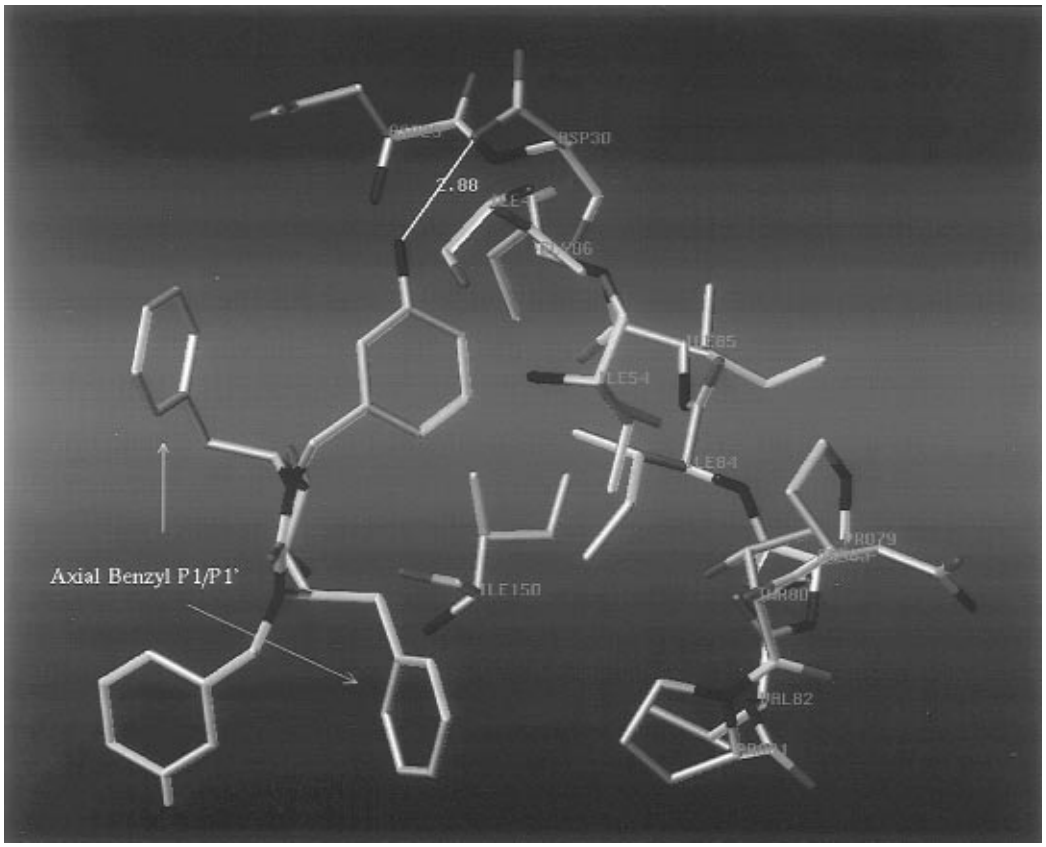
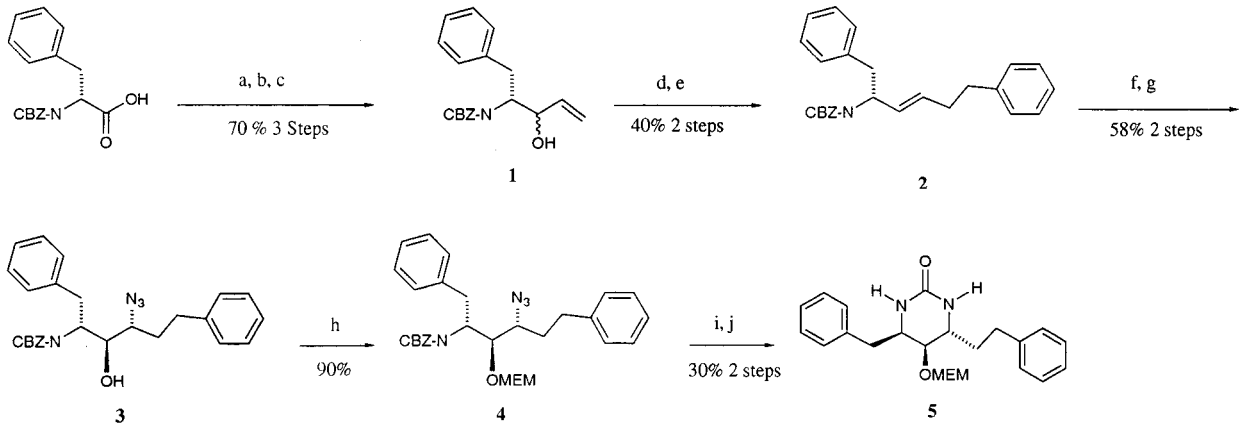


Figure 3. X-ray structure of the complex of DMP450 with HIV-1PR showing the important trans diaxial conformation of the P1/P1′ benzyl groups. The figure also shows the interactions of the *N*-benzyl substituent with the S2 binding pocket.

Scheme 1[a]



[a] Key: (a) isobutyl chloroformate/THF/0 °C/*N*,*O*-dimethylhydroxylamine; (b) vinylmagnesium bromide; (c) $NaBH_4/CeCl_3$; (d) MsCl; (e) BnMgCl/CuCN; (f) MCPBA/CH_2Cl_2; (g) NH_4Cl/NaN_3/DMF; (h) MEM-Cl; (i) H_2, Pd/C; (j) CDI/THF.

However, if one changes the equatorial P1′ benzyl group into a phenethyl group, then, although this substituent is still equatorial, the benzyl portion can take an axial-like position. The phenethyl group can then interact with the enzyme in the same way that the benzyl group on the 7-membered ring cyclic urea interacts. This becomes apparent when computer models are examined as shown in Figure 6. In green is the 7-membered cyclic urea DMP450 in its bound conformation, and overlapped in white is a model of the P1/P1′ benzyl/benzyl (Figure 6A) and P1/P1′ benzyl/phenethyl tetrahydropyrimidinones (Figure 6B). If the 7-membered ring cyclic urea serves as a template of an optimally complementary scaffolding for HIVPR, then these modeling studies suggested that in the tetrahydropyrimidinone, the P1′ phenethyl analog should be a better inhibitor than the P1′ benzyl analog. In order to test these design and modeling predictions, the synthesis of tetrahydropyrimidinones was undertaken.

Synthesis of Tetrahydropyrimidinones. The methods used to synthesize the desired analogs are summarized in Schemes 1 and 2. The synthesis of the tetrahydropyrimidinone is achieved by modification[13] of the procedure developed by researchers at Abbott[11] for the synthesis of the diamine alcohol isostere core with defined stereochemistry at the three asymmetric centers. However, since we desire the opposite stereochemistry, we start with the enantiomeric Cbz-D-phenylalanine as summarized in Scheme 1. The unnatural amino acid is converted to the corresponding Weinreb amide[12] and then treated with vinyl Grignard to give the vinyl ketone. This is reduced with $NaBH_4$ to give the allylic alcohol **1** in 70% yield over the three steps. The alcohol is converted to the mesylate and then

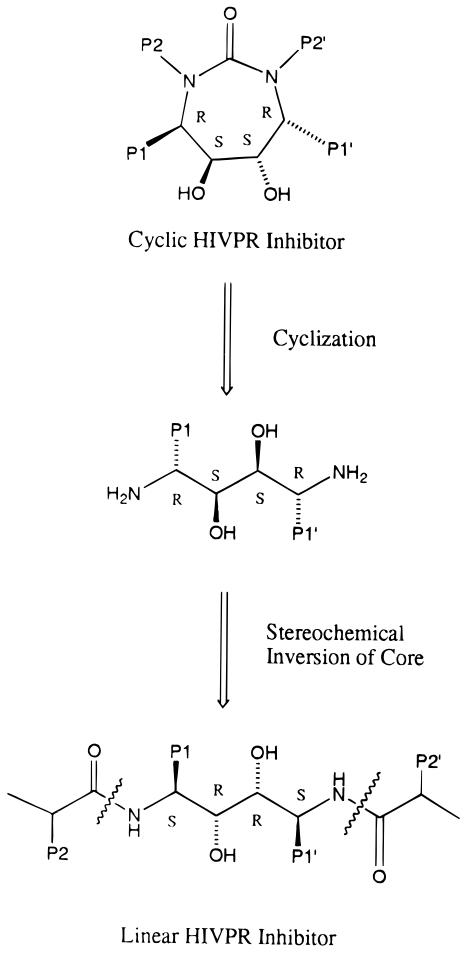
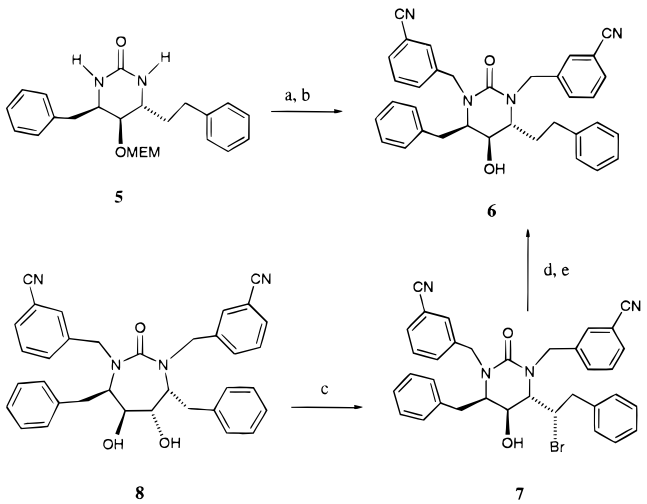


Figure 4. Retro-design analysis of the steps which are needed to convert to the cyclic HIVPR inhibitor from the linear HIVPR inhibitor.

Scheme 2[a]



[a] Key: (a) NaH/DMF/4-CNBnBr; (b) HCl/MeOH; (c) 2-acetoxyisobutyryl bromide/CH_2Cl_2; (d) Zn/AcOH; (e) NaOH/MeOH.

treated with the cuprate derived from benzyl Grignard and copper cyanide to give the olefin **2** in 40% yield over two steps. The olefin is converted to the epoxide and opened using sodium azide to give the azido alcohol **3** as a major isomer (4:1 by NMR)[14] in 58% yield over two steps. The alcohol is protected as the MEM ether and then converted to the diamine by catalytic hydrogenation. The diamine is cyclized with CDI to give the desired tetrahydropyrimidinone **5**. The urea nitrogens are then alkylated using standard conditions of NaH/DMF[8] and appropriate alkylating agent (Scheme 2). Although it is a little long, the synthesis provided sufficient material of defined stereochemistry to enable the validation of the design ideas.

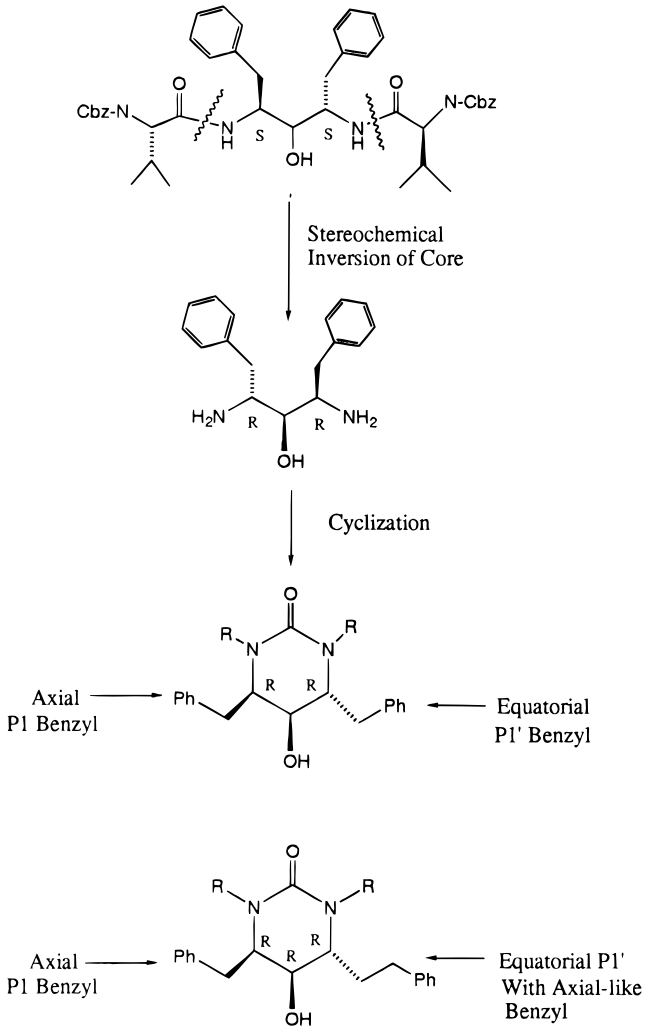


Figure 5. Outline of steps needed to convert the linear diamine alcohol class of HIVPR inhibitors to the tetrahydropyrimidinone class of HIVPR inhibitors.

While this synthesis was progressing we discovered that the 7-membered ring cyclic urea has a tendency to undergo a novel rearrangement ring-contraction reaction to give the desired tetrahydropyrimidinone. The scope and details of this rearrangement will be published elsewhere. However, we were able to take advantage of this tendency to design an efficient synthesis of the desired tetrahydropyrimidinones as shown in Scheme 2. For example, when the diol **8** is treated with 2-acetoxyisobutyryl bromide,[15] a nearly quantitative yield of the 6-membered ring bromo acetate **7** is obtained. The bromide of **7** is reduced with zinc dust/acetic acid and the acetate hydrolyzed to give the desired corresponding alcohol **6** in an overall 90% yield, identical in every way to that obtained from the tetrahydropyrimidinone **5** synthesized from Cbz-D-phenylalanine (Scheme 1). This rearrangement is a very efficient method to synthesize the tetrahydropyrimidinone analogs starting from the symmetrically N-substituted 7-membered ring cyclic ureas. This allowed us to fully explore the SAR of this series of compounds and was the method used for the synthesis of all the compounds reported in this paper.

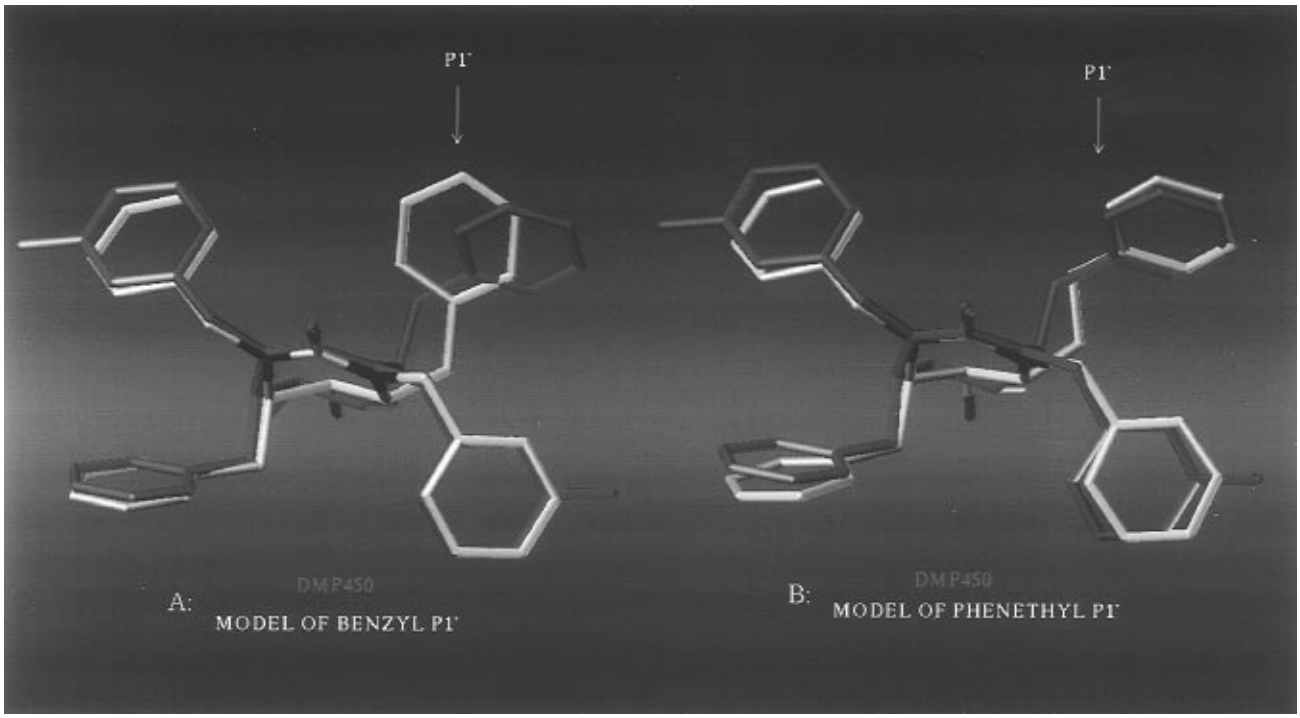


Figure 6. Bound conformation of DMP450 (green), obtained from X-ray analysis of the complex with HIVPR, overlapped (A) with a model of the tetrahydropyrimidinone inhibitor having a P1′ benzyl substituent (white) and (B) with a model of the tetrahydropyrimidinone inhibitor having a P1′ phenethyl substituent (white).

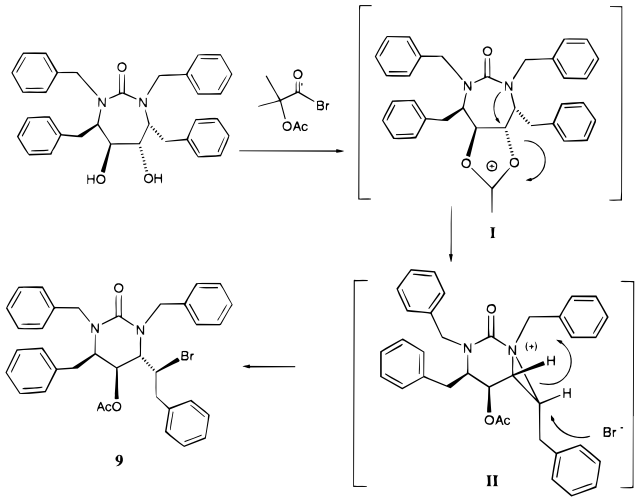


Figure 7.

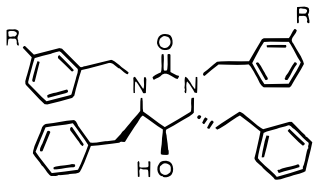
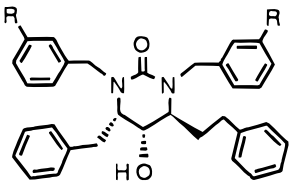
This rearrangement can be envisioned as proceeding first through the acetoxonium ion **I** (Figure 7), which has been proposed as an intermediate in the reaction of diols with acetoxyisobutyryl halides.[15] The urea nitrogen then participates to give the aziridinium cationic intermediate **II**. Attack by bromide ion opens the aziridine ring to give the observed bromo acetate **9** (Figure 7) as the only product in quantitative yield. The structure and stereochemistry of the bromo acetate intermediate **9** were confirmed by X-ray analysis (see Supporting Information).

Evaluation of Tetrahydropyrimidinones. As the modeling studies suggested, the SAR of the tetrahydropyrimidinone closely parallels the SAR found for the 7-membered ring cyclic ureas. As it is with the cyclic ureas,[8] the stereochemistry of the tetrahydropyrimidinones is of critical importance for activity. Table 1 summarizes the effect of stereochemistry on the HIVPR inhibitory activity. Analogous to the 7-membered ring cyclic ureas, only the corresponding tetrahydropyrimidinones with *RRR* configuration are active. In each case shown the *RRR* isomer is at least 800 times more potent than corresponding *SSS* isomer. The *SSS* isomers were obtained from the corresponding enantiomeric *SRRS* 7-membered ring cyclic urea.

Table 2 summarizes the effect of N-substitution on the activity of the tetrahydropyrimidinones that were synthesized in this study. The parent N,N-unsubstituted compound **17** is a weak (K_i = 1 μM) inhibitor of the enzyme. However, even small N-substituents that can interact with the lipophilic S2 enzyme sites greatly increase activity. The cyclopropylmethyl analog **18** is a very potent inhibitor with a K_i of 3.8 nM. The benzyl analog **19** shows excellent potency (K_i 15 nM) making it a good skeleton for further analoging. Substituting the meta position of the *N*-benzyl ring of **19** with hydrogen bond donor/acceptor groups gives further increases in potency. The addition of one heteroatom capable of donating/accepting a hydrogen bond gives a 50-fold increase in potency (for the phenol **11** with a K_i of 0.30 nM). The amide **23** with two heteroatoms capable of donating/accepting a hydrogen bond gives a further increase in potency with a K_i of 0.088 nM. Finally, the amidoxime **24** with more opportunities for hydrogen bonding has a K_i of 0.018 nM.

The crystal structure of the amidoxime **24** complexed with HIVPR was solved and is shown in Figure 8, top. The binding mode is, as expected, very similar to that found with the 7-membered ring cyclic ureas. There is a network of hydrogen bonds between the urea carbonyl and the flap residues Ile50/50′ and between the alcohol and the catalytic Asp25/25′. Analysis of the X-ray structure shows that in order to maximize the S1/S1′ interactions, the alcohol of the tetrahydropyrimidinone binds asymmetrically and is displaced closer to one of the aspartates as shown in Figure 8. The amidoxime functionality also has hydrogen-bonding interactions

Table 1

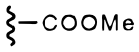
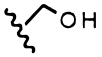
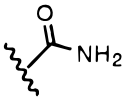
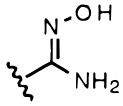
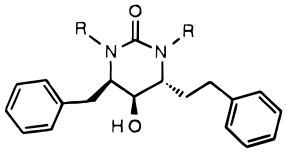
R Substituent	RRR Isomer		SSS Isomer	
	**6**	K_i = 11 nM IC_{90} = 1600 nM	**31**	K_i = 8000 nM IC_{90} > 5000 nM
	**20**	K_i = 1.5 nM IC_{90} > 5000 nM	**34**	K_i = 3300 nM IC_{90} > 5000 nM
	**21**	K_i = 0.49 nM IC_{90} = 109 nM	**35**	K_i = 550 nM IC_{90} > 5000 nM
	**23**	K_i = 0.088 nM IC_{90} = 35 nM	**32**	K_i = 4800 nM IC_{90} > 5000 nM
	**24**	K_i = 0.018 nM IC_{90} = 49 nM	**33**	K_i = 780 nM IC_{90} > 5000 nM

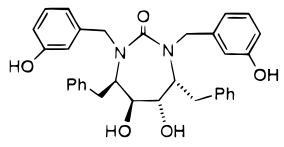
Table 2



compd	R	K_i (nM)	IC_{90} (nM)
17	H	970	>5000
18	cyclopropylmethyl	3.8	5200
19	benzyl	15	2800
6	3-cyanobenzyl	11	1600
20	3-(carbomethoxy)benzyl	1.5	>5000
11	3-hydroxybenzyl	0.3	115
21	3-(hydroxymethyl)benzyl	0.49	109
22	3-amino-4-fluorobenzyl	0.25	36
23	3-benzamido	0.088	35
24	3-benzamido oxime	0.018	49
25	3-aminobenzyl	1.7	365
26	3-(*N*-methylamino)benzyl	4.9	328
27	4-fluoro-3-benzamido	1.4	490
28	4-amino-3-fluorobenzyl	8.0	540
29	4-(hydroxymethyl)benzyl	2.5	3600
30	4-carbomethoxybenzyl	1970	>5000

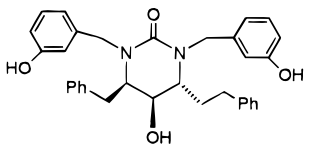
with Asp30 and Gly48. The X-ray structure suggests that the amidoxime binds in both possible tautomer forms as shown in Figure 8, bottom. This ability to form many hydrogen-bonding tautomer forms probably accounts for the great potency of **24**. Superposition of the bound conformation of the tetrahydropyrimidinone **24** with the bound conformation of the 7-membered ring cyclic urea DMP450 (Figure 9) shows the excellent overlap of all four phenyl rings and confirms the initial design considerations.

Chart 1



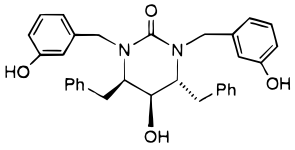
K_i = 0.12 nM

10



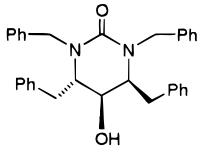
K_i = 0.28 nM

11



K_i = 33 nM

12

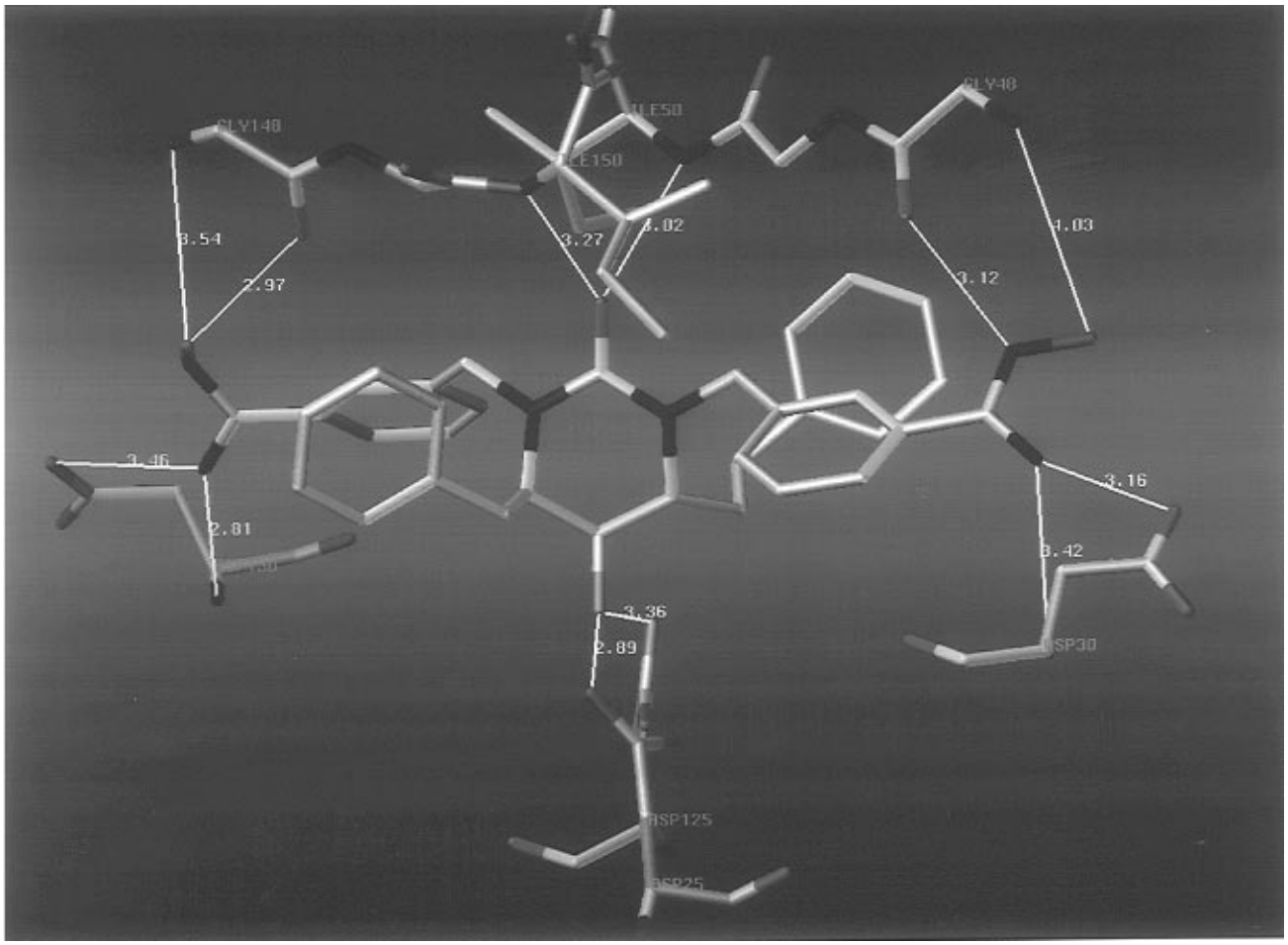


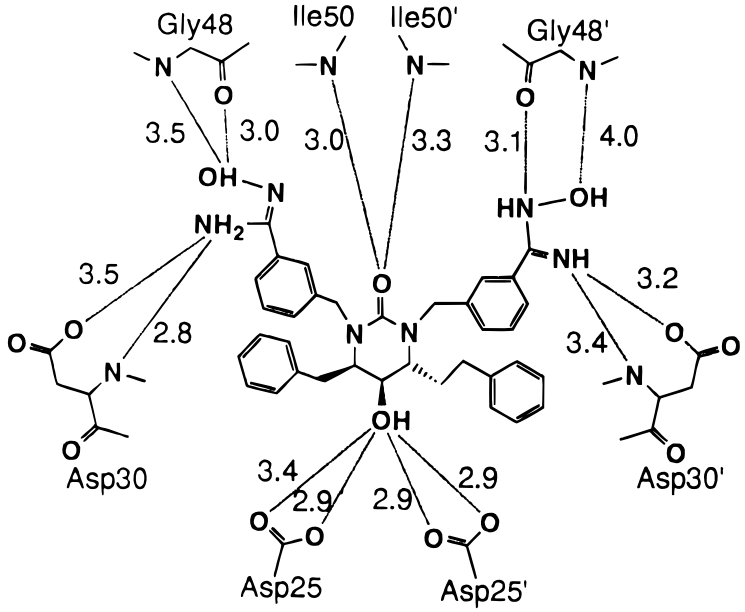
IC_{50} = 80,000 nM (ref. 16)

13

The importance of the phenethyl group for the activity is further exemplified in Chart 1. Whereas the P1′ phenethyl tetrahydropyrimidinone **11** is nearly equipotent to the analogous 7-membered ring cyclic urea **10**,[8a] the P1/P1′ benzyl/benzyl analog **12** is about 100 times less active than the P1/P1′ benzyl/phenethyl analog **11**. If, in addition, the wrong stereochemistry is used, as exemplified by the tetrahydropyrimidinone **13**,[16] the potency is reduced even further.

Although in general the SAR of tetrahydropyrimidinones closely parallels that of the 7-membered ring cyclic ureas, there are some noticeable differences. In every case the K_i of the tetrahydropyrimidinone analog





24

Figure 8. (Top) X-ray structure of the complex of **24** with HIV-1PR showing the hydrogen-bonding interactions. The urea oxygen accepts hydrogen bonds from the protease flaps Ile50/50′ with the exclusion of the intervening structural water molecule. The hydroxyl group is asymmetrically bound to the two catalytic aspartate residues. (Bottom) Hydrogen-bonding scheme of **24** with HIV-1PR with distance shown in Å. Note that the amidoxime substituent seems to bind in two different tautomeric forms based on the distance to the Gly48 carbonyl.

is always 2−5-fold weaker than that of the corresponding 7-membered cyclic urea with the same (P2) substituents. This may be due to the fact that in order for the phenethyl side chain of the tetrahydropyrimidinone to interact optimally with the enzyme it has to be in a conformation in which there is an eclipsing interaction that is nearly anticlinal and *not* in the energy minimum antiperiplanar conformation. The 7-membered ring cyclic ureas, on the other hand, bind in their lowest energy conformer. In addition there is an entropic

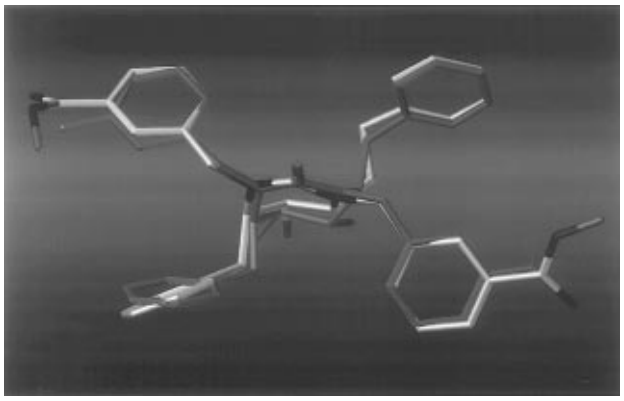


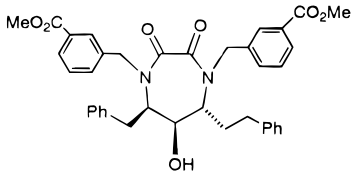
Figure 9. Overlapped DMP450 (green) and **24** (white) in their bound conformations obtained from X-ray analysis of their respective complexes with HIVPR. There is an extremely good fit of all four phenyl groups suggesting the need to maximize S1/S1′ interactions.

penalty,[25] due to the extra rotatable bond of the phenethyl compared to the benzyl group. Thus, the tetrahydropyrimidinone would always have to pay this small energy cost even when its interaction with the enzyme is the same as the 7-membered ring cyclic urea (as pictured in Figure 9). This energy difference (enthalpic and entropic) would result in the observed weaker K_i values.

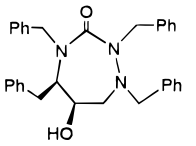
The other influence on the SAR seems to be due differences in the enzyme's ability to tolerate substitution from the para position from the *N*-benzyl P2 group of the tetrahydropyrimidinones. Since the 6-membered ring is smaller, the enzyme conformation may change slightly to accommodate the difference. However, the X-ray structures we have obtained (at the current 2 Å resolution) do not show significant differences in the enzyme conformation when complexed with tetrahydropyrimidinones compared to the 7-membered ring cyclic ureas. The net effect, however, is that substituents at the para position of the P2 benzyl groups are less well tolerated in the tetrahydropyrimidinone analogs compared to the 7-membered ring cyclic ureas. For example, the *p*-hydroxymethyl analog **29** is 10 times less potent than the corresponding 7-membered ring cyclic urea DMP323.[8c] In contrast the *m*-hydroxymethyl tetrahydropyrimidinone analog **21** is nearly equipotent to the corresponding 7-membered ring cyclic urea analog.[8c] An even more dramatic difference is seen with the meta- and para-substituted methyl esters **20** and **30**, which show a 1000-fold difference in binding. In the corresponding 7-membered ring cyclic ureas both isomers are equipotent[8c] (data not shown). Another manifestation of this seems to extend to the directionality of hydrogen-bonding interactions at the meta position. Whereas the *m*-hydroxy-substituted analogs **10** and **11** are nearly equivalent (Chart 1), the *m*-amino analog **25** is 10 times less potent that the cyclic urea analog DMP450. This may be due to the rotational freedom of a phenol compared to an aniline in their hydrogen-bonding capabilities. Thus, although the SAR of the tetrahydropyrimidinones parallels that of the cyclic ureas, there are some subtle differences that can be rationally explained.

Various cyclic structures, other than a cyclic urea, can also be envisioned with the diamino alcohol core. For example, following the same strategy used for the tetrahydropyrimidinones discussed above, one can cyclize the diamino alcohol core using oxalyl chloride

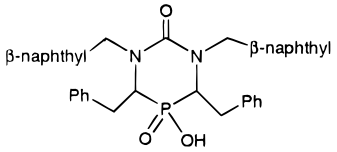
Chart 2. Other Cyclized Linear HIVPR Inhibitors



14
K_i = 40 nM (ref. 17)



15
K_i = 2.0 nM (ref. 18)



16
IC_{50} = 260 nM (ref. 21)

instead of CDI to yield the 7-membered cyclic oxamide **14**, which is also a good inhibitor of HIVPR.[17] Since DuPont Merck disclosed its work on the 7-membered ring cyclic ureas, there have been other examples of linear HIVPR inhibitors that have been cyclized to give potent cyclic compounds (Chart 2). Researchers at Abbott,[18] Ciba,[19] and DuPont Merck[20] have disclosed the cyclization of linear hydrazine inhibitors to give the azacyclic ureas **15**. Work published by Abbott shows these to be potent inhibitors of HIVPR. In addition, X-ray structures of complexes with HIV protease show that the azacyclic ureas have a similar conformation and binding mode as the cyclic ureas.[18] Researchers at Hoechst have cyclized their linear diamino phosphinic acids to give the 6-membered ring urea phosphinic acids **16**.[21] Although the cyclic phosphinic acids are mixtures of isomers and they do not have the optimal phenethyl P1′ substituent, they show surprisingly good activity.

Conclusion

The work reported here and the examples cited show that in general one can convert a linear HIVPR inhibitor into a potent cyclic inhibitor as long as one takes into account the conformation of the resulting cyclic compound and how that conformation will interact with the enzyme active site. In certain cases that will necessitate a modification of the substituents on the inhibitor for optimum interaction with the enzyme (for example, changing a benzyl into a phenethyl group). This method may be able to produce a larger diversity of potent, nonpeptide HIVPR inhibitors than are now available. We are continuing our efforts in expanding the scope of this method and will report on other examples in the near future.[26]

Experimental Section

Biological Methods. Inhibition of HIVPR was measured by the assay of the cleavage of a fluorescent substrate using HPLC as described previously.[9b] The antiviral activity potency of compounds was assessed by measuring their effect on the accumulation of viral RNA transcripts 3 days after infection of MT-2 cells with HIV-1RF as described previously.[22] The concentration of test compound which reduced the concentration of HIV viral RNA by 90% from the level measured in an untreated infected culture is designated IC_{90}.

Molecular Modeling. Molecular modeling studies were performed using SYBYL version 6.0, commercially available from Tripos Associates, Inc. and viewed on a Silicon Graphics Indigo^2 workstation. Models of tetrahydropyrimidinones were

built using SYBYL's build feature (Sketch Molecule and the Fragment library) and energy minimized to convergence using the MAXIMIN standard options (forcefield, Tripos; method, Powell; charge, Gasteiger−Huckel; dielectric constant, 1.0; termination, gradient 0.05 kcal/mol Å). Using the X-ray structure of DMP323 and/or DMP450 the tetrahydropyrimidinone models were manually docked to give the best overlap. Then an iterative process of manually adjusting the rotatable bonds on the models to best overlap with the 7-membered ring cyclic ureas was used followed by minimization using MAXIMIN until the difference was as small as possible. The final dihedral angle for the phenethyl side chain in the model was 127°, and the energy difference from the energy minimum was about 3 kcal. In the X-ray structure of **24**/HIVPR complex this angle was found to be 116°.

X-ray Crystallography. The complex of **24** with HIV-1 protease was crystallized as described previously.[8a] The unit cell dimensions of the complex are $a = b = 63.2$ Å and $c = 83.9$ Å. The diffraction data were collected with a R-AXIS II imaging plate mounted on an RU200 Rigaku rotating anode generator operating at 50 kV and 100 mA. Total 27 445 reflections were collected resulting in 11 937 unique reflections, and R_{sym} was 12.7%. The data-extended 2.0 Å resolution was 92% complete. The difference maps calculated with the proton coordinate of XK263[8a] revealed the corresponding inhibitor position. The structure was refined using the simulated annealing method, XPLOR.[24] The final *R*-factor using the reflections with intensities greater than 2s(*I*) was 0.215.

General. All reactions were carried out under an atmosphere of dry nitrogen. Commercial reagents were used without purther purification. ^{1}H NMR (300 MHz) spectra were recorded using tetramethylsilane as an internal standard. 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). All final targets were obtained as noncrystalline amorphous solids unless specified otherwise. Mass spectra were measured with a HP5988A mass spectrometer with particle beam interface using NH_3 for chemical ionization or a Finnigan MAT 8230 mass spectrometer with NH_3−DCI or VG TRIO 2000 for ESI. High-resolution mass spectra were measured on a VG 70-VSE instrument with NH_3 chemical ionization. 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%.

(4*R*,5*R*,6*R*)-Tetrahydro-5-*O*-[(2-methoxyethoxy)methyl]-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (5). A solution of D-Z-Phe (11.0 g, 0.037 mol) in THF was cooled to −20 °C and treated with *N*-methylmorpholine (4.0 g, 0.04 mol) followed by dropwise addition of isobutyl chloroformate (5.0 g, 0.037 mol), and the resulting solution was allowed to stir for 20 min. Then a slurry of *N*,*O*-dimethylhydroxylamine·HCl (4.9 g, 0.05 mol) in DMF (and neutralized with *N*-methylmorpholine) was added, and the resulting reaction mixture was stirred for 30 min. The volume was reduced at room temperature on a rotary evaporator and the residue dissolved in ethyl acetate, washed successively with water, 10% HCl, 10% $NaHCO_3$, and brine, and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure to give 12.6 g of the amide.

The crude amide was dissolved in ether, cooled to 0 °C (ice bath), and treated with vinylmagnesium bromide (120 mL, 1 M THF). The reaction mixture was stirred for 30 min at 0 °C. The reaction mixture was then poured while stirring into a mixture of HCl (concentrated) (30 mL)/ice/water (200 mL) and then extracted into ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated to give 11.5 g of the vinyl ketone as a pale yellow oil: CIMS (NH_3) *m*/*z* 327 ($M + NH_4^+$, 100).

A solution of the crude vinyl ketone in methanol was treated at room temperature with $CeCl_3 \cdot 7H_2O$ (13.8 g, 0.037 mol). The resultant solution was stirred vigorously while $NaBH_4$ (1.4 g, 0.037 mol) was added in very small portions (caution: vigorous foaming). After the addition was complete the reaction mixture was stirred at room temperature for 30 min and then concentrated on a rotary evaporator to one-third of the volume. The resulting solution was neutralized with 1 N HCl and the precipitate formed extracted into ethyl ether. The extracts were washed with water and brine, then dried over $MgSO_4$, and concentrated to give a white solid. This was chromatographed (MPLC, silica gel, 30% EtOAc/hexane) to give 7.5 g (65%, three steps) of the allylic alcohol **1** as a mixture of diastereomers: CIMS (NH_3) *m*/*z* 312 ($M + H^+$, 100).

A solution of the allylic alcohol **1** (31 g, 0.1 mol) in CH_2Cl_2 was cooled to 0 °C (ice bath) and treated with diisopropylethylamine (30 g, 0.23 mol). Then methanesulfonyl chloride (26 g, 0.23 mol) was added slowly and the mixture stirred for 1 h. The reaction mixture was transferred to a separatory funnel and washed with 1 N HCl, water, and brine. The solution was dried ($MgSO_4$) and concentrated to give the mesylate as an oil, which was used without further purification.

CuCN (12 g, 0.14 mol) in THF (100 mL) was cooled to −70 °C and treated slowly with benzylmagnesium chloride (360 mL, 2 M THF, 0.72 mol) via syringe. The solution was stirred at −70 °C for 20 min and then at 0 °C for 30 min and then cooled at −70 °C again before adding the mesylate above as a solution in THF (130 mL) via syringe. The reaction mixture was stirred at −70 °C for 60 min, poured into a mixture of 1 N HCl/ice, and extracted into EtOAc. The extract was washed with NH_4Cl (aqueous), NH_4OH, and brine, then dried over $MgSO_4$, and concentrated. The residue was chromatographed (MPLC, silica gel, 10% EtOAc/hexane) to give 11.7 g (30%, two steps) of the trans olefin **2** as a white solid: CIMS (NH_3) *m*/*z* 386 ($M + H^+$, 98), 403 ($M + NH_4^+$, 100).

A solution of the olefin **2** (11.0 g, 0.029 mol) in CH_2Cl_2 (75 mL) was cooled to 0 °C in an ice bath, treated with MCPBA (60%, 14 g, 0.048 mol), and stirred at 0 °C for 7 h. After the reaction was complete the solution was diluted with 100 mL of CH_2Cl_2 and washed successively with 1 N $Na_2S_2O_3$, 1 N NaOH, water, and brine. The solution was dried over $MgSO_4$ and concentrated to give 11.6 g of the epoxide as a thick oil, which was used without further purification.

To a solution of the epoxide in DMF (80 mL) were added NaN_3 (20 g, 0.3 mol), NH_4Cl (2.6 g, 0.05 mol), and 20 mL of water, and the resulting solution was heated at 85 °C for 3 h and then stirred overnight at room temperature. The solution was concentrated on a rotary evaporator under high vacuum at 60 °C and the resulting residue partitioned between water and CH_2Cl_2. The organic extract was washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed (MPLC, silica gel, 20% EtOAc/hexane) to give 7.4 g (58%, two steps) of the azido alcohol **3** as a white solid as the major isomer (about 4:1 ratio by NMR): CIMS (NH_3) *m*/*z* 445 ($M + H^+$).

A solution of the above azido alcohol **3** (7.2 g, 0.016 mol) in CH_2Cl_2 was treated with diisopropylamine (4.2 g, 0.032 mol) and MEM-Cl (4.0 g, 0.032 mol) and heated to reflux overnight. The solution was concentrated in vacuo, and the residue was chromatographed (MPLC, silica gel, 20% EtOAc/hexane) to give 7.7 g (90%) of the azido MEM ether **4** as a colorless oil: CIMS (NH_3) *m*/*z* 533 ($M + H^+$, 100).

A solution of azido MEM ether **4** (5.7 g, 0.0107 mol) in EtOAc was treated with 2 mL of acetic acid and 1 g of Pearlman's catalyst, and the mixture was hydrogenated at 55 psi of H_2 for 20 h. The solution was filtered (Celite) and then extracted with 1 N HCl (3 × 100 mL). The aqueous extract was made basic with 50% NaOH while cooling in an ice bath, and the resulting precipitate was extracted into EtOAc. The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to give 2.5 g of the diamine as a colorless oil: CIMS (NH_3) *m*/*z* 373 ($M + H^+$, 100).

A solution of the diamine (2.5 g, 0.0067 mol) in THF (75 mL) was treated with CDI (1.1 g, 0.0067 mol) and stirred at room temperature overnight. The reaction mixture was concentrated, and the residue was chromatographed (HPLC, silica gel, 5% MeOH/$CHCl_3$) to give 1.3 g (30%, two steps) of the tetrahydropyrimidinone **5**: ^{1}H NMR ($CDCl_3$) δ 7.37−7.15 (m, 10 H), 5.41 (bs, 1 H), 4.87 (d, $J = 8$ Hz, 1 H, ab), 4.78 (d, $J = 8$ Hz, 1 H, ab), 4.72 (bs, 1 H), 3.82 (m, 1 H), 3.72 (m, 2 H), 3.60 (bm, 2 H), 3.38 (s, 3 H), 2.97 (dd, $J = 5, 13$ Hz, 1 H, abx),

2.81 (m, 2 H, abx), 2.57 (m, 1 H, abx), 1.74 (m, 2 H); CIMS (NH_3) *m/z* 399 (M + H^+, 100); HRMS calcd for $C_{23}H_{32}N_2O_4$ (M + H^+) 399.2284, found 399.2279.

(4*R*,5*R*,6*R*)-Tetrahydro-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (17). A solution of tetrahydropyrimidinone **5** (30 mg) in methanol (2 mL) was treated with a saturated HCl/methanol solution (5 mL) and stirred at room temperature for 5 h. The mixture was evaporated to dryness in vacuo and the residue chromatographed (HPLC, Zorbax NH_2 column, 7% MeOH/CH_2Cl_2) to give 20 mg of a white solid: 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. ($C_{19}H_{22}N_2O_2$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis(cyclopropylmethyl)-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (18). Method 1: From Tetrahydropyrimidinone 5. To a suspension of NaH (60 mg, 1.5 mmol, 60% oil dispersion) in DMF was added tetrahydropyrimidinone **5** (100 mg, 0.27 mmol), and the mixture was stirred at room temperature for 30 min. To the resulting solution was added (bromomethyl)cyclopropane (250 mg, 1.8 mmol), and the mixture was stirred at room temperature for 30 min and then at 60 °C for 30 min. The reaction mixture was diluted with 5% HCl (aqueous) and extracted into EtOAc. The organic extracts were washed with water and brine, then dried ($MgSO_4$), and concentrated. The residue was chromatographed (HPLC, silica gel, 50% EtOAc/hexane) to give 35 mg of the N,N-dialkylated tetrahydropyrimidinone as a colorless film: CIMS (NH_3) *m/z* 507 (M + H^+, 100).

A solution of the N,N-dialkylated tetrahydropyrimidinone (25 mg) in MeOH was treated with HCl (gas) for 20 min and then stirred at room temperature for 1 h. The solution was evaporated to dryness in vacuo, and the residue was chromatographed (HPLC, silica gel, 10% MeOH/$CHCl_3$) to give 20 mg of **18** as a colorless film: ^{1}H NMR ($CDCl_3$) δ 7.38−7.12 (m, 8 H), 7.05 (d, *J* = 7 Hz, 2 H), 3.92 (dd, *J* = 7, 14 Hz, 1 H, abx), 3.85 (dd, *J* = 7, 14 Hz, 1 H, abx), 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, abx), 2.67 (dd, *J* = 7, 14 Hz, 1 H, abx), 2.51 (m, 2 H), 2.30 (d, 10 Hz, 1 H), 2.96 (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.

Method 2: From 7-Membered Cyclic Urea. To 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-diazapin-2-one (200 mg, 0.46 mmol) in CH_2Cl_2 (6 mL) at room temperature was added 2-acetoxyisobutyryl bromide (300 mg, 1.4 mmol), and the solution was stirred at room temperature for 15 min at which time TLC showed complete conversion. The reaction was quenched with saturated $NaHCO_3$, and the organic layer was separated, washed with water and brine, dried, and concentrated to give 250 mg of the corresponding bromo acetate. The crude bromo acetate was dissolved in 10 mL of acetic acid, treated with 2 g of Zn (dust), 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, dried, and evaporated to give the acetate as an oil. The crude acetate was dissolved in MeOH, treated with 1 N NaOH, and stirred at room temperature. The mixture was concentrated, and the residue was partitioned between 1 N HCl and EtOAc. The organic extract was washed with water and brine, dried, and concentrated, and the resulting residue was chromatographed (HPLC, silica gel, 10% MeOH/$CHCl_3$) to give 20 mg of **18** as a colorless film identical in every respect with that obtained via method 1.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis[(3-cyanophenyl)methyl]-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (6). Method 1: From Tetrahydropyrimidinone 5. To a suspension of NaH (200 mg, 5 mmol, 60% oil dispersion) in DMF was added tetrahydropyrimidinone **5** (500 mg, 1.3 mmol), and the mixture was stirred at room temperature for 30 min. To the resulting solution was added 3-cyanobenzyl bromide (800 mg, 4 mmol), and the mixture was stirred at room temperature for 45 min. The reaction mixture was diluted with 5% HCl (aqueous) and extracted into EtOAc. The organic extracts were washed with water and brine, then dried ($MgSO_4$), and concentrated. The residue was chromatographed (HPLC, silica gel, 50% EtOAc/hexane) to give 560 mg of the N,N-dialkylated tetrahydropyrimidinone: CIMS (NH_3) *m/z* 629 (M + H^+, 100).

A solution of the N,N-dialkylated tetrahydropyrimidinone (75 mg) in MeOH was treated with 4 N HCl/dioxane and stirred at room temperature overnight. The solution was evaporated to dryness in vacuo, and the residue was chromatographed (HPLC, silica gel, 50% EtOAc/hexane) to give 35 mg of **6** as a foam.

Method 2: From 7-Membered Cyclic Urea. To a solution of (4*R*,5*S*,6*S*,7*R*)-hexahydro-5,6-dihydroxy-1,3-bis[(3-cyanophenyl)methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazapin-2-one[8c] (1.0 g, 1.8 mmol) in CH_2Cl_2 (20 mL) at room temperature was added 2-acetoxyisobutyryl bromide (0.56 g, 2.7 mmol), and the solution was stirred at room temperature for 15 min at which time TLC showed complete conversion. The reaction was quenched with saturated $NaHCO_3$, and the organic layer was separated, washed with water and brine, dried, and concentrated to give 1.1 g of the rearranged bromo acetate. The crude bromo acetate (1.0 g) was dissolved in 50 mL of acetic acid, treated with 7 g of Zn (dust), and vigorously stirred at room temperature until TLC analysis showed complete conversion. The mixture was filtered, and the solid was washed thoroughly with EtOAc. The filtrate was washed with water, saturated $NaHCO_3$, and brine, dried, and evaporated to give the acetate. The crude acetate was chromatographed (MPLC, silica gel, 65% EtOAc/hexane) to give 820 mg of acetate as a white foam. The pure acetate (400 mg, 0.68 mol) was dissolved in MeOH, treated with 1 N NaOH, and stirred at room temperature. The mixture was concentrated, and the residue was partitioned between 1 N HCl and EtOAc. The organic extract was washed with water and brine, dried, and concentrated and the resulting residue chromatographed (MPLC, silica gel, 65% EtOAc/hexane) to give 300 mg of **6** as a foam identical in every respect with that obtained via method 1: ^{1}H NMR ($CDCl_3$) δ 7.59−7.41 (m, 8 H), 7.38−7.21 (m, 6 H), 7.00 (dd, *J* = 7, 16 Hz, 4 H), 5.23 (d, *J* = 15 Hz, 1 H), 5.13 (d, *J* = 16 Hz, 1 H), 4.25 (d, *J* = 16 Hz, 1 H), 3.91 (d, *J* = 15 Hz, 1 H), 3.56 (m, 2 H), 3.14 (m, 1 H), 2.88 (m, 2 H), 2.40 (m, 2 H), 1.90 (m, 1 H), 1.76 (d, *J* = 8 Hz, 1 H), 1.62 (m, 2 H); CIMS (NH_3) *m/z* 541 (M + H^+, 100); HRMS calcd for $C_{35}H_{33}N_4O_2$ (M + H^+) 541.2604, found 541.2587; $[\alpha]^{25}_D$ −10.38° (*c* 0.212, $CHCl_3$). Anal. ($C_{35}H_{32}N_4O_2 \cdot 0.33H_2O$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3,6-tris(phenylmethyl)-5-hydroxy-4-(2-phenylethyl)-2(1*H*)-pyrimidinone (19). To a solution of (4*R*,5*S*,6*S*,7*R*)-hexahydro-5,6-dihydroxy-1,3,4,7-tetrakis(phenylmethyl)-2*H*-1,3-diazapin-2-one[8c] (1.3 g, 2.6 mmol) in CH_2Cl_2 (40 mL) at room temperature was added 2-acetoxyisobutyryl bromide (1.7 g, 8.1 mmol), and the solution was stirred at room temperature for 15 min at which time TLC showed complete conversion. The reaction was quenched with saturated $NaHCO_3$, and the organic layer was separated, washed with water and brine, dried, and concentrated to the rearranged bromo acetate. The crude bromo acetate was chromatographed (MPLC, silica gel, 30% EtOAc/hexane) to give 1.4 g of **9**. A small fraction of the eluent from this chromatography was allowed to evaporate slowly to give crystals of the bromo acetate **9** that were of sufficient quality for single-crystal X-ray analysis. For **9**: mp 178−180 °C. Anal. ($C_{35}H_{35}N_2O_3Br \cdot 0.2C_6H_{14}$) C, H, N.

The bromo acetate **9** (1.0 g) was dissolved in 50 mL of acetic acid, treated with Zn (dust) (7 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, dried, and evaporated to give the acetate. The crude acetate was chromatographed (MPLC, silic gel, 65% EtOAc/hexane) to give 820 mg of acetate as a

white foam. The pure acetate (400 mg, 0.68 mol) was dissolved in MeOH, treated with 1 N NaOH (5 mL), and stirred at room temperature. The mixture was concentrated, and the residue was partitioned between 1 N HCl and EtOAc. The organic extract was washed with water and brine, dried, and concentrated, and the resulting 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. ($C_{33}H_{34}N_2O_2$) C, H, N.

Crystallographic Data for 9. Empirical formula: $C_{35}H_{35}N_2O_3Br$, from 30% EtOAc/hexane, colorless, flat needle, 0.07 × 0.15 × 0.90 mm, monoclinic, $P2_1$ (No. 4); a = 11.131(1), b = 11.908(1), c = 12.776(1) Å; β = 111.747(5)°; T = −51 °C; V = 1572.9 Å^3, Z = 2; FW = 611.59, D_c = 1.291 g/cc, μ(Mo) = 13.27 cm^{-1}. Data were collected on a Rigaku RU300, R-AXIS image plate area detector, Mo Kα radiation, anode power = 50 Kv × 120 ma, crystal to plate distance = 85.0 mm, 210 μm pixel raster, number of frames = 31, oscillation range = 6.0°/frame, exposure = 4.0 min/frame, box sum integration, 8344 data collected, 3.4° ≤ 2θ ≤ 48.3°, maximum h, k, l = 12, 13, 14, no absorption correction, 2332 duplicates, 7.4% R-merge, 1880 unique reflections with $I \geq 3.0\sigma(I)$. Structure was solved by direct methods (MULTAN) [difficult solution complicated by disorder in one of the phenyl rings. The asymmetric unit consists of one molecule in a general position. Hydrogen atoms are idealized with C−H = 0.95 Å. The acentric space group indicates an enantiomeric isomer which is in agreement with the calculated intensity differences for the anomalous terms of bromine (R, R_w = 6.29/5.82 vs 6.57/6.31 for the inverted structure)], refinement by full-matrix least-squares on F, scattering factors from *International Tables for X-ray Crystallography*, Vol. IV, including anomalous terms for Br, biweight α [$\sigma^2(I) + 0.0009(I)^2$]^2 (excluded 20); refined anisotropic, all nonhydrogen atoms; fixed atoms, H; 369 parameters, data/parameter ratio = 5.04, R = 0.063, R_w = 0.058, error of fit = 1.82, max Δ/σ = 0.15, largest residual density = 0.40 e/Å^3.

(4*S*,5*S*,6*S*)-Tetrahydro-1,3-bis[(3-cyanophenyl)methyl]-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (31). Same procedure as that used to synthesize **6** (using method 2) but starting with the enantiomeric cyclic urea (4*S*,5*R*,6*R*,7*S*)-hexahydro-5,6-dihydroxy-1,3-bis[(3-cyanophenyl)methyl]-4,7-bis(phenylmethyl)-2*H*-1,3-diazapin-2-one was used to give **31**: ^{1}H NMR ($CDCl_3$) δ 7.59−7.41 (m, 8 H), 7.38−7.21 (m, 6 H), 7.00 (dd, J = 7, 16 Hz, 4 H), 5.23 (d, J = 15 Hz, 1 H), 5.13 (d, J = 16 Hz, 1 H), 4.25 (d, J = 16 Hz, 1 H), 3.91 (d, J = 15 Hz, 1 H), 3.56 (m, 2 H), 3.14 (m, 1 H), 2.88 (m, 2 H), 2.40 (m, 2 H), 1.90 (m, 1 H), 1.76 (d, J = 8 Hz, 1 H), 1.62 (m, 2 H); CIMS (NH_3) m/z 541 (M + H^+, 100); HRMS calcd for $C_{35}H_{33}N_4O_2$ (M + H^+) 541.2604, found 541.2584; [α]$^{25}_D$ +6.84° (*c* 0.190, $CHCl_3$). Anal. ($C_{35}H_{32}N_4O_2 \cdot 0.2H_2O$) C, H, N.

(4*S*,5*S*,6*S*)-Tetrahydro-1,3-bis[(3-benzamido)methyl]-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (32). The cyano group of **31** was converted to the amide using the DMSO/H_2O_2 procedure[23] to give **32**: ^{1}H NMR ($CDCl_3$) δ 7.97 (s, 1 H), 7.84 (s, 1 H), 7.66 (bm, 2 H), 7.32−7.12 (m, 12 H), 7.05 (d, J = 7 Hz, 2 H), 6.93 (d, J = 16 Hz, 2 H), 6.88 (bs, 1 H), 6.57 (bs, 1 H), 5.23 (d, J = 16 Hz, 1 H), 4.80 (d, J = 16 Hz, 1 H), 4.58 (d, J = 16 Hz, 1 H), 4.30 (bs, 1 H), 3.96 (d, J = 16 Hz, 1 H), 3.60 (m, 2 H), 3.22 (m, 1 H), 2.82 (d, J = 7 Hz, 2 H), 2.32 (t, J = 8 Hz, 2 H), 1.94 (m, 1 H), 1.57 (m, 1 H); CIMS (NH_3) m/z 577 (M + H^+, 100); HRMS calcd for $C_{35}H_{37}N_4O_4$ (M + H^+) 577.2815, found 577.2809. Anal. ($C_{35}H_{36}N_4O_4 \cdot C_2H_5OH$) C, H, N.

(4*S*,5*S*,6*S*)-Tetrahydro-1,3-bis[(3-benzamide oxime)-methyl]-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (33). An ethanol solution of **31** was treated with excess $NH_2OH \cdot HCl/Et_3N$ and heated (EtOH) to reflux for 4 h to give the amidoxime **33**: ^{1}H NMR ($CDCl_3/CD_3OD$) δ 7.67 (bs, 1 H), 7.52 (bs, 1 H), 7.45 (m, 2 H), 7.30−7.12 (m, 10 H), 6.98 (m, 4 H), 6.10 (bs, 2 H), 5.22 (d, J = 15 Hz, 1 H), 4.87 (d, J = 15 Hz, 1 H), 4.11 (d, J = 15 Hz, 1 H), 3.94 (d, J = 15 Hz, 1 H), 3.51 (m, 2 H), 3.21 (m, 1 H), 2.78 (m, 2 H, abx), 2.36 (t, J = 8 Hz, 2 H), 1.90 (m, 1 H), 1.65 (m, 2 H); ESIMS m/z 304 (M + 2H^{2+}, 100); HRMS calcd for $C_{35}H_{39}N_6O_4$ (M + H^+) 607.3033, found 607.3016.

(4*S*,5*S*,6*S*)-Tetrahydro-1,3-bis[(3-carbomethoxyphenyl)-methyl]-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (34). A solution of **32** in methanol was treated with H_2SO_4 and heated at reflux for 24 h to give the methyl ester **34**: ^{1}H NMR ($CDCl_3$) δ 7.95 (m, 4 H), 7.56 (m, 1 H), 7.42 (m, 3 H), 7.22 (m, 6 H), 7.00 (dd, J = 7, 16 Hz, 4 H), 5.39 (d, J = 15 Hz, 2 H), 3.98 (d, J = 15 Hz, 1 H), 3.93 (d, J = 15 Hz, 1 H), 3.91 (s, 3 H), 3.84 (s, 3 H), 3.52 (m, 1 H), 3.41 (m, 1 H), 3.19 (m, 1 H), 2.87 (m, 2 H), 2.41 (m, 2 H) 1.90 (m, 1 H), 1.87−1.59 (m, 2 H); CIMS (NH_3) m/z 607 (M + H^+, 100); HRMS calcd for $C_{37}H_{39}N_2O_6$ (M + H^+) 607.2808, found 607.2787. Anal. ($C_{37}H_{38}N_2O_6$) C, H, N.

(4*S*,5*S*,6*S*)-Tetrahydro-1,3-bis[[3-(hydroxymethyl)-phenyl]methyl]-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (35). A solution of **34** in THF was treated with LAH at 0 °C for 3 h to give the alcohol **35**: ^{1}H NMR ($CDCl_3$) δ 7.36−7.08 (m, 14 H), 6.95 (dd, J = 7, 16 Hz, 4 H), 5.21 (d, J = 15 Hz, 1 H), 5.19 (d, J = 15 Hz, 1 H), 4.61 (bm, 4 H), 4.01 (d, J = 15 Hz, 1 H), 3.95 (d, J = 15 Hz, 1 H), 3.41 (m, 2 H), 3.18 (m, 1 H), 2.90 (m, 2 H), 2.79 (bm, 1 H), 2.50 (bm, 1 H), 2.33 (m, 3 H), 1.85 (m, 1 H), 1.57 (m, 1 H); CIMS (NH_3) m/z 551 (M + H^+, 100); HRMS calcd for $C_{35}H_{39}N_2O_4$ (M + H^+) 551.2910, found 551.2894. Anal. ($C_{35}H_{38}N_2O_4 \cdot 0.75H_2O$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis[(3-carbomethoxyphenyl)-methyl]-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (20). The same procedure described for **19** above was used: mp 156−158 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (m, 4 H), 7.56 (m, 1 H), 7.42 (m, 3 H), 7.22 (m, 6 H), 7.00 (dd, J = 7, 16 Hz, 4 H), 5.39 (d, J = 15 Hz, 2 H), 3.98 (d, J = 15 Hz, 1 H), 3.93 (d, J = 15 Hz, 1 H), 3.91 (s, 3 H), 3.84 (s, 3 H), 3.52 (m, 1 H), 3.41 (m, 1 H), 3.19 (m, 1 H), 2.87 (m, 2 H), 2.41 (m, 2 H), 1.90 (m, 1 H), 1.87−1.59 (m, 2 H); CIMS (NH_3) m/z 607 (M + H^+, 100); HRMS calcd for $C_{37}H_{39}N_2O_6$ (M + H^+) 607.2808, found 607.2808. Anal. ($C_{37}H_{38}N_2O_6$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis[[3-(hydroxymethyl)-methyl]-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (21). A solution of **20** in THF was treated with LAH at 0 °C for 3 h to give the alcohol **21**: mp 58−61 °C; ^{1}H NMR ($CDCl_3$) δ 7.36−7.08 (m, 14 H), 6.95 (dd, J = 7, 16 Hz, 4 H), 5.22 (d, J = 15 Hz, 1 H), 5.18 (d, J = 15 Hz, 1 H), 4.61 (bm, 4 H), 4.01 (d, J = 15 Hz, 1 H), 3.95 (d, J = 15 Hz, 1 H), 3.41 (m, 2 H), 3.18 (m, 1 H), 2.90 (m, 2 H), 2.79 (bm, 1 H), 2.50 (bm, 1 H), 2.33 (m, 3 H), 1.85 (m, 1 H), 1.57 (m, 1 H); CIMS (NH_3) m/z 551 (M + H^+, 100); HRMS calcd for $C_{35}H_{39}N_2O_4$ (M + H^+) 551.2910, found 551.2886. Anal. ($C_{35}H_{38}N_2O_4 \cdot 0.5H_2O$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis[(3-benzamido)methyl]-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (23). The cyano group of **6** was converted to the amide using the DMSO/H_2O_2 procedure to give **23**: mp 105−108 °C; ^{1}H NMR ($CDCl_3$) δ 7.97 (s, 1 H), 7.84 (s, 1 H), 7.66 (bm, 2 H), 7.32−7.12 (m, 12 H), 7.05 (d, J = 7 Hz, 2 H), 6.93 (d, J = 16 Hz, 2 H), 6.88 (bs, 1 H), 6.57 (bs, 1 H), 5.23 (d, J = 16 Hz, 1 H), 4.80 (d, J = 16 Hz, 1 H), 4.58 (d, J = 16 Hz, 1 H), 4.30 (bs, 1 H), 3.96 (d, J = 16 Hz, 1 H), 3.60 (m, 2 H), 3.22 (m, 1 H), 2.82 (d, J = 7 Hz, 2 H), 2.32 (t, J = 8 Hz, 2 H), 1.94 (m, 1 H), 1.57 (m, 1 H); CIMS (NH_3) m/z 577 (M + H^+, 100). Anal. ($C_{35}H_{36}N_4O_4 \cdot H_2O$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis[(4-fluoro-3-benzamido)-methyl]-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (27). The cyano group was converted to the amide using the DMSO/H_2O procedure to give **27**: mp 106−109 °C; ^{1}H NMR ($CDCl_3$) δ 8.00 (m, 2 H), 7.50 (m, 1 H), 7.40 (m, 1 H), 7.26−6.96 (m, 12 H), 6.70 (bd, J = 11 Hz, 2 H), 6.13 (bs, 2 H), 5.22 (d, J = 15 Hz, 1 H), 5.06 (d, J = 15 Hz, 1 H), 4.09 (d, J = 15 Hz, 1 H), 3.99 (d, J = 15 Hz, 1 H), 3.47 (m, 2 H), 3.22 (m, 1 H), 2.85 (m, 2 H), 2.38 (m, 2 H), 1.90 (m, 1 H), 1.86 (bs, 1 H), 1.63 (m, 1 H); CIMS (NH_3) m/z 613 (M + H^+, 100). Anal. ($C_{35}H_{34}N_4O_4F_2$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis[(4-carbomethoxyphenyl)-methyl]-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (30). The same procedure described for

20 above was used: mp 72−75 °C; ^{1}H NMR ($CDCl_3$) δ 8.0 (m, 4 H), 7.2 (m, 10 H), 7.0 (m, 4 H), 5.4 (d, J = 16 Hz, 1 H), 5.3 (d, J = 15 Hz, 1 H), 4.1 (d, J = 16 Hz, 1 H), 3.96 (d, J = 15 Hz, 1 H), 3.96 (s, 3 H), 3.93 (s, 3 H), 3.45 (m, 1 H), 3.40 (m, 1 H), 3.15 (m, 1 H), 2.95 (m, 2 H), 2.40 (m, 2 H), 1.90 (m, 1 H), 1.76 (d, J = 8 Hz, 1 H), 1.61 (m, 2 H); CIMS (NH_3) m/z 607 (M + H^+, 100); HRMS calcd for $C_{37}H_{39}N_2O_6$ (M + H^+) 607.2808, found 607.2797. Anal. ($C_{37}H_{38}N_2O_6 \cdot 0.15H_2O$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis[[4-(hydroxymethyl)phenyl]methyl]-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (29). A solution of **30** in THF was treated with LAH at 0 °C for 3 h to give the alcohol **29**: ^{1}H NMR ($CDCl_3$) δ 7.32−7.18 (m, 14 H), 7.03−6.97 (m, 4 H), 5.33 (d, J = 15 Hz, 2 H), 4.66 (s, 2 H), 4.63 (s, 2 H), 3.83 (d, J = 15 Hz, 1 H), 3.80 (d, J = 15 Hz, 1 H), 3.41 (m, 1 H), 3.35 (m, 1 H), 3.15 (m, 1 H), 2.85 (m, 1 H), 2.40 (m, 1 H), 2.14 (bs, 1 H), 1.95 (bs, 1 H), 1.85 (m, 1 H), 1.70 (bs, 1 H), 1.60 (m, 1 H); CIMS (NH_3) m/z 551 (M + H^+, 100). Anal. ($C_{35}H_{38}N_2O_4 \cdot 0.25H_2O$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis[(3-hydroxyphenyl)methyl]-5-hydroxy-4-(2-phenylethyl)-6-(phenylethyl)-2(1*H*)-pyrimidinone (11): mp 93−95 °C; ^{1}H NMR ($CDCl_3$) δ 7.91 (bs, 2 H), 7.25−6.84 (m, 14 H), 6.73−6.59 (m, 4 H), 5.07 (d, J = 15 Hz, 1 H), 4.98 (d, J = 16 Hz, 1 H), 3.95 (d, J = 16 Hz, 1 H), 3.85 (d, J = 15 Hz, 1 H), 3.40 (m, 2 H), 3.15 (m, 1 H), 2.8 (m, 2 H), 2.3 (bs, 1 H), 2.25 (m, 2 H), 1.78 (m, 1 H), 1.48 (m, 1 H); CIMS (NH_3) m/z 523 (M + H^+, 100). Anal. ($C_{33}H_{34}N_2O_4 \cdot 0.25H_2O$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis[(3-aminophenyl)methyl]-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (25): mp 89−92 °C; ^{1}H NMR ($CDCl_3$) δ 7.29−7.00 (m, 14 H), 6.64−6.54 (m, 6 H), 5.37 (d, J = 15 Hz, 1 H), 5.32 (d, J = 15 Hz, 1 H), 3.77 (d, J = 16 Hz, 1 H), 3.70 (d, J = 15 Hz, 1 H), 3.63 (bs, 2 H), 3.41 (bm, 1 H), 3.34 (m, 1 H), 3.18 (m, 1 H), 2.90 (m, 2 H, abx), 2.42 (m, 2 H), 1.95 (bs, 1 H), 1.85 (m, 1 H), 1.62 (m, 1 H); CIMS (NH_3) m/z 523 (M + H^+, 100). Anal. ($C_{33}H_{36}N_4O_2 \cdot 0.1C_4H_8O_2$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis[(4-amino-3-fluorophenyl)methyl]-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (28): mp 68−70 °C; ^{1}H NMR ($CDCl_3$) δ 7.29−7.17 (m, 6 H), 7.07−6.95 (m, 4 H), 6.92−6.81 (m, 4 H), 6.76−6.68 (m, 2 H), 5.33 (d, J = 16 Hz, 1 H), 5.28 (d, J = 15 Hz, 1 H), 3.76 (d, J = 16 Hz, 1 H), 3.67 (d, J = 15 Hz, 1 H), 3.71 (bs, 4 H), 3.40 (m, 1 H), 3.30 (m, 1 H), 3.15 (m, 1 H), 2.88 (m, 2 H, abx), 2.41 (t, J = 8 Hz, 2 H), 1.85 (m, 1 H), 1.61 (m, 1 H), 1.61 (bs, 1 H); CIMS (NH_3) m/z 557 (M + H^+, 100). Anal. $C_{33}H_{34}N_4O_2F_2$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis[(3-amino-4-fluorophenyl)methyl]-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (22): mp 68−70 °C; ^{1}H NMR ($CDCl_3$) δ 7.30−7.17 (m, 6 H), 7.06−6.85 (m, 6 H), 6.72−6.64 (m, 2 H), 6.58−6.50 (m, 2 H), 5.32 (d, J = 15 Hz, 1 H), 5.24 (d, J = 15 Hz, 1 H), 3.83 (d, J = 15 Hz, 1 H), 3.68 (d, J = 15 Hz, 1 H), 3.60 (bs, 4 H), 3.41 (m, 1 H), 3.35 (m, 1 H), 3.16 (m, 1 H), 2.90 (m, 2 H, abx), 2.41 (t, J = 8 Hz, 2 H), 1.83 (m, 1 H), 1.70 (bs, 1 H), 1.60 (m, 1 H); CIMS (NH_3) m/z 557 (M + H^+, 100). Anal. ($C_{33}H_{34}N_4O_2F_2 \cdot 0.5H_2O$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis[[3-(*N*-methylamino)phenyl]methyl]-5-hydroxy-4-(2-phenylethyl)-6-(phenylmethyl)-2(1*H*)-pyrimidinone (26): mp 65−66 °C deg; ^{1}H NMR ($CDCl_3$) δ 7.28−7.00 (m, 12 H), 6.62−6.46 (m, 6 H), 5.44 (d, J = 15 Hz, 1 H), 5.39 (d, J = 14 Hz, 1 H), 3.79 (d, J = 15 Hz, 1 H), 3.72 (d, J = 14 Hz, 1 H), 3.70 (bs, 2 H), 3.4 (bm, 1 H), 3.35 (m, 1 H), 3.31 (m, 1 H), 3.00−2.83 (m, 2 H, abx), 2.80 (s, 3 H), 2.76 (s, 3 H), 2.44 (t, J = 7 Hz, 2 H), 1.85 (m, 1 H), 1.75 (bs, 1 H), 1.65 (m, 1 H); CIMS (NH_3) m/z 549 (M + H^+, 100). Anal. ($C_{35}H_{40}N_4O_2 \cdot 0.25H_2O$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis[(3-benzamide oxime)methyl]-5-hydroxy-4-(2-phenylethyl)-6-(phenylethyl)-2-(1*H*)-pyrimidinone (24). The cyano group of **6** was converted to the amidoxime by treatment with $NH_2OH \cdot HCl/Et_3N$ in refluxing EtOH to give **24**: mp 119−121 °C; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 7.67 (bs, 1 H), 7.52 (bs, 1 H), 7.45 (m, 2 H), 7.30−7.12 (m, 10 H), 6.98 (m, 4 H), 6.10 (bs, 2 H), 5.22 (d, J = 15 Hz, 1 H), 4.87 (d, J = 15 Hz, 1 H), 4.11 (d, J = 15 Hz, 1 H), 3.94 (d, J = 15 Hz, 1 H), 3.51 (m, 2 H), 3.21 (m, 1 H), 2.78 (m, 2 H, abx), 2.36 (t, J = 8 Hz, 2 H), 1.90 (m, 1 H), 1.65 (m, 2 H); ESIMS m/z 304 (M + $2H^{2+}$, 100). Anal. ($C_{35}H_{38}N_6O_4 \cdot 0.25H_2O$) C, H, N.

(4*R*,5*R*,6*R*)-Tetrahydro-1,3-bis[(3-hydroxyphenyl)methyl]-5-hydroxy-4,6-bis(phenylmethyl)-2(1*H*)-pyrimidinone (13). The procedure described by Abbott[11b] was used to obtain the azido alcohol, and then following the procedure described above for **5** and **6** (method 1, using 3-benzoxybenzyl chloride as the alkylating agent) gave, after hydrogenolysis, the desired phenol **13**: ^{1}H NMR ($CDCl_3$) δ 7.13−6.98 (m, 8 H), 6.93−6.71 (m, 3 H), 6.69 (s, 1 H), 6.67−6.64 (m, 6 H), 5.07 (d, J = 16 Hz, 1 H), 4.94 (d, J = 15 Hz, 1 H), 4.13 (d, J = 16 Hz, 1 H), 3.86 (d, J = 15 Hz, 1 H), 3.50 (m, 1 H), 3.30 (m, 1 H), 3.21 (m, 1 H), 2.92 (m, 1 H, abx), 2.71 (m, 2 H, 2 overlapping abx), 2.29 (m, 1 H, abx), 1.70 (bs, 3 H); CIMS (NH_3) m/z 509 (M + H^+, 100); HRMS calcd for $C_{32}H_{33}N_2O_4$ (M + H^+) 509.2440, found 509.2456.

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Supporting Information Available: Text describing single-crystal X-ray analysis of **9** and tables giving fractional coordinates, thermal parameters, bond distances and angles, and nonbonding distances (6 pages). Ordering information is given on any current masthead page.

References

(1) (a) Questions regarding the single-crystal X-ray structure of compound **9** should be addressed to J. Calabrese at DuPont, CR&D Experimental Station, P.O. Box 80228, Wilmington, DE 19880−0228. (b) Questions regarding the X-ray structure of **24**/HIVPR complex should be addressed to C.-H. Chang at DuPont Merck Pharmaceutical Co., Experimental Station, P.O. Box 80228, Wilmington, DE 19880−0228.

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