Discovery of Potent Isoxazoline Glycoprotein IIb/IIIa Receptor Antagonists

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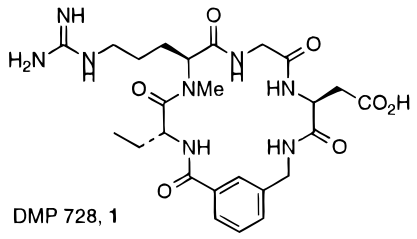
Using the isoxazoline as a common structural feature, three series of glycoprotein IIb/IIIa receptor antagonists were evaluated, culminating in the discovery of XR299 (**30**). In an *in vitro* assay of platelet inhibition, XR299 had an IC_{50} of 0.24 μM and was a potent antiplatelet agent when dosed intravenously in a canine model. It was shown through X-ray studies of the cinchonidine salt **49** that the receptor required the 5(*R*)-stereochemistry for high potency. The ethyl ester prodrug of XR299, XR300 (**29**), was orally active in the dog.

Introduction

Platelet adhesion and aggregation are important events in the pathophysiology of thrombosis.[1] Upset of the delicate balance of hemostasis can result in the uncontrolled deposition of platelets on thrombogenic surfaces. This may be followed by distal embolization of platelet−fibrin thrombi, leading to the occlusion of vessels,[2−4] a condition associated with unstable angina, myocardial infarction, transient ischemic attack, stroke, and other thromboembolic disorders.

Platelets are activated by a wide variety of agonists, including adenosine diphosphate (ADP), serotonin, arachidonic acid, thrombin, and collagen. The process of platelet activation typically involves the participation of several signal transduction pathways. Currently prescribed antiplatelet agents, such as aspirin, are of limited efficacy as they can only block one of the pathways involved. An antiplatelet drug which prevents platelet aggregation induced by all agonists should, in principle, represent a more efficacious antiplatelet therapy. Glycoprotein IIb/IIIa (GPIIb/IIIa, $\alpha_{IIb}\beta_3$) is a platelet membrane-bound receptor which upon activation binds fibrinogen, a necessary and sufficient prelude to platelet aggregation.[5,6] Recent clinical results have demonstrated the utility of GPIIb/IIIa antagonists in man for the treatment of arterial thrombosis.[7] The intense level of interest in this area may be best appreciated through a perusal of several reviews describing peptide, cyclic peptide, and small molecule GPIIb/IIIa antagonists.[8−11]

Previous reports from these laboratories described the discovery of novel, template-constrained peptides containing the Arg-Gly-Asp (RGD) recognition sequence, represented by DMP 728 (**1**).[12−14] As a highly potent and selective GPIIb/IIIa antagonist, DMP 728 provided a useful starting point for the design of a non-peptide agent. Additional structure−function information was also available in the form of several low molecular weight, non-peptide GPIIb/IIIa antagonists.[15−21] After consideration of the structural information contained in these and in **1**, it was assumed that the bound conformation of **1** required an extended glycine conformation and a distance of 15−17 Å between the basic and acidic groups. The structures of potent, non-peptide GPIIb/IIIa antagonists suggested that a Gly carbonyl mimic such as an aryl group or amide was important for good binding. In simplest terms, it was envisioned that high receptor affinity could be achieved with a non-peptide through proper positioning of the important basic and acidic pharmacophore moieties on a suitable core structure.



DMP 728, **1**

After consideration of the attributes of a number of heterocycles as a core structure, the 3,5-disubstituted isoxazoline was selected since a diverse array of structural types could be rapidly evaluated through the facility and generality of 1,3-dipolar cycloaddition chemistry.[22] Isoxazolines also serve as versatile synthons for numerous functional groups, and if necessary this aspect of the rich chemistry of isoxazolines could be exploited. In this account, we describe the synthesis and antiplatelet activity of three series of isoxazolines, culminating with the discovery of a potent, orally active series of isoxazolinylacetamides.

Chemistry

A representative synthetic route used to prepare 3-(4-alkoxyphenyl)isoxazolines **2**−**6** is depicted in Scheme 1. Alkylation of 4-hydroxybenzaldehyde with 2-(Boc-piperidin-4-yl)ethanol (**7a**)[23] under Mitsunobu conditions followed by reaction with hydroxylamine hydrochloride afforded oxime **8a**. 1,3-Dipolar cycloaddition of the nitrile oxide formed *in situ*[24] from **8a** and methyl pent-4-enoate, or *via* treatment of the corresponding oximinoyl chloride[25] with triethylamine in the presence of methyl pent-4-enoate, afforded isoxazoline **9**. Saponification of **9** followed by Boc cleavage gave **2**.

Isoxazolineacetic acids **10a**,**b**, bearing lipophilic groups α to the carboxylate, were prepared from L-vinylglycine (**11**).[26] As shown in Scheme 2, cycloaddition of this material with oxime **8a** afforded isoxazolines **12a,b** as a 2.5:1 mixture of diastereomers, as determined using ^{1}H NMR. The mixture was saponified and partially separated using flash chromatography, giving the major

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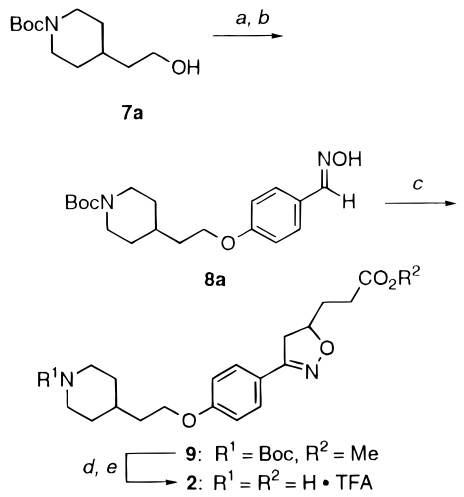
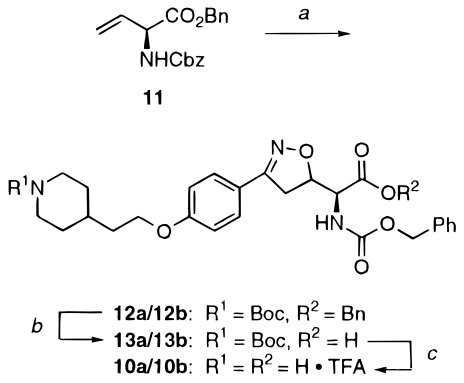
Scheme 1[a]



[a] Reagents: (a) PPh_3, *p*-hydroxybenzaldehyde, DEAD, THF; (b) NH_2OH·HCl, EtOH/pyr; (c) methyl pent-4-enoate, bleach, CH_2Cl_2; (d) LiOH, THF/H_2O; (e) TFA/CH_2Cl_2.

Scheme 2[a]



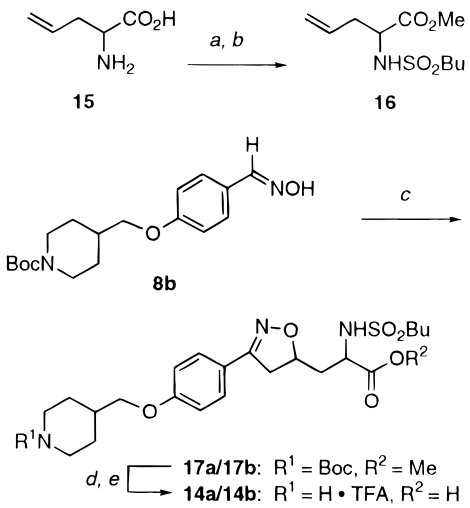
[a] Reagents: (a) **8a**, bleach, CH_2Cl_2; (b) LiOH, THF/H_2O; (c) 33% TFA/CH_2Cl_2.

diastereomer **13a** and a 1:1 mixture of **13a,b** (stereochemistry unassigned). These materials were then Boc deprotected, affording **10a** and a 1:1 mixture of **10a**,**b**.

The synthesis of the allylglycine-derived isoxazolines **14a**,**b** is depicted in Scheme 3. D,L-2-Amino-4-pentenoic acid (**15**) was first rendered soluble through silylation using *N*,*O*-bis(trimethylsilyl)(trifluoromethyl)acetamide (BSTFA).[27] Reaction with butanesulfonyl chloride afforded the sulfonamide, which was desilylated and isolated as the crystalline dicyclohexylammonium salt. Esterification then afforded methyl ester **16**. Attempts to prepare the sulfonamide with omission of the silylation resulted in poor yields. Dipolar cycloaddition of this material with oxime **8b** gave a 1:1 mixture of diastereomers (stereochemistry unassigned). The diastereomers were separated using flash chromatography, giving **17a**,**b**. Separate processing afforded **14a**,**b**.

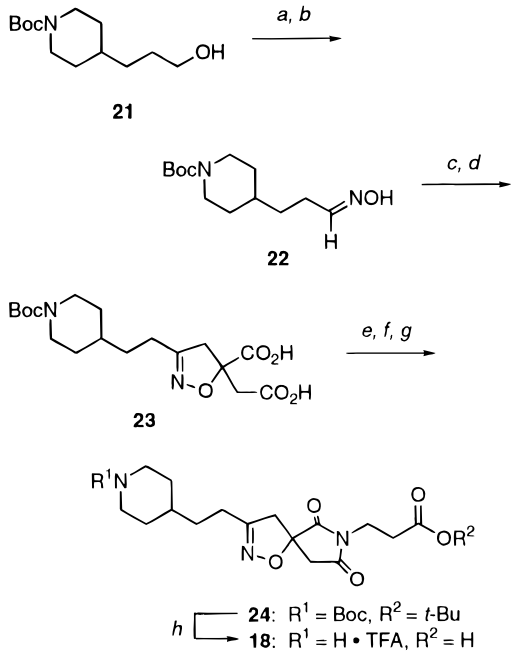
A general route to the spiro-isoxazolinylimides **18**−**20** is shown in Scheme 4. Oxidation of 3-(Boc-piperidin-4-yl)propanol[19,28] (**21**) using buffered PCC followed by reaction with hydroxylamine hydrochloride afforded oxime **22**. Oxidation to the nitrile oxide in the presence of dimethyl itaconate gave the isoxazoline, which was saponified to afford diacid **23**. Formation of the anhydride was followed by reaction with *β*-alanine *tert*-butyl ester, activation of the free carboxylate as the hydroxysuccinimide ester, and ring closure, affording imide **24**. Global deprotection gave **18**.

Scheme 3[a]



[a] Reagents: (a) i. BSTFA, MeCN, 55 °C, 2 h, ii. $BuSO_2Cl$, pyr, 70 °C, 18 h, iii. DCHA, Et_2O; (b) MeOH, HCl; (c) **16**, bleach, CH_2Cl_2; (d) LiOH, THF/H_2O; (e) 33% TFA/CH_2Cl_2.

Scheme 4[a]

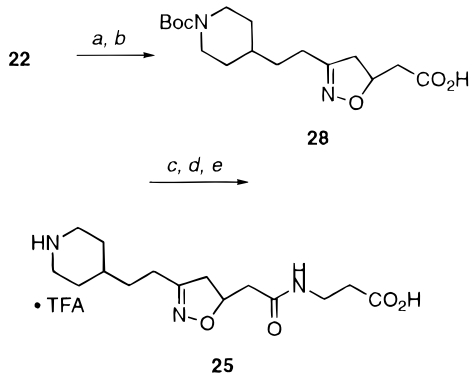


[a] Reagents: (a) PCC, NaOAc, CH_2Cl_2; (b) NH_2OH·HCl, EtOH/pyr; (c) dimethyl itaconate, NaOCl, CH_2Cl_2; (d) LiOH, THF/H_2O; (e) DCC, *β*-alanine *tert*-butyl ester, THF; (f) DCC, HOSuc, THF; (g) NaH, DMF; (h) 33% TFA/CH_2Cl_2.

A general route for the synthesis of the isoxazolinylacetamides **25**−**27** is depicted in Scheme 5. Dipolar cycloaddition of the nitrile oxide prepared *in situ* from oxime **22** with methyl 3-butenoate followed by saponification gave carboxylic acid **28**. Coupling of **28** with *β*-alanine methyl ester followed by saponification and Boc cleavage afforded **25**.

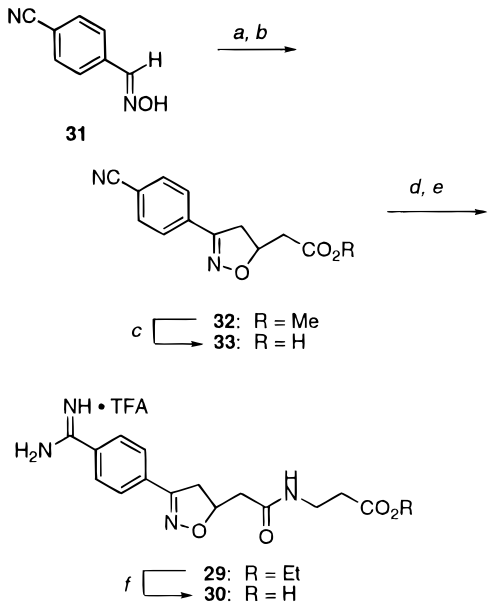
Benzamidines **29** and **30** were prepared using the route shown in Scheme 6. Conversion of *p*-cyanobenzaldoxime (**31**) to the oximinoyl chloride followed by dipolar cycloaddition with methyl 3-butenoate gave isoxazoline **32**. Saponification to give acid **33**, coupling with *β*-alanine methyl ester, and subsequent Pinner reaction gave the imidate, which was immediately reacted with ammonium carbonate to afford the amidine XR300 (**29**). Saponification of the ester gave the carboxylate XR299 (**30**).

Scheme 5[a]



[a] Reagents: (a) methyl but-3-enoate, bleach, CH_2Cl_2; (b) LiOH, THF/H_2O; (c) H-β-Ala-OMe, TBTU, Et_3N, DMF; (d) TFA/CH_2Cl_2; (e) rabbit liver esterase, pH 7.1.

Scheme 6[a]



[a] Reagents: (a) NCS, DMF; (b) methyl but-3-enoate, Et_3N, CH_2Cl_2; (c) LiOH, THF/H_2O; (d) H-β-Ala-OEt, TBTU, Et_3N, DMF; (e) HCl, EtOH, then $(NH_4)_2CO_3$, MeOH; (f) LiOH, MeOH.

Results and Discussion

In designing the 3-(4-alkoxyphenyl)isoxazoline series, it was envisioned that a piperidine could function as a conformationally constrained arginine guanidine mimic,[19] while an aryl moiety could act as a glycine carbonyl mimic.[19] Our initial efforts resulted in the 3-(5-isoxazolinyl)propionic acid (**2**). In an *in vitro* aggregation assay,[29] **2** afforded an IC_{50} of 48 μM, approximately 2-fold less potent than Arg-Gly-Asp-Ser. Analogs of **2** were then prepared to determine the optimum through-bond distance between the amino and carboxylate functionality and the optimal spatial relationship between the 3-arylisoxazoline core and the carboxy terminus (Table 1). The overall length was shortened by one methylene unit in **3** and **4**, resulting in a 3−6-fold increase in potency. This proved to be the optimum length for the series, as further reduction in length by one methylene unit afforded **5** and **6**, which were less potent. The effect of core positioning within the overall structure (**3** *vs* **4**) appeared to be small.

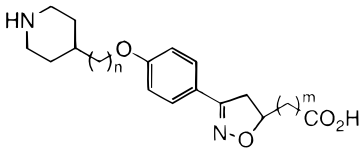
To test the possibility that a lipophilic group positioned α to the carboxylate might result in a potency increase,[19] compounds **10** and **14** were prepared (Table 2). The 5(*R*,*S*)-2(*S*)-diastereomers **10a**,**b** were 2−3-fold less potent than the unsubstituted and racemic **3**. As **10b** was a 1:1 mixture of diastereomers, the estimated activity of the second diastereomer, free of the first, was likely to be in the low-micomolar range; therefore, no further attempts were made to separate them.

Unlike the relationship between the isoxazolineacetic acids **10a**,**b** and their unsubstituted counterpart **3**, the diastereomeric pair **14a**,**b** was 2−3-fold more potent than the unsubstituted counterpart **4**. Again, the diastereomers had similar potencies.

The modest potencies observed thus far prompted the design of a spiro-isoxazolinylimide series. The spirocyclic core provided a rigid framework upon which to append the basic and acidic groups and retained a Gly carbonyl mimic in the form of the imide carbonyl groups. In addition, the isoxazoline moiety was positioned further from the acidic terminus.

Spirocycles **18**−**20** were prepared to establish the optimum distance between the basic and acidic termini (Table 3). Unfortunately, none of the compounds from this series proved to be active *in vitro*. It seemed plausible that the steric bulk and/or rigidity of the spiro-fused core resulted in poor complementarity with the receptor.

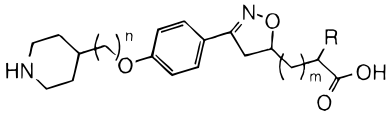
Table 1. Effect of Overall Length and Core Position



compd	*n*	*m*	hPRP $IC_{50} \pm (\mu M)$[a]
2	2	2	48 ± 8.4
3	2	1	8.3 ± 0.72
4	1	2	18 ± 3.6
5	1	1	36.6 ± 11.2
6	2	0	38.2 ± 8.2

[a] Inhibition of ADP-induced aggregation was determined in three donors.

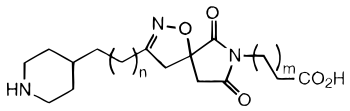
Table 2. Effect of α-Substitution



compd	*n*	*m*	R	hPRP $IC_{50} \pm (\mu M)$[a]
10a,b	2	0	$NHCO_2Bn$	13 ± 1.5
10a	2	0	$NHCO_2Bn$	23 ± 5.9
14a	1	1	$NHSO_2Bu$	2.7 ± 0.32
14b	1	1	$NHSO_2Bu$	8.4 ± 2.2

[a] See corresponding footnote in Table 1.

Table 3. Spiro-Isoxazolinylimides



compd	*n*	*m*	hPRP % inhib @ 100 μM ± SEM[a]
18	1	1	16.6 ± 4.9
19	1	2	16.3 ± 6.1
20	2	2	24 ± 10.9

[a] See corresponding footnote in Table 1.

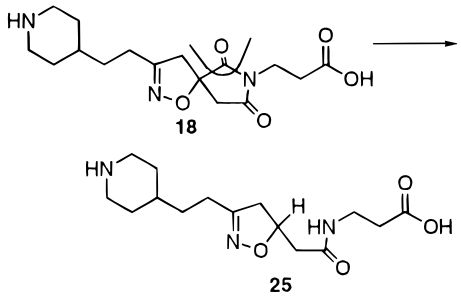
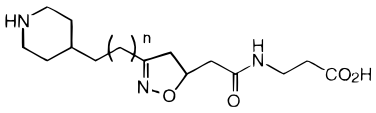


Figure 1. Design of the isoxazolinylacetamide series.

Table 4. Effect of Overall Length and Core Position



compd	*n*	hPRP $IC_{50} \pm$ SEM (μM)[a]
25	1	0.63 ± 0.043
26	2	16.0 ± 1.0
27	0	>100

[a] See corresponding footnote in Table 1.

Reasoning that the spiro-fused core had restricted the available conformational space of the side chains too severely, we relaxed the constraints imposed by the spiro-fused core by deleting an imide carbonyl from **18**, to give **25** (Figure 1). This modification afforded an amide N-H that could be useful as a hydrogen bond-donating group and allowed greater conformational sampling of the amide carbonyl and the acidic side chain.

As shown in Table 4, **25** was more than 100-fold more potent than **18** and possessed an IC_{50} of 0.63 μM in the PRP assay. Increasing or decreasing the length of the linker unit bearing the piperidine by one methylene unit (in **26** and **27**, respectively) resulted in large losses in potency. A further increase in potency relative to **25** was then achieved by replacement of the (piperidin-4-yl)ethyl moiety with a benzamidin-4-yl group, resulting in XR299 (**30**). From the study of serine protease inhibitors, the benzamidine moiety was a known mimetic of the arginine side chain.[30] XR299 was 2−3-fold more potent than **25** and had an IC_{50} of 0.24 μM. This increase could perhaps be attributed to a tighter control of conformational mobility or a beneficial hydrophobic shielding and/or reinforced ionic bonding effect afforded by the benzamidin-4-yl moiety.[31]

Upon examination of the antiplatelet efficacy of XR299, it was found that it inhibited the binding of [^{125}I]fibrinogen to activated human platelets[29] with an IC_{50} of 10.0 ± 3.0 nM (Figure 2). In this assay it was approximately 3 orders of magnitude more potent than RGDS. In a GPIIb/IIIa ELISA assay,[29] the IC_{50} of XR299 was 1.1 ± 0.8 nM, demonstrating that it had high affinity for GPIIb/IIIa. Additionally, it was found to inhibit platelet aggregation irrespective of the agonist used,[32] consistent with antagonism of the platelet GPIIb/IIIa receptor. As Table 5 demonstrates, XR299 very selectively antagonizes GPIIb/IIIa. In the other integrin-based adhesion assay systems examined,[29] the IC_{50} of XR299 exceeded 100 μM.

The administration of an oral dose of 1 mg/kg XR299 to dogs resulted in little antiplatelet effect.[33] However, at the same oral dose the ethyl ester XR300 (**29**) gave a 90−100% inhibition of *ex vivo* ADP (100 μM)-mediated

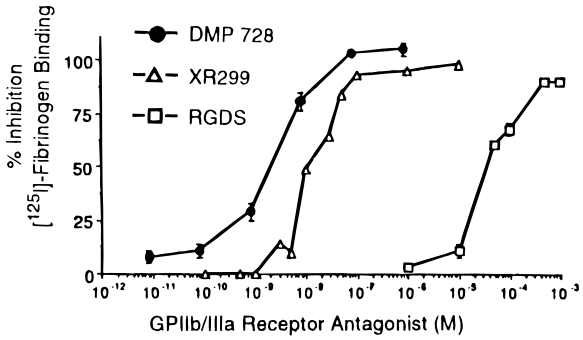
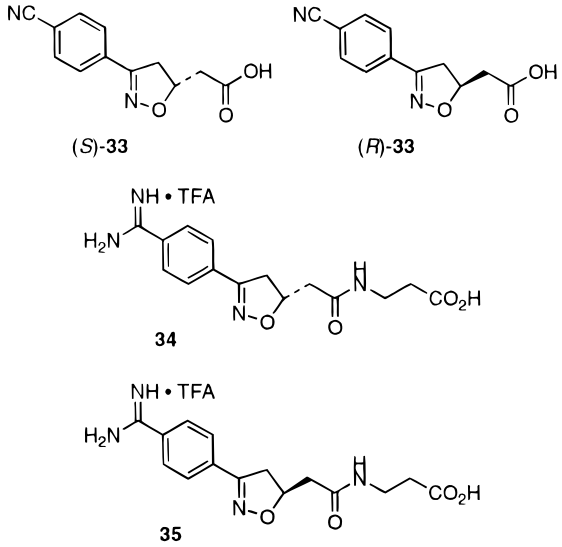


Figure 2. Antiplatelet efficacy of XR299 (**29**) in inhibiting [^{125}I]fibrinogen binding to activated human platelets.

platelet aggregation which declined to approximately 70% over 6 h (Figure 3).

Isoxazoline Absolute Stereochemistry. Chiral HPLC resolution of **29** and saponifications of the individual isomers afforded the carboxylic acids **34** and **35**. In the PRP assay, it was found that **34** had an IC_{50} of 0.86 ± 0.022 μM, while **35** had an IC_{50} of 0.06 ± 0.0092 μM, establishing the importance of the absolute configuration of the isoxazoline stereocenter.

An optically active isoxazoline synthetic intermediate was prepared from ester **32** or acid **33** through resolution using chiral preparative HPLC. Alternatively, it was conveniently obtained through fractional crystallization of the diastereomeric cinchonidine salts of acid **33**. Upon X-ray crystallographic analysis of **49**, the less soluble of the salts, it was found that the isoxazoline possessed the 5(*S*)-configuration (Figure 4). Amide formation between (*S*)-**33** and β-alanine methyl ester was accomplished using a standard peptide-coupling protocol (TBTU, Et_3N, DMF). The nitrile was then converted to the amidine and processed as before to afford **34**, which was optically pure, as determined using chiral HPLC. In a similar manner, 5(*R*)-**33** gave **35**, establishing that the receptor required the 5(*R*)-stereochemistry for high potency.



Conclusions

In conclusion, XR299 is a prototype isoxazolinylacetamide having excellent affinity and selectivity for the GPIIb/IIIa receptor. Classical resolution through crystallization of the diastereomeric cinchonidine salts of **33**, X-ray crystallographic analysis, and synthesis of

Table 5. Selectivity of XR299

assay system	IC_{50} (μM)
GPIIb/IIIa ELISA	0.0011
hPRP	0.24
Huvec-Vitronectin	200
Huvec-Fibronectin	180
Mac-1	>100
VLA4/VCAM	>100
Mac-1/ICAM	100

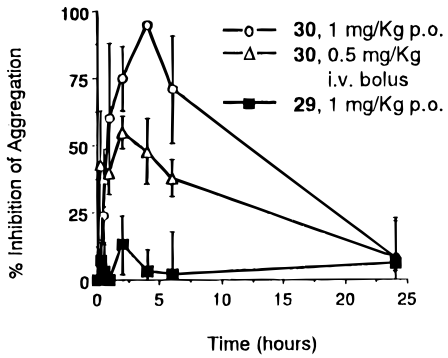


Figure 3. Canine model of antiplatelet efficacy of XR299 and XR300 in inhibiting ADP (10−4 M)-induced aggregation (n = 3).

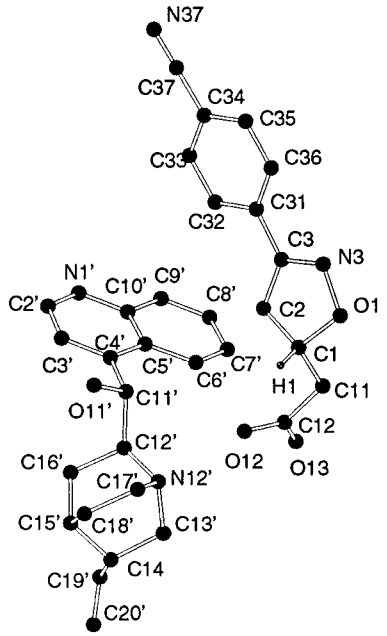


Figure 4. View of the structure of **49** as determined by single-crystal X-ray diffraction. Most hydrogen atoms have been omitted for clarity.

the 5(*R*)-isomer **35** established the importance of absolute configuration to *in vitro* antiplatelet potency. The ethyl ester prodrug of XR299, XR300, afforded excellent levels of platelet inhibition and good duration of action when dosed orally in a canine model.

Experimental Section

General Experimental. Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Unless otherwise stated, preparative HPLC separations were accomplished on a Vydac C18 column operated at room temperature and eluted at a 10 mL/min flow rate, using a linear gradient of 100% H_2O containing 0.05% TFA-20% H_2O/MeCN containing 0.05% TFA over 60 min, with UV detection at 254 nm. ^1H, and ^{13}C NMR data were obtained using Varian Unity 300, Unity 400, or VXR400 spectrometers and referenced to TMS or residual HOD. Mass spectral data were obtained on either VG 70-VSE (FAB, high-resolution FAB, high-resolution DCI) or Finnigan MAT 8230 (DCI) mass spectrometers. Combustion analyses were performed by Quantitative Technologies, Inc., Bound Brook, NJ. Solvents and reagents were used as purchased from Aldrich Chemical Co. unless otherwise stated. The yields quoted in this paper are isolated yields.

Ethyl Ester 36. To a stirred solution of ethyl isonipecotate (20.01 g, 0.1273 mol) in EtOAc (100 mL) at 0 °C was added dropwise a solution of Boc_2O (27.76 g, 0.1272 mol) in EtOAc (50 mL). The mixture was allowed to warm to room temperature overnight. After 20 h, the solution was poured into water, washed with water, 0.1 M HCl, saturated $NaHCO_3$, and saturated NaCl, and dried ($MgSO_4$). After filtration and washing the solid with EtOAc, the filtrate was concentrated *in vacuo* and placed under vacuum until constant weight was achieved to give 32.54 g (99%) of the desired carbamate **36** as a mobile oil: ^1H NMR (300 MHz, $CDCl_3$) δ 4.13 (q, J = 7.0 Hz, 2H), 4.03 (dm, J = 13.6 Hz, 2H), 2.81 (m, 2H), 2.41 (m, 1H), 1.86 (dm, J = 13.6 Hz, 2H), 1.62 (m, 2H), 1.44 (s, 9H), 1.24 (t, J = 7.0 Hz, 3H); CIMS (NH_3) m/z 275 ($M + NH_4^+$, 100), 258 ($M + H^+$, 15). Anal. ($C_{13}H_{23}NO_4$) C, H, N.

Preparation of Piperidine 7b. To a solution of **36** (32.34 g, 0.1257 mol) in THF (100 mL) at 0 °C was added dropwise 1 M LAH in THF (87.9 mL, 0.0879 mol). After 2 h, excess hydride was quenched by the addition of water (3.2 mL), 2 M NaOH (3.2 mL), and water (10 mL). The mixture was filtered and washed with EtOAc, and the filtrate was washed with water and saturated NaCl and dried over $MgSO_4$. After filtration and washing the solid with EtOAc, the filtrate was concentrated *in vacuo* and placed under vacuum until constant weight was achieved to give 22.72 g (84%) of alcohol **7b** as a white solid: mp 79.2−81.1 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 4.12 (bd, J = 12.8 Hz, 2H), 3.49 (d, J = 6.2 Hz, 2H), 2.68 (dt, J = 13.2, 1.8 Hz, 2H), 1.69 (m, 3H), 1.44 (s, 9H, coincident with m, 1H), 1.14 (m, 2H); CIMS (NH_3) m/z 233 ($M + NH_4^+$, 100), 216 ($M + H^+$, 85). Anal. ($C_{11}H_{21}NO_3$) C, H, N.

Preparation of Ether 37a. To a solution of **7a** (7.71 g, 33.6 mmol), 4-hydroxybenzaldehyde (4.11 g, 33.6 mmol), and PPh_3 (8.82 g, 33.6 mmol) in THF (60 mL) at −20 °C (bath temperature) was added a solution of DEAD (5.3 mL, 33.7 mmol) in THF (30 mL) over 2 h. During the addition, a deep red solution resulted, which changed to a golden color upon warming to room temperature overnight (18 h). The solution was concentrated and redissolved in EtOAc. It was then washed with water, 0.1 M HCl, 1 M NaOH, and saturated NaCl and dried over $MgSO_4$. Concentration *in vacuo* gave a solid (~20 g), which was purified using flash chromatography (10−20% EtOAc/hexanes step gradient), affording 7.82 g (70%) of **37a** as a white solid after drying under vacuum to constant weight: mp 82.1−82.9 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.83 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 4.10 (bd, J = 12.8 Hz, 2H), 4.04 (t, J = 6.6 Hz, 2H), 2.69 (bt, 2H), 1.84 (m, 2H), 1.70 (bd, J = 14.3 Hz, 2H), 1.46 (s, 9H, coincident with m, 2H), 1.10 (m, 2H). Anal. ($C_{19}H_{27}NO_4$) C, H, N.

Also prepared in this fashion from **7b** was **37b**: 8.14 g (70%) as a white solid; mp 115.6−116.8 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.81 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 4.15 (bd, J = 13.2 Hz, 2H), 3.87 (d, J = 6.6 Hz, 2H), 2.74 (dt, J = 12.4, 1.8 Hz, 2H), 1.97 (m, 1H), 1.81 (bd, J = 12.8 Hz, 2H), 1.45 (s, 9H), 1.27 (dq, J = 12.1, 4.0 Hz, 2H); CIMS (NH_3) m/z 351 ($M + NH_4^+$, 100).

Preparation of Oxime 8a. To a solution of **37a** (3.16 g, 9.48 mmol) in MeOH (20 mL) were added hydroxylamine hydrochloride (1.27 g, 18.3 mmol) and 2 M NaOH (7 mL, 14 mmol). The resulting suspension was stirred overnight at room temperature (18 h). The mixture was brought to pH 4 using 1 M HCl and filtered and the filter cake washed with water. The product was dried under vacuum over P_2O_5, affording 2.88 g (87%) of the desired oxime as a white solid: mp 114.4−116.1 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 2H), 7.51 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 4.10 (m, 2H), 4.03 (t, J = 6.2 Hz, 2H), 2.71 (bt, 2H), 1.73 (m, 4H), 1.46 (s, 9H), 1.19 (m, 2H); CIMS (NH_3) m/z 366 ($M + NH_4^+$, 100), 349 ($M + H^+$, 25). Anal. ($C_{19}H_{28}N_2O_4$) C, H, N.

Preparation of Oxime 8b. A mixture of **37b** (3.16 g, 9.89 mmol) and hydroxylamine hydrochloride (1.27 g, 18.3 mmol)

in 9:1 MeOH/pyridine (30 mL) was heated at reflux for 18 h. The mixture was cooled to room temperature and concentrated to dryness. The residue was dissolved in EtOAc, washed with 0.1 M HCl, water, saturated $CuSO_4$, water, and saturated NaCl, and dried over $MgSO_4$. After filtration and washing the solid with EtOAc, the filtrate was concentrated *in vacuo* and placed under vacuum until constant weight was achieved to give 3.19 g (96%) of oxime **8b** as a white solid: mp 140.1−141.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.48 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 4.14 (bs, 2H), 3.80 (d, J = 6.2 Hz, 2H), 2.71 (bt, J = 12.4 Hz, 2H), 1.95 (m, 1H), 1.80 (bd, J = 12.4 Hz, 2H), 1.45 (s, 9H), 1.26 (m, 2H).

Preparation of Oximinoyl Chloride 38a. To a solution of **8a** (955 mg, 2.74 mmol) in DMF (5 mL) was added NCS (366 mg, 2.74 mmol) in three portions. After 3 h, the solution was diluted with EtOAc, washed with water and saturated NaCl, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting solid was crystallized from ether/hexanes to give 548 mg (52%) of the oximinoyl chloride as a white solid: mp 119.3−119.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (bs, 1H), 7.77 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 4.12 (bd, J = 13.2 Hz, 2H), 4.04 (t, J = 6.2 Hz, 2H), 2.72 (bt, J = 12.1 Hz, 2H), 1.70 (m, 5H), 1.46 (s, 9H), 1.10 (m, 2H); CIMS (NH_3) m/z 400 (M + NH_4^+, 18), (M + NH_4 − HCl^+, 100). Anal. ($C_{19}H_{27}ClN_2O_4$) C, H, N, Cl.

Also prepared in this fashion from **8b** was oximinoyl chloride **38b**: white solid, 1.17 g (33%); mp 178.0−179.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 9.0 Hz, 2H), 4.17 (bd, J = 12.4 Hz, 2H), 3.80 (d, J = 6.2 Hz, 2H), 2.74 (dt, J = 12.8, 1.8 Hz, 2H), 1.95 (m, 1H), 1.81 (bd, J = 12.1 Hz, 2H), 1.46 (s, 9H), 1.27 (dq, J = 12.5, 4.0 Hz, 2H); CIMS (NH_3) did not afford product-derived M + NH_4^+ or M + H^+ ions.

Also prepared in this fashion from **31** was **39**: white solid, 572 mg (93%); mp >300 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.89 (s, 1H), 7.96 (m, 4H); CIMS (NH_3) m/z 198 (M + NH_4^+, 80), 181 (M + H^+, 30), 136 (100). Anal. ($C_8H_5ClN_2O$) C, H, N, Cl.

Preparation of Isoxazoline 9a. To a solution of **38a** (500 mg, 1.43 mmol) and methyl 4-pentenoate (245 mg, 2.15 mmol) in CH_2Cl_2 (7 mL) was added a 5% solution of NaOCl (Clorox; 5 mL, 3.5 mmol). The mixture was stirred rapidly at room temperature for 18 h, diluted with water, and washed with CH_2Cl_2. The combined organic was dried over $MgSO_4$. After filtration and washing the solid with EtOAc, the filtrate was concentrated *in vacuo* giving a yellow solid. Crystallization from EtOAc/hexanes afforded 500 mg (76%) of isoxazoline **9a** as a white solid: mp 104.1−104.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 4.75 (m, 1H), 4.10 (bs, 2H), 4.04 (t, J = 5.9 Hz, 2H), 3.69 (s, 3H), 3.42 (dd, J = 16.5, 10.3 Hz, 1H), 2.97 (dd, J = 16.5, 7.3 Hz, 1H), 2.71 (bt, J = 12.5 Hz, 2H), 2.53 (t, J = 7.3 Hz, 2H), 2.01 (q, J = 7.3 Hz, 2H), 1.72 (m, 4H), 1.46 (s, 9H), 1.17 (m, 2H); CIMS (NH_3) m/z 478 (M + NH_4^+, 100). Anal. ($C_{25}H_{36}N_2O_6$) C, H, N.

Also prepared in this fashion from **38a** was **9e**: white solid, 409 mg (66%); mp 71.8−73.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 8.6 Hz, 2H), 6.91 (d, J = 8.6 Hz, 2H), 5.17 (dd, J = 10.2, 7.7 Hz, 1H), 4.10 (bs, 2H), 4.04 (t, J = 5.9 Hz, 2H), 3.82 (s, 3H), 3.64 (s, 1H), 3.61 (d, J = 3.3 Hz, 1H), 2.71 (bt, J = 12.4 Hz, 2H), 1.72 (m, 4H), 1.46 (s, 9H, coincident with m, 1H), 1.17 (m, 2H); MS (ESI) m/z 433 (M + H^+, 39), 377 (M + H − $C_4H_8^+$, 100), 333 (M + H − $C_4H_8CO_2^+$, 42). Anal. ($C_{23}H_{32}N_2O_6$) C, H, N.

Also prepared in this fashion from **22** and methyl 3-butenoate was **40**, except that **22** was added to the reaction mixture over 15 h. The crude isoxazoline was purified using flash chromatography (10−50% EtOAc/hexanes), giving 10.35 g (42%) of a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.89 (m, 1H), 4.09 (bd, J = 5.5 Hz, 2H), 3.71 (s, 3H), 3.13 (dd, J = 16.8, 9.9 Hz, 1H), 2.79 (dd, J = 15.8, 6.0 Hz, 1H), 2.67 (m, 3H), 2.55 (dd, J = 15.8, 7.7 Hz, 1H), 2.38 (t, J = 7.3 Hz, 2H), 1.68 (bd, J = 10.6 Hz, 2H), 1.52 (m, 2H), 1.45 (s, 9H, coincident with m, 1H), 1.10 (dq, J = 11.7, 3.7 Hz, 2H); MS (ESI) m/z 355 (M + H^+, 100). Anal. ($C_{18}H_{30}N_2O_5$) C, H, N.

Preparation of Isoxazoline 9b. To a solution of **38a** (400 mg, 1.045 mmol) and methyl 3-butenoate (200 mg, 2.00 mmol) in benzene (5 mL) was added Et_3N (0.15 mL, 1.1 mmol). The resulting suspension was heated at reflux for 5 h, cooled to room temperature, and diluted with EtOAc. It was washed with 0.1 M HCl, water, and saturated NaCl, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting solid was crystallized from CH_2Cl_2/hexanes to give 357 mg (77%) of isoxazoline **9b** as a white solid: mp 139.1−140.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 5.08 (m, 1H), 4.10 (bd, J = 13.2 Hz, 2H), 4.04 (t, J = 5.9 Hz, 2H), 3.73 (s, 3H), 3.53 (dd, J = 16.5, 10.1 Hz, 1H), 3.10 (dd, J = 16.8, 7.1 Hz, 1H), 2.88 (dd, J = 16.1, 5.9 Hz, 1H), 2.71 (bt, J = 12.8 Hz, 2H), 2.64 (dd, J = 15.8, 7.7 Hz, 1H), 1.72 (m, 5H), 1.46 (s, 9H), 1.08 (m, 2H); CIMS (NH_3) m/z 464 (M + NH_4^+, 1), 447 (M + H^+, 31), 391 (M + H − $C_4H_8^+$, 100). Anal. ($C_{24}H_{34}N_2O_6$) C, H, N.

Also prepared in this fashion from **38b** was **9c**: white solid, 537 mg (60%); mp 97.9−99.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 4.74 (m, 1H), 4.15 (bd, J = 13.2 Hz, 2H), 3.81 (d, J = 6.2 Hz, 2H), 3.67 (s, 3H), 3.40 (dd, J = 16.5, 10.2 Hz, 1H), 2.95 (dd, J = 16.5, 7.3 Hz, 1H), 2.73 (dt, J = 13.2, 1.1 Hz, 2H), 2.52 (t, J = 7.3 Hz, 2H), 1.98 (q, J = 7.0 Hz, 2H, overlapping m, 1H), 1.81 (bd, J = 12.8 Hz, 2H), 1.45 (s, 9H), 1.26 (dq, J = 12.4, 3.7 Hz, 2H); CIMS (NH_3) m/z 464 (M + NH_4^+, 2), 447 (M + H^+, 31), 408 (M + NH_4 − $C_4H_8^+$, 11), 391 (M + H − $C_4H_8^+$, 100). Anal. ($C_{24}H_{34}N_2O_6$) C, H, N.

Also prepared in this fashion from **38b** was **9d**: white solid, 329 mg (68%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.04 (m, 1H), 4.15 (bd, J = 13.2 Hz, 2H), 3.81 (d, J = 6.2 Hz, 2H), 3.71 (s, 3H), 3.54 (dd, J = 16.8, 10.3 Hz, 1H), 3.08 (dd, J = 16.8, 7.3 Hz, 1H), 2.86 (dd, J = 16.1, 5.9 Hz, 1H), 2.73 (dt, J = 12.8, 1.8 Hz, 2H), 2.62 (dd, J = 15.8, 7.7 Hz, 1H), 1.95 (m, 1H), 1.81 (bd, J = 13.2 Hz, 2H), 1.45 (s, 9H), 1.25 (dq, J = 12.8, 4.4 Hz, 2H); CIMS (NH_3) m/z 450 (M + NH_4^+, 100), 433 (M + H^+, 25), 394 (M + NH_4 − $C_4H_8^+$, 20).

Also prepared in this fashion from **39** was **32**. The crude product was purified using flash chromatography (0−50% EtOAc/hexanes), giving 3.68 g (81%) as a white solid: mp 120.1−120.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (AB quartet, Δ = 22.7 Hz, J = 8.4 Hz, 4H), 5.16 (m, 1H), 3.72 (s, 3H), 3.54 (dd, J = 16.8, 10.6 Hz, 1H), 3.13 (dd, J = 16.8, 7.7 Hz, 1H), 2.90 (dd, J = 16.1, 5.7 Hz, 1H), 2.67 (dd, J = 16.1, 7.7 Hz, 1H); CIMS (NH_3) m/z 262 (M + NH_4^+, 100), 245 (M + H^+, 45). Anal. ($C_{13}H_{12}N_2O_3$) C, H, N.

Preparation of Carboxylic Acid 41a. To a solution of **9a** (350 mg, 0.760 mmol) in THF (5 mL) was added 0.5 M LiOH (3 mL, 1.5 mmol). The reaction mixture was stirred at room temperature for 4 h, the pH was adjusted to 3 using 0.1 M HCl, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and filtered, the solid was washed with EtOAc, and the filtrate was concentrated *in vacuo*. Purification of the residue using flash chromatography ($CHCl_3$−20% MeOH/$CHCl_3$ gradient) afforded 261 mg (77%) of carboxylic acid **41a** after crystallization from EtOAc/hexanes as a white solid: mp 119.4−119.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 4.08 (bs, 2H), 4.04 (bt, J = 5.9 Hz, 2H), 3.44 (dd, J = 16.5, 10.3 Hz, 1H), 2.98 (dd, J = 16.5, 7.3 Hz, 1H), 2.71 (bt, J = 12.1 Hz, 2H), 2.59 (t, J = 7.3 Hz, 2H), 2.00 (m, 2H), 1.72 (m, 4H), 1.46 (s, 9H), 1.19 (m, 2H); MS (ESI) m/z 447 (M + H^+, 100). Anal. ($C_{24}H_{34}N_2O_6 \cdot 0.33\ H_2O$) C, H, N.

Also prepared in this fashion from **9b** was **41b**: white solid, 34 mg (74%); mp 169.1−170.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 5.10 (m, 1H), 4.08 (m, 2H, coincident with t, J = 5.9 Hz, 2H), 3.55 (dd, J = 16.5, 10.2 Hz, 1H), 3.11 (dd, J = 16.8, 7.0 Hz, 1H), 2.93 (dd, J = 16.1, 6.2 Hz, 1H), 2.71 (m, 3H), 2.00 (m, 2H), 1.72 (m, 5H), 1.46 (s, 9H); CIMS (NH_3) m/z 450 (M + NH_4^+, 100), 433 (M + H^+, 7). Anal. ($C_{23}H_{32}N_2O_6$) C, H, N.

Also prepared in this fashion from **9c** was **41c**: crystallized from CH_2Cl_2/hexanes to give 163 mg (67%) as a white solid; mp 146.5−147.7 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 4.75 (m, 1H), 3.81 (d, J = 6.2 Hz, 2H), 3.41 (dd, J = 16.5, 10.3 Hz, 1H), 2.95 (dd, J = 16.5, 7.3 Hz, 1H), 2.75 (bt, J = 12.4 Hz, 2H), 2.57 (t, J = 7.3 Hz, 2H), 1.97 (m, 3H), 1.81 (bd, J = 12.1 Hz, 2H), 1.45 (s, 9H),

1.24 (m, 2H); CIMS (NH_3) *m/z* 450 ($M + NH_4^+$, 100). Anal. ($C_{23}H_{32}N_2O_6$) C, H, N.

Also prepared in this fashion from **9d** was **41d**: 72 mg (22%) as a white solid; mp 164.0−164.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.07 (m, 1H), 4.15 (bd, J = 13.6 Hz, 2H), 3.82 (d, J = 6.2 Hz, 2H), 3.53 (dd, J = 16.8, 10.3 Hz, 1H), 3.10 (dd, J = 16.8, 7.0 Hz, 1H), 2.91 (dd, J = 16.1, 5.9 Hz, 1H), 2.73 (dt, J = 14.6, 1.8 Hz, 2H), 2.68 (dd, J = 16.1, 7.3 Hz, 1H), 1.97 (m, 1H), 1.81 (bd, J = 13.2 Hz, 2H), 1.45 (s, 9H), 1.26 (dq, J = 12.8, 4.4 Hz, 2H); CIMS (NH_3) *m/z* 436 ($M + NH_4^+$, 100), 419 ($M + H^+$, 20), 380 ($M + NH_4 - C_4H_8^+$, 25). Anal. ($C_{22}H_{30}N_2O_6$) C, H, N.

Also prepared in this fashion from **9e** was **41e**: 376 mg (99%) as a white foam; mp 60.2−60.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 9.0 Hz, 2H), 6.91 (d, J = 9.0 Hz, 2H), 5.19 (dd, J = 9.2, 8.4 Hz, 1H), 4.10 (bs, 2H), 4.04 (t, J = 5.9 Hz, 2H), 3.70 (d, J = 1.1 Hz, 1H), 3.67 (s, 1H), 2.71 (bt, J = 12.4 Hz, 2H), 1.72 (m, 4H), 1.46 (s, 9H), 1.19 (m, 3H); MS (ESI) *m/z* 419 ($M + H^+$, 36), 363 ($M + H - C_4H_8^+$, 100), 319 ($M + H - C_4H_8CO_2^+$, 30). Anal. ($C_{22}H_{30}N_2O_6$) C, H, N.

Also prepared in this fashion from **40** was **28**: 0.22 g (100%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.92 (m, 1H), 4.08 (m, 2H), 3.76 (m, 3H), 3.14 (dd, J = 17.2, 10.3 Hz, 1H), 2.82 (dd, J = 16.1, 6.2 Hz, 1H), 2.67 (m, 4H), 2.38 (t, J = 7.3 Hz, 2H), 1.86 (m, 2H), 1.68 (bd, J = 11.0 Hz, 2H), 1.51 (m, 2H, coincident with 1.45 (s, 9H) and (m, 1H)), 1.10 (dq, J = 12.1, 4.0 Hz, 2H); CIMS (NH_3) *m/z* 358 ($M + NH_4^+$, 100). Anal. ($C_{17}H_{28}N_2O_5$) C, H, N.

Also prepared in this fashion from **32** was **33**: 62 mg (67%) as a white solid; mp 179.2−181.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (m, 4H), 5.17 (m, 1H), 3.56 (dd, J = 16.8, 10.6 Hz, 1H), 3.13 (dd, J = 16.8, 7.7 Hz, 1H), 2.94 (dd, J = 16.5, 6.2 Hz, 1H), 2.73 (dd, J = 16.5, 7.0 Hz, 1H); CIMS (NH_3) *m/z* 248 ($M + NH_4^+$, 100), 231 ($M + H^+$, 5). Anal. ($C_{12}H_{10}N_2O_3$) C, H, N.

(±)-4,5-Dihydro-3-[4-[2-(4-piperidinyl)ethoxy]phenyl]-5-isoxazolepropanoic Acid Mono(trifluoroacetate) (2). To a solution of **41a** (150 mg, 0.336 mmol) in CH_2Cl_2 (2 mL) was added TFA (1 mL, 13 mmol). After 1.5 h, the product was precipitated by the addition of ether, affording 65 mg (42%) of the TFA salt as a white solid: mp 114.8−115.7 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.59 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 4.72 (m, 1H), 4.07 (t, J = 5.9 Hz, 2H), 3.47 (dd, J = 16.8, 10.2 Hz, 1H), 3.37 (dd, J = 16.8, 7.7 Hz, 1H), 2.98 (m, 2H), 2.44 (t, J = 7.3 Hz, 2H), 2.01 (bd, J = 15.0 Hz, 2H), 1.93 (m, 3H), 1.80 (m, 2H), 1.44 (m, 2H); MS (ESI) *m/z* 347 ($M + H^+$, 100). Anal. ($C_{19}H_{26}N_2O_4 \cdot CF_3CO_2H$) C, H, N.

(±)-4,5-Dihydro-3-[4-[2-(4-piperidinyl)ethoxy]phenyl]-5-isoxazoleacetic Acid Mono(trifluoroacetate) (3). 3 was prepared in a similar fashion to **2**: 33 mg (60%) as a white solid; mp 142.4−143.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, J = 8.8, 2.6 Hz, 2H), 6.96 (dd, J = 8.8, 2.6 Hz, 2H), 5.03 (m, 1H), 4.10 (m, 2H), 3.55 (ddd, J = 16.8, 10.3, 2.2 Hz, 1H), 3.38 (bd, J = 12.4 Hz, 2H), 3.16 (ddd, J = 17.2, 7.7, 2.2 Hz, 1H), 2.98 (bt, J = 13.2 Hz, 2H), 2.69 (m, 2H), 2.01 (bd, J = 14.3 Hz, 2H), 1.91 (m, 1H), 1.80 (m, 2H), 1.46 (m, 2H); CIMS (NH_3) *m/z* 333 ($M + H^+$, 100). Anal. ($C_{18}H_{24}N_2O_4 \cdot CF_3CO_2H$) C, H, N.

(±)-4,5-Dihydro-3-[4-(4-piperidinylmethoxy)phenyl]-5-isoxazolepropanoic Acid Mono(trifluoroacetate) (4). 4 was prepared in a similar fashion to **2**: 88 mg (83%) as a white solid; mp 179.1−181.8 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.60 (d, J = 9.0 Hz, 2H), 6.97 (d, J = 9.0 Hz, 2H), 4.73 (m, 1H), 3.94 (d, J = 6.1 Hz, 2H), 3.46 (m, 3H), 3.06 (m, 3H), 2.45 (dt, J = 7.3, 1.2 Hz, 2H), 2.16 (m, 1H), 2.08 (bd, J = 15.4 Hz, 2H), 1.94 (q, J = 6.6 Hz, 1H), 1.64 (dq, J = 14.2, 4.2 Hz, 2H); CIMS (NH_3) *m/z* 333 ($M + H^+$, 100). Anal. ($C_{18}H_{24}N_2O_4 \cdot CF_3CO_2H$) C, H, N.

(±)-4,5-Dihydro-3-[4-(4-piperidinylmethoxy)phenyl]-5-isoxazoleacetic Acid Mono(trifluoroacetate) (5). 5 was prepared in a similar fashion to **2**: 64 mg (94%) as a white solid; mp 220 °C dec; ^{1}H NMR (300 MHz, CD_3OD) δ 7.61 (d, J = 9.2 Hz, 2H), 6.97 (d, J = 9.2 Hz, 2H), 5.04 (m, 1H), 3.95 (d, J = 5.9 Hz, 2H), 3.56 (dd, J = 17.2, 10.2 Hz, 1H), 3.45 (bd, J = 12.8 Hz, 2H), 3.18 (dd, J = 17.2, 7.3 Hz, 1H), 3.04 (dt, J = 10.2, 2.9 Hz, 2H), 2.69 (m, 2H), 2.18 (m, 1H), 2.08 (bd, J = 14.6 Hz, 2H), 1.63 (m, 2H); HRMS (CI-NH_3) *m/z* 319.1658 [($M + H)^+$, calcd for $C_{17}H_{22}N_2O_4$ 319.1654]. Anal. ($C_{17}H_{22}N_2O_4 \cdot CF_3CO_2H$) C, H, N.

(±)-4,5-Dihydro-3-[4-[2-(4-piperidinyl)ethoxy]phenyl]-5-isoxazolecarboxylic Acid Mono(trifluoroacetate) (6). 6 was prepared in a similar fashion to **2**: 254 mg (76%) as a white solid; mp 156.8 °C dec; ^{1}H NMR (300 MHz, D_2O + TFA-d_1) δ 7.26 (d, J = 8.8 Hz, 2H), 6.68 (d, J = 8.8 Hz, 2H), 4.97 (dd, J = 11.7, 6.6 Hz, 1H), 4.97 (t, J = 6.2 Hz, 2H), 3.48 (dd, J = 17.6, 11.7 Hz, 1H), 3.33 (dd, J = 17.6, 6.6 Hz, 1H), 3.13 (bd, J = 12.8 Hz, 2H), 2.68 (dt, J = 12.8, 2.2 Hz, 2H), 1.68 (bd, J = 13.9 Hz, 2H), 1.56 (m, 1H), 1.47 (m, 2H), 1.15 (m, 2H); MS (ESI) *m/z* 319 ($M + H^+$, 100). The analytical sample was recrystallized from MeOH/ether. Anal. ($C_{17}H_{22}N_2O_4 \cdot CF_3CO_2H \cdot 0.5\ H_2O$) C, H, N.

Preparation of Isoxazolines 12a,b. To a solution of **8a** (852 mg, 2.44 mmol) and vinylglycine (**11**) (612 mg, 1.88 mmol) in CH_2Cl_2 (10 mL) was added 5% NaOCl (Clorox, 4 mL, 2.8 mmol). The mixture was rapidly stirred at room temperature for 22 h, after which time it was diluted with water and CH_2Cl_2. After separation of the layers, the aqueous was washed with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and washed with CH_2Cl_2, and the filtrate was concentrated *in vacuo*, giving 1.4 g. Purification using flash chromatography (10% EtOAc/hexanes−30% EtOAc/hexanes) then afforded 886 mg (70%) of the isoxazolines as an oily product (2.5:1 mixture of the *erythro*- and *threo*-isomers by ^{1}H NMR); ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.34 (m, 5H), 7.23 (m, 5H), 6.87 (d, J = 8.8 Hz, 2H), 5.47 (m, 1H), 5.12 (m, 5H), 4.60 (m, 1H), 4.07 (m, coincident with 4.03 (t, J = 6.1 Hz, 4H)), 3.36 (m, 2H), 2.71 (bt, J = 12.7 Hz, 2H), 1.70 (m, 5H), 1.45 (s, 9H), 1.18 (m, 2H); MS (ESI) *m/z* 672 ($M + H^+$, 100), 616 ($M + H - C_4H_8^+$, 87). Anal. ($C_{38}H_{45}N_3O_8$) C, H, N.

Preparation of Carboxylic Acids 13a,b. To a solution of **12a**,**b** (875 mg, 1.302 mmol) in THF (5 mL) was added 0.5M LiOH (3.5 mL). After 5 h at room temperature, the pH was adjusted to 3 using 0.1M HCl and the mixture extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and washed with CH_2Cl_2, and the filtrate was concentrated *in vacuo*, giving an oil. To the crude product was added methanol, causing selective crystallization of diastereomer **13a**. Collection of the solid by filtration and drying under vacuum until constant weight was achieved gave 295 mg (39%) as a white solid: mp 216.1−216.2 °C; TLC (silica gel 60, 20% MeOH/$CHCl_3$) R_f = 0.23; ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C) δ 7.50 (d, J = 8.9 Hz, 2H), 7.23 (s, 5H), 6.96 (d, J = 8.9 Hz, 2H), 6.17 (bs, 1H), 4.99 (m, 3H), 4.07 (t, J = 6.1 Hz, 2H), 3.90 (m, 3H), 3.35 (d, J = 9.3 Hz, 2H), 2.72 (bt, J = 12.4 Hz, 2H), 1.67 (m, 5H), 1.39 (s, 9H), 1.08 (m, 2H); MS (ESI) *m/z* 582 ($M + H^+$, 32), 526 ($M + H - C_4H_8^+$, 100), 482 ($M + H\text{-}C_4H_8\text{-}CO_2^+$, 91). This material failed combustion analysis and was recrystallized from MeOH. Anal. Calcd for $C_{31}H_{39}N_3O_8$: C, 64.01; H, 6.76; N, 7.22. Found: C, 57.05; H, 6.69; N, 6.29.

The filtrate was concentrated *in vacuo* and placed under vacuum until constant weight was achieved, giving 200 mg (26%) of **13a,b** as a white solid. This material was a 1:1 mixture of *erythro*- and *threo*-isomers (by ^{1}H NMR). Anal. ($C_{31}H_{39}N_3O_8$) C, H, N.

4,5-Dihydro-α-[[(phenylmethoxy)carbonyl]amino]-3-[4-[2-(4-piperidinyl)ethoxy]phenyl]-5-isoxazoleacetic Acid Mono(trifluoroacetate) (Mixture of isomers 10a,b). To a solution of **13a**,**b** (23 mg, 0.039 mmol) in CH_2Cl_2 (1 mL) was added TFA (0.5 mL, 6.5 mmol). After 1 h at room temperature, the mixture was concentrated *in vacuo* and crystallized from MeOH/ether, giving 15 mg (79%) as a white solid: mp 302 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6, 60 °C) δ 7.57 (d, J = 8.8 Hz, 2H), 7.30 (s, 5H), 6.99 (d, J = 8.8 Hz, 2H), 5.05 (s, 2H, coincident with m, 1H), 4.35 (d, J = 4.9 Hz, 1H), 4.09 (t, J = 6.1 Hz, 2H), 3.52 (dd, J = 17.3, 10.7 Hz, 1H), 3.26 (m, 3H), 2.88 (dt, J = 12.7, 2.7 Hz, 2H), 1.88 (bd, J = 14.4 Hz, 2H), 1.80 (m, 1H), 1.72 (m, 2H), 1.38 (m, 2H); MS (ESI) *m/z* 482 ($M + H^+$, 100). Anal. ($C_{26}H_{31}N_3O_6 \cdot 0.5\ H_2O$) C, H, N.

4,5-Dihydro-α-[[(phenylmethoxy)carbonyl]amino]-3-[4-[2-(4-piperidinyl)ethoxy]phenyl]-5-isoxazoleacetic Acid Mono(trifluoroacetate) (Isomer 10a). To a solution of **13a** (177 mg, 0.304 mmol) in CH_2Cl_2 (1 mL) was added TFA (0.5

mL, 6.5 mmol). After 1 h at room temperature, the mixture was concentrated *in vacuo* and crystallized from MeOH/ether, giving 3 mg (2%) of the TFA salt as a white solid: mp >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6, 60 °C) δ 8.48 (bs, 0.5H), 8.15 (bs, 0.5H), 7.55 (d, J = 8.9 Hz, 2H), 7.30 (m, 5H), 6.97 (d, J = 8.9 Hz, 2H), 5.05 (s, 2H), 4.96 (m, 1H), 4.33 (m, 1H), 4.07 (t, J = 6.3 Hz, 2H), 3.38 (m, 2H), 3.26 (bd, J = 12.0 Hz, 2H), 2.87 (m, 2H), 1.86 (bd, J = 14.2 Hz, 2H), 1.78 (m, 1H), 1.70 (apparent q, J = 6.3 Hz, 2H), 1.36 (bq, J = 13.2 Hz, 2H).

Dicyclohexylammonium D,L-2-[(Butylsulfonyl)amino]-4-pentenoate (42). To a suspension of **15** (2.54 g, 22.06 mmol) in acetonitrile (35 mL) was added BSTFA (7.3 mL, 27.5 mmol). The suspension was heated at 55 °C for 2 h, after which time a golden yellow solution resulted. To this solution were added pyridine (2.2 mL, 27.2 mmol) and *n*-butanesulfonyl chloride (3.0 mL, 23.1 mmol). The mixture was heated at 70 °C for 20 h and then cooled to room temperature. Concentration *in vacuo* afforded a brown oil, to which was added 15% $KHSO_4$ (5 mL). The mixture was stirred for 1 h and extracted with EtOAc (3×). The combined organic extracts were washed with saturated NaCl, dried ($MgSO_4$), and concentrated, and the resulting oil was dissolved in ether (5 mL). To this solution was added DCHA (4.38 mL, 22.0 mmol), causing immediate precipitation of the dicyclohexylammonium salt. The white solid was collected by filtration and placed under vacuum until constant weight was achieved, giving 8.42 g (92%): mp 207.1−208.6 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 5.84 (m, 1H), 5.09 (dm, J = 17.1 Hz, 1H), 5.04 (dm, J = 10.2 Hz, 1H), 3.80 (dd, J = 7.1, 5.1 Hz, 1H), 3.18 (m, 2H), 3.02 (m, 2H), 2.49 (m, 2H), 2.06 (m, 4H), 1.78 (m, 8H), 1.55 (m, 12H), 0.94 (t, J = 7.3 Hz). Anal. ($C_{21}H_{40}N_2O_4S$) C, H, N, S.

Methyl D,L-2-[(Butylsulfonyl)amino]-4-pentenoate (16). Into a solution of **42** (8.36 g, 20.07 mmol) in MeOH (50 mL) at 5 °C was bubbled dry HCl for 5 min. The resulting stirred suspension was allowed to warm to room temperature for 18 h, diluted with ether, and filtered. Concentration of the filtrate *in vacuo* was followed by the addition of ether, a second filtration, and washing of the filtrate with 0.1 M HCl, saturated $NaHCO_3$, and saturated NaCl. The solution was dried ($MgSO_4$) and filtered, the solid washed with ether, the filtrate concentrated *in vacuo*, and the residue placed under vacuum until constant weight was achieved to give 4.49 g (90%) of the desired ester as a light brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.68 (m, 1H), 5.19 (bd, J = 1.5 Hz, 1H), 5.15 (m, 1H), 4.78 (bd, J = 8.4 Hz, 1H), 4.20 (dt, J = 8.8, 5.8 Hz, 1H), 3.77 (s, 3H), 2.99 (m, 2H), 2.54 (t, J = 6.6 Hz, 2H), 1.76 (m, 2H), 1.42 (sextuplet, J = 7.3 Hz, 2H), 0.93 (t, J = 7.3 Hz, 3H); CIMS (NH_3) m/z 267 (M + NH_4^+, 100), 250 (M + H^+, 51). Anal. ($C_{10}H_{19}NO_4S$) C, H, N, S.

Preparation of Isoxazolines 17a,b. To a solution of **8b** (1.95 g, 5.83 mmol) and **16** (1.45 g, 5.82 mmol) in CH_2Cl_2 (10 mL) was added a 5% solution of NaOCl (Clorox; 16 mL, 11.2 mmol). The resulting mixture was rapidly stirred at room temperature for 2 days. The mixture was diluted with EtOAc and water and the layers were separated. The aqueous portion was washed with EtOAc, and the combined organic fraction was washed with saturated NaCl and dried over $MgSO_4$. Filtration, washing with EtOAc, and concentration *in vacuo* afforded a light brown oil, which was purified using flash chromatography (0−50% EtOAc/hexanes five-step gradient), giving four components. As determined using ^{1}H NMR, the least polar of these materials was the starting olefin and oxime. The next components isolated were the less polar (**17a**, fraction 11−12, 0.97 g, 29%) and more polar (**17b**, fractions 14−16, 1.04 g, 31%) diastereomers.

For **17a**: white solid; mp 125.2−126.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 5.21 (d, J = 7.7 Hz, 1H), 4.95 (m, 1H), 4.18 (m, 3H), 3.82 (s, 3H, coincident with m, 2H), 3.47 (dd, J = 16.5, 6.2 Hz, 1H), 3.01 (m, 3H), 2.75 (bt, J = 12.1 Hz, 2H), 2.24 (m, 2H), 1.96 (m, 1H), 1.82 (m, 4H), 1.47 (s, 9H, coincident with m, 2H), 1.27 (m, 2H), 0.95 (t, J = 7.0 Hz, 3H); CIMS (NH_3) m/z 599 (M + NH_4^+, 100). Anal. ($C_{28}H_{43}N_3O_8S$) C, H, N, S.

For **17b**: white solid; mp 131.8−132.7 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 5.25 (d, J = 9.5 Hz, 1H), 4.87 (m, 1H), 4.35 (dt, J = 9.2, 3.7 Hz, 1H), 4.15 (bs, 2H), 3.81 (d, J = 6.2 Hz, 2H), 3.78 (s, 3H), 3.49 (dd, J = 16.5, 10.3 Hz, 1H), 3.05 (t, J = 7.7 Hz, 2H), 2.97 (dd, J = 16.5, 7.0 Hz, 1H), 2.73 (bt, J = 12.1 Hz, 2H), 2.21 (m, 1H), 1.94 (m, 2H), 1.82 (m, 4H), 1.45 (s, 9H), 1.24 (m, 3H), 0.92 (t, J = 7.3 Hz, 3H); CIMS (NH_3) m/z 599 (M + NH_4^+, 100). Anal. ($C_{28}H_{43}N_3O_8S$) C, H, N, S.

Preparation of Carboxylic Acid 43a. To a solution of **17a** (320 mg, 0.550 mmol) in THF (5 mL) was added 0.5 M LiOH (2 mL, 1 mmol). After 6 h at room temperature, the pH was adjusted to 3 using 0.1 M HCl and the mixture extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and filtered, the solid was washed with CH_2Cl_2, and the filtrate was concentrated *in vacuo*. The crude carboxylic acid was purified using flash chromatography (0−15% MeOH/$CHCl_3$ step gradient) followed by crystallization from EtOAc/hexanes, affording 271 mg (87%) of the desired material as a white solid: mp 156.9−157.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C) δ 7.56 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 4.80 (m, 1H), 3.96 (bd, J = 13.2 Hz, 2H), 3.90 (d, J = 6.3 Hz, 2H), 3.77 (bs, 3H), 3.52 (t, J = 7.8 Hz, 1H), 3.38 (dd, J = 14.4, 10.0 Hz, 1H), 2.98 (t, J = 7.8 Hz, 2H), 2.76 (dt, J = 12.2, 1.7 Hz, 2H), 1.95 (m, 2H), 1.75 (m, 4H), 1.41 (s, 9H), 1.38 (d, J = 7.6 Hz, 1H), 1.25 (m, 4H), 0.88 (t, J = 7.3 Hz, 3H); CIMS (NH_3) m/z 467 (M + H − $C_4H_8CO_2$ $^{+\ +}$, 10), 171 (100). Anal. ($C_{27}H_{41}N_3O_8S$) C, H, N, S.

Prepared in a similar fashion to **17b** was **43b**: 262 mg (83%) as a white solid; mp 149.7−149.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.45 (d, J = 9.5 Hz, 1H), 4.92 (m, 1H), 4.37 (m, 1H), 4.15 (bs, 2H), 3.81 (d, J = 6.2 Hz, 2H), 3.47 (dd, J = 16.5, 9.9 Hz, 1H), 3.08 (t, J = 8.1 Hz, 2H), 3.01 (dd, J = 16.5, 7.0 Hz, 1H), 2.74 (bt, J = 12.1 Hz, 2H), 2.26 (m, 1H), 2.01 (m, 2H), 1.81 (m, 4H), 1.45 (s, 9H, coincident with m, 1H), 1.24 (m, 3H), 0.91 (t, J = 7.3 Hz, 3H); CIMS (NH_3) m/z 467 (M + + H − $C_4H_8CO_2^+$, 10), 171 (100). Anal. ($C_{27}H_{41}N_3O_8S\cdot 2H_2O$) C, H, N, S.

α-[(Butylsulfonyl)amino]-4,5-dihydro-3-[4-(4-piperidinylmethoxy)phenyl]-5-isoxazolepropanoic Acid Mono(trifluoroacetate) (Isomer 14a). To a solution of **43a** (98 mg, 0.173 mmol) in CH_2Cl_2 (1 mL) was added TFA (0.5 mL, 6.5 mmol). After 1 h at room temperature, the mixture was concentrated *in vacuo*, giving an oily residue. Crystallization from MeOH then afforded 28 mg (29%) of the desired product as a white solid: mp 239.4−240.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 6.58 (bs, 1H), 4.75 (m, 1H), 3.87 (d, J = 6.1 Hz, 2H), 3.51 (t, J = 6.1 Hz, 2H), 3.05 (dd, J = 17.1, 8.3 Hz, 1H), 2.97 (m, 2H), 2.83 (bt, J = 11.6 Hz, 2H), 1.93 (m, 4H), 1.63 (m, 2H), 1.48 (m, 2H), 1.34 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H); CIMS (NH_3) m/z 468 (M + H^+, 100). Anal. ($C_{24}H_{34}F_3N_3O_8S$) C, H, N, S.

α-[(Butylsulfonyl)amino]-4,5-dihydro-3-[4-(4-piperidinylmethoxy)phenyl]-5-isoxazolepropanoic Acid Mono(trifluoroacetate) (Isomer 14b). 14b was prepared in a similar fashion to **14a**: 67 mg (34%) as a white solid; mp 263.5 °C dec; ^{1}H NMR (400 MHz, DMSO-d_6 + TFA-d_1, 60 °C) δ 7.58 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.8 Hz, 1H), 7.00 (d, J = 8.8 Hz, 2H), 4.77 (m, 1H), 4.00 (dd, J = 10.3, 3.9 Hz, 1H), 3.92 (d, J = 6.1 Hz, 2H), 3.48 (dd, J = 16.8, 10.3 Hz, 1H), 3.31 (bd, J = 12.7 Hz, 2H), 3.09 (dd, J = 17.1, 7.3 Hz, 1H), 3.00 (m, 2H), 2.91 (m, 2H), 1.92 (bd, J = 14.2 Hz, 2H), 1.82 (m, 1H), 1.69 (m, 2H), 1.49 (m, 2H), 1.39 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H); CIMS (NH_3) m/z 468 (M + H^+, 100).

Preparation of Aldehyde 44a. To a suspension of PCC (11.52 g, 53.44 mmol) and NaOAc (4.38 g, 53.4 mmol) in CH_2Cl_2 (60 mL) at room temperature was added a solution of **21a** (10.00 g, 41.09 mmol) in CH_2Cl_2 (20 mL). After 4 h, the mixture was diluted with ether and filtered through a short column of Florisil. The eluent was concentrated *in vacuo* and placed under vacuum until constant weight was achieved, giving 8.32 g (84%) of the desired aldehyde as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (t, J = 1.5 Hz, 1H), 4.05 (bs, 2H), 2.64 (bt, J = 11.7 Hz, 2H), 2.45 (dt, J = 7.3, 1.5 Hz, 2H), 1.60 (m, 3H), 1.43 (s, 9H, coincident with m, 2H), 1.08 (dq, J = 12.1, 4.0 Hz, 2H); HRMS (CI-NH_3) m/z 242.1746 [(M + H)$^+$, calcd for $C_{13}H_{23}NO_3$ 242.1756].

Prepared in a similar fashion from **21b** was **44b**: 10.03 g (80%) as an oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (t, J = 1.5 Hz, 1H), 4.07 (bs, 2H), 2.67 (bt, 2H), 2.44 (dt, J = 7.3, 1.5 Hz,

2H), 1.64 (m, 4H), 1.45 (s, 9H), 1.37 (m, 1H), 1.27 (m, 2H), 1.10 (m, 2H); CIMS (NH_3) *m/z* 273 ($M + NH_4^+$, 100), 256 ($M + H^+$, 10).

Preparation of Oxime 22a. To a solution of **44a** (4.06 g, 16.8 mmol) in 50% EtOH/pyridine (20 mL) was added hydroxylamine hydrochloride (1.77 g, 25.5 mmol). After 20 h at room temperature, the mixture was diluted with ice−water, causing the product to separate as an oil. The oil was dissolved in ether, washed with 0.1 M HCl, water, saturated $CuSO_4$, water, and saturated NaCl, and dried over $MgSO_4$. Filtration and washing of the solids using ether and concentration of the filtrate *in vacuo* followed by purification using flash chromatography (10−50% EtOAc/hexanes) afforded 4.19 g (97%) of the oily oxime as a 1:1 mixture of *E*/*Z*-isomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (t, J = 6.2 Hz, 0.5H), 6.70 (t, J = 5.5 Hz, 0.5H), 4.06 (bs, 2H), 2.67 (bt, J = 12.8 Hz, 2H), 2.41 (m, 1H), 2.23 (m, 1H), 1.66 (bs, 2H), 1.45 (s, 9H, coincident with m, 4H), 1.08 (m, 2H); CIMS (NH_3) *m/z* 274 ($M + NH_4^+$, 50), 257 ($M + H^+$, 40), 256 (100). Anal. ($C_{13}H_{24}N_2O_3$) C, H, N.

Prepared in a similar fashion from **44b** was **22b**: 2.96 g (30%) as an oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (bs, 0.5H), 7.65 (bs, 0.5H), 7.42 (t, J = 5.9 Hz, 0.5H), 6.71 (t, J = 5.5 Hz, 0.5H), 4.08 (bs, 2H), 2.66 (bt, J = 12.1 Hz, 2H), 2.37 (m, 1H), 2.19 (m, 1H), 1.64 (bd, J = 12.4 Hz, 2H), 1.52 (m, 2H), 1.45 (s, 9H), 1.31 (m, 2H), 1.09 (m, 2H); CIMS (NH_3) *m/z* 274 ($M + NH_4^+$, 50), 257 ($M + H^+$, 40), 256 (100). Anal. ($C_{14}H_{26}N_2O_3$) C, H, N.

Preparation of Isoxazoline 45a. This material was prepared from **22a** and dimethyl itaconate in a fashion similar to **9a**, affording after purification using flash chromatography (0−50% EtOAc/hexanes) 510 mg (63%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06 (bd, J = 13.6 Hz, 2H), 3.78 (s, 3H), 3.67 (s, 3H), 3.57 (d, J = 17.6 Hz, 1H), 3.15 (d, J = 16.5 Hz, 1H), 3.06 (d, J = 17.6 Hz, 1H), 2.86 (d, J = 16.1 Hz, 1H), 2.65 (bt, J = 12.1 Hz, 2H), 2.36 (m, 2H), 1.65 (m, 2H, coincident with residual H_2O), 1.51 (bq, J = 7.7 Hz, 2H), 1.43 (s, 9H, coincident with m, 1H), 1.07 (m, 2H); CIMS (NH_3) *m/z* 430 ($M + NH_4^+$, 13), 413 ($M + H^+$, 18), 374 ($M + NH_4 - C_4H_8^+$, 100), 357 ($M + H - C_4H_8^+$, 34). Anal. ($C_{20}H_{32}N_2O_7$) C, H, N.

Prepared in a similar fashion from **22b** was **45b**: 1.82 g (70%) of 70% pure material, as an oil containing dimethyl itaconate; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07 (bs, 2H), 3.80 (s, 3H), 3.70 (s, 3H), 3.59 (d, J = 17.6 Hz, 1H), 3.18 (d, J = 16.5 Hz, 1H), 3.07 (d, J = 17.6 Hz, 1H), 2.88 (d, J = 16.5 Hz, 1H), 2.66 (bt, J = 12.5 Hz, 2H), 2.34 (t, J = 7.3 Hz, 2H), 1.62 (m, 4H), 1.45 (s, 9H), 1.41 (m, 1H), 1.30 (m, 2H), 1.07 (dq, J = 12.1, 4.0 Hz, 2H); CIMS (NH_3) *m/z* 444 ($M + NH_4^+$, 100).

Preparation of Dicarboxylic Acid 23a. This material was prepared from **45a** in a fashion similar to **41a**: 240 mg (68%) as a white solid after crystallization from EtOAc/hexanes; mp 154.4−154.9 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 4.04 (bd, J = 13.2 Hz, 2H), 3.52 (d, J = 17.8 Hz, 1H), 3.18 (d, J = 17.8 Hz, 1H), 2.97 (AB quartet, Δ = 32.6 Hz, J = 16.8 Hz, 2H), 2.72 (b, 2H), 2.39 (m, 2H), 1.71 (bd, J = 13.2 Hz, 2H), 1.51 (m, 3H), 1.43 (s, 9H), 1.05 (m, 2H); CIMS (NH_3) *m/z* 402 ($M + NH_4^+$, 100), 385 ($M + H^+$, 30). Anal. ($C_{18}H_{28}N_2O_7$) C, H, N.

Prepared in a similar fashion from **45b** was **23b**: 1.21 g (78%) as a white solid; mp 139.0 °C dec; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.08 (bs, 2H), 4.06 (m, 2H), 3.57 (d, J = 17.9 Hz, 1H), 3.19 (d, J = 16.8 Hz, 1H), 3.07 (d, J = 17.9 Hz, 1H), 2.99 (d, J = 16.8 Hz, 2H), 2.68 (bt, J = 12.1 Hz, 2H), 2.36 (m, 2H), 1.62 (m, 4H), 1.45 (s, 9H), 1.40 (m, 1H), 1.26 (m, 2H), 1.07 (m, 2H); MS (ESI) *m/z* 399 ($M + H^+$, 100), 343 ($M + H - C_4H_8^+$, 89). Anal. ($C_{19}H_{30}N_2O_7$) C, H, N.

Preparation of Isoxazolinylimide 24a. To a solution of **23a** (700 mg, 1.82 mmol) in THF (5 mL) was added DCC (378 mg, 1.83 mmol). After 20 min at room temperature, β-alanine *tert*-butyl ester hydrochloride (372 mg, 2.05 mmol) was added followed by Et_3N (0.30 mL, 2.1 mmol). After 3 h, the mixture was diluted with ether and filtered and the filtrate concentrated *in vacuo*. To the crude amide (430 mg) in THF (5 mL) was added *N*-hydroxysuccinimide (100 mg, 0.869 mmol) followed by DCC (180 mg, 0.872 mmol), and the resulting mixture was stirred at room temperature for 20 h. After the addition of ether, the mixture was filtered and the filtrate concentrated *in vacuo*. To the crude succinimide (402 mg) in DMF (5 mL) at 0 °C was added pentane-washed NaH (16 mg, 0.66 mmol). After 3 h, the reaction was quenched with HOAc and the mixture diluted with EtOAc. The mixture was washed with water followed by saturated $NaHCO_3$, water, 0.1 M HCl, and saturated NaCl and dried over $MgSO_4$. Filtration and washing of the solids with EtOAc and concentration of the filtrate *in vacuo* afforded an oily residue, which was purified using flash chromatography (0−5% MeOH/$CHCl_3$) to give 149 mg (46%) of the desired product as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09 (bs, 2H), 3.82 (t, J = 7.3 Hz, 2H), 3.54 (d, J = 17.2 Hz, 1H), 3.12 (d, J = 18.7 Hz, 1H), 2.98 (d, J = 17.2 Hz, 1H), 2.83 (d, J = 18.7 Hz, 1H), 2.69 (m, 1H), 2.57 (t, J = 7.3 Hz, 2H), 2.42 (m, 2H), 1.68 (m, 2H), 1.57 (m, 2H), 1.45 (s, 9H), 1.43 (s, 9H, coincident with m, 1H), 1.11 (m, 2H); MS (ESI) *m/z* 494 ($M + H^+$, 79), 225 (100). Anal. ($C_{25}H_{39}N_3O_7$) C, H, N.

Prepared in a similar fashion from **23a** and *tert*-butyl 4-aminobutanoate was **24b**: 96 mg (10%) as an oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.08 (bs, 2H), 3.61 (t, J = 7.0 Hz, 2H), 3.57 (d, J = 17.2 Hz, 1H), 3.11 (d, J = 18.5 Hz, 1H), 2.98 (d, J = 17.2 Hz, 1H), 2.81 (d, J = 18.5 Hz, 1H), 2.69 (bt, J = 11.7 Hz, 2H), 2.26 (t, J = 7.3 Hz, 2H), 1.89 (m, 2H), 1.68 (bs, 2H, coincident with H_2O), 1.57 (q, J = 7.3 Hz, 2H), 1.46 (s, 9H), 1.44 (s, 9H), 1.26 (m, 1H), 1.11 (m, 2H); CIMS (NH_3) *m/z* 525 ($M + NH_4^+$, 100). Anal. ($C_{26}H_{41}N_3O_7$) C, H, N.

Prepared in a similar fashion from **23b** and *tert*-butyl 4-aminobutanoate was **24c**: 101 mg (8%) as an oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.08 (bs, 2H), 3.60 (t, J = 7.0 Hz, 2H), 3.56 (d, J = 17.2 Hz, 1H), 3.11 (d, J = 18.7 Hz, 1H), 2.97 (d, J = 17.2 Hz, 1H), 2.81 (d, J = 18.7 Hz, 1H), 2.67 (m, 2H), 2.39 (bt, J = 8.0 Hz, 2H), 2.26 (t, J = 7.0 Hz, 2H), 1.89 (m, 2H), 1.64 (m, 4H), 1.46 (s, 9H), 1.44 (s, 9H), 1.33 (m, 2H), 1.12 (m, 2H); CIMS (NH_3) *m/z* 539 ($M + NH_4^+$, 100). Anal. ($C_{27}H_{43}N_3O_7$) C, H, N.

(±)-6,8-Dioxo-3-[2-(4-piperidinyl)ethyl]-1-oxa-2,7-diazaspiro[4.4]non-2-ene-7-propanoic Acid Mono(trifluoroacetate) (18). To a solution of **24a** (75 mg, 0.152 mmol) in CH_2Cl_2 (0.5 mL) was added TFA (0.5 mL). After 2 h at room temperature, the solution was concentrated *in vacuo* and the residue diluted with toluene and evaporated (2×). The oily residue was crystallized from MeOH/ether, affording 10 mg (15%) as a white solid after drying under vacuum: mp 178.0−179.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6, 60 °C) δ 12.15 (bs, 1H), 8.26 (bs, 2H), 3.64 (m, 2H), 3.64 (m, 2H), 3.39 (d, J = 17.8 Hz, 1H), 3.26 (m, 3H), 2.98 (AB quartet, Δ = 71.3 Hz, J = 18.3 Hz, 2H), 2.85 (m, 2H), 2.5 (m, 1H, coincident with DMSO-d_5), 2.37 (t, J = 7.6 Hz, 2H), 1.84 (bd, J = 11.7 Hz, 2H), 1.58 (m, 2H), 1.52 (t, J = 7.6 Hz, 2H), 1.29 (m, 2H); CIMS (NH_3) *m/z* 338 ($M + H^+$, 100). Anal. ($C_{18}H_{24}F_3N_3O_7$) C, H, N.

(±)-6,8-Dioxo-3-[2-(4-piperidinyl)ethyl]-1-oxa-2,7-diazaspiro[4.4]non-2-ene-7-butanoic Acid Mono(trifluoroacetate) (19). 19 was prepared in a similar fashion to **18**: 18 mg (31%) as a white solid; mp 133.4−135.1 °C; ^{1}H NMR (400 MHz, CD_3OD, 55 °C) δ 3.59 (t, J = 6.8 Hz, 2H), 3.64 (d, J = 17.7 Hz, 1H), 3.38 (bd, J = 12.9 Hz, 2H), 3.18 (d, J = 17.7 Hz, 1H), 2.98 (m, 4H), 2.45 (m, 2H), 2.31 (t, J = 7.1 Hz, 2H), 2.00 (m, 2H), 1.89 (pentuplet, J = 7.1 Hz, 2H), 1.40 (m, 2H); CIMS (NH_3) *m/z* 352 ($M + H^+$, 100). Anal. ($C_{17}H_{25}N_3O_5 \cdot CF_3CO_2H$) C, H, N.

(±)-6,8-Dioxo-3-[3-(4-piperidinyl]propyl]-1-oxa-2,7-diazaspiro[4.4]non-2-ene-7-butanoic Acid Mono(trifluoroacetate) (20). 20 was prepared in a similar fashion to **18**: 50 mg (58%) as a white solid; mp 104.9−106.7 °C; ^{1}H NMR (400 MHz, CD_3OD, 55 °C) δ 3.59 (t, J = 6.8 Hz, 2H), 3.49 (d, J = 17.7 Hz, 1H), 3.37 (bd, J = 12.7 Hz, 2H), 3.17 (d, J = 17.7 Hz, 1H), 2.97 (m, 4H), 2.41 (m, 2H), 2.32 (t, J = 7.3 Hz, 2H), 2.96 (bd, J = 14.6 Hz, 2H), 1.89 (m, 2H), 1.65 (m, 3H), 1.39 (m, 4H); MS (ESI) *m/z* 366 ($M + H^+$, 100). Anal. ($C_{19}H_{27}N_3O_5 \cdot CF_3CO_2H \cdot H_2O$) C, H, N.

Preparation of Isoxazolinylacetamide 46. To a solution of **28** (644 mg, 1.89 mmol), β-alanine methyl ester hydrochloride (280 mg, 2.00 mmol), and TBTU (1.272 g, 3.96 mmol) in DMF (15 mL) was added Et_3N (0.80 mL, 5.7 mmol). The resulting mixture was stirred at room temperature for 3 h and then diluted with EtOAc, washed with water, saturated $NaHCO_3$, 0.1 M HCl, and saturated NaCl, and dried over $MgSO_4$. Filtration and washing of the solids with EtOAc and

concentration of the filtrate *in vacuo* was followed by purification using flash chromatography (0−4% MeOH/$CHCl_3$) to give 504 mg (63%) of the desired amide as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (bt, 1H), 4.85 (m, 1H), 4.07 (bs, 2H), 3.71 (s, 3H), 3.52 (q, J = 6.1 Hz, 2H), 3.08 (dd, J = 17.1, 10.3 Hz, 1H), 2.75 (dd, J = 17.1, 7.3 Hz, 1H), 2.68 (bt, J = 11.7 Hz, 2H), 2.54 (m, 3H), 2.44 (dd, J = 14.6, 5.4 Hz, 1H), 2.36 (bt, J = 6.4 Hz, 2H), 1.65 (m, 2H), 1.52 (q, J = 7.6 Hz, 2H), 1.45 (s, 9H, coincident with m, 1H), 1.12 (m, 2H); MS (ESI) m/z 426 ($M + H^+$, 100). Anal. ($C_{21}H_{35}N_3O_6 \cdot 0.5\ H_2O$) C, H, N.

Prepared in a similar fashion from **33** and β-alanine ethyl ester hydrochloride was **47**: 1.387 g (48%) as a white solid; mp 102.0−102.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (AB quartet, Δ = 21.2 Hz, J = 8.8 Hz, 4H), 6.36 (bt, J = 4.8 Hz, 1H), 5.16 (m, 1H), 4.16 (q, J = 7.0 Hz, 2H), 3.54 (m, 3H), 3.22 (dd, J = 16.8, 7.7 Hz, 1H), 2.68 (dd, J = 14.6, 6.2 Hz, 1H), 2.57 (dd, J = 14.6, 6.2 Hz, 1H), 2.52 (m, 2H), 1.28 (t, J = 7.0 Hz, 3H); MS (ESI) m/z 330 ($M + H^+$, 100). Anal. ($C_{17}H_{19}N_3O_4$) C, H, N.

Preparation of Amine 48. To a solution of **46** (504 mg, 1.18 mmol) in CH_2Cl_2 (4 mL) was added TFA (2 mL). After 1 h, the mixture was concentrated *in vacuo* and purified twice using reverse phase preparative HPLC (220 nm detection), affording 71 mg (14%) of the desired amine as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.53 (bt, J = 5.8 Hz, 1H), 4.88 (m, 1H), 3.71 (s, 3H), 3.52 (q, J = 6.2 Hz, 2H), 3.41 (bd, J = 12.4 Hz, 2H), 3.09 (dd, J = 17.2, 10.2 Hz, 1H), 2.88 (bq, J = 11.0 Hz, 2H), 2.77 (dd, J = 17.6, 7.7 Hz, 1H), 2.52 (m, 3H), 2.46 (dd, J = 14.6, 5.5 Hz, 1H), 2.37 (bt, J = 7.0 Hz, 2H), 1.91 (bd, J = 10.6 Hz, 2H), 1.58 (m, 5H); MS (ESI) m/z 312 ($M + H^+$, 100). Anal. ($C_{16}H_{27}N_3O_4 \cdot CF_3CO_2H \cdot H_2O$) C, H, N:

(±)-*N*-[[4,5-Dihydro-3-[2-(4-piperidinyl)ethyl]-5-isoxazolyl]acetyl]-β-alanine Mono(trifluoroacetate) (25). To a solution of **48** (38 mg, 0.089 mmol) in 0.3 N HEPES buffer (pH = 7.1) was added rabbit liver esterase (Sigma; 20 μL, 9 units). After 5 days at 37 °C, protein was removed using ultrafiltration, and the filtrate was purified using reverse phase preparative HPLC (220 nm detection), affording 13 mg (34%) of the desired acid as a colorless amorphous solid: ^{1}H NMR (300 MHz, CD_3OD) δ 4.84 (m, 1H, coincident with H_2O), 3.40 (m, 4H), 3.12 (dd, J = 17.6, 10.2 Hz, 1H), 2.95 (dt, J = 12.8, 2.9 Hz, 2H), 2.80 (dd, J = 17.2, 7.3 Hz, 1H), 2.51 (dd, J = 14.3, 6.6 Hz, 1H), 2.49 (t, J = 6.6 Hz, 2H), 2.39 (m, 3H), 1.57 (m, 3H), 1.35 (m, 2H); MS (ESI) m/z 312 ($M + H^+$, 100). Anal. ($C_{15}H_{25}N_3O_4 \cdot 1.14\ CF_3CO_2H$) C, H, N.

(±)-*N*-[[4,5-Dihydro-3-[3-(4-piperidinyl)propyl]-5-isoxazolyl]acetyl]-β-alanine Mono(trifluoroacetate) (26). 26 was prepared in a similar fashion to **25** as a colorless oil: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.77 (bs, 1H), 8.49 (bs, 1H), 8.04 (bt, J = 5.5 Hz, 2H), 4.71 (m, 1H), 3.20 (m, 5H), 3.03 (dd, J = 17.2, 10.2 Hz, 1H), 2.81 (bq, J = 11.0 Hz, 2H), 2.67 (dd, J = 17.2, 7.0 Hz, 1H), 2.39 (m, 3H), 2.26 (m, 4H), 1.78 (bd, J = 12.4 Hz, 2H), 1.49 (m, 3H), 1.24 (m, 4H); MS (ESI) m/z 326 ($M + H^+$, 100). Anal. ($C_{16}H_{27}N_3O_4 \cdot 0.8\ CF_3CO_2H \cdot 4\ H_2O$) C, H, N.

(±)-*N*-[[4,5-Dihydro-3-(4-piperidinylmethyl)-5-isoxazolyl]acetyl]-β-alanine Mono(trifluoroacetate) (27). 27 was prepared in a similar manner to **25** as a colorless oil: ^{1}H NMR (300 MHz, CD_3OD) δ 4.85 (m, 1H, coincident with H_2O), 3.41 (m, 4H), 3.14 (dd, J = 17.2, 10.2 Hz, 1H), 3.00 (bt, J = 12.8 Hz, 2H), 2.83 (dd, J = 17.2, 7.1 Hz, 1H), 2.50 (m, 3H), 2.41 (dd, J = 14.2, 6.2 Hz, 1H), 2.34 (d, J = 6.6 Hz, 2H), 1.97 (m, 3H), 1.44 (m, 2H); MS (NH_3-DCI) m/z 298 ($M + H^+$, 100). Anal. ($C_{14}H_{23}N_3O_4 \bullet 1.4\ CF_3CO_2H$) C, H , N.

Preparation of Benzamidine 29. Into a solution of **47** (1.65 g, 5.01 mmol) in EtOH (150 mL) at 0 °C (bath temperature) was bubbled H_2SO_4-dried HCl gas for 2 h. The ice−water bath was removed, and the resulting solution was allowed to stand at room temperature overnight (18 h). After concentration *in vacuo*, the resulting solid was redissolved in EtOH (100 mL) and $(NH_4)_2CO_3$ (14.41 g, 0.150 mol) added. The suspension was stirred at room temperature for 20 h, the solids were collected by filtration and washed with EtOH, and the filtrate was concentrated *in vacuo*. Purification using flash chromatography (0−20% MeOH/$CHCl_3$) afforded 713 mg (41%) of the desired amidine as a white solid: mp 152.0−152.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (AB quartet, Δ = 16.8 Hz, J = 8.4 Hz, 4H), 5.13 (m, 1H), 4.12 (q, J = 7.3 Hz, 2H), 3.58 (dd, J = 17.2, 10.6 Hz, 1H), 3.44 (m, 2H), 3.26 (dd, J = 17.2, 7.3 Hz, 1H, coincident with $CHCl_3$), 2.57 (m, 4H), 1.25 (t, J = 7.3 Hz, 2H); MS (ESI) m/z 347 ($M + H^+$, 100). The analytical sample was obtained after purification using reverse phase preparative HPLC. Anal. ($C_{17}H_{22}N_4O_4 \cdot 1.5\ CF_3CO_2H$) C, H, N.

(±)-*N*-[[3-[4-(Aminoiminomethyl)phenyl]-4,5-dihydro-5-isoxazolyl]acetyl]-β-alanine (30). To a solution of **29** (346 mg, 1.00 mmol) in EtOH (6 mL) was added 0.5 M LiOH (6 mL, 3 mmol). Upon mixing, the zwitterionic product began to separate from solution. After stirring for 18 h at room temperature, the solid was collected by filtration, washed with water, and dried under vacuum until constant weight was achieved, affording 365 mg (115%) of the desired acid as a white solid: ^{1}H NMR (300 MHz, CD_3OD) δ 7.86 (AB quartet, Δ = 18.3 Hz, J = 8.4 Hz, 4H), 5.21 (m, 1H), 3.57 (dd, J = 17.2, 10.6 Hz, 1H), 3.43 (m, 2H), 3.25 (dd, J = 17.2, 7.3 Hz, 1H, coincident with CHD_2OD), 2.64 (dd, J = 14.6, 6.8 Hz, 1H), 2.52 (m, 3H); MS (ESI) m/z 319 ($M + H^+$, 100); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.22, 169.13, 165.48, 156.50, 129.51, 129.06, 127.23, 79.16, 41.06, 39.34, 35.18, 34.28. The analytical sample was purified using preparative reverse phase HPLC. Anal. ($C_{15}H_{18}N_4O_4 \cdot CF_3CO_2H$) C, H, N.

Chiral Resolution of XR300 (29). The resolution of XR300 was accomplished using chiral HPLC on a Chiracel OJ-50 column at 35 °C that was eluted at a 10 mL/min flow rate under isocratic conditions using 0.1% TFA−15% EtOH−85% hexanes. Isomer 1: retention time = 17.5 min, $[\alpha]_D$ +75.28° (c 0.360, $CHCl_3$). Isomer 2: retention time = 21.9 min, $[\alpha]_D$ −66.18° (c 0.340, $CHCl_3$).

Classical Resolution of Acid 33 *via* Crystallization of the Cinchonidine Salts. Isoxazoline (*R,S*)-**33** (2.3 g, 10 mmol) was dissolved in hot acetone (50 mL), cinchonidine (2.9 g, 9.8 mmol) added, and the solution allowed to stand at 5 °C overnight. The resulting solid was filtered to give 4.4 g of **49** as a white crystalline material. Recrystallization from acetone (70 mL) gave 2.0 g of **49** (92% ee by HPLC). A second recrystallization from acetone (30 mL) then afforded 1.5 g (29%) of **49** (98% ee by HPLC). To **49** (260 mg, 0.50 mmol) in chloroform (3 mL) was added 1 M HCl in ether (3 mL, 3 mmol), and the resulting precipitate was collected by filtration. The filtrate was concentrated *in vacuo* to give (*S*)-**33** (120 mg, quantitative), $[\alpha]_D$ +138.38 (c 0.198, $CHCl_3$).

The mother liquor was concentrated to a volume of approximately 35 mL. The solution was cooled to room temperature and the resulting solid filtered. The mother liquor was concentrated *in vacuo* and placed under vacuum to give 1.2 g (23%) of **50** (90% ee by HPLC). Processing of **50** in a fashion similar to **49** then gave (*R*)-**33** (122 mg, quantitative), $[\alpha]_D$ −142.93 (c 0.184, $CHCl_3$).

X-ray Crystallography of $C_{34}H_{38}N_4O_5$ (49). Crystal data: $C_{34}H_{38}N_4O_5$ from acetone (cooling), colorless, thin needles, −0.08 × 0.43 × 0.55 mm, orthorhombic, $P2_12_12_1$ (No. 19); a = 16.349(1), b = 30.235(3), c = 6.333(1) Å; T = −48 °C, V = 3130.5 Å^3, Z = 4; FW = 582.70, d_{calc} = 1.236 g/cm^3, μ(Mo) = 0.78 cm^{-1}.

The data were collected on a Rigaku RU300 diffractometer, *R*-axis image plate area detector, Mo Kα radiation, filament size = 0.5 mm × 1.0 cm, anode power = 5050 kV × 120 mA, crystal to plate distance = 85.0 mm, 210 μm pixel raster, number of frames = 45, oscillation range = 4.0°/frame, exposure = 4.0 min/frame, box sum, integration, 12 551 data collected, 2.8° ≤ 2θ ≥ 48.3°, maximum h, k, l = 18, 34, 7, no absorption correction, 3852 duplicates, 5.0% *R*-merge, 1935 unique reflections with $I \geq 3.0\sigma(I)$.

The structure was solved and refined by direct methods (MULTAN). The asymmetric unit consists of one ion pair and one acetone solvate in general positions. The hydrogen atoms were idealized from observed positions, while the enantiomorph was fixed from the known configuration of cinchonidine. Refinement was by full-matrix least-squares on F, with scattering factors from the *International Tables for X-ray Crystallography*,[34] biweight = $[\sigma^2(I) + 0.0009(I)^2]^{-1/2}$ (excluded 13); refined anisotropic, all non-hydrogen atoms; fixed atoms, hydrogen atoms; 388 parameters, data/parameter ratio = 4.95,

$R = 0.050$, $R_w = 0.044$, error of fit = 1.33, max D/s = 0.30, largest residual density = 0.18 q/Å^3 (background).

From the known stereochemistry of cinchonidine (C11′(*R*), C12′(*S*), C14″(*R*), C15′(*S*)), the stereochemistry of the isoxazoline was determined to be the (*S*)-configuration. In the lattice, the anion strongly hydrogen bonds to the hydroxy and amine groups of the cation. The acetone is easily lost through channels along the c-axis.

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Supporting Information Available: Tables of relevant details of the X-ray crystallographic studies, tables of final atomic parameters, anisotropic thermal parameters, and selected bond distances and angles, structure amplitudes, a table of elemental analysis data, a 400 MHz ^{1}H NMR spectrum of **10a**, and chiral phase HPLC chromatograms of **34** and **35** (13 pages). Ordering information is given on any current masthead page.

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