Stereoisomers of Cyclic Urea HIV-1 Protease Inhibitors: Synthesis and Binding Affinities

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Stereoisomers of Cyclic Urea HIV-1 Protease Inhibitors: Synthesis and Binding Affinities

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We have synthesized stereoisomers of cyclic urea HIV-1 protease inhibitors to study the effect of varying configurations on binding affinities. Four different synthetic approaches were used to prepare the desired cyclic urea stereoisomers. The original cyclic urea synthesis using amino acid starting materials was used to prepare three isomers. Three additional isomers were prepared by synthetic routes utilizing L-tartaric acid and D-sorbitol as chiral starting materials. A stereoselective hydroxyl inversion of the cyclic urea *trans*-diol was used to prepare three additional isomers. In all 9 of the 10 possible cyclic urea stereoisomers were prepared, and their binding affinities are described.

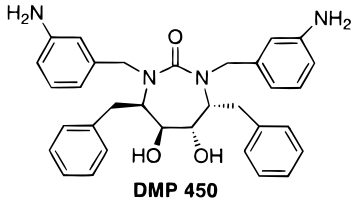
Introduction

Human immunodeficiency virus (HIV) has been shown to be the causative agent of acquired immunodeficiency syndrome (AIDS). There has been an intense effort to find inhibitors of the HIV-1-encoded aspartyl protease (HIV-Pr) which plays an essential role in the maturation of immature virion proteins. We have described a novel series of highly potent cyclic urea HIV-Pr inhibitors which were designed to displace the active site structural water.[1] Compounds of this class have shown picomolar binding affinities and good oral bioavailability in animals. Currently clinical candidate DMP 450 (Chart 1) has been shown to be a potent HIV-Pr inhibitor with a good pharmacokinetic profile in humans and will be entering further clinical trials.[2]

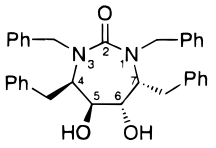
Cyclic ureas were designed to bind to HIV-Pr with the diol oxygens symmetrically hydrogen binding to the catalytic Asp 25/25′. The rigid cyclic urea scaffold allows for the optimal binding interactions of the P1/P1′ and P2/P2′ residues with their corresponding pockets in the active site. Modeling studies have predicted the optimal stereochemistry for substituted cyclic ureas to be 4*R*,5*S*,6*S*,7*R*. This allows a conformation where pseudodiaxial benzyl groups project into the S1/S1′ pockets and pseudodiequatorial hydroxyl groups bind with the Asp 25/25′ residues. The importance of the correct absolute stereochemistry was demonstrated by the 1000-fold difference in potency between the P2/P2′ allyl-substituted *RSSR* cyclic urea and its enantiomer.[1] We have attempted to synthesize each remaining cyclic urea isomer to study the effect of varying stereochemistry on binding affinities.

The relationship between binding affinity and stereochemistry has recently been demonstrated for a series of P1/P1′ phenoxymethyl-substituted cyclic urea analogues.[3] A series of four C_2-symmetrical stereoisomers were prepared, and their activity against HIV-Pr was compared to the calculated binding free energies. As predicted, the *RSSR* isomer was most active with a reported K_i = 12 nM. The *SRRS*, *SSSS*, and *RRRR* isomers showed a large decrease in binding with little or no activity at micromolar concentrations.

Chart 1



DMP 450



1: (4R, 5S, 6S, 7R)

Although our molecular modeling predicts the cyclic urea *RSSR* stereoisomer to be the most potent, multiple binding modes to HIV-Pr might exist. There are a number of examples of nonspecific binding of stereoisomers to HIV-Pr in other protease inhibitor classes. Nonspecific binding to the catalytic aspartate residues has been described for the hydroxyethylamine dipeptide isosteres[4] and the C_2-symmetry-based diaminodiol[5] inhibitors of HIV-Pr. In both cases a conformational shift yields an alternate binding mode allowing the hydroxyl residues to bind to the catalytic site.[6] Recently, the lack of stereospecificity in binding of a diastereomer of Ritonavir was described.[7] Inversion of the valinyl P2 side chain of Ritonavir did not change the inhibitory potency or the pharmacokinetic properties. Comparing the diastereomer's X-ray crystal structures bound to HIV-Pr showed a backbone conformational shift permitting the valine residues of both inhibitors to bind to the S2 pocket. This shift preserved other important hydrogen-bonding interactions giving equivalent binding affinities. We desired to synthesize all possible cyclic urea stereoisomers to determine if a conformational shift or alternate binding mode could yield an isomer with equal or greater binding affinity.

Chemistry

With 4 contiguous chiral centers, there are 10 possible symmetrically substituted cyclic urea stereoisomers.

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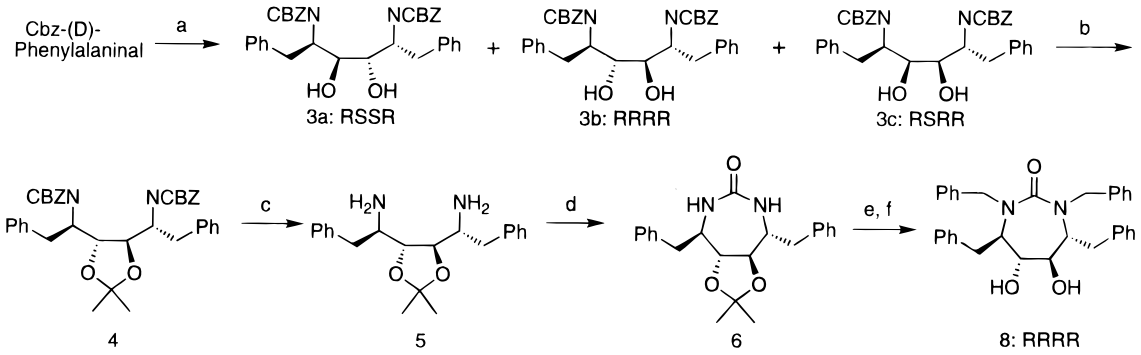
Scheme 1[a]



[a] Reagents: (a) VCl_3·$(THF)_3$, Zn, THF; (b) 2,2-dimethoxypropane, (±)-camphorsulfonic acid, CH_2Cl_2, filter; (c) $Pd(OH)_2$/C, H_2, 98%; (d) 1,1′-CDI, CH_2Cl_2, 81%; (e) NaH, BnBr, DMF, 79%; (f) HCl, MeOH, H_2O, 95%.

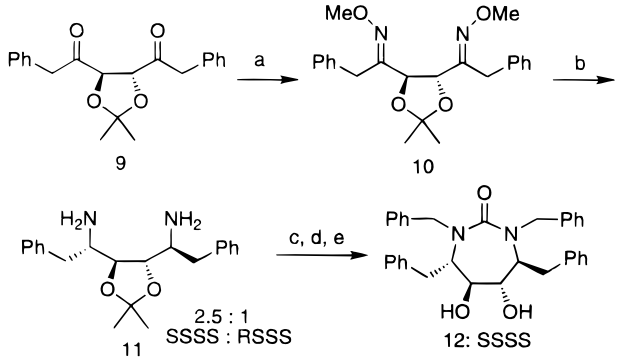
The original cyclic urea synthesis used amino acid starting materials and was only practical for the *RSSR* cyclic urea stereoisomer **1** (Chart 1) and its enantiomer **2**. We used three additional synthetic approaches in an attempt to prepare all possible stereoisomers. Although there are many P2/P2′ substituents which give subnanomolar binding affinities, we chose the benzyl group as a constant P2/P2′ substituent for we were only concerned with relative changes in activity.

Cyclic urea **1** and its enantiomer **2** were prepared by the procedure of Lam et al.[8] The chiral centers of **1** were derived from a Pedersen pinacol coupling of Cbz-D-phenylalaninal.[9] This coupling was highly stereoselective yielding predominantly the protected *RSSR* diaminodiol **3a**; however, minor amounts of the *RRRR* (**3b**) and *RSRR* (**3c**) isomers were also generated (Scheme 1). After removal of the *RSSR* stereoisomer by recrystallization,[8] the *RRRR* isomer could be isolated from the filtrate as the isopropylidine-protected diol **4** by the procedure of Kempf et al.[10] Hydrogenolysis of **4** gave the diamine **5** which was cyclized with 1,1′-carbonyldiimidazole (1,1′-CDI) in methylene chloride to give the cyclic urea **6**. Alkylation with benzyl bromide followed by deprotection gave the *RRRR* cyclic urea **8**.

Although the Pedersen coupling methodology could have been used to prepare the *SSSS*, *RSRR*, and *SRSS* stereoisomers, the diaminodiol isomers recovered were minor components of the pinacol reaction mixture. In addition, tedious purification procedures were required to isolate the *RSRR* and *SRSS* isomers, and a more efficient synthesis was desired. Alternate synthetic routes were also needed to prepare the four isomers with (4*S*,7*R*)-P1/P1′ configurations. A crossed Pedersen coupling of the two Cbz-phenylalaninal enantiomers would be impractical due to the complex mixture of possible stereoisomers.

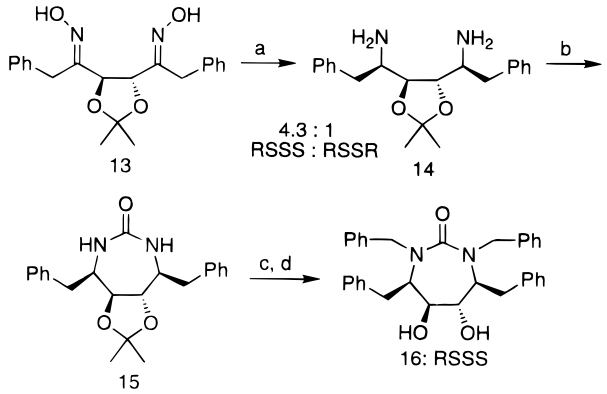
To synthesize the two additional (5*S*,6*S*)-diol diastereomers, we chose an approach starting from L-tartaric acid. We have previously described an alternate synthetic route to P1/P1′-substituted cyclic ureas where L-tartaric acid was used as the source of the (5*S*,6*S*)-diol stereochemistry.[11] The P1/P1′ residues were introduced by addition of substituted benzyl Grignard reagents to activated tartrate amides to give the diketone **9**. Conversion to an oxime followed by a stereoselective reduction generated the (4*R*,7*R*)-P1/P1′ chiral centers resulting in the desired *RSSR* configuration. During the course of these studies we found that by modifying the reduction conditions varying amounts of the *SSSS* and *RSSS* diaminodiol stereoisomers **11** and **14** could be obtained. We have optimized these conditions to synthesize the *SSSS* and *RSSS* cyclic urea isomers as shown in Schemes 2 and 3.

Scheme 2[a]



[a] Reagents: (a) H_2NOMe·HCl, EtOH, H_2O, 93%; (b) BH_3·THF, THF, 54%; (c) 1,1′-CDI, CH_2Cl_2, 83%; (d) KO*t*-Bu, BnBr, THF, 81%; (e) HCl, MeOH, H_2O, 92%.

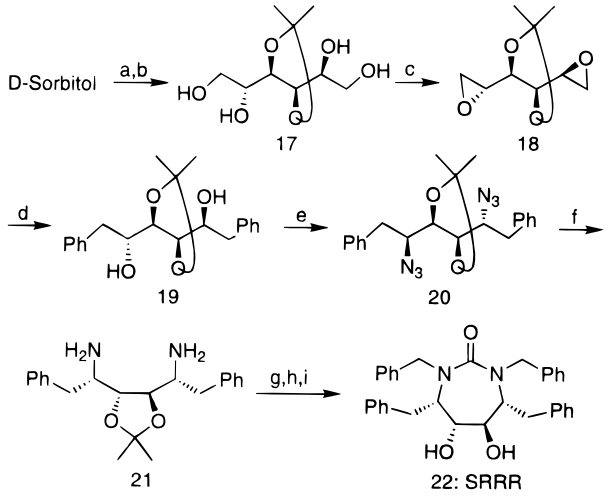
Scheme 3[a]



[a] Reagents: (a) RaNi, H_2, MeOH, NH_4OH, 92%; (b) 1,1′-CDI, tetrachloroethane, reflux, 75%; (c) NaH, BnBr, DMF, 68%; (d) HCl, MeOH, H_2O, 91%.

The *SSSS* isomer **12** was synthesized as illustrated in Scheme 2. The diketone **9** was treated with methoxylamine hydrochloride in ethanol/water to give the bis-oxime ether **10** as a mixture of oxime isomers. Reduction with borane·THF afforded the diamine as a 2.5:1 mixture of the *SSSS* and *RSSS* isomers which were separated by column chromatography. The resulting diamine **11** was cyclized, alkylated, and deprotected

Scheme 4[a]



[a] Reagents: (a) 2,2-dimethoxypropane, H_2SO_4, acetone, 80%; (b) 70% AcOH, 45 °C, 81%; (c) Ph_3P, DEAD, toluene, reflux, 65%; (d) PhLi, CuCN, THF, −78−0 °C, 90%; (e) Ph_3P, DEAD, $(PhO)_2P(O)N_3$, THF, 0−25 °C, 20%; (f) $LiAlH_4$, THF, quant.; (g) 1,1′-CDI, tetrachloroethane, rt−reflux, 78%; (h) KO*t*-Bu, BnBr, THF, 78%; (i) 20% concd HCl, CH_3CN, 75%.

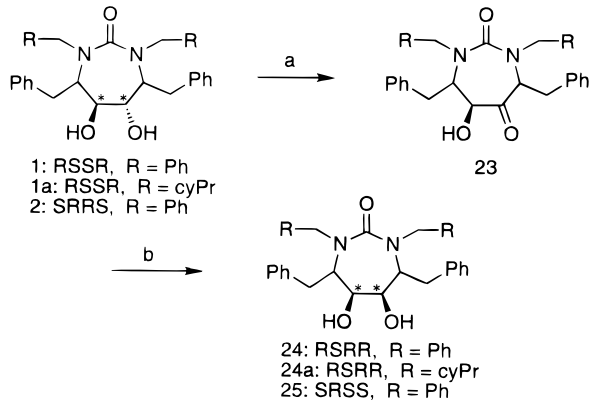
as previously described[11] to give the *SSSS* cyclic urea **12**. The configuration of **12** was confirmed by comparison to the *RRRR* isomer **8**. The spectral properties (^{1}H NMR, IR, MS) of **12** were identical to those of **8** with the exception of an opposite optical rotation.

Although the route illustrated in Scheme 2 could have been used to prepare the *RSSS* isomer, a more efficient synthesis was realized by again modifying the reduction conditions as shown in Scheme 3. Hydrogenation of the bis-oxime **13** with Raney nickel gave the diamine as a 4.3:1 mixture of the *RSSS* and *RSSR* isomers. After separation by column chromatography the *RSSS* diamine **14** was cyclized with 1,1′-CDI in refluxing 1,1,2,2-tetrachloroethane to give cyclic urea **15**. Alkylation followed by deprotection gave the *RSSS* stereoisomer **16**.

Rather than synthesizing the *SRRR* isomer utilizing the tartrate-based route shown in Scheme 3, an alternate approach was desired to unambiguously confirm the configuration generated by the stereoselective reduction. Scheme 4 describes the preparation of the *SRRR* cyclic urea isomer **22** starting from commercially available D-sorbitol. Treatment of D-sorbitol with 2,2-dimethoxypropane and concentrated H_2SO_4 in acetone followed by partial deprotection gave the monoacetonide **17**. Treatment of **17** with triphenylphosphine and diethyl azodicarboxylate (DEAD) in toluene provided the diepoxide **18**. Subsequent treatment of this epoxide with excess phenyl cuprate gave the desired diol **19**. Displacement of the two hydroxyl groups with an azide source provided the diazide **20**. Reduction of the diazide using lithium aluminum hydride provided the diamine **21** which was converted to the *SRRR* cyclic urea **22**. The spectral properties of **22** are consistent with the *SRRR* configuration being identical to the *RSSS* isomer **16** with the exception of an opposite optical rotation.

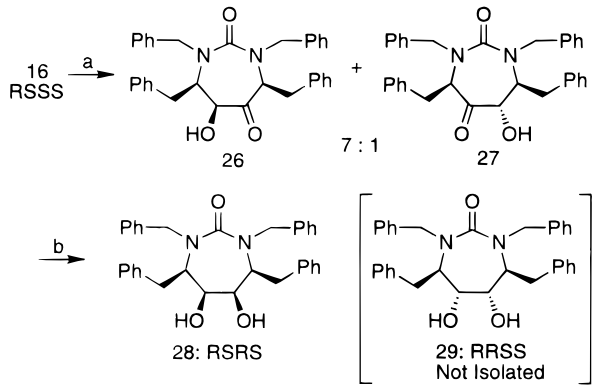
Our approach to the synthesis of the four *cis*-diol cyclic urea isomers was through a stereoselective hydroxyl inversion of the *trans*-diol (Scheme 5). The *RSSR* urea **1** was oxidized to the ketol **23** via a modified Swern

Scheme 5[a]



[a] Reagents: (a) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; (b) $NaBH_4$, EtOH; * indicates relative stereochemistry.

Scheme 6[a]



[a] Reagents: (a) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 90%; (b) $NaBH_4$, EtOH.

oxidation. Reduction with $NaBH_4$ in ethanol was highly selective giving an 11:1 ratio of the *RSRR* stereoisomer and regenerated *RSSR* cyclic urea. Purification by column chromatography gave the *RSRR* stereoisomer **24**. Enantiomer **25** was prepared analogously from **2**.

To unambiguously confirm the stereochemical assignments, an X-ray analysis was desired. Because we could not obtain a suitable crystal from the P2/P2′ benzyl-substituted analogue, the diol inversion was repeated with the highly crystalline cyclopropylmethyl-substituted cyclic urea **1a**.[8] Single-crystal X-ray analysis of **24a** confirmed the stereochemical assignments as *RSRR*.

To synthesize the two remaining *meso* diastereomers, we attempted the diol inversion on the *RSSS* isomer **16** in hopes of obtaining a mixture of the *RSRS* **28** and *RRSS* **29** stereoisomers (Scheme 6). Oxidation of **16** selectively oxidized the 6-hydroxyl giving a 7:1 mixture of ketols **26** and **27**. Reduction of this mixture gave the *RSRS* cyclic urea **28** along with recovered **16**; no *RRSS* **29** was isolated. The selectivity of the oxidation can be rationalized assuming the conformation of the *RSSS* isomer to be 4ax,5eq,6eq,7eq; therefore, the 5-hydroxyl is sterically hindered by the 4-axial benzyl group, and the 6-hydroxyl is preferentially oxidized yielding ketol **26**. Reduction of ketol **26** with sodium borohydride gave the *RSRS* stereoisomer **28.** Although the minor ketol **27** could have been reduced to the *RRSS* isomer **29**, the 4-axial benzyl group may block attack from the β-face so reduction regenerates the *RSSS* isomer. It is inter-

Table 1. Binding Affinity of the Cyclic Urea Diastereomers

compd	configuration	K_i (nM)[a]
1	*RSSR*	3.6 ± 1.1
2	*SRRS*	3810 ± 1580
8	*RRRR*	1350 ± 310
12	*SSSS*	560 ± 100
16	*RSSS*	64 ± 30
22	*SRRR*	6700 ± 210
24	*RSRR*	6.0 ± 2.2
25	*SRSS*	1710 ± 220
28	*RSRS*	250 ± 55

[a] Values are expressed as the mean ± SD, $n = 2-4$.

esting to note that the *RSRS* cyclic urea displayed an extremely broad and complex ^{1}H NMR spectrum at room temperature. Although **28** is symmetrical, either conformer is ax,eq,ax,eq, and due to slow ring inversion an averaged spectra is only obtained at high temperatures. The stereochemical assignments of **28** were confirmed by single-crystal X-ray analysis.

Results and Discussion

The cyclic urea stereoisomers were tested for binding affinity,[12] and the results are shown in Table 1. As predicted the *RSSR* cyclic urea **1** was the most potent with a $K_i = 3.6$ nM. As originally designed, the *RSSR* stereochemistry allows a conformation where the ring substituents obtain an ax,eq,eq,ax orientation. This allows the diols to symmetrically bind to the aspartate residues and the P1/P1′ and P2/P2′ side chains to optimally project into their respective pockets. The *RSRR* isomer **24** showed similar activity with a $K_i =$ 6.0 nM. With one hydroxyl group inverted, this isomer can maintain a conformation with the ring substituents in an ax,eq,ax,ax orientation. The catalytic aspartate residues can bind to the one remaining equatorial hydroxyl group, and the P1/P1′ and P2/P2′ side chains can interact with their respective binding pockets. This is consistent with the binding of C_2-symmetrical diaminodiol inhibitors where inversion of one hydroxyl group was also tolerated.[5] Although one cyclic urea hydroxyl group can be inverted with little loss in binding, the inversion of both hydroxyls is not tolerated as shown by the *RRRR* isomer **8** with a $K_i = 1350$ nM.

Inverting the stereochemistry of the P1/P1′ substituents is undesirable as demonstrated by the *RSSS* isomer **16** with a $K_i = 64$ nM. Inversion to an equatorial P1 side chain results in a 10-fold loss in activity. Similarly the *meso RSRS* isomer **28** with its ax,eq,ax,eq orientation loses almost 2 orders of magnitude in activity with a $K_i = 250$ nM. The remaining diastereomers were shown to be seriously mismatched, and they lose over 2−3 orders of magnitude in potency versus the originally designed *RSSR* cyclic urea.

Conclusion

In summary, we have prepared 9 of the 10 possible cyclic urea stereoisomers. Three alternate synthetic routes were required in addition to the original synthesis of cyclic ureas using amino acid starting materials. Two of the synthetic routes used L-tartaric acid or D-sorbitol as starting materials. The third general route exploited a stereoselective hydroxyl inversion of the cyclic urea *trans*-diol to the *cis*-diol isomers. The alternate synthetic routes described may be useful for the preparation and design of future cyclic urea-based HIV-Pr inhibitors.

The effect of varying stereochemistry on binding was described. As originally predicted, the *RSSR* isomer **1** was the most active in our binding assay. Of comparable activity was the *RSRR* isomer **24** which differs by one inverted hydroxyl group. The other diastereomers were substantially less potent demonstrating the importance of substituent orientation on cyclic urea-based HIV-Pr inhibitor potency.

Experimental Section

All reactions were carried out with continuous stirring under an atmosphere of dry nitrogen. Unless otherwise specified, all solvents and commercial reagents were used as received without additional purification. Chromatography was performed with solvents indicated using EM Science silica gel 60 (230−400 mesh). ^{1}H (300-MHz) NMR spectra were recorded with $CDCl_3$ as solvent using tetramethylsilane as an internal standard. Infrared spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrometer, and optical rotations were obtained on a Perkin-Elmer 241 polarimeter. Melting points are uncorrected. Elemental analysis was performed on all target compounds by Quantitative Technologies, Inc., Bound Brook, NJ.

(3*S*,4*S*)-2,5-Bis(methoxyimino)-1,6-diphenyl-3,4-*O*-isopropylidenehexanediol (10). To a solution of bis-ketone **9** (1.76 g, 5.20 mmol) in ethanol (100 mL) and water (33 mL) was added methoxylamine hydrochloride (1.06 g, 3.95 mmol). After stirring overnight the reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, 15% ethyl acetate/hexane) to give bis-oxime **10** as a mixture of oxime isomers (1.92 g, 93%): CIMS (NH_3) *m*/*z* 397 ($M + H^+$, 100%).

(4*S*,5*S*,6*S*,7*S*)-Hexahydro-5,6-dihydroxy-1,3,4,7-tetrakis(phenylmethyl)-2*H*-1,3-diazapin-2-one (12). To a solution of bis-oxime **10** (1.92 g, 4.8 mmol) in THF (35 mL) at 0 °C was added borane−tetrahydrofuran complex (18 mL, 18 mmol, 1.0 M in THF) dropwise. The solution was allowed to warm to room temperature and then refluxed for 2 h. The solution was cooled to 0 °C and carefully quenched with water (9 mL) and then 15% aqueous NaOH (9 mL). The solution was gently refluxed for 10 min, cooled, and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, 10% methanol/CH_2Cl_2) to give the diamine as a 2.5:1 mixture of the *SSSS* and *RSSS* isomers (887 mg, 54%). The mixture of isomers could be separated by chromatography (silica gel, 10% methanol/CH_2Cl_2) to give the *SSSS* diamine **11**. The diamine was converted to the *SSSS* cyclic urea **12** as described: yield 62% (from **11**); mp 66−68 °C; ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 16 H), 7.08 (d, $J = 7.0$ Hz, 4 H), 4.75 (d, $J = 14.3$ Hz, 2 H), 3.56 (s, 2 H), 3.51 (d, $J = 14.3$ Hz, 2 H), 3.21 (m, 2 H), 2.97 (A of ABX, $J_{AB} = 13.2$ Hz, $J_{AX} = 6.6$ Hz, 2 H), 2.77 (B of ABX, $J_{AB} = 13.2$ Hz, $J_{BX} = 7.2$ Hz, 2 H), 1.61 (br s, 2 H); IR (KBr) ν 3590, 3566, 1630, 1210 cm^{-1}; CIMS (NH_3) *m*/*z* 507 ($M + H^+$, 100%); $[\alpha]^{25}_D = +52.50°$ ($c = 0.600$, $CHCl_3$). Anal. ($C_{33}H_{34}N_2O_3$) C,H,N.

(4*R*,5*S*,6*S*,7*S*)-Hexahydro-5,6-dihydroxy-1,3,4,7-tetrakis(phenylmethyl)-2*H*-1,3-diazapin-2-one (16). To a solution of bis-oxime **13** (2.20 g, 6.0 mmol) in methanol (150 mL) and ammonium hydroxide (20 mL, 28% in water) was added Raney nickel (11 g, 50% slurry). The suspension was charged with hydrogen (50 psi) for 20 h. The suspension was carefully filtered through Celite, and the solvent was removed under reduced pressure. Chromatography (silica gel, 10% methanol/CH_2Cl_2) gave the diamine as a 4.3:1 mixture of the *RSSS* and *RSSR* isomers (1.86 g, 92%). The mixture of isomers could be separated by chromatography (silica gel, 10% methanol/CH_2Cl_2) to give the *RSSS* diamine **14**. The diamine was

converted to the *RSSS* cyclic urea **16** as described: yield 46% (from **14**); mp 87−90 °C; ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 16 H), 7.07 (m, 4 H), 4.72 (br d, J = 14.3 Hz, 1 H), 4.53 (br s, 2 H), 4.19 (m, 1 H), 3.76 (br d, J = 14.3 Hz, 1 H), 3.44 (br s, 3 H), 2.98 (m, 4 H), 1.73 (d, J = 5.1 Hz, 1 H), 1.35 (br s, 1 H); IR (KBr) ν 3410, 1620, 1450 cm^{-1}; CIMS (NH_3) m/z 507 ($M + H^+$, 100%); $[\alpha]^{25}_D = +77.00°$ (c = 0.600, $CHCl_3$). Anal. ($C_{33}H_{34}N_2O_3$) C,H,N.

(4*R*,5*S*,7*R*)-Hexahydro-5-hydroxy-1,3,4,7-tetrakis(phenylmethyl)-2*H*-1,3-diazapine-2,6-dione (23). To a solution of oxalyl chloride (83 mg, 0.65 mmol) in CH_2Cl_2 (2.5 mL) at −78 °C was added methyl sulfoxide (105 mg, 0.98 mmol). The solution was stirred for 20 min, and cyclic urea **1** (250 mg, 0.49 mmol) in THF (2 mL) was added dropwise. After 20 min, triethylamine (198 mg, 1.96 mmol) was added, and the reaction mixture was allowed to warm to room temperature. Water was added, and the suspension was extracted with EtOAc. The combined organic layers were washed with dilute HCl and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, 25% ethyl acetate/hexane) to give ketol **23** as a glass (203 mg, 82%): ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 16 H), 7.03 (m, 2 H), 6.90 (m, 2 H), 5.00 (d, J = 14.3 Hz, 1 H), 4.75 (d, J = 14.3 Hz, 1 H), 4.29 (dd, J = 5.9, 4.0 Hz, 1 H), 4.11 (m, 1 H), 4.03 (d, J = 14.3 Hz, 1 H), 3.77 (m, 1 H), 3.49 (d, J = 4.0 Hz, 1 H), 3.10−2.69 (m, 5 H); IR (KBr) ν 3410, 3030, 1720, 1650, cm^{-1}; CIMS (NH_3) m/z 505 ($M + H^+$, 100%).

(4*R*,5*S*,6*R*,7*R*)-Hexahydro-5,6-dihydroxy-1,3,4,7-tetrakis(phenylmethyl)-2*H*-1,3-diazapin-2-one (24). To a solution of ketol **23** (140 mg, 0.28 mmol) in ethanol (10 mL) was added sodium borohydride (26 mg, 0.69 mmol). After 45 min dilute HCl was carefully added, and the reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, 33% ethyl acetate/hexane) to give the *RSRR* urea **24** as a white solid (112 mg, 80%): mp 138−139 °C; ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 18 H), 6.92 (m, 2 H), 4.89 (d, J = 14.3 Hz, 1 H), 4.87 (d, J = 14.3 Hz, 1 H), 3.92 (d, J = 14.3 Hz, 1 H), 3.57 (m, 4 H), 3.15−2.75 (m, 5 H), 2.62 (d, J = 8.1 Hz, 1 H), 1.60 (d, J = 5.5 Hz, 1 H); IR (KBr) ν 3290, 3030, 1600, 1450 cm^{-1}; CIMS (NH_3) m/z 507 ($M + H^+$, 100%); $[\alpha]^{25}_D = -17.50°$ (c = 0.600, $CHCl_3$). Anal. ($C_{33}H_{34}N_2O_3$) C,H,N.

(4*R*,5*S*,6*R*,7*S*)-Hexahydro-5,6-dihydroxy-1,3,4,7-tetrakis(phenylmethyl)-2*H*-1,3-diazapin-2-one (28). Starting with **16**, following the procedure described for the synthesis of **23** gave the ketols **26** and **27** as a 7:1 mixture of isomers (225 mg, 90%). Reduction following the procedure of **24** and recrystallization with ethyl acetate/hexane gave the *RSRS* urea **28** as a white solid (154 mg, 71%). The stereochemistry was confirmed as *RSRS* by a single-crystal X-ray analysis (see Supporting Information): mp 176−177 °C; ^{1}H NMR (DMSO-d_6, 140 °C) δ 7.20 (m, 20 H), 4.58 (d, J = 15.1 Hz, 2 H), 4.40 (m, 2 H), 3.78 (br s, 2 H), 3.65 (br s, 2 H), 3.41 (br s, 2 H), 3.11 (A of ABX, J_{AB} = 13.9 Hz, J_{AX} = 6.6 Hz, 2 H), 2.89 (B of ABX, J_{AB} = 13.9 Hz, J_{BX} = 7.6 Hz, 2 H); IR (KBr) ν 3390, 3030, 2930, 1610, 1450 cm^{-1}; CIMS (NH_3) m/z 507 ($M + H^+$, 100%). Anal. ($C_{33}H_{34}N_2O_3$) C,H,N.

Supporting Information Available: Experimental procedures for the synthesis of compounds **8** and **22** and atomic coordinates for the X-ray crystal structures of compounds **24a** and **28** (16 pages). Ordering information is given on any current masthead page.

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