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Synthetic Chemical Diversity: Solid Phase Synthesis of Libraries of C_2 Symmetric Inhibitors of HIV Protease Containing Diamino Diol and Diamino Alcohol Cores

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Solid phase synthesis of non-oligomeric organic compounds has been pursued for high-efficiency generation of large numbers of structurally diverse compounds for drug screening. Known as chemical diversity libraries or combinatorial libraries (when the synthesis is carried out in a combinatorial fashion), these compounds can be used for *de novo* discovery of drug leads or for expedient structure–activity relationship (SAR) studies. To expand the scope of solid phase synthesis beyond the capability of the traditional method of solid phase synthesis for peptides, a strategy was developed for bi-directional solid phase synthesis starting with diamino alcohol or diamino diol core structures. The strategy relies on using bifunctional linkers to modify the core structures, simultaneously protecting the hydroxyl group or the diol moiety of the core and providing a carboxyl group for attachment of the modified cores to a solid support. The two NH_2 groups of the modified cores attached to the solid support were then deprotected and reacted with a wide variety of amine-reactive reagents (carboxylic acids, sulfonyl chlorides, isocyanates, chloroformates, etc.) to extend the molecule in both directions. This strategy was successfully applied to automated parallel synthesis of a library of C_2 symmetric inhibitors of HIV protease containing the known symmetry-based diamino diol and diamino alcohol core structures, thus enabling expedient access of large numbers of analogs in this series. A library of over 300 discrete compounds was synthesized using this methodology in order to identify potent (IC_{50} < 100 nM) HIV protease inhibitors with reduced size. This paper describes the technical aspects of this technology.

Introduction

High-through-put screening has played an important role in drug discovery by providing drug leads or, in some instances, drug candidates.[1] Traditionally, the samples for screening have come from either natural sources (*e.g.*, plant or soil extracts and fermentation broth) or existing collections of pure synthetic compounds. Recent approaches in this area have utilized the preparation of large libraries of structurally diverse compounds primarily using a variety of polymer-supported (solid phase) synthetic techniques, known as synthetic chemical diversity libraries.[2] High expectations have been bestowed to this new approach to drug discovery for a number of reasons. First, the techniques of solid phase synthesis have been greatly advanced due to the improvement in the chemistry and instrumentation of solid phase peptide synthesis during past several decades[3] and the adoption of combinatorial synthesis which can produce combinatorial mixtures of vast numbers of compounds in a short period of time.[4] Several technical approaches have been developed for combinatorial synthesis.[5] Second, it is now recognized

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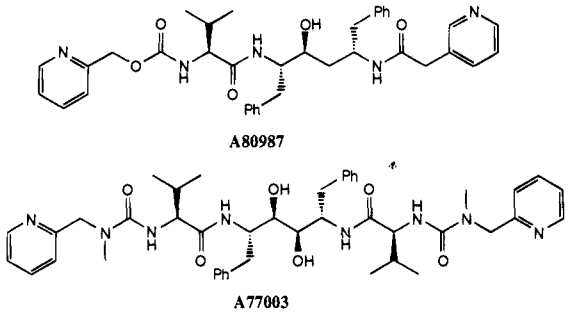


Figure 1. Structures of representative HIV protease inhibitors containing the diamino diol core (A77003) and diamino alcohol core (A80987).

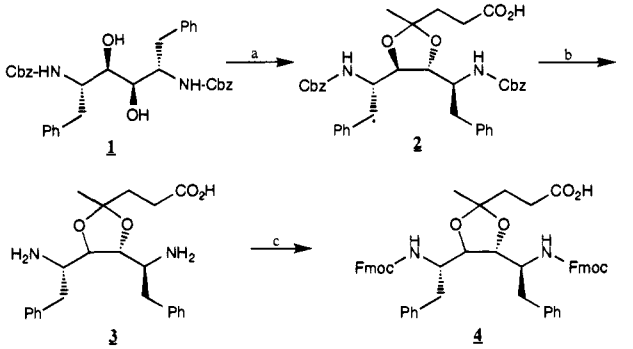


Figure 2. Synthesis of modified diamino diol core (1). Reagents and conditions: (a) levulinic acid, concentrated H_2SO_4 (catalytic), room temperature, overnight, 95–100%; (b) EtOAc, Pd/C, H_2, 95–100%; (c) H_2O/dioxane, $NaHCO_3$, Fmoc-OSu, 85%.

that unpurified samples of synthetic individual compounds or combinatorial mixtures can be treated similarly to natural products as valid sources of compounds for screening, although they are not subjected to the vigorous characterization or purification required for typical synthetic compounds. Despite the apparent potentials, several obstacles to the success of this approach remain. One of the challenges is to expand the scope of solid phase synthesis to allow preparation of compound libraries based on non-oligomeric small organic molecules, since early libraries are mostly composed of peptides which have limited usefulness as drugs.[6] Some progress has been made in this area[7] with several recent papers describing solid phase synthesis of nonpeptidic organic compounds, including benzodiazepines and hydantoins[8,9] and inhibitors of aspartic proteases.[10]

In terms of application, a diversity library can be designed for general screening to test activity against a variety of biological targets for *de novo* discovery of drug leads (universal libraries). Alternatively, a library can be designed to encompass analogs based on existing core structures for expedient structure–activity relationship studies (targeted or focused libraries). In this report, we describe a method for automated solid phase synthesis of targeted diversity libraries based on the C_2 symmetric HIV protease inhibitors containing diamino alcohol or diamino diol core units. The method employs a strategy of bi-directional solid phase synthesis using a hydroxyl group or diol moiety as the attachment point. We have synthesized a library of over 300 compounds using this methodology in order to identify potent (IC_{50} < 100 nM) HIV protease inhibitors with reduced size.

Rationale. HIV protease has been shown to be a viable target for therapeutic intervention of HIV infection, and extensive efforts have been directed toward developing clinically effective inhibitors of this enzyme.[11] Compounds containing the C_2 symmetric or pseudosymmetric diamino alcohol or diamino diol core units, as exemplified by A80987[12] and A77003[13] (Figure 1), are among the most potent HIV protease inhibitors reported. Several compounds of these classes are currently in clinical trials.[14] Our effort to develop diversity libraries containing these two classes of compounds is motivated by two considerations. First, despite the success these compounds have achieved, there is considerable need to discover compounds with improved potency and enhanced bioavailability and pharmacokinetics. This point is underscored by the fact that several clinical candidates have developed viral resistance *in vitro* and that uninterrupted inhibition of viral replication with more potent and bioavailable inhibitors is believed to be the most promising way of overcoming the onset of viral resistance.[15] Furthermore, there is a strong incentive to uncover potent compounds with reduced size, which, in principle, are more likely to be bioavailable and more economical to produce.

The most prominent structural feature of A80987, A77003, and their analogs is that the molecules extend in *both directions* starting from the central diamino alcohol or diamino diol core unit. While the phenyl groups of the core interact with the P1/P1′ binding pockets of the enzyme, the ligands for the P2/P2′ and P3/P3′ binding pockets of the enzyme are attached sequentially to the amino groups of the core via amide, carbamate, urea, or sulfonamide linkages.[16] This geometry contradicts the scheme of conventional solid phase (peptide) synthesis, which starts from the carboxyl terminus and proceeds unidirectionally to the aminoterminus. Furthermore, traditional solid phase synthesis also requires a carboxyl group for attachment to the resin.[17]

We anticipated that this obstacle could be overcome by functionalization of the central diamino alcohol or diamino diol core units with a bifunctional linker which simultaneously provides hydroxyl protection and a carboxylic group for attaching the modified cores to the solid support. The two NH_2 groups of the modified cores attached to the solid support could then be deprotected and allowed to react with a wide variety of amine-reactive reagents (carboxylic acids, sulfonyl chlorides, isocyanates, chloroformates, etc.) in order to extend the molecule in both directions, thus enabling automated solid phase synthesis of analogs of A80987 or A77003.

Results

The structures and synthesis of modified diamino diol core (**4**) and diamino alcohol core (**10**) are presented in Figures 2 and 3, respectively. We chose to use Fmoc as the protection group for the amino groups to take advantage of the mild conditions for its removal (weak base).[18] The key features of compounds **4** and **10** are the bifunctional linkers and the bond linkage between the linkers and the core units. For the modified cores to be useful in solid phase synthesis, this linkage must be stable under the conditions of solid phase synthesis and cleavable by treatment with a mild acid such as trifluoroacetic acid (TFA) to release the final products from the solid support. The commercially available

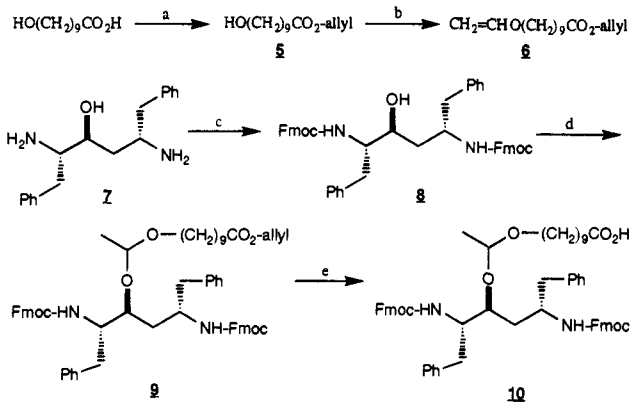


Figure 3. Synthesis of the modified diamino alcohol core (**2**). Reagents and conditions: (a) allyl alcohol (excess), CH_2Cl_2, 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride, 4-(dimethylamino)pyridine (catalytic), 3 h, 75%; (b) ethyl vinyl ether, $Hg(OAc)_2$, reflux, overnight, 60–75%; (c) Fmoc-OSu, CH_2Cl_2, pyridine, overnight, 80-95%; (d) **6**, pyridinium *p*-toluenesulfonate, CH_2Cl_2, 3 h, 85%; (e) dimedone, $Pd[PPh_3]_4$, THF, overnight, 85%.

levulinic acid served as a convenient linker for the diamino diol core, allowing synthesis of the Fmoc-protected modified diamino diol core (**4**) from the bis-Cbz protected diamino diol core (**1**) in three steps in about 80% overall yield (Figure 2). For the diamino alcohol core, a variety of potential bifunctional linkers were designed and synthesized. Terminal olefinic acid, exemplified by benzyl 7-methyl-7-octenoate, represents one class of potential alcohol linkers which can be used to convert the hydroxyl group of the bis-Fmoc-protected diamino alcohol core (**8**) into a tertiary ether under acid catalysis. However, benzyl 7-methyl-7-octenoate failed to react with **8** in the desired fashion under a variety of conditions. Several likely linkers based on 3,4-dihydro-2*H*-pyran, similar to the linker described by Ellman and co-workers,[19] were also synthesized. However, the hydroxyl group of **8** was apparently too sterically hindered to react with 5-substituted 3,4-dihydro-2*H*-pyran.[20] These results led to the design of a linear vinyloxy carboxylic acid, namely allyl 10-(vinyloxy)-decanoate (**6**, Figure 3), as a linker. Indeed, compound **6** reacted smoothly with the bis-Fmoc-protected diamino alcohol core (**8**) under very mild acidic conditions using pyridinium *p*-toluenesulfonate to give acetate **9**, which led to the desired diamino alcohol core **10** after removal of the allyl group. We anticipated that the ketal linkage of the diamino diol core **4** and the acetal linkage for the diamino alcohol core **10** should satisfy the requirements of solid phase synthesis.

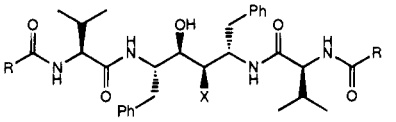
Having developed the modified cores, we then set out to establish the feasibility of a solid phase synthesis of analogs of A80987 and A77003 by synthesizing a panel of model compounds (Table 1). To start, the modified cores (**4** and **10**) were coupled to the NovaBead 4-methylbenzhydramine (MBHA) resin (substitution level: 0.45–0.8 mmol/g) in large batches via amide bond formation using the standard carbodiimide-catalyzed activation of **4** and **10**. The actual loading level was estimated by the weight gain or more quantitatively by spectrometric quantitation of dibenzofulvene after subjecting a portion of the resins to deprotection by piperidine. A number of commercially available resins were evaluated, and the MBHA resin was chosen since the amide bond between the cores (**4** and **10**) and MBHA resin is expected to be resistant to trifluoroacetic acid. Thus, only cleavage of the ketal (for the diamino diol series) and acetal (for the diamino alcohol series) linkage is expected during the postsynthesis cleavage step with TFA, and the linkers will stay attached to the resin, eliminating a source of contamination.

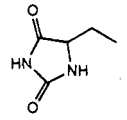
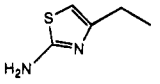
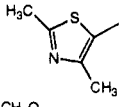
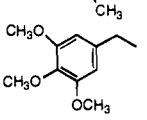
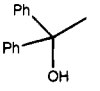
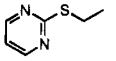
The remaining synthesis involves Fmoc removal (piperidine in DMF), coupling of Fmoc amino acids, Fmoc removal, and coupling to carboxylic acids or sulfonyl chlorides. For high-through-put automated synthesis, these steps can be conveniently performed in a completely automated fashion on one of several commercially available multiple-peptide synthesizers, capable of synthesizing 48 or 96 compounds in parallel in a single run (6–8 h of instrument time). Most of these instruments can accommodate a variety of chemistries for activation of carboxyl group. We obtained satisfactory results with the Abimed AMS422 instrument employing PyBOP–HOBt chemistry.[21] At the completion of the synthesis, the dried resins were subjected to acid-mediated cleavage, and the products were obtained by evaporation of the filtered cleavage solutions. The overall process of solid phase synthesis is illustrated in Figure 4.

The product cleavage step merits further comments. We initially anticipated that the acid sensitivity of the acetal linkage of **4** and the ketal linkage of **10** would allow facile cleavage of the finished products from the resin with TFA. This turned out to be the case for the diamino alcohol series, for which resin-bound products can be cleaved completely with 30% aqueous TFA for 3 h. For the diamino diol series, however, the cleavage required much more drastic conditions, due to poor acid-sensitivity of the ketal linkage of **10**. A variety of conditions were attempted to effect this cleavage. The best result was obtained with 95% TFA overnight at room temperature, which gave the desired products (**11**, X = OH) as well as significant amount of contaminating compounds still carrying the levulinic acid linker (cleaved but not deprotected), as evident from the mass spectra (*vide infra*).

Several criteria were employed to judge the performance of the solid phase synthesis approach: formation of the expected products, product purity, and yield. The goal was to obtain the expected products in purity acceptable for screening without further purification and in quantities sufficient for multiple testings. For all the model compounds, unpurified product was obtained in amounts close to the theoretical yield based on the amount of resin used after drying the samples to a constant weight. Thus, using 60–70 mg of the loaded resins (maximum amount allowed by the instrument we employed, loading level: 0.5 mmol/g), 25–30 mg of the unpurified products were obtained. Mass spectrometry was then employed for identification of the products. Molecular ions were observed for all the model compounds (supporting information). For several compounds in the diol series, a (M + 97) peak derived from the expected product still coupled to the linker was also observed. The purity of the samples was then assessed with thin-layer chromatography (TLC) or more quantitatively with HPLC analysis, which revealed purity ranging from 30% to 70% for the mono-ol series and from 20% to 50% for the diol series. In general, purity of the mono-ol compounds was better than the corre-

Table 1. Structures and Biological Activity of Model HIV Protease Inhibitors Synthesized Using the Process of Solid Phase Synthesis (Figure 4)[a]



Entry	R	Mono-ol (X=H) M.W	Mono-ol (X=H) IC_{50} (nM)[a]	Diol (X=OH) M.W	Diol (X=OH) IC_{50} (nM)[a]
1		762	<1[b]	778	9.6
2		762	<1[c]	778	12
3		760	13	776	860
4		898	<1[d]	914	3.4
5		902	160	918	6400
6		786	<1[e]	802	16

[a] Concentration was based on the weight of unpurified samples and not corrected for impurities. Each compound was assayed at 3–5 concentrations where feasible and the IC_{50} values were determined from the percentage of inhibition data, [b] 43% inhibition at 0.5 nM. [c] 40% inhibition at 0.5 nM. [d] 71% inhibition at 0.5 nM. [e] 33% inhibition at 0.5 nM.

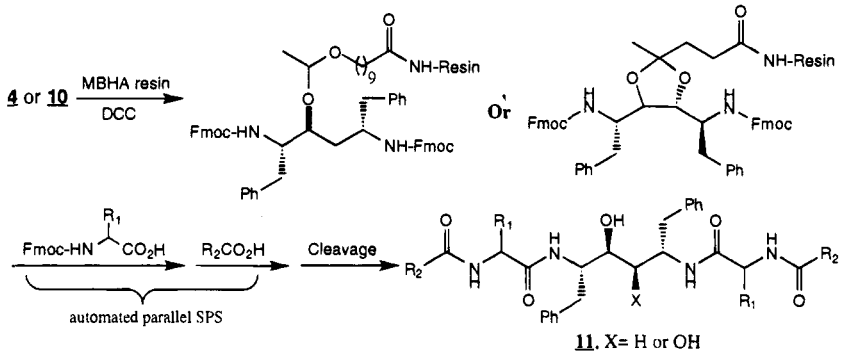


Figure 4. Scheme of solid phase synthesis of analogs of A77003 and A80987.

sponding compound in the diol series, apparently due to the long reaction time required for cleavage of the diol products with 95% aqueous TFA.

The unpurified samples of the model compounds were tested for HIV protease inhibition. In a fluorometric HIV protease activity assay,[22] these compounds inhibit HIV protease with IC_{50} ranging from <1 nM to 6.4 μM (Table 1). The data in Table 1 indicated that compounds containing the mono-ol core are consistently more potent inhibitors than the corresponding compounds containing the diol core. This result is in agreement with the conclusion of previous studies using compounds obtained via traditional solution synthesis.[23]

Having established the feasibility of our approach, we proceeded to synthesize diversity libraries of compounds containing the diamino diol and diamino alcohol cores. Our initial attention has been focused on compounds lacking the valine residues present in A80987 and A77003 (Figure 1) or the model compounds (Table 1). This decision was based on a previous study of analogs

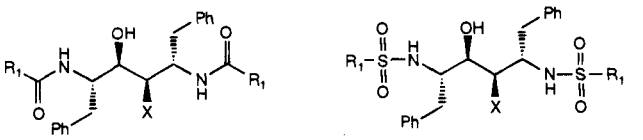


Figure 5. Generic structures of the first library of half-sized inhibitors of HIV protease.

of A77003 and A80987 which showed that molecular size was an important determinant of oral bioavailability.[12] We started by selecting a diverse set of monomers (building blocks) from a large pool of commercially available carboxylic acids and sulfonyl chlorides. A library of 300 compounds (150 compounds each containing the diol and mono-ol core, respectively), with generic structures as shown in Figure 5, was then synthesized. With the Abimed AMS422 synthesizer, up to 48 compounds (24 compounds each of the diol series and mono-ol series) can be synthesizer per run which can be completed in a day. Since our primary application for

this library is to search for inhibitors with activity above a set threshold, routine chromatographic purification of the samples was not pursued. However, all samples were subjected to FAB mass spectrometry analysis. Screening of this library for HIV protease inhibition is on-going, and the results will be reported in the future.

Discussion

With the exception of the unexpected harsh conditions required for cleavage of the products in the diol series (95% TFA, overnight), the solid phase synthesis strategy we envisioned for the C_2 symmetric or pseudosymmetric HIV protease inhibitors was successful. The method is efficient and flexible, allowing incorporation of wide varieties of functionalities.

The essence of the synthetic chemical diversity approach for drug discovery is rapid synthesis and screening of large numbers of compounds as collections of individual compounds (often unpurified) or combinatorial mixtures. Thus, product purity (for individual compounds) or integrity (for combinatorial mixtures) becomes an important issue. Currently, there is no consensus to the minimum purity required. Besides the obvious requirement that one should exercise all the chemistry diligence to improve the integrity of the library, the exact requirement of purity (for libraries of individual compounds) apparently depends on the intended application of the library (or conversely, the purity level of a library will dictate its application). A powerful application of synthetic diversity libraries is for the discovery of drug leads or for the identification of compounds with potency above a given level, which permits rapid identification of the most potent compounds in a series. In this scenario, the purity or integrity of the library is of minor concern since the lead compounds discovered by the initial screening can be followed up by more meticulous characterization using traditional methods. If, however, the library is designed for quantitative SAR studies, far more stringent requirements clearly need to be placed on the product purity, likely requiring chematographic purification.

Given the significant variation in the purity of the model compounds, the library we have synthesized will be limited to qualitative or semiquantitative applications. Since the concentrations of the samples were calculated based on the weight of the unpurified samples and not corrected for impurity, the IC_{50} values in Table 1 probably underestimated the true potency of these compounds. Significantly, the mono-ol series and diol series gave an identical activity trend (for both series, entry 4 was the most active; followed by entries 1, 2, and 6 with similar activities; followed by entry 3; followed by entry 5). These results demonstrated that this approach can be used at least to obtain preliminary SAR data that establishes the gross trend (*i.e.*, effects of >1 order of magnitude) for a given series (mono-ol or diol).

A variety of factors can affect the product purity from a solid phase synthesis, including the intrinsic yield of the chemical transformations involved and the properties of the monomers (building blocks). Often, the solid phase chemistry employed for the synthesis of a library is optimized using a limited number of model monomers, leaving the properties of the monomers used for the synthesis of the actual library the most significant variable. Such variability can arise from variable reactivity of the reacting functional group of the monomers, potential interference of side-chain functional groups with the desired reactions, and the unknown stability of the monomers under the TFA or other cleavage conditions. For solid phase synthesis of standard peptides, all these variables have been carefully examined over the past several decades, and vast amount of information is available regarding reactivity of various standard amino acids, their stability under the cleavage conditions, etc. However, for a synthesis employing building blocks other than standard amino acids, such experimental information is largely lacking. Since it is often not practical to investigate the suitability of individual monomers, only empirical predictions can be relied upon as the guidance.

The synthetic process illustrated in Figure 4 starting with modified diamino diol core (**4**) and diamino monool core (**10**) leads to formation of C_2 symmetric molecules. However, it would be relatively easy to adapt this methodology for solid phase synthesis of HIV protease inhibitors of other structural types. As one example, unsymmetric inhibitor molecules can be synthesized by protecting the amino groups of the cores orthogonally using protecting groups removable under different conditions (*e.g.*, a combination of Fmoc and Alloc group) which permits sequential deprotection and acylation of each amino group. Furthermore, our strategy could potentially be adapted for solid phase synthesis of other HIV protease inhibitors, such as the seven-membered ring cyclic ureas described recently by Lam *et al.*[24]

Although we have only used the solid phase synthesis process shown in Figure 4 for parallel synthesis of individual compounds, it should be applicable for *combinatorial synthesis* as well. However, combinatorial synthesis will pose a number of unique problems, not the least of which is the issue that library integrity can be compromised due to the formation of side products. It is logical that stringent requirements need to be placed on a solid phase synthesis process in order to carry out the process in a combinatorial fashion. Otherwise, identification of library components that exhibit biological activities would become exceedingly difficult, even with the aid of various encoding tactics described recently.[25]

In summary, we have developed technologies for solid phase synthesis of compounds containing diamino diol and diamino alcohol core structures as potential HIV protease inhibitors. The methods have been adapted on a commercially available instrument for parallel synthesis of a diversity library containing these structures. This represented one of the first examples of applying solid phase synthesis technique toward multiple, parallel synthesis of compound analogs, and the approach will be broadly applicable to many other classes of compounds.

Experimental Section

General Methods. Commercially available solvents were used as received, and reagents were purchased from Aldrich Chemical Co. (Milwaukee, WI) unless noted otherwise. Column chromatography was performed with the solvent systems indicated using E. Merck silica gel 60 (70–230 mesh). ^1H NMR spectra were recorded on a GE AE-300 (300 MHz) using tetramethylsilane as an internal standard. Abbreviations:

Cbz, (benzyloxy)carbonyl; MBHA, 4-methylbenzhydrylamine; Fmoc, fluorenylemthyloxycarbonyl; DMF, *N,N*-dimethylformamide; NMP, *N*-methylpyrrolidone; HOBt, 1-hydroxybenzotriazole hydrate; DMAP, 4-(dimethylamino)pyridine; PyBOP, (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate. The starting materials for synthesis of the modified cores, compound 1 and **7**, were obtained from Department of Process Chemistry, Abbott Laboratories. The Abimed AMS 422 Multiple Peptide Synthesizer was acquired via Gilson Medical Electronics Co. (Middleton, WI).

Preparation of (4*R*,5*R*,1″*S*)-1-Methyl-1-(3′-carboxypropyl)-4,5-bis[1″-[(benzyloxycarbonyl)amino]-2″-phenylethyl]-1,3-dioxolane (2). A suspension of compound 1 (10.0 g, 17.62 mmol) in 60 mL of levulinic acid and 0.8 mL of concentrated H_2SO_4 was stirred at ambient temperature for 24–48 h or until the mixture turned into a homogeneous yellow solution. The reaction mixture was taken up in 200 mL of ether, and the solution was washed repeatedly with saturated NaCl solution to remove excess levulinic acid. Upon complete removal of levulinic acid (TLC), the etheral solution was dried ($MgSO_4$), filtered, evaporated, and dried *in vacuo* to give a white solid, 11.43 g, 97.3%. ^{1}H NMR ($CDCl_3$): δ 1.40 (s, 3H), 2.0–2.1 (m, 2H), 2.35–2.50 (m, 2H), 2.70–2.90 (m, 4H), 3.65–3.75 (m, 2H), 3.95 (m, 1H), 4.10 (m, 1H), 4.70–5.00 (m, 6H), 7.00–7.30 (m, 20H). FAB-MS: m/z 667 $(M + H)^+$, 623 $(M - CO_2)^+$, base peak.

Preparation of (4*R*,5*R*,1″*S*)-1-Methyl-1-(3′-carboxypropyl)-4,5-bis[1″-[1″-amino-2″-phenylethyl]-1,3-dioxolane (3). Compound **2** (11.4 g, 17.14 mmol) was hydrogenated in EtOAc or MeOH with 10% Pd/C as the catalyst at ambient temperature. The catalyst was filtered and washed extensively with MeOH. Concentration of the solution gave 6.64 g (97.2%) of a white solid. ^{1}H NMR (MeOH-d_4): δ 1.40 (s, 3H), 2.10 (m, 2H), 2.30 (m, 2H), 2.55–2.70 (m, 2H), 2.90 (d, 2H), 3.10 (m, 1H), 3.45 (m, 1H), 3.95 (m, 1H), 4.10 (m, 1H), 7.10–7.40 (m, 10H). CIMS: m/z 399 $(M + H)^+$, base peak.

Preparation of (4*R*,5*R*,1″*S*)-1-Methyl-1-(3′-carboxypropyl)-4,5-bis[1″-[(fluorenylmethyloxycarbonyl)amino]-2″-phenylethyl]-1,3-dioxolane (4). To a solution of the diamino ketal **3** (3.79 g, 9.52 mmol), a mixture of 55 mL of dioxane, and 50 mL of water containing sodium bicarbonate (1.639 g, 19.5 mmol) was added a solution of Fmoc-OSu (NovaBiochem, 6.48 g, 19.23 mmol) in 50 mL of dioxane over several minutes. After the mixture was stirred at ambient temperature overnight, water (300 mL) was added, and the mixture was carefully acidified to pH 2 with 1 N HCl and extracted with EtOAC (5 × 100 mL). The combined organic solution was worked up routinely and evaporated to give an off-white solid. Column chromatography using 60% EtOAc in hexane as the solvent afforded 7.5 g (93.5%) of the title compound as a white solid. ^{1}H NMR (MeOH-d_4): δ 1.48 (s, 3H), 1.98 (d, 2H), 2.10 (t, 2H), 2.48 (m, 2H), 2.80 (m, 4H), 3.90–4.15 (m, 8H), 6.8–7.8 (m, 26H). FAB-MS: m/z 843 $(M + H)^+$, 881 $(M + K)^+$.

Preparation of Allyl 10-Hydroxydecanoate (5). To a solution of 10-hydroxydecanoic acid (5.0 g, 26.5 mmol) and allyl alcohol (15.5 g, 265 mmol) in 100 mL of CH_2Cl_2 was added 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (Sigma Chemical Co., 6.15 g, 31.8 mmol) and DMAP (100 mg). After stirring for 2 h, the solution was washed with 0.1 N HCl (3 × 50 mL), 5% aqueous $NaHCO_3$ (3 × 50 mL), and brine (3 × 50 mL), dried ($MgSO_4$), filtered, and concentrated. The crude product was passed through a silica gel plug using 40% EtOAc in hexane to remove the baseline contamination. Concentration of the solution gave 4.5 g of an oil (75.0%). ^{1}H NMR ($CDCl_3$): δ 5.92 (m, 1H), 5.32 (dq, 1H), 5.23 (dq, 1H), 4.58 (dt, 2H), 3.63 (t, 2H), 3.65 (t, 2H), 2.35 (t, 2H), 1.5–1.7 (m, 4H), 1.3 (m, 8H). CIMS (NH_3): m/z 229 $(M + H)^+$, 246 $(M + NH_4)^+$.

Preparation of Allyl 10-(Vinyloxy)decanoate (6). Mercury acetate (2.44 g, 7.7 mmol) was added to a solution of allyl 10-hydroxydecanoate (3.5 g, 15.4 mmol) in 80 mL of distilled ethyl vinyl ether. The solution was purged with argon and refluxed under argon atmosphere overnight. After cooling to ambient temperature, K_2CO_3 (1.0 g) was added and the mixture stirred for 30 min. EtOAc (100 mL) was added, and the solution was washed with saturated NaCl (4 × 80 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography using 30% EtOAc–hexane as the solvent to give 3.0 g of a liquid (61%). ^{1}H NMR ($CDCl_3$): δ 6.45 (dd, 1H), 5.92 (m, 1H), 5.32 (d.q, 1H), 5.23 (d.q, 1H), 4.58 (d.t, 2H), 4.18 (d.d, 1H), 3.97 (d.d, 1H), 3.63 (t, 2H), 2.35 (t, 2H), 1.5–1.7 (m, 4H), 1.3 (m, 8H). CIMS (NH_3): m/z 255 $(M + H)^+$, 272 $(M + NH_4)^+$.

Preparation of (2*S*,3*S*,5*S*)-3-Hydroxy-2,5-bis[(fluorenylmethyloxycarbonyl)amino]-1,6-diphenylhexane (8). To a solution of diamino alcohol **7** (2.84 g, 10.0 mmol) in CH_2Cl_2 (150 mL) was added Fmoc-OSu (NovaBiochem, 6.75 g, 20.0-mmol) and diisopropylethylamine (3.4 mL, 20 mmol). The solution was stirred at room temperature overnight. The solid formed was collected by filtration, washed five times with aqueous NaCl solution, and dried under vacuum to give the first crop of product. The mother liquor was concentrated and the residue taken up in EtOAc (200 mL). The solution was washed with saturated NaCl (3 × 100 mL), dried, and filtered. Solvent evaporation gave additional product. Total yield was 6.13 g (84.2%). ^{1}H NMR (DMSO-d_6): δ 1.60 (bt, 2H), 2.50 (m, 2H), 2.55–2.80 (m, 4H), 3.65 (m, 1H), 3.8–4.2 (m, 9H), 7.05–7.45 (m, 18H), 7.60–7.70 (m, 4H), 7.86 (d, 4H). FAB-MS: m/z 729 $(M + H)^+$.

Preparation of Allyl 10-{1′-[[(2′*S*,3″*S*,5″*S*)-2″,5″-Bis[(fluorenylmethyloxycarbonyl)amino]-1″,5″-diphenylhex-3″-yl]oxy]ethoxy}decanoate (9). To a suspension of the Fmoc-protected diamino alcohol **9** (3.28 g, 4.5 mmol) in CH_2Cl_2 (300 mL) was added allyl 10-(vinyloxy)decanoate (**6**, 1.7 g, 6.7 mmol), followed by pyridinium *p*-toluenesulfonate (0.113 g, 0.45 mmol). The mixture turned clear in about 1 h. The reaction was monitored frequently by TLC (40% EtOAc–hexane). Additional linker **6** was added (~20% each time) if necessary until complete conversion of the starting core was observed. The solution was then washed with pH 7.0 Na_2HPO_4 (0.1 M) buffer (2 × 150 mL) and saturated NaCl (2 × 100 mL) and then dried ($MgSO_4$). Filtration and solvent evaporation gave a clear oil which was chromatographed on a silica gel column, using 40% EtOAc–hexane solvent to give a foamy solid, 3.0 g, 67%. ^{1}H NMR (DMSO-d_6): δ 1.20–1.35 (m, 10 H), 1.48 (m, 2H), 1.60–1.70 (m, 4H), 2.32 (t, 2H), 2.60–2.95 (m, 4H), 3.30–3.45 (m, 2H), 3.60–3.70 (m, 1H), 3.90–4.45 (m, 9H), 4.58 (dt, 2H), 4.60–4.70 (m, 2H), 4.80–5.00 (m, 1H), 5.20–5.35 (ddd, 2H), 5.85–6.00 (m, 1H), 7.05–7.45 (m, 18H), 7.60–7.70 (m, 4H), 7.85 (d, 4H). FAB-MS (with K^+): m/z 1021 $(M + K)^+$.

Preparation of 10-{1′-[[(2′*S*,3″*S*,5″*S*)-2″,5″-Bis[(fluorenylmethyloxycarbonyl)amino]-1″,5″-diphenylhex-3″-yl]oxy]ethoxy}decanoic Acid (10). To a solution of compound **9** (4.8 g, 4.9 mmol) in 200 mL of anhydrous THF (Aldrich Gold Label) was added dimedone (6.85 g, 49 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.56 g, 0.49 mmol). The solution was purged with nitrogen and then stirred under nitrogen at room temperature overnight. The solution was then concentrated, and the residue was taken up in EtOAc (200 mL) and washed with pH 7.0 Na_2HPO_4 (0.1 M) buffer (2 × 150 mL). The organic solution was then treated repeatedly by mixing with saturated $NaHSO_3$ (150 mL) followed by vigorous stirring for 15–30 min until essentially all dimedone was removed (2–3 treatments required). The organic solution was then washed with saturated NaCl (2 × 150 mL) and worked up routinely. The crude product was purified by column chromatography using 50% EtOAc–hexane solvent, which afforded 3.8 g of white solid (84.0%). ^{1}H NMR ($CDCl_3$): δ 1.20–1.35 (m, 10 H), 1.48 (m, 2H), 1.65–1.75 (m, 4H), 2.32 (t, 2H), 2.60–2.95 (m, 4H), 3.30–3.45 (m, 2H), 3.60–3.70 (m, 1H), 3.90–4.45 (m, 9H), 4.60–4.70 (m, 2H), 4.75–4.90 (dd, 1H), 7.05–7.45 (m, 18H), 7.60–7.70 (m, 4H), 7.85 (d, 4H). FAB-MS (with K^+): m/z 981 $(M + K)^+$.

Coupling of the Diamino Diol Core 4 and Diamino Alcohol Core 10 to MBHA Resin. The modified diamino diol core **4** or the modified diamino alcohol core **10** (5.0 mmol, ~1.5 equiv relative to the resin) was dissolved in 10 mL of *N*-methylpyrrolidone (NMP) and 10 mL of CH_2Cl_2. To the solution was added diisopropylcarbodiimide (0.79 mL, 5.0 mmol) and 0.68 g of of HOBt. After stirring for 30–60 min,

the solution was mixed with 5.0 g of NovaBead MBHA resin (NovaBiochem, La Jolla, CA; substitution, 0.65 mmol/g) which was pretreated with NMP. The mixture was shaken overnight and then filtered. The resin was washed with NMP (5 times), NMP–CH_2Cl_2 (1:1) mixture (5 times), and CH_2Cl_2 (5 times) and vacuum dried. The actual loading level was then determined based on the observed weight gain to be 0.5–0.55 mmol/g.

Automated Solid Phase Synthesis. The automated solid phase synthesis was carried out on an Abimed AMS422 Multiple Peptide Synthesizer (Gilson, Middleton, WI). Activation of carboxylic acids was accomplished by *in situ* formation of HOBt ester with PyBOP in the presence of *N*-methylmorpholine (NMM). This instrument has 24 discrete monomer vessels and 48 reaction vessels. For each run, 60–70 mg (~0.03 mmol) of the diamino diol resin was added to each of the first 24 reaction vessels and about same amount of the diamino alcohol resin was added to the second 24 reaction vessels. The instrument software was then modified, and solutions of the reagents and monomers were prepared, all according to the instrument operation manual. The chemistry protocols are highlighted as follows. The resins were first washed with NMP (3 × 1.5 mL), deprotected by two treatments with 20% piperidine in NMP (20 min each time), and then washed with NMP (6 × 1.5 mL). A solution of Fmoc-amino acids or carboxylic acids in NMP (0.3 mL, ~0.24 mmol), a solution of PyBOP in NMP (0.22 mL, ~0.22 mmol), and a solution of NMM (0.1 mL, ~0.4 mmol) were delivered to each reaction vessel. The mixture was then allowed a coupling time of 60 min. The coupling was then repeated for the second time (double coupling). For the synthesis of the model compounds, the deprotection and coupling were repeated as described above. After the final coupling, resins were washed with NMP (6 × 1.5 mL each reaction vessel) and CH_2Cl_2 (6 × 1.5 mL each reaction vessel) and dried. The resin containing molecules with the diamino diol core were then cleaved by treating the resins with 95% aqueous TFA overnight, and the inhibitor molecules containing the diamino alcohol core were cleaved by treating the resin with 30% TFA in CH_2Cl_2 for 3 h. Solutions of the released compounds were then evaporated in a speedvac and the products characterized by TLC and FAB-MS.

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Supporting Information Available: FAB mass spectra of unpurifird samples of the model HIV protease inhibitors shown in Table 1 (12 pages). Ordering information is given on any current masthead page.

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