Identification and Initial Structure−Activity Relationships of a Novel Class of Nonpeptide Inhibitors of Blood Coagulation Factor Xa

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The discovery and some of the basic structure−activity relationships of a series of novel nonpeptide inhibitors of blood coagulation Factor Xa is described. These inhibitors are functionalized β-alanines, exemplified by **2a**. Docking experiments placing **2a** in the active site of Factor Xa implied that the most expeditious route to enhancing in vitro potency was to modify the group occupying the S3 site of the enzyme. Increasing the hydrophobic contacts between the inhibitor and the enzyme in this region led to **8**, which has served as the prototype for this series. In addition, an enantioselective synthesis of these substituted β-alanines was also developed.

Introduction

Normal hemostasis is required for proper maintenance of the vasculature in response to routine injury. When an imbalance occurs in this process a thrombotic state is often the result.[1] Thrombotic disease is a major cause of death and morbidity. Since blood coagulation is a vital component of normal hemostasis and, as a consequence, thrombotic processes, anticoagulants have long been a part of the regimen of drugs used to treat thrombotic disease.[2] New members of this therapeutic class may offer significant benefits over some of the agents presently in use. Currently prescribed drugs present a number of problems including low bioavailability, endogenous inhibitors, and the need for cofactors (heparin);[3] delayed onset of action and the need for extensive patient monitoring (coumarins);[4] as well as limited efficacy and bleeding complications (both).

The conversion of the zymogen Factor X into its enzymatically active form, Factor Xa, is the point at which the intrinsic and extrinsic pathways of blood coagulation converge.[5] Factor Xa is the active enzyme present in the prothrombinase complex, which is responsible for the conversion of prothrombin into thrombin (Factor IIa).[6] As the final enzymatic product of blood coagulation and the agent which converts the glycoprotein fibrinogen to fibrin, which is one of the primary components of blood clots,[7] inhibition of thrombin has been the target of extensive research into the development of new anticoagulant agents.[8]

Direct thrombin inhibitors, while potentially very promising therapeutic agents,[9] may also have a number of potential drawbacks. The prothrombinase complex, present at the site of vascular injury, is unaffected by direct thrombin inhibitors and maintains a pro-thrombotic state by continually producing a supply of thrombin.[10] A rebound in the generation of thrombin has been observed following the discontinuation of therapy with direct thrombin inhibitors,[11] leading to a possible reestablishment of the original thrombotic state. Thrombin itself has some anticoagulant functions[12] that may be desirable to retain. In a number of direct comparisons between direct thrombin inhibitors and direct Factor Xa inhibitors in animal models, inhibitors of Factor Xa have been shown to be superior antithrombotic agents.[13] Taken together, all of these issues make the development of small molecule direct Factor Xa inhibitors an attractive alternative to current anticoagulant therapy.[14]

Compared to the thrombin literature, there are relatively few reports of small molecule inhibitors of Factor Xa. Many of these describe small peptide transition-state inhibitors.[15] Descriptions of nonpeptide inhibitors are limited primarily to a group of well-known bis-amidines,[16] the related DX-9065a,[17] and similar compounds.[18] Most recently, several reports of nonpeptide Factor Xa inhibitors of other structural types have appeared in the patent literature.[19] We describe the discovery and some of the preliminary structure−activity relationships of a new class of potent and selective Factor Xa inhibitors based upon a series of 2,3-disubstituted β-alanines.

Results and Discussion

All of the compounds illustrated in Tables 1−3 were initially prepared as racemic mixtures (vide infra) and tested for their ability to inhibit human Factor Xa in a purified enzyme system. Assays were run in triplicate, and IC_{50} values were reproducible with a correlation variance of <10%. In addition, the compounds described in Tables 2 and 3 were assayed against human thrombin and bovine trypsin.

During an investigation into some β-lactam-based serine protease inhibitors, the undesired ring-opened product **1** was obtained (Figure 1). This material was

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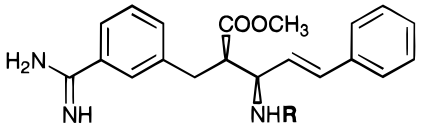
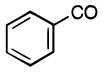
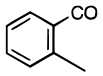
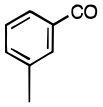
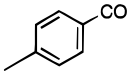
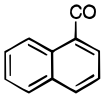
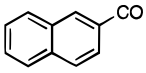
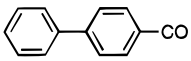
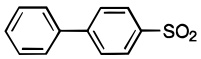
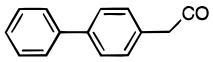
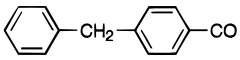
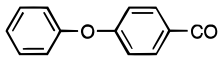
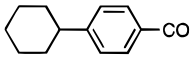
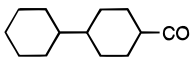
Table 1. Aromatic P3 Substitutions

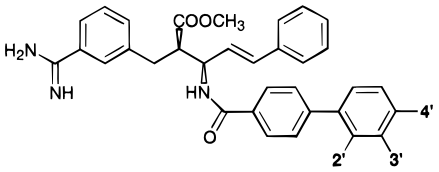


	R	Inhibition of FactorXa (IC_{50} in μM)
2a		0.70
3		1.20
4		1.10
5		0.60
6		0.79
7		0.16
8		0.11
9		1.97
10		1.13
11		0.46
12		1.22
13		0.58
14		1.12

screened for inhibitory activity against a variety of serine proteases and found to be a very modest inhibitor of Factor Xa (IC_{50} = 5 μM). Considering this unexpected result, a simple analogue of **1** was prepared in which the carboxylic acid was esterified and the *p*-nitrophenyl group replaced with an unsubstituted phenyl ring. The resulting compound, **2a**, had an IC_{50} for the inhibition of Factor Xa of 0.70 μM. This nearly 10-fold increase in in vitro potency led us to begin an investigation into the potential use of this novel class of substituted β-alanines as anticoagulants.

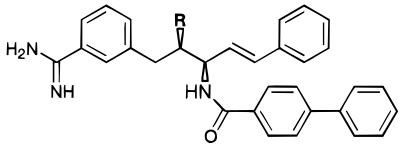
3-Substituted benzamidines are typically preferred over 4-substituted benzamidines as Factor Xa inhibitors.[20] The 4-substituted benzamidine analogue of **2a**, **2b**, was synthesized and was found to be a 50-fold less potent inhibitor of Factor Xa. Thus work was generally confined to 3-substituted benzamidines.

Table 2. Substituted Biphenyls



				IC_{50} (μM)		
compd	2′	3′	4′	Factor Xa	Factor IIa	trypsin
8	H	H	H	0.11	18	5.3
15	CH_3	H	H	0.09	9.0	3.1
16	H	CH_3	H	0.12	7.2	2.7
17	H	H	CH_3	0.24	4.8	2.8
18	CH_2CH_3	H	H	0.38	5.3	2.5
19	H	CH_2CH_3	H	0.39	1.7	2.6
20	H	H	CH_2CH_3	0.89	nd	nd
21	OCH_3	H	H	0.05	3.3	1.8
22	H	OCH_3	H	0.11	2.4	2.2
23	H	H	OCH_3	0.08	2.7	2.9
24	OCH_3	H	OCH_3	0.09	3.5	2.9
25	H	OCH_3	OCH_3	0.03	4.7	2.5
26	OCH_2CH_3	H	H	0.06	3.8	1.8
27	H	OCH_2CH_3	H	0.18	4.3	3.6
28	H	H	OCH_2CH_3	0.36	2.0	2.8

Table 3. Ester Modifications



		IC_{50} (μM)		
compd	R	Factor Xa	Factor IIa	trypsin
8	$COOCH_3$	0.11	18	5.3
29	$CON(CH_3)_2$	4.4	nd	nd
30	COOH	2.7	7.7	22
31	CH_2OH	0.65	nd	nd
32	CH_2OCH_3	0.54	8.7	10
33	CH_2OCOCH_3	0.36	3.8	1.4
34	H	0.95	31	6.6

By analogy to well-known thrombin inhibitors,[21] it was assumed that the benzamidine of **2a** bound in the S1 pocket of Factor Xa in the vicinity of Asp189. Either of the lipophilic portions of **2a**, the phenyl or styryl group, was assumed to be located in the S3 pocket of the enzyme, defined by the three aromatic amino acids Phe174, Tyr99, and Trp215. The methyl ester was assumed to be in the vicinity of the active site, near Ser195. These assumptions were lent some validity by utilizing the crystal structure of des-1−45 Factor Xa[22] and docking **2a** into the active site of the enzyme using FastDocking, an automated protocol developed in-house.[23] Figure 2 shows the results of this docking experiment.

In the model of **2a** bound in the Factor Xa active site, the inhibitor amidine group forms twin hydrogen bonds with the side chain of Asp189, as well as additional hydrogen bonds with the carbonyl oxygen of Gly218 and a water molecule deep within the S1 site. Similar types

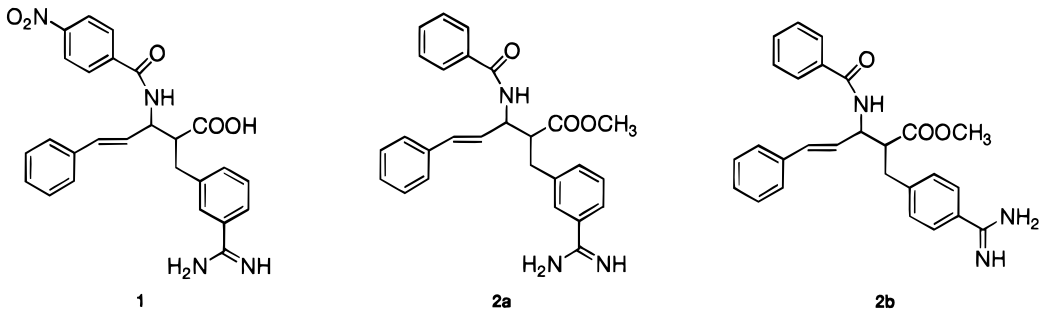


Figure 1.

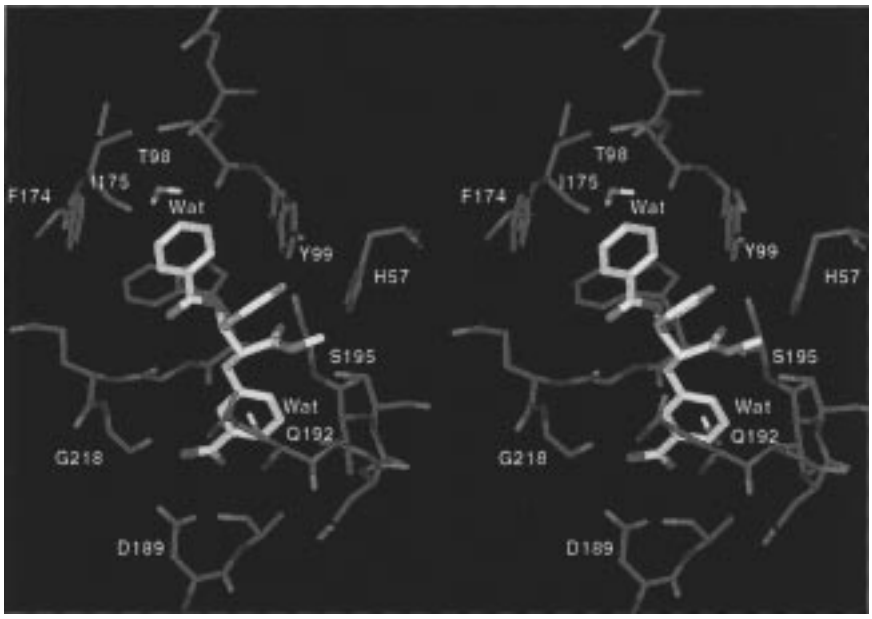


Figure 2. Stereoview of **2a** docked into the active site of Factor Xa.

of hydrogen-bonding networks are well-established for benzamidine-based inhibitors of thrombin.[24] The ester group is postioned near the catalytic triad, which is rich with potential hydrogen bonding sites. The amide NH may be capable of forming a weak intramolecular hydrogen bond with the carbonyl oxygen of the methyl ester. No direct interaction with the active site serine is implicated. Likewise, no significant role for protein binding is indicated for the styryl group of **2a**. Importantly, the model suggests that the benzamide phenyl group only partially fills the S3 site and is therefore amenable to modifications that would increase the size of this group, resulting in enhanced hydrophobic contacts in this region.

Following the identification of **2a** as a reasonably potent inhibitor of Factor Xa, and with a working model of its interactions with the enzyme in hand, initial efforts were concentrated on improving in vitro potency. As the model suggested, this could most readily be accomplished by examining a variety of aromatic substitutions for the benzoyl group of **2a** (Table 1) in an attempt to maximize interactions in the S3 site. The primary focus of this paper is the result of that effort.

Neither the toluyl derivatives **3**−**5** nor the 1-naphthyl derivative **6** provided any significant enhancement. However, both the 2-naphthyl and biphenyl analogues (**7** and **8**, respectively) led to significant increases in in vitro activity. Biphenyl derivative **8** was chosen as the starting point for subsequent work in this series both because of the novelty of the biphenyl system as an aromatic P3 group in serine protease inhibitors and the ease of synthesis of biphenyl systems relative to naphthyl systems.

Figure 3 shows the results of a second docking experiment placing **8** in the active site of Factor Xa. In this model similar interactions for the amidine, styryl, and ester groups are observed. In addition, the amide oxygen of **8** can be seen to be within hydrogen-bonding range of Gly218NH. The *p*-biphenyl group is indeed inserted deep within the S3 site.

Compounds **9**−**14** in Table 1 illustrate the effects of simple structural modifications to the biphenyl system. The model shown in Figure 3 suggests that the planar geometry of the carboxamide of **8** is important in optimally positioning the biphenyl system in S3. Sulfonamide **9**, which led to the greatest drop in potency, introduces a nonplanar geometry and causes a disruption in the manner in which the biphenyl is presented to the S3 site. Changing the trajectory of either the entire biphenyl system (**10**), or of only the distal phenyl ring (**11** or **12**), into the S3 pocket causes a steric conflict with the three aromatic residues forming the walls of the pocket. This results in a 4−10-fold loss in potency. Increasing the bulk of the biphenyl group by saturating one (**13**) or both (**14**) rings gave similar results.

The binding model illustrated in Figure 3 also implies that, in its present location in S3, there may be sufficient room for the placement of small substituents

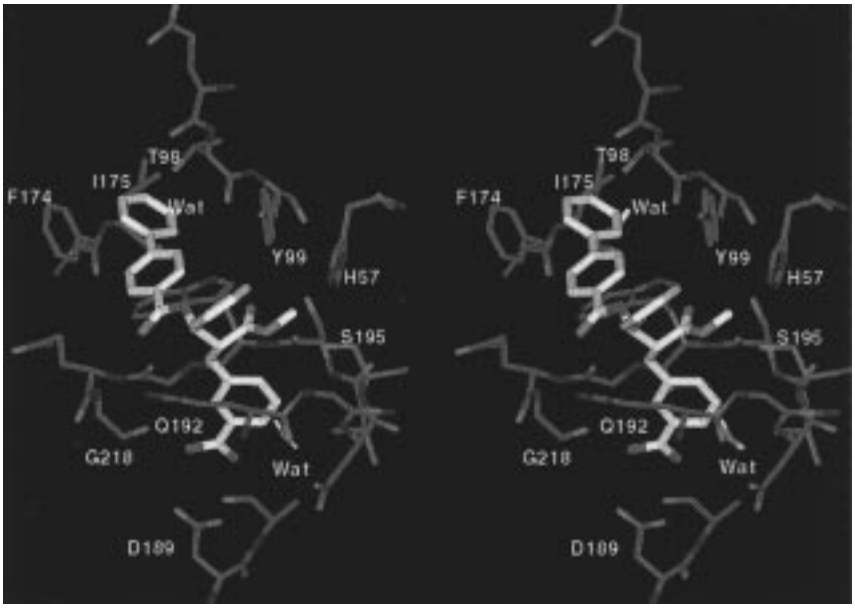


Figure 3. Stereoview of the proposed model of **8** bound in the active site of Factor Xa.

at specific points around the distal ring of the biphenyl system. Table 2 describes a group of analogues designed to demonstrate the effect of simple alkyl and alkoxy substituents on this phenyl ring.

The addition of a methyl group at either the 2′- or 3′-position has little or no effect on in vitro potency. A methyl group at the 4′-position or an ethyl group at either the 2′- or 3′-position causes a modest loss of potency, while an ethyl group at the 4′-position results in a much more dramatic decline in activity. The proposed binding model offers a reasonable explanation for much of this. Aliphatic substitution at the 3′- or especially the 4′-position of the distal phenyl ring results in moderate steric conflicts with the side chain of Phe174 and/or Thr98Ca. An ethyl group at the 4′-position (**20**) would be predicted to undergo particulary severe steric clashes with the side chain of Phe174, and **20** is indeed the least potent of these analogues.

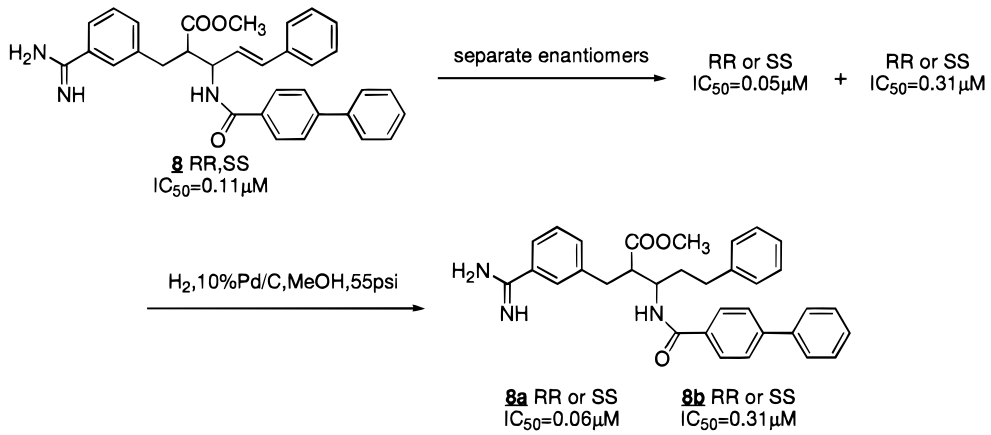
By contrast, addition of a small alkoxy group to the distal phenyl ring generally results in a modest enhancement in in vitro potency. The most dramatic example of this is the 3′,4′-dimethoxy derivative **25**, which shows a 4-fold increase in activity against Factor Xa, relative to the unsubstituted biphenyl **8**. This may be explained by the preferred geometry of the alkoxy groups in which, unlike the ethyl groups, the alkoxy substituents are coplanar with respect to the distal ring of the biphenyl system. By assuming such a geometry, the compounds containing alkoxy substituents avoid the steric clashes experienced by those with ethyl groups. The 4′-methoxy group also has the potential to form hydrogen bonds with the side chain of Thr98, as well as the structural water bridging the Ile175 and Thr98 backbone oxygen atoms.

The compounds illustrated in Table 2 show a very modest level of selectivity versus either thrombin or trypsin. For example, **21** was roughly 25-fold more selective against Factor Xa than against thrombin and 10-fold more selective than against trypsin (selectivity based on a ratio of the K_i values for inhibition of each enzyme).[25] Along with these two enzymes, **21** was also assayed for its ability to inhibit a number of related serine proteases that are involved in the body's endogenous anticoagulant and fibrinolytic systems. This analogue showed 150-fold and 300-fold selectivities versus plasmin and activated protein C, respectively. There was no observable inhibition of tissue type plasminogen activator, at concentrations of inhibitor up to 31 μM.

A number of changes to the ester functionality of **8** were also explored in an attempt to exploit the hydrogen-bonding potential of the region it was predicted to occupy by our model. These are illustrated in Table 3. The original methyl ester proved to be the most potent analogue of the functional groups listed. Certain functionality, notably the dimethylamide **29** and the carboxylic acid **30**, provided analogues that were significantly less potent. The loss of activity seen for the dimethylamide can be attributed to negative steric interactions. The observed loss in activity for the carboxylic acid may indicate that the desolvation energy of this highly polar group is poorly compensated for in terms of the potential hydrogen-bonding interactions. This is consistent with the prediction of the model which indicates that the ester group is sequestered from solvent by His57, Tyr99, Ser195, and Gln192 side chains as well as by the adjacent styryl substituent of **8** itself. Likewise, elimination of the ester group entirely (**34**) led to a 10-fold loss in in vitro activity, possibly a reflection of the loss of all hydrogen bonding potential. Alcohol **31**, ether **32**, and acetate **33** all show more modest drops in activity. This again may be a reflecion of reduced hydrogen-bonding potential and/or a high desolvation energy.

The structure−activity relationships described in Table 3 do not necessarily support the suggestion of our model that there is no direct interaction between the methyl ester of the inhibitor and the active site serine of Factor Xa. To clarify this point, **8** was incubated with Factor Xa and was recovered intact, with no observable formation of the corresponding carboxylic acid **30**. This result supports the hypothesis that no covalent interaction between the inhibitor and enzyme occurs.

Scheme 1. Preparation of Single Enantiomers Related to **8**



All of the compounds illustrated in Tables 1-3 were prepared as racemic mixtures. This was a result of their preparation using well-established β-lactam chemistry. The synthetic route that was used (vide infra) not only led to racemic mixtures but also suffered from generally low yields and cumbersome reactions.

Accordingly, the required stereochemistry at the two chiral centers in these compounds was deduced and a more efficient, enantioselective route to substituted β-alanines was devised starting from commercially available α-amino acids.

To have a point of reference from the original synthetic route, racemic **8** was separated into its enantiomers by chiral HPLC. The styryl group of each enantiomer was then independently reduced to the corresponding phenylethyl group to give **8a** and **8b** (Scheme 1). Both **8a** and **8b** are equipotent in vitro to the styryl analogues from which they are derived.

Given the syn relationship between the ester group and the amine in **8** and consequently in **8a** and **8b**, one of these two materials must possess a 2*R*,3*R* stereochemistry and the other must be 2*S*,3*S*. Each of these compounds could then be independently prepared as a single enantiomer from suitably protected, readily available homophenylalanine and compared to the compounds obtained from the original synthetic sequence.

N−α-Boc-D-homophenylalanine was converted to the 2*R*,3*R* enantiomer of **8** (vide infra). This provided a compound that was equipotent in vitro to the more active of the two enantiomers obtained from separation and reduction of racemic **8**. Thus, **8a** was presumed to be the *R*,*R* enantiomer.

N−α-Boc-L-homophenylalanine was subjected to the same process and afforded a compound, presumably the 2*S*,3*S* enantiomer, which was equipotent in vitro to **8b**, the less active of the enantiomers obtained from the original sequence.

In addition, the materials obtained from the two routes (**8a** and **35**) were identical spectroscopically. It was assumed that the active configuration of these novel Factor Xa inhibitors was 2*R*,3*R*, and this information, along with the improved enantioselective synthesis, has been applied to all of our subsequent work in this area.

In summary, these substituted β-alanines exemplify a new class of readily accessible, potent, selective inhibitors of Factor Xa. This class of compounds may represent a point of departure for the development of new anticoagulant agents.

Chemistry

Racemic Synthesis. The two starting materials needed to assemble the β-lactams were easily prepared using standard methods. The thiopyridyl ester of 3-(3-cyanophenyl)propionic acid and the imine formed from the condensation of cinnamaldehyde with *p*-anisidine underwent condensation[26] in the presence of titanium tetrachloride[27] to provide a 95:5 mixture of *trans*- to *cis*-β-lactams (Scheme 2). The two β-lactams could be separated by flash chromatography at this point. However, separation proved to be more facile after removal of the N-*p*-methoxyphenyl protecting group.

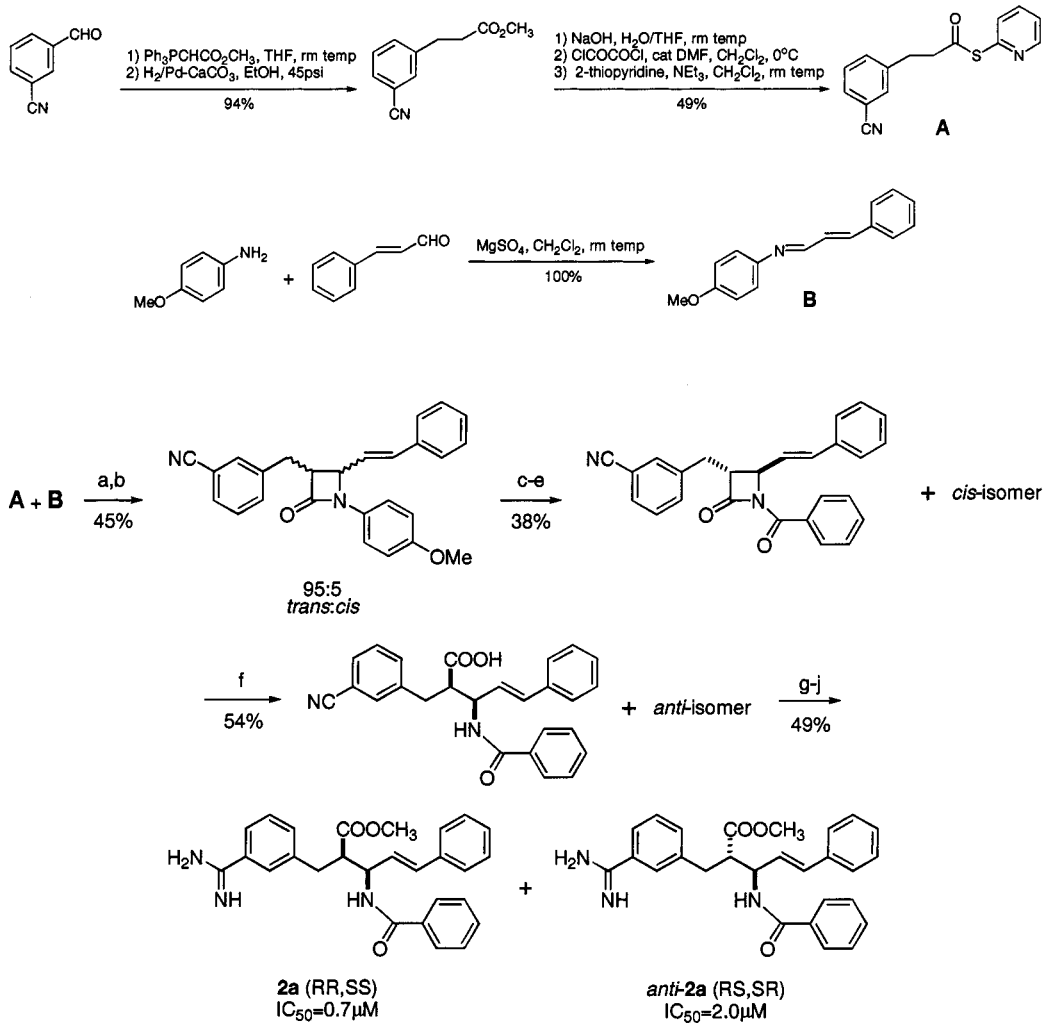
Following deprotection of the β-lactam nitrogen with cerric ammonium nitrate,[28] the *cis*- and *trans*-β-lactam intermediates were separated from one another and independently acylated with the desired acid chloride,[29] illustrated in Scheme 2 for **2a**. Any of the required acyl groups that were not commercially available were prepared by well-established methods.[30] The β-lactams then underwent ring opening with aqueous base, the *trans*-β-lactam giving rise to the diastereomer bearing a *syn* relationship between the carboxylic acid and *N*-benzoyl group. Conversely, the *cis*-β-lactam provided the anti-diastereomer.

To complete the synthesis of the compounds shown in Tables 1 and 2, the benzonitrile was converted to the corresponding benzamidine using a well-known sequence[31] and the carboxylic acid converted to its methyl ester. The syn diastereomer, which is derived from the predominant product of the initial condensation, was found to be the better inhibitor of Factor Xa in vitro.

For the compounds **29**−**33**, shown in Table 3, the free carboxylic acid obtained from the ring opening of the appropriately substituted β-lactam was modified as shown in Scheme 3. The acid, amide, alcohol, and methyl ether were all prepared by well-known methods and independently taken on to their respective benzamidines. The acetate was not stable to the conditions used for preparation of the amidine and was prepared directly from the benzamidine of the alcohol, with the amidine protected as its hydrochloride salt.

The synthesis of **34** was accomplished in a straightforward manner as illustrated in Scheme 4. Methyl 4-(3-cyanophenyl)butyrate was prepared starting from

Scheme 2. Synthesis of Racemic Substituted β-Alanine Derivatives



(a)$TiCl_4$, NEt_3, CH_2Cl_2, -78°C; (b)flash chromatography; (c)CAN, CH_3CN/THF, -20°C to rm temp; (d)separate by flash cromatography: from this point forward the *cis* and *trans* isomers were handled separately; (e)PhCOCl, NEt_3, DMAP, CH_2Cl_2, rm temp; (f)NaOH, H_2O/THF, rm temp; (g)H_2S, pyr, NEt_3, rm temp; (h)CH_3I, CH_2Cl_2, reflux; (i) NH_4OAc, MeOH, reflux; (j) HCl, MeOH, rm temp

3-cyanobromobenzene by standard manipulations. This material was converted to 3-cyanohomophenylalanine by azidation via 2,4,6-triisopropylbenzenesulfonyl azide[32] followed by reduction to the amine. Following acylation with 4-biphenylcarboxylic acid, standard methods were used to convert the ester group to an aldehyde that underwent Wittig reaction to introduce the styryl group. A 4:1 ratio of trans to cis olefin was obtained and could be readily separated by flash chromatography. Conversion of the nitrile to the corresponding benzamidine gave **34**.

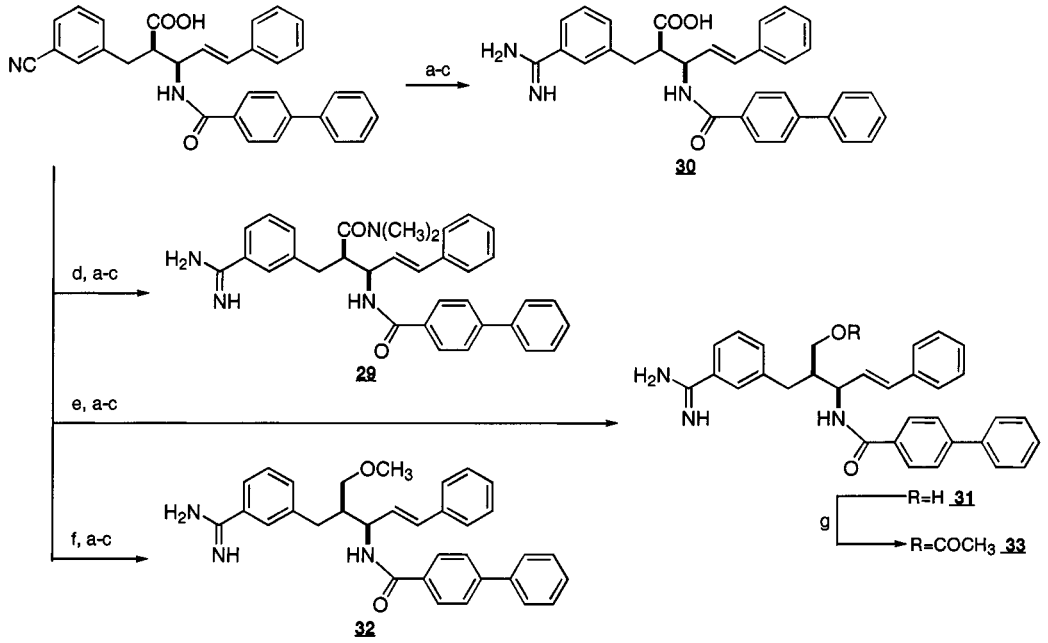
Enantioselective Synthesis. For the preparation of the *R,R* enantiomers, *N*-α-Boc-D-homophenylalanine was subjected to one carbon homologation[33] with retention of configuration to give *N*-Boc-3(*R*)-amino-5-phenylpentanoic acid methyl ester (Scheme 5). Alkylation with 3-cyanobenzyl bromide then afforded a single diastereomer in >96% ee by chiral HPLC. This result was expected based on literature precedent for the α-alkylation of β-alanine derivatives.[34] The alkylation is presumably chelation controlled, with the electrophile approaching the enolate dianion from the face opposite the bulky phenylethyl group to give what is assumed to be the 2*R*,3*R* derivative. Subsequent manipulations similar to those described in Scheme 2 provided the desired 2*R*,3*R* enantiomer.

Experimental Section

In Vitro Assays for the Inhibition of Factor Xa, Thrombin, and Trypsin. Human factor Xa and thrombin were obtained from Enzyme Research Laboratories, Inc. (South Bend, IN). Bovine trypsin was obtained from Sigma Chemical Co. (St. Louis, MO). The chromogenic substrates used were Spectrozyme FXa (American Diagonostica Inc., Greenwich, CT), Pefachrome TH (Centerchem, Inc., Stamford, CT), and S-2765 (Diapharma Group Inc., Franklin, OH) for FXa, thrombin, and trypsin, respectively. FXa and thrombin were assayed in a buffer containing 0.05 M Tris, 0.15 M NaCl, and 0.1% PEG-8000 at pH 7.5. Trypsin was assayed in the aforementioned buffer with addition of 0.02 M $CaCl_2$.

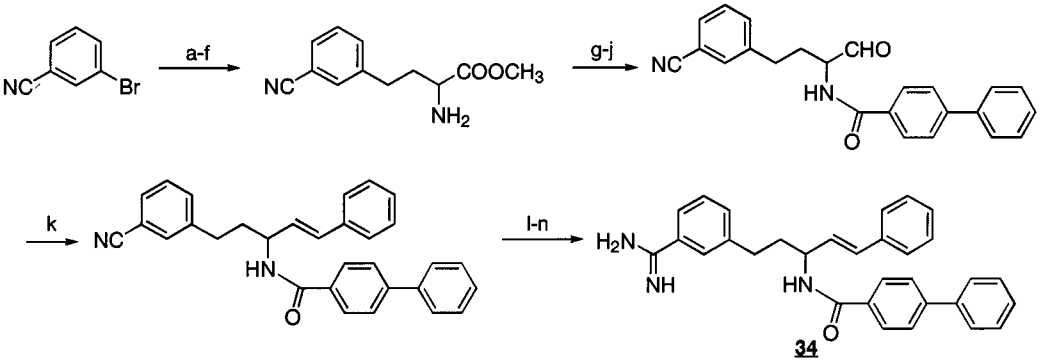
The final substrate concentrations in the reactions were 200 μM, 50 μM, and 250 μM for Spectrozyme FXa, Pefachrome TH, and S-2765, respectively. All enzyme assays were carried out at room temperature in 96-well microtiter plates with a final enzyme concentration of 1 nM. Compound dilutions were added to the wells containing buffer and enzyme, and preincubated for 30 min. The enzymatic reactions were initiated by the addition of substrate. The color developed from the

Scheme 3. Synthesis of Carboxylic Acid Derivatives



(a) H_2S, NEt_3, pyridine, rt; (b) CH_3I, CH_2Cl_2, reflux; (c) NH_4OAc, methanol, reflux, 62%(a,b,and c); (d) oxalyl chloride, cat. DMF, CH_2Cl_2, 0°C, then $NH(CH_3)_2$, 0°C, 80%; (e) isobutyl chloroformate, NEt_3, THF, 0°C then $NaBH_4$, H_2O, rt, 76%; (f) NaH, CH_3I, THF/DMF, 40°C, 23%; (g) acetyl chloride, pyridine, CH_2Cl_2, 0°C, 90%.

Scheme 4. Synthesis of **34**



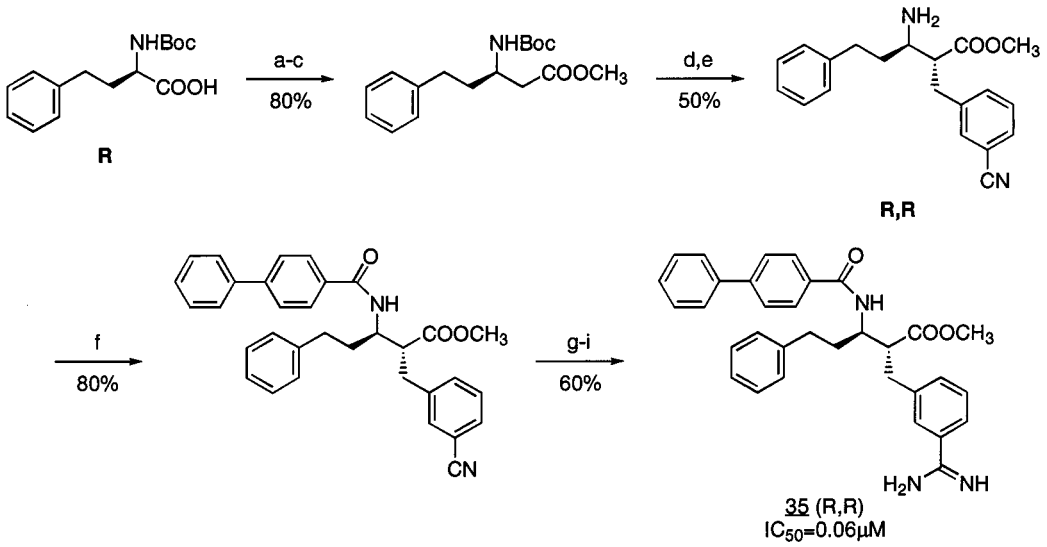
(a) $Pd(Ph_3P)_4$,homopropargyl alcohol,piperidine,80°C; (b) H_2,Pd/$CaCO_3$,ethanol,45psi; (c) Jones reagent,acetone,rt; (d) CH_2N_2,ether,rt, 42%(4 steps); (e)KHMDS,THF,-78°C then 2,4,6-triisopropylbenzene sulfonyl azide,THF,-70°C; (f) H_2,Pd/$CaCO_3$,ethanol,45psi, 95% (2 steps); (g) 4-biphenyl carboxylic acid,TBTU,NEt_3,DMF,rt,90%; (h) NaOH,methanol,water,0°C; (i) isopropyl chloroformate,NEt_3,THF,0°C then $NaBH_4$,H_2O; (j) oxalyl chloride,DMSO,NEt_3,CH_2Cl_2,-78°C to rt, 60% (3 steps); (k) Ph_3P=CHPh,THF,rt,70%; (l) H_2S,NEt_3,pyridine,rt; (m) CH_3I,CH_2Cl_2,reflux; (n) NH_4OAc,methanol,reflux, 65% (3 steps)

release of *p*-nitroanilide from each chromogenic substrate was monitored continuously for 5 min at 405 nm on a Thermomax microtiter plate reader (Molecular Devices, Sunnyvale, CA). Under the experimental conditions, less than 10% of the substrate was consumed in all assays. The initial velocities measured were used to determine the amount of inhibitor required to diminish 50% of the control velocity and defined as the IC_{50} of the inhibitor. Assuming the kinetic mechanisms were competitive inhibition, the apparent K_i values could then be calculated according to the Cheng−Prusoff equation, $K_i = IC_{50}/1 + [S]/K_m$.

Docking of 2a and 8 into the Active Site of Factor Xa. Lower energy conformations of the ligand are generated using a modified version of a rule-based method implemented in Chem-X (Chemical Design Ltd., Chipping Norton, Oxfordshire, OX7 5SR, UK). Using ChemDBS-3D (Chemical Design Ltd.), in-house customization was designed to fit each generated conformation onto a predefined, minimal pharmacophore model using a steric shell of the active site as an added constraint. Matching conformations are then passed to the program DISCOVER (Chemical Design Ltd.) for optimization in a partially relaxed active site model using the CFF97 forcefield (Potential Energy Functions Consortium, Msi, 9685 Scranton Rd, San Diego, CA 92121). The resulting docked complexes are scored on the basis of total force field energy and empirical rules. This method has been validated against several known protein/ligand systems, having reproduced in all cases to date the correct bound conformation of the ligand within 0.7 Å RMS.

Chemistry. All starting materials not described below were purchased from commercial sources. All reagents and solvents were used as received from commercial sources without additional purification. Proton NMRs were recorded on a Bruker ARX 300 MHz spectrometer. Mass spectra were

Scheme 5. Enantioselective Synthesis of Substituted β-Alanines



(a)iBuCOCl, NMM, THF, 0°C; (b)CH_2N_2, ether; (c)PhCOOAg, NEt_3, MeOH; (d)LHMDS, THF, -78°C to -35°C;then 4-cyanobenzyl bromide; (e)25%TFA/CH_2Cl_2, 0°C; (f)4-biphenylcarboxylic acid, TBTU, DMF, DIPEA, room temp; (g)H_2S, pyr, NEt_3, room temp; (h) CH_3I, acetone, reflux; (i)NH_4OAc, methanol, reflux

obtained from a Varian VG-70SE spectrometer. Optical rotations were recorded on a Perkin-Elmer Model 241 polarimeter. Elemental analyses were performed by Quantitative Technologies of Whitehorse, NJ. Preparative reverse phase HPLC was performed with a Rainin SD-1 Dynamax system and a 2-in. C-18 reverse phase Dynamax 60A column using a gradient of 20% acetonitrile/0.1% TFA in water to 100% acetonitrile and a flow rate of 50 mL/min. Analytical reverse phase HPLC was performed with a Rainin HPX system and an analytical C-18 reverse phase Dynamax 60A column using the same gradient system used for preparative work and a flow rate of 1 mL/min.

Workup means drying over magnesium sulfate, filtering, and concentrating in vacuo. All final products (**2a**−**35**) were obtained as hygroscopic white solids following purification by reverse phase HPLC and lyophilization of the aqueous portions of those fractions containing the desired product. All compounds were of a final purity of >95 area % by analytical HPLC.

4-Cyclohexylcyclohexane Carboxylic Acid. To a solution of methyl 4-phenylbenzoate (10 mmol) in 20 mL of methanol and 10 mL of glacial acetic acid was added 5% rhodium on alumina (1 g, 50 wt %). The reaction mixture was placed on a Parr shaker and left under a positive pressure of hydrogen (45 psi) for 72 h. The reaction mixture was filtered and the filtrate concentrated in vacuo. The residue was suspended in 20 mL of tetrahydrofuran and 10 mL of 2 N sodium hydroxide was added dropwise at room temperature. The resulting solution was stirred at room temperature for 2 h. Tetrahydrofuran was removed in vacuo and the aqueous phase was brought to pH 2 by the dropwise addition of 1 N hydrochloric acid at 0 °C. The precipitate was filtered off and dried under vacuum. ^{1}H NMR (DMSO-d_6) δ 1.95 (br t, J = 4.2 Hz, 1H), 1.50−1.72 (m, 10H), 1.06−1.31 (m, 10H).

Preparation of 4-(2-Methylphenyl)benzoic Acid. Representative Synthesis of Biphenyls. (A) To a solution of 11.8 mL of *n*-butyllithium in hexanes (19 mmol) in 13 mL of tetrahydrofuran was added a solution of 1-bromo-2-methylbenzene (19 mmol) in 2 mL of tetrahydrofuran, dropwise via syringe at −78 °C. Stirring was continued for 1 h at −78 °C. A solution of zinc chloride (19 mmol) in 38 mL of tetrahydrofuran was added over 2 min at −78 °C. The resulting solution was allowed to come to room temperature over 40 min.

(B) To a solution of bis(triphenylphosphine)palladium dichloride (1 mmol) in 11 mL of tetrahydrofuran was added diisobutylaluminum hydride (1 mmol) as a solution in hexanes, at room temperature, followed by ethyl iodobenzoate (16 mmol) in a single portion at room temperature.

Solution A was added to solution B and the reaction mixture allowed to stir at room temperature overnight. The reaction mixture was diluted with 300 mL of diethyl ether and washed with 1 N hydrochloric acid (3 × 75 mL) and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was suspended in 20 mL of tetrahydrofuran, and 10 mL of 2 N sodium hydroxide was added dropwise at room temperature. The resulting solution was stirred at room temperature for 2 h. Tetrahydrofuran was removed in vacuo, and the aqueous phase was brought to pH 2 by the dropwise addition of 1 N hydrochloric acid at 0 °C. The precipitate was filtered off and dried under vacuum. ^{1}H NMR (DMSO-d_6): δ 7.96 (d, J = 10.8 Hz, 2H), 7.45 (d, J = 10.8 Hz, 2H), 7.15−7.32 (m, 4H), 2.21 (s, 3H).

4-(3-Methylphenyl)benzoic Acid. ^{1}H NMR (DMSO-d_6): δ 7.96 (d, J = 10.8 Hz, 2H), 7.75 (d, J = 10.8 Hz, 2H), 7.42−7.55 (m, 2H), 7.28−7.40 (m, 1H). 7.21 (d, J = 9.6 Hz, 1H), 2.21 (s, 3H).

4-(4-Methylphenyl)benzoic Acid. ^{1}H NMR (DMSO-d_6): δ 7.95 (d, J = 9.6 Hz, 2H), 7.72 (d, J = 9.6 Hz, 2H), 7.67 (d, J = 9.6 Hz, 2H), 7.01 (d, J = 9.6 Hz, 2H), 2.40 (s, 3H).

4-(2-Ethylphenyl)benzoic Acid. ^{1}H NMR (DMSO-d_6): δ 7.96 (d, J = 10.8 Hz, 2H), 7.40 (d, J = 10.8 Hz, 2H), 7.28−7.35 (m, 2H), 7.20−7.27 (m, 1H), 7.10−7.18 (m, 1H), 2.55 (q, J = 12.0 Hz, 2H), 0.97 (t, J = 12.0 Hz, 3H).

4-(3-Ethylphenyl)benzoic Acid. ^{1}H NMR (DMSO-d_6): δ 7.96 (d, J = 10.8 Hz, 2H), 7.75 (d, J = 10.8 Hz, 2H), 7.42−7.55 (m, 2H), 7.28−7.40 (m, 1H), 7.21 (d, J = 9.6 Hz, 1H), 2.66 (q, J = 12.0 Hz, 2H), 1.18 (t, J = 12.0 Hz, 3H).

4-(2-Methoxyphenyl)benzoic Acid. ^{1}H NMR (DMSO-d_6): δ 7.93 (d, J = 10.8 Hz, 2H), 7.56 (d, J = 10.8 Hz, 2H), 7.22−7.40 (m, 2H), 7.12 (d, J = 8.4 Hz, 1H), 7.04−7.16 (m, 1H), 3.74 (s, 3H).

4-(3-Methoxyphenyl)benzoic Acid. ^{1}H NMR (DMSO-d_6): δ 7.97 (d, J = 10.8 Hz, 2H), 7.75 (d, J = 10.8 Hz, 2H), 7.32−7.42 (m, 1H), 7.18−7,28 (m, 2H), 6,91−7.00 (m, 1H), 3.81 (s, 3H).

4-(2.4-Dimethoxyphenyl)benzoic Acid. ^{1}H NMR (DMSO-d_6): δ 7.95 (d, J = 10.8 Hz, 2H), 7.55 (d, J = 10.8 Hz, 2H), 7.25 (s, 1H), 6.57−6.53 (m, 2H), 3.85 (s, 3H), 3.82 (s, 3H).

4-(3.4-Dimethoxyphenyl)benzoic Acid. ^{1}H NMR (DMSO-d_6): δ 8.16 (d, J = 10.8 Hz, 2H), 7.76 (d, J = 10.8 Hz, 2H), 7.42 (s, 1H), 7.28 (d, J = 9.6 Hz, 1H), 7.08 (d, J = 9.6 Hz, 1H), 3.74 (s, 3H), 3.78 (s, 3H).

4-(2-Ethoxyphenyl)benzoic Acid. ^{1}H NMR (DMSO-d_6): δ 7.93 (d, J = 10.8 Hz, 2H), 7.56 (d, J = 10.8 Hz, 2H), 7.22−7.40 (m, 2H), 7.12 (d, J = 8.4 Hz, 1H), 7.00−7.12 (m, 1H), 4.22 (q, J = 12.0 Hz, 2H), 1.28 (t, J = 12.0 Hz, 3H).

4-(3-Ethoxyphenyl)benzoic Acid. ^{1}H NMR (DMSO-d_6): δ 7.97 (d, J = 10.8 Hz, 2H), 7.75 (d, J = 10.8 Hz, 2H), 7.32−7.42 (m, 1H), 7.18−7.28 (m, 2H), 6.91−7.00 (m, 1H), 4.20 (q, J = 12.0 Hz, 2H), 1.30 (t, J = 12.0 Hz, 3H).

4-(4-Ethoxyphenyl)benzoic Acid. ^{1}H NMR (DMSO-d_6): δ 7.95 (d, J = 9.6 Hz, 2H), 7.72 (d, J = 9.6 Hz, 2H), 7.42 (d, J = 9.6 Hz, 2H), 7.01 (d, J = 9.6 Hz, 2H), 4.06 (q, J = 12.0 Hz, 2H), 1.30 (t, J = 12.0 Hz, 3H).

Representative Synthesis of Acid Chlorides. To a solution of the carboxylic acid (5 mmol) in 15 mL of tetrahydrofuran and 15 mL of methylene chloride was added oxalyl chloride (10 mmol) dropwise via syringe at 0 °C, followed by several drops of dimethylformamide in a similar fashion. Stirring was continued 1 h at room temperature. Solvents were removed in vacuo and the acid chloride dried under vacuum prior to use.

3-(3-Cyanophenyl)propionic Acid Thiopyridyl Ester. To a stirred solution of 3-cyanobenzaldehyde (153 mmol) in 100 mL of dry tetrahydrofuran under N_2 at room temperature was added methyl (triphenylphosphoranylidene)acetate (183 mmol). The mixture was allowed to stir overnight at room temperature and then concentrated in vacuo. The crude residue was chromatographed (40% ethyl acetate/hexanes) to give methyl 3-(3-cyanophenyl)acrylate. ^{1}H NMR ($CDCl_3$): δ 7.43−7.8 (m, 5H), 6.47 (d, J = 12 Hz, 1H), 3.8 (s, 3H).

To a stirred solution of the acrylate (145 mmol) in 150 mL of ethanol was added 2 g of 10% Pd/$CaCO_3$. The reaction mixture was held under a positive pressure of hydrogen (45 psi) on a Parr shaker for 8 h. The reaction mixture was filtered through Celite and the filtrate concentrated in vacuo to give methyl 3-(3-cyanophenyl)propionate. ^{1}H NMR ($CDCl_3$): δ 7.33−7.72 (m, 4H), 3.66 (s, 3H), 2.97 (t, J = 7.8 Hz, 2H), 2.62 (t, J = 7.8 Hz, 2H).

To a stirred solution of the methyl ester (89 mmol) in 100 mL of tetrahydrofuran and 50 mL of methanol was added 10 mL of 10 N sodium hydroxide dropwise at room temperature. The resulting solution was stirred for 2 h at room temperature and the volume of the reaction mixture concentrated by about half in vacuo. Then 30 mL of 5 N hydrochloric acid was added. The resulting suspension was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were worked up to give 3-(3-cyanophenyl)propionic acid. ^{1}H NMR ($CDCl_3$): δ 7.35−7.55 (m, 4H), 2.98 (t, J = 7.9 Hz, 2H), 2.7 (t, J = 7.9 Hz, 2H).

To a stirred solution of the propionic acid (47 mmol) in 100 mL of methylene chloride was added dimethylformamide (0.5 mL) in a single portion at room temperature followed by oxalyl chloride (70 mmol) dropwise via syringe. After 1 h, gas evolution had ceased and the solvent and excess oxalyl chloride were removed in vacuo. The residue was redissolved in 100 mL of methylene chloride and cooled to 0 °C. Mercaptopyridine (50 mmol) was added portionwise, followed by triethylamine (56 mmol) in a similar fashion. The reaction mixture was allowed to come to room temperature and stirred for an additional 1 h. The reaction mixture was diluted with methylene chloride and washed with 1 N sodium hydroxide (1 × 25 mL). The organic layer was worked up and the residue subjected to flash chromatography using 1:1 ethyl acetate−hexanes to give 3-(3-cyanophenyl)propionic acid thiopyridyl ester. 1H NMR ($CDCl_3$): δ 8.63 (d, J = 9 Hz, 1H), 7.7−7.8 (m, 1H), 7.27−7.62 (m, 6H), 3.05 (s, 4H).

[(4-Methoxyphenyl)imino]cinnamaldehyde. To a stirred solution of cinnamaldehyde (81 mmol) and *p*-anisidine (81 mmol) in 200 mL of methylene chloride was added magnesium sulfate (162 mmol) portionwise at 0 °C. After 4 h, the mixture was filtered and the filtrate concentrated in vacuo to give [(4-methoxyphenyl)imino]cinnamaldehyde. ^{1}H NMR ($CDCl_3$): δ 8.28 (m, 1H), 7.52 (m, 2H), 7.38 (m, 3H), 7.2 (m, 2H), 7.12 (m, 2H), 6.93 (m, 2H), 3.82 (s, 3H).

Preparation of Compound 2a. *N*−Benzoyl-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-β-alanine Methyl Ester. Representative Synthesis of Compounds 2−28. To a stirred solution of the 3-(3-cyanophenyl)propionic acid thiopyridyl ester (26 mmol) in 120 mL of methylene chloride was added titanium tetrachloride (26 mmol) as a 1 M solution in methylene chloride, dropwise via syringe at −78 °C. After 15 min, triethylamine (26 mmol) was added, dropwise via syringe at −78 °C. The resulting mixture was allowed to stir for 30 min at −78 °C, and then a solution of 4-methoxyphenylimino cinnamaldehyde (19 mmol) in 20 mL of methylene chloride was added dropwise via syringe at −78 °C. The reaction mixture was warmed to 0 °C. After 1.5 h at this temperature, the reaction was quenched by the slow addition of a saturated sodium bicarbonate solution and partitioned with water. The organic layer was washed with 1 N sodium hydroxide (2 × 50 mL) and worked up. The crude β-lactams were subjected to flash chromatography using 2:3 ethyl acetate−hexanes to give a 5:1 mixture of *trans*-/*cis*- β-lactams. Major (trans) isomer: ^{1}H NMR ($CDCl_3$): δ 7.2−7.6 (m, 11H), 6.8 (d, J = 11 Hz, 2H), 6.65 (d, J = 15.8 Hz, 1H), 6.2 (dd, J = 15.8, 7.9 Hz, 1H), 4.32 (m, 1H), 3.72 (s, 3H), 3.0−3.42 (m, 3H).

To a stirred solution of a mixture of *trans*-/*cis*-β-lactams (3.8 mmol) in 45 mL of acetonitrile and 15 mL of tetrahydrofuran at −20 °C was added a solution of cerric ammonium nitrate (CAN, 5.7 mmol) in 10 mL of water. After 15 min, another 1.5 g of CAN in 5 mL of water was added. After a further 30 min, the mixture was quenched by the slow addition of a saturated sodium bicarbonate solution and allowed to come to room temperature. The resulting suspension is filtered through Celite. The Celite was washed several times with methylene chloride (total ca. 200 mL). The filtrate layers are separated and the organic layer worked up. The crude product was chromatographed using 3:2 ethyl acetate−hexanes to give, separately, pure *cis*- and *trans*-3-(3-cyanobenzyl)-4-(*trans*-styryl) β-lactam. Major (trans) isomer: ^{1}H NMR ($CDCl_3$): δ 7.17−7.65 (m, 9H), 6.52 (d, J = 15.8 Hz, 1H), 6.25 (s, 1H), 6.14 (dd, J = 15.8, 7.9 Hz, 1H), 3.97 (m, 1H), 3−3.33 (m, 3H). Minor (cis) isomer: ^{1}H NMR ($CDCl_3$) δ: 7.21−7.52 (m, 9H), 6.62 (d, J = 15.8 Hz, 1H), 6.45 (s, 1H), 6.1 (dd, J = 15.8, 7.9 Hz, 1H), 4.46 (m, 1H), 3.7 (m, 1H), 3.02−3.17 (m, 1H), 2.8−2.93 (m, 1H).

To a stirred solution of the *trans*-β-lactam (23.2 mmol) in 50 mL of methylene chloride was added triethylamine (29 mmol) dropwise at room temperature. Benzoyl chloride (23.2 mmol) was then added portionwise followed by (dimethylamino)pyridine (2.3 mmol) all at once. After 30 min the mixture was diluted with 100 mL of methylene chloride and washed with 1 N hydrochloric acid (1 × 50 mL). The organic layer was then worked up. The crude product was subjected to flash chromatography using 3:7 ethyl acetate−hexanes to give *trans*-*N*-benzoyl-3-(3-cyanobenzyl)-4-(*trans*-styryl) β-lactam. ^{1}H NMR ($CDCl_3$): δ 8.06 (m, 2H), 7.2−7.75 (m, 12H), 6.67 (d, J = 15.8 Hz, 1H), 6.23 (dd, J = 15.8, 7.9 Hz, 1H), 4.63 (m, 1H), 3.46 (m, 1H), 3.1−3.3 (m, 2H).

To a stirred solution of the *trans*-β-lactam (4.7 mmol) in 50 mL of tetrahydrofuran was added 13.6 mL of a 1 N sodium hydroxide solution, dropwise at room temperature. After 2 h, most of the THF was removed in vacuo and 20 mL of 1 N hydrochloric acid was slowly added at 0 °C. The resulting suspension was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were worked up. The crude product was purified by reverse phase HPLC using a gradient of 40% acetonitrile/0.1% trifluoroacteic acid in water to 100% acetonitrile. The fractions containing product were lyophilized to give *N*-benzoyl-*syn*-(2-(3-cyanobenzyl)-3-*trans*-styryl)-β-alanine. ^{1}H NMR ($CDCl_3$): δ 7.18−7.97 (m, 14H), 6.61 (d, J = 15.8 Hz, 1H), 6.2 (dd, J = 15.8, 7.9 Hz, 1H), 5.14 (m, 1H), 3.00−3.22 (m, 3H).

To a solution of *N*-benzoyl-*syn*-(2-(3-cyanobenzyl)-3-*trans*-styryl)-β-alanine (2 mmol) in 25 mL of pyridine and 5 mL of triethylamine was bubbled in hydrogen sulfide for 10 min at room temperature. The solution was allowed to stir at room temperature overnight. Nitrogen gas was bubbled through the

reaction for 5 min, and solvents were removed *in vacuo*. The residue was dried under vacuum and then dissolved in 15 mL of dry acetone. To this solution was added 5 mL of methyl iodide, and this solution was heated at 50 °C for 1 h and then concentrated in vacuo. The residue was dissolved in 20 mL of methanol, and ammonium acetate (4 mmol) was added in a single portion at room temperature. The reaction mixture was heated at 65 °C for 2 h. After cooling, methanol was removed in vacuo and the residue dissolved in 30 mL of dry methanol at room temperature. Molecular sieves (ca. 50 mg) were added, and gaseous hydrogen chloride was bubbled through the solution for 2 min. The mixture was stirred for 10 min at room temperature and concentrated in vacuo. The crude ester was purified by reverse phase HPLC using a gradient of 40% acetonitrile in water buffered with 0.1% trifluoroacetic acid to 100% acetonitrile. Acetonitrile was removed in vacuo, and the aqueous phase was lyophilized to provide the desired product, *N*-benzoyl-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine methyl ester, as its trifluoroacetate salt. ^{1}H NMR (DMSO-d_6): δ 8.70 (d, J = 8.6 Hz, 1H), 7.92 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.75−7.21 (m, 10H), 6.67 (d, J = 16.1 Hz, 1H), 6.40 (dd, J = 16.1, 7.8 Hz, 1H), 4.98 (dd, J = 16.1, 7.8 Hz, 1H), 3.46 (s, 3H), 3.18−3.25 (m, 1H), 3.05−2.88 (m, 2H). MS: *m*/*z* (FAB) 442 (M + H)$^+$. Anal. ($C_{27}H_{27}N_3O_3$·TFA·1.5H_2O) C, H, N.

***N*-Benzoyl-*anti*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Methyl Ester (*anti*-2a).** The minor isomer from the *β*-lactam formation described above, *trans*-3-(3-cyanobenzyl)-4-*trans*-styryl *β*-lactam, was taken through the same sequence of steps to provide the *anti* isomer of **2a**. ^{1}H NMR (DMSO-d_6): δ 8.64 (d, J = 8.6 Hz, 1H), 7.86 (d, J = 9.0 Hz, 2H), 7.18−7.52 (m, 12H), 6.67 (d, J = 15.6 Hz, 1H), 6.30 (dd, J = 15.6, 7.8 Hz, 1H), 4.95 (m, 1H), 3.50 (s, 3H), 3.22−3.28 (m, 2H), 3.05−3.12 (m, 1H). MS: *m*/*z* (FAB) 442 (M + H)$^+$. Anal. ($C_{27}H_{27}N_3O_3$·TFA·1.5H_2O) C, H, N.

***N*-(2-Methylbenzoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Methyl Ester (3).** ^{1}H NMR (DMSO-d_6): δ 9.3 (s, 1H), 9.15 (s, 1H), 8.7 (d, J = 7.6 Hz, 1H), 7.2−7.6 (m, 13H), 6.9 (d, J = 8 Hz, 1H), 6.6 (d, J = 15 Hz, 1H), 6.35 (dd, J = 15, 6 Hz, 1H), 4.9 (dd, J = 15, 6 Hz, 1H), 3.55 (s, 3H), 3.2−3.3 (m, 1H), 2.8−3 (m, 1H), 2.3 (s, 3H). MS: *m*/*z* (FAB) 456 (M + H)$^+$. Anal. ($C_{28}H_{29}N_3O_3$·TFA·0.25H_2O) C, H, N.

***N*-(3-Methylbenzoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Methyl Ester (4).** ^{1}H NMR (DMSO-d_6): δ 9.3 (s, 1H), 9.2 (s, 1H), 8.7 (d, J = 7.6 Hz, 1H), 7.2−7.7 (m, 13H), 6.9 (d, J = 8 Hz, 1H), 6.6 (d, J = 15 Hz, 1H), 6.35 (dd, J = 15, 6 Hz, 1H), 4.9 (dd, J = 16, 6 Hz, 1H), 3.6 (s, 3H), 3.2−3.3 (m, 1H), 2.8−3 (m, 1H), 2.35 (s, 3H). MS: *m*/*z* (FAB) 456 (M + H)$^+$. Anal. ($C_{28}H_{29}N_3O_3$·TFA·3.0H_2O) C, H, N.

***N*-(4-Methylbenzoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Methyl Ester (5).** ^{1}H NMR (DMSO-d_6): δ 9.25 (s, 1H), 8.93 (s, 1H), 8.55 (d, J = 12.0 Hz, 1H), 7.72 (d, J = 10.8 Hz, 2H), 7.65−7.55 (m, 2H), 7.52−7.20 (m, 9H), 6.64 (d, J = 19.2 Hz, 1H), 6.39 (dd, J = 19.2, 9.6 Hz, 1H), 5.02−4.90 (m, 1H), 3.44 (s, 3H), 3.28−3.15 (m, 2H), 2.88−3.07 (m, 2H), 2.33 (s, 3H). MS: *m*/*z* (FAB) 456 (M + H)$^+$. Anal. ($C_{28}H_{29}N_3O_3$·TFA·3.0H_2O) C, H, N.

***N*-1-Naphthoyl-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Methyl Ester (6).** ^{1}H NMR (DMSO-d_6): δ 9.27 (s, 1H), 9.11 (s, 1H), 8.88 (d, J = 8.67 Hz, 1H), 8.18−8.07 (m, 1H), 8.05−7.9 (m, 2H), 7.7−7.2 (m, 13H), 6.73 (d, J = 15.9 Hz, 1H), 6.4 (dd, J = 15.9, 7.8 Hz, 1H), 5.07 (dd, J = 16, 7.9 Hz, 1H), 3.52 (s, 3H), 3.28−3.17 (m, 1H), 3.12−2.95 (m, 2H). MS: *m*/*z* (FAB) 493 (M + H)$^+$. Anal. ($C_{31}H_{29}N_3O_3$·TFA·0.5H_2O) C, H, N.

***N*-2-Naphthoyl-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Methyl Ester (7).** ^{1}H NMR (DMSO-d_6): δ 9.24 (s, 1H), 9.02 (s, 1H), 8.83 (d, J = 8.6 Hz, 1H), 8.4 (s, 1H), 8.08−7.85 (m, 4H), 7.68−7.2 (m, 12H), 6.68 (d, J = 15.8 Hz, 1H), 6.43 (dd, J = 15.8, 7.8 Hz, 1H), 5.03 (dd, J = 15.8, 7.8 Hz, 1H), 3.46 (s, 3H), 3.28−3.2 (m, 1H), 3.13−2.95 (m, 2H). MS: *m*/*z* (FAB) 493 (M + H)$^+$. Anal. ($C_{31}H_{29}N_3O_3$·TFA·0.5H_2O) C, H, N.

***N*-(4-Phenylbenzoyl)-*syn*-(2-(3-amidinobenzyl)-3-(*trans*-styryl)-*β*-alanine Methyl Ester (8).** ^{1}H NMR (DMSO-d_6): δ 7.90 (d, J = 10.8 Hz, 2H), 7.79 (d, J = 10.8 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 7.65−7.58 (m, 2H), 7.55−7.20 (m, 10H), 6.67 (d, J = 19.2 Hz, 1H), 6.42 (dd, J = 19.2, 9.6 Hz, 1H), 5.05−4.94 (m, 1H), 3.47 (s, 3H), 3.25−3.15 (m, 2H), 3.08−2.92 (m, 2H). MS: *m*/*z* (FAB) 519 (M + H)$^+$. Anal. ($C_{33}H_{31}N_3O_3$·TFA·1.5H_2O) C, H, N.

***N*-(4-Phenylbenzenesulfonyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Methyl Ester (9).** ^{1}H NMR (DMSO-d_6): δ 9.50 (s, 2H), 9.30 (s, 2H), 8.40 (d, J = 7.0 Hz, 1H), 8.05 (d, J = 7.0 Hz, 2H), 7.90 (d, J = 7.0 Hz, 2H), 7.40−7.80 (m, 4H), 7.10−7.40 (m, 4H), 6.40 (d, J = 10.0 Hz, 1H), 6.00 (dd, J = 10.0, 5.0 Hz, 1H), 4.40−4.60 (m, 1H), 3.80 (s, 3H), 3.10−3.30 (m, 3H). MS: *m*/*z* (FAB) 555 (M + H)$^+$. Anal. ($C_{32}H_{31}N_3O_4S$·TFA·2.0H_2O) C, H, N.

***N*-(4-Phenylphenylacetoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Methyl Ester (10).** ^{1}H NMR (DMSO-d_6): δ 9.50 (s, 2H), 9.30 (s, 2H), 8.80 (d, J = 5.0 Hz, 1H), 8.00 (d, J = 7.0 Hz, 2H), 7.90 (s, 2H), 7.80 (s, 2H), 7.70 (d, J = 5.0 Hz, 2H), 7.40−7.60 (m, 5H), 6.80 (d, J = 10.0 Hz, 1H), 6.60 (dd, J = 10.0,5.0 Hz, 1H), 5.10−5.30 (m, 1H), 3.80 (s, 3H), 3.60 (s, 2H), 3.40−3.50 (m, 1H), 3.10−3.30 (m, 3H). MS: *m*/*z* (FAB) 533 (M + H)$^+$. Anal. ($C_{34}H_{33}N_3O_3$·TFA·1.5H_2O) C, H, N.

***N*-(4-Benzylbenzoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Methyl Ester (11).** ^{1}H NMR (DMSO-d_6): δ 9.50 (s, 2H), 9.30 (s, 2H), 8.70 (d, J = 5.0 Hz, 1H), 8.10 (d, J = 5.0 Hz, 2H), 7.90 (s, 2H), 7.80 (s, 2H), 7.70 (s, 2H), 7.30−7.70 (m, 5H), 6.90 (d, J = 10.0 Hz, 1H), 6.60 (dd, J = 10.0, 5.0 Hz, 1H), 5.10−5.30 (m, 1H), 4.70 (s, 2H), 3.60 (s, 3H), 3.50−3.60 (m, 1H), 3.20−3.40 (m, 2H). MS *m*/*z* (FAB) 533 (M + H)$^+$. Anal. ($C_{34}H_{33}N_3O_3$·TFA·1.5H_2O) C, H, N.

***N*-(4-Phenoxybenzoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Methyl Ester (12).** ^{1}H NMR (DMSO-d_6): δ 9.50 (s, 2H), 9.30 (s, 2H), 8.72 (d, J = 5.0 Hz, 1H), 8.42 (d, J = 5.0 Hz, 2H), 7.93 (s, 2H), 7.80 (s, 2H), 7.70 (s, 2H), 7.31−7.70 (m, 5H), 6.90 (d, J = 10.0 Hz, 1H), 6.60 (dd, J = 10.0, 5.0 Hz, 1H), 5.10−5.30 (m, 1H), 3.64 (s, 3H), 3.50−3.65 (m, 1H), 3.17−3.43 (m, 2H). MS: *m*/*z* (FAB) 535 (M + H)$^+$. Anal. ($C_{33}H_{31}N_3O_4$·TFA) C, H, N.

***N*-(4-Cyclohexylbenzoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Methyl Ester (13).** ^{1}H NMR (DMSO-d_6): δ 9.50 (s, 2H), 9.30 (s, 2H), 8.75 (d, J = 7.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2H), 7.80 (s, 2H), 7.70 (s, 2H), 7,60 (d, J = 7.0 Hz, 2H), 7.40−7.65 (m, 4H), 6.85 (d, J = 10.0 Hz, 1H), 6.60 (dd, J = 10.0, 5.0 Hz, 1H), 5.10−5.30 (m, 1H), 3.70 (s, 3H), 3.40−3.60 (m, 2H), 3.10−3.30 (m, 2H), 2.00−2.20 (m, 5H), 1.40−1.80 (m, 6H). MS: *m*/*z* (FAB) 525 (M + H)$^+$. Anal. ($C_{33}H_{37}N_3O_3$·TFA·1.5H_2O) C, H, N.

***N*-(4-Cyclohexylcyclohexanoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Methyl Ester (14).** ^{1}H NMR (DMSO-d_6): δ 8.00 (d, J = 7.0 Hz, 1H), 7.50−7.70 (m, 4H), 7.20−7.50 (m, 5H), 6.70 (d, J = 10.0 Hz, 1H), 6.30 (dd, J = 10.0, 5.0 Hz, 1H), 4.80−5.00 (m, 1H), 3.60 (s, 3H), 2.90−3.20 (m, 3H), 1.40−2.20 (m, 13H), 0.90−1.40 (m, 12H). MS: *m*/*z* (FAB) 531 (M + H)$^+$. Anal. ($C_{33}H_{43}N_3O_3$·TFA·1.5H_2O) C, H, N.

***N*-(4-(2-(Methylphenyl)benzoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Methyl Ester (15).** ^{1}H NMR (DMSO-d_6): δ 9.25 (s, 1H), 9.03 (s, 1H), 8.71 (d, J = 8.7 Hz, 1H), 7.86 (d, J = 8 Hz, 2H), 7.61 (d, J = 8 Hz, 2H), 7.6−7.12 (m, 13H), 6.67 (d, J = 15.9 Hz, 1H), 6.42 (dd, J = 15.9, 7.8 Hz, 1H), 5.0 (dd, J = 16, 7.9 Hz, 1H), 3.32 (s, 3H), 3.3−3.15 (m, 1H), 3.11−2.9 (m, 2H), 2.21 (s, 3H). MS: *m*/*z* (FAB) (M + H)$^+$. Anal. ($C_{34}H_{33}N_3O_3$·TFA·0.5H_2O) C, H, N.

***N*-(4-(3-Methylphenyl)benzoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Methyl Ester (16).** ^{1}H NMR (DMSO-d_6): δ 9.25 (s, 1H), 8.99 (s, 1H), 8.68 (d, J = 8.7 Hz, 1H), 7.9 (d, J = 9 Hz, 1H), 7.75 (d, J = 9 Hz, 1H), 7.68−7.15 (m, 13H), 6.68 (d, J = 15.9 Hz, 1H), 6.4 (dd, J = 15.9, 7.8 Hz, 1H), 5.0 (dd, J = 16, 7.9 Hz, 1H), 3.46 (s, 3H), 3.28−3.18 (m, 1H), 3.1−2.9 (m, 2H), 2.36 (s, 3H). MS: *m*/*z* (FAB) 533 (M + H)$^+$. Anal. ($C_{34}H_{33}N_3O_3$·TFA·1.5H_2O) C, H, N.

***N*-(4-(4-Methylphenyl)benzoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Methyl Ester (17).** ^{1}H NMR (DMSO-d_6): δ 9.22 (s, 1H), 8.91 (s, 1H), 8.68 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 9 Hz, 2H), 7.75 (d, J = 9 Hz, 2H), 7.65−7.2 (m, 13H), 6.65 (d, J = 15.9 Hz, 1H), 6.39 (dd, J = 15.9, 7.8 Hz, 1H), 4.99 (dd, J = 16, 7.9 Hz, 1H), 3.46 (s, 3H), 3.28−3.18 (m, 1H), 3.08−2.88 (m, 2H), 2.35 (s, 3H). MS: *m*/*z* (FAB) 533 (M + H)$^+$. Anal. ($C_{34}H_{33}N_3O_3$·TFA·2.25H_2O) C, H, N.

***N*−(4-(2-Ethylphenyl)benzoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Methyl Ester (18).** ^{1}H NMR (DMSO-d_6): δ 9.25 (s, 1H), 9.05 (s, 1H), 8.68 (d, J = 8.6 Hz, 1H), 7.88 (d, J = 9 Hz, 2H), 7.76 (d, J = 9 Hz, 2H), 7.62 (m, 2H), 7.55−7.15 (m, 11H), 6.66 (d, J = 16 Hz, 1H), 6.4 (dd, J = 16, 7.8 Hz, 1H), 4.96 (dd, J = 16, 7.8 Hz, 1H), 3.47 (s, 3H), 3.3−3.18 (m, 1H), 3.1−2.88 (m, 2H), 2.67 (q, J = 8.5 Hz, 2H), 1.22 (t, J = 8.5 Hz, 3H). MS: *m*/*z* (FAB) 547 (M + H)$^+$. Anal. ($C_{35}H_{35}N_3O_3$·TFA·0.5H_2O) C, H, N.

***N*−(4-(3-Ethylphenyl)benzoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Methyl Ester (19).** ^{1}H NMR (DMSO-d_6): δ 9.25 (s, 1H), 9.08 (s, 1H), 8.72 (d, J = 12.0 Hz, 1H), 7.88 (d, J = 10.8 Hz, 2H), 7.75 (d, J = 10.8 Hz, 2H), 7.68−7.55 (m, 2H), 7.53−7.15 (m, 11H), 6.66 (d, J = 19.2 Hz, 1H), 6.41 (dd, J = 19.2, 9.6 Hz, 1H), 5.07−4.92 (m, 1H), 3.45 (s, 3H), 3.28−3.16 (m, 2H), 3.08−2.88 (m, 2H), 2.66 (q, J = 9.6 Hz, 2H), 1.23 (t, J = 9.6 Hz, 3H). MS: *m*/*z* (FAB) 547 (M + H)$^+$. Anal. ($C_{35}H_{35}N_3O_3$·TFA·0.5H_2O) C, H, N.

***N*-(4-(4-Ethylphenyl)benzoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Methyl Ester (20).** ^{1}H NMR (DMSO-d_6): δ 9.3 (s, 1H), 9.15 (s, 1H), 8.9 (d, J = 7.6 Hz, 1H), 8.2 (d, J = 8 Hz, 2H), 8 (d, J = 9 Hz, 2H), 7.4−7.9 (m, 12H), 7.2 (d, J = 8 Hz, 1H), 6.9 (d, J = 15 Hz, 1H), 6.6 (dd, J = 15, 6 Hz, 1H), 5.2 (dd, J = 16, 6 Hz, 1H), 3.7 (s, 3H), 3.4−3.5 (m, 1H), 3.1−3.2 (m, 1H), 2.85 (q, 2H), 1.4 (t, 3H). MS: *m*/*z* (FAB) 547 (M + H)$^+$. Anal. ($C_{35}H_{35}N_3O_3$.TFA·1.5H_2O) C, H, N.

***N*-(4-(2-Methoxyphenyl)benzoyl)-*syn*-(2-(3-amidinobenzyl)-3-trans-styryl)-*β*-alanine Methyl Ester (21).** ^{1}H NMR (DMSO-d_6): δ 9.25 (s, 1H), 9.03 (s, 1H), 8.76 (d, J = 8.7 Hz, 1H), 7.83 (d, J = 9.5 Hz, 2H), 7.65−6.95 (m, 15H), 6.64 (d, J = 15.9 Hz, 1H), 6.4 (dd, J = 15.9, 7.8 Hz, 1H), 4.99 (dd, J = 16, 7.9 Hz, 1H), 3.75 (s, 3H), 3.46 (s, 3H), 3.3−3.17 (m, 1H), 3.1−2.9 (m, 2H). MS: *m*/*z* (FAB) 549 (M + H)$^+$. Anal. ($C_{34}H_{33}N_3O_4$·TFA·1.0H_2O) C, H, N.

***N*-(4-(3-Methoxyphenyl)benzoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Methyl Ester (22).** ^{1}H NMR (DMSO-d_6): δ 9.23 (s, 1H), 8.96 (s, 1H), 8.69 (d, J = 8.7 Hz, 1H), 7.9 (d, J = 9.6 Hz, 2H), 7.68−7.18 (m, 12H), 6.96 (dd, J = 9.6, 2 Hz, 1H), 6.64 (d, J = 15.9 Hz, 1H), 6.39 (dd, J = 15.9, 7.8 Hz, 1H), 4.98 (dd, J = 16, 7.9 Hz, 1H), 3.81 (s, 3H), 3.47 (s, 3H), 3.28−3.17 (m, 1H), 3.08−2.86 (m, 2H). MS: *m*/*z* (FAB) 549 (M + H)$^+$. Anal. ($C_{34}H_{33}N_3O_4$·TFA·1.25H_2O) C, H, N.

***N*-(4-(4-Methoxyphenyl)benzoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Methyl Ester (23).** ^{1}H NMR (DMSO-d_6): δ 9.23 (s, 1H), 8.96 (s, 1H), 8.66 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 9.1 Hz, 2H), 7.72−7.22 (m, 11H), 7.03 (d, J = 8.7 Hz, 2H), 6.64 (d, J = 16.1 Hz, 1H), 6.4 (dd, J = 16.1, 7.9 Hz, 1H), 4.97 (dd, J = 16.1, 7.9 Hz, 1H), 3.77 (s, 3H), 3.46 (s, 3H), 3.28−3.15 (m, 1H), 3.08−2.88 (m, 2H). MS: *m*/*z* (FAB) 549 (M + H)$^+$. Anal. ($C_{34}H_{33}N_3O_4$·TFA·1.25H_2O) C, H, N.

***N*-(4-(2,4-Dimethoxyphenyl)benzoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Methyl Ester (24).** ^{1}H NMR (DMSO-d_6): δ 9.23 (s, 1H), 9.07 (s, 1H), 8.63 (d, J = 9 Hz, 1H), 7.81 (d, J = 8.9 Hz, 2H), 7.68−7.15 (m, 14H), 6.72−6.52 (m, 1H), 6.45−6.3 (m, 1H), 5.04−4.9 (m, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.51 (s, 3H), 3.21−3.15 (m, 1H), 3.08−2.85 (m, 2H). MS: *m*/*z* (FAB) 579 (M + H)$^+$. Anal. ($C_{35}H_{35}N_3O_5$·TFA·1.0H_2O) C, H, N.

***N*-(4-(3,4-Dimethoxyphenyl)benzoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Methyl Ester (25).** ^{1}H NMR (DMSO-d_6): δ 9.5 (s, 1H), 9.3 (s, 1H), 8.9 (d, J = 7.6 Hz, 1H), 8.1 (d, J = 8 Hz, 2H), 7.9 (d, J = 9 Hz, 2H), 7.8 (s, 2H), 7.4−7.7 (m, 11H), 7.25 (d, J = 8 Hz, 1H), 6.6 (d, J = 15 Hz, 1H), 6.4 (dd, J = 15, 6 Hz, 1H), 4 (s, 3H), 3.9 (s, 3H), 3.7 (s, 3H), 3.4−3.5 (m, 1H), 3.2−3.4 (m, 1H). MS: *m*/*z* (FAB) 579 (M + H)$^+$. Anal. ($C_{35}H_{35}N_3O_5$·TFA·2.5H_2O) C, H, N.

***N*-(4-(2-Ethoxyphenyl)benzoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Methyl Ester (26).** ^{1}H NMR (DMSO-d_6): δ 9.24 (s, 1H), 9.11 (s, 1H), 8.68 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 9 Hz, 2H), 7.6 (d, J = 9 Hz, 2H), 7.59−6.95 (m, 13H), 6.65 (d, J = 15.9 Hz, 1H), 6.39 (dd, J = 15.9, 7.8 Hz, 1H), 4.98 (dd, J = 16, 7.8 Hz, 1H), 4.03 (q, J = 8.1 Hz, 2H), 3.47 (s, 3H), 3.28−3.18 (m, 1H), 3.1−2.88 (m, 2H), 1.24 (t, J = 8.1 Hz, 3H). MS: *m*/*z* (FAB) 563 (M + H)$^+$. Anal. ($C_{35}H_{35}N_3O_4$·TFA·0.5H_2O) C, H, N.

***N*-(4-(3-Ethoxyphenyl)benzoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Methyl Ester (27).** ^{1}H NMR (DMSO-d_6): δ 9.22 (s, 1H), 9.05 (s, 1H), 8.7 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 9 Hz, 2H), 7.76 (d, J = 9 Hz, 2H), 7.68−7.12 (m, 12H), 6.98−6.85 (m, 1H), 6.67 (d, J = 16 Hz, 1H), 6.4 (dd, J = 16, 7.8 Hz, 1H), 5.01 (dd, J = 16, 7.8 Hz, 1H), 4.08 (q, J = 7.5 Hz, 2H), 3.45 (s, 3H), 3.25−3.15 (m, 1H), 3.08−2.89 (m, 2H), 1.32 (t, J = 7.5 Hz, 2H). MS: *m*/*z* (FAB) 563 (M + H)$^+$. Anal. ($C_{35}H_{35}N_3O_4$·TFA·1.5H_2O) C, H, N.

***N*-(4-(4-Ethoxyphenyl)benzoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Methyl Ester (28).** ^{1}H NMR (DMSO-d_6): δ 9.26 (s, 1H), 9.02 (s, 1H), 8.64 (d, J = 8.7 Hz, 1H), 7.86 (d, J = 9 Hz, 2H), 7.72 (d, J = 9 Hz, 2H), 7.7−7.22 (m, 11H), 7.01 (d, J = 10.4 Hz, 2H), 6.64 (d, J = 15.9 Hz, 1H), 6.38 (dd, J = 15.9, 7.8 Hz, 1H), 4.98 (dd, J = 16, 7.8 Hz, 1H), 4.06 (q, J = 8.2 Hz, 2H), 3.45 (s, 3H), 3.3−3.18 (m, 1H), 3.08−2.85 (m, 2H), 1.32 (t, J = 8.2 Hz, 3H). MS: *m*/*z* (FAB) 563 (M + H)$^+$. Anal. ($C_{35}H_{35}N_3O_4$·TFA·1.0H_2O) C, H, N.

***N*-(4-Phenylbenzoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Dimethyl Amide (29).** To a solution of *N*-(4-phenylbenzoyl)-*syn*-(2-(3-cyanobenzyl)-3-*trans*-styryl)-*β*-alanine (see above) (2 mmol) in 20 mL of methylene chloride was added two drops of dimethylformamide, followed by oxalyl chloride (4 mmol) dropwise via syringe at 0 °C. After 20 min, dimethylamine was bubbled through the solution for 2 min at 0 °C. Stirring was continued for 30 min, during which time the reaction mixture was allowed to come to room temperature. Solvents were removed in vacuo, and the residue was converted to the corresponding amidine as described above. ^{1}H NMR (DMSO-d_6): δ 8.06 (d, J = 7.8 Hz, 2H), 7.82 (d, J =7.8 Hz, 2H), 7.25−7.77 (m, 14H), 6.73 (d, J = 15.8 Hz, 1H), 6.4 (dd, J = 15.8, 7.9 Hz, 1H), 5.13 (m, 1H), 3.27 (s, 3H), 3.22 (s, 3H), 3.08−3.45 (m, 3H). MS: *m*/*z* (FAB) 532 (M + H)$^+$. Anal. ($C_{34}H_{34}N_4O_2$·TFA·3.0H_2O) C, H, N.

***N*-(4-Phenylbenzoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine (30).** *N*-(4-Phenylbenzoyl)-*syn*-(2-(3-cyanobenzyl)-3-*trans*-styryl)-*β*-alanine (see above) is converted to the corresponding amidine as described above. ^{1}H NMR (DMSO-d_6): δ 8.00 (d, J = 9 Hz, 2H), 7.82 (d, J = 9 Hz, 2H), 7.22−7.77 (m, 14H), 6.73 (d, J = 15.8 Hz, 1H), 6.4 (dd, J = 15.8, 7.9 Hz, 1H), 4.95 (m, 1H), 3.08−3.45 (m, 3H). MS: *m*/*z* (FAB) 505 (M + H)$^+$. Anal. ($C_{32}H_{29}N_3O_3$·TFA·0.5H_2O) C, H, N.

***N*-(4-Phenylbenzoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alaninol (31).** To a stirred solution of *N*-(4-phenylbenzoyl)-*syn*-(2-(3-cyanobenzyl)-3-*trans*-styryl)-*β*-alanine (see above) (2 mmol) and triethylamine (3.2 mmol) in dry tetrahydrofuran at 0 °C was added isobutyl chloroformate (3 mmol) dropwise via syringe. After 15 min, the reaction mixture was filtered into a solution of sodium borohydride (4 mmol) in 5 mL of water at 0 °C. The mixture was allowed to warm to room temperature. After 1 h, tetrahydrofuran was removed in vacuo. Water was added, and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were worked up. The crude product was purified by flash chromatography (1:2 ethyl acetate−hexanes). The nitrile was then converted to the corresponding amidine as described above. ^{1}H NMR ($CDCl_3$): δ 7.92 (d, J = 9 Hz, 2H), 7.2−7.72 (m, 16H), 6.67 (d, J = 15.5 Hz, 1H), 6.27 (dd, J = 15.5, 7.8 Hz, 1H), 4.94 (m, 1H), 3.88 (m, 1H), 3.5 (m, 1H), 3.12 (m, 1H), 2.82−3.03 (m, 2H), 1.95 (m, 1H). MS: *m*/*z* (FAB) 491 (M + H)$^+$. Anal. ($C_{32}H_{31}N_3O_2$·TFA·1.5H_2O) C, H, N.

***N*−(4-Phenylbenzoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-*β*-alanine Methyl Ether (32).** To a stirred solution of *N*-(4-phenylbenzoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-

β-alaninol (see **31**) (0.2 mmol) in 2 mL of a 2:1 solution of tetrahydrofuran−dimethylformamide at 0 °C was added sodium hydride (60% dispersion; 0.4 mmol) in a single portion. After 15 min, methyl iodide (0.3 mmol) was added, and the reaction mixture was allowed to warm to room temperature. After 2 h, unreacted sodium hydride was quenched by the careful addition of a saturated sodium bicarbonate solution. Tetrahydrofuran was removed in vacuo and the residue diluted with water (100 mL) and extracted with methylene chloride (3 × 50 mL). The combined organic extracts were worked up. The crude methyl ether was subjected to flash chromatograpy (1:2 ethyl acetate−hexanes). ^{1}H NMR (DMSO-d_6): δ 7.93 (d, J = 9.3 Hz, 2H), 7.15−7.83 (m, 16H), 6.57 (d, J = 15.8 Hz, 1H), 6.22 (dd, J = 15.8, 6.8 Hz, 1H), 5 (m, 1H), 3.75 (m, 1H), 3.42 (s, 3H), 3.27 (m, 1H), 2.87−3.03 (m, 2H), 2.12 (m, 1H).

The nitrile was then converted to the corresponding amidine as described above. ^{1}H NMR ($CDCl_3$): δ 7.93 (d, J = 9.3 Hz, 2H), 7.15−7.83 (m, 16H), 6.57 (d, J = 15.8 Hz, 1H), 6.22 (dd, J = 15.8, 6.8 Hz, 1H), 5 (m, 1H), 3.75 (m, 1H), 3.42 (s, 3H), 3.27 (m, 1H), 2.87−3.03 (m, 2H), 2.12 (m, 1H). MS: *m*/*z* (FAB) 505 $(M + H)^+$. Anal. ($C_{33}H_{33}N_3O_2$·TFA·1.0H_2O) C, H, N.

***N*-(4-Phenylbenzoyl)-*syn*-(2-(3-amidinobenzyl)-3-*trans*-styryl)-β-alanine Methyl Acetate (33).** A mixture of alcohol **31** (1 mmol), pyridine (4.9 mmol), (dimethylamino)pyridine (0.1 mmol), and acetic anhydride (1.2 mmol) was stirred 24 h at room temperature. The mixture was diluted with methylene chloride (50 mL) and washed with 0.1 N hydrochloric acid (2 × 10 mL). The organic layer was worked up and directly purified by reverse phase HPLC. ^{1}H NMR (DMSO-d_6): δ 7.98 (d, J = 8 Hz, 2H), 7.73 (d, J = 8 Hz, 2H), 7.67 (d, J = 8 Hz, 2H), 7.17−7.58 (m, 12H), 6.94 (d, 1H), 6.55 (d, J = 18 Hz, 1H), 6.21 (dd, J = 18, 5 Hz, 1H), 5.1 (m, 1H), 4.38 (m, 1H), 4.08 (m, 1H), 2.68−2.97 (m, 2H), 2.51 (m, 1H). MS: *m*/*z* (FAB) 533 $(M + H)^+$. Anal. ($C_{34}H_{33}N_3O_3$·TFA·1.0H_2O) C, H, N.

***N*-(4-Phenylbenzoyl)-2-*trans*-styryl-4-(3-amidinophenyl)propylamine (34).** To a solution of 3-cyano-1-bromobenzene (55 mmol) and 3-butyn-1-ol (55 mmol) in 40 mL of piperidine was added tetrakis(triphenylphosphine)palladium (6 mmol) in a single portion at room temperature. The reaction mixture was heated at 80 °C for 2 h. After cooling, solvents were removed in vacuo and the residue was subjected to flash chromatography (1:1 ethyl acetate−hexanes) to provide 4-(3-cyanophenyl)-3-butyn-1-ol. To this material (44 mmol) in 100 mL of ethanol was added palladium on calcium carbonate (0.5 g). The reaction mixture was shaken (Parr shaker) under a positive pressure of hydrogen (45psi) for 3 h. Catalyst was removed by filtration through Celite and the filtrate concentrated in vacuo. The residue was dissolved in 50 mL of acetone and 16 mL of freshly prepared Jones reagent was added dropwise at room temperature. Stirring was continued 15 min at room temperature. The supernatant was decanted, the residue was stirred with 50 mL of fresh acetone, and the supernatant was decanted again. The supernatants were combined and concentrated in vacuo. The residue was diluted with water (100 mL) and washed with ethyl acetate (3 × 100 mL). The combined organic extracts were worked up and treated with an excess of ethereal diazomethane. Excess diazomethane was decomposed by the dropwise addition of glacial acetic acid and the reaction mixture worked up and purified by flash chromatography (1:9 ethyl acetate−hexanes) to give methyl 4-(3-cyanophenyl)butanoate. ^{1}H NMR ($CDCl_3$): δ 7.30−7.50 (m, 4H), 3.64 (s, 3H), 2.68 (t, J = 9.6 Hz, 2H), 2.30 (t, J = 9.6 Hz, 2H), 1.95 (m, 2H).

To a solution of the ester (9.8 mmol) in 50 mL of tetrahydrofuran was added lithium hexamethyldisilazide (12.8 mmol, 1.0M solution in tetrahydrofuran) dropwise via syringe at −78 °C. After 15 min, a solution of triisopropylbenzenesulfonyl azide (12.8 mmol) in 20 mL of tetrahydrofuran was added via cannula at −78 °C. The reaction mixture was allowed to slowly warm to 0 °C and stirred an additional 15 min. Saturated sodium bicarbonate solution (10 mL) was added and tetrahydrofuran was removed in vacuo. The residue was diluted with water (100 mL) and extracted with methylene chloride (3 × 100 mL). The combined organic extracts were worked up. To this material (9.0 mmol) in 50 mL of ethanol was added palladium on calcium carbonate (0.5 g). The reaction mixture was shaken (Parr shaker) under a positive pressure of hydrogen (45psi) for 1 h. Catalyst was removed by filtration through Celite and the filtrate concentrated in vacuo. Purification by reverse phase HPLC (10% acetonitrile/0.1% trifluoroacetic acid in water to 100% acetonitrile) afforded methyl 2-amino-4-(3-cyanophenyl)butanoate. ^{1}H NMR ($CDCl_3$): δ 7.32−7.50 (m, 4H), 3.72 (s, 3H), 3.42 (t, J = 7.2 Hz, 1H), 2.56−2.64−2.70 (m, 2H), 2.08−2.18 (m, 1H), 1.85−1.95 (m, 1H).

To a solution of 4-biphenylcarboxylic acid (6 mmol) in 30 mL of dimethylformamide was added diisopropylethylamine (6 mmol) in a single portion at room temperature, followed by 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (6 mmol) in a similar fashion. The reaction mixture was stirred for 2 min at room temperature, and a solution of the free amine (6 mmol) in 15 mL of dimethylformamide was added in a single portion. Stirring was continued overnight at room temperature. The reaction mixture was diluted with 300 mL of ethyl acetate and washed sequentially with 1 N hydrochloric acid (3 × 75 mL), water, saturated sodium bicarbonate (3 × 75 mL), and brine. The organic phase was worked up to give methyl 2-((4-phenylbenzoyl)amino)-4-(3-cyanophenyl)butanoate. ^{1}H NMR ($CDCl_3$): δ 7.87 (d, J = 13.2 Hz, 2H), 7.66 (d, J = 13.2 Hz, 2H), 7.60 (d, J = 12.0 Hz, 1H), 7.35−7.50 (m, 8H), 4.78−4.85 (m, 1H), 3.66 (s, 3H), 2.72−2.83 (m, 2H), 2.40−2.54 (m, 1H), 2.00−2.18 (m, 1H).

To a solution of this methyl ester (6 mmol) in 20 mL of methanol was added 20 mL of 1 N sodium hydroxide slowly at 0 °C. The reaction mixture was allowed to come to room temperature and stirred for an additional 1 h. The reaction mixture was brought to pH 7 by the slow addition of 1 N hydrochloric acid. Tetrahydrofuran was removed in vacuo and the residue diluted with water (100 mL), brought to pH 3 with 1 N hydrochloric acid, and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were worked up to give 2-((4-phenylbenzoyl)amino)-4-(3-cyanophenyl)butanoic acid. This material was dissolved in 25 mL of tetrahydrofuran and triethylamine (9 mmol) was added in a single portion at room temperature. The reaction mixture was cooled to 0 °C, and isobutyl chloroformate (6 mmol) was added dropwise via syringe. Stirring was continued for 20 min at 0 °C. The reaction mixture was filtered into a solution of sodium borohydride (6 mmol) in 5 mL of water at 0 °C. The mixture was allowed to warm to room temperature. After 1 h, tetrahydrofuran was removed in vacuo. Water was added (50 mL), and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were worked up to give 2-((4-phenylbenzoyl)amino)-4-(3-cyanophenyl)-1-butanol. The crude alcohol, as a solution in 10 mL of methylene chloride, was added to a solution of oxalyl chloride (18 mmol) and dimethyl sulfoxide (18 mmol) in 100 mL of methylene chloride, dropwise via addition funnel at −78 °C. The reaction mixture was allowed to warm to −30 °C, then recooled to −78 °C, and stirred for an additional 1 h. Triethylamine (60 mmol) was added dropwise and the reaction mixture warmed to room temperature and stirred an additional 1 h. All solvents were removed in vacuo, and the residue was taken up in methylene chloride (100 mL) and washed with water (3 × 50 mL). The organic layer was worked up and purified by flash chromatography (1:4 ethyl acetate−hexanes) to provide 2-((4-phenylbenzoyl)amino)-4-(3-cyanophenyl)-1-butanal. ^{1}H NMR ($CDCl_3$): δ 9.68 (s, 1H), 7.87 (d, J = 13.2 Hz, 2H), 7.66 (d, J = 13.2 Hz, 2H), 7.58 (d, J = 12.0 Hz, 1H), 7.35−7.46 (m, 8H), 4.84−4.90 (m, 1H), 2.72−2.83 (m, 2H), 2.40−2.54 (m, 1H), 2.00−2.18 (m, 1H).

To a suspension of benzyltriphenylphosphonium chloride (4.2 mmol) in 20 mL of tetrahydrofuran was added *n*-butyllithium (4.5 mmol, 1.6 M solution in hexanes) dropwise at room temperature. Stirring was continued for 30 min at room temperature. The solution of the ylide was cannulated into a solution of 2-((4-phenylbenzoyl)amino)-4-(3-cyanophenyl)-1-butanal (1.7 mmol) in 50 mL of tetrahydrofuran at room

temperature. Stirring was continued for 3.5 h and a solution of saturated sodium bicarbonate carefully added. Tetrahydrofuran was removed in vacuo, and the residue was diluted with water (100 mL) and extracted with methylene chloride (3 × 100 mL). The combined organic extracts were worked up. ^{1}H NMR of the crude material showed a 4:1 ratio of *trans*- to *cis*-olefin. Pure *N*-(4-phenylbenzoyl)-2-*trans*-styryl-4-(3-cyanophenyl)propylamine was obtained by recrystallization from ethyl acetate−hexanes. ^{1}H NMR ($CDCl_3$): δ 7.85 (d, J = 13.2 Hz, 2H), 7.66 (d, J = 13.2 Hz, 2H), 7.60 (d, J = 12.0 Hz, 1H), 7.35−7.46 (m, 13H), 6.64 (d, J = 26.4 Hz, 1H), 6.20 (dd, J = 26.4, 12.0 Hz, 1H), 4.84−4.96 (m, 1H), 2.82 (t, J = 10.8 Hz, 2H), 2.05−2.15 (m, 2H).

To a solution of this material (1 mmol) in 20 mL of pyridine and 4 mL of triethylamine was bubbled in hydrogen sulfide for 10 min at room temperature. The solution was allowed to stir at room temperature overnight. Nitrogen gas was bubbled through he reaction for 5 min, and solvents were removed in vacuo. The residue was dried under vacuum and then dissolved in 15 mL of dry acetone. To this solution was added 5 mL of methyl iodide, and this solution was heated at 50 °C for 1 h and then concentrated in vacuo. The residue was dissolved in 20 mL of methanol, and ammonium acetate (2 mmol) was added in a single portion at room temperature. The reaction mixture was heated at 65 °C for 2 h. After cooling, methanol was removed in vacuo and the residue purified by reverse phase HPLC to provide compound **34**. ^{1}H NMR (DMSO-d_6): δ 7.90 (d, J = 13.2 Hz, 2H), 7.66 (d, J = 13.2 Hz, 2H), 7.62 (d, J = 12.0 Hz, 1H), 7.39−7.58 (m, 13H), 6.64 (d, J = 26.4 Hz, 1H), 6.24 (dd, J = 26.4, 12.0 Hz, 1H), 4.84−4.96 (m, 1H), 2.82 (t, J = 10.8 Hz, 2H), 2.05−2.15 (m, 2H). MS: m/z (FAB) 461 (M + H)$^+$. Anal. ($C_{31}H_{29}N_3O$·TFA·0.5H_2O) C, H, N.

Synthesis of 2(*R*)-((3-Amidinophenyl)methyl)-3(*R*)-(*N*-(4-phenylbenzoyl)amino)-5-phenylpentanoic Acid Methyl Ester (35). To a solution of *N*-α-Boc-D-homophenylalanine (38 mmol) in 80 mL of dry tetrahydrofuran was added *N*-methylmorpholine (38 mmol) in a single portion, followed by isobutyl chloroformate (38 mmol) in a similar fashion, at −20 °C. The reaction mixture was stirred for 10 min at −20 °C and filtered into a preformed ethereal solution of diazomethane (∼70 mmol) at 0 °C. The resulting solution was allowed to stand at 0 °C for 20 min. Excess diazomethane was decomposed by the dropwise addition of glacial acetic acid, and solvents were removed in vacuo. The resulting oil was dissolved in 150 mL of dry methanol. A solution of silver bezoate (8 mmol) in 17 mL of triethylamine was slowly added with stirring at room temperature. The resulting black reaction mixture was stirred for 45 min at room temperature. Methanol was removed in vacuo and the residue taken up in 700 mL of ethyl acetate. The mixture was filtered through Celite and washed sequentially with saturated sodium bicarbonate (3 × 150 mL), water (1 × 150 mL), 1 N potassium bisulfate (3 × 150 mL), and brine (1 × 150 mL). The organic layer was worked up and purified by flash chromatography (3:1 hexanes−ethyl acetate) to give methyl *N*-Boc-3(*R*)-amino-5-phenylpentanoate. ^{1}H NMR ($CDCl_3$): δ 7.21−7.31 (m, 2H), 7.11−7.20 (m, 3H), 4.92−5.05 (m. 1H), 3.88−4.02 (m, 1H), 3.67 (s, 3H), 2.59−2.78 (m, 2H), 2.45−2.58 (m, 2H), 1.72−1.93 (m, 2H), 1.43 (s, 9H).

A solution of the homologated amino ester (11 mmol) in 70 mL of dry tetrahydrofuran was cooled to −78 °C, and a solution of lithium hexamethyldisilazide in tetrahydrofuran (33 mmol) was added via syringe at such a rate that the temperature did not rise above −60 °C. The reaction mixture was warmed to −25 °C over 40 min and recooled to −78 °C. A solution of 3-cyanobenzyl bromide (27 mmol) in 20 mL of tetrahydrofuran was added via syringe at such a rate that the temperature did not rise above −60 °C. The reaction mixture was allowed to come to room temperature and stirred at room temperature for 1 h. Then 125 mL of saturated sodium bicarbonate was added, and tetrahydrofuran was removed in vacuo. The remaining material was partitioned between 500 mL of ethyl acetate and 150 mL of saturated sodium bicarbonate. The organic phase was further washed with saturated sodium bicarbonate (2 × 100 mL) and brine. The organic layer was worked up. The residue was triturated with 40 mL of 4:1 hexanes−ethyl acetate. The solid material was filtered off and discarded. The filtrate, containing the desired product, was concentrated *in vacuo*. To a solution of this material (5 mmol) in 60 mL of methylene chloride was added 20 mL of trifluoroacetic acid dropwise at 0 °C. The resulting solution was stirred for 2 h at 0 °C. Solvents were removed in vacuo, and the residue was purified by reverse phase HPLC using a gradient of 30% to 70% acetonitrile in water containing 0.1% trifluoroacetic acid. Acetonitrile was removed in vacuo and the remaining material partitioned between saturated sodium bicarbonate and ethyl acetate. The aqueous layer was extracted twice with ethyl acetate, and the combined organic layers were worked up to give 2(*R*)-((3-cyanophenyl)methyl)-3(*R*)-amino-5-phenylpentanoic acid methyl ester. ^{1}H NMR ($CDCl_3$): δ 7.11−7.51 (m, 9H), 3.55 (s, 3H), 2.91−3.12 (m, 3H), 2.75−2.88 (m, 2H), 2.60−2.73 (m, 1H), 1.72−1.95 (m, 2H).

To a solution of 4-biphenylcarboxylic acid (2 mmol) in 10 mL of DMF was added diisopropylethylamine (2 mmol) in a single portion at room temperature, followed by 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (2 mmol) in a similar fashion. The reaction mixture was stirred for 2 min at room temperature, and a solution of the free amine (2 mmol) in 15 mL of dimethylformamide was added in a single portion. Stirring was continued overnight at room temperature. The reaction mixture was diluted with 300 mL of ethyl acetate and washed sequentially with 1 N hydrochloric acid (3 × 75 mL), water, saturated sodium bicarbonate (3 × 75 mL), and brine. The organic phase was worked up to give 2(*R*)-((3-cyanophenyl)methyl)-3(*R*)-(*N*-(4-phenylbenzoyl)amino)-5-phenylpentanoic acid methyl ester. ^{1}H NMR ($CDCl_3$): δ 7.94 (d, J = 10.8 Hz, 2H), 7.72 (d, J = 10.8 Hz, 2H), 7.63 (d, J = 9.6 Hz, 2H), 7.35−7.54 (m, 7H), 7.21−7.32 (m, 2H), 7.11−7.20 (m, 3H), 4.41−4.56 (m, 1H), 3.64 (s, 3H), 2.88−3.05 (m, 3H), 2.60−2.77 (m, 2H), 1.75−1.95 (m, 2H).

To a solution of this material (1 mmol) in 20 mL of pyridine and 4 mL of triethylamine was bubbled in hydrogen sulfide for 10 min at room temperature. The solution was allowed to stir at room temperature overnight. Nitrogen gas was bubbled through the reaction for 5 min, and solvents were removed *in vacuo*. The residue was dried under vacuum and then dissolved in 15 mL of dry acetone. To this solution was added 5 mL of methyl iodide, and this solution was heated at 50 °C for 1 h and then concentrated in vacuo. The residue was dissolved in 20 mL of methanol, and ammonium acetate (2 mmol) was added in a single portion at room temperature. The reaction mixture was heated at 65 °C for 2 h. After cooling, methanol was removed in vacuo and the residue purified by reverse phase HPLC using a gradient of 20% to 80% acetonitrile in water buffered with 0.1% trifluoroacetic acid. Acetonitrile was removed in vacuo and the aqueous phase lyophilized to provide the desired product, 2(*R*)-((3-amidinophenyl)methyl)-3(*R*)-(*N*-(4-phenylbenzoyl)amino)-5-phenylpentanoic acid methyl ester, as its trifluoroacetate salt. ^{1}H NMR ($CDCl_3$): δ 9.23 (s, 2H), 9.01 (s, 2H), 8.35 (d, J = 13.2 Hz, 1H), 7.94 (d, J = 13.2 Hz, 1H), 7.77 (d, J = 10.8 Hz, 2H), 7.72 (d, J = 10.8 Hz, 2H), 7.57 (s, 2H), 7.42−7.52 (m, 4H), 7.33−7.41 (m, 1H), 7.20−7.28 (m, 2H), 7.10−7.19 (m, 3H), 4.38−4.42 (m, 1H), 3.45 (s, 3H), 3.02−3.12 (m, 1H), 2.85−2.98 (m, 2H), 2.58−2.75 (m, 1H), 2.45−2.56 (m, 1H), 1.75−2.06 (m, 2H). MS: m/z (FAB) 521 (M + H)$^+$. $[\alpha]_D$ (methanol) = +19.7°. Anal. ($C_{33}H_{33}N_3O_3$·TFA·2.5H_2O) C, H, N.

2(*S*)-((3-Amidinophenyl)methyl)-3(*S*)-(*N*-(4-phenylbenzoyl)-amino)-5-phenylpropionic acid methyl ester was prepared in an identical fashion from *N*-α-Boc-L-homophenylalanine. ^{1}H NMR ($CDCl_3$): δ 9.23 (s, 2H), 9.15 (s, 2H), 8.35 (d, J = 13.2 Hz, 1H), 7.94 (d, J = 13.2 Hz, 1H), 7.76 (d, J = 10.8 Hz, 2H), 7.72 (d, J = 10.8 Hz, 2H), 7.57 (s, 2H), 7.42−7.52 (m, 4H), 7.33−7.41 (m, 1H), 7.24 (d, J = 10.8 Hz, 2H), 7.10−7.19 (m, 3H), 4.38−4.42 (m, 1H), 3.45 (s, 3H), 3.02−3.12 (m, 1H), 2.85−3.01 (m, 2H), 2.58−2.73 (m, 1H), 2.45−2.56 (m, 1H), 1.75−

2.06 (m, 2H). MS: *m/z* (FAB) 521 $(M + H)^+$. $[\alpha]_D$ (methanol) = −19.2°. Anal. ($C_{33}H_{33}N_3O_3$·TFA·2.5H_2O) C, H, N.

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