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Diversity-Oriented Synthesis of a Drug-Like System Displaying the Distinctive N→C═O Interaction

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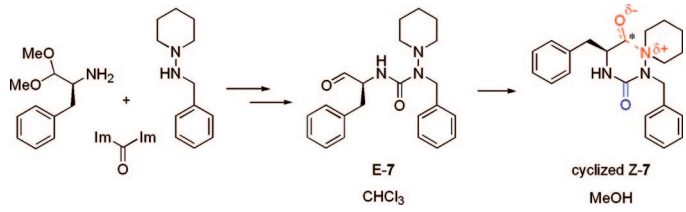

This study describes the syntheses and characterization of two hydrazino ureas. These fold into a six-membered ring by virtue of the infrequently observed $^{\delta+}$N→C═O$^{\delta-}$ interaction when solvated by polar protic media. The highly polar functional group resulting from this interaction is hypothesized to especially reproduce electronic but also steric features of the transition states of peptide hydrolysis. The urea moiety constitutes an additional key element of modern HIV-1 protease (HIV PR) inhibitors and is meant to interact with the enzyme flaps. We have developed an efficient, convergent synthetic route to enantiopure compounds that uses CDI to couple two independent building blocks, one derived from amino acids and the other one from easily accessible hydrazines. It is thus amenable to rapid generation of diversity in order to screen for novel HIV PR inhibitors. A complete study using one- and two-dimensional NMR as well as UV spectroscopy confirmed the sole existence of the cyclic constitution of target compounds **7** and **8** in methanol. Total reversal to the linear aldehydic form is observed upon passage to apolar media.

Introduction

The design of transition state (TS) analogs of enzymatic reactions has proved to be a powerful strategy for the development of potent enzyme inhibitors on the one hand as well as for the creation of artificial catalysts on the other.[1–3] Inhibitors of aspartic proteases (PR) have great importance for the treatment of a variety of diseases including malaria, cancer, hypertension, AIDS, and Alzheimer's disease.[4,5]A common approach in designing inhibitors for HIV-1 protease (HIV PR) has been the incorporation of a TS isostere into a peptidomimetic that reflects the linear shape of the biologically occurring peptide substrate. Several isosteric moieties have been explored, for example, hydroxyethylamine, hydroxyethylene, statine, phosphinate, reduced amide, α-ketoamide, and more recently a silicon-based unit.[6–8]

An alternative approach has been the use of heterocyclic nonpeptidic templates, such as a cyclic urea (**1**)[9] or a 5,6-dihydro-4-hydroxy-2-pyrone (**2**).[10,11] While the hydroxyl group(s) interact(s) with the catalytic aspartyl diad of HIV PR, the carbonyl function on the opposite side engages in hydrogen bonding with two protein flaps of the enzyme. Incorporation of heterocycles displaying such features into an inhibitor can yield higher affinities due to a favorable entropic effect in that (a) the carbonyl function replaces a key enzyme-bound water molecule that is usually attached to the flaps,[9,12] and (b) fewer degrees of freedom have to be frozen during complexation, due to the elevated rigidity of the core.[9,13] Repression of conformational freedom is also known to lead to better oral bioavail-

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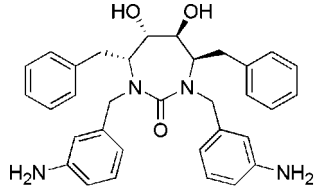
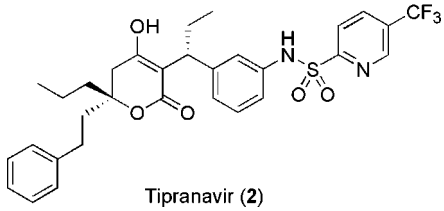
ability.[14] Generally, the search for potent enzyme inhibitors as well as the design of artifical enzymes has greatly benefited from two complementary strategies, one based on structural considerations and the other on the generation and screening of combinatorial libraries.[15,16]

We have been interested in exploring the moiety resulting from a tertiary amine-carbonyl interaction ($^{\delta+}$N→C=O$^{\delta-}$, see examples **3**,[17] **4**,[18] and **5**[19]) for its capacity to reproduce steric and electronic properties of the transition states of peptide hydrolysis (for comparison see the second TS (**6**) of the preferred dipeptide sequence of HIV PR[20,21]).



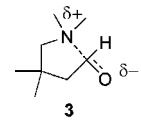
DMP450 (**1**)



Tipranavir (**2**)

Historically, the $^{\delta+}$N→C=O$^{\delta-}$ interaction was observed in a rare class of alkaloids as a transannular contact across medium-sized rings.[22,23] It has been described as a through-space homoconjugation where electron density is shifted from the *n* nitrogen orbital to the carbonyl π^* orbital,[24] giving rise to an enhanced dipole moment and a hypsochromic shift of the carbonyl UV absorption.[25,26] Studies on natural and synthetic examples have shown that the interaction is favored in polar protic media and when incorporated into preorganized, often multicyclic frameworks.[17,19,27] Recently, the $^{\delta+}$N→C=O$^{\delta-}$ moiety has featured prominently in the total synthesis of the marine natural product (−)-sarain A (**4**).[18]

With respect to the strategy of transition-state mimicry, we find the following of its characteristics particularly attractive: (a) an N−C bond order between 0 and 1; (b) a carbon hybridization between sp^2 and sp^3; (c) a C−O bond order between 1 and 2; and (d) partial charges on the oxygen and the nitrogen, resulting in an enhanced dipole moment.[25] This strongly polarized unit may thus form particularly strong hydrogen bonds and electrostatic interactions with the catalytic diad of the two aspartate residues. Our first-generation prototype **5** showed the $^{\delta+}$N→C=O$^{\delta-}$ interaction to a degree of 70% at 20 °C in MeOH.[19] The resulting non-zero fraction of the (unfolded) aldehydic form not only complicates analysis of the system but also rules out any exploration as a drug candidate, since aldehydes are justly regarded as too reactive toward nitrogen nucleophiles present in living organisms.



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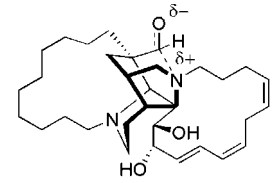
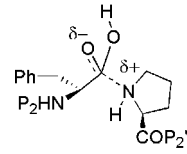
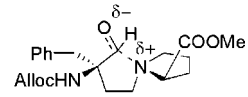


(-)Sarain A (**4**)



TS (**6**)



5

In this study it was our objective to identify a core unit that would show total $^{\delta+}$N→C=O$^{\delta-}$ interaction, while offering a nonreactive carbonyl group on the opposite side of the molecule to satisfy the hydrogen-bonding partners on the enzyme flaps. This core unit should be of reduced molecular complexity and should be easily assembled to allow for the subsequent hunt for a promising lead structure by a combined computational and combinatorial tactic.

Results and Discussion

Compound Design and Synthetic Strategy. A urea moiety not only proved to interact well with the flaps but offers the advantage to largely rigidify a cyclic system. Grafting an aldehyde group and a tertiary amine moiety on each nitrogen, respectively, the preorganizing effect of a *Z*/*Z*-configured urea should greatly favor the $^{\delta+}$N→C=O$^{\delta-}$ interaction. Also, use of a tertiary hydrazine as the nitrogen donor was expected to favor the interaction due to its enhanced nucleophilicity and could be introduced by creating a urea hydrazide. We quickly realized that such features would not allow us to assemble a five-membered heterocycle resulting from the $^{\delta+}$N→C=O$^{\delta-}$ interaction, but a six-membered one. Yet $^{\delta+}$N→C=O$^{\delta-}$ interactions have never been observed in six-membered rings outside the context of multicyclic systems. It remained to be seen whether such a compound shows a strong propensity to fold.

From a synthetic point of view, the urea moiety may ultimately be very useful for the creation of a combinatorial library, since rapid, convergent assembly from three building blocks can be envisaged (Scheme 1). We chose to connect two types of building blocks via the urea carbonyl group in which one contains the (protected) carbonyl acceptor and the other one the tertiary-nitrogen donor in the form of a hydrazine. Numerous substituants (R_1−R_6) may be introduced. However, at least two limitations need to be put forward here: (a) not unexpectedly, we have found that if R_6 represents a hydrogen

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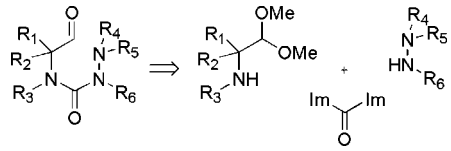
SCHEME 1. Retrosynthetic Assembly of the Target and Opportunities for Generating Diversity



atom, a spontaneous cyclization reaction takes place, furnishing a five-membered ring that displays no $^{\delta+}N{\rightarrow}C{=}O^{\delta-}$ interaction; we thus concluded that R_6 has to be a substituent other than hydrogen; (b) for the time being, we only succeeded in our synthetic efforts if R_3 = H, most likely for steric reasons.

The aldehyde building block can be conveniently generated from an amino acid precursor, thus allowing for an enormous choice of substitution and stereoconfiguration patterns in view of the market size of this commodity. We initially chose phenylalanine as this precursor. The hydrazine building block may be generated (a) from secondary amines of any kind[28] with subsequent reductive alkylation of the newly introduced primary nitrogen, or (b) by consecutive alkylation of commercially available hydrazines,[29] once again demonstrating the immense potential of this scheme for the generation of diversity. The use of carbonyl di-imidazole (CDI) as the connecting reagent appeared ideal for two reasons: (a) the desired urea function is formed without further manipulations; (b) two independent nucleophiles can be introduced consecutively, since the product of the initial step (e.g., **12**, Scheme 2) is much less reactive than CDI itself and will not react with a second amino nucleophile.[30] The remaining imidazole unit can however be methylated to produce the corresponding, highly reactive imidazolium salt that was shown to react with various nucleophiles under mild conditions.[31] In the following, we describe the synthesis and the configurational and constitutional analysis of two independent manifestations (**7**, Scheme 2, and **8**, Scheme 4) of the generic structure in Scheme 1.

Synthesis of Piperidyl Hydrazino Urea 7. In the synthesis of the phenylalanine part of **7** (Scheme 2), aldehyde **9** was prepared as previously described from commercially available Cbz-protected phenylalaninol.[32] The following protection step by acid-catalyzed acetalization furnished compound **10** in a convenient overnight reaction at room temperature. Removal of the Cbz group using straightforward catalytic hydrogenation quantitatively furnished amine **11**. Reaction with CDI yielded carbamoylimidazole **12** as the only product in only 15 min. Compound **12** is not stable on silica, but the conversion is clean and quantitative, making purification unnecessary. Intermediate **12** can thus be produced in a very efficient four-step synthesis from commercial sources.

Benzyl hydrazine **14** was obtained by reacting commercially available hydrazine **13** with benzaldehyde, followed by in situ reduction of the intermediate hydrazone. Although imines are commonly reduced with $NaBH_4$ or $NaCNBH_3$, their application to conjugated hydrazones has not been described. The common reagent for this task is reported to be borane,[33] which is also known for its capacity to reduce amides.[34] Since we intended to apply the same reduction step to the synthesis of the second target compound of this study, bearing an amide moiety (**8**, Scheme 4), we searched for milder conditions to prevent amide reduction. Catalytic hydrogenation at room temperature and atmospheric pressure gave low yields. LC-MS monitoring of the reaction indicated that the desired product was formed within a few hours, but during the same time it underwent side reactions to a significant degree. Despite its literature absence, we then attempted the application of $NaCNBH_3$ under neutral conditions and also in the presence of stoichiometric amounts of acetic acid, to no avail. On the other hand, using a large excess of acetic acid at room temperature produced the desired hydrazine **14** in only 30 min.

The reaction of primary hydrazines with carbamoylimidazoles, such as **12**, has been reported, but secondary hydrazine **14** did not react with compound **12**, even when refluxing the mixture.[30] The imidazole unit was thus activated with excess MeI to produce a highly reactive imidazolium intermediate.[31] Subsequently, treatment of activated **12** with **14** gave hydrazino urea **15** in a convenient overnight reaction. The three-step reaction sequence from **11** to **15** (reaction of **11** with CDI, activation with MeI, and reaction with **14**) effectively couples the amino acid with the hydrazine building block and may be regarded as central to the synthesis of the target system. It offers an overall yield of 71%, while requiring just one purification step by column chromatography for **15**. Removal of the dimethyl acetal protecting group was achieved by exposure to in situ generated TMSI,[35] furnishing desired target compound **7** in excellent yield. The *E*/*Z*-configuration of **7** as depicted in Scheme 2 is the only one observed (see section on configurational analysis). All reaction conditions applied in the synthesis of **7** are also included in that of **8** (see below). Since no diastereomer formation (racemization) was observed in the preparation of **8**, we suggest that racemization also does not occur in the assembly of **7**.

Synthesis of Prolyl Hydrazino Urea 8. In order to demonstrate the potential for structural diversification, we established the synthesis of a second target compound (**8**, Scheme 4) where the hydrazine unit is derived from an amino acid (proline). By synthesizing **8**, we would simultaneously be able to prove that ring sizes other than that of a piperidyl ring give equally reliable folding and that sterically more demanding substitution patterns on this ring do not impair the $^{\delta+}N{\rightarrow}C{=}O^{\delta-}$ interaction. We would also show that amino acid derivatives are a suitable starting material to establish elevated molecular complexity in our system. The preparation of **8** necessitated the elaboration of a synthetic sequence toward the second hydrazine building block. The common way of making hydrazino acids from amino acids is to reduce nitrosated amino acids by use of Zn/HOAc.[36] Even though this procedure has been for years the only reported method for this task, no explanation has been given for the low yields that are generally disclosed. Nevertheless, we embarked on its application for its straightforward character. Nitroso

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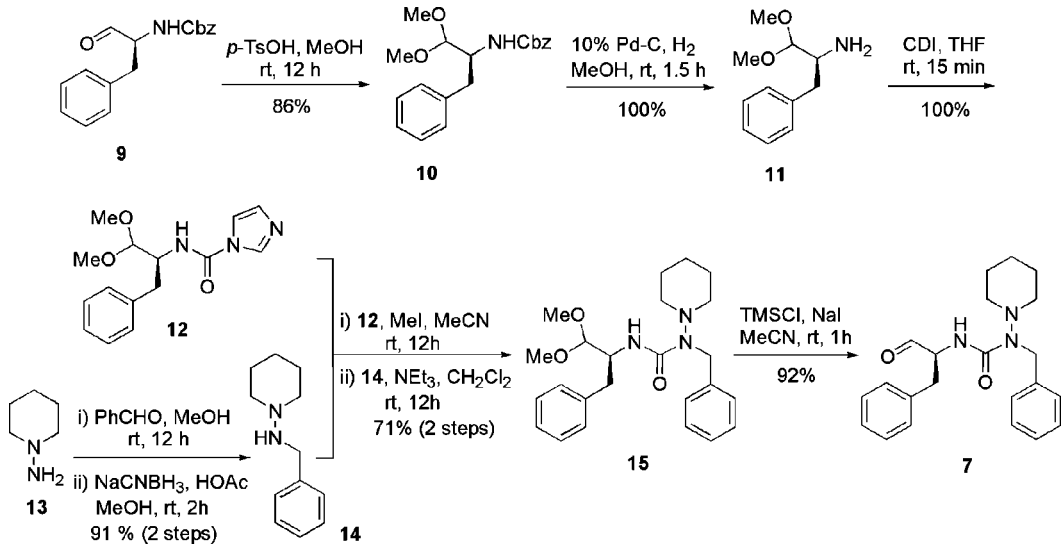
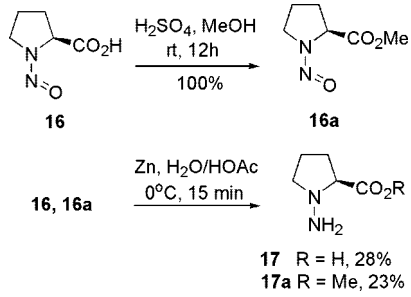
SCHEME 2. Preparation of Target Compound 7



SCHEME 3. Classical Approach in the Synthesis of Hydrazino Proline Derivatives



proline **16**[36] was converted into its methyl ester **16a**, and subsequently the two served as model compounds to test the Zn/HOAc reduction (see Scheme 3). In both cases, LC-MS analysis of samples directly taken from the crude reaction mixture showed clean conversion to **17** and **17a** (see S39−S43 in Supporting Information), however low yields were obtained after reaction workup. The generally described workup procedure consists of saturating the reaction solution with H_2S, which results in the precipitation of large amounts of colloidal zinc sulfide. The resulting slurry was filtered, but only traces of compounds **17** and **17a** were obtained. In light of the LC-MS data, we suggest that the inherent problem of this procedure is the encapsulation of the target compound by the considerable amounts of colloidal zinc sulfide. We do not rule out that a method might eventually be found to overcome this problem.

In order to obtain good yields of the hydrazino acid building block, we turned to a rather recent innovation. The oxaziridine reagent **18** (Scheme 4) effectively transfers an NH-Boc moiety to an amino acid.[28,37] Treatment of (*S*)-proline with freshly prepared **18** gave thus *N*-Boc-protected hydrazino proline **19** in good yield. In order to prepare hydrazino dipeptide **20**, compound **19** was reacted with H-Val-NH^{t}Bu using EDC and HOBt as coupling reagents.[38] The Boc group was then removed in a matter of 2 h by use of TFA before applying the reductive amination step toward **21**, as worked out in the preparation of **14**. The overall yield of deprotection, hydrazone formation, and reduction was 93%, while purification by column chromatography was only necessary following the last step. The preparation of urea **22** was carried out in a manner identical to that of **15** by reacting hydrazine **21** with methylated **12**. Deprotection of the dimethyl acetal using NaI and TMSCl gave the second target compound **8** in excellent yield. Since diastereomer formation was not observed during this reaction sequence, we conclude that the assembly of **8** occurred without racemization. As in the synthesis of **7**, most steps are high-yielding, do not require purification by column chromatography, and except for the amination of proline, are performed at room temperature.

Configurational and Constitutional Analysis. The cyclization tendency of compounds **7** and **8** was studied by NMR and UV spectroscopy. The ^{1}H NMR spectrum of **7** in $CDCl_3$ showed only one set of signals, including the one of the aldehydic proton (Figure 1), thus indicating that only one of the four possible configurational isomers is present. The corresponding ^{1}H−^{1}H NOESY spectrum revealed contacts of the urea proton (position 3 of *E*-**7** in Scheme 5, 6.85 ppm) with the piperidine protons (position 8, 2.64−2.62 ppm and 2.48−2.36 ppm; see S28 in Supporting Information), while no interaction with the benzylic protons (position 6, 4.51 ppm) was observed. These data suggest that **7** adopts the *E*/*Z* configuration as shown in Scheme 5. The ^{13}C NMR spectrum of **7** in $CDCl_3$ revealed only one set of signals with the characteristic signal of the aldehyde carbon at 200.7 ppm

By contrast, in MeOH-d_4 this signal disappeared in favor of two signals further upfield. At 100.5 and 100.1 ppm, they are plainly centered in the zone between the olefinic/aromatic and the aliphatic region, suggesting a partial change in hybridization from sp^2 to sp^3. It may be assumed that these signals correspond to the newly formed pseudotetrahedral carbon, resulting from the $^{\delta+}$N→C=O$^{\delta-}$ interaction (cyclized *Z*-**7** in Scheme 5). Their splitting can be explained with the fact that a new stereogenic center has been formed without any particular stereoselectivity and that two diasteromers were generated as it was previously observed.[27c] This is supported by the splitting of most of the other carbon signals in the spectrum. These observations are reflected in the ^{1}H NMR spectrum taken in MeOH-d_4, where the signal corresponding to the aldehyde proton has disappeared. A ^{1}H−^{13}C HMBQ spectrum revealed that the signal of the

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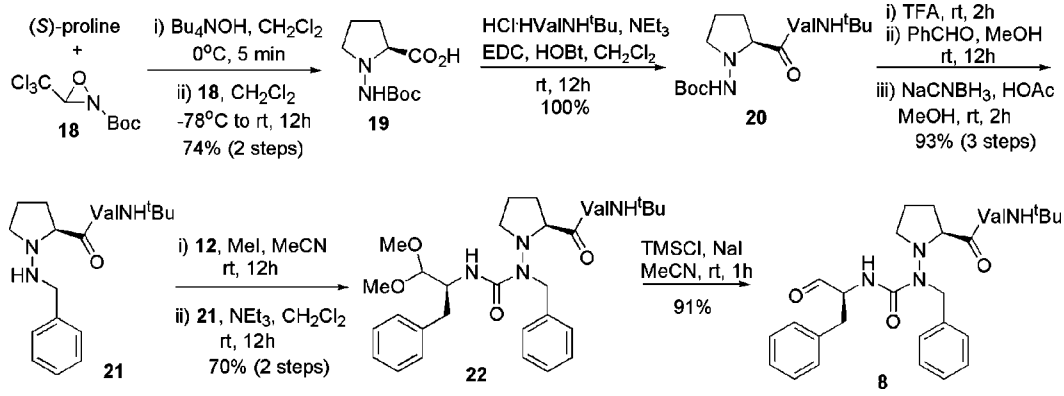
SCHEME 4. Preparation of Target Compound 8



methine proton of the newly formed pseudotetrahedral center (position 1, Scheme 5) is located right underneath the signal of the benzylic protons (position 6, δ 4.61−4.57). Futher evidence for the $^{\delta+}N{\rightarrow}C{=}O^{\delta-}$ interaction in MeOH-d_4 could be obtained from a $^1H-^{13}C$ HMBC spectrum (see S29 and S30 in Supporting Information for the HMBQ and HMBC spectra). The spectrum showed ^3J coupling between the methine proton and the carbon atoms adjacent to the piperidine nitrogen (positions 8, δ 55.41, 55.38, 54.92, and 54.86 ppm). To our knowledge, this is the first time that the $^{\delta+}N{\rightarrow}C{=}O^{\delta-}$interaction has been characterized by 2D NMR spectroscopy and that actual coupling through this weak bond has been demonstrated.

Interestingly, upon dissolution in MeOH-d_4, the "folding" of **7** can be monitored by NMR. Figure 1 demonstrates that about 40% is cyclized after 10 min at room temperature, 70% conversion is reached after 30 min, and cyclization is complete in 3 h. These kinetics might be explained with the existence of a configurational equilibrium present in **7** (Scheme 5). In the absence of a polar protic medium, the thermodynamic form is *E*-**7**, where the planar secondary amide of the urea moiety is *E*-configured. In MeOH-d_4, this configurational equilibrium is shifted completely to the *Z* form by the coupled constitutional equilibrium in favor of the cyclized *Z* form. The activation barrier of the *E*/*Z* equilibrium of regular ureas has been determined to be approximately 13 kcal/mol[39] and thus signficantly lower than that of carboxamide bonds (around 20 kcal/mol).[40,41] Still, a barrier of 13 kcal/mol explains the relative slowness of the process observed here at room temperature. Compound **8** showed a behavior identical to that of **7** when being examined by ^1H and ^{13}C NMR. The open aldehydic form was the only one present in $CDCl_3$, whereas time-resolved folding occurred in MeOH-d_4 to give cyclized *Z*-**8** in the form of two diastereomers (Scheme 5). Interestingly, when samples of **7** or **8** in MeOH-d_4 are evaporated to dryness and redissolved in $CDCl_3$, only the linear aldehydic form is detected, thus demonstrating that this unique cyclization process is completely reversible.

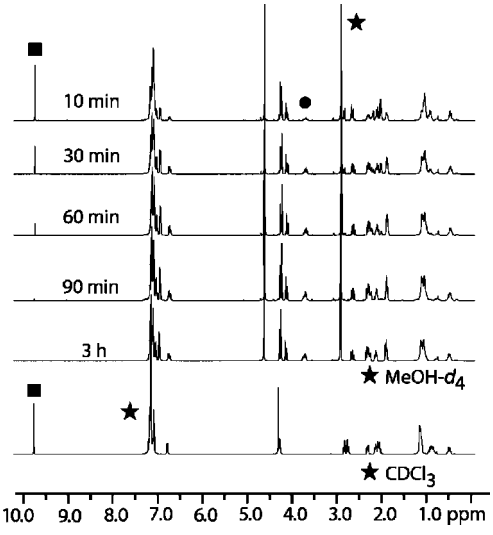


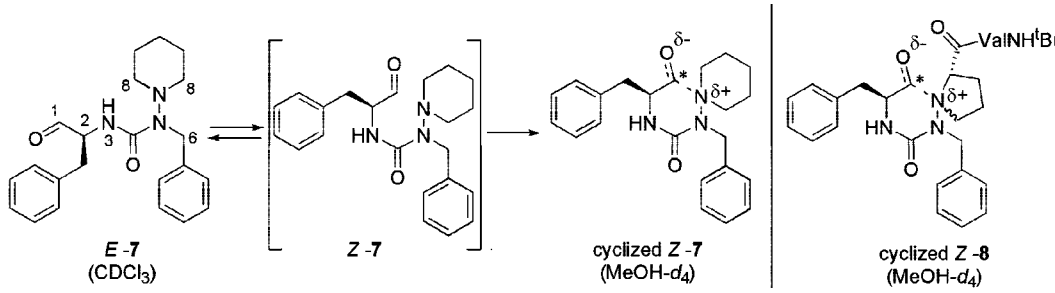
FIGURE 1. ^1H spectra (500 MHz) of **7** in $CDCl_3$, and at certain time intervals beginning with initial dissolution in MeOH-d_4. (■) *E*-**7** (position 1 proton), (●) cyclized *Z*-**7** (position 2 proton).

The above observation that the $^{\delta+}N{\rightarrow}C{=}O^{\delta-}$ interaction is especially favored in polar protic media is in complete agreement with literature data.[17,19,27] It is however the first time that such an interaction is observed in the formation of a six-membered ring outside the context of multicyclic or macrocyclic systems that benefit from elevated levels of preorganization. Up until now, linear systems were only known to fold to five-membered rings.[17,27c] This leads us to conclude that there are no principal obstacles to the formation of a six-membered ring brought about by an $^{\delta+}N{\rightarrow}C{=}O^{\delta-}$ interaction, aside from an unfavorable entropic term. Our system benefits from a urea moiety that, once *Z*-configured, endows the molecule with a considerable degree of preorganization thanks to its coplanarity.

UV spectroscopy is an alternative means to detect the $^{\delta+}N{\rightarrow}C{=}O^{\delta-}$ interaction.[19,26] It is characterized by a band that is significantly more intense and found at a shorter wavelength than the one of the aldehyde function. This band can be ascribed to the transition between the bonding and antibonding molecular orbitals newly formed by the through-space interaction of the *n* nitrogen orbital and the π orbitals of the carbonyl function (Figure 2).[24] Figure 3 shows two diagrams, each depicting two UV spectra taken from compounds **7** and **8** in $CHCl_3$ and MeOH, respectively. In $CHCl_3$, the spectra have their maximum at 241 nm, corresponding to the absorption of the aldehyde function. The extinction coefficients were calculated to be ϵ = 877 L mol^{-1} cm^{-1} for **7**, and ϵ = 733 L mol^{-1} cm^{-1} for **8**. In MeOH, the spectra show the intense $^{\delta+}N{\rightarrow}C{=}O^{\delta-}$ band at 208 nm, while no aldehyde absorption can be observed. The

(39) Zhao, Y. M.; Raymond, M. K.; Tsai, H.; Roberts, J. D. *J. Phys. Chem.* **1993**, *97*, 2910–2913.
(40) Drakenberg, T.; Dahlqvist, K.-I.; Forsen, S. *J. Phys. Chem.* **1972**, *76*, 2178–2183.
(41) Scherer, G.; Kramer, M. L.; Schutkowski, M.; Reimer, U.; Fischer, G. *J. Am. Chem. Soc.* **1998**, *120*, 5568–5574.

SCHEME 5. Equilibria between the *E* Configuration and the Putative *Z* Configuration (Not Observed) of the Open Form, and the Cyclic Constitution Z-7



extinction coefficients corresponding to this band were determined to be $\epsilon = 21200$ and 18082 L mol^{-1} cm^{-1} for **7** and **8**, respectively. These results are in accord with previous reports[19,26] and support the observations of the NMR investigations of the present study.

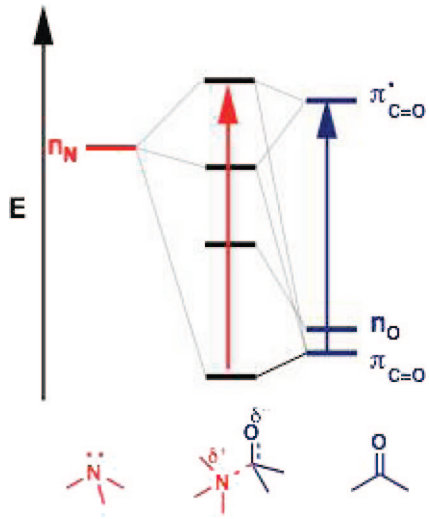


FIGURE 2. Energy levels of the $^{\delta+}$N→C═O$^{\delta-}$ molecular orbitals, constructed from the nitrogen *n* orbital and the carbonyl π orbitals; and observed transitions.

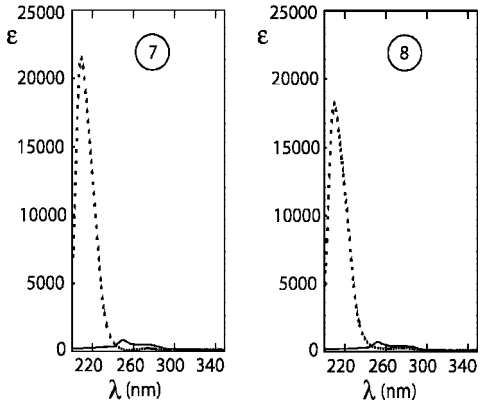


FIGURE 3. UV spectra of compounds **7** and **8** in MeOH (dotted line) and in $CHCl_3$ (continuous line).

Conclusion

We have integrated the unusual $^{\delta+}$N→C═O$^{\delta-}$ moiety into a drug-like molecule (low molecular weight, rigid, and largely inert) that displays key elements present in well-known HIV PR inhibitors, while offering unique hydrogen bonding properties yet to be explored. The rigidity provided by the urea core as well as the nucleophilicity of the hydrazine nitrogen make the cyclic form the only constitutional isomer present in methanol. This may likely be extended to aqueous media but remains to be verified by investigating derivatives with increased water solubility. Importantly, the absence of any aldehydic form is essential to any exploration of the $^{\delta+}$N→C═O$^{\delta-}$ moiety as a possible pharmacophore. Both target molecules revert completely and rapidly to the linear, aldehydic form when redissolved in chloroform, thus making this system an attractive starting point for the development of a molecular switch.

The synthetic pathway elaborated here allows for fast and economical generation of diversity using commercially available enantiopure amino acid derivatives and secondary amines as building blocks. All reactions but one were carried out at room temperature, are high-yielding, and in most cases do not require purification by column chromatography. These assets make the pathway particularly attractive for a combinatorial approach to the discovery of novel HIV PR inhibitors, or of antagonists to any other drug target for that matter. In silico screening by QM/MM methods of selected candidates based on our system in complex with HIV PR is currently in progress. The results will be applied to the generation of promising lead structures in due course.

Experimental Section

(*S*)-(1-Benzyl-2,2-dimethoxy-ethyl)-carbamic Acid Benzyl Ester (10). Aldehyde **9** (625 mg, 2.21 mmol) was dissolved in anhydrous MeOH (20 mL), and *p*-toluenesulfonic acid monohydrate (40 mg, 0.21 mmol) was added. The reaction was stirred overnight, and then most of the solvent was removed under vacuum. $NaHCO_3$ (saturated aqueous solution, 20 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4, and the solvent was evaporated under vacuum. Purification by flash chromatography (33% EtOAc/cyclohexane) gave **10** as a white solid (625 mg, 86%). Mp 75 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.19 (m, 10H), 5.07 (d, J = 12.4 Hz, 1H), 5.01 (d, J = 12.4 Hz, 1H), 4.94 (d, J = 9.2 Hz, 1H), 4.17 (d, J = 3.3 Hz, 1H), 4.11−4.09 (m, 1H), 3.43 (s, 3H), 3.39 (s, 3H), 2.93 (dd, J = 13.8, 6.1 Hz, 1H), 2.79 (dd, J = 13.8, 8.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.9, 137.7, 136.5, 129.2, 128.3, 127.8, 127.7, 126.2, 104.6, 66.4, 55.6, 55.4, 53.4, 35.8; HRMS (ESI) calcd for $C_{19}H_{23}NO_4Na$ $[M + Na]^+$ 352.1525, found 352.1526.

(*S*)-Imidazole-1-carboxylic Acid (1-Benzyl-2,2-dimethoxy-ethyl)-amide (12). CDI (457 mg, 2.82 mmol) was suspended in anhydrous THF (3 mL), and a solution of amine **11** (500 mg, 2.56 mmol) in THF (2 mL) was added dropwise at room temperature. The reaction was stirred for 30 min, and then the solvent was evaporated. The residue was redissolved in CH_2Cl_2 (10 mL) and washed with water (2 × 5 mL). The organic phase was dried over

Na_2SO_4, and the solvent was evaporated under vacuum to give pure **12** as colorless oil (814 mg, quant yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.33−7.22 (m, 6H), 7.07 (s, 1H), 5.90 (d, J = 8.5 Hz, 1H), 4.42−4.37 (m, 1H), 4.26 (d, J = 2.7 Hz, 1H), 3.49 (s, 3H), 3.39 (s, 3H), 3.02−2.94 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.6, 137.0, 135.9, 130.5, 129.2, 128.7, 126.8, 115.8, 104.1, 56.0, 55.7, 53.5, 36.0; HRMS (ESI) calcd for $C_{15}H_{20}N_3O_3$ $[M + H]^+$ 290.1505, found 290.1505.

Benzyl-piperidin-1-yl-amine (14). Benzaldehyde (2.44 g, 23.02 mmol) and hydrazine **13** (2.00 g, 20.00 mmol) were stirred at room temperature in anhydrous MeOH (150 mL) overnight. Acetic acid (30 mL, 525 mmol) and $NaCNBH_3$ (6.30 g, 100 mmol) were added, and stirring was continued for 2 h. Most of the solvent was removed under vacuum. Then a pH value around 8 was adjusted by adding $NaHCO_3$ (saturated aqueous solution, 40 mL) and NaOH (aqueous solution, 10 mL), and the mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4, and the solvent was evaporated under vacuum. After purification by flash chromatography (50% EtOAc/cyclohexane), **14** was obtained as a colorless oil (3.44 g, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.23 (m, 5H), 3.97 (s, 2H), 2.67 (br s, 4H), 1.66−1.62 (m, 4H), 1.57−1.52 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.9, 128.3, 128.0, 126.7, 57.3, 52.6, 25.8, 23.7; HRMS (CI) calcd for $C_{12}H_{19}N_2$ $[M + 1]^+$ 191.1548, found 191.1549.

(*S*)-1-Benzyl-3-(1-benzyl-2,2-dimethoxy-ethyl)-1-piperidin-1-yl-urea (15). Compound **12** (257 mg, 0.89 mmol) was dissolved in anhydrous acetonitrile (1.6 mL), and iodomethane (215 μL, 3.45 mmol) was added. The reaction was stirred overnight at room temperature, then the solvent was evaporated, and the yellow oil was dried under vacuum. The residue was redissolved in anhydrous CH_2Cl_2 (9 mL), and benzylhydrazine **14** (169 mg, 0.89 mmol) and triethylamine (123 μL, 0.89 mmol) were added. After stirring overnight at room temperature, the reaction was quenched by adding $NaHCO_3$ (saturated aqueous solution, 10 mL), and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, and the solvent was removed under vacuum. After purification by flash chromatography (33% EtOAc/cyclohexane), urea **15** was obtained as a colorless oil (260 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.13 (m, 10H), 6.61 (d, J = 9.0 Hz, 1H), 4.60 (d, J = 16.3 Hz, 1H), 4.45 (d, J = 16.3 Hz, 1H), 4.31−4.27 (m, 2H), 3.473 (s, 3H), 3.468 (s, 3H), 3.06 (dd, J = 13.9, 4.5 Hz, 1H), 2.78 (dd, J = 13.9, 8.9 Hz, 1H), 2.71−2.69 (m, 1H), 2.52−2.48 (m, 1H), 2.42−2.40 (m, 1H), 2.36−2.32 (m, 1H), 1.65−1.42 (m, 5H), 1.03−0.95 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.8, 140.5, 138.6, 129.4, 128.2, 128.1, 127.2, 126.4, 126.0, 105.9, 56.3, 55.0, 53.4, 53.1, 52.1, 42.0, 35.3, 26.4, 23.2; HRMS (ESI) calcd for $C_{24}H_{33}N_3O_3Na$ $[M + Na]^+$ 434.2420, found 434.2421.

(*S*)-1-Benzyl-3-(1-benzyl-2-oxo-ethyl)-1-piperidin-1-yl-urea (7). To a solution of compound **15** (120 mg, 0.29 mmol) in anhydrous acetonitrile (6 mL) were added NaI (110 mg, 0.73 mmol) and TMSCl (93 μL, 0.73 mmol). The reaction was stirred at room temperature for 1 h and was then quenched by adding $NaHCO_3$ (saturated aqueous solution, 5 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were washed with $Na_2S_2O_3$ (saturated aqueous solution, 10 mL) and then with water (10 mL). The organic phase was dried over Na_2SO_4, and the solvent was evaporated under vacuum. After purification by flash chromatography (50% EtOAc/cyclohexane), **7** was obtained as a colorless oil (97 mg, 92%). $[\alpha]^{25}_D$ −30.6 (c 1.086, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.66 (s, 1H; CHO), 7.25−7.12 (m, 10H; Ar), 6.85 (d, J = 6.9 Hz, 1H; NH), 4.51 (s, 2H; NCH_2Ph), 4.50−4.46 (m, 1H; NHCH), 3.12 (dd, J = 14.0, 6.0 Hz, 1H; CH_2Ph), 3.05 (dd, J = 14.0, 7.4 Hz, 1H; CH_2Ph), 2.64−2.62 (m, 1H; $NNCH_{2piperidine}$), 2.48−2.36 (m, 3H; $NNCH_{2pip}$), 1.54−1.50 (m, 3H; CH_{2pip}), 1.36−1.22 (m, 2H; CH_{2pip}), 0.95−0.87 (m, 1H; CH_{2pip}); ^{13}C NMR (127 MHz, $CDCl_3$) δ 200.7 (CHO), 158.0 (NCON), 140.0 (Ar), 136.4 (Ar), 129.3 (Ar), 128.6 (Ar), 128.3 (Ar), 127.4 (Ar), 126.9 (Ar), 126.7 (Ar), 60.2 (NHCH), 53.5 ($NNCH_{2pip}$), 53.4 ($NNCH_{2pip}$), 42.3 (NCH_2Ph), 35.3 (CH_2Ph), 26.3 (CH_{2pip}), 26.2 (CH_{2pip}), 23.1 (CH_{2pip}); ^{1}H NMR (500 MHz, MeOH-d_4), (1:1 mixture of two diasteromers) δ 7.33−7.10 (m, 18H; Ar), 6.94−6.88 (m, 2H; Ar), 4.61−4.57 (m, 4H; NCH_2Ph, $^{\delta+}N{\rightarrow}CH{=}O^{\delta-}$), 4.49−4.45 (m, 2H; NCH_2Ph), 4.14−4.05 (m, 2H; NHCH), 3.12−3.05 (m, 2H; CH_2Ph), 2.81−2.72 (m, 4H; CH_2Ph, $NNCH_{2pip}$), 2.64−2.58 (m, 2H; $NNCH_{2pip}$), 2.41−2.37 (m, 4H; $NNCH_{2pip}$), 1.67−1.60 (m, 10H; CH_{2pip}), 1.11−1.04 (m, 2H; CH_{2pip}); ^{13}C NMR (127 MHz, MeOH-d_4) δ 160.9 (NCON), 160.8 (NCON), 142.4 (Ar), 140.9 (Ar), 131.39 (Ar), 131.37 (Ar), 130.2 (Ar), 130.0 (Ar), 129.03 (Ar), 129.02 (Ar), 128.4 (Ar), 128.1 (Ar), 100.5 ($^{\delta+}N{\rightarrow}CH{=}O^{\delta-}$), 100.1 ($^{\delta+}N{\rightarrow}CH{=}O^{\delta-}$), 57.5 (NHCH), 57.4 (NHCH), 55.41 ($NNCH_{2pip}$), 55.38 ($NNCH_{2pip}$), 54.92 ($NNCH_{2pip}$), 54.86 ($NNCH_{2pip}$), 43.9 (NCH_2Ph), 37.44 (CH_2Ph), 37.36 (CH_2Ph), 28.36 (CH_{2pip}), 28.34 (CH_{2pip}), 28.30 (CH_{2pip}), 28.24 (CH_{2pip}), 25.1 (CH_{2pip}); MS (ESI) m/z 366.2 ($[M + H]^+$, 100). HRMS (ESI) calcd for $C_{22}H_{28}N_3O_2$ $[M + H]^+$ 366.2182, found 366.2187. Anal. Calcd for $C_{22}H_{27}N_3O_2$: C, 72.30; H, 7.45; N, 11.50. Found: C, 72.19; H, 7.48; N 11.46.

(*S*,*S*)-[2-(1-*tert*-Butylcarbamoyl-2-methyl-propylcarbamoyl)-pyrrolidin-1-yl]-carbamic Acid *tert*-Butyl Ester (20). Compound **19** (1.94 g, 8.43 mmol) was dissolved in CH_2Cl_2 (60 mL), and EDC (2.26 g, 11.77 mmol) and then HOBt (12.65 mL of a 1 N solution in *N*-methylmorpholine, 12.65 mmol) were added. After 5 min, a suspension of HValNH^{t}Bu·HCl (1.75 g, 8.43 mmol) and triethylamine (1.17 mL, 8.43 mmol) in CH_2Cl_2 (20 mL) was added, and the reaction was stirred overnight. $NaHCO_3$ (saturated aqueous solution, 80 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic extracts were dried over Na_2SO_4, and the solvent was evaporated under vacuum. Purification by flash chromatography (50% EtOAc/CH_2Cl_2) gave **20** as colorless oil (3.24 g, quant yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (br s, 1H), 6.01 (br s, 1H), 5.82 (br s, 1H), 4.05−4.02 (m, 1H), 3.56 (dd, J = 10.2, 4.8 Hz, 1H), 3.41−3.38 (m, 1H), 2.87 (dd, J = 16.4, 9.4 Hz, 1H), 2.35−2.27 (m, 2H), 2.01−1.85 (m, 2H), 1.82−1.72 (m, 1H), 1.45 (s, 9H), 1.32 (s, 9H), 0.95 (d, J = 6.7 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.0, 170.2, 155.6, 80.1, 68.2, 59.3, 55.7, 50.9, 29.8, 29.5, 28.5, 28.2, 23.1, 19.4, 17.6; HRMS (ESI) calcd for $C_{19}H_{36}N_4O_4Na$ $[M + Na]^+$ 407.2634, found 407.2633.

(*S*,*S*)-1-Benzylamino-pyrrolidine-2-carboxylic Acid (1-*tert*-Butylcarbamoyl-2-methyl-propyl)-amide (21). Compound **20** (1.48 g, 3.85 mmol) was dissolved in TFA (80 mL) and stirred for 2 h at room temperature. The solvent was evaporated, and the yellow oil was dried under vacuum. The residue was redissolved in MeOH (30 mL), and according to the preparation of **14**, reacted with benzaldehyde (471 mg, 4.44 mmol), followed by treatment with $NaCNBH_3$ (1.22 g, 19.30 mmol) and acetic acid (6 mL, 105 mmol). After reaction workup (see synthesis of compound **14**), and purification by flash chromatography (5% MeOH/CH_2Cl_2), **21** was obtained as a white solid (1.34 g, 93%). Mp 82 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 9.0 Hz, 1H), 7.35−7.22 (m, 5H), 5.93 (br s, 1H), 4.06−3.98 (m, 3H), 3.55−3.52 (m, 1H), 3.24 (dd, J = 9.6, 5.8 Hz, 1H), 2.36 (dd, J = 16.5, 8.2 Hz, 1H), 2.27−2.13 (m, 2H), 1.89−1.75 (m, 3H), 1.31 (s, 9H), 0.95 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.7, 170.2, 138.2, 128.7, 128.2, 127.1, 69.6, 58.3, 56.1, 54.8, 51.0, 30.8, 28.4, 28.1, 22.2, 19.2, 18.0; HRMS (ESI) calcd for $C_{21}H_{35}N_4O_2$ $[M + H]^+$ 375.2760, found 375.2761.

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spectra, respectively. This work was supported by the Rhone-Alpes Region through research cluster 5, and by the French Research Ministry and the CNRS. M.W. acknowledges a European Doctoral Fellowship from the Research Ministry.

Supporting Information Available: General experimental procedures. Experimental protocols and characterization data for compounds **8**, **9**, **11**, **16**, **16a**, **17**, **17a**, **19**, and **22**. ^{1}H NMR and ^{13}C NMR spectra of compounds **7**−**22**. ^{1}H NMR spectral monitoring of the cyclization process of **7** in MeOH-d_4. ^{1}H−^{1}H NOESY, ^{1}H−^{13}C HMBQ, and ^{1}H−^{13}C HMBC spectra of **7**. LC-MS analyses (chromatograms, mass spectra) of the conversions of **16** to **17** and **16a** to **17a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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